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Dinuclear zinc catalyzed asymmetric tandem Michael addition/acetalization reactions of cyclic diketones and β,γ-unsaturated α-ketoesters

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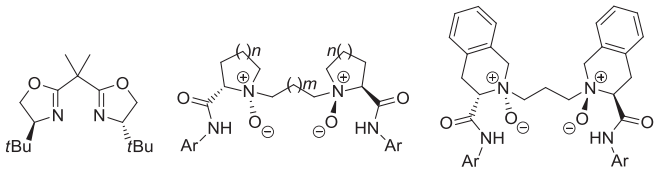
ABSTRACT

The dinuclear zinc–ProPhenol complex is applied as efficient catalyst in the highly stereoselective tandem Michael addition/acetalization reactions of cyclic 1,3-diketones and β,γ-unsaturated α-ketoesters. A variety of substrates are well-tolerated, and a broad range of synthetically and pharmaceutically useful chiral chromene derivatives are directly produced in good yields of up to 96% and good enantioselectivities of up to 96% ee.

1. Introduction

The six-membered oxygenated heterocycles, such as tetrahydropyrans, chromenes, and flavanones, are one of the most common natural product frameworks, which exhibit numerous biological and physiological activities.[1] The structural motifs, especially the optically active ones, are widely utilized as important building blocks for natural product syntheses and pharmaceutical elaborations.[1a–d,f] Among various asymmetric synthetic strategies developed to prepare the chiral motifs, the catalytic tandem Michael addition/acetalization reaction of cyclic 1,3-dicarbonyl compound with α,β-unsaturated carbonyl compound is considered as one of the highly efficient approaches.[1d,e]

Comparing with other commonly used α,β-unsaturated carbonyl derivatives, such as alkenals and enones, the β,γ-unsaturated α-ketoesters demonstrate specific advantages in substrate activation and stereo-induction owing to the presence of bidentate 1,2-dicarbonyl moiety, which can form multiple effective associations with different types of chiral catalysts.[2] As early as in 2003, Jørgensen and co-workers reported the asymmetric tandem Michael addition/acetalization reactions of cyclic 1,3-dicarbonyl compounds and β,γ-unsaturated α-ketoesters catalyzed by chiral bisoxazoline–copper(II) complexes.[3] By using (*S*)-*t*-Bu-Box (Fig. 1) as the optimal chiral ligand, a variety of synthetically and pharmaceutically useful chiral chromene derivatives[4] were directly produced in almost quantitative yields and good stereoselectivities up to 92% ee.[3] Following the early pioneering work, the asymmetric tandem processes have drawn intensive studies in recent years.[5] Calter and co-worker demonstrated that cinchona alkaloid-derived pyrimidine organocatalysts could efficiently catalyze the tandem reactions to afford excellent enantioselectivities ranging from 94% to 99% ee.[5a] Subsequently, a variety of chiral squaramide-



(*S*)-*t*-Bu-Box | *N*,*N*′-dioxide Ligand (*n* = 1 or 2; *m* = 0 or 1) (by Feng) | tetrahydroisoquinoline-derived *N*,*N*′-dioxide Ligand (by Govender)

Fig. 1. Previously used chiral ligands for the asymmetric tandem reactions of 1,3-dicarbonyl compounds and β,γ-unsaturated α-ketoesters.

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or/and thiourea-derived H-bonding organocatalysts have also been utilized as effective catalyst by the groups of Cao, Wang, and Xu, respectively.[5b–d,g] However, the development of chiral metal catalysts is yet to be investigated. In 2011, Feng and co-workers communicated the highly enantioselective tandem Michael addition/acetalization reactions of various cyclic 1,3-dicarbonyl compounds and β,γ-unsaturated α-ketoesters catalyzed by *N*,*N*′-dioxide–nickel(II)/copper(II) complexes (Fig. 1).[5e,f] Recently, Govender and co-workers also described the application of tetrahydroisoquinoline-derived *N*,*N*′-dioxide ligands (Fig. 1) to the tandem transformations, but only moderate to good enantioselectivities were obtained.[5h] Since the effective metal catalysts are majorly limited to bisoxazoline and *N*,*N*′-dioxide mononuclear metal complexes, the development of efficient metal catalysts is in demand and rewarding, given the synthetic usefulness of chiral chromene products.

Meanwhile, as a well-developed bifunctional metal catalyst, the Trost's dinuclear zinc–ProPhenol complex (Fig. 2) has demonstrated remarkable catalytic efficiency and stereoselectivity in asymmetric Michael additions of carbo- and phospho-nucleophiles to α,β-unsaturated carbonyl compounds and nitroalkenes.[6,7] The self-assembled dinuclear metal complex displays complementary reactivity at the two metal centers, and allows for dual activation of both Michael donor and acceptor. Comparing with the broad applications of the dinuclear metal catalyst in single-step reactions, its use in synthetically useful tandem processes has been rarely reported. Recently, Trost and Hirano demonstrated that the dinuclear zinc complex was capable of catalyzing tandem Michael addition/transesterification reactions to produce spirocyclic oxindoles in good yields and excellent stereoselectivities.[6e] Moreover, bidentate enolate surrogate, for example, α-hydroxyketone,[6a] 2(5*H*)-furanone,[6c] or 3-hydroxyoxindole,[6e] is usually required as effective Michael donor, and the use of monodentate one is less documented. In these contexts, we herein report the dinuclear zinc–ProPhenol-catalyzed highly enantioselective tandem Michael addition/acetalization reactions of cyclic 1,3-diketones and β,γ-unsaturated α-ketoesters, and a wide range of optically active chromene derivatives are directly produced in good yields (up to 96%) and good enantioselectivities (up to 96% ee) with a catalyst loading of 5 mol %.

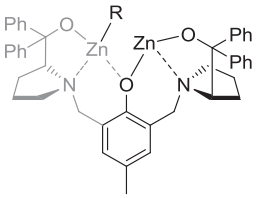
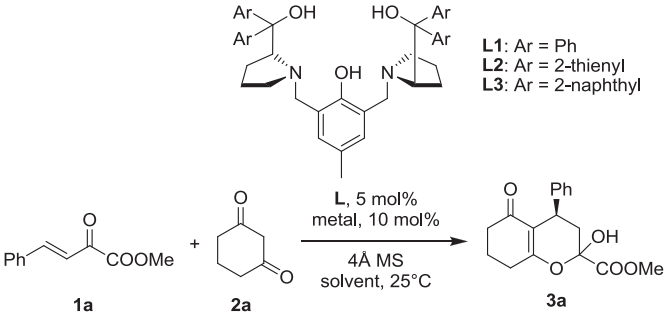


Fig. 2. Trost's dinuclear zinc–ProPhenol complex.

