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Organocatalytic Asymmetric Decarboxylative Cyanomethylation of Isatins using L-Proline Derived Bifunctional Thiourea

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First asymmetric decarboxylative cyanomethylation of isatins is reported herewith using bifunctional thiourea derived from L-proline in good yields and enantioselectivities. This strategy enables the construction of various cyanomethylene substituted 3-hydroxy oxindoles in enantioelective manner. Enantioselective synthesis of alkaloid CPC-1 has been accomplished in fewer steps.

Introduction

Pharmacologically active scaffolds present in natural products inspire the synthetic chemists to synthesize analogs of the same to increase molecular diversity. 3-Hydroxy oxindole is one such scaffold which received much attention due to its wide biological activity.[1]

Intermediate I is a versatile building block to various natural products. The reported methods to enantiopure 3-hydroxy oxindoles can be broadly cla metal catalysis[2] and organocatalysis.[3] Decarboxylative addit of malonic acid half thioester (MAHT)[4] or ketoacid which is an effective way of forming C-C bond enantioselectively wa to synthesize intermediate I[5] and II.[6] A recent communicat discloses the use of Ytterbium complex of I construction of 3-hydroxy oxindoles.[7] Hayashi and co-workers accomplished the synthesis of intermediate I using asymmetri aldol reaction.[8] The resulting intermediates of the protocols require multiple synthetic trans accomplish the synthesis of natural products such 1, etc.

Existence of few methods for synthesizing intermediate I stimulated us to develop a methodology for the hydroxy oxindoles. Moreover, devoid of nitroge intermediate I demand multiple synthetic steps to total synthesis of natural products (Fig 1). Introduction of group as shown in intermediate II, would definitely shor synthesis of natural products e.g. Alline, CPC-1, etc. (Fig I).

Although decarboxylative addition using MAH ketoacids is well explored, there are only fe literature for the enantioselective decarboxylative addition of cyanoacetic acid.[9] Only achiral version of cyanomethylatio isatins had been reported recently.[10] To the best of our knowledge there is no report on enantioselective synthesis of natural products. Herein we disclose the first enantioselective decarboxylative cyanomethylation of isatins with good yield enantioselectivities using L-proline derived thiourea catalyst.

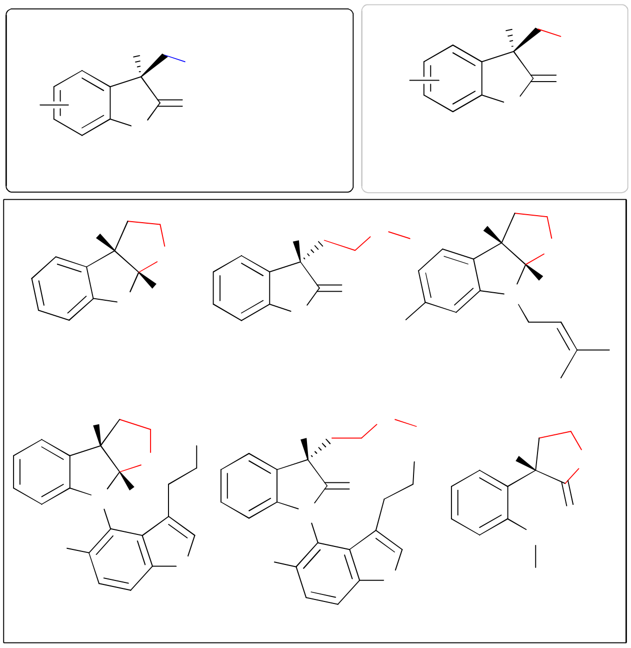

Fig 1 Selected examples of bioactive molecules which can be s from intermediate II in fewer steps

Results and discussion

Initially decarboxylative cyanomethylation was in using cinchona bases and its derivatives. Isatin (1) was treated with 1.1 equivalent of cyanoacetic acid (2) in the presence chiral base (5 mol %) in THF at 25 °C (Table 1, entries 1-7). Except ICD, these chiral bases catalysed the formati

