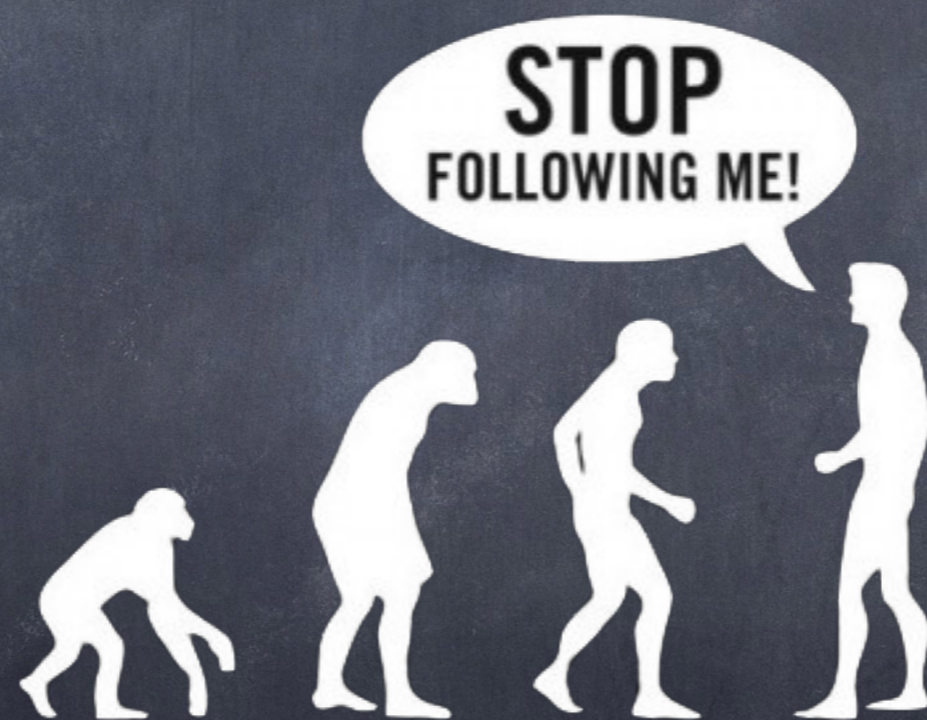
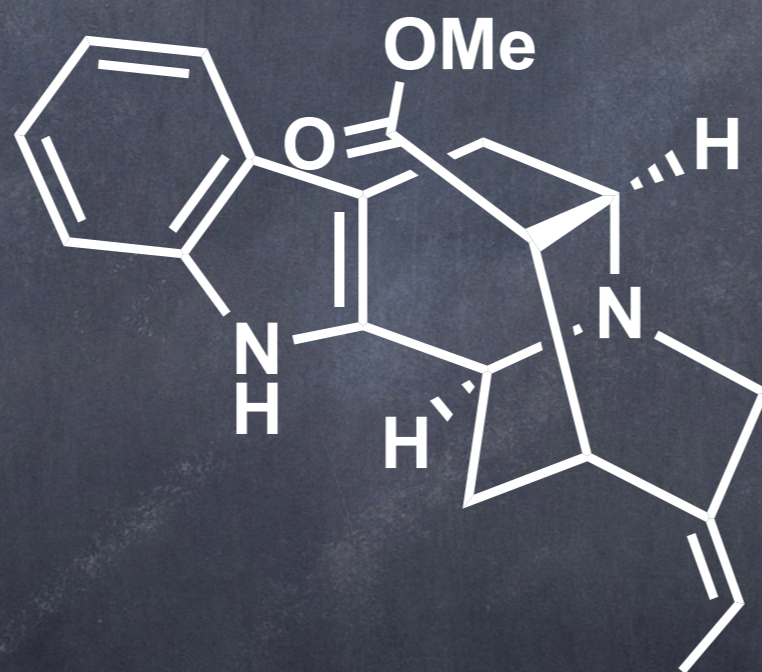
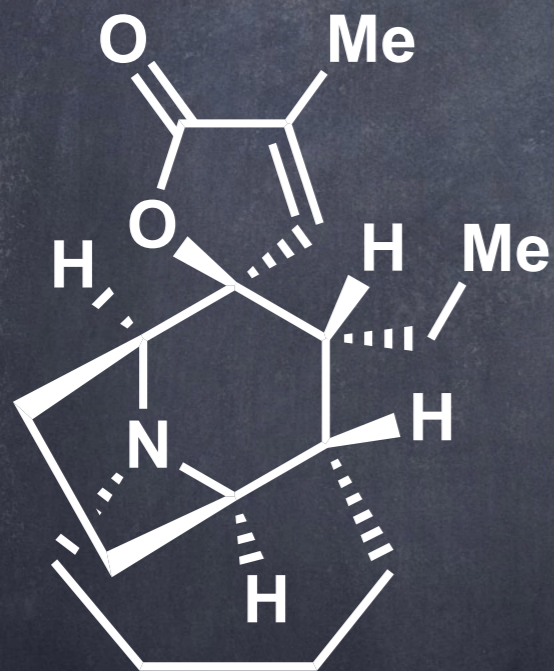

Total Synthesis of polycyclic Natural Products – beyond Biogenetic Relationships



IASOC 2016
Sept 28th 2016
Tanja Gaich
University of Konstanz

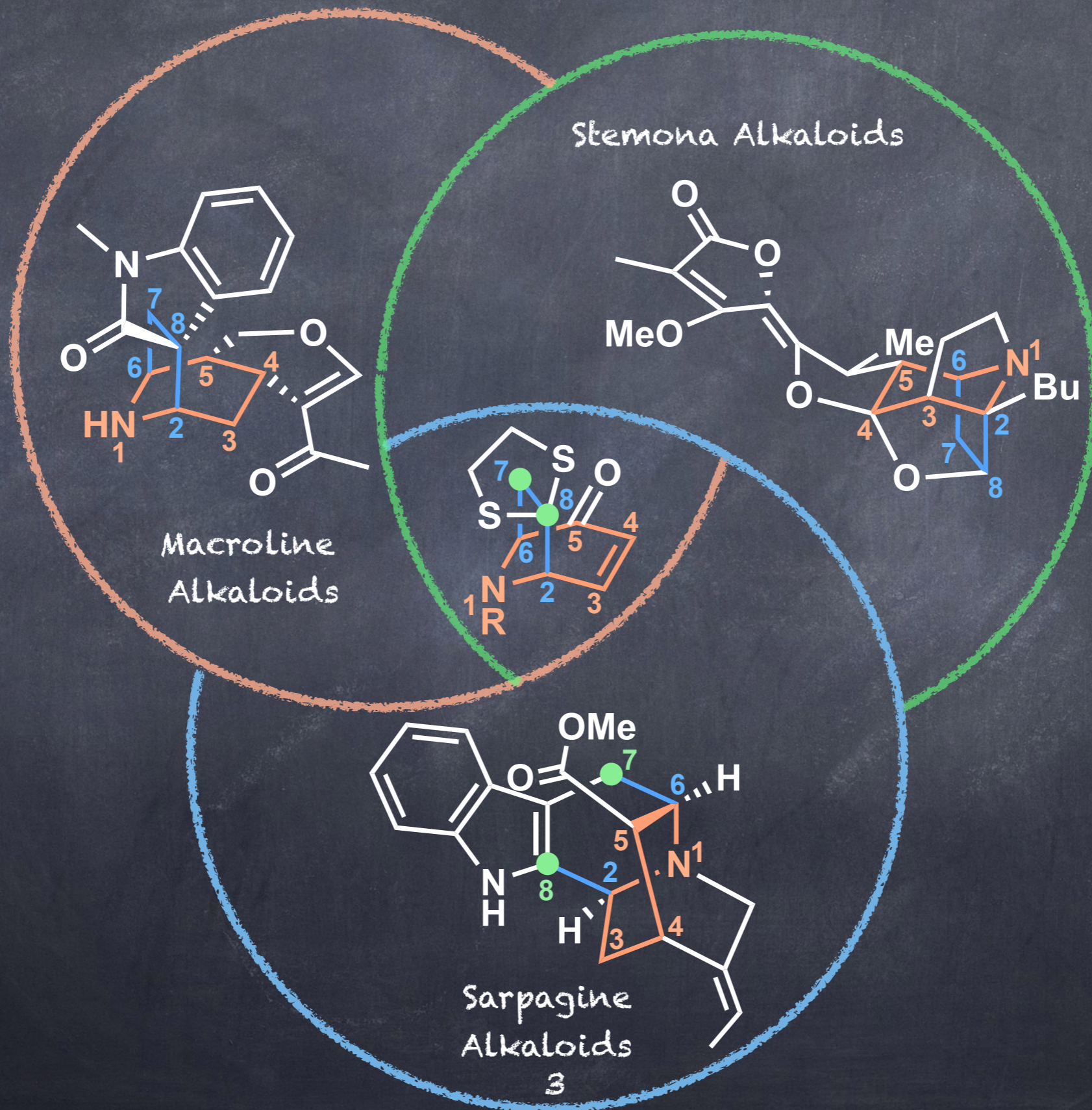
Generalized Total Synthesis of Sarpagine and Stemona Alkaloids



S. Krüger

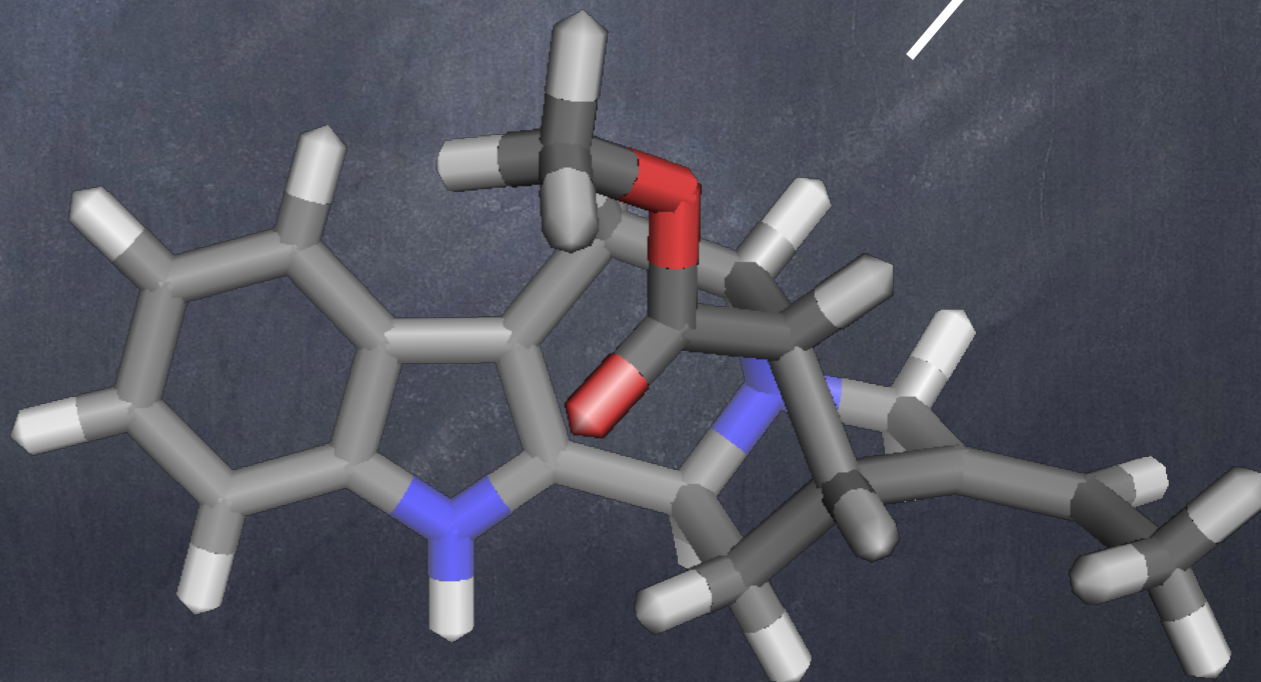
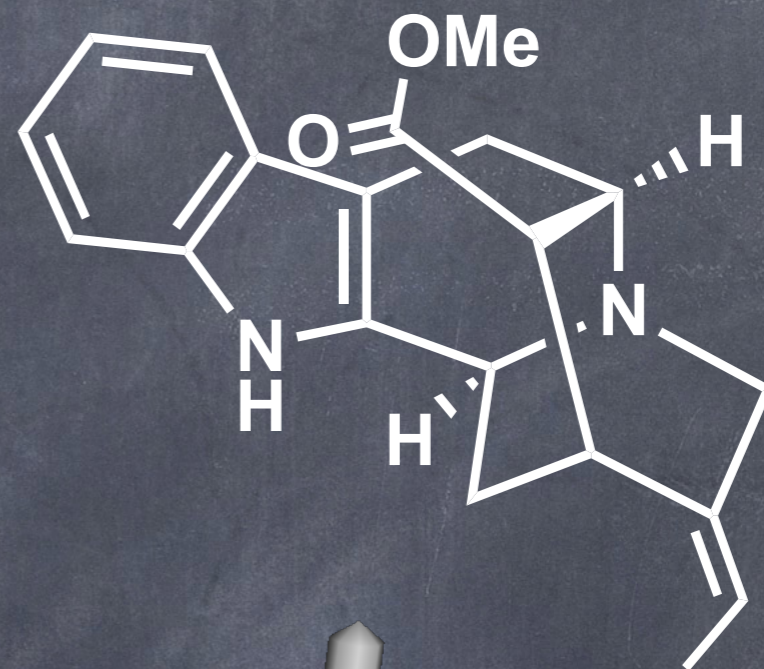
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Tanja Gaich
University of Konstanz

Privileged Intermediate



Isolation Sarpagines

- Apocynaceae (Catharanthus roseus)
- "Rosy-periwinkle" or "old maid"
- Madagascar (endemic)
- Ethnomedicine: Diabetes, Malaria, Hodgkin's Lymphoma

