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PAPER

Enantioselective organocatalytic Michael-hemiketalization catalyzed by a *trans*-bifunctional indane thiourea catalyst†

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An efficient, convenient and enantioselective Michael-hemiketalization reaction has been developed for the synthesis of naphthoquinones. In this work, a novel *trans*-bifunctional indane thiourea catalyst has been reported to promote this process to afford high yields (up to 99%) and high to excellent enantiomeric excesses (90–98% ee).

Introduction

Naphthoquinones occur in various families of plants, fungi, bacteria and insects linking the electron transport chains in the metabolic pathway with the oxidative processes.[1] Many of these naturally occurring naphthoquinones and their synthetic analogues are important precursors for the synthesis of natural products and pharmaceuticals.[2] Therefore, naphthoquinones have been broadly explored for their anti-inflammatory,[3] antifungal,[4] trypanocida,[5] molluscicidal,[6] leishmanicidal[7] and antitumor biological activities.[4,8]

Lapachol **1** (Fig. 1) is a natural naphthoquinone that occurs naturally in the grain of many wooden trees and is widely applied in American folk medicine.[9] It is because lapachol **1** and its derivatives (for example, antitumor agent **3** and kalafungin **4**, Fig. 1) were found to exhibit a wide spectrum of biological activities, such as anticancer, antimicrobial and anti-inflammatory functions.[10] Recent progress has shown that the biological activities of lapachol and derivatives are associated with their promising structure and ability to induce oxidative stress at the level of the enzyme P450 reductase.[11] In this regard, an exploration of potential anti-malarial agents was carried out. Gratifyingly, this discovery resulted in a highly lipophilic drug, Atovaquone **2** that closely resembles the structure of an ubiquinone.[12] Currently, a combination of atovaquone and makarone is being used to treat malaria, and also is useful for the treatment of illnesses caused by *Pneumocystis carinii*.[13]

In view of the significance of the framework, efficient syntheses of naphthoquinones are of great interest. Although asymmetric organocatalysis as a powerful tool in particular has proven itself to be a valuable instrument in the preparation of enantiomerically enriched compounds,[14] the examples that generated optical

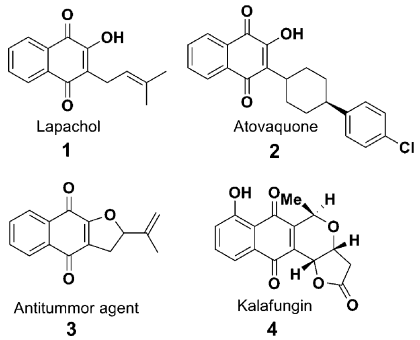
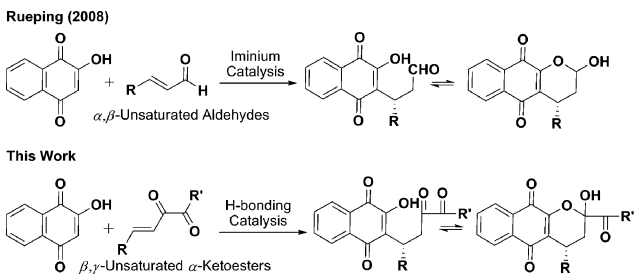


Fig. 1 Examples of naphthoquinones as pharmaceutical drugs.

pure naphthoquinone *via* an organocatalytic asymmetric manner are still extremely rare. In 2008, Rueping *et al.* first reported the example of diaryl-prolinol ether organocatalyst promoted asymmetric Michael reaction of 2-hydroxy-1,4-naphthoquinone and α-unsaturated aldehydes (Scheme 1).[15] In brief, this strategy employed iminium ion catalysis process to promote the key C–C bond-forming. Recently, H-bonding mediated catalysis for C–C bond formation has been discovered as a new powerful tool and mild synthetic method for the efficient construction of molecular architectures.[16] Especially, there was a remarkable development and application on chiral bifunctional thiourea catalysis.[16] The utilization of inexpensive and readily synthesized chiral thiourea catalysts attracted considerable interest and proved to be effective



Scheme 1 Organocatalyst promoted Michael addition of 2-hydroxy-1,4-naphthoquinone to unsaturated system.

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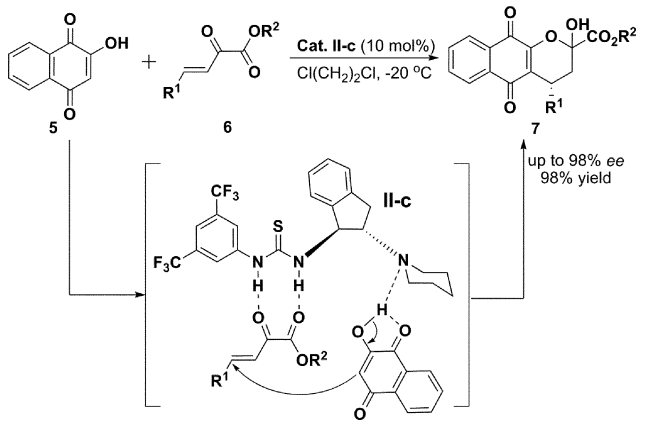
in several asymmetric transformations. Herein, we wish to report a novel strategy for the preparation of chiral naphthoquinones through H-bonding mediated enantioselective Michael addition reaction and a novel chiral *trans*-indane thiouea catalyst (Scheme 2). Surprisingly this catalyst has a *trans*-configuration, in contrast to the successful indane thiourea catalysts developed by our group.[17] Moreover, this strategy allowed a quick construction of diversely functionalized naphthoquinones under mild reaction conditions and achieved high to excellent enantioselectivities (90–98% ee) and excellent yields (94–99%).



Scheme 2 Strategy for enantioselective synthesis of naphthoquinones.

