# A Concise Enantiospecific Synthesis of Nuphar Piperidine Alkaloids: Total Synthesis of (−)-Anhydronupharamine, (−)-Nupharamine, (−)-Nuphenine and (+)-3-Epinupharamine

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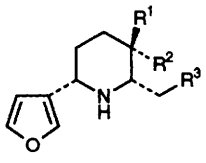
Enantiospecific syntheses of (−)-anhydronupharamine, (−)-nupharamine, (−)-nuphenine, and (+)-3-epinupharamine are achieved starting from (−)- or (+)-carvone as chiral sources, in which a regioselective reductive fragmentation of the cyclopentane derivatives and an intramolecular aza–Wittig reaction were involved as key reactions.

(−)-Anhydronupharamine **1**[1] and (−)-nupharamine **2**,[2] having sesquiterpenoid structures with furan and piperidine rings, are isolated from the dried rhizome of *Nuphar japonicum* DC. Although the absolute stereochemistry of natural nupharamine was initially assigned as 2*R*,3*S*,6*R*,[3] it was revised later to its antipodal form[4] as depicted in Fig. 1. Since dehydration of nupharamine provided anhydronupharamine, the absolute configuration of anhydronupharamine was confirmed as the same as those of nupharamine. Nuphenine **3**[5] and 3-epinupharamine **4**,[6,7] isolated from *Nuphar variegatum* Engelm, are other members of the family of nuphar piperidine alkaloids with the epimeric methyl group at C-3. The absolute configuration of 3-epinupharamine **4** was recently determined to be 2*S*,3*S*,6*S* by its non-stereoselective synthesis.[8] With regards to the chiral synthesis[9] of nuphar piperidine alkaloids, only two syntheses for nupharamine[8,10] and one for 3-epinupharamine[8] have so far been reported and none of the chiral synthesis for anhydronupharamine and nuphenine has appeared to date. We are therefore interested in developing a general synthetic path to those alkaloids starting from the readily available monoterpene carvone as a chiral source, and here report their enantiospecific syntheses.



**1** $R^1$ = Me, $R^2$ = H, $R^3$ = CH=$CMe_2$
**2** $R^1$ = Me, $R^2$ = H, $R^3$ = $CH_2C(OH)Me_2$
**3** $R^1$ = H, $R^2$ = Me, $R^3$ = CH=$CMe_2$
**4** $R^1$ = H, $R^2$ = Me, $R^3$ = $CH_2C(OH)Me_2$

Fig. 1

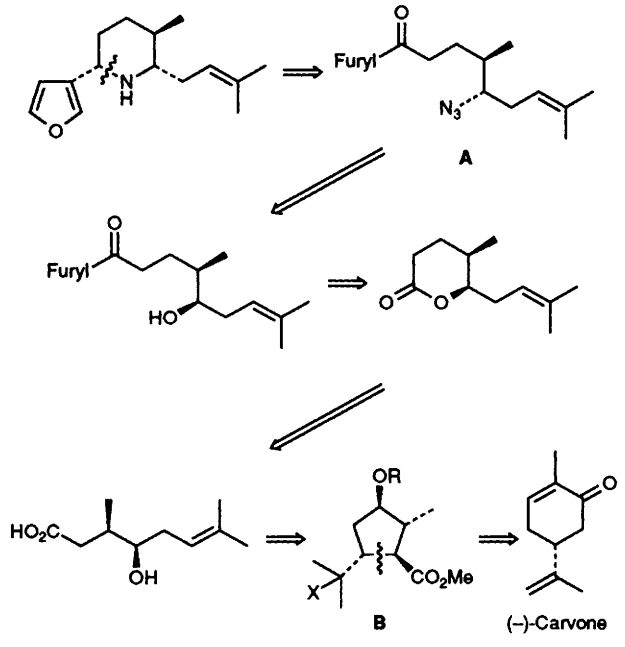
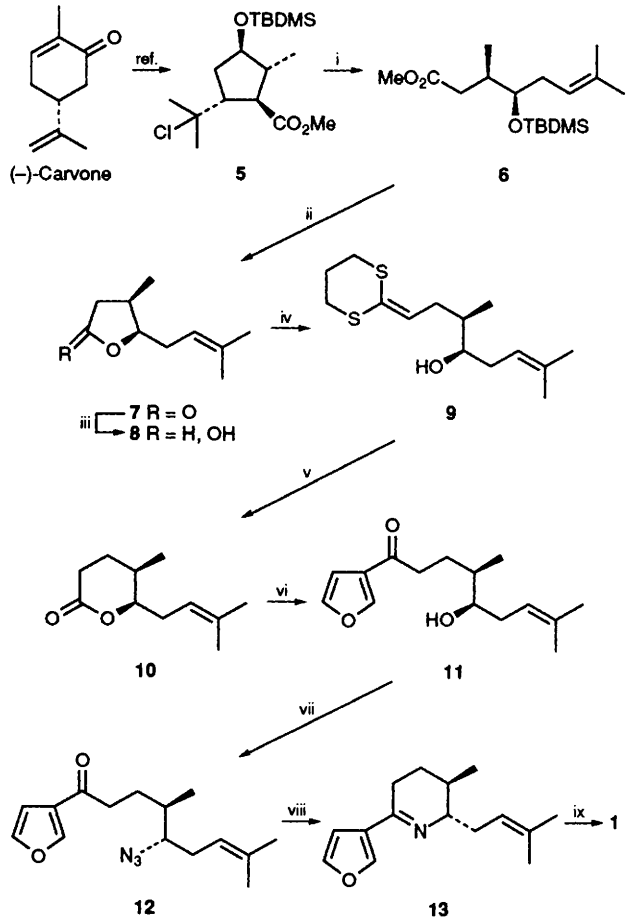


