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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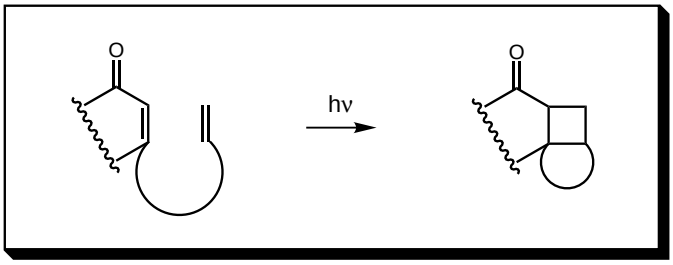


Lead References:

- 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

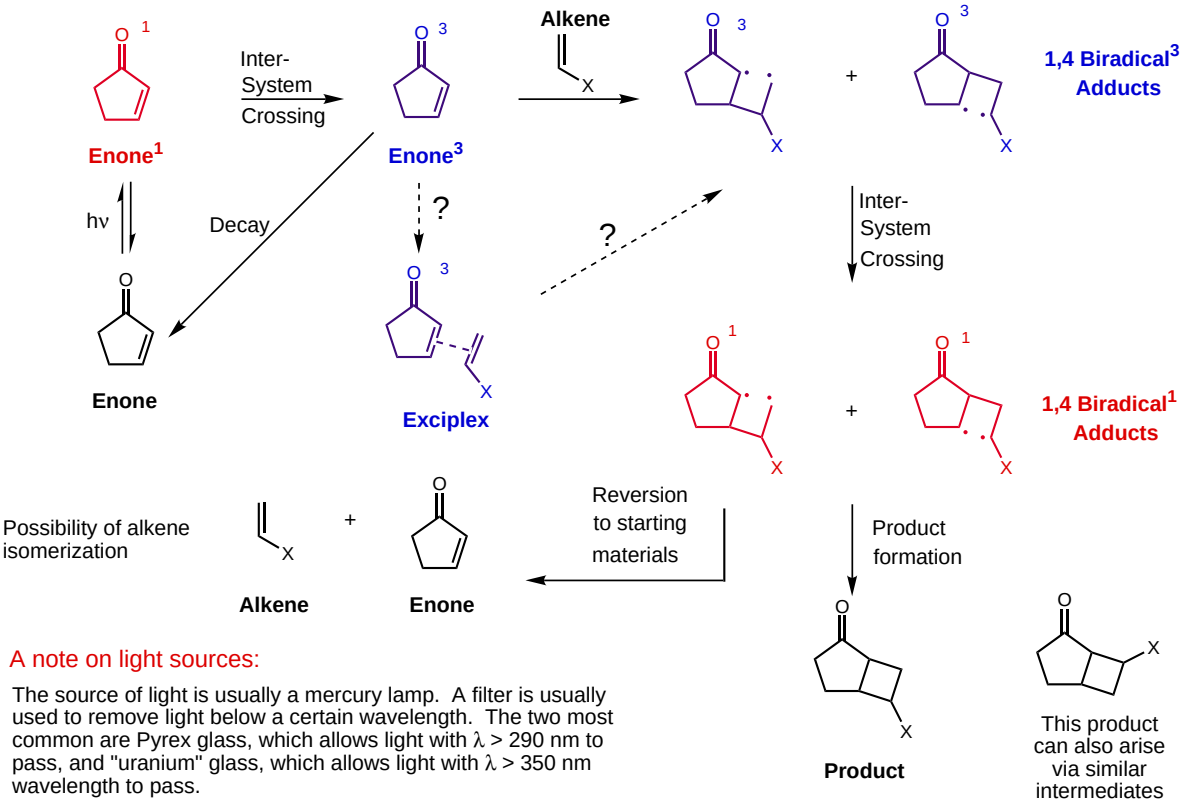
II) Selected synthetic examples:

- 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

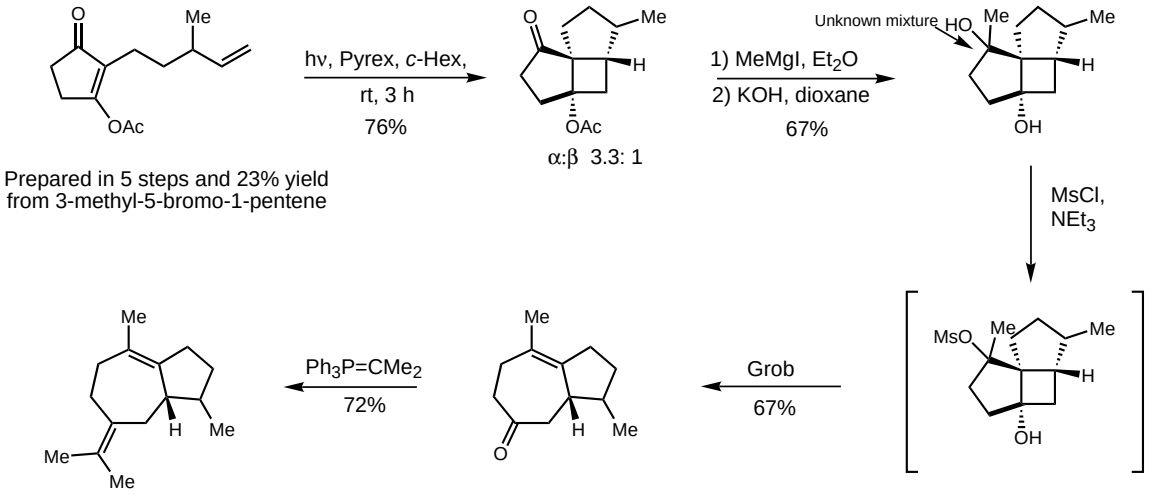


A note on light sources:

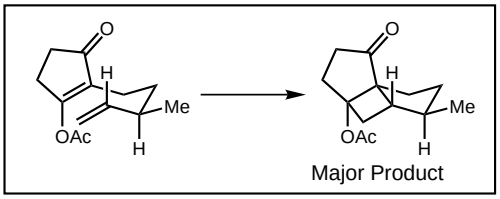
The source of light is usually a mercury lamp. A filter is usually used to remove light below a certain wavelength. The two most common are Pyrex glass, which allows light with $\lambda > 290$ nm to pass, and "uranium" glass, which allows light with $\lambda > 350$ nm wavelength to pass.

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

(±) β-Bulnesene and Epi-β-bulnesene

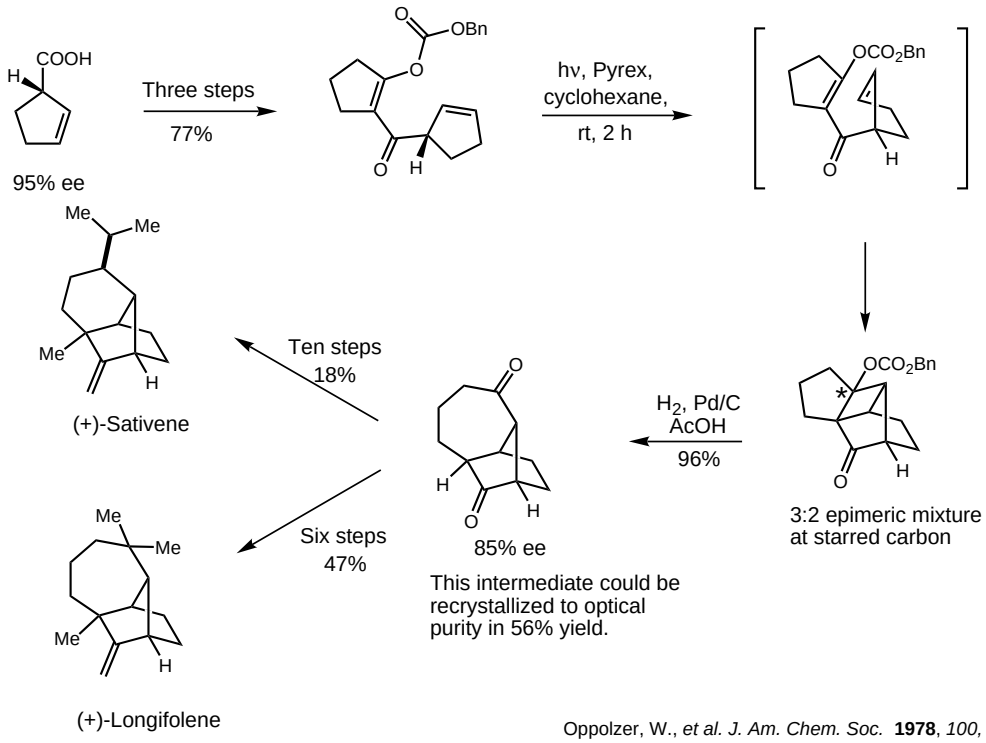


Stereochemical rationale (TBD)



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

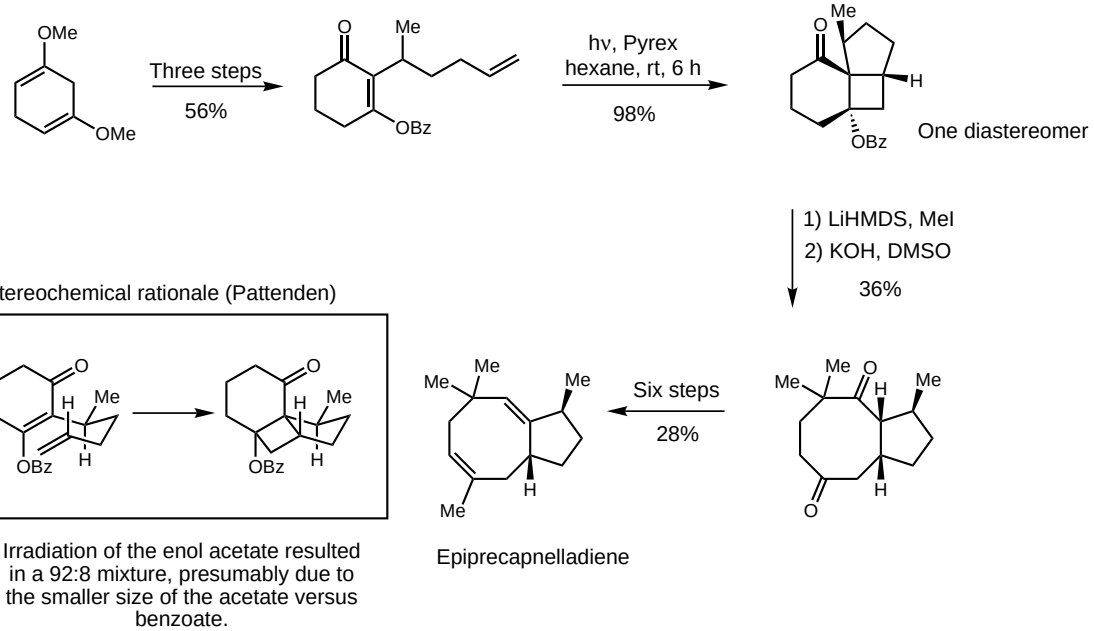
(+)-Longifolene and (+)-Sativene



Oppolzer, W., *et al. J. Am. Chem. Soc.* **1978**, *100,* 2583.

