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Studies of New Indole Alkaloid Coupling Methods for the Synthesis of Haplophytine

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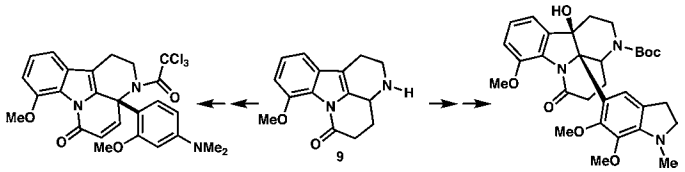
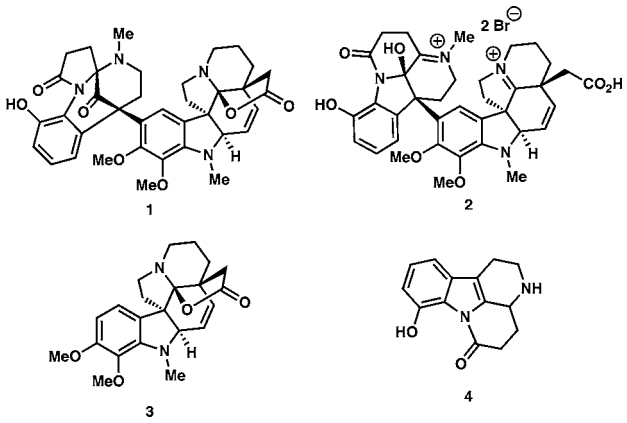
ABSTRACT



The two novel bisindole alkaloid structures shown can be synthesized in a few steps from the canthiphytine derivative 9.

Haplophytine (**1**) is a potent insecticidal alkaloid isolated from the Central American plant *Haplophyton cimicidum* that consists of two alkaloidal subunits joined together in a highly unusual way.[1−4] Upon exposure to HBr, haplophytine undergoes a unique 1,2-cationic shift to generate the rearranged iminium bromide structure **2**, which clearly contains two indole moieties that are the most likely building blocks for the biosynthetic pathway. The more complex of these building blocks, aspidophytine (**3**), which is also naturally occurring,[4] has previously been synthesized in these laboratories.[5] The other coupling component may be a canthiphytine[4] derivative derived from the tetracyclic indole alkaloid **4**. The chemical synthesis of haplophytine from aspidophytine and a derivative of canthiphytine represents a major challenge because of the obvious steric impediments to such a coupling process and also the complete lack of any precedent. In this paper we report on studies directed toward this objective using a canthiphytine derivative and an aspidophytine mimic.



(1) (a) Crosby, D. G. In *Naturally Occurring Insecticides*; Jacobson, M., Crosby, D. G., Eds; Marcel Dekker: New York, 1991; p 213. (b) Sukh Dev; Koul, O. In *Insecticides of Natural Origin*; Harwood Academic Publishers: Amsterdam, The Netherlands, 1997; pp 250 and 251.

(2) (a) Rogers, E. F.; Snyder, H. R.; Fischer, R. F. *J. Am. Chem. Soc.* **1952**, *74*, 1987. (b) Snyder, H. R.; Fischer, R. F.; Walker, J. F.; Els, H. E.; Nussberger, G. A. *J. Am. Chem. Soc.* **1954**, *76*, 2819, 4601. (c) Synder, H. R.; Strohmayer, H. F.; Mooney, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 3708.

(3) (a) Cava, M. P.; Talapatra, S. K.; Nomura, K.; Weisback, J. A.; Douglas, B.; Shoop, E. C. *Chem. Ind.* (*London*) **1963**, 1242. (b) Cava, M. P.; Talapatra, S. K.; Yates, P.; Rosenberger, M.; Szabo, A. G.; Douglas, B.; Raffauf, R. F.; Shoop, E. C.; Weisbach, J. A. *Chem. Ind.* (*London*) **1963**, 1875. (c) Rae, I. D.; Rosenberger, M.; Szabo, A. G.; Willis, C. R.; Yates, P.; Zacharias, D. E.; Jeffrey, G. A.; Douglas, B.; Kirkpatrick, J. L.; Weisbach, J. A. *J. Am. Chem. Soc.* **1967**, *89*, 3061. (d) Zacharias, D. E. *Acta Crystallogr., Sect. B* **1970**, *26*, 1455.

