# Total Synthesis of (–)-Chanoclavine I and an Oxygen-Substituted Ergoline Derivative

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**Supporting Information** 

**ABSTRACT:** An efficient and direct route to ergot alkaloid (-)-chanoclavine I (3) is described using the inexpensive compound (2R)-(+)-phenyloxirane (15) as a chiral pool in 13 steps with 17% overall yield. Key features of the synthesis include a palladium-catalyzed intramolecular aminoalkynylation of terminal olefin and a rhodium-catalyzed intramolecular [3 + 2] annulation. An oxygen-substituted ergoline derivative (-)-25 was also achieved by using the same strategy.



# INTRODUCTION

Ergot alkaloids are a class of indole compounds biosynthetically derived from L-tryptophan. Most of the ergot alkaloids are isolated from various *Claviceps* species, although they can also be isolated from other fungi and higher plants.<sup>1</sup> Ergot alkaloids are popular among researchers because of their multimodal biological activities<sup>2–4</sup> and interesting molecular architectures, which present practical challenges in synthesis. The characteristic structural feature of all ergot alkaloids is the tetracyclic ergoline skeleton (see 1, Figure 1).<sup>5</sup> The 3,4-fused tricyclic indole skeleton is a key feature of all ergot alkaloids, including lysergic acid (2), chanoclavine I (3), cycloclavine (4), agroclavine (5), pergolide (6), etc. Nearly all ergot alkaloids are derived from a common biosynthetic intermediate chanoclavine I (3), and the structural diversity within the ergot alkaloids results from the elaborate chemical derivatiza-



Figure 1. Structures of several typical ergot alkaloids.

tion of this intermediate.<sup>6</sup> Developing a more efficient total synthesis strategy in obtaining chanoclavine I (3) has potential in simplifying the process of ergot alkaloid biosynthesis and chemical synthesis study.

The common strategy in synthesizing ergot alkaloids typically begins with a preformed indole; our search team<sup>7</sup> has successfully formal synthesized  $(\pm)$ -cycloclavine (4) using this indole-derived method. Several transformations were needed because of the low reactivity at the 4-position of indole core. Therefore, a later stage indole synthesis provided an alternative to accomplish natural products possessing 3,4-fused indole skeleton in a more concise manner. Over the past decade, improvements toward a more efficient and direct formation of iodole and its derivatives have been made, and new methodologies have been successfully applied into total synthesis.<sup>8</sup> In 2006, Funk<sup>9</sup> reported a  $6\pi$  electrocyclic reactions strategy to construct the skeleton of dragmacidin E. In 2009 and 2017, Wipf<sup>10,11</sup> reported an intramolecular Diels-Alder reaction of furan to furnish total synthesis of  $(\pm)$ -cycloclavine and (-)-cycloclavine. In 2011, Jia<sup>12</sup> reported the total synthesis of (+)-lysergic acid by using the intramolecular Larock indolization process. In 2016, Cho<sup>13</sup> reported intramolecular Fisher indole synthesis and subsequent Claisen rearrangement that resulted in total synthesis of (-)-aurantioclavine. Based on the previous research, we were interested in developing a more efficient strategy to construct the ergot alkaloids.

The current study focuses on the synthesis of (-)-chanoclavine I (3),<sup>14,15</sup> the biosynthetic processor of ergot alkaloids. Previous research has reported two strategies (Scheme 1) for optical total syntheses of (-)-chanoclavine I (3), both of which start from the 4-substituted indole derivatives. In 1994, Genet<sup>16</sup> first reported the total synthesis of (-)-chanoclavine I (3) in a 12-step process, with 1.6% overall yield, stemming from indole-

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# Scheme 1. Previous Optical Synthetic Approaches to (-)-Chanoclavine I

(a) Genet's approach



(b) Yokoyama and Murakami's approach



4-carboxaldehyde. The key step of the synthesis was a chiral BINAP-palladium complex catalyzed cyclization reaction with nitroacetate 7 to construct trans-substituted tricyclic compound 8, resulting in a 60% yield and 95% ee. After the six-step manipulation from intermediate 8, the target molecule was produced. Two years later, Yokoyama and Murakami<sup>1</sup> reported an additional approach, using 16 linear steps with 9% overall yield stemming from a tryptophan derivative. The synthesis was based on a PdCl<sub>2</sub>-BPPP (1,3-bisdiphenylphosphinopropane)-catalyzed intramolecular cyclization (Heck-Mizoroki reaction) on 9, used to establish the key Z-selective olefin intermediate 10 with 77% yield. The target molecular was produced after the 11-step manipulation from intermediate 10. These routes were not efficient, and more research was needed to increase efficiency. The current synthetic design was primarily based on two papers. In 2011, Waser<sup>18</sup> reported the exceptional efficiency of lithium palladate catalysts for the intramolecular aminoalkynylation of terminal olefins using hypervalent iodine reagents. This novel strategy allowed both C-N formation and introduced a terminal alkyne in a single transformation. In 2014, Murakami<sup>19</sup> reported a novel construction strategy for a 3,4-fused indole skeleton that

Scheme 2. Retrosynthetic Analysis

exhibited an intramolecular [3 + 2] cycloaddition of the  $\alpha$ imino rhodium carbene complexes with aryl groups and subsequent oxidative aromatization to produce the indole core. This methodology was successfully applied in the total synthesis of (+)-lysergol by Luo.<sup>20</sup> These work provided the groundwork for a concise and efficient route for the total synthesis of (-)-chanoclavine I (3) based on palladiumcatalyzed intramolecular aminoalkynylation, followed by intramolecular [3 + 2] annulation reaction. The synthesis of an oxygen-substituted ergoline derivative was also demonstrated in the same manner.

# RESULTS AND DISCUSSION

It was suggested that (-)-chanoclavine I (3) would be formed in the late stage by rhodium-catalyzed intramolecular [3 + 2]annulation of compound 11 retrosynthetically (Scheme 2). In turn, intermediate 11 would be derived from compound 12 using a Wittig reaction and a subsequent Cu(I)-catalyzed click reaction with tosyl azide (TsN<sub>3</sub>). Cyclic carbamate 12 could be prepared from 14 using a lithium palladate catalyzed intramolecular aminoalkynylation. The hypervalent iodine reagent triisopropylsilyl ethynylbenziodoxolone (TIPS-EBX, 13) is considered an effective reagent for this transformation due to its mild reaction conditions and high stereoselectivity. The Ntosylcarbamate 14 should be accessible from commercially available (2R)-(+)-phenyloxirane 15.

