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An expeditious route to the synthesis of the enantioenriched tetracyclic core of ergot alkaloids *via* an organocatalytic aldol reaction†‡

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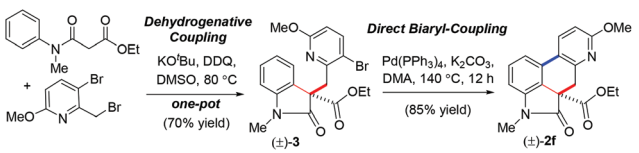
The synthesis of the tetracyclic skeleton of ergot alkaloids has been developed *via* a key organocatalytic enantioselective aldol reaction using paraformaldehyde as the C1-unit in the presence of thiourea catalyst followed by a key Pd-catalyzed directed coupling accelerated by the DavePhos ligand. Utilizing the aforementioned strategy, we have synthesized a key tetracyclic intermediate in up to 95% ee with high yield.

Introduction

Ergot alkaloids are typically designated as ergoline alkaloids having the characteristic structure of a tetracyclic indole ring system.[1] The potential of this group of alkaloids as medicinal agents is very high based on their broad pharmacological activity.[2]

Indeed, several ergot alkaloids (**1a–j**) and their synthetic analogues such as terguride (**1a**) and pergolide (**1b**) are clinically used for treating a diverse array of human maladies (*e.g.*, as a vasodilator, a prolactin inhibitor, and an anti-Parkinsonian's disease drug).[2] Because of their unique tetracyclic ergoline skeleton containing a tetrahydropyridine and a [cd]-fused indole, in addition to important biological activities, a variety of total syntheses and synthetic studies toward lysergic acid and the related ergot alkaloids have been reported to date.[3–6]

Towards this direction, we have recently reported a racemic approach to the synthesis of the tetracyclic core of ergot alkaloids **2f** *via* an oxidative coupling to synthesize **3** followed by a Pd(0)-catalyzed directed coupling as shown in Scheme 1.[7a] Herein, we report an efficient strategy for the synthesis of the enantioenriched core of these alkaloids *via* a TU-catalyzed efficient aldol reaction using paraformaldehyde as the C1-unit[7b] followed by a key Pd-catalyzed directed coupling (Scheme 1).



Scheme 1 Our report on the synthesis of the tetracyclic core of **2f**.

Results and discussion

Retrosynthetically, we envisioned that the enantioenriched tetracyclic core of type **2e** (Fig. 1) could be an advanced intermediate for the total synthesis of a variety of ergot alkaloids

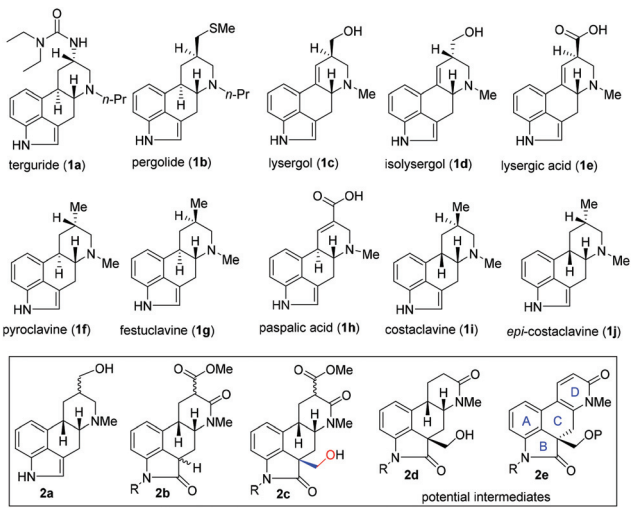


Fig. 1 Representative ergot alkaloids (**1a–j**) and potential intermediates **2a–e**.

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†This paper is dedicated to Professor V. Chandrasekhar on the occasion of his 60th birthday.

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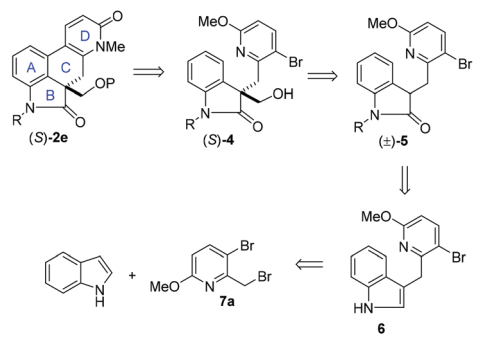
and their synthetic analogues *via* a directed hydrogenation of the α-pyridone of **2e** to afford δ-lactam **2d** (Fig. 1),[8] α-functionalization of δ-lactam **2d** using cyanomethylformate to afford ester **2c**,[9] followed by base mediated de-hydromethylation of ester **2c** to afford 2-oxindole **2b** *via* a *retro*-aldol reaction,[10] and finally reduction and aromatization to form indole ring **2a** (Fig. 1).[11] Enantioenriched **2e** could be obtained from enantioenriched **4** sharing the all-carbon quaternary stereogenic center (Scheme 2) *via* a Pd(0)-catalyzed directed coupling reaction[7] followed by demethylation to form α-pyridone.[12]

We thought to access enantioenriched **4** from 3-substituted 2-oxindole **5** following a Dynamic Kinetic Asymmetric Transformation (DYKAT)[13] involving a hydroxymethylation reaction using paraformaldehyde as the C1-unit[14] in the presence of a suitable bifunctional thiourea catalyst.[15] Furthermore, 3-substituted 2-oxindole **5** could be accessed from 3-substituted indole **6**, which in turn could be synthesized from 5-bromo 2-methoxy 2-picolyl bromide **7a**[12b] *via* the base promoted alkylation of indole.

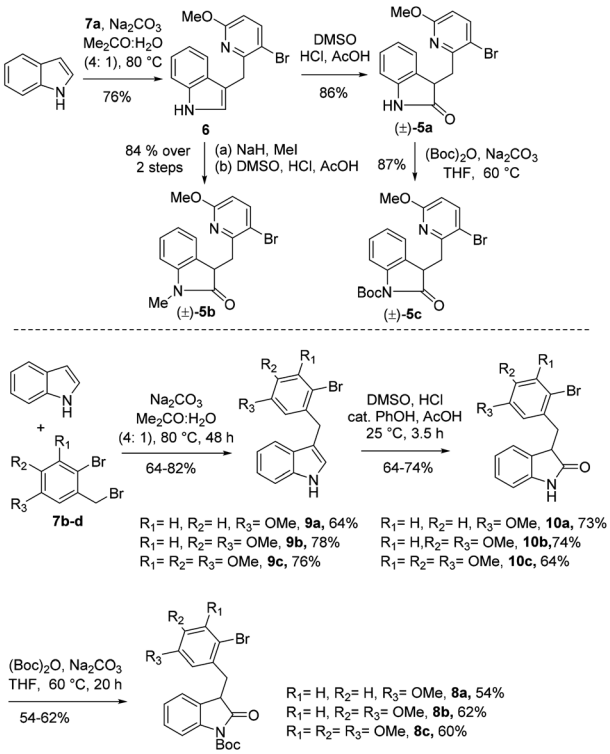
With the above hypothesis, we synthesized 2-oxindoles **5** with few different protecting groups starting from 3-substituted indole **6**. As per Scheme 3, indole was reacted with bromide **7a** in the presence of Na_2CO_3 to afford **6** in 76% yield (Scheme 3). The latter was then reacted with DMSO in HCl/AcOH[16] to afford 2-oxindole **5a** in 86% yield. In another sequence, **6** was methylated with MeI followed by reaction with DMSO in HCl/AcOH to afford **5b** in 84% overall yield in 2 steps. In addition, a variety of 3-(2-bromoaryl)methyl-2-oxindoles **8a–c** were also synthesized following a similar reaction sequence (Scheme 3).

Initially, the enantioselective organocatalytic hydroxymethylation of 2-oxindoles **5a–b** was carried out using paraformaldehyde in the presence of bifunctional thiourea ligand **L1** (Scheme 4). However, the reaction was not successful and starting materials were isolated quantitatively. We imagined that the pK_a of the methine proton in **5a–b** might be responsible for this failure.[17]

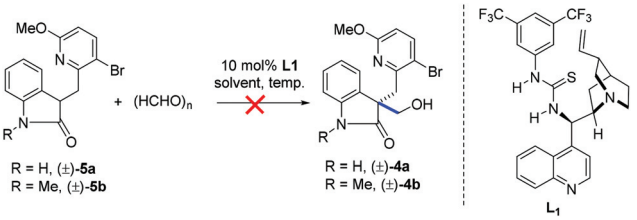
To circumvent this, we changed the protecting group to an electron-withdrawing Boc-group which may enhance the acidity of the methine proton sufficiently, thereby allowing a facile enolization of compound **5c**.[18] The latter was obtained



Scheme 2 Retrosynthetic analysis of intermediate **2e**.



Scheme 3 Synthesis of *N*-Boc protected 3-substituted 2-oxindoles **5b** and **8a–c**.



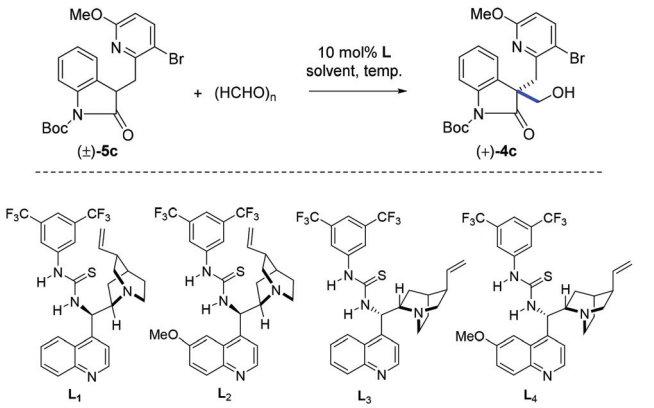
Scheme 4 Initial attempt of TU-catalyzed aldol reactions of compounds **5a–b**.

in 87% yield from a reaction of **5a** with $(Boc)_2O$. With **5c** in hand, we then carried out the catalytic enantioselective aldol reaction using paraformaldehyde in the presence of bifunctional thiourea catalysts **L1–L4** (Table 1).