(4) Yates, P.; MacLachlan, F. N.; Rae, I. D.; Rosenberger, M.; Szabo, A. G.; Willis, C. R.; Cava, M. P.; Behforouz, M.; Lakshmikantham, M. V.; Zeigler, W. *J. Am. Chem. Soc.* **1973**, *95*, 7842.

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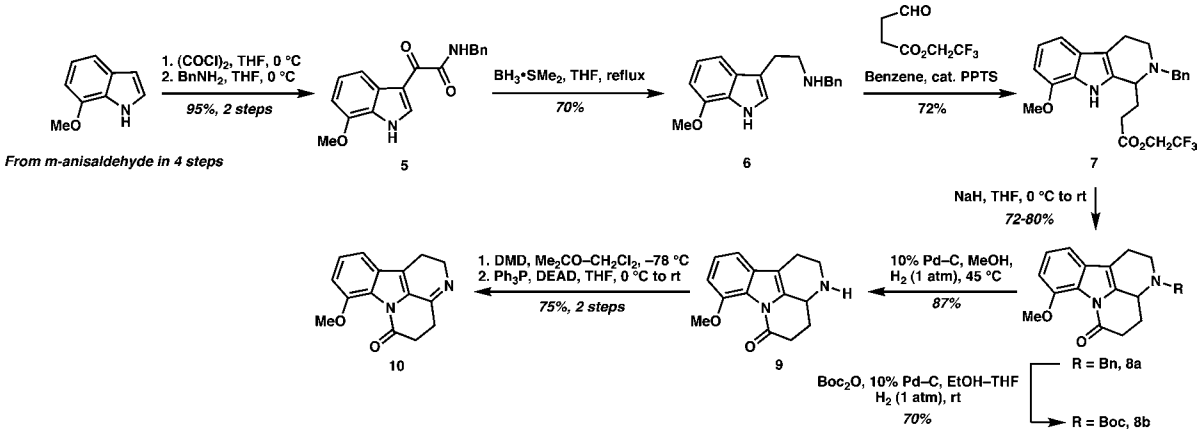
Scheme 1

