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Enantioselective Synthesis of Dihydropyran-Fused Indoles through [4+2] Cycloaddition between Allenoates and 3-Olefinic Oxindoles

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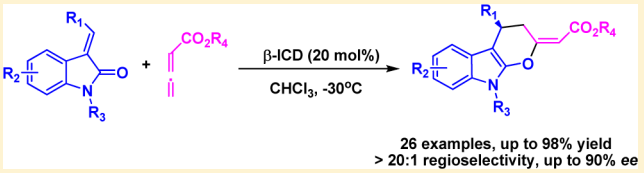
Supporting Information

ABSTRACT: A highly enantioselective [4+2] annulation with respect to allenoates and 3-olefinic oxindoles catalyzed by Lewis base was reported, which proved to be an efficient way to synthesize chiral dihydropyran-fused indoles. The cycloaddition products were generally obtained in high yields (up to 98%) with very good enantioselectivities (up to 94% enantiomeric excess).



Dihydropyran-fused indoles, which are important structural motifs in natural products and biologically active molecules, have attracted wide synthetic interest.[1] Great efforts have been devoted to the construction of this valuable scaffold.[2] However, the study of direct asymmetric catalysis processes for these compounds, to the best of our knowledge, has been very limited. In 2010, Ye reported the first example of a chiral N-heterocyclic carbene (NHC)-catalyzed [4+2] cycloaddition reaction of ketenes and 3-alkylenyloxindoles to give the corresponding 3,4-dihydropyrano[2,3-*b*]indol-2-ones in excellent yields with good diastereo- and enantioselectivities.[3] In 2012, Zhong developed a chiral NHC-catalyzed Diels–Alder reaction of 2-oxindolin-3-ylidenes and α-chloroaldehydes, which synthesized the fused pyrano[2,3-*b*]indoles in good to excellent yields with very good stereoselectivities.[4] In 2013, Zhu and Cheng presented the example of accessing optically active dihydropyran-fused indoles through chiral calcium phosphate-catalyzed enantioselective hetero-Diels–Alder reactions between 2-oxoindlin-3-ylidenes and alkyl vinyl ethers (Figure 1).[5] Despite these elegant contributions, the catalytic asymmetric synthesis of chiral dihydropyran-fused indole derivatives is still in its infancy, and novel catalytic processes are highly desirable.

Allenoates as an attractive substrate class, which can be catalyzed by Lewis base, have become an integral part of the synthesis of cyclic compounds in recent years.[6] After the pioneering phosphine-catalyzed [3+2] cycloaddition of allenoates with alkenes by Lu in 1995,[7] a large number of annulations between allenoates and electron-deficient olefins or imines were developed, providing a variety of carbocycles and heterocycles with multifunctional groups.[8] However, examples of the construction of six-membered oxygenated heterocycles, such as dihydropyrans and dihydropyranones, which are privileged structural motifs in biological and medicinal molecules,[9] are very limited.[10] To the best of our knowledge, there is only one report of the synthesis of chiral dihydropyran skeletons catalyzed by chiral phosphine.[11] On the other hand, amine-catalyzed cycloadditions to allenoates have been disclosed by at least four groups over the past few years.[12] In

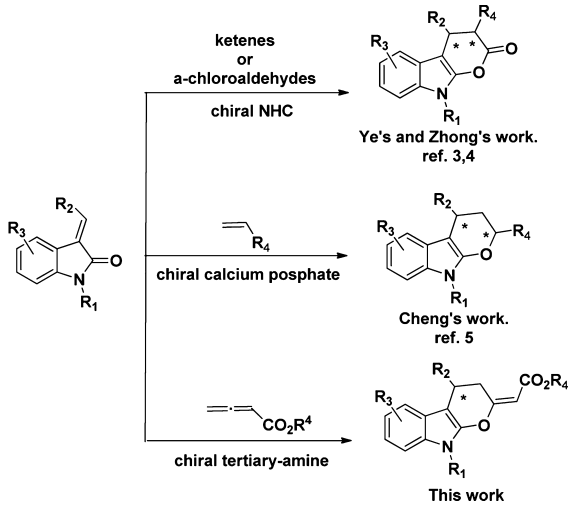


Figure 1. Application of 3-alkenyloxindoles in asymmetric synthesis of dihydropyran-fused indoles.

2011, Tong and Borhan reported an asymmetric [4+2] cycloaddition of allenoates with α,β-unsaturated ketone, which afforded dihydropyran derivatives in high yields and enantioselectivities.[12a,b] More recently, Shi and Wei developed an asymmetric [4+2] cycloaddition of β,γ-unsaturated α-ketoesters and α-ketophosphonates with allenic esters by the amine type organocatalysts.[12c,d] Furthermore, Shi and Wei also realized a highly enantioselective [2+2] annulation of allenoates with trifluoromethyl ketones using an analogous cinchona alkaloid-derived catalyst.[12f] In addition, Sasai reported a chiral amine-catalyzed [2+2] cycloaddition of ketimines with allenoates.[12g]

According to the consideration mentioned above, the Lewis base-catalyzed [4+2] cycloadditions of 3-olefinic oxindoles with

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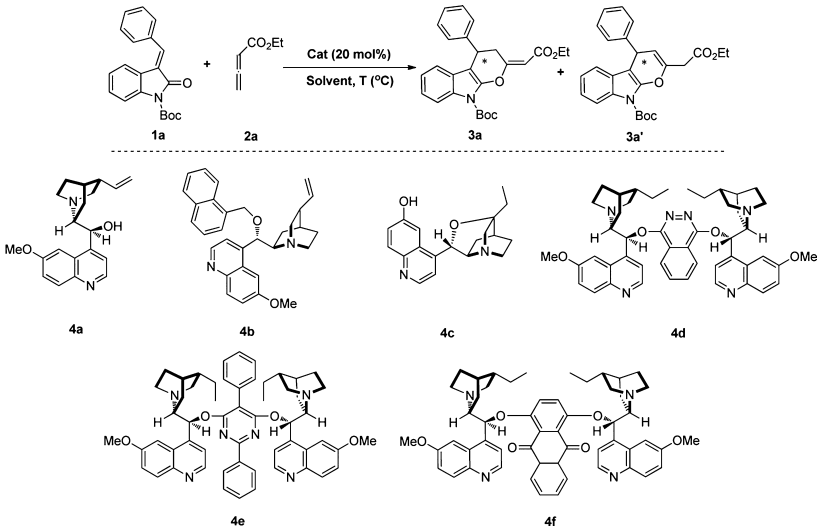
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	T (°C)	solvent	time (h)	yield[b] (%)	3a:3a′[c]	ee[d] (%)
1	**4a**	rt	$CHCl_3$	96	18	>20:1	−38
2	**4b**	rt	$CHCl_3$	96	48	18:1	4
3	**4c**	rt	$CHCl_3$	48	90	>20:1	64
4	**4d**	rt	$CHCl_3$	96	21	>20:1	55
5	**4e**	rt	$CHCl_3$	96	65	>20:1	35
6	**4f**	rt	$CHCl_3$	96	71	15:1	10
7	**4c**	rt	CH_2Cl_2	24	92	>20:1	65
8	**4c**	rt	CH_3CN	1	91	9:1	42
9	**4c**	rt	THF	3	86	>20:1	67
10	**4c**	rt	ether	3	89	>20:1	71
11	**4c**	rt	toluene	4	94	>20:1	74
12	**4c**	rt	chlorobenzene	12	90	>20:1	70
13	**4c**	rt	benzotrifluoride	6	93	>20:1	74
14	**4c**	rt	xylene	3	86	>20:1	74
15	**4c**	−30	toluene	96	92	>20:1	70
16	**4c**	−30	$CHCl_3$	144	80	>20:1	87