At the outset, we carried out the optimization of **5c** with paraformaldehyde in the presence of catalytic **L1** in different solvents (Table 1). Following exhaustive optimization, we observed that a maximum of 94% ee of the product can be achieved when the reaction was carried out using 10 mol% of **L1** in acetonitrile at room temperature in 16 h (entry 7). Gratifyingly, 5 mol% **L1** also afforded **4c** in 93% ee in 28 h. It was also observed that the enantioselectivity can be enhanced to 94% and 95% while performing the reaction at 0 °C (48 h) and −10 °C (60 h), respectively (entries 20 and 23).

Interestingly, we found that the enantioselective organocatalytic hydroxymethylation of 2-oxindoles **8a–c** can be carried

Table 1 Optimization of the thiourea catalyzed aldol reaction

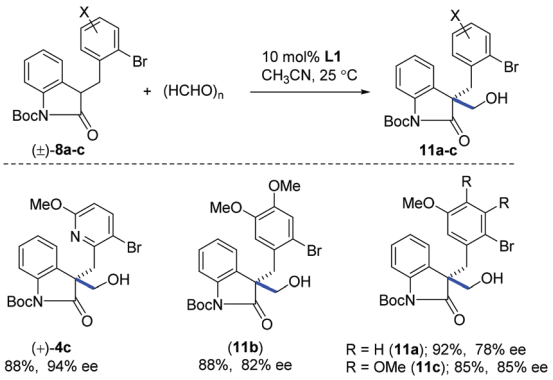


S. no.[a]	Catalyst	Solvent	Temp	Time	% **4c**[b]	% ee[c]
1	10 mol% **L1**	CH_2Cl_2	25 °C	15 h	94%	92%
2	10 mol% **L1**	$CHCl_3$	25 °C	15 h	92%	91%
3	10 mol% **L1**	$(CH_2Cl)_2$	25 °C	16 h	89%	89%
4	10 mol% **L1**	DME	25 °C	6 d	91%	80%
5	10 mol% **L1**	EtOAc	25 °C	16 h	90%	91%
6	10 mol% **L1**	THF	25 °C	17 h	91%	86%
7	10 mol% **L1**	CH_3CN	25 °C	16 h	88%	94%
8	10 mol% **L1**	dioxane	25 °C	17 h	92%	89%
9	10 mol% **L1**	Et_2O	25 °C	18 h	93%	92%
10	10 mol% **L1**	DMF	25 °C	18 h	86%	29%
11	10 mol% **L1**	PhMe	25 °C	18 h	91%	74%
12	10 mol% **L1**	DMSO	25 °C	17 h	85%	29%
13	5 mol% **L1**	CH_2Cl_2	25 °C	30 h	94%	93%
14	5 mol% **L1**	$CHCl_3$	25 °C	29 h	92%	90%
15	**5 mol% L1**	**CH_3CN**	**25 °C**	**28 h**	**90%**	**93%**
16	5 mol% **L1**	EtOAc	25 °C	30 h	90%	85%
17	5 mol% **L1**	Et_2O	25 °C	32 h	91%	87%
18	10 mol% **L1**	CH_2Cl_2	0 °C	60 h	92%	90%
19	10 mol% **L1**	$CHCl_3$	0 °C	60 h	92%	89%
20	10 mol% **L1**	CH_3CN	0 °C	48 h	90%	94%
21	10 mol% **L1**	EtOAc	0 °C	90 h	55%	93%
22	10 mol% **L1**	Et_2O	0 °C	90 h	50%	90%
23	10 mol% **L1**	CH_3CN	−10 °C	60 h	91%	95%
24	10 mol% **L1**	CH_2Cl_2	−10 °C	90 h	70%	95%
25	10 mol% **L1**	Et_2O	−10 °C	90 h	30%	94%
26	10 mol% **L2**	CH_2Cl_2	25 °C	14 h	87%	91%
27	10 mol% **L2**	CH_3CN	25 °C	16 h	94%	89%
28	10 mol% **L2**	Et_2O	25 °C	15 h	87%	90%
29	10 mol% **L3**	CH_2Cl_2	25 °C	14 h	94%	−89%
30	10 mol% **L3**	CH_3CN	25 °C	14 h	91%	−93%
31	10 mol% **L3**	Et_2O	25 °C	15 h	87%	−91%
32	10 mol% **L4**	CH_2Cl_2	25 °C	14 h	91%	−86%
33	10 mol% **L4**	CH_3CN	25 °C	14 h	94%	−89%
34	10 mol% **L4**	Et_2O	25 °C	15 h	94%	−88%

[a] Reactions were carried out with 0.02 mmol of (±)-**5c** in 2 mL of solvent at a specified temperature and specified time. [b] Isolated yields of (+)-**4c** after column chromatography. [c] Enantiomeric excess are determined by chiral column using iso-propanol and *n*-hexane as solvent system.

out under standard conditions using paraformaldehyde in the presence of bifunctional thiourea ligand **L1** to achieve products **11a–c** in 78–85% ee (Scheme 5).

The stereochemical rationale for our hypothesized catalytic aldol process following a DYKAT process in the presence of thiourea ligand **L1** is shown in Fig. 2. It has been proposed that if the enolate of **5c** can establish H-bonding with ligand **L1** and activate the nucleophile **5c** and electrophile (formaldehyde), favorable stereoselectivity could be obtained *via* the *Re*-face approach of 2-oxindole leading to the formation of enantioenriched hydroxyl methylated product **4c** (Fig. 2).



Scheme 5 Substrates scope of organocatalytic aldol. Reactions were carried out with 0.02 mmol of (±)-**8a–c** in 2 mL of acetonitrile at room temperature. Isolated yields of (+)-**4c** and **11a–c** are reported after column chromatography.

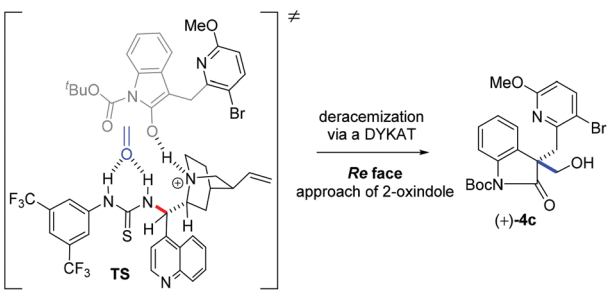
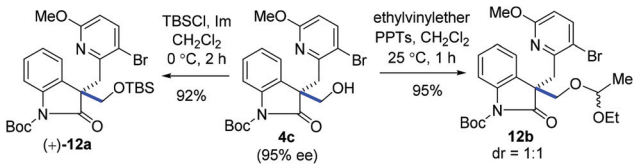


Fig. 2 Proposed transition state.

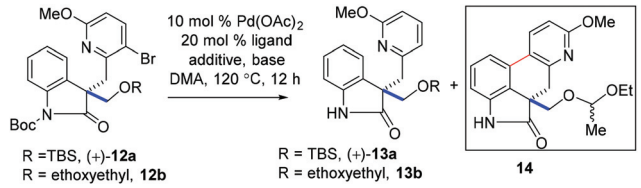
With the enantioenriched **4c** in hand, our effort was thereafter to elaborate this to the enantioenriched tetracyclic core of type **2a**. Towards this, we tried a directed coupling of Boc-protected aldol product **4c** using 10 mol% of $Pd(OAc)_2$ and 20 mol% of DavePhos in *N*,*N*-dimethylacetamide (DMA) at different temperatures. However, all efforts to forge the biaryl connection led to the multiple spots on TLC and we could isolate 39% of dehydroxymethylation (*retro*-aldol) product **5a**, when the reaction was carried out at 120 °C for 12 h. Later, 30 mol% pivalic acid as an additive also didn't help, which afforded 46% of **5a**. We imagined that this reaction proceeds through K_2CO_3-promoted *retro*-aldol followed by the decomposition of the Boc group.

Our failure of directed coupling *via* the *retro*-aldol process led us to think of the protecting hydroxymethyl group of **4c**. Towards this, we protected the hydroxymethyl group as TBS and ethoxyethyl ether using TBSCl and ethyl vinyl ether, respectively, to obtain products **12a** and **12b** (Scheme 6). These compounds were then used for directed coupling reactions for the key biaryl ring formation and the results are summarized in Table 2. It was observed that TBS ether protected enantioenriched **12a** was not a good substrate which afforded only



Scheme 6 Substrate preparation for biaryl coupling.

