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Synthesis of *Amaryllidaceae* alkaloids, siculine, oxocrinine, epicrinine, and buflavine

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Abstract—Three crinane type of alkaloids isolated from *Amaryllidaceae* family were synthesized by taking advantage of the PIFA-mediated intramolecular *p*-*p*′ diphenol coupling reaction of norbelladine derivatives. Furthermore, buflavine was also prepared by using the *p*-*p*′ diphenol coupling followed by dienone–phenol rearrangement as a key step.

1. Introduction

Amaryllidaceae family is an attractive source of alkaloids,[1] which are valuable as targets for total synthesis because of their unique structures, limited supply, and promising bioactivities such as cholinesterase inhibition which has being found in galanthamine.[2,3] The alkaloids are, in the metabolic pathways, synthesized at least by three different types of intramolecular phenol coupling, that is, the coupling between the positions of *p*-*o*′, *p*-*p*′, and *o*-*p*′ (phenol–*O*-methylcathecol) in *O*-methylnorbelladine (**1**). Galanth-amine, for example, is one of the *p*-*o*′ coupling products while lycoline is generated via the *o*-*p*′ coupling.[4] By mimicking the biosynthetic phenol coupling, we have recently attained the total syntheses of galanthamine and narwedine, in which *O*-methylcathecol ring of **1** was replaced with 2-*O*-methylpyrogarrole in order to avoid the mixture of two products resulting from the *p*-*o*′ and the *p*-*p*′ coupling.[5] The *p*-*p*′ phenol coupling of **1** would generate maritidine (**2**), which was synthesized by several groups taking advantage of effective carbon–carbon bond formation such as oxidative phenol coupling[6] and Heck reaction[7] as key steps. Demethylation, epimerization, and/or formal oxidation of methoxy groups of maritidine (**2**) would provide crinine (**3**)[8] and its derivatives, for example, siculine (**4**) from *Sternbergia sicula*,[9] oxocrinine (**5**) isolated from *Crinum americanum*,[10] and epicrinine (**6**) from *Nerine bowdenii*[11] (Fig. 1).

These could be promising candidates as excellent lead compounds for pharmaceutical research since crinane,[12] the common structure of the crinine alkaloids, exhibited antivirus, antitumor, and anticholinergic activities.[13] Furthermore, it is also an acceptable hypothesis that buflavine (**7**) isolated from *Boophane flava*[14] might be also generated by the *p*-*p*′ coupling followed by dienone–phenol rearrangement. In this paper, we would like to report

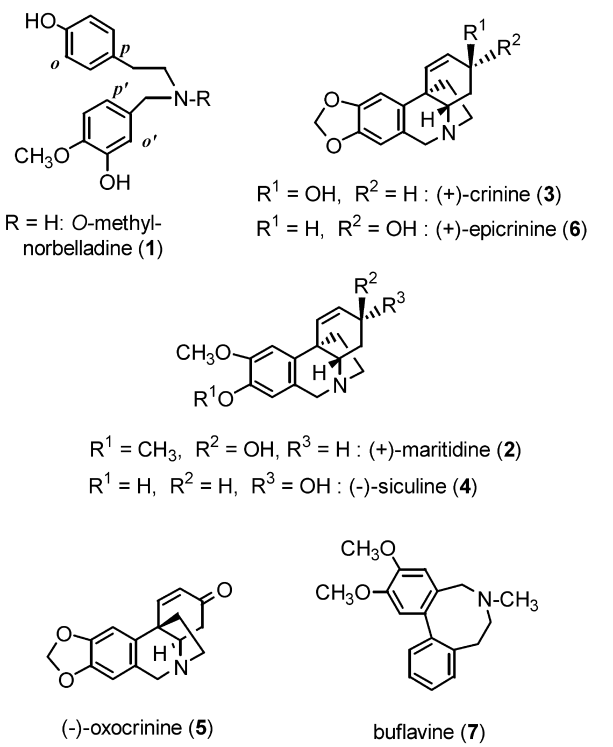

Figure 1. Structures of *Amaryllidaceae* alkaloids.

Keywords: Phenol coupling; Phenyliodine(III) bis(trifluoroacetate) (PIFA); Siculine; Oxocrinine; Epicrinine; Buflavine.
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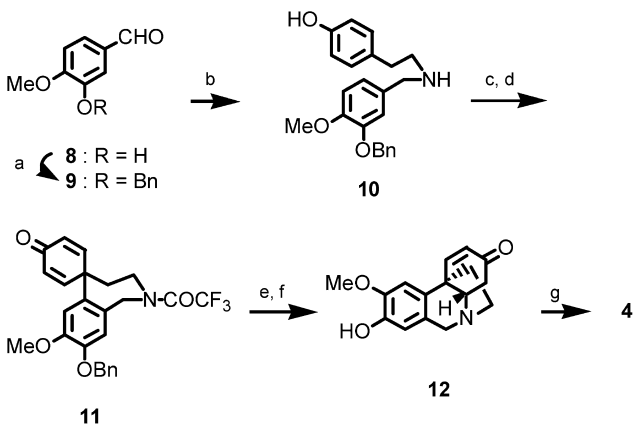


a: BnCl, K_2CO_3, DMF, 90 °C, 20 min., **b**: 1) tyramine, 2) $NaBH_4$, r.t., 1h. (82 % from **8**), **c**: $(CF_3CO)_2O$, pyridine, r.t., 1d. (quant.), **d**: PIFA, CF_3CH_2OH, -25 °C, 30 min. (78 %), **e**: BCl_3, CH_2Cl_2, -78 °C, 3d. (79 %), **f**: 10% KOH aq., r.t., 10 min. (87 %), **g**: L-Selectride, THF, - 78 °C, 1d. (53 %).

