A TOTAL SYNTHESIS OF (±)-LYSERGENE AND (±)-AGROCLAVINE

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Abstract——— A preliminary study on the exploitation of a general synthetic route to the ergoline group of alkaloids on the despyrrole analogs was successfully extended to the first total synthesis of racemic lysergene and agroclavine via the route involving reductive photocyclization of the furylenamide (10) followed by ring opening of the resulting dihydrofuran ring (11).

Although we have reported a total synthesis of (±)-lysergic acid[1] via the route involving reductive photocyclization of enamide, some important ergot alkaloids having a common ergoline skeleton, for example, lysergene, agroclavine, and lysergol, have yet been eluded from attack by total synthesis except some partial and formal synthesis[2-4]. Our programme of synthesizing ergot alkaloids by the utilization of reductive photocyclization of enamide has now enabled us to attack these alkaloids. We now report upon establishment of a simple and general synthetic route by using their despyrrole analogs, the first total synthesis of (±)-lysergene and (±)-agroclavine.

Establishment of A General Synthetic Route (Preliminary Study)

By using the despyrrole analogs of these ergoline alkaloids, benzo[f]quinoline derivatives, which lack only a pyrrole ring from the parent alkaloids, the establishment of a general synthetic route has been investigated. The starting photocyclized product (2) was prepared from the enamide (1) as reported previously[5] with a slight modification of the irradiation condition as follows. The photocyclized lactam was best prepared in 84 % yield by the irradiation of a 0.006 M solution of the enamide (1) in benzene-methanol (1 : 1, v/v) in the presence of

0.048 M sodium borohydride to afford the trans-lactam (2) in 76 % and the cis-lactam (3) in 8 % yields respectively. Ozonolysis of the lactam (2) at a temperature below -30°C in methanol followed by reduction with lithium aluminum hydride afforded the 1,3-diol (4) in 64 % yield, which was then mesylated with methanesulfonyl chloride in pyridine at room temperature to give the dimesylate (5) in a quantitative yield. Treatment of the dimesylate (5) with potassium t-butoxide in DMSO brought about smooth double elimination of two mesylate groups to afford the strongly fluorescent diene derivative (6) in 50 % yield, which showed nmr, δ 6.84 (1H, br s, 1-H), 5.04 and 4.94 (each 1H, br s, =CH), 2.97 (1H, br d, J=11 Hz, 4a-H), and 2.49 (3H, s, NMe), assignable to the despyrrole analog of lysergene. Furthermore, reduction of the diene (6) under Birch condition gave, upon 1,4-reduction, a mixture of the unsaturated amines (7) and (8) in 30 % and 45 % yields respectively, of which the B/C-trans compound (7) was identical with the despyrrole analog of agroclavine which we had reported previously[6]. The latter compound (8) exhibited nmr, δ 5.48 (1H, br s, 1-H), 3.66 (1H, br, W1/2=11 Hz, 10b-H), 2.52(3H, s, NMe), and 1.64 (3H, br s, 2-Me), thus established its B/C-cis structure.

Total Synthesis of Lysergene and Agroclavine

According to the synthetic route explored on the despyrrole analogs of the ergoline alkaloids, the first total synthesis of (±)-lysergene and (±)-agroclavine was accomplished as follows. The starting enamide (10) was prepared in 90 % yield by the usual method from the known tricyclic ketone (9)[1] which carries a p-methoxybenzenesulfonyl group (MBS) on nitrogen. Irradiation of the enamide (10) was carried out in the presence of sodium borohydride in a solution of benzene and methanol (10 : 1, v/v) at 4-5°C by using a high pressure mercury lamp with an uranyl glass filter[7]. The photocyclized products were obtained as a mixture of two stereoisomeric lactams (11) with respect to the C/D-ring juncture in a 80 % combined yield. Ozonolysis of this mixture (11) in dichloromethane at -60°C followed by reduction with lithium aluminum hydride afforded a mixture of two 1,3-diols (12) and (13) which were then readily separated. The desired C/D-trans-1,3-diol (12) was obtained by crystallization from dichloromethane in 26 % yield, while the C/D-cis-1,3-diol (13) was isolated by column chromatography of the above mother liquor in 13 % yield. The

trans-diol (12) showed nmr ($CDCl_3$-CD_3OD), δ 3.98 (1H, dd, J= 11, 5 Hz, 9-H), 2.31 (3H, s, NMe), 2.02 (1H, br t, J= 11 Hz, 5-H), and 1.21 (1H, br q, J= 12 Hz, 4ax-H), and the cis-diol (13) had nmr, δ 3.71 (1H, dd, J= 9 and 5 Hz, 9-H), 2.41 (3H, s, NMe), and 1.44 (1H, q, J= 111.5 Hz, 4ax-H). These two 1,3-diols (12) and (13) afforded the same diene (14) with the yields of 44 % from (12) and 41 % from (13), upon treatment with methanesulfonyl chloride in pyridine at room temperature followed by potassium t-butoxide in DMSO. Reductive cleavage of the protective group from the diene (14) was achieved with lithium aluminum hydride in dimethoxyethane to give the N-norindoline (15) in 47 % yield, which was converted into (±)-lysergene (16) in 50 % yield upon dehydrogenation with phenylseleninic anhydride[8]. Alternatively, Birch reduction of the diene (14) brought about reductive cleavage of the protective group and reduction of the diene structure to afford the C/D-trans-amine (17) and the cis-amine (18) in 50 % and 25 % yields respectively. The trans-amine (17) showed nmr, δ 6.02 (1H, br s, 9-H), 2.45 (3H, s, NMe), 1.74 (3H, br s, CMe), while the cis-congener (18) exhibited nmr, δ 5.39 (1H, br s, 9-H), 2.60 (3H, s, NMe), and 1.64 (3H, br s, CMe). The C/D-trans-amine (17) was then dehydrogenated by phenylseleninic anhydride to give (±)-agroclavine (19) in 56 % yield. These compounds (16) and (19) were identical with natural alkaloids lysergene and agroclavine upon direct comparisons with respective authentic specimen.

