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Partial Synthesis of the Antiamoebic Bisindole Alkaloid (-)-Macrocarpamine.

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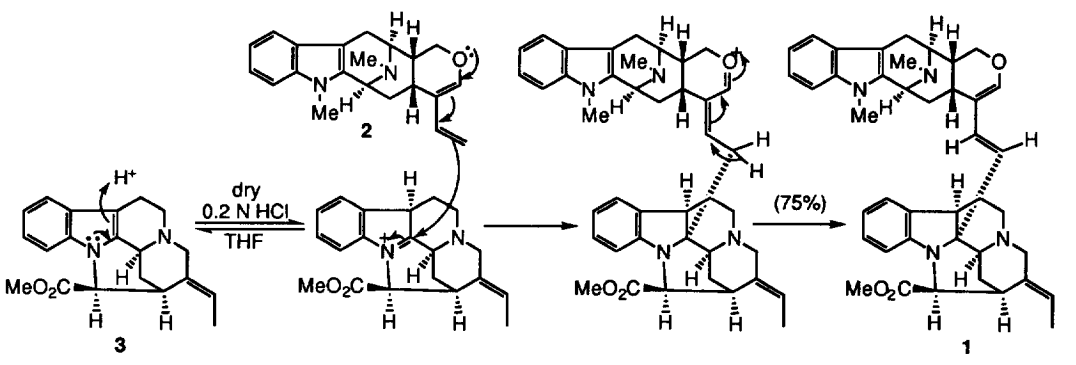
Abstract: *The partial synthesis of the antiamoebic bisindole alkaloid (-)-macrocarpamine* ***1*** *has been completed by coupling (-)-anhydromacrosalhine-methine* ***2*** *with plant-derived (+)-pleiocarpamine* ***3*** *in anhydrous 0.2 N HCl in THF in 75% yield.* Copyright © 1996 Elsevier Science Ltd

Diseases caused by protozoa are responsible for considerable mortality and morbidity in the tropics and subtropics, consequently, there is a need for new therapeutic agents.[1,2] With respect to the *Alstonia* alkaloids, Wright *et al.* recently reported that nine alkaloids from *Alstonia angustifolia* had antiprotozoal activity *in vitro* against *Entamoeba histolytica* and *Plasmodium falciparum.* Three bisindole alkaloids, macrocarpamine **1**, macralstonine acetate (semisynthetic), and villastonine were found to possess significant activity against both protozoa mentioned above. Moreover, **1** was found to be the most active antiamoebic compound but was four times less potent than the standard antiamoebic drug, emetine. The results of these *in vitro* studies provide some basis for the traditional use of *Alstonia angustifolia* in the treatment of amoebic dysentery and malaria by the people of Malaya.[1,2] (-)-Macrocarpamine **1** was first isolated from the bark of *Alstonia macrophylla* Wall by Hesse *et al.* in 1978.[3] Furthermore, in 1988 Ghedira *et al.* reported the isolation of the related bisindoles 10-methoxymacrocarpamine and 10-methoxymacrocarpamine-N-4'-oxide from the leaves of *Alstonia angustifolia.*[4]

Scheme 1



Recently (-)-anhydromacrosalhine-methine **2** was synthesized enantiospecifically from D-(+)-tryptophan (see the previous paper). When **2** was coupled with natural pleiocarpamine **3** under aqueous acidic conditions (0.2 N aq. HCl), the enol ether **2** was converted into products of hydration. However, treatment of **3** with 6 equivalents of **2** (added portionwise over a 48 hour period) in 0.2 N anhydrous HCl/THF provided (-)-macrocarpamine **1** in 75% yield. Nucleophilic attack of the diene **2** did occur on pleiocarpamine **3** from the α-face of the 2,3-indole double bond as planned.[5] The spectroscopic properties (MS, NMR) of synthetic **1** were virtually identical to those reported by Mayerl and Hesse.[3] The structure of **1** was further confirmed by 2D NMR (HMQC, COSY) experiments. Although at least four bisindoles[1,2,4,6] have been isolated which could presumably be formed by condensation of a diene such as **2** with another monomeric indole unit, to our knowledge this is the first example of a coupling reaction between a vinylogous enol ether (diene **2**) of this type and an iminium ion. Moreover, this sequence serves as the first example of a proton-mediated coupling reaction between two monomeric units in the *Alstonia* series to provide a bisindole alkaloid. In the biomimetic syntheses of LeQuesne,[7] the Michael acceptor (macroline) served as the electrophile and its addition to pleiocarpamine was not readily reversible in acidic solution. In contrast, in the condensation between pleiocarpamine **3** and the diene **2**, the electrophile is a proton. Since protonation of the indole double bond of **3** is a readily reversible process, the sequence illustrated here is unique. The diene **2** must be added to an acidic solution of **3** in small portions to immediately quench the iminium ion intermediate, otherwise only products of diene decomposition are observed.

The work described above constitutes the first partial synthesis of the antiamoebic alkaloid (-)-macrocarpamine **1** and supports the earlier biogenetic proposal of Hesse in regard to the origin of bisindole **1**.[3]

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