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A general approach to crinine-type *Amaryllidaceae* alkaloids: total syntheses of (±)-haemanthidine, (±)-pretazettine, (±)-tazettine, and (±)-crinamine

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Abstract—A general strategy for synthesizing the crinine-type *Amaryllidaceae* alkaloids was developed. And total syntheses of four representative crinine-type *Amaryllidaceae* alkaloids: (±)-haemanthidine, (±)-pretazettine, (±)-tazettine, and (±)-crinamine, were accomplished via a common intermediate **17**. This crucial precursor was achieved on the basis of the NBS-promoted semipinacol rearrangement recently developed by our group and an intramolecular Michael addition, which efficiently constructed the sterically congested quaternary carbon center and the hydroindole skeleton of the crinine-type alkaloids, respectively.

1. Introduction

The crinine-type *Amaryllidaceae* alkaloids possess a wide range of biological activities.[1,2] For example, (±)-haemanthidine (**1**),[3] (±)-tazettine (**3**),[4] and (±)-crinamine (**4**)[5] show high analgesic, mild anticancer, and cytotoxic activities, respectively. In particular, (±)-pretazettine (**2**),[3] which exhibits high anticancer activity, has recently stimulated extremely the interest of chemists.[3,6] The important structural features of these alkaloids include an arylhydroindole core and a *cis* or *trans* hydroxyl group in the pyrrolidine ring, which represent central synthetic challenges. To date, several creative strategies had emerged to address these problems.[3–5,7] Despite the availability of many synthetic methods, it is necessary to develop more general procedures.

As a part of our ongoing research program for synthesizing *Amaryllidaceae* alkaloids,[8] we report herein a new general approach to the more complex crinine-type alkaloid members **1**–**4** (Fig. 1).

Our retrosynthetic analysis is shown in Scheme 1. We envisioned that all four target molecules could be synthesized from the same crucial arylhydroindole enone **5**, which might be prepared from **6** through an intramolecular Michael addition. The requisite double bond and 1,2-amino alcohol unit of intermediate **6** would be derived from the bromine and aldehyde functions in compound **7**, respectively. The key sterically congested quaternary carbon center in **7** could be constructed by the NBS-promoted semipinacol rearrangement of allylic alcohol **8**.

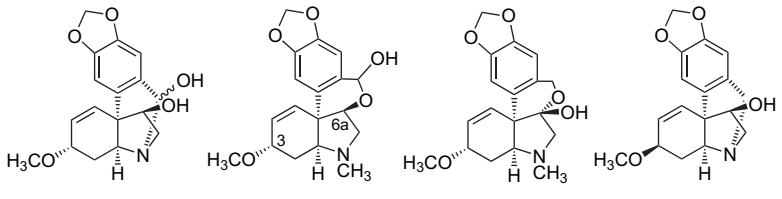

Figure 1. Representative member of the crinine-type *Amaryllidaceae* alkaloids.

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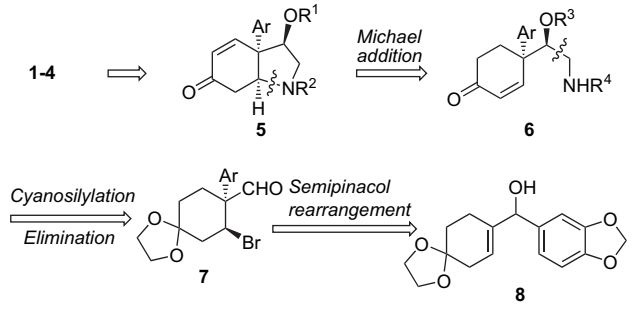
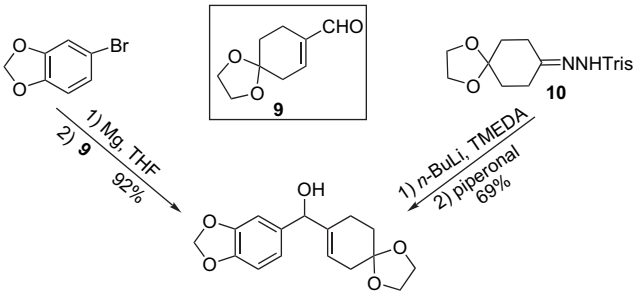


Scheme 1. Retrosynthetic analysis of target molecules **1**–**4**; Ar=3,4-methylenedioxyphenyl.

2. Results and discussion

2.1. Preparation of allylic alcohol 8

The starting allylic alcohol **8** was prepared by two means. One was the addition of aldehyde **9**[9] to the Grignard reagent of 4-bromo-1,2-(methylenedioxy)benzene, the other was the Shapiro reaction between **10**[8d] and piperonal (Scheme 2).



Scheme 2. Preparation of allylic alcohol **8**.

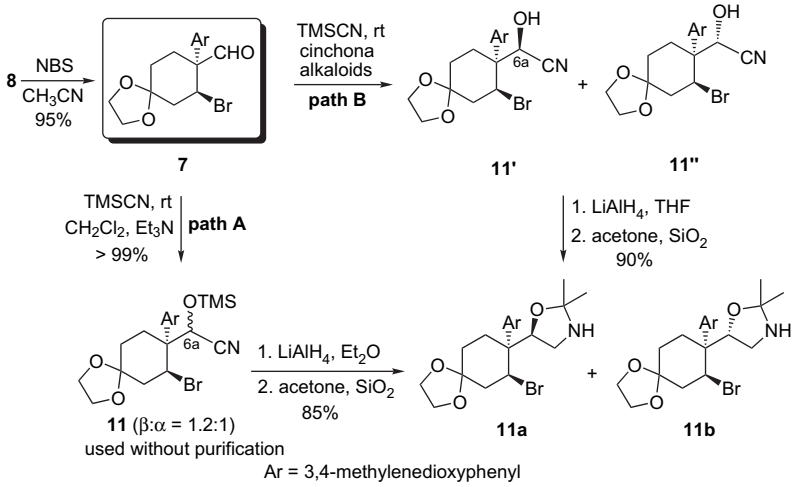
2.2. Preparation of aldehyde 7 and compounds 11a and 11b

By utilizing the work recently developed by our group on the use of *N*-bromosuccinimide (NBS)-promoted semipinacol rearrangement to build the quaternary carbon center,[8b] the aldehyde **7** was easily prepared from the alcohol **8** in excellent yield (95%) and with high diastereoselectivity (d.r.>99:1). In order to introduce the hydroxyl group at C-6a position and extend a nitrogen-containing carbon chain, the cyanation method was applied. The addition of trimethylsilylcyanide (TMSCN) to the aldehyde **7** set the hydroxyl group at C-6a position, and the corresponding trimethylsilyl ether adducts (**11**, a mixture of two isomers), which could not be separated by silica gel chromatography, were then reduced with $LiAlH_4$. After protection of the amino alcohol with acetone, two separable diastereoisomers (**11a** and **11b**) were obtained in 85% yield over three steps (path A in Scheme 3). However, the diastereoselectivity was very low (**11a/11b**=1.2:1) when triethylamine (Et_3N) was used as a base. To increase the diastereoselectivity of the initial addition reaction, other conditions were investigated (Table 1). The cinchona alkaloids were selected as the base in place of Et_3N. Notably, in all tests with different cinchona alkaloids, only the cyanohydrin products, but none of the corresponding TMS adduct were isolated (Scheme 3). The use of a stoichiometric quantity of the hydroquinine was necessary (entries 9–11, Table 1). Evaluation of bases and solvents showed that the best conditions for the reaction,

Table 1. Preparation of cyanohydrin in different conditions[a]

Entry	Solvent	Base/equiv	Time	Ratio[b] **11′**/**11″**	Yield[c] (%)
1	Et_2O	Quinine/1	2 d	—[d]	Trace
2	THF	Quinine/1	2 d	—[d]	Trace
3	Toluene	Quinine/1	2 d	2.1:1	62
4	CH_2Cl_2	Quinine/1	2 d	2.8:1	83
5	CH_2Cl_2	Quinidine/1	2 d	2.3:1	81
6	CH_2Cl_2	Cinchonine/1	2 d	2.0:1	78
7	CH_2Cl_2	Cinchonidine/1	2 d	2.6:1	76
8	CH_2Cl_2	Hydroquinidine/1	2 d	3.28:1	79
9	CH_2Cl_2	Hydroquinine/0.1	4 d	1.61:1	56
10	CH_2Cl_2	Hydroquinine/0.5	3 d	1.88:1	63
11	CH_2Cl_2	Hydroquinine/1	2 d	3.5:1	82
12	CH_2Cl_2	Hydroquinine/2	10 h	2.7:1	90

[a] Reaction was carried out on a 0.1 mmol scale with 1.2 equiv of TMSCN in 2 mL of solvent for 2 d, unless noted otherwise.
[b] Determined by ^1H NMR.
[c] The yield was overall yields of **11′** and **11″**, based on the recovered material.
[d] Not determined.

