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# Enantiospecific total synthesis of the enantiomer of the indole alkaloid intermediate macroline

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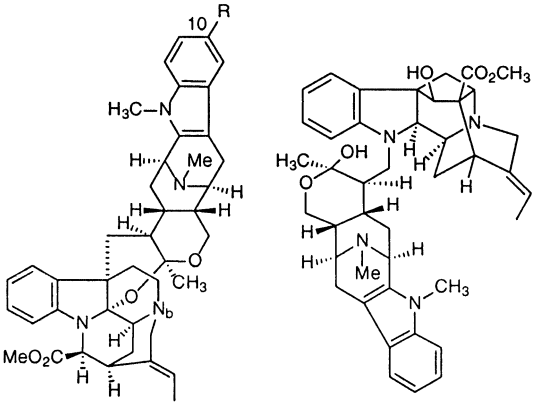
**Abstract**—The total synthesis of the enantiomer **3En** of macroline **3** was completed (from L-tryptophan methyl ester **6**) in an overall yield of 12.3% (11 isolated intermediates). The corresponding macroline equivalent **18** was prepared in 14.3% yield. This work provides, for the first time, an opportunity to synthesize mismatched bisindole alkaloids for studies on the mechanism of action of *Alstonia* antimalarial alkaloids at the receptor level. © 2002 Elsevier Science Ltd. All rights reserved.

Malaria is the world's most important tropical parasitic disease and there are an estimated 300–500 million cases of malaria each year. The emergence of multidrug resistant strains of the parasite is exacerbating the situation. Various naturally occurring compounds have been isolated and shown to exhibit antimalarial activity. In regard to the present work, indole alkaloids isolated from *Alstonia* species have shown important antiprotozoal activity.[1–3] In 1992, Wright et al.[1] reported significant activity of *Alstonia* bisindole alkaloids against protozoa and against the resistant strains of *Plasmodia falciparum* parasites. To date, it is clear that the dimeric alkaloids are much more potent than the monomeric units which comprise them against *P. falciparum* malaria. More recently, Houghton et al.[2,3] have shown that the bisindoles are of particular interest for their unique selectivity against the multidrug resistant K1 strain versus the chloroquine sensitive T9-96 strain of *P. falciparum*. Although the naturally occurring bisindole alkaloids have shown promising results, the antimalarial mechanism of action of these bases is not understood. As a consequence, the synthesis of the natural alkaloids and the antipodes as well as the mismatched[4] bisindoles including analogs have become important. It is necessary to prepare a number of structural analogs of these bisindoles to search for enhanced activity/selectivity; moreover, analogs are required to study SAR at the receptor level. Potential new drug candidates could emerge from this work as well as tools to study the mechanism of action of these dimeric bases at the cellular level.

Represented in Fig. 1 are two bisindole alkaloids (**1a** and **2**) that exhibit potent antimalarial activity. From the pioneering biomimetic coupling processes of LeQuesne,[5–7] these bisindole alkaloids can be envisaged to arise from condensation of a unit of macroline with another monomeric alkaloid. For this reason, the synthesis of the enantiomer **3En** of macroline on a large scale is key to the preparation of mismatched[4] bisindoles. Mismatched bisindoles would arise from the condensation of the enantiomer of macroline with pleiocarpamine or vice versa. This approach is built on a common strategy to synthesize both the natural and unnatural antipodes and to generate a bisindole alkaloid library (Scheme 1). The antipodes of the bisindoles