[a]The reactions were conducted with 0.1 mmol of **1a**, 0.15 mmol of **2a**, and 20 mol % catalyst in 0.5 mL of solvent. [b]Isolated yields. No *Z*-isomer of the cycloadduct was detected. [c]Determined by ^{1}H NMR of the crude product. [d]Determined by chiral HPLC analysis.

allenoates have been studied, but their asymmetric syntheses are being explored.[13] We report herein a transformation of 3-olefinic oxindole by tertiary amine type Lewis base catalyst (Figure 1). In practice, an asymmetric [4+2] annulation between allenoates and 3-olefinic oxindoles was achieved, thus generating enantiomerically enriched dihydropyran-fused indole derivatives.[14]

We initiated the study with six widely used tertiary amine catalysts **4a**−**f** (20 mol %) in $CHCl_3$ at room temperature and investigated the reaction between (*E*)-*tert*-butyl 3-benzylidene-2-oxindoline-1-carboxylate **1a** and ethyl 2,3-butadienoate **2a** as a model (Table 1, entries 1−6). To our delight, all the catalysts promoted the reaction with different yields, very good regioselectivities, and moderate to good enantioselectivities.

Among the six catalysts examined, *β*-isocupreidine (**4c**) was identified as the optimal one because of its stereoselectivity and efficiency (Table 1, entry 3).

A solvent screening was then conducted (Table 1, entries 3 and 7−14). It was found that benzene type solvents gave relatively good results. Among the screened benzene type solvents, toluene gave the best result, in which cyclization product **3a** was obtained in 94% yield, with >20:1 regioselectivity and 74% enantiomeric excess (ee) (Table 1, entry 11). Unfortunately, lowering the reaction temperature in toluene decreases the enantioselectivity (Table 1, entry 15). Via further exploration of the reaction conditions, the employment of $CHCl_3$ at −30 °C was found to afford optimal results with an 80% yield, a >20:1 regioselectivity, and an 87% ee (Table 1, entry 16).

Having established the optimal reaction conditions, we subsequently turned our attention to examining the substrate scope with respect to a variety of arylidenoxindoles. As shown in Table 2, the corresponding cyclization products **3** were generally obtained in high yields (71−98%) with good enantioselectivities (76−90% ee) (Table 2, entries 1−13). Substrates containing strong electron-withdrawing groups at the *para* positions of the benzene rings of **1** exhibited higher reactivities (**1e** and **1f**). A larger aromatic ring could also be accommodated in the reaction, giving good yield and excellent enantioselectivity (Table 2, entry 14). When the substrates were heterocyclic rings (**1n** and **1o**), the [4+2] cycloaddition could also work; however, lower yields and moderate enantioselectivities were obtained (Table 2, entrise 15 and 16). To our disappointment, when R_1 is an ester or aliphatic group (**1p** and **1q**), corresponding cyclization products **3p** and **3q** were obtained with low yields and bad enantioselectivities

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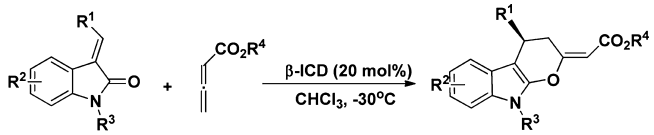
Table 2. Substrates scope[a]



1 2 3

entry	R^1	R^2	R^3	R^4	t (days)	yield[b] (%)	ee[c] (%)
1	**1a**, C_6H_5	H	Boc	Et	6	80	**3a**, 87
2	**1b**, 4-$CH_3C_6H_4$	H	Boc	Et	10	82	**3b**, 87
3	**1c**, 4-ClC_6H_4	H	Boc	Et	8	94	**3c**, 90
4	**1d**, 4-BrC_6H_4	H	Boc	Et	5	82	**3d**, 89
5	**1e**, 4-CNC_6H_4	H	Boc	Et	2	98	**3e**, 87
6	**1f**, 4-$NO_2C_6H_4$	H	Boc	Et	2	98	**3f**, 87
7	**1g**, 3-FC_6H_4	H	Boc	Et	5	84	**3g**, 89
8	**1h**, 3-ClC_6H_4	H	Boc	Et	5	85	**3h**, 90
10	**1i**, 3-BrC_6H_4	H	Boc	Et	4	90	**3i**, 88
11	**1j**, 3,4-diClC_6H_3	H	Boc	Et	5	96	**3j**, 87
12	**1k**, 2-FC_6H_4	H	Boc	Et	8	84	**3k**, 76
13	**1l**, 2-$NO_2C_6H_4$	H	Boc	Et	6	71	**3l**, 84
14	**1m**, 2-naphthyl	H	Boc	Et	7	93	**3m**, 88
15	**1n**, 2-thienyl	H	Boc	Et	10	11	**3n**, 65
16	**1o**, 2-furyl	H	Boc	Et	8	19	**3o**, 61
17	**1p**, CO_2Et	H	Boc	Et	7	47	**3p**, 15
18[d]	**1q**, ^{t}Bu	H	Boc	Et	1	19	**3q**, 38
19	**1r**, C_6H_5	5-Cl	Boc	Et	2	92	**3r**, 86
20	**1s**, C_6H_5	6-Cl	Boc	Et	4	88	**3s**, 85
21[e]	**1t**, C_6H_5	H	CO_2Et	Et	4	87	**3t**, 82
22	**1u**, C_6H_5	H	Ac	Et	7	61	**3u**, 83
23[f]	**1v**, C_6H_5	H	Bn	Et	1	19	**3v**, 7
24	**1a**, C_6H_5	H	Boc	**2b**, Me	6	36	**3w**, 87
25	**1a**, C_6H_5	H	Boc	**2c**, ^{i}Pr	6	27	**3x**, 83
26	**1a**, C_6H_5	H	Boc	**2d**, Bn	6	83	**3y**, 84

[a]The reactions were conducted with 0.1 mmol of **1**, 0.15 mmol of **2**, and 20 mol % β-ICD in 0.5 mL of $CHCl_3$ at −30 °C. [b]Isolated yields (regioselectivities of >20:1, determined by ^{1}H NMR analysis of the crude product). [c]Determined by chiral HPLC analysis. [d]The reactions were conducted with 0.1 mmol of **1**, 0.15 mmol of **2**, and 20 mol % β-ICD in 0.5 mL of toluene at 80 °C. [e]The racemic product has been previously reported in ref 13a. [f]The reactions were conducted with 0.1 mmol of **1**, 0.15 mmol of **2**, and 20 mol % β-ICD in 0.5 mL of $CHCl_3$ at 80 °C.