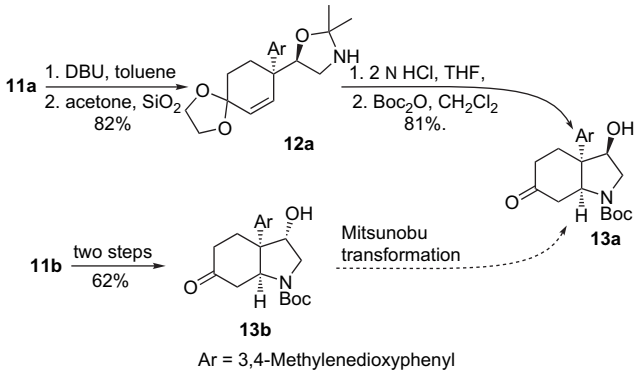


Scheme 3. Preparation of aldehyde **7** and compounds **11a** and **11b**.

which provided product **11′** and **11″** (ratio=3.5:1), were hydroquinine as base and CH_2Cl_2 as solvent (entry 11, Table 1). Interestingly, the decrease in diastereoselectivity was observed when a twofold hydroquinine was employed (entry 12, Table 1). As shown in Scheme 3, **11a** and **11b** were also obtained from **11′** and **11″** under the similar reaction conditions. The major isomer **11a** was identified to be the desired intermediate (as will be discussed below).

2.3. Construction of arylhydroindole framework 13a

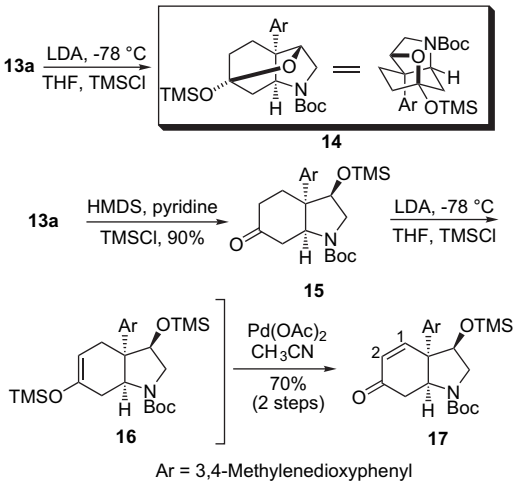
The major isomer **11a** was dehydrobrominated by treatment with 1,8-diazabicyclo[5.4.0]under-7-ene (DBU) in refluxing toluene, and the requisite double bond of **12a** was introduced in 82% yield. Under acidic condition, **12a** was deprotected and transformed into the corresponding secondary amine in nearly quantitative yield,[4c] and without purification this Michael addition product was treated with di-*tert*-butyl dicarbonate (Boc_2O) to provide the crucial intermediate **13a** in 81% yield (Scheme 4).[10] Successively, the transformation of the minor isomer **11b** into the intermediate **13a** was also investigated (Scheme 4). The diastereoisomer **13b** (6a-*epi*-**13a**) was prepared in the same fashion from **11b** in 62% yield (two steps). With the isomer **13b** in hand, we next focused on the inversion of the configuration at C-6a position. Under the standard Mitsunobu conditions,[11] the reactions did not provide the expected product **13a**, but resulted only in the decomposition of the starting material.



Scheme 4. Construction of the arylhydroindole framework (**13a** and **13b**).

2.4. Preparation of enone 17 and determination of β-OH at C-6a position

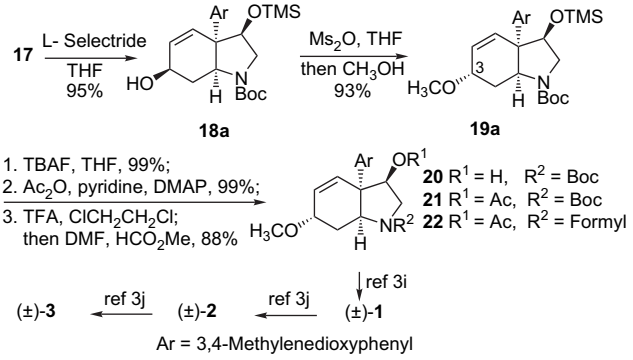
With the rapid construction of the arylhydroindole framework **13a**, installation of the C1–C2 double bond was investigated. Initially we anticipated that the silyl enol ether **16** could be synthesized from **13a** by silylation of the hydroxyl group and enolization of the carbonyl group in a one-pot process (Scheme 5). However, unexpected compound **14** was isolated in excellent yield under the conditions of lithium diisopropylamine (LDA) and chlorotrimethylsilane (TMSCl). The formation of **14** is a fortuitous proof of the relative stereochemistry of the hydroxyl group at C-6a position, since the secondary alcohol of opposite configuration cannot form an oxygen bridge at C-3 position.[12] To our knowledge, as an efficient chemical method to determine the key hydroxyl group configuration at C-6a position in this hydroindoline system, this conversion is first reported by our group.[13] Due to the failure of the one-pot operation, the hydroxyl of **13a** was first protected as the silyl ether under the Sweeley's condition,[14] giving compound **15** in excellent yield. Enolization of **15** and trapping with TMSCl afforded the silyl enol ether **16**, which was oxidized directly by $Pd(OAc)_2$[15] to furnish the desired enone **17** in 70% yield (Scheme 5).



Scheme 5. Determination of β-OH at C-6a position and preparation of enone **17**.

2.5. Total syntheses of haemanthidine (1), pretazettine (2), and tazettine (3)

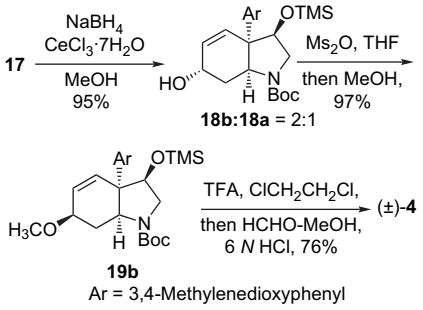
Having introduced the correct C1–C2 double bond, we then proceeded to set the methyloxy group at the C-3 position in stereoselective manner. Enone **17** was reduced with L-Selectride in THF at −78 °C to afford allylic alcohol **18a** as a single diastereoisomer in excellent yield, whose formation arose from the attack of hydride on the *exo* face of the hydroindole system. Using Whitlock's method,[16] we inverted the β-hydroxyl group of **18a** into the required α-methoxy derivative **19a** in 93% yield. The alcohol **20** was easily prepared from compound **19a** and converted into the *N*-formyl derivative **22** via acetate **21** (86% yield for four steps). Following the known procedures,[3i,3j] we achieved the total syntheses of **1**, **2**, and **3** from derivative **22** (Scheme 6), whose spectral data were identical to those reported in the literature.[3i,3j]



Scheme 6. Total syntheses of haemanthidine (**1**), pretazettine (**2**), and tazettine (**3**).

2.6. Total synthesis of crinamine (4)

Additionally, enone **17** was reduced under Luche condition[17] at room temperature to afford allylic alcohol **18** in 95% yield (**18b**/**18a**=2:1), albeit with disappointing diastereoselectivity. Allylic ether **19b** was obtained from **18b** using the same method as in the preparation of **19a**. After removal of the Boc and TMS protecting groups of **19b** with CF_3COOH, the followed Pictet–Spengler reaction in a one-pot procedure readily gave crinamine **4** in 76% yield, whose spectral data were agreed with those reported in the literature (Scheme 7).[3i,2b]



Scheme 7. Total synthesis of crinamine (**4**).

3. Conclusion

In summary, we successfully synthesized the crinine-type *Amaryllidaceae* alkaloids including (±)-haemanthidine, (±)-pretazettine, (±)-tazettine, and (±)-crinamine using an NBS-promoted semipinacol rearrangement developed by our group and a Michael addition as the key steps, and disclosed a general strategy for synthesizing the crinine-type *Amaryllidaceae* alkaloids.