Results and discussion

Recently, we uncovered an interesting indane thiourea catalytic system which sufficiently promoted several asymmetric transformations.[17] Having established the capacity of chiral indane thioureas to catalyze asymmetric cascade processes by using varied nucleophiles and electrophiles for new bond formation, we sought to utilize this indane catalytic system for the construction of novel and useful complexes.

To probe the feasibility of the proposed reaction, 2-hydroxy-1,4-naphthoquinone **5** was treated with β–unsaturated α–keto ester **6a** in the presence of catalyst **I** (Fig. 2), developed by Soós[18] and Dixon[19] and Connon[20] groups respectively (Table 1). As shown in Table 1, catalyst **I** exhibited an excellent catalytic

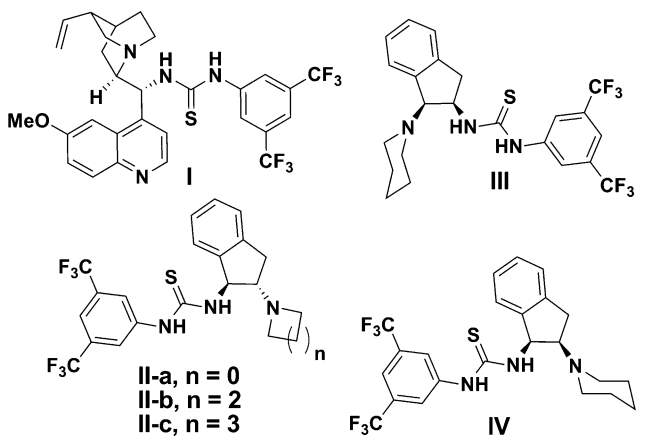
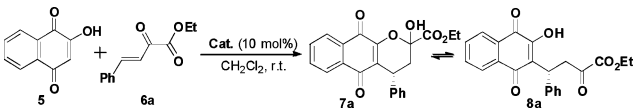


Fig. 2 Evaluated chiral thiourea catalysts.

Table 1 Evaluation of chiral thiourea catalysts[a]



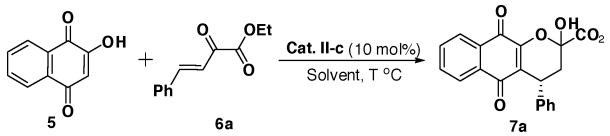
Entry	Cat.	t (h)	Yield (%)[b]	ee (%)[c]
11	**I**	2	97	74
22	**II-a**	2	96	55
33	**II-b**	2	96	64
44	**II-c**	**2**	**98**	**87**
55	**III**	2	97	71
66	**IV**	2	96	9

[a] Reaction was conducted on 0.1 mmol scale in CH_2Cl_2 (0.5 mL) at r.t. for 2 h, and the ratio of **6a/5** is 1 : 1.1. [b] Yield of isolated product aftercolumn chromatography. [c] Enantiomeric excess (ee) was determined by HPLC.

activity to offer a 97% yield in 2 h. However, only a moderate enantioselectivity (74% ee) was achieved. Therefore, development of a novel and active chiral catalyst which can promote a reaction with a result of both high efficiency and excellent stereo-control is our current main focus. In planning our catalyst investigation, we decided to firstly examine the indane bifunctional amine-thiourea catalytic system developed and reported by our group. This kind of system has demonstrated some unique aspects, such as higher activity, excellent stereo-control, and flexible skeleton. Based on our previous experience, catalyst **III** and **IV** (Fig. 2) both exhibited high stereo-control in Michael reaction related cascade processes. We assumed that they might also promote this reaction and generate some surprising results. Unfortunately, the promising catalyst **III** just provided a very general result (Table 1, 97%, 71% ee). Catalyst **IV**, the similar analogue of catalyst **III** with a switch of amine and thiourea functional groups, totally lost the stereo-control for this reaction (Table 1, 96%, 9% ee). Meanwhile, our previous experience in using indane thiourea catalyst told us that the dihedral angle is one of the critical factors for stereochemistry control. In view of the structures of catalyst **III** and **IV**, we found that amine and thiourea groups are in the *syn* position. We then suspected if the *syn* position of two functional groups had an influence on stereoselectivity improvement. Consequently, catalysts **II** (Fig. 2) were synthesized evaluated. In contrast to catalyst **IV**′s structure, catalysts **II** just have a chiral inversion on the amine part while maintaining all the other features. Gratifyingly, catalyst **II-c** demonstrated a superior stereo-control in enantioselectivity (Table 1, 98%, 87% ee). These results fully proved our catalyst design is on the right track. Obviously, the ring size played an important role in improving enantioselectivity. The most bulky six member ring based amine is the most favored in comparison with three and five member rings.

For further optimization, solvent, as well as reaction temperature, was examined (Table 2). These experiments revealed that the best results with regards to reactivity and enantioselectivity were obtained with $Cl(CH_2)_2Cl$ at −20 °C (Table 2, entry 6). The process was completed within 24 h and afforded naphthoquinone derivative **7a** (compound **7a** was coexisted with anomer **8a** in $CDCl_3$, see ESI† for details) in 97% yield and with an excellent enantioselectivity (96% ee). In varying reaction temperature, the enantioselectivity can be dramatically enhanced by an appropriate reduction on temperature. Most importantly, there is not any yield

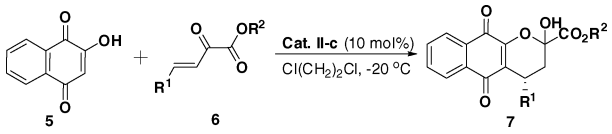
Table 2 Optimization of reaction conditions[a]



Entry	Solvent	*T*/°C	t (h)	Yield (%)[b]	ee (%)[c]
1	DMSO	r.t.	2	92	45
2	CH_2Cl_2	r.t.	2	98	87
3	$CHCl_3$	r.t.	2	97	80
4	$Cl(CH_2)_2Cl$	r.t.	2	98	89
5	$Cl(CH_2)_2Cl$	0 °C	5	98	94
6	**$Cl(CH_2)_2Cl$**	**–20 °C**	**24**	**97**	**96**
7	Et_2O	r.t.	2	96	87
8	Anisole	r.t.	2	96	83
9	Toluene	r.t.	2	96	82
10	Xylene	r.t.	2	97	83
11	$PhCF_3$	r.t.	2	96	85

[a] Unless specified, see the Experimental section for reaction conditions. [b] Yield of isolated product. [c] Enantiomeric excess (ee) was determined by HPLC analysis.