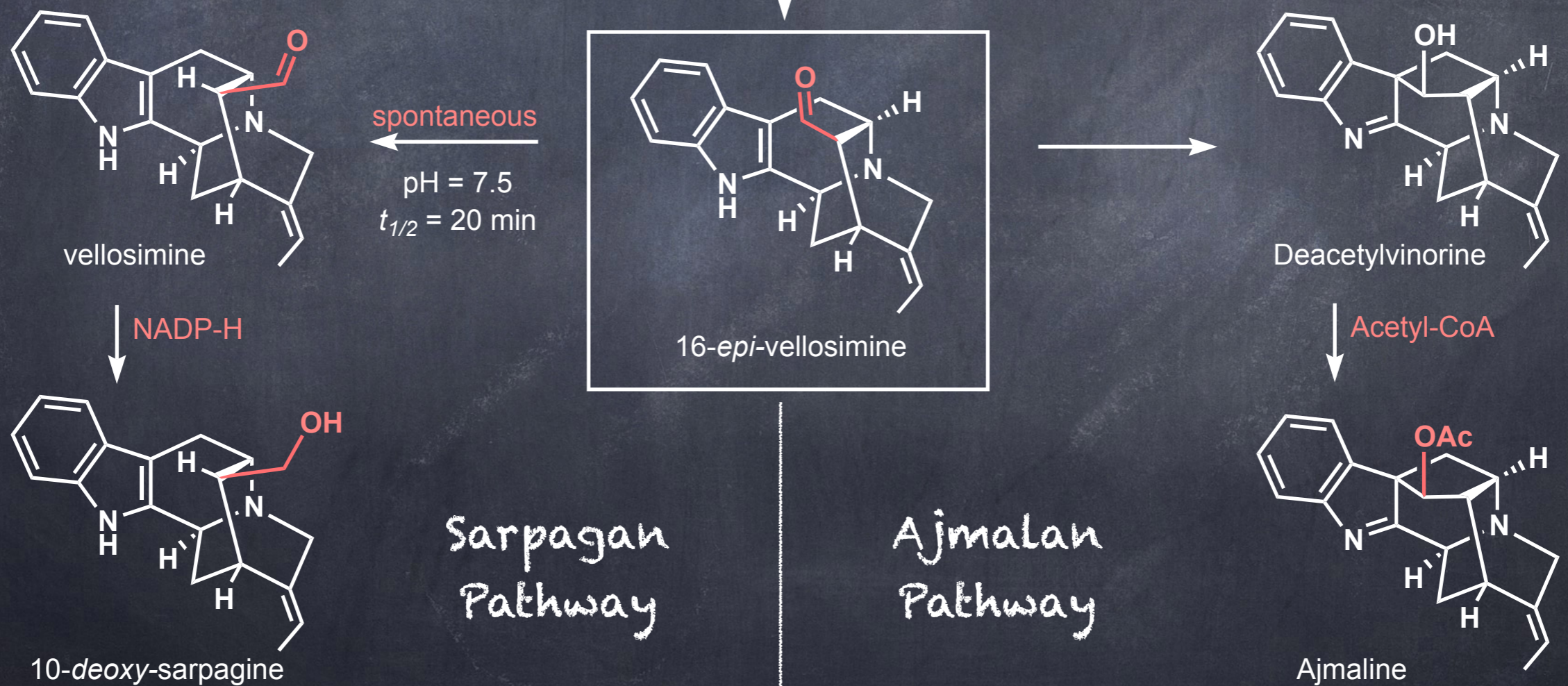
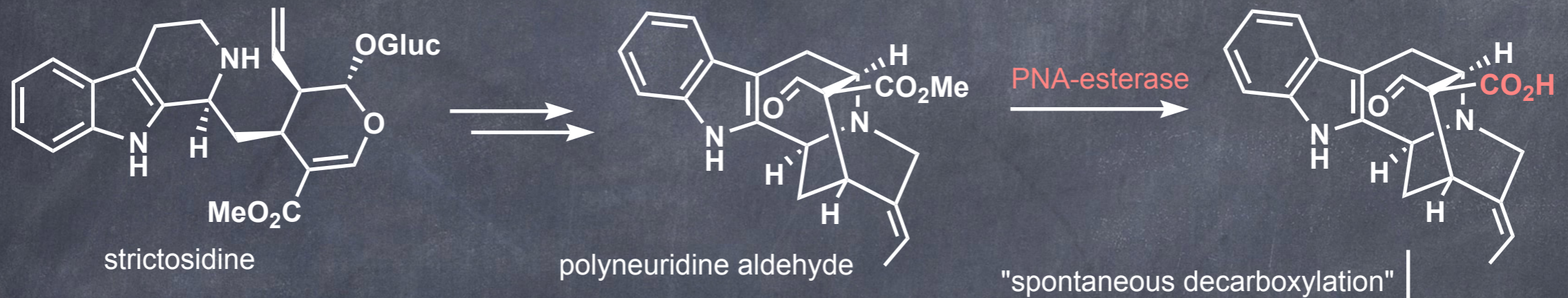


Isolation of Pericyclivine: Farnsworth, N. R.; *et al.* J. Pharm. Sci., 1964, (12) 53, 1558.

Syntheses: J. Cook *J. Org. Chem.*, 2013, 6756.

S. F. Martin *et al.*, *J. Am. Chem. Soc.*, 2003, 125, 15, 4541-4550.

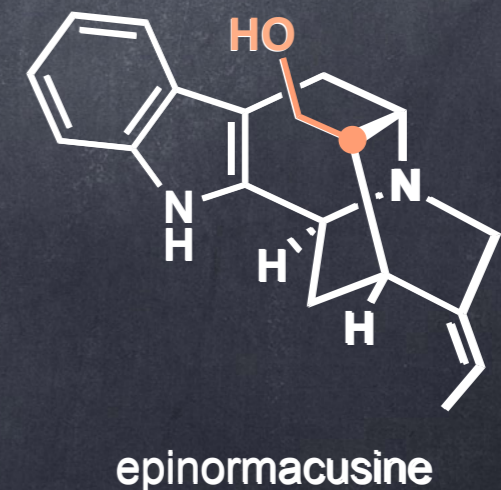
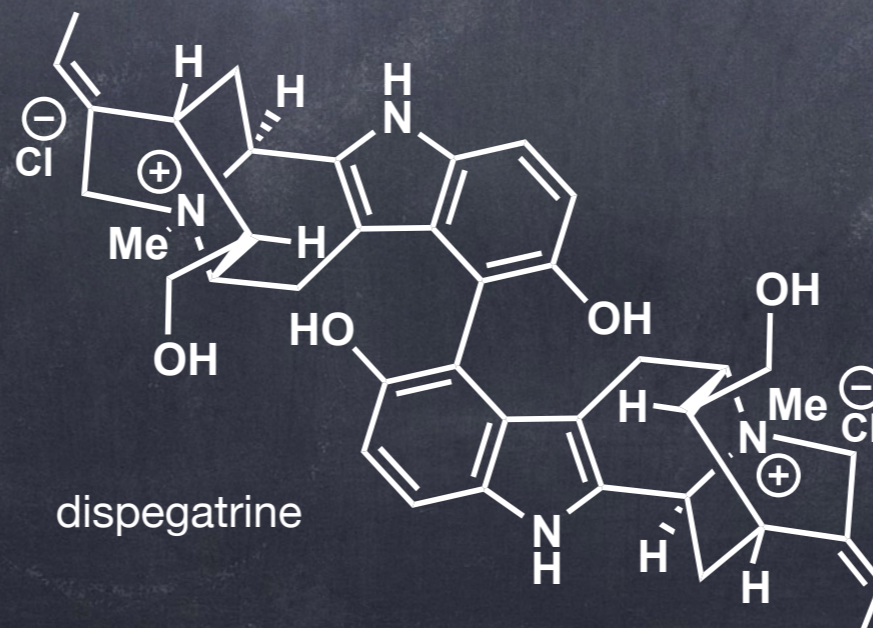
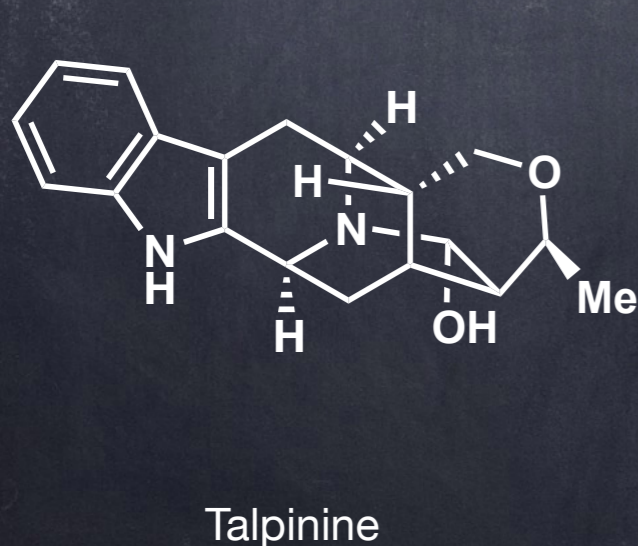
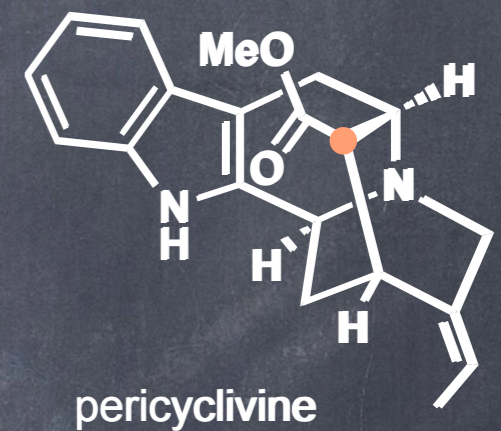
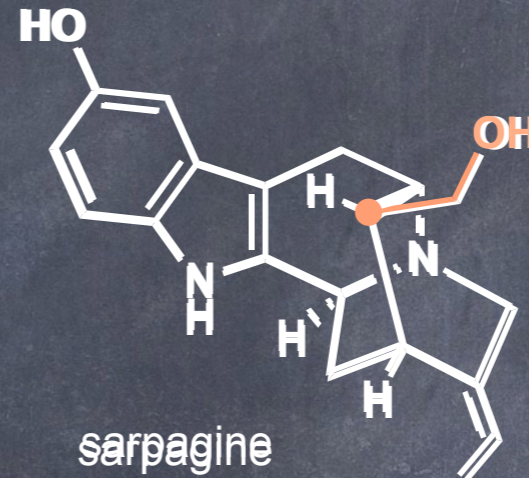
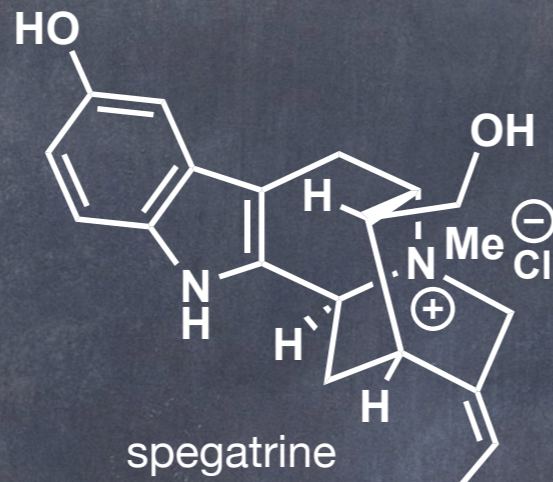
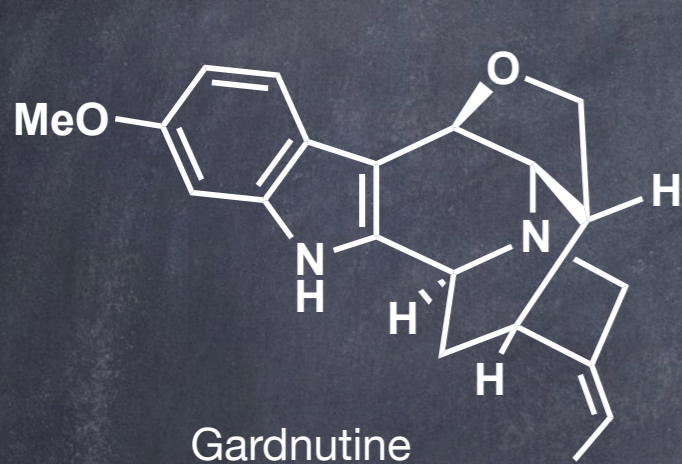
Biosynthesis



Sarpagine Family Members

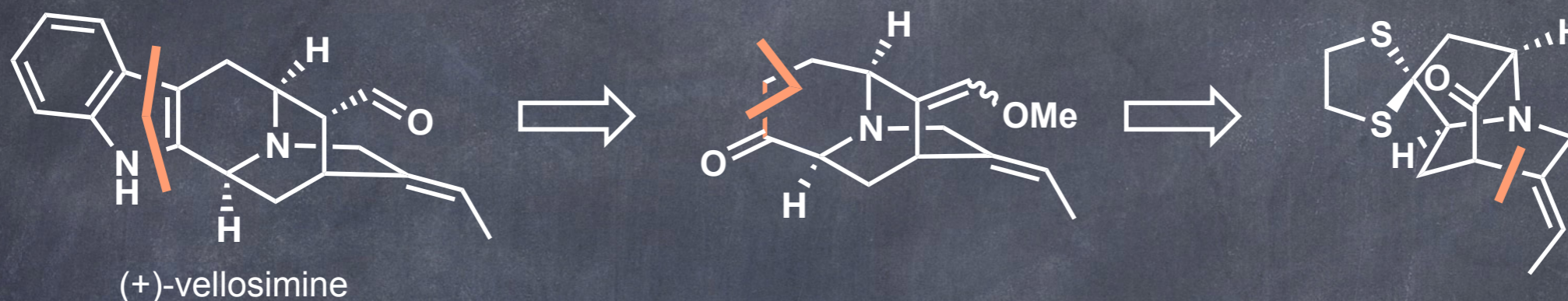
- Additional Rings
- Variation at C-16

- Oxidation of Indole
- Dimer-products



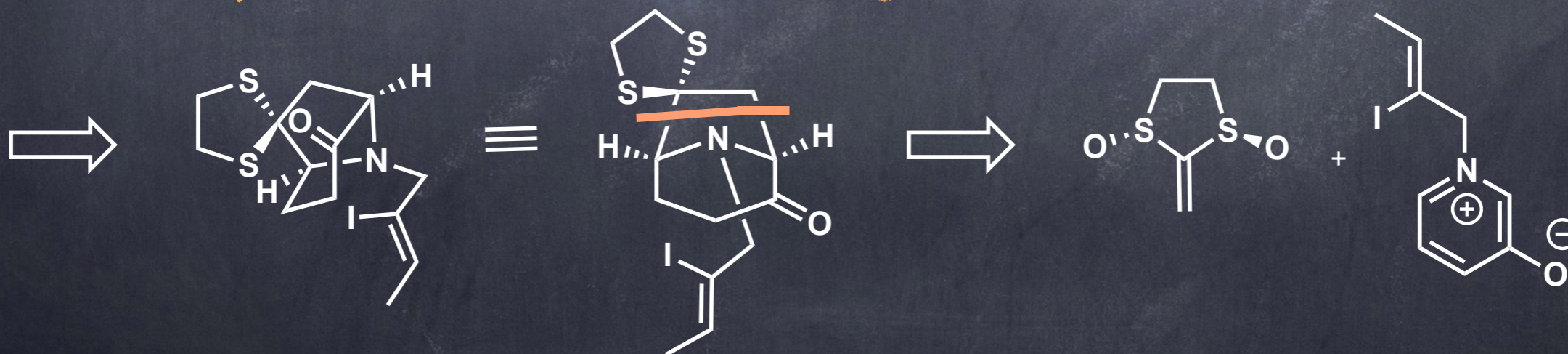
Retrosynthesis

Fischer Indole Ring enlargemnet



Pd-catalyzed enolate coupling

[S+2]-oxido-pyridinium ion cycloaddition



M. Braun, *et al. Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 6952.

A. R. Katritzky *et al. Chem. Rev.*, 1989, **89**, 827–861.

Synthesis of (Z)-1-bromo-2-iodo-2-butene:

a) Ensley, H. E.; *et al. J. Org. Chem.* **1982**, *47*, 404.

