SIMPLE TOTAL SYNTHESES OF (–)-ERGOT ALKALOIDS AND THEIR (+)-ENANTIOMERS BY A COMMON SYNTHESIS METHOD UTILIZING OPTICAL RESOLUTION[1]

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Abstract——The first and simple total syntheses of (–)-isochanoclavine-I ((–)-**1b**), (–)-agroclavine ((–)-**3**), (–)-agroclavine-I ((–)-**4**), and (–)-norchanoclavine-I ((–)-**5c**) and their (+)-enantiomers are achieved from indole-3-carboxaldehyde (**8**) by a common synthesis method utilizing optical resolution. Absolute configuration of (–)-*agroclavine-I is determined to be 5R and 10S for the first time.* Preparations of both enantiomers of chanoclavine-I (**1c**) are also included.

The first enantioselective total synthesis of (+)-paliclavine was achieved in 1984 by Kozikowski and co-workers.[2a] Since that time, several additional enantioselective total syntheses of ergot alkaloids have been reported.[2b-d] Although these syntheses are wonderful and artistic, there remains conspicuous need of a simple and general method for preparing optically active ergot alkaloids.

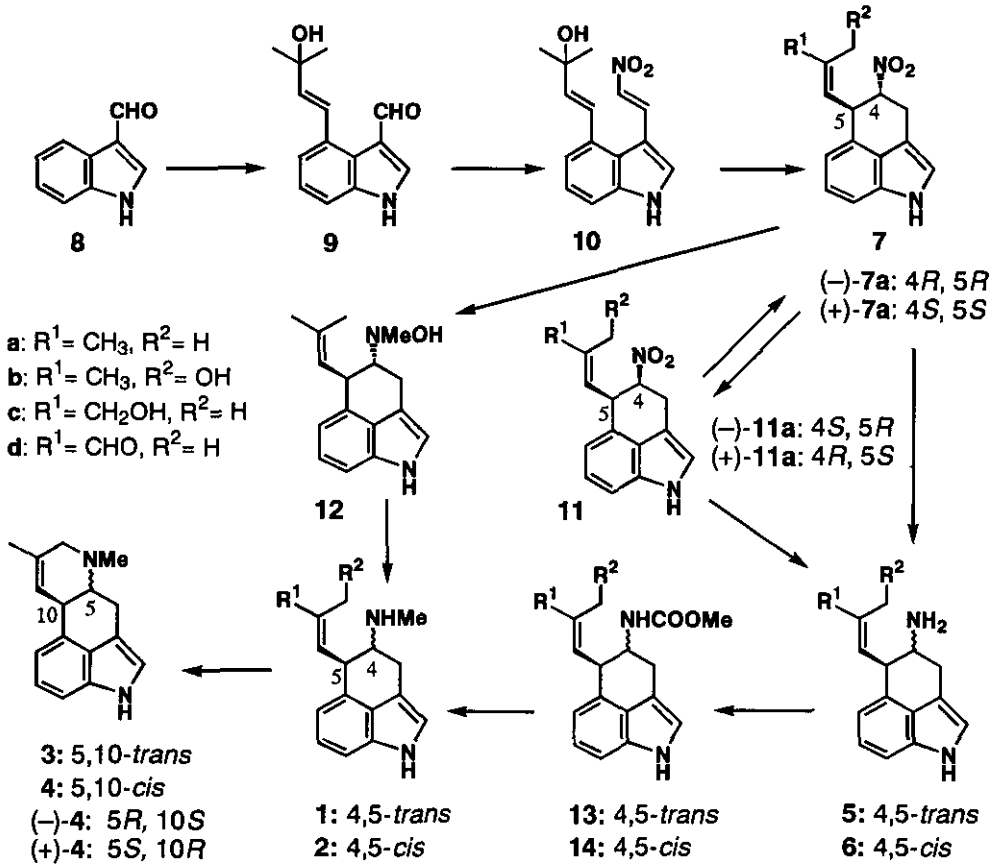
We have realized simple total syntheses of various (±)-ergot alkaloids establishing a common synthesis method for them.[3] The method was also effective for the first syntheses of (–)- and (+)-6,7-seco-agroclavine ((–)- and (+)-**1a**)[4] and for determining their absolute configurations.[4] Thus, (±)-4,5-*trans*-5-(2-methyl-1-propenyl)-4-nitro-1,3,4,5-tetrahydrobenz[*cd*]indole ((±)-**7a**) was prepared through **9** and **10** in three steps in 34% overall yield from indole-3-carboxaldehyde (**8**, Scheme 1).[3] After establishing interconversion method between (±)-**7a** and (±)-4,5-*cis*-isomer ((±)-**11a**),[3f] both enantiomers of **7a** and **11a** were obtained using preparative chiral column chromatography.[4] Then, (–)-**7a** and (+)-**7a** were converted in one pot operation to (–)- and (+)-6,7-secoagroclavine ((–)- and (+)-**1a**) by the reaction with MeMgI, followed by the reduction of the resultant 4-*N*-methylhydroxyamine ((–)- and (+)-**12**) with Zn-HCl. Alternative three steps synthesis route to (–)-**1a** and (+)-**1a** was also established from (–)-**7a** and (+)-**7a**, respectively, through (–)-**5a** and (–)-**13a**, and (+)-**5a** and (+)-**13a**.[4]

