JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

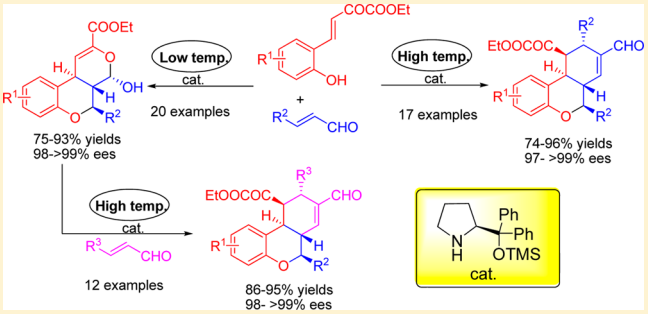
Organocatalytic Diversity-Oriented Asymmetric Synthesis of Tricyclic Chroman Derivatives

Zhi-Cong Geng, Shao-Yun Zhang, Nai-Kai Li, Ning Li, Jian Chen, Hai-Yan Li, and Xing-Wang Wang*

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, People's Republic of China

Supporting Information

ABSTRACT: The tandem *oxo*-Michael-IED/HDA and *oxo*-Michael-IED/HDA-Michael-Aldol condensation transformations between (*E*)-2-hydroxyaryl-2-oxobut-3-enoate derivatives with enals have been developed in the presence of (*S*)-diphenylprolinol trimethylsilyl ether as an organocatalyst. Two types of tricyclic chroman derivatives were, respectively, obtained, by adjusting the reactant ratio and reaction temperature, in good yields (up to 96%) with excellent enantioselectivities (up to >99%) and good diastereoselectivities (up to >30/1). It should be noted that the divergent chiral chroman derivatives were obtained by successive reaction of (*E*)-2-hydroxyaryl-2-oxobut-3-enoate derivatives with two different enal substrates in highly catalytic results.



INTRODUCTION

The chiral functionalized chromans are found in many natural products and synthetic molecules, which exhibit broad-spectrum biological activities.[1] The synthesis of the optically active chroman derivatives has attracted much attention from both academia and the pharmaceutical industry. Some multistep synthetic strategies have been developed to construct bioactive chroman complexes,[2] in which asymmetric induction was realized by the use of chiral building blocks,[3] kinetic resolution,[4] and transition-metal-mediated asymmetric catalysis.[5]

The first organocatalytic enantioselective synthesis of a chromene skeleton was reported by Arvidsson et al. in 2006 using salicylaldehyde as the substrate.[6a] Since then, asymmetric syntheses of chroman or chromene skeletons via organocatalysis attracted great attention for research groups worldwide.[6] Although great progress in the syntheses of those two kinds of skeletons via an organocatalytic domino reaction[7,8] has been made in recent several years, the access to tricyclic compounds containing chroman units has been scarcely reported in the literature. Some important tricyclic compounds with chroman units have displayed extensive biological activities (Figure 1). For example, Calyxin I is the natural compound extracted from seeds of *Alpinia blepharocalyx*, which is used for the treatment of stomach disorders.[9] Bispyran SCH 900229 is a γ-secretase inhibitor.[10] Epiconicol, isolated from ascidians *Aplidium conicum* and *Synoicum castellatum*, exhibits cytotoxic activities against P388, A549.[11] The last compound in Figure 1 is the CB1 full agonist.[12]

In view of the significance of those tricyclic chroman compounds, the development of new divergent and efficient synthetic strategies to enantiomerically enriched chroman derivatives with tricyclic structures remains highly demanding and challenging. Herein, we report our preliminary results on the facile and efficient synthesis of optically active tricyclic chroman derivatives by organocatalytic tandem *oxo*-Michael-IED/HDA or *oxo*-Michael-IED/HDA-Michael-Aldol condensation (IED/HAD: inverse-electron-demand hetero-Diels–Alder[13−15]) transformation between (*E*)-2-hydroxyaryl-2-oxo-

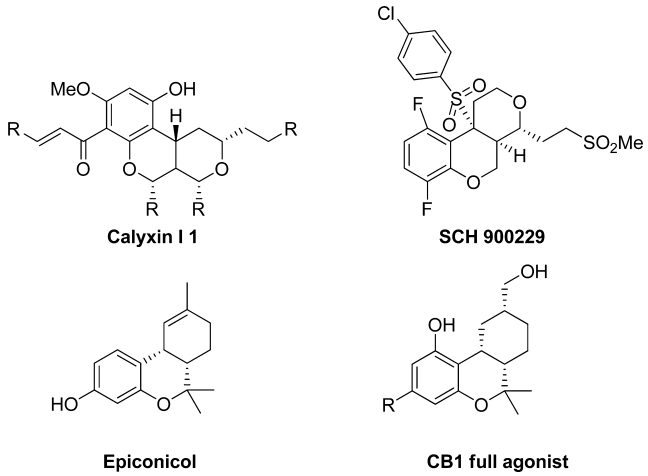


Figure 1. Some bioactive tricyclic compounds containing a chroman backbone.

Received: July 21, 2014
Published: October 16, 2014

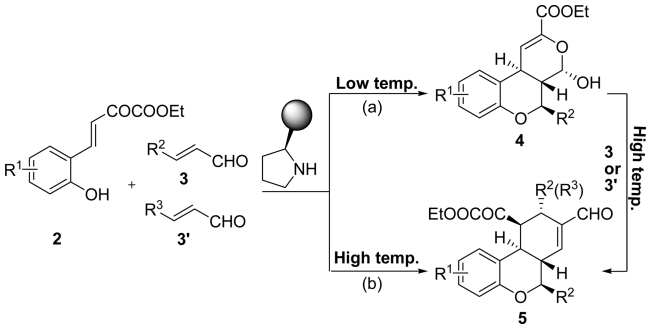
   dx.doi.org/10.1021/jo501560m | J. Org. Chem. 2014, 79, 10772–10785

but-3-enoates and enals in very good yields with excellent diastereo- and enantioselectivities.

RESULTS AND DISCUSSION

The 4-substituted (*E*)-2-oxo-3-butenoates are important substrates due to their versatile reaction sites.[16] It was envisioned that the *oxo*-Michael addition reaction between the designed (*E*)-2-hydroxyaryl-2-oxobut-3-enoate **2a** and cinnamaldehyde **3a** would be initiated through iminium catalysis by a secondary amine, and subsequent cyclization leads to access to the chroman skeleton. To our delight, it was found that two types of chiral tricyclic chroman derivatives **4** and **5** were obtained, respectively, through organocatalytic domino *oxo*-Michael-IED/HDA and *oxo*-Michael-IED/HDA-Michael-Aldol condensation reactions by readily adjusting both reactant ratio and reaction temperature (Scheme 1).

Scheme 1. Synthesis of Two Types of Tricyclic Chroman Derivatives



First, the reaction between **2a** and **3a** was investigated in the presence of 20 mol % of (*S*)-proline or its derivatives **1a**–**e** and the same amount of benzoic acid **A1** as organocatalyst in toluene.[17] (*S*)-Proline **1c** and its derivatives **1a** and **1b** were found to be ineffective for the reaction, because they afforded either trace or racemic products after 12 h (Table 1, entries 1–3). When α,α-diphenylprolinol **1d** was used as an organocatalyst, **4a** as the major product was obtained in 35% yield and 95% enantioselectivity (Table 1, entry 4). With (*S*)-diphenylprolinol trimethylsilyl ether **1e** as the organocatalyst, **5a** as the major product was obtained in 89% yield with >99% enantioselectivity and 19/1 diastereoselectivity (Table 1, entry 5). In order to improve the catalytic results for product **5a**, the other reaction parameters, including reaction solvents and additives, were investigated. After screening several commmon solvents for this reaction, chlorobenzene was proved to the optimal reaction medium in consideration of yield, diastereoselectivity, and enantioselectivity (Table 1, entries 6–9). The product **5a** could be obtained in 80% yield and >99% enantioselectivity under additive-free conditions after 18 h (Table 1, entry 10). Subsequently, two other Brønsted acids **A2** and **A3** were tested as additives for this transformation (Table 1, entries 11 and 12). With **A2** as additive, the product **5a** was afforded in only 45% yield (Table 1, entry 11). Finally, **A3** was selected as the optimal additive in regard to the reactivity. In addition, we attempted to reduce the catalyst loading of **1e**; the product **5a** was obtained in 87% yield and >99% enantioselectivity with a prolonged reaction time of 24 h (Table 1, entry 13). Thus, the optimal reaction conditions for **5a** were finally established as the reaction being performed in the presence of **1e** (20 mol %) as the catalyst and **A3** (20 mol %) as the additive in PhCl at 30 °C.

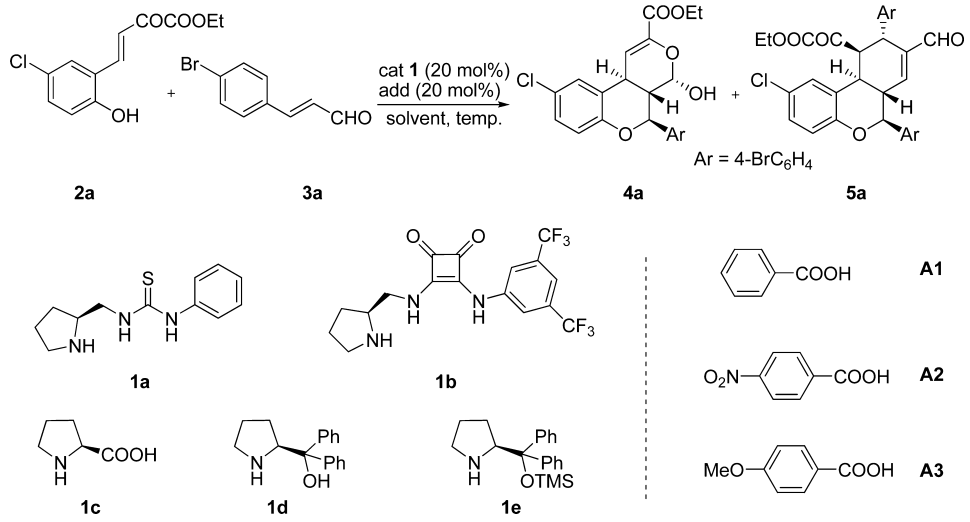
On the other hand, if the reaction time was changed from 12 h to 40 min under the optimal reaction conditions to **5a**, we found that product **4a** could be isolated in 40% yield with 99% enantioselectivity (Table 1, entry 14). It was considered that the yield of **4a** might be improved by tuning the ratio of **2a** to **3a** at high reaction temperature (Table 1, entries 15 and 16). Gratefully, the yield of **4a** could be increased to 64% with a 1.5/1 molar ratio of **2a** to **3a** at 30 °C (Table 1, entry 16). Subsequently, the reaction temperature was investigated. It was found that the yield of **4a** could be further increased to 80% by lowering the reaction temperature to −5 °C within 20 h (Table 1, entry 17). A slight increase of the yield from 80% to 87% was observed by reducing the reactant concentration (Table 1, entry 18). From the catalytic result, it was observed that low temperature could efficiently inhibit the transformation of **4a** to **5a**. In view of both the instability of cinnamaldehyde derivatives and the relatively complex synthesis route for **2a**, decreasing the loading of substrate **2a** was reasonable. Subsequently, the reactant loading of **3a** was increased at −5 °C (Table 1, entries 19–21), and the best results (89% yield and >99% ee) for **4a** were obtained with a 1/2 molar ratio of **2a** to **3a** at −5 °C (Table 1, entry 20). When the catalyst loading was reduced to 10 mol %, only 67% yield for **4a** was obtained even after 36 h (Table 1, entry 22).

With the optimized reaction conditions in hand, the substrate scope for **4** was first explored, and the results are summarized in Table 2. With the use of **2a** as the nucleophilic reagent, a series of α,β-unsaturated aldehydes **3** were examined to study the effects of electronic and steric properties on both enantioselectivity and reactivity. For aryl-substituted α,β-unsaturated aldehydes **3** bearing either electron-withdrawing or electron-donating groups in the *m*- or *p*-position of aromatic rings, all the reactions gave the desired products **4a**–**4h** in good yields (78–91%) with excellent enantioselectivities (>99%) (Table 2, entries 1–8). Aromatic heterocyclic α,β-unsaturated aldehydes such as 3-(1-tosyl-1*H*-indol-3-yl)acrylaldehyde **3j** showed good performance and provided product **4i** in 75% yield with >99% enantioselectivity (Table 2, entry 9). To our delight, aliphatic α,β-unsaturated aldehydes also exhibited promising results. With crotonaldehyde **3k** as substrate, the product **4j** was obtained in 93% yield with >99% enantioselectivity (Table 2, entry 10). The other alkyl-substituted α,β-unsaturated aldehydes, such as *trans*-2-pentenal **3l**, *trans*-2-hexenal **3m**, *trans*-2-octenal **3n**, *trans*-2-decenal **3o**, and *trans*, *cis*-2, 6-nonadienal **3p**, were also tolerated and provided the desired products **4k**–**4o** in 82–90% yields with >99% enantioselectivities, respectively (Table 2, entries 11–15). In addition, nucleophilic reagents **2b**–**2f** with different kinds of substituents in aryl rings were investigated, and the products **4p**–**4t** were obtained in good yields (78–87%) with excellent enantioselectivities (98–>99%), regardless of electronic features and the position of the substituents on the aromatic rings of (*E*)-2-hydroxyaryl-2-oxobut-3-enoate **2** (Table 2, entries 16–20).

