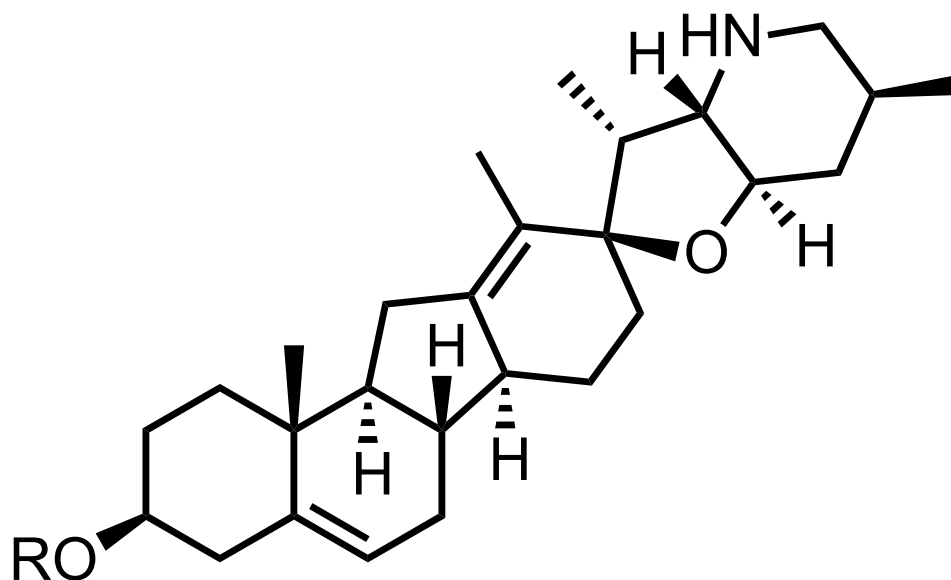


# Jerveratrum Alkaloids: Total & Semi-Synthesis

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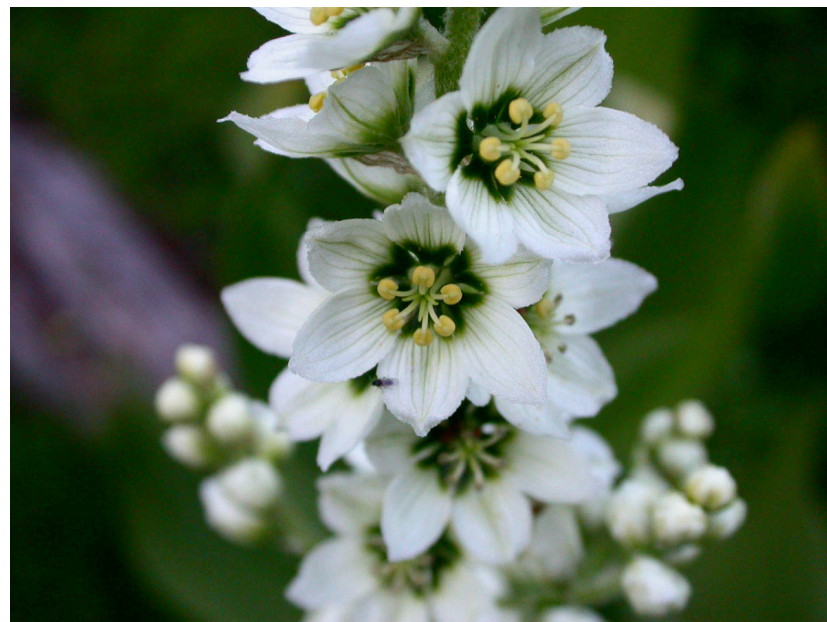


Jeremy Roach  
Shenvi Lab Group Meeting  
August 8, 2013

# Outline

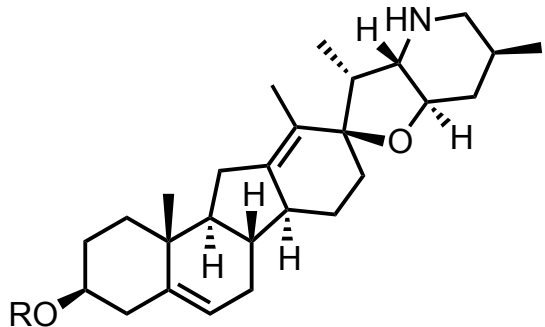
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1. Structure & Family
2. Discovery & Biological Impact
3. Syntheses of Natural Products
4. Medicinal Chemistry & Drug Development

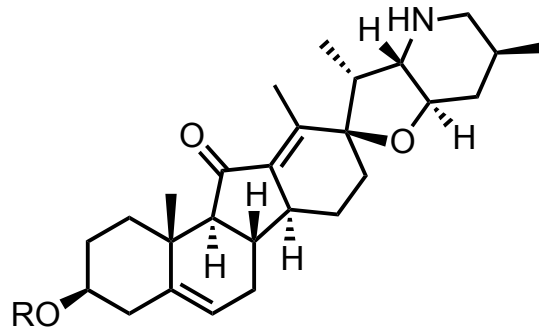


# Members of the Jerveratrum family

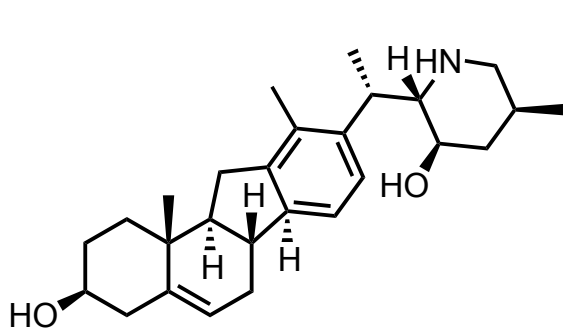
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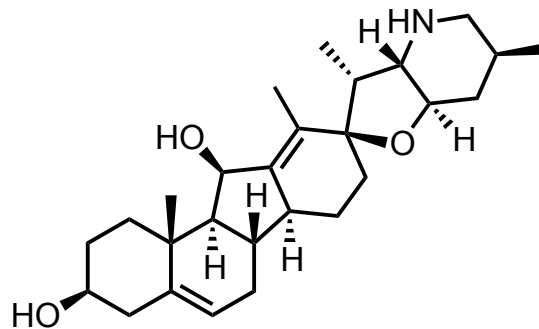
R = H **Cyclopamine**  
R = sug **Cycloposine**



R = H **Jervine**  
R = sug **Pseudojervine**



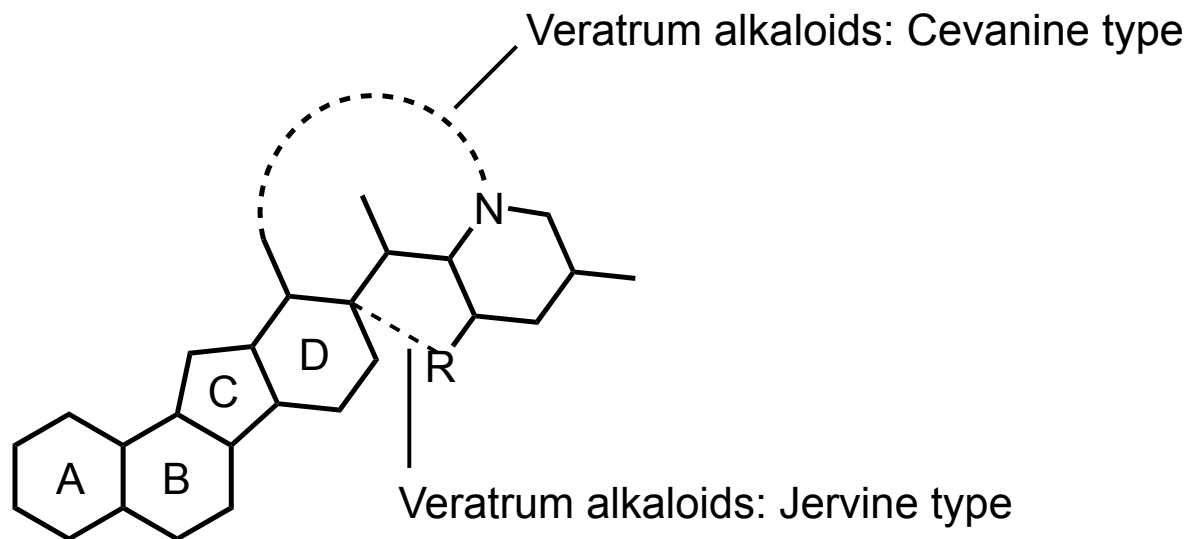
**Veratramine**



**Veratrobazine**

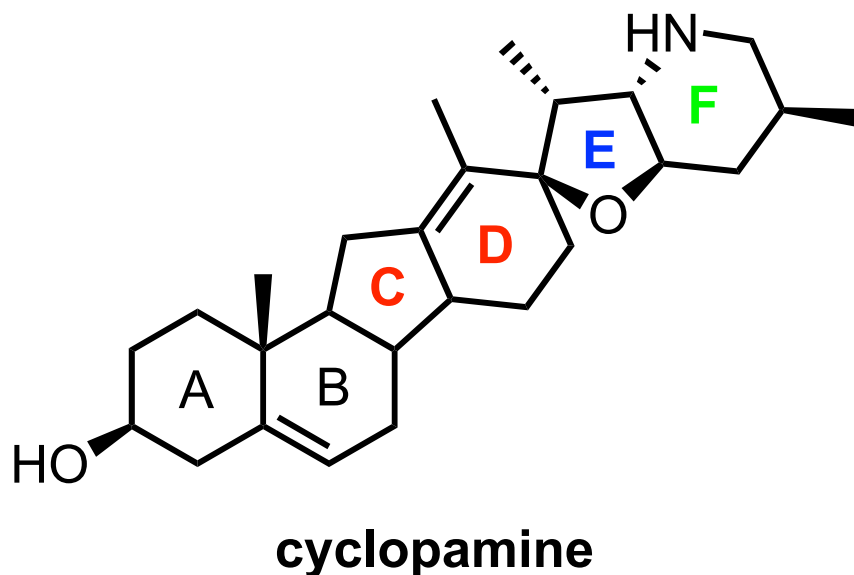
# Veratrum Alkaloids

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# Structural Highlights

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- C-nor-D-homo steroidal framework
- Spiro-connected, highly substituted THF ring E
- Fused piperidine ring F, containing a secondary basic nitrogen

# Homer's *Odyssey*

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Via: [www.dinojim.com](http://www.dinojim.com)