Table 3 Substrate scope[a]



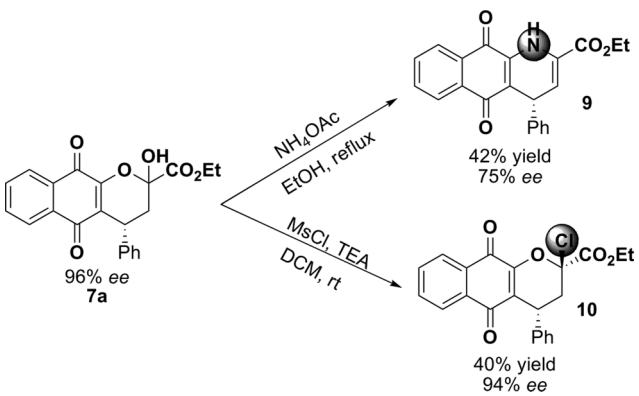
Entry	R^1	R^2	t (h)	Yield (%)[b]	ee (%)[c]
1	Ph (**7a**)	Et	24	97	96
2	4-FC_6H_4 (**7b**)	Et	24	99	96
3	4-ClC_6H_4 (**7c**)	Et	24	99	97
4	3-ClC_6H_4 (**7d**)	Et	24	98	97
5	2-ClC_6H_4 (**7e**)	Et	36	95	95
6	2-BrC_6H_4 (**7f**)	Et	36	95	94
7	4-$MeOC_6H_4$ (**7g**)	Et	36	98	90
8	4-$MeSC_6H_4$ (**7h**)	Et	36	98	93
9	4-$AllyloxyC_6H_4$ (**7i**)	Et	36	97	90
10	4-$BnOC_6H_4$ (**7j**)	Et	36	97	90
11	3-$PhOC_6H_4$ (**7k**)	Et	36	96	96
12	4-*i*PrC_6H_4 (**7l**)	Et	36	97	94
13	1-Naphthyl (**7m**)	Et	36	95	91
14	2-Thiophene (**7n**)	Et	24	96	95
15	Et (**7o**)	Et	36	94	98
16	Ph (**7p**)	Me	24	97	96

[a] Unless specified, see the Experimental section for reaction conditions. [b] Yield of isolated product. [c] Enantiomeric excess (ee) was determined by HPLC analysis.

loss penalty in the process (Table 2, entries 4–6, 2 to 24 h, 97% to 98% yield, 89% to 96% ee). Furthermore, less polar solvents are fundamental for obtaining relatively higher enantioselectivities at room temperature (Table 2, entries 2–4 and 7–11, 80–89% ee). For high polar solvent, a relatively low enantioselectivity was observed by potentially destroying the H-bonding interaction (Table 2, entry 1, 45% ee).

Under the optimized reaction conditions, the generality of our process was tested by using various β–unsaturated α–keto esters **6** (Table 3). Aromatic β–unsaturated α–keto esters having both neutral (Table 3, entry 1), electron-withdrawing (Table 3, entries 2–6) and electron-donating substituents (Table 3, entries 7–12) can effectively be applied to this transformation; the substitution pattern of the arene had limited influence on the enantioselectivity of the reaction (Table 3, entries 2–13, 90–97% ee). In addition, it was possible to use both heteroaromatic (Table 3, entry 14) and aliphatic β–unsaturated α–keto ester (Table 3, entry 15) in this reaction. Meanwhile, the ester modification (Me replaced Et) also had no obvious effect on the enantioselectivity (Table 3, entry 16). The ability permitted the assembly of a diverse of functionalized naphthoquinone complexes in excellent yields (Table 3, 94–99%) and with high to excellent enantioselectivities (Table 3, 90–98% ee). The absolute configuration of the product **7f** was determined by single-crystal X-ray analysis (See ESI†).

Furthermore, the highly enantiomerically enriched naphthoquinone complexes obtained by this method can be easily converted into dihydropyridine naphthoquinones. As an example, **7a** was converted to dihydropyridine naphthoquinone **9** in 42% yield and 75% ee by a simple one-step treatment (Scheme 3). Surprisingly, there is a reduction of the ee value within this conversion process. In addition, naphthoquinone complex **7a** also can react with methanesulfonyl chloride to afford complex **10** under the condition of triethyl amine (Scheme 3, 40% and 94% ee). In this case, a halogen, chloride, was introduced to replace hydroxyl group. More importantly, ee value was remained in this process.



Scheme 3 Structure elaboration of **7a**.

Conclusions

In summary, we have developed an efficient and convenient enantioselective Michael-hemiketalization reaction for the synthesis of naphthoquinone complexes with excellent yields (94–99%) and high to excellent enantioselectivities (90–98% *ee*). This protocol proceeded through a new and simple *trans*–amine–thiourea indane catalyst promoted conjugated addition strategy. We hope that the catalytic system and strategy demonstrated here could be applied to other asymmetric transformations to efficiently assemble chiral materials with complex structures. Further elaboration of the products to other types of biologically active compounds and the potential application of the catalytic system are now ongoing in our group.

Experimental

General methods

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 (300 MHz) or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL-T mass spectrometer in EI mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T mass spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with $KMnO_4$ solution, or ninhydrin followed by heating using a heat gun. Flash chromatography separations were performed on Merck 60 (0.040–0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral phase HPLC analysis. Optical rotations were recorded on Jasco DIP-1000 polarimeter.

