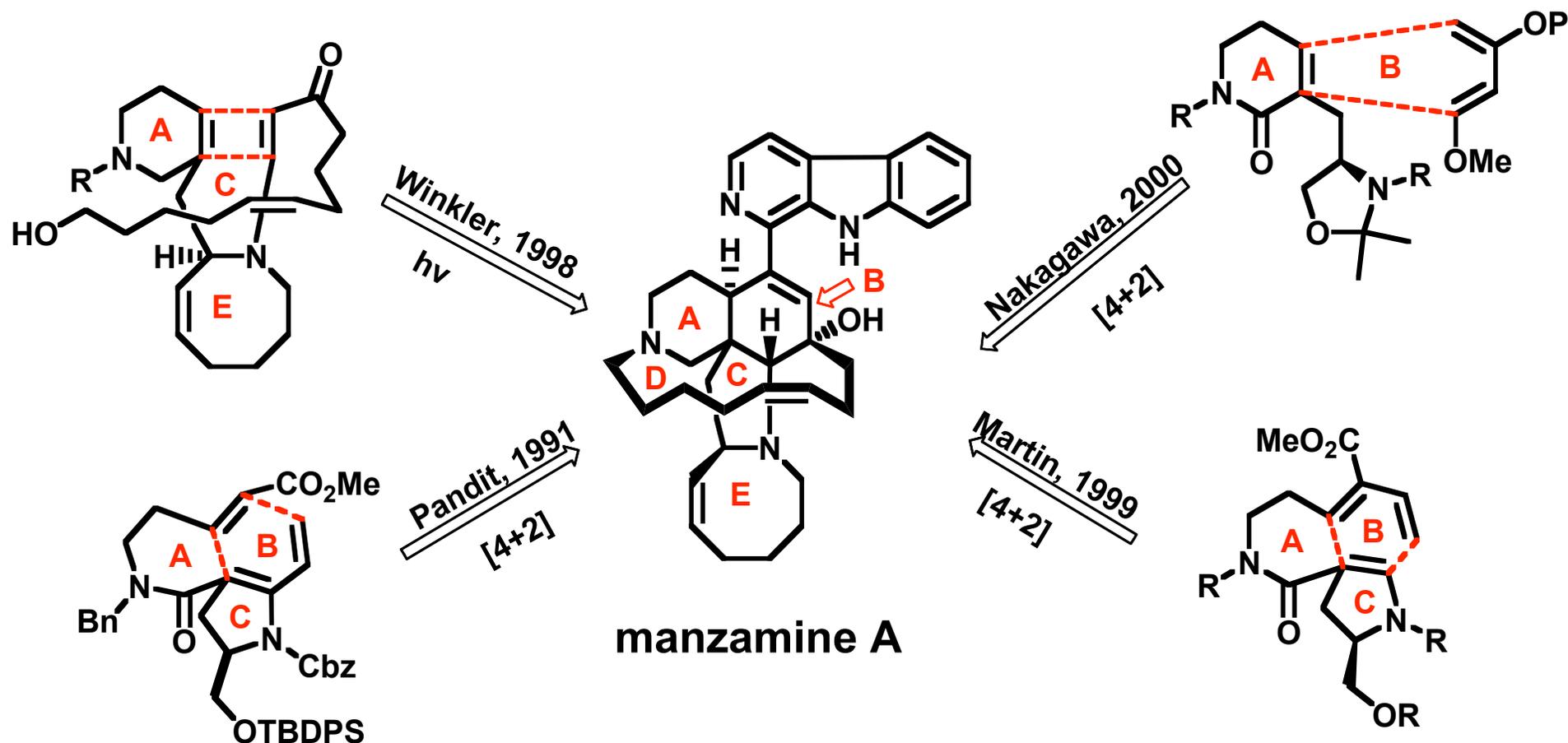


Total Syntheses of Manzamine A.



Ramil Baiazitov. SED group meeting. February 21, 2006

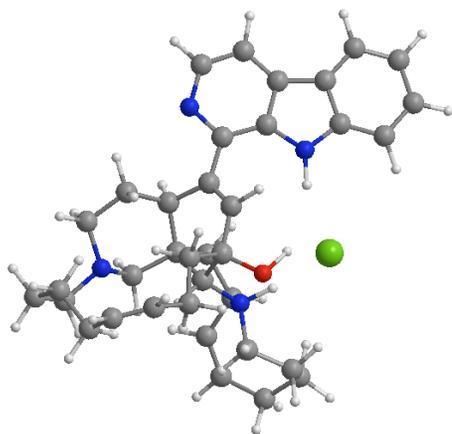
Manzamine A



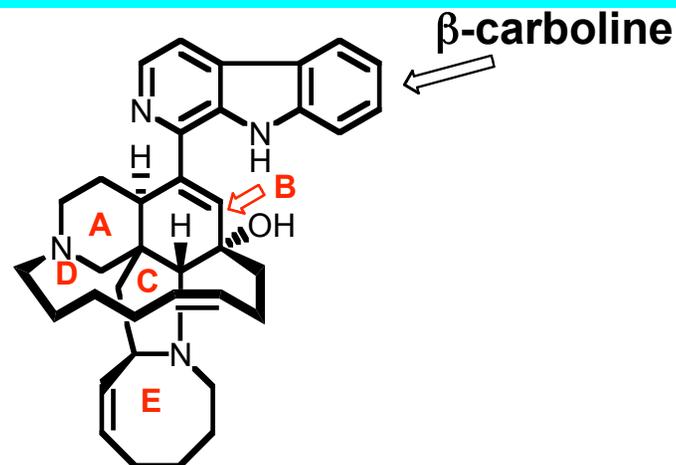
Haliclona (Sigmadocia) caerulea
Blue Caribbean sponge

Caribbean and Hawaiian Islands

Isolated: Higa, T. et al *JACS*, 1986, 108, 6404



X-ray of
HCl salt



manzamine A

$C_{36}H_{44}N_4O$

Exact Mass: 548.3515

Rings:

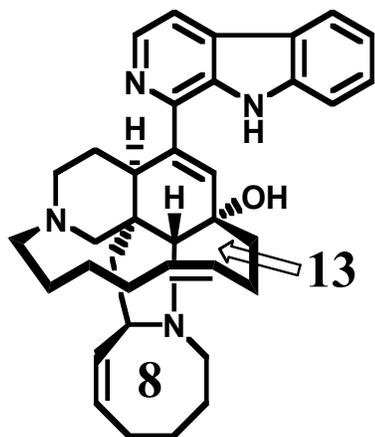
eight total, five aliphatic (ABCDE),
one 13-membered, one 8-membered,
 β -carboline

Two Z-double C-C bonds

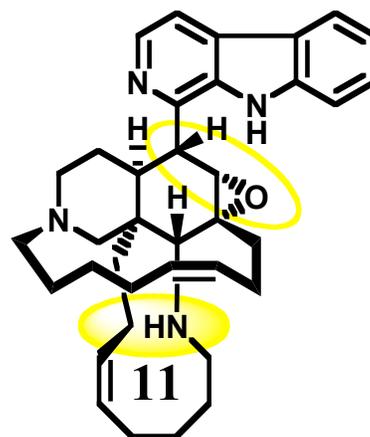
Stereocenters:

five on carbon, four contiguous,
one quaternary, one tetrasubstituted

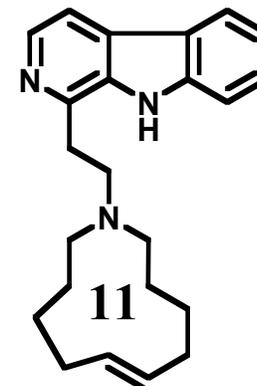
Manzamine Alkaloids



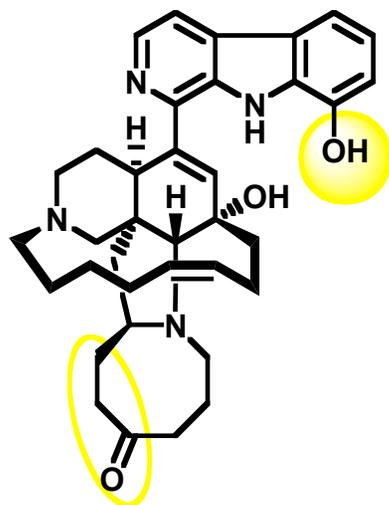
manzamine A



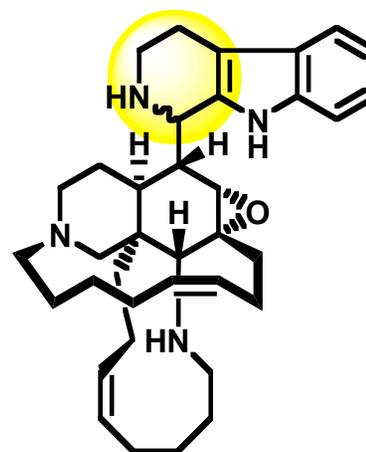
manzamine B



manzamine C

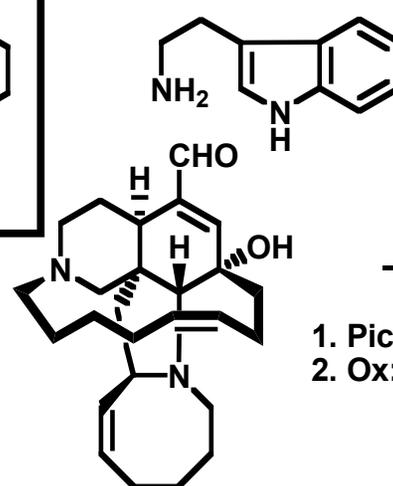
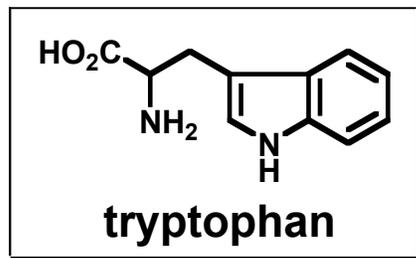
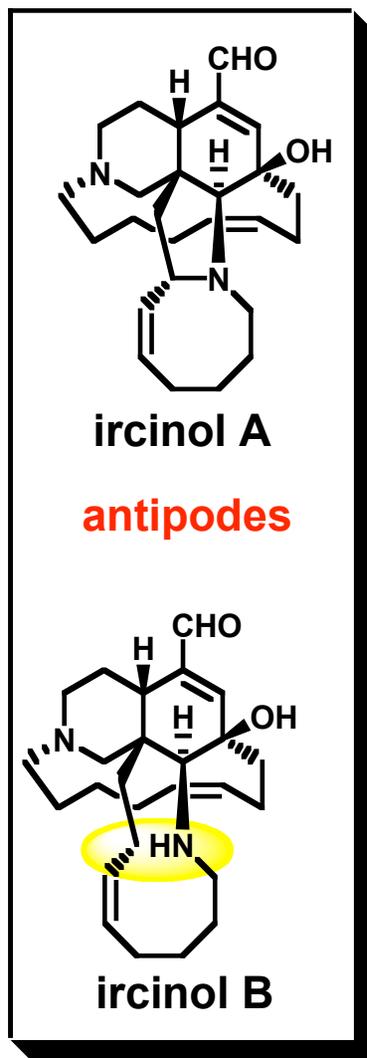


