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Enantioselective Synthesis of Coumarin Derivatives by PYBOX-DIPH-Zn(II) Complex Catalyzed Michael Reaction

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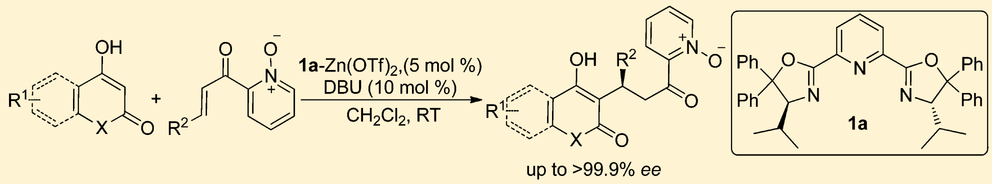
S Supporting Information



ABSTRACT: A potential pharmacologically active chiral 3-substituted 4-hydroxy-2-oxo-2*H*-chromene skeleton has been synthesized by enantioselective Michael addition catalyzed by PYBOX-DIPH-Zn$(OTf)_2$ complex. The methodology has successfully been employed in the synthesis of (*R*)-Warfarin and another related compounds.

Coumarin derivatives are an important class of compounds having a broad range of biological activities such as antibiotic, antifungal, antipsoriasis, cytotoxic, anti-HIV, anticoagulant and anti-inflammatory activity.[1] Currently, most of the drugs containing coumarin derivatives are administered in the form of racemate. Since the activity metabolism and pharmacological effects of the two enantiomers are different, the development of efficient enantioselective methods for the synthesis of enantioenriched coumarin derivatives is of utmost importance. Several new asymmetric synthetic routes to coumarin derivatives has been reported in literature.[2,3] Among them, the Michael reaction of 4-hydroxycoumarin to α,β-unsaturated carbonyls is of great interest because the products obtained are direct precursors to various other biological active compounds like warfarin, acenocoumarol, etc.[3]

Recently, 2-enoylpyridine *N*-oxide has been proved to be an excellent prochiral template for various enantioselective reactions.[4] In this direction, we have reported enantioselective conjugate addition of indoles, pyrroles and dialkylmalonates with these substrates and achieved excellent yields and enantioselectivities.[5] The attractive features associated with 2-enoylpyridin *N*-oxide as Michael acceptor are higher reactivity and enantioselectivity, easy cleavage of pyridine *N*-oxide ring of product and characteristic chemistry of pyridine *N*-oxide ring to perform several transformations.[6] This led us to evaluate 2-enoylpyridine *N*-oxides in other asymmetric transformation like enantioselective Michael reaction of cyclic 1,3-dicarbonyl compounds. In this paper, we wish to report the Michael addition of cyclic 1,3-dicarbonyl compounds to 2-enoylpyridine *N*-oxide catalyzed by bisoxazoline-Zn$(OTf)_2$ complexes (Figure 1).

From our earlier studies, *ip*-pybox-diph (**1a**)−Zn $(OTf)_2$ complex was found to be an excellent catalyst;[7] initial studies were conducted between 4-hydroxycoumarin (**2a**) and benzylidene-2-acetylpyridine-*N*-oxide (**3a**) in the presence of 5 mol % of catalyst (**1a**)−Zn$(OTf)_2$ complex and 10 mol % triethylamine.

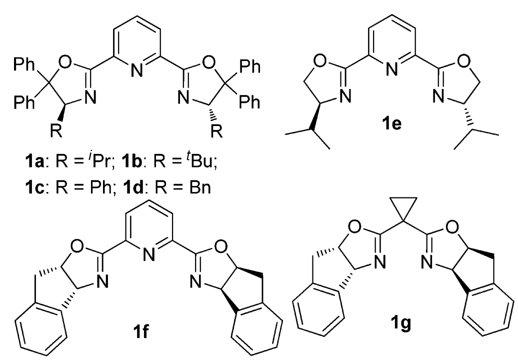


Figure 1. Bisoxazoline ligands used in enantioselective Michael reaction.

To our delight, the corresponding Michael product **4a** was isolated in 97% yield and 83% *ee* (Table 1, entry 1). The Michael addition product **4a** was found to exist in rapid equilibrium with the two diastereomeric forms of the hemiketal **4a′** in solution.[3f] The equilibrium is very rapid, and therefore no diastereomers were observed during HPLC analysis using the mixture of hexane/2-propanol containing 0.1% TFA as the eluent. However, it gave highly complicated and concentration-dependent NMR spectra. Having this encouraging result in hand, various bisoxazoline ligands (**1a**−**1g**) were screened, and results are summarized in Table 1. Among various pybox-diph ligands (**1a**−**1d**) used, *ip*-pybox-diph (**1a**) gave the best results. Poor enantioselectivities and lower reaction rate with *ip*-pybox **1e** (entry 5) and *cis*-1-amino-2-indanol derived pybox **1f** (entry 6) clearly indicate the beneficial effect of *gem*-diphenyl groups at C5 of oxazoline rings.[7] Surprisingly, the bidentatebisoxazoline **1g**, which was used by us in Michael reaction of dialkylmalonate to

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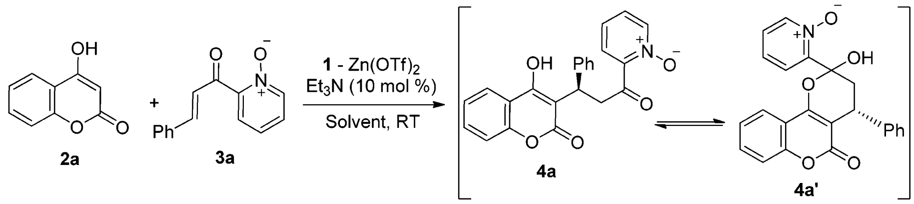
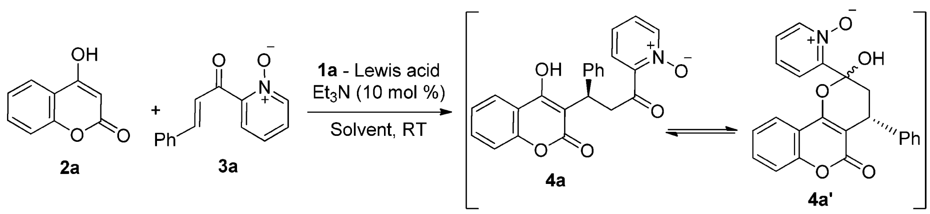
Table 1. Enantioselective Michael Reaction of 4-Hydroxycoumarin Catalyzed by Various Bisoxazoline−Zn(OTf)$_2$ Complexes[a]



entry	ligand	catalyst loading (mol %)	time (h)	yield (%)[b]	*ee* (%)[c]
1	**1a**	5	2	97	83
2	**1b**	5	2	95	80
3	**1c**	5	2	87	15
4	**1d**	5	5	86	29
5	**1e**	5	20	90	7
6	**1f**	5	6	92	15
7	**1g**	5	6	90	0
8	**1a**	10	2	96	80
9	**1a**	2	3	96	79
10[d]	**1a**	5	15	90	60

[a]All reactions were run on a 0.2 mmol scale in 1.0 mL of dichloromethane, 10 mol % Et_3N. [b]Isolated yield. [c]Determined by chiral HPLC using Chiralcel OD-H column. [d]Reaction was carried at −5 °C.

