Chemistry 206

Advanced Organic Chemistry

Handout–36A

Intramolecular Enone-Olefin Photocycloadditions Directed Toward Natural Product Synthesis

Travis Dunn

Evans Group Seminar, March 31, 2000

DAE Group Friday Afternoon Seminar

March 31, 2000

D. A. Evans

Monday
September 27, 1999

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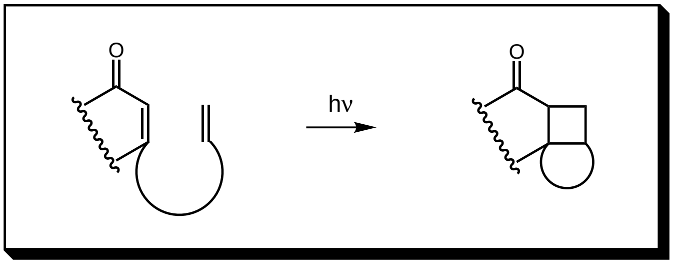


Lead References:

- Intramolecular Enone-Olefin Photocycloaddition
  Crimmins, M.T. *Chem. Rev.* **1988**, *88*, 1453-1473.
- Cycloaddition/Fragmentation Strategies in Synthesis
  Winkler, J.D., *et al. Chem. Rev.* **1995**, *95*, 2003-2020.
- Mechanism of Enone-Olefin Photocycloaddition
  Schuster, D.I., *et al. Chem. Rev.* **1993**, *93*, 3-22.

Introduction and Scope

I) Mechanistic considerations of the enone-olefin photocycloaddition

II) Selected synthetic examples:

A) The Oppolzer syntheses

B) The Pattenden syntheses

C) The Pirrung syntheses

D) One hit wonders

E) The Crimmins syntheses

F) The Winkler syntheses

The following will not be covered in this seminar:

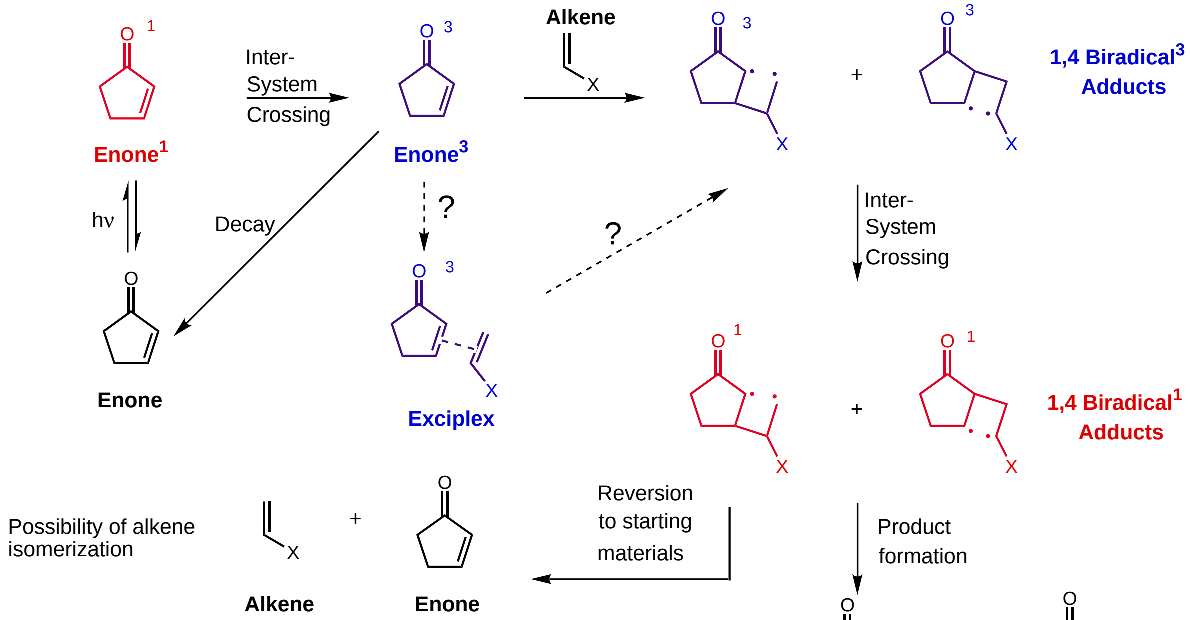
I) Non-target motivated studies of the intramolecular photocycloaddition

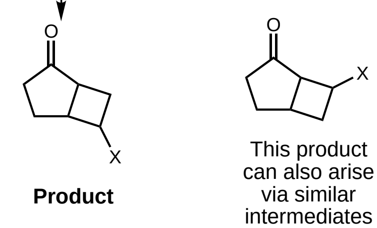
II) Intramolecular Paterno-Büchi reactions

III) Intramolecular ketene cycloadditions

IV) Other intramolecular photocycloadditions (e.g. arene-olefin meta cycloadditions)

Mechanistic Considerations of the Enone-Olefin Photocycloaddition



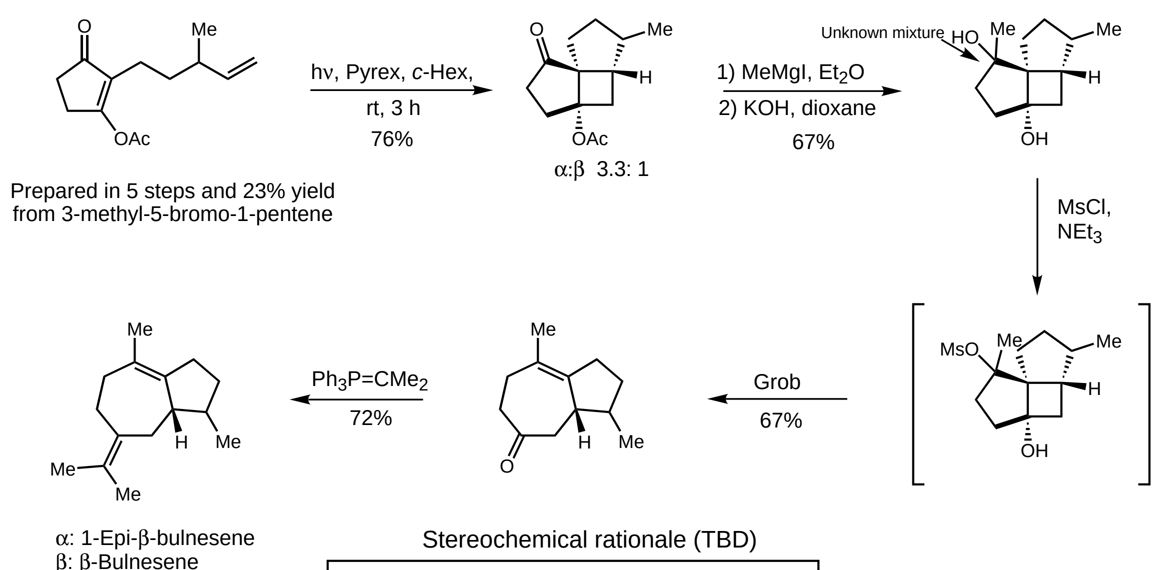


A note on light sources:

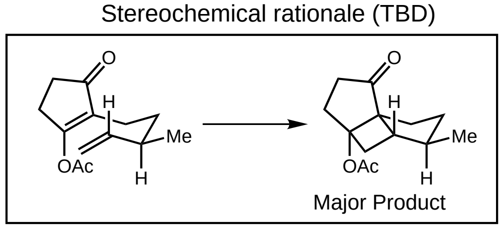
The source of light is usually a mercury lamp. A filter is usually used to remove light below a certain wavelength. The two most common are Pyrex glass, which allows light with $\lambda > 290$ nm to pass, and "uranium" glass, which allows light with $\lambda > 350$ nm wavelength to pass.

Schuster, D.I., *et al. Chem. Rev.* **1993**, *93*, 3.

(±) β-Bulnesene and Epi-β-bulnesene

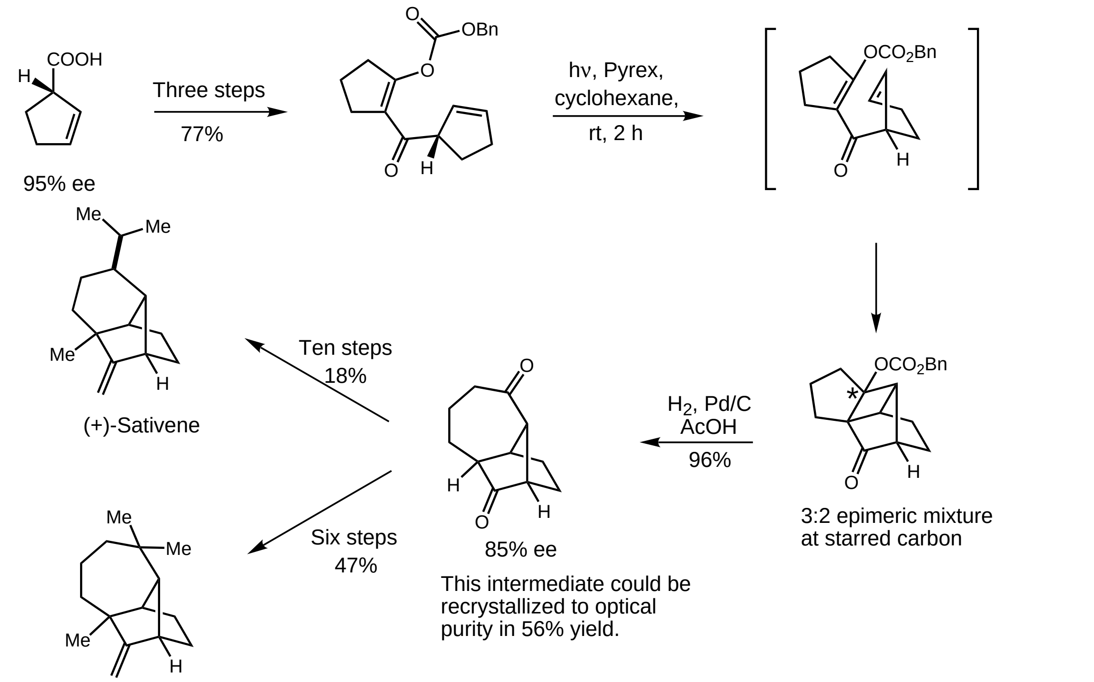


Stereochemical rationale (TBD)



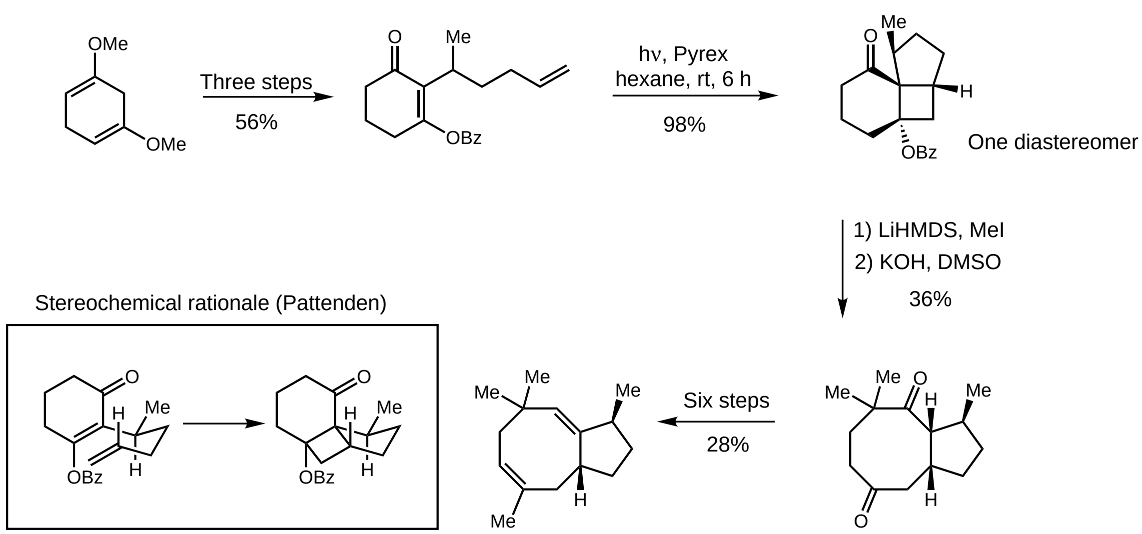
Oppolzer, W., *et al. Helv. Chim. Acta.*, **1980**, *63*, 1198.

