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# Two new tryptamine-derived alkaloids from *Chimonanthus praecox* f. concolor

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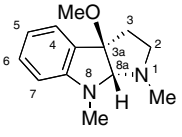
**Abstract**—A new pyrrolidinoindoline-type alkaloid, CPC-1, and a new tryptamine-derived dimeric alkaloid, CPC-2, were isolated from the seeds and rinds of *Chimonanthus praecox* f. concolor. The structure including the absolute configuration of CPC-1 was determined by chiral total synthesis. CPC-2 has a unique hexahydropyrroloquinoline skeleton.


Pyrrolidinoindoline-type alkaloids have been isolated from plants belonging to genera *Chimonanthus*, *Calycanthus*, *Psychotria*, *Calycodendron*, and *Idiospermum*,[1] and some of their important biological activities, such as antinociceptive or antibacterial activity, have been reported.[2] In our continuing chemical studies on pyrrolidinoindoline-type alkaloids,[3] we investigated the alkaloidal constituents in the seeds and rinds of *Chimonanthus praecox* (L.) f. concolor Makino (Calycanthaceae), and isolated two new compounds: a pyrrolidinoindoline-type alkaloid, CPC-1 (**1**), and a tryptamine-derived dimeric alkaloid, CPC-2 (**10**). We report herein the structure elucidation of these new alkaloids.

From the hot MeOH extract of the seeds and rinds of *C. praecox* f. concolor,[4] CPC-1 (**1**) and CPC-2 (**10**) were isolated as minor constituents together with eight known alkaloids, (+)-calycanthine (**11**), (−)-chimonanthine (**12**), *meso*-chimonanthine, (−)-folicanthine, (−)-calycanthidine, (−)-chimonanthidine, tryptamine, and $N_a$,$N_b$-dimethyltryptamine, by a combination of column chromatographies.

The HR-FAB-MS spectrum of the new compound, CPC-1 (**1**),[5] which exhibited $[\alpha]_D^{26}$ −88 (*c* 0.1, MeOH), gave a protonated molecular ion peak at *m*/*z* 219.1489 ($[MH]^+$) that corresponded to the molecular formula $C_{13}H_{19}N_2O$ (*m*/*z* 219.1497). The UV absorption bands (301.5, 251.0, 205.5 nm) and the characteristic aminoacetal proton ($\delta$ 4.36, H-8a) and carbon ($\delta$ 91.7, C-8a) signals in the NMR spectra indicated that **1** was a pyrrolidinoindoline-type compound. The $^1$H NMR spectrum also demonstrated the presence of a methoxy group at $\delta$ 3.04 together with one methyl group each on aniline nitrogen ($\delta$ 2.97, $N_8$-$CH_3$) and aliphatic nitrogen ($\delta$ 2.58, $N_1$-$CH_3$), four aromatic protons of the indoline nucleus, and four protons of the ethane bridge. The $^{13}$C NMR spectrum pointed to the presence of an $sp^3$ quaternary carbon bearing an oxygen function at $\delta$ 94.1. HMBC correlations between the methoxy proton at $\delta$ 3.04 and the oxygenated quaternary carbon indicated that the methoxy group was attached to C-3a. Therefore, the structure of CPC-1 was deduced to be that shown as formula **1** (Fig. 1).

To confirm the structure proposed by the spectroscopic analyses above, the synthesis of racemic CPC-1 was




CPC-1 (**1**)

**Figure 1.** Structure of CPC-1 (**1**).

*Keywords*: Alkaloid; Pyrrolidinoindoline; Dimeric alkaloid; *Chimonanthus*; Structure elucidation; Chiral total synthesis.
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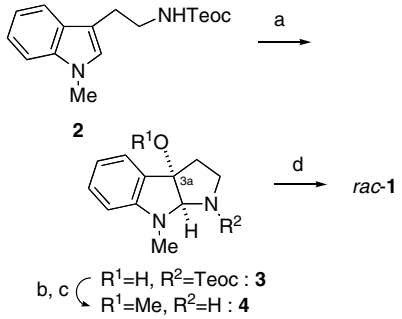



**Scheme 1.** Reagents and conditions: (a) *m*-CPBA, TFA (excess), $CH_2Cl_2$, −40 °C, 1.5 h, yield 92%; (b) $CH_3I$, NaH, DMF, 0 °C, 3 h, rt, 4.5 h, yield 72%; (c) TBAF, THF, 0 °C, 1.5 h, rt, 16.5 h, yield 83%; (d) HCHO aq then $NaBH_3CN$, MeOH, rt, 1 h, yield 71%.

initially performed. $N_a$-Methyl-$N_b$-trimethylsilylethoxycarbonyl (Teoc) tryptamine (**2**) was treated with *m*-CPBA in the presence of excess trifluoroacetic acid[6] in $CH_2Cl_2$ to give 3a-hydroxypyrrolidinoindoline **3** in 92% yield. Methylation of the hydroxy group on 3a position (MeI, NaH, DMF, yield 72%) and removal of the $N_b$-Teoc group (TBAF, THF, yield 83%) gave secondary amine **4**. Finally, **4** was treated with formalin and then $NaBH_3CN$ in MeOH to afford *rac*-**1** in 71% yield. All spectral data (UV, NMR, MS) except the optical property of synthetic *rac*-**1** were identical with those of natural **1** (Scheme 1).

Next, we planned the chiral total synthesis of **1** to establish the absolute configuration of the natural product. According to the procedure for asymmetric allylation developed by Walsh and co-workers,[6] isatin (**5**) was treated with (*R*)-(+)-binol, $Ti(O^iPr)_4$, 2-propanol, and tetraallylstannane to give allylated compound **6** in 89% yield with 42% ee based on chiral HPLC analysis. Two times recrystallization of the product from AcOEt provided enantiomerically pure (*S*)-**6**.[7] The absolute configuration at C-3 in **6** was deduced to be *S* by comparing its CD spectrum (Fig. 2) with those of (*S*)- and (*R*)-**9**,[3a] whose absolute configurations have been established.[3a] Next, the $N_a$ and hydroxyl groups in (*S*)-**6** were methylated with NaH and $CH_3I$ in DMF to give dimethyl compound **7** in 94% yield. Subsequently, **7** was treated with cat. $OsO_4$ and *N*-methylmorpholine *N*-oxide (NMO) followed by $NaIO_4$[8] to afford the aldehyde. Then, the crude aldehyde was directly subjected to reductive amination by condensing with $CH_3NH_2$ and the resulting imine was reduced with $NaBH_3CN$ to give **8**[9] in 28% yield from **7**. The CD spectrum of **8** (Fig. 2) was again compared with those of (*S*)- and (*R*)-**9**, and the absolute configuration at C-3 in **8** was confirmed. Finally, the reductive cyclization of **8** with $LiAlH_4$ in THF[10] afforded (3a*S*,8a*S*)-**1**[11] in 37% yield. Synthetic **1** showed $[\alpha]_D^{24}$ +101 (*c* 0.53, MeOH), whereas natural **1** exhibited $[\alpha]_D^{26}$ −88 (*c* 0.1, MeOH).[12] Therefore, the structure including the absolute configuration of natural CPC-1 was determined to be formula **1** having the 3a*R*,8a*R* configuration (Scheme 2).

The molecular formula of the second new alkaloid, CPC-2 (**10**),[13] was established to be $C_{22}H_{26}N_4$ from

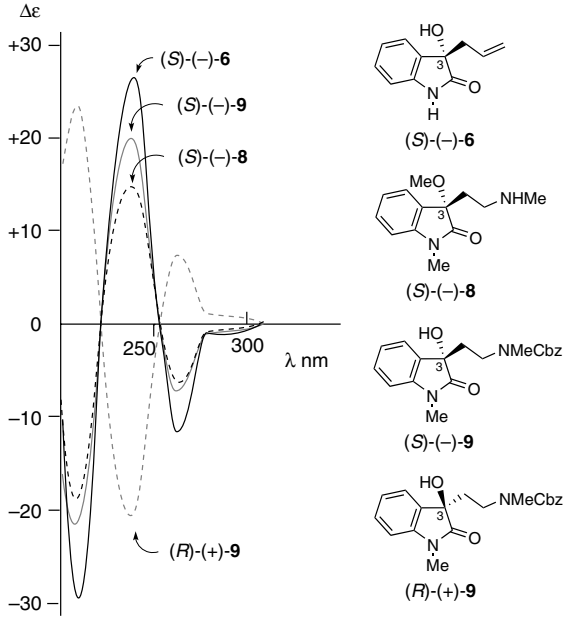
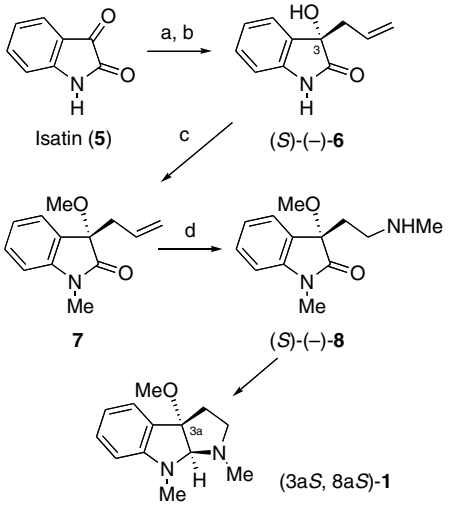



**Figure 2.** CD spectra of **6**, **8**, (*S*)- and (*R*)-3-hydroxyoxindoles (**9**).




**Scheme 2.** Reagents and conditions: (a) tetraallylstannane, (*R*)-(+)-binol, $Ti(O^iPr)_4$, 2-propanol, 0 °C, 2 h, 0 °C to rt, 10 h, yield 89%, 42% ee; (b) recrystallization from AcOEt, >99% ee; (c) $CH_3I$, NaH, DMF, rt, 3.5 h, yield 94%; (d) (i) $OsO_4$, NMO, $CH_3CN$, $H_2O$, rt, 65 h, (ii) $NaIO_4$, 1,4-dioxane, $H_2O$, rt, 30 min, (iii) $CH_3NH_2$·HCl, $MgSO_4$, MeOH, rt, 1 h, then $NaBH_3CN$, rt, 3 h, yield 28% from **7**; (e) $LiAlH_4$, THF, 0 °C, 1.5 h, rt, 2.5 h, yield 37%, 99.4% ee.

the HR-FAB-MS spectrum (*m*/*z*: 347.2246 $[MH]^+$). The $^{13}C$ NMR spectrum showed 11 signals only, indicating that **10** was a dimeric compound having a symmetrical structure.

The $^1H$ NMR spectrum indicated the presence of a methyl group on aliphatic nitrogen ($\delta$ 2.35, $N_1$-$CH_3$), four aromatic protons, and four protons on the ethane bridge. Furthermore, the characteristic proton signal at $\delta_H$ 3.97 and the carbon signal at $\delta_C$ 82.8 in the NMR spectra, as well as the UV spectrum ($\lambda_{max}$ 295.5, 250.0, 208.5 nm),[14] indicated the existence of the partial

structure of Ph–N–CH–N. HMBC correlation between protons at $\delta$ 7.22 (H-4, 4′) and $\delta$ 1.81 (H-3, 3′) and the $sp^3$ quaternary carbon at $\delta$ 53.7 suggested that CPC-2 had a tryptamine-derived dimeric structure. As the spectroscopic data of this compound were different from those of known calycanthine (**11**) or chimonanthine (**12**), four other candidates, **10**, **15**, **16**, and **17**, were considered for the structure of CPC-2. These hypothetical structures were discussed extensively in literature during the structure elucidation of chimonanthine (**12**)[15] or in the biogenetic speculation and total synthesis of calycanthaceous alkaloids.[16,17] Thus, these compounds including calycanthine (**11**) and chimonanthine (**12**) were thought to be equivalent to the tetraaminodialdehyde intermediate (**14**), which would be formed by the oxidative dimerization of $N_b$-methyltryptamine (**13**) in the plants. In the differential NOE experiments of CPC-2, irradiation of H-4 ($\delta$ 7.22) led to enhancement of the signal intensities of H-3 and H-3′ protons at $\delta$ 2.27, and H-2 and H-2′ protons at $\delta$ 2.85 (Fig. 3). The Dreiding-model study indicated that structure **10** was an exclusive isomer that satisfied the above NOE experiments. Further, $S_2$-type symmetrical isomers corresponding to each $C_2$-type candidate (**10**, **15**, **16**, **17**), for example, compound **18**, could be excluded from the list of the possible structures of CPC-2, because CPC-2 exhibited optical activity ($[\alpha]_D^{26}$ +57 (*c* 0.04, EtOH)). The isolation of *iso*-calycanthine,[18] which had the same skeleton as that of CPC-2, was reported previously. Although the stereochemistry of *iso*-calycanthine was not elucidated in the literature, its spectral data were completely different from those of CPC-2. If CPC-2 were biogenetically related to co-existing alkaloids, (+)-calycanthine (**11**) and (−)-chimonanthine (**12**), its absolute configuration would be 3a*S*,3′a*S* based on the biogenetic speculation above, which allows for the retention of configuration of the carbons at 3a and 3′a. Taken together, the structure of CPC-2 was proposed to be that shown as formula **10** (Fig. 4).

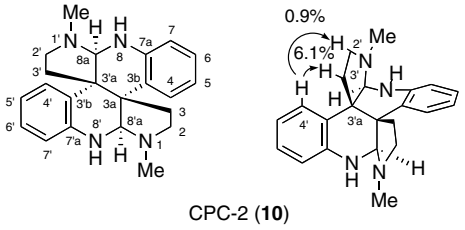



**Figure 3.** Structure and differential NOE data of CPC-2 (**10**).

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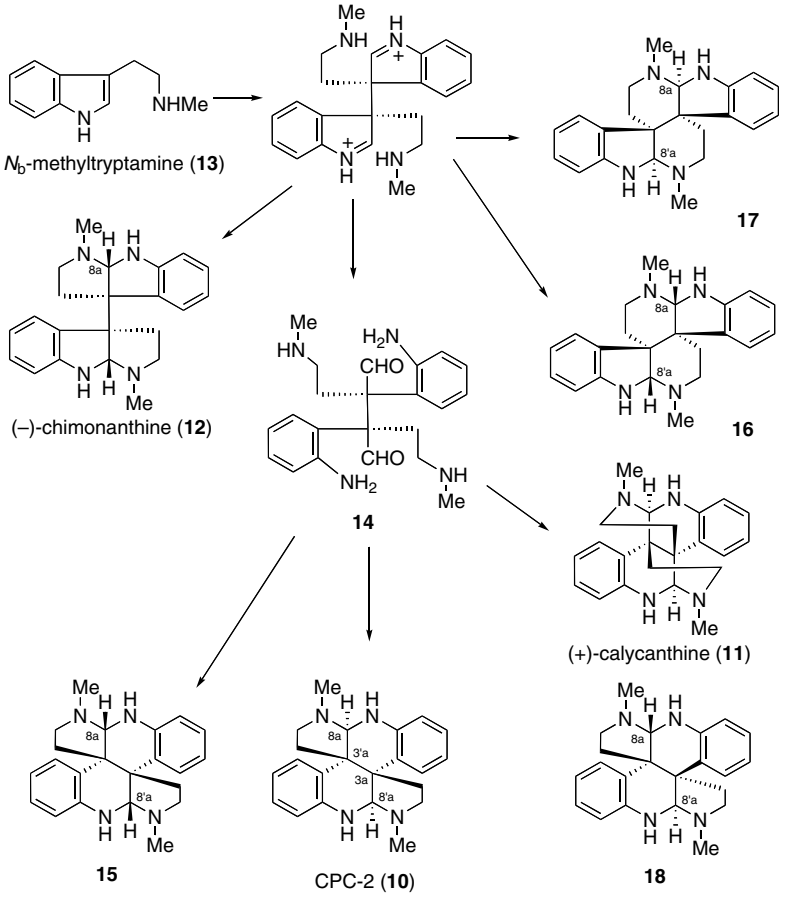


**Figure 4.** Biogenetic speculation of tryptamine-derived known dimeric alkaloids and hypothetical compounds.

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4. The seeds and rinds of *Chimonanthus praecox* f. concolor were collected from Tsukuba Botanical Garden, The National Science Museum, Tokyo. The seeds (268.2 g) and rinds (828.8 g) were extracted with hot MeOH to give the extract (89.8 g). The MeOH extract was dissolved in 90% MeOH–$H_2O$ and washed with *n*-hexane. After evaporation, the 90% MeOH–$H_2O$ layer was dissolved in $H_2O$. The aqueous layer was extracted with AcOEt and then *n*-BuOH to give the AcOEt (5.7 g) and *n*-BuOH (19.5 g) extracts, respectively, which were purified by a combination of column chromatographies to afford two new alkaloids, CPC-1 (2.2 mg from the AcOEt extract) and CPC-2 (0.9 mg, from the *n*-BuOH extract).
5. CPC-1 (**1**), amorphous, $[\alpha]_D^{26}$ −88 (*c* 0.1, MeOH). UV (MeOH) $\lambda_{max}$ nm (log ε): 301.5 (3.14), 251.0 (3.72), 205.5 (4.15). IR ($CHCl_3$) $\nu_{max}$ $cm^{-1}$: 2941, 1608, 1490. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.20 (1H, td, *J* = 7.6, 1.1 Hz, H-6), 7.16 (1H, dd, *J* = 7.6, 1.1 Hz, H-4), 6.75 (1H, td, *J* = 7.6, 1.1 Hz, H-5), 6.51 (1H, d, *J* = 7.6 Hz, H-7), 4.36 (1H, s, H-8a), 3.04 (3H, s, $OCH_3$), 2.97 (3H, s, $N_8$-$CH_3$), 2.80 (1H, ddd, *J* = 9.2, 6.8, 4.5 Hz, H-2), 2.62 (1H, br-td, *J* = 8.8, 6.0 Hz, H-2), 2.58 (3H, s, $N_1$-$CH_3$), 2.35 (1H, ddd, *J* = 12.3, 8.3, 6.8 Hz, H-3), 2.13 (1H, ddd, *J* = 12.3, 6.0, 4.5 Hz, H-3). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 153.1 (C-7a), 129.7 (C-6), 128.1 (C-3b), 124.1 (C-4), 117.9 (C-5), 107.8 (C-7), 94.1 (C-3a), 91.7 (C-8a), 52.5 ($OCH_3$), 52.4 (C-2), 39.4 (C-3), 38.7 ($N_1$-$CH_3$), 36.3 ($N_8$-$CH_3$). EI-MS *m*/*z* (%): 218 ($M^+$, 100), 203 (85), 160 (76), 144 (52), 83 (43), 71 (46). HR-FAB-MS (NBA/PEG) *m*/*z*: 219.1489 ($MH^+$, calcd for $C_{13}H_{19}N_2O$ 219.1497). CD (*c* = 0.37 mmol/L, MeOH, 23 °C) Δε (λ nm): 0 (350), −1.0 (307), −0.3 (280), −3.4 (257), 0 (241), +2.4 (218), +3.6 (205).
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7. Data of **6**, mp 132–135 °C (AcOEt). $[\alpha]_D^{26}$ −10 (*c* 1.3, MeOH). CD (*c* = 0.68 mmol/L, MeOH, 24 °C) Δε (λ nm): 0 (309), −1.8 (291), −11.2 (263), 0 (253), +27.2 (238), 0 (222), −29.7 (211). Racemate **6** has been reported; Nair, V.; Jayan, C. N.; Ros, S. *Tetrahedron* **2001**, *57*, 9453–9459.
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9. Data of (*S*)-(−)-**8**, $[\alpha]_D^{24}$ −29.0 (*c* 0.89, MeOH). CD (*c* = 0.28 mmol/L, MeOH, 24 °C) Δε (λ nm): 0 (319), −6.0 (265), 0 (256), +14.0 (241), 0 (224), −18.7 (212).
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11. Data of (3a*S*,8a*S*)-**1**, $[\alpha]_D^{24}$ +101 (*c* 0.53, MeOH). CD (*c* = 0.39 mmol/L, MeOH, 24 °C) Δε (λ nm): 0 (354), +1.1 (305), +0.2 (274), +4.0 (255), 0 (240), −0.7 (229), −1.9 (219), −4.3 (205).
12. Enantiomeric purity of natural **1** was examined by chrial HPLC analysis, demonstrating that it does not contain the enantiomer.
13. CPC-2 (**10**), amorphous, $[\alpha]_D^{26}$ +57 (*c* 0.04, EtOH). UV (MeOH) $\lambda_{max}$ nm (log ε): 295.5 (3.59), 250.0 (4.12), 208.5 (4.53). $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.22 (2H, dd, *J* = 7.7, 1.3 Hz, H-4, 4′), 7.10 (2H, ddd, *J* = 7.7, 7.7, 1.3 Hz, H-6, 6′), 6.79 (2H, ddd, *J* = 7.7, 7.7, 1.3 Hz, H-5, 5′), 6.65 (2H, dd, *J* = 7.7, 1.3 Hz, H-7, 7′), 3.97 (2H, s, H-8a, 8′a), 2.85 (2H, ddd, *J* = 8.7, 8.7, 6.7 Hz, H-2, 2′), 2.78 (2H, ddd, *J* = 8.7, 8.7, 3.1 Hz, H-2, 2′), 2.35 (6H, s, $N_1$-$CH_3$, $N_{1'}$-$CH_3$), 2.27 (2H, ddd, *J* = 13.2, 6.7, 3.1 Hz, H-3, 3′), 1.81 (2H, ddd, *J* = 13.2, 8.7, 8.7 Hz, H-3, 3′). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 144.3 (C-7a, 7′a), 130.9 (C-3b, 3′b), 127.6 (C-6, 6′), 125.9 (C-4, 4′), 118.4 (C-5, 5′), 115.6 (C-7, 7′), 82.8 (C-8a, 8′a), 53.7 (C-3a, 3′a), 53.0 (C-2, 2′), 38.6 ($N_1$-$CH_3$, $N_{1'}$-$CH_3$), 31.1 (C-3, 3′). FAB-MS (NBA) *m*/*z*: 347 ($MH^+$). HR-FAB-MS (NBA/PEG) *m*/*z*: 347.2246 ($MH^+$, calcd for $C_{22}H_{27}N_4$ 347.2236). CD (*c* = 0.44 mmol/L, EtOH, 9 °C) Δε (λ nm): 0 (327), +2.0 (307), 0 (279), −7.1 (260), 0 (249), +1.7 (244), 0 (231), −3.2 (217), 0 (212), +2.3 (207).
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