Ergot alkaloids : the first and five step total syntheses of (-)-and (+)-6,7-secoagroclavines, and syntheses of (-)-and (+)-6-nor-6-propyl-6, 7-secoagroclaines ((-)-and (+)-kstu 1415)

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ERGOT ALKALOIDS: THE FIRST AND FIVE STEP TOTAL SYNTHESES OF (-)- AND (+)-6,7-SECOAGROCLAVINES, AND THE SYNTHESES OF (-)- AND (+)-6-NOR-6-PROPYL-6,7-SECOAGROCLAVINES ((-)- AND (+)-KSU 1415)[1]

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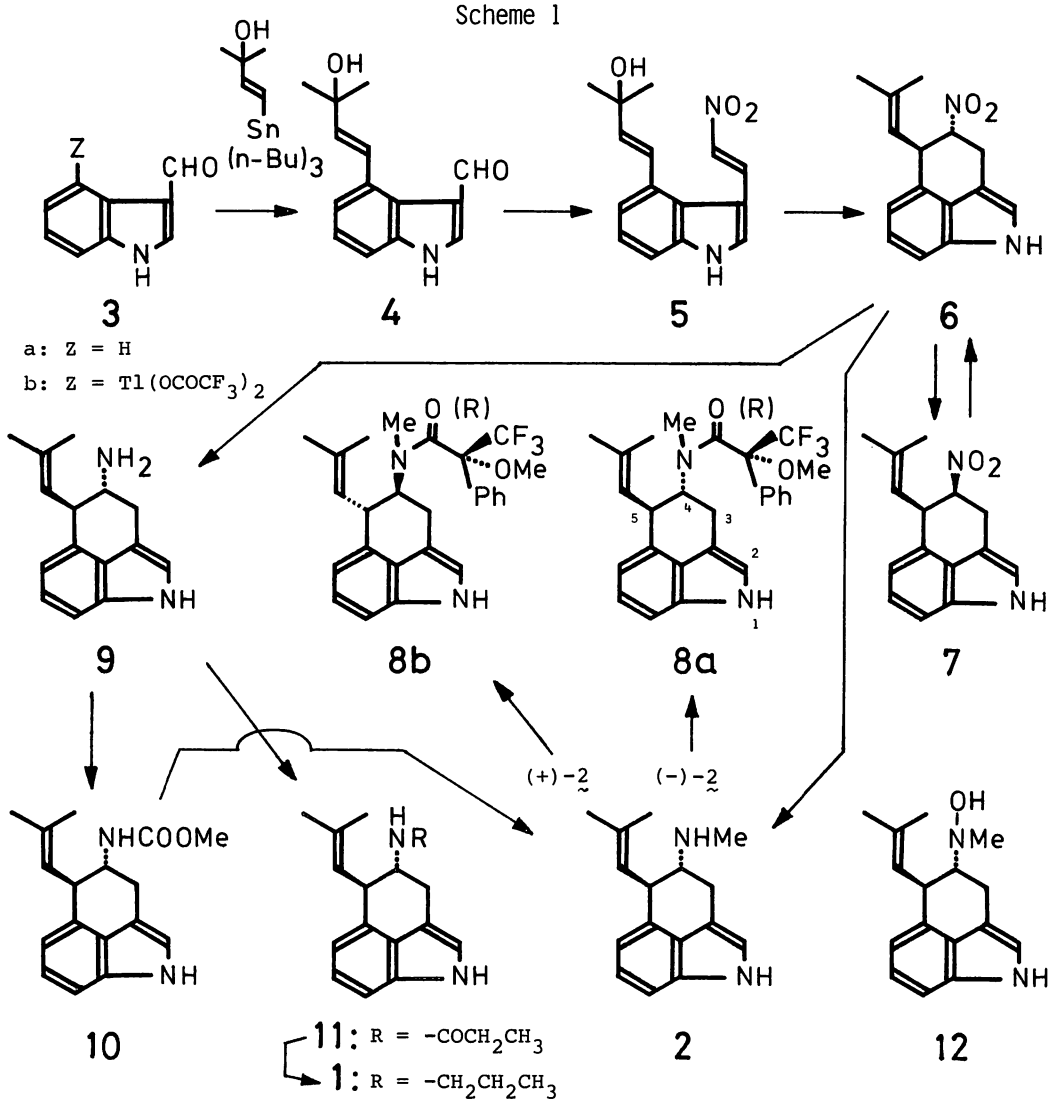
Abstract——Simple synthetic method for optically active 4,5-trans-((-)- and (+)-6) and 4,5-cis-5-(2-methyl-1-propen-1-yl)-4-nitro-1,3,4,5-tetrahydrobenz[cd]indoles ((-)- and (+)-7) was developed. Using these chiral common synthetic intermediates, the first total syntheses of (-)- and (+)-6,7-secoagroclavines were achieved in only five steps. Preparations of (-)- and (+)-6-nor-6-propyl-6,7-secoagroclavines ((-)- and (+)-KSU 1415) are also described.

