Synthesis T. Abe et al. Special Topic

C4 Pictet–Spengler Reactions for the Synthesis of Core Structures in Hyrtiazepine Alkaloids

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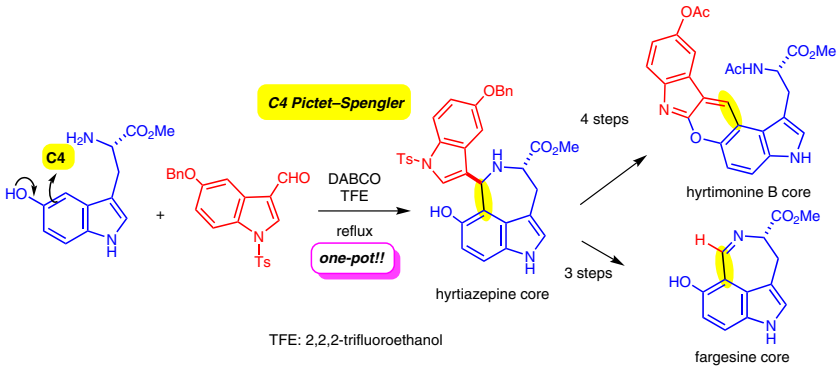

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Abstract The hyrtiazepine alkaloids are a family of bisindole natural products that have the azepinoindole backbone. We developed a biomimetic approach by constructing the azepinoindole core in a one-pot manner through 1,4-diazabicyclo[2.2.2]octane/2,2,2-trifluoroethanol (DABCO/TFE) promoted Pictet–Spengler reaction onto the C-4 position of tryptophan. This strategy allowed the synthesis of common key structures of these families. The key intermediate can be converted into the 3*H*-pyrano[2,3-*b*:5,6-*e*′]diindol intermediate present in hyrtimomines A and B, as well as the azepinoindole core present in fargesine.

Key words Pictet–Spengler reaction, indole alkaloids, azepinoindoles, biomimetic synthesis, cyclizations, stereoselectivities

The hyrtiazepine alkaloids, hyrtiazepine,[1] hyrtimomine A–C,[2a] and F,[2b] and hyrtinadine C and D,[3] are a family of bisindole natural products containing azepinoindole core structures (Figure 1). These bisindoles display promising biological activity, such as cytotoxity against human epidermoid carcinoma KB cells and muline leukemia L1210 cells,[2a] and antimicrobial[3] activities. Their complex structure and interesting biological properties has prompted investigations on the synthesis of these alkaloids.[4] Ito and Yamaguchi reported the first total synthesis of (±)-hyrtiazepine by using *ortho*-selective α-hydroxyalkylation/intramolecular imine formation.[5] Given their complexity, to date, there is no precedent for the total synthesis of these natural products except for Ito and Yamaguchi's milestone.

The structural relationship between these natural products inspired us to develop a biomimetic strategy for their synthesis. These alkaloids can plausibly be biosynthesized by the oxidative Pictet–Spengler reaction (Scheme 1). First, a condensation of tryptophan and 5-hydroxy-indole-3-carbaldehyde affords the iminium ion. Subsequently, an oxidative Pictet–Spengler reaction at the C-4 position of the indole ring affords hyrtiazepine. After the formation of hyrtiazepine, a cascade sequence would occur. Thus, oxidation sequences could afford hyrtinadines C, D and hyrtimomine C, whereas hyrtimomines A and B would be produced by an intramolecular oxa-Michael addition of hyrtiazepine.

Previously, we reported a base-promoted C-4 Pictet–Spengler reaction of serotonines, which enable azepinoindoles to be afforded in one pot.[6] Furthermore, the concise synthesis of (±)-aurantioclavine was also accomplished in

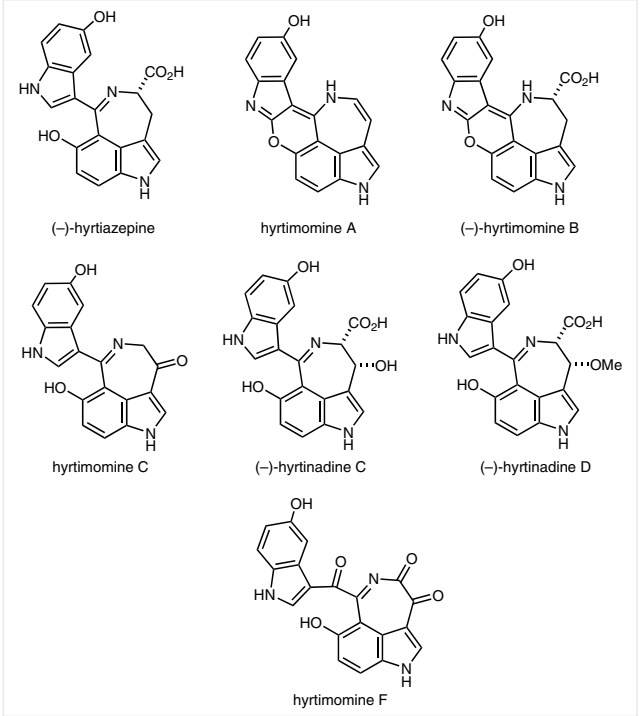

Figure 1 Members of the hyrtiazepine family

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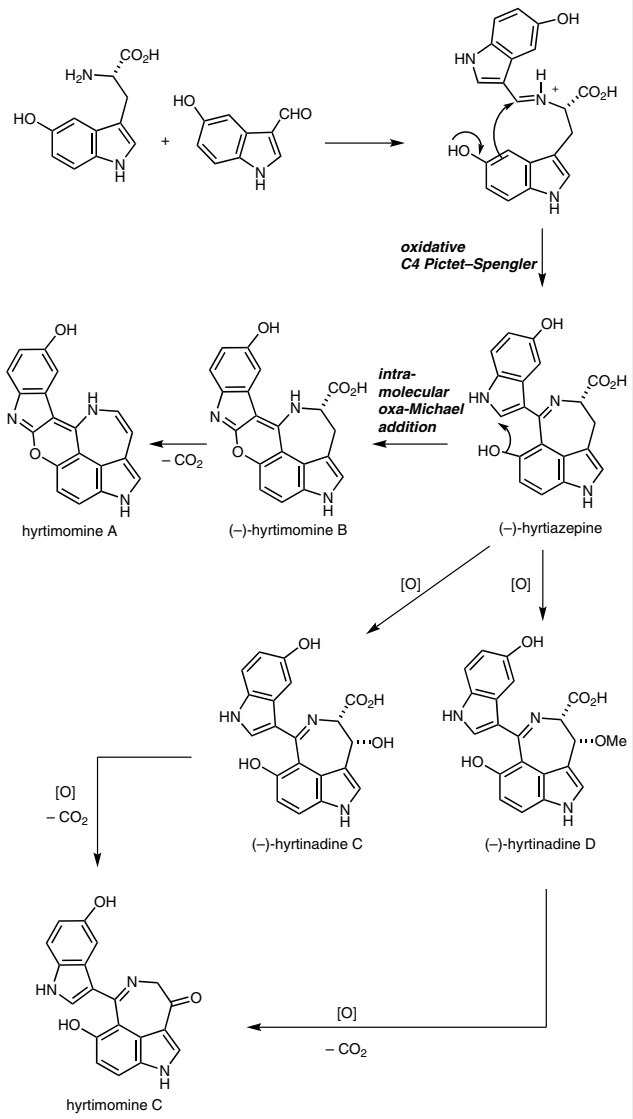
only three steps from N_b-benzyl-serotonine and alkylaldehydes by using this strategy.[7] Recently, we reported the first synthesis of the azepinoindole alkaloid hyrtioreticulins C and D through a base-promoted C-4 Pictet–Spengler reaction between tryptophan and acetaldehyde.[8] Although these results demonstrated that such a biomimetic cascade toward hyrtiazepines was possible, there were a few challenges in the synthesis of these alkaloids. To obtain azepinoindoles from the C-4 Pictet–Spengler reaction, the reaction with tryptophan and 5-hydroxyindole-3-carbaldehyde must proceed smoothly. However, in the preliminary experiments, this scenario would not be easy to achieve under the previously reported conditions.[6–8] Therefore, alternative and appropriate reaction conditions for the C-4 Pictet–Spengler reaction would be necessary to supply a common hyrtiazepine core structure. As an outgrowth of our investigations in the area of indole alkaloids,[9] we envisioned that the C-4 Pictet–Spengler reaction of tryptophans with 5-hydroxyindole-3-carbaldehydes would allow a concise approach to these alkaloids under new reaction conditions.

