

SIMPLE TOTAL SYNTHESSES OF (–)-ERGOT ALKALOIDS AND THEIR (+)-ENANTIOMERS BY A COMMON SYNTHESIS METHOD UTILIZING OPTICAL RESOLUTION¹

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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 5*R* and 10*S* 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.

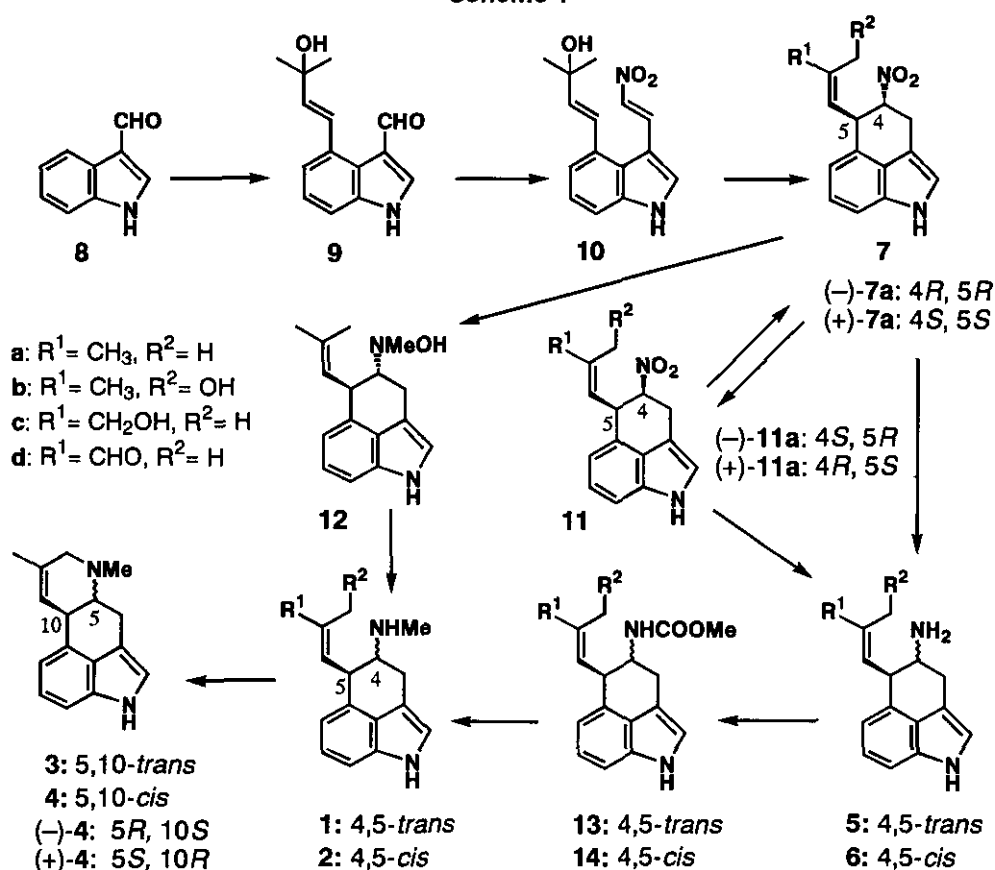
We have realized simple total syntheses of various (±)-ergot alkaloids establishing a common synthesis method for them.³ The method was also effective for the first syntheses of (–)- and (+)-6,7-secoagroclavine ((–)- and (+)-**1a**)⁴ and for determining their absolute configurations.⁴ Thus, (±)-4,5-*trans*-5-(2-methyl-1-propenyl)-4-nitro-1,3,4,5-tetrahydrobenz[*c*]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 extension 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 route³ 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, $[\alpha]_{\text{D}}^{25}$ –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, $[\alpha]_{\text{D}}^{25}$ +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, $[\alpha]_{\text{D}}^{19}$ –183.0° ($c = 0.30$, pyridine)) and (+)-agroclavine ((+)-3, mp 210–211°C, $[\alpha]_{\text{D}}^{20}$ +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, $[\alpha]_{\text{D}}^{25}$ –258.8° ($c = 0.30$, 99.5% EtOH)) and (+)-6a (mp 157.0–157.5°C, $[\alpha]_{\text{D}}^{25}$ +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, $[\alpha]_{\text{D}}^{22}$ –224.8° ($c = 0.30$, 99.5% EtOH)) and (+)-14a (mp 169–

170°C, $[\alpha]_D^{22} +226.8^\circ$ ($c = 0.30$, 99.5% EtOH)) in 86 and 86% yields, respectively. Further reductions of (–)-**14a** and (+)-**14a** with LiAlH_4 in refluxing THF afforded (–)-**2a** (caramel, $[\alpha]_D^{28} -282.8^\circ$ ($c = 0.30$, 99.5% EtOH)) and (+)-**2a** (caramel, $[\alpha]_D^{27} +286.7^\circ$ ($c = 0.30$, 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, $[\alpha]_D^{18} -302.2^\circ$ ($c = 0.30$, 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, $[\alpha]_D^{18} +301.0^\circ$ ($c = 0.30$, 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_2CO_3 in MeCN giving (+)-agroclavine-I ((+)-**4**, viscous oil, $[\alpha]_D^{17} +157.3^\circ$ ($c = 0.28$, pyridine)) in 86% yield. (–)-Agroclavine-I ((–)-**4**, viscous oil, $[\alpha]_D^{22} -157.3^\circ$ ($c = 0.27$, 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 $^1\text{H-NMR}$ comparison studies.^{5d}