Table 2 Optimization of directed coupling



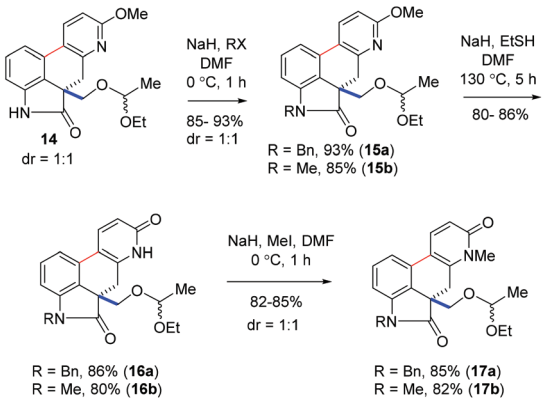
Entry	12a–b	Ligand	Base (2.5 equiv.)	Additive	13a–b	14[a,b]
1	**12a**	Ph_3P	K_2CO_3	None	17% (**13a**)[c]	—
2	**12a**	Ph_3P	Na_2CO_3	None	15% (**13a**)[c]	—
3	**12b**	Ph_3P	K_2CO_3	None	42% (**13b**)	35%
4	**12b**	Ph_3P	K_2CO_3	Piv. acid[d]	42% (**13b**)	51%
5	**12b**	Ph_3P	$^iPr_2NEt$	Piv. acid[d]	50% (**13b**)	19%
6	**12b**	Ph_3P	K_3PO_4	Piv. acid[d]	35% (**13b**)	42%
7[e]	**12b**	DavePhos	Na_2CO_3	Piv. acid[d]	24% (**13b**)	62%
8[e]	**12b**	DavePhos	K_2CO_3	Piv. acid[d]	10% (**13b**)	81%
9[f]	**12b**	**DavePhos**	**K_2CO_3**	**Piv. acid[d]**	**15% (13b)**	**79%**

[a] Reactions were carried out with 0.3 mmol of **12** in 1.0 mL of solvent in a sealed tube under an argon atmosphere. [b] Isolated yields after column chromatography. [c] 36–38% yields of 2-oxindole **12a** were isolated. [d] 30 mol% pivalic acid was used as an additive. [e] 10 mol% DavePhos was used. [f] 5 mol% $Pd(OAc)_2$/6 mol% DavePhos and reaction run for 18 h.

dehalogenated product **13a** in 15–17% yields along with 36–38% yields of 2-oxindole **5a** (entries 1 and 2). Interestingly, by changing the substrate from **12a** to **12b**, we found that biaryl coupling product **14** can be obtained in 35% yield along with 42% yield of dehalogenated product **13b**, when no additive was used (entry 3).

The yield of **14** was further increased to 51% when 30 mol% pivalic acid was used as an additive.[19,20] Gratifyingly, biaryl product **14** was obtained in 62% yield when 12 mol% DavePhos was used as a ligand and Na_2CO_3 as a base (entry 7). The yield was further increased to 81% when K_2CO_3 was used as a base (entry 8). In fact, among all bases used, K_2CO_3 gave a satisfactory result compared to Na_2CO_3, K_2PO_4, and $^iPr_2NEt$ (entries 5–7). It is noteworthy that the biaryl coupling can afford **14** in 79% yield, when the reaction was carried out in the presence of 5 mol% $Pd(OAc)_2$ and 6 mol% DavePhos (entry 9).

Having the biaryl coupling product **14** in hand, we then elaborated this to a number of important intermediates (Scheme 7). It was *N*-alkylated with benzyl bromide and methyl iodide to afford **15a** and **15b** in 93% and 85% yields, respectively. These 2-methoxy pyridine compounds (**15a–b**) were treated with NaSEt under refluxing DMF to afford α-pyridones



Scheme 7 Synthesis of advanced intermediate α-pyridones for ergot alkaloids.

16a and **16b** in 86% and 80% yields, respectively. Later, α-pyridones were *N*-methylated with methyl iodide to furnish *N*-methylated α-pyridones **17a** and **17b** in 85% and 82% yields, respectively.

Conclusions

In conclusion, we have reported an efficient entry to the tetracyclic enantioenriched core of ergoline structural motifs of ergot alkaloids. This synthetic strategy features a catalytic enantioselective hydroxymethylation reaction following a Dynamic Kinetic Asymmetric Transformation (DYKAT) using paraformaldehyde as the C1 unit in the presence of thiourea catalyst **L1** followed by an another key directed coupling catalyzed by only 5 mol% of $Pd(OAc)_2$ and 6 mol% DavePhos ligand. Further exploration of this strategy is currently under active investigations in our laboratory.

Experimental

Materials and methods

Unless otherwise stated, reactions were performed in oven-dried glassware fitted with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred *via* a syringe using standard Schlenk techniques. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium/benzophenone ketyl. Acetonitrile, dichloromethane (CH_2Cl_2), toluene, and benzene were distilled over calcium hydride. All other solvents such as chloroform, methanol, ethanol and DMSO and reagents such as tryptamine, phthalic anhydride, succinic anhydride, sodium borohydride, methyl chloroformate, benzyl chloroformate, *p*-toluenesulfonyl chloride, $LiAlH_4$, triethylamine, acetic acid, di-*tert*-butyl dicarbonate, paraformaldehyde, *etc*. were used as received, unless otherwise noted. Thin layer chromatography was performed using Merck Silicagel 60 F-254 precoated plates (0.25 mm) and visualized by

UV irradiation, 2,4-DNP, anisaldehyde stain and other stains. Silica gel from Merck (particle size 100–200 mesh) was used for flash chromatography. Melting points were recorded on a digital melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on 400 and 500 MHz spectrometers at ^{13}C operating frequencies of 100 and 125 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 7.24 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR). Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogen). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were recorded on a FT-IR system (Spectrum BX) and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High-resolution mass spectrometry (HRMS) data were recorded on a MicrOTOF-Q-II mass spectrometer using methanol as the solvent. High resolution mass spectra and NMR data were obtained from the Central Instrumentation Facility (CIF) at the Indian Institute of Science Education and Research (IISER) Bhopal.

Synthesis and characterization of 6. In a round bottom flask, indole (5.85 g, 50.0 mmol; 2.0 equiv.), picolyl bromide and **7a** (7.0 g, 25.0 mmol; 1.0 equiv.) were dissolved in 125 mL acetone and water (4 : 1). To this solution, Na_2CO_3 (5.3 g, 50.0 mmol; 2.0 equiv.) was added, the reaction mixture was placed in an oil bath maintaining a temperature of 80 °C and heating was continued up to 48 h until picolyl bromide was completely consumed. Upon completion of the reaction (TLC shows complete consumption), the reaction mixture was diluted with water and ethyl acetate, and the organic layer was separated through a separatory funnel. The organic layer was washed with water, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by column chromatography with *n*-hexane–EtOAc (47 : 3) to afford **6** as brown gel.

3-((3-Bromo-6-methoxypyridin-2-yl)methyl)-1*H*-indole (6). 5.15 g (65% yield) as yellow gel. R_f = 0.35 (5% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.98 (m, 1H), 7.95 (brs, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.33 (m, 1H), 7.24 (m, 1H), 7.13 (m, 1H), 6.51 (d, J = 8.6 Hz, 1H), 4.40 (s, 2H), 3.97 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 162.5, 156.2, 142.7, 136.1, 127.7, 122.7, 122.0, 119.9, 119.3, 11.0, 111.5, 110.0, 53.7, 33.6; **IR** (film) ν_{max} 3412, 2945, 1576, 1457, 1416, 1319, 1262, 1034, 1010, 819, 742 cm^{-1}; **HRMS** (ESI) m/z 317.0285 $[M + H]^+$; calculated for $[C_{15}H_{13}BrN_2O + H]^+$: 317.0284.

Synthesis and characterization of (±)-5a. In a round bottom flask, compound **6** (5.0 g, 15.7 mmol; 1.0 equiv.) was dissolved in acetic acid (50 mL), and DMSO (3.0 mL, 39.4 mmol; 2.5 equiv.), conc. HCl (7.2 mL, 86.3 mmol; 5.5 equiv.) and PhOH (73 mg, 0.785 mmol; 0.05 equiv.) were added successively at room temperature. The reaction mixture was then stirred for 3.5 h. Upon completion of the reactions (TLC showed complete consumption of the starting material), the reaction mixture was diluted with EtOAc (100 mL) and extracted with saturated ammonium chloride (75 mL × 2 times). The organic layer was separated through a separatory funnel, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was then purified by flash column chromatography with *n*-hexane–EtOAc (3 : 2) to afford (±)-**5a** as brown gel.

3-((3-Bromo-6-methoxypyridin-2-yl)methyl)indolin-2-one (±)-5a. 4.5 g (86% yield) as a pale yellow solid. R_f = 0.40 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.60 (s, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.14 (m, 1H), 6.85–6.91 (m, 3H), 6.45 (d, J = 8.7 Hz, 1H), 4.16 (dd, J = 7.8, 4.3 Hz, 1H), 3.71 (s, 3H), 3.67 (dd, J = 16.7, 4.3 Hz, 1H), 3.41 (dd, J = 16.7, 7.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 180.3, 162.3, 153.1, 142.3, 141.5, 129.7, 127.7, 124.0, 122.1, 112.1, 110.5, 109.5, 53.5, 44.0, 36.2; **IR** (film) ν_{max} 3224, 2942, 1078, 1574, 1462, 1417, 1296, 1014, 821, 750 cm^{-1}; **MP** 127–129 °C; **HRMS** (ESI) m/z 333.0237 $[M + H]^+$; calculated for $[C_{15}H_{13}BrN_2O_2 + H]^+$: 333.0233.

Synthesis and characterization of (±)-5b. Step 1: In a round bottom flask, compound **6** (1.23 g, 3.92 mmol; 1.0 equiv.) was dissolved in DMF (10 mL), and NaH (188 mg, 4.7 mmol; 1.2 equiv.) was added to the solution portionwise at 0 °C. After stirring for 5 minutes at the same temperature, MeI (257 μL, 4.11 mmol; 1.05 equiv.) was added dropwise and stirring was continued for another 30 minutes. Upon completion of the reactions (TLC showed complete consumption of the starting material), the reaction mixture was quenched with water (20 mL) and diluted with EtOAc (40 mL). The organic layer was separated through a separatory funnel and washed with brine twice (20 mL × 2). Then, the entire organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was directly charged for the next step without purification.