Table 2. Effect of Lewis Acids and Solvents[a]



entry	Lewis acid	solvent	time (h)	yield (%)[b]	*ee* (%)[c]
1	$Zn(OTf)_2$	CH_2Cl_2	2	97	83
2	$Cu(OTf)_2$	CH_2Cl_2	5	92	68
3	$Cu(OTf)_2{\cdot}PhCH_3$	CH_2Cl_2	3	95	65
4	$Sc(OTf)_3$	CH_2Cl_2	9	82	5
5	$Yb(OTf)_3$	CH_2Cl_2	6	86	3
6	$In(OTf)_3$	CH_2Cl_2	6	84	11
7	$Zn(OTf)_2$	$CHCl_3$	2	96	75
8	$Zn(OTf)_2$	THF	2	94	74
9	$Zn(OTf)_2$	$(CH_2Cl)_2$	2	95	81
10	$Zn(OTf)_2$	toluene	12	91	53
11	$Zn(OTf)_2$	CH_3CN	15	90	72

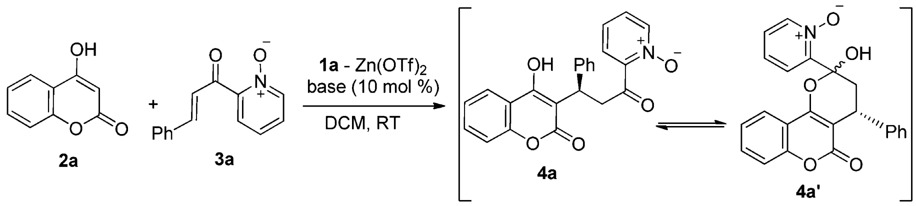
[a]All reactions were run on a 0.2 mmol scale in 1.0 mL of solvent, 5 mol % catalyst, 10 mol % Et_3N. [b]Isolated yield. [c]Determined by chiral HPLC using Chiralcel OD-H column.

2-enoylpyridine *N*-oxide, yielded racemic product with 4-hydroxycoumarin (Table 1, entry 7).[5c]

Studies investigating the effect of catalyst loading and temperature showed that 5 mol % catalyst loading and room temperature is the best combination for this reaction (Table 1, entries 1 and 8−10). Among various Lewis acids and solvents screened, $Zn(OTf)_2$ gave the best results when the reaction was conducted in dichloromethane (Table 2). Next, we investigated the effect of various basic additives in the reaction (Table 3). A control experiment (Table 3, entry 1) showed that the basic additive enhanced the rate as well as enantioselectivity of the product. The bulky Hünig's base improved the enantioselectivity to 86% (Table 3, entry 3). Interestingly, use of DBU further improved the rate as well as enantioselectivity of the reaction (88% *ee*, Table 3, entry 4). Other bases afforded products in the range of 67−82% *ee* with high yields (Table 3, entries 5−10).

Under optimized condition, we further looked forward for substrates scope. A series of cyclic 1.3-dicarbonyl compounds (**2a**−**2f**) were used as nucleophile in the Michael reaction with benzylidene-2-acetylpyridine-*N*-oxide (Table 4, entries 1−6). We observed that this catalytic protocol works well with significant structural variations, and thus a variety of 4-hydroxycoumarin derivatives (**2a**−**2c**) as well as other analogues such as 4-hydroxy-1-methyl-2(1*H*)-quinolone (**2d**), 4-hydroxy-2*H*-thiochromen-2-one (**2e**) and 4-hydroxy-6-methyl-2*H*-pyranone (**2f**) furnished the corresponding products (**4d**−**4f**) in good yields and high level of enantioselectivities. Next, the effect of substitutions on electrophile was studied (Table 4, entries 7−16). The reaction proceeded smoothly with aromatic, heteroaromatic and aliphatic substrates as well. A substrate having ester group at *β*-position (**3j**) worked well, leading to a highly functionalized coumarin derivative (**4o**) (Table 4, entry 15).

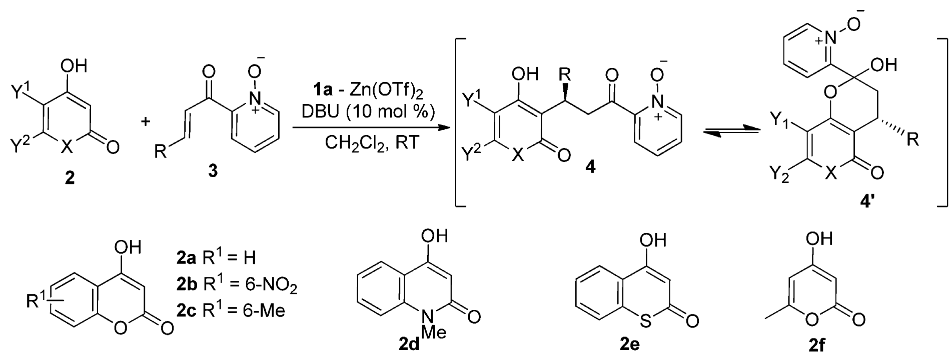
Table 3. Effect of Base Additives[a]



entry	base	time (h)	yield (%)[b]	*ee* (%)[c]
1		12	90	74
2	Et_3N	2	97	83
3	$^{i}Pr_2NEt$	2	96	86
4	DBU	1.5	99	88
5	NMM	4	96	80
6	K_2CO_3	6	80	79
7	1-Me-Im	2	95	81
8	pyridine	2	90	73
9	DMAP	3	94	82
10	DBN	2	95	67

[a]All reactions were run on a 0.2 mmol scale in 1.0 mL of dichoromethane, 5 mol % catalyst **1a**–Zn(OTf)$_2$, 10 mol % base. [b]Isolated yield. [c]Determined by chiral HPLC using Chiralcel OD-H column.

Table 4. Substrates Scope of Enantioselective Michael Addition[a]



entry	2	R	4	time (h)	yield (%)[b]	*ee* (%)[c]
1	**2a**	Ph (**3a**)	**4a**	2	99 (70)	88 (97)[f]
2	**2b**	Ph (**3a**)	**4b**	2	97 (65)	85 (98)[f]
3	**2c**	Ph (**3a**)	**4c**	2	93 (63)	80 (96)[g]
4	**2d**	Ph (**3a**)	**4d**	2	93	97
5	**2e**	Ph (**3a**)	**4e**	4	87 (55)	70 (81)[g]
6	**2f**	Ph (**3a**)	**4f**	1.5	90	96
7	**2a**	2-$NO_2C_6H_4$ (**3b**)	**4g**	3	95 (63)	91 (96)[f]
8	**2a**	3-$NO_2C_6H_4$ (**3c**)	**4h**	1	96 (70)	89 (96)[g]
9	**2a**	4-$NO_2C_6H_4$ (**3d**)	**4i**	1	98 (62)	89 (>99)[f]
10	**2a**	3-ClC_6H_4 (**3e**)	**4j**	2	98 (45)	88 (>99.9)[f]
11	**2a**	4-$MeOC_6H_4$ (**3f**)	**4k**	3	87 (55)	67 (75)[g]
12	**2a**	1-naphthyl (**3g**)	**4l**	9	95 (60)	53 (84)[f]
13	**2a**	2-furyl (**3h**)	**4m**	5	99 (45)	78 (96)[g]
14	**2a**	(*E*)-PhCHCH (**3i**)	**4n**	2	85 (74)	69 (87)[g]
15	**2a**	COOEt (**3j**)	**4o**	7	80 (66)	79 (83)[g]
16	**2a**	^{t}Bu (**3k**)		72	nr[d]	nd[e]

[a]All reactions were run on a 0.2 mmol scale in 1.0 mL of dichloromethane, 5 mol % catalyst **1a**–Zn(OTf)$_2$, 10 mol % DBU. [b]Isolated yield. [c]Determined by chiral HPLC; yield and *ee* in parentheses is *ee* after ethyl acetate treatment. [d]nr = no reaction. [e]nd = not determined. [f]*ee* of collected solid after washing with ethyl acetate. [g]*ee* of filtrate after washing with ethyl acetate.

