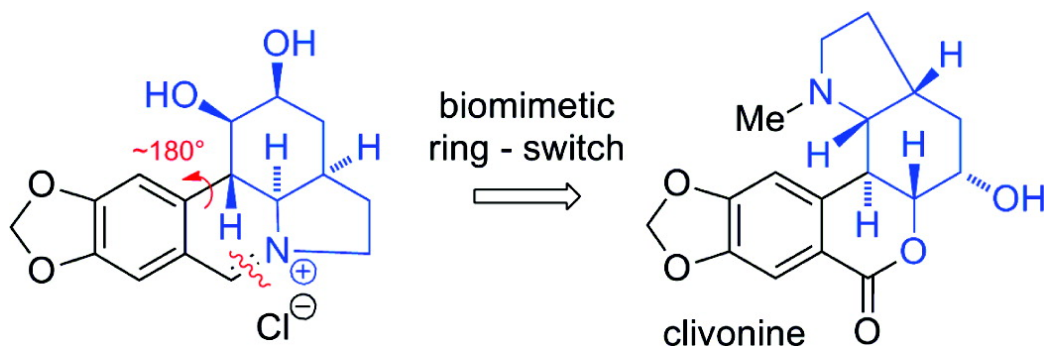


# Total Synthesis of the Lycorenine-Type Amaryllidaceae Alkaloid ( $\pm$ )-Clivonine via a Biomimetic Ring-Switch from a Lycorine-Type Progenitor

Carles Giró Mañas, Victoria L. Paddock, Chrostan G. Bochet, Alan C. Spivey,\* Andrew J. P. White, Inderjit Mann, and Wolfgang Oppolzer  
*J. Am. Chem. Soc.* Article ASAP DOI: 10.1021/ja910184j

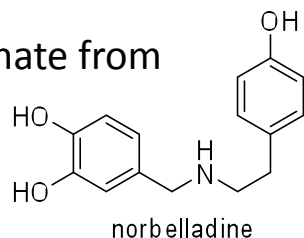


Marija Manojlović  
Wipf Group Current Literature Meeting  
3/27/2010

# Amaryllidaceae Alkaloids

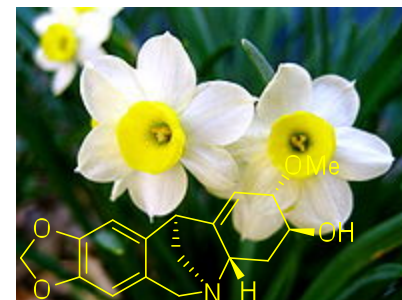
- Amaryllidaceae family: *ca.* 85 genera and 1100 species distributed throughout tropic and warm temperate regions
- Widely used in folk medicine
- Nearly 500 structurally diverse alkaloids isolated so far
- 18 different skeleton types
- Biological activities: antitumor, antibacterial, antifungal, antimalarial, antiviral, analgesic and AChE inhibitory activity

- Biosynthetically originate from norbelladine



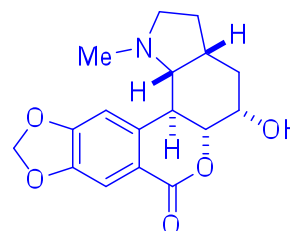
*Nat. Prod. Rep.* **2009**, 26, 363.

*J. Am. Chem. Soc.* **1956**, 78, 2899.

