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Article

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Azetidine Derived Dinuclear Zinc Catalyzed Asymmetric Conjugate Addition of Bioactive Heterocycles to β,γ-Unsaturated α-Ketoesters

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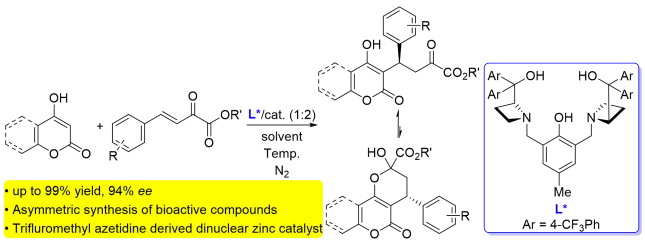
Abstract:



A general AzePhenol dinuclear zinc catalytic system has successfully developed and applied into the asymmetric Michael addition of 4-hydroxyl pyrones and 4-hydroxy coumarins to *β*,*γ*-unsaturated *α*-keto esters. Excellent yields (up to 99%) and high enantioselectivities (up to 94% *ee*) are obtained for a wide range of substrates under mild conditions in absence of additives. This bimetallic catalytic approach represents a new and effective asymmetric synthetic protocol to access a variety of bioactive compounds with pharmacological interest. The possible mechanism is proposed to explain the origin of the asymmetric induction.

Introduction

Coumarin and pyranone moieties have been well recognized as the key structural scaffolds in several bioactive compounds.[1] In particular, their derivatives have been established as potential antimalarial, anticoagulant, and anti-HIV agents.[2] As a consequence of the structural importance, methods for the synthesis of this kind of heterocycles have gained considerable attention. The direct asymmetric Michael addition of coumarins/pyranones to *α*,*β*-unsaturated carbonyl compound is considered as one of the most convenient approaches to furnish the chiral drug, warfarin, which is an effective anticoagulant for preventing thrombosis and embolism.[3] As a class of activated *α*,*β*-unsaturated carbonyl systems, *β*,*γ*-unsaturated *α*-ketoesters are very attractive Michael acceptors due to their high reactivity and their potential to transform into a range of different functionalities. Furthermore, the *α*-oxo ester moiety can form multiple effective associations with chiral catalysts.

Numerous catalytic strategies for enantioselective modifications of coumarins/pyranones have been developed over the past decades. Among them, organocatalytic process has proved to be efficient.[4] As a subfield of organocatalysis, bifunctional catalyst has emerged as an especially important tool for this transformation. The previous work has disclosed the highly enantioselective Michael addition of 4-hydroxycoumarins and *β*,*γ* unsaturated *α*-ketoesters catalyzed by an array of chiral squaramide and thiourea-derived organocatalysts.[5−13] The privilege of bifunctional systems probably associates with the compatibility for simultaneous activation of both the electrophile and the nucleophile. In contrast, the application of metal catalyst in enantioselective Michael addition of coumarins/pyranones appears scarce. In 2003, Jørgensen and co-workers reported the first transition metal catalyzed asymmetric Michael addition of 4-hydroxycoumarins to *β*,*γ*-unsaturated *α*-ketoesters by using chiral bisoxazoline-copper(II) complexes,[14] moderate to good enantioselectivities (up to 86% *ee*) were obtained in the presence of diethyl ether in

the reflux condition. While a significant decrease both in yield and enantioselectivity was observed under ambient condition and using other solvents, which limited the application of this approach in practical utility. Subsequently, *N,N'*-dioxide–nickel(II) complex was employed as a metal catalyst for this type of reaction by the Feng group to afford good enantioselectivities ranging from 85% to 90% *ee* in the presence of 4Å MS (molecular sieve).[15] Despite the achievements to date, the metal catalytic system towards this transformation still have some drawbacks in terms of general limitation to mononuclear metallic catalyst, relatively lower stereoselectivity, and the requirements of extra additives. Additionally, enantioselective manipulation of pyrones *via* metal catalysis has not been well documented. Therefore, the development of novel and effective activation strategies for the metal catalytic process to access a wide range of bioactive heterocycles with coumarin and pyranone structure units is highly desirable in this area.

In recent years, our group has developed a dinuclear zinc-AzePhenol catalyst and it has demonstrated remarkable catalytic efficiency and stereoselectivities in a number of catalytic enantioselective transformations.[16] Enlightened by this, we envisaged that coumarins/pyrones and *β*,*γ*-unsaturated *α*-ketoesters might be suitably activated and orientated by our dual Lewis acid/Lewis base functionality, and it is possible that the azetidine ring skeleton provides the appropriate sterically hindered microenvironment to promote the stereoselectivity of the target Michael addition. Herein, we report the successful application of a trifluoromethyl substituted dinuclear zinc-AzePhenol in the asymmetric Michael addition of 4-hydroxycoumarins and a 4-hydroxypyrones to *β*,*γ*-unsaturated *α*-ketoesters. The combination of broad substrates scope, high enantioselectivities, and mild conditions, represent an efficient metallic catalytic approach for the synthesis of bioactive warfarin analogues.

Results and Discussion

Figure 1. Chiral Ligands Candidates

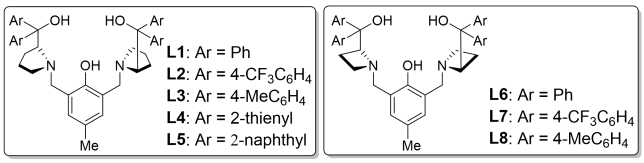
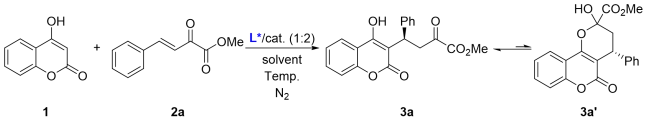


Table 1. Optimization of Reaction Conditions[a]



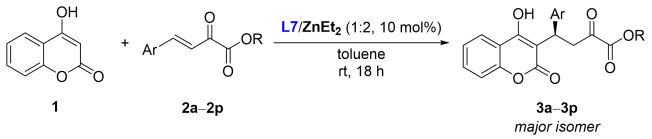
Entry	L*	Cat.	Solvent	Temp. (°C)	Additive	Yield (%)[b]	*ee* (%)[c]
1	L_1	$ZnEt_2$	CH_2Cl_2	rt	-	82	80
2	L_2	$ZnEt_2$	CH_2Cl_2	rt		86	82
3	L_3	$ZnEt_2$	CH_2Cl_2	rt		89	63
4	L_4	$ZnEt_2$	CH_2Cl_2	rt		83	81
5	L_5	$ZnEt_2$	CH_2Cl_2	rt		81	71
6	L_6	$ZnEt_2$	CH_2Cl_2	rt		68	60
7	L_7	$ZnEt_2$	CH_2Cl_2	rt		89(87[d])	86(85[d])
8	L_8	$ZnEt_2$	CH_2Cl_2	rt		74	70
9	L_7	$ZnMe_2$	CH_2Cl_2	rt		92	82
10	L_7	$MgBu_2$	CH_2Cl_2	rt		94	43
11	L_7	$ZnEt_2$	Et_2O	rt		68	84
12	L_7	$ZnEt_2$	$CHCl_3$	rt		91	82
13	L_7	$ZnEt_2$	CH_3CN	rt		78	75
14	L_7	$ZnEt_2$	1,4-dioxane	rt		57	62
15	L_7	$ZnEt_2$	DCE	rt		74	71
16	L_7	$ZnEt_2$	benzene	rt		76	78
17	L_7	$ZnEt_2$	toluene	rt		96	89
18	L_7	$ZnEt_2$	toluene	-20		81	81
19	L_7	$ZnEt_2$	toluene	0		95	85
20	L_7	$ZnEt_2$	toluene	40		89	78
21	L_7	$ZnEt_2$	toluene	rt	4Å MS (25 mg)	92	84
22	L_7	$ZnEt_2$	toluene	rt	Et_3N	86	56
23	L_7	$ZnEt_2$	toluene	rt	Na_2CO_3	89	84
24	L_7	$ZnEt_2$	toluene	rt	K_2CO_3	83	83

[a] Unless noted, all reactions were conducted with **1** (0.125 mmol), **2a** (0.125 mmol), and catalyst (20 mol%) in toluene (1.5 mL) under N_2 at room temperature (rt). [b] Isolated yield. [c] Determined by HPLC analysis, the absolute configurations were assigned by comparison to literature values. [d]10 mol% catalyst was used.