(+)-Longifolene and (+)-Sativene



Oppolzer, W., *et al. J. Am. Chem. Soc.* **1978**, *100,* 2583.
Oppolzer, W., *et al. Helv. Chim. Acta.* **1984**, *67*, 1154.

(±)-Epiprecapnelladiene

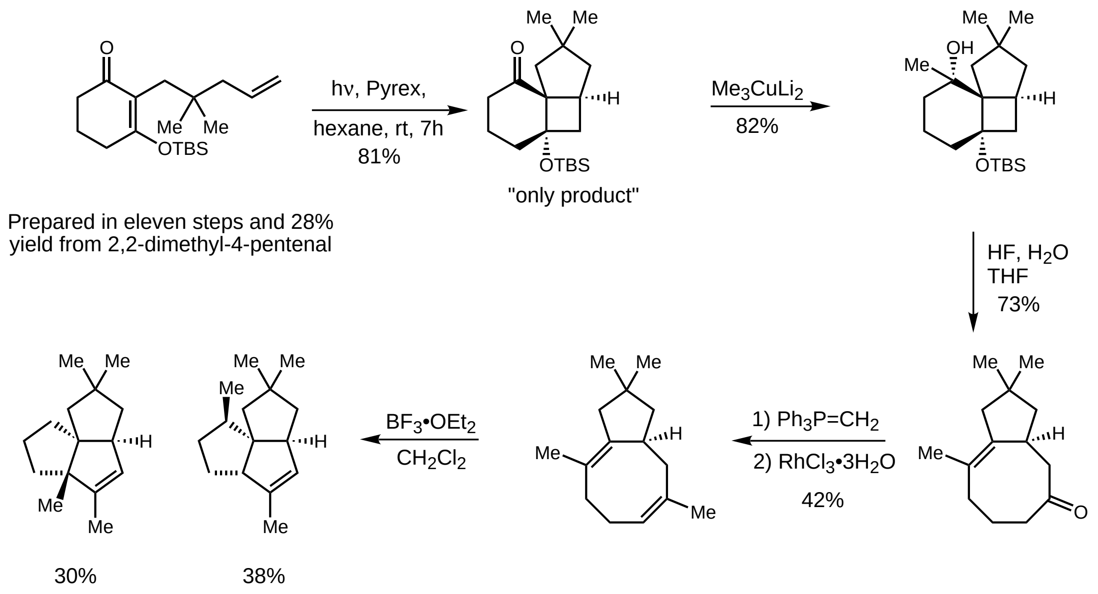


Irradiation of the enol acetate resulted in a 92:8 mixture, presumably due to the smaller size of the acetate versus benzoate.

Epiprecapnelladiene

Pattenden, G., *et al. J. Chem. Soc., Chem. Comm.* **1980**, 1195.
Pattenden, G., *et al. J. Chem. Soc., Perkin Trans. I* **1983**, 1913.

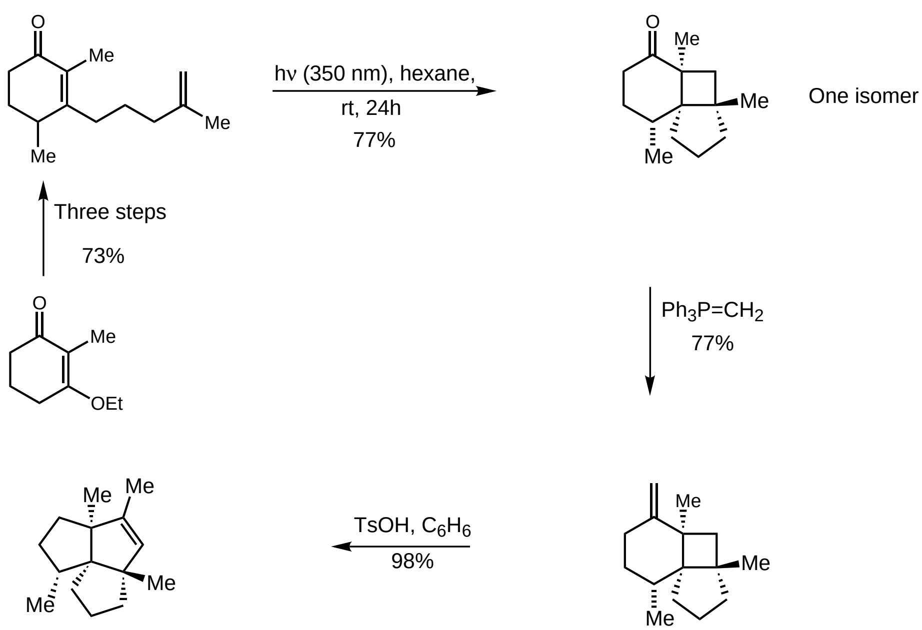
(±)-Pentalenene



(±) Pentalenene

Pattenden, G., *et al. Tetrahedron Lett.* **1984**, *25*, 3021.
Pattenden, G., *et al.Tetrahedron* **1987**, *43*, 5637.

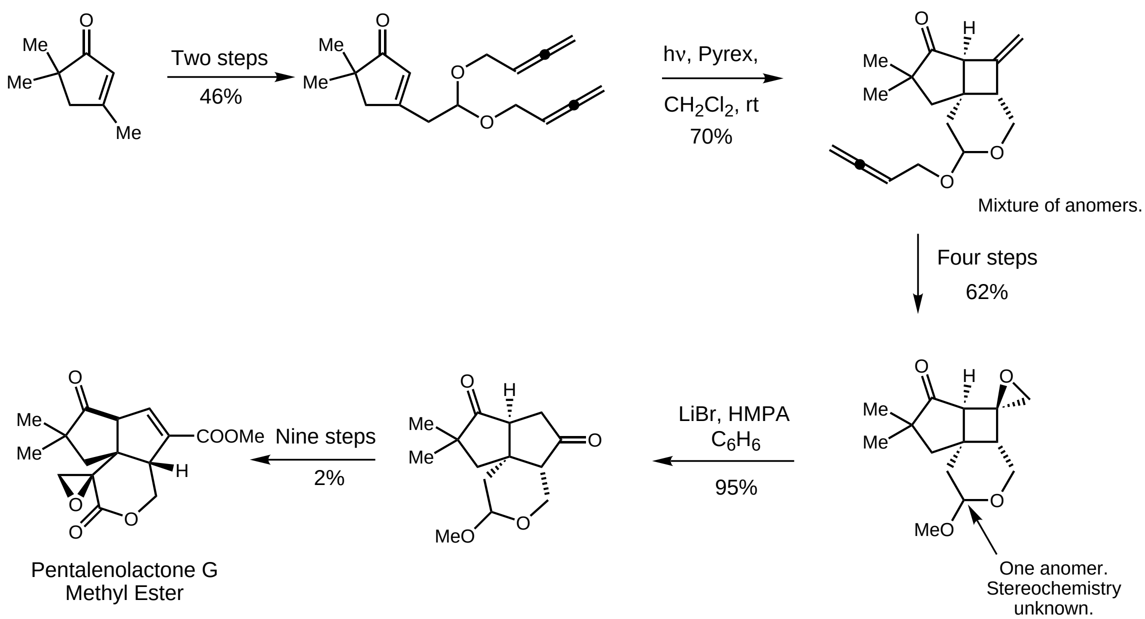
(±)-Isocomene



Isocomene

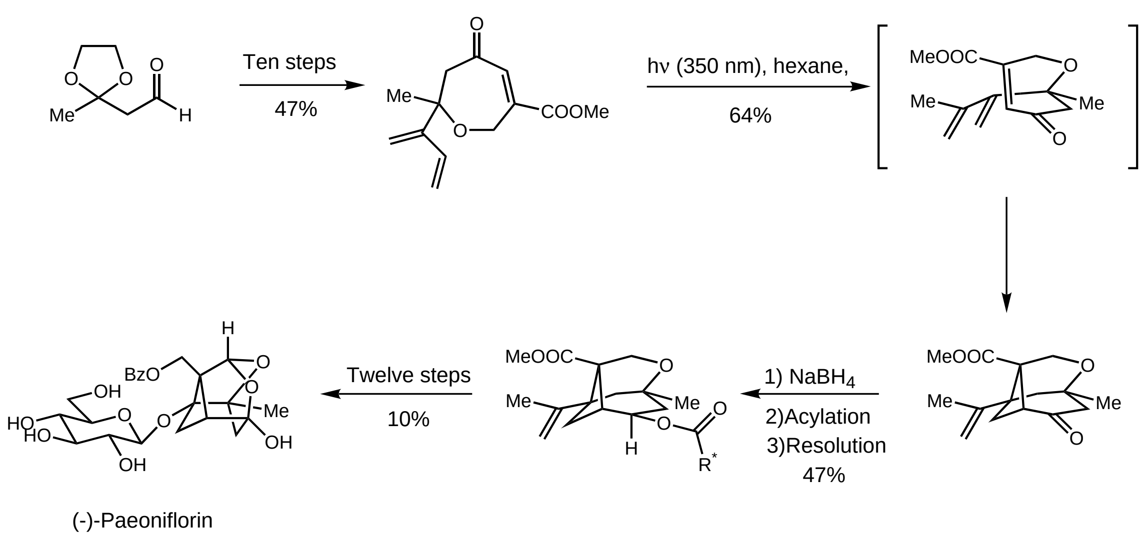
Pirrung, M.C. *J. Am. Chem. Soc.* **1979**, *101*, 7130.
Pirrung, M.C. *J. Am. Chem. Soc.* **1981**, *103*, 82.

