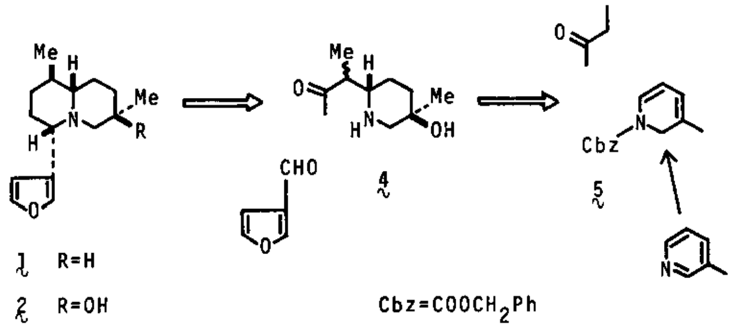
A FACILE SYNTHESIS OF A NUPHAR ALKALOID, NUPHAROLUTINE

Mitsutaka Natsume* and Masashi Ogawa
Research Foundation Itsuu Laboratory
Tamagawa 2-28-10, Setagaya-ku, Tokyo 158, Japan

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.



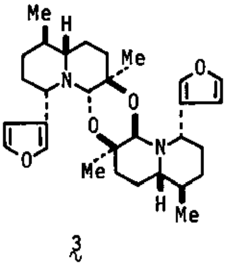
1 R=H

2 R=OH

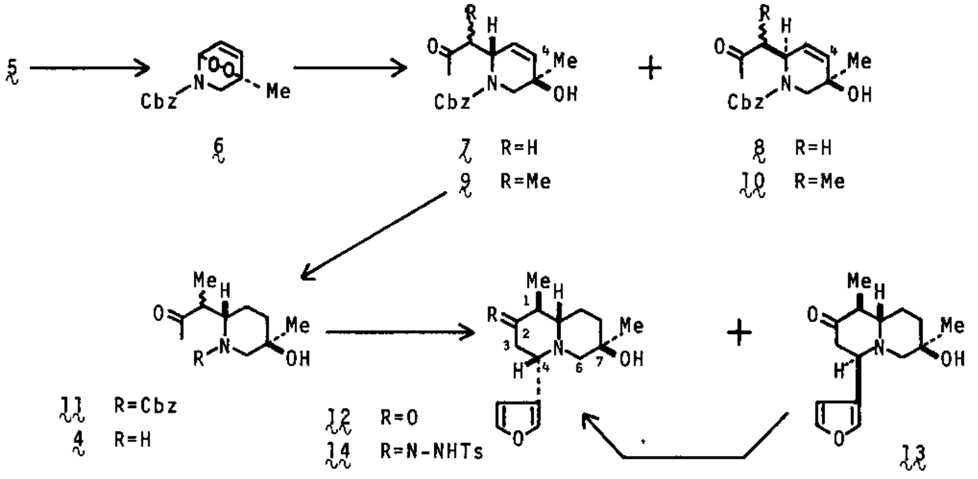
4

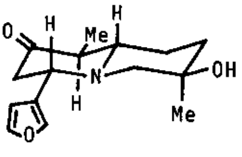
5

Cbz=COOCH$_2$Ph

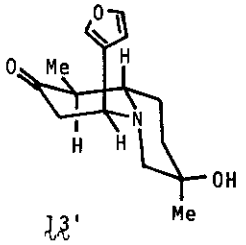


3

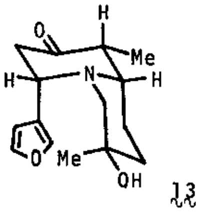




12'



13'



13"

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 ^{1}H 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 ^{1}H 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] ^{1}H 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**.

Acknowledgement —— We wish to express our deep gratitude to Professor R.T.

LaLonde for making the identification and sending us the spectral data of nupharolutine. Thanks are due to Professor M. Hanaoka for providing the manuscript of his original paper prior to its publication. A part of this work was supported by Grant-in-Aid for Special Project Research from the Ministry of Education, Science and Culture, which is gratefully acknowledged.

REFERENCES AND NOTES

1. T. Matsunaga, I. Kawasaki, and T. Kaneko, *Tetrahedron Lett.*, 2471 (1967).
2. Reviews: M. Hanaoka, *Yuki Gosei Kyokai-shi*, 35, 465 (1977).
3. S. Yasuda, M. Hanaoka, and Y. Arata, *Heterocycles*, 6, 391 (1977); *Chem. Pharm. Bull.*, 28, 831 (1980).
4. J.T. Wrobel, A. Iwanow, C. Braekman-Danheux, T.I. Martin, and D.B. MacLean, *Can. J. Chem.*, 50, 1831 (1972).
5. R.T. LaLonde, C.F. Wong, and K.C. Das, *J. Am. Chem. Soc.*, 94, 8522 (1972).
6. M. Natsume, Y. Sekine, M. Ogawa, H. Soyagimi, and Y. Kitagawa, *Tetrahedron Lett.*, 3473 (1979).
7. M. Natsume and M. Ogawa, *Heterocycles*, 14, 615 (1980).
8. M.S. Newman and M.C. Vander Zwan, *J. Org. Chem.*, 38, 2910 (1973).
9. H.O. House, L.J. Czuba, M. Gall, and H.D. Olmstead, *J. Org. Chem.*, 34, 2324 (1969).
10. Satisfactory result of elementary analysis was obtained for C, H, N.
11. F. Bohlmann, *Chem. Ber.*, 91, 2157 (1958).
12. L. Caglioti and M. Magi, *Tetrahedron*, 19, 1127 (1963).
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).
15. R.T. LaLonde, T.N. Donvito, and A. I-M. Tsai, *Can. J. Chem.*, 53, 1714 (1975).
16. Y. Arata and T. Ugai, *Yakugaku Zasshi*, 66B, 138 (1946).
17. R.T. LaLonde, E. Auer, C.F. Wong, and V.P. Muralidharan, *J. Am. Chem. Soc.*, 93, 2501 (1971).
18. T. Ohashi, *Yakugaku Zasshi*, 79, 729 (1959).

Received, 16th June, 1980