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Construction of the Erythrinane Core Skeleton via Asymmetric Catalytic Cascade Reaction of Tertiary Enamides

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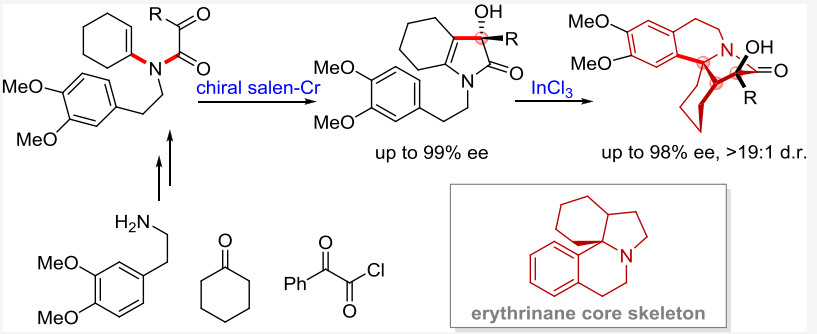

ABSTRACT: We report herein an efficient cascade strategy for the rapid construction of a highly enantioenriched erythrinane core skeleton. Under the sequential catalysis of a chiral Cr(III)(salen)Cl and $InCl_3$, cyclohexanone-derived tertiary enamides undergo an intramolecular enantioselective nucleophilic addition followed by diastereoselective Pictet−Spengler cyclization. This method is highly enantio- and diastereoselective, leading to diverse erythrina alkaloid derivatives as the sole diastereoisomer with up to 98% ee.

INTRODUCTION

The erythrina alkaloids contain a unique tetracyclic spiroamine scaffold and display remarkable curare-like and hypnotic activities.[1] Many compounds containing the erythrinane skeleton also possess interesting biological activities, including sedative, hypotensive, and CNS depressant properties.[2] Because of distinctive molecular structures and diverse pharmacological activities, these alkaloids are very attractive targets for synthetic organic chemists. Despite many elegant synthetic methods documented in the literature,[3,4] the catalytic enantioselective synthesis of erythrina alkaloids and their analogues is rare. In the synthesis of (+)-dihydro-*β*-erythroidine, Kristensen and Vital reported a Pd/(*S*,*S*-salen)-catalyzed enantioselective allylation to produce allyl prolinone, this chiral key intermediate then went through a 12-step synthetic sequence to finally deliver the lactonic erythrina alkaloid.[5] You's group developed a Pd(0)-catalyzed intramolecular dearomative arylation of 5-hydroxyl indoline, which produces an erythrinane derivative in 31% yield and 86% ee.[6] Nevertheless, the de novo construction of the erythrinane skeleton allowing structurally diverse modification in the catalytic enantioselective manner remains a big challenge and in great demand.

As an enamine variant, tertiary enamides are stable compounds and they show diminished enaminic (nucleophilic) reactivity because of the electron-withdrawing nature of the N-acyl group. Therefore, tertiary enamides have long been known as inert chemicals in organic transformations. However, this conventional notion has been challenged in recent years. Due to the cross-conjugation system within tertiary enamides, there will be two resonance structures that can be obtained by conjugation of the long-pair electrons of nitrogen with carbon−carbon double bond and carbon−oxygen double bond, respectively. The enabled regulation of the cross-conjugation system by means of the nature of the EWG on the nitrogen atom as well as the reaction media could revive and modulate the nucleophilicity of tertiary enamides. We have long been interested in exploring the nucleophilic reaction and synthetic application of tertiary eamides,[7−14] thus demonstrating that tertiary enamides are unique, shelf-stable, and versatile synthons in organic synthesis.[15] Following the reactivity of the parent enamine with electrophiles, tertiary enamides generally produce the expected monofunctionalized products. The reactions are believed to proceed through an iminium intermediate, followed by iminium−enamine tautomerization (Scheme 1a). Based on this hypothesis, we have recently developed a catalytic asymmetric cascade reaction involving the nucleophilic addition of tertiary enamides to ketonic carbonyls and the trapping of acyliminium by a benzene moiety (Scheme 1b). We envisioned

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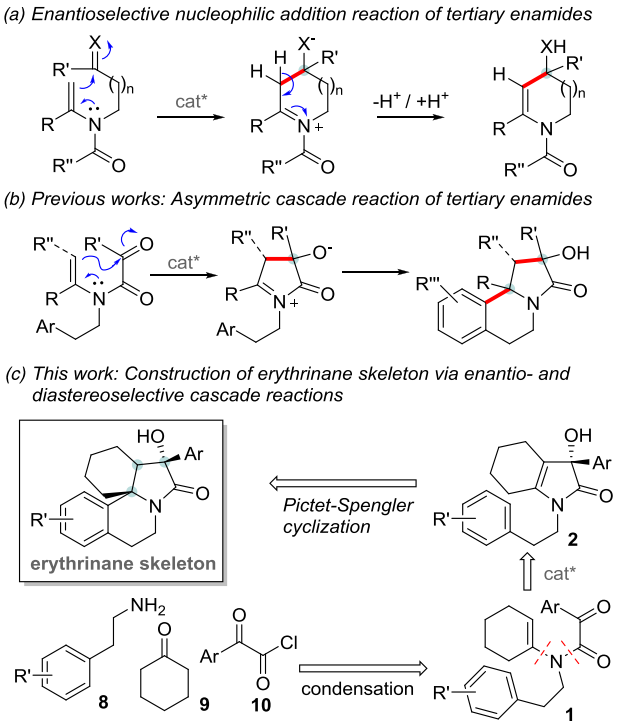
Scheme 1. Design of a Catalytic Asymmetric Cascade Reaction for the Construction of Erythrinane Skeleton

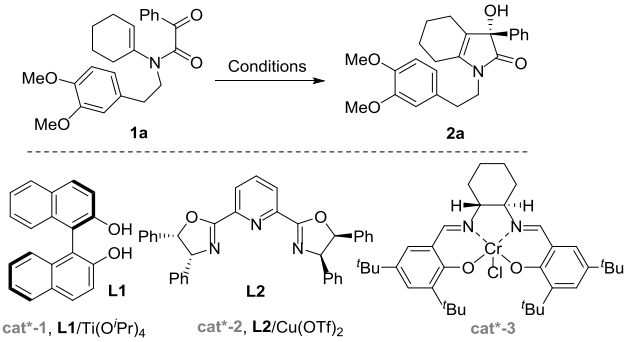


that the use of cyclohexanone-derived tertiary enamides **1** bearing an electron-rich aryl moiety would first lead to the formation of 5−6 fused ring system **2**. Had this been the case, a cascade intramolecular Pictet−Spengler cyclization could be expected, leading eventually to ABCD ring-fused erythrinane core skeleton **3** in a very short synthetic sequence.[16] Disconnection of both the C−N bond of amide and enamine function in **1** would afford phenethylamine **8**, cyclohexanone (**9**), and 2-oxo-2-arylacetylchloride **10**, three simple reagents all being commercially available (Scheme 1c). We report herein a catalytic asymmetric reaction cascade involving the nucleophilic addition of tertiary enamides to ketone carbonyls and the trapping of acyliminium by Pictet−Spengler cyclization. This method is highly efficient and enantio- and diastereoselective, thus leading to diverse erythrina alkaloid derivatives as the sole diastereoisomers with up to 98% ee.

RESULTS AND DISCUSSION

To begin with, condensation between alkyl amine **8** and cyclohexanone (**9**) followed by acylation of the resulting imine afforded tertiary enamide **1a** as our starting reagent. Exploring the reaction of **1a**, we first looked at the performance of the complexation of chiral binol-Ti(O^iPr)$_4$ and Pybox with copper, which were validated in catalyzing the enantioselective addition of tertiary enamides to ketones.[12a,17] Surprisingly, they both gave low yields of the desired product and low enantioselective control (Table 1, entries 1−2), indicating that the structure of enamides may have a great influence on their reactivity. The combination of (*R*,*R*)-Cr(III)(salen)Cl and Na_2CO_3 were then tested because in our previous result they also performed well in the enantioselective addition of tertiary enamides to ketonic carbonyls.[12c] Stirring a benzene solution of **1a** in the presence of (*R*,*R*)-Cr(III)(salen)Cl (0.2 equiv) and Na_2CO_3 (0.2 equiv) at room temperature for 60 h afforded **2a** as the only product in

Table 1. Condition Optimization for Enantioselective Intramolecular Addition of 1a−2a



entry	cat*	solvent	temp. (°C)	time (h)	**2a** (%)[d]	ee (%)[e]
1[a]	cat*-1	xylenes	rt	12	28	25
2[b]	cat*-2	DCM	rt	12	35	13
3[c]	cat*-3	benzene	rt	60	83	50
4[c]	cat*-3	toluene	rt	12	90	77
5[c]	cat*-3	xylenes	rt	24	86	59
6[c]	cat*-3	DCM	rt	24	99	15
7[c]	cat*-3	DCE	rt	24	98	40
8[c]	cat*-3	CCl_4	rt	12	86	66
9[f]	cat*-3	toluene	rt	12	90	86
10[f]	cat*-3	toluene	10	18	99	94
11[f]	cat*-3	toluene	0	12	trace	n.d.[g]

[a]Conditions: **1a** (0.2 mmol), cat*-1 (20 mol %), xylenes (6 mL), RT. [b]Conditions: **1a** (0.2 mmol), cat*-2 (10 mol %), DCM, RT. [c]Conditions: **1a** (0.2 mmol), (*R*,*R*)-Cr(III)(salen)Cl (0.04 mmol, 0.2 equiv), Na_2CO_3 (0.04 mmol, 0.2 equiv), solvent (6 mL). [d]Yield of the isolated product. [e]Measured by chiral-phase high-performance liquid chromatography (HPLC). [f]100 mg 4 Å MS was added. [g]n.d. not determined.