The total synthesis of (-)-chanoclavine I (3) began by preparing (2S)-(+)-phenylbut-3-en-1-ol (16, Scheme 3) according to the literature procedure<sup>21</sup> using an inexpensive (2R)-(+)-phenyloxirane (15) as the chiral pool. The chloro-(1,5-cyclooctadiene)copper(I) dimer [CuCl(COD)]<sub>2</sub> catalyzed vinylation of (2R)-(+)-phenyloxirane (15), resulting in alcohol (+)-16 with a 71% yield. Subsequently, the carbamation from the obtained alcohol (+)-16 was prepared by exposing (+)-16 to p-tosyl isocyanate (p-Ts-NCO) in DCM to provide (2S)-(+)-phenylbut-3-en-1-yl tosylcarbamate (14) with a 97% yield. The substrate (+)-14 was now present, allowing the key aminoalkynylation to be investigated by utilizing the procedure that was described by Waser.<sup>18</sup> The phenyl-substituted homoallyl carbamate (+)-14 was then treated with TIPS-EBX (13), palladium(II) chloride (PdCl<sub>2</sub>), and lithium chloride (LiCl) in EtOH for 5 h at room temperature where the desired 4,5-trans-substituted 1,3-oxazinan-2-one product (-)-12 was



### Scheme 3. Synthesis of (-)-Chanoclavine I



produced as the sole rearrangement product with a 87% yield (>99% ee was determined by chiral HPLC, see the Supporting Information, S21). The relative stereochemistry of (-)-12 was confirmed by an X-ray crystallographic analysis of the final natural product obtained, although the exact mechanism for this transformation was unclear. The LiAlH<sub>4</sub> reduction of the cyclic carbamate (-)-12 in THF at 0 °C for 30 min resulted in the cleavage of the carbamate ring that yielded an amino alcohol that subsequently oxidized with Dess-Martin periodinane (DMP) to result in the aldehyde (+)-17 with 84% yield. Note that the ee (%) was not determined by chiral HPLC as the sample was unstable and had a weak absorption signal; see the Supporting Information, S22. The nitrogen atom of the original methyl group from the natural product was originally going to be produced via reduction of the cyclic carbamate ring of (-)-12. Unfortunately, only the decarboxylation product was obtained under different reaction conditions such as NaBH<sub>4</sub>, LiBH<sub>4</sub>, DIBAL-H, BH<sub>3</sub>·SMe<sub>2</sub>, and L-Selectride, and the methyl group was rebuilt afterward. This produced the (+)-17, where the Wittig olefination of aldehyde reacted with Ph<sub>3</sub>P= C(CH<sub>3</sub>)CO<sub>2</sub>Me in THF after 50 °C for 5 h, which produced the *E*-selective  $\alpha_{\beta}$ -unsaturated ester (+)-18 with a 82% yield (80% ee was determined by chiral HPLC; see the Supporting Information, S23). From the obtained (+)-18 we were able to rebuild the methyl group at the nitrogen atom, resulting in a reaction of (+)-18 with MeI and K2CO3 in DMF at room temperature. This produced a methylation product (+)-19 with a 98% yield. Subsequently, desilylation of the triple bond of compound (+)-19 using tetrabutylammonium fluoride (TBAF) was carried out successfully, resulting in terminal alkyne (-)-20

with a 80% yield. Utilizing the well-established method,<sup>22</sup> copper(I) thiophene-2-carboxylate (CuTC) catalyzed the click reaction of (-)-20 with TsN<sub>3</sub> in toluene at room temperature, which formed 1,2,3-triazoles (+)-11 with 90% yield. With (+)-11, we were able to produce the 3,4-fused indole skeleton through the crucial [3 + 2] annulation based on the Murakami<sup>19</sup> protocol. By heating the (+)-11 to rhodium(II) pivalate dimer  $Rh_2(OCO^tBu)_4$  and 4 Å molecular sieves (MS) in 1,2-dichloroethane (DCE) at 85 °C for 3 h, the desired [3 +2] annulation product (dihydroindole) was obtained. After the compounds were confirmed by TLC spectra, the solvent was evaporated and the pale residue was obtained. The residue was treated with manganese dioxide (MnO<sub>2</sub>) in DCM at room temperature for 24 h, which yielded the tricyclic indole compound (-)-21 with 77% yield within this two-step process without intermediate separation or identification. The single crystal of the  $(\pm)$ -21 was obtained from the synthesis scheme starting from the  $(\pm)$ -2-phenyloxirane (see Figure 2 and ref 23). Compound (-)-21 possessed the framework of the nature product. The last stage was simply a reduction of the ester to



Figure 2. Single crystal of  $(\pm)$ -21 from  $(\pm)$ -15.

alcohol and deprotection of tosyl group. Hence, DIBAL-H reduction of the  $\alpha_{\beta}$ -unsaturated ester (-)-21 in THF at -78 °C resulted in a primary allylic alcohol, where the direct removal of the tosyl group with freshly prepared lithium naphthalenide at -78 °C produced (–)-chanoclavine I (3) with a 77% yield (>99% ee, see Supporting Information, S20). The absolute configuration of (-)-3 was confirmed through a single-crystal X-ray crystallographic analysis (see ref 24). The (-)-chanoclavine I (3) was synthesized in this 13-step process, with a 17% overall yield from (R)-(+)-phenyloxirane (15). The spectroscopic data, i.e., <sup>1</sup>H NMR (see Table S1) and IR spectra of the synthetic sample, were in agreement with the reported data.<sup>16,25</sup> The optical rotation of the synthetic sample was  $[\alpha]_D^{16}$ -196.0 (c 1.5, pyridine), which is analogous with the isolation literature <sup>14,15</sup> reported  $[\alpha]_D^{20}$  –240 (c 1, pyridine) and the synthetic literature<sup>16</sup> reported  $[\alpha]_D^{20}$  –213 (*c* 0.4, pyridine).

To investigate the further applicability of the strategy, total synthesis of an oxygen-substituted ergoline derivative was performed. Various cases<sup>19</sup> have shown that intramolecular [3 + 2] annulation is a versatile synthetic strategy within the construction of the 3,4-fused indole skeleton on various linear substrates. Considering that most of the ergot alkaloids contained a trans-substituted D ring, we postulated that a substrate containing a trans-six-membered ring between the phenyl and alkynyl groups would be tolerated. To answer this, we designed a module experiment on substrate (-)-12 (Scheme 4) that contained a trans-substituted D ring (in contrast with the ergoline skeleton). Thus, exposure of (-)-12 to TBAF in THF at 0 °C for 2 h resulted in cleavage of the silicon protecting group quantitatively. Following the same protocol as above, the obtained terminal alkyne (-)-22 was

Scheme 4. Synthesis of (-)-25 and (+)-26



converted to the 1,2,3-triazole (-)-23 with a 95% yield via copper(I) thiophene-2-carboxylate (CuTC) catalyzed click reaction with  $TsN_3$ . The treatment of (-)-23 with rhodium(II) pivalate dimer Rh<sub>2</sub>(OCO<sup>t</sup>Bu)<sub>4</sub> and 4 Å MS in DCE at 85 °C for 3 h resulted in the formation of the [3 + 2] product. The dihydroindole compound was directly oxidized with MnO2 in DCM without intermediate separation or purification. After being stirred at room temperature for 24 h, the tetracyclic 3,4fused indole skeleton (-)-24 was achieved with a 74% yield over the two steps. Eventually, the tosyl group of (-)-24 was removed with a 59% yield with freshly prepared lithium naphthalenide in THF at -78 °C. An oxygen-substituted ergoline derivative (-)-25 was obtained in the eight-step process with a 24% overall yield from the (R)-(+)-phenyloxirane (15). This synthesis lays the foundation for total synthesis of other ergot alkaloids in a novel and efficient manner. Compounds (-)-24 and (-)-25 were believed to be useful intermediates for the total synthesis of many other ergot alkaloids. For example, in 2013, Jia<sup>12</sup> reported an unfinished scheme for the total synthesis of (+)-lysergic acid. Baylis-Hillman reaction was designed to construct the D ring of lysergic acid in later stage, although this design fell short, as the key substrate of the Baylis-Hillman reaction could not be prepared. However, compound (-)-24 could be transferred to a cyclic amino aldehyde (+)-26, the necessary substrate of the Baylis-Hillman reaction, by cleavage of the cyclic carbamate ring by LiAlH<sub>4</sub> reduction followed by a Dess-Martin oxidation of the resulting hydroxyl group with a 64% yield over a twostep process. Thus, the synthesis of the (+)-lysergic acid should be achieved.

