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Stereoselective Synthesis of Fused Spiroindolines via Tandem Mannich/Intramolecular Aminal Formation

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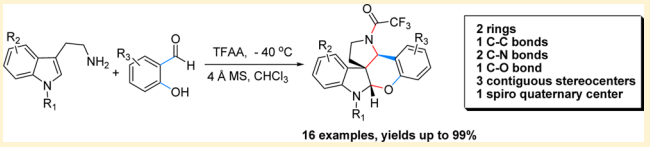
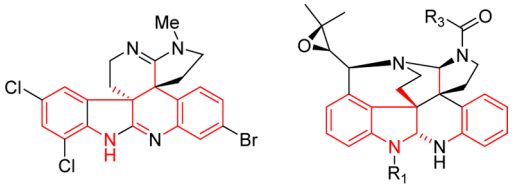
Supporting Information

ABSTRACT: A novel tandem Mannich/intramolecular aminal formation between tryptamines and salicylaldehydes was reported. This strategy provides a promising approach for the stereoselective synthesis of a range of complex fused spiroindolines, which bear a highly congested contiguous spiro quaternary center and two tertiary stereocenters, in a highly economical and effective fashion.



The pursuit of synthetic efficiency continues to stimulate the design and development of new concepts and innovative synthetic strategies in both academic research and industrial applications. One of the most effective ways to improve synthetic efficiency is to implement reaction cascades, which have emerged as powerful tools to give a rapid increase in molecular complexity from simple and readily available starting materials. It is obvious that such transformations require fewer solvents and adsorbents and less energy, hence minimizing waste management in comparison to a series of individual stepwise reactions. In recent years, considerable efforts have been devoted to the development of tandem or domino reactions.[1]

The spiroindoline[2] unit is a privileged heterocyclic motif that is commonly encountered in naturally occurring indole alkaloids and synthetic analogues with interesting biological activities, such as perophoramidine[3] and communesin[4] (Figure 1). A hexacyclic framework containing a spiro quaternary center and two adjacent stereocenters was elucidated for the both indole alkaloids. The novel architecture together with their biological activities made such a skeleton an appealing target for synthetic chemists. In the last few decades, more than 20 synthetic works have been published dealing with diverse synthetic strategies,[5−9] such as intramolecular hetero Diels−Alder reactions,[6] stepwise alkylation/cyclization,[7] intramolecular Heck coupling/reductive cyclizations,[8] and so on.[9] However, it is still desirable and challengeable as before to develop a more concise approach for synthesis of such a skeleton. Herein we report a highly economical and effective method to construct the fused spiroindolines via a novel tandem Mannich/intramolecular aminal formation between tryptamines and salicylaldehydes.



1 2

Figure 1. Examples of biologically important molecules containing polycyclic spiroindoline motifs.

Our work was inspired by Bailey's recent report concerning a TFA-catalyzed Pictet−Spengler reaction between tryptophan (**3**) and salicylaldehyde (**4**) to afford tetrahydroisoquinoline (**6**) (Scheme 1).[10] Connecting with the mechanism studies, including Bailey's previous work, concerning the Pictet−Spengler reaction between the tryptamine derivative and aldehydes, this reaction may proceed by both two possible pathways after the formation of the iminium ion **5**: (a) C-2 of indole attacks the imine to directly afford the tetrahydroisoquinoline **6**, and (b) C-3 of indole attacks the imine to give the spirocyclic intermediate **7**, which subsequently rearrangea to **6**.[11] In our opinion, if an electron-rich group such as an alkyl group attaches to the nitrogen atom of indole, then the nucleophilic activity of C-3 of the indole will be enhanced, which favors the formation of spirocyclic intermediate **7**. Sequentially the imine cation **7** could be captured by the adjacent phenoxyl group to undergo an intramolecular aminal formation, and the fused spiroindoline **8** as the final product will be obtained.

With this idea in mind, tryptamine derivative **3** and salicylaldehyde **4** were chosen as model substrates to investigate the tandem reaction. Several Lewis or Brønsted acids[12] for promoting this transformation were screened, which proved to be unfruitful (Table 1, entries 1−3). These results led us to explore more active

