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General Approach for the Synthesis of Sarpagine/Macroline Indole Alkaloids. Enantiospecific Total Synthesis of the Indole Alkaloid Trinervine

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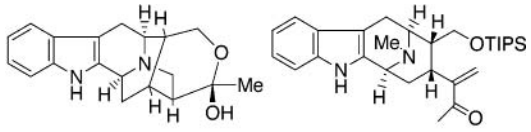
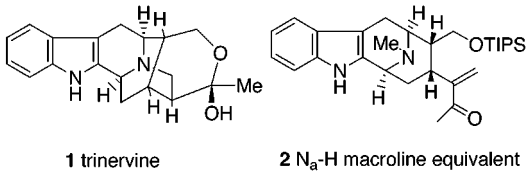
ABSTRACT



1 trinervine **2** N_a-H macroline equivalent

The total synthesis of the indole alkaloid trinervine 1 was accomplished in enantiospecific fashion in an overall yield of 20% (from the tetracyclic ketone 8) in 10 reaction vessels (12.5% from tryptophan methyl ester). The synthesis of the N_a-H substituted macroline equivalent 2 was also completed in high yield via the same intermediate 13. The unique protection/hydroboration process developed here should provide a method to functionalize the C(19)–C(20) double bond in similar systems.

During the past few decades more than 90 macroline/sarpagine-related indole alkaloids have been isolated from various species of *Alstonia*.[1−3] Although the biological activity of some of these alkaloids is known,[1−3] most of them remain unexplored as a result of the paucity of isolated material. Trinervine **1** was first isolated in 1990 from the ethanolic extract of the roots of *Strychnos trinervis*,[4] and its structure was assigned on the basis of 2D NMR experiments. As illustrated in Figure 1, trinervine retains the basic sarpagine skeleton while containing a unique hemiketal ring juncture that is not found in other sarpagine bases.[1−3] The sarpagine alkaloids are closely related to the macroline bases, and the four stereocenters in the N_a-H macroline equivalent **2** are identical to those in **1**. In 1980 the synthesis of macroline from normacusine B by LeQuesne et al.[5] provided direct proof for the close biogenetic relationship of the macroline bases to the sarpagine alkaloids.[5] However, the difficulty in functionalization of the double bond in normacusine B has prevented extensive use of this strategy for the synthesis of other alkaloids.[1−3]



1 trinervine **2** N_a-H macroline equivalent

Figure 1.

(1) Lounasmaa, M.; Hanhinen., P.; Westersund, M. The Sarpagine Group of Indole Alkaloids. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1999; Vol. 52.

(2) Bi,Y.; Hamaker, L. K.; Cook, J. M. The Synthesis of Macroline Related Alkaloids. In *Studies in Natural Products Chemistry, Bioactive Natural Products, Part A*; Basha, F. Z., Rahman, A., Eds.; Elsevier Science: Amsterdam, 1993; Vol. 13, p 383.

(3) Hamaker, L. K.; Cook, J. M. The Synthesis of Macroline Related Sarpagine Alkaloids. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier Science: New York, 1995; Vol. 9, p 23.

(4) Mukherjee, R.; Melo, M. de F. F.; Santos, Cid A. deM.; Gaittet, E.; Das, B. C. *Heterocycles* **1990**, *31*, 1819.

(5) Esmond, R. W.; LeQuesne, P. W. *J. Am. Chem. Soc.* **1980**, *102*, 7116.

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Recently, Houghton et al.[6,7] have demonstrated the bisindole alkaloids villalstonine **3** (Figure 2), *O*-acetyl macral-