Oppolzer, W., *et al. Helv. Chim. Acta.* **1984**, *67*, 1154.

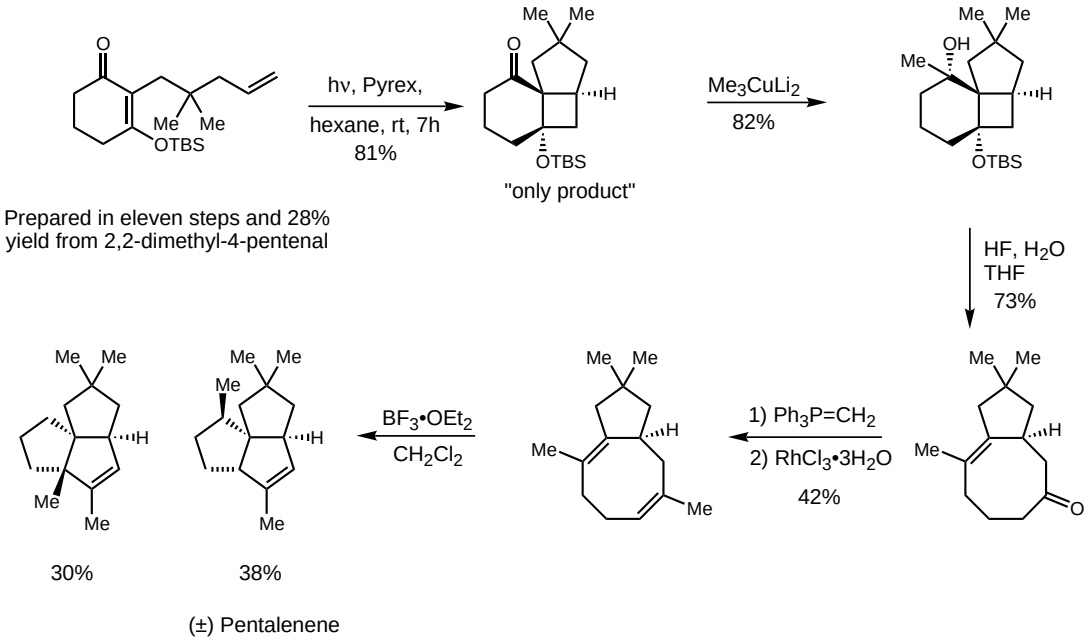
(±)-Epiprecapnelladiene



Pattenden, G., *et al. J. Chem. Soc., Chem. Comm.* **1980**, 1195.

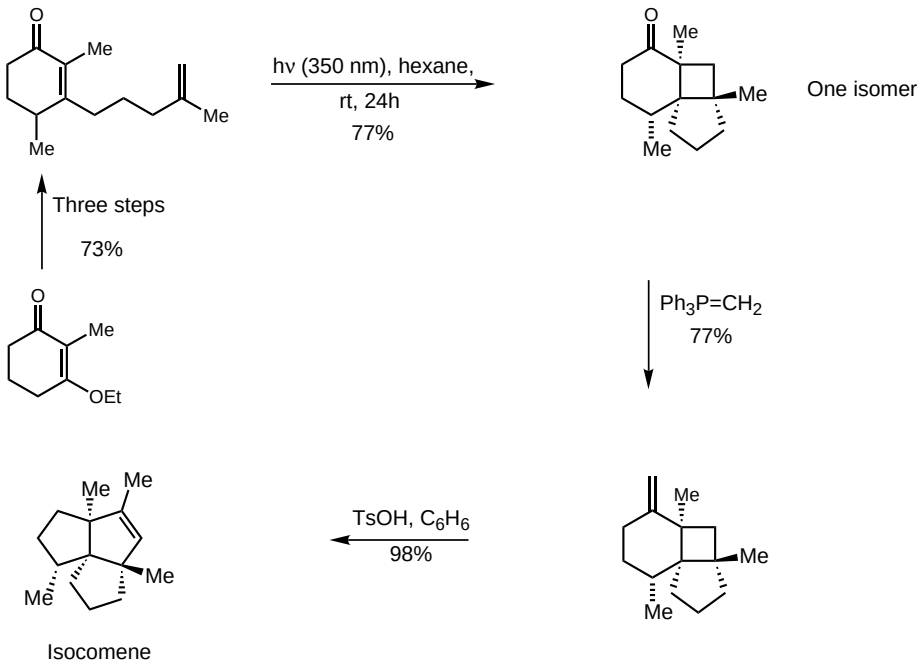
Pattenden, G., *et al. J. Chem. Soc., Perkin Trans. I* **1983**, 1913.

(±)-Pentalenene



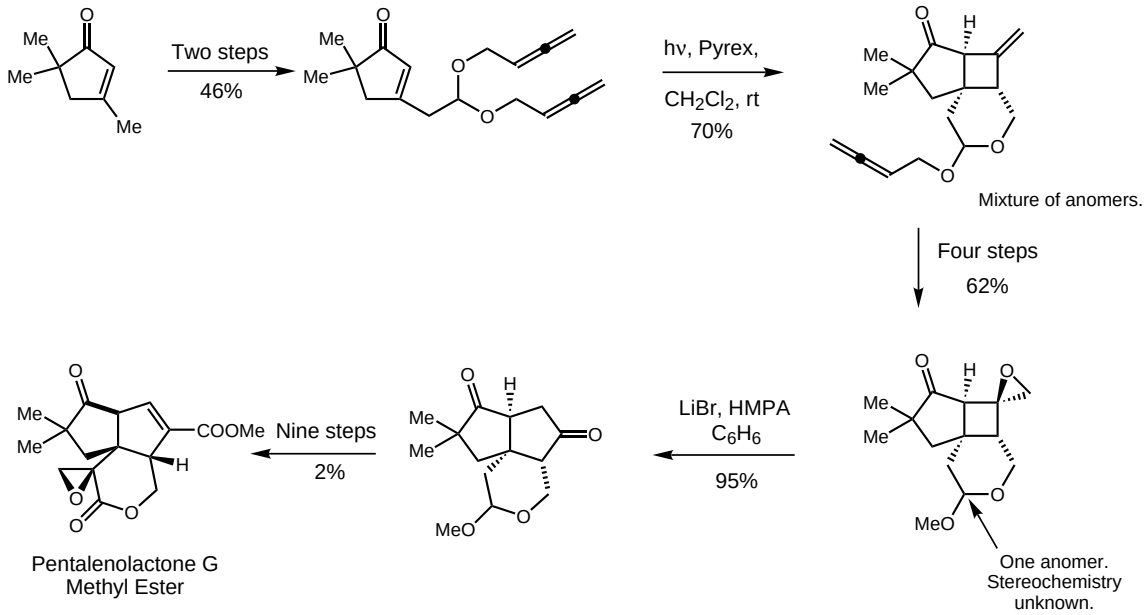
Pattenden, G., *et al. Tetrahedron Lett.* **1984**, *25*, 3021.
Pattenden, G., *et al.Tetrahedron* **1987**, *43*, 5637.

(±)-Isocomene



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

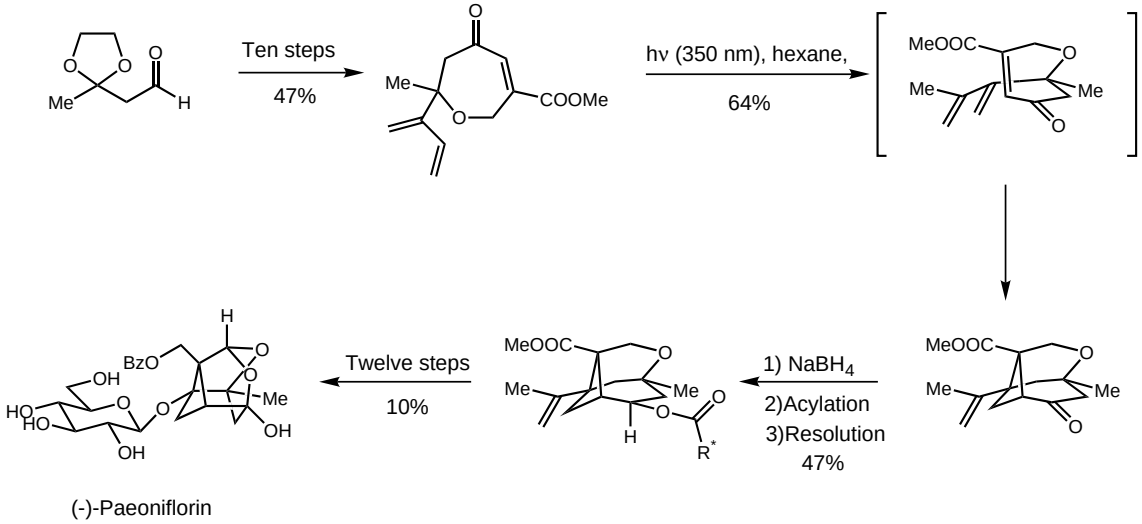
(±)-Pentalenolactone G Methyl Ester



Pirrung, M.C., *et al.Tetrahedron Lett.* **1986**, *27*, 2703.

