Oxidative Cyclization Reactions of Tryptamine Utilizing Hypervalent Iodobenzene in Routes for Pyrroloindole Alkaloid Synthesis

Daichi Kajiyama, Tsuyoshi Saitoh, Satoshi Yamaguchi, Shigeru Nishiyama*

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223-8522, Japan
Fax +81(45)5661717; E-mail: nisiyama@chem.keio.ac.jp

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Abstract: Oxidative cyclization of *N*-acetyltryptamine by using iodobenzene diacetate (PIDA) provided the corresponding 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-3a-ol derivative, which could be derivatized following appropriate protection of the two amino and *tert*-hydroxyl groups. The facile one-pot procedure for cyclization and introduction of the oxygen functionality was applied in concise routes for the synthesis of the natural products CPC-1 and debromoflustraminol B.

Key words: cyclization, fused ring systems, indole, natural products, oxidation

The pyrroloindole (1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole) structure, biogenetically synthesized from tryptophan, is found as the fundamental framework in a variety of natural products that contain prenyl, indole, and/or hydroxyl functionalities at the C-3 position (Figure 1).[1] From the viewpoint of diversity oriented synthesis, 3-hydroxylpyrroloindoles, which posses three polar functional groups giving a variety of functionalities, have previously been produced using peroxide,[2a] singlet oxygen,[2b] *N*-phenylselenophthalimide,[2c,d] pyridine *N*-oxide with *hv*,[2e] and phenyliodine(III) diacetate (PIDA, also known as diacetoxyiodobenzene, DAIB) oxidation-based processes.[2f] Ciufolini[3a] and Padwa[3b] described hypervalent iodine promoted oxidation reactions of oxazoline-containing indole derivatives that led to the introduction of C-2 oxygen and C-3 nitrogen functionality. In addition, a method using a hypervalent iodine oxidant for the introduction of oxygen functions at C-2 and C-3 of the indole framework was developed by Takayama et al.[4] During a recent investigation exploring methods for oxidative construction of heterocycles,[5] we developed a new process that generates pyrroloindoles through cyclization reactions of iminium ion intermediates. The results of studies leading to the development of this process and its applications to natural product synthesis are described herein.

Oxidation reactions of *N*-acetyltryptamine (**1**; R^1 = H, R^2 = Ac) using hypervalent iodine oxidants were explored in this effort with the expectation that they would generate pyrroloindoles through cyclization of iminium ion intermediates (Table 1). In the initial phase of this effort, we observed that the oxidant PhI(OTFAc)$_2$ (PIFA), generally employed in oxidation reactions of indoles, transformed **1** (**1**; R^1 = H, R^2 = Ac) into a complex mixture of products (entry 1). In contrast, when PIDA was used to oxidize **1**, the 3-acetoxy derivative **2a** was generated along with 2-acetoxytryptamine (**3a**; Table 1, entry 2). Moreover, electrochemically generated PhI(OTFEt)$_2$ (PIFE)[6] was found to promote the reaction of the tryptamine derivative to form **2b**, possessing a trifluoroethoxy group at C-3 (Table 1, entry 3), whereas the Koser reagent [PhI(OTs)OH] did not affect the desired cyclization process (Table 1, entry 4). Because **2a** was particularly well suited as an intermediate in natural product synthesis, optimization of the conditions for the oxidative cyclization reaction was performed (Table 1, entry 2). To examine the effects of solvents, reactions were carried out in non-alcoholic solvents such as dichloromethane and acetonitrile, as well as in methanol. As the data displayed in Table 1 (entries 5–7) shows, these processes did not produce the desired cyclization product.