As the products were solid, washing the products with ethyl acetate improved the enantioselectivities to excellent level (up to >99.9%). It was observed that in some cases (**4a, 4b, 4g, 4i, 4j, 4l**), collected solids show higher enantioselectivities; however, in another set of products (**4c, 4e, 4h, 4k, 4m, 4n, 4o**) the filtrate exhibited higher *ee* values. This is predominantly due to the self-purification of enantioenriched compounds through the self-disproportionation of enantiomers, which is well documented in the literature.[8]

Single crystal X-ray analysis of compound **4j** (see the Supporting Information; CCDC 888974 also contains the supplementary crystallographic data), which was crystallized from enantiopure compound, established the absolute configuration of Michael product to be (*R*). To rationalize the observed absolute configuration of the Michael reaction, a plausible transition state model has been proposed.[7a] The coordination of 2-enoylpyridine-*N*-oxide (**2a**) to **1a**−Zn(II) complex led to two transition states **TS1** and **TS2** as shown in Figure 2. Among two transition states, **TS1** will be more reactive because of the *trans*-influence of pyridine. In transition state **TS2**, the reacting center of 2-enoylpyridine-*N*-oxide **3a** is less accessible to nucleophile because of the steric hindrance of phenyl rings at C5 of oxazoline ring. Thus, in favored transition state **TS1**, nucleophile attacks the 2-enoylpyridine-*N*-oxide from *Re* face leading to (*R*)-enantiomer of the product. *Si* face attack is hindered by the presence of isopropyl group at the C4 of the oxazoline ring.

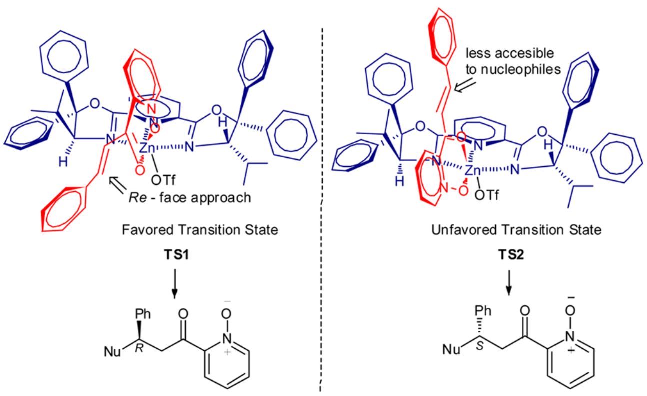
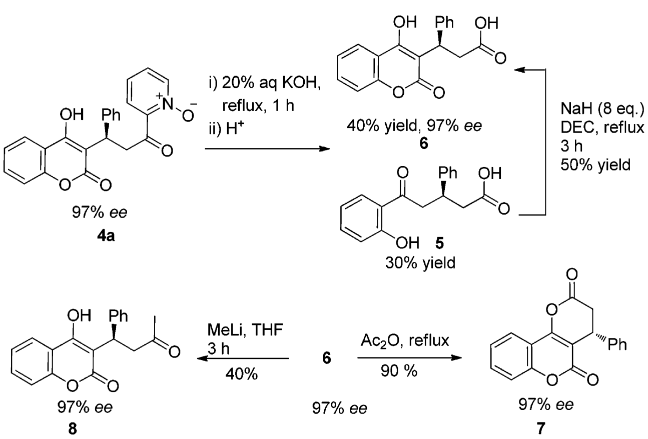


Figure 2. Plausible transition state model for PYBOX-DIPH−Zn(II) catalyzed enantioselective Michael reaction.

To illustrate the synthetic utility of this method, we have cleaved the pyridine-*N*-oxide ring of Michael product **4a** in refluxing 20% aqueous KOH to afford corresponding acid **6** in 40% yield without loss of enantiopurity (Scheme 1). It was found that the poor yield of **6** was due to the formation of the unwanted decarboxylated product **5**. However, compound **5** could be converted to the desired hydroxycoumarin derivative **6** when treated with sodium hydride and diethyl carbonate (DEC). The acid **6** was then converted into (*R*)-Warfarin **8** in 97% *ee*, which is a potent anticoagulant. The lactonization of **6** with acetic anhydride afforded enol lactone **7**, an important functionalized substructure, which shows a variety of interesting biological and pharmaceutical activities, in 90% yields without losing the enantiopurity.[9]

Scheme 1. Synthetic Applications of Our Methodology



In conclusion, we have developed an enantioselective route to access optically active hydroxycoumarin derivatives in excellent enantioselectivities via asymmetric Michael reaction. The present catalytic methodology can tolerate a significant structural variation in cyclic 1,3-dicarbonyl compounds. The stereochemistry of the chiral product has been unambiguously confirmed by single X-ray crystallography. We have synthesized various biologically active compounds such as Warfarin **8** and enol lactone **7** from the Michael product illustrating the importance of the method. Furthermore, a transition state model has been proposed to explain the stereochemical outcome of the reaction.

■ EXPERIMENTAL SECTION

General Remarks. Reagents were used as supplied. NMR spectra were determined at 500 MHz for ^{1}H and 125 MHz for ^{13}C in $CDCl_3$ solvent. IR spectra were recorded with an FT-IR spectrometer. HRMS were performed on TOF MS ES+ mass instrument.

Procedure for the Synthesis of (*E*)-2-(4-Ethoxy-4-oxobut-2-enoyl)pyridine-*N*-oxide (3j). Ethyl glyoxalate solution (50% in toluene), (1.6 mL, 8 mmol) was added dropwise to a solution of 2-acetylpyridine-*N*-oxide (0.915 g, 6.7 mmol) and pyrolidine (110 μL, 1.34 mmol) in dichloromethane (50 mL) at rt and stirred for 4 days. The mixture was concentrated in vacuo and purified by column chromatography to give 0.5928 g (40% yield) of product as semisolid: ^{1}H NMR (500 MHz; $CDCl_3$) δ 1.27−1.31 (m, 3H), 4.21−4.26 (m, 2H), 6.81 (dd, J = 2.0, 15.8 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.41−7.44 (m, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.86 (dd, J = 2.0, 15.8 Hz, 1H), 8.21 (d, J = 6.6, Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 61.6, 125.4, 125.8, 127.4, 128.7, 130.7, 137.8, 140.4, 165.4, 186.2; HRMS (ES+) calc for $C_{11}H_{12}NO_4$ $[M + H]^+$ 222.0766, found 222.0764.

