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Highly enantioselective aldol reaction of acetaldehyde and isatins only with 4-hydroxydiarylprolinol as catalyst: concise stereoselective synthesis of (*R*)-convolutamydines B and E, (−)-donaxaridine and (*R*)-chimonamidine

Wen-Bing Chen [a,b], Xi-Lin Du [c], Lin-Feng Cun [a], Xiao-Mei Zhang [a], Wei-Cheng Yuan [a,*]

[a] *Key Laboratory for Asymmetric Synthesis & Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, PR China*
[b] *Graduate School of Chinese Academy of Sciences, Beijing 100049, PR China*
[c] *Department of General Surgery, Tangdu Hospital, The Fourth Military Medical University, Xi'an 710038, PR China*

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ABSTRACT

A highly enantioselective aldol reaction of acetaldehyde and a wide scope of isatins has been presented only using readily available 4-hydroxydiarylprolinol as catalyst, affording various desired 3-substituted 3-hydroxyindolin-2-one adducts with moderate to high yield (up to 95%) and good enantioselectivities (up to 98% ee). This method not only represents an example of concise stereoselective synthesis of enantiopure (*R*)-convolutamydines B and E, but also firstly exhibits expedient asymmetric synthesis optically active (−)-donaxaridine and (*R*)-chimonamidine.

1. Introduction

3-Substituted-3-hydroxyindolin-2-ones are useful synthetic intermediates for alkaloids and biologically active compounds, such as convolutamydines A–E,[1] donaxaridine,[2] chimonamidine,[2] 3′-hydroxyglucoisatisin,[3] and TMC-95s[4] (Fig. 1). Convolutamydines A–E are members of a class of oxindole alkaloids having 4,6-dibromo-3-hydroxyoxindole as a common motif and differ each other in a side chain moiety at C-3 (Fig. 1). Notably, the interest in their skeletal structures and the potent biological activities of convolutamydines A and B[1a,b] are reflected by some methodologies that have been developed and continue to be explored for their synthesis.[5–7] However, as for convolutamydines A–E, there are only few reports for the synthesis of optically active convolutamydines B and E through an enantioselective reaction so far[6,7], moreover, the potential biological effects of convolutamydine B or E have not been sufficiently evaluated due to the scarcity of them. At the same time, we also amazedly note that there no any catalytic asymmetric synthetic methods reported for the synthesis of optically active donaxaridine[2c] (Fig. 1), which is a very important alkaloid isolated from *Arundo donax*, and chimonamidine[2b] (Fig. 1), which is a novel tryptamine-related alkaloid isolated from the seeds of *Chimonanthus Precox Link*. In this context, it should be importance to develop efficient and practical methods for the synthesis of optically active convolutamydines B and E, chimonamidine, and donaxaridine.

In the last years, organocatalysis has proved to be a powerful tool in the development of a large number of enantioselective reactions.[8] There have been ample reports on the reaction employing various aldehydes as nucleophiles.[9] However, until recently, using acetaldehyde as a nucleophile has been identified as a powerful, metal-free method for the synthesis of 1,3-diols, β-amino aldehydes, and β-substituted-γ-nitroaldehydes.[7,10] In spite of this, the aldol reaction of acetaldehyde with ketones is strongly desired since the resulting tertiary products are valuable building blocks for the subunits. Consequently, it is interesting that developing an asymmetric aldol reaction between acetaldehyde with high reactive ketones. Isatin and its derivatives are susceptible to nucleophilic attack at C-3 ketone carbonyl and aldol type condensations are readily performed under a variety of conditions.[11,12] Based on this chem-information and our interest in the investigation into the reactivity of isatins,[12] we envision that the asymmetric aldol reaction between acetaldehyde and isatins should be achievable, and thus provide various chiral 3-substituted-3-hydroxyindolin-2-ones. Recently, Nakamura and co-workers firstly reported the asymmetric aldol reaction of acetaldehyde and isatin catalyzed by *N*-(2-thiophenesulfonyl)prolinamide and its synthetic applications

* Corresponding author: Fax: +86 28 85229250.
E-mail address: yuanwc@cioc.ac.cn (W.-C. Yuan).

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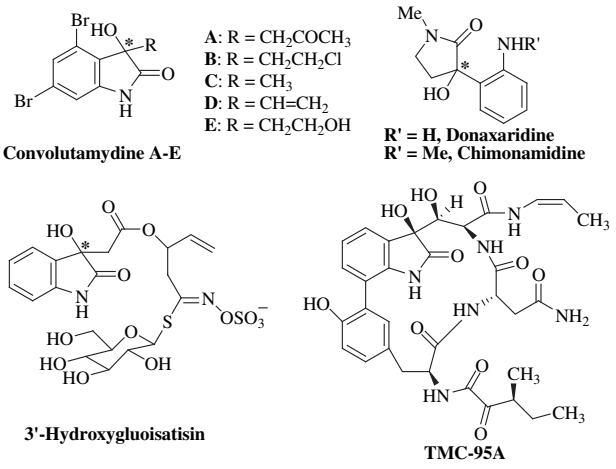