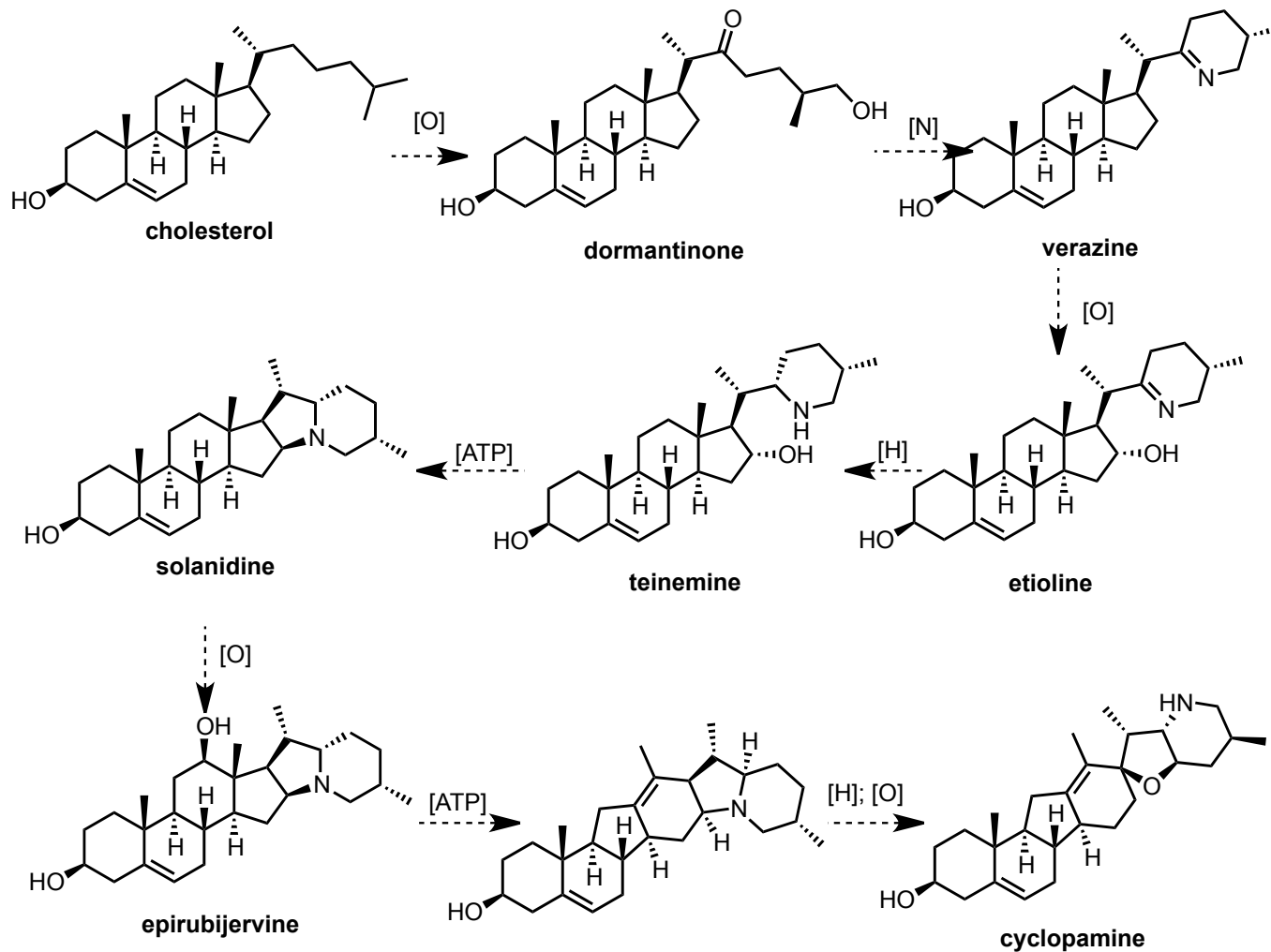
# Discovery of Teratogenic Compounds

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- 1950's – Cyclops Sheep found
- Holoprosencephaly
- Department of Agriculture sent scientists to observe
- Pregnant sheep who grazed upon *Veratrum californicum* had a high occurrence of cyclopia in their offspring

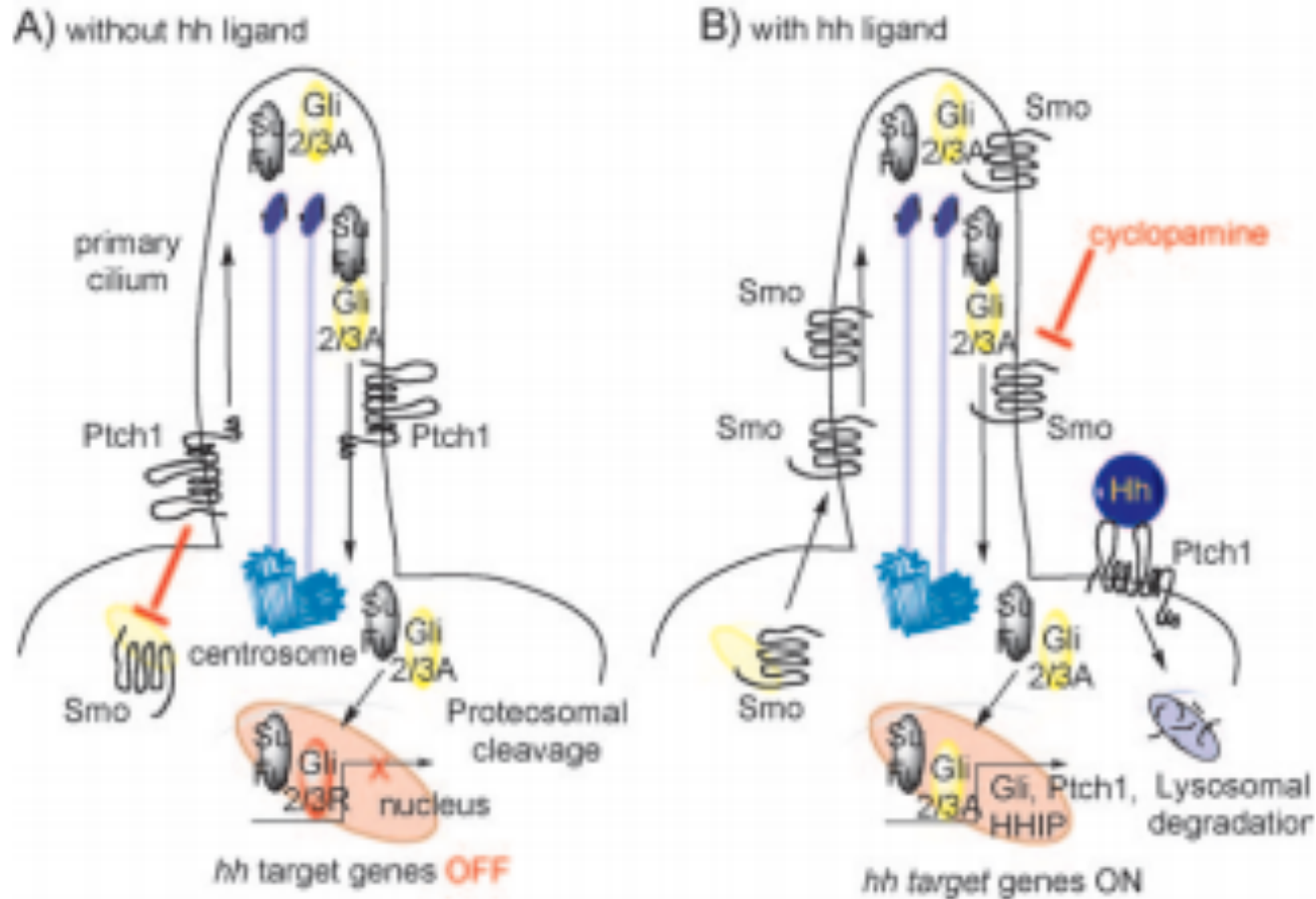


# Biosynthesis





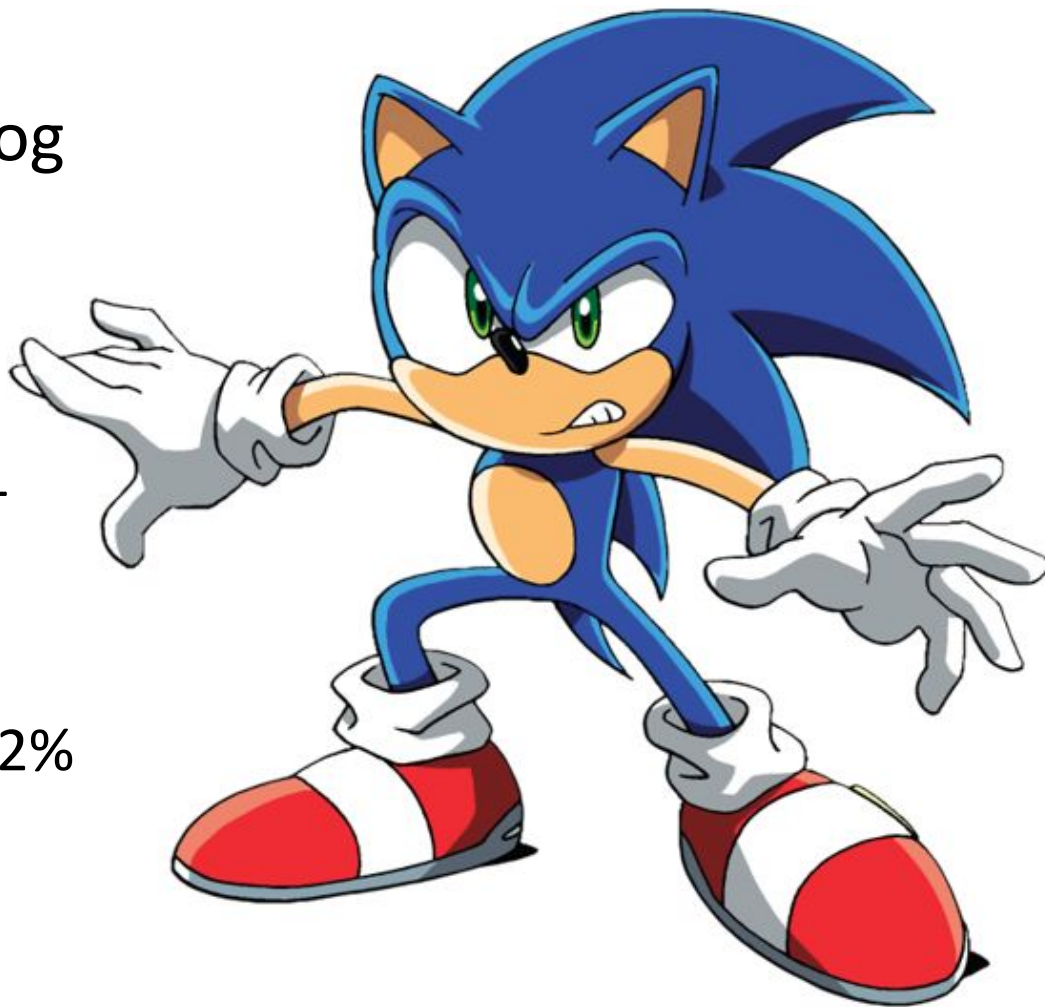
# Mechanism of Action



# Renewed Interest- Antitumor Activity

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- Activation of Hedgehog pathway leads to malignancies
  - Type 1- Gorlin syndrome (BCC) Inactivation of Patched
  - Type 2- Colon
  - Type 3- Pancreas (< 2% survival)



