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Enantioselective Total Synthesis of (+)-Amabiline

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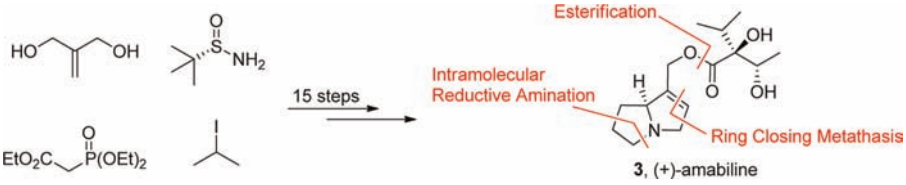
ABSTRACT



The first total synthesis of (+)-amabiline, an unsaturated pyrrolizidine alkaloid from *Cynoglossum amabile*, is reported. This convergent, enantioselective synthesis proceeds in 15 steps (10-step longest linear sequence) in 6.2% overall yield and features novel methodology to construct the unsaturated pyrrolizidine or (−)-supinidine core.

Pyrrolizidine alkaloids (**1**), historically referred to as necine bases, share a common azabicyclo[3.3.0]octane core but differ based on the oxygenation pattern and whether or not C1−C2 is saturated (Figure 1).[1] While the amine bases themselves are rarely isolated in nature, the corresponding mono- and diesters are more common, as either the tertiary amine or the *N*-oxide, **2**−**5**.[1] Members of this family of alkaloids possess a wide range of biological activities including antitumor, antibacterial, anti-inflammatory, carcinogenic, and hepatotoxic activity, with several members entering human clinical trials.[1−5] Plants containing pyrrolizidine alkaloids are toxic to humans and animals, but several insect species have evolved to employ them for their own chemical defense.[6] Interestingly, the toxicity has been attributed to liver metabolism of the C1−C2 unsaturated congeners leading to the generation of highly reactive alkylating agents.[7]

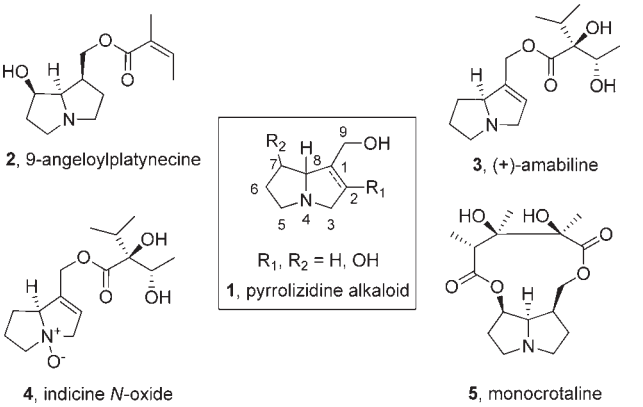


Figure 1. Structures and numbering convention of pyrrolizidine alkaloids **1**, and representative examples **2**−**4**.

A number of racemic routes to the pyrrolizidine alkaloid core (**1**) have been developed, but recent efforts have focused on asymmetric approaches.[1−5] The majority of these approaches rely on the chiral pool, employing L-proline, malic acid, or carbohydrates as chiral starting materials.[1] Based on the synthetic challenge, the diverse

(1) For reviews on the pyrrolizidine alkaolids, see: (a) Robins, D. J. *J. Nat. Prod. Rep.* **1989**, *6*, 221. (b) Ikeda, M.; Sato, T.; Ishibashi, H. *Heterocycles* **1988**, *27*, 1465. (c) Dai, W.-M.; Nagao., Y. *Heterocycles* **1990**, *30*, 1231–1261.

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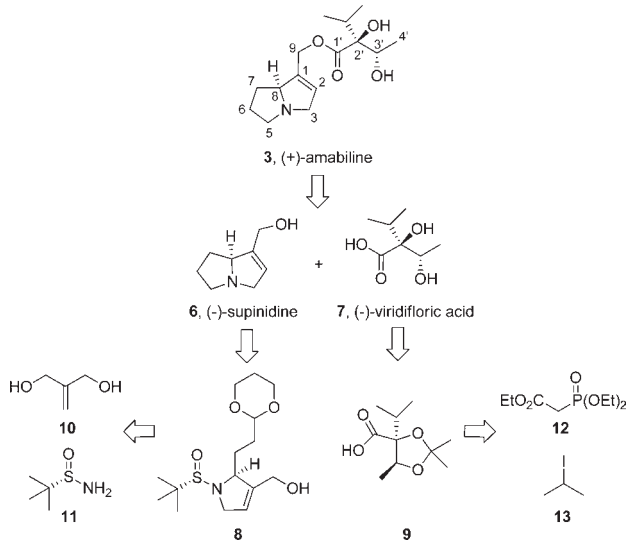
biological activity, and our recently reported methodology to construct multiple bicyclic azacine systems,[8] we decided to apply our methodology toward the enantioselective synthesis of (+)-amabiline (**3**), an unsaturated pyrrolizidine alkaloid, isolated in 1967 from *Cynoglossum amabile*, that has yet to be the subject of a total synthesis.[7,9–12]

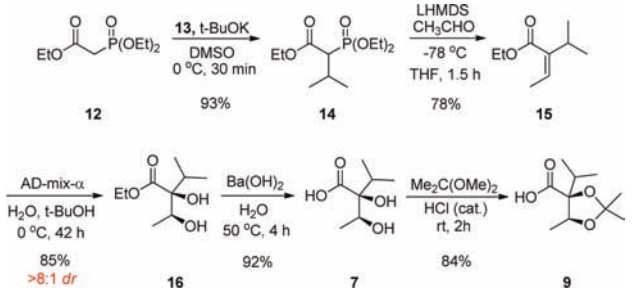
Scheme 1. Retrosynthetic Analysis of (+)-Amabiline (**3**)



Our retrosynthesis first cleaved the ester bond to liberate the necine base (−)-supinidine (**6**) and (−)-viridifloric acid (**7**) (Scheme 1). **6** has been synthesized previously, but the most expedient route required 18 steps.[13] By employing a novel extension of our newly developed azacine methodology,[8] **6** would be accessed from **8**, which would be derived from commercial diol **10** and (*S*)-*tert*-butyl sulfinimine **11**. (−)-Viridifloric acid (**7**) would be prepared as prescribed by Schulz,[14] via **9**, from commercial **12** and **13**.

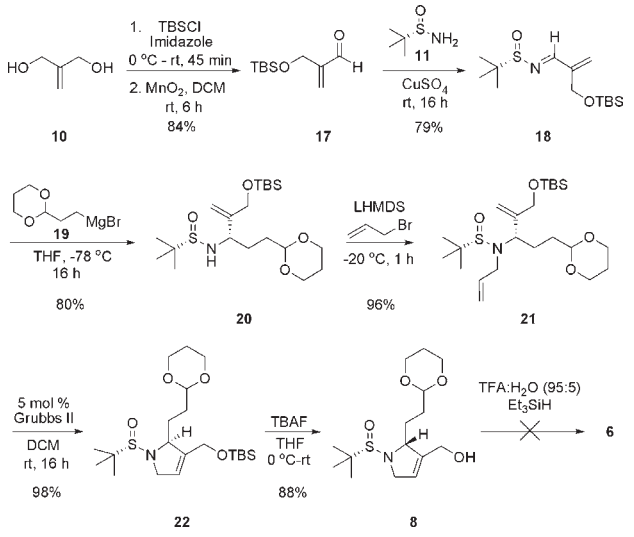
Efforts initially focused on the synthesis of **7** (Scheme 2).[14] Alkylation of phosphonate ester **12** with **13** provided **14** in 93% yield. A Horner–Wadsworth–Emmons reaction with acetaldehyde provided alkene **15**, which then underwent a Sharpless dihydroxylation to afford (*S*,*S*)-diol **16** in >8:1 *dr*. Ester hydrolysis gave the (−)-viridifloric acid (**7**), idenitical in all respects to the natural acid, which was then protected as the dioxolane congener **9**. Thus, the synthesis of **9** required five steps and proceeded in 48% overall yield.

Scheme 2. Synthesis of protected (−)-viridifloric acid (**9**)



With **7** in hand, attention was now directed to the synthesis of key intermediate **8** (Scheme 3). Commercial diol **10** was monosilylated. MnO_2 oxidation of the allylic alcohol then delivered aldehyde **17** in 84% yield for the two steps. Condensation of **17** with (*S*)-*tert*-butyl sulfinimine **11** gave **18** in 79% yield.[8,15–17] Addition of Grignard reagent **19** provides **20** in >9:1 *dr*,[8,15–21] which is

Scheme 3. Synthesis of Key Intermediate **8** and Attempted Synthesis of **6**



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(12) In 1993, a strucuturally unrelated *Amaryllidaceae* alkaloid was isolated and also named amabiline. However, the moniker of amabiline has been applied to **3** in multiple manuscripts over the past 45 years. For the isolation and synthesis of the *Amaryllidaceae* alkaloid also named amabiline, see: (a) Likhitwitayawuid, K.; Angerhofer, C. K.; Pezzuto, J. M.; Cordell, G. A.; Ruangrungsi, N. *J. Nat. Prod.* **1993**, *56*, 1331. (b) Findlay, A. D.; Banwell, M. G. *Org. Lett.* **2009**, *11*, 3160–3162.

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subsequently allylated to deliver **21** in 77% yield for the two steps. A ring closing metathasis reaction employing Grubbs II[22] smoothly led to pyrrolidine **22**, and a TBAF deprotection generated the key intermediate **8**. Single X-ray crystallography (Figure 2) confirmed the absolute stereochemistry of **8** as (*S*,*S*).[23] Here, we anticipated that deprotection of the acetal and the sulfinamine would liberate the free aldehyde and amine, respectively, followed by an intramolecular condensation to form the imine that would then be reduced *in situ* to provide (−)-supinidine (**6**). However, classical Ellman conditions and a number of other variants failed to facilitate this transformation, affording complex mixtures of polar species.

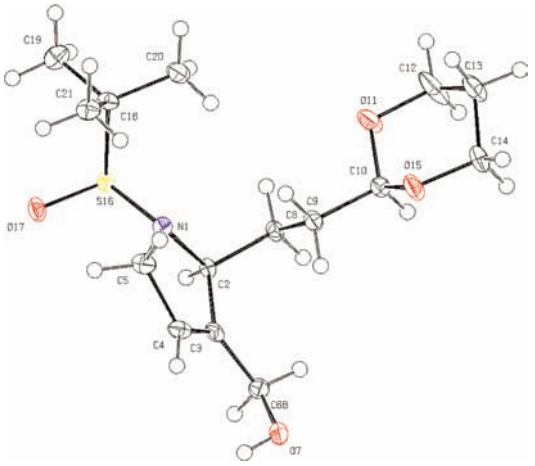
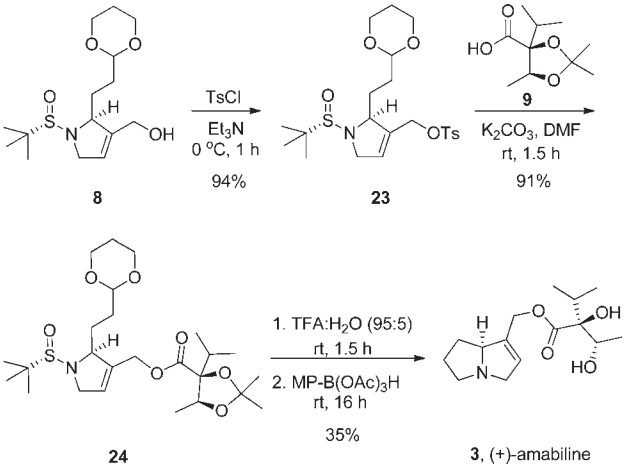


Figure 2. X-ray structure (ORTEP) of key intermediate **8**, confirming the correct (*S*,*S*)-stereochemistry.

Therefore, we elected to first couple **8** and **9**, followed by global deprotection and intramolecular reductive amination. However, this too proved difficult, due to the sterically hindered acid **9**. We evaluated several coupling reagents (EDCI/DMAP, TBTU/DBU, DCC/DMAP, HATU/DIEA) and protocols, but none provided any trace of the ester product. Therefore, we decided to convert the hydroxyl of **8** into a leaving group and attempt to install the ester linkage by emloying the acid as a nucleophile. A mesylate derivative afforded a 45% conversion to the desired ester, but **23**, a tosylate variant, afforded the desired ester in 82% yield (Scheme 4). A final acid-mediated global deprotection of the acetal, the dioxolane, and the sulfinamine enabled the intramolecular condensation to form the imine, which was then reduced *in situ* by MP-BH(OAc)$_3$ to deliver amabiline (**3**) in 37% yield in a five-step, one-pot reaction cascade (an average of 82% yield/transformation). Thus, the first total synthesis of (+)-amabiline (**3**) was completed in 15 synthetic steps (10-step longest linear sequence) and in 6.2% overall yield. Our synthetic amabiline was identical in all respects to the data reported for natural **3**. Moreover, this represents a notable improvement, as previous efforts have required up to 18 steps to deliver (−)-supinidine (**6**), the parent necine base.[13]

Scheme 4. Synthesis of (+)-Amabiline (**3**)



Based on the strucutral similarity of **3** to other pyrrolizidine alklaoids with anticholinergic activity,[1−5] we evaluated our synthetic **3** against all five human mAChR receptors (hM$_1$−M$_5$). Interestingly, **3** possessed no activity at any of the mAChRs ($IC_{50} > 10\,\mu M$), as well as a larger collection of GPCRs, ion channels, and transporters.

In summary, we have completed the first total synthesis of (+)-amabiline (**3**), requiring only 15 synthetic steps (10-step longest linear sequence) in 6.2% overall yield. This highly convergent and concise synthesis will enable the preparation of unnatural, unsaturated pyrrolizidine alkaloids for additional biological evaluation. Further refinements are in progress and will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. This manuscript was published ASAP on March 20, 2011. Due to a production error, Scheme 3 was not updated. The corrected version was posted on March 23, 2012.

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(23) See the Supporting Information for full details.

The authors declare no competing financial interest.