We have developed the idea of common synthetic method[2a] and proved it to be versatile for preparing various (±)-ergot alkaloids only by changing reagents without altering synthetic route.[2b,c] During the synthetic study, we also disclosed that (±)-6-nor-6-propyl-6,7-secoagroclavine ((±)-KSU 1415, (±)-1), an analogue of an ergot alkaloid 6,7-secoagroclavine,[3] was a potent dopamine agonist.[4] Since then, we needed both enantiomers of optically active KSU 1415 for evaluating their biological activities. In this communication, we report that our method is also effective for the short step syntheses of both enantiomers of optically active 6,7-secoagroclavine ((-)- and (+)-2), and (-)- and (+)-KSU 1415.

We found that our tin-thall reaction[2c,5] was successfully applied for the synthesis of 4-(3-hydroxy-3-methyl-1-buten-1-yl)indole-3-carboxaldehyde (4). Thus, the treatment of (3-formylindol-4-yl)thallium bis(trifluoroacetate) (3b), prepared almost quantitatively from indole-3-carboxaldehyde (3a) and thallium tris(trifluoroacetate), with tributyl(3-hydroxy-3-methyl-1-buten-1-yl)stannane[6] in the presence of tetra-n-butylammonium chloride and a catalytic amount of palladium acetate in N,N-dimethylformamide at 100°C for 6 h afforded 4 in 49% yield (Scheme 1). These

Scheme 1



two steps could be carried out in one pot operation in the same overall yield. Next, the compound (4) was converted to (±)-4,5-trans-5-(2-methyl-1-propen-1-yl)-4-nitro-1,3,4,5-tetrahydrobenz[cd]indole (6) in two steps through 5 in 70% overall yield as reported previously.[7] While (±)-4,5-cis isomer (7) was obtained by the established interconversion method between (±)-6 and (±)-7.[7]

Since (±)-6 and (±)-7 are common synthetic intermediates for (±)-ergot alkaloids and thus readily available, we planned their optical resolution by applying chiral column chromatography. After various examinations, we found that both enantiomers of 4,5-trans-compound ((±)-6) were separable with base-line resolution on chiralpak AS column (Daicel Chemical Ind., Ltd.) using isopropanol-hexane (1:9, v/v) as an

