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A TOTAL SYNTHESIS OF (±)-DIHYDROPALUSTRINE.

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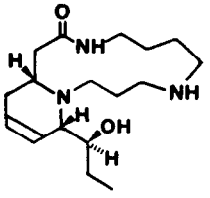
Abstract: Dihydropalustrine has been synthesized by a β-lactam-imino ether coupling route. A dehydro precursor previously considered to represent palustrine has now been shown to be nonidentical with the natural product.

Palustrine is the main alkaloid of Equisetum palustre L.,[1] one of several species of the marsh horsetail. Structural and synthetic investigations by Eugster led to its formulation as structure (1).[2,4] In addition to the chemical and spectroscopic evidence, this assignment was based on an elegant synthesis of (±)-dihydropalustrine (3).[3] We now report a total synthesis of compound (1) in racemic form and its conversion to (±)-dihydropalustrine (3).



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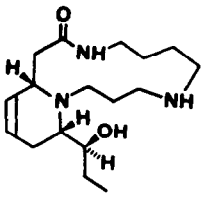

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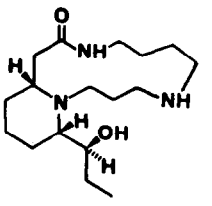
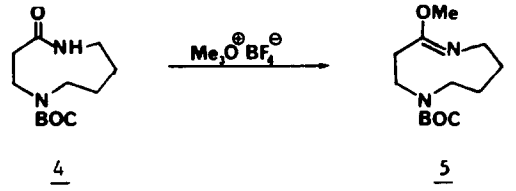


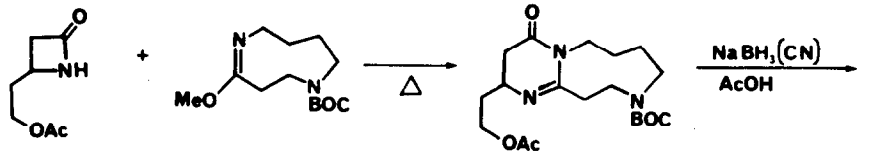
3

Our synthesis began with the protected nine-membered amino lactam (4) which we have previously employed in the synthesis of the alkaloids chaenorhine[6] and verbascenine.[7] The methyl imino ether (5), formed from 4 (97%) using trimethyloxonium tetrafluoroborate, was heated at 145° in mesitylene with the known β-lactam (6).[8] The coupled product (7) (65%) was then reduced using sodium cyanoborohydride in acetic acid[9] to form the thirteen-membered lactam (8)(90%), and the newly generated amino group was protected by conversion to the trichloroethoxycarbamate (9)(90%). Deacetylation with sodium methoxide yielded the alcohol (10) (95%) which was then converted to the bromide (11) using triphenylphosphite dibromide.[10] Heating the bromide with triphenylphosphine produced the phosphonium salt (12)(50% from 10).

