A SIMPLE FOUR STEP SYNTHESIS AND OPTICAL RESOLUTION OF 4-NITRO-1, 3, 4, 5-TETRAHYDROBENZ[*cd*]INDOLE, AND THE SYNTHESES OF 1-HYDROXY DERIVATIVES OF 4-NITRO- AND 4-AMINO-1, 3, 4, 5-TETRAHYDROBENZ[*cd*]INDOLES[1]

Kyoko Nakagawa, Naokatsu Aoki, Harunobu Mukaiyama, and Masanori Somei*

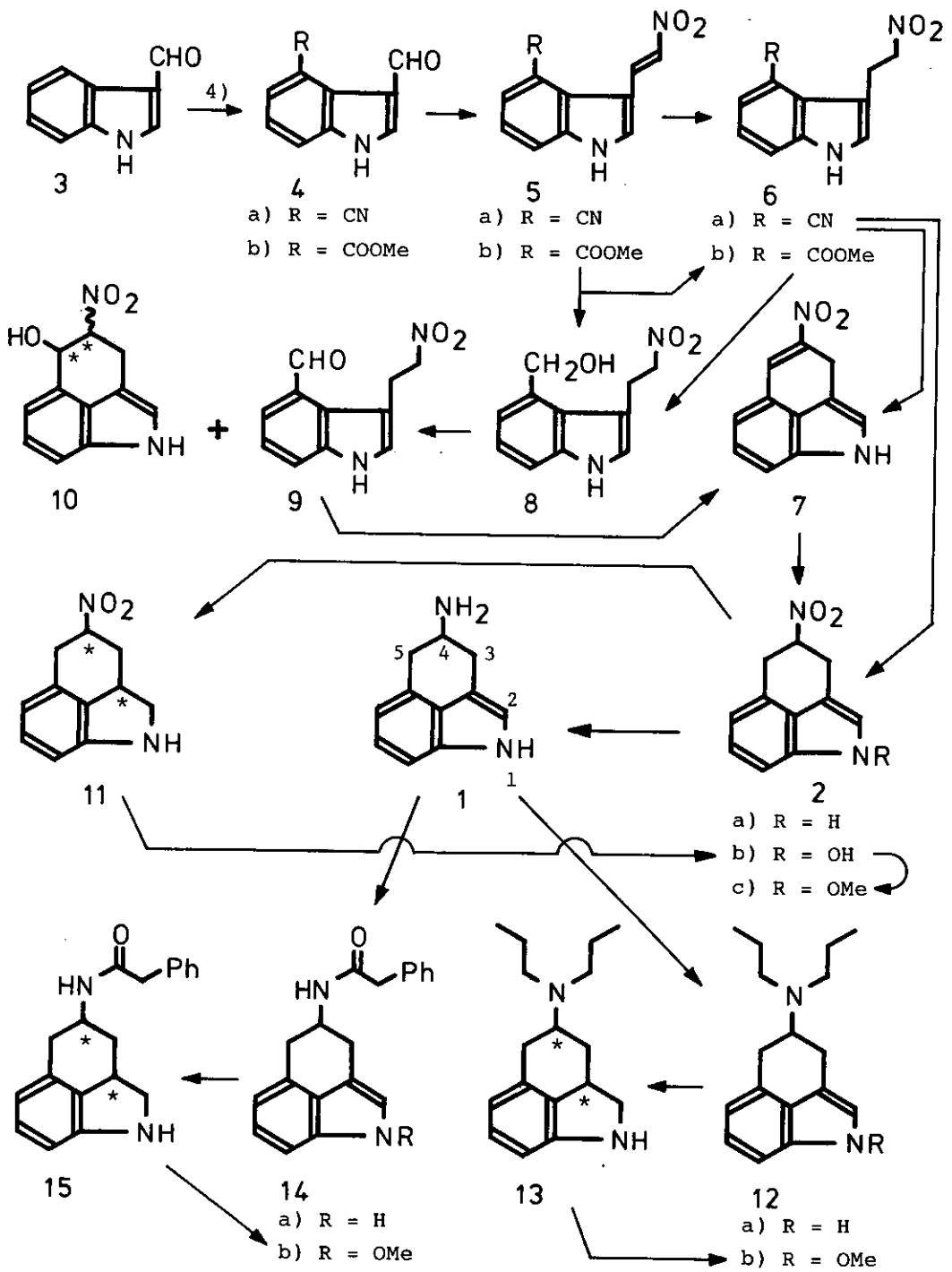
Faculty of Pharmaceutical Sciences, Kanazawa University, 13-1 Takara-machi, Kanazawa 920, Japan

Abstract ——— 4-Nitro-1, 3, 4, 5-tetrahydrobenz[*cd*]indole was synthesized from indole-3-carboxaldehyde in four steps with an overall yield of 30%. Optical resolution of its enantiomers by chiral column chromatography was successful. Syntheses of 1-hydroxy derivatives of 4-nitro- and 4-amino-1, 3, 4, 5-tetrahydrobenz[*cd*]indoles are also reported.