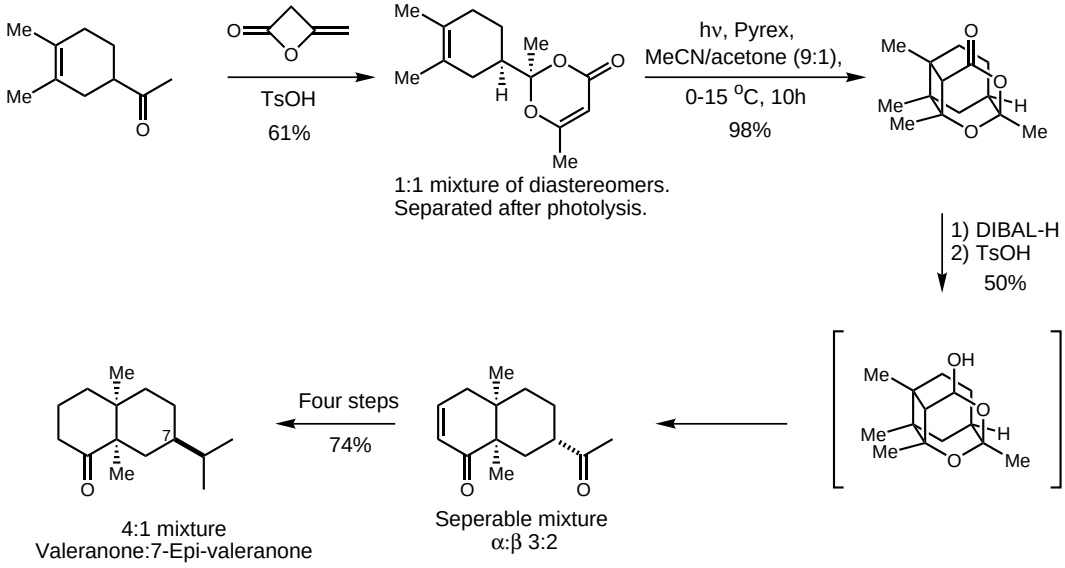
Pirrung, M.C., *et al. J. Org. Chem.* **1988**, *53*, 227.

(-)-Paeoniflorin



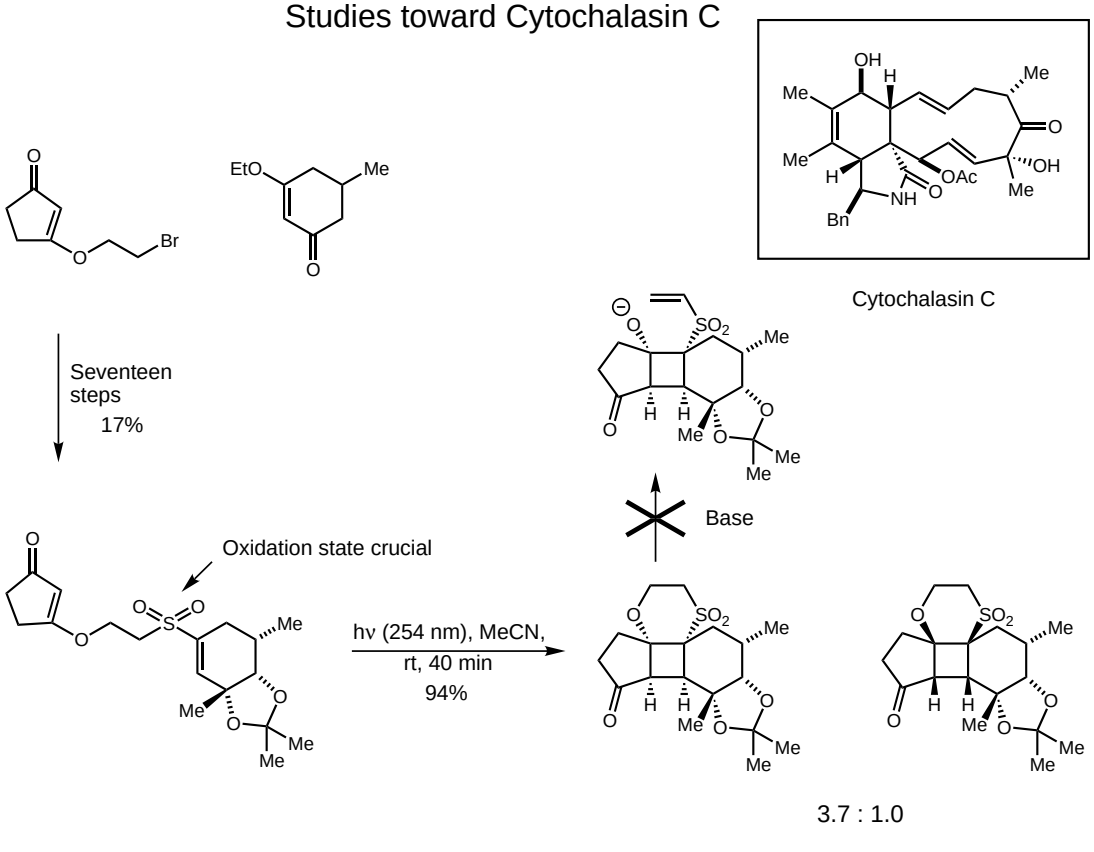
Hatakeyama, S., Takano, S., *et al. J. Am. Chem. Soc.* **1994**, *116,* 4081.

(±)-Valeranone



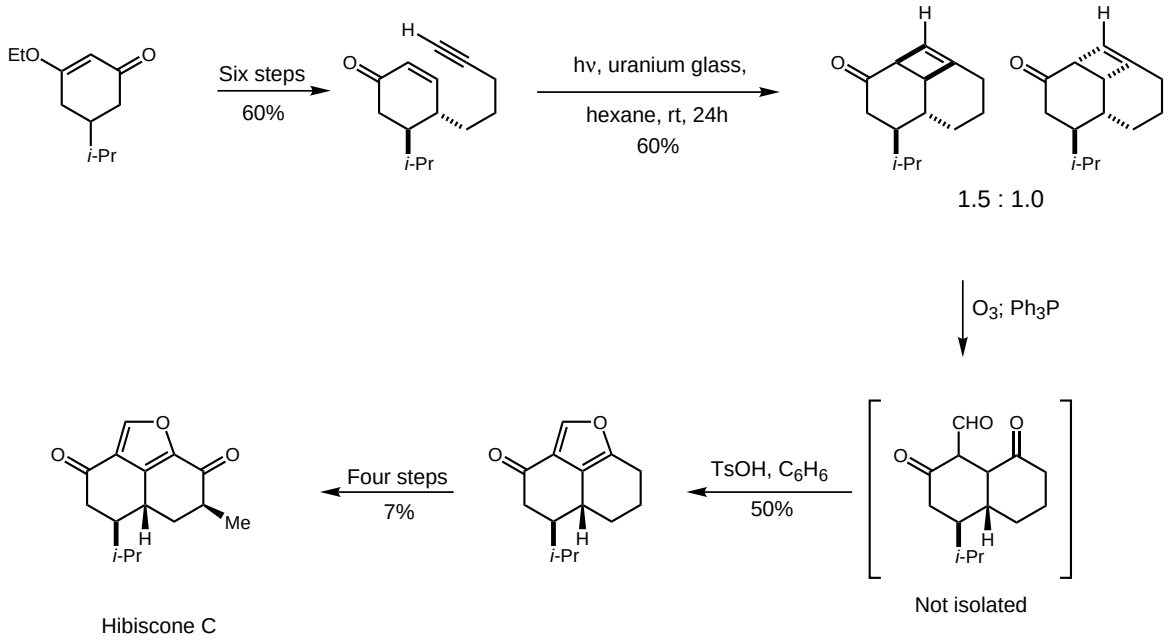
Takeshita, H. *et al*. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2699.

Studies toward Cytochalasin C



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

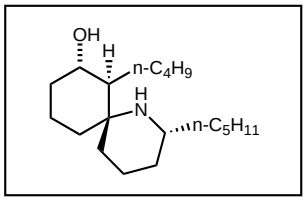
(±)-Hibiscone C



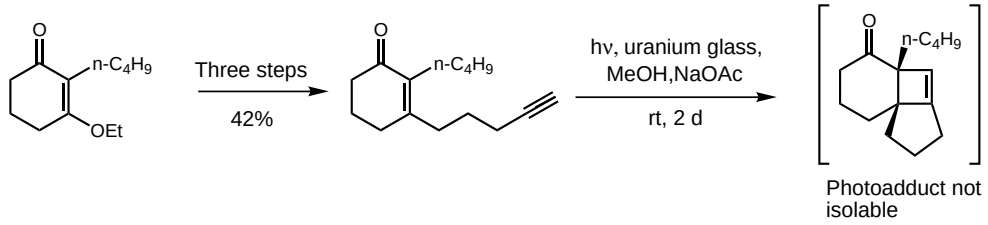
Smith, A.B., III, *et al. J. Am. Chem. Soc.* **1982**, *104,* 5568.

