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Chiral Synthesis of (-)-Nupharamine

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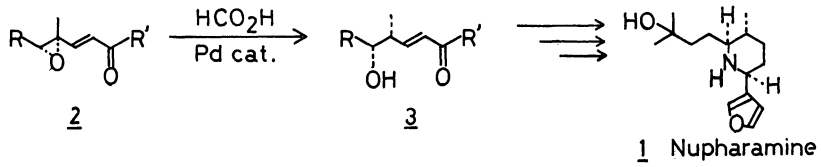
Reaction of the optically active alkenyloxirane with formic acid in the presence of palladium(0)-phosphine catalyst gave the homoallylic alcohol selectively, which was converted to (-)-nupharamine.

Sesquiterpene quinolizidine alkaloids and piperidine alkaloids have been isolated from genus Nuphar.[1] Although several synthetic works for these compounds have appeared, synthesis of nuphar alkaloids as chiral forms has not been reported. Recently we have reported that hydrogenolysis of alkenyloxiranes using formic acid in presence of palladium catalyst to give homoallylic alcohols proceeds with high regio- and stereoselectivity under mild conditions.[2] This method is considered to be useful for synthesis of piperidine and quinolizidine alkaloids, because the 3-methylpiperidine skeleton is easily formed from 3 generated by the hydrogenolysis of **2**. In this paper we wish to report a synthesis of the sesquiterpene alkaloid, (-)-nupharamine (**1**), which was isolated from *Nuphar japonicium* DC.



2 **3** **1** Nupharamine

The alkenyloxirane **7** was prepared in three steps from the allylic alcohol **4**. Thus, epoxydation of **4** with t-BuOOH using $Ti(O^iPr)_4$-(-)-diethyl tartarate in dichloromethane at -23 °C gave the optically active oxirane **5** in 92% yield.[3] Swern oxidation of **5** gave the aldehyde **6** in 91% yield followed by Emmons-Horner reaction using the phosphonate **12** to give the alkenyloxirane **7** in 87% yield. Conversion of **7** to **8** was carried out with formic acid in the presence of $Pd_2(dba)_3CHCl_3$ (2.5 mol%) and PPh_3 (2.5 mol%) in dioxane at room temperature for 8 h. The homoallylic alcohol **8** was obtained as a major product with its regio isomer **9** (90% yield as a

mixture; **8**:**9**=4:1). Hydrogenation of **8** followed by azidation using diphenylphosphonoazide gave the azide **10** stereoselectively.[4] The azide **10** was treated with triphenylphosphine to give the cyclic imine **11** in 90% yield by intramolecular aza Wittig reaction via an iminophosphorane intermediate. Finally, reduction of the imine **11** with $NaBH_4$ followed by removal of the protecting group gave (-)-nupharamine (**1**), whose optical rotation and ^{13}C-NMR spectrum[5] are identical with those in the literature.[6]

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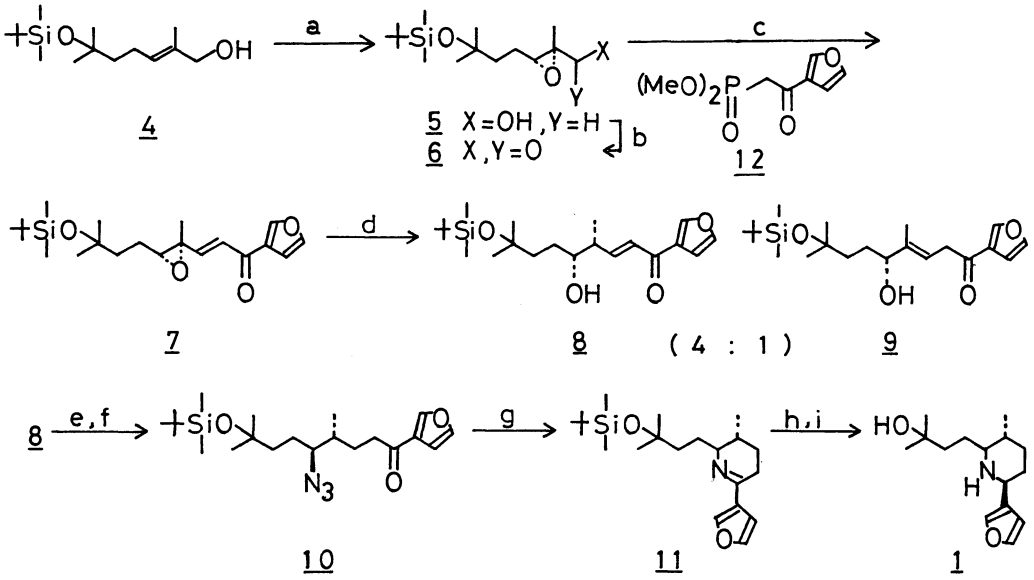

(a) ^tBuOOH, $Ti(O^iPr)_4$, D-(-)-DET, CH_2Cl_2, -23 °C, 92% (b) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C, 91% (c) **12**, NaH, THF, 0°C, 87% (d) $Pd_2(dba)_3CHCl_3$, Ph_3P, HCO_2H, Et_3N, dioxane, r.t., 90% (**8**:**9**=4:1) (e) H_2, Pd/C, AcOEt/Et_3N, 96% (f) $(=NCO_2Et)_2$, Ph_3P, $(PhO)_2P(O)N_3$, THF, 50% (g) Ph_3P, THF, reflux, 90% (h) $NaBH_4$, EtOH, 0 °C, 84% (i) HF, MeOH, 73%

References
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2) M. Oshima, H. Yamazaki, I. Shimizu, M. Nisar, and J. Tsuji, J. Am. Chem. Soc., 111, 6280 (1989).
3) T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980). R. M. Hanson and K. B. Sharpless, J. Org. Chem., 51, 1922 (1986).
4) B. Lal, B. N. Pramanik, M. S. Manhas, and A. K. Bose, Tetrahedron Lett., 23, 1977 (1977).
5) $[\alpha]_D^{24.5}$ -36.5° (c 0.52 $CHCl_3$); ^{13}C-NMR (22.4 MHz, $CDCl_3$) 18.55(q), 28.43(t), 29.28(q), 30.23(q), 33.64(t), 33.98(t), 34.31(d), 39.68(t), 53.10(d), 62.94(d), 68.92(s), 109.14(d), 128.77(s), 138.32(d), 142.86(d).
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