Step 2: In a round bottom flask, the crude *N*-methylated compound (3.92 mmol; 1.0 equiv.) was dissolved in acetic acid (50 mL), and DMSO (750 μL, 9.85 mmol; 2.5 equiv.), conc. HCl (1.8 mL, 21.6 mmol; 5.5 equiv.) and PhOH (20 mg, 0.2 mmol; 0.05 equiv.) were added successively at room temperature. The reaction mixture was then stirred for 3.5 h at the same temperature. Upon completion of the reactions, the reaction mixture was concentrated under reduced pressure and diluted with EtOAc (100 mL). Then, the excess acid was quenched with aqueous $NaHCO_3$ solution and the organic layer was washed with brine, respectively. The organic layer was then separated through a separatory funnel, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was then purified by flash column chromatography with *n*-hexane–EtOAc (7 : 3) to afford (±)-**5b** as yellow gel.

3-((3-Bromo-6-methoxypyridin-2-yl)methyl)-1-methylindolin-2-one (5b). 1.13 g (84% yield) as yellow gel. R_f = 0.45 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.60 (d, J = 8.6 Hz, 1H), 7.22 (m, 1H), 6.88 (m, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.46 (d, J = 8.6 Hz, 1H), 4.18 (dd, J = 8.4, 4.2 Hz, 1H), 3.69 (s, 3H), 3.64 (dd, J = 16.5, 4.3 Hz, 1H), 3.32 (dd, J = 16.4, 8.4 Hz, 1H), 3.23 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 177.8, 162.3, 155.3, 144.3, 142.4, 129.2, 127.7, 123.8, 122.2, 112.2, 110.5, 107.8, 53.5, 43.6, 36.5, 26.; **IR** (film) ν_{max} 2920, 2725, 1596, 1411, 1372, 1189, 1172, 1087, 982, 773 cm^{-1}; **HRMS** (ESI) m/z 347.0391 $[M + H]^+$; calculated for $[C_{16}H_{15}BrN_2O_2 + H]^+$: 347.0390.

Synthesis and characterization of (±)-5c. In an oven dried round bottom flask, compound (±)-**5a** (2.5 g, 7.5 mmol;

1.0 equiv.) was taken and dissolved in dry THF (25 mL) under a nitrogen atmosphere. To this, $(Boc)_2O$ (1.8 mL, 8.25 mmol; 1.1 equiv.) and Na_2CO_3 (6.4 g, 60.0 mmol; 8.0 equiv.) were added successively and placed in a preheated oil bath maintaining 80 °C and stirring was continued up to 20 h until the starting material was fully consumed. Upon completion of the reaction (TLC shows complete consumption), the reaction mixture was diluted with water and ethyl acetate, and the organic layer was separated through a separatory funnel. The organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography with *n*-hexane–EtOAc (9 : 1) to afford (±)-**5c** as brown gel.

***tert*-Butyl 3-((3-bromo-6-methoxypyridin-2-yl)methyl)-2-oxoindoline-1-carboxylate (±)-5c.** 2.5 g (77% yield) as yellow gel. R_f = 0.45 (10% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.80 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.21 (m, 1H), 7.00 (m, 2H), 6.37 (d, J = 8.6 Hz, 1H), 4.08 (t, J = 5.5 Hz, 1H), 3.73 (dd, J = 17.3, 4.7 Hz, 1H), 3.57 (m, 4H), 1.62 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 176.0, 162.3, 152.3, 149.6, 142.2, 140.3, 127.9, 127.8, 124.1, 123.0, 114.7, 111.9, 110.6, 84.0, 53.3, 44.0, 35.8, 28.1; **IR** (film) ν_{max} 2924, 1775, 1728, 1574, 1578, 1463, 1353, 1296, 1014, 752 cm^{-1}; **HRMS** (ESI) m/z 455.0567 $[M + H]^+$; calculated for $[C_{20}H_{21}N_2O_4 + H]^+$: 455.0577.

General procedure for organocatalytic aldol. In a screw cap vial, substrate (±)-**5c** (15 mg, 0.035 mmol; 1.0 equiv.) was charged in 1 mL MeCN at 25 °C. Paraformaldehyde (30 mg) and catalyst (1.9 mg, 0.0035 mmol; 0.1 equiv.) were added successively and stirring was continued at the same temperature until the starting material was fully consumed. Upon completion of the reaction, the product was purified through column chromatography with *n*-hexane–EtOAc (3 : 2) to afford (+)-**4c** as colorless gel.

***tert*-Butyl (*S*)-3-((3-bromo-6-methoxypyridin-2-yl)methyl)-3-(hydroxymethyl)-2-oxoindoline-1-carboxylate (+)-4c.** 15 mg (94% yields) as colourless gel. R_f = 0.35 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.84 (d, J = 8.1 Hz, 1H), 7.50 (m, 1H), 7.25 (m, 1H), 7.14 (m, 1H), 7.07 (m, 1H), 6.32 (d, J = 8.7 Hz, 1H), 3.80–3.91 (m, 2H), 3.69 (s, 2H), 3.57 (s, 3H), 2.63 (brs, 1H), 1.65 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 177.5, 162.1, 151.9, 149.5, 142.2, 140.3, 128.9, 128.8, 128.4, 124.3, 122.5, 114.9, 110.6, 84.2, 68.7, 53.7, 53.3, 38.7, 28.1; **IR** (film) ν_{max} 3367, 2979, 2925, 1782, 1729, 1577, 1465, 1351, 1294, 1150, 752 cm^{-1}; **HRMS** (ESI) m/z 485.0698 $[M + Na]^+$; calculated for $[C_{21}H_{23}BrN_2O_5 + Na]^+$: 485.0683. Enantiomeric excess was determined to be 95% ee *via* HPLC analysis using a Chiralpak IB column; solvent: 2-propanol/hexane = 1/19; flow rate: 0.5 mL min^{-1}; detection: at 254 nm: t_R major = 20.51 min, t_R minor = 23.87 min; $[\alpha]_{589}^{23.7°C}$ = +57.3 (c = 0.26, $CHCl_3$).

Synthesis and characterization of (+)-12a. In an oven-dried round-bottom flask, compound (+)-**4c** (420 mg, 0.907 mmol; 1.0 equiv.) was dissolved in 10 mL CH_2Cl_2. After this, imidazole (123 mg, 1.81 mmol; 2.0 equiv.) and *tert*-butyldimethylsilyl chloride (204 mg, 1.36 mmol; 1.5 equiv.) were added successively at room temperature and stirring was continued for 2 h. Upon completion of the reactions, the reaction mixture was quenched with water and 10 mL CH_2Cl_2 was added to it. The organic layer was separated through a separatory funnel and the water layer was washed with CH_2Cl_2 (10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was then purified by flash chromatography with *n*-hexane–EtOAc (19 : 1) to afford (+)-**12a** colorless gel.

***tert*-Butyl (*R*)-3-((3-bromo-6-methoxypyridin-2-yl)methyl)-3-(((*tert*-butyldimethyl-silyl)oxy)methyl)-2-oxoindoline-1-carboxylate (+)-12a.** 482 mg (92% yield) as colorless gel. R_f = 0.6 (5% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.81 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.21 (td, J = 7.6, 1.4 Hz, 1H), 7.13 (dd, J = 7.4, 1.0 Hz, 1H), 7.02 (td, J = 7.5, 0.8 Hz, 1H), 6.29 (d, J = 8.7 Hz, 1H), 3.88 (ABq, J = 14.8, 9.0 Hz, 2H), 3.77 (d, J = 17.0 Hz, 1H), 3.54 (s, 3H), 3.46 (d, J = 19.6 Hz, 1H), 1.64 (s, 9H), 0.79 (s, 9H), −0.04 (s, 3H), −0.11 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 177.2, 162.1, 152.1, 149.6, 142.0, 140.7, 130.1, 127.8, 123.7, 122.7, 114.4, 111.6, 110.4, 83.6, 69.8, 54.2, 53.2, 38.2, 28.1, 25.6, 17.9, −5.7, −5.9; **IR** (film) ν_{max} 2929, 2856, 1770, 1726, 1579, 1463, 1355, 1298, 1152, 1117, 838, 750 cm^{-1}; **HRMS** (ESI) m/z 615.1315 $[M + K]^+$; calculated for $[C_{27}H_{37}BrN_2O_5Si + K]^+$: 615.1287; $[\alpha]_{589}^{24.7°C}$ = +26.8 (c = 0.22, $CHCl_3$).

Synthesis and characterization of (12b). Enantioenriched (+)-**4c** (2.0 g, 4.3 mmol; 1.0 equiv.) was charged in 30 mL CH_2Cl_2 and ethyl vinyl ether (8.2 mL, 86.0 mmol; 20.0 equiv.) was then added to it at room temperature. To the reaction mixture, pyridinium *p*-toluenesulfonate (2.1 g, 8.6 mmol; 2.0 equiv.) was added and the reaction mixture was stirred at the same temperature for 1 h. After complete consumption of the starting material, the reaction mixture was concentrated under reduced pressure and was then directly purified by flash chromatography with *n*-hexane–EtOAc (9 : 1) to afford **12b** as colorless gel.

