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## SIMPLE TOTAL SYNTHESSES OF (–)-ERGOT ALKALOIDS AND THEIR (+)-EN-ANTIOMERS BY A COMMON SYNTHESIS METHOD UTILIZING OPTICAL RESOLUTION<sup>1</sup>

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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.<sup>2a</sup> Since that time, several additional enantioselective total syntheses of ergot alkaloids have been reported.<sup>2b-d</sup> Although these syntheses are wonderful and artistic, there remains conspicuous need of a simple and general method for preparing optically active ergot alkaloids.

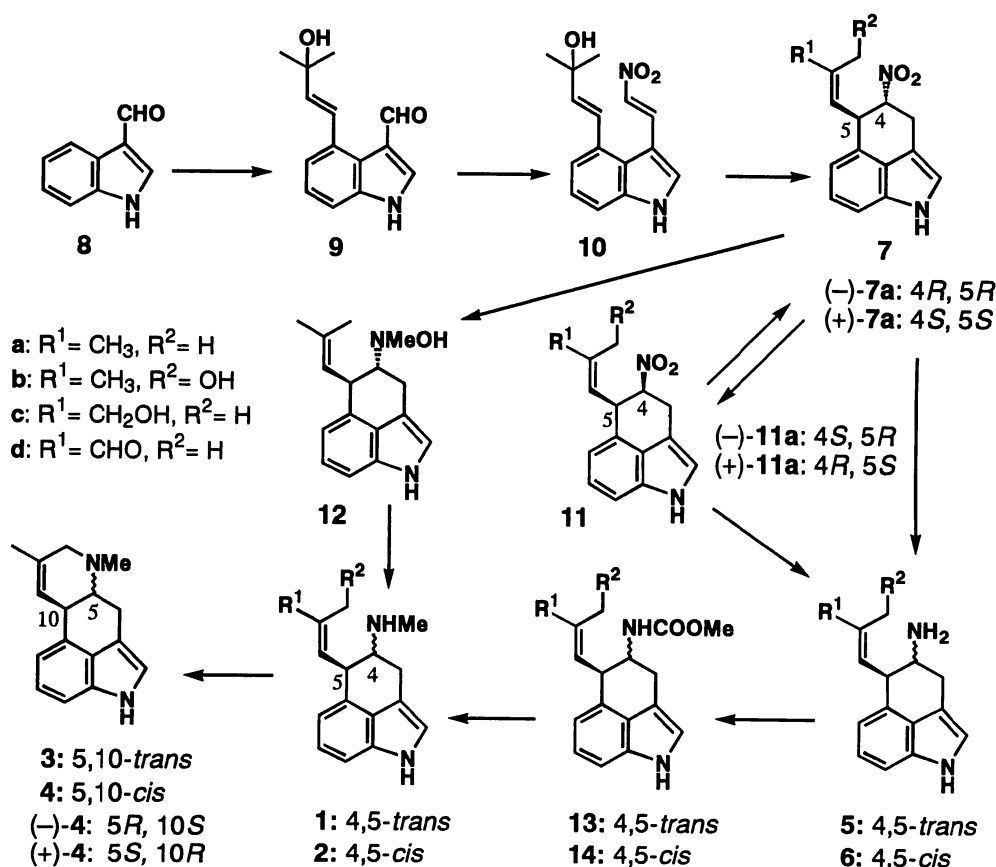
We have realized simple total syntheses of various (±)-ergot alkaloids establishing a common synthesis method for them.<sup>3</sup> The method was also effective for the first syntheses of (–)- and (+)-6,7-secoagroclavine ((–)- and (+)-**1a**)<sup>4</sup> and for determining their absolute configurations.<sup>4</sup> 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).<sup>3</sup> After establishing interconversion method between (±)-**7a** and (±)-4,5-*cis*-isomer ((±)-**11a**),<sup>3f</sup> both enantiomers of **7a** and **11a** were obtained using preparative chiral column chromatography.<sup>4</sup> 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**.<sup>4</sup>

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**),<sup>5a</sup> chanoclavine-I (**1c**),<sup>5a,b</sup> agroclavine (**3**),<sup>5c</sup> agroclavine-I (**4**),<sup>5d</sup> and norchanoclavine-I (**5c**)<sup>5e</sup> only by changing reagents without altering the synthesis route<sup>3</sup> as shown below.

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

treatment with  $\text{SeO}_2$  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  $\text{SeO}_2$  close to the (Z)-methyl group.<sup>3f</sup> 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  $\text{POCl}_3$  in the presence of  $\text{K}_2\text{C}_2\text{O}_3$  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-tetrahydrobenzo[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 ( $\text{ClCO}_2\text{Me}$ ) in the presence of  $\text{Et}_3\text{N}$  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,  $[\alpha]_D^{22} +226.8^\circ$  ( $c = 0.30$ , 99.5% EtOH)) in 86 and 86% yields, respectively. Further reductions of (-)-**14a** and (+)-**14a** with  $\text{LiAlH}_4$  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%  $\text{SeO}_2$  on celite in dioxane and  $\text{Et}_3\text{N}$  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  $\text{POCl}_3$  in the presence of  $\text{K}_2\text{C}_2\text{O}_3$  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*.<sup>4</sup> Since the treatment of (-)-**11a** and (+)-**11a** with  $\text{Et}_3\text{N}$  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 <sup>1</sup>H-NMR comparison studies.<sup>5d</sup>

Oxidation of (-)-**7a** with *t*-BuO<sub>2</sub>H in the presence of 5% $\text{SeO}_2$  on  $\text{SiO}_2$ <sup>6</sup> in dioxane, followed by the reduction of the resultant mixture of (-)-**7c** and overoxidized aldehyde compound ((-)-**7d**) with  $\text{NaBH}_4$ , 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  $\text{ClCO}_2\text{Me}$  in the presence of  $\text{Et}_3\text{N}$  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  $\text{LiAlH}_4$  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.<sup>5,7</sup> In literatures,<sup>5c,8</sup> agroclavine ((-)-enantiomer) had already been led to festuclavine, costaclavine, isetoclavine, 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.

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