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CONCISE SYNTHESIS OF (±)-AURANTIOCLAVINE

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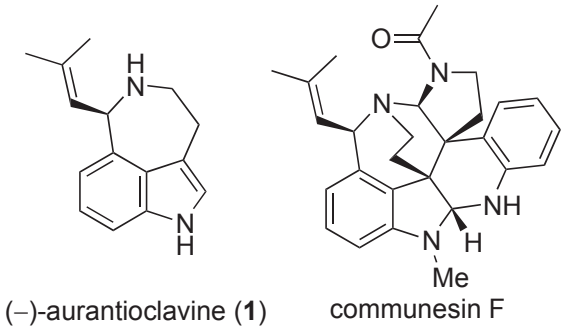
Abstract – A synthetic route to (±)-aurantioclavine has been established using a six-step transformation without toxic metal reagents. This synthetic route is useful because it is not only a short-step synthesis but is applicable to gram-scale synthesis of a protected (±)-aurantioclavine.

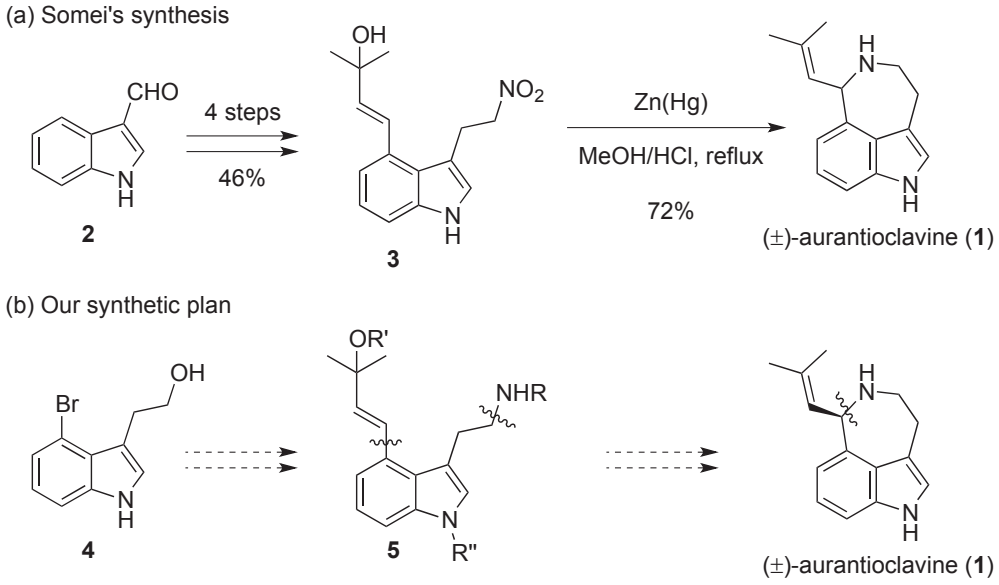
(−)-Aurantioclavine (**1**) was originally isolated from *Penicillium aurantiovirens* in 1981 by Kozlovskii and coworkers (Figure 1).[1] This compound is characterized by a nitrogen atom-containing seven-membered ring (an azepane ring) fused with indole. Recently, it was reported that aurantioclavine is a biosynthetic intermediate for communesins, which is a family of complex heptacyclic alkaloids.[2] To investigate synthetic routes, inspired by the biosynthesis, for related natural products from aurantioclavine and its protected form, a large-scale synthesis of these compounds would be important. Therefore, many groups have focused on aurantioclavine as a synthetic target. The first total synthesis was reported by Somei and co-workers based on a reductive amino cyclization (Scheme 1a).[3] Stoltz and co-workers reported the first enantioselective synthesis and determination of the absolute stereochemistry.[4] To date, several racemic and enantioselective total syntheses have been reported.[5–12] We have also reported an asymmetric synthesis via palladium-catalyzed intramolecular allylic amination.[10]



