THE TOTAL SYNTHESIS OF (±)-EPI-IBOGAMINE USING THE DIELS-ALDER REACTION OF 2-PYRIDONE

Hiroshi Tomisawa, Hiroshi Hongo, Hideki Kato, Reiko Fujita,
Takafumi Naraki, and Kumi Sato
Tohoku College of Pharmacy,
Komatsushima, Sendai 983, Japan

The Diels-Alder reactions of 1-methyl- and 1-benzyl-2(1H)-pyridone (I and II) with methyl acrylate (III) and acrylonitrile produced mainly the appropriate substituted isoquinuclidine derivatives which are easily accessible to iboga alkaloids. The short total synthesis of (±)-*epi-ibogamine* and the formal total synthesis of (±)-desethylibogamine employing the adducts were achieved as outlined below.

The adduct (IV) obtained by the Diels-Alder reaction (17% yield) of II with III was reduced with $LiAlH_4$ to give the methylol (V) in 80% yield. Tosylation (94%) and Grignard reaction (72%) gave the isoquinuclidine (VIa). Treatment of VIa with 2-(3-indolyl)ethyl bromide (90%) and subsequent debenzylation with C_3H_7SLi (33%) afforded the indolylethylisoquinuclidine (VIIa). Cyclization to (±)-epi-ibogamine was performed by the reaction of VIIa with $(MeCN)_2PdCl_2$, $AgBF_4$, and Et_3N, followed by $NaBH_4$ reduction in 20% yield. The formal total synthesis of (±)-desethylibogamine was accomplished using the dicarboxylic acid (VIII)(41%) prepared by hydrolysis of the Diels-Alder adduct of II and maleic anhydride. Catalytic reduction (99%) of VIII and subsequent decarboxylation with $Pb(OAc)_4$ (43%) gave the olefin (IX). The isoquinuclidine (VIb) obtained by reduction (90%) of IX was converted by the above-mentioned sequences into the indolylethylisoquinuclidine (VIIb)(3.7% from VIb), which had already been transformed into (±)-desethylibogamine by Trost and Genêt.