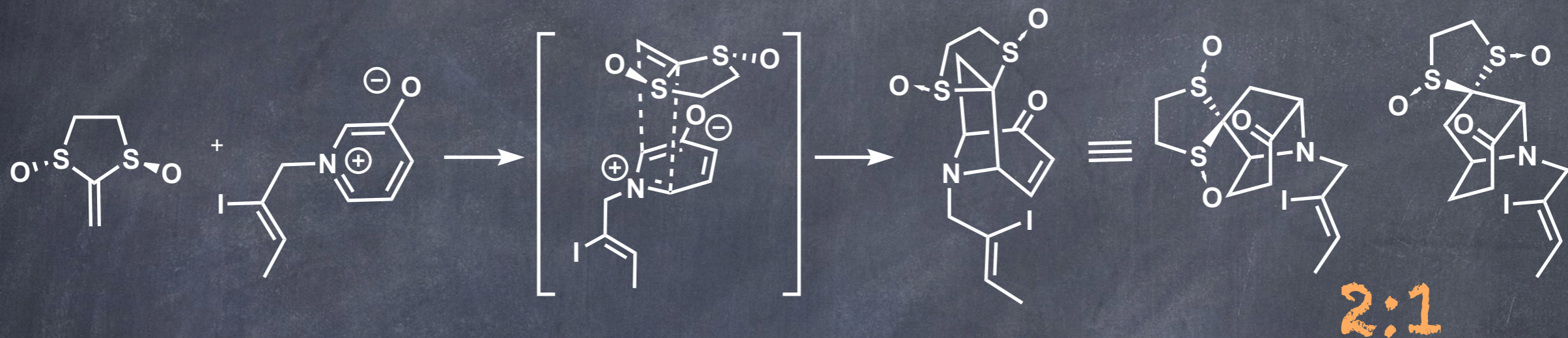
b) Corey, E. J.; *et al. J. Am. Chem. Soc.* **1970**, *92*, 6314.

Synthesis of vinyl-sulfoxide:

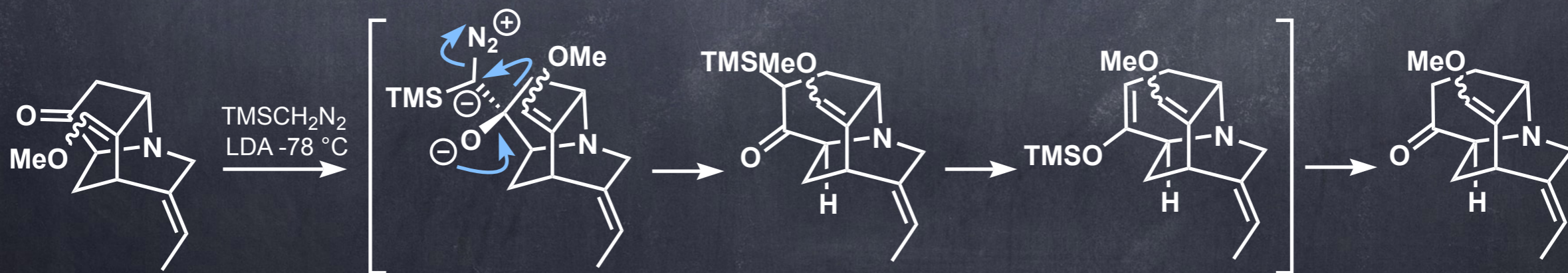
V. K. Aggarwal, *et al. Org. Biomol. Chem.*, **2003**, *1*, 1884-1893.

Key-Steps

[5+2]-oxido-pyridiniumion cycloaddition

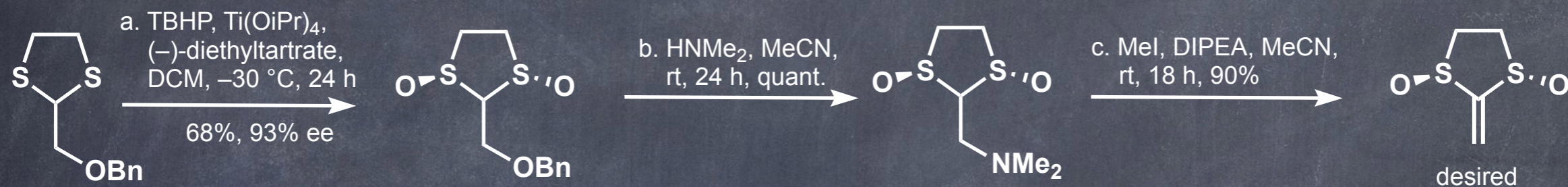


Ring-enlargement (Tiffeneau-Demjanov)

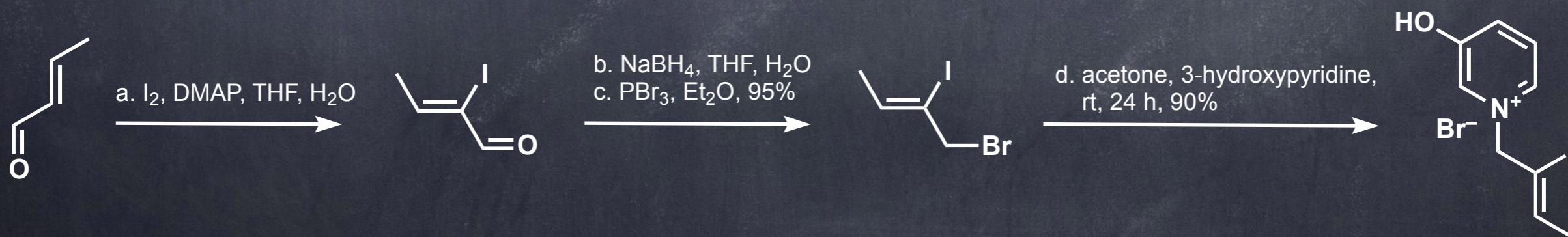


Synthesis of [5+2]-Precursors

Enantioselective Synthesis of dipolarophile



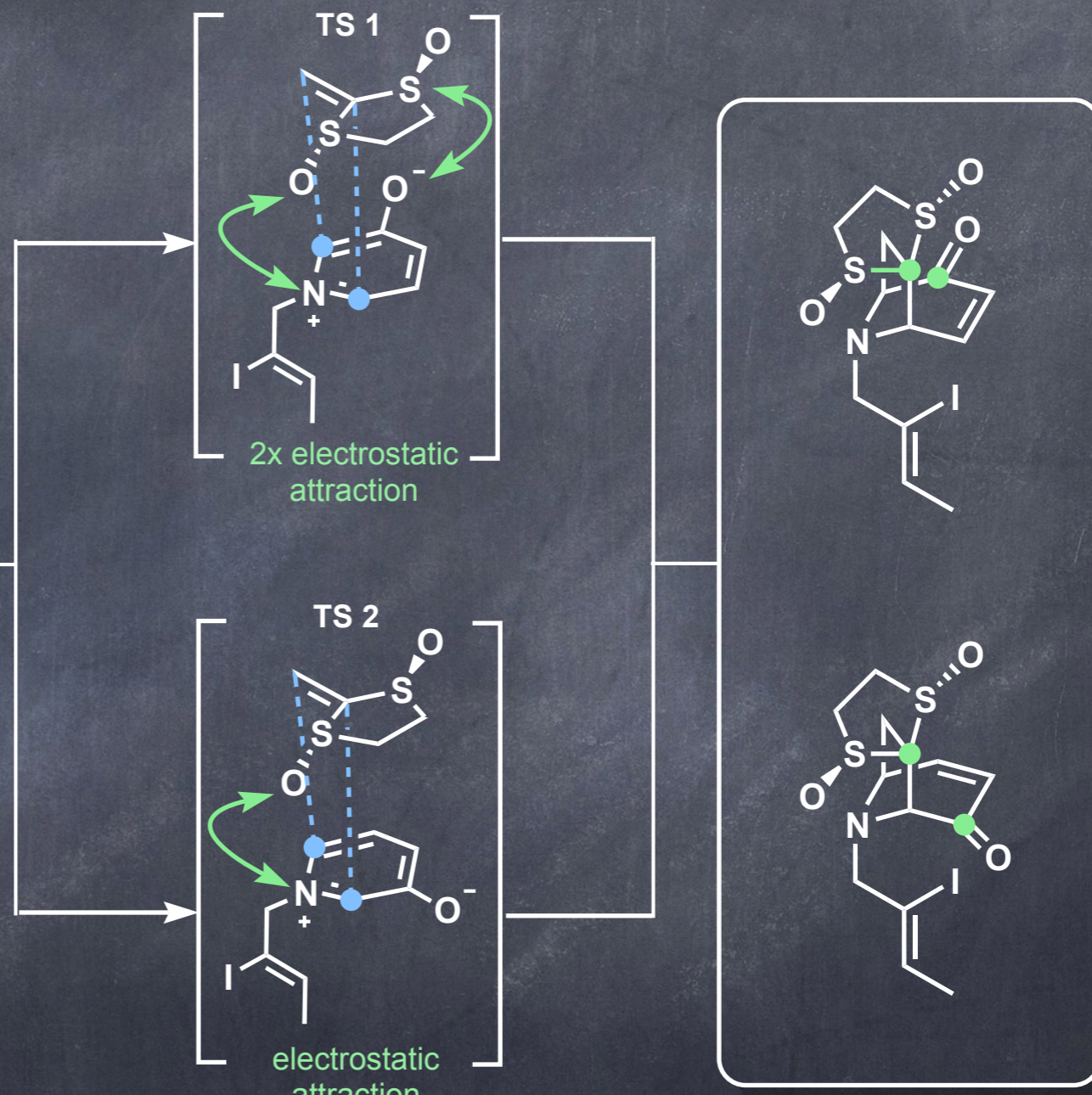
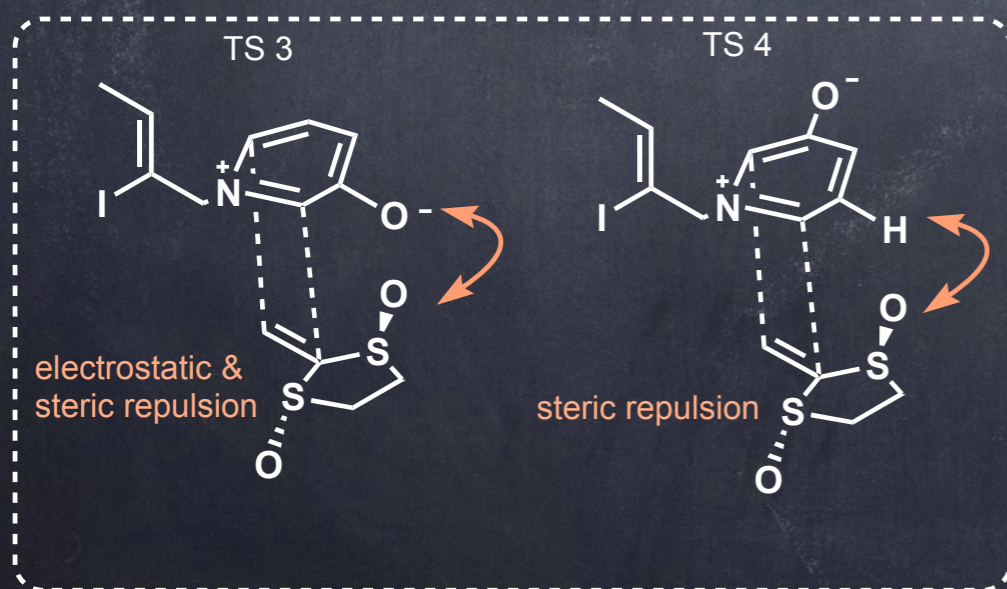
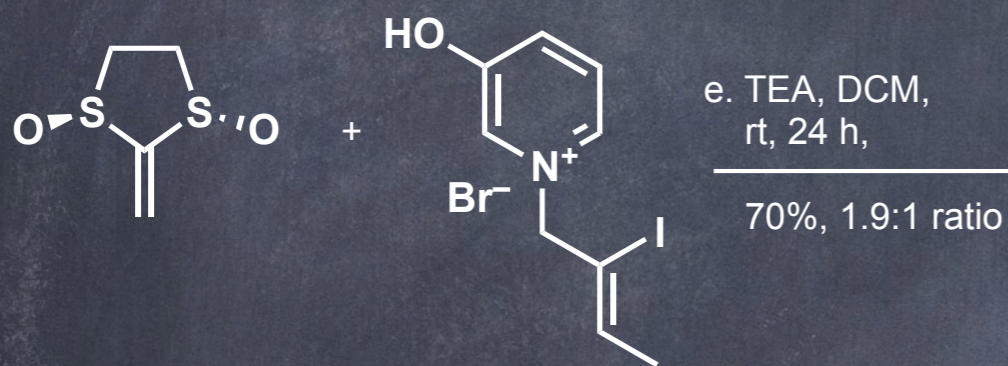
Synthesis of the dipole