General Procedure for Enantioselective Michael Reaction. A solution of a ligand **1a** (7.3 mg, 0.012 mmol) and $Zn(OTf)_2$ (3.6 mg, 0.01 mmol) in dry dichloromethane (1 mL) was stirred at rt for 1 h under nitrogen atmosphere. *trans*-2-Enoylpyridine-*N*-oxide (0.20 mmol) was added, and mixture was stirred for additional 15 min at rt. Then cyclic 1,3-dicarbonyl compound (0.24 mmol) was added, and the reaction mixture was stirred at rt until the completion of the reaction (monitored by TLC). The mixture was concentrated in vacuo and purified over silica gel by column chromatography (methanol/ethyl acetate 1:20) to afford the product. It was further purified by washing with EtOAc (4 mL). Yield in parentheses is after ethyl acetate treatment. Enantiomeric excess was determined by HPLC analysis on Daicel Chiralcel OD-H column (**4a**, **4g**, **4i**, **4k**, **4m**) and Daicel Chiralpack AD-H column (**4b**, **4c**, **4d**, **4e**, **4f**, **4h**, **4j**, **4l**, **4n**, **4o**) using *n*-hexane/2-propanol (contains 0.1% TFA) as eluent.

(*R*)-2-(3-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-3-phenylpropanoyl)pyridine-1-oxide (4a). Light yellow solid, 0.0767 g, 99% yield (0.0542 g, 70% yield): mp 160−162 °C; $[\alpha]_D^{25}$ +19.7 (c 2.4, $CHCl_3$ for 97% *ee*); HPLC t_R(major) = 36.67 min, t_R(minor) = 58.18 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.38 (dd, J = 11.6, 13.2, 0.83 H), 2.75 (dd, J = 7.3, 13.7 Hz, 0.17H), 2.87 (dd, J = 6.5, 13.5 Hz, 0.83 H), 3.04 (dd, J = 2.7, 13.7 Hz, 0.17 H), 4.33 (dd, J = 2.3, 7.2 Hz, 0.17H), 4.43 (dd, J = 6.3, 11.5 Hz, 0.83 H), 7.19−7.63 (m, 11 H), 7.84 (dd, J = 1.5, 6.6 Hz, 0.83 H), 7.92 (d, J = 6.4 Hz, 0.17 H), 8.30 (dd, J = 1.0, 6.6 Hz, 0.17 H), 8.35 (dd, J = 1.0, 6.4 Hz 0.83 H), 9.42 (s, 0.11 H), 10.25 (s, 0.62 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.4, 35.3, 37.1, 40.7, 98.6, 98.8, 105.1, 115.8, 116.6, 116.7, 123.1, 123.2, 123.3, 123.7, 123.9, 124.1, 126.3, 126.4, 126.8, 127.1, 127.7, 128.3, 128.5, 128.7, 128.9, 131.9, 132.2, 140.9, 142.7, 147.0, 153.1, 158.3, 160.9; IR (thin film) ν 3403, 1710, 1628, 1573 cm^{-1}; HRMS (ES+) calc for $C_{23}H_{18}NO_5$ $[M + H]^+$ 388.1185, found 388.1187.

(*R*)-2-(3-(4-Hydroxy-6-nitro-2-oxo-2*H*-chromen-3-yl)-3-phenylpropanoyl)pyridine-1-oxide (4b). Light yellow solid, 0.0839 g, 97% yield (0.0562 g, 65% yield): mp 153−155 °C; $[\alpha]_D^{25}$ +15.2 (c 2.0, $CHCl_3$ for 98% *ee*); HPLC t_R(major) = 15.98 min, t_R(minor) = 35.30 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.39−2.44 (m, 0.83H), 2.76

(dd, J = 7.5, 13.8 Hz, 0.17H), 2.86 (dd, J = 6.6, 13.2 Hz, 0.83H), 3.02 (dd, J = 2.3, 13.8 Hz, 0.17H), 4.32 (d, J = 5.2 Hz, 0.17H), 4.42 (dd, J = 6.6, 11.5 Hz, 0.83H), 5.70 (s, 0.17H), 7.15−7.54 (m, 10H), 7.60 (dd, J = 2.0, 8.0 Hz, 0.83H), 7.64 (dd, J = 1.7, 8.0 Hz, 0.17H), 8.34 (d, J = 5.7 Hz, 0.83H), 8.29 (d, J = 6.6 Hz, 0.17H), 9.25 (s, 0.16H), 10.25 (s, 0.4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.3, 35.5, 37.7, 40.7, 92.2, 98.6, 98.8, 103.0, 105.0, 115.4, 115.7, 116.2, 116.5, 116.7, 123.0, 123.1, 123.3, 123.5, 123.7, 123.8, 123.9, 124.1, 126.3, 126.4, 126.8, 127.1, 127.7, 128.2, 128.8, 128.9, 131.9, 132.1, 132.3, 140.8, 141.9, 146.9, 147.4, 152.9, 153.0, 154.0, 158.4, 158.8, 161.0, 162.0, 164.0, 166.0; IR (thin film) ν 3396, 1710, 1628, 1582 cm^{-1}; HRMS (ES+) calc for $C_{23}H_{17}N_2O_7$ [M + H]$^+$ 433.1036, found 433.1033.

(*R*)-2-(3-(4-Hydroxy-6-methyl-2-oxo-2*H*-chromen-3-yl)-3-phenylpropanoyl)pyridine-1-oxide (4c). White solid, 0.0747 g, 93% yield (0.0506 g, 63% yield): mp 168−169 °C; $[\alpha]_D^{25}$ −4.0 (c 0.8, $CHCl_3$ for 96% *ee*); HPLC t_R(major) = 11.69 min, t_R(minor) = 22.54 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.39 (s, 2.49H), 2.41 (s, 0.51H), 2.43 (m, 0.83 H), 2.75 (dd, J = 7.4, 13.5 Hz, 0.13H), 2.86 (dd, J = 6.4, 13.1 Hz, 0.83H), 3.02(dd, J = 3.4, 14.4 Hz, 0.17H), 4.30 (dd, J = 3.0, 7.5 Hz, 0.17H), 4.42 (dd, J = 6.4, 11.3 Hz, 0.83H), 7.18−7.68 (m, 11H), 8.30 (d, J = 7.3 Hz, 0.17H), 8.34 (d, J = 6.4 Hz, 0.83H), 9.27 (s, 0.15H), 10.24 (s, 0.74H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.4, 34.4, 35.4, 37.2, 40.8, 98.5, 104.9, 115.3, 116.4, 122.5, 123.7, 126.4, 126.7, 127.1, 127.6, 128.2, 128.7, 128.8, 132.9, 133.6, 140.8, 142.7, 147.0, 151.2, 158.4, 161.1; IR (thin film) ν 3396, 1710, 1628, 1582 cm^{-1}; HRMS (ES+) calc for $C_{24}H_{20}NO_5$ [M + H]$^+$ 402.1341, found 402.1346.