Initially, the addition of 4-hydroxycoumarin **1** to the *α*-ketoester **2a** was employed as a model reaction to explore the effect of the various chiral dinuclear zinc catalysts. Notably, an equilibrium between Michael adduct **3a** and cyclic hemiketal **3a'** was observed in NMR, which existed predominantly in their open (keto-**3a**) form. However, The equilibrium was sufficiently rapid that only two peaks from enantiomers were detected during chiral HPLC analysis, which was in accordance with earlier observations by Jørgensen for similar compounds.[14] A series of chiral ligands were prepared in our laboratory (Figure 1, **L1**−**L8**).[17] Our previous work showed the reaction was ineffective by using Trost's ligand in THF,[18] therefore the preliminary study was conducted in DCM. As shown in Table 1, the results revealed that good yield and moderate *ee* were observed in the presence of **L1** (entry 1). However, additional efforts to modulate the electronic and steric effect on aryl framework did not increase the enantiomeric excess significantly (entries 2−5). To our delight, replacing the AzePhenol **L1** by **L6**, the enantioseletivity was improved (entry 6). Encouraged by this result, the different substitution on aryl ring of **L6** was investigated, the electron-withdrawing trifluoromethyl substitution was superior to electron-donating methyl substitution with 87% yields and 85% *ee*, which probably owing to the effective activation of *α*-ketoester by the increased electrophility of zinc catalyst (entry 7). Accordingly, ligand **L7** was then used for further reaction conditions screening. The reaction was found to be dependent on metal counterion. A dramatic diminishment in both yield and enantioselectivity was observed when alkali magnesium counterion was employed (entry 10). It was worth to mention that the high yield and enantioselectivity were maintained with a reduced catalyst loading from 20 to 10 mol% (entry 7). The solvent effect was subsequent to be assessed. In general, the reaction in polar solvent led to a reduction of the asymmetric induction compared to that in non-polar solvent. Toluene was identified as the choice of solvent to deliver the adducts in excellent enantiomeric excess. Further screening of the reaction temperature and additives for stereoselectivity enhancement was conducted. Gratifyingly, the reaction proceeded smoothly at room temperature in the absence of additives without any detriment of yield as well as enantiomeric excess, 96% yield and

89% *ee* were achieved in the optimal conditions, which exhibited the effective and convenience of our approach (entry 17).

Table 2. Variation of the *α*-Ketoesters for the Asymmetric Conjugate Addition with Coumarin Catalyzed by Dinuclear Zinc Catalyst[a]



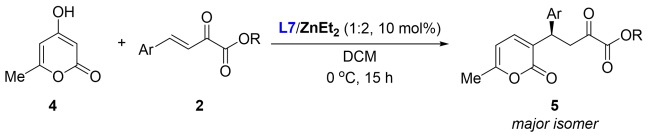
Entry	**2**	Ar	R	t (h)	Product	Yield (%)[b]	*ee* (%)[c]
1	**2a**	C_6H_5	Me	18	**3a**	96	89
2	**2b**	4-FC_6H_4	Me	18	**3b**	76	92
3	**2c**	4-ClC_6H_4	Me	18	**3c**	70	93
4	**2d**	4-BrC_6H_4	Me	18	**3d**	86	90
5	**2e**	4-MeC_6H_4	Me	24	**3e**	99	92
6	**2f**	3-ClC_6H_4	Me	24	**3f**	70	83
7	**2g**	3-BrC_6H_4	Me	24	**3g**	78	84
8	**2h**	3-MeC_6H_4	Me	24	**3h**	90	92
9	**2i**	3-$OMeC_6H_4$	Me	24	**3i**	99	88
10	**2j**	2-ClC_6H_4	Me	12	**3j**	85	86
11	**2k**	2-BrC_6H_4	Me	12	**3k**	84	91
12	**2l**	2-naphthyl	Me	18	**3l**	72	92
13	**2m**	2-thienyl	Me	18	**3m**	63	83
14	**2n**	C_6H_5	Et	18	**3n**	96	94
15	**2o**	C_6H_5	*i*-Pr	36	**3o**	98	93
16	**2p**	C_6H_5	*t*-Bu	36	**3p**	96	94

a. Unless noted, all reactions were conducted with **1** (0.125 mmol), **2a−2p** (0.125 mmol), and catalyst (10 mol%) in toluene (1.5 mL) under N_2 at room temperature. b. Isolated yield. c. Determined by HPLC analysis. The absolute configurations were assigned by comparison to literature values. In all cases, the product chromatograms were compared against a known racemic mixture. The absolute configuration of **3a** was assigned by comparison of optical rotation and chiral HPLC traces with the literature.[14] The other products were tentatively assigned by analogy.

Under the optimized conditions, we explored the generality of this reaction with a spectrum of *β*,*γ*-unsaturated *α*-ketoesters. The results are summarized in Table 2. The similar high level of enantioselectivities were achieved by employing a wide array of aromatic *β*,*γ*-unsaturated *α*-oxoesters. It appears that the electronic nature and position on aryl substitution had negligible effects on either the yields or stereoselectivities (entries 2−11). However, the methoxyl and thienyl substituents on

phenyl ring afforded slightly lower enantiomeric excess, which might be attributed to the competitive coordination interaction between the methoxyl or thienyl group and the catalyst (entries 9 and 13). Notably, the reactivity was sensitive to the electronic property of the substituents on the phenyl ring, the electron-deficient halogen substituted *α*-ketoesters were outperformed by the electron-rich methyl substituent to deliver the products in lower yields (entries 2−6). Gratifyingly, the *β*,*γ*-unsaturated *α*-ketoesters bearing various ester groups provided warfarin analogues in nearly quantitative yields and excellent enantioselectivities, irrespective of the steric property of the ester substitution (entries 14−16).

Table 3. Variation of the *α*-Ketoesters for the Asymmetric Conjugate Addition with Pyrones Catalyzed by Dinuclear Zinc Catalyst[a]

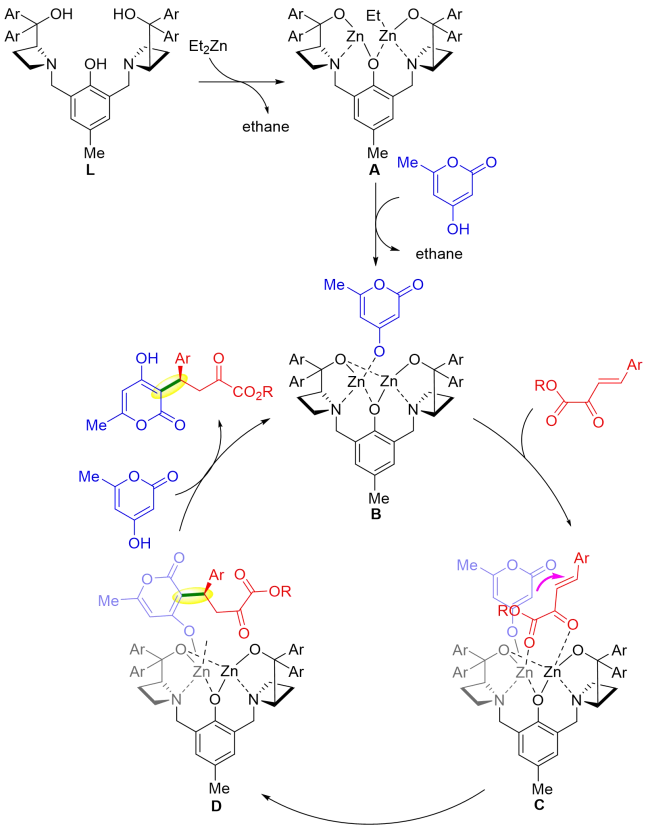


Entry	**2**	Ar	R	t (h)	Product	Yield (%)[b]	*ee* (%)[c]
1	**2a**	C_6H_5	Me	15	**5a**	96	83
2	**2b**	4-FC_6H_4	Me	15	**5b**	84	75
3	**2c**	4-ClC_6H_4	Me	18	**5c**	98	81
4	**2d**	4-BrC_6H_4	Me	15	**5d**	86	76
5	**2e**	4-MeC_6H_4	Me	15	**5e**	92	88
6	**2f**	3-ClC_6H_4	Me	24	**5f**	95	75
7	**2g**	3-BrC_6H_4	Me	15	**5g**	81	84
8	**2h**	3-MeC_6H_4	Me	15	**5h**	95	90
9	**2i**	3-OMeC_6H_4	Me	15	**5i**	92	80
10	**2j**	2-ClC_6H_4	Me	18	**5j**	68	60
11	**2k**	2-BrC_6H_4	Me	12	**5k**	68	72
12	**2l**	2-naphthyl	Me	15	**5l**	93	80
13	**2m**	2-thienyl	Me	20	**5m**	94	78
14	**2n**	C_6H_5	Et	15	**5n**	94	81
15	**2o**	C_6H_5	*i*-Pr	15	**5o**	86	80
16	**2p**	C_6H_5	*t*-Bu	15	**5p**	91	76

a. Unless otherwise noted, all reactions were conducted with **4** (0.125 mmol), **2a**, **2b**, **2d**, **2e**, **2g−2j**, **2l−2p** (0.125 mmol), and catalyst (10 mol%) in DCM (1.5 mL) under N_2 at 0 °C. b. Isolated yield. c. Determined by chiral HPLC. The absolute configurations were assigned by comparison to literature values. In all cases, the product chromatograms were compared against a known racemic mixture. The absolute configuration of 4aa was assigned by comparison of optical rotation and chiral HPLC traces with the literature.[14]

4-Hydroxyl pyrones are less nucleophilic compared to 4-hydroxy coumarins, which led to the lower reactivity of Michael-addition. Consequently, only 72% yield and 70% *ee* was observed in this case. High yield and enantioselectivity was restored after a screening of reaction conditions (see the Supporting Information for detail), 96% yield and 83% *ee* was obtained in DCM and 0 °C (Table 3, entry 1). With the optimal reaction conditions, various pyrones were prepared in high yields and good enantioselectivities. Satisfyingly, the *β*,*γ*-unsaturated *α*-ketoesters bearing naphthyl and thienyl substituents (**5l** and **5m**), respectively, were compatible in this reaction. The electron-donating methyl substituents on the phenyl ring (**5e** and **5h**) had a pronounced effect on both the asymmetric induction and the reactivity compared to the electron-withdrawing halogen group (**5b, 5c,** 5**d** and **5f**), since the *α*-ketoesters bearing electron-rich substituents would facilitate the electrons shift to carbonyl group, which made it more easier to coordinate with chiral zinc catalyst. In addition, the steric effect was obvious as well, a diminishment of *ee* was observed when bulkyl *tert*-butyl ester group **5p** was used. It was found that *ortho*- halogen substitution **5j** or **5k** resulted in a reduced yield and *ee*, which probably was attributed to the steric effect and thus led to a competing 1,2-addition process (entry 8).