(−)-aurantioclavine (**1**) communesin F

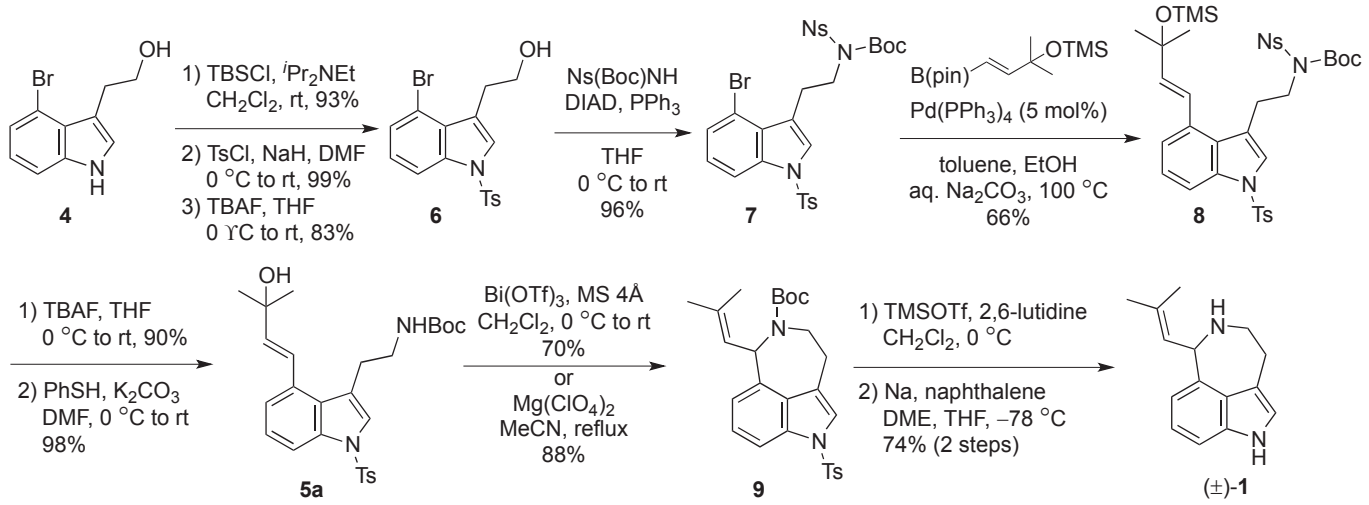
Figure 1. Aurantioclavine (**1**) and communesin F

The shortest-step synthesis is Ishikura's racemic synthesis from serotonin through a base-promoted Pictet–Spengler reaction, while the deoxygenation of a hydroxy group on the indole ring was problematic.[7] Somei's first total synthesis required five steps from indole-3-carboxaldehyde (**2**) (Scheme 1a).[3a] This synthesis appeared to be scalable, but it requires the use of a zinc-mercury amalgam. For a concise and scalable synthesis of **1** without toxic metal reagents, we planned an intramolecular S_N2' reaction of compound **5** (Scheme 1b). The cyclization precursor **5** would be prepared through introduction of a nitrogen atom and an allyl alcohol unit into an indole derivative **4**. In the current study, we will report a concise synthesis of (±)-**1** based on an intramolecular S_N2' reaction.



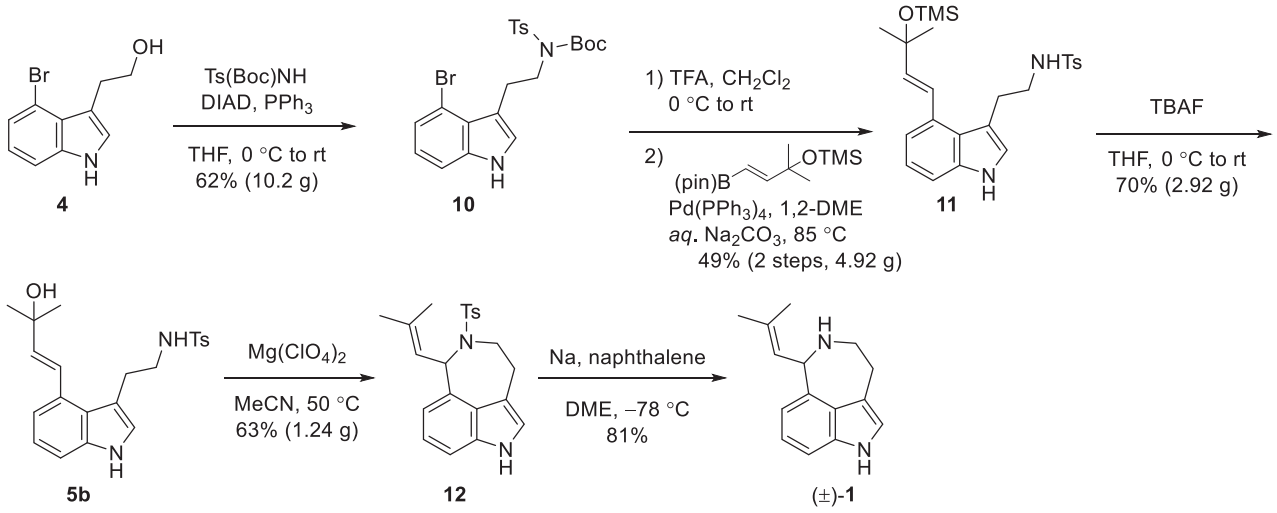
Scheme 1. (a) Somei's synthesis, and (b) our synthetic plan for aurantioclavine (**1**)

