A SIMPLE SYNTHESIS OF A PHYTOALEXIN, METHOXYBRASSININ[1]

Masanori Somei,* Kensuke Kobayashi, Kazuhisa Shimizu, and Toshiya Kawasaki

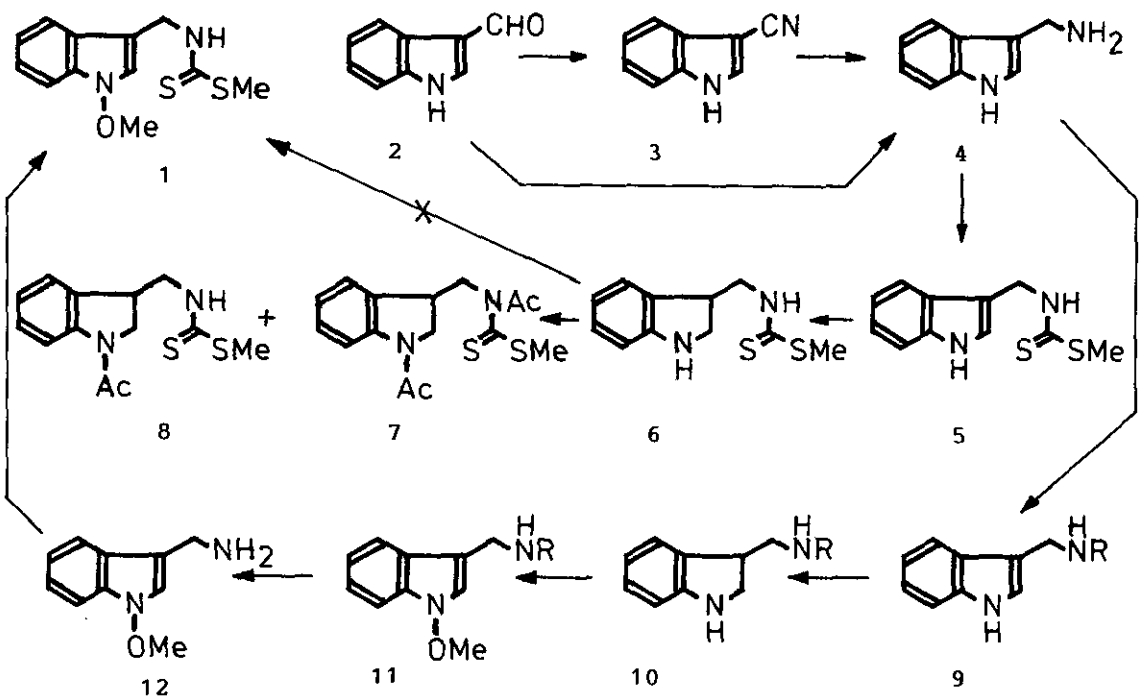
Faculty of Pharmaceutical Sciences, Kanazawa University
13-1 Takara-machi, Kanazawa 920, Japan

Abstract ——— A simple and an alternative multi-gram scale synthetic method for methoxybrassinin is developed starting from indole-3-carboxaldehyde.

Methoxybrassinin (1) is a phytoalexin isolated by Takasugi and co-workers[2] from Chinese cabbage Brassica campestris L. ssp. pekinensis and has a unique structure involving thiocarbamate side chain and 1-methoxyindole skeleton. Since the compound (1) is an example of methylated derivatives[3] of 1-hydroxyindoles, we have been much interested in it because we have a hypothesis[4] that 1-hydroxyindoles would be in vivo intermediates in the metabolism of indole compounds. Furthermore, considering that 1 and various 1-methoxyindole derivatives are contained in the plant family Cruciferae[2,5] and we take them from daily vegetables (cabbage, radish, turnip, etc.) in a significant quantity,[5] it is quite important and urgent to study their biological activities. For pursuing the study, we need much quantity of 1. Now, we report an alternative[6] and a simple multi-gram scale synthetic method for 1.

Reduction of indole-3-carbonitrile (3),[7] with lithium aluminum hydride in tetrahydrofuran (THF) afforded 3-aminomethylindole[6,8] (4, mp 89-90.5°C) in 69% yield (Scheme 1). The compound (4) could also be produced directly

from indole-3-carboxaldehyde (2) in 13% yield by the treatment with ammonium acetate and sodium cyanoborohydride ($NaBH_3CN$) in acetic acid (AcOH). The reaction of 4 with carbon disulfide (CS_2), followed by the treatment with methyl iodide (MeI), afforded brassinin[2] (5) in 89% yield. Subsequent reduction of 5 with $NaBH_3CN$ in AcOH produced 2,3-dihydroindole (6, oil) in 87% yield. Its structure was confirmed by the acetylation with acetic anhydride (Ac_2O) resulting in the formation of diacetyl (7, oil) and monoacetyl compound (8, mp 153-154°C) in 31% and 65% yields, respectively. Unfortunately, sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$) catalyzed oxidation[3,4] of 6 with 30% hydrogen peroxide (H_2O_2) and subsequent treatment with diazomethane (CH_2N_2) did not produce the desired 1.



a: R = $-COCH_3$, b: R = $-COCF_3$

Scheme 1

Therefore, 3-aminomethylindole (4) was converted to its acetyl (9a, mp 135.0-136.5°C) or trifluoroacetyl derivative (9b, mp 113-114°C) in 88% or 91% yield by treatment with either Ac_2O or ethyl trifluoroacetate[9] in THF. Trifluoroacetylation of 4 with trifluoroacetic anhydride and pyridine afforded rather poor result (57%). Although reduction of 9a with $NaBH_3CN$ in AcOH afforded 2,3-dihydroindole (10a, mp 90-91.5°C) in 93% yield, the reduction of 4 gave many unidentified products under the same reaction conditions. Treatment of 9b with triethylsilane[10] in trifluoroacetic acid afforded 2,3-dihydroindole (10b, mp 100.5-101.0°C) in 82% yield. Catalytic oxidation of 10a or 10b with $Na_2WO_4 \cdot 2H_2O$ and 30% H_2O_2, followed by methylation of the resultant 1-hydroxyindole with CH_2N_2, produced 11a (mp 132.5-133°C) or 11b (mp 70.5-71°C) in 59% or 77% yields, respectively. Subsequent alkaline hydrolysis of 11a and 11b in methanol-water produced 3-aminomethyl-1-methoxyindole (12, oil) in 34% and 98% yields, respectively. The compound (12) was readily converted to 1 with CS_2 and MeI by the reported procedure[2,6] in 64% yield.

In conclusion, methoxybrassinin (1) is readily available from indole-3-carboxaldehyde (2) in seven (or six) steps in 12% overall yield with an originality rate[11] of 25%. Preparation of various derivatives of 1 and 12, and their biological evaluations are in progress.

REFERENCES AND NOTES

1. Dedicated to Prof. M. Hamana on the occasion of his 75th birthday. This report is part 58 of a series entitled "The Chemistry of Indoles". Part 57: See reference 4b.
2. M. Takasugi, N. Katsui, and A. Shirata, J. Chem. Soc., Chem. Comm., 1986, 1077; M. Takasugi, K. Monde, N. Katsui, and A. Shirata, Bull. Chem. Soc. Japan, 1988, 61, 285.
3. References are cited in the following paper's reference number 3: M. Somei and T. Kawasaki, Heterocycles, 1989, 29, 1251.

4. 1-Hydroxytryptophan[4b] would initially be produced from tryptophan in vivo and become a common intermediate for the biosynthesis of various indole alkaloids, such as pyrrolo[2,3-b]indoles, 4-substituted indoles, 4-oxoazetizin-2-spiro-3'-(2'-oxindole) derivatives, and so on. 1-Hydroxytryptophan could also play a role in vivo for detoxification of alkylating substances, forming 1-alkoxytryptophan. a) Review: M. Somei, Yuki Gosei Kagaku Kyokai Shi, 1991, 49, 205; b) M. Somei, T. Kawasaki, K. Shimizu, Y. Fukui, and T. Ohta, Chem. Pharm. Bull., 1991, 39, 1905; c) T. Kawasaki, A. Kodama, T. Nishida, K. Shimizu, and M. Somei, Heterocycles, 1991, 32, 221.

5. G. R. Fenwick, R. K. Heaney, and W. J. Mullin, CRC Critical Rev. Food Sci. Nutr., 1983, 18, 123; A. B. Hanley, P. S. Belton, G. R. Fenwick, and N. F. Janes, Phytochemistry, 1985, 24, 598; R. McDanell, A. E. M. McLean, A. B. Hanley, R. K. Heaney, and G. R. Fenwick, Fd. Chem. Toxic., 1988, 26, 59; A. B. Hanley and K. R. Parsley, Phytochemistry, 1990, 29, 769 and references cited therein.

6. T. Kawasaki and M. Somei, Heterocycles, 1990, 31, 1605.

7. H. M. Blatter, H. Lukaszewski, and G. de Stevens, "Organic Syntheses", Coll. Vol. 5, ed. by H. E. Baumgarten, John Wiley and Sons, Inc., New York, 1973, p. 656.

8. J. Schallenberg and E. Meyer, Z. Naturforsch., 1983, 38b, 108.

9. T. J. Curphey, J. Org. Chem., 1979, 44, 2805.

10. Z. N. Parnes, V. A. Budylin, E. Y. Beilinson, and A. N. Kost, Zhur. Org. Khim., 1972, 8, 2564 [Chem. Abstr., 1973, 78, 84176h].

11. M. Somei, Yuki Gosei Kagaku Kyokai Shi, 1982, 40, 387; M. Somei, Advances in Pharmaceutical Sciences, The Research Foundation for Pharmaceutical Sciences, 1985, 1, 45; M. Somei, Yakugaku Zasshi, 1988, 108, 361 and references cited therein.

Received, 17th October, 1991