Scheme 1. Proposed Catalytic Cycle of the Asymmetric Conjugate Addition



To explain the high levels of stereoselectivity, we propose the following plausible mechanism based on bifunctional activation strategy. As illustrated in Scheme 1, the deprotonation occurred by the other Brønsted basic zinc nucleus to form the zinc enolate **B**. On the other hand, the *β*,*γ*-unsaturated *α*-ketoester was activated and oriented by the Lewis acidic zinc nucleus *via* bidentate coordination of the 1,2-dicarbonyl moiety to form the intermediate **C**. The benzo-fused conjugation system of 4-hydroxy coumarin facilitates the deprotonation step, which account for the observed higher enantioselectivities compared to 4-hydroxyl pyrones. Ultimately, the well-induced transition state promotes the nucleophile **1** to attack the oxoester **2a** from the *Re* face and to justify the observed stereochemical outcome.

Conclusion

In conclusion, we have developed a dinuclear zinc catalyzed enantioselective Michael addition of 4-hydroxyl pyrones and 4-hydroxy coumarins to *β*,*γ*-unsaturated *α*-ketoesters. This catalytic method allows access to a series of optically active coumarin and pyrone derivatives with pharmaceutical interest. Compared to the previous metallic process, the higher yields and enantioselectivities can be achieved under mild reaction conditions and in the absence of additives. Further applications of the dinuclear metal catalytic system for the preparation of valuable chiral products are currently underway.

Experimental Section

General Remarks. All reactions were performed in flame-dried glassware using conventional Schlenk techniques under a static pressure of argon. All starting materials, ligands, and racemic products were prepared according to known procedures. Liquids and solutions were transferred with (micro)syringes. Solvents were purified and dried following standard procedures. Technical grade solvents for extraction and chromatography were distilled prior to use. Analytical thin-layer chromatography (TLC) and flash column chromatography were performed on silica gel using the indicated solvents. ^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{1H\}$ NMR spectra were recorded in $CDCl_3$ on *Bruker DPX 400* (400 MHz). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual solvent resonance as the internal standard (δ = 7.26 ppm for ^{1}H and δ = 77.16 ppm for $^{13}C\{^{1}H\}$). Data are reported as follows: chemical shift, multiplicity (br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. Optical rotations were recorded on a *Perkin-Elmer 341* polarimeter. Infrared (IR) spectra were recorded on a *Thermo Nicolet IR 200* spectrophotometer and reported in wavenumbers (cm^{-1}). High resolution mass spectrometry (HRMS) analyses were performed on an *Agilent LC-MSAD-Trap-XCT* instrument. Melting

points (m.p.) were determined with a Stuart SMP20 apparatus and are not corrected. The *ee* value determination was carried out using chiral HPLC on a *Chiralcel ID*, A*D-H, or OD-H Column* (for all the columns: 4.6 mmφ × 250 mm, Daicel Chemical Ind., LTD, Japan) combined with a *JASCO model PU-1580 intelligent HPLC pump* and a *JASCO model UV-1575 intelligent UV-vis detector* (254nm).

General Procedure for the Catalytic Asymmetric Conjugate Addition of Bioactive Heterocycles to *β*,*γ*-Unsaturated *α*-Ketoesters: In a flame-dried 10 mL Schlenk tube equipped with a magnetic stir bar, chiral ligand **L7** (0.00625 mmol, 5 mol%) in dry toluene or DCM (0.8 mL) is added under nitrogen. Then a solution of dimethylzinc (0.0105 mL, 1.2 mol/L in hexane, 0.0125 mmol, 10 mol%) is added through a micro syringe to the system at 0 °C and the resulting mixture is stirred at room temperature for 30 min. Afterwards, cooling the system to 0 °C again and 4-hydroxy coumarins **1** or 4-hydroxyl pyrones **4** (0.125 mmol, 1.0 equiv.), *β*,*γ*-unsaturated *α*-keto esters (**2a**–**2p**, 0.125 mmol, 1.0 equiv.) and dry toluene or DCM (0.7 mL) are added successively. The solution is stirred at indicated temperature for indicated reaction time. After complete consumption of the imine starting material, as monitored by TLC analysis, saturated NH_4Cl (2.0 mL) is added and the mixture is extracted with ethyl acetate (3 × 10 mL). The combined organic phases are washed with brine (5.0 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, purification of the residue by column chromatography on silica gel using mixtures of petroleum ether and ethyl acetate as eluents affords the analytically pure title compounds.

(*R*)-Methyl 4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-phenylbutanoate[14] (**3a**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 42.4 mg, 96% yield, exists in an equilibrium with cyclic hemiketal **3a'**; $[\alpha]_D^{20}$ = -24.6 (c 1.0, $CHCl_3$); HPLC (Chiralpak ID column, hexane/*i*-PrOH = 70/30, flow rate = 2.0 mL/min, λ = 254 nm; Retention time: *t*r(major) = 5.33 min, *t*r(minor) = 7.20 min, 89% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.8 Hz, 0.3H), 7.78 (d, *J* = 7.8 Hz, 0.7H), 7.53 (dd, *J* = 17.3, 8.8 Hz, 1H), 7.26 (dt, *J* = 17.1, 6.5 Hz, 7H), 5.00 (s, 0.7H), 4.66 (s, 0.3H), 4.33 (d, *J* = 6.4 Hz, 0.3H), 4.19 (t, *J* = 9.0 Hz, 0.7H), 3.86 (d, *J* =

27.9 Hz, 3H), 2.78 (dd, *J* = 14.2, 7.4 Hz, 0.3H), 2.53 (dd, *J* = 14.3, 3.0 Hz, 0.3H), 2.45 (d, *J* = 8.9 Hz, 1.4H) ppm. HRMS (ESI) exact mass for $[M+Na]^+$ ($C_{20}H_{16}O_6Na$): calcd m/z 375.0839, found: 375.0838; IR (neat) $\tilde{\nu}$/cm^{-1} = 3440, 3132, 2854, 1741, 1626, 1400, 1159, 1091, 827, 766, 699, 595; m.p.: 170 – 172 °C.

(*R*)-Methyl 4-(4-fluorophenyl)-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxobutanoate[6] (**3b**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 35.2 mg, 76% yield, exists in an equilibrium with cyclic hemiketal **3b'**; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm; Retention time: *t*r(major) = 16.02 min, *t*r(minor) = 34.20 min, 92% *ee*); $[\alpha]_D^{20}$ = -10.2 (c 0.3, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 – 7.76 (m, 1H), 7.64 – 7.53 (m, 1H), 7.40 – 7.27 (m, 4H), 7.23 – 7.16 (m, 2H), 4.32 (dd, *J* = 7.3, 2.6 Hz, 0.3H), 4.20 (dd, *J* = 11.1, 7.2 Hz, 0.7H), 3.97 – 3.90 (m, 3H), 2.81 (dd, *J* = 14.3, 7.6 Hz, 0.3H), 2.53 – 2.38 (m, 1.7H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 169.0, 168.9, 162.8, 161.7, 159.5 (d, *J* = 210 Hz), 159.4 (d, *J* = 260 Hz),152.8, 138.0, 137.3, 132.3, 132.1, 129.0 (d, *J* = 10 Hz), 128.5 (d, *J* = 11 Hz), 124.1, 123.9, 122.9, 116.7, 116.6, 115.5 (d, *J* = 21 Hz), 115.1 (d, *J* = 21 Hz), 104.6, 102.8, 96.0, 95.5, 54.1, 54.0, 38.1, 35.5, 33.9, 33.1 ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = -116.2, -116.5 ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{20}H_{16}FO_6$): calcd m/z 371.0925, found: 371.0926; IR (neat) $\tilde{\nu}$/cm^{-1} = 3421, 3132, 2923, 1746, 1715, 1698, 1624, 1399, 1224, 760; m.p.: 195 – 197 °C.