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

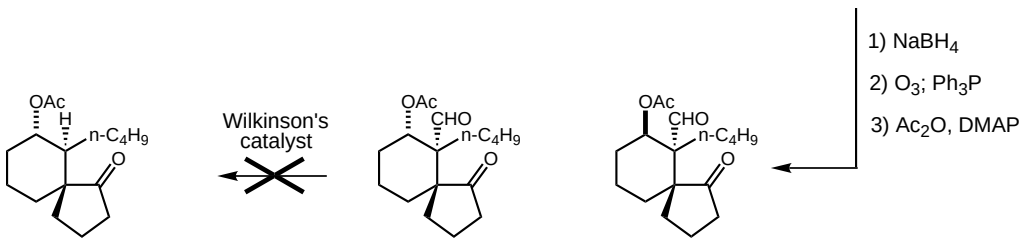
Studies toward Perhydrohistrionicotoxin



Perhydrohistrionicotoxin



Photoadduct not isolable

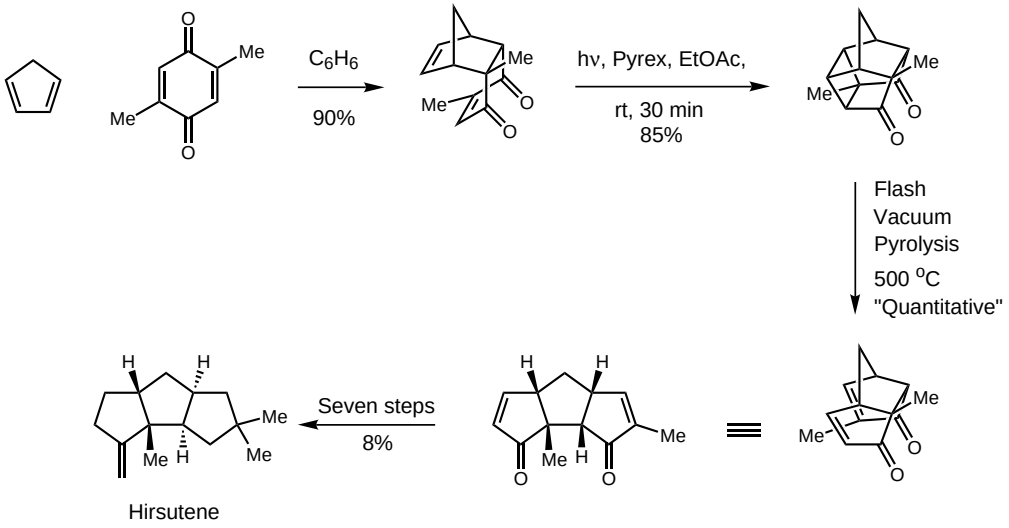


9%

17%

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

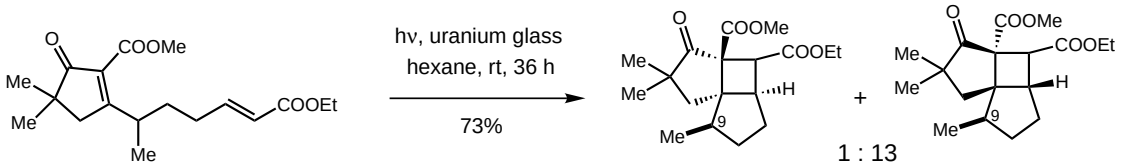
(±)-Hirsutene



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.

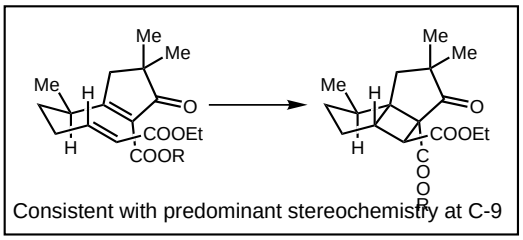


The stereochemistry at the starred carbon was not determined, but the products were isolated as a mixture.

Stereochemical rationale (Crimmins)

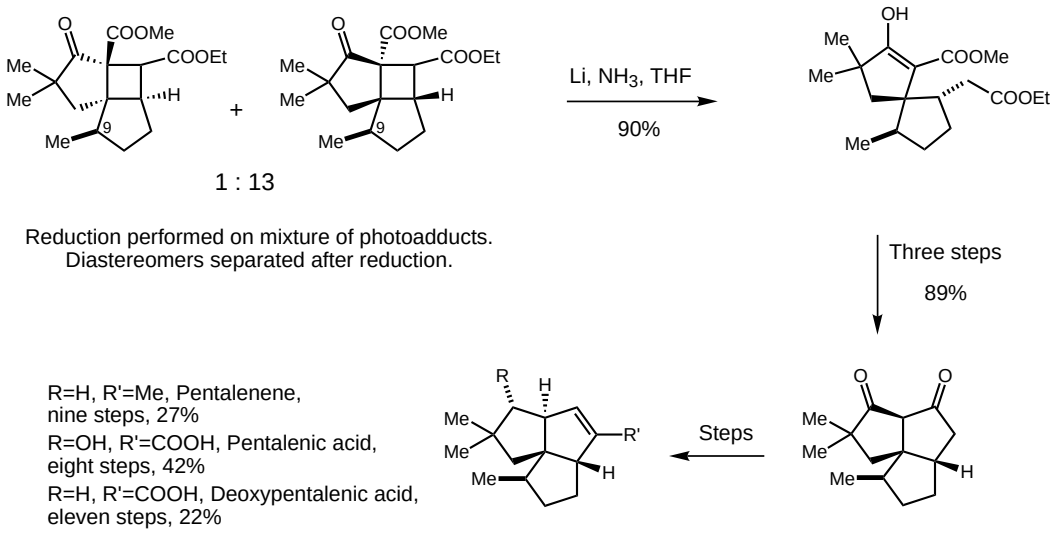
R	C-9 dr
Me	13:1
Et	17:1
i-Pr	>20:1

Varying the size of the indicated alkyl group influenced the stereoselectivity



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.



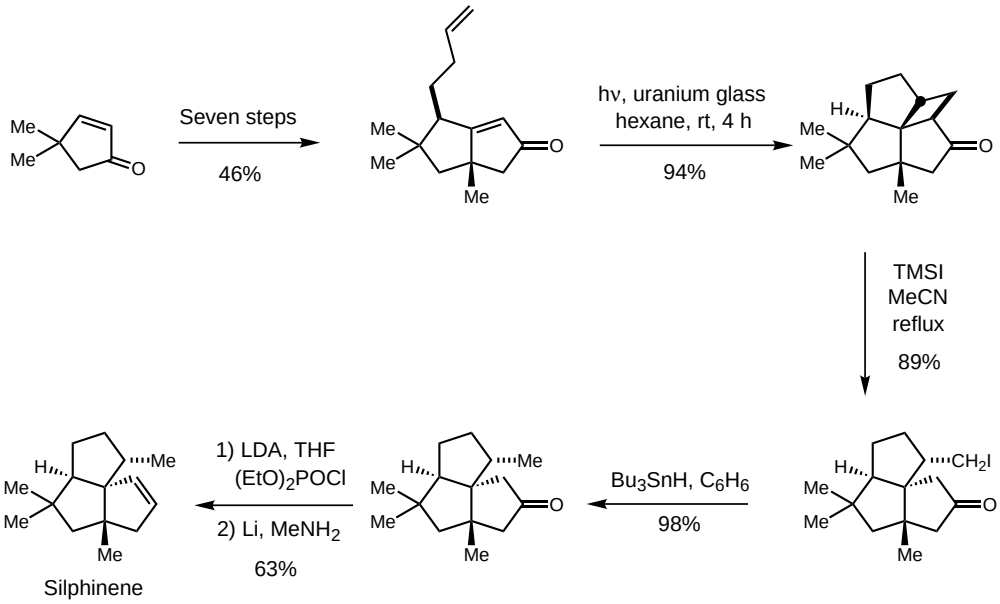
1 : 13

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

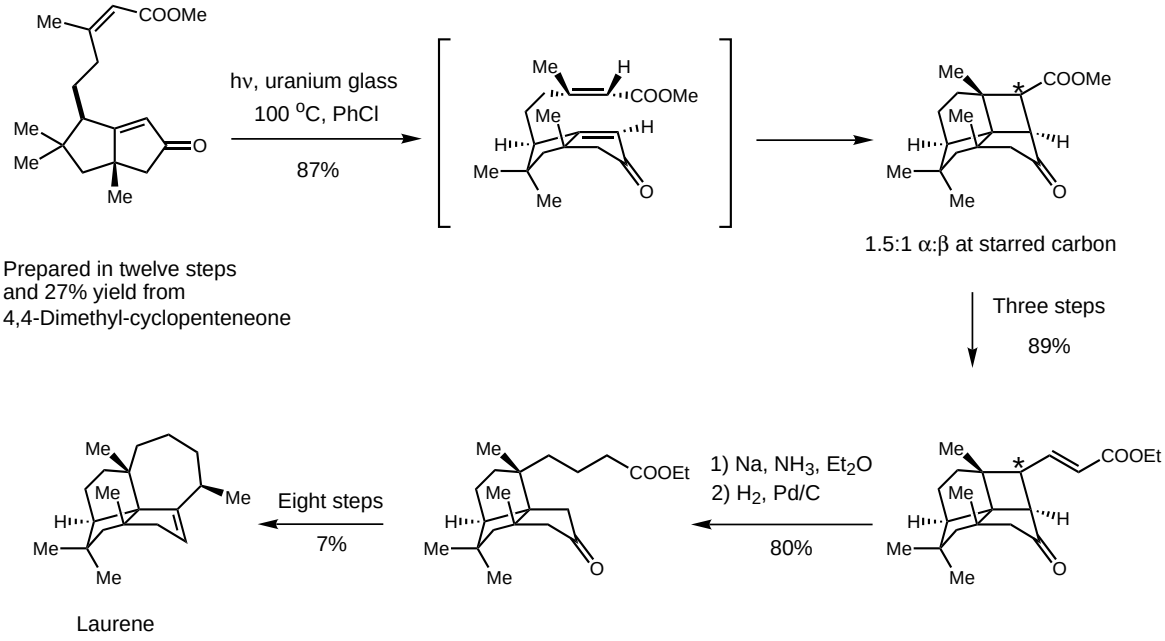


Silphinene

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

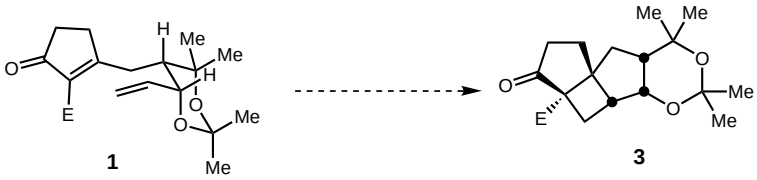


Prepared in twelve steps
and 27% yield from
4,4-Dimethyl-cyclopenteneone

Laurene

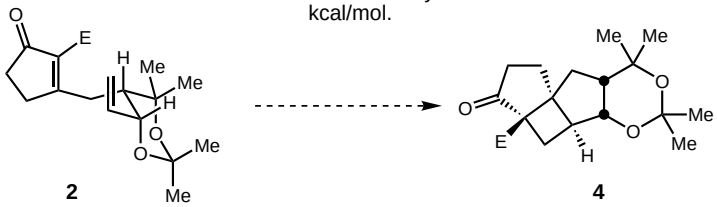
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1987**, *109*, 6199.
Crimmins, M.T., *et al. Tetrahedron Lett.* **1985**, *26*, 997.