(*R*)-2-(3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3-phenylpropanoyl)pyridine-1-oxide (4d). White solid, 0.0745 g, 93% yield: mp 184−185 °C; $[\alpha]_D^{25}$ −3.7 (c 0.4, $CHCl_3$ for 97% *ee*); HPLC t_R(major) = 17.90 min, t_R(minor) = 45.66 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.46 (dd, J = 10.9, 13.2 Hz, 0.79H), 2.71 (dd, J = 7.5, 13.8 Hz, 0.21H), 2.89 (dd, J = 6.9, 13.5 Hz, 0.79H), 3.04 (dd, J = 3.2, 13.7 Hz, 0.21H), 3.61 (s, 2.4H), 3.70 (s, 0.60H), 4.38 (dd, J = 2.9, 7.2 Hz, 0.21H), 4.48 (dd, J = 6.7, 10.9 Hz, 0.79H), 7.15−7.65 (m, 11H), 8.04 (dd, J = 1.4, 8.0 Hz, 0.79H), 8.12 (d, J = 8.0 Hz, 0.21H), 8.27−8.30 (m, 1H), 8.98 (s, 0.23H), 9.73 (s, 0.73H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 29.4, 29.5, 35.0, 36.1, 37.6, 40.9, 97.6, 97.9, 110.4, 113.9, 114.0, 116.1, 121.7, 121.9, 123.2, 123.7, 125.8, 126.0, 126.3, 127.0, 127.7, 128.1, 128.3, 128.6, 130.7, 130.9, 139.4, 140.6, 144.2, 148.0, 154.7, 161.8; IR (thin film) ν 3397, 1636, 1595 cm^{-1}; HRMS (ES+) calc for $C_{24}H_{21}N_2O_4$ [M + H]$^+$ 401.1501, found 401.1507.

(*R*)-2-(3-(4-Hydroxy-2-oxo-2*H*-thiochromen-3-yl)-3-phenylpropanoyl)pyridine-1-oxide (4e). White solid, 0.0702 g, 87% yield (0.0444 g, 55% yield): mp 176−178 °C; $[\alpha]_D^{25}$ + 4.9 (c 1.6, $CHCl_3$ for 81% *ee*); HPLC t_R(major) = 16.16 min, t_R(minor) = 24.01 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.42−2.49 (m, 0.80H), 2.72−2.75 (m, 0.20 H), 2.86 (dd, J = 7.1, 13.2 Hz, 0.79H), 3.02 (dd, J = 2.8, 13.5 Hz, 0.21H), 4.53 (dd, J = 6.7, 11.3 Hz, 1H), 7.16−7.63 (m, 11H), 8.18 (d, J = 8.2 Hz, 0.79H), 8.27 (d, J = 8.2 Hz, 0.21H), 8.30 (d, J = 6.4 Hz, 0.21H), 8.35 (d, J = 6.4 Hz, 0.79H), 9.23 (s, 0.12H), 9.98 (s, 0.51H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 34.7, 36.4, 40.6, 97.9, 116.3, 123.6, 123.8, 125.3, 126.1, 126.2, 126.5, 126.9, 127.6, 128.1, 128.5, 128.7, 129.9, 136.0, 140.8, 143.8, 147.3, 158.6, 182.8; IR (thin film) ν 3397, 1710, 1594, 1549 cm^{-1}; HRMS (ES+) calc for $C_{23}H_{18}NO_4S$ [M + H]$^+$ 404.0957, found 404.0952.

(*R*)-2-(3-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-3-phenylpropanoyl)pyridine-1-oxide (4f). Semisolid, 0.0632 g, 90% yield: $[\alpha]_D^{25}$ + 29.3 (c 2.8, $CHCl_3$ for 96% *ee*); HPLC t_R(major) = 9.37 min, t_R(minor) = 13.12 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.18 (s, 0.27H), 2.20 (s, 2.40H), 2.25 (s, 0.33H), 2.29 (d, J = 11.8 Hz, 0.83H), 2.64 (dd, J = 7.4, 13.7 Hz, 0.17H), 2.75 (dd, J = 6.3, 13.1 Hz, 0.83H), 2.93 (dd, J = 2.9, 13.8 Hz, 0.17H), 4.15 (m, 0.17H), 4.26 (dd, J = 6.3, 11.5 Hz, 0.83H), 5.75 (s, 0.12H), 5.89 (s, 0.77H), 5.97(s, 0.16H), 7.18−7.55 (m, 8H), 8.24 (d, J = 6.6 Hz, 0.17H), 8.28 (d, J = 6.3 Hz, 0.83H), 9.09 (s, 0.14H), 10.09 (s, 0.74H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 19.9, 33.6, 34.7, 37.1, 40.6, 98.2, 100.3, 100.4, 101.8, 123.2, 123.6, 126.1, 126.2, 126.3, 126.7, 127.1, 127.6, 128.2, 128.5, 128.7, 140.7, 142.6, 146.9, 161.6, 162.8, 163.2; IR (thin film) ν 3419, 1691, 1579 cm^{-1}; HRMS (ES+) calc for $C_{20}H_{18}NO_5$ [M + H]$^+$ 352.1185, found 352.1185.

(*R*)-2-(3-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-3-(2-nitrophenyl)-propanoyl)pyridine-1-oxide (4g). Light yellow solid, 0.0821 g, 95% yield (0.0544 g, 63% yield): mp 178−180 °C; $[\alpha]_D^{25}$ = −62.1 (c 0.3, $CHCl_3$ for 96% *ee*); HPLC t_R(major) = 28.28 min, t_R(minor) = 70.64 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ = 2.35 (bs, 0.48 H), 2.90 (dd, J = 8.1, 14.4 Hz, 0.52 H), 3.03 (d, J = 14.4 Hz, 0.53 H), 3.32 (bs, 0.47 H), 5.00 (d, J = 8.1 Hz, 0.18 H), 5.06 (bs, 0.52 H), 7.21−7.69 (m, 9 H), 7.84 (d, J = 7.8 Hz, 0.52 H), 7.90−7.94 (m, 1 H), 8.07 (d, J = 8.3 Hz, 0.4 8 H), 8.32 (d, J = 6.6 Hz, 0.48 H), 8.39 (d, J = 6.4 Hz, 0.52 H), 10.08 (s, 0.41 H), 10.40 (s, 0.48 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.2, 35.9, 99.2, 102.4, 116.6, 116.8, 123.1, 123.3, 123.4, 123.6, 124.0, 124.2, 124.9, 125.3, 126.4, 126.5, 127.7, 128.8, 131.7, 132.1, 132.4, 132.9, 133.2, 137.5, 140.9, 141.0, 146.8, 153.0, 159.4, 161.7; IR (thin film) ν 3390,1708, 1628, 1576, cm^{-1}; HRMS (ES+) calc for $C_{23}H_{17}N_2O_7$ [M + H]$^+$ 433.1036, found 433.1030.