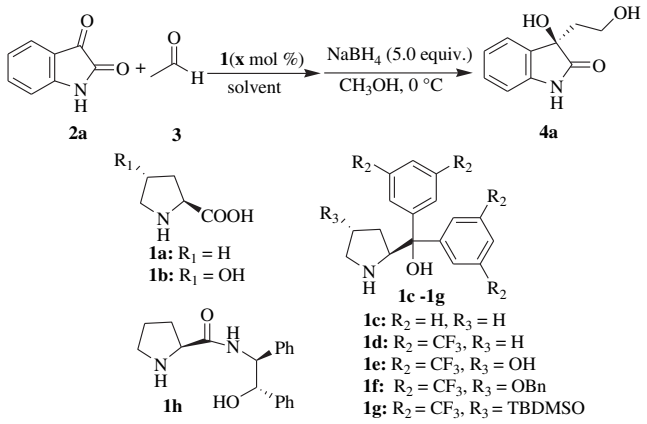
Figure 1. Representative examples of biologically active 3-substituted-3-hydroxy-indolin-2-ones.

to chiral convolutamydine B and E.[7a] However, in this method, the gainable high enantioselectivities were only limited to halogen-substituted isatin substrates. Shortly after this, while our this manuscript was soon ready to submit, Hayashi and co-workers also reported the asymmetric aldol reaction of acetaldehyde and isatin derivatives with 4-hydroxydiarylprolinol as catalyst.[7b] In this report, it was inevitable that using 30 mol % catalysts loading and the same amount $ClCH_2CO_2H$ as additive for completion the aldol reactions, which only tolerated limited *N*-protected isatin derivatives generating desired adducts in moderate yields with the highest 85% ee. Despite this, herein, we also hope to report our highly enantioselective aldol reaction of acetaldehyde with a wide scope of isatins only use 4-hydroxydiarylprolinol as catalyst for smoothly providing desired products with good yields (up to 95%) and good enantioselectivities (up to 98% ee), which is further used for concise stereoselective synthesis of optically active convolutamydines B and E, donaxaridine and chimonamidine.

2. Results and discussion

As a model reaction, we studied the reactivity of free isatin (**2a**) with acetaldehyde (**3**) in the presence of various catalysts and under different reaction conditions, and the aldol adduct was reduced by $NaBH_4$ in methanol at 0 °C giving optically active product **4a** as aim product to facilitate the separation and detection[13] (Table 1). Initial experiments were performed with **2a**, 5.0 equiv **3** and 10 mol % catalysts in 1,2-dimethoxyethane (DME) at 15 °C to screen catalysts, It was appeared from the results given in entries 1–8 (Table 1) that catalyst **1e** was the most effective catalyst for the reaction in terms of reactivity and selectivity (Table 1, entry 5). And then, the screening of solvents showed that the model reaction proceeded smoothly in a variety of reaction medium, significantly, 1,2-dimethoxyethane (DME) was found to be superior to other solvents in terms of yield and ee value (Table 1, entries 5 and 9–15). Interestingly, we found that the reaction even proceeded smoothly only with catalyst **1e** in DME, however, in Hayashi's system,[7b] the reaction must be catalyzed by catalyst **1e** and with acid as additive in DMF. Through the further investigation to catalysts loading, we found that very low yield was observed when the reaction was carried out with 5 mol % **1e**, albeit giving almost unchanged ee value (Table 1, entry 16). On the other hand, increasing the catalyst loading to 20 mol %, the reaction completed in shorter reaction time and furnished product **4a** in 93% isolated yield and 72% ee (Table 1, entry 17). Further optimization to reaction temperature, no significant change was found in enantioselectivity when the

Table 1
Screening of various reaction conditions[a]



Entry	**1** (x)	Solvent	Time (h)	T (°C)	Yield[b] (%)	ee[c] (%)
1	**1a** (10)	DME	24	15	25	(−)15
2	**1b** (10)	DME	24	15	50	17
3	**1c** (10)	DME	36	15	70	(−)25
4	**1d** (10)	DME	36	15	87	67
5	**1e** (10)	DME	24	15	90	70
6	**1f** (10)	DME	24	15	83	69
7	**1g** (10)	DME	24	15	83	66
8	**1h** (10)	DME	24	15	77	53
9	**1e** (10)	THF	24	15	70	62
10	**1e** (10)	DCM	36	15	80	32
11	**1e** (10)	CH_3CN	24	15	71	35
12	**1e** (10)	Et_2O	24	15	66	55
13	**1e** (10)	Dioxane	24	15	84	55
14	**1e** (10)	C_2H_5OH	24	15	39	39
15	**1e** (10)	AcOEt	24	15	61	60
16	**1e** (5)	DME	24	15	21	71
17	**1e** (20)	DME	15	15	93	72
18	**1e** (20)	DME	24	0	85	72
19	**1e** (20)	DME	40	−10	90	74
20	**1e** (20)	DME	72	−20	25	75
21[d]	**1e** (20)	DME	96	−10	90	80
22	**1e** (20)	DME	90	−10	80	66[e]
23	**1e** (20)	DME	90	−10	80	66[f]
24	**1e** (20)	DME	90	−10	62	70[g]
25	**1e** (20)	DME	90	−10	90	59[h]

[a] Unless otherwise noted, reactions were performed with **2a** (0.5 mmol), **3** (2.5 mmol), and catalysts **1** in the corresponding solvent (0.5 mL). *c*=1.0 M. DME=1,2-Dimethoxyethane, DCM=Dichloromethane.