Chart 1.
Optical Resolution by Chiral Column Chromatography

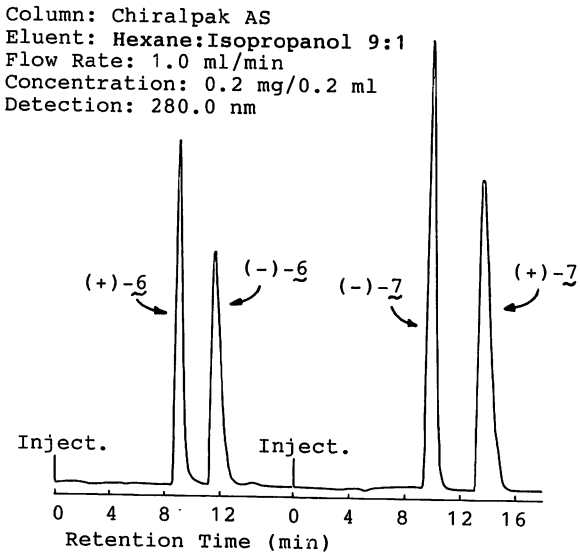
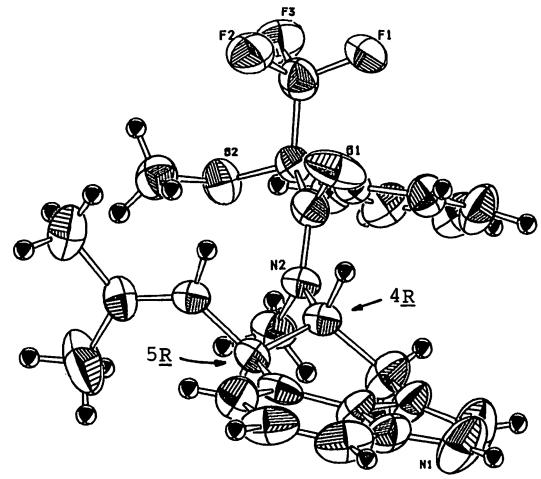


Figure 1.
Stereoscopic View of the (R)-(+)-MTPA amide of (-)-2 (8a)



eluent. As can be seen in Chart 1, the early part of the two peaks was proved to be pure (+)-6 (mp 178-179°C, $[\alpha]_D^{21}$ +109.5° (c=0.30, 99.5% EtOH was used throughout the present study)). The latter part was pure (-)-6 (mp 177-178°C, $[\alpha]_D^{21}$ -109.8° (c=0.30)). Under similar separating conditions, the 4,5-cis-compound ((±)-7) revealed better optical resolution than the 4,5-trans-isomer (Chart 1). On the preparative scale chiralpak AS column, almost the same optical resolution patterns were obtained and one injection of 22.5 mg of (±)-7 afforded 11.0 mg each of pure (-)-7 (mp 133-134°C, $[\alpha]_D^{25}$ -399.0° (c=0.31)) and (+)-7 (mp 134.5-136°C, $[\alpha]_D^{25}$ +407.1° (c=0.30)) within 40 min operation with an excellent reproducibility.

Finally, (-)-6 and (+)-6 were converted in one pot operation to (-)- ((-)-2, mp 137.5-139°C, $[\alpha]_D^{25}$ -212.6° (c=0.35)) and (+)-6,7-secoagroclavine ((+)-2, mp 135-135.5°C, $[\alpha]_D^{28}$ +211.3° (c=0.30)) in 55 and 50% yields, respectively, by the reaction with an excess amount of methylmagnesium iodide, followed by the reduction of the resultant unstable methylhydroxylamine[8] (12) with zinc (Zn) in methanolic hydrochloric acid (HCl) at reflux.

On the other hand, reduction of (-)-6 and (+)-6 with amalgamated Zn in methanolic HCl afforded (-)-9 (hard caramel, $[\alpha]_D^{21}$ -159.2° (c=0.31)) and (+)-9 (hard caramel,

$[\alpha]_D^{20}$ +159.6° (c=0.22)) in 98 and 96% yields, respectively. Treatment of (-)-9 and (+)-9 with methyl chloroformate in the presence of triethylamine afforded (-)-10 (mp 166-167.5°C, $[\alpha]_D^{27}$ -84.4° (c=0.30)) and (+)-10 (mp 167.5-169°C, $[\alpha]_D^{27}$ +86.6° (c=0.30)) in 89 and 84% yields, respectively. Further reduction of (-)-10 and (+)-10 with lithium aluminum hydride ($LiAlH_4$) in refuxing tetrahydrofuran (THF) afforded (-)-2 and (+)-2 in 98 and 92% yields, respectively.

