FORMAL TOTAL SYNTHESES OF DITERPENE ALKALOIDS ATISINE, GARRYINE AND VEATCHINE

Tetsuji Kametani, Keiichiro Fukumoto, Yasuyuki Kato,
Toshio Honda, and Fumio Satoh
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980

Hydrophenanthrene synthesis was examined by thermolysis of 1-cyano-4-methoxy-1-(4-methoxycarbonyl-4-vinyl)pentylbenzocyclobutene (1) which was prepared as follows. 2-Bromo-5-methoxybenzaldehyde was treated with cyanoacetic acid to give the corresponding cinnamic acid, whose reduction with sodium borohydride, followed by decarboxylation, afforded 2-bromo-5-methoxyphenylpropiononitrile. Treatment of this nitrile with sodium amide in liq. ammonia gave 1-cyano-4-methoxybenzocyclobutene (2). The condensation of 2 with mehtyl 4-iodo-1-methyl-1-vinylvalerate, prepared from methyl methylacetoacetate in four steps, in the presence of sodium amide furnished the starting material (1). Thermolysis of 1 in dry benzene below 230° in an autoclave gave (±)-4aα-cyano-1,2,3,4,4a,9,10,10aα-octahydro-7-methoxy-1α-methoxycarbonyl-1β-methylphenanthrene (3) in stereoselective and regioselective manner. On the other hand, thermolysis of 1 over 230° afforded regioselectively 3 and 10aβ-epimer (4). The former product (3) was converted into the latter (4) by oxidation with chromic acid, followed by bromination, dehydrobromination with N-phenylbenzamidine and hydrogenation. The structure of 4 was confirmed by conversion into the known (±)-1α-carboxy-1,2,3,4,4aα,10,10aβ-octahydro-7-methoxy-1β-methylphenanthrene.

Catalytic reduction of 4 gave the lactam, which was reduced with lithium aluminum hydride to afford 16,17-imino-13-methoxy-5β,10α-podocarpane-8,11,13-triene. This compound was correlated with diterpene alkaloids, atisine, garryine and veatchine. Thus, a formal total synthesis of these alkaloids has been accomplished.