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Synthesis of Pancratistatin Models

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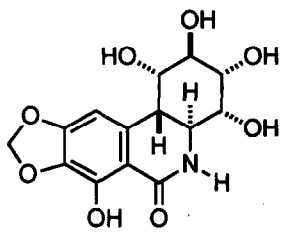
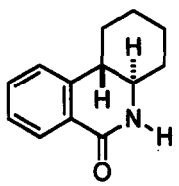
Abstract: Two model syntheses for the phenanthridone core of the cytotoxic alkaloid pancratistatin are reported. The key maneuver in these syntheses is 1,4-addition of an ortho-lithiated benzamide derivative to 1-nitrocyclohexene. The resulting 2-aryl-1-nitrocyclohexanes (**6** and **11**) are further transformed into the pancratistatin models **2** and **3**.

Pancratistatin (**1**), a phenanthridone alkaloid from the roots of *Pancratium littorale* Jacq.,[2] has shown promising in vitro anticancer activity.[3] In spite of a pioneering total synthesis of **1**[4] and several imaginative approaches to the general skeleton,[5] there is still room for an economical, 'low-tech' route to the alkaloid, one that could be used to prepare sufficient quantities of the material for use in clinical trials. In this Letter, we report syntheses of the tricyclic models (±)-**2** and (±)-**3**.



1



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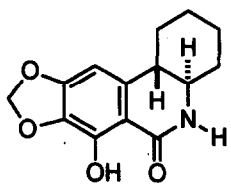
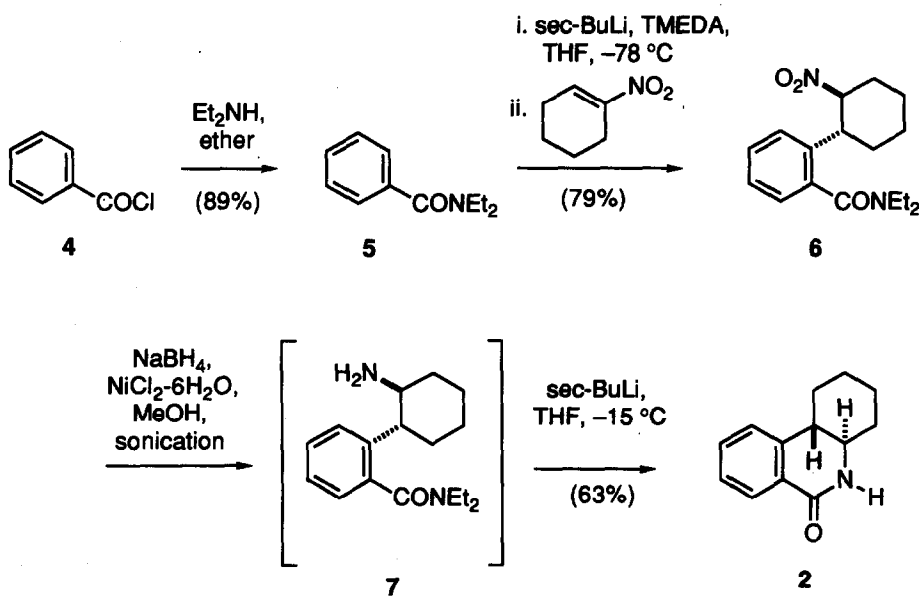


3

The synthesis of (±)-**2** (Scheme 1) began with benzoyl chloride (**4**), which was converted into its diethylamide (**5**) by reaction with diethylamine in ether. Metallation of **5** at the *ortho* position[6] was accomplished by reaction with sec-butyllithium in a mixture of TMEDA and THF at –78 °C. The resulting yellow solution was added through a cannula to a solution of 1-nitrocyclohexene in THF at –78 °C to afford the trans 1,4-addition product **6** in excellent yield. Reduction of the nitro group was accomplished with sodium borohydride–nickel chloride[7] to provide the unstable amine **7**. Without purification, **7** was dissolved in THF, cooled to –15 °C, and treated with 1.2 equivalents

of sec-butyllithium; lactam **2** (mp 207-208 °C) was obtained in 63% yield. Substitution of sec-butyllithium by *n*-butyllithium led to complex mixtures and low yields of lactam. Weaker bases were ineffective in bringing about the cyclization.

