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# Concise Synthesis of the Hasubanan Alkaloid (±)-Cepharatine A Using a Suzuki Coupling Reaction To Effect *o,p*-Phenolic Coupling

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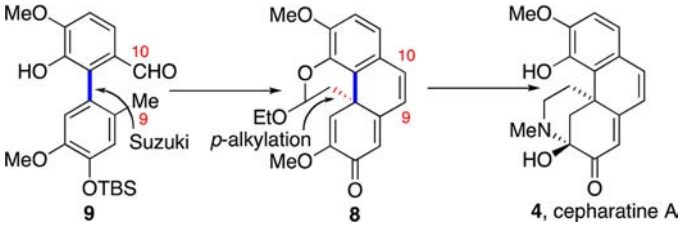
## ABSTRACT




**Suzuki coupling of 10 and 11 resulted in 9, which was *O*-alkylated to provide 12. Treatment of 12 with CsF in DMF resulted in the formation of the completed core structure 13 in a single step. Reductive amination of 13 completed the synthesis of (±)-cepharatine A, 4.**

The hasubanan alkaloids, exemplified by the structures of hasubanonine **1** and cepharamine **2**,[1] have attracted the attention of synthetic organic chemists because of their obvious structural relationship to morphine **3** (opioid), Figure 1.[2a−d,3a−3c]

Recently, the structures of the cepharatines A (**4**), B (**6**), C (**5**), and D (**7**), Figure 2, have been reported,[4] and this has generated a successful enantioselective synthesis of cepharatines A, C, and D.[5]

In 2009 we reported a new strategy for the synthesis of codeine and galanthamine that involved a Suzuki reaction

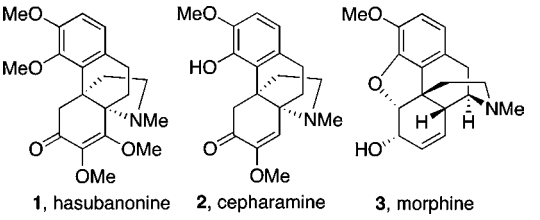



**Figure 1.** Structures of hasubanonine **1**, cepharamine **2**, and morphine **3**.

to establish the key *o,p*-phenolic coupling structural feature, followed by intramolecular phenol alkylation resulting in a cross conjugated cyclohexa-2,5-dienone.[6] Application of this concise strategy leads to the retrosynthetic pathway for the construction of cepharatine A **4**, Scheme 1.

It was anticipated that construction of the adduct **9** by a Suzuki coupling reaction would solve the *o,p*-phenolic coupling problem, Scheme 2 (formation of the blue biaryl bond). Intramolecular alkylation of **9** (formation

(1) Matsui, M. *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 33, pp 307−347(see also earlier vols. 13 and 16).

(2) (a) (±)-Cepharamine synthesis: Inubushi, Y.; Ibuka, T.; Kitano, M. *Tetrahedron Lett*. **1969**, 1611–1614. (b) (±)-Hasubanonine synthesis: Ibuka, T.; Tanaka, K.; Inubushi, Y. *Tetrahedron Lett*. **1970**, *13*, 1393–1396. (c) (+)-Cepharamine Synthesis: Schultz, A. G.; Wang, A. *J. Am. Chem. Soc*. **1998**, *120*, 8259–8260. (d) (−)-Hasubanonine synthesis: Herzon, S. B.; Calandra, N. A.; King, S. A. *Angew. Chem., Int. Ed*. **2011**, *50*, 8863–8866.

(3) (a) (−)-Acutumine synthesis: Li, F.; Tartakoff, S. S.; Castle, S. L. *J. Am. Chem. Soc*. **2009**, *131*, 6674–6675. (b) Li, F.; Tartakoff, S. S.; Castle, S. L. *J. Org. Chem*. **2009**, *74*, 9082–9093. (c) Jones, S. B.; He, L.; Castle, S. L. L. *Org. Lett*. **2006**, *8*, 3757–3760.

(4) He, L.; Zhang, Y.-H.; Guan, H.-Y.; Zhang, J.-X.; Sun, Q.-Y.; Hao, X.-J. *J. Nat. Prod*. **2011**, *74*, 181–184.

(5) Chuang, K. V.; Navarro, R.; Reisman, S. E. *Angew. Chem., Int. Ed*. **2011**, *50*, 9447–9451.

(6) Magnus, P.; Sane, N.; Fauber, B. P.; Lynch, V. *J. Am. Chem. Soc*. **2009**, *131*, 16045–16047.

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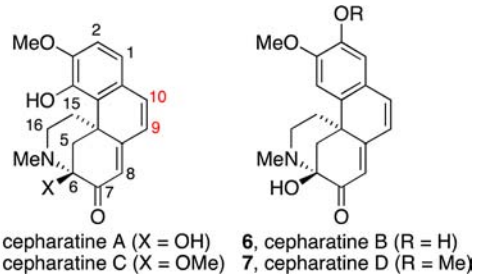
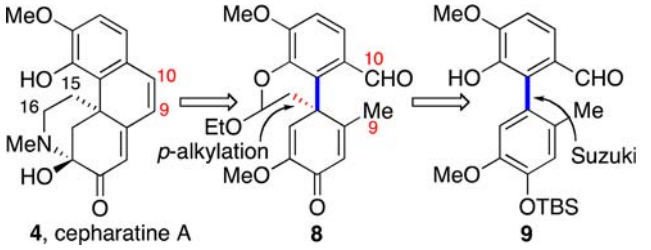



**Figure 2.** Structures of cepharatines A, B, C, and D respectively.

**Scheme 1.** Retrosynthetic Strategy for the Construction of *o,p*-Phenol Coupling Intermediate **8** from **9**

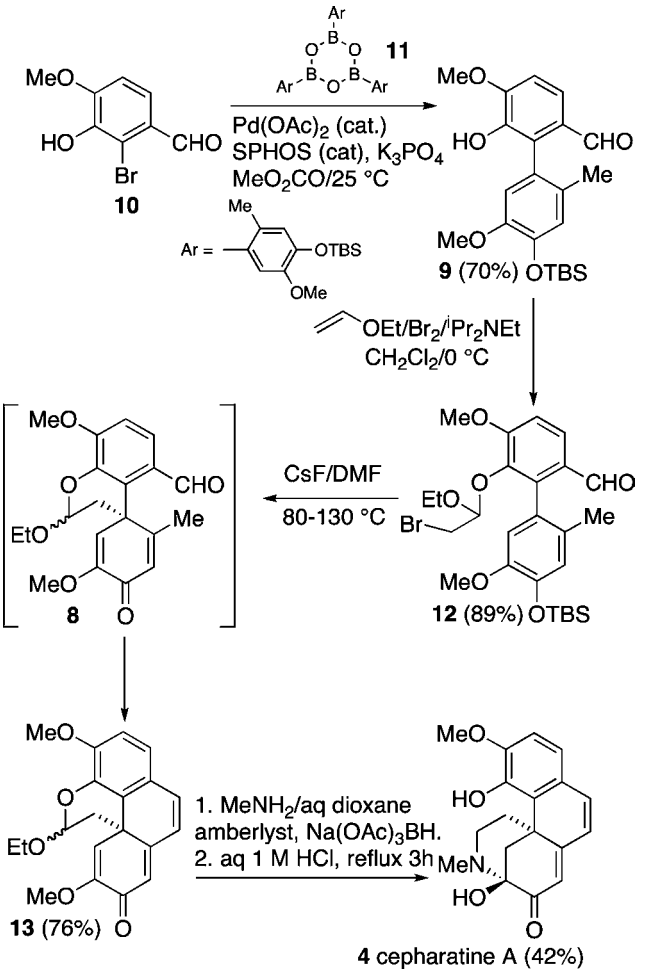



of the red bond) leads to the cross conjugated cyclohexa-2,5-dienone **8**. The enolizable C-9 methyl group in **8** is poised to undergo condensation with the C-10 aldehyde to give cepharatine A **4** after reductive amination and acidic treatment. It is noteworthy that, in principle, this strategy forms the phenathrenone skeleton directly in the correct oxidation state. Castle adopted a Suzuki coupling strategy to form the biaryl bond and subsequent RCM to establish the C9−C10 double bond.[3a−c]

Treatment of the boronic ester derivative **11** (available in three steps from 2-methoxy-5-methylphenol in overall 78% yield; see Supporting Information for its synthesis) with 2-bromo-isovanillin **10** under Suzuki coupling reaction conditions provided **9** (70%), Scheme 2. The final two carbon atoms were obtained from bromination of ethyl vinyl ether and exposure of **9** to the in situ generated dibromide in the presence of $^{i}Pr_2NEt$ resulting in **12** (89%).

When **12** was treated with CsF in DMF at 80 °C it was converted into **8** (colorless), which on further warming to 130 °C generated a bright yellow solution characteristic of the fully conjugated chromophore associated with the cepharatines ($\lambda_{max}$ 388 nm). After workup **13** was isolated as a canary yellow solid (mp 147−150 °C), and its structure was confirmed by single crystal X-ray crystallography. To complete the synthesis **13** was reductively aminated, and

**Scheme 2.** Conversion of **10** into Cepharatine A




the crude product was treated with aqueous 1 M HCl to give cepharatine A (42%).

The synthesis of (±)-cepharatine A proceeds in 7 steps from commercially available 2-methoxy-5-methylphenol in 16% overall yield. The key transformation was the conversion of **12** into **13**, where the C-15 and C9−C10 carbon−carbon bonds are formed in a single step.

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**Supporting Information Available.** Complete experimental details and compound characterization. This information is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.