83% yield but with only moderate ee (entry 3). Gratifyingly, other aromatic solvents such as toluene (entry 4) and xylenes (entry 5) could dramatically improve both the conversion and stereoselectivity, with toluene being the best to obtain **2a** in 90% yield with 77% ee. However, switching to halogen-containing solvents like dichloromethane (DCM, entry 6), 1,2-dichloroethane (DCE, entry 7), and CCl_4 (entry 8) diminished the enantioselectivity. Toluene was chosen for further optimization. It is noteworthy that the use of 4 Å MS as an additive plays a decisive role in improving the stereocontrol (entry 9). Evidently, the ee value of this (*R*,*R*)-Cr(III)(salen)Cl-catalyzed cyclization was further increased to 94% when the reaction was performed at a lower temperature of 10 °C (entry 10). Nevertheless, further decreasing the temperature to 0 °C led to a much slower reaction (entry 11). Overall, the optimum conditions found consisted of stirring a toluene solution of **1a** (c = 0.033 M) at 10 °C in the presence of (*R*,*R*)-Cr(III)(salen)Cl (0.2 equiv), Na_2CO_3 (0.2 equiv), and 4 Å MS (500 mg/mmol) for 18 h. Under these conditions, compound **2a** was isolated in 99% yield with 94% ee.

With the optimized conditions in hand, the scope of this catalytic enantioselective cyclization was briefly examined. As shown in Scheme 2, tertiary enamides having both an electron-withdrawing (**1b**, **1c**) or an electron-donating group (**1d**) on the aromatic ring afforded the corresponding fused bicyclic product **2b**−**2d** in 86−95% yields and 93−99% ees. Analogously, a highly enantiopure 2-naphthyl-substituted product **2e** was synthesized in 80% yield and 92% ee. It is worth noting that 4,4-dimethylcyclohexanone and monoprotected cyclohexane-

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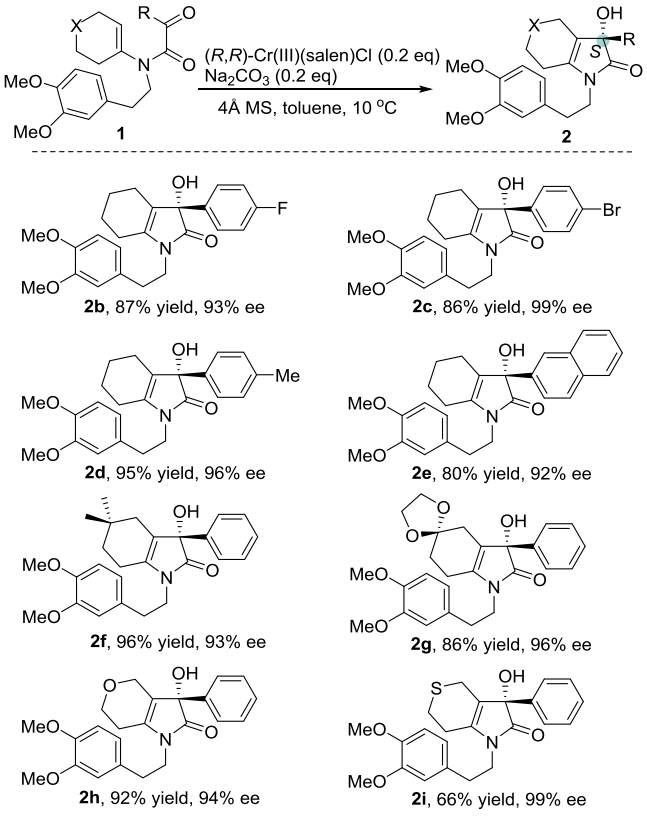
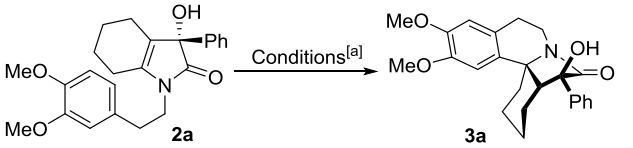
Scheme 2. Scope of Cr(III)(salen)Cl-Catalyzed Enantioselective Intramolecular Addition of Tertiary Enamides for the Formation of 5−6 Fused Ring System 2



1,4-dione were also found to be well tolerated to afford the functionalized enantioenriched products **2f** and **2g** in good yields and excellent enantiopurities. In addition, compounds **1h** and **1i** bearing dihydropyran (**1h**) and dihydrothiopyran (**1i**) were also suitable substrates, affording the fused bicyclic products in good yields and excellent ees (**2h**, 92% yield, 94% ee; **2i**, 66% yield, 99% ee), which highly enriched the diversity of the heteroskeleton. The absolute configuration of **2a** was determined by X-ray crystallography, and the configurations of the other 5−6 bicyclic products **2** were assigned accordingly (Supporting Information).[17]

During the experiment, we found that further intramolecular cyclization from **2a** to **3a** was not going well under the current catalyst system. To facilitate the sequential diastereoselective Pictet−Spengler cyclization and thus access the erythrinane core skeleton, an additional Lewis acid or Brønsted acid was added. After screening a series of acid promoters and reaction conditions, $InCl_3$ stood out as the best to afford ABCD ring-fused erythrinane core skeleton **3a** as the sole diastereomer but only in 35% yield (Table 2, entry 1−6). Evidently, decreasing the reaction temperature from rt to 5 °C dramatically improved the yield of **3a** from 35 to 56% (entry 7). Lowering the catalyst loading led to a slower reaction with a diminished yield (entry 8), while the reaction was further accelerated when it was executed at a higher catalyst loading (entry 9). Overall, the optimum conditions were to stir a CH_2Cl_2 solution of **2a** (*c* 0.033 M) in the presence of $InCl_3$ (1 equiv) at 0 °C for 18 h. Under these conditions, highly enantioenriched **3a** was isolated in 64% yield with excellent enantioselectivity (98% ee) and diastereoselectivity (>19:1 d.r.). The absolute configuration of **3a** was determined by X-ray crystallographic analysis to be (4a*R*, 5*R*, 13b*S*) and is consistent with erythrina-type alkaloid (Supporting Information).[17]

Table 2. Condition Optimization for Diastereoselective Pictet−Spengler Cyclization[a]



entry	cat. (eq)	solv.	temp. (°C)	time (h)	**3a** (%)[b]	ee (%)[c]
1	*p*-TSA (0.5)	tol	rt	0.5	2	93
2	$InCl_3$ (0.5)	tol	rt	0.5	20	93
3	$BF_3{\cdot}Et_2O$ (0.5)	tol	rt	0.5	3	94
4	$AlCl_3$ (0.5)	tol	rt	0.5	8	93
5	$InCl_3$ (0.5)	$CHCl_3$	rt	0.5	10	92
6	$InCl_3$ (0.5)	DCM	rt	0.5	35	95
7	$InCl_3$ (0.5)	DCM	5	3	56	94
8	$InCl_3$ (0.2)	DCM	5	72	36	93
9	$InCl_3$ (1.0)	DCM	5	3	51	92
10	$InCl_3$ (1.0)	DCM	0	18	64	98
11	$InCl_3$ (1.0)	DCM	−10	72	0	

[a]Conditions: **2a** (0.2 mmol), catalyst, solvent (6 mL). [b]Yield of the isolated product. [c]Measured by chiral-phase HPLC.

The scope of the diastereoselective Pictet−Spengler cyclization promoted by $InCl_3$ was next examined. As shown in Scheme 3, tertiary enamides having both an electron-withdrawing (**2b**, **2c**) and electron-donating (**2d**) group on the aromatic ketones are compatible with the reaction conditions, affording the desired products (**3b**−**3d**) in good enantiopurities (84−90% ee) and moderate yield (31−65%). The 2-naphthyl substituted product **3e** was synthesized analogously in 39% yield and 91% ee. Pleasingly, 4,4-dimethylcyclohexanone-derived **2f** participated in the reaction smoothly to afford the desired erythrina derivative **3f** in 31% yield and 91% ee. When a keto-protected cyclohexanone (**2g**) was subjected to the reaction, a diminished yield of **3g** was observed. This was mainly due to the partial deprotection that occurred spontaneously during the diastereoselective cyclization in the presence of $InCl_3$. However, the enantioselectivity of **3g** was maintained at a high level (96% ee). Tertiary enamides bearing dihydropyran (**2h**) and dihydrothiopyran (**2i**) followed the same reaction route to produce the corresponding heterocyclic product **3h** (44% yield, 95% ee) and **3i** (47% yield, 86% ee), respectively. Pleasingly, all products were obtained with high diastereomeric purity. The moderate yields were mainly attributed to the undesired competitive dehydration and double bond migration byproduct **4** during the Pictet−Spengler cyclization (Scheme 3).

The obtained fused tetracyclic compounds **3** not only resemble the structure of erythrina alkaloids but they are also invaluable platforms for the synthesis of diverse complicated N-heterocyclic compounds potentially useful in drug discovery. To further illustrate the synthetic potential of the present method, post functionalization of **3a** was undertaken. As shown in Scheme 4, using an excess amount of $LiAlH_4$, chemoselective lactam reduction of **3a** afforded **5** in 90% yield. On the other hand, α,β-unsaturated lactam **6** was obtained upon dehydration in the yield of 89%. Finally, the hydrogenation of **6** in the presence of Pd/C produces **7** as the sole diastereoisomer in 81% yield.