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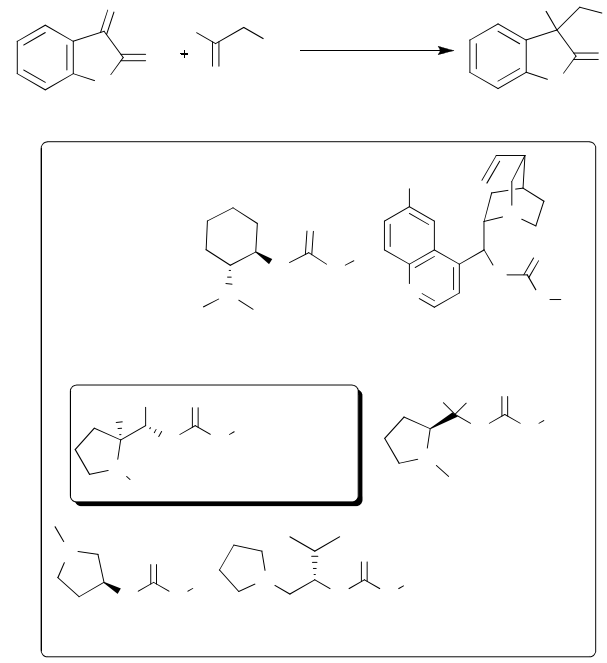
cyanomethylated product 3a. Although satisfactory yields were obtained, the enantioselectivities were found to be poor (Table 1, entries 1-7). Since we explored chiral bases failed to deliver the expected outcome, we turned our attention to covalent bifunctional thiourea organocatalysts. Widely used bifunctional thioureas (4c, 4d, 4h, 4i and 4j) were employed (5 mol %) to accomplish enantioselective cyanomethylation. Among various bifunctional thiourea organocatalysts tested, quinine derived thiourea yielded the product with better enantioselectivity (Table 1, entry 9), but still there is a lot of room for improvement in enantioselectivity.

Table 1 Screening of organocatalysts for the enantioselective decarboxylative cyanomethylation[a] of isatins

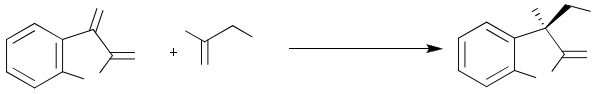


Entry	catalyst	Time (days)	Yield[b] (%)	ee[c] (%)
1	4a	3	78	11 (S)
2	4b	3	79	rac
3	4c	3	76	16 (R)
4	4d	3	81	07 (R)
5	4e	3	79	10 (S)
6	4f	3	trace	–
7	4g	3	78	rac
8	4h	3	79	48 (S)
9	4i	3	79	57 (R)
10	4j	3	79	42 (S)
11	5a	3	77	74 (S)
12	5b	3	79	80 (S)
13	5c	3	79	75 (S)
14	6a	5	trace	–
15	6b	3	81	55 (R)
16	7	3	trace	–
17	8	3	76	54 (R)

[a] The reactions were carried out with 1a (0.1 mmol), 2 (0.11 mmol), and catalyst (0.005 mmol) in 0.5 ml of THF at 25 °C. [b] Isolated yield. [c] Determined by chiral HPLC.

