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Antimalarial Activity of a New Family of Analogues of Manzamine A

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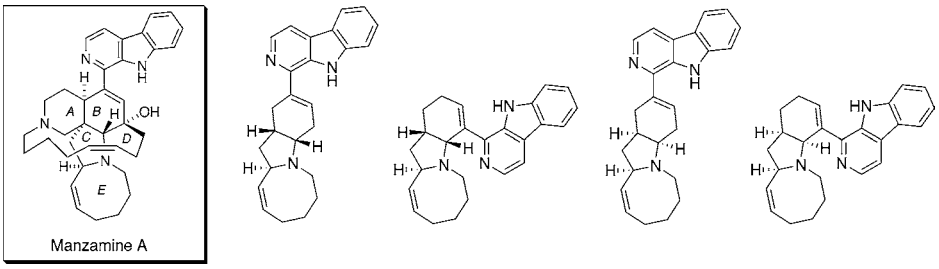
ABSTRACT



Manzamine A represents an important lead structure for the development of novel antimalarial chemotherapies. The synthesis and biological evaluation of a group of simplified analogues of manzamine A, which were designed to examine the roles of the A and D rings and of both the relative stereochemistry and the orientation of the β-carboline heterocycle on the antimalarial activity of manzamine A, are described.

Malaria is a disease that affects 300−500 million people each year and results annually in 1−2 million deaths, mostly among children. Structurally and functionally novel antimalarial agents with new mechanisms of action are needed as monotherapeutic agents or for use in combined chemotherapy with other presently available drugs. The urgent need for new and effective antimalarials escalates as *Plasmodium falciparum* and other human malaria parasite species have developed resistance to most commercially available antimalarial agents.[1]

The manzamine alkaloids represent important lead structures for the development of antiinfectives. Manzamine A and related structures represent highly potent, orally bioavailable[2] antimalarial substances that are more effective than most currently available therapeutics, i.e., chloroquine and artemisinin. In addition, some of the manzamine classes have also demonstrated activity against AIDS-opportunistic infectious diseases including tuberculosis and toxoplasmosis.

The low isolated yield of **1** that was originally reported from a natural source, the Okinawan sponge *Haliclona* sp.,[3] prompted us to examine the SAR of manzamine A in an effort to develop simpler structural analogues with comparable antimalarial properties. We describe herein the synthesis and biological evaluation of a "minilibrary" of analogues of manzamine A that was designed to probe the roles of the A and D rings as well as the relative stereochemistry and β-carboline orientation on the antimalarial pharmacophore. The retention of the β-carboline moiety was deemed critical as the antimalarial activity of ircinol A (**2**, Figure 1) is ca. 400 times less than that of manzamine A.[4]

On the basis of the approach that was featured in our total synthesis of manzamine A,[5] we reasoned that the readily

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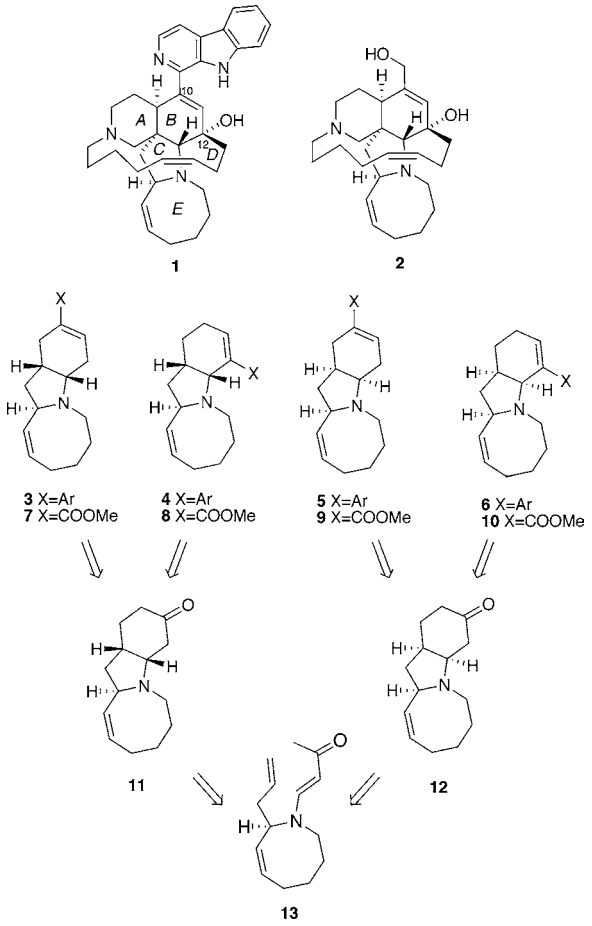
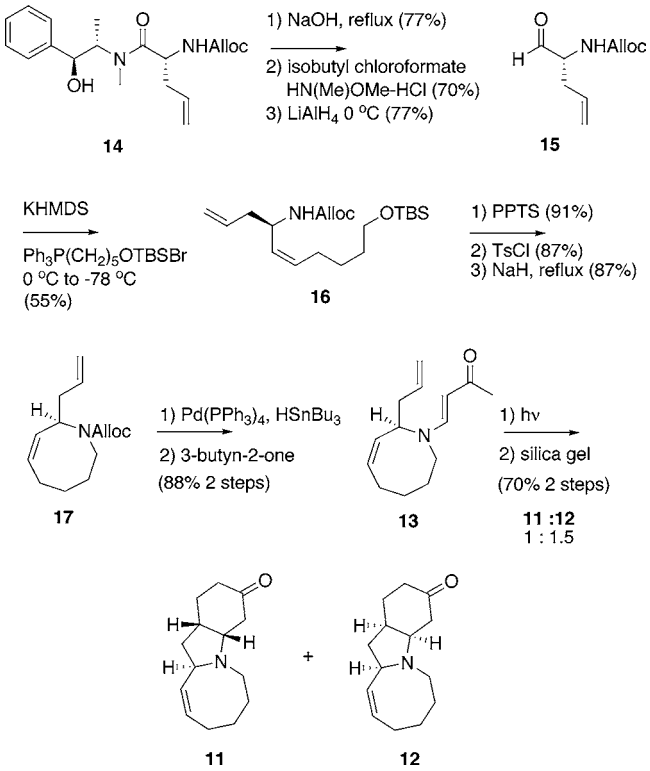


Figure 1. Retrosynthetic analysis.

available photosubstrate **13** could serve as a source of a family of analogues in which both the relative stereochemistry and the orientation of the β-carboline heterocyclic ring could be varied. The synthesis and irradiation of photosubstrate **13** are outlined in Scheme 1. The absolute stereochemistry of **13** was established via the alkylation of Myers pseudoephedrine glycinamide[6] with allyl bromide to give **14**. Hydrolysis of **14**, followed by Weinreb amide formation, and $LiAlH_4$ reduction afforded aldehyde **15**, which was subjected without purification to Wittig olefination to produce **16** as the desired *cis*-alkene. Silyl ether deprotection, followed by tosylation, and NaH-mediated ring closure yielded azocine **17**. Alloc removal in the presence of Pd(0) followed by alkylation of the resulting secondary amine with 3-butyn-2-one[7] afforded photosubstrate **13**. Irradiation of **13** through a Pyrex photoreaction vessel (8 mM in acetonitrile)

Scheme 1. Photosubstrate Synthesis and Irradiation



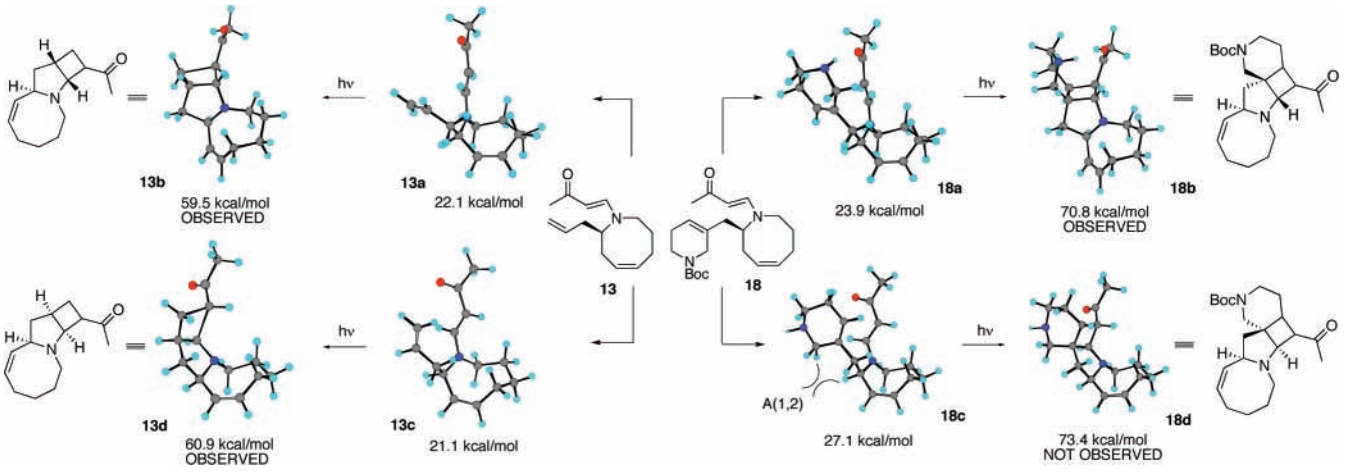


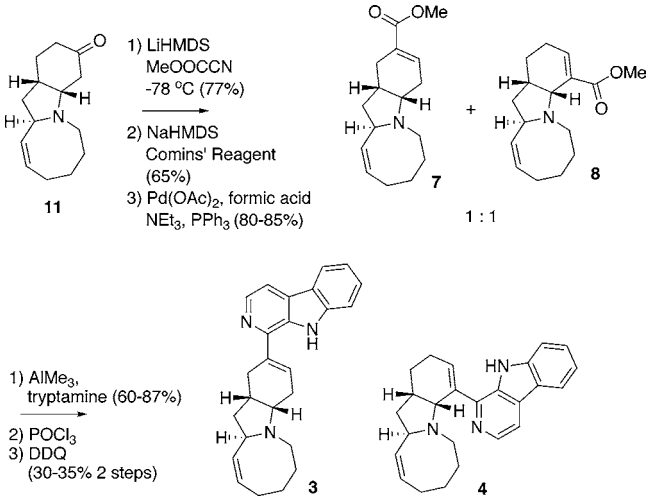
Figure 2. Stereochemistry of [2+2] photoaddition of BCE vs ABCE photosubstrates.

yielded a diastereomeric mixture of intermediate aminals, which in the presence of silica gel afforded tricyclic ketones **11** and **12** in a 1:1.5 ratio, respectively.

The lack of diastereoselectivity in the photocycloaddition of **13** stands in marked contrast to the highly selective formation of the manzamine core that we have described.[8] This difference can be understood as a function of the presence or absence of the tetrahydropyridine manzamine A ring in the photocycloaddition reaction. In the case of **18a**, the orientation of the A ring is locked as shown in Figure 2. The alternative cyclohexene ring conformation **18c** suffers from an internal A(1,2) strain interaction, which accounts for the ca. 3.2 kcal/mol difference in energy between **18a** and **18c**. The absence of the A ring in **13** significantly decreases the energy difference between the two possible reacting conformers **13a** and **13c**, and our calculations (MM2) indicate only a ca. 1.0 kcal/mol difference in energy between **13a** and **13c**, a result that is consistent with the observed 1:1.5 ratio of products.

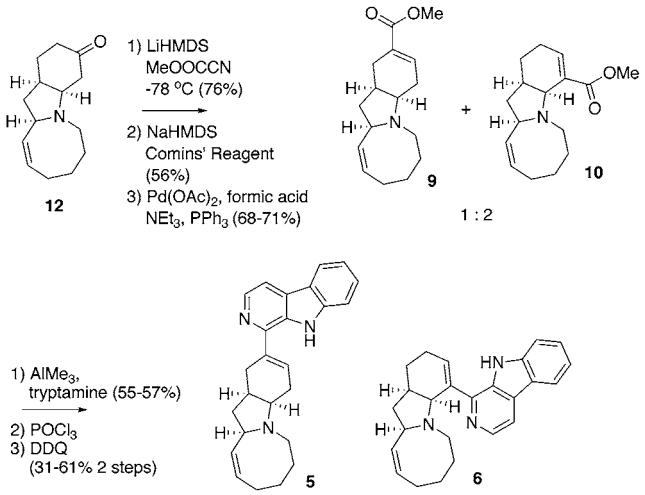
The syntheses of BCE analogues **3**−**6** were completed as shown in Schemes 2 and 3. Enolization of **11** led to the

Scheme 2. Synthesis of Analogues **3** and **4**



formation of a mixture of enolates, which afforded an inseparable mixture of ketoesters (not shown). We were delighted to find that conversion of the ketoester mixture to the corresponding enol triflates (NaHMDS, Comins' reagent) facilitated the separation of the diastereomeric products, which on reduction gave, separately, each of the unsaturated esters **7** and **8** in a ca. a 1:1 ratio. Weinreb aminolysis of each of the unsaturated esters with trimethylaluminum and tryptamine, followed by Bischler−Napieralski cyclization and DDQ-mediated oxidation, afforded the desired BCE

Scheme 3. Synthesis of Analogues **5** and **6**



analogues **3** and **4**. Similar treatment of **12**, as outlined in Scheme 3, gave the isomeric β-carboline-containing analogues **5** and **6**.

These four novel structures facilitated an interrogation of the role of both the A and D rings and of the relative stereochemistry and β-carboline orientation on the antimalarial activity of **3**−**6**. We note that **3**, which embodies both the same relative stereochemistry (cis-exo orientation of the azocine ring relative to the BC ring system) and the same β-carboline orientation (C-10) as that of manzamine A, exhibits the most potent antimalarial activity of the new structures, all of which are significantly less active than manzamine A itself (see Table 1). These results underscore the importance of the A and D rings on the antimalarial activity of manzamine A. We observe a ca. 8-fold decrease in activity with **5** relative to **3**, an indication of the significance of the manzamine relative stereochemistry for the antimalarial activity of **3**. In contrast, changing the β-carboline orientation, i.e., **4** vs **3**, leads to a more modest 2-fold decrease in activity, suggesting a greater role for the manzamine relative stereochemistry in the observed activity of these novel structures. It is more difficult to make direct comparisons with **6**, which embodies neither the manzamine relative stereochemistry nor the orientation of the β-carboline found in the natural product.

Table 1. Antimalarial Activity Against *P. falciparum*

compound	IC_{50} (ng/mL) W2 clone	IC_{50} (ng/mL) D6 clone
manzamine A	13.5	25.0
3	310	300
4	630	640
5	2500	1800
6	1300	1500

These simplified analogues (**3**−**6**) of manzamine A provide valuable insight into the structural and stereochemical

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requirements for biological activity in this system. Further studies are currently underway in our laboratory, and our results will be reported in due course.

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

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