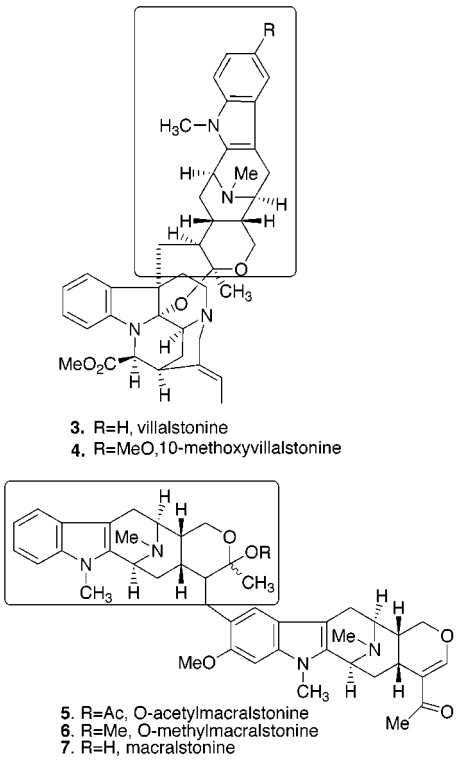


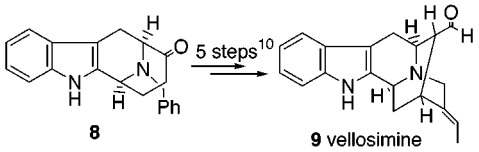
Figure 2.

stonine **5**, and *O*-methyl macralstonine **6** exhibited pronounced antiplasmodial activity against cerebral malaria (*Plasmodia falciparum*). Interestingly, in contrast to chloroquine, they exhibited significantly higher affinity against the drug-resistant K1 strain than to the chloroquine-sensitive T9-96 strain of this parasite.[6,7] As illustrated in Figure 2, the northern portion of these three bisindoles can be envisaged to originate from macroline or an analogue, as indicated from the earlier work of LeQuesne[8] and others.[9] To obtain a better understanding of the mechanism of antiplasmodial activity of these bisindoles at drug resistant strains, the synthesis of macroline analogues has become important in order to generate different structural patterns for SAR studies. Herein, we wish to report a concise synthesis of the related indole alkaloid trinervine **1**, as well as the preparation of the stable N_a-H macroline equivalent **2** through a common intermediate. Condensation of **2** with the obligatory monomeric alkaloid (southern unit), analogous to the biomimetic approach of LeQuesne,[5] would provide new bisindoles for the study of drug resistance.

(6) Keawpradub, N.; Eno-Amooquaye, E.; Burke, P. J.; Houghton, P. J. *Planta Med.* **1999**, *65*, 311.
(7) Keawpradub, N.; Kirby, G. C.; Steele, J. C. P.; Houghton, P. J. *Planta Med.* **1999**, *65*, 690.
(8) Burke, D. E.; DeMarkey, C. A.; LeQuesne, P. W.; Cook, J. M. *J. Chem. Soc., Chem. Commun.* **1972**, 1346.
(9) Bi, Y.; Zhang, L. H.; Hamaker, L. K.; Cook, J. M. *J. Am. Chem. Soc.* **1994,** *116*, 9027.

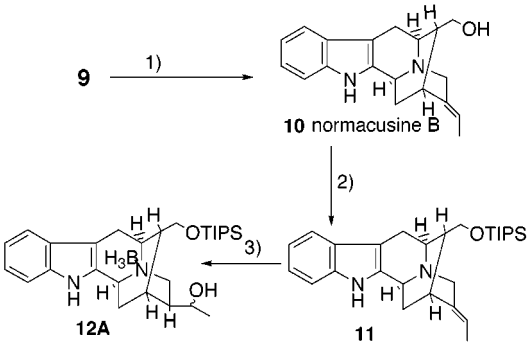
Recently, a synthesis of vellosimine **9** was accomplished by Wang[10] via an enolate-driven palladium-catalyzed cyclization as a key step.[10] The synthesis (Scheme 1) enabled

Scheme 1



the conversion of the tetracyclic ketone[11] into vellosimine **8** stereospecifically in five steps.[10] With vellosimine **9** in hand in gram quantities, this material was reduced with $NaBH_4$ in EtOH to provide normacusine B[12] **10** in 95% yield (Scheme 2). Treatment of the alcohol moiety of **10** with

Scheme 2



1)$NaBH_4$, EtOH, 95%. 2)TIPSCl, imidazole, DMF, rt, 90%. 3)9 equiv BH_3-DMS, THF, rt, 3h; 3N NaOH, H_2O_2, 2h, 90%.