(Table 2, entries 17 and 18). Higher yields and ee values could also be achieved when 5- or 6-chloro-substituted (*E*)-*tert*-butyl 3-benzylidene-2-oxindoline-1-carboxylate (**1r** or **1s**, respectively) was introduced to the substrates (Table 2, entry 19 or 20, respectively). Further examination of the N-protecting group of oxindole shows that **1t** and **1u** can also work in this cyclization reactions smoothly with good ee values (Table 2, entries 21 and 22, respectively). When R^3 is a benzyl group, [4+2] cycloaddition product **3v** was isolated in an almost racemic fashion in very low yield.[15]

To explore the substrate scope of the [4+2] cycloaddition, different substituted allenoates (**2b**−**d**) were further examined. As shown in Table 2, the result for **3y** is good (Table 2, entry 26). The enantioselectivities of **3w** and **3x** were very good; however, bad yields were obtained (Table 2, entries 24 and 25).[16]

The absolute configuration of products **3j** and **3t** was determined by X-ray analysis (Figures S1 and S2 of the Supporting Information).[17] The configurations of other products were tentatively assigned by referring to that of **3j** and **3t**.

On the basis of the crystal structure of **3j** and **3t** and previous reports,[12] we proposed a transition structure shown in Figure 2 for the [4+2] cycloaddition reactions. We hypothesize that both

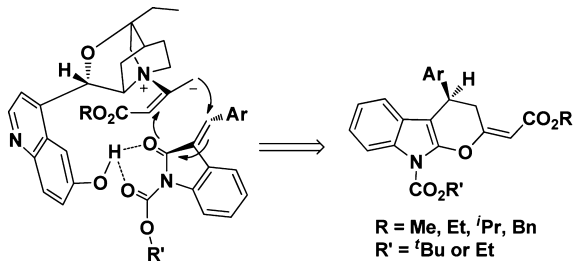


Figure 2. Proposed transition-state assembly.

of the carbonyl oxygen atoms of substrate **1** can bond with the phenolic hydroxyl group of β-ICD through hydrogen bonding, which could be stabilized as a six-membered ring. The zwitterion homoenolate then may preferentially attack from the *re* face to minimize the steric repulsion. The inferior enantioselectivities catalyzed by **4g** (Figure 3), in which the OH group of β-ICD was protected by methyl, further prove the important role of the phenolic hydroxyl in enantiocontrol.

Furthermore, the methodology can also work with (*E*)-1-acetyl-2-benzylideneindolin-3-ones (Figure 4), which give products **5**−**8** through the α-carbon of the allenoate as the nucleophilic carbon in passable yields with excellent ee values. We assumed that the steric interactions between the ester

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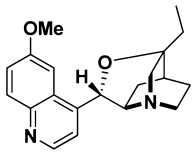
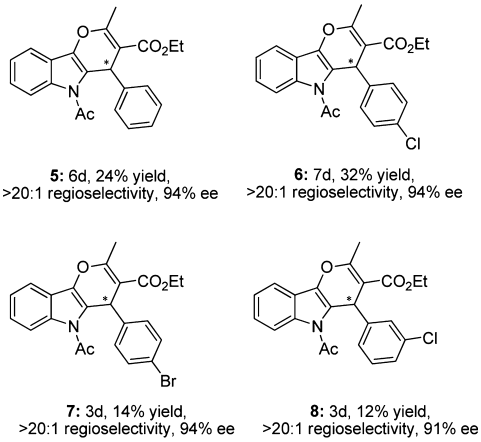


4g

3a: 1d, 92% yield, 3% *ee*;
3t: 1d, 89% yield, 2% *ee*.

Figure 3. Formal [4+2] cycloaddition of **1a** and **1q** with **2a** catalyzed by **4g**.



5: 6d, 24% yield, >20:1 regioselectivity, 94% ee

6: 7d, 32% yield, >20:1 regioselectivity, 94% ee

7: 3d, 14% yield, >20:1 regioselectivity, 94% ee

8: 3d, 12% yield, >20:1 regioselectivity, 91% ee

Figure 4. Results for (*E*)-1-acetyl-2-benzylideneindolin-3-ones.

group of allenoate and the aromatic ring may attribute to the observed regioselectivity.

In summary, we have developed an asymmetric [4+2] cycloaddition reaction of allenoates with 3-olefinic oxindoles catalyzed by tertiary amine type Lewis base. Remarkably, in the presence of a commercially available catalyst, β-ICD, a wide range of 3-arylidenoxindoles and substituted allenoates underwent the reaction smoothly, providing a number of dihydropyran-fused indole derivatives in good yields (up to 98%), excellent regioselectivities (>20:1), and good enantioselectivities (up to 94% ee).

EXPERIMENTAL SECTION

General Information. Commercial reagents were used as received, unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift mutiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted were designated as multiplet (m). Mass spectra were obtained using electrospray ionization (ESI-TOF), electron impact ionization (EI-TOF), or matrix-assisted laser desorption ionization (MALDI-TOF) mass spectrometry. 3-Olefinic oxindoles were synthesized according to the literature procedure.[18]

General Experimental [4+2] Cycloaddition Reaction Procedure. To a stirred solution of (*E*)-*tert*-butyl 3-benzylidene-2-oxindoline-1-carboxylate **1a** (0.1 mmol) and β-ICD (0.02 mmol) in dry $CHCl_3$ (0.5 mL) at −30 °C was added ethyl 2,3-butadienoate **2a** (0.15 mmol, 1.5 equiv). The reactions were monitored by TLC. After **1a** was consumed, the reaction solution was concentrated *in vacuo* and the crude was purified by flash chromatography to afford product **3a**. The regioselectivity was determined by ^{1}H NMR spectroscopy of the crude product. The ee value was determined by chiral HPLC analysis.

*(R,E)-tert-Butyl 2-(2-Ethoxy-2-oxoethylidene)-4-phenyl-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3a**).* White solid: 34.6 mg, 80% yield; mp 107−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.3 Hz, 1H), 7.31−7.20 (m, 5H), 7.20−7.12 (m, 1H), 7.09−7.00 (m, 1H), 6.83 (d, J = 7.5 Hz, 1H), 5.81 (s, 1H), 4.24 (t, J = 6.4 Hz, 1H), 4.20−4.05 (m, 2H), 3.71−3.59 (m, 2H), 1.70 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 165.4, 148.9, 144.6, 141.9, 131.6, 128.8, 127.8, 127.2, 126.4, 123.2, 122.8, 118.2, 115.1, 102.7, 96.4, 84.3, 60.2, 34.9, 31.9, 28.4, 14.4; HRMS (EI-TOF) calcd for $C_{26}H_{27}NO_5$ $(M)^+$ m/z 433.1889, found m/z 433.1896. The enantiomeric excess was determined by HPLC with an IA-H column at 210 nm (1:19 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 4.4 min (minor) and 4.7 min (major). $[\alpha]^{25}_D$ −54.3° (c 1.0, $CHCl_3$).

