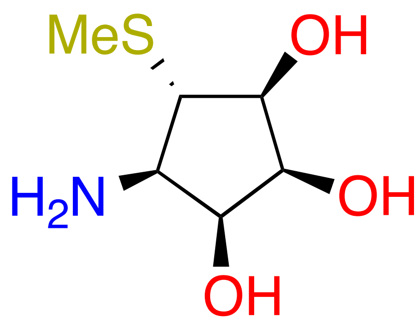
Total Synthesis of (+)-Mannostatin A



Rong Ling and Patrick S. Mariano*
J. Org. Chem. **1998**, *63*, 6072

Kristen DeMeester
March 4, 2014

Patrick S. Mariano

Education

•B.S. in Chemistry, 1964, Fairleigh Dickinson University

•Ph.D. in Chemistry, 1969, **Advisor** H-Zimmerman University of Wisconsin NIH Predoctoral Fellow

The Di-π-Methane Rearrangement. Interaction of Electronically Excited Vinyl Chromophores

•Postdoctoral Fellowship in Chemistry, **Advisor** H-Wasserman 1968-1970, Yale University

Career

•1970-1976; Assistant Professor, Texas A&M University

•1976-1979; Associate Professor, Texas A&M University

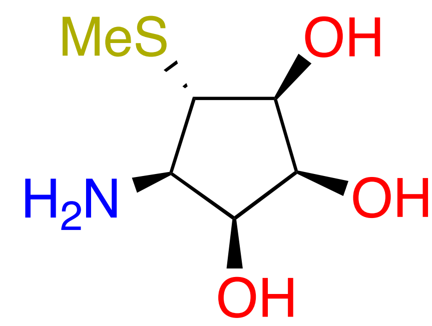
•1978; Visiting Professor of Chemistry, Cornell University

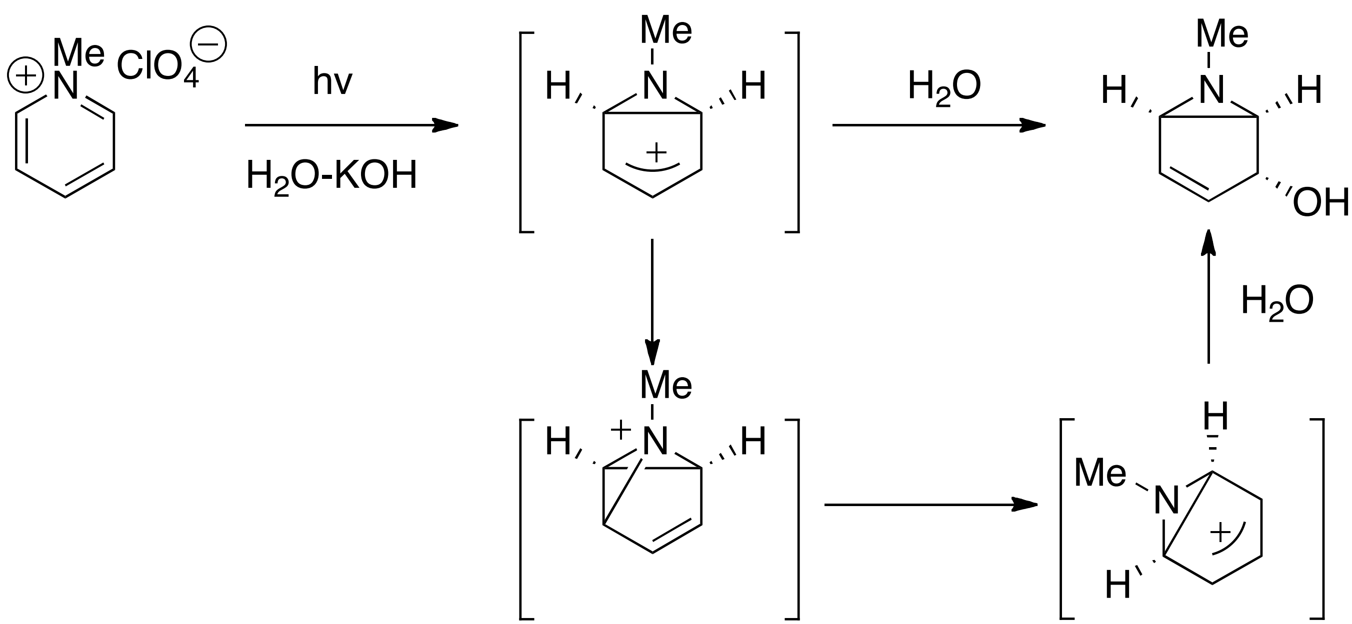
•1979-1997; Professor of Chemistry, University of Maryland