These results indicate that, identification of a suitable catalyst for enantioselective transformation is an ongoing challenge for synthetic chemists. In order to identify a suitable catalyst for cyanomethylation reaction we employed the proline derived non-covalent bifunctional organocatalyst containing tertiary amine and thiourea functionality which has been developed in our laboratory[11] (unpublished results). We hope that proline derived bifunctional organocatalysts will emerge as an efficient catalyst for enantioselective reactions. In addition the modular synthesis would allow the possibility of altering electronic properties at stereogenic centre bearing the functionality. We were delighted to observe that synthesized thiourea 5a efficiently catalyzed the formation of product 3a with good yield and enantioselectivity (Table 1, entries 11). N-Me derivative of organocatalyst 5a was found to be the most suitable organocatalyst which yielded 3a with 80% ee (entry 12). To ascertain the requirement of newly created stereogenic centre in 5a, thiourea 6a and 6b were also employed. A more sterically hindered thiourea 6a which has no stereogenic centre at the carbon bearing moiety was unable to catalyze cyanomethylation of isatin (Table 1, entry 14). Although prolinol derived thiourea 6b afforded the product 3a in 81% yield but moderate enantioselectivity (55%) was observed (Table 1, entry 15). To prove the worth of newly employed thiourea 5a, we evaluated two more thiourea catalysts 7 and 8 that contain N-alkyl pyrrolidine ring.[12] While catalyst 7 failed to promote the cyanomethylation, product 3a was isolated in 76% yield with low enantioselectivity in the case of thiourea 8 (Table 1, entries 16 and 17). The absolute configuration of the product 3a formed by organocatalyst 5a and 6b was found to be (S) and (R) respectively (Table 1, entries 12 and 15).[13] The results indicate

Table 2 Optimization studies of enantioselective decarboxylative cyanomethylation of isatins using 5b organocatalyst



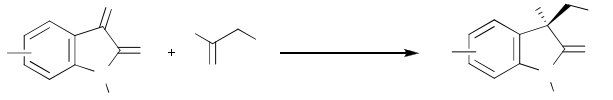
Entry	Solvent	mol %	Time (days)	Yield[b] (%)	ee[c] (%)
1	THF	5	5	78	81
2	CH_2Cl_2	5	5	70	33
3	DCE	5	4	trace	–
4	$CHCl_3$	5	4	trace	–
5	CH_3CN	5	4	trace	–
6	MTBE	5	4	82	86
7	Et_2O	5	4	81	73
8	Acetone	5	4	60	44
9	EtOAc	5	4	63	60
10	$PhCH_3$	5	4	trace	–
11	DMF	5	6	85	07
12[d]	MTBE	5	6	trace	–
13	MTBE	2	6	76	75
14	MTBE	10	4	80	80

[a] The reactions were carried out with 1a (0.1 mmol), 2 (0.12 mmol), and 5b (0.005 mmol) in 0.5 ml of solvent at mentioned temperature. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Reaction was carried out at 5 °C.

that, the newly created stereogenic bearing carbon (Table 3, entries 3). Various N-substituted isatins thiourea moiety not only dictates the stereochemical outcome of the reaction but it is also essential for effective asymmetric induction.

Further optimizations of reaction medium, catalyst loading, and temperature resulted in only marginal improvement of enantioselectivity and the details are listed in Table 2. 5 mol % of catalyst 5b, ambient temperature and MTBE as the reaction medium were identified as optimized reaction conditions to afford the product 3a in 82% yield and 84% ee. Thus we identified suitable bifunctional thiourea catalyst 5b which outperformed widely used chiral bases and thiourea catalysts in cyanomethylation of isatin.

Table 3 Substrate scope of enamide derived oxidative cyanomethylation of isatins using 5b organocatalyst

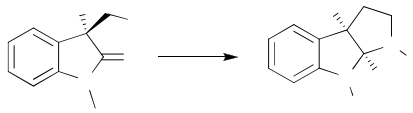


Entry	R_1, R_2	Product	Time (days)	Yield[b] (%)	ee[c] (%)
1	H, H	3a	4	82	84
2	5-Br, H	3b	3.5	78	82
3	5-Cl, H	3c	4	82	84
4	5-F, H	3d	3.5	76	87(98)
5	5-NO_2, H	3e	3.5	78	84(99)
6	5-OCH_3, H	3f	6	72	75
7	5,7-di Br, H	3g	3	78	86
8	5,7-di Cl, H	3h	4	72	90
9	5,7-di Me, H	3i	6	72	81
10	H, Bn	3j	4	75	70
11	H, Me	3k	4	81	80
12	H, tert-butylacetate	3l	4	76	80
13	H, Propargy	3m	4	80	72

[a]The reactions were carried out with 1 (0.11 mmol), 2 (0.11 mmol), 5a and (0.005 mmol) in 0.5 ml of MTBE at rt. [b]Isolated yield. [c]Determined by chiral HPLC. Enantiomeric excess in the parenthesis was obtained after single recrystalisation.