2. Results and discussion

We started our investigations by examining the cascade Michael reaction of cyclic 1,3-diketone **2a** and β,γ-unsaturated α-ketoester **1a** under the catalysis of dinuclear metal–ProPhenol complex (Table 1). The chiral complex was in situ generated by treating (*S*,*S*)-Bis-ProPhenol ligand **L** with 2 equiv metal reagent in the presence of 4 Å MS.[6] Early optimization with various ligand–metal combinations (Table 1, entries 1–6) proved that the complex of ligand **L1** and Et_2Zn was the optimal catalyst in promoting the desired conjugate addition in anhydrous THF at 25 °C. The Michael reaction was followed with a favored tandem acetalization to afford hexahydrochromene **3a** in 94% yield and 93% ee (Table 1, entry 1).[8] Some typical solvents, such as toluene and acetonitrile, which had been previously used in the dinuclear catalytic system, were also screened, and anhydrous THF gave the optimal results in both yield and enantioselectivity (Table 1, entries 7–12). When the catalyst loading was decreased from 5 to 3 mol %, reaction yield was decreased to 80% with a slight sacrifice in stereoselectivity (Table 1, entry 13). When reaction temperature was lowered to 10 °C, the enantioselectivity increased to 94% ee, but at the cost of extended reaction time (Table 1, entry 14). Furthermore, when the reaction was performed at 0 °C, the decreases of both reaction efficiency and stereoselectivity were observed (Table 1, entry 15).

Table 1
Optimization of reaction conditions for the cascade Michael reaction of **2a** and **1a**[a]



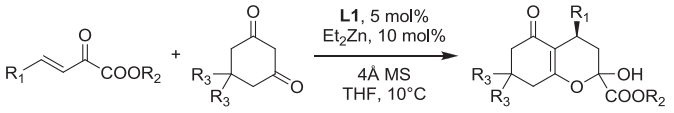
Entry	L	Metal reagent	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	**L1**	Et_2Zn	THF	20	94	93
2	**L2**	Et_2Zn	THF	15	62	4
3	**L3**	Et_2Zn	THF	15	90	89
4	**L1**	Me_2Zn	THF	21	90	91
5[d]	**L1**	Et_2Zn+Bu_2Mg	THF	21	54	36
6	**L1**	Bu_2Mg	THF	21	80	5
7	**L1**	Et_2Zn	Toluene	20	53	81
8	**L1**	Et_2Zn	CH_2Cl_2	20	46	75
9	**L1**	Et_2Zn	$CHCl_3$	20	48	70
10	**L1**	Et_2Zn	Et_2O	20	50	61
11	**L1**	Et_2Zn	MeCN	20	42	76
12	**L1**	Et_2Zn	1,4-Dioxane	20	92	77
13[e]	**L1**	Et_2Zn	THF	20	80	92
14[f]	**L1**	Et_2Zn	THF	24	94	94
15[g]	**L1**	Et_2Zn	THF	26	87	89

[a] Unless otherwise noted, the reaction were performed with **1a** (0.125 mmol), **2a** (0.125 mmol), ligand **L** (5 mol %), metal reagent (10 mol %), and 10 mg 4 Å MS in solvent (1.3 mL) at 25 °C.
[b] Yield of the isolated product **3a**.
[c] Determined by chiral HPLC analysis using the Chiralpak AD column. And the absolute configuration of **3a** was determined by comparison to literature data.[5b]
[d] The 5 mol % Et_2Zn and 5 mol % Bu_2Mg were used as metal reagents.
[e] The 3 mol % ligand **L1** and 6 mol % Et_2Zn were used.
[f] The reaction was performed at 10 °C.
[g] The reaction was performed at 0 °C.

After the optimal reaction conditions were established, the substrate scope and limitation of the tandem reaction were further investigated by using various β,γ-unsaturated α-ketoesters and cyclic 1,3-diketones (Table 2). It was found that the catalytic tandem process is sensitive to spatial hindrance. If a substrate, either a Michael donor or acceptor, possesses even a small steric hindrance group, a change of reaction efficiency or/and stereoselectivity would be observed.

The β,γ-unsaturated α-ketoesters bearing different substituent on ester moiety (R^2) was initially examined. A relative big substituent, such as ethyl or isopropyl, would result in decreased yield and prolonged reaction time comparing with methyl substituent (Table 2, entries 1–3). The substrates **1** bearing *para*- or/and *meta*-substituted γ-aryl moiety (R^1) could smoothly react with 1,3-cyclohexanedione (R^3=H) to afford chiral chromene derivatives **3** in good yields and excellent enantioselectivities of more than 90% ee (Table 2, entries 4–14). A broad range of substituents on the γ-aromatic ring were well tolerated, including both electronic donating groups, such as methyl and methoxyl, and electronic withdrawing groups, such as fluoro, chloro, and bromo. Whereas,

Table 2
Substrate scope of the catalytic asymmetric Michael addition/acetalization reactions of cyclic diketones and β,γ-unsaturated α-ketoesters[a]



1 2 3

Entry	R^1	R^2	R^3	Time (h)	3	Yield (%)[b]	ee (%)[c]
1	Ph	Me	H	24	**3a**	94	94
2	Ph	Et	H	27	**3b**	79	91
3	Ph	^{i}Pr	H	30	**3c**	79	92
4	4-MeC_6H_4	Me	H	26	**3d**	95	91
5	4-MeOC_6H_4	Me	H	28	**3e**	89	91
6	4-FC_6H_4	Me	H	21	**3f**	96	91
7	4-ClC_6H_4	Me	H	24	**3g**	87	90
8	4-BrC_6H_4	Me	H	26	**3h**	96	92
9	3-MeC_6H_4	Me	H	30	**3i**	67	91
10	3-MeOC_6H_4	Me	H	30	**3j**	65	89
11	3,4-OCH_2O–C_6H_3	Me	H	28	**3k**	87	93
12	3-ClC_6H_4	Me	H	27	**3l**	77	91
13	3-BrC_6H_4	Me	H	24	**3m**	87	91
14	3-Br–4-Cl–C_6H_3	Me	H	28	**3n**	75	91
15	2-ClC_6H_4	Me	H	48	**3o**	16	16
16	2-BrC_6H_4	Me	H	48	**3p**	7	12
17	2,6-$(MeO)_2$–C_6H_3	Me	H	72	**3q**	0	n.d.[d]
18	2-Naphthyl	Me	H	28	**3r**	80	93
19	2-Thienyl	Me	H	30	**3s**	84	96
20	Ph	Me	Me	20	**3t**	98	89
21	4-MeC_6H_4	Me	Me	28	**3u**	90	76
22	4-MeOC_6H_4	Me	Me	30	**3v**	94	74
23	4-ClC_6H_4	Me	Me	30	**3w**	85	75
24	4-BrC_6H_4	Me	Me	30	**3x**	85	76

[a] Unless otherwise noted, the reaction were performed with **1** (0.125 mmol), **2** (0.125 mmol), ligand **L1** (5 mol %), Et_2Zn (10 mol %), and 10 mg 4 Å MS in anhydrous THF (1.3 mL) at 10 °C.
[b] Yield of the isolated product **3**.
[c] Determined by chiral HPLC analysis using the Chiralpak AD or OD column. And the absolute configurations of **3** were determined by comparison to literature data.[5a,b,f,g]
[d] Not determined.

compared with *para*-substituted substrate, the *meta*-substituted one usually gave reduced yield (Table 2, entry 4 vs 9, entry 5 vs 10, entry 7 vs 12, and entry 8 vs 13).