(*R*)-Methyl 4-(4-chlorophenyl)-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxobutanoate[6] (**3c**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 33.8 mg, 70% yield, exists in an equilibrium with cyclic hemiketal **3c'**; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm; Retention time: *t*r(major) = 16.27 min, *t*r(minor) = 36.27 min, 93% *ee*); $[\alpha]_D^{20}$ = -27.7 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 – 7.76 (m, 1H), 7.64 – 7.53 (m, 1H), 7.41 – 7.27 (m, 4H), 7.23 – 7.18 (m, 2H), 4.32 (dd, *J* = 7.3, 2.6 Hz, 0.3H), 4.20 (dd, *J* = 11.1, 7.2 Hz, 0.7H), 3.97 – 3.91 (m, 3H), 2.81 (dd, *J* = 14.3, 7.6 Hz, 0.4H), 2.53 – 2.37 (m, 1.6H) ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{20}H_{16}ClO_6$): calcd m/z 387.0630, found: 387.0631; IR (neat) $\tilde{\nu}$/cm^{-1} = 3184, 2954, 2926, 2853, 1750, 1716, 1697, 1625, 1437, 1111, 1108, 759; m.p.: 191 – 193 °C.

(*R*)-Methyl 4-(4-bromophenyl)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxobutanoate[6] (**3d**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 46.2 mg, 86% yield, exists in an equilibrium with cyclic hemiketal **3d'**; HPLC (Chiralpak ID column, hexane/*i*-PrOH = 70/30, flow rate = 2.0 mL/min, λ = 254 nm; Retention time: *t*r(major) = 4.79 min, *t*r(minor) = 7.66 min, 90% *ee*); $[\alpha]_D^{20}$ = -28.6 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 – 7.76 (m, 1H), 7.63 – 7.52 (m, 1H), 7.46 – 7.27 (m, 4H), 7.18 – 7.12 (m, 2H), 4.29 (dd, *J* = 7.3, 2.7 Hz, 0.3H), 4.22 – 4.11 (m, 0.7H), 3.92 (d, *J* = 12.1 Hz, 3H), 2.80 (dd, *J* = 14.3, 7.5 Hz, 0.3H), 2.55 – 2.33 (m, 1.7H) ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{20}H_{16}BrO_6$): calcd m/z 431.0125, found: 431.0126; IR (neat) $\tilde{\nu}$/cm^{-1} = 3420, 3143, 1715, 1696, 1683, 1624, 1488, 1400, 1111, 759; m.p.: 197 – 199 °C.

(*R*)-Methyl 4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-(*p*-tolyl)butanoate[6] (**3e**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 45.3 mg, 99% yield, exists in an equilibrium with cyclic hemiketal **3e'**; HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *t*r(major) = 7.30 min, *t*r(minor) = 13.59 min, 92% *ee*); $[\alpha]_D^{20}$ = -20.3 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 – 7.76 (m, 1H), 7.71 – 7.43 (m, 2H), 7.29 (dd, *J* = 12.0, 7.5 Hz, 1H), 7.13 (d, *J* = 11.1 Hz, 4H), 4.32 (s, 0.3H), 4.19 (t, *J* = 8.9 Hz, 0.7H), 3.89 (s, 3H), 2.52 (d, *J* = 23.5 Hz, 0.3H), 2.51 (dd, *J* = 29.3, 11.3 Hz, 1.7H), 2.34 (s, 3H) ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{21}H_{19}O_6$): calcd m/z 367.1176, found: 367.1174; IR (neat) $\tilde{\nu}$/cm^{-1} = 3420, 3133, 2956, 2854, 1731, 1715, 1625, 1574, 1491, 1455, 1399, 1111, 759; m.p.: 171 – 173 °C.

(*R*)-Methyl 4-(3-chlorophenyl)-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxobutanoate[6] (**3f**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 33.8 mg, 70% yield, exists in an equilibrium with cyclic hemiketal **3f'**; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm; Retention time: *t*r(major) = 13.49 min, *t*r(minor) = 26.75 min, 83% *ee*); $[\alpha]_D^{20}$ = -19.6 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 – 7.75 (m, 1H), 7.67 – 7.52 (m, 1H), 7.44 – 7.12 (m, 6H), 4.31 (dd, *J* = 7.2, 2.5 Hz, 0.3H), 4.20 (dd, *J* = 11.0, 7.2 Hz, 0.7H), 3.92 (d, *J* = 11.3 Hz, 3H), 2.81 (dd, *J* = 14.3, 7.5 Hz, 0.3H), 2.60 – 2.38 (m,

1.7H) ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{20}H_{16}ClO_6$): calcd m/z 387.0630, found: 387.0631; IR (neat) $\tilde{\nu}$/cm^{-1} = 3339, 3016, 2954, 2852, 1753, 1715, 1626, 1574, 1327, 1112, 760, 736; m.p.: 140 – 142 °C.

(*R*)-Methyl 4-(3-bromophenyl)-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxobutanoate[15] (**3g**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 41.9 mg, 78% yield, exists in an equilibrium with cyclic hemiketal **3g'**; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm; Retention time: *t*r(major) = 15.99 min, *t*r(minor) = 29.50 min, 84% *ee*); $[\alpha]_D^{20}$ = -22.8 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.2 Hz, 1H), 7.54 (dd, *J* = 23.0, 17.0 Hz, 1H), 7.42 – 7.29 (m, 4H), 7.20 (s, 2H), 4.29 (s, 0.27H), 4.13 (q, *J* = 7.1 Hz, 0.73H), 3.89 (s, 3H), 2.78 (s, 0.3H), 2.43 (dd, *J* = 21.0, 9.8 Hz, 1.7H) ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{20}H_{16}BrO_6$): calcd m/z 431.0125, found: 431.0126; IR (neat) $\tilde{\nu}$/cm^{-1} = 3419, 3143, 2953, 2953, 2924, 1747, 1714, 1624, 1573, 1398, 1165, 1111, 759; m.p.: 130 – 132 °C.

(*R*)-Methyl 4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-(*m*-tolyl)butanoate[15] (**3h**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid 41.2 mg, 90% yield, exists in an equilibrium with cyclic hemiketal **3h'**; HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *t*r(major) = 8.06 min, *t*r(minor) = 16.06 min, 92% *ee*); $[\alpha]_D^{20}$ = -13.2 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.79 (m, 1H), 7.57 (dddd, *J* = 17.4, 8.6, 7.4, 1.6 Hz, 1H), 7.42 – 7.29 (m, 2H), 7.25 – 7.03 (m, 4H), 4.18 (dd, *J* = 16.1, 7.5 Hz, 0.67H), 4.09 – 3.99 (m, 0.33H), 3.95 – 3.85 (m, 3H), 2.60 – 2.53 (m, 0.33H), 2.49 – 2.44 (m, 1.67H), 2.33 (d, *J* = 4.3 Hz, 3H) ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{21}H_{19}O_6$): calcd m/z 367.1176, found: 367.1175; IR (neat) $\tilde{\nu}$/cm^{-1} = 3147, 2955, 2925, 2854, 1715, 1625, 1574, 1435, 1398, 1111, 759, 703; m.p.: 167 – 169 °C.

(*R*)-Methyl 4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-4-(3-methoxyphenyl)-2-oxobutanoate[15] (**3i**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 47.3 mg, 99% yield, exists in an equilibrium with cyclic hemiketal **3i'**; HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *t*r(major) = 6.70 min, *t*r(minor) = 10.98 min, 88% *ee*); $[\alpha]_D^{20}$ = -12.8

(c 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.0 Hz, 1H), 7.63 – 7.49 (m, 0.8H), 7.36 – 7.19 (m, 3.2H), 6.91 – 6.73 (m, 3H), 4.52 (s, 0.2H), 4.18 – 4.06 (m, 2.8H), 3.88 – 3.75 (m, 4H), 2.78 (s, 0.2H), 2.48 (d, *J* = 8.1 Hz, 1,8H) ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{21}H_{19}O_7$): calcd m/z 383.1125, found: 383.1126; IR (neat) $\tilde{\nu}$/cm^{-1} = 3338, 3196, 3005, 2954, 1717, 1626, 1554, 1394, 1265, 1111, 761, 736; m.p.: 147 – 149 °C.

(*S*)-Methyl 4-(2-chlorophenyl)-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxobutanoate[8] (**3j**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 41.0 mg, 85% yield, exists in an equilibrium with cyclic hemiketal **3j'**; HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *tr*(major) = 9.36 min, *tr*(minor) = 19.77 min, 86% *ee*); $[\alpha]_D^{20}$ = -13.1 (c 0.3, in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (dd, *J* = 12.3, 8.0 Hz, 1H), 7.63 – 7.53 (m, 1H), 7.43 – 7.25 (m, 3H), 7.15 (dt, *J* = 14.3, 6.6 Hz, 3H), 4.75 (s, 0.47H), 4.66 (d, *J* = 5.7 Hz, 0.51H), 3.90 (d, *J* = 35.0 Hz, 3H), 2.78 (dd, *J* = 14.4, 7.6 Hz, 0.46H), 2.68 – 2.36 (m, 1.51H) ppm; HRMS (ESI) exact mass for $[M+Na]^+$ ($C_{20}H_{15}ClNaO_6$): calcd m/z 409.0449, found: 409.0448; IR (neat) $\tilde{\nu}$/cm^{-1} = 3422, 3134, 2917, 2850, 1735, 1725, 1698, 1693, 1625, 1399, 757; m.p.: 149 – 151 °C.