# First Syntheses

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- W. S. Johnson
  - Stanford University
  - Steroid Guru
- Veratramine
- Tadashi Masamune
  - Hokkaido University
- Jervine

# First Syntheses

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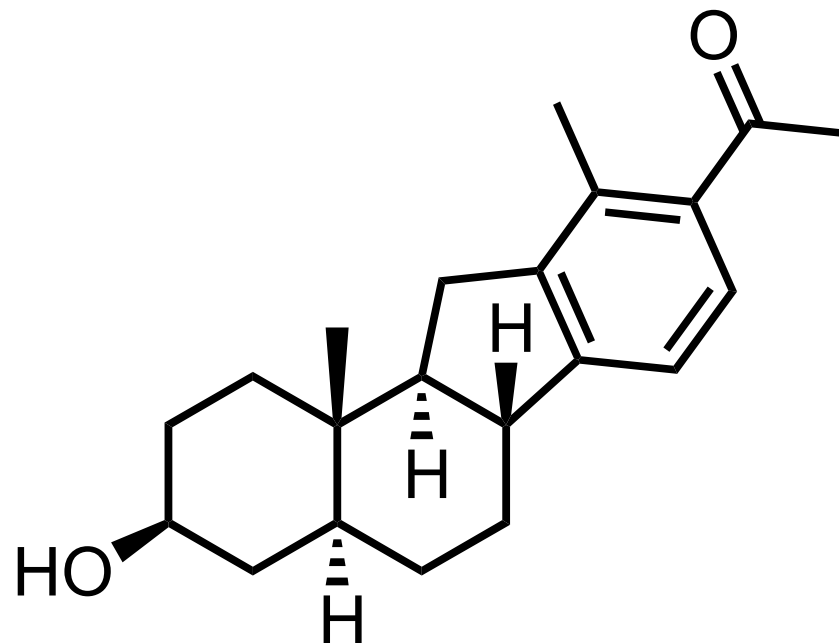
- W. S. Johnson
  - Stanford University
  - Steroid Guru
- Veratramine



- Tadashi Masamune  
(Visual Approximation)
  - Hokkaido University
- Jervine

# Common Intermediate

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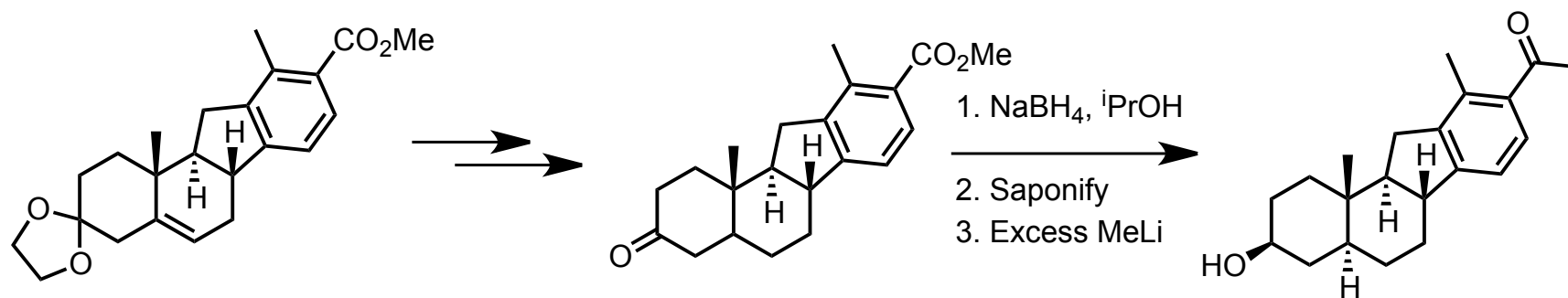


- W. S. Johnson
  - Stanford University
  - Steroid Guru
- Veratramine
- 17-Acetyl-5 $\alpha$ -etiojerva-12,14,16-trien-3 $\beta$ -ol
- Available from Hecogenin degradation



# WS Johnson Intermediate

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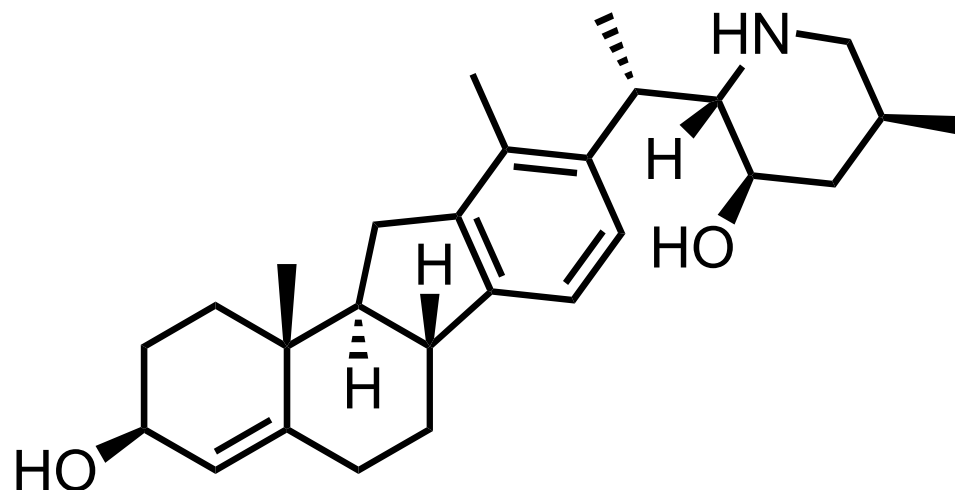
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Johnson, W.S.; Cox, J.M.; Graham, D.W.; Whitlock, H.W. *J. Am. Chem. Soc.* **1967**, *89*, 4524-4526.

Johnson, W.S.; deJongh, A.P; Coverdale, C.E.; Scott, J.W.; Burckhardt, U. . *J. Am. Chem. Soc.* **1967**, *89*, 4523-4524.

# Veratramine

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- W. S. Johnson
  - Stanford University
  - Steroid Guru
- Veratramine

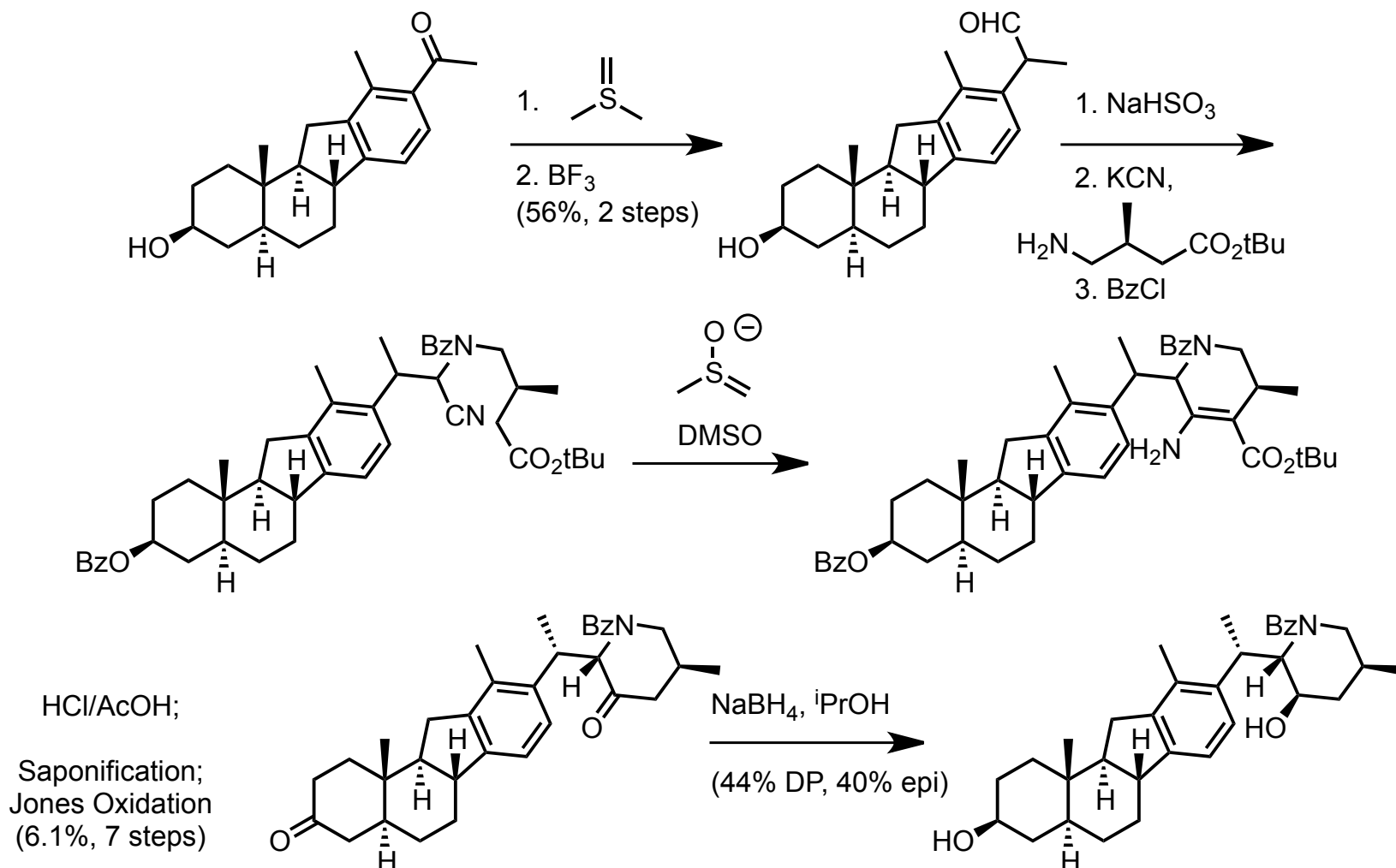
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Johnson, W.S.; Cox, J.M.; Graham, D.W.; Whitlock, H.W. *J. Am. Chem. Soc.* **1967**, *89*, 4524-4526.