Scheme 1. Synthetic route of siculine (**4**).

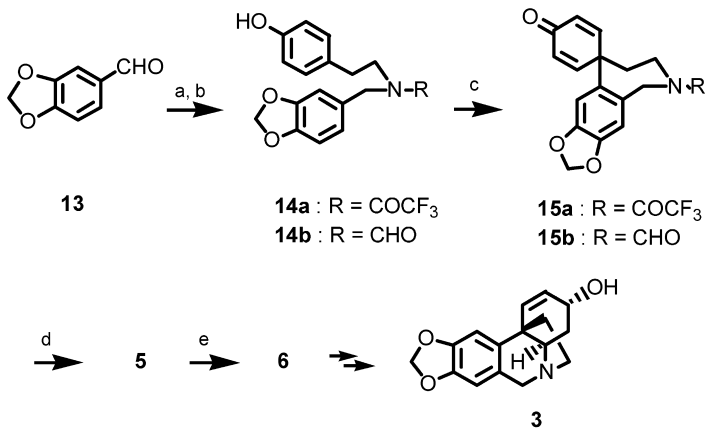
the facile synthesis of the alkaloids generated via the *p-p′* oxidative phenol coupling as a part of our synthetic studies of *Amaryllidaceae* alkaloids.

2. Result and discussion

We started our synthetic study of these alkaloids with the synthesis of siculine (**4**), of which synthetic studies have not been reported so far. After the protection of phenolic group of isovanillin (**8**) with benzyl group, obtained 3-*O*-benzylisovanillin (**9**) was exposed by reductive amination with tyramine in the presence of sodium borohydride to afford phenethylbenzylamine (**10**). Protection of the amino group of **10** with trifluoroacetyl group, followed by the oxidation with phenyliodine(III) bis(trifluoroacetate) (PIFA)[5,6c,d,15] proceeded the phenol coupling to afford dienone (**11**). Deprotection of the benzyl group of **11** with boron trichloride and successive hydrolysis of trifluoroacetylamide group with 10% potassium hydroxide in methanol gave the intramolecular Michael adduct (**12**). Reduction of **12** with L-Selectride afforded siculine (**4**) (Scheme 1).

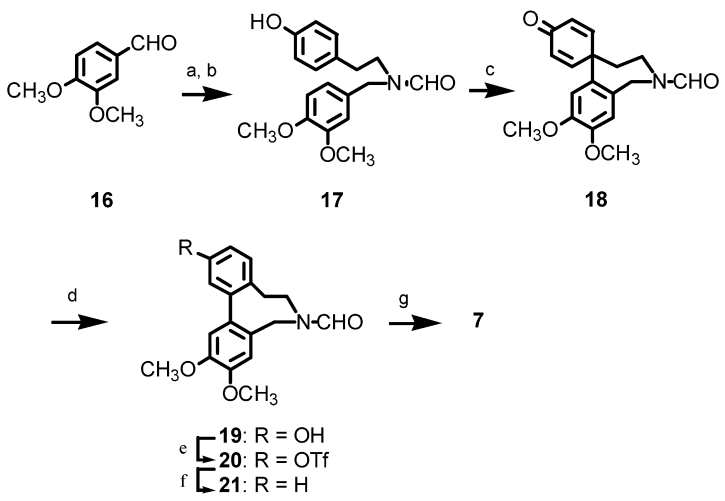
This strategy is also applicable to the synthesis of oxocrinine (**5**)[6i,16] and its related alkaloids. Reductive amination of piperonal (**13**) and tyramine was followed by *N*-acylation with either trifluoroacetic anhydride or ethyl formate to give **14a**, **14b**. The obtained **14a**, **14b** were, respectively, allowed to the oxidative coupling with PIFA giving the desired coupled products **15a**, **15b** in excellent yields. Respective hydrolysis of the protecting groups of **15a** and **15b** with 10% potassium hydroxide in methanol followed by spontaneous intramolecular Michael addition afforded oxocrinine (**5**), and successive reduction with L-Selectride gave epicrinine (**6**)[16a,17] that can be converted to crinine (**3**) by the known method (Scheme 2).[18]