*(R,E)-tert-Butyl 2-(2-Ethoxy-2-oxoethylidene)-4-(p-tolyl)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3b**).* Pale yellow solid: 36.7 mg, 82% yield; mp 97−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.3 Hz, 1H), 7.21−7.03 (m, 6H), 6.87 (d, J = 7.7 Hz, 1H), 5.82 (s, 1H), 4.22 (t, J = 6.4 Hz, 1H), 4.19−4.08 (m, 2H), 3.71−3.58 (m, 2H), 2.33 (s, 3H), 1.71 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 165.5, 148.8, 144.5, 138.8, 136.7, 131.5, 129.4, 127.6, 126.4, 123.2, 122.7, 118.2, 115.1, 102.6, 96.6, 84.3, 60.1, 34.5, 32.0, 28.3, 21.2, 14.4; HRMS (ESI-TOF) calcd for $C_{27}H_{29}NO_5Na$ $(M + Na)^+$ m/z 470.1943, found m/z 470.1940. The enantiomeric excess was determined by HPLC with an IA-H column at 210 nm (3:97 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 4.6 min (minor) and 4.9 min (major). $[\alpha]^{25}_D$ −83.0° (c 1.0, $CHCl_3$).

*(R,E)-tert-Butyl 4-(4-Chlorophenyl)-2-(2-ethoxy-2-oxoethylidene)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3c**).* White solid: 43.9 mg, 94% yield; mp 95−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.3 Hz, 1H), 7.34−7.28 (m, 2H), 7.26−7.19 (m, 3H), 7.13 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 7.7 Hz, 1H), 5.88 (s, 1H), 4.29 (t, J = 6.1 Hz, 1H), 4.26−4.12 (m, 2H), 3.74 (dd, J = 15.2, 6.0 Hz, 1H), 3.64 (dd, J = 15.2, 6.3 Hz, 1H), 1.76 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 164.8, 148.8, 144.7, 140.4, 132.9, 131.6, 129.1, 128.9, 126.2, 123.4, 123.0, 118.0, 115.2, 103.0, 95.8, 84.5, 60.3, 34.3, 31.7, 28.3, 14.3; HRMS (ESI-TOF) calcd for $C_{26}H_{26}ClNO_5Na$ $(M + Na)^+$ m/z 490.1397, found m/z 490.1395. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (3:97 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 5.5 min (minor) and 8.6 min (major). $[\alpha]^{25}_D$ −65.6° (c 1.0, $CHCl_3$).

*(R,E)-tert-Butyl 4-(4-Bromophenyl)-2-(2-ethoxy-2-oxoethylidene)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3d**).* White solid: 41.9 mg, 82% yield; mp 89−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.3 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 7.8 Hz, 1H), 7.10 (dd, J = 16.4, 8.0 Hz, 3H), 6.86 (d, J = 7.7 Hz, 1H), 5.83 (s, 1H), 4.23 (t, J = 6.1 Hz, 1H), 4.20−4.06 (m, 2H), 3.69 (dd, J = 15.2, 6.0 Hz, 1H), 3.58 (dd, J = 15.3, 6.3 Hz, 1H), 1.71 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 164.8, 148.8, 144.7, 140.9, 131.9, 131.6, 129.5, 126.1, 123.4, 123.0, 121.0, 118.0, 115.2, 103.0, 95.7, 84.5, 60.3, 34.3, 31.6, 28.3, 14.3; HRMS (ESI-TOF) calcd for $C_{26}H_{26}BrNO_5Na$ $(M + Na)^+$ m/z 534.0892, found m/z 534.0888. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (3:97 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 5.8 min (minor) and 8.9 min (major). $[\alpha]^{25}_D$ −65.4° (c 1.0, $CHCl_3$).

*(R,E)-tert-Butyl 4-(4-Cyanophenyl)-2-(2-ethoxy-2-oxoethylidene)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3e**).* Pale yellow solid: 44.9 mg, 98% yield; mp 97−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.24−7.17 (m, 1H), 7.09 (t, J = 7.4 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H), 5.84 (s, 1H), 4.33 (t, J = 5.9 Hz, 1H), 4.18−4.05 (m, 2H), 3.81 (dd, J = 15.2, 5.5 Hz, 1H), 3.54 (dd, J = 15.3, 6.3 Hz, 1H), 1.70 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 164.1, 148.6, 147.4, 144.9, 132.6, 131.5, 128.5, 125.8, 123.5, 123.2, 118.9, 117.6, 115.3, 111.1, 103.4, 94.8, 84.6, 60.3, 34.8, 31.1, 28.3, 14.3; HRMS (ESI-TOF) calcd for $C_{27}H_{26}N_2O_5Na$ $(M + Na)^+$ m/z 481.1739, found m/z 481.1738. The enantiomeric excess was

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determined by HPLC with an OD-H column at 210 nm (1:4 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 5.8 min (minor) and 10.5 min (major). $[\alpha]^{25}_D$ −82.4° (*c* 1.0, $CHCl_3$).

*(R,E)-tert-Butyl 2-(2-Ethoxy-2-oxoethylidene)-4-(4-nitrophenyl)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3f**).* Pale yellow solid: 46.8 mg, 98% yield; mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.8 Hz, 2H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.24−7.16 (m, 1H), 7.13−7.05 (m, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 5.85 (s, 1H), 4.39 (t, *J* = 5.9 Hz, 1H), 4.19−4.05 (m, 2H), 3.85 (dd, *J* = 15.2, 5.4 Hz, 1H), 3.62−3.51 (m, 1H), 1.71 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 164.0, 149.5, 148.6, 147.2, 145.0, 131.5, 128.6, 125.8, 124.1, 123.5, 123.2, 117.6, 115.4, 103.5, 94.8, 84.7, 60.4, 34.6, 31.1, 28.3, 14.3; HRMS (ESI-TOF) calcd for $C_{26}H_{25}N_2O_7$ $(M - H)^-$ *m*/*z* 477.1662, found *m*/*z* 477.1662. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (1:4 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 6.0 min (minor) and 11.4 min (major). $[\alpha]^{25}_D$ −78.6° (*c* 1.0, $CHCl_3$).

*(R,E)-tert-Butyl 2-(2-Ethoxy-2-oxoethylidene)-4-(3-fluorophenyl)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3g**).* White solid: 37.9 mg, 84% yield; mp 87−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.3 Hz, 1H), 7.32−7.25 (m, 1H), 7.25−7.18 (m, 1H), 7.15−7.06 (m, 2H), 6.98−6.91 (m, 3H), 5.87 (s, 1H), 4.29 (t, *J* = 6.1 Hz, 1H), 4.23−4.09 (m, 2H), 3.77 (dd, *J* = 15.3, 5.9 Hz, 1H), 3.61 (ddd, *J* = 15.4, 6.3, 0.6 Hz, 1H), 1.74 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.8, 163.1 (d, $^1J_{CF}$ = 245.0 Hz), 148.8, 144.7, 144.6 (d, $^3J_{CF}$ = 6.7 Hz), 131.6, 130.2 (d, $^3J_{CF}$ = 8.2 Hz), 126.1, 123.4 (d, $^4J_{CF}$ = 2.7 Hz), 123.0, 117.9, 115.2, 114.6 (d, $^2J_{CF}$ = 21.6 Hz), 114.1 (d, $^2J_{CF}$ = 21.0 Hz), 103.0, 95.7, 84.4, 60.2, 34.7, 34.6, 31.5, 28.3, 14.3; HRMS (ESI-TOF) calcd for $C_{26}H_{26}FNO_5Na$ $(M + Na)^+$ *m*/*z* 474.1693, found *m*/*z* 474.1690. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (3:97 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 5.6 min (minor) and 9.0 min (major). $[\alpha]^{25}_D$ −61.2° (*c* 1.0, $CHCl_3$).