[b] Yield of isolated product by column chromatography after the aldol adduct was reduced.

[c] The ee values were determined by chiral stationary phase HPLC.

[d] The reaction was performed with **2a** (0.1 mmol), **3** (0.5 mmol), and catalyst **1e** (20 mol %) in DME (1.2 mL) at −10 °C for 96 h. *c*=0.08 M.

[e] The reaction was conducted as Table 1, entry 21 for 90 h, and using 20 mol % PhCOOH as additive.

[f] The reaction was conducted as Table 1, entry 21 for 90 h, and using 20 mol % AcOH as additive.

[g] The reaction was conducted as Table 1, entry 21 for 90 h, and using 20 mol % $Cl_2CHCOOH$ as additive.

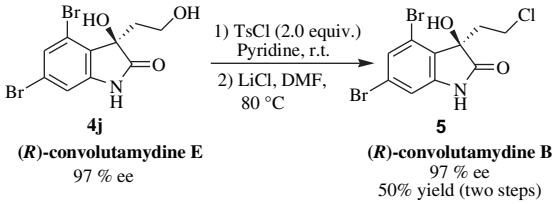
[h] The reaction was conducted as Table 1, entry 21 for 90 h, and using 20 mol % 3,5-dinitrobenzoic acid as additive.

reaction was run at 0 °C (Table 1, entry 18), and slighter higher ee value was observed for the reaction carried out at −10 °C with prolonged reaction time (Table 1, entry 19). However, the product only in 25% yield was obtained with further decreasing temperature to −20 °C even though prolonging reaction time to 72 h (Table 1, entry 20). Gratifying, the reaction proceeded also smoothly under low concentration at −10 °C and provided **4a** in 80% ee and 90% isolated yield with longer reaction time (Table 1, entry 21). Subsequently, we tried to further improve the enantioselectivity through adding PhCOOH, AcOH, $Cl_2CHCOOH$, and 3,5-dinitrobenzoic acid as additive, respectively (Table 1, entries 22–25), it revealed that with the addition of various acid, the reactions were

slightly faster but the enantioselectivities significantly decreased (Table 1, entries 22–25 vs entry 21).

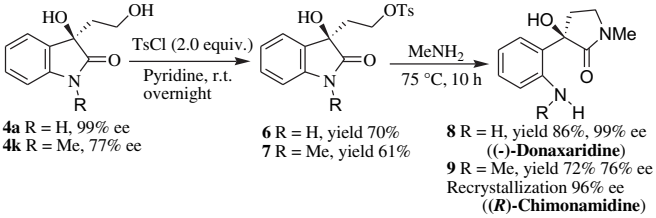
Having established what we believed to be the optimal reaction conditions,[14] we next examined the scope of this methodology with a variety of isatin derivatives to establish the generality of the process. The scope of the reaction was summarized in Table 2. It was found that various isatin derivatives **2b–j** and **2n** bearing either electro-donating or electron-withdrawing substituent on the phenyl ring could be well tolerated, and the corresponding products were obtained in good to excellent enantioselectivities (84–98% ee) and moderate to very high yield (50–95%, Table 2, entries 2–10 and 14). It should be noted that incorporation of substituent at the C-4 position of isatins showed obvious improvement to the enantioselectivity of the reaction (Table 2, entries 5, 8, and 10). Importantly, the enantiomeric excesses could be readily improved to 99% from 80% after a single recrystallization (Table 2, entry 1). The reaction also took place well with substrates bearing methyl, allyl, and benzyl substituents at the N-1 position with good yields and ee values (Table 2, entries 11–13). Gratifyingly, (*R*)-convolutamydine E (**4j**) could be easily obtained in 97% ee with this approach (Table 2, entry 10). Furthermore, we also showed that this reaction could be performed in scale up to 1.0 mmol giving (*R*)-convolutamydine E with the same excellent enantioselectivity and good yield under the same reaction conditions (Table 2, entries 10 vs 15).[15]

On the base of the successful synthesis of (*R*)-convolutamydine E, an application of this methodology was investigated with a concise synthesis of (*R*)-convolutamydine B. As illustrated in Scheme 1, the optically (*R*)-convolutamydine E (**4j**) could be readily transformed into (*R*)-convolutamydine B (**5**) with sequence of tosylation and chlorination without racemization (Scheme 1).[16]



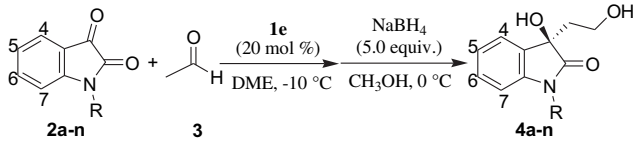
Scheme 1. The synthesis of optically active (*R*)-convolutamydine B.

To further illustrate the synthetic potential of this methodology, we undertook the formal synthesis of chiral (−)-donaxaridine and (*R*)-chimonamidine. As shown in Scheme 2, **4a** and **4k** were first, respectively, protected with 4-methylbenzene-1-sulfonyl (Ts) group by exposure to 4-methylbenzene-1-sulfonyl chloride (TsCl) and pyridine, to give the corresponding tosylation products (**6** and **7**), and then treated in the methylamine solution in alcohol to undergo a transamidation of methylamino intermediate to successfully generate high enantiopurity (−)-donaxaridine (**8**) in 99% ee and (*R*)-chimonamidine (**9**) in 96% ee.[17] To the best of our knowledge, this is the first report on the synthesis of optically active (−)-donaxaridine and (*R*)-chimonamidine through catalytic asymmetric approach.[16]



Scheme 2. The synthesis of optically active (−)-donaxaridine and (*R*)-chimonamidine.