Then, we turned our attention to the substrate scope of the desired products **5**. First, with **2a** as the substrate, structural variation of α,β-unsaturated aldehydes was investigated. As shown in Table 3, the electronic nature of the aryl rings of α,β-unsaturated aldehydes seemed to have limited influences on the enantioselectivities. Regardless of electronic property and the steric hindrance of substituents attached to the aryl rings, all the reactions proceeded well to afford the products in good yields

dx.doi.org/10.1021/jo501560m | J. Org. Chem. 2014, 79, 10772–10785

Table 1. Conditions Screening[a]



entry	cat.	solvent	add.	temp. (°C)	time (h)	yield **4a**/**5a** (%)[b]	dr[c]	ee (%)[d]
1	**1a**	PhMe	**A1**	30	12	<10/<10	−/−	−/−
2	**1b**	PhMe	**A1**	30	12	<10/<10	−/−	−/−
3	**1c**	PhMe	**A1**	30	12	32/<10	>30:1/−	0/−
4	**1d**	PhMe	**A1**	30	12	35/<10	>30:1/−	95/−
5	**1e**	PhMe	**A1**	30	12	<10/89	−/19:1	−/>99
6	**1e**	PhCl	**A1**	30	12	<10/86	−/>30:1	−/>99
7	**1e**	$PhCF_3$	**A1**	30	12	<10/70	−/>30:1	−/>99
8	**1e**	$CHCl_3$	**A1**	30	12	<10/86	−/19:1	−/>99
9	**1e**	THF	**A1**	30	12	<10/50	−/24:1	−/>99
10	**1e**	PhCl	−	30	18	<10/80	−/>30:1	−/>99
11	**1e**	PhCl	**A2**	30	12	<10/45	−/>30:1	−/>99
12	**1e**	PhCl	**A3**	30	12	<10/90	−/>30:1	−/>99
13[e]	**1e**	PhCl	**A3**	30	24	<10/87	−/>30:1	−/>99
14	**1e**	PhCl	**A3**	30	40 min	40/34	>30:1/−	>99/−
15[f]	**1e**	PhCl	**A3**	30	50 min	56/<10	>30:1/−	>99/−
16[g]	**1e**	PhCl	**A3**	30	80 min	64/<10	>30:1/−	>99/−
17[g]	**1e**	PhCl	**A3**	−5	20	80/<10	>30:1/−	>99/−
18[g,h]	**1e**	PhCl	**A3**	−5	20	87/<10	>30:1/−	>99/−
19[h,i]	**1e**	PhCl	**A3**	−5	10	83/<10	>30:1/−	>99/−
20[h,j]	**1e**	PhCl	**A3**	−5	18	89/<10	>30:1/−	>99/−
21[h,k]	**1e**	PhCl	**A3**	−5	24	86/<10	>30:1/−	>99/−
22[e,h,j]	**1e**	PhCl	**A3**	−5	36	67/<10	>30:1/−	>99/−

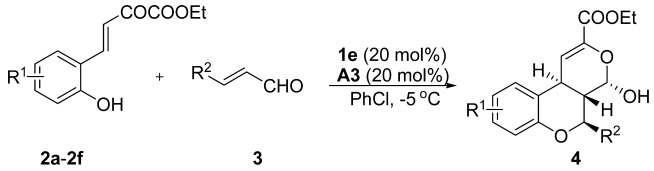
[a]Unless noted, reactions were carried out with **2a** (0.10 mmol), **3a** (0.3 mmol), cat. (20 mol %), and additive (20 mol %) and in solvent (1.0 mL). The yield was based on **2a**. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Determined by chiral HPLC analysis. [e]With 10 mol % **1e**. [f]**2a** (0.10 mmol), **3a** (0.11 mmol). [g]**2a** (0.15 mmol), **3a** (0.10 mmol). The yield was based on **3a**. [h]In 2 mL of PhCl. [i]**2a** (0.10 mmol), **3a** (0.30 mmol). [j]**2a** (0.10 mmol), **3a** (0.20 mmol). [k]**2a** (0.10 mmol), **3a** (0.15 mmol).

ranging from 80% to 95% with excellent enantioselectivities (Table 3, entries 1−9). The catalytic results of 74% yield with >99% enantioselectivity were obtained with aromatic heterocyclic α,β-unsaturated aldehyde **3j** as substrate (Table 3, entry 10). In addition, the electronic features and the position of the substituents on the aromatic rings of **2** also showed marginal influence on the yields and level of the enantioselectivities. The desired products **5k**−**5p** were afforded in 90−96% yields with 97% to >99% enantioselectivities (Table 3, entries 11−17). Good diastereoselectivities (>10/1 dr) were obtained for all of the above cases. Fortunately, the single crystals of **4a** and **5c** were obtained by recrystallization from petroleum ether/CH_2Cl_2, and the configurations of the products were unambiguously determined by X-ray analysis (see the Supporting Information).[18]

When **4a** was treated under identical reaction conditions, product **5a** was obtained in 88% yield with 99% enantioselectivity (Scheme 2). We thought that this phenomenon could provide important synthetic strategy to obtain diverse products by combinations of different reaction conditions of products **4** and **5**. In order to test the potential of this synthetic strategy, both **2a** and four α,β-unsaturated aldehydes **3a**, **3f**, **3h**, and **3i** were chosen as the substrates. Sixteen diverse products might be obtained theoretically by different combinations of α,β-unsaturated aldehydes. Gratefully, all of these possibilities were realized, and the results are summarized in Table 4. The desired products **5a**, **5f**, **5h** and **5i** with the same aryl substituents on the tricyclic skeletons were obtaind in 89−95% yields with >99% enantioselectivities under the identical reaction conditions for the synthesis of **5**. For the synthesis of the products

dx.doi.org/10.1021/jo501560m | J. Org. Chem. 2014, 79, 10772−10785

Table 2. Substrates Scope for 4[a]



2a-2f **3** **4**

R^1 = 5-Cl, **2a**; R^1 = 5-NO_2, **2b**
R^1 = 5-Me, **2c**; R^1 = 4-Me, **2d**
R^1 = 3,5-Br_2, **2e**; R^1 = H, **2f**

entry	R^1	R^2	time (h)	product	yield (%)[b]	ee (%)[c]
1	**2a**	4-BrC_6H_4/**3a**	18	**4a**	89	>99
2	**2a**	4-ClC_6H_4/**3b**	18	**4b**	86	>99
3	**2a**	4-CNC_6H_4/**3c**	6	**4c**	85	>99
4	**2a**	4-$NO_2C_6H_4$/**3d**	6	**4d**	90	>99
5	**2a**	3-$NO_2C_6H_4$/**3e**	6	**4e**	91	>99
6	**2a**	4-$MeOC_6H_4$/**3f**	36	**4f**	80	>99
7	**2a**	4-MeC_6H_4/**3h**	24	**4g**	78	>99
8	**2a**	C_6H_5/**3i**	18	**4h**	88	>99
9	**2a**	*N*-Ts-3-indolyl/**3j**	24	**4i**	75	>99
10[d]	**2a**	Me/**3k**	18	**4j**	93	>99
11[d]	**2a**	Et/**3l**	18	**4k**	90	>99
12[d]	**2a**	*n*-Pr/**3m**	18	**4l**	88	>99
13[d]	**2a**	*n*-pentyl/**3n**	18	**4m**	83	>99
14[d]	**2a**	*n*-heptyl/**3o**	18	**4n**	85	>99
15[d]	**2a**	(*Z*)-hex-3-en-1-yl/**3p**	18	**4o**	82	>99
16[d]	**2b**	Me/**3k**	20	**4p**	78	>99
17[d]	**2c**	Me/**3k**	18	**4q**	85	98
18[d]	**2d**	Me/**3k**	18	**4r**	82	>99
19	**2e**	4-CNC_6H_4/**3c**	20	**4s**	84	>99
20	**2f**	4-BrC_6H_4/**3a**	18	**4t**	87	>99

[a]Unless noted, reactions were carried out with **2a** (0.10 mmol), **3a** (0.20 mmol), **1** (20 mol %), and *p*-$MeOC_6H_4COOH$ (20 mol %) and in PhCl (2.0 mL) at −5 °C. [b]Isolated yield. [c]Determined by chiral HPLC analysis; the products were obtained with >10/1 dr. [d]**3** (0.50 mmol).

5aa−**5ac** with the different aryl substituents on the tricyclic skeletons, the compound **4a** was first synthesized by the reaction between **2a** and *α*,*β*-unsaturated aldehyde **3a**. Subsequently, **4a** was employed to react with *α*,*β*-unsaturated aldehyde **3f**, **3h**, and **3i**, respectively, which provided the desired products **5aa**−**5ac** in 89−90% yields with >99% enantioselectivities. The products **5fa**−**5fc**, **5ha**−**5hc**, and **5ia**−**5ic** could be obtained with the same procedure. All the products were obtained in good yields (86−95%) with excellent enantioselectivities (98−>99%) and good diastereoselectivities (>10/1).

In order to further extend the functional groups of the desired products, it was found that the chiral product **5a** could be converted to the corresponding hydrazine **6** and mercaptal **7** in 88% and 86% yield, respectively, without any loss of enantiopurity (Scheme 3). Furthermore, compound **7** could be converted into the useful *α*-hydroxy acid ester **8** in 99% yield with 99% enantioselectivity and 3/1 diastereoselectivity by asymmetric hydrogenation transformation (Scheme 4).

A plausible mechanism was proposed and is shown in Scheme 5. The enal **2a** was activated by the catalyst **1e** and formed an iminium ion **I-1**. Subsequently, an intermediate **I-2** was generated through the reaction of chiral iminium ion **I-1** and **3a**. The resulting **I-2** then underwent intramolecular IED/HDA reaction to provide an intermediate **I-3**. The hydrolysis of the intermediate **I-3** yielded the corresponding product **4a**. If the reaction proceeded at a higher reaction temperature, **4a** further reacted with another iminium ion **I-1** to generate an intermediate **I-4**. The resulting **I-4** then underwent intramolecular aldol reaction to furnish the intermediate **I-5**, which successively conducted dehydration and hydrolysis reactions to provide the desired product **5a**. Several critical intermediates were detected by ESI-MS analysis of the reaction mixture, which verified the aminocatalytic nature of this reaction (Scheme 5).

CONCLUSION

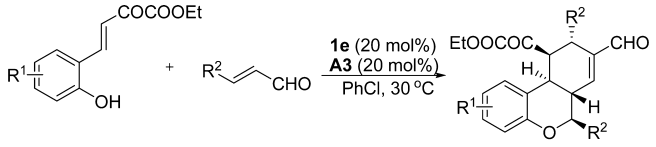
In conclusion, a facile and efficient procedure has been developed for the synthesis of two types of tricyclic chroman derivatives by tandem *oxo*-Michael-IED/HDA and *oxo*-Michael-IED/HDA-Michael-Aldol condensation transformations in the presence of (*S*)-diphenylprolinol trimethylsilyl ether as an organocatalyst. The corresponding optically active chroman derivatives were obtained in good yields with excellent stereoselectivities. Structures of the final products were confirmed by X-ray diffraction analysis. This reported synthetic method provides an easy access to chroman derivatives with remarkable structural complexity by taking advantage of these silent features: readily available starting materials, operational simplicity, short reaction time, high yields, and excellent stereoselectivity. Further exploitation of this method and application of these products are underway.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further

dx.doi.org/10.1021/jo501560m | J. Org. Chem. 2014, 79, 10772−10785

Table 3. Substrates Scope for 5[a]



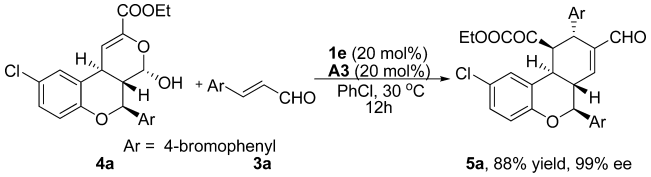
2a-2f **3** **5**

R^1 = 5-Cl, **2a**; R^1 = 5-NO_2, **2b**
R^1 = 5-Me, **2c**; R^1 = 4-Me, **2d**
R^1 = 3,5-Br_2, **2e**; R^1 = H, **2f**

entry	R^1	R^2	time (h)	product	yield (%)[b]	ee (%)[c]
1	**2a**	4-BrC_6H_4/**3a**	12	**5a**	90	>99
2	**2a**	4-ClC_6H_4/**3b**	12	**5b**	91	>99
3	**2a**	4-CNC_6H_4/**3c**	12	**5c**	90	>99
4	**2a**	4-$NO_2C_6H_4$/**3d**	12	**5d**	93	>99
5	**2a**	3-$NO_2C_6H_4$/**3e**	12	**5e**	92	>99
6	**2a**	4-$MeOC_6H_4$/**3f**	12	**5f**	92	>99
7	**2a**	2-$MeOC_6H_4$/**3g**	12	**5g**	80	97
8	**2a**	4-MeC_6H_4/**3h**	12	**5h**	95	>99
9	**2a**	C_6H_5/**3i**	12	**5i**	93	>99
10	**2a**	*N*-Ts-3-indolyl/**3j**	12	**5j**	74	>99
11	**2b**	4-$NO_2C_6H_4$/**3d**	12	**5k**	91	>99
12	**2c**	4-$NO_2C_6H_4$/**3d**	12	**5l**	90	>99
13	**2d**	4-$NO_2C_6H_4$/**3d**	12	**5m**	94	>99
14	**2e**	4-CNC_6H_4/**3c**	12	**5n**	93	>99
15	**2e**	4-$NO_2C_6H_4$/**3d**	12	**5o**	90	>99
16	**2f**	4-BrC_6H_4/**3a**	12	**5p**	95	97
17	**2f**	4-$NO_2C_6H_4$/**3d**	12	**5q**	96	>99

[a]Unless noted, reactions were carried out with **2a** (0.10 mmol), **3a** (0.30 mmol), **1** (20 mol %), and *p*-$MeOC_6H_4COOH$ (20 mol %) and in PhCl (1.0 mL) at 30 °C. [b]Isolated yield. [c]Determined by chiral HPLC analysis; the products were obtained with >10/1 dr.

Scheme 2. Synthesis of 5a by the Reaction of 4a and 3a



Ar = 4-bromophenyl

4a **3a** **5a**, 88% yield, 99% ee

purification. All reactions were carried out in air and using undistilled solvent, without any precautions to exclude moisture unless otherwise noted. Organic solutions were concentrated under reduced pressure on a rotary evaporator. Reactions were monitored by thin-layer chromatography (TLC) on silica gel precoated glass plates (0.2 ± 0.03 mm thickness, GF-254, particle size: 0.01−0.04 mm). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm. Flash column chromatography was performed using silica gel (particle size: 0.04−0.05 mm). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a spectrometer (400 or 300 MHz and 100 or 75 MHz, respectively). Chemical shifts (δ ppm) are relative to the resonance of the deuterated solvent as the internal standard ($CDCl_3$, δ 7.27 ppm, DMSO-d_6, δ 2.50 ppm for proton NMR, $CDCl_3$, δ 77.23 ppm, DMSO-d_6, δ 39.51 ppm for carbon NMR). ^1H NMR data are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet), coupling constants (J) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). High-resolution mass spectra (HRMS) for all the compounds were determined on an electron spray ionization time-of-flight (ESI-TOF) mass spectrometer. High-performance liquid chromatography (HPLC) was performed on chromatographs using chiral columns. X-ray data were recorded on a diffractometer. Optical rotations are reported as follows: $[\alpha]_D^{rt}$ (*c* in g per 100 mL, solvent).

General Procedure For Asymmetric Synthesis of Chroman Derivatives 4 and 5. In an ordinary tube equipped with a magnetic stirring bar, the solution of catalyst **1e** (20 mol %), and additive **A3** (20 mol %) in PhCl (2.0 mL) was stirred at room temperature; then, α,β-unsaturated aldehyde **3** (2 equiv) was added. Subsequently, the reaction mixture was dropped to −5 °C and stirred for 30 min. At last, (*E*)-ethyl 4-(2-hydroxyphenyl)-2-oxobut-3-enoate derivative **2** (1 equiv) was added. Afterward, the reaction mixture was stirred for 6−36 h at −5 °C. The reaction mixture was directly loaded onto a silica gel and purified by flash chromatography (petroleum ether/dichloromethane) to give desired products **4a**−**4t**.

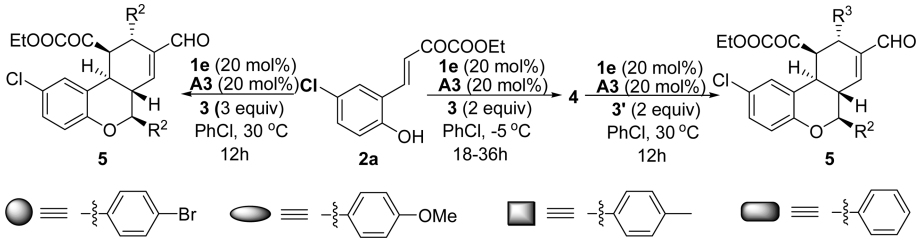
In an ordinary tube equipped with a magnetic stirring bar, the solution of catalyst **1e** (20 mol %), and additive **A3** (20 mol %) in PhCl (1.0 mL) was stirred at 30 °C; then, α, β-unsaturated aldehyde **3** (3 equiv) was added. Subsequently, (*E*)-ethyl 4-(2-hydroxyphenyl)-2-oxobut-3-enoate derivative **2** (1 equiv) was added. Afterward, the reaction mixture was stirred for 12 h at 30 °C. The reaction mixture was directly loaded onto a silica gel and purified by flash chromatography (petroleum ether/dichloromethane) to give desired products **5a**−**5q**.