4. Experimental

4.1. General

Melting points were measured on X-4 melting point apparatus and are uncorrected. IR spectra were measured on KBr disks by using a Nicolet NEXUS 670 FTIR spectrometer. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Mercury-plus 300BB spectrometer (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR spectra), a Brucker AM-400 spectrometer (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR spectra). The EIMS spectra were recorded on a HP5988A mass spectrometer, and the high-resolution mass spectra were recorded on Brucker Daltonics APEX II 49e spectrometer by means of the ESI technique. Silica gel (200–300 mesh) for column chromatography and silica GF_{254} for TLC were produced by Qingdao Marine Chemical Company (China). Solvents for reaction were distilled prior to use: THF and Et_2O from Na and benzophenone, MeOH from Mg and I_2, CH_2Cl_2, Et_3N, and DMF from CaH_2, and toluene from $LiAlH_4$. All air- or moisture-sensitive reactions were conducted under an argon atmosphere.

4.1.1. Benzo[1,3]dioxol-5-yl-(1,4-dioxa-spiro[4.5]dec-7-en-8-yl)-methanol (8).

Process A: to a stirred suspension of magnesium turnings 240 mg (10 mmol) in dry THF (20 mL) was added 1.2 mL 4-bromo-1,2-(methylenedioxyl)benzene (10 mmol) in 10 mL THF at room temperature. The reaction mixture was stirred for 2 h until the magnesium turnings had disappeared. Then a solution of aldehyde **9**[9] 1.7 g (10 mmol) in THF (20 mL) was added to the above mixed solution at 0 °C. After 30 min, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (30 mL) and allowed to stir for another 1 h. The aqueous solution was extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with water, brine, and dried over Na_2SO_4, then concentrated under reduced pressure. Recrystallization from petroleum/EtOAc afforded the allylic alcohol **8** (2.67 g, 92%) as a white crystal. Mp 104–106 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 6.86–6.75 (m, 3H), 5.95 (d, J=2.7 Hz, 2H), 5.77 (s, 1H), 5.05 (s, 1H), 3.98–3.95 (m, 4H), 2.35 (br s, 2H), 2.10–2.08 (m, 2H), 1.71 (t, J=6.6 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6, 146.8, 139.3, 136.2, 120.1, 119.9, 108.0, 107.9, 107.0, 100.9, 77.0, 64.3, 35.4, 30.8, 23.5 ppm; IR (KBr): ν 3418, 1500, 1488, 1442, 1251, 1231, 1115, 1051, 1037, 938, 926 cm^{-1}; MS (70 eV, EI): *m/z* (%) 290 (M^+, 12), 272 (1), 226 (3), 151 (23), 122 (24), 99 (16), 93 (15), 86 (100), 77(11); HRMS (ESI) calcd for $C_{16}H_{18}O_5Na$: 313.1046 $[M+Na]^+$; found: 313.1044.

Process B: to a cold (−78 °C) suspension of **10** (4.36 g, 10 mmol) in dried tetramethylethylenediamine (TMEDA, 30 mL) was added dropwise *n*-BuLi (2.0 M in hexane, 12.0 mL, 24 mmol) under an argon atmosphere (10 min). The reaction mixture was stirred at room temperature for 4 h, and then cooled to −78 °C again. The solution of piperonal (3.0 g, 20 mmol) in dried TMEDA (15 mL) was added dropwise. After 1 h, the mixture was poured into saturated aqueous solution of NH_4Cl (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum/EtOAc=5:1) provided the allylic alcohol **8** (2.0 g, 69%).

4.1.2. 8-Benzo[1,3]dioxol-5-yl-7β-bromo-1,4-dioxa-spiro[4.5]decane-8-carbaldehyde (7).

To a solution of allylic alcohol **8** (290 mg, 1 mmol) in CH_3CN (15 mL) was added NBS (196 mg, 1.1 mmol) at room temperature. The reaction mixture was stirred for 6 h until the allylic alcohol had disappeared completely as monitored by TLC. The solution was concentrated in vacuum and the residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=6:1) to give the aldehyde **7** as a white crystal (350 mg, 95%). Mp 84–86 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 9.93 (s, 1H), 6.80–6.75 (m, 2H), 6.63 (dd, J=8.3, 2.3 Hz, 1H), 5.96 (s, 2H), 4.71 (dd, J=12.9, 4.2 Hz, 1H), 3.99–3.90 (m, 4H), 2.52–2.47 (m, 1H), 2.35–2.31 (m, 1H), 2.22 (t, J=12.9 Hz, 1H), 1.84 (dd, J=12.9, 9.9 Hz, 2H), 1.67–1.64 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.1, 148.3, 147.0, 132.1, 120.3, 108.4, 108.0, 107.0, 101.3, 64.6, 64.4, 56.5, 51.0, 43.6, 32.1, 31.8 ppm; IR (KBr): ν 3405, 1712, 1501, 1439, 1241, 1150, 1093, 1036, 938, 622 cm^{-1}; MS (70 eV, EI): *m/z* (%) 370 (M^+, 3), 368

(M^+, 3), 289 (9), 260 (41), 259 (34), 215 (37), 187 (57), 174 (100), 157 (26), 128 (43), 115 (63), 108 (52), 99 (70), 80 (93), 63 (33); HRMS (ESI) calcd for $C_{16}H_{17}O_5BrNa$: 391.0152 $[M+Na]^+$; found: 391.0158.

4.1.3. 5-(8-Benzo[1,3]dioxol-5-yl-7β-bromo-1,4-dioxa-spiro[4.5]decane-8-yl)-2,2-dimethyl-oxazolidine (11a and 11b). *Path A*: to a solution of the above aldehyde **7** (1.11 g, 3 mmol) in CH_2Cl_2 (30 mL) was added dropwise TMSCN (0.48 mL, 3.6 mmol) at room temperature, and then Et_3N (0.52 mL, 3.8 mmol) was added. The mixture was stirred and the reaction was monitored by ^1H NMR. After the material had disappeared completely, the reaction mixture was concentrated in vacuo. The solution of the residue in Et_2O (30 mL) was added dropwise to a solution of $LiAlH_4$ (228 mg, 6 mmol) in dry Et_2O (50 mL) at 0 °C. After the mixture was stirred for 2 h at room temperature, the reaction mixture was quenched with H_2O, 15% NaOH, and H_2O, and the resulting mixture was filtered. The solid residue was washed well with $CHCl_3$, and the combined organic phases were concentrated. The residue was purified by flash column chromatography silica gel (petroleum/acetone=5:1) to give white gem **11a** (612 mg, 46.4%) and **11b** (510 mg, 38.6%). Compound **11a**: ^1H NMR (400 MHz, $CDCl_3$): δ 6.89 (br, 2H), 6.79 (d, J=8.0 Hz, 1H), 5.96 (d, J=3.6 Hz, 2H), 5.22 (s, 1H), 4.26 (dd, J=7.4, 4.2 Hz, 1H), 4.05–3.98 (m, 2H), 3.82–3.78 (m, 2H), 3.03 (dd, J=12.6, 7.4 Hz, 1H), 2.70 (dd, J=12.4, 4.4 Hz, 1H), 2.15 (dd, J=11.4, 3.0 Hz, 2H), 2.05–2.01 (m, 1H), 1.92–1.81 (m, 2H), 1.74 (d, J=14 Hz, 1H), 1.20 (s, 3H), 1.18 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 146.4, 129.6, 122.4, 109.6, 107.7, 107.3, 101.1, 95.5, 82.1, 77.2, 64.4, 63.4, 56.6, 47.5, 47.0, 37.9, 30.7, 26.5, 25.3 ppm; IR (KBr): ν 3304, 1491, 1434, 1374, 1243, 1093, 1040, 933, 911, 732, 644 cm^{-1}; MS (70 eV, EI): m/z (%) 360 (1), 260 (23), 174 (41), 115 (8), 100 (100), 71 (25), 70 (16), 43 (15); HRMS (ESI) calcd for $C_{20}H_{27}NBrO_5$: 440.1067 $[M+H]^+$; found: 440.1073. Compound **11b**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.01 (d, J=1.8 Hz, 1H), 6.91 (d, J=8.1 Hz, 1H), 6.77 (d, J=8.4 Hz, 1H), 5.94–5.93 (m, 2H), 4.85 (t, J=7.3 Hz, 1H), 4.33 (dd, J=7.4, 5.0 Hz, 1H), 4.02–3.94 (m, 2H), 3.87–3.83 (m, 2H), 3.21 (dd, J=12.5, 7.7 Hz, 1H), 2.79 (dd, J=12.6, 5.1 Hz, 1H), 2.40–2.31 (m, 3H), 2.16 (br, 1H), 1.83–1.80 (m, 1H), 1.61–1.54 (m, 2H), 1.51 and 1.11 (2s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 146.1, 133.5, 120.6, 108.9, 107.8, 107.6, 101.0, 95.1, 80.1, 65.8, 64.5, 63.8, 54.4, 47.9, 47.5, 41.1, 31.0, 26.6, 25.0 ppm; IR (KBr): ν 3307, 1712, 1490, 1435, 1240, 1038, 940, 827, 662 cm^{-1}; MS (70 eV, EI): m/z (%) 360 (1), 292 (1), 260 (24), 174 (42), 115 (9), 100 (100), 71 (26), 70 (16), 55 (9), 43 (13).