If the spatial hindrance of γ-aryl moiety was large enough, the conjugate addition could be severely prohibited. When either *ortho*-chloro or *ortho*-bromo substituted substrate was used, a competing 1,2-addition/condensation process was identified as major reaction, and the desired Michael addition/acetalization product was afforded in very poor yield and enantioselectivity (Table 2, entries 15 and 16). Moreover, the 2,6-dimethoxyl substituted β,γ-unsaturated α-ketoester was not able to react with 1,3-cyclohexanedione, and reactants were almost fully recovered after days (Table 2, entry 17).

The scope of cyclic 1,3-diketone was also extended to dimedone (R^3=Me) to further explore the potential of the catalytic system. Compared with the results obtained by using 1,3-cyclohexanedione, the reaction efficiency of dimedone remained almost the same, but the enantioselectivities were decreased (Table 2, entries 20–24). Furthermore, a series of different 1,3-dicarbonyl compounds (Fig. 3), such as 2-methyl-1,3-cyclohexanedione **4a**, 1,3-cyclopentanedione **4b**, 2,4-pentanedione **4c**, and Meldrum's acid **4d** were also applied as Michael donors to react with β,γ-unsaturated α-ketoester **1a**

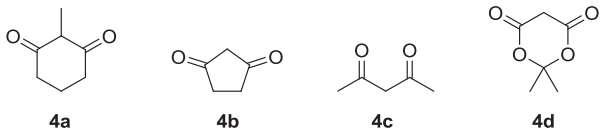
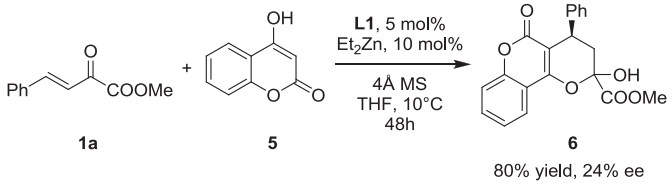
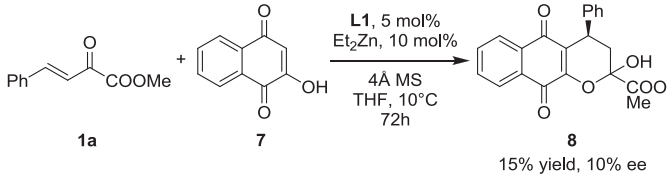


Fig. 3. A series of 1,3-dicarbonyl compounds.

under the optimal reaction conditions. But, surprisingly, no significant conversion was observed in each case, and the reactants were almost untouched even after prolonged reaction time. Additionally, the reaction of 4-hydroxycoumarine **5** was examined, and the corresponding cascade product **6** was obtained in 80% yield, but the enantioselectivity is as low as 24% ee (Scheme 1). When 2-hydroxy-1,4-naphthoquinone **7** was utilized as 1,3-diketone surrogate, the reaction could not be driven to a completion even after three days, and the tandem product **8** was isolated in very poor yield and enantioselectivity (Scheme 2).

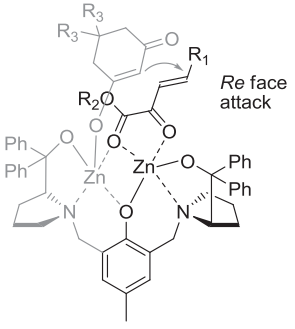


Scheme 1. Asymmetric cascade Michael reaction by using 4-hydroxycoumarin as Michael donor.



Scheme 2. Asymmetric cascade Michael reaction by using 2-hydroxy-1,4-naphthoquinone as Michael donor.

In order to understand the catalytic process, the transition state model of the conjugate addition process (Scheme 3) was proposed based on the dual activation mechanism of dinuclear zinc catalysis[6a–c,e,7a] and the bidentate coordination mode of β,γ-unsaturated α-ketoesters.[2] As illustrated, the cyclic 1,3-diketone was activated by the Brønsted basic zinc nucleus, and the zinc enolate was formed. Meanwhile, the β,γ-unsaturated α-ketoester was activated by the other Lewis acidic zinc nucleus via bidentate coordination of the 1,2-dicarbonyl moiety. With the spatial alignment, the zinc enolate would attack from the *Re* face of the coordinated Michael acceptor to give the observed stereo-chemical outcome.



Scheme 3. Proposed transition state model.

3. Conclusion

In summary, we reported the dinuclear zinc–ProPhenol complex catalyzed highly efficient asymmetric tandem Michael addition/acetalization reactions of cyclic 1,3-diketones and β,γ-unsaturated α-ketoesters. A broad range of substrates are well-tolerated, and synthetically and pharmaceutically useful chiral chromene derivatives were directly produced in good yields up to 96% and good enantioselectivities up to 96% ee. In the detailed study of substrate scope, a steric hindrance effect was observed. If a substrate, either

a Michael donor or acceptor, possesses a spatial hindrance group, the reaction efficiency or/and stereoselectivity would decrease. Besides six-membered cyclic 1,3-diketones, the 4-hydroxycoumarin was also used as an alternative Michael donor to produce the desired six-membered oxygenated heterocycle. The stereoselective outcome of the asymmetric catalysis was also explained by a proposed transition state model of the conjugate addition process.

4. Experimental

4.1. General methods

NMR spectra (^{1}H and ^{13}C) were performed on a commercial spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) using solution in $CDCl_3$ (referenced internally to Me_4Si); the *J* values were given in Hertz. IR Spectra were determined on a commercial spectrophotometer. TLC was performed on dry silica gel plates developed with petroleum ether (60–90 °C) and ethyl acetate, and spots were visualized with UV light. The mass spectra were obtained using a commercial instrument with an electrospray ionization source (ESI). The ionization method for HRMS was electrospray ionization (ESI), and the mass analyzer type was the time of flight (TOF). All the mass spectra were performed using anhydrous MeOH as solvent. Melting points were determined using melting point apparatus. The chiral ProPhenol ligands (**L1**,[6d] **L2**,[7d] and **L3**[6d]) and various γ-aryl β,γ-unsaturated α-ketoesters **1**[9] were synthesized according to reported procedures.