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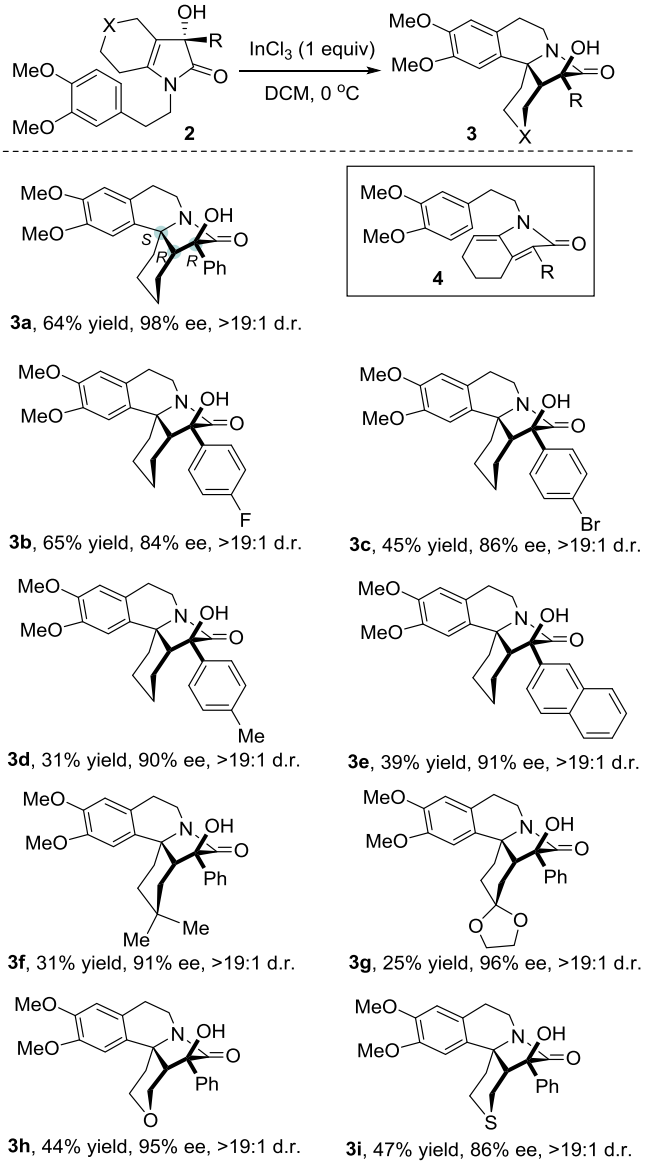
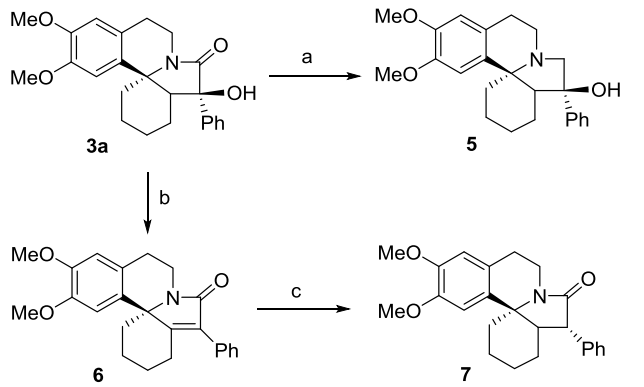
Scheme 3. Scope of $InCl_3$-Promoted Diastereoselective Pictet–Spengler Cyclization



Scheme 4. Post Functionalization of 3a



[a]Conditions: (a) $LiAlH_4$ (5 equiv), tetrahydrofuran (THF), reflux, 8 h, 90%; (b) MsCl (3.6 equiv), Et_3N (7 equiv), DCM, RT, 12 h, 89%; (c) Pd/C (20% w/w), H_2 (1 atm), MeOH, RT, 12 h, 81%, >19:1 d.r.

CONCLUSIONS

In summary, we have developed an efficient two-step strategy for the rapid construction of the erythrinane core skeleton from cyclohexanone-derived tertiary enamides. This method comprises a chiral Cr(III)(salen)Cl-catalyzed enantioselective intramolecular addition of tertiary enamides to ketone carbonyls with subsequent $InCl_3$-promoted diastereoselective Pictet–Spengler cyclization processes. The cascade asymmetric double intramolecular cyclization reactions produce diverse erythrina alkaloids in moderate yields with good enantioselectivity and excellent diastereoselectivity. Synthetic application of the method by transforming the resulting products into various erythrina-type core skeleton derivatives was also included. The synthesis of erythrina-type and iboga-type alkaloids based on this methodology is currently under development in our laboratory.

EXPERIMENTAL SECTION

General Remarks. All chemicals were dried or purified according to standard procedures prior to use. Flash column chromatography was performed on silica gel (100–200 mesh). Reactions were monitored using precoated, glass-backed silica gel plates and visualized by means of UV irradiation (254 nm) or $KMnO_4$, phosphomolybdic acid. ^1H NMR and ^{13}C NMR spectra were recorded using a JEOL EXC-400 MHz spectrometer at ambient temperature. ^1H frequency is at 400.13 MHz and ^{13}C frequency is at 100.62 MHz. Chemical shifts are reported in ppm with either tetramethylsilane or the residual solvent resonance used as an internal standard. Abbreviations are used in the description of NMR data as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), and coupling constant (J, Hz). Melting points are uncorrected. Infrared spectra were recorded using an FT-IR spectrometer with KBr discs in the 4000–400 cm^{-1} region. The high-resolution mass spectra (HRMS) were recorded on a Q Exactive Orbitrap Mass Spectrometer (Orbitrap). All yields reported were isolated yields, and ee values were determined by HPLC using Daicel ADH or ODH chiral columns eluted with a mixture of isopropanol and hexane at 25 °C. The optical rotation was determined by a Rudolph Autopol IV Automatic polarimeter. Crystallographic data were collected on a Rigaku XtaLAB Synergy (Cu) X-ray single crystal diffractometer.

General Procedure for the Synthesis of Tertiary Enamides 1. A dichloromethane solution of amine (0.5 M), ketone (0.5 M), and 4 Å MS (1:1 w/w) was vigorously stirred at 25 °C until the conversion of amine to imine was completed. The mixture was filtered through a pad of Celite and washed with DCM. The filtrate was concentrated in vacuo to give a crude imine product, which was used immediately without further purification. Under an argon atmosphere, imine (5 mmol) was dissolved in *N*,*N*-dimethylformamide (DMF, 10 mL), and then Et_3N (0.834 ml, 6 mmol, 1.2 equiv) was added. After cooling to −20 °C, acyl chloride (6 mmol, 1.2 equiv) was added dropwise for 20 min. The resulting mixture was kept stirring at −20 °C for another 20 min. A saturated aqueous $NaHCO_3$ solution (20 mL) was added to quench the reaction at −20 °C. The mixture was extracted with ethyl acetate (3 × 50 mL) and washed with brine (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give the pure enamide product **1**.

*N-(Cyclohex-1-en-1-yl)-N-(3,4-dimethoxyphenethyl)-2-oxo-2-phenylacetamide (**1a**).* Purified by column chromatography on silica gel (hexane/AcOEt/Et_3N = 20:1:0.5): white solid (687.8 mg, 35%); m.p. 92–94 °C; IR(KBr) 2933, 2849, 1642, 1516 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.68 (t, 1H, J = 7.3 Hz), 7.64 (d, 2H, J = 7.3 Hz), 7.48–7.52 (m, 2H), 6.88 (s, 1H), 6.87 (d, 1H, J = 6.4 Hz), 6.79 (dd, 1H, J = 8.0, 1.6 Hz), 5.24–5.26 (m, 1H), 3.81 (t, 2H, J = 7.1 Hz), 3.75 (s, 3H), 3.75 (s, 3H), 2.81 (t, 2H, J = 7.1 Hz), 1.98–2.02 (m, 2H), 1.67–1.71 (m, 2H), 1.40–1.42 (m, 2H), 1.24–1.27 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 191.5, 165.6, 148.6, 147.5, 135.8, 134.3,

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133.3, 130.76, 128.9, 128.6, 120.9, 112.9, 111.8, 55.6, 55.4, 43.4, 32.6, 26.0, 24.1, 21.7, 20.6; HRMS (ESI-Orbitrap) calcd for $C_{24}H_{28}NO_4^+$ $[M + H]^+$ 394.2018; found: 394.2013.

*N-(Cyclohex-1-en-1-yl)-N-(3,4-dimethoxyphenethyl)-2-(4-fluorophenyl)-2-oxoacetamide (**1b**).* Purified by column chromatography on silica gel (hexane/AcOEt/Et_3N = 20:1:0.5): white solid (904.0 mg, 44%); m.p. 71−72 °C; IR(KBr) 2935, 1643, 1515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.72−7.76 (m, 2H), 7.30−7.35 (m, 2H), 6.90 (d, 1H, J = 8.2 Hz), 6.90 (s, 1H), 6.79 (d, 1H, J = 8.2 Hz), 5.25−5.27 (m, 1H), 3.79 (t, 2H, J = 7.3 Hz), 3.75 (s, 3H), 3.75 (s, 3H), 2.81 (t, 2H, J = 7.1 Hz), 1.98−2.04 (m, 2H), 1.68−1.73 (m, 2H), 1.40−1.46 (m, 2H), 1.25−1.28 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 189.9, 165.4 (d, J = 255.1 Hz), 165.3, 148.6, 147.5, 135.9, 131.7 (d, J = 10.6 Hz), 130.8, 130.1 (d, J = 1.9 Hz), 128.8, 120.8, 116.1 (d, J = 22.2 Hz), 112.9, 111.8, 55.6, 55.4, 43.6, 32.6, 26.1, 24.1, 21.7, 20.7; HRMS (ESI-Orbitrap) calcd for $C_{24}H_{26}FNNaO_4^+$ $[M + Na]^+$ 434.1738; found: 434.1736.

*2-(4-Bromophenyl)-N-(cyclohex-1-en-1-yl)-N-(3,4-dimethoxyphenethyl)-2-oxoacetamide (**1c**).* Purified by column chromatography on silica gel (hexane/AcOEt/Et_3N = 20:1:0.5): white solid (708.6 mg, 30%); m.p. 81−83 °C; IR(KBr) 2936, 2933, 1643, 1515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.72 (d, 2H, J = 8.7 Hz), 7.56 (d, 2H, J = 8.7 Hz), 6.89−6.91 (m, 2H), 6.78 (dd, 1H, J = 8.2, 1.4 Hz), 5.23−5.25 (m, 1H), 3.79 (t, 2H, J = 7.3 Hz), 3.75 (s, 3H), 3.75 (s, 3H), 2.80 (t, 2H, J = 6.9 Hz), 1.98−2.02 (m, 2H), 1.69−1.72 (m, 2H), 1.40−1.45 (m, 2H), 1.24−1.30 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 190.5, 165.1, 148.6, 147.4, 135.9, 132.3, 132.2, 130.7, 130.5, 129.0, 128.6, 120.9, 112.8, 111.7, 55.5, 55.4, 43.5, 32.6, 26.1, 24.2, 21.8, 20.7; HRMS (ESI-Orbitrap) calcd for $C_{24}H_{26}BrNNaO_4^+$ $[M + Na]^+$ 494.0937; found: 494.0936.

