A NOVEL AND STEREOSELECTIVE SYNTHESIS OF CIS-1,8-H-1-HYDROXYPYRROLIZIDINE

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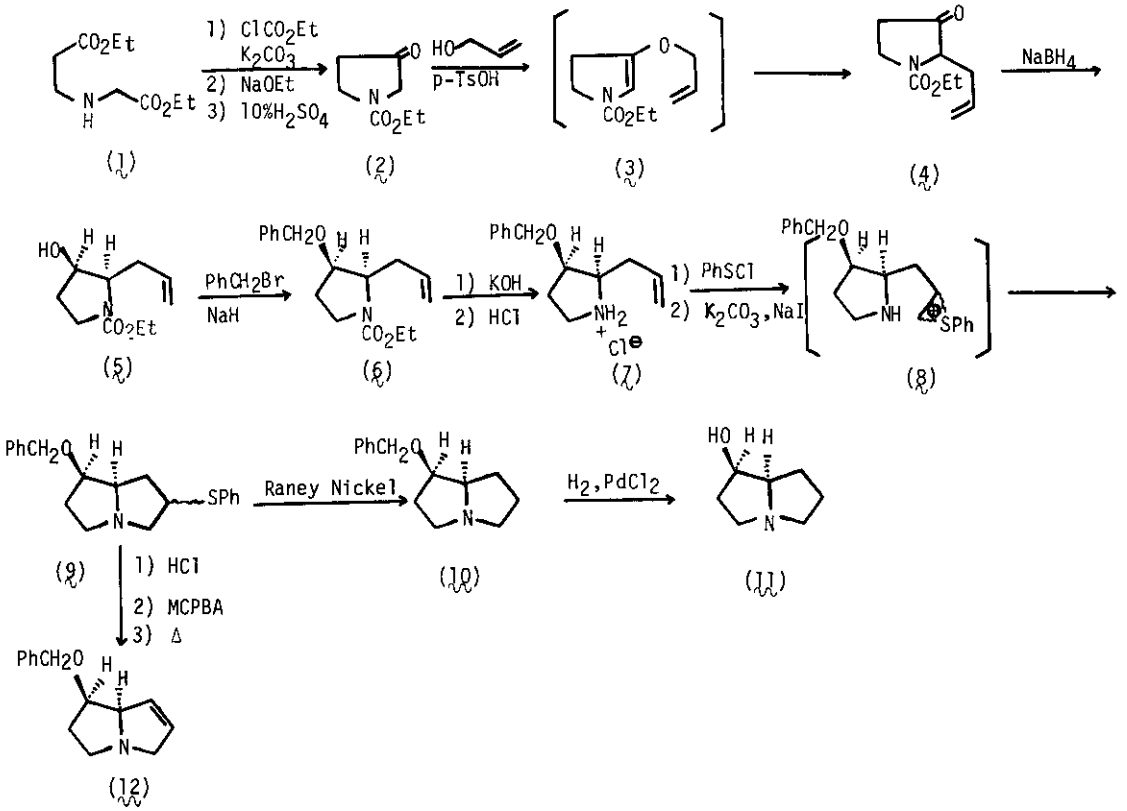
Abstract — The title compound was synthesized through a regioselective introduction of allyl group at the C_2 position of the 3-oxopyrrolidine derivative (2) by [3,3] sigmatropic rearrangement and an amino cyclization via the episulfonium intermediate (8) by key steps.

Recently, there are many reports concerning with syntheses of pyrrolizidine alkaloids and their derivatives. Their wide range of biological activities has made them particularly attractive synthetic target.[1] We have been also interested in a facile and general method for constructing their ring system. In the course of this investigation, we disclosed a regioselective allyl introduction to the 3-oxopyrrolidine (2) by [3,3] sigmatropic rearrangement and amino cyclization of olefinic amines by addition of benzenesulfenyl chloride followed by base-induced ring closure.[2] Here we report a novel stereoselective synthesis of cis-1,8-H-1-hydroxypyrrolizidine (11) using above reactions as key reactions.

The 3-oxopyrrolidine derivative (2), readily prepared from the amino diester (1)[3] in a high yield, was refluxed in xylene with allyl alcohol in the presence of catalytic amount of p-toluenesulfonic acid and sodium sulfate[4] to afford, most probably through an allyl ether intermediate (3), a single product in 48.8 % yield (based on unrecovered starting material), whose structure (4)[5] was assigned on the basis of the spectral data [IR ($CHCl_3$) 1695, 1760 (C=O); NMR (CCl_4) δ 1.27 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 4.13 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$), 4.83 ~ 6.10 (3H, m, olefinic protons)] and the observation that one of hydrogens at the C_2 position of the starting pyrrolidine (2) disappeared in the NMR spectrum of (4). The ketone (4) was subsequently reduced stereoselectively to give the alcohol (5)[5] in 62 % yield. The stereochemistry was assumed to be cis, which was established by its conversion to the known final product (11). The alcohol (5) was protected as the benzyl ether (6)[5] by a reaction with benzyl bromide and sodium hydride in dimethylformamide with a yield of 79.3 %. After hydrolysis of the carbamate (6) with potassium hydroxide in diethylene glycol, the hydrochloride (7) of the resulting amine, without purification, was treated with benzenesulfenyl chloride in dry methylene chloride to

produce adducts as a mixture of regioisomers in 73.5 % yield from (6), which was immediately cyclised by a treatment with potassium carbonate and sodium iodide in refluxing acetonitrile to furnish the desired pyrrolizidine (9)[5] as a mixture of two stereoisomers in 66 % yield after purification by chromatography on silica gel. This reaction was presumed to proceed via an episulfonium intermediate such as (8). The benzenesulfenyl group was easily removed by Raney nickel in ethanol to afford the compound (10)[5], which was subsequently debenzylated by hydrogenolysis on palladium chloride in methanol and a few drops of chloroform under hydrogen atmosphere. The product so obtained in 72 % yield after chromatography on neutral alumina (grade III), was ascertained to be cis-1,8-H-1-hydroxypyrrolizidine (11)[5] because of the identity with the authentic one prepared by the known method.[6] Furthermore, the hydrochloride of the sulfide (9) could be converted to the olefinic compound (12)[5] by a treatment with m-chloroperbenzoic acid in methylene chloride at -20° followed by heating in xylene.

Thus a regioselective [3,3] sigmatropic rearrangement and an amino cyclization induced by the addition of benzenesulfenyl chloride followed by base treatment provide a new entry for the construction of pyrrolizidine ring system. Syntheses of pyrrolizidine alkaloids using this methodology are under investigation.



(1) (2) (3) (4) (5) (6) (7) (8) (9) (10) (11) (12)

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