In the next stage of this effort, we assessed the effect of functional groups on the oxidative cyclization reactions of substituted tryptamines (Table 2). Whereas the presence of an electron-withdrawing group at N-1 was found to retard the reaction (Table 2, entries 2 and 3), the related N-1 methyl derivative participated in a low-yielding cyclization process (Table 2, entry 4). In contrast to tryptamines containing H and Me groups at N-1 (Table 2, entries 1 and 4), the derivative with Bn and at N-1 and the Ac substituent in side chain nitrogen position (Table 2, entry 5) un-

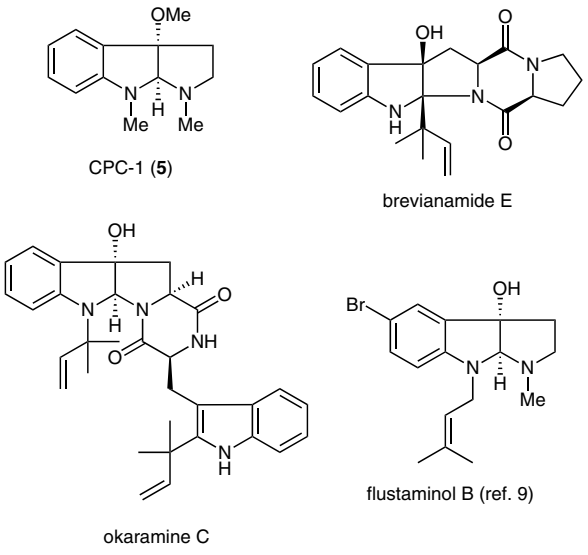

Figure 1 Structures of 3-hydroxylpyrroloindole natural products

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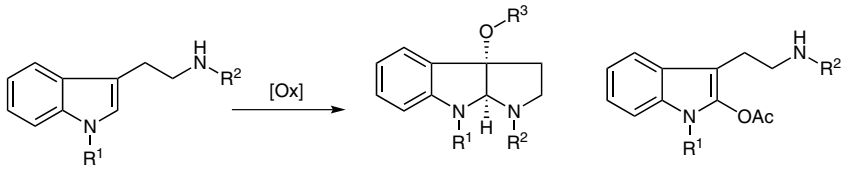
Table 1 Oxidant and Solvent Dependence of Oxidation Reactions of *N*-Acetyltryptamine **1**[a]



1 **2** **3**

Entry	Oxidant[b]	R^1	R^2	R^3	Solvent	Yield (%)[c]		
						2	**3**	**1**
1	$PhI(OTFAc)_2$	H	Ac		TFE[b]	dec.		–
2	$PhI(OAc)_2$	H	Ac	Ac		38 (**2a**)	16 (**3a**)	–
3	$PhI(OTFEt)_2$	H	Ac	TFEt		30 (**2b**)	–	–
4	PhI(OTs)OH	H	Ac			–	–	65
5	$PhI(OAc)_2$	H	Ac		MeCN	complex mixture[d]		19
6	$PhI(OAc)_2$	H	Ac		CH_2Cl_2	complex mixture[d]		24
7	$PhI(OAc)_2$	H	Ac		MeOH	dec.		–

[a] Reaction conditions: **1** (15 mM), oxidant (1.2 equiv), 0 °C, solvent.
[b] TFAc: trifluoroacetyl, TFE: 2,2,2-trifluoroethanol, TFEt: trifluoroethyl.
[c] Isolated yield.
[d] Compounds **2** and **3** were not observed. Oxidized N–C2 bond.

derwent PIDA-promoted reactions to form the corresponding 2-acetoxy derivatives **3** as the major products along with lower amounts of **2**. Reactions of substrates bearing Boc, Ts, and Me protecting groups at the side chain amine center did not yield identifiable products (Table 2, entries 6–8).[7] Finally, the reaction of the side chain benzoylamide derivative (Table 2, entry 9) proceeded in a similar manner to that of the corresponding acetyl analogue (Table 2, entry 1), however, the cyclization product to α-oxidation product ratio **2**/**3** now favored the latter.

Table 2 Oxidation Reactions of Tryptamines **1**[a]

Entry	Tryptamine **1**		Yield (%)[b]		
	R^1	R^2	**2**	**3**	**1**
1	H	Ac	38	16	–
2	Boc	Ac	–	–	100
3	Ts	Ac	–	–	100
4	Me	Ac	13	–	–
5	Bn	Ac	3	23	–
6	H	Boc	dec.		
7	H	Ts	dec.		
8	H	Me	dec.		
9	H	Bz	28	34	–