Our racemic synthesis was initiated from the silylation of a known indole derivative **4** (Scheme 2).[13] After tosylation of the indole nitrogen, the *tert*-butyldimethylsilyl (TBS) group was removed to produce alcohol **6**. The Mitsunobu reaction of **6** with NsNHBoc gave compound **7** in excellent yield. The Suzuki–Miyaura coupling reaction of **7** with (*E*)-(3-hydroxy-3-methylbutenyl)boronic acid pinacol ester in the presence of a catalytic amount of $Pd(PPh_3)_4$ and Na_2CO_3 as a base proceeded smoothly to give compound **8** in 66% yield. After the trimethylsilyl (TMS) and nosyl (Ns) groups were removed, the formation of an azepane ring was examined. A treatment of **5a** using a catalytic amount (10 mol%) of $Bi(OTf)_3$ in the presence of MS 4Å in CH_2Cl_2 gave a cyclized product **9** in 70% yield without removal of the Boc group. Use of $Mg(ClO_4)_2$, which was employed by Jia in a related cyclization,[9] gave a better yield (88%). Finally, *tert*-butoxycarbonyl (Boc) and tosyl (Ts) groups were removed stepwise through treatment using TMSOTf and sodium naphthalenide to give racemic aurantioclavine (**1**). The spectral data including ^1H and ^{13}C NMR spectra of **1** are identical to previously reported data.[1,10a]



Scheme 2. Initial route to (±)-aurantioclavine (**1**)

Although we identified the cyclization conditions for compound **5a**, the synthetic route was lengthy because of protecting group manipulation, which required seven steps. Therefore, the initial synthetic route was revised by minimizing these protecting group manipulations. The nitrogen unit could be introduced to compound **4** without the Ts group on the indole nitrogen atom (Scheme 3). After deprotection of the Boc group of **10** through treatment using trifluoroacetic acid (TFA), an allyl alcohol unit was introduced through Suzuki–Miyaura coupling with (*E*)-(3-hydroxy-3-methylbutenyl)boronic acid pinacol ester to give compound **11**. Removal of the TMS group was followed by formation of an azepane ring using $Mg(ClO_4)_2$ to give a protected aurantioclavine **12**. Finally, racemic aurantioclavin was accessed through treatment using sodium naphthalenide to remove the Ts group. This synthetic route was robust, and 1.24 g of protected aurantioclavine **12** could be synthesized.



Scheme 3. Concise and scalable synthesis of aurantioclavine (**1**)

In summary, we have developed a concise synthetic route to (±)-aurantioclavine by minimizing protecting group manipulations. The synthesis requires only a six-step transformation without toxic metal reagents. Additionally, this synthetic route could be used for gram-scale synthesis of a protected (±)-aurantioclavine. Therefore, it is likely to be useful in preparing not only aurantioclavine but synthetic analogues.

EXPERIMENTAL

General. Unless otherwise noted, all reactions were performed under argon atmosphere. Analytical thin-layer chromatography was performed using Merck Silica gel 60 and Merck 25 DC-Alufolein. Flash silica gel column chromatography was performed using Kanto Silica gel 60 N (spherical, neutral, 40–100 μm) or Fuji Silysia NH silica gel. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a JEOL JNM-ECA500 KP at 500 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00) or C_6H_6 (δ 7.16). Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); dd (double doublet); ddd (double double doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a JEOL JNM-ECA500 KP at 125 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0). Infrared spectra were recorded using a FT/IR-4100 (JASCO). Low resolution mass spectra and high resolution mass spectra (HRMS) were recorded on JMS-700 mass spectrometer (JEOL) for FAB-MS and a LCMS-IT-TOF (Shimadzu) for ESI-MS.

4-Bromo-3-(2-hydroxyethyl)-1-tosyl-1*H*-indole (6)

To a solution of indole **6** (3.80 g, 15.8 mmol) in CH_2Cl_2 (70 mL) were added *N*-ethyldiisopropylamine (5.50 mL, 31.6 mmol) and *tert*-butyldimethylchlorosilane (2.86 g, 19.0 mmol). After the reaction mixture was stirred at room temperature for 7 h, the reaction mixture was diluted with EtOAc, and washed with saturated *aq*. NH_4Cl and then *aq*. $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/EtOAc = 9/1 to 8/2) to give a silyl ether (5.20 g, 93%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.08 (1H, s), 7.31–7.25 (2H, m), 7.10 (1H, m), 6.99 (1H, dd, J = 7.7, 7.7 Hz), 3.93 (2H, t, J = 7.2 Hz), 3.24 (2H, t, J = 7.2 Hz), 0.89 (9H, s), 0.01 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.4, 125.6, 124.4, 123.8, 122.6, 114.2, 113.7, 110.4, 64.8, 29.7, 26.0, 18.4, –5.2.

To a solution of the above silyl ether (2.32 g, 6.55 mmol) in DMF (32 mL) were added sodium hydride (60% wt, 314 mg, 7.21 mmol) and *p*-toluenesulfonyl chloride (1.37 g, 7.21 mmol) at 0 °C. After 10 min, the reaction mixture was stirred at room temperature for additional 4 h. The reaction was quenched with saturated *aq*. NH_4Cl. The aqueous layer was extracted with mixed solution of hexane/EtOAc (3/2) twice.