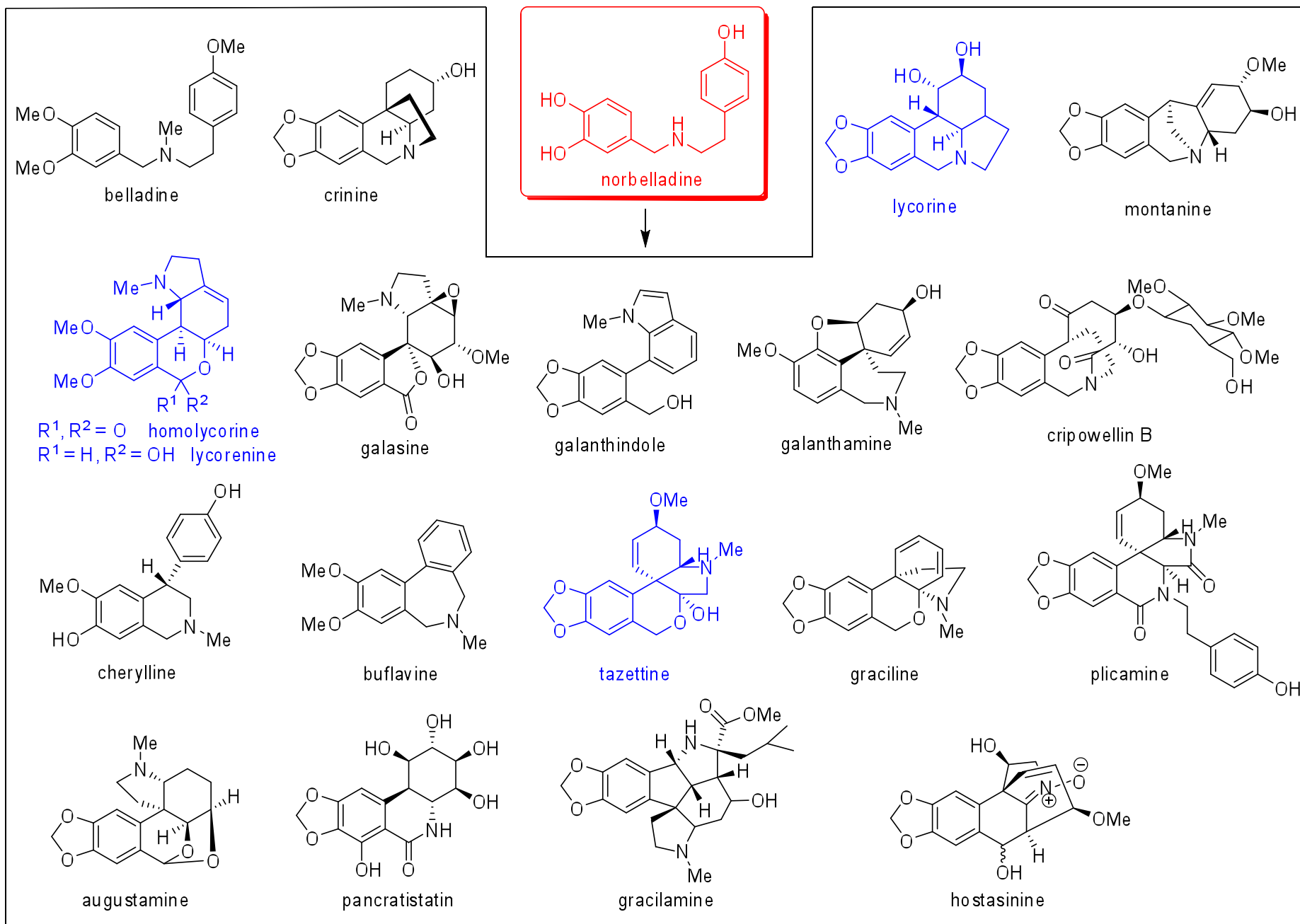


## Clivonine:

- Isolated from *Clivia miniata* (bush lily) in 1956 by Wildman
- Structure determined by Jeffs in 1971



<http://en.wikipedia.org/wiki/Amaryllidaceae>



Nat. Prod. Rep. 2009, 26, 363.

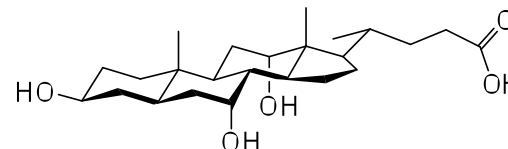
# Sir Derek H. R. Barton



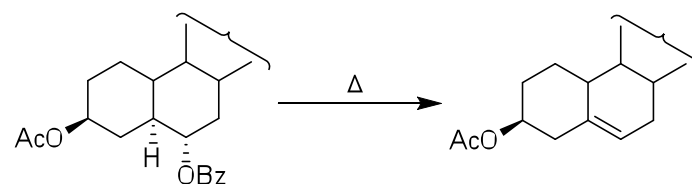
- One-electron oxidative coupling of phenols in synthesis and biosynthesis

**Barton's hypothesis (1957):  
Phenolic oxidative coupling is  
critical diversifying step in alkaloid  
biosynthesis!**

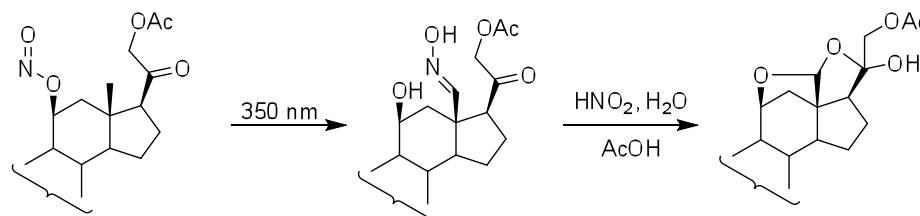
- Conformational analysis (Nobel prize 1969)



- Discovery of *cis*-elimination



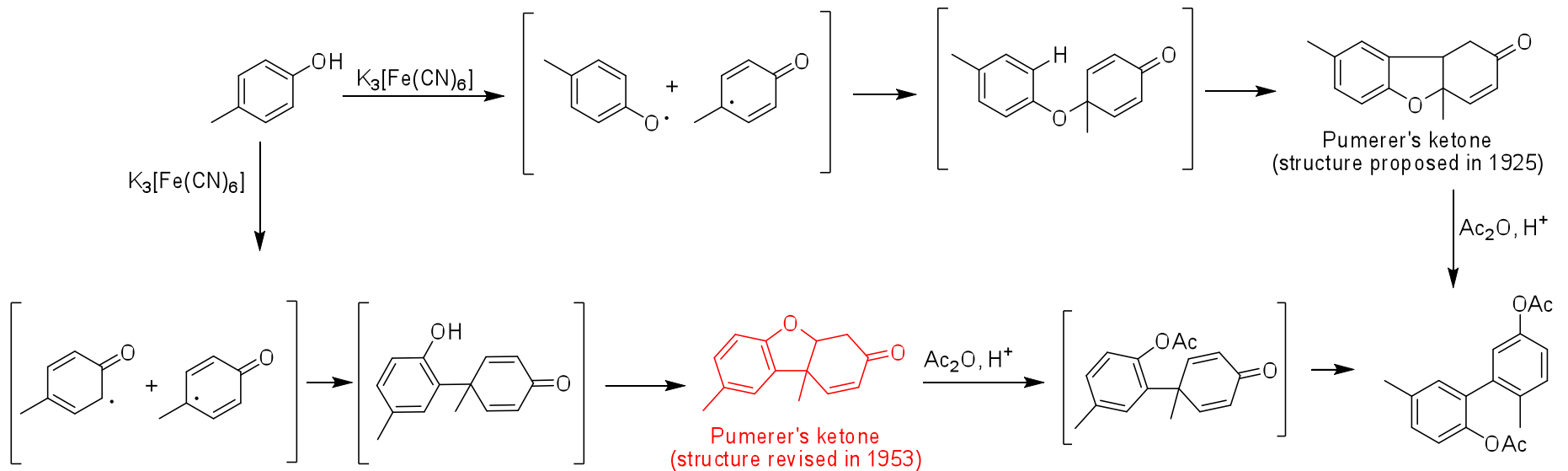
- Photochemical reactions (synthesis of aldosterone by nitrite photolysis)