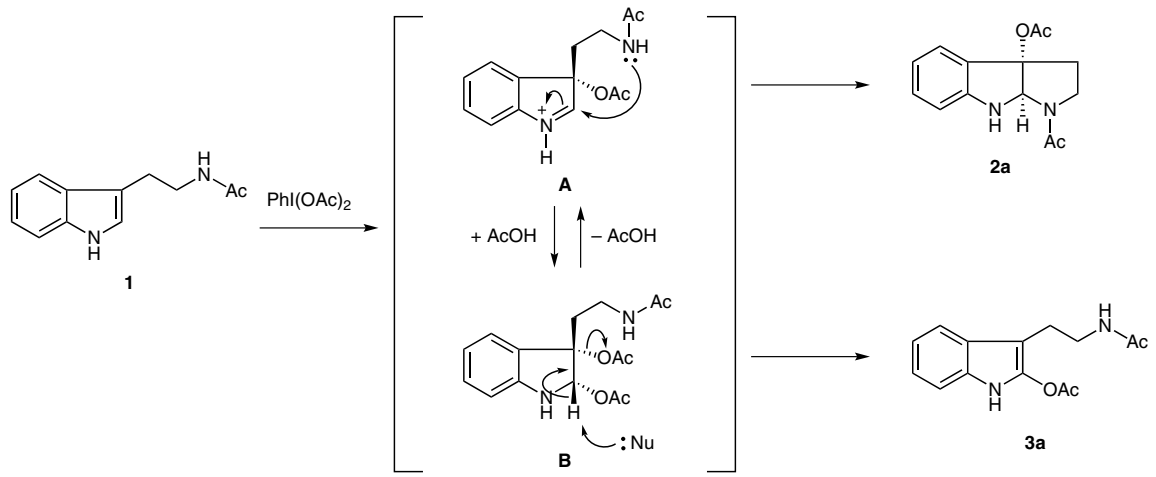
[a] Reaction conditions: **1** (15 mM) in TFE, PIDA (1.2 equiv).
[b] Isolated yield.

With the expectation that an improvement in the yield could be achieved, additives were employed in the oxidation reaction (Table 3). However, the use of Lewis acids (entries 1 and 2) or strong Brønsted acids such as TFA and TsOH (entries 3 and 4) did not promote the desired reaction of *N*-acetyltryptamine (**1**; R^1 = H, R^2 = Ac). In contrast to its use as solvent (entry 7), the presence of AcOH in a mixed solvent system facilitated the formation of the cyclization product **2a** in 53% yield (entry 6). The addition of NaOAc effected recovery of the starting material, together with the formation of **2a** (conversion yield 71%;

Table 3 Use of Additives in the Oxidation Reactions of *N*-Acetyltryptamine (**1**; R^1 = H, R^2 = Ac)[a]

Entry	Additive	Solv.	Yield (%)[b]		
			2a	**3a**	**1**
1	$Cu(OTf)_2$ (5 mol%)	TFE	dec.		
2	$BF_3{\cdot}OEt_2$ (3 equiv)		dec.		
3	TFA (3 equiv)		dec.		
4	TsOH (3 equiv)		dec.		
5	AcOH (3 equiv)		38	–	–
6	AcOH (150 equiv)		53	–	–
7	–	AcOH	6	–	16
8	NaOAc (3 equiv)[c]	TFE	58	–	24

[a] Reaction conditions: **1** (15 mM) in TFE, PIDA (1.2 equiv).
[b] Isolated yield.
[c] PIDA (0.8 equiv).