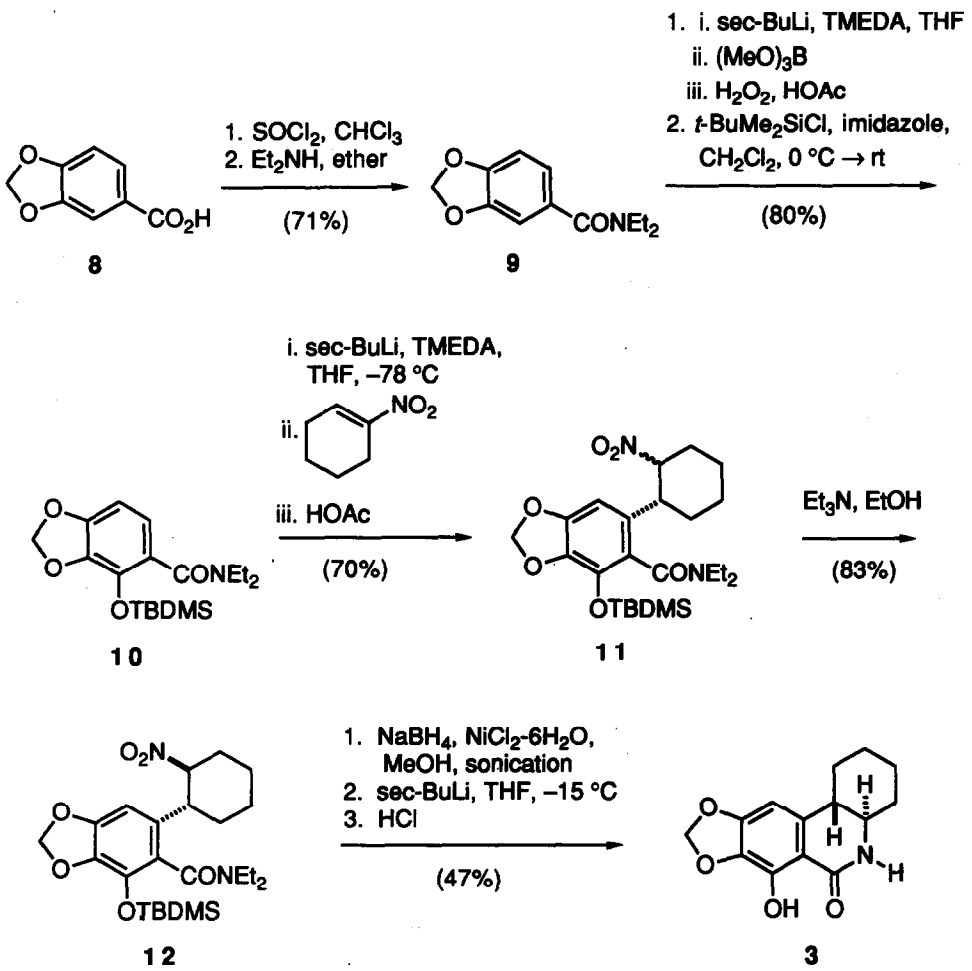
Scheme 1



A more complete model synthesis is summarized in Scheme 2. The diethylamide of piperonylic acid (**9**) was metallated as in the first model and the resulting aryllithium derivative treated with trimethyl borate to obtain the derived boronate. This intermediate was oxidized with 30% hydrogen peroxide in acetic acid and worked up by the procedure of Beak and Brown.[8] The resulting crude phenol was protected as the *tert*-butyldimethylsilyl ether[9] **10** in the normal manner.[10] Compound **10** has also been synthesized in five steps from pyrogallol[4] by a route that employs the Snieckus carbamoyl rearrangement.[11] Metallation of **10** under the normal conditions gave a deep red solution that was added by cannula to 1-nitrocyclohexene to obtain a mixture of cis and trans 1-aryl-2-nitrocyclohexanes. Treatment of this mixture with triethylamine in refluxing ethanol caused epimerization of the cis isomer and delivered the pure trans isomer **12** in good yield. The nitro group was reduced, again with sodium borohydride–nickel chloride,[7] to give an

amine that was cyclized by treatment with *sec*-butyllithium in THF at –15 °C. Removal of the *tert*-butyldimethylsilyl group provided tricyclic lactam **3**, mp 288-89 °C.

Scheme 2



The model studies reported here establish a simple process that can be used to elaborate the phenanthridone nucleus. Efforts are currently being directed at the synthesis of a suitably protected 3,4,5,6-tetrahydroxy-1-nitrocyclohexene so that this approach can be used to synthesize pancratistatin itself.

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References and Notes

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