*N-(Cyclohex-1-en-1-yl)-N-(3,4-dimethoxyphenethyl)-2-oxo-2-(p-tolyl)acetamide (**1d**).* Purified by column chromatography on silica gel (hexane/AcOEt/Et_3N = 20:1:0.5): white solid (753.0 mg, 37%); m.p. 100−101 °C; IR(KBr) 2932, 1642, 1516 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.53 (d, 2H, J = 8.2 Hz), 7.30 (d, 2H, J = 7.8 Hz), 6.91 (s, 1H), 6.90 (d, 1H, J = 8.0 Hz), 6.78 (dd, 1H, J = 8.0, 1.6 Hz), 5.23−5.25 (m, 1H), 3.80 (t, 2H, J = 7.1 Hz), 3.75 (s, 3H), 3.75 (s, 3H), 2.80 (t, 2H, J = 7.1 Hz), 2.38 (s, 3H), 1.99−2.02 (m, 2H), 1.68−1.69 (m, 2H), 1.41−1.44 (m, 2H), 1.25−1.28 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 191.1, 165.8, 148.6, 147.4, 145.0, 135.9, 131.0, 130.8, 129.5, 128.8, 128.7, 120.9, 112.8, 111.7, 55.5, 55.4, 43.3, 32.7, 26.1, 24.2, 21.8, 21.3, 20.7; HRMS (ESI-Orbitrap) calcd for $C_{25}H_{29}NNaO_4^+$ $[M + Na]^+$ 430.1989; found: 430.1988.

*N-(Cyclohex-1-en-1-yl)-N-(3,4-dimethoxyphenethyl)-2-(naphthalen-2-yl)-2-oxoacetamide (**1e**).* Purified by column chromatography on silica gel (hexane/AcOEt/Et_3N = 20:1:0.5): white solid (909.2 mg, 41%); m.p. 115−116 °C; IR(KBr) 2932, 1642, 1515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.20 (s, 1H), 8.06−8.08 (m, 1H), 8.00−8.03 (m, 2H), 7.69−7.75 (m, 2H), 7.62−7.66 (m, 1H), 6.97 (d, 1H, J = 1.8 Hz), 6.92 (d, 1H, J = 8.2 Hz), 6.81 (dd, 1H, J = 8.2, 1.8 Hz), 5.23−5.25 (m, 1H), 3.88 (t, 2H, J = 7.1 Hz), 3.77 (s, 3H), 3.77 (s, 3H), 2.85 (t, 2H, J = 7.1 Hz), 2.01−2.04 (m, 2H), 1.62−1.66 (m, 2H), 1.37−1.40 (m, 2H), 1.17−1.24 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 191.5, 165.6, 148.6, 147.3, 135.9, 135.5, 131.9, 131.3, 130.7, 129.7, 129.4, 128.9, 127.9, 127.3, 123.1, 121.0, 112.7, 111.7, 55.5, 55.4, 43.1, 32.6, 26.0, 24.1, 21.8, 20.7; HRMS (ESI-Orbitrap) calcd for $C_{28}H_{29}NNaO_4^+$ $[M + Na]^+$ 466.1989; found: 466.1988.

*N-(3,4-Dimethoxyphenethyl)-N-(4,4-dimethylcyclohex-1-en-1-yl)-2-oxo-2-phenylacetamide (**1f**).* Purified by column chromatography on silica gel (hexane/AcOEt/Et_3N = 20:1:0.5): white solid (927.4 mg, 44%); m.p. 110−111 °C; IR(KBr) 2921, 2848, 1644, 1516 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.63−7.69 (m, 3H), 7.47−7.51 (m, 2H), 6.90 (d, 1H, J = 7.6 Hz), 6.91 (s, 1H), 6.79 (dd, 1H, J = 8.2, 1.8 Hz), 5.14−5.16 (m, 1H), 3.84 (t, 2H, J = 7.1 Hz), 3.75 (s, 3H), 3.75 (s, 3H), 2.82 (t, 2H, J = 6.9 Hz), 2.02−2.06 (m, 2H), 1.48−1.49 (m, 2H), 1.22−1.25 (m, 2H), 0.69 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 191.2, 165.6, 148.6, 147.5, 134.6, 134.4, 133.2, 130.7, 128.9, 128.7, 128.2, 120.9, 112.9, 111.8, 55.6, 55.4, 43.4, 38.0, 34.6, 32.7, 27.7, 27.4, 23.5; HRMS (ESI-Orbitrap) calcd for $C_{26}H_{31}NNaO_4^+$ $[M + Na]^+$ 444.2145; found: 444.2143.

*N-(3,4-Dimethoxyphenethyl)-2-oxo-2-phenyl-N-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)acetamide (**1g**).* Purified by column chromatography on silica gel (hexane/AcOEt/Et_3N = 20:1:0.5): white solid (1.1 g, 49%); m.p. 113−114 °C; IR(KBr) 2959, 2935, 1641, 1516 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.63−7.66 (m, 1H), 7.57−7.59 (m, 2H), 7.44−7.48 (m, 2H), 6.86−6.88 (m, 2H), 6.75 (dd, 1H, J = 8.2, 1.8 Hz), 5.08−5.10 (m, 1H), 3.78 (t, 2H, J = 7.3 Hz), 3.75−3.76 (m, 4H), 3.71 (s, 3H), 3.71 (s, 3H), 2.76 (t, 2H, J = 7.1 Hz), 2.13−2.14 (m, 2H), 1.86−1.87 (m, 2H), 1.43−1.46 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 191.3, 165.6, 148.6, 147.5, 135.1, 134.4, 133.3, 130.7, 128.9, 128.7, 126.6, 120.9, 112.8, 111.7, 105.7, 63.8, 55.6, 55.4, 43.5, 34.7, 32.5, 30.2, 25.1; HRMS (ESI-Orbitrap) calcd for $C_{26}H_{29}NNaO_6^+$ $[M + Na]^+$ 474.1887; found: 474.1884.

*N-(3,6-Dihydro-2H-pyran-4-yl)-N-(3,4-dimethoxyphenethyl)-2-oxo-2-phenylacetamide (**1h**).* Purified by column chromatography on silica gel (hexane/AcOEt/Et_3N = 20:1:0.5): white solid (830.4 mg, 42%); m.p. 107−109 °C; IR(KBr) 2922, 1645, 1515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.70 (t, 1H, J = 7.1 Hz), 7.66 (d, 2H, J = 6.9 Hz), 7.49−7.53 (m, 2H), 6.93 (d, 1H, J = 1.8 Hz), 6.91 (d, 1H, J = 8.2 Hz), 6.81 (dd, 1H, J = 8.2, 1.8 Hz), 5.32−5.33 (m, 1H), 3.86 (t, 2H, J = 7.3 Hz), 3.76−3.77 (m, 2H), 3.75 (s, 3H), 3.75 (s, 3H), 3.53 (t, 2H, J = 5.5 Hz), 2.84−2.86 (m, 2H), 2.11−2.15 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 191.2, 165.6, 148.7, 147.5, 134.5, 133.4, 133.1, 130.6, 129.0, 128.8, 126.9, 121.0, 112.9, 111.8, 63.8, 63.2, 55.6, 55.5, 43.4, 32.6, 26.6; HRMS (ESI-Orbitrap) calcd for $C_{23}H_{25}NNaO_5^+$ $[M + Na]^+$ 418.1625; found: 418.1624.

*N-(3,6-Dihydro-2H-thiopyran-4-yl)-N-(3,4-dimethoxyphenethyl)-2-oxo-2-phenylacetamide (**1i**).* Purified by column chromatography on silica gel (hexane/AcOEt/Et_3N = 20:1:0.5): yellow solid (616.5 mg, 30%); m.p. 107−108 °C; IR(KBr) 2922, 1644, 1515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.70 (t, 1H, J = 7.3 Hz), 7.64 (d, 2H, J = 7.8 Hz), 7.49−7.52 (m, 2H), 6.93 (s, 1H), 6.92 (d, 1H, J = 8.7 Hz), 6.81 (d, 1H, J = 7.8 Hz), 5.46−5.49 (m, 1H), 3.84 (t, 2H, J = 7.1 Hz), 3.76 (s, 3H), 3.76 (s, 3H), 2.81−2.86 (m, 4H), 2.55−2.58 (m, 2H), 2.29−2.33 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 191.2, 165.6, 148.6, 147.5, 136.7, 134.6, 133.2, 130.6, 129.0, 128.9, 126.5, 120.9, 112.8, 111.7, 55.6, 55.5, 43.7, 32.5, 27.6, 24.5, 24.1; HRMS (ESI-Orbitrap) calcd for $C_{23}H_{25}NNaO_4S^+$ $[M + Na]^+$ 434.1397; found: 434.1398.

General Procedure for (*R,R*)-Cr(III)(salen)Cl-Catalyzed Enantioselective Synthesis of 2. Under argon protection, enamide **1** (0.2 mmol), (*R,R*)-Cr(III)(salen)Cl (0.2 equiv, 0.04 mmol, 25.3 mg), 4 Å MS (100 mg), and Na_2CO_3 (0.2 equiv, 4.2 mg) were added in dry toluene (6 mL) and the resulting mixture was stirred at 10 °C. After a period of time (18−48 h), 4 Å MS was filtered and the reaction was quenched by saturated $NaHCO_3$ solution. The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography to afford pure product **2**.