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Scheme 1. Original Proposal

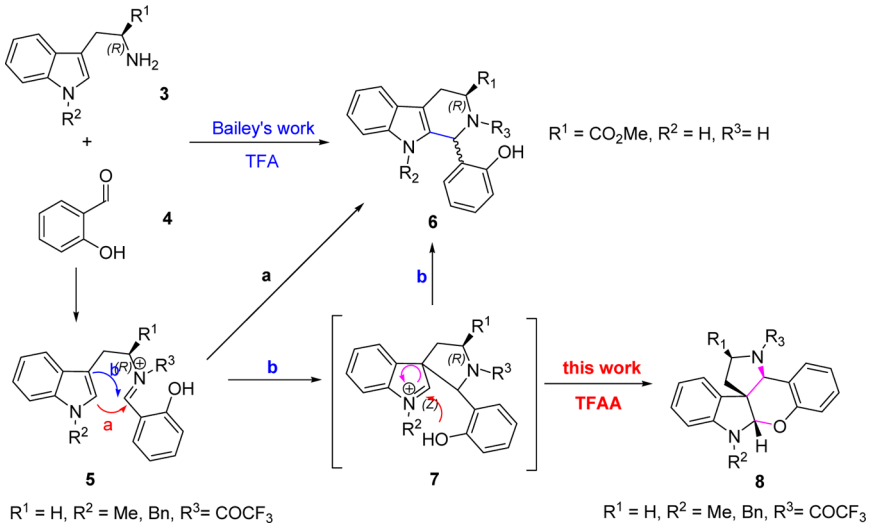
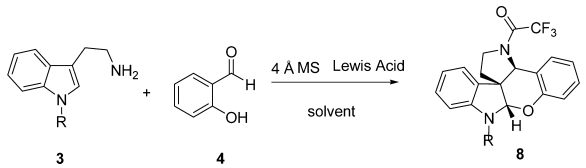


Table 1. Optimization of the Reaction Conditions



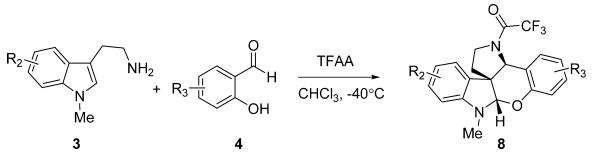
entry[a]	activator	addictive	solvent	temp (°C)	yield (%)[b]
1	$TiCl_4$		CH_2Cl_2	room temp	0
2	TFA		CH_2Cl_2	room temp	0
3	$BF_3.Et_2O$		CH_2Cl_2	room temp	0
4	TFAA		CH_2Cl_2	room temp	60
5	TFAA		$CHCl_3$	room temp	80
6	TFAA		CCl_4	room temp	0
7	TFAA		DCE	room temp	0
8	TFAA		toluene	room temp	0
9	TFAA		CH_3CN	room temp	0
10	TFAA		$CHCl_3$	−20	85
11	TFAA		$CHCl_3$	−40	88
12	TFAA	4 Å MS	$CHCl_3$	−40	96
13[c]	TFAA	4 Å MS	$CHCl_3$	−40	60

[a]Unless otherwise mentioned, R = CH_3. All the reactions were carried out with **5** (0.2 mmol), **4** (0.24 mmol), and Lewis acid (1.2 equiv), 4 Å MS (30 mg), solvent (2.0 mL). Abbreviations: TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride, DCE = 1,2-dichloroethane. [b]Isolated yield. [c]R = benzyl.

reaction intermediates; to enhance the reactivity of imine or iminium intermediates, we chose trifluoroacetic anhydride (TFAA) as activator to reinvestigate the tandem reaction. Fortunately, the reaction did occur and the desired spiro cyclization product **8** was obtained in 60% yield (Table 1, entry 4). Varying the solvent influenced the outcome considerably; CH_2Cl_2 (DCM) provided the product in moderate yield, albeit inferior to that for $CHCl_3$ (Table 1, entries 4 and 5). Also, in CCl_4, 1,2-dichloroethane (DCE), toluene, and CH_3CN, no formation of the product was detected (Table 1, entries 6−9). The optimal result was further obtained in 88% yield at −40 °C (Table 1, entries 10 and 11). Meanwhile, using 4 Å MS as an additive was favorable to the reaction (Table 1, entry 12). Notably, when the benzyl-protected tryptamine **3** was utilized, the corresponding fused spiroindoline **8** was obtained in 60% yield, probably due to steric hindrance (Table 1, entry 13).