*(R,E)-tert-Butyl 4-(3-Chlorophenyl)-2-(2-ethoxy-2-oxoethylidene)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3h**).* White solid: 39.7 mg, 85% yield; mp 113−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 1H), 7.25−7.16 (m, 4H), 7.16−7.12 (m, 1H), 7.09 (td, *J* = 7.7, 0.8 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 5.84 (s, 1H), 4.24 (t, *J* = 6.2 Hz, 1H), 4.21−4.07 (m, 2H), 3.71 (dd, *J* = 15.3, 6.0 Hz, 1H), 3.60 (ddd, *J* = 15.4, 6.3, 0.7 Hz, 1H), 1.71 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.7, 148.8, 144.8, 144.0, 134.5, 131.6, 130.1, 127.8, 127.4, 126.1, 126.0, 123.4, 123.0, 117.9, 115.2, 103.1, 95.5, 84.5, 60.3, 34.6, 31.6, 28.3, 14.3; HRMS (ESI-TOF) calcd for $C_{26}H_{26}ClNO_5Na$ $(M + Na)^+$ *m*/*z* 490.1397, found *m*/*z* 490.1399. The enantiomeric excess was determined by HPLC with an IA-H column at 210 nm (2:98 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 5.5 min (minor) and 6.0 min (major). $[\alpha]^{25}_D$ −64.0° (*c* 1.0, $CHCl_3$).

*(R,E)-tert-Butyl 4-(3-Bromophenyl)-2-(2-ethoxy-2-oxoethylidene)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3i**).* White solid: 46.0 mg, 90% yield; mp 125−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 1H), 7.41−7.34 (m, 2H), 7.23−7.12 (m, 3H), 7.12−7.06 (m, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 5.84 (s, 1H), 4.23 (t, *J* = 6.2 Hz, 1H), 4.19−4.09 (m, 2H), 3.69 (dd, *J* = 15.3, 6.0 Hz, 1H), 3.65−3.56 (m, 1H), 1.71 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.7, 148.7, 144.8, 144.3, 131.6, 130.7, 130.4, 130.3, 126.4, 126.1, 123.4, 123.0, 122.8, 118.0, 115.2, 103.1, 95.5, 84.5, 60.3, 34.6, 31.6, 28.3, 14.3; HRMS (ESI-TOF) calcd for $C_{26}H_{26}BrNO_5Na$ $(M + Na)^+$ *m*/*z* 534.0892, found *m*/*z* 534.0890. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2:98 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 6.0 min (minor) and 6.5 min (major). $[\alpha]^{25}_D$ −57.8° (*c* 1.0, $CHCl_3$).

*(R,E)-tert-Butyl 4-(3,4-Dichlorophenyl)-2-(2-ethoxy-2-oxoethylidene)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3j**).* White solid: 48.1 mg, 96% yield; mp 104−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.23−7.17 (m, 1H), 7.14−7.06 (m, 2H), 6.89 (d, *J* = 7.5 Hz, 1H), 5.84 (s, 1H), 4.23 (t, *J* = 6.0 Hz, 1H), 4.19−4.09 (m, 2H), 3.75 (dd, *J* = 15.2, 5.6 Hz, 1H), 3.53 (ddd, *J* = 15.2, 6.3, 0.6 Hz, 1H), 1.71 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.3, 148.7, 144.9, 142.3, 132.8, 131. 6, 131.2, 130.7, 129.7, 127.1, 125.9, 123.5, 123.1, 117.8, 115.3, 103.4, 95.1, 84.6, 60.3, 34.0, 31.4, 28.3, 14.3; HRMS (ESI-TOF) calcd for $C_{26}H_{25}Cl_2NO_5Na$ $(M + Na)^+$ *m*/*z* 524.1007, found *m*/*z* 524.1005. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (1:99 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 10.8 min (minor) and 25.7 min (major). $[\alpha]^{25}_D$ −89.3° (*c* 1.0, $CHCl_3$).

*(S,E)-tert-Butyl 2-(2-Ethoxy-2-oxoethylidene)-4-(2-fluorophenyl)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3k**).* White solid: 37.9 mg, 84% yield; mp 104−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.23−7.16 (m, 2H), 7.11−7.06 (m, 2H), 7.0−6.92 (m, 3H), 5.82 (s, 1H), 4.63 (t, *J* = 5.9 Hz, 1H), 4.19−4.02 (m, 2H), 3.85 (dd, *J* = 15.3, 5.2 Hz, 1H), 3.49 (dd, *J* = 15.3, 6.5 Hz, 1H), 1.70 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 164.8, 160.8 (d, $^1J_{CF}$ = 244.8 Hz), 148.8, 145.1, 131.6, 129.3 (d, $^3J_{CF}$ = 3.7 Hz), 128.8 (d, $^3J_{CF}$ = 8.2 Hz), 128.6 (d, $^2J_{CF}$ = 13.7 Hz), 126.1, 124.3 (d, $^4J_{CF}$ = 3.3 Hz), 123.3, 122.9, 117.8, 115.6 (d, $^2J_{CF}$ = 21.7 Hz), 115.2, 103.2, 94.9, 84.4, 60.2, 30.3, 28.3, 27.7 (d, $^3J_{CF}$ = 3.3 Hz), 14.3; HRMS (ESI-TOF) calcd for $C_{26}H_{26}FNO_5Na$ $(M + Na)^+$ *m*/*z* 474.1693, found *m*/*z* 474.1692. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (1:99 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 7.5 min (minor) and 8.8 min (major). $[\alpha]^{25}_D$ −46.2° (*c* 1.0, $CHCl_3$).

*(R,E)-tert-Butyl 2-(2-Ethoxy-2-oxoethylidene)-4-(2-nitrophenyl)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3l**).* Brown oil: 34.0 mg, 71% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.3 Hz, 1H), 7.98 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.40 (pd, *J* = 7.3, 1.6 Hz, 2H), 7.22−7.12 (m, 2H), 7.08 (dd, *J* = 11.1, 4.0 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 5.85 (s, 1H), 4.93 (dd, *J* = 6.7, 4.7 Hz, 1H), 4.17−4.01 (m, 2H), 3.88 (dd, *J* = 15.4, 4.7 Hz, 1H), 3.60 (ddd, *J* = 15.4, 6.8, 0.9 Hz, 1H), 1.71 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 163.8, 149.3, 148.7, 145.7, 136.5, 133.2, 131.6, 130.2, 128.2, 125.7, 125.0, 123.5, 123.3, 117.7, 115.3, 104.1, 94.7, 84.7, 60.4, 31.1, 30.1, 28.4, 14.3; HRMS (ESI-TOF) calcd for $C_{26}H_{25}N_2O_7$ $(M - H)^-$ *m*/*z* 477.1662, found *m*/*z* 477.1665. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (2:98 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 12.0 min (minor) and 13.9 min (major). $[\alpha]^{25}_D$ −80.2° (*c* 1.0, $CHCl_3$).