Given that we envisioned a biomimetic approach, we started our venture by preparing the starting materials. Thus, we synthesized tryptophan methyl ester **6** from tryptophan by following a reported procedure;[10] the other starting materials, indole-3-carbaldehydes, were synthesized from 5-hydroxyindole (**1**) (Scheme 2). First, compound **1** was reacted with BnBr in the presence of K_2CO_3 and *N*,*N*-dimethylformamide (DMF) under reflux conditions, which led to the formation of O-protected indole **2**.[11] Next, treatment of **2** with Vilsmeier–Haack reagent[12] at room temperature furnished the desired aldehyde **4a**.[13] The latter was transformed into **4b**[14] and **4c** by using TsCl and $(Boc)_2O$, respectively. The *N*-methoxyindole **5** was obtained from **2**, via indoline **3**[15] followed by Somei oxidation[16] using Na_2WO_4 and methylation. Finally, the Vilsmeier–Haack reaction of **5** afforded the desired aldehyde **4d**.

With the starting materials in hand, we next set out to investigate the reaction between tryptophan **6** and aldehyde **4b** (Scheme 3). Initially, **6** and **4b** were subjected to the previously reported reaction conditions ($MeOH/Et_3N$ under microwave irradiation).[8] Unfortunately, unexpected **4a** was mainly produced via detosylation under basic conditions, and neither the desired azepinoindole **7** nor β-carboline **8** could be obtained.

Having encountered difficulties in obtaining **7**, we investigated the use of milder reaction conditions that were compatible with aldehyde **4b** (Table 1). To our delight, conducting the reaction in MeOH at reflux afforded the desired azepinoindole **7** in 29% yield (*cis*/*trans* = 0:100), along with **8** in 4% yield (*cis*/*trans* = 75:25) and unstable imine **9** in 8% yield (entry 1). Among the various bases screened, 1,4-diazabicyclo[2.2.2]octane (DABCO) was most effective (entries 2–4). However, although the yield increased, the diastereoselectivity dropped off significantly. The *cis* stereochemistry of **7a** was established by ^{1}H NOE experiments, which revealed a strong NOE interaction (Figure 2). To improve the diastereoselectivity, we probed the solvents in the reaction (entries 5–8). However, none of the attempts were successful. For example, when MeOH was replaced with DMF, imine **9** was mainly isolated (entry 5). Among these solvents, alcohols seemed to be diastereoselective (entries 7 and 8). At this stage, we hypothesized that the C-4 Pictet–Spengler reaction would be promoted if a corresponding iminium ion derived from **9** could be stabilized.



Scheme 1 Biosynthesis of the azepinoindole alkaloids

Based on our hypothesis and on previous reports,[17] we next conducted a polar solvent screen. Among the solvents examined, 2,2,2-trifluoroethanol (TFE)[17] resulted in the formation of **7b** in 74% yield with high diastereoselectivity (Table 1, entry 9).

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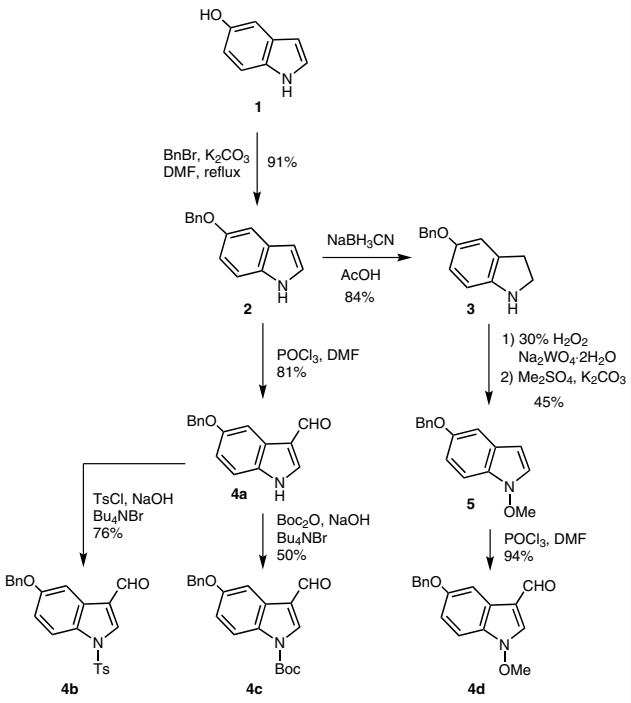
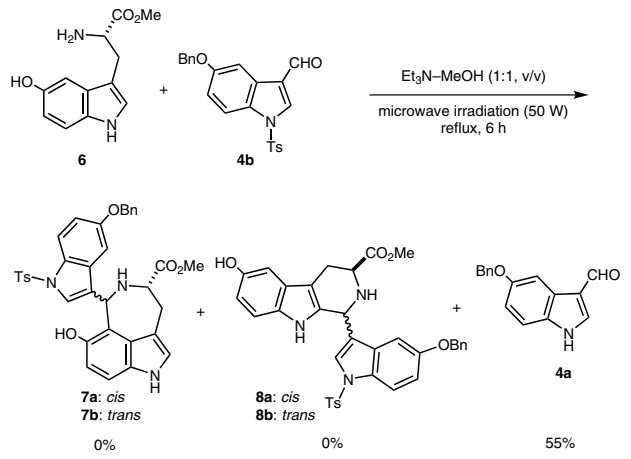


Scheme 2 Synthesis of 3-formylindoles



Scheme 3 Attempted synthesis of azepinoindole **7** by using our previously developed conditions

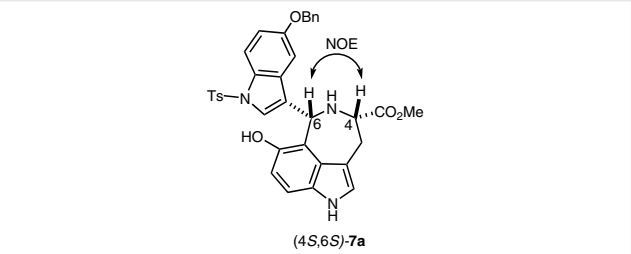


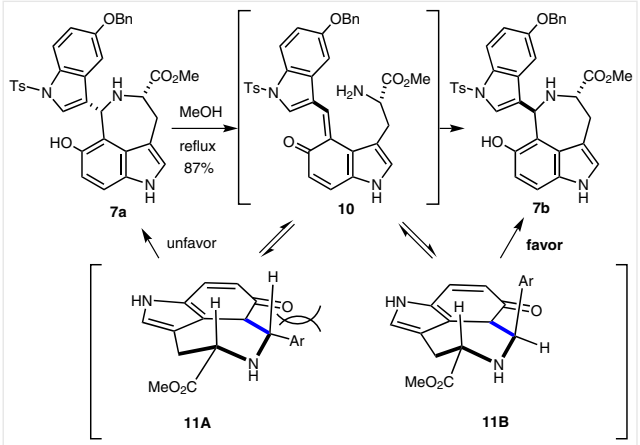
Figure 2 ^{1}H NOE experiments with **7a**

Furthermore, the use of a combination of DABCO and TFE provided **7b** in 84% yield as the only product (Table 1, entry 10). TFE has several unique properties,[18] which include high polarity, high ionization power,[19] high ability to make hydrogen bonds,[20] and low nucleophilicity.[21] These properties of TFE would enhance the reactivity of the iminium ion in the C-4 Pictet–Spengler reaction.

To confirm the origin of diastereoselectivity, we carried out isomerization experiments (Scheme 4). Subjecting the *cis*-isomer to the reaction in MeOH under reflux conditions led to the production of the *trans*-isomer in 87% yield. This sequence would be initiated by retro-Mannich reaction, forming the quinodimehane intermediate **10**.

