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Synthesis of 2-Oxindoles Sharing Vicinal All-Carbon Quaternary Stereocenters via Organocatalytic Aldol Reaction

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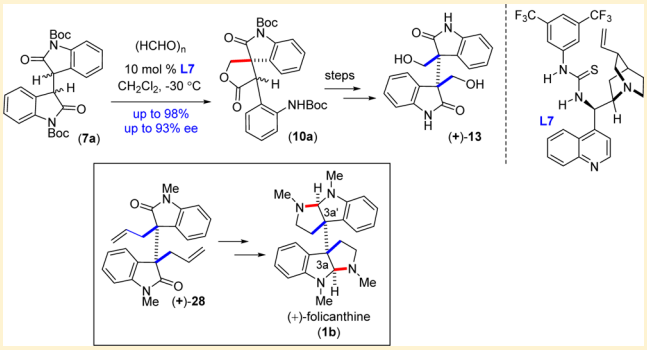
Supporting Information

ABSTRACT: An organocatalytic enantioselective aldol reaction using paraformaldehyde as C1-unit has been developed for the synthesis of 2-oxindoles sharing vicinal all-carbon quaternary stereocenters. The methodology is eventually employed in the formal total synthesis of (+)-folicanthine (**1b**).



INTRODUCTION

Stereoselective construction of sterically congested vicinal all-carbon quaternary stereocenters has gained widespread interest owing to the prevalence of such structural arrangements in natural products and bioactive compounds.[1] Particularly, alkaloids containing rigid stereocenters, such as chimonanthine (**1a**), folicanthine (**1b**), calycanthine (**1c**), communesins A (**1d**), and E (**1e**), caught our attention for their unique structural features as well as interesting bioactivities.[2] These alkaloids are found in a number of different types of plants and animals and are associated with a wide array of biological activities.[3] Consequently, a number of asymmetric strategies have been developed to synthesize vicinal all-carbon quaternary centers,[4,5] including catalytic asymmetric processes.[6] Recently, Trost[7a] and our group[7b] reported a Pd-catalyzed sequential 2-fold decarboxylative allylations for an efficient synthesis of C_2-symmetric bis-2-oxindole of the type **2a**.[8] Herein, we envisioned that enantioenriched (*R*,*R*)-**2b** would serve as an advanced intermediate for the synthesis of dimeric indole alkaloids shown in Figure 1.

Inspired by the dramatic progress of organocatalysis utilizing chiral bifunctional urea and thiourea (TU) catalysts,[9] recently, we have reported TU-catalyzed efficient aldol reaction using paraformaldehyde as C1-unit for total syntheses of alkaloids sharing 2-oxindoles (**4a**,**b**) and pyrroloindoline scaffolds (**5a**,**b** and **6a**,**b**) (Scheme 1).[10]

We envisioned that retrosynthetically, racemic and *meso*-diastereomers of bis-amides 7 of any diastereomeric ratio could effectively undergo organocatalytic enantioselective double aldol reactions following a dynamic kinetic asymmetric transformation (DYKAT)[11] involving sequential hydroxymethylation using paraformaldehyde as C1 unit[10,12] to afford a mixture of diastereomers, (*R*,*R*)-**8** and *meso*-**8** (Scheme 2) in the presence of an optimized thiourea (TU) catalyst. The major obstacle in realizing this transformation was the presence of pre-existing stereocenters in the substrates that might be interfering with the inherent catalyst selectivity and the potential for developing mismatched catalyst−substrate interactions that can negatively impact the chemical yield. Thus, use of such a complex mixture of substrates in an asymmetric transformation is quite interesting and stands as a challenge worth testing (Scheme 2).

RESULTS AND DISCUSSION

The stereochemical rationale of our hypothesized catalytic sequential aldol reactions following a dynamic kinetic asymmetric transformation (DYKAT) using thiourea ligand **L7** is shown in Figure 2. It has been proposed that if bis-enol **7** (Scheme 2) can establish H-bonding with ligand **L7** (see, transition state **9**), then *Re*-face is accessible for the aldol reactions leading to the formation of C_2-symmetric bis-2-oxindoles (*R*,*R*)-**8a** over *meso*-**8a** (Figure 2).

With above hypothesis, we carried out an asymmetric hydroxymethylation of **7a** using paraformaldehyde as the C1 unit using various enantioenriched catalysts such as **L1**-**L14** (Scheme 3). After exhaustive optimization (Scheme 3), it was noticed the formation of a diastereomeric mixture of spirolactone products with one all-carbon quaternary stereocenter (*S*,*S*)-**10a** and (*S*,*R*)-**10a** in 1:1 dr with up to 75% ee, when the reaction was carried out in the presence of 10 mol% of **L7** in CH_2Cl_2 at 25 °C.[13] This could be due to the higher reactivity of

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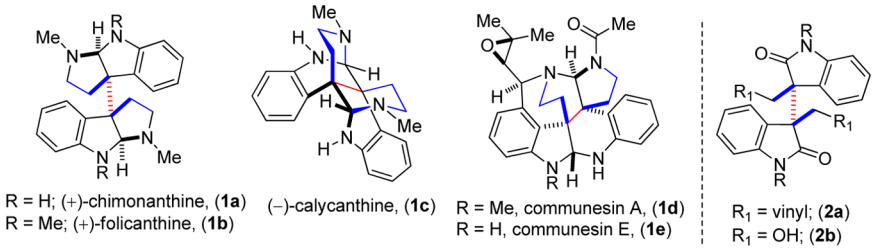
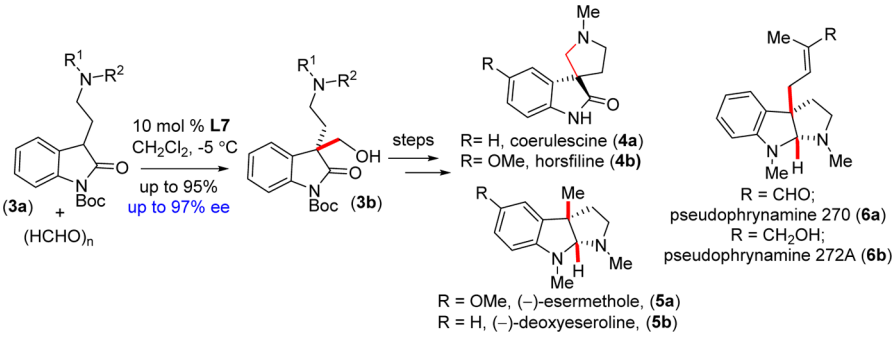


Figure 1. Alkaloids containing vicinal all-carbon quaternary stereocenters.

Scheme 1. Our Approach to 2-Oxindole and Pyrroloindoline Alkaloids



Scheme 2. Our Working Hypothesis Utilizing a DYKAT Concept

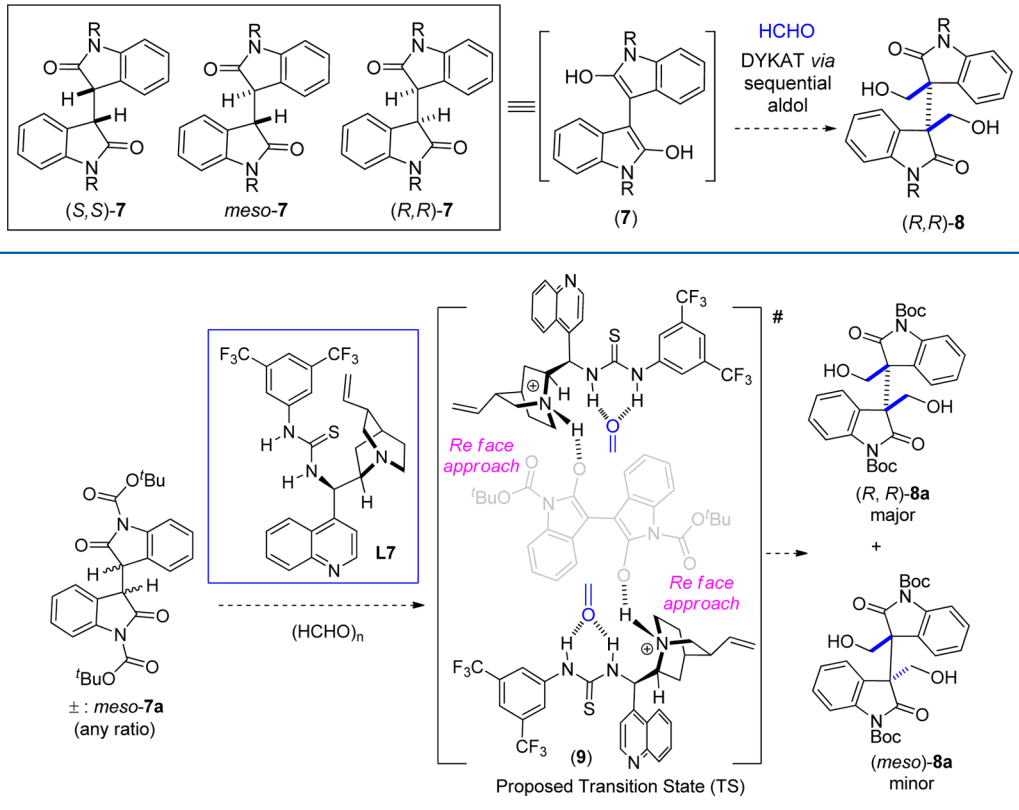


Figure 2. Our hypothesis of DYKAT via sequential aldol processes.

carbonyl of *N*-Boc 2-oxindoles, which upon reaction with hydroxymethyl group forms a lactone ring after first aldol reaction is completed. However, we thought of exploring this product to C_2-symmetric bis-2-oxindole in few steps.

Further optimization was carried out using various solvents and temperature and the results are shown in Table 1. It was observed that, 10 mol% of **L7** afforded product **10a** in 1:1 dr with excellent yields (90−98%) in chloroform, dichloroethane, ethyl acetate, acetonitrile, and diethyl ether and afforded product with 74% ee, 77% ee, 72% ee, 75% ee, and 73% ee, respectively, at room temperature (entries 1−7, Table 1). The enantioselectivity was increased to 82% ee by lowering the reaction temperature to 0 °C (entry 10). On further decreasing the temperature to −20 °C, the enantioselectivity was also

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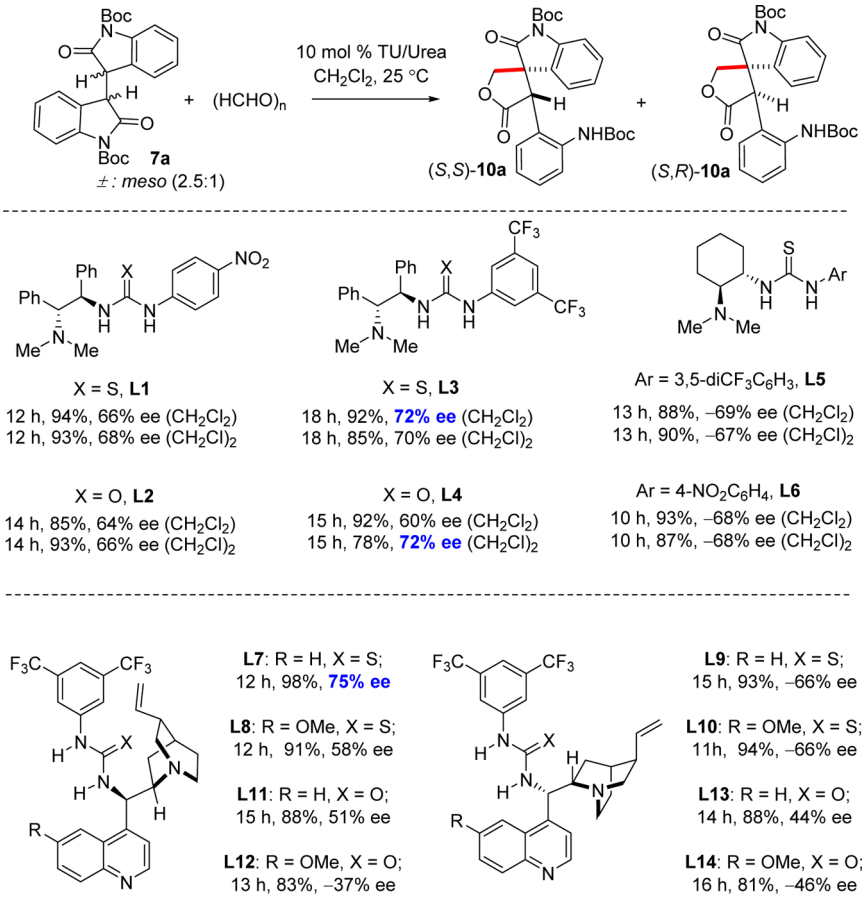
Scheme 3. Optimization of L1-L14-Catalyzed Aldol Reaction of Dimeric 2-Oxindoles 7a



[a]Reactions were carried out using 0.03 mmol of **7a** with paraformaldehyde (30 mg) in 1.5 mL solvent at room temperature.

increased to 89% ee (25 h, 97% yield; entry 12). Gratifyingly, we observed that, 93% ee of **10a** can be achieved by performing the reaction using **L7** as catalyst in CH_2Cl_2 at −30 °C (entry 15). However, on further decreasing the temperature to −40 °C, the reaction became very sluggish (entries 17 and 18).

Further, in order to find optimized catalyst, we carried out asymmetric hydroxymethylation of **7a** at −30 °C using various enantioenriched catalysts such as **L1-L4** and **L7-L10** (Scheme 4). Based on our extensive studies, it was decided to **L7** is the best catalyst for asymmetric hydroxymethylation of dimeric 2-oxindoles of type **7** using paraformaldehyde in CH_2Cl_2 at −30 °C.

Further substrate studies in the asymmetric hydroxymethylation using paraformaldehyde afforded us the diastereomeric mixture of lactone products (*S*,*S*)-**10b−d** and (*S*,*R*)-**10b−d** (maximum of ∼1.2:1 dr) were obtained in 82−90% ee (Figure 3).

Since the asymmetric hydroxymethylation of dimeric 2-oxindoles **7a−d** using paraformaldehyde did not occur in sequential manner as expected (Figure 2), we thought to install second C−C bond in diastereoselective fashion (Scheme 5). To realize this, the diastereomeric mixture of spiro-lactone products (*S*,*S*)-**10a** and (*S*,*R*)-**10a** (∼1:1 dr) was treated with trifluoroacetic acid (TFA), which was then followed by TBS-protection of hydroxymethyl group and Boc-protection of NH of 2-oxindoles affording bis-Boc protected **11** in 91% ee with 1:1 dr (Scheme 5). It was then decided to carry out diastereoselective hydroxymethylation using bifunctional thio-urea ligands **L7**.[14] Gratifyingly, a second diastereoselective aldol with paraformaldehyde worked very well in the presence of 10 mol% of **L7** in CH_2Cl_2 at 25 °C to afford pseudo-C_2-symmetric **12** in 85% yield and ∼12:1 dr with 91% ee, which in turn afforded C_2-symmetric bis-2-oxindoles (+)-**13** in ∼12:1 dr and 91% ee (Scheme 5).