General procedure

To a solution of 2-hydroxynaphthalene-1,4-dione **5** (17.5 mg, 0.1 mmol) in 0.45 mL of DCE was added (*E*)-Ethyl 2-oxo-4-phenylbut-3-enoate **6a** (23 mg, 0.11 mmol) at –20 °C, followed by adding of 50 μL of pre-cooled catalyst **II-c** solution (4.2 mg in 50 μL of DCE, 0.01 mmol). The mixture was stirred at –20 °C for 24 h. The crude product was purified by column chromatography on silica gel, eluted by hexane–EtOAc = 2 : 1 to afford 36.7 mg (97% yield) of the desired product **7a** as yellow solid.

(4*R*)-Ethyl 2-hydroxy-5,10-dioxo-4-phenyl-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7a). (Table 3, entry 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15–8.08 (m, 1H), 8.03–8.0 (m, 0.44 H), 7.90 (dt, J = 6.6, 3.0 Hz, 0.48 H), 7.75–7.63 (m, 2.3H), 7.47 (d, J = 7.3 Hz, 0.6 H), 7.33–7.18 (m, 4.4 H), 5.01–4.95 (m, 0.74 H), 4.72 (s, 0.16 H), 4.45 (dd, J = 7.6, 3.5 Hz, 0.19 H), 4.38–4.25 (m, 2.5 H), 4.15 (dd, J = 19.2, 9.8 Hz, 0.32 H), 3.67 (dd, J = 19.2, 5.7 Hz, 0.30 H), 2.74 (dd, J = 14.3, 7.7 Hz, 0.19 H), 2.46–2.36 (m, 1.27 H), 1.32 (dd, J = 9.0, 5.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.66, 183.97, 183.24, 183.12, 181.50, 179.30, 178.98, 168.19, 160.68, 153.56, 153.06, 152.57, 142.84, 141.94, 140.99, 135.11, 134.22, 134.15, 133.34, 133.17, 132.96, 132.76, 132.07, 131.89, 130.94, 130.83, 129.07, 128.76, 128.57, 128.33, 128.16, 127.57, 127.22, 127.07, 126.93, 126.68, 126.58, 126.49, 126.43, 126.39, 126.21, 126.05, 125.10, 123.73, 122.98, 95.96, 95.23, 63.54, 63.44, 62.48, 42.24, 37.83, 35.74, 35.28, 34.74, 33.54, 13.93, 13.89; HRMS (ESI) calcd for $C_{22}H_{18}NaO_6$ (M + Na$^+$) 401.1001, found 401.0999; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 15.37 min, t_{minor} = 20.34 min, *ee* = 96%; $[\alpha]_D^{25}$ = +26.7 (c = 1.13 in $CHCl_3$).

(4*R*)-Ethyl 4-(4-fluorophenyl)-2-hydroxy-5,10-dioxo-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene -2-carboxylate (7b). (Table 3, entry 2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 94.9 Hz, 2H), 7.69 (d, J = 22.1 Hz, 2H), 7.44 (bs, 0.67 H), 7.24 (d, J = 23.6 Hz, 1.21 H), 6.98 (bs, 2H), 4.92 (d, J = 49.2 Hz, 0.73 H), 4.69 (bs, 0.19 H), 4.32 (t, J = 25.7 Hz, 2.63 H), 4.11–4.07 (m, 0.36 H), 3.67 (d, J = 14.8 Hz, 0.33 H), 2.72 (bs, 0.19 H), 2.38 (bs, 1 H), 1.34 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.15, 183.13, 181.41, 179.21, 168.11, 162.52, 160.75, 160.70, 160.57, 153.06, 138.47, 135.18, 134.24, 133.25, 132.07, 130.85, 129.77, 129.18, 128.74, 126.39, 126.25, 115.74, 115.57, 115.27, 95.21, 63.62, 62.53, 42.31, 37.82, 35.07, 34.09, 29.67, 13.93; HRMS (ESI) calcd for $C_{22}H_{17}FNaO_6$ (M + Na$^+$) 419.0907, found 419.0895; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 10.88 min, t_{minor} = 15.99 min, *ee* = 96%; $[\alpha]_D^{25}$ = +27.7 (c = 1.37 in $CHCl_3$).

(4*R*)-Ethyl 4-(4-chlorophenyl)-2-hydroxy-5,10-dioxo-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7c). (Table 3, entry 3). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15–8.01 (m, 1.5 H), 7.92–7.90 (m, 0.48 H), 7.75–7.67 (m, 2 H), 7.40 (t, J = 8.2 Hz, 0.69 H), 7.24 (ddd, J = 29.3, 18.3, 8.0 Hz, 3.58 H), 4.86 (d, J = 109.7 Hz, 1 H), 4.40–4.24 (m, 2.74 H), 4.07 (dd, J = 19.5, 9.5 Hz, 0.32 H), 3.68 (dd, J = 18.9, 5.7 Hz, 0.31 H), 2.72 (dd, J = 14.0, 7.7 Hz, 0.22 H), 2.42–2.30 (m, 1.22 H), 1.34 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.37, 179.74, 153.11, 140.67, 134.58, 133.28, 132.49, 132.19, 130.37, 129.01, 128.77, 126.64, 126.30, 123.78, 63.31, 34.29, 13.92; HRMS (ESI) calcd for $C_{22}H_{17}ClNaO_6$ (M + Na$^+$) 435.0611, found 435.0598; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 10.77 min, t_{minor} = 15.66 min, *ee* = 97%; $[\alpha]_D^{25}$ = +18.7 (c = 1.37 in $CHCl_3$).

