SYNTHETIC APPROACH TO DITERPENE ALKALOIDS —— A SIMPLE AND NOVEL SYNTHESIS OF THE A,B,C AND D RING PART FROM 1-BENZYL-1,2,3,4-TETRAHYDROISOQUINOLINE

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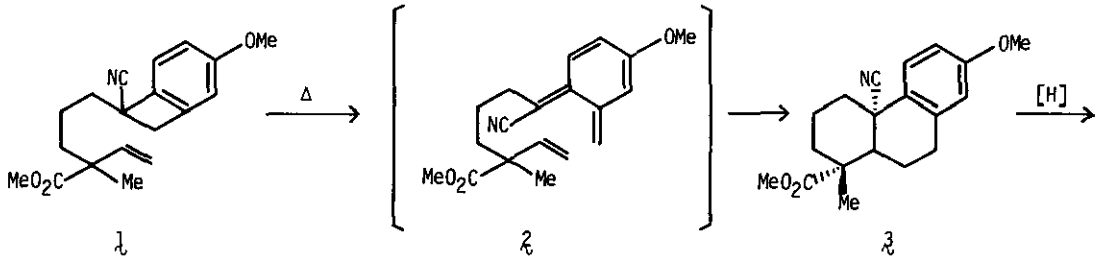
Abstract —— The synthesis of the A,B,C and D ring part (13) of diterpene alkaloid atisine (5) from 1-benzyl-1,2,3,4-tetrahydroisoquinoline (6) by use of an intramolecular Diels-Alder reaction is described.

Previously we[1] reported a new construction of A,B,C and E ring part (4) of diterpene alkaloids, which had been correlated to atisine (5)[2], by an intramolecular Diels-Alder reaction of the o-quinodimethane (2) derived from the benzocyclobutene (1) and then a reduction of the resulting tricyclic compound (3). Continuing a synthetic approach to diterpene alkaloids, we have been investigating a new construction of diterpene alkaloid ring system, and here report a simple synthesis of the A,B,C and D ring part of atisine (5) from 1-benzyl-1,2,3,4-tetrahydroisoquinoline (6), easily available, using an intramolecular Diels-Alder reaction as a key step.

Chart 1



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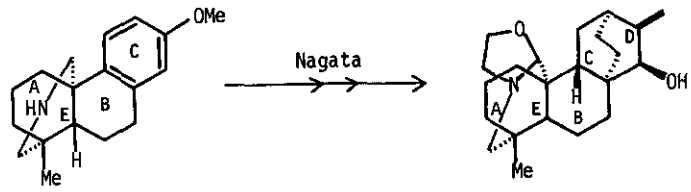
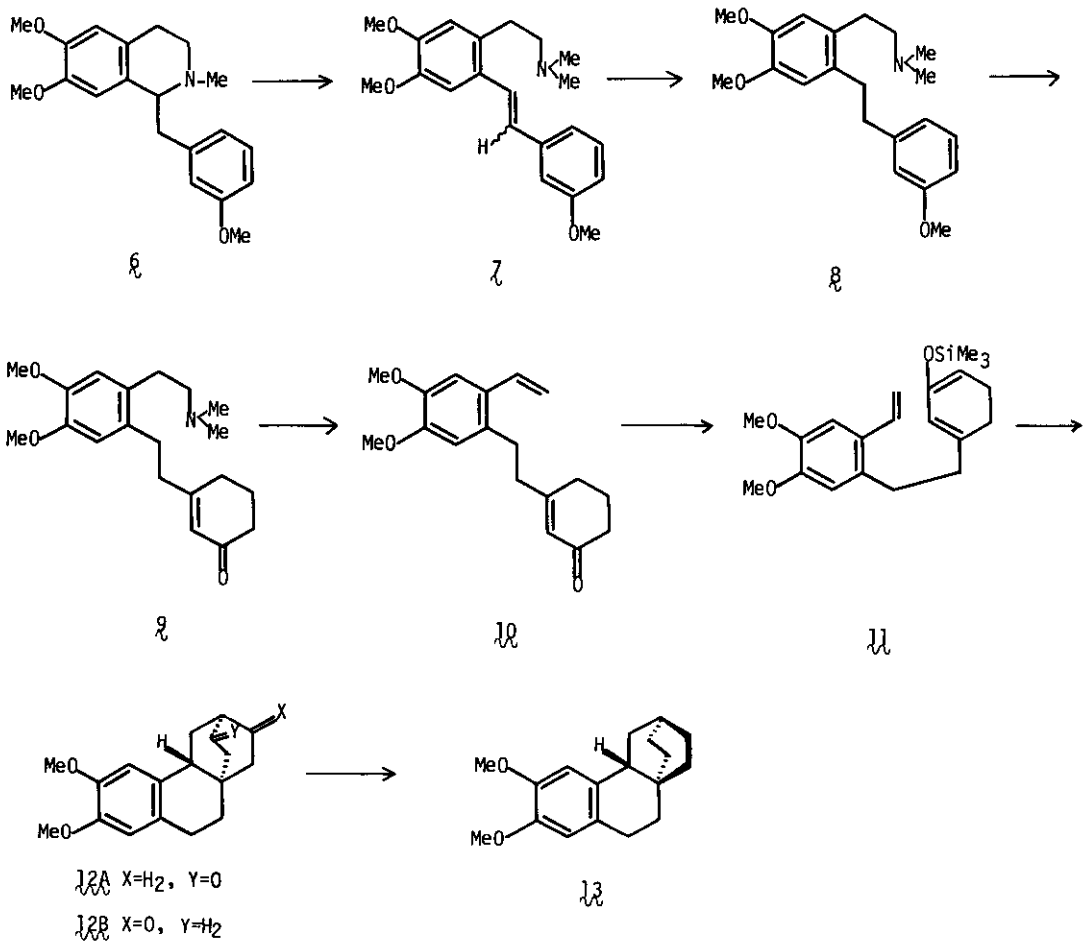