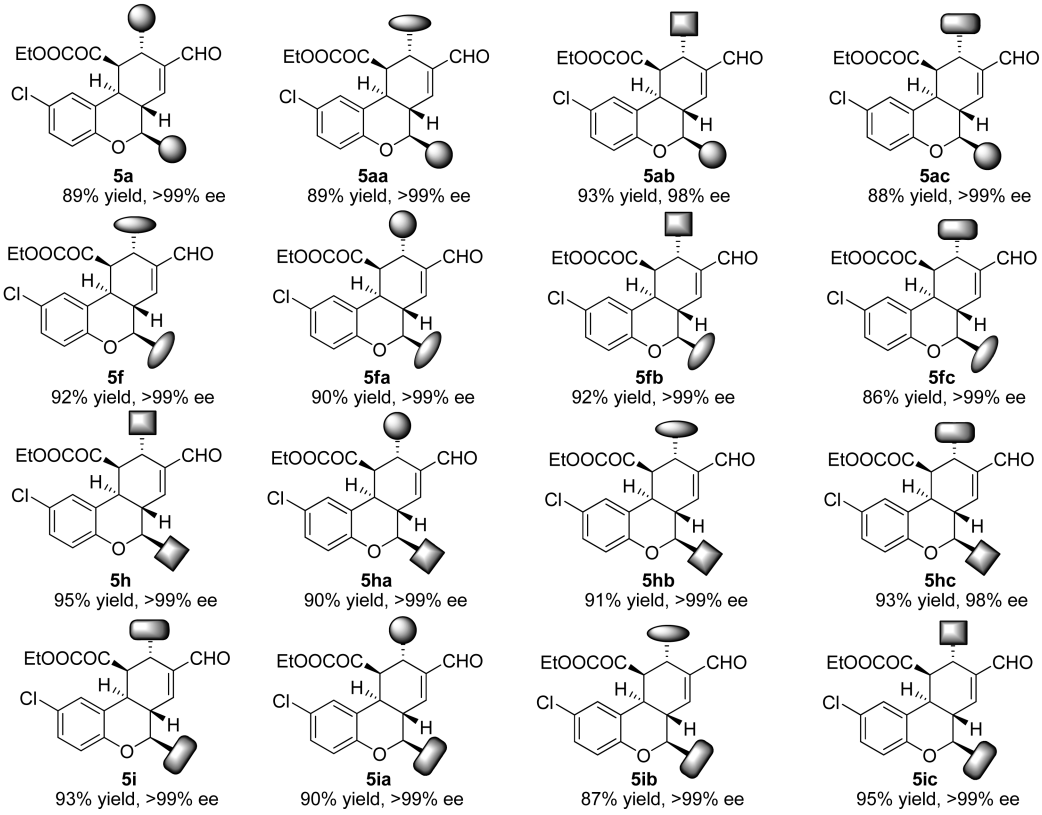
General Experimental Procedure for Synthesis of Compounds 5aa−5ac, 5fa−5fc, 5ha−5hc, 5ia−5ic. In an ordinary tube equipped with a magnetic stirring bar, the solution of catalyst **1e** (20 mol %), and additive **A3** (20 mol %) in PhCl was stirred at 30 °C; then, α,β-unsaturated aldehyde **3** (2 equiv) was added. Subsequently, **4** (1 equiv) was added. Afterward, the reaction mixture was stirred for 12 h at 30 °C. The reaction mixture was directly loaded onto a silica gel and purified by flash chromatography (petroleum ether/dichloromethane) to give the desired product.

General Experimental Procedure for Synthesis of Compounds 6−8. In an ordinary tube equipped with a magnetic stirring bar, *p*-toluenesulfonohydrazide (1.1 equiv) was dissolved in methonol. Subsequently, the solution of **5a** (1.0 equiv in CH_2Cl_2) was added. The reaction mixture was heated to 60 °C and stirred for 2 h at 60 °C. The reaction mixture was directly loaded onto a silica gel and purified by flash chromatography (petroleum ether/EtOAc) to give the desired product **6**.

dx.doi.org/10.1021/jo501560m | J. Org. Chem. 2014, 79, 10772−10785

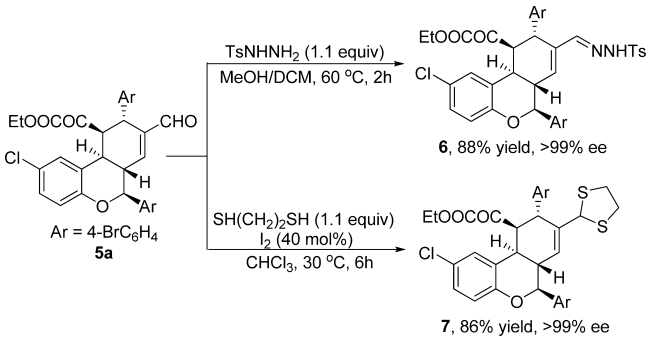
Table 4. Diversity-Oriented Synthesis of Chiral Chroman Derivatives[a]



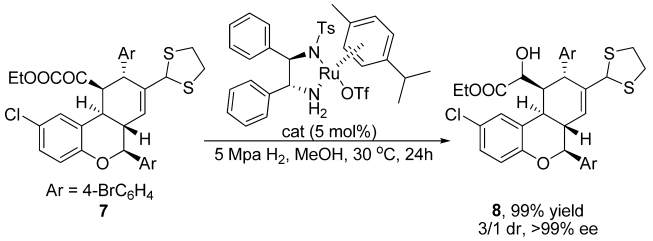


[a]The yield was isolated yield, and the ee was determined by chiral HPLC analysis. All the products were obtained with >10/1 dr.

Scheme 3. Synthetic Transformation



Scheme 4. Conversion of 7 into Functionalized α-Hydroxy Acid Ester



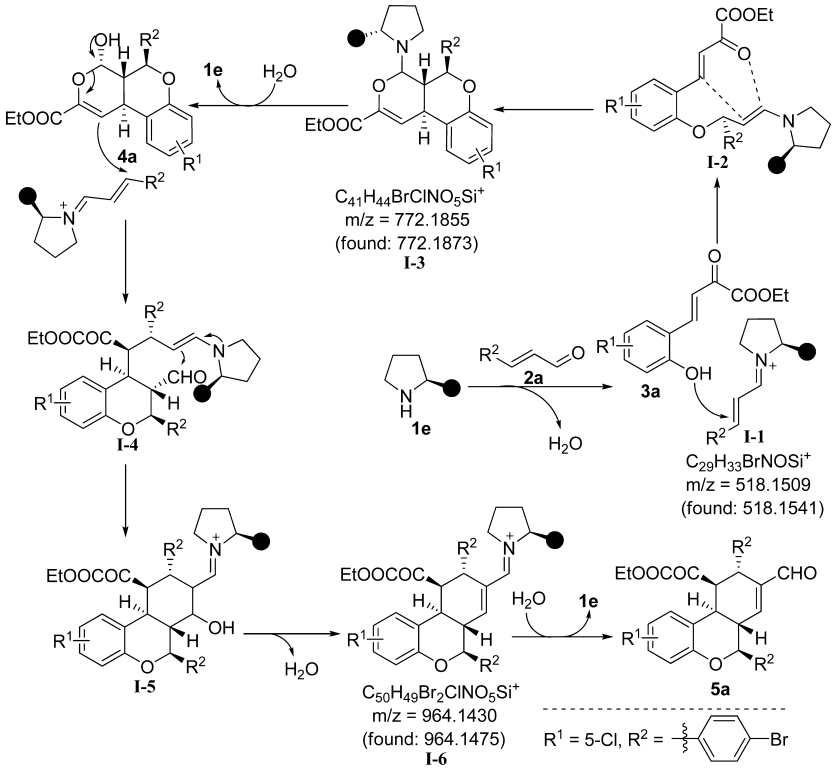
1,2-Ethanedithiol (1.1 equiv) was dissolved in $CHCl_3$ at 30 °C. Subsequently, **5a** (1 equiv) was added. At last, I_2 (40 mol %) was added. The reaction mixture was stirred for 6 h at 30 °C. The reaction mixture was directly loaded onto a silica gel and purified by flash chromatography (petroleum ether/EtOAc) to give the desired product **7**.

Compound **7**, catalyst (5 mol %), and degassed MeOH were added to a glass tube under nitrogen. The tube was then placed into a stainless steel autoclave, which was purged with hydrogen gas for three times before it was pressurized with H_2 to 50 atm. Subsequently, the mixture was stirred under this H_2 pressure at 30 °C for 24 h. After careful release of the hydrogen, methanol was concentrated to afford the crude product. The reaction mixture was directly loaded onto a silica gel and purified by flash chromatography (petroleum ether/EtOAc) to give the desired product **8**.

(4S,4aS,5S,10bS)-Ethyl-5-(4-bromophenyl)-9-chloro-4-hydroxy-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate (***4a***). 89% yield (41.5 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 5.862, t (minor) = 5.267]; $[\alpha]_D^{26}$ = 124.00 (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.70 (d, *J* = 3.6 Hz, 1H), 7.68–

dx.doi.org/10.1021/jo501560m | J. Org. Chem. 2014, 79, 10772–10785

Scheme 5. Proposed Mechanism



7.58 (m, 3H), 7.43 (d, J = 8.4 Hz, 2H), 7.19 (dd, J = 8.4, 1.6 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 6.60 (d, J = 2.0 Hz, 1H), 5.04 (d, J = 10.4 Hz, 1H), 4.89 (dd, J = 4.0, 2.0 Hz, 1H), 4.25−4.10 (m, 2H), 3.93 (d, J = 12.0 Hz, 1H), 2.14 (t, J = 11.2 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 152.5, 141.4, 136.9, 131.6, 129.9, 127.6, 126.0, 124.8, 124.3, 122.0, 118.2, 109.3, 90.5, 79.0, 60.8, 40.7, 28.5, 14.1; IR (KBr) ν_{max}: 3454.64, 2976.45, 1714.17, 1578.35, 1487.62, 1456.29, 869.30, 856.54, 811.88, 777.16, 747.27 cm^{-1}; HRMS (EI): m/z = 464.0018 (calcd for $C_{21}H_{18}BrClO_5$ = 464.0026).

(4S,4aS,5S,10bS)-Ethyl-9-chloro-5-(4-chlorophenyl)-4-hydroxy-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4b)***. 86% yield (36.2 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 5.996, t (minor) = 4.888]; $[\alpha]_D^{26}$ = 142.40 (c 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72−7.69 (m, 1H), 7.61 (d, J = 1.2 Hz, 1H), 7.54−7.48 (m, 4H), 7.19 (dd, J = 8.8, 2.0 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 6.60 (d, J = 2.4 Hz, 1H), 5.05 (d, J = 10.0 Hz, 1H), 4.89 (dd, J = 4.0, 2.0 Hz, 1H), 4.26−4.12 (m, 2H), 3.93 (d, J = 12.0 Hz, 1H), 2.14 (t, J = 11.2 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 152.5, 141.4, 136.5, 133.4, 129.6, 128.6, 127.6, 126.0, 124.8, 124.3, 118.2, 109.3, 90.5, 78.9, 60.8, 40.7, 28.5, 14.1; IR (KBr) ν_{max}: 3451.89, 2983.50, 1712.77, 1602.97, 1477.18, 1409.03, 865.47, 834.30, 813.45, 783.43, 754.06 cm^{-1}; HRMS (EI): m/z = 420.0530 (calcd for $C_{21}H_{18}Cl_2O_5$ = 420.0531).

(4S,4aS,5S,10bS)-Ethyl-9-chloro-5-(4-cyanophenyl)-4-hydroxy-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4c)***. 85% yield (35.0 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 9.579, t (minor) = 8.026]; $[\alpha]_D^{26}$ = 121.18 (c 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96−7.88 (m, 2H), 7.75 (dd, J = 4.4, 1.2 Hz, 1H), 7.72−7.65 (m, 2H), 7.64−7.60 (m, 1H), 7.23−7.18 (m, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 5.16 (d, J = 10.0 Hz, 1H), 4.86 (dd, J = 4.4, 2.0 Hz, 1H), 4.25−4.14 (m, 2H), 3.94 (d, J = 12.0 Hz, 1H), 2.18 (t, J = 11.6 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.0, 152.3, 142.8, 141.4, 132.6, 128.6, 127.7, 126.0, 124.7, 124.5, 118.6, 118.2, 111.7, 109.2, 90.3, 78.9, 60.8, 40.7, 28.4, 14.1; IR (KBr) ν_{max}: 3459.72, 2970.88, 2230.29, 1712.73, 1609.73, 1505.50, 1482.40, 1447.64, 865.86, 842.77, 825.88, 812.16, 779.91, 758.27 cm^{-1}; HRMS (EI): m/z = 411.0868 (calcd for $C_{22}H_{18}ClNO_5$ = 411.0874).

(4S,4aS,5S,10bS)-Ethyl-9-chloro-4-hydroxy-5-(4-nitrophenyl)-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4d)***. 90% yield (38.9 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 11.024, t (minor) = 9.087]; $[\alpha]_D^{26}$ = 104.00 (c 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (d, J = 8.4 Hz, 2H), 7.85−7.70 (m, 3H), 7.64 (s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.60−6.55 (m, 1H), 5.23 (d, J = 10.0 Hz, 1H), 4.95−4.75 (m, 1H), 4.26−4.10 (m, 2H), 3.96 (d, J = 12.0 Hz, 1H), 2.19 (t, J = 11.2 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.0, 152.2, 147.8, 144.8, 141.4, 129.0, 127.7, 126.0, 124.8, 124.6, 123.8, 118.2, 109.1, 90.3, 78.6, 60.8, 40.9, 28.4, 14.1; IR (KBr) ν_{max}: 3422.51, 2980.06, 1707.86, 1607.63, 1517.61, 1480.62, 1444.5, 858.02, 845.74, 820.47, 751.17, 718.33 cm^{-1}; HRMS (EI): m/z = 431.0768 (calcd for $C_{21}H_{18}ClNO_7$ = 431.0772).

