

A simple synthesis of a phytoalexin, methoxybrassinin

著者	Somei Masanori, Kobayashi Kensuke, Shimizu Kazuhisa, Kawasaki Toshiya
journal or publication title	Heterocycles
volume	33
number	1
page range	77-80
year	1992-01-01
URL	http://hdl.handle.net/2297/4323

doi: <https://doi.org/10.3987/com-91-s20>

A SIMPLE SYNTHESIS OF A PHYTOALEXIN, METHOXYBRASSININ¹

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

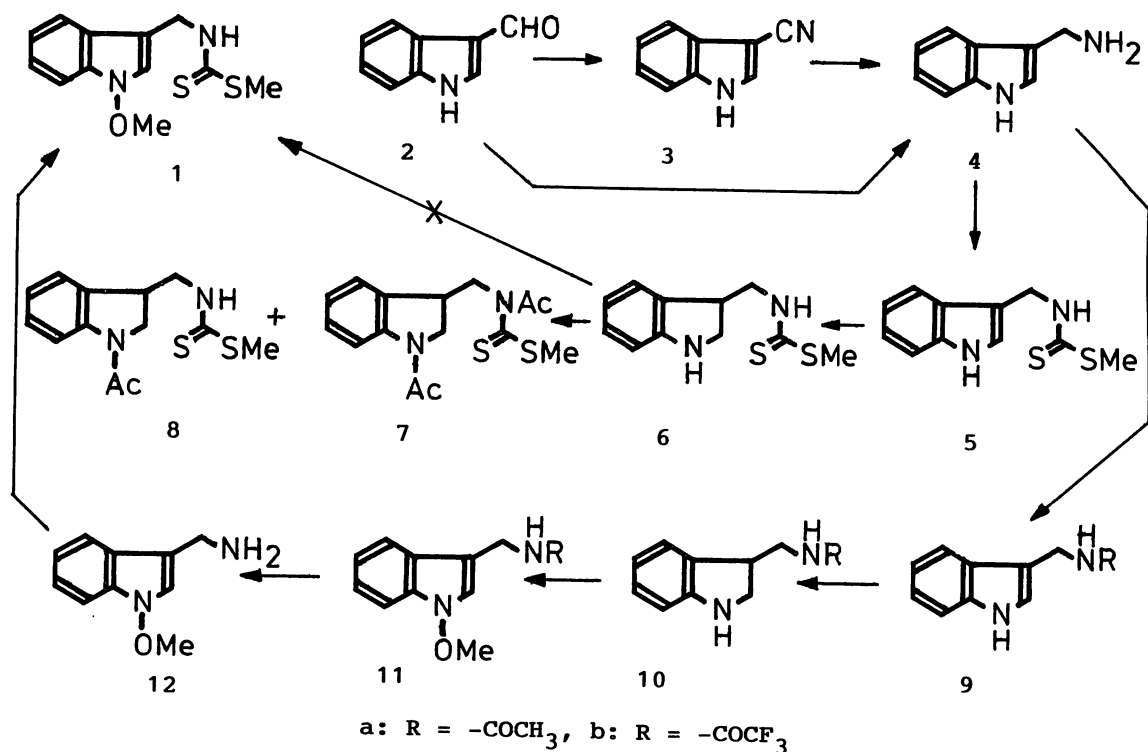
Faculty of Pharmaceutical Sciences, Kanazawa University
13-1 Takara-machi, Kanazawa 920, Japan

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-workers² 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 derivatives³ of 1-hydroxyindoles, we have been much interested in it because we have a hypothesis⁴ 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 alternative⁶ 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 brassinin² (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 ($\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$) 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.



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 Ac₂O or ethyl trifluoroacetate⁹ in THF. Trifluoroacetylation of 4 with trifluoroacetic anhydride and pyridine afforded rather poor result (57%). Although reduction of 9a with NaBH₃CN 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 triethylsilane¹⁰ in trifluoroacetic acid afforded 2,3-dihydroindole (10b, mp 100.5–101.0°C) in 82% yield. Catalytic oxidation of 10a or 10b with Na₂WO₄·2H₂O and 30% H₂O₂, followed by methylation of the resultant 1-hydroxyindole with CH₂N₂, 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 CS₂ 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 rate¹¹ 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