JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

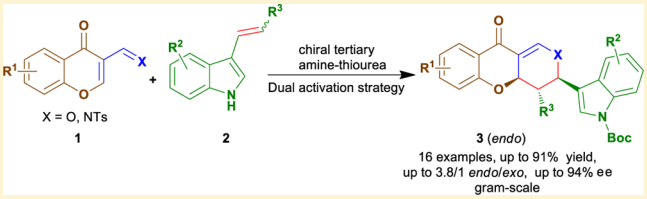
Chiral Tertiary Amine Thiourea-Catalyzed Asymmetric Inverse-Electron-Demand Diels–Alder Reaction of Chromone Heterodienes Using 3-Vinylindoles as Dienophiles

Zhijie Mao, Aijun Lin, Yan Shi, Haibin Mao, Weipeng Li, Yixiang Cheng, and Chengjian Zhu*

State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, People's Republic of China

Supporting Information

ABSTRACT: A straightforward and efficient protocol for the construction of structurally and biologically interesting chiral flavanoids incorporating three privileged structures, i.e., chromanone, dihydropyran, and indole, has been developed on the basis of chiral bifunctional tertiary amine thiourea-catalyzed asymmetric inverse-electron-demand Diels–Alder reaction of chromone heterodienes and 3-vinylindoles, which were used as dienophiles.



INTRODUCTION

Flavanoids with chromanone or chromone as the structural scaffold represent an important class of naturally occurring structures characterized by their ability to interact with a number of different receptors in the body (Figure 1).[1] Due to

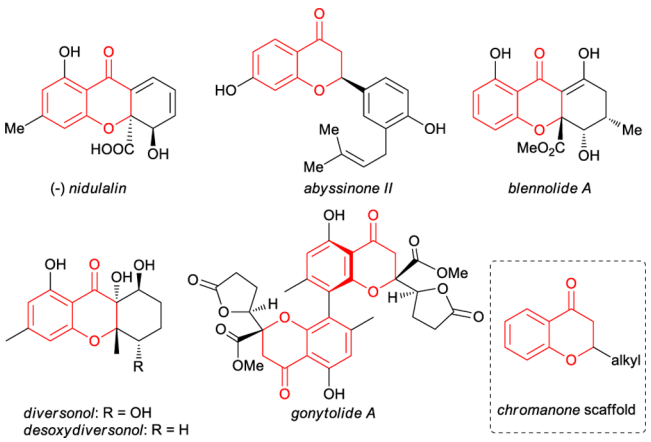


Figure 1. Chiral flavanoid natural products with chromanone as the structural scaffold.

their attractive pharmacological and biological properties, such as anticancer, antitumor, and antibacterial, etc., great efforts have been devoted to the synthesis of this class of compounds during the past several years.[2] Despite the important advances, catalytic stereoselective construction of chromanones and related structures still remains a challenge, especially when chromones are used as precursors.[3]

Indole is regarded as a privileged structure due to its existence in a huge number of alkaloids and natural products.[4] The catalytic asymmetric Diels–Alder (DA) cycloadditions of vinylindoles provide a straightforward route to introduce a chiral indole skeleton with highly functional and stereogenic complexity. However, it is difficult to find a compatible catalyst system due to the instability and high reactivity of vinylindoles. In 2008, Ricci and co-workers developed the first organocatalyzed asymmetric normal-electron-demand DA reaction of vinylindoles based on the interaction between tertiary amine catalysts and the indole NH moiety.[5] In recent years, vinylindoles have commonly been used as conjugated dienes in normal-electron-demand DA reaction,[6] and fewer studies have focused on the catalytic asymmetric inverse-electron-demand Diels–Alder (IEDDA) reaction[7] using vinylindoles as dienophiles.

To the best of our knowledge, there was only one example reported in 2010 in which the acid-sensitive 3-vinylindoles were used in chiral phosphoric acid-catalyzed asymmetric Povarov reaction through a syringe pump (Scheme 1).[6a] To simplify the experimental operation and continue our research on the IEDDA reaction,[8] herein we report a bifunctional tertiary amine thiourea-catalyzed IEDDA reaction of chromone heterodienes with 3-vinylindoles as dienophiles, leading to natural product-like chromanone derivatives containing a tricyclic hetero-system.

RESULTS AND DISCUSSION

To probe the feasibility of IEDDA reaction of 3-formylchromone (**1a**) and 3-vinylindole (**2a**), we initially carried out the reaction at 10 °C in CH_2Cl_2 in the presence of 20 mol % quinine-derived catalyst **I** (Table 1, entry 1, and Figure 2). Although the reaction proceeded smoothly to give the adducts as a mixture of two diastereoisomers in high yield, the poor

Received: July 25, 2013
Published: September 5, 2013

   dx.doi.org/10.1021/jo401592w | J. Org. Chem. 2013, 78, 10233–10239

Scheme 1. Vinylindoles Used as Dienophiles in Asymmetric IEDDA Reaction

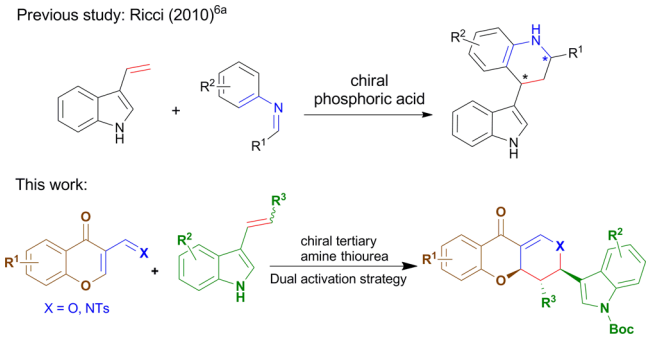
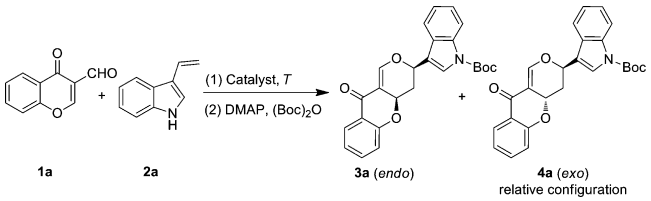


Table 1. Catalyst Screening and Optimization Studies[a]



entry	catalyst	T (°C)	yield[b] (%)	dr[c] (*endo*/*exo*)	ee[c] (%)
1	**I**	10	86	3.5/1	−65 (−64)
2	**IIIa**	10	83	3.2/1	−50 (−49)
3	**IIIb**	10	78	3.3/1	−45 (−42)
4	**IIIc**	10	87	3.2/1	−51 (−48)
5	**IV**	10	90	3.2/1	−76 (−74)
6	**V**	10	46	3.3/1	55 (64)
7	**VIa**	10	90	3.3/1	75 (85)
8	**VIb**	10	91	3.0/1	83 (90)
9	**VIc**	10	90	2.8/1	83 (92)
10	**VIb**	0	88	3.4/1	85 (96)
11	**VIb**	−20	85	3.4/1	86 (96)
12[d]	**VIb**	−20	83	2.8/1	86 (96)
13	**VIb**	−40	84	3.4/1	87 (94)
14[e]	**VIb**	−40	85	3.0/1	90 (94)
15[e]	**VIc**	−40	88	3.2/1	92 (96)
16[f]	**VIc**	−40	87	3.4/1	94 (97)