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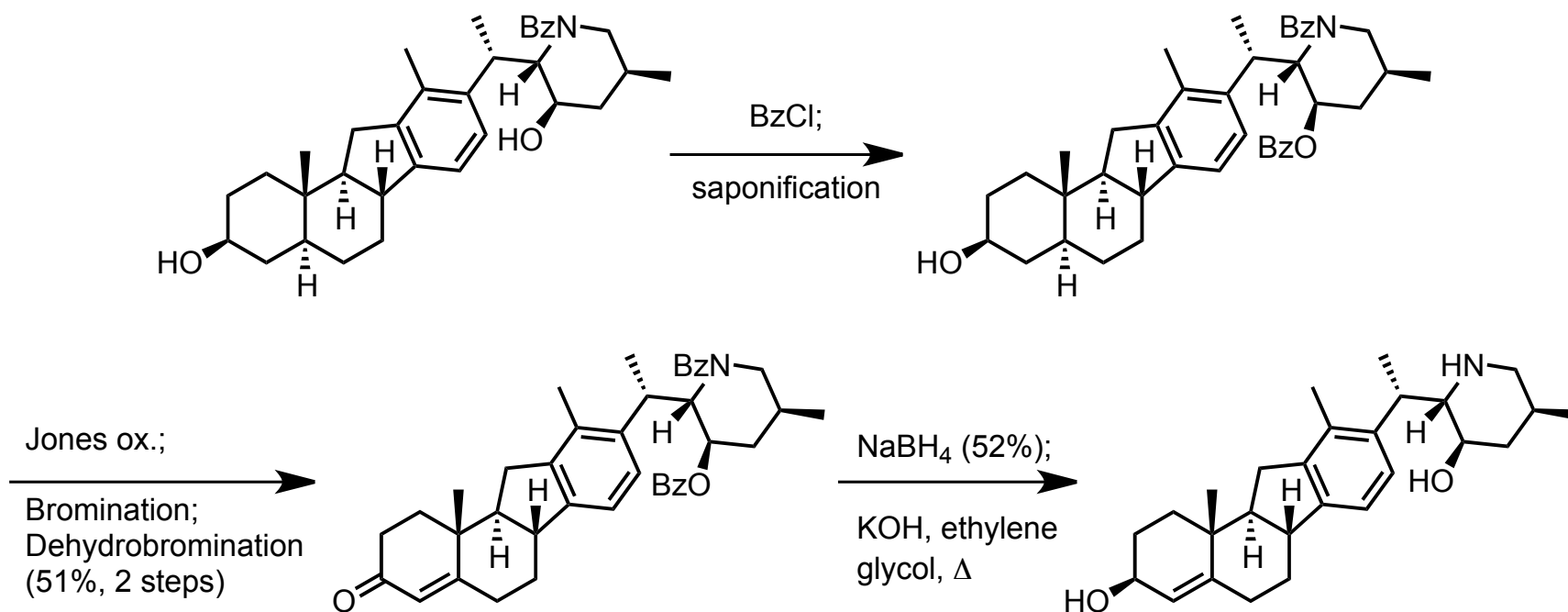
# WS Johnson Veratramine



Johnson, W.S.; Cox, J.M.; Graham, D.W.; Whitlock, H.W. *J. Am. Chem. Soc.* **1967**, *89*, 4524-4526.

Johnson, W.S.; deJongh, A.P.; Coverdale, C.E.; Scott, J.W.; Burckhardt, U. *J. Am. Chem. Soc.* **1967**, *89*, 4523-4524.

# WS Johnson Veratramine



Johnson, W.S.; Cox, J.M.; Graham, D.W.; Whitlock, H.W. *J. Am. Chem. Soc.* **1967**, *89*, 4524-4526.

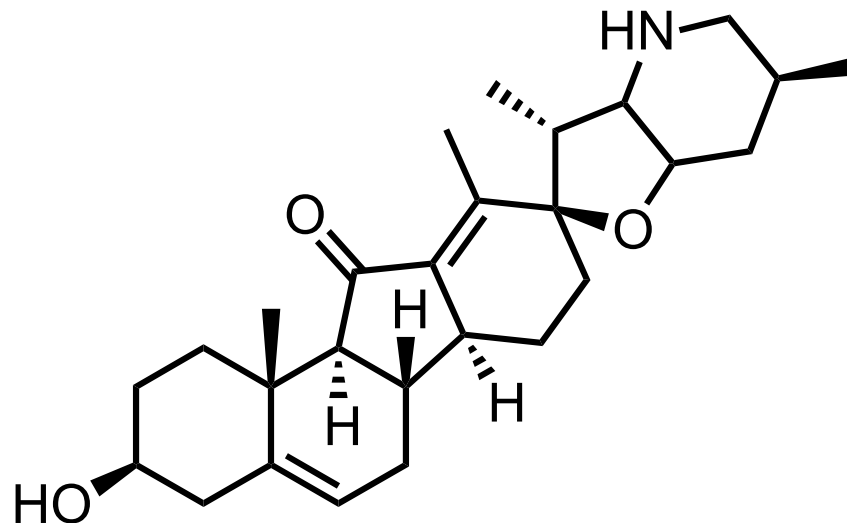
Johnson, W.S.; deJongh, A.P.; Coverdale, C.E.; Scott, J.W.; Burckhardt, U. *J. Am. Chem. Soc.* **1967**, *89*, 4523-4524.

# Jervine

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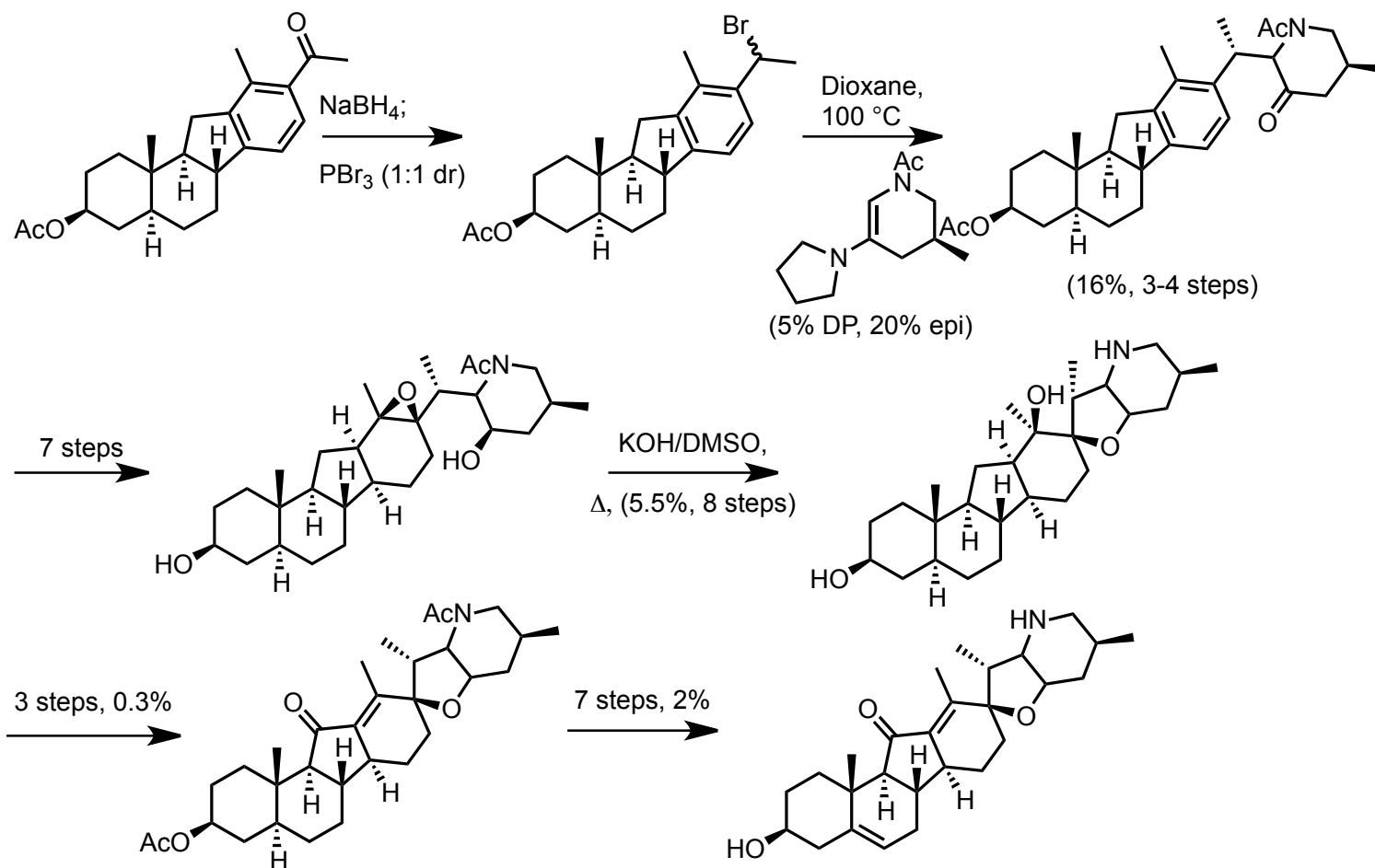
- Tadashi Masamune
  - Hokkaido University
- Jervine



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Johnson, W.S.; Cox, J.M.; Graham, D.W.; Whitlock, H.W. *J. Am. Chem. Soc.* **1967**, *89*, 4524-4526.  
Masamune, T.; Takasugi, M.; Murai, A.; Kobayashi, K. *J. Am. Chem. Soc.* **1967**, *89*, 4521-4523.

# Masamune Jervine

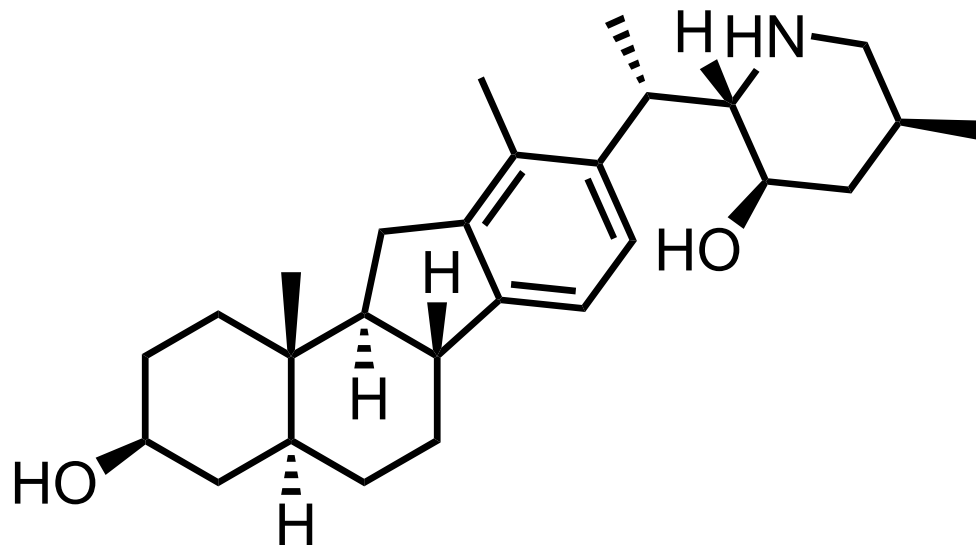


Johnson, W.S.; Cox, J.M.; Graham, D.W.; Whitlock, H.W. *J. Am. Chem. Soc.* **1967**, *89*, 4524-4526.

