TOTAL SYNTHESIS OF ERGOT ALKALOID (±)-FUMIGACLAVINE B

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Abstract————The synthetic route developed on the despyrrole analogs of clavines was successfully applied to the first total synthesis of (±)-fumigaclavine B (1) and (±)-isolysergine (2), thus firmly established the structure of the former alkaloid (1).

Two clavines, fumigaclavine B (1)[1] and isolysergine (2),[2] have eluded the attack of synthetic chemists. Therefore, the structure of the former alkaloid (1) has awaited its conclusive establishment by total synthesis. We now report the first total synthesis of (±)-fumigaclavine B (1), an ergot alkaloid, and (±)-isolysergine (2), an unnatural isomer of the alkaloid lysergine,[2] from the common intermediate (7a)[3] via the route developed on the despyrrole analogs of these clavines. As a result, we have firmly established and also revised the n.m.r. assignment[1b] on fumigaclavine B (1).

Synthesis of Despyrrole Analogs of the Alkaloids

In order to establish a potent synthetic route to the target alkaloids, two despyrrole analogs (5 and 6) were synthesized from the cis-1,3-diol (3a),[3] which was mesylated at an ice-cooling temperature to give the monomesylate (3b) in 95% yield, which was then converted into the cis-2-methyl-1-ol (4a), mp 97.5-98.5°C, by reduction with lithium aluminum hydride in tetrahydrofuran in 69% yield. Its structure was confirmed from the n.m.r. peaks at δ 4.15 (dd, J=10 and 5 Hz, 1-H), 2.70 (t, J=10 Hz, 10b-H), and 1.27 (d, J=7 Hz, CMe). Mesylation of the 1-hydroxy group in 4a was performed with mesyl chloride in pyridine at room temperature to yield the corresponding mesylate (4b) in 80% yield. Inversion of the 1α-hydroxy group into 1β-orientation was performed on the 1α-mesylate (4b) by the treatment with potassium superoxide in dimethyl sulfoxide in the presence of 18-crown-6-ether[4] at room temperature to give the 1β-hydroxy-2α-methylbenzo-[f]quinoline (despyrrolofumigaclavine B) (5), mp 164-165°C, in 50% yield, which

showed n.m.r. peaks at δ 4.32 (br s, 1-H), 2.97 (br d, J=11 Hz, 10b-H), and 1.17 (d, J=7 Hz, CMe). On the other hand, introduction of a double bond into 1,10b-position was achieved by the treatment of 4b with potassium tert-butoxide in dimethyl sulfoxide at room temperature to give the 2α-methyl-1,10b-didehydrobenzo[f]quinoline (despyrroloisolysergine) (6) [oxalate, mp 188-190°C] in 51% yield which showed n.m.r. peaks at δ 6.25 (br d, J=5 Hz, 1-H) and 1.21 (d, J=7 Hz, CMe). Thus a synthetic route to two clavines (1 and 2) was established.

Total Synthesis of (±)-Fumigaclavine B and (±)-Isolysergine

According to the route developed on their despyrrole analogs (5 and 6), total synthesis of the hitherto untouched alkaloid (±)-fumigaclavine B (1) and unnatural clavine (±)-isolysergine (2) has been successfully achieved. The starting cis-1,3-diol (7a)[3] was mesylated to the monomesylate (7b), which was then reduced with lithium aluminum hydride to give the 8α-methyl-9α-ol (8a), mp 199-200°C, in 70% yield, which showed n.m.r. peaks at δ 3.89 (dd, J=11 and 5 Hz, 9-H), 2.86 (t, J=11 Hz, 10-H), and 1.19 (d, J=7 Hz, CMe). Inversion of the 9α-hydroxy group into the epimeric β-orientation was performed according to the procedure applied to the despyrrole analog (4a) to afford the 9β-ol (9a), mp 241-242°C, in 54% yield which showed n.m.r. peaks at δ 4.32 (br s, 9-H), 2.95 (br d, J=10 Hz, 10-H), and 1.20 (d, J=7 Hz, CMe), thus confirmed its stereochemistry. The treatment of 9a with sodium in liquid ammonia removed a protective group on nitrogen to afford the 8α-methyl-9β-ol (9b) in 86% yield which showed n.m.r. peaks at δ($CDCl_3$-CD_3OD) 4.36 (br s, 9-H), 2.96 (br d, J=10 Hz, 10-H), and 1.23 (d, J=7 Hz, CMe). Dehydrogenation of the indoline (9b) into the indole (1) was performed by the treatment with phenylseleninic anhydride[5] in the presence of three equivalent amount of indole in 89% yield. The indole (1), mp 199-200°C (dec.), was found to be identical with natural fumigaclavine B[1d] upon comparison of their spectral data. On the other hand, the base treatment (potassium tert-butoxide in dimethyl sulfoxide) of the 9α-mesylate (8b) afforded the 9-ergolene (10a), mp 159-160°C, in 52% yield, which showed n.m.r. peaks at δ 6.39 (br d, J=5 Hz, 9-H) and 1.18 (d, J=7 Hz, CMe) and was then treated with lithium aluminum hydride in dimethoxyethane to afford the 2,3-dihydroisolysergine (10b) in 76% yield. Dehydrogenation of 10b with phenylseleninic anhydride as above completed the synthesis of (±)-isolysergine (2),[2] mp 112-114°C, in 90% yield, which showed n.m.r. peaks at δ 6.94 (br s, 2-H), 6.43 (br dd, J=5 and