manzamine F



manzamine H

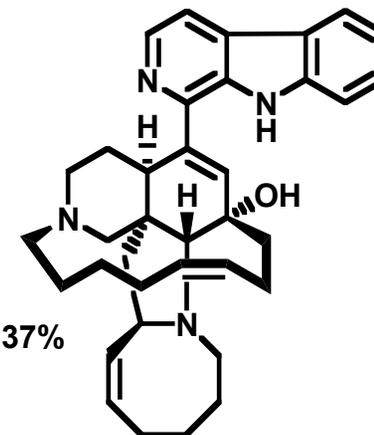
Manzamine Alkaloids



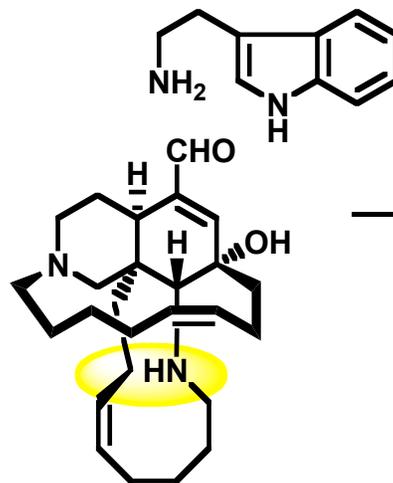
ircinal A

DDQ

1. Pictet-Spengler: 37%
2. Ox: 54%

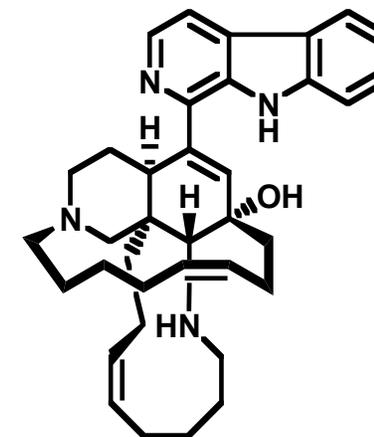


manzamine A



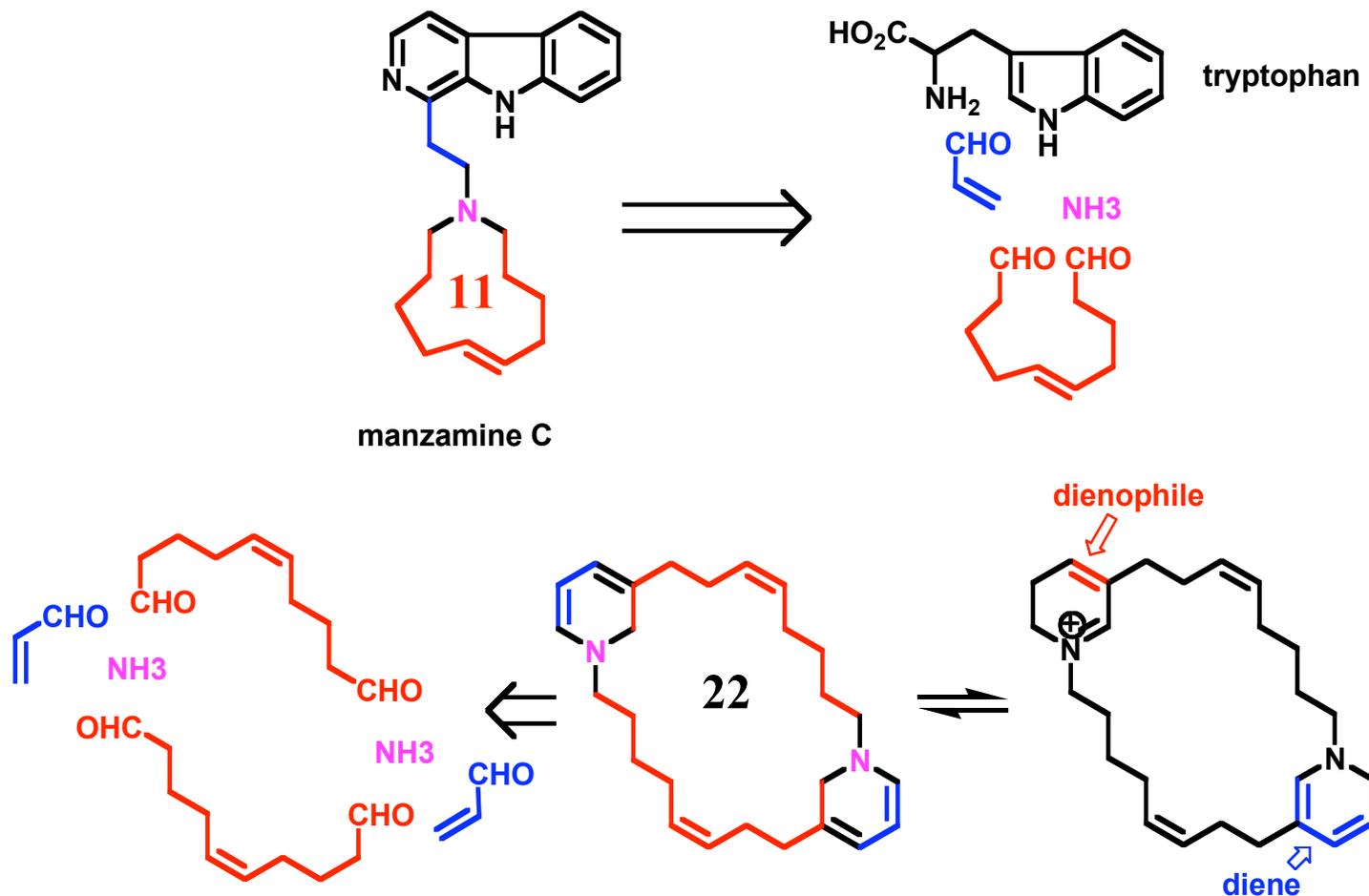
ircinal B

DDQ



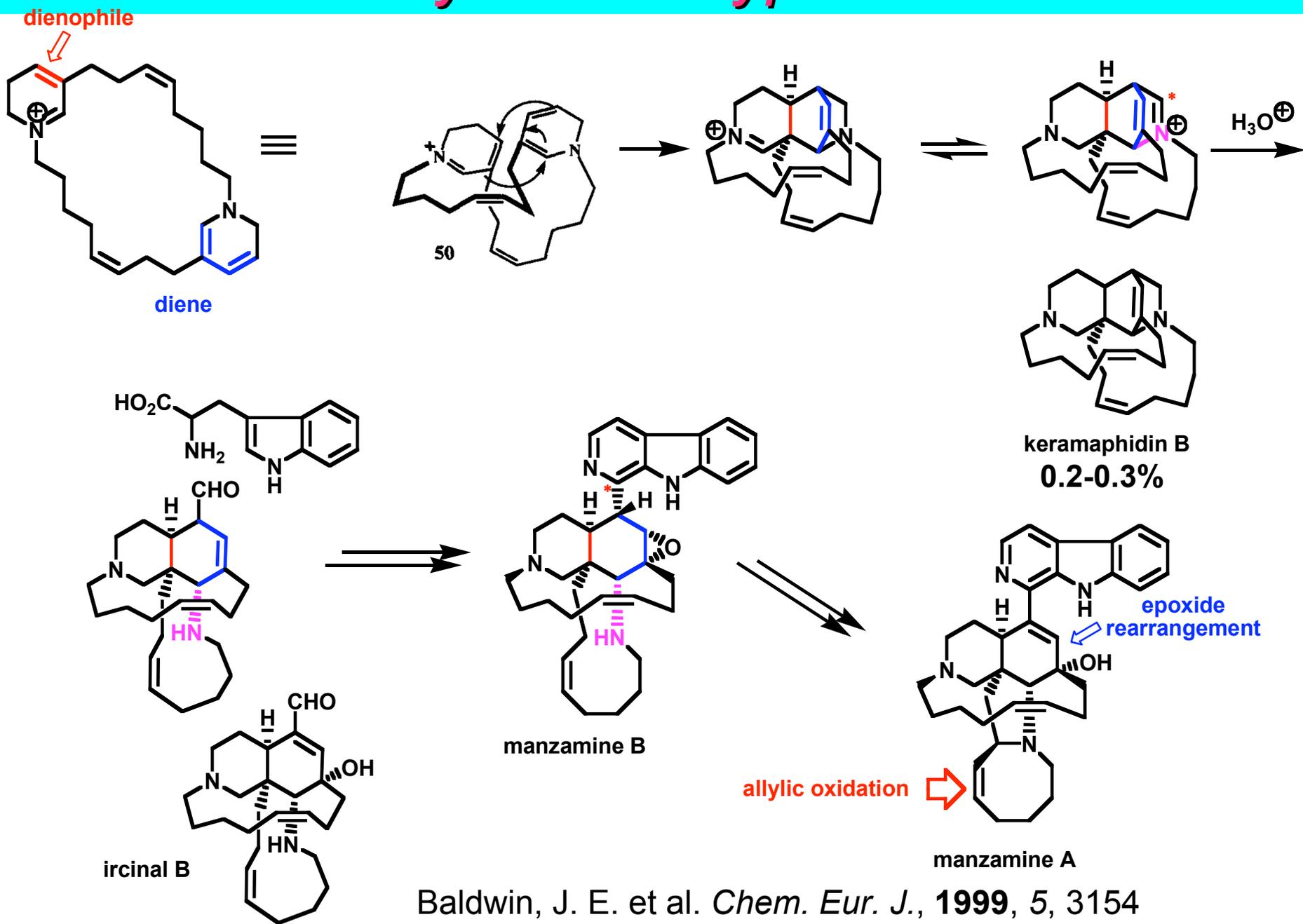
manzamine J

Biosynthetic Hypothesis



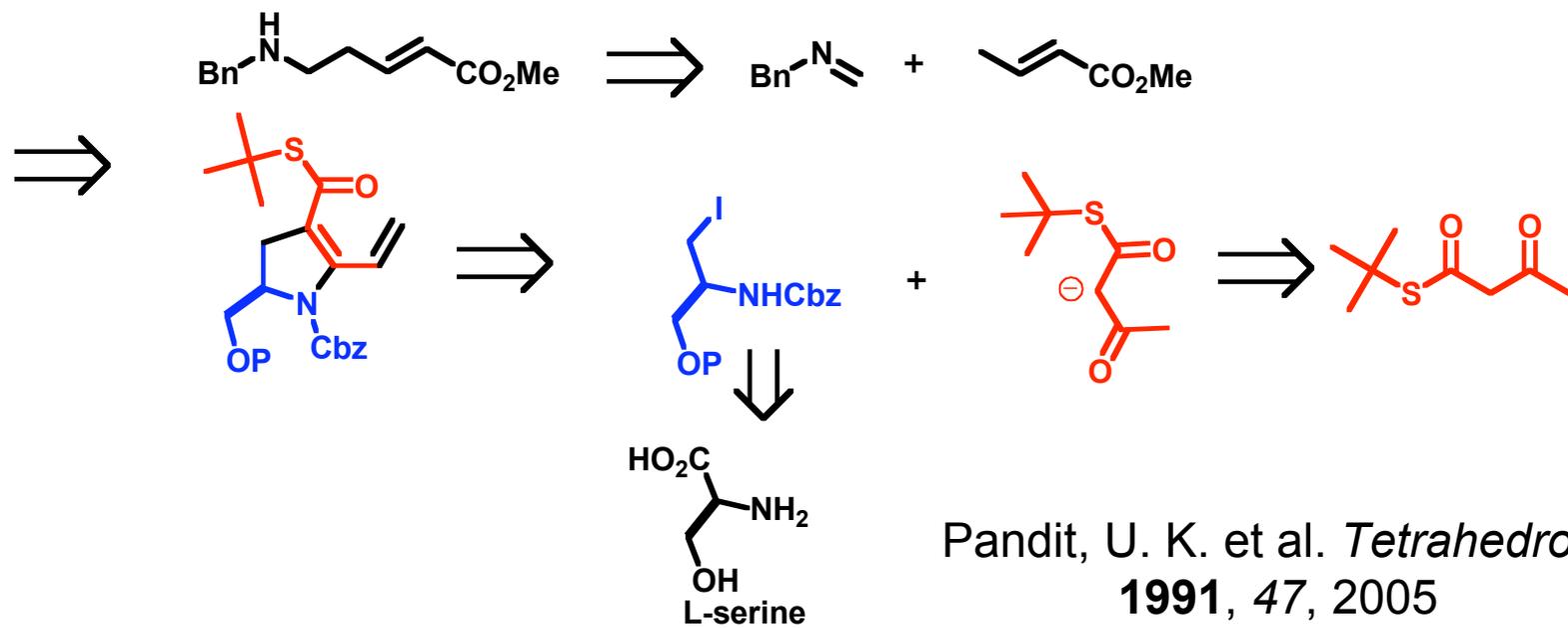
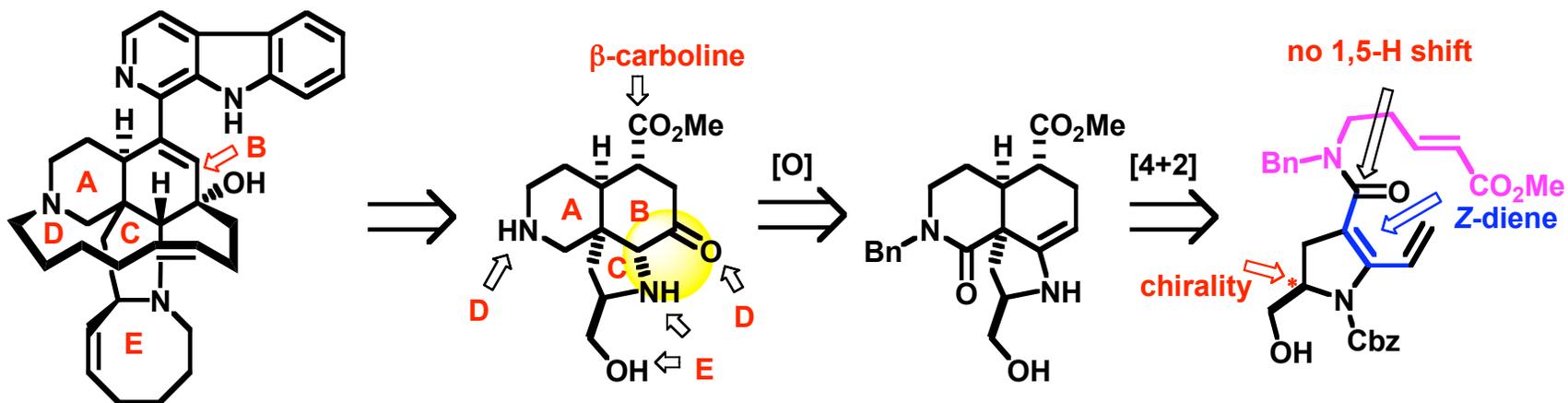
Baldwin, J. E.; Whitehead, R. C. *Tet. Lett.*, **1992**, 33, 2059

Biosynthetic Hypothesis

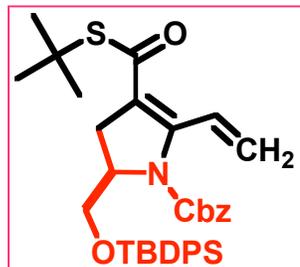


Baldwin, J. E. et al. *Chem. Eur. J.*, **1999**, 5, 3154

Pandit's Synthesis of the ABCDE fragment. Retrosynthesis.

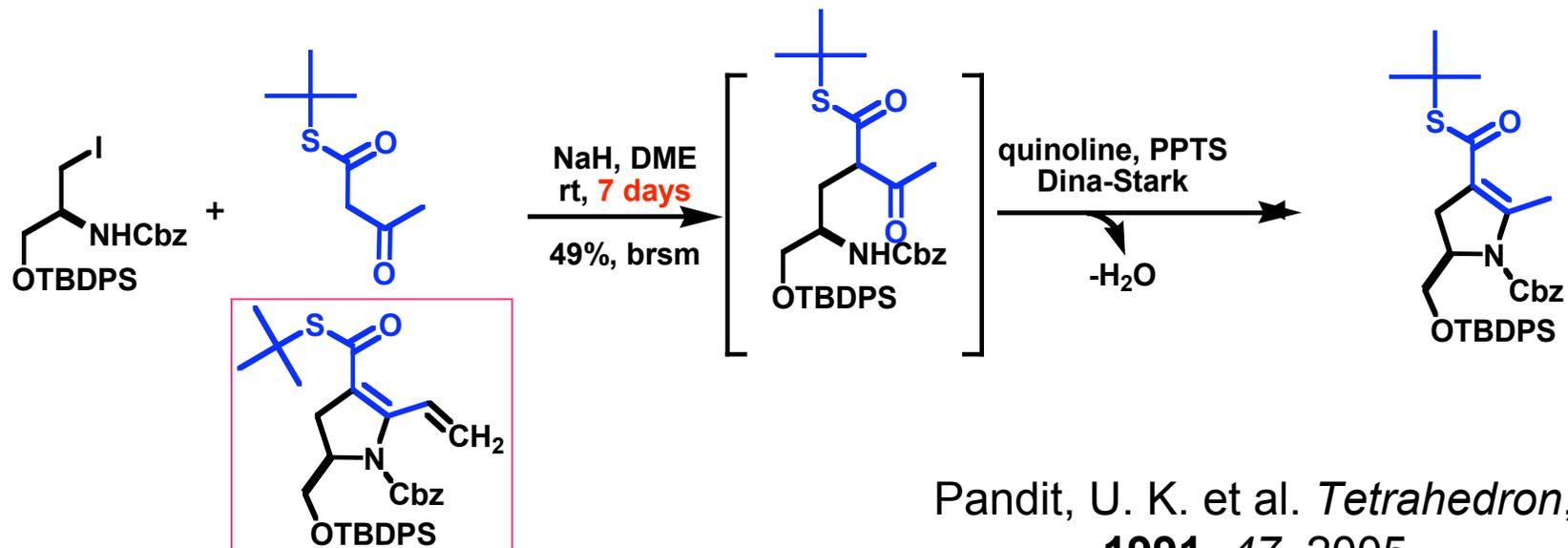
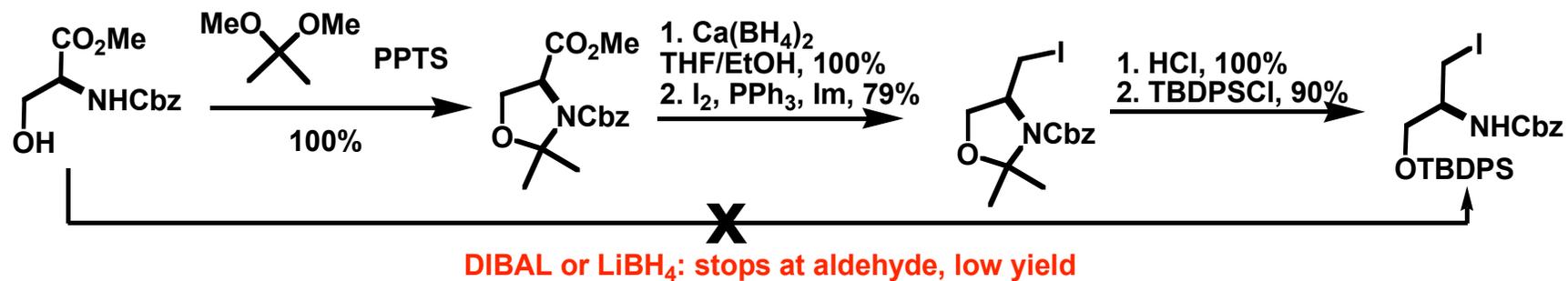