# CONCLUSION

A straightforward asymmetric total synthesis of (-)-chanoclavine I (3) in a 13-step process with a 17% overall yield was developed. Our synthesis featured an efficient construction of the trans-substituted cyclic carbamate ring via a palladium-catalyzed intramolecular aminoalkynylation of terminal alkene and a rhodium-catalyzed intramolecular [3 + 2] annulation to construct the 3,4-fused indole skeleton. The highly efficient total synthesis of (-)-chanoclavine I (3) provided the basis for an extended study both the biosynthesis and chemical synthesis pathway for ergot alkaloids. An additional oxygen-substituted ergoline derivative (-)-25 was synthesized that has potential application in the synthesis of various ergot alkaloids including lysergic acid (2). At this time, further studies are underway.

#### EXPERIMENTAL SECTION

General Information. All reactions that required anhydrous conditions were carried out by standard procedures under argon. Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying reagents. Petroleum ether (PE) used had a boiling range of 60-90 °C. Reactions were monitored by TLC on silica gel GF 254 plates. Column chromatography was generally performed through silica gel (200-300 mesh). IR spectra were recorded on an FT-IR spectrophotometer and reported in wavenumbers (cm<sup>-1</sup>). Melting points were determined by use of a microscope apparatus and are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a 400 MHz spectrometer, as were the DEPT 135 experiments, except for the NMR experiment on compound (+)-26 which was recorded on a 300 MHz spectrometer. Chemical shift values were given in ppm and coupling constants (J) in Hz. Except for the <sup>1</sup>H NMR spectra experiments made in CDCl<sub>3</sub> which used TMS as an internal standard, in the other <sup>1</sup>H and <sup>13</sup>C NMR spectra experiments, solvent residue signals were used as an internal references (CDCl<sub>3</sub>:  $\delta_{\rm C} = 77.00$  ppm; C<sub>5</sub>D<sub>5</sub>N:  $\delta_{\rm H} = 8.74$  ppm,  $\delta_{\rm C} = 150.35$  ppm). Accurate mass measurements were obtained on a 7.0 T FT-ICR or 4G mass spectrometer or on a double-focusing sector-field instrument. Singlecrystal X-ray diffraction measurements were performed with a diffractometer working with graphite-monochromated Mo K $\alpha$ radiation. TIPS-EBX (13)<sup>18</sup> and Rh<sub>2</sub>(OCO'Bu)<sub>4</sub><sup>26</sup> were synthesized according to the reported procedure.



1-[(Triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (TIPS-EBX, **13**). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.43–8.41 (m, 1H), 8.32–8.29 (m, 1H), 7.78–7.76 (m, 2H), 1.16–1.15 (m, 21H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 166.4 (C), 134.7 (CH), 132.4 (CH), 131.5 (CH), 131.4 (C), 126.0 (CH), 115.6 (C), 114.2 (C), 64.6 (C), 18.5 (CH<sub>3</sub>), 11.1 (CH). The NMR data are in accordance with the literature values.<sup>18</sup>



(+)-(S)-2-Phenyl-but-3-en-1-ol (16). Following the literature procedure,<sup>21</sup> to a suspension of (+)-(R)-phenyloxirane (15) (1.99 g, 16.56 mmol, 1.0 equiv) and chloro(1,5-cyclooctadiene)copper(I) dimer [CuCl(COD)]<sub>2</sub> (344 mg, 0.83 mmol, 0.05 equiv) in THF (24 mL) was added vinylmagnesium bromide (20.0 mL, 20.0 mmol, 1.0 M solution in THF, 1.2 equiv) at -78 °C. The reaction mixture was then allowed to warm to room temperature overnight and quenched by the addition of a saturated solution of NH<sub>4</sub>Cl (60 mL). The aqueous layer was extracted with ethyl acetate  $(3 \times 50 \text{ mL})$ . The combined organic layers were dried over MgSO4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (PE/EtOAc 10/1) to afford the title compound as a colorless oil (1.75 g, 71%). R<sub>f</sub> = 0.6 (PE/EtOAc 4/ 1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.34–7.31 (m, 2H), 7.25–7.21 (m, 3H), 6.03-5.95 (m, 1H), 5.19 (d, 1H, 8.0 Hz), 5.16 (d, 1H, 15.6 Hz), 3.80–3.78 (m, 2H), 3.54 (q, 1H, J = 7.3 Hz), 1.53 (br s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 140.6 (C), 138.2 (CH), 128.7 (CH), 127.9 (CH), 126.8 (CH), 117.0 (CH<sub>2</sub>), 66.0 (CH<sub>2</sub>), 52.4 (CH). The spectroscopic properties of this compound are consistent with the literature reported value.



(+)-(S)-2-Phenylbut-3-en-1-yl Tosylcarbamate (14). To a solution of alcohol (+)-16 (1.86 g, 12.55 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (32 mL) was added p-tosyl isocyanate (p-Ts-NCO) (3.71 g, 18.83 mmol, 1.5 equiv) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 30 min, and then diluted with H<sub>2</sub>O (15 mL). The resulting mixture was extracted with  $CH_2Cl_2$  (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (PE/EtOAc 4:1) to provide compound (+)-14 as a white solid (4.20 g, 97%).  $R_f = 0.4$ (PE/EtOAc 4/1). Mp: 79–81 °C.  $[\alpha]_{D}^{16}$  +22.3 (c 1.1, MeOH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.19-8.11 (br, 1H), 7.86-7.83 (m, 2H), 7.29-7.20 (m, 5H), 7.13-7.11 (d, 2H, J = 7.4 Hz), 5.92-5.83 (m, 1H), 5.09-5.00 (m, 2H), 4.36-4.23 (m, 2H), 3.61 (q, 1H, J = 7.2Hz), 2.42 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 150.5 (C), 144.9 (C), 139.3 (C), 136.8 (CH), 135.3 (C), 129.5 (CH), 128.6 (CH), 128.2 (CH), 127.7 (CH), 127.0 (CH), 117.0 (CH<sub>2</sub>), 68.9 (CH<sub>2</sub>), 48.2

(CH), 21.6 (CH<sub>3</sub>). IR (KBr, neat): 3241, 1751, 1452, 1350, 1162, 702, 663 cm<sup>-1</sup>. HRMS (ESI-ToF) m/z:  $[M + NH_4]^+$  calcd for  $C_{18}H_{23}N_2O_4S$  363.1373, found 363.1375.