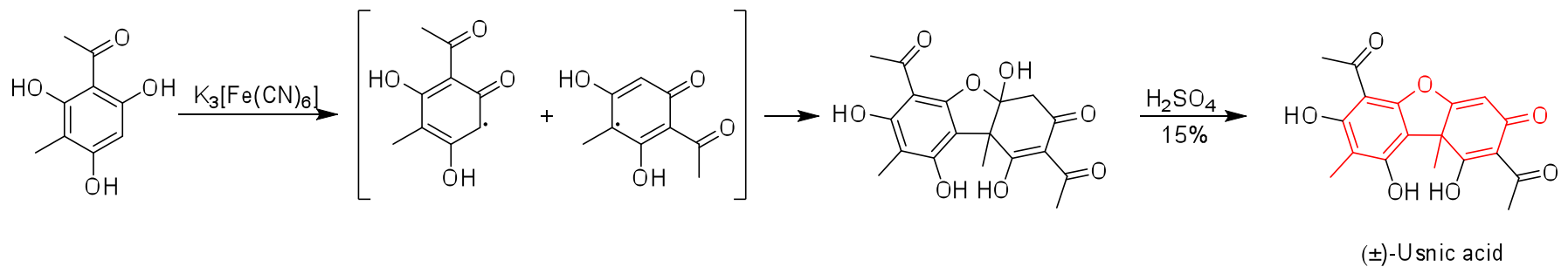
- Radical chemistry: Barton-McCombie deoxygenation
- Radical decarboxylation

Barton, D. H. R. *Some Recollections of Gap Jumping*, American Chemical Society: Washington 1991.

# Pumerer's ketone structure



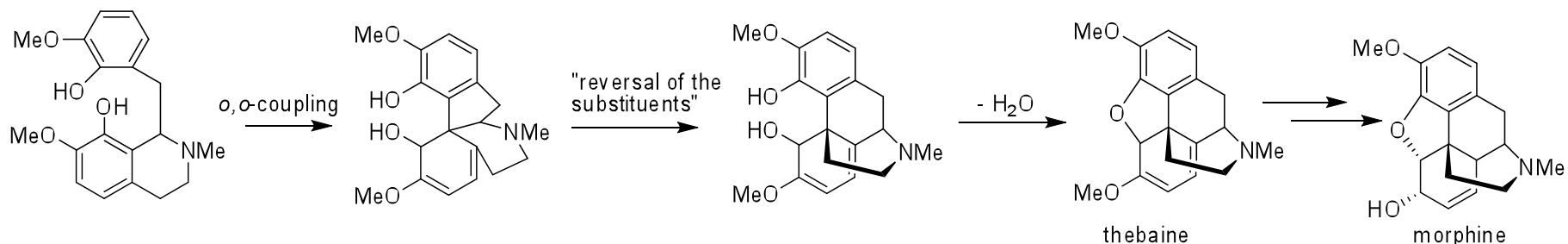
# (±)-Usnic Acid



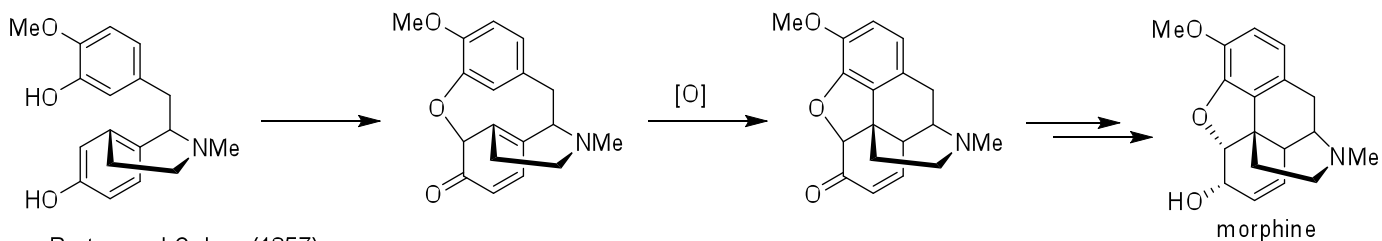
Barton, D. H. R. *Some Recollections of Gap Jumping*, American Chemical Society: Washington 1991.

# Biosynthesis of Morphine

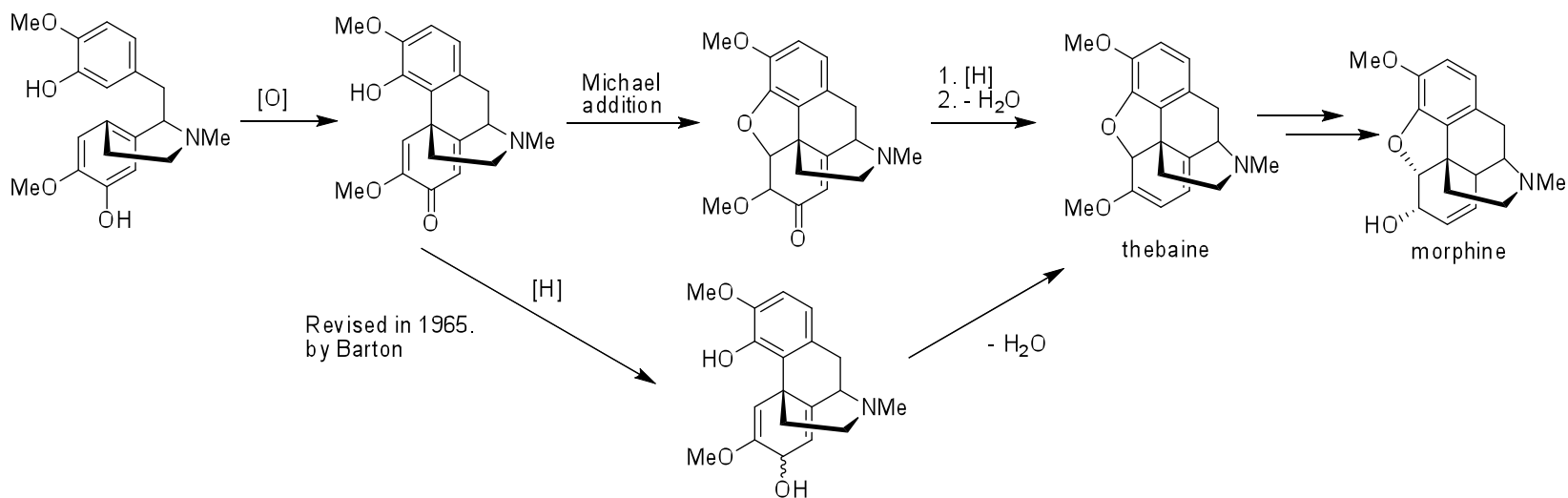
Robinson, 1931.



