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CONSTRUCTION OF THE TRICYCLIC ABC RING SUBUNIT OF MANZAMINE A VIA A NOVEL INTRAMOLECULAR DIELS-ALDER REACTION

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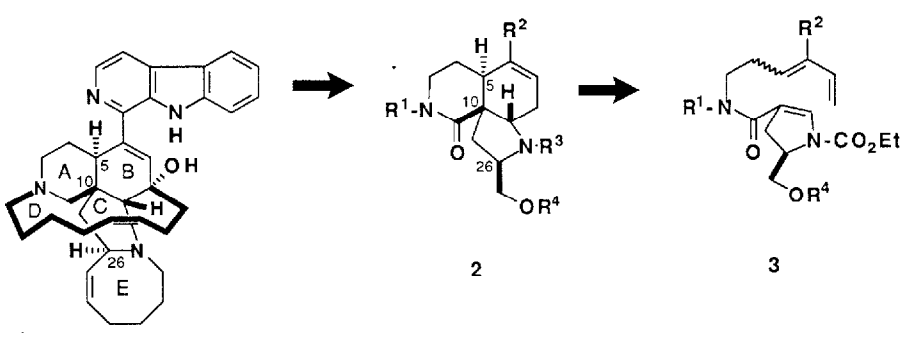
Abstract. A novel entry to the manzamine A (**1**) has been designed that features an intramolecular Diels-Alder reaction of a vinylogous imide for the facile construction of the tricyclic core of **1** as illustrated by the conversions **8** and **16** → **9**.

Manzamine A (**1**) belongs to a novel class of β-carboline alkaloids that were isolated from marine sponges of genera *Haliclona* and *Pellina* found off the coast of Okinawa.[1] The complex structure of this alkaloid, which is unprecedented in nature, coupled with its antitumor activity has served as an impetus for an increasing number of interesting synthetic investigations. Most of the reported activity thus far has been focused upon constructing the central pyrrolo[2,3-*j*]isoquinoline tricyclic core.[2] Some years ago we first disclosed the utility of intramolecular Diels-Alder[3] reactions for the facile formation of hydroisoquinolines[4] and have since exploited such processes in the design of concise approaches to a number of important alkaloid natural products.[5] As an extension of these investigations, it occurred to us that a variant of the intramolecular Diels-Alder reaction involving either a vinylogous amide or imide as the dienophile might provide an efficacious entry to the ABC skeletal subunit of manzamine A. Specifically, we envisioned that the cyclization of substrates such as **3** would proceed to deliver cycloadducts such as **2**, thereby creating the tricyclic core of manzamine A in a single step (Scheme 1). We report herein the successful realization of this preliminary objective.

Scheme 1



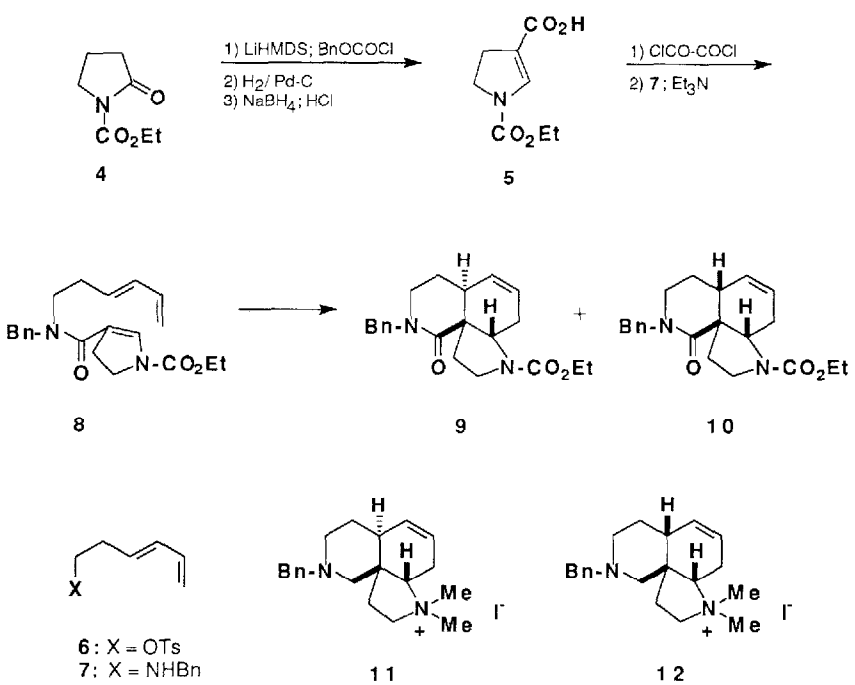
1 **2** **3**

Prior to embarking upon a major effort to prepare manzamine A (**1**) according to the strategy formulated in Scheme 1, it was necessary to evaluate two critical issues. First, it was mandatory to establish the feasibility of the key cycloaddition step, since there existed scant precedent for the participation of vinylogous imides as dienophiles in intramolecular Diels-Alder reactions.[6] Having verified the viability of the cycloaddition, it would be necessary to

define those stereochemical control elements that would guarantee the stereoselective production of the requisite *cis*-hydroisoquinoline ring system as well as the correct relationship between the centers at C(10) and C(26) in **2**.

We have examined several methods to construct vinylogous imides related to that present in **3**, but the most effective tactic developed thus far entails reaction of acid chlorides derived from the mono acids of vinylogous imides.[7] Thus, *N*-ethoxycarbonyl-2-pyrrolidinone (**4**)[8] was transformed in 72% overall yield in three steps into the acid **5** (Scheme 2). Subsequent reaction of **7**, which was prepared by aminolysis ($BnNH_2$/MeCN/Δ; 14 h; 83%) of the known tosylate **6**,[4] with the acid chloride generated from **5** (ClCO-COCl/CH_2Cl_2; 25 °C) furnished the vinylogous imide **8** in 84% yield. When **8** was simply heated in mesitylene at reflux, a mixture (ca. 2:1) of the two cycloadducts **9**, which corresponds to the tricyclic ABC subunit of manzamine A (**1**), and **10** was obtained (81%). The structures of **9** and **10** were initially assigned on the basis of a series of NOE studies, but the veracity of these assignments were later confirmed by single crystal X-ray analyses[9] of the two quaternary salts **11** and **12**, which were prepared from **9** and **10**, respectively, by sequential hydride reduction and methylation [(1) $LiAlH_4$/THF; Δ. (2) MeI/MeOH; 25 °C]. This critical experiment thus convincingly supported the earlier hypothesis that a vinylogous imide array could participate as the dienophile in an intramolecular Diels-Alder reaction. More importantly this cyclization also firmly established the feasibility of the key step in our novel strategy for the synthesis of **1**.

Scheme 2

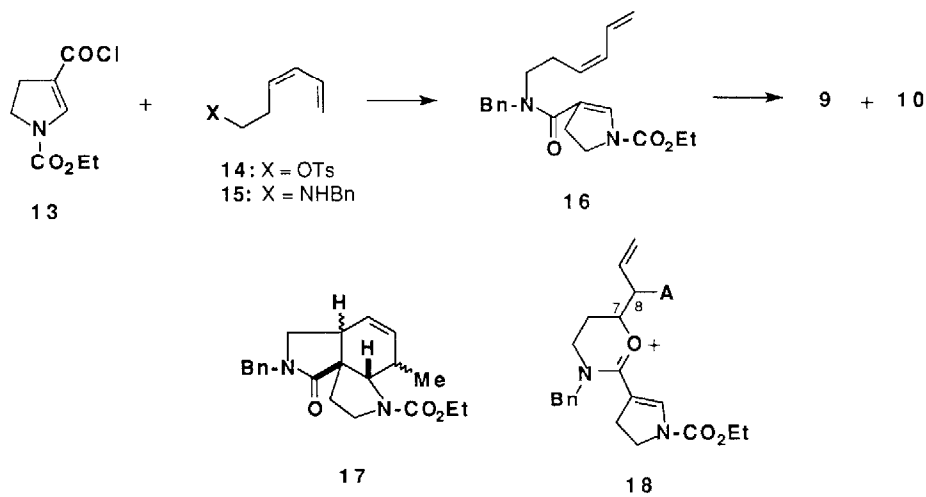


We then explored various means to enhance the stereoselectivity of the intramolecular Diels-Alder reaction of trienes related to **8**. In the first series of experiments, we examined the effect of Lewis acids on the reaction and found that heating **8** in the presence of $EtAlCl_2$ (1.5 equiv/toluene/110 °C; 72 hr; 71%) provided a mixture (5.7:1) of

9 and **10**. That $EtAlCl_2$ served a catalytic role was clearly evident based upon the observation that the cyclization was markedly slower at this temperature in the absence of $EtAlCl_2$. Other Lewis acids ($TiCl_4$ and $BF_3{\cdot}Et_2O$) were found to be less effective than $EtAlCl_2$, but Et_2AlCl may also be used. Further studies are in progress.

The intramolecular [4+2] cycloadditions of trienes in which the internal double bond is *Z* are more stereoselective than the cyclizations of the corresponding trienes having an *E* internal double bond.[10] Since examination of molecular models revealed that only the transition state leading to the desired *cis*-fused product **9** would be accessible to the *Z*-triene **16**, we set to the task of preparing **16** by straightforward modification of the procedures developed previously for the synthesis of **8**. In the event, the unsaturated amine **15**, which was formed in 78% yield upon treatment of the tosylate **14**[4] with benzylamine, was allowed to react with the acid chloride **13** (**5**, ClCO-COCl) to furnish **16** in 77% yield (Scheme 3). Surprisingly, when **16** was heated in the presence of $EtAlCl_2$ (1.5 equiv/toluene; 120 °C; 100 h; 70%), a mixture (ca. 8:1) of cycloadducts was obtained that contained the expected **9** as the major product, but the isomeric adduct **10** was also formed. The cyclization of **16** could also be induced thermally (180 °C, 20 h), but a mixture (4:1:7; 83% combined yield) of **9**, **10**, and two isomers (ca. 3:1) of **17**, which ostensibly arose by cyclization of an isomeric triene derived from **16** via a 1,5-hydrogen shift, was obtained.

Scheme 3



We tentatively speculate that those quantities of **10** that were produced upon thermolysis of **16** arose from the cyclization of **8** that is formed under the reaction conditions by isomerization of **16**. Presumably **16** undergoes acid-catalyzed cyclization to an intermediate of type **18** (A = Lewis acid or H); rotation about the C(7)-C(8) bond of the trienic array then ensues followed by elimination to provide **8**. In support of this hypothesis, we recently found that **16** does undergo partial equilibration to **8** in the presence of catalytic amounts of $EtAlCl_2$ (toluene, 72 h, 40 °C; ca. 30% conversion). We are exploring a variety of modifications of experimental parameters in an effort to define those conditions in which the cyclizations of *Z*-trienes related to **16** will not be accompanied by the deleterious isomerization to the corresponding *E*-trienes.

In these preliminary investigations, we have established the applicability of intramolecular Diels-Alder reactions of vinylogous imides to the facile construction of the pyrrolo[2,3-*j*]hydroisoquinoline ring system that

constitutes the central tricyclic core of manzamine A (**1**). These results pave the way for future investigations toward the total synthesis of **1**, which are presently underway in our laboratories.

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