(*S*)-Methyl 4-(2-bromophenyl)-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxobutanoate (**3k**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 45.2 mg, 84% yield, exists in an equilibrium with cyclic hemiketal **3k'**; $[\alpha]_D^{20}$ = -10.2 (c 0.3, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *tr*(major) = 10.74 min, *tr*(minor) = 22.06 min, 91% *ee*); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (dd, *J* = 15.8, 7.9 Hz, 1H), 7.56 (dd, *J* = 16.1, 7.5 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 0.5H), 7.35 – 7.28 (m, 1.5H), 7.16 (d, *J* = 5.9 Hz, 1H), 7.11 – 7.06 (m, 1H), 4.83 (s, 1H), 4.61 (s, 1H), 3.94 (s, 1H), 3.90 (s, 1H), 2.77 (dd, *J* = 14.5, 7.6 Hz, 0.5H), 2.63 (d, *J* = 16.9 Hz, 1H), 2.21 (s, 1H), 2.02 (s, 0.5H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 169.2, 168.8, 161.3, 160.4, 157.3, 152.8, 140.1, 139.9, 133.0, 132.2, 132.0, 131.1, 129.9, 129.4, 128.4, 128.3, 127.8, 126.9, 124.0, 124.0, 123.9, 122.9, 122.7, 116.7, 116.6, 115.2, 114.9, 102.6, 96.0, 95.5, 54.1, 54.0, 33.5, 29.3, 27.2, 22.7 ppm; HRMS (ESI) exact mass for $[M+H]^+$

($C_{20}H_{16}BrO_6$): calcd m/z 431.0125, found: 431.0126; IR (neat) $\tilde{\nu}$/cm^{-1} = 3420, 3134, 2924, 2853, 1746, 1715, 1626, 1574, 1459, 1166, 1109, 757, 721; m.p.: 86 – 87 °C.

(*R*)-Methyl 4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-4-(naphthalen-2-yl)-2-oxobutanoate[15] (**3l**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 36.2 mg, 72% yield, exists in an equilibrium with cyclic hemiketal **3l'**; HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *tr*(major) = 11.44 min, *tr*(minor) = 22.10 min, 92% *ee*); $[\alpha]_D^{20}$ = -10.1 (c 0.2, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 – 7.68 (m, 5H), 7.64 – 7.53 (m, 1H), 7.48 – 7.29 (m, 5H), 4.52 (dd, *J* = 7.4, 3.4 Hz, 0.3H), 4.39 (dd, *J* = 10.7, 7.3 Hz, 1.7H), 3.87 (d, *J* = 44.1 Hz, 3H), 2.87 (dd, *J* = 14.3, 7.4 Hz, 0.3H), 2.69 – 2.48 (m, 1.7H) ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{24}H_{19}O_6$): calcd m/z 403.1176, found: 403.1176; IR (neat) $\tilde{\nu}$/cm^{-1} = 3420, 3134, 2925, 2852, 1747, 1715, 1624, 1399, 1110, 819, 759; m.p.: 107 – 108 °C.

(*S*)-Methyl 4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-(thiophen-2-yl)butanoate[6] (**3m**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 28.2 mg, 63% yield, exists in an equilibrium with cyclic hemiketal **3m'**; HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *tr*(major) = 5.89 min, *tr*(minor) = 7.80 min, 83% *ee*); $[\alpha]_D^{20}$ = +22.7 (c 0.3, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (dd, *J* = 14.1, 7.9 Hz, 1H), 7.65 – 7.52 (m, 1H), 7.32 (tt, *J* = 14.4, 7.3 Hz, 2H), 7.21 – 7.15 (m, 1H), 6.93 (dd, *J* = 8.6, 4.2 Hz, 2H), 4.65 – 4.53 (m, 1H), 3.95 – 3.85 (m, 3H), 2.80 (dd, *J* = 14.4, 6.9 Hz, 0.3H), 2.73 – 2.52 (m, 1.7H) ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{18}H_{15}SO_6$): calcd m/z 359.0584, found: 359.0586; IR (neat) $\tilde{\nu}$/cm^{-1} = 3430, 3132, 2849, 1683, 1624, 1399, 1172, 1024, 761; m.p.: 112 – 114 °C.

(*R*)-Ethyl 4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-phenylbutanoate[14] (**3n**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 43.9 mg, 96% yield,exists in an equilibrium with cyclic hemiketal **3n'**; HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *tr*(major) = 9.12 min, *tr*(minor) = 21.24 min, 94% *ee*); $[\alpha]_D^{20}$ = -30.1 (c 0.3, in $CHCl_3$); ^{1}H NMR(400 MHz, $CDCl_3$): δ = 7.80 (dd, *J* = 19.5, 7.7 Hz, 1H), 7.65 –

7.45 (m, 1H), 7.39 – 7.15 (m, 7H), 4.39 – 4.24 (m, 2H), 4.20 (dd, *J* = 10.3, 7.9 Hz, 0.3H), 4.07 – 3.95 (m, 0.7H), 2.80 (dd, *J* = 14.2, 7.4 Hz, 0.3H), 2.57 – 2.37 (m, 1.7H), 1.33 (dd, *J* = 15.3, 8.1 Hz, 3H) ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{21}H_{19}O_6$): calcd m/z 367.1176, found: 367.1174; IR (neat) $\tilde{\nu}$/cm^{-1} = 3420, 3333, 3145, 3028, 1746, 1695, 1625, 1398, 1111, 758, 700. m.p.: 167 – 169 °C.

(*R*)-Isopropyl 4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-phenylbutanoate[6] (**3o**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 46.6 mg, 98% yield, exists in an equilibrium with cyclic hemiketal **3o'**; HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *tr*(major) = 6.71 min, *tr*(minor) = 16.24 min, 93% *ee*); $[\alpha]_D^{20}$ = -13.5 (c 0.3, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (dd, *J* = 22.7, 7.8 Hz, 1 H), 7.62 – 7.46 (m, 1H), 7.40 – 7.17 (m, 7H), 5.16 (dt, *J* = 11.4, 5.7 Hz, 1H), 4.33 (d, *J* = 4.7 Hz, 0.3H), 4.20 (dd, *J* = 11.3, 7.2 Hz, 0.7H), 2.79 (dd, *J* = 14.2, 7.5 Hz, 0.3H), 2.56 – 2.32 (m, 0.7H), 1.28 – 1.15 (m, 6H) ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{22}H_{21}O_6$): calcd m/z 381.1333, found: 381.1333; IR (neat) $\tilde{\nu}$/cm^{-1} = 3443, 3132, 1734, 1716, 1698, 1614, 1440, 780, 720; m.p.: 140 – 142 °C.

(*R*)-*tert*-Butyl 4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-phenylbutanoate[6] (**3p**): Purified by flash chromatography (petroleum ether : EtOAc = 2 : 1) to afford a white solid, 47.3 mg, 96% yield, exists in an equilibrium with cyclic hemiketal **3p'**; HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *tr*(major) = 5.89 min, *tr*(minor) = 12.63 min, 94% *ee*); $[\alpha]_D^{20}$ = -14.2 (c 0.3, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (dd, *J* = 24.8, 7.9 Hz, 1H), 7.61 – 7.47 (m, 1H), 7.41 – 7.15 (m, 7H), 4.32 (dd, *J* = 7.3, 3.2 Hz, 0.3H), 4.19 (dd, *J* = 12.0, 6.8 Hz, 0.7H), 2.76 (dd, *J* = 14.3, 7.5 Hz, 0.3H), 2.53 – 2.28 (m, 1.7H), 1.53 (d, *J* = 9.7 Hz, 9H) ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{23}H_{23}O_6$): calcd m/z 395.1489, found: 395.1490; IR (neat) $\tilde{\nu}$/cm^{-1} = 3394, 3131, 2925, 2850, 1733, 1716, 1698, 1624, 1136, 758; m.p.: 151 – 153 °C.

(*R*)-Methyl 4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-4-phenylbutanoate[14] (**5a**): Purified by flash chromatography using petroleum ether with EtOAc to afford a colorless oil 37.9 mg, 96% yield, exists in an equilibrium with cyclic hemiketal **5a'**;

$[\alpha]_D^{20}$ = +17.1 (c 1.72, in $CHCl_3$); HPLC (Chiralpak OD, hexane/*i*-PrOH = 70/30, flow rate = 2.0 mL/min, λ = 254 nm; Retention time: *tr*(major) = 6.50 min, *tr*(minor) = 10.06 min, 83% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.16 (m, 5H), 5.88 (s, 0.3H), 5.82 (s, 0.7H), 4.95 (s, 0.7H), 4.56 (s, 0.3H), 4.18 – 3.99 (m, 1H), 3.85 (s, 1H), 3.74 (s, 2H), 2.66 (dd, *J* = 14.3, 7.4 Hz, 0.3H), 2.41 (dd, *J* = 14.3, 3.7 Hz, 0.3H), 2.32 (d, *J* = 8.8 Hz, 1.4H), 2.24 (s, 1H), 2.20 (s, 2H) ppm. HRMS (ESI) exact mass for $[M+H]^+$ ($C_{17}H_{16}O_6$): calcd m/z 317.1020, found: 317.1023; IR (neat) $\tilde{\nu}$/cm^{-1} = 3268, 2916, 2847, 1683, 1574, 1449, 1230, 1194, 1141, 757, 696.