4.1.4. (8-Benzo[1,3]dioxol-5-yl-7β-bromo-1,4-dioxa-spiro[4.5]decane-8-yl)-hydroxy-acetonitrile (11′ and 11″). To a solution of the above aldehyde **7** (312 mg, 0.85 mmol) in CH_2Cl_2 (10 mL) was added dropwise TMSCN (0.14 mL, 1.05 mmol) at room temperature, and then hydroquinine (278 mg, 0.85 mmol) was added. The mixture was stirred for 2 d at room temperature, and then concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=5:1) to give 263 mg white solid (**11′** and **11″**, ratio=3.5:1) and recovered the starting material 12 mg. ^1H NMR (300 MHz, $CDCl_3$): δ 6.85–6.78 (m, 3H), 6.01 and 6.00 (2s, 2H), 5.20 (m, 1H), 4.96 (d, J=11.4 Hz, 0.67H), 4.76 (d, J=10.8 Hz, 0.19H), 4.07–4.00 (m, 2H), 3.85–3.81 (m, 2H), 2.27–2.09 (m, 4H), 1.83–1.79 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 148.5, 147.8, 147.6, 127.0, 121.7, 117.9, 117.6, 108.9, 108.6, 107.0, 101.6, 101.5, 70.2, 69.7, 64.5, 63.6, 60.5, 53.2, 52.7, 48.9, 48.8, 38.4, 38.0, 31.0, 30.5, 24.8, 24.3 ppm; IR (KBr): ν 3389, 1710, 1506, 1437, 1244, 1091, 1039, 940, 845 cm^{-1}; MS (70 eV, EI): m/z (%) 259 (1), 174 (1), 88 (11), 86 (69), 84 (100), 82 (15), 80 (13), 49 (16), 47 (18), 43 (13).

4.1.5. 5-(8-Benzo[1,3]dioxol-5-yl-7β-bromo-1,4-dioxa-spiro[4.5]decane-8-yl)-2,2-dimethyl-oxazolidine (11a and 11b). *Path B*: to a solution of $LiAlH_4$ (32 mg, 0.84 mmol) in THF (10 mL) was added dropwise a solution of the mixtures of **11′** and **11″** (160 mg, 0.4 mmol) in THF (10 mL) at 0 °C. After 20 min, the reaction was quenched with H_2O, 15% NaOH, and H_2O, and the resulting mixture was filtered. The solid residue was washed well with $CHCl_3$, the combined organic phases were concentrated, and the residue was purified by silica gel (petroleum/acetone=5:1) to give white gem **11a** (124 mg, 70%) and **11b** (35 mg, 20%).

4.1.6. 5-(8-Benzo[1,3]dioxol-5-yl-1,4-dioxa-spiro[4,5]-dec-6-en-8-yl)-2,2-dimethyl-oxazolidine (12a). A mixture of **11a** (516 mg, 1.18 mmol) and DBU (1.8 mL, 11.8 mmol) in toluene (20 mL) was refluxed for 2 d. The mixture was concentrated in vacuo. The residue was purified directly by flash column chromatography on silica gel (petroleum/acetone=3:1) to afford compound **12a** (347 mg, 82%, two steps) as a white gum. ^1H NMR (400 MHz, $CDCl_3$): δ 7.00 (s, 1H), 6.80 (dd, J=8.2, 3.0 Hz, 1H), 6.69 (dd, J=8.2, 3.0 Hz, 1H), 6.02 (dd, J=11.2, 2.4 Hz, 1H), 5.90 (t, J=2.8 Hz, 2H), 5.75 (d, J=10.8 Hz, 1H), 4.04–3.83 (m, 5H), 3.01–2.95 (m, 1H), 2.89–2.83 (m, 1H), 2.00–1.95 (m, 2H), 1.78–1.75 (m, 1H), 1.65–1.58 (m, 2H), 1.28 (s, 3H), 1.25 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 145.9, 136.9, 135.3, 128.6, 120.9, 108.6, 107.5, 105.4, 100.8, 95.8, 83.1, 64.6, 64.3, 47.7, 45.8, 30.0, 29.8, 27.1, 25.7 ppm; IR (KBr): ν 3313, 1487, 1434, 1240, 1099, 1038, 936, 814 cm^{-1}; MS (70 eV, EI): m/z (%) 260 (3), 187 (2), 128 (3), 115 (3), 100 (100); HRMS (ESI) calcd for $C_{20}H_{26}NO_5$: 360.1805 $[M+H]^+$; found: 360.1801.

4.1.7. 5-(8-Benzo[1,3]dioxol-5-yl-1,4-dioxa-spiro[4,5]-dec-6-en-8-yl)-2,2-dimethyl-oxazolidine (12b). The same method was applied to the preparation of compound **12b** (79%, two steps). ^1H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, J=1.6 Hz, 1H), 6.80 (dd, J=8.2, 1.4 Hz, 1H), 6.70 (dd, J=7.8, 3.0 Hz, 1H), 5.99 (d, J=10.0 Hz, 1H), 5.90 (s, 2H), 5.86 (d, J=10.0 Hz, 1H), 4.15–4.12 (m, 1H), 4.00–3.94 (m, 3H), 3.86 (dd, J=6.4, 5.8 Hz, 1H), 3.16 (dd, J=12.0, 7.2 Hz, 1H), 2.91 (dd, J=12.0, 5.4 Hz, 1H), 2.00–1.92 (m, 2H), 1.69–1.65 (m, 2H), 1.58–1.52 (m, 1H), 1.33 (s, 3H), 1.27 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 145.9, 136.4, 134.3, 130.3, 121.1, 108.3, 107.5, 105.3, 100.8, 95.6, 82.3, 64.7, 64.3, 47.8, 46.1, 31.9, 29.5, 26.8, 25.2 ppm; IR (KBr): ν 3313, 1653, 1610, 1487, 1434, 1240, 1038, 936, 814 cm^{-1}; MS (70 eV, EI): m/z (%) 360 (M^+, 1), 260 (23), 174 (41), 115 (8), 100 (100), 71 (25), 70

(16), 43 (15); HRMS (ESI) calcd for $C_{20}H_{26}NO_5$: 360.1805 $[M+H]^+$; found: 360.1801.

4.1.8. 3a-Benzo[1,3]dioxol-5-yl-3β-hydroxy-6-oxo-octahydro-indole-1-carboxylic acid *tert*-butyl ester (13a). A solution of the above protected amino alcohol **12a** (277 mg, 0.77 mmol), THF (15 mL), and 2 N HCl (2.2 mL) was heated at reflux for 6 h. After cooled to room temperature, the reaction was quenched by addition solid of K_2CO_3 until pH=8. The resulting layers were separated and the aqueous layer was extracted with $CHCl_3$ (5×10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL), and triethylamine (0.33 mL, 2.4 mmol) was added to the solution. The solution was stirred for 10 min, then added $(Boc)_2O$ 252 mg (1.16 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, whereupon H_2O (3 mL) was added and the organic layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=1:1) to give **13a** as a white gum (234 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (br, 0.64H), 6.78 (br, 2.30H), 5.96 (s, 2H), 4.64–4.58 (br, 0.74H), 4.46 (br, 0.60H), 4.28 (br, 0.64H), 3.67 (br, 0.56H), 3.34 (d, J=10.4 Hz, 1H), 3.06–2.85 (br, 2H), 2.60 (br, 0.77H), 2.38 (br, 1H), 2.23–1.85 (br, 3H), 1.15 and 1.42 (2s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.1, 154.4, 148.3, 148.0, 146.5, 137.1, 134.8, 119.1, 118.9, 108.2, 106.9, 106.5, 106.3, 101.2, 94.9, 94.6, 81.0, 80.1, 79.7, 77.2, 59.4, 56.9, 56.2, 53.0, 52.5, 52.2, 51.6, 51.1, 45.6, 45.1, 43.5, 43.0, 42.7, 42.1, 36.5, 33.3, 33.2, 28.4, 26.4 ppm; IR (KBr): ν 3405, 1689, 1506, 1488, 1402, 1237, 1167, 1039, 932, 732 cm^{-1}; MS (70 eV, EI): *m/z* (%) 375 (M^+, 3), 319 (3), 229 (4), 216 (8), 188 (9), 174 (14), 115 (11), 77 (10), 57 (100); HRMS (ESI) calcd for $C_{20}H_{25}NO_6Na$: 398.1574 $[M+Na]^+$; found: 398.1580.