Table 2
Scope of aldol reaction with isatins **2a**–**m** and acetaldehyde **3**[a]



2a: 4,5,6,7 = H, R = H
2b: 4,6,7 = H, 5 = Me, R = H
2c: 4,6,7 = H, 5 = Cl, R = H
2d: 4,5,7 = H, 6 = Cl, R = H
2e: 5,6,7 = H, 4 = Cl, R = H
2f: 4,6,7 = H, 5 = Br, R = H
2g: 4,5,7 = H, 6 = Br, R = H
2h: 5,6,7 = H, 4 = Br, R = H
2i: 4,6 = H, 5,7 = Br, R = H
2j: 5,7 = H, 4,6 = Br, R = H
2k: 4,5,6,7 = H, R = Me
2l: 4,5,6,7 = H, R = allyl
2m: 4,5,6,7 = H, R = Bn
2n: 4,6,7 = H, 5 = MeO, R = H

Entry	2	Time (h)	4	Yield[b] (%)	ee[c] (%)
1	**2a**	96	**4a**	90	80(99)[d]
2	**2b**	108	**4b**	87	88
3	**2c**	96	**4c**	90	87
4	**2d**	96	**4d**	80	84
5	**2e**	96	**4e**	92	95
6	**2f**	108	**4f**	93	90
7	**2g**	120	**4g**	70	83[e]
8	**2h**	100	**4h**	74	98
9	**2i**	96	**4i**	92	88[e]
10	**2j**	108	**4j**	73	97[f]
11	**2k**	96	**4k**	75	77
12	**2l**	96	**4l**	73	77
13	**2m**	96	**4m**	95	78
14	**2n**	108	**4n**	50	84
15	**2j**	108	**4j**	70	97[f,g]

[a] Unless otherwise noted, reaction were performed with **2** (0.1 mmol), **3** (0.5 mmol), and **1e** (20 mol %) in DME (1.2 mL) at −10 °C.
[b] Yield of isolated product by column chromatography after the aldol adducts were reduced.
[c] The ee values were determined by chiral stationary phase HPLC.
[d] ee value in parentheses is that obtained after single recrystallization.
[e] Reaction were performed with **2** (0.2 mmol), **3** (1.0 mmol), and **1e** (20 mol %) in the DME (2.4 mL) at −10 °C.
[f] The absolute configuration of **4j** was *R* assigned by comparison of the sign of the optical rotation with reported data.[7a] The other products were assigned by analogy by assuming a similar catalytic mechanism.
[g] Reaction was performed in scale up to 1.0 mmol.

3. Conclusions

In conclusion, we have presented a highly enantioselective aldol reaction of acetaldehyde with isatins catalyzed by organocatalyst. As for this method, several advantages are worthy to be mentioned: (1) only using readily available 4-hydroxydiarylprolinol as catalyst and needless for any other additive;[14] (2) wide scope of substrates, not only free isatin but also various substituted isatins;[7] (3) moderate to high yield (up to 95%) and good enantioselectivities (up to 98% ee) for various 3-substituted 3-hydroxyindolin-2-ones; (4) an example of concise stereoselective synthesis of enantiopure (*R*)-convolutamydines B and E; (5) the first example of expedient asymmetric synthesis of optically active (−)-donaxaridine and (*R*)-chimonamidine.

4. Experimental

4.1. General remarks

Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Reactions were monitored by thin layer chromatography using silica gel $HSGF_{254}$ plates. ^1H NMR and ^{13}C NMR (300 and 75 MHz, respectively) spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$. ^1H NMR chemical shifts are reported in parts per million relative to tetramethylsilane

(TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2SO$ at 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in parts per million from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.20 ppm, $(CD_3)_2SO$ at 39.51 ppm).

4.2. Typical procedure for the aldol reaction of acetaldehyde and isatin

Acetaldehyde (30 μL, 0.5 mmol purity 98.5%) was added to a mixture of **1e** (0.02 mmol, 11 mg) and isatin (0.1 mmol, 15 mg) in DME (1.2 mL) at −10 °C. After the reaction mixture had been stirred for four days, methanol (2 mL) and $NaBH_4$ (20 mg, 5.0 equiv) were added at 0 °C ($NaBH_4$ was slowly added portions). The resulting reaction mixture was stirred for additional 30 min at 0 °C, before it was quenched with saturated NH_4Cl solution. The mixture was extracted with ethyl acetate, and the combined organic phase was dried over Na_2SO_4. Purification by flash column chromatography on silica gel (ethyl acetate/hexane 1:2–2:1) to gave product **4a**.