Scheme 1 A plausible oxidation mechanism

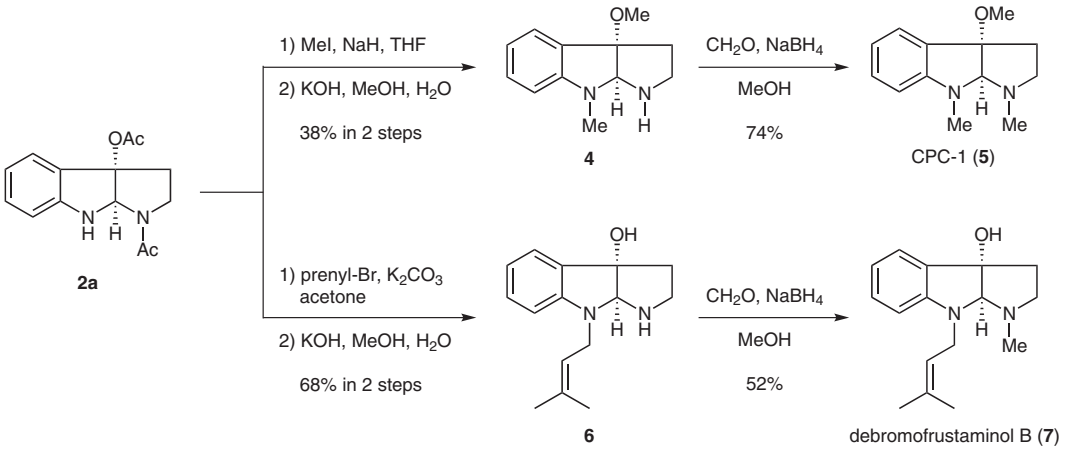
Table 3, entry 8). The presence of acetate ions seems to support the stability of the intermediate (see **A** in Scheme 1 below), which provides the desired oxidation process, leading to **2a**.

A plausible mechanism for the cyclization reaction is summarized in Scheme 1. In a manner similar to that described previously,[3] the process begins with oxidation of **1** to form the iminium intermediate **A**, bearing an acetoxyl group at C-3. Addition of the terminal amide then gives the cyclization product **2a**. In competition with the cyclization process, addition of acetate to the C-2 position of iminium intermediate **A** provides the 2,3-diacetoxy derivative **B**, which then undergoes elimination to produce **3a**.

In studies aimed at developing the synthetic potential of the cyclization process and, in particular, its applications to the preparation of members of the 3-hydroxypyrroloindole natural product family (Scheme 2), we explored methods to differentiate between the three polar functional groups present in the pyrroloindole **2a**. This effort led to the observation that treatment of **2a** with iodomethane and sodium hydride, followed by removal of the amide acetyl group, afforded *N*-methylpyrroloindole **4**, which, on reductive methylation, yielded CPC-1 (**5**), a natural product isolated from *Chimonanthus praecox* f.[8] In addition, prenylation of **2a**, followed by exhaustive deacylation, generated *N*-prenylpyrroloindole **6**, which, upon reductive methylation, formed debromoflustraminol B (**7**),[9] a debromo derivative of the marine alkaloid from *Flustra foliacea* (L.).

In the study described above, a method for the facile synthesis of 3-hydroxypyrroloindole **2a**, employing PIDA-promoted oxidation of readily available *N*-acetyltryptamine (**1**), was developed. Differentiation between the three polar functional groups in **2a** was then accomplished as part of a concise synthetic pathway for the preparation of naturally occurring CPC-1 (**5**) and debromofrustaminol B (**7**).

IR spectra were recorded with a JASCO Model FT/IR-4200 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained with JEOL JNM AL-400, JEOL JNM ECX-400, or JEOL JNM α-400 spectrometers in $CDCl_3$ solution using tetramethylsilane as an internal standard. HRMS were obtained with a Waters LCT Premier XE (ESI). Preparative and analytical TLC were carried out on silica gel plates (Kieselgel 60 F_{254}, E. Merck AG, Germany) using UV (254 nm) irradiation or 5% phosphomolybdic acid in EtOH for detection. Kanto Chemical silica 60N (spherical, neutral; 63–210 μm)



Scheme 2 Synthesis of CPC-1 (**5**) and debromofrustaminol B (**7**)

was used for column chromatography. All reactions were carried out under an argon atmosphere. When necessary, solvents were dried prior to use. Anhydrous solvents were purchased from Kanto Chemical Co. Inc. and stored over 4Å MS under an Ar atmosphere.

Oxidation to 1-Acetyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-3a-yl acetate (2a); Typical Procedure

To a stirred solution of **1** (R^1 = H, R^2 = Ac; 44 mg, 0.22 mmo1) in TFE (22 mL) and NaOAc (54 mg, 0.66 mmol), was added PIDA (56 mg, 0.17 mmo1) at 0 °C. The resulting mixture was stirred at the same temperature for 2 h. Concentration in vacuo gave a residue that was subjected to silica gel column chromatography ($CHC1_3$–MeOH, 15:1) to give **2a**.

