Organocatalytic asymmetric conjugate addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-ketoesters

Jin-jia Wang, Jin-hua Lao, Zhi-peng Hu, Rui-Jiong Lu, Shao-zhen Nie, Quan-sheng Du, and Ming Yan*

Institute of Drug Synthesis and Pharmaceutical Process, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China
E-mail: yanming@mail.sysu.edu.cn

Abstract
The conjugate addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-keto-esters was studied using a series of chiral bifunctional organocatalysts. Takemoto's catalyst was found to be most efficient for this transformation. Excellent yields and good enantioselectivities were achieved for a variety of β,γ-unsaturated α-keto-esters and cyclic 1,3-dicarbonyl compounds. A bifunctional catalytic mechanism is proposed. The method provides a new asymmetric synthetic route for chiral courmarin derivatives.

Keywords: Asymmetric conjugate addition, organocatalyst, cyclic 1,3-dicarbonyl compound, β,γ-unsaturated α-keto-ester

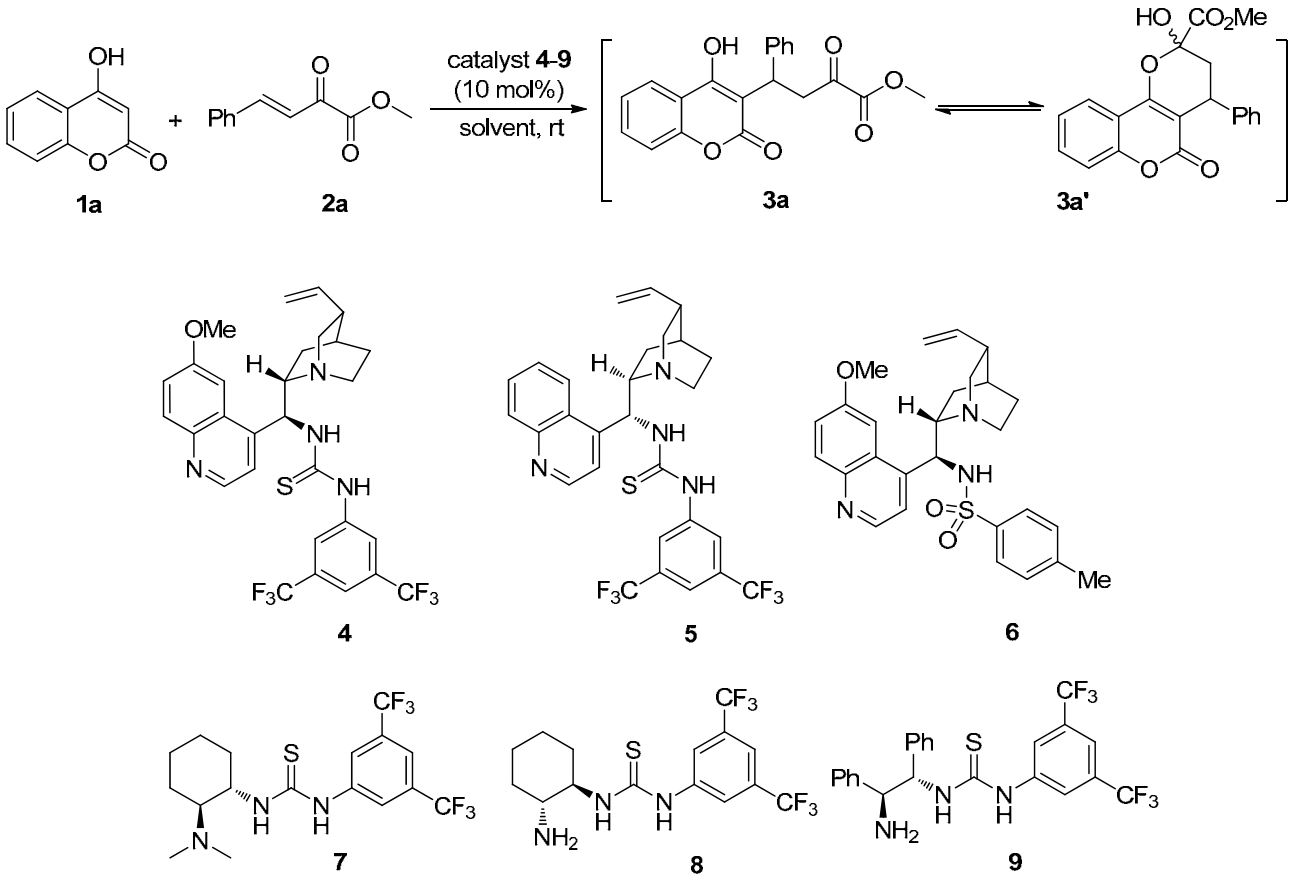
Introduction

Asymmetric conjugate addition of 1,3-dicarbonyl compounds to various Michael acceptors is an important method for the preparation of chiral compounds.[1] Although chiral metal catalysts have been applied successfully for a number of transformations, great efforts are continuing to develop more efficient, cheaper catalysts and to expand the substrate scope. In recent years asymmetric organocatalysis has emerged as a powerful tool for the synthesis of chiral compounds.[2] Organocatalytic asymmetric conjugate additions of nucleophiles to Michael acceptors have been studied extensively.[3] Excellent enantioselectivities have been obtained for the organocatalytic conjugate addition of 1,3-dicarbonyl compounds to α,β-unsaturated aldehydes, ketones and nitro compounds. Although β,γ-unsaturated α-keto-esters are highly reactive Michael acceptors, their reactions with 1,3-dicarbonyl compounds have been seldom studied. To the best of our

knowledge, only a few papers concerning this reaction have appeared. Jørgensen *et al*. found that chiral bisoxazoline-copper catalysts are efficient for the asymmetric conjugate addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-keto-esters.[4] Calter and Wang reported that pyrimidinyl-cinchona alkaloid derivatives are suitable organocatalysts for the reaction, however the substrates were limited to cyclohexane-1,3-dione and 5,5-dimethylcyclohexane-1,3-dione.[5] Feng, Liu and co-workers found that chiral *N,N*′-dioxide-yttrium(III) complexes catalyze the conjugate addition of malonates to β,γ-unsaturated α-keto-esters with excellent yields and enantioselectivities.[6] Very recently Xu and co-workers reported that chiral squaramides are highly enantioselective catalysts for the conjugate addition of 4-hydroxycoumarins and 4-hydroxypyrone to β,γ-unsaturated α-keto-esters.[7] In recent years, chiral bifunctional organocatalysts combining hydrogen-bond donors (such as thioureas, ureas, sulfonamides) and amine groups have been proved to be extremely efficient catalysts for many reactions.[8] We initiated a series of studies on the design and application of chiral bifunctional organocatalysts for asymmetric conjugate additions.[9] Herein we report the asymmetric conjugate addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-keto-esters. Chiral bifunctional thioureas were found to be efficient catalysts for the reaction.