*4.2.1. (R)-3-Hydroxy-3-(2-hydroxyethyl)indolin-2-one (**4a**).* White solid, mp 139–140 °C; 90% yield, 80% ee; $[\alpha]_D^{25}$ +15.6 (*c* 1.25, MeOH); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.21 (br s, 1H), 7.27–7.22 (m, 1H), 7.18 (d, *J*=7.5 Hz, 1H), 6.98–6.93 (m, 1H), 6.79 (d, *J*=7.5 Hz, 1H), 5.89 (br s, 1H), 4.40 (t, *J*=5.1 Hz, 1H), 3.52–3.24 (m, 2H), 1.97 (dd, *J*=6.0 and 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 40.6, 56.3, 74.3, 109.5, 121.6, 124.0, 128.9, 132.0, 141.6, 179.2; IR (KBr) ν 3336, 3172, 2920, 1705, 1626, 1475 cm^{-1}; HRMS (ESI) Calculated for $C_{10}H_{11}NO_3$ $[M+Na]^+$: 216.06311, found: 216.06189.;HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)=7.8 min, t_R (major)=9.5 min.

*4.2.2. (R)-3-Hydroxy-3-(2-hydroxyethyl)-5-methylindolin-2-one (**4b**).* White solid, mp 120–121 °C; 87% yield, 88% ee; $[\alpha]_D^{25}$ +16.5 (*c* 0.34, MeOH); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.09 (br s, 1H), 7.08 (s, 1H), 6.99 (d, *J*=7.8 Hz, 1H), 6.68 (d, *J*=7.8 Hz, 1H), 5.84 (br s, 1H), 4.38 (t, *J*=5.1 Hz, 1H), 3.31–3.22 (m, 2H), 2.25 (s, 3H), 1.96 (t, *J*=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 20.7, 40.6, 56.4, 74.4, 109.3, 124.7, 129.1, 130.4, 132.1, 139.1, 179.3; IR (KBr) ν 3455, 3205, 2923, 1699, 1625, 1492 cm^{-1}; HRMS (ESI) Calculated for $C_{11}H_{13}NO_3$ $[M+Na]^+$: 230.07876, found: 230.07817; HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)=7.6 min, t_R (major)=9.8 min.

*4.2.3. (R)-5-Chloro-3-hydroxy-3-(2-hydroxyethyl)indolin-2-one (**4c**).* White solid, mp 141–143 °C; 90% yield, 87% ee; $[\alpha]_D^{25}$ +8.2 (*c* 0.42, MeOH); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.31 (br s, 1H), 7.31–7.22 (m, 2H), 6.80 (d, *J*=8.1 Hz, 1H), 6.00 (br s, 1H), 4.38 (t, *J*=4.8 Hz, 1H), 3.38–3.28 (m, 2H), 2.01–1.97 (m, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 40.3, 56.2, 74.5, 111.0, 124.3, 125.6, 128.7, 134.1, 140.6, 178.9; IR (KBr) ν 3254, 3070, 2937, 1730, 1675, 1624 cm^{-1}; HRMS (ESI) Calculated for $C_{10}H_{10}ClNO_3$ $[M+Na]^+$: 250.02390, found: 250.02414; HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)=7.1 min, t_R (major)=8.9 min.

*4.2.4. (R)-6-Chloro-3-hydroxy-3-(2-hydroxyethyl)indolin-2-one (**4d**).* White solid, mp 129–130 °C; 80% yield, 84% ee; $[\alpha]_D^{25}$ +5.7 (*c* 0.50, MeOH); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.32 (br s, 1H), 7.26 (d, *J*=7.8 Hz, 1H), 7.00 (dd, *J*=1.8 and 7.8 Hz, 1H), 6.80 (d, *J*=1.8 Hz, 1H), 5.94 (br s, 1H), 4.36 (t, *J*=5.1 Hz, 1H), 3.30–3.24 (m, 2H), 2.02–1.94 (m, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 40.2, 56.2, 73.9, 109.5, 121.1, 125.5, 130.8, 132.9, 143.2, 179.0; IR (KBr) ν 3372, 2955, 1732, 1618, 1488 cm^{-1}; HRMS (ESI) Calculated for $C_{10}H_{10}ClNO_3$ $[M+Na]^+$: 250.02390, found: 250.02414; HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)=8.9 min, t_R (major)=10.2 min.

*4.2.5. (R)-4-Chloro-3-hydroxy-3-(2-hydroxyethyl)indolin-2-one (**4e**).* White solid, mp 182–183 °C; 92% yield, 95% ee; $[\alpha]_D^{25}$ −2.8 (*c* 0.40, MeOH); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.38 (br s, 1H), 7.23–7.18 (m, 1H), 6.93 (d, *J*=8.1 Hz, 1H), 6.74 (d, *J*=7.5 Hz, 1H), 5.96 (br s, 1H), 4.37 (t, *J*=4.8 Hz, 1H), 3.15–3.07 (m, 2H), 2.34–2.30 (m, 1H), 2.23–2.16 (m, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 37.9, 56.3, 75.3, 108.5, 122.3, 127.5, 130.3, 130.6, 143.9, 178.3; IR (KBr) ν 3404, 3295, 3110, 2935, 1720, 1621, 1592 cm^{-1}; HRMS (ESI) Calculated for $C_{10}H_{10}ClNO_3$ $[M+Na]^+$: 250.02390, found: 250.02414; HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)=8.5 min, t_R (major)=10.4 min.

