CHEMISTRY LETTERS, pp. 615-618, 1981.

TOTAL SYNTHESIS OF ERGOT ALKALOID, (±)-6,7-SECOAGROCLAVINE[1]

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Ergot alkaloid, (±)-6,7-secoagroclavine was synthesized from 2-methyl-5-nitroisoquinolinium iodide by three routes. In the course of the study, a novel intra-molecular γ-alkylation of allyl alcohol was found. Reaction of Grignard reagents with nitroalkanes to afford N-alkyl hydroxylamines was effectively used in the present synthesis.

In the previous papers,[2] we described a two step synthesis of 4-(indol-4-yl)-3-buten-2-one (2) from 2-methyl-5-nitroisoquinolinium iodide (1) and its conversion to 5-acetonyl-1,3,4,5-tetrahydro-4-nitrobenz[cd]indole (4t and 4c in ca. 3:1 ratio) via Mannich base (3).

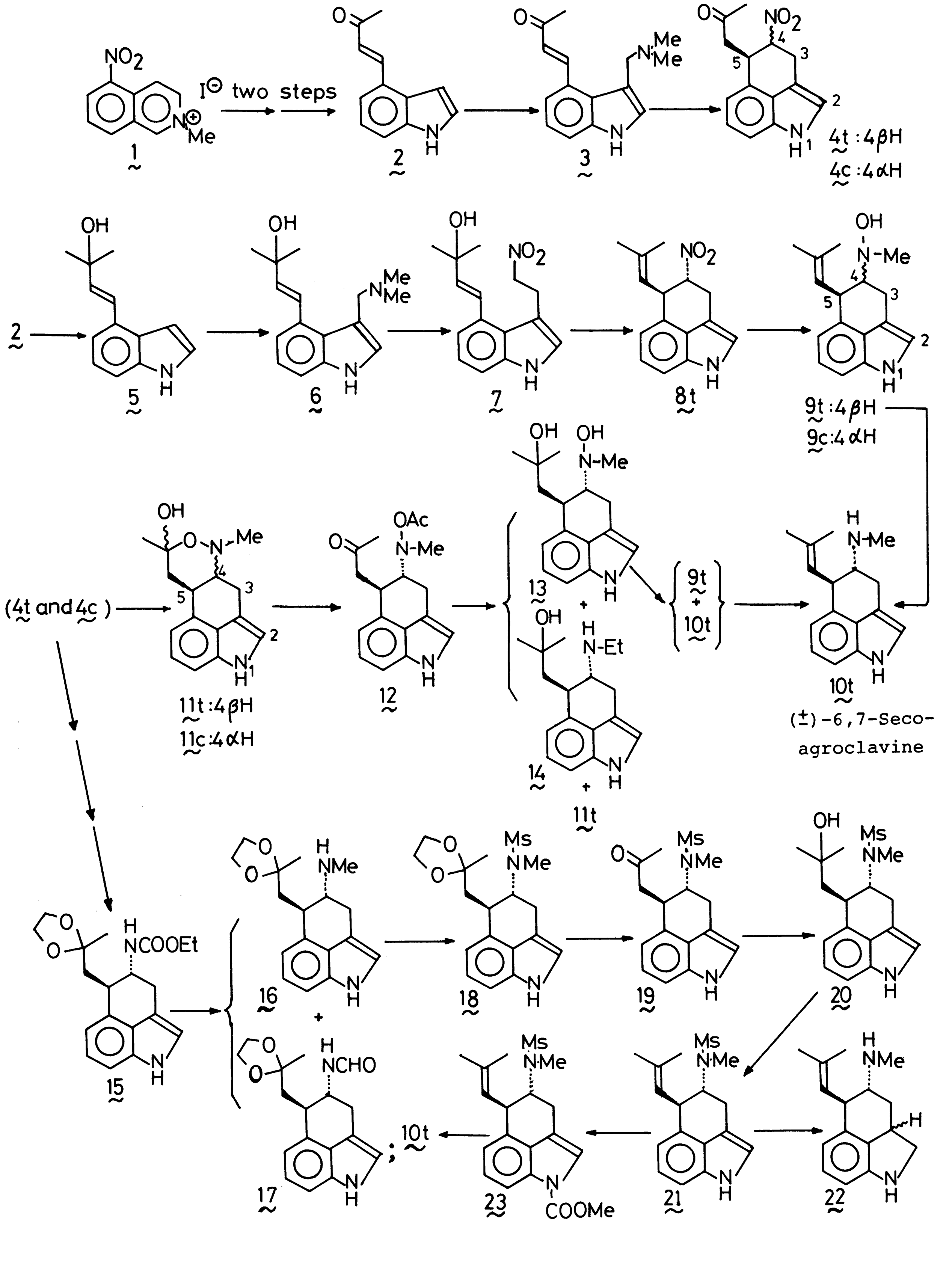
Now, we wish to report a total synthesis of ergot alkaloid, (±)-6,7-seco-agroclavine[3] by three routes starting from 2 or 4t.