**1a.** R=H, villalstonine
**1b.** R=H, villalstonine $N_b$-oxide
**1c.** R=OMe, 10-methoxyvillalstonine

**2.** alstomacroline

**Figure 1.**

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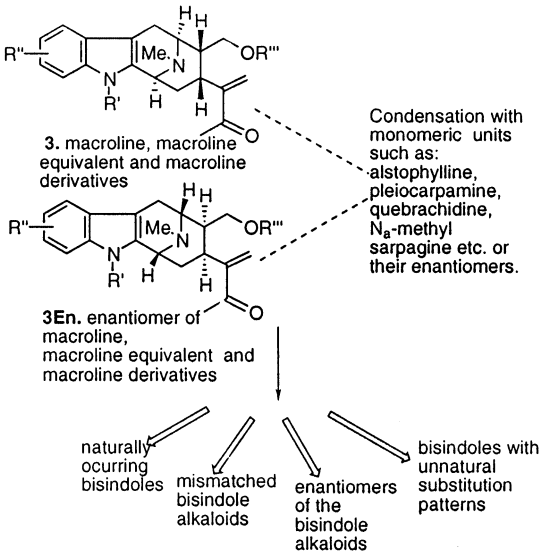
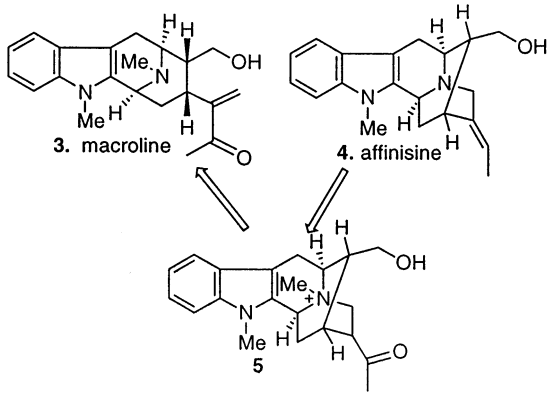



**Scheme 1.** Potential generation of the bisindole alkaloid library.

would also be readily available via this approach. From the earlier work of LeQuesne,[6] the biosynthesis of macroline **3** could be envisaged to arise from affinisine **4** through intermediate **5** (Scheme 2). In an earlier communication, we reported the enantiospecific total synthesis of the enantiomer of the indole alkaloid affinisine;[8] herein, we wish to report a concise, enantiospecific approach to the synthesis of the enantiomer of macroline and its equivalent through the enantiomer of affinisine in support of the previous hypothesis.[6,8]

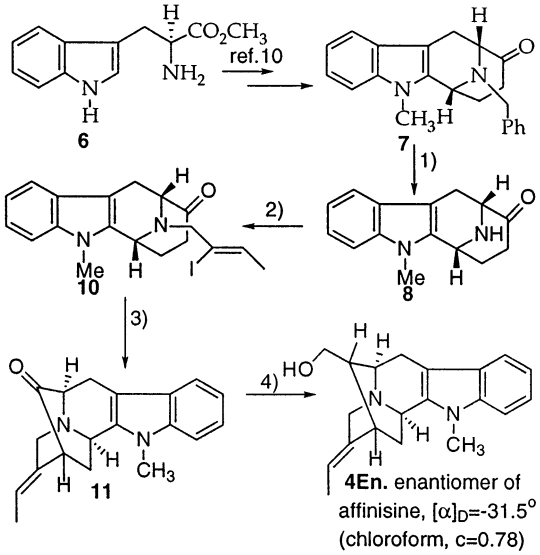
Recently, the synthesis of (+)-$N_a$-methyl tetracyclic ketone **7** was improved by taking advantage of the 100% diastereoselective Pictet–Spengler reaction in the $N_a$-H series. Analogous to the two-pot synthesis of the (−)-$N_a$-H tetracyclic ketone,[9] the (+)-$N_a$-methyl tetracyclic ketone **7** could be prepared in a short synthetic sequence,[10] which provided hundreds of grams of the desired template **7**. This material was debenzylated via catalytic hydrogenation to afford the $N_b$-H ketone **8** in 85% yield. This base was stirred with the *Z*-1-bromo-2-iodo-2-butene **9** in the presence of $K_2CO_3$ to give