The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/EtOAc = 95/5 to 85/15) to give 4-bromo-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-tosyl-*1H*-indole (3.30 g, 99%) as a white amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94 (1H, dd, *J* = 8.0, 0.6 Hz), 7.73 (2H, d, *J* = 8.3 Hz), 7.46 (1H, s), 7.36 (1H, dd, *J* = 8.0, 0.6 Hz), 7.21 (2H, d, *J* = 8.3 Hz), 7.10 (1H, dd, *J* = 8.0, 8.0 Hz), 3.90 (2H, t, *J* = 6.6 Hz), 3.14 (2H, t, *J* = 6.6 Hz), 2.34 (3H, s), 0.88 (9H, s), 0.01 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 145.1, 136.2, 134.9, 129.9, 129.0, 127.6, 126.8, 125.6, 125.1, 120.0, 114.4, 112.8, 63.0, 29.8, 25.9, 21.5, 18.2, –5.3.

To a solution of the above 4-bromo-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-tosyl-*1H*-indole (3.09 g, 6.08 mmol) in THF (120 mL) was added tetrabutylammonium fluoride (1.0 M in THF soln., 7.30 mL, 7.30 mmol) at 0 °C. After 10 min, the reaction mixture was stirred at room temperature for additional 40 min and then saturated *aq*. NH_4Cl was added to the reaction mixture. The aqueous layer was extracted with EtOAc twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/EtOAc = 7/3 to 6/4) to give titled compound **6** (2.00 g, 83%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.97 (1H, d, *J* = 8.0 Hz), 7.74 (2H, d, *J* = 8.0 Hz), 7.50 (1H, s), 7.37 (1H, d, *J* = 8.0 Hz), 7.23 (2H, d, *J* = 8.0 Hz), 7.12 (1H, dd, *J* = 8.0, 8.0 Hz), 3.96–3.92 (2H, m), 3.21 (2H, t, *J* = 6.4 Hz), 2.34 (3H, s), 1.65 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 145.3, 136.5, 134.8, 130.0, 128.7, 127.8, 126.8, 125.7, 125.4, 119.3, 114.5, 112.9, 62.5, 29.6, 21.6; HRMS (ESI): calcd. for $C_{17}H_{17}NO_3S^{79}Br$ $[M+H]^+$ 394.0113, found 394.0105.

tert-Butyl (2-(4-bromo-1-tosyl-*1H*-indol-3-yl)ethyl)((4-nitrophenyl)sulfonyl)carbamate (7)

To a solution of indole **6** (1.98 g, 5.02 mmol), *tert*-butyl(2-nitrophenyl)carbamate (1.82 g, 6.02 mmol), and triphenylphosphine (2.62 g, 10.0 mmol) in THF (60 mL) was added diisopropyl azodicarboxylate (1.78 mL, 9.04 mmol) at 0 °C. After 10 min, the reaction mixture was stirred at room temperature for additional 12 h and then the reaction was quenched with water. The aqueous layer was extracted with EtOAc twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/$CHCl_3$ = 2/8 to 0/10) to give titled compound **7** (3.25 g, 96%) as a white amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.34 (1H, m), 7.95 (1H, dd, *J* = 8.0, 0.9 Hz), 7.80 (2H, d, *J* = 8.6 Hz), 7.75–7.74 (3H, m), 7.62 (1H, s), 7.38 (1H, dd, *J* = 8.0, 0.9 Hz), 7.25 (2H, d, *J* = 8.6 Hz), 7.12 (1H, dd, *J* = 8.0, 8.0 Hz), 4.20 (2H, t, *J* = 6.6 Hz), 3.37 (2H, t, *J* = 6.6 Hz), 2.35 (3H, s), 1.03 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 150.2, 147.6, 145.1, 136.3, 134.8, 134.1, 133.54, 133.48, 131.7, 130.0, 128.9, 127.6, 127.0, 126.7, 125.3, 124.3, 118.7, 114.6, 112.7, 84.6, 48.3, 27.3, 27.0, 21.6; HRMS (FAB): calcd. for $C_{28}H_{28}N_3O_8S_2^{79}BrNa$ $[M+Na]^+$ 700.0399, found 700.0395.

