SYNTHESES OF (±)-4-AMINO-1,3,4,5-TETRAHYDROBENZ[*cd*]INDOLE-4-CARBOXYLIC ACID, (±)-4-*N*,*N*-DIPROPYLAMINO-4-HYDROXYMETHYL- AND (±)-4-PROPYLOXY-1,3,4,5-TETRAHYDROBENZ[*cd*]INDOLE[1]

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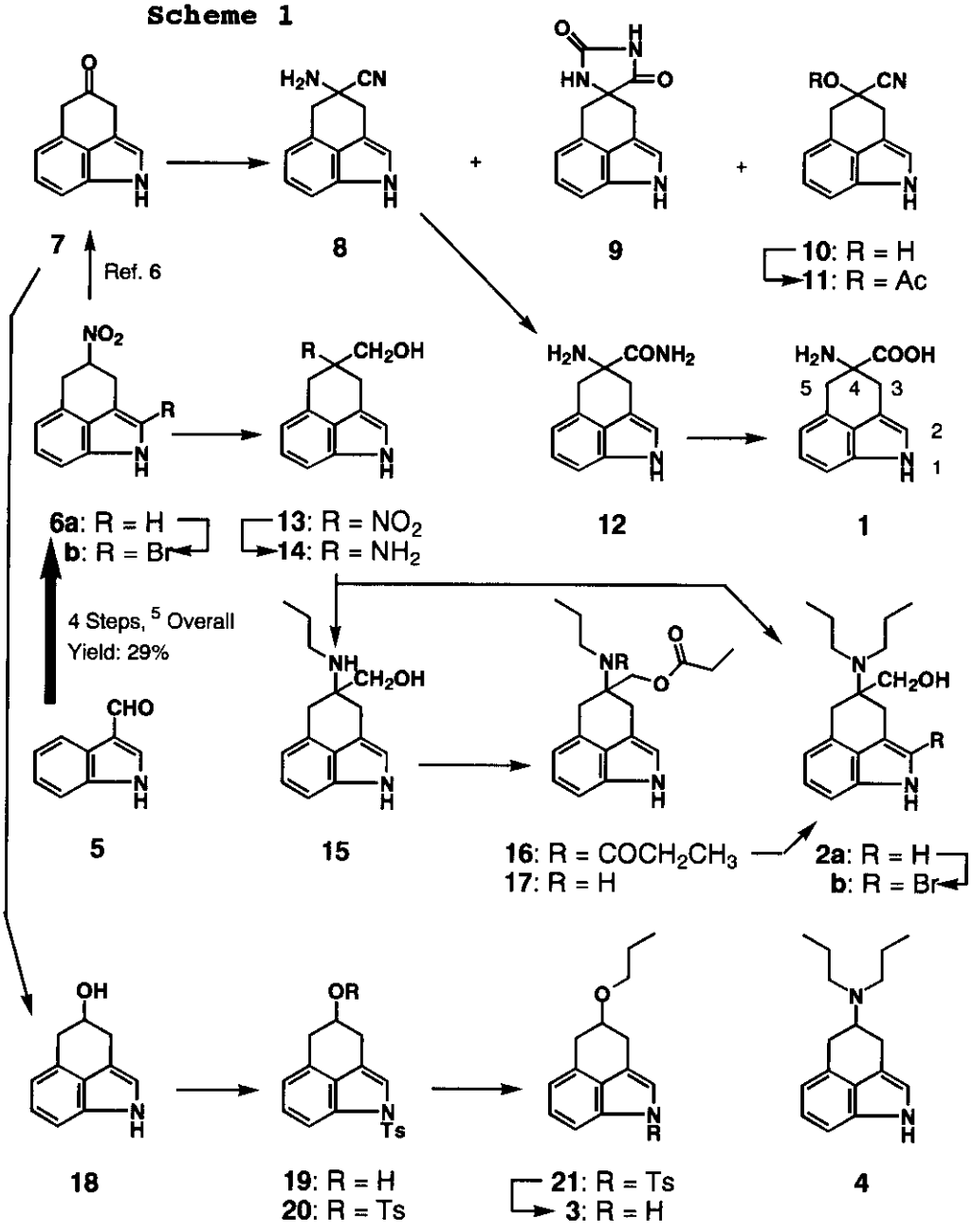
Abstract----Simple syntheses of the title compounds are reported starting from indole-3-carboxaldehyde.