With the optimized conditions in hand, various tryptamine derivatives **3** and salicylaldehydes **4** were used for the preparation of densely functionalized polycyclic indole derivatives and the reactions were found to be broadly applicable to a wide variety of substituted **3** and **4** species, which are presented in Table 2. Tryptamine derivatives

Table 2. Reaction Scope



entry	R^2	R^3	product	yield (%)
1	H	H	**8a**	96
2	7-CH_3	H	**8b**	98
3	5-CH_3	H	**12c**	95
4	5-Br	H	**8d**	88
5	5-OCH_3	4-Br	**8e**	66
6	7-CH_3	4-^{t}Bu	**8f**	96
7	5-Br	4-^{t}Bu	**8g**	73
8	5-Br	4-Br	**8h**	86
9	4-CH_3	6-CH_3	**8i**	73
10	7-CH_3	4,6-Cl_2	**8j**	78
11	H	4-OCH_3	**8k**	72
12	H	4-^{t}Bu	**8l**	73
13	H	4,6-Br_2	**8m**	73
14	H	5-OCH_3	**8n**	99
15	H	6-CH_3	**8o**	77
16	H	4,6-Cl_2	**8p**	82

bearing either electron-withdrawing or electron-donating groups proceeded smoothly to the corresponding products in terms of chemical yields: specifically, electron-rich tryptamines **3** gave high yields (Table 2, entries 2 and 3), whereas electron-deficient tryptamines **3** generated the spiro product in slightly lower yield (Table 2, entry 4) . To further illustrate the power of this tandem reaction, salicylaldehydes with various substituents, irrespective of the position at the aryl ring, were also examined. Meta methyl, methoxyl, *tert*-butyl, and halogen substituents had no significant impact, and the corresponding products were obtained in up to 99% yield (Table 2, entries 5−8 and 11−13). Moreover, salicylaldehyde **4**

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with a methoxyl group at the ortho position proved to be the most suitable substrate and afforded the corresponding spiroindoline in 99% yield (Table 2, entry 14). Electron-deficient salicylaldehydes (substituted with dibromo or dihalogen) all led to their products in moderate to good yields (Table 2, entries 10, 13, and 16).

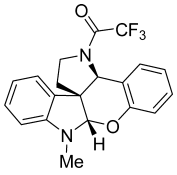
The relative configuration of the product **8a** was unambiguously determined by X-ray single crystallographic analysis.

In summary, we have developed a novel tandem Mannich/intramolecular aminal formation between tryptamines and salicylaldehydes. This tandem reaction started from easily available materials to afford highly functionalized spiro-fused six-membered indolines in good to excellent yields with the generation of up to three new stereogenic centers (a highly congested continuous spiro quaternary center and two tertiary stereocenters) in excellent regio- and diastereoselectivities.

EXPERIMENTAL SECTION

A flame-dried 10 mL round-bottom flask equipped with a rubber septum and magnetic stir bar was charged with 4 Å molecular sieves (30 mg); the corresponding tryptamine **3** (0.2 mmol, 1.0 equiv, 1.0 M in chloroform) and salicylaldehyde **4** (0.24 mmol, 1.20 equiv, 1.0 M in chloroform) were added sequentially at −40 °C. The resulting mixture was stirred for 8 h at −40 °C, and then TFAA (0.24 mmol, 1.2 equiv, 1.0 M in chloroform) was added. This mixture was then stirrred at −40 °C and monitored by TLC. On completion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with ethyl acetate (3 × 20 mL). The mixture was washed with brine (2 × 5 mL), and the organic extracts were dried over sodium sulfate and filtered. Concentration of the solution by rotary evaporation under reduced pressure gave a residue, which was purified by flash column chromatography (petroleum ether/EtOAc 10/1) to afford the product **8**.

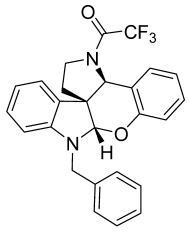
Spectroscopic Data for Products 8a−p. Compound **8a**:



8a

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 130−132 °C. Yield: 96% (72 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.40−7.19 (m, 1H), 7.13−7.05 (m, 2H, 6.97−6.93 (m, 2H), 6.72 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 4.0 Hz, 1H), 5.30 (s, 1 H), 5.03 (s, 1H), 4.12 (t, J = 8.8 Hz, 1H), 3.99−3.92 (m, 1H), 2.89 (s, 3H), 2.49−2.41 (m, 1H), 2.29−2.23 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 156.5−155.4, 152.1, 149.9, 131.5, 129.7, 129.4, 129.3, 128.7, 123.8, 122.5, 122.2, 118.6, 118.5, 106.0, 101.2, 62.6, 55.2, 46.6, 38.4, 31.0. HRMS (ESI): calcd for $C_{20}H_{17}F_3N_2O_2$ $[M + H]^+$ 375.1242, found 375.1240.