4.1.9. 3a-Benzo[1,3]dioxol-5-yl-3α-hydroxy-6-oxo-octahydro-indole-1-carboxylic acid *tert*-butyl ester (13b). The same method was applied to the preparation of compound **13b** (yield: 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86–6.79 (m, 3H), 5.99 (s, 2H), 4.62 (br, 1H), 4.13 (br, 1H), 3.70 (br, 2H), 3.26 (br, 0.5H), 2.99 (br, 0.5H), 2.81 (br, 1H), 2.25–2.00 (m, 4H), 1.48 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.9, 155.4, 148.9, 147.1, 131.7, 120.8, 108.9, 107.4, 101.4, 80.6, 77.4, 57.8, 54.2, 53.2, 43.1, 41.4, 36.2, 31.4, 28.4 ppm; IR (KBr): ν 3426, 1711, 1690, 1490, 1396, 1235, 1037, 931 cm^{-1}; MS (70 eV, EI): *m/z* (%) 375 (M^+, 1), 229 (4), 216 (40), 174 (14), 115 (5), 70 (8), 57 (84), 43 (100).

4.1.10. 7-Benzo[1,3]dioxol-5-yl-1β-trimethylsilanyloxy-2-oxa-5-aza-tricyclo[4.3.1.0^{3,7}]decane-5-carboxylic acid *tert*-butyl ester (14). A solution of *n*-butyllithium (2 M solution in hexane, 0.3 mL) was added dropwise to a solution of diisopropylamine (0.084 mL, 0.6 mmol) in THF (5 mL) at 0 °C under argon atmosphere. The solution was stirred at 0 °C for 45 min before being cooled to −78 °C and treated with a solution of **13a** (101 mg, 0.27 mmol) in THF (2 mL). After 30 min, TMSCl (0.080 mL, 0.63 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min, then slowly warmed to −20 °C, and quenched after 1 h with saturated $NaHCO_3$ solution (2 mL). After dilution with ether (30 mL), the organic layer was separated, and the aqueous layer was extracted with ether (3×10 mL). The combined organic layers were washed successively with saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4, and concentrated in vacuum. Purification of the residue by flash column chromatography on silica gel (petroleum/EtOAc=10:1) provided the acetal **14** (109 mg, 90%) as a white film. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73–6.63 (m, 3H), 5.90 (s, 2H), 4.60 (dd, J=3.6, 1.6 Hz, 1H), 4.52 (d, J=6.8 Hz, 0.59H), 4.39 (d, J=7.6 Hz, 0.42H), 3.31 (d, J=11.4 Hz, 0.5H), 3.26 (d, J=11.6 Hz, 0.5H), 2.95–2.87 (m, 1H), 2.28–2.24 (m, 1H), 2.16–2.13 (m, 1H), 2.10–2.02 (m, 1H), 1.98–1.86 (m, 2H), 1.79–1.72 (m, 1H), 1.48 (s, 4H), 1.39 (s, 5H), 0.14 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4, 154.0, 147.9, 146.3, 135.2, 118.8, 108.2, 106.5, 106.3, 101.0, 96.4, 96.2, 80.6, 79.9, 79.5, 79.4, 60.2, 57.0, 56.5, 52.9, 52.4, 45.4, 44.9, 43.7, 43.2, 34.8, 34.7, 28.5, 28.3, 1.89 ppm; IR (KBr): ν 1693, 1402, 1245, 1174, 1041, 923, 873, 844 cm^{-1}; MS (70 eV, EI): *m/z* (%) 447 (M^+, 1), 288 (14), 246 (19), 202 (22), 73 (49), 57 (100); HRMS (ESI) calcd for $C_{23}H_{34}NSiO_6$: 448.2150 $[M+H]^+$; found: 448.2150.

4.1.11. 3a-Benzo[1,3]dioxol-5-yl-6-oxo-3β-trimethylsilanyloxy-octahydro-indole-1-carboxylic acid *tert*-butyl ester (15). To a solution of **13a** (107 mg, 0.29 mmol) in dried pyridine (1.5 mL) were added hexamethyl disilazane (HMDS) (0.4 mL, 1.92 mmol) and TMSCl (0.3 mL, 2.36 mmol) subsequently. The reaction mixture was stirred for 30 min and H_2O (0.5 mL) was added carefully. After dilution with CH_2Cl_2 (30 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with saturated $CuSO_4$ solution, water, brine, dried over Na_2SO_4, and concentrated in vacuum. Purification of the residue by flash column chromatography on silica gel (petroleum/EtOAc=12:1) provided **15** (115 mg, 90%) as a white film. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81–6.74 (m, 3H), 5.95 (s, 2H), 4.68–4.59 (br, 1H), 3.99 (s, 1H), 3.67 (br, 1H), 3.41–3.34 (br, 1H), 3.21 (br, 0.4H), 3.04 (br, 0.5H), 2.68 (dd, J=16.8, 5.2 Hz, 1H), 2.23–2.09 (m, 4H), 1.49 (s, 9H), −0.10 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.2, 155.9, 148.1, 146.5, 133.4, 121.0, 108.4, 108.2, 101.3, 80.6, 77.4, 59.1, 55.1, 53.7, 42.6, 41.4, 36.9, 31.0, 28.7, 0.00 ppm; IR (KBr): ν 1693, 1491, 1393, 1250, 1167, 936, 845 cm^{-1}; MS (70 eV, EI): *m/z* (%) 447 (M^+, 0.5), 216 (100), 174 (16), 73 (30), 57 (50); HRMS (ESI) calcd for $C_{23}H_{33}NSiO_6Na$: 470.1969 $[M+Na]^+$; found: 470.1960.

4.1.12. 3a-Benzo[1,3]dioxol-5-yl-6-oxo-3β-trimethylsilanyloxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (17). A solution of *n*-butyllithium (2 M solution in hexane, 0.23 mL) was added dropwise to a solution of diisopropylamine (0.065 mL, 0.46 mmol) in THF (5 mL) at 0 °C under argon atmosphere. The solution was stirred at 0 °C for 45 min before being cooled to −78 °C and treated with a solution of silyl ether **15** (195 mg, 0.44 mmol) in THF (2 mL). After 30 min, TMSCl (0.07 mL, 0.55 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min, slowly warmed to −20 °C, and quenched with saturated $NaHCO_3$ solution (2 mL) after 1 h. After diluting with

ether (30 mL), the organic layer was separated, and the aqueous layer was extracted with ether (3×10 mL). The combined organic layers were washed successively with saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4, and concentrated in vacuum to give the silyl enol ether **16**, which was used in the next reaction without further purification. A mixture of this residue, $Pd(OAc)_2$ (160 mg, 0.71 mmol) in CH_3CN (20 mL) was stirred at room temperature overnight. The mixture was then concentrated and the brown residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=3:1) to afford enone **17** as a white foamy solid (137 mg, 70%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.11 (d, J=10.5 Hz, 1H), 6.84 (s, 1H), 6.78 (s, 2H), 6.29 (d, J=10.8 Hz, 1H), 5.95 (s, 2H), 4.51–4.46 (m, 1H), 4.24 (br, 0.45H), 4.11 (br, 0.76H), 3.89–3.81 (m, 1H), 3.67 (br, 0.44H), 3.30–3.24 (br, 0.61H), 3.09–2.94 (m, 1H), 2.45–2.30 (br, 1H), 1.44 (s, 9H), 0.05 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.7, 197.4, 154.4, 148.3, 147.7, 147.4, 147.0, 132.2, 132.0, 130.8, 120.5, 108.3, 107.1, 101.3, 80.7, 80.1, 76.6, 75.7, 61.7, 54.0, 52.9, 52.3, 52.0, 37.8, 36.4, 28.3, −0.23 ppm; IR (KBr): ν 1697, 1504, 1488, 1394, 1250, 1164, 1113, 1040, 934, 912, 844, 733 cm^{-1}; MS (70 eV, EI): m/z (%) 215 (14), 214 (100), 73 (27), 57 (43), 41 (13); HRMS (ESI) calcd for $C_{23}H_{31}NSiO_6Na$: 468.1813 $[M+Na]^+$; found: 468.1817.