Yield: 32.8 mg (58%); yellow oil.

IR (film): 3315, 2953, 2879, 1740 cm^{-1}.

^{1}H NMR: δ = 7.54 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.17 (td, *J* = 7.6, 0.8 Hz, 1 H), 6.77 (td, *J* = 7.6, 1.2 Hz, 1 H), 6.63 (d, *J* = 8.0 Hz, 1 H), 5.62 (s, 1 H), 5.31 (br s, 1 H), 3.72 (ddd, *J* = 10.0, 8.8, 1.6 Hz, 1 H), 3.30 (td, *J* = 11.0, 6.8 Hz, 1 H), 3.05 (ddd, *J* = 12.9, 6.4, 1.6 Hz, 1 H), 2.61 (ddd, *J* = 13.6, 8.8, 2.4 Hz, 1 H), 2.02 (s, 3 H), 2.01 (s, 3 H).

^{13}C NMR: δ = 170.2, 169.9, 150.7, 131.0, 126.6, 125.3, 119.0, 110.1, 919, 79.7, 47.0, 35.0, 22.1, 21.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_3$: 261.1239; found: 261.1233.

1-{3a-(2-Trifluoroethoxy)-3,3a-dihydropyrrolo[2,3-*b*]indol-1(2*H*)-yl}acetate (2b)

Yield: 10.8 mg (30%); yellow oil.

IR (film): 2933, 2869, 1653, 1173 cm^{-1}.

^{1}H NMR: δ = 7.35 (td, *J* = 8.0, 1.2 Hz, 1 H), 7.30–7.27 (m, 2 H), 7.17 (td, *J* = 8.0, 1.2 Hz, 1 H), 4.95–4.71 (m, 2 H), 3.71 (m, 2 H), 2.13–1.93 (m, 2 H), 2.01 (s, 3 H).

^{13}C NMR: δ = 176.5, 156.3, 150.0, 136.4, 130.6, 125.4, 122.8, 119.5, 80.8, 65.3, 64.9, 38.4, 25.6, 21.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}F_3N_2O_2$: 299.1007; found: 299.1015.

3-(2-Acetamidoethyl)-1*H*-indol-2-yl Acetate (3a)

Yield: 6.8 mg (16%); pale yellow oil.

IR (film): 3285, 1772, 1654, 1496, 1364 cm^{-1}.

^{1}H NMR: δ = 8.48 (s, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.20 (td, *J* = 8.0, 0.8 Hz, 1 H), 7.14 (td, *J* = 8.0, 0.8 Hz, 1 H), 5.68 (s, 1 H), 3.56 (q, *J* = 6.0 Hz, 2 H), 2.86 (t, *J* = 6.0 Hz, 2 H), 2.37 (s, 3 H), 1.88 (s, 3 H).

^{13}C NMR: δ = 174.6, 170.1, 131.5, 128.3, 126.3, 122.0, 120.2, 118.5, 111.0, 97.6, 39.0, 23.2, 22.6, 20.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_3$: 261.1239; found: 261.1230.

3a-Methoxy-8-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]lindole (4)

To a solution of **2a** (16 mg, 0.062 mmo1) in THF (0.5 mL) at 0 °C, was added, in portions, NaH (60% in mineral oil, 12 mg, 0.25 mmol). After 10 min, MeI (15 μL, 0.25 mmo1) was added slowly, and the mixture was stirred at 60 °C overnight. Addition of H_2O (3 mL) followed by extraction with EtOAc (3 × 3 mL) gave organic extracts that were dried (Na_2SO_4), and concentrated in vacuo. The residue was subjected to silica gel column chromatography (EtOAc) to give acetamide.

Yield: 6.2 mg (41%); pale yellow oil.

IR (film): 2933, 2825, 1651, 1610 cm^{-1}.