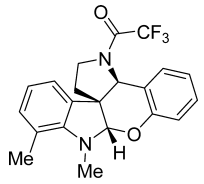
Compound **8a′**:



8a'

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 232−234 °C. Yield: 60% (54 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, J = 7.2 Hz, 1H), 7.26 (d, J = 3.6 Hz, 1H), 7.13 (t, J = 7.2 Hz, 3H), 7.17 (d, J = 5.6 Hz, 3H), 7.04 (t, J = 7.6 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.79 (d, J = 4.0 Hz, 1H), 6.73 (t, J = 7.6 Hz, 1H), 6.29 (d, J = 8.0 Hz, 1H), 5.40 (s, 1H), 5.08 (s, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.44 (d, J = 16.0 Hz, 1H), 4.17 (t, J = 9.6 Hz 1H), 3.96−3.89 (m, 1H), 2.48−2.40 (m, 1H), 2.26−2.20 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 156.5−155.4, 152.1, 149.5, 137.2, 131.5, 129.6, 129.3, 128.7, 128.6, 128.5, 127.4, 127.2, 123.8, 122.5, 122.4, 119.0, 118.8, 106.6, 99.4, 62.7, 55.5, 48.6, 46.6, 38.7. HRMS (ESI): calcd for $C_{26}H_{21}F_3N_2O_2$ $[M + H]^+$ 451.1555, found 451.1550.

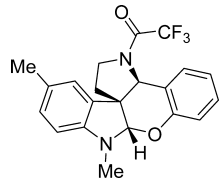
Compound **8b**:



8b

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 140−142 °C. Yield: 98% (76 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.25−7.12 (m, 1H), 7.03−6.92 (m, 3H), 6.50 (d, J = 8.0 Hz, 1H), 6.22 (d, J = 7.6 Hz, 1H), 5.39 (s, 1H), 5.21 (s, 1H), 4.22−4.13 (m, 1H), 3.92−3.79 (m, 1 H), 2.87 (s, 3H), 2.78−2.69 (m, 1H), 2.33 (s, 3H), 2.25−2.21 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 155.8−155.1, 152.5, 150.6, 133.8, 131.5, 131.0, 129.7, 129.2, 125.3, 123.8, 122.5, 121.7, 118.6, 104.2, 101.6, 59.0, 56.3, 46.1, 37.0, 31.1, 18.2. HRMS (ESI): calcd for $C_{21}H_{19}F_3N_2O_2$ $[M + H]^+$ 389.1399, found 389.1395.

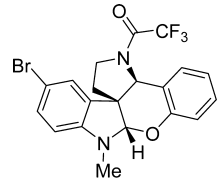
Compound **8c**:



8c

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 141−143 °C. Yield: 95% (74 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 7.24−7.18 (m, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.96−6.91 (m, 2H), 6.49 (d, J = 7.6 Hz, 1H), 6.21 (d, J = 7.6 Hz, 1H), 5.38 (s, 1H), 5.12 (s, 1H), 4.16 (t, J = 9.6 Hz, 1H), 3.88−3.79 (m, 1H), 2.86 (s, 3H), 2.77−2.69 (m, 1H), 2.32 (s, 3H), 2.24−2.20 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 156.1−155.1, 152.5, 150.5, 133.8, 131.5, 129.7, 129.2, 125.3, 123.9, 122.5, 121.7, 118.5, 117.7, 104.2, 101.5, 59.0, 56.3, 46.1, 37.0, 31.1, 18.2. HRMS (ESI): calcd for $C_{21}H_{19}F_3N_2O_2$ $[M + H]^+$ 389.1399, found 389.1395.

Compound **8d**:



8d

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 137−139 °C. Yield: 88% (80 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31 (d, J = 4.4 Hz, 1H), 7.25−7.20 (m, 1H), 7.13−6.94 (m, 2H), 6.95 (t., J = 4.4 Hz, 1H), 6.72 (t, J = 5.2 Hz, 1H), 6.35 (d, J = 8.0 Hz, 1H), 6.31(s, 1H), 5.03 (s, 1H),

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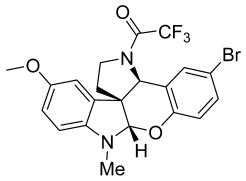
4.23−4.16 (m, 1H), 4.04−3.93 (m, 1H), 2.89 (s, 3H), 2.49−2.39 (m, 1 H), 2.33−2.24 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 154.9, 152.1, 150.0, 132.3, 131.5, 129.7, 129.4, 123.8, 122.5, 122.2, 118.7, 118.5, 117.1, 112.6, 106.0, 101.2, 62.7, 55.3, 46.6, 38.4, 31.0. HRMS (ESI): calcd for $C_{20}H_{16}BrF_3N_2O_2$ $[M + H]^+$ 453.0347, found 453.0344.

