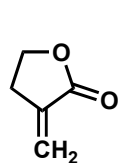


# Total Synthesis of Nuphar Thioalkaloids

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1) 0.9 mol-% [Ru(C<sub>6</sub>H<sub>6</sub>)Cl((S)-BINAP)]Cl  
H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>  
2) DIBALH, CH<sub>2</sub>Cl<sub>2</sub>, -78°C  
3) Ph<sub>3</sub>PCH<sub>2</sub>, Et<sub>2</sub>O, 0°C  
4) I<sub>2</sub>, PPh<sub>3</sub>, ImH, CH<sub>2</sub>Cl<sub>2</sub>, 0°C  
71% o4s, 96% ee

**A**

5) **1**, **2**, <sup>n</sup>BuLi, THF, 0°C  
then **A**, THF, -78°C

**B**

7) acrolein diethyl acetal  
5 mol-% HG-II, CH<sub>2</sub>Cl<sub>2</sub>, 40°C  
E:Z 10:1  
8) Ph<sub>3</sub>PCHCO<sub>2</sub>Me, CH<sub>2</sub>Cl<sub>2</sub>, 40°C  
E:Z 5:1

**C**

9) Cd-Pb couple,  
THF/1 M NH<sub>4</sub>OAc(aq), 23°C  
10) 5 mol-% [RhCl(PPh<sub>3</sub>)<sub>3</sub>],  
H<sub>2</sub>, PhMe  
41% o4s

**C**

11a) AcOH, PhMe  
110°C  
91%

**D**

12a) 4 eq. LDA,  
10 eq. 4-MeOC<sub>6</sub>H<sub>4</sub>OCOCI  
THF, -78°C

**E**

13a) NaBH<sub>4</sub>, MeOH, 23°C  
43% o2s

14a) 3 eq. MsCl, Hünig's Base  
CH<sub>2</sub>Cl<sub>2</sub>, 0°C

**F**

15a) 5 eq. Na<sub>2</sub>S x 9 H<sub>2</sub>O,  
0.2 eq. TBAI  
16a) DIBALH, PhMe, 0°C  
73% o3s

**C**

11b) AllocCl,  
Hünig's Base  
THF, rflux  
90%

**G**

12b) KHMDS, methyl benzoate  
THF, -78°C to 0°C

**H**

13b) (4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>)SO<sub>2</sub>N<sub>3</sub>, DBU  
CH<sub>2</sub>Cl<sub>2</sub>, 23°C  
78% o2s

**H**

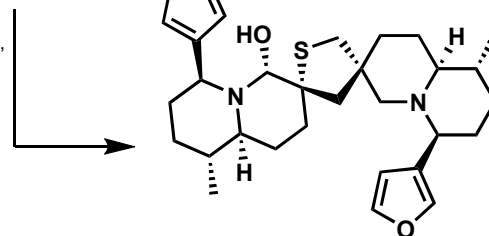
17) 0.83 eq. **F**  
5 mol-% [Cu(hfacac)<sub>2</sub>]  
CH<sub>2</sub>Cl<sub>2</sub>, 100°C (μW)  
55% (82% brsm **F**)

**I**  
29%

and

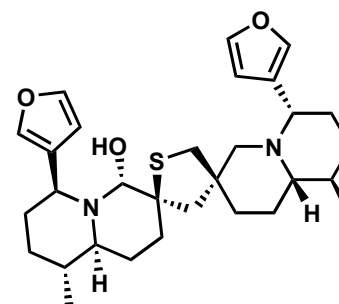
**J**  
26%

18) 5 mol-% [Pd(PPh<sub>3</sub>)<sub>4</sub>],  
PhSiH<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 23°C  
19) DIBALH, -89°C  
33% o2s

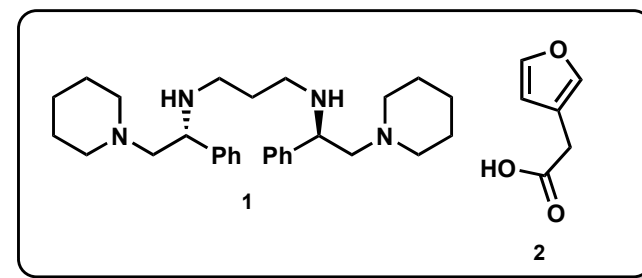


(+)-6-Hydroxythiobinupharidine

18) + 19)  
59% o2s



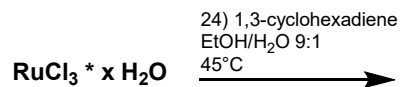
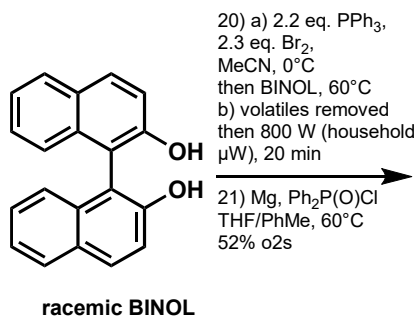
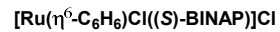
(-)-6-Hydroxythionuplutine



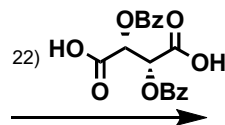
## Hints:

- 9) 1 new ring formed
- 15a) only 1 eq. sulfide gets incorporated

**Total synthesis of Nuphar thioalkaloids**  
**Synthesis of organometallic compounds & catalysts**



K



$\text{CHCl}_3/\text{EtOAc}$ , reflux  
 then filter  
 then  $\text{NaOH}_{(\text{aq})}$   
 89%

L

23) 4.3 eq.  $\text{NEt}_3$ ,  
 4.2 eq.  $\text{HSiCl}_3$   
 $100^\circ\text{C}$  to  $120^\circ\text{C}$ ,  
 xylenes  
 97%

M

N

25) 2 eq. M  
 EtOH/ $\text{C}_6\text{H}_6$  8:1  
 $50^\circ\text{C}$ , 40 min