(4S,4aS,5S,10bS)-Ethyl-9-chloro-4-hydroxy-5-(3-nitrophenyl)-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4e)***. 91% yield (39.3 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 11.560, t (minor) = 7.949]; $[\alpha]_D^{26}$ = 92.00 (c 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40−8.20 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H), 7.83−7.72 (m, 2H), 7.64 (d, J = 1.2 Hz, 1H), 7.22 (dd, J = 8.8, 2.0 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 5.26 (d, J = 10.4 Hz, 1H), 4.90 (dd, J = 4.0, 2.4 Hz, 1H), 4.26−4.10 (m, 2H), 3.96 (d, J = 12.4 Hz, 1H), 2.26 (t, J = 11.2 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 152.3, 148.0, 141.4, 139.6, 134.3, 130.3, 127.7, 126.0, 124.8, 124.5, 123.8, 122.4, 118.3, 109.2, 90.3, 78.6, 60.8, 40.7, 28.5, 14.1; IR (KBr) ν_{max}: 3408.31, 2980.85, 1713.59, 1533.28, 1445.00, 862.58, 813.53, 787.73, 753.22, 737.68, 721.97 cm^{-1}; HRMS (EI): m/z = 431.0781 (calcd for $C_{21}H_{18}ClNO_7$ = 431.0772).

(4S,4aS,5S,10bS)-Ethyl-9-chloro-4-hydroxy-5-(4-methoxyphenyl)-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4f)***. 80% yield (33.3 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 8.665, t (minor) = 5.998]; $[\alpha]_D^{26}$ = 143.08 (c 0.13, $CHCl_3$);

dx.doi.org/10.1021/jo501560m | J. Org. Chem. 2014, 79, 10772−10785

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.65−7.61 (m, 1H), 7.61−7.57 (m, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.17 (dd, J = 4.8, 2.0 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 4.97 (d, J = 10.4 Hz, 1H), 4.92 (dd, J = 4.0, 2.0 Hz, 1H), 4.24−4.12 (m, 2H), 3.92 (d, J = 12.4 Hz, 1H), 3.79 (s, 3H), 2.14 (t, J = 11.2 Hz, 1H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2, 159.6, 152.7, 141.5, 129.4, 129.1, 127.6, 125.9, 124.8, 124.1, 118.2, 114.0, 109.4, 90.7, 79.4, 60.8, 55.2, 40.7, 28.6, 14.1; IR (KBr) ν_{max}: 3422.86, 2941.41, 1707.48, 1615.73, 1587.12, 1515.82, 1478.91, 875.42, 863.96, 826.12, 815.85, 799.15, 753.49 cm^{-1}; HRMS (EI): m/z = 416.1021 (calcd for $C_{22}H_{21}ClO_6$ = 416.1027).

(4S,4aS,5S,10bS)-Ethyl-9-chloro-4-hydroxy-5-p-tolyl-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4g)***. 78% yield (31.3 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min−*1*, λ = 254 nm, t (major) = 6.220, t (minor) = 4.539]; $[\alpha]_D^{26}$ = 167.41 (c 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.64 (d, J = 4.0 Hz, 1H), 7.60 (s, 1H), 7.35 (d, J = 7.6 Hz, 2H), 7.24 (d, J = 7.6 Hz, 2H), 7.20−7.14 (m, 1H), 6.83 (d, J = 8.8 Hz, 1H), 6.65−6.55 (m, 1H), 4.98 (d, J = 10.4 Hz, 1H), 4.90 (s, 1H), 4.28−4.10 (m, 2H), 3.92 (d, J = 12.0 Hz, 1H), 2.34 (s, 3H), 2.12 (t, J = 11.2 Hz, 1H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 152.7, 141.4, 138.2, 134.5, 129.1, 127.6, 126.0, 124.8, 124.1, 118.2, 109.4, 90.7, 79.6, 60.8, 40.7, 28.6, 20.8, 14.1; IR (KBr) ν_{max}: 3456.43, 2980.11, 1717.99, 1516.95, 1478.19, 869.84, 843.98, 811.30, 795.00, 765.02 cm^{-1}; HRMS (EI): m/z = 400.1068 (calcd for $C_{22}H_{21}ClO_5$ = 400.1078).

(4S,4aS,5S,10bS)-Ethyl-9-chloro-4-hydroxy-5-phenyl-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4h)***. 88% yield (34.0 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 5.438, t (minor) = 4.623]; $[\alpha]_D^{26}$ = 141.82 (c 0.06, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.67 (d, J = 4.0 Hz, 1H), 7.64−7.58 (m, 1H), 7.52−7.40 (m, 5H), 7.19 (dd, J = 4.4, 2.0 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 6.60 (d, J = 1.6 Hz, 1H), 5.03 (d, J = 10.0 Hz, 1H), 4.89 (dd, J = 4.0, 2.0 Hz, 1H), 4.30−4.10 (m, 2H), 3.94 (d, J = 12.0 Hz, 1H), 2.14 (t, J = 11.2 Hz, 1H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 152.6, 141.4, 137.5, 128.9, 128.6, 127.61, 127.58, 126.0, 124.8, 124.2, 118.2, 109.3, 90.6, 79.7, 60.8, 40.9, 28.5, 14.1; IR (KBr) ν_{max}: 3427.62, 2957.26, 1715.90, 1478.40, 1455.88, 863.11, 817.26, 757.66, 699.66 cm^{-1}; HRMS (EI): m/z = 386.0924 (calcd for $C_{21}H_{19}ClO_5$ = 386.0921).

(4S,4aS,5S,10bS)-Ethyl-9-chloro-4-hydroxy-5-(1-tosyl-1H-indol-3-yl)-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4i)***. 75% yield (43.5 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 26.733, t (minor) = 9.425]; $[\alpha]_D^{26}$ = 97.78 (c 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 3.6 Hz, 1H), 7.65−7.58 (m, 2H), 7.46−7.34 (m, 3H), 7.28−7.16 (m, 2H), 6.82 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 2.0 Hz, 1H), 5.39 (d, J = 10.8 Hz, 1H), 4.97 (dd, J = 4.4, 2.0 Hz, 1H), 4.26−4.10 (m, 2H), 3.95 (d, J = 12.0 Hz, 1H), 2.42 (t, J = 11.6 Hz, 1H), 2.34 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 152.3, 145.7, 141.5, 134.5, 133.9, 130.4, 128.5, 127.7, 126.9, 126.1, 125.9, 125.2, 124.9, 124.3, 123.6, 120.7, 118.7, 118.2, 113.4, 109.2, 90.7, 73.0, 60.8, 54.9, 28.5, 21.1, 14.1; IR (KBr) ν_{max}: 3424.08, 2980.23, 1716.02, 1478.50, 1446.45, 861.41, 812.25, 746.93, 703.42 cm^{-1}; HRMS (EI): m/z = 579.1132 (calcd for $C_{30}H_{26}ClNO_7S$ = 579.1119).

(4S,4aS,5R,10bS)-Ethyl-9-chloro-4-hydroxy-5-methyl-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4j)***. 93% yield (30.2 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 4.812, t (minor) = 5.790]; $[\alpha]_D^{26}$ = 250.00 (c 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.70−7.62 (m, 1H), 7.54−7.46 (m, 1H), 7.15 (dd, J = 8.8, 2.4 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H), 5.65 (dd, J = 4.0, 2.4 Hz, 1H), 4.25−4.15 (m, 2H), 4.15−4.05 (m, 1H), 3.71 (d, J = 12.0 Hz, 1H), 1.60 (t, J = 11.2 Hz, 1H), 1.37 (d, J = 6.4 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2, 152.4, 141.3, 127.5, 125.9, 124.9, 123.9, 118.0, 109.3, 90.6, 73.9, 60.8, 41.2, 28.1, 18.0, 14.1; IR (KBr) ν_{max}: 3404.60, 2981.81, 1716.31, 1616.63, 1517.62, 1483.10, 876.34, 861.72, 843.98, 748.30, 718.61 cm^{-1}; HRMS (EI): m/z = 324.0757 (calcd for $C_{16}H_{17}ClO_5$ = 324.0765).

(4S,4aS,5R,10bS)-Ethyl-9-chloro-5-ethyl-4-hydroxy-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4k)***. 90% yield (30.5 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 4.441, t (minor) = 5.750]; $[\alpha]_D^{26}$ = 250.40 (c 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68 (dd, J = 4.0, 1.2 Hz, 1H), 7.54−7.48 (m, 1H), 7.15 (dd, J = 8.8, 2.0 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.53 (d, J = 2.0 Hz, 1H), 5.65 (dd, J = 8.8, 2.0 Hz, 1H), 4.25−4.13 (m, 2H), 4.06−3.88 (m, 1H), 3.71 (d, J = 12.4 Hz, 1H), 1.90−1.80 (m, 1H), 1.70−1.50 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2, 152.5, 141.3, 127.4, 125.8, 125.0, 123.8, 118.1, 109.3, 90.4, 78.0, 60.8, 28.1, 24.3, 14.1, 8.7; IR (KBr) ν_{max}: 3440.01, 2973.28, 1709.95, 1631.38, 1480.01, 1405.99, 860.10, 819.29, 795.67, 771.41, 754.50, 720.72 cm^{-1}; HRMS (EI): m/z = 338.0917 (calcd for $C_{17}H_{19}ClO_5$ = 338.0921).

(4S,4aS,5R,10bS)-Ethyl-9-chloro-4-hydroxy-5-propyl-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4l)***. 88% yield (31.0 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 4.203, t (minor) = 5.614]; $[\alpha]_D^{26}$ = 237.39 (c 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.67 (d, J = 3.2 Hz, 1H), 7.53−7.48 (m, 1H), 7.16 (dd, J = 8.4, 2.0 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H), 5.65 (dd, J = 4.4, 2.4 Hz, 1H), 4.30−4.10 (m, 2H), 4.09−4.35 (m, 1H), 3.71(d, J = 12.4 Hz, 1H), 1.78−1.70 (m, 1H), 1.66−1.54 (m, 3H), 1.50−1.34 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2, 152.4, 141.3, 127.4, 125.8, 125.0, 123.8, 118.1, 109.3, 90.5, 76.9, 60.8, 33.4, 28.2, 17.4, 14.1, 13.9; IR (KBr) ν_{max}: 3453.61, 2956.78, 1731.45, 1479.47, 1368.60, 888.30, 859.61, 817.76, 794.54, 742.79 cm^{-1}; HRMS (EI): m/z = 352.1074 (calcd for $C_{18}H_{21}ClO_5$ = 352.1078).

(4S,4aS,5R,10bS)-Ethyl-9-chloro-4-hydroxy-5-pentyl-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4m)***. 83% yield (31.6 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 4.068, t (minor) = 5.457]; $[\alpha]_D^{26}$ = 127.70 (c 1.48, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66 (dd, J = 4.0, 0.8 Hz, 1H), 7.52−7.48 (m, 1H), 7.17−7.11 (m, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H), 5.65 (dd, J = 4.4, 2.4 Hz, 1H), 4.26−4.11 (m, 2H), 4.07−3.92 (m, 1H), 3.71 (d, J = 12.4 Hz, 1H), 1.84−1.69 (m, 1H), 1.68−1.48 (m, 3H), 1.47−1.36 (m, 1H), 1.35−1.18 (m, 7H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2, 152.4, 141.2, 127.4, 125.8, 125.0, 123.8, 118.1, 109.3, 90.5, 77.1, 60.8, 31.2, 31.2, 28.2, 23.6, 22.0, 14.1, 13.9; IR (KBr) ν_{max}: 3450.62, 2932.14, 1726.12, 1480.18, 1384.31, 925.42, 813.32, 758.67 cm^{-1}; HRMS (ESI): m/z = 381.1487 (calcd for $C_{20}H_{25}ClO_5$ + H^+ = 381.1469).

(4S,4aS,5R,10bS)-Ethyl-9-chloro-5-heptyl-4-hydroxy-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4n)***. 85% yield (34.8 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 3.939, t (minor) = 5.056]; $[\alpha]_D^{26}$ = 124.60 (c 1.26, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68−7.64 (m, 1H), 7.54−7.44 (m, 1H), 7.17−7.09 (m, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H), 5.64 (dd, J = 4.2, 2.4 Hz, 1H), 4.24−4.15 (m, 2H), 4.06−3.92 (m, 1H), 3.71 (d, J = 12.4 Hz, 1H), 1.83−1.69 (m, 1H), 1.69−1.49 (m, 3H), 1.48−1.36 (m, 1H), 1.35−1.19 (m, 11H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 152.4, 141.2, 127.4, 125.8, 125.0, 123.8, 118.1, 109.3, 90.5, 77.1, 60.8, 31.3, 31.2, 29.0, 28.6, 28.2, 24.0, 22.1, 14.1, 13.9; IR (KBr) ν_{max}: 3447.17, 2962.41, 1732.53, 1480.22, 1309.76, 1219.53, 771.92 cm^{-1}; HRMS (EI): m/z = 408.1711 (calcd for $C_{22}H_{29}ClO_5$ = 408.1704).

(4S,4aS,5R,10bS)-Ethyl-9-chloro-5-((Z)-hex-3-enyl)-4-hydroxy-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate ***(4o)***. 82% yield (32.2 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 4.133, t (minor) = 5.194]; $[\alpha]_D^{26}$ = 123.25 (c 1.36, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.67 (dd, J = 4.4, 0.8 Hz, 1H), 7.51 (dd, J = 2.4, 0.8 Hz, 1H), 7.21−7.11 (m, 1H), 6.81 (d, J = 8.8 Hz, 1H),

6.52 (d, J = 2.0 Hz, 1H), 5.65 (dd, J = 4.0, 2.4 Hz, 1H), 5.45−5.29 (m, 2H), 4.25−4.16 (m, 2H), 4.04−3.94 (m, 1H), 3.71 (d, J = 12.0 Hz, 1H), 2.25 (q, J = 7.2 Hz, 2H), 2.10−1.99 (m, 2H), 1.87−1.73 (m, 1H), 1.72−1.58 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 152.3, 141.3, 132.1, 128.0, 127.5, 125.8, 124.9, 123.9, 118.1, 109.3, 90.5, 76.4, 60.8, 31.2, 28.2, 21.8, 20.0, 14.2, 14.1; IR (KBr) ν_{max}: 3446.64, 2936.79, 1723.76, 1480.48, 1384.33, 1236.14, 862.79, 751.58 cm^{-1}; HRMS (EI): m/z = 392.1394 (calcd for $C_{21}H_{25}ClO_5$ = 392.1391).

*(4S,4aS,5R,10bS)-Ethyl-4-hydroxy-5-methyl-9-nitro-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate (**4p**).* 78% yield (26.2 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 8.336, t (minor) = 11.016]; $[\alpha]_D^{26}$ = 263.45 (*c* 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.03 (dd, J = 8.8, 2.4 Hz, 1H), 7.75 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 9.2 Hz, 1H), 6.57 (d, J = 1.6 Hz, 1H), 5.70−5.60 (m, 1H), 4.35−4.15 (m, 3H), 3.78 (d, J = 12.0 Hz, 1H), 1.68 (t, J = 11.2 Hz, 1H), 1.42 (d, J = 6.4 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 159.3, 141.5, 140.4, 124.0, 123.9, 122.3, 117.2, 108.5, 90.4, 75.4, 60.9, 40.7, 28.0, 17.9, 14.1; IR (KBr) ν_{max}: 3404.60, 2981.81, 1716.31, 1616.63, 1517.62, 1483.10, 876.34, 861.72, 843.98, 748.30, 718.61 cm^{-1}; HRMS (ESI): m/z = 334.0930 (calcd for $C_{16}H_{17}NO_7 - H^+$ = 334.0932).