(*R*)-Methyl 4-(4-fluorophenyl)-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxobutanoate (**5b**): Purified by flash chromatography using petroleum ether with EtOAc to afford a colorless oil, 35.1 mg, 84% yield, exists in an equilibrium with cyclic hemiketal **5b'**; $[\alpha]_D^{20}$ = +23 (c 0.034, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *tr*(major) = 8.65 min, *tr*(minor) = 14.63 min, 75% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 – 7.10 (m, 2H), 7.02 – 6.93 (m, 2H), 5.87 (s, 0.3H), 5.82 (s, 0.7H), 4.81 (s, 0.7H), 4.52 (s, 0.3H), 4.19 – 3.99 (m, 1H), 3.87 (s, 1H), 3.81 (s, 2H), 2.66 (dd, *J* = 14.3, 7.4 Hz, 0.3H), 2.37 (dd, *J* = 11.5, 2.8 Hz, 0.3H), 2.34 – 2.27 (m, 1.4H), 2.25 (s, 1H), 2.20 (s, 2H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 169.0, 168.9, 163.5, 163.1, 162.6, 161.7, 161.6 (d, *J* = 243 Hz) , 161.5 (d, *J* = 241 Hz), 137.9, 137.8, 137.4, 137.3, 130.0, 129.9, 129.0 (d, *J* = 8 Hz), 128.6 (d, *J* = 8 Hz), 115.4 (d, *J* = 21 Hz), 115.1 (d, *J* = 21 Hz), 101.5, 99.9, 99.8, 95.7, 95.2, 53.9, 53.8, 38.1, 35.5, 33.2, 32.4, 29.3, 19.9 ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = -116.4, -116.7 ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{17}H_{16}FO_6$): calcd m/z 335.0925, found: 335.0924; IR (neat) $\tilde{\nu}$/cm^{-1} = 3276, 2957, 2920, 2847, 1687, 1574, 1509, 1444, 1222, 1137, 1036, 1012, 826, 802, 781.

(*R*)-Methyl 4-(4-chlorophenyl)-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxobutanoate (**5c**): Purified by flash chromatography using petroleum ether with EtOAc to afford a yellow solid, 42.9 mg, 98% yield, exists in an equilibrium with cyclic hemiketal **5c'**; $[\alpha]_D^{20}$ = +27.1 (c 0.034, in $CHCl_3$); HPLC (Chiralpak ID, hexane/*i*-PrOH = 70/30, flow rate = 2.0 mL/min, λ = 254 nm; Retention time: *tr*(major) = 5.47 min, *tr*(minor) = 8.86 min, 81% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 – 7.23 (m, 2H),

7.14 (d, *J* = 8.3 Hz, 2H), 5.87 (s, 0.3H), 5.82 (s, 0.7H), 4.83 (s, 0.7H), 4.55 (s, 0.3H), 4.12 (dd, *J* = 7.2, 2.7 Hz, 0.3H), 4.02 (dd, *J* = 11.0, 7.0 Hz, 0.7H), 3.87 (s, 1H), 3.82 (s, 2H), 2.66 (dd, *J* = 14.2, 7.5 Hz, 0.3H), 2.38 (d, *J* = 3.1 Hz, 0.3H), 2.35 – 2.32 (m, 0.3H), 2.32 – 2.28 (m, 0.7H), 2.26 (s, 1.4H), 2.21 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 169.0, 168.8, 163.5, 163.2, 163.0, 162.6, 161.8, 140.8, 140.3, 132.3, 132.2, 128.9, 128.8, 128.5, 128.4, 101.2, 100.0, 99.9, 99.5, 95.7, 95.1, 77.1, 53.9, 53.8, 37.9, 35.4, 33.3, 32.5, 19.9. ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{17}H_{16}ClO_6$): calcd m/z 351.0630, found: 351.0634; IR (neat) $\tilde{\nu}$/cm^{-1} = 3321, 2950, 2930, 2867, 1687, 1570, 1512, 1444, 1222, 1137, 1076, 1012, 846, 791; m.p.: 97 – 99 ^{o}C.

(*R*)-Methyl 4-(4-bromophenyl)-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxobutanoate (**5d**): Purified by flash chromatography using petroleum ether with EtOAc to afford a colorless oil, 37.4 mg, 86% yield, exists in an equilibrium with cyclic hemiketal **5d'**; $[\alpha]_D^{20}$ = +17.2 (c 0.318, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *t*r(major) = 9.15 min, *t*r(minor) = 15.66 min, 76% *ee*); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 – 7.35 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.87 (s, 0.3H), 5.81 (s, 0.7H), 4.77 (s, 0.7H), 4.51 (s, 0.3H), 4.17 – 4.07 (m, 1H), 3.87 (s, 1H), 3.82 (s, 2H), 2.66 (dd, *J* = 14.3, 7.5 Hz, 0.3H), 2.36 (dd, *J* = 11.9, 2.4 Hz, 0.3H), 2.34 – 2.28 (m, 1.4H), 2.25 (s, 1H), 2.21 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 168.9, 168.7, 163.4, 163.2, 162.9, 162.4, 161.8, 141.3, 140.8, 131.7, 131.3, 129.2, 128.8, 120.3, 120.2, 101.1, 99.9, 99.9, 99.4, 95.6, 95.0, 53.9, 53.8, 37.8, 35.2, 33.4, 32.5, 19.9, 19.8 ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{17}H_{16}BrO_6$): calcd m/z 395.0125, found: 395.0122; IR (neat) $\tilde{\nu}$/cm^{-1} = 3292, 2956, 2916, 2851, 1683, 1582, 1485, 1440, 1230, 1194, 1141, 1008, 818, 781.

(*R*)-Methyl 4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-4-(p-tolyl)butanoate (**5e**): Purified by flash chromatography using petroleum ether with EtOAc to afford a white solid, 37.9 mg, 92% yield, exists in an equilibrium with cyclic hemiketal **5e'**; $[\alpha]_D^{20}$ = +44.2 (c 1.99, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *t*r(major) = 8.41 min, *t*r(minor) = 15.58

min, 88% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (s, 4H), 5.87 (s, 0.3H), 5.80 (s, 0.7H), 4.66 (s, 0.7H), 4.35 (s, 0.3H), 4.12 – 4.00 (m, 1H), 3.86 (s, 1H), 3.79 (s, 2H), 2.65 (dd, *J* = 14.3, 7.3 Hz, 0.3H), 2.41 (dd, *J* = 14.4, 3.0 Hz, 0.3H), 2.36 – 2.27 (m, 4.4H), 2.25 (s, 1H), 2.20 (s, 2H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 169.0, 168.9, 163.5, 163.0, 162.6, 162.5, 161.4, 139.1, 138.4, 136.1, 129.3, 129.2, 127.1, 126.9, 101.8, 99.9, 95.8, 95.1, 53.8, 53.7, 38.2, 35.6, 33.3, 21.1, 19.9, 19.8 ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{18}H_{19}O_6$): calcd m/z 331.1176, found: 331.1179; IR (neat) $\tilde{\nu}$/cm^{-1} = 3264, 2952, 2924, 2856, 1683, 1574, 1444, 1400, 1230, 1190, 1141, 1036, 814, 781; m.p.: 99 – 101 °C.

(*R*)-methyl 4-(3-chlorophenyl)-4-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-2-oxobutanoate (**5f**):Purified by flash chromatography using petroleum ether with EtOAc to afford a white solid, 42 mg, 95% yield, exists in an equilibrium with cyclic hemiketal **5f'**; $[\alpha]_D^{20}$ = +22.2 (c 0.034, in $CHCl_3$); HPLC (Chiralpak ID, hexane/*i*-PrOH = 70/30, flow rate = 2.0 mL/min, λ = 254 nm; Retention time: *t*r(major) = 5.51 min, *t*r(minor) = 9.50 min, 75% *ee*);^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 – 7.15 (m, 3H), 7.11 (d, *J* = 7.1 Hz, 1H), 5.88 (s, 0.3H), 5.83 (s, 0.7H), 4.91 (s, 0.7H), 4.60 (s, 0.3H), 4.12 (dd, *J* = 7.1, 2.7 Hz, 0.3H), 4.05 – 3.97 (m, 0.7H), 3.87 (s, 1H), 3.81 (s, 2H), 2.66 (dd, *J* = 14.3, 7.5 Hz, 0.3H), 2.35 (d, *J* = 7.2 Hz, 0.3H), 2.31 (d, *J* = 7.6 Hz, 1H), 2.27 (d, *J* = 4.7 Hz, 1.4H), 2.22 (s, 2H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 168.9, 168.8, 163.5, 163.4, 163.1, 162.6, 161.9, 144.4, 143.9, 134.3, 134.0, 129.9, 129.5, 127.7, 127.1, 126.9, 126.7, 125.8, 125.6, 100.9, 100.0, 99.2, 95.7, 95.1, 77.1, 53.9, 53.8, 37.9, 35.3, 33.6, 32.8, 20.0, 19.9 ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{17}H_{16}ClO_6$): calcd m/z 351.0630, found: 351.0626; IR (neat) $\tilde{\nu}$/cm^{-1} = 3266, 2986, 2920, 2847, 1687, 1574, 1522, 1444, 1222, 1137, 1036, 1022, 832, 802, 781; m.p.: 92 – 94 °C.