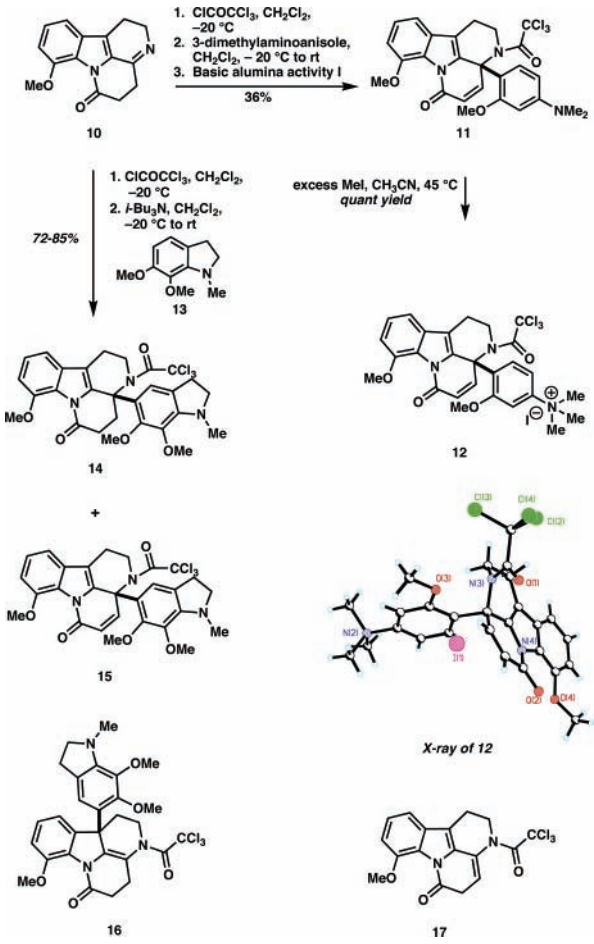


As the canthiphytine coupling components we selected the tetracyclic 7-methoxyindole derivatives **8b** and **10**. These were synthesized from 7-methoxyindole via the keto amide **5** as shown in Scheme 1. Reduction of **5** to the tryptamine **6** was best accomplished by heating with $BH_3{\cdot}SMe_2$ in THF at reflux for 6 h with subsequent purification by rapid flash chromatography on silica gel. Pictet−Spengler condensation of **6** with trifluoroethyl 3-formylpropionate (from the mono-acid chloride by reduction with 1 atm of H_2 and 10% Pd−C catalyst in dry THF in the presence of 2,6-lutidine) afforded the tricyclic ester **7**. Treatment of **7** with sodium hydride in THF at 0 °C yielded the *N*-protected canthiphytine derivative **8a**, which was then transformed into the key intermediates **8b**, **9**, and **10** as shown in Scheme 1.

The oxidation of amine **9** to imine **10** initially proved difficult because of the propensity of the imine to undergo further oxidation to a carbazole-type compound. However, this conversion was efficiently accomplished (after examination of numerous alternative methods) in 2 steps via the *N*-hydroxylamine derivative of **9** in 75% overall yield. Treatment of amine **9** with 1 equiv of freshly prepared dimethyldioxirane in acetone−CH_2Cl_2 provided the corresponding *N*-hydroxylamine compound. Dehydration of the latter with PPh_3−DEAD (Mitsunobu reagent) afforded the desired imine **10**. The imine **10** could be activated for coupling with π-electron-rich aromatic substrates after *N*-acylation with 2 equiv of trichloroacetyl chloride in CH_2Cl_2 at −20 °C.[6,7] The results of coupling experiments with two model substrates are summarized in Scheme 2.

The *N*-trichloroacetyl iminium derivative of **10** underwent coupling with the simple aspidophytine model 3-dimethylaminoanisole in CH_2Cl_2 at −20 °C to give **11** as an oil in 36% yield after rapid chromatography on basic alumina (activity I). The structure of **11** was established by reaction with methyl iodide to give a crystalline methiodide derivative **12** and subsequent X-ray crystallographic analysis. Unfortunately, the occurrence of coupling α to the iminium

Scheme 2

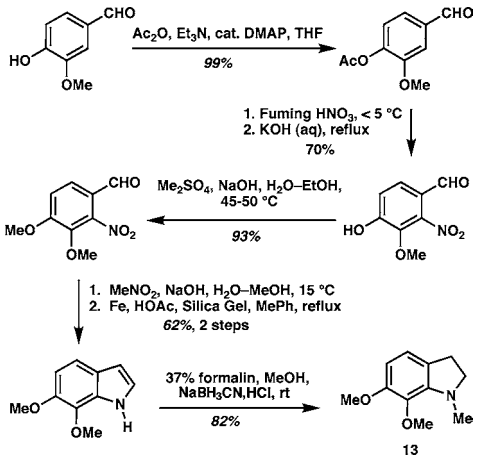


(5) (a) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771. (b) For another synthesis see also: Sumi S.; Matsumoto K.; Tokuyama H.; Fukuyama T. *Org Lett.* **2003**, *5*, 1891.

(6) One equivalent of Cl_3CCOCl was suboptimal for the subsequent coupling reactions, presumably because of attachment of Cl_3CCO to the lactam carbonyl oxygen as well as to the imine nitrogen.

(7) A variety of other imine activating reagents did not promote coupling: e.g., CH_3I, $CH_3OSO_2CF_3$, BF_3, Ph_3CBF_4, $(CF_3SO_2)_2O$, and $Me_3SiOSO_2CF_3$. *p*-Nitrophenylchloroformate and $(CF_3CO)_2O$ did afford the coupling product with **13** but only in lower yield.

