

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

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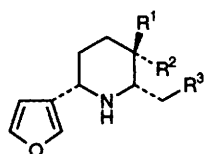
Enantiospecific syntheses of (–)-anhydronupharamine, (–)-nupharamine, (–)-nuphenine, and (+)-3-epinupharamine are achieved starting from (–)- or (+)-carvone as chiral sources, in which a regioselective reductive fragmentation of the cyclopentane derivatives and an intramolecular aza-Wittig reaction were 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 form⁴ 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 synthesis⁹ of nuphar piperidine alkaloids, only two syntheses for nupharamine^{8,10} and one for 3-epinupharamine⁸ 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.

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



- 1** $R^1 = \text{Me}, R^2 = \text{H}, R^3 = \text{CH}=\text{CMe}_2$
2 $R^1 = \text{Me}, R^2 = \text{H}, R^3 = \text{CH}_2\text{C}(\text{OH})\text{Me}_2$
3 $R^1 = \text{H}, R^2 = \text{Me}, R^3 = \text{CH}=\text{CMe}_2$
4 $R^1 = \text{H}, R^2 = \text{Me}, R^3 = \text{CH}_2\text{C}(\text{OH})\text{Me}_2$

Fig. 1

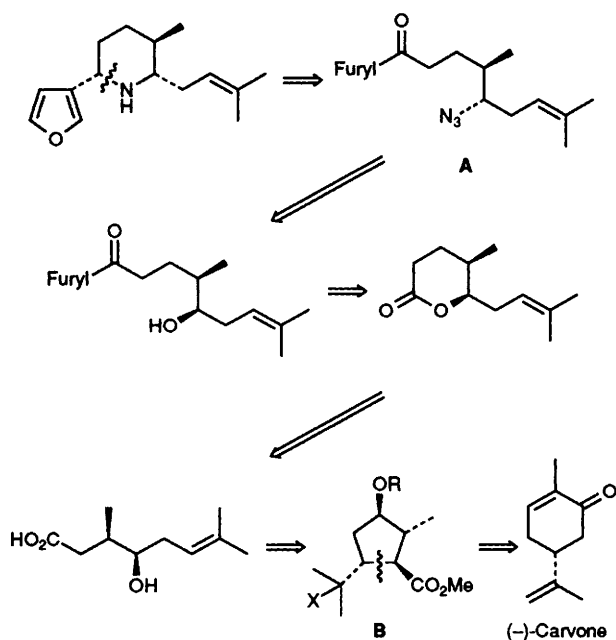
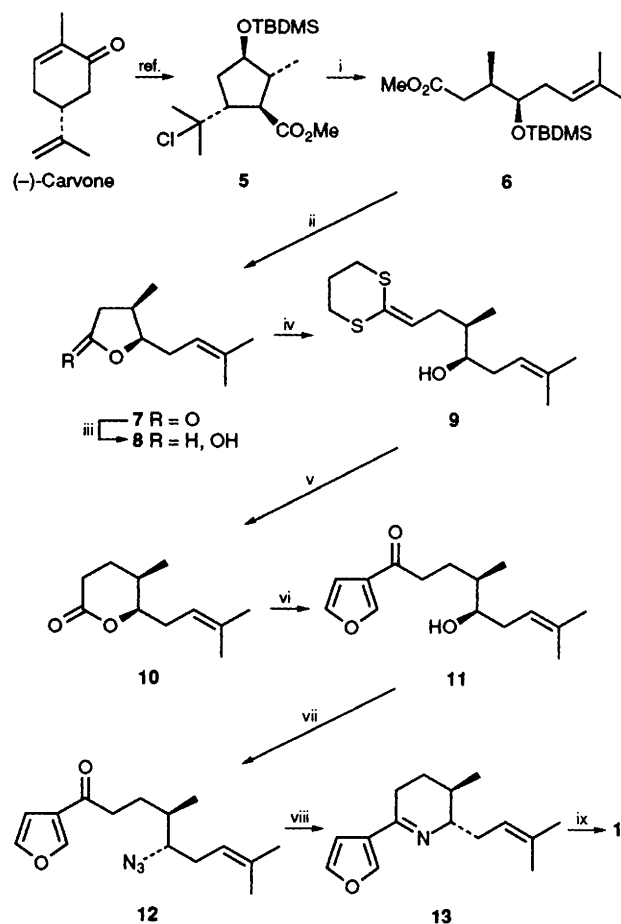


Fig. 2



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, Bu₄NF, THF, room temp.; iii, DIBAL, THF, –78 °C (97.2% from **6**); iv, 2-trimethylsilyl-1,3-dithiane, BuⁿLi, THF, –15 °C; v, *p*-TsOH, CH₂Cl₂, room temp. (69.5% from **8**); vi, 3-bromofuran, BuⁿLi, THF, –78 °C (92.1%); vii, Ph₃P, DEAD, (PhO)₂P(O)N₃, THF, 0 °C (88% from **11**); viii, Ph₃P, THF, reflux; ix, NaBH₄, 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 procedure¹³ 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, CHCl₃) {lit.,¹⁴ $[\alpha]_D -62.5$ (CHCl₃)}, 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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