The sense of asymmetric induction in the second diastereoselective aldol reaction with paraformaldehyde is shown in Figure 4. C_2−symmetric bis-2-oxindole (+)-**13** could in fact be an advanced intermediate for total syntheses of **1a**,**b** and related alkaloids (Figure 1).

In order to synthesize *meso*-bis-2-oxindoles (*meso*-**13**), a second diastereoselective aldol of **11** was performed in the presence of 10 mol% of pseudo enantiomeric ligand of **L7**, i.e., **L10** in CH_2Cl_2 at 25 °C to afford enantioenriched bis-2-oxindole **12** in 81% yield with ∼10:1 dr and 91% ee, which in turn afforded *meso*-**13** in 77% yield with ∼10:1 dr (Scheme 6).

The stereochemical induction during second diastereoselective aldol with paraformaldehyde is shown in Figure 5. Compound *meso*-**13** could be an advanced intermediate for total synthesis of *meso*-chimonanthine (*meso*-**1a**).

For synthetic elaboration to the total synthesis of (+)-folicanthine (**1b**), C_2-symmetric bis-2-oxindole (+)-**13** was protected with TBS group to form (+)-**14a**, from where an *N*-methylation followed by deprotection of TBS leads to the formation of (+)-**14b** in 51% over 2 steps (Scheme 7). The latter was then converted to bis-mesylate (+)-**15a**. However, to our disappointment, cyanation reaction of (+)-**15a** was not

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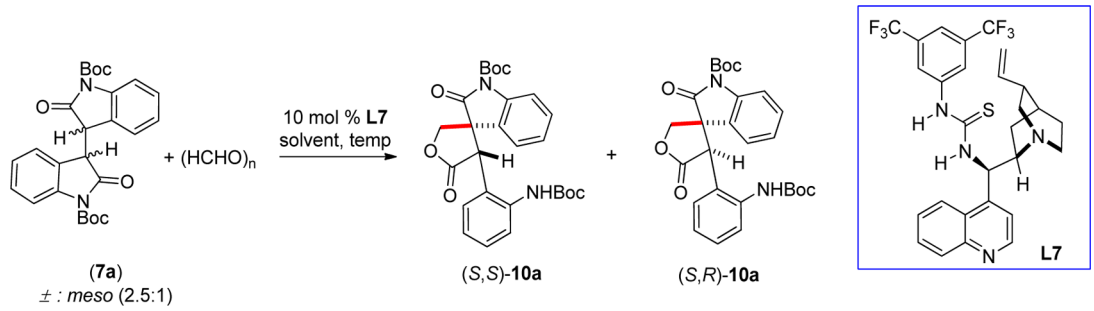
Table 1. Optimization of L7-Catalyzed Aldol Reaction of Dimeric 2-Oxindoles 7a



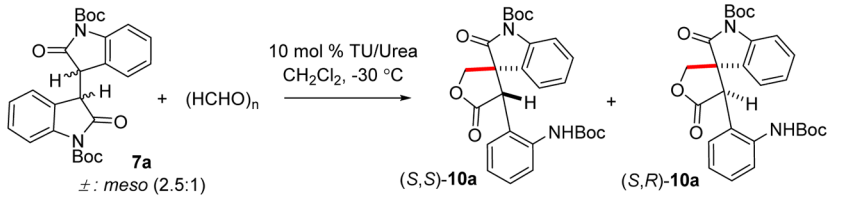
(**7a**)
± : *meso* (2.5:1)

(*S*,*S*)-**10a** (*S*,*R*)-**10a**

entry[a]	solvent	temp	time	%yield[b]	%ee[c]
1	$CHCl_3$	25 °C	12 h	98%	74%
2	$ClCH_2CH_2Cl$	25 °C	11 h	95%	77%
3	EtOAc	25 °C	14 h	91%	72%
4	PhMe	25 °C	18 h	82%	56%
5	THF	25 °C	15 h	10%	ND
6	CH_3CN	25 °C	12 h	90%	75%
7	Et_2O	25 °C	15 h	93%	73%
8	Me_2CO	25 °C	14 h	14%	ND
9	CH_3CN	0 °C	17 h	15%	ND
10	CH_2Cl_2	0 °C	18 h	97%	82%
11	Et_2O	0 °C	36 h	91%	61%
12	CH_2Cl_2	−20 °C	25 h	97%	89%
13	$ClCH_2CH_2Cl$	−20 °C	28 h	11%	ND
14	$CHCl_3$	−20 °C	28 h	95%	79%
15	CH_2Cl_2	−30 °C	68 h	96%	93%
16	$CHCl_3$	−30 °C	70 h	94%	82%
17	CH_2Cl_2	−40 °C	60 h	18%	ND
18	$CHCl_3$	−40 °C	60 h	16%	ND

[a]Reactions were carried out using 0.03 mmol of **7a** with paraformaldehyde (30 mg) in 1.5 mL solvent at room temperature. [b]Isolated yields after column purification. [c]ee's were determined by chiralpak IB column (5% isopropanol in *n*-hexane and 1 mL/min flow rate). ND stands for not determined.

Scheme 4. Optimization of Aldol Reaction of Dimeric 2-Oxindoles 7a with Paraformaldehyde



7a
± : *meso* (2.5:1)

(*S*,*S*)-**10a** (*S*,*R*)-**10a**

L1: 80 h, 90%, −88% ee
L2: 80 h, 88%, −86% ee
L3: 80 h, 89%, 86% ee
L4: 80 h, 92%, 82% ee
L7: 68 h, 96%, **93% ee**
L8: 68 h, 91%, 89% ee
L9: 68 h, 90%, −88% ee
L10: 68 h, 92%, −89% ee

[a]Reactions were carried out using 0.03 mmol of **7a** with paraformaldehyde (30 mg) in 1.5 mL solvent at room temperature.

successful, probably due to neopentyl type effect (Scheme 7). Further, in another sequence, we wanted to do bis-iodination of C_2-symmetric bis-2-oxindole (+)-**14b**. Efforts toward this direction simply afforded a spiro-fused 5-membered ether sharing vicinal all-carbon quaternary stereocenter (+)-**15b** in 74% yield (Scheme 7).

Therefore, we followed an alternative route for the synthesis of (+)-folicanthine (**1b**). Toward this direction, diastereomeric mixture of bis-2-oxindole **11** was reacted with allylchloroformate in the presence of triethylamine to afford allylcarbonate (+)-**16** in 89% yield (Table 2). The latter was then treated in the presence of $Pd_2(dba)_3$ in combination with dppp to affect the decarboxylative allylation (DcA) to afford product (+)-**17** in up to ∼6.1:1 dr at −25 °C (entries 1−3). We then thought of utilizing ligand accelerated diastereoselective DcA in the presence of (*R*,*R*)-**18** and (*S*,*S*)-**18**. The DcA afforded (+)-**17** in ∼4.5:1 dr when carried out in the presence of (*S*,*S*)-**18**. This is probably due to the formation of a "match−mismatch" pair of stereochemistry of (+)-**16** with ligand (*S*,*S*)-**18**. As expected, to our delight, we could achieve (+)-**17** in ∼11.5:1 dr, when the

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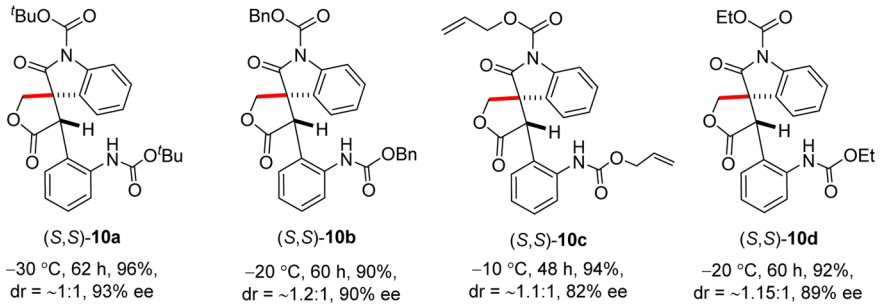
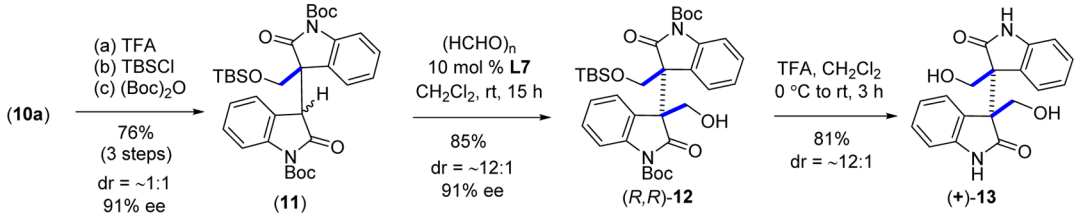


Figure 3. Substrates scope of unprecedented aldol reaction catalyzed by **L7**.

Scheme 5. Synthesis of (+)-13 *via* Aldol Reaction Catalyzed by L7



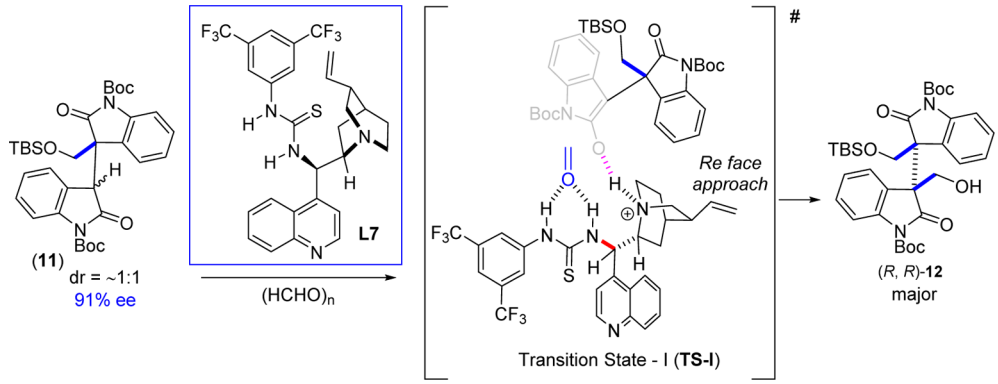
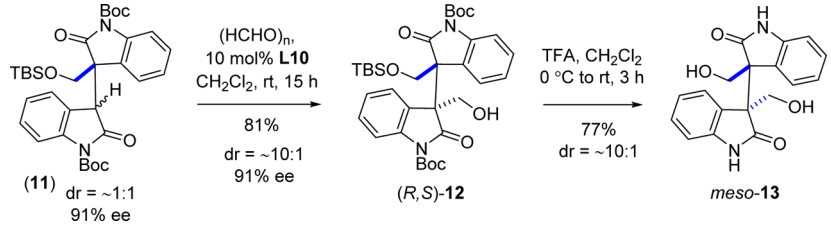


Figure 4. Stereochemistry rationale of diastereoselective aldol processes.

Scheme 6. Synthesis of *meso*-13 *via* Aldol Reaction Catalyzed by L10



DcA was carried out in the presence of (*R*,*R*)-**18** (Table 2), probably due to the formation of a "match−match" pair of stereochemistry of (+)-**16** with (*R*,*R*)-**18**.

With enantioenriched unsymmetrical bis-2-oxindole (+)-**17** in hand, we ventured into the possibility of its use in the total synthesis of natural products. Toward this, compound (+)-**17** was treated with trifluoroacetic acid (TFA) for cleavage of TBS as well as Boc groups to furnish bis-2-oxindole (+)-**19** in 80% yield (Scheme 8), which was then followed by *N*-methylation to afford expected bis-2-oxindole (+)-**20** (62%) along with unexpected diastereomeric mixture of **21** (11%). The formation of **21** is due to the dehydroxymethylation (a *retro*-aldol process)[15] in the presence of NaH, which is probably because of electron-withdrawing nature of amide functionality at α-position that accelerates the dehydroxymethylation of (+)-**19**.

Next, (+)-**20** was oxidized with Dess-Martin periodinane (DMP) to afford aldehyde (+)-**22** in 75% yield. The X-ray structure of (+)-**22** unambiguously proved bis-2-oxindole structure (Scheme 8). However, to our surprise, an attempt to do Wittig olefination of aldehyde (+)-**22** in the presence of $MeOCH{=}PPh_3$ led to deformylation to furnish diastereomeric mixture of **23**. Even a similar dehydroxymethylation of (+)-**24** was observed when we tried to oxidize with Dess-Martin periodinane (DMP), which furnished diastereomeric mixture (~1:1) of (+)-**25** (Scheme 9).[16] Compound (+)-**24** was synthesized from bis-Boc protected 2-oxindole (+)-**17** in the presence of catalytic camphor sulfonic acid (CSA). Next,

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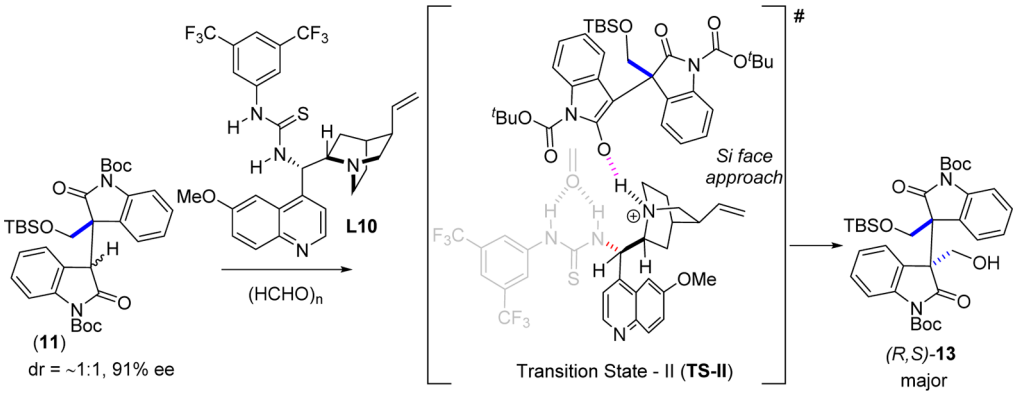


Figure 5. Stereochemistry rationale of DYKAT via sequential aldol processes.