Schöpf, 1952. (based on the wrong structure of Pumerer's ketone)



Barton and Cohen (1957)



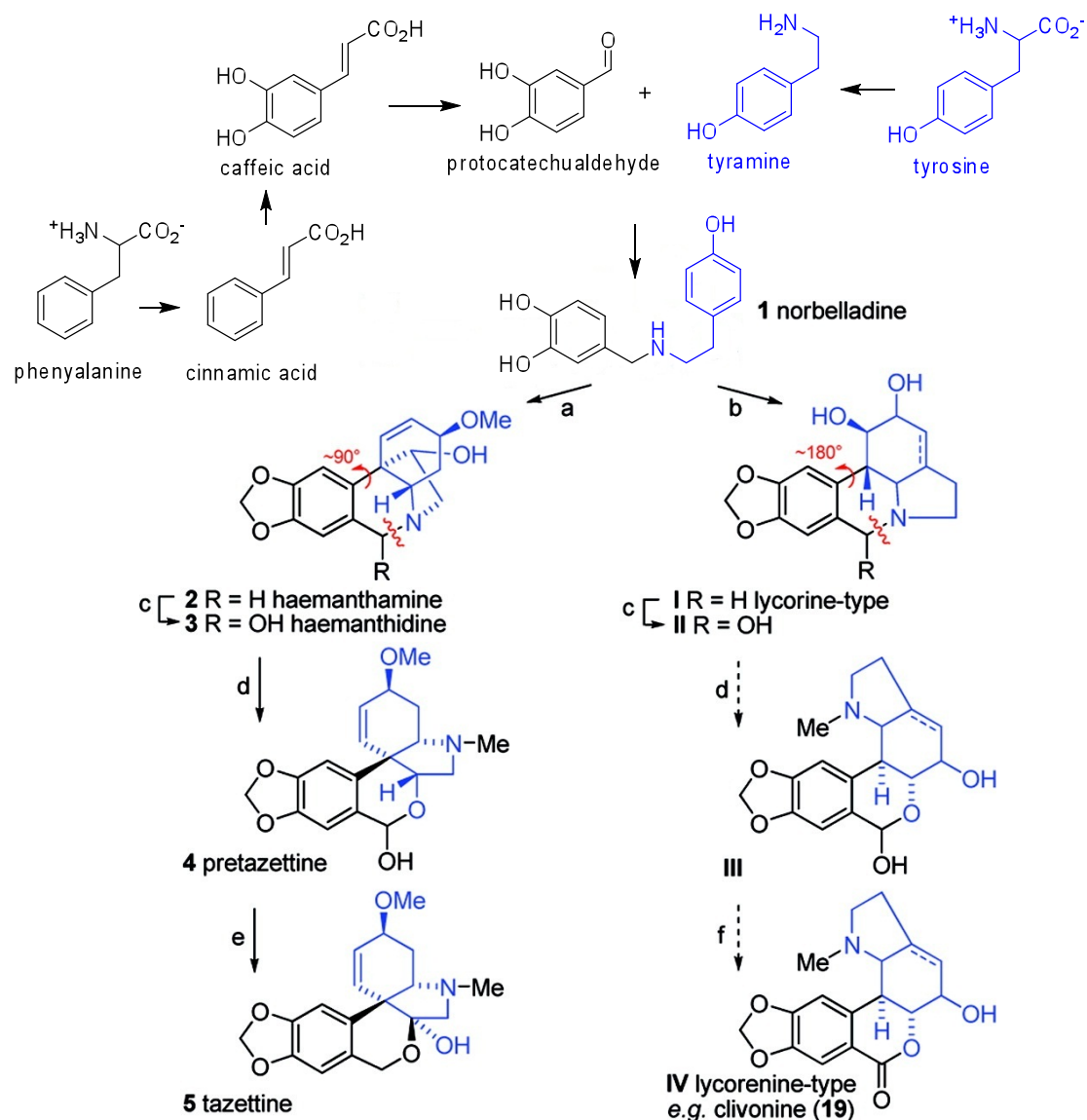
Bentley, K. W. *Kurtze Mitteilungen – Brief Reports* **1956**, 251.

Barton, D. H. R., Cohen, T., *Festschrift Arthur Stoll* **1957**, 117.

Barton, D. H. R. *et al. J. Chem. Soc.* **1965**, 2423.

