

SYNTHESIS OF AN AMARYLLIDACEAE ALKALOID, ($\pm$)-HIPPEASTRINE

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Abstract — Total synthesis of one of Amaryllidaceae alkaloids, hippeastrine, was accomplished starting from methyl 2- $\underline{c}$ -(N-methoxycarbonylamino)-3- $\underline{t}$ -(3,4-methylenedioxyphenyl)cyclohex-4-enyl-r-acetate in stereoselective manner.

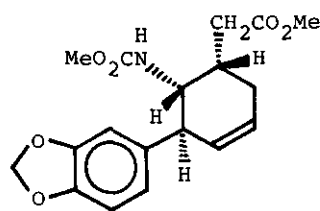
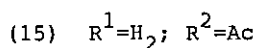
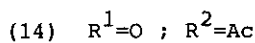
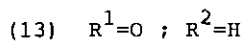
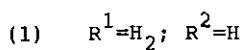
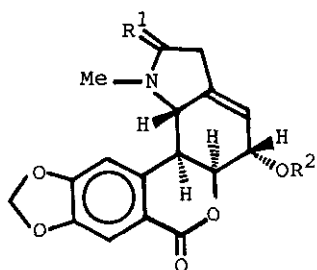
Although there have been several reports concerning the syntheses of Amaryllidaceae alkaloids, straightforward synthesis of hippeastrine (1),¹ one of the lactonic alkaloids, occurring in Amaryllidaceae plants, has not been completed so far.² We report here a synthesis of ($\pm$)-hippeastrine as continuation of our synthetic work of Amaryllidaceae alkaloids.

Hydrolysis of the urethane-ester (2)³ in 2N aqueous sodium hydroxide and toluene (two phase) at reflux overnight gave an aqueous solution of the corresponding amino acid sodium salt, which was, after adjusting pH 5 with concentrated hydrochloric acid, treated with water soluble DCC [1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide] to furnish the nor-lactam (3) in 80% overall yield. Methylation of (3) with sodium hydride and methyl iodide gave the lactam (4) in good yield. Treatment of (4) with chloromethyl methyl ether in acetic acid in the presence of zinc chloride followed by silver acetate gave the acetoxy-lactam (5) in 45% yield. Epoxidation of (5) with *m*-chloroperbenzoic acid in methylene chloride gave the oxide (6) as a sole product in 75% yield. ¹H-nmr(400MHz) of (6) showed a signal of a doublet at δ (CDCl₃) 3.46ppm (J=9.5Hz) assigned to a benzylic proton. Dreiding model examination indicated that when the oxide was conferred as the structure (6) depicted in chart, the dihedral angle between H_b and H_c was nearly 90°, suggesting the

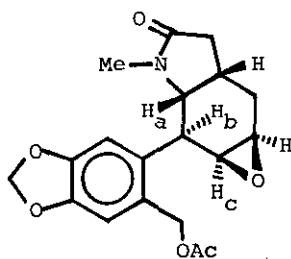
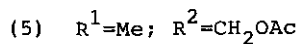
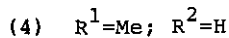
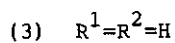
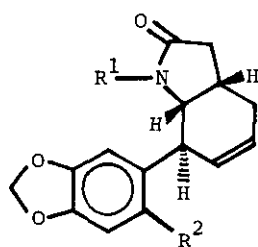
structure of the oxide (6).

Treatment of the oxide (6) with acetic acid and acetic anhydride in the presence of boron trifluoride etherate gave the triacetate (7) in good yield. Alkaline hydrolysis of (7) in ethanol gave the triol, which was, without further characterization, transformed to dihydrohippeastrine lactam (8) with manganese dioxide in chloroform. Treatment of (8) with Meerwein reagent ($\text{Et}_3\text{O}^+\text{BF}_4^-$) followed by sodium borohydride gave (+)-dihydrohippeastrine [(+)-cliviasine]⁴ (9), mp 151-153°C in 58% yield. Its spectral data [¹H-nmr and ir (CHCl_3)] and behaviour on thin layer chromatography were identical with those of dihydrohippeastrine derived from hipp-eastrine, the facts confirming the synthesis of the alkaloid and, in turn, the structure of the triacetate (7).

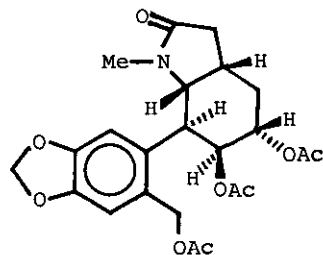
Treatment of the hydroxy-lactam (8) with methanesulfonyl chloride in pyridine gave the mesylate (10) which was, without further purification, heated with lithium chloride and lithium carbonate in dimethylformamide under argon to give the dehydro-lactam (11) in 85% yield. Oxidation of (11) with *m*-chloroperbenzoic acid in dichloroethane in the presence of 4,4'-thiobis-(6-*tert*-butyl-*m*-cresol)⁵ under reflux for 2 days gave the oxide (12) in 80% yield. The stereostructure of the oxide (12) was ultimately disclosed by synthesis of (+)-hippeastrine. Thus, application of Sharpless method⁶ to convert an oxide into an allyl alcohol furnished hippeastrine lactam (13) in 45% yield. Attempt to reduce the lactam carbonyl was made in the same manner as the reduction of dihydrohippeastrine lactam (8) using ($\text{Et}_3\text{O}^+\text{BF}_4^-$) followed by sodium borohydride, but (+)-hippeastrine was not detected even on thin layer chromatography. Reduction of the lactam (13) with lithium aluminium hydride in tetrahydrofuran followed by oxidation of the resulting product(s) with manganese dioxide gave no fruitful result. Furthermore, attempt to transform the lactam (13) to the corresponding thio-lactam was also unsuccessful. Eventually we found that treatment of (+)-hippeastrine lactam acetate (14) with trimethyloxonium fluoroborate⁷ in place of triethyloxonium fluoroborate followed by zinc borohydride⁸ furnished (+)-hippeastrine acetate (15) in low yield (13% yield), the ir (CHCl_3), and its ¹H-nmr spectra were superimposable upon those of hippeastrine acetate. Hydrolysis of the acetate (14) with potassium carbonate in aqueous methanol gave (+)-hippeastrine (mp 210-211°C, from ethanol). The ir (CHCl_3) and ¹H-nmr spectra of the latter were identical with those of hippeastrine, indicating accomplishment of the synthesis of the alkaloid.



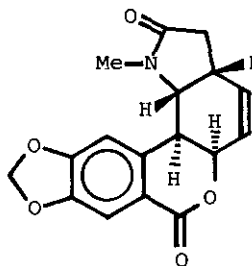
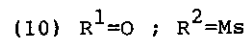
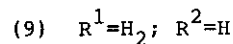
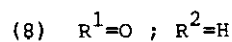
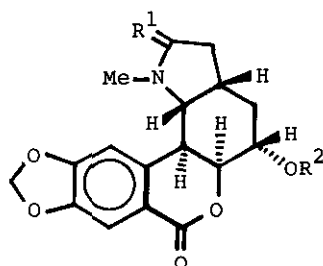
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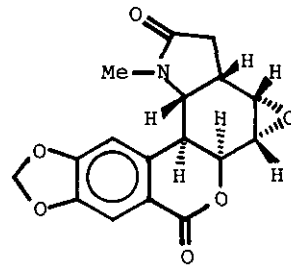
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(7)



(11)



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