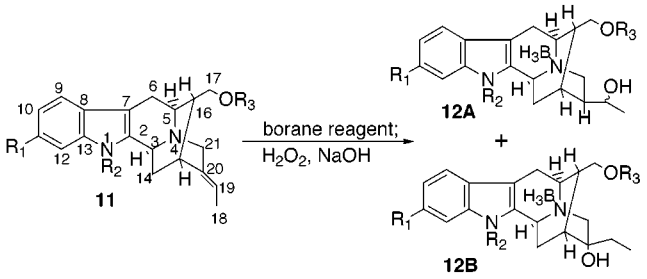
TIPSCl in DMF in the presence of imidazole provided the silyl ether **11**[13] in 90% yield. With this ether **11** in hand, functionalization of the C(19)−C(20) olefinic bond was attempted via hydroboration. A number of these experiments are detailed in Table 1 with respect to regioselectivity of the process.

As illustrated, treatment of the N_a-methyl *O*-TBDMS ether (entry 1) of **11** with 9 equiv of BH_3·THF at 0 °C for 10 h followed by the standard workup[14] provided **12A**/**12B** surprisingly in a ratio of 7:3 (70% yield).

The low yield was due in part to cleavage of the TBDMS group; the use of $NaBO_3$·$4H_2O$ in the workup did not improve the yield significantly. A change in the borane

(10) Wang, T.; Cook, J. M. *Org. Lett.* **2000**, *2*, 2057.
(11) Yu, P.; Cook, J. M. *J. Org. Chem.* **1998**, *63*, 9160.
(12) The X-ray crystal structure of normacusine B was obtained by Dr.Judy Flippen-Anderson (unpublished results) and confirms the stereochemistry as illustrated here.
(13) The TBDMS ether shown in Table 1 was synthesized by the same method. For the N_a-methyl cases, see: Liu, X.; Wang, T.; Xu, Q.; Ma, C.; Cook, J. M. *Tetrahedron Lett.* **2000**, *41*, 6299.
(14) Brown, H. C. *Organic Synthesis via Boranes*; Wiley: New York, 1975.

Table 1. Regioselective Hydroboration



entry	R_2	R_3	T (°C)	borane reagent[a]	yield (%)	**12A**[b]:**12B**
1	Me	TBDMS	0	BH_3·THF	70	7:3[c]
2	Me	TBDMS	0	BH_3·DMS	65	4:1
3	Me	TBDMS	rt	9-BBN	0	
4	Me	TBDMS	rt	thexyl borane	0	
5	Me	TBDMS	rt	BH_2Cl·DM_S	0	
6	Me	TBDMS	−20 to 0	BH_3·THF	70	1:1
7	H	TIPS	0	BH_3·DMS	85	1:1
8	**H**	**TIPS**	**rt**	**BH_3·DMS**	**90**	**>25:1**
9	H	TIPS	rt	BH_3·THF	86	>25:1
10	H	TBDMS	rt	BH_3·DMS	70	20:1
11[d]	H	TIPS	rt	BH_3·DMS	81	**no 12B detected**
12	H	TIPS	40	BH_3·DMS	78	**no 12B detected**
13	Me	TIPS	rt	BH_3·DMS	85	9:1
14	Boc	TIPS	rt	BH_3·DMS	88	8:1
15[e]	Me	TIPS	rt	BH_3·DMS	90	15:1

[a] In all cases, 9 equiv of the borane reagent was used. [b] **12A** consists of a mixture of two isomers, both of which have the same stereochemistry at C20. When subjected to Swern oxidation, they both gave the same ketone **13**; no further studies on the stereochemistry at C(19) have been carried out. [c] The ratio was based on the isolated yield and analysis of the ^{1}H NMR spectrum of the mixture. [d] In this case, CH_2Cl_2 was used as the solvent instead of THF. [e] In this case, R_1 = OMe, whereas in all other cases, R_1 = H.