Results and Discussion

The conjugate addition of 4-hydroxycoumarin **1a** to (*E*)-methyl 2-oxo-4-phenylbut-3-enoate **2a** was examined with chiral bifunctional organocatalysts **4-9** (Scheme 1). The experimental results are summarized in Table 1. Quinine-derived thiourea **4** provided the expected product **3a** in excellent yield and with moderate enantioselectivity (Table 1, entry 1). The product **3a** was found to be in a rapid equilibrium with cyclic hemiketal **3a'**. The equilibrium is sufficiently rapid that only two peaks from enantiomers were observed during chiral HPLC analysis. The same phenomenon was observed by Jørgensen and his co-workers.[4] Cinchonine-derived thiourea **5** also gave **3a** in excellent yield, but with lower enantioselectivity (Table 1, entry 2). Quinine-derived sulfonamide **6** also catalyzed the reaction with low enantioselectivity (Table 1, entry 3). Further study showed that Takemoto's catalyst **7** is a more efficient catalyst and **3a** could be obtained with better enantioselectivity and excellent yield (Table 1, entry 4).[10] Good yields were also achieved with chiral thiourea-primary amines **8** and **9**, however the enantioselectivities were low (Table 1, entries 5, 6). A screening of reaction solvents with catalyst **7** indicated that THF is optimal in terms of best enantioselectivity (Table 1, entries 4, 7-9). Decrease of reaction temperature resulted in the loss of enantioselectivity (Table 1, entries 10, 11). Using 5 mol% catalyst **7** provided the product **3a** in lower yield, but the enantioselectivity was almost unchanged (Table 1, entry 12). On the other hand, higher catalyst loading (20 mol% **7)** also did not provide substantial improvement (Table 1, entry 13).


OH
Ph
O
O
O
catalyst 4-9
(10 mol%)
solvent, rt
Ph
HO
CO2Me
1a
2a
3a
3a'
OMe
H
N
NH
S
F3C
CF3
4
5
6
Me
7
8
9
NH2

Scheme 1

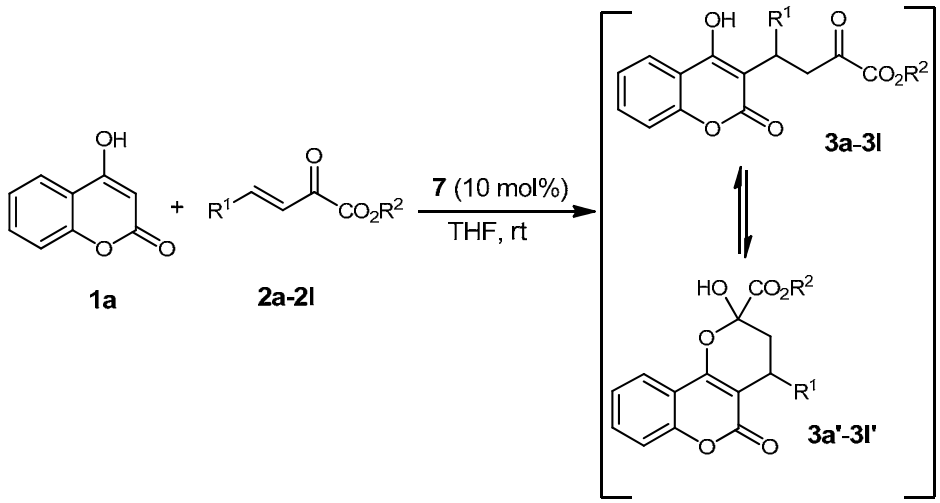
Table 1. Catalyst screening and optimization of reaction conditions[a]

Entry	Catalyst	Solvent	Time (h)	Yield(%)[b]	Ee(%)[c]
1	**4**	CH_2Cl_2	1	99	59 (R)
2	**5**	CH_2Cl_2	1	99	-32 (S)
3	**6**	CH_2Cl_2	1	99	30 (R)
4	**7**	CH_2Cl_2	1	99	63 (R)
5	**8**	CH_2Cl_2	3	89	-23 (S)
6	**9**	CH_2Cl_2	3	97	20 (R)
7	**7**	THF	3	99	76 (R)
8	**7**	$CHCl_3$	1	99	64 (R)
9	**7**	toluene	1	99	50 (R)
10[d]	**7**	THF	12	97	74 (R)
11[e]	**7**	THF	48	94	53 (R)
12[f]	**7**	THF	6	71	75 (R)
13[g]	**7**	THF	2.5	99	77 (R)

[a]Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol) and catalyst (0.01 mmol) in solvent (1.0 mL) at room temperature;
[b]Isolated yields;
[c]Determined by chiral HPLC on a chiralpak AD-H column. The absolute configurations of **3a** were assigned by comparing the optical rotations with the reported data (ref. 8);
[d]The reaction was conducted at 0 °C;
[e]The reaction was conducted at -30 °C;
[f]5 mol % **7** was used.
[g]20 mol % **7** was used.

The scope of β,γ-unsaturated α-keto-esters was examined and the results are summarized in Table 2. The β,γ-unsaturated α-keto-esters **2a-2k** bearing various γ-aryl and heteroaryl substitutions afforded the desired adduct products **3a-3k** in excellent yields and with good enantioselectivities (74-79% ee). The electronic property of the substituents on the phenyl ring exerted negligible effects on either the yields or enantioselectivities (Table 2, entries 1-8). Bulky ester groups of β,γ-unsaturated α-keto-esters were also well tolerated (Table 2, entries 9-11). Furthermore γ-alkyl unsaturated keto-ester **2l** is also compatible with this reaction. The product **3l** was obtained in good yield and enantioselectivity after a prolonged reaction time (Table 2, entry 12). It should be noted that many optically active coumarin derivatives, such as **3a-3l**, possess various interesting biological activities.[11]

Table 2. Asymmetric conjugate addition of **1a** to **2a-2k** catalyzed by **7**[a]



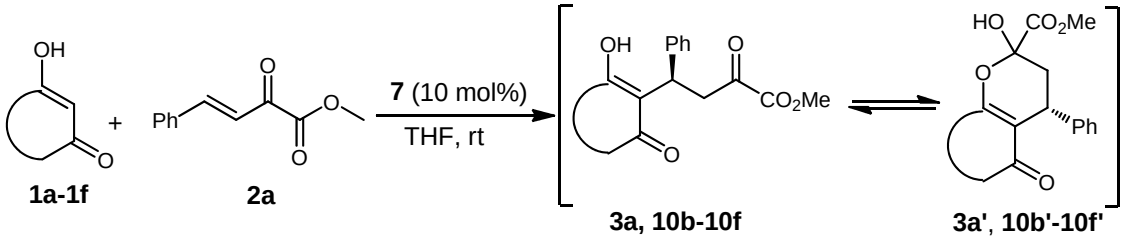
Entry	**2**	R^1	R^2	Time (h)	Product	Yield (%)[b]	Ee (%)[c]
1	**2a**	Ph	Me	3	**3a/3a'**	99	76
2	**2b**	4-MeC_6H_4	Me	3	**3b/3b'**	98	75
3	**2c**	4-$MeOC_6H_4$	Me	3	**3c/3c'**	99	75
4	**2d**	4-FC_6H_4	Me	1	**3d/3d'**	99	75
5	**2e**	4-ClC_6H_4	Me	1	**3e/3e'**	99	79
6	**2f**	3-ClC_6H_4	Me	1	**3f/3f'**	99	75
7	**2g**	4-BrC_6H_4	Me	1	**3g/3g'**	98	76
8	**2h**	2-thienyl	Me	3	**3h/3h'**	95	77
9	**2i**	Ph	Et	3	**3i/3i'**	96	76
10	**2j**	Ph	*i*-Pr	3	**3j/3j'**	95	74
11	**2k**	Ph	Allyl	3	**3k/3k'**	99	77
12	**2l**	*i*-Pr	Et	9	**3l/3l'**	74	80