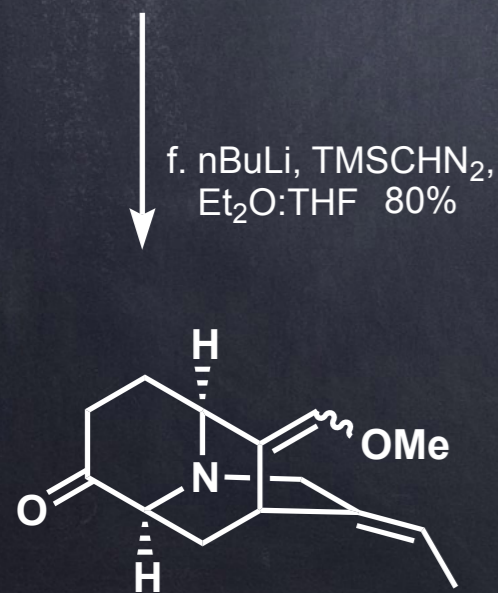
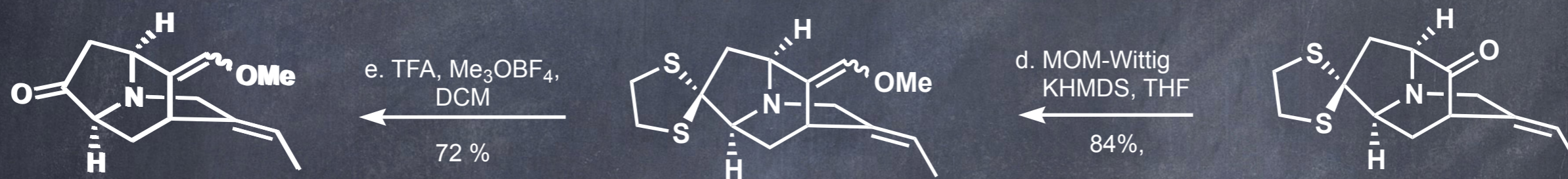
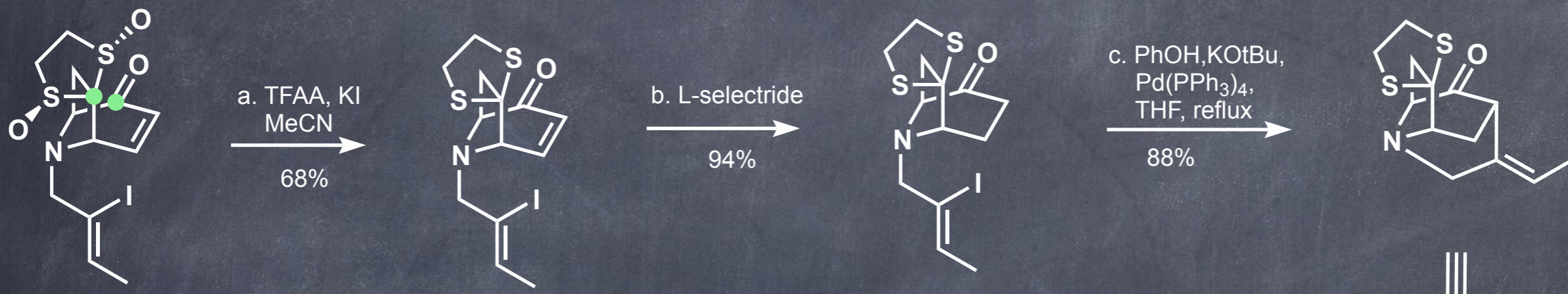
a. H. Firouzabadi et al., *JOC*, **2001**, 66, 7527-7529 b. V. K. Aggarwal et al., *JOC*, **1995**, 60, 4962-4963 c. M. E. Krafft, J. W. Cran, *Synlett*, **2005**, 8, 1263-1266
d. J. M. Cook et al., *TL*, **2010**, 51, 815-817 e. T. P. Loh et al., *TL*, **1998**, 39, 1453-1456 f. J. M. Cook et al., *TL*, **2003**, 44, 8013-8017

Selectivity in the [S+2]-CA

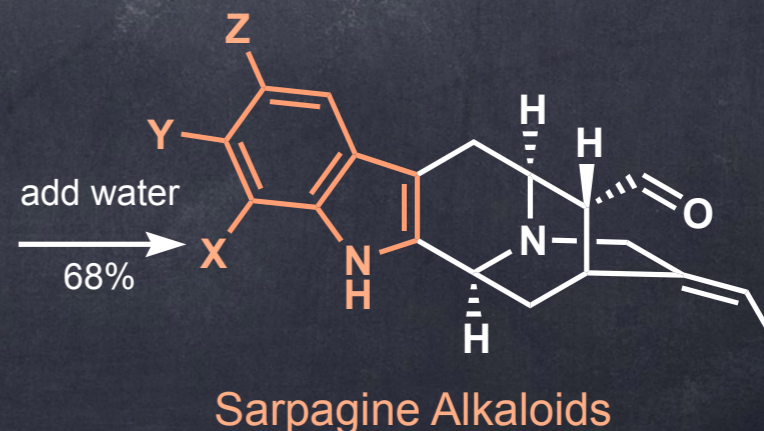
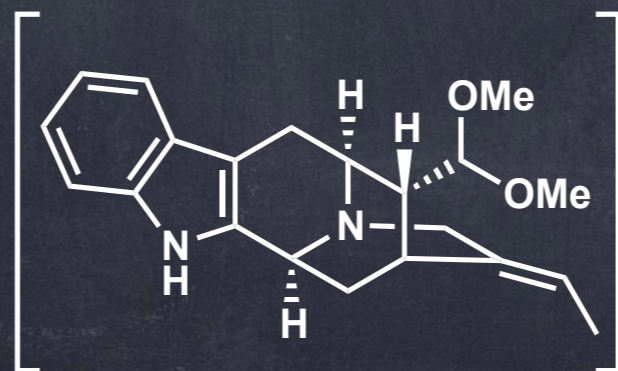
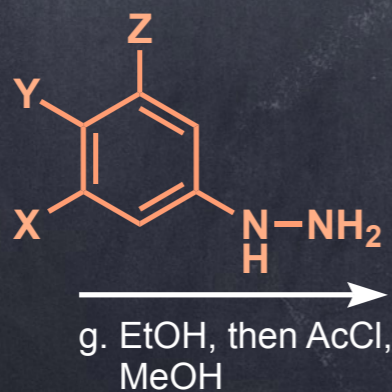
Regioselectivity
(2 synergistic electronic effects)
Stereoselectivity



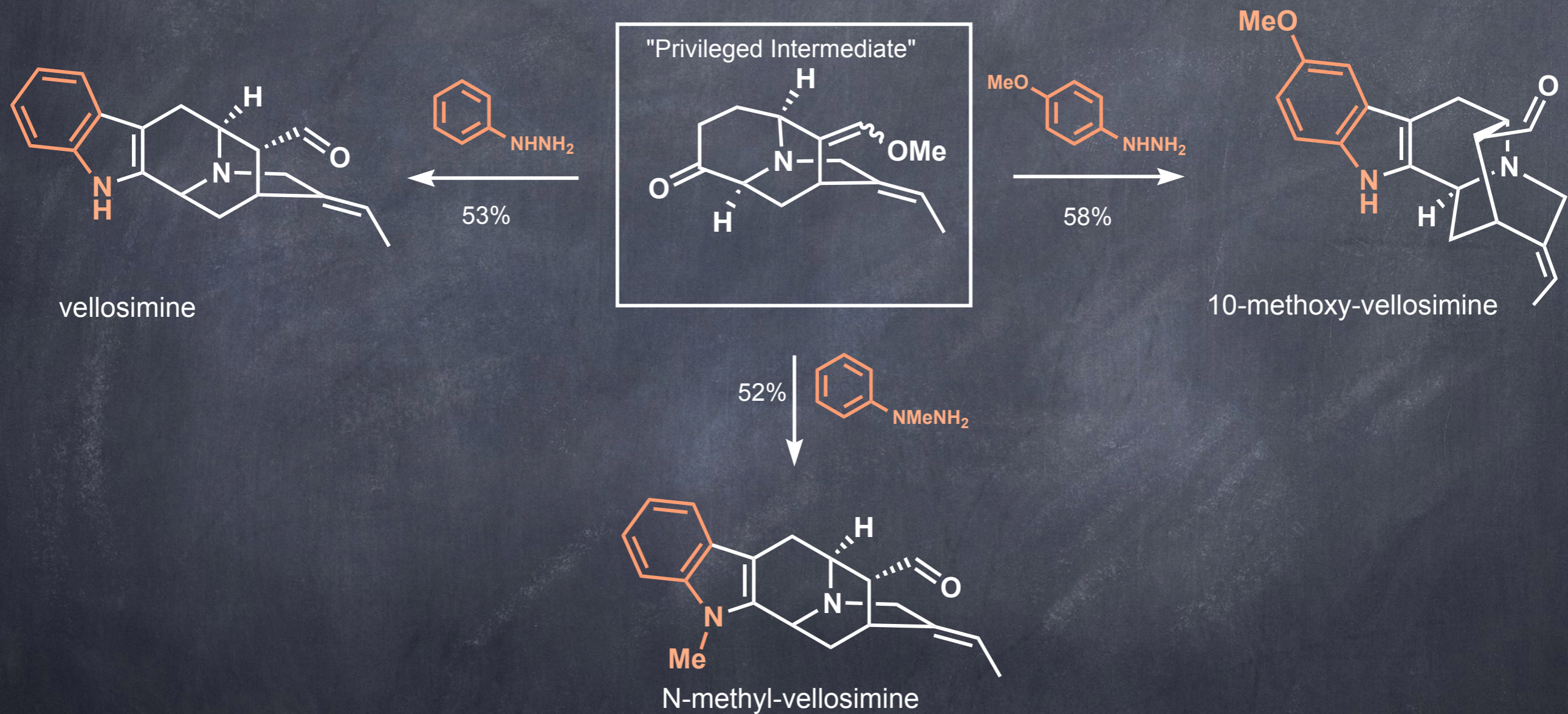
The Total Synthesis



Target Differentiation 8 steps 18% over all yield



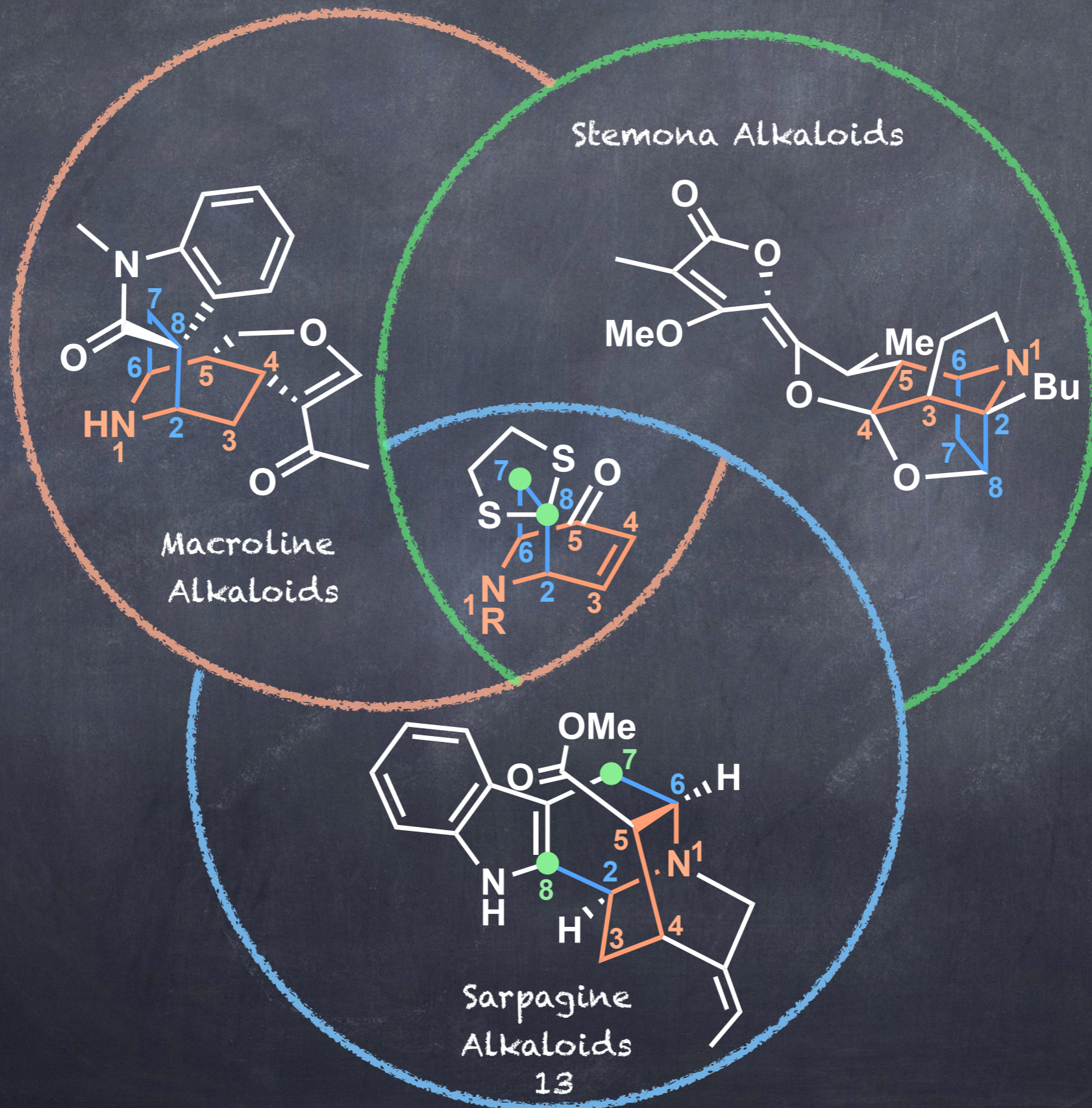
Generalized Synthesis



catalytic enantioselective
joint-synthetic route

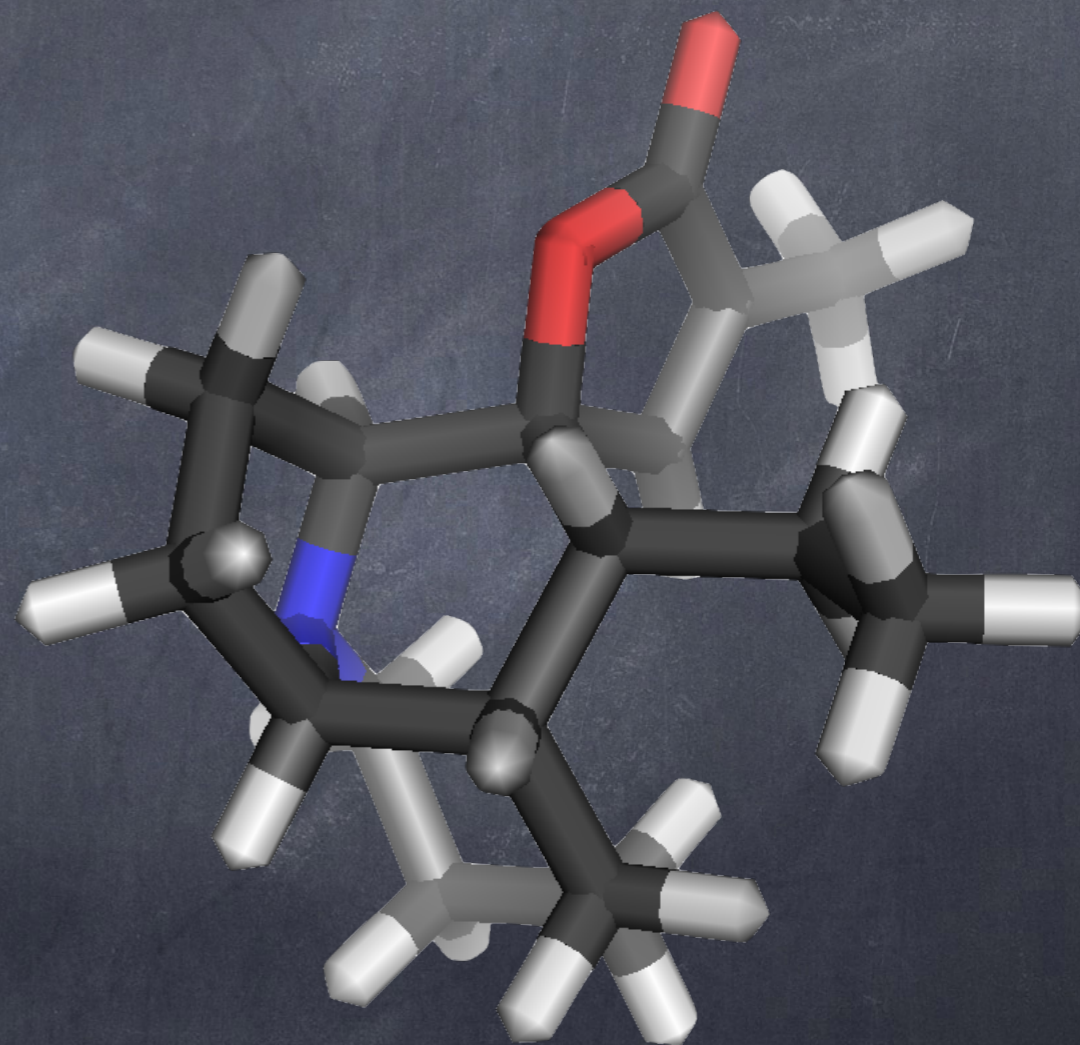
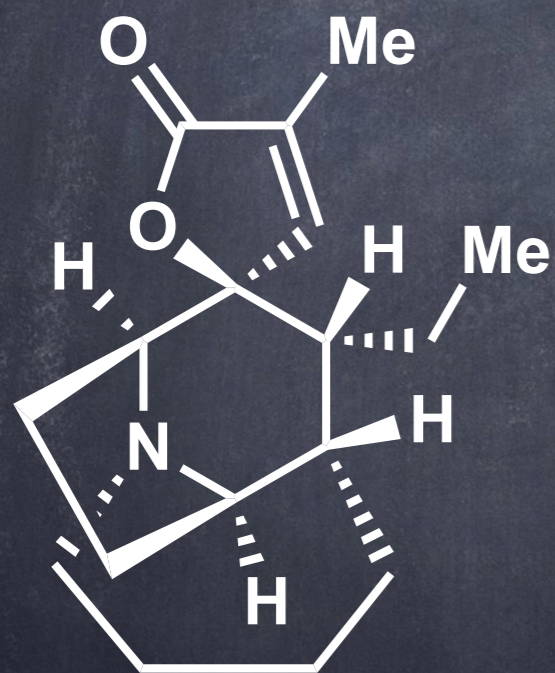
8 steps (ex known compounds)
12 steps from commercial