(4*R*)-Ethyl 4-(3-chlorophenyl)-2-hydroxy-5,10-dioxo-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7d). (Table 3, entry 3).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14–7.91 (m, 2 H), 7.70 (d, J = 23.3 Hz, 2 H), 7.40 (d, J = 51.7 Hz, 0.68 H), 7.22–7.14 (m, 3.22 H), 4.99 (d, J = 20.5 Hz, 0.77 H), 4.79 (s, 0.18 H), 4.40–4.23 (m, 2.69 H), 4.13–4.05 (m, 0.35 H), 3.67 (d, J = 14.5 Hz, 0.31H), 2.71 (d, J = 6.9 Hz, 0.19 H), 2.37 (dt, J = 25.9, 10.2 Hz, 1.16 H), 1.34 (t, J = 7.1 Hz, 3 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 192.28, 182.98, 179.11, 168.02, 153.24, 144.93, 135.19, 134.23, 133.29, 131.99, 130.84, 130.00, 128.28, 127.28, 127.13, 126.95, 126.43, 126.29, 125.61, 124.28, 95.19, 63.62, 62.55, 41.95, 37.60, 35.43, 35.41, 34.90, 34.56, 13.91; HRMS (ESI) calcd for $C_{22}H_{17}ClNaO_6$ (M + Na$^+$) 435.0611, found 435.0601; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 11.07 min, t_{minor} = 13.40 min, *ee* = 97%; $[\alpha]_D^{25}$ = +7.1 (c = 1.47 in $CHCl_3$).

(4*S*)-Ethyl 4-(2-chlorophenyl)-2-hydroxy-5,10-dioxo-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7e). (Table 3, entry 3).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11–7.92 (m, 2 H), 7.68 (s, 2 H), 7.40 (d, J = 6.0 Hz, 1 H), 7.13 (d, J = 32.8 Hz, 3 H), 4.94–4.74 (m, 2 H), 4.36–4.33 (m, 2 H), 2.69 (s, 0.35 H), 2.42 (d, J = 65.3 Hz, 1.39 H), 1.34 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.89, 179.14, 168.07, 154.00, 153.33, 140.21, 138.83, 134.23, 133.27, 131.89, 130.90, 129.90, 129.60, 127.96, 127.25, 126.44, 126.32, 124.75, 95.91, 95.31, 63.58, 35.11, 32.50, 30.86, 29.66, 13.92; HRMS (ESI) calcd for $C_{22}H_{17}ClNaO_6$

(M + Na^+) 435.0611, found 435.0611; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 13.36 min, t_{minor} = 16.31 min, *ee* = 95%; $[\alpha]_D^{25}$ = +29.6 (*c* = 1.33 in $CHCl_3$).

(4*S*)-Ethyl 4-(2-bromophenyl)-2-hydroxy-5,10-dioxo-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7f). (Table 3, entry 6).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 85.6, 26.6 Hz, 2 H), 7.70–7.58 (m, 3 H), 7.19–7.07 (m, 3 H), 4.87–4.72 (m, 2H), 4.34 (dd, *J* = 15.9, 7.4 Hz, 2 H), 2.55 (dt, *J* = 212.8, 59.1 Hz, 2 H), 1.34 (t, *J* = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.81, 179.10, 168.03, 154.00, 140.46, 134.19, 133.40, 133.26, 132.91, 131.95, 130.91, 129.72, 128.26, 128.18, 127.92, 126.97, 126.43, 126.30, 124.86, 123.79, 122.63, 95.96, 95.31, 63.61, 60.37, 33.46, 32.76, 21.00, 13.93; HRMS (ESI) calcd for $C_{22}H_{17}BrNaO_6$ (M + Na^+) 479.0106, found 479.0101; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 14.23 min, t_{minor} = 16.53 min, *ee* = 94%; $[\alpha]_D^{25}$ = +13.3 (*c* = 0.87 in $CHCl_3$).

(4*R*)-Ethyl 2-hydroxy-4-(4-methoxyphenyl)-5,10-dioxo-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7g). (Table 3, entry 7).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14–7.90 (m, 2 H), 7.68 (d, *J* = 24.9 Hz, 2 H), 7.39 (d, *J* = 7.6 Hz, 0.69 H), 7.16 (d, *J* = 7.9 Hz, 1.26 H), 6.85–6.82 (m, 2 H), 4.86 (d, *J* = 88.3 Hz, 0.85 H), 4.39–4.23 (m, 2.59 H), 4.09 (dd, *J* = 18.8, 9.3 Hz, 0.35 H), 3.76 (d, *J* = 10.7 Hz, 3 H), 3.65 (d, *J* = 19.2 Hz, 0.41 H), 2.69 (d, *J* = 7.3 Hz, 0.18 H), 2.39 (d, *J* = 7.9 Hz, 1 H), 1.33 (t, *J* = 6.9 Hz, 3 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 192.78, 184.03, 183.21, 181.56, 179.33, 168.21, 160.77, 158.47, 158.23, 152.89, 152.40, 135.05, 134.72, 134.10, 133.29, 133.11, 132.92, 132.80, 132.14, 130.85, 129.22, 128.61, 128.22, 127.03, 126.36, 126.17, 126.00, 125.32, 124.03, 123.27, 114.19, 113.95, 113.79, 96.02, 95.34, 63.45, 63.37, 62.42, 55.16, 42.44, 37.92, 35.37, 35.00, 33.92, 32.81, 13.91; HRMS (ESI) calcd for $C_{23}H_{20}NaO_7$ (M + Na^+) 431.1107, found 431.1101; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 23.49 min, t_{minor} = 44.30 min, *ee* = 90%; $[\alpha]_D^{25}$ = +58.7 (*c* = 1.37 in $CHCl_3$).