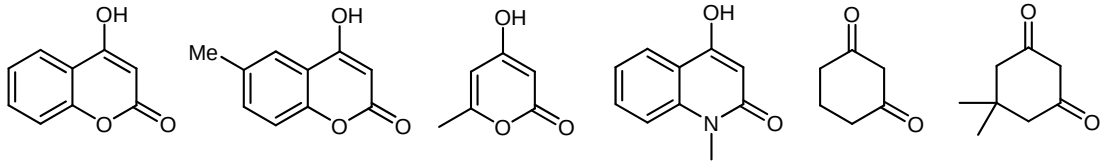
[a]Reactions were carried out with **1a** (0.1 mmol), **2a-2k** (0.1 mmol), and **7** (0.01 mmol) in THF (1.0 mL) at room temperature;
[b]Isolated yields;
[c]Determined by chiral HPLC with a chiralpak AD-H column.

Furthermore cyclic 1,3-dicarbonyl compounds **1a-1f** were examined as the nucleophiles in the reaction with **2a**. The results are summarized in Table 3. 6-Methyl-4-hydroxycoumarin **1b** and 4-hydroxy-6-methyl-2*H*-pyranone **1c** provided similar yields and enantioselectivities with **1a** (Table 3, entries 1-3). 4-Hydroxy-6-methylpyrone **1d** and cyclohexane-1,3-dione **1e** were also suitable substrates. Excellent yields and enantioselectivities were achieved (Table 3, entries 4-5).

5,5-Dimethylcyclohexane-1,3-dione **1f** afforded better enantioselectivity (Table 3, entry 6). The results imply that the present catalytic method is generally applicable for various cyclic 1,3-dicarbonyl compounds.

Table 3. Asymmetric conjugate addition of **1a-f** to **2a**[a]



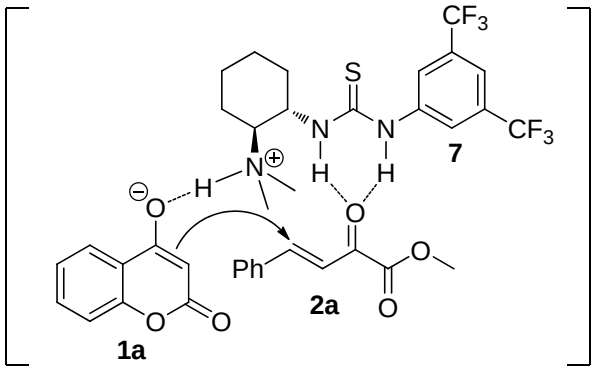


1a **1b** **1c** **1d** **1e** **1f**

Entry	Substrate	Time (h)	Product	Yield (%)[b]	Ee (%)[c]
1	**1a**	3	**3a/3a'**	99	76
2	**1b**	3	**10b/10b'**	99	79
3	**1c**	3	**10c/10c'**	99	74
4	**1d**	3	**10d/10d'**	92	74
5	**1e**	3	**10e/10e'**	99	79
6	**1f**	3	**10f/10f'**	97	85

[a]Reactions were carried out with **1a-1f** (0.1 mmol), **2a** (0.1 mmol), and **7** (0.01 mmol) in THF (1.0 mL) at room temperature;
[b]Isolated yields;
[c]Determined by HPLC with a chiralpak AD-H column.

The reaction is proposed to proceed via a bifunctional catalytic mechanism (Scheme 2).[8] β,γ-unsaturated α-keto-ester **2a** is activated to nucleophilic attack through double hydrogen-bonding interactions with the thiourea group of catalyst **7**. On the other hand, the tertiary amine group of **7** removes one proton of 4-hydroxycoumarin **2a**. The resulting amino cation forms another hydrogen bond with the oxygen ion. The consequent nucleophilic attack gives (*R*)-**3a** as the major product.



Scheme 2

Conclusions

We have developed an efficient asymmetric conjugate addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-keto-esters. Bifunctional thiourea-tertiary amines were found to be suitable organocatalysts. The reaction provided the products in excellent yields and with good enantioselectivities for a variety of β,γ-unsaturated α-keto-esters and cyclic 1,3-dicarbonyl compounds. Further attempts to improve the enantioselectivity and to apply this method for the preparation of valuable chiral products are currently underway.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE 400 spectrometer. Chemical shifts of protons are reported in parts per million downfield from tetramethylsilane (δ = 0). Chemical shifts of carbon are referenced to the carbon resonances of the solvent ($CHCl_3$: δ = 77.0). Peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Optical rotations were measured on a Perkin-Elmer 341 digital polarimeter. Melting points were measured on a WRS-2A melting point apparatus and are uncorrected. The high resolution mass spectroscopic data were obtained at Shimadazu LCMS-IT-TOF spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak). Enantiomeric excesses were determined by HPLC using a Daicel Chiralpak AD-H column and eluting with a *n*-hexane/*i*-PrOH solution. Flash chromatography was performed over silica gel (230-400 mesh), purchased from Qingdao Haiyang Chemical Co., Ltd. Commercial reagents were used as received. β,γ-Unsaturated α-keto-esters **2a**-**2k**,[12] **2l**[13] and catalysts **4**-**9**[14] were prepared

according to the reported procedures.

Typical procedure for organocatalytic asymmetric conjugate addition

A solution of 4-hydroxycoumarin **1a** (0.1 mmol), (*E*)-methyl 2-oxo-4-phenylbut-3-enoate **2a** (0.1 mmol), Takemoto's catalyst **7** (0.01 mmol) in THF (1.0 mL) was stirred at room temperature for 3 h. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel to afford **3a** as a white solid. Compound **3a** was found to be in equilibrium with cyclic hemiketal **3a'**. These two isomers were observed as separate compounds in ^{1}H and ^{13}C NMR spectra, but were not resolved by HPLC analysis.

4-(4-Hydroxy-oxo-2*H*-chromen-3-yl)- 4-phenyl-2-oxo-butyric acid methyl ester (3a). White solid (99% yield), exists in an equilibrium with cyclic hemiketal **3a'**, m.p. 170-172 °C, $[\alpha]_D^{20}$= -19.6 (c 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (d, *J* = 8.8 Hz, 1.34 H), 2.55 (dd, *J* = 14.4, 3.2 Hz, 0.33 H), 2.80 (ddd, *J* = 14.4, 7.2, 1.2 Hz, 0.33 H), 3.90 (s, 2.01 H), 3.92 (s, 0.99 H), 4.20 (t, *J* = 9.2 Hz, 0.67 H), 4.36 (dd, *J* = 7.2, 3.2 Hz, 0.33 H), 4.46 (d, *J* = 1.2 Hz, 0.33 H, OH, the position is concentration dependent), 4.66 (s, 0.67H, OH, the position is concentration dependent), 7.23-7.38 (m, 7 H), 7.51-7.58 (m, 1 H), 7.78 (dd, *J* = 8.0, 1.6 Hz, 0.67 H), 7.83 (dd, *J* = 8.0, 1.6 Hz, 0.33 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.7, 34.5, 35.6, 38.1, 53,8, 53.9, 95.5, 96.2, 102.9, 104.7, 115.0, 115.3, 116.5, 116.6, 122.8, 122.9, 123.8, 124.0, 126.6, 126.7, 127.1, 127.3, 128.4, 128.6, 131.8, 132.1, 141.5, 142.2, 152.8, 158.1, 158.5, 160.7, 161.6, 168.8, 168.9; IR (KBr): 3459 (s), 3181 (m), 3022 (w), 2952(w), 1756 (s), 1618(s), 1572 (s), 1491(s), 1453 (m), 699 (s) cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{16}O_6Na$ $(M + Na)^+$: 375.0845, found: 375.0838. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R(major enantiomer) = 6.59 min, t_R(minor enantiomer) = 9.90 min, 76% ee.

