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

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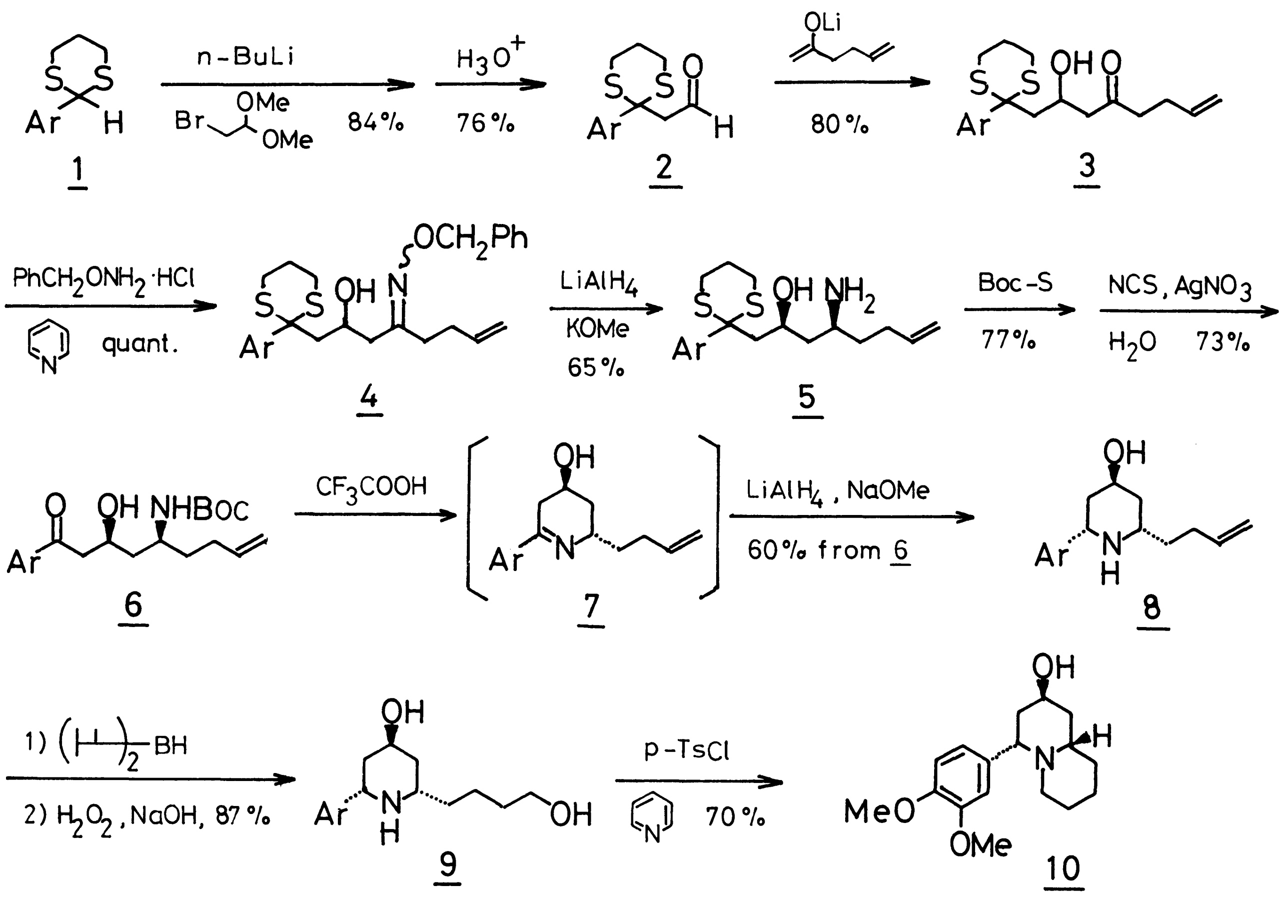
A lythraceae alkaloid, (±)-lasubine II, is synthesized via an acyclic *syn*-1,3-amino alcohol which is derived stereoselectively from a β-hydroxy ketone.

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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References

1) W. M. Golebiewski and J. T. Wrobel, "The Alkaloids," ed by R. G. A. Rodrigo, Academic Press, Inc. New York (1981), Vol. 18, Chap. 4.
2) H. Iida, M. Tanaka, and C. Kibayashi, J. Org. Chem., 49, 1909 (1984) and the references cited therein.
3) K. Narasaka, S. Yamazaki, and Y. Ukaji, Chem. Lett., 1984, 2065.
4) For the isolation of lasubine II, see: K. Fuji, T. Yamada, E. Fujita, and H. Murata, Chem. Pharm. Bull., 26, 2515 (1978).
5) H. Raumz, Arzneim.-Forsch., 28, 2048 (1978).
6) The *anti*-1,3-amino alcohol was not detectable by ^{13}C NMR spectrum.
7) Y. Matsumura, K. Maruoka, and H. Yamamoto, Tetrahedron Lett., 23, 1929 (1982).
8) ^1H 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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