*(R,E)-tert-Butyl 2-(2-Ethoxy-2-oxoethylidene)-4-(naphthalen-2-yl)-3,4-dihydropyrano[2,3-b]-indole-9(2H)-carboxylate (**3m**).* White solid: 44.9 mg, 93% yield; mp 150−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 1H), 7.86−7.73 (m, 3H), 7.73 (s, 1H), 7.51−7.43 (m, 3H), 7.25−7.18 (m, 1H), 7.07−7.04 (m, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 5.91 (s, 1H), 4.47 (t, *J* = 6.3 Hz, 1H), 4.23−4.07 (m, 2H), 3.87−3.74 (m, 2H), 1.77 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 165.2, 148.8, 144.7, 139.3, 133.5, 132.7, 131.6, 128.6, 127.9, 127.7, 126.4, 126.3, 126.1, 125.8, 125.7, 123.3, 122.8, 118.2, 115.1, 102.7, 96.1, 84.3, 60.1, 35.0, 31.8, 28.3, 14.3; HRMS (ESI-TOF) calcd for $C_{30}H_{29}NO_5Na$ $(M + Na)^+$ *m*/*z* 506.1943, found *m*/*z* 506.1942. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (3:97 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 5.9 min (minor) and 6.5 min (major). $[\alpha]^{25}_D$ −112.3° (*c* 1.0, $CHCl_3$).

*(S,E)-tert-Butyl 2-(2-Ethoxy-2-oxoethylidene)-4-(thiophen-2-yl)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3n**).* Pale yellow solid: 4.8 mg, 11% yield; mp 111−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.1 Hz, 1H), 7.24−7.11 (m, 4H), 6.93−6.86 (m, 2H), 5.85 (s, 1H), 4.58 (t, *J* = 5.4 Hz, 1H), 4.23−4.07 (m, 3H), 3.40 (dd, *J* = 15.3, 6.2 Hz, 1H), 1.69 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 164.7, 148.8, 145.9, 144.1, 131.5, 126.9, 126.2, 124.8, 124.4, 123.4, 123.0, 117.8, 115.2, 103.4, 96.7, 84.4, 60.3, 31.6, 30.0, 28.3, 14.4; HRMS (ESI-TOF) calcd for $C_{24}H_{25}NO_5SNa$ $(M + Na)^+$ *m*/*z* 462.1351, found *m*/*z* 462.1348. The enantiomeric excess was determined by HPLC with an IA-H column at 210 nm (2:98 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 6.3 min (minor) and 6.8 min (major). $[\alpha]^{25}_D$ −6.18° (*c* 0.5, $CHCl_3$).

*(S,E)-tert-Butyl 2-(2-Ethoxy-2-oxoethylidene)-4-(furan-2-yl)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3o**).* Yellow solid:

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8.1 mg, 19% yield; mp 69−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.7 Hz, 1H), 7.33 (s, 1H), 7.25−7.14 (m, 3H), 6.27 (s, 1H), 6.10 (d, J = 2.9 Hz, 1H), 5.85 (s, 1H), 4.37 (t, J = 5.4 Hz, 1H), 4.27−4.12 (m, 3H), 3.31 (dd, J = 15.3, 6.3 Hz, 1H), 1.69 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 164.9, 154.6, 148.8, 144.2, 142.0, 131.5, 126.4, 123.4, 122.9, 117.7, 115.2, 110.3, 106.2, 103.1, 94.7, 84.3, 60.3, 28.4, 28.3, 28.0, 14.4; HRMS (ESI-TOF) calcd for $C_{24}H_{26}NO_6$ $(M + H)^+$ m/z 424.1760, found m/z 424.1756. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (3:97 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 6.1 min (minor) and 7.9 min (major). $[\alpha]^{20}_D$ −25.7° (c 0.405, $CHCl_3$).

*(E)-9-tert-Butyl 4-Ethyl 2-(2-Ethoxy-2-oxoethylidene)-3,4-dihydropyrano[2,3-b]indole-4,9(2H)-dicarboxylate (**3p**).* Colorless oil: 20.2 mg, 47% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 5.7, 3.2 Hz, 1H), 7.46−7.44 (m, 1H), 7.23−7.20 (m, 2H), 5.86 (s, 1H), 4.40 (dd, J = 15.6, 2.8 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.94 (dd, J = 6.5, 2.9 Hz, 1H), 2.90 (dd, J = 15.5, 5.8 Hz, 1H), 1.67 (s, 9H), 1.31 (t, J = 7.1 Hz, 4H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 166.7, 164.3, 148.7, 144.6, 131.4, 126.1, 123.5, 123.1, 117.8, 115.2, 103.1, 91.4, 84.5, 61.5, 60.3, 34.3, 28.3, 24.8, 14.4, 14.2; HRMS (ESI-TOF) calcd for $C_{23}H_{28}NO_7$ $(M + H)^+$ m/z 430.1866, found m/z 430.1866. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (1:19 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 5.8 min (major) and 6.5 min (minor). $[\alpha]^{20}_D$ +4.2° (c 1.0, $CHCl_3$).

*(E)-tert-Butyl 4-(tert-Butyl)-2-(2-ethoxy-2-oxoethylidene)-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3q**).* Colorless oil: 7.8 mg, 19% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, J = 8.5, 4.6 Hz, 1H), 7.44−7.37 (m, 1H), 7.23−7.14 (m, 2H), 5.15 (d, J = 5.2 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.41−3.24 (m, 3H), 1.65 (s, 9H), 1.27 (t, J = 7.1 Hz, 4H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 149.1, 146.4, 146.1, 132.2, 128.0, 122.7, 122.4, 119.1, 114.7, 104.7, 95.0, 83.7, 61.2, 42.4, 39.3, 38.1, 28.3, 27.7, 14.3; HRMS (ESI-TOF) calcd for $C_{24}H_{32}NO_5$ $(M + H)^+$ m/z 414.2280, found m/z 414.2279. The enantiomeric excess was determined by HPLC with an IC-H column at 210 nm (1:19 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 5.3 min (major) and 6.7 min (minor). $[\alpha]^{20}_D$ +6.7° (c 0.39, $CHCl_3$).