# Biosynthesis of Tazettine and Lycorenine-Type Alkaloids

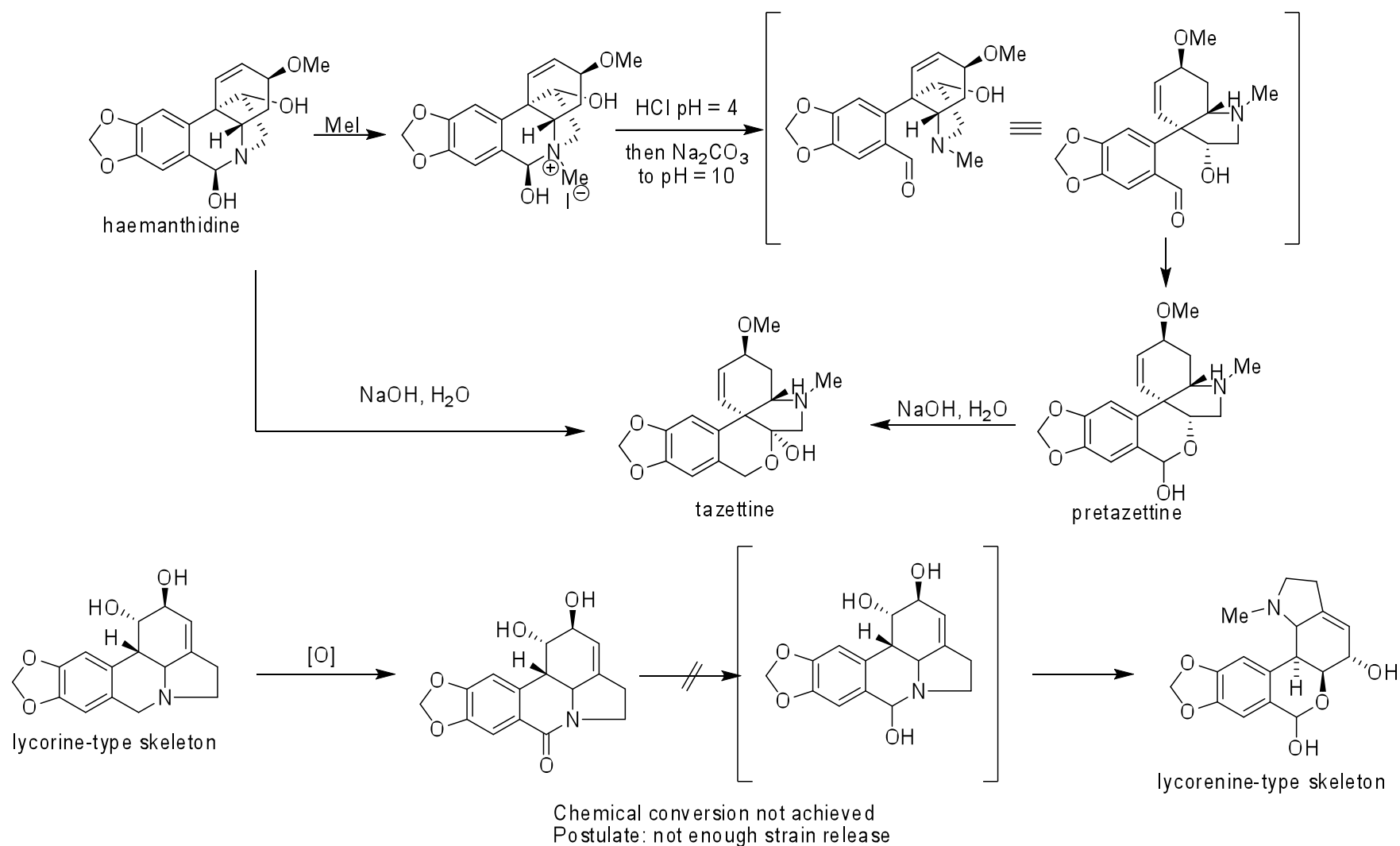
- Norbelladine is biosynthesized from tyrosine and phenylalanine
- Further transformations of norbelladine first proposed by Barton in 1957 – tazettine is formed by intermolecular phenolic coupling
- Revised in 1960 – “ring switching” proposed
- Confirmed by Wildman by tritium feeding experiments
- Biomimetic protocol for the synthesis of pretazettine known since 1969
- No biomimetic protocol for the conversion of lycorine to lycorenine-type skeleton until now



Spivey *et al.* *J. Am. Chem. Soc.* ASAP

Herbert, R. B. *The Biosynthesis of Secondary Metabolites*, 2<sup>nd</sup> ed.; Springer: Berlin 1989.