•1997-present; Professor of Chemistry, University of New Mexico

https://chemistry.unm.edu/people/faculty/members/patrick-mariano.html

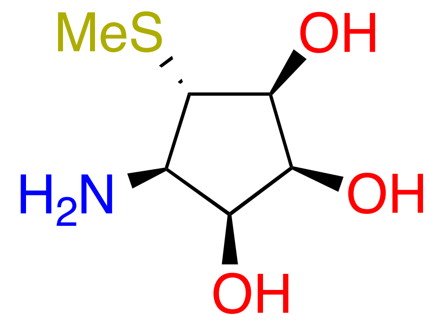
Early Pyridinium Photochemistry Inspiration

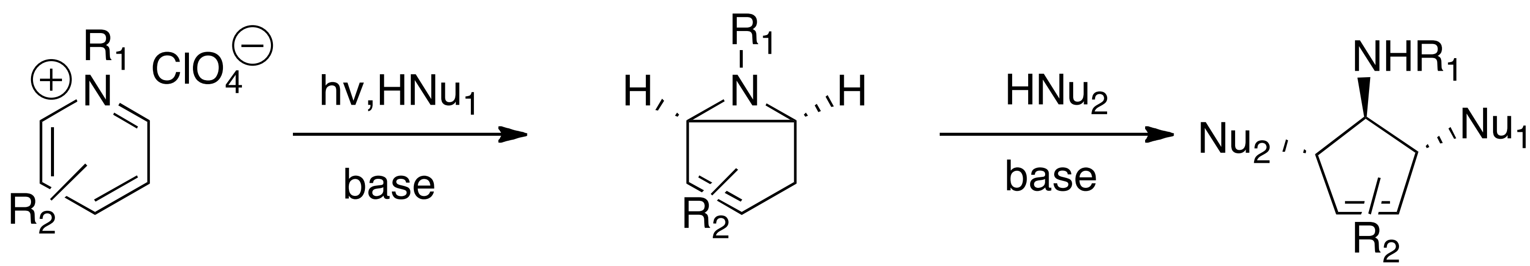




L. Kaplan, J. W. Pavlik and K. E. Wilzbach, Photohydration of Pyridinium Ions, J. Am. Chem. Soc., 1972, 94, 3283–3284; Mariano, P. *J. Org. Chem.* **1996,** *61,* 4439-4449

