A simple synthesis of a phytoalexin, methoxybrassinin

A SIMPLE SYNTHESIS OF A PHYTOALEXIN, METHOXYBRASSININ[1]

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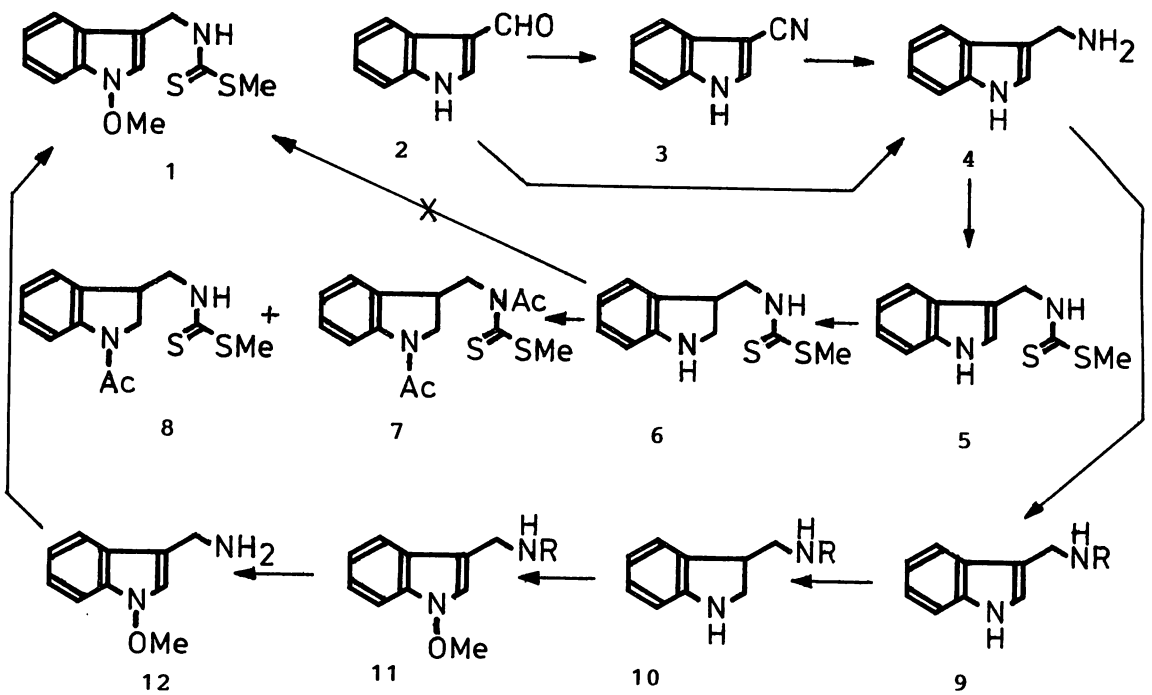
Abstract ——— A simple and an alternative multi-gram scale synthetic method for methoxybrassinin is developed starting from indole-3-carboxaldehyde.

Methoxybrassinin (1) is a phytoalexin isolated by Takasugi and co-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.

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