The intramolecular Mannich reaction then afforded the *trans*-isomer via intermediate **11B**. Due to steric repulsion at **11A**, the thermodynamically unstable *cis*-isomer is not dominant in the Pictet–Spengler reaction at the C-4 position of the indole ring. These trends are similar to the majority of the syntheses of clavicipitic acids,[22] except for Piersanti's *cis*-selective synthesis using Rh(I)-catalyzed intramolecular 1,2-additions of boronic acids to imines.[23] These results suggests that the high *trans*-diastereoselectivity would result from isomerization under reflux conditions. However, in these isomerization experiments, the *cis*-diastereoselectivity[22] could not be explained (Table 1, entry 4). To obtain some clues for the origin of this *cis*-diastereoselectivity, further investigations must be conducted.

We then investigated the protective group on the indole nitrogen on **4** under the optimized conditions (Table 2). No reaction occurred in the absence of a protective group on the indole nitrogen atom (entry 1). In the case of the electron-withdrawing group, the desired products **7b** and **7d** were obtained in 85% and 66% yield, respectively (entries 2 and 3). No product could be obtained when *N*-methoxyaldehyde **4d** was used (entry 4).



Scheme 4 Isomerization of **7a** into **7b** via **10** and possible origin of diastereoselectivity

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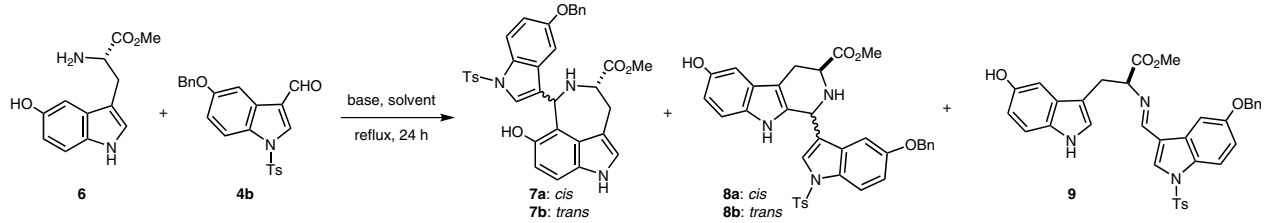
Table 1 Reaction of **6** with Aldehyde **4b** for the Construction of Hyrtiazepine Skeleton



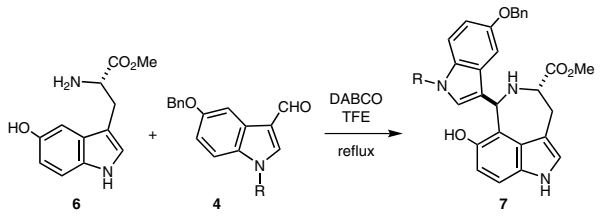
Entry	Base	Solvent	Yields (%)[a]			
			7 (*cis*/*trans*)[b]	**8** (*cis*/*trans*)[b]	**9**	**6**
1	–	MeOH	29 (0:100)	4 (75:25)	8	18
2	DABCO	MeOH	56 (39:61)	–	–	15
3	Et_3N	MeOH	37 (35:65)	–	–	60
4	DIEA	MeOH	39 (72:28)	–	–	31
5	–	DMF	–	12 (58:42)	54	26
6	–	MeCN	5 (25:75)	16 (53:47)	17	32
7	–	EtOH	7 (0:100)	7 (34:66)	14	49
8	–	^{i}PrOH	22 (12:88)	10 (32:68)	12	40
9	–	TFE	74 (0:100)	–	9	7
10	DABCO	TFE	85 (1:99)	–	–	–

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopic analysis.

With the precursor **7b** in hand, we planned to use the approach for the synthesis of the hyrtiazepine cores (Scheme 5). The tosyl group on the indole nitrogen was removed by using magnesium powder in MeOH[24] to provide amine **7c** in 73% yield. Subsequent reduction with 10% Pd-C and hydrogen gas provided phenol **12** in 70% yield.

With **12** in hand, we then turned our attention to the synthesis of hyrtiazepine using an unprecedented late-stage imine formation of azepinoindoles. We attempted to realize this strategy by employing the oxidation conditions, but all failed. 5-Hydroxyindole was mainly obtained via retro-Mannich type fragmentation.

Table 2 Reaction of **6** with Aldehydes **4**



Entry	**4**	R	Time (h)	**7**	R	Yield (%)[a]
1	**4a**	H	24	**7c**	H	0
2	**4b**	Ts	4	**7b**	Ts	85
3	**4c**	Boc	4	**7d**	Boc	66
4	**4d**	OMe	24	**7e**	OMe	0

[a] Isolated yield.

Next, the azepinoindole intermediate **12** was used to test the formation of the alkylidene indolenine core present in hyrtiazepine alkaloids such as hyrtimomines A and B. Intensive investigations provided a solution for this problem. Thus, intermediate **12**, on exposure to TfOH in the presence of 10% Pd-C at room temperature, followed by acetylation, afforded the desired pyranodiindole **13** in 47% yield through an intramolecular oxa-Michael addition/ring opening of the azepane ring (Scheme 5). This is the first example of the synthesis of 3*H*-pyrano[2,3-*b*:5,6-*e*′]diindol. We also tried to synthesize hyrtimonime B from **12** without cleaving the C–N bond of the azepine-ring according to the precedents for the hemiaminal formation.[25] However, all attempts failed to obtain hyrtimonime B.

During the attempted synthesis of hyrtimonine B, we encountered an unexpected reaction. The treatment of compound **12** in MeOH under reflux conditions afforded an unstable cyclic imine **14** in 61% yield through retro-Mannich reaction. This framework is present in azepinoindole alkaloids such as fargesine[26] and cimitrypazepine.[27]

Finally, the imine formation of model substrate **15** was investigated because of the difficulty encountered in the imine formation of **12** (Scheme 6). Disappointingly, the imine formation could not be achieved and decomposition

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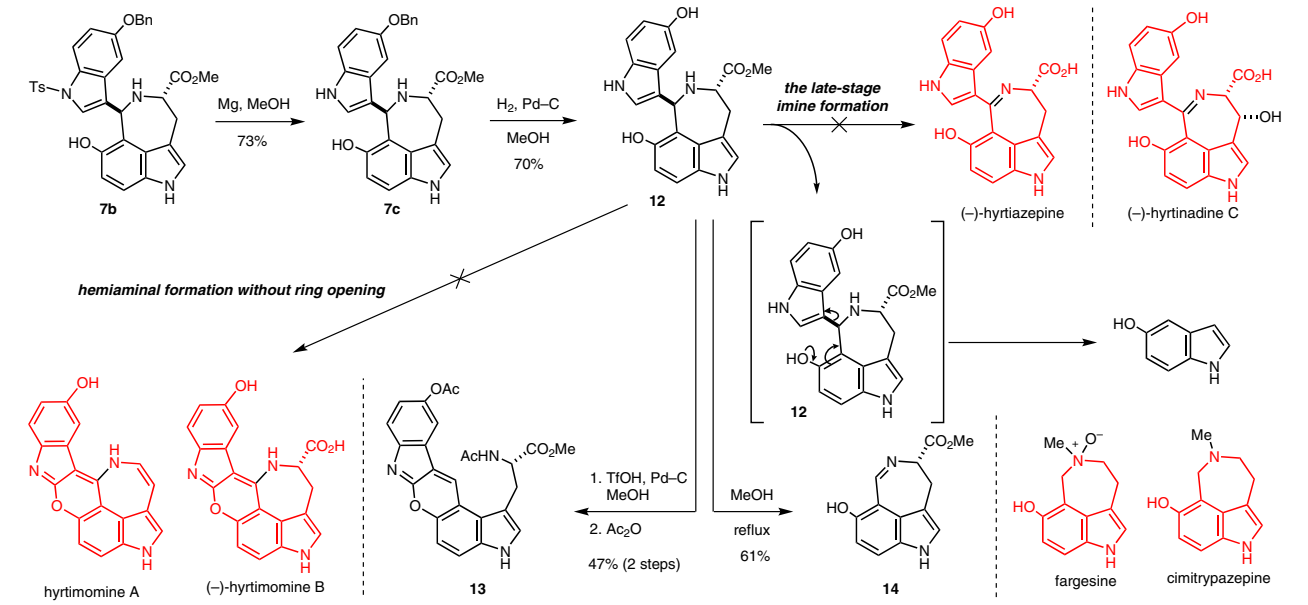
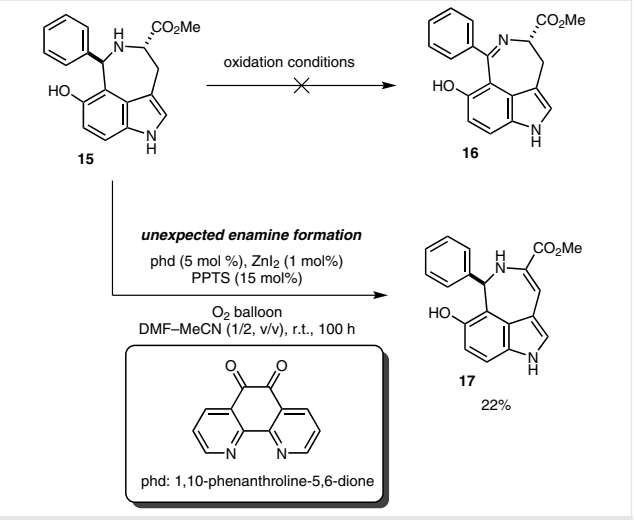