4.1.13. 3a-Benzo[1,3]dioxol-5-yl-6β-hydroxy-3β-trimethylsilanyloxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (18a). To a well-stirred solution of enone **17** (24 mg, 0.054 mmol) in THF (2 mL) at −78 °C under argon atmosphere was added dropwise a solution of L-Selectride (1.0 M solution in THF, 0.07 mL, 0.07 mmol) by syringe and the resulting solution was stirred for 15 min at this temperature. The reaction mixture was quenched by the addition of CH_3OH (0.2 mL) over 1 min. The resulting slurry was allowed to warm to room temperature slowly, and H_2O (3 mL) was added. The aqueous layer was extracted with $CHCl_3$ (3×20 mL), and the combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (petroleum/EtOAc 10:1) afforded the allylic alcohol **18a** as white crystal (24 mg, 95%). Mp 168–170 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.81 (s, 1H), 6.75 (s, 2H), 6.26 (dd, J=9.9, 3.6 Hz, 1H), 6.20 (d, J=9.9 Hz, 1H), 5.94 (s, 2H), 4.40 (t, J=10.0 Hz, 1H), 4.10 (br, 1H), 3.94 (br, 1H), 3.73 (br, 1H), 3.07 (dd, J=13.6, 8.4 Hz, 1H), 2.60 (br, 0.7H), 1.84 (br, 0.6H), 1.68–1.47 (m, 1H), 1.48 (s, 9H), −0.02 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 148.0, 146.5, 135.1, 131.8, 128.3, 120.5, 108.1, 107.6, 101.1, 80.3, 77.3, 63.6, 60.3, 52.9, 51.8, 29.7, 28.5, −0.11 ppm; IR (KBr): ν 3424, 1690, 1399, 1248, 1111, 1037, 936, 844 cm^{-1}; MS (70 eV, EI): m/z (%) 447 (M^+, 0.2), 198 (100), 199 (14), 73 (21), 57 (31), 41 (10); HRMS (ESI) calcd for $C_{23}H_{33}NSiO_6Na$: 470.1969 $[M+Na]^+$; found: 470.1974.

4.1.14. 3a-Benzo[1,3]dioxol-5-yl-6α-methoxy-3β-trimethylsilanyloxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (19a). To a solution of allylic alcohol **18a** (22 mg, 0.049 mmol) and NEt_3 (0.10 mL, 0.72 mmol) in THF (2 mL) was added Ms_2O (54 mg, 0.31 mmol) at 0 °C and the solution was stirred for 1 h. To this solution was added MeOH (2 mL) and the solution was stirred at 0 °C for 3 d. Ethyl acetate (30 mL) was added to this solution, and the organic layer was washed with saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=3:1) to give **19a** as a colorless amorphous (21 mg, 93%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.90 (d, J=1.6 Hz, 1H), 6.63 (dd, J=10.0, 1.8 Hz, 1H), 6.76 (d, J=7.2 Hz, 1H), 6.20 (d, J=10.5 Hz, 1H), 5.95 (d, J=10.5 Hz, 1H), 5.95 (s, 2H), 4.49–4.44 (m, 1H), 4.05 (br, 0.4H), 3.88–3.78 (m, 2.3H), 3.68–3.61 (m, 0.4H), 3.38–3.32 (m, 3H), 2.98 (t, J=10.0 Hz, 1H), 2.85 (br, 0.33H), 2.60 (br, 0.64H), 1.48 (s, 9H), 0.067 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 154.3, 147.8, 146.3, 135.3, 131.7, 131.3, 128.3, 127.9, 120.9, 108.0, 107.8, 101.1, 80.0, 79.6, 76.1, 75.3, 72.6, 61.5, 56.0, 53.4, 52.5, 51.9, 51.3, 28.5, 27.2, 25.8, −0.11 ppm; IR (KBr): ν 1694, 1488, 1395, 1249, 1101, 936, 879, 843 cm^{-1}; MS (70 eV, EI): m/z (%) 231 (9), 199 (13), 198 (51), 73 (48), 57 (100), 41 (27); HRMS (ESI) calcd for $C_{24}H_{35}O_6NSiNa$: 484.2126 $[M+Na]^+$; found: 484.2129.

4.1.15. 3a-Benzo[1,3]dioxol-5-yl-3β-hydroxy-6α-methoxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (20). To a solution of silyl ether **19a** (43 mg, 0.095 mmol) in THF (3 mL) was added dropwise a solution of Bu_4NF (1 M solution in THF, 0.1 mL, 0.10 mmol) at room temperature. After 10 min, the solution was concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (petroleum/EtOAc=1:1) afforded the alcohol **20** (36.5 mg, 99%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.94 (s, 1H), 6.88 (d, J=8.1 Hz, 1H), 6.78 (d, J=8.4 Hz, 1H), 6.26 (d, J=10.5 Hz, 1H), 5.96 (s, 2H), 5.92 (d, J=11.1 Hz, 1H), 4.60 (br, 1H), 4.06 (br, 0.7H), 3.93–3.86 (br, 2.73H), 3.40 (s, 3H), 3.13 (t, J=9.3 Hz, 1H), 2.77 (br, 0.6H), 2.57 (br, 0.8H), 1.76 (br, 1H), 1.54 (s, 1H), 1.48 (s, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.5, 148.1, 146.7, 134.8, 132.4, 127.6, 120.7, 109.8, 108.3, 107.6, 101.2, 80.1, 74.7, 72.4, 61.2, 56.1, 53.6, 50.8, 28.5, 27.6 ppm; IR (KBr): ν 3404, 1674, 1605, 1487, 1409, 1320, 1132, 930 cm^{-1}; MS (70 eV, EI): m/z (%) 389 (M^+, 1), 259 (1), 249 (21), 230 (19), 199 (10), 198 (13), 115 (10), 57 (100), 41 (26); HRMS (ESI) calcd for $C_{21}H_{31}N_2O_6$: 407.2177 $[M+NH_4]^+$; found: 407.2174.

4.1.16. 3β-Acetoxy-3a-benzo[1,3]dioxol-5-yl-6α-methoxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (21). A solution of alcohol **20** (30 mg, 0.077 mmol), DMAP (2 mg), pyridine (0.03 mL), and Ac_2O (0.04 mL) in CH_2Cl_2 (2 mL) was stirred at 0 °C for 2 h. Ethyl acetate (20 mL) was added to the solution and the organic phase was washed with 1 N HCl, water, saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. Purification of the residue by flash column chromatography on silica gel (petroleum/EtOAc=2:1) provided **21** (33 mg, 99%). ^1H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, J=1.6 Hz, 1H), 6.87 (dd, J=8.2, 1.8 Hz, 1H), 6.77 (d, J=8.2 Hz, 1H), 6.17 (dd, J=10.2, 2.8 Hz, 1H), 5.96 (s, 2H), 5.86 (d, J=10.2 Hz, 1H), 5.59 (t, J=6.4 Hz, 0.5H), 5.52 (t, J=6.4 Hz, 0.5H), 4.12 (d, J=3.6 Hz, 0.5H), 4.05 (d, J=4.4 Hz, 0.5H), 3.98–3.92 (m, 1H), 3.85 (br, 1H), 3.40 (s, 3H), 3.17 (dd, J=11.2, 6.0 Hz, 0.5H), 3.08 (dd, J=10.8, 7.2 Hz, 0.5H), 2.61 (t, J=6.0 Hz, 0.5H),

2.40–2.33 (m, 0.5H), 2.02 (s, 3H), 1.86–1.81 (m, 0.5H), 1.76–1.71 (m, 0.5H), 1.47 and 1.25 (2s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 154.2, 148.1, 146.8, 134.5, 131.3, 130.5, 129.3, 128.5, 120.4, 108.2, 107.6, 101.2, 80.2, 75.8, 75.1, 72.0, 59.8, 56.2, 49.3, 49.1, 28.5, 27.8, 26.5, 20.9 ppm; IR (KBr): ν 2975, 1744, 1694, 1489, 1392, 1238, 1039, 935 cm^{-1}; MS (70 eV, EI): *m/z* (%) 431 (M^+, 1), 291 (13), 198 (20), 71 (20), 57 (100), 43 (54), 41 (26); HRMS (ESI) calcd for $C_{23}H_{33}N_2O_7$: 449.2282 $[M+NH_4]^+$; found: 449.2276.

