Synthesis of Two Nuphar Alkaloids by Allenic Hydroxylamine Cyclisation

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Abstract: A highly diastereoselective silver-catalysed cyclisation of a 2-substituted β-allenic hydroxylamine is reported. The resulting *trans*-isoxazolidine is converted into two Nuphar alkaloids by a sequence involving cross-metathesis and intramolecular reductive amination.

Key words: piperidines, allenes, cyclisation, silver, alkaloids

Most of the Nuphar alkaloids, trisubstituted piperidine alkaloids, were isolated from the Japanese water lily, *Nuphar japonica*. One member of the family was isolated from the scent glands of the North American beaver.[1] A number of syntheses of these alkaloids in both racemic and optically active forms have been reported.[2] In this letter, we wish to report racemic syntheses of nupharamine (**1**, Figure 1) and the otherwise unnamed bicyclic Nuphar alkaloid, 5-(3-furyl)-8-methyloctahydroindolizidine (**2**), using the Claesson cyclisation[3] of an allenic hydroxylamine to control the 2,3-stereochemistry. We have previously shown in the syntheses of sedamine[4] and porantheridine[5] that this cyclisation is a useful and practical route to stereochemically defined 1,3-amino alcohols. These cyclisations employed a β-allenic hydroxylamine derivative with a substituent at the 1-position. In contrast, the allenic hydroxylamine required for Nuphar synthesis would have a methyl group at the 2-position.

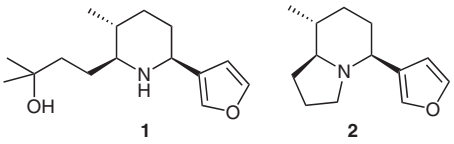
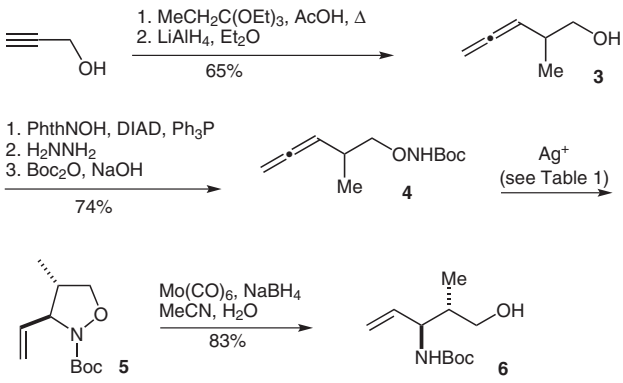


Figure 1

The desired allenic substrate was easily prepared on a multigramme scale by a Johnson–Claisen rearrangement[6] involving propargyl alcohol and triethyl orthopropionate catalysed by acetic acid (Scheme 1). This reaction proceeded in essentially quantitative yield. Reduction of the resulting ester group with lithium aluminium hydride gave the primary allenic alcohol **3**[6b,c] which was converted into the Boc-protected hydroxylamine **4** by the usual sequence of Mitsunobu reaction with *N*-hydroxyphthalimide (78%),[7] dephthaloylation (quantitative), and acylation (95%). Several catalysts were screened for the Claesson cyclisation (Table 1). The highest yield and highest selectivity for the *trans*-isoxazolidine **5**[8] was achieved using silver triflate in anhydrous dichloromethane. Due to the hygroscopic nature of this salt, molecular sieves were added to the reaction mixture. It was found that the diastereoselectivity was distinctly lower when water was present. To eliminate the possibility that the cyclisation is due to acid generated by hydrolysis of the salt,[9] the allenic hydroxylamine was treated with tetrafluoroboric acid. No cyclisation was observed. The two isomers of the isoxazolidine **5** were inseparable at this stage, but could be separated by chromatography after cleavage of the N–O bond using molybdenum hexacarbonyl.[10] The major isomer of amino alcohol derivative **6** proved to be crystalline, and its structure could be confirmed by X-ray crystallography (Figure 2).[11]



Scheme 1 Allene synthesis and cyclisation

Table 1 Cyclisation of Allene **4**

Entry	Catalyst (mol%)	Solvent	*trans*/*cis*	Yield (%)
1	$AgNO_3$ (20)	acetone–H_2O	1.7:1	45
2	$AgBF_4$ (35)	CH_2Cl_2	10:1	46
3	$AgNO_3/SiO_2$ (20)	CH_2Cl_2	7:1	23
4	AgOTf (20)	acetone–H_2O	1:1	96
5	AgOTf (20)	CH_2Cl_2	22:1	91
6	HBF_4 (30)	CH_2Cl_2	–	0

