

Syntheses of ( $\pm$ )  
)-4-amino-1,3,4,5-tetrahydrobenz[cd]indole-4-carboxylic acid, ( $\pm$ )  
)-4-N,N-dipropylamino-4-hydroxymethyl- and ( $\pm$ )  
)-4-propyloxy-1,3,4,5-tetrahydrobenz[cd]indole

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SYNTHESES OF ( $\pm$ )-4-AMINO-1,3,4,5-TETRAHYDROBENZ[*cd*]INDOLE-4-CARBOXYLIC ACID, ( $\pm$ )-4-*N,N*-DIPROPYLAMINO-4-HYDROXYMETHYL- AND ( $\pm$ )-4-PROPYLOXY-1,3,4,5-TETRAHYDROBENZ[*cd*]INDOLE<sup>1</sup>

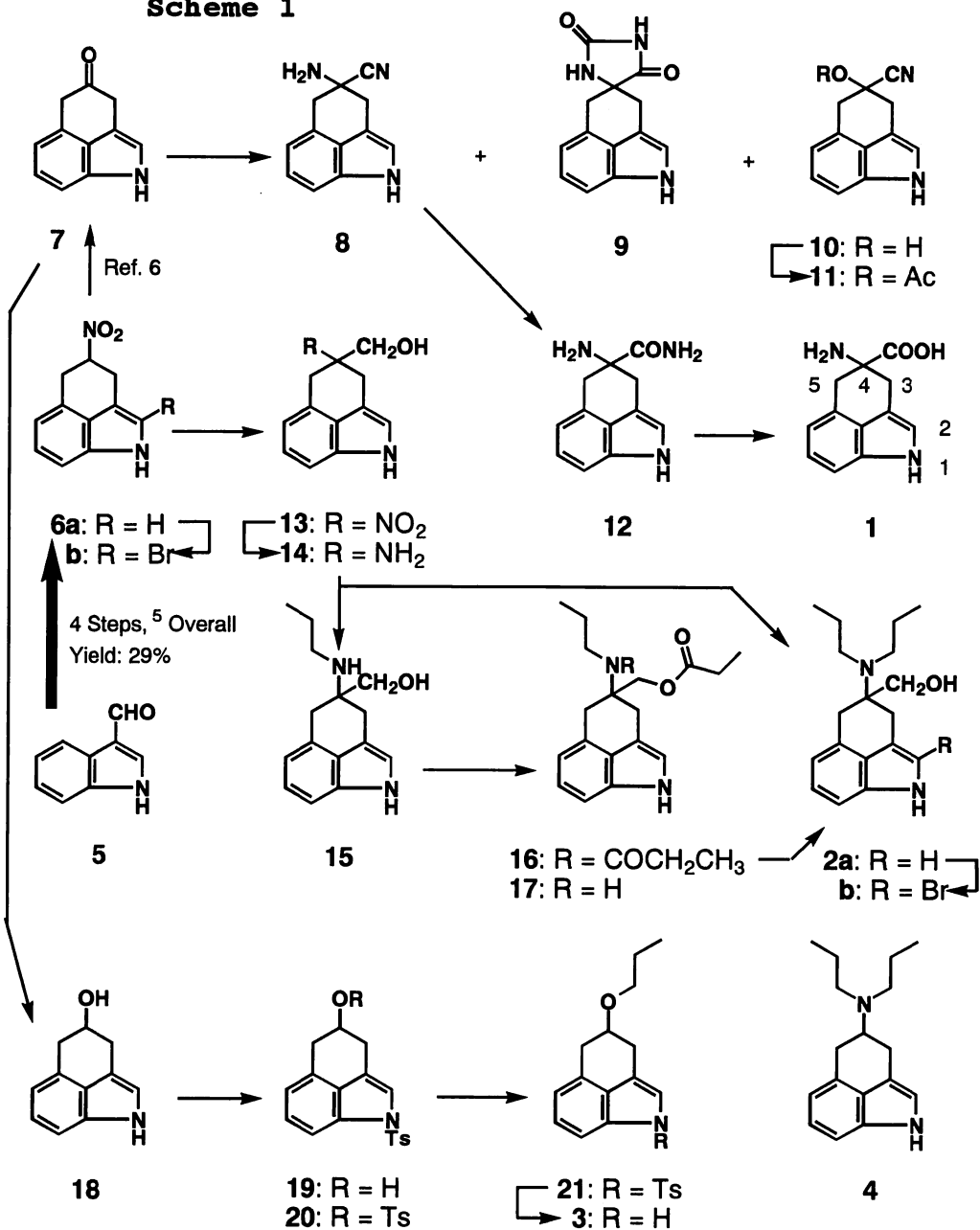
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*Abstract*---Simple syntheses of the title compounds are reported starting from indole-3-carboxaldehyde.

In our synthetic project to develop biologically active indole compounds,<sup>2</sup> we have been much interested in 4-amino-1,3,4,5-tetrahydrobenz[*cd*]indole-4-carboxylic acid (**1**, Scheme 1), 4-*N,N*-dipropylamino-4-hydroxymethyl- (**2 a**), and 4-propyloxy-1,3,4,5-tetrahydrobenz[*cd*]indole (**3**). The amino acid (**1**) has a conformationally constrained structure<sup>3</sup> of tryptophan as well as a part of skeleton of ergot alkaloids.<sup>4</sup> Therefore, we could expect **1** not only as a dopamine agonist but also as a useful probe to obtain information about the bioactive conformation of a neuropeptide, such as cholecystokinin (CCK),<sup>3</sup> by incorporating **1** into the peptide. While the compound (**2 a**) is an analog of a potent dopamine agonist, 4-*N,N*-dipropylamino-1,3,4,5-tetrahydrobenz[*cd*]indole<sup>5</sup> (**4**), and **3** is its oxa-analog. In this communication, we wish to report facile syntheses of the title compounds in ( $\pm$ )-form from indole-3-carboxaldehyde (**5**).