^{1}H NMR: δ = 7.24 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.16 (dd, *J* = 7.4, 0.8 Hz, 1 H), 6.76 (td, *J* = 7.4, 0.8 Hz, 1 H), 6.48 (d, *J* = 8.0 Hz, 1 H), 5.68 (s, 1 H), 3.73 (ddd, *J* = 14.0, 8.8, 4.0 Hz, 1 H), 3.31 (td, *J* = 9.2, 6.8 Hz, 1 H), 3.08 (s, 3 H), 3.03 (s, 3 H), 2.39–2.31 (m, 2 H), 2.11 (s, 3 H).

^{13}C NMR: δ = 170.6, 152.2, 130.4, 125.5, 123.8, 117.8, 107.8, 92.2, 82.0, 52.7, 46.7, 38.7, 33.8, 22.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_2$: 247.1450; found: 247.1447.

To a solution of the acetamide (13 mg, 0.052 mmo1) in MeOH (1.0 mL) and H_2O (0.2 mL) was added KOH (397 mg, 7.08 mmol). After stirring at reflux for 20 h, the mixture was diluted with H_2O (1 mL) and extracted with EtOAc (3 × 1 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated in vacuo. The residue was subjected to silica gel column chromatography ($CHC1_3$–MeOH, 10:1) to give **4**.

Yield: 10.1 mg (95%); colorless oil.

IR (film): 2934, 2825, 1609 cm^{-1}.

^{1}H NMR: δ = 7.26–7.16 (m, 2 H), 6.71 (td, *J* = 7.6, 0.8 Hz, 1 H), 6.43 (d, *J* = 7.6 Hz, 1 H), 4.82 (s, 1 H), 3.20–3.14 (m, 1 H), 3.09 (s, 3 H), 2.89 (s, 3 H), 2.77 (td, *J* = 13.8 H, 1 H), 2.49 (br s, 1 H), 2.25–2.21 (m, 2 H).

^{13}C NMR: δ = 152.3, 129.8, 126.8, 124.4, 117.0, 105.9, 94.7, 86.4, 52.9, 45.5, 42.0, 31.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{17}N_2O$: 205.1341; found: 205.1318.

CPC-1 (5)

To a solution of **4** (6 mg, 0.026 mmo1) in MeOH (0.35 mL) was added CH_2O (37% aqueous solution, 20 μL, 0.26 mmol) at 0 °C. The resulting mixture was stirred at r.t. for 5 h. $NaBH_3CN$ (12.7 mg, 0.195 mmo1) was added at 0 °C and the mixture was stirred at r.t. for 4 h, then diluted by addition of H_2O (2 mL) and extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was subjected to silica gel preparative thin layer chromatography ($CHC1_3$–MeOH, 10:1) to give **5**.

Yield: 4.2 mg (74%); colorless oil.

IR (film): 2927, 2790, 1608 cm^{-1}.

^{1}H NMR: δ = 7.19 (td, *J* = 7.6, 0.9 Hz, 1 H), 7.15 (dd, *J* = 7.5, 0.9 Hz, 1 H), 6.74 (td, *J* = 7.5, 0.9 Hz, 1 H), 6.50 (d, *J* = 8.2 Hz, 1 H), 4.36 (s, 1 H), 3.03 (s, 3 H), 2.96 (s, 3 H), 2.80 (ddd, *J* = 11.9, 4.5, 2.5 Hz, 1 H), 2.62 (td, *J* = 8.8, 4.8 Hz, 1 H), 2.57 (s, 3 H), 2.35 (ddd, *J* = 13.8, 6.2, 2.8 Hz, 1 H), 2.13 (ddd, *J* = 12.4, 6.2, 2.0 Hz, 1 H).

^{13}C NMR: δ = 153.1, 129.7, 128.0, 124.0, 117.9, 107.8, 94.0, 91.6, 52.5, 52.4, 39.3, 38.6, 36.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{19}N_2O$: 219.1497; found: 219.1493.

8-(3-Methylbut-2-en-1-yl)-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-*b*]indo-3a-ol (6)

To a solution of **2a** (14 mg, 0.05 mmol) in acetone (0.5 mL) were added prenyl bromide (18 μL, 0.156 mmol) and K_2CO_3 (22 mg, 0.16 mmol). The resulting mixture was stirred at r.t. overnight, diluted by the addition of H_2O (3 mL), and extracted with EtOAc (3 × 3 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in MeOH (0.5 mL) and H_2O (0.1 mL) containing KOH (624 mg, 11 mmol). The mixture was stirred at reflux for 20 h, cooled, and partitioned between H_2O (3 mL) and EtOAc (3 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo, giving a residue that was subjected to silica gel column chromatography ($CHC1_3$–MeOH, 10:1) to give **6**.