[a]To a solution of **1a** (0.1 mmol) and catalyst (0.02 mmol) in CH_2Cl_2 (0.5 mL) at the indicated temperature was added **2a** (0.12 mmol), and the mixture was stirred for 12 h. After the solvent was evaporated, THF (2.0 mL), DMAP (10 mol %), and $(Boc)_2O$ (0.15 mmol) were added sequentially at room temperature, and the mixture was stirred at room temperature for another 6 h. [b]Isolated total yield of **3a** and **4a** after two steps. [c]Determined by HPLC analysis. The first value in each entry is the ee value of the *endo* product, and the value in parentheses is the ee value of the *exo* product. [d]The solution of **2a** (0.12 mmol) in CH_2Cl_2 (0.5 mL) was added by syringe pump in 2 h. [e]Two pellets of 4 Å molecular sieves were added at the first step. [f]Two pellets of 4 Å molecular sieves were added to 1.0 mL of CH_2Cl_2 at the first step.

solubility in most organic solvents made us take a further protection on the indole NH with $(Boc)_2O$. To our delight, the two diastereoisomers showed better solubility and could be separated by flash chromatography after the protection, giving **3a** as the major product with a 65% ee value (Table 1, entry 1). Next, several common chiral tertiary amine thiourea catalysts were introduced, and their performance was tested (Figure 2). Compared with chiral aminoindanol-derived tertiary amine thioureas **IIIa**−**V**, Takemoto's catalysts **VIa**−**VIc** gave better enantioselectivities, particularly for catalysts **VIb** and **VIc**

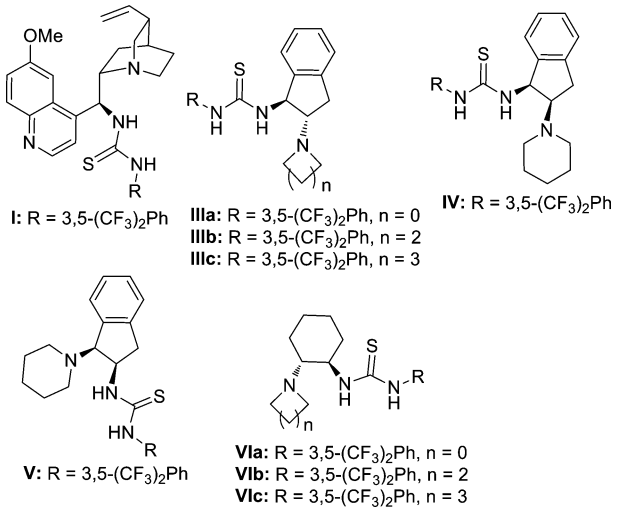


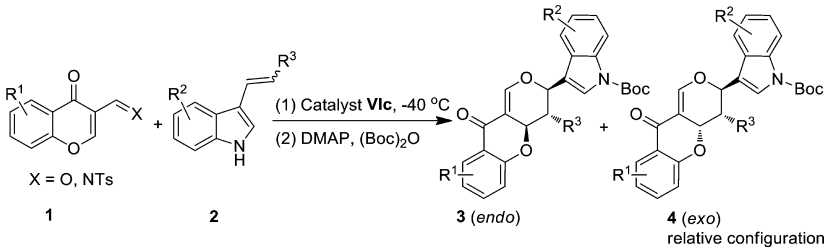
Figure 2. Chiral tertiary amine thiourea catalysts.

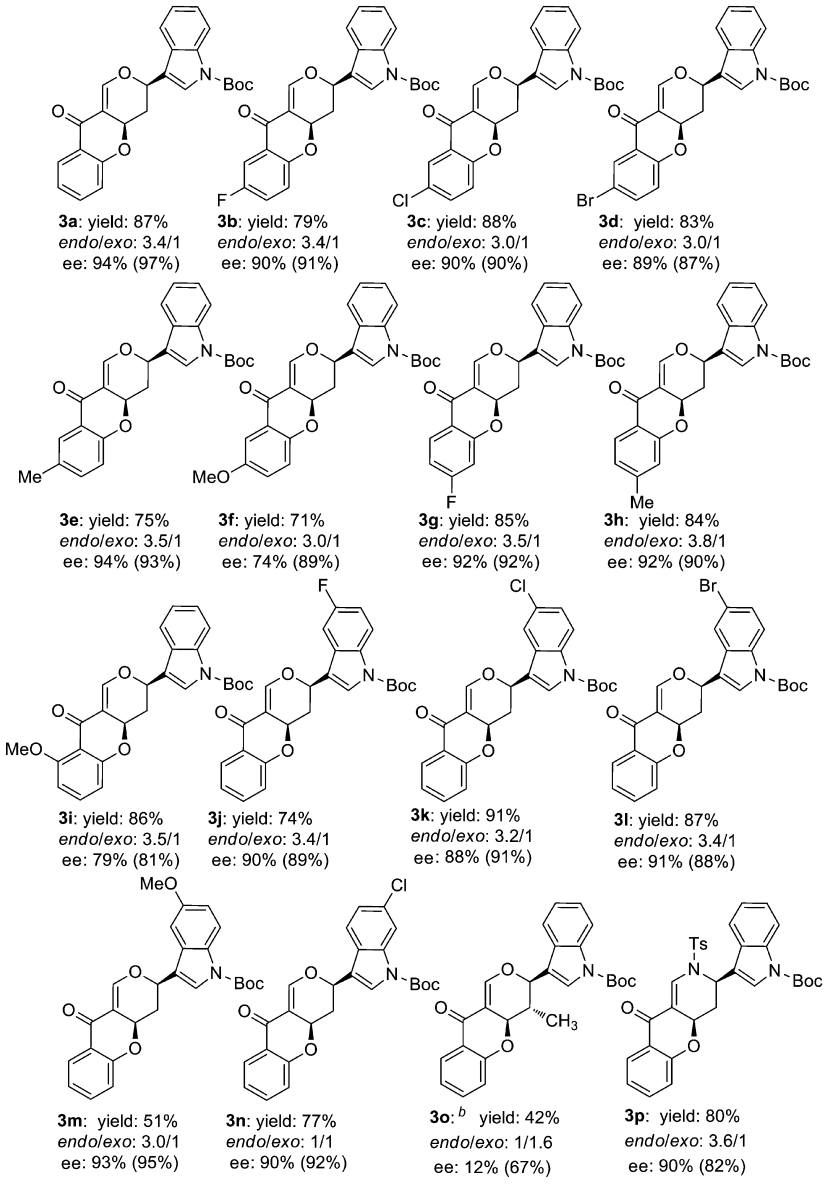
(Table 1, entries 2−6 vs entries 7−9). With the best catalysts, **VIb** and **VIc**, in hand, we further optimized the reaction conditions. In all the solvents screened (see the Supporting Information), CH_2Cl_2 turned out to be the best solvent, giving 91% total yield with a 3.0/1 *endo*/*exo* ratio and 83% ee for *endo* product **3a** (Table 1, entry 8). Lowering the temperature was favorable to improve the ee value, and 87% ee for **3a** was obtained when the reaction was carried out at −40 °C (Table 1, entry 13). When 4 Å molecular sieves were added, the ee value was improved, and 92% ee for **3a** was obtained when catalyst **VIc** was introduced under the same conditions (Table 1, entry 15). Further lowering the concentration gave **3a** with a 94% ee value (Table 1, entry 16).

