TOTAL SYNTHESIS OF OPTICALLY ACTIVE PROTOBERBERINE ALKALOID, XYLOPININE, BY 1,3-ASYMMETRIC INDUCTION IN PHOTOLYSIS

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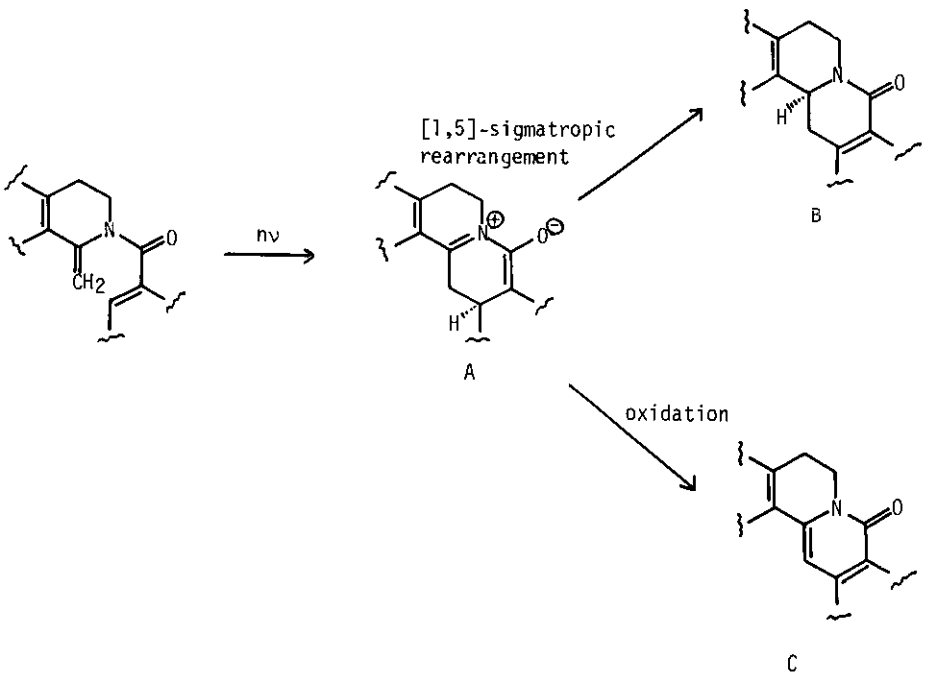
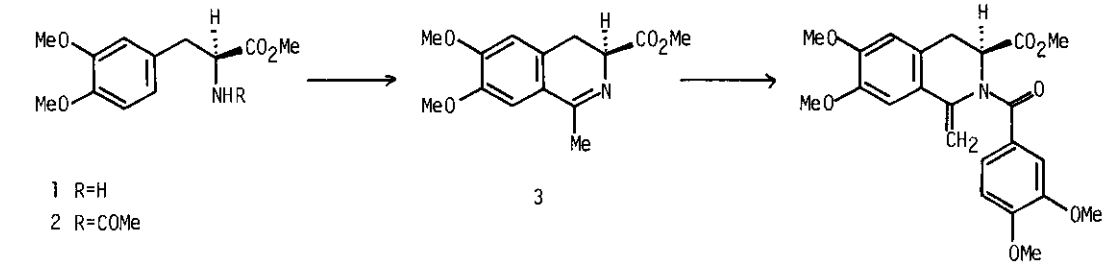
Abstract —— Total synthesis of optically active xylopinine (11) was achieved by irradiation of the enamide (4) as a key reaction.