Pandit's Synthesis of the Diene.

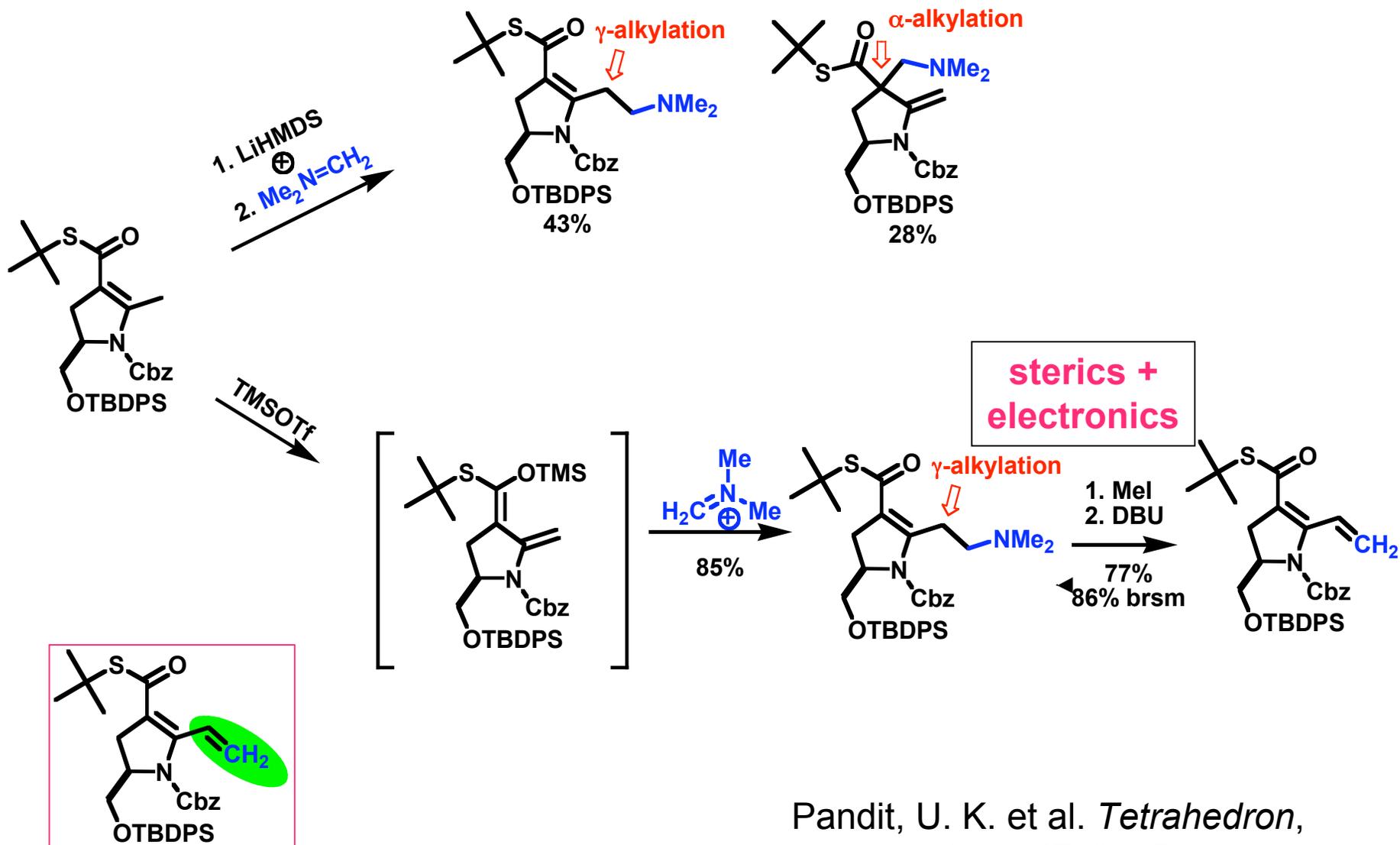


Pandit, U. K. et al. *Tetrahedron*,
1991, 47, 2005

Pandit's Synthesis of the Diene.

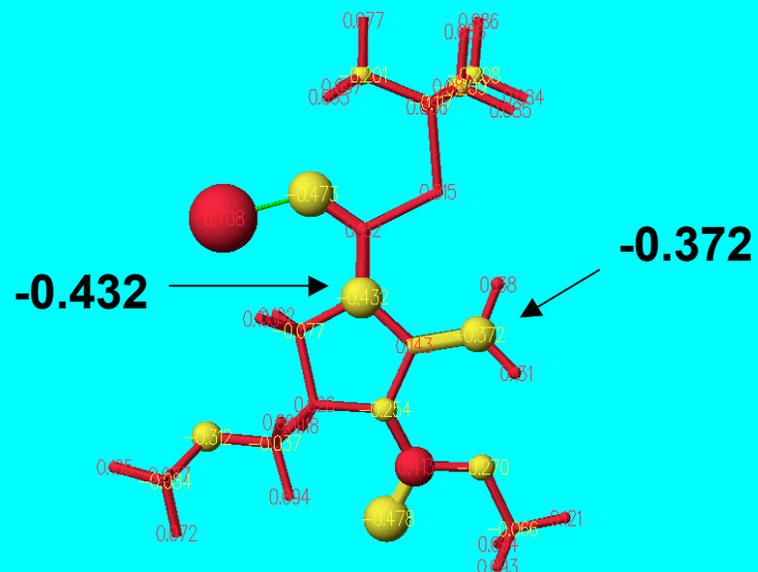
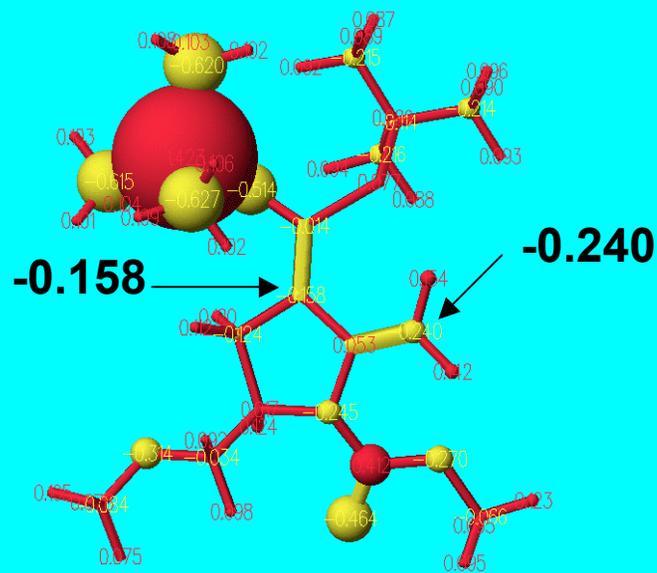
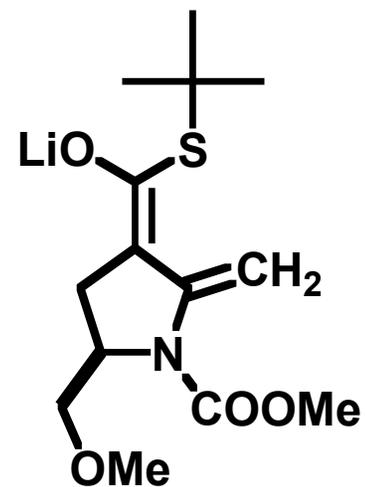
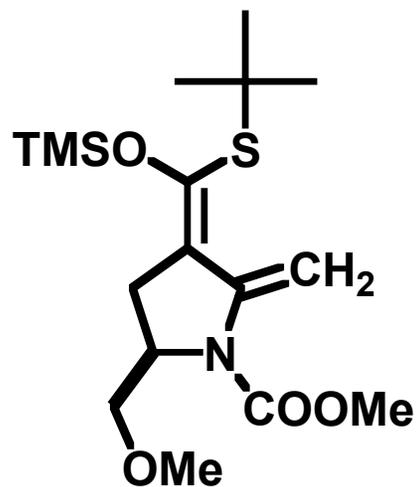


Pandit's Synthesis of the Diene. Methylenation.