4.2. Representative procedure for the dinuclear zinc–ProPhenol complex catalyzed tandem Michael addition/acetalization reactions

Diethylzinc (1 M in hexane, 13 μL, 13 μmol, 10 mol %) was added via microsyringe to a stirred solution of chiral ligand **L1** (6 μmol, 5 mol %) in freshly distilled anhydrous THF (0.3 mL) under a nitrogen atmosphere, and the mixture was stirred at room temperature for 30 min to generate the zinc catalyst. The resulting solution was cooled to 10 °C, and was quickly added into a stirred solution of β,γ-unsaturated α-ketoester **1** (0.125 mmol), cyclic 1,3-diketone **2** (0.125 mmol), and 10 mg 4 Å MS in freshly distilled anhydrous THF (1.0 mL) at 10 °C under a nitrogen atmosphere. The reaction mixture was stirred at 10 °C, and was monitored by TLC analysis. After total consumption of reactants, the reaction was quenched using saturated aqueous solution of NH_4Cl, and was extracted with ethyl acetate for three times. The combined organic layer was washed with saturated aqueous solution of Na_2CO_3 and brine, and dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel using a mixture of petroleum ether and ethyl acetate as eluent. Absolute configurations of the tandem reaction products were assigned by correlation to literature data and considering the similarity in the stereochemical reaction pathway.[5a,b,f,g]

4.3. Characterization of the tandem reaction products

*4.3.1. (4R)-Methyl 2-hydroxy-5-oxo-4-phenyl-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3a**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 94% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=7.75 min, t_R(minor)=10.56 min, 94.3% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27–7.24 (m, 2.15H), 7.17–7.14 (m, 3H), 4.83 (s, 0.64H), 4.40 (s, 0.30H), 4.09–4.13 (m, 0.33H), 3.89 (m, 0.70H), 3.84 (s, 0.97H), 3.71 (s, 2.04H), 2.56–2.22 (m, 6.26H), 2.17–1.99 (m, 2.15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.1, 196.5, 169.4, 168.8, 143.9, 142.7, 128.4, 128.3, 127.2, 126.9, 126.3, 126.1, 115.3, 113.1, 95.7, 94.8, 38.3, 36.9, 36.9, 35.8, 33.2, 31.6, 28.8, 28.7, 20.7, 20.2 ppm; IR (neat): 3433, 3130, 2927, 2852, 1744, 1615, 1400, 1162, 776, 561 cm^{-1}; MS (ESI): *m*/*z*=303.1 $[M+H]^+$.

*4.3.2. (4R)-Ethyl 2-hydroxy-5-oxo-4-phenyl-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3b**).*[5a,f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 79% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=7.40 min, t_R(minor)=10.00 min, 90.3% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.28–7.23 (m, 2.17H), 7.17–7.15 (m, 3.0H), 4.78 (br s, 0.54H), 4.40 (br s, 0.26H), 4.29–4.11 (m, 2.42H), 3.89 (m, 0.69H), 2.58–2.34 (m, 6.30H), 2.28–1.99 (m, 2.18H), 1.33–1.30 (m, 1.15H), 1.27–1.24 (m, 2.15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.1, 196.5, 169.5, 169.0, 168.9, 168.8, 144.1, 142.8, 128.4, 128.2, 127.2, 126.9, 126.2, 126.1, 115.3, 113.1, 95.6, 94.7, 63.2, 63.0, 38.3, 37.0, 36.9, 35.8, 33.3, 31.8, 29.7, 28.9, 28.8, 20.7, 20.2, 14.0, 13.9 ppm; IR (neat): 3439, 3131, 2853, 1741, 1662, 1400, 1161, 910, 880, 776, 561 cm^{-1}; MS (ESI): *m*/*z*=317.1 $[M+H]^+$, 339.1 $[M+Na]^+$, 655.2 $[2M+Na]^+$.

*4.3.3. (4R)-Isopropyl 2-hydroxy-5-oxo-4-phenyl-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3c**).* Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 79% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=6.68 min, t_R(minor)=9.16 min, 91.4% ee; $[\alpha]_D^{25}$ +16.4 (*c* 0.52, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.29–7.24 (m, 2.22H), 7.20–7.16 (m, 3.06H), 5.12–5.02 (m, 0.99), 4.81 (s, 0.55H), 4.48 (s, 0.21H),4.08–4.09 (m, 0.32H), 3.91–3.87 (m, 0.67H), 2.59–2.17 (m, 6.36H), 2.08–1.99 (m, 2.26H), 1.31–1.25 (m, 6.37H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.0, 196.5, 169.6, 168.9, 168.5, 168.4, 144.3, 142.9, 128.4, 128.2, 127.2, 126.9, 126.2, 126.1, 115.4, 113.2, 95.6, 94.6, 38.3, 37.0, 36.9, 35.8, 33.4, 31.9, 28.9, 28.8, 25.3, 21.6, 21.5, 21.4, 20.7, 20.2 ppm; IR (neat): 3423, 3131, 2927, 2853, 1744, 1662, 1619, 1400, 1225, 1078, 828, 561 cm^{-1}; MS (ESI): *m*/*z*=331.1 $[M+H]^+$, 353.1 $[M+Na]^+$; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$, calcd for $C_{19}H_{23}O_5^+$ 331.1545, found 331.1541.

*4.3.4. (4R)-Methyl 2-hydroxy-5-oxo-4-p-tolyl-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3d**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 95% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=8.72 min, t_R(minor)=10.42 min, 91.5% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.05 (s, 4H), 5.0(s, 0.59H), 4.51 (s, 0.29H),4.07 (br s, 0.37H), 3.88–3.82 (m, 0.57H), 3.82 (s, 1.01H), 3.70 (s, 1.95H), 2.58–2.33 (m, 4.13H), 2.28(s, 3H), 2.25–2.20 (m, 1.66H), 2.07–1.97 (m, 2.29H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.2, 196.6, 196.5, 169.4, 169.3, 168.8, 140.9, 139.6, 135.8, 135.5, 129.1, 127.0, 126.8, 115.4, 113.2, 95.7, 94.8, 38.3, 36.9, 35.8, 32.8, 31.2, 28.9, 28.8, 21.0, 20.7, 20.2 ppm; IR (neat): 3423, 3131, 2958, 2927, 2853, 1744, 1615, 1400, 1162, 1080, 775, 561 cm^{-1}; MS (ESI): *m*/*z*=317.1 $[M+H]^+$, 339.1 $[M+Na]^+$, 655.3 $[2M+Na]^+$.