(±)-Lubiminol

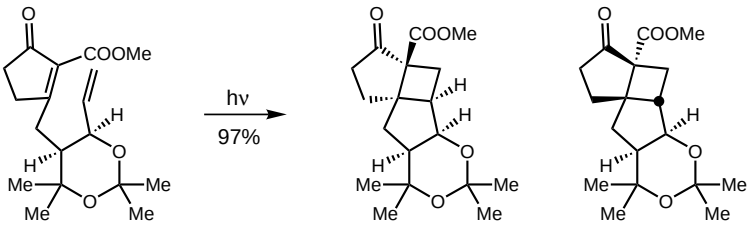


1 **3**

For E=Me, MM2 calculations suggest that **1** should be more stable than **2** by 1.1 kcal/mol.



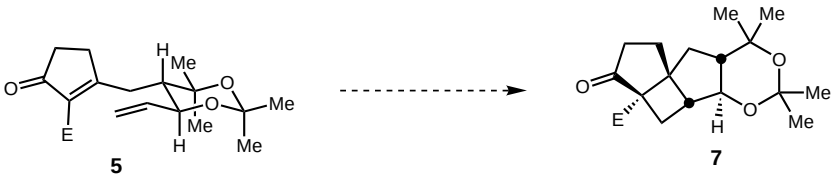
2 **4**



3 83:17 **4**

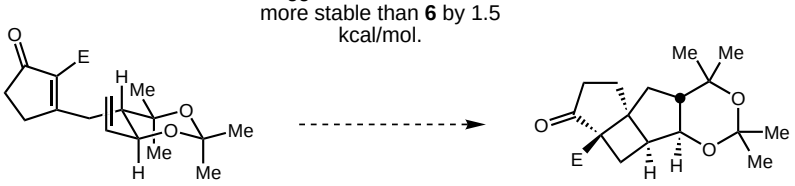
Crimmins, M.T., *et al. Tetrahedron Lett.* **1996**, *37,* 8703.
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1998**, *120,* 1747.

(±)-Lubiminol

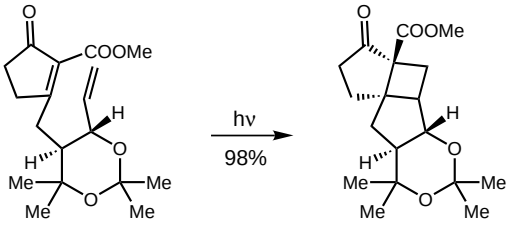


5 **7**

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



6 **8**



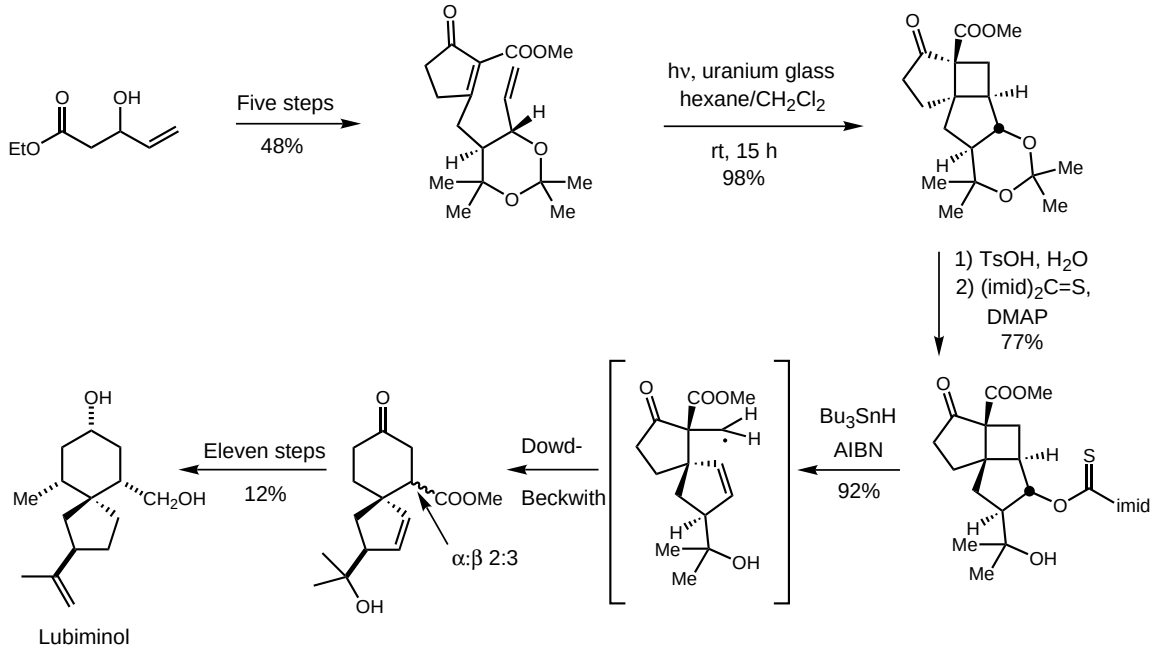
7

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.

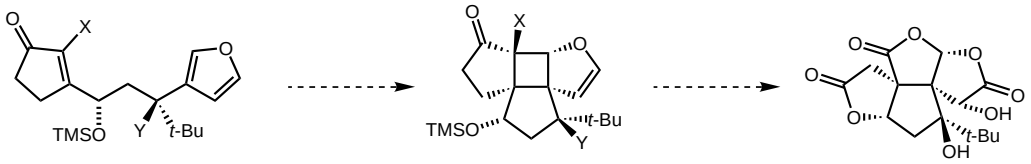
(±)-Lubiminol



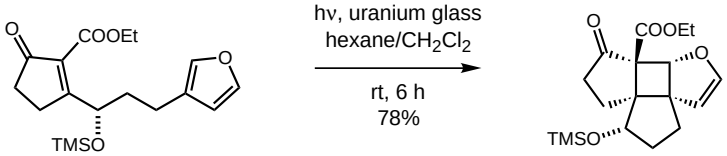
Crimmins, M.T., *et al. Tetrahedron Lett.* **1996**, *37,* 8703.

Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1998**, *120,* 1747.