Fig. 2

We first attempted the synthesis of anhydronupharamine **1**. Our synthetic strategy, shown in Fig. 2, hinges upon the formation of an acyclic precursor **A** with the desired stereochemistry in the correct chirality, *via* a regioselective fragmentation reaction of the γ-halo-ester **B**, developed by us recently,[11] followed by introduction of an azido group under the Mitsunobu reaction condition.

Thus, the γ-halo-ester **5**, readily accessible from (−)-carvone based on our earlier work,[11] was subjected to a regioselective fragmentation reaction with samarium diiodide to afford the acyclic ester **6**, in 85.5% yield, having the desired



**Scheme 1** *Reagents and conditions*: i, 3.7 equiv. Sm, 3.5 equiv. 1,2-diiodoethane, THF–HMPA (20:1), room temp. (85.5%); ii, $Bu_4NF$, THF, room temp.; iii, DIBAL, THF, −78 °C (97.2% from **6**); iv, 2-trimethylsilyl-1,3-dithiane, $Bu^nLi$, THF, −15 °C; v, *p*-TsOH, $CH_2Cl_2$, room temp. (69.5% from **8**); vi, 3-bromofuran, $Bu^nLi$, THF, −78 °C (92.1%); vii, $Ph_3P$, DEAD, $(PhO)_2P(O)N_3$, THF, 0 °C (88% from **11**); viii, $Ph_3P$, THF, reflux; ix, $NaBH_4$, EtOH, room temp. (77.4% from **12**)

chirality. Desilylation of the ester **6** with tetra-n-butylammonium fluoride in THF gave rise to the γ-lactone **7**, which on reduction with diisobutylaluminium hydride (DIBAL) afforded the lactol **8** in 97.2% yield from **6**. Ring-expansion reaction of the lactol **8** was achieved by treatment with 6 equiv. of 2-lithio-2-trimethylsilyl-1,3-dithiane,[12] prepared from 2-trimethylsilyl-1,3-dithiane and n-butyllithium, in THF and subsequent hydrolysis of the resulting thioacetal **9** with a catalytic amount of toluene-*p*-sulfonic acid in dichloromethane to give the δ-lactone **10** in 69.5% yield. Reaction of the δ-lactone **10** with 3-lithiofuran, prepared from 3-bromofuran and n-butyllithium, in THF underwent smoothly to provide the alcohol **11**, in 92.1% yield, which was further converted into the azide **12** according to the Lal's procedure[13] using diethyl azodicarboxylate (DEAD), triphenylphosphine and diphenylphosphoryl azide, in 88% yield. Since the desired acyclic precursor with the correct chirality for anhydronupharanine was thus synthesized stereoselectively, we focused our attention to a construction of a piperidine ring by adopting an aza–Wittig reaction.[10] Treatment of the azide **12** with triphenylphosphine in refluxing THF afforded the imine **13**, which without purification, was reduced with sodium borohydride in ethanol to give anhydronupharamine **1** as the single stereoisomer, in 77.4% yield from **12**, whose spectroscopic data including its specific optical rotation, $[\alpha]_D$ −64.9 (*c* 0.1, $CHCl_3$) {lit.,[14] $[\alpha]_D$ −62.5 $(CHCl)_3$)}, were identical with those reported.[14] Since anhydronupharamine **1** was already converted into nupharamine **2** by treatment with hydrochloric acid,[14] this synthesis constitutes its chiral synthesis.

Nuphenine **3**, $[\alpha]_{Hg}$ (365 nm) −23.4 (MeOH) {lit.,[5] $[\alpha]_{Hg}$ −23 (MeOH)}, was also synthesized starting from (+)-eldanolide,[11,15] easily derived from (+)-carvone, by following essentially the same synthetic scheme as for the preparation of **1**. Since the hydration of nuphenine **3** giving 3-epi-nupharamine **4** has already been reported by Forrest and Ray,[6] this synthesis also constitutes its chiral synthesis.

In summary, we could develop efficient stereoselective syntheses of nuphar piperidine alkaloids starting from (−)- or (+)-carvone as chiral sources and this synthetic strategy should be applicable to the chiral synthesis of other naturally occurring nuphar alkaloids.

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