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A NEW APPROACH TO THE SYNTHESIS OF A LYTHRACEAE ALKALOID, LASUBINE II

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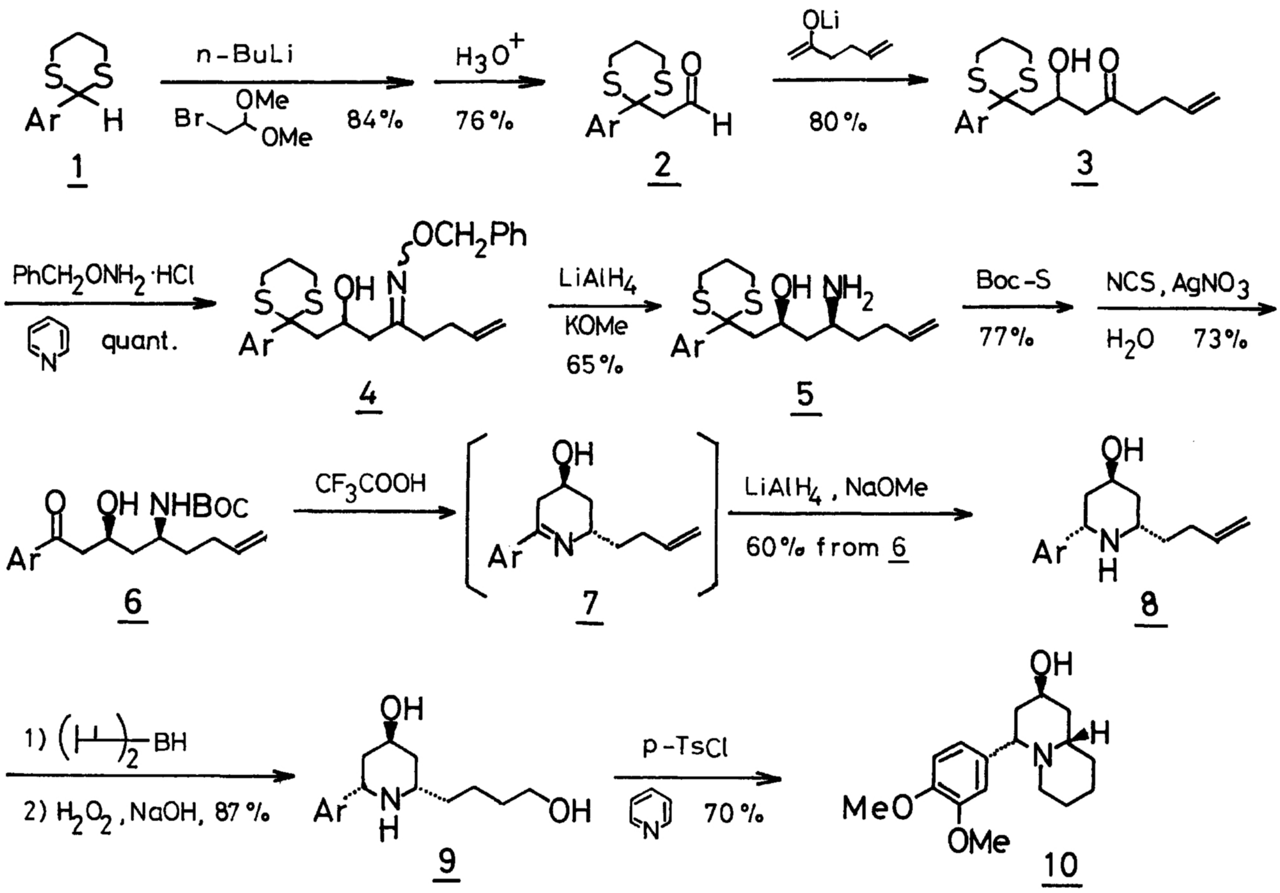
A lythraceae alkaloid, (±)-lasubine II, is synthesized via an acyclic *syn*-1,3-amino alcohol which is derived stereoselectively from a β-hydroxy ketone.

Generally, lythraceae alkaloids have been synthesized by the condensation of isopelletierine with aromatic aldehydes[1] or a [2+3] cycloaddition of tetrahydropyridine N-oxide.[2] Recently, we reported an efficient method for the preparation of *syn*-1,3-amino alcohols by the stereoselective reduction of acyclic β-hydroxy ketone O-benzyloximes.[3] By applying this method, a new route to the synthesis of a lythraceae alkaloid, lasubine II (10),[4] has been accomplished. In this strategy, the key intermediate, an acyclic *syn*-1,3-amino alcohol 5, was prepared stereoselectively from a β-hydroxy ketone 3, and successive cyclization processes afforded (±)-lasubine II in a stereoselective manner.

Firstly, the β-hydroxy ketone 3 was prepared from veratraldehyde. 2-(3,4-Dimethoxyphenyl)-1,3-dithiane (1) derived from veratraldehyde[5] was alkylated with 2-bromo-1,1-dimethoxyethane and the product was hydrolyzed to an aldehyde 2. Then the aldol reaction of the aldehyde 2 with the kinetic enolate of 5-hexen-2-one afforded the β-hydroxy ketone 3 in 80% yield, in which the whole carbon skeleton for lasubine II (10) was arranged. The aldol product 3 was converted to the corresponding O-benzyloxime 4 as an almost 1:1 mixture of *syn* and *anti*-O-benzyloximes. Stereoselective reduction of 4 was achieved by the treatment with lithium aluminum hydride (LAH) in the presence of potassium methoxide in THF (-78 → -15 °C) to yield the *syn*-1,3-amino alcohol 5 in 65% yield.[6]

The ring construction to a quinolizidine skeleton was performed by the following procedures. After the protection of the amino group of 5 by t-butoxycarbonyl group, the thioacetal group was hydrolyzed to generate a hydroxy ketone 6. Deprotection of the amino group with trifluoroacetic acid in dichloromethane spontaneously yielded a labile cyclic imine 7, which was immediately reduced with LAH in the presence of sodium methoxide to furnish the 2,6-*cis*-piperidine 8 stereoselectively.[7] Hydroboration utilizing disiamylborane and the successive oxidation afforded a diol 9, and the treatment with p-toluenesulfonyl chloride in pyridine gave (±)-lasubine II (10).[8]

Thus the stereoselective synthesis of lasubine II has been achieved via an acyclic intermediate, demonstrating a new and useful strategy for the preparation of lythraceae alkaloids.



Ar= 3,4-dimethoxyphenyl

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8) ^{1}H NMR (400 MHz) and IR spectra of the synthetic (±)-lasubine II (10) was identical with those of the natural lasubine II. And Mass spectrum completely agreed with those values reported by C. Kibayashi.[2]

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