TOTAL SYNTHESIS OF ERGOT ALKALOIDS, (±)-ELYMOCLAVINE AND (±)-ISOLYSERGOL

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Abstract —— Two of the hitherto untouched ergot alkaloids, (±)-elymoclavine and (±)-isolysergol, were synthesized according to the synthetic route involving enamide photocyclization.

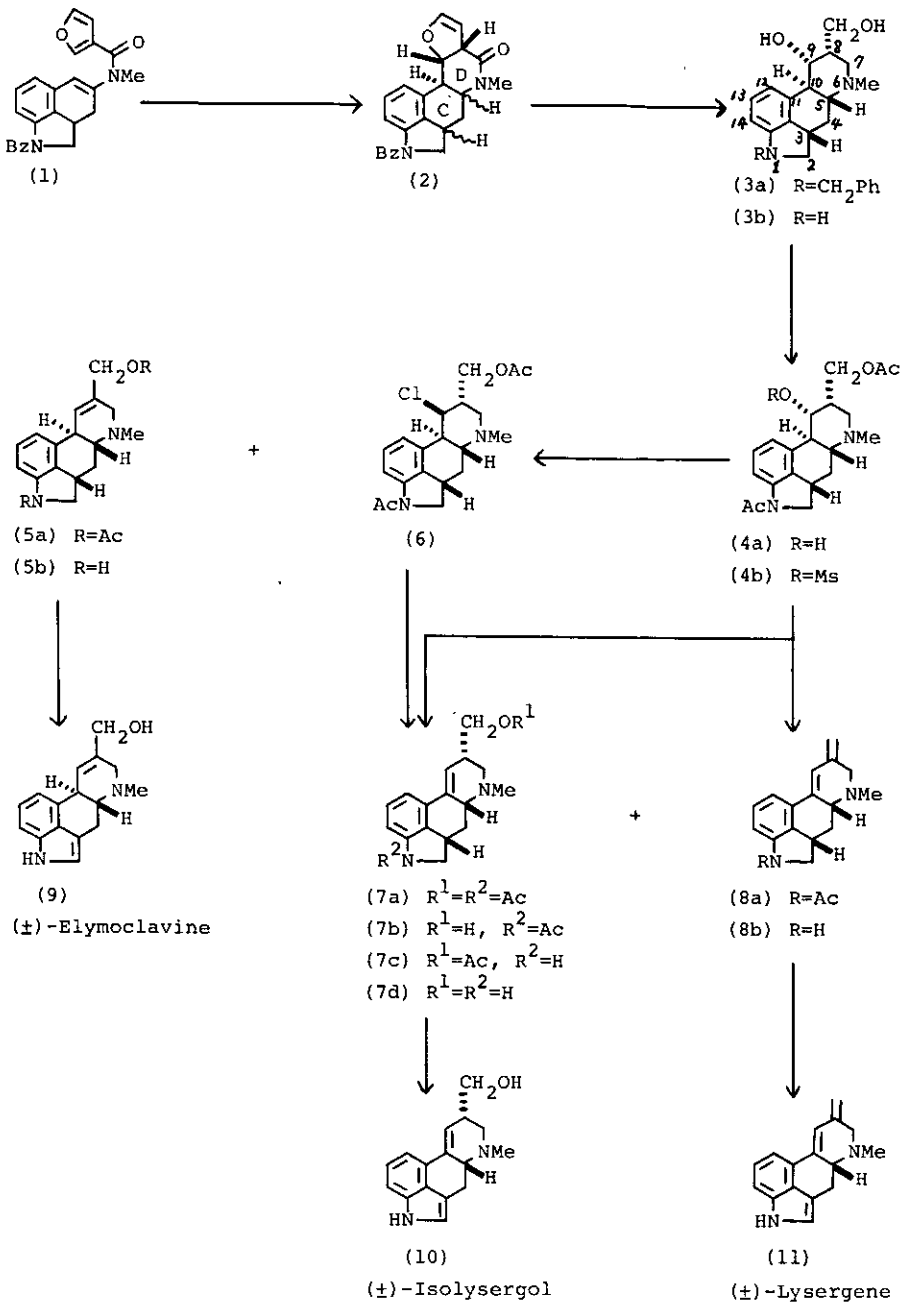
There are two types of ergot alkaloids having an ergoline skeleton depending on the position of double bond, namely, 8- and 9-ergolene structures[1], of which the stable alkaloids having 9-ergolene structure form a major group including lysergic acid, lysergol, and lysergine, thus having been picked as the major targets for their syntheses. On the contrary, the unstable group of alkaloids having 8-ergolene structure contain relatively few members of alkaloids such as paspalic acid, elymoclavine and agroclavine, of which only agroclavine had been synthesized[2] while the other two have so far eluded from attack of synthetic chemists. Furthermore, elymoclavine is regarded as a key intermediate in the biosynthetic pathways to ergot alkaloids[1]. We now report the first total synthesis of two alkaloids, (±)-elymoclavine and (±)-isolysergol, in addition to an alternative synthesis[2] of (±)-lysergene.