Under the optimized reaction conditions, we next examined the substrate scope, and the results are summarized in Table 2. In general, all of the chromone oxadienes with electron-withdrawing or electron-donating substituents could undergo IEDDA reaction to afford the desired adducts in moderate to good yields with about 3.0−4.0/1 *endo*/*exo* ratios and good to excellent enantioselectivities (Table 2, **3a**−**3i**). MeO-substituted 3-formylchromones gave products with lower ee values compared with other substituted 3-formylchromones (Table 2, **3f** and **3i**), probably caused by their negative effect on the hydrogen-bonding interaction between the tertiary amine thiourea catalyst and chromone oxadienes. Furthermore, different substituted 3-vinylindoles were also employed to test the substrate compatibility of 3-vinylindole. Generally speaking, the IEDDA reaction of 3-formylchromone and different substituted 3-vinylindoles progressed smoothly, giving satisfactory yields and stereochemical outcomes (Table 2, **3j**−**3n**). When heterodiene **1** was treated with 2 equiv of methyl-substituted vinylindole **2** (E/Z = 1/1), only the E isomer underwent the IEDDA reaction, giving the *endo* product with only 12% ee (Table 2, **3o**), which was in accordance with previous reports.[5] Moreover, the chromone azadiene gave a similar result, although attempts to separate the two diastereoisomers by column chromatography failed (Table 2, **3p**). A control experiment showed that only 28% yield was obtained and no ee values for the two diastereoisomers were observed when the nitrogen on 3-vinylindole was protected by a benzyl (Bn) group, indicating that the interaction between the tertiary amine catalyst and the indole NH moiety is necessary for the stereoselective outcome (results not shown in Table 2).

dx.doi.org/10.1021/jo401592w | J. Org. Chem. 2013, 78, 10233−10239

Table 2. Substrate Scope of the Reaction[a]





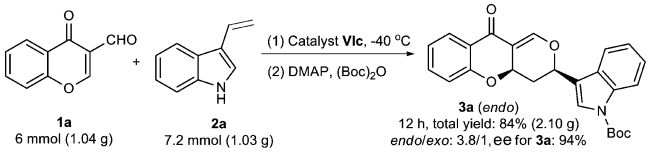
[a]Reaction conditions: To a solution of **1** (0.1 mmol) and **VIc** (0.02 mmol) in CH_2CI_2 (1.0 mL) containing two pellets of molecular sieves at −40 °C was added **2a** (0.12 mmol), and the mixture was stirred for 12 h. After the solvent was evaporated, THF (2.0 mL), DMAP (10 mol %), and $(Boc)_20$ (0.15 mmol) were added sequentially at room temperature, and the mixture was stirred at room temperature for another 6 h. Yields refer to the isolated total yield of **3** and **4** after two steps. The *endo*/*exo* ratios and ee values were determined by HPLC analysis, and the data in parentheses are the ee values of the *exo* products. The absolute configuration of **3a** was determined by X-ray analysis of its derivative **5a** and NOE analysis, and other *endo* products were assigned by analogy. [b]A 2 equiv portion of methyl-substituted vinylindole **2** (E/Z = 1/1) was used.

An additional scaled-up experiment (Scheme 2) showed that this reaction could be performed on the gram scale without obvious loss of diastereoselectivity and enantioselectivity (6 mmol, 84% total yield, 3.8/1 *endo*/*exo*, 94% ee for the *endo* product).

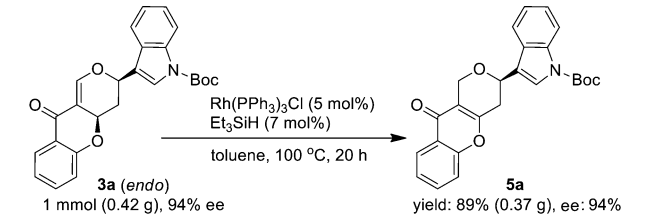
To determine the absolute configurations of the major enantiomers and their potential application, compound **3a** was subjected to catalytic isomerization in the presence of Wilkinson's catalyst (5 mol %) and 7 mol % Et_3SiH (Scheme 3).[9] The exocyclic to endocyclic migration of the double bond

dx.doi.org/10.1021/jo401592w | J. Org. Chem. 2013, 78, 10233−10239

Scheme 2. Scaled-Up Experiment



Scheme 3. Conversion of 3a to Chromone Derivative 5a



in **3a** took place smoothly to give chromone-derived product **5a** in 89% yield without obvious loss of enantioselectivity. The absolute configuration of **5a** was unambiguously determined to be *R* by single-crystal X-ray structural analysis (see the Supporting Information),[10] which allowed us to assign the absolute configuration of **3a** as 3*R*,4a*R* according to its relative configuration analysis. On the basis of these results, we proposed a synergistic interaction for the catalytic asymmetric IEDDA reaction between the catalyst and the two reactants, as shown in Figure 3. The process was directed by multiple hydrogen-bonding interactions between the chromone oxadienes and 3-vinylindoles (Figure 3).

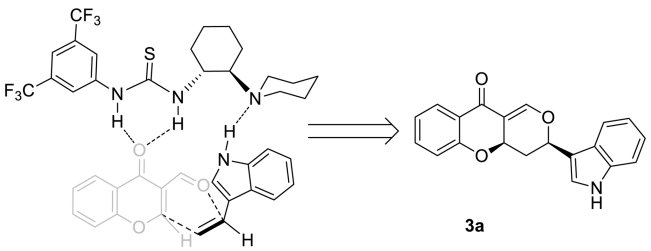


Figure 3. Proposed reaction mode between the substrates and catalyst **VIc**.

CONCLUSION

In summary, a novel class of structurally and biologically interesting chiral flavanoids incorporating three privileged structures, i.e., chromanone, dihydropyran, and indole, have been constructed through catalytic asymmetric IEDDA reaction of chromone oxadienes and 3-vinylindoles for the first time. The reaction proceeded smoothly to afford the IEDDA adducts with good to high yields and enantioselectivities (up to 91% total yield, up to 94% ee for the *endo* product). Although the *endo*/*exo* ratios of the product are moderate, the two diastereoisomers could be easily separated by flash chromatography in most cases, which still makes it desirable in practical application. Remarkably, such reaction could be performed on the gram scale, and the product could be easily transformed to equally biologically significant chromone-derived products without obvious loss of enantioselectivity. The generated chiral flavanoids with chromanone and indole as the structural scaffolds in the current catalytic asymmetric reaction will be useful to advance chemical research of the indole-containing flavonoid compounds as drug candidates. The biological evaluation of these compounds and further study of IEDDA reaction of 3-vinylindoles with other heterodienes are currently under way in our laboratory.

EXPERIMENTAL SECTION

Typical Procedure for Chiral Bifunctional Tertiary Amine Thiourea VIc Catalyzed Asymmetric IEDDA Reaction of 3-Formylchromone (1a) and 3-Vinylindole (2a). To a solution of **1a** (17.4 mg, 0.1 mmol) and **VIc** (9.0 mg, 0.02 mmol) in CH_2Cl_2 (1.0 mL) containing two pellets of 4 Å molecular sieves at −40 °C was added **2a** (17.1 mg, 0.12 mmol), and the mixture was stirred for 12 h. After the solvent was evaporated, THF (2.0 mL), DMAP (1.2 mg, 0.01 mol), and $(Boc)_2O$ (26.1 mg, 0.12 mmol) were added sequentially at room temperature, and the mixture was stirred at room temperature for another 6 h. After evaporation of the solvent under reduced pressure, the crude product was directly purified by flash chromatography (ethyl acetate/petroleum ether = 1/9) to afford the IEDDA adducts containing a mixture of two diastereoisomers for HPLC analysis. Further separation by flash chromatography gave the pure compound **3a** for NMR analysis.