4-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-4-(4-methylphenyl)-2-oxo-butyric acid methyl ester (3b). White solid, 98% yield, exists in an equilibrium with cyclic hemiketal **3b'**. m.p. 171-173 °C, $[\alpha]_D^{20}$= -25.7 (c 0.44, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 1.02 H), 2.31 (s, 1.98 H), 2.43 (d, *J* = 8.8 Hz, 1.32 H), 2.51 (dd, *J* = 14.4, 3.2 Hz, 0.34 H), 2.76 (dd, *J* = 14.4, 7.2 Hz, 0.34 H), 3.84 (s, 1.98 H), 3.89 (s, 1.02 H), 4.16 (t, *J* = 8.8 Hz, 0.66 H), 4.31 (dd, *J* = 7.2, 3.2 Hz, 0.34 H), 4.61 (s, 0.34 H, OH, the position is concentration dependent), 4.92 (s, 0.66 H, OH, the position is concentration dependent), 7.07-7.11 (m, 4 H), 7.23-7.35 (m, 2 H), 7.48-7.57 (m, 1 H), 7.77 (d, *J* = 8.0 Hz, 0.66 H), 7.83 (d, *J* = 8.0 Hz, 0.34 H); ^{13}C NMR ($CDCl_3$): δ = 20.1, 33.2, 34.1, 35.6, 38.2, 53.8, 53.9, 95.4, 96.1, 103.0, 105.2, 115.1, 115.3, 116.6, 116.7, 122.7, 122.9, 123.7, 124.0, 126.9, 127.2, 129.3, 129.4, 131.8, 132.0, 136.2, 136.3, 138.3, 139.3, 152.9, 157.8, 158.3, 160.6, 161.6, 168.9, 169.0; IR (KBr): 3182 (m), 2920 (m), 2851 (w), 1753 (s), 1680 (s), 1619 (s), 1573 (s), 1513 (m), 1454 (m), 760 (m) cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{19}O_6$ $(M + H)^+$: 367.1182, found: 367.1180. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R (major enantiomer) = 7.01 min, t_R (minor enantiomer) =10.90 min, 75% ee.

4-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-4-(4-methoxyphenyl)- 2-oxo-butyric acid methyl ester (3c). White solid, 99% yield, exists in an equilibrium with cyclic hemiketal **3c'**. m.p.

147-148 °C, $[\alpha]_D^{20}$ = -35.6 (c 0.50, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (d, *J* = 8.8 Hz, 1.80 H), 2.50 (dd, *J* = 14.4, 3.2 Hz, 0.10 H), 2.75 (dd, *J* = 14.4, 7.6 Hz, 0.10 H), 3.76 (s, 0.30 H), 3.77 (s, 2.70 H), 3.86 (s, 2.70 H), 3.90 (s, 0.30 H), 4.15 (t, *J* = 8.8 Hz, 0.90 H), 4.29 (dd, *J* = 7.2, 3.2 Hz, 0.10 H), 4.58 (s, 0.10 H, OH, the position is concentration dependent), 4.84 (s, 0.90 H, OH, the position is concentration dependent), 6.81-6.86 (m, 2 H), 7.13-7.17 (m, 2 H), 7.24-7.35 (m, 2 H), 7.49-7.53 (m, 1 H), 7.77 (dd, *J* = 8.0, 3.2 Hz, 0.90 H), 7.83 (dd, *J* = 8.0, 3.2 Hz, 0.10 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.9, 33.7, 35.6, 38.2, 53.8, 53.9, 55.1, 55.2, 95.1, 96.2, 103.1, 105.1, 113.9, 114.1, 115.0, 115.3, 116.5, 116.6, 122.7, 122.9, 123.7, 124.0, 128.1, 128.4, 131.8, 132.0, 133.4, 134.2, 152.7, 152.8, 157.9, 158.3, 160.7, 161.6, 168.9; IR (KBr): 3204 (m), 2997 (w), 2952 (w), 2840 (w), 1761 (s), 1681 (s), 1573 (s), 1511 (m), 1455 (m), 759 (s) cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{19}O_7$ $(M + H)^+$: 383.1131, found: 383.1142. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R (major enantiomer) = 8.36 min, t_R (minor enantiomer) =14.06 min, 75% ee.

4-(4-Fluoro-phenyl)-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-butyric acid methyl ester (3d). White solid, 99% yield, exists in an equilibrium with cyclic hemiketal **3d'**. m.p. 195-197 °C, $[\alpha]_D^{20}$ = -26.2 (c 0.58, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42-2.50 (m, 1.65 H), 2.79 (dd, *J* = 14.4, 7.6 Hz, 0.35 H), 3.91 (s, 1.95 H), 3.93 (s, 1.05 H), 4.19 (dd, *J* = 10.8, 7.6 Hz, 0.65 H), 4.31 (dd, *J* = 7.2, 2.8 Hz, 0.35 H), 4.55 (s, 0.35 H, OH, the position is concentration dependent), 4.74 (s, 0.65 H, OH, the position is concentration dependent), 6.94-7.01 (m, 2 H), 7.19-7.21 (m, 2 H), 7.31-7.37 (m, 2 H), 7.52-7.59 (m, 1 H), 7.78 (d, *J* = 8.0 Hz, 0.65 H), 7.82 (d, *J* = 8.0 Hz, 0.35 H); ^{13}C NMR ($CDCl_3$): δ = 33.0, 33.9, 35.4, 38.1, 54.0, 54.1, 95.4, 95.9, 102.8, 104.8, 115.0, 115.1, 115.2, 115.3, 115.4, 115.7, 116.6, 116.7, 122.8, 122.9, 123.8, 124.1, 128.5, 128.6, 128.9, 129.0, 132.0, 132.2, 137.2, 137.9, 138.0, 152.8, 152.9, 158.0, 158.4, 160.4, 160.5, 161.5, 162.8, 162.9, 168.9, 169.0; IR (KBr): 3420 (s), 2956 (w), 2925(w), 2853 (w), 1717 (s), 1626 (s), 1575 (m), 1509 (s), 1456 (w), 761 (m) cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{16}O_6F$ $(M + H)^+$: 371.0931, found: 371.0939. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R (major enantiomer) = 6.51 min, t_R (minor enantiomer) =10.27 min, 75% ee.

