A Short and Enantiospecific Synthesis of (–)-Nupharamine

Julian Gebauer, Siegfried Blechert*

Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 135, 10623 Berlin, Germany
Fax +49(30)31423619; E-mail: blechert@chem.tu-berlin.de

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Abstract: A short and convergent synthesis of the naturally occurring sesquiterpenoid piperidine alkaloid (–)-nupharamine is presented starting from (–)-isopinocampheol via cross metathesis and reductive amination as the key steps.

Key words: catalysis, reductive amination, terpenes, alkaloids, cross metathesis

Aquatic plants of the genus *Nuphar* (*Nymphaeaceae*) have shown to be the source of a large class of terpenoid alkaloids some of which exhibit immunosuppressive, antifungal or insecticidal activity.[1] As a unique structural motif, the *Nuphar* alkaloids share a 3-furyl group and almost all display a quinolizidine core (Figure 1).

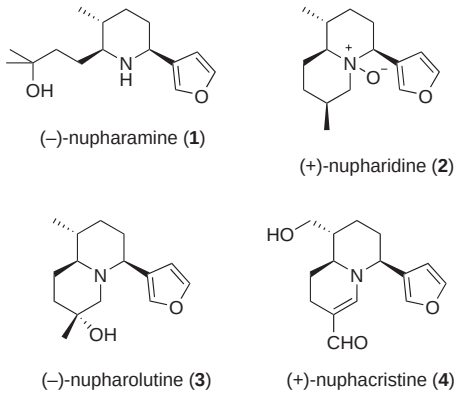
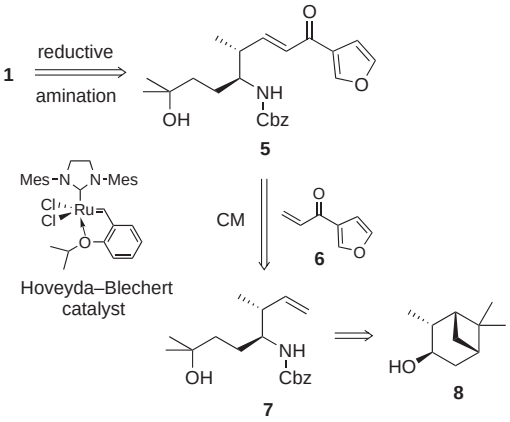


Figure 1 Selected *Nuphar* alkaloids.

Isolated from the rhizome of the yellow water lily *Nuphar japonica*,[2] a perennial herb used as diuretic and stomach analgesic, (–)-nupharamine (**1**) is one of only a few sesquiterpenoid piperidines and has served as an attractive target in several enantioselective syntheses.[3] On the basis of our previous work towards the synthesis of substituted N-heterocycles[4] we herein wish to report a short and convergent synthesis of **1** via an olefin cross metathesis (CM) – reductive amination sequence starting from furyl vinyl ketone **6** and enantiopure amino alcohol **7**, the latter being derived in three steps from (–)-isopinocampheol (**8**) as an inexpensive chiral building block (Scheme 1).

The strategies for the preparation of both CM partners are outlined in Scheme 2. Since regioselective thermal frag-



Scheme 1 Retrosynthetic analysis.

mentation of the cyclobutane ring of several pinanes including (+)-isopinocampheol has been reported,[5] we envisaged that thermolysis of **8** would furnish dienol **9a** as an adequate substrate for the preparation of the desired metathesis precursor **7**.

Although the yield of dienol has been rather modest[5a] (25%) the multigram availability of enantiopure **8** and its one-step conversion into **9a** as an appropriately substituted precursor of the correct absolute configuration should be a fair compensation.

In our hands flash pyrolysis at 480 °C and 15 mbar in the gas phase gave a 20:1 mixture[6] of the isomeric dienols **9a** and **9b** in 23% yield together with 50% of recovered starting material. Since removal of **9b** was difficult by column chromatography we chose to proceed with the mixture and attempt separation at a later stage. The selective hydration of trisubstituted double bonds yielding tertiary alcohols has been successfully achieved either by epoxidation and subsequent ring-opening[7] or addition of trifluoro acetic acid (TFA) and subsequent acetate cleavage.[8] For the latter purpose we considered phthalimide **10** to be an ideal intermediate as it would allow the introduction of nitrogen under the required inversion of configuration through a Mitsunobu reaction and at the same time eliminate the possibility of acid-promoted intramolecular N-alkylation. Simultaneous N,O-deprotection and N-reprotection should in turn afford the desired CM precursor **7**.

Unfortunately, Mitsunobu reaction of **9a**,**b** with 1.1 equivalents of phthalimide, DEAD and PPh_3 in THF led to extensive elimination (ca. 60%) probably due to the high steric demand of the intermediate phosphonium species.

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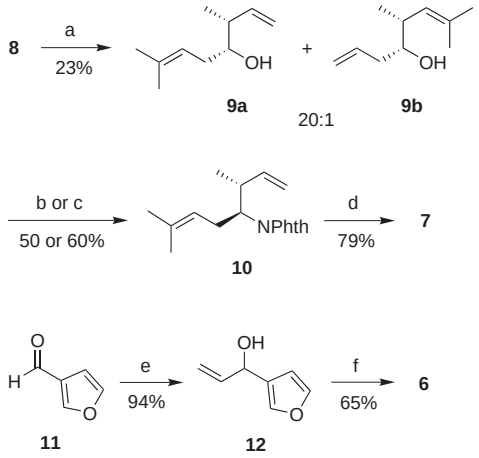
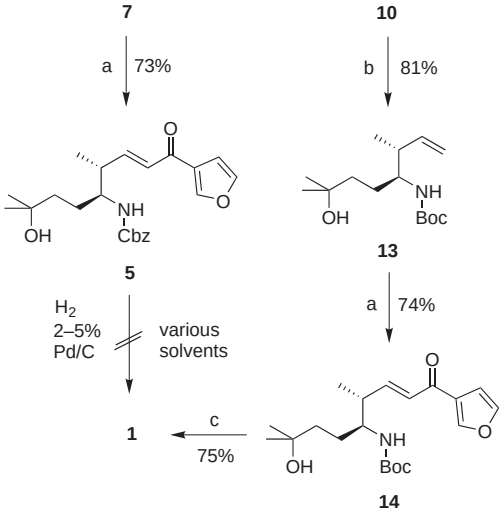


Scheme 2 *Reagents and conditions*: a) 480 °C, 15 mbar, gas phase; b) phthalimide, $MePPh_2$, DEAD (1.1 equiv each), THF, 0 °C, 1 h; c) (i) MsCl (1.2 equiv), pyridine, r.t., 2 h; (ii) NaN_3 (5 equiv), DMF, 50 °C, 60 h; (iii) LAH (4 equiv), Et_2O, 0 °C, 1 h; (iv) phthalic anhydride (1 equiv), THF, 60 °C, 2 h; (v) CDI (2 equiv), THF, r.t., 1 h; d) (i) 30% TFA (10 equiv) in $CHCl_3$, r.t., 16 h; (ii) $MeNH_2$ (50 equiv), EtOH, 55 °C, 24 h; (iii) Cbz-Cl (1.1 equiv), aq $NaHCO_3$, $CHCl_3$, r.t., 16 h; e) vinyl magnesium bromide (1.1 equiv), Et_2O, 0 °C, 1 h; f) MnO_2 (10 equiv), CH_2Cl_2, 40 °C, 24 h.



Scheme 3 *Reagents and conditions*: a) **6** (1.2 equiv), 10 mol% (2-isopropoxyphenylmethylene)–[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]ruthenium dichloride, CH_2Cl_2, 40 °C, 72 h; b) (i) 30% TFA (10 equiv) in $CHCl_3$, r.t., 16 h; (ii) $MeNH_2$ (50 equiv), EtOH, 55 °C, 24 h; (iii) Boc_2O (1.1 equiv), aq $NaHCO_3$, $CHCl_3$, r.t., 16 h; c) (i) H_2 (1 atm), 5 mol% Pd/C, acetone, r.t., 15 min; (ii) 10% TFA in CH_2Cl_2, r.t., 1 h; (iii) $NaBH_4$ (1 equiv), EtOH, 0 °C, 1 h.

Thus, slightly better results were obtained by using $MePPh_2$ as the phosphine component, whereas Me_2PPh gave no further improvement.

In order to overcome this drawback, an alternative two-step S_N2-process was investigated. While mesylation of **9a**,**b** and reaction with phthalimide potassium salt (2 equiv, DMF, 50 °C, 72 h) failed completely, substitution using sodium azide under the same conditions occurred smoothly, showing only small amounts of elimination product. The LAH reduction of the crude azide, treatment with phthalic anhydride and cyclization of the resulting phthalamic acid using carbonyldiimidazole (CDI)[9] was therefore found to be an alternative route affording **10** in 60% yield over five steps.

In both cases **10** was obtained as a single diastereomer after column chromatography.[10] Finally, treatment with TFA in $CHCl_3$, aminolysis with excess methylamine in EtOH and introduction of the benzyl carbamate furnished **7** in high overall yield.