Next, we tried to synthesize buflavine (**7**), which was prepared by Kobayashi 25 years prior to its isolation and characterization.[19] Since it has been isolated in 1995, buflavine (**7**) was synthesized by three groups using the biaryl coupling, that is, Meyers' coupling[20] and Suzuki–Miyaura coupling reactions.[21] However, tedious procedures were required to prepare arylborate or polymethoxybenzene derivatives before employing the coupling reactions. Being encouraged by the usefulness of the *p-p′* phenol coupling with PIFA for the synthesis of *Amallylidaceae* alkaloids as mentioned above, in addition to the previous reports,[5] we confirmed that applying the phenol coupling could effectively revise the synthetic route of **7**. Reductive amination of 3,4-dimethoxybenzaldehyde (**16**) with tyramine in the presence of sodium borohydride was first conducted to give the amine, and successive protection of the amino group with ethyl formate gave **17**. Unfortunately, oxidative coupling reactions that are reported to accompany



a: 1) tyramine, 2) $NaBH_4$, r.t., 1d., **b**: $(CF_3CO)_2O$ or HCO_2Et (quant. from **13**), **c**: PIFA, CF_3CH_2OH (**14a**: - 40 °C, 20 min., 74 %, **14b**: 0 °C, 30 min., 91 %), **d**: 10% KOH aq., MeOH (87 % from **15a**, 61 % from **15b**), **e:** L-Selectride, THF, - 78 °C, 1d. (82 %).

Scheme 2. Synthetic route of oxocrinine (**5**) and epicrinine (**6**).



a: 1) tyramine, r.t., 6h., 2) $NaBH_4$, r.t., 4h., **b**: HCO_2Et, reflux, 1d., (96 % from **16**), **c**: PIFA, r.t., 30 min., (92 %), **d**: methanesulfonic acid, r.t., 1d., (92 %), **e**: Tf_2O, 0 °C to r.t., 8h., (96 %), **f**: $Pd(OAc)_2$, PPh_3, Et_3N, HCO_2H, 60 °C, 2d., (87 %), **g**: $LiAlH_4$, r.t., 15h., (94 %).

Scheme 3. Synthetic route of buflavine (**7**).

eight-membered ring formation, for example, PIFA-mediated reaction with boron trifluoride etherate,[22] did not give any satisfactory results in this case. Therefore, the seven-membered product **18** of the *p*-*p*′ oxidative coupling of **17** with PIFA[18] was treated with methanesulfonic acid to convert it to **19** by dienone–phenol rearrangement.[6h] In order to deoxygenate the phenolic hydroxyl group, **19** was converted to triflate (**20**) followed by palladium-catalyzed reduction to afford **21**. Reduction of formamide group of **21** with lithium aluminum hydride gave buflavine (**7**) (Scheme 3). As expected, the overall yield of this synthetic route (64%) is much higher than those reported so far in the literatures.[20,21]

3. Conclusion

As mentioned above, we have succeeded in the first synthesis of siculine (**4**), the synthesis of buflavine (**7**) with the highest overall yield reported so far, and the short step synthesis of oxocrinine (**5**) and epicrinine (**6**), by applying the PIFA-mediated *p*-*p*′ diphenol coupling of norbelladine derivatives. The coupling reaction is applicable even on the industrial scale since it generates only volatile iodobenzene and trifluoroacetic acid. Further study on the synthesis of chiral compounds of **3**–**6** is now in progress.

4. Experimental

4.1. General

Melting points were taken on a micro hot-stage apparatus (Yanagimoto) and were uncorrected. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8300 diffraction grating infrared spectrophotometer and ^1H- and ^{13}C NMR spectra were obtained on a JEOL JNM-AL300, a Varian Unity INOVA-400 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-SX 102A QQ or a JEOL JMS-GC-mate mass spectrometer. Combustion analysis was done on a Perkin–Elmer Series II CHNS/O Analyzer 2400. Specific rotations were recorded on a Horiba SEPA-200 automatic digital polarimeter. Their data were recorded with Shimadzu C-R6A Chromatopac. Acetate buffer was adjusted with a Horiba pH meter F-13. Wakogel C-200 (silica gel) (100–200 mesh, Wako) was used for open column chromatography. Flash column chromatography was performed with Silica Gel 60N (Kanto Chemical Co., Inc.). Silica gel 60 F-254 plates (Merck) were used for thin layer chromatography (TLC). Preparative TLC (PTLC) was done with Silica gel 60 F-254 plate (0.25 mm, Merck) or Silica gel 60 F-254 plate (0.5 mm, Merck). When necessary, compounds were further purified by a recycle HPLC (JAI LC-908) on GPC column (JAIGEL 1H and 2H) after purification on silica gel.

4.2. Materials

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl, and dichloromethane was distilled from CaH_2, after washing with water 10 times, to remove methanol contaminants. Most of the reagents were obtained from Wako Pure Chemical Industries, Ltd., Nakalai Tesque, Inc., Aldrich Chemical Inc.

