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THE SYNTHESIS OF (±)-VERBASCENINE

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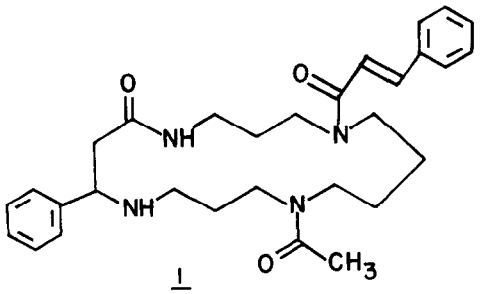
Abstract: A synthesis of (±)-verbascenine is described which includes,as the key step, the coupling of 4-phenylazetidin-2-one with an imino ether derivative of a protected thirteen-membered diamino lactam.

Verbascenine is a member of the family of spermine and spermidine alkaloids recently isolated from plant sources. Based on the results of chemical degradation and spectroscopic studies carried out by Hesse and coworkers[1] it was assigned the seventeen-membered lactam structure (1) incorporating cinnamic acid residues along with a spermine backbone.



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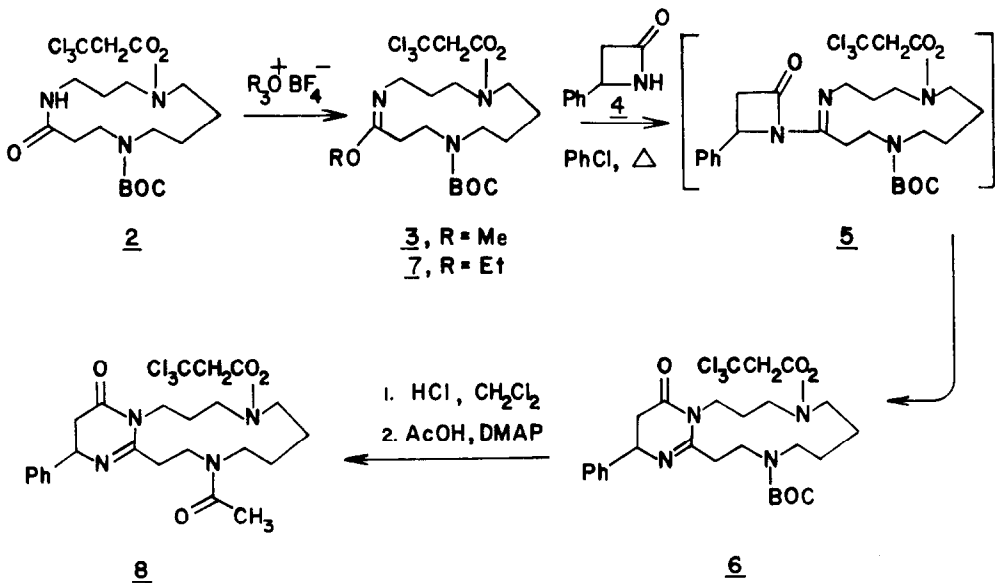
In connection with our studies on the synthesis of macrocyclic lactams in the polyamine field,[2,3,4,5] we have explored the generality of the ring expansion process recently utilized in the synthesis of dihydroperiphylline[3] and chaenorhine.[5] This method utilizes, as a key step, the coupling of a β-lactam with a cyclic imino ether.[6,7] In our synthetic work, this ring enlargement, followed by reductive cleavage, has served to incorporate substituted β-amino-β-phenylpropionyl residues into amino lactams of various sizes. While previous ring expansions of azetidinones have been used in the formation of

8,9 and 13-membered lactams, the synthesis of (±)-verbascenine outlined below represents the first use of a β-lactam for the generation of a 17-membered ring in this series.

