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# Stereoselective synthesis of *Nuphar* quinolizidine alkaloid, (−)-deoxynupharidine

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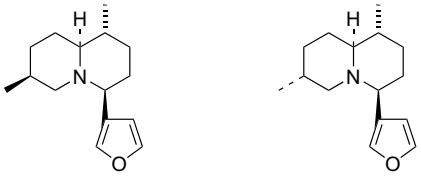
**Abstract**—A stereoselective synthetic route to *Nuphar* quinolizidine alkaloid, (−)-deoxynupharidine, was established by employing reductive carbon–nitrogen bond cleavage, followed by simultaneous recyclization of a proline derivative with samarium diiodide, and an intramolecular ring-closing metathesis, as the key steps.


(−)-Deoxynupharidine **1** and (−)-7-*epi*-deoxynupharidine **2**, isolated from plants of the genus *Nuphar*,[1] are sesquiterpene alkaloids based on a quinolizidine core with a furan ring. The dried rhizomes of *Nuphar japonicum* DC. and *Nuphar pumilum* (TIMM.) DC., are used in folk medicine for tonic, haemostatic and diuretic purposes in China and Japan. It has also been recognized that (−)-deoxynupharidine exhibited an immunosuppressive effect,[2] a central paralysis effect[3] and weak anti-metastitic activity,[4] and (−)-7-*epi*-deoxynupharidine showed insecticidal activity[1] (Fig. 1).

Although several syntheses of deoxynupharidine **1** have been achieved, most of them led to the synthesis of the target compound in racemic form.[5] Very recently, Harrity and co-workers published a stereocontrolled chiral synthesis of **1** by employing a formal [3+3] cycloaddition reaction to obtain a piperidine nucleus.[6] We have recently developed a general strategy for stereoselective construction of an optically pure 5,6-disubstituted piperidone ring system starting from pyroglutamic acid,[7] where a reductive carbon–nitrogen bond cleavage reaction of α-amino carbonyl compounds with samarium diiodide, was involved as a key reaction.[8] As part of our continuing effort to synthesize biologically active natural products utilizing the reductive carbon–nitrogen bond cleavage reaction,[7,9] we are interested in a stereoselective synthesis of (−)-deoxynupharidine.

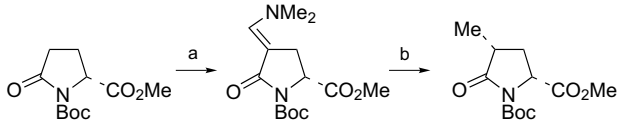



**1.** Deoxynupharidine **2.** 7-*epi*-Deoxynupharidine

**Figure 1.** Structures of deoxynupharidine and 7-*epi*-deoxynupharidine.

*N*-Boc-D-pyroglutamic acid methyl ester **3**, readily accessible from commercially available (*R*)-pyroglutamic acid, was converted to (2*R*,4*R*)-*N*-Boc-4-methyl-D-pyroglutamic acid methyl ester **5**, via the enaminone **4**, by using the literature procedures for the preparation of its antipode, as shown in Scheme 1.[10]

For introduction of an alkyl side chain at the 5-position of **5** stereoselectively, we adopted a tandem Horner–Emmons–Michael reaction, as previously described in the synthesis of (+)-febrifugine.[7]




**3** **4** **5**

**Scheme 1.** Reagents and conditions: (a) *tert*-BuOCH(NMe)$_2$, toluene, 100 °C (96%); (b) 10% Pd–C, *i*-PrOH–AcOEt (5:1), rt (91%.)

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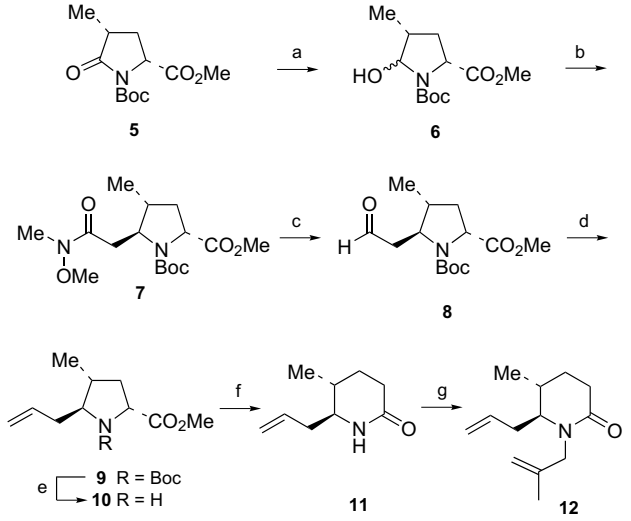
Reduction of the lactam **5** with lithium triethylborohydride, followed by treatment of the resulting aminal **6** with the Wittig reagent, prepared from NaH and diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate, gave the amide **7** with the desired stereochemistry, as the sole product.