(-)-(4R,5R)-5-Phenyl-3-tosyl-4-(3-(triisopropylsilyl)prop-2-ynyl)-1,3-oxazinan-2-one (12). To a solution of tosyl amide (+)-14 (2.21 g, 6.37 mmol, 1.0 equiv) in EtOH (160 mL) was added LiCl (972 mg, 22.93 mmol, 3.6 equiv) followed by PdCl<sub>2</sub> (113 mg, 0.64 mmol, 0.1 equiv) and benziodoxolone reagent triisopropylsilyl ethynylbenziodoxolone (TIPS-EBX, 13, 3.27 g, 7.64 mmol, 1.2 equiv). The reaction mixture was stirred for 5 h at room temperature. The solvent was then removed under reduced pressure to give a dark residue, which was subsequently suspended in Et<sub>2</sub>O (50 mL). The organic layer was washed with a saturated solution of Na2CO3 (50 mL). The aqueous layer was extracted with Et<sub>2</sub>O ( $3 \times 50$  mL). The combined organic layers were dried over MgSO4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by flash chromatography (PE/EtOAc 4/1) to give the product (-)-12 as a colorless needle crystal (2.92 g, 87%).  $R_f = 0.5$  (PE/EtOAc 4/1). Mp: 121–127 °C.  $[\alpha]_D^{16}$  –4.0 (c 2.0, DCM). <sup>1</sup>H NMR (400 MHz, CDCl<sub>2</sub>):  $\delta$  7.49 (d, 2H, J = 8.0 Hz), 7.34–7.31 (m, 3H), 7.26–7.23 (m, 2H), 7.11 (d, 2H, J = 8.0 Hz), 4.78–4.74 (m, 1H), 4.65–4.55 (m, 2H), 3.78 (q, 1H, J = 4.7 Hz), 2.92–2.90 (m, 2H), 2.37 (s, 3H), 1.05 (m, 21H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  148.3 (C), 144.6 (C), 137.8 (C), 135.1 (C), 129.3 (CH), 129.1 (CH), 128.7 (CH), 127.9 (CH), 127.3 (CH), 101.5 (C), 86.3 (C), 67.7 (CH<sub>2</sub>), 61.0 (CH), 40.3 (CH), 26.2 (CH<sub>2</sub>), 21.5 (CH<sub>3</sub>), 18.3 (CH<sub>3</sub>), 11.1 (CH). IR (KBr, neat): 3412, 2943, 2864, 2175, 1711, 1355, 1172, 1153 cm<sup>-1</sup>. HRMS (ESI-ToF) *m*/ z:  $[M + H]^+$  calcd for  $C_{29}H_{40}NO_4SSi$  526.2442, found 526.2447.



(+)-(25,3R)-3-(4-Methylphenylsulfonamido)-2-phenyl-6-(triisopropylsilyl)hex-5-ynal (17). To a solution of compond (-)-12 (1.81 g, 3.44 mmol, 1 equiv) in THF (20 mL) was added LiAlH<sub>4</sub> (95%, 0.68 g, 17.2 mmol, 5 equiv) at 0 °C. After the solution was stirred for 1 h, water (0.7 mL) and a solution of NaOH (10%, 1.4 mL) were added dropwise carefully at the same temperature, and the mixture was filtered over Celite. The filter was extracted with methyl *tert*-butyl ether (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to give a white solid, which was used in the next step directly without further purification.

To a solution of the above product in DCM (20 mL) was added Dess-Martin periodinane (1.75 g, 4.13 mmol, 1.2 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h shielded from light. The reaction mixture was quenched with a solution of saturated NaHCO<sub>3</sub> solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with the DCM (3  $\times$  50 mL). The combined organic layers were dried over MgSO4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (PE/EtOAc 4/1) to give aldehyde (+)-17 as a white solid (1.44 g, 84%).  $R_f = 0.3$  (PE/EtOAc 2/1). Mp: 86–89 °C.  $[\alpha]_D^{16}$ +10.0 (c 0.6, MeOH). <sup>1</sup>H NMR (400 MHz,  $CDC\bar{l}_3$ ):  $\delta$  9.65 (s, 1H), 7.68 (d, 2H, J = 8.4 Hz), 7.32-7.30 (m, 3H), 7.24 (s, 1H), 7.15-7.12 (m, 2H), 5.10 (d, 1H, J = 9.6 Hz), 4.00 (br s, 2H), 2.42 (s, 3H), 2.39-2.35 (m, 1H), 2.20-2.15 (m, 1H), 1.09 (m, 21H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 198.8 (CH), 143.6 (C), 137.6 (C), 132.9 (C), 129.7 (CH), 129.3 (CH), 129.2 (CH), 128.3 (CH), 126.9 (CH), 102.3 (C), 85.9 (C), 60.6 (CH), 53.1 (CH), 24.3 (CH<sub>2</sub>), 21.5 (CH<sub>3</sub>), 18.6 (CH<sub>3</sub>), 11.2 (CH). IR (KBr, neat): 3241, 2941, 2173, 1731, 1461,

1432, 1332, 1167, 698, 661 cm<sup>-1</sup>. HRMS (ESI-ToF) m/z: [M + H]<sup>+</sup> calcd for C<sub>28</sub>H<sub>40</sub>NO<sub>3</sub>SSi 498.2493, found 498.2495.



(+)-(4R,5R,E)-Methyl 2-Methyl-5-(4-methylphenylsulfonamido)-4-phenyl-8-(triisopropylsilyl)oct-2-en-7-ynoate (18). To a solution of aldehyde (+)-17 (1.40 g, 2.81 mmol, 1 equiv) in dry THF (35 mL) was added crystalline ( $\alpha$ -carbomethoxyethylidene)triphenylphosphorane (1.96 g, 5.62 mmol, 2 equiv). The reaction mixture was stirred and heated from room temperature to 50 °C for 2 h under argon. The solvent was then removed under reduced pressure. The residue was purified by flash chromatography (PE/EtOAc 4/1) to give the ester (+)-18 as a white solid (1.31 g, 82%).  $R_f = 0.6$  (PE/EtOAc 2/ 1). Mp: 34–38 °C.  $[\alpha]_{D}^{16}$  +17.6 (*c* 0.9, MeOH). <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ ):  $\delta$  7.72 (d, 2H, J = 8.4 Hz), 7.29–7.21 (m, 5H), 7.17–7.15 (m, 2H), 6.87-6.84 (dd, 1H, J = 10.0, 1.6 Hz), 4.75 (d, 1H, J = 9.6Hz), 3.95 (t, 1H, J = 10.0 Hz), 3.70 (s, 3H), 2.43 (s, 3H), 2.28-2.23 (m, 1H), 2.28–2.03 (m, 1H), 1.79 (d, 3H, J = 1.3 Hz), 1.11 (m, 21H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 167.9 (C), 143.5 (C), 140.7 (CH), 139.4 (C), 137.6 (C), 129.74 (C), 129.71 (CH), 129.0 (CH), 127.9 (CH), 127.4 (CH), 127.0 (CH), 102.5 (C), 85.5 (C), 56.1 (CH), 51.8 (CH<sub>3</sub>), 47.7 (CH), 24.1 (CH<sub>2</sub>), 21.6 (CH<sub>3</sub>), 18.7 (CH<sub>3</sub>), 12.8 (CH<sub>3</sub>), 11.2 (CH); IR (KBr, neat): 3259, 2945, 2170, 1714, 1435, 1334, 1162, 735, 622 cm<sup>-1</sup>. HRMS (ESI-ToF) m/z:  $[M + NH_4]^+$  calcd for C32H49N2O4SSi 585.3177, found 585.3178.