*(S)-1-(3,4-Dimethoxyphenethyl)-3-hydroxy-3-phenyl-4,5,6,7-tetrahydro-1H-indol-2(3H)-one (**2a**).* Purified by column chromatography on silica gel (hexane/AcOEt = 3:1): white solid (77.9 mg, 99%); m.p. 143−145 °C; $[\alpha]_D^{25}$ = −152.0 (*c* 0.25, $CHCl_3$); ee = 94% (DAICEL Chiralpak AD-H, hexane/2-propanol = 70/30, λ = 207 nm, flow rate = 0.5 mL/min); IR(KBr) 3374, 2932, 1703, 1681, 1515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.28−7.32 (m, 2H), 7.23−7.25 (m, 1H), 7.20 (d, 2H, J = 7.3 Hz), 6.86 (d, 1H, J = 8.2 Hz), 6.81 (d, 1H, J = 1.8 Hz), 6.71 (dd, 1H, J = 8.0, 1.6 Hz), 6.02 (s, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.55−3.62 (m, 1H), 3.44−3.51 (m, 1H), 2.71 (t, 2H, J = 6.9 Hz), 1.95−2.04 (m, 3H), 1.53−1.64 (m, 5H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 178.8, 148.7, 147.4, 140.3, 138.3, 131.2, 127.9, 126.9, 125.3, 120.8, 117.5, 112.9, 112.0, 79.0, 55.6, 55.4, 40.7, 34.5, 22.0, 21.9, 20.5, 19.0; HRMS (ESI-Orbitrap) calcd for $C_{24}H_{26}NO_4^-$ $[M - H]^-$ 392.1867; found: 392.1872.

*(S)-1-(3,4-Dimethoxyphenethyl)-3-(4-fluorophenyl)-3-hydroxy-4,5,6,7-tetrahydro-1H-indol-2(3H)-one (**2b**).* Purified by column chromatography on silica gel (hexane/AcOEt = 3:1): white solid (71.6 mg, 87%); m.p. 236−237 °C; $[\alpha]_D^{25}$ = −58.8 (*c* 0.25, $CHCl_3$); ee = 93% (DAICEL Chiralpak AD-H, hexane/2-propanol = 70/30, λ = 254 nm, flow rate = 0.5 mL/min); IR(KBr) 3364, 2932, 1703, 1682, 1515

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cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.19−7.22 (m, 2H), 7.09−7.13 (m, 2H), 6.86 (d, 1H, J = 8.2 Hz), 6.80 (d, 1H, J = 1.8 Hz), 6.70 (dd, 1H, J = 8.0, 1.6 Hz), 6.09 (s, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.57−3.61 (m, 1H), 3.48−3.51 (m, 1H), 2.71 (t, 2H, J = 6.6 Hz), 1.99−2.07 (m, 3H), 1.54−1.64 (m, 5H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 178.6, 161.3 (d, J = 243.6 Hz), 148.7, 147.4, 138.5, 136.4, 131.1, 127.3 (d, J = 7.8 Hz), 120.8, 117.2, 114.7 (d, J = 22.1 Hz), 112.9, 112.0, 78.5, 55.6, 55.4, 40.6, 34.4, 22.0, 21.9, 20.5, 19.0; HRMS (ESI-Orbitrap) calcd for $C_{24}H_{25}FNO_4^-$ $[M - H]^-$ 410.1773; found: 410.1775.

(S)-3-(4-Bromophenyl)-1-(3,4-dimethoxyphenethyl)-3-hydroxy-4,5,6,7-tetrahydro-1H-indol-2(3H)-one (**2c**). Purified by column chromatography on silica gel (hexane/AcOEt = 3:1): white solid (81.2 mg, 86%); m.p. 111−112 °C; $[\alpha]_D^{25}$ = −128.4 (c 0.25, $CHCl_3$); ee = 99% (DAICEL Chiralpak AD-H, hexane/2-propanol = 70/30, λ = 254 nm, flow rate = 0.5 mL/min); IR(KBr) 3359, 2931, 1703, 1681, 1515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.48 (d, 2H, J = 8.2 Hz), 7.11 (d, 2H, J = 7.8 Hz), 6.86 (d, 1H, J = 8.2 Hz), 6.80 (d, 1H, J = 1.8 Hz), 6.69 (dd, 1H, J = 8.0, 1.6 Hz), 6.13 (s, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.56−3.63 (m, 1H), 3.46−3.51 (m, 1H), 2.69−2.75 (m, 2H), 2.06−2.08 (m, 2H), 1.96−1.99 (m, 1H), 1.59−1.63 (m, 2H), 1.53−1.54 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 178.3, 148.7, 147.4, 139.7, 138.8, 131.1, 130.9, 127.6, 120.8, 120.2, 117.1, 112.9, 112.0, 78.6, 55.6, 55.4, 40.6, 34.4, 21.9, 21.8, 20.5, 18.9; HRMS (ESI-Orbitrap) calcd for $C_{24}H_{25}BrNO_4^-$ $[M - H]^-$ 470.0972; found: 470.0972.

(S)-1-(3,4-Dimethoxyphenethyl)-3-hydroxy-3-(p-tolyl)-4,5,6,7-tetrahydro-1H-indol-2(3H)-one (**2d**). Purified by column chromatography on silica gel (hexane/AcOEt = 3:1): white solid (77.4 mg, 95%); m.p. 91−93 °C; $[\alpha]_D^{25}$ = −119.6 (c 0.25, $CHCl_3$); ee = 96% (DAICEL Chiralpak AD-H, hexane/2-propanol = 70/30, λ = 254 nm, flow rate = 0.5 mL/min); IR(KBr) 3359, 2922, 1703, 1681, 1515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.08−7.11 (m, 4H), 6.86 (d, 1H, J = 8.2 Hz), 6.80 (s, 1H), 6.71 (d, 1H, J = 7.8 Hz), 5.95 (s, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.54−3.60 (m, 1H), 3.45−3.50 (m, 1H), 2.70 (t, 2H, J = 6.6 Hz), 2.27 (s, 3H), 1.95−2.03 (m, 3H), 1.53−1.62 (m, 5H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 178.9, 148.7, 147.4, 138.1, 137.3, 136.0, 131.2, 128.5, 125.2, 120.8, 117.6, 112.9, 112.0, 78.9, 55.6, 55.4, 40.7, 34.5, 22.0, 21.9, 20.6, 20.5, 19.0; HRMS (ESI-Orbitrap) calcd for $C_{25}H_{28}NO_4^-$ $[M - H]^-$ 406.2024, found: 406.2026.

(S)-1-(3,4-Dimethoxyphenethyl)-3-hydroxy-3-(naphthalen-2-yl)-4,5,6,7-tetrahydro-1H-indol-2(3H)-one (**2e**). Purified by column chromatography on silica gel (hexane/AcOEt = 3:1): white solid (71.0 mg, 80%); m.p. 203−205 °C; $[\alpha]_D^{25}$ = −87.2 (c 0.25, $CHCl_3$); ee = 92% (DAICEL Chiralpak AD-H, hexane/2-propanol = 70/30, λ = 254 nm, flow rate = 0.5 mL/min); IR(KBr) 3365, 2930, 1703, 1681, 1515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.85−7.91 (m, 3H), 7.81 (d, 1H, J = 8.2 Hz), 7.48−7.50 (m, 2H), 7.19 (dd, 1H, J = 8.7, 1.4 Hz), 6.86 (d, 1H, J = 8.2 Hz), 6.84 (d, 1H, J = 1.8 Hz), 6.73 (dd, 1H, J = 8.1, 1.7 Hz), 6.24 (s, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.61−3.66 (m, 1H), 3.49−3.56 (m, 1H), 2.75 (t, 2H, J = 6.9 Hz), 1.99−2.11 (m, 3H), 1.54−1.64 (m, 5H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 178.8, 148.7, 147.4, 138.6, 137.9, 132.8, 132.2, 131.2, 127.9, 127.6, 127.4, 126.1, 125.8, 124.0, 123.6, 120.9, 117.6, 112.8, 111.9, 79.3, 55.5, 55.4, 40.8, 34.5, 22.04, 21.98, 20.6, 19.2; HRMS (ESI-Orbitrap) calcd for $C_{28}H_{28}NO_4^-$ $[M - H]^-$ 442.2024; found: 442.2025.

(S)-1-(3,4-Dimethoxyphenethyl)-3-hydroxy-5,5-dimethyl-3-phenyl-4,5,6,7-tetrahydro-1H-indol-2(3H)-one (**2f**). Purified by column chromatography on silica gel (hexane/AcOEt = 3:1): white solid (404.7 mg, 96%); m.p. 236−237 °C; $[\alpha]_D^{25}$ = −58.8 (c 0.25, $CHCl_3$); ee = 93% (DAICEL Chiralpak AD-H, hexane/2-propanol = 70/30, λ = 254 nm, flow rate = 0.5 mL/min); IR(KBr) 3353, 2952, 1682, 1508 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.27−7.30 (m, 2H), 7.22 (t, 1H, J = 7.3 Hz), 7.16 (d, 2H, J = 6.9 Hz), 6.86 (d, 1H, J = 8.2 Hz), 6.81 (d, 1H, J = 1.8 Hz), 6.71 (dd, 1H, J = 7.8, 1.8 Hz), 5.98 (s, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.61−3.66 (m, 1H), 3.47−3.53 (m, 1H), 2.73 (t, 2H, J = 6.9 Hz), 1.97−2.01 (m, 2H), 1.76 (d, 1H, J = 16.5 Hz), 1.34 (t, 2H, J = 6.2 Hz), 1.29 (d, 1H, J = 16.5 Hz), 0.84 (s, 3H), 0.74 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 179.0, 148.7, 147.4, 140.2, 137.0, 131.2, 127.8, 126.9, 125.1, 120.9, 116.7, 112.9, 112.0, 79.0, 55.6, 55.4, 40.8, 34.8, 34.4, 32.9, 29.0, 28.2, 27.1, 18.4; HRMS (ESI-Orbitrap) calcd for $C_{26}H_{30}NO_4^-$ $[M - H]^-$ 420.2180; found: 420.2184.