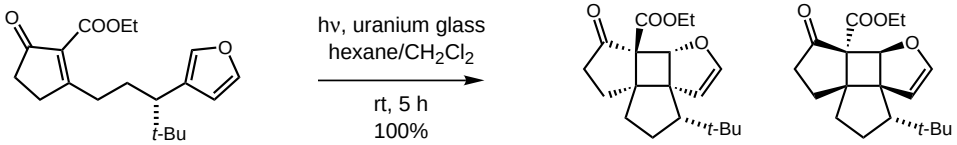
(±)-Bilobalide



Bilobalide



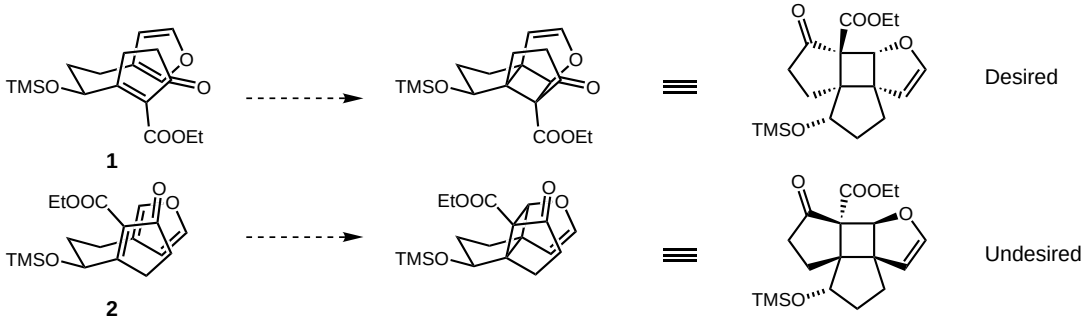
one diastereomer

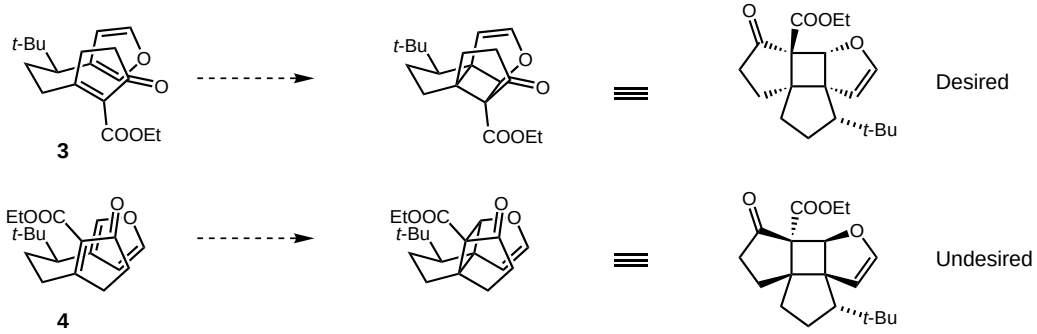


1.5 1.0

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

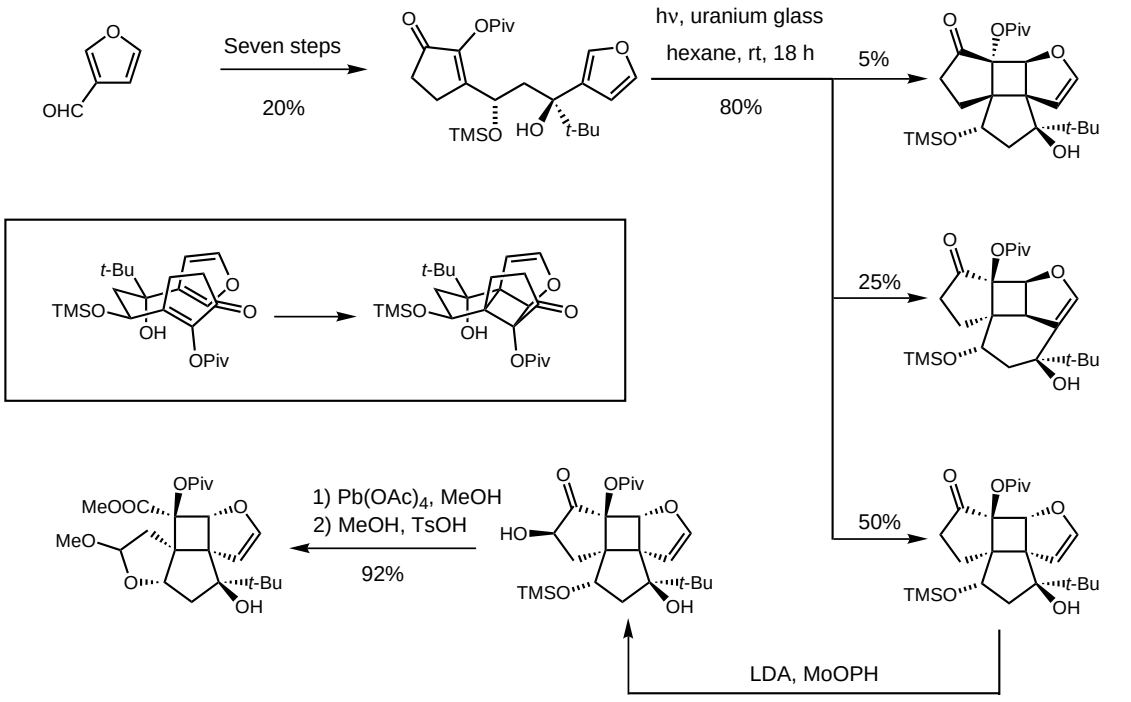




MM2 calculations suggested that **1** was more favored than **2** by approximately 1.6 kcal/mol, while there was almost no difference in energy between **3** and **4** (0.2 kcal/mol).

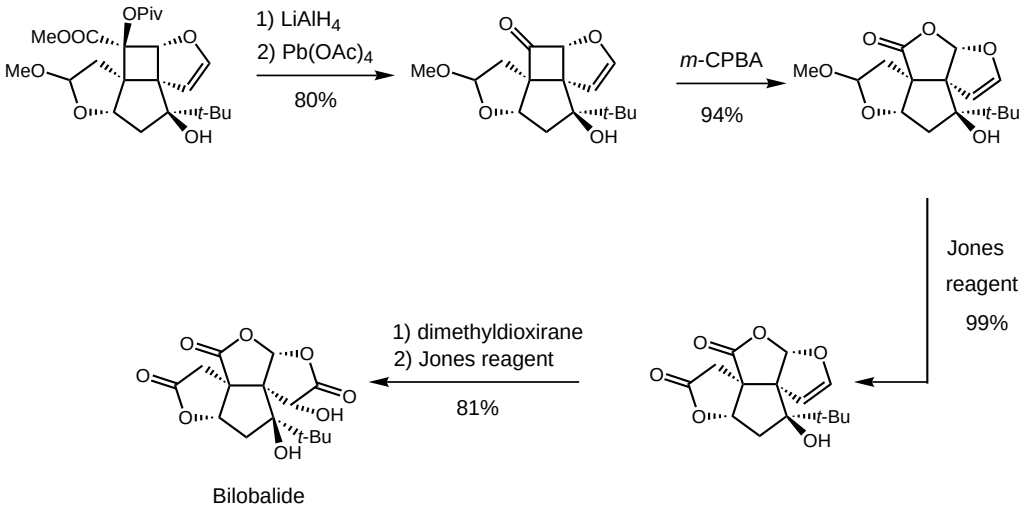
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1992**, *114*, 5445.
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1993**, *115*, 3146.

(±)-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.

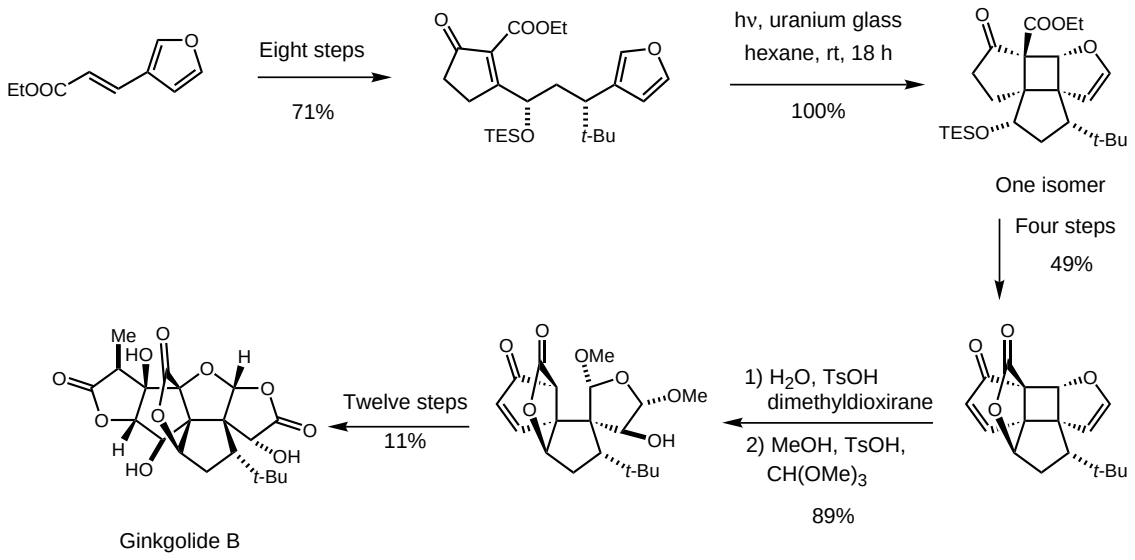
(±)-Bilobalide



Bilobalide

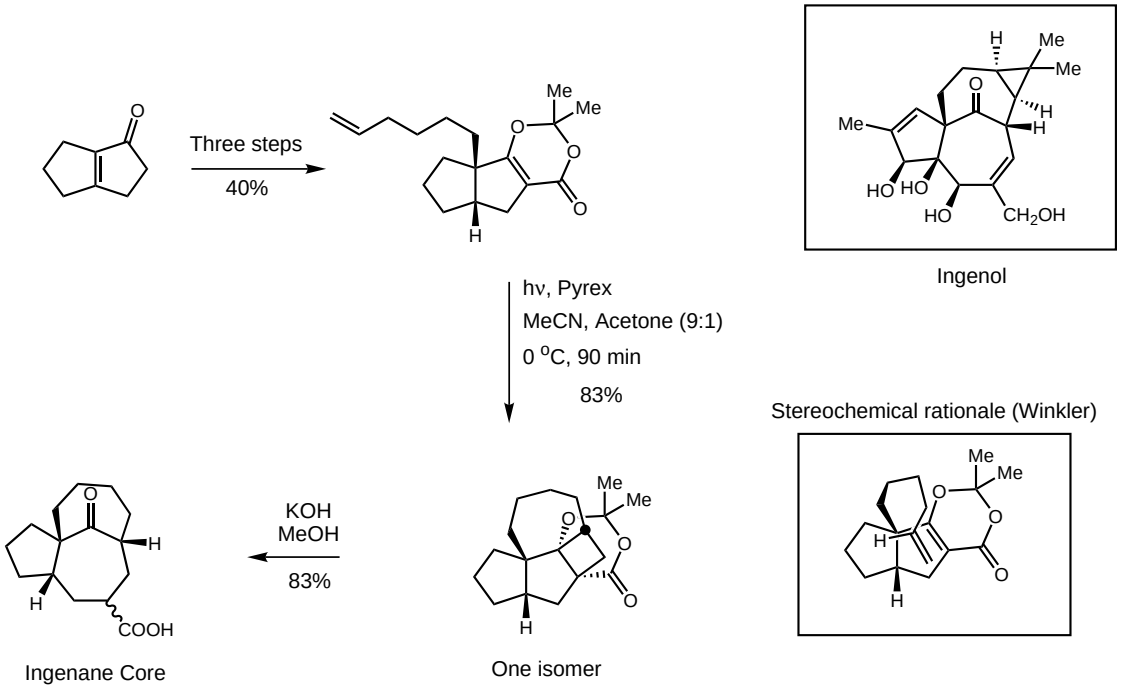
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1992**, *114*, 5445.
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1993**, *115*, 3146.

(±)-Ginkgolide B



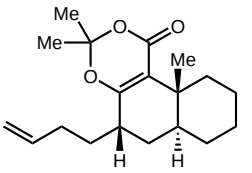
Crimmins, M.T. *et al. J. Am. Chem. Soc.* **1999**, *121*, 10249.
Crimmins, M.T. *et al. Tetrahedron Lett.* **1989**, *30*, 5997.