The enantiomer excesses of (-)-2 and (+)-2 were determined to be more than 99%, respectively, in the following way. First, (-)-2 and (+)-2 were converted to the corresponding diastereomeric Mosher amides, 8a (mp 238.5-239°C (decomp.), $[\alpha]_D^{23}$ +25.5° (c=0.20)) and 8b (mp 232-233°C (decomp.), $[\alpha]_D^{26}$ +98.5° (c=0.31)) in 90 and 82% yields, respectively, by the reaction with acid chloride derived from (R)-(+)-2-methoxy-2-trifluoromethylphenylacetic acid ((R)-(+)-MTPA). Both diastereoisomers, (8a) and (8b), did not exhibit the existence of the other diastereoisomer on the ^{1}H-nmr (400 MHz)[9] and hplc analyses.[9] Similar analyses of (R)-(+)-MTPA amide of (-)-9 (mp 186-187°C, $[\alpha]_D^{21}$ -39.0° (c=0.30)) and that of (+)-9 (mp 155-156°C, $[\alpha]_D^{26}$ +26.1° (c=0.31)) proved that (-)-9 and (+)-9 were also optically pure.[9] Based on the above data, (R)-(+)-MTPA amide of (-)-2 (8a) was subjected to X-ray crystallographic analysis[10] for establishing the absolute configuration at the 4- and 5-positions of (-)-2. The results shown in Figure 1 proved unequivocally that 8a was 4R,5R-4,5-trans-4-[N-((R)-2-methoxy-2-trifluoromethyl)phenylacetyl-N-methylamino]-5-(2-methyl-1-propen-1-yl)-1,3,4,5-tetrahydrobenz[cd]indole.

Treatment of (-)-9 and (+)-9 with propionyl chloride afforded (-)-11 (mp 193.5-194.5°C, $[\alpha]_D^{29}$ -74.6° (c=0.30)) and (+)-11 (mp 193-194°C, $[\alpha]_D^{28}$ +80.2° (c=0.50)) in 90 and 91% yields, respectively. Reduction of (-)-11 and (+)-11 with $LiAlH_4$ produced (-)-KSU 1415 ((-)-1, mp 135-136°C, $[\alpha]_D^{28}$ -185.6° (c=0.30)) and (+)-KSU 1415 ((+)-1, mp 134-135°C, $[\alpha]_D^{28}$ +195.2° (c=0.30)) in 64 and 63% yields, respectively.

In conclusion, the first total syntheses of (-)- and (+)-6,7-secoagroclavines were achieved in only five (or four) steps and their absolute stereochemistries were established unequivocally. Both enantiomers of KSU 1415 were also prepared. Hundreds mg of optically pure enantiomers of 6 and 7 are now obtainable in a day, syntheses of other ergot alkaloids and their derivatives are currently in progress.

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9. Although 1:1 mixture of pure 8a and 8b showed clearly resolved peaks ascribed for each isomer in the ^{1}H-nmr (400 MHz) spectrum, a mixture of them in the ratio of 99.5:0.5 (w/w) did not exhibit the peaks of 8b. However, hplc analysis of the mixture on silica gel (C.I.G. column, Kusano Kagakukikai Co.) clearly showed the existence of 8b. Similarly, diastereomer excesses of (R)-(+)-MTPA amides of (-)-9 and (+)-9 were established to be more than 99%, respectively. These results suggest that judgement of optical purity based on ^{1}H-nmr analysis using only one enantiomer should be done very carefully.

10. Crystal data for 8a: $C_{26}H_{27}F_3N_2O_2$, M=456.51, orthorhombic, space group $P2_12_12_1$, with unit cell dimensions a=16.874(2), b=22.364(5), c=6.240(1) Å, V=2354.6(8) $Å^3$, Z=4, and D (calcd.)=1.29g/cm^3. The reflection data were collected on a Rigaku AFC-5 diffractometer for $3°<2\theta<55°$ using MoKα radiation (λ=0.71069Å) and the ω-2θ scan method at a 2θ scan speed of 6°/min. The structure was solved by the direct method using MITHRIL program and refined by full-matrix least-squares. The final R value was 0.039 for 1101 independent reflections [$I>3\sigma(I)$].

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