4.2.1. *N*-3′-Benzyloxy-4′-methoxyphenylmethyl-[2-(4-hydroxyphenyl)]ethylamine (10). Potassium carbonate (4.4 g, 32.0 mmol) and benzyl chloride (2.3 mL, 19.6 mmol) were successively added to a solution of isovanillin (**8**) (2.5 g, 16.3 mmol) in *N*,*N*-dimethylformamide (16 mL), and the reaction mixture was stirred for 3 h at 90 °C. After the reaction, the mixture was concentrated in vacuo and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and

concentrated in vacuo. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 3/1) afforded 3′-*O*-benzylisovanillin (**9**). Tyramine (2.9 g, 21.0 mmol) was added to a solution of **9** in methanol (40 mL), and the reaction mixture was stood to stir for 1 day. Sodium borohydride (728.2 mg, 19.2 mmol) was added to the reaction mixture at 0 °C and the mixture was stirred for another 3 h at room temperature. Crystal needles (**10**) (4.8 g, 82%) appearing in the reaction vessel were collected by filtration. Mp 135–136 °C (methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.23 (m, 5H), 6.96 (d, J=8.6 Hz, 2H), 6.86 (s, 1H), 6.78 (s, 2H), 6.65 (d, J=8.6 Hz, 2H), 4.98 (s, 2H), 3.83 (s, 3H), 3.68 (s, 2H), 2.81 (t, J=6.8 Hz, 2H), 2.71 (t, J=6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.23, 148.80, 148.12, 137.02, 131.50, 130.22, 129.71, 128.42, 127.73 127.38 121.13, 115.71, 114.17, 111.62, 70.69, 56.00, 53.25, 49.92, 34.60; IR ($CHCl_3$): 1612, 1593, 1514 cm^{-1}; HRMS calcd for $C_{23}H_{25}NO_3$ (M^+): 363.1834, found: 363.1838. Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 76.02; H, 6.94; N, 3.82.

4.2.2. Preparation of dienone (11). Trifluoroacetic anhydride (0.93 mL, 6.6 mmol) was added to a solution of **10** (1.0 g, 2.8 mmol) in pyridine (10 mL) at 0 °C. The reaction mixture was stirred for 1 day at 0 °C, and then the methanol was added to quench the reaction. The mixture was concentrated in vacuo and extracted with ethyl acetate. The organic layer was successively washed with 1 M HCl, saturated $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 1/1) afforded trifluoroacetamide (1.3 g, 100%) as a colorless oil. ^{1}H NMR spectral and HRMS data were completely coincided with those in the literature;[6g] ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.89, 154.69, 149.59, 149.46, 148.15, 148.13, 136.58, 136.52, 129.75, 129.70, 129.63, 128.88, 128.55, 128.46, 127.95, 127.84, 127.63, 127.27, 127.21, 126.70, 121.24, 120.65, 115.60, 115.44, 113.96, 113.41, 111.74, 111.66, 71.01, 70.84, 55.96, 55.93, 51.13, 49.40, 48.22, 48.19, 48.11, 34.14, 31.73; IR ($CHCl_3$): 1686, 1516 cm^{-1}. To a solution of the trifluoroacetamide (1.2 g, 2.5 mmol) in CF_3CH_2OH (12 mL), was added a solution of phenyliodine(III) bis(trifluoroacetate) (1.2 g, 2.8 mmol) in CF_3CH_2OH (12 mL) at −25 °C. The reaction mixture was stirred for 30 min, and then concentrated in vacuo. Purification of the residue by column chromatography (silica gel, ethyl acetate) afforded **11** (0.9 g, 78%) as an amorphous powder. ^{1}H NMR, IR spectral and HRMS data were completely coincided with those in the literature;[6g] ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.23, 185.09, 152.88, 152.46, 149.34, 149.20, 147.40, 147.14, 136.43, 136.37, 128.58, 128.53, 128.42, 128.33, 128.01, 127.98, 127.91, 127.67, 127.38, 127.26, 127.16, 127.10, 116.48, 115.91, 113.32, 113.26, 71.12, 70.94, 56.10, 55.97, 48.63, 48.42, 48.28, 48.14, 45.30, 45.27, 44.17, 35.81, 33.83.