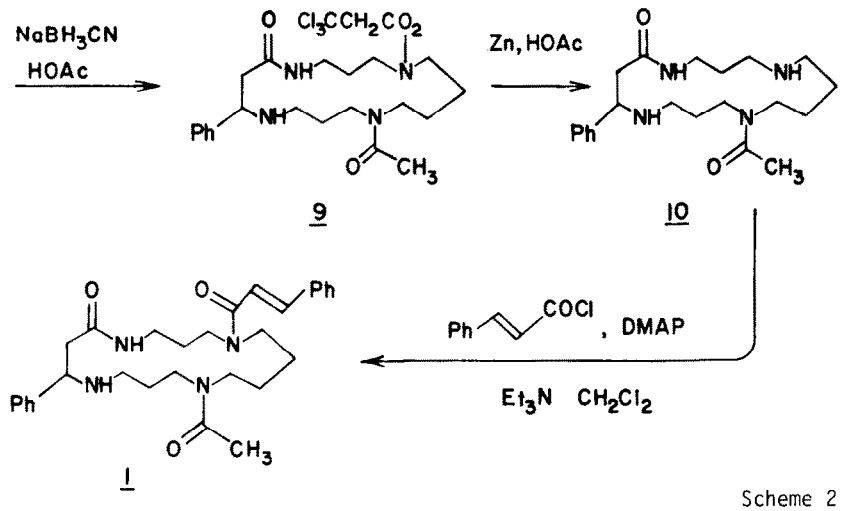
The imino ether (3) previously prepared (91%) from 2 as an intermediate in the synthesis of chaenorhine[5] was warmed with 4-phenylazetidin-2-one (4) in refluxing chlorobenzene to form the 4-oxo-tetrahydropyrimidine (6). In our early experiments, the yield of 6 was low (16%) and this product was accompanied by a substantial amount of the 13-membered lactam (2). The fact that an appreciable quantity of lactam (2) was regenerated from 3 in this reaction suggested that demethylation of the methyl imino ether



Scheme 1

was competing with the initial addition-elimination step which presumably forms the intermediate (5)[6] (not isolated).[8] We therefore sought to minimize the dealkylation side-reaction by the use of the corresponding ethyl imino ether (7) prepared from 2 in 95% yield. Thus, when 7 was allowed to react with 4-phenylazetidin-2-one (4) the desired product (6) was isolated in 60% yield. Only a trace of the lactam (2) could be detected by TLC. Removal of the BOC group ($HCl/CH_2Cl_2/0°C$) and introduction of the acetyl group ($AcCl/DMAP/CH_2Cl_2/25°C$) provided the fused ring system (8) in 80% yield. (Scheme 1).

The synthesis of verbascenine was completed as follows: (Scheme 2) Treatment of 8 with $NaBH_3CN$ (3 equiv) in AcOH (2h at 25°C, 1h at 50°C, 12h at 25°C) [2,3,5.] gave the 17-membered lactam (9) (88%). After removal of the 2,2,2-trichloroethoxycarbonyl protecting group (Zn/AcOH/25°C) to form 10, the trans-cinnamoyl residue was selectively introduced[9] by low temperature acylation of the less-hindered secondary amino function (trans-Ph-CH=CH-COCl/Et_3N/DMAP/-78°) yielding (±)-verbascenine (1) (58% from 9).



Scheme 2

With the aid of Professor M. Hesse, University of Zurich, we were able to obtain a sample of pure, natural verbascenine from Professor K. Seifert, Institut fur Biochemie der Pflanzen Halle, Akademie der Wissenschaften der DDR. The synthetic product (1) was identical in all respects (TLC, 500 MHz NMR, MS, IR) with the natural material.

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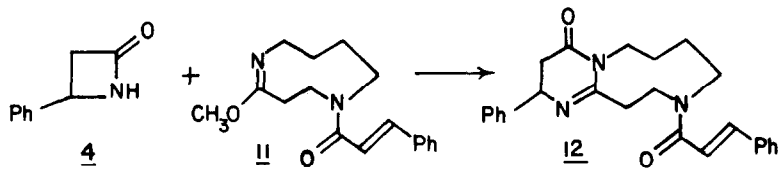
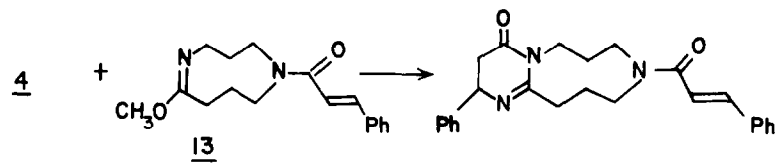
7. A related reaction which we have employed as the convergent step in our recent chaenhorine synthesis utilizes a β-amino ester in place of the β-lactam.

8. In our synthesis of dihydroperiphylline [3] involving the conversion of a 9-membered ring to a 13-membered ring, the coupling of 4 with the methyl imino ether (11) to form 12 took place in 67% yield. On the other hand, the reaction of 4 with 13 during an attempted celacinnine synthesis gave very low yields of the analogous coupling product. We are investigating the possibility that geometric effects associated with the syn vs. anti configurations of the cyclic imino ether groups may affect the course of this reaction. (See R. M. Moriarty, C.-L. Yeh, K. C. Ramey and P. W. Whitehurst, J. Am. Chem. Soc., 92, 6360 (1970).)





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