*tert-Butyl 3-((3R,4aR)-10-Oxo-3,4,4a,10-tetrahydropyrano[4,3-b]-chromen-3-yl)-1H-indole-1-carboxylate (**3a**).* Total yield: 87% (36.2 mg, *endo*/*exo* = 3.4/1). White solid. Mp: 167.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.18 (d, J = 8.0 Hz, 1H), 7.98 (dd, J = 8.0, 2.0 Hz, 1H), 7.76 (s, 1H), 7.69 (s, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.48−7.43 (m, 1H), 7.39−7.34 (m, 1H), 7,30−7.26 (m, 1H), 7,09−7.05 (m, 1H), 6.97−6.95 (m, 1H), 5.46 (dt, J = 12.0, 1.2 Hz, 1H), 5.37 (ddd, J = 10.0, 6.8, 1.2 Hz, 1H), 2.81 (ddd, J = 13.2, 6.8, 2.0 Hz, 1H), 2.68 (td, J = 12.6, 10.0 Hz, 1H), 1.68 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.2, 160.7, 154.0, 149.5, 135.8, 135.4, 128.1, 127.4, 125.1, 123.8, 123.1, 122.9, 122.1, 119.5, 118.1, 117.7, 115.7, 112.0, 84.4, 72.3, 71.0, 32.9, 28.3. HRMS: exact mass calcd for $C_{25}H_{23}NNaO_5$ 440.1474 $[M + Na]^+$, found 440.1471. HPLC (Chiralpak IA-H, hexane/i-PrOH = 80/20, flow rate 0.5 mL/min, λ = 238 nm): retention time 19.8 min (major), 24.0 min (minor). $[\alpha]_D^{20.0}$ = −27.4 (c = 0.25, $CHCl_3$, 94% ee).

*tert-Butyl 3-((3R,4aS)-10-Oxo-3,4,4a,10-tetrahydropyrano[4,3-b]-chromen-3-yl)-1H-indole-1-carboxylate (**4a**).* Total yield: 87% (36.2 mg, *endo*/*exo* = 3.4/1). Yellow solid. Mp: 97.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16 (d, J = 7.6 Hz, 1H), 7.99 (dd, J = 7.6, 1.6 Hz, 1H), 7.81 (d, J = 1.2 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.59 (s, 1H), 7.48−7.43 (m, 1H), 7,38−7.34 (m, 1H), 7.30−7.26 (m, 1H), 7,08−7.04 (m, 1H), 6.97 (dd, J = 8.4, 0.8 Hz, 1H), 5.51 (dd, J = 7.2, 2.8 Hz, 1H), 4.93 (td, J = 5.6, 1.6 Hz, 1H), 2.82−2.75 (m, 1H), 2.75−2.66 (m, 1H), 1.67 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.9, 160.8, 153.3, 149.6, 135.9, 135.3, 128.0, 127.7, 125.1, 123.1, 123.1, 123.1, 122.0, 119.6, 118.2, 117.9, 115.7, 112.2, 84.4, 71.6, 68.9, 33.0, 28.3. HRMS: exact mass calcd for $C_{25}H_{23}NNaO_5$ 440.1474 $[M + Na]^+$, found 440.1485. HPLC (Chiralpak IA-H, hexane/i-PrOH = 80/20, flow rate 0.5 mL/min, λ = 238 nm): retention time 17.96 min (major), 18.74 min (minor). $[\alpha]_D^{25.5}$ = 220.1 (c = 0.3, $CHCl_3$, 97% ee).

*tert-Butyl 3-((3R,4aR)-8-Fluoro-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (**3b**).* Total yield: 79% (34.3 mg, *endo*/*exo* = 3.4/1). White solid. Mp: 117.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.18 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 7.69 (s, 1H), 7.64−7.61 (m, 2H), 7.39−7.35 (m, 1H), 7,30−7.26 (m, 1H), 7,19−7.15 (m, 1H), 6.96−6.92 (m, 1H), 5.49−5.46 (m, 1H), 5.35 (ddd, J = 10.0, 6.6, 1.2 Hz, 1H), 2.81 (ddd, J = 13.2, 7.4, 2.0 Hz, 1H), 2.68 (td, J = 12.6, 10.0 Hz, 1H), 1.68 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 180.4 (d, J_{C-F} = 1.5 Hz), 159.0, 156.9 (d, J_{C-F} = 1.9 Hz), 154.6, 149.5, 135.8, 128.1, 125.2, 123.8, 123.6 (d, J_{C-F} = 2.0 Hz), 123.1, 122.7, 122.5, 119.5 (d, J_{C-F} = 4.9 Hz), 119.3 (d, J_{C-F} = 7.2 Hz), 117.9, 115.7, 112.7 (d, J_{C-F} = 23.6 Hz), 111.5, 84.4, 72.5, 71.2, 32.9, 28.3. HRMS: exact mass calcd for $C_{25}H_{23}FNO_5$ 436.1560 $[M + H]^+$, found 436.1544. HPLC (Chiralpak IA-H, hexane/i-PrOH = 90/10, flow rate 0.5 mL/min, λ = 238 nm): retention time 29.4 min (major), 31.7 min (minor). $[\alpha]_D^{26.5}$ = −8.4 (c = 0.27, $CHCl_3$, 90% ee).

tert-Butyl 3-((3R,4aR)-8-Chloro-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate

dx.doi.org/10.1021/jo401592w | J. Org. Chem. 2013, 78, 10233−10239

(3c). Total yield: 88% (39.6 mg, *endo*/*exo* = 3.0/1). White solid. Mp: 119.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.18 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 2.8 Hz, 1H), 7.78 (s, 1H), 7.69 (s, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.41−7.35 (m, 2H), 7.30−7.26 (m, 1H), 6.91 (d, J = 8.4 Hz, 1H), 5.50−5.49 (m, 1H), 5.37 (ddd, J = 10.0, 6.4, 1.2 Hz, 1H), 2.82 (ddd, J = 13.2, 6.6, 2.0 Hz, 1H), 2.69 (td, J = 12.6, 10.0 Hz, 1H), 1.68 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 180.1, 159.2, 154.7, 149.5, 135.8, 135.1, 128.0, 127.6, 126.9, 125.2, 123.9, 123.8, 123.1, 119.4, 119.4, 117.9, 115.7, 111.3, 84.5, 72.5, 71.3, 32.8, 28.3. HRMS: exact mass calcd for $C_{26}H_{26}ClNNaO_6$ 506.1346 [M + CH_3OH + Na]$^+$, found 506.1340. HPLC (Chiralpak IA-H, hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 238 nm): retention time 16.02 min (major), 18.12 min (minor). $[\alpha]_D^{27.1}$ = 25.3 (c = 0.33, $CHCl_3$, 90% ee).

tert-Butyl 3-((3R,4aR)-8-Bromo-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (3d). Total yield: 83% (41.1 mg, *endo*/*exo* = 3.0/1). White solid. Mp: 168.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.18 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 2.4 Hz, 1H), 7.78 (s, 1H), 7.69 (s, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.53 (dd, J = 8.8, 2.4 Hz, 1H), 7.39−7.35 (m, 1H), 7.30−7.26 (m, 1H), 6.86 (d, J = 8.8 Hz, 1H), 5.50−5.47 (m, 1H), 5.37 (ddd, J = 10.0, 6.8, 1.2 Hz, 1H), 2.82 (ddd, J = 13.2, 6.6, 2.0 Hz, 1H), 2.69 (td, J = 12.8, 10.0 Hz, 1H), 1.68 (s, 9H). ^{13}C NMR (100 MHz, CDC_{l3}): δ (ppm) 179.9, 159.6, 154.7, 149.6, 138.0, 135.8, 130.0, 128.0, 125.2, 124.2, 123.9, 123.1, 119.8, 119.5, 117.9, 115.7, 114.8, 111.3, 84.5, 72.5, 71.3, 32.8, 28.3. HRMS: exact mass calcd for $C_{25}H_{22}BrNNaO_5$ 518.0579 [M + Na]$^+$, found 518.0573. HPLC (Chiralpak IA-H, hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 238 nm): retention time 16.89 min (major), 19.74 min (minor). $[\alpha]_D^{19.8}$ = 17.3 (c = 0.25, $CHCl_3$, 89% ee).