(+)-(4R,5R,E)-Methyl 5-(N,4-Dimethylphenylsulfonamido)-2methyl-4-phenyl-8-(triisopropylsilyl)oct-2-en-7-ynoate (19). To a solution of compound (+)-18 (1.30 g, 2.29 mmol, 1 equiv) in freshly distilled N,N-dimethylformamide (10 mL) were added methyl iodide (2.60 g, 18.32 mmol, 8 equiv) and potassium carbonate (633 mg, 4.58 mmol, 2 equiv). The reaction mixture was stirred vigorously at room temperature for 20 h, quenched with water (5 mL), and then diluted with EtOAc (150 mL). The organic phase was washed with water (5  $\times$ 30 mL) and then a solution saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (30 mL), dried over anhydrous MgSO4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (PE/EtOAc 4/1) to afford compound (+)-19 as a white solid (1.31 g, 98%).  $R_f = 0.6$ (PE/EtOAc 2/1). Mp: 70–73 °C.  $[\alpha]_{D}^{16}$  +11.4 (c 0.4, MeOH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.74 (d, 2H, J = 8.0 Hz), 7.35–7.27 (m, 6H), 7.25-7.23 (m, 1H), 6.97-6.95 (m, 1H), 4.47-4.42 (m, 1H), 4.23 (t, 1H, J = 10.6 Hz), 3.70 (s, 3H), 2.94 (s, 3H), 2.42 (s, 3H), 2.38–2.33 (m, 1H), 2.20–2.15 (m, 1H), 1.84 (d, 3H, J = 0.8 Hz), 1.09 (s, 21H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  167.8 (C), 143.2 (C), 141.5 (CH), 139.5 (C), 136.6 (C), 129.6 (CH), 128.9 (CH), 128.3 (C), 128.2 (CH), 127.3 (CH), 127.2 (CH), 104.2 (C), 85.5 (C), 58.2 (CH), 51.7 (CH<sub>3</sub>), 45.6 (CH), 30.1 (CH<sub>3</sub>), 22.7 (CH<sub>2</sub>), 21.4 (CH<sub>3</sub>), 18.5 (CH<sub>3</sub>), 12.3 (CH<sub>3</sub>), 11.2 (CH). IR (KBr, neat): 3360, 2928, 2864, 2170, 1718, 1598, 1460, 1343, 1162, 739, 677 cm<sup>-1</sup>. HRMS (ESI-ToF) m/z:  $[M + NH_4]^+$  calcd for  $C_{33}H_{51}N_2O_4SSi$  599.3333, found 599.3331.

(-)-(4R,5R,E)-Methyl 5-(N,4-Dimethylphenylsulfonamido)-2methyl-4-phenyloct-2-en-7-ynoate (20). To a solution of compound (+)-19 (930 mg, 1.60 mmol, 1.0 equiv) in THF (10 mL) was added a solution of TBAF (1.0 M in THF, 4.8 mL, 4.80 mmol, 3.0 equiv) dropwise at 0 °C. The mixture was allowed to warm to room temperature over 2 h. The reaction was quenched with a solution of NaHCO<sub>3</sub> (1 M, 10 mL) and extracted with EtOAc ( $3 \times 20$  mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (PE/EtOAc 4/1) to afford compound (-)-20 as a white solid (544 mg, 80%).  $R_f = 0.3$  (PE/EtOAc 4/1). Mp: 101–103 °C.  $[\alpha]_D^{16}$  –137.3 (č 0.5, MeOH). <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ ):  $\delta$  7.75 (d, 2H, J = 8.4 Hz) 7.35–7.25 (m, 7H), 7.04–7.01 (m, 1H), 4.52–4.47 (m, 1H), 4.00 (t, 1H, J = 10.4 Hz), 3.71 (s, 3H), 2.80 (s, 3H), 2.42 (s, 3H), 2.25-2.19 (m, 1H), 2.14-2.08 (m, 1H), 1.89 (t, 1H, J = 2.7 Hz), 1.85 (d, 3H, J = 1.4 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 168.0 (C), 143.2 (C), 141.3 (CH), 139.4 (C), 136.8 (C), 129.5 (CH), 129.1 (CH), 128.5 (C), 128.2 (CH), 127.48 (CH), 127.46 (CH), 80.1 (C), 72.1 (CH), 59.1 (CH), 51.9 (CH<sub>3</sub>), 47.0 (CH), 29.4 (CH<sub>3</sub>), 21.5 (CH<sub>3</sub>), 20.9 (CH<sub>2</sub>), 12.6 (CH<sub>3</sub>). IR (KBr, neat): 3265, 2953, 2109, 1703, 1435, 1334, 1166, 1073, 667 cm<sup>-1</sup>. HRMS (ESI-ToF) m/z:  $[M + NH_4]^+$  calcd for  $C_{24}H_{31}N_2O_4S$ 443.1999, found 443.1998.



(+)-(4R,5R,E)-Methyl 5-(N,4-Dimethylphenylsulfonamido)-2methyl-4-phenyl-6-(1-tosyl-1H-1,2,3-triazol-4-yl)hex-2-enoate (11). To a solution of compound (-)-20 (787 mg, 1.85 mmol, 1.0 equiv) in toluene (10 mL) were added copper(I) thiophene-2-carboxylate (CuTC) (36 mg, 0.19 mmol, 0.1 equiv) and a solution of TsN<sub>3</sub> (365 mg, 1.85 mmol, 1.0 equiv) in toluene (10 mL) in room temperature. The reaction mixture was stirred for 12 h at the same temperature. The mixture was then quenched with a saturated solution of NH<sub>4</sub>Cl (30 mL) and extracted with EtOAc (3  $\times$  20 mL). The combined organic layers were washed with brine, dried over MgSO4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (PE/EtOAc 4/1) to give 1,2,3-triazole (+)-11 as a white powder (1.02 g, 90%).  $R_f = 0.5$  (PE/EtOAc 1/1). Mp: 101–104 °C. $[\alpha]_{D}^{16}$  +28.7 (c 1.2, DCM). <sup>1</sup>H NMR (400 MHz,  $\dot{CDCl}_3$ :  $\delta$  7.9 (d, 2H, J = 8.4 Hz), 7.62 (s, 1H), 7.49 (d, 2H, J = 8.2 Hz), 7.32 (d, 2H, J = 8.2 Hz), 7.28–7.26 (m, 4H), 7.20–7.18 (m, 3H), 7.02 (d, 1H, J = 8.4 Hz), 4.80-4.74 (m, 1H), 3.86-3.81 (t, 1H, J = 10.4 Hz), 3.70 (s, 3H), 2.80-2.69 (m, 2H), 2.58 (s, 3H), 2.40 (d, 6H), 1.82 (d, 3H, J = 1.2 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  167.9 (C), 147.0 (C), 143.7 (C), 143.3 (C), 141.4 (CH), 139.5 (C), 136.6 (C), 133.1 (C), 130.2 (CH), 129.5 (CH), 129.2 (CH), 128.6 (CH), 128.4 (C), 128.2 (CH), 127.5 (CH), 126.9 (CH), 122.0 (CH), 61.5 (CH), 51.9 (CH<sub>3</sub>), 49.1 (CH), 26.8 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 21.5 (CH<sub>3</sub>), 12.5 (CH<sub>3</sub>). IR (KBr, neat): 2951, 1712, 1597, 1494, 1437, 1392, 1268, 736, 672 cm<sup>-1</sup>. HRMS (ESI-ToF) m/z:  $[M + H]^+$  calcd for C31H35N4O6S2 623.1993, found 623.1994.