(4*R*)-Ethyl 2-hydroxy-4-(4-(methylthio)phenyl)-5,10-dioxo-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene -2-carboxylate (7h). (Table 3, entry 8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 74.2, 37.4 Hz, 2 H), 7.68 (d, *J* = 23.0 Hz, 2 H), 7.39–7.17 (m, 4 H), 5.04 (d, *J* = 83.9 Hz, 1 H), 4.38–4.09 (m, 3 H), 3.67 (d, *J* = 17.0 Hz, 0.27 H), 2.71 (bs, 0.19 H), 2.45–2.36 (m, 4 H), 1.32 (bs, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.11, 179.26, 168.09, 153.04, 139.68, 136.51, 134.19, 133.15, 130.79, 127.74, 127.05, 126.35, 126.17, 124.89, 95.26, 63.47, 42.07, 37.73, 35.14, 34.21, 15.85, 13.88; HRMS (ESI) calcd for $C_{23}H_{20}NaO_6S$ (M + Na^+) 447.0878, found 447.0873; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 19.14 min, t_{minor} = 31.89 min, *ee* = 93%; $[\alpha]_D^{25}$ = +52.9 (*c* = 1.43 in $CHCl_3$).

(4*R*)-Ethyl 4-(4-(allyloxy)phenyl)-2-hydroxy-5,10-dioxo-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7i). (Table 3, entry 9). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16–7.90 (m, 1.66 H), 7.92–7.91 (m, 0.42 H), 7.75–7.58 (m, 2.34 H), 7.38 (d, *J* = 8.5 Hz, 0.73 H), 7.16 (d, *J* = 8.2 Hz, 1 H), 6.87–6.82 (m, 2 H), 6.03 (dt, *J* = 24.3, 9.6 Hz, 1 H), 5.32 (ddd, *J* = 27.4, 24.3, 10.7 Hz, 2 H), 4.94 (dd, *J* = 9.6, 5.8 Hz, 0.29 H), 4.74 (s, 0.35 H), 4.45–4.22 (m, 4.56 H), 4.10 (dd, *J* = 19.1, 9.6 Hz, 0.34 H), 3.64 (dd, *J* = 19.2, 6.0 Hz, 0.35 H), 2.38 (d, *J* = 9.5 Hz, 1 H), 1.34 (t, *J* = 7.1 Hz, 3 H);^{13}C NMR (75 MHz, $CDCl_3$) δ 192.79, 184.06, 183.24, 181.60, 179.36, 168.27, 157.55, 157.35, 152.89, 152.35, 135.11, 134.91, 134.15, 133.36, 133.28, 133.17, 132.98, 132.16, 131.72, 130.87, 130.70, 129.25, 128.63, 128.24, 127.09, 126.40, 126.23, 126.06, 125.40, 124.06, 118.04, 117.62, 115.01, 114.79, 114.58, 114.45, 95.91, 95.25, 68.81, 63.60, 63.48, 62.47, 42.47, 37.89, 35.20, 35.03, 33.94, 32.69, 29.68, 13.95; HRMS (ESI) calcd for $C_{25}H_{22}NaO_7$ (M + Na^+) 457.1263, found 457.1251; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 20.60 min, t_{minor} = 39.69 min, *ee* = 90%; $[\alpha]_D^{25}$ = +53.9 (*c* = 1.5 in $CHCl_3$).

(4*R*)-Ethyl 4-(4-(benzyloxy)phenyl)-2-hydroxy-5,10-dioxo-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7j). (Table 3, entry 10).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15–7.90 (m, 2 H), 7.74–7.63 (m, 2.59 H), 7.43–7.28 (m, 6.20 H), 7.17–7.15 (m, 1.62 H), 6.93–6.88 (m, 2 H), 5.02–4.93 (m, 3 H), 4.41–4.23 (m, 2.76 H), 4.10 (dd, *J* = 19.1, 9.6 Hz, 0.35 H), 3.64 (dd, *J* = 19.2, 6.0 Hz, 0.32 H), 2.73–2.68 (m, 0.19 H), 2.43–2.37 (m, 1 H), 1.35–1.31(m, 3 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 192.78, 184.04, 183.22, 181.57, 179.32, 168.23, 160.77, 157.76, 157.56, 152.91, 152.39, 137.05, 135.07, 135.02, 134.19, 134.12, 133.35, 133.31, 133.14, 132.94, 132.83, 132.16, 130.87, 129.28, 129.12, 128.90, 128.66, 128.54, 128.52, 128.38, 128.27, 128.11, 127.92, 127.88, 127.48, 127.40, 127.24, 127.06, 126.49, 126.38, 126.20, 126.03, 125.32, 124.01, 115.09, 114.90, 114.67, 95.98, 95.31, 70.01, 63.51, 63.42, 62.43, 42.46, 37.91, 35.29, 35.04, 33.95, 32.78, 13.93, 13.91; HRMS (ESI) calcd for $C_{29}H_{24}NaO_7$ (M + Na^+) 507.1420, found 507.1414; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 24.43 min, t_{minor} = 41.02 min, *ee* = 90%; $[\alpha]_D^{25}$ = +42.2 (*c* = 1.53 in $CHCl_3$).

(4*R*)-Ethyl 2-hydroxy-5,10-dioxo-4-(3-phenoxyphenyl)-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7k). (Table 3, entry 11). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (ddd, *J* = 47.3, 11.5, 7.4 Hz, 2 H), 7.73–7.66 (m, 2 H), 7.31–7.18 (m, 3.55 H), 7.08–6.80 (m, 5.3 H), 4.96 (t, *J* = 64.9 Hz, 1 H), 4.41–4.07 (m, 2.7 H), 4.10 (dd, *J* = 18.8, 9.3 Hz, 0.28 H), 3.66 (dd, *J* = 19.2, 5.0 Hz, 0.27 H), 2.72 (dd, *J* = 13.9, 7.6 Hz, 0.19 H), 2.45–2.33 (m, 1.26 H), 1.33 (t, *J* = 7.1 Hz, 3 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 183.19, 179.16, 168.10, 157.01, 153.01, 144.89, 134.16, 133.15, 129.63, 126.22, 123.16, 118.75, 116.90, 95.24, 63.45, 42.08, 37.67, 34.63, 29.64, 13.90; HRMS (ESI) calcd for $C_{28}H_{22}NaO_7$ (M + Na^+) 493.1263, found 493.1258; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 14.18 min, t_{minor} = 17.62 min, *ee* = 96%; $[\alpha]_D^{25}$ = +11.7 (*c* = 1.73 in $CHCl_3$).