*(R,E)-tert-Butyl 6-Chloro-2-(2-ethoxy-2-oxoethylidene)-4-phenyl-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3r**).* White solid: 43.0 mg, 92% yield; mp 133−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.8 Hz, 1H), 7.33−7.23 (m, 3H), 7.23−7.18 (m, 2H), 7.11 (dd, J = 8.8, 2.1 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 5.81 (s, 1H), 4.21 (t, J = 6.3 Hz, 1H), 4.18−4.05 (m, 2H), 3.64 (qd, J = 15.3, 6.0 Hz, 2H), 1.69 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.9, 148.6, 145.4, 141.4, 129.9, 128.9, 127.7, 127.6, 127.4, 122.8, 117.8, 116.2, 103.1, 95.9, 84.8, 60.3, 34.8, 31.8, 28.3, 14.3; HRMS (ESI-TOF) calcd for $C_{26}H_{26}ClNO_5Na$ $(M + Na)^+$ m/z 490.1397, found m/z 490.1394. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (3:97 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 5.0 min (minor) and 6.2 min (major). $[\alpha]^{25}_D$ −21.6° (c 1.0, $CHCl_3$).

*(R,E)-tert-Butyl 7-Chloro-2-(2-ethoxy-2-oxoethylidene)-4-phenyl-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3s**).* White solid: 41.1 mg, 88% yield; mp 138−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 1.8 Hz, 1H), 7.32−7.23 (m, 3H), 7.23−7.18 (m, 2H), 7.00 (dd, J = 8.3, 1.9 Hz, 1H), 6.67 (d, J = 8.3 Hz, 1H), 5.80 (s, 1H), 4.20 (t, J = 6.6 Hz, 1H), 4.17−4.09 (m, 2H), 3.73 (dd, J = 15.4, 6.1 Hz, 1H), 3.54 (dd, J = 15.4, 7.0 Hz, 1H), 1.70 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 165.0, 148.5, 144.8, 141.5, 131.9, 128.8, 128.5, 127.7, 127.3, 124.8, 123.6, 118.9, 115.6, 102.9, 96.2, 84.8, 60.2, 34.9, 31.9, 28.3, 14.3; HRMS (ESI-TOF) calcd for $C_{26}H_{26}ClNO_5Na$ $(M + Na)^+$ m/z 490.1397, found m/z 490.1397. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (3:97 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 4.5 min (minor) and 4.9 min (major). $[\alpha]^{25}_D$ −42.8° (c 1.0, $CHCl_3$).

*(R,E)-Ethyl 2-(2-Ethoxy-2-oxoethylidene)-4-phenyl-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3t**).* White solid: 35.2 mg, 87% yield; mp 121−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.3 Hz, 1H), 7.32−7.21 (m, 5H), 7.20−7.15 (m, 1H), 7.06 (td, J = 7.7, 0.9 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 5.84 (s, 1H), 4.52 (q, J = 7.1 Hz, 2H), 4.25 (t, J = 6.4 Hz, 1H), 4.19−4.06 (m, 2H), 3.73−3.58 (m, 2H), 1.50 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 165.1, 150.4, 144.5, 141.7, 131.5, 128.8, 127.7, 127.2, 126.6, 123.5, 123.0, 118.3, 115.2, 102.9, 96.8, 63.5, 60.2, 35.0, 31.9, 14.5, 14.3; HRMS (MALDI-TOF) calcd for $C_{24}H_{23}NO_5Na$ $(M + Na)^+$ m/z 428.1474, found m/z 428.1469. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (3:97 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 6.2 min (minor) and 6.8 min (major). $[\alpha]^{25}_D$ −1.50° (c 0.8, $CHCl_3$).

*(R,E)-Ethyl 2-[9-Acetyl-4-phenyl-3,4-dihydropyrano[2,3-b]indol-2(9H)-ylidene]acetate (**3u**).* White solid: 22.9 mg, 61% yield; mp 115−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 8.3, 0.5 Hz, 1H), 7.32−7.23 (m, 5H), 7.22−7.16 (m, 1H), 7.08 (td, J = 7.6, 0.8 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 5.83 (s, 1H), 4.26 (t, J = 6.4 Hz, 1H), 4.20−4.07 (m, 2H), 3.73−3.60 (m, 2H), 2.71 (s, 3H), 1.25 (td, J = 7.1, 0.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 166.2, 164.7, 143.6, 141.4, 131.8, 128.8, 127.7, 127.3, 126.5, 124.1, 123.7, 118.1, 116.6, 103.2, 96.9, 60.4, 34.9, 31.8, 26.6, 14.3; HRMS (MALDI-TOF) calcd for $C_{23}H_{21}NO_4Na$ $(M + Na)^+$ m/z 398.1368, found m/z 398.1366. The enantiomeric excess was determined by HPLC with an IA-H column at 210 nm (1:19 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 7.3 min (minor) and 8.1 min (major). $[\alpha]^{20}_D$ −37.0° (c 1.0, $CHCl_3$).

*(R,E)-Ethyl 2-[9-Benzyl-4-phenyl-3,4-dihydropyrano[2,3-b]indol-2(9H)-ylidene]acetate (**3v**).* Yellow solid: 7.9 mg, 19% yield; mp 65−66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.14 (m, 11H), 7.02 (t, J = 7.3 Hz, 1H), 6.97−6.86 (m, 2H), 5.76 (s, 1H), 5.27 (s, 2H), 4.33 (t, J = 6.5 Hz, 1H), 4.19−4.05 (m, 2H), 3.78 (dd, J = 15.2, 5.9 Hz, 1H), 3.53 (dd, J = 15.2, 7.1 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 166.0, 145.5, 142.9, 137.2, 132.0, 128.9, 128.6, 127.8, 127.7, 127.0, 126.9, 125.2, 120.3, 120.2, 118.4, 109.4, 102.3, 90.8, 60.1, 45.5, 35.7, 33.0, 14.4; HRMS (ESI-TOF) calcd for $C_{28}H_{26}NO_3$ $(M + H)^+$ m/z 424.1913, found m/z 424.1915. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (3:97 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 12.2 min (major) and 16.2 min (minor). $[\alpha]^{20}_D$ +2.02° (c 0.395, $CHCl_3$).

*(R,E)-tert-Butyl 2-(2-Methoxy-2-oxoethylidene)-4-phenyl-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3w**).* White solid: 15.1 mg, 36% yield; mp 112−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.3 Hz, 1H), 7.35−7.26 (m, 5H), 7.23−7.16 (m, 1H), 7.12−7.05 (m, 1H), 6.87 (d, J = 7.6 Hz, 1H), 5.86 (s, 1H), 4.28 (t, J = 6.4 Hz, 1H), 3.76−3.63 (m, 5H), 1.74 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 165.7, 148.8, 144.5, 141.8, 131.6, 128.8, 127.7, 127.2, 126.4, 123.3, 122.8, 118.2, 115.1, 102.2, 96.5, 84.4, 51.4, 34.9, 31.9, 28.3; HRMS (ESI-TOF) calcd for $C_{25}H_{25}NO_5Na$ $(M + Na)^+$ m/z 442.1630, found m/z 442.1630. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2:98 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 6.4 min (minor) and 7.0 min (major). $[\alpha]^{25}_D$ −94.1° (c 0.75, $CHCl_3$).