The scope of the reaction was investigated after establishing the optimal reaction condition. Since better pharmacological activity is expected with unprotected oxindole derivatives than their protected counterparts, various substituted oxindoles were examined as substrates. Isatins (1) were treated with cyanoacetic acid (2) in the presence of 5 mol % 5b in MTBE at 25 °C. The corresponding cyanomethylated products (3) were obtained in good yields in all the cases (72-82%). Notably, halogen substituents are well tolerated in this cyanomethylation reaction in which the respective products were isolated in very good enantioselectivities (Table 3, entries 1-2). Reaction proceeded efficiently with good yield and enantioselectivity in the presence of electron withdrawing substituent (NO_2 in isatin, Table 3, entry 5). A slight diminish in enantioselectivity was noticed in the presence of electron releasing OMe substituent (Table 3, entry 6). 5,7-Disubstituted isatins were successfully used as substrates; corresponding cyanomethylated oxindoles were obtained in comparable yields and enantioselectivities of mono substituted

derivatives (Table 3, entries 7-10). Thus we accomplished the first enantioselective cyanomethylation of isatins in good yields and enantioselectivites for the substrates bearing halogens, electron withdrawing and electron releasing group.



Scheme 2 Enantioselective synthesis of CPC-1

Reagents and conditions: (i) LiAlH$_4$, HCl, NaCNBH$_3$, MeOH, rt, 4h; (ii) NaH, MeI, dry DMF, rt, 2h, 70% yield (over 3 steps).

There are only two reports on enantioselective synthesis of CPC-1. Kitajima *et al.* employed Ti(O^iPr)$_4$ mediated asymmetric allylation route to accomplish the total synthesis.[15] Hayashi applied covalent organocatalysis to achieve using enantioselective enamine addition to isatin.[8] Herein, we demonstrated asymmetric oxidative cyanomethylation method to synthesize CPC-1 using a covalent thiourea organocatalyst with comparable enantioselectivity in and with better overall yield.

Conclusions

In summary, we successfully applied an organocatalyst enantioselective cyanomethylation of isatins for the first the literature. It is noteworthy that, the well k systems such as chiral bases, privileged thioureas f this transformation when compared to bifunctional t developed in our laboratory. We further substantiate intermediate II to synthesize CPC-1 in three steps. Due to th importance of substituted 3-hydroxy oxindole scaffold in th field of medicinal chemistry, we are confident intermediate II will play vital role in the synthes bioactive small molecules. Furthermore, exploration of organocatalysis in new enantioselective reactions is being carried out in our laboratory.

Experimental

General remarks

All reactions were carried out in an oven dried flask. S used for reactions and column chromatography were co grade and distilled prior to use. Toluene and THF were Sodium/Benzophenone, CH_2Cl_2 and $CHCl_3$ over CaH_2. Solvents for HPLC bought as analytical grade and used without fur purification. TLC was performed on pre-coated silica gel aluminium plates with F-254 indicator, visualised by irradi with UV light. Column chromatography was performed silica gel (100-60 mesh). ^{1}H-NMR and ^{13}C-NMR were recorded o a 500 MHz instrument using DMSO-d_6 and $CDCl_3$ as solvent and multiplicity is as follows: s (singlet), d (doublet), t (quartet), m (multiplet), dd (doublet of doublet),

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triplet) bs (broad singlet). Coupling constants J were reported in Hertz. High resolution mass spectra were obtained by ESI using Q-TOF mass spectrometer. IR spectra were reported in terms of frequency of absorption (cm^{-1}). The enantiomeric excess is obtained by HPLC analysis using a chiral stationary phase column (CHIRALPAK AD-H, AS-H and OD-H). Optical rotation was recorded using polarimeter at a wavelength of 589 nm.