(±)-Pentalenolactone G Methyl Ester



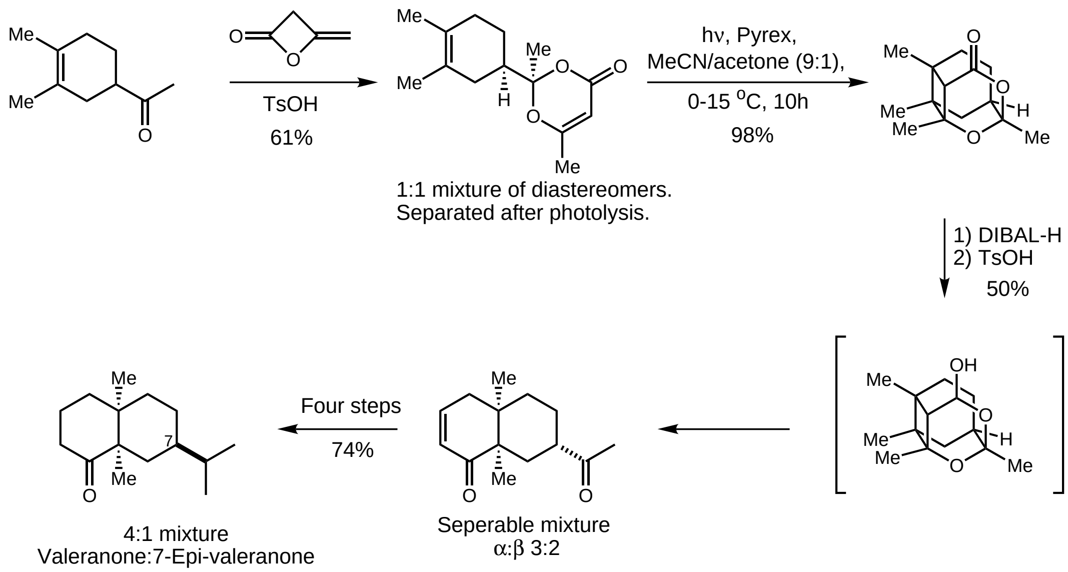
Pirrung, M.C., *et al.Tetrahedron Lett.* **1986**, *27*, 2703.
Pirrung, M.C., *et al. J. Org. Chem.* **1988**, *53*, 227.

(-)-Paeoniflorin



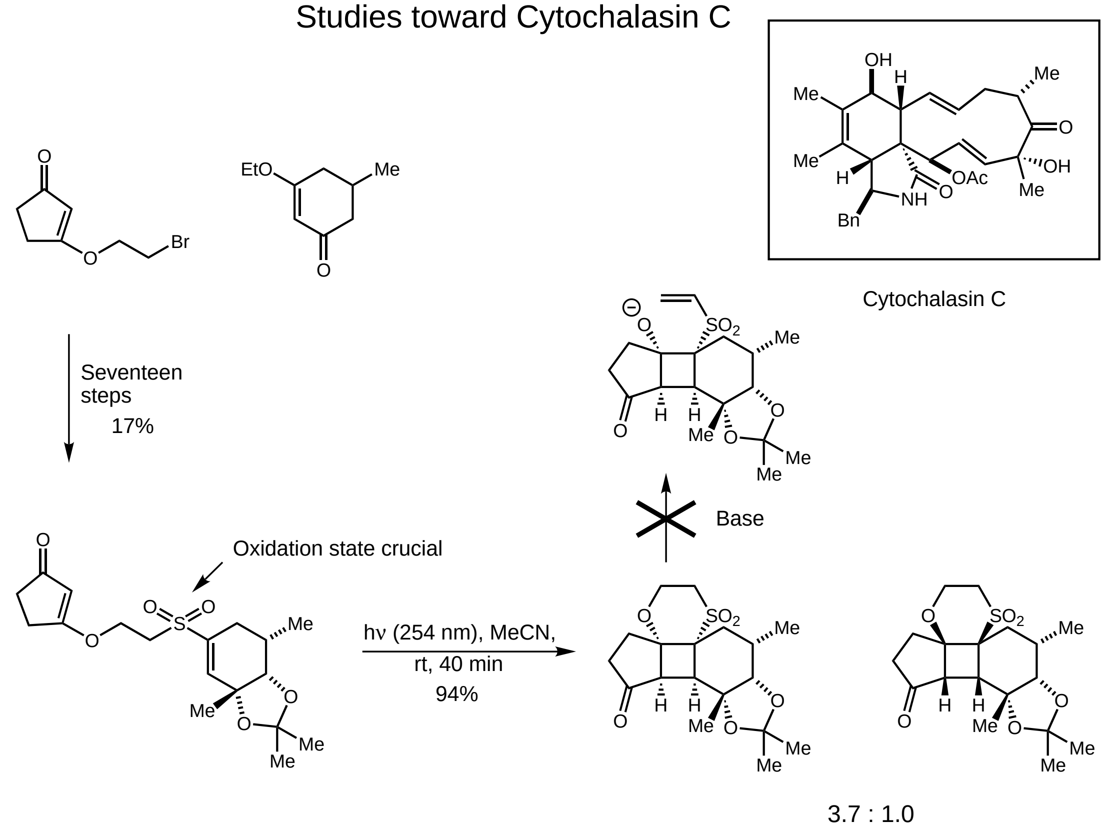
Hatakeyama, S., Takano, S., *et al. J. Am. Chem. Soc.* **1994**, *116*, 4081.

(±)-Valeranone



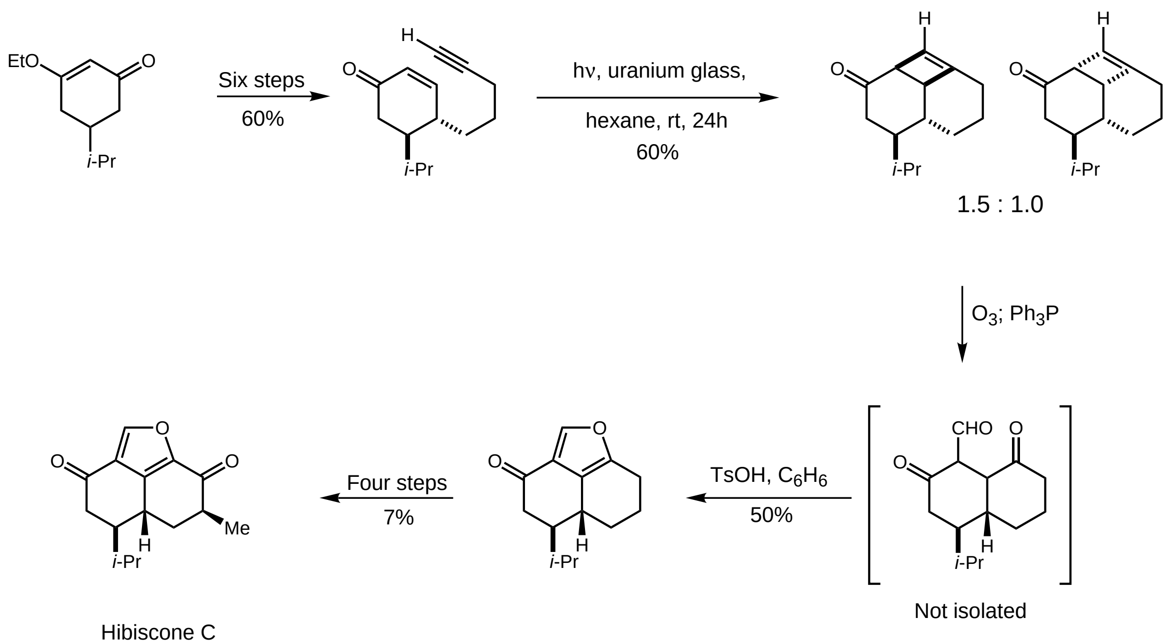
Takeshita, H. *et al*. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2699.

Studies toward Cytochalasin C



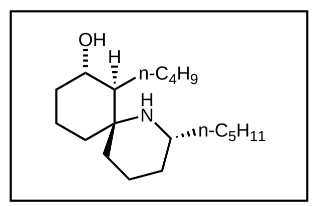
Fuchs, P.L., *et al. J. Org Chem.* **1982**, *47,* 3121.

(±)-Hibiscone C

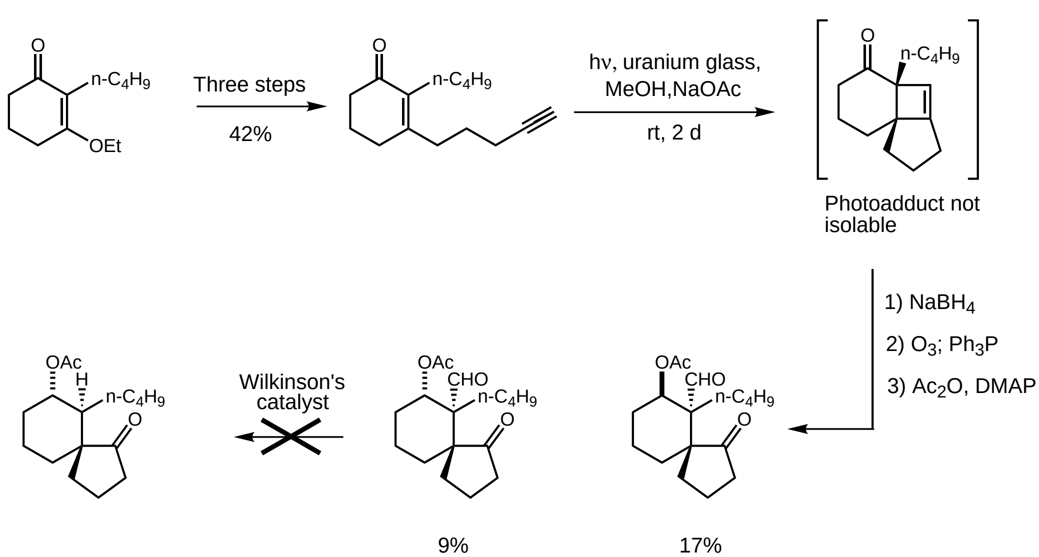


Smith, A.B., III, *et al. J. Am. Chem. Soc.* **1982**, *104,* 5568.
Smith, A.B., III, *et al. J. Am. Chem. Soc.* **1984**, *106,* 2115.

Studies toward Perhydrohistrionicotoxin

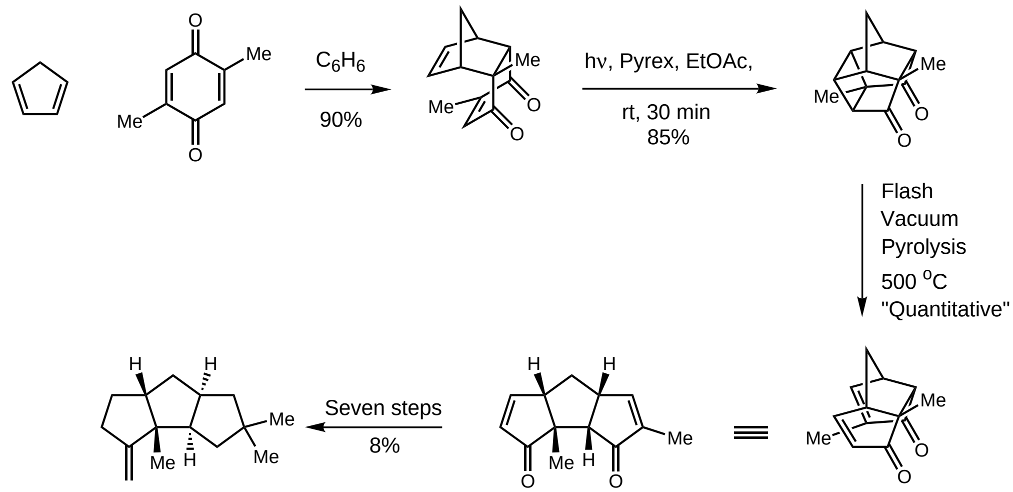


Perhydrohistrionicotoxin



Smith, A.B., III, *et al. J. Org. Chem.* **1984**, *49*, 832.