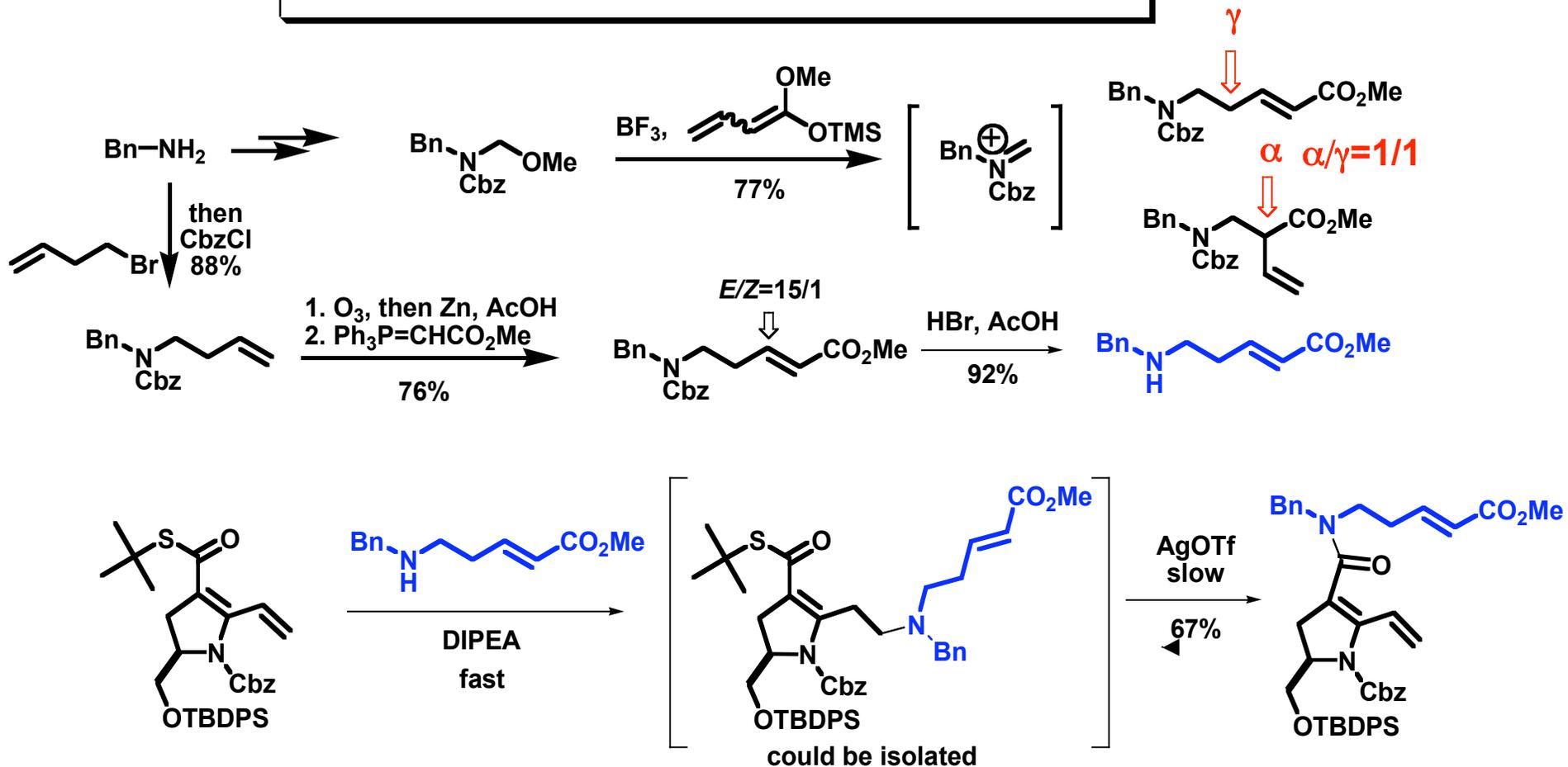
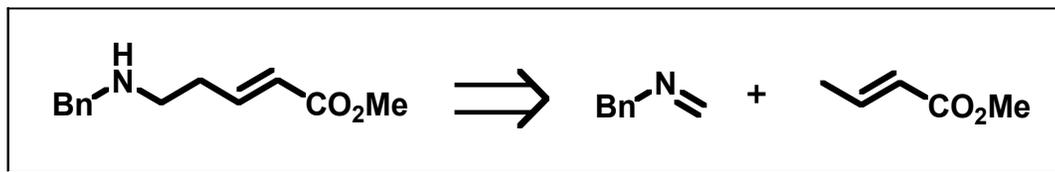


Pandit, U. K. et al. *Tetrahedron*,
1991, 47, 2005

Regioselectivity (α vs. γ)

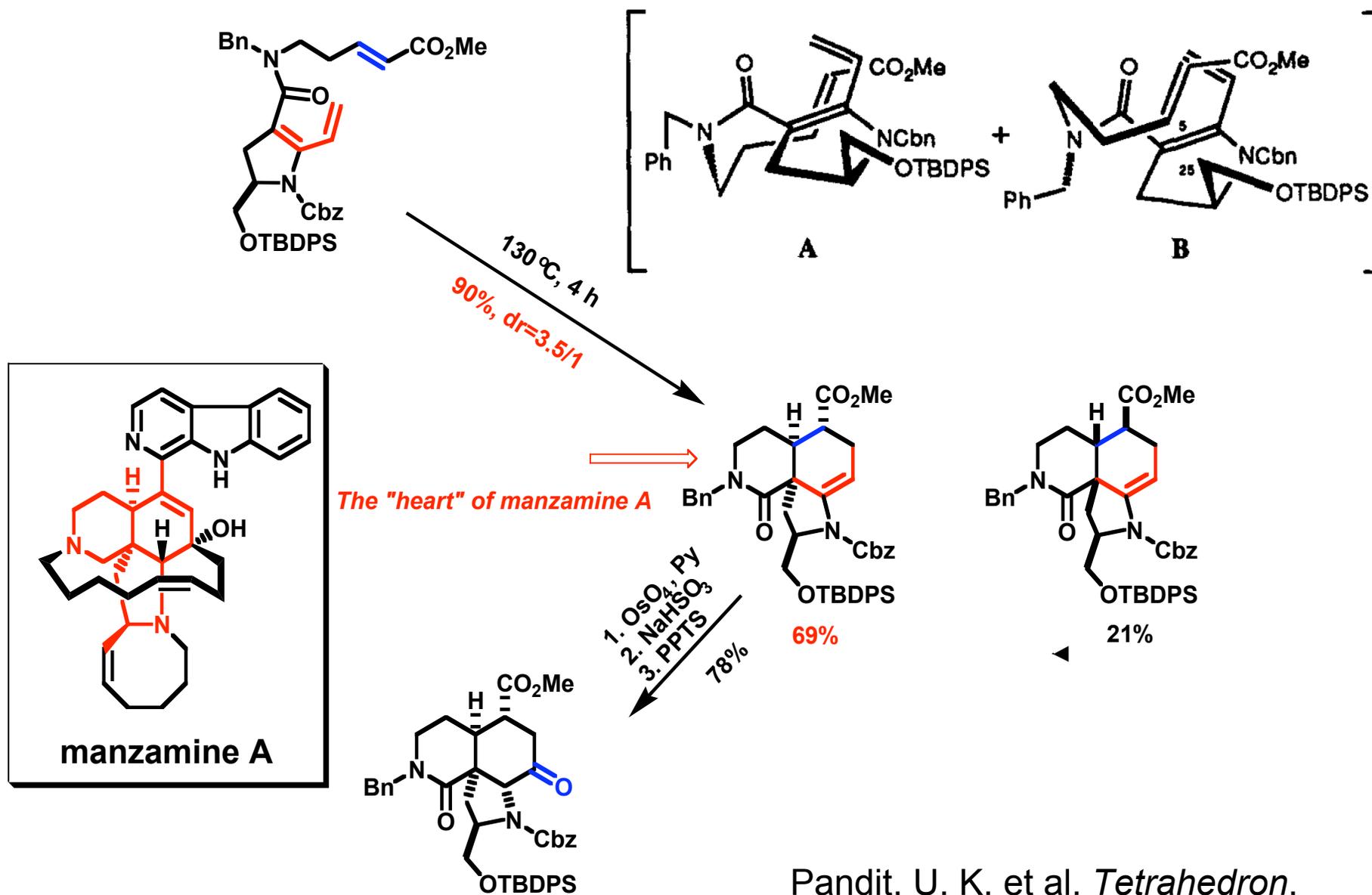


Pandit's Synthesis of the DA-Substrate.



Pandit, U. K. et al. *Tetrahedron*,
1991, 47, 2005

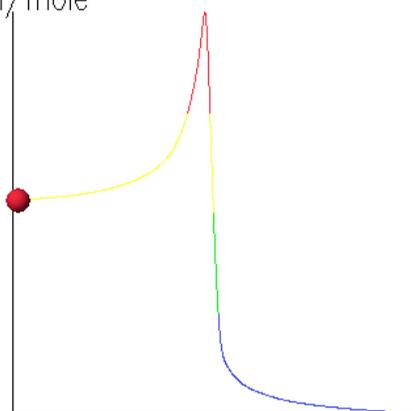
Pandit. Making the "Heart" of Manzamine A.