4.2.3. 8-Demethyl-3-oxomaritidine (12). Boron trichloride (0.78 mL, 1.0 M solution in dichloromethane, 0.78 mmol) was added to a solution of **11** (238 mg, 0.52 mmol) in dichloromethane (3 mL) at −78 °C. The reaction mixture was stirred for 3 days at −78 °C, and then water was added to quench the reaction. The mixture was extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 2/3) afforded a debenzylated compound (150.9 mg, 79%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, J=10.3 Hz, 1H), 6.95 (d, J=10.3 Hz, 1H), 6.90 and 6.74 (s, 1H), 6.51 (s, 1H), 6.33 (d, J=6.2 Hz, 1H), 6.31 (d, J=6.2 Hz, 1H), 5.76 (brs, 1H, OH), 4.77 and 4.74 (s, 2H), 3.86 (dd, J=12.5, 8.1 Hz, 2H), 3.76 and 3.75 (s, 3H), 2.44–2.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.39, 185.26, 153.15, 152.76, 146.33, 144.92, 144.90, 128.63, 128.50, 127.15, 127.01, 117.61, 117.53, 116.31, 112.02, 111.94, 55.97, 55.91, 48.51, 48.22 48.13, 45.34, 45.30, 44.23, 35.83, 33.89; IR ($CHCl_3$): 3541, 1690, 1665, 1626, 1591, 1516 cm^{-1}; HRMS calcd for $C_{18}H_{16}NO_4F_3$ (M^+): 367.1031, found: 367.1034. To a solution of the debenzylated compound (25 mg, 0.07 mmol) in methanol (0.5 mL), was added 10% aqueous solution of potassium hydroxide (0.5 mL) and stirred for 30 min at room temperature. The reaction mixture was concentrated in vacuo and extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 10/1) afforded **12** (16.1 mg, 87%) as colorless crystals; mp 252–255 °C (decomp.) (*n*-hexane) (lit.,[6a,c] mp 250–252 °C, decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J=10.3 Hz, 1H), 6.88 (s, 1H), 6.61 (s, 1H), 6.11 (d, J=10.3 Hz, 1H), 4.40 (d, J=16.8 Hz, 1H), 3.92 (s, 3H), 3.81 (d, J=16.8 Hz, 1H), 3.67 (dd, J=12.9, 5.6 Hz, 1H), 3.56 (ddd, J=13.3, 10.1, 3.5 Hz, 1H), 3.03 (ddd, J=14.2, 7.9, 5.3 Hz, 1H), 2.71 (dd, J=16.8, 5.7 Hz, 1H), 2.49 (dd, J=16.8, 13.0 Hz, 1H), 2.40 (ddd, J=12.4, 9.0, 3.7 Hz, 1H), 2.19 (ddd, J=12.1, 10.5, 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.17, 149.56, 145.29, 144.59, 134.17, 128.74, 125.78, 113.26, 104.53, 68.94, 61.32, 56.10, 54.05, 44.77, 44.46, 40.12; IR ($CHCl_3$): 3543, 1680, 1506 cm^{-1}; HRMS calcd for $C_{16}H_{17}NO_3$ (M^+): 271.1208, found: 271.1205.

4.2.4. Siculine (4). Lithium tri-*sec*-buthylborohydride (L-Selectride®) (0.22 mL, 1.0 M solution in THF, 0.22 mmol) was added to a solution of **12** (24.4 mg, 0.09 mmol) in THF (5 mL) at −78 °C, and the reaction mixture was stirred for 1 day at −78 °C. After quenching the reaction with aqueous solution of Na_2SO_4, the mixture was extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 5/1) afforded siculine (**4**) (13.1 mg, 53%) as colorless crystals. ^{1}H NMR spectral and EI-MS data were completely coincided with those in the literature;[9] mp 235–239 °C (decomp.) (chloroform); ^{13}C NMR (100 MHz, CD_3OD): δ 148.32, 146.79, 135.70, 133.08, 129.11, 128.07, 122.28, 114.75, 107.36, 68.23, 67.45, 60.99, 56.61, 53.56, 44.38, 33.93; IR ($CHCl_3$): 3331, 2963, 2934, 1506, 1466, 1447, 1315, 1275, 1240, 1198, 1128, 1094, 1026, 868 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO_3$ (M^+): 273.1365, found: 273.1370.

4.2.5. *N*-Trifluoroacetyl-*N*-3′, 4′-methylenedioxyphenylmethyl-[2-(4-hydroxyphenyl)]ethylamine (14a). Tyramine (1.1 g, 8.0 mmol) was added to a solution of piperonal (**13**) (1.0 g, 6.7 mmol) in methanol (8 mL), and the reaction mixture was stirred for 6 h at room temperature.

Sodium borohydride (277.3 mg, 7.3 mmol) was added to the mixture and stirred for 1 day. The reaction mixture was concentrated in vacuo, and extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo and treated for further reaction without purification. Trifluoroacetic anhydride (2.4 mL, 16.8 mmol) was added to a solution of the residue in pyridine (18 mL) and the mixture was stirred for 2 h at 0 °C. After quenching the reaction with methanol, the mixture was concentrated in vacuo and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 2/1) afforded **14a** (3.0 g, 100%) as colorless crystals. All the spectral data was coincided with those in the literature.[23]