(±)-Hirsutene

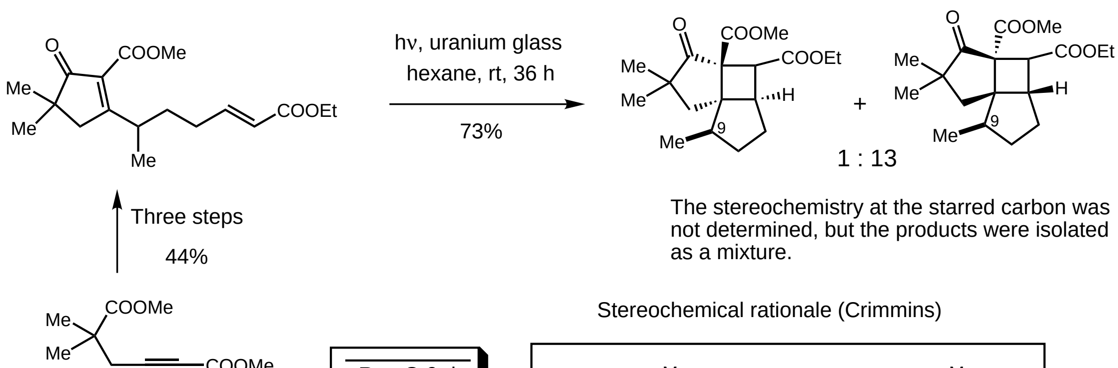


Hirsutene

Formal syntheses of capnellene and coriolin were reported using a similar photoaddition/fragmentation reaction.

Mehta, G., *et al. J. Am. Chem. Soc.* **1986**, *108*, 3443.
Mehta, G., *et al. J. Chem. Soc., Chem. Comm.* **1981**, 756.

(±)-Pentalenene, (±)-Pentalenic Acid and (±)-Deoxypentalenic Acid from a Common Precursor.

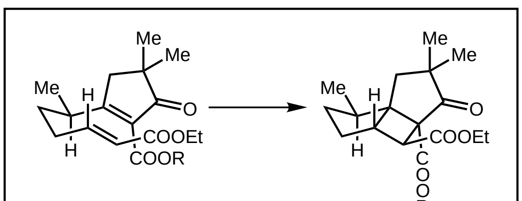


The stereochemistry at the starred carbon was not determined, but the products were isolated as a mixture.

Stereochemical rationale (Crimmins)

R	C-9 dr
Me	13:1
Et	17:1
i-Pr	>20:1

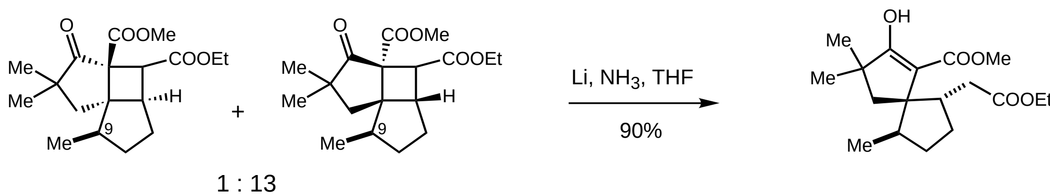
Varying the size of the indicated alkyl group influenced the stereoselectivity



Consistent with predominant stereochemistry at C-9

Crimmins, M.T., *et al. J. Org. Chem.* **1984**, *49,* 2076.
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1986**, *108,* 800.

(±)-Pentalenene, (±)-Pentalenic Acid and (±)-Deoxypentalenic Acid from a Common Precursor.



Reduction performed on mixture of photoadducts.
Diastereomers separated after reduction.

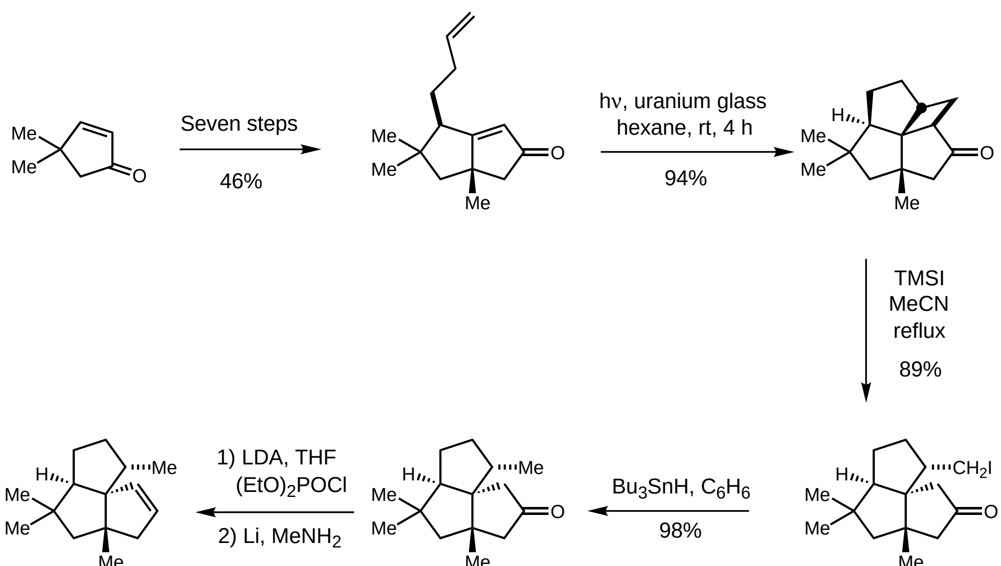
R=H, R'=Me, Pentalenene, nine steps, 27%

R=OH, R'=COOH, Pentalenic acid, eight steps, 42%

R=H, R'=COOH, Deoxypentalenic acid, eleven steps, 22%

Crimmins, M.T., *et al. J. Org. Chem.* **1984**, *49,* 2076.
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1986**, *108,* 800.

(±)-Silphinene

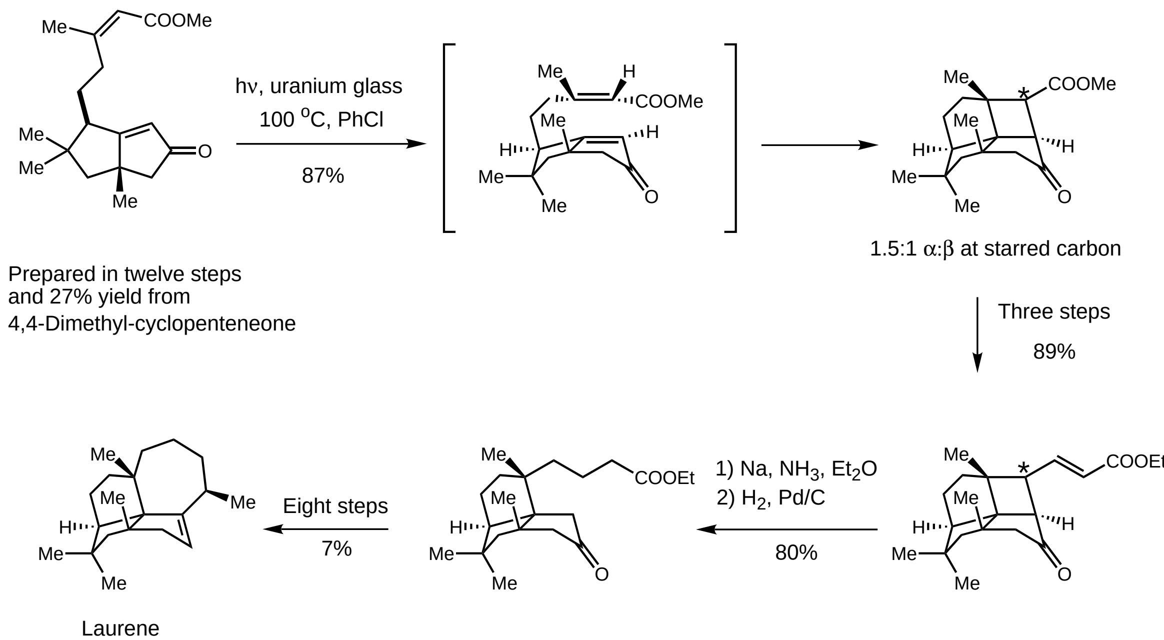


Silphinene

Plus a 14% yield of isosilphinene

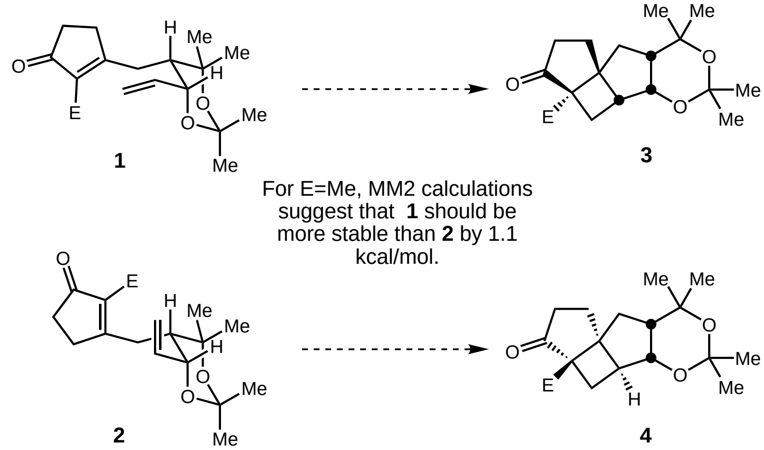
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1986**, *108*, 3435.
Crimmins, M.T., *et al. Tetrahedron Lett.* **1985**, *26*, 997.

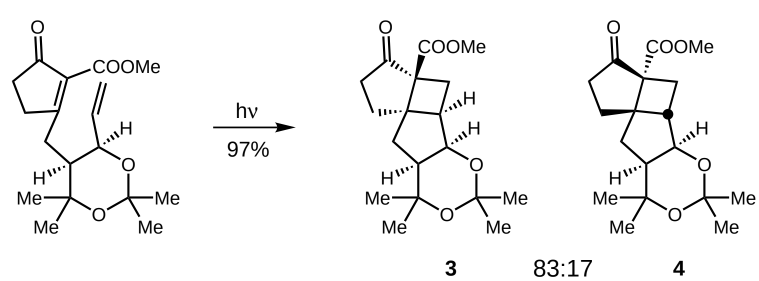
(±)-Laurenene



Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1987**, *109*, 6199.
Crimmins, M.T., *et al. Tetrahedron Lett.* **1985**, *26*, 997.

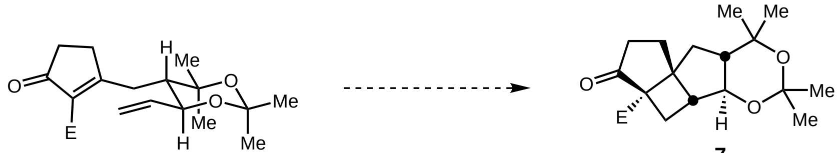
(±)-Lubiminol





Crimmins, M.T., *et al. Tetrahedron Lett.* **1996**, *37,* 8703.
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1998**, *120,* 1747.