***tert*-Butyl 3-((3-bromo-6-methoxypyridin-2-yl)methyl)-3-((1-ethoxyethoxy)methyl)-2-oxoindoline-1-carboxylate (12b).** 2.18 g (95% yield) as colorless gel. R_f = 0.55 (10% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ: 7.80 (d, J = 8.3 Hz, 2H) (both isomers), 7.47 (d, J = 8.7 Hz, 2H) (both isomers), 7.20 (m, 2H) (both isomers), 7.15 (d, J = 7.6 Hz, 2H) (both isomers), 7.00 (t, J = 7.4 Hz, 2H) (both isomers), 6.27 (d, J = 8.6 Hz, 2H) (both isomers), 4.59 (m, 2H) (both isomers), 3.70–3.87 (m, 6H) (both isomers), 3.32–3.56 (m, 10H) (both isomers), 3.26 (m, 2H) (both isomers), 1.63 (s, 9H) (one isomer), 1.62 (s, 9H) (other isomers), 1.12 (d, J = 5.4 Hz, 3H) (one isomer), 1.18 (d, J = 5.4 Hz, 3H) (other isomers), 1.10 (t, J = 7.1 Hz, 3H) (one isomer), 1.07 (t, J = 7.1 Hz, 3H) (other isomers); **^{13}C NMR** (100 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ: 199.9, 177.4, 162.1, 152.0, 151.9, 149.5, 142.3, 142.1, 140.3, 128.9, 128.4, 127.9, 124.3, 123.8, 122.9, 122.8, 122.5, 114.9, 110.7, 110.5, 110.4, 99.9, 99.7, 84.2, 68.7, 61.2, 61.0, 58.5, 53.7, 53.3, 53.2, 52.7, 38.8, 38.7, 28.1, 19.4, 19.3, 18.4, 15.3, 15.2; **IR** (film) ν_{max} 2979, 2929, 1771, 1725, 1579, 146, 1297, 1152, 750 cm^{-1}; **HRMS** (ESI) m/z 573.1026 $[M + K]^+$; calculated for $[C_{25}H_{31}BrN_2O_6 + K]^+$: 573.0997.

Synthesis and characterization of 13a–b. In an oven-dried sealed tube, compound **12a** (108 mg, 0.187 mmol; 1.0 equiv.) was added to dry DMA (*N*,*N*-dimethylacetamide) (1.0 mL) and degassed under an argon atmosphere at room temperature for 20 minutes. To this solution, $Pd(OAc)_2$ (4.2 mg, 0.0187 mmol; 0.1 equiv.), PPh_3 (9.8 mg, 0.0374 mmol; 0.2 equiv.) and K_2CO_3 (64.6 mg, 0.467 mmol; 2.5 equiv.) were added successively and sealed under an argon atmosphere. The reaction mixture was then placed in an oil bath maintaining 120 °C and stirring was continued at the same temperature for 12 h. Then, the reaction mixture was quenched with water (2 mL) and then diluted with 5 mL of EtOAc. The organic layer was washed with water (2 × 5 mL) and brine (5 mL), respectively, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was directly purified by flash chromatography with *n*-hexane–EtOAc (4 : 1) to afford **13a** as yellow gel. A similar procedure was followed for the synthesis of **13b** starting from compound **12b** (100 mg, 0.187 mmol; 1.0 equiv.).

(*S*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-((6-methoxypyridin-2-yl)methyl)indolin-2-one (+)-13a. 13 mg (17% yield) as yellow gel (entry 1, Table 2). R_f = 0.28 (20% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.16 (d, J = 7.3 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.90 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.59 (d, J = 7.2 Hz, 1H), 6.39 (d, J = 8.1 Hz, 1H), 3.97 (d, J = 9.3 Hz, 1H), 3.86 (d, J = 9.3 Hz, 1H), 3.63 (s, 3H), 3.34 (q, J = 14.2 Hz, 2H), 0.79 (s, 9H), −0.04 (s, 3H), −0.10 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 180.8, 163.1, 154.7, 141.4, 138.5, 131.4, 127.6, 124.9, 121.7, 116.3, 109.2, 108.4, 68.4, 55.7, 53.1, 39.9, 25.8, 18.3, −5.4, −5.6; **IR** (film) ν_{max} 2939, 2836, 1772, 1736, 1533, 1403, 1305, 1258, 1102, 1007, 938, 780 cm^{-1}; HRMS (ESI) m/z 421.1921 $[M + Na]^+$; calculated for $[C_{22}H_{30}N_2O_3Si + Na]^+$: 421.1918.

3-((1-Ethoxyethoxy)methyl)-3-((6-methoxypyridin-2-yl)methyl)indolin-2-one 13b. 28 mg (42% yield) as yellow gel (entry 3, Table 2). R_f = 0.29 (20% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ 8.42 (s, 1H), 8.36 (s, 1H), 7.35–7.28 (m, 2H), 7.15 (t, J = 7.0 Hz, 2H), 7.09 (t, J = 7.7 Hz, 2H), 6.91 (t, J = 7.5 Hz, 2H), 6.75 (d, J = 7.7 Hz, 2H), 6.57 (d, J = 7.2 Hz, 2H), 6.42 (d, J = 3.7 Hz, 1H), 6.40 (d, J = 3.7 Hz, 1H), 4.61 (q, J = 5.4 Hz, 1H), 4.58 (q, J = 5.5 Hz, 1H), 3.98 (d, J = 9.1 Hz, 1H), 3.94–3.82 (m, 2H), 3.66–3.65 (m, 6H), 3.53–3.47 (m, 1H), 3.37–3.22 (m, 7H), 1.21 (d, J = 5.4 Hz, 3H), 1.19 (d, J = 5.4 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 180.3, 180.2, 162.9, 162.9, 154.2, 154.1, 141.2, 141.2, 141.1, 141.1, 138.4 (2C), 131.0, 131.0, 127.7, 127.6, 124.5, 124.4, 124.4, 121.7, 121.6, 116.3, 116.3, 109.2, 108.4, 108.4, 99.8, 99.6, 69.3, 68.7, 61.1, 60.9, 54.0, 54.0, 53.0, 40.5, 19.5, 19.3, 15.2, 15.1; **IR** (film) ν_{max} 2909, 2826, 1771, 1726, 1543, 1401, 1315, 1248, 1092, 1006, 948, 790 cm^{-1}; HRMS (ESI) m/z 379.1631 $[M + Na]^+$; calculated for $[C_{20}H_{24}N_2O_4 + Na]^+$: 379.1628.

Synthesis and characterization of 14. In an oven-dried sealed tube, compound **12b** (1.0 g, 1.87 mmol; 1.0 equiv.) was taken in dry DMA (*N*,*N*-dimethylacetamide) (8 mL) and degassed under an argon atmosphere at room temperature for 20 minutes. To this solution, $Pd(OAc)_2$ (20 mg, 0.093 mmol; 0.05 equiv.), DavePhos (36 mg, 0.093 mmol; 0.06 equiv.), pivalic acid (57 mg, 0.56 mmol; 0.3 equiv.) and K_2CO_3 (640 mg, 4.67 mmol; 2.5 equiv.) were added successively and sealed under an argon atmosphere. The reaction mixture was then placed in an oil bath maintaining 120 °C and stirring was continued at the same temperature for 12 h. Upon completion of the reaction (TLC showed complete consumption of the starting material), the reaction mixture was quenched with water and then diluted with 30 mL of EtOAc. The organic layer was washed with water (2 × 20 mL) and brine (15 mL), respectively, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was directly purified by flash chromatography with *n*-hexane–EtOAc (3 : 1) to afford 79% yield of **14** as yellow gel along with 15% yield of **13b** (entry 9, Table 2).

5a-((1-Ethoxyethoxy)methyl)-8-methoxy-5a,6-dihydroindolo[4,3-*fg*]quinolin-5(4*H*)-one (14). 522 mg (79% yield) as yellow gel (entry 9, Table 2). R_f = 0.30 (20% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ 7.91 (d, J = 8.4 Hz, 4H), 7.32–7.21 (m, 3H), 7.15 (d, J = 7.9 Hz, 2H), 6.77 (d, J = 7.6 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 4.59 (q, J = 5.4 Hz, 1H), 4.47 (q, J = 5.4 Hz, 1H), 3.96 (s, 6H), 3.85–3.72 (m, 4H), 3.49–3.41 (m, 1H), 3.20–3.06 (m, 7H), 1.09 (d, J = 5.4 Hz, 3H), 1.06 (d, J = 5.4 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 181.5, 181.4 (2C), 163.7 (2C), 154.1, 140.8, 140.7, 133.7, 133.7, 130.9, 130.8, 129.6, 129.5, 127.0, 126.9, 121.6, 121.5, 115.8, 115.7, 109.2, 109.1, 108.2, 108.1, 99.5, 99.4, 65.9, 65.6, 60.9, 60.8, 53.8, 53.8, 47.8, 47.8, 34.5, 34.4, 19.3, 19.3, 15.2, 15.2; **IR** (film) ν_{max} 2930, 2853, 1769, 1721, 1555, 1400, 1317, 1250, 1080, 1016, 908, 780 cm^{-1}; **HRMS** (ESI) m/z 377.1471 $[M + Na]^+$; calculated for $[C_{20}H_{22}N_2O_4 + Na]^+$: 377.1500; $[\alpha]_{589}^{17.8°C}$ = −12.6 (c = 0.54, $CHCl_3$).

Synthesis and characterization of 15a–b. In an oven dried round-bottom flask, compound **14** (410 mg, 1.158 mmol; 1.0 equiv.) was dissolved in dry DMF (5 mL) under nitrogen and NaH (60% in mineral oil) (56 mg, 1.39 mmol; 1.2 equiv.) was added portionwise at 0 °C and stirring was continued at the same temperature for 5 minutes until the color changed to brown. Then, BnBr (144 μL, 1.21 mmol; 1.05 equiv.) was transferred dropwise and stirring was continued for 30 minutes while the temperature of the reaction was allowed to increase from 0 °C to room temperature. Upon completion of the reaction, the reaction mixture was quenched with water (5 mL) and partitioned between water and EtOAc. The organic layer was then separated and the water layer was washed with 2 × 15 mL EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography with *n*-hexane–EtOAc (4 : 1) to afford **15a** as yellow gel. The same reaction was performed using MeI (145 μL, 1.21 mmol; 1.05 equiv.) as an alkylating agent to afford **15b**.

4-Benzyl-5a-((1-ethoxyethoxy)methyl)-8-methoxy-5a,6-dihydroindolo[4,3-*fg*]quinolin-5(4*H*)-one (15a). 550 mg (93% yield) as yellow gel. R_f = 0.35 (20% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ: 7.48 (d, J =

8.6 Hz, 2H), 7.24 (m, 10 H), 2.15 (d, J = 7.3 Hz, 2H), 6.99–7.04 (m, 2H), 6.86 (t, J = 7.5 Hz, 2H), 6.53 (d, J = 4.5 Hz, 1H), 6.51 (d, J = 4.5 Hz, 1H), 6.31 (d, J = 8.7 Hz, 2H), 5.30 (d, J = 5.3 Hz, 2H), 4.61 (q, J = 5.4 Hz, 1H), 4.52 (q, J = 5.5 Hz, 1H), 4.50 (d, J = 15.6 Hz, 2H), 4.01 (m, 2H), 3.91 (d, J = 9.0 Hz, 1H), 3.83 (d, J = 8.7 Hz, 1H), 3.62 (m, 2H), 3.49 (m, 8H), 3.39 (m, 1H), 3.16–3.27 (m, 2H), 3.12 (m, 1H), 1.18 (d, J = 5.3 Hz, 3H), 1.12 (d, J = 5.4 Hz, 3H), 1.01–1.06 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ: 178.14, 178.12, 161.9, 152.50, 152.47, 143.5, 143.4, 142.2, 135.9, 130.73, 130.71, 128.55, 128.52, 127.6, 127.3, 127.1, 127.0, 123.33, 123.29, 121.81, 121.79, 112.23, 112.21, 110.50, 110.49, 108.47, 99.62, 99.57, 70.2, 70.0, 60.7, 60.3, 53.3, 53.0, 52.9, 43.72, 43.70, 38.5, 38.4, 19.4, 19.3, 15.2, 15.1; **IR** (film) ν_{max} 2920, 2846, 1699, 1593, 1464, 1295, 1021, 750 cm^{-1}; **HRMS** (ESI) m/z 445.2151 $[M + H]^+$; calculated for $[C_{27}H_{28}N_2O_4 + H]^+$: 445.2122.

((1-Ethoxyethoxy)methyl)-8-methoxy-4-methyl-5a,6-dihydroindolo[4,3-*fg*]quinolin-5(4*H*)-one (15b). 396 mg (93% yield) as yellow gel. R_f = 0.32 (20% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ 7.91 (s, 1H), 7.89 (s, 1H), 7.31 (t, J = 7.8 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 6.70 (dd, J = 10.9, 8.1 Hz, 4H), 4.53 (q, J = 5.4 Hz, 1H), 4.40 (q, J = 5.4 Hz, 1H), 3.95 (s, 6H), 3.82–3.68 (m, 4H), 3.41 (d, J = 2.3 Hz, 1H), 3.24 (d, J = 1.5 Hz, 6H), 3.13 (dt, J = 10.1, 6.6 Hz, 5H), 3.01 (d, J = 16.3 Hz, 2H), 1.04 (d, J = 5.4 Hz, 3H), 1.03–0.97 (m, 6H), 0.94 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 180.2, 180.1, 164.2 (2C), 155.1, 155.0, 144.5, 144.5, 134.4, 134.4, 131.1, 131.0, 130.2, 130.2, 127.0, 126.9, 122.4, 122.3, 116.5, 116.4, 109.7, 109.6, 107.0, 106.9, 100.2, 100.0, 67.0, 66.5, 61.4 (2C), 54.4, 54.4, 48.2 (2C), 35.2, 35.1, 27.2, 27.1, 19.9, 19.9, 15.8 (2C); **IR** (film) ν_{max} 2920, 2843, 1755, 1727, 1565, 1410, 1347, 1240, 1060, 1006, 938, 710 cm^{-1}; **HRMS** (ESI) m/z 391.1634 $[M + Na]^+$; calculated for $[C_{21}H_{24}N_2O_4 + Na]^+$: 391.1628.

Synthesis and characterization of 16a–b. In an oven dried sealed tube, EtSH (132 μL, 1.79 mmol; 10.0 equiv.) was added to dry DMF (3 mL) under nitrogen and NaH (60% in mineral oil) (40 mg, 0.90 mmol; 5.0 equiv.) was added portionwise at 0 °C and stirring was continued at the same temperature for 20 minutes. Then, compound **15a** (80 mg, 0.18 mmol; 1.0 equiv.) was transferred to the reaction mixture at room temperature and sealed under a nitrogen atmosphere. The reaction was then heated at 130 °C for 6 h until the starting material was completely consumed. Upon completion of the reaction, the reaction mixture was quenched with water (5 mL) and diluted with 10 mL EtOAc. The organic layer was then separated and the water layer was washed with 2 × 5 mL EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography with EtOAc to afford **16a** as yellow gel. Product **16b** was obtained under the same reaction conditions using **15b**.

4-Benzyl-5a-((1-ethoxyethoxy)methyl)-5a,7-dihydroindolo[4,3-*fg*]quinoline-5,8(4*H*,6*H*)-dione (16a). 66 mg (86% yield) as yellow gel. R_f = 0.25 (EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ: 7.91 (m, 2H), 7.41 (m, 4H), 7.34 (m, 4H), 7.28 (m, 2H), 7.08 (m, 2H), 6.64 (m, 2H), 6.53 (m, 2H), 4.58 (m, 3H), 4.48 (m, 1H), 3.97 (m, 2H), 3.87 (m, 2H), 3.34 (m, 1H), 3.06–3.21 (m, 4H), 3.08 (m, 3H), 1.10 (m, 6H), 0.98 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ: 178.4, 178.3, 165.2, 144.0, 143.9, 137.3, 135.8, 129.8, 129.7, 129.0, 128.9, 128.7, 128.6, 127.5, 127.3, 127.2, 124.3, 118.3, 118.2, 115.0, 114.9, 113.1, 113.0, 107.3, 99.4, 99.2, 66.2, 65.9, 60.5, 60.1, 46.6, 46.5, 44.0, 30.1, 30.0, 19.2, 19.1, 15.1; **IR** (film) ν_{max} 3383, 2920, 1847, 1651, 1559, 1456, 1248, 1117, 1045 cm^{-1}; **HRMS** (ESI) m/z 453.1784 $[M + Na]^+$; calculated for $[C_{26}H_{26}N_2O_4 + Na]^+$: 587.1645.

5a-((1-Ethoxyethoxy)methyl)-4-methyl-5a,7-dihydroindolo[4,3-*fg*]quinoline-5,8(4*H*,6*H*)-dione (16b). 17 mg (80% yield) as yellow gel. R_f = 0.25 (5% MeOH in EtOAc). **^{1}H NMR** (700 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ: 7.90 (d, J = 9.3 Hz, 2H), 7.34 (td, J = 7.8, 1.0 Hz, 2H), 6.62 (ddd, J = 9.3, 3.5, 0.7 Hz, 2H), 5.58 (q, J = 5.4 Hz, 1H), 4.47 (q, J = 5.4 Hz, 1H), 3.87 (m, 2H), 3.80 (m, 2H), 3.44 (m, 2H), 3.26 (m, 1H), 3.25 (s, 3H), 3.24 (s, 3H), 3.20 (m, 6H), 3.00 (m, 2H), 1.10 (d, J = 5.5 Hz, 3H), 1.07 (d, J = 5.5 Hz, 3H), 1.04 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (175 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ: 178.5, 178.4, 165.2, 165.1, 144.2, 144.1, 143.8, 143.7, 137.3, 137.2, 129.85, 129.84, 129.0, 112.9, 106.3, 106.2, 99.7, 99.5, 66.4, 65.8, 60.8, 46.6, 46.5, 29.8, 29.7, 26.6, 26.5, 19.3, 19.2, 15.1; **IR** (film) ν_{max} 3392, 1705, 1596, 1436, 1373, 1174, 1120, 721 cm^{-1}.

Synthesis and characterization of 17a–b. In an oven dried round-bottom flask, compound **16a** (50 mg, 0.116 mmol; 1.0 equiv.) was charged under a nitrogen atmosphere and dissolved in 1 mL DMF. NaH (6 mg, 0.151 mmol; 1.3 equiv.) was added to a stirred solution at 0 °C and stirring was continued for another 5 minutes before the addition of MeI (8 μL, 0.121 mmol; 1.05 equiv.). Stirring was continued at the same temperature for an hour before being quenched with water (2 mL) and partitioned with EtOAc (6 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography with EtOAc to afford **17a** as yellow gel.