*4.2.6. (R)-5-Bromo-3-hydroxy-3-(2-hydroxyethyl)indolin-2-one (**4f**).* White solid, mp 143–147 °C; 93% yield, 90% ee; $[\alpha]_D^{25}$ +4.5 (*c* 1.10, MeOH); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.29 (br s, 1H), 7.40–7.33 (m, 2H), 6.73 (d, *J*=8.1 Hz, 1H), 5.99 (br s, 1H), 4.37 (t, *J*=4.8 Hz, 1H), 3.25 (d, *J*=4.8 Hz, 2H), 1.98–1.94 (m, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 40.3, 56.2, 74.5, 111.6, 113.3, 126.9, 131.6, 134.5, 141.0, 178.7; IR (KBr) ν 3311, 2919, 1719, 1622, 1474 cm^{-1}; HRMS (ESI) Calculated for $C_{10}H_{10}BrNO_3$ $[M+Na]^+$: 293.97363, found: 293.97317; HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)=7.2 min, t_R (major)=9.3 min.

*4.2.7. (R)-6-Bromo-3-hydroxy-3-(2-hydroxyethyl)indolin-2-one (**4g**).* White solid, mp 134–135 °C; 70% yield, 83% ee; $[\alpha]_D^{25}$ +7.5 (*c* 0.35, MeOH); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.31 (br s, 1H), 7.22–7.12 (m, 2H), 6.93 (s, 1H), 5.94 (br s, 1H), 4.35 (br s, 1H), 3.32–3.27 (m, 2H), 2.00–1.97 (m, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 40.3, 56.1, 74.0, 112.3, 121.3, 124.0, 125.9, 131.3, 143.4, 178.9; IR (KBr) ν 3523, 3346, 1919, 1731, 1678, 1614 cm^{-1}; HRMS (ESI) Calculated for $C_{10}H_{10}BrNO_3$ $[M+Na]^+$: 293.97363, found: 293.97317; HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)=8.4 min, t_R (major)=9.7 min.

*4.2.8. (R)-4-Bromo-3-hydroxy-3-(2-hydroxyethyl)indolin-2-one (**4h**).* White solid, mp 160–161 °C; 74% yield, 98% ee; $[\alpha]_D^{25}$ +1.0 (*c* 0.36, MeOH); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.32 (br s, 1H), 7.20–7.15 (m, 2H), 7.02 (d, *J*=1.8 Hz, 1H), 5.95 (br s, 1H), 4.37 (br s, 1H), 3.38–3.28 (m, 2H), 2.12–2.10 (m, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 40.2, 56.2, 74.1, 112.4, 121.4, 124.1, 125.9, 131.3, 143.3, 178.9; IR (KBr) ν 3404, 3104, 2940, 1713, 1617, 1586 cm^{-1}; HRMS (ESI) Calculated for $C_{10}H_{10}BrNO_3$ $[M+Na]^+$: 293.97363, found: 293.97317; HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)=8.8 min, t_R (major)=10.8 min.

*4.2.9. (R)-5,7-Dibromo-3-hydroxy-3-(2-hydroxyethyl)indolin-2-one (**4i**).* White solid, mp 188–189 °C; 92% yield, 88% ee; $[\alpha]_D^{25}$ −0.1 (*c* 0.69, MeOH); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.65 (br s, 1H), 7.63 (d, *J*=1.8 Hz, 1H), 7.45 (d, *J*=1.8 Hz, 1H), 6.14 (br s, 1H), 4.38 (t, *J*=5.1 Hz, 1H), 3.28–3.24 (m, 2H), 2.06–1.98 (m, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 40.0, 56.1, 75.4, 102.7, 113.7, 126.2, 133.3, 135.7, 140.7, 178.5; IR (KBr) ν 3525, 3340, 2912, 1708, 1614, 1581 cm^{-1}; HRMS (ESI) Calculated for $C_{10}H_9Br_2NO_3$ $[M+Na]^+$: 371.88414, found: 371.88359; ee was determined with the corresponding tosylation product. HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)=8.2 min, t_R (major)=10.1 min.

*4.2.10. (R)-4,6-Dibromo-3-hydroxy-3-(2-hydroxyethyl)indolin-2-one (**4j**)*[7a]. White solid, mp 206–208 °C; 71% yield, 97% ee; $[\alpha]_D^{25}$ −9.3 (*c* 1.00, MeOH); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.49 (br s, 1H), 7.31 (d, *J*=1.2 Hz, 1H), 6.93 (d, *J*=1.2 Hz, 1H), 6.00 (br s, 1H), 4.38 (t, *J*=4.8 Hz, 1H), 3.17–3.06 (m, 2H), 2.37–2.33 (m, 1H), 2.18–2.08 (m,

1H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 37.5, 56.2, 75.7, 111.8, 119.7, 122.2, 126.9, 128.7, 145.5, 178.3; IR (KBr) ν 3349, 3222, 2937, 1739, 1611, 1577 cm^{-1}; HRMS (ESI) Calculated for $C_{10}H_9Br_2NO_3$ $[M+Na]^+$: 371.88414, found; 371.88359; HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)-=8.8 min, t_R (major)=11.1 min.

