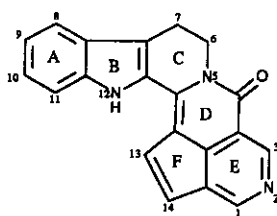


SYNTHETIC STUDIES ON NAULAFINE¹David B. Repke*, Jahangir², Robin D. Clark, and Janis T. Nelson

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Abstract—The first synthesis of Naulafine, 7,12-dihydrocyclopent[de]indolo-[2',3':3,4]pyrido[1,2-b][2,7]-naphthyridin-4(6H)-one, is described.

We have previously demonstrated the utility of lithiated toluamides^{3,4} and lithiated cyanopicolines⁵⁻⁶ for the production of polycyclic heterocycles such as 8-oxoberbines⁴, 10-azaberbines, and indolo[2:3, 3':4']pyrido[1,2-b]naphthyridines. Thus, condensation of these lithium species with TMS triflate-activated cyclic imines has led to the synthesis of alamaridine⁵, alangimaridine and alangimarine⁶, nauclefine, angustine, and angustidine^{7,8}. Using this methodology, we then turned our attention to the synthesis of another Nauclea alkaloid, the hexacyclic naulafine 1. Herein we report the total synthesis of this natural product.



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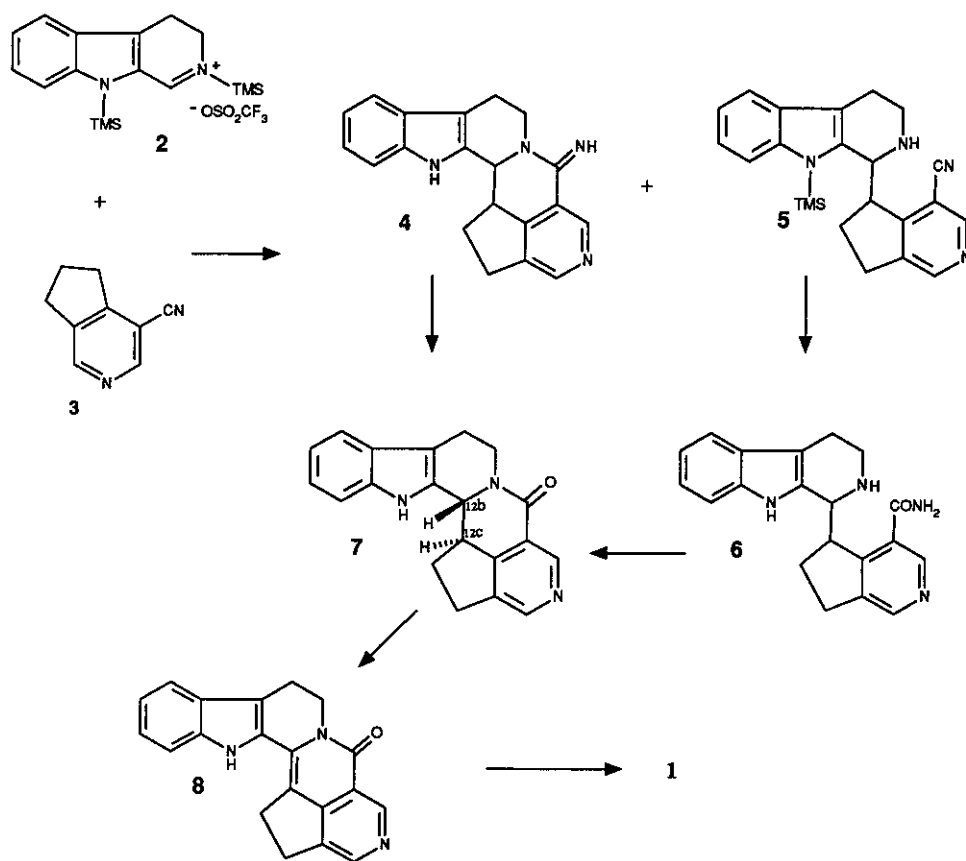
First isolated from Nauclea latifolia Smith by Hotellier, Delaveau, and Pousset⁹, naulafine is unique among the Nauclea alkaloids in that it contains a sixth fused, five-membered ring (ring F).

When a solution of the anion of 6,7-dihydro-5H-2-pyridine-4-carbonitrile 3^{10} (generated in THF at -78°C using 1 equivalent of LDA) was added to a suspension of 2,9-bis-(trimethylsilyl)-3,4-dihydropyrido[3,4-b]indolium trifluoromethane sulfonate 2^8 in THF at -78°C , the expected cyclic amidine **4** was obtained in only 19% yield. The major product of this reaction was the trimethylsilyl aminonitrile **5** (39% yield). The structure of **5** was determined by ir, ^1H nmr, ms, and elemental analysis.¹¹ When either **4** or **5** was heated at reflux with potassium hydroxide in aqueous dioxane for two days the lactam **7** (tetrahydronaulafine) resulted. If the reaction of **5** was interrupted prematurely, significant amounts of the amide **6** were also isolated. The ^1H nmr spectrum of **7** indicates that it is one diastereomer. The hydrogen at C-12b appears as a doublet at 4.86 ppm with $J_{12b,12c} = 11.29$ Hz clearly indicating a trans relationship to the hydrogen at C-12c. Similar coupling constants of analogous protons in tetrahydroprotoberberines have been observed^{12,13}.

The stereoselectivity observed in the formation of **7** can be justified by either thermodynamic or kinetic arguments. Examination of molecular models indicated that the trans isomer appears to be more stable; any cis isomer formed could be equilibrated under the strongly basic reaction conditions. The kinetic argument invokes what appears to be, on examination of molecular models, the most favorable endo transition state for the two reactants. A similar argument has been proposed to explain the stereospecificity observed in the addition of lithiated phthalides to dihydroisoquinolines¹⁴.

The tetrahydro compound **7** was readily converted to dihydronaulafine¹⁵ **8** by reaction with iodine⁶ in ethanol at reflux. There is no evidence of further oxidation of compound **8** to naulafine under these conditions. In fact, compound **8** proved remarkably resistant to further dehydrogenation. The conversion of **8** to **1** could not be effected with a variety of reagents and conditions¹⁶. However, the transformation was realized by heating **8** with 20% Pd/C¹⁷ in p-cymene under reflux for 16 hours. The yield of **1** was 30%; 60% of **8** was recovered. Longer reaction periods led not only to the formation of **1** but also to the production of numerous by-products. The ^1H nmr and mass spectral data for **1** were identical to that reported⁹.

SCHEME I



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2. Syntex Postdoctoral Fellow 1987-1988.

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11. Compound 5 exhibited a sharp ir nitrile band at 2240 cm^{-1} (KBr), a singlet for the indole-TMS group at 0.66 ppm, and a lack of the indole N-H proton which re-appeared as a sharp, D_2O -exchangable singlet at 11.32 ppm upon treatment of 5 with acid. EI MS showed the parent peak at m/z 386.
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15. Compound 8: mp $> 300^\circ\text{C}$ (MeOH), ^1H nmr (Bruker WM 500, 500 MHz, $\text{DMSO}-d_6$, ppm δ): 10.82 (s, 1H, indole N-H, exchanges with D_2O), 8.97 (s, 1H), 8.54 (s, 1H), 7.58 (d, 1H), 7.08 (t, 1H), 4.38 (t, 2H, $J=6.4\text{ Hz}$), 3.49 (d, 2H, $J=4.2\text{ Hz}$), 3.37 (d, 2H, $J=4.2\text{ Hz}$), 3.05 (t, 2H, $J=6.3\text{ Hz}$). High Resolution ms (Finnigan Mat 311A): Theoretical Mass: 313.121511, Measured Mass: 313.120192.
16. Reagents and conditions: DDQ in benzene, reflux; selenium dioxide, glacial acetic acid, reflux; sulfur, 225°C ; platinum oxide in xylene, reflux; manganese dioxide in dioxane, reflux; $n\text{-BuLi/TMEDA}$ in cyclohexane, reflux. For reviews on dehydrogenation, see P.P. Fu and R.G. Harvey, Chem. Rev., 1978, 78, 317 and P.N. Rylander, "Organic Syntheses with Noble Metal Catalysts", Academic Press, New York, 1973.
17. The catalyst was prepared by stirring 20% $\text{Pd}(\text{OH})_2/\text{C}$ (Pearlman's Catalyst) in xylene under H_2 at atmospheric pressure for 14 hours and then concentrating to dryness under reduced pressure at 50°C .

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