Oxidation of (–)-**7a** with *t*-BuO₂H 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, $[\alpha]_D^{20} -113.3^\circ$ ($c = 0.29$, 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, $[\alpha]_D^{21} +112.4^\circ$ ($c = 0.27$, 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, $[\alpha]_D^{25} -178.0^\circ$ ($c = 0.30$, pyridine)) and (+)-**5c** (mp 205.5–207°C, $[\alpha]_D^{24} +179.6^\circ$ ($c = 0.30$, pyridine)) in 98 and 100% yields, respectively. Treatment of (–)-**5c** and (+)-**5c** with ClCO_2Me in the presence of Et_3N produced (–)-**13c** (oil, $[\alpha]_D^{21} -80.4^\circ$ ($c = 0.23$, 99.5% EtOH)) and (+)-**13c** (oil, $[\alpha]_D^{21} +80.3^\circ$ ($c = 0.23$, 99.5% EtOH)) in 89 and 88% yields, respectively. (–)-Chanoclavine-I ((–)-**1c**, mp 221–222°C, $[\alpha]_D^{24} -241.6^\circ$ ($c = 0.18$, pyridine)) and (+)-**1c** (mp 222–223°C, $[\alpha]_D^{23} +242.7^\circ$ ($c = 0.18$, 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

1. This report is Part 82 of a series entitled "The Chemistry of Indoles". Part 81: M. Somei, F. Yamada, and H. Morikawa, *Heterocycles*, 1997, **46**, in press.
2. a) A. P. Kozikowski, Y. -Y. Chen, B. C. Wang, and Z. B. Xu, *Tetrahedron*, 1984, **40**, 2345; b) N. Kardos and J. -P. Genet, *Tetrahedron Asymmetry*, 1994, **5**, 1525; c) Y. Yokoyama, T. Matsumoto, and Y. Murakami, *J. Org. Chem.*, 1995, **60**, 1486; d) Y. Yokoyama, K. Kondo, M. Mitsuhashi, and Y. Murakami, *Tetrahedron Lett.*, 1996, **37**, 9309.
3. a) M. Somei and F. Yamada, *Chem. Pharm. Bull.*, 1984, **32**, 5064; b) F. Yamada, Y. Makita, T. Suzuki, and M. Somei, *ibid.*, 1985, **33**, 2162; c) M. Somei, Y. Makita, and F. Yamada, *ibid.*, 1986, **34**, 948; d) M. Somei, F. Yamada, and Y. Makita, *Heterocycles*, 1987, **26**, 895; e) M. Somei, F. Yamada, H. Ohnishi, Y. Makita, and M. Kuriki, *ibid.*, 1987, **26**, 895; f) M. Somei, *Yakugaku Zasshi*, 1988, **108**, 361 and references cited therein.
4. K. Nakagawa and M. Somei, *Heterocycles*, 1991, **32**, 873; K. Nakagawa and M. Somei, Abstracts of Papers, 91th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Toyama, December 1994, p.10; M. Somei, K. Nakagawa, F. Yamada, and S. Hamamoto, Abstracts, 15th International Congress of Heterocyclic Chemistry, Taipei, August 1995, OP-II-8.
5. a) D. Stauffacher and H. Tschertter, *Helv. Chim. Acta*, 1964, **47**, 2186; b) A. Hofmann, R. Brunner, H. Kobel, and A. Brack, *Helv. Chim. Acta*, 1957, **40**, 1358; c) M. Abe, *Ann. Rep. Takeda Res. Lab.*, 1951, **10**, 73; M. Abe and S. Yamatodani, *J. Agr. Chem. Soc. Japan*, 1954, **28**, 501; d) V. G. Sakharovsky and A. G. Kozlovsky, *Tetrahedron Lett.*, 1984, **25**, 109; A. G. Kozlovskii, T. F. Solo'eva, V. G. Sakharovskii, and V. M. Adanin, *Prikl. Biokim. Mikrobiol.*, 1982, **18**, 535; e) J. M. Cassady, C. I. Abou-Chaar, and H. G. Floss, *Lloydia*, 1973, **36**, 390.
6. B. R. Chhabra, K. Hayano, T. Ohtsuka, H. Shirahama, and T. Matsumoto, *Chem. Lett.*, 1981, 1703.
7. Reported data⁵ for optical rotations and melting points of natural alkaloids: (–)-isochanoclavine-I ((–)-**1b**): mp 181°C, $[\alpha]_D^{20} +216^\circ$ (c = 0.50, pyridine); (–)-chanoclavine-I ((–)-**1c**): mp 220–222°C, $[\alpha]_D^{20} -240^\circ$ (c = 1.0, pyridine); (–)-agroclavine ((–)-**3**): mp 210–212°C, $[\alpha]_D^{20} -183^\circ$ (pyridine), (–)-agroclavine-I ((–)-**4**): amorphous powder, $[\alpha]_D^{22} -155^\circ$ (c = 0.15, pyridine).
8. M. Abe and S. Yamatodani, *J. Agr. Chem. Soc. Japan*, 1959, **33**, 1031; S. Yamatodani and H. Abe, *ibid.*, 1960, **34**, 366.

Received, 9th April, 1997