( $\pm$ )-4-Nitro-1,3,4,5-tetrahydrobenz[*cd*]indole (**6 a**) was obtained in four steps in 29% overall yield from **5** according to our synthetic method,<sup>5</sup> and then **6 a** was converted to **7** by the procedure of Kruse and co-worker<sup>6</sup> in 88% yield. Since **7** is known to isomerize to 1,2-dihydro-4-hydroxybenz[*cd*]indole having stabler naphthalene skeleton than indole isomer,<sup>6</sup> Bucherer reaction of **7** was investigated under careful control of reaction conditions and the results are summarized in Table I. As can be seen in the Table,  $\alpha$ -aminonitrile<sup>7a</sup> (**8**), hydantoin<sup>7b</sup> (**9**), and cyanohydrin<sup>7c</sup> (**10**) were produced using (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> and KCN (Entries 1-4), and under the

## Scheme 1



reaction conditions of Entry 2, **9** was obtained as major product. While, Strecker type reaction of **7** with  $\text{NH}_4\text{Cl}$  and  $\text{KCN}$  produced **8** as major product under the reaction conditions of Entry 6. Although **10** was a crystalline solid, it was unstable and gradually changed back to **7**. Isolation of stable 4-acetoxy-4-cyano compound<sup>7d</sup> (**11**) in 43% yield by the treatment of **7** with  $\text{KCN}$  in  $\text{AcOH}$ , followed by the reaction of the resulting **10** with  $\text{Ac}_2\text{O}$  and pyridine, clearly established the structure of **10**. Next, **8** was converted to amide<sup>7e</sup> (**12**) in 84% yield by the reaction with 2N- $\text{NaOH}$  in the presence of 30%  $\text{H}_2\text{O}_2$ . Subsequent hydrolysis of **12** with 2N- $\text{NaOH}$  in  $\text{MeOH}$  produced the desired amino acid<sup>7f</sup> (**1**) in a quantitative yield.

Table I. Bucherer and Strecker Type Reactions of **7**

$\text{7} \xrightarrow[\text{MeOH, } 60^\circ\text{C}]{\text{Ammonium Salt}} \text{8} + \text{9} + \text{10} + \text{Recovery}$						
Entry	Ammonium Salt (mol)	Reaction Time (h)	<b>8</b>	Yield (%) <b>9</b>	of <b>10</b>	Recovery
1	$(\text{NH}_4)_2\text{CO}_3$ (10.5)	5	2	49	0	0
2	"	2	11	59	0	0
3	"	1	51	23	6	16
4	"	0.5	40	10	19	31
5	$\text{NH}_4\text{Cl}$ (10.5)	2	15	0	7	6
6	"	1	56	0	10	26

For the synthesis of the target compound (**2a**), **6a** was initially treated with  $\text{KO}^t\text{Bu}$  and 37% formalin to afford **13**<sup>7g</sup> in 73% yield, which was reduced with  $\text{Zn}(\text{Hg})\text{-HCl}$  to give **14**<sup>7h</sup> in 94% yield. The reaction of **14** with propyl iodide (2 mol) in the presence of  $\text{K}_2\text{CO}_3$  produced the mono-propyl<sup>7i</sup> (**15**) and the target compound<sup>7j</sup> (**2a**) in 87 and 6% yields, respectively. Various attempts to improve the yield of **2a** were unsuccessful. While, treatment of **15** with propionyl chloride afforded **16**<sup>7k</sup> and **17**<sup>7l</sup> in 89 and 8% yields, respectively. Subsequent reduction of **16** with  $\text{LiAlH}_4$  afforded **2a** in 91% yield. Furthermore, the 2-bromo compounds, (**2b**)<sup>7m</sup> and (**6b**)<sup>7n</sup> were obtained in 92 and 87% yields, respectively, by reacting **2a** and **6a** with NBS.

The third target compound (**3**) was produced as follows. Reduction of **7** with  $\text{NaBH}_4$  afforded 4-hydroxy-1,3,4,5-tetrahydrobenz[*cd*]indole<sup>70</sup> (**18**) in 99% yield. Successive treatment of **18** with  $\text{NaH}$ , and then with tosyl chloride produced *N*-tosyl<sup>7p</sup> (**19**) and *N,O*-ditosyl compound<sup>7q</sup> (**20**) in 37 and 27% yields, respectively, together with 34% recovery of unreacted starting material. Treatment of **19** with  $\text{KH}$  in DMF, and then with propyl iodide afforded 47% yield of the 4-propyloxy compound<sup>7r</sup> (**21**), which was successfully converted to **37s** in 86% yield by hydrolysis with 2N-NaOH.

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7. All new compounds gave satisfactory spectral and elemental analysis data for crystals or high resolution mass data for oils. a) mp 129.0-132.0°C; b) mp 295.0-297.0°C; c) unstable crystals; d) mp 161.0-162.0°C; e) mp 81.0-82.0°C; f) mp 275.0-278.0°C (decomp.); g) mp 154.0-155.0°C; h) mp 173.5-174.0°C; i) mp 132.0-133.0°C; j) mp 93.5-95.0°C; k) mp 165.0-166.0°C; l) oil; m) mp 160.0-163.0°C (decomp.); n) mp 125.0-135.0°C (decomp.); o) mp 87.0-88.0°C; p) oil; q) oil; r) oil; s) oil.