(S)-1′-(3,4-Dimethoxyphenethyl)-3′-hydroxy-3′-phenyl-3′,4′,6′,7′-tetrahydrospiro[[1,3]dioxolane-2,5′-indol]-2′ (1′H)-one (**2g**). Purified by column chromatography on silica gel (hexane/AcOEt = 3:1): yellow solid (77.7 mg, 86%); m.p. 121−122 °C; $[\alpha]_D^{25}$ = −57.2 (c 0.25, $CHCl_3$); ee = 96% (DAICEL Chiralpak AD-H, hexane/2-propanol = 70/30, λ = 254 nm, flow rate = 0.5 mL/min); IR(KBr) 3364, 2925, 1716. 1683, 1515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.28−7.32 (m, 2H), 7.24−7.26 (m, 1H), 7.21−7.23 (m, 2H), 6.85 (d, 1H, J = 8.2 Hz), 6.79 (d, 1H, J = 1.8 Hz), 6.70 (dd, 1H, J = 8.2, 1.8 Hz), 6.15 (s, 1H), 3.82−3.89 (m, 3H), 3.76−3.80 (m, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.55−3.63 (m, 1H), 3.45−3.51 (m, 1H), 2.69 (t, 2H, J = 7.1 Hz), 2.18−2.25 (m, 3H), 1.70−1.78 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 178.7, 148.7, 147.4, 139.8, 137.7, 131.1, 128.1, 127.2, 125.4, 120.8, 114.9, 112.7, 112.0, 107.4, 78.9, 63.8, 63.7, 55.6, 55.3, 41.0, 34.6, 30.6, 30.2, 19.9; HRMS (ESI-Orbitrap) calcd for $C_{26}H_{28}NO_6^-$ $[M - H]^-$ 450.1922; found: 450.1926.

(S)-1-(3,4-Dimethoxyphenethyl)-3-hydroxy-3-phenyl-3,4,6,7-tetrahydropyrano[4,3-b]pyrrol-2(1H)-one (**2h**). Purified by column chromatography on silica gel (hexane/AcOEt = 3:1): white solid (72.8 mg, 92%); m.p. 121−122 °C; $[\alpha]_D^{25}$ = −271.2 (c 0.25, $CHCl_3$); ee = 94% (DAICEL Chiralpak AD-H, hexane/2-propanol = 70/30, λ = 254 nm, flow rate = 0.5 mL/min); IR(KBr) 3363, 2932, 1717, 1515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.30−7.33 (m, 2H), 7.26−7.28 (m, 1H), 7.22 (d, 2H, J = 6.9 Hz), 6.87 (d, 1H, J = 7.8 Hz), 6.82 (d, 1H, J = 1.8 Hz), 6.71 (dd, 1H, J = 8.2, 1.8 Hz), 6.28 (s, 1H), 4.10 (dt, 1H, J = 14.7, 2.7 Hz), 3.72−3.76 (m, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.60−3.67 (m, 1H), 3.47−3.54 (m, 1H), 2.73 (t, 2H, J = 7.1 Hz), 2.17−2.20 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 178.5, 148.7, 147.5, 139.7, 137.1, 131.0, 128.1, 127.3, 125.2, 120.9, 116.0, 112.9, 112.0, 78.4, 63.4, 61.3, 55.6, 55.4, 40.8, 34.3, 21.6; HRMS (ESI-Orbitrap) calcd for $C_{23}H_{24}NO_5^-$ $[M - H]^-$ 394.1660; found: 394.1661.

(S)-1-(3,4-Dimethoxyphenethyl)-3-hydroxy-3-phenyl-3,4,6,7-tetrahydrothiopyrano[4,3-b]pyrrol-2(1H)-one (**2i**). Purified by column chromatography on silica gel (hexane/AcOEt = 3:1): white solid (54.3 mg, 66%); m.p. 163−165 °C; $[\alpha]_D^{25}$ = −80.8 (c 0.25, $CHCl_3$); ee = 99% (DAICEL Chiralpak AD-H, hexane/2-propanol = 70/30, λ = 254 nm, flow rate = 0.5 mL/min); IR(KBr) 3373, 2928, 1704, 1681, 1515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.30−7.34 (m, 2H), 7.26−7.28 (m, 1H), 7.22 (d, 2H, J = 7.8 Hz), 6.86 (d, 1H, J = 8.2 Hz), 6.82 (d, 1H, J = 1.4 Hz), 6.71 (dd, 1H, J = 8.2, 1.4 Hz), 6.30 (s, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.59−3.66 (m, 1H), 3.47−3.54 (m, 1H), 3.09 (d, 1H, J = 16.5 Hz), 2.77 (t, 2H, J = 5.5 Hz), 2.71 (t, 2H, J = 8.0 Hz), 2.66 (d, 1H, J = 16.5 Hz), 2.35−2.39 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 177.9, 148.7, 147.5, 139.6, 139.1, 131.0, 128.2, 127.4, 125.3, 120.8, 115.0, 112.8, 111.9, 79.1, 55.6, 55.4, 40.7, 34.4, 24.1, 22.2, 20.4; HRMS (ESI-Orbitrap) calcd for $C_{23}H_{26}NO_4S^+$ $[M + H]^+$ 412.1577; found: 412.1569.

General Procedure for Diastereoselective Synthesis of Product 3. Under argon protection, product **2** (0.2 mmol) and $InCl_3$ (1 equiv, 44.2 mg) were added in dry DCM (6 mL) and the resulting mixture was stirred at 0 °C. After a period of time, the solvent was removed in vacuo and the residue was chromatographed on a silica gel column to give pure product **3**.

(S)-1-(2-(4aR,5R,13bS)-5-Hydroxy-11,12-dimethoxy-5-phenyl-3,4,4a,5,8,9-hexahydro-1H-indolo[7a,1-a]isoquinolin-6(2H)-one (**3a**). Purified by column chromatography on silica gel (hexane/AcOEt = 4:1): white solid (50.4 mg, 64%); m.p. 227−228 °C; $[\alpha]_D^{25}$ = −33.2 (c 0.25, $CHCl_3$); ee = 98% (DAICEL Chiralpak OD-H, hexane/2-propanol = 75/25, λ = 207 nm, flow rate = 0.5 mL/min); IR(KBr) 3342, 2938, 1678 cm^{-1}; d.r. >19:1; ^1H NMR (400 MHz, chloroform-d): δ 7.48 (d, 2H, J = 6.9 Hz), 7.30−7.38 (m, 3H), 6.93 (s, 1H), 6.64 (s, 1H), 4.15−4.21 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.53−3.60 (m, 1H), 3.02−3.10 (m, 1H), 2.88−2.92 (m, 1H), 2.83−2.87 (m, 1H), 2.50 (s, 1H), 1.98−2.07 (m, 2H), 1.77−1.92 (m, 2H), 1.35−1.37 (m, 2H), 1.21−1.26 (m, 1H), 0.18−0.27 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-d): δ 173.8, 148.0, 147.5, 140.6, 135.8, 128.2, 127.6, 125.1, 112.2, 109.0, 81.8, 60.3, 56.4, 56.1, 49.5, 36.5, 36.3, 27.2, 24.7, 20.6,

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20.3; HRMS (ESI-Orbitrap) calcd for $C_{24}H_{26}NO_4^-$ $[M - H]^-$ 392.1867; found: 392.1863.

*1-(3,4-Dimethoxyphenethyl)-3-phenyl-5,6-dihydro-1H-indol-2(4H)-one (**4**).* Purified by column chromatography on silica gel (hexane/AcOEt = 4:1): colorless oil (22.5 mg, 30%); IR(KBr) 2933, 1682, 1515 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.57 (d, 2H, J = 7.3 Hz), 7.41−7.44 (m, 2H), 7.33 (t, 1H, J = 7.3 Hz), 6.84 (d, 1H, J = 8.2 Hz), 6.79 (s, 1H), 6.73 (d, 1H, J = 7.3 Hz), 5.96 (t, 1H, J = 4.4 Hz), 3.74−3.78 (m, 2H), 3.70 (s, 3H), 3.70 (s, 3H), 2.73−2.79 (m, 4H), 2.32−2.37 (m, 2H), 1.71−1.77 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 167.8, 148.6, 147.4, 140.4, 137.8, 131.5, 131.1, 128.6, 128.2, 127.6, 124.3, 120.7, 112.6, 111.9, 111.3, 55.5, 55.3, 33.9, 23.9, 23.5, 23.2; HRMS (ESI-Orbitrap) calcd for $C_{24}H_{26}NO_3^+$ $[M + H]^+$ 376.1907; found: 376.1903.

*(4aR,5R,13bS)-5-(4-Fluorophenyl)-5-hydroxy-11,12-dimethoxy-3,4,4a,5,8,9-hexahydro-1H-indolo[7a,1-a]isoquinolin-6(2H)-one (**3b**).* Purified by column chromatography on silica gel (hexane/AcOEt = 4:1): white solid (53.5 mg, 65%); m.p. 238−240 °C; $[\alpha]_D^{25}$ = −84.8 (c 0.25, $CHCl_3$); ee = 84% (DAICEL Chiralpak OD-H, hexane/2-propanol = 75/25, λ = 220 nm, flow rate = 0.5 mL/min); IR(KBr) 3329, 2936, 1678, 1508 cm^{-1}; d.r. >19:1; ^1H NMR (400 MHz, chloroform-d): δ 7.43−7.46 (m, 2H), 7.02−7.06 (m, 2H), 6.91 (s, 1H), 6.63 (s, 1H), 4.15−4.18 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.49−3.55 (m, 1H), 3.01−3.09 (m, 1H), 2.86−2.89 (m, 1H), 2.81−2.83 (m, 1H), 2.50 (br s, 1H), 1.90−2.00 (m, 2H), 1.73−1.87 (m, 2H), 1.34−1.43 (m, 2H), 1.24−1.30 (m, 1H), 0.32−0.38 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-d): δ 173.8, 162.6 (d, J = 248.5 Hz), 148.1, 147.6, 136.4, 135.7, 129.4 (d, J = 7.7 Hz), 125.1, 115.1 (d, J = 21.2 Hz), 112.2, 109.0, 81.4, 60.4, 56.4, 56.1, 49.5, 36.6, 36.4, 27.2, 24.8, 20.5; HRMS (ESI-Orbitrap) calcd for $C_{24}H_{27}FNO_4^+$ $[M + H]^+$ 412.1919; found: 412.1920.

