A FACILE SYNTHESIS OF A NUPHAR ALKALOID, NUPHAROLUTINE

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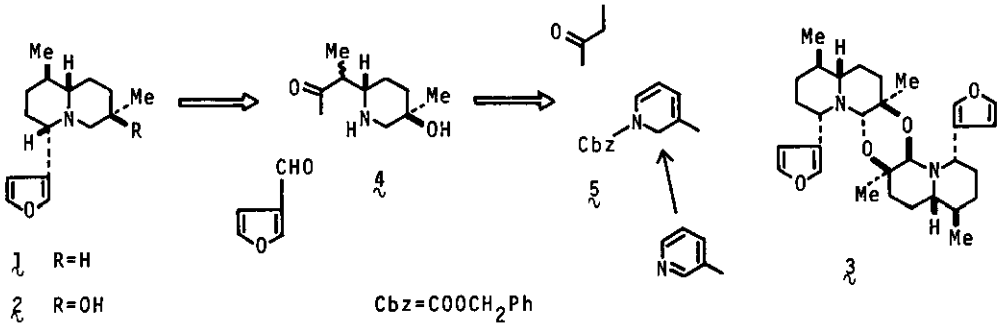
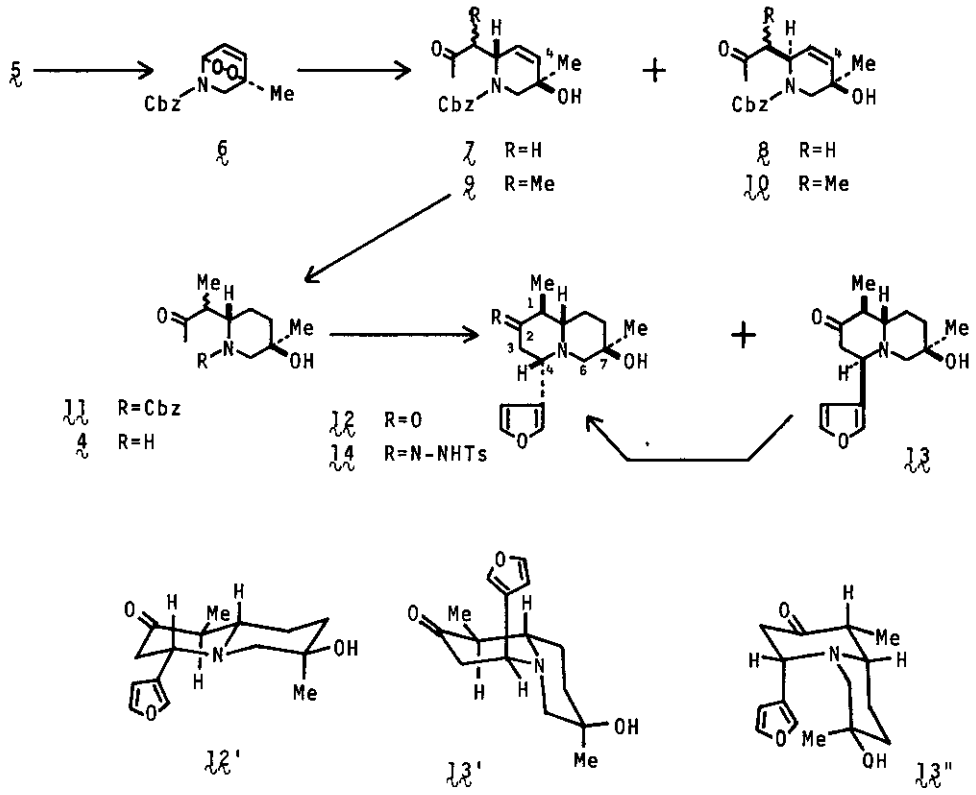
Abstract: A regio- and stereoselective synthesis of (±)-nupharolutine (2) was achieved starting from 3-methylpyridine by utilizing the $SnCl_2$-effected reaction of endoperoxide of a 1,2-dihydropyridine derivative 5.

An alkali catalyzed condensation of isopelletierine with aromatic aldehydes[1] is a well-studied procedure for the syntheses of *Lythraceae* alkaloids[2] and its application to the synthesis of *Nuphar* alkaloids, deoxynupharidine (1) and its epimers has been reported by Hanaoka and co-workers.[3]

When one considers the same condensation for a synthesis of nupharolutine (2), which is isolated from the rhizomes of *Nuphar luteum*[4] and also is a $NaBH_4$ reduction product of a dimeric alkaloid 3 from *Nuphar luteum* subsp. *macrophyllum*,[5] an effective method for the preparation of an isopelletierine derivative 4 seems to be essential. Our $SnCl_2$-effected reaction[6] of an endoperoxide of a dihydropyridine derivative[7] 5 is quite suitable for the regio- and stereoselective production of 4, and we wish to describe here the first synthesis of (±)-2 from 3-methylpyridine, MeCOEt, and 3-furylaldehyde.