Privileged Intermediate



Isolation and Origin

- From *Stemona parviflora* 2003
China (endemic)
- Chinese medicine: antitussive, and insecticide



1 completed racemic total synthesis:

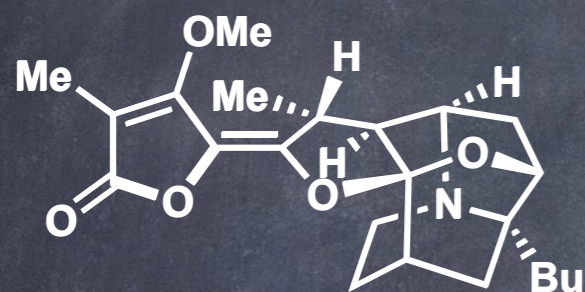
Chen, Z.-H.; Tian, J.-M.; Chen, Z.-M.; Tu, Y.-Q. *Chem. Asian J.*, **2012**, *7*, 2199-2202

Isolation of Parvineostemonine:

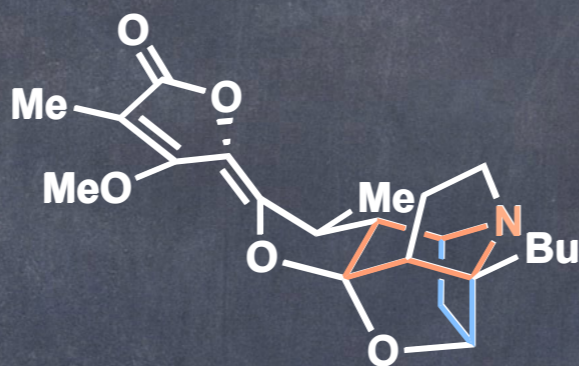
C. Q. Ke, Z. S. He, Y. P. Yang, and Y. Ye, *Chin. Chem. Lett.*, **2003**, *14*, 173.

Stemona Family Members

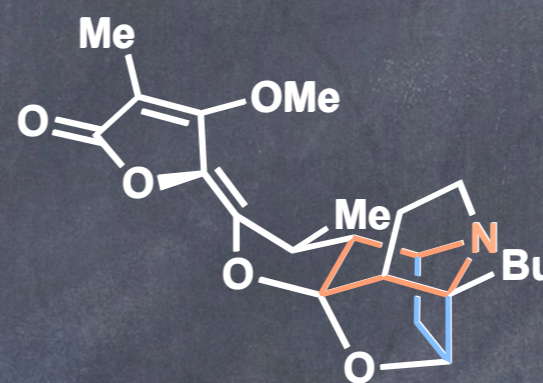
- Diverse skeleton
- ca. 130 Congeners
- Tropan system



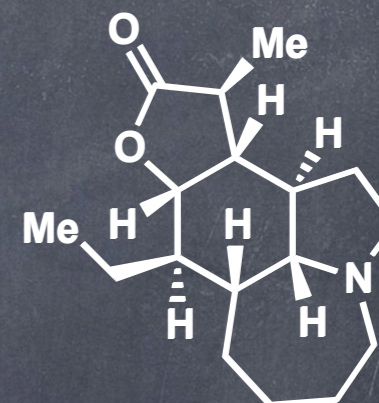
parvistemoninine



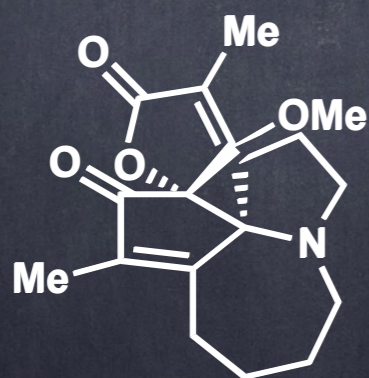
iso-stemofoline



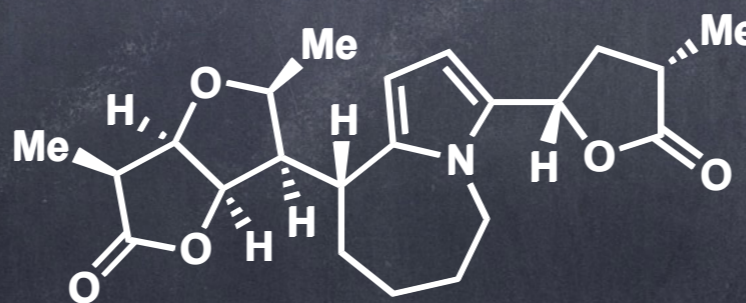
stemofoline



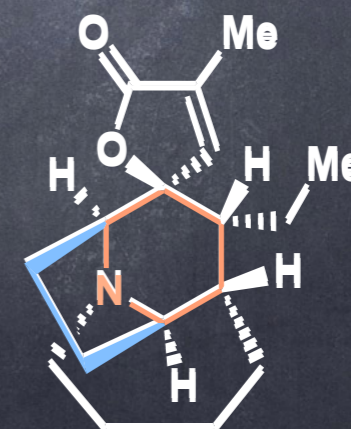
stenine



Stemonamine



Didehydroparvistemonine

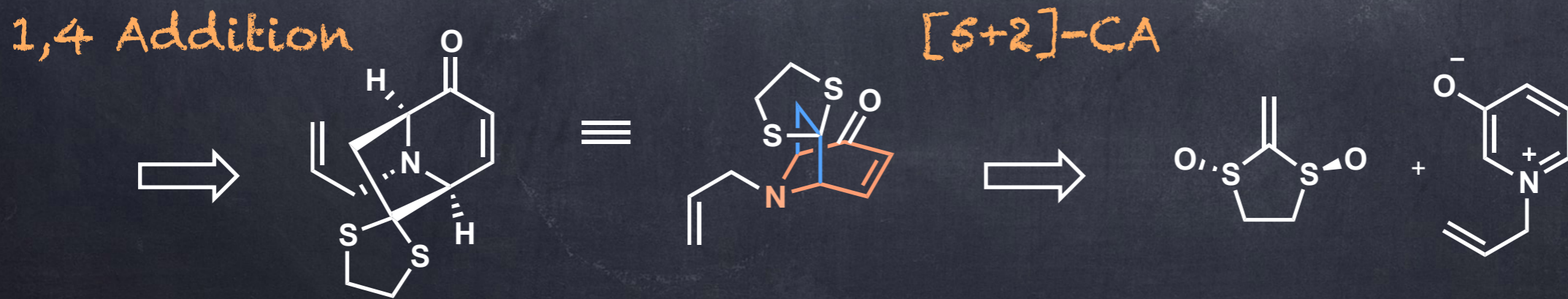
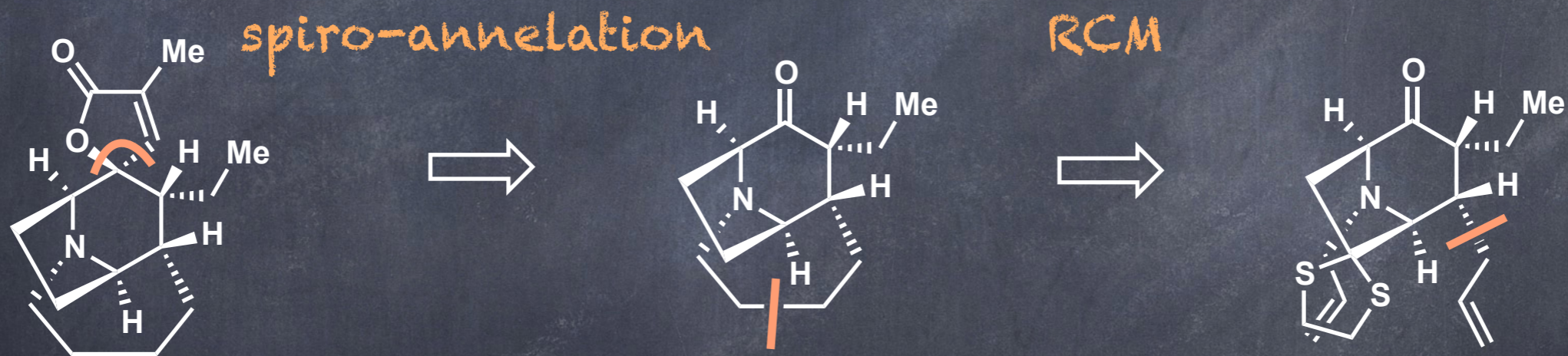


parvineostemonine

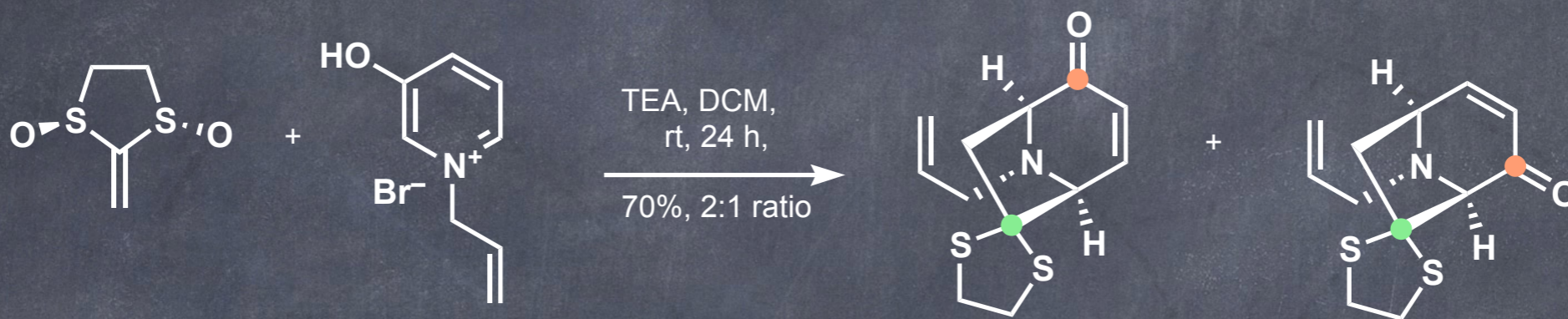
- a.) Pilli, R. A.; Rosso, G. B.; Ferreira de Oliveira, M. da C. *Nat. Prod. Rep.* **2010**, 27(12), 1908-1937. b.) Greger, H. *Planta Med.* **2006**, 72, 99-113.
c.) Pyne, S. G.; Ung, A. T.; Jatisatienr, A.; Mungkornasakwakul, P. *International Journal of Science and Technology*, **2007**, 1(2), 157-165.
d.) R. A. Pilli, G. B. Rosso, M. C. F. de Oliveira in *The Alkaloids*, Vol. 62 (Ed.: G. A. Cordell), Elsevier, New York, 2005, pp. 77-173;

Retrosynthesis

Tropan System:



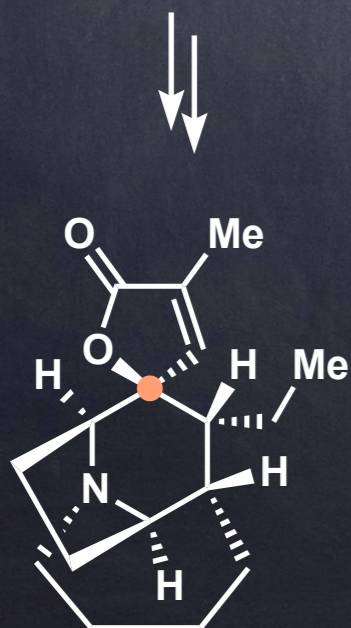
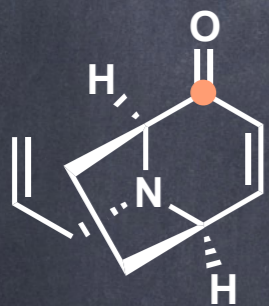
Symmetry Properties of Regioisomers



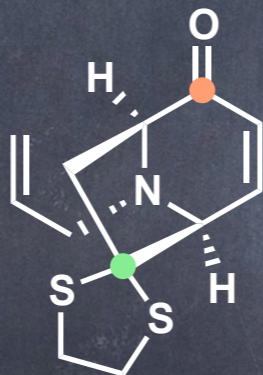
Enantioselective !