4 5

Hofmann reaction of 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3-methoxybenzyl)-2-methylisoquinoline (6)[3], followed by a catalytic hydrogenation of the resulting methine base (7)[4] on 10 % Pd-C under 5 atoms of hydrogen in methanol, gave the dihydromethine base (8)[4] [m/e 343 (M^+)]. Birch reaction of 8 with lithium in liquid ammonia in the presence of isopropanol afforded the reduction product which was hydrolized with 10 % hydrochloric acid in methanol at room temperature to furnish the enone (9)[4] [m/e 331 (M^+); ν_{max} ($CHCl_3$) 1660 and 1620 cm^{-1}; δ($CDCl_3$) 2.30 (6H, s, NMe_2), 5.91 (1H, s, olefinic H)]. Treatment of 9 with m-chloroperbenzoic acid in methylene dichloride at 0°C gave the corresponding N-oxide which was without purification thermolyzed at 110°C in xylene for 2 h in a current of nitrogen to afford the des N-methine type of compound (10)[4] [m.p. 77.5 ∿ 78.0°C; m/e 286 (M^+); ν_{max} ($CHCl_3$) 1660 and 1620 cm^{-1}; δ($CDCl_3$) 5.16 (1H, dd J 10 and 2 Hz, $H\rangle C=C\langle \underline{H}$), 5.66 (1H, dd, J 12 and 2 Hz, $H\rangle C=C\langle \underline{H}$), 5.76 (1H, s, CH=CO)]. This olefin (10) was also obtained from 9 by a usual Hofmann degradation through the methiodide of 9. A kinetically controlled enolization[5] of the enone system of 10 with LDA in THF at 0°C for 2 h, followed by a treatment with trimethylsilyl chloride gave the unstable diene (11) which was immediately heated at 200°C in toluene for 9.5 h in a sealed tube and then hydrolyzed with 1 % hydrochloric acid in methanol to afford the cycloaddition compound (12A)[4] [m.p. 137 ∿ 138°C; m/e 286 (M^+); ν_{max} ($CHCl_3$) 1720 cm^{-1}; δ($CDCl_3$) 1.22 ∿ 3.10 (14H, m), 3.85 (6H, s, 2 x OMe), 6.54 and 6.60 (each 1H, s, aromatic H)] and its stereoisomer (12B) (oil)[6] in a ratio[7] of 5 : 2 in 57 % yield[8]. Treatment of 12A with ethanedithiol in the presence of boron trifluoride etherate in methylene dichloride at room temperature for 1 h gave the dithio ketal [δ($CDCl_3$) 3.10 ∿ 3.40 (4H, $-SCH_2CH_2S-$)] which was subjected to desulfurization reaction with Raney nickel in ethanol to afford in 92 % yield the tetracyclic compound (13)[4] [m.p. 72 ∿ 73°C; m/e 272 (M^+); δ($CDCl_3$) 0.90 ∿ 2.96 (16H, m), 3.84 (6H, s, 2 x OMe), 6.52 and 6.68 (each 1H, s, aromatic H)]. This compound was also prepared from a mixture of 12A and 12B by the same treatment

with the case of 12A. Thus we could achieve a novel conversion of 1-benzyl-isoquinoline into atisine system, and now we are investigating a synthesis of atisirene by the intramolecular cycloaddition.

Chart 2



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3. I. Baxter, L. T. Allan, and G. A. Swan, J. Chem. Soc., 1965, 3645.

4. All new compounds revealed a correct microanalysis and a reasonable i.r. and n.m.r. spectra for the assigned structure.
5. H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, J. Org. Chem., 1969, 34, 232.
6. The compound (12B) was inseparable from 12A by ordinary chromatographies.
7. This is determined by a comparison of the ratio of methyl resonances [the acetates from 12A: $\delta(CDCl_3)$ 1.96 and 2.05; the acetates from 12B: $\delta(CDCl_3)$ 2.07 and 2.10] of acetoxyl group of the acetates, which were prepared by a reduction of the crude mixture of 12A and 12B with sodium borohydride, followed by an acetylation of the resulting crude alcohol with acetic anhydride and pyridine.
8. The yield is not optimized.

Received, 12th June, 1981