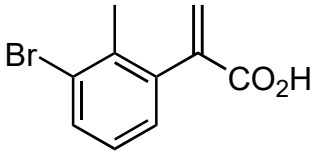
Asymmetric Synthesis of Cyclopamine, a Hedgehog (Hh) Signaling Pathway Inhibitor

Shao, A.; Liu, W.; Liu, M.; He, H.; Zhou, Q.-L.; Zhu, S.-F.; Gao, S.

J. Am. Chem. Soc. **2023**. DOI:10.1021/jacs.3c10362



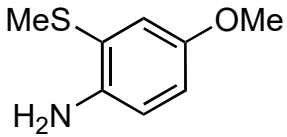
1-3

A

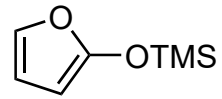
4-9

B

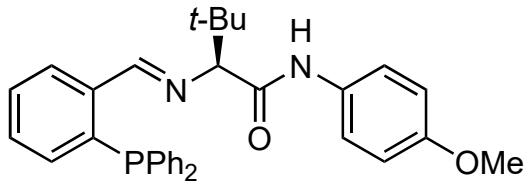
1) H_2, [Ir-SpiroBAP]$^+$, Cs_2CO_3
2) $TMSCHN_2$, DIBALH *then* DMP
3) **1**, **2**, **3**, *i*-PrOH, AgOAc



1



2



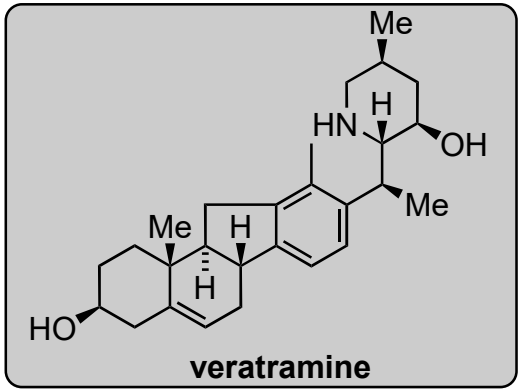
3

4) $Cu(OAc)_2$, $PhSiH_3$
5) LiHMDS, MeI, 1,3-dimethyl-2-imidazolidinone
6) CAN *then* HCl
7) NaOH
8) BH_3•SMe_2 *then* Boc_2O, Na_2CO_3
9) NaH, BnBr, TBAI

1) HINT: Stereochem. maps onto natural product

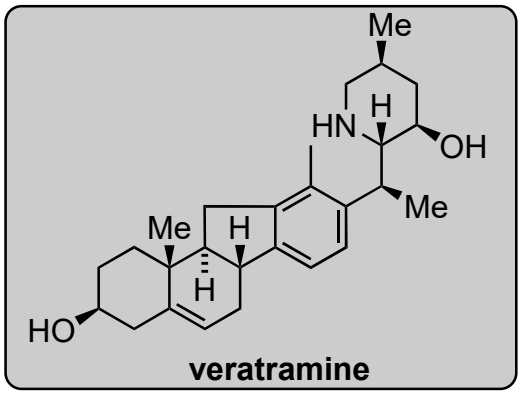
3) HINT: Product has ^{13}C signal at 173.5 ppm, 8 ^1H signals >6 ppm

7) HINT: Product has two exchangeable protons



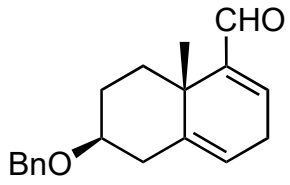
veratramine

10-14



veratramine

10) *t*-BuLi *then* **4**
11) DMP
12) *hv* (366 nm)
13) LAH, $AlCl_3$
14) Na, NH_3 *then* HCl

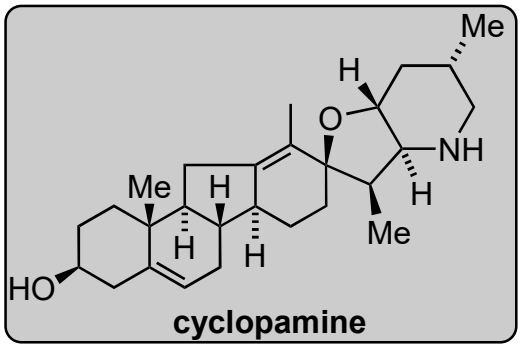


4

15-20

15) Li, NH_3 *then* PtO_2, H_2
16) Fmoc-OSu
17) *m*-CPBA
18) HCl (aq.)
19) TMSOTf
20) Et_2NH

15) HINT: ^{13}C signals at 143.1, 134.8, 132.0, 123.2



cyclopamine