4-(4-Chloro-phenyl)-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-butyric acid methyl ester (3e). White solid, 99% yield, exists in an equilibrium with cyclic hemiketal **3e'**. m.p. 192-194 °C, $[\alpha]_D^{20}$ = -37.6 (c 0.45, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36-2.49 (m, 1.64 H), 2.79 (dd, *J* = 14.4, 7.2 Hz, 0.36 H), 3.90 (s, 1.92 H), 3.92 (s, 1.08 H), 4.18 (dd, *J* = 11.2, 7.2 Hz, 0.64 H), 4.29 (dd, *J* = 7.6, 2.8 Hz, 0.36 H), 4.60 (d, *J* = 0.8 Hz, 0.36 H, OH, the position is concentration dependent), 4.80 (s, 0.64 H, OH, the position is concentration dependent), 7.17-7.36 (m, 6 H), 7.51-7.59 (m, 1 H), 7.77 (dd, *J* = 8.0, 1.6 Hz, 0.64 H), 7.82 (dd, *J* = 8.0, 1.6 Hz, 0.36 H); ^{13}C NMR ($CDCl_3$): δ = 33.1, 34.1, 35.2, 37.9, 54.0, 54.1, 95.4, 95.9, 102.5, 104.4, 114.9, 115.2, 116.6, 116.7, 122.8, 122.9, 123.9, 124.1, 128.4, 128.5, 128.8, 128.9, 132.0, 132.2, 132.3, 132.4, 140.2, 140.9, 152.8, 152.9, 158.2, 158.5, 160.6, 161.5, 168.8, 168.9; IR (KBr): 3210 (m), 2958 (w), 2853 (w), 1756 (s), 1679 (s), 1619 (s), 1492 (m), 1456 (m), 767 (m) cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{16}O_6Cl$ $(M + H)^+$: 387.0635, found: 387.0636. The enantiometric excess was determined by

HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R (major enantiomer) = 6.74 min, t_R (minor enantiomer) =10.45 min, 79% ee.

4-(3-Chloro-phenyl)-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-butyric acid methyl ester (3f). White solid, 99% yield, exists in an equilibrium with cyclic hemiketal **3f'**. m.p. 140-141 °C, $[\alpha]_D^{20}$=-29.7 (c 0.72, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 2.41-2.48 (m, 1.68 H), 2.75 (dd, *J* = 14.4, 7.6 Hz, 0.32 H), 3.81 (s, 2.04 H), 3.88 (s, 0.96 H), 4.16 (dd, *J* = 10.6, 7.2 Hz, 0.68 H), 4.25 (dd, *J* = 7.2, 3.2 Hz, 0.32 H), 4.94 (s, 0.32 H, OH, the position is concentration dependent), 5.30 (s, 0.68 H, OH, the position is concentration dependent), 7.10 (m, 6 H), 7.48-7.57 (m, 1 H), 7.77 (dd, *J* = 8.0, 1.2 Hz, 0.68 H), 7.80 (dd, *J* = 8.0, 1.2 Hz, 0.32 H); ^{13}C NMR ($CDCl_3$): δ = 33.5, 34.3, 35.3, 37.8, 537, 53.9, 95.5, 96.0, 102.1, 103.8, 114.8, 115.1, 116.4, 116.6, 122.8, 122.9, 123.9, 124.0, 125.5, 125.7, 126.6, 126.9, 127.1, 127.6, 129.4, 129.8, 132.0, 132.2, 133.9, 134.2, 143.9, 144.3, 152.7, 158.5, 158.8, 160.8, 161.6, 168.6, 168.8; IR (KBr): 3401 (s), 2926 (w), 2853 (w), 1682 (s), 1621 (s), 1574 (m), 1492 (m), 1456 (m), 759 (m) cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{16}O_6Cl$ $(M + H)^+$: 387.0635, found: 387.0638. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R (major enantiomer) = 5.89 min, t_R (minor enantiomer) = 8.54 min, 75% ee.

4-(4-Bromo-phenyl)-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-butyric acid methyl ester (3g). White solid, 98% yield, exists in an equilibrium with cyclic hemiketal **3g'**. m.p. 198-199 °C, $[\alpha]_D^{20}$ = - 42.0 (c 0.40, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36-2.49 (m, 1.64 H), 2.79 (ddd, *J* = 14.4, 7.2, 1.6 Hz, 0.36 H), 3.90 (s, 1.92 H), 3.92 (s, 1.08 H), 4.16 (dd, *J* = 11.2, 7.2 Hz, 0.64 H), 4.28 (dd, *J* = 7.2, 2.8 Hz, 0.36 H), 4.58 (d, *J* = 1.6 Hz, 0.36 H, OH, the position is concentration dependent), 4.77 (d, *J* = 1.6 Hz, 0.64 H, OH, the position is concentration dependent), 7.12-7.14 (m, 2 H), 7.28-7.43 (m, 4 H), 7.51-7.60 (m, 1 H), 7.77 (dd, *J* = 8.0, 1.6 Hz, 0.64 H), 7.81 (dd, *J* = 8.0, 1.6 Hz, 0.36 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.2, 34.2, 35.1, 37.9, 54.0, 54.1, 95.3, 95.9, 102.5, 104.4, 114.9, 115.2, 116.6, 116.8, 120.4, 120.5, 122.8, 122.9, 123.9, 124.1, 128.9, 129.3, 131.4, 131.8, 132.1, 132.3, 140.8, 141.5, 152.8, 152.9, 158.1, 158.5, 160.5, 161.5, 168.8, 168.9; IR (KBr): 3205 (m), 2956 (w), 1757 (s), 1678 (s), 1618 (s), 1571 (s), 1491 (m), 1456 (m), 766 (s) cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{16}O_6Br$ $(M + H)^+$: 431.0130, found: 431.0148. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R (major enantiomer) = 7.04 min, t_R (minor enantiomer) =11.30 min, 76% ee.

4-Furan-2-yl-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-butyric acid methyl ester (3h). White solid, 95% yield, exists in an equilibrium with cyclic hemiketal **3h'**. m.p. 147-149 °C, $[\alpha]_D^{20}$ = 19.6 (c 0.66, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 2.53 (dd, *J* = 14.0, 6.8 Hz, 0.60 H), 2.59-2.69 (m, 1 H), 2.78 (dd, *J* = 14.4, 6.8 Hz, 0.40 H), 3.82 (s, 1.80 H), 3.92 (s, 1.20 H), 4.53 (dd, *J* = 10.4, 6.8 Hz, 0.60 H), 4.60 (dd, *J* = 6.8, 2.4 Hz, 0.40 H), 4.69 (s, 0.40H, OH, the position is concentration dependent), 5.00 (s, 0.60 H, OH, the position is concentration dependent), 6.89-6.91 (m, 2 H), 7.13-7.17 (m, 1 H), 7.27-7.35 (m, 2 H), 7.50-7.77 (m, 1 H), 7.78 (dd, *J* = 8.0, 1.6 Hz, 0.60 H), 7.82 (dd, *J* = 8.0, 1.6 Hz, 0.40 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.0, 30.1, 35.5, 38.5, 53.8, 54.0, 95.6, 95.9, 102.9, 104.4, 114.9, 115.1, 116.5, 116.7, 122.9, 123.0, 123.5,

123.8, 124.0, 124.1, 124.8, 125.1, 126.6, 132.1, 132.3, 145.1, 152.7, 152.8, 157.7, 157.9, 160.6, 161.6, 168.6; IR (KBr): 3353 (s), 3110 (w), 3075 (w), 2952 (w), 1739 (s), 1682 (s), 1625 (s), 1608 (m), 1491 (m), 1455 (m), 769 (m), 719 (m) cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{15}O_6S$ $(M + H)^+$: 359.0589, found: 359.0587. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R (major enantiomer) = 9.99 min, t_R (minor enantiomer) =14.56 min, 77% ee.