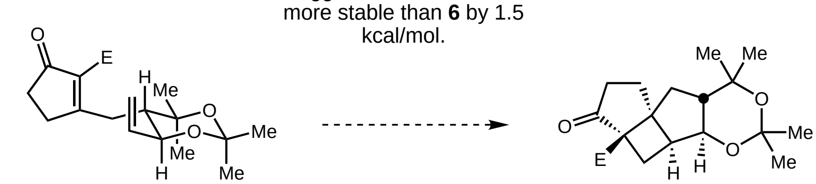
(±)-Lubiminol



5

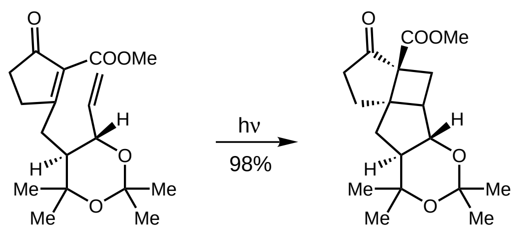
7

For E=Me, MM2 calculations suggest that **5** should be more stable than **6** by 1.5 kcal/mol.



6

8

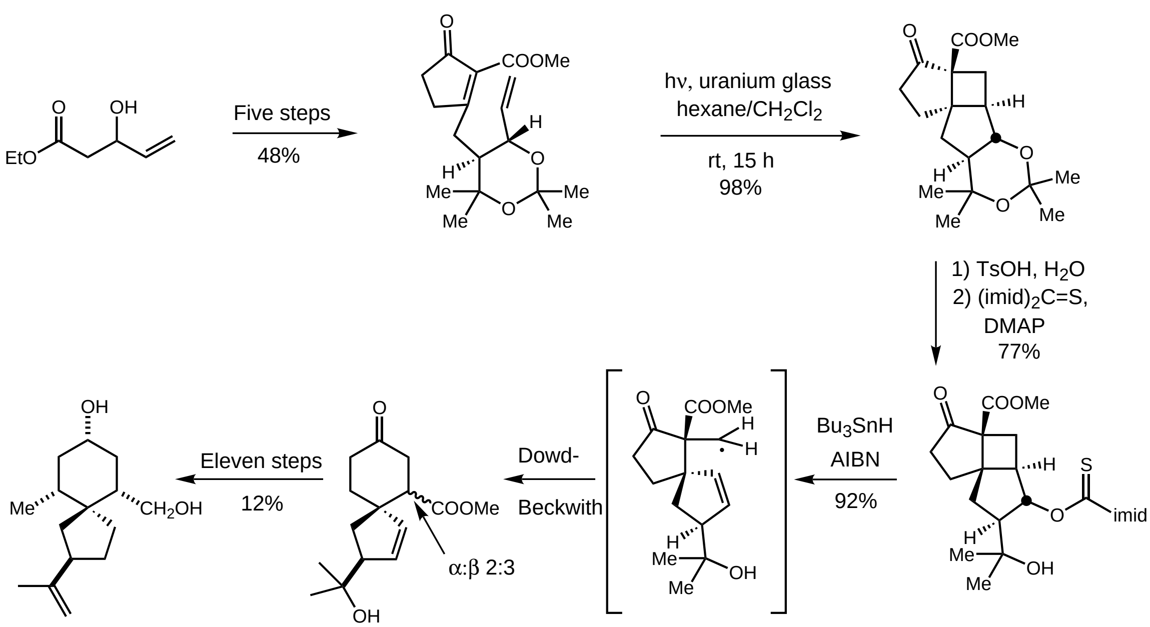


7

Only isolated product

Crimmins, M.T., *et al. Tetrahedron Lett.* **1996**, *37,* 8703.
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1998**, *120,* 1747.

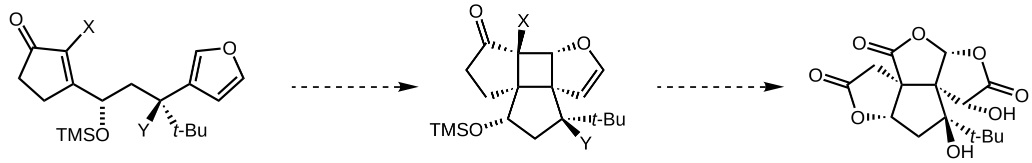
(±)-Lubiminol



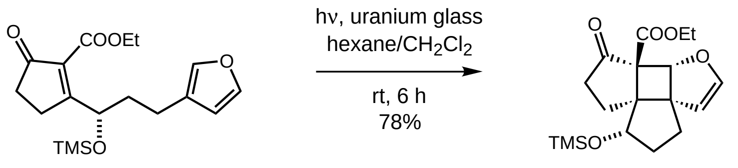
Lubiminol

Crimmins, M.T., *et al. Tetrahedron Lett.* **1996**, *37,* 8703.
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1998**, *120,* 1747.

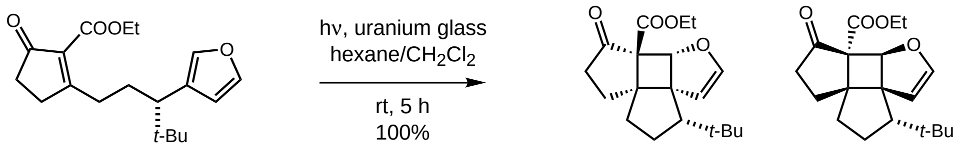
(±)-Bilobalide



Bilobalide



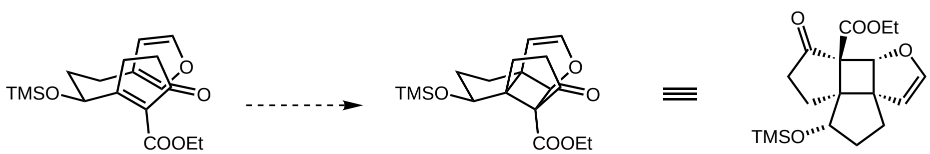
one diastereomer



1.5 1.0

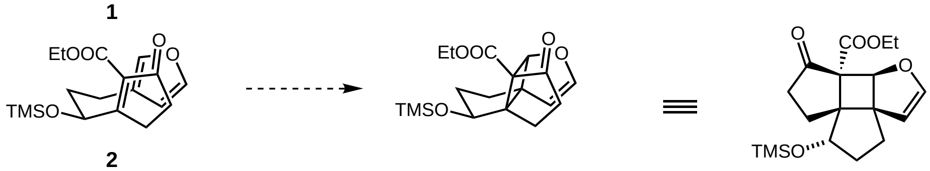
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1992**, *114*, 5445.
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1993**, *115*, 3146.

(±)-Bilobalide



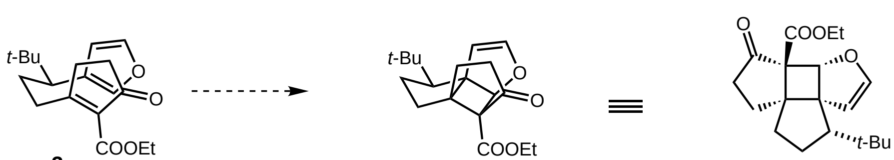
1

Desired



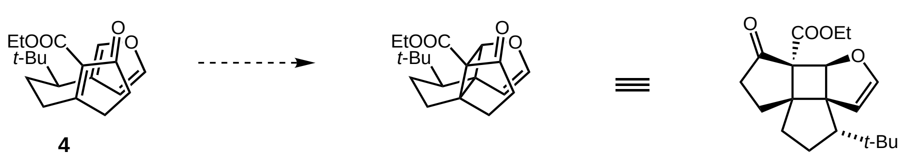
2

Undesired



3

Desired



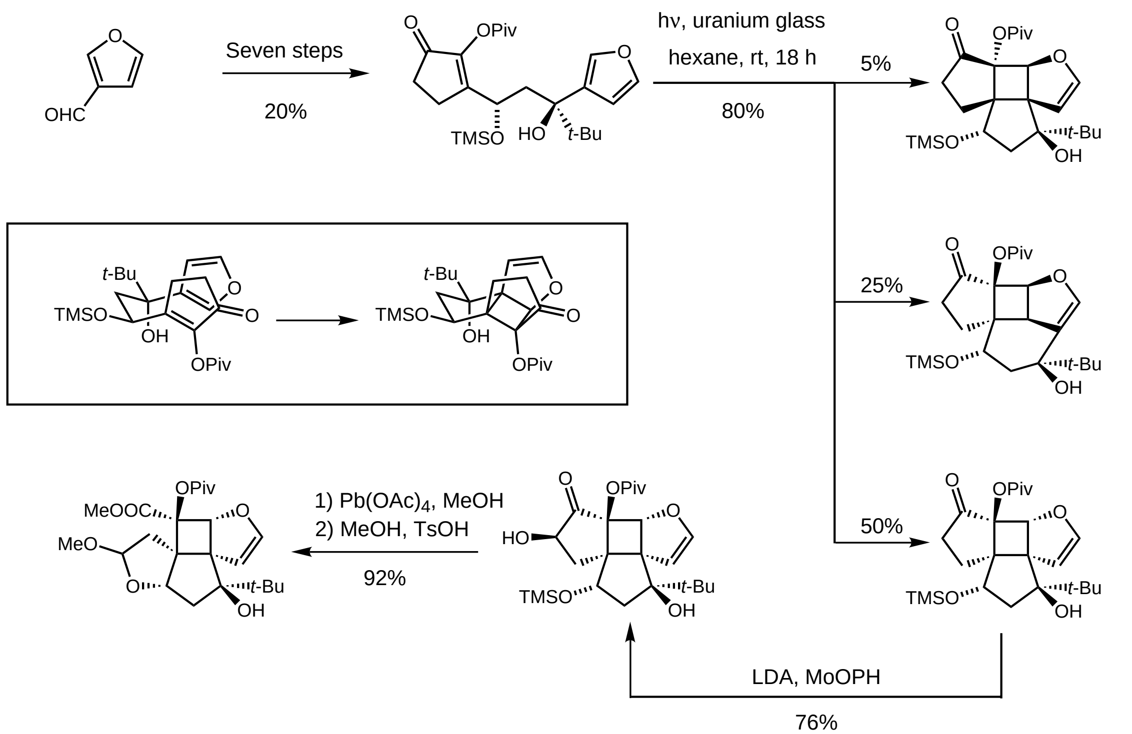
4

Undesired

MM2 calculations suggested that **1** was more favored than **2** by approximately 1.6 kcal/mol, while there was almost no difference in energy between **3** and **4** (0.2 kcal/mol).

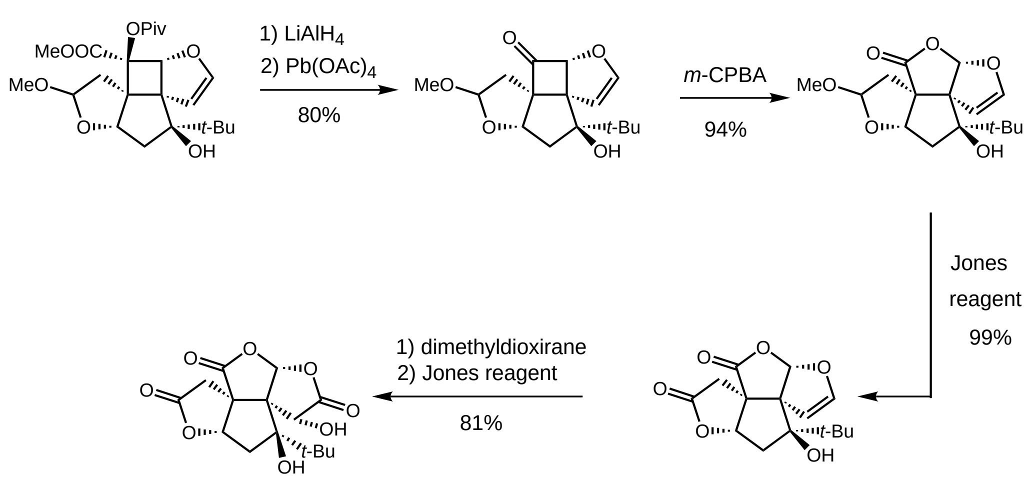
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1992**, *114*, 5445.
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1993**, *115*, 3146.

(±)-Bilobalide



Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1992**, *114*, 5445.
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1993**, *115*, 3146.

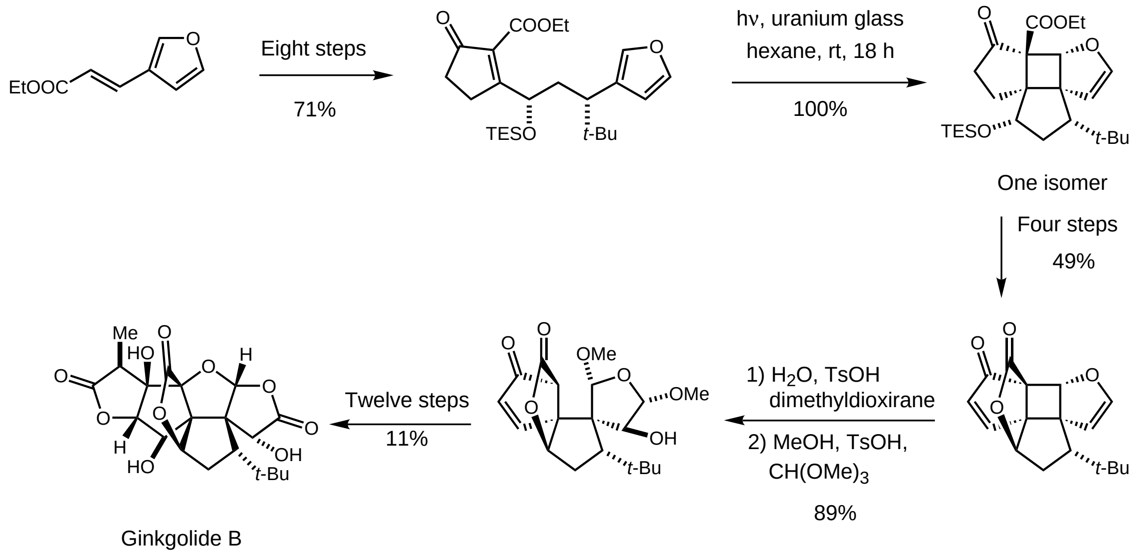
(±)-Bilobalide



Bilobalide

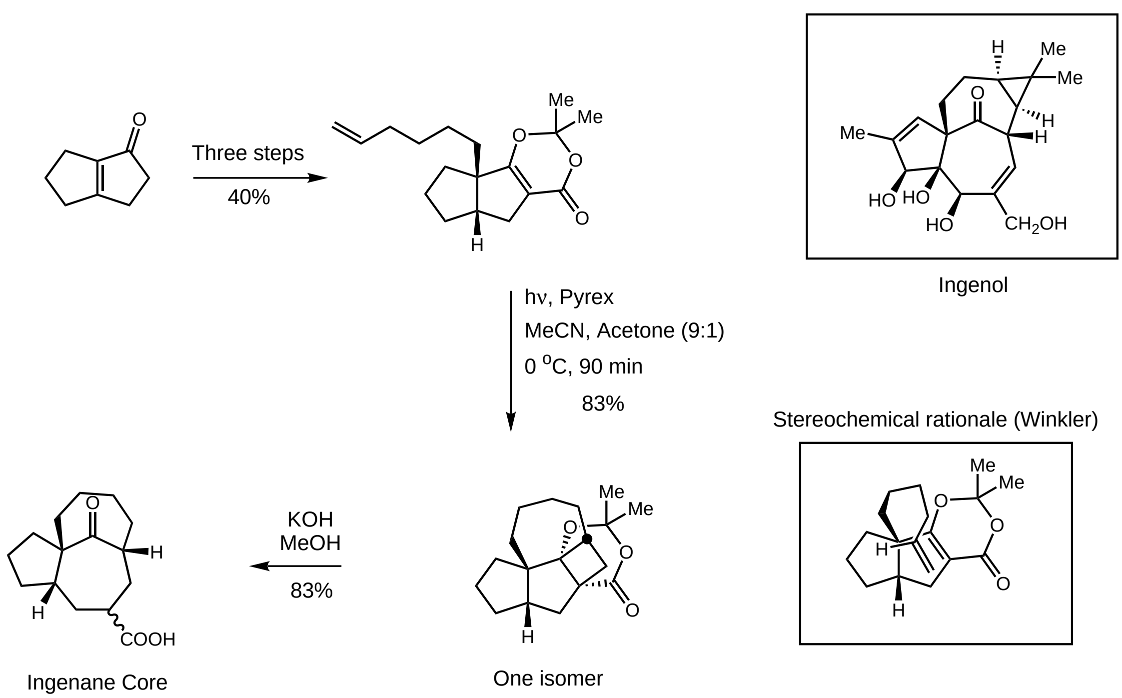
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1992**, *114*, 5445.
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1993**, *115*, 3146.

(±)-Ginkgolide B



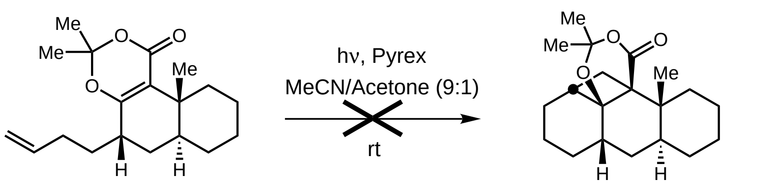
Crimmins, M.T. *et al. J. Am. Chem. Soc.* **1999**, *121*, 10249.
Crimmins, M.T. *et al. Tetrahedron Lett.* **1989**, *30*, 5997.

Synthesis of the Core of the Ingenane Diterpenes

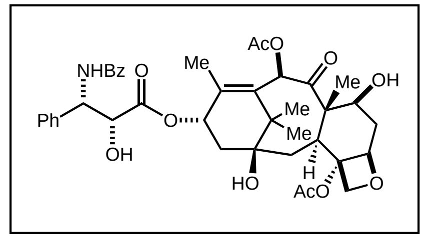


Winkler, J.D., *et al. J. Am. Chem. Soc.* **1987**, *109*, 2850.

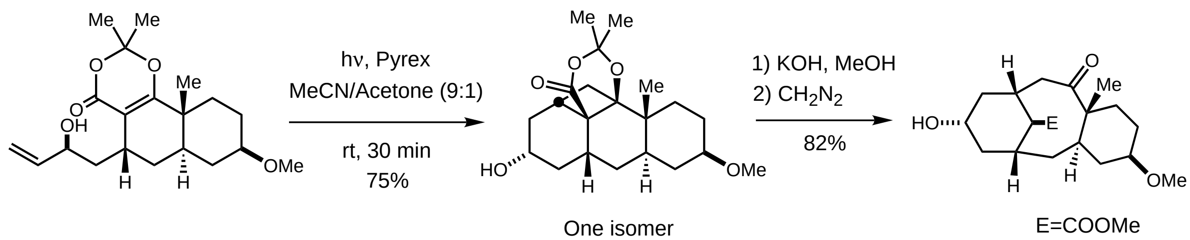
Synthetic Studies Toward the Taxane Core



None of the desired photoadduct could be isolated.

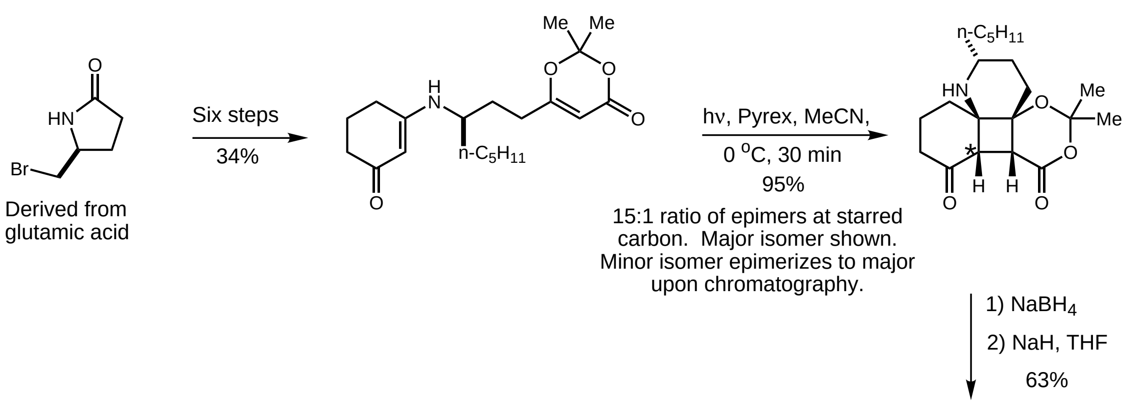


Taxol

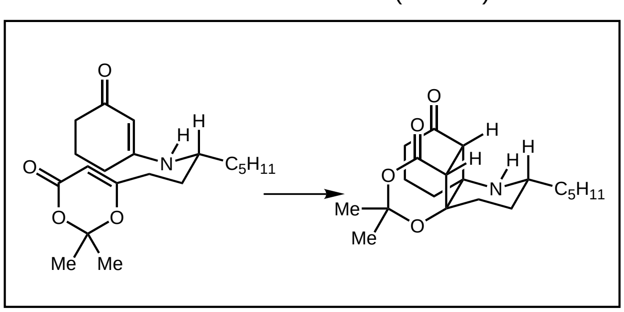


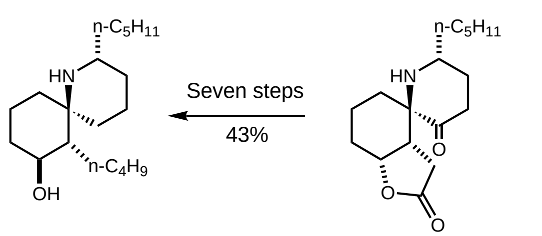
Winkler, J.D., *et al.Tetrahedron Lett.* **1986**, *27*, 5959.
Winkler, J.D., *et al. J. Org. Chem.* **1989**, *54*, 4491.
Winkler, J.D., *et al.Tetrahedron* **1992**, *48*, 7049.