In the synthesis of a wide range of alkaloids, a photolysis of enamides has been proved to be a very powerful tool,[1-3] and the reaction mechanism, shown in scheme 1, has also been investigated in details.[4] A [1,5]-sigmatropic rearrangement of a



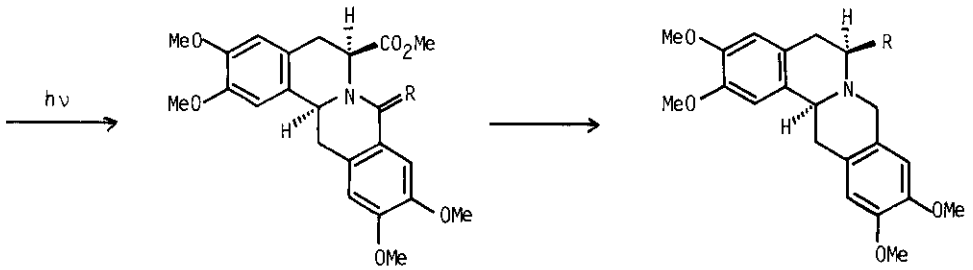
Scheme 1



1 R=H
2 R=COMe

3

4



5 R=O
6 R=H_2

7 R=CO_2H
8 R=CO_2CO_2Et
9 R=$CONH_2$
10 R=CN
11 R=H

Scheme 2

photo-cyclised product (A) leads to a lactam (B), whereas oxidation provides a dehydro-lactam (C). Though optically active isoquinoline alkaloids, i.e. (s)-laudanosine and (s)-reticuline, have been synthesised[5,6] by the asymmetric Pictet-Spengler reaction (1,3-asymmetric induction) of L-phenylalanine derivatives with sodium glycidates, the photochemical asymmetric induction in the synthesis of isoquinoline alkaloids has not been reported up to date. On a consideration of these reactions, it would be a reasonable assumption that the 1,3-asymmetric induction would occur during the photolysis of the enamide prepared from an optically active amino acid, followed by a [1,5]-sigmatropic rearrangement. Thus, the requisite enamide (4) was prepared as follows. Treatment of L-3,4-dimethoxyphenylalanine (1)[7] with acetic anhydride in pyridine afforded the amide (2), which was then cyclised with phosphoryl chloride in acetonitrile at 60°C to give the 3,4-dihydro-1-methylisoquinoline (3). The enamide (4) was synthesised by treatment of 3 with 3,4-dimethoxybenzoyl chloride according to Ninomiya's method.[1] Irradiation of a solution of the enamide (4) in benzene with a high-pressure mercury lamp equipped with a Pyrex filter at room temperature for 5 h furnished the 8-oxoprotoberberine (5)[8] as a main product in 73.3 % yield. Treatment of the lactam (5) with phosphoryl chloride gave the quaternary chloride, which without isolation was reduced with sodium borohydride in methanol to give the amine (6) in 88.8 % yield. Removal of the C_1-unit at the C_6-position from 6 was achieved by adoption of Yamada's procedure[5,6] with slight modification. The ester (6) was hydrolysed with sodium hydroxide in ethanol to the carboxylic acid (7), which was then converted to the amide (9) via the corresponding mixed anhydride (8) in 45.1 % over-all yield from 6. Dehydration of the amide (9) with phosphorus pentoxide and celite in pyridine afforded the nitrile (10), whose decyanation with sodium borohydride furnished xylopinine (11), m.p. 160 - 163°C (EtOH) $[\alpha]_D$ -281° (c = 0.19, $CHCl_3$) [lit.,[9] -297° ($CHCl_3$)] in 66.1 % yield. Thus, the synthesis of optically active xylopinine (optical purity 94.7 %) (11) was achieved by an irradiation of the enamide (4), and this is the first application of 1,3-asymmetric induction in photolysis to the isoquinoline alkaloid synthesis. Thermolysis of the optically active enamide (4) is also under investigation.

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8 M.p. 157 - 158° (MeOH); $\nu_{max.}$ ($CHCl_3$) 1730, 1640 cm^{-1}; δ($CDCl_3$) 3.33 (2H, m, C_5-H); 3.55 (3H, s, CO_2CH_3), 3.75 - 3.93 (12H, 4 x OCH_3), 5.77 (br, 1H, t, J = 8 Hz), C_{13a}-H), 5.55 (1H, m, C_6-H), 6.69 (1H, s, aromatic proton), 6.73 (1H, s, aromatic proton), 6.85 (1H, s, aromatic proton), 8.60 (1H, s, C_9-H).

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