We picked the photocyclized pentacyclic lactam (2) as our starting compound which, as described previously, was readily prepared by reductive photocyclization of the enamide (1) in good yield[3]. Oxidative ring opening of the dihydrofuran ring was achieved first by ozonolysis followed by lithium aluminum hydride reduction to yield the N-benzyl-1,3-diols (3) as a C/D-*cis* and *trans*-mixture, which were separated. The C/D-*trans*-N-benzyl derivative (3a) thus obtained in 56 % yield [δ 4.45 and 3.86 (each d, J=14.5Hz, CH_2Ph), 4.02 (dd, J=10 and 5Hz, 9-H), 3.10 (t, J=10Hz, 10-H), 2.10 (ddd, J=12, 10, and 2Hz, 5-H), and 1.36 (q, J=12Hz, 4ax-H)], was treated with palladium on charcoal in hydrogen stream for

debenzylation to give the debenzylated amine (3b) [δ [$CDCl_3$-CD_3OD (1:1)] 4.02 (dd, J=10 and 5Hz, 9-H), 3.00 (t, J=10Hz, 10-H), 2.15 (ddd, J=12, 10, and 2Hz, 5-H), and 1.37 (q, J=12Hz, 4ax-H)], which was acetylated in the presence of pyridine under an ice-cooling temperature to afford the corresponding N,O-diacetate (4a) [ν max 1730 (OAc) and 1650 (NAc) cm^{-1}; δ 4.01 (m, 9-H), 2.84 (t, J=10 Hz, 10-H), and 1.39 (q, J=12Hz, 4ax-H)] in 89 % yield. Treatment of this N,O-diacetate (4a) with thionyl chloride in a benzene solution under refluxing temperature for 1 h afforded the 9β-chloro substituted derivative (6) [ν max 1740 (OAc) and 1660 (NAc) cm^{-1}; δ 4.96 (br s, 9-H), 3.25 (br d, J=10Hz, 10-H), and 1.41 (q, J=12Hz, 4ax-H)] as a major product in 65 % yield along with the dehydrated 8-ergolene derivative (5a) [ν max 1730 (OAc) and 1650 (NAc) cm^{-1}; δ 6.31 (br s, 9-H) and 1.51 (q, J=12Hz, 4ax-H)] as a minor in 18 % yield, which were separated by preparative t.l.c. Removal of two acetyl groups on both nitrogen and oxygen in (5a) was readily achieved by the treatment with small amount of hydrochloric acid in methanol. The product (5b) thus obtained has the structure corresponding to 2,3-dihydroelymoclavine (5b) [δ 6.30 (br s, 9-H) and 1.55 (q, J=12Hz, 4ax-H)]. The conversion of (5b) into elymoclavine (9) was done by dehydrogenation with phenylseleninic anhydride[4] in 20 % yield. Thus, the final product (9) was found to be completely identical with the authentic sample of natural alkaloid elymoclavine[5] upon direct comparison.

On the other hand, the major product (6) obtained by the treatment with thionyl chloride on the N,O-diacetate (4a) was used for its conversion into (±)-isolysergol (10). Treatment of the 9β-chloro derivative (6) with DBU afforded the eliminated diacetate (7a) [ν max 1740 (OAc) and 1660 (NAc) cm^{-1}; δ 6.38 (br s, J(W1/2)=10Hz, 9-H), 2.84 (br d, J=12Hz, 5-H), and 1.36 (q, J=12Hz, 4ax-H)] with a 9-ergolene structure in 98 % yield. *Deacetylation of (7a) with hydrochloric* acid in methanol yielded the corresponding deacetylated product (7d), [δ [$CDCl_3$ -CD_3OD (2:1)] 6.41 (br d, J=5Hz, 9-H), 2.97 (br d, J=12Hz, 5-H), and 1.34 (q, J=12Hz, 4ax-H)], which was dehydrogenated with phenylseleninic anhydride to give (±)-isolysergol (10) in 30 % yield. The identity of the product (10) with natural alkaloid[6] was established by direct comparison.

Alternatively, the conversion of (7d) into (±)-isolysergol (10) was conveniently achieved by the following treatments. Partial acetylation of (7d) with ace-


(1)
(2)
(3a) R=CH2Ph
(3b) R=H
(4a) R=H
(4b) R=Ms
(5a) R=Ac
(5b) R=H
(6)
(7a) R1=R2=Ac
(7b) R1=H, R2=Ac
(7c) R1=Ac, R2=H
(7d) R1=R2=H
(8a) R=Ac
(8b) R=H
(9)
(±)-Elymoclavine
(10)
(±)-Isolysergol
(11)
(±)-Lysergene

tic anhydride in acetic acid in the presence of conc hydrochloric acid[7] afforded the O-acetate (7c) which was then dehydrogenated by the treatment with a mixture of tert-butyl hypochlorite, dimethyl sulfide and triethylamine in a dichloromethane solution followed by the sodium ethoxide treatment[8], thus completed the preparation of (±)-isolysergol (10) in 46 % overall yield.

In addition to the above first synthesis of two alkaloids, we have added an alternative synthesis[2] of (±)-lysergene from the intermediary N,O-diacetate (4a). Mesylation of (4a) afforded the corresponding 9-mesylate (4b). Base treatment of the 9-mesylate (4b) yielded the doubly eliminated N-acetate (8a) [νmax 1650 (NAc) cm^{-1}; δ6.82 (br s, 9-H), 5.10 and 4.99 (each br s, $C=CH_2$), and 1.50 (q, J=12Hz, 4ax-H)] and the N-acetate (7b) [νmax 1650 (NAc) cm^{-1}; δ6.42 (br d, J=6Hz, 9-H), 2.88 (br d, J=12Hz, 5-H), and 1.41 (q, J=12Hz, 4ax-H)] in 16 and 24 % respective yields, the former (8a) of which was then readily deacetylated to give the dihydrolysergene (8b). The conversion of the indoline moiety into the indole, therefore, to (±)-lysergene was similarly[4] achieved. The product (11) was identical with natural lysergene upon direct comparison.

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N.m.r. spectra were measured at 200 MHz in $CDCl_3$ solution with TMS as internal standard, unless otherwise noted.

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