General procedure for asymmetric decarboxylative cyanomethylation of isatin

To a stirred solution of 5b (2.31 mg, 0.005 mmol, 5 mol%) and isatin 1 (0.1 mmol) in MTBE (0.5 mL), cyanoacetic acid 2 (10.2 mg, 0.12 mmol) was added. The solution was stirred at ambient temperature for mentioned days. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified through column chromatography on silica gel to give the product 3.

(S)-2-(3-Hydroxy-2-oxoindolin-3-yl)acetonitrile (3a)[10a] Prepared according to the general procedure using isatin 1a (29.4 mg, 0.2 mmol) and the reaction completed after 4 days. After column chromatography, the desired product was obtained (30.54 mg, 82% yield). $[\alpha]^{25}_{D}$ = −58.8 (c = 1.0, MeOH); Analytical data matches with previously reported values. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.54 (s, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.29 (t, J = 9.5 Hz, 1H), 7.05 (t, J = 9.5 Hz, 1H), 6.88 (d, J = 9.5 Hz, 1H), 6.66 (s, 1H), 3.10 (d, J = 20.5 Hz, 1H), 2.96 (d, J = 20.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.7, 141.6, 130.0, 129.7, 124.9, 122.1, 117.0, 110.0, 71.7, 26.1; HPLC (90 : 10, n-hexane : i-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD-H column, t_R = 21.3 (major), t_R = 23.9 (minor), 84% ee.

(S)-2-(5-Bromo-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (3b)[10a]. Prepared according to the general procedure using isatin 1b (22.6 mg, 0.1 mmol) and the reaction completed after 3.5 days. After column chromatography, the desired product was obtained (20.84 mg, 78% yield). $[\alpha]^{25}_{D}$ = −18.72 (c = 1.0, MeOH); Analytical data matches with previously reported values. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.80 (s, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.49 (dd, J = 8.5, 2.0 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 3.05 (d, J = 14.5 Hz, 1H), 3.03 (d, J = 14.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.1, 140.9, 132.6, 132.1, 127.0, 116.8, 113.6, 112.1, 72.2, 25.7; HPLC (90 : 10, n-hexane : i-PrOH, 220 nm, 1 mL/min) Chiralpak AD-H column, t_R = 21.5 (major), t_R = 25.8 (minor), 82% ee.

(S)-2-(5-Chloro-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (3c)[10a]. Prepared according to the general procedure using isatin 1c (18.16 mg, 0.1 mmol) and the reaction completed after 4 days. After column chromatography, the desired product was obtained (18.26 mg, 82% yield). $[\alpha]^{25}_{D}$ = −26.0 (c = 1.0, MeOH); Analytical data matches with previously reported values. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.67 (s, 1H), 7.48 (d, J = 2.5 Hz, 1H), 7.35 (dd, J = 8.5, 2.5 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 6.74 (s, 1H), 3.11 (d, J = 16.5 Hz, 1H), 3.02 (d, J = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.2, 140.5, 131.7, 129.8, 125.9, 124.3, 116.8, 111.6, 72.0, 25.7; HPLC (90 : 10, n-hexane : i-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD-H column, t_R = 20.5 (major), t_R = 24.3 (minor), 84% ee.

(S)-2-(5-Fluoro-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (3d)[10a]. Prepared according to the general procedure using isatin 1d (16.51 mg, 0.1 mmol) and the reaction completed after 3.5 days. After column chromatography, the desired product was obtained (15.67 mg, 76% yield). $[\alpha]^{25}_{D}$ = −31.10 (c = 1.0, $CHCl_3$); Analytical data matches with previously reported va[illegible] NMR (500 MHz, DMSO-d_6): δ = 10.54 (s, 1H), 7.18 (d, J = 8.0, 2.5 Hz, 1H), 7.12 (m, 1H), 6.85 (dd, [illegible]), 6.76 (s, 1H), 3.15 (d, J = 16.5 Hz, 1H), 3.09 (d, J = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 17[illegible] 137.73, 137.72, 131.3, 131.[illegible] 111.0, [illegible]; HPLC (95 : 5, n-hexane : i-PrOH, 220 nm, 0.5 mL/min) Chiralpak AD-H column, t_R = 41.73 (major), t_R = 46.1 (minor), 98% ee.

