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REDUCTIVE PHOTOCYCLIZATION OF ENAMIDE IN THE PRESENCE OF A CHIRAL METAL HYDRIDE COMPLEX----- ASYMMETRIC SYNTHESIS OF XYLOPININE

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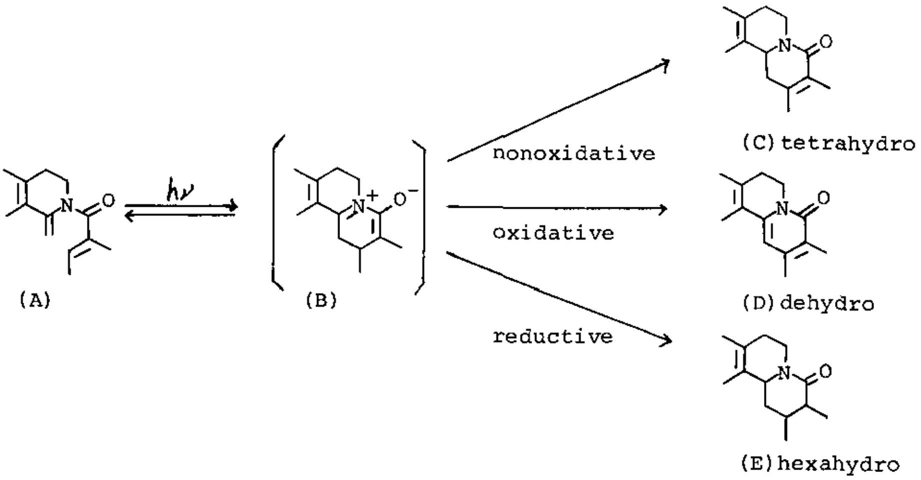
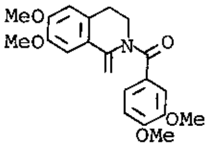
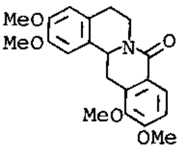
Abstract----- Total synthesis of optically active xylopinine (3b) was achieved by reductive photocyclization of enamide (1) in the presence of a chiral hydride complex.

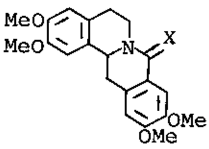
The development of enamide photocyclization as a synthetic strategy has seen rapid growth in the past several years particularly in the field of research on alkaloid synthesis.[1] Under nonoxidative[1], oxidative[1], and reductive[2] conditions, enamide (A) undergoes smooth photochemical cyclization via a common intermediate (B) to afford the tetrahydrolactam (C), dehydrolactam (D), and hexahydrolactam (E), respectively. On an assumption that asymmetric reduction of an intermediate (B) by a chiral metal hydride complex would occur during the course of photolysis of the enamide (A), as exemplified by reductive photocyclization[2], we have undertaken the reductive photocyclization of the enamide (1)[3] in the presence of a chiral metal hydride complex and completed the photochemical asymmetric synthesis of xylopinine.



Among a number of the asymmetric reductions[4] of ketones, enamines, and imines with chiral metal hydride complexes, we chose the well-studied lithium aluminum hydride-quinine complex which is readily prepared from commercially available quinine.


(1)


(2)


(3a) X= O
(3b) X= H_2

To a solution of lithium aluminum hydride (380 mg, 0.01M) in ether (100 ml), a solution of quinine (3.24 g, 0.01M) in tetrahydrofuran (50 ml) was added dropwise at room temperature under nitrogen atmosphere. After stirring at room temperature for 20 min., the enamide (1)[3] (369 mg, 0.001M) dissolved in benzene (350 ml) was added to the above hydride solution at 0°. Irradiation of the resulting solution at 0° with high pressure mercury lamp (with pyrex filter) under nitrogen atmosphere for 75 min. led to the formation of two lactams (2) [22 mg, 6 %, $[\alpha]_D$ -63° (c=0.48, $CHCl_3$)] and (3a)[48 mg, 13 %, $[\alpha]_D$ -102° (c=0.44, $CHCl_3$)], which were separated by column chromatography on silica-gel with ether as eluant and exhibited identical n.m.r. spectra with the authentic lactams[3] respectively. Reduction of the lactam (3a) with lithium aluminum hydride furnished xylopinine (3b), m.p. 159-162°(Et_2O), $[\alpha]_D$ -109° (c=0.06, $CHCl_3$) (lit.[5] $[\alpha]_D$ -297° ($CHCl_3$) in 48 % yield.

Similar irradiation (27 min) of a mixture of the enamide (1)(0.001M) and the dilute solution (500 ml) of the chiral complex (0.01M) of lithium aluminum hydride-quinine (1:1) in a mixture of benzene-tetrahydrofuran (15:1) afforded the lactam (3a)[10 %, $[\alpha]_D$ -71° (c=0.63, $CHCl_3$)] and the amine (3b) [38%, $[\alpha]_D$ -16° (c=1.75, $CHCl_3$)], of which the latter amine was found to be identical with xylopinine upon direct comparison with the authentic sample[3]. Thus, this direct formation of the amine (3b) from the enamide (1), presumably via the optically active lactam (3a) upon reduction with lithium aluminum hydride-quinine complex in benzene-tetrahydrofuran solution, provided a useful synthesis of xylopinine in one manipulation.

In conclusion, the synthesis of optically active xylopinine (3b)(optical activity; 37 %) was achieved by reductive photocyclization of the enamide (1) in the presence of a chiral metal hydride complex and this is the first application of the phtochemical asymmetric synthesis in the isoquinoline alkaloids except the recent report[6] by Kametani and coworkers. Mechanistic study and further application of other chiral metal hydride complexes to reductive photocyclization of enamides are now in progress.

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