Addition of vinyl magnesium bromide to 3-furfural (**11**) and mild oxidation of the crude carbinol **12** gave rise to enone **6**, which decomposed even at low temperature and was preferably prepared freshly before use.

With both coupling partners in hands, CM reaction of **7** using 10 mol% of the Hoveyda–Blechert catalyst[11] and a slight excess (1.2 equiv) of **6** proceeded slowly, giving the desired amino enone **5** in 73% yield (Scheme 3). It should be noted that the application of higher temperatures (60–80 °C in dichloroethane), larger amounts (2–5 equiv) of **6** or the use of other commercial catalysts gave no improvement in this case.

In course of the finishing piperidine formation we were surprised to find that various attempts to achieve the intended reductive amination by means of hydrogenolysis failed due to concomitant reduction of the 3-acyl furan moiety. As reduction of the conjugated double bond in **5** was fortunately the most rapid process, we reasoned that its selective hydrogenation followed by N-deprotection and final diastereoselective hydride reduction of the resulting imine should constitute a simple alternative for construction of the piperidine ring.[12] In consequence, Boc protection of the crude amino alcohol derived from **10**[13] followed by CM reaction under the approved conditions provided the suitable cyclization precursor **14** in good overall yield.[14] Finally, careful hydrogenation of **14** in aprotic media, Boc cleavage with 10% TFA in CH_2Cl_2 and treatment of the imine intermediate with $NaBH_4$ in EtOH produced **1** as a single stereoisomer[3c] in 75% yield,[15] whose spectroscopic data[3d,16] and optical rotation[2] {$[\alpha]_D^{20}$ –38.7 (*c* 0.75, $CHCl_3$)} were in accordance with the ones reported.

In conclusion, we have described an exceptionally short and efficient (27% overall yield from **9a**,**b**) approach to (–)-nupharamine, utilizing commercially available (–)-isopinocampheol as the only source of chirality. Furthermore, our convergent strategy should enable easy access to derivatives bearing substituents other than the 3-furyl group, as well as their enantiomers when starting from (+)-isopinocampheol.

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(10) **Preparation and Spectral Data of 10.**
To a stirred solution of alcohol **9a**,**b** (154 mg, 1.0 mmol), phthalimide (162 mg, 1.1 mmol) and $MePPh_2$ (220 mg, 1.1 mmol) in dry THF (5 mL) under nitrogen was added DEAD (191 mg, 1.1 mmol) dropwise at 0 °C. The mixture was allowed to warm to r.t. over a period of 1 h before it was diluted with Et_2O, filtered and concentrated. Flash chromatography (SiO_2) of the resulting residue gave 140 mg (50%) of **10** as a colorless oil. $[\alpha]_D^{20}$ –18.8 (*c* 0.85, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (m, 2 H), 7.67 (m, 2 H), 5.58 (m, 1 H), 4.97 (t, *J* = 7.0 Hz, 1 H), 4.91 (dd, *J* = 16.9, 1.0 Hz, 1 H), 4.76 (dd, *J* = 10.1, 1.0 Hz, 1 H), 3.99 (dt, *J* = 11.0, 4.1 Hz, 1 H), 3.00 (m, 1 H), 2.85 (m, 1 H), 2.45 (m, 1 H), 1.53 (s, 3 H), 1.52 (s, 3 H), 1.14 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8, 141.2, 134.6, 133.7, 131.8, 123.0, 120.3, 115.1, 56.8, 41.1, 28.4, 25.7, 18.4, 17.8 ppm. IR (ATR): ν = 2973, 2928, 1772, 1710, 1390, 1361, 1088, 919, 874, 721 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{18}H_{21}NO_2$ [M^+]: 283.1572; found: 283.1577. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 75.92; H, 7.55; N, 4.64.