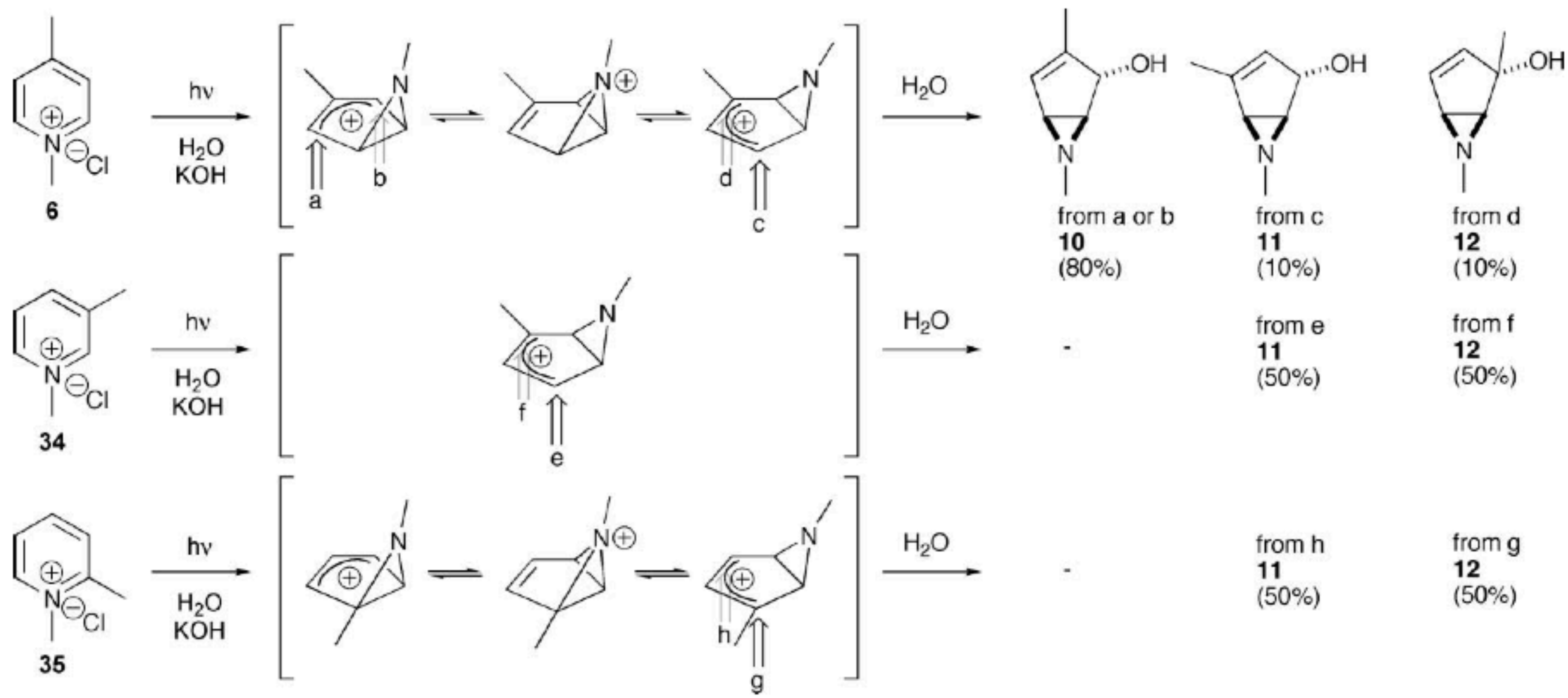
Early Pyridinium Photochemistry Inspiration