Scheme 5 Synthesis of diverse hyrtiazepine alkaloid core structures from the common intermediate **7b**

of **15** was observed. To avoid the decomposition, milder conditions for imine formations were also attempted. To our surprise, enamine **17** was obtained when the Stahl's oxidation conditions were applied.[28] These results suggest that it is difficult to accomplish the synthesis of hyrtiazepine by the late-stage imine formation strategy.



Scheme 6 Attempted imine formation using model substrate **15**

In conclusion, we have developed a biomimetic approach employing a C-4 Pictet–Spengler reaction using DABCO and TFE that provides access to the azepinoindole core in a one-pot operation. The key feature in this reaction is biomimetic cyclizations onto the C-4 position of tryptophan. The common intermediate can be converted into the alkylidene indolenine core present in hyrtimomines A and B, as well as the azepinoindole core present in fargesine and cimitrypazepine. We found that the imine formation of azepinoindoles is difficult to achieve. Our campaign for the total synthesis of hyrtiazepine alkaloids using the C-4 Pictet–Spengler reaction is in progress and the results will be reported in due course.

Optical rotations were recorded with a JASCO P-2200 polarimeter. Melting points were recorded with a Yamato MP21 and are uncorrected. IR spectra were measured with a Shimadzu IRAffinity-1 spectrometer and absorbance bands are reported in wavenumbers (cm^{-1}). NMR experiments were performed with a JEOL JNM-ECA500 (500 MHz) spectrometer. Chemical shifts in ^1H and ^{13}C NMR are expressed in ppm (δ). All ^{13}C NMR spectra were determined with complete proton decoupling. Column chromatography and Flash column chromatography were performed on silica gel (Silica Gel 60N, Kanto Chemical Co., Ltd.). High-resolution MS spectra were recorded with Micromass AutoSpec 3100 and JEOL JMS-T100LP mass spectrometers. Microwave irradiation was performed with a Green-Motif I (IMCR-25003) monomode microwave reactor (IDX Corporation). All microwave irradiation experiments were carried out in glass tubes with microwave power at 50 W. All reagents were obtained from commercial suppliers and used without further purification.

5-Benzyloxy-1*H*-indole (2)[11]

Benzylbromide (2.0 mL, 16.8 mmol) and K_2CO_3 (3.1 g, 22.5 mmol) were added to a solution of 5-hydroxyindole **1** (2.0 g, 15.0 mmol) in DMF (10 mL) and the mixture was stirred and heated at reflux. After 24 h, the mixture was cooled to r.t. and the reaction was quenched with 10% aq HCl. The mixture was extracted with EtOAc (3 × 50 mL),

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washed with H_2O (30 mL) and brine (2 × 20 mL), and dried over $MgSO_4$. The solvent was removed and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:6) to give **2**.

Yield: 3 g (91%); colorless solid; mp 97–100 °C ($CHCl_3$).

IR ($CHCl_3$): 3483, 1626, 1581, 1477, 1452, 1281, 1153 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.03 (br. s, 1 H), 7.52 (d, *J* = 7.5 Hz, 2 H), 7.43 (t, *J* = 7.5 Hz, 2 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 7.27 (d, *J* = 8.6 Hz, 1 H), 7.24 (d, *J* = 2.3 Hz, 1 H), 7.15 (t, *J* = 2.8 Hz, 1 H), 6.99 (dd, *J* = 8.6, 2.3 Hz, 1 H), 6.51 (t, *J* = 2.3 Hz, 1 H), 5.15 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.5, 137.8, 131.3, 128.7, 128.4, 127.9, 127.7, 125.1, 113.2, 111.9, 104.1, 102.5, 71.1.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{15}H_{13}NO$: 223.0997; found: 223.1028.

5-Benzyloxy-1*H*-indole-3-carboxaldehyde (4a)[13]

Phosphoryl chloride (0.4 mL, 4.3 mmol) was added to DMF (2.7 mL) at –30 °C and the mixture was stirred at r.t. for 0.5 h. A solution of **2** (536 mg, 2.4 mmol) in DMF (3 mL) was added and the mixture was stirred at r.t. for 1 h. The mixture was cooled to 0 °C and the reaction was quenched with 10% aq NaOH, and stirred at r.t. for 0.5 h. The mixture was neutralized with 10% aq HCl, and the resulting precipitate was separated by filtration, washed with H_2O, and dried under vacuum to give **4a**.

Yield: 489 mg (81%); colorless solid; mp 242–244 °C ($CHCl_3$).

IR (KBr): 3152, 1632, 1616, 1585, 1522, 1493, 1479, 1468, 1449, 1395, 1261, 1204, 1140 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 12.01 (br. s, 1 H), 9.85 (s, 1 H), 8.19 (d, *J* = 1.9 Hz, 1 H), 7.65 (d, *J* = 2.3 Hz, 1 H), 7.45 (d, *J* = 8.1 Hz, 2 H), 7.34–7.40 (m, 3 H), 7.29 (t, *J* = 6.9 Hz, 1 H), 6.93 (dd, *J* = 8.6, 2.3 Hz, 1 H), 5.09 (s, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 185.3, 155.2, 139.2, 138.0, 132.6, 128.9, 128.2, 128.1, 125.4, 118.6, 114.3, 113.8, 104.6, 70.1.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{13}NO_2$: 251.0946; found: 251.0942.

5-Benzyloxy-1-tosyl-1*H*-indole-3-carboxaldehyde (4b)[14]

Tetrabutylammonium bromide (97 mg, 0.3 mmol) was added to a solution of **4a** (251 mg, 1.0 mmol) and 50% aq NaOH (2 mL) in CH_2Cl_2 (2 mL). After stirring at r.t. for 10 min, TsCl (210 mg, 1.1 mmol) was added and the mixture was stirred at r.t. for 0.5 h. The mixture was diluted with EtOAc (50 mL) and washed with H_2O (15 mL) and brine (2 × 10 mL), and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography ($CHCl_3$) to give **4b**.

Yield: 308 mg (76%); colorless solid; mp 170–171 °C (EtOAc–hexane).