(*R*)-2-(3-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-3-(3-nitrophenyl)-propanoyl)pyridine-1-oxide (4h). White solid 0.0830 g, 96% yield (0.0605 g, 70% yield): mp 167−170 °C; $[\alpha]_D^{25}$ −36.4 (c 0.3, $CHCl_3$ for 96% *ee*); HPLC t_R(major) = 24.19 min, t_R(minor) = 35.75; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.37 (t, J = 12.5 Hz, 0.70 H), 2.78 (dd, J = 8.9, 13.8 Hz, 0.30 H), 2.90 (dd, J = 6.4, 13.1 Hz, 0.70 H), 3.01 (d, J = 13.5 Hz, 0.30 H), 4.42 (d, J = 7.0 Hz, 0.30 H), 4.54 (dd, J = 6.2, 11.7 Hz, 0.70 H), 7.25−7.68 (m, 8 H), 7.85 (d, J = 7.7 Hz, 0.70 H), 7.89 (d, J = 8.0 Hz, 0.30 H), 8.03−8.08 (m, 1.7 H), 8.20 (bs, 0.30 H), 8.30 (d, J = 6.1 Hz 0.30 H), 8.36 (d, J = 6.1 Hz 0.70 H), 9.75 (s, 0.23 H), 10.37 (s, 0.56 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.1, 35.4, 36.5, 40.2, 98.5, 98.9, 101.5, 103.6, 115.3, 115.5, 116.7, 116.8, 121.6, 121.8, 122.0, 123.2, 123.3, 123.3, 123.4, 123.7, 124.2, 124.3, 126.5, 126.6, 128.9, 129.0, 129.7, 132.3, 132.6, 134.2, 134.4, 140.9, 144.4, 145.0, 146.5, 146.7, 148.2, 148.6, 153.0, 159.1, 159.4, 160.9, 162.1; IR (thin film) ν 3405, 1708, 1626, 1573 cm^{-1}; HRMS (ES+) calc for $C_{23}H_{17}N_2O_7$ [M + H]$^+$ 433.1036, found 433.1035.

(*R*)-2-(3-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-3-(4-nitrophenyl)-propanoyl)pyridine-1-oxide (4i). White solid 0.0847 g, 98% yield (0.0536 g, 62%): mp 193−195 °C; $[\alpha]_D^{25}$ −69.2 (c 0.7, $CHCl_3$ for >99% *ee*); HPLC t_R(major) = 27.46 min, t_R(minor) = 51.75 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.30−2.35 (m, 0.7 H), 2.76 (dd, J = 7.6, 13.7 Hz, 0.70 H), 2.89 (dd, J = 6.4, 13.2 Hz, 0.70 H), 3.05 (d, J = 13.7 Hz, 0.30 H), 4.42 (d, J = 7.1 Hz, 0.30 H), 4.56 (dd, J = 6.4, 12.0 Hz, 0.70 H), 7.26−7.66 (m, 8 H), 7.85 (d, J = 7.8 Hz, 0.70 H), 7.91 (d, J = 7.8 Hz, 0.30 H), 8.14 (d, J = 8.8 Hz, 0.6 H), 8.18 (d, J = 8.8 Hz, 1.4 H), 8.31 (d, J = 6.4 Hz 0.30 H), 8.37 (d, J = 6.6 Hz, 0.70 H), 9.64 (s, 0.24 H), 10.36 (s, 0.53 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.2, 35.6, 36.6, 40.2, 98.4, 98.7, 103.7, 115.4, 116.7, 123.1, 123.2, 123.5, 123.6, 124.2, 124.3, 124.4, 126.5, 126.6, 128.1, 128.8, 132.4, 132.6, 140.9, 146.5, 146.8, 150.7, 153.1, 159.0, 160.9; IR (thin film) ν 3423, 1709, 1627 cm^{-1}; HRMS (ES+) calc for $C_{23}H_{17}N_2O_7$ [M + H]$^+$ 433.1036, found 433.1035.

(*R*)-2-(3-(3-Chlorophenyl)-3-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)propanoyl)pyridine-1-oxide (4j). White solid, 0.0827 g, 98% yield (0.0380 g, 45% yield): mp 165−167 °C; $[\alpha]_D^{25}$ −13.9 (c 0.3, $CHCl_3$ for >99.9% *ee*); HPLC t_R(major) = 11.56 min, t_R(minor) =18.24 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.31−2.39 (m, 0.78 H), 2.72 (dd, J = 7.4, 13.5 Hz, 0.22 H), 2.86 (dd, J = 6.4, 13.5 Hz, 0.78 H), 3.00 (d, J = 15.8 Hz, 0.22 H), 4.31 (d, J = 5.5 Hz, 0.22 H), 4.41 (dd, J = 6.4, 11.6 Hz, 0.78 H), 7.17−7.63 (m, 10 H), 7.84 (dd, J = 1.6, 8.0 Hz, 0.78 H), 7.90 (d, J = 8.0 Hz, 0.22 H), 8.07 (d, J = 7.1 Hz, 0.22 H), 8.32 (d, J = 5.5 Hz, 0.22 H), 8.36 (d, J = 5.8 Hz, 0.58 H), 9.44 (s, 0.22 H), 10.23 (s, 0.52 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.1, 35.3, 36.8, 40.5, 42.1, 98.6, 104.3, 115.6, 116.7, 116.8, 123.1, 123.2, 123.6, 124.0, 124.2, 125.7, 126.1, 126.3, 126.5, 126.7, 127.1, 128.1, 128.5, 128.6, 128.8, 129.4, 130.1, 132.1, 132.3, 134.5, 140.9, 144.8, 146.7, 153.1, 158.6, 160.8; IR (thin film) ν 3397, 1708, 1626, 1573 cm^{-1}; HRMS (ES+) calc for $C_{23}H_{17}ClNO_5$ [M + H]$^+$ 422.0795, found 422.0797.

(*R*)-2-(3-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-3-(4-methoxy-phenyl)propanoyl)pyridine-1-oxide (4k). Light yellow solid, 0.0726 g, 87% yield (0.0459 g, 55% yield): mp 160−161 °C; $[\alpha]_D^{25}$ + 12.4 (c 0.6, $CHCl_3$ for 75% ee); HPLC t_R(major) = 23.49 min, t_R(minor) = 42.30 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.37−2.42 (m, 0.82 H), 2.73 (dd, J = 7.7, 14.0 Hz, 0.18 H), 2.84 (dd, J = 6.8, 13.5 Hz, 0.82 H), 2.97(dd, J = 2.5, 13.8 Hz, 0.18 H), 3.75 (s, 0.54 H), 3.76 (s, 2.46 H), 4.28 (d, J = 7.7 Hz, 0.18 H), 4.38 (dd, J = 6.4, 11.6 Hz, 0.82 H), 6.80−6.84 (m, 2H), 7.12−7.64 (m, 8H), 7.83(d, J = 7.9 Hz, 0.82H), 7.90(d, J = 7.9 Hz, 0.18H), 8.30 (d, J = 5.8 Hz, 0.18H), 8.34(d, J = 5.8 Hz, 0.82H), 9.31(s, 0.17H), 10.23(s, 0.68H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.6, 34.6, 37.1, 40.8, 55.2, 55.3, 98.6, 98.8, 105.2, 113.7, 114.2, 115.7, 116.5, 116.7, 123.0, 123.1, 123.2, 123.7, 123.9, 124.1, 126.3, 126.4, 128.1, 128.7, 128.8, 131.8, 132.1, 134.6, 140.8, 146.9, 153.0, 158.2, 158.3, 160.9; IR (thin film) ν 3416, 1711, 1625, 1573 cm^{-1}; HRMS (ES+) calc for $C_{24}H_{20}NO_6$ [M + H]$^+$ 418.1291, found 418.1297.