***tert*-Butyl (*E*)-(2-(4-(3-hydroxy-3-methylbut-1-en-1-yl)-1-tosyl-*1H*-indol-3-yl)ethyl)carbamate (5a)**

To a solution of indole **7** (3.18 g, 4.69 mmol), and boronic ester (1.60 g, 5.63 mmol) in toluene (25 mL), EtOH (5 mL) and aq. Na_2CO_3 (2.0 M, 25 mL) was added tetrakis(triphenylphosphine)palladium (272 mg, 0.235 mmol). The reaction mixture was heated to 100 °C for 21 h. The reaction mixture was gradually cooled to room temperature. After addition of water, the aqueous layer was extracted with EtOAc twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/EtOAc = 8/2 to 6/4) to give compound **8** (2.35 g, 66%) as a white amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.32 (1H, m), 7.87 (1H, m), 7.80 (2H, d, *J* = 8.3 Hz), 7.76–7.72 (3H, m), 7.52 (1H, s), 7.25–7.21 (4H, m), 7.08 (1H, d, *J* = 15.8 Hz), 6.18 (1H, d, *J* = 15.8 Hz), 4.13 (2H, t, *J* = 6.5 Hz), 3.25 (2H, t, *J* = 6.5 Hz), 2.34 (3H, s), 1.45 (6H, s), 1.05 (9H, s), 0.17 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 150.1, 147.6, 144.7, 142.1, 135.7, 135.1, 134.1, 133.52, 133.48, 132.7, 131.7, 129.9, 128.0, 127.0, 125.0, 124.6, 124.3, 123.3, 121.2, 119.0, 112.4, 84.8, 73.8, 47.5, 30.5, 28.4, 27.4, 21.5, 2.6.

To a solution of the above compound **8** (2.35 g, 3.11 mmol) in THF (50 mL) was added tetrabutylammonium fluoride (1.0 M in THF sol., 3.73 mL, 3.73 mmol) at 0 °C. After the reaction mixture was stirred at 0 °C for 1 h, saturated *aq*. NH_4Cl was added to the mixture. The aqueous layer was extracted with EtOAc twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/EtOAc = 6/4 to 5/5) to give an alcohol (1.92 g, 90%) as a white amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.28 (1H, m), 7.90 (1H, m), 7.79–7.73 (5H, m), 7.52 (1H, s), 7.28–7.21 (5H, m), 6.27 (1H, d, *J* = 15.5 Hz), 3.95 (2H, t, *J* = 7.7 Hz), 3.28 (2H, t, *J* = 7.7 Hz), 3.06 (1H, s), 2.34 (3H, s), 1.40 (6H, s), 1.28 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 150.3, 147.4, 144.9, 142.2, 135.8, 135.0, 134.4, 133.4, 132.9, 132.5, 131.8, 129.9, 127.6, 126.8, 125.5, 124.7, 124.5, 122.7, 121.7, 119.1, 112.5, 86.0, 70.9, 48.7, 29.8, 28.2, 27.7, 21.5.

To a solution of the above alcohol (705 mg, 1.03 mmol) in DMF (4 mL) were added potassium carbonate (427 mg, 3.09 mmol) and thiophenol (127 μL, 1.24 mmol) at 0 °C. After 10 min, the reaction mixture was stirred at room temperature for additional 12 h. After addition of water, the aqueous layer was extracted with EtOAc twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/EtOAc = 7/3 to 6/4) to give the titled compound **5a** (503 mg, 98%) as a white amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.86 (1H, dd, *J* = 7.7, 1.4 Hz), 7.73 (2H, d, *J* = 8.0 Hz), 7.36 (1H, s), 7.29 (1H, d, *J* = 15.8 Hz), 7.27–7.22 (2H, m), 7.20 (2H, d, *J* = 8.0 Hz), 6.27 (1H, d, *J* = 15.8 Hz), 4.92 (1H, s), 3.97 (1H, s), 3.30–3.24 (2H, m), 3.02–2.97 (2H, m), 2.33 (3H, s), 1.46 (9H, s), 1.40 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 155.9, 144.9, 142.2, 135.9, 135.0, 132.7, 129.8, 127.7, 126.8, 124.7, 124.6, 122.8, 1215, 120.1, 112.3, 79.9, 70.6, 42.1,

29.8, 28.8, 28.4, 21.5; HRMS (ESI): calcd. for $C_{27}H_{35}N_2O_5S$ $[M+H]^+$ 499.2267, found 499.2258.