tert-Butyl 3-((3R,4aR)-8-Methyl-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (3e). Total yield: 75% (32.3 mg, *endo*/*exo* = 3.5/1). White solid. Mp: 131.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.19 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 1.6 Hz, 1H), 7.75 (s, 1H), 7.69 (s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.39−7.35 (m, 1H), 7.30−7.26 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 5.48−5.44 (m, 1H), 5.34 (ddd, J = 10.0, 6.6, 1.2 Hz, 1H), 2.80 (ddd, J = 13.2, 6.8, 2.0 Hz, 1H), 2.68 (td, J = 12.4, 10.0 Hz, 1H), 2.33 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.4, 158.8, 153.9, 149.5, 136.3, 135.8, 131.6, 128.1, 127.1, 125.1, 123.8, 123.1, 122.5, 119.5, 118.2, 117.5, 115.7, 112.2, 84.4, 72.3, 71.0, 33.0, 28.3, 20.6. HRMS: exact mass calcd for $C_{26}H_{25}NNaO_5$ 454.1630 [M + Na]$^+$, found 454.1635. HPLC (Chiralpak IA-H, hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 238 nm): retention time 13.07 min (major), 17.14 min (minor). $[\alpha]_D^{28.2}$ = 16.9 (c = 0.33, $CHCl_3$, 94% ee).

tert-Butyl 3-((3R,4aR)-8-Methoxy-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (3f). Total yield: 71% (31.7 mg, *endo*/*exo* = 3.0/1). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.18 (d, J = 8.4 Hz, 1H), 7.75 (s, 1H), 7.69 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 3.6 Hz, 1H), 7.39−7.35 (m, 1H), 7.30−7.26 (m, 1H), 7.06 (dd, J = 9.2, 3.2 Hz, 1H) 6.89 (d, J = 8.8 Hz, 1H), 5.48−5.44 (m, 1H), 5.32 (ddd, J = 9.8, 6.6, 1.2 Hz, 1H), 3.83 (s, 3H), 2.80 (ddd, J = 13.2, 6.8, 2.0 Hz, 1H), 2.68 (td, J = 12.6, 10.0 Hz, 1H), 1.68 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.2, 155.3, 154.7, 154.1, 149.5 135.8, 128.1, 125.1, 124.1, 123.8, 123.1, 123.0, 119.5, 119.0, 118.1, 115.7, 112.1, 108.3, 84.4, 72.4, 71.1, 55.9, 33.0, 28.3. HRMS: exact mass calcd for $C_{27}H_{29}NNaO_7$ 502.1842 [M + CH_3OH + Na]$^+$, found 502.1841. HPLC (Chiralpak IA-H, hexane/i-PrOH = 90/10, flow rate 0.5 mL/min, λ = 238 nm): retention time 36.34 min (major), 43.83 min (minor). $[\alpha]_D^{28.7}$ = 17.3 (c = 0.24, $CHCl_3$, 74% ee).

tert-Butyl 3-((3R,4aR)-7-Fluoro-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (3g). Total yield: 85% (36.9 mg, *endo*/*exo* = 3.5/1). White solid. Mp: 162.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.18 (d, J = 8.4 Hz, 1H), 8.00 (dd, J = 8.4, 6.4 Hz, 1H), 7.76 (s, 1H), 7.69 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.39−7.35 (m, 1H), 7.30−7.26 (m, 1H), 6.78 (td, J = 8.0, 2.0 Hz, 1H) 6.65 (dd, J = 9.6, 2.4 Hz, 1H), 5.49−5.46 (m, 1H), 5.41 (ddd, J = 10.0, 6.8, 1.2 Hz, 1H), 2.82 (ddd, J = 13.6, 6.8, 2.0 Hz, 1H), 2.69 (td, J = 12.8, 10.0 Hz, 1H), 1.68 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 180.0, 168.4, 165.9, 162.4 (d, J_{C-F} = 10.6 Hz), 154.3, 149.5, 135.8, 129.9 (d, J_{C-F} = 10.5 Hz), 128.0, 125.2, 123.8, 123.1, 119.6 (d, J_{C-F} = 3.4 Hz), 119.5, 118.0, 115.7, 111.3, 110.3 (d, J_{C-F} = 22.3 Hz), 104.8 (d, J_{C-F} = 24.3 Hz), 84.4, 72.4, 71.6, 32.9, 28.3. HRMS: exact mass calcd for $C_{25}H_{25}FNO_6$ 454.1666 [M + H_2O + H]$^+$, found 454.1666. HPLC (Chiralpak IA-H, hexane/i-PrOH = 95/5, flow rate 1.0 mL/min, λ = 238 nm): retention time 24.96 min (major), 28.08 min (minor). $[\alpha]_D^{29.2}$ = 5.0 (c = 0.38, $CHCl_3$, 92% ee).

tert-Butyl 3-((3R,4aR)-7-Methyl-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (3h). Total yield: 84% (36.2 mg, *endo*/*exo* = 3.8/1). White solid. Mp: 172.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.18 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.69 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 3.6 Hz, 1H), 7.39−7.35 (m, 1H), 7.30−7.26 (m, 1H), 6.90−6.87 (m, 1H), 6.76 (s, 1H), 5.48−5.44 (m, 1H), 5.35 (ddd, J = 10.0, 6.8, 1.2 Hz, 1H), 2.80 (ddd, J = 13.2, 6.4, 2.0 Hz, 1H), 2.67 (td, J = 12.8, 10.0 Hz, 1H), 2.36 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.0, 160.8, 153.6, 149.5, 146.9, 135.8, 128.1, 127.3, 125.1, 123.8, 123.4, 123.1, 120.5, 119.5, 118.2, 117.8, 115.7, 112.0, 84.4, 72.3, 71.0, 33.0, 28.3, 22.0. HRMS: exact mass calcd for $C_{27}H_{29}NNaO_6$ 486.1893 [M + CH_3OH + Na]$^+$, found 486.1895. HPLC (Chiralpak IA-H, hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 238 nm): retention time 19.86 min (major), 26.86 min (minor). $[\alpha]_D^{29.6}$ = 15.7 (c = 0.22, $CHCl_3$, 92% ee).