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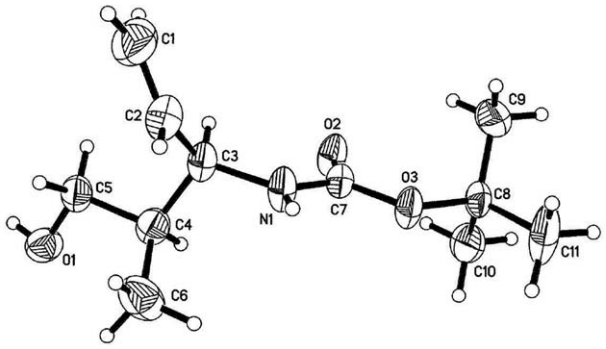


Figure 2 X-ray crystal structure of amino alcohol derivative **6**

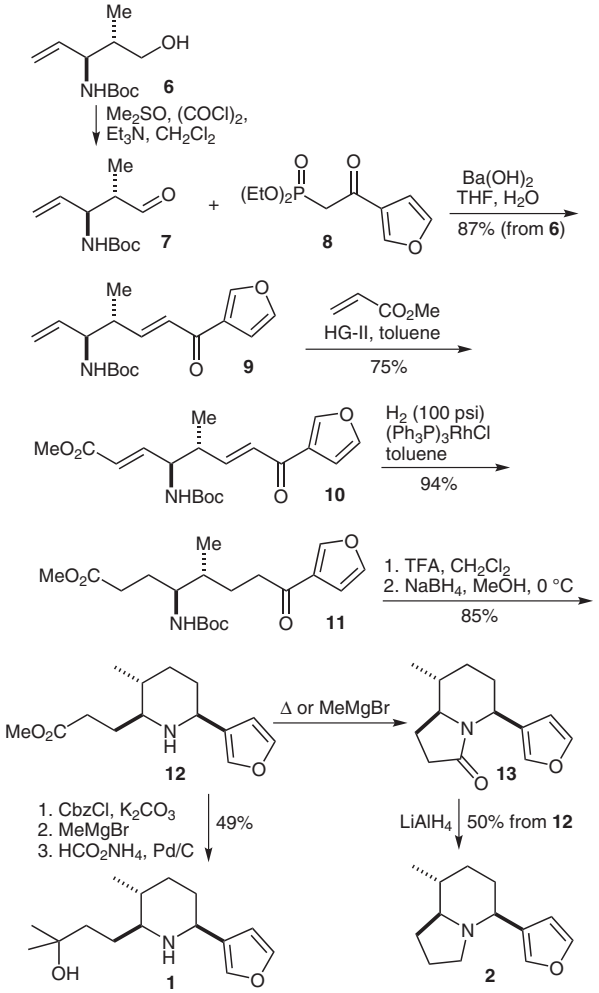
Attempts to convert the alcohol group of **6** into a bromide or iodide were unsuccessful as the halo compounds proved to be unstable during handling. Therefore, to achieve the required chain elongation, alcohol **6** was oxidized to aldehyde **7** (Scheme 2). The Swern oxidation proved to be the best method for this transformation. This compound, which would undergo epimerization at C2 on prolonged standing, was immediately coupled with the furyl phosphonate **8**[12] in a Horner–Wadsworth–Emmons reaction to give diene **9** in 87% yield from alcohol **6**. Use of barium hydroxide[13] proved to be superior to the Masamune–Roush modification.[14] In the latter case, the reaction failed to go to completion.

The synthesis of nupharamine (**1**) then required cross-metathesis[15] with commercially available 2-methylbut-3-en-2-ol. Our attempts to achieve this transformation were uniformly disappointing due to the steric hindrance encumbering both partners. Cross-metathesis with methyl acrylate, on the other hand, worked satisfactorily to give ester **10**, although it was necessary to employ the second-generation Hoveyda–Grubbs catalyst (HG-II, 5 mol%) by gradual addition to a toluene solution of the substrates at 70 °C[16] with continuous bubbling of nitrogen[17] to obtain optimum yield (75%) and conversion. No metathesis was observed at the internal alkene of **9**.

Reduction of the two alkenes of ester **10** proved troublesome. Both are somewhat hindered and, with palladium on carbon as the catalyst, hydrogenation even at atmospheric pressure, resulted in reduction of the furan in addition to the alkenes. Use of Wilkinson's catalyst with hydrogen at ambient pressure (balloon) resulted in partial reduction of the double bond conjugated to the ester. Clean and complete reduction of both alkenes, without detectable furan reduction was finally achieved using Wilkinson's catalyst under hydrogen at 100 psi, cleanly giving ester **11** in 94% yield.

Removal of the Boc group in the usual way, followed by a mildly basic workup yielded a crude tetrahydropyridine which was directly reduced with sodium borohydride to give the desired piperidine **12**[18] as a single diastereomer, following the procedure of Blechert.[2j]

Piperidine **12** was converted into nupharamine (**1**) using a slight modification of the literature method: N-protection as a benzyl carbamate, formation of the tertiary alcohol using excess methylmagnesium bromide, and deprotection by palladium-catalysed reduction with ammonium formate.[2i] Alternatively, heating ester **12** in toluene at reflux[2i,19] yielded the known lactam **13** which was converted into 5-(3-furyl)-8-methyloctahydroindolizidine (**2**) by reduction with lithium aluminium hydride in 50% yield (two steps).[2i]



Scheme 2 Nuphar alkaloid synthesis

Racemic, but highly diastereoselective, syntheses of two Nuphar alkaloids have been completed with a common isoxazolidine intermediate, generated by a highly stereoselective silver-catalysed allenic hydroxylamine cyclisation, have been completed. Studies on the asymmetric synthesis are in hand.