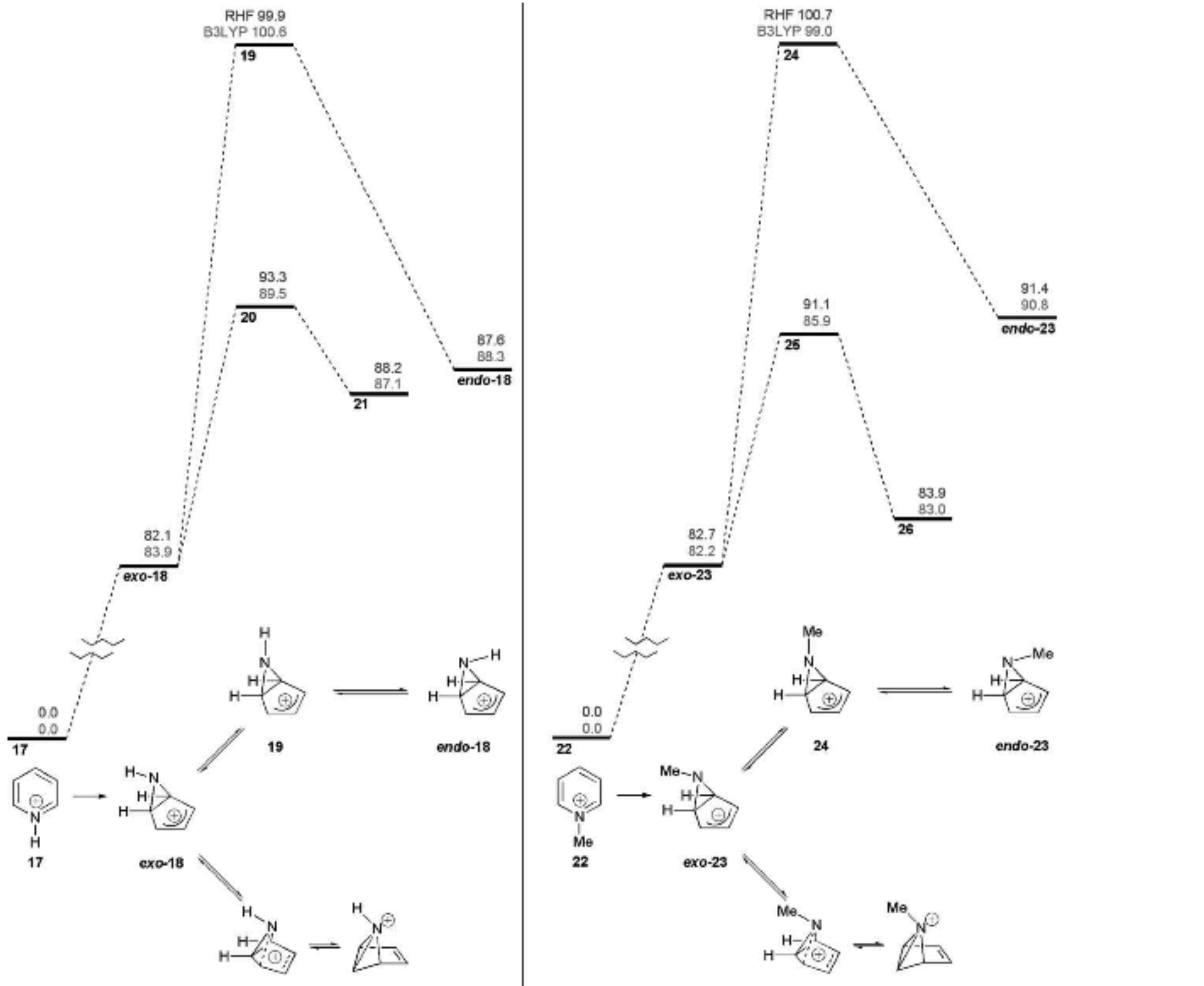


Mariano, P. *J. Org. Chem.* **1996,** *61,* 4439-4449

Mechanistic Insight



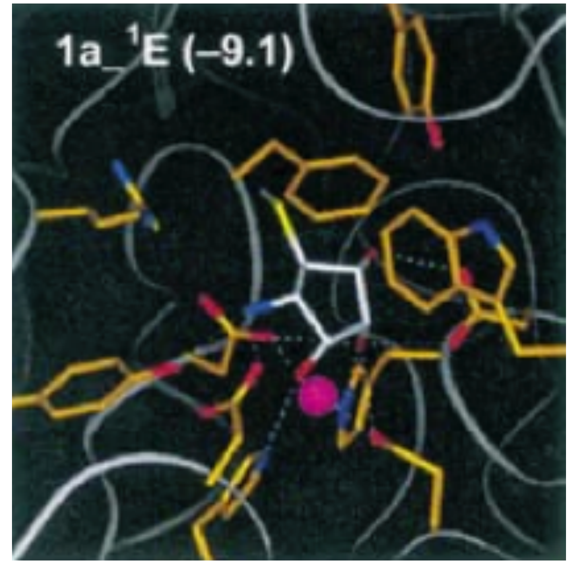
Damiano, Org. Biomol. Chem., 2007, 5, 2735–2752