4-Benzyl-5a-((1-ethoxyethoxy)methyl)-7-methyl-5a,7-dihydroindolo[4,3-*fg*]quinoline-5,8(4*H*,6*H*)-dione (17a). 46 mg (82% yield) as yellow gel. R_f = 0.3 (EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ: 7.78 (d, J = 8.6 Hz, 2H), 7.37 (m, 4H), 7.34 (m, 4H), 7.29 (m, 2H), 7.07 (d, J = 7.9 Hz, 2H), 6.64 (m, 2H), 6.54 (m, 2H), 5.24 (d, J = 4.4 Hz, 1H), 5.21 (d, J = 4.9 Hz, 1H), 4.7 (d, J = 6.4 Hz, 1H), 4.68 (d, J = 6.4 Hz, 1H), 4.60 (q, J = 5.3 Hz, 1H), 4.51 (q, J = 5.4 Hz, 1H), 3.87 (m, 2H), 3.74 (m, 8H), 3.58 (q, J = 7.0 Hz, 1H), 3.54 (q, J = 7.1 Hz, 1H), 3.35 (m, 2H), 3.19 (q, J = 7.1 Hz, 2H), 1.13 (d, J = 5.3 Hz, 3H), 1.10 (d, J = 5.4 Hz, 3H), 0.99 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ: 177.7, 149.5, 149.4, 143.4, 143.3, 135.73, 135.72, 135.1, 129.8, 128.9, 128.7, 128.6, 127.62, 127.61, 177.3, 127.2, 121.9, 121.8, 115.2, 115.1, 107.2, 99.4, 99.1, 65.9, 65.4, 60.6, 60.0, 51.83, 51.82, 44.02, 44.0, 34.3, 34.1, 31.1, 19.2, 19.1, 15.1; **IR** (film) ν_{max} 2914, 1690, 1457, 1368, 1248, 1174, 1123, 1022, 983, 750 cm^{-1}; **HRMS** (ESI) m/z 445.2117 $[M + H]^+$; calculated for $[C_{27}H_{28}N_2O_4 + H]^+$: 445.2122.

5a-((1-Ethoxyethoxy)methyl)-4,7-dimethyl-5a,7-dihydroindolo[4,3-*fg*]quinoline-5,8(4*H*,6*H*)-dione (17b). 9.0 mg (75% yield) as yellow gel. R_f = 0.3 (5% MeOH in EtOAc). **^{1}H NMR** (700 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ: 7.79 (d, J = 9.5 Hz, 2H), 7.35 (td, J = 7.8, 1.1 Hz, 2H), 7.11 (d, J = 2H), 6.74 (m, 2H), 6.64 (m, 2H), 4.56 (q, J = 5.4 Hz, 1H), 4.51 (q, J = 5.4 Hz, 1H), 3.78 (m, 2H), 3.72 (s, 3H), 3.71 (s, 3H), 3.67 (m, 2H), 3.60 (m, 1H), 3.56 (m, 1H), 3.41 (m, 2H), 3.26 (s, 6H), 3.19–3.24 (m, 4H), 1.14 (d, J = 5.4 Hz, 3H), 1.08 (d, J = 5.4 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (175 MHz, $CDCl_3$) (diastereomeric ratio ~1 : 1) δ: 177.8, 177.7, 168.3, 149.7, 149.6, 144.1, 135.1, 135.0, 132.1, 132.0, 129.9, 129.2, 129.1, 128.6, 128.5, 121.8, 121.7, 118.3, 118.2, 115.1, 115.0, 114.4, 111.3, 106.2, 106.1, 99.5, 99.4, 66.0, 65.3, 60.9, 60.6, 51.8, 51.7, 34.0, 33.8, 31.0, 26.6, 26.5, 19.3, 19.2, 15.1, 15.0; **IR** (film) ν_{max} 2928, 2097, 1712, 1596, 1412, 1373, 1248, 1174, 1097, 984, 749 cm^{-1}; **HRMS** (ESI) m/z 369.1837 $[M + H]^+$; calculated for $[C_{21}H_{24}N_2O_4 + H]^+$: 369.18.09.

Synthesis and characterization of 9a–c. The procedure is same as shown for compound **6**.

3-(2-Bromo-5-methoxybenzyl)-1*H*-indole (9a). 2.1 g (66% yields) as yellow gel. R_f = 0.65 (10% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.93 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.20 (m, 1H), 7.12 (m, 1H), 6.90 (d, J = 2.6 Hz, 1H), 6.78 (d, J = 3.1 Hz, 1H), 6.64 (dd, J = 8.7, 3.1 Hz, 1H), 4.18 (s, 2H), 3.66 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.0, 141.5, 136.4, 133.2, 127.4, 122.8, 122.1, 119.5, 119.1, 116.6, 115.1, 113.9, 113.1, 111.2, 55.3, 32.0; **IR** (film) ν_{max} 3414, 2904, 2833, 2667, 1593, 1570, 1469, 1238, 1053, 1014 cm^{-1}; **HRMS** (ESI) m/z 316.0309 $[M + H]^+$; calculated for $[C_{16}H_{14}BrNO + H]^+$: 316.0332.

3-(2-Bromo-4,5-dimethoxybenzyl)-1*H*-indole (9b). 3.02 g (78% yield) as yellow gel. R_f = 0.45 (20% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.99 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.05 (s, 1H), 6.90 (s, 1H), 6.75 (s, 1H), 4.15 (s, 2H), 3.86 (s, 3H), 3.69 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.4, 147.9, 136.4, 132.4, 127.3, 122.5, 122.1, 119.5, 119.1, 115.5, 114.7, 114.2, 113.4, 111.1, 56.2, 55.9, 31.5; **IR** (film) ν_{max} 3373, 2907, 2839, 1504, 1456, 1436, 1257, 1215, 775 cm^{-1}; **HRMS** (ESI) m/z 368.0239 $[M + Na]^+$; calculated for $[C_{17}H_{16}BrNO_2 + Na]^+$: 368.0257.

3-(2-Bromo-3,4,5-trimethoxybenzyl)-1*H*-indole (9c). 2.52 g (76% yield) as yellow gel. R_f = 0.35 (20% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.15 (s, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.15 (dt, J = 34.4, 7.6 Hz, 2H), 6.93 (s, 1H), 6.61 (s, 1H), 4.19 (s, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 3.66 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.5, 150.8, 141.4, 136.4, 136.2, 127.4, 122.9, 122.1, 119.4, 119.1, 113.9, 111.2, 110.7, 109.5, 61.1, 61.0, 56.0, 32.1; **IR** (film) ν_{max} 3392, 2935, 2846, 2665, 1568, 1481, 1456, 1332, 1105, 1008 cm^{-1}; **HRMS** (ESI) m/z 376.0548 $[M + H]^+$; calculated for $[C_{18}H_{18}BrNO_3 + H]^+$: 376.0543.

Synthesis and characterization of 10a–c. The procedure is same as shown for compound **5a**.

3-(2-Bromo-5-methoxybenzyl)indolin-2-one (10a). 1.2 g (76% yield) as a pale yellow solid. R_f = 0.30 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.70 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.18 (m, 1H), 6.89–6.96 (m, 3H), 6.48 (d, J = 8.6 Hz, 1H), 4.18 (dd, J = 7.6, 4.3 Hz, 1H), 3.74 (m, 4H), 3.46 (dd, J = 16.6 Hz, 7.7 Hz, 1H) 8.60 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 181.2, 162.3, 153.0, 142.3, 141.8, 129.7, 127.7, 123.8, 122.1, 112.1, 110.5, 109.8, 53.6, 44.2, 36.1; **IR** (film) ν_{max} 3224, 2901, 1706, 1471, 1240, 765 cm^{-1}; **MP** 126–127 °C; **HRMS** (ESI) m/z 332.0273 $[M + H]^+$; calculated for $[C_{16}H_{14}BrNO_2 + H]^+$: 332.0281.

3-(2-Bromo-4,5-dimethoxybenzyl)indolin-2-one (10b). 1.0 g (83% yield) as a pale yellow solid. R_f = 0.35 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.07 (s, 1H), 7.16 (t, J = 7.3 Hz, 1H), 7.02 (s, 1H), 6.88 (m, 2H), 6.70 (m, 2H), 3.85 (m, 4H), 3.74 (s, 3H), 3.51 (dd, J = 13.9, 5.5 Hz, 1H), 2.93 (dd, J = 14.0, 9.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 179.8, 148.4, 148.0, 141.5, 129.4, 128.7, 128.1, 125.2, 121.9, 115.6, 114.7, 114.4, 109.8, 56.1, 56.0, 45.9, 36.8; **IR** (film) ν_{max} 2835, 1706, 1506, 1257, 1215, 785 cm^{-1}; **MP** 150–152 °C; **HRMS** (ESI) m/z 362.0370 $[M + H]^+$; calculated for $[C_{17}H_{16}BrNO_3 + H]^+$: 362.0386.

3-(2-Bromo-3,4,5-trimethoxybenzyl)indolin-2-one (10c). 1.25 g (64% yield) as a pale yellow solid. R_f = 0.30 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.45 (s, 1H), 7.15 (t, J = 7.7 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 6.68 (d, J = 7.4 Hz, 1H), 6.57 (s, 1H), 3.87 (m, 7H), 3.74 (s, 3H), 3.53 (dd, J = 13.9, 5.7 Hz, 1H), 2.92 (dd, J = 13.8, 9.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 180.1, 152.2, 151.0, 142.1, 141.6, 133.1, 128.7, 128.1, 125.1, 121.9, 111.2, 110.7, 110.0, 61.2, 61.0, 56.1, 45.6, 37.5; **IR** (film) ν_{max} 2926, 2843, 2366, 1706, 1477, 1338, 1105, 754 cm^{-1}; **MP** 88–90 °C; **HRMS** (ESI) m/z 392.0495 $[M + H]^+$; calculated for $[C_{18}H_{18}BrNO_4 + H]^+$: 392.0492.

Synthesis and characterization of 8a–c. The procedure is same as shown for compound **5c**.