Major 2 : 1 Minor

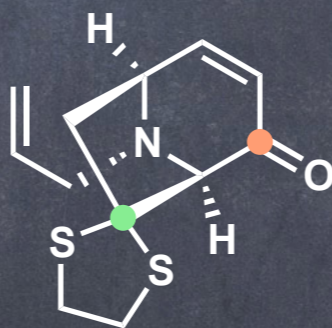
Enantiomers



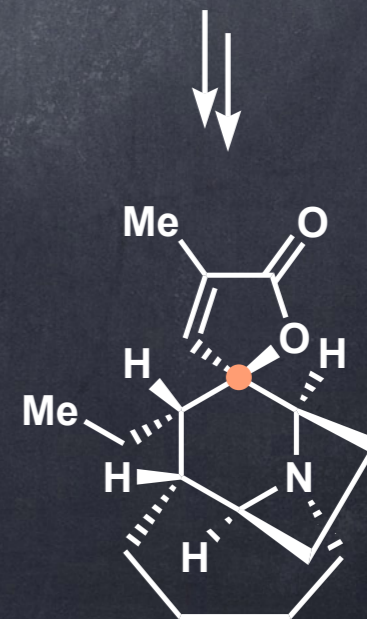
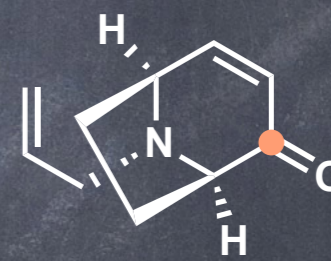
Regioisomers



+



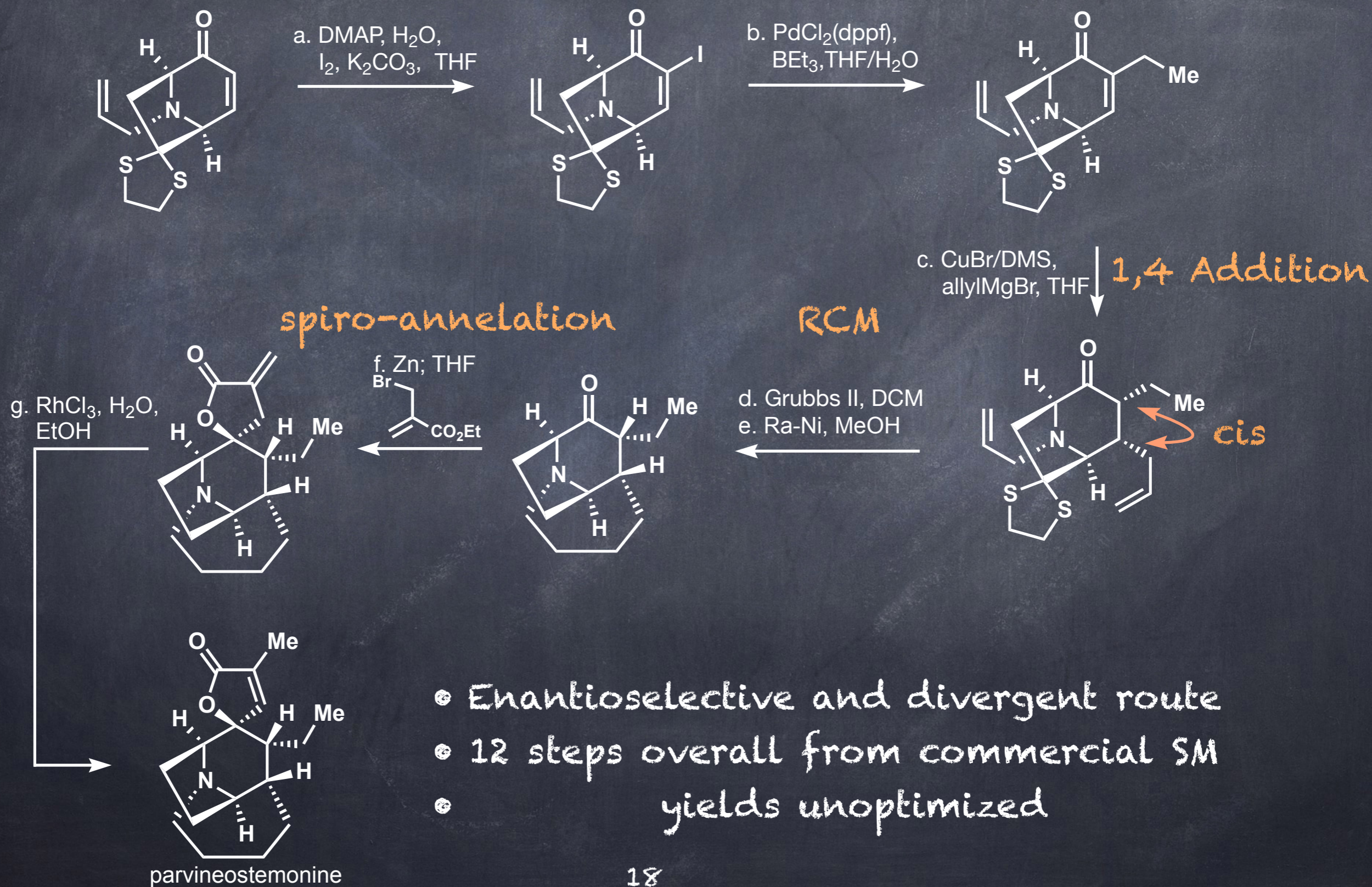
Enantiomers



Both Regiomers used

=> Enantiodivergent Synthesis

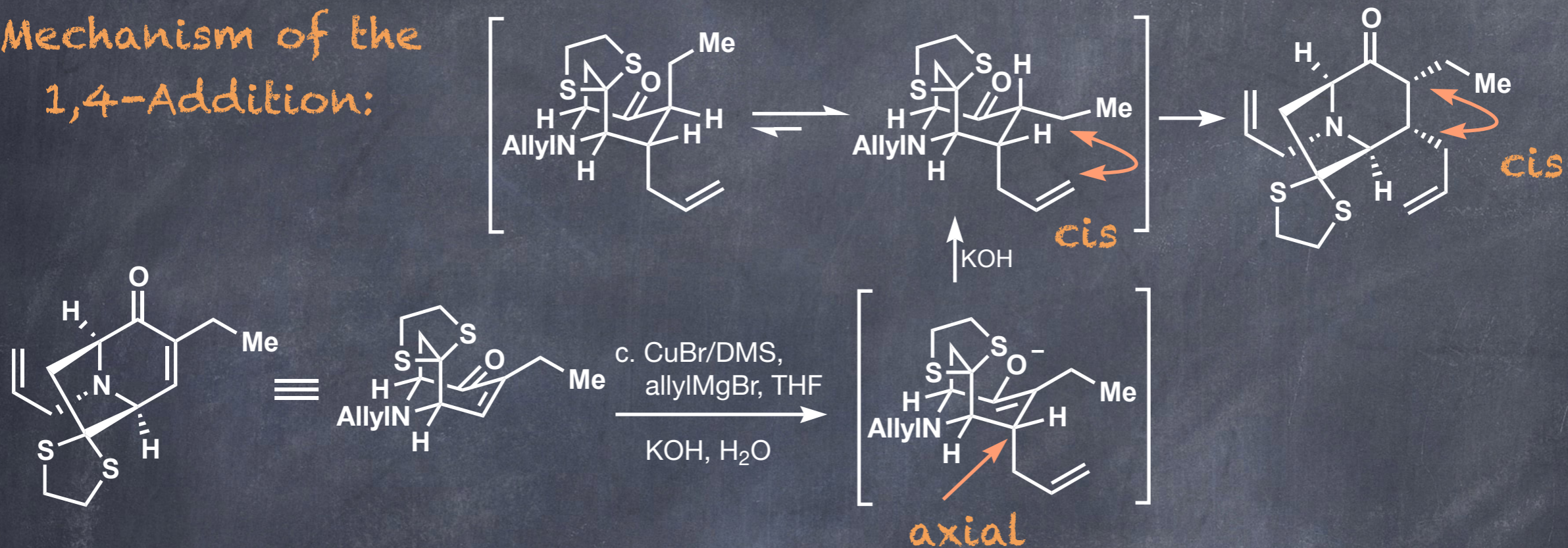
The Total Synthesis



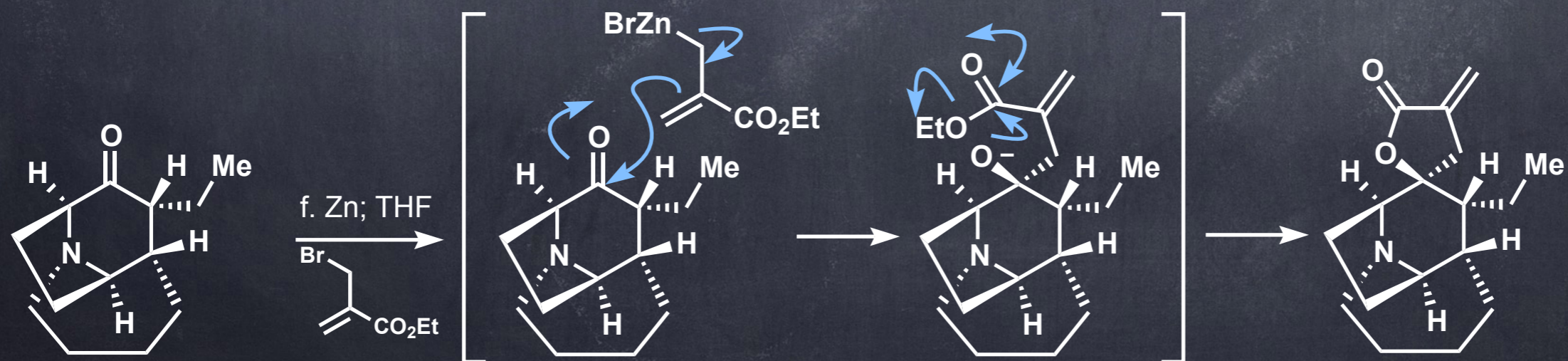
- Enantioselective and divergent route
- 12 steps overall from commercial SM
- yields unoptimized

The Total Synthesis

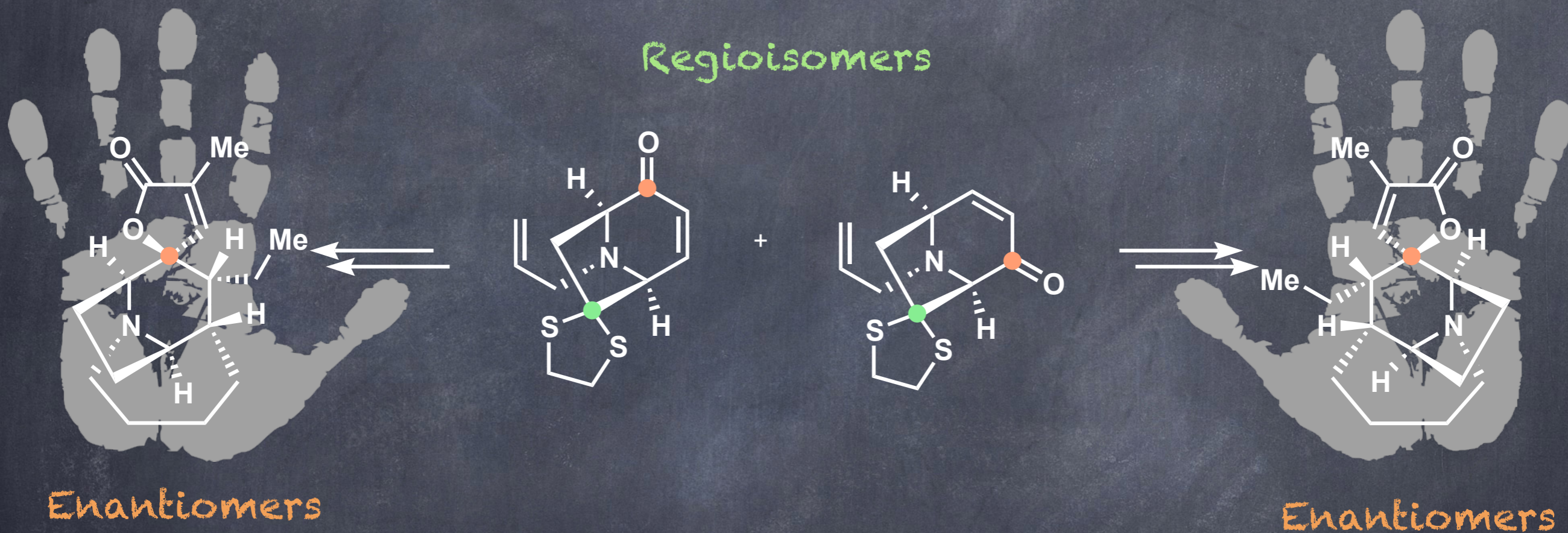
Mechanism of the
1,4-Addition:



Mechanism of spiro-annelation



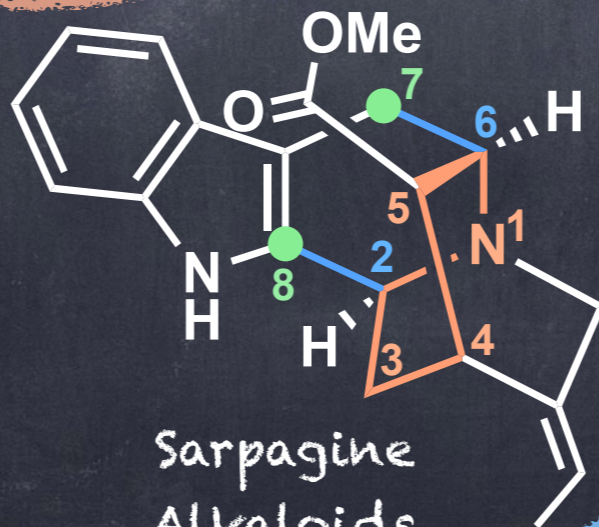
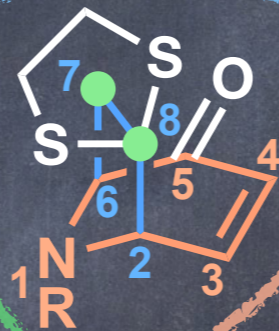
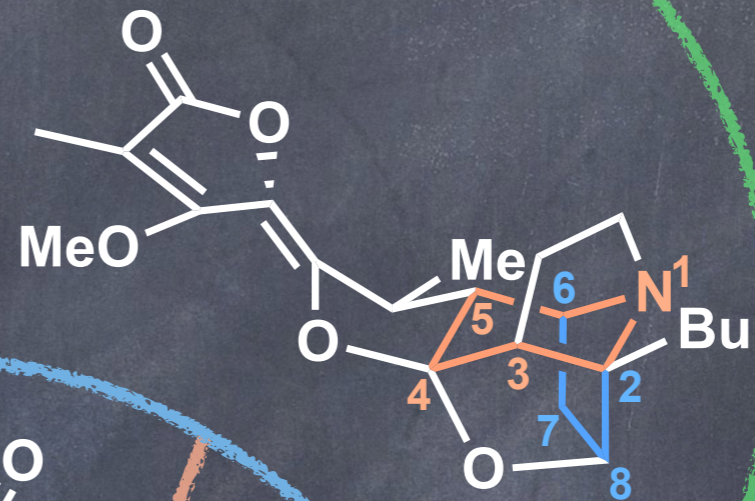
Conclusion I