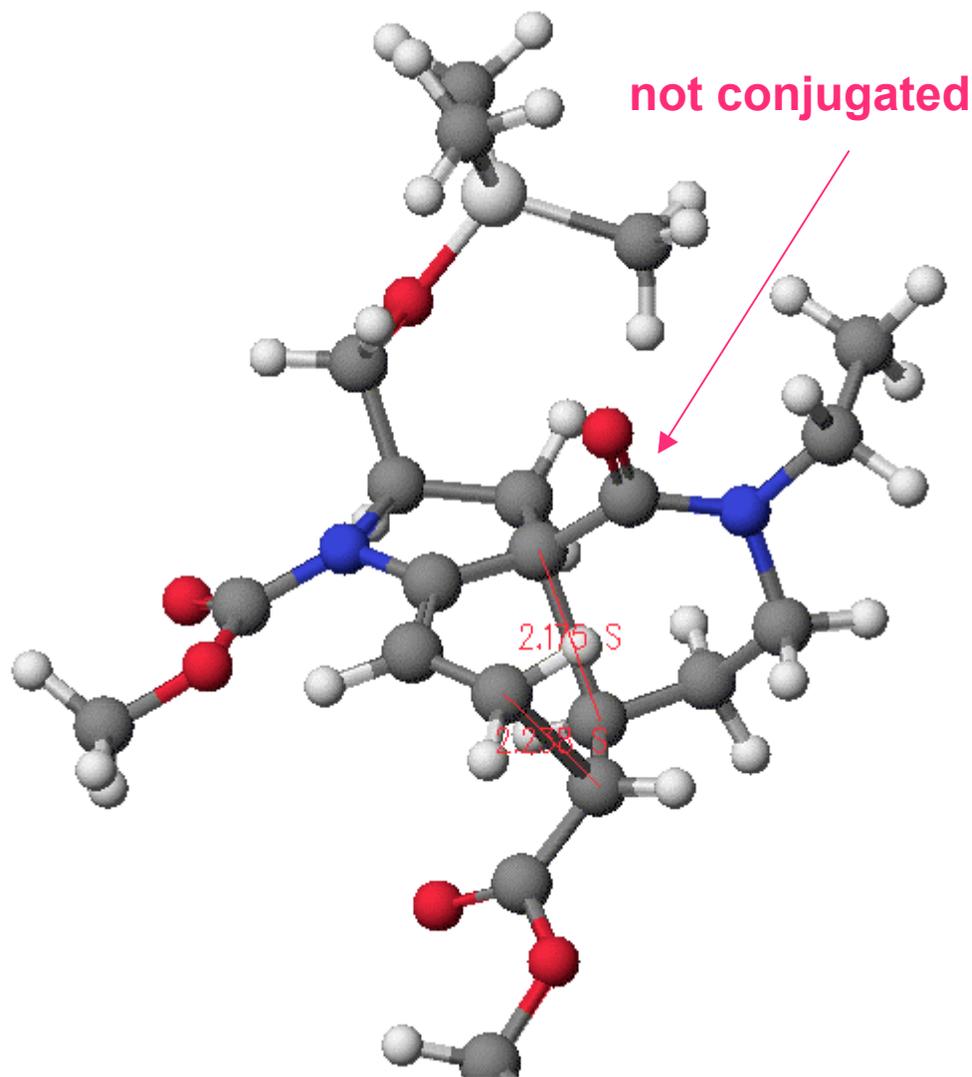
Pandit, U. K. et al. *Tetrahedron*,
1991, 47, 2005

The Transition State.

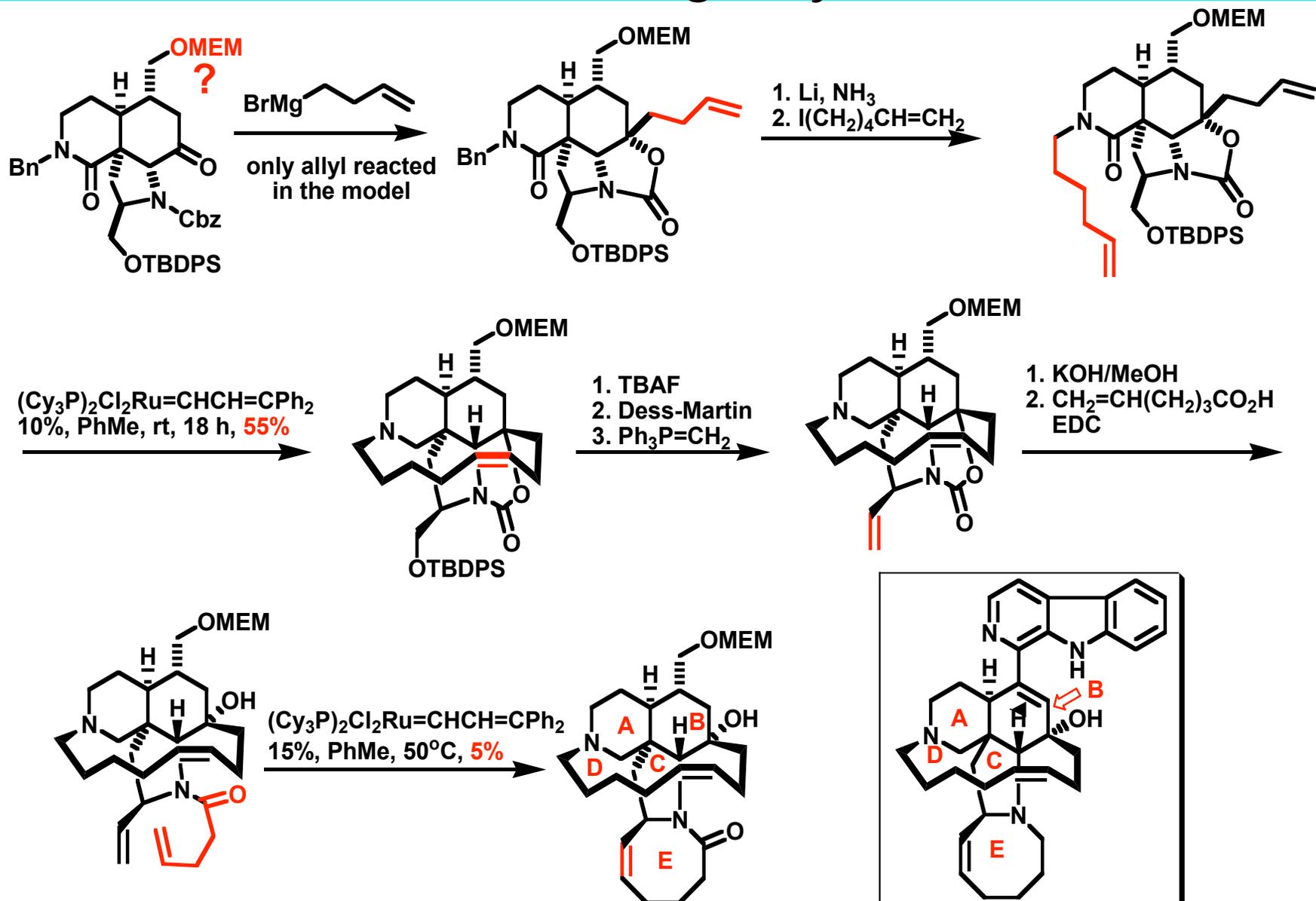
Potential_Energy
-306.24 to
-234.71 kcal/mole



Distance
0.04 to
53.76 Angstroms

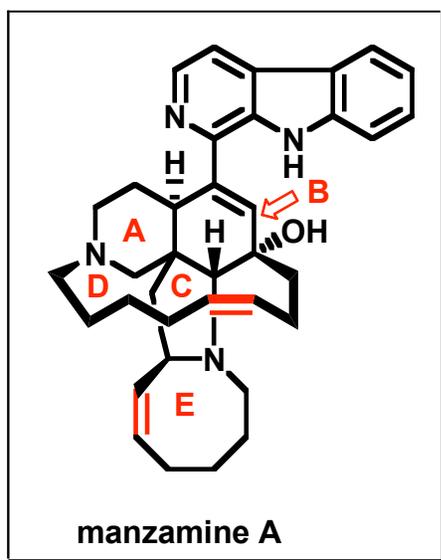
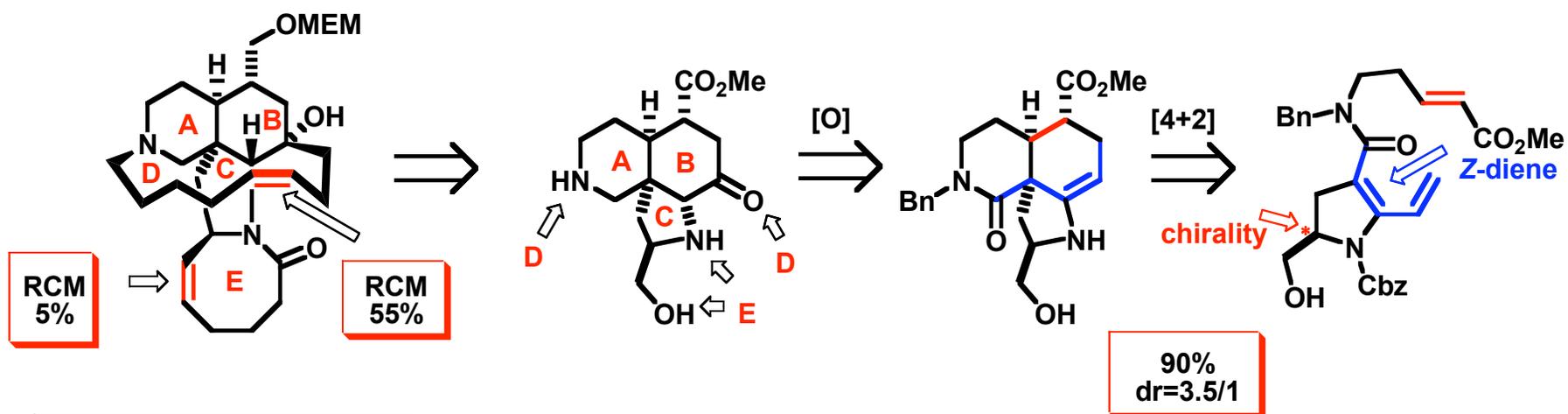


Pandit. DE Rings Synthesis.