*(4aR,5R,13bS)-5-(4-Bromophenyl)-5-hydroxy-11,12-dimethoxy-3,4,4a,5,8,9-hexahydro-1H-indolo[7a,1-a]isoquinolin-6(2H)-one (**3c**).* Purified by column chromatography on silica gel (hexane/AcOEt = 4:1): white solid (42.5 mg, 45%); m.p. 258−259 °C; $[\alpha]_D^{25}$ = −165.2 (c 0.25, $CHCl_3$); ee = 86% (DAICEL Chiralpak OD-H, hexane/2-propanol = 75/25, λ = 220 nm, flow rate = 0.5 mL/min); IR(KBr) 3329, 2931, 1677, 1511 cm^{-1}; d.r. >19:1; ^1H NMR (400 MHz, chloroform-d): δ 7.49 (d, 2H, J = 8.7 Hz), 7.36 (d, 2H, J = 8.2 Hz), 6.90 (s, 1H), 6.63 (s, 1H), 4.09−4.20 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.49−3.56 (m, 1H), 3.01−3.09 (m, 1H), 2.88 (t, 1H, J = 5.3 Hz), 2.82−2.84 (m, 1H), 1.97−2.01 (m, 1H), 1.88−1.94 (m, 1H), 1.71−1.84 (m, 2H), 1.37−1.40 (m, 2H), 1.24−1.31 (m, 1H), 0.34−0.42 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-d): δ 173.5, 148.1, 147.5, 139.7, 135.5, 131.4, 129.4, 125.0, 122.3, 112.1, 108.8, 81.5, 60.4, 56.4, 56.0, 49.4, 36.7, 36.3, 27.2, 24.8, 20.6, 20.5; HRMS (ESI-Orbitrap) calcd for $C_{24}H_{27}BrNO_4^+$ $[M + H]^+$ 472.1118; found: 472.1119.

*(4aR,5R,13bS)-5-Hydroxy-11,12-dimethoxy-5-(p-tolyl)-3,4,4a,5,8,9-hexahydro-1H-indolo[7a,1-a]isoquinolin-6(2H)-one (**3d**).* Purified by column chromatography on silica gel (hexane/AcOEt = 4:1): purified by column chromatography on silica gel (hexane/AcOEt = 4:1 to 2:1): white solid (25.3 mg, 31%); m.p. 244−246 °C; $[\alpha]_D^{25}$ = −63.2 (c 0.25, $CHCl_3$); ee = 90% (DAICEL Chiralpak OD-H, hexane/2-propanol = 75/25, λ = 230 nm, flow rate = 0.5 mL/min); IR(KBr) 3331, 2931, 1678, 1512 cm^{-1}; d.r. >19:1; ^1H NMR (400 MHz, chloroform-d): δ 7.36 (d, 2H, J = 7.8 Hz), 7.16 (d, 2H, J = 7.8 Hz), 6.94 (s, 1H), 6.64 (s, 1H), 4.11−4.20 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.52−3.58 (m, 1H), 3.01−3.09 (m, 1H), 2.86−2.91 (m, 1H), 2.81−2.84 (m, 1H), 2.31−2.51 (br s, 1H), 2.35 (s, 3H), 1.97−2.05 (m, 2H), 1.77−1.91 (m, 2H), 1.35−1.37 (m, 2H), 1.22−1.27 (m, 1H), 0.25−0.34 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-d): δ 174.1, 148.0, 147.5, 138.0, 137.5, 135.9, 129.0, 127.5, 125.1, 112.2, 109.1, 81.7, 60.4, 56.4, 56.1, 49.5, 36.5, 36.4, 27.3, 24.7, 21.3, 20.6, 20.4; HRMS (ESI-Orbitrap) calcd for $C_{25}H_{30}NO_4^+$ $[M + H]^+$ 408.2169; found: 408.2172.

*(4aR,5R,13bS)-5-Hydroxy-11,12-dimethoxy-5-(naphthalen-2-yl)-3,4,4a,5,8,9-hexahydro-1H-indolo[7a,1-a]isoquinolin-6(2H)-one (**3e**).* Purified by column chromatography on silica gel (hexane/AcOEt = 4:1): white solid (34.6 mg, 39%); m.p. 228−229 °C; $[\alpha]_D^{25}$ = −74.0 (c 0.25, $CHCl_3$); ee = 91% (DAICEL Chiralpak OD-H, hexane/2-propanol = 75/25, λ = 254 nm, flow rate = 0.5 mL/min); IR(KBr) 3343, 2936, 1678 cm-1; d.r. >19:1; ^1H NMR (400 MHz, chloroform-d): δ 7.88 (s, 1H), 7.80−7.85 (m, 3H), 7.65 (d, 1H, J = 8.2 Hz), 7.47−7.50 (m, 2H), 6.93 (s, 1H), 6.63 (s, 1H), 4.18−4.24 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.56−3.63 (m, 1H), 3.01−3.09 (m, 1H), 2.83−2.93 (m, 2H), 2.20−2.80 (br s, 1H), 1.98−2.07 (m, 2H), 1.78−1.90 (m, 2H), 1.23−1.39 (m, 2H), 1.15−1.19 (m, 1H), 0.18−0.27 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-d): δ 174.0, 147.9, 147.5, 137.9, 135.7, 133.0, 132.9, 128.5, 127.9, 127.7, 126.8, 126.4, 126.2, 125.4, 125.1, 112.1, 108.8, 81.9, 60.5, 56.3, 56.0, 49.7, 36.6, 36.4, 27.2, 24.7, 20.53, 20.46; HRMS (ESI-Orbitrap) calcd for $C_{28}H_{30}NO_4^+$ $[M + H]^+$ 444.2169; found: 444.2169.

*(4aR,5R,13bS)-5-Hydroxy-11,12-dimethoxy-3,3-dimethyl-5-phenyl-3,4,4a,5,8,9-hexahydro-1H-indolo[7a,1-a]isoquinolin-6(2H)-one (**3f**).* Purified by column chromatography on silica gel (hexane/AcOEt = 4:1): white solid (26.1 mg, 31%); m.p. 230−231 °C; $[\alpha]_D^{25}$ = −182.4 (c 0.25, $CHCl_3$); ee = 91% (DAICEL Chiralpak OD-H, hexane/2-propanol = 75/25, λ = 220 nm, flow rate = 0.5 mL/min); IR(KBr) 3352, 2927, 1681, 1507 cm^{-1}; d.r. >19:1; ^1H NMR (400 MHz, chloroform-d): δ 7.48 (d, 2H, J = 7.3 Hz), 7.32−7.35 (m, 2H), 7.28−7.30 (m, 1H), 6.79 (s, 1H), 6.55 (s, 1H), 4.28−4.33 (m, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.34 (td, 1H, J = 12.5, 5.2 Hz), 3.13−3.22 (m, 1H), 2.81−2.86 (m, 1H), 2.58 (dd, 1H, J = 16.3, 4.8 Hz), 2.34 (s, 1H), 2.01−2.07 (m, 1H), 1.82−1.90 (m, 1H), 1.25−1.29 (m, 2H), 1.00 (s, 3H), 0.86−0.93 (m, 1H), 0.79 (s, 3H), 0.58 (dd, 1H, J = 14.0, 5.7 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-d): δ 175.9, 148.0, 147.6, 139.1, 136.2, 128.0, 125.2, 112.3, 108.3, 82.9, 61.6, 56.3, 56.0, 46.7, 39.8, 35.6, 34.1, 34.0, 32.3, 29.6, 26.1, 24.8; HRMS (ESI-Orbitrap) calcd for $C_{26}H_{32}NO_4^+$ $[M + H]^+$ 422.2326; found: 422.2325.

*(4a′R,5′R,13b′S)-5′-Hydroxy-11′,12′-dimethoxy-5′-phenyl-1′,2′,4a′,5′,8′,9′-hexahydrospiro[[1,3]dioxolane-2,3′-indolo[7a,1-a]isoquinolin]-6′ (4′H)-one (**3g**).* Purified by column chromatography on silica gel (hexane/AcOEt = 4:1): white solid (22.6 mg, 25%); m.p. 229−231 °C; $[\alpha]_D^{25}$ = −139.2 (c 0.25, $CHCl_3$); ee = 96% (DAICEL Chiralpak OD-H, hexane/2-propanol = 75/25, λ = 220 nm, flow rate = 0.5 mL/min); IR(KBr) 2935, 1644, 1516 cm^{-1}; d.r. >19:1; ^1H NMR (400 MHz, chloroform-d): δ 7.45 (d, 2H, J = 7.3 Hz), 7.33−7.36 (m, 2H), 7.29−7.31 (m, 1H), 6.96 (s, 1H), 6.56 (s, 1H), 4.33−4.38 (m, 1H), 3.93 (s, 3H), 3.86−3.91 (m, 2H), 3.85 (s, 3H), 3.73−3.82 (m, 2H), 3.38 (td, 1H, J = 12.5, 5.2 Hz), 3.16−3.25 (m, 1H), 3.04−3.09 (m, 1H), 2.64 (dd, 1H, J = 16.3, 4.8 Hz), 2.12 (t, 2H, J = 6.6 Hz), 1.69−1.93 (br s, 1H), 1.69−1.80 (m, 2H), 1.29−1.36 (m, 1H), 1.06 (dd, 1H, J = 13.7, 6.0 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-d): δ 175.2, 147.9, 147.5, 139.07, 134.9, 128.2, 128.1, 127.6, 124.7, 111.9, 108.8, 108.4, 82.8, 64.5, 64.3, 61.1, 56.2, 55.9, 48.4, 35.9, 35.3, 35.0, 30.9, 26.3; HRMS (ESI-Orbitrap) calcd for $C_{26}H_{30}NO_6^+$ $[M + H]^+$ 452.2068; found: 452.2061.