*4.3.5. (4R)-Methyl 2-hydroxy-4-(4-methoxyphenyl)-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3e**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 89% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=12.49 min, t_R(minor)=20.34 min, 91.2% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.09–7.06 (m, 1.99H), 6.81–6.79 (d, *J*=8.3 Hz, 2H), 4.91 (br s, 0.53H), 4.44 (br s, 0.32H), 4.05 (br s, 0.36H), 3.88–3.84 (m, 1.78H), 3.76–3.71 (m, 4.97H), 2.49–2.19 (m, 6.32H), 2.07–1.99 (m, 2.36H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ=197.2, 196.7, 169.4, 169.3, 168.8, 158.0, 157.8, 135.9, 134.8, 128.1, 127.9, 115.4, 113.8, 113.8, 113.4, 95.8, 94.9, 55.2, 55.2, 53.6, 53.5, 38.3, 37.0, 36.9, 35.9, 32.4, 30.8, 28.9, 28.8, 20.7, 20.2 ppm; IR (neat): 3423, 3130, 2957, 2924, 2853, 1745, 1614, 1615, 1245, 1400, 1225, 1078, 1040, 776, 561 cm^{-1}; MS (ESI): *m*/*z*=333.2 $[M+H]^+$, 687.3 $[2M+Na]^+$.

*4.3.6. (4R)-Methyl 4-(4-fluorophenyl)-2-hydroxy-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3f**).*[5f] Purified by flash

chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 96% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=9.07 min, t_R(minor)=14.26 min, 90.9% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.13–7.10 (m, 2.00H), 6.96–6.92 (m, 1.94H), 4.82 (s, 0.52H), 4.50 (s, 0.37H), 4.06–4.04 (m, 0.37H), 3.90–3.89 (m, 0.71H), 3.85 (s, 1.05H), 3.76 (s, 1.95H), 2.57–2.19 (m, 6.27H), 2.09–1.99 (m, 2.49H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.6, 196.5, 169.4, 169.3, 169.0, 162.4, 159.9, 139.6, 139.5, 138.6, 128.8, 128.7, 128.3, 128.3, 115.3, 115.2, 115.0, 114.9, 114.8, 95.5, 94.7, 53.7, 53.6, 38.3, 36.9, 36.9, 36.8, 35.6, 32.6, 31.0, 28.8, 28.7, 20.7, 20.2 ppm; IR (neat): 3430, 3130, 2853, 1742, 1663, 1621, 1400, 1159, 1083, 776, 561 cm^{-1}; MS (ESI): *m*/*z*=321.1 $[M+H]^+$, 343.1 $[M+Na]^+$, 359.1 $[M+K]^+$.

*4.3.7. (4R)-Methyl 4-(4-chlorophenyl)-2-hydroxy-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3g**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 87% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=10.36 min, t_R(minor)=15.65 min, 90.3% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.22–7.18 (m, 2H), 7.10–7.07 (m, 1.99H), 4.90 (s, 0.53H), 4.58 (s, 0.27H), 4.02 (br s, 0.32H), 3.88–3.83 (m, 1.70H), 3.75 (s, 2.01H), 2.40–1.96 (m, 8.38H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.2, 196.6, 169.7, 169.4, 169.2, 142.6, 141.6, 131.7, 128.8, 128.6, 128.3, 128.2, 115.0, 112.9, 95.5, 94.8, 53.8, 53.7, 38.1, 36.9, 36.9, 35.6, 32.8, 31.3, 28.9, 28.8, 20.7, 20.2 ppm; IR (neat): 3422, 3130, 2958, 2924, 2853, 1744, 1659, 1615, 1400, 1225, 1078, 927, 776, 561 cm^{-1}; MS (ESI): *m*/*z*=337.1 $[M+H]^+$.

*4.3.8. (4R)-Methyl 4-(4-bromophenyl)-2-hydroxy-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3h**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 96% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=10.84 min, t_R(minor)=16.51 min, 90.5% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.38–7.34 (m, 2H), 7.05–7.03 (m, 2H), 4.77–4.70 (br s, 0.64H), 4.13–4.12 (m, 0.39H), 4.02–4.00 (br s, 0.32H), 3.85 (s, 1.69H), 3.75 (s, 2.01H), 2.56–1.97 (m, 8.49H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ=196.0, 195.5, 170.3, 168.8, 168.3, 168.1, 142.0, 141.1, 130.4, 130.1, 128.1, 127.7, 118.7, 118.6, 113.8, 111.8, 94.5, 93.7, 52.7, 52.5, 37.0, 35.8, 35.8, 34.5, 31.8, 30.4, 27.8, 27.7, 19.6, 19.1 ppm; IR (neat): 3421, 3130, 2927, 2853, 1744, 1615, 1400, 1225, 1078, 776, 561 cm^{-1}; MS (ESI): *m*/*z*=381.0 $[M+H]^+$, 402.9 $[M+Na]^+$.

*4.3.9. (4R)-Methyl 2-hydroxy-5-oxo-4-m-tolyl-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3i**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 67% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=7.12 min, t_R(minor)=11.16 min, 89.9% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.16–7.12(m, 1.03H), 6.98–6.93(m, 3H), 4.73 (s, 0.65H), 4.31 (s, 0.33H), 4.07–4.06 (m, 0.47H), 3.88–3.87 (m, 0.62H), 3.83(s, 1.18H), 3.75 (s, 2.11H), 2.57–2.35 (m, 4.37H), 2.30 (s, 3.16H), 2.22 (d, *J*=9.0 Hz, 1.62H), 2.02–1.99(m, 2.18H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.0, 196.5, 169.4, 168.7, 143.9, 142.5, 137.8, 128.3, 127.7, 127.0, 124.0, 123.9, 115.4, 113.1, 95.8, 94.8, 38.3, 37.0, 36.9, 35.9, 33.1, 31.5, 28.9, 28.8, 21.6, 20.2 ppm; IR (neat): 3423, 3131, 2927, 2853, 1744, 1661, 1617, 1400, 1159, 1078, 776, 662, 561 cm^{-1}; MS (ESI): *m*/*z*=317.1 $[M+H]^+$, 339.1 $[M+Na]^+$, 655.3 $[2M+Na]^+$.

*4.3.10. (4R)-Methyl 2-hydroxy-4-(3-methoxyphenyl)-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3j**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 65% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=10.67 min, t_R(minor)=14.30 min, 86.1% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.19–7.15 (m, 1H), 6.77–6.70(m, 3.05H), 4.84 (br s, 0.47H), 4.41 (br s, 0.22H), 4.07–3.88 (m, 0.99H), 3.84 (s, 1.14H), 3.78–3.75 (m, 5H), 2.58–2.22 (m, 6.27H), 2.10–1.98 (m, 2.22H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.1, 196.6, 169.5, 169.4, 169.3, 168.8, 159.5, 159.5, 145.7, 144.4, 129.4, 129.3, 119.5, 119.4, 115.2, 113.6, 112.9, 111.1, 95.7, 94.8, 38.3, 36.9, 36.9, 35.8, 33.2, 31.6, 28.9, 28.8, 20.7, 20.2 ppm; IR (neat): 3424, 3131, 2853, 1744, 1664, 1662, 1400, 1161, 1078, 776, 619, 561 cm^{-1}; MS (ESI): *m*/*z*=333.2 $[M+H]^+$, 355.2 $[M+Na]^+$, 687.3 $[2M+Na]^+$.