4.2.6. *N*-Formyl-*N*-3′,4′-methylenedioxyphenylmethyl-[2-(4-hydroxyphenyl)]ethylamine (14b). Tyramine (2.2 g, 16.0 mmol) was added to a solution of piperonal (**13**) (2.0 g, 13.3 mmol) in methanol (32 mL) and the mixture was stirred at room temperature for 3 h. Sodium borohydride (553.4 mg, 14.6 mmol) was added and stirred for 1 h at room temperature. After the reaction, the mixture was concentrated in vacuo, and extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo and treated for further reaction without purification. The residue was dissolved in ethyl formate (40 mL) and refluxed for 2 days, and the mixture was concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 30/1) afforded **14b** (4.3 g, 100%) as colorless crystals; mp 113–115 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 and 7.80 (s, 1H), 7.01 (d, J=8.4 Hz, 1H), 6.92 (d, J=8.4 Hz, 1H), 6.78–6.71 (m, 4H), 6.63 and 6.61 (s, 2H), 4.46 (s, 1H), 4.15 (s, 1H), 3.43 (t, J=7.4 Hz, 1H), 3.33 (t, J=6.5 Hz, 1H), 2.72 (t, J=7.0 Hz, 1H), 2.70 (t, J=6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.35, 162.91, 155.34, 154.89, 148.24, 148.05, 147.57, 147.21, 129.90, 129.85, 129.35, 128.80, 121.81, 121.18, 115.73, 115.43, 108.77, 108.41, 108.24, 107.86, 101.28, 101.12, 51.68, 48.58, 45.34, 43.58, 33.71, 32.33; IR ($CHCl_3$): 1665, 1516, 1504 cm^{-1}; HRMS calcd for $C_{17}H_{17}NO_4$ (M^+): 299.1157, found: 299.1153. Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.30; H, 5.77; N, 4.71.

PIFA oxidation of **14a**. Phenyliodine(III) bis(trifluoroacetate) (64 mg, 0.15 mmol) in CF_3CH_2OH (2 mL) was added to a solution of **14a** (50 mg, 0.14 mmol) in CF_3CH_2OH (3 mL) at −40 °C. The reaction mixture was stirred for 20 min at −40 °C, and then concentrated in vacuo. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 1/1) afforded **15a** (36.9 mg, 74%) as a colorless crystals. All the spectral data was coincided with those in the literature.[6g]

PIFA oxidation of **14b**. Phenyliodine(III) bis(trifluoroacetate) (790.2 mg, 1.8 mmol) in CF_3CH_2OH (10 mL) was added to a solution of **14b** (0.5 g, 1.7 mmol) in CF_3CH_2OH (20 mL) at 0 °C. The reaction mixture was stirred for 30 min and then concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 20/1) afforded **15b** (0.45 g, 91%) as colorless crystals; mp 195–198 °C (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 and 8.18 (s, 1H), 7.03 (d, J=10.3 Hz, 1H), 6.95 (d, J=10.3 Hz, 1H), 6.80 and 6.65 (s, 1H), 6.56 and 6.54 (s, 1H), 6.32–6.27 (m, 2H), 5.95 and 5.92 (s, 2H), 4.56 and 4.60 (s, 2H), 3.79 and 3.74 (t, J=6.1 Hz, 2H), 2.36–2.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.30, 185.18, 162.60, 161.56, 153.05, 152.46, 147.61, 147.41, 147.06, 147.02, 130.85, 130.75, 129.52, 129.45, 127.24, 127.03, 110.87, 110.18, 109.58, 109.26, 101.73, 101.60, 49.93, 48.50, 48.40, 45.62, 45.30, 40.33, 36.06, 34.23; IR ($CHCl_3$): 1666, 1626, 1506 cm^{-1}; HRMS calcd for $C_{17}H_{15}NO_4$ (M^+): 297.1001, found: 297.1006. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.41; H, 5.07; N, 4.63.

4.2.7. Oxocrinine (5) from 15a. 10% aqueous solution of potassium hydroxide (1.5 mL) was added to a solution of **15a** (110 mg, 0.30 mmol) in methanol (1.5 mL) at room temperature. The reaction mixture was stirred for 9 h at room temperature, and then concentrated in vacuo. The residue was extracted with chloroform and the organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 10/1) afforded **5** (70.6 mg, 87%) as colorless crystals, accompanied with the starting material **15a** (7.0 mg, 6%). Mp 171–173 °C (ethyl acetate) (lit.,[16a] mp 175–178 °C; lit.,[16b] 170–172 °C). All the spectral data of **5** was completely coincided with those in the literature.[10,16]

4.2.8. Preparation of oxocrine (5) from 15b. 10% aqueous solution of potassium hydroxide (1.0 mL) was added to a solution of **15b** (45.5 mg, 0.15 mmol) in methanol (1.5 mL) at room temperature. The reaction mixture was stirred for 9 h at 60 °C, and then concentrated in vacuo. The residue was extracted with chloroform and the organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 10/1) afforded **5** (25.3 mg, 61%) as colorless crystals. All the spectral data of **5** was completely coincided with those in the literature.[10,16]

4.2.9. Epicrinine (6). Lithium tri-*sec*-buthylborohydride (L-Selectride®) (0.37 mL, 1.0 M solution in THF, 0.37 mmol) was added to a solution of **5** (42 mg, 0.16 mmol) in THF (1 mL) at −78 °C, and the reaction mixture was stirred for 1 day at −78 °C. The reaction was quenched with saturated aqueous Na_2SO_4, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 5/1) afforded epicrinine (**6**) (34.6 mg, 82%) as colorless crystals. Mp 232–235 °C (decomp.) (ethyl acetate) (lit.,[16a] mp 235–239 °C; lit.,[18] 234–235 °C). All the spectral data was coincided with those in the literature.[11,17]