***tert*-Butyl 3-(2-bromo-5-methoxybenzyl)-2-oxoindoline-1-carboxylate (8a).** 240 mg (65% yield) as pale yellow gel. R_f = 0.55 (10% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.80 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 8.7 Hz, 1H), 7.27 (m, 1H), 6.99 (td, J = 7.5, 1.1 Hz, 1H), 6.75 (d, J = 3.2 Hz, 1H), 6.71 (m, 2H), 3.98 (dd, J = 9.6, 5.6 Hz, 1H), 3.73 (s, 3H), 3.56 (dd, J = 13.8, 5.6 Hz, 1H), 2.96 (dd, J = 14.0, 9.5 Hz, 1H), 1.63 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 175.2, 158.7, 149.3, 139.9, 138.1, 133.6, 128.2, 127.0, 124.6, 123.9, 117.3, 115.2, 114.8, 114.7, 84.4, 55.5, 45.3, 38.3, 28.1; **IR** (film) ν_{max} 2960, 2929, 2850, 1791, 1768, 1732, 1477, 1352, 1296, 1251, 1149, 754 cm^{-1}; **HRMS** (ESI) m/z 454.0639 $[M + Na]^+$; calculated for $[C_{21}H_{22}BrNO_4 + Na]^+$: 454.0624.

***tert*-Butyl 3-(2-bromo-4,5-dimethoxybenzyl)-2-oxoindoline-1-carboxylate (8b).** 520 mg (71% yield) as colorless gel. R_f = 0.45 (20% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.77 (d, J = 8.20 Hz, 1H), 7.24 (t, J = 7.3 Hz, 1H), 7.01 (s, 1H), 6.98 (td, J = 7.5, 1.0 Hz, 1H), 6.73 (d, J = 7.5 Hz, 1H), 6.66 (s, 1H), 3.92 (dd, J = 9.1, 5.7 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.52 (dd, J = 13.9, 5.5 Hz, 1H), 2.96 (dd, J = 14.0, 9.2 Hz, 1H), 1.62 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 175.4, 149.2, 148.6, 148.1, 131.9, 128.9, 128.2, 126.9, 124.8, 123.8, 115.6, 114.8, 114.7, 114.4, 84.4, 56.1, 56.0, 45.8, 37.6, 28.1; **IR** (film) ν_{max} 2922, 2848, 1732, 1506, 1257, 1506, 1257, 1149, 790 cm^{-1}; **HRMS** (ESI) m/z

484.0729 [M + Na]$^+$; calculated for [$C_{22}H_{24}BrNO_5$ + Na]$^+$: 484.0730.

***tert*-Butyl 3-(2-bromo-3,4,5-trimethoxybenzyl)-2-oxoindoline-1-carboxylate (8c).** 359 mg (60% yield) as pale yellow gel. R_f = 0.50 (30% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.79 (d, J = 8.1 Hz, 1H), 7.27 (m, 1H), 6.77 (td, J = 7.7, 1.0 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.55 (s, 1H), 3.94 (dd, J = 9.1, 5.7 Hz, 1H), 3.88 (s, 6H), 3.76 (s, 3H), 3.53 (dd, J = 13.9, 5.8 Hz, 1H), 3.01 (dd, J = 13.9, 8.9 Hz, 1H), 1.63 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 175.3, 152.3, 151.1, 149.2, 142.2, 139.9, 132.6, 128.3, 127.0, 124.7, 123.9, 114.8, 111.2, 110.7, 84.4, 61.2, 61.0, 56.1, 45.5, 38.3, 28.1; **IR** (film) ν_{max} 2920, 2850, 1708, 1471, 1267, 1169, 1045, 754 cm^{-1}; **HRMS** (ESI) m/z 514.0809 [M + Na]$^+$; calculated for [$C_{23}H_{26}BrNO_6$ + Na]$^+$: 514.0836.

Synthesis and characterization of 11a–c. The procedure is same as shown for compound (+)-**4c**.

***tert*-Butyl (*S*)-3-(2-bromo-4,5-dimethoxybenzyl)-3-(hydroxymethyl)-2-oxoindoline-1-carboxylate (+)-11b.** 15 mg (94% yield) as colourless gel. R_f = 0.3 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.67 (d, J = 8.1 Hz, 1H), 7.23 (m, 1H), 7.09 (m, 2H), 6.80 (s, 1H), 6.61 (s, 1H), 4.01 (d, J = 11.2 Hz, 1H), 3.85 (d, J = 11.2 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.35 (ABq, J = 14.0 Hz, 2H), 2.36 (s, 1H), 1.59 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 178.2, 148.8, 148.2, 147.9, 139.9, 128.7, 127.3, 126.9, 124.3, 124.2, 115.5, 115.2, 114.8, 113.1, 84.6, 66.6, 55.9, 55.7, 55.6, 37.7, 28.1; **IR** (film) ν_{max} 3425, 2922, 2848, 1786, 1732, 1508, 1149, 775 cm^{-1}; **HRMS** (ESI) m/z 514.0811 [M + Na]$^+$; calculated for [$C_{23}H_{26}BrNO_6$ + Na]$^+$: 514.0836. Enantiomeric excess was determined to be 82% ee *via* HPLC analysis using a Chiralpak IA column; solvent: 2-propanol/hexane = 1/9; flow rate: 1.0 mL min^{-1}; detection: at 254 nm: t_R minor = 14.10 min, t_R major = 16.83 min; $[\alpha]_{589}^{25.4^\circ C}$ = +15.3 (c = 1.0, $CHCl_3$).

***tert*-Butyl (*S*)-3-(2-bromo-5-methoxybenzyl)-3-(hydroxymethyl)-2-oxoindoline-1-carboxylate (+)-11a.** 23 mg (92% yield) as colorless gel. R_f = 0.42 (40% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.71 (d, J = 8.1 Hz, 1H), 7.24 (m, 2H), 7.01–7.08 (m, 2H), 6.69 (d, J = 3.0 Hz, 1H), 6.55 (dd, J = 8.8 Hz, 1H), 4.03 (d, J = 11.2 Hz, 1H), 3.85 (d, J = 11.2 Hz, 1H), 3.64 (s, 3H), 3.41 (d, J = 13.9 Hz, 1H), 3.34 (d, J = 13.9 Hz, 1H), 2.36 (brs, 1H), 1.60 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 178.1, 158.5, 148.9, 139.9, 135.9, 133.3, 128.8, 127.2, 124.2, 124.1, 116.2, 115.6, 115.4, 114.8, 84.5, 66.4, 55.3, 55.2, 38.1, 28.0; **IR** (film) ν_{max} 3444, 2922, 2850, 1735, 1597, 1469, 1153, 750 cm^{-1}; **HRMS** (ESI) m/z 484.0760 [M + Na]$^+$; calculated for [$C_{22}H_{24}BrNO_5$ + Na]$^+$: 484.0730. Enantiomeric excess was determined to be 78% ee *via* HPLC analysis using a Chiralpak IA column; solvent: 2-propanol/hexane = 1/9; flow rate: 1.0 mL min^{-1}; detection: at 254 nm: t_R minor = 9.72 min, t_R major = 12.17 min; $[\alpha]_{589}^{25.5^\circ C}$ = +5.3 (c = 1.0, $CHCl_3$).

***tert*-Butyl (*S*)-3-(2-bromo-3,4,5-trimethoxybenzyl)-3-(hydroxymethyl)-2-oxoindoline-1-carboxylate (+)-11c.** 20 mg (95% yield) as colourless gel. R_f = 0.35 (50% EtOAc in hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.66 (d, J = 8.2 Hz, 1H), 7.20 (td, J = 8.8, 1.8 Hz, 1H), 7.00–7.07 (m, 2H), 6.47 (s, 1H), 3.98 (d, J = 11.2 Hz, 1H), 3.84 (d, J = 11.3 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.65 (s, 3H), 3.45 (d, J = 14.6 Hz, 1H), 3.35 (d, J = 14.0 Hz, 1H), 2.47 (brs, 1H), 1.57 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 178.1, 152.0, 150.6, 148.8, 142.0, 139.8, 130.7, 128.7, 127.3, 124.3, 124.1, 114.7, 112.4, 109.3, 84.6, 66.5, 61.0, 60.7, 55.8, 55.5, 38.0, 28.0; **IR** (film) ν_{max} 3436, 2933, 1784, 1732, 1483, 1463, 1149, 765 cm^{-1}; **HRMS** (ESI) m/z 544.0920 [M + Na]$^+$; calculated for [$C_{24}H_{28}BrNO_7$ + Na]$^+$: 544.0941. Enantiomeric excess was determined to be 85% ee *via* HPLC analysis using a Chiralpak IA column; solvent: 2-propanol/hexane = 3/17; flow rate: 1.0 mL min^{-1}; detection: at 254 nm: t_R minor = 6.34 min, t_R major = 7.63 min; $[\alpha]_{589}^{23.7^\circ C}$ = +8.5 (c = 0.23, $CHCl_3$).

Conflicts of interest

There are no conflicts to declare.

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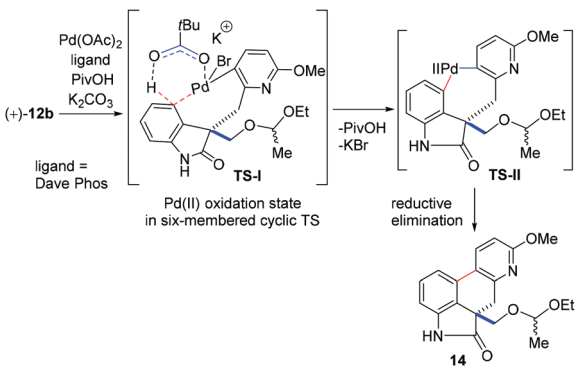

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