*(4S,4aS,5R,10bS)-Ethyl-4-hydroxy-5,9-dimethyl-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate (**4q**).* 85% yield (25.9 mg), 98% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 4.553, t (minor) = 5.690]; $[\alpha]_D^{26}$ = 197.69 (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60 (dd, J = 4.2, 0.8 Hz, 1H), 7.23 (s, 1H), 6.94−6.88 (m, 1H), 6.65 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 5.65 (dd, J = 4.0, 2.4 Hz, 1H), 4.27−4.15 (m, 2H), 4.09−3.97 (m, 1H), 3.68 (d, J = 12.4 Hz, 1H), 2.24 (s, 3H), 1.62−1.50 (m, 1H), 1.36 (d, J = 6.4 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.3, 151.3, 141.2, 128.7, 128.1, 126.2, 122.2, 116.0, 110.0, 90.8, 73.3, 60.7, 41.7, 27.9, 20.2, 18.1, 14.1; IR (KBr) ν_{max}: 3397.82, 2983.66, 1714.67, 1496.62, 1462.75, 1344.72, 1130.49, 976.63, 908.95, 857.88, 790.02, 756.23 cm^{-1}; HRMS (EI): m/z = 304.1314 (calcd for $C_{17}H_{20}O_5$ = 304.1311).

*(4S,4aS,5R,10bS)-Ethyl-4-hydroxy-5,8-dimethyl-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate (**4r**).* 82% yield (25.0 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 4.671, t (minor) = 6.155]; $[\alpha]_D^{26}$ = 148.30 (*c* 1.27, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60 (d, J = 4.0 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 6.59 (s, 1H), 6.49 (d, J = 2.0 Hz, 1H), 5.64 (dd, J = 4.0, 2.4 Hz, 1H), 4.26−4.14 (m, 2H), 4.11−3.99 (m, 1H), 3.65 (d, J = 12.0 Hz, 1H), 2.21 (s, 3H), 1.54 (t, J = 11.2 Hz, 1H), 1.36 (d, J = 6.0 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2, 153.3, 141.1, 136.9, 125.8, 120.9, 119.6, 116.6, 110.0, 90.8, 73.4, 60.7, 41.8, 27.6, 20.6, 18.2, 14.1; IR (KBr) ν_{max}: 3421.94, 2978.38, 1716.53, 1574.36, 1522.68, 1448.46, 1384.08, 1130.70, 754.61 cm^{-1}; HRMS (EI): m/z = 304.1312 (calcd for $C_{17}H_{20}O_5$ = 304.1311).

*(4S,4aS,5S,10bS)-Ethyl-7,9-dibromo-5-(4-cyanophenyl)-4-hydroxy-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate (**4s**).* 84% yield (45.0 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 9.306, t (minor) = 7.898]; $[\alpha]_D^{26}$ = 16.98 (*c* 0.53, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (d, J = 8.4 Hz, 2H), 7.83 (dd, J = 4.4, 1.2 Hz, 1H), 7.80−7.76 (m, 1H), 7.72−7.66 (m, 3H), 6.62 (d, J = 2.0 Hz, 1H), 5.29 (d, J = 10.4 Hz, 1H), 4.87 (dd, J = 4.0, 2.4 Hz, 1H), 4.25−4.10 (m, 2H), 3.99 (d, J = 12.0 Hz, 1H), 2.18 (t, J = 11.6 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.0, 149.5, 142.5, 141.5, 133.0, 132.7, 128.4, 126.9, 118.6, 112.1, 111.8, 111.1, 108.7, 90.2, 79.8, 60.9, 40.7, 28.7, 14.1; IR (KBr) ν_{max}: 3453.41, 2986.99, 2957.74, 2230.30, 1716.44, 1608.71, 1589.04, 1505.07, 1452.17, 884.61, 856.03, 841.65, 763.03, 752.06, 736.05 cm^{-1}; HRMS (EI): m/z = 532.9468 (calcd for $C_{22}H_{17}Br_2NO_5$ = 532.9473).

*(4S,4aS,5S,10bS)-Ethyl-5-(4-bromophenyl)-4-hydroxy-4,4a,5,10b-tetrahydropyrano[3,4-c]chromene-2-carboxylate (**4t**).* 87% yield (37.5 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 6.179, t (minor) = 5.726]; $[\alpha]_D^{26}$ = 76.92 (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.70−7.60 (m, 3H), 7.51 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.16 (t, J = 7.6 Hz, 1H), 6.97 (t, J = 7.2 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 5.03 (d, J = 10.4 Hz, 1H), 4.91 (dd, J = 4.0, 2.0 Hz, 1H), 4.25−4.05 (m, 2H), 3.93 (d, J = 12.0 Hz, 1H), 2.12 (t, J = 11.6 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 153.5, 141.4, 137.2, 131.5, 129.9, 127.8, 126.1, 122.5, 121.9, 120.5, 116.5, 109.7, 90.6, 78.7, 60.8, 41.2, 28.2, 14.1; IR (KBr) ν_{max}: 3454.64, 2976.45, 1714.17, 1578.35, 1487.62, 1456.29, 869.30, 856.54, 811.88, 777.16, 747.27 cm^{-1}; HRMS (EI): m/z = 430.0406 (calcd for $C_{21}H_{19}BrO_5$ = 430.0416).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-6,9-bis(4-bromophenyl)-2-chloro-8-formyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5a**).* 90% yield (59.3 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 10.253, t (minor) = 7.959]; $[\alpha]_D^{26}$ = −54.71 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.08 (dd, J = 8.8, 1.6 Hz, 1H), 6.95−6.85 (m, 1H), 6.80 (d, J = 8.8 Hz, 1H), 6.55−6.50 (m, 1H), 4.97 (d, J = 10.4 Hz, 1H), 4.39−4.28 (m, 4H), 3.53 (t, J = 10.8 Hz, 1H), 3.28 (dd, J = 11.0, 3.6 Hz, 1H), 1.37 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 191.9, 161.3, 153.3, 148.1, 140.8, 140.4, 136.8, 132.5, 132.3, 129.5, 129.4, 128.7, 126.0, 124.6, 123.7, 123.2, 121.8, 118.5, 82.1, 63.5, 48.4, 40.3, 38.5, 34.3, 14.1; IR (KBr) ν_{max}: 2980.85, 1725.64, 1690.65, 1593.99, 1486.26, 1406.50, 972.12, 855.13, 821.10 cm^{-1}; HRMS (EI): m/z = 655.9606 (calcd for $C_{30}H_{23}Br_2ClO_5$ = 655.9601).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-6,9-bis(4-chlorophenyl)-8-formyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5b**).* 91% yield (51.9 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 9.291, t (minor) = 7.367]; $[\alpha]_D^{26}$ = −66.37 (*c* 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 7.55−7.45 (m, 4H), 7.35 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.08 (dd, J = 8.6, 2.4 Hz, 1H), 6.95−6.85 (m, 1H), 6.80 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 1.6 Hz, 1H), 4.99 (d, J = 10.4 Hz, 1H), 4.40−4.25 (m, 4H), 3.54 (t, J = 10.4 Hz, 1H), 3.29 (dd, J = 12.0, 2.8 Hz, 1H), 1.37 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 192.0, 161.4, 153.4, 148.1, 140.9, 139.8, 136.3, 135.6, 133.8, 129.6, 129.5, 129.2, 129.1, 128.7, 126.0, 124.6, 123.3, 118.6, 82.1, 63.5, 48.5, 40.4, 38.5, 34.3, 14.1; IR (KBr) ν_{max}: 2957.55, 1726.28, 1690.40, 1490.97, 1480.36, 1409.43, 888.04, 856.32, 824.47, 735.73, 711.53, 695.13 cm^{-1}; HRMS (ESI): m/z = 586.0972 (calcd for $C_{30}H_{23}Cl_2ClO_5 + NH_4^+$ = 586.0949).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-6,9-bis(4-cyanophenyl)-8-formyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5c**).* 90% yield (49.6 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (70:30), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 17.078, t (minor) = 12.334]; $[\alpha]_D^{26}$ = −59.29 (*c* 0.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35 (s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.68 (t, J = 8.0 Hz, 4H), 7.42 (d, J = 8.4 Hz, 2H), 7.11 (dd, J = 8.8, 1.6 Hz, 1H), 6.92−6.88 (m, 1H), 6.83 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H), 5.07 (d, J = 10.4 Hz, 1H), 4.41−4.30 (m, 4H), 3.59 (t, J = 10.8 Hz, 1H), 3.27 (dd, J = 12.0, 3.2 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0, 191.6, 161.2, 153.0, 147.8, 146.5, 142.7, 140.6, 133.2, 133.1, 129.0, 128.6, 126.4, 124.6, 122.8, 118.7, 118.5, 118.3, 113.8, 112.0, 81.8, 63.7, 47.9, 40.3, 39.1, 34.3, 14.1; IR (KBr) ν_{max}: 2957.55, 1726.28, 1690.40, 1599.66, 1490.97, 1480.36, 1409.43, 888.04, 856.32, 824.47, 735.73, 711.53, 695.13 cm^{-1}; HRMS (ESI): m/z = 568.1639 (calcd for $C_{32}H_{23}ClN_2O_5 + NH_4^+$ = 568.1634).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-8-formyl-6,9-bis(4-nitrophenyl)-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5d**).* 93% yield (55.0 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (70:30), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 27.896, t (minor) = 20.937]; $[\alpha]_D^{26}$ = −55.00 (*c* 0.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1H), 8.42 (d, J

= 8.8 Hz, 2H), 8.26 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.12 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.91 (d, *J* = 1.6 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 6.55 (d, *J* = 1.6 Hz, 1H), 5.15 (d, *J* = 10.4 Hz, 1H), 4.46−4.29 (m, 4H), 3.63 (t, *J* = 10.8 Hz, 1H), 3.30 (dd, *J* = 11.2, 3.6 Hz, 1H), 1.39 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0, 191.6, 161.2, 153.0, 148.9, 148.5, 147.7, 147.6, 144.6, 140.7, 129.1, 128.9, 128.8, 126.5, 124.63, 124.58, 124.5, 122.7, 118.7, 81.5, 63.8, 47.9, 40.4, 38.9, 34.4, 14.1; IR (KBr) ν_{max}: 2954.30, 1727.69, 1690.24, 1606.51, 1522.05, 1478.87, 1413.61, 854.31, 753.53 cm^{-1}; HRMS (ESI): *m*/*z* = 608.1444 (calcd for $C_{30}H_{23}ClN_2O_9$ + NH_4^+ = 608.1430).

Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-8-formyl-6,9-bis(3-nitrophenyl)-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5e**). 92% yield (54.4 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (70:30), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 21.739, t (minor) = 18.931]; $[\alpha]_D^{26}$ = −58.86 (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 8.45 (s, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.21 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.06 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 8.0 Hz, 2H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.92 (d, *J* = 1.2 Hz, 1H), 6.84 (*J* = 8.8 Hz, 1H), 6.58 (d, *J* = 1.2 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 4.49−4.32 (m, 4H), 3,66 (t, *J* = 10.8 Hz, 1H), 3.33 (dd, *J* = 12.0, 3.6 Hz, 1H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0, 191.7, 161.2, 153.1, 149.0, 148.8, 148.0, 143.5, 140.6, 139.9, 134.3, 134.0, 130.6, 130.5, 129.1, 126.5, 124.8, 124.6, 123.1, 123.0, 122.7, 122.3, 118.8, 81.5, 63.8, 48.2, 40.2, 38.8, 34.3, 14.1; IR (KBr) ν_{max}: 2927.04, 1727.43, 1690.21, 1530.43, 1478.24, 1414.87, 878.81, 811.22, 764.27, 733.69 cm^{-1}; HRMS (ESI): *m*/*z* = 608.1456 (calcd for $C_{30}H_{23}ClN_2O_9$ + NH_4^+ = 608.1430).

Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-8-formyl-6,9-bis(4-methoxyphenyl)-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5f**). 92% yield (51.6 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 11.404, t (minor) = 10.874]; $[\alpha]_D^{26}$ = −75.72 (*c* 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 7.10−7.01 (m, 3H), 6.97−6.86 (m, 3H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.52 (d, *J* = 1.6 Hz, 1H), 4.97 (d, *J* = 10.4 Hz, 1H), 4.37−4.27 (m, 4H), 3.89 (s, 3H), 3.80 (s, 3H), 3.54 (d, *J* = 11.2 Hz, 1H), 3.34 (dd, *J* = 11.6, 3.2 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 192.3, 161.6, 160.7, 159.2, 153.7, 148.5, 141.1, 133.4, 129.9, 129.2, 128.9, 128.5, 125.6, 124.7, 123.8, 118.5, 114.72, 114.66, 82.6, 63.4, 55.6, 55.5, 49.0, 40.4, 38.4, 34.5, 14.1; IR (KBr) ν_{max}: 2957.29, 1725.65, 1691.07, 1612.86, 1585.09, 1511.12, 1477.86, 1413.80, 831.87, 717.61 cm^{-1}; HRMS (ESI): *m*/*z* = 578.1966 (calcd for $C_{32}H_{29}ClO_7$ + NH_4^+ = 578.1940).

Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-8-formyl-6,9-bis(2-methoxyphenyl)-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5g**). 80% yield (44.9 mg), 97% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 6.291, t (minor) = 8.000]; $[\alpha]_D^{26}$ = −24.29 (*c* 0.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.33−7.27 (m, 1H), 7.20−7.10 (m, 2H), 7.10−7.00 (m, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.90−6.83 (m, 1H), 6.82−6.76 (m, 2H), 6.58 (s, 1H), 5.55 (s, 1H), 4.61 (s, 1H), 4.40−4.20 (m, 3H), 3.98 (s, 3H), 3.92 (s, 3H), 3.34 (s, 2H), 1.34 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1, 192.5, 162.7, 157.0, 156.7, 154.0, 150.2, 140.3, 130.3, 129.2, 129.0, 128.4, 128.0, 127.9, 126.3, 125.4, 125.3, 124.1, 121.7, 120.4, 118.5, 111.1, 111.0, 76.2, 62.9, 55.8, 55.7, 45.8, 40.7, 35.7, 33.2, 14.2; IR (KBr) ν_{max}: 2936.16, 1735.81, 1722.40, 1685.47, 1599.99, 1588.34, 1490.01, 1478.76, 1463.66, 888.29, 876.30, 861.58, 829.97, 814.74, 783.21, 751.86 cm^{-1}; HRMS (ESI): *m*/*z* = 578.1965 (calcd for $C_{32}H_{29}ClO_7$ + NH_4^+ = 578.1940).

Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-8-formyl-6,9-di-p-tolyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5h**). 95% yield (50.3 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 6.484, t (minor) = 5.653]; $[\alpha]_D^{26}$ = −69.77 (*c* 0.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.19−7.12 (m, 4H), 7.05 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.92 (d, *J* = 1.2 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 1H), 4.97 (d, *J* = 10.0 Hz, 1H), 4.39−4.27 (m, 4H), 3.54 (t, *J* = 11.6 Hz, 1H), 3.34 (dd, *J* = 11.6, 3.2 Hz, 1H), 2,44 (s, 3H), 2.33 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 192.3, 161.6, 153.7, 148.5, 141.0, 139.6, 138.4, 137.5, 134.9, 130.0, 129.9, 128.5, 127.8, 127.7, 125.6, 124.7, 123.8, 118.5, 82.9, 63.3, 48.8, 40.4, 38.7, 34.4, 21.5, 21.2, 14.1; IR (KBr) ν_{max}: 2963.15, 1725.62, 1691.72, 1512.18, 1478.20, 1412.84, 858.94, 802.58, 711.98 cm^{-1}; HRMS (ESI): *m*/*z* = 546.2056 (calcd for $C_{32}H_{29}ClO_5$ + NH_4^+ = 546.2042).

Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-8-formyl-6,9-diphenyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5i**). 93% yield (46.6 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 210 nm, t (major) = 6.929, t (minor) = 8.017]; $[\alpha]_D^{26}$ = −92.63 (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 7.56−7.46 (m, 5H), 7.38 (d, *J* = 9.6 Hz, 2H), 7.32−7.22 (m, 3H), 7.07 (dd, *J* = 8.6, 1.6 Hz, 1H), 6.93 (s, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.53 (d, *J* = 1.6 Hz, 1H), 5.02 (d, *J* = 10.4 Hz, 1H), 4.42−4.29 (m, 4H), 3.57 (t, *J* = 10.8 Hz, 1H), 3.36 (dd, *J* = 12.0, 3.2 Hz, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 192.2, 161.6, 153.6, 148.4, 141.3, 140.9, 137.9, 129.7, 129.4, 129.3, 128.5, 127.83, 127.80, 125.7, 124.6, 123.7, 118.5, 83.0, 63.4, 48.7, 40.5, 39.0, 34.4, 14.1; IR (KBr) ν_{max}: 2956.32, 1725.84, 1691.00, 1600.45, 1477.68, 1454.01, 887.08, 854.92, 818.07, 761.27, 727.92 cm^{-1}; HRMS (ESI): *m*/*z* = 518.1751 (calcd for $C_{30}H_{25}ClO_5$ + NH_4^+ = 518.1729).

Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-8-formyl-6,9-bis(1-tosyl-1H-indol-3-yl)-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5j**). 74% yield (65.7 mg), >99% ee, >10/1 dr [Daicel Chiralcel OD-H, hexane/*i*-PrOH (75:25), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 20.478, t (minor) = 24.067]; $[\alpha]_D^{26}$ = 10.82 (*c* 0.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.06−7.96 (m, 2H), 7.95−7.84 (m, 3H), 7.63 (t, *J* = 7.5 Hz, 3H), 7.49−7.38 (m, 3H), 7.37−7.28 (m, 3H), 7.15 (d, *J* = 7.2 Hz, 2H), 7.11−7.12 (m, 2H), 6,83 (s, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.54 (s, 1H), 5.28 (d, *J* = 10.8 Hz, 1H), 4.53 (s, 1H), 4.46 (s, 1H), 4.33 (d, *J* = 7.2 Hz, 2H), 3.89 (t, *J* = 10.8 Hz, 1H), 3.30 (d, *J* = 11.2 Hz, 1H), 2.40 (s, 3H), 2.25 (s, 3H), 1.36 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 191.7, 161.7, 153.2, 148.1, 145.8, 145.5, 140.6, 136.2, 136.0, 135.2, 134.7, 130.4, 130.1, 129.2, 128.8, 128.2, 127.3, 126.8, 126.00, 125.95, 125.9, 125.8, 125.1, 124.6, 124.3, 124.1, 123.8, 123.5, 121.0, 120.0, 118.8, 118.6, 114.4, 114.2, 76.7, 63.6, 45.0, 38.5, 35.4, 31.2, 21.9, 21.7, 14.1; IR (KBr) ν_{max}: 2960.56, 1725.65, 1694.20, 1637.31, 1478.08, 1447.83, 884.25, 812.28, 747.60, 703.54 cm^{-1}; HRMS (ESI): *m*/*z* = 904.2159 (calcd for $C_{48}H_{39}ClN_2O_9S_2$ + NH_4^+ = 904.2124).

Ethyl-2-((6S,6aS,9R,10R,10aR)-8-formyl-2-nitro-6,9-bis(4-nitrophenyl)-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5k**). 91% yield (54.7 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (70:30), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 56.542, t (minor) = 21.952]; $[\alpha]_D^{26}$ = −108.72 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.39 (s, 1H), 8.44 (d, *J* = 8.8 Hz, 2H), 8.28 (d, *J* = 8.8 Hz, 2H), 8.09 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.87 (d, *J* = 1.6 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.56 (d, *J* = 1.6 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 4.54 (t, *J* = 3.6 Hz, 2H), 4.46−4.34 (m, 2H), 3.76 (t, *J* = 11.2 Hz, 1H), 3.34 (dd, *J* = 11.0, 3.6 Hz, 1H), 1.40 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 191.4, 160.6, 159.5, 149.1, 148.2, 147.6, 146.7, 143.7, 141.9, 140.8, 128.9, 128.8, 125.1, 124.7, 124.6, 122.5, 121.0, 118.0, 82.5, 64.0, 47.8, 40.0, 38.9, 34.2, 14.1; IR (KBr) ν_{max}: 2958.74, 1727.70, 1690.97, 1606.73, 1584.02, 1481.71, 898.34, 856.60, 839.78, 749.79 cm^{-1}; HRMS (ESI): *m*/*z* = 640.0976 (calcd for $C_{30}H_{23}N_3O_{11}$ + K^+ = 640.0964).

Ethyl-2-((6S,6aS,9R,10R,10aR)-8-formyl-2-methyl-6,9-bis(4-nitrophenyl)-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5l**). 90% yield (51.3 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (70:30), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 26.007, t (minor) = 18.391]; $[\alpha]_D^{26}$ = −24.62 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1H), 8.39 (d, *J* = 8.8 Hz, 2H), 8.23 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.48

dx.doi.org/10.1021/jo501560m | J. Org. Chem. 2014, 79, 10772−10785

(d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.75 (s, 1H), 6.58 (s, 1H), 5.14 (d, J = 10.4 Hz, 1H), 4.48 (d, J = 3.6 Hz, 1H), 4.42 (s, 1H), 4.34−4.22 (m, 2H), 3.64−3.52 (m, 1H), 3.33 (dd, J = 11.2, 3.2 Hz, 1H), 2.20 (s, 3H), 1.34 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 191.8, 161.5, 152.2, 148.9, 148.7, 148.4, 147.5, 145.2, 140.7, 130.8, 129.7, 128.9, 128.8, 125.1, 124.5, 124.4, 120.4, 117.1, 81.2, 63.5, 48.0, 40.9, 39.0, 34.4, 20.8, 14.1; IR (KBr) ν_{max}: 2957.06, 1725.98, 1689.81, 1606.08, 1521.91, 1494.56, 1417.48, 855.04, 749.55 cm^{-1}; HRMS (ESI): m/z = 593.1517 (calcd for $C_{31}H_{26}N_2O_9$ + Na^+ = 593.1531).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-8-formyl-3-methyl-6,9-bis(4-nitrophenyl)-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5m**).* 94% yield (53.6 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (70:30), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 26.238, t (minor) = 21.868]; $[\alpha]_D^{26}$ = −37.02 (c 0.81, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (s, 1H), 8.40 (d, J = 8.8 Hz, 2H), 8.24 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.0 Hz, 1H), 6.73 (s, 1H), 6.70−6.65 (m, 1H), 6.57 (d, J = 1.2 Hz, 1H), 5.15 (d, J = 10.4 Hz, 1H), 4.80 (d, J = 3.6 Hz, 1H), 4.40 (s, 1H), 4.35−4.23 (m, 2H), 3.59 (t, J = 11.2 Hz, 1H), 3.32 (dd, J = 11.2, 3.2 Hz, 1H), 2.25 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.3, 191.8, 161.3, 154.2, 148.9, 148.8, 148.4, 147.5, 145.2, 140.7, 139.3, 128.9, 128.8, 124.5, 124.45, 124.43, 122.4, 117.9, 117.7, 81.3, 63.5, 47.9, 41.0, 38.9, 34.2, 21.2, 14.1; IR (KBr) ν_{max}: 2924.22, 1727.53, 1690.16, 1606.26, 1574.70, 1521.99, 1455.73, 855.84, 803.27, 742.97 cm^{-1}; HRMS (ESI): m/z = 593.1523 (calcd for $C_{31}H_{26}N_2O_9$ + Na^+ = 593.1531).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-2,4-dibromo-6,9-bis(4-cyanophenyl)-8-formyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5n**).* 93% yield (62.7 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (70:30), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 20.336, t (minor) = 11.670]; $[\alpha]_D^{26}$ = −94.19 (c 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 8.09 (dd, J = 8.0, 2.0 Hz, 4H), 7.56 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 1.2 Hz, 1H), 6.55 (d, J = 1.6 Hz, 1H), 6.15 (d, J = 10.8 Hz, 1H), 4.42−4.32 (m, 4H), 3,56 (t, J = 11.2 Hz, 1H), 3.26 (dd, J = 11.4, 3.6 Hz, 1H), 1.40 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 191.4, 161.0, 150.3, 147.2, 146.3, 142.3, 140.5, 134.9, 133.21, 133.17, 128.6, 128.5, 126.6, 124.8, 118.5, 118.3, 113.9, 113.5, 112.4, 112.1, 82.6, 63.9, 47.8, 40.4, 39.1, 34.4, 14.1; IR (KBr) ν_{max}: 2958.94, 2228.63, 1726.77, 1690.80, 1608.38, 1555.76, 1502.90, 1448.24, 888.99, 835.91, 771.85, 735.96, 720.26 cm^{-1}; HRMS (ESI): m/z = 1372.9677 (calcd for $(C_{30}H_{22}Br_2N_2O_9)_2$ + Na^+ = 1372.9627).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-2,4-dibromo-8-formyl-6,9-bis(4-nitrophenyl)-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5o**).* 90% yield (64.3 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (70:30), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 38.287, t (minor) = 19.703]; $[\alpha]_D^{26}$ = −108.33 (c 0.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.39 (s, 1H), 8.43 (d, J = 8.8 Hz, 2H), 8.26 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 1.6 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 0.8 Hz, 1H), 6.59 (d, J = 1.6 Hz, 1H), 5.24 (d, J = 10.4 Hz, 1H), 4.49−4.34 (m, 4H), 3.60 (t, J = 10.8 Hz, 1H), 3.30 (dd, J = 11.2, 3.6 Hz, 1H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 191.4, 161.0, 150.3, 148.9, 148.3, 147.7, 147.1, 144.1, 140.7, 135.0, 128.8, 128.7, 126.7, 124.7, 124.6, 113.6, 112.5, 82.4, 63.9, 47.8, 40.5, 39.0, 34.4, 14.1; IR (KBr) ν_{max}: 2985.27, 1726.92, 1690.47, 1606.33, 1522.07, 1491.87, 1448.43, 854.27, 753.55, 720.14, 697.29 cm^{-1}; HRMS (ESI): m/z = 734.9585 (calcd for $C_{30}H_{22}Br_2N_2O_9$ + Na^+ = 734.9584).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-6,9-bis(4-bromophenyl)-8-formyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5p**).* 95% yield (59.3 mg), 97% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (70:30), flow rate: 1.0 mL·min^{-1}, λ = 210 nm, t (major) = 9.570, t (minor) = 8.847]; $[\alpha]_D^{26}$ = −30.42 (c 0.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.20−7.07 (m, 3H), 6.95 (d, J = 11.6 Hz, 1H), 6.89−6.78 (m, 2H), 6.55 (d, J = 1.6 Hz, 1H), 4.99 (d, J = 10.4 Hz, 1H), 4.44 (d, J = 3.6 Hz, 1H), 4.33−4.19 (m, 3H), 3.54 (t, J = 11.2 Hz, 1H), 3.33 (dd, J = 11.6, 3.2 Hz, 1H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 192.1, 161.5, 154.8, 148.7, 140.8, 140.6, 137.2, 132.5, 132.3, 129.5, 128.8, 124.7, 123.6, 121.8, 121.5, 121.1, 117.2, 82.0, 63.3, 48.3, 40.8, 38.6, 34.4, 14.1; IR (KBr) ν_{max}: 2958.03, 1725.81, 1689.95, 1581.62, 1487.49, 1455.52, 881.47, 852.35, 820.35, 752.62, 707.15 cm^{-1}; HRMS (EI): m/z = 621.9977 (calcd for $C_{30}H_{24}Br_2O_5$ = 621.9990).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-8-formyl-6,9-bis(4-nitrophenyl)-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5q**).* 96% yield (53.4 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (70:30), flow rate: 1.0 mL·min^{-1}, λ = 210 nm, t (major) = 26.720, t (minor) = 29.564]; $[\alpha]_D^{26}$ = −27.50 (c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1H), 8.41 (d, J = 8.4 Hz, 2H), 8.25 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.17 (t, J = 7.6 Hz, 1H), 6.98−6.82 (m, 3H), 6.57 (d, J = 1.6 Hz, 1H), 5.16 (d, J = 10.0 Hz, 1H), 4.56 (d, J = 3.6 Hz, 1H), 4.41 (s, 1H), 4.36−4.24 (m, 2H), 3.64 (t, J = 11.2 Hz, 1H), 3.35 (dd, J = 11.4, 3.2 Hz, 1H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2, 191.8, 161.3, 154.4, 148.8, 148.3, 147.5, 145.1, 140.7, 129.1, 128.9, 128.8, 124.63, 124.55, 124.5, 121.5, 121.0, 117.3, 81.4, 63.6, 47.8, 40.8, 38.9, 34.4, 14.1; IR (KBr) ν_{max}: 2986.17, 1726.88, 1682.00, 1607.27, 1583.52, 1521.83, 1488.72, 1456.03, 858.43, 832.72, 802.15, 762.45, 751.46 cm^{-1}; HRMS (ESI): m/z = 574.1836 (calcd for $C_{30}H_{24}N_2O_9$ + NH_4^+ = 574.1820).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-6-(4-bromophenyl)-2-chloro-8-formyl-9-(4-methoxyphenyl)-6a,9,10,10a-tetrahydro-6H-benzo[c]-chromen-10-yl)-2-oxoacetate (**5aa**).* 89% yield (54.3 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 10.613, t (minor) = 9.544]; $[\alpha]_D^{26}$ = −57.43 (c 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.20−7.13 (m, 2H), 7.06 (dd, J = 8.8, 2.0 Hz, 1H), 6.94−6.86 (m, 3H), 6.79 (d, J = 8.8 Hz, 1H), 6.48 (d, J = 2.0 Hz, 1H), 4.97 (d, J = 10.4 Hz, 1H), 4.40−4.26 (m, 4H), 3.79 (s, 3H), 3.56−3.49 (m, 1H), 3.33 (dd, J = 11.4, 3.2 Hz, 1H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 192.1, 161.5, 159.2, 153.4, 147.4, 141.4, 137.0, 133.2, 132.5, 129.5, 128.8, 128.6, 125.9, 124.6, 123.73, 123.70, 118.5, 114.7, 82.3, 63.4, 55.5, 48.8, 40.4, 38.4, 34.3, 14.1; IR (KBr) ν_{max}: 2956.30, 1725.57, 1692.13, 1609.90, 1510.44, 1478.85, 887.40, 855.68, 732.30, 713.31 cm^{-1}; HRMS (EI): m/z = 608.0621 (calcd for $C_{31}H_{26}BrClO_6$ = 608.0601).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-6-(4-bromophenyl)-2-chloro-8-formyl-9-p-tolyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5ab**).* 93% yield (55.2 mg), 98% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 7.982, t (minor) = 6.680]; $[\alpha]_D^{26}$ = −41.74 (c 0.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.25 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.12−7.02 (m, 4H), 6.97 (dd, J = 8.6, 1.6 Hz, 1H), 6.85−6.81 (m, 1H), 6.70 (d, J = 8.8 Hz, 1H), 6.42−6.38 (m, 1H), 4.90 (d, J = 10.4 Hz, 1H), 4.32−4.28 (m, 4H), 3.44 (t, J = 11.2 Hz, 1H), 3.25 (dd, J = 11.4, 3.2 Hz, 1H), 2.26 (s, 3H) 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 192.1, 161.5, 153.4, 147.5, 141.3, 138.2, 137.6, 137.0, 132.5, 130.0, 129.5, 128.5, 127.6, 125.9, 124.7, 123.72, 123.69, 118.5, 82.3, 63.4, 48.7, 40.4, 38.7, 34.3, 21.2, 14.1; IR (KBr) ν_{max}: 2956.96, 1725.75, 1693.22, 1594.41, 1575.57, 1479.56, 887.24, 819.56, 756.25, 712.13 cm^{-1}; HRMS (EI): m/z = 592.0630 (calcd for $C_{31}H_{26}BrClO_5$ = 592.0652).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-6-(4-bromophenyl)-2-chloro-8-formyl-9-phenyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5ac**).* 88% yield (51.0 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 8.973, t (minor) = 7.347]; $[\alpha]_D^{26}$ = −36.60 (c 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.65−7.35 (m, 4H), 7.31 (d, J = 7.2 Hz, 1H), 7.07 (dd, J = 8.4, 1.6 Hz, 1H), 6.92 (d, J = 1.2 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 1.6 Hz, 1H), 4.99 (d, J = 10.4 Hz, 1H), 4.44−4.28 (m, 4H), 3.54 (t, J = 11.2 Hz, 1H), 3.34 (dd, J = 11.6, 3.6 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 192.1, 161.5, 153.4, 147.7, 141.22, 141.18, 137.0, 132.6, 129.5, 129.3, 128.6, 127.9, 127.8, 126.0, 124.6, 123.74, 123.66, 118.5, 82.3, 63.5, 48.6, 40.4, 39.1, 34.3, 14.1; IR (KBr) ν_{max}: 2957.53, 1725.70, 1692.19, 1595.60, 1479.61, 1451.72, 886.74, 855.39, 815.80, 769.73, 734.07,