I. Eight step synthesis of (±)-6,7-secoagroclavine from 1

Grignard reaction of 2 with MeMgI in THF/Et_2O afforded allyl alcohol derivative [5, mp 97-98°C, MS m/e: 201 (M^+), NMR (CD_3OD) δ: 1.41 (6H, s), 6.37 (1H, d, J=15.6 Hz), 6.90 (1H, d, J=15.6 Hz)] in 84% yield. Subsequent treatment of 5 with dimethyl-(methylene)ammonium chloride[4] in CH_3CN gave Mannich base [6, oil, MS m/e: 258 (M^+), NMR ($CDCl_3$) δ: 2.23 (6H, s), 3.53 (2H, s)] in 70% yield. Monoalkylation of 6 with nitromethane in the presence of (n-Bu)$_3$P as a catalyst[2b] afforded nitroallyl alcohol [7, mp 106-107°C, MS m/e: 274 (M^+), IR (KBr): 1562, 1537, 1382, 1370 cm^{-1}] in 55% yield. The required intra-molecular γ-alkylation of allylic moiety of 7 was then achieved by the action of anhydrous $ZnCl_2$ and NEt_3 in abs. THF to produce 8 in 18% yield, together with 29% yield of the recovery. The NMR spectrum of 8 established predominent formation of trans isomer (trans and cis in ca. 9:1 ratio), whose coupling constant between H-4 and H-5 protons was 9.5 Hz.

Since simple nitroalkanes can be converted to alkylhydroxylamines by the reaction with Grignard reagents,[5] we have applied this reaction in the next step. Thus, by the action of a large excess of MeMgI in THF/Et_2O to the nitro compound [8t, mp 158-160°C, MS m/e: 256 (M^+), NMR ($CDCl_3$) δ: 1.78 (3H, s), 1.83 (3H, s), 5.13 (1H, d, J=10 Hz)], the desired methylhydroxylamines, [9t, oil, MS m/e: 256 (M^+), NMR ($CDCl_3$) δ: 2.66 (3H, s, N-Me)] and [9c, oil, MS m/e: 256 (M^+), NMR ($CDCl_3$) δ: 2.77 (3H, s, N-Me)], were obtained in 19% and 20% yields, respectively. Final conversion of trans isomer (9t) to the corresponding amine (10t) was achieved in 27% yield by the reduction with aq. $TiCl_3$[6] in the presence of $AcONH_4$.

The synthetic material (10t) was identified as (±)-6,7-secoagroclavine by mix-


I⊖ two steps
4t : 4βH
4c : 4αH
9t : 4βH
9c : 4αH
11t : 4βH
11c : 4αH
(4t and 4c)
(±)-6,7-Seco-
agroclavine

ture melting point, spectral (IR, UV, MS, and ^{1}H-NMR), and tlc comparison with an authentic sample, which was kindly supplied by Dr. M. Natsume.

II. Nine step synthesis of (±)-6,7-secoagroclavine from 1

A mixture of 4t and 4c (in ca. 3:1 ratio) was converted with excess MeMgI in THF/Et_2O to the cyclic hemiketal (11) in 94% yield. The compound (11) was found to be a mixture of 11t and 11c in ca. 2:1 ratio, from which 11t [mp 207-209°C (dec.), MS m/e: 258 (M^+), NMR (10% CD_3OD in $CDCl_3$) δ: 1.47 (3H, s), 2.74 (3H, s, N-Me)] was separated out by crystallization from MeOH. Subsequent acetylation with Ac_2O/pyridine converted 11t into 12 [mp 136.5-137.5°C, MS m/e: 300 (M^+), IR (KBr): 1733, 1710 cm^{-1}] in 99% yield.

Grignard reaction was again employed on 12 with an excess of MeMgI in THF/Et_2O to produce the desired methylhydroxylamine [13, oil, MS m/e: 274 (M^+), NMR ($CDCl_3$) δ: 1.36 (6H, s), 2.72 (3H, s, N-Me)], ethylamino compound[7] [14, mp 185.5-186.5°C, MS m/e: 272 (M^+), NMR (10% CD_3OD in $CDCl_3$) δ: 1.10 (3H, t, J=7 Hz), 2.73 (2H, q, J=7 Hz)], and 11t in 6%, 16%, and 59% yields, respectively. Although the yield of 13 is low, this difficulty can be overcome by repetition of the above reaction sequences using the recovered 11t. Dehydration of 13 with p-TsOH in benzene afforded a mixture of 9t and 10t.[8] Since the separation of them was rather difficult, the mixture was immediately reduced with aq. $TiCl_3$ in the presence of $AcONH_4$ to produce the alkaloid (10t) in 42% overall yield from 13.

III. Fourteen step synthesis of (±)-6,7-secoagroclavine from 1

The ethyl carbamate (15) was prepared from the compound (4t) through three steps as previously reported.[2b] Reduction of 15 with $LiAlH_4$ in Et_2O afforded methylamino compound [16, oil, MS m/e: 286 (M^+), NMR ($CDCl_3$) δ: 2.30 (3H, s, N-Me)][3b] and N-formyl compound [17, oil, MS m/e: 300 (M^+), NMR ($CDCl_3$) δ: 7.78 (1H, s, N-CHO)][3b] in 51% and 37% yields, respectively. Treatment of 16 with MsCl in Et_3N/pyridine produced the sulfonamide [18, mp 222-223°C, MS m/e: 364 (M^+), IR (KBr): 1319, 1138 cm^{-1}] in 79% yield. The corresponding ketone [19, mp 166.5-167°C, MS m/e: 320 (M^+), IR (KBr): 1718 cm^{-1}], obtained in 86% yield after deketalization with 1N-HCl in acetone, was then allowed to react with MeMgI to afford the tertiary alcohol [20, mp 194-195°C, MS m/e: 336 (M^+), NMR ($CDCl_3$) δ: 1.35 (3H, s), 1.47 (3H, s)] in 85% yield. Dehydration of 20 with p-TsOH in benzene gave the olefin [21, mp 171-172°C, MS m/e: 318 (M^+), NMR ($CDCl_3$) δ: 1.83 (3H, d, J=1.6 Hz), 1.90 (3H, d, J=1.6 Hz), 5.20 (1H, d, J=10 Hz)] in 85% yield.

It is noteworthy that in the final step an attempted demesylation of 21 by Birch reduction resulted in the formation of the indoline [22, in ca. 1:1 mixture of diastereoisomers, MS m/e: 242 (M^+)] regardless of the presence or absence of proton sources under various reaction conditions.[9] This undesired over-reduction was prevented by the use of 1-methoxycarbonyl compound [23, oil, MS m/e: 376 (M^+), IR (film): 1740 cm^{-1}, NMR ($CDCl_3$) δ: 3.98 (3H, s, COOMe)], which was obtained from 21 in 86% yield by the reaction with NaH/ClCOOMe in abs. DMF. Removal of both N-mesyl and 1-methoxycarbonyl groups of 23 was successfully carried out with Li in liq. NH_3 at -33°C and subsequent work-up to afford the alkaloid 10t and 22 in 50% and

37% yields, respectively.

Further study for the synthesis of other ergot alkaloids is currently in progress.

Acknowledgement

The authors express their cordial gratitude to Dr. Mitsutaka Natsume, Research Foundation ITSUU Laboratory, for kindly suppling a precious authentic (±)-6,7-seco-agroclavine and its spectral data. This work was supported in part by the Grant-in-Aid of the Ministry of Education, Science and Culture, Japan (No. 447111).

References and Notes

All new compounds gave satisfactory analytical and spectral data. Efforts to attain the optimum reaction conditions have not been made for any of the reaction steps described.

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7. The formation of 14 would be explained by the initial elimination of AcOH from 12 and subsequent attack of MeMgI on the resultant N-methylene intermediate.
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(Received February 17, 1981)