In the previous paper,[7] we reported the formation of 7 (32%) and 8 (6%) by the $SnCl_2$-effected reaction of 2-methoxypropene[8] on the endoperoxide 6, which was prepared by the sensitized photooxygenation of 5. This time, 2-trimethylsilyloxy-2-butene, derived from MeCOEt,[9] was utilized as a nucleophile, and the similar reaction on 6 afforded 9 and 10 in respective yields of 35% and 4%, based on the dihydropyridine derivative 5. Both 9 and 10 were mixtures of diastereomers concerning to the secondary Me group on the side chain, and the major product 9 exhibited ^{13}C NMR signals of C-4 at 133.4 ppm and 134.3 ppm, whereas the minor product 10 showed the corresponding signals at the same chemical shift at 136.0 ppm. This phenomenon agreed well with the criterion[7] for the stereochemical assignment of the hydroxyl group with respect to the side chain. Catalytic hydrogenation of 9 over PtO_2 in dimethoxyethane produced a dihydro derivative 11 in 85% yield.

Removal of the protecting group from the nitrogen atom was carried out as usual (H_2, 10% Pd-C, MeOH) and the resulting isopelletierine derivative 4 was submitted to the condensation with 3-furylaldehyde by catalysis of alkali. Presence

of the hydroxyl function β to the secondary amino group required a critical reaction condition to furnish the aimed product and stirring a solution of 4 and 3-furylaldehyde in 1% NaOH-MeOH-H_2O (3:1) at room temperature (21-22°C) for 15 hr afforded two crystalline products, 12,[10] mp 110-111.5°, and 13,[10] mp 101-103°, in 20% and 16% yields, respectively, from 11. In the ^1H NMR spectrum of 12, H-4 was observed at δ 3.58 as a double doublet having J=10, 4 Hz and existence of the Bohlmann bands[11] in its IR spectrum at 2800 and 2780 cm^{-1} concluded that 12 possessed the trans quinolizidine ring system and the furyl moiety was situated in the equatorial configuration as illustrated in the formula 12'. On treatment with hot alkali, 12 was recovered in 75% yield, meaning that Me group at C-1 was oriented in the stable configuration.

On the other hand, 13 exhibited no Bohlmann bands in the IR spectrum and the ^1H NMR signal of H-4 appeared at δ 4.18 in the shape of broad doublet with J=7 Hz. When 13 was refluxed in 5% NaOH-MeOH-H_2O (3:1) for 12 hr, conversion into 12 was observed in 53% yield, together with the recovery of 13 in 18% yield. These facts clearly showed that the cis quinolizidine structure 13', having furan substituent in the axial configuration was assigned to 13 and the Me group at C-1 was equatorially oriented. Another cis quinolizidine form 13" would be conceivable, but close proximity of C-7 Me group and furan ring seemed to enable this form to be unlikely. A direct synthesis of 12 and 13 from 9 was carried out by catalytic hydrogenation over 10% Pd-C in MeOH to produce 4, followed by the alkali catalyzed condensation with 3-furylaldehyde. 12 and 13 were obtained in 17% and 15% yields, respectively.

In order to complete the synthesis, 12 was transformed to an amorphous tosylhydrazone 14 in 96% yield, and 14 was treated with $LiAlH_4$[12] in THF at room temperature for 3 hr and then at reflux for 3 hr. (±)-2,[10] mp 86.5-88.5°, was obtained in 40% yield and identical with natural nupharolutine by comparison of MS,[4] ^1H NMR (100 MHz, $CDCl_3$), IR,[13] and ^{13}C NMR[14] spectra, which were kindly supplied by Professor LaLonde. As nupharolutine has already been converted[4] to deoxynupharidine (1), which was oxidized[16] to nupharidine (15), and the latter has been transformed[17] by way of dehydrodeoxynupharidine into 7-epideoxynupharidine (16) and nupharamine (17), whose dehydration has been carried out[18] to furnish anhydronupharamine (18), the present synthesis of (±)-nupharolutine constitutes the formal syntheses of 1, 15, 16, 17, and 18.

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13. IR $\nu_{max}^{CCl_4}$ cm^{-1} (in part) synthetic material (values in literature[5]): 3560-3120 (3571-3125), 2798 (2805), 2775 (2782), 1501 (1502), 1461 (1458), 1438 (1439), 1378 (1377), 1158 (1160), 1060 (1064), 1032 (1038), 868 (875).
14. ^{13}C NMR ($CDCl_3$, 25.16 MHz) ppm of synthetic material (of natural product[15]): 19.25 (19.30), 25.44 (25.48), 27.97 (28.21), 33.62 (33.78), 34.16 (34.43), 34.84 (35.11), 38.30 (38.55), 59.65 (59.87), 63.06 (63.45), 68.17 (68.51), 69.20 (69.48), 109.25 (109.64), 129.04 (129.65), 139.22 (139.68), 142.78 (143.25).
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