tert-Butyl 3-((3R,4aR)-9-Methoxy-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (3i). Total yield: 86% (38.4 mg, *endo*/*exo* = 3.5/1). White solid. Mp: 131.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.18 (d, J = 8.0 Hz, 1H), 7.72 (s, 1H), 7.67 (s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.38−7.33 (m, 2H), 7.28 (d, J = 7.2 Hz, 1H), 6.60−6.54 (m, 2H), 5.41 (d, J = 11.6 Hz, 1H), 5.25 (dd, J = 9.6, 6.8, Hz, 1H), 3.93 (s, 3H), 2.77 (ddd, J = 13.2, 6.4, 2.0 Hz, 1H), 2.61 (td, J = 12.8, 9.6 Hz, 1H), 1.68 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 180.2, 162.6, 161.2, 153.5, 149.5, 135.8, 135.2, 128.1, 125.1, 123.7, 123.0, 119.6, 118.3, 115.6, 113.4, 113.0, 110.2, 105.3, 84.3, 72.0, 70.8, 56.3, 33.0, 28.3. HRMS: exact mass calcd for $C_{27}H_{29}NNaO_7$ 502.1842 [M + CH_3OH + Na]$^+$, found 502.1841. HPLC (Chiralpak IA-H, hexane/i-PrOH = 80/20, flow rate 1.0 mL/min, λ = 238 nm): retention time 25.20 min (major), 40.33 min (minor). $[\alpha]_D^{29.9}$ = 96.2 (c = 0.30, $CHCl_3$, 79% ee).

tert-Butyl 5-Fluoro-3-((3R,4aR)-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (3j). Total yield: 74% (32.2 mg, *endo*/*exo* = 3.4/1). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.15−8.13 (m, 1H), 7.98 (dd, J = 7.6, 1.6 Hz, 1H), 7.75 (s, 1H), 7.71 (s, 1H), 7.49−7.44 (m, 1H), 7.28 (dd, J = 8.8, 2.4 Hz, 1H), 7.12−7.05 (m, 2H), 6.97−6.95 (m, 1H), 5.44−5.40 (m, 1H), 5.37 (ddd, J = 10.0, 6.8, 1.2 Hz, 1H), 2.80 (ddd, J = 13.2, 6.8, 2.0 Hz, 1H), 2.66 (td, J = 12.8, 10.0 Hz, 1H), 1.68 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.1, 160.6 (d, J_{C-F} = 18.2 Hz), 158.2, 153.8, 149.2, 135.4, 132.2, 129.0 (d, J_{C-F} = 9.3 Hz), 127.5, 125.2, 122.8, 122.2, 117.9 (d, J_{C-F} = 3.2 Hz), 117.7, 116.7 (d, J_{C-F} = 9.1 Hz), 113.0 (d, J_{C-F} = 24.6 Hz), 112.1, 105.3 (d, J_{C-F} = 24.7 Hz), 84.7, 72.1, 70.9, 32.8, 28.2. HRMS: exact mass calcd for $C_{25}H_{23}FNO_5$ 436.1560 [M + H]$^+$, found 436.1567. HPLC (Chiralpak IA-H, hexane/i-PrOH = 80/20, flow rate 0.5 mL/min, λ = 238 nm): retention time 21.12 min (major), 26.08 min (minor). $[\alpha]_D^{30.8}$ = 22.9 (c = 0.20, $CHCl_3$, 90% ee).

tert-Butyl 5-Chloro-3-((3R,4aR)-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (3k). Total yield: 91% (41.0 mg, *endo*/*exo* = 3.2/1). White solid. Mp: 143.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.11 (d, J = 8.8 Hz, 1H), 7.98 (dd, J = 8.0, 2.0 Hz, 1H), 7.76 (s, 1H), 7.70 (s, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.49−7.45 (m, 1H), 7.32 (dd, J = 8.8, 2.0 Hz, 1H), 7.10−7.06 (m, 1H), 6.96 (d, J = 8.4 Hz, 1H), 5.45−5.41 (m, 1H), 5.38 (ddd, J = 10.0, 6.8, 1.2 Hz, 1H), 2.81 (ddd, J = 13.2, 6.8, 2.0 Hz, 1H), 2.66 (td, J = 12.8, 10.4 Hz, 1H), 1.68 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.1, 160.7, 153.8, 149.1, 135.5, 131.8, 129.2, 128.9, 127.5, 125.4, 125.0, 122.8, 122.2, 119.3, 117.7, 117.6, 116.7, 112.1, 84.9, 72.0, 70.9, 32.9, 28.2. HRMS: exact mass calcd for $C_{25}H_{22}ClNNaO_5$ 474.1084 [M + Na]$^+$, found 474.1085. HPLC (Chiralpak IA-H, hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ =

238 nm): retention time 15.76 min (major), 19.93 min (minor). $[\alpha]_D^{30.4}$ = 5.8 (*c* = 0.57, $CHCl_3$, 88% ee).

*tert-Butyl 5-Bromo-3-((3R,4aR)-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (**3l**).* Total yield: 87% (43.1 mg, *endo*/*exo* = 3.4/1). White solid. Mp: 147.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (d, *J* = 8.8 Hz, 1H), 7.98 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.76−7.75 (m, 2H), 7.68 (s, 1H), 7.49−7.45 (m, 2H), 7.10−7.06 (m, 1H), 6.96 (dd, *J* = 8.0, 0.8 Hz, 1H), 5.44−5.41 (m, 1H), 5.38 (ddd, *J* = 10.0, 6.8, 1.2 Hz, 1H), 2.80 (ddd, *J* = 13.6, 6.8, 2.0 Hz, 1H), 2.65 (td, *J* = 12.8, 10.0 Hz, 1H), 1.68 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.1, 160.7, 153.8, 149.1, 135.5, 134.6, 129.8, 128.1, 127.5, 124.8, 122.9, 122.3, 122.2, 117.7, 117.5, 117.1, 116.5, 112.1, 84.9, 72.0, 70.9, 32.9, 28.2. HRMS: exact mass calcd for $C_{25}H_{22}BrNNaO_5$ 518.0579 $[M + Na]^+$, found 518.0580. HPLC (Chiralpak IB-H, hexane/i-PrOH = 95/5, flow rate 1.0 mL/min, λ = 238 nm): retention time 17.12 min (major), 23.44 min (minor). $[\alpha]_D^{30.1}$ = 8.6 (*c* = 0.68, $CHCl_3$, 91% ee).

*tert-Butyl 5-Methoxy-3-((3R,4aR)-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (**3m**).* Total yield: 51% (22.8 mg, *endo*/*exo* = 3.0/1). White solid. Mp: 120.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (d, *J* = 8.8 Hz, 1H), 7.99 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.77 (s, 1H), 7.66 (s, 1H), 7.49−7.44 (m, 1H), 7.09−7.05 (m, 2H), 6.99−6.95 (m, 2H), 5.46−5.42 (m, 1H), 5.38 (ddd, *J* = 10.4, 6.8, 1.2 Hz, 1H), 3.87 (s, 3H), 2.81 (ddd, *J* = 13.6, 6.8, 2.0 Hz, 1H), 2.69 (td, *J* = 12.8, 10.0 Hz, 1H), 1.67 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.2, 160.8, 156.2, 154.0, 149.5, 135.4, 130.5, 129.0, 127.5, 124.4, 122.9, 122.2, 117.8, 117.7, 116.4, 113.9, 112.0, 102.2, 84.2, 72.3, 71.1, 55.9, 32.7, 28.3. HRMS: exact mass calcd for $C_{26}H_{25}NNaO_6$ 470.1580 $[M + Na]^+$, found 470.1580. HPLC (Chiralpak IB-H, hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 238 nm): retention time 14.26 min (major), 21.12 min (minor). $[\alpha]_D^{30.7}$ = 1.8 (*c* = 0.42, $CHCl_3$, 93% ee).

