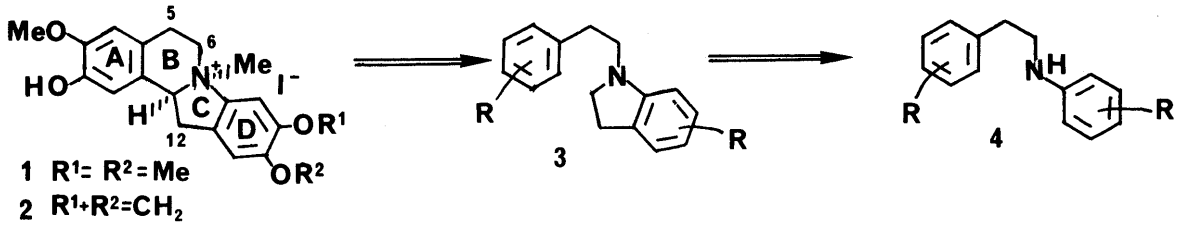
A NOVEL TOTAL SYNTHESIS OF (±)-CRYPTAUSTOLINE, A DIBENZOPYRROCOLINE ALKALOID

Shingo YASUDA, Taeko HIRASAWA, Shuji YOSHIDA, and Miyoji HANAOKA*
Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan

(±)-Cryptaustoline (**1**), a dibenzopyrrocoline alkaloid, was efficiently synthesized from the readily available N-phenethylaniline (**7**) via the N-phenethyloxindole (**12**) or the N-phenethylindole (**14**) by the Bischler-Napieralski reaction or by radical cyclization.

KEYWORDS dibenzopyrrocoline alkaloid; cryptaustoline; Bischler-Napieralski reaction; radical cyclization; reductive bond cleavage; α-chloro-α-methylthioacetyl chloride; tributyltin hydride

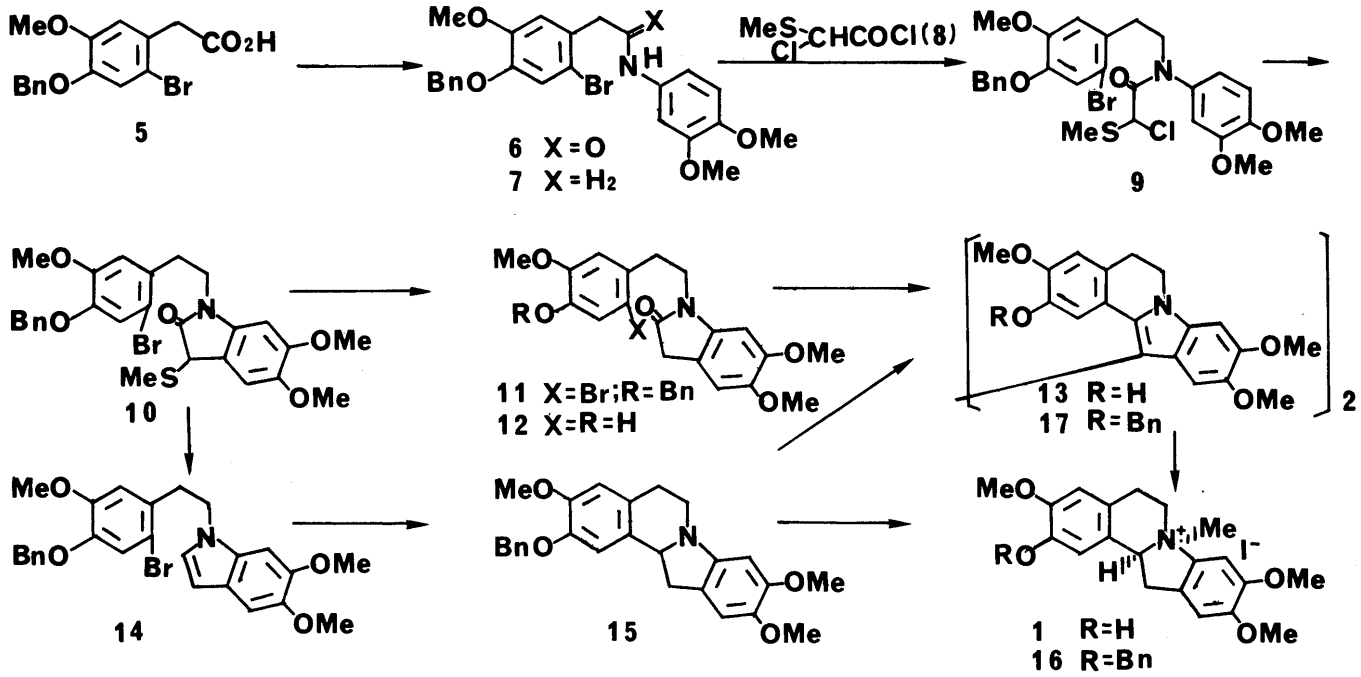
Only two dibenzopyrrocoline alkaloids, cryptaustoline (**1**) and cryptowoline (**2**) have been known.[1] Their skeleton had been synthesized before they were isolated.[2] And several syntheses of the alkaloids have so far been reported[1,3] because of their biogenetic and structural interest. The methodologies of these syntheses were based principally on the construction of the five-membered ring (C-ring) from an appropriate isoquinoline (A,B,D-ring). We report here a novel synthesis of (±)-cryptaustoline (**1**) by forming of the B-ring via an N-phenethylindole (**3**) (A,C,D-ring) obtained from a readily available N-phenethylaniline (**4**).



On treatment with oxalyl chloride, 4-benzyloxy-2-bromo-5-methoxyphenylacetic acid (**5**)[4] was converted to the acid chloride, which was treated with 3,4-dimethoxyaniline in the presence of triethylamine to give the amide (**6**, 76%, mp 171-172°C). Reduction of **6** with aluminum hydride in tetrahydrofuran (THF) afforded the N-phenethylaniline (**7**, 78%, mp 124-125°C). Conversion of **7** to the expected N-phenethylindole was realized by application of Tamura's procedure.[5] Condensation of **7** with α-chloro-α-methylthioacetyl chloride (**8**)[5] in dichloromethane under nitrogen followed by treatment with stannic chloride provided exclusively the desired N-phenethyloxindole (**10**, 84%, mp 108-110°C) via the intermediary amide (**9**). The presence of the bromine in the A ring completely prevented the formation of an undesired seven-membered benzazepine product.

Initially, transformation of the oxindole (**10**) to the alkaloid was carried out through the Bischler-Napieralski reaction. Reduction of **10** with zinc dust in refluxing acetic acid afforded the desulfurization product (**11**). Catalytic hydrogenolysis of **11** over 10% Pd-C in acetic acid effected debromination and debenzylation to give the phenolic oxindole (**12**, 77% form **10**). The Bischler-Napieralski reaction of **12** with phosphorus oxychloride in refluxing acetonitrile produced the unexpected dimeric cyclization product [**13**, 78%, mp 217-218°C; m/z 648 (M^+); δ 7.26, 7.07, 6.79, 6.73 (each 1H, s), 4.16 (2H, t, J=7), 3.95 (3H, s), 3.93 (6H, s), 3.10 (2H, t, J=7)]. The dimeric structure of **13** was proved by the lack of the vinylic proton at C-12 in its ^{1}H-NMR spectrum[6] and further by the appearance in its ^{13}C-NMR spectrum of the C-12 signal as a singlet instead of a doublet. Similar dimeric compounds were reported by Brossi[7] and Hess.[8] On treatment with borane-dimethyl sulfide complex in THF in the presence of trifluoroacetic acid,[9] the dimer (**13**) underwent reduction of the double bond and concomitant reductive C-C bond cleavage to afford the monomeric product. As the product was so labile to revert back to the starting dimer, the crude product was immediately quaternized with methyl iodide to provide (±)-cryptaustoline [**1**, 65%, mp 250-252°C, (lit.[3a] mp 260°C, lit.[3d] mp 255-256°C); δ 7.41, 6.91, 6.83, 6.77 (each 1H, s), 5.04 (1H, t, J=8), 4.02 (3H, s), 3.93 (6H, s), 3.65 (3H, s)]. The synthetic (±)-**1** was identical with the authentic sample.

Alternatively and more conveniently, the B-ring was constructed through radical cyclization by



efficient utilization of the bromine in the A ring previously used as a blocking group. Reduction of the oxindole (**10**) with aluminum hydride in THF gave the indole (**14**, 80%). This was treated with tributyltin hydride in the presence of azobisisobutyronitrile in benzene under reflux to afford the unstable cyclization product (**15**), quaternization of which with methyl iodide produced (±)-O-benzylcryptaustoline [**16**, 72% from **14**, mp 223-225°C, (lit.[3a] mp 224-226°C)]. The amine (**15**) was easily air-oxidized to the dimeric product (**17**) similar to **13**. Finally, according to Kametani's procedure,[3a] heating of **16** with concentrated hydrochloric acid followed by potassium iodide in ethanol furnished (±)-cryptaustoline in 66% yield.

Thus, we have accomplished a novel and efficient synthesis of (±)-cryptaustoline (**1**) starting from the N-phenethylaniline (**7**) via the N-phenethyloxindole (**10**) by two different routes.

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