Masamune, T.; Takasugi, M.; Murai, A.; Kobayashi, K. *J. Am. Chem. Soc.* **1967**, *89*, 4521-4523.

# Formal Synthesis of Family

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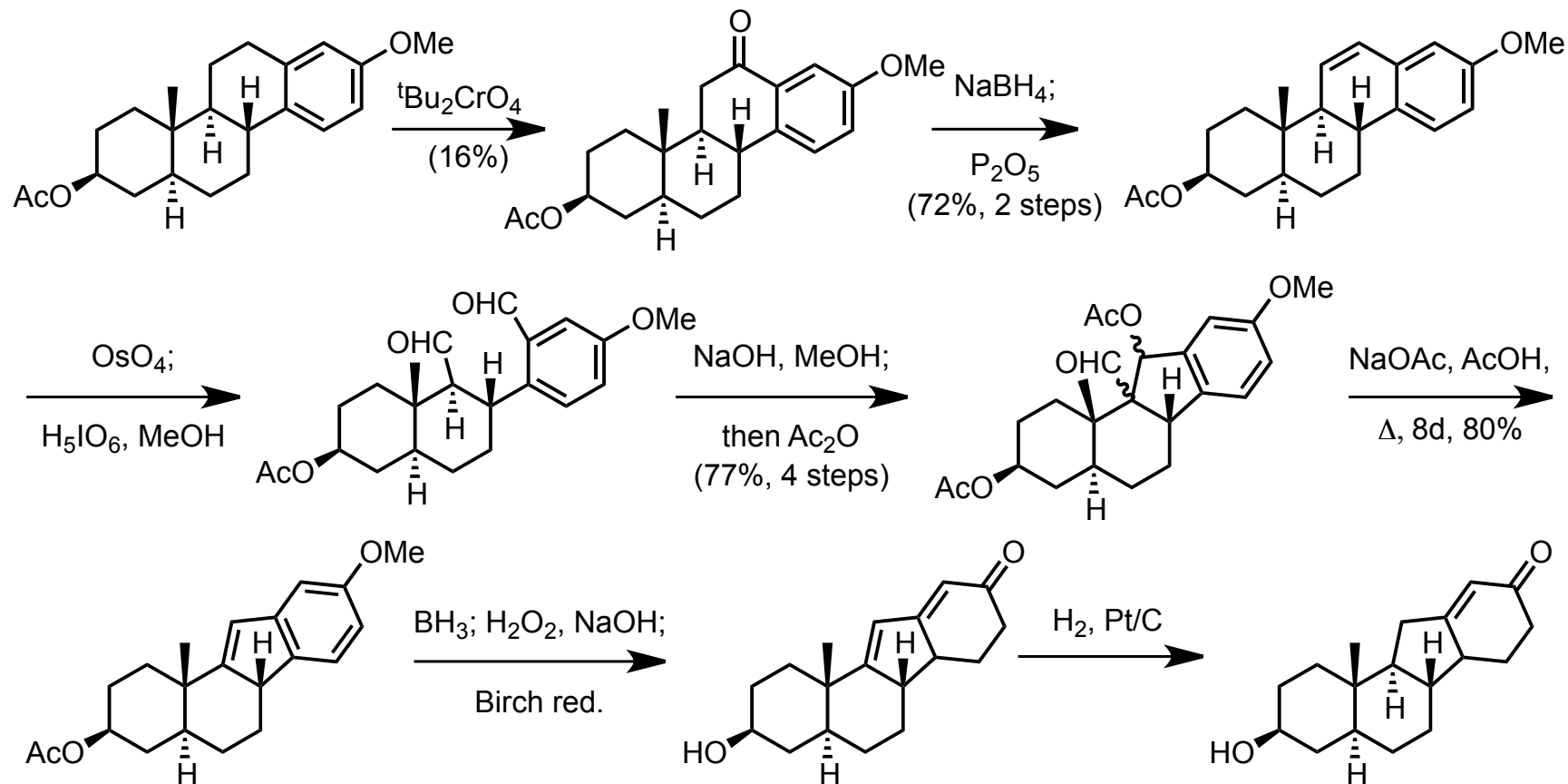
- James P. Kutney
  - University of British Columbia
- Advanced Jervine Intermediate

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Kutney, *et. al. Can. J. Chem.* **1975**, *53*, 1775-1795.

Kutney, *et. al. Can. J. Chem.* **1975**, *53*, 1796-1817.

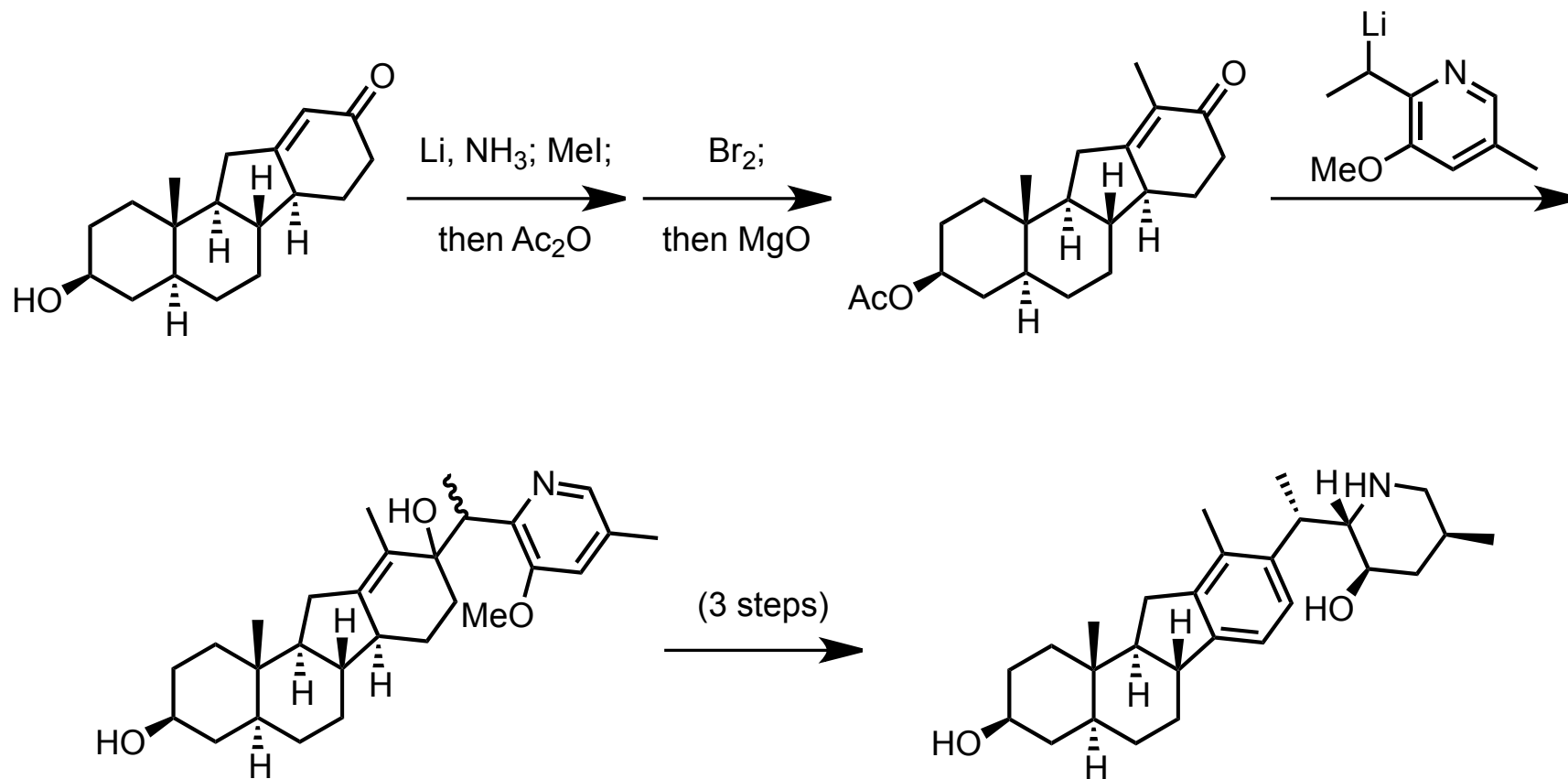
# Kutney Formal



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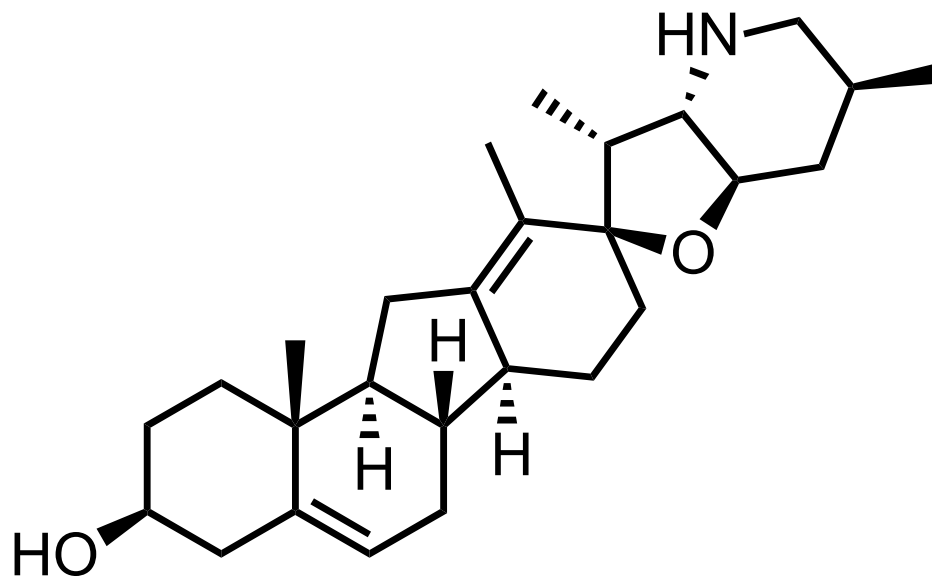
# Kutney Formal



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Kutney, *et. al. Can. J. Chem.* **1975**, *53*, 1796-1817.