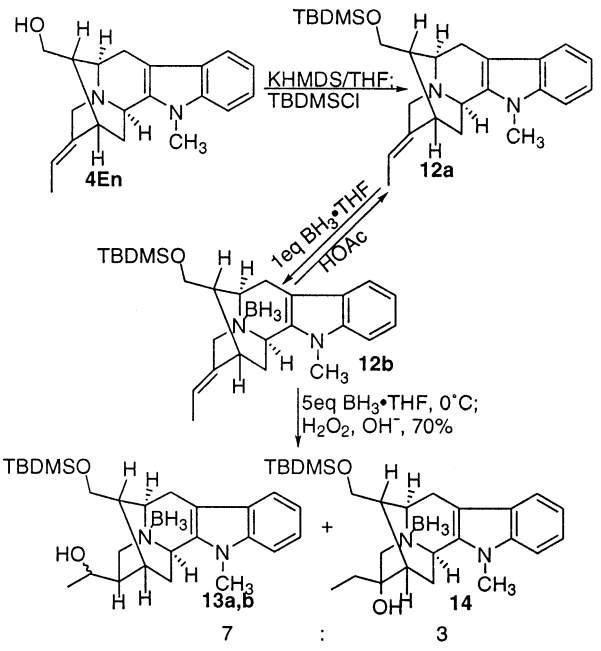

**Scheme 2.** Proposed relationship between macroline and affinisine.

ketone **10** in 83% yield. When ketone **10** was heated to 65°C in DMF/$H_2O$ (9:1) in the presence of palladium(II) acetate, triphenyl phosphine, $Bu_4NBr$ and $K_2CO_3$, the intramolecular cyclization took place to afford the desired ketone **11** in stereospecific fashion (80% yield). With the cyclized ketone **11** in hand, the synthesis was completed in simple fashion (Scheme 3). Wittig reaction of **11** was followed by acidic hydrolysis of the enol ether so generated to afford the enantiomer of $N_a$-methylvellosimine. Reduction of the aldehyde function of the enantiomer of $N_a$-methylvellosimine with $NaBH_4$ then gave the enantiomer **4En** of affinisine with 100% diastereoselectivity.[8]

Based on a retrosynthetic analysis, it was decided to use a hydroboration/oxidation sequence to gain entry into the ketone function in the enantiomer of **5**. As illustrated in Scheme 4, the hydroxyl group of the enantiomer **4En** of affinisine was protected as the *t*-butyldimethylsilyl ether to afford **12a**. However, the yield of the desired *sec*-ol via the hydroboration/oxidation process was low (49%).[8] To understand the low yield of this process, amine **12a** was treated with 1 equiv. of $BH_3$·THF to furnish a new component which exhibited a higher $R_f$ value than **12a** on TLC. Analysis of the $^1H$ NMR and $^{13}C$ NMR spectra of the crude reaction product indicated the olefinic peaks were intact. The spectral data were also very similar to the starting olefinic derivative **12a**. Furthermore, when this compound was heated in THF with 1 equiv. of acetic acid, the original olefinic amine **12a** was recovered (TLC and NMR). Based on the above data, it was believed this newly formed material (which surprisingly had a higher $R_f$ than **12a**) was an $N_b$-$BH_3$ complex **12b**. With this in mind, the origin of the low yield of the




**Scheme 3.** *Reagents and conditions*: (1) Pd/C, EtOH/HCl, 85%. (2) *Z*-1-Bromo-2-iodo-2-butene **9**, THF, $K_2CO_3$, 83%. (3) 5 mol% $Pd(OAc)_2$, 20 mol% $Ph_3P$, 1 equiv. $Bu_4NBr$, 4 equiv. $K_2CO_3$, DMF/$H_2O$ (9:1), 65°C, 8 h, 80%. (4) $MeOCH_2PPh_3Cl$, KO*t*-Bu, benzene, rt, 24 h; 2N HCl/THF, 55°C, 5 h, 90%; $NaBH_4$/EtOH, 0°C, 90%.




**Scheme 4.**

hydroboration reaction was now reinvestigated. A byproduct was isolated and analysis of the spectral data permitted the assignment of this material as tertiary alcohol **14** (shown in Scheme 4). The results of NOESY experiments[11] permitted the assignment of the stereochemistry of the *tert*-ol **14** and the *sec*-ols **13a**,**b** as shown in Scheme 4. It was well known that hydroboration of a trisubstituted olefin was highly regioselective (>97%)[12] to provide the *sec*-ols in high yield. In contrast, regioselective hydroboration (borane) in the styrene system[12] as well as with allylic tosylates and allylic chlorides[13] has been shown to be less straightforward for electronic reasons. Brown et al.[12] have proposed a transition state for the hydroboration of the styrene system to rationalize these results. It was believed that partial positive character would be developed near the hydrogen atom while a partial negative charge would be developed adjacent to the attacking boron atom. In an attempt to understand the origin of the tertiary alcohol **14** from hydroboration of the C(19)–C(20) double bond in **12**, the TS analysis of Brown was applied to the existing system (Fig. 2). As discussed earlier, the N–$BH_3$ complex **12b** would form from amine **12a** before attack on the C(19)–C(20) double bond takes place. The $N_b$-complexation would provide a partial positive charge in the vicinity of the $N_b$-nitrogen atom. This partially developed positive charge would destabilize the developing positive charge in the transition state during hydroboration. Consequently, the transition state **T2**, which gave rise to the desired *sec*-ols **13a**,**b** although sterically favored, was electronically disfavored in comparison to the free amine via this interaction. This electronic interaction, presumably, would provide some explanation for the unexpected attack (30%) on the olefinic carbon atom at C(20). The origin of the epimeric hydroxyls at C(19) in **13a**,**b**, arises presumably from an elimination/rehydroboration sequence. Further work will be necessary to confirm this.

With the understanding of the possible origin of the low yield and regioselectivity in mind, a recent modification of the reaction conditions has resulted in high yield access to the key intermediate **16** (Scheme 5). The TIPS group was now chosen to protect the alcohol function at C(17) to prevent base-mediated hydrolysis of the silyl ether during the oxidation following hydroboration. As shown in Scheme 5, when the hydroboration of **15** was conducted with 9 equiv. of $BH_3$/DMS at room temperature, the desired *sec*-ols **16** were obtained in 80% yield after oxidative workup. The origin of the change in selectivity in going from 0°C to rt is still under study. The Swern oxidation of **16** went smoothly to furnish ketones **17a** and **b** (85%), the structures of which were studied in detail.[11] The mixture of ketones **17a** and **b** was then heated in THF in the presence of 1.5 equiv. of HCl (1N aq.) for 3 h, after which ketone **18**, which was devoid of the boron species, was produced in 90% yield. The methylation of **18** with methyl iodide went smoothly to give the $N_b$-methiodide salt which was originally treated with $K_2CO_3$ in refluxing benzene to afford the enantiomer **19** of the macroline equivalent.[6,10] This retro-Michael reaction was later improved and became more reproducible by modification of the original conditions. The $N_b$-methyl salt was stirred with *t*-BuOK in refluxing THF/EtOH (6:1) to provide the enantiomer **18** of the macroline equivalent in greater than 95% yield. The difficulty in reproducing the earlier procedure arose because $K_2CO_3$ was not soluble in the benzene layer. Sometimes the concentration of the base was not high enough to effect the retro-Michael reaction. The success of the earlier conditions rested largely on the water content present in the system which was hard to control. The modified system (*t*-BuOK, THF/EtOH) does not suffer from this disad-

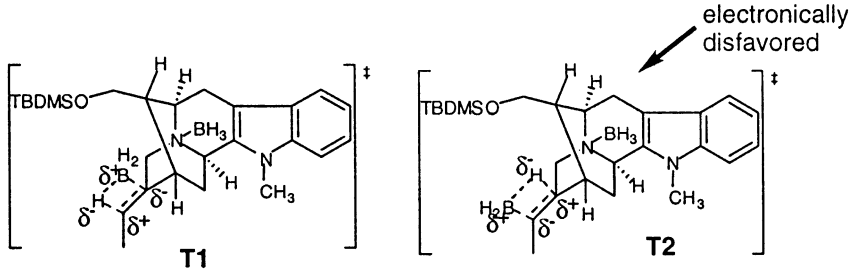
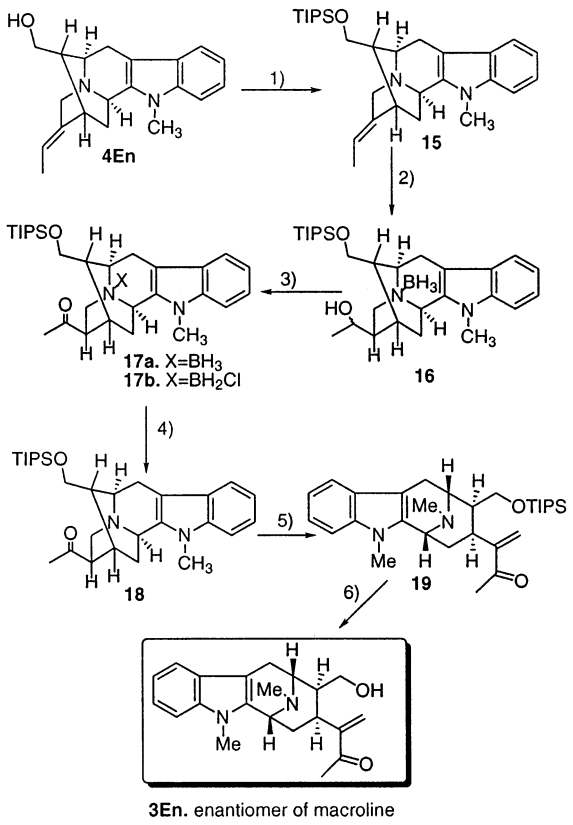
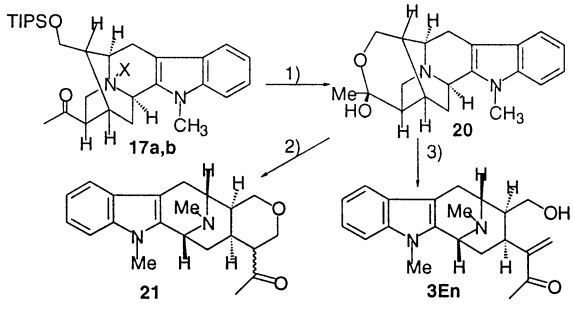



**Figure 2.**




**Scheme 5.** *Reagents and conditions*: (1) 3 equiv. KHMDS, 3 equiv. TIPSCl, THF, 0°C to rt, 90%; or 3 equiv. TIPSCl, 3 equiv. imidazole, DMF, 90%. (2) 9 equiv. $BH_3$/DMS, THF, rt, 3 h; $NaOH/H_2O_2$, rt 2 h, 80%. (3) $(COCl)_2$, DMSO, −78°C; $Et_3N$, 85%. (4) 1.5 equiv. HCl (1N, aq.), THF, reflux, 3 h, 90%. (5) MeI, THF; THF/EtOH (6:1), *t*-BuOK, reflux, 95%. (6) $NBu_4F$, THF, 86%.




**Scheme 6.** *Reagents and conditions*: (1) 10 equiv. HCl (1N aq), THF, reflux, 85%. (2) MeI, THF; 1.5 equiv. KO*t*-Bu, THF/EtOH (1:1) reflux, 95%. (3) MeI, THF; 0.95 equiv. KO*t*-Bu, THF/EtOH (1:1) reflux, 75%.

vantage. The silyl ether was then removed from olefin **18** by stirring in TBAF/THF to furnish the enantiomer **3En** of macroline in 86% yield. The spectral data for the enantiomer **3En** of macroline were in complete agreement with the literature;[14,15] the optical rotation was equal in magnitude and opposite in sign.

More recently, another transformation from the sarpagine alkaloids to the macroline alkaloids was developed. As illustrated in Scheme 6, the $N_b$-boron complexes were treated with 10 equiv. of HCl (1N aq.) in THF to furnish the trinervine analog **20(En)** in 85% yield. When the $N_b$-methyl analog of this compound was treated with 1.5 equiv. of base (KO*t*-Bu), dihydroalstonerine **21(En)** was produced in 95% yield; however, when 0.9 equiv. of KO*t*-Bu was employed, the enantiomer **3En** of macroline was produced in 75% yield. This sequence provided an alternative route to the desired enantiomer **3En**.

In conclusion, the total synthesis of the enantiomer **3En** of macroline was completed (from L-tryptophan methyl ester **6**) in 11 isolated intermediates. The overall yield of (+)-macroline (**3En**) was 12.3% and the corresponding macroline equivalent **18** was prepared in 14.3% yield. Since the total synthesis of the enantiomer **3En** of macroline and the macroline equivalent **18(En)** have been completed, they can be employed to prepare the mismatched bisindole alkaloids analogous to the coupling reaction of Bi et al.[16] under the biomimetic conditions of LeQuesne.[5–7] Therefore, both natural and unnatural bisindole alkaloids can be obtained by this chemistry. This will provide additional tools with which to study drug resistance in *P. falciparum* (K1 vs. T9-96 strain) malaria, as mentioned previously.

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