dx.doi.org/10.1021/jo501560m | J. Org. Chem. 2014, 79, 10772−10785

700.34 cm^{-1}; HRMS (EI): m/z = 578.0502 (calcd for $C_{30}H_{24}BrClO_5$ = 578.0496).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-9-(4-bromophenyl)-2-chloro-8-formyl-6-(4-methoxyphenyl)-6a,9,10,10a-tetrahydro-6H-benzo[c]-chromen-10-yl)-2-oxoacetate (**5fa**).* 90% yield (54.9 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 11.189, t (minor) = 8.932]; $[\alpha]_D^{26}$ = −63.01 (*c* 0.37, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.10−7.08 (m, 3H), 6.92−6.90 (m, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.56 (d, *J* = 1.6 Hz, 1H), 5.00 (d, *J* = 10.4 Hz, 1H), 4.35−4.28 (m, 4H), 3.89 (s, 3H), 3.60−3.51 (m, 1H), 3.29 (dd, *J* = 11.4, 3.6 Hz, 1H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 192.2, 161.5, 160.7, 153.7, 149.2, 140.5, 132.4, 129.7, 129.5, 129.2, 128.7, 125.7, 124.6, 123.3, 121.8, 118.7, 114.8, 82.5, 63.5, 55.7, 48.6, 40.3, 38.6, 34.5, 14.1; IR (KBr) ν_{max}: 2961.44, 1726.36, 1690.24, 1613.54, 1586.84, 1515.70, 1480.23, 1407.31, 888.91, 859.23, 732.79, 705.35 cm^{-1}; HRMS (EI): m/z = 608.0612 (calcd for $C_{31}H_{26}BrClO_6$ = 608.0601).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-8-formyl-6-(4-methoxyphenyl)-9-p-tolyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5fb**).* 92% yield (50.1 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 8.518, t (minor) = 7.292]; $[\alpha]_D^{26}$ = −71.58 (*c* 0.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.19−7.10 (m, 4H), 7.05−7.03 (m, 3H), 6.94−6.89 (m, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.53 (d, *J* = 1.6 Hz, 1H), 4.96 (d, *J* = 10.0 Hz, 1H), 4.44−4.28 (m, 4H), 3.88 (s, 3H), 3.60−3.50 (m, 1H), 3.34 (dd, *J* = 11.4, 3.6 Hz, 1H), 2.33 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 192.3, 161.6, 160.6, 153.7, 148.5, 141.1, 138.4, 137.5, 129.94, 129.91, 129.2, 128.5, 127.7, 125.6, 124.7, 123.8, 118.5, 114.7, 82.6, 63.4, 55.6, 48.9, 40.4, 38.7, 34.5, 21.3, 14.1; IR (KBr) ν_{max}: 2925.02, 1725.72, 1691.35, 1613.53, 1586.55, 1514.99, 1477.88, 888.44, 858.78, 732.28, 716.35 cm^{-1}; HRMS (EI): m/z = 544.1657 (calcd for $C_{32}H_{29}ClO_6$ = 544.1653).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-8-formyl-6-(4-methoxyphenyl)-9-phenyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5fc**).* 86% yield (45.7 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 9.081, t (minor) = 8.047]; $[\alpha]_D^{26}$ = −47.11 (*c* 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.32−7.24 (m, 3H), 7.07−7.02 (m, 3H), 6.92 (d, *J* = 1.2 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.55 (d, *J* = 1.0 Hz, 1H), 4.98 (d, *J* = 10.4 Hz, 1H), 4,40−4.26 (m, 4H), 3.89 (s, 3H), 3.61−3.56 (m, 1H), 3.35 (dd, *J* = 11.4, 3.6 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 192.3, 161.6, 160.7, 153.7, 148.7, 141.4, 140.9, 129.9, 129.3, 129.2, 128.5, 127.81, 127.78, 125.6, 124.6, 123.7, 118.6, 114.7, 82.6, 63.4, 55.6, 48.7, 40.4, 39.1, 34.5, 14.1; IR (KBr) ν_{max}: 2959.33, 1725.57, 1690.97, 1613.51, 1586.16, 1477.46, 1414.06, 858.59, 821.80, 763.67, 741.96 cm^{-1}; HRMS (EI): m/z = 530.1501 (calcd for $C_{31}H_{27}ClO_6$ = 530.1496).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-9-(4-bromophenyl)-2-chloro-8-formyl-6-p-tolyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5ha**).* 90% yield (53.5 mg), >99% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 8.298, t (minor) = 6.777]; $[\alpha]_D^{26}$ = −84.14 (*c* 0.44, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.31 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.06 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.91 (d, *J* = 1.6 Hz, 1H), 6.79 (d, *J* = 1.6 Hz, 1H), 6.56 (d, *J* = 2.0 Hz, 1H), 4.96 (d, *J* = 6.4 Hz, 1H), 4.35−4.27 (m, 4H), 3.60−3.50 (m, 1H), 3.28 (dd, *J* = 11.4, 3.6 Hz, 1H), 2.44 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 192.1, 161.5, 153.7, 149.1, 140.5, 139.8, 134.7, 132.4, 130.1, 129.5, 128.6, 127.8, 125.7, 124.6, 123.3, 121.8, 118.6, 82.7, 63.5, 48.5, 40.3, 38.6, 34.4, 21.5, 14.1; IR (KBr) ν_{max}: 2960.66, 1726.22, 1690.50, 1573.22, 1515.73, 1481.67, 1407.22, 888.95, 819.40, 706.10 cm^{-1}; HRMS (EI): m/z = 592.0656 (calcd for $C_{31}H_{26}BrClO_5$ = 592.0652).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-8-formyl-9-(4-methoxyphenyl)-6-p-tolyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5hb**).* 91% yield (49.6 mg), >99% ee, >10/1 dr [Daicel Chiralcel OD-H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 8.009, t (minor) = 10.669]; $[\alpha]_D^{26}$ = −109.27 (*c* 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.31 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.19−7.15 (m, 2H), 7.05 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.93−6.86 (m, 3H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 4.97 (d, *J* = 10.4 Hz, 1H), 4.40−4.35 (m, 4H), 3.79 (s, 3H), 3.60−3.48 (m, 1H), 3.34 (dd, *J* = 11.4, 3.6 Hz, 1H), 2.44 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 192.3, 161.6, 159.2, 153.7, 148.4, 141.1, 139.7, 134.9, 133.4, 130.0, 128.8, 128.5, 127.8, 125.6, 124.6, 123.8, 118.5, 114.6, 82.9, 63.3, 55.5, 48.9, 40.4, 38.4, 34.4, 21.5, 14.1; IR (KBr) ν_{max}: 2931.59, 1724.85, 1693.07, 1610.29, 1581.62, 1509.76, 1477.03, 889.37, 825.65, 727.76, 710.87 cm^{-1}; HRMS (EI): m/z = 544.1664 (calcd for $C_{32}H_{29}ClO_6$ = 544.1653).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-8-formyl-9-phenyl-6-p-tolyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5hc**).* 93% yield (47.9 mg), 98% ee, >10/1 dr [Daicel Chiralpak IA, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 6.968, t (minor) = 6.266]; $[\alpha]_D^{26}$ = −60.00 (*c* 0.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 7.46−7.20 (m, 8H), 7.04 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.91 (d, *J* = 1.2 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.55 (d, *J* = 2.0 Hz, 1H), 4.98 (d, *J* = 10.0 Hz, 1H), 4.41−4.26 (m, 4H), 3.60−3.51 (m, 1H), 3.34 (dd, *J* = 11.4, 3.6 Hz, 1H), 2.44 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 192.3, 161.6, 153.7, 148.7, 141.4, 140.9, 139.7, 134.9, 130.0, 129.3, 128.5, 127.81, 127.77, 125.6, 124.6, 123.7, 118.5, 82.9, 63.4, 48.7, 40.4, 39.1, 34.4, 21.5, 14.1; IR (KBr) ν_{max}: 2957.10, 1725.67, 1690.82, 1515.69, 1477.41, 1451.81, 888.09, 858.14, 742.01, 726.88 cm^{-1}; HRMS (EI): m/z = 514.1542 (calcd for $C_{31}H_{27}ClO_5$ = 514.1547).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-9-(4-bromophenyl)-2-chloro-8-formyl-6-phenyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5ia**).* 90% yield (52.2 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 10.330, t (minor) = 11.507]; $[\alpha]_D^{26}$ = −109.23 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 7.55−7.46 (m, 7H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.10−7.04 (m, 1H), 6.92 (dd, *J* = 2.4, 1.2 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 6.54 (d, *J* = 6.0 Hz, 1H), 5.00 (d, *J* = 10.0 Hz, 1H), 4.38−4.25 (m, 4H), 3.62−3.51 (m, 1H), 3.30 (dd, *J* = 11.6, 3.6 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 192.1, 161.5, 153.6, 148.8, 140.6, 140.5, 137.7, 132.4, 129.8, 129.5, 129.4, 128.7, 127.8, 125.8, 124.6, 123.3, 121.9, 118.7, 82.9, 63.5, 48.5, 40.4, 38.6, 34.4, 14.1; IR (KBr) ν_{max}: 2956.59, 1726.08, 1690.61, 1642.92, 1481.12, 1455.52, 888.07, 854.79, 840.49, 816.09, 761.32, 727.06, 700.25 cm^{-1}; HRMS (EI): m/z = 578.0492 (calcd for $C_{30}H_{24}BrClO_5$ = 578.0496).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-8-formyl-9-(4-methoxyphenyl)-6-phenyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5ib**).* 87% yield (46.2 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 10.864, t (minor) = 12.482]; $[\alpha]_D^{26}$ = −111.11 (*c* 0.27, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.31 (s, 1H), 7.55−7.46 (m, 5H), 7.20−7.15 (m, 2H), 7.06 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.95−6.87 (m, 3H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 5.01 (d, *J* = 10.0 Hz, 1H), 4.38−4.27 (m, 4H), 3.80 (s, 3H), 3.60−3.50 (m, 1H), 3.36 (dd, *J* = 11.4, 3.6 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 192.3, 161.6, 159.2, 153.6, 148.2, 141.2, 137.9, 133.4, 129.7, 129.4, 128.9, 128.5, 127.8, 125.7, 124.7, 123.8, 118.5, 114.7, 83.0, 63.4, 55.5, 48.9, 40.5, 38.4, 34.4, 14.1; IR (KBr) ν_{max}: 2998.38, 1722.58, 1693.59, 1610.20, 1583.97, 1456.07, 887.82, 824.07, 729.79, 703.28 cm^{-1}; HRMS (EI): m/z = 530.1511 (calcd for $C_{31}H_{27}ClO_6$ = 530.1496).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-2-chloro-8-formyl-6-phenyl-9-p-tolyl-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**5ic**).* 95% yield (48.9 mg), >99% ee, >10/1 dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 8.119, t (minor) = 9.778]; $[\alpha]_D^{26}$ = −121.24 (*c* 0.49, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.31 (s, 1H), 7.54−7.46 (m, 4H), 7.20−7.12 (m, 4H), 7.05 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.93−6.91 (m, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 1H),

dx.doi.org/10.1021/jo501560m | J. Org. Chem. 2014, 79, 10772−10785

5.01 (d, J = 10.0 Hz, 1H), 4.44−4.25 (m, 4H), 3.60−3.50 (m, 1H), 3.35 (dd, J = 11.4, 3.6 Hz, 1H), 2.34 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 192.3, 161.6, 153.6, 148.2, 141.1, 138.4, 137.9, 137.5, 129.9, 129.7, 129.3, 128.5, 127.8, 127.7, 125.7, 124.7, 123.8, 118.5, 83.0, 63.4, 48.8, 40.5, 38.7, 34.4, 21.2, 14.1; IR (KBr) ν_{max}: 2980.88, 1723.71, 1686.58, 1634.80, 1510.54, 1477.66, 1456.11, 867.82, 831.51, 731.80, 700.83 cm^{-1}; HRMS (EI): m/z = 514.1557 (calcd for $C_{31}H_{27}ClO_5$ = 514.1547).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-6,9-bis(4-bromophenyl)-2-chloro-8-((2-tosylhydrazono)methyl)-6a,9,10,10a-tetrahydro-6H-benzo[c]-chromen-10-yl)-2-oxoacetate (**6**).* 88% yield (72.8 mg), >99% ee, >10/1dr [Daicel Chiralpak IA, hexane/*i*-PrOH (70:30), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 22.966, t (minor) = 6.511]; $[\alpha]_D^{26}$ = −45.63 (c 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.4 Hz, 2H), 7.50 (s, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.18−7.10 (m, 3H), 7.08−6.98 (m, 3H), 6.87 (d, J = 1.2 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 5.72 (d, J = 2.0 Hz, 1H), 4.82 (d, J = 10.4 Hz, 1H), 4.45 (s, 1H), 4.35 (dd, J = 14.4, 7.2 Hz, 2H), 4.31 (d, J = 3.2 Hz, 1H), 3.39 (t, J = 11.2 Hz, 1H), 3.18 (dd, J = 11.2, 3.2 Hz, 1H), 2.42 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 161.5, 153.4, 147.7, 144.2, 141.7, 137.2, 135.6, 134.9, 134.7, 132.4, 132.1, 129.7, 129.5, 128.5, 127.3, 125.8, 124.5, 123.7, 123.5, 121.4, 118.4, 82.8, 63.5, 48.4, 40.0, 39.9, 34.1, 21.9, 14.1; IR (KBr) ν_{max}: 2981.34, 1725.63, 1596.01, 1484.29, 1406.96, 880.97, 854.03, 814.84, 703.54 cm^{-1}; HRMS (ESI): m/z = 825.0043 (calcd for $C_{37}H_{31}Br_2ClN_2O_6S$ + H^+ = 825.0031).