Synthesis of the Core of the Ingenane Diterpenes

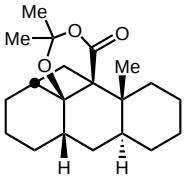


Winkler, J.D., *et al. J. Am. Chem. Soc.* **1987**, *109*, 2850.

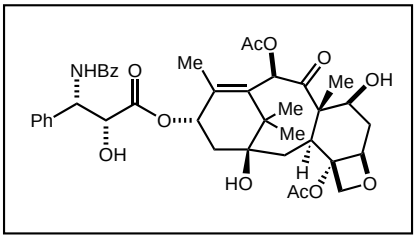
Synthetic Studies Toward the Taxane Core



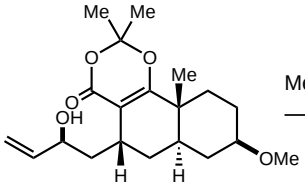
hν, Pyrex
MeCN/Acetone (9:1)
rt



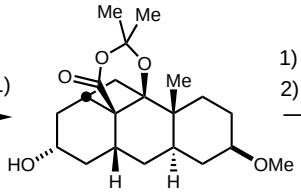
None of the desired photoadduct could be isolated.



Taxol

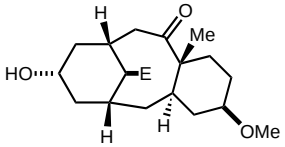


hν, Pyrex
MeCN/Acetone (9:1)
rt, 30 min
75%



One isomer

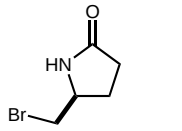
1) KOH, MeOH
2) CH_2N_2
82%



E=COOMe

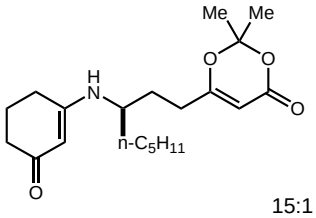
Winkler, J.D., *et al.Tetrahedron Lett.* **1986**, *27*, 5959.
Winkler, J.D., *et al. J. Org. Chem.* **1989**, *54*, 4491.
Winkler, J.D., *et al.Tetrahedron* **1992**, *48*, 7049.

(-)-Perhydrohistrionicotoxin

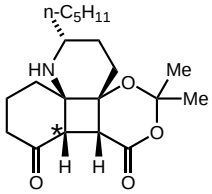


Derived from glutamic acid

Six steps
34%



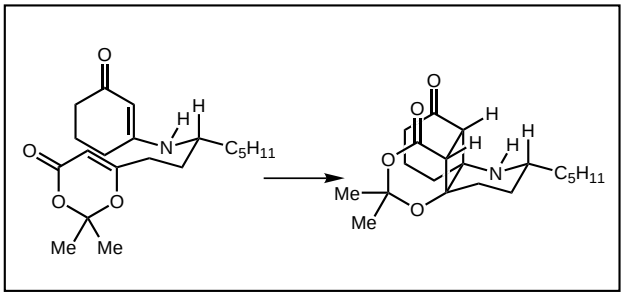
hν, Pyrex, MeCN,
0 °C, 30 min
95%

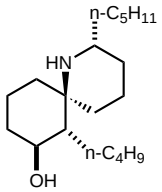


15:1 ratio of epimers at starred carbon. Major isomer shown. Minor isomer epimerizes to major upon chromatography.

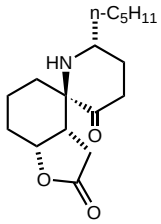
1) $NaBH_4$
2) NaH, THF
63%

Stereochemical rationale (Winkler)





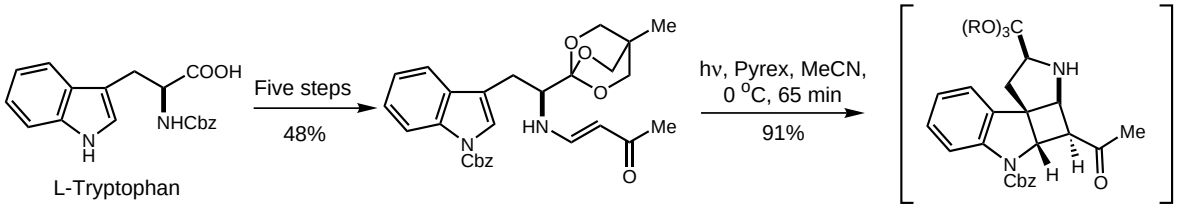
Seven steps
43%



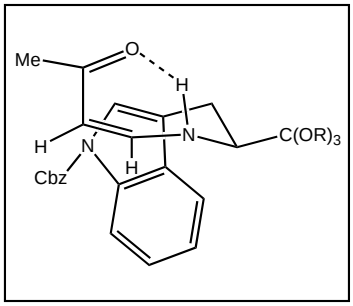
Perhydrohistrionicotoxin

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

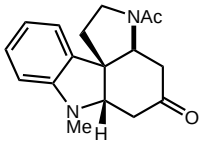
Formal Synthesis of Vindorosine



Stereochemical rationale (Winkler)

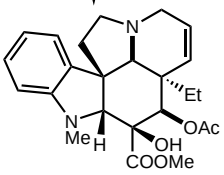


Intermediate in Büchi's racemic synthesis



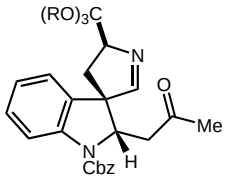
>97%ee

Büchi
Eight steps
3%

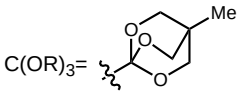


Vindorosine

Eight steps
20%

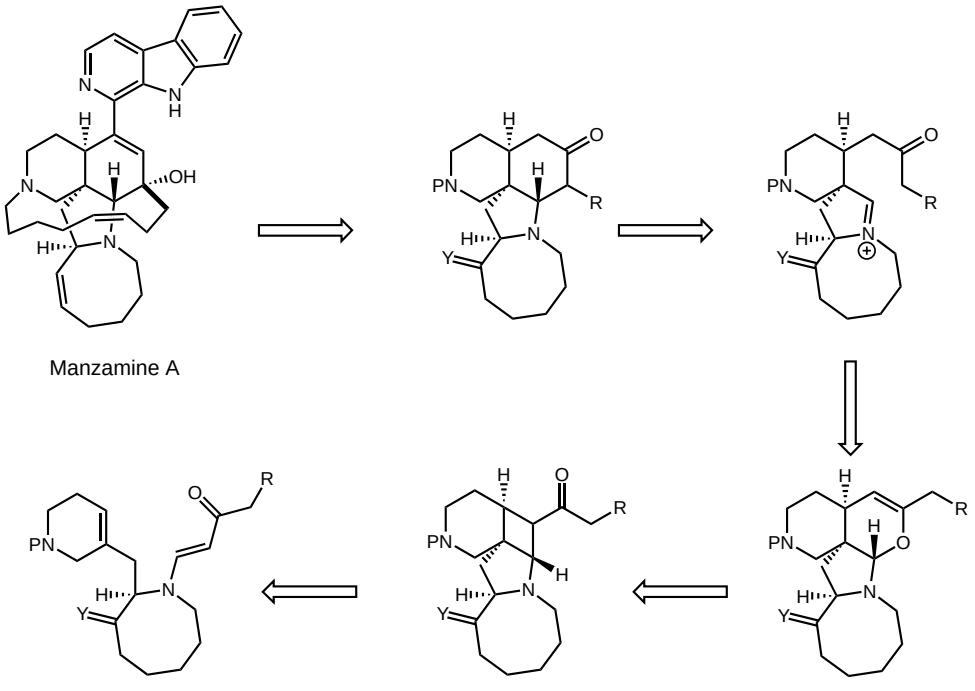


One diastereomer



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



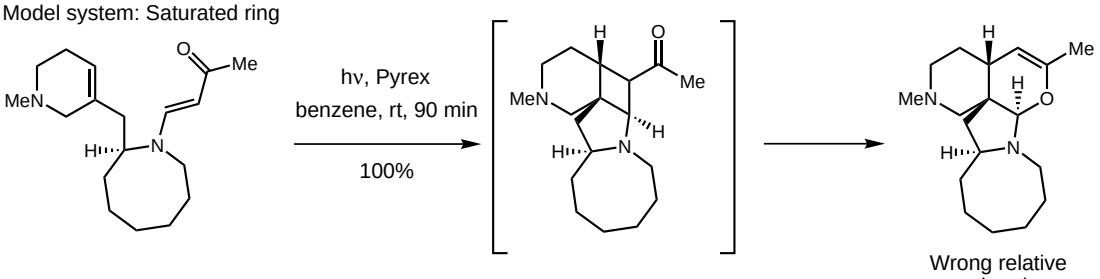
Manzamine A

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.

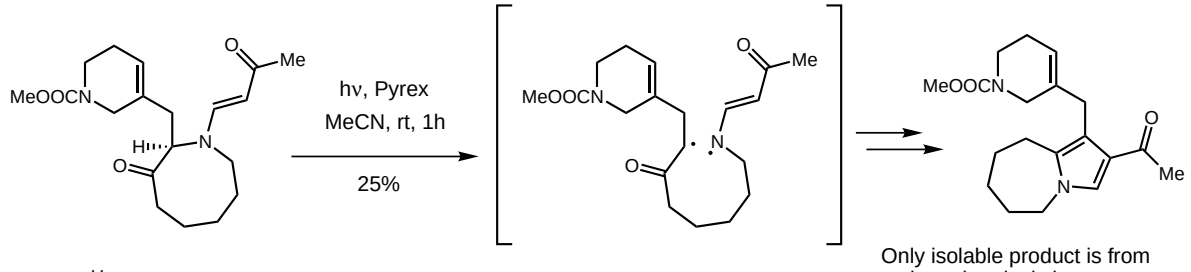
Winkler, J.D., *et al. Tetrahedron Lett.* **1993**, *34*, 6509.
Winkler, J.D., *et al. Isr. J. Chem.* **1997**, *37*, 47.
Winkler, J.D., *et al.Tetrahedron* **1998**, *54*, 7045.
Winkler, J.D., *et al. J. Am. Chem. Soc.* **1998**, *120*, 6425.