# Wildman's Biomimetic Conversion of Haemanthidine to Tazettine and Pretazettine

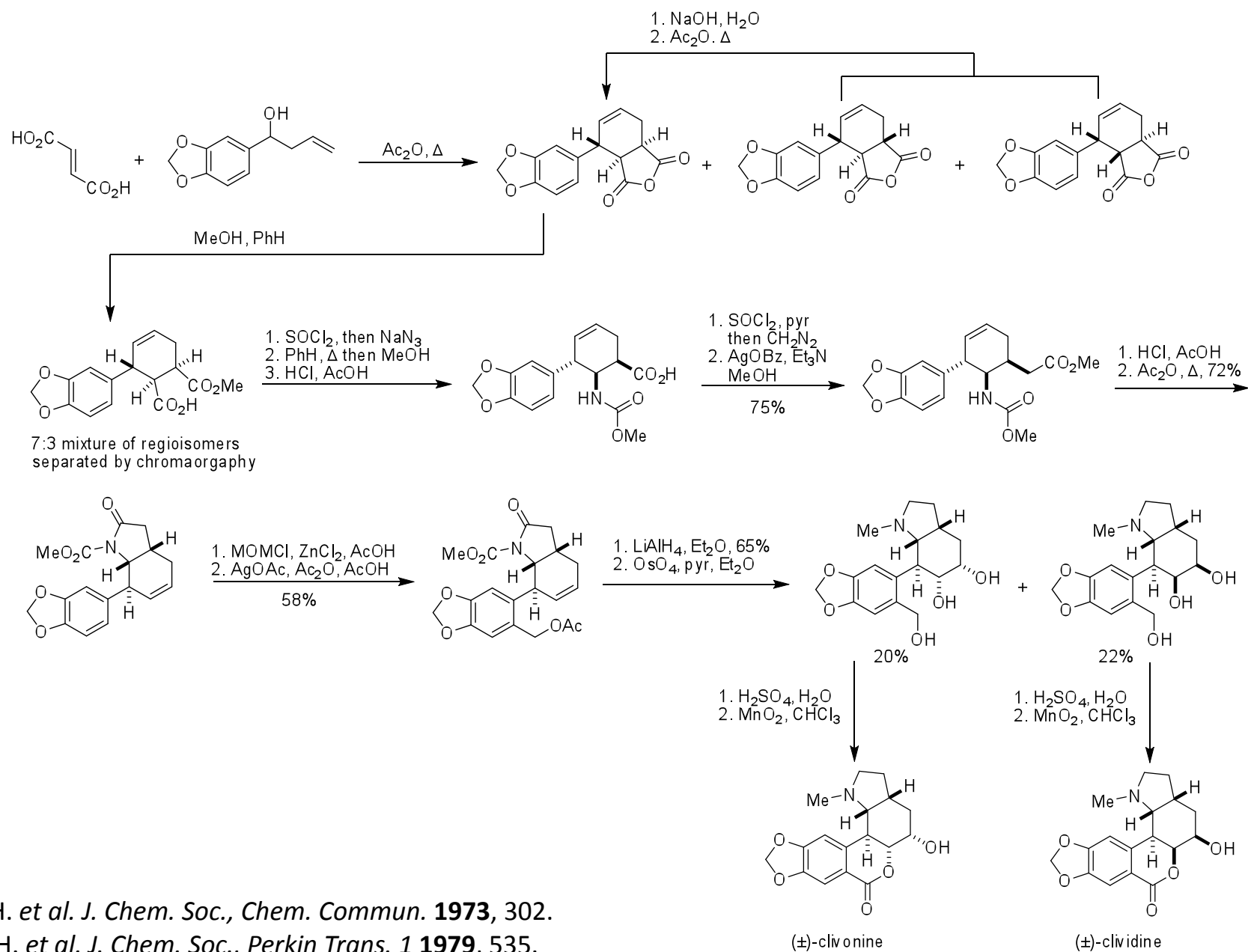


Wildman, W. C.; Bailey, D. T. *J. Am. Chem. Soc.* **1969**, *91*, 150.

Harken, R. D.; Christensen, C. P.; Wildman, W. C. *J. Org. Chem.* **1976**, *41*, 2450.



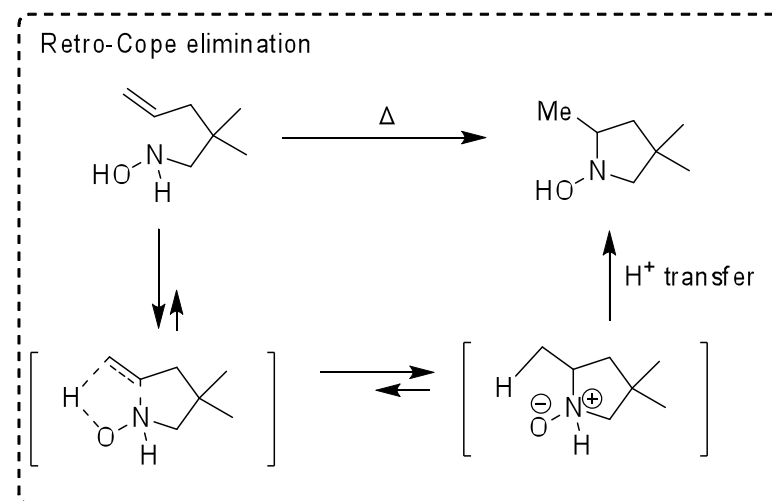
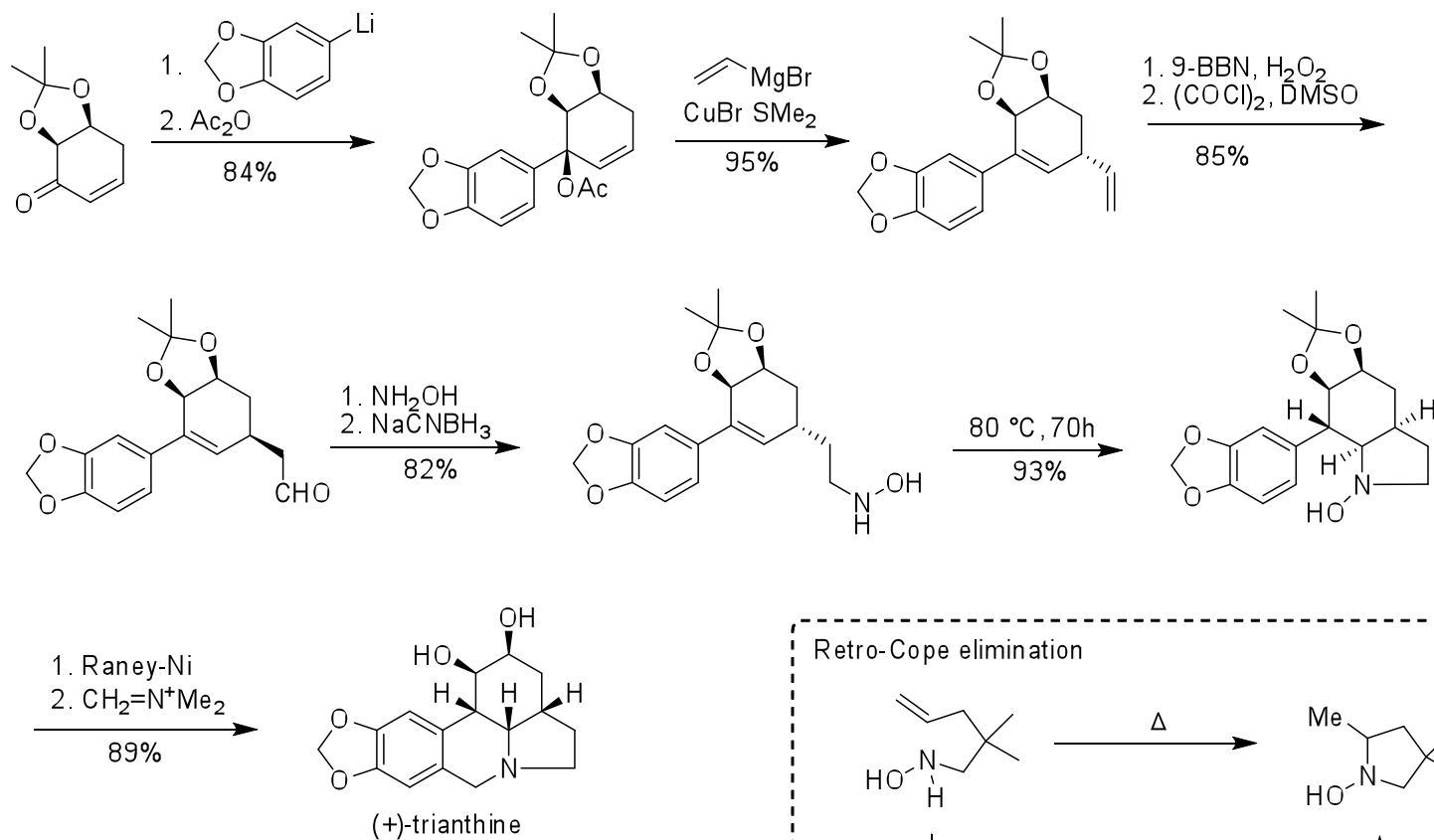
# Irie's Synthesis of Clivonine