Scheme 3



nitrogen, rather than γ (i.e., at C(3) of the indole moiety), appears to preclude the use of this approach for the synthesis of haplophytine. This point was reinforced by our results with an even closer model of aspidophytine, *N*-methyl-6,7-dimethoxy-2,3-dihydroindole (**13**), which was synthesized from 3-methoxy-4-hydroxybenzaldehyde as shown in Scheme 3.

Treatment of the *N*-trichloroacetyl iminium derivative of **10** with **13** in the presence of 2 equiv of the hindered base *i*-Bu_3N led to a facile union of the two components.[8] A nonaqueous workup followed by flash chromatography on silica gel afforded a 1:1 mixture of **14** and **15** in a combined yield of 84%. When the crude coupling product was passed through a column of basic alumina (activity I) it was totally converted to **15**.

Given the close correlation between the NMR spectra for **15** and **11** (see Figure 1) as well as their methiodide derivative (see the Supporting Information), **15** is assigned the structure shown in Scheme 2. Unfortunately, none of the desired coupling product **16** was detected even on HPLC analysis of the crude reaction mixture (see the Supporting Information for the HPLC trace). The only other product, detected in trace amounts, is **17**, formed by deprotonation of the intermediate acyliminium ion. This result clearly showed that this approach is not applicable to the synthesis of haplophytine and led to the study of other ways to accomplish the required C−C coupling reaction.

Coupling products **11** and **14** exhibit unusual behavior. As evident from the above discussion, compounds of this type show an unusually strong tendency to undergo aerial oxidation in the presence of even a mild base. This process is facilitated by easy enolization of the amidic carbonyl. In fact enol ester **11a** can be isolated from the reaction of Cl_3CCOCl and imine **10** with 3-dimethylaminoanisole. Furthermore, treatment of iodide salt **14a** with Et_3N in air leads to quantitative conversion of **14a** to **15a**.[8]

(8) See the Supporting Information for details.

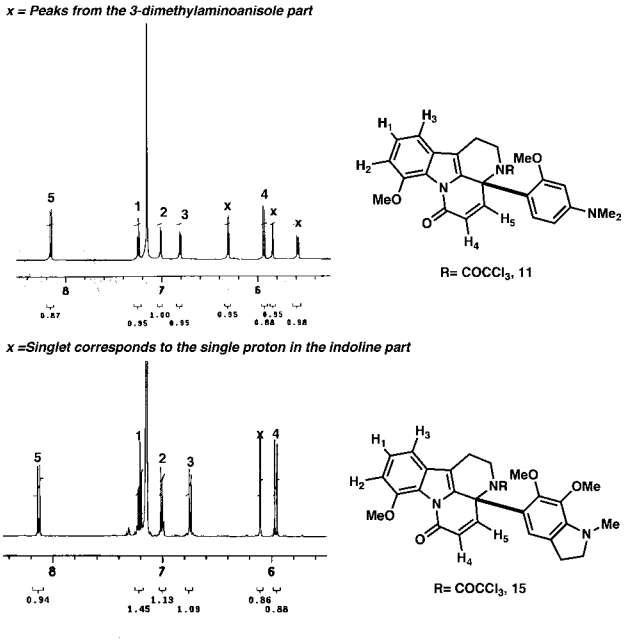
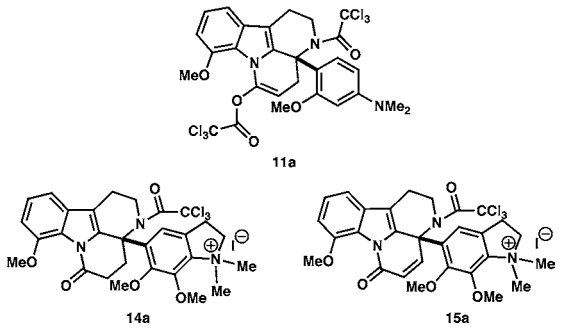


Figure 1. ^1H NMR spectra of coupling products **11** and **15**.[9]

Compounds **11** and **14** are also unstable to strongly basic aqueous conditions which lead to very complex mixtures. Finally, treatment of **14** with acid causes dearylation (C−C cleavage) to form **10**.