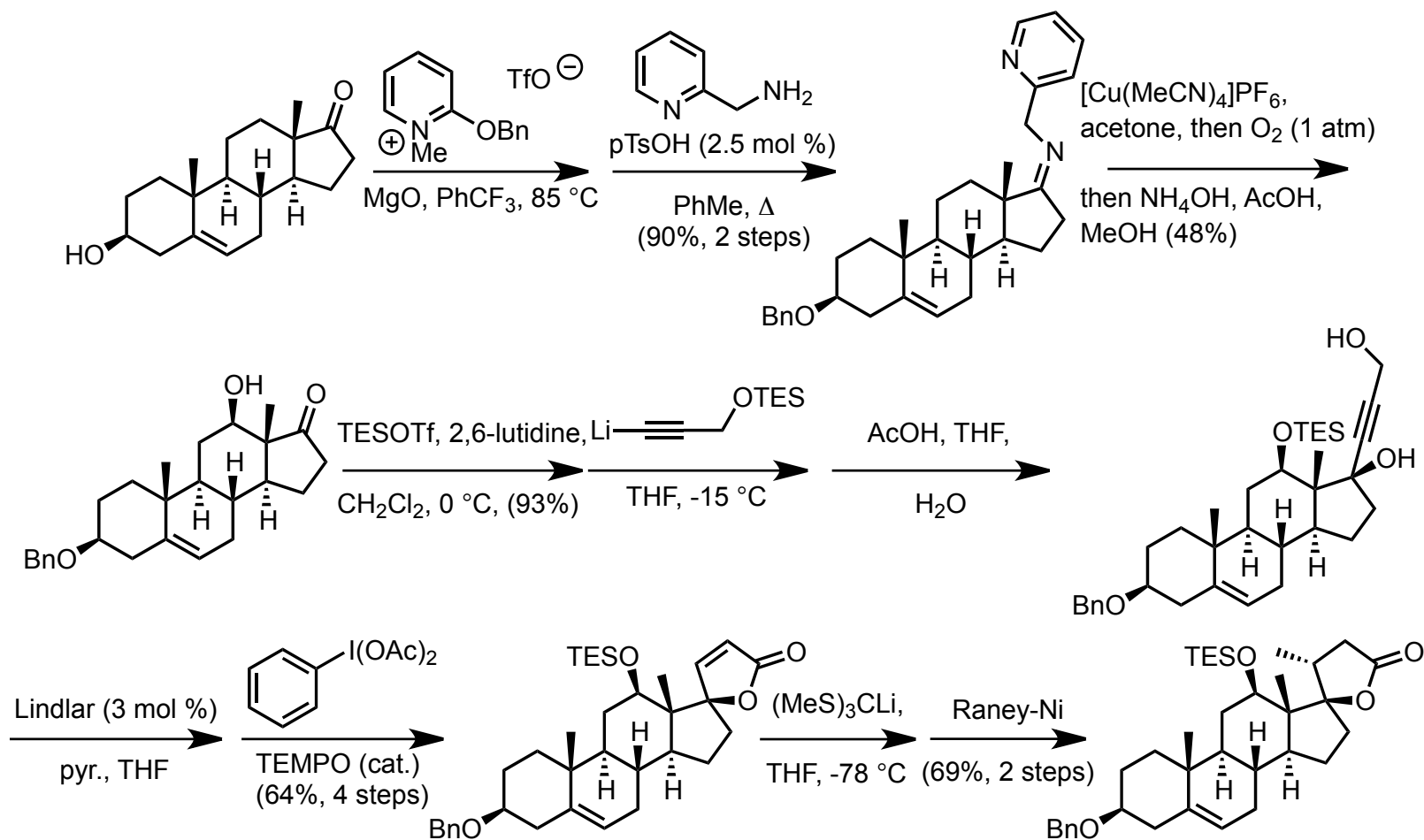
# Cyclopamine



- Athanassios Giannis
  - University of Leipzig
- Cyclopamine
- 20 linear steps, 1% yield

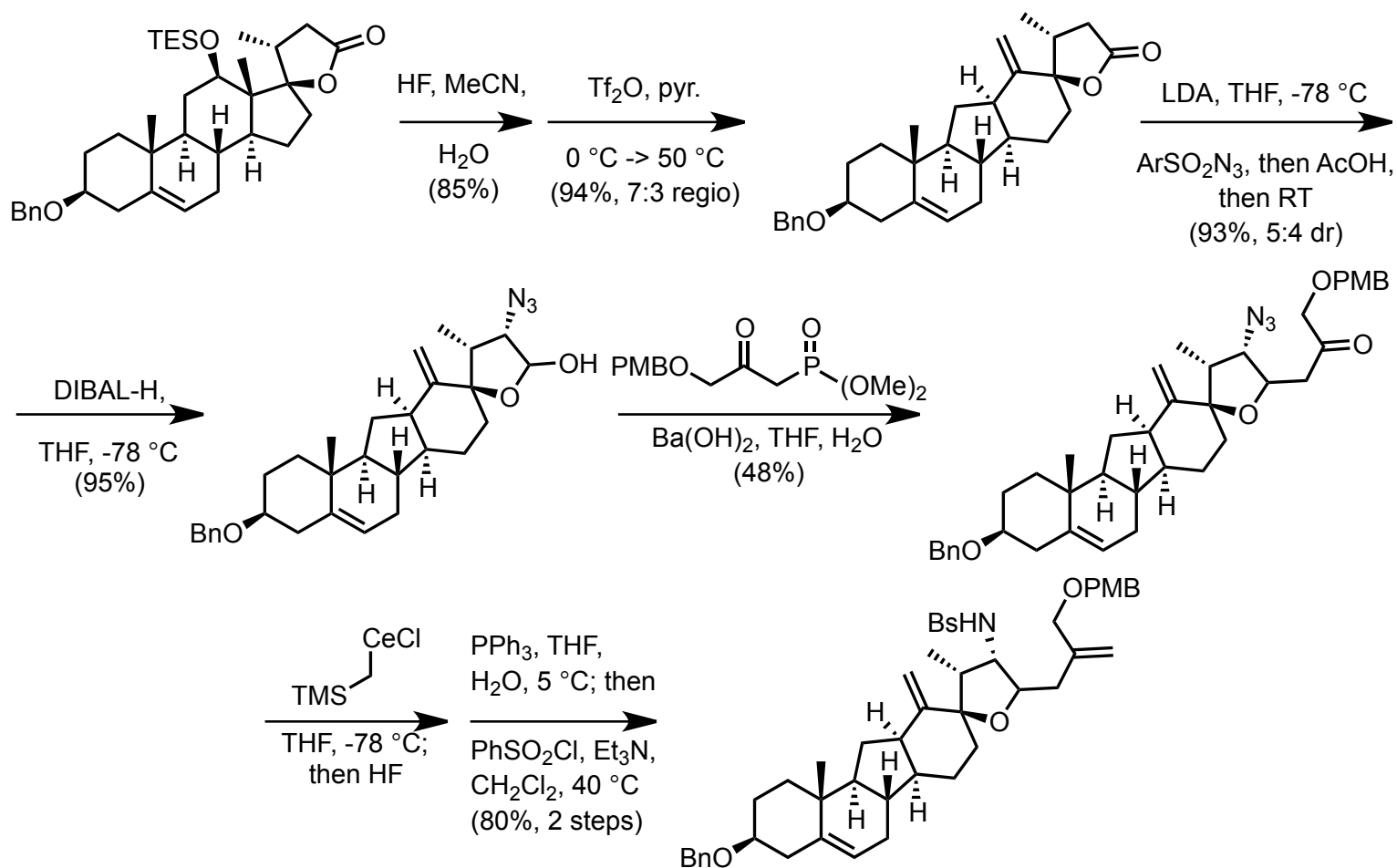


# Giannis Cyclopamine

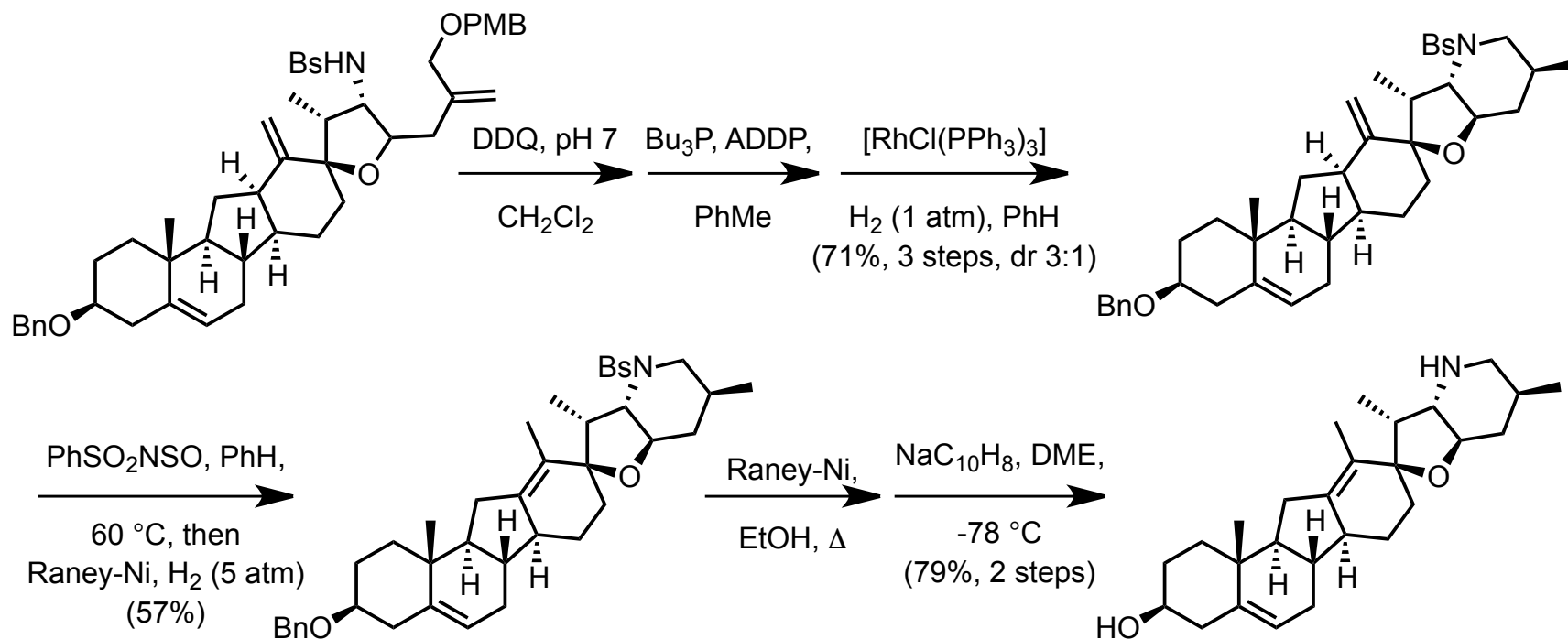


Giannis, A.; Heretsch, P.; Sarli, V.; Stöbel, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 7911-7914.