(4*R*)-Ethyl 2-hydroxy-4-(4-isopropylphenyl)-5,10-dioxo-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7l). (Table 3, entry 12).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09–7.91 (m, 2 H), 7.68 (d, *J* = 20.8 Hz, 2 H), 7.38 (s, 1 H), 7.15 (bs, 3 H), 4.81 (d, *J* = 154.8 Hz, 1 H), 4.42–4.14 (m, 2.89 H), 3.64 (d, *J* = 15.8 Hz, 0.31 H), 2.78 (d, *J* = 72.2 Hz, 1 H), 2.40 (d, *J* = 8.2 Hz, 1 H), 1.32 (bs, 3 H), 1.22 (bs, 6 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 192.81, 184.01, 183.14, 181.59, 179.35, 168.25, 160.76, 152.98, 147.47, 147.00, 139.96, 138.28, 135.05, 134.09, 133.11, 132.91, 132.17, 130.89, 129.13, 128.08, 127.40, 127.11, 126.79, 126.62, 126.40, 126.19, 126.02, 125.35, 123.95, 104.97, 95.34, 63.46, 62.42,

42.41, 37.94, 35.44, 34.32, 33.61, 23.87, 13.91; HRMS (ESI) calcd for $C_{25}H_{24}NaO_6$ (M + Na^+) 443.1471, found 443.1465; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 14.02 min, t_{minor} = 18.78 min, *ee* = 94%; $[\alpha]_D^{25}$ = +39.6 (*c* = 1.0 in $CHCl_3$).

(4*R*)-Ethyl 2-hydroxy-4-(naphthalen-1-yl)-5,10-dioxo-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7m). (Table 3, entry 13). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28–7.07 (m, 11 H), 5.71 (s, 0.13 H), 5.02 (d, *J* = 96.2 Hz, 1 H), 4.54 (bs, 0.20 H), 4.23–4.13 (m, 2 H), 3.63 (d, *J* = 16.7 Hz, 0.14 H), 2.80 (dd, *J* = 13.7, 8.0 Hz, 0.23 H), 2.53–2.39 (m, 1 H), 1.21 (ddd, *J* = 14.5, 10.6, 6.3 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.63, 183.10, 183.00, 179.25, 178.94, 168.15, 154.00, 139.31, 136.93, 135.14, 134.23, 134.15, 133.36, 133.21, 132.97, 132.08, 131.95, 131.00, 130.92, 130.53, 129.41, 129.13, 127.72, 127.53, 127.22, 126.47, 126.42, 126.29, 126.09, 125.73, 125.52, 125.42, 125.28, 125.07, 123.40, 122.58, 95.96, 95.53, 63.44, 62.49, 60.38, 42.95, 36.94, 33.40, 31.95, 29.65, 21.00, 14.15, 13.92, 13.80; HRMS (ESI) calcd for $C_{26}H_{20}NaO_6$ (M + Na^+) 451.1158, found 451.1152; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 21.03 min, t_{minor} = 29.86 min, *ee* = 91%; $[\alpha]_D^{25}$ = +45.2 (*c* = 1.5 in $CHCl_3$).

(4*S*)-Ethyl 2-hydroxy-5,10-dioxo-4-(thiophen-2-yl)-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7n). (Table 3, entry 14). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18–8.04 (m, 1.62 H), 7.97–7.95 (m, 0.27 H), 7.71 (ddd, *J* = 29.0, 15.3, 6.9 Hz, 2.42 H), 7.14 (d, *J* = 5.0 Hz, 0.81 H), 7.06 (d, *J* = 3.5 Hz, 0.53 H), 6.94–6.88 (m, 1.25 H), 5.29 (dd, *J* = 9.5, 6.0 Hz, 0.46 H), 4.86–4.62 (m, 0.77 H), 4.33 (ddd, *J* = 21.4, 10.6, 5.2 Hz, 2 H), 4.12 (dd, *J* = 19.1, 9.3 Hz, 0.55 H), 3.77 (dd, *J* = 19.2, 6.0 Hz, 0.51 H), 2.73 (dd, *J* = 14.5, 7.3 Hz, 0.16 H), 2.59–2.48 (m, 0.73 H), 1.34 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.16, 183.61, 183.08, 181.45, 160.53, 152.46, 143.49, 135.22, 134.25, 133.43, 133.23, 133.07, 132.73, 130.79, 129.12, 128.77, 127.15, 126.81, 126.64, 126.56, 126.43, 126.28, 126.16, 125.40, 125.14, 124.89, 124.46, 124.25, 123.78, 123.54, 122.97, 95.64, 95.26, 63.64, 62.56, 43.43, 38.24, 34.94, 30.94, 29.88, 28.36, 13.93; HRMS (ESI) calcd for $C_{20}H_{16}NaO_6S$ (M + Na^+) 407.0565, found 407.0560; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 19.84 min, t_{minor} = 26.87 min, *ee* = 95%; $[\alpha]_D^{25}$ = +52.6 (*c* = 1.17 in $CHCl_3$).