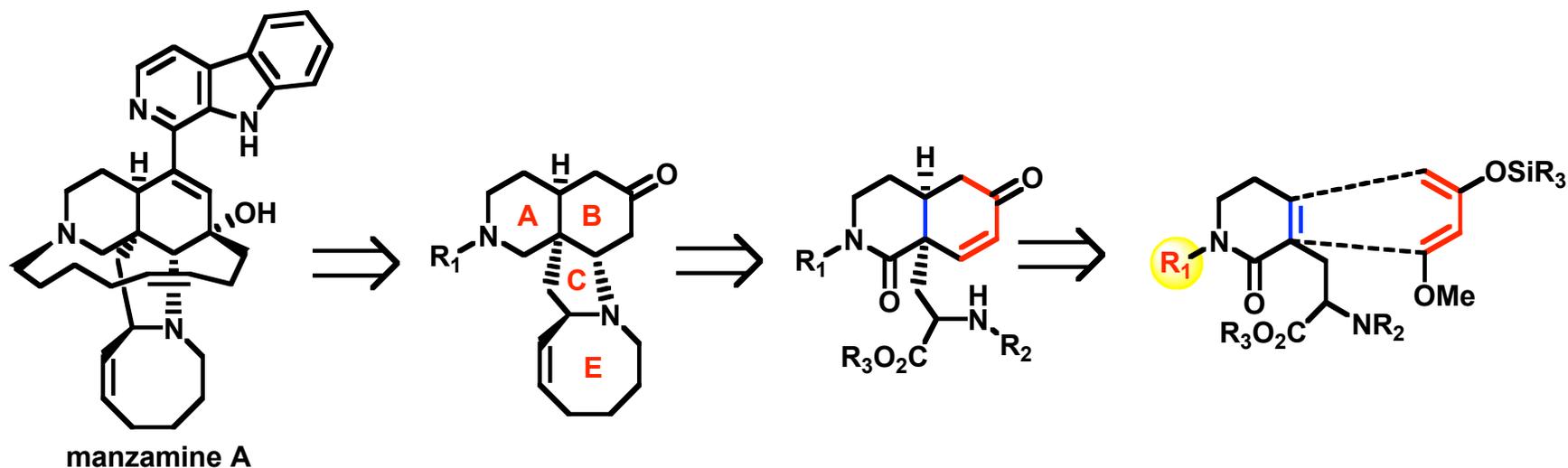


Pandit, U. K. et al. *Pure&Appl. Chem.* First synthesis of the ABCDE system
 1996, 68, 659

Pandit's Synthesis of the ABCDE fragment. Summary.



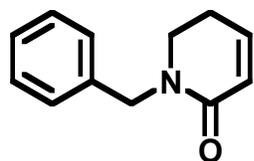
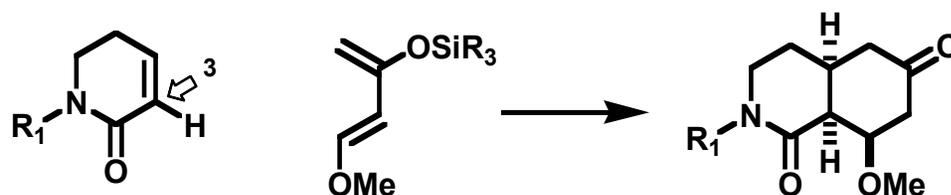
Nakagawa's *ABCE* Synthesis. Retrosynthesis.



How does the substituent **R₁** on the nitrogen effect the electrophilicity of the dienophile?

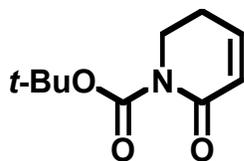
Nakagawa's Total Synthesis. Models.

electronics of the 3-unsubstituted dienophile



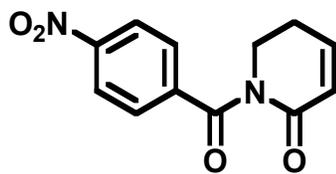
HOMO: -9.314
LUMO: -0.026

xylene, reflux, 5 h
NR



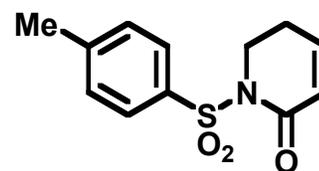
HOMO: -9.907
LUMO: -0.295

xylene, reflux, 5 h
NR



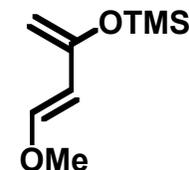
HOMO: -10.165
LUMO: -1.684

xylene, reflux, 5 h
57%



HOMO: -10.201
LUMO: -0.629

xylene, reflux, 5 h
50%

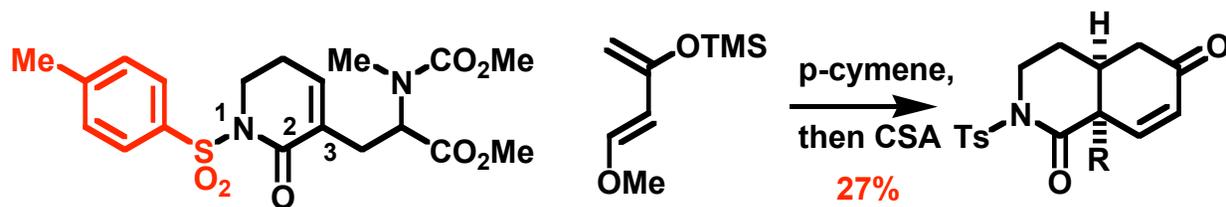
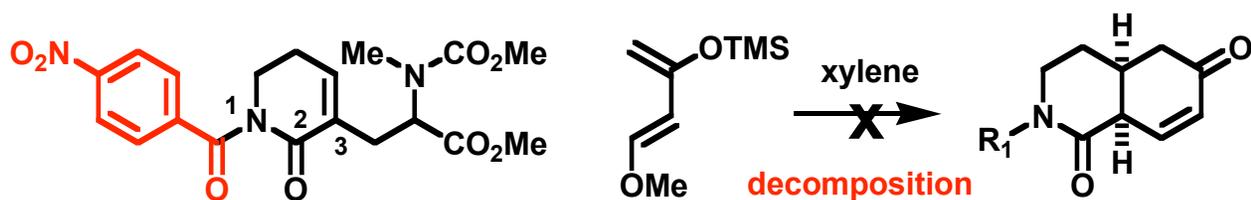


HOMO: -8.416
LUMO: 0.653

How e-poor the dienophile is?

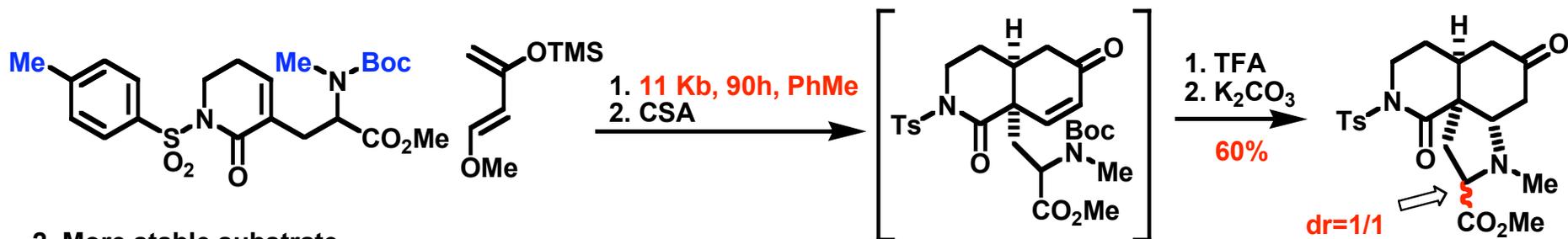
Nakagawa's Total Synthesis. Models.

3-alkyl substituted dienophile

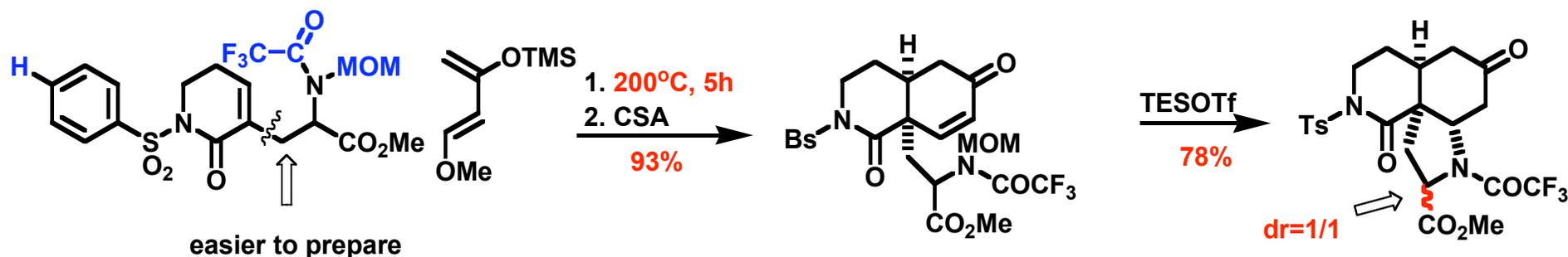


Nakagawa. Further Optimization.