Yield: 8.6 mg (68%); colorless oil.

IR (film): 3242, 2967, 2927, 2855, 1608 cm^{-1}.

^{1}H NMR: δ = 7.25 (dd, *J* = 7.6, 0.8 Hz, 1 H), 7.14 (td, *J* = 7.6, 1.2 Hz, 1 H), 6.69 (td, *J* = 7.6, 0.8 Hz, 1 H), 6.44 (d, *J* = 8.0 Hz, 1 H), 5.22 (br t, *J* = 6.8 Hz, 1 H), 4.70 (s, 1 H), 3.88–3.76 (m, 2 H), 3.13 (ddd, *J* = 10.4, 7.2, 3.2 Hz, 1 H), 2.83 (ddd, *J* = 15.6, 8.8, 3.2 Hz, 1 H), 2.59 (br s, 2 H), 2.21–2.17 (m, 2 H), 1.73 (s, 3 H), 1.71 (s, 3 H).

^{13}C NMR: δ = 150.4, 135.7, 131.4, 129.8, 123.6, 119.8, 117.4, 106.7, 90.6, 88.5, 45.7, 43.1, 42.2, 25.7, 18.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{21}N_2O$: 245.1654; found: 245.1652.

Debromoflustraminol B (7)

To a solution of **6** (27 mg, 0.11 mmo1) in MeOH (1 mL) was added CH_2O (37% aqueous solution, 78 μL, 0.99 mmol). The resulting mixture was stirred at r.t. for 5.5 h and cooled to 0 °C before adding $NaBH_4$ (18.8 mg, 0.51 mmol). The mixture was warmed to r.t. and stirred for 2.5 h. After addition of H_2O (3 mL), the mixture was extracted with Et_2O (3 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo, giving a residue that was subjected to silica gel column chromatography (EtOAc) to give **7**.

Yield: 14.9 mg (52%); yellow oil.

IR (film): 3357, 3049, 2968, 2930, 1671, 1608 cm^{-1}.

^{1}H NMR: δ = 7.24 (dd, *J* = 7.6, 0.8 Hz, 1 H), 7.16 (td, *J* = 7.0, 1.2 Hz, 1 H), 6.74 (td, *J* = 8.0, 0.8 Hz, 1 H), 6.52 (d, *J* = 8.0 Hz, 1 H), 5.21 (br t, *J* = 7.2 Hz, 1 H), 4.33 (s, 1 H), 3.90–3.81 (m, 2 H), 2.84 (ddd, *J* = 10.8, 4.4, 2.0 Hz, 1 H), 2.68 (ddd, *J* = 11.2, 6.4, 2.0 Hz, 1 H), 2.56 (s, 3 H), 2.32 (ddd, *J* = 13.8, 6.8, 2.0 Hz, 1 H), 2.18 (ddd, *J* = 12.2, 6.4, 1.2 Hz, 1 H), 1.72 (s, 3 H), 1.71 (s, 3 H).

^{13}C NMR: δ = 151.2, 134.8, 132.3, 129.8, 123.3, 120.5, 118.2, 108.6, 95.5, 88.4, 53.1, 46.9, 40.1, 38.6, 25.7, 18.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{23}N_2O$: 259.1810; found: 259.1797.

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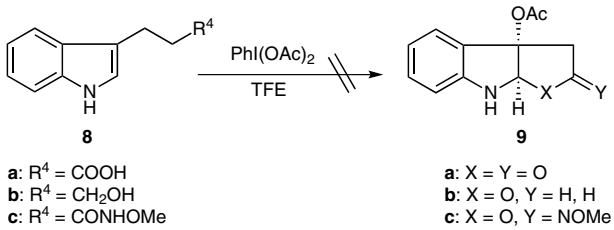
(7) Oxidations of tryptamines **8** that did not possess an acetamide group provided none of the desired cyclized products **9** (Scheme 3).



Scheme 3

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