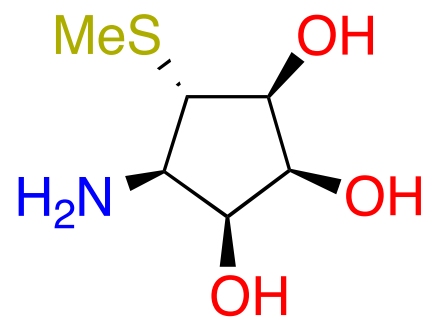


Damiano, Org. Biomol. Chem., 2007, 5, 2735–2752

(+)-Mannostatin A

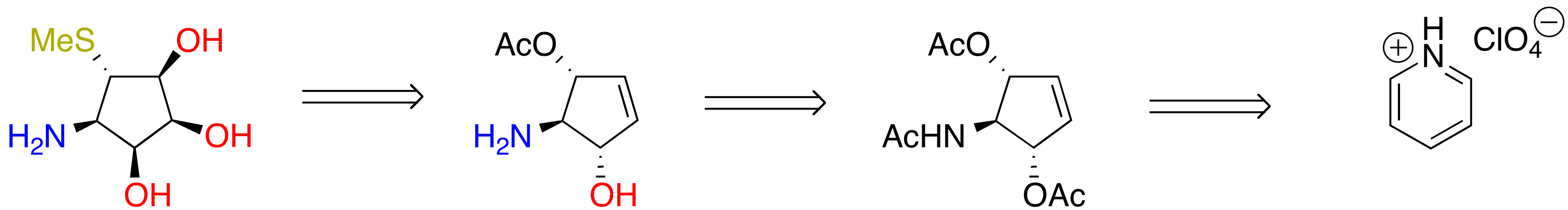
- Metabolite isolated from microorganism *Streptoverticillium verticillus* in 1989
- Competitive inhibitor of glycoprotein-processing enzyme mannosidase II
- Glycosidase inhibitors act as anitviral, antitumor proliferative or immunoregulatory agents





Elbein, Alan***. Biochemistry* 1990, *29,*** 10062-1 0069; Trost, B. ***J. Am. Chem. SOC.*1991, 113,**
6317-6318; Kawatkar, S. ***ChemBioChem,* 2004, *5,*** 1220