Irie, H. *et al.* *J. Chem. Soc., Chem. Commun.* **1973**, 302.

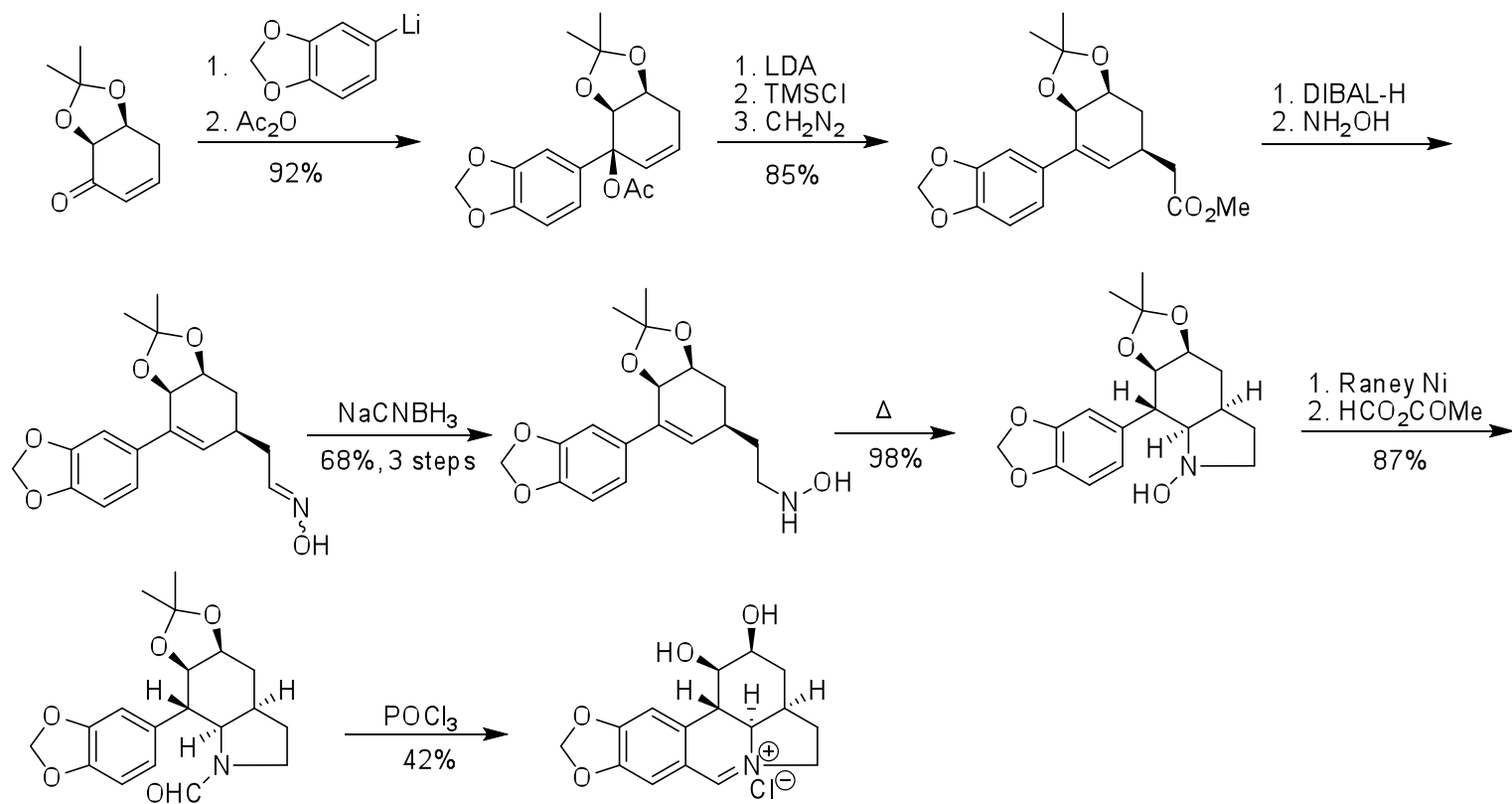
Irie, H. *et al.* *J. Chem. Soc., Perkin Trans. 1* **1979**, 535.