(-)-Perhydrohistrionicotoxin



Stereochemical rationale (Winkler)

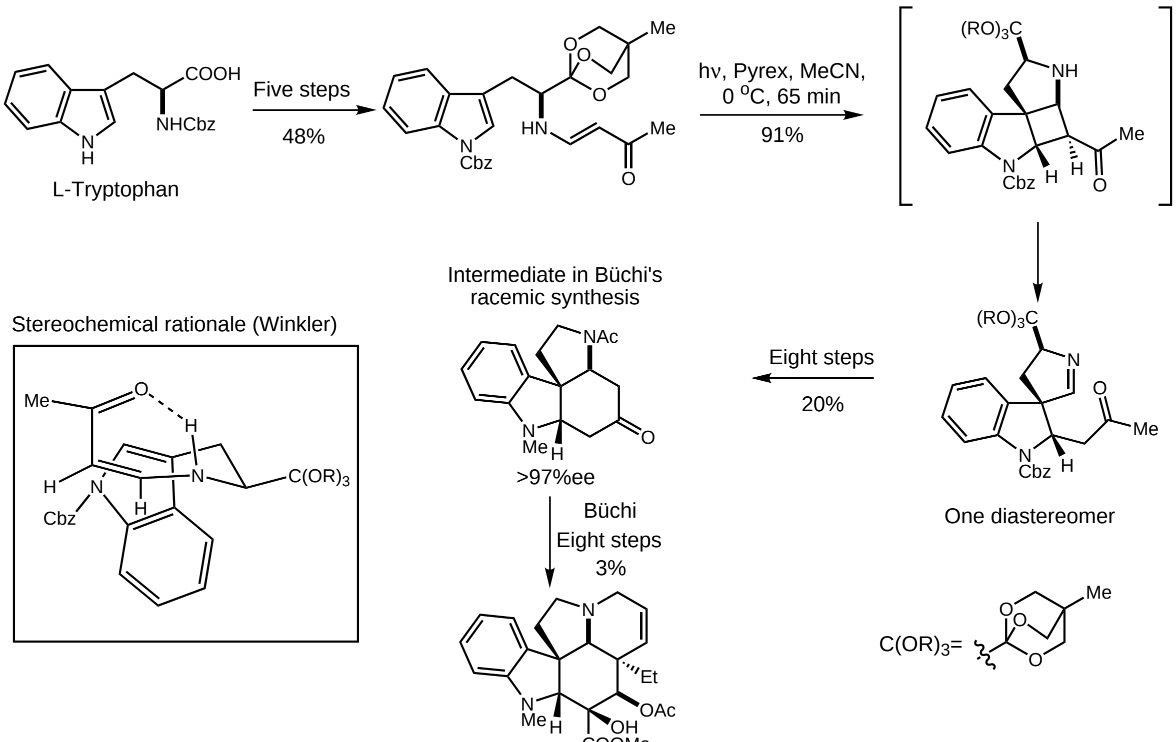




Perhydrohistrionicotoxin

Winkler, J.D., *et al. Tetrahedron Lett.* **1986**, *27*, 5177.
Winkler, J.D., *et al. J. Am .Chem. Soc.* **1989**, *111*, 4852.

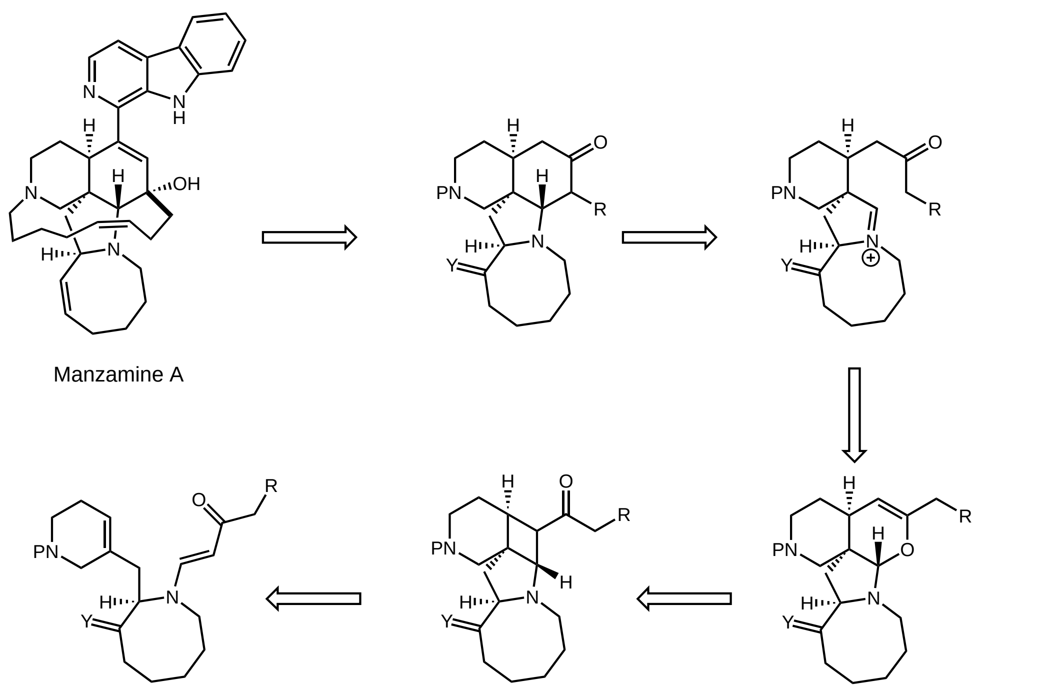
Formal Synthesis of Vindorosine



Vindorosine

Winkler, J. D., *et al*. *J. Am. Chem. Soc.* **1990** *112*, 8971.
Büchi, G., *et al. J. Am. Chem. Soc.* **1971**, *93*, 3299.

(±)-Manzamine A

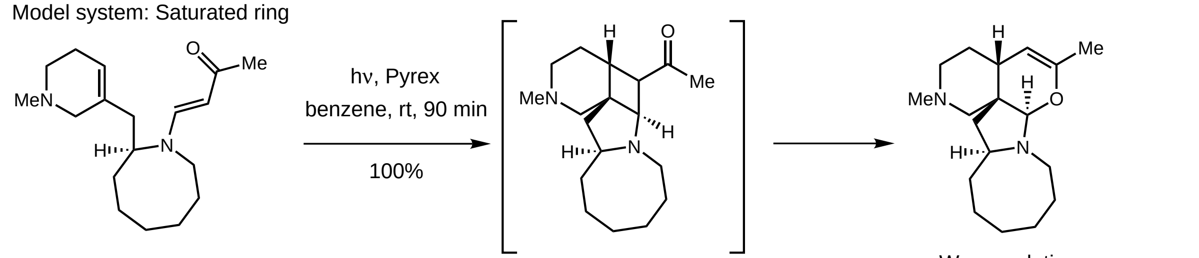


For an analysis of the total synthesis of Manzamine A, see the Evans Group Seminar "Approaches the the Total Synthesis of the Manzamine Alkaloids," Hemaka Rajapakse, Jan. 21, 2000.

Winkler, J.D., *et al. Tetrahedron Lett.* **1993**, *34*, 6509.
Winkler, J.D., *et al. Isr. J. Chem.* **1997**, *37*, 47.
Winkler, J.D., *et al.Tetrahedron* **1998**, *54*, 7045.
Winkler, J.D., *et al. J. Am. Chem. Soc.* **1998**, *120*, 6425.

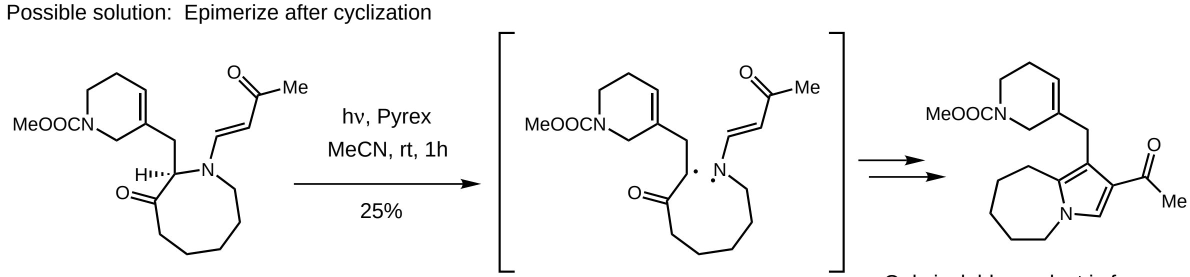
(±)-Manzamine A

Model system: Saturated ring

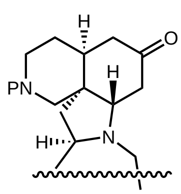


Wrong relative stereochemistry at three new centers.

Possible solution: Epimerize after cyclization



Only isolable product is from photochemical cleavage, rearrangement.

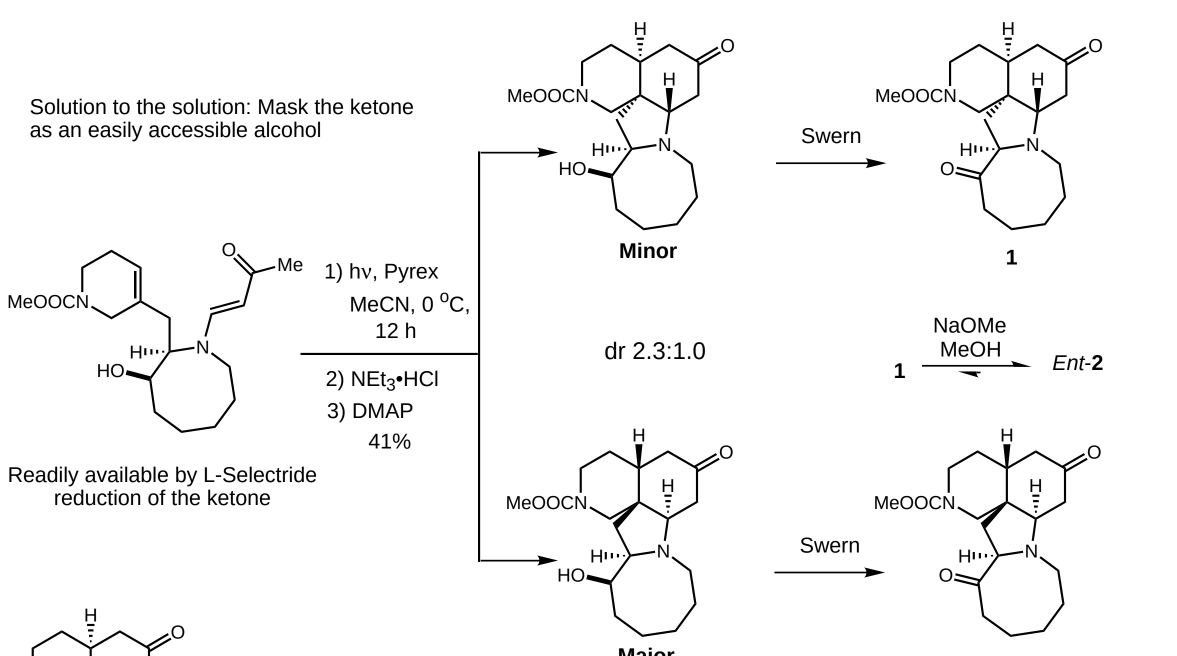


Manzamine Core

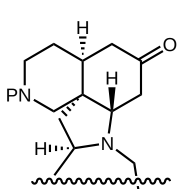
Winkler, J.D., *et al. Tetrahedron Lett.* **1993**, *34*, 6509.
Winkler, J.D., *et al. Isr. J. Chem.* **1997**, *37*, 47.
Winkler, J.D., *et al.Tetrahedron* **1998**, *54*, 7045.
Winkler, J.D., *et al. J. Am. Chem. Soc.* **1998**, *120*, 6425.

