A TOTAL SYNTHESIS OF (±)-AGROCLAVINE-I. A NEW C/D-*cis*-8-ERGOLENE ALKALOID

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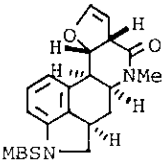
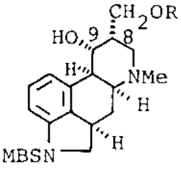
Abstract —— A new total synthesis of (±)-agroclavine-I was described.

In continuation of our synthetic work[1-5] on ergoline type of alkaloids, we now report a new synthesis of (±)-agroclavine-I,[6] which was isolated from a Penicillium kapuscinski strain as one of metabolites and proposed its structure (1) as having a novel C/D-*cis* ring juncture from its n.m.r. analysis. Very recently the first total syntheses had been reported.[7] Our synthetic strategy was based on the another utilization of the key intermediate (3) which was prepared from the photocyclized lactam (2) and successively applied to total synthesis of some ergolene type of alkaloids including (±)-lysergene and (±)-agroclavine.[2] The key intermediate, C/D-*cis*-9-hydroxy-8-methylol (3), was mesylated in pyridine at an ice-cooling temperature to give the monomesylate (4) in 90% yield which was then reduced with lithium aluminum hydride in tetrahydrofuran to give the 8-methyl-9-ol (5) in 41% yield. The structure of (5) was established from its n.m.r. spectrum which exhibited signals of hydrogen at 9-position at δ 3.60 as a doublet of doublets with the coupling constants of 8 and 5 Hz, two geminal hydrogens at 7-position at δ 2.61 and 2.36 as each doublet of doublets, with *J* values of 12 and 4 Hz, and a methyl group at δ 1.07 as a doublet with *J* value of 7 Hz, thus also suggesting the conformation of this compound (5) as shown by (A).

Dehydration of the 8-methyl-9-ol (5) with thionyl chloride in benzene proceeded smoothly to give the 8-ergolene type of compound (6) in 64% yield, which showed n.m.r. signals of hydrogen at 9-position at δ 5.28 as a broad singlet and methyl

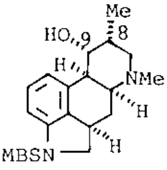


(2)

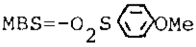


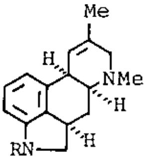
(3) R=H

(4) R=Ms



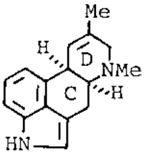
(5)



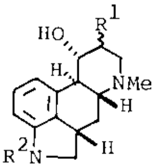


(6) R=MBS

(7) R=H

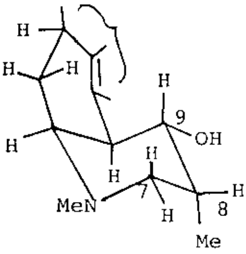


(1)

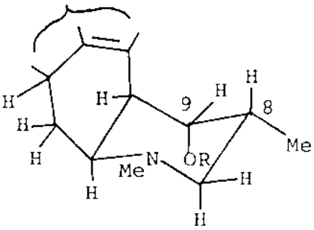


(8) R^1= α-CH_2OAc
R^2=Ac

(9) R^1=β-CH_2OAc
R^2=Bz



(A)



(B)

group at δ 1.60 as a broad singlet. This facile formation of the dehydrated product (6) under the above procedure was phenomenal and quite a contrast to the previous results. Thus, it had been observed that under similar treatment with thionyl chloride, the 8α-acetate (8) yielded the 9β-chloro derivative as the major and the 8-ergolene derivative as the minor products,[3] while the 8β-acetate (9) gave only the 9β-chloro derivative.[4] These results suggest that the C/D-ring juncture of (5) makes the conformation (B) favorable, thereby facilitating diaxial elimination between 8β-axial hydrogen and the intermediary 9α-axial group.

Removal of the protective group on the indole nitrogen was achieved by reduction with lithium aluminum hydride in tetrahydrofuran to give the indoline (7) in 67% yield which showed n.m.r. signals of 9-hydrogen at δ 5.40 as a broad singlet and 8-methyl group at δ 1.63 as a broad singlet.

Conversion of the indoline (7) into the indole (1) was achieved by dehydrogenation with phenylseleninic anhydride in the presence of indole[8] to yield (1) in 90% yield, which showed identical n.m.r. signals and u.v. absorptions as those reported on natural agroclavine-I,[6] thereby completed the total synthesis of the alkaloid and also established the proposed structure of the alkaloid.

REFERENCES

N.m.r. spectra were measured in $CDCl_3$ with TMS as internal standard on a Varian XL-200 at 200 MHz.

1 I. Ninomiya, C. Hashimoto, T. Kiguchi, and T. Naito, J. Chem. Soc., Perkin Trans. 1, 1985, 2911.

2 T. Kiguchi, C. Hashimoto, and I. Ninomiya, Heterocycles, 1984, **22**, 43.

3 I. Ninomiya, C. Hashimoto, and T. Kiguchi, Heterocycles, 1984, **22**, 1035.

4 T. Kiguchi, C. Hashimoto, and I. Ninomiya, Heterocycles, 1985, **23**, 1377.

5 T. Kiguchi, C. Hashimoto, and I. Ninomiya, Heterocycles, in press.

6 V. G. Sakharovsky and A. G. Kozlovsky. Tetrahedron Lett., 1984, **25**, 109.

7 A. P. Kozikowski and P. D. Stein, J. Am. Chem. Soc., 1985, **107**, 2569.

8 I. Ninomiya, C. Hashimoto, T. Kiguchi, D. H. R. Barton, X. Lusinchi, and P. Milliet, Tetrahedron Lett., in press.

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