To construct a quinolizidine ring skeleton, we decided to utilize ring closing metathesis (RCM).[11] Thus, the amide **7** was transformed into the olefin **9** by DIBAL reduction and subsequent treatment of the resulting aldehyde **8** with the Wittig reagent. Deprotection of the Boc group of **9** with trifluoroacetic acid afforded the amine **10**, which on reductive deamination with samarium diiodide in THF–HMPA in the presence of methanol as the proton source, yielded the desired piperidone **11** stereoselectively, where a carbon–nitrogen bond cleavage reaction and subsequent recyclization took place simultaneously, as expected. *N*-Alkylation of **11** with 3-bromo-2-methylpropene in the presence of sodium hydride provided the RCM precursor **12** (Scheme 2).

RCM of **12** was successfully achieved by using 2 mol % of Grubbs' second-generation catalyst in refluxing benzene for 2 h to furnish the bicyclic lactam **13** in 96% yield. Treatment of **13** with 3-lithiofuran in THF, followed by reduction of the resulting enamine with sodium borohydride afforded the furan derivative **14**[12] and its diastereomer **15**,[13] in 57% yield from **13** in a ratio of ca. 5:1. Harrity and co-workers reported a similar installation of a furan ring to a lactam in their synthesis of (−)-deoxynupharidine, in which DIBAL was employed as the reducing agent for reduction of a proposed intermediate, a carbinolamine.[6] However, in our experiments, we could confirm the presence of an enamine as an intermediate by the analysis of its NMR spectra.[14]




**Scheme 2.** Reagents and conditions: (a) $LiBEt_3H$, THF, −78 °C; (b) NaH, THF, $(EtO)_2P(O)CH_2CON(Me)OMe$, rt (96% from **5**); (c) DIBAL, THF, −78 °C; (d) NaHMDS, $Ph_3PCH_3^+Br^-$, THF, −78 °C to rt (95% from **7**); (e) TFA, $CH_2Cl_2$, 0 °C to rt; (f) $SmI_2$, THF, HMPA, MeOH, 0 °C to rt (90% from **9**); (g) 3-bromo-2-methylpropene, NaH, DMF, 0 °C to rt (87%).

Actually, our attempted reduction of the crude product in this addition reaction with DIBAL was unsuccessful.

Although the stereochemistry of the products **14** and **15** could not be determined at this stage, the major compound **14** was assumed to have the desired stereochemistry based on consideration of the molecular models for a subsequent reduction of the intermediate. This speculation was unambiguously confirmed by further conversion of **14** into the target compound **1**. The observed stereoselectivity for the reduction can be rationalized by assuming a stable conformation of the imine as depicted in Figure 2, where the hydride attack occurs from axial orientation.

Finally, a catalytic reduction of **14** over palladium hydroxide provided (−)-deoxynupharidine **1** in 68% yield together with (−)-7-*epi*-deoxynupharidine **2** in 11% yield[15] (Scheme 3). The spectroscopic data of the synthesized compound **1** were identical with those reported;[5b] $[\alpha]_D$ −105.4 (*c* 0.33, EtOH), lit.,[16] $[\alpha]_D$ −109.86 (*c* 1.16, EtOH).

Although the optical rotation of **2**, exhibiting the same spectroscopic data as those reported[17,18] was slightly different from the reported value; $[\alpha]_D$ −109.3 (*c* 0.46, EtOH), lit.,[17] $[\alpha]_D$ −89 (*c* 3.5, EtOH), we believe that our synthesized compound must be optically pure based on consideration of our synthetic schemes.

In summary, we were able to establish a stereoselective chiral synthesis of (−)-deoxynupharidine **1** by employ-

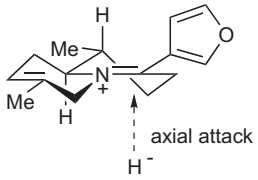
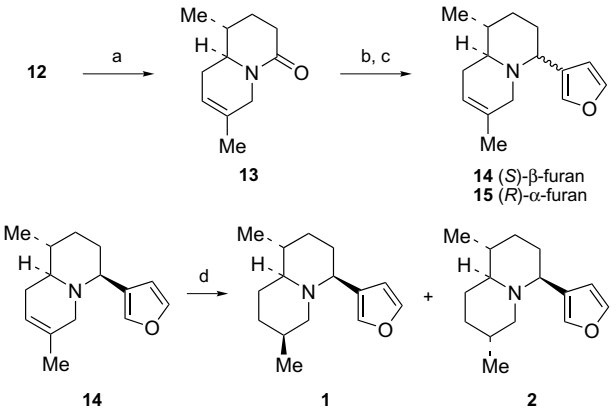