*(R,E)-tert-Butyl 2-(2-Isopropoxy-2-oxoethylidene)-4-phenyl-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3x**).* White solid: 12.1 mg, 27% yield; mp 101−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.3 Hz, 1H), 7.31−7.20 (m, 5H), 7.19−7.12 (m, 1H), 7.08−7.01 (m, 1H), 6.83 (d, J = 7.6 Hz, 1H), 5.78 (s, 1H), 4.99 (dt, J = 12.5, 6.3 Hz, 1H), 4.24 (t, J = 6.3 Hz, 1H), 3.64 (d, J = 6.4 Hz, 2H), 1.70 (s, 9H), 1.23−1.19 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.0, 148.9, 144.7, 141.9, 131.6, 128.7, 127.7, 127.1, 126.4, 123.2, 122.8, 118.2, 115.1, 103.3, 96.3, 84.3, 67.5, 34.9, 31.9, 28.3, 22.0; HRMS (ESI-TOF) calcd for $C_{27}H_{29}NO_5Na$ $(M + Na)^+$ m/z 470.1943, found m/z 470.1942. The enantiomeric excess was determined by HPLC with an IA-H column at 210 nm (3:97 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 5.1 min (minor) and 6.7 min (major). $[\alpha]^{25}_D$ −4.67° (c 0.6, $CHCl_3$).

*(R,E)-tert-Butyl 2-[2-(Benzyloxy)-2-oxoethylidene]-4-phenyl-3,4-dihydropyrano[2,3-b]indole-9(2H)-carboxylate (**3y**).* Pale yellow solid: 41.1 mg, 83% yield; mp 72−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.3 Hz, 1H), 7.39−7.19 (m, 10H), 7.17 (t, J =

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7.8 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 5.87 (s, 1H), 5.17−5.06 (m, 2H), 4.24 (t, J = 6.3 Hz, 1H), 3.67 (d, J = 6.4 Hz, 2H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 166.0, 148.8, 144.5, 141.8, 136.2, 131.6, 128.8, 128.7, 128.3, 128.2, 127.7, 127.2, 126.3, 123.3, 122.9, 118.2, 115.1, 102.3, 96.4, 84.4, 66.0, 34.8, 32.0, 28.3; HRMS (MALDI-TOF) calcd for $C_{31}H_{29}NO_5Na$ $(M + Na)^+$ m/z 518.1943, found m/z 518.1940. The enantiomeric excess was determined by HPLC with an IA-H column at 210 nm (2:98 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 7.6 min (minor) and 9.1 min (major). $[\alpha]^{25}_D$ −47.6° (c 1.0, $CHCl_3$).

*Ethyl 5-Acetyl-2-methyl-4-phenyl-4,5-dihydropyrano[3,2-b]-indole-3-carboxylate (**5**).* Yellow solid: 9.0 mg, 24% yield; mp 83−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.82 (m, 1H), 7.71−7.62 (m, 1H), 7.37−7.29 (m, 2H), 7.26−7.17 (m, 4H), 7.17−7.10 (m, 1H), 5.75 (s, 1H), 4.22−4.09 (m, 2H), 2.57 (s, 3H), 2.49 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 167.2, 158.8, 143.9, 136.6, 134.0, 128.9, 128.2, 126.9, 125.5, 123.5, 120.9, 120.5, 117.4, 115.4, 108.1, 60.6, 40.4, 27.1, 19.8, 14.3; HRMS (MALDI-TOF) calcd for $C_{23}H_{21}NO_4Na$ $(M + Na)^+$ m/z 398.1368, found m/z 398.1366. The enantiomeric excess was determined by HPLC with an IA-H column at 210 nm (2:98 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 17.6 min (minor) and 18.8 min (major). $[\alpha]^{25}_D$ −38.5° (c 0.4, $CHCl_3$).

*Ethyl 5-Acetyl-4-(4-chlorophenyl)-2-methyl-4,5-dihydropyrano-[3,2-b]indole-3-carboxylate (**6**).* Brown solid: 13.1 mg, 32% yield; mp 70−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.72 (m, 1H), 7.71−7.64 (m, 1H), 7.39−7.29 (m, 2H), 7.23−7.13 (m, 4H), 5.76 (s, 1H), 4.19−4.10 (m, 2H), 2.60 (s, 3H), 2.49 (s, 3H), 1.27 (t, J = 7.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 167.0, 159.2, 142.7, 136.4, 133.8, 132.5, 130.5, 128.3, 125.6, 123.6, 121.0, 120.6, 117.6, 115.0, 107.8, 60.7, 39.9, 27.3, 19.8, 14.3; HRMS (MALDI-TOF) calcd for $C_{23}H_{20}ClNO_4Na$ $(M + Na)^+$ m/z 432.0979, found m/z 432.0981. The enantiomeric excess was determined by HPLC with an IA-H column at 210 nm (2:98 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 17.1 min (major) and 19.5 min (minor). $[\alpha]^{20}_D$ −16.0° (c 0.65, $CHCl_3$).

*Ethyl 5-Acetyl-4-(4-bromophenyl)-2-methyl-4,5-dihydropyrano-[3,2-b]indole-3-carboxylate (**7**).* Brown solid: 6.3 mg, 14% yield; mp 90−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 6.8 Hz, 1H), 7.39−7.29 (m, 4H), 7.13 (d, J = 8.1 Hz, 2H), 5.75 (s, 1H), 4.19−4.09 (m, 2H), 2.60 (s, 3H), 2.49 (s, 3H), 1.27 (t, J = 7.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 167.0, 159.2, 143.3, 136.4, 133.8, 131.2, 130.9, 125.6, 123.6, 121.0, 120.8, 120.5, 117.7, 115.0, 107.7, 60.7, 40.0, 27.3, 19.8, 14.3; HRMS (ESI-TOF) calcd for $C_{23}H_{22}BrNO_4$ $(M + H)^+$ m/z 454.0654, found m/z 454.0641. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2:98 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 19.3 min (minor) and 20.6 min (major). $[\alpha]^{20}_D$ −17.3° (c 0.3, $CHCl_3$).

*Ethyl 5-Acetyl-4-(3-chlorophenyl)-2-methyl-4,5-dihydropyrano-[3,2-b]indole-3-carboxylate (**8**).* Colorless oil: 4.9 mg, 12% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.5 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.39−7.29 (m, 2H), 7.22 (s, 1H), 7.19−7.08 (m, 3H), 5.76 (s, 1H), 4.25−4.06 (m, 2H), 2.60 (s, 3H), 2.51 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 166.9, 159.4, 146.2, 136.5, 133.9, 133.8, 129.3, 129.2, 127.4, 127.1, 125.6, 123.5, 120.9, 120.3, 117.7, 115.0, 107.6, 60.7, 40.2, 27.2, 19.8, 14.3; HRMS (ESI-TOF) calcd for $C_{23}H_{22}ClNO_4$ $(M + H)^+$ m/z 410.1159, found m/z 410.1156. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (2:98 2-propanol:hexane) at a rate of 1.0 mL/min. t_R = 11.2 min (major) and 12.0 min (minor). $[\alpha]^{20}_D$ −20.4° (c 0.245, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra, HPLC data, and X-ray crystal data of compounds **3j** and **3t** (cif). 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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