Various biologically active compounds[2] have been derived from 4-amino-1, 3, 4, 5-tetrahydrobenz[*cd*]indole (**1**, Scheme 1) as a parent compound, and much efforts have been devoted on developing a simple synthetic method for **1**.[2] Its shortest synthetic route among thus far known[2,3] is the one through indole-4-carboxaldehyde[3] using 2-methyl-3-nitrobenzoic acid as a starting material. Nevertheless, it still requires cumbersome nine steps with low overall yield.[2]

In this communication, we describe a simple four step synthetic method of 4-nitro-1, 3, 4, 5-tetrahydrobenz[*cd*]indole[2g] (**2a**), a synthetic precursor of **1**, from indole-3-carboxaldehyde (**3**). We also succeeded in the optical res-

Scheme 1


CHO
4)
3
R
CHO
4
a) R = CN
b) R = COOMe
NO2
5
a) R = CN
b) R = COOMe
6
a) R = CN
b) R = COOMe
HO
NO2
NH
10
CHO
9
CH2OH
8
7
NH2
5 4 3 2
1
11
2
a) R = H
b) R = OH
c) R = OMe
HN
O
Ph
15
14
a) R = H
b) R = OMe
N
13
12
a) R = H
b) R = OMe

olution of both enantiomers of **2a** by chiral column chromatography and in the syntheses of 1-hydroxy derivatives of 4-nitro- and 4-amino-1,3,4,5-tetrahydrobenz[*cd*]indoles.

I. A simple four step synthesis of 4-nitro-1,3,4,5-tetrahydrobenz[*cd*]-indole (**2a**)

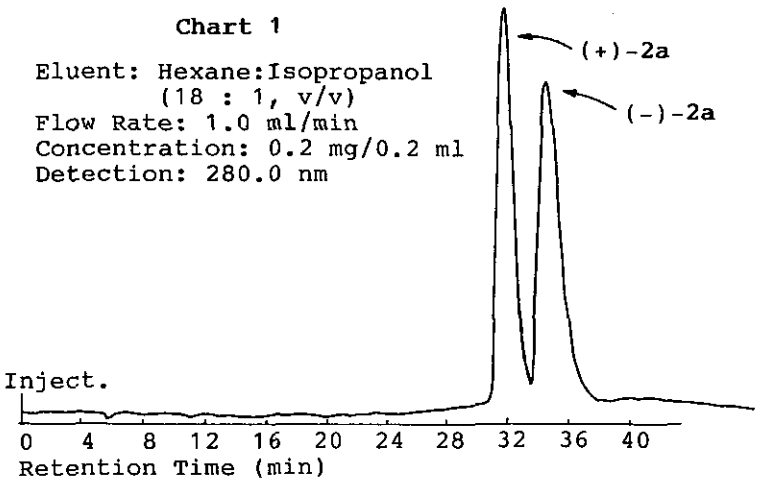
4-Cyano-3-(2-nitroethyl)indole (**6a**) was prepared through **4a** and **5a** in three steps from **3**, according to the reported procedure[4] in 53% oveall yield. Next, sequential treatment of **6a**, initially with diisobutylaluminum hydride (DIBAL) in anhydrous tetrahydrofuran (THF) at room temperature for 30 min, then with methanol (MeOH)-water at reflux for 30 min, was found to produce 1,3-dihydro-4-nitrobenz[*cd*]indole (**7**, mp 190-190.5°C) in 52% yield. Since the compound (**7**) was cleanly reduced to **2a** (mp 138.5-139°C, lit.,[2g] mp 134-135°C) in 80% yield with sodium borohydride ($NaBH_4$) in MeOH, the attempt at effecting one pot conversion of **6a** to **2a** was readily attained in 57% yield by adding the $NaBH_4$ reduction procedure to the above DIBAL and MeOH-water treatment. Consequently, a simple four step synthetic method for **2a** from **3** with an overall yield of 30% was established with the originality rate[5] of 60%. However, every attempt to convert **5a** into **2a** in one pot operation was unsuccessful at present. Finally, **2a** was reduced to **1** (mp 125-126°C, lit.,[2g] mp 119-121°C) with amalgamated zinc-aqueous hydrogen chloride at reflux in 99.5% yield.

