Communications to the Editor

Short, Efficient Syntheses of the Amaryllidaceae Alkaloids (−)-Amabiline and (−)-Augustamine *via* Intramolecular 2-Azaallyl Anion Cycloadditions

William H. Pearson* and Frank E. Lovering

Department of Chemistry, The University of Michigan Ann Arbor, Michigan 48109-1055

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The Amaryllidaceae alkaloids continue to be of interest as synthetic targets due to the wide range of biological activities exhibited by these bases.[1] We report exceptionally short and efficient total syntheses of the Amaryllidaceae alkaloids (−)-amabiline (**1**) and (−)-augustamine (**2**) (Figure 1), neither of which have been previously synthesized. In addition to providing further evidence of the utility of 2-azaallyl anion cycloadditions, this work serves to confirm the absolute stereochemistry of these two alkaloids.

We have previously shown that the intramolecular cycloaddition of 2-azaallyl anions with alkenes[2] is a useful method for the assembly of the octahydro- or hexahydroindole ring system often found embedded in the polycyclic Amaryllidaceae alkaloids (e.g., crinine[3] and epipretazettine[4]). The 2-azaallyl anions are readily generated by tin−lithium exchange of (2-azaallyl)-stannanes with *n*-butyllithium.[2b−f] In order to better understand the scope and stereoselectivity of these cycloadditions, we chose to explore the synthesis of the alkaloids (−)-amabiline (**1**) and (−)-augustamine (**2**), both of which were proposed to be available from the same 2-azaallyl anion **4** *via* similar octahydroindoles **3** (Figure 1). Amabiline (**1**) is a new alkaloid isolated from the bulbs of *Crinum amabile*.[5] Its absolute configuration presumably was assigned as that shown in Figure 1 by comparison of the direction of its optical rotation with that of other alkaloids containing the 5,10-ethanophenanthridine ring system. Augustamine (**2**) has an octahydroindole core identical to that of amabiline. Augustamine was isolated from *Crinum augustum* in 1981 and characterized in 1983,[6] and interest in its pharmacological properties persists.[7] Its absolute stereochemistry was not assigned. We are not aware of any other Amaryllidaceae alkaloids with a similar arrangement of hydroxyl groups in the cyclohexane ring as that found in these two alkaloids, and no related synthetic studies have been reported.[8]

We chose the lactone **5** as the starting material for our synthesis, since it has the correct relative configuration at the two oxygen-bearing stereocenters for amabiline and augustamine (Scheme 1). It also seemed likely that the enantiomer of **5**

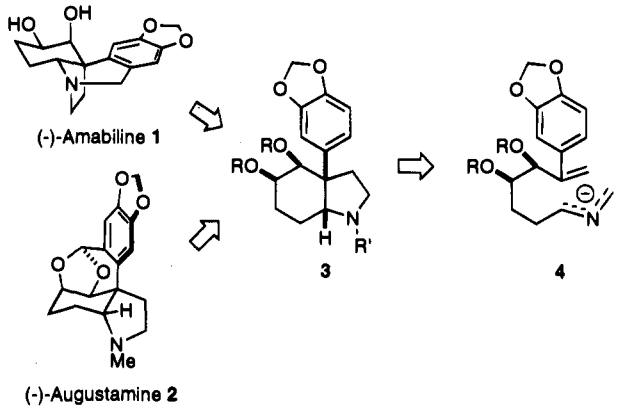
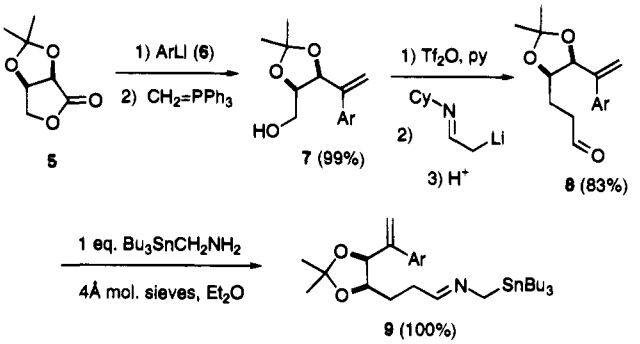


Figure 1. Retrosynthetic analysis of (−)-amabiline (**1**) and (−)-augustamine (**2**).

Scheme 1. Synthesis of the (2-Azaallyl)stannane **9**



shown would lead to the natural enantiomers of both target molecules. The lactone **5** is commercially available (Aldrich) or may be prepared in large quantities from inexpensive D-isoascorbic acid.[9] Lithium−halogen exchange of 4-bromo-1,2-(methylenedioxy)benzene with *n*-butyllithium in THF gave the aryllithium **6**, which was added to the lactone **5**. Without purification, the resultant lactol was subjected to Wittig methylenation to give the alcohol **7** in nearly quantitative yield for the two-step sequence. Chain extension of **7** to the aldehyde **8** was accomplished in an efficient manner using metalloenamine chemistry.[10] Thus, the alcohol **7** was converted to its triflate and then treated with the metalloenamine derived from *N*-cyclohexylacetaldimine and LDA. The resultant imine was hydrolyzed under mildly acidic conditions to give aldehyde **8** in 83% yield from the alcohol **7**, a sequence requiring no purification of intermediates. The aldehyde **8** was then condensed with (aminomethyl)tri-*n*-butylstannane[2d] to give the (2-azaallyl)stannane **9** in quantitative yield.

Addition of the (2-azaallyl)stannane **9** to a solution of *n*-butyllithium in THF at −78 °C effected transmetalation to the 2-azaallyl anion, which participated in an intramolecular cycloaddition with the alkene (Scheme 2). Quenching the resultant *N*-lithiopyrrolidine with water afforded two diastereomers, **10a** and **10b**, of the cycloadduct in a 5:1 ratio. While exposure of **10a** to classic Pictet−Spengler conditions (HCl,

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(8) Many synthetic studies on structurally related alkaloids such as crinine, pretazettine, and mesembrine have been published.[1,3,4]

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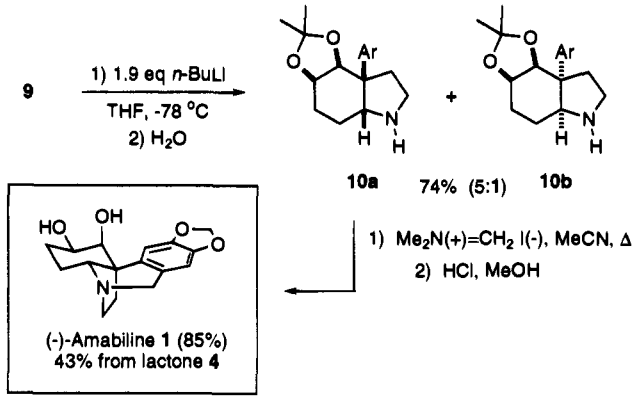
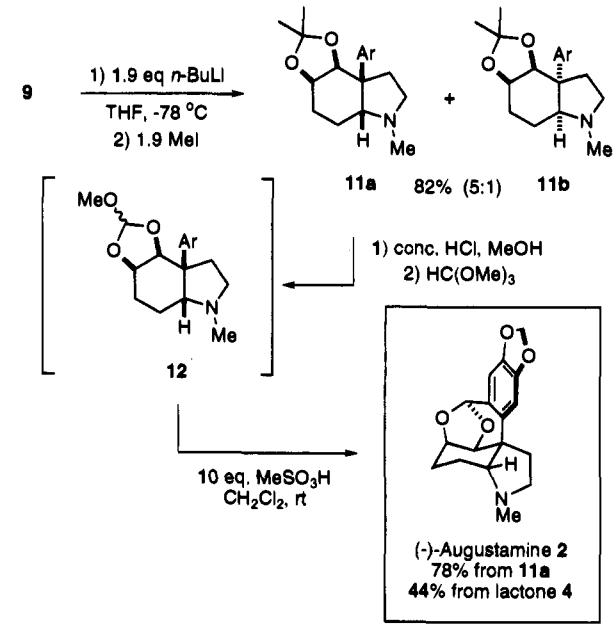
Scheme 2. Synthesis of (−)-Amabiline (**1**)



formaldehyde) did not promote the desired transformation, treatment of **10a** with Eschenmoser's salt[11] in refluxing acetonitrile followed by removal of the acetonide under acidic conditions gave (−)-amabiline (**1**) in 92% yield. The spectral data of synthetic (−)-amabiline were consistent with those provided by Professor Cordell.[12] The optical rotation, $[\alpha]^{20}_D$ −31.6° (c = 0.28, EtOH), matched the literature value of $[\alpha]^{20}_D$ −32° (c = 0.3, EtOH),[5] verifying the absolute configuration of the natural alkaloid. The synthesis of (−)-amabiline required eight steps from the lactone **5**, required only four purifications, and proceeded in 43% overall yield.

For the synthesis of (−)-augustamine, the 2-azaallyl anion cycloaddition was repeated as described above, except that the workup was carried out with iodomethane to provide a 5:1 ratio of **11a** and **11b** in 82% yield (Scheme 3). Removal of the acetonide with methanolic HCl provided the diol. Initial attempts to form the bicyclic ketal of augustamine directly using a related protocol developed by Danishefsky[13] in his work on tazettine and pretazettine (PPA, trimethyl orthoformate, reflux) proved unsuccessful. However, a stepwise approach proceeding through the orthoester **12** was fruitful. Evaporation of the reaction mixture resulting from the HCl cleavage of **11a** left the hydrochloride salt of the diol, which was mixed with trimethyl orthoformate to produce **12**. Without purification, **12** was treated with methanesulfonic acid to afford (−)-augustamine (**2**) in 78% yield from **11a**. The spectral data of synthetic (−)-augustamine matched that reported in the literature.[6b] The optical

Scheme 3. Synthesis of (−)-Augustamine (**2**)



rotation of synthetic **2**, $[\alpha]^{20}_D$ −80.1° (c = 1.42, $CHCl_3$), was also consistent with the literature value of $[\alpha]^{20}_D$ −83° (c = 1.4, $CHCl_3$),[6b] thus determining the absolute configuration of the natural product. The synthesis of (−)-augustamine required nine steps from the lactone **5**, required only four purifications, and proceeded in 44% overall yield.

The first asymmetric syntheses of (−)-amabiline (**1**) and (−)-augustamine (**2**) have been accomplished in overall yields of 43% and 44%, respectively, from the readily available lactone **5**, thus confirming or determining the absolute stereochemistry of the natural products. The syntheses illustrate the efficiency of the 2-azaallyl anion cyclization for the assembly of polycyclic ring systems with multiple stereogenic centers.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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