***tert*-Butyl 1-(2-methylprop-1-en-1-yl)-6-tosyl-1,3,4,6-tetrahydro-*2H*-azepino[5,4,3-cd]indole-2-carboxylate (9)**

To a solution of compound **5a** (1.25 g, 2.51 mmol) in MeCN (30 mL) was added magnesium perchlorate (672 mg, 3.01 mmol). The reaction mixture was refluxed for 4 h. The reaction mixture was gradually cooled to room temperature and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (hexane/EtOAc = 9/1 to 8/2) to give titled compound **9** (1.06 g, 88%, mixture of two rotamers (3:2)) as a white amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.84 (1H, dd, *J* = 11.7, 8.3 Hz), 7.76 (2H, dd, *J* = 11.0, 8.4 Hz), 7.34 (1H, d, *J* = 9.5 Hz), 7.25-7.18 (3H, m), 6.96 (0.6H, d, *J* = 7.7 Hz), 6.90 (0.4H, d, *J* = 7.7 Hz), 6.42 (0.6H, d, *J* = 7.7 Hz), 6.23 (0.4H, d, *J* = 8.3 Hz), 5.26 (0.4H, d, *J* = 8.3 Hz), 5.22 (0.6H, d, *J* = 8.0 Hz), 4.01 (0.4H, d, *J* = 14.0 Hz), 3.85 (0.6H, d, *J* = 14.0 Hz), 3.42–3.30 (1H, m), 3.21–3.07 (1H, m), 2.97–2.91 (1H, m), 2.35 (3H, s), 1.70 (3H, s), 1.58 (3H, s), 1.45 (5.4H, s), 1.41 (3.6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.7, 154.3, 144.8, 138.4, 138.2, 136.7, 136.0, 135.7, 135.3, 135.2, 129.8, 127.6, 126.91, 126.86, 125.0, 124.8, 124.4, 124.1, 122.7, 122.5, 122.3, 121.8, 121.1, 120.9, 111.52, 111.47, 80.0, 79.6, 58.0, 56.8, 42.1, 41.7, 28.5, 28.4, 27.6, 26.9, 25.7, 25.6, 21.6, 18.5, 18.4; HRMS (ESI): calcd. for $C_{27}H_{33}N_2O_4S$ $[M+H]^+$ 481.2161, found 481.2177.

(±)-Aurantioclavine (1)

To a solution of compound **9** (228 mg, 0.474 mmol) in CH_2Cl_2 (5.3 mL) were added 2,6-lutidine (0.280 mL, 2.37 mmol) and trimethylsilyl trifluoromethanesulfonate (0.34 mL, 1.90 mmol) at 0 °C. After the reaction mixture was stirred at 0 °C for 20 min, saturated *aq*. NH_4Cl was added to the reaction mixture. The aqueous layer was extracted with EtOAc twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by NH silica gel column chromatography (hexane/EtOAc = 8/2 to 6/4) to give a Ts-protected aurantioclavine (172 mg, 96%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (1H, dd, *J* = 8.0, 0.9 Hz), 7.73 (2H, d, *J* = 8.3 Hz), 7.36 (1H, s), 7.21–7.17 (3H, m), 6.95 (1H, dd, *J* = 8.0, 0.9 Hz), 5.36 (1H, d, *J* = 8.9 Hz), 4.80 (1H, d, *J* = 8.9 Hz), 3.47 (1H, m), 3.04 (1H, m), 2.95 (2H, m), 2.33 (3H, s), 1.82 (3H, s), 1.79 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 144.7, 139.2, 136.1, 135.3, 134.2, 129.8, 128.9, 127.1, 126.8, 124.0, 122.5, 122.3, 121.9, 111.7, 62.1, 47.8, 30.6, 25.8, 21.5, 18.3.

To a solution of naphthalene (800 mg, 6.24 mmol) in DME (5 mL) was added a sodium metal (160 mg, 6.96 mmol). The mixture was stirred at room temperature for 3 h. This solution was added dropwise to the solution of the above Ts-protected aurantioclavine (172 mg, 0.452 mmol) in THF (35 mL) at –78 °C until dark green color persisted. After 10 min, the reaction was quenched with saturated *aq*. NH_4Cl. The

aqueous layer was extracted with EtOAc twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by NH silica gel column chromatography (hexane/EtOAc = 6/4 to 4/6) to give (±)-aurantioclavine (**1**) (75.8 mg, 74%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (1H, s), 7.23 (1H, d, *J* = 7.7 Hz), 7.10 (1H, dd, J = 7.7, 7.7 Hz), 7.03 (1H, s), 6.84 (1H, d, *J* = 7.7 Hz), 5.46 (1H, dt, *J* = 9.2, 1.1 Hz), 4.89 (1H, d, *J* = 9.2 Hz), 3.56 (1H, m), 3.12 (1H, m), 3.07–2.99 (2H, m), 1.85 (6H, dd, *J* = 5.2, 1.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 138.5, 137.1, 133.2, 127.7, 125.3, 121.5, 120.9, 117.8, 115.7, 109.1, 62.6, 48.9, 31.0, 25.8, 18.3; IR (ATR): 3400, 3145, 2933, 2725, 1615, 1440, 1337, 1263, 1158 cm^{-1}; HRMS (FAB): calcd. for $C_{15}H_{19}N_2$ $[M+H]^+$ 227.1548, found 227.1574.

tert-Butyl (2-(4-bromo-*1H*-indol-3-yl)ethyl)(tosyl)carbamate (10)