Acknowledgment

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(8) NMR spectroscopic data for the *trans* isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (3 H, d, *J* = 6.8 Hz, CH_3), 1.45 (9 H, s, *t*-Bu), 2.39 (1 H, m, CH), 3.41 (1 H, t, *J* = 8.3 Hz, CH_2), 3.93 (1 H, t, *J* = 6.9 Hz, CH), 4.10 (1 H, t, *J* = 7.2 Hz,CH_2), 5.13 (1 H, *J* = 10.1 Hz, =CH), 5.22 (1 H, *J* = 17.0 Hz, =CH), 5.76 (1 H, ddd, *J* = 7.2, 10.2, 16.8 Hz, =CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 28.2, 43.8, 69.1, 75.0, 81.8, 115.8, 136.7, 157.0.

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(11) A suitable crystal was obtained from EtOAc–hexane. Empirical formula: $C_{11}H_{21}NO_3$; formula weight: 215.29; temp: 173 (2) K; wavelength: 0.71073 Å; crystal system: monoclinic; space group: P2 (1)/n; unit cell dimensions: *a* = 11.1651 (4) Å, *α* = 90°, *b* = 11.2768 (4) Å, *β* = 115.343 (2)°, *c* = 11.1785 (5) Å, *γ* = 90°; volume: 1272.00(9) Å^3; *Z*: 4; density(calcd): 1.124 Mg/m^3; absorption coefficient: 0.081 mm^{-1}; *F*(000): 472; crystal size: 0.30 × 0.30 × 0.14 mm^3; *c* range for data collection: 2.16–27.67°; index ranges: –14 ≤ *h* ≤ 14, –12 ≤ *k* ≤ 14, –14 ≤ *l* ≤ 14; reflections collected: 12787; independent reflections: 2983 [*R*(int) = 0.0586]; completeness to *c* = 27.67°: 99.9%; absorption correction; semi-empirical from equivalents; max. and min. transmission: 0.9888 and 0.9762; refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 2983/0/144; goodness-of-fit on F^2; 1.067; final *R* indices [I > 2σ(*I*)]*R*1 = 0.0652, *wR*2 = 0.1952; *R* indices (all data); *R*1 = 0.1041, *wR*2 = 0.2283; largest diff. peak and hole; 0.425 and –0.298 e Å^{-3}. Details have been deposited with the Cambridge Crystallographic Data Centre, CCDC 764203, and may be obtained at http://www.ccdc.cam.ac.uk.

(12) Diethyl methylphosphonate (8.71 g, 57.3 mmole) in THF (30 mL) and added via cannula to a solution of *n*-BuLi (48 mL of a 1.6 M solution in hexane, 71.6 mmol) in THF (50 mL) at –78 °C. A solution of the Weinreb amide of 3-furoic acid (6.64 g, 47.7 mmol) in THF (20 mL) and added via cannula to the mixture. The mixture was stirred for 2 h. 2 M HCl was added to the mixture, and it was extracted twice with Et_2O. The combined organic layers were dried ($MgSO_4$), and concentrated to give phosphonate **8** as a brown oil (15 g, 1.29 mmol, 72%), which was used without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.05 Hz, 6 H, CH_3), 3.39 (d, *J* = 22.7 Hz, 2 H, PCH_2), 4.14 (m, 4 H, CH_2), 6.80 (t, *J* = 1.2 Hz, 1 H, CH), 7.43 (s, 1 H, CH), 8.16 (s, 1 H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2 (d, *J* = 5.7 Hz), 40.6 (d, *J* = 127.8 Hz), 62.7, 108.8, 127.7, 144.2, 149.1, 185.6 (d, *J* = 6.7 Hz).

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(18) NMR data for piperidine **12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.4 Hz, 3 H), 1.10–1.30 (m, 3 H), 1.35–1.50 (1 H, m), 1.55–1.70 (1 H, m), 1.75–1.85 (2 H, m), 1.95–2.05 (1 H, m), 2.25–2.32 (1 H, m), 2.40–2.45 (2 H, m), 3.57 (m, 1 H), 3.65 (s, 3 H), 6.37 (s, 1 H), 7.33 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 28.6, 30.2, 33.9, 34.1, 35.5, 51.5, 53.2, 62.3, 109.1, 129.5, 138.3, 142.7, 174.5.

(19) Lactam **13** is also obtained if ester **12** is treated directly with methylmagnesium bromide.