(S)-2-(3-Hydroxy-5-nitro-2-oxoindolin-3-yl)acetonitrile[10a] (3e) Prepared according to the general procedure using isatin 1e (19.21 mg, 0.1 mmol) and the reaction completed after 3.5 days. After column chromatography, the desired product was obtained (18.19 mg, 78% yield). $[\alpha]^{25}_{D}$ = −11.2 (c = 1.0, MeOH); Analytical data matches with previously reported va[lues]. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.26 (s, 1H), 8.34 (d, J = 2.5 Hz, 1H), 8.27 (dd, J = 8.5, 2.5 Hz, 1H), 7.09 (d, J = 8.5 Hz, 1H), 6.93 (s, 1H), 3.21 (d, J = 16 Hz, 1H), 3.14 (d, J = 17.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.9, 148.1, 142.3, 130.6, 127.2, 119.9, 116.7, 110.4, 71.6, 25.4; HPLC (90 : 10, n-hexane : i-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD-H column, t_R = 28.6 (major), t_R = 34.13 (minor), 99% ee.

(S)-2-(3-Hydroxy-5-methoxy-2-oxoindolin-3-yl)acetonitrile (3f)[10a]. Prepared according to the general procedure using isatin 1f (17.71 mg, 0.1 mmol) and the reaction completed after 6 d[ays]. After column chromatography, the desired product wa[s obtained] (15.71 mg, 72% yield). $[\alpha]^{25}_{D}$ = −44.2 (c = 1.0, MeOH); Analytical data matches with previously reported va[lues]. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.35 (s, 1H), 7.07 (d, J = 2.5 Hz, 1H), 6.84 (dd, J = 8.5, 2.5 Hz, 1H), 6.76 (d, J = 8.5 Hz, 1H), 6.59 (s, 1H), 3.70 (s, 3H), 3.03 (d, J = 17.0 Hz, 1H), 2.95 (d, J = 17.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.5, 155.0, 134.6, 130.8, 116.9, 114.5, 111.1, 110.4, 72.3, 55.5, [illegible]; HPLC (90 : 10, n-hexane : i-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD-H column, t_R = 22.9 (major), t_R = 28.17 (minor), 75% ee.

(S)-2-(5,7-Dibromo-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (3g)[10a]. Prepared according to the general procedure using isatin 1g (30.49 mg, 0.1 mmol) and the reaction completed after 3 d[ays]. After column chromatography, the desired product was obtained (26.98 mg, 78% yield). $[\alpha]^{25}_{D}$ = −28.01 (c = 1.0, $CHCl_3$); Analytical data matches with previously reported va[lues]. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.06 (s, 1H), 7.76 (d, J = 1.5 Hz, 1H), 7.67 (d, J = 1.5 Hz, 1H), 6.87 (s, 1H), 3.15–3.07 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 176.0, 140.6, 134.4, 133.2, 126.2, 116.6, 114.0, 103.2, 72.7, 25.6; HPLC (90 : 10, n-hexane : i-PrOH, 254 nm, 1.0 mL/min) Chiralpak AS-H column,

t_R = 39.3 (minor), 44.8 (major), ee.

(*S*)-2-(5,7-Dichloro-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (3h). Prepared according to the general procedure using isatin (21.60 mg, 0.1 mmol) and the reaction completed after 4 days. After column chromatography, the desired product was obtained (18.50 mg, 72% yield). $[\alpha]_D^{25}$ = −16.10 (c = 1, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) = 11.21 (s, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.22 (s, 1H), 3.15 (d, J = 16.5 Hz, 1H), 3.10 (d, J = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) = 176.3, 138.6, 133.0, 129.2, 123.2, 121.6, 116.7, 115.1, 112.7, 25.6; HRMS (ESI) m/z calculated $C_{10}H_6O_2N_2Cl_2+Na^+$: 278.9695, found: 278.9698. HPLC (90 : 10, hexane : PrOH, 220 nm, 1.0 mL/min) Chiralpak AD column, t_R = 33.2 (major), t_R = 36.9 (minor), 90% ee.