To a solution of indole derivative **4** (8.09 g, 33.7 mmol), Ts(Boc)NH (11.0 g, 40.4 mmol), and triphenylphosphine (17.7 g 67.4 mmol) in 240 mL of THF at 0 °C, a solution of diisopropyl azodicarboxylate (12.0 mL, 60.7 mmol) was added in a dropwise manner. After 30 min, the reaction mixture was warmed up to ambient temperature and was stirred for an additional 12 h. The reaction mixture was quenched using H_2O. The aqueous layer was extracted twice using EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using flash silica gel column chromatography (hexane/EtOAc = 8/2 to 7/3) to give titled compound **10** (10.2 g, 62%) as a white amorphous substance; ^{1}H NMR ($CDCl_3$) δ: 8.94 (1H, s), 7.81 (2H, d, *J* = 8.0 Hz), 7.32 (1H, d, *J* = 8.3 Hz), 7.25–7.23 (3H, m), 7.18 (1H, s), 6.95 (1H, dd, *J* = 8.0, 8.0 Hz), 4.32 (2H, t, *J* = 6.2 Hz), 3.45 (2H, t, *J* = 6.2 Hz), 2.39 (3H, s), 0.92 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 151.3, 144.1, 137.8, 137.0, 129.1, 128.0, 126.1, 125.6, 123.4, 122.4, 114.1, 111.9, 110.8, 83.4, 49.0, 27.2, 27.0, 21.5; IR (ATR): 3375, 1709, 1341, 1084 cm^{-1}; HRMS (FAB): calcd. for $C_{22}H_{25}N_2O_4S^{79}BrNa$ $[M+Na]^+$ 515.0616, found 515.0613.

(*E*)-4-Methyl-*N*-(2-(4-(3-methyl-3-((trimethylsilyl)oxy)but-1-en-1-yl)-*1H*-indol-3-yl)ethyl)benzenesulfonamide (11)

To a solution of indole **10** (10.5 g, 21.3 mmol) in 720 mL of CH_2Cl_2 at 0 °C, 80 mL of trifluoroacetic acid was added. After 1 h, the reaction mixture was warmed up to ambient temperature and stirred for an additional 5 h. The reaction mixture was neutralized using *aq*. Na_2CO_3. The aqueous layer was extracted using CH_2Cl_2 twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a crude material.

The solution of this crude material, boronic ester (7.28 g, 25.6 mmol), and tetrakis(triphenylphosphine)palladium (1.24 g, 1.07 mmol) in 130 mL of 1,2-dimethoxyethane and 65 mL

of *aq*. Na_2CO_3 (2.0 M) was warmed up to 85 °C. After 16 h, the reaction mixture was gradually cooled to the ambient temperature and diluted using H_2O. The aqueous layer was extracted twice using EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude substance was purified using flash silica gel column chromatography (hexane/EtOAc = 8/2 to 6/4) to give titled compound **11** (4.92 g, 49%, two steps) as an orange amorphous substance; ^{1}H NMR ($CDCl_3$) δ: 8.19 (1H, s), 7.53 (2H, d, *J* = 8.3 Hz), 7.21 (1H, d, *J* = 7.7 Hz), 7.12–7.07 (4H, m), 7.02 (1H, d, *J* = 15.8 Hz), 6.92 (1H, s), 6.07 (1H, d, *J* = 15.8 Hz), 4.54 (1H, t, *J* = 6.3 Hz), 3.23 (2H, dt, *J* = 6.3, 6.3 Hz), 3.04 (2H, t, *J* = 6.3 Hz), 2.34 (3H, s), 1.36 (6H, s), 0.15 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 143.1, 140.0, 137.2, 136.5, 131.3, 129.5, 126.8, 124.1, 123.9, 122.3, 117.1, 111.7, 110.4, 73.7, 43.3, 30.6, 27.5, 21.4, 2.6; IR (ATR): 3734, 3392, 2980, 2870, 1156, 837 cm^{-1}; HRMS (FAB): calcd. for $C_{25}H_{34}N_2O_3SSiNa$ $[M+Na]^+$ 493.1957, found 493.1954.

(*E*)-*N*-(2-(4-(3-Hydroxy-3-methylbut-1-en-1-yl)-*1H*-indol-3-yl)ethyl)-4-methylbenzenesulfonamide (5b)