Scheme 7. Synthetic Elaboration of C_2-Symmetric Diol (+)-13

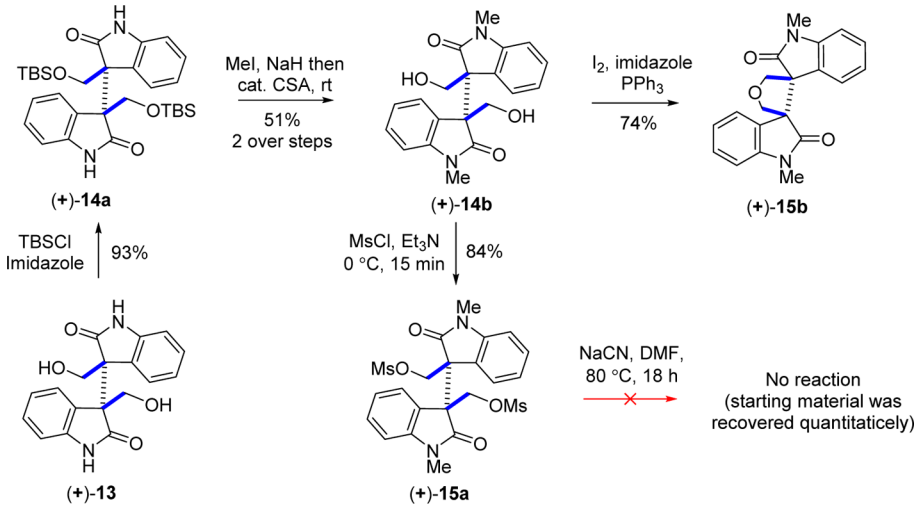
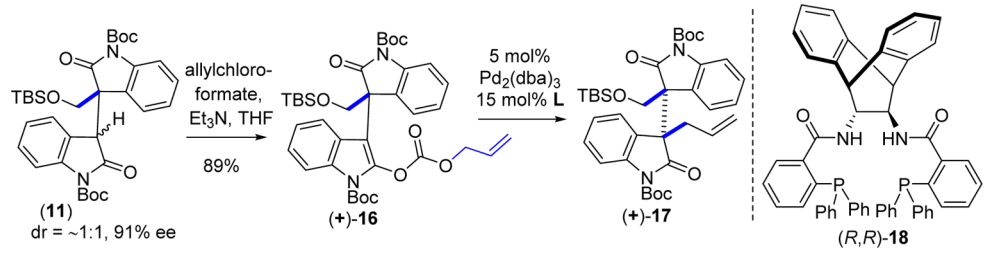


Table 2. Catalytic Diastereoselective DcA of (+)-16



entry	L	solvent	temp	time	%yield[a,b]	dr[c]
1	[d]	THF	25 °C	4 h	75	3.3:1
2	dppp	THF	25 °C	4 h	78	3.8:1
3	dppp	THF	−25 °C	10 h	72	6.1:1
4	(*S*,*S*)-**18**	Et_2O	−25 °C	9 h	81	4.5:1
5	(*R*,*R*)-**18**	Et_2O	−25 °C	10 h	83	11.5:1

[a]Reactions were carried out using 0.04 mmol of **16** scale in 2.0 mL solvent at specified temperature. [b]Isolated yields after column purification. [c]dr were determined from crude ^{1}H NMR. [d]5 mol% $Pd(PPh_3)_4$ was used as catalyst.

diastereomeric mixture (~1:1) of (+)-**25** was reacted with allylchloroformate to furnish allyl carbonate (+)-**26** in 84% yield.

Later, we envisioned another set of ligand assisted decarboxylative allylation (DcA) in the presence of (*R*,*R*)-**18** and (*S*,*S*)-**18** (Table 3). The DcA afforded (+)-**27** only in ~4.5:1 dr, when carried out in the presence of (*S*,*S*)-**18** at −25 °C (entry 2). However, the diastereoselectivities can be enhanced to ~11:1,[17] when DcA was carried out in the presence of (*R*,*R*)-**18** at −25 °C (entry 3), due to the formation of a "match−match" pair of stereochemistry of substrate (+)-**26** and ligand (*R*,*R*)-**18**.

With C_2-symmetric bis-2-oxindole (+)-**27** secure, our effort was thereafter to elaborate this intermediate for formal total

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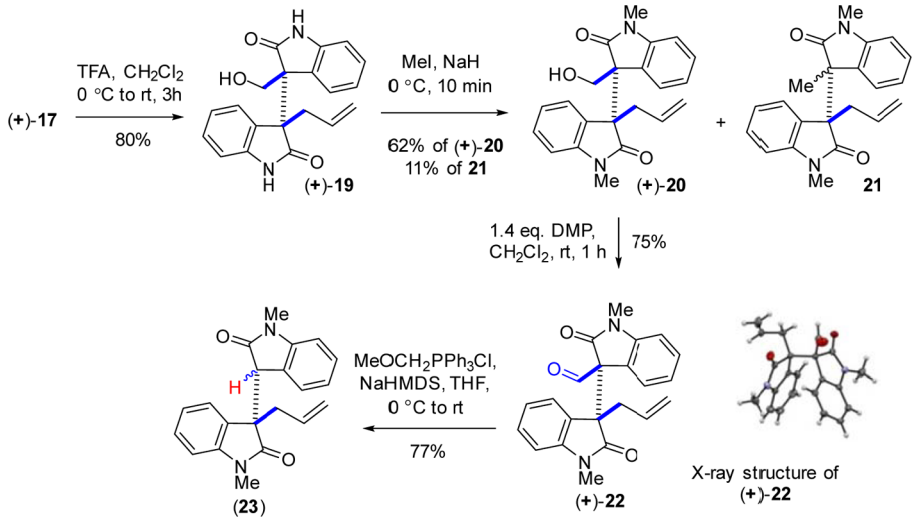
Scheme 8. Unexpected Deformylation of 22 and X-ray Structure [CCDC: 1485561]



Scheme 9. Synthetic Elaboration of Compound 17

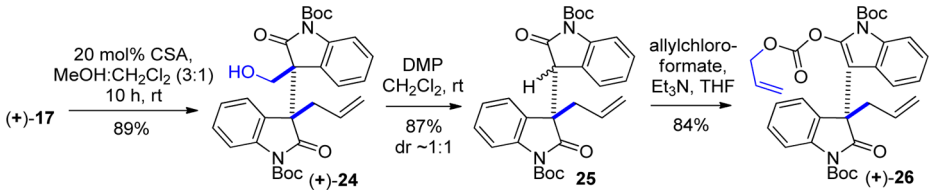
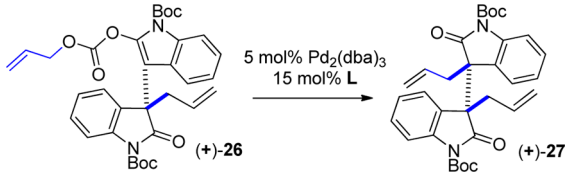


Table 3. Catalytic Diastereoselective DcA of (+)-26



entry	L	solvent	temp	time	%yield[a,b]	dr[c]
1	[d]	THF	25 °C	4 h	88	1.6:1
2	(*S*,*S*)-**18**	Et_2O	−25 °C	9 h	87	4.5:1
3	(*R*,*R*)-**18**	Et_2O	−25 °C	10 h	90	11:1

[a]Reactions were carried out using 0.03 mmol of **26** in 1 mL solvent at indicated temperature. [b]Isolated yields after column purification. [c]dr were determined from crude ^{1}H NMR. [d]5 mol % $Pd(PPh_3)_4$ was used as catalyst.

synthesis of (+)-folicanthine (**1b**) (Figure 1). Treatment of (+)-**27** with TFA, followed by *N*-methylation afforded C_2-symmetric bis-2-oxindole (+)-**28** (Scheme 10). The latter was converted to enantioenriched C_2-symmetric bis-aldehyde (+)-**29** following oxidative cleavage. As, total synthesis of (+)-folicanthine (**1b**) is known from (+)-**29** in 5 steps from our previous report,[6d] this effort culminated as the formal total synthesis of (+)-folicanthine (**1b**).

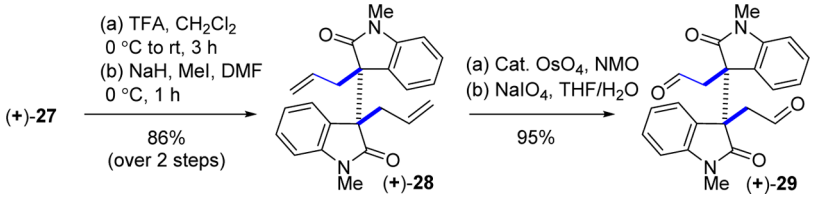
CONCLUSIONS

In conclusion, we have shown that bifunctional TU-catalyzed hydroxymethylation can efficiently be utilized as key enantioselective reaction to synthesize dimeric 2-oxindoles having vicinal all-carbon quaternary stereocenter. This process goes through an unprecedented hydroxymethylation followed by ring cleavage of amide functionality to produce spiro-lactone ring. Utilizing above method, we have synthesized C_2-symmetric as well as *meso*-dimeric 2-oxindole **13**. In order to show the synthetic versatility of this approach, we have synthesized enantioenriched carbonates (+)-**16** and (+)-**26** and utilized in highly diastereoselective DcA to complete the formal total synthesis of (+)-folicanthine (**1b**). Further exploration of this strategy is currently under active investigation in our laboratory.

EXPERIMENTAL SECTION

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 syringe

Scheme 10. Formal Total Synthesis of (+)-Folicanthine (1b)



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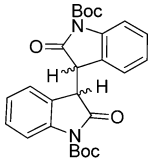
using standard Schlenk techniques. Tetrahydrofuran (THF), diethyl ether (Et_2O) was distilled over sodium/benzophenone ketyl. Acetonitrile, dichloromethane (CH_2Cl_2), toluene, and benzene were distilled over calcium hydride. All other solvents and reagents were used as received unless otherwise noted. Reaction temperatures above 23 °C refer to oil bath temperature. Thin layer chromatography was performed using Silicagel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation, 2,4-dinitrophenylhydrazine, anisaldehyde stain, and other stains. Silicagel of 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 with ^{13}C operating frequencies of 100, 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, numbers 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 and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High-resolution mass spectrometry (HRMS) data were recorded using methanol as solvent. Optical rotations were measured on an automatic polarimeter. Enantiomeric excess was determined by chiral HPLC analysis performed on Chiralpak IB column.

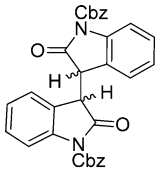
Synthetic Procedure and Characterization of (7a). To a solution of 2-oxindole (14.2 g, 106.7 mmol) and isatin (15.7 g, 106.7 mmol) in AcOH (150 mL) was added conc. aq. HCl (15 mL) at room temperature. The reaction mixture was stirred at 120 °C for 15 h. After the mixture was cooled down to room temperature, the precipitate was filtrated and dried over reduced pressure. Then, the crude solid residue was dissolved in CH_2Cl_2 (300 mL), and Boc_2O (53.9 mL, 234.74 mmol) and DMAP (2.6 g, 21.34 mmol) were added. After stirring for 5 h at room temperature, the reaction mixture was evaporated under reduced pressure. Then, the reaction mixture was taken in AcOH (150 mL) and Zn-dust (27.9 g, 426.8 mmol) was added, and the mixture was stirred for 6 h at room temperature. The precipitate was filtrated and dried over reduced pressure and purified by silica gel column chromatography using 10% EtOAc in hexane. Recrystallization from diethyl ether gave the title bis-Boc compound, **7a** as a ∼ 2.5:1 diastereomeric ratio, which was used for the next step.



± : meso -**7a**

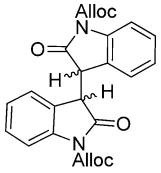
*Di-tert-butyl 2,2′-dioxo-[3,3′-biindoline]-1,1′-dicarboxylate (**7a**).*[6b] 30.7 g (62% yields over 3 steps) as amorphous white powder. R_f = 0.40 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$, spectrum contains ∼2.5:1 diastereomers) δ: 7.82 (d, J = 8.2 Hz, 1H for major diastereomer), 7.65 (d, J = 8.2 Hz, 1H for minor diastereomer), 7.30 (t, J = 7.7 Hz, 1H for major diastereomer), 7.13 (td, J = 1.5, 8.5 Hz, 1H for minor diastereomer), 7.03 (t, J = 7.4 Hz, 1H for major diastereomer), 6.95−6.89 (m, 2H for minor diastereomer), 6.79 (d, J = 7.4 Hz, 1H for major diastereomer), 4.42 (s, 1H for minor diastereomer), 4.32 (s, 1H for major diastereomer), 1.66 (s, 9H for minor diastereomer), 1.56 (s, 9H for major diastereomer); ^{13}C NMR (100 MHz, $CDCl_3$, spectrum contains ∼2.5:1 diastereomers) δ: 174.2, 172.8, 148.9, 148.9, 141.0, 140.1, 129.1, 128.9, 124.5, 124.5, 124.3, 123.2, 123.2, 123.1, 115.5, 114.9, 84.8, 84.4, 47.5, 47.3, 28.1, 28.0; IR (film) υ_{max} 2990, 1734, 1633, 1484, 1367, 1292, 1260, 1149, 843 cm^{-1}; mp 149−151 °C.

Synthetic Procedure and Characterization of (7b−d). To a solution of 2-oxindole (2 g, 15 mmol; 1.0 equiv) and isatin (2.2 g, 15 mmol; 1.0 equiv) in AcOH (20 mL) was added conc. aq. HCl (1 mL) at room temperature. The reaction mixture was stirred at 120 °C for 15 h. After the mixture was cooled down to room temperature, the precipitate was filtrated and dried over reduced pressure. Then, the crude solid residue, isoindigo was dissolved in DMF (10 mL), and NaH (60 wt%, 1.32 g, 33 mmol; 2.2 equiv) was added at 0 °C and stirred it for 10 min. Then, chloroformate (allyl or benzyl or ethyl) (31.5 mmol; 2.1 equiv) was added at 0 °C. The suspension was stirred for 1 h. Upon completion of the reaction (monitoring by TLC), the reaction mixture was poured into ice−water and the filtered solid residue. Then, the solid residue was taken in AcOH (15 mL) and Zn-dust (3.9 g, 60 mmol; 4.0 equiv) was added, and the mixture was stirred for 6 h at room temperature. The precipitate was filtered and dried over reduced pressure and purified by silica gel column chromatography using 20% EtOAc in hexane. Recrystallization from diethyl ether gave the title compound as diastereomeric ratio, which was used for the next step.



± : meso -**7b**

*Dibenzyl 2,2′-Dioxo-[3,3′-biindoline]-1,1′-dicarboxylate (**7b**).* 4.7 g (59% yields) as light red color solid. R_f = 0.50 (30% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$, spectrum contains ∼3.3:1 diastereomers) δ: 7.89 (d, J = 7.8 Hz, 1H for major diastereomer), 7.72 (d, J = 7.9 Hz, 1H for minor diastereomer), 7.54−7.52 (m, 2H for minor diastereomer), 7.43−7.29 (m, 6H for major +3H for minor diastereomer), 7.12 (t, J = 7.3 Hz, 1H for minor diastereomer), 7.05 (t, J = 7.0 Hz, 1H for major diastereomer), 6.92−6.79 (m, 1H for major +2H for minor diastereomer), 5.49 (brs, 2H for minor diastereomer), 5.37 (ABq, J = 36.0 Hz, 2H for major diastereomer), 4.48 (s, 1H for minor diastereomer), 4.39 (s, 1H for major diastereomer); ^{13}C NMR (100 MHz, $CDCl_3$, spectrum contains ∼3.3:1 diastereomers) δ: 173.9, 172.5, 150.4, 140.6, 139.7, 134.9, 134.8, 129.4, 129.1, 128.8, 128.7, 128.6, 128.4, 128.2, 128.0, 125.0, 124.1, 123.2, 123.1, 115.7, 115.2, 68.9, 68.6, 47.5, 47.4; IR (film) υmax 2970, 2899, 1635, 1448, 1207, 744, 673 cm-1; MP 158−160 ∘C. IR (film) υ_{max} 2970, 2899, 1635, 1448, 1207, 744, 673 cm^{-1}; mp 158−160 °C.



