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A Chemoenzymatic Total Synthesis of (+)-Amabiline

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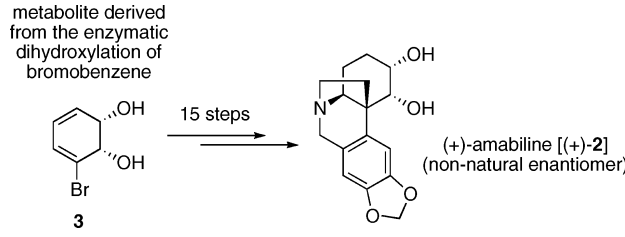
ABSTRACT



The readily available and enzymatically derived *cis*-1,2-dihydrocatechol 3 has been converted, over 15 steps, into (+)-amabiline, the non-natural enantiomeric form of a crinine-type alkaloid.

Crinine [(−)-**1**, Figure 1] is the parent member of a significant class of *Amaryllidaceae* alkaloids characterized by the presence of a 5,10b-ethanophenanthridine ring system. Vittatine [(+)-**1**] is another member of the class and one that embodies the alternate enantiomeric form of the constituent framework. A broad range of biological activities have been attributed to these natural products, including antitumor, antiviral and immunostimulant properties.[1] (−)-Amabiline [(−)-**2**], which was isolated during a search for new, plant-derived antimalarial agents,[2] is a further example of a crinine alkaloid and one that possesses a novel oxygenation pattern in the six-membered D-ring. Thus far, it has been the subject of a single synthetic study that served to confirm the proposed structure.[3] Herein we outline a chemoenzymatic approach to (+)-amabiline [(+)-**2**)], the non-natural enantiomeric form of the alkaloid, that makes use of an Eschenmoser−

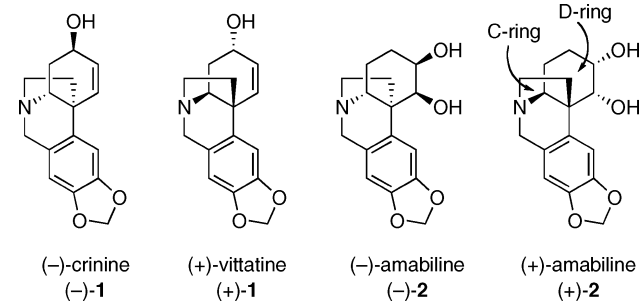


Figure 1. Structures of the alkaloids (−)-crinine, (+)-vittatine, (−)-amabiline and (+)-amabiline.

Claisen rearrangement,[4] an intramolecular S_N' displacement process and a Pictet−Spengler cyclization reaction to assemble the requisite framework. The route described, which allows for the introduction of functionality at all relevant positions on the D-ring of the crinine alkaloid

(1) For reviews on the crinine alkaloids see: (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 30, p 251. (b) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 51, p 323. (c) Lewis, J. R. *Nat. Prod. Rep.* **1998**, *15*, 107.

(2) Likhitwitayawuid, K.; Angerhofer, C. K.; Chai, H.; Pezzuto, J. M.; Cordell, G. A.; Ruangrungsi, N. *J. Nat. Prod.* **1993**, *56*, 1331.

(3) (a) Pearson, W. H.; Lovering, F. E. *J. Am. Chem. Soc.* **1995**, *117*, 12336. (b) Pearson, W. H.; Lovering, F. E. *J. Org. Chem.* **1998**, *63*, 3607.

(4) (a) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425. Muxfeldt and co-workers employed this reaction in developing the first total synthesis of (±)-crinine: (b) Muxfeldt, H.; Schneider, R. S.; Mooberry, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3670.

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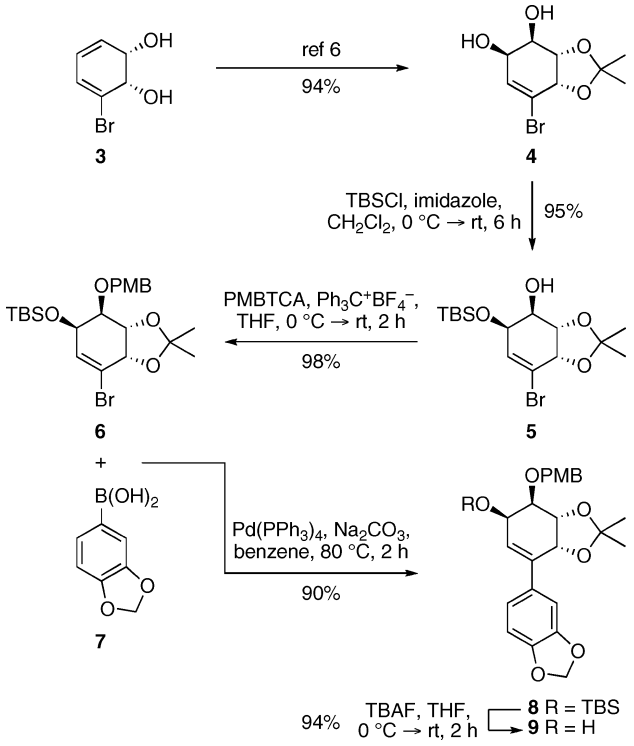
framework, should be useful in preparing many other members of the family.

The early stages of our approach to (+)-amabiline involved functionalization of the non-halogenated double bond within the *cis*-1,2-dihydrocatechol **3** (Scheme 1), a

Scheme 1. Synthesis of Substrate **9** for the Eschenmoser−Claisen Rearrangement Reaction



commodity chemical that can be obtained in large quantity and enantiomerically pure form via the whole-cell mediated biotransformation of bromobenzene.[5] Thus, the conversion of compound **3** into diol **4**[6] was readily achieved by initial formation of the corresponding acetonide followed by dihydroxylation of this intermediate (94% yield, 2 steps). Selective protection (TBSCl, imidazole) of the allylic hydroxyl group within product **4** was readily achieved under conventional conditions and so afforded monoether **5**. Conversion of the latter compound into the corresponding PMB ether **6** (93%, 2 steps) required the use of *p*-methoxybenzyl trichloroacetimidate (PMBTCA) in combination with $Ph_3C^+BF_4^{-}$[7] so as to prevent cleavage of the TBS ether. The stage was now set for a Suzuki−Miyaura cross coupling[8] of compound **6** with the commercially available boronic acid **7** which proceeded smoothly [using ($Pd(PPh_3)_4$, Na_2CO_3 and benzene] to give the desired product **8** in 90% yield. Removal of the TBS ether within the last compound was readily achieved using TBAF and so generating allylic alcohol **9** in 94% yield.

With compound **9** in hand, the construction of the quaternary carbon center associated with (+)-amabiline could now be addressed (Scheme 2). We envisaged that the Eschenmoser variant of the Claisen rearrangement reaction[4] would provide an effective means for doing so. Pleasingly, exposure of substrate **9** to *N*,*N*-dimethylacetamide dimethyl acetal in toluene at 120 °C for 16 h resulted in the generation of the expected product **10** in 95% yield. Reduction of the newly introduced tertiary amide moiety was effected by treating compound **10** with lithium triethylborohydride, and in this manner the corresponding primary alcohol, **11**, could be obtained in 94% yield. A short sequence of steps was now required to obtain a substrate capable of engaging in an intramolecular S_N' reaction to establish the 5-membered C-ring of the target framework. Toward such ends (Scheme 2), alcohol **11** was converted (using I_2 and PPh_3) into the corresponding iodide **12** which was, in turn, treated with sodium azide to give compound **13** (85% yield, 2 steps). DDQ-mediated cleavage of the PMB ether moiety within azide **13** then gave allylic alcohol **14** in 92% yield. Conversion of compound **14** into the corresponding mesylate **15** (MsCl, Et_3N) proved straightforward and set the stage for a Staudinger reduction.[9] It was anticipated this would generate a primary amine capable of engaging in a spontaneous intramolecular S_N'-reaction, thereby forming the C-ring of target (+)-**2**. In accord with such expectations, treatment of azide **15** with PPh_3 in THF/H_2O resulted in the formation of the 3a-arylhexahydroindole **16** in good yield (70%, over 2 steps). Subjection of compound **16** to treatment with paraformaldehyde and formic acid at 80 °C for 16 h effected a Pictet−Spengler cyclization reaction, accompanied by cleavage of the acetonide residue and formylation of the resulting diol, to give **17** (70%). Completion of the synthesis of (+)-amabiline required reduction of the Δ^3-double bond and hydrolysis of the formate ester moieties within **17**. Conveniently, this could be achieved in a one-pot process, whereby K_2CO_3 was added to the reaction mixture used for effecting hydrogenation (H_2, 5% Pd/C, MeOH). In this manner (+)-amabiline was obtained directly and in 93% yield from precursor **17**. The spectral data (NMR, MS, IR) derived from this material were in full accord with the assigned structure and in excellent agreement with the literature

(5) Compound **3** can be obtained from the Aldrich Chemical Co. (Catalogue Number 489492) or from Questor, Queen's University of Belfast, Northern Ireland (http://questor.qub.ac.uk/newsite/contact.htm). For reviews on methods for generating *cis*-1,2-dihydrocatechols by microbial dihydroxylation of the corresponding aromatics, as well as the synthetic applications of these metabolites, see: (a) Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichim. Acta* **1999**, *32*, 35. (b) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A.; McLeod, M. D.; McRae, K. J.; Stewart, S. G.; Vögtle, M. *Pure Appl. Chem.* **2003**, *75*, 223. (c) Johnson, R. A. *Org. React.* **2004**, *63*, 117. (d) Hudlicky, T.; Reed, J. W. *Synlett* **2009**, 685.

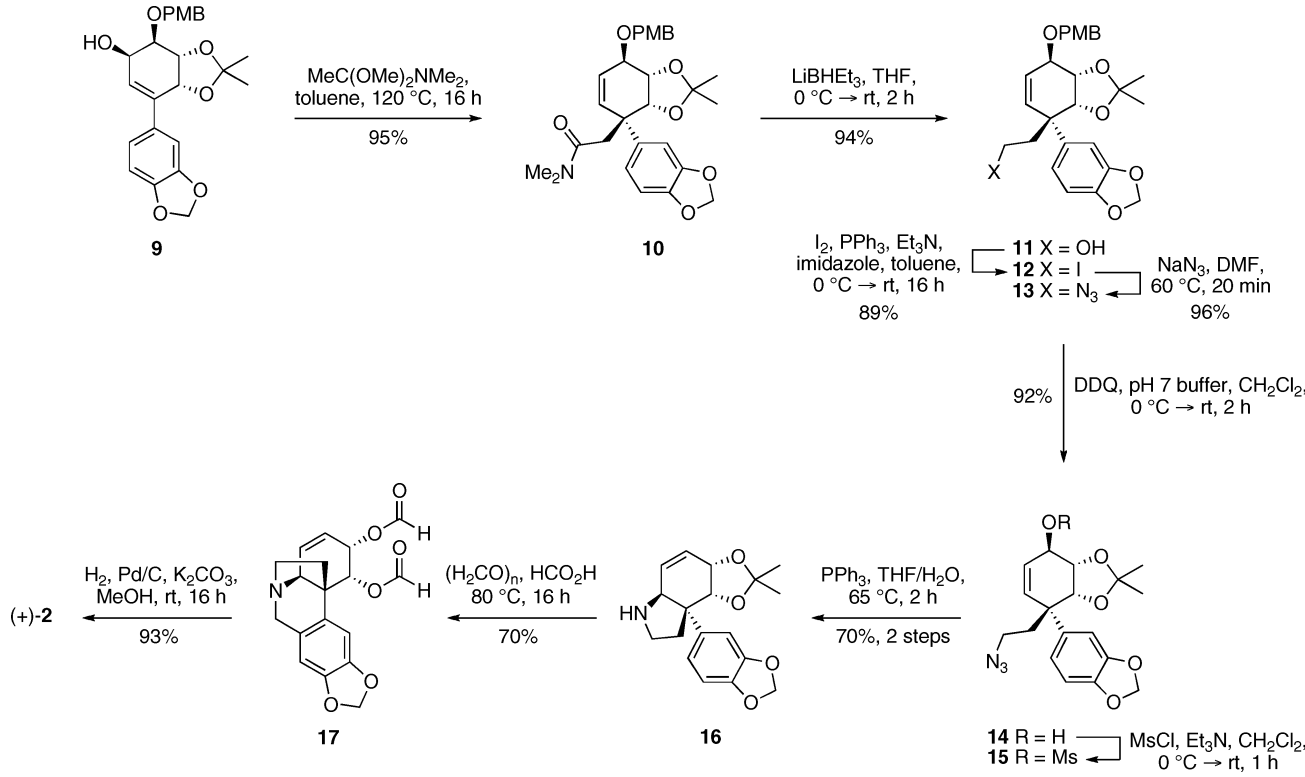
(6) (a) Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439. (b) Hudlicky, T.; Rulin, F.; Tsunoda, T.; Luna, H.; Andersen, C.; Price, J. D. *Isr. J. Chem.* **1991**, *31*, 229.

(7) (a) Ireland, R. E.; Liu, L.; Roper, T. D. *Tetrahedron* **1997**, *53*, 13221. (b) Paterson, I.; Coster, M. J.; Chen, D. Y.-K.; Aceña, J. L.; Bach, J.; Keown, L. E.; Trieselmann, T. *Org. Biomol. Chem.* **2005**, *3*, 2420.

(8) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.

(9) For a useful point-of-entry into the literature on the Staudinger reaction see: Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic: Burlington, MA, 2005; pp 428−429.

Scheme 2. Completion of the Synthesis of (+)-Amabiline



data available for the natural product.[2,3] Furthermore, the specific rotation of (+)-amabiline {$[\alpha]_D$ +31.8 (*c* 0.25, EtOH)} was of similar magnitude but opposite sign to that reported[2] for the naturally occurring enantiomer {$[\alpha]_D$ −32 (*c* 0.3, EtOH)}.

It is anticipated that minor modifications to the reaction sequence presented here should provide access to related members of the crinine alkaloid family. Work toward such ends is now underway and results will be reported in due course.

Acknowledgment. We thank the Institute of Advanced Studies and the Australian Research Council for generous financial support.

Supporting Information Available: Full experimental procedures; ^{1}H and/or ^{13}C NMR spectra of compounds (+)-**2**, **5**, **6**, **8**−**10**, **12**−**14**, **16** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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