4.1.17. 3β-Acetic acid-3a-benzo[1,3]dioxol-5-yl-1-formyl-6α-methoxy-2,3,3a,6,7,7a-hexahydro-1*H*-indol-3-yl ester (22). To a solution of **21** (26 mg, 0.06 mmol) in $ClCH_2CH_2Cl$ (2 mL) was added CF_3COOH (0.1 mL, 1.3 mmol) at room temperature. After 3 h, solid K_2CO_3 (ca. 200 mg) was added to the solution, and a small amount of Na_2SO_4 was also added. The undissolved material was filtered off and the solvent was removed. DMF (1 mL) and HCO_2Me (2 mL) were added to this crude amine and the solution was warmed at 90 °C for 6 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel (petroleum/EtOAc=3:1) to give **22** as a white film (19 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 0.62H), 8.25 (s, 0.46H), 6.89 (dd, *J*=4.8, 1.6 Hz, 1H), 6.86–6.83 (m, 1H), 6.77 (dd, *J*=8.4, 2.8 Hz, 1H), 6.24–6.19 (m, 1H), 5.96 (s, 2H), 5.88 (d, *J*=10.4 Hz, 1H), 5.67 (t, *J*=6.0 Hz, 0.63H), 5.50 (t, *J*=7.2 Hz, 0.5H), 4.22 (dd, *J*=8.0, 3.4 Hz, 1H), 4.09–4.02 (m, 1H), 3.89 (dd, *J*=12.4, 4.0 Hz, 1H), 3.40 (s, 1.35H), 3.39 (s, 1.70H), 3.31–3.25 (m, 1H), 2.75 (t, *J*=8.4 Hz, 0.48H), 2.31–2.24 (m, 0.56H), 2.03 (s, 1.75H), 1.99 (s, 1.35H), 1.99–1.95 (m, 0.64H), 1.69–1.65 (m, 0.68H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 170.0, 161.6, 160.6, 148.3, 147.0, 133.9, 133.6, 132.3, 129.6, 129.3, 127.7, 120.3, 120.0, 108.4, 108.3, 107.4, 101.3, 75.0, 74.9, 71.6, 71.1, 59.5, 59.4, 56.5, 56.3, 52.8, 51.5, 48.5, 47.3, 30.9, 26.1, 20.9, 20.8 ppm; IR (KBr): ν 3385, 2922, 1741, 1668, 1378, 1237, 1069, 1037 cm^{-1}; MS (70 eV, EI): *m/z* (%) 359 (M^+, 2), 198 (8), 115 (8), 84 (67), 49 (35), 47 (42), 43 (100); HRMS (ESI) calcd for $C_{19}H_{22}NO_6$: 360.1442 $[M+H]^+$; found: 360.1437.

4.1.18. (±)-Haemanthidine (1). A solution of formamide **22** (15 mg, 0.042 mmol) in freshly distilled $POCl_3$ (0.5 mL) was stirred at 80 °C under sealed tube. After 4 h, the mixture was cooled to room temperature and the excess $POCl_3$ was removed in vacuum. Aqueous THF (1:1, 1.0 mL) was added and the solution was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in MeOH (1.0 mL), and K_2CO_3 (50 mg, 0.36 mmol) was added to the solution. The mixture was stirred at room temperature for additional 1 h, and filtered. The filtrate was removed under vacuum and the resulted crude product was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH=6:1) to give **1** (10 mg, 76%) as an opaque film. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (s, 0.40H), 6.83 (s, 0.50H), 6.81 (s, 0.41H), 6.78 (s, 0.48H), 6.44–6.35 (m, 2H), 5.94–5.92 (m, 2H), 5.76 (s, 0.42H), 5.11 (s, 0.47H), 4.24 (dd, *J*=14.4, 7.0 Hz, 0.43H), 3.95–3.90 (m, 2.5H), 3.66 (dd, *J*=12.8, 4.4 Hz, 0.5H), 3.40 and 3.39 (2s, 3H), 3.42–3.38 (m, 0.5H), 3.28 (dd, *J*=12.4, 2.8 Hz, 0.5H), 3.03 (dd, *J*=13.6, 2.0 Hz, 0.5H), 2.36 (td, *J*=13.6, 4.4 Hz, 0.6H), 2.24 (td, *J*=13.6, 4.4 Hz, 1H), 2.05 (dd, *J*=13.6, 4.0 Hz, 1H), 2.02 (br, 0.5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 147.8, 146.9, 146.6, 135.7, 134.1, 132.9, 132.5, 128.0, 127.3, 126.2, 126.0, 109.5, 108.4, 102.9, 102.8, 101.1, 88.4, 85.8, 78.6, 78.1, 72.4, 72.1, 62.0, 58.0, 56.9, 56.6, 56.5, 51.9, 50.7, 50.3, 27.7, 27.4 ppm; IR (KBr): ν 3383, 2924, 1482, 1246, 1087, 1036, 933, 732 cm^{-1}; MS (70 eV, EI): *m/z* (%) 317 (M^+, 9), 284 (14), 268 (16), 227 (11), 209 (17), 201 (11), 200 (13), 199 (11), 103 (12), 102 (11), 88 (28), 73 (38), 71 (44), 47 (55), 41 (71), 39 (24); HRMS (ESI) calcd for $C_{17}H_{20}NO_5$: 318.1337 $[M+H]^+$; found: 318.1334.

4.1.19. (±)-Pretazettine (2). To a well-stirred solution of **1** (7.0 mg, 0.022 mmol) in MeOH (3 mL) was added methyl iodine (0.38 mL, 6.2 mmol). The reaction mixture was stirred for 6 h before removing the methanol in vacuum. The residue was treated with aqueous hydrochloric acid (2 mL, 0.01 M) for 1 min and the pH of the solution was adjusted to 8 with saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$ (6×5 mL), and the organic portions were combined, dried, and concentrated. The crude product was purified by flash column chromatography on silica gel ($MeOH/Et_3N/CHCl_3$=10:3:87) to afford **2** as a white film (6.9 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 1H), 6.77 (s, 1H), 6.13 (s, 1H), 5.93 (s, 2H), 5.89 (d, *J*=10.8 Hz, 1H), 5.52 (d, *J*=10.4 Hz, 1H), 4.34 (dd, *J*=11.2, 7.2 Hz, 1H), 4.18–4.14 (m, 1H), 3.44 (s, 3H), 3.01–2.96 (m, 2H), 2.67 (dd, *J*=9.6, 8.0 Hz, 1H), 2.55–2.48 (m, 1H), 2.50 (s, 3H), 1.77 (dd, *J*=11.2, 10.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 146.5, 135.4, 129.1, 128.9, 127.4, 108.1, 104.9, 101.2, 93.9, 73.9, 73.1, 64.1, 56.1, 54.1, 46.2, 43.3, 30.2 ppm; IR (KBr): ν 3350, 1482, 1254, 1089, 1036, 934 cm^{-1}; MS (70 eV, EI): *m/z* (%) 331 (M^+, 4), 316 (3), 247 (25), 225 (7), 201 (9), 139 (8), 128 (9), 115 (18), 85 (60), 83 (100), 82 (10), 77 (12), 74 (18), 70 (27), 57 (16), 55 (16), 44 (37), 42 (31); HRMS (ESI) calcd for $C_{18}H_{22}NO_5$: 332.1492 $[M+H]^+$; found: 332.1486.