4-(4-Hydroxy-oxo-2*H*-chromen-3-yl)-2-oxo-4-phenylbutyric acid ethyl ester (3i). White solid, 96% yield, exists in an equilibrium with cyclic hemiketal **3i'**. m.p. 167-168 °C, $[\alpha]_D^{20}$= -20.9 (c 0.33, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (dt, *J* = 7.2, 2.0 Hz, 3 H), 2.44 (d, *J* = 9.2 Hz, 1.12 H), 5.07 (dd, *J* = 14.4, 3.2 Hz, 0.44 H), 2.80 (ddd, *J* = 14.4, 7.2, 0.8 Hz, 0.44 H), 4.20 (t, *J* = 9.2 Hz, 0.56 H), 4.30-4.39 (m, 2.44 H), 4.53 (d, *J* = 0.8 Hz, 0.44 H, OH, the position is concentration dependent), 4.76 (s, 0.56 H, OH, the position is concentration dependent), 7.21-7.37 (m, 7 H), 7.50-7.59 (m, 1 H), 7.77 (dd, *J* = 8.0, 1.6 Hz, 0.56 H), 7.82 (dd, *J* = 8.0, 1.6 Hz, 0.44 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.0, 33.7, 34.6, 35.5, 38.1, 63.4, 63.5, 95.4, 96.1, 102.9, 104.9, 115.1, 115.3, 116.5, 115.7, 122.7, 122.8, 127.3, 124.0, 126.6, 126.7, 127.1, 127.4, 128.4, 128.7, 131.8, 132.0, 141.6, 142.4, 152.7, 152.8, 158.1, 158.5, 160.7, 161.6, 168.4, 168.5; IR (KBr): 3454 (m), 3084 (w), 3026 (w), 2986 (w), 2926 (w), 1751 (s), 1713 (s), 1681 (s), 1492 (m), 1454 (m), 756 (s), 699 (m) cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}O_5$ $(M + H)^+$: 303.1232, found: 303.1233. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R (major enantiomer) = 5.90 min, t_R (minor enantiomer) =8.70 min, 76% ee.

4-(4-Hydroxy-oxo-2*H*-chromen-3-yl)-2-oxo-4-phenylbutyric acid isobutyl ester (3j). White solid, 95% yield, exists in an equilibrium with cyclic hemiketal **3j'**. m.p. 140-141 °C, $[\alpha]_D^{20}$ = -24.2 (c 0.36, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29-1.33 (m, 6 H), 2.35-2.46 (m, 1.36 H), 2.50 (dd, *J* = 14.4, 3.2 Hz, 0.32 H), 2.78 (dd, *J* = 14.4, 7.2 Hz, 0.32 H), 4.19 (dd, *J* = 11.2, 7.2 Hz, 0.68 H), 4.32 (dd, *J* = 7.2, 3.2 Hz, 0.32 H), 4.74 (s, 0.32 H, OH, the position is concentration dependent), 5.05 (s, 0.68 H, OH, the position is concentration dependent), 5.13-5.16 (m, 1 H), 7.19-7.35 (m, 7 H), 7.49-7.57 (m, 1 H), 7.75 (dd, *J* = 8.0, 1.2 Hz , 0.68 H), 7.80 (dd, *J* = 8.0, 1.2 Hz, 0.32 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 33.7, 34.7, 38.0, 71.8, 71.9, 95.3, 96.0, 102.9, 104.9, 115.1, 115.4, 116.5, 116.6, 122.7, 122.8, 123.7, 124.0, 126.6, 126.7, 127.1, 127.4, 128.3, 128.7, 131.8, 132.0, 141.6, 142.6, 152.8, 158.1, 160.6, 167.9, 168.0; IR (KBr): 3316 (s), 3058 (w), 2985 (w), 2942 (w), 1753 (s), 1674 (s), 1620 (s), 1492 (m), 1451 (m), 765 (s), 700 (m) cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{19}O_6$ $(M - H)^+$: 379.1182, found: 379.1180. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R (major enantiomer) = 5.90 min, t_R (minor enantiomer) = 8.70 min, 74% ee.

4-(4-Hydroxy-oxo-2*H*-chromen-3-yl)-2-oxo-4-phenylbutyric acid allyl ester (3k). White solid, 99% yield, exists in an equilibrium with cyclic hemiketal **3k'**. m.p. 108-109 °C, $[\alpha]_D^{20}$ = -18.6 (c 0.72, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (d, *J* = 8.8 Hz, 1.34 H), 2.55 (dd, *J* = 14.4, 3.2 Hz, 0.33 H), 2.81 (dd, *J* = 14.4, 6.8 Hz, 0.33 H), 4.20 (t, *J* = 8.8 Hz, 0.67 H), 4.33-4.36 (dd, *J* = 7.2, 3.2 Hz, 0.33 H), 4.55 (s, 0.33 H, OH, the position is concentration dependent), 4.70-4.79 (m,

2 H), 4.83 (s, 0.67 H, OH, the position is concentration dependent), 5.30-5.40 (m, 2 H), 5.86-5.96 (m, 1 H), 7.21-7.26 (m, 7 H), 7.34-7.56 (m, 1 H), 7.77 (dd, *J* = 8.0, 1.2 Hz, 0.67 H), 7.82 (dd, *J* = 8.0, 1.2 Hz, 0.33H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.6, 34.6, 35.5, 38.1, 67.5, 67.6, 95.5, 96.1, 102.9, 104.9, 115.1, 115.3, 116.5, 116.7, 119.9, 120.0, 122.7, 122.8, 123.8, 124.0, 126.7, 126.8, 127.1, 127.4, 128.4, 128.7, 130.5, 131.8, 132.1, 141.5, 142.3, 152.8, 152.9, 158.0, 158.4, 160.6, 161.6, 168.1, 168.2; IR (KBr): 3349 (m), 2929 (w), 1759 (s), 1678 (s), 1619 (s), 1572 (m), 1493 (m), 1454 (m), 786 (s), 698 (m) cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{17}O_6$ (M - H)$^+$: 377.1025, found: 377.1032. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R(major enantiomer) = 6.42 min, t_R(minor enantiomer) = 10.19 min, 77% ee.

