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A SIMPLE SYNTHESIS OF A PHYTOALEXIN, METHOXYBRASSININ¹

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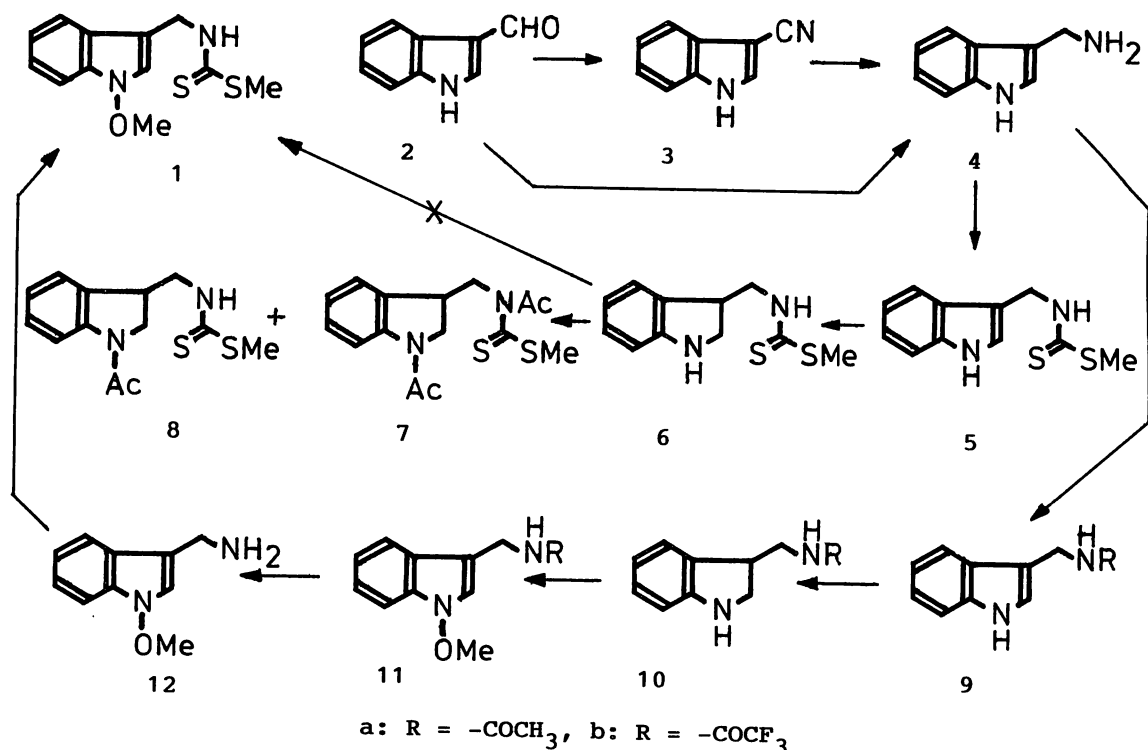
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Abstract ——— A simple and an alternative multi-gram scale synthetic method for methoxybrassinin is developed starting from indole-3-carboxaldehyde.

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.

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