(-)-(E)-Methyl 3-((4R,5R)-4-(N,4-Dimethylphenylsulfonamido)-1tosyl-1,3,4,5- tetrahydrobenzo[cd]indol-5-yl)-2-methylacrylate (**21**). To solution of 1,2,3-triazole (+)-**11** (765 mg, 1.25 mmol, 1.0 equiv) in 1,2-dichloroethane (20 mL) were added rhodium(II) pivalate dimer Rh<sub>2</sub>(OCO<sup>t</sup>Bu)<sub>4</sub> (7.6 mg, 12.5  $\mu$ mol, 0.01 equiv) and 4 Å MS (200 mg) under argon. It was note that the reaction vessel was evacuated and

refilled with argon five times before the reaction. The reaction mixture was heated to 85 °C under argon for 3 h. After being cooled to room temperature, the molecular sieves were filtered off, and the remaining solution was concentrated to a viscous residue. To a suspension of the crude residue in anhydrous DCM (20 mL) was added activated MnO2 (1.09 g, 12.50 mmol, 10 equiv) at room temperature. After being stirred at room temperature for 20 h, the reaction mixture was passed through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (PE/ EtOAc 4/1) to give the product (-)-21 as colorless needle crystals (570 mg, 77%).  $R_f = 0.6$  (PE/EtOAc 1/1). Mp: 168–174 °C.  $[\alpha]_D^{16}$ -43.9 (c 2.2, DCM). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.78-7.74 (m, 3H), 7.67 (d, 2H, J = 8.4 Hz), 7.27-7.20 (m, 5H), 7.16 (d, 1H, J = 1.2 Hz), 6.75 (d, 1H, J = 7.6 Hz), 6.60-6. 57 (m, 1H), 4.41-4.35 (m, 1H), 4.09–4.04 (t, 1H, J = 10.2 Hz), 3.76 (s, 3H), 2.99–2.82 (m, 2H), 2.74 (s, 3H), 2.43 (s, 3H), 2.35 (s, 3H), 1.93 (d, 3H, J = 1.2 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 167.7 (C), 144.9 (C), 143.4 (C), 139.6 (CH), 136.6 (C), 135.2 (C), 133.3 (C), 131.1 (C), 130.0 (C), 129.9 (CH), 129.6 (CH), 128.0 (C), 127.3 (CH), 126.7 (CH), 125.7 (CH), 120.1 (CH), 120.0 (CH), 117.4 (C), 112.3 (CH), 57.9 (CH), 52.0 (CH<sub>3</sub>), 40.9 (CH), 28.7 (CH<sub>3</sub>), 25.3 (CH<sub>2</sub>), 21.6 (CH<sub>3</sub>), 12.8 (CH<sub>3</sub>). IR (KBr, neat): 2943, 1709, 1598, 1165, 674 cm<sup>-1</sup>. HRMS (ESI-ToF) m/z:  $[M + Na]^+$  calcd for  $C_{31}H_{32}N_2O_6S_2Na$  615.1594, found 615.1592.



(-)-(E)-2-Methyl-3-((4R,5R)-4-(methylamino)-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)prop-2-en-1-ol (3). To a solution of compound (-)-21 (231 mg, 0.39 mmol, 1.0 equiv) in dry DCM (50 mL) was added DIBAL-H (1 M in THF, 0.78 mL, 0.78 mmol, 2.0 equiv) at -78 °C, and the resulting mixture was stirred for 1.5 h at the same temperature. Then methanol (2 mL) and a solution of saturated potassium tartrate (10 mL) were added dropwise sequentially. The mixture was allowed to warm to room temperature and stirred for a further 10–15 min. The obtained white precipitate was filtered through a pad of Celite, and the aqueous phase was extracted with DCM. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude residue was used directly in the next step without further purification.

To a solution of naphthalene (1.12 g, 8.75 mmol) in previously degassed THF (17 mL) was added lithium (61 mg, 8.75 mmol). The mixture was sonicated for 30 min and then stirred at room temperature for another 2 h in order to obtain a dark green (lithium naphthalenide) solution of 0.5 M.<sup>18</sup> To a solution of the previously obtained alcohol in THF (5 mL) was added the freshly prepared solution of lithium naphthalenide dropwise at -78 °C until the reaction mixture stayed permanently dark green (3 mL, 4.0 equiv). The reaction mixture was stirred at -78 °C for 30 min and warmed to room temperature for another 30 min. The reaction mixture was quenched with a solution of NaHCO<sub>3</sub> (1 M, 3 mL) and extracted with DCM ( $3 \times 10$  mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to give a pale residue. The crude residue was purified by flash chromatography (CHCl<sub>3</sub>/MeOH/NH<sub>4</sub>OH 46/5/0.5) and recrystallized in acetone to give (-)-chanoclavine I (3) as a pale crystal (77 mg, 77%).  $R_f = 0.2$  (CHCl<sub>3</sub>/MeOH/NH<sub>4</sub>OH 46/5/0.5). Mp: 216– 220 °C (lit.<sup>14</sup> mp 220–222 °C, lit.<sup>15</sup> mp 222 °C, lit.<sup>16</sup> mp 192 °C).  $[\alpha]_D^{16} - 196.0$  (*c* 1.5, pyridine) [lit.<sup>14,15</sup>  $[\alpha]_D^{20} - 240$  (*c* 1, pyridine), lit.<sup>16</sup>  $[\alpha]_D^{20} - 213$  (*c* 0.4, pyridine)]. <sup>1</sup>H NMR (400 MHz, C<sub>5</sub>D<sub>5</sub>N):  $\delta$  11.63 (br, s, 1H), 7.43 (d, 1H, J = 8.0 Hz), 7.29–7.25 (m, 2H), 7.04 (d, 1H, J = 7.2 Hz), 6.56 (t, 1H, J = 6.0 Hz, disappeared on addition of  $D_2O$ ) 5.91 (dd, 1H, J = 10.0, 1.4 Hz), 4.46 (m, 2H), 4.21 (t, 1H, 8.8 Hz), 3.43 (dd, 1H, J = 14.8, 4.0 Hz), 3.05-3.02 (m, 1H), 2.94-2.88 (m, 1H), 2.41 (s, 3H), 2.04 (d, 3H, J = 1.2 Hz). <sup>13</sup>C NMR (100 MHz, C<sub>5</sub>D<sub>5</sub>N): δ 140.7 (C), 135.6 (C), 133.5 (C), 127.9 (C), 125.8 (CH),

123.4 (CH), 119.9 (CH), 116.6 (CH), 111.8 (C), 109.9 (CH), 68.3 (CH<sub>2</sub>), 62.8 (CH), 44.1 (CH), 34.7 (CH<sub>3</sub>), 27.5 (CH<sub>2</sub>), 15.1 (CH<sub>3</sub>). IR (KBr, neat): 3418, 2923, 1616, 1444, 1072, 744 cm<sup>-1</sup>. HRMS (ESI-ToF) m/z: [M + H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>21</sub>N<sub>2</sub>O 257.1648, found 257.1647. (The <sup>1</sup>H NMR data of the synthetic sample are agreement with the literature reported value, <sup>16,25</sup> and the detailed comparison is listed in the Supporting Information. To the best of our knowledge, there was no <sup>13</sup>C NMR data reported before.)