*4.2.11. (R)-3-Hydroxy-3-(2-hydroxyethyl)-1-methylindolin-2-one (**4k**).* White solid, mp 99–101 °C; 75% yield, 78% ee; $[\alpha]_D^{25}$ +14.0 (*c* 0.28, MeOH); ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 7.33–7.28 (m, 2H), 7.07–7.02 (m, 1H), 6.97 (d, *J*=7.8 Hz, 1H), 5.95 (br s, 1H), 4.38 (t, *J*=5.1 Hz, 1H), 3.28–3.21 (m, 2H), 3.08 (s, 3H), 2.00 (dd, *J*=6.6, 12.6 Hz, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 25.8, 40.6, 56.3, 74.1, 108.4, 122.3. 123.6, 129.1, 131.4, 143.2, 177.4; IR (KBr) ν 3386, 3322, 2956, 1704, 1614, 1488 cm^{-1}; HRMS (ESI) Calculated for $C_{11}H_{13}NO_3$ $[M+Na]^+$: 230.07876, found: 230.07817; HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, 25 °C: t_R (minor)=8.1 min, t_R (major)=8.7 min.

*4.2.12. (R)-1-Allyl-3-hydroxy-3-(2-hydroxyethyl)indolin-2-one (**4l**).* White solid, mp 86–88 °C; 73% yield, 77% ee; $[\alpha]_D^{25}$ +28.2 (*c* 0.34, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J*=7.2 Hz, 1H), 7.28–7.23 (m, 1H), 7.09–7.04 (m, 1H), 6.79 (d, *J*=7.8 Hz, 1H), 5.78 (dt, *J*=5.1, 17.1 Hz, 1H), 5.28–5.17 (m, 2H), 4.98 (br s, 1H), 4.33 (dd, *J*=4.8, 16.2 Hz, 1H), 4.18 (dd, *J*=4.8, 16.2 Hz, 1H), 3.87 (s, 2H), 3.50 (br s, 1H), 2.23–2.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.4, 42.2, 58.2, 75.7, 109.3, 117.6, 122.9, 123.1, 129.4, 130.7, 130.9, 141.9, 178.2; IR (KBr) ν 3500, 2952, 2929, 1685, 1616, 1468 cm^{-1}; HRMS (ESI) Calculated for $C_{13}H_{15}NO_3$ $[M+Na]^+$: 256.09441, found: 256.09416; HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)=7.5 min, t_R (major)=8.9 min.

*4.2.13. (R)-1-Benzyl-3-hydroxy-3-(2-hydroxyethyl)indolin-2-one (**4m**).* Sticky liquid, 95% yield, 77% ee; $[\alpha]_D^{25}$ +27.1 (*c* 0.52, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J*=7.2 Hz, 1H), 7.33–7.17 (m, 6H), 7.08–7.03 (m, 1H), 6.70 (d, *J*=7.8 Hz, 1H), 4.95 (d, *J*=15.6 Hz, 1H), 4.75 (d, *J*=15.6 Hz, 1H), 4.60 (br s, 1H), 3.96 (t, *J*=5.7 Hz, 2H), 3.15 (br s, 1H), 2.31–2.24 (m, 1H), 2.14–2.04 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.3, 43.8, 58.5, 76.1, 109.6, 123.3, 123.9, 127.2, 127.7, 128.8, 129.6, 130.6, 135.3, 141.9, 178.5; IR (KBr) ν 3388, 3060, 2925, 1705, 1614, 1488 cm^{-1}; HRMS (ESI) Calculated for $C_{17}H_{17}NO_3$ $[M+Na]^+$: 306.11006, found: 306.10980; HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)-=10.6 min, t_R (major)=11.8 min.

*4.2.14. (R)-3-Hydroxy-3-(2-hydroxyethyl)-5-methoxyindolin-2-one (**4n**).* Sticky colorless oil, 50% yield, 84% ee; $[\alpha]_D^{25}$ +2.0 (*c* 0.27, Me_2CO); ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 10.05 (br s, 1H), 6.88 (s, 1H), 6.75–6.78 (m, 2H), 5.91 (br s, 1H), 4.42 (t, *J*=4.8 Hz, 1H), 3.69 (s, 3H), 3.26–3.22 (m, 2H), 1.95–1.95 (m, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 40.6, 55.5, 563, 74.8, 110.0, 110.9, 113.6, 133.3, 134.8, 154.9, 179.2; IR (KBr)ν 3369, 2924, 2854, 1730, 1607, 1462 cm^{-1}; HRMS (ESI) Calculated for $C_{11}H_{13}NO_4$ $[M+Na]^+$: 246.07368, found: 246.07342; ee was determined with the corresponding tosylation product; HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)=9.4 min, t_R (major)=17.0 min.

4.3. Synthesis of (*R*)-convolutamdine B (5)

To a solution of **4j** (100 mg, 0.285 mmol) in dry pyridine (1.0 mL) was added *p*-toluenesulfonyl chloride (110 mg, 0.576 mmol) at room temperature. After stirring at room temperature overnight, quenched with 1.0 M HCl and extracted with ethyl acetate, washed with a saturated Na_2CO_3 and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in low pressure. A residue that was purified by column chromatography (ethyl acetate/hexane 1:4–1:2) to afford corresponding tosylation product. The mixture of the resulting tosylation product (43 mg, 0.085 mmol) and LiCl (22 mg, 0.512 mmol) in DMF (1 mL) was stirred at 80 °C for 12 h. After complete conversation, DMF was removed in low pressure and the product was purified by flash column chromatography on silica gel (ethyl acetate/hexane 1:4–1:2), 50% yield for two steps.