# Oppolzer's Synthesis of (+)-Trianthine



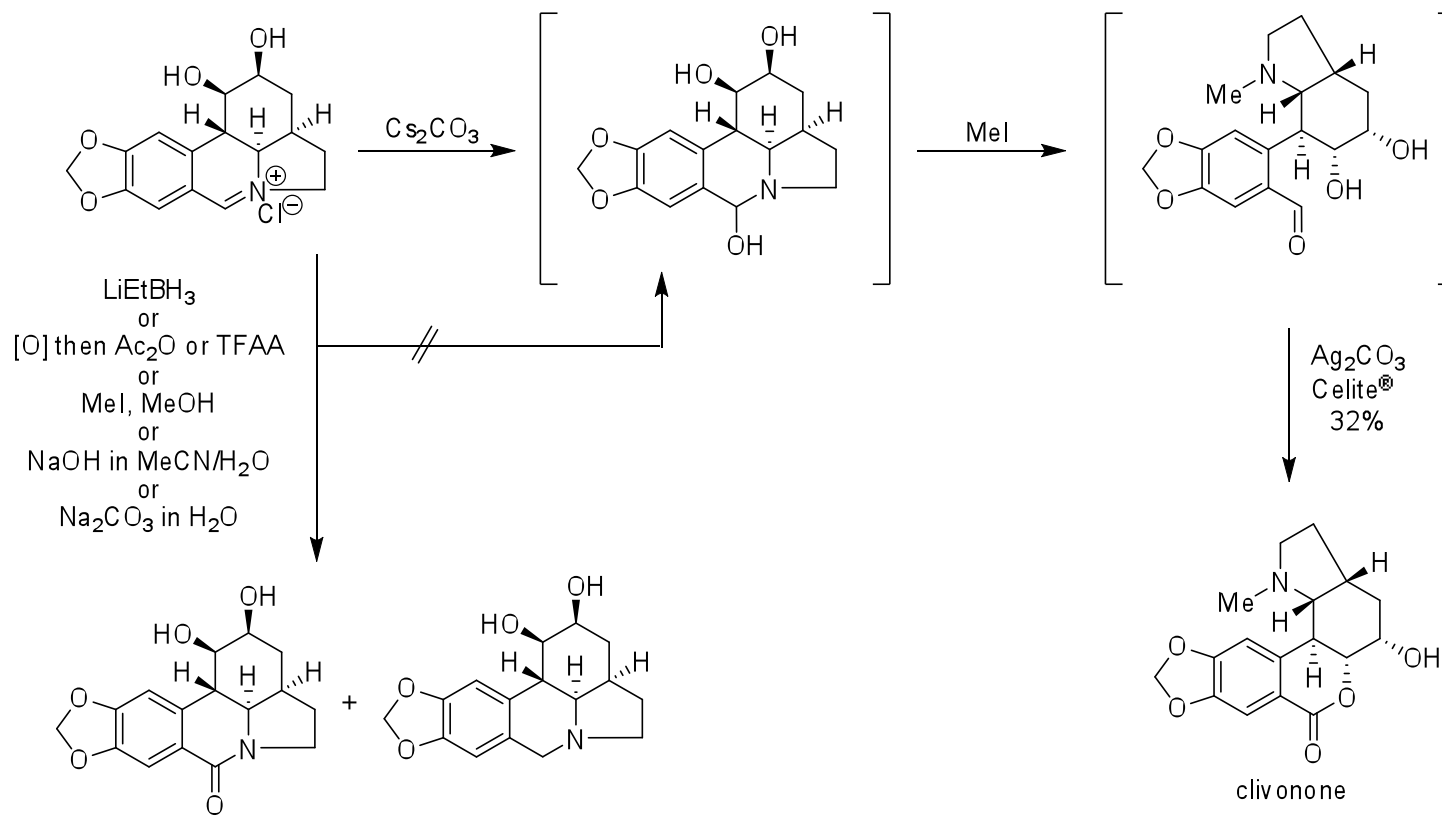
Oppolzer, W.; Spivey A. C.; Bochet, C.B. *J. Am. Chem. Soc.* **1994**, *116*, 3139.

# Title Paper



Spivey *et al.* *J. Am. Chem. Soc.* ASAP

# Title Paper



Spivey *et al.* *J. Am. Chem. Soc.* ASAP

# Conclusions

- Total synthesis of ( $\pm$ )-clivonine was achieved in 12 steps (6.1% overall yield)
- Biomimetic transformation of lycorine-type intermediate to lycorenine-type product corroborated Barton's 50 years old hypothesis
- Synthesis of other members of this type of *Amaryllidaceae* alkaloids is currently being explored
- Sir Derek H. C. Barton on alkaloid biosynthesis:

*"...the last paper on this subject was in 1974. One day this theme will be developed elsewhere. It was, however, very satisfying to see how much elegant work came out of my original disbelief in the long-accepted formula of Pumerer's ketone."*

Barton, D. H. R. *Some Recollections of Gap Jumping*, American Chemical Society: Washington 1991.