IR ($CHCl_3$): 1678, 1541, 1476, 1450, 1383, 1177 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 10.01 (s, 1 H), 8.79 (s, 1 H), 7.94 (d, *J* = 8.6 Hz, 1 H), 7.83 (d, *J* = 9.2 Hz, 1 H), 7.64 (d, *J* = 2.3 Hz, 1 H), 7.39–7.43 (m, 4 H), 7.34 (t, *J* = 7.4 Hz, 2 H), 7.28 (t, *J* = 7.4 Hz, 1 H), 7.10 (dd, *J* = 9.2, 2.3 Hz, 2 H), 5.09 (s, 2 H), 2.30 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 187.3, 156.8, 147.0, 139.5, 137.4, 133.9, 131.1, 129.5, 129.0, 128.4, 128.2, 127.7, 127.4, 122.0, 116.3, 114.7, 105.7, 70.2, 21.6.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{23}H_{19}NO_4S_2$: 405.1035; found: 405.1005.

tert-Butyl 5-Benzyloxy-3-formyl-1*H*-indole-1-carboxylate (4c)

Tetrabutylammonium bromide (97 mg, 0.3 mmol) was added to a solution of **4a** (48 mg, 0.19 mmol) and 50% aq NaOH (2 mL) in CH_2Cl_2 (2 mL). After stirring at r.t. for 10 min, di-*tert*-butyl dicarbonate (84 mg, 0.38 mmol) was added and the mixture was stirred at r.t. for 8 h. The mixture was diluted with EtOAc (50 mL) and washed with H_2O (15 mL) and brine (2 × 10 mL), and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography (EtOAc–hexane, 1:10) to give **4c**.

Yield: 34 mg (50%); colorless solid; mp 248–249 °C ($CHCl_3$–hexane).

IR ($CHCl_3$): 1744, 1674, 1454, 1256, 1148, 1088 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 10.06 (s, 1 H), 8.19 (s, 1 H), 8.02 (d, *J* = 9.2 Hz, 1 H), 7.88 (d, *J* = 2.3 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.33 (t, *J* = 7.5 Hz, 1 H), 7.09 (dd, *J* = 9.2, 2.8 Hz, 1 H), 5.14 (s, 2 H), 1.70 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.0, 156.5, 148.8, 137.0, 136.9, 130.7, 128.7, 128.1, 127.8, 127.1, 121.4, 116.2, 116.1, 105.3, 85.7, 70.6, 28.2.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{21}H_{21}NO_4$: 351.1471; found: 351.1475.

5-Benzyloxyindoline (3)[15]

$NaBH_3CN$ (602 mg, 9.1 mmol) was added to a solution of **2** (1.0 g, 4.5 mmol) in AcOH (50 mL). After stirring at r.t. for 10 min, the mixture was cooled to 0 °C and the reaction was quenched with H_2O (50 mL) and 40% aq NaOH. The mixture was extracted with EtOAc (3 × 50 mL), washed with H_2O (30 mL) and brine (2 × 20 mL), and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH–29% NH_4OH, 46:1:0.1) to give **3**.

Yield: 844 mg (84%); pale-yellow oil.

IR ($CHCl_3$): 1492, 1140 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.5 Hz, 2 H), 7.38 (t, *J* = 7.5 Hz, 2 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 6.84 (t, *J* = 2.8 Hz, 1 H), 6.67 (dd, *J* = 8.6, 2.8 Hz, 1 H), 6.58 (d, *J* = 8.1 Hz, 1 H), 4.99 (s, 2 H), 3.53 (t, *J* = 8.3 Hz, 2 H), 3.01 (t, *J* = 8.2 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.8, 145.7, 137.8, 131.2, 128.6, 127.9, 127.6, 113.5, 112.8, 110.1, 71.1, 47.9, 30.5.

HRMS (ESI): *m*/*z* [MH^+]: calcd for $C_{15}H_{16}NO$: 226.1232; found 226.1186.

5-Benzyloxy-1-methoxy-1*H*-indole (5)

A solution of 30% H_2O_2 (510 mg, 4.5 mmol) in MeOH (1 mL) was added to a mixture of **3** (100 mg, 0.45 mmol) and $Na_2WO_4{\cdot}2H_2O$ (31 mg, 0.09 mmol) in MeOH–H_2O (8:1 v/v, 4.5 mL) at 0 °C under stirring at r.t. After 15 min, a solution of K_2CO_3 (315 mg, 2.3 mmol) and dimethyl sulfate (121 mg, 0.9 mmol) in MeOH (1 mL) was added to the mixture. After stirring at r.t. for 0.5 h, the reaction was quenched with H_2O (30 mL) and the mixture was extracted with $CHCl_3$ (3 × 50 mL), washed with H_2O (30 mL) and brine (2 × 20 mL), and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography (EtOAc–hexane, 1:5) to give **5**.

Yield: 51 mg (45%); colorless solid; mp 56–58 °C ($CHCl_3$–hexane).

IR ($CHCl_3$): 1460, 1144 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.5 Hz, 2 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.32–7.36 (m, 2 H), 7.24 (d, *J* = 3.4 Hz, 1 H), 7.14 (d, *J* = 2.3 Hz, 1 H), 7.01 (dd, *J* = 9.2, 2.3 Hz, 1 H), 6.27 (dd, *J* = 3.5, 1.2 Hz, 1 H), 5.11 (s, 2 H), 4.07 (s, 3 H).

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^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.7, 137.7, 128.6, 127.9, 127.6, 127.6, 124.8, 123.7, 113.6, 109.2, 104.5, 97.7, 71.0, 66.0.

HRMS (ESI): *m*/*z* [MNa^+] calcd for $C_{16}H_{15}NO_2Na$: 276.1001; found: 276.0986.

5-Benzyloxy-1-methoxy-1*H*-indole-3-carboxaldehyde (4d)

Phosphoryl chloride (0.24 mL, 2.6 mmol) was added to DMF (1.5 mL) at –30 °C and the solution was stirred at r.t. for 0.5 h. A solution of **5**(321 mg, 1.3 mmol) in DMF (0.5 mL) was added and the mixture was stirred at r.t. for 1 h. The mixture was cooled to 0 °C and the reaction was quenched with 10% aq NaOH, and stirred at r.t. for 0.5 h. The mixture was extracted with EtOAc (3 × 50 mL), washed with H_2O (30 mL) and brine (2 × 20 mL), and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography (EtOAc–hexane, 1:2) to give **4d**.

Yield: 334 mg (94%); colorless solid; mp 108–109 °C ($CHCl_3$–hexane).

IR ($CHCl_3$): 1661, 1458, 1368, 1103 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.90 (s, 1 H), 7.91 (d, *J* = 2.3 Hz, 1 H), 7.82 (s, 1 H), 7.49 (d, *J* = 6.9 Hz, 2 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 7.37 (d, *J* = 9.2 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz, 1 H), 7.09 (dd, *J* = 9.2, 2.3 Hz, 1 H), 5.14 (s, 2 H), 4.16 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 185.2, 156.3, 137.1, 131.8, 128.7, 128.1, 127.8, 122.5, 116.0, 113.8, 109.8, 104.7, 70.7, 67.1.

HRMS (ESI): *m*/*z* [MNa^+] calcd for $C_{17}H_{15}NNaO_3$: 304.0950; found: 304.0901.

Pictet–Spengler Reaction of 6 with 4 under Microwave Irradiation (Scheme 3)

To a solution of tryptophan **6** (47 mg, 0.2 mmol) in Et_3N–MeOH (1:1, v/v, 2 mL), **4b** (89 mg, 0.22 mmol) was added and the mixture was stirred for 5 min at r.t. The mixture was heated under reflux for 6 h using microwave irradiation (50 W). After the mixture had cooled, the mixture was evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 2:1) to give **4a**.

Yield: 28 mg (55%).

Pictet–Spengler Reaction of 6 with 4; Typical Procedure (Table 1)

To a solution of **6** (47 mg, 0.2 mmol) in MeOH (2 mL), **4b** (89 mg, 0.22 mmol) was added. After stirring at reflux for 24 h, the mixture was cooled to r.t. and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH–29% NH_4OH, 46:1:0.1) to give **7**(36 mg, 29% yield),**8**(5 mg, 4% yield), and**9** (10 mg, 8% yield). Analytical samples**7a**, **7b**, **8a** and**8b** were obtained by further purification using silica gel column chromatography ($CHCl_3$–MeOH–29% NH_4OH, 46:1:0.1).

Methyl (4*S*,6*S*)-6-(5-Benzyloxy-1-tosyl-1*H*-indol-3-yl)-7-hydroxy-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole-4-carboxylate (7a)

Colorless solid; mp 108–111 °C ($CHCl_3$–hexane); $[\alpha]_D^{24}$ = 4.5 (*c* = 0.10 in MeOH).

