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GENERAL APPROACH FOR THE SYNTHESIS OF MACROLINE/SARPAGINE ALKALOIDS. THE TOTAL SYNTHESIS OF (+)-MACROLINE

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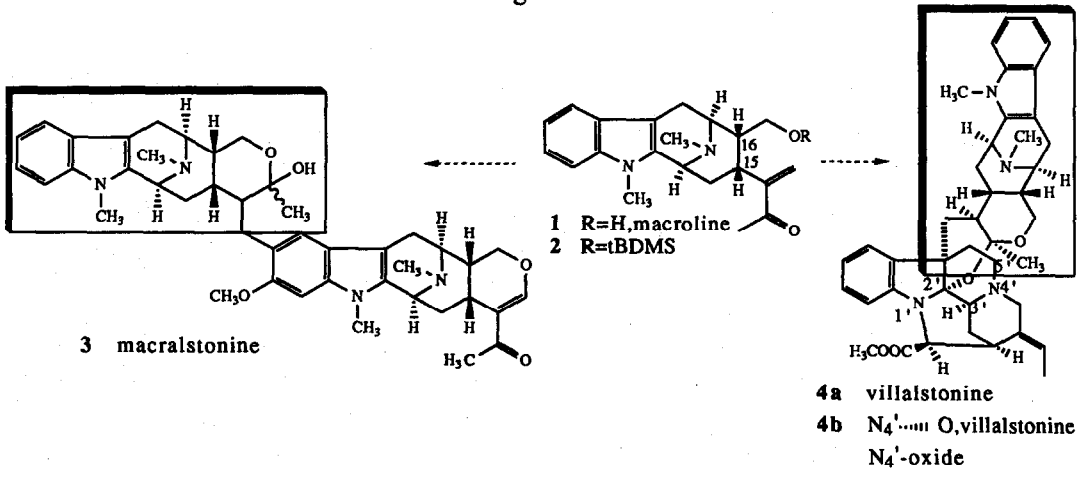
Abstract: *(+)-Macroline **1** and a more stable equivalent **2** were synthesized from the tetracyclic ketone **5**. The key steps in the synthesis involved a stereoselective Claisen rearrangement followed by hydroboration-oxidation of the resulting olefin **14** to set the correct stereochemistry at C-15 and C-16.*

During the last several years, over sixty indole alkaloids have been isolated from *Alstonia macrophylla* Wall, *Alstonia muelleriana* Domin, and other *Alstonia* species.[1,2] At least eighteen of these alkaloids are bisindoles including the hypotensive base macralstonine **3**[3] and the related villalstonine **4a**,[4] depicted in Figure 1. A unit derived from macroline comprises one portion of the structure of a number of these alkaloids, although **1** has been obtained only as a degradation product of villalstonine **4a**.[4] In addition, **1** has been shown to be a biomimetic precursor of the bisindole alkaloids alstonisidine,[5] macralstonidine[6] and alkaloid-H,[7] as well as that of **3**,[8] **4**,[5] and the monomeric base alstonerine.[6] It has been proposed by LeQuesne[6] that **1** or a suitable equivalent serves as a biogenetic precursor for one portion of most of these *Alstonia* bisindole alkaloids.[1] In keeping with our interest in the total synthesis of *Alstonia* bisindole alkaloids including **3**, we wish to report an enantiospecific synthesis of (+)-macroline **1**, as well as of the more stable macroline equivalent **2**.

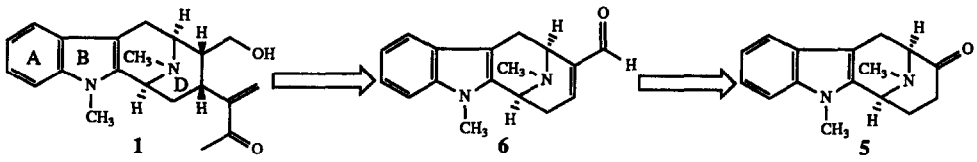
Figure 1



Examination of the structure of **1** clearly illustrates this base contains a tetracyclic ring system, (ABCD) identical to that in alstonerine and suaveoline.[9,11,12] This suggests that the synthetic intermediate, *(6S, 10S)*-(-)-5-methyl-9-oxo-12-benzyl-6, 7, 8, 9, 10, 11-hexahydro-6, 10-imino-*5H*-

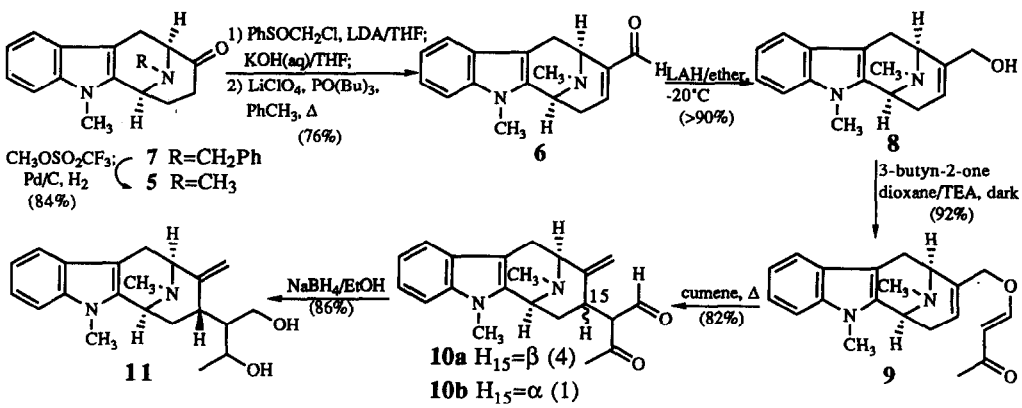
cyclooct[*b*]indole **5**, employed for the preparation of the latter two monomeric alkaloids could be used for the preparation of (+)-**1**. This optically active tetracyclic ketone **5** was prepared according to the chemistry developed *en route* to alstonerine and is now readily available.[10] Based on this, a retrosynthetic analysis of macroline is depicted in Figure 2.

Figure 2



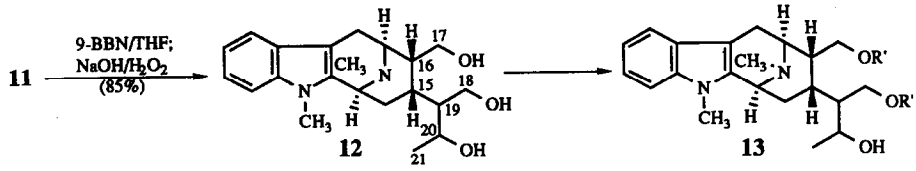
The synthesis began with **7**, which was converted into N_b-methyl ketone **5** in 84% yield by methylation with methyl triflate followed by catalytic debenzylation (H_2, Pd/C). Ketone **5** was then converted into the α,β-unsaturated aldehyde **6**, as illustrated in Scheme 1, analogous to published methods.[11] Numerous attempts have been made to effect a 1,4 addition to **6**, but with one notable exception,[12] all have failed.[13] Consequently, an intramolecular approach (Claisen rearrangement) was employed to introduce the four carbon chain at C-15. The aldehyde **6** was reduced to allylic alcohol **8** with lithium aluminum hydride. Michael addition of the allylic alcohol **8** to 3-butyn-2-one in the dark provided the desired pre-Claisen intermediate, enone ether **9**, in 92% yield. The Claisen rearrangement (150°C) took place stereoselectively, as illustrated in Scheme 1, from the desired α face (4:1) of **9** in 82% yield.[9] The β-dicarbonyl compound **10a** was reduced to the diol **11** with sodium borohydride.

Scheme 1



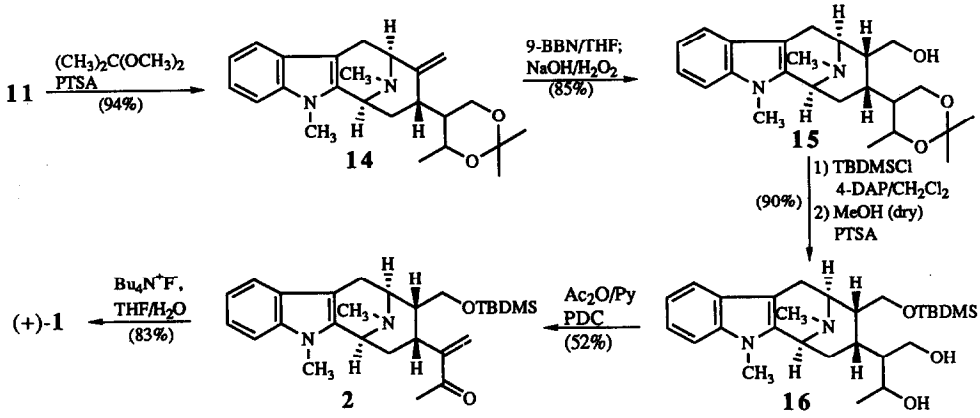
Stereoselective hydroboration-oxidation of intermediate **11** provided the triol **12**, which had earlier been converted into alstonerine.[9] Attempts to employ **12** for the synthesis of **1** were not successful in a practical sense. Tosylation of the primary hydroxyl groups at C-17 and C-18 while successful also resulted in intramolecular cyclization which furnished two additional components, one

Scheme 2



of which contained the ring system present in the related alkaloid talcarpine.[1] Protection of the two primary hydroxyl groups as the stable t-butyldimethylsilyl ethers rendered the generation of the C(18-19) olefinic double bond of **1** more difficult. A number of other methods were attempted but proved unsatisfactory. The sequence outlined in Scheme 3 was, therefore, designed to circumvent the above mentioned problems.

Scheme 3



The 1,3-diol **11** was converted into the acetonide **14** in 94% yield. Hydroboration-oxidation of **14** occurred exclusively from the β-face of the C(16-17) olefinic bond to furnish the desired primary alcohol **15** at C(17). The hydroxyl group at C(17) of **15** was converted into its *t*-butyldimethylsilyl ether afterwhich the acetonide was selectively removed by stirring with p-toluenesulfonic acid in dry methanol. The diol **16** which resulted was treated with tosyl chloride in pyridine-methylene chloride at 20°C for 48h and later at 35°C for 24h. Unfortunately, only starting **16**, accompanied by a small amount of unresolved alkaloidal material, was isolated from this process. Mesylation of **16** did take place but, as expected, with very little regioselectivity.

Based on a report by Helquist[14] in 1981, acetic anhydride was then employed as both the protecting group at C(18) and as the desired leaving group. The primary hydroxyl group in **16** at C(18) was converted into the monoacetate afterwhich the mixture was exposed to oxidation with PDC (methylene chloride). Elimination of the acetate function occurred spontaneously upon oxidation of the secondary alcohol to provide the α,β-unsaturated ketone present in the stable macroline equivalent **2**.

Both transformations were carried out in a one-pot process to provide enone **2** in 52% yield. When **2** was stirred in THF with tetrabutylammonium fluoride,[15] (+)-macroline **1** was obtained in 83% yield. The spectral properties of **1** were identical to those reported earlier by Schmid *et al.*[4]

In summary, the enantiospecific synthesis of (+)-macroline **1** and a suitable "stable equivalent" **2** has been accomplished. It is known that macroline, when exposed to alkali, will cyclize to dihydroalstonerine,[6] consequently, the synthesis of **2** was designed to enhance the shelf-life of this macroline equivalent. With (+)-**1** or **2** in hand, the synthesis of the bisindoles depicted in Figure 1 now reverts to the preparation of alstophylline[8] and pleiocarpamine,[5] respectively.

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