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著者	Somei Masanori, Funamoto Tetsuo, Ohta Toshiharu
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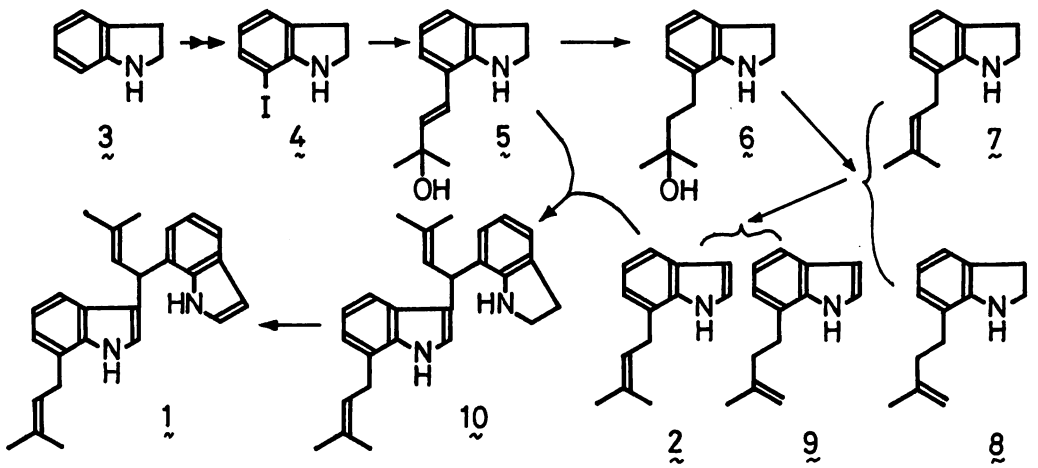
TOTAL SYNTHESES OF INDOLE ALKALOIDS, ANNONIDINE A AND 7-(3-METHYL-2-BUTEN-1-YL)INDOLE[1]

Masanori Somei,* Tetsuo Funamoto, and Toshiharu Ohta
Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1 Takara-machi, Kanazawa 920, Japan

Abstract ——— Practical total syntheses of annonidine A and 7-(3-methyl-2-buten-1-yl)indole are reported.

Achenbach and co-workers[2] isolated annonidine A (1) and 7-(3-methyl-2-buten-1-yl)-indole[3a] (2) from the stem bark of the west african medicinal plant, Annonidium Mannii Engl. & Diels (Annonaceae) in 1985. We are much interested in annonidine A because of its hitherto unknown prenylated bisindole structure. In this report, we describe the total syntheses of annonidine A and 7-(3-methyl-2-buten-1-yl)indole.[3b] We have already reported a convenient and practical synthetic method for 2,3-dihydro-7-iodoindole (4) from 2,3-dihydroindole (3) in three steps in 62% overall yield.[4] Heck reaction of 4 with 2-methyl-3-buten-2-ol in the presence of a catalytic amount of palladium acetate in N,N-dimethylformamide afforded 4-(2,3-dihydroindol-7-yl)-2-methyl-3-buten-2-ol (5, mp 85.0-86.5°C) in 74% yield.[4b] Catalytic hydrogenation of 5 over 10% palladium/carbon at an atmospheric pressure produced 4-(2,3-dihydroindol-7-yl)-2-methyl-3-butanol (6, mp 88-90°C) in 87% yield. Subsequent treatment of 6 with p-toluenesulfonic acid in refluxing benzene afforded 95% yield of an inseparable mixture of 2,3-dihydro-7-(3-methyl-2-buten-1-yl)indole (7) and its double bond isomer (8) in the ratio of 13:1. Oxidation of the mixture with dioxygen in the presence of a catalytic amount of salcomine[5] in methanol at room temperature for 2 h afforded 7-(3-methyl-2-buten-1-yl)indole [2, mp 43.5-44.0°C (lit.[2] mp 43-44 °C)] and its double bond isomer (9, mp 18-19°C) in 75% and 3% yields, respectively. Condensation of 2 and 5 in tetrahydrofuran by the action of 2N-hydrochlolic acid produced regiospecifically 3-[1-(2,3-dihydroindol-7-yl)-3-methyl-2-buten-1-yl]-7-(3-methyl-2-buten-1-yl)indole (10, viscose oil) in 78% yield. Subsequent salcomine[5] catalyzed oxidation with dioxygen afforded 3-[1-(indol-7-yl)-3-methyl-2-buten-1-yl]-

7-(3-methyl-2-buten-1-yl)indole [1, mp 105-108°C (lit.[2] mp 106-108°C)] in 65% yield. Spectral data of 1 and 2 were identical with those of the natural alkaloids. Since the present method is simple and practical, synthesis of various derivatives and evaluations of their pharmacological activities are currently in progress.



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