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(13) **Preparation and Spectral Data of 13.**
To a stirred solution of **10** (140 mg, 0.5 mmol) in $CHCl_3$ (1.2 mL) was added TFA (0.4 mL, 5.0 mmol) dropwise at 0 °C. After 16 h at r.t. the volatiles were removed in vacuo. To the residue was added a 8 M solution of $MeNH_2$ in EtOH (3 mL, 24 mmol) and the mixture was stirred at 55 °C for 24 h. Evaporation of the volatiles gave the crude amino alcohol which was dissolved in $CHCl_3$ (4 mL) and treated with sat. $NaHCO_3$ solution (0.5 mL) followed by Boc_2O (120 mg, 0.54 mmol) in 1 mL $CHCl_3$. After 16 h at r.t. H_2O (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried, concentrated, diluted with Et_2O and filtered. Flash chromatography (SiO_2) of the concentrate gave 97 mg (81%) of **13** as a clear viscous oil. $[\alpha]_D^{20}$ –7.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.76 (m, 1 H), 5.08 (m, 2 H), 4.29 (br d, *J* = 8.4 Hz, 1 H), 3.57 (m, 1 H), 2.34 (m, 1 H), 1.60–1.30 (m, 5 H), 1.44 (s, 9 H), 1.21 (s, 6 H), 1.03 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.2, 139.5, 115.9, 79.1, 70.7, 54.8, 41.6, 39.9, 29.6, 29.4, 28.5, 27.9, 16.3 ppm. IR (ATR): ν = 3345, 2969, 2932, 1690, 1504, 1365, 1250, 1173, 913 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{14}H_{26}NO_3$ [$M^+ - CH_3$]: 256.1913; found: 256.1929. Anal. Calcd for $C_{15}H_{29}NO_3$: C, 66.38; H, 10.77; N, 5.16. Found: C, 66.67; H, 10.58; N, 5.45.

(14) **Preparation and Spectral Data of 14.**
A solution of amine **13** (27 mg, 0.10 mmol), enone **6** (15 mg, 0.12 mmol) and the Hoveyda–Blechert catalyst (6.3 mg, 0.01 mmol) in dry CH_2Cl_2 (2 mL) under nitrogen was stirred for 72 h at 40 °C. The solvent was evaporated and the residue was purified by flash chromatography (SiO_2) to give 27 mg (74%) of **14** as a brownish solid. Mp 92–94 °C. $[\alpha]_D^{20}$ –24.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.45 (s, 1 H), 6.95 (dd, *J* = 15.5, 8.0 Hz, 1 H), 6.83 (s, 1 H), 6.56 (d, *J* = 8.0 Hz, 1 H), 4.44 (br d, *J* = 9.4 Hz, 1 H) 3.69 (m, 1 H), 2.58 (m, 1 H), 1.60–1.30 (m, 5 H), 1.42 (s, 9 H), 1.20 (s, 6 H), 1.13 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 184.4, 156.1, 148.9, 147.6, 144.3, 128.0 127.7, 109.2, 79.4, 70.6, 54.8, 41.6, 39.8, 29.6, 29.4, 28.4, 27.7, 16.3 ppm. IR (ATR): ν = 3345, 2970, 2932, 1692, 1668, 1619, 1512, 1365, 1250, 1158, 1055, 873 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{16}H_{23}NO_5$ [$MH^+ - C(CH_3)_3$]: 309.1576; found: 309.1580. Anal. Calcd for $C_{20}H_{31}NO_5$: C, 65.73; H, 8.55; N, 3.83. Found: C, 65.28; H, 8.07; N, 3.63.

(15) **Preparation and Spectral Data of (–)-Nupharamine (1)**.
To a solution of aminoenone **14** (35 mg, 0.096 mmol) in acetone (2 mL) was added 10% Pd/C (6 mg, 0.005 mmol) at r.t. and the heterogeneous mixture was stirred under 1 atm of hydrogen for 15 min. Filtration and evaporation of the solvent gave a residue which was dissolved in CH_2Cl_2 (1 mL), treated with TFA (0.1 mL) and stirred for 1 h. The solution was then diluted with CH_2Cl_2 (20 mL), washed with sat. $NaHCO_3$ solution (5 mL), dried and concentrated. To the crude imine were added EtOH (1 mL) and at 0 °C $NaBH_4$ (4 mg, 0.1 mmol). After 1 h the solvent was evaporated and the residue was purified by flash chromatography (Al_2O_3) to give 18 mg (75%) of a yellow oil. $[\alpha]_D^{20}$ –38.7 (*c* 0.75, $CHCl_3$), {lit.[2] $[\alpha]_D^{22}$ –35.4 ($CHCl_3$)}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (m, 2 H), 6.41 (s, 1 H), 3.61 (dd, *J* = 11.5, 2.0 Hz, 1 H), 2.38 (m, 1 H), 1.85 (m, 2 H), 1.75 (m, 2 H), 1.57 (m, 2 H), 1.45 (m, 2 H), 1.23 (m, 1 H), 1.21 (s, 3 H), 1.19 (s, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.1, 138.5, 129.0, 109.3, 68.9, 63.0, 53.1, 39.7, 34.3, 34.0, 33.7, 30.3, 29.3, 28.5, 18.6 ppm. IR (ATR): ν = 3385, 2966, 2926, 2871, 2850, 1458, 1377, 1161, 1025, 912, 874, 794, 765 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{15}H_{25}NO_2$ [M^+]: 251.1885; found: 251.1890..

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