In our synthetic project to develop biologically active indole compounds,[2] 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[3] of tryptophan as well as a part of skeleton of ergot alkaloids.[4] 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),[3] 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[5] (**4**), and **3** is its oxa-analog. In this communication, we wish to report facile syntheses of the title compounds in (±)-form from indole-3-carboxaldehyde (**5**).

(±)-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,[5] and then **6 a** was converted to **7** by the procedure of Kruse and co-worker[6] in 88% yield. Since **7** is known to isomerize to 1,2-dihydro-4-hydroxybenz[*cd*]indole having stabler naphthalene skeleton than indole isomer,[6] 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, α-aminonitrile[7a] (**8**), hydantoin[7b] (**9**), and cyanohydrin[7c] (**10**) were produced using $(NH_4)_2CO_3$ and KCN (Entries 1-4), and under the

Scheme 1


7
Ref. 6
8
9
10: R = H
11: R = Ac
6a: R = H
b: R = Br
13: R = NO2
14: R = NH2
12
1
4 Steps, 5 Overall
Yield: 29%
5
15
16: R = COCH2CH3
17: R = H
2a: R = H
b: R = Br
18
19: R = H
20: R = Ts
21: R = Ts
3: R = H
4

reaction conditions of Entry 2, **9** was obtained as major product. While, Strecker type reaction of **7** with NH_4Cl and 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[7d] (**11**) in 43% yield by the treatment of **7** with KCN in AcOH, followed by the reaction of the resulting **10** with Ac_2O and pyridine, clearly established the structure of **10**. Next, **8** was converted to amide[7e] (**12**) in 84% yield by the reaction with 2N-NaOH in the presence of 30% H_2O_2. Subsequent hydrolysis of **12** with 2N-NaOH in MeOH produced the desired amino acid[7f] (**1**) in a quantitative yield.

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

7 —(Ammonium Salt; KCN (3.5 mol), MeOH, 60°C)→ **8** + **9** + **10** + **Recovery**

Entry	Ammonium Salt (*mol*)	Reaction Time (h)	Yield (%) of **8**	**9**	**10**	**Recovery**
1	$(NH_4)_2CO_3$ (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	NH_4Cl (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 KO^tBu and 37% formalin to afford **13**[7g] in 73% yield, which was reduced with Zn(Hg)-HCl to give **14**[7h] in 94% yield. The reaction of **14** with propyl iodide (2 mol) in the presence of K_2CO_3 produced the mono-propyl[7i] (**15**) and the target compound[7j] (**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**[7k] and **17**[7l] in 89 and 8% yields, respectively. Subsequent reduction of **16** with $LiAlH_4$ afforded **2a** in 91% yield. Furthermore, the 2-bromo compounds, (**2b**)[7m] and (**6b**),[7n] 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 $NaBH_4$ afforded 4-hydroxy-1,3,4,5-tetrahydrobenz[*cd*]indole[7o] (**18**) in 99% yield. Successive treatment of **18** with NaH, and then with tosyl chloride produced *N*-tosyl[7p] (**19**) and *N,O*-ditosyl compound[7q] (**20**) in 37 and 27% yields, respectively, together with 34% recovery of unreacted starting material. Treatment of **19** with KH in DMF, and then with propyl iodide afforded 47% yield of the 4-propyloxy compound[7r] (**21**), which was successfully converted to **3**[7s] 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.

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