4-(4-Hydroxy-oxo-2*H*-chromen-3-yl)-5-methyl-2-oxo-hexanoic acid ethyl ester (3l). Colorless oil**,** 74% yield, exists in an equilibrium with cyclic hemiketal **3l'**. $[\alpha]_D^{20}$ = 81.8 (c 0.44, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (d, *J* = 6.8 Hz, 2.1 H), 0.95 (d, *J* = 6.8 Hz, 0.9 H), 1.00-1.03 (m, 3 H), 1.26 (t, *J* = 7.2 Hz, 0.9 H), 1.43 (t, *J* = 7.2 Hz, 2.1 H), 2.11 (dd, *J* = 7.2, 13.6 Hz, 0.7 H), 2.17-2.24 (m, 0.7 H), 2.34 (d, *J* = 5.6 Hz, 0.7 H), 2.59-2.67 (m, 0.3 H), 2.91-2.96 (m, 0.3 H), 3.07-3.13 (m, 0.3 H), 3.28-3.36 (m, 0.3 H), 4.30 (q, *J* = 7.2 Hz, 0.6 H), 4.44 (qd, *J* = 0.4, 7.2 Hz, 1.4 H), 4.76 (d, *J* = 2.0 Hz, 0.7 H, OH, the position is concentration dependent), 5.10 (s, 0.3 H, OH, the position is concentration dependent), 7.21-7.31 (m, 2 H), 7.47-7.53 (m, 1 H), 7.69 (dd, *J* = 1.6, 8.0 Hz, 0.7 H), 7.74 (dd, *J* = 1.6, 8.0 Hz, 0.3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.0, 15.8, 19.1, 20.3, 21.0, 25.2, 27.0, 29.1, 29.4, 32.6, 34.9, 63.4, 63.5, 95.8, 97.0, 105.5, 105.7, 115.2, 115.5, 116.2, 116.4, 122.6, 123.6, 123.8, 131.5, 131.6, 152.4, 152.5, 157.7, 157.9, 161.3, 162.4, 169.0, 169.2; HRMS (ESI) calcd for $C_{18}H_{19}O_6$ (M - H)$^+$: 331.1182, found: 331.1188. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R(major enantiomer) = 5.31 min, t_R(minor enantiomer) = 6.57 min, 80% ee.

4-(6-Methyl-4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-phenyl-butyric acid methyl ester (10b). White solid, 99% yield, exists in an equilibrium with cyclic hemiketal **10b'**. m.p. 182-183 °C, $[\alpha]_D^{20}$= -30.4 (c 0.70, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 2.58 H), 2.43 (s, 0.42 H), 2.44 (d, *J* = 8.8 Hz, 1.72 H), 2.52 (dd, *J* = 14.4, 3.6 Hz, 0.14 H), 2.78 (ddd, *J* = 14.4, 7.2, 1.2 Hz, 0.14 H), 3.85 (s, 2.68 H), 3.91 (s, 0.42 H), 4.18 (t, *J* = 8.8 Hz, 0.86 H), 4.32 (dd, *J* = 7.2, 3.2 Hz, 0.14 H), 4.53 (d, *J* = 1.2 Hz, 0.14 H, OH, the position is concentration dependent), 4.82 (s, 0.86 H, OH, the position is concentration dependent), 7.17 -7.37 (m, 7 H), 7.55 (d, *J* = 1.2 Hz, 0.86 H), 7.60 (d, *J* = 1.6 Hz, 0.14 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 33.7, 34.6, 35.6, 38.1, 53.8, 53.9, 95.4, 96.1, 102.7, 104.7, 114.7, 114.9, 116.3, 116.4, 122.4, 122.5, 126.7, 127.1, 127.3, 128.4, 128.6, 132.9, 133.1, 133.5, 133.8, 141.6, 142.4, 150.9, 151.0, 158.0, 158.4, 160.9, 161.8, 169.0; IR (KBr): 3298 (s), 3065 (w), 2999 (w), 2951 (w), 2924 (w), 1761 (s), 1672 (s), 1623 (s), 1494 (m), 1449 (m), 780 (m), 699 (m) cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{17}O_6$ (M - H)$^+$: 365.1025, found: 365.1031. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R(major enantiomer) = 6.37 min, t_R(minor enantiomer) = 13.62 min, 79% ee.

4-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-4-phenyl-butyric acid methyl ester (10c). White solid, 99% yield, exists in an equilibrium with cyclic hemiketal **10c'**. m.p. 50-52 °C, $[\alpha]_D^{20}$= 32.5 (c 0.60, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19 (s, 2.10 H), 2.22 (s, 0.90 H), 2.31 (d, *J* = 8.4 Hz, 1.40 H), 2.38 (dd, *J* = 14.4, 4.4 Hz, 0.30 H), 2.64 (dd, *J* = 14.4, 7.2 Hz, 0.30 H), 3.66(s, 2.10 H), 3.81 (s, 0.90 H), 4.01 (t, *J* = 8.4 Hz, 0.70 H), 4.11 (dd, *J* = 7.2, 4.4 Hz, 0.30 H), 4.76 (s, 0.30 H, OH, the position is concentration dependent), 5.23 (s, 0.70 H, OH, the position is concentration dependent), 5.83 (s, 0.70 H), 5.87 (s, 0.30 H), 7.14-7.28 (m, 5 H); ^{13}C NMR ($CDCl_3$): δ = 19.6, 19.7, 33.1, 33.6, 36.0, 37.9, 53.4, 53.6, 95.3, 96.0, 99.8, 99.9, 100.0, 101.1, 126.4, 126.5, 127.0, 127.2, 128.2, 128.4, 141.6, 141.9, 161.3, 161.4, 162.8, 163.1, 163.3, 163.5, 168.6, 168.8; IR (KBr): 3391 (s), 3028 (w), 2955 (w), 2925 (w), 1690 (s), 1579 (s), 1494 (m), 1447 (m), 761 (m), 701 (m) cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}O_6$ (M - H)$^+$: 315.0869, found: 315.0862. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R(major enantiomer) = 6.44 min, t_R(minor enantiomer) = 8.51 min, 74% ee.

4-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-2-oxo-4-phenylbutyric acid methyl ester (10d). White solid, 99% yield, exists in an equilibrium with cyclic hemiketal **10d'**. m.p. 208-210 °C, $[\alpha]_D^{20}$ = 26.3 (c 0.38, CH_3OH). ^{1}H NMR (400 MHz, $(CD_3)CO$): δ = 2.41 (dd, *J* = 14.0, 5.6 Hz, 0.30 H), 2.52 (d, *J* = 7.6 Hz, 1.40 H), 2.76 (dd, *J* = 14.0, 7.6 Hz, 0.30 H), 3.51 (s, 2.10 H), 3.57 (s, 2.10 H), 3.58 (s, 0.90 H), 3.80 (s, 0.90 H), 4.26 (t, *J* = 7.6 Hz, 1 H), 6.69 (s, 0.30 H, OH, the position is concentration dependent), 6.93 (s, 0.70 H, OH, the position is concentration dependent), 7.10-7.30 (m, 6 H), 7.50-7.52 (m, 1 H), 7.62-7.67 (m, 1 H), 7.98-8.00 (m, 1 H); (100 MHz, DMSO-d_6): δ = 28.9, 34.7, 35.4, 38.3, 38.5, 38.9, 52.0, 52.7, 95.6, 96.9, 107.3, 108.1, 114.5, 114.8, 121.5, 122.4, 125.4, 125.6, 127.1, 127.3, 1277.8, 130.9, 138.7, 138.8, 142.9, 144.2, 154.8, 160.8, 168.5, 168.9; HRMS (ESI) calcd for $C_{21}H_{18}NO_5$ (M - H)$^+$: 364.1185, found: 364.1190. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 220 nm, 0.7 ml/min); t_R(major enantiomer) = 8.38 min, t_R(minor enantiomer) = 14.3 min, 74% ee.