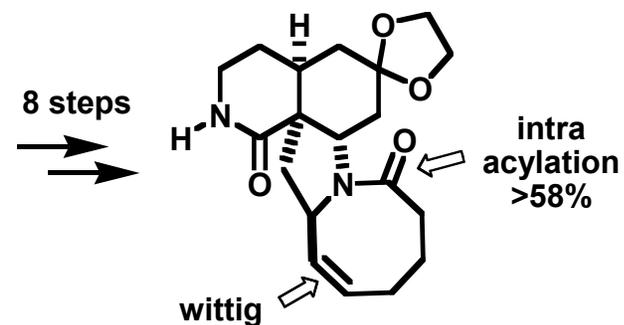
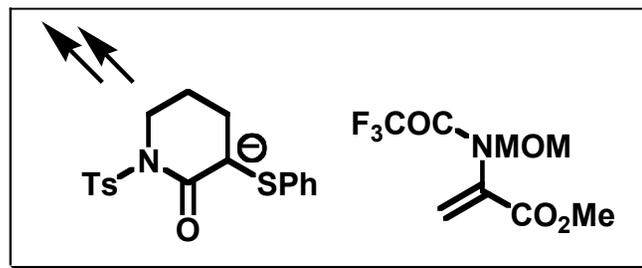
1. High Pressure DA



2. More stable substrate

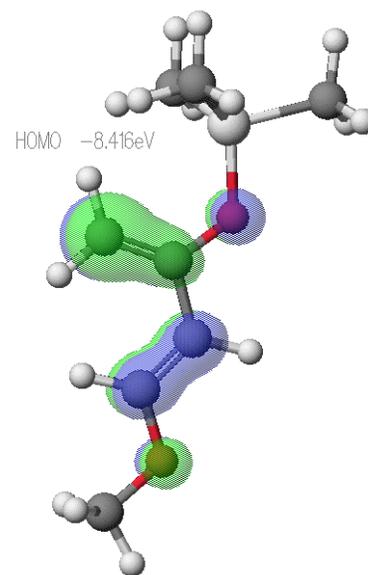
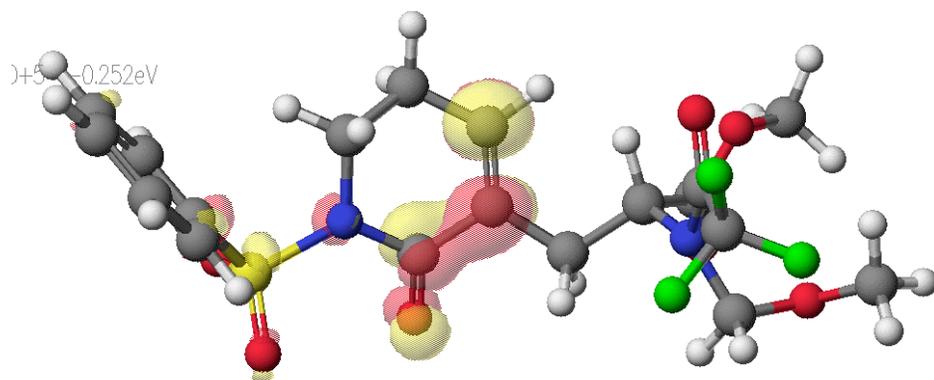
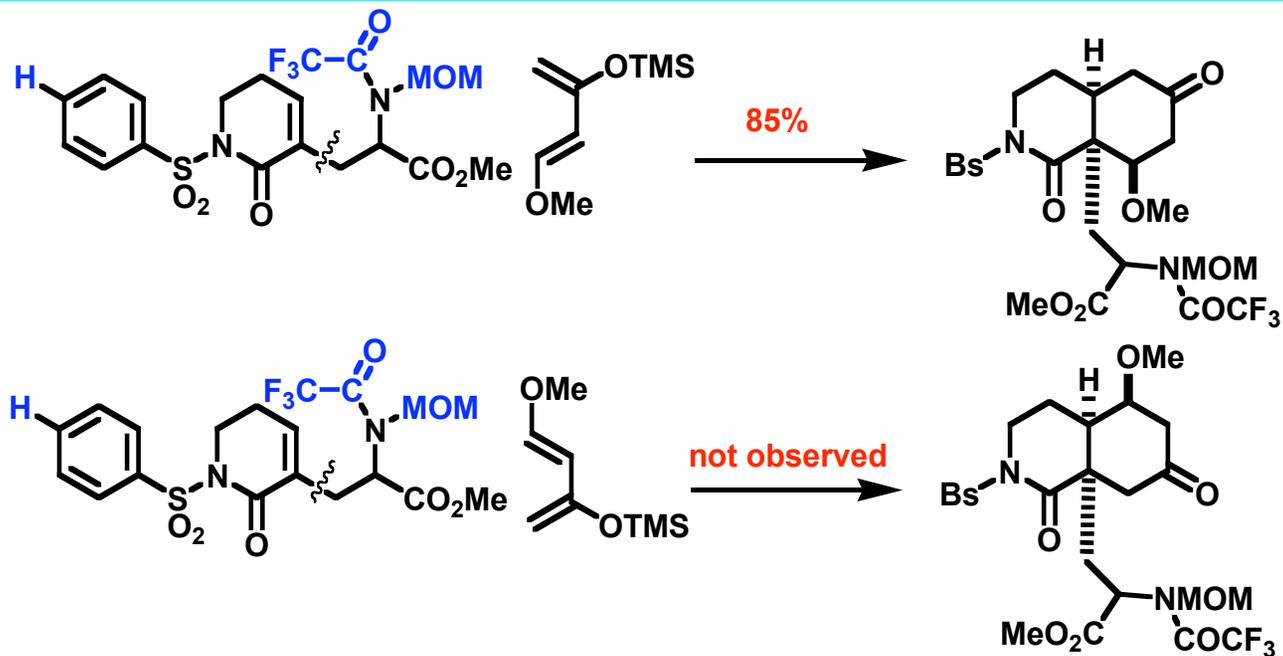


easier to prepare

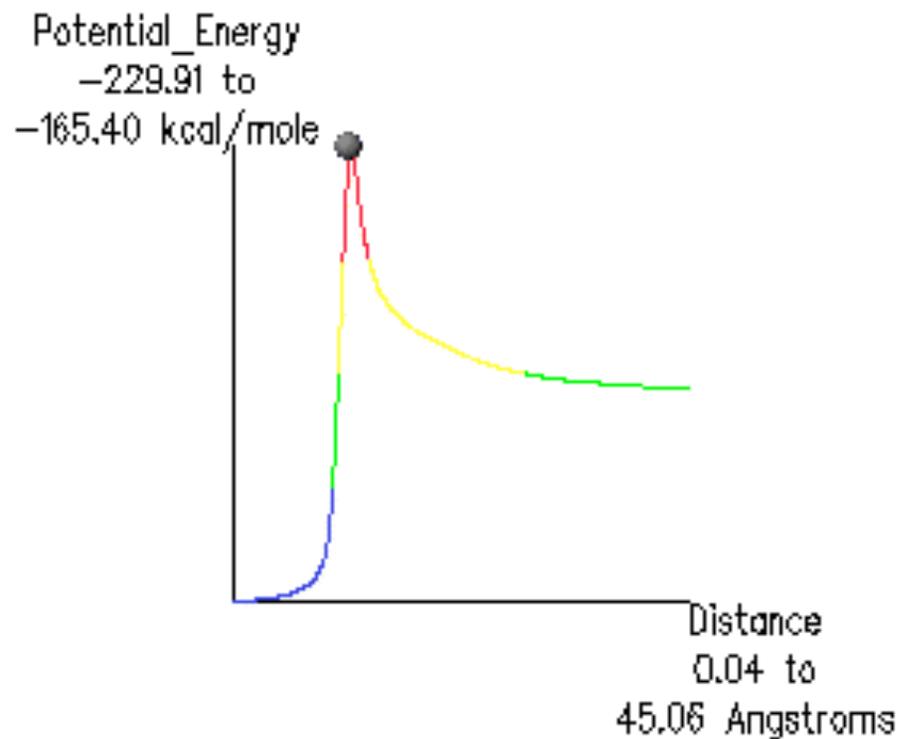
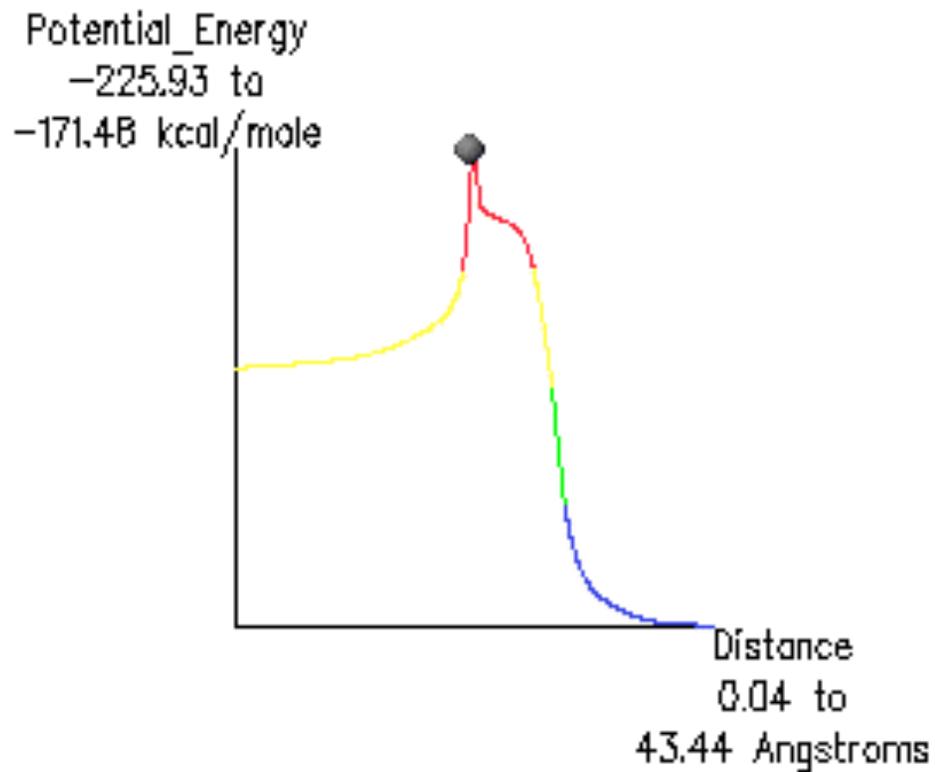