*4.3.11. (4R)-Methyl 4-(benzo[d][1,3]dioxol-5-yl)-2-hydroxy-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3k**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 87% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=15.04 min, t_R(minor)=18.78 min, 92.5% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.71–6.69 (m, 0.99H), 6.66–6.63 (m, 2.03H), 5.89 (s, 2H), 4.05–3.93 (m, 0.55H), 3.84 (s, 1.19H), 3.82–3.79 (m, 0.55H), 3.79 (s, 1.95H), 2.56–2.18 (m, 6.48H), 2.07–1.97 (m, 2.31H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.2, 196.7, 169.5, 169.4, 169.3, 168.8, 147.5, 145.7, 137.9, 136.8, 120.1, 115.4, 113.2, 108.2, 108.1, 107.9, 107.3, 100.9, 100.8, 95.7, 94.8, 53.7, 53.6, 38.3, 36.9, 36.9, 35.8, 32.8, 31.5, 28.9, 20.7, 20.2 ppm; IR (neat): 3424, 3131, 2927, 2853, 1744, 1659, 1615, 1400, 1225, 1078, 929, 776, 561 cm^{-1}; MS (ESI): *m*/*z*=347.1 $[M+H]^+$, 369.1 $[M+Na]^+$.

*4.3.12. (4R)-Methyl 4-(3-chlorophenyl)-2-hydroxy-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3l**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 77% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=8.63 min, t_R(minor)=11.87 min, 90.3% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.19–7.12 (m, 2.94H), 7.06–7.05 (m, 1H), 5.00 (s, 0.60H), 4.58 (s, 0.30H), 4.03 (br s, 0.39H), 3.88–3.84 (m, 1.68H), 3.77 (s, 2H), 2.56–2.18 (m, 6.25H), 2.09–1.99 (m, 2.25H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ=197.0, 196.5, 169.8, 169.3, 169.3, 146.3, 145.3, 134.1, 133.8, 129.7, 129.3, 127.6, 126.9, 126.3, 126.3, 125.7, 125.4, 114.8, 112.6, 95.5, 94.7, 53.8, 53.7, 38.0, 36.9, 36.8, 35.5, 33.2, 31.6, 28.9, 28.7, 20.7, 20.1 ppm; IR (neat): 3424, 3131, 2958, 2923, 2853, 1744, 1615, 1400, 1225, 1078, 928, 776, 629, 561 cm^{-1}; MS (ESI): *m*/*z*=337.1 $[M+H]^+$.

*4.3.13. (4R)-Methyl 4-(3-bromophenyl)-2-hydroxy-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3m**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 87% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=9.48 min, t_R(minor)=12.92 min, 91.7% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.29–7.26 (m, 2H), 7.13–7.09 (m, 1.89H), 4.88 (s, 0.53H), 4.56 (br s, 0.25H), 4.03–4.02 (m, 0.46H), 3.85 (s, 1.57H), 3.78 (s, 1.89H), 2.57–1.99 (m, 7.85H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.1, 196.5, 169.8, 169.3, 169.3, 146.5, 130.5, 130.0, 129.8, 129.6, 129.3, 129.1, 126.1, 125.9, 122.4, 122.2, 114.7, 112.6, 95.5, 94.7, 53.8, 53.7, 38.1, 36.9, 36.8, 35.4, 33.1, 31.5, 28.9, 28.7, 20.6, 20.1 ppm; IR (neat): 3432, 3130, 2852, 1744, 1662, 1618, 1400, 1225, 1078, 776, 561 cm^{-1}; MS (ESI): *m*/*z*=381.1 $[M+H]^+$, 403.1 $[M+Na]^+$.

*4.3.14. (4R)-Methyl 4-(3-bromo-4-chlorophenyl)-2-hydroxy-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3n**).* Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 75% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=11.30 min, t_R(minor)=15.49 min, 90.7% ee; $[\alpha]_D^{25}$ −13.6 (*c* 0.67, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40 (m, 0.99H), 7.34–7.27(m, 1.15H), 7.08–7.05 (m, 1H), 4.93 (br s, 0.52H), 4.67 (br s, 0.30H), 4.05–3.99 (m, 0.58H), 3.85 (s, 1.28H), 3.81 (s, 2.03H), 2.56–2.14 (m, 6.31H), 2.10–2.00 (m, 2.29H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.1, 196.5, 169.9, 169.5, 169.3, 169.2, 144.7, 143.7, 132.8, 132.0, 131.8, 130.2, 129.7, 127.8, 127.4, 122.3, 121.9, 116.0, 114.6, 112.4, 95.3, 94.7, 38.0, 36.9, 36.8, 35.2, 32.7, 28.9, 28.8, 25.3, 20.7, 20.1 ppm; IR (neat): 3426, 3130, 2927, 2852, 1743, 1659, 1620, 1400, 1225, 1078, 928, 777, 561 cm^{-1}; MS (ESI): *m*/

z=414.9 $[M+H]^+$, 436.9 $[M+Na]^+$; HRMS (ESI-TOF): m/z $[M+H]^+$, calcd for $C_{17}H_{17}BrClO_5^+$ 414.9948, found 414.9943.

*4.3.15. (4S)-Methyl 4-(2-chlorophenyl)-2-hydroxy-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3o**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 16% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=90/10, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=16.18 min, t_R(minor)=18.89 min, 16.7% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34–7.32 (d, J=6.64 Hz, 1H), 7.13–7.07 (m, 2.91H), 4.69 (s, 0.48H), 4.39–4.37 (m, 1.32H), 3.87 (s, 1.26H), 3.78 (s, 1.68H), 2.59–2.28 (m, 5.70H), 2.12–2.00 (m, 2.40H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.6, 196.1, 169.7, 169.6, 169.3, 133.3, 129.7, 129.5, 129.0, 127.5, 127.3, 126.8, 126.1, 114.8, 112.6, 95.5, 94.8, 53.8, 53.6, 37.0, 36.9, 32.7, 29.2, 28.9, 28.8, 20.7, 20.2 ppm; IR (neat): 3421, 3130, 2927, 2853, 1744, 1662, 1621, 1400, 1225, 1078, 772, 563 cm^{-1}; MS (ESI): m/z=337.1 $[M+H]^+$, 359.1 $[M+Na]^+$, 375.0 $[M+K]^+$.