Both Regiomers used
12 over all steps
=> Enantiodivergent Synthesis

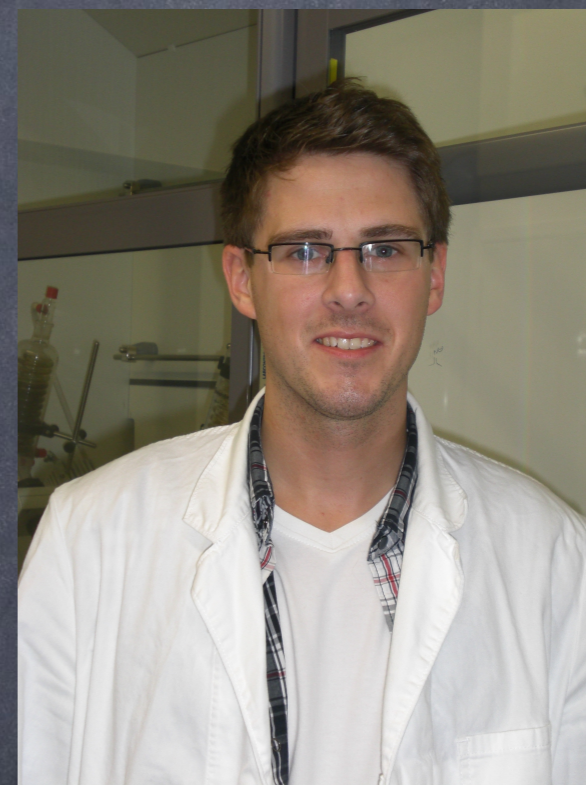
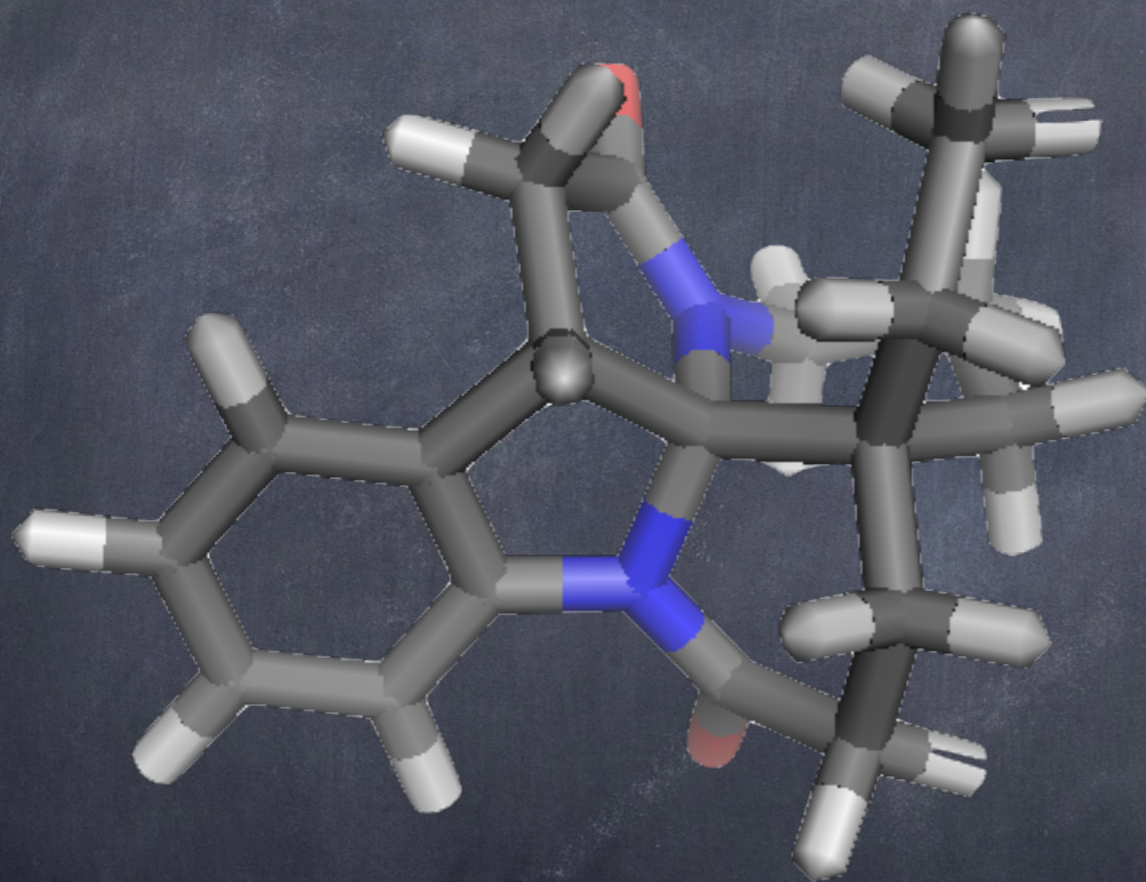
Conclusion II

Stemona Alkaloids



Sarpagine Alkaloids

The Leuconoxine Family – Photochemical C–H–Activation



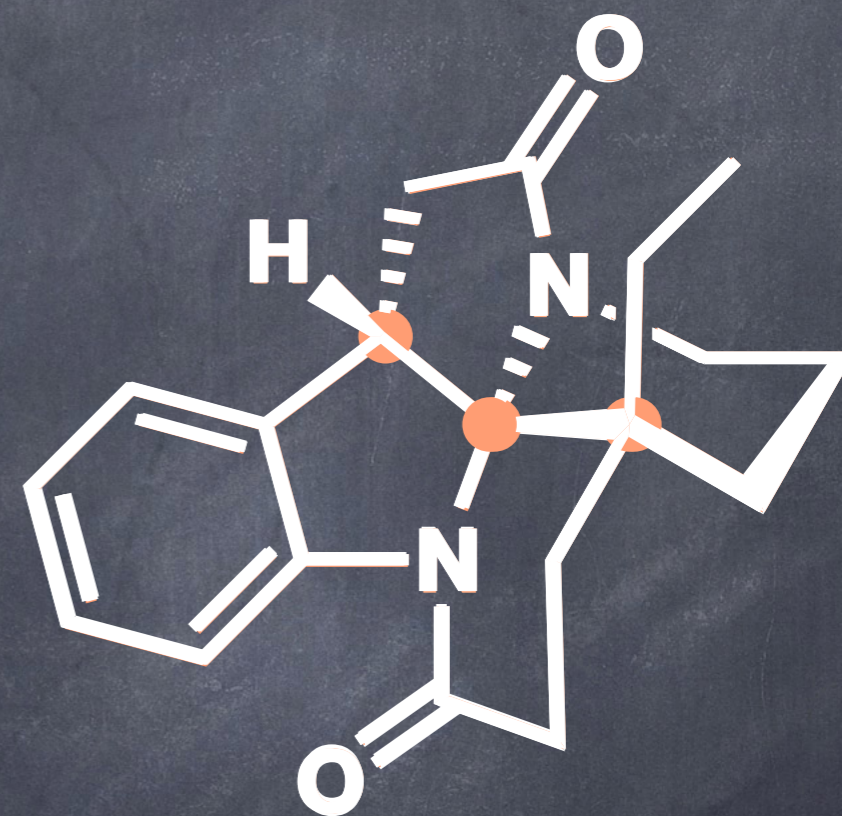
M. Pfaffenbach

IASOC 2016
Sept 28th 2016
Tanja Gaich
University of Konstanz

Structural Analysis

Signature Structure Elements:

- [5.5.6.6]fenestrane structure
- Indole / tryptamine unit
- Secologanin sub-unit
- 3 Stereocenters
- 1 Quaternary carbon atom
- Central Amino of fenestrane



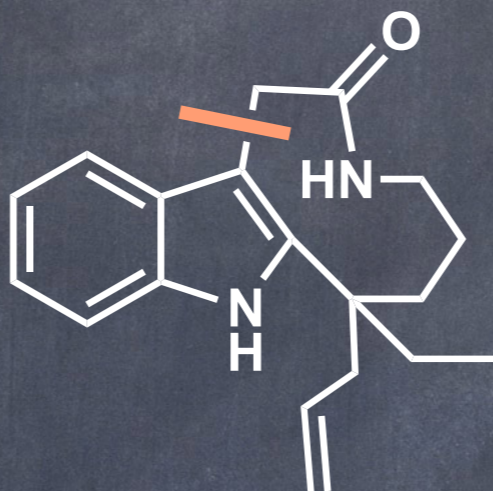
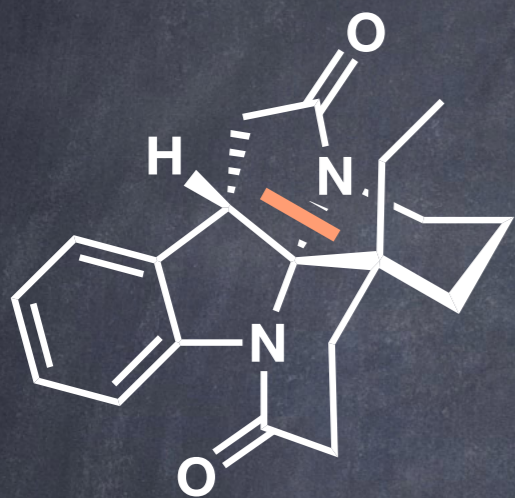
leuconoxine

Completed total syntheses:

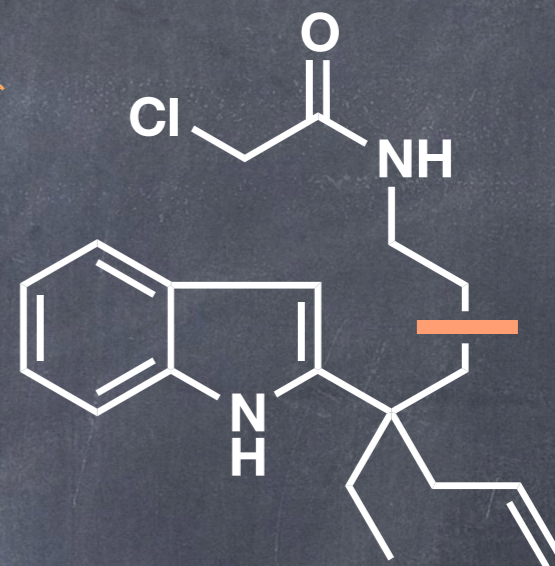
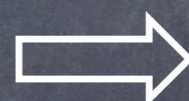
- a) Z. Xu, Q. Wang, J. Zhu, J. Am. Chem. Soc. 2013, 135, 19127 – 19130;
- b) A. Umehara, H. Ueda, H. Tokuyama, Org. Lett. 2014, 16, 2526 – 2529;
- c) Y. Yang, Y. Bai, S. Sun, M. Dai, Org. Lett. 2014, 16, 6216 – 6219;
- d) K. Higuchi, S. Suzuki, R. Ueda, N. Oshima, E. Kobayashi, M. Tayu, T. Kawasaki, Org. Lett. 2015, 17, 154 – 157.

Retrosynthesis I

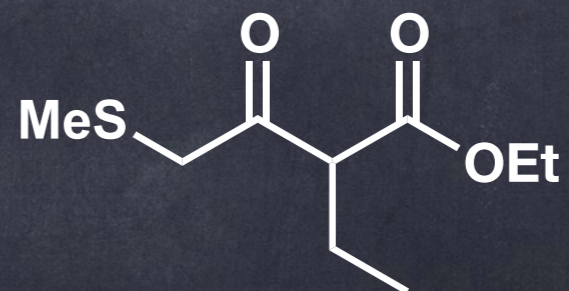
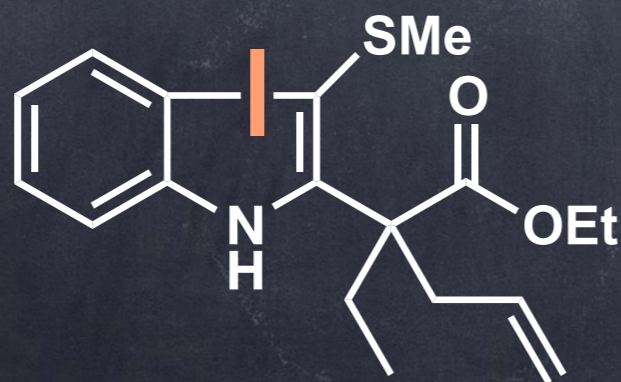
transannular
cyclization



Wittkop
cyclization



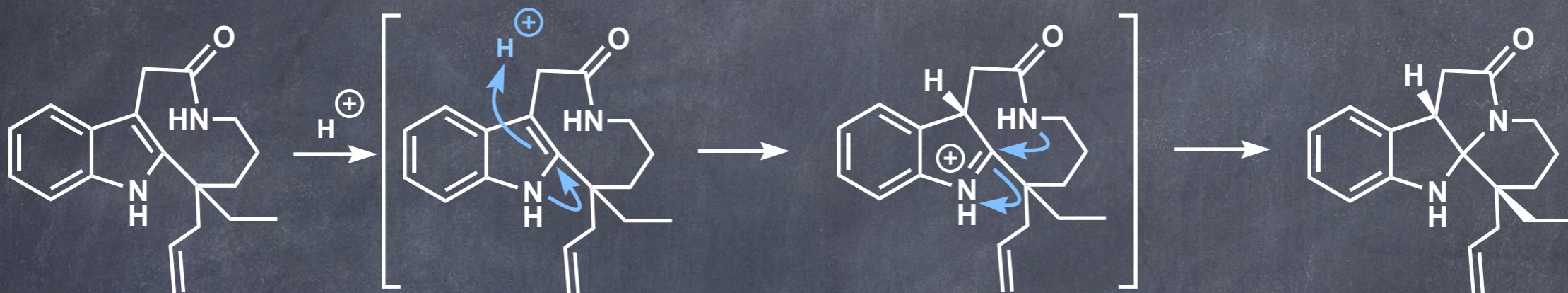
Wittig-Olefination



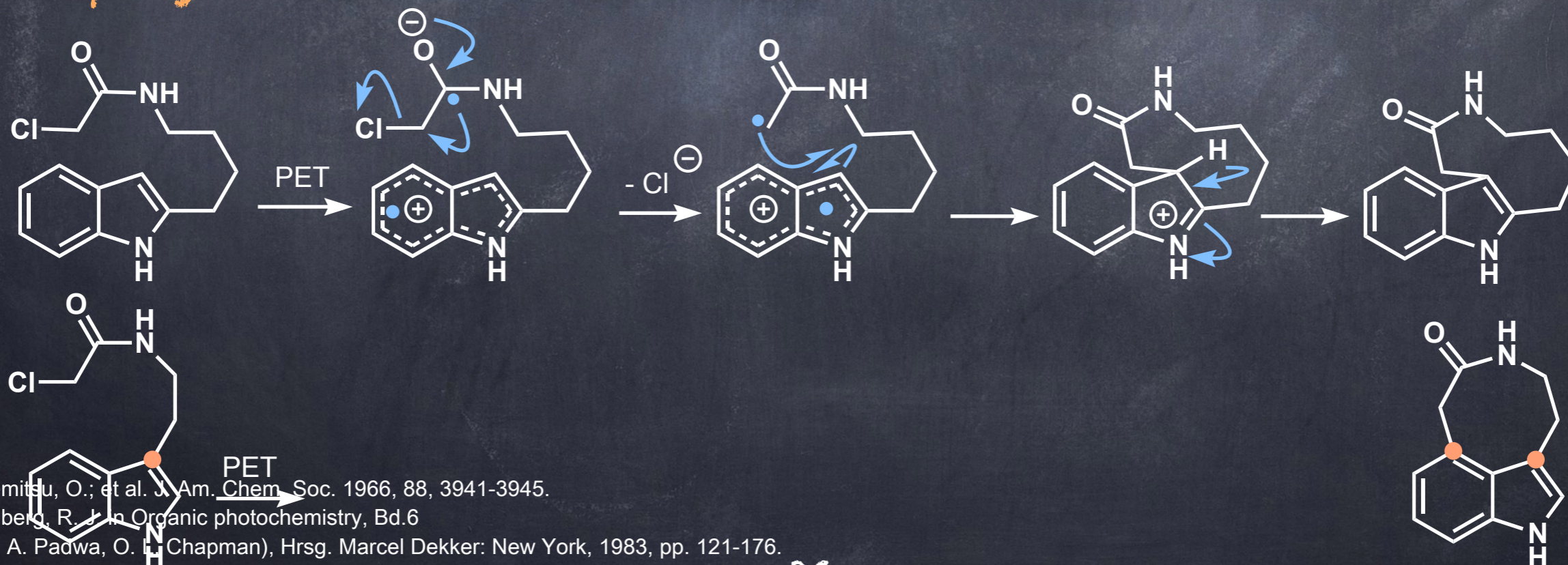
Gassman indole
synthesis

Key Features

Transannular Cyclization



Witkop Cyclization



Yonemitsu, O.; et al. *J. Am. Chem. Soc.* 1966, 88, 3941-3945.