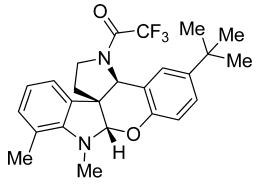
Compound **8e**:



8e

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 142−144 °C. Yield: 66% (64 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (s,1 H), 7.19(d, J = 4.0 Hz, 1H), 6.96−6.94 (m, 2H), 6.66 (d, J = 4.0 Hz. 1H), 6.28 (d, J = 8.0 Hz, 1H), 5.23 (s, 1H), 4.95 (s, 1H), 4.18 (d, J = 8.0 Hz, 1 H), 3.95−3.87 (m,4H), 2.82 (s, 3H), 2.47−2.39 (m, 1H), 2.27−2.18 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 159.0−157.9, 153.6, 151.3, 143.9, 134.1, 132.9, 132.8, 131.9, 129.6, 125.9, 120.6, 114.0, 112.6, 108.2, 100.4, 62.1, 56.0, 49.8, 40.6, 38.2, 29.8, HRMS (ESI): calcd for $C_{21}H_{18}BrF_3N_2O_3$ $[M + H]^+$ 483.0453, found 483.0450.

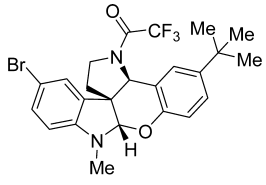
Compound **8f**:



8f

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 108−110 °C. Yield: 96% (85 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (s,1H), 7.23 (s, 1H), 6.92−6.86 (m, 2H), 6.74−6.65 (m, 2H), 5.11 (s, 1H), 5.03 (s, 1H), 4.15 (t, J = 7.6 Hz, 1H), 3.94−3.85 (m, 1H), 3.17 (s, 3H), 2.45−2.37 (m, 1H), 2.34 (s, 3H), 2.27−2.19 (m, 1H), 1.26 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): 156.1, 155.7, 149.6, 147.8, 145.0, 132.6, 130.4, 127.8, 126.5, 126.3, 120.2, 119.4, 118.7, 117.7, 114.7, 102.2, 62.4, 54.7, 46.3, 38.7, 35.5, 31.5, 31.4, 19.2. HRMS (ESI): calcd for $C_{25}H_{27}F_3N_2O_2$ $[M + H]^+$ 445.2025, found 445.2021.

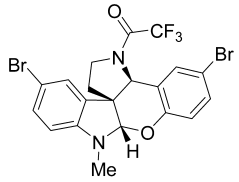
Compound **8g**:



8g

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 105−107 °C. Yield: 73% (74 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, J = 2.4 Hz, 1H), 7.26−7.15 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.22 (d, J = 8.4 Hz, 1H), 5.28 (s, 1H), 5.00 (s, 1H), 4.19−4.14 (m, 1H), 4.00−3.88 (m, 1H), 2.86 (s, 3H), 2.46−2.38 (m, 1H), 2.29−2.16 (m, 1H), 1.27 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): 153.1, 149.4, 149.1, 145.3, 143.4, 131.9, 131.2, 128.8, 126.7, 126.4, 125.5, 122.4, 117.8, 107.5, 100.9, 62.6, 54.9, 46.5, 38.7, 34.3, 31.5, 31.4. HRMS (ESI): calcd for $C_{24}H_{24}BrF_3N_2O_2$ $[M + H]^+$ 509.0973, found 509.0971.

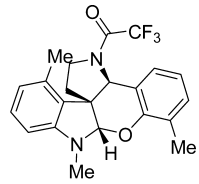
Compound **8h**:



8h

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 135−137 °C. Yield: 86% (91 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (dd, J = 4.0 Hz, J = 8.0 Hz, 1H), 7.28−7.14 (m, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.83 (t, J = 4.0 Hz, 1H), 6.71 (d, J = 4.0 Hz, 1H), 6.21 (d, J = 8.0 Hz, 1H), 5.33 (s, 1H), 4.91 (s, 1H), 4.21 (d, J = 6.0 Hz, 1H), 3.97−3.90 (m, 1H), 2.84 (s, 3H), 2.47−2.41 (m, 1H), 2.28−2.19 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 154.7, 154.4, 151.2, 148.9, 142.4, 134.7, 134.2, 133.0, 132.4, 125.5, 120.8, 120.7, 120.5, 117.2, 107.5, 101.2, 62.4, 55.2, 46.5, 38.4, 31.9. HRMS (ESI): calcd for $C_{20}H_{15}Br_2F_3N_2O_2$ $[M + H]^+$ 530.9452, found 530.9450.

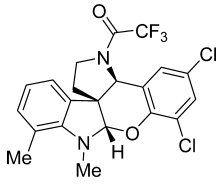
Compound **8i**:



8i

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 138−140 °C. Yield: 73% (59 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25−7.23 (m, 1H), 7.08−6.99 (m, 2H), 6.84 (t, J = 7.6 Hz, 1H), 6.50 (d, J = 7.6 Hz, 1H), 6.23 (d, J = 7.6 Hz, 1H), 5.38 (s, 1H), 5.22 (s, 1 H), 4.16 (t, J = 10.0 Hz, 1H), 3.88−3.81 (m, 1H), 2.91(s, 3H), 2.76−2.70 (m, 1H), 2.32−2.20 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): 155.7, 155.3, 150.6, 150.5, 133.9, 132.1, 131.0, 129.2, 128.9, 127.6, 125.5, 123.4, 121.9, 120.9, 104.3, 101.8, 59.2, 56.3, 46.1, 37.1, 31.7, 18.2, 15.3. HRMS (ESI): calcd for $C_{22}H_{21}F_3N_2O_2$ $[M + H]^+$ 403.1555, found 403.1552.

Compound **8j**:



8j

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 151−152 °C. Yield: 78% (71 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (s, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.33−7.30 (m, 1H), 6.91 (dd, J = 8.0 Hz, J = 16.0 Hz, 1H), 6.73−6.67 (m, 1H), 5.36 (s, 1H), 4.85 (s, 1H), 4.21−4.15 (m, 1H), 4.00−3.92 (m, 1H), 3.19 (s, 1H), 2.55−2.47 (m, 1H), 2.33−2.26 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): 156.1, 147.8, 147.1, 133.2, 132.4, 131.1, 130.8, 130.0, 127.3, 126.9, 120.3, 119.7, 118.7, 104.3, 63.0, 55.0, 46.9, 39.0, 35.6, 19.2. HRMS (ESI): calcd for $C_{21}H_{17}Cl_2F_3N_2O_2$ $[M + H]^+$ 457.0619, found 457.0617.

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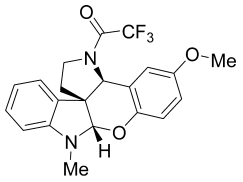
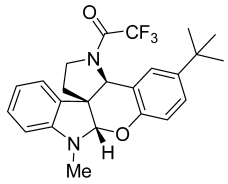
Compound **8k**:



8k

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 138−139 °C. Yield: 72% (58 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56−7.53 (m, 1H), 7.51 (d, J = 4.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 2H), 6.50 (d, J = 8.0 Hz, 1H), 6.22 (d, J = 8.0 Hz, 1H), 5.33 (s, 3H), 5.22 (s,1H), 4.17−4.11 (m,1H), 3.89−3.82 (m, 1H), 3.75 (s, 3H), 2.87 (s, 3H), 2.80−2.71 (m, 1H), 2.23−2.18 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 161.84, 160.84, 155.5, 153.5, 133.7m 132.5, 130.7, 130.4, 129.1, 124.6, 122.4, 121.6, 120.9, 119.9, 107.0, 101.7, 58.7, 56.0, 55.3, 45.8, 37.0, 31.3. HRMS (ESI): calcd for $C_{21}H_{19}F_3N_2O_3$ $[M + H]^+$ 405.1348, found 405.1344.

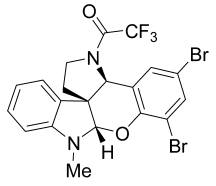
Compound **8l**:



8l

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 100−102 °C. Yield: 73% (63 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, J = 2.0 Hz, 1H), 7.25−7.22 (m, 1H), 7.14−7.06 (m, 2H), 6.87 (d, J = 8.4 Hz, 1H), 6.75 (t, J = 8.0 Hz 1H), 6.37 (d, J = 7.6 Hz, 1H), 5.26 (s, 1H), 5.05 (s, 1H), 4.17 (t, J =9.6 Hz, 1H), 4.00−3.90 (m, 1H), 2.89 (s, 3H), 2.46−2.39 (m, 1 H), 2.29−2.23 (m, 1H), 1.25 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): 156.1, 155.7, 150.0, 149.6, 145.0, 129.2, 128.4, 126.5, 126.4, 122.8, 122.3, 119.0, 118.5, 117.7, 106.1, 101.0, 62.6, 54.9, 46.5, 38.6, 34.2, 31.4, 31.2. HRMS (ESI): calcd for $C_{24}H_{25}F_3N_2O_2$ $[M + H]^+$ 431.1868, found 431.1864.

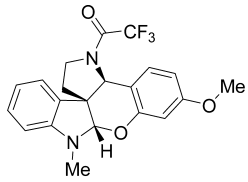
Compound **8m**:



8m

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 132−134 °C. Yield: 73% (77 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (d, J = 4.0 Hz, 1H), 7.28 (t, J = 4.0 Hz, 1H), 7.07(d, J = 8.0 Hz, 1H), 6.96 (t, J = 8.0 Hz, 1H), 6.73 (t, J = 4.0 Hz, 1H), 6.35 (d, J = 8.0 Hz, 1H), 5.31 (s, 1H), 5.03 (s, 1H), 4.18 (d, J = 6.0 Hz, 1H), 4.00−3.90 (m, 1H), 2.90 (s, 3H), 2.49−2.42 (m, 1H), 2.30−2.24 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 155.2, 152.1, 150.0, 131.4, 131.0, 129.8, 129.7, 129.4, 122.4, 122.2, 120.3, 119.7, 118.5, 106.0, 101.2, 62.7, 55.3, 46.5, 38.4, 31.0. HRMS (ESI): calcd for $C_{20}H_{15}Br_2F_3N_2O_2$ $[M + H]^+$ 530.9452, found 530.9450.

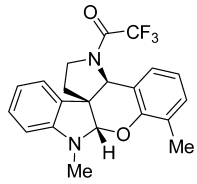
Compound **8n**:



8n

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 138−140 °C. Yield: 99% (80 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 4.0 Hz, 1H), 7.00 (d, J = 4.0 Hz, 2H), 6.89 (d, J = 4.0 Hz, 1H), 6.51 (t, J = 6.0 Hz, 1H), 6.22 (d, J = 8.0 Hz, 1H), 5.33 (s, 1H), 5.22 (s, 1H), 4.15−4.11 (m, 1H), 3.89−3.75 (m, 1H), 3.75 (s, 1H), 2.87 (s, 3H), 2.80−2.72 (m, 1H), 2.23−2.18 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 161.8, 160.8, 156.5, 153.5, 133.9, 133.7, 132.5, 130.8, 129.2, 122.6, 122.3, 121.5, 120.9 119.8, 107.0, 101.7, 58.8, 56.0, 55.3, 46.0, 37.0, 31.3. HRMS (ESI): calcd for $C_{21}H_{19}F_3N_2O_3$ $[M + H]^+$ 405.1348, found 405.1346.

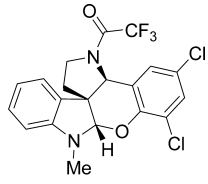
Compound **8o**:



8o

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 140−142 °C. Yield: 77% (60 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26 (m, 2H), 7.13−7.11 (m, 2H), 7.07 (t, J = 8.4 Hz, 1H), 6.86 (t, J = 8.0 Hz, 1H), 6.36 (d, J = 8.0 Hz, 1H), 5.32 (s, 1H), 5.03 (s, 1H), 4.20−4.15 (m, 1H), 4.00−3.91 (m, 1H), 2.93 (s, 3H), 2.49−2.42 (m, 1H) 2.29−2.23 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): 153.4, 150.2, 150.0, 132.1, 131.1, 129.3, 129.0, 127.8, 123.5, 122.3, 121.9, 120.0, 118.6, 106.1, 101.5, 63.0, 55.4, 46.5, 38.6, 31.5, 15.4. HRMS (ESI): calcd for $C_{21}H_{19}F_3N_2O_2$ $[M + H]^+$ 389.1399, found 389.1395.

Compound **8p**:



8p

analytical TLC on silica gel, petroleum ether/ethyl acetate (10/1), yellow crystalline solid, mp 145−147 °C. Yield: 82% (73 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (d, J = 4.0 Hz, 1H), 7.40 (d, J = 4.0 Hz, 1H), 7.30 (d, J = 4.0 Hz, 1H), 7.08 (t, J = 4.0 Hz, 1H), 6.68 (s, 1H), 6.36 (t, J = 6.0 Hz, 1 H), 5.49 (s, 1H), 4.90 (s, 1H), 4.22−4.18 (m, 1H), 4.01−3.94 (m, 1H),2.93 (s, 3H), 2.56−2.48 (m, 1 H), 2.32−2.24 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 159.1−158.0, 150.1, 149.0, 131.0, 130.0, 129.7, 128.7, 127.8, 124.2, 122.8, 122.4, 119.9, 118.5, 109.4, 102.6, 62.9, 55.6, 46.9, 38.7, 29.7. HRMS (ESI): calcd for $C_{20}H_{15}Cl_2F_3N_2O_2$ $[M + H]^+$ 443.0463, found 443.0461.