(*S*)-2-(3-Hydroxy-5,7-dimethyl-2-oxoindolin-3-yl)acetonitrile (3i). Prepared according to the general procedure using isatin (17.52 mg, 0.1 mmol) and the reaction completed after 4 days. After column chromatography, the desired product was obtained (15.57 mg, 72% yield). $[\alpha]_D^{25}$ = −48.0 (c = 1, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) = 10.48 (s, 1H), 7.09 (s, 1H), 6.92 (d, J = 0.5 Hz, 1H), 6.50 (s, 1H), 3.00 (d, J = 16.5 Hz, 1H), 2.90 (d, J = 16.5 Hz, 1H), 2.24 (s, 1H), 2.16 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) = 177.1, 137.6, 131.5, 130.8, 129.5, 122.0, 119.1, 117.1, 72.2, 26.2, 20.8, 16.5; HRMS (ESI) m/z calculated for $C_{12}H_{12}O_2N_2+Na^+$: 239.0791, found: 239.0794. HPLC (90 : 10, hexane : PrOH, 254 nm, 1.0 mL/min) Chiralpak AD, t_R = 10.6 (minor), 11.7 (major), ee.

(*S*)-2-(1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)acetonitrile (3j)[10a]. Prepared according to the general procedure using isatin (23.72 mg, 0.1 mmol) and the reaction completed after 4 days. After column chromatography, the desired product was obtained (26.87% yield). $[\alpha]_D^{25}$ = −51.0 (c = 1, MeOH); Analytical data matches with previously reported values. ^{1}H NMR (500 MHz, $CDCl_3$): = 7.65 (d, J = 7.5 Hz, 1H), 7.37-7.24 (m, 6H), 7.14 (t, J = 7.5 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 4.92 (d, J = 16.5 Hz, 1H), 4.87 (d, J = 16.0 Hz, 1H), 4.03 (d, J = 16.5, Hz, 1H), 3.52 (d, J = 16.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): = 175.5, 142.0, 130.8, 128.6, 126.7, 127.4, 127.2, 124.0, 123.1, 109.8, 51.4, 44.7, 27.4. HPLC (70 : 30, hexane : PrOH, 220 nm, 1.0 mL/min) Chiralpak AS, t_R = 12.7 (minor), 23.7 (major), 70% ee.

2-(3-Hydroxy-1-methyl-2-oxoindolin-3-yl)acetonitrile[10a] (3k). Prepared according to the general procedure using isatin (16.11 mg, 0.1 mmol) and the reaction completed after 4 days. After column chromatography, the desired product was obtained (16.37 mg, 81% yield). $[\alpha]_D^{25}$ = −30.0 (c = 1.0, MeOH); Analytical data matches with previously reported values. ^{1}H NMR (500 MHz, $CDCl_3$): = 7.65 (d, J = 7.5 Hz, 1H), 7.37 (td, J = 8.0, 1.0 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 3.40 (s, 1H), 3.23 (s, 3H), 3.03 (d, J = 16.5, 1Hz, 1H), 2.71 (dd, J = 16.5, 1Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): = 175.5, 142.7, 130.9, 127.5, 124.2, 123.2, 116.3, 109.3, 26.5. HPLC (95 : 5, hexane : PrOH, 254 nm, 1.0 mL/min) Chiralpak AD, t_R = 18.7 (major), 21.3 (minor), 80% ee.

(*S*)-Tert-butyl 2-(3-(cyanomethyl)-3-hydroxy-2-oxoindolin-1-yl)acetate (3l). Prepared according to the general procedure using isatin (26.12 mg, 0.1 mmol) and the reaction completed after 4 days. After column chromatography, the desired product was obtained (22.98% yield). $[\alpha]_D^{25}$ = −68.20 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): = 7.64 (d, J = 7.5 Hz, 1H), 7.36 (td, J = 7.5, 1.0 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 4.34 (d, J = 17.5 Hz, 1H), 4.27 (d, J = 17.5 Hz, 1H), 2.93 (d, J = 16.5 Hz, 1H), 2.66 (d, J = 16.5 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): = 175.5, 166.5, 141.6, 130.8, 127.8, 124.6, 124.1, 115.6, 109.0, 83.6, 72.4, 42.2, 27.7. HRMS (ESI) m/z calculated $C_{16}H_{18}O_4N_2+Na^+$: 325.1159, found: 325.1166. HPLC (90 : 10, hexane : PrOH, 220 nm, 1.0 mL/min) Chiralpak AD column, t_R = 22.4 (major), t_R = 27.4 (minor), 98% ee.