*Ethyl-2-((6S,6aS,9R,10R,10aR)-6,9-bis(4-bromophenyl)-2-chloro-8-(1,3-dithiolan-2-yl)-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-oxoacetate (**7**).* 86% yield (63.2 mg), >99% ee, >10/1dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL·min^{-1}, λ = 254 nm, t (major) = 18.486, t (minor) = 10.153]; $[\alpha]_D^{26}$ = 6.50 (c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.04 (dd, J = 8.8, 2.0 Hz, 1H), 6.81 (d, J = 1.6 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 5.83 (d, J = 1.2 Hz, 1H), 4.86 (d, J = 9.6 Hz, 1H), 4.80 (s, 1H), 4.40−4.28 (m, 3H), 4.24−4.16 (m, 1H), 3.30−3.00 (m, 5H), 2.95−2.80 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 161.6, 153.4, 141.0, 137.9, 137.2, 132.4, 132.1, 130.1, 129.4, 128.2, 126.0, 125.5, 124.4, 124.2, 123.1, 121.9, 118.2, 83.5, 63.2, 56.9, 49.5, 43.2, 39.6, 39.3, 38.3, 33.6, 14.2; IR (KBr) ν_{max}: 2955.52, 1724.29, 1593.68, 1483.50, 1405.11, 888.93, 858.74, 822.62, 740.73, 716.71 cm^{-1}; HRMS (ESI): m/z = 749.9780 (calcd for $C_{32}H_{27}Br_2ClO_4S_2$ + NH_4^+ = 749.9744).

*Ethyl-2-((6S,6aS,9R,10R,10aS)-6,9-bis(4-bromophenyl)-2-chloro-8-(1,3-dithiolan-2-yl)-6a,9,10,10a-tetrahydro-6H-benzo[c]chromen-10-yl)-2-hydroxyacetate (**8**).* 99% yield (73.0 mg), >99% ee, 3/1dr [Daicel Chiralpak AD-H, hexane/*i*-PrOH (90:10), flow rate: 0.8 mL·min^{-1}, λ = 210 nm, t (major) = 33.188, t (minor) = 24.255]; $[\alpha]_D^{26}$ = 26.67 (c 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.4 Hz, 2H), 7.52−7.43 (m, 2H), 7.41−7.33 (m, 2H), 7.12−6.98 (m, 3H), 6.96−6.90 (m, 1H), 6.83−6.73 (m, 1H), 5.96−5.84 (m, 1H), 5.96−5.83 (m, 1H), 4.85 (d, J = 10.4 Hz, 1H), 4.82−4.76 (m, 1H), 4.40−4.20 (m, 2H), 4.05−3.85 (m, 2H), 3.25−2.85 (m, 6H), 2.70 (t, J = 7.2 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 154.1, 142.1, 138.9, 137.8, 132.2, 132.1, 130.1, 129.6, 128.0, 125.7, 125.5, 125.4, 124.0, 123.0, 121.3, 118.4, 82.9, 69.8, 62.4, 57.0, 46.3, 43.6, 39.4, 39.3, 38.2, 34.5, 14.4; IR (KBr) ν_{max}: 3446.27, 2924.31, 1730.52, 1594.15, 1481.68, 1404.89, 862.52, 821.42, 716.84 cm^{-1}; HRMS (ESI): m/z = 751.9906 (calcd for $C_{32}H_{29}Br_2ClO_4S_2$ + NH_4^+ = 751.9901).

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic data of **4a** and **5c**, the copies of ^{1}H and ^{13}C NMR spectra of the products, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Fax: +(86)512-6588-0378. E-mail: wangxw@suda.edu.cn (X.-W.W.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support of the National Natural Science Foundation of China (21272166), the Major Basic Research Project of the Natural Science Foundation of the Jiangsu Higher Education Institutions (13KJA150004), the Program for New Century Excellent Talents in University (NCET-12-0743), and a Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD), and also the Project of Scientific and Technologic Infrastructure of Suzhou (SZS201207).

■ REFERENCES

(1) (a) Buckner, S. A.; Milicic, I.; Daza, A.; Taber, R. D.; Scott, V. E. S.; Sullivan, J. P.; Brioni, J. D. *Eur. J. Pharmacol.* **2000**, *400*, 287−295. (b) Khelili, S.; Florence, X.; Bouhadja, M.; Abdelaziz, S.; Mechouch, N.; Mohamed, Y.; Tullio, P. D.; Lebrun, P.; Pirotte, B. *Bioorg. Med. Chem.* **2008**, *16*, 6124−6130. (c) Coi, A.; Bianucci, A. M.; Calderone, V.; Testai, L.; Digiacomo, M.; Rapposelli, S.; Balsamo, A. *Bioorg. Med. Chem.* **2009**, *17*, 5565−5571. (d) Trenor, S. R.; Shultz, A. R.; Love, B. J.; Long, T. E. *Chem. Rev.* **2004**, *104*, 3059−3077. (e) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953. (f) Breschi, M. C.; Calderone, V.; Martelli, A.; Minutolo, F.; Rapposelli, S.; Testai, L.; Tonelli, F.; Balsamo, A. *J. Med. Chem.* **2006**, *49*, 7600−7602.

(2) Shen, H.-C. *Tetrahedron* **2009**, *65*, 3931−3952.

(3) (a) Iwasaki, K.; Nakatani, M.; Inoue, M.; Katoh, T. *Tetrahedron* **2003**, *59*, 8763−8773. (b) Kurdyumov, A. V.; Hsung, R. P. *J. Am. Chem. Soc.* **2006**, *128*, 6272−6273. (c) Deng, W.-P.; Zhong, M.; Guo, X.-C.; Kende, A. S. *J. Org. Chem.* **2003**, *68*, 7422−7427. (d) Hua, D.-H.; Huang, X.-D.; Chen, Y.; Battina, S. K.; Tamura, M.; Noh, S. K.; Koo, S. I.; Namatame, I.; Tomoda, H.; Perchellet, E. M.; Perchellet, J. P. *J. Org. Chem.* **2004**, *69*, 6065−6078. (e) Mikoshiba, H.; Mikami, K.; Nakai, T. *Synlett* **2001**, *SI*, 989−990. (f) Song, Y.-L.; Hwang, S.; Gong, P.; Kim, D.; Kim, S. *Org. Lett.* **2008**, *10*, 269−271.

(4) (a) Holmberg, P.; Tedenborg, L.; Rosqvist, S.; Johansson, A. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 747−750. (b) Kawasaki, M.; Kakuda, H.; Goto, M.; Kawabata, S.; Kometani, T. *Tetrahedron: Asymmetry* **2003**, *14*, 1529−1534. (c) Rein, C.; Demel, P.; Outten, R. A.; Netscher, T.; Breit, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 8670−8673.

(5) (a) Chandrasekhar, S.; Reddy, M. V. *Tetrahedron* **2000**, *56*, 6339−6344. (b) Cassman, P. G.; Amick, D. R. *J. Am. Chem. Soc.* **1978**, *100*, 7611−7619. (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074−9075. (d) Marcos, R.; Escrich, C. R.; Herrerías, C. I.; Pericás, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 16838−16839. (e) Mente, N. R.; Neighbors, J. D.; Wiemer, D. F. *J. Org. Chem.* **2008**, *73*, 7963−7970.

(6) For selected examples of syntheses of chroman or chromene derivatives, see: (a) Govender, T.; Hojabri, L.; Moghaddam, F.; Arvidsson, P. *Tetrahedron:Asymmetry* **2006**, *17*, 1763−1767. (b) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem.—Eur. J.* **2007**, *13*, 574−581. (c) Luo, S.-P.; Li, Z.-B.; Wang, L.-P.; Guo, Y.; Xia, A.-B.; Xu, D.-Q. *Org. Biomol. Chem.* **2009**, *7*, 4539−4546. (d) Lu, D.-F.; Li, Y.-J.; Gong, Y.-F. *J. Org. Chem.* **2010**, *75*, 6900−6907. (e) Hong, L.; Wang, L.; Sun, W.-S.; Wong, K.; Wang, R. *J. Org. Chem.* **2009**, *74*, 6881−6884. (f) Liu, C.-L.; Zhang, X.-S.; Wang, R.; Wang, W. *Org. Lett.* **2010**, *12*, 4948−4951. (g) Zu, L.-S.; Zhang, S.-L.; Xie, H.-X.; Wang, W. *Org. Lett.* **2009**, *11*, 1627−1630. (h) Ramachary, D. B.; Prasad, M. S.; Laxmi, S. V.; Madhavachary, R. *Org. Biomol. Chem.* **2014**, *12*, 574−580. (i) Enders, D.; Wang, C.; Yang, X.-N.; Raabe, G.

Adv. Synth. Catal. **2010**, *352*, 2869−2874. (j) Ramachary, D. B.; Madhavachary, R.; Prasad, M. S. *Org. Biomol. Chem.* **2012**, *10*, 5825−5829. (k) Enders, D.; Yang, X.-N.; Wang, C.; Raabe, G.; Runsik, J. *Chem.—Asian J.* **2011**, *9*, 2255−2259. (l) Zhang, X.-S.; Zhang, S.-L.; Wang, W. *Angew. Chem., Int. Ed.* **2010**, *8*, 1481−1484. (m) Li, H.; Wang, J.; Nunu, T. E.; Zu, L.-S.; Jiang, W.; Wei, S.-H.; Wang, W. *Chem. Commun.* **2007**, 507−509. (n) Rueping, M.; Dufour, J.; Maji, M. S. *Chem. Commun.* **2012**, *48*, 3406−3408. (o) Li, W.-J.; Liu, H.; Jiang, X.-F.; Wang, J. *ACS Catal.* **2012**, *2*, 1535−153. (p) Ren, Q.; Siau, W.; Du, Z.-Y.; Zhang, K.; Wang, J. *Chem.—Eur. J.* **2011**, *17*, 7781−7785. (q) Kotame, P.; Hong, B. C.; Liao, J. H. *Tetrahedron Lett.* **2009**, *50*, 704−707. (r) Liu, L.-Y.; Zhu, Y.-N.; Huang, K.-M.; Wang, B.; Chang, W.-X.; Li, J. *Eur. J. Org. Chem.* **2014**, *20*, 4342−4350. (s) Mao, H.-B.; Lin, A.-J.; Tang, Y.; Shi, Y.; Hu, H.-W.; Cheng, Y.-X.; Zhu, C.-J. *Org. Lett.* **2013**, *15*, 4062−4065. (t) Enders, D.; Urbanietz, G. *synthesis* **2011**, *12*, 1905−1911. (u) Enders, D.; Urbanietz, G. *synthesis* **2012**, *5*, 773−782. (v) Xie, J.-W.; Huang, X.; Fan, L.-P.; Xu, D.-C.; Li, X.-S.; Su, H.; Wen, Y.-H. *Adv. Synth. Catal.* **2009**, *351*, 3077−3082. (w) Alemán, J.; Núñez, A.; Marzo, L.; Marcos, V.; Alvarado, C.; José Luis, G. *Chem.—Eur. J.* **2010**, *16*, 9453−9456. (x) Alemán, J.; Cuauhtémoc, A.; Vanesa, M.; Alberto, N.; José Luis, G. *Synthesis* **2011**, *12*, 1840−1846.

(7) For selected reviews on organocatalytic domino reactions, see: (a) Yu, X.-H.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037−2046. (b) Pellisier, H. *Chem. Rev.* **2013**, *113*, 442−524. (c) Pellisier, H. *Adv. Synth. Catal.* **2012**, *354*, 237−294. (d) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570−1581. (e) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248−264. (f) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492−8509. (g) Xu, L.-W.; Li, L.; Shi, Z.-H. *Adv. Synth. Catal.* **2010**, *352*, 243−279. (h) Alemán, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774−793. (i) Figueiredo, R.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575−2600. (j) Marqués-López, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *27*, 1138−1167.

(8) For selected reviews on syntheses of chroman derivatives with organocatalysis, see: (a) Bhanja, C.; Jena, S.; Nayak, S.; Mohapatra, S. *Beilstein J. Org. Chem.* **2012**, *8*, 1668−1694. (b) Núñez, M. G.; García, P.; Moro, R. F.; Díez, D. *Tetrahedron* **2010**, *66*, 2089−2109. (c) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2012**, *41*, 988−999.

(9) Cakir, S. P.; Stokes, S.; Sygula, A.; Mead, K. T. *J. Org. Chem.* **2009**, *74*, 7529−7532.

(10) Wu, W.-L.; Asberom, T.; Bara, T.; Bennett, C.; D. Burnett, A.; Clader, J.; Domalski, M.; Greenlee, W. J.; Josien, H.; McBriar, M.; Rajagopalan, M.; Vicarel, M.; Xu, R.; Hyde, L. A.; Vecchio, R. A. D.; Williams, M. E. C.; Song, L.-X.; Lee, J. L.; Terracina, G.; Zhang, Q.; Nomeir, A.; Parker, E. M.; Zhang, L.-L. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 844−849.

(11) Cheng, L.-J.; Xie, J.-H.; Chen, Y.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2013**, *4*, 764−767.

(12) Thakur, G. A.; Bajaj, S.; Paronis, C.; Peng, Y.; Bowman, A. L.; Arak, L. S.; Caron, M. G.; Parrish, D.; Deschamps, J. R.; Makriyannis, A. *J. Med. Chem.* **2013**, *56*, 3904−3921.

(13) (a) Li, J.-L.; Liu, T.-Y.; Chen, Y.-C. *Acc. Chem. Res.* **2012**, *45*, 1491−1500. (b) Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359−5406. (c) Jiang, X.-X.; Wang, R. *Chem. Rev.* **2013**, *113*, 5515−5546. (d) Wessig, P.; Müller, G. *Chem. Rev.* **2008**, *108*, 2051−2063.

(14) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498−1501.

(15) Xu, Z.-H.; Liu, L.; Wheeler, K.; Wang, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 3484−3488.

(16) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2013**, *113*, 5924−5988.

(17) (a) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901−2904. (b) Albrecht, Ł.; Dickmeiss, G.; Acosta, F. C.; Rodríguez-Escrich, C.; Davis, R. L.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543−2546. (c) Lattanzi, A. *Chem. Commun.* **2009**, 1452−1463. (d) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964−6965.

(18) Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC 997475 for **4a** and CCDC 997476 for **5c**).