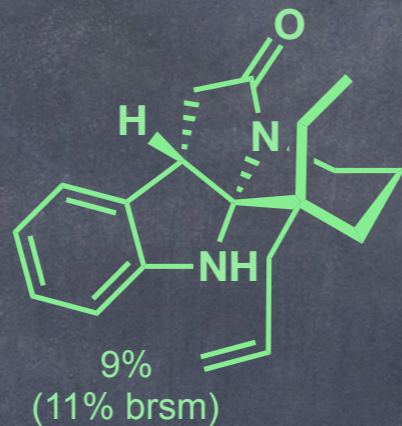
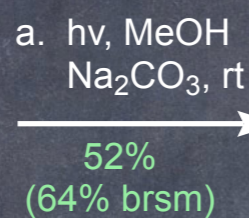
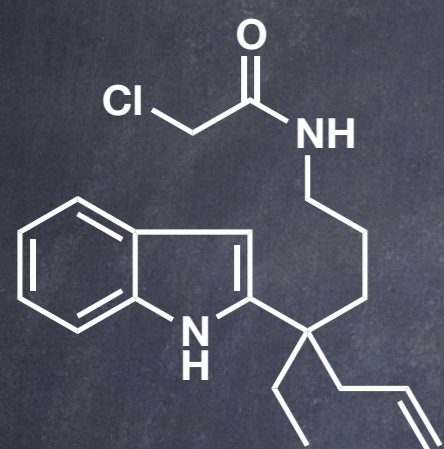
Sundberg, R. J. in *Organic photochemistry*, Bd.6

(Eds: A. Padwa, O. I. Chapman), Hrsg. Marcel Dekker: New York, 1983, pp. 121-176.

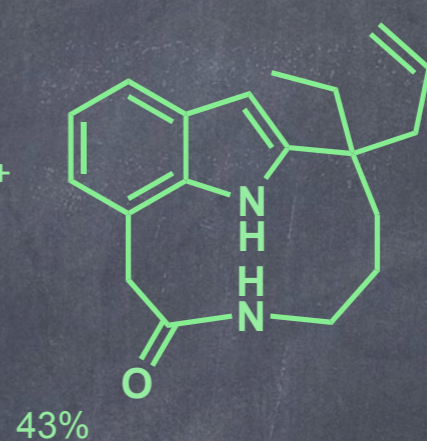
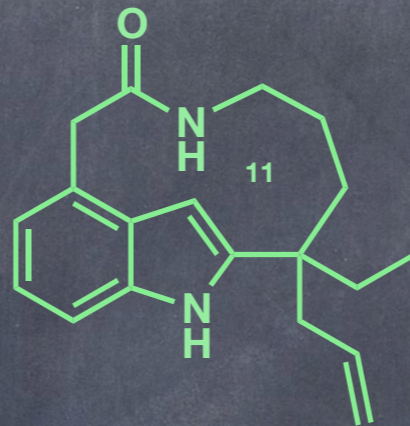
Huisgen, R. *Angew. Chem. Int. Ed.* 2011, 25, 5609-5610.

Witkop Cyclization

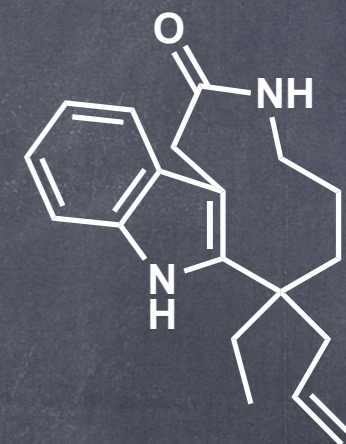
Obtained Products



Indolo-cyclophane

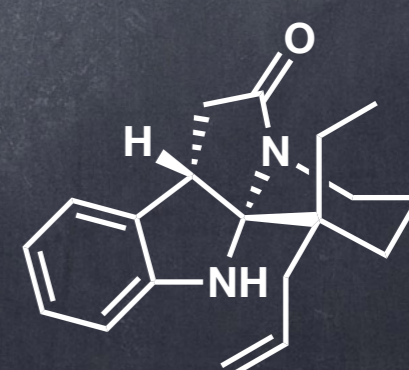
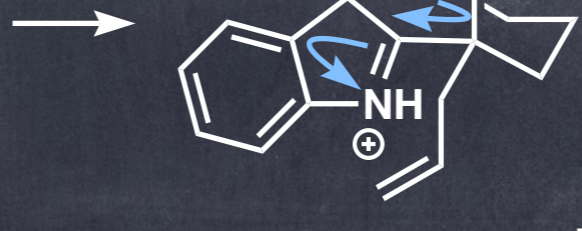
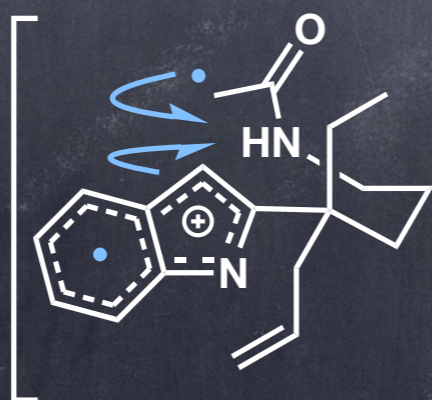
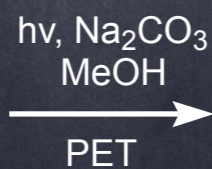
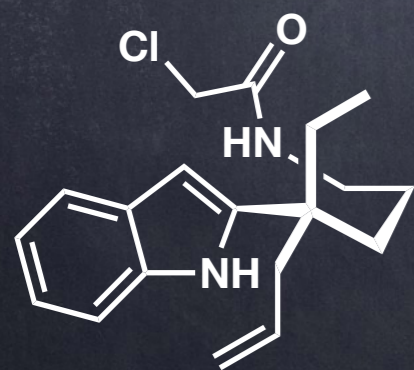


Expected



Mechanism

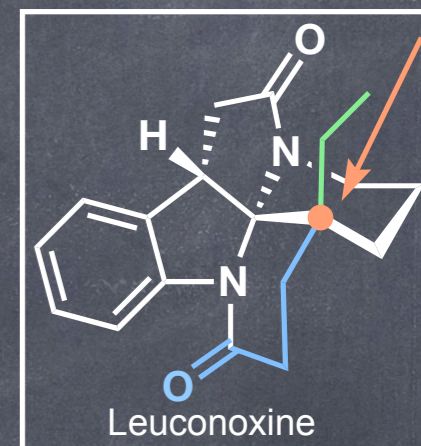
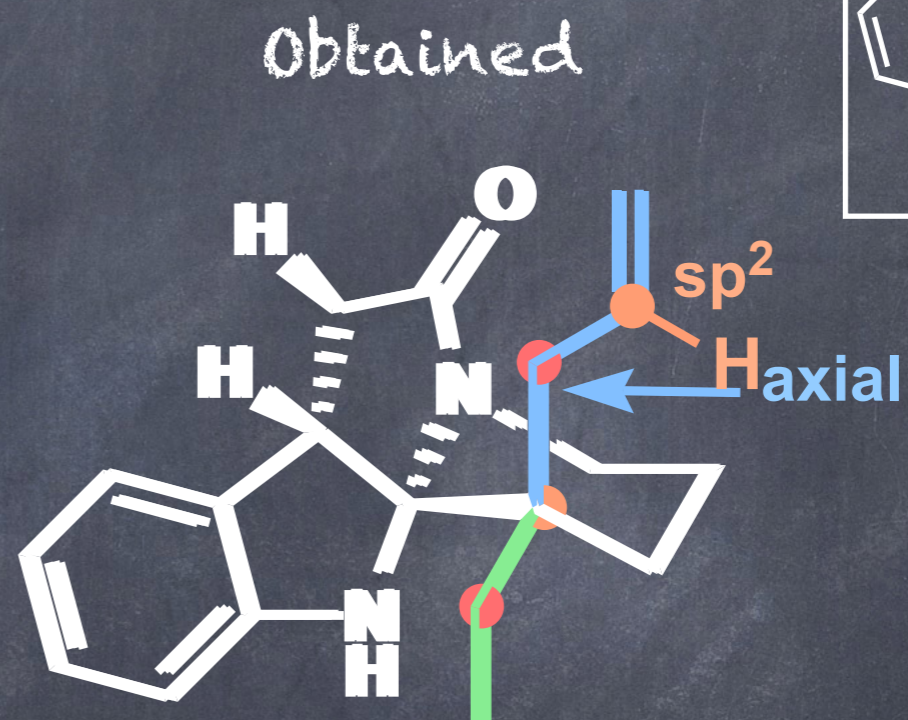
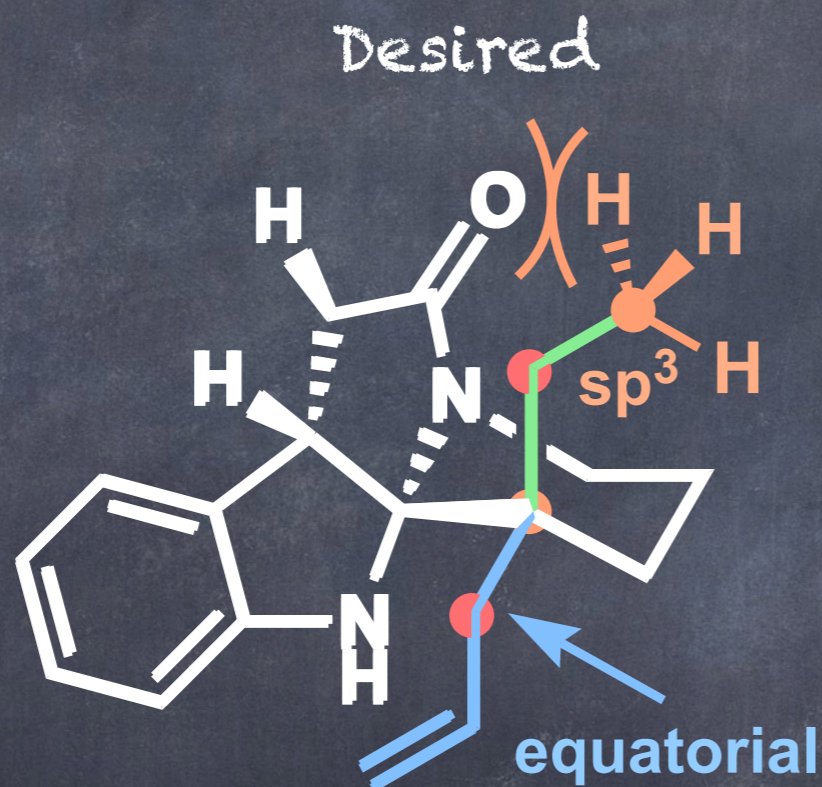
Cascade Witkop-transannular cyclization



Completely
diastereoselective !

An Analysis Attempt...

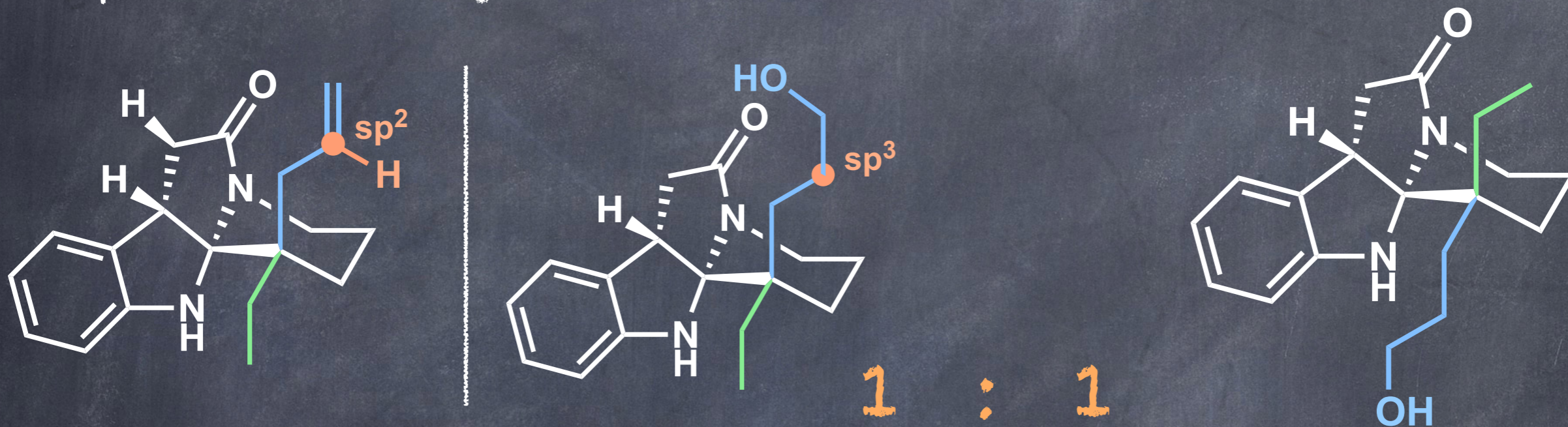
Where does the selectivity come from?



- Allyl preferred in axial
- neo-Pentyl positions identical
- steric hindrance sp^2 vs sp^3
- and/or Π - Π -interaction

2nd Approach

Adaptation of the System:



Completion of the Total Synthesis:

