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TOTAL SYNTHESIS OF N-NORNITIDINE

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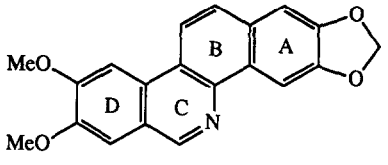
Summary: The benzo[c]phenanthridine alkaloid, N-nornitidine has been synthesized employing a benzyne-vinyl isocyanate cycloaddition as the key transformation.

The tetracyclic benzo[c]phenanthridines constitute an important sub-class of the isoquinoline alkaloid family[1] and a number of these species have elicited considerable synthetic[1c,2] interest due to demonstrated anticancer activity.[3,4] Although several representatives of this group of alkaloids display significant biological activity and progress toward understanding their mode of action has been made,[5] clinical utility has been limited by the acute toxicity exhibited by many of these materials.[3a]



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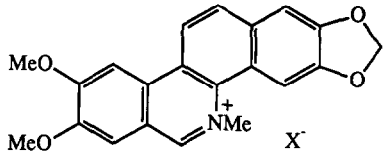
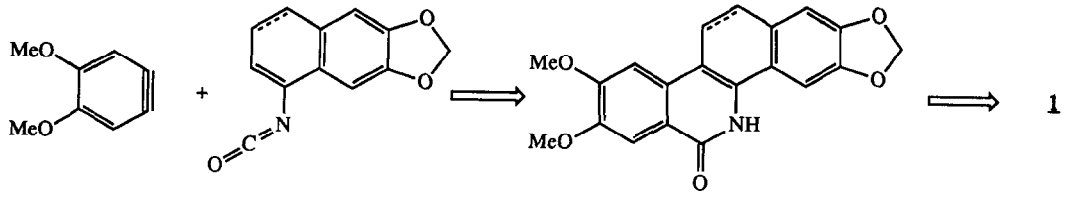


2

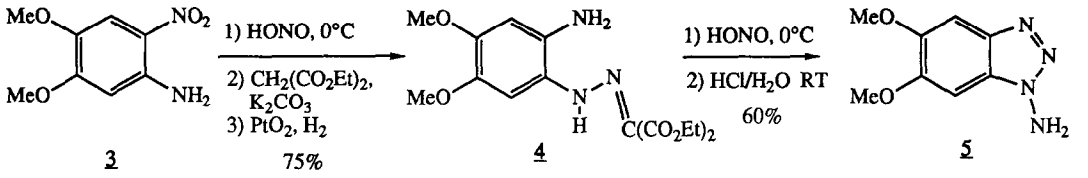
The bulk of reported benzophenanthridine synthetic studies to date have involved multistep sequences for assembly of the target molecules by fusing the tetracyclic framework together at the B or C ring juncture. A cycloaddition protocol for construction of these alkaloids would be particularly attractive due to the high level of convergency that this class of reactions affords.[2a] We report herein a novel and convergent total synthesis of the benzophenanthridine alkaloid, N-nornitidine employing the cycloaddition of a substituted benzyne with an appropriately substituted vinyl isocyanate partner.[6]



Scheme I

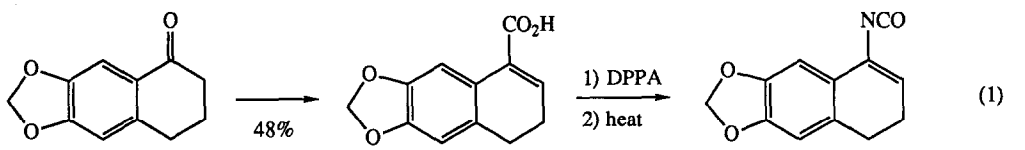
N-Nornitidine (**1**) represents an interesting example of this group of alkaloids in that it was known for some time as a synthetic intermediate[7] prior to its isolation from the tropical American *Zanthoxylum* species in 1981 by Boulware and Stermitz.[8] In addition, compound **1** is a useful point of departure for accessing several N-alkylated alkaloids such as the potent anticancer species, nitidine (**2**).[9]

The strategy envisioned for the total synthesis of N-nornitidine is based on the cycloaddition of a substituted benzyne with an appropriate vinyl or aryl isocyanate partner as depicted in Scheme I. An experimentally convenient method for effecting this type of benzyne-vinyl isocyanate cycloaddition employing a $Pb(OAc)_4$ decomposition of N-aminobenzotriazole has been recently developed in our laboratory.[10]



3 **4** **5**

The D-ring portion of the N-nornitidine target in the form of a substituted N-aminobenzotriazole is furnished in good overall yield by exploiting a modification of a sequence originated by Campbell and Rees.[11] In this instance, the readily available nitroaniline (**3**) is conveniently converted, via intermediate **4** (mp: 103-5°C),[12] into the requisite benzyne precursor, N-aminobenzotriazole **5** (mp: 185-86°C)[12] in 45% overall yield. We have found

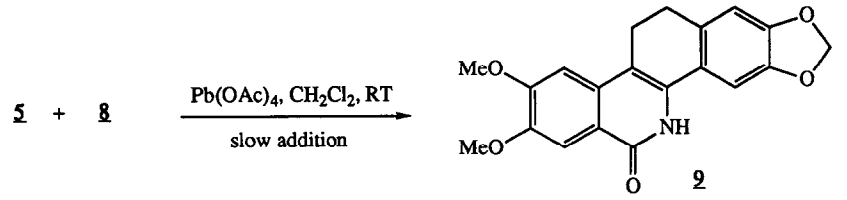


6 **7** **8** (1)

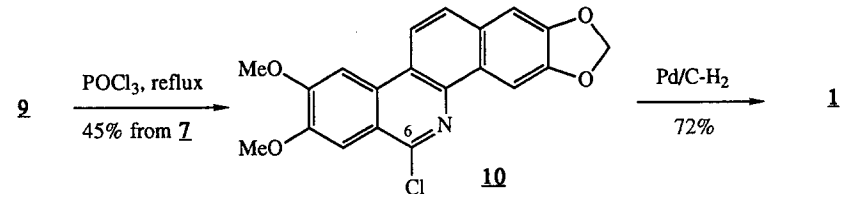
that employing K_2CO_3 as the base in this process greatly increases the efficiency of the diazonium coupling step critical to the conversion of **3** into compound **4**. We have previously established that Pb(IV) mediated decomposition of aminobenzotriazoles for the production of benzyne suitable for cycloaddition with vinyl isocyanates is superior to other methods currently available for this purpose.[10] Interestingly, attempted cycloaddition with benzyne generated by thermal decomposition of the corresponding arene diazonium carboxylate resulted principally in the production of the substituted biphenylene.

Readily available tetralone **6**[13] serves as the building block for the A-B ring substructure of the target molecule as outlined in equation (1). Palladium mediated carboalkoxylation[14] of the vinyl triflate derived from **6** (LDA, -70°; $(Tf)_2NPh$) followed by saponification of the resultant α,β-unsaturated methyl ester provided the acid **7** (mp: 207-210°C)[12] in 48% overall yield for the three step sequence. Nearly quantitative conversion of **7** into the corresponding vinyl isocyanate **8** via a modified Curtius rearrangement (diphenyl phosphorazidate (DPPA), toluene, reflux)[15] completed the elaboration of the A-B ring precursor. This particular vinyl isocyanate was neither isolated nor characterized, but was immediately subjected to the benzyne cycloaddition conditions.

The final assembly of the tetracyclic framework was effected by combining crude vinyl isocyanate **8** with a slight excess of $Pb(OAc)_4$ and N-aminobenzotriazole **5** in freshly distilled CH_2Cl_2 at room temperature. The reaction was complete within 15 min at this temperature. The maximum yields for this transformation were



obtained when CH_2Cl_2 solutions of the aminobenzotriazole and $Pb(OAc)_4$ were added simultaneously via dual syringe pumps to a solution of the vinyl isocyanate in a small quantity of the same solvent.[16] The resultant, highly insoluble pyridinone **9** was carried onto the next step without benefit of purification. This species was exposed to excess $POCl_3$ at reflux affording directly the *fully aromatic* chlorobenzophenanthridine **10** (mp >300°C, IR (nujol), 1618, 1575 cm^{-1})[12] in 45% overall yield for the three step sequence. Routine hydrogenolysis (Pd/C-H_2, atm. pressure) of the chloro substituent in tetracycle **10** followed to give N-nornitidine (**1**) (mp: 278-280°C, lit.,[8] mp: 279-281°C) in 72% yield.



The synthetic material produced in this manner exhibited spectral data (^1H NMR, UV, mass spect.) identical to those obtained for the authentic natural product as provided by Professor Stermitz.

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