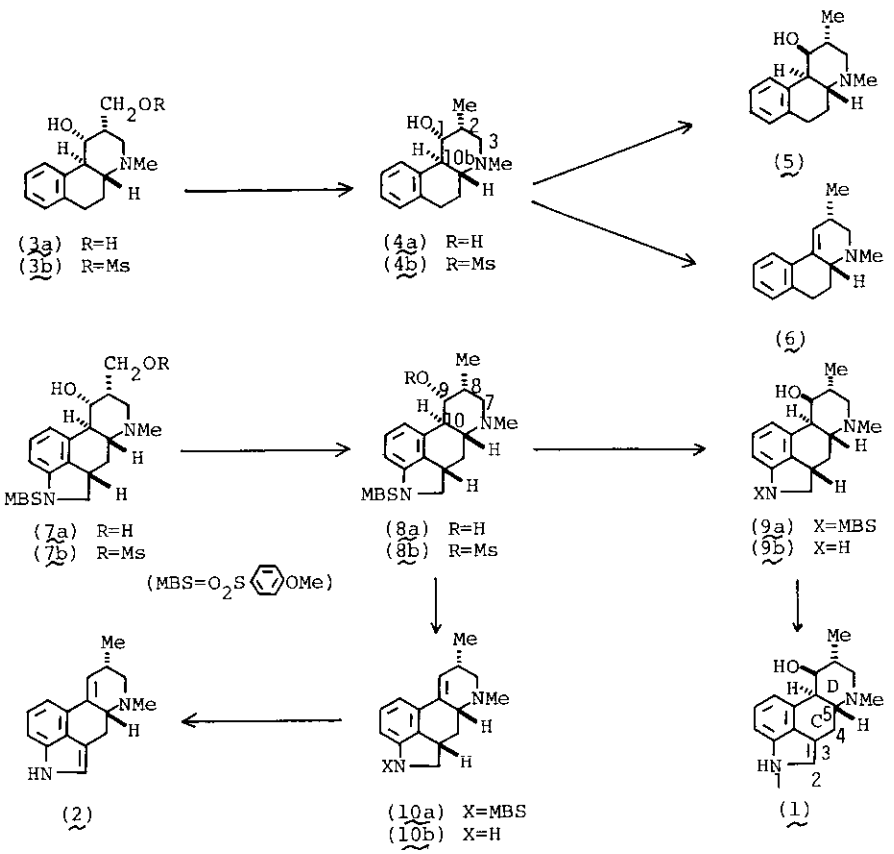

Table N.m.r. data of (±)-fumigaclavine B (1)

Protons	δ		Multiplicity	J Hz (Coupled proton)
1-H	8.02		br s	
2-H	6.86		br s	
4-Heq	3.34	(3.29)*	d	11(4-Hax)
4-Hax	2.68	(2.58)	td	11(4-Heq); 11(5-H); 1.5(2-H)
5-H	2.58	(2.66)	m	
7-Heq**	2.58	(3.38)	dd	11(7-Hax); 2(8-H)
7-Hax**	2.81	(2.82)	dd	11(7-Heq); 4(8-H)
8-H	2.12	(2.15)	m	
9-H	4.50	(4.51)	br s	
10-H	3.29	(2.58)	dm	9(5-H)
8-Me	1.26	(1.25)	d	7(8-H)
NMe	2.41	(2.39)	s	

*Values in parentheses were reported by Bach et al.[1b]

**Assignments of these two geminal protons were established from n.O.e. measurement.

2 Hz, 9-H), and 1.21 (d, J=7 Hz, CMe) and was identical with the sample prepared from natural lysergene[2] upon comparison of their spectral data.

The Structure of the Alkaloid Fumigaclavine B

Fumigaclavine B (1) was first isolated in 1961 by Spilsbury and Wilkinson[1a] who proposed its structure having an 8β-methyl configuration from its conversion into lysergine upon soda-lime distillation. Later in 1974, this proposed structure was revised by Bach and his coworkers[1b] from the n.m.r. analysis, as having an 8-methyl group in α-axial and a 9-hydroxy group in β-axial orientation with C/D-trans ring juncture without any chemical evidences. By taking advantage of the synthesis of (±)-fumigaclavine B (1), we have rechecked its n.m.r. assignment and found that Bach's assignment must be revised as summarized in the Table though the proposed structure (1) for this alkaloid happened to be valid.

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Unless otherwise mentioned, n.m.r. spectra were measured in $CDCl_3$ with TMS as internal standard on a Varian XL-200 at 200MHz.

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