*4.3.16. (4S)-Methyl 4-(2-bromophenyl)-2-hydroxy-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3p**).* Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 7% yield; $[\alpha]_D^{25}$ +8.5 (c 0.75, CH_2Cl_2); HPLC (Chiralpak AD, hexane/*i*-PrOH=90/10, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=16.75 min, t_R(minor)=19.88 min, 6.5% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.53–7.51 (d, J=6.64 Hz, 1H), 7.17–7.00 (m, 3.05H), 4.86 (s, 0.49H), 4.52 (s, 0.35H), 4.34–4.33 (m, 0.98H), 3.87 (s, 1.28H), 3.76 (s, 1.80H), 2.58–2.28 (m, 5.78H), 2.10–2.01 (m, 2.49H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.6, 196.1, 169.7, 169.6, 169.3, 141.2, 132.9, 132.8, 129.1, 127.8, 127.6, 127.5, 126.7, 124.0, 114.8, 112.9, 95.5, 94.8, 53.8, 53.6, 37.0, 36.9, 33.1, 31.8, 29.7, 28.9, 28.8, 25.3, 20.7, 20.2 ppm; IR (neat): 3431, 3131, 2584, 1741, 1658, 1628, 1400, 1227, 1078, 922, 776, 561 cm^{-1}; MS (ESI): m/z=381.0 $[M+H]^+$, 402.9 $[M+Na]^+$; HRMS (ESI-TOF): m/z $[M+H]^+$, calcd for $C_{17}H_{18}BrO_5^+$ 381.0338, found 381.0332.

*4.3.17. (4R)-Methyl 2-hydroxy-4-(naphthalen-2-yl)-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3r**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 80% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=13.68 min, t_R(minor)=20.61 min, 93.3% ee; ^{1}H NMR (400 MHz, CDCl3): δ=7.76–7.71 (m, 2.94H), 7.60–7.56 (d, 1H), 7.41–7.25 (m, 3.17H), 4.90 (br s, 0.56H), 4.44 (s, 0.23H), 4.23 (br s, 0.23H), 4.12–4.05 (m, 1.06H), 3.82 (s, 0.91H), 3.67 (s, 1.95H), 2.60–2.26 (m, 6.09H), 2.04–1.99 (m, 2.18H) ppm; ^{13}C NMR (100 MHz, CDCl3): δ=197.2, 196.6, 169.7, 169.4, 169.0, 141.4, 140.4, 133.6, 133.4, 132.3, 128.1, 128.0, 127.8, 127.6, 125.9, 125.8, 125.6, 125.5, 125.4, 125.3, 125.2, 115.2, 113.2, 95.7, 94.8, 53.7, 53.7, 38.2, 37.0, 36.9, 35.8, 33.4, 32.0, 28.9, 28.8, 20.7, 20.2 ppm; IR (neat): 3422, 3131, 2958, 2927, 2853, 1744, 1659, 1615, 1400, 1225, 1078, 1043, 928, 770, 559 cm^{-1}; MS (ESI): m/z=353.2 $[M+H]^+$, 727.3 $[2M+Na]^+$.

*4.3.18. (4S)-Methyl 2-hydroxy-5-oxo-4-(thiophen-2-yl)-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3s**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 84% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=90/10, flow rate=0.5 mL/min, λ=254 nm) t_R(major)=53.21 min, t_R(minor)=63.20 min, 95.9% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.12–7.07 (dd, J=5.1 Hz, 1H), 6.89–6.85 (m, 1.05H), 6.79–6.77 (m, 0.99H), 5.18 (s, 0.46H), 4.56 (s, 0.35H), 4.38 (br s, 0.41H), 4.28–4.23 (m, 0.62H), 3.85 (s, 1.27H), 3.68 (s, 1.85H), 2.58–2.26 (m, 6.32H), 2.09–1.99 (m, 2.21H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.0, 196.7, 169.2, 169.1, 169.0, 168.9, 147.2, 146.9, 126.6, 126.4, 124.2, 124.1, 123.6, 122.9, 115.0, 113.4, 95.6, 95.0, 53.7, 53.5, 38.5, 36.9, 35.7, 28.8, 28.7, 28.7, 26.8, 20.6, 20.1 ppm; IR (neat): 3423, 3131, 2927, 2853, 1741, 1663, 1622, 1400, 774, 561 cm^{-1}; MS (ESI): m/z=309.1 $[M+H]^+$, 331.1 $[M+Na]^+$, 347.1 $[M+K]^+$, 639.1 $[2M+Na]^+$.

*4.3.19. (4R)-Methyl 2-hydroxy-7,7-dimethyl-5-oxo-4-phenyl-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3t**).*[5f] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 98% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=6.48 min, t_R(minor)=10.45 min, 90.1% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27–7.24 (t, J=7.2 Hz, 2.26H), 7.17–7.13 (t, J=7.2 Hz, 3.09H), 5.00 (s, 0.54H), 4.50 (s, 0.37H), 4.07 (br s, 0.37H), 3.91–3.87 (m, 0.72H), 3.84 (s, 0.98H), 3.70 (s, 1.95H), 2.58–2.21 (m, 6.36H), 1.19 (d, J=9.6 Hz, 3.25H), 1.10 (d, J=9.2 Hz, 3.05H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.3, 197.9, 170.7, 169.0, 168.5, 145.2, 144.2, 129.7, 129.6, 128.6, 128.4, 127.5, 127.4, 115.1, 97.2, 97.2, 96.3, 96.3, 54.9, 54.7, 52.1, 52.1, 43.8, 43.7, 39.6, 37.4, 37.4, 34.6, 33.4, 33.3, 33.2, 33.0, 31.0, 30.6, 30.1, 29.6, 29.0 ppm; IR (neat): 3418, 3130, 2927, 2853, 1742, 1661, 1621, 1400, 1161, 1074, 776, 562 cm^{-1}; MS (ESI): m/z=331.2 $[M+H]^+$, 683.3 $[2M+Na]^+$.

*4.3.20. (4R)-Methyl 2-hydroxy-7,7-dimethyl-5-oxo-4-p-tolyl-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3u**).* Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 90% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=7.34 min, t_R(minor)=10.62 min, 75.7% ee; $[\alpha]_D^{25}$ −11.4 (c 0.39, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.07–7.01 (m, 4H), 4.97 (s, 0.50H), 4.56 (s, 0.27H), 4.07–3.99 (m, 0.69H), 3.84–3.88 (m, 0.51H), 3.83 (s, 1.07H), 3.69 (s, 1.88H), 2.56–2.29 (m, 3.39H), 2.28 (m, 3.16H), 2.25–2.20 (m, 2.6H), 1.19 (d, J=9.6 Hz, 3.45H), 1.10 (d, J=9.2 Hz, 2.85H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.2, 197.8, 170.7, 170.6, 168.9, 168.3, 142.2, 141.2, 137.0, 136.8, 130.4, 128.4, 128.3, 115.3, 113.5, 97.3, 96.4, 54.9, 54.8, 52.1, 43.7, 43.7, 39.7, 37.5, 34.2, 33.4, 33.0, 31.0, 30.6, 30.1, 29.6, 29.0, 26.6, 22.4 ppm; IR (neat): 3426, 3132, 2956, 2923, 1750, 1617, 1400, 1225, 1072, 819, 793, 561 cm^{-1}; MS (ESI): m/z=345.1 $[M+H]^+$, 367.1 $[M+Na]^+$, 383.0 $[M+K]^+$; HRMS (ESI-TOF): m/z $[M+H]^+$, calcd for $C_{20}H_{25}O_5^+$ 345.1702, found: 345.1698.