(*R*)-Methyl 4-(3-bromophenyl)-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxobutanoate (**5g**): Purified by flash chromatography using petroleum ether with EtOAc to afford a colorless oil, 39.9 mg, 81% yield, exists in an equilibrium with cyclic hemiketal **5g'**; $[\alpha]_D^{20}$ = +25.3 (c 0.44, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *t*r(major)

= 11.25 min, *t*r(minor) = 22.82 min, 84% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 – 7.28 (m, 2H), 7.20 – 7.10 (m, 2H), 5.87 (s, 0.3H), 5.82 (s, 0.7H), 4.15 – 3.96 (m, 2H), 3.87 (s, 1H), 3.83 (s, 2H), 2.66 (dd, *J* = 14.3, 7.5 Hz, 0.3H), 2.42 – 2.29 (m, 1.7H), 2.26 (s, 1H), 2.22 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 168.7, 163.4, 163.2, 162.4, 161.8, 144.7, 144.2, 130.6, 130.2, 129.9, 129.8, 129.7, 129.6, 126.2, 126.1, 122.6, 122.3, 100.9, 99.9, 99.2, 95.6, 95.0, 53.9, 53.8, 37.9, 35.2, 33.6, 32.7, 19.9, 19.9 ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{17}H_{16}BrO_6$): calcd m/z 395.0125, found: 395.0127; IR (neat) $\tilde{\nu}$/cm^{-1} = 3248, 2952, 2924, 2847, 1679, 1578, 1440, 1230, 1190, 1137, 781, 692.

(*R*)-Methyl 4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-4-(*m*-tolyl)butanoate (**5h**): Purified by flash chromatography using petroleum ether with EtOAc to afford a white solid, 39.2 mg, 95% yield, exists in an equilibrium with cyclic hemiketal **5h'**; $[\alpha]_D^{20}$ = +43.6 (c 1.60, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *t*r(major) = 9.15 min, *t*r(minor) = 19.20 min, 90% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 – 7.11 (m, 1H), 7.00 (t, *J* = 7.0 Hz, 3H), 5.88 (s, 0.3H), 5.82 (s, 0.7H), 4.86 (s, 0.7H), 4.48 (s, 0.3H), 4.16 – 4.07 (m, 0.3H), 4.00 (t, *J* = 8.9 Hz, 0.7H), 3.85 (s, 1H), 3.77 (s, 2H), 2.65 (dd, *J* = 14.3, 7.3 Hz, 0.3H), 2.42 (dd, *J* = 14.3, 3.7 Hz, 0.3H), 2.31 (t, *J* = 4.2 Hz, 4.4H), 2.25 (s, 1H), 2.21 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 169.0, 168.9, 163.5, 163.1, 162.8, 162.6, 161.5, 161.4, 142.1, 141.4, 138.0, 138.0, 128.4, 128.3, 128.0, 127.8, 127.6, 127.5, 124.2, 124.1, 101.6, 100.0, 99.9, 95.9, 95.2, 53.8, 53.6, 38.2, 35.9, 33.7, 32.9, 21.5, 19.9, 19.8 ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{18}H_{19}O_6$): calcd m/z 331.1176, found: 331.1176; IR (neat) $\tilde{\nu}$/cm^{-1} = 3292, 2956, 2920, 2847, 1687, 1578, 1444, 1400, 1181, 1137, 1040, 1008, 987, 777, 701; m.p.: 105 – 107 °C.

(*R*)-Methyl 4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-4-(3-methoxyphenyl)-2-oxobutanoate (**5i**): Purified by flash chromatography using petroleum ether with EtOAc to afford a colorless oil 39.8 mg, 92% yield, exists in an equilibrium with cyclic hemiketal **5i'**; $[\alpha]_D^{20}$ = +32.2 (c 0.466, in $CHCl_3$); HPLC (Chiralpak ID, hexane/*i*-PrOH = 70/30, flow rate = 2.0 mL/min, λ = 254 nm; Retention time: *t*r(major) = 9.74 min, *t*r(minor) = 16.62 min, 80% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 – 7.18 (m, 1H),

6.87 – 6.72 (m, 3H), 5.87 (s, 0.3H), 5.80 (s, 0.7H), 4.70 (s, 0.7H), 4.40 (s, 0.3H), 4.17 – 3.94 (m, 1H), 3.87 (s, 1H), 3.81 (s, 2H), 3.77 (d, *J* = 5.1 Hz, 3H), 2.66 (dd, *J* = 14.3, 7.4 Hz, 0.3H), 2.44 (dd, *J* = 14.3, 3.3 Hz, 0.3H), 2.37 – 2.30 (m, 1.4H), 2.25 (s, 1H), 2.21 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): *δ* = 169.0, 168.9, 163.4, 163.1, 162.7, 162.5, 161.5, 159.7, 159.6, 144.0, 143.2, 129.6, 129.4, 119.7, 119.5, 113.8, 113.2, 111.7, 111.5,101.6, 99.9, 99.7, 95.8, 95.1, 55.2, 53.8, 53.8, 38.1, 35.6, 33.8, 32.9,19.9, 19.9 ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{18}H_{19}O_7$): calcd m/z 347.1125, found: 347.1130; IR (neat) $\tilde{\nu}$/cm^{-1} = 3252, 2956, 2920, 2839, 1683, 1578, 1440, 1226, 1186, 1137, 1036, 777, 696.

(*S*)-Methyl 4-(2-chlorophenyl)-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxobutanoate (**5**j): Purified by flash chromatography using petroleum ether with EtOAc to afford a colorless oil, 29.8 mg, 68% yield, exists in an equilibrium with cyclic hemiketal **5j'**; $[\alpha]_D^{20}$ = +44.4 (c 1.04, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, *λ* = 254 nm; Retention time: *t*r(major) = 11.29 min, *t*r(minor) = 19.68 min, 60% *ee*); ^1H NMR (400 MHz, $CDCl_3$): *δ* = 7.35 (d, *J* = 7.2 Hz, 1H), 7.20 – 7.08 (m, 3H), 5.88 (s, 0.5H), 5.83 (s,0.5H), 4.58 (s, 0.5H), 4.47 (d, *J* = 7.5 Hz, 0.5H), 4.12 (q, *J* = 7.1 Hz, 0.5H), 3.89 (s, 1.5H), 3.81 (s, 2H), 2.64 (dd, *J* = 14.5, 7.6 Hz, 0.5H), 2.56 – 2.41 (m, 1H), 2.26 (s, 1.5H), 2.22 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): *δ* = 169.1, 168.8, 163.4, 163.1, 162.2, 161.7 161.6, 138.4, 133.3, 129.6, 129.2, 127.9, 127.8, 127.0, 126.2, 100.0, 99.9, 99.3, 95.7, 95.2, 53.9, 53.8, 32.6, 30.4, 19.9, 19.8 ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{17}H_{16}ClO_6$): calcd m/z 351.0630, found: 351.0634; IR (neat) $\tilde{\nu}$/cm^{-1} = 3276, 2956, 2924, 2851, 1683, 1578, 1440, 1230, 1190, 1141, 1032, 943, 814, 757, 692.

(*S*)-Methyl 4-(2-bromophenyl)-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxobutanoate (**5k**): Purified by flash chromatography using petroleum ether with EtOAc to afford a white solid, 33.4 mg, 68% yield, exists in an equilibrium with cyclic hemiketal **5k'**; HPLC (Chiralpak ID, hexane/*i*-PrOH = 70/30, flow rate = 2.0 mL/min, *λ* = 254 nm; Retention time: *t*r(major) = 7.39 min, *t*r(minor) = 6.55 min, 72% *ee*); $[\alpha]_D^{20}$ = +59.7 (c 0.03, in $CHCl_3$);^1H NMR (400 MHz, $CDCl_3$): *δ* = 7.55 (d, *J* = 8.9 Hz, 1H), 7.24 – 7.18 (m, 0.5H), 7.18 – 7.11 (m, 1H), 7.10 – 7.03 (m, 1.5H), 5.85 (d, *J* = 21.2 Hz, 1H),

4.67 (s, 1H), 4.58 (s, 0.5H), 3.86 (d, *J* = 27.7 Hz, 3H), 2.64 (dd, *J* = 14.4, 7.6 Hz, 0.5H), 2.56 – 2.45 (m, 1H), 2.24 (d, *J* = 16.3 Hz, 3H), 2.20 – 2.11 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 169.14, 168.82, 163.46, 163.19, 162.33, 161.73, 161.67, 140.97, 139.95, 133.04, 132.97, 129.98, 129.42, 128.30, 128.20, 127.75, 127.29, 126.90, 124.20, 124.01, 101.06, 100.05, 99.92, 99.52, 95.80, 95.28, 54.02, 53.80, 32.88, 29.72, 29.34, 27.23, 22.71, 19.92. ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{17}H_{16}BrO_6$): calcd m/z 395.0125, found: 395.0126; IR (neat) $\tilde{\nu}$/cm^{-1} = 3239, 2962, 2935, 2849, 1680, 1578, 1440, 1232, 1192, 1139, 782, 692; m.p.: 117 – 119 °C.