***(R)*-2-(3-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-3-(naphthalen-1-yl)propanoyl)pyridine-1-oxide (4l).** Light yellow solid, 0.0831 g, 95% yield (0.525 g, 60% yield): mp 160−162 °C; $[\alpha]_D^{25}$ + 117.1 (c 1.5, $CHCl_3$ for 84% *ee*); HPLC t_R(major) = 36.18 min. t_R(minor) = 28.01 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.43 (bs, 0.67 H), 2.83−2.86 (m, 0.33 H), 3.03 (bs, 0.68 H), 3.12 (d, J = 13.5 Hz, 0.32 H), 5.04 (d, J = 6.9 Hz, 0.32 H), 5.32 (bs, 0.68 H), 5.58 (s, 0.28 H), 7.19−8.07 (m, 13 H), 8.20 (d, J = 6.3 Hz, 0.64 H), 8.30 (d, J = 5.5 Hz, 1.46 H), 9.29 (s, 0.19 H), 10.48 (s, 0.66 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.7, 34.9, 92.1, 98.8, 98.9, 103.1, 105.4, 115.5, 115.9, 116.1, 116.6, 116.7, 122.6, 122.7, 123.1, 123.2, 123.3, 123.5, 123.7, 124.0, 124.2, 125.1, 125.3, 125.8, 125.9, 126.1, 126.3, 126.4, 126.5, 127.5, 128.9, 129.1, 129.2, 129.5, 130.7, 131.2, 131.9, 132.2, 132.3, 134.2, 134.3, 136.4, 140.8, 146.6, 147.2, 152.9, 153.0, 153.9, 159.2, 161.0, 162.1, 164.1, 166.0; IR (thin film) ν 3405, 1712, 1627, 1574 cm^{-1}; HRMS (ES+) calc for $C_{27}H_{20}NO_5$ [M + H]$^+$ 438.1341, found 438.1349.

***(S)*-2-(3-(Furan-2-yl)-3-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-propanoyl)pyridine-1-oxide (4m).** Yellow solid, 0.0747 g, 99% yield (0.0340 g, 45% yield): mp 142−143 °C; $[\alpha]_D^{25}$ −6.7 (c 1.0, $CHCl_3$ for 96% *ee*); HPLC t_R(major) = 19.76 min, t_R(minor) = 29.16; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.54 (dd, J = 6.8, 13.7 Hz, 0.27 H), 2.75 (m, 1.45 H), 3.29 (dd, J = 1.7, 13.5 Hz, 0.28 H), 4.42 (d, J = 6.6 Hz, 0.28 H), 4.54 (dd, J = 7.8, 9.0 Hz, 0.72 H), 6.09 (d, J = 3.2 Hz, 0.28 H), 6.22 (d, J = 3.2 Hz, 0.76 H), 6.28 (dd, J = 2.0, 3.5 Hz, 0.72 H), 6.30 (dd, J = 2.0, 3.5 Hz, 0.28 H), 7.22−7.57(m, 6.75 H), 7.65 (dd, J = 1.7, 8.0 Hz, 0.25 H), 7.82 (dd, J = 1.5, 8.0 Hz, 0.75 H), 7.85 (dd, J = 1.5, 7.8 Hz, 0.25 H), 8.32−8.33 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2, 29.1, 33.0, 36.5, 98.4, 98.5, 101.1, 102.7, 110.6, 110.7, 115.4, 115.5, 116.6, 116.7, 123.1, 123.2, 123.3, 123.7, 123.9, 124.1, 126.4, 128.6, 128.8, 132.1, 132.3, 140.7, 140.8, 140.9, 141.2, 146.8, 147.1, 152.9, 153.7, 154.2, 158.0, 158.4, 160.8, 162.1; IR (thin film) ν 3413, 1713, 1629, 1611, 1575 cm^{-1}; HRMS (ES+) calc for $C_{21}H_{16}NO_6$ [M + H]$^+$ 378.0978, found 378.0975.

***(R)*-*(E)*-2-(3-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-5-phenyl-pent-4-enoyl)pyridine-1-oxide (4n).** Yellow solid, 0.0703 g, 85% yield (0.0612 g, 74% yiled): mp 127−129 °C; $[\alpha]_D^{25}$ −64.7 (c 1.5, $CHCl_3$ for 88% *ee*); HPLC t_R(major) = 15.14 min, t_R(minor) = 31.36 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ = 2.44−2.53 (m, 1H), 2.74(dd, J = 6.5, 13.5 Hz, 0.49H), 2.87 (dd, J = 1.6, 13.5 Hz, 0.51H), 3.86−3.88 (m, 0.51H), 4.02−4.06 (m, 0.49H), 6.32(dd, J = 7.7, 15.9 Hz, 0.51H), 6.59 (d, J = 15.9 Hz, 0.49H), 6.69−6.78 (m, 1H), 7.12−7.54 (m, 10H), 7.62(dd, J = 1.9, 8.0 Hz, 0.49H), 7.67(dd, J = 1.9, 8.0 Hz, 0.51H),7.83 (dd, J = 1.5, 8.0 Hz, 0.49H), 8.35 (dd, J = 6.4, 9.1 Hz, 1H), 9.91 (s, 0.38H), 10.12(s, 0.42 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.8, 32.9, 35.3, 37.2, 98.3, 98.6, 103.5, 104.5, 115.5, 116.5, 116.6, 123.0, 123.3, 123.7, 123.9, 126.3, 126.4, 126.5, 127.2, 127.3, 128.4, 128.5, 128.7, 129.6, 130.4, 131.1, 131.6, 131.9, 137.1, 137.4, 140.8, 140.9, 147.2, 147.5, 152.7, 152.9, 157.0, 157.6, 161.4, 162.0; IR (thin film) ν 3420, 1705, 1625, 1573 cm^{-1}; HRMS (ES+) calc for $C_{25}H_{20}NO_5$ [M + H]$^+$ 414.1341, found 414.1345.

***(S)*-2-(4-Ethoxy-3-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-4-oxobutanoyl)pyridine-1-oxide (4o).** Yellow semisolid, 0.0613 g, 80% yield (0.0506 g, 66% yield): $[\alpha]_D^{25}$ −8.7 (c 0.6, $CHCl_3$ for 83% *ee*); HPLC t_R(major) = 16.21 min, t_R(minor) = 20.82 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ 1.23−1.32 (m, 3H), 2.44−2.50 (m, 1.0 H), 2.90 (dd, J = 5.8, 11.7 Hz, 0.42H), 3.31 (d, J = 12.9 Hz, 0.58 H), 3.92 (d, J = 5.8 Hz, 0.58H), 4.08 (dd, J = 6.0, 11.9 Hz, 0.42H), 4.17−4.27 (m, 2.0 H), 7.21−7.57(m, 5H), 7.66 (dd, J = 7.7, 15.6 Hz, 1.0H), 7.78 (d, J = 7.7 Hz, 1.0H), 8.35−8.37 (m, 1.0H), 10.26 (s, 0.42 H), 10.29 (s, 0.58H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 14.2, 32.0, 33.6, 34.0, 35.6, 61.6, 61.7, 98.1, 115.3, 116.7, 122.9, 123.1, 123.5, 123.6, 124.0, 126.6, 128.7, 128.9, 132.2, 140.9, 146.5, 152.9, 156.9, 161.6, 186.3; IR (thin film) ν 3396, 1713, 1633, 1611, 1576 cm^{-1}; HRMS (ES+) calc for $C_{20}H_{18}NO_7$ [M + H]$^+$ 384.1083, found 384.1087.