# Giannis Cyclopamine



# Giannis Cyclopamine



# A Failed Convergent Approach?

## Synthesis of All Diastereomers of the Piperidine–Alkaloid Substructure of Cyclopamine

2009  
Vol. 11, No. 23  
5410–5412

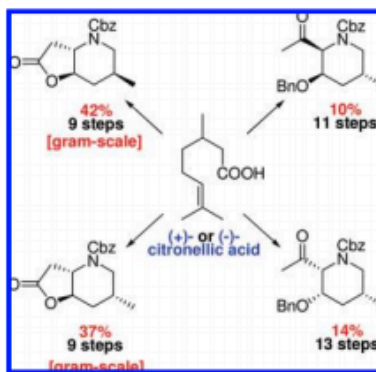
Philipp Heretsch, Sebastian Rabe, and Athanassios Giannis\*

*Institut für Organische Chemie, Universität Leipzig, 04103 Leipzig, Germany*

*giannis@uni-leipzig.de*

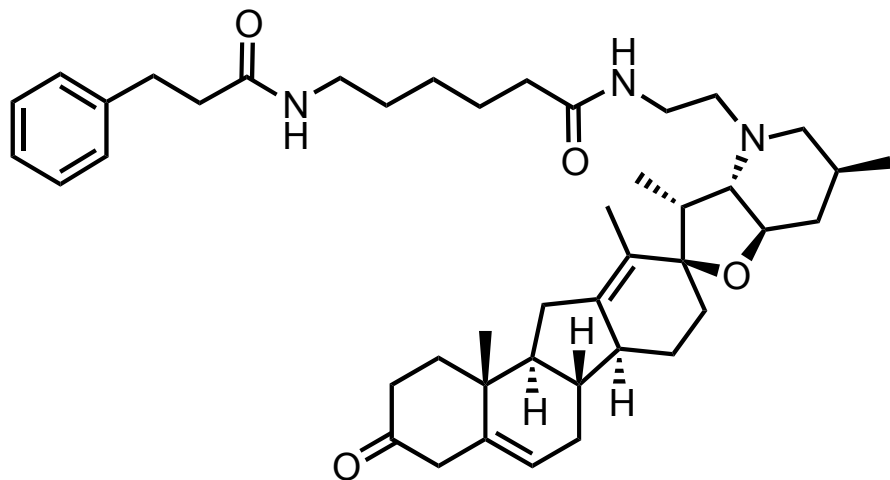
Received September 30, 2009

### ABSTRACT

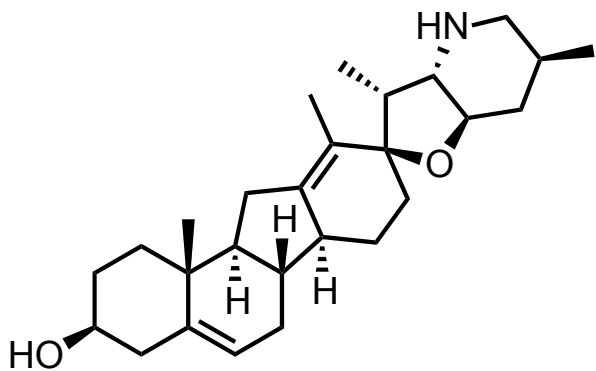


# Medicinal Chemistry

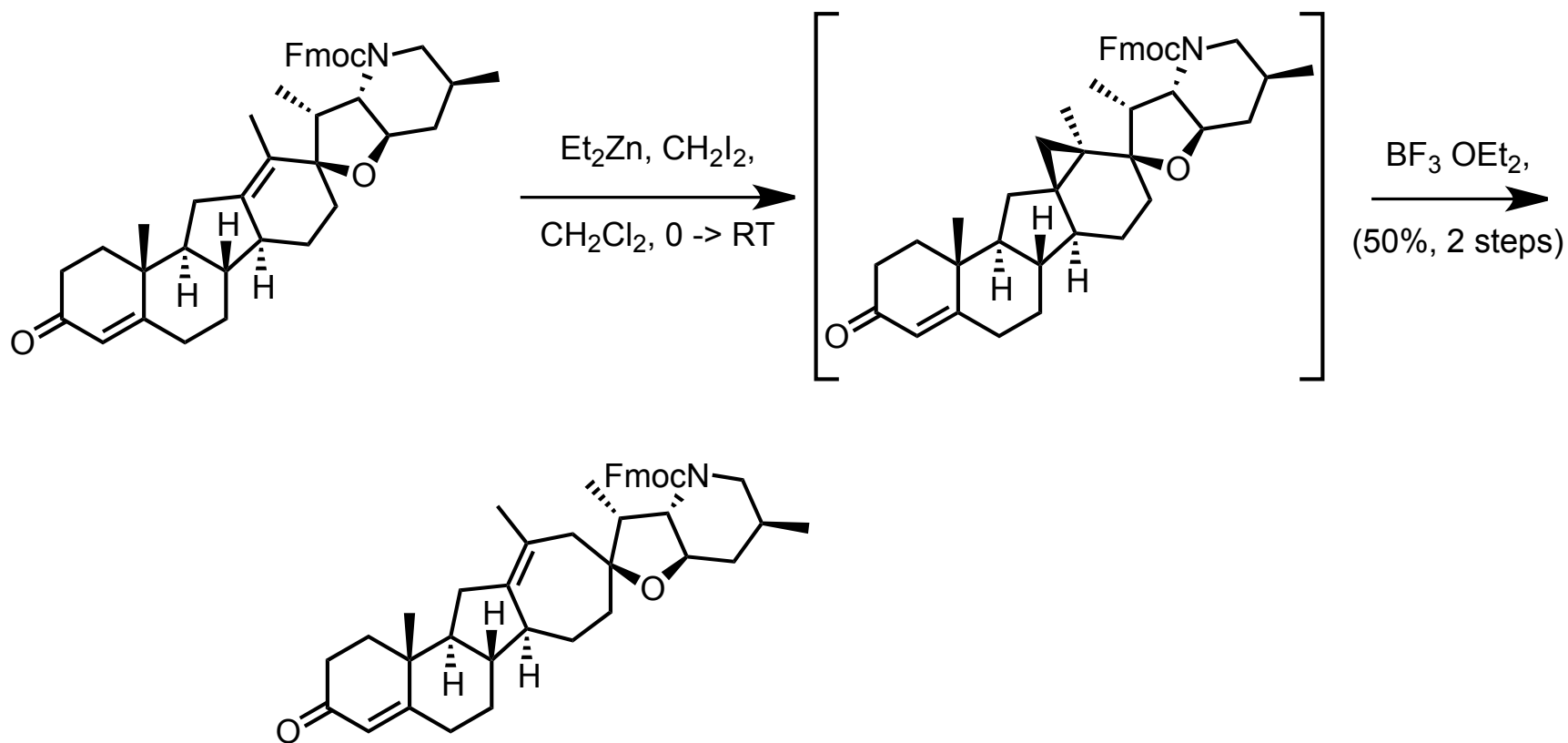
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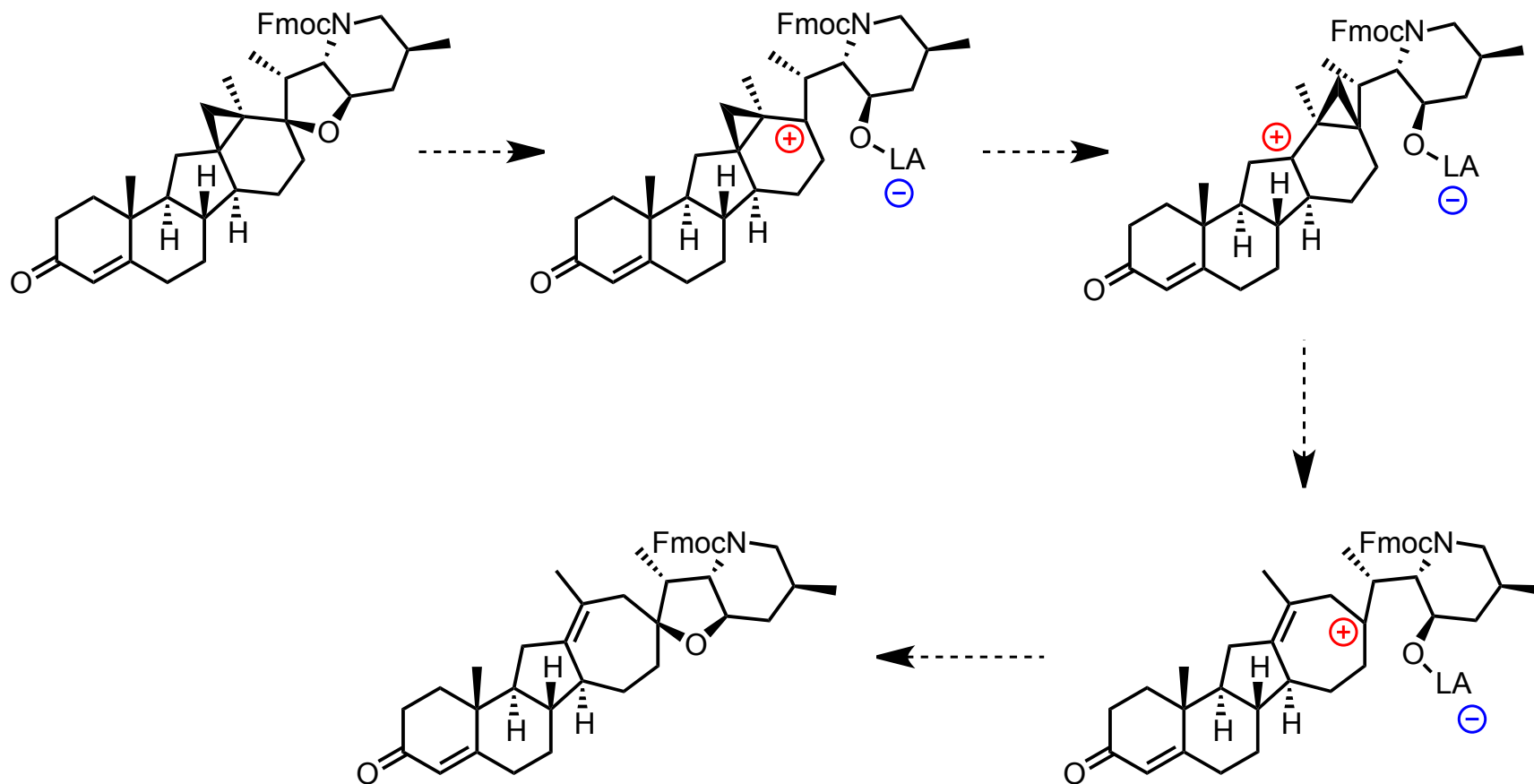
- Solubility
- Acid Sensitivity
- Effective Inhibition

