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Concise Synthesis of (±)-Aurantioclavine through a Base-Promoted Pictet–Spengler Reaction

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A concise total synthesis of (±)-aurantioclavine (**1**) was completed in three steps through the base-promoted Pictet–Spengler reaction of N_b-benzylserotonin with 3-methylbut-2-enal.

Introduction

Aurantioclavine (**1**),[1] clavicipitic acid (**2**),[2] and hyrtiazepine (**3**)[3] (Figure 1) are members of a unique class of indole alkaloids characterized by a novel azepino[5,4,3-*cd*]-indole ring system. (–)-Aurantioclavine (**1**) was first isolated in 1981 from *Penicillium aurantiovirens*,[1] and the absolute configuration was confirmed to be (*R*) in 2008.[4]

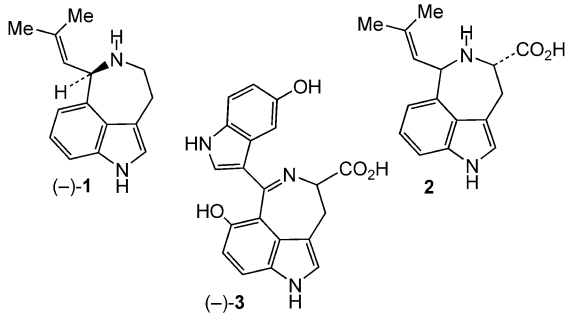
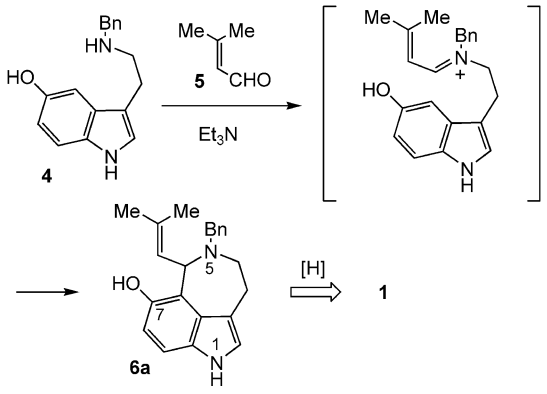


Figure 1. Azepinoindole alkaloids.

Previously, two racemic[5] syntheses and one enantioselective[4] synthesis of **1** were achieved in multiple steps through the preparation of properly functionalized 3,4-disubstituted indoles, with subsequent ring closure to form the azepane ring. In the context of our interest in indole alkaloid synthesis,[6] we developed a novel one-pot procedure for the assembly of the azepino[5,4,3-*cd*]indole ring system through the base-promoted Pictet–Spengler reaction of N_b-benzylserotonin (**4**) with aldehydes.[7] This prompted us to devise a straightforward strategy for the synthesis of azepinoindole alkaloids (Scheme 1). Our synthetic route to (±)-**1** involves the one-pot assembly of azepinoindole **6a** from **4** and 3-methylbut-2-enal (**5**) as the key step and the subsequent removal of the OH group at the 7-position and the N_b-benzyl (Bn) group at the 5-position (Scheme 1). This paper describes a novel and concise total synthesis of (±)-aurantioclavine (**1**) and expands upon our previous communication.[7]



Scheme 1.

Results and Discussion

Although the Pictet–Spengler reaction has been extensively investigated,[8] the one-pot construction of the azepinoindole moiety is a remarkable finding for this reaction. The study was initially undertaken to probe the conditions for the reaction of **4** with various α,β-unsaturated aldehydes. Initial treatment of **4** with acrolein (**7a**; 3 equiv.) in the presence of Et_3N in MeOH at room temperature for 24 h under a nitrogen atmosphere resulted in the addition of MeOH to afford azepinoindole **8a** in 41% yield

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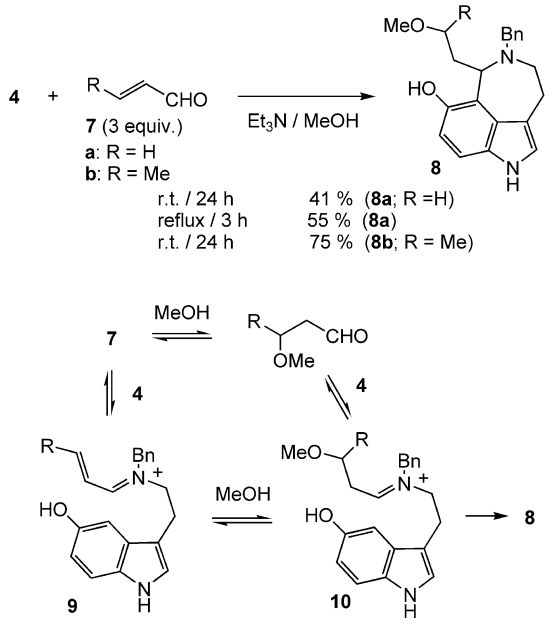
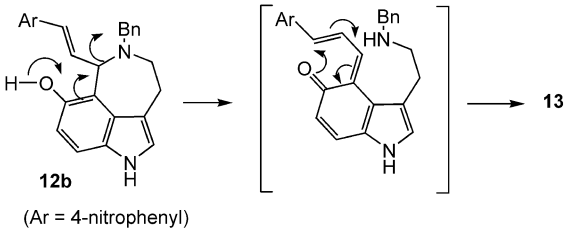
(Scheme 2). The yield was increased slightly to 55% by heating the reaction mixture at reflux for 3 h. The reaction proceeded similarly in the case of crotonaldehyde (**7b**) at room temperature for 24 h, and MeOH adduct **8b** was obtained as a separable mixture of two diastereomers in 75% yield. The production of **8** can conceivably occur through the addition of MeOH to **7** and/or to iminium ion **9** followed by the cyclization of **10**.



Scheme 2.

Under the same conditions, carrying out the reaction with cinnamaldehyde (**11a**) at room temperature for 6 h provided **12a** in 84% yield without the formation of MeOH adduct, whereas pyranocarboline **14** was obtained as an inseparable mixture of two diastereomers in 80% yield by refluxing for 24 h. On the other hand, the reaction with 4-nitrocinnamaldehyde (**11b**) was more facile; the reaction was complete within 1 h at room temperature, producing **12b** in 53% yield along with pyranoindole **13** in 14% yield. Under reflux for 20 min, the reaction afforded **12b** in 69% yield and **13** in 11% yield (Scheme 3).

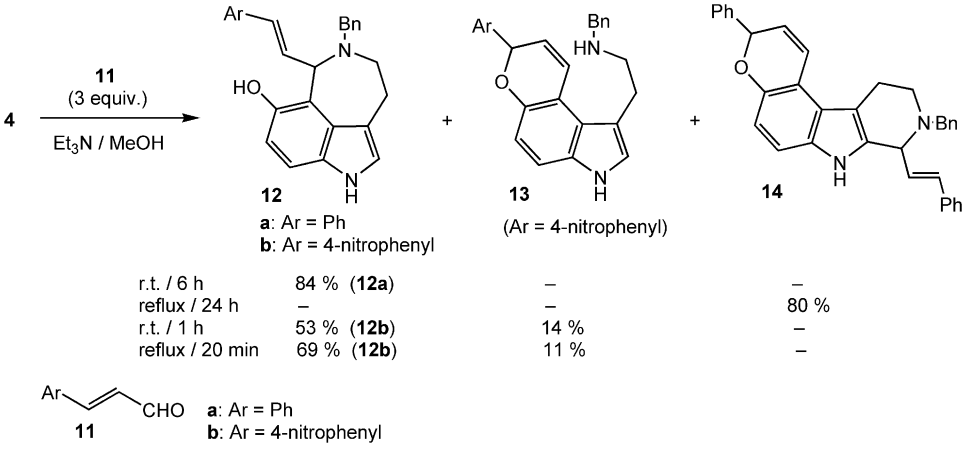
Azepinoindoles **12** were likely precursors of **13** and **14**. A series of ring-opening and ring-closing sequences triggered by the unprotected OH group in **12b** likely account for the generation of **13** (Scheme 4). It is also possible that, in boiling MeOH, **12a** underwent this series of transformations accompanied by the Pictet–Spengler reaction with **11a**, leading to **14**.



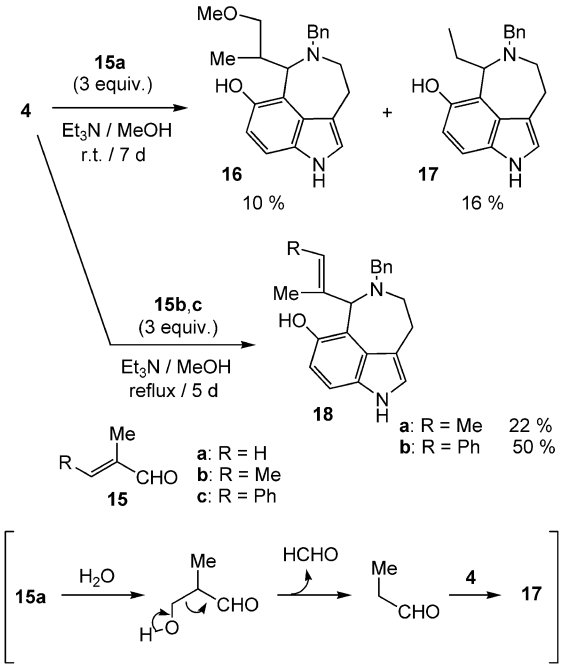
Scheme 4.

Serious retardation of the reaction was observed in the reaction with α-methyl-substituted aldehydes **15**. Running the reaction with methacrolein (**15a**) at room temperature for 7 d resulted in the isolation of **16** in 10% yield and **17** in 16% yield along with the recovery of unreacted **4** in 30% yield (Scheme 5). The formation of **17** can be explained by the reaction of **4** with propionaldehyde generated from **15a** and H_2O in situ. Heating **4** at reflux with 2-methyl-2-butenal (**15b**) and α-methylcinnamaldehyde (**15c**) for 5 d resulted in the isolation of **18a** and **18b** in 22 and 50% yield, respectively.

The successful formation of azepinoindoles in one pot prompted us to extend the reaction to the synthesis of (±)-aurantioclavine (**1**). Similarly, the reaction of **4** with 3-methylbut-2-enal (**5**) (3 equiv.) was first conducted in the presence of Et_3N in MeOH at room temperature for 10 h (Scheme 6). The separation of the reaction mixture by silica gel column chromatography resulted in the isolation of two products, azepinoindole **6a** and pyranoindole **19**, in an al-

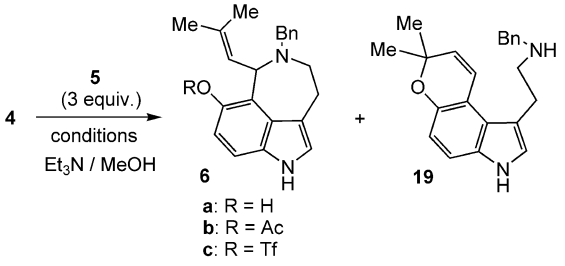


Scheme 3.



Scheme 5.

most 1:1 ratio (Table 1, Entry 1). Because the TLC of the reaction mixture showed only a single spot that was attributable to **6a**, **19** was possibly formed from **6a** during silica gel chromatography. When conducting the reaction in refluxing MeOH, **6a** was not formed and only **19** was observed on the TLC plate of the reaction mixture; **19** was then isolated in 62% yield after column chromatography (Table 1, Entry 2). After conducting the reaction at room temperature for 10 h, the mixture was immediately evaporated under reduced pressure and then treated with AcCl/Et_3N in CH_2Cl_2 or Tf_2O/Et_3N in CH_2Cl_2, giving rise to the isolation of **6b** and **6c** in 58 and 60% yield, respectively, without the formation of **19** (Table 1, Entries 3 and 4).[7]



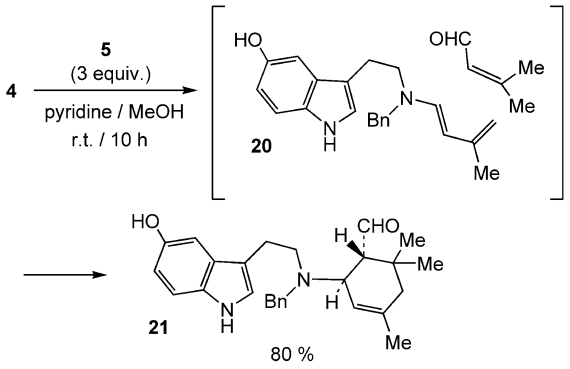
Scheme 6.

In contrast, an alternative reaction outcome was the result of using pyridine as the base; treatment of **4** with **5** (3 equiv.) in pyridine/MeOH (1:1) at room temperature for 10 h produced **21** in 80% yield (Scheme 7). The reaction path accounting for the formation of **21** possibly involved a [4π+2π] cycloaddition between **5** and dienamine **20**.

Table 1. Reaction of **4** with **5** in Et_3N/MeOH (1:1).[a]

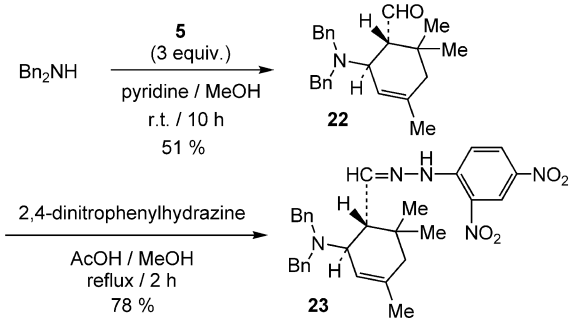
Entry	Conditions	Yield [%][b]	
		6	**19**
1	r.t./10 h	34 (**6a**: R = H)	35
2	reflux/0.5 h	–	62
3	r.t./10 h, then AcCl/Et_3N/DMAP/CH_2Cl_2	58 (**6b**: R = Ac)	–
4	r.t./10 h, then Tf_2O/Et_3N/CH_2Cl_2	60 (**6c**: R = Tf)	–

[a] Compounds **4** and **5** (3 equiv.) in Et_3N/MeOH (1:1). [b] Isolated yield based on **4**.



Scheme 7.

To evaluate the feasibility of the process, the reaction was carried out with the use of dibenzylamine and **5** (3 equiv.) under the same conditions, leading to the isolation of **22** in 51% yield (Scheme 8).



Scheme 8.

The structure of **21** was determined on the basis of ^1H NMR NOESY experiments, in which no NOE correlation between H^a (δ = 2.17 ppm) and H^b (δ = 3.88 ppm) was observed. The assignment was further confirmed by comparison with **22** (Figure 2). Moreover, conversion of **22** into hydrazone **23** permitted the unequivocal structural confirmation of **23** by X-ray crystal structure analysis,[9] whereas formation of hydrazone of **21** was not successful due to its instability under acidic conditions.

With azepinoindole **6c** in hand, attention was then shifted to selective removal of the OTf and *N*-Bn groups of **6c**. Preliminary experiments revealed that a catalytic reduction of **24** (derived from **4** and 3-methylbutanal followed

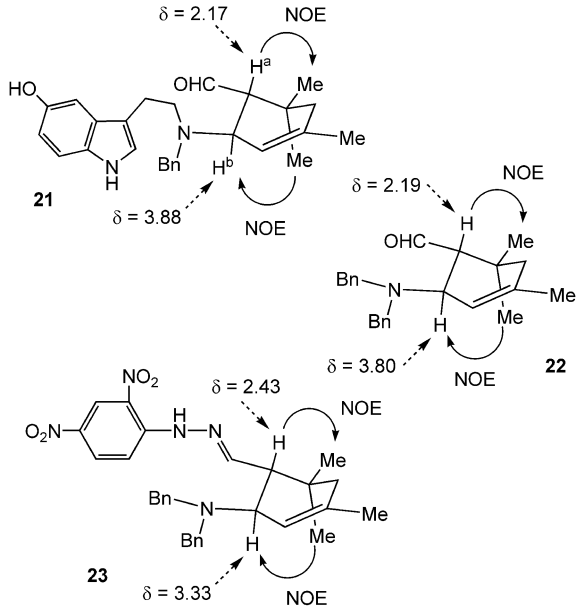
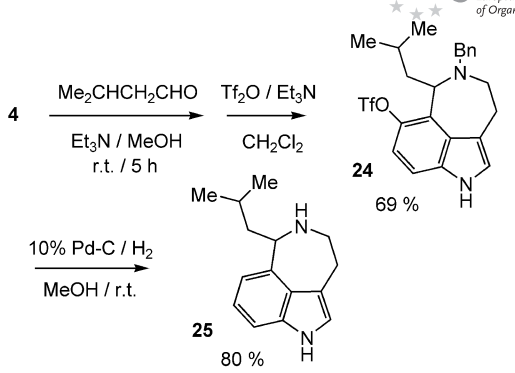


Figure 2. Diagnostic NOE correlations of **21**, **22**, and **23**.

by treatment with Tf_2O in 69% yield) with 10% Pd-C[10] in MeOH under atmospheric pressure of hydrogen was successful in producing dihydroaurantioclavine **25** in 80% yield (Scheme 9).[11]

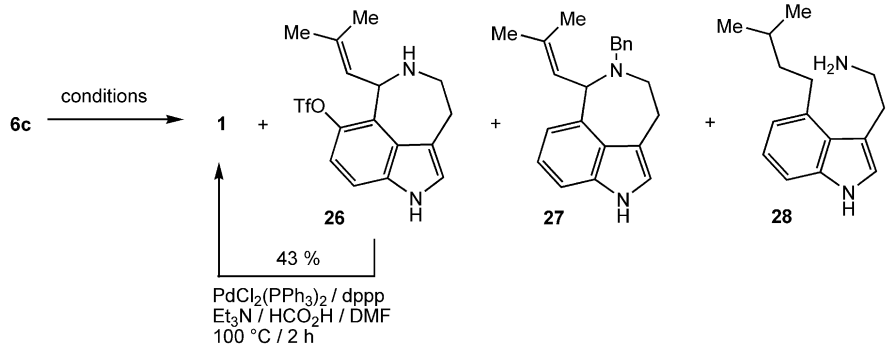
Nevertheless, attempted reduction of **6c** under similar conditions proved to be problematic due to the susceptibility of the isobutenylamine moiety to the reduction conditions (Scheme 10). This susceptibility resulted in the generation of over-reduced product **28** (Table 2, Entry 1). Thus, Pd-catalyzed hydrogenolysis of **6c** with HCO_2H as a hydride source in the presence of $PdCl_2(PPh_3)_2$ with diphenylphosphanylpropane (dppp) was performed,[12] producing **27** in low yield (Table 2, Entry 2). After several experiments, (±)-aurantioclavine (**1**) was obtained in 35% yield by the reduction of **6c** with the use of HCO_2NH_4 (4 equiv.) in the presence of 10% Pd-C[10] in MeOH at room temperature for 30 min, along with **26** and **28** (Table 2, Entry 4).[13] Conversion of **26** into **1** was also accomplished by heating with formic acid in the presence of $PdCl_2(PPh_3)_2$, dppp, and Et_3N in DMF at 100 °C for 2 h, giving (±)-**1** in 43% yield.



Scheme 9.

Conclusions

In summary, a concise total synthesis of (±)-aurantioclavine (**1**) was completed in three steps from N_b-benzylserotonin (**4**). A base-promoted Pictet–Spengler reaction was the key step of the synthesis. Further studies directed to the synthesis of other azepinoindole alkaloids with the use of this methodology are in progress.



Scheme 10.

Table 2. Conversion of **6c in**to (±)-aurantioclavine (**1**).

Entry	Conditions	Yield [%][a]			
		1	**26**	**27**	**28**
1	10% Pd-C[b]/H_2 (1 atm)/MeOH/0.5 h	–	–	–	90
2	$PdCl_2(PPh_3)_2$/dppp/HCO_2H/Et_3N/DMF/100 °C/7 h	–	–	22	–
3	10% Pd-C/HCO_2NH_4 (2 equiv.)/MeOH/r.t./0.5 h	9	21	–	2
4	10% Pd-C/HCO_2NH_4 (4 equiv.)/MeOH/r.t./0.5 h	35	18	–	28

[a] Isolated yield based on **6c**. [b] 10% Pd-C (K-type) purchased from N.E. CHEMCAT Inc., Japan.

Experimental Section

General: Melting points were recorded with a Yamato MP21 and are uncorrected. MS and HRMS spectra were recorded with a Micromass AutoSpec 3100 mass spectrometer. IR spectra were measured with a Hitachi Model 270–30 spectrometer. The NMR experiments were performed with a Jeol JNM-ECA500 (500 MHz) spectrometer, and chemical shifts are expressed in ppm (δ) with TMS as an internal reference. Column chromatography was performed on silica gel (Silica Gel 60N, Kanto Chemical Co., Ltd.).

General Procedure for the Reaction of N_b-Benzylserotonin 4 with Aldehydes 7, 11, and 15 in the Presence of Et_3N in MeOH: To a solution of **4** (0.4 mmol) in Et_3N (5 mL) and MeOH (5 mL) was added aldehyde (**7**, **11**, or **15**; 1.2 mmol), and the mixture was stirred at room temperature or heated under reflux. The mixture was concentrated under reduced pressure, and the residue was separated by column chromatography on SiO_2 to give **8**, **12**, **16**, **17**, and **18** with AcOEt/hexane, 1:3; **14** with AcOEt/hexane, 1:9; or **13** with $CHCl_3$/MeOH/28% NH_4OH, 46:3:0.3.

5-Benzyl-6-(2-methoxyethyl)-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]-indol-7-ol (8a): Yield: 55 mg (41%), after treatment at room temperature for 24 h; 74 mg (55%), after heating under reflux for 3 h; yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3480 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.85 (m, 1 H), 2.33 (m, 1 H), 2.89 (dt, J = 16.0, 3.0 Hz, 1 H), 3.15 (m, 1 H), 3.27 (td, J = 14.4, 6.0 Hz, 1 H), 3.28 (s, 3 H), 3.43–3.50 (m, 2 H), 3.60 (ddd, J = 14.4, 11.8, 3.0 Hz, 1 H), 3.82 (d, J = 13.7 Hz, 1 H), 3.98 (d, J = 13.7 Hz, 1 H), 4.49 (t, J = 6.3 Hz, 1 H), 6.40 (s, 1 H), 6.78 (d, J = 8.6 Hz, 1 H), 6.93 (s, 1 H), 7.10 (d, J = 8.6 Hz, 1 H), 7.24 (t, J = 7.4 Hz, 1 H), 7.31 (t, J = 7.4 Hz, 2 H), 7.33 (d, J = 7.4 Hz, 2 H), 7.89 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.3, 35.2, 45.0, 56.2, 57.1, 58.6, 70.6, 109.9, 113.4, 115.0, 121.5, 122.0, 125.8, 126.8, 128.1, 128.9, 131.8, 140.2, 147.0 ppm. HRMS (EI): calcd. for $C_{21}H_{24}N_2O_2$ $[M]^+$ 336.1838; found 336.1824.

5-Benzyl-6-(2-methoxypropyl)-3,4,5,6-tetrahydro-1*H*-azepino-[5,4,3-*cd*]indol-7-ol (8b, Less Polar): Yield: 52.5 mg (37.5%); pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3484 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.10 (d, J = 5.7 Hz, 3 H), 1.41 (dd, J = 15.5, 10.9 Hz, 1 H), 2.24 (dd, J = 15.5, 8.6 Hz, 1 H), 2.92 (d, J = 16.6 Hz, 1 H), 3.03 (s, 3 H), 3.41–3.26 (m, 3 H), 3.68 (td, J = 13.7, 3.0 Hz, 1 H), 3.82 (d, J = 13.2 Hz, 1 H), 4.00 (d, J = 13.2 Hz, 1 H), 4.33 (d, J = 8.6 Hz, 1 H), 6.79 (d, J = 8.6 Hz, 1 H), 6.92 (br. s, 1 H), 7.05 (br. s, 1 H), 7.10 (d, J = 8.6 Hz, 1 H), 7.24 (m, 1 H), 7.30–7.34 (m, 4 H), 7.87 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.6, 25.5, 43.8, 46.4, 55.7, 56.3, 56.7, 76.2, 109.7, 113.5, 114.9, 121.1, 122.4, 125.4, 126.9, 128.1, 129.4, 131.4, 140.4, 147.0 ppm. HRMS (EI): calcd. for $C_{22}H_{26}N_2O_2$ $[M]^+$ 350.1994; found 350.1973.

5-Benzyl-6-(2-methoxypropyl)-3,4,5,6-tetrahydro-1*H*-azepino-[5,4,3-*cd*]indol-7-ol (8b, More Polar): Yield: 52.5 mg (37.5%); colorless crystals. M.p. 185–187 °C ($CHCl_3$/hexane). IR ($CHCl_3$): $\tilde{\nu}$ = 3484 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21 (d, J = 5.7 Hz, 3 H), 1.84 (ddd, J = 14.0, 7.0, 6.7 Hz, 1 H), 2.27 (ddd, J = 14.0, 7.4, 6.0 Hz, 1 H), 2.87 (dt, J = 16.6, 2.9 Hz, 1 H), 3.09 (ddd, J = 14.9, 5.1, 2.9 Hz, 1 H), 3.22 (ddd, J = 16.6, 11.5, 4.6 Hz, 1 H), 3.32 (s, 3 H), 3.54–3.62 (m, 2 H), 3.79 (d, J = 13.7 Hz, 1 H), 3.96 (d, J = 13.7 Hz, 1 H), 4.59 (dd, J = 7.4, 7.0 Hz, 1 H), 6.74 (d, J = 8.6 Hz, 1 H), 6.93 (s, 1 H), 7.09 (d, J = 8.6 Hz, 1 H), 7.23 (m, 1 H), 7.28–7.32 (m, 4 H), 8.53 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.0, 24.8, 40.0, 43.9, 54.6, 56.0, 57.4, 74.6, 109.6, 112.8, 114.4, 121.6, 122.1, 125.9, 126.7, 128.0, 128.8, 131.8, 139.7, 146.4 ppm. HRMS (EI): calcd. for $C_{22}H_{26}N_2O_2$ $[M]^+$ 350.1994; found 350.1974. $C_{22}H_{26}N_2O_2$ (350.46): calcd. C 75.39, H 7.47, N 7.99; found C 75.25, H 7.56, N 7.97.

5-Benzyl-6-[(*E*)-2-phenylethenyl]-3,4,5,6-tetrahydro-1*H*-azepino-[5,4,3-*cd*]indol-7-ol (12a): Yield: 128 mg (84%); pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3484 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.56 (br. s, 1 H), 2.85 (dt, J = 16.6, 2.4 Hz, 1 H), 3.07 (ddd, J = 13.7, 3.2, 2.4 Hz, 1 H), 3.20 (ddd, J = 16.6, 13.7, 3.2 Hz, 1 H), 3.59 (td, J = 13.7, 3.2 Hz, 1 H), 3.94 (d, J = 13.7 Hz, 1 H), 4.10 (d, J = 13.7 Hz, 1 H), 5.18 (d, J = 5.7 Hz, 1 H), 6.16 (d, J = 16.0 Hz, 1 H), 6.58 (dd, J = 16.0, 5.2 Hz, 1 H), 6.78 (d, J = 8.6 Hz, 1 H), 6.98 (s, 1 H), 7.19 (d, J = 8.6 Hz, 1 H), 7.24–7.27 (m, 5 H), 7.30–7.34 (m, 3 H), 7.41 (d, J = 7.4 Hz, 2 H), 7.96 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.4, 46.2, 56.6, 63.3, 110.2, 113.0, 115.5, 119.9, 121.9, 126.6, 126.9, 127.4, 128.3, 128.4, 128.8, 130.5, 131.6, 132.4, 136.9, 140.0, 146.3 ppm. HRMS (EI): calcd. for $C_{26}H_{24}N_2O$ $[M]^+$ 380.1889; found 380.1890.

5-Benzyl-6-[(*E*)-2-(4-nitrophenyl)ethenyl]-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-7-ol (12b): Yield: 90 mg (53%), after treatment at room temperature for 1 h; 117 mg (69%), after heating under reflux for 20 min; pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3484 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.56 (br. s, 1 H), 2.87 (dt, J = 15.0, 2.9 Hz, 1 H), 3.17 (dt, J = 14.2, 2.9 Hz, 1 H), 3.25 (ddd, J = 15.0, 14.2, 2.9 Hz, 1 H), 3.54 (td, J = 14.2, 2.9 Hz, 1 H), 3.94 (d, J = 13.6 Hz, 1 H), 4.09 (d, J = 13.6 Hz, 1 H), 4.27 (s, 1 H), 5.28 (d, J = 4.0 Hz, 1 H), 6.11 (d, J = 16.4 Hz, 1 H), 6.75 (d, J = 8.5 Hz, 1 H), 6.79 (dd, J = 16.4, 4.0 Hz, 1 H), 7.01 (s, 1 H), 7.21 (d, J = 8.5 Hz, 1 H), 7.34 (t, J = 7.1 Hz, 2 H), 7.39–7.43 (m, 4 H), 8.01 (s, 1 H), 8.10 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.1, 46.8, 56.1, 62.8, 110.6, 112.6, 115.5, 119.2, 122.4, 123.9, 126.9, 127.1, 127.2, 128.5, 128.9, 129.1, 132.4, 137.2, 139.9, 143.9, 146.2, 146.7 ppm. HRMS (EI): calcd. for $C_{26}H_{23}N_3O_3$ $[M]^+$ 425.1739; found 425.1806.

***N*-Benzyl-2-[7-(4-nitrophenyl)-3,7-dihydropyrano[3,2-*e*]indol-1-yl]-ethanamine (13):** Yield: 23.8 mg (14%), after treatment at room temperature for 1 h; 18.7 mg (11%), after heating under reflux for 20 min; pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3485 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.89 (s, 1 H), 2.98 (t, J = 7.1 Hz, 2 H), 3.09 (t, J = 7.1 Hz, 2 H), 3.84 (s, 2 H), 5.83 (dd, J = 9.6, 4.0 Hz, 1 H), 5.89 (d, J = 4.0 Hz, 1 H), 6.77 (d, J = 8.5 Hz, 1 H), 7.00 (d, J = 1.7 Hz, 1 H), 7.13 (d, J = 8.5b Hz, 1 H), 7.19 (d, J = 9.6 Hz, 1 H), 7.24 (m, 1 H), 7.30–7.35 (m, 4 H), 7.64 (d, J = 8.5 Hz, 2 H), 7.93 (s, 1 H), 8.19 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.7, 49.6, 53.9, 74.9, 112.2, 112.3, 113.4, 114.0, 122.2, 123.1, 123.4, 123.8, 124.2, 127.2, 127.6, 128.3, 128.5, 132.9, 146.9, 147.4, 147.7, 148.4 ppm. HRMS (EI): calcd. for $C_{26}H_{23}N_3O_3$ $[M]^+$ 425.1739; found 425.1740.

9-Benzyl-3-phenyl-8-[(*E*)-2-phenylethenyl]-3,7,8,9,10,11-hexahydro-pyrano[3,2-*e*]pyrido[3,4-*b*]indole (14): Yield: 158 mg (80%); pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3464 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.62 (dt, J = 19.5, 6.2 Hz, 1 H), 2.93–3.02 (m, 2 H), 3.20 (m, 1 H), 3.49 (dd, J = 13.7, 8.0 Hz, 1 H), 4.16 (dd, J = 13.7, 8.0 Hz, 1 H), 4.28 (d, J = 8.6 Hz, 1 H), 5.80–5.85 (m, 2 H), 6.35 (ddd, J = 15.8, 8.6, 2.0 Hz, 1 H), 6.68 (dd, J = 8.6, 1.7 Hz, 2 H), 6.72 (dd, J = 15.8, 10.6 Hz, 2 H), 6.99 (dd, J = 8.6, 2.9 Hz, 1 H), 7.07 (d, J = 8.0 Hz, 1 H), 7.25–7.36 (m, 7 H), 7.42 (dd, J = 12.9, 7.7 Hz, 4 H), 7.50 (d, J = 7.4 Hz, 2 H), 7.56 (d, J = 3.4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.6, 48.2, 58.6, 63.0, 76.4, 76.7, 108.32, 111.2, 111.5, 113.3, 122.1, 122.4, 123.5, 123.6, 123.7, 126.6, 127.0, 127.1, 128.1, 128.3, 128.5128.7, 129.7, 131.9, 133.9, 134.8, 136.1, 139.1, 141.1, 147.2 ppm. HRMS (EI): calcd. for $C_{35}H_{30}N_2O$ $[M]^+$ 494.2350; found 494.2358.

5-Benzyl-6-(1-methoxypropan-2-yl)-3,4,5,6-tetrahydro-1*H*-azepino-[5,4,3-*cd*]indol-7-ol (16): Yield: 14 mg (10%); pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3484 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.63 (d,

J = 7.4 Hz, 3 H), 2.40 (m, 1 H), 2.94 (dt, *J* = 16.4, 3.6 Hz, 1 H), 3.17 (dt, *J* = 14.0, 3.5 Hz, 1 H), 3.25 (m, 1 H), 3.29 (s, 3 H), 3.50 (d, *J* = 2.8 Hz, 2 H), 3.56 (m, 1 H), 3.79 (d, *J* = 13.2 Hz, 1 H), 3.93 (d, *J* = 13.2 Hz, 1 H), 4.36 (d, *J* = 5.7 Hz, 1 H), 6.78 (d, *J* = 8.5 Hz, 1 H), 6.92 (s, 1 H), 6.93 (s, 1 H), 7.13 (d, *J* = 8.5 Hz, 1 H), 7.24 (t, *J* = 7.0 Hz, 1 H), 7.30–7.35 (m, 4 H), 7.89 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6, 25.5, 38.5, 46.1, 56.2, 58.9, 61.6, 77.6, 110.0, 113.5, 115.2, 119.9, 121.2, 126.6, 126.7, 128.1, 128.9, 131.6, 140.3, 147.9 ppm. HRMS (EI): calcd. for $C_{22}H_{26}N_2O_2$ $[M]^+$ 350.1994; found 350.1992.

5-Benzyl-6-ethyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-7-ol (17): Yield: 19.5 mg (16%); pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3480 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 7.4 Hz, 3 H), 1.77–1.86 (m, 2 H), 2.85 (dt, *J* = 16.4, 2.3 Hz, 1 H), 3.10 (ddd, *J* = 14.0, 4.2, 2.3 Hz, 1 H), 3.26 (ddd, *J* = 16.4, 14.0, 4.4 Hz, 1 H), 3.51 (td, *J* = 14.0, 4.2 Hz, 1 H), 3.84 (d, *J* = 14.2 Hz, 1 H), 4.04 (d, *J* = 14.2 Hz, 1 H), 4.21 (br. s, 1 H), 4.34 (dd, *J* = 10.2, 5.1 Hz, 1 H), 6.66 (d, *J* = 8.5 Hz, 1 H), 6.95 (s, 1 H), 7.07 (d, *J* = 8.5 Hz, 1 H), 7.24 (t, *J* = 7.4 Hz, 1 H), 7.31 (t, *J* = 7.4 Hz, 2 H), 7.38 (d, *J* = 7.4 Hz, 2 H), 7.89 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.0, 25.0, 26.8, 42.9, 55.6, 62.5, 109.2, 112.4, 115.6, 122.0, 124.7, 126.2, 126.7, 128.2, 128.7, 132.2, 140.7, 145.5 ppm. HRMS (EI): calcd. for $C_{20}H_{22}N_2O$ $[M]^+$ 306.1732; found 306.1732.

5-Benzyl-6-[(2*E*)-but-2-en-2-yl]-3,4,5,6-tetrahydro-1*H*-azepino-[5,4,3-*cd*]indol-7-ol (18a): Yield: 29.2 mg (22%); pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3480 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.56 (d, *J* = 6.8 Hz, 3 H), 1.91 (s, 3 H), 2.81 (dt, *J* = 15.9, 2.0 Hz, 1 H), 3.01 (ddd, *J* = 13.7, 3.8, 2.0 Hz, 1 H), 3.24 (td, *J* = 15.9, 3.8 Hz, 1 H), 3.37 (td, *J* = 13.7, 3.8 Hz, 1 H), 3.85 (d, *J* = 14.2 Hz, 1 H), 4.06 (d, *J* = 14.2 Hz, 1 H), 4.27 (br. s, 1 H), 4.77 (s, 1 H), 4.93 (q, *J* = 6.8 Hz, 1 H), 6.80 (d, *J* = 8.5 Hz, 1 H), 6.96 (s, 1 H), 7.17 (d, *J* = 8.5 Hz, 1 H), 7.24 (t, *J* = 7.4 Hz, 1 H), 7.31 (t, *J* = 7.4 Hz, 2 H), 7.37 (d, *J* = 7.4 Hz, 2 H), 7.95 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6, 16.0, 25.0, 43.3, 55.3, 68.8, 110.0, 113.2, 115.2, 120.8, 122.0, 122.2, 126.8, 126.9, 128.2, 128.8, 132.3, 136.4, 140.5, 146.5 ppm. HRMS (EI): calcd. for $C_{22}H_{24}N_2O$ $[M]^+$ 332.1889; found 332.1880.

5-Benzyl-6-[(1*E*)-1-phenylprop-1-en-2-yl]-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-7-ol (18b): Yield: 78.8 mg (50%); pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3484 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.17 (s, 3 H), 2.85 (d, *J* = 16.4 Hz, 1 H), 3.08 (ddd, *J* = 14.4, 4.5, 2.3 Hz, 1 H), 3.28 (ddd, *J* = 16.4, 14.4, 4.5 Hz, 1 H), 3.49 (td, *J* = 14.4, 4.5 Hz, 1 H), 3.90 (d, *J* = 13.6 Hz, 1 H), 4.10 (d, *J* = 13.6 Hz, 1 H), 4.25 (s, 1 H), 4.95 (s, 1 H), 5.88 (s, 1 H), 6.81 (d, *J* = 8.5 Hz, 1 H), 6.98 (s, 1 H), 7.15 (d, *J* = 7.4 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 1 H), 7.23–7.27 (m, 4 H), 7.33 (t, *J* = 7.4 Hz, 2 H), 7.40 (d, *J* = 6.8 Hz, 2 H), 7.96 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.2, 25.0, 43.8, 55.5, 69.2, 110.3, 113.1, 115.3, 120.4, 122.1, 126.3, 126.9, 127.1, 127.4, 128.0, 128.3, 128.8, 129.1, 132.3, 138.1, 139.4, 140.3, 146.6 ppm. HRMS (EI): calcd. for $C_{27}H_{26}N_2O$ $[M]^+$ 394.2045; found 394.2038.

Reaction of 4 with 3-Methylbut-2-enal (5): To a solution of **4** (53 mg, 0.2 mmol) in Et_3N (5 mL) and MeOH (5 mL) was added **5** (0.05 mL, 0.6 mmol), and the mixture was stirred at room temperature for 10 h. The mixture was concentrated under reduced pressure, and the residue was separated by column chromatography on SiO_2. The first elution (AcOEt/hexane, 1:2) gave **6a** (45 mg, 34%) and the second elution ($CHCl_3$/MeOH/28% NH_4OH, 46:3:0.3) gave **19** (46 mg, 35%).

5-Benzyl-6-(2-methylprop-1-en-1-yl)-3,4,5,6-tetrahydro-1*H*-azepino-[5,4,3-*cd*]indol-7-ol (6a): Pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3480 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.77 (s, 3 H), 1.79 (s, 3 H), 2.86 (dt, *J* = 16.1, 2.7 Hz, 1 H), 3.01 (m, 1 H), 3.17 (m, 1 H), 3.55 (td, *J* = 13.6, 2.7 Hz, 1 H), 3.84 (d, *J* = 13.2 Hz, 1 H), 4.00 (d, *J* = 13.2 Hz, 1 H), 4.39 (br. s, 1 H), 5.03 (d, *J* = 9.2 Hz, 1 H), 5.44 (dd, *J* = 9.2, 1.1 Hz, 1 H), 6.77 (d, *J* = 8.6 Hz, 1 H), 6.96 (s, 1 H), 7.12 (d, *J* = 8.6 Hz, 1 H), 7.24 (t, *J* = 8.3 Hz, 1 H), 7.30 (t, *J* = 7.4 Hz, 2 H), 7.38 (d, *J* = 7.4 Hz, 2 H), 7.93 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.2, 26.1, 26.8, 46.1, 57.1, 59.3, 109.7, 113.2, 115.5, 121.8, 122.5, 124.2, 125.8, 126.9, 128.2, 129.0, 132.4, 137.3, 140.1, 146.3 ppm. HRMS (EI): calcd. for $C_{22}H_{24}N_2O$ $[M]^+$ 332.18898; found 332.1887.

***N*-Benzyl-2-(7,7-dimethyl-3,7-dihydropyrano[3,2-*e*]indol-1-yl)ethanamine (19):** Colorless crystals. M.p. 120–123 °C (AcOEt/hexane). IR ($CHCl_3$): $\tilde{\nu}$ = 3480 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.43 (2 × s, 6 H), 1.60 (br. s, 1 H), 2.97 (t, *J* = 6.9 Hz, 2 H), 3.07 (t, *J* = 6.9 Hz, 2 H), 3.83 (s, 2 H), 5.60 (d, *J* = 9.7 Hz, 1 H), 6.71 (d, *J* = 8.6 Hz, 1 H), 6.92 (d, *J* = 9.7 Hz, 1 H), 6.95 (d, *J* = 2.3 Hz, 1 H), 7.08 (d, *J* = 8.6 Hz, 1 H), 7.23 (m, 1 H), 7.28–7.31 (m, 4 H), 7.86 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.2, 27.8, 49.7, 54.0, 74.8, 111.1, 112.9, 113.1, 113.9, 120.2, 122.8, 123.5, 126.9, 128.1, 128.4, 129.6, 132.5, 140.4, 146.8 ppm. HRMS (EI): calcd. for $C_{22}H_{24}N_2O$ $[M]^+$ 332.1889; found 332.1885. $C_{22}H_{24}N_2O$ (332.44): calcd. C 79.48, H 7.27, N 8.42; found C 79.65, H 7.20, N 8.45.

5-Benzyl-6-(2-methylprop-1-en-1-yl)-3,4,5,6-tetrahydro-1*H*-azepino-[5,4,3-*cd*]indol-7-yl Acetate (6b): To a solution of **4** (106 mg, 0.4 mmol) in Et_3N (5 mL) and MeOH (5 mL) was added **5** (0.12 mL, 1.3 mmol), and the mixture was stirred at room temperature for 10 h under a nitrogen atmosphere. After evaporation of the solvent, CH_2Cl_2 (10 mL), Et_3N (0.16 mL, 1.2 mmol), and DMAP (10 mg, 0.08 mmol) were added to the residue. Then, AcCl (55 mg, 0.7 mmol) was added to the mixture under ice-cooling. After stirring for 1 h, the mixture was diluted with AcOEt (100 mL) and washed with brine, and the organic layer was dried with $MgSO_4$. The solvent was removed, and the residue was separated by column chromatography on SiO_2 (AcOEt/hexane, 1:2) to give **6b** (87 mg, 58%) as a pale yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3480, 1742 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.66 (s, 3 H), 1.67 (s, 3 H), 2.08 (s, 3 H), 2.88 (dt, *J* = 16.0, 3.4 Hz, 1 H), 3.06 (dd, *J* = 13.2, 3.4 Hz, 1 H), 3.22 (ddd, *J* = 16.0, 13.2, 3.4 Hz, 1 H), 3.61 (td, *J* = 13.2, 3.4 Hz, 1 H), 3.79 (d, *J* = 13.2 Hz, 1 H), 3.93 (d, *J* = 13.2 Hz, 1 H), 4.99 (d, *J* = 8.6 Hz, 1 H), 5.22 (d, *J* = 8.6 Hz, 1 H), 6.80 (d, *J* = 8.6 Hz, 1 H), 6.94 (s, 1 H), 7.14 (d, *J* = 8.6 Hz, 1 H), 7.24 (t, *J* = 7.4 Hz, 1 H), 7.29 (t, *J* = 7.4 Hz, 2 H), 7.34 (d, *J* = 7.4 Hz, 2 H), 8.11 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.3, 21.0, 25.8, 45.8, 55.9, 58.7, 109.6, 116.5, 117.2, 122.2, 125.6, 125.9, 126.9, 128.2, 129.3, 129.5, 134.7, 134.8, 140.0, 141.3, 170.3 ppm. HRMS (EI): calcd. for $C_{24}H_{26}N_2O_2$ $[M]^+$ 374.1994; found 374.1990.

5-Benzyl-6-(2-methylprop-1-en-1-yl)-3,4,5,6-tetrahydro-1*H*-azepino-[5,4,3-*cd*]indol-7-yl Trifluoromethanesulfonate (6c): To a solution of **4** (300 mg, 1.1 mmol) in Et_3N (15 mL) and MeOH (15 mL) was added **5** (0.32 mL, 3.3 mmol), and the mixture was stirred at room temperature for 10 h under a nitrogen atmosphere. After evaporation of the solvent, CH_2Cl_2 (30 mL) and Et_3N (0.78 mL, 5.6 mmol) were added to the residue. Then, Tf_2O (0.28 mL, 1.7 mmol) was added to the solution under ice-cooling, and the mixture was stirred for 30 min. The mixture was diluted with AcOEt (200 mL) and washed with brine, and the organic layer was dried with $MgSO_4$. The solvent was removed, and the residue was separated by column chromatography on SiO_2 (AcOEt/hexane, 1:5) to give **6c** (306 mg, 60%) as colorless crystals. M.p. 127–128 °C (AcOEt/hexane). IR ($CHCl_3$): $\tilde{\nu}$ = 3480 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.71 (s, 3 H), 1.82 (s, 3 H), 2.85 (d, *J* = 16.6 Hz, 1 H), 2.97 (dd, *J* = 3.6, 14.2 Hz, 1 H), 3.21 (ddd, *J* = 3.6, 14.2, 16.6 Hz, 1 H),

3.57 (dt, J = 3.6, 14.2 Hz, 1 H), 3.88 (1d, J = 13.7 Hz, 1 H), 3.95 (d, J = 13.7 Hz, 2 H), 5.17 (d, J = 8.0 Hz, 1 H), 5.28 (d, J = 8.0 Hz, 1 H), 7.04 (s, 1 H), 7.04 (d, J = 9.0 Hz, 1 H), 7.20 (d, J = 9.0 Hz, 1 H), 7.24 (t, J = 7.4 Hz, 1 H), 7.31 (t, J = 7.4 Hz, 2 H), 7.37 (d, J = 7.4 Hz, 2 H), 8.21 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.5, 25.3, 25.8, 44.2, 55.6, 60.6, 110.1, 114.8, 115.2, 117.3, 117.4, 120.0, 122.5, 123.3, 124.4, 126.1, 127.0, 128.3, 128.9, 132.2, 135.4, 137.2, 139.6, 140.8 ppm. MS (EI): m/z = 464 [M^+]. $C_{23}H_{23}F_3N_2O_3S$ (464.50): calcd. C 59.47, H 4.99, N 6.03; found C 59.60, H 4.85, N 6.00.

***rel*-(1*S*,2*S*)-2-{Benzyl[2-(5-hydroxy-1*H*-indol-3-yl)ethyl]amino}-4,6,6-trimethylcyclohex-3-ene-1-carbaldehyde (21):** To a solution of **4** (51 mg, 0.2 mmol) in pyridine (5 mL) and MeOH (5 mL) was added **5** (0.06 mL, 0.6 mmol), and the mixture was then stirred at room temperature for 10 h under a nitrogen atmosphere. The mixture was concentrated under reduced pressure, and the residue was separated by column chromatography on SiO_2 (hexane/AcOEt, 3:1) to give **21** (64 mg, 80%) as a pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1706 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (s, 3 H), 0.96 (s, 3 H), 1.53 (d, J = 17.8 Hz, 1 H), 1.68 (s, 3 H), 1.70 (br. s, 1 H), 1.93 (d, J = 17.8 Hz, 1 H), 2.17 (dd, J = 5.2, 10.9 Hz, 1 H, 1 H), 2.87–2.64 (m, 4 H), 3.53 (d, J = 13.7 Hz, 1 H), 3.84 (d, J = 13.7 Hz, 1 H), 3.88 (d, J = 10.9 Hz, 1 H), 5.56 (s, 1 H), 6.67 (d, J = 2.3 Hz, 1 H), 6.73 (dd, J = 2.3, 8.6 Hz, 1 H), 6.87 (d, J = 2.3 Hz, 1 H), 7.15 (d, J = 8.6 Hz, 1 H), 7.24 (t, J = 8.2 Hz, 1 H), 7.33–7.29 (m, 4 H), 7.77 (s, 1 H), 9.43 (d, J = 5.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 23.4, 25.4, 29.4, 34.3, 46.6, 51.1, 55.4, 55.9, 58.9, 103.2, 111.6, 111.7, 113.6, 117.6, 122.7, 126.8, 128.1, 128.2, 129.0, 131.4, 136.1, 140.4, 149.4, 208.1 ppm. HRMS (EI): calcd. for $C_{27}H_{32}N_2O_2$ [$M]^+$ 416.2464; found 416.2453.

***rel*-(1*S*,2*S*)-2-(Dibenzylamino)-4,6,6-trimethylcyclohex-3-ene-1-carbaldehyde (22):** To a solution of dibenzylamine (260 mg, 1.3 mmol) in pyridine (1 mL) and MeOH (5 mL) was added **5** (0.28 mL, 2.9 mmol), and the mixture was then stirred at room temperature for 10 h under a nitrogen atmosphere. The mixture was concentrated under reduced pressure, and the residue was separated by column chromatography on SiO_2 (hexane/AcOEt, 10:1) to give **22** (232 mg, 51%) as a pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1712 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (s, 3 H), 0.94 (s, 3 H), 1.54 (d, J = 17.0 Hz, 1 H), 1.73 (s, 3 H), 1.96 (d, J = 17.0 Hz, 1 H), 2.19 (dd, J = 5.1, 10.8 Hz, 1 H), 3.42 (d, J = 13.8 Hz, 2 H), 3.71 (d, J = 13.8 Hz, 2 H), 3.80 (d, J = 10.8 Hz, 1 H), 5.66 (s, 1 H), 7.22–7.18 (m, 2 H), 7.24–7.29 (m, 8 H), 9.17 (d, J = 5.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 23.6, 29.4, 34.2, 46.6, 53.8, 54.2, 58.7, 116.8, 127.0, 128.2, 129.0, 136.4, 139.7, 207.3 ppm. HRMS (EI): calcd. for $C_{24}H_{29}NO$ [$M]^+$ 347.2249; found 347.2250.

***rel*-(1*S*,2*S*)-*N*,*N*-Dibenzyl-6-{(*E*)-[2-(2,4-dinitrophenyl)hydrazinylidene]methyl}-3,5,5-trimethylcyclohex-2-en-1-amine (23):**[9] To a solution of **22** (232 mg, 0.7 mmol) in AcOH (1 mL) and MeOH (5 mL) was added 2,4-dinitrophenylhydrazine (159 mg, 0.8 mmol), and the mixture was heated under reflux for 2 h under a nitrogen atmosphere. The mixture was concentrated under reduced pressure, and the residue was separated by column chromatography on SiO_2 (hexane/AcOEt, 10:1) to give **23** (276 mg, 78%) as red prisms. M.p. 190–191 °C (decomp.) ($CHCl_3$/MeOH). IR ($CHCl_3$): $\tilde{\nu}$ = 1614 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77 (s, 3 H), 0.92 (s, 3 H), 1.64 (d, J = 17.3 Hz, 1 H), 1.77 (s, 3 H), 2.02 (d, J = 17.3 Hz, 1 H), 2.43 (dd, J = 7.9, 10.8 Hz, 1 H), 3.33 (d, J = 10.8 Hz, 1 H), 3.44 (d, J = 13.6 Hz, 2 H), 3.73 (d, J = 13.6 Hz, 2 H), 5.66 (s, 1 H), 6.69 (d, J = 7.9 Hz, 1 H), 7.19–7.22 (m, 6 H), 7.25–7.28 (m, 4 H), 8.06 (d, J = 9.6 Hz, 1 H), 8.34 (dd, J = 2.8, 9.6 Hz, 1 H), 9.20 (d, J = 2.8 Hz, 1 H), 10.96 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 23.7, 30.0, 34.1, 45.9, 50.7, 54.5, 55.8, 116.6, 117.3, 123.7, 127.1, 128.0, 128.7, 128.9, 130.0, 136.3, 137.7, 140.3, 145.1, 155.5 ppm. HRMS (EI): calcd. for $C_{30}H_{33}N_5O_4$ [$M]^+$ 527.2533; found 527.2541. $C_{30}H_{33}N_5O_4$ (527.62): calcd. C 68.29, H 6.30, N 13.27; found C 68.36, H 6.15, N 1311.

5-Benzyl-6-(2-methylpropyl)-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]-indol-7-yl Trifluoromethanesulfonate (24): To a solution of **4** (106 mg, 0.4 mmol) in Et_3N (5 mL) and MeOH (5 mL) was added 3-methylbutanal (1.3 mL, 1.2 mmol), and the mixture was stirred at room temperature for 5 h under a nitrogen atmosphere. After the mixture was concentrated under reduced pressure, CH_2Cl_2 (10 mL) and Et_3N (0.3 mL, 2.0 mmol) were added to the residue. Then, Tf_2O (0.08 mL, 0.5 mmol) was added to the mixture under ice-cooling, and the mixture was stirred for 30 min. The mixture was diluted with AcOEt (100 mL), washed with brine, and dried with $MgSO_4$. The solvent was removed, and the residue was separated by column chromatography on SiO_2 (hexane/AcOEt, 5:1) to give **24** (124 mg, 69%) as a colorless solid. M.p. 113–114 °C ($CHCl_3$/hexane). IR (KBr): $\tilde{\nu}$ = 3440 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (d, J = 6.9 Hz, 3 H), 1.01 (d, J = 6.9 Hz, 3 H), 1.29 (ddd, J = 14.2, 11.0, 4.3 Hz, 1 H), 1.92 (ddd, J = 14.2, 11.7, 2.9 Hz, 1 H), 1.97–2.05 (m, 1 H), 2.80 (ddd, J = 16.6, 3.4, 2.2 Hz, 1 H), 3.02 (ddd, J = 14.3, 4.6, 2.2 Hz, 1 H), 3.25 (ddd, J = 16.6, 14.3, 4.6 Hz, 1 H), 3.41 (td, J = 14.3, 3.4 Hz, 1 H), 3.89 (d, J = 14.0 Hz, 1 H), 4.04 (d, J = 14.0 Hz, 1 H), 4.67 (dd, J = 11.7, 4.3 Hz, 1 H), 7.04 (s, 1 H), 7.06 (d, J = 8.8 Hz, 1 H), 7.20 (d, J = 8.8 Hz, 1 H), 7.24 (t, J = 7.4 Hz, 1 H), 7.31 (t, J = 7.4 Hz, 2 H), 7.36 (d, J = 7.4 Hz, 2 H), 8.17 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.4, 23.7, 24.3, 24.6, 41.7, 43.4, 55.4, 60.6, 109.8, 114.8, 115.3, 116.8, 117.3, 119.9, 122.0, 123.1, 126.0, 126.8, 128.2, 128.6, 133.6, 135.3, 139.6, 139.7 ppm. HRMS (EI): calcd. for $C_{23}H_{25}F_3N_2O_2S$ [$M]^+$ 466.1538; found 466.1492. $C_{23}H_{25}F_3N_2O_2S$ (450.52): calcd. C 61.32, H 5.59, N 6.22; found C 61.22, H 5.70, N 6.32.

6-(2-Methylpropyl)-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-7-ol (25): A mixture of **24** (75 mg, 0.16 mmol) and 10% Pd-C[10] (35 mg) in MeOH (5 mL) was stirred at room temperature under atmospheric pressure of hydrogen for 5 h. The catalyst and solvent were removed, and the residue was separated by column chromatography on SiO_2 ($CHCl_3$/MeOH/28% NH_4OH, 46:2:0.2) to give **25** (29 mg, 80%) as a colorless solid. M.p. 121–123 °C (hexane/$CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3136, 3088 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (d, J = 6.3 Hz, 3 H), 1.03 (d, J = 6.3 Hz, 3 H), 1.57 (ddd, J = 14.6, 10.3, 4.5 Hz, 1 H), 1.83–1.91 (m, 2 H), 2.46 (br. s, 1 H), 2.98–3.16 (m, 3 H), 3.35 (ddd, J = 13.0, 9.2, 3.4 Hz, 1 H), 4.40 (dd, J = 10.3, 4.5 Hz, 1 H), 6.85 (d, J = 7.8 Hz, 1 H), 6.94 (s, 1 H), 7.09 (t, J = 7.8 Hz, 1 H), 7.17 (d, J = 7.8 Hz, 1 H), 8.17 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 23.7, 25.0, 30.7, 43.8, 45.2, 59.4, 108.8, 115.2, 116.9, 120.9, 121.5, 125.2, 137.1, 140.6 ppm. HRMS (EI): calcd. for $C_{15}H_{20}N_2$ [$M]^+$ 228.1626; found 228.1658. $C_{15}H_{20}N_2$ (228.34): calcd. C 78.90, H 8.83, N 12.27; found C 78.77, H 8.90, N 12.31.

Conversion of 6c into (±)-Aurantioclavine (1): A mixture of **6c** (100 mg, 0.2 mmol), HCO_2NH_4 (55.1 mg, 0.9 mmol), and 10% Pd-C[10] (200 mg) in MeOH (5 mL) was stirred for 30 min under a nitrogen atmosphere. The resulting suspension was passed over SiO_2 and washed with $CHCl_3$/MeOH/28% NH_4OH (46:5:0.5). The filtrate was evaporated, and the residue was separated by column chromatography on SiO_2 ($CHCl_3$/MeOH/28% NH_4OH, 46:3:0.3) to give (±)-**1** (16 mg, 35%), **26** (13 mg, 18%), and **28** (13 mg, 28%).

(±)-Aurantioclavine (1): M.p. 186–188 °C ($CHCl_3$) (ref.[1] m.p. 188–189 °C). IR ($CHCl_3$): $\tilde{\nu}$ = 3480 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$):

δ = 1.78 (br. s, 1 H), 1.84 (s, 3 H), 1.85 (s, 3 H), 3.00–3.14 (m, 3 H), 3.54–3.58 (m, 1 H), 4.89 (d, J = 9.1 Hz, 1 H), 5.46 (dd, J = 9.1, 1.1 Hz, 1 H), 6.84 (dd, J = 7.6, 1.1 Hz, 1 H), 7.01 (s, 1 H), 7.09 (t, J = 7.6 Hz, 1 H), 7.22 (d, J = 7.6 Hz, 1 H), 8.11 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.3, 25.9, 31.0, 48.9, 62.6, 109.1, 115.8, 117.8, 120.9, 121.5, 125.3, 127.7, 133.1, 137.0, 138.5 ppm. HRMS (EI): calcd. for $C_{15}H_{18}N_2$ $[M]^+$ 226.1470; found 226.1471.

6-(2-Methylprop-1-en-1-yl)-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]-indol-7-yl Trifluoromethanesulfonate (26): Colorless crystals. M.p. 124–126 °C (AcOEt/hexane). IR ($CHCl_3$): $\tilde{\nu}$ = 3480 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73 (d, J = 1.1 Hz, 3 H), 1.86 (d, J = 1.1 Hz, 3 H), 1.91 (br. s, 1 H), 2.96 (m, 1 H), 3.07–3.15 (m, 2 H), 3.40 (m, 1 H), 5.32 (dtt, J = 9.6, 1.1, 1.1 Hz, 1 H), 5.41 (d, J = 8.5 Hz, 1 H), 7.02 (d, J = 9.1 Hz, 1 H), 7.07 (br. s, 1 H), 7.19 (d, J = 9.1 Hz, 1 H), 8.30 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1, 25.7, 31.2, 42.7, 55.4, 109.9, 114.9, 117.2, 118.6, 123.2, 125.0, 125.8, 132.6, 135.7, 136.1, 140.0 ppm. HRMS (EI): calcd. for $C_{16}H_{17}F_3N_2O_3S$ $[M]^+$ 374.0912; found 374.0912. $C_{16}H_{17}F_3N_2O_3S$ (374.38): calcd. C 51.33, H 4.58, N 7.48; found C 51.00, H 4.46, N 7.42.

2-[4-(3-Methylbutyl)-1*H*-indol-3-yl]ethanamine (28): Colorless crystals. M.p. 84–86 °C ($CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3480 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (2 × d, J = 6.2 Hz, 6 H), 1.42 (br. s, 2 H), 1.56–1.61 (m, 2 H), 1.65–1.75 (m, 1 H), 2.95–2.98 (m, 2 H), 3.01 (s, 4 H), 6.87 (d, J = 7.4 Hz, 1 H), 6.96 (s, 1 H), 7.08 (t, J = 7.4 Hz, 1 H), 7.17 (d, J = 7.4 Hz, 1 H), 8.20 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.7, 28.3, 31.4, 31.5, 41.6, 43.0, 109.0, 113.8, 120.0, 122.0, 122.3, 125.0, 136.3, 137.2 ppm. HRMS (EI): calcd. for $C_{15}H_{22}N_2$ $[M]^+$ 230.1783; found 230.1793. $C_{15}H_{22}N_2$ (230.35): calcd. C 78.21, H 9.62, N 12.16; found C 78.35, H 9.76, N 12.22.

Conversion of 26 into (±)-Aurantioclavine (1): A mixture of **26** (90.4 mg, 0.2 mmol), $PdCl_2(PPh_3)_2$ (33.9 mg, 0.05 mmol), dppp (40.4 mg, 0.1 mmol), Et_3N (0.17 mL, 1.2 mmol), and formic acid (0.02 mL, 0.5 mmol) in DMF (2 mL) was heated at 100 °C for 2 h under an argon atmosphere. The solvent was removed, and the residue was separated by column chromatography on SiO_2 ($CHCl_3$/MeOH/28% NH_4OH, 23:1:0.1) to give **1** (23.4 mg, 43%).

5-Benzyl-6-(2-methylprop-1-en-1-yl)-3,4,5,6-tetrahydro-1*H*-azepino-[5,4,3-*cd*]indole (27): A mixture of **6c** (101 mg, 0.22 mmol), $PdCl_2(PPh_3)_2$ (31 mg, 0.04 mmol), dppp (36 mg, 0.09 mmol), Et_3N (0.26 mL, 1.1 mmol), and formic acid (0.02 mL, 0.44 mmol) in DMF (3 mL) was heated at 100 °C for 7 h under an argon atmosphere. The solvent was removed, and the residue was separated by column chromatography on SiO_2 (hexane/AcOEt, 4:1) to give **27** (15 mg, 22%) as a pale-yellow oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3480 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73 (s, 3 H), 1.74 (s, 3 H), 2.95 (dt, J = 16.4, 4.0 Hz, 1 H), 3.06 (dt, J = 14.5, 4.0 Hz, 1 H), 3.16 (ddd, J = 16.4, 11.0, 4.0 Hz, 1 H), 3.60 (ddd, J = 14.5, 11.0, 4.0 Hz, 1 H), 3.82 (d, J = 13.6 Hz, 1 H), 3.94 (d, J = 13.6 Hz, 1 H), 4.96 (d, J = 8.5 Hz, 1 H), 5.46 (d, J = 8.5 Hz, 1 H), 6.75 (d, J = 7.4 Hz, 1 H), 6.99 (s, 1 H), 7.09 (t, J = 7.4 Hz, 1 H), 7.22 (d, J = 7.4 Hz, 1 H), 7.24 (t, J = 7.4 Hz, 1 H), 7.30 (t, J = 7.4 Hz, 2 H), 7.38 (d, J = 7.4 Hz, 2 H), 8.04 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.4, 25.9, 26.1, 46.9, 55.5, 64.9, 108.9, 115.8, 118.7, 120.8, 121.9, 125.4, 126.4, 126.7, 128.1, 128.9, 133.4, 136.8, 138.9, 140.3 ppm. HRMS (EI): calcd. for $C_{22}H_{24}N_2$ $[M]^+$ 316.1939; found 316.1954.

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