SYNTHESIS OF AN AMARYLLIDACEAE ALKALOID, (±)-HIPPEASTRINE

Jun'ichi Katakawa and Haruo Meguri

Faculty of Pharmaceutical Sciences, Setsunan University, 45-1,

Nagaotoge-cho, Hirakata, Osaka 573-01, Japan

Hiroshi Irie[*]

Faculty of Pharmaceutical Sciences, Nagasaki University,

Bunkyo-machi, Nagasaki 852, Japan

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

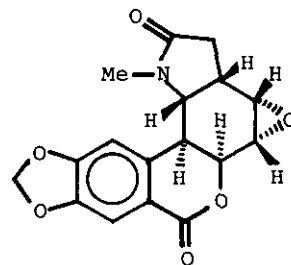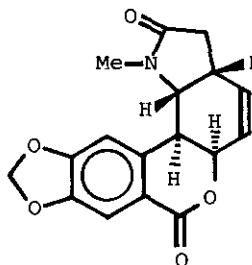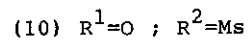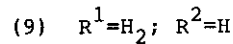Although there have been several reports concerning the syntheses of Amaryllidace-
ae alkaloids, straightforward synthesis of hippeastrine (1),[1] one of the lactonic
alkaloids, occurring in Amaryllidaceae plants, has not been completed so far.[2]
We report here a synthesis of (±)-hippeastrine as continuation 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 hydroch-
loric acid, treated with water soluble DCC [1-ethyl-3-(3'-dimethylaminopropyl)car-
bodiimide] 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 chlo-
ride followed by silver acetate gave the acetoxy-lactam (5) in 45% yield. Epoxida-
tion of (5) with m-chloroperbenzoic acid in methylene chloride gave the oxide (6)
as a sole product in 75% yield. ^{1}H-nmr(400MHz) of (6) showed a signal of a doublet
at δ(CDCl$_3$) 3.46ppm (J=9.5Hz) assigned to a benzylic proton. Dreiding model exami-
nation 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 character-
ization, transformed to dihydrohippeastrine lactam (8) with manganese dioxide in
chloroform. Treatment of (8) with Meerwein reagent ($Et_3O^+BF_4^-$) followed by sodium
borohydride gave (±)-dihydrohippeastrine [(±)-cliviasine][4] (9), mp 151-153°C in
58% yield. Its spectral data [^{1}H-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 dehyd-
ro-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, appli-
cation of Sharpless method[6] 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
($Et_3O^+BF_4^-$) followed by sodium borohydride, but (±)-hippeastrine was not detected
even on thin layer chromatography. Reduction of the lactam (13) with lithium alum-
inium 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 trimethyloxo-
nium fluoroborate[7] in place of triethyloxonium fluoroborate followed by zinc boro-
hydride[8] furnished (±)-hippeastrine acetate (15) in low yield (13% yield), the ir
($CHCl_3$), and its ^{1}H-nmr spectra were superimposable upon those of hippeastrine
acetate. Hydrolysis of the acetate (14) with potassium carbonate in aqueous metha-
nol gave (±)-hippeastrine (mp 210-211°C, from ethanol). The ir ($CHCl_3$) and ^{1}H-nmr
spectra of the latter were identical with those of hippeastrine, indicating accom-
plishment of the synthesis of the alkaloid.

(1) $R^1=H_2$; $R^2=H$

(13) $R^1=O$; $R^2=H$

(14) $R^1=O$; $R^2=Ac$

(15) $R^1=H_2$; $R^2=Ac$

(2)

(3) $R^1=R^2=H$

(4) $R^1=Me$; $R^2=H$

(5) $R^1=Me$; $R^2=CH_2OAc$

(6)

(7)

(8) $R^1=O$; $R^2=H$

(9) $R^1=H_2$; $R^2=H$

(10) $R^1=O$; $R^2=Ms$

(11)

(12)
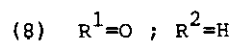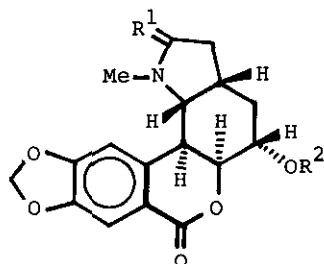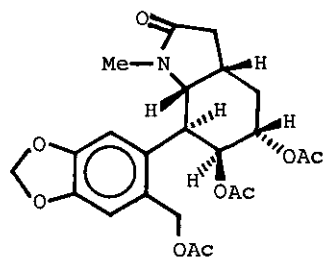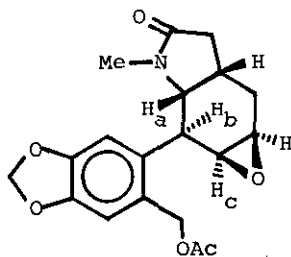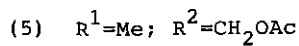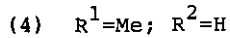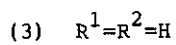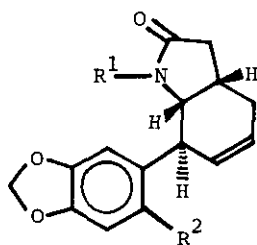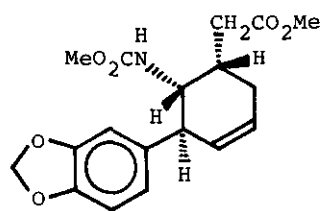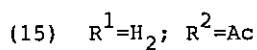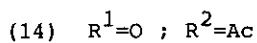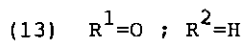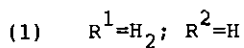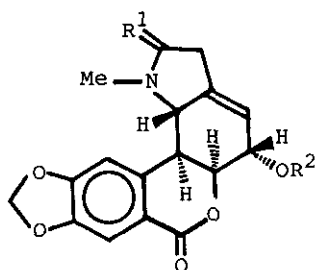
REFERENCES

1. H. G. Boit, <u>Chem. Ber.</u>, 1956, 89, 1129.

2. Transformation of lycorine to hippeastrine has been reported by K. Kotera and his associates, K. Kotera, Y. Yamada, and R. Nakane, <u>Tetrahedron</u>, 1968, 24, 759.

3. Y. Tsuda, T. Sano, J. Taga, K. Isobe, J. Toda, S. Takagi, M. Yamaki, M. Murata, H. Irie, and H. Tanaka, <u>J. Chem. Soc. Perkin I</u>, 1979, 1358.

4. W. Döpke and M. Bienert, <u>Pharmazie</u>, 1970, 25, 700.

5. Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, and T. Goto, <u>J. Chem. Soc. Chem. Comm.</u>, 1972, 64.

6. K. B. Sharpless and R. F. Lauer, <u>J. Am. Chem. Soc.</u>, 1973, 95, 2697; K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, <u>ibid.</u>, 1973, 95, 6137.

7. T. J. Curphey, <u>Org. Syn.</u>, 1968, 51, 142.

8. W. J. Gensler, F. Johnson, and A. D. B. Sloan, <u>J. Am. Chem. Soc.</u>, 1960, 82, 6074.