(4*S*)-Ethyl 4-ethyl-2-hydroxy-5,10-dioxo-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7o). (Table 3, entry 15). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 20.8, 9.8 Hz, 2 H), 7.76–7.66 (m, 2 H), 4.68 (d, *J* = 84.2 Hz, 0.55 H), 4.40–4.26 (m, 2H), 3.63 (bs, 0.47 H), 3.50 (dd, *J* = 18.0, 8.8 Hz, 0.49 H), 3.30 (dd, *J* = 18.1, 5.5 Hz, 0.50 H), 3.10–2.98 (m, 0.57 H), 2.33–2.15 (m, 1.39 H), 1.90–1.61 (m, 4.47 H), 1.35 (ddd, *J* = 46.0, 25.4, 18.3 Hz, 3.83 H), 1.05 (t, *J* = 7.4 Hz, 1.17 H), 0.96–0.84 (m, 2.52 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.49, 184.26, 183.85, 181.27, 179.19, 169.00, 160.91, 153.19, 151.68, 135.03, 134.02, 133.18, 133.09, 132.90, 132.08, 130.91, 129.23, 127.03, 126.57, 126.29, 126.23, 126.07, 125.74, 124.34, 95.96, 63.47, 62.38, 42.30, 32.97, 32.21, 29.21, 28.79, 27.73, 25.79, 25.23, 24.97, 13.94, 12.13, 11.94, 10.65; HRMS (ESI) calcd for $C_{18}H_{18}NaO_6$ (M + Na^+) 353.1001, found 353.0996; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 10.50 min, t_{minor} = 12.10 min, *ee* = 98%; $[\alpha]_D^{25}$ = +18.5 (*c* = 1.17 in $CHCl_3$).

(4*R*)-Methyl 2-hydroxy-5,10-dioxo-4-phenyl-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (7p). (Table 3, entry 16).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 77.6, 37.5 Hz, 2 H), 7.68 (d, *J* = 23.6 Hz, 2 H), 7.46 (bs, 0.67 H), 7.30–7.22 (m, 4.4 H), 4.89 (d, *J* = 117.6 Hz, 1 H), 4.43–4.11 (m, 1 H), 3.86 (d, *J* = 15.1 Hz, 3 H), 3.67 (d, *J* = 16.4 Hz, 0.28 H), 2.72 (bs, 0.18 H), 2.46–2.37 (m, 1.22 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.20, 183.98, 183.09, 181.46, 179.31, 168.60, 152.94, 142.65, 140.95, 135.09, 134.17, 133.33, 133.16, 132.95, 132.73, 132.05, 130.78, 129.05, 128.72, 128.56, 128.34, 128.12, 127.53, 127.20, 127.05, 126.91, 126.67, 126.39, 126.21, 126.04, 125.02, 123.65, 95.39, 53.79, 52.94, 42.32, 37.86, 35.69, 35.46, 34.64, 33.58, 29.62; HRMS (ESI) calcd for $C_{21}H_{16}NaO_6$ (M + Na^+) 387.0845, found 387.0839; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{major} = 12.76 min, t_{minor} = 18.37 min, *ee* = 96%; $[\alpha]_D^{25}$ = +28.7 (*c* = 1.17 in $CHCl_3$).

(*R*)-Ethyl 5,10-dioxo-4-phenyl-1,4,5,10-tetrahydrobenzo[g]-quinoline-2-carboxylate (9). A solution of **7a** (38 mg, 0.1 mmol) and ammonium acetate (77 mg, 1.0 mmol) in ethanol (0.5 mL) was heated at 70 °C for 30 min. The solvent was evaporated and the mixture was purified by column chromatography on silica gel, eluted by hexane–EtOAc = 10 : 1 to provide **9** as a red solid (15 mg, 42% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 7.6, 0.9 Hz, 1 H), 8.00 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.70–7.61 (m, 3 H), 7.36 (dd, *J* = 8.2, 0.9 Hz, 2 H), 7.31 (dd, *J* = 10.4, 5.0 Hz, 2 H), 7.21 (dd, *J* = 10.2, 4.3 Hz, 1 H), 6.18 (dd, *J* = 5.4, 1.9 Hz, 1 H), 5.05 (d, *J* = 5.4 Hz, 1 H), 4.38–4.27 (m, 2 H), 1.34 (t, *J* = 7.1 Hz, 3 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 182.48, 180.11, 162.13, 144.91, 138.86, 134.69, 132.96, 132.49, 130.36, 128.77, 128.25, 127.22, 126.49, 126.30, 126.10, 115.44, 113.69, 62.04, 38.50, 14.13; HRMS (ESI) calcd for $C_{22}H_{17}NNaO_4$ (M + Na^+) 382.1055, found 382.1050; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{minor} = 20.62 min, t_{major} = 26.70 min, *ee* = 75%; $[\alpha]_D^{25}$ = +180.7 (*c* = 0.27 in $CHCl_3$).

(2*R*,4*R*)-Ethyl 2-chloro-5,10-dioxo-4-phenyl-3,4,5,10-tetrahydro-2*H*-benzo[g]chromene-2-carboxylate (10). To a solution of **7a** (76 mg, 0.2 mmol) in DCM (1 mL) were added triethylamine (0.1 mL) and methanesulfonyl chloride (0.05 mL) at room temperature. After 12 h, the mixture was purified by column chromatography on silica gel, eluted by hexane–EtOAc = 7 : 1 to provide **10** as yellow oil (32 mg, 40% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20–8.18 (m, 1 H), 7.80–7.98 (m, 1 H), 7.76–7.70 (m, 2 H), 7.31–7.28 (m, 2 H), 7.23 (dd, *J* = 7.1, 5.2 Hz, 3 H), 4.38–4.30 (m, 3 H), 3.00 (dd, *J* = 14.7, 7.7 Hz, 1 H), 2.83 (dd, *J* = 14.7, 6.1 Hz, 1 H), 1.34 (t, *J* = 7.3 Hz, 3 H);^{13}C NMR (126 MHz, $CDCl_3$) δ 182.91, 177.67, 165.40, 153.12, 141.28, 134.37, 133.69, 131.84, 130.85, 128.65, 127.51, 126.92, 126.64, 126.62, 123.77, 91.46, 63.62, 40.77, 34.96, 13.89; HRMS (ESI) calcd for $C_{22}H_{17}ClNaO_5$ (M + Na^+) 419.0662, found 419.0659; HPLC (Chiralpak IC, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_{minor} = 32.20 min, t_{major} = 37.06 min, *ee* = 94%; $[\alpha]_D^{25}$ = +149.7 (*c* = 0.33 in $CHCl_3$).

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Notes and references

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