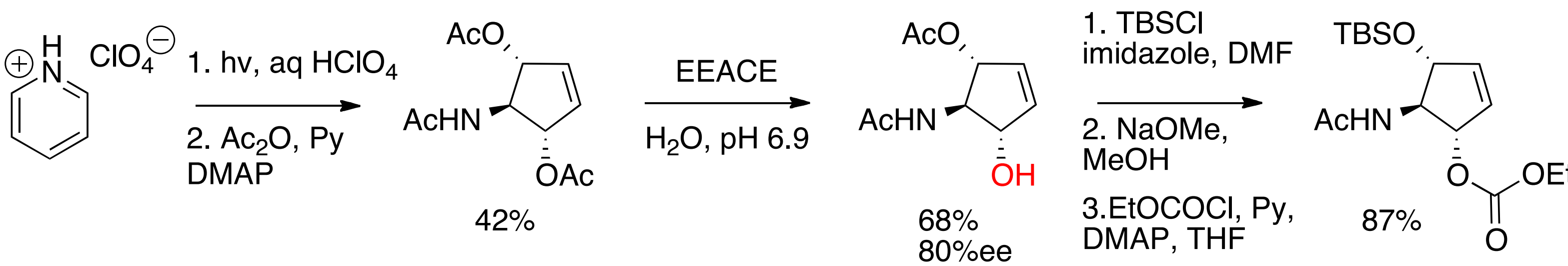
Retrosynthesis

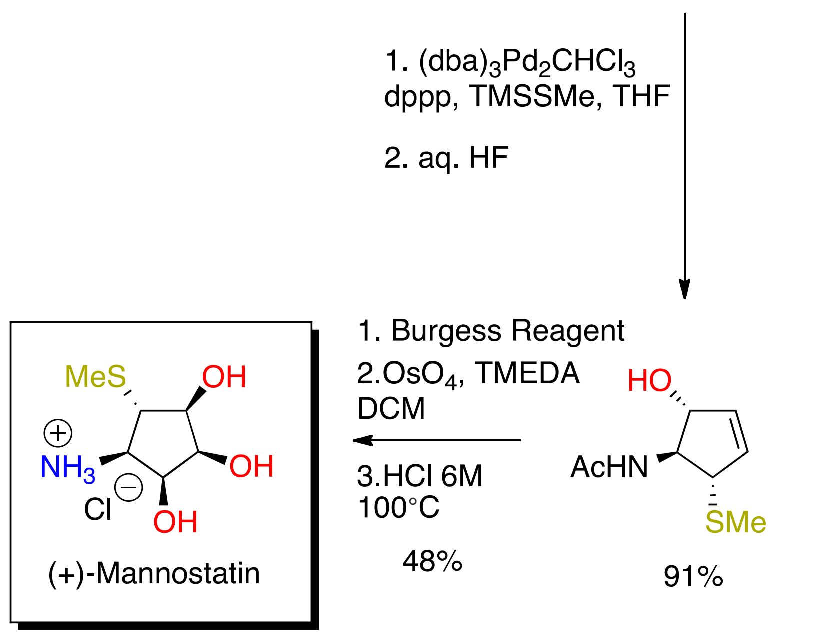


(+)-Mannostatin A

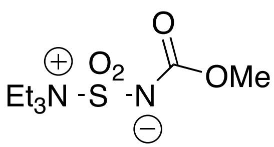
Rong Ling and Patrick S. Mariano* *J. Org. Chem.* **1998**, *63*, 6072

