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Regiospecific, Enantiospecific Total Synthesis of the Alkoxy-Substituted Indole Bases, 16-*epi*-N_a-Methylgardneral, 11-Methoxyaffinisine, and 11-Methoxymacroline as Well as the Indole Alkaloids Alstophylline and Macralstonine

Xiaoxiang Liu,[†] Jeffrey R. Deschamp,[‡] and James M. Cook*[,†]

Department of Chemistry, University of Wisconsin−Milwaukee, Milwaukee, Wisconsin 53201, and Laboratory for the Structure of Matter, Code 6030, Naval Research Laboratory, 4555 Overlook Ave., SW, Washington, DC 20375

capncook@uwm.edu

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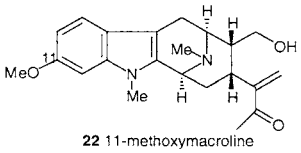
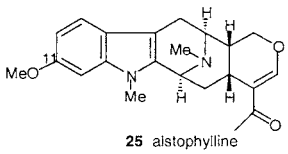
ABSTRACT



22 11-methoxymacroline



25 alstophylline

A regiospecific, enantiospecific approach to the synthesis of ring-A-substituted indole alkaloids was developed via a doubly convergent strategy. The asymmetric Pictet–Spengler reaction and enolate-driven palladium cross-coupling processes were both executed in stereospecific fashion and served as the stereochemical basis of this approach. The synthesis of 16-*epi*-N_a-methylgardneral (15), 11-methoxyaffinisine (16), and 11-methoxymacroline (22) has been accomplished in high yield and in enantiospecific fashion. Moreover, the key C-19 ketosarpagine system (borane adducts) 19a,b employed for the construction of 11-methoxymacroline (22) was also transformed into alstophylline 25, which resulted in completion of the total synthesis of the bisindole macralstonine (1).

Indole alkaloids of the sarpagine/macroline-type comprise one of the largest groups of structurally related indole natural products.[1−3] Interest in the macroline/sarpagine alkaloids originated as a result of folk tales that described the medicinal properties of the plants from which these alkaloids were isolated.[1−3] Malaria is the world's most common 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. In regard to the present work, various indole alkaloids isolated from *Alstonia* species have shown important anti-protozoal activity.[4,5] To date, it is clear the dimeric alkaloids are much more potent than the monomeric units that comprise them against *Plasmodia falciparum* malaria. More

[†] University of Wisconsin−Milwaukee.
[‡] Naval Research Laboratory.

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recently, Houghton et al.[5] showed that the bisindoles are of particular interest for their unique selectivity against the multidrug resistant K1 strain vs the chloroquine sensitive T9-96 strain of *P. falciparum*. As a consequence, the synthesis of the natural alkaloids and the antipodes as well as the mismatched bisindoles,[6] including analogues, has become important. It is necessary to prepare a number of structural analogues of these bisindoles to search for enhanced activity/selectivity; moreover, analogues are required to study SAR at the receptor level.

Many bisindole alkaloids isolated from Alstonia species contain a ring-A-substituted methoxyl unit as illustrated in the structures of macralstonine **1**,[7] 19-*O*-methylmacralstonine **2**,[5] and 10-methoxyvillastonine **3** (Figure 1).[8] It is important