*4.3.21. (4R)-Methyl 2-hydroxy-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3v**).* Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 94% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=9.48 min, t_R(minor)=18.23 min, 76.5% ee; $[\alpha]_D^{25}$ −19.7 (c 0.55, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.10–7.06 (m, 2H), 6.82–6.79 (d, J=8.3 Hz, 2H), 4.61 (s, 0.57H), 4.29 (s, 0.36H), 4.13–4.04 (m, 0.55H), 3.87–3.83 (m, 1.48H), 3.76–3.75 (m, 5.16H), 2.52–2.20 (m, 6.14H), 1.17 (d, J=9.6 Hz, 3.18H), 1.10 (d, J=9.2 Hz, 3.15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.2, 197.8, 170.7, 170.6, 168.7, 168.1, 159.3, 159.1, 137.3, 136.1, 129.6, 129.3, 115.5, 115.2, 115.1, 97.1, 96.3, 56.5, 56.5, 54.9, 54.8, 52.2, 43.7, 43.7, 39.6, 37.1, 33.8, 33.4, 33.0, 32.2, 31.0, 30.6, 30.1, 29.5, 29.0 ppm; IR (neat): 3425, 3133, 2957, 2925, 2853, 1750, 1615, 1510, 1400, 1245, 1078, 828, 764, 611 cm^{-1}; MS (ESI): m/z=361.1 $[M+H]^+$, 383.1 $[M+Na]^+$, 399.0 $[M+K]^+$; HRMS (ESI-TOF): m/z $[M+H]^+$, calcd for $C_{20}H_{25}O_6^+$ 361.1651, found: 361.1649.

*4.3.22. (4R)-Methyl 4-(4-chlorophenyl)-2-hydroxy-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3w**).* Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 85% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=7.79 min, t_R(minor)=15.53 min, 72.1% ee; $[\alpha]_D^{25}$ −31.7 (c 0.89, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.26–7.19 (m, 2.05H), 7.10–7.08 (d, 2H), 4.71 (s, 0.57H), 4.46 (s, 0.57H), 4.13–4.11 (m, 0.31H), 4.04–4.02 (m, 0.41H), 3.84 (s, 1.24H), 3.78 (s, 1.90H), 2.58–2.19 (m, 6.77H), 1.17 (d, J=9.6 Hz, 3.23H), 1.10 (d, J=9.2 Hz, 3.05H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.1, 197.6, 170.7, 170.6, 169.1, 168.5, 143.9, 143.0, 133.0, 132.9, 130.2,

129.8, 129.7, 129.5, 114.9, 113.1, 96.8, 96.1, 55.0, 54.9, 52.0, 43.7, 43.7, 39.4, 36.8, 34.2, 33.4, 33.0, 32.8, 31.0, 30.6, 30.1, 29.5, 29.0 ppm; IR (neat): 3423, 3130, 2927, 2852, 1743, 1662, 1621, 1400, 1226, 1078, 828, 776, 561 cm^{-1}; MS (ESI): m/z=365.1 $[M+H]^+$, 387.1 $[M+Na]^+$, 403.1 $[M+K]^+$; HRMS (ESI-TOF): m/z $[M+H]^+$, calcd for $C_{17}H_{18}ClO_5^+$ 365.1153, found: 365.1153.

*4.3.23. (4R)-Methyl 4-(4-bromophenyl)-2-hydroxy-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-2-carboxylate (**3x**).* Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 85% yield; HPLC (Chiralpak AD, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=8.23 min, t_R(minor)=16.65 min, 77.5% ee; $[\alpha]_D^{25}$ −25.5 (*c* 0.49, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ=7.38–7.34 (m, 2H), 7.04–7.02 (d, 2.02H), 4.84 (s, 0.52H), 4.57 (s, 0.30H), 4.03–3.98 (m, 0.73H), 3.84 (s, 1.41H), 3.76 (s, 1.93H), 2.57–2.19 (m, 6.40H), 1.19 (d, J=9.6 Hz, 2.95H), 1.10 (d, J=9.2 Hz, 3.07H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.1, 197.6, 170.7, 170.6, 169.1, 168.7, 144.5, 143.7, 132.8, 132.5, 130.6, 130.2, 121.1, 121.0, 114.8, 113.0, 96.9, 96.1, 55.0, 54.9, 52.0, 43.7, 43.7, 39.3, 36.9, 34.2, 33.4, 33.0, 32.9, 31.0, 30.6, 30.1, 29.5, 29.0, 26.6 ppm; IR (neat): 3439, 3127, 2957, 2923, 2850, 1744, 1619, 1400, 1225, 1071, 826, 776, 561 cm^{-1}; MS (ESI): m/z=409.0 $[M+H]^+$, 431.0 $[M+Na]^+$, 447.0 $[M+K]^+$; HRMS (ESI-TOF): m/z $[M+H]^+$, calcd for $C_{17}H_{18}BrO_5^+$ 409.0651, found: 409.0647.

*4.3.24. (4R)-Methyl 2-hydroxy-5-oxo-4-phenyl-2,3,4,5-tetrahydropyrano[3,2-c]chromene-2-carboxylate (**6**).*[5b] Purified by flash chromatography (petroleum ether/EtOAc=2/1) to afford a white solid in 80% yield; HPLC (Chiralpak OD-H, hexane/*i*-PrOH=80/20, flow rate=1.0 mL/min, λ=254 nm): t_R(major)=11.69 min, t_R(minor)=21.67 min, 23.9% ee; ^1H NMR (400 MHz, $CDCl_3$): δ=7.81 (dt, J=16.4, 8.0 Hz, 1H), 7.59–7.52 (m, 1H), 7.31–7.23 (m, 7H), 4.89 (d, J=8.8, 0.56H), 4.61 (s, 0.27H), 4.36–4.17 (m, 1H), 3.92–3.87 (dd, J=32.2, 9.5 Hz, 3.06H), 2.83–2.78 (dd, J=14.0, 7.4 Hz, 0.33H), 2.57–2.45 (m, 1.76H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.7, 161.7, 160.9, 158.6, 158.2, 152.8, 142.2, 141.6, 132.1, 131.9, 128.6, 128.4, 127.4, 127.1, 126.7, 124.0, 123.8, 122.9, 116.6, 116.5, 115.2, 115.0, 104.6, 102.9, 96.2, 95.6, 53.9, 53.8, 38.1, 35.8, 34.6, 33.8 ppm; IR (neat): 3440, 3132, 2854, 1741, 1626, 1400, 1159, 1091, 827, 766, 699, 595 cm^{-1}; MS (ESI): m/z=353.1 $[M+H]^+$, 375.0 $[M+Na]^+$.

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Supplementary data

Copies of ^1H NMR and ^{13}C NMR spectra of products of tandem reactions are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.06.109.

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