reagent from BH_3·THF to BH_3·DMS did not improve the ratio (entry 2), which is in agreement with the earlier work of Brown.[14] These initial results prompted a more detailed study of this process, especially since trisubstituted olefins generally provide the secondary alcohols with high regioselectivity.[15] From this study, it was determined that the first equivalent of borane reacted at the N_b-nitrogen atom, a phenomena that has also been reported in other systems.[16] In addition, in the earlier work of Brown[17] the regioselectivity observed in the hydroboration of allylic chlorides or tosylates with BH_3 was very low. It was postulated[17] that electron withdrawal by the substituent had altered the electronic character of the olefin. Certainly, after the N_b−borane complex had formed, this moiety would function as an electron-withdrawing group that may be the origin of the poor selectivity observed in this system. Electron withdrawal by the N_b−borane function would be expected to destabilize the developing positive charge at C(20), if the desired attack of boron took place at C(19). To minimize the formation of the tertiary alcohol **12B**, hindered boranes were employed; however, all of these were ineffective. No reaction was observed when 9-BBN or thexylborane were employed (entries 3 and 4). When BH_2Cl·DMS was used, only the BH_2Cl-N_b complex (entry 5) was observed.[18] If the temperature was lowered, this did not improve the regioselectivity(entry 6); either no reaction took place or the conversion was very slow. To promote hydroboration at C(19) in preference to C(20) the bulkier TIPS group was chosen to replace the TBDMS protecting group. It was felt the yields would also be higher because the TIPS group would be more stable under the reaction conditions. Treatment of this compound with BH_3·DMS at 0 °C gave **12A**/**12B** (entry 7) in a 1:1 ratio. Again, when this procedure was carried out at lower temperature, the ratio did not improve. It was decided to promote kinetic control of this process by carrying out the hydroboration at room temperature. Indeed, when the reaction was carried out at room temperature with 9 equiv of BH_3·DMS, a 90% yield was obtained and the ratio dramatically improved to >25:1 **12A**/**12B**(entry 8). As shown in entry 9, the reaction employing BH_3·THF at room temperature provided a similar yield and regioselectivity; replacement of the TIPS group with TBDMS (entry10) did not affect the ratio significantly as long as the process was carried out at room temperature, albeit the yield was lower. When the process was carried out in CH_2Cl_2 (entry 11) or at an elevated temperature (entry 12), as expected, the *tert*-ol **12B** was detected by neither TLC nor analysis of the crude material by NMR spectroscopy. Although the mechanism is not clear at this point, two possible pathways could be ruled out: (1) The stereochemistry of the hydroxyl function in **12B** was determined by 2D NOESY experiments to be in the α configuration. This is inconsistent with the intramolecular delivery of the borane from the C-17-oxygen atom via a six-membered transition state, for a *β*-hydroxyl function would be expected. In addition, since the ratio of **12A**/**12B** was very similar (entries 8 and 10) when the TBDMS moiety was replaced with a bulkier group (TIPS), this suggests complexation of the attacking BH_3 to the C-17 oxygen atom was not a controlling factor. (2) It is known that alkyl boranes can undergo rearrangement at higher temperature and eventually provide the least substituted boranes. When this hydroboration was done at 0 °C followed by stirring at room temperature overnight, the ratio of **12A**:**12B** was still approximately 7:3. This result suggests that under these conditions, the rearrangement of the *tert*-alkyl borane to the *sec*-alkyl borane either did not take place or was at a very slow rate.

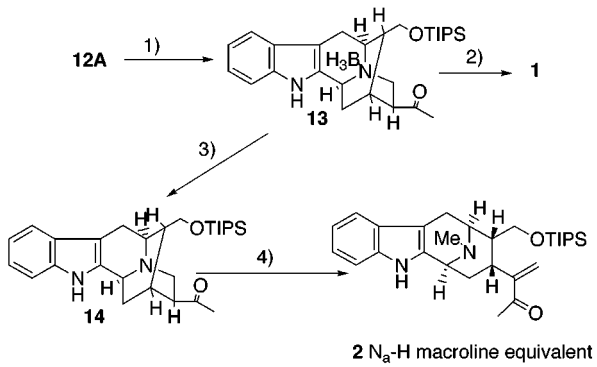
It is possible at higher temperature (rt) in THF that the BH_3-N_b complex is not as stable as it is at 0 °C, and consequently, **11** behaves as the free base rather than the N_b-BH_3 complex. This would permit the normal addition of BH_3 to the trisubstituted olefin.[15] However, other more

(15) Zweifel, G.; Brown, H. C. *Org. React.* **1963**, *13*, 1.
(16) Stotter, P. L.; Friedman, M. D.; Dorsey, G. O.; Shiely, R. W.; Williams, R. F. and Minter, D. E. *Heterocycles* **1987**, *25*, 251.
(17) Brown, H. C.; Keblys, K. A. *J, Am. Chem. Soc.* **1964**, *86*, 1791.
(18) We did not run a ^{11}B NMR on this compound; however, on the basis of its polarity and analysis of the crude material by NMR spectroscopy, this is the most reasonable structure.

subtle factors may be controlling the difference in regioselectivity at room temperature and 0 °C in these systems. While it may appear that the indole ring is too far from the site of reaction to have an effect, the results of experiments in entries 8 and 13−15 put this into question. When the N_a-H function was substituted with a methyl function (entry 13) or an N_a-Boc function was employed, at room temperature the ratio of **12A**:**12B** was still only 9:1. However, when the electron-rich 6-methoxy-substituted indole was employed as a substrate (entry 15), the ratio again increased to 15:1. It appears the more electron-rich indole systems gave better ratios of **12A**:**12B**, suggesting the intermediacy of an N_b−boron mediated cleavage of the C(3)−N_b bond.[19] However, products of reduction of an incipient carbocation[19] were not observed. Further work on the mechanism of this hydroboration process is required before meaningful conclusions can be reached. Suffice it to say the regioselectivity of **12A**:**12B** has been increased from 7:3 to 9:1 in the N_a-methyl case and to greater than 25:1 in the important N_a-H series.

With the *sec*-ol **12A** in hand, this monol was subjected to the conditions of the Swern oxidation[20] to provide the desired ketone **13** (Scheme 3) in 75% yield. To achieve the enantiospecific total synthesis of the indole alkaloid trinervine **1**, the ketone **13** was stirred with 10 equiv of 1 N aqueous HCl in refluxing THF. In this process the borane complex was removed, as well as the TIPS protecting group, followed by cyclization to provide trinervine **1** in 80% yield. The spectral data for **1** were in excellent agreement with the natural product.[4] Since no other diastereomers were isolated from this process, **1** is clearly the most stable hemiketal. Furthermore, treatment of the same ketone **13** with only 1.5 equiv of 1 N aqueous HCl in refluxing THF[21] provided the free base **14** in 90% yield. When the free base **14** was treated with MeI, followed by a base-induced retro-Michael[5] reaction, this gave the key N_a-H macroline equivalent **2** in 90% yield.

Scheme 3[a]



[a] 1) DMSO, $(COCl)_2$, −78 °C; Et_3N, 75%. 2) 10 equiv of HCl (1 N aq), THF, reflux, 3 h, 80%. 3) 1.5 equiv of HCl (1 N aq), THF, reflux, 3 h, 90%. 4) MeI, THF; K_2CO_3, THF, reflux, 90%.

In summary, the total synthesis of trinervine **1** was completed in enantiospecific fashion in an overall yield of 20% (from the ketone **8**) in 10 reaction vessels. From the same intermediate **13** employed to prepare **1**, the synthesis of the N_a-H macroline equivalent **2** was completed in high overall yield. The synthesis of **2** provides a stable material that can be employed to prepare bisindole alkaloids analogous to the work of Bi et al. [9] under the biomimetic conditions of LeQuesne.[8] Since both enantiomers of **2** can be prepared by the asymmetric Pictet−Spengler reaction,[13] natural or unnatural bisindole alkaloids can be obtained by this chemistry. This will provide additional tools with which to study drug resistance in *Plasmodia falciparum* (K1 vs T9-96 strain) malaria. The hydroboration/oxidation sequence developed here (90% yield, > 25:1) should also be applicable to the synthesis of *Strychnos* alkaloids that possess the *sec*-ol or a ketone function at the position analogous to C(19) in the sarpagine system.[22]

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

OL0101990

(19) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennett, D. W.; Cook, J. M.; Watson, W. H.; Krawiec, M. *J. Org. Chem.* **1997**, *62*, 44.

(20) Tidwell, T. T. *Org. React* **1990**, *39*, 297.

(21) Other methods to remove the borane from the complex included reagents such as acetic acid, DMAP, etc. (Liu, X.; Cook, J. M. Unpublished results).

(22) Many alkaloids in the *Strychnos* family contain the side chain featured in compounds **11** and **12**. For details, see: Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455.