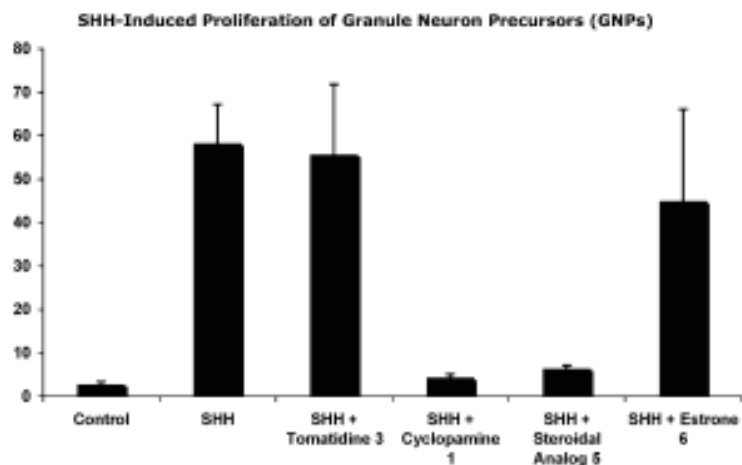
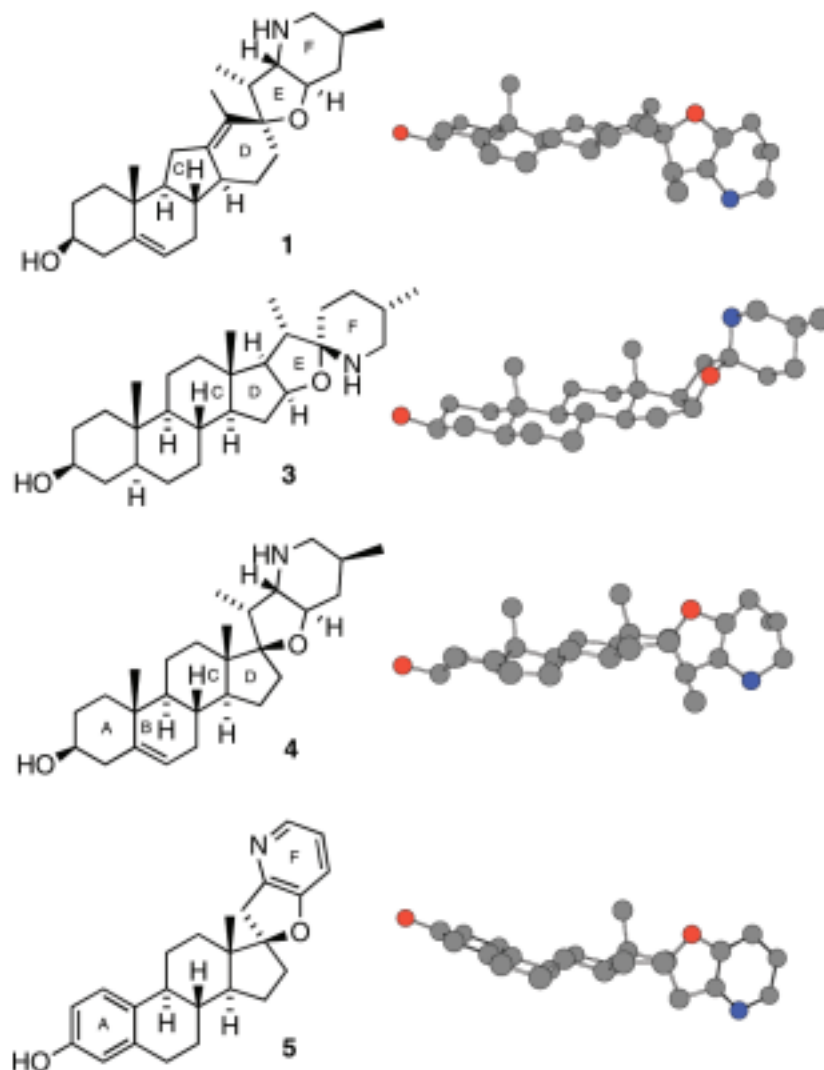
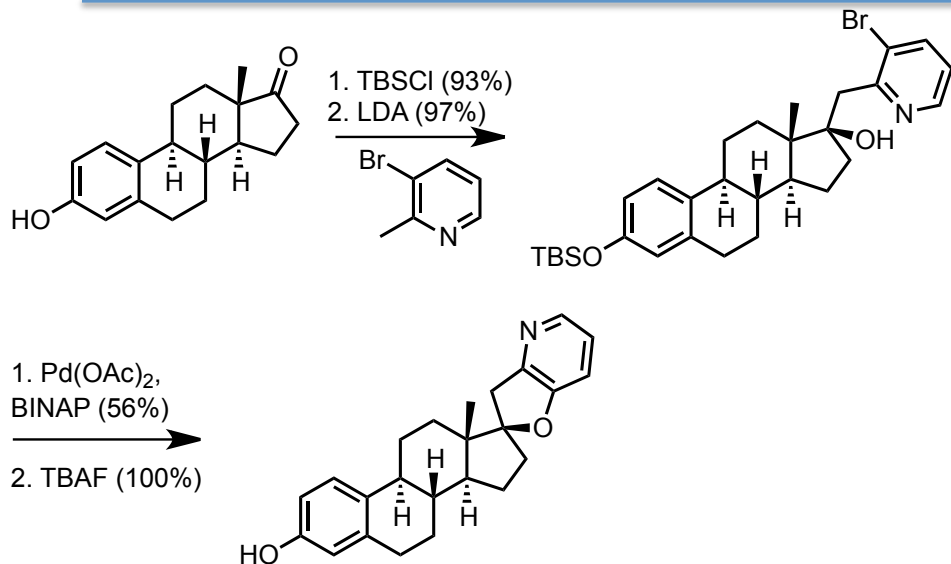


# Semi-Synthesis of a New Framework



# Mechanism



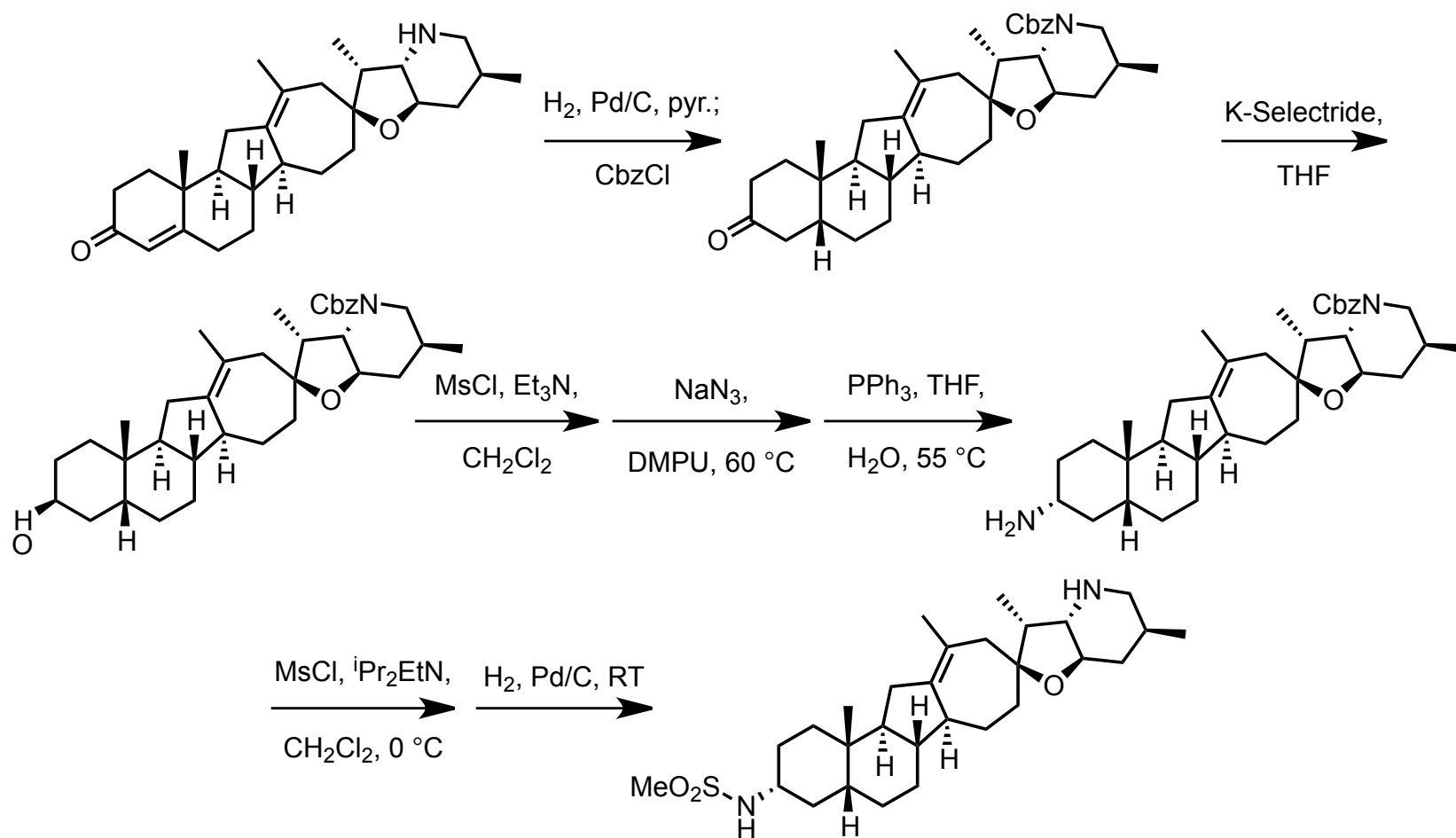


**Figure 4.** Compound **5** inhibits SHH-induced proliferation of granule neuron precursors (GNPs).

**Figure 3.** Structures and three-dimensional models of cycloamine **1**, tomatidine **3**, androstrane analogue **4**, and estrone analogue **5**.



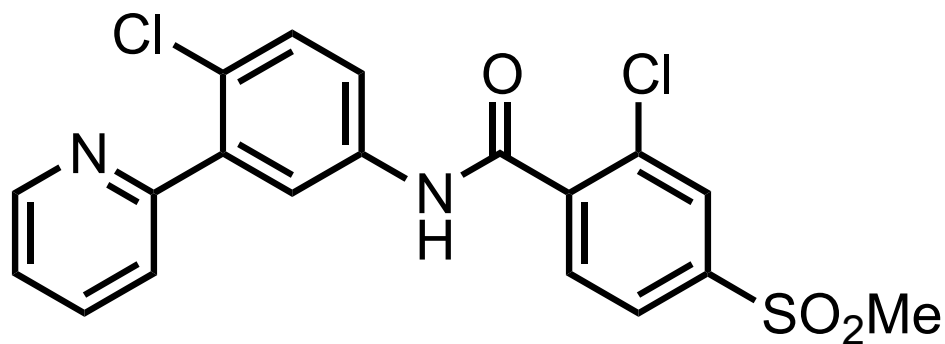
# A Final Drug Candidate



# Vismodegib (Erivedge<sup>®</sup>)

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- Genentec
- Approved January 30, 2012, for BCC
  - More trials underway
    - Pancreatic
    - Stomach
    - Colorectal



Thanks for your attention!