**Figure 2.** Stereoselective reduction of the intermediate.




**Scheme 3.** Reagents and conditions: (a) 2 mol % Grubbs' 2nd cat, benzene, 60 °C (96%); (b) 3-lithiofuran, THF, −78 °C; (c) $NaBH_4$, MeOH, rt (57% from **13**); (d) $H_2$, $Pd(OH)_2$, MeOH, rt (68% for **1**, 11% for **2**).

ing reductive deamination of α-amino carbonyl compound with samarium diiodide and RCM as the key reactions. The methodology described here is obviously applicable to the stereoselective synthesis of other *Nuphar* alkaloids in optically active forms.

## Acknowledgements

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12. Selected data for compound **14**: $[\alpha]_D$ −162.3 (*c* 0.57, $CHCl_3$). $^1H$ NMR ($CDCl_3$) $\delta$ 0.93 (3H, d, $J = 6.6$ Hz), 1.16–1.29 (1H, m), 1.35–1.54 (4H, m), 1.66–2.02 (5H, m), 2.27–2.40 (2H, m), 2.93–3.03 (2H, m), 5.36 (1H, m), 6.48 (1H, dd, $J = 0.8$, 1.5 Hz), 7.33–7.37 (2H, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 18.8, 20.7, 31.9, 33.4, 34.4, 37.5, 56.9, 61.2, 64.2, 109.5, 118.3, 128.4, 131.4, 139.3, 142.8; IR (thin film) 1596, 1573, 1501, 1450, 1439, 1377, 1349, 1330, 1308, 1292, 1250, 1219, 1184, 1163, 1125, 1097, 1070, 1033, 1020, 977, 874 $cm^{-1}$; HRMS *m/z* found: 231.1646 (calcd for $C_{15}H_{21}NO$: 231.1623).
13. Selected data for compound **15**: $[\alpha]_D$ −104.4 (*c* 0.16, $CHCl_3$). $^1H$ NMR ($CDCl_3$) $\delta$ 1.02 (3H, d, $J = 6.1$ Hz), 1.35–1.66 (6H, m), 1.67–1.79 (1H, m), 1.88–2.11 (2H, m), 2.18–2.32 (1H, m), 2.48 (1H, ddd, $J = 4.7$, 8.2, 9.2 Hz), 2.84 (1H, d, $J = 16.6$ Hz), 2.94 (1H, dt, $J = 1.2$, 16.6 Hz), 4.03 (1H, t, $J = 4.1$ Hz), 5.37 (1H, m), 6.37 (1H, m), 7.35 (1H, s), 7.39 (1H, t, $J = 1.6$ Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 18.9, 20.7, 27.6, 30.6, 31.2, 36.7, 54.4, 54.7, 56.8, 111.9, 118.0, 124.9, 131.5, 139.9, 142.3; IR (thin film) 1499, 1458, 1439, 1377, 1261, 1188, 1176, 1160, 1130, 1108, 1061, 1045, 1028, 972, 874 $cm^{-1}$; HRMS *m/z* found: 231.1643 (calcd for $C_{15}H_{21}NO$: 231.1623).
14. Although the enamine was found to be unstable towards isolation, $^1H$ and $^{13}C$ NMR spectra were obtained. $^1H$ NMR data for the enamine: $^1H$ NMR ($CDCl_3$) $\delta$ 0.98 (3H, d, $J = 6.4$ Hz), 1.58 (3H, d, $J = 0.8$ Hz), 1.69–2.14 (4H, m), 2.19–2.33 (1H, m), 2.52 (1H, ddd, $J = 3.8$, 9.7, 9.9 Hz), 2.89 (1H, dt, $J = 1.2$, 16.8 Hz), 3.52 (1H, d, $J = 16.8$ Hz), 4.78 (1H, dd, $J = 2.3$, 6.3 Hz), 5.43–5.49 (1H, m), 6.41 (1H, dd, $J = 0.8$, 1.8 Hz), 7.35 (1H, dd, $J = 1.6$, 1.8 Hz), 7.39 (1H, s); $^{13}C$ NMR ($CDCl_3$) $\delta$ 18.5, 20.6, 30.9, 31.1, 32.7, 53.9, 60.5, 102.3, 110.7, 119.1, 124.8, 132.2, 138.9, 139.5, 142.3.
15. The diastereoselectivity for the hydrogenation of compound **14** was observed to be ca. 4:1 (**1**:**2**) by the analysis of $^1H$ NMR spectrum of the crude products.
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