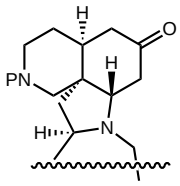
(±)-Manzamine A

Model system: Saturated ring



Possible solution: Epimerize after cyclization

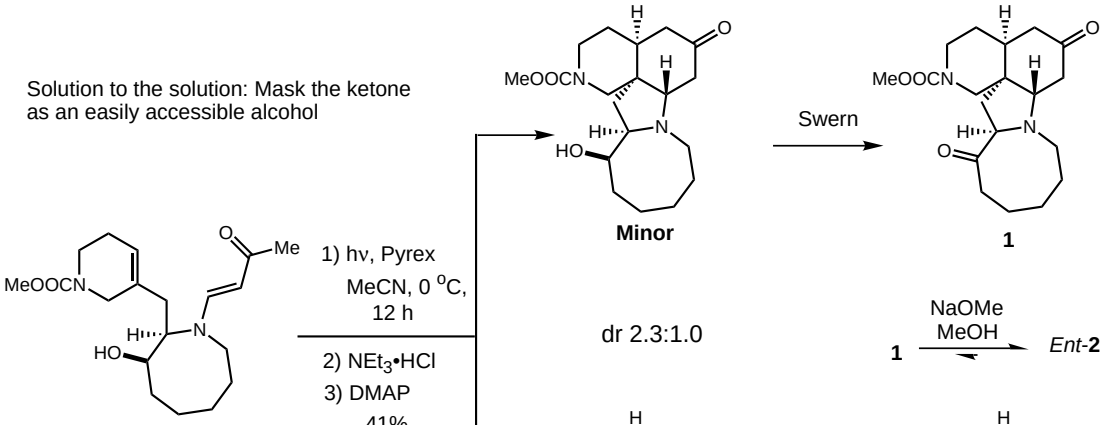




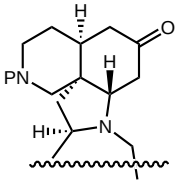
Winkler, J.D., *et al. Tetrahedron Lett.* **1993**, *34*, 6509.
Winkler, J.D., *et al. Isr. J. Chem.* **1997**, *37*, 47.
Winkler, J.D., *et al.Tetrahedron* **1998**, *54*, 7045.
Winkler, J.D., *et al. J. Am. Chem. Soc.* **1998**, *120*, 6425.

(±)-Manzamine A

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



Readily available by L-Selectride
reduction of the ketone

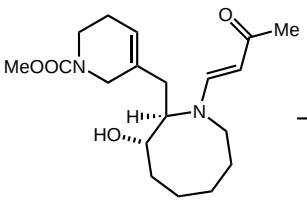


Again, the predominant product has
the wrong stereochemistry and
cannot be isomerized to the correct
stereochemistry.

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

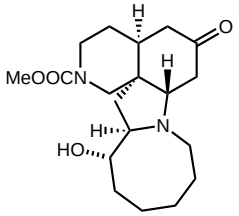
Partial solution: The opposite diastereomer provides the desired stereochemistry



Minor diastereomer of ketone reduction with $NaBH_4$.

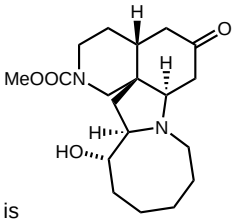
1) hν, Pyrex
MeCN, 0 °C,
3 h

2) NEt_3•HCl
3) DMAP
50%



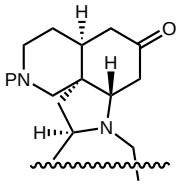
Major

dr 2.5:1.0



Minor

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

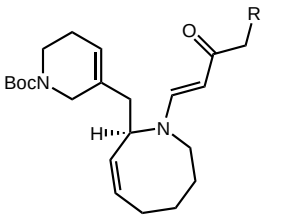


Manzamine Core

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.

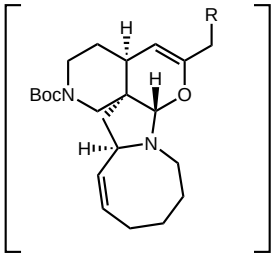
(±)-Manzamine A

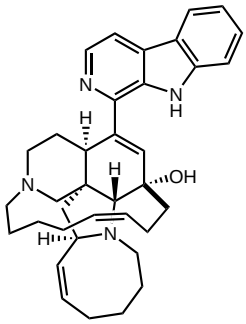
Ultimate solution: The olefinic linkage in the natural product provides for the correct stereoinduction



1) hν, Pyrex
MeCN, rt,
6 h

2) Pyr•AcOH
20%

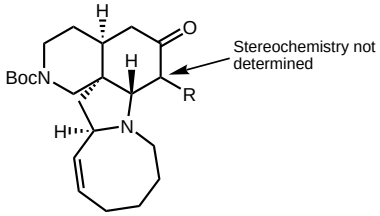




Manzamine A

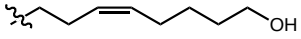
Steps

See Rajapakse seminar

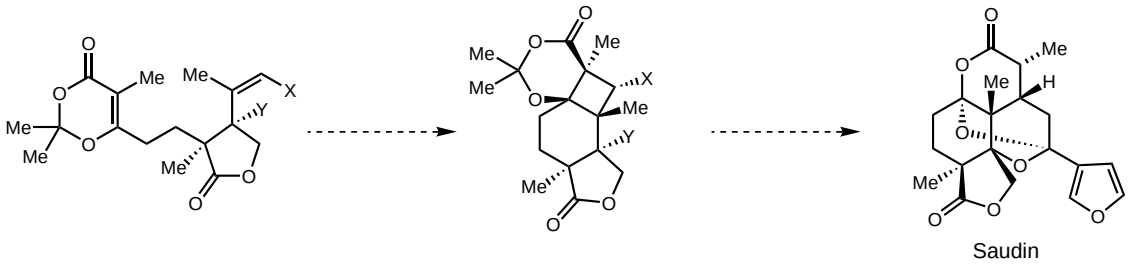


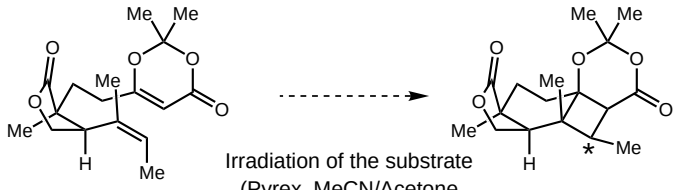
One diastereomer

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



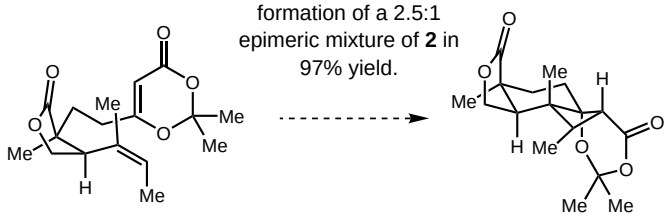


1

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 °C, 2 h) led to the formation of a 2.5:1 epimeric mixture of **2** in 97% yield.

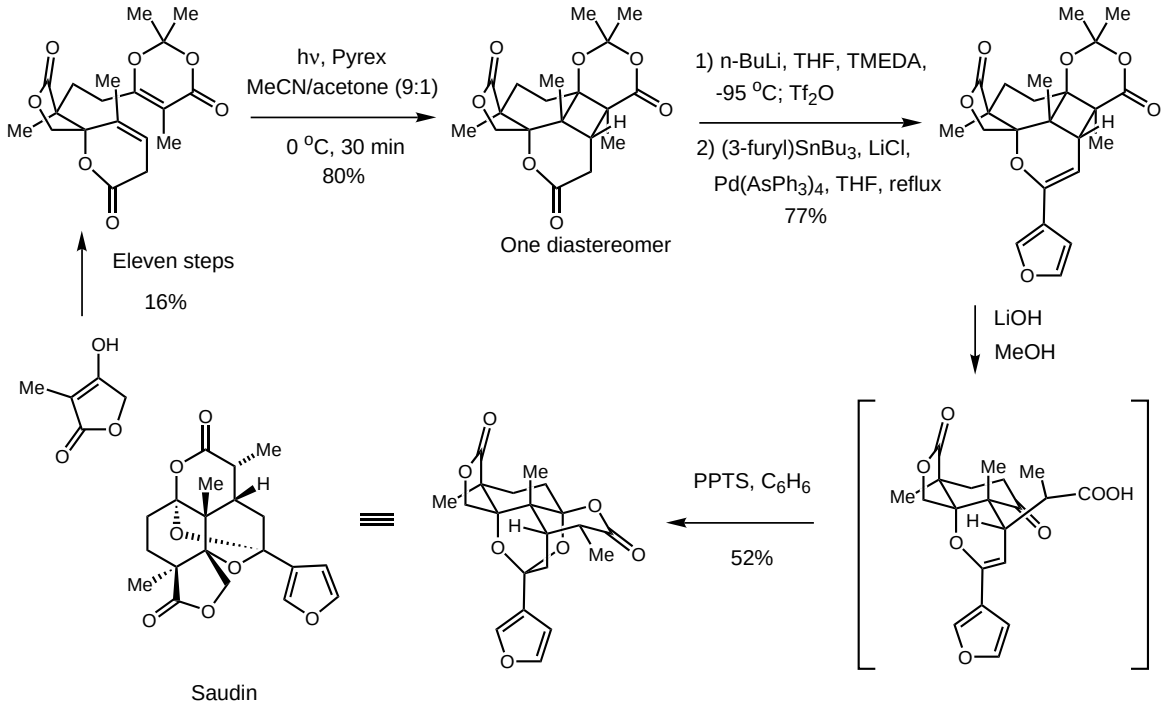
2



3 **4**

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

(±)-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.