To a solution of indole **11** (4.90 g, 10.4 mmol) in 170 mL of THF at 0 °C, a solution of tetrabutylammonium fluoride (1.0 M in THF sol., 11.4 mL, 1.1 mmol) was added in a dropwise manner. After 15 min, the reaction mixture was warmed up to ambient temperature and stirred for an additional 1 h. The reaction mixture was quenched using saturated *aq*. NH_4Cl. The aqueous layer was extracted twice using EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude substance was purified using flash silica gel column chromatography (hexane/EtOAc = 7/3 to 5/5) to give titled compound **5b** (2.92 g, 70%) as a yellow amorphous substance; ^{1}H NMR ($CDCl_3$) δ: 8.31 (1H, s), 7.60 (2H, d, *J* = 8.3 Hz), 7.24 (1H, m), 7.20 (1H, d, *J* = 15.8 Hz), 7.14 (2H, d, *J* = 8.3 Hz), 7.12–7.09 (2H, m), 6.91 (1H, s), 6.19 (1H, d, *J* = 15.8 Hz), 5.26 (1H, m), 3.16 (2H, dt, *J* = 7.0, 7.0 Hz), 3.03 (2H, t, *J* = 7.0 Hz), 2.57 (1H, br), 2.34 (3H, s), 1.41 (6H, s); ^{13}C NMR ($CDCl_3$) δ: 143.2, 139.4, 137.1, 136.6, 131.0, 129.5, 126.8, 124.4, 124.3, 123.7, 122.2, 117.2, 112.1, 110.5, 71.2, 44.2, 30.0, 28.0, 21.4; IR (ATR): 3393, 1318, 1304, 1152 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{26}N_2O_3SNa$ $[M+Na]^+$ 421.1556, found 421.1555.

***N*-Ts Aurantioclavine (12)**

The solution of indole **5b** (2.05 g, 5.14 mmol) and magnesium perchlorate (1.38 g, 6.17 mmol) in 200 mL of MeCN was warmed up to 50 °C. After 12 h, the reaction mixture was gradually cooled to ambient temperature and concentrated under reduced pressure. The crude substance was purified using flash silica gel column chromatography (hexane/EtOAc = 8/2 to 6/4) to give titled compound **12** (1.24 g, 63%) as a white amorphous substance; ^{1}H NMR ($CDCl_3$) δ: 8.06 (1H, s), 7.54 (2H, d, *J* = 8.3 Hz), 7.15 (1H, d, *J* =

7.8 Hz), 7.05 (1H, dd, *J* = 7.8, 7.8 Hz), 7.03 (2H, d, *J* = 8.3 Hz), 6.86 (1H, s), 6.77 (1H, d, *J* = 7.8 Hz), 6.25 (1H, d, *J* = 9.0 Hz), 5.35 (1H, dt, *J* = 9.0, 1.4 Hz), 4.00 (1H, dt, *J* = 14.9, 3.6 Hz), 3.72 (1H, ddd, *J* = 14.9, 11.8, 3.6 Hz), 3.22 (1H, ddd, *J* = 16.2, 11.8, 3.6 Hz), 3.01 (1H, dt, *J* = 16.2, 3.6 Hz), 2.29 (3H, s), 1.83 (3H, d, *J* = 1.4 Hz), 1.63 (3H, s); ^{13}C NMR ($CDCl_3$) δ: 142.3, 138.2, 137.0, 136.0, 135.4, 128.8, 127.0, 124.3, 123.3, 121.6, 121.3, 117.8, 113.6, 109.4, 59.7, 44.0, 28.4, 25.8, 21.3, 18.6; IR (ATR): 3405, 1435, 1321, 1152 cm^{-1}; HRMS (FAB): calcd. for $C_{22}H_{25}N_2O_2S$ $[M+H]^+$ 381.1637, found 381.1634.

(±)-Aurantioclavine (1)

To a solution of naphthalene (800 mg, 6.25 mmol) in DME (5 mL) a sodium metal was added (0.160 g, 6.96 mmol). The mixture was stirred at ambient temperature for 1.5 h. This solution was added dropwise to a solution of **12** (246.8 mg, 0.649 mmol) in DME (6 mL) at –78 °C until a dark green color persisted. After 25 min, the reaction mixture was quenched using saturated *aq*. NH_4Cl. The aqueous layer was extracted twice using EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude substance was purified using NH silica gel column chromatography (hexane/EtOAc = 8/2 to 5/5) to give (±)-aurantioclavine (**1**) (118.9 mg, 81%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (1H, s), 7.23 (1H, d, *J* = 7.7 Hz), 7.10 (1H, dd, J = 7.7, 7.7 Hz), 7.03 (1H, s), 6.84 (1H, d, *J* = 7.7 Hz), 5.46 (1H, dt, *J* = 9.2, 1.1 Hz), 4.89 (1H, d, *J* = 9.2 Hz), 3.56 (1H, m), 3.12 (1H, m), 3.07–2.99 (2H, m), 1.85 (6H, dd, *J* = 5.2, 1.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 138.5, 137.1, 133.2, 127.7, 125.3, 121.5, 120.9, 117.8, 115.7, 109.1, 62.6, 48.9, 31.0, 25.8, 18.3; IR (ATR): 3400, 3145, 2933, 2725, 1615, 1440, 1337, 1263, 1158 cm^{-1}; HRMS (FAB): calcd. for $C_{15}H_{19}N_2$ $[M+H]^+$ 227.1548, found 227.1574.

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