(*R*)-Methyl 4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-4-(naphthalen-2-yl)-2-oxobutanoate (**5l**): Purified by flash chromatography using petroleum ether with EtOAc to afford a yellow solid, 36.6 mg, 93% yield, exists in an equilibrium with cyclic hemiketal **5l'**; $[\alpha]_D^{20}$ = +17.6 (c 0.828, in $CHCl_3$); HPLC (Chiralpak ID, hexane/*i*-PrOH = 70/30, flow rate = 2.0 mL/min, λ = 254 nm; Retention time: *tr*(major) = 8.75 min, *tr*(minor) = 14.83 min, 80% *ee*); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 – 7.69 (m, 3H), 7.63 (s, 0.7H), 7.62 (s, 0.3H), 7.41 (m, 2H), 7.34 (dd, *J* = 8.5, 1.8 Hz, 0.3H), 7.29 (dd, *J* = 8.5, 1.8 Hz, 0.7H), 5.90 (s, 0.3H), 5.83 (s, 0.7H), 4.98 (s, 0.7H), 4.57 (s, 0.3H), 4.22 – 4.08 (m, 1H), 3.83 (s, 1H), 3.67 (s, 2H), 2.70 (dd, *J* = 14.3, 7.4 Hz, 0.3H), 2.50 (dd, *J* = 14.3, 3.7 Hz, 0.3H), 2.43 – 2.30 (m, 1.4H), 2.26 (s, 1H), 2.20 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 168.9, 168.8, 163.6, 163.3, 163.1, 162.7, 161.6, 139.5, 139.1, 133.5, 133.4, 132.5, 132.4, 128.3, 128.1, 127.8, 127.7, 127.6, 125.9, 125.7, 125.4, 125.4, 125.3, 101.3, 100.0, 99.8, 95.9, 95.3, 53.8, 53.6, 38.0, 35.7, 33.9, 33.2, 19.9, 19.8 ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{21}H_{19}O_6$): calcd m/z 367.1176, found: 367.1174; IR (neat) $\tilde{\nu}$/cm^{-1} = 3280, 2952, 2924, 2851, 1687, 1574, 1444, 1396, 1226, 1181, 1137, 1040, 959, 822, 745; m.p.: 131 – 133 °C.

(*S*)-Methyl 4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-4-(thiophen-2-yl)-butanoate (**5m**): Purified by flash chromatography using petroleum ether with EtOAc to afford a colorless oil, 37.8 mg, 94% yield, exists in an equilibrium with cyclic hemiketal **5m'**; $[\alpha]_D^{20}$ = +78.5 (c 2.0, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *tr*(major) = 11.36 min, *tr*(minor) = 14.94 min, 78% *ee*); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.17 –

7.12 (m, 1H), 6.93 – 6.85 (m, 2H), 5.86 (s, 0.3H), 5.81 (s, 0.7H), 4.95 (s, 0.7H), 4.56 (s, 0.3H), 4.43 (dd, *J* = 6.7, 2.7 Hz, 0.3H), 4.37 (dd, *J* = 10.0, 6.7 Hz, 0.7H), 4.15 – 4.09 (m, 0.3H), 3.88 (s, 1H), 3.75 (s, 1.7H), 2.66 (dd, *J* = 14.4, 6.9 Hz, 0.3H), 2.57 (dd, *J* = 14.4, 2.9 Hz, 0.3H), 2.53 – 2.36 (m, 1.4H), 2.25 (s, 1H), 2.21 (s, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 168.6, 162.6, 162.5, 161.9, 161.8, 145.4, 145.3, 126.5, 125.0, 124.6, 123.9, 123.4, 101.3, 99.9, 95.7, 95.2, 53.8, 53.7, 38.5, 35.6, 29.4, 28.4, 19.9, 19.8 ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{15}H_{15}O_6S$): calcd m/z 323.0584, found: 323.0580; IR (neat) $\tilde{\nu}$/cm^{-1} = 3260, 2952, 2920, 2847, 1683, 1574, 1440, 1404, 1185, 1137, 1028, 801, 785, 696.

(*R*)-Ethyl 4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-4-phenylbutanoate[8] (**5n**): Purified by flash chromatography using petroleum ether with EtOAc to afford a white solid, 38.7 mg, 94% yield, exists in an equilibrium with cyclic hemiketal **5n'**; m.p. = 57−60 °C; $[\alpha]_D^{20}$ = +34.1 (c 1.0, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *t*r(major) = 8.61 min, *t*r(minor) = 17.30 min, 81% *ee*); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32 – 7.26 (m, 2H), 7.24 – 7.18 (m, 3H), 5.88 (s, 0.3H), 5.82 (s, 0.7H), 4.90 (s, 0.7H), 4.55 (s, 0.3H), 4.34 – 4.17 (m, 2.3H), 4.06-4.00 (m, 0.7H), 2.67 (dd, *J* = 14.3, 7.4 Hz, 0.3H), 2.41 (dd, *J* = 14.3, 3.5 Hz, 0.3H), 2.35 – 2.28 (m, 1.4H), 2.25 (s, 1H), 2.20 (s, 2H), 1.32 (t, *J* = 7.1 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 2H) ppm. HRMS(EI): calcd for $C_{18}H_{19}O_6$ $[M+H]^+$: 331.1176, found 331.1179; IR (neat) $\tilde{\nu}$/cm^{-1} = 3284, 2920,2852, 1683, 1574, 1449, 1396, 1226, 1190, 1141, 1040, 1004, 757, 696; m.p.: 95 – 97 °C.

(*R*)-Isopropyl 4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-4-phenylbutanoate (**5o**): Purified by flash chromatography using petroleum ether with EtOAc to afford a colorless oil, 37.0 mg, 86% yield, exists in an equilibrium with cyclic hemiketal **5o'**; $[\alpha]_D^{20}$ = +24 (c 0.274, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *t*r(major) = 6.97 min, *t*r(minor) = 14.86 min, 80% *ee*); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.16 (m, 5H), 5.88 (s, 0.3H), 5.81 (s, 0.7H), 4.68 (s, 0.7H), 4.41 (s, 0.3H), 4.24 – 3.98 (m, 1H), 2.67 (dd, *J* = 14.3, 7.5 Hz, 0.3H), 2.40 (dd, *J* = 14.3, 3.2 Hz, 0.3H), 2.35 – 2.28 (m, 1.4H), 2.25 (s, 1H), 2.20 (s, 2H), 1.30 (dt, *J* = 11.0, 5.5 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$):

δ = 168.1, 168.0, 163.5, 163.2, 162.9, 162.4, 161.4, 142.5, 141.7, 128.6, 128.3, 127.3, 127.1, 126.7, 126.6, 101.8, 100.0, 99.9, 99.8, 95.6, 94.9, 71.8, 71.7, 38.0, 35.4, 33.9, 33.0, 21.6, 21.5, 21.4, 19.9, 19.8 ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{19}H_{21}O_6$): calcd m/z 345.1333, found: 345.1338; IR (neat) $\tilde{\nu}$/cm^{-1} = 3171, 2977, 1756, 1675, 1638, 1574, 1444, 1287, 1230, 1149, 1105, 1050, 1012, 838, 769, 701.

(*R*)-*tert*-Butyl 4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-4-phenylbutanoate (**5p**): Purified by flash chromatography using petroleum ether with EtOAc to afford a colorless oil, 40.7 mg, 91% yield, exists in an equilibrium with cyclic hemiketal **5p'**; $[\alpha]_D^{20}$ = +4.6 (c 0.828, in $CHCl_3$); HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; Retention time: *t*r(major) = 7.73 min, *t*r(minor) = 15.63 min, 76% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.27 (m, 2H), 7.22 (dd, *J* = 16.4, 6.3 Hz, 3H), 5.88 (s, 0.3H), 5.82 (s, 0.7H), 4.67 (s, 0.7H), 4.45 (s, 0.3H), 4.25-3.87 (m, 1H), 2.64 (d, *J* = 6.8 Hz, 1H), 2.43 – 2.28 (m, 1H), 2.25 (s, 1H), 2.20 (s, 2H), 1.51 (s, 9H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 167.6, 167.5, 163.4, 163.3, 163.0, 162.4, 161.3, 142.7, 141.8, 128.6, 128.4, 128.2, 127.3, 127.0, 126.5, 126.4, 101.8, 100.1, 100.0, 99.9, 95.8, 95.1, 85.0, 84.8, 38.2, 35.6, 34.0, 33.3, 27.7, 19.9, 19.8 ppm; HRMS (ESI) exact mass for $[M+H]^+$ ($C_{20}H_{23}O_6$): calcd m/z 359.1489, found: 359.1486; IR (neat) $\tilde{\nu}$/cm^{-1} = 3236, 2973, 2924, 2847, 1748, 1679, 1642, 1574, 1444, 1400, 1295, 1141, 1056, 951, 842, 773, 696.

Supporting Information

Chiral HPLC chromatograms data and copies of NMR spectra for the asymmetric conjugate adducts. This material is available free of charge *via* the Internet at http://pubs.acs.org.

Notes

The authors declare no competing financial interest.

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