Now, we wish to report that the community of the above method is further heightened by its extention to the total syntheses of both enantiomers of isochanoclavine-I (**1b**),[5a] chanoclavine-I (**1c**),[5a,b] agroclavine (**3**),[5c] agroclavine-I (**4**),[5d] and norchanoclavine-I (**5c**)[5e] only by changing reagents without altering the synthesis route[3] as shown below.

Oxidation of (*Z*)-methyl on the isobutenyl group at the 5-position of (–)-**1a** was attained by the

treatment with SeO_2 in dioxane to produce (–)-isochanoclavine-I ((–)-**1b**, mp 183.5–185.0°C, $[\alpha]_D^{25}$ –212.8° (c = 0.50, pyridine)) in 29% yield together with unreacted (–)-**1a** in 41% yield. This regioselective functionalization can be explained by the coordination of the 4-methylamino group to selenium, putting SeO_2 close to the (*Z*)-methyl group.[3f] Similar oxidation of (+)-**1a** afforded (+)-**1b** (mp 179.5–181.0°C, $[\alpha]_D^{25}$ +210.8° (c = 0.50, pyridine)) in 31% yield together with unreacted (+)-**1a** in 39% yield. Subsequent cyclization of (–)-**1b** and (+)-**1b** with $POCl_3$ in the presence of K_2CO_3 in MeCN proceeded smoothly to give (–)-agroclavine ((–)-**3**, mp 209–210°C, $[\alpha]_D^{19}$ –183.0° (c = 0.30, pyridine)) and (+)-agroclavine ((+)-**3**, mp 210–211°C, $[\alpha]_D^{20}$ +185.2° (c = 0.31, pyridine)) in 90 and 88% yields, respectively.

Scheme 1



On the other hand, reduction of 4,5-*cis*-4-nitro compounds ((–)-**11a** and (+)-**11a**) with amalgamated Zn in methanolic HCl afforded (–)-4,5-*cis*-4-amino-5-(2-methyl-1-propenyl)-1,3,4,5-tetrahydrobenz[*cd*]indole ((–)-**6a**, mp 156–157°C, $[\alpha]_D^{25}$ –258.8° (c = 0.30, 99.5% EtOH)) and (+)-**6a** (mp 157.0–157.5°C, $[\alpha]_D^{25}$ +259.4° (c = 0.30, 99.5% EtOH)) in 95 and 96% yields, respectively. Treatment of (–)-**6a** and (+)-**6a** with methyl chloroformate ($ClCO_2Me$) in the presence of Et_3N afforded the corresponding carbamates, (–)-**14a** (mp 169–170°C, $[\alpha]_D^{22}$ –224.8° (c = 0.30, 99.5% EtOH)) and (+)-**14a** (mp 169–

170°C, $[\alpha]_D^{22}$ +226.8° (c = 0.30, 99.5% EtOH)) in 86 and 86% yields, respectively. Further reductions of (–)-**14a** and (+)-**14a** with $LiAlH_4$ in refluxing THF afforded (–)- **2a** (caramel, $[\alpha]_D^{28}$ –282.8° (c = 0.30, 99.5% EtOH)) and (+)-**2a** (caramel, $[\alpha]_D^{27}$ +286.7° (c = 0.30, 99.5% EtOH)) in 99 and 98% yields, respectively. Regioselective allylic oxidation of (–)-**2a** with 30% SeO_2 on celite in dioxane and Et_3N afforded the corresponding (*Z*)-hydroxymethyl compounds, (–)-**2b** (mp 178–179°C, $[\alpha]_D^{18}$ –302.2° (c = 0.30, 99.5% EtOH)) in 29% yield together with unreacted (–)-**2a** in 32% yield. Similar oxidation of (+)-**2a** afforded (+)-**2b** (mp 178.5–180.0°C, $[\alpha]_D^{18}$ +301.0° (c = 0.30, 99.5% EtOH)) in 24% yield together with unreacted (+)-**2a** in 45% yield. It should be mentioned that the change in sign of optical rotation was observed in the case of ring closure of (–)-**2b** with $POCl_3$ in the presence of $K_2C\,O_3$ in MeCN giving (+)-agroclavine-I ((+)-**4**, viscous oil, $[\alpha]_D^{17}$ +157.3° (c = 0.28, pyridine)) in 86% yield. (–)-Agroclavine-I ((–)-**4**, viscous oil, $[\alpha]_D^{22}$ –157.3° (c = 0.27, pyridine)) was also obtained by the similar cyclization of (+)-**2b** in 83% yield.