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■ ASSOCIATED CONTENT

Supporting Information

Figures, tables, text, and a CIF file giving experimental details, ^{1}H and ^{13}C NMR spectra of all new compounds, and X-ray data of compound **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.*. **2006**, *45*, 354. (c) Nicolaou, K. C.; Chen, J.-S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (d) Poulin, J.; Grisé-Bard, C. M.; Barriault, L. *Chem. Soc. Rev.* **2009**, *38*, 3092. (e) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

(2) (a) Chou, T.-Q.; Chin, J. *Physiology* **1931**, *5*, 345. (b) Moncrief, J. M.; Beer, C, T.; Cutts, J, H. *Ann. N.Y. Acad. Sci.* **1958**, *84*, 4963. (c) Gorman, M.; Neuss, N.; Biemann, K. *J. Am. Chem. Soc.* **1962**, *84*, 1058. (d) Liu, C.-T.; Wang, Q.-W.; Wang, C.-H. *J. Am. Chem. Soc.* **1981**, *103*, 4634. (e) Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355. (f) Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124. (g) Kato, D.; Sasaki, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3685.

(3) For a mini-review of methods of perophoramidine and communesin, see: Siengalewicz, P.; Gaith, T.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8170.

(4) For the isolation of (+)-communesins A−C and E−H and (+)-communesin D, see: (a) Hayashi, H.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355. (b) Jadulco, R.; Edrada, R. A.; Ebel, R.; Berg, A .; Schaumann, k.; Wray, V.; Steube, K.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 78. (c) Hayashi, H.; Matsumoto, H.; Akiyama, K. *Biosci., Biotechnol., Biochem.* **2004**, *68*, 753. (d) Dalsgaard, P. W.; Blunt, J. W.; Munro, M. H. G; Frisvad, J. C.; Christophersen, C. *J. Nat. Prod.* **2005**, *68*, 258.

(5) Selected examples in total synthesis: (a) IbacetaLizana, J. S. L.; Jackson, A. H.; Prasitpan, N.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans.2* **1987**, 1221. (b) Magnus, P.; Mugrage, B.; DeLuca, M. R.; Cain, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 786. (c) Magnus, P.; Mugrage, B.; DeLuca, M.; Cain, G. A. *J. Am. Chem. Soc.* **1990**, *112*, 5220. (d) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068. (e) Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 4317. (f) Linnepe, P.; Schmidt, A. M.; Eilbracht, P. *Org. Biomol. Chem.* **2006**, *4*, 302. (g) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794. (h) Ishikawa, H.; Colby, D, A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T, A.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 4904.

(6) (a) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2003**, *5*, 3169. (b) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068.

(7) (a) Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 4317. (b) Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8170. (c) Fu, L. F. *Heterocycl. Chem.* **2010**, *26*, 433.

(8) Liu, P.; Seo, J. H.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2000.

(9) (a) Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem., Int. Ed.* **2010**, *47*, 8170. (b) Wu, H.-X,.; Xue, F.; Xiao, X.; Qin, Y. *J. Am. Chem. Soc.* **2010**, *132*, 14052. (c) Zuo, Z,-W.; Xie, W.-Q.; Ma, D.-W. *J. Am. Chem. Soc.* **2010**, *132*, 13226.

(10) Bailey, P. D.; Cochrane, P. J.; Forster, A. H.; Morgana, K. M.; Pearson, D. P. J. *Tetrahedron Lett.* **1999**, *40*, 4597.

(11) (a) Jackson, A. H.; Naidoo, B. J. *J. Chem. Soc., Perkin Trans. 2* **1973**, 548. (b) Ungemach, F.; Cook, J. M. *Heterocycles* **1978**, *9*, 1089. (c) Bailey, P. D. *J. Chem. Res., Synop.* **1987**, 202. (d) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (e) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

(12) (a) Van Tamelen, E. E.; Dolby, L. J.; Lawton, R. G. *Tetrahedron Lett.* **1960**, *40*, 30. (b) Buechi, G.; Matsumoto, K. E.; Nishimura, H. *J. Am. Chem. Soc.* **1971**, *93*, 3299. (c) Ando, M.; Buechi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880. (d) Wenkert, E.; Orito, K.; Simmons, D. P.; Ardisson, J.; Kunesch, N.; Poisson, J. *J. Org. Chem.* **1983**, *48*, 5006.