4.2.10. *N*-Formyl-*N*-3′,4′-dimethoxyphenylmethyl-[2-(4-hydroxyphenyl)]ethylamine (17). Tyramine (990.6 mg, 7.22 mmol) was added to a solution of 3,4-dimethoxybenzaldehyde (**16**) (1.0 g, 6.02 mmol) in methanol (12 mL), and the reaction was stirred for 6 h at room temperature. Sodium borohydride (250.5 mg, 6.62 mmol) was added to the mixture, and it was stirred for 4 h at room temperature

and concentrated in vacuo. The residue was extracted with chloroform and the organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo, and treated for further reaction without purification. The residue was dissolved in ethyl formate (30 mL) and refluxed for 1 day, and then concentrated in vacuo. Crystallization of the residue from diethyl ether afforded **17** (1.82 g, 96%) as colorless crystals; mp 95–97 °C (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 and 7.81 (s, 1H), 6.99 (d, J=8.6 Hz, 1H), 6.89 (d, J=8.6 Hz, 1H), 6.84–6.61 (m, 5H), 4.50 and 4.20 (s, 2H), 3.869 and 3.866 (s, 3H), 3.84 and 3.83 (s, 3H), 3.45 and 3.34 (t, J=6.9 Hz, 2H), 2.71 and 2.70 (t, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.39, 163.01, 155.51, 155.13, 149.29, 149.21, 148.90, 149.61, 129.78, 129.69, 129.55, 128.59, 127.86, 120.82, 120.15, 115.68, 115.41, 111.46, 111.18, 110.93, 110.41, 55.88, 55.83, 51.70, 48.69, 45.45, 43.65, 33.68, 32.33; IR ($CHCl_3$): 1663, 1614, 1595 cm^{-1}; HRMS calcd for $C_{18}H_{21}NO_4$ (M^+): 315.1470, found: 315.1465. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.70; H, 6.70; N, 4.59.

PIFA oxidation of **17**. Phenyliodine(III) bis(trifluoroacetate) (1.5 g, 3.49 mmol) in CF_3CH_2OH (10 mL) was added to a solution of **17** (1.0 g, 3.17 mmol) in CF_3CH_2OH (20 mL). The reaction mixture was stirred for 30 min at room temperature, and then concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 50/1) afforded **18** (912.8 mg, 92%) as colorless crystals; mp 187–189 °C (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 and 8.20 (s, 1H), 7.09 and 6.99 (d, J=10.2 Hz, 2H), 6.82 and 6.66 (s, 1H), 6.54 and 6.53 (s, 1H), 6.32 and 6.31 (d, J=10.2 Hz, 2H), 4.12 and 4.65 (s, 2H), 3.891 and 3.885 (s, 3H), 3.82 and 3.77 (t, J=6.2 Hz, 2H), 3.734 and 3.731 (s, 3H), 2.38–2.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.40, 185.28, 162.57, 161.53, 153.25, 152.66, 148.30, 148.05, 147.99, 147.97, 129.62, 129.51, 128.10, 127.97, 127.11, 126.89, 113.64, 113.01, 112.62, 112.25, 55.93, 55.91, 55.87, 49.83, 48.39, 48.26, 45.65, 45.15, 40.31, 36.24, 34.38; IR ($CHCl_3$): 1666, 1624, 1609, 1522 cm^{-1}; HRMS calcd for $C_{18}H_{19}NO_4$ (M^+): 313.1314, found: 313.1317. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.71; H, 6.12; N, 4.60.

4.2.11. Dienone–phenol rearrangement of 18. Methanesulfonic acid (1.5 mL) was added to **18** (50 mg, 0.16 mmol) at room temperature, and stirred for 1 day. The mixture was neutralized with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, ethyl acetate) afforded **19** (45.9 mg, 92%) as colorless crystals; mp 229–231 °C (methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 and 8.12 (s, 1H), 7.33 (s, 1H), 7.14 and 7.11 (d, J=8.2 Hz, 1H), 6.91 and 6.88 (d, J=2.6 Hz, 1H), 6.83 and 6.80 (d, J=2.7 Hz, 1H), 6.82 and 6.77 (s, 1H), 6.47 and 6.45 (brs, 1H, OH), 5.11 and 5.07 (s, 1H), 3.93 and 3.89 (s, 3H), 3.88 and 3.86 (s, 3H), 3.84–3.81 (m, 1H), 3.22 and 3.19 (d, J=10.9, 1H), 3.22 and 3.18 (s, 1H), 2.91 and 2.88 (d, J=6.4 Hz, 1H), 2.35 and 2.32 (d, J=11.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.57, 162.07, 154.73, 148.62, 148.13, 141.36, 140.91, 132.54, 131.11, 130.66, 128.03, 127.87, 116.50, 116.06, 115.47, 115.29, 113.62, 112.38, 111.81, 111.42, 60.49, 55.94, 55.92, 50.18, 49.85, 44.55, 43.17, 34.32, 32.41; IR ($CHCl_3$): 1659, 1607, 1578, 1518 cm^{-1}, HRMS calcd for $C_{18}H_{19}NO_4$ (M^+): 313.1314, found: 313.1318. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.71; H, 6.12; N, 4.42.

4.2.12. *N*-Formyl-2,3-dimethoxy-10-trifluoromethanesulfonyloxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (20). Trifluoromethanesulfonic anhydride (0.065 mL, 0.38 mmol) was added to a solution of **19** (50 mg, 0.16 mmol) in pyridine (1 mL) at 0 °C. The reaction mixture was stirred for 5 h at 0 °C and then continued to stir for another 3 h at room temperature. The reaction was quenched with water and the mixture was extracted with ethyl acetate. The organic layer was washed with 1 M HCl, saturated $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 10/1) afforded **20** (44.9 mg, 63%) as colorless crystals, accompanied with the starting material **19** (17 mg, 34%); mp 124–125 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 and 8.13 (s, 1H), 7.41–7.25 (m, 4H), 6.76 and 6.73 (s, 1H), 5.16 and 5.13 (s, 1H), 3.95 (s, 3H), 3.93 (m, 1H), 3.92 and 3.91 (s, 3H), 3.25 and 3.22 (d, J=10.8 Hz, 1H), 3.11 and 3.08 (s, 1H), 3.03 and 3.00 (d, J=6.6 Hz, 1H), 2.45 and 2.41 (dd, J=11.1, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.23, 161.75, 149.56, 149.34, 148.99, 148.41, 147.83, 147.75, 142.61, 142.10, 140.48, 139.73, 131.38, 131.27, 130.87, 130.48, 128.44, 128.29, 122.46, 122.09, 120.90, 120.73, 120.32, 117.13, 113.94, 112.23, 111.64, 111.57, 56.11, 56.07, 56.01, 50.03, 48.88, 44.39, 42.30, 34.83, 32.96; IR ($CHCl_3$): 1665, 1607, 1574, 1518 cm^{-1}; HRMS calcd for $C_{19}H_{18}NO_4SF_3$ (M^+): 445.0807, found: 445.0804. Anal. Calcd for $C_{19}H_{18}NO_4SF_3$: C, 51.23; H, 4.07; N, 3.14. Found: C, 51.49; H, 4.25; N, 3.12.

4.2.13. *N*-Formyl-2,3-dimethoxy-5,6,7,8-tetrahydrodibenz-[*c*,*e*]azocine (21). Palladium acetate (4.3 mg, 0.019 mmol), triphenylphosphine (10.1 mg, 0.039 mmol), formic acid (0.007 mL, 0.193 mmol) and triethylamine (0.041 mL, 0.291 mmol) were added to a solution of **20** (43.0 mg, 0.097 mmol) in *N*,*N*-dimethylformamide (1 mL), and then the reaction mixture was stirred for 2 days at 60 °C. The mixture was concentrated in vacuo and the residue was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 5/1) afforded **21** (25.0 mg, 87%) as colorless crystals; mp 185–187 °C (methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 and 8.13 (s, 1H), 7.40–7.26 (m, 5H), 6.79 (s, 1H), 5.13 and 5.10 (s, 1H), 3.95 (s, 3H), 3.91–3.86 (m, 1H), 3.90 and 3.89 (s, 3H), 3.26 and 3.22 (d, J=11.1 Hz, 1) 3.16 and 3.12 (s, 1H), 2.98 and 2.95 (d, J=6.6 Hz, 1H), 2.44 and 2.40 (dd, J=11.0, 1.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.25, 161.76, 148.81, 148.68, 148.56, 148.08, 140.13, 139.98, 139.68, 139.18, 132.98, 132.54, 129.82, 129.49, 129.40, 128.35, 128.33, 128.18, 128.13, 126.74, 126.60, 113.64, 112.44, 111.87, 111.41, 56.02, 55.95, 55.88, 49.99, 49.29, 44.39, 42.66, 35.25, 33.37; IR ($CHCl_3$): 1661, 1607, 1518 cm^{-1}; HRMS calcd for $C_{18}H_{19}NO_3$ (M^+): 297.1365, found: 297.1361. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.70; H, 6.35; N, 4.74.

4.2.14. Buflavine (7). A suspension of $LiAlH_4$ (4.5 mg, 0.12 mmol) in THF was added to a solution of **21** (23.4 mg, 0.08 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred for 15 h at room temperature, and then the reaction was quenched with saturated solution of Na_2SO_4, extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 5/1) afforded **7** (21.1 mg, 94%) as a viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.22 (m, 4H), 6.91 (s, 1H), 6.80 (s, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.54 (d, J=13.6 Hz, 1H), 3.27 (t, J=9.3 Hz, 1H), 3.08 (d, J=13.6 Hz, 1H), 2.77–2.66 (m, 1H), 2.60–2.49 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.41, 147.89, 141.22, 140.00, 132.96, 132.35, 129.65, 129.44, 129.02, 127.88, 126.08, 113.58, 112.14, 58.65, 58.29, 55.93, 45.82, 32.49; IR ($CHCl_3$): 1607, 1522 cm^{-1}; HRMS calcd for $C_{18}H_{21}NO_2$ (M^+): 283.1572, found: 283.1566.

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