Alternatively, the compound (**7**) could be prepared by the following route. 4-Methoxycarbonylindole-3-carboxaldehyde (**4b**), obtained in 53% yield from **3** by one pot procedure,[4] was converted into 4-methoxycarbonyl-3-(2-nitrovinyl)indole (**5b**, mp 121-122°C) in 91% yield by the aldol reaction with nitromethane. Subsequent reduction of **5b** with $NaBH_4$ in *N,N*-dimethylformamide-MeOH afforded 4-methoxycarbonyl-3-(2-nitroethyl)indole (**6b**, mp 106-107 °C) in 83% yield. DIBAL (3 mol eq.) reduction of **6b** in THF afforded 4-hydroxymethyl-3-(2-nitroethyl)indole (**8**, mp 118-119°C) in 99% yield, nevertheless attempts to convert **5b** directly to **8** by DIBAL (3 mol eq.) reduc-

tion were unsuccessful, giving **6b** in 31% yield in addition to 35% yield of starting material. On the other hand, lithium borohydride ($LiBH_4$) reduction of **5b** in THF at reflux did not realize complete conversion of **5b** into **8**, instead **6b** and **8** were produced in 36 and 33% yields, respectively. Similar behavior was observed on the reduction of **6b** with $LiBH_4$ (20 mol eq.), resulting in the formation of **8** in 31% yield together with 55% yield of recovery. Though oxidation of **8** with either active manganese dioxide or dimethyl sulfoxide-acetic anhydride afforded poor results, pyridinium chlorochromate (3 mol eq.) in pyridine produced 3-(2-nitroethyl)indole-4-carboxaldehyde (**9**, mp 159-160°C) and 5-hydroxy-4-nitro-1,3,4,5-tetrahydrobenz[*cd*]indole (**10**, as a mixture of diastereoisomers) in 32 and 13% yields, respectively. Subsequent treatment of **9** with triethylamine in MeOH at reflux for 1 h afforded **7** in 87% yield.

Ⅱ. Optical resolution of 4-nitro-1,3,4,5-tetrahydrobenz[*cd*]indole (**2a**)

With the desired compound (**2a**) in hand, we next tried its optical resolution on chiral column chromatography, and finally found that (+)-**2a** (mp 126.5-127.0°C, $[\alpha]_D^{23}$ +7.12° (99.5% EtOH, c=0.24)) and (-)-**2a** (mp 125.0-126.0°C, $[\alpha]_D^{23}$ -7.38° (99.5% EtOH, c=0.25)) were separable on chiralpak AS column (Daicel Kagaku) using isopropanol-hexane (1:18, v/v) as an



eluent, and the results are shown in Chart 1. Determination of their absolute configuration and syntheses of optically active derivatives of **2a** and **1** are currently under investigation.

Ⅲ. Syntheses of 1-hydroxy derivatives of 4-nitro- and 4-amino-1,3,4,5-tetrahydrobenz[*cd*]indoles

We suppose that **1**, **2a**, and related indole compounds would be metabolized into the corresponding 1-hydroxyindoles *in vivo*.[1b,6] Therefore, preparations of the expected compounds are of much interest.

Treatment of **2a** with sodium cyanoborohydride ($NaBH_3CN$) in trifluoroacetic acid (TFA) and acetic acid (AcOH) (2:3 mixture) produced 95% yield of indoline (**11**), which was an inseparable 2:1 mixture of diastereoisomers. Similarly, 4-dipropylamino-1,3,4,5-tetrahydrobenz[*cd*]indole (**12a**), readily obtainable from **1** by treatment with propyl iodide,[2j] was converted to the corresponding indoline (**13**, 6:1 mixture of diastereoisomers) in 86% yield. Subsequent oxidation of **11** with sodium tungstate·dihydrate ($Na_2WO_4 \cdot 2H_2O$) and urea hydrogen peroxide addition compound[6c] ($urea \cdot H_2O_2$) afforded 52% yield of the desired 1-hydroxy-4-nitro-1,3,4,5-tetrahydrobenz[*cd*]indole (**2b**) as prisms (mp 134.0-134.5°C), which could be stored at room temperature for 1 week without any decomposition. The reaction of **2b** with ethereal diazomethane afforded the corresponding 1-methoxy derivative (**2c**) in 64 % yield as a stable oil. By carrying out the above two procedures successively, one pot preparation of **2c** was realized in 33% yield. Similar one pot oxidation of the diastereoisomers (**13**) with $Na_2WO_4 \cdot 2H_2O$ and $urea \cdot H_2O_2$, followed by the methylation of the resultant 1-hydroxyindole with diazomethane afforded 4-dipropylamino-1-methoxy-1,3,4,5-tetrahydrobenz[*cd*]indole (**12b**) in 46% yield as an unstable oil.