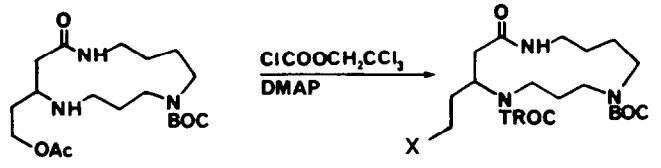


4 5

BOC = COOt-Bu
TROC = $COOCH_2CCl_3$



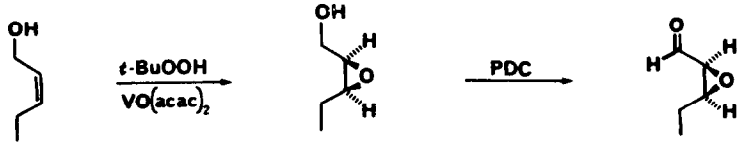
6 5 7



8 9

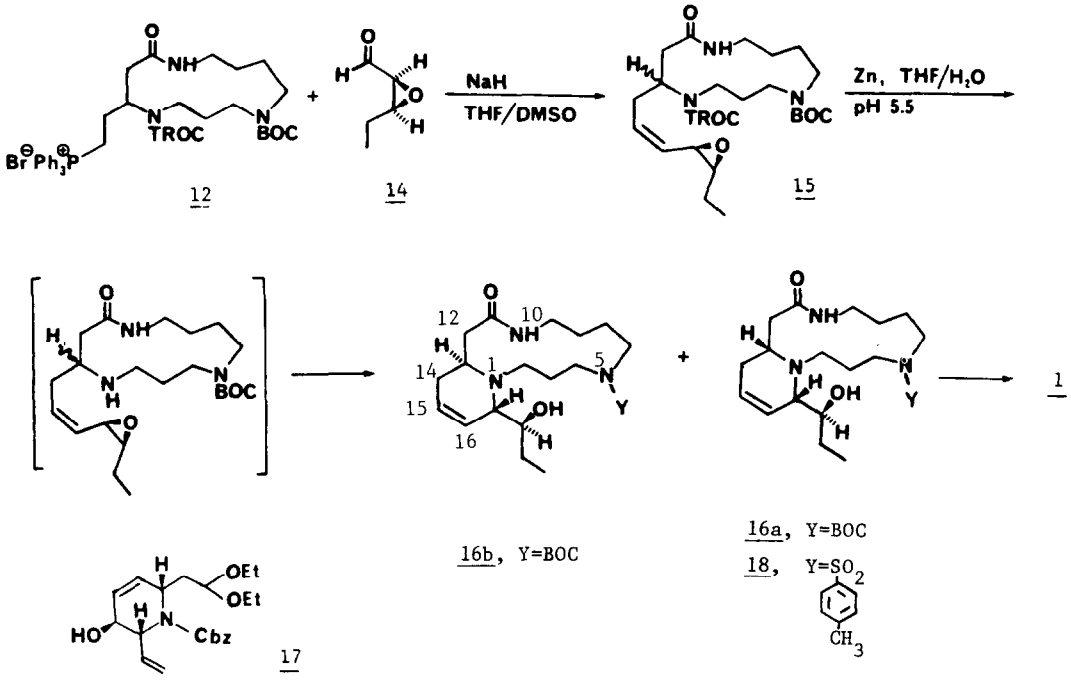
9, X=OAc
10, X=OH
11, X=Br
12, X=Ph_3P^+, Br^-

To incorporate the remaining part of the tetrahydropyridine framework, a Wittig reaction (NaH, TMF/DMSO)[11] was carried out with 12 and the epoxy aldehyde (14) forming 15 (70%). Epoxide 14 was prepared from the allylic alcohol (13) [12] utilizing the Sharpless procedure [13] ($VO(acac)_2$, t-butyl hydroperoxide) followed by oxidation with pyridinium dichromate. Assignment of the cis configuration to the newly formed double bond in 15 was consistent with the NMR spectrum (δ5.39,d of d, $J_{A,B}$=10 Hz) (δ5.75, d of t, $J_{B,A}$=10 Hz). Removal of the trichloroethoxycarbonyl group (Zn, THF/H_2O, pH 5.5)[14] resulted in concurrent intramolecular opening of the epoxide ring by the deprotected secondary amino group and afforded the alcohols (16a and 16b) having the desired stereochemical relationship at position C-17 and C-18 with a mixture of α and β hydrogens at C-13.



13 14

The two diastereomeric products were then separated by flash chromatography, yielding the BOC protected derivatives having the natural configuration (16a) (41%), and unnatural (16b) (46%). Removal of the BOC group from 16a (HCl/CH_2Cl_2) yielded compound 1, identical (comparison of high field NMR spectra) with the same substance independently synthesized by Natsume starting from the piperidino derivative (17).[5] Natsume was able to verify the structure of his product by X-ray crystallographic analysis of the sulfonamide derivative (18).



With the availability of a fresh sample of palustrine recently isolated by Professor Eugster, we were able to show that compound 1 is not the same as the natural material. However, hydrogenation of natural palustrine ($Pd/BaSO_4$)[2] and of our synthetic product (1) gave the identical dihydro derivative (TLC, 500 MHz NMR), thus confirming all structural and stereochemical aspects of Eugster's original assignment, except for the position of the double bond. The likely possibility that palustrine may be represented by structure (2) having an alternative location of the double bond at C_{14}-C_{15} in the six-membered ring is under active investigation.[15]

Acknowledgement: We are most grateful to Professor C.H. Eugster, University of Zurich, for providing an authentic sample of palustrine and for helpful private discussions on the structural problem. We also wish to thank Professor M. Natsume, Research Foundation, Itsuu Laboratory, for the opportunity to make comparisons of our products with his synthetic material and for sharing his NMR and X-ray evidence with us.

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15. This alternative structure (2) was previously considered by Eugster: C. Mayer, W. Trueb, J. Wilson and C.H. Eugster, Helv. Chim. Acta, 51, 661 (1968). The possibility that the double bond may be incorporated in the thirteen-membered ring is highly unlikely, based on Eugster's degradative work.[2]
16. All new compounds gave satisfactory IR, NMR and mass spectra consistent with their structures.

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