*4.3.1. (R)-4,6-Dibromo-3-(2-chloroethyl)-3-hydroxyindolin-2-one ((R)-convolutamdine B (**5**))*[7a]. White solid, 97% ee; $[\alpha]_D^{25}$ +0.5 (*c* +0.35, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.70 (br s, 1H), 7.37 (s, 1H), 7.98 (s, 1H), 6.30 (br s, 1H), 3.50–3.44 (m, 1H), 3.18–3.16 (m, 1H), 2.50–2.45 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 37.3, 39.2, 75.8, 112.4, 119.9, 122.9, 127.5, 128.0, 145.4, 177.7; IR (KBr) ν 3328, 3220, 2921, 1713, 1609 cm^{-1}; HPLC Chiralpak AD-H, *i*-propanol/hexane=20/80, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)-=8.2 min, t_R (major)=10.2 min.

4.4. Synthesis of (−)-donaxaridine (8) and (*R*)-chimonamidine (9)

To a solution of **4a** or **4k** (0.67 mmol) in dry pyridine (4.0 mL) was added *p*-toluenesulfonyl chloride (1.35 mmol) at room temperature and stirred at room temperature overnight. 1 N HCl was added to quench the reaction, which was then extracted with ethyl acetate. The combined extract was washed with saturated Na_2CO_3 and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a residue that was purified by flash column chromatography on silica gel (ethyl acetate/hexane 1:3–1:2) to afford corresponding product **6** (yield 70%) or **7** (yield 61%).

The mixture of **6** or **7** (0.25 mmol) in methylamine solution (40 wt % in absolute ethanol) (8 mL) was stirred at 75 °C. After disappearance of **6** or **7** was confirmed by TLC (10 h), the reaction mixture was concentrated under reduced pressure. The residue was directly purified by flash column chromatography on silica gel (ethyl acetate/hexane 1:2) to afford the corresponding product **8** (yield 86%, ee 99%) or **9** (yield 72%, ee 76%). After single recrystallization, the ee value of product **9** was improved to 96% from 76%.

*4.4.1. (−)-Donaxaridine (**8**)*[2f]. White solid, 99% ee; $[\alpha]_D^{25}$ −162 (*c* 0.40, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11–7.05 (m, 1H), 6.83 (d, *J*=6.6 Hz, 1H), 6.69–6.64 (m, 1H), 4.60 (br s, 2H), 4.57 (br s, 1H), 3.32–3.21 (m, 2H), 2.95 (s, 3H), 2.72 (dt, *J*=5.1, 6.3 Hz, 1H), 2.45–2.38 (m, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 30.1, 32.9, 45.6, 19.4, 117.9, 118.2, 125.1, 125.6, 129.1, 145.8, 175.1; IR (KBr) ν 3492, 3396, 3304, 1668, 1617, 1496, 1310 cm^{-1}; HPLC Chiralpak AD-H, ethanol/hexane=30/70, flow rate 1.0 mL/min, λ=254 nm, t_R (minor)-=12.8 min, t_R (major)=15.5 min.

*4.4.2. (R)-Chimonamidine (**9**)*[2b]. White solid, 96% ee; $[\alpha]_D^{20}$ −153 (*c* 0.18, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.19 (m, 1H), 6.83 (dd, *J*=1.2, 7.5 Hz 1H), 6.72 (d, *J*=8.1 Hz 1H), 6.66–6.11 (m, 1H), 5.81 (br s, 1H), 4.31 (br s, 1H), 3.31–3.20 (m, 2H), 2.97 (s, 3H), 2.84 (s, 3H), 2.71 (dd, *J*=5.1, 12.9 Hz, 1H), 2.45–2.38 (m, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 30.1, 30.2, 33.1, 45.7, 79.7, 111.7, 116.6, 124.6, 125.4, 129.4, 148.3, 175.2; HPLC Chiralpak AD-H, ethanol/hexane=30/70, flow rate 1.0 mL/min, λ=254 nm, t_R (major)=5.4 min, t_R (minor)=6.2 min.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2009.12.041.

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12. Chen, W.-B.; Liao, Y.-H.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *Green Chem.* **2009**, *11*, 1465–1476 and relevant reference therein.
13. After the aldol reaction, the aldol adduct was reduced by $NaBH_4$ (5.0 equiv to isatin) in methanol to give **4a**. In this reduction steps, the $NaBH_4$ should be added slowly in portions at 0 °C.
14. Comparing with Hayashi's system,[7b] we use 1,2-dimethoxyethane (DME) as solvent only with 20 mol % 4-hydroxydiarylprolinol as catalyst under −10 °C, but Hayashi applied DMF as solvent with 30 mol % 4-hydroxydiarylprolinol as catalyst and 30 mol % $ClCH_2CO_2H$ as necessary additive under 4 °C.
15. The optically active (*R*)-convolutamydine E was obtained with 250 mg (white solid).
16. About the detailed procedure, see Experimental section.
17. The absolute configuration of chimonamidine (**9**) was *R* assigned by comparison of the sign of the optical rotation with reported data in Ref. 2b.