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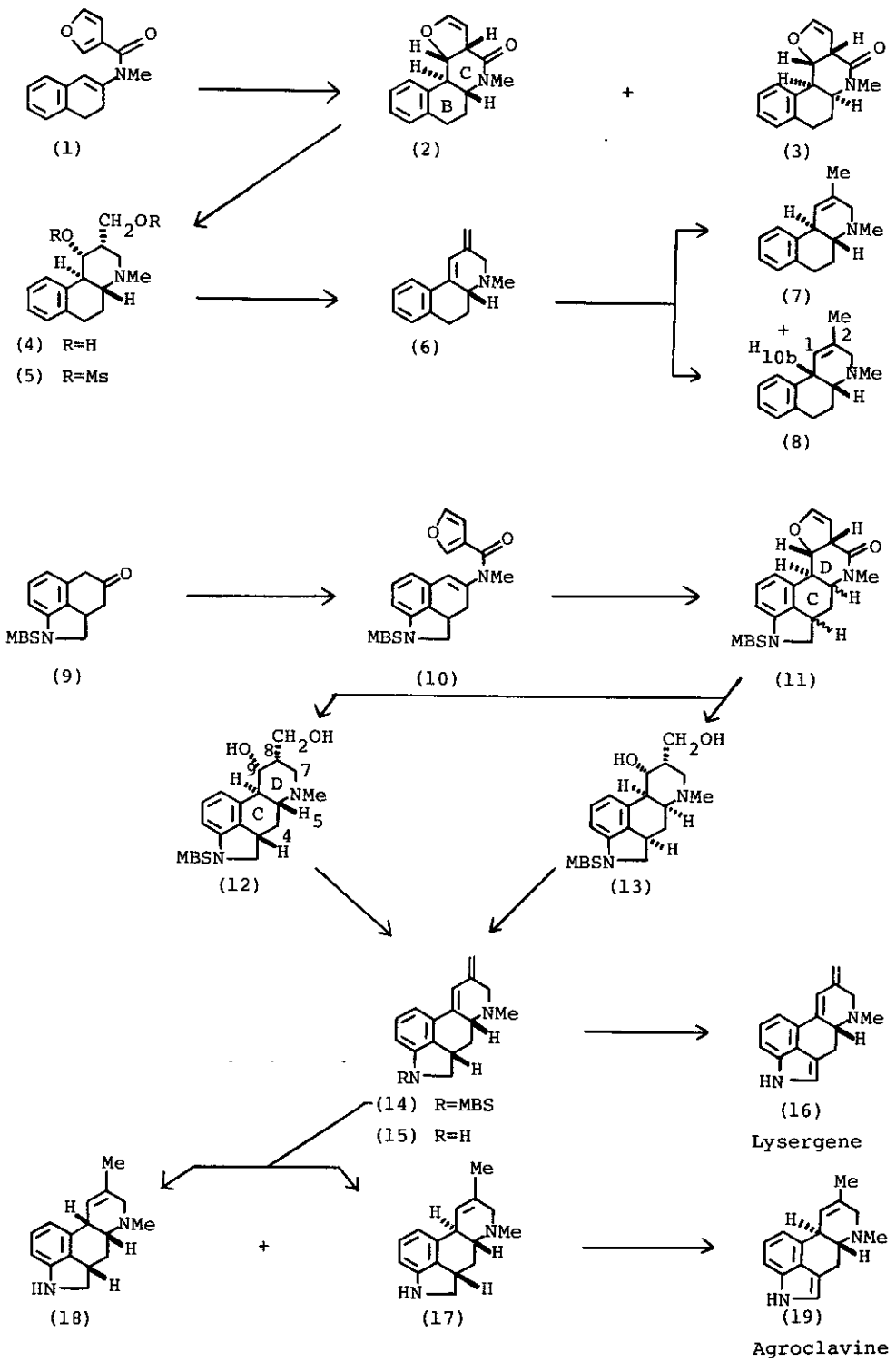
(1)
(2)
(3)
(4) R=H
(5) R=Ms
(6)
(7)
(8)
(9)
(10)
(11)
(12)
(13)
(14) R=MBS
(15) R=H
(16)
Lysergene
(17)
(18)
(19)
Agroclavine

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Unless otherwise mentioned, nmr spectra were measured in $CDCl_3$ with TMS as internal standard on a Varian XL-20 at 200 MHz.

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