*tert-Butyl 6-Chloro-3-((3R,4aR)-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (**3n**).* Total yield: 77% (34.7 mg, *endo*/*exo* = 1/1). White solid. Mp: 160.5 °C. ^{1}H NMR (400 MHz, CDCl3): δ (ppm) 8.23 (s, 1H), 7.98 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.75 (s, 1H), 7.66 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.47 (t, *J* = 8.4 Hz, 1H), 7.28−7.27 (m, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 5.44 (d, *J* = 13.2 Hz, 1H), 5.40−5.36 (m, 1H), 2.80 (ddd, *J* = 13.2, 6.8, 2.0 Hz, 1H), 2.66 (td, *J* = 12.4, 10.4 Hz, 1H), 1.68 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.1, 160.7, 153.8, 149.1, 136.3, 135.5, 131.3, 127.5, 126.6, 124.2, 123.7, 122.9, 122.2, 120.3, 118.0, 117.8, 116.0, 112.1, 85.0, 72.1, 70.9, 33.0, 28.2. HRMS: exact mass calcd for $C_{26}H_{26}ClNNaO_6$ 506.1346 $[M + CH_3OH + Na]^+$, found 506.1347. HPLC (Chiralpak IB-H, hexane/i-PrOH = 95/5, flow rate 1.0 mL/min, λ = 238 nm): retention time 13.36 min (minor), 14.95 min (major). $[\alpha]_D^{30.9}$ = 13.4 (*c* = 0.36, $CHCl_3$, 90% ee).

*tert-Butyl 3-((3R,4S,4aR)-4-Methyl-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (**3o**).* Total yield: 42% (18.1 mg, *endo*/*exo* = 1/1.6). White solid. Mp: 158.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.19 (d, *J* = 8.0 Hz, 1H), 7.98 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.77 (s, 1H), 7.69 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.48−7.44 (m, 1H), 7.39−7.35 (m, 1H), 7.28−7.24 (m, 1H), 7.09−7.05 (m, 1H), 6.98 (dd, *J* = 8.4, 0.8 Hz, 1H), 5.05 (d, *J* = 11.6 Hz, 1H), 4.87 (dd, *J* = 9.2, 2.0 Hz, 1H), 2.88−2.81 (m, 1H), 1.69 (s, 9H), 1.09 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.4, 160.8, 154.0, 149.5, 136.0, 135.3, 128.0, 127.4, 125.6, 125.1, 123.1, 122.7, 122.1, 119.9, 117.8, 116.4, 115.7, 111.8, 84.4, 78.2, 77.0, 36.4, 28.3, 14.6. HRMS: exact mass calcd for $C_{27}H_{29}NNaO_6$ 486.1893 $[M + CH_3OH + Na]^+$, found 486.1879. HPLC (Chiralpak IA-H, hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 238 nm): retention time 11.89 min (major), 17.11 min (minor). $[\alpha]_D^{25.2}$ = −9.2 (*c* = 0.20, $CHCl_3$, 12% ee).

*tert-Butyl 3-((3R,4S,4aS)-4-Methyl-10-oxo-3,4,4a,10-tetrahydropyrano[4,3-b]chromen-3-yl)-1H-indole-1-carboxylate (**4o**).* Total yield: 42% (18.1 mg, *endo*/*exo* = 1/1.6). Yellow solid. Mp: 155.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.15 (d, *J* = 7.6 Hz, 1H), 7.96 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.80 (d, *J* = 1.6 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.53 (s, 1H), 7.45−7.41 (m, 1H), 7.37−7.34 (m, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 5.34 (d, *J* = 5.2 Hz, 1H), 4.91 (dd, *J* = 5.6, 1.6 Hz, 1H), 2.97−2.92 (m, 1H), 1.67 (s, 9H), 1.29 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 181.4, 160.8, 152.2, 135.8, 135.1, 135.0, 127.6, 127.2, 124.9, 123.3, 122.8, 122.7, 121.6, 119.4, 117.8, 117.6, 115.5, 110.3, 84.3, 74.3, 71.3, 34.2, 28.0, 11.8. HRMS: exact mass calcd for $C_{26}H_{25}NNaO_5$ 454.1630 $[M + Na]^+$, found 454.1632. HPLC (Chiralpak IA-H, hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 238 nm): retention time 8.55 min (major), 12.70 min (minor). $[\alpha]_D^{25.0}$ = 26.2 (*c* = 0.20, $CHCl_3$, 67% ee).

*tert-Butyl 3-(10-Oxo-2-tosyl-3,4,4a,10-tetrahydro-2H-chromeno-[3,2-c]pyridin-3-yl)-1H-indole-1-carboxylate (**3p**).* Total yield: 80% (45.6 mg, *endo*/*exo* = 3.6/1). Yellow oil. Attempts to separate the two diastereoisomers by column chromatography failed, and the ^{1}H NMR and ^{13}C NMR spectra were recorded for the mixture containing *endo* and *exo* products. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.28−8.27 (m, 1H), 8.08−7.93 (m, 2H), 7.61 (d, *J* = 8.0 Hz, 1.1H), 7.47 (d, *J* = 7.6 Hz, 0.6H), 7.42−7.30 (m, 3H), 7.24−7.16 (m, 2H), 7.09−6.98 (m, 2H), 6.84−6.78 (m, 2H), 5.67 (s, 0.5H), 5.40 (dd, *J* = 8.4, 4.2 Hz, 0.5H), 5.12−5.09 (m, 0.5H), 4.77 (dd, *J* = 10.4, 5.6 Hz, 0.5H), 2.93−2.85 (m, 0.5H), 2.76 (ddd, *J* = 12.4, 5.6, 2.4 Hz, 0.5H), 2.62−2.56 (m, 0.5H), 2.35 (s, 1.6H), 2.20 (s, 1.3H), 2.17−2.10 (m, 0.5H), 1.62 (s, 5H), 1.58 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 180.6, 179.9, 160.6, 160.5, 149.2, 149.1, 145.0, 144.2, 135.7, 135.3, 135.2, 135.0, 134.6, 133.4, 130.0, 129.0, 128.1, 127.6, 127.5, 127.3, 127.0, 125.4, 125.0, 124.4, 123.4, 123.0, 122.9, 122.7, 122.0, 119.5, 118.6, 117.8, 117.7, 116.4, 115.7, 115.2, 113.1, 112.2, 84.4, 84.0, 70.2, 69.8, 50.6, 50.5, 36.0, 31.6, 28.2, 28.1, 21.7, 21.5. HRMS: exact mass calcd for $C_{32}H_{30}N_2NaO_6S$ 593.1722 $[M + Na]^+$, found 593.1726. HPLC (Chiralpak IA-H, hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 238 nm): retention time 14.08 min (major for *endo* product), 17.58 min (minor for *endo* product), 90% ee for *endo* product.

Typical Procedure for the Transformation of *endo* Product 3a to Chromone-Derived Product 5a. To a solution of **3a** (0.42 g, 1 mmol) and Wilkinson's catalyst (46 mg, 0.05 mmol) in toluene (20.0 mL) was added a solution of triethylsilane in toluene (12 μL, 0.07 mmol, in 5 mL of toluene) under an Ar atmosphere, and the mixture was stirred at 100 °C for 20 h. After evaporation of the solvent under reduced pressure, the crude product was directly purified by flash chromatography (ethyl acetate/petroleum ether = 1/4) to afford **5a** as a white solid.