*(4aS,5R,13bS)-5-Hydroxy-11,12-dimethoxy-5-phenyl-1,2,4a,5,8,9-hexahydropyrano[4′,3′:2,3]pyrrolo[2,1-a]isoquinolin-6(4H)-one (**3h**).* Purified by column chromatography on silica gel (hexane/AcOEt = 4:1): white solid (34.8 mg, 44%); m.p. 226−229 °C; $[\alpha]_D^{25}$ = −160.0 (c 0.25, $CHCl_3$); ee = 95% (DAICEL Chiralpak OD-H, hexane/2-propanol = 75/25, λ = 214 nm, flow rate = 0.5 mL/min); IR(KBr) 3347, 2926, 1682, 1513 cm^{-1}; d.r. >19:1; ^1H NMR (400 MHz, chloroform-d): δ 7.46 (d, 2H, J = 8.2 Hz), 7.30−7.39 (m, 3H), 6.94 (s, 1H), 6.61 (s, 1H), 4.28−4.33 (m, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.57−3.71 (m, 3H), 3.39−3.50 (m, 2H), 3.09−3.17 (m, 1H), 2.94 (t, 1H, J = 6.4 Hz), 2.75 (d, 1H, J = 16.0 Hz), 2.50 (br s, 1H), 2.04−2.17 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-d): δ 174.4, 148.3, 148.0, 139.2, 134.5, 128.44, 128.36, 127.2, 125.2, 112.2, 108.8, 81.0, 65.0, 62.8, 58.9, 56.3, 56.1, 49.8, 36.3, 35.7, 27.0; HRMS (ESI-Orbitrap) calcd for $C_{23}H_{26}NO_5^+$ $[M + H]^+$ 396.1805; found: 396.1804.

*(4aR,5R,13bS)-5-Hydroxy-11,12-dimethoxy-5-phenyl-1,2,4a,5,8,9-hexahydrothiopyrano[4′,3′:2,3]pyrrolo[2,1-a]isoquinolin-6(4H)-one (**3i**).* Purified by column chromatography on silica gel (hexane/AcOEt = 4:1): white solid (38.4 mg, 47%); m.p. 226−228 °C; $[\alpha]_D^{25}$ = −236.0 (c 0.25, $CHCl_3$); ee = 86% (DAICEL Chiralpak OD-H, hexane/2-propanol = 75/25, λ = 220 nm, flow rate = 0.5 mL/min); IR(KBr) 3350, 2922, 1680, 1514 cm^{-1}; d.r. >19:1; ^1H NMR (400 MHz, chloroform-d): δ 7.41 (d, 2H, J = 6.9 Hz), 7.29−7.37 (m, 3H), 7.34 (s, 1H), 6.60 (s, 1H), 4.38−4.44 (m, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.38−3.45 (m, 1H), 3.19 (dd, 1H, J = 9.8, 5.7 Hz), 3.10−

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3.15 (m, 1H), 2.73−2.77 (m, 2H), 2.60 (td, 1H, J = 11.9, 4.1 Hz), 2.24−2.49 (br s, 1H), 2.24−2.37 (m, 3H), 2.04−2.12 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-d): δ 148.2, 147.6, 139.6, 133.2, 128.4, 126.9, 124.7, 112.1, 109.4, 82.4, 60.3, 56.2, 56.0, 52.4, 36.0, 33.5, 26.9, 25.3, 21.0; HRMS (ESI-Orbitrap) calcd for $C_{23}H_{26}NO_4S^+$ $[M + H]^+$ 412.1577; found: 412.1571.

Synthesis of 5. To a stirred suspension of $LiAlH_4$ (57 mg, 1.5 mmol) in THF (10 mL) was added **3a** (118 mg, 0.3 mmol) and the resulting mixture was refluxed for 8 h. The solution was cooled to rt and quenched by successive addition of water (0.2 mL) and 20% aqueous NaOH solution (0.2 mL) under vigorous stirring. The mixture was filtered through a pad of Celite, and the white precipitate was washed several times with THF containing ∼1% of concentrated ammonium hydroxide. The combined filtrates were concentrated and purified by flash column chromatography on silica gel (PE/EA = 3:1) to give product **5**. White solid (102.5 mg, 90%); m.p. 241−243 °C; IR(KBr) 2923, 1509 cm^{-1}; ^1H NMR (400 MHz, chloroform-d): δ 7.49−7.78 (m, 2H), 7.13−7.38 (m, 3H), 6.79 (s, 1H), 6.65 (s, 1H), 4.32 (s, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.38−3.47 (m, 2H), 3.20−3.28 (m, 1H), 2.71−2.79 (m, 2H), 1.69−1.78 (m, 2H), 1.57−1.64 (m, 2H), 1.20−1.26 (m, 3H), 1.08−1.11 (m, 1H), 0.84−0.90 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-d): δ 146.5, 141.7, 139.3, 127.8, 127.1, 127.0, 111.8, 108.9, 91.6, 83.6, 60.4, 56.1, 56.0, 51.2, 40.9, 38.1, 29.3, 24.0, 20.8, 20.3; HRMS (ESI-Orbitrap) calcd for $C_{24}H_{30}NO_3^+$ $[M + H]^+$ 380.2220; found: 380.2210.

Synthesis of 6. To a solution of **3a** (157 mg, 0.4 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added MsCl (165 mg, 111 μL, 1.44 mmol) and Et_3N (283 mg, 389 μL, 2.8 mmol). The solution was stirred at 0 °C for 1 h and allowed to warm to rt and stirred overnight. Water was added, and the mixture was extracted with CH_2Cl_2 and washed with brine. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (PE/EA = 3:1) affords **6**. White solid (133.7 mg, 89%); m.p. 148−150 °C IR(KBr) 2921, 1679, 1510 cm^{-1}; ^1H NMR (400 MHz, chloroform-d): δ 7.44−7.46 (m, 2H), 7.38−7.42 (m, 2H), 7.30−7.34 (m, 1H), 7.21 (s, 1H), 6.71 (s, 1H), 4.23−4.29 (m, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.46−3.53 (m, 1H), 3.25 (dd, 1H, J = 14.4, 4.8 Hz), 2.97−3.05 (m, 1H), 2.91 (t, 1H, J = 5.3 Hz), 2.85 (dd, 1H, J = 14.9, 5.7 Hz), 2.49 (d, 1H, J = 12.4 Hz), 2.14 (d, 1H, J = 13.3 Hz), 1.82−1.92 (m, 1H), 1.76 (d, 1H, J = 13.7 Hz), 1.64 (td, 1H, J = 13.2, 4.3 Hz), 1.36−1.49 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-d): δ 169.2, 157.1, 148.2, 146.7, 131.8, 131.4, 130.6, 129.8, 128.3, 128.0, 127.3, 112.6, 110.6, 64.8, 56.6, 56.0, 41.5, 36.4, 28.5, 27.8, 27.6, 21.5; HRMS (ESI-Orbitrap) calcd for $C_{24}H_{26}NO_3^+$ $[M + H]^+$ 376.1907; found: 376.1903.

Synthesis of 7. To a two-necked round bottom flask equipped with a magnetic stirrer were added compound **6** (94 mg, 0.25 mmol), Pd/C catalyst (18.8 mg, 20% w/w), and CH_3OH (5 mL). The reaction mixture was stirred at room temperature under a hydrogen atmosphere overnight. The mixture was filtered through Celite, and the filtrate was evaporated under vacuum. Flash chromatography on silica gel (PE/EA = 3:1) affords **7**. White solid (76.4 mg, 81%); m.p. 91−93; IR(KBr) 2929, 1692, 1508 cm^{-1}; ^1H NMR (400 MHz, chloroform-d): δ 7.19−7.30 (m, 5H), 6.80 (s, 1H), 6.54 (s, 1H), 4.29−4.34 (m, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 3.67 (d, 1H, J = 6.9 Hz), 3.25−3.33 (m, 1H), 3.14−3.22 (m, 1H), 2.77−2.83 (m, 1H), 2.55 (dd, 1H, J = 16.3, 4.8 Hz), 2.21 (d, 1H, J = 13.7 Hz), 1.56−1.67 (m, 3H), 1.18−1.37 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-d): δ 177.7, 148.1, 147.5, 135.4, 133.8, 129.7, 128.2, 126.8, 126.8, 112.3, 107.9, 62.2, 56.4, 56.0, 52.0, 42.9, 36.7, 35.3, 26.0, 25.97, 24.1, 21.6; HRMS (ESI-Orbitrap) calcd for $C_{24}H_{28}NO_3^+$ $[M + H]^+$ 378.2064; found: 378.2058.

Synthetic Procedure for Gram Scale Synthesis of 2h. Under argon protection, enamide **1h** (7.37 mmol, 2.91 g), (*R*,*R*)-Cr(III)-(salen)Cl (0.2 equiv, 1.47 mmol, 931.6 mg), 4 Å MS (3.69 g), and Na_2CO_3 (0.2 equiv, 154.8 mg) were added in dry toluene (221 mL) and the resulting mixture was stirred at 10 °C. After 48 h, 4 Å MS was filtered and the reaction was quenched by saturated $NaHCO_3$ solution. The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EA = 2:1) to afford pure product **2h** (yield: 74%, 2.16 g; ee: 84%).

Synthetic Procedure for Gram Scale Synthesis of 3h. Under argon protection, product **2h** (5.47 mmol, 2.16 g) and $InCl_3$ (1 equiv, 1.21 g) were added in dry DCM (164 mL) and the resulting mixture was stirred at 0 °C. After 12 h, the solvent was removed in vacuo and the residue was chromatographed on a silica gel column eluted with a mixture of petroleum ether and ethyl acetate (2:1) to give pure product **3h** (yield: 1.11 g, 51%; ee: 74%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01992.

HPLC data; crystal data; and copies of ^1H NMR and ^{13}C NMR spectra of products (PDF)
Crystallographic data for **2a** (TX1109-2a) (CIF)
Crystallographic data for **3a** (TX1069-3a) (CIF)

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This manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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