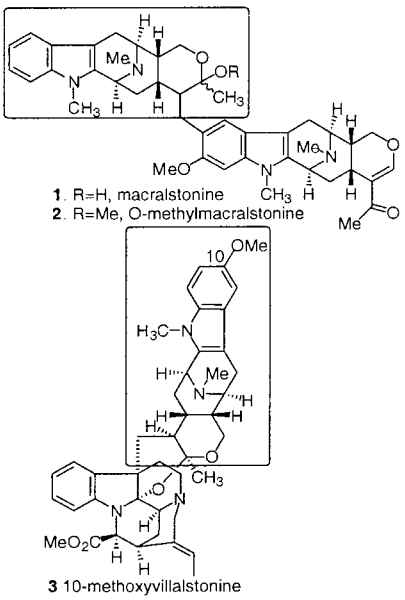
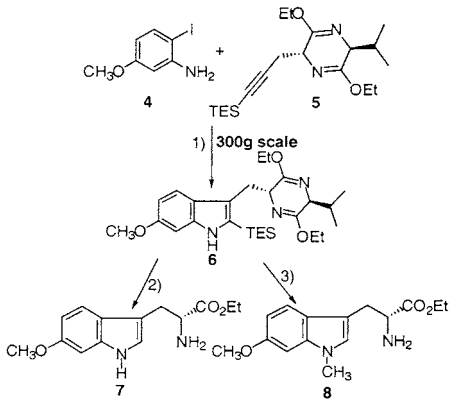


Figure 1.

to note that a minor change in structure resulted in significantly enhanced antiplasmodial activity for 19-*O*-methylmacralstonine **2** in comparison to the parent **1**.[5] From the pioneering biomimetic coupling process of LeQuesne,[9,10] these bisindole alkaloids can be envisaged to arise from condensation of a unit of macroline with another monomeric alkaloid. Since the coupling of macroline and alstophylline was previously carried out by LeQuesne et al.[10] to provide macralstonine **1**, the synthesis of this bisindole would now rest on the synthesis of these two monomeric units. Herein, the regiospecific synthesis of 11-methoxymacroline is reported, which was later transformed into alstophylline and culminated in the total synthesis of the bisindole macralstonine **1**.

Examination of the structure of bisindole **1** or **2** clearly indicated that functionalization of ring-A with an alkoxy group in the latter stages of the synthesis would be a difficult process. For this reason, a strategy was adopted to incorporate the 11-alkoxy group into ring-A of **1** from the beginning. If successful, this would also provide a method for the synthesis of many other 11-methoxy-substituted sarpagine- and ajmaline-related indole alkaloids. On the basis of previous work on the total synthesis of indole alkaloids via the asymmetric Pictet−Spengler reaction,[11] the 6-methoxy-D-tryptophan was chosen as the chiral transfer agent and starting material. Because of this, the Schöllkopf chiral auxiliary required for the asymmetric induction was prepared from the inexpensive L-valine. As shown in Scheme 1,

Scheme 1[a]



[a] Reaction conditions: (1) 1% $Pd(OAc)_2$, Na_2CO_3, LiCl, DMF, 100 °C, 77%. (2) 2 N aqueous HCl, EtOH, THF, from 78 to 0 °C, 86%. (3) NaH, DMF, MeI, 95%; aqueous 2 N HCl/THF, rt, 2 h, 93%.

iodoaniline **4** and the propargyl unit **5**,[12] which had been prepared on a 200 g scale with high diastereoselectivity from the readily available Schöllkopf chiral auxiliary (from L-valine),[13] underwent Larock heteroannulation[15] to provide the protected 6-methoxy tryptophan **6** in 77% yield (300 g scale). Hydrolysis of the Schöllkopf chiral auxiliary followed by the removal of the triethylsilyl group was realized in 90% yield in a single step to provide **7**. Because the Schöllkopf chiral auxiliary served as an excellent protecting group (no racemization) for the amino acid portion of a tryptophan, the intermediate **6** also served as the precursor to the required N_a-methyl analogue **8**. The N_a-methyl-6-methoxy-D-tryp-

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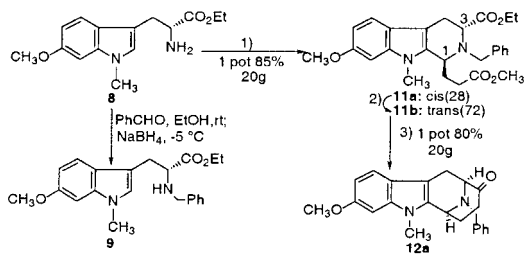
tophan **8**, employed here for the synthesis of the N_a-methyl bases, was prepared by a two step transformation from **6** in >90% overall yield (see Scheme 1).

With the desired tryptophan unit **8** in hand, attention was turned to the construction of the rigid 11-methoxytetracyclic ketone, which could serve as the key template for the synthesis of the 11-methoxyindole alkaloids. As illustrated in Scheme 2, the primary amine in **10** was converted into

Scheme 2[a]

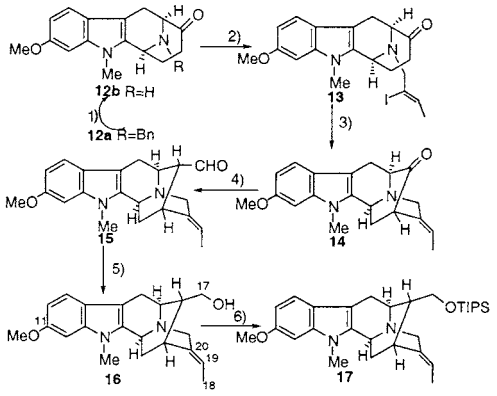


[a] Reaction conditions: (1) PhCHO, EtOH, rt; $NaBH_4$, −5 °C; $HCOCH_2CH_2CO_2Et$ (**10**), CH_2Cl_2, rt; 1% TFA/CH_2Cl_2 (∼1 equiv TFA), rt, 12 h. (2) CF_3CO_2H, CH_2CHCl_2. (3) NaH (60%, 3.2 equiv), MeOH (3.5 equiv), toluene, reflux; 33% KOH, dioxane, reflux.

the N_b-benzyl ester **9** by reductive amination in high yield. The optical purity of this N_b-benzyltryptophan **9** was determined to be greater than 98% ee by comparison of the optical rotation with that of an authentic sample. The Pictet−Spengler condensation between the aldehyde **10** and the N_b-benzylamine **9** took place in the presence of the catalyst (acetic acid/CH_2Cl_2) to afford a mixture (at C-1) of trans (**11b**) and cis (**11a**) diesters in nearly quantitative yield in a ratio of 72:28. If TFA/CH_2Cl_2 was employed in this process, significant decomposition of the starting 6-methoxytryptophan took place.[14] Consequently, after the Pictet−Spengler cyclization was complete, a small amount of TFA was added to the reaction mixture after which epimerization of the stereocenter at C(1) of the cis diastereomer took place to give the desired trans diester **11b** as the single isolable diastereomer. Dieckmann cyclization of the trans diester **11b** followed by base-mediated hydrolysis/decarboxylation in a one-pot process then provided the key tetracyclic ketone **12a** in 85% overall yield. The synthesis of this key ketone **12a** could then be carried out in a two-pot fashion (from **6**) and was accomplished (from iodoaniline **4**) in five reaction vessels and an overall yield of 46%.

With an efficient synthesis of the 11-methoxytetracyclic ketone **12a** in hand, attention was turned to the synthesis of the alkoxylated sarpagine system, 16-*epi*-N_a-methyl gardneral **15**,[15] a base previously obtained by Sakai from the degradation of gardnerine.[16] It was felt that gardneral **15** as well as 16-*epi*-N_a-methyl-gardnerine will be implicated as key biogenetic or synthetic intermediates on the route to bisindoles or to ajmaline alkaloids such as rauflexine.[17] The stereospecific construction of the (*E*)-ethylidene function in these sarpagine bases was first realized in the 10-methoxylated sarpagine series by employing the Pd-catalyzed (enolate-driven) intramolecular cyclization.[18,19] This important stereoconstruction of the C(19)−C(20) olefinic bond avoids the formation of the olefinic isomer (koumidine series), which is the thermodynamically more stable olefin.[19] As illustrated in Scheme 3, the N_b-benzyl function was

Scheme 3[a]



[a] Reaction conditions: (1) Pd/C, EtOH/HCl, 87%. (2) (*Z*)-1-Bromo-2-iodo-2-butene, THF, K_2CO_3, reflux, 85%. (3) 5% $Pd(OAc)_2$, 20% PPh_3, 1 equiv Bu_4NBr, 4 equiv K_2CO_3, DMF/H_2O (9:1), 65 °C, 8 h, 82%. (4) $MeOCH_2PPh_3Cl$, KOtBu, benzene, rt, 24 h; 2 N HCl/THF, 55 °C, 5 h, 85%. (5) $NaBH_4$/EtOH, 90%. (6) KHMDS, TIPSCI, THF, 90%.

removed under the conditions of catalytic hydrogenation. The N_b-H function was readily alkylated with (*Z*)-1-bromo-2-iodo-2-butene to provide the N_b-alkylated ketone **13** in an overall yield of 83%. When this ketone **13** was subjected to the conditions of the palladium-catalyzed intramolecular cyclization, the pentacyclic ketone **14** was obtained in 82% yield in stereospecific fashion.[19] This ketone **14** was then converted into 16-*epi*-N_a-methyl gardneral **15** in 90% yield via a Wittig reaction followed by hydrolysis. This could be carried out in a one-pot process if the reaction mixture was extracted with ether before the alkaline/CH_2Cl_2 workup. This removed the phosphorus byproducts before isolation of **15**. The spectral data of **15** were identical to those reported by Sakai.[15] Reduction of the aldehyde function in gardneral **15** with $NaBH_4$ then provided the 11-methoxy affinisine **16** in 95% yield. Although neither **15** nor **16** have been isolated from natural sources, to date, it is felt that their structures and expected biosynthesis bode well for their eventural isolation from the *Apocynaceae*. Protection of the hydroxyl function of **16** with TIPSCl then gave the *O*-TIPS ether **17** in 90% yield.

With the *O*-TIPS ether **17** in hand, the regioselective hydroboration was then carried out. As illustrated in Scheme

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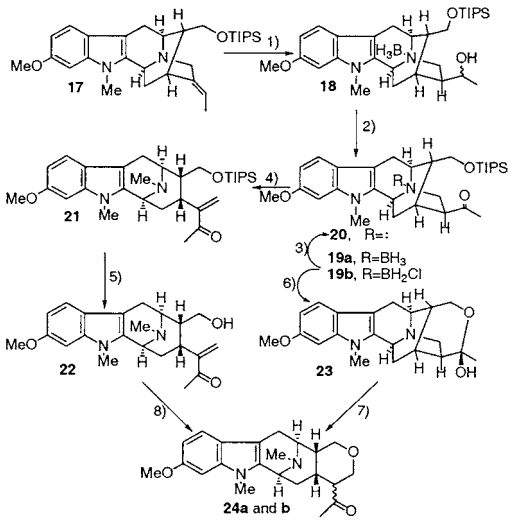
Scheme 4[a]



[a] Reaction conditions: (1) 9 equiv BH_3−DMS, THF, rt; H_2O_2, NaOH, 90%. (2) DMSO, $(COCl)_2$; Et_3N; 1.5 equiv HCl, THF, reflux, 80%. (3) 1.5 equiv HCl, THF, reflux, 90%. (4) MeI, THF; KOtBu, THF/EtOH (6:1), reflux, 90%. (5) TBAF, THF, rt, 6 h, 86%. (6) 10 equiv HCl (1 N, aqueous), THF, reflux, 85%. (7) MeI, THF; 1.5 equiv KOtBu, THF/EtOH (1:1) reflux, 95%. (8) NaOEt, THF/EtOH.

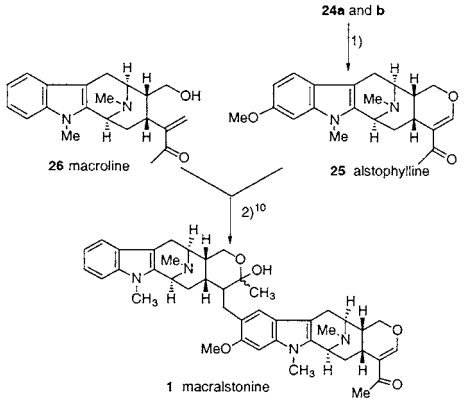
4, the hydroboration went smoothly to give the C(19) mixture of *sec*-ols **18** in 90% yield accompanied by only 6% of the *tert*-ol.[20] The regioselectivity has been increased to 100:0 in a related system.[19] Examination of the NOESY spectrum of these two *sec*-ols indicated that the stereochemistry was identical at C(19) but epimeric at C(20). The origin of this interesting epimeric/scrambling at C(20) in this series is under study.[19] The Swern oxidation of the mixture of these two *sec*-ols then gave the ketones **19a**,**b** in 80% yield. Examination of the two-dimensional COSY and NOESY NMR experiments indicated that **19a**,**b** contained the same stereochemistry at C(19).[20] When this mixture of ketones **19a**,**b** was stirred with 1 equiv of aqueous HCl (1 N) in refluxing THF, the N_b-boron-free ketone **20** was isolated in 90% yield; however, when the mixture of ketones **19a**,**b** was treated with 5 equiv of aqueous HCl (1 N) in refluxing THF, the cyclized 11-methoxy-N_a-methyl-trinervine **23** was isolated in 85% yield. Modification of the original conditions of LeQuesne[21] for the ring-opening process (**20** to **21**, Scheme 4) reported for the parent system gave the key 11-methoxymacroline equivalent **21** in 90% yield. This stable macroline equivalent was converted into 11-methoxymacroline **22** on stirring with TBAF in THF.

When the trinervine **23** was subjected to the ring-opening conditions (MeI/THF; KOtBu/THF/EtOH), dihydroalstophyllines **24a**,**b** were isolated in 95% yield. This provided the first example of interconversion of a trinervine base to a macroline alkaloid that was in agreement with biogenetic proposals by LeQuesne.[21]

Conversion of dihydroalstophylline **24a**,**b** into alstophylline **25** was recently accomplished by employing the IBX reagent of Nicolaou,[20] although the yield has not yet been maximized.[19] The mass spectral fragmentation pattern of **25** and the NMR spectra were in good agreement with that of Schmid.[23] This completed the total synthesis of alstophylline, which had earlier been converted into the bisindole macralstonine **1**. Since (+)-macroline was previously synthesized by Bi and improved in the enantiomeric series by Liu[19] (12.3% overall yield) via the exact route illustrated in Scheme 4 (to **22**) in the parent (11-H system), this served as a doubly convergent route to macralstonine **1**.

In summary, a new efficient route to the parent 6-methoxytryptophan ethyl ester was developed and scaled up to 300 g via a palladium-catalyzed heteroannulation process. The synthesis of 16-*epi*-N_a-methyl-gardneral **15** and 16-*epi*-N_a-methylgardnerine has been accomplished in high yield and in stereospecific fashion via a Pd-catalyzed (enolate-driven) intramolecular cyclization. The coupling of alstophylline **25** and macroline **26** (Scheme 5) was carried out

Scheme 5[a]



[a] Reaction conditions: (1) IBX, pTSA, toluene/DMSO (2:1), 70 °C. (2) 0.2 N HCl; see ref 10.

previously by LeQuesne and Cook et al.;[10] consequently, this completed the total synthesis of the antimalarial bisindole alkaloid macralstonine **1**.

Acknowledgment. We acknowledge the Office of Naval Research, NIDA, and NIMH for support of this work.

Supporting Information Available: X-ray structural data on the N_a-H analogue of the trans diester **11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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