(-)-(4*R*,5*R*)-5-Phenyl-4-(prop-2-yn-1-yl)-3-tosyl-1,3-oxazinan-2one (**22**). In analogy to the synthesis of compound (-)-**20**, the desilylation was carried out by starting from cyclic carbamate (-)-**12** (646 mg, 1.23 mmol, 1.0 equiv) to give compound (-)-**22** (445 mg, 98%) as a white solid.  $R_f = 0.2$  (PE/EtOAc 4/1). Mp: 187–194 °C.  $[\alpha]_{D}^{16}$  -63.2 (*c* 0.02, MeOH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.44 (d, 2H, *J* = 8.4 Hz), 7.35–7.33 (m, 3H), 7.27–7.24 (m, 2H), 7.11 (d, 2H, *J* = 8.4 Hz), 4.81–4.77 (m, 1H), 4.67–4.55 (m, 2H), 3.7 (q, 1H, *J* = 4.4 Hz), 2.91–2.79 (m, 2H), 2.38 (s, 3H), 2.19 (t, 1H, *J* = 2.8 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  148.3 (C), 144.8 (C), 137.7 (C), 134.8 (C), 129.3 (CH), 129.1 (CH), 128.6 (CH), 127.9 (CH), 127.3 (CH), 78.0 (C), 73.3 (CH), 67.7 (CH<sub>2</sub>), 60.8 (CH), 40.0 (CH), 25.1 (CH<sub>2</sub>), 21.6 (CH<sub>3</sub>). IR (KBr, neat): 3431, 2957, 2864, 2176, 1762, 1369, 1135, 676 cm<sup>-1</sup>. HRMS (ESI-TOF) *m*/*z*: [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>20</sub>NO<sub>4</sub>S 370.1108, found 370.1110.



(-)-(4R,5R)-5-Phenyl-3-tosyl-4-((1-tosyl-1H-1,2,3-triazol-4-yl)methyl)-1,3-oxazinan-2-one (23). In analogy to the synthesis of compound (+)-11, this click reaction was carried out by starting from terminal alkyne (-)-22 (919 mg, 2.49 mmol, 1.0 equiv) to give 1,2,3,triazole (-)-23 (1.34 g, 95%) as a white powder.  $R_f = 0.4$  (PE/EtOAc 1/1). Mp: 206 °C dec.  $[\alpha]_D^{16}$  -57.4 (c 0.5, DCM). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.99-7.97 (m, 3H), 7.43-7.38 (m, 4H), 7.32-7.26 (m, 3H), 7.19–7.17 (m, 2H), 7.13 (d, 2H, J = 8 Hz), 4.93 (dd, 1H, J = 10.8, 6.0 Hz), 4.62-4.58 (m, 1H), 4.50-4.46 (m, 1H), 3.50 (q, 1H, J = 4.4 Hz), 3.36 (d, 2H, J = 6.0 Hz), 2.44 (s, 3H), 2.40 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 148.4 (C), 147.4 (C), 145.1 (C), 141.8 (C), 137.7 (C), 134.6 (C), 132.8 (C), 130.5 (CH), 129.3 (CH), 128.8 (CH), 128.7 (CH), 127.9 (CH), 127.4 (CH), 123.1 (CH), 67.9 (CH<sub>2</sub>), 62.1 (CH), 39.8 (CH), 30.8 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>); IR (KBr, neat): 3122, 1713, 1396, 1197, 670 cm<sup>-1</sup>. HRMS (ESI-ToF) m/z: [M + H]<sup>+</sup> calcd for C<sub>27</sub>H<sub>27</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub> 567.1367, found 567.1368.



(-)-(6*a*R,10*a*R)-4,7-Ditosyl-4,6,6*a*,7,10,10*a*-hexahydro-8*H*-[1,3]oxazino[5',4':4,5]benzo[1,2,3-cd]indol-8-one (**24**). In analogy to the synthesis of compound (-)-**21**, [3 + 2] annulation reaction was carried out by starting from 1,2,3,-triazole (-)-**23** (1.29 g, 2.27 mmol, 1.0 equiv) to give tetracyclic indole compound (-)-**24** (901 mg, 74%) as a white powder.  $R_f = 0.6$  (PE/EtOAc 1/1). Mp: >300 °C.[ $\alpha$ ]<sup>D</sup><sub>D</sub> -103.1 (*c* 1.0, DCM). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.00 (d, 2H, *J* = 8.0 Hz), 7.85 (d, 1H, *J* = 8.4 Hz), 7.80 (d, 2H, *J* = 8.4 Hz), 7.37-

7.30 (m, 4H), 7.27–7.24 (m, 2H), 6.90 (d, 1H, *J* = 7.2 Hz), 4.87 (dd, 1H, *J* = 10.8, 3.6 Hz), 4.38–4.27 (m, 2H), 4.09 (dd, 1H, *J* = 14.4, 3.2 Hz), 3.50–3.44 (m, 1H), 2.82–2.75 (m, 1H), 2.46 (s, 3H), 2.37 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  149.5 (C), 145.3 (C), 145.2 (C), 136.0 (C), 135.3 (C), 133.1 (C), 130.0 (CH), 129.6 (CH), 128.9 (CH), 128.5 (C), 126.8 (CH), 126.5 (C), 125.7 (CH), 121.1 (CH), 116.42 (CH), 116.39 (C), 113.3 (CH), 66.3 (CH<sub>2</sub>), 61.4 (CH), 40.6 (CH), 30.2 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>). IR (KBr, neat): 3430, 1735, 1350, 1166, 607 cm<sup>-1</sup>. HRMS (ESI-ToF) *m*/*z*: [M + Na]<sup>+</sup> calcd for C<sub>27</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>Na 559.0968, found 559.0952.