4-(2-Hydroxy-6-oxocyclohex-1-enyl)-2-oxo-4-phenyl-butyric acid methyl ester (10e). White solid, 99% yield, exists in an equilibrium with cyclic hemiketal **10e'**. m.p. 144-145 °C, $[\alpha]_D^{20}$ = 12.8 (c 0.58, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98-2.12 (m, 2 H), 2.23-2.59 (m, 6 H), 3.78 (s, 2.34 H), 3.85 (s, 0.66 H), 3.90 (dt, *J* = 8.8, 1.6 Hz, 0.78 H), 4.10-4.13 (m, 0.22 H), 4.16 (s, 0.22 H, OH, the position is concentration dependent), 4.48 (s, 0.78 H, OH, the position is concentration dependent), 7.14-7.18 (m, 3 H), 7.24-7.28 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2, 20.7, 28.7, 28.9, 31.5, 33.2, 35.7, 36.9, 37.0, 38.31, 53.5, 53.6, 94.7, 95.6, 113.1, 115.5, 126.1, 126.3, 126.9, 127.2, 128.3, 128.4, 142.7, 144.0, 168.5, 169.4, 196.2, 196.8; IR (KBr): 3066 (m), 2952 (m), 1759 (s), 1637 (s), 1609 (s), 1496 (m), 1454 (m), 760 (m), 705 (m) cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}O_5$ (M + H)$^+$: 303.1232, found: 303.1233. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 70:30, λ = 254 nm, 0.8 ml/min); t_R(major enantiomer) = 6.07 min, t_R(minor enantiomer) = 7.43 min, 79% ee.

4-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-2-oxo-4-phenyl-butyric acid methyl ester (10f). White solid, 97% yield, exists in an equilibrium with cyclic hemiketal **10f'**. m.p. 161-162 °C, $[\alpha]_D^{20}$ = -15.0 (c 0.28, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 1.95 H), 1.11 (s, 1.05 H), 1.17 (s, 1.95 H), 1.19 (s, 1.05 H), 2.01-2.58 (m, 6 H), 3.72 (s, 1.95 H), 3.84 (s, 1.05 H), 3.86-3.91 (m, 0.65 H), 4.07-4.08 (m, 0.35 H), 4.32 (s, 0.35 H, OH, the position is concentration dependent), 4.68 (s, 0.65 H, OH, the position is concentration dependent), 7.13-7.17 (m, 3 H), 7.23-7.27 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7, 28.2, 28.8, 29.3, 29.7, 31.7, 31.9, 32.1, 33.3, 36.0, 38.3, 42.3,42.4, 50.8, 53.5, 53.6, 94.9, 95.8, 112.0, 113.9, 126.1, 126.3, 12.0, 127.3, 128.3, 128.4, 142.9, 144.0, 166.9, 167.5, 169.3, 169.4, 196.3, 196.8; IR (KBr): 3129 (s), 2953 (w), 2932 (w), 2887 (w), 1756 (s), 1596 (s), 1494 (s), 1451 (m), 762 (m), 696 (m) cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{21}O_5$ $(M - H)^+$: 329.1389, found: 329.1396. The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane: 2-propanol = 70: 30, λ = 254 nm, 0.7 ml/min); t_R(major enantiomer) = 6.22 min, t_R(minor enantiomer) = 8.69 min, 85% ee.

Acknowledgements

Financial support of this study from the National Natural Science Foundation of China (No. 20772160, 20972195), the Ministry of Science and Technology of China (No. 2009ZX09501-017) and the Zhuhai Bureau of Science and Technology is gratefully acknowledged.

References

1. For the reviews of catalytic asymmetric conjugate addition, see: (a) Yamaguchi, M.; Jacobsen, E. N.; Pfalz, A.; Yamamoto, H.; Eds. *Comprehensive Asymmetric Catalysis*, Springer: Berlin, 1999, Ch. 31. p. 2. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (c) Krause, N.; Hoffmann-Roeder, A. *Synthesis* **2001**, 171.
2. For the general reviews of asymmetric organocatalysis, see: (a) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (b) Yu, X.-H.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (c) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (c) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249.
3. For the recent reviews of organocatalytic asymmetric conjugate addition, see: (a) Almasi, D.; Alonso, D. A.; Najera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, *11*, 1701. (c) Chen, Y.-C. *Synlett* **2008**, 1919. (d) Mukherjee, S.; Yang, J.-W.; Hoffman, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (e) Pellissier, H.; *Tetrahedron* **2007**, *63*, 9267.
4. Halland, N.; Velgaard, T.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 5067.

5. Calter, M. A.; Wang, J. *Org. Lett.* **2009**, *11*, 2205.
6. Zhou, L.; Lin, L. L.; Wang, W. T.; Ji, J.; Liu, X. H.; Feng, X. M. *Chem. Commun.* **2010**, 3601.
7. Xu, D.-Q.; Wang, Y.-F.; Zhang, W.; Luo, S.-P.; Zhong, A.-G.; Xia, A.-B.; Xu, Z.-Y. *Chem. Eur. J.* **2010**, ASAP (DOI: 10.1002/chem.201000094).
8. For the reviews of bifunctional organocatalysts: see: (a) Connon, S. J. *Chem.Commun.* **2008**, 2499. (b) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.
9. (a) Zhang, X.-J.; Liu, S.-P.; Li, X.-M.; Yan, M; Chan, A. S. C. *Chem. Commun.* **2009**, 833; (b) Xuan,Y.-N.; Nie, S.-Z.; Dong, L.-T.; Zhang, J.-M.; Yan, M. *Org. Lett.* **2009**, *11*, 1583; (c) Liu, S.-P.; Zhang,X.-J.; Lao, J.-H.; Yan, M. *Arkivoc* **2009**, *7*, 268. (d) Zhang, X.-J.; Liu, S.-P.; Lao, J.-H.; Du, G.-J.; Yan, M.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2009**, *20*, 1451.
10. (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032.
11. For the biological and pharmaceutical activities of coumarin deratives, see: (a) Murray, R. D. H.; Medez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*, Wiley: New York, 1982. (b) *The Handbook of Natural Flavonoids*, Harborne, J. B.; Baxter H.; Eds. Wiley: Chichester, UK, 1999. (c) Manolov, I.; Danchev, N. D. *Eur. J. Med. Chem*. **1995**, *30*, 531. (d) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; Lee, K. H. *J. Med. Chem*. **1999**, *42*, 2662. (e) Ishikawa, T. *Heterocycles* **2000**, *53*, 453. (f) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; McPhail, A. T.; Lee, K. H. *J. Med. Chem.* **2001**, *44*, 664. (g) Melliou,E.; Magiatis, P.; Mitaku, S.; Skaltsounis, A. L.; Chinou, E.; Chinou, I. *J. Nat. Prod.* **2005**, *68*, 78.
12. (a) Stecher, E. D.; Ryder, H. F. *J. Am. Chem. Soc.* **1952**, *74*, 4392. (b) Audrain,H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *65*, 4487.
13. Sugimura, H.; Miura, M.; Yamada, N. *Tetrahedron: Asymmetry* **1997**, *8,* 4089.
14. (a) Kaik, M.; Gawroński, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1559. (b) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (c) Okino, T.; Hoashi,Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (d) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (e) Luo, J.; Xu, L.-W.; Hay, R. A. S.; Lu, Y.-X. *Org. Lett.* **2009**, *11*, 437.