(±)-Manzamine A

Solution to the solution: Mask the ketone as an easily accessible alcohol



2



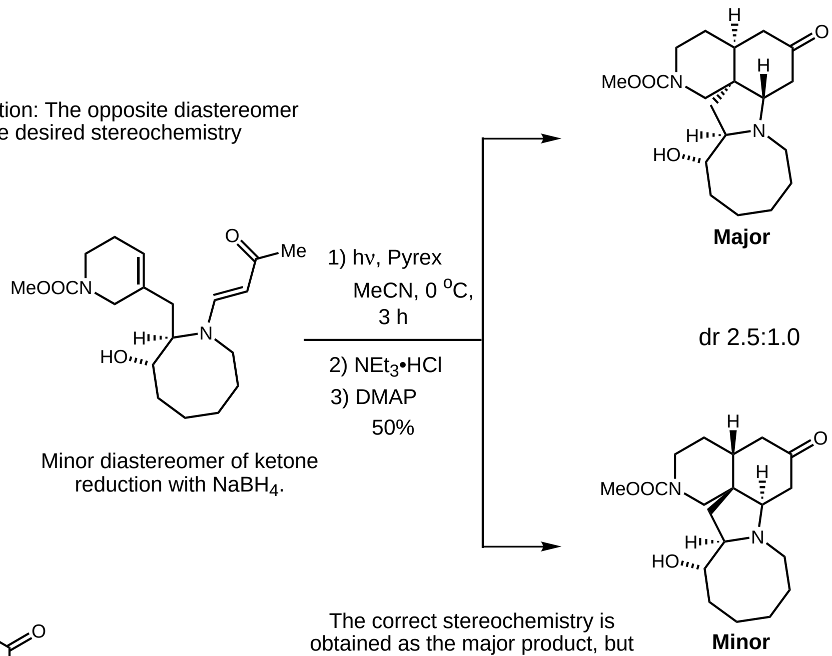
Manzamine Core

Again, the predominant product has the wrong stereochemistry and cannot be isomerized to the correct stereochemistry.

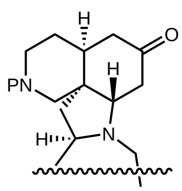
Winkler, J.D., *et al. Tetrahedron Lett.* **1993**, *34*, 6509.
Winkler, J.D., *et al. Isr. J. Chem.* **1997**, *37*, 47.
Winkler, J.D., *et al.Tetrahedron* **1998**, *54*, 7045.
Winkler, J.D., *et al. J. Am. Chem. Soc.* **1998**, *120*, 6425.

(±)-Manzamine A

Partial solution: The opposite diastereomer provides the desired stereochemistry



Minor diastereomer of ketone reduction with $NaBH_4$.



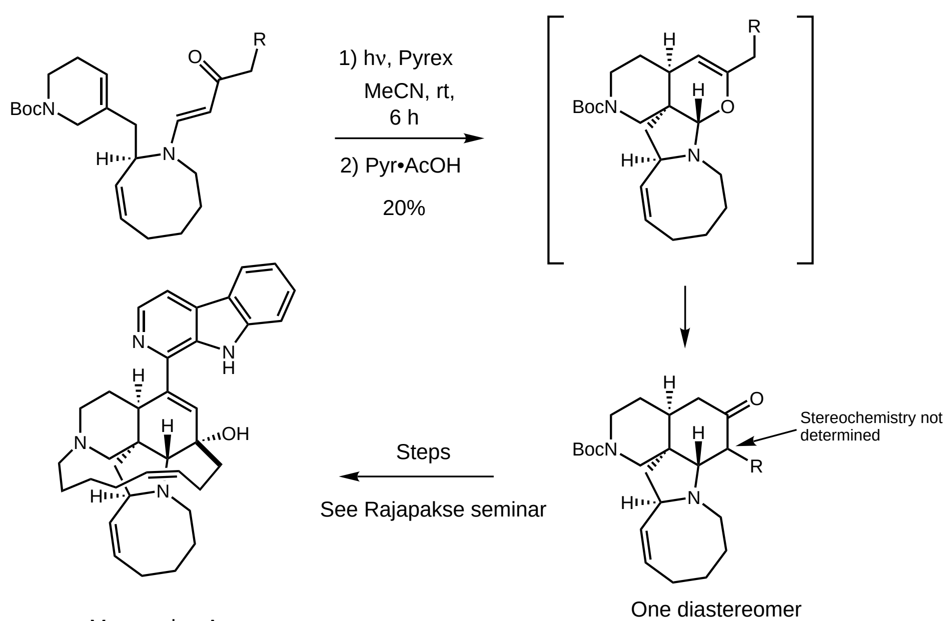
Manzamine Core

The correct stereochemistry is obtained as the major product, but this substrate is synthetically inaccessible in high yield.

Winkler, J.D., *et al. Tetrahedron Lett.* **1993**, *34*, 6509.
Winkler, J.D., *et al. Isr. J. Chem.* **1997**, *37*, 47.
Winkler, J.D., *et al.Tetrahedron* **1998**, *54*, 7045.
Winkler, J.D., *et al. J. Am. Chem. Soc.* **1998**, *120*, 6425.

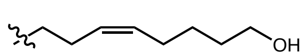
(±)-Manzamine A

Ultimate solution: The olefinic linkage in the natural product provides for the correct stereoinduction

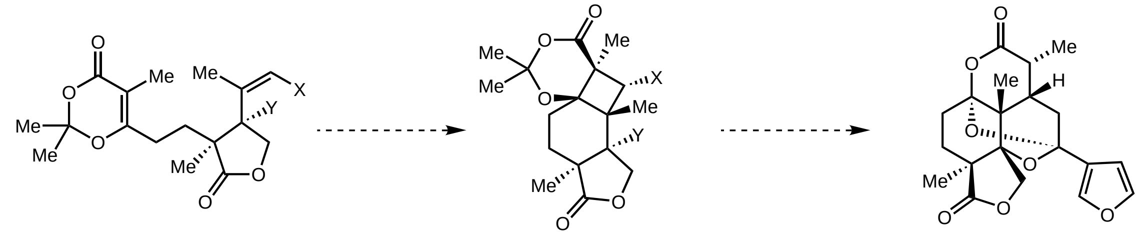


Winkler, J.D., *et al. Tetrahedron Lett.* **1993**, *34*, 6509.
Winkler, J.D., *et al. Isr. J. Chem.* **1997**, *37*, 47.
Winkler, J.D., *et al.Tetrahedron* **1998**, *54*, 7045.
Winkler, J.D., *et al. J. Am. Chem. Soc.* **1998**, *120*, 6425.

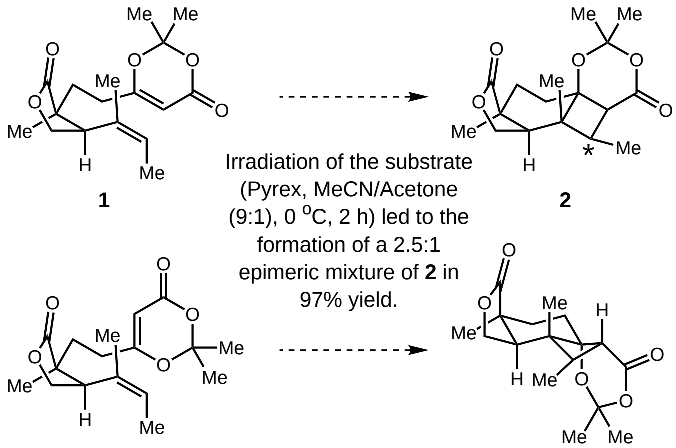
R=



(±)-Saudin



Saudin



1

2

3

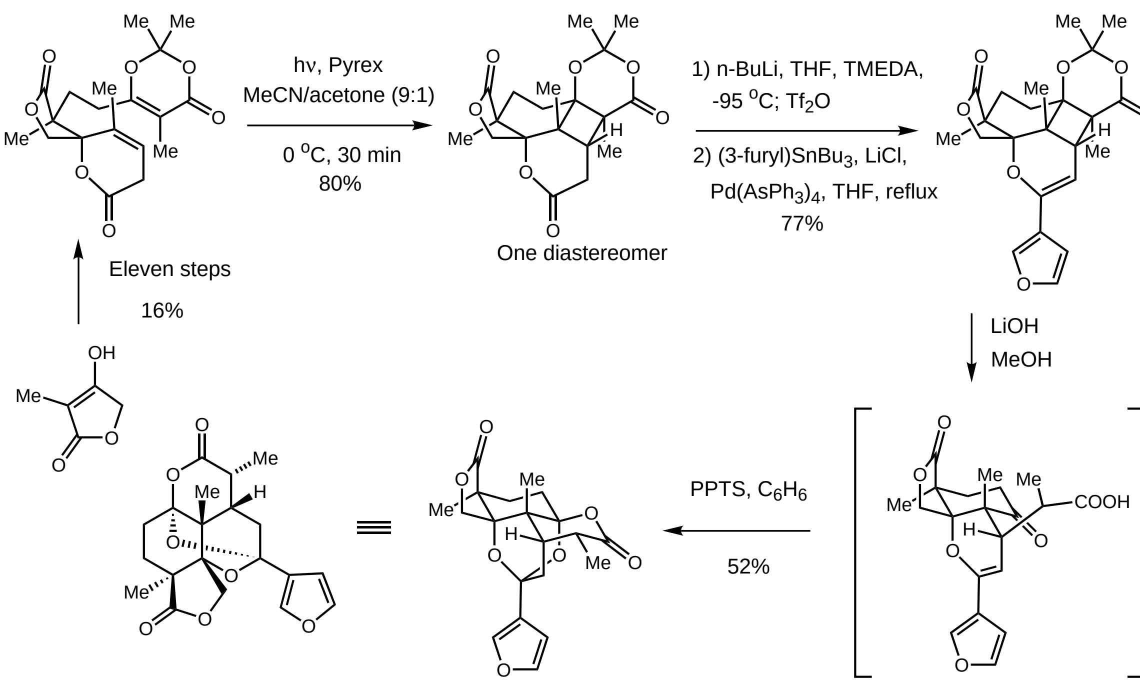
4

MM2 calculations suggest that **1** should be approximately 1.6 kcal/mol more stable than **3.**

Irradiation of the substrate (Pyrex, MeCN/Acetone (9:1), 0 ^{o}C, 2 h) led to the formation of a 2.5:1 epimeric mixture of **2** in 97% yield.

Winkler, J.D., *et al*. *J. Am. Chem. Soc.* **1999**, *121*, 7425.
Winkler, J.D., *et al*. *Tetrahedron Lett.* **1998**, *39*, 2253.

(±)-Saudin



One diastereomer

Saudin

Winkler, J.D., *et al*. *J. Am. Chem. Soc.* **1999**, *121*, 7425.
Winkler, J.D., *et al*. *Tetrahedron Lett.* **1998**, *39*, 2253.

Conclusions

- A lack of complete mechanistic understanding has not prevented the successful application of the enone-olefin photocycloaddition to a great many synthetic challenges.

- Intramolecular enone-olefin photocycloaddition is useful for the stereoselective contruction of carbocycles, especially five membered rings.

- Multiple quaternary and congested centers can be constructed in a single operation.

- Great creativity is possible in the fragmentation of the derived cyclobutane to access useful synthetic intermediates.

- Stereoinduction from existing stereocenters is usually explicable in a rational and satisfying manner.

- Molecular modeling simulations have proven useful in predicting the stereoselectivity of several photocycloadditions.