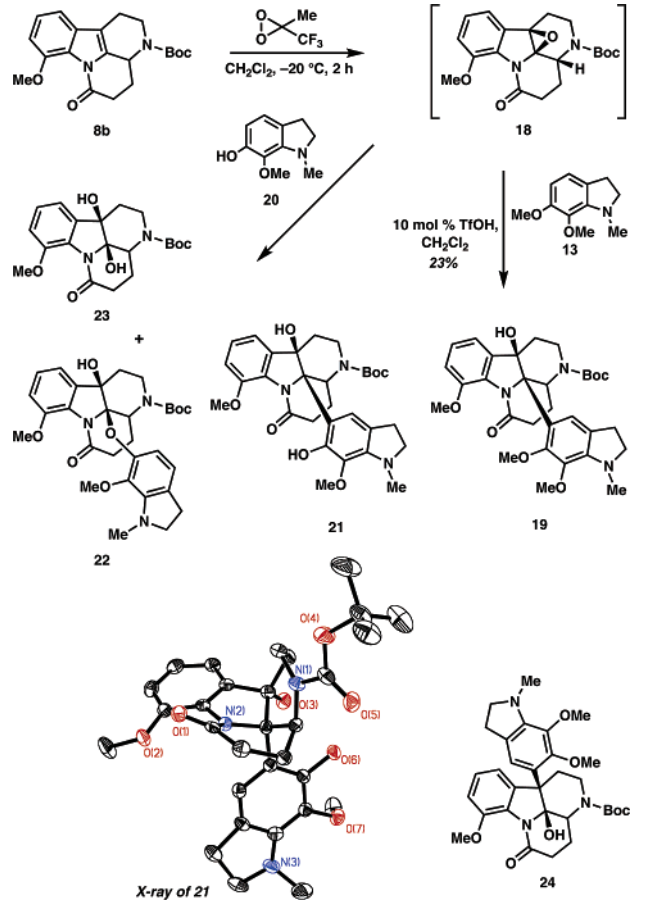


The second approach investigated for the coupling of the two components involved selective epoxidation of the indole double bond in **8b** (Scheme 4). Treatment of **8b** with 2,2,2-trifluorodimethyldioxirane (TFMD) at −20 °C for 2 h afforded the desired epoxide **18** (determined by NMR). (Dimethyldioxirane gave no epoxide under these conditions.) Exposure of the latter to catalytic Bronsted acid such as TfOH[10] and the 2,3-dihydroindole **13** led to 23% isolated yield of the coupling product **19**. The ^{13}C NMR spectrum of **19** revealed the chemical

(9) The peak assignment is based on comparison with similar compounds and their splitting pattern.

(10) It was found that protic acids seem to work best for this type of reaction. Use of Lewis acid did not lead to high desired product formation. The major product in these cases was the diol.

Scheme 4



shifts of the newly formed quaternary carbons (C(2) and C(3) in the indole system) to be in the region of 80−82 ppm instead of two peaks at ca. 95 and 67 ppm as one would expect in the desired C(3) coupling product,[11] thus indicating that the coupling had occurred at the C(2) carbon.

Our ^{13}C NMR analysis was confirmed when the coupling reaction was performed with the hydroxyindoline **20** to afford a crystalline coupling product (25%) that was shown to be **21** by X-ray crystallographic analysis. Along with the C−C coupling product, 5% of the C−O coupling product **22** was obtained from this reaction along with diol **23**.

The experimental results reported in this paper provide additional indications of the difficulty of achieving by chemical means a biomimetic synthesis of haplophytine by the direct coupling of two indole alkaloid precursors. Nonetheless, we think that this challenge to synthesis can be met and that the process of finding a solution to this problem will be informed by the research described herein.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H NMR, ^{13}C NMR, IR for the new compounds described herein; X-ray crystal data for **12** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) On the basis of comparison with closely related natural product cimilophytine. See: Adesomoju, A. A.; Rawal, V. H.; Lakshmikantham, M. V.; Cava, M. P. *J. Org. Chem.* **1983**, *48*, 3015.