Cleavage of Pyridine N-Oxide Ring (Scheme 1). **4a** (387.4 mg, 1 mmol) was suspended in 5 mL of 20% aqueous KOH, and mixture was refluxed for 1 h. The reaction mixture was acidified with concentrated HCl at 0 °C and extracted with EtOAc. The organic layer was concentrated in vacuo and purified column chromatography to afford the product **5** and **6**.

Data for 5. Semisolid, 0.0852 g, 30% yield: $[\alpha]_D^{25}$ = +15.5 (c 3.5, acetone); ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.71−2.75 (m, 1H), 2.82−2.87 (m, 1H), 3.37−3.42 (m, 1H), 3.82−3.88 (m, 1H), 6.85−6.88 (m, 1H), 7.94 (dd, J = 1.0, 8.5 Hz, 1H), 7.19−7.31(m, 5H), 7.43−7.46 (m, 1H), 7.73 (dd, J = 1.5, 8.0 Hz, 1H), 12.12 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.1, 40.4, 44.2, 118.7, 119.1, 119.4, 127.2, 127.4, 128.8, 129.9, 136.6, 142.6, 162.5, 177.9, 204.2; IR (thin film) ν = 3030, 1706, 1639, 1614, 1580 cm^{-1}; HRMS (ES+) calc for $C_{17}H_{17}O_4$ [M + H]$^+$ 285.1127, found 285.1125.

Data for 6. Semisolid, 0.0124 g, 40% yield (overall 0.0171 g, 55% yield): $[\alpha]_D^{25}$ +72.5 (c 1.3, acetone); ^{1}H NMR (500 MHz; $CDCl_3$) δ 3.20−3.23 (m, 1H), 3.53−3.59 (m, 1H), 4.12 (dd, J = 7.0, 14.0 Hz, 1H), 4.78 (dd, J = 3.5, 9.5 Hz, 1H), 7.17−7.32 (m, 7H), 7.43−7.49 (m, 1H), 7.87(d, J = 8.0 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 35.2, 36.1, 37.1, 40.3, 44.1, 107.5, 116.4, 118.6, 119.4, 123.8, 124.0, 127.1, 127.2, 127.4, 127.8, 128.6, 128.9, 129.8, 132.0, 136.6, 139.4, 142.6, 161.1, 162.5, 177.4, 177.6, 204.2; IR (thin film) ν = 3225, 1704, 1609, 1565 cm^{-1}; HRMS (ES+) calc for $C_{18}H_{15}O_5$ [M + H]$^+$ 311.0919, found 311.0919.

Transformation of Compound 5 to Compound 6. A solution of **5** (57 mg, 0.2 mmol) in diethylcarbonate (1 mL) was added to a suspension of NaH (60% dispersion in mineral oil) in diethylcarbonate (1 mL) at 0 °C. The mixture was heated at 100 °C for 4 h and then cooled to 0 °C and quenched by water. The mixture was extracted by diethyl ether, and aqueous phase was acidified with 2 N HCl to pH 3. The resulting mixture was extracted with dichloromethane, concentrated in vacuo and purified by column chromatography to give 31.1 mg (50%) of **6**.

Synthesis of Enol Lactone and Warfarin (Scheme 1). *Enol Lactone 7.*[9a] A solution of **6** (62.2 mg, 0.2 mmol) in 0.2 mL of acetic anhydride was refluxed for 5 min and poured into ice water. Then the resulting mixture was extracted with dichloromethane, concentrated in vacuo and purified by column chromatography to give 52.8 mg (90%) of **7**: mp 138−141 °C; $[\alpha]_D^{25}$ −151.3 (c 1.0, $CHCl_3$ for 97% ee); [lit[9a]]$[\alpha]_D^{25}$ −164.9 (c 0.33, $CHCl_3$ for 91% *ee R* isomer)]; HPLC Daicel Chiralpack AD-H column, *n*-hexane/2-propanol (90:10), flow rate 1.0 mL/min. t_R(major) = 19.85 min, t_R(minor) = 29.14 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ 3.13 (dd, J = 1.8, 16.2 Hz, 1H), 3.21(dd, J = 7.5, 16.2 Hz, 1H), 4.52 (dd, J = 7.7, 1.9 Hz, 1H), 7.24−7.39 (m, 7H), 7.60−7.63 (m, 1H), 7.91(dd, J = 1.5, 8.0 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) HRMS (ES+) calc for $C_{18}H_{13}O_4$ [M + H]$^+$ 293.0814, found 293.0816.

(R)-Warfarin 8.[3a,c,d] 1.6 mmol of methyllithium was added to a stirred solution of **6** (62.2 mg, 0.2 mmol) in 1 mL of dry THF at 0 °C. After 3 h at 0 °C, 6 mmol of Me_3SiCl was added while stirring continued. The reaction mixture was allowed to warm to rt. Then 1 mL of 1 N HCl was added and stirred at rt for 1 h. The mixture was then extracted with dichloromethane; organic layer was concentrated in vacuo and purified by column chromatography to give **8**. White solid, 0.0250 g, 40% yield: mp 156−159 °C; $[\alpha]_D^{25}$ +12.1 (c 0.5, acetonitrile for 97% *ee*); [lit[3d]]$[\alpha]_D^{22}$ = −12.0 (c 0.3, acetonitrile for 96% *ee S* isomer]; HPLC Daicel Chiralpack AD-H column, *n*-hexane/2-propanol (80:20), flow rate 1.0 mL/min. t_R(major) = 5.67 min, t_R(minor) = 15.21 min; ^{1}H NMR (500 MHz; $CDCl_3$) δ 1.65 (s, 1.40H), 1.67 (s, 1.60H), 1.94−1.99 (m, 0.47H), 2.27(s, 0.3H), 2.36−2.52 (m, 1.3H), 3.30 (d, J = 18.0 Hz, 0.1H), 3.44 (bs, 0.33H), 3.83 (dd, J = 10.1, 19.6 Hz, 0.1H), 3.91 (s, 0.52H), 4.15 (dd, J = 6.7, 11.3 Hz, 0.53H), 4.25 (dd, J = 3.4, 6.7 Hz, 0.37H), 4.70 (d, J = 8.0 Hz, 0.1H), 7.19−7.35 (m, 7H), 7.46 (t, J = 7.9 Hz, 0.55H), 7.53−7.56 (m, 0.34H), 7.79 (d, J = 8.3 Hz, 0.46H), 7.88 (d, J = 7.7 Hz, 0.33H), 7.92 (d, J = 7.7 Hz, 0.1H); HRMS (ES+) calc for $C_{19}H_{17}O_4$ [M + H]$^+$ 309.1127, found 309.1124.

ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra and HPLC chromatograms for all new compounds and crystal data (CIF) for **4j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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