(-)-(6aR,10aR)-4.6.6a,7,10,10a-Hexahvdro-8H-[1,3]oxazino-[5',4':4,5]benzo[1,2,3-cd]indol-8-one (25). To a solution of naphthalene (4.49 g, 35.0 mmol) in previously degassed THF (70 mL) was added lithium (243 mg, 35.0 mmol), and the mixture was sonicated for 30 min and then stirred at room temperature for 2 h in order to obtain a 0.5 M dark green (lithium naphthalenide) solution.<sup>18</sup> To a solution of (-)-24 (826 mg, 1.54 mmol, 1.0 equiv) in THF (20 mL) at -78 °C was added the freshly prepared lithium naphthalenide dropwise until the reaction mixture stayed permanently dark green (11 mL, 4.0 equiv). The mixture was stirred at -78 °C for 30 min and at room temperature for another 30 min. The mixture was quenched with 1 M NaHCO<sub>3</sub> (11 mL) and extracted with AcOEt ( $3 \times 20$  mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The provided residue was purified by flash chromatography (PE/AcOEt 4/1) to give (-)-25 as a white powder (207 mg, 59%).  $R_f = 0.3$  (EtOAc). Mp: >300 °C.  $[\alpha]_D^{16}$  -50.0 (*c* 0.06, pyridine). <sup>1</sup>H NMR (400 MHz, C<sub>5</sub>D<sub>5</sub>N)  $\delta$  11.87 (br s, 1H), 8.97 (br s, 1H), 7.45 (d, 1H, J = 8 Hz), 7.28-7.26 (m, 2H), 6.91 (d, 1H, J = 6.8 Hz), 5.20 (dd, 1H, J = 10.8, 4.4 Hz), 4.46 (t, 1H, J = 10.8 Hz), 3.89–3.82 (m, 1H), 3.47 (dd, 2H, J = 14.2, 4.6 Hz), 3.00 (t, 1H, J = 12.8 Hz). <sup>13</sup>C NMR (100 MHz, C<sub>5</sub>D<sub>5</sub>N)  $\delta$  154.2 (C), 135.4 (C), 128.0 (C), 127.5 (C), 123.4 (CH), 120.6 (CH), 113.6 (CH), 111.2 (CH), 110.5 (C), 69.6 (CH<sub>2</sub>), 55.8 (CH), 39.1 (CH), 29.8 (CH<sub>2</sub>). IR (KBr, neat): 3397, 1718, 1367, 1044, 746 cm<sup>-1</sup>. HRMS (ESI-ToF) m/z:  $[M + Na]^+$  calcd for  $C_{13}H_{12}N_2O_2Na$  251.0791, found 251.0790.



(+)-N-((4R,5R)-5-Formyl-1-tosyl-1,3,4,5-tetrahydrobenzo[cd]indol-4-yl)-4-methylbenzenesulfonamide (**26**). In analogy to the synthesis of compound (+)-17, to a solution of (-)-24 (28 mg, 5.1 ×  $10^{-2}$  mmol, 1.0 equiv) in THF (2 mL) at 0 °C was added LiAlH<sub>4</sub> (95%, 22.7 mg, 0.26 mmol, 5 equiv) at 0 °C. After the mixture was stirred for 20 min, water (0.03 mL) and a solution of NaOH (10%, 0.06 mL) were carefully added dropwise careful at the same temperature, and the mixture was filtered over Celite. The filter cake was washed with DCM (50 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give a white solid, which was used in the next step directly without further purification.

To a solution of the above product in DCM (2 mL) was added Dess-Martin periodinane (27.0 mg,  $6.1 \times 10^{-2}$  mmol, 1.2 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h shielded from light. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (PE/EtOAc 2/1) to give aldehyde (+)-**26** as a white solid (16.6 mg, 64%).  $R_f = 0.7$  (PE/EtOAc 2/1). Mp: 37–41 °C.  $[\alpha]_{23}^{23}$  +100.0 (*c* 0.01, DCM). <sup>1</sup>H NMR (300

MHz, CDCl<sub>3</sub>):  $\delta$  9.46 (s, 1H), 7.87 (d, 1H, *J* = 8.1 Hz), 7.79 (d, 2H, *J* = 8.4 Hz), 7.68 (d, 2H, *J* = 8.1 Hz), 7.21–7.39 (m, 6H), 7.10 (d, 1H, *J* = 7.2 Hz), 4.54–4.57 (m, 1H), 4.40–4.46 (m, 1H), 3.89 (d, 1H, *J* = 2.7 Hz), 2.92–2.98 (m, 1H), 2.62–2.68 (m, 1H), 2.45 (d, 3H), 2.36 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  197.9, 145.2, 143.9, 137.5, 135.2, 133.4, 130.1, 129.9, 128.3, 127.0, 126.8, 126.3, 122.5, 122.13, 122.10, 113.7, 113.4, 56.9, 48.2, 26.2, 21.60, 21.57. IR (neat): 3286, 2924, 1728, 1460, 1262, 1119, 795, 684, 582 cm<sup>-1</sup>. HRMS (ESI-ToF) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>26</sub>H<sub>25</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub> 509.1199, found 509.1196.

# ASSOCIATED CONTENT

#### **S** Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00573.

<sup>1</sup>H, <sup>13</sup>C NMR (DEPT 135) spectra for known compounds  $(13,^{18} (+)-16,^{21} (-)-3^{14-17,25})$  and unknown compounds [(+)-14, (-)-12, (+)-17, (+)-18, (-)-19, (-)-20, (+)-11, (-)-21, (-)-22, (-)-23, (-)-24, (-)-25, and (+)-26]; HPLC spectra of 12, 17, 18, and 3 (PDF) X-ray crystallographic data for  $(\pm)-21$  (CIF)

X-ray crystallographic data for (-)-3 (CIF)

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#### Notes

The authors declare no competing financial interest.

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- (23) X-ray crystal data for  $(\pm)$ -21 from ethyl acetate/petroleum ether:  $C_{31}H_{32}N_2O_6S_2$  (M = 592.71 g/mol): monoclinic, space group  $P2_1/n$  (no. 14), a = 20.918(2) Å, b = 6.0208(6) Å, c = 25.025(2) Å,  $\beta = 111.139(10)^\circ$ , V = 2939.6(5) Å<sup>3</sup>, Z = 4, T = 290.0(4) K,  $\mu$ (Mo K $\alpha$ ) = 0.228 mm<sup>-1</sup>,  $D_{calc} = 1.339$  g/cm<sup>3</sup>, 11607 reflections measured ( $6.72^\circ \le 2\Theta \le 52.04^\circ$ ), 5795 unique ( $R_{int} = 0.0473$ ,  $R_{sigma} = 0.0873$ ) which were used in all calculations. The final  $R_1$  was 0.0598 (>  $2\sigma(9I)$ ) and w $R_2$  was 0.1476 (all data). CCDC-1528617 contains the supplementary crystallographic data for  $(\pm)$ -21.
- (24) X-ray crystal data for (-)-3 from chloroform/methanol/ ammonia-water/acetone:  $C_{16}H_{20}N_2O$  (M = 256.34 g/mol): orthorhombic, space group  $P2_12_12_1$  (no. 19), a = 8.7997(4) Å, b =10.3121(5) Å, c = 15.5615(9) Å, V = 1412.10(13) Å<sup>3</sup>, Z = 4, T =293(2) K,  $\mu$ (Mo K $\alpha$ ) = 0.076 mm<sup>-1</sup>,  $D_{calc} = 1.206$  g/cm<sup>3</sup>, 3705 reflections measured ( $6.99^{\circ} \le 2\Theta \le 52.042^{\circ}$ ), 2370 unique ( $R_{int} =$ 0.0289,  $R_{sigma} = 0.0663$ ) which were used in all calculations. The final  $R_1$  was 0.0593 ( $I > 2\sigma(I)$ ) and w $R_2$  was 0.1324 (all data). CCDC-1536231 contains the supplementary crystallographic data for (-)-3.

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