± : meso -**7c**

*Diallyl 2,2′-Dioxo-[3,3′-biindoline]-1,1′-dicarboxylate (**7c**).* 4.3 g (67% yields over 3 steps) as white powder. R_f = 0.55 (30% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$, spectrum contains ∼3.3:1 diastereomers) δ: 7.91 (d, J = 8.2 Hz, 1H for minor diastereomer), 7.75 (d, J = 8.2 Hz, 1H for major diastereomer), 7.34 (t, J = 7.7 Hz, 1H for minor diastereomer), 7.19−7.15 (m, 1H for major diastereomer), 7.07 (t, J = 7.4 Hz, 1H for minor diastereomer), 6.95−6.92 (m, 2H for major diastereomer), 6.82 (d, J = 7.4 Hz, 1H for minor diastereomer), 6.12−6.02 (m, 1H for major diastereomer), 6.00−5.92 (m, 1H for minor diastereomer), 5.55 (dd, J = 1.3, 17.2 Hz, 1H for major diastereomer), 5.42 (dd, J = 1.3, 17.2 Hz, 1H for minor diastereomer), 5.38 (dd, J = 1.0, 10.5 Hz, 1H for major diastereomer), 5.28 (dd, J = 1.0, 10.4 Hz, 1H for minor diastereomer), 4.95−4.93 (m, 2H for major diastereomer), 4.87−4.77 (m, 2H for minor diastereomer), 4.50 (s, 1H for major diastereomer), 4.39 (s, 1H for minor diastereomer); ^{13}C NMR (100 MHz, $CDCl_3$, spectrum contains ∼3.3:1 diastereomers) δ: 173.9, 172.5, 150.3, 150.3, 140.6, 139.7, 130.9, 130.9, 129.4, 129.1, 125.0, 124.9, 124.1, 123.2, 123.2, 119.6, 119.3, 115.7, 115.2, 67.9, 67.6, 47.4, 47.4; IR (film) υ_{max} 2993, 2924, 1725, 1697, 1621, 1476, 1399, 1201, 979, 889 cm^{-1}; mp 147−149 °C.

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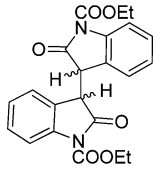
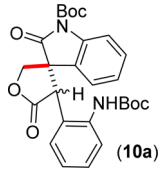


± : meso -**7d**

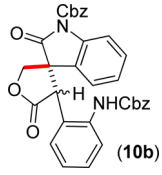
*Diethyl 2,2′-Dioxo-[3,3′-biindoline]-1,1′-dicarboxylate (**7d**).* 3.4 g (55% yields) as white powder. R_f = 0.45 (40% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$, spectrum contains ∼1:1 diastereomers) δ: 7.90 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.18−7.14 (m, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.94−6.93 (m, 2H), 6.81 (d, J = 7.4 Hz, 1H), 4.51 (q, J = 7.1 Hz, 2H), 4.48 (s, 1H), 4.44−4.34 (m, 3H), 1.48 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, spectrum contains ∼1:1 diastereomers) δ: 174.0, 172.6, 150.6, 150.5, 140.7, 139.8, 129.8, 129.1, 124.9, 124.8, 124.1, 123.2, 123.2, 123.1, 115.7, 115.1, 63.7, 63.5, 47.4, 47.3, 14.3, 14.2; IR (film) υ_{max} 2997, 1738, 1628, 1468, 1359, 1232, 1045, 846, 752 cm^{-1}; mp 184−185 °C.

General Procedure for Organocatalytic Unprecedented Aldol Reaction. In a sealed tube equipped with a magnetic stirring bar, to the mixture of **7** (0.03 mmol; 1.0 equiv) and paraformaldehyde solid (30 mg) were taken in 1.5 mL of HPLC grade CH_2Cl_2 and the reaction mixture was kept in −30 °C. After that, **L7** (0.005 mmol; 0.1 equiv) was added and reaction mixture was stirred for indicated times. Upon completion of the reactions, (TLC showed complete consumption of starting material) the reaction mixture was directly loaded onto silica gel and purified by flash chromatography using 10−20% EtOAc in hexane to give the desired products **10**.



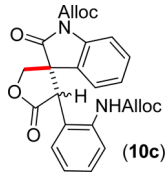
(**10a**)

*(3S)-tert-Butyl 4-(2-((tert-Butoxycarbonyl)amino)phenyl)-2′,5-dioxo-4,5-dihydro-2H-spiro[furan-3,3′-indoline]-1′-carboxylate (**10a**).* 23.7 mg (96% yields) as white powder. R_f = 0.3 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$, spectrum contains ∼1:1 diastereomers) δ: 7.81 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.58 (dd, J = 2.3,7.6 Hz, 1H), 7.47−7.41 (m, 2H), 7.37−7.32 (m, 2H), 7.27−7.20 (m, 4H), 7.15 (t, J = 7.7 Hz, 1H), 7.05−7.00 (m, 3H), 6.84 (d, J = 7.3 Hz, 1H), 6.21 (brs, 1H), 5.62 (brs, 1H), 4.73 (d, J = 6.1 Hz, 1H), 4.71 (d, J = 6.5 Hz, 1H), 4.69 (s, 1H), 4.58−4.54 (m, 2H), 4.42 (d, J = 9.2 Hz, 1H), 1.66 (s, 9H), 1.49 (d, J = 9.7 Hz, 18H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, spectrum contains ∼1:1 diastereomers) δ: 175.1, 174.0, 173.5, 173.1, 153.0, 153.0, 148.4, 142.2, 140.0, 139.1, 136.8, 136.7, 131.1, 130.4, 129.8, 129.8, 129.1, 129.0, 125.6, 125.5, 124.9,124.8, 124.7, 123.8, 122.2, 115.8, 115.1, 85.3, 84.9, 81.3, 80.7, 80.4, 72.9, 71.0, 57.1, 56.8, 51.8, 50.5, 28.2, 28.2, 28.0, 27.9; IR (film) υ_{max} 3499, 2979, 2960, 1711, 1669, 1634, 1600, 1501, 1434, 1114, 1100, 978, 852 cm^{-1}; HRMS (ESI) m/z 517.1931 [M+Na]$^+$; calculated for [$C_{27}H_{30}N_2O_7$ + Na]$^+$: 517.1945; mp 178−181 °C; Enantiometric excess was determined to be 93% ee via HPLC analysis using a Chiralpak IB column; solvent: 2-propanol/hexane =1/19; flow rate: 1.0 mL/min; detection: at 254 nm): t_R major =22.37 min, t_R minor =35.37 min.



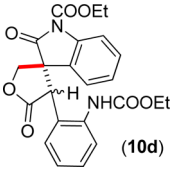
(**10b**)

*(3S)-Benzyl 4-(2-(((benzyloxy)carbonyl)amino)phenyl)-2′,5-dioxo-4,5-dihydro-2H-spiro[furan-3,3′-indoline]-1′-carboxylate (**10b**).* 25.3 mg (90% yields) as white amorphous. R_f = 0.27 (30% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$, spectrum contains major diastereomer) δ: 7.81 (d, J = 8.1 Hz, 1H), 7.44−7.33 (m, 13H), 7.28−7.27 (m, 1H), 7.21 (t, J = 6.9 Hz, 2H), 7.11 (t, J = 7.7 Hz, 1H), 5.93 (brs, 1H), 5.32−5.25 (m, 2H), 5.03 (brs, 2H), 4.67 (d, J = 9.6 Hz, 1H), 4.66 (s, 1H), 4.46 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, spectrum contains major diastereomer) δ: 173.5, 173.1, 153.9, 149.8, 139.6, 136.1, 134.6, 131.3, 130.4, 129.3, 128.7, 128.6, 128.6, 128.5, 128.3, 128.2, 127.9, 125.9, 122.5, 115.9, 71.1, 68.7, 67.1, 57.2, 51.5; IR (film) υ_{max} 3489, 2938, 2897, 1754, 1689, 1650, 1400, 1413, 1250, 742 cm^{-1}; HRMS (ESI) m/z 563.1827 [M+H]$^+$; calculated for [$C_{33}H_{26}N_2O_7$ + H]$^+$: 563.1813; mp 64−66 °C; Enantiometric excess was determined to be 89% ee via HPLC analysis using a Chiralpak IB column; solvent: 2-propanol/hexane =3/22; flow rate: 1.0 mL/min; detection: at 254 nm): t_R major =27.38 min, t_R minor =32.49 min.



(**10c**)

*(3S)-Allyl 4-(2-((((allyloxy)carbonyl)amino)phenyl)-2′,5-dioxo-4,5-dihydro-2H-spiro[furan-3,3′-indoline]-1′-carboxylate (**10c**).* 21.7 mg (94% yields) as white solid. R_f = 0.25 (20% EtOAc in hexane). dr =1.1:1 (determined from unpurified reaction mixture] of (10c) as a solid, dr =10:1 (after recrystallization)] ^{1}H NMR (400 MHz, $CDCl_3$, spectrum contains ∼10:1 diastereomers) δ: 7.81 (d, J = 7.9 Hz, 1H for major diastereomer), 7.74 (d, J = 8.0 Hz, 1H for minor diastereomer), 7.54 (d, J = 7.5 Hz, 1H for major diastereomer), 7.39 (t, J = 8.0 Hz, 1H for major diastereomer), 7.31 (t, J = 7.8 Hz, 2H for major diastereomer), 7.22 (d, J = 8.14 Hz, 2H for major diastereomer), 7.20 (d, J = 8.0 Hz, 2H for minor diastereomer), 7.14 (d, J = 7.2 Hz, 1H for major diastereomer), 7.03 (t, J = 8.2 Hz, 2H for minor diastereomer), 6.98 (d, J = 7.4 Hz, 1H for minor diastereomer), 6.16 (brs, 1H for minor diastereomer), 6.05−5.95 (m, 2H for minor diastereomer), 5.93−5.81 (m, 2H for major diastereomer), 5.51 (d, J = 18 Hz, 2H for minor diastereomer), 5.34 (d, J = 18.2 Hz, 2H for major diastereomer), 5.24 (d, J = 10.3 Hz, 2H for major diastereomer), 5.20 (d, J = 10.0 Hz, 2H for minor diastereomer), 4.86−4.80 (m, 4H for minor diastereomer), 4.72−4.64 (m, 4H for major diastereomer), 4.56 (d, J = 7.2 Hz, 1H for minor diastereomer), 4.50 (d, J = 7.9 Hz, 1H for major diastereomer), 4.45 (s, 2H for major diastereomer), 4.41 (s, 2H for minor diastereomer); ^{13}C NMR (100 MHz, $CDCl_3$, spectrum contains ∼10:1 diastereomers) δ: 173.8, 173.6, 173.4, 173.2, 153.9, 153.8, 149.8, 149.7, 139.6, 138.7, 136.3, 136.2, 132.4, 132.3, 131.3, 130.6, 130.6, 130.4, 130.2, 130.0, 129.4, 129.3, 126.3, 125.9, 125.1, 123.9, 122.5, 119.7, 119.2, 118.1, 117.9, 116.0, 115.4, 74.0, 73.3, 71.3, 70.8, 68.1, 67.7, 66.1, 66.0, 57.4, 50.7; IR (film) υ_{max} 3499, 2987, 2870, 1703, 1649, 1601, 1399, 1279, 1101, 980 cm^{-1}; HRMS (ESI) m/z 463.1478 [M+H]$^+$; calculated for [$C_{25}H_{22}N_2O_7$ + H]$^+$: 463.1500; mp 105−107 °C; Enantiometric excess was determined to be 81% ee via HPLC analysis using a Chiralpak IB column; solvent: 2-propanol/hexane =3/22; flow rate: 1.0 mL/min; detection: at 254 nm): t_R major =17.02 min, t_R minor =21.18 min.



(**10d**)

*(3S)-Ethyl 4-(2-((ethoxycarbonyl)amino)phenyl)-2′,5-dioxo-4,5-dihydro-2H-spiro[furan-3,3′-indoline]-1′-carboxylate (**10d**).* 21.2 mg (92% yields) as white solid. R_f = 0.20 (40% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$, spectrum contains ∼1.2:1 diastereomers) δ: 7.81 (d, J = 8.1 Hz, 1H for minor diastereomer), 7.73 (d, J = 8.2 Hz, 1H for major diastereomer), 7.54 (d, J = 7.2 Hz, 1H for minor

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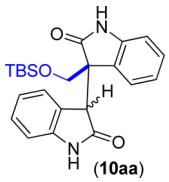
diastereomer), 7.42−7.12 (m, 10H for major + minor diastereomer), 7.06−6.94 (m, 5H for major + minor diastereomer), 6.34 (brs, 1H for major diastereomer), 5.87 (brs, 1H for minor diastereomer), 4.77 (s, 1H for major diastereomer), 4.71−4.63 (m, 3H for minor diastereomer), 4.50 (d, J = 9.6 Hz, 1H for minor diastereomer), 4.47−4.40 (m, 3H for major + minor diastereomer), 4.29 (q, J = 7.1 Hz, 2H for minor diastereomer), 4.12 (q, J = 7.0 Hz, 2H for major diastereomer), 4.02−4.00 (m, 2H for major diastereomer), 1.42 (t, J = 7.1 Hz, 3H for minor diastereomer), 1.28 (t, J = 7.1 Hz, 3H for major diastereomer); ^{13}C NMR (100 MHz, $CDCl_3$, spectrum contains ∼1.2:1 diastereomers) δ: 174.7, 173.8, 173.6, 173.2, 154.2, 150.0, 149.9, 139.8, 138.8, 136.5, 136.3, 131.3, 130.4, 130.2, 129.9, 129.3, 125.8, 125.4, 125.2, 125.0, 123.9, 122.5, 115.9, 115.3, 73.3, 71.3, 64.0, 63.7, 61.5, 57.2, 57.1, 50.7, 14.5, 14.4, 14.1, 14.0; IR (film) υ_{max} 3441 (br), 2976, 2899, 1731, 1669, 1634, 1509, 1481, 1207, 1108, 1076, 937, 921 cm^{-1}; HRMS (ESI) m/z 439.1482 $[M+H]^+$; calculated for $[C_{23}H_{22}N_2O_7 + H]^+$: 439.1500; mp 147−149 °C; Enantiometric excess was determined to be 89% ee via HPLC analysis using a Chiralpak IB column; solvent: 2-propanol/hexane =3/22; flow rate: 1.0 mL/min; detection: at 254 nm): t_R major =18.39 min, t_R minor =22.00 min.

Synthetic procedure and characterization of (10aa). *Step 1.* In an oven-dried round-bottom flask, enantioenriched compound **10a** (100 mg, 0.202 mmol; 1.0 equiv) was taken in dichloromethane (4 mL). To this solution was added trifluoroacetic acid (1 mL) at 0 °C and was stirred for 1 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, and the organic phase was extracted with dichloromethane. The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was directly treated for next step without purification.

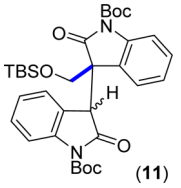
Step 2. The crude material (0.202 mmol; 1.0 equiv. as prepared earlier) was taken in dichloromethane (3 mL) under argon atmosphere and the reaction vessel was cooled to 0 °C. To this reaction mixture imidazole (55 mg 0.808 mmol; 4.0 equiv) and TBSCl (91 mg, 0.606 mmol; 3.0 equiv) were added and stirred it at room temperature for 1 h. Upon completion of the reaction (monitoring by TLC), it was quenched with water and extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude products were purified by flash chromatography using 15% EtOAc in hexane to afford **10aa**.



(**10aa**)

*(3S)-3-(((tert-Butyldimethylsilyl)oxy)methyl)-[3,3′-biindoline]-2,2′-dione (**10aa**).* 77.5 mg (94% yields over 2 steps) as light yellow solid. R_f = 0.32 (30% EtOAc in hexane). ^{1}H NMR (500 MHz, $CDCl_3$, spectrum contains major diastereomer) δ: 8.64 (d, J = 14.7 Hz, 2H), 7.29−7.26 (m, 2H), 7.10−7.06 (m, 2H), 6.90−6.85 (m, 2H), 6.74−6.71 (m, 2H), 4.84 (d, J = 9.7 Hz, 1H), 4.38 (d, J = 9.7 Hz, 1H), 4.01 (s, 1H), 0.70 (s, 9H), −0.01 (s, 3H), −0.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, spectrum contains major diastereomer) δ: 179.5, 177.7, 141.8, 141.3, 128.4, 128.3, 125.2, 124.7, 123.4, 123.4, 122.5, 122.3, 109.5, 109.4, 65.4, 57.1, 47.7, 25.5, 17.9, −5.5, −5.8; IR (film) υ_{max} 3511, 3470, 2976, 2899, 1699, 1635, 1511, 1439, 1321, 1177, 1001, 937, 831, 721 cm^{-1}; mp 217−219 °C; HRMS (ESI) m/z 409.1971 $[M+H]^+$; calculated for $[C_{23}H_{28}N_2O_3Si + H]^+$: 409.1942.

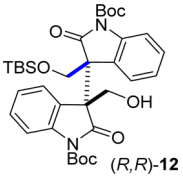
Synthetic Procedure and Characterization of (11). In an oven-dried round-bottom flask, the compound **10aa** (50 mg, 0.122 mmol; 1.0 equiv) was taken in dry THF (3 mL) under argon atmosphere. To this reaction mixture NaH (60 wt%, 11 mg, 0.268 mmol; 2.2 equiv) was added portion wise at 0 °C and it was stirred for another 5 min at same temperature. Then, $(Boc)_2O$ (59 μL, 0.256 mmol; 2.1 equiv) was added to the reaction mixture at 0 °C and it was stirred for 30 min. Upon completion of the reactions, (TLC showed complete consumption of starting material) the reaction mixture was quenched with ice−water and extracted with EtOAc (2 × 5 mL), dried over anhydrous Na_2SO_4, evaporated under rotary evaporator, and the crude products were purified by column chromatography using 10% EtOAc in hexane to afford **11**.



(**11**)

*(3S)-Di-tert-butyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-2,2′-dioxo-[3,3′-biindoline]-1,1′-dicarboxylate (**11**).* 60 mg (81% yields) as yellow gel. R_f = 0.3 (10% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$, spectrum contains ∼1.2:1 diastereomers) δ: 7.78 (dd, J = 8.2, 12.9 Hz, 2H for major diastereomer), 7.56 (d, J = 8.1 Hz, 1H for major diastereomer), 7.50 (d, J = 8.1 Hz, 1H for major diastereomer), 7.28 (m, 2H for minor diastereomer), 7.13−7.07 (m, 5H for minor diastereomer), 7.04−6.89 (m, 4H for major diastereomer), 6.81 (d, J = 7.5 Hz, 1H for minor diastereomer), 6.66 (d, J = 7.4 Hz, 1H for minor diastereomer), 4.66 (d, J = 9.5 Hz, 1H for minor diastereomer), 4.40 (s, 1H for minor diastereomer), 4.14 (d, J = 9.6 Hz, 1H for minor diastereomer), 4.07 (s, 1H for major diastereomer), 1.63 (s, 9H for major diastereomer), 1.62 (s, 9H for major diastereomer), 1.50 (s, 9H for minor diastereomer), 1.49 (s, 9H for minor diastereomer), 0.71 (s, 9H for minor diastereomer), 0.60 (s, 9H for major diastereomer), −0.03 (s, 3H for minor diastereomer), −0.07 (s, 3H for major diastereomer), −0.14 (s, 3H for minor diastereomer), −0.29 (s, 3H for major diastereomer); ^{13}C NMR (100 MHz, $CDCl_3$, spectrum contains ∼1.2:1 diastereomers) δ: 175.7, 174.5, 173.6, 171.9, 149.0, 148.8, 148.7, 148.7, 141.2, 141.2, 140.9, 140.0, 129.0, 128.8, 126.9, 126.2, 128.8, 124.3, 124.1, 124.0, 114.6, 114.5, 85.2, 84.7, 84.2, 83.9, 66.4, 66.2, 58.0, 56.7, 48.6, 48.4, 28.1, 28.0, 28.0, 27.9, 25.6, 25.4, 17.9, 17.7, −5.6, −5.7, −5.7, −5.9; IR (film) υ_{max} 2997, 2968, 1701, 1689, 1621, 1551, 1421, 1106, 970, 679 cm^{-1}; HRMS (ESI) m/z 631.2795 $[M+Na]^+$; calculated for $[C_{33}H_{44}N_2O_7Si + Na]^+$: 631.2810.

Synthetic Procedure and Characterization of (*R*,*R*)-12. In an oven-dried round-bottom flask equipped with a magnetic stirring bar, to the mixture of **11** (20 mg, 0.03 mmol; 1.0 equiv) and paraformaldehyde solid (20.0 mg) were taken in 2 mL of HPLC grade CH_2Cl_2 at room temperature. After that **L7** (1.8 mg, 0.003 mmol; 0.1 equiv) was added and reaction mixture was stirred at room temperature for 15 h. Upon completion of the reactions, (TLC showed complete consumption of starting material) the reaction mixture was directly loaded onto silica gel and purified by flash chromatography using 10−15% EtOAc in hexane to give the desired products (*R*,*R*)-**12**.



(*R*,*R*)-**12**

*(3R,3′R)-Di-tert-butyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-3′-(hydroxymethyl)-2,2′-dioxo-[3,3′-biindoline]-1,1′-dicarboxylate (R,R)-**12**.* 16.3 mg (85% yields) as white solid. R_f = 0.22 (20% EtOAc in hexane). [dr = 12:1 (determined from unpurified reaction mixture) of (*R*,*R*)-12 as a solid, dr = 6.7:1 (after column chromatography)]. ^{1}H NMR (400 MHz, $CDCl_3$, spectrum contains ∼6.7:1 diastereomers) δ: 7.75 (d, J = 8.0 Hz, 1H for minor diastereomer), 7.71 (d, J = 8.0 Hz, 1H for minor diastereomer), 7.44 (d, J = 8.0 Hz, 1H for major diastereomer), 7.39 (d, J = 8.1 Hz, 1H for major diastereomer), 7.27−7.25 (m, 1H for major +2H for minor diastereomer), 7.16 (d, J = 7.8 Hz, 1H for major diastereomer), 7.10−7.01 (m, 2H for major +2H for

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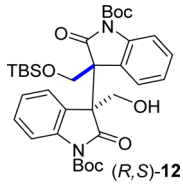
minor diastereomer), 6.95 (td, J = 0.7, 7.8 Hz, 1H for major diastereomer), 6.89 (td, J = 7.6, 0.7 Hz, 1H for major +1H for minor diastereomer), 6.52 (d, J = 7.4 Hz, 1H for minor diastereomer), 4.68 (dd, J = 11.3, 3.7 Hz, 1H for major diastereomer), 4.60 (d, J = 9.3 Hz, 1H for major diastereomer), 4.52 (d, J = 9.5 Hz, 1H for minor diastereomer), 4.42 (d, J = 9.2 Hz, 1H for major diastereomer), 4.31 (d, J = 9.2 Hz, 1H for minor diastereomer), 4.27−4.20 (m, 1H for major diastereomer), 4.07 (d, J = 7.0 Hz, 1H for minor diastereomer), 2.72 (dd, J = 9.0, 4.2 Hz, 1H for minor diastereomer), 2.35 (dd, J = 9.0, 3.6 Hz, 1H for major diastereomer), 1.61 (s, 9H for major diastereomer), 1.58 (s, 9H for major diastereomer), 1.51 (s, 9H for minor diastereomer), 1.46 (s, 9H for minor diastereomer), 0.58 (s, 9H for minor diastereomer), 0.51 (s, 9H for major diastereomer), −0.08 (s, 3H for major diastereomer), −0.10 (s, 3H for minor diastereomer), −0.24 (s, 3H for minor diastereomer), −0.28 (s, 3H for major diastereomer); ^{13}C NMR (100 MHz, $CDCl_3$, spectrum contains ∼12:1 diastereomers) δ: 175.9, 175.3, 174.7, 174.0, 148.6, 148.6, 148.5, 148.4, 141.5, 140.8, 140.4, 140.0, 129.4, 129.2, 129.0, 129.0, 128.7, 128.2, 126.6, 126.2, 125.6, 125.4, 125.3, 124.2, 124.1, 124.0, 123.7, 123.7, 123.3, 122.7, 115.3, 114.8, 114.6, 114.1, 84.6, 84.2, 84.2, 83.7, 64.1, 62.4, 62.2, 59.2, 57.7, 28.1, 28.1, 28.0, 27.9, 25.4, 25.3, 17.7, 17.6, −5.7, −5.7, −5.8, −5.9; IR (film) υ_{max} 3466 (br), 2989, 2918, 1648, 1601, 1321, 1299, 926, 702 cm^{-1}; mp 247−249 °C; HRMS (ESI) m/z 661.2914 $[M+Na]^+$; calculated for $[C_{34}H_{46}N_2O_8Si + Na]^+$: 661.2916; Enantiometric excess was determined to be 91% ee via HPLC analysis using a Chiralpak IB column; solvent: 2-propanol/hexane =1/99; flow rate: 1.0 mL/min; detection: at 254 nm): t_R major =23.30 min, t_R minor =15.82 min.

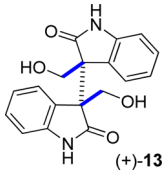
Synthetic Procedure and Characterization of (*R,S*)-12. In an oven-dried round-bottom flask equipped with a magnetic stirring bar, to the mixture of **11** (20 mg, 0.03 mmol; 1.0 equiv) and paraformaldehyde solid (20.0 mg) were taken in 2 mL of HPLC grade CH_2Cl_2 at room temperature. After that **L10** (1.8 mg, 0.003 mmol; 0.1 equiv) was added and reaction mixture was stirred at room temperature for 15 h. Upon completion of the reactions, (TLC showed complete consumption of starting material) the reaction mixture was directly loaded onto silica gel and purified by flash chromatography using 15−20% EtOAc in hexane to give the desired product (*R,S*)-**12**.



(*R,S*)-**12**

*(3R, 3′S)-Di-tert-butyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-3′-(hydroxymethyl)-2,2′-dioxo-[3,3′-biindoline]-1,1′-dicarboxylate (R,S)-**12**.* 15.5 mg (81% yields) as white solid. R_f = 0.2 (30% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$, spectrum contains diastereomeric ratio) δ: 7.82 (d, J = 8.2 Hz, 1H for major diastereomer), 7.77 (d, J = 8.2 Hz, 1H for major diastereomer), 7.51 (d, J = 8.2 Hz, 1H for minor diastereomer), 7.45 (d, J = 8.2 Hz, 1H for minor diastereomer), 7.35−7.30 (m, 2H for major +2H for minor diastereomer), 7.22 (d, J = 7.8 Hz, 1H for minor diastereomer), 7.16 (d, J = 7.8 Hz, 1H for minor diastereomer), 7.10 (t, J = 7.5 Hz, 1H for major +1H for minor diastereomer), 7.01 (d, J = 7.6 Hz, 1H for major diastereomer), 6.96 (d, J = 8.1 Hz, 1H for major +1H for minor diastereomer), 6.57 (d, J = 7.5 Hz, 1H for major diastereomer), 4.73 (d, J = 11.3 Hz, 1H for minor diastereomer), 4.65 (d, J = 9.3 Hz, 1H for minor diastereomer), 4.58 (d, J = 9.4 Hz, 1H for major diastereomer), 4.49 (d, J = 9.3 Hz, 1H for minor diastereomer), 4.45−4.40 (m, 1H for major diastereomer), 4.37 (d, J = 9.4 Hz, 1H for major diastereomer), 4.31 (m, 1H for minor diastereomer), 4.12 (d, J = 11.6 Hz, 1H for major), 2.67 (brs, 1H for major diastereomer), 2.23 (brs, 1H for minor diastereomer), 1.67 (s, 9H for minor diastereomer), 1.64 (s, 9H for minor diastereomer), 1.58 (s, 9H for major diastereomer), 1.52 (s, 9H for major diastereomer), 0.63 (s, 9H for major diastereomer), 0.57 (s, 9H for minor diastereomer), −0.03 (s, 3H for minor diastereomer), −0.05 (s, 3H for major diastereomer), −0.19 (s, 3H for major diastereomer), −0.23 (s, 3H for minor diastereomer); ^{13}C NMR (100 MHz, $CDCl_3$, spectrum contains one diastereomers) δ: 175.8, 174.1, 148.7, 148.6, 141.5, 140.8, 129.4, 129.1, 126.6, 125.5, 124.2, 124.0, 123.8, 123.7, 115.3, 114.9, 84.3, 83.8, 64.3, 64.2, 59.2, 57.1, 28.0, 27.9, 25.4, 17.8, −5.7, −5.9; IR (film) υ_{max} 3466 (br), 2932, 1770, 1734, 1613, 1481, 1466, 1366, 1292, 1153, 841 cm^{-1}; mp 165−168 °C. Enantiometric excess was determined to be 91% ee via HPLC analysis using a Chiralpak IB column; solvent: 2-propanol/hexane =1/99; flow rate: 1.0 mL/min; detection: at 254 nm): t_R major =11.07 min, t_R minor =13.18 min.

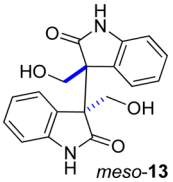
Synthetic Procedure and Characterization of (+)-13. In a solution of enantioenriched compound (*R,R*)-**12** (418 mg, 0.655 mmol; 1.0 equiv) in dichloromethane (20 mL), trifluoroacetic acid (5 mL) was added at 0 °C and was stirred for 1 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, and the organic phase was extracted with dichloromethane. The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude material was purified by flash chromatography using 50−75% EtOAc in hexane to furnish (+)-**13**.



(+)-**13**

*(3R,3′R)-3,3′-Bis(hydroxymethyl)-[3,3′-biindoline]-2,2′-dione (+)-**13**.* 172 mg (81% yields) as white solid. R_f = 0.3 (in EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.35 (brs, 1H), 7.07 (d, J = 7.5 Hz, 1H), 6.91 (t, J = 7.7 Hz, 1H), 6.73 (t, J = 7.4 Hz, 1H), 6.44 (d, J = 7.6 Hz, 1H), 4.51 (d, J = 10.1 Hz, 1H), 3.95 (d, J = 10.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 179.0, 143.1, 129.3, 128.2, 123.8, 121.3, 109.0, 60.5, 57.7; IR (film) υ_{max} 3611 (br), 3411 (br), 2990, 1630, 1500, 1419, 750 cm^{-1}; mp 95−96 °C; HRMS (ESI) m/z 325.1170 $[M+H]^+$; calculated for $[C_{18}H_{16}N_2O_4 + H]^+$: 325.1183; $[\alpha]_{589}^{24.8}$ = +159.9 (c = 0.113, MeOH).

Synthetic Procedure and Characterization of *meso*-13. In a solution of enantioenriched compound (*R,S*)-**12** (100 mg, 0.157 mmol; 1.0 equiv) in dichloromethane (5 mL), trifluoroacetic acid (1.5 mL) was added at 0 °C and was stirred for 1 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, and the organic phase was extracted with dichloromethane. The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude material was purified by flash chromatography using 60−80% EtOAc in hexane to afford *meso*-**13**.



meso-**13**

*(3R,3′S)-3,3′-Bis(hydroxymethyl)-[3,3′-biindoline]-2,2′-dione (meso-**13**).* 39 mg (77% yields) as colorless solid. R_f = 0.2 (in EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$:DMSO-d6 = 3:2) δ: 9.96 (s, 1H), 7.10 (t, J = 7.2 Hz, 1H), 6.78 (d, J = 7.0 Hz, 1H), 6.72 (d, J = 7.4 Hz, 1H), 6.63 (brs, 1H), 4.73 (brs, 1H), 4.40 (d, J = 7.2 Hz, 1H), 4.13 (d, J = 9.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$:DMSO-d6 = 3:2) δ: 178.3, 143.3, 129.0, 128.5, 124.6, 121.3, 109.8, 62.4, 57.8; IR (film) υ_{max} 3449 (br), 3400 (br), 2979, 2899, 1701, 1649, 1599, 1441, 1279, 738 cm^{-1}; mp 125−127 °C.

Synthetic Procedure and Characterization of (+)-14a. Compound (+)-**13** (196 mg, 0.605 mmol; 1.0 equiv) was dissolved in DMF (5 mL). Imidazole (247 mg, 3.63 mmol; 6.0 equiv) and TBSCl (273 mg, 1.82 mmol; 3.0 equiv) were added at 0 °C to this

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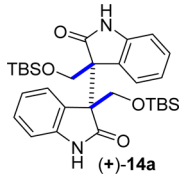
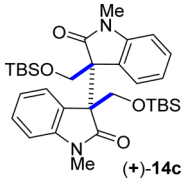
solution and the mixture was stirred for 2 h at room temperature. The reaction was quenched with water; the organic phase was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography using 10% EtOAc in hexane to furnish (+)-**14a**.



*(3R,3′R)-3,3′-Bis(((tert-butyldimethylsilyl)oxy)methyl)-[3,3′-biindoline]-2,2′-dione (+)-**14a***. 304 mg (91% yields) as colorless solid. R_f = 0.5 (20% EtOAc in hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.85 (brs, 1H), 7.17 (td, J = 1.0, 7.7 Hz, 1H), 6.87 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.72 (d, J = 7.4 Hz, 1H), 4.51 (d, J = 9.6 Hz, 1H), 4.39 (d, J = 9.6 Hz, 1H), 0.70 (s, 9H), −0.05 (s, 3H), −0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.4, 142.3, 128.8, 128.5, 124.9, 121.4, 109.4, 63.6, 57.7, 25.5, 17.9, −5.6, −5.8; IR (film) υ_{max} 3479 (br), 2971, 2952, 1700, 1690, 1611, 1531, 1479, 1076, 937 cm^{-1}; mp 258−261 °C; $[\alpha]_{589}^{22.6}$ = +79 (c = 0.13, MeOH).

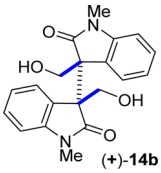
Synthetic Procedure and Characterization of (+)-14c. In an oven-dried round-bottom flask, the compound (+)-**14a** (206 mg, 0.37 mmol; 1.0 equiv) was taken in DMF (7 mL) under argon atmosphere and the reaction vessel was cooled to 0 °C. To this reaction mixture was added NaH (60 wt%, 36 mg, 0.89 mmol; 2.4 equiv) portionwise, and stirred for another 5 min. Then MeI (51 μL, 0.82 mmol; 2.2 equiv) was added to the reaction mixture at 0 °C and the mixture warmed to room temperature and stirring continued for another 30 min. The reaction was quenched with water; the organic phase was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with water and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography using 5% EtOAc in hexane to furnish product (+)-**14c**.



*(3R,3′R)-3,3′-Bis(((tert-butyldimethylsilyl)oxy)methyl)-1,1′-dimethyl-[3,3′-biindoline]-2,2′-dione (+)-**14c***. 176 mg (82% yields) as white powder. R_f = 0.7 (10% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.03 (d, J = 7.4 Hz, 1H), 6.97 (td, J = 0.8, 7.7 Hz, 1H), 6.77 (t, J = 7.3 Hz, 1H), 6.42 (d, J = 7.7 Hz, 1H), 4.79 (d, J = 9.3 Hz, 1H), 4.34 (d, J = 9.3 Hz, 1H), 3.08 (s, 3H), 0.49 (s, 9H), −0.1 (s, 3H), −0.3 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.9, 144.5, 128.3, 128.0, 122.8, 121.7, 107.1, 61.8, 57.6, 25.7, 25.3, 17.5, −5.6, −5.9; IR (film) υ_{max} 2998, 2900, 1714, 1631, 1258, 1093, 833 cm^{-1}; mp 50−52 °C; HRMS (ESI) m/z 581.3221 $[M+H]^+$; calculated for $[C_{32}H_{48}N_2O_4Si_2 + H]^+$: 581.3225; $[\alpha]_{589}^{23.6}$ = +80 (c = 0.1, MeOH).

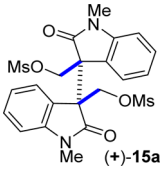
Synthetic Procedure and Characterization of (+)-14b. To a solution of compound (+)-**14c** (161 mg, 0.28 mmol; 1.0 equiv) in MeOH: CH_2Cl_2 (3:1) (7 mL), camphor sulfonic acid (13 mg, 0.056 mmol; 0.2 equiv) was added and stirred it for 15 h at room temperature. Upon completion of the reactions, (TLC showed complete consumption of starting material) the reaction mixture was directly evaporated and loaded onto silica gel and purified by flash chromatography using 50−75% EtOAc in hexane to furnish (+)-**14a** to give the desired product (+)-**14b**.

*(3R,3′R)-3,3′-Bis(hydroxymethyl)-1,1′-dimethyl-[3,3′-biindoline]-2,2′-dione (+)-**14b***. 68 mg (69% yields) as white solid. R_f = 0.2 (75% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16 (d, J = 7.5 Hz, 1H), 7.08 (t, J = 7.7 Hz, 1H), 6.88 (t, J = 7.6 Hz, 1H), 6.53 (d, J =



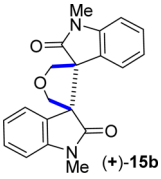
7.8 Hz, 1H), 4.68 (d, J = 11.6 Hz, 1H), 4.12 (d, J = 11.6 Hz, 1H), 3.62 (brs, 1H), 3.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.1, 143.3, 128.9, 126.8, 123.9, 122.6, 108.1, 63.2, 57.1, 26.1; IR (film) υ_{max} 3551 (br), 2999, 2903, 1669, 1630, 1425, 1221, 900, 703 cm^{-1}; mp 146−148 °C; HRMS (ESI) m/z 353.1489 $[M+H]^+$; calculated for $[C_{20}H_{20}N_2O_4 + H]^+$: 353.1496; $[\alpha]_{589}^{23.9}$ = +186.7 (c = 0.16, MeOH).

Synthetic Procedure and Characterization of (+)-15a. In an oven-dried round-bottom flask, diol (+)-**14b** (55 mg, 0.16 mmol; 1.0 equiv) was taken in CH_2Cl_2 (4 mL). The flask was cooled to 0 °C, and Et_3N (89 μL, 0.64 mmol; 4.0 equiv) was added in one portion. The suspension was stirred at 0 °C for 2 min, and then MsCl (31 μL, 0.40 mmol; 2.5 equiv) was added dropwise. The mixture was stirred at 0 °C for another 15 min. The reaction mixture was quenched water and diluted with brine (5 mL), was extracted with CH_2Cl_2 (2 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resultant crude mixture was purified by flash chromatography on silica gel using 40−50% EtOAc in hexane to afford (+)-**15a**.



*((3R,3′R)-1,1′-Dimethyl-2,2′-dioxo-[3,3′-biindoline]-3,3′-diyl)bis-(methylene) Dimethanesulfonate (+)-**15a***. 68 mg (84% yields) as white solid. R_f = 0.3 (50% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11−7.06 (m, 2H), 6.88 (t, J = 7.1 Hz, 1H), 6.49 (d, J = 7.8 Hz, 1H), 5.45 (d, J = 9.8 Hz, 1H), 4.86 (d, J = 9.8 Hz, 1H), 3.12 (s, 3H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.0, 143.8, 129.8, 124.0, 123.0, 122.6, 108.3, 67.2, 55.0, 37.1, 26.2; IR (film) υ_{max} 2990, 2880, 1700, 1632, 1599, 1481, 1400, 1300, 1179, 989 cm^{-1}; mp 228−230 °C; HRMS (ESI) m/z 509.1045 $[M+H]^+$; calculated for $[C_{22}H_{24}N_2O_8S_2 + H]^+$: 509.1047.

Synthetic Procedure and Characterization of (+)-15b. In an oven-dried round-bottom flask, the compound (+)-**14b** (118 mg, 0.34 mmol; 1.0 equiv) was taken in dry toluene (7 mL) under argon atmosphere. To this reaction mixture, imidazole (114 mg, 1.67 mmol; 5.0 equiv), PPh_3 (439 mg, 1.67 mmol; 5.0 equiv), and iodine (340 mg, 1.34 mmol; 4.0 equiv) were added respectively at room temperature and then refluxed it for 8 h. The reaction was quenched with saturated aq. $Na_2S_2O_3$ solution, the organic phase was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with water and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography using 20% EtOAc in hexane afforded product (+)-**15b**.



*Cyclic Ether (+)-**15b***. 84 mg (74% yields) as colorless solid. R_f = 0.4 (40% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, J = 7.5 Hz, 1H), 7.15 (td, J = 0.8, 7.7 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H), 6.57 (d, J = 7.8 Hz, 1H), 4.82 (d, J = 8.6 Hz, 1H), 4.28 (d, J = 8.6 Hz, 1H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.6, 144.3, 129.3, 124.4, 123.0, 122.6, 108.0, 73.2, 60.2, 25.9; IR (film) υ_{max} 2939, 1691, 1649, 1297, 1163, 910, 721 cm^{-1}; mp 280−281 °C; HRMS

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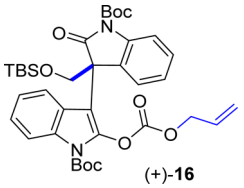
(ESI) m/z 357.1237 $[M+Na]^+$; calculated for $[C_{20}H_{18}N_2O_3 + Na]^+$: 357.1210; $[\alpha]_{589}^{24.5}$= +353.3 (c = 0.052, MeOH).

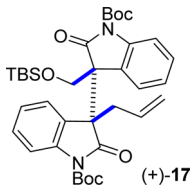
Synthetic Procedure and Characterization of (+)-16. In an oven-dried round-bottom flask was charged with compound **11** (1.0 g, 1.64 mmol; 1.0 equiv) in dry THF (20 mL) under nitrogen atmosphere at 0 °C. Then triethyl amine (686 μL; 4.92 mmol; 3.0 equiv) was added to the solution. After 5 min of stirring allyl chloroformate (686 μL; 1.97 mmol; 1.2 equiv) was added dropwise over a period of 2 min at 0 °C and stirring was continued for 30 min. Upon completion of the reaction (judged by TLC analysis) diluted with EtOAc (30 mL) and quenched with H_2O. The whole reaction mixture was taken in a separatory funnel to separate the organic layer. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using 5% EtOAc and hexane mixture as eluent to afford the desired product (+)-**16**.



(+)-**16**

*(R)-tert-Butyl 2-((((allyloxy)carbonyl)oxy)-3-(1-(tert-butoxycarbonyl)-3-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxoindolin-3-yl)-1H-indole-1-carboxylate (+)-**16**.* 1.01 g (89% yields) as white foam. R_f = 0.27 (10% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.28 (td, J = 1.4, 8.7 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 6.4 Hz, 1H), 7.10−7.0 (m, 2H), 6.86 (brs, 1H), 6.02−5.92 (m, 1H), 5.43 (d, J = 17.1 Hz, 1H), 5.32 (d, J = 10.4 Hz, 1H), 4.71 (brs, 3H), 4.34 (m, 1H), 1.62 (s, 9H), 1.61 (s, 9H), 0.65 (s, 9H), −0.09 (s, 3H), −0.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.2, 149.3, 148.5, 140.8, 139.5, 132.3, 130.6, 130.1, 128.5, 125.0, 124.5, 124.0, 123.3, 120.3, 120.3, 119.7, 115.4, 114.6, 104.4, 84.9, 84.0, 70.2, 67.0, 55.7, 28.1, 28.1, 25.5, 17.8, −5.8, −6.1; IR (film) υ_{max} 2999, 2989, 2876, 1736, 1700, 1633, 1601, 1499, 1400, 1311, 900, 699 cm^{-1}; mp 68−70 °C; HRMS (ESI) m/z 715.3000 $[M+Na]^+$; calculated for $[C_{37}H_{48}N_2O_9Si + Na]^+$: 715.3021; $[\alpha]_{589}^{22.7}$= +40 (c = 0.44, MeOH).

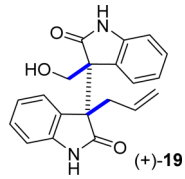
Procedure for Pd-Catalyzed Decarboxylative Allylation of Compound 16. In an oven-dried sealed tube, solvent (2 mL) was degassed by using nitrogen balloon at room temperature over a period of 10 min. $Pd_2(dba)_3$ (5 mol%) and 15 mol% of ligand were added to it and stirring was continued for 20 min to make the complex mixture. After that reaction mixture was cooled at −25 °C. Then, enantioenriched compound **16** was added to the complex solution and stirring was continued for specified time at same temperature. After complete consumption of starting material (monitored by TLC) the reaction mixture was concentrated and purified by column chromatography using 5% EtOAc in hexane to afford the desired enantioenriched compound (+)-**17**.



(+)-**17**

*(3R, 3′R)-Di-tert-butyl 3-allyl-3′-(((tert-butyldimethylsilyl)oxy)-methyl)-2,2′-dioxo-[3,3′-biindoline]-1,1′-dicarboxylate (+)-**17**.* 15.6 mg (83% yields, 0.029 mmol scale) as colorless solid. R_f = 0.4 (10% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (t, J = 7.3 Hz, 2H), 7.19 (t, J = 8.3 Hz, 2H), 7.07−7.00 (m, 2H), 6.95−6.87 (m, 2H), 5.09−4.95 (m, 2H), 4.80−4.77 (m, 1H), 4.62 (d, J = 9.2 Hz, 1H), 4.48 (d, J = 9.3 Hz, 1H), 3.59 (dd, J = 5.4, 13.0 Hz, 1H), 2.90 (dd, J = 6.1, 13.0 Hz, 1H), 1.62 (s, 9H), 1.60 (s, 9H), 0.52 (s, 9H), −0.07 (s, 3H), −0.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.7, 175.3, 148.7, 148.5, 140.4, 139.3, 131.5, 128.7, 128.5, 126.7, 126.4, 124.0, 123.5, 123.4, 122.9, 119.9, 114.3, 114.0, 84.4, 84.0, 62.3, 58.8, 56.6, 34.1, 28.1, 25.3, 17.6, −5.7, −5.8; IR (film) υ_{max} 2911, 2900, 1703, 1641, 1601, 1379, 1211, 1001, 727 cm^{-1}; mp 69−71 °C; HRMS (ESI) m/z 671.3150 $[M+Na]^+$; calculated for $[C_{36}H_{48}N_2O_7Si + Na]^+$: 671.3123; $[\alpha]_{589}^{25.3}$= +173.7 (c = 0.12, MeOH).

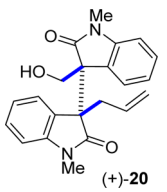
Synthetic Procedure and Characterization of (+)-19. In an oven-dried round-bottom flask, enantioenriched compound (+)-**17** (524 mg, 0.81 mmol; 1.0 equiv) was taken in dichloromethane (10 mL). To this solution was added trifluoroacetic acid (2 mL) at 0 °C and was stirred for 1 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, and the organic phase was extracted with dichloromethane. The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by flash chromatography using 50−75% EtOAc in hexane to afford product (+)-**19**.



(+)-**19**

*(3R,3′R)-3-Allyl-3′-(hydroxymethyl)-[3,3′-biindoline]-2,2′-dione (+)-**19**.* 215 mg (80% yields) as colorless solid. R_f = 0.45 (75% EtOAc in hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.54 (brs, 1H), 8.49 (brs, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 7.06 Hz, 1H), 7.02 (q, J = 8.3 Hz, 2H), 6.89 (t, J = 7.7 Hz, 2H), 6.62 (d, J = 7.2 Hz, 1H), 6.58 (d, J = 7.7 Hz, 1H), 5.10−5.09 (m, 2H), 4.82−4.77 (m, 2H), 4.06 (d, J = 11.6 Hz, 1H), 3.71 (dd, J = 5.7, 13.3 Hz, 1H), 2.97 (dd, J = 7.2, 13.3 Hz, 1H), 2.55 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 180.3, 178.3, 140.6, 140.2, 131.6, 128.7, 128.6, 128.4, 127.7, 124.6, 124.0, 122.7, 122.4, 119.6, 109.6, 109.5, 63.1, 57.1, 56.8, 34.6; IR (film) υ_{max} 3497 (br), 2956, 2921, 1732, 1701, 1635, 1601, 1483, 773 cm^{-1}; mp 200−201 °C; HRMS (ESI) m/z 335.1409 $[M+H]^+$; calculated for $[C_{20}H_{18}N_2O_3 + H]^+$: 335.1390; $[\alpha]_{589}^{24.1}$= +133 (c = 0.183, MeOH).

Synthetic Procedure and Characterization of (+)-20. In an oven-dried round-bottom flask, the compound (+)-**19** (205 mg, 0.61 mmol; 1.0 equiv) was taken in DMF (7 mL) under argon atmosphere and the reaction vessel was cooled to 0 °C. To this reaction mixture was added NaH (60 wt%, 54 mg, 1.35 mmol; 2.2 equiv) portionwise, and stirred for another 5 min. Then MeI (80 μL, 1.29 mmol; 2.1 equiv) was added to the reaction mixture at 0 °C and the mixture warmed to room temperature and stirring continued for another 30 min. The reaction was quenched with water; the organic phase was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with water and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography using 50% EtOAc in hexane giving product (+)-**20** and **21**.



(+)-**20**

*(3R,3′R)-3-Allyl-3′-(hydroxymethyl)-1,1′-dimethyl-[3,3′-biindoline]-2,2′-dione (+)-**20**.* 137 mg (62% yields) as colorless crystalline solid. R_f = 0.3 (50% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (d, J = 7.2 Hz, 1H), 7.07−7.00 (m, 3H), 6.86−6.82 (m, 2H), 6.46 (ABq, J = 16.2 Hz, 2H), 5.01−4.98 (m, 2H), 4.78−4.73 (m, 2H), 3.93−3.90 (m, 2H), 3.73−3.69 (m, 1H), 3.08 (s, 3H), 3.07 (s, 3H), 3.03−2.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.4, 175.8, 143.4, 143.2, 131.8, 128.6, 128.5, 127.8, 127.2, 124.1, 123.4, 122.4, 122.1, 119.3, 107.7, 107.7, 63.1, 56.9, 56.1, 34.1, 25.9, 25.8; IR (film)

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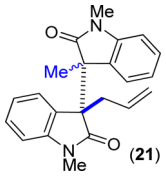
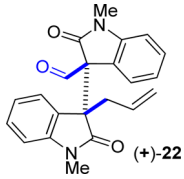
υ_{max} 3456 (br), 2998, 2900, 1699, 1610, 1480, 1369, 1259, 1106, 1047, 932 cm^{-1}; mp 194−196 °C; HRMS (ESI) *m/z* 363.1714 $[M+H]^+$; calculated for $[C_{22}H_{22}N_2O_3 + H]^+$: 363.1703; $[\alpha]_{589}^{23.1}$= +114 (*c* = 0.136, MeOH).



(21)

(R)-3-Allyl-1,1′,3′-trimethyl-[3,3′-biindoline]-2,2′-dione (***21***). 23 mg (11% yields) as yellow solid. R_f = 0.75 (50% EtOAc in hexane). ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.08−7.0 (m, 4H), 6.83 (td, *J* = 1.0, 7.6 Hz, 2H), 6.44 (ddt, *J* = 0.7, 7.8,16.5 Hz, 2H), 5.10−4.98 (m, 2H), 4.77−4.74 (m, 1H), 3.64−3.60 (m, 1H), 3.10 (s, 3H), 3.07 (m, 3H), 3.06−3.02 (m, 1H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 178.1,176.8, 143.4, 142.5, 132.6, 131.0, 128.2, 128.1, 128.1, 123.3, 122.9, 121.8, 121.6, 118.7, 107.4, 107.2, 55.5, 51.4, 33.3, 25.7, 25.6, 16.0; IR (film) υ_{max} 2997, 2971, 1700, 1679, 1479, 1126, 1003, 978 cm^{-1}; mp 182−184 °C; HRMS (ESI) *m/z* 369.1589 $[M+Na]^+$; calculated for $[C_{22}H_{22}N_2O_2 + Na]^+$: 369.1573.

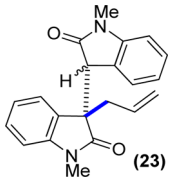
Synthetic Procedure and Characterization of (+)-22. Dess-Martin periodinane (116 mg, 0.274 mmol; 1.4 equiv) was added to a solution of primary alcohol (+)-**20** (71 mg, 0.195 mmol; 1.0 equiv) and CH_2Cl_2 (5 mL) at rt. After 1 h, the reaction mixture was poured into a mixture of CH_2Cl_2 (15 mL) and 10% aqueous $NaHSO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (5 mL), H_2O (10 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using 10% EtOAc in hexane to afford the title compounds (+)-**22**.



(+)-22

*(3R,3′R)-3′-Allyl-1,1′-dimethyl-2,2′-dioxo-[3,3′-biindoline]-3-carbaldehyde (+)-**22***. 53 mg (75% yields) as crystalline solid. R_f = 0.5 (30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) *δ*: 10.48 (s, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.12−7.04 (m, 3H), 6.86 (q, *J* = 7.9 Hz, 2H), 6.55−6.50 (m, 2H), 5.14−4.99 (m, 2H), 4.81 (dd, *J* = 2.3, 9.8 Hz, 1H), 3.88 (ABq, *J* = 13.7 Hz, 1H), 3.13 (d, *J* = 1.9 Hz, 6H), 3.02 (ABq, *J* = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 194.3, 176.4, 171.2, 143.6, 143.5, 131.1, 129.5, 128.9, 126.4, 124.3, 123.2, 122.9, 122.6, 122.4, 119.8, 108.3, 107.9, 65.3, 57.4, 35.0, 26.1, 25.9; IR (film) υ_{max} 2989, 2904, 1781, 1701, 1659, 1304, 1179, 1002, 769 cm^{-1}; mp 172−173 °C; HRMS (ESI) *m/z* 361.1560 $[M+H]^+$; calculated for $[C_{22}H_{20}N_2O_3 + H]^+$: 361.1547; $[\alpha]_{589}^{22}$= +141 (*c* = 0.107, MeOH).

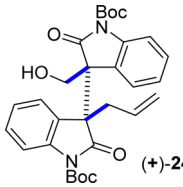
Synthetic Procedure and Characterization of (23). An oven-dried round-bottom flask was charged with the Wittig reagent (51 mg, 0.148 mmol, 1.3 equiv) and THF (2 mL) and cooled to 0 °C followed by addition of NaHMDS, 2(M) in THF (80 μL, 0.159 mmol, 1.4 equiv) dropwise. The resulting reddish brown solution was stirred at 0 °C for 30 min and then a solution of compound (+)-**22** (41 mg, 0.114 mmol, 1.0 equiv) in THF (2 mL) was added dropwise via syringe to the reaction vessel. The reaction mixture was stirred for another 2.5 h at 0 °C and quenched with 2N HCl (5 mL) at 0 °C. Stirring was continued for 1 h and then the reaction mixture was warmed to room temperature and neutralized by the addition of saturated $NaHCO_3$ (7 mL). The resulting mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography by silica gel using 20% EtOAc in hexane to give compound **23**.



(23)

(3S)-3-Allyl-1,1′-dimethyl-[3,3′-biindoline]-2,2′-dione (***23***). This compound was obtained as a colorless oil. R_f = 0.54 (one isomer) (30% EtOAc in hexane); ^1H NMR (500 MHz, $CDCl_3$, for one isomer) *δ* 7.10−7.05 (m, 3H), 7.04−7.02 (m, 1H), 6.85 (tb, *J* = 1.1, 7.60 Hz, 1H), 6.80 (tb, *J* = 1.1, 7.65 Hz, 1H), 6.59 (m, 2H), 5.35−5.27 (m, 1H), 5.07 (ddt, *J* = 1.2, 2.2, 17.0 Hz, 1H), 4.86 (ddd, *J* = 1.0, 2.1, 10.1 Hz, 1H), 3.91 (s, 1H), 3.64 (ddt, *J* = 1.1, 6.9, 13. Seven Hz, 1H), 3.17 (s, 3H), 3.16 (s, 3H), 3.05−3.01 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, for one isomer) *δ* 177.3,175.1,143.9, 143.5, 132.0, 128.3, 127.8, 124.7, 124.0, 122.9, 122.3, 122.0, 119.1, 107.7, 107.6, 54.7, 49.1, 37.8, 25.9, 25.9; IR (film) υ_{max} 3055, 2888, 1714, 1610, 1466, 1355, 1176, 1077, 992, 922, 745 cm^{-1}.

Synthetic Procedure and Characterization of (+)-24. To a solution of compound (+)-**17** (520 mg, 0.801 mmol; 1.0 equiv) in MeOH: CH_2Cl_2 (3:1) (15 mL), camphorsulfonic acid (37 mg, 0.16 mmol; 0.2 equiv) was added and stirred it for 15 h at room temperature. Upon completion of the reactions, (TLC showed complete consumption of starting material) the reaction mixture was directly evaporated and loaded onto silica gel and purified by flash chromatography using 20% EtOAc in hexane to afford desired product (+)-**24**.



(+)-24

*(3R,3′R)-Di-tert-butyl 3-allyl-3′-(hydroxymethyl)-2,2′-dioxo-[3,3′-biindoline]-1,1′-dicarboxylate (+)-**24***. 381 mg (89% yields) as white powder. R_f = 0.3 (30% EtOAc in hexane). ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.49 (d, *J* = 8.3 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.16−7.09 (m, 2H), 7.02−7.00 (m, 2H), 5.11−5.02 (m, 2H), 4.85 (ddd, *J* = 1.5, 3.4, 8.5 Hz, 1H), 4.76 (dd, *J* = 1.9, 11.1 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 3.58−3.54 (m, 1H), 3.01−2.97 (m, 1H), 1.66 (s, 9H), 1.65 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 176.0, 175.0, 148.4, 148.3, 140.1, 139.3, 131.2, 129.3, 129.0, 125.8, 125.2, 123.9, 123.9, 123.5, 123.4, 120.2, 114.6, 114.4, 84.6, 84.5, 62.0, 58.2, 57.3, 33.9, 28.1, 28.1; IR (film) υ_{max} 3591 (br), 2995, 1635, 1497, 1153, 925 cm^{-1}; mp 137−139 °C; HRMS (ESI) *m/z* 557.2281 $[M+Na]^+$; calculated for $[C_{30}H_{34}N_2O_7 + Na]^+$: 557.2258; $[\alpha]_{589}^{24.3}$= +228.9 (*c* = 0.103, MeOH).

Synthetic Procedure and Characterization of (25). Dess-Martin periodinane (222 mg, 0.52 mmol; 1.4 equiv) was added to a solution of primary alcohol (+)-**24** (200 mg, 0.37 mmol; 1.0 equiv) and CH_2Cl_2 (7 mL) at rt. After 1 h, the reaction mixture was poured into a mixture of CH_2Cl_2 (20 mL) and 10% aqueous NaHSO3 (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (10 mL), H_2O (20 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using 5% EtOAc in hexane to afford the title compounds **25**.

(3S)-Di-tert-butyl 3-allyl-2,2′-dioxo-[3,3′-biindoline]-1,1′-dicarboxylate (***25***). 162 mg (87% yields) as colorless gel. R_f = 0.55 (10% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$, spectrum contains ∼1:1 diastereomers) *δ*: 7.77 (t, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.33−7.24 (m, 2H), 7.17−7.14 (m, 2H), 7.10−6.94 (m, 5H), 6.91−6.86 (m, 2H), 6.57 (d, *J* = 7.3 Hz, 1H), 5.45−5.29 (m, 2H), 5.05 (t, *J* = 18.2 Hz, 2H), 4.96−4.89 (m,

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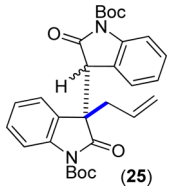
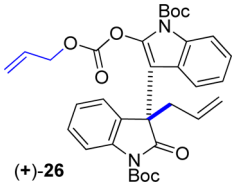


(25)

2H), 4.03 (s, 1H), 3.97 (s, 1H), 3.46 (ABq, J = 13.8 Hz, 1H), 3.06−2.99 (m, 2H), 2.97−2.92 (m, 1H), 1.63 (s, 9H), 1.62 (s, 9H), 1.56 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, spectrum contains ∼1:1 diastereomers) δ: 175.9, 175.4, 173.2, 171.8, 148.9, 148.7, 148.6, 141.2, 140.5, 139.9, 139.6, 131.2, 130.8, 129.2, 129.0, 128.9, 127.2, 126.1, 125.0, 124.3, 124.2, 124.0, 123.9, 123.8, 123.4, 123.0, 122.9, 122.7, 120.4, 120.1, 115.4, 115.3, 114.7, 114.5, 84.5, 84.5, 84.1, 84.0, 56.0, 55.1, 51.4, 50.6, 39.9, 38.3, 28.1, 28.0, 27.9; IR (film) υ_{max} 2976, 2930, 1774, 1741, 1616, 1469, 1346, 1296, 1258, 1160, 1099, 927, 840, 754 cm^{-1}; HRMS (ESI) m/z 527.2141 [M+Na]$^+$; calculated for [$C_{29}H_{32}N_2O_6$ + Na]$^+$: 527.2153.

Synthetic Procedure and Characterization of (+)-26.[7a] An oven-dried round-bottom flask was charged with compound **25** (138 mg, 0.27 mmol; 1.0 equiv) in dry THF (5 mL) under nitrogen atmosphere at 0 °C. Then triethyl amine (114 μL; 0.82 mmol; 3.0 equiv) was added to the solution. After 5 min of stirring allyl chloroformate (38 μL; 0.33 mmol; 1.2 equiv) was added dropwise over a period of 2 min at 0 °C and stirring was continued for 30 min. Upon completion of the reaction (judged by TLC analysis) diluted with EtOAc (15 mL) and quenched with H_2O. The whole reaction mixture was taken in a separatory funnel to separate the organic layer. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography using 10% EtOAc and hexane mixture as eluent to afford the desired product (+)-**26**.

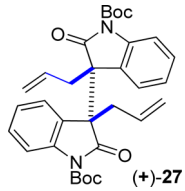


(+)-26

*(R)- tert-Butyl 3-(3-allyl-1-(tert-butoxycarbonyl)-2-oxoindolin-3-yl)-2-(((allyloxy)carbonyl)oxy)-1H-indole-1-carboxylate (+)-**26**.*[7a] 133 mg (84% yields) as colorless gel. R_f = 0.3 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.30 (td, J = 1.2, 8.6 Hz, 1H), 7.24−7.18 (m, 2H), 7.10 (d, J = 7.5 Hz, 1H), 7.07−7.05 (m, 2H), 5.98−5.88 (m, 1H), 5.45−5.35 (m, 2H), 5.30 (d, J = 10.4 Hz, 1H), 5.03 (d, J = 17.0 Hz, 1H), 4.97 (d, J = 10.2 Hz, 1H), 4.66 (d, J = 3.8 Hz, 2H), 3.30−3.20 (m, 2H), 1.61 (s, 9H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.3, 149.3, 148.5, 139.5, 139.4, 132.1, 131.0, 130.7, 130.4, 128.6, 125.3, 124.7, 124.5, 124.4, 123.2, 120.4, 120.1, 119.8, 115.4, 114.9, 105.8, 84.9, 84.3, 70.1, 53.0, 40.9, 28.1, 28.1; IR (film) υ_{max} 2976, 1734, 1628, 1458, 1361, 1149, 1066, 932, 836 cm^{-1}; HRMS (ESI) m/z 611.2394 [M+Na]$^+$; calculated for [$C_{33}H_{36}N_2O_8$ + Na]$^+$: 611.2364; $[\alpha]_{589}^{24.1}$ = +61.8 (c = 0.088, MeOH).

Procedure for Pd(0)-Catalyzed Decarboxylative Allylation. In an oven-dried sealed tube, solvent (2 mL) was degassed by using nitrogen balloon at room temperature over a period of 10 min. $Pd_2(dba)_3$ (5 mol%) and 15 mol% of ligand were added to it and stirring was continued for 20 min to make the complex mixture. After that reaction mixture was cooled at −25 °C. Then, enantioenriched compound (+)-**26** was added to the complex solution and stirring was continued for specified time at same temperature. After complete consumption of starting material (monitored by TLC) the reaction mixture was concentrated and purified by column chromatography using 5% EtOAc in hexane to afford the desired enantioenriched compound (+)-**27**.

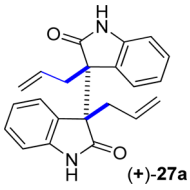
*(3R,3′R)-Di-tert-butyl 3,3′-diallyl-2,2′-dioxo-[3,3′-biindoline]-1,1′-dicarboxylate (+)-**27**.* 14.7 mg (88% yields, 0.027 mmol scale) as



(+)-27

colorless solid. R_f = 0.4 (10% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.04 (t, J = 8.2 Hz, 1H), 6.92 (t, J = 8.2 Hz, 1H), 5.1−4.98 (m, 2H), 4.81 (dd, J = 3.3, 9.5 Hz, 1H), 3.46 (dd, J = 5.9, 13.6 Hz, 1H), 3.05 (dd, J = 6.0, 13.0 Hz, 1H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.3, 148.5, 139.3, 131.7, 128.8, 126.3, 123.6, 123.6, 119.8, 114.2, 84.3, 57.1, 33.5, 28.1; IR (film) υ_{max} 2996, 2930, 1770, 1723, 1637, 1475, 1339, 1259, 1153, 1087, 605 cm^{-1}; mp 131−132 °C; HRMS (ESI) m/z 567.2444 [M+Na]$^+$; calculated for [$C_{32}H_{36}N_2O_6$ + Na]$^+$: 567.2466; $[\alpha]_{589}^{23.3}$= +232 (c = 0.152, MeOH).[7a]

Synthetic Procedure and Characterization of (+)-27a. In a solution of enantioenriched compound (+)-**27** (200 mg, 0.368 mmol; 1.0 equiv) in dichloromethane (5 mL), trifluoroacetic acid (1 mL) was added at 0 °C and was stirred for 2 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, and the organic phase was extracted with dichloromethane. The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude material was purified by flash chromatography using 10% EtOAc in hexane to furnish (+)-**27a**.



(+)-27a

*(3R,3′R)-3,3′-Diallyl-[3,3′-biindoline]-2,2′-dione (+)-**27a**.* 116 mg (92% yields) as colorless solid. R_f = 0.15 (20% EtOAc in hexane). ^{1}H NMR [500 MHz, CD_3CN:DMSO-d_6 (4:1)] δ: 9.90 (brs, 1H), 7.20 (d, J = 7.6 Hz, 1H), 6.99 (td, J = 1.1, 7.7 Hz, 1H), 6.84 (t, J = 7.6 Hz, 1H), 6.54 (d, J = 7.7 Hz, 1H), 5.13−5.05 (m, 2H), 4.96 (dd, J = 1.3, 17.0 Hz, 1H), 4.78 (dd, J = 2.3, 10.0 Hz, 1H), 3.58 (dd, J = 6.9, 13.3 Hz, 1H), 2.92 (dd, J = 7.4, 13.3 Hz, 1H); ^{13}C NMR [125 MHz, CD_3CN:DMSO-d_6 (4:1)] δ: 178.5, 141.9, 133.0, 129.1, 128.1, 124.1, 121.3, 118.2, 108.8, 55.4, 33.7; IR (film) υ_{max} 3218(br), 3081, 1704, 1698, 1619, 1470, 1336, 1232, 1284, 1108, 994, 919 cm^{-1}; mp 210−211 °C; HRMS (ESI) m/z 367.1433 [M+Na]$^+$; calculated for [$C_{22}H_{20}N_2O_2$ + Na]$^+$: 367.1417; $[\alpha]_{589}^{23.3}$ = +195 (c = 0.101, MeOH).

Synthetic Procedure and Characterization of (+)-28.[6d] In an oven-dried round-bottom flask, the compound (+)-**27a** (55 mg, 0.16 mmol; 1.0 equiv) was taken in DMF (3 mL) under argon atmosphere and the reaction vessel was cooled to 0 °C. To this reaction mixture was added NaH (60 wt%, 14 mg, 0.352 mmol; 2.2 equiv) portionwise, and stirred for another 5 min. Then MeI (21 μL, 0.336 mmol; 2.1 equiv) was added to the reaction mixture at 0 °C and the mixture warmed to room temperature and stirring continued for another 30 min. The reaction was quenched with water; the organic phase was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography using 10% EtOAc in hexane to afford product (+)-**28**.

*(3R,3′R)- 3,3′-Diallyl-1,1′-dimethyl-[3,3′-biindoline]-2,2′-dione (+)-**28**.* 55 mg (93% yields) as crystalline solid. R_f = 0.65 (20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.01 (d, J = 7.5 Hz, 1H), 6.97 (td, J = 1.0, 7.7 Hz, 1H), 6.79 (t, J = 7.5 Hz, 1H), 6.38 (d, J = 7.8 Hz, 1H), 5.05−4.92 (m, 2H), 4.73−4.70 (m, 1H), 3.61 (dd, J = 5.6, 12.8 Hz, 1H), 3.03 (s, 3H), 3.05−2.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.9, 143.3, 132.5, 128.2, 128.1, 123.4, 121.7, 118.8, 107.2, 55.9, 33.2, 25.6; IR (film) υ_{max} 2926, 2852, 1705, 1693,

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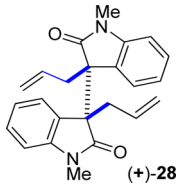
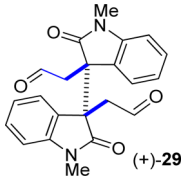


(+)-28

1610, 1374, 1354, 1124, 922, 759 cm^{-1}; HRMS (ESI) *m/z* 373.1924 $[M+H]^+$; calculated for $[C_{24}H_{24}N_2O_2 + H]^+$: 373.1911; mp 219−221 °C; $[\alpha]_{589}^{25.2}$ = +249 (*c* = 0.520, $CHCl_3$).[6d]

Synthetic Procedure and Characterization of (+)-29.[6d] To a stirred solution of compound (+)-**28** (45 mg, 0.121 mmol; 1.0 equiv) in CH_2Cl_2 (5 mL) at room temperature, *N*-methyl morpholine-*N*-oxide (66 mg, 0.605 mmol; 5.0 equiv) followed by catalytic OsO_4 (0.3 mL, 4% solution in water) were added to it. Then the reaction mixture was stirred for 5 h at room temperature. Upon completion of starting material (monitored by TLC), the reaction mixture was quenched with saturated Na_2SO_3 and extracted with CH_2Cl_2 (3 × 15 mL). The extracted organic layer was concentrated under reduced pressure. The crude material was directly dissolved in 10 mL THF:H_2O (2:1) mixture. To that reaction mixture, $NaIO_4$ (120 mg, 0.605 mmol; 5.0 equiv) was added at 0 °C and stirred for 1 h. The reaction mixture was diluted with EtOAc (10 mL) and water (5 mL) and organic layers were separated. The extracted organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid crude material was washed with ether (2 × 10 mL) and dried under reduced pressure. After removal of the solvent, the residue was purified by flash column chromatography using 30% EtOAc in hexane to afford (+)-**29**.



(+)-29

*2,2′-((3R,3′R)-1,1′-Dimethyl-2,2′-dioxo-[3,3′-biindoline]-3,3′-diyl)diacetaldehyde (+)-**29***. 43 mg (95% yields) as white crystalline solid. R_f = 0.4 (50% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 9.31 (d, *J* = 1.10 Hz, 2H), 7.02 (td, *J* = 7.76, 0.99 Hz, 2H), 6.92 (d, *J* = 7.11 Hz, 2H), 6.79 (d, *J* = 7.49 Hz, 2H), 6.41 (d, *J* = 7.80 Hz, 2H), 4.16 (dd, *J* = 17.73, 1.47 Hz, 2H), 3.27 (d, *J* = 17.74 Hz, 2H), 3.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 176.3, 143.6, 129.0, 126.2, 122.5, 121.8, 107.7, 51.5, 43.1, 25.9; IR (film) υ_{max} 3059, 2931, 1697, 1612, 1471, 1374, 1096, 755 cm^{-1}; HRMS (ESI) *m/z* 377.1514 $[M+H]^+$; calculated for $[C_{22}H_{20}N_2O_4 + H]^+$: 377.1496; mp 163−165 °C; $[\alpha]_{589}^{27.0}$ = +125 (*c* = 0 0.56, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02195.

Copies of ^1H, ^{13}C NMR spectra, and HRMS for all new compounds (PDF)

X-ray crystallographic data of compound **22** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) Dimeric 2-oxindole (similar to that of **7a**) with the *N*-methyl protecting group (**7e**) failed to afford product. This is probably due to the Boc protecting group in **7a** enhanced the acidity of the methine proton, thereby allowing the enolization of **7a** to be more facile (Figure 2).

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(14) A 2 step protocol with first step enantioselective and second diastereoselective process has been utilized in total synthesis. For reference, see ref 6b.
(15) A first methylation using MeI followed by a *retro*-aldol in presence of NaH could account for the formation of **21**.
(16) The reaction of Dess-Martin Periodinane probably affords an aldehyde, which then undergoes a deformylation reaction in the presence of AcOH produced in this reaction (MeCOOCHO as byproduct).
(17) A sequential allylation via DcA (decarboxylative allylation) afforded (+)-**27** in maximum of 3.3:1 dr from bis-carbonate substrate. For reference, see ref 7a.

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