On the other hand, treatment of **1** with phenylacetyl chloride afforded 73% yield of amide compound (**14a**, oil). Reduction of **14a** with $NaBH_3CN$ in TFA and AcOH (1:4, v/v) produced the corresponding diastereoisomers, **15a** (mp 159-160°C) and **15b** (oil), in 41 and 47% yields, respectively. Subsequent

oxidation of the mixture of **15a** and **15b** with $Na_2WO_4 \cdot 2H_2O$ and urea$\cdot H_2O_2$, followed by the methylation of the resultant unstable 4-dipropylamino-1-hydroxy-1, 3, 4, 5-tetrahydrobenz[*cd*]indole with dimethyl sulfate and potassium carbonate afforded 40% yield of the desired stable 1-methoxyindole derivative (**14b**, mp 138-139°C).

Reactivity and biological evaluations of the above mentioned 1-hydroxyindole derivatives are in progress.

ACKNOWLEDGMENT

This report is partly supported by a Grant-in-Aid for Scientific Research (Grant No. 04771872) from the Ministry of Education, Science, and Culture which is gratefully acknowledged.

REFERENCES AND NOTES

1. a) This report is partly presented, Book of Abstracts, 22nd Congress of Heterocyclic Chemistry, Sendai, Japan, October, 1991, p. 259, and Part 62 of a series entitled "The Chemistry of Indoles". b) Part 61: M. Somei, T. Kawasaki, Y. Fukui, F. Yamada, T. Kobayashi, H. Aoyama, and D. Shinmyo, *Heterocycles*, 1992, **34**, 1887.
2. a) A. Stoll and T. Petrzilka, *Helv. Chim. Acta*, 1952, **35**, 148; b) L. S. Harris, and F. C. Uhre, *J. Pharmacol. Exp. Ther.*, 1960, **128**, 358; c) N. J. Bach, E. C. Kornfeld, N. D. Jones, M. O. Chaney, D. E. Dorman, J. W. Paschal, J. A. Clemens, and E. B. Smalstig, *J. Med. Chem.*, 1980, **23**, 481; d) N. J. Bach, E. C. Kornfeld, J. A. Clemens, and E. B. Smalstig, *ibid.*, 1980, **23**, 812; e) J. R. Boissier, L. Nedelec, C. Oberlander, and F. Labrie, *Acta Pharm. Suec.*, Suppl. 2, 1983, 120; f) L. Nedelec, A. Pierdet, P. Fauveau, C. Euvard, L. Proulx-Ferland, C. Dumont, F. Labrie, and L. R. Boissier, *J. Med. Chem.*, 1983, **26**, 522; g) L. I. Kruse and M. D. Meyer, *J. Org. Chem.*, 1984, **49**, 4761; h) M. E. Flaugh, D. L. Mullen, R. W. Fuller, and N. R. Mason, *J. Med. Chem.*, 1988, **31**, 1746; i) C. J.

Moody, A. L. Beck, and W. J. Coates, *Tetrahedron Lett.*, 1989, **30**, 4017; j) M. J. Martinelli, M. R. Leanna, D. L. Varie, B. C. Peterson, T. J. Kress, J. P. Wepsiec, and V. V. Khau, *ibid.*, 1990, **31**, 7579; k) D. L. Varie, *ibid.*, 1990, **31**, 7583.

3. H. Plieninger, M. Hobel, and V. Liede, *Chem. Ber.*, 1963, **96**, 1618; M. Somei, Y. Karasawa, and C. Kaneko, *Chemistry Lett.*, 1980, 813; A. P. Kozikowski, H. Ishida, and Y-Y. Chen, *J. Org. Chem.*, 1980, **45**, 3350; M. Somei, F. Yamada, Y. Karasawa, and C. Kaneko, *Chemistry Lett.*, 1981, 615; M. Somei, Y. Karasawa, T. Shoda, and C. Kaneko, *Chem. Pharm. Bull.*, 1981, **29**, 249; M. Somei and T. Shoda, *Heterocycles*, 1982, **17**, 417.
4. M. Somei, F. Yamada, M. Kunimoto, and C. Kaneko, *Heterocycles*, 1984, **22**, 797; F. Yamada and M. Somei, *ibid.*, 1987, **26**, 1173; M. Somei, M. Wakida, and T. Ohta, *Chem. Pharm. Bull.*, 1988, **36**, 1162.
5. Definition of originality rate was proposed: M. Somei, *Yuki Gosei Kagaku Kyokai Shi*, 1982, **40**, 387; M. Somei, *Yakugaku Zasshi*, 1988, **108**, 361.
6. a) Review: M. Somei, *Yuki Gosei Kagaku Kyokai Shi*, 1991, **49**, 205 and references cited therein. b) M. Somei, T. Kawasaki, K. Shimizu, Y. Fukui, and T. Ohta, *Chem. Pharm. Bull.*, 1991, **39**, 1905. c) M. Somei and T. Kobayashi, *Heterocycles*, 1992, **34**, 1295.

Received, 22nd July, 1992