4.1.20. (±)-Tazettine (3). To a well-stirred solution of **2** (6.9 mg, 0.0208 mmol) in MeOH (1.0 mL) was added 0.1 M NaOH (0.7 mL, 0.07 mmol), and the reaction mixture was stirred for 30 min before removing the MeOH in vacuum. The aqueous layer was extracted with $CHCl_3$ (7×5 mL), and the organic portions were combined, dried, and concentrated. The crude product was purified by flash column chromatography on silica gel ($MeOH/CHCl_3$=1:9) to afford **3** as a white film (6.3 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (s, 1H), 6.51 (s, 1H), 6.16 (d, *J*=10.2 Hz, 1H), 5.91 (s, 2H), 5.62 (d, *J*=10.2 Hz, 1H), 4.97 (d, *J*=15.0 Hz, 1H), 4.65 (d, *J*=15.0 Hz, 1H), 4.16–4.13 (m, 1H), 3.47 (s, 3H), 3.32 (d, *J*=10.2 Hz, 1H), 2.88 (br, 1H), 2.70 (d, *J*=10.2 Hz, 1H), 2.42 (s, 3H), 2.28–2.22 (m, 1H), 1.67–1.60 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 146.5, 130.8, 128.6, 128.1, 125.5, 109.3, 104.0, 102.1, 101.0, 72.9, 70.1, 65.6, 62.1, 56.1, 49.9, 41.9, 26.8 ppm; IR (KBr): ν 3196, 1475, 1453, 1380, 1127, 883, 706 cm^{-1}; MS (70 eV, EI): *m/z* (%) 331 (M^+, 6), 316 (3), 298 (5), 247 (56), 201 (13), 199 (15), 185 (10), 152 (20), 113 (12), 112 (11), 97 (23), 71 (64), 57 (87), 55 (51), 49 (60), 43 (100), 42 (95), 41 (80); HRMS (ESI) calcd for $C_{18}H_{22}NO_5$: 332.1492 $[M+H]^+$; found: 332.1490.

4.1.21. 3a-Benzo[1,3]dioxol-5-yl-6α-hydroxy-3β-trimethylsilanyloxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (18b). To a solution of **17** (150 mg, 0.52 mmol) in methanol (10 mL) was added $CeCl_3 \cdot 7H_2O$ (193 mg, 0.52 mmol) at room temperature and then $NaBH_4$ (49 mg, 1.3 mmol) was added. After stirring for 5 min, the reaction mixture was quenched with H_2O (0.5 mL). The solution was concentrated, and the residue was dissolved in CH_2Cl_2 (50 mL) and washed with H_2O (10 mL) back extracting the aqueous phase with CH_2Cl_2 (50 mL). The combined organic portions were concentrated and the residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=3:1) to give **18b** as a white amorphous (90 mg, 63%) and **18a** as white crystal (46 mg, 32%). Compound **18b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (d, J=1.6 Hz, 1H), 6.85 (dd, J=8.0, 2.0 Hz, 1H), 6.78 (br, 1H), 6.11 (d, J=10.8 Hz, 1H), 5.92 (d, J=10.0 Hz, 1H), 5.92 (s, 2H), 4.41 (br, 1H), 4.28 (br, 1H), 3.99 (br, 0.5H), 3.88 (br, 0.5H), 3.81 (dd, J=10.0, 7.2 Hz, 1H), 3.63 (br, 0.5H), 2.95 (t, J=10.0 Hz, 1H), 2.79 (br, 0.5H), 2.57 (d, J=12.4 Hz, 0.5H), 1.62 (br, 1H), 1.46 (s, 9H), −0.08 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 147.9, 146.4, 135.5, 133.9, 128.0, 127.7, 120.8, 118.9, 108.0, 107.7, 106.8, 101.1, 80.1, 79.6, 76.2, 75.5, 61.6, 53.1, 53.0, 52.3, 51.9, 51.4, 28.54, 28.46, −0.12 ppm; IR (KBr): ν 3405, 1690, 1488, 1397, 1250, 879, 843 cm^{-1}; MS (70 eV, EI): m/z (%) 447 (M^+, 0.3), 216 (100), 198 (37), 73 (45), 57 (78); HRMS (ESI) calcd for $C_{23}H_{33}NSiO_6Na$: 470.1969 $[M+Na]^+$; found: 470.1977.

4.1.22. 3a-Benzo[1,3]dioxol-5-yl-6β-methoxy-3β-trimethylsilanyloxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (19b). To a solution of **18b** (34 mg, 0.076 mmol) and NEt_3 (0.15 mL, 1.08 mmol) in THF (2 mL) was added Ms_2O (92 mg, 0.53 mmol) at 0 °C and the solution was stirred for 1 h. To this solution was added MeOH (2 mL) and the solution was stirred at 0 °C for 3 d. Ethyl acetate (50 mL) was added to this solution, and the organic layer was washed with saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=3:1) to give **19b** as a colorless amorphous (34 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82 (d, J=8.1 Hz, 1H), 6.76 (s, 2H), 6.16 (dd, J=12.3, 4.2 Hz, 1H), 6.01 (d, J=11.7 Hz, 1H), 5.95 (s, 2H), 4.34 (t, J=6.3 Hz, 1H), 4.05–3.96 (br, 1H), 3.71–3.66 (m, 2H), 3.55 (dd, J=10.5, 6.3 Hz, 0.5H), 3.38–3.34 (m, 0.32H), 3.34 (s, 3H), 3.19–3.06 (m, 1H), 2.83–2.78 (m, 0.55H), 2.50–2.45 (m, 0.33H), 1.49 and 1.46 (2s, 9H), −0.01 (s, 5H), −0.04 (s, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.32, 154.26, 147.9, 146.2, 136.4, 136.0, 130.0, 129.7, 129.6, 129.3, 120.2, 120.0, 108.0, 107.8, 107.6, 107.4, 101.1, 79.5, 79.1, 72.6, 72.4, 72.3, 61.5, 59.8, 59.4, 56.4, 55.9, 53.8, 52.7, 52.0, 28.5, 27.2, −0.07 ppm; IR (KBr): ν 1693, 1399, 1249, 1107, 1038, 936, 843 cm^{-1}; MS (70 eV, EI): m/z (%) 461 (M^+, 0.1), 230 (12), 199 (15), 198 (100), 73 (20), 57 (29), 41 (8); HRMS (ESI) calcd for $C_{24}H_{36}NSiO_6$: 462.2306 $[M+H]^+$; found: 462.2302.

4.1.23. (±)-Crinamine (4). To a solution of compound **19b** (20 mg, 0.043 mmol) in dry $ClCH_2CH_2Cl$ (2 mL) was added trifluoroacetic acid (0.1 mL, 1.3 mmol) at 0 °C. After the mixture was stirred for 8 h at room temperature, saturated aqueous $NaHCO_3$ (1 mL) was added, and the organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3×5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give crude amine. A solution of formalin (0.05 mL) in MeOH (0.1 mL) was added to this amine. After the solution was stirred for 10 min, 6 M aqueous hydrochloric acid (2.5 mL) was added. The mixture was warmed to 40 °C for 10 h, cooled to room temperature, and then basified by the dropwise addition of $NH_3 \cdot H_2O$. The resultant mixture was extracted with $CHCl_3$ (5×10 mL), and the organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=10:1) to afford **4** (10 mg, 76%, two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (s, 1H), 6.49 (s, 1H), 6.27 (s, 2H), 5.91 (d, J=2.0 Hz, 2H), 4.34 (d, J=17.0 Hz, 1H), 4.02 (dd, J=10.0, 6.0 Hz, 1H), 3.98–3.97 (m, 1H), 3.72 (d, J=17.0 Hz, 1H), 3.41 (s, 3H), 3.39–3.37 (m, 2H), 3.23 (dd, J=13.2, 4.4 Hz, 1H), 2.15–2.05 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6, 146.3, 136.2, 135.5, 126.8, 123.6, 106.9, 103.2, 100.9, 80.1, 76.1, 66.2, 63.6, 61.3, 55.8, 50.3, 30.3 ppm; IR (KBr): ν 3363, 2920, 1654, 1481, 1238, 1036, 935 cm^{-1}; MS (70 eV, EI): m/z (%) 270 (17), 269 (87), 268 (30), 240 (40), 224 (27), 211 (19), 181 (84), 153 (26), 115 (47), 77 (31), 71 (40), 69 (44), 57 (59), 55 (63), 43 (100), 41 (48); HRMS (ESI) calcd for $C_{17}H_{20}NO_4$: 302.1387 $[M+H]^+$; found: 302.1382.

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