*(R)-tert-Butyl 3-(10-Oxo-1,3,4,10-tetrahydropyrano[4,3-b]-chromen-3-yl)-1H-indole-1-carboxylate (**5a**).* Yield: 89% (0.37 g). White solid. Mp: 172.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.22 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.70−7.63 (m, 3H), 7.47−7.33 (m, 3H), 7.29−7.27 (m, 1H), 5.11 (dd, *J* = 9.6, 3.2 Hz, 1H), 4.97 (d, *J* = 15.2 Hz, 1H), 4.77 (td, *J* = 15.2, 2.0 Hz, 1H), 3.28−3.20 (m, 1H), 3.06−3.01 (m, 1H), 1.67 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 175.7, 160.4, 156.2, 149.7, 135.9, 133.6, 128.5, 125.7, 125.1, 125.0, 123.7, 123.0, 123.0, 119.9, 119.8, 117.9, 117.0, 115.6, 84.1, 69.6, 62.8, 33.0, 28.3. HRMS: exact mass calcd for $C_{25}H_{23}NNaO_5$ 440.1474 $[M + Na]^+$, found 440.1470. HPLC (Chiralpak IB-H, hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 238 nm): retention time 13.21 min (major), 18.26 min (minor). $[\alpha]_D^{26.4}$ = 47.9 (*c* = 0.35, $CHCl_3$, 94% ee).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization (^{1}H NMR, ^{13}C NMR, HPLC) for all new compounds, including X-ray data and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cjzhu@nju.edu.cn. Fax/phone: (+86) 25-83594886.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (Grants 21172106 and 21074054), the National Basic Research Program of China (Grant 2010CB923303), and the Research Fund for the Doctoral Program of Higher Education of China (Grant 20120091110010) for their financial support.

■ REFERENCES

(1) (a) Ellis, G. P. *Chromenes, Chromanones, and Chromones*; Wiley: New York, 1977. (b) Ellis, G. P.; Lockhart, I. M. *Chromans and Tocopherols*; Wiley: New York, 1981. (c) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939. (d) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P.; Sylvain, C. *J. Am. Chem. Soc.* **2004**, *126*, 11966. (e) Sharma, S. K.; Kumar, S.; Chand, K.; Kathuria, A.; Gupta, A.; Jain, R. *Curr. Med. Chem.* **2011**, *18*, 3825. (f) Kikuchi, H.; Isobe, M.; Sekiya, M.; Abe, Y.; Hoshikawa, T.; Ueda, K.; Kurata, S.; Katou, Y.; Oshima, Y. *Org. Lett.* **2011**, *13*, 4624. (g) Goel, R.; Sharma, V.; Budhiraja, A.; Ishar, M. P. S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4665.

(2) (a) Dang, A.-T.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *Org. Lett.* **2007**, *10*, 233. (b) Park, J. Y.; Ullapu, P. R.; Choo, H.; Lee, J. K.; Min, S.-J.; Pae, A. N.; Kim, Y.; Baek, D.-J.; Cho, Y. S. *Eur. J. Org. Chem.* **2008**, 5461. (c) Baskar, B.; Dakas, P.-Y.; Kumar, K. *Org. Lett.* **2011**, *13*, 1988. (d) Liu, T.-L.; He, Z.-L.; Wang, C.-J. *Chem. Commun.* **2011**, *47*, 9600. (e) Baskar, B.; Wittstein, K.; Sankar, M. G.; Khedkar, V.; Schürmann, M.; Kumar, K. *Org. Lett.* **2012**, *14*, 5924. (f) Eleya, N.; Malik, I.; Reimann, S.; Wittler, K.; Hein, M.; Patonay, T.; Villinger, A.; Ludwig, R.; Langer, P. *Eur. J. Org. Chem.* **2012**, 1639. (g) Beekman, A. M.; Castillo Martinez, E.; Barrow, R. A. *Org. Biomol. Chem.* **2013**, *11*, 1109.

(3) (a) Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830. (b) Wang, H.-F.; Cui, H.-F.; Chai, Z.; Li, P.; Zheng, C.-W.; Yang, Y.-Q.; Zhao, G. *Chem.—Eur. J.* **2009**, *15*, 13299. (c) Zu, L.; Zhang, S.; Xie, H.; Wang, W. *Org. Lett.* **2009**, *11*, 1627. (d) Butler, J. D.; Conrad, W. E.; Lodewyk, M. W.; Fettinger, J. C.; Tantillo, D. J.; Kurth, M. J. *Org. Lett.* **2010**, *12*, 3410. (e) Gao, Y.; Ren, Q.; Wu, H.; Li, M.; Wang, J. *Chem. Commun.* **2010**, *46*, 9232. (f) Dückert, H.; Khedkar, V.; Waldmann, H.; Kumar, K. *Chem.—Eur. J.* **2011**, *17*, 5130. (g) Wang, H.; Luo, J.; Han, X.; Lu, Y. *Adv. Synth. Catal.* **2011**, *353*, 2971. (h) Li, J.-L.; Zhou, S.-L.; Chen, P.-Q.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Chem. Sci.* **2012**, *3*, 1879. (i) Nibbs, A. E.; Scheidt, K. A. *Eur. J. Org. Chem.* **2012**, 449.

(4) (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970. (b) Thomson, R. H. *The Chemistry of Natural Products*; Blackie and Son: Glasgow, Scotland, 1985; (c) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S. *J. Med. Chem.* **1988**, *31*, 2235. (d) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179. (e) Bondensgaard, K.; Ankersen, M.; Thøgersen, H.; Hansen, B. S.; Wulff, B. S.; Bywater, R. P. *J. Med. Chem.* **2004**, *47*, 888. (f) Chen, F.-E.; Huang, J. *Chem. Rev.* **2005**, *105*, 4671. (g) Marsault, E.; Peterson, M. L. *J. Med. Chem.* **2011**, *54*, 1961. (h) Adams, G. L.; Carroll, P. J.; Smith, A. B. *J. Am. Chem. Soc.* **2012**, *135*, 519. (i) Johansson, H.; Jørgensen, T. B.; Gloriam, D. E.; Brauner-Osborne, H.; Pedersen, D. S. *RSC Adv.* **2013**, *3*, 945.

(5) Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9236.

(6) (a) Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. *Chem. Commun.* **2010**, *46*, 327. (b) Gioia, C.; Bernardi, L.; Ricci, A. *Synthesis* **2010**, 161. (c) Wang, X.-F.; Chen, J.-R.; Cao, Y.-J.; Cheng, H.-G.; Xiao, W.-J. *Org. Lett.* **2010**, *12*, 1140. (d) Zheng, C.; Lu, Y.; Zhang, J.; Chen, X.; Chai, Z.; Ma, W.; Zhao, G. *Chem.—Eur. J.* **2010**, *16*, 5853. (e) Tan, B.; Hernández-Torres, G.; Barbas, C. F. *J. Am. Chem. Soc.* **2011**, *133*, 12354. (f) Liu, W.; Lim, H. J.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2012**, *134*, 5496. (g) Xiao, Y.-C.; Zhou, Q.-Q.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Org. Lett.* **2012**, *14*, 5940.

(7) For selected reviews, see: (a) Jørgensen, K. A. *Eur. J. Org. Chem.* **2004**, 2093. (b) Lin, L.; Liu, X.; Feng, X. *Synlett* **2007**, 2147. (c) Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P. *Synthesis* **2010**, 1. (d) Núñez, M. G.; García, P.; Moro, R. F.; Díez, D. *Tetrahedron* **2010**, *66*, 2089. (e) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703. (f) Jiang, X.; Wang, R. *Chem. Rev.* **2013**, *113*, 5515.

(8) Mao, Z.; Li, W.; Shi, Y.; Mao, H.; Lin, A.; Zhu, C.; Cheng, Y. *Chem.—Eur. J.* **2013**, *19*, 9754.

(9) Tanaka, M.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *Chem. Lett.* **1994**, *23*, 1455.

(10) CCDC-927360 (**5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.