(*S*)-2-(3-Hydroxy-2-oxo-1-(prop-2-ynyl)indolin-3-yl)acetonitrile (3m). Prepared according to the general procedure using isatin (18.52 mg, 0.1 mmol) and ethyl reaction completed after 4 days. After column chromatography, the desired product was obtained (18.10% yield). $[\alpha]_D^{25}$ = −41.0 (c = 1, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): = 7.69 (dd, J = 7.0, 0.5 Hz, 1H), 7.45 (td, J = 7.0, 1.5 Hz, 1H), 7.23 (td, J = 7.5, 1.0 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 4.53 (dd, J = 17.5, 2.5 Hz, 1H), 4.47 (dd, J = 17.5, 2.5 Hz, 1H), 3.18 (s, 1H), 3.04 (d, J = 16.5 Hz, 1H), 2.71 (d, J = 16.5 Hz, 1H), 2.29 (t, J = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): = 174.7, 141.1, 131.1, 127.7, 124.6, 124.5, 115.5, 110.4, 76.1, 73.4, 28.7, 20.9. HRMS (ESI) m/z calculated $C_{13}H_{10}O_2N_2+Na^+$: 249.0634, found: 249.0635. HPLC (90 : 10, hexane : PrOH, 220 nm, 1.0 mL/min) Chiralpak AD column, t_R = 34.6 (major), t_R = 41.8 (minor), 74% ee.

Synthesis of LPC[10b]

A solution of (1.0 g, 5.3 mmol) in THF (25 mL) was cooled to 0 °C and $LiAlH_4$ (0.605 g, 15.9 mmol) was added in portions. After stirred at room temperature for 3 hours, the reaction was quenched with 50% of sodium potassium tartrate solution, filtered over celite with EtOAc. The crude product was used for next step without further purification. To a solution of (422 mg, 5.2 mmol) was added to a solution of crude material in MeOH (25 mL) at 0 °C, then $NaCNBH_3$ (658 mg, 10.4 mmol) was added portion wise and the reaction mixture was stirred for 2 h at room temperature. The resulting mixture was quenched with pH 7.0 phosphate buffer solution and organic materials were extracted with ethyl acetate three times, and the combined organic extracts were dried over Na_2SO_4, and concentrated to N-dimethylated product. The crude material was dissolved in THF (15 mL) and added dropwise to NaH (60% dispersion in mineral oil, 100 mg) in dry THF at 0 °C. When the gas evolution was stopped, methyl iodide (0.6 mL, 3 mmol) was added slowly and stirred at room temperature for 12 hours, the reaction was quenched with water and filtered over celite with EtOAc. The crude product was purified by column chromatography to afford (+)-LPC-1 as oil (0.298 g, 27% yield over 3 steps). Analytical data was matched with previously reported values. $[\alpha]_D^{25}$ = +98.4 (c = 0.73, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) = 7.24 – 7.10 (m, 2H), 6.74 (d, J = 7.0 Hz, 1H), 6.51 (d,

1H), 4.35 (s, 1H), 3.04 (s, 3H), 2.97 (s, 3H), 2.85 (m, 1H), 2.67 2.52 (m, 4H), 2.35 (dd, J = 12.5, 8.0, 1H), 2.11 (ddd, J = 12.5, 6.0, 4.5 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) = 153.2, 129.8, 128.1, 124.1, 118.0, 107.9, 94.1, 91.8, 52.5, 52.0, 39.4, 38.7, 36.3.

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