Synthesis of (+)-Mannostatin A

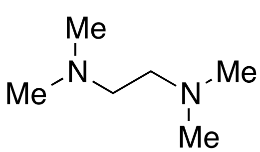




Burgess Reagent

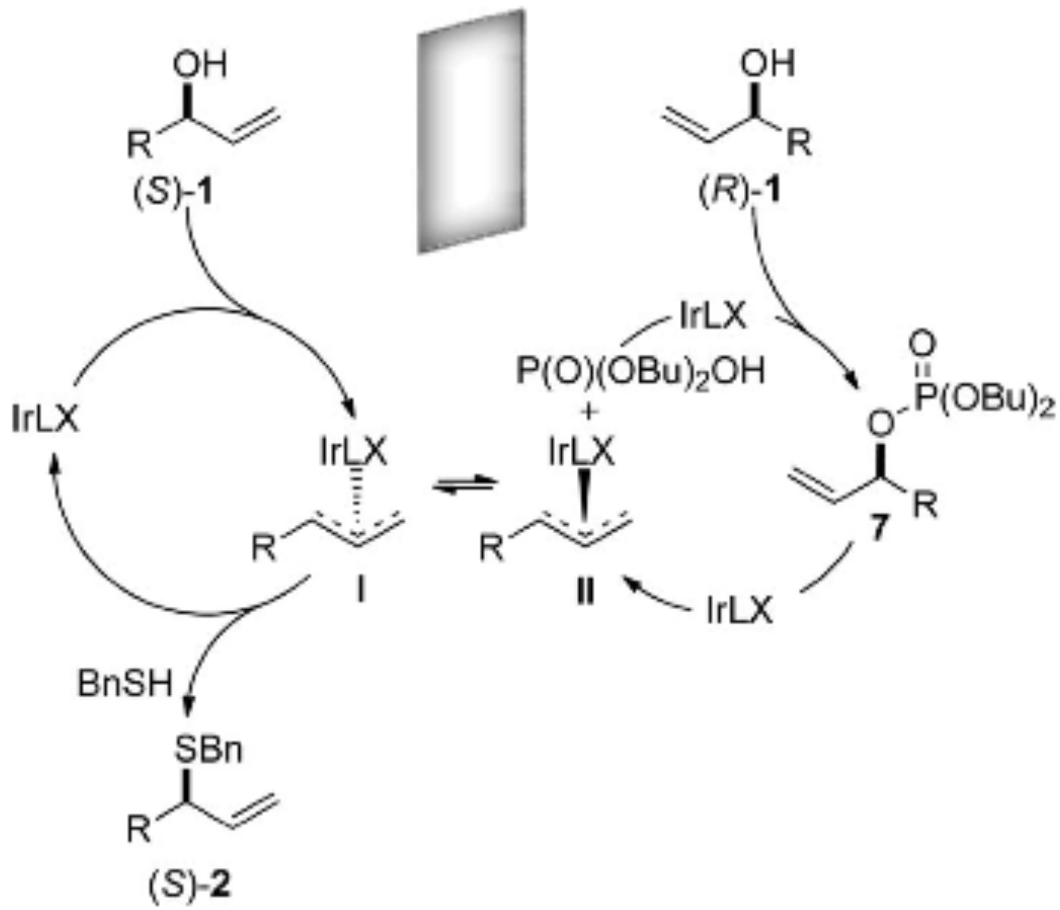


TMEDA=Tetramethylethylenediamine



EEACE = Electric Eel Acetylcholine Esterase

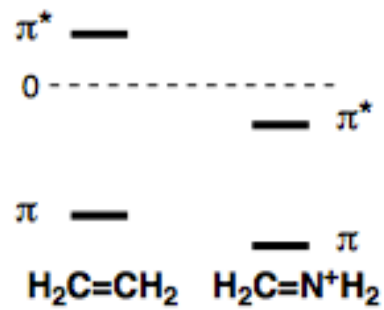
Mechanisms



Carreira. Angew. Chem. Int. Ed. 2012, 51, 8652 –8655

Rationale

Only one photochemical transition possible: π - π^*. Occurs in the UV and visible regions (similar to olefins).
Pyridiniums and phenyl substituted iminiums have long-lived singlet excited states.
HOMO and LUMO π-orbitals much lower than the corresponding olefins.



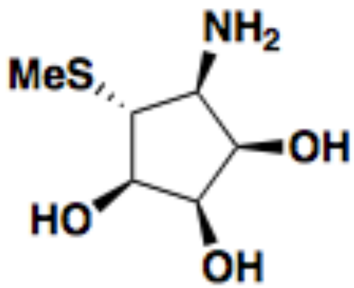
Ground state reactions observed: nucleophilic attack or deprotonation adjacent to the nitrogen atom.
Excited state reactions observed: cis-trans isomerization (C=C not C=N), electrocyclizations, and cycloadditions. Note: Due to the increased electron density on carbon, nucleophilic additions should not be possible.
Low LUMO allows easy single-electron reduction to form α-amino radicals.
Great receptors in SET processes. Unique reactivity available for such excited states (depending on ionization energies and electron affinities:

$$A^* + B \longrightarrow A^{\bullet -} B^{\bullet +}$$

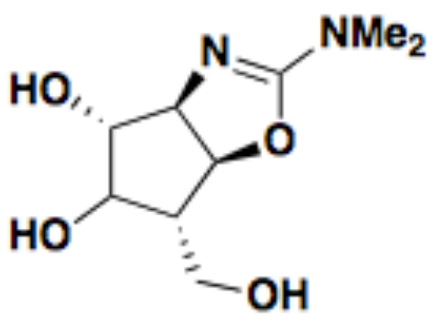
http://www.scripps.edu/baran/images/grpmtgpdf/Richter_July_05.pdf

Other Synthetic Applications

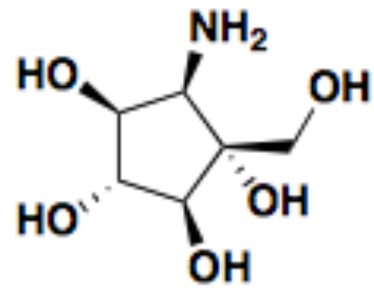
– Mannostatin A
(*J. Org. Chem.* **1998**, *63*, 6072)



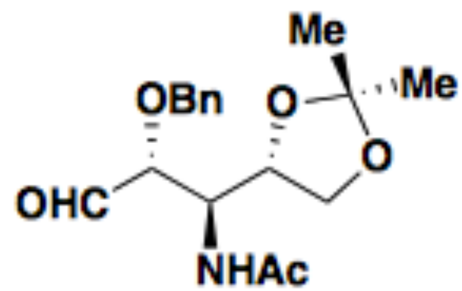
– Allosamizoline
(*Tetrahedron Lett.* **2001**, *42*, 4755)



– Trehazolamine
(*J. Org. Chem.* **2005**, *70*, 5618)



– Protected Pentoses
(*J. Org. Chem.* **2002**, *67*, 3525).



http://www.scripps.edu/baran/images/grpmtgpdf/Richter_July_05.pdf

Summary

- Route to syntehsize (+)-Mannostatin A highlights pyridinium salkt photochemistry
  - » Concise, economical
- 11 Step synthesis with overall 11% yield
- Stereo & regioselectivity used to prepare other biologically active natural products

Questions

Early Pyridinium Photochemistry – backup cis,trans