We have already proved unequivocally that the absolute configuration of (–)-**7a** is 4*R* and 5*R*.[4] Since the treatment of (–)-**11a** and (+)-**11a** with Et_3N afforded (–)-**7a** and (+)-**7a** in 79% and 80% yields, respectively, the absolute configuration of (+)-**11a** is proved to be 4*R* and 5*S*. The compound ((+)-**11a**) is chemically correlated with (+)-**2b** as described above. Consequently, the absolute configuration of a natural product, (–)-agroclavine-I ((–)-**4**), is determined to be 5*R* and 10*S* for the first time, though it had been deduced based on ^{1}H-NMR comparison studies.[5d]

Oxidation of (–)-**7a** with *t*-BuO_2H in the presence of 5%SeO_2 on SiO_2[6] in dioxane, followed by the reduction of the resultant mixture of (–)-**7c** and overoxidized aldehyde compound ((–)-**7d**) with $NaBH_4$, produced (–)-(*E*)-hydroxymethyl compound ((–)-**7c**, mp 133–134°C, $[\alpha]_D^{20}$ –113.3° (c = 0.29, 99.5% EtOH)) in 53% yield together with unreacted (–)-**7a** in 22% yield. Under similar reaction conditions, (+)-**7a** was converted to the corresponding (+)-(*E*)-hydroxymethyl compound ((+)-**7c**, mp 132– 133°C, $[\alpha]_D^{21}$ +112.4° (c = 0.27, 99.5% EtOH) in 43% yield together with unreacted (+)-**7a** in 25% yield. Reduction of (–)-**7c** and (+)-**7c** with amalgamated Zn in methanolic HCl afforded (–)-norchanoclavine-I ((–)-**5c**, mp 207– 208°C, $[\alpha]_D^{25}$ –178.0° (c = 0.30, pyridine)) and (+)-**5c** (mp 205.5–207°C, $[\alpha]_D^{24}$ +179.6° (c = 0.30, pyridine)) in 98 and 100% yields, respectively. Treatment of (–)-**5c** and (+)-**5c** with $ClCO_2Me$ in the presence of Et_3N produced (–)-**13c** (oil, $[\alpha]_D^{21}$ –80.4° (c = 0.23, 99.5% EtOH)) and (+)-**13c** (oil, $[\alpha]_D^{21}$ +80.3° (c = 0.23, 99.5% EtOH)) in 89 and 88% yields, respectively. (–)-Chanoclavine-I ((–)-**1c**, mp 221–222°C, $[\alpha]_D^{24}$ –241.6° (c = 0.18, pyridine)) and (+)-**1c** (mp 222–223°C, $[\alpha]_D^{23}$ +242.7° (c = 0.18, pyridine)) were obtained by reducing (–)-**13c** and (+)-**13c** with $LiAlH_4$ in refluxing THF in 90 and 88% yields, respectively.

The data of optical rotations of our synthetic (–)-compounds were identical with those of natural alkaloids.[5,7] In literatures,[5c,8] agroclavine ((–)-enantiomer) had already been led to festuclavine, costaclavine, isosetoclavine, and setoclavine. Therefore, formal total syntheses of them are also

achieved.

In conclusion, both enantiomers of isochanoclavine-I (**1b**), agroclavine (**3**), agroclavine-I (**4**), and norchanoclavine-I (**5c**) are now readily available in less than nine steps from indole-3-carboxaldehyde (**8**) utilizing our common synthesis method. In seven steps (–)- and (+)-chanoclavine-I ((–)- and (+)-**1c**) can be obtained. Preparations of various optically active derivatives of ergot alkaloids are now in progress.

REFERENCES AND NOTES

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7. Reported data[5] for optical rotations and melting points of natural alkaloids: (–)-isochanoclavine-I ((–)-**1b**): mp 181°C, $[\alpha]_D^{20}$ +216° (c = 0.50, pyridine); (–)-chanoclavine-I ((–)-**1c**): mp 220–222°C, $[\alpha]_D^{20}$ –240° (c = 1.0, pyridine); (–)-agroclavine ((–)-**3**): mp 210–212°C, $[\alpha]_D^{20}$ –183° (pyridine), (–)-agroclavine-I ((–)-**4**): amorphous powder, $[\alpha]_D^{22}$ –155° (c = 0.15, pyridine).
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