IR ($CHCl_3$): 3480, 1757, 1452, 1371, 1171 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (br. s, 1 H), 7.80 (d,*J* = 9.2 Hz, 1 H), 7.69 (d, *J* = 8.6 Hz, 2 H), 7.48 (s, 1 H), 7.25–7.34 (m, 5 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.12 (d, *J* = 8.5 Hz, 2 H), 7.02 (s, 1 H), 6.92 (dd, *J* = 9.2, 2.5 Hz, 1 H), 6.87 (d, *J* = 2.5 Hz, 1 H), 6.64 (d, *J* = 8.5 Hz, 1 H), 5.72 (s, 1 H), 4.74 (s, 2 H), 3.93 (dd, *J* = 12.0, 2.3 Hz, 1 H), 3.67 (s, 3 H), 3.41 (dd, *J* = 14.9, 2.3 Hz, 1 H), 3.11 (dd, *J* = 14.9, 12.9 Hz, 1 H), 2.32 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.3, 155.5, 146.5, 145.1, 137.0, 135.0, 132.5, 130.5, 130.2, 130.0, 128.6, 128.0, 127.7, 126.9, 126.2, 125.5, 124.7, 122.8, 119.5, 115.1, 114.6, 113.6, 112.9, 110.0, 104.1, 70.2, 59.8, 55.3, 52.4, 34.0, 21.7.

HRMS (ESI): *m*/*z* [MH^+] calcd for $C_{35}H_{32}N_3O_6S$: 622.2012; found: 622.2012.

Methyl (4*S*,6*R*)-6-(5-Benzyloxy-1-tosyl-1*H*-indol-3-yl)-7-hydroxy-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole-4-carboxylate (7b)

Colorless solid; mp 138–141 °C ($CHCl_3$–hexane); $[\alpha]_D^{24}$ = –5.6 (*c* = 0.11 in MeOH).

IR ($CHCl_3$): 3484, 1734, 1460, 1371, 1172 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (br. s, 1 H), 7.81 (d, *J* = 9.2 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 2 H), 7.45 (d, *J* = 7.4 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.31–7.34 (m, 2 H), 7.21 (d, *J* = 8.6 Hz, 1 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.05 (s, 1 H), 6.98 (dd, *J* = 9.1, 2.3 Hz, 1 H), 6.79 (s, 1 H), 6.75 (d, *J* = 8.6 Hz, 1 H), 6.07 (s, 1 H), 5.02 (s, 2 H), 3.66 (dd, *J* = 12.3, 2.8 Hz, 1 H), 3.52 (s, 3 H), 3.43 (dd, *J* = 16.0, 2.8 Hz, 1 H), 3.02 (dd, *J* = 15.5, 12.6 Hz, 1 H), 2.32 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5, 155.9, 145.2, 144.7, 137.2, 134.8, 132.7, 131.3, 131.0, 129.8, 128.7, 128.1, 127.8, 127.1, 126.7, 126.1, 123.5, 122.9, 120.7, 115.0, 114.9, 112.7, 112.5, 110.8, 104.2, 70.6, 54.9, 53.1, 52.1, 34.3, 21.6.

HRMS (ESI): *m*/*z* [MH^+] calcd for $C_{35}H_{32}N_3O_6S$: 622.2012; found: 622.2036.

Methyl (1*S*,3*S*)-1-(5-Benzyloxy-1-tosyl-1*H*-indol-3-yl)-6-hydroxy-2,3,4,9-tetrahydro-9*H*-β-carboline-3-carboxylate (8a)

Colorless solid; mp 132–137 °C ($CHCl_3$–hexane); $[\alpha]_D^{24}$ = –20.0 (*c* = 0.11 in MeOH).

IR ($CHCl_3$): 3456, 1736, 1597, 1452, 1372, 1171 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 9.2 Hz, 1 H), 7.76 (d, *J* = 8.0 Hz, 2 H), 7.61 (s, 1 H), 7.37 (s, 1 H), 7.21–7.27 (m, 7 H), 6.99 (d, *J* = 8.6 Hz, 1 H), 6.95 (dd, *J* = 9.2, 2.3 Hz, 1 H), 6.92 (d, *J* = 2.3 Hz, 1 H), 6.75 (d, *J* = 2.3 Hz, 1 H), 6.71 (dd, *J* = 8.6, 2.3 Hz, 1 H), 5.41 (s, 1 H,), 4.76 (s, 2 H), 3.95 (dd, *J* = 10.9, 4.0 Hz, 1 H), 3.78 (s, 3 H), 3.13 (dd, *J* = 13.8, 4.0 Hz, 1 H), 2.88 (ddd, *J* = 14.9, 11.5, 2.3 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.1, 155.5, 149.7, 145.3, 136.8, 135.1, 134.5, 131.4, 130.4, 130.1, 129.9, 128.6, 127.9, 127.9, 127.5, 127.0, 125.8, 121.2, 115.1, 114.6, 111.8, 111.6, 108.1, 104.2, 103.1, 70.4, 56.9, 52.4, 50.8, 25.7, 21.7.

HRMS (ESI): *m*/*z* [MH^+] calcd for $C_{35}H_{32}N_3O_6S$: 622.2012; found: 622.2009.

Methyl (1*R*,3*S*)-1-(5-Benzyloxy-1-tosyl-1*H*-indol-3-yl)-6-hydroxy-2,3,4,9-tetrahydro-9*H*-β-carboline-3-carboxylate (8b)

Colorless solid; mp 129–132 °C ($CHCl_3$–hexane); $[\alpha]_D^{24}$ = –6.9 (*c* = 0.11 in MeOH).

IR ($CHCl_3$): 3462, 1734, 1597, 1452, 1371, 1173 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 9.2 Hz, 1 H), 7.70 (d, *J* = 8.6 Hz, 2 H), 7.60 (s, 1 H), 7.27–7.32 (m, 6 H), 7.19 (d, *J* = 8.6 Hz, 2 H), 7.00 (d, *J* = 8.6 Hz, 1 H), 6.98 (dd, *J* = 9.2, 2.9 Hz, 1 H), 6.89 (d, *J* = 2.3 Hz, 1 H), 6.85 (br. s, 1 H), 6.69 (dd, *J* = 9.2, 2.3 Hz, 1 H), 5.57 (s, 1 H), 4.81 (s, 2 H), 3.85 (t, *J* = 6.3 Hz, 1 H), 3.68 (s, 3 H), 3.07 (dd, *J* = 15.5, 5.2 Hz, 1 H), 3.00 (dd, *J* = 14.9, 6.9 Hz, 1 H), 2.32 (s, 3 H).

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^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2, 155.6, 149.8, 145.2, 136.9, 135.0, 133.2, 131.4, 130.4, 130.2, 130.0, 128.6, 128.0, 127.7, 126.9, 125.8, 123.0, 115.0, 114.8, 111.8, 107.8, 103.7, 103.3, 70.4, 53.0, 52.3, 47.2, 24.6, 21.7.

HRMS (ESI): *m*/*z* [MH$^+$] calcd for $C_{35}H_{32}N_3O_6S$: 622.2012; found: 622.2007.

Methyl *N*-(5-Benzyloxy-1-tosyl-1*H*-indol-3-yl)methylene-5-hydroxytryptophanate (9)

Colorless solid; mp 97–102 °C ($CHCl_3$–hexane); $[\alpha]_D^{24}$ = –147.6 (*c* = 0.10 in MeOH).

IR ($CHCl_3$): 3480, 1736, 1641, 1450, 1379, 1173 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (br. d, *J* = 2.3 Hz, 1 H), 7.91 (s, 1 H), 7.84 (br. s, 1 H), 7.81 (d, *J* = 9.2 Hz, 1 H),7.70 (d, *J* = 8.6 Hz, 2 H), 7.60 (br. s, 1 H), 7.46 (d, *J* = 7.5 Hz, 2 H), 7.37 (t, *J* = 7.5 Hz, 2 H), 7.29 (t, *J* = 7.5 Hz, 1 H), 7.19 (d,*J* = 8.6 Hz, 2 H), 7.10 (d, *J* = 8.6 Hz, 1 H), 7.03 (dd, *J* = 9.2, 2.9 Hz, 1 H), 6.92 (d, *J*= 2.3 Hz, 1 H), 6.83 (d, *J* = 2.3 Hz, 1 H), 6.66 (dd, *J* = 8.6, 2.3 Hz, 1 H), 5.09 (dd, *J* = 18.3, 12.1 Hz, 2 H), 4.12 (dd, *J* = 8.6, 4.5 Hz, 1 H), 3.74 (s, 3 H), 3.43 (dd, *J* = 14.3, 4.6 Hz, 1 H), 3.19 (dd, *J* = 14.3, 8.6 Hz, 1 H), 2.33 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 156.6, 156.1, 149.5, 145.5, 137.2, 134.9, 131.4, 130.8, 130.1, 130.1, 129.0, 128.7, 128.1, 127.8, 127.0, 124.6, 119.9, 115.6, 114.2, 111.9, 111.8, 111.0, 106.7, 103.7, 74.3, 70.5, 52.3, 29.9, 21.7.

HRMS (ESI): *m*/*z* [MH$^+$] calcd for $C_{35}H_{32}N_3O_6S$: 622.2012; found: 622.2005.

Isomerization of *cis*-Isomer 7a to *trans*-Isomer 7b

After a solution of**7a** (19 mg, 0.03 mmol) in MeOH (3 mL) was stirred and heated at reflux for 30 h, the mixture was cooled to r.t. and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH–29% NH_4OH, 46:1:0.1) to give **7b**.

Yield: 16 mg (87%).

Base-Promoted*trans*-Selective Pictet–Spengler Reaction of 6 with 4; Typical Procedure

1,4-Diazabicyclo[2.2.2]octane (67 mg, 0.6 mmol) was added to a mixture of **6** (47 mg, 0.2 mmol) and **4c** (77 mg, 0.22 mmol) in 2,2,2-trifluoroethanol (2 mL). After stirring at reflux for 4 h, the mixture was cooled to r.t. and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH–29% NH_4OH, 46:1:0.1) to give **7d**.

Yield: 75 mg (66%).

Methyl (4*S*,6*R*)-6-(5-Benzyloxy-1-*tert*-butoxycarbonyl-1*H*-indol-3-yl)-7-hydroxy-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole-4-carboxylate (7d)

Yield: 75 mg (66%); colorless solid; mp 133–135 °C ($CHCl_3$–hexane); $[\alpha]_D^{24}$ = 5.2 (*c* = 0.11 in MeOH).

IR ($CHCl_3$): 3480, 1723, 1381, 1157 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.09 (br. s, 1 H), 7.90 (br. s, 1 H), 7.48 (d, *J* = 7.5 Hz, 2 H), 7.41 (t, *J* = 7.5 Hz, 2 H), 7.31–7.37 (m, 2 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 6.97–6.99 (m, 2 H,), 6.93 (br. s, 1 H), 6.73 (d, *J* = 8.6 Hz, 1 H), 6.13 (s, 1 H), 5.05 (s, 2 H), 3.88 (dd, *J* = 12.6, 2.9 Hz, 1 H), 3.58 (s, 3 H), 3.48 (dd, *J* = 15.5, 2.9 Hz, 1 H), 3.06 (ddd, *J* = 14.9, 12.6, 1.1 Hz, 1 H), 1.58 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.8, 155.1, 149.9, 145.3, 137.4, 132.7, 130.9, 130.6, 128.6, 128.0, 127.7, 126.1, 122.8, 121.1, 120.6, 116.0, 114.5, 112.9, 112.5, 110.6, 104.2, 83.9, 70.6, 55.1, 53.2, 52.2, 34.3, 28.3.

HRMS (ESI): *m*/*z* [MH$^+$] calcd for $C_{33}H_{34}N_3O_6$: 568.2448; found: 568.2434.

Methyl (4*S*,6*R*)-6-(5-Benzyloxy-1*H*-indol-3-yl)-7-hydroxy-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole-4-carboxylate (7c)

Magnesium turnings (242 mg, 10 mmol) was added to a solution of **7b** (250 mg, 0.4 mmol) in MeOH (20 mL). After stirring at r.t. for 1 h under N_2 atmosphere, the mixture was quenched by addition of sat. aq NH_4Cl (50 mL). The mixture was extracted with EtOAc (3 × 50 mL), washed with brine (2 × 20 mL), and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography (EtOAc–hexane, 1:2) to give **7c**.

Yield: 137 mg (73%); colorless solid; mp 127–129 °C ($CHCl_3$–MeOH); $[\alpha]_D^{24}$ = –2.1 (*c* = 0.11 in MeOH).

IR ($CHCl_3$): 3478, 1732, 1583, 1483, 1454, 1439, 1192 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.46 (br s, 1 H), 10.31 (br s, 1 H), 7.98 (s, 1 H), 7.41 (d, *J* = 7.5 Hz, 2 H), 7.37 (t, *J* = 7.5 Hz, 2 H), 7.29 (t, *J* = 7.5 Hz, 1 H), 7.15 (br s, 1 H), 7.13 (d, *J*= 9.2 Hz, 1 H), 7.05 (d, *J*= 8.6 Hz, 1 H), 7.00 (s, 1 H), 6.69 (dd, *J* = 9.2, 2.3 Hz, 1 H), 6.61 (d, *J* = 8.6 Hz, 1 H), 6.22 (s, 1 H), 6.05 (s, 1 H), 4.69 (dd, *J* = 21.2, 12.6 Hz, 2 H), 3.68 (dd, *J* = 12.1, 2.9 Hz, 1 H), 3.48 (s, 3 H), 3.26 (dd, *J* = 15.5, 2.9 Hz, 1 H), 2.85 (dd, *J* = 15.5, 12.0 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 175.3, 152.3, 146.1, 138.3, 132.5, 132.1, 128.9, 128.2, 128.2, 127.8, 126.9, 125.9, 123.2, 122.3, 116.6, 112.3, 111.9, 111.6, 111.5, 109.9, 103.7, 70.2, 55.3, 53.2, 52.1, 34.8.

HRMS (ESI): *m*/*z* [MH$^+$] calcd for $C_{28}H_{26}N_3O_4$: 468.1923; found: 468.1911.

Methyl (4*S*,6*R*)-6-(5-Hydroxy-1*H*-indol-3-yl)-7-hydroxy-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole-4-carboxylate (12)

10% Pd-C (49 mg, 0.05 mmol) was added to a solution of **7c** (50 mg, 0.1 mmol) in MeOH (5 mL). After stirring at r.t. for 0.5 h under H_2 atmosphere, the mixture was filtered through a pad of Celite and the precipitates were washed with MeOH. The solvent was removed, and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH–29% NH_4OH, 46:1:0.1) to give **12**.

Yield: 28 mg (70%); colorless solid; mp 159–160 °C ($CHCl_3$–MeOH); $[\alpha]_D^{24}$ = 19.1 (*c* = 0.11 in MeOH).

IR ($CHCl_3$): 3418, 1732, 1483, 1454, 1437, 1192 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.42 (br. s, 1 H), 10.09 (br. s, 1 H), 8.29 (s, 1 H), 7.92 (s, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 6.97 (br. s, 1 H), 6.59 (d, *J* = 8.6 Hz, 1 H), 6.53 (dd, *J* = 8.6, 2.3 Hz, 1 H), 6.04 (d, *J* = 1.7 Hz, 1 H), 6.00 (s, 1 H), 3.71 (dd, *J* = 11.5, 2.9 Hz, 1 H), 3.49 (s, 3 H), 3.25 (dd, *J* = 14.9, 2.9 Hz, 1 H), 2.83 (dd,*J* = 14.9, 12.6 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 175.1, 150.6, 146.1, 132.3, 132.0, 128.2, 127.0, 125.5, 123.0, 122.6, 116.1, 111.8, 111.8, 111.6, 111.6, 109.8, 104.4, 55.3, 53.1, 52.0, 34.6.

HRMS (ESI): *m*/*z* [MH$^+$] calcd for $C_{21}H_{20}N_3O_4$: 378.1454; found: 378.1429.

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Methyl (*S*)-2-Acetamino-3-(10-acetoxy-3*H*-pyrano[2,3-*b*:5,6-*e*′]diindol-1-yl)propanoate (13)

Compound **12** (38.0 mg, 0.10 mmol) was added to a suspension of 10% Pd-C (53.2 mg, 0.05 mmol) and TfOH (0.02 mL, 0.23 mmol) in MeOH (4 mL) under N_2 atmosphere. After stirring at r.t. for 20 h, the mixture was filtered and the precipitates were washed with MeOH, and evaporated in vacuo. Ac_2O (0.05 mL, 0.53 mmol), Et_3N (0.08 mL, 0.58 mmol) and DMAP (14.0 mg, 0.01 mmol) were added to a solution of obtained crude product in THF (2 mL). After stirring at r.t. for 2 h, the reaction was quenched with H_2O. The mixture was extracted with EtOAc (3 × 10 mL), washed with brine (10 mL), and dried over K_2CO_3. The solvent was removed, and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH–29% NH_4OH, 46:3:0.3) to give **14**.

Yield: 22 mg (47%); orange solid; mp 280–285 °C ($CHCl_3$–hexane); $[\alpha]_D^{24}$ = –23.6 [*c* = 0.10 in MeOH–TFA, 99:1, v/v)].

IR ($CHCl_3$): 1740, 1647, 1427, 1319, 1184 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 11.62 (br. s, 1 H), 9.35 (s, 1 H), 8.50 (d, *J* = 7.5 Hz, 1 H), 7.98 (d, *J* = 2.3 Hz, 1 H), 7.83 (d, *J* = 8.6 Hz, 1 H), 7.56 (d, *J* = 9.2 Hz, 1 H), 7.55 (d, *J* = 8.6 Hz, 1 H), 7.45 (d, *J* = 2.3 Hz, 1 H), 7.21 (dd, *J* = 8.6, 2.3 Hz, 1 H), 4.65—4.69 (m, 1 H), 3.64 (s, 3 H), 3.55 (dd, *J* = 15.5, 5.8 Hz, 1 H), 2.94 (dd, *J* = 15.5, 8.6 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.7, 170.4, 170.3, 164.5, 150.2, 148.2, 145.7, 133.4, 130.6, 128.3, 124.5, 123.0, 123.0, 122.4, 119.1, 117.8, 115.8, 112.1, 111.9, 111.8, 53.4, 52.6, 29.7, 22.9, 21.4.

HRMS (ESI): *m*/*z* [MH^+] calcd for $C_{25}H_{25}N_3O_6$: 462.1665; found: 460.1527.

Methyl (*S*)-7-Hydroxy-3,4-dihydro-1*H*-azepino[5,4,3-*cd*]indole-4-carboxylate (14)

A solution of **12** (18.6 mg, 0.05 mmol) in MeOH (2.5 mL) was heated at reflux for 10 h. The mixture was cooled to r.t. and concentrated in vacuo, and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH–29% NH_4OH, 46:3:0.3) to give **1**(4 mg, 53% yield) and **14**.

Yield: 7 mg (61%); yellow solid; mp 136–140 °C ($CHCl_3$–hexane); $[\alpha]_D^{24}$ = –10.8 [*c* = 0.02 in MeOH–TFA, 99:1, v/v)].

IR (KBr): 3198, 1742, 1609, 1435, 1252, 1231, 1165 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 10.71 (br. s, 1 H), 8.42 (br. s, 1 H), 7.24 (d, *J* = 9.2 Hz, 1 H), 6.97 (s, 1 H), 6.37 (br. d, *J* = 7.5 Hz, 1 H), 4.31 (d, *J* = 7.5 Hz, 1 H), 3.64 (s, 3 H), 3.23 (d, *J* = 15.5 Hz, 1 H), 2.94 (dd, *J* = 15.5, 8.1 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.6, 154.9, .8, 125.3, 122.5, 121.4, 115.9, 4.0, 110.1, 62.6, 52.5, 31.1.

HRMS (ESI): *m*/*z* [MH^+] calcd for $C_{13}H_{13}N_2O_3$: 245.0926; found: 245.0923.

Methyl (4*S*,6*R*)-7-Hydroxy-6-phenyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole-4-carboxylate (15)

1,4-Diazabicyclo[2.2.2]octane (70 mg, 0.6 mmol) was added to a mixture of **6** (468 mg, 2 mmol) and benzaldehyde (0.6 mL, 6 mmol) in 2,2,2-trifluoroethanol (20 mL). After stirring at reflux for 4 h, the mixture was cooled to r.t. and concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc–hexane, 1:1) to give **15**.

Yield: 400 mg (62%); colorless solid; mp 215–218 °C ($CHCl_3$–hexane); $[\alpha]_D^{24}$ = –46.2 (*c* = 0.10 in MeOH).

IR ($CHCl_3$): 3478, 1732, 1438 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 10.63 (d, *J* = 2.3 Hz, 1 H), 8.31 (s, 1 H), 7.13 (t, *J* = 7.5 Hz, 2 H), 7.06–7.09 (m, 1 H), 7.06 (d, *J* = 8.6 Hz, 1 H), 7.02 (br. s, 1 H), 6.93 (d, *J* = 7.5 Hz, 2 H), 6.59 (d, *J* = 8.6 Hz, 1 H), 5.78 (s, 1 H), 3.53 (s, 3 H), 3.36 (dd, *J* = 12.6, 2.3 Hz, 1 H), 3.22 (dd, *J* = 15.5, 2.3 Hz, 1 H), 2.82 (ddd, *J* = 15.5, 12.6, 1.2 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 174.8, 146.4, 144.1, 132.0, 128.8, 128.1, 127.1, 126.7, 123.3, 120.0, 111.4, 111.4, 110.4, 59.2, 55.3, 52.3, 34.4.

HRMS (ESI): *m*/*z* [MH^+] calcd for $C_{19}H_{19}N_2O_3$: 323.1396; found: 323.1367.

Methyl (*R*)-7-Hydroxy-6-phenyl-5,6-dihydro-1*H*-azepino[5,4,3-*cd*]indole-4-carboxylate (17)

To a solution of 5 mol% 1,10-phenanthroline-5,6-dione (phd, 2 mg, 0.01 mmol), 2.5 mol% ZnI_2 (1.6 mg, 0.005 mmol), and 15 mol% PPTS (7.5 mg, 0.03 mmol) in DMF (1 mL) and MeCN (2 mL) was added **15** (65 mg, 0.2 mmol). After stirring at r.t. for 100 h under an O_2 atmosphere (1 atm), the mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc–hexane, 1:2) to give **17**.

Yield: 14 mg (22%); colorless solid; mp 260–266 °C ($CHCl_3$–hexane); $[\alpha]_D^{24}$ = 165.6 (*c* = 0.10 in MeOH).

IR (KBr): 3314, 1667, 1632, 1462, 1427, 1246 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 11.17 (d, *J* = 1.7 Hz, 1 H), 8.73 (s, 1 H), 7.39 (d, *J* = 2.9 Hz, 1 H), 7.11 (d, *J* = 8.6 Hz, 1 H), 7.06 (t, *J* = 7.5 Hz, 2 H), 6.98—7.02 (m, 1 H), 6.89 (d, *J* = 7.5 Hz, 2 H), 6.78 (d, *J* = 1.7 Hz, 1 H), 6.68 (d, *J* = 8.6 Hz, 1 H), 6.03 (d, *J* = 6.3 Hz, 1 H), 5.83 (dd, *J* = 6.3, 1.7 Hz, 1 H), 3.61 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.1, 146.5, 145.2, 131.6, 128.2, 128.2, 128.0, 126.9, 126.4, 125.9, 119.4, 113.8, 112.3, 111.1, 110.9, 56.6, 52.4.

HRMS (ESI): *m*/*z* [MH^+] calcd for $C_{19}H_{17}N_2O_3$: 321.1239; found: 321.1256.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588438.

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