Pergamon

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A Partial Synthesis of the *Alstonia* Bisindole Alkaloid Villalstonine

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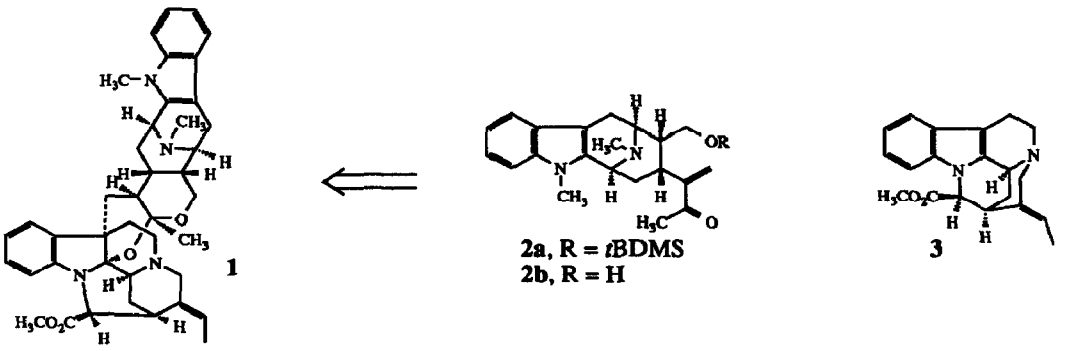
Abstract: *The partial synthesis of villalstonine 1 has been completed by coupling the macroline equivalent 2a with plant-derived (+)-pleiocarpamine 3 in 0.2N aq. hydrochloric acid in the presence of fluoride ion.*

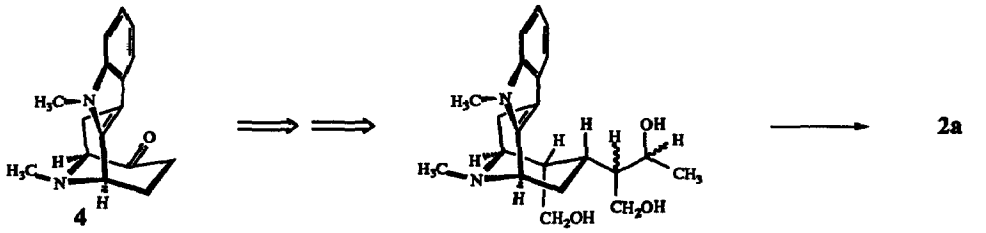
Since *Cinchona* bark became known to the Europeans three centuries ago, its preparations and its principle alkaloid, quinine, have been used in the treatment of malaria.[1,2] During an epidemic in Manila, dita bark, an extract of *Alstonia scholaris* was said to have surpassed quinine as a drug to treat malaria. With respect to the macroline/sarpagine alkaloids, Wright et al.[3] recently reported their findings on the antiprotozoal activity of nine alkaloids from *Alstonia angustifolia* against *Entamoeba histolytica* and *Plasmodium falciparum* in vitro. Three bisindole alkaloids, macralstonine acetate, macrocarpamine and villalstonine **1** were found to exhibit significant activity against both protozoa mentioned above. Villalstonine **1**, in fact, was found to be the most potent alkaloid of the three against *P. falciparum* and was about one fifteenth as potent as the antimalarial drug chloroquine. These results, therefore, explain the use of



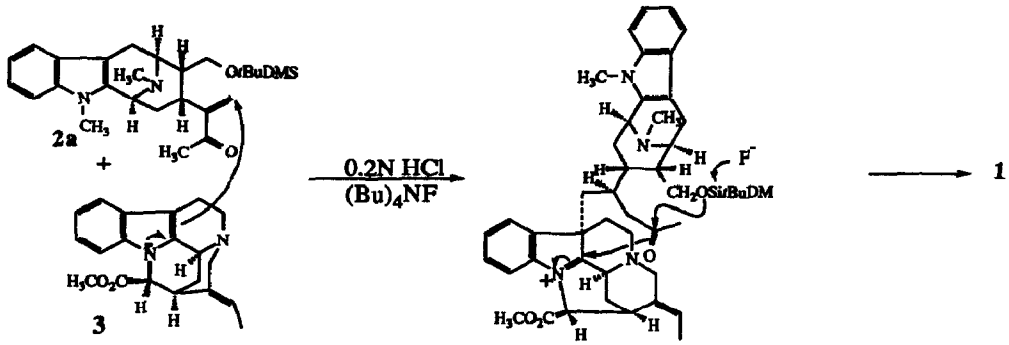
Scheme 1

Alstonia angustifolia in traditional medicine for treatment of amoebic dysentery and the treatment of malaria, although the potencies of even the most active alkaloids were less than the standard drugs tested.[3]

Recently the (-)-tetracyclic ketone **4** has been converted enantiospecifically into the macroline equivalent **2a** *via* a series of stereocontrolled steps outlined in reference 4. We wish to report that stirring the synthetic macroline equivalent (+)-**2a** with plant-derived pleiocarpamine **3** in 0.2N aqueous hydrochloric acid in the presence of fluoride ion provided villalstonine **1** as the only observable product. It is believed that this biomimetic[5]-type coupling process occurred as illustrated in Scheme 3. Since synthetic (+)-macroline **2b**[4] also underwent this same condensation in 60% yield, it is difficult to determine whether initial condensation between **2a** and **3** took place before or after the fluoride-mediated scission of the silicon oxygen bond in **2a**. Irregardless of this, both approaches led to the stereospecific formation of **1**. Villalstonine prepared *via* this route was identical in all respects (TLC, MS, IR NMR) with an authentic sample of **1** isolated from *A. muelleriana*.[6-8] This constitutes the first partial synthesis of any of the *Alstonia* bisindole alkaloids.



Scheme 2



Scheme 3

References and notes:

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8. Villalstonine (from Scheme 3) was shown to be pure by NMR spectroscopy.

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