JOC The Journal of Organic Chemistry

Article

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Synthesis of *S*-(−)-5,6-Dihydrocanthin-4-ones via a Triple Cooperative Catalysis-Mediated Domino Reaction

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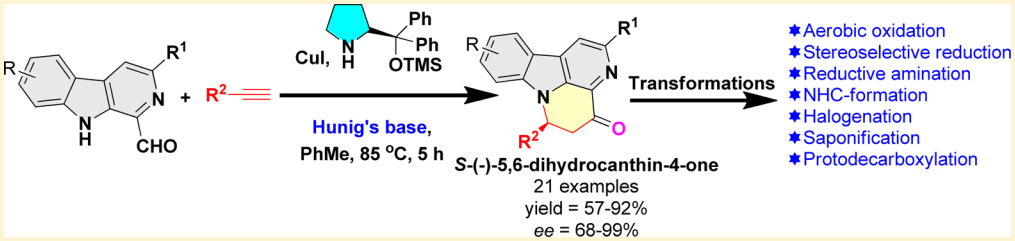
Supporting Information



ABSTRACT: An enantioselective synthesis of *S*-(−)-5,6-dihydrocanthin-4-ones via a triple cooperative catalysis-mediated domino reaction having a broad substrate scope is reported. The reaction between substituted 1-formyl-9*H*-*β*-carbolines and terminal alkynes in the presence of catalytic amounts of Jorgensen−Hayashi catalyst, copper iodide, and Hunig base proceeded via a multicascade route, affording the title compounds in good yields and excellent ees with interesting mechanistic features. These compounds were assessed for in vitro antiplasmodial activity against *P. falciparum* strains. Additionally, 5,6-dihydrocanthin-4-ones are demonstrated to be a versatile precursor to different fused *β*-carboline derivatives via simple synthetic transformations.

INTRODUCTION

The *β*-carboline core represents a privileged structural motif that is found in a number of natural products and compounds endowed with diverse biological activities.[1,2] Among them, the tetracyclic canthin-4-one group of alkaloids is represented by three natural analogues: viz., tuboflavine (5-ethylcanthin-4-one), isotuboflavine (R = methyl), and norisotuboflavine (R = H) (Figure 1).[3] Whereas significant antimicrobial activity is

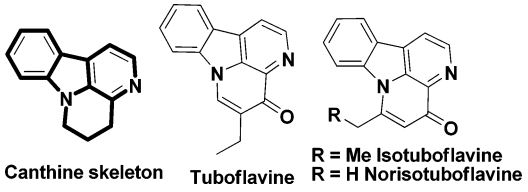


Figure 1. Canthin-4-one group of alkaloids.

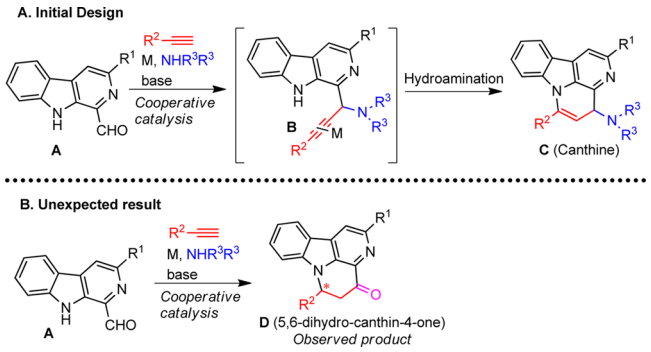
reported for the natural canthin-4-one and some of its derivatives,[4] the synthetic canthin-4-ones exhibit phosphodiesterase-inhibitory activity.[5] The canthin-4-one was also demonstrated to be precursor to fused *β*-carbolines, including the alkaloid annomontine and its synthetic analogue C-117, which were reported to display potent antimicrobial, anxiolytic, and antimalarial activities.[6] However, the chemistry of the parent scaffold remains underdeveloped, since most of the methods reported involve either multistep procedures or precursors which are not readily available. Bracher and co-workers demonstrated new alternative routes either via 1,3-diketones or from isoxazole derivatives, but these methods included only two or three examples, respectively.[7] Whereas the 1,3-diketone route failed for bulkier substitution, the isoxazole route required drastic conditions for the transformation. Therefore, a more practical and one-step route with options to introduce diversity for assessing the medicinal potential of this class is desired. One of the attractive options to approach this objective is via a domino reaction, the worthiness of which for generating architectural complexity present in natural products is widely known.[8] Several such cascade sequences are catalyzed by either a single chemical entity or multiple catalysts, though later a more powerful tool has emerged for achieving the synthesis of a variety of complex scaffolds.[9] In one of our research programs to study the synthetic applications of 1-formyl-9*H*-*β*-carboline for preparing fused *β*-carbolines,[10] we have reported a cascade approach to 3-aminoindolizino[8,7-*b*]indoles via copper-mediated A^3-coupling between N-substituted 1-formyl-9*H*-*β*-carbolines and terminal alkynes in the presence of a secondary amine.[11] Unfortunately, the reaction was unsuccessful with a substrate having a free NH group. Aiming to circumvent this

Received: March 30, 2016
Published: May 9, 2016

DOI: 10.1021/acs.joc.6b00613
J. Org. Chem. 2016, 81, 4751−4761

limitation and expand the scope, we reasoned that A^3-coupling of N-unsubstituted 1-formyl-9*H*-β-carboline **A** with terminal alkyne would furnish **B**, wherein the free NH under the influence of an additional base may trigger intramolecular cyclization, offering the canthine core **C** (Scheme 1). Working

Scheme 1. Initial Design of Experiment and Unexpected Results



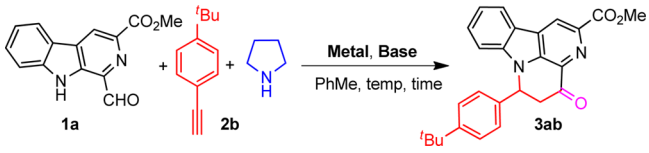
toward this goal, we fortuitously discovered that treating the substituted 1-formyl-9*H*-β-carbolines with terminal alkynes in the presence of three cooperative catalysts, viz. CuI, secondary amine, and DIEA (Hunig's base), resulted in the synthesis of diverse 5,6-dihydrocanthin-4-ones instead of the expected substituted canthines. This unique domino transformation allowed the development of a preparative and enantioselective route to useful 5,6-dihydrocanthin-4-ones, which were demonstrated to be apposite precursors to canthin-4-one analogues and other novel fused β-carbolines. In addition, the synthesized compounds were screened in vitro against *P. falciparum* to assess their antiplasmodial efficacy. The detailed results of this study are disclosed herein.

RESULTS AND DISCUSSION

Initially, in a pilot reaction methyl 1-formyl-9*H*-β-carboline ester (**1a**) was reacted with 1-(*tert*-butyl)-4-ethynylbenzene (**2b**) in the presence of CuI, morpholine, and Cs_2CO_3 at 90 °C using toluene as the medium. The reaction was completed in 12 h, affording a mixture of products from which the major component (15%) was established as 5,6-dihydrocanthin-4-one (**3ab**). Replacing morpholine with pyrrolidine in the reaction enhanced the yield of **3ab** to 32%. Spurred by this success and the possibility of achieving better yields of **3ab**, we considered optimizing the reaction conditions with respect to different bases and metal catalysts (Table 1). It was observed that, in comparison to the inorganic bases, the use of tertiary amines was more suited for the reaction (compare entries 2−4 with entries 5−7). Further, it was found that DIEA not only gave a better yield of **3ab** but also reduced the reaction time to 5 h (compare entry 7 with entries 5 and 6). Titrating the amount of DIEA made it apparent that 35% of the base is optimum for the success of this reaction (entry 11). Among the metal catalysts, CuI was found to be superior in comparison to all other catalysts investigated during the study. Thus, the optimized conditions for the reaction that worked best in our hands was **1a** (1.0 equiv) and **2b** (1.2 equiv) in the presence of CuI (10 mol %), pyrrolidine (20 mol %), and DIEA (35 mol %) in toluene at 85 °C for 5 h (94%, entry 11).

On the basis of preliminary results and our previous work,[11] a plausible mechanism for **3ab** is outlined in Scheme 2. Initially,

Table 1. Optimization of the Reaction Conditions[a] for the Synthesis of 3ab



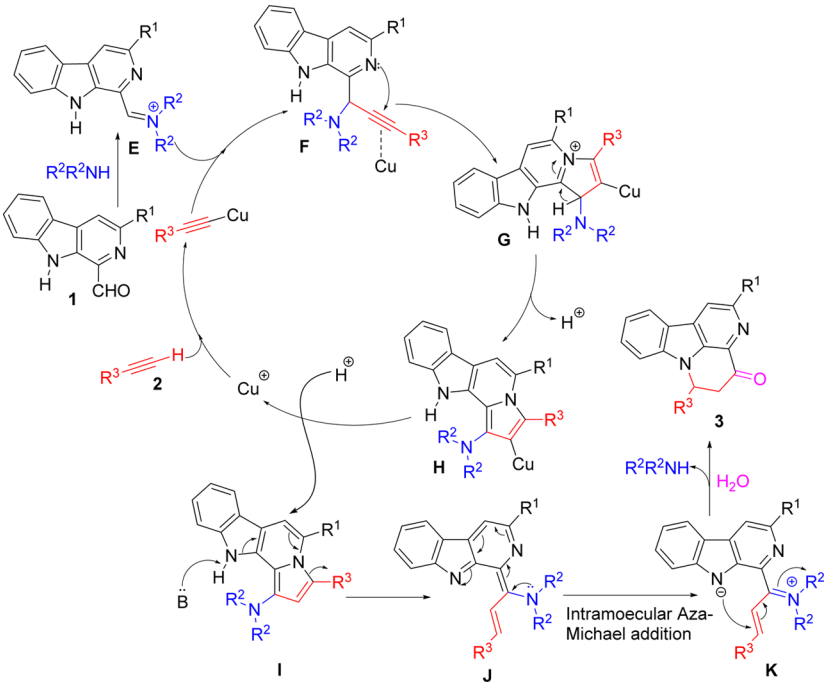
entry	base (amt (equiv))	catalyst (amt (mol %))	temp (°C)	time (h)	yield (%)[b]
1		CuI (10)	90	12	NR
2	Cs_2CO_3 (0.5)	CuI (10)	90	12	32
3	K_2CO_3 (0.5)	CuI (10)	90	12	40
4	Na_2CO_3 (0.5)	CuI (10)	90	12	26
5	DBU (0.5)	CuI (10)	90	12	62
6	TEA (0.5)	CuI (10)	90	12	74
7	DIEA (0.5)	CuI (10)	90	5	92
8	DIEA (0.4)	CuI (10)	90	5	92
9	DIEA (0.35)	CuI (10)	90	5	92
10	DIEA (0.3)	CuI (10)	90	5	86
11	**DIEA (0.35)**	**CuI (10)**	**85**	**5**	**94**
12	DIEA(0.35)	CuBr (10)	85	5	78
13	DIEA (0.35)	$CuBr_2$ (10)	85	5	65
14	DIEA (0.35)	CuCl (10)	85	5	53
15	DIEA (0.35)	Cu_2O (10)	85	5	15
16	DIEA (0.35)	$Cu(OAc)_2$ (10)	85	5	22
17	DIEA (0.35)	$AgBF_4$ (10)	85	5	45
18	DIEA (0.35)	$AuCl(PPh_3)$ (10)	85	5	62
19	DIEA (0.35)	$AuCl_3$ (10)	85	12	21
20	DIEA (0.35)	$AgNO_3$	85	12	34

[a]The reactions were performed using **1a** (0.1 g, 0.39 mmol), **2b** (86 μL, 0.47 mmol), and pyrrolidine (7.0 μL, 0.08 mmol) in PhMe (5.0 mL). [b]Isolated yields after purification. NR = no reaction.

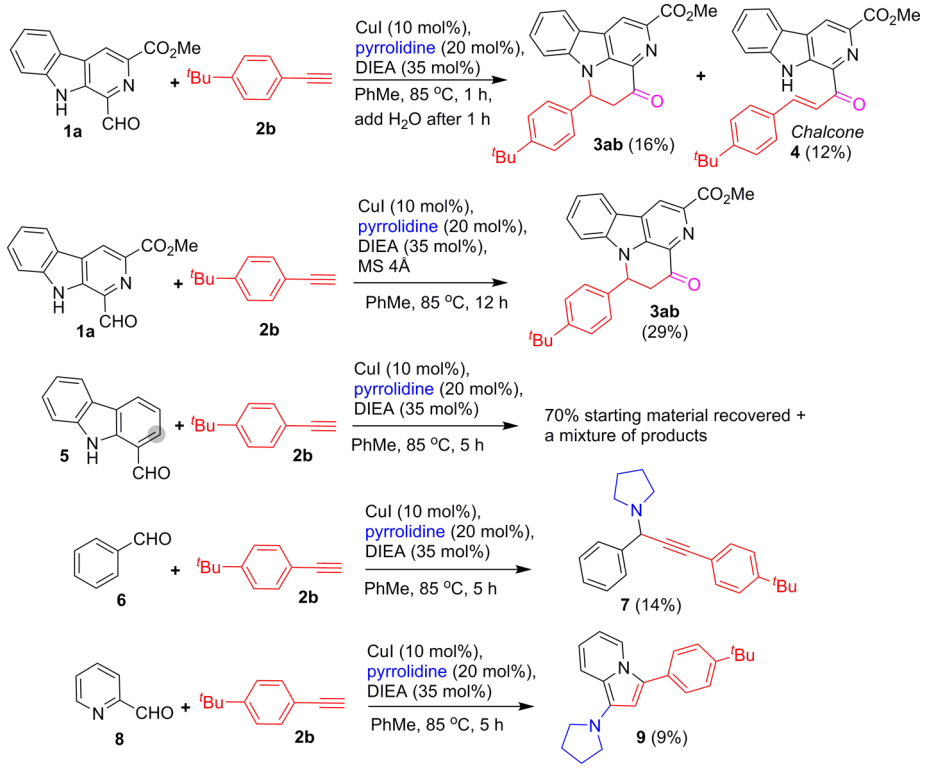
the aldehyde **1** reacts with pyrrolidine to form iminium ion **E**. Thereafter, in situ formed Cu-coordinated alkyne reacts with **E**, leading to the formation of propargylic amine **F**, wherein a nucleophilic attack of the pyridyl nitrogen on the Cu-coordinated allenyl double bond occurs, resulting in the formation of cationic intermediate **G**, which on protonolysis is converted to 3-aminoindolizino[8,7-*b*]indole **I**. Next, attack of the base on the NH of indole of intermediate **I** leads to fissure of the pyrrole ring, offering the intermediate **J**. The intermediate **J** undergoes an intramolecular aza-Michael reaction to afford **K**, which upon hydrolysis furnishes the product **3**. To ascertain the cleavage of the pyrrole subunit in **I** leading to **J**, in a control experiment the progress of the reaction among **1a**, **2a**, and pyrrolidine was arrested with water after 1 h, leading to isolation of chalcone **4** (12%) in addition to **3ab** and other materials (Scheme 3). Furthermore, to establish that the water released during the imine formation induces hydrolysis in the final step, in another control experiment molecular sieves were added to the reaction of **1a** and **2b**, which produced **3ab** in 29% yield in only 12 h. Additionally **1a** was heated with **2b**, pyrrolidine, and DIEA in dry toluene in the presence of $H_2{}^{18}O$ (97%) under inert conditions. On completion the reaction mixture was directly subjected to mass spectral analysis and displayed the presence of a mixture of ^{16}O-**3ab** (413 amu) and ^{18}O-**3ab** (415 amu), suggesting that the water released during the imine formation is used for the hydrolysis step (see the Supporting Information). To unequivocally ascertain the participation of the pyridyl nitrogen of β-carboline for the initial nucleophilic attack onto the triple

DOI: 10.1021/acs.joc.6b00613
J. Org. Chem. 2016, 81, 4751−4761

Scheme 2. Plausible Mechanism for the Formation of the Product



Scheme 3. Control Experiments

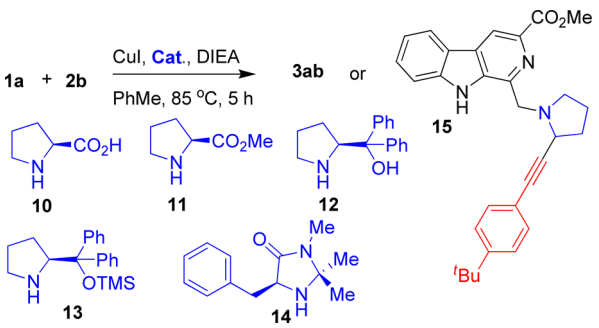


bond, we prepared the 9*H*-carbazole-1-carbaldehyde **5** and subjected it to reaction with **2b** under standard reaction conditions, but the starting material (70%) was recovered unreacted along with a mixture of products. Finally, to provide additional evidence for the formation of intermediates **F** and **I** in the proposed route, benzaldehyde (**6**) and 2-pyridinecarbaldehyde (**8**) were reacted with **2b** independently under the optimized conditions. Whereas benzaldehyde **6** afforded the propargylamine **7** (14%), 2-pyridinecarbaldehyde **8** gave the indolizine **9** (9%), corresponding to intermediates **F** and **I**, respectively.

The mechanistic insight into this practical and highly efficient route to 5,6-dihydrocanthin-4-one generated interest in studying the fate of the reaction in the presence of chiral amino catalysts.[12] Accordingly, the reaction of **1a** with **2b** was probed in the presence of chiral secondary amines **10**−**14** (Table 2).

DOI: 10.1021/acs.joc.6b00613
J. Org. Chem. 2016, 81, 4751−4761

Table 2. Optimization Study for the Enantioselective Synthesis of 5,6-Dihydrocanthin-4-one (3ab)



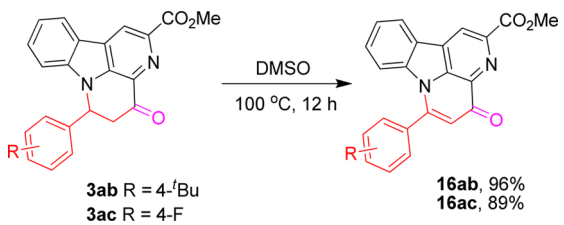
entry[a]	catalyst (20 mol %)	yield of **3ab** (%)[b]	ee (%)[c]	yield of **15** (%)[b]
1	**10**			36
2	**11**	90	40	
3	**12**	NR		
4	**13**	87	95	
5	**14**	NR		

[a]The reactions were carried out with **1a** (0.39 mmol), **2b** (0. mmol), CuI (0.04 mmol), and DIEA (0.14 mmol) in solvent (5.0 mL) for 5 h under N_2. [b]Isolated yields after column chromatography. [c]Calculated via HPLC on a ChiraDex column.

We were delighted to discover that the reaction was successful in the presence of Jorgensen−Hayashi catalyst (**13**)[13] to offer **3ab** in 87% yield with 95% ee. The reaction was also successful in the presence of methyl proline ester (**11**), but **3ab** was formed in only 40% ee. Unlike the reaction in the presence of proline, **10** afforded the product **15** (36%), while reactions were unsuccessful with diphenylprolinol **12** and the MacMillan catalyst **14**.[14] The yield of **15** was improved to 85% when the proline-mediated reaction was performed in the presence of 20 mol % of AcOH. The formation of **15** was attributed to the decarboxylative coupling of alkyne with proline **10**.[15]

Attempts to assign the absolute stereochemistry of **3ab** on the basis of X-ray analysis were unsuccessful. Although a single crystal of **3ab** was obtained from a solution of dimethyl sulfoxide (DMSO), X-ray analysis revealed it to be the oxidized product methyl 6-(4-(*tert*-butyl)phenyl)-4-oxo-4*H*-indolo-[3,2,1-*de*][1,5]naphthyridine-2-carboxylate (substituted canthin-4-one derivative **16ab**) (see the Supporting Information). Previously the oxidation of 5,6-dihydrocanthin-4-one to canthin-4-one was reported to be a two-step process via α-halogenation of ketone followed by dehalogenation.[16] We discovered that heating **3ab** in DMSO in air expedited the oxidation, offering **16ab** quantitatively. This oxidation was observed to be general, as exemplified by transformation of **3ac** to **16ac** under identical conditions (Scheme 4). Fortunately, however, on the basis of the CD spectral analysis of **3ab** the absolute stereochemistry was assigned as *S* (see the Supporting Information). The two possible transition states for the formation of the product is delineated in Figure 2, but as the *Si*-face attack is sterically less hindered, only the *S* enantiomer of **3** is formed.

Scheme 4. Oxidation of 5,6-Dihydrocanthin-4-one (3) into Canthin-4-one (16)



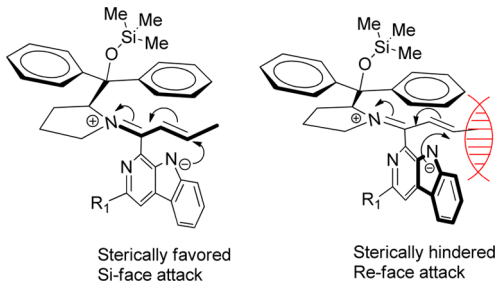


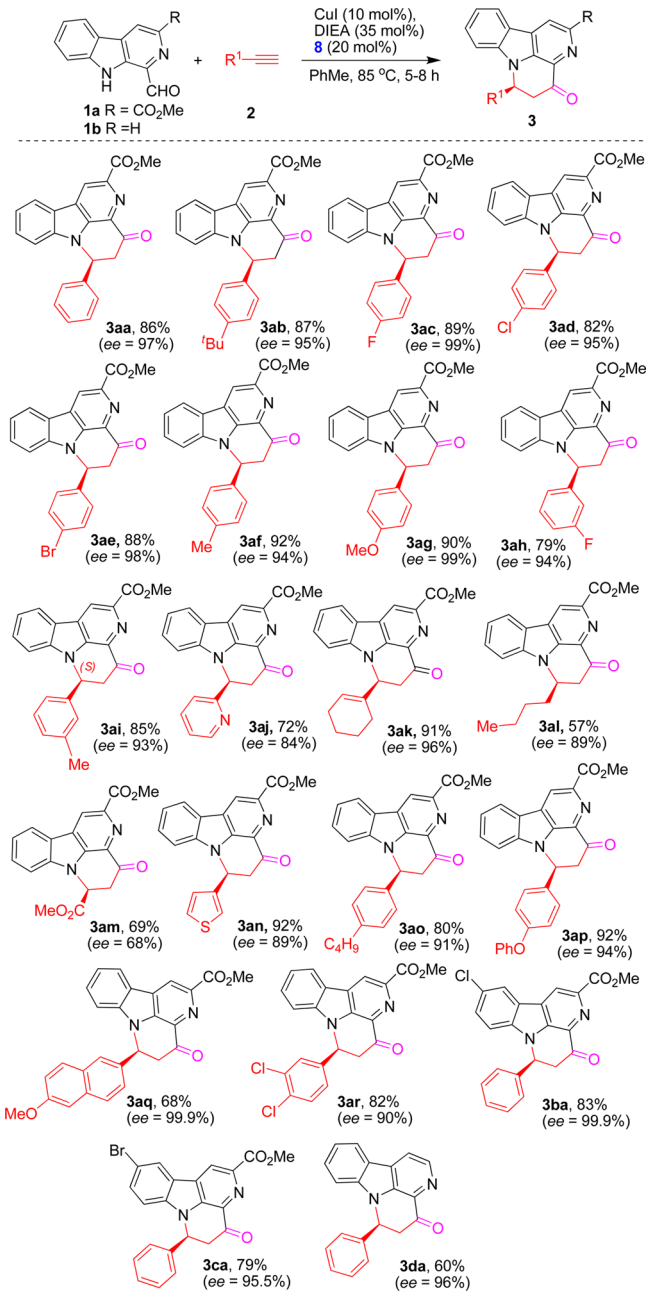
Figure 2. Two possible transition states for the formation of **3**.

Subsequently, we investigated the scope of the protocol with respect to β-carbolines and terminal alkynes, and the results are summarized in Scheme 5. In the first set of reactions methyl formyl-9*H*-β-carboline ester **1a** was treated with different terminal alkynes **2a−r**, and it was found that all reactions were successful, affording the respective products **3aa−3ar** in good yields with high ee. However, the product **3am**, originating from methyl propiolate (**2m**), was obtained in a moderate ee of only 68%. In a second set of reactions, changes were made to β-carboline **1**, and accordingly substrates **1b−d** were reacted with **2a** under the optimized conditions, leading to the synthesis of **3ba−3da**, respectively. The absolute configurations of all other products were assigned by analogy to that of compound **3ab**. Since the canthinone groups of alkaloids are reported to show antimalarial activity, we evaluated these compounds for in vitro antiplasmodial effects against chloroquine-sensitive 3D-7 and chloroquine-resistant K1 *P. falciparum* strain (see the Supporting Information). It was evident that no compound showed better activity than the standard drug chloroquine used in the bioassay.

Finally, we explored the utility of these compounds as starting materials for accessing differently substituted fused β-carbolines. In this context, first **3ab** was subjected to reduction with sodium borohydride to give **17** as a diastereomeric mixture (syn:anti 85:15) (Scheme 6). We were pleased to discover that a similar reduction in the presence of K-Selectride was diastereoselective, affording **17** as the syn isomer (ee = 66%) which was only ascertained via detailed NMR experiments (see the Supporting Information). Likewise, the reductive amination of (*S*)-**3aa** with 4-methoxyaniline in the presence of AcOH and sodium borohydride was diastereoselective to furnish **18** as the syn isomer only (ee = 54%). Recently, we have reported that β-carboline-fused N-heterocyclic carbenes (NHCs) display potent antitumor activity.[2c] In our objective to prepare new β-carboline-based NHCs, in a model experiment, **3ab** was treated with 4-(trifluoromethyl)aniline in the presence of ethanolic hydrochloric acid, which resulted in the formation of **19** in 98% yield. Aiming at accessing products with pharmacophores for further extension using some robust reactions, we performed the lithium hydroxide mediated hydrolysis of the ester group in **3ab** to give the acid **20**. On the other hand, brominating **3ab**,**ah**,**ao** with NBS in AcOH as the medium resulted in the corresponding dibromo derivatives **21ab**,**ah**,**ao**. Finally treating compound **3ab** with potassium

DOI: 10.1021/acs.joc.6b00613
J. Org. Chem. 2016, 81, 4751−4761

Scheme 5. Scope of the Protocol for the Enantioselective Synthesis of *S*-(−)-5,6-Dihydrocanthin-4-ones[a]



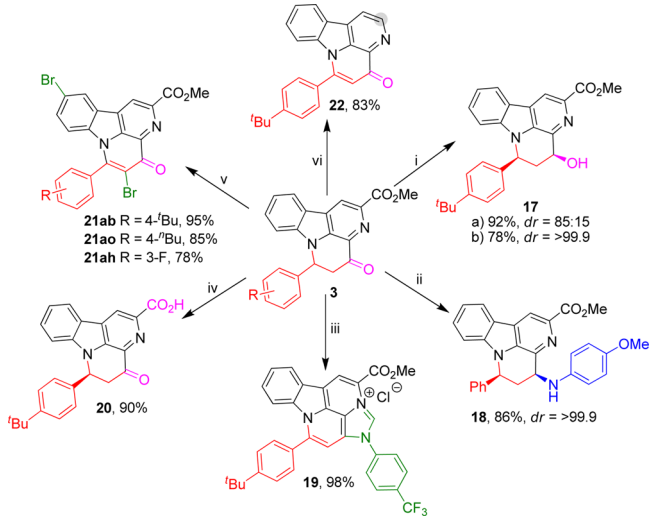
[a]All the reactions were carried out with **1** (0.39 mmol) and **2** (0.47 mmol) in PhMe (10 mL).

hydroxide in ethanol followed by treatment with silver carbonate in DMSO furnished **22** (83%) via protodecarboxylation.

CONCLUSIONS

In summary, we have disclosed an enantioselective route for obtaining diverse *S*-(−)-5,6-dihydrocanthin-4-ones from the reactions of 1-formyl-9*H*-*β*-carbolines with terminal alkynes via triple cooperative catalysis. This efficient multicascade protocol was found to be general over a broad range of substrates, and most of the products were isolated in good ee. The 5,6-dihydrocanthin-4-ones were found to be versatile starting materials for accessing canthin-4-ones and expanding to novel

Scheme 6. Synthetic Transformations of 5,6-Dihydrocanthin-4-one[a]



[a]Conditions: (i) reduction in the presence of (a) $NaBH_4$, EtOH, 0 °C, 2 h and (b) K-Selectride 1 M solution in THF, dry THF, −78 °C, 6 h, (ii) 4-methoxyaniline, AcOH, $NaBH_4$, dry CH_2Cl_2, 0 °C, 2 h, (iii) AcCl, HCHO, 4-(trifluoromethyl)aniline, EtOH (2.0 mL), room temperature, 12 h, (iv) LiOH, THF/H_2O, room temperature, 12 h, (v) NBS, AcOH, room temperature, 4 h, and (vi) KOH, Ag_2CO_3, DMSO, 110 °C, 12 h.

substituted fused *β*-carboline derivatives. The synthesis of libraries of these new *β*-carbolines for biological evaluation is underway and will be reported elsewhere.

EXPERIMENTAL SECTION

General Considerations. Unless otherwise noted, all reactions were assembled under a nitrogen atmosphere and were monitored by thin-layer chromatography (TLC). TLC was performed on precoated silica gel plates. After elution, plates were visualized under UV illumination at 254 nm for UV-active materials. Further visualization was achieved by staining with $KMnO_4$ or charring on a hot plate. The melting points were recorded on a hot-stage apparatus and are uncorrected. IR spectra were recorded using a FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on 300, 400, and 500 MHz spectrometers with $CDCl_3$ or DMSO-d_6 as solvent, using TMS as an internal standard (chemical shifts in δ). Peak multiplicities of ^1H NMR signals were designated as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet), etc. Coupling constants (J) are in Hz. The LC-ESI-MS were recorded on a triple-quadrupole (TQD) mass spectrometer, and the HRMS spectra were recorded as ESI-HRMS on a Q-TOF LC-MS/MS mass spectrometer. The optical rotations were measured on an automatic polarimeter at 25 °C. Column chromatography was performed using silica gel having particle size 100−200 mesh. Analytical grade solvents for the column chromatography were used as received. Commercial grade reagents and solvents were used without further purification. The enantiomeric excesses (ees) were determined by HPLC analysis employing a ChiraDex column, by comparing the samples with the appropriate racemic mixtures. Diastereomeric ratios were determined by ^1H NMR analysis of crude reaction mixtures.

General Procedure for the Synthesis of *S*-(−)-5,6-Dihydrocanthin-4-ones 3 As Exemplified by 3ab. In a reaction vessel containing 10 mL of toluene were placed **1a** (0.1 g, 0.39 mmol), **8** (0.05 M solution in toluene, 16 μL, 0.08 mmol), **2b** (86 μL, 0.47 mmol), CuI (7.0 mg, 0.04 mmol), and DIEA (24 μL, 0.14 mmol) at room temperature under a nitrogen atmosphere. The resulting solution was stirred at 85 °C for 5 h. On completion, the excess

DOI: 10.1021/acs.joc.6b00613
J. Org. Chem. 2016, 81, 4751−4761

solvent was removed and the residue was directly subjected to column chromatography on silica gel using hexanes/EtOAc (60/40, v/v) as eluent to obtain 0.141 g (87%) pure *S*-(−)-**3ab** as a yellow solid. (*S*)-Methyl 6-(4-*tert*-butylphenyl)-4-oxo-5,6-dihydro-4*H*-indolo[3,2,1-*de*]-[1.5]naphthyridine-2-carboxylate (**3ab**): mp 171−173 °C; $[\alpha]^{25}_{D}$ = −19.2 (*c* = 1.0, $CHCl_3$); R_f = 0.52 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1219, 1409, 1540, 1625, 1690, 1753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (s, 9H), 3.52 (dd, J_1 = 4.4 Hz, J_2 = 16.4 Hz, 1H), 3.46 (dd, J_1 = 6.5 Hz, J_2 = 16.6 Hz, 1H), 4.07 (s, 3H), 6.02 (m, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 7.9 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 9.05 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.4, 34.8, 47.7, 53.1, 57.6, 111.8, 121.6, 122.1, 122.4, 123.4, 125.7, 126.5, 130.3, 130.5, 133.7, 135.5, 139.6, 141.8, 142.2, 152.2, 166.7, 190.2. MS (ESI +): *m*/*z* 412.1. ESI-HR-MS: calculated for $C_{26}H_{24}N_2O_3$ (M^+ + H) 412.1787, found 412.1785. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 6.11 and 6.77 min.

General Procedure for the Synthesis of Racemic 5,6-Dihydrocanthin-4-ones As Exemplified by the Synthesis of 3ab. In a reaction vessel charged with 10 mL of dry toluene under a nitrogen atmosphere were placed **1a** (0.1 g, 0.39 mmol), pyrrolidine (7.0 μL, 0.08 mmol), 4-*tert*-butylphenylacetylene (**2b**; 86 μL, 0.47 mmol), CuI (7.0 mg, 0.04 mmol), and DIEA (24 μL, 0.14 mmol). The reaction mixture was further purged with nitrogen for 5.0 min to deoxygenate it completely. Thereafter the resulting solution was heated with stirring at 85 °C for 5 h. On completion, the reaction mixture was cooled to room temperature and directly subjected to silica gel column chromatography (hexanes/EtOAc, 60/40, v/v) to obtain pure **3ab** as a yellow solid (152 mg, 94%). *The same protocol was applied for the synthesis of other analogues of racemic 5,6-dihydrocanthin-4-ones* **3**.

*(S)-Methyl 4-Oxo-6-phenyl-5,6-dihydro-4H-indolo[3,2,1-de][1,5]-naphthyridine-2-carboxylate (**3aa**).* Yield: 86% (0.12 g from 0.1 g); yellow solid, mp 163−165 °C; $[\alpha]^{25}_{D}$ = −16.6 (*c* = 1.0, $CHCl_3$); R_f = 0.58 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1217, 1520, 1690, 1734, 2850 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.48 (dd, J_1 = 4.8 Hz, J_2 = 16.5 Hz, 1H), 3.73 (dd, J_1 = 6.8 Hz, J_2 = 16.5 Hz, 1H), 4.07 (s, 3H), 6.04 (t, *J* = 5.2 Hz, 1H), 7.02 (t, *J* = 5.4 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 7.26−7.29 (m, 3H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 8.22 (d, *J* = 7.7 Hz, 1H), 9.06 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 47.6, 52.9, 57.9, 111.7, 121.4, 122.0, 122.2, 123.2, 125.9, 129.0, 129.5, 130.2, 130.3, 133.3, 138.5, 139.3, 141.6, 142.0, 166.4, 189.9. MS (ESI+): *m*/*z* 357.1. ESI-HR-MS: calculated for $C_{22}H_{16}N_2O_3$ (M^+ + H) 357.1239, found 357.1241. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 6.25 and 7.40 min.

*(S)-Methyl 6-(4-Fluorophenyl)-4-oxo-5,6-dihydro-4H-indolo-[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3ac**).* Yield: 89% (0.131 g from 0.1 g); yellow solid, mp 171−173 °C; $[\alpha]^{25}_{D}$ = −15.5 (*c* = 1.0, $CHCl_3$); R_f = 0.50 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 998, 1198, 1295, 1563, 1621, 1706, 1741, 2840 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.43 (dd, J_1 = 5.1 Hz, J_2 = 16.5 Hz, 1H), 3.72 (dd, J_1 = 6.8 Hz, J_2 = 16.5 Hz, 1H), 4.03 (s, 3H), 6.03 (t, *J* = 5.5 Hz, 1H), 6.95−7.04 (m, 4H), 7.12 (d, *J* = 8.1 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 8.26 (d, *J* = 7.9 Hz, 1H), 9.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.5, 52.9, 57.2, 111.5, 116.5 (d, *J* = 21.9 Hz), 121.4, 122.1, 122.3, 123.3, 127.6 (d, *J* = 8.3 Hz), 130.2, 130.3, 133.2, 134.3, (d, *J* = 3.1 Hz), 139.5, 141.4, 141.9, 162.8, (d, *J* = 249.3 Hz), 166.3, 189.6. MS (ESI+): *m*/*z* 375.1. ESI-HR-MS: calculated for $C_{22}H_{15}FN_2O_3$ (M^+ + H) 375.1145, found 375.1144. The product was analyzed by HPLC to determine the enantiomeric excess: 99.9% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 5.72 min.

*(S)-Methyl 6-(4-Chlorophenyl)-4-oxo-5,6-dihydro-4H-indolo-[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3ad**).* Yield: 82% (0.125 g from 0.1 g); yellow solid, mp 190−192 °C; $[\alpha]^{25}_{D}$ = −16.5 (*c* = 1.0, $CHCl_3$); R_f = 0.52 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1175, 1286, 1489, 1587, 1693, 1755, 2853 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.45−3.50 (m, 1H), 3.74−3.81 (m, 1H), 4.08 (s, 3H), 6.06 (bs, 1H), 6.71 (d, *J* = 9.1 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 7.01 (t, *J* = 8.1 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.37−7.47 (m, 2H), 7.61 (t, *J* = 7.9 Hz, 1H), 8.30 (d, *J* = 7.7 Hz, 1H), 9.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.3, 52.6, 58.6, 111.4, 117.8, 120.7, 122.3, 122.4, 126.1, 126.5, 128.4, 134.9, 136.0, 141.1, 143.8, 166.8, 189.1. MS (ESI +): *m*/*z* 391.1. ESI-HR-MS: calculated for $C_{22}H_{15}ClN_2O_3$ (M^+ + H) 391.0849, found 391.0851. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 6.21 and 7.62 min.

*(S)-Methyl 6-(4-Bromophenyl)-4-oxo-5,6-dihydro-4H-indolo-[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3ae**).* Yield: 88% (0.15 g from 0.1 g); yellow solid, mp 184−186 °C; $[\alpha]^{25}_{D}$ = −26.2 (*c* = 1.0, $CHCl_3$); R_f = 0.50 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1198, 1286, 1575, 1630, 1685, 1741, 3035 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.45 (dd, J_1 = 4.7 Hz, J_2 = 16.4 Hz, 1H), 3.75 (dd, J_1 = 6.8 Hz, J_2 = 16.4 Hz, 1H), 4.07 (s, 3H), 6.03 (dd, J_1 = 4.7 Hz, J_2 = 6.6 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 7.3 Hz, 1H), 7.42−7.46 (m, 3H), 7.57−7.62 (m, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 9.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 47.4, 53.1, 57.4, 111.6, 121.6, 122.3, 122.4, 123.1, 123.5, 127.6, 130.4, 130.5, 132.8, 133.4, 137.6, 139.8, 141.4, 142.0, 166.4, 189.4. MS (ESI+): *m*/*z* 435.2. ESI-HR-MS: calculated for $C_{22}H_{15}BrN_2O_3$ (M^+ + H) 435.0344, found 435.0341. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 5.83 and 6.79 min.

*(S)-Methyl 4-Oxo-6-p-tolyl-5,6-dihydro-4H-indolo[3,2,1-de][1,5]-naphthyridine-2-carboxylate (**3af**).* Yield: 92% (0.134 g from 0.1 g); yellow solid, mp 164−166 °C; $[\alpha]^{25}_{D}$ = −17.3 (*c* = 1.0, $CHCl_3$); R_f = 0.56 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1456, 1576, 1690, 1745, 2845 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H), 3.46 (dd, J_1 = 5.1 Hz, J_2 = 16.4 Hz, 1H), 3.69 (dd, J_1 = 6.6 Hz, J_2 = 16.4 Hz, 1H), 4.06 (s, 3H), 5.98 (t, *J* = 5.7 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 2H), 7.06−7.14 (m, 3H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 9.07 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 47.7, 52.9, 57.9, 111.9, 121.4, 121.9, 122.3, 123.2, 125.9, 130.1, 130.2, 130.4, 133.4, 135.6, 138.9, 139.3, 141.7, 142.1, 166.5, 190.1. MS (ESI+): *m*/*z* 371.2. ESI-HR-MS: calculated for $C_{23}H_{18}N_2O_3$ (M^+ + H) 371.1396, found 371.1397. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 6.62 and 8.28 min.

*(S)-Methyl 6-(4-Methoxyphenyl)-4-oxo-5,6-dihydro-4H-indolo-[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3ag**).* Yield: 90% (0.151 g from 0.1 g); yellow solid, mp 186−188 °C; $[\alpha]^{25}_{D}$ = −24.4 (*c* = 1.0, $CHCl_3$); R_f = 0.49 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1186, 1269, 1462, 1570, 1691, 1740, 2843 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.28 (dd, J_1 = 3.0 Hz, J_2 = 16.4 Hz, 1H), 3.51 (dd, J_1 = 6.1 Hz, J_2 = 16.4 Hz, 1H), 3.88 (s, 3H), 3.93 (s, 3H), 5.80 (t, *J* = 6.0 Hz, 1H), 6.75 (d, *J* = 6.0 Hz, 2H), 6.88−6.96 (m, 3H), 7.22 (t, *J* = 6.0 Hz, 1H), 7.36 (t, *J* = 6.0 Hz, 1H), 8.07 (d, *J* = 9.0 Hz, 1H), 8.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$): δ 52.7, 55.2, 57.4, 111.9, 121.6, 122.1, 123.4, 125.9, 129.6, 130.3, 130.5, 133.5, 135.7, 139.5, 141.7, 142.2, 144.1, 159.8, 166.4, 190.7. MS (ESI+): *m*/*z* 387.1. ESI-HR-MS: calculated for $C_{23}H_{18}N_2O_4$ (M^+ + H) 387.1345, found 387.1341. The product was analyzed by HPLC to determine the enantiomeric excess: 99.9% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 5.41 min.

*(S)-Methyl 6-(3-Fluorophenyl)-4-oxo-5,6-dihydro-4H-indolo-[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3ah**).* Yield: 79% (0.116g from 0.1 g); yellow solid, mp 152−154 °C; $[\alpha]^{25}_{D}$ = −12.7 (*c* = 1.0, $CHCl_3$); R_f = 0.51 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1198, 1565, 1630, 1702, 1752, 2896 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.48 (dd, J_1 = 4.4 Hz, J_2 = 16.4 Hz, 1H), 3.77 (dd, J_1 = 6.9 Hz, J_2 = 16.4 Hz, 1H), 4.08 (s, 3H), 6.07 (dd, J_1 = 6.8 Hz, J_2 = 16.4 Hz, 1H), 6.70−6.73 (m, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 6.99−7.04 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.24−7.29 (m, 1H), 7.44−7.48 (m, 1H), 7.58−7.63 (m, 1H), 8.31(d, *J* = 7.8 Hz, 1H), 9.08 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.5, 52.9, 57.3, 108.8 (d, *J* = 22.8 Hz), 112.4, 113.9 (d, *J* = 21.3 Hz), 116.9 (d, *J* = 2.9 Hz), 119.5, 121.3, 121.5, 122.1, 129.5, 130.6 (d, *J* = 9.8 Hz), 136.3 (d, *J* = 24.5 Hz),

DOI: 10.1021/acs.joc.6b00613
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137.8, 141.2, 163.4 (d, J = 246.0 Hz), 166.3, 188.9. MS (ESI+): m/z 375.1. ESI-HR-MS: calculated for $C_{22}H_{15}FN_2O_3$ (M^+ + H) 375.1145, found 375.1141. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 5.90 and 7.20 min.

*(S)-Methyl 4-Oxo-6-m-tolyl-5,6-dihydro-4H-indolo[3,2,1-de][1,5]-naphthyridine-2-carboxylate (**3ai**).* Yield: 85% (0.123 g from 0.1 g); a yellow solid, mp 148−150 °C; $[\alpha]^{25}_D$ = −18.6 (c = 1.0, $CHCl_3$); R_f = 0.55 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 989, 1289, 1456, 1630, 1698, 1734, 3012 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H), 3.45 (dd, J_1 = 4.8 Hz, J_2 = 16.4 Hz, 1H), 3.69 (dd, J_1 = 6.7 Hz, J_2 = 16.5 Hz, 1H), 4.05 (s, 3H), 5.97 (t, J = 5.5 Hz, 1H), 6.79 (d, J = 7.4 Hz, 1H), 6.87 (s, 1H), 7.09−7.16 (m, 3H), 7.39 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 5 7. Hz, 1H), 8.26 (d, J = 7.8 Hz, 1H), 9.03 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 47.5, 52.9, 57.9, 111.7, 121.4, 121.9, 122.2, 122.9, 123.1, 126.4, 129.3, 129.8, 130.1, 130.3, 133.3, 138.5, 139.3, 139.4, 141.6, 142.0, 166.4, 189.9. MS (ESI+): m/z 371.0. ESI-HR-MS: calculated for $C_{23}H_{18}N_2O_3$ (M^+ + H) 371.1396, found 371.1393. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 6.36 and 7.42 min.

*(S)-Methyl 4-Oxo-6-(pyridin-2-yl)-5,6-dihydro-4H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3aj**).* Yield: 72% (0.101 g from 0.1 g); yellow solid, mp 123−125 °C; $[\alpha]^{25}_D$ = −10.8 (c = 1.0, $CHCl_3$); R_f = 0.32 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1185, 1256, 1453, 1590, 1697, 1758, 2932 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.61 (d, J = 16.2 Hz, 1H), 3.76 (dd, J_1 = 7.1 Hz, J_2 = 15.9 Hz, 1H), 4.06 (s, 3H), 6.15 (d, J = 4.7 Hz, 1H), 6.83 (d, J = 7.4 Hz, 1H), 7.16 (d, J = 4.9 Hz, 1H), 7.42 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 6.6 Hz, 1H), 7.64 (t, J = 6.9 Hz, 1H), 8.27 (d, J = 7.6 Hz, 1H), 8.45 (s, 1H), 9.03 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.9, 53.1, 58.4, 111.1, 120.2, 121.4, 122.0, 122.0, 122.3, 123.4, 123.8, 130.1, 134.1, 137.4, 139.3, 141.2, 141.7, 150.5, 157.2, 166.7, 189.8. MS (ESI+): m/z 358.0. ESI-HR-MS: calculated for $C_{21}H_{15}N_3O_3$ (M^+ + H) 358.1192, found 358.1196. The product was analyzed by HPLC to determine the enantiomeric excess: 84% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 3.83 and 5.04 min.

*(S)-Methyl 6-Cyclohexenyl-4-oxo-5,6-dihydro-4H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3ak**).* Yield: 91% (0.128 g from 0.1 g); yellow solid, mp 140−142 °C; $[\alpha]^{25}_D$ = −45.1 (c = 1.0, $CHCl_3$); R_f = 0.53 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1269, 1456, 1586, 1694, 1736, 3241 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.47−1.54 (m, 4H), 1.86−1.95 (m, 4H), 3.33 (dd, J_1 = 3.3 Hz, J_2 = 16.5 Hz, 1H), 3.48−3.56 (m, 1H), 4.06 (s, 3H), 5.38 (dd, J_1 = 3.0 Hz, J_2 = 16.5 Hz, 1H), 5.52 (bs, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 8.27 (d, J = 7.9 Hz, 1H), 9.01 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 22.2, 24.2, 24.9, 44.5, 52.9, 60.1, 111.5, 121.4, 121.8, 122.1, 123.3, 126.5, 129.9, 130.1, 133.3, 134.9, 139.0, 141.7, 141.9, 166.6, 190.8. MS (ESI+): m/z 360.1. ESI-HR-MS: calculated for $C_{22}H_{20}N_2O_3$ (M^+ + H) 360.1474, found 360.1477. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 5.88 and 6.75 min.

*(R)-Methyl 6-Butyl-4-oxo-5,6-dihydro-4H-indolo[3,2,1-de][1,5]-naphthyridine-2-carboxylate (**3al**).* Yield: 57% (0.075 g from 0.1 g); yellow oil; $[\alpha]^{25}_D$ = −38.1 (c = 1.0, $CHCl_3$); R_f = 0.48 (hexanes/EtOAc, 5/5, v/v); IR (neat) ν_{max} 1261, 1483, 1572, 1692, 1739, 3865 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, J = 6.5 Hz, 3H), 1.21 (t, J = 6.7 Hz, 4H), 1.80−1.84 (m, 2H), 3.46−3.54 (m, 1H), 3.68−3.93 (m, 1H), 4.07 (s, 3H), 4.57−4.61 (m, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 8.29 (d, J = 8.2 Hz, 1H), 9.03 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 13.9, 22.5, 28.9, 31.6, 43.5, 52.9, 53.6, 110.7, 121.4, 121.7, 122.0, 122.1, 123.4, 130.0, 133.2, 138.9, 141.1, 166.6, 190.9. MS (ESI+): m/z 337.0. ESI-HR-MS: calculated for $C_{20}H_{20}N_2O_3$ (M^+ + H) 337.1552, found 337.1555. The product was analyzed by HPLC to determine the enantiomeric excess: 89% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 6.75 and 8.80 min.

*(S)-Dimethyl 4-Oxo-5,6-dihydro-4H-indolo[3,2,1-de][1,5]-naphthyridine-2,6-dicarboxylate (**3am**).* Yield: 59% (0.078 g from 0.1 g); brown oil; $[\alpha]^{25}_D$ = −23.3 (c = 1.0, $CHCl_3$); R_f = 0.61 (hexanes/EtOAc, 5/5, v/v); IR (Neat) ν_{max} 1560, 1620, 1686, 1730, 2854 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.81−3.87 (m, 1H), 3.92−3.95 (m, 4H), 4.12 (s, 3H), 6.22 (t, J = 5.7 Hz, 1H), 7.42−7.46 (m, 1H), 7.68 (t, J = 7.3 Hz, 2H), 8.25 (d, J = 7.6 Hz, 1H), 9.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.9, 52.3, 52.6, 52.8, 111.3, 120.9, 121.7, 122.2, 130.1, 132.3, 135.3, 141.4, 160.7, 166.1, 188.3. MS (ESI+): m/z 339.0. ESI-HR-MS: calculated for $C_{18}H_{14}N_2O_5$ (M^+ + H) 339.0981, found 339.0985. The product was analyzed by HPLC to determine the enantiomeric excess: 68% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 6.22 and 7.32 min.

*(S)-Methyl 4-Oxo-6-(thiophen-3-yl)-5,6-dihydro-4H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3an**).* Yield: 92% (0.131 g from 0.1 g); gray solid, mp 138−140 °C; $[\alpha]^{25}_D$ = −32.0 (c = 1.0, $CHCl_3$); R_f = 0.48 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1259, 1458, 1580, 1685, 1753, 3098 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.55 (dd, J_1 = 4.0 Hz, J_2 = 16.3 Hz, 1H), 3.72 (dd, J_1 = 6.4 Hz, J_2 = 16.3 Hz, 1H), 4.06 (s, 3H), 6.18 (d, J = 5.7 Hz, 1H), 6.85−6.92 (m, 2H), 7.25−7.28 (m, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 8.27 (t, J = 7.8 Hz, 1H), 9.03 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.5, 52.9, 53.4, 11.4, 121.4, 122.0, 122.2, 122.5, 123.3, 125.1, 127.9, 130.2, 130.5, 133.3, 139.2, 139.5, 141.4, 141.5, 166.4, 189.9. MS (ESI+): m/z 363.2. ESI-HR-MS: calculated for $C_{20}H_{14}N_2O_3S$ (M^+ + H) 363.0803, found 363.0807. The product was analyzed by HPLC to determine the enantiomeric excess: 89% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 5.80 and 6.89 min.

*(S)-Methyl 6-(4-Butylphenyl)-4-oxo-5,6-dihydro-4H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3ao**).* Yield: 80% (0.129 g from 0.1 g); yellow solid, mp 178−180 °C; $[\alpha]^{25}_D$ = −27.7 (c = 1.0, $CHCl_3$); R_f = 0.54 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1187, 1452, 1530, 1698, 1739, 2850 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, J = 7.3 Hz, 3H), 1.25−1.37 (m, 2H), 1.48 (m, 2H), 2.55 (t, J = 7.6 Hz, 2H), 3.49 (dd, J_1 = 4.7 Hz, J_2 = 16.4 Hz, 1H), 3.72 (dd, J_1 = 6.6 Hz, J_2 = 16.4 Hz, 1H), 4.08 (s, 3H), 6.02 (t, J = 5.5 Hz, 1H), 6.94 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 7.16 (d, J = 8.3 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H), 9.07 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.4, 33.5, 35.3, 47.7, 53.0, 57.8, 111.8, 121.5, 122.0, 122.3, 123.3, 125.9, 129.5, 130.2, 130.4, 133.5, 135.7, 139.4, 141.7, 142.1, 144.0, 166.6, 190.1. MS (ESI +): m/z 412.2. ESI-HR-MS: calculated for $C_{26}H_{24}N_2O_3$ (M^+ + H) 412.1787, found 412.1783. The product was analyzed by HPLC to determine the enantiomeric excess: 91% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 6.14 and 7.21 min.

*(S)-Methyl 4-Oxo-6-(4-phenoxyphenyl)-5,6-dihydro-4H-indolo-[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3ap**).* Yield: 92% (0.162 g from 0.1 g); yellow solid, mp 202−204 °C; $[\alpha]^{25}_D$ = −29.4 (c = 1.0, $CHCl_3$); R_f = 0.38 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 968, 1428, 1530, 1695, 1743, 2901 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.48 (dd, J_1 = 4.6 Hz, J_2 = 16.4 Hz, 1H), 3.73 (dd, J_1 = 6.6 Hz, J_2 = 16.4 Hz, 1H), 4.07 (s, 3H), 6.04 (t, J = 5.1 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.3 Hz, 4H), 7.11 (t, J = 7.3 Hz, 1H), 7.15 (d, J = 8.3 Hz, 1H), 7.26−7.34 (m, 2H), 7.43 (t, J = 7.5 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H), 9.05 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 47.8, 53.2, 57.5, 111.8, 119.3, 119.6, 121.7, 122.2, 122.5, 123.5, 124.1, 127.5, 130.1, 130.4, 130.6, 132.9, 139.6, 141.7, 142.1, 156.4, 158.3, 166.7, 190.1. MS (ESI+): m/z 449.1. ESI-HR-MS: calculated for $C_{28}H_{20}N_2O_4$ (M^+ + H) 449.1501, found 449.1503. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 5.75 and 6.53 min.

*(S)-Methyl 6-(6-Methoxynaphthalen-2-yl)-4-oxo-4H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3aq**).* Yield: 68% (0.116 g from 0.1 g); white solid, mp 198−200 °C; $[\alpha]^{25}_D$ = −22.2 (c = 1.0, $CHCl_3$); R_f = 0.34 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1247, 1458, 1590, 1697, 1757, 2821 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.56 (dd, J_1 = 5.1 Hz, J_2 = 16.5 Hz, 1H), 3.75 (dd, J_1 = 6.5 Hz, J_2 = 16.5 Hz, 1H), 3.89 (s, 3H), 4.07 (s, 3H), 6.14 (t, J = 5.5 Hz, 1H), 7.09−7.19 (m, 4H), 7.36−7.50 (m, 3H), 7.58 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 7.6 Hz, 1H), 9.04 (s, 1H). ^{13}C NMR

DOI: 10.1021/acs.joc.6b00613
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(100 MHz, $CDCl_3$): δ 47.6, 52.9, 55.4, 58.2, 105.7, 111.8, 119.7, 121.4, 121.9, 122.3, 123.1, 123.7, 125.1, 128.5, 128.6, 129.5, 130.1, 130.4, 133.3, 133.5, 134.6, 139.3, 141.7, 142.1, 158.3, 166.4, 189.9. MS (ESI +): *m/z* 411.1. ESI-HR-MS: calculated for $C_{27}H_{20}N_2O_4$ (M^+ + H): 437.1501, found 437.1505. The product was analyzed by HPLC to determine the enantiomeric excess: 87% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 4.83 and 8.25 min.

*(S)-Methyl 6-(3,4-Dichlorophenyl)-4-oxo-5,6-dihydro-4H-indolo-[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3ar**).* Yield: 82% (0.136 g from 0.1 g); a yellow solid, mp 191−193 °C; $[\alpha]^{25}_D$ = −20.4 (*c* = 1.0, $CHCl_3$); R_f = 0.49 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1123, 1298, 1465, 1583, 1696, 1756, 2932 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.40−3.46 (m, 1H), 3.78 (dd, J_1 = 7.2 Hz, J_2 = 16.4 Hz, 1H), 4.07 (s, 3H), 6.05, (bs, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.28−7.37 (m, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 8.29 (d, *J* = 7.6 Hz, 1H), 9.07 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 47.1, 53.1, 56.6, 111.3, 121.6, 122.2, 122.4, 123.4, 124.9, 127.9, 130.5, 131.4, 131.6, 133.1, 133.3, 133.8, 138.7, 139.6, 141.1, 141.8, 166.3, 189.2. MS (ESI+): *m/z* 425.1. ESI-HR-MS: calculated for $C_{22}H_{14}Cl_2N_2O_3$ (M^+ + H) 425.0460, found 425.0463. The product was analyzed by HPLC to determine the enantiomeric excess: 90% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 5.60 and 6.31 min.

*(S)-Methyl 10-Chloro-4-oxo-6-phenyl-5,6-dihydro-4H-indolo-[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3ba**).* Yield: 83% (0.112 g from 0.1 g); gray solid, mp 182−184 °C; $[\alpha]^{25}_D$ = −21.6 (*c* = 1.0, $CHCl_3$); R_f = 0.51 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1140, 1280, 1502, 1609, 1697, 1738, 3058 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.41 (dd, J_1 = 4.2 Hz, J_2 = 16.4 Hz, 1H), 3.66 (dd, J_1 = 6.6 Hz, J_2 = 16.8 Hz, 1H), 3.98 (s, 3H), 5.96 (t, *J* = 5.1 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.94−6.96 (m, 2H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.19−7.21 (m, 2H), 7.46 (d, *J* = 7.8 Hz, 1H), 8.18 (s, 1H) 8.97 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.6, 53.1, 57.9, 112.2, 121.6, 122.1, 123.3, 125.4, 125.9, 129.1, 129.6, 130.2, 130.4, 133.4, 138.5, 139.4, 141.6, 142.1, 168.4, 191.9. MS (ESI+): *m/z* 391.1. ESI-HR-MS: calculated for $C_{22}H_{15}ClN_2O_3$ (M^+ + H) 391.0849, found 391.0853. The product was analyzed by HPLC to determine the enantiomeric excess: 99.9% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 5.25 and 6.68 min.

*(S)-Methyl 10-Bromo-4-oxo-6-phenyl-5,6-dihydro-4H-indolo-[3,2,1-de][1,5]naphthyridine-2-carboxylate (**3ca**).* Yield: 79% (0.103 g from 0.1 g); brown solid, mp 168−170 °C; $[\alpha]^{25}_D$ = −18.8 (*c* = 1.0, $CHCl_3$); R_f = 0.52 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 986, 1158, 1458, 1632, 1685, 1741, 3256 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.51 (dd, J_1 = 4.1 Hz, J_2 = 16.3 Hz, 1H), 3.90 (dd, J_1 = 6.7 Hz, J_2 = 16.3 Hz, 1H), 4.07 (s, 3H), 6.07 (t, *J* = 5.6 Hz, 1H), 6.63 (d, *J* = 7.1 Hz, 1H), 7.14−7.21 (m, 5H), 7.91 (d, *J* = 1 7. Hz, 1H), 8.41 (d, *J* = 1.7 Hz, 1H), 9.04 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.6, 52.6, 53.6, 111.9, 116.2, 118.5, 119.8, 126.4, 128.5, 129.7, 130.0, 133.9, 135.3, 139.3, 145.9, 146.5, 147.1, 165.6, 188.8. MS (ESI+): *m/z* 435.2. ESI-HR-MS: calculated for $C_{22}H_{15}BrN_2O_3$ (M^+ + H) 435.0344, found 435.0341. The product was analyzed by HPLC to determine the enantiomeric excess: 95.5% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 4.17 and 5.21 min.

*(S)-6-Phenyl-5,6-Dihydro-4H-indolo[3,2,1-de][1,5]naphthyridin-4-one (**3da**).* Yield: 62% (0.091 g from 0.1 g); yellow solid, mp 134−136 °C; $[\alpha]^{25}_D$ = −41.1 (*c* = 1.0, $CHCl_3$); R_f = 0.59 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1158, 1469, 1596, 1640, 1689, 3025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.53 (dd, J_1 = 4.6 Hz, J_2 = 16.3 Hz, 1H), 3.77 (dd, J_1 = 6.6 Hz, J_2 = 16.3 Hz, 1H), 6.10 (t, *J* = 5.6 Hz, 1H), 7.24−7.28 (m, 1H), 7.44−7.47 (m, 2H), 7.51−7.54 (m, 3H), 8.07−8.11 (m, 2H), 8.23−8.26 (m, 2H), 8.53 (d, *J* = 4.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.7, 52.3, 110.9, 118.5, 120.8, 121.8, 128.1, 129.3, 131.2, 132.4, 138.1, 141.1, 187.6. MS (ESI+): *m/z* 299.2. ESI-HR-MS: calculated for $C_{20}H_{14}N_2O$ (M^+ + H) 299.1184, found 299.1187. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 6.05 and 7.46 min.

*(E)-Methyl 1-(3-(4-tert-Butylphenyl)acryloyl)-9H-pyrido[3,4-b]-indole-3-carboxylate (**4**).* Yield: 12% (0.019 g from 0.1 g); yellow solid, mp 207−209 °C; R_f = 0.53 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 968, 1189, 1389, 1621, 1696, 1701, 1756, 3265 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 9H), 4.12 (s, 3H), 7.45−7.47 (m, 3H), 7.65−7.67 (m, 2H), 7.81 (dd, J_1 = 2.7 Hz, J_2 = 7.6 Hz, 2H), 8.07 (d, *J* = 16.1 Hz, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 8.62 (d, *J* = 16.1 Hz, 1H), 9.06 (s, 1H), 10.74 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 30.1, 52.8, 112.4, 120.8, 121.2, 121.6, 122.1, 128.9, 129.1, 129.7, 130.7, 144.8, 193.7. MS (ESI+): *m/z* 413.1. ESI-HR-MS: calculated for $C_{26}H_{24}N_2O_3$ (M^+ + H) 413.1865, found 413.1861.

*1-(3-(4-tert-Butylphenyl)-1-phenylprop-2-ynyl)pyrrolidine (**7**).* Yield: 14% (0.125 g from 0.3 g); a colorless oil; R_f = 0.62 (Hexanes: EtOAc, 8:2, v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H), 1.71 (bs, 4H), 2.63 (bs, 4H), 4.85 (s, 1H), 7.17−7.25 (m, 5H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.52 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 23.4, 31.2, 34.8, 50.1, 59.1, 85.7, 87.3, 120.2, 125.3, 126.5, 127.3, 127.6, 128.3, 128.4, 131.6, 139.3, 151.4. MS (ESI+): *m/z* 318.1. ESI-HR-MS: calculated for $C_{23}H_{27}N$ (M^+ + H): 318.2222, found 318.2219.

*1-(3-(4-tert-Butylphenyl)-1-phenylprop-2-ynyl)pyrrolidine (**9**).* Yield: 9% (0.08 g from 0.3 g); light yellow oil; R_f = 0.62 (Hexanes: EtOAc, 8:2, v/v); ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H), 1.71 (bs, 4H), 2.63 (bs, 4H), 4.85 (s, 1H), 7.17−7.25 (m, 5H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.52 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5, 31.2, 31.4, 106.7, 110.2, 114.5, 118.5, 122.1, 125.1, 125.2, 125.8, 127.9, 128.7, 131.5, 136.9, 154.2. MS (ESI+): *m/z* 319.2. ESI-HR-MS: calculated for $C_{22}H_{26}N_2$ (M^+ + H) 319.2174, found 319.2177.

*Methyl 1-((2-((4-tert-Butylphenyl)ethynyl)pyrrolidin-1-yl)methyl)-9H-pyrido[3,4-b]indole-3-carboxylate (**15**).* Yield: 36% (0.065 g from 0.1 g); colorless oil; R_f = 0.31 (hexanes/EtOAc, 5/5, v/v); IR (Neat) ν_{max}: 689, 898, 1136, 1286, 1423, 1590, 1753, 2356, 3025 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 9H), 1.91(m, 2H), 2.16 (m, 1H), 2.31 (m, 1H), 2.56 (m, 1H), 2.93 (m, 1H), 3.78 (t, *J* = 6.9 Hz, 1H), 4.06 (s, 3H), 4.22 (d, *J* = 14.5 Hz, 1H), 4.83 (d, *J* = 14.5 Hz, 1H), 7.28−7.36 (m, 5H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 8.84 (s, 1H), 10.26 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.3, 34.7, 52.8, 116.3, 122.2, 122.4, 124.4, 125.6, 126.5, 126.8, 129.9, 130.6, 132.9, 136.5, 139.2, 141.5 (d, *J* = 44 Hz), 151.3, 166.2. MS (ESI+): *m/z* 466.3. ESI-HR-MS: calculated for $C_{30}H_{31}N_3O_2$ (M^+ + H) 466.2495, found 466.2491. The yield of compound **15** was improved to 85% by performing the identical reaction (on a 0.1 g scale) in the presence of 20 mol % of AcOH.

General Procedure for DMSO-Mediated Aerobic Oxidation of 3 As Exemplified by the Synthesis of 16ab. A solution of **3ab** (0.1 g, 0.24 mmol) in DMSO (4.0 mL) was heated at 100 °C with stirring in the presence of air for 12 h. After the reaction was complete (as determined by TLC), water was added to the reaction mixture, from which the crude product separated out as a solid. The crude product was passed through a small band of silica gel using hexanes/ethyl acetate (40/60, v/v) as the eluent to furnish 0.095 g (96%) of analytically pure **16ab** as a white solid. Methyl 6-(4-*tert*-butylphenyl)-4-oxo-4*H*-indolo[3,2,1-*de*][1.5]naphthyridine-2-carboxylate (**16ab**): mp 210−212 °C; R_f = 0.48 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 969, 1145, 1258, 1456, 1596, 1710, 1740, 3025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 9H), 4.12 (s, 3H), 6.56 (s, 1H), 6.57 (d, *J* = 8.5 Hz, 1H), 7.36−7.55 (m, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 8.21 (d, *J* = 7.4 Hz, 1H), 9.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.4, 35.2, 53.3, 115.2, 119.4, 119.8, 123.6, 124.9, 125.1, 126.2, 128.7, 129.6, 130.9, 134.9, 136.8, 137.8, 140.5, 145.2, 149.5, 1547, 166.2, 178.2. MS (ESI+): *m/z* 411.1. ESI-HR-MS: calculated for $C_{26}H_{22}N_2O_3$ (M^+ + H) 411.1709, found 411.1713.

*Methyl 6-(4-Fluorophenyl)-4-oxo-4H-indolo[3,2,1-de][1,5]-naphthyridine-2-carboxylate (**16ac**).* Yield: 89% (0.088 g from 0.1 g); yellow solid, mp 204−206 °C; R_f = 0.44 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1219, 1521, 1715, 1750, 3021, 3345 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 4.03 (s, 3H), 6.37 (s, 1H), 6.39 (s, 1H), 7.48−7.56 (m, 4H), 7.86 (dd, J_1 = 5.4 Hz, J_2 = 8.4 Hz, 2H), 8.57−8.59 (m, 1H), 9.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.2, 114.7, 116.6 (d, *J* = 21.8 Hz), 119.8 (d, *J* = 35.4), 123.7, 125.0, 125.1, 128.5, 130.9, 131.1, 134.9, 136.7, 140.2, 145.2, 148.1, 164.2 (d, *J* = 250.1), 165.9, 177.98. MS (ESI+): *m/z* 373.2. ESI-HR-MS: calculated for $C_{22}H_{13}FN_2O_3$ (M^+ + H) 373.0988, found 373.0992.

DOI: 10.1021/acs.joc.6b00613
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Typical Procedure for $NaBH_4$-Mediated Reduction of 3ab for the Synthesis of 17. To a stirred solution of **3ab** (0.1 g, 0.24 mmol) in EtOH (5.0 mL) was added $NaBH_4$ (10 mg, 0.24 mmol) at 0 °C, and the reaction was continued for 2 h. On completion (as determined by TLC), the solvent was removed under reduced pressure and thereafter water (10 mL) was added. The precipitated solid was filtered and dried to give **17** (0.092 g, 92%) as a white solid.

Typical Procedure for K-Selectride-Mediated Reduction of 3ab for the Synthesis of 17. To a stirred solution of **3ab** (0.1 g, 0.24 mmol) in dry THF (5.0 mL) was added a 1 M K-Selectride solution in THF (28 μL, 0.28 mmol) at −78 °C, and the reaction was continued for 6 h. On completion (as determined by TLC), the solvent was removed under reduced pressure and thereafter 10 mL of water was added. The precipitated solid was filtered and dried to afford **17** (0.078 g, 78%) as a white solid. (*4S,6S*)-methyl 6-(4-*tert*-butylphenyl)-4-hydroxy-5,6-dihydro-4*H*-indolo[3,2,1-*de*][1.5]-naphthyridine-2-carboxylate (**17**): mp 167−169 °C; $[\alpha]^{25}_{D}$ = +21.3 (*c* = 1.0, $CHCl_3$); R_f = 0.35 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 988, 1269, 1543, 1601, 1665, 1745, 2322, 3345 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H), 2.76 (m, 1H), 2.90 (m, 1H), 3.62 (bs, 1H), 4.05 (s, 3H), 5.36 (bs, 1H), 5.66 (dd, J_1 = 9.9 Hz, J_2 = 3.8 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.26−7.30 (m, 4H), 8.19 (d, *J* = 7.6 Hz, 1H), 8.85 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$-DMSO-d_6): δ 31.3, 34.7, 41.6, 52.7, 57.6, 65.9, 112.7, 117.5, 120.8, 122.3, 122.4, 126.1, 126.8, 128.4, 135.4, 135.8, 136.3, 141.2, 144.5, 151.8, 166.9. ESI-HR-MS: calculated for $C_{26}H_{26}N_2O_3$ (M^+ + H) 415.2022, found 415.2027. The product was analyzed by HPLC to determine the enantiomeric excess: 66% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 3.12 and 4.99 min. *The diastereomeric ratio in both cases was determined on the basis of ^1H NMR of the crude sample.*

Typical Procedure for Reductive Amination of 3aa for the Synthesis of 18. To a stirred solution of (*S*)-**3aa** (0.1 g, 0.28 mmol) and 4-methoxyaniline (0.041 g, 0.34 mmol) in dry CH_2Cl_2 (5.0 mL) was added AcOH (3.4 μL, 0.055 mmol) at room temperature, and the reaction was continued for 6 h (until formation of the imine was complete). Thereafter, $NaBH_4$ (11 mg, 0.28 mmol) was added at 0 °C and the reaction was continued for 2 h. On completion the solvent was removed under reduced pressure and the reaction mixture was quenched by adding aqueous saturated $NaHCO_3$; the separated solid was filtered out and dried to furnish **18** (0.111 g, 86%) as a brown solid. Methyl 4-(4-methoxyphenylamino)-6-phenyl-5,6-dihydro-4*H*-indolo[3,2,1-*de*][1.5]naphthyridine-2-carboxylate (**18**): $[\alpha]^{25}_{D}$ = +10.8 (*c* = 1.0, $CHCl_3$); mp 145−147 °C; R_f = 0.32 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1125, 1298, 1463, 1582, 1642, 1743, 2823, 3243 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.75−2.83 (m, 1H), 2.92−2.97 (m, 1H), 3.76 (s, 3H), 3.88 (bs, 1H), 4.07 (s, 3H), 5.39 (dd, J_1 = 4.8 Hz, J_2 = 8.3 Hz, 1H), 5.70 (dd, J_1 = 4.3 Hz, J_2 = 8.5 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.75−6.78 (m, 1H), 7.28−7.41 (m, 10H), 8.22 (d, *J* = 7.1 Hz, 1H), 8.87 (s, 1H);. ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.6, 52.9, 55.9, 57.3, 60.5, 111.6, 119.1, 119.4, 121.4, 122.1, 122.2, 123.2, 123.9, 127.3, 129.8, 130.2, 130.3, 132.7, 133.3, 139.4, 141.5, 141.9, 158.1, 166.4. MS (ESI+): *m*/*z* 464.1. ESI-HR-MS: calculated for $C_{29}H_{25}N_3O_3$ (M^+ + H) 464.1974, found 464.1979. The product was analyzed by HPLC to determine the enantiomeric excess: 54% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 3.38 and 4.01 min.

Typical Procedure for the Synthesis of N-Heterocyclic Carbene 19 from 3ab. In a round-bottom flask containing dry ethanol (5.0 mL) was placed acetyl chloride (25 μL, 0.36 mmol) at 0 °C with stirring. After 5 min formaldehyde (14 μL, 0.36 mmol) and 4-(trifluoromethyl)aniline (39 μL, 0.28 mmol) were added dropwise at the same temperature. The reaction was allowed to proceed further for 20 min, after which **3ab** (0.1 g, 0.24 mmol) was added with stirring. The reaction mixture was warmed to room temperature, and the reaction continued for 12 h. The separated solid in the reaction mixture was filtered and washed with ice-cold ethanol (2 mL) to give the analytically pure **19** (0.334 g, 98%) as a yellow solid. 7-(4-*tert*-Butylphenyl)-2-(methoxycarbonyl)-5-(4-(trifluoromethyl)phenyl)-5*H*-imidazo[4,5,1-*de*]indolo[3,2,1-*ij*][1.5]naphthyridin-3-ium chloride (**19**): mp 242−244 °C; R_f = 0.20 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 868, 1123, 1216, 1545, 1640, 1746, 2345, 2869, 3345 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.15 (s, 9H), 3.97 (s, 3H), 6.38 (d, *J* = 1.5 Hz, 1H), 6.73 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.45 (dt, J_1 = 0.6 Hz, J_2 = 7.6 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.65−7.69 (m, 1H), 8.61 (d, *J* = 7.9 Hz, 1H), 9.24 (s, 1H), 10.07 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 31.3, 34.7, 52.8, 116.3, 122.2, 122.4, 124.4, 125.6, 126.5, 126.8, 129.9, 130.6, 132.9, 136.5, 139.2, 141.5 (d, *J* = 44 Hz), 151.3, 166.2. MS (ESI+): *m*/*z* 567.1. ESI-HR-MS: calculated for $C_{34}H_{27}F_3N_3O_2$ (M^+ + H) 567.2134, found 567.2130.

Typical Procedure for Saponification of 3ab for the Synthesis of Acid 20. To a stirred solution of **3ab** (0.1 g, 0.24 mmol) in THF/H_2O, (1/1 v/v, 6.0 mL) was added LiOH (10 mg, 0.36 mmol) at room temperature, and the reaction was continued for 12 h. On completion, the reaction mixture was quenched by adding 1 N HCl to adjust the pH to 7.0. The resulting mixture was purified by silica gel column chromatography (hexanes/EtOAc, 4:6) to give **20** (0.086 g, 90%) as a yellow solid. 6-(4-*tert*-Butylphenyl)-4-oxo-5,6-dihydro-4*H*-indolo[3,2,1-*de*][1.5]naphthyridine-2-carboxylic acid (**20**): $[\alpha]^{25}_{D}$ = −17.2 (*c* = 1.0, $CHCl_3$); mp 224−226 °C; R_f = 0.24 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1498, 1563, 1698, 1776, 3219, 3314 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 9H), 3.51 (dd, J_1 = 4.4 Hz, J_2 = 16.3 Hz, 1H), 3.74 (dd, J_1 = 6.8 Hz, J_2 = 16.4 Hz, 1H), 6.05 (dd, J_1 = 4.6 Hz, J_2 = 6.5 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 8.1 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 9.07 (s, 1H), 11.94 (bs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 32.8, 35.9, 47.5, 57.4, 113.3, 121.4, 121.9, 122.2, 123.2, 125.4, 126.3, 130.1, 130.3, 133.4, 135.3, 139.3, 141.6, 141.9, 152.1, 169.7, 190.1. MS (ESI+): *m*/*z* 399.2. ESI-HR-MS: calculated for $C_{25}H_{22}N_2O_3$ (M^+ + H) 399.1709, found 399.1713. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (ChiraDex; MeCN/H_2O (95/5, v/v), flow rate 1.0 mL/min, λ 254 nm); t_r = 2.71 and 3.66 min.

General Procedure for NBS-Mediated Bromination of 3 As Exemplified by the Synthesis of 21ab. To a mixture of compound **3ab** (0.1 g, 0.24 mmol) and NBS (0.09 g, 0.51 mmol) was added 2 mL of AcOH wtih stirring, and the reaction mixture was allowed to continue at room temperature for 4 h. On completion, the reaction mixture was neutralized with an aqueous solution of $NaHCO_3$ and extracted with EtOAc (15 mL × 3). The solvent was removed in vacuo, and the residue was purified by silica gel using a hexane/ethyl acetate mixture (6/4) as eluent to afford **21ab** (0.131 g, 95%) as a yellow solid. Methyl 5,10-dibromo-6-(4-*tert*-butylphenyl)-4-oxo-4*H*-indolo[3,2,1-*de*][1.5]naphthyridine-2-carboxylate (**21ab**): mp 202−204 °C; R_f = 0.58 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 985, 1236, 1526, 1624, 1726, 2298, 3152 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (s, 9H), 4.17 (s, 3H), 7.02 (t, *J* = 8.1 Hz, 2H), 7.20−7.28 (m, 2H), 7.40−7.48 (m, 1H), 8.39 (s, 1H), 8.29 (d, *J* = 7.6 Hz, 2H), 9.07 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 33.3, 53.4, 116.2, 118.5, 119.8, 126.4, 128.4, 128.5, 129.7, 130.0, 130.1, 133.9, 143.2, 146.5, 147.6, 166.2, 173.9. MS (ESI+): *m*/*z* 567.2. ESI-HR-MS: calculated for $C_{26}H_{20}Br_2N_2O_3$ (M^+ + H) 566.9919, found 566.9921.

*Methyl 5,10-Dibromo-6-(4-butylphenyl)-4-oxo-4H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate (**21ao**).* Yield: 89% (0.122 g from 0.1 g); yellow solid, mp 195−197 °C; R_f = 0.56 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1284, 1472, 1582, 1623, 1721, 2350, 3014 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (t, *J* = 7.4 Hz, 3H), 1.48 (hex, *J* = 7.3 Hz, 2H), 1.77 (qu, *J* = 7.6 Hz, 2H), 2.84 (t, *J* = 7.6 Hz, 2H), 4.12 (s, 3H), 5.85 (d, *J* = 8.7 Hz, 1H), 7.41−7.53 (m, 5H), 8.30 (d, *J* = 1.4 Hz, 1H), 8.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.4, 33.4, 35.7, 53.4, 115.8, 116.2, 118.5, 119.8, 126.4, 128.5, 129.7, 130.0, 133.9, 135.3, 135.4, 139.3, 145.9, 146.5, 147.1, 165.6, 172.6. MS (ESI+): *m*/*z* 567.1. ESI-HR-MS: calculated for $C_{26}H_{20}Br_2N_2O_3$ (M^+ + H): 566.9919, found 566.9923.

*Methyl 5,10-Dibromo-6-(3-fluorophenyl)-4-oxo-4H-indolo[3,2,1-de][1,5]naphthyridine-2-carboxylate (**21ah**).* Yield: 78% (0.109 g from 0.1 g); yellow solid, mp 208−210 °C; R_f = 0.53 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1452, 1528, 1615, 1724, 2156, 2989 3058 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.02 (s, 3H), 5.76 (d, *J* = 8.3

DOI: 10.1021/acs.joc.6b00613
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Hz, 1H), 7.32−7.51 (m, 4H), 7.61−7.71 (m, 1H), 8.23 (s, 1H), 8.89 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 53.4, 116.2, 118.2, (d, J = 58.6 Hz), 119.8, 126.3 (d, J = 6.9 Hz), 128.5, 129.7, 130.0, 133.6, 133.9, 135.2 (d, J = 23.4 Hz), 139.3, 145.8, 146.5, 147.2, 165.5, 172.6, 177.4. MS (ESI+): m/z 529.1. ESI-HR-MS: calculated for $C_{22}H_{11}Br_2FN_2O_3$ (M^+ + H) 528.9199, found 528.9203.

Typical Procedure for Protodecarboxylation of 3ab for the Synthesis of 22. To a solution of **3ab** (0.1 g, 0.24 mmol) in isopropyl alcohol (5 mL) was added KOH (0.02 g, 0.36 mmol), and the mixture was heated at 70 °C for 3 h. The solvent was removed under reduced pressure, and the solid was filtered out and dried under vacuum to afford the corresponding potassium salt. The potassium salt was taken up in DMSO (5.0 mL), and to it was added Ag_2CO_3 (0.1 g, 0.36 mmol; the reaction mixture was heated at 110 °C for 12 h. Thereafter water (10 mL) was added followed by the addition of EtOAc (30 mL). The organic layer was separated, and the water layer was extracted with EtOAc (2 × 25 mL). The organic layers were pooled and dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain a residue which was purified by silica gel column chromatography (hexanes/EtOAc, 6/4) to give **22** (70 mg, 83%) as a yellow solid. (6-(4-*tert*-Butylphenyl)-4*H*-indolo[3,2,1-*de*][1.5]-naphthyridin-4-one (**22**): mp 138−140 °C; R_f = 0.46 (hexanes/EtOAc, 5/5, v/v); IR (KBr) ν_{max} 1258, 1453, 1652, 1714, 2850, 3018 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 9H), 6.36 (s, 1H), 7.32−7.38 (m, 1H), 7.55−7.64 (m, 4H), 8.07−8.18 (m, 2H), 8.29 (d, J = 7.6 Hz, 2H), 8.62 (t, J = 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.2, 35.1, 112.1, 113.9, 118.4, 120.7, 121.8, 125.1, 129.2, 131.2, 138.1, 141.1, 176.8. MS (ESI+): m/z 353.0. ESI-HR-MS: calculated for $C_{24}H_{20}N_2O$ (M^+ + H) 353.1654, found 353.1651.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00613.

Details of the X-ray crystallographic analysis of **16ab**, CD spectral data of **3ab**, ^{1}H and ^{13}C NMR and 2D NMR (**3ab**, **15**, and **17**) spectra, and HPLC chromatograms (PDF)

X-ray crystallographic data for **16ab** (CIF)

Additional structural data (ZIP)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.U.D. and R.M. gratefully acknowledge financial support from the Council of Scientific and Industrial Research, New Delhi, India, and University Grants Commission, New Delhi, India, respectively, in the form of a fellowship. The authors acknowledge the SAIF Division of CDRI for providing the spectroscopic data. The authors also acknowledge Dr. Pratik Sen, IIT Kanpur, for performing CD spectral studies toward determining the absolute stereochemistry. S.B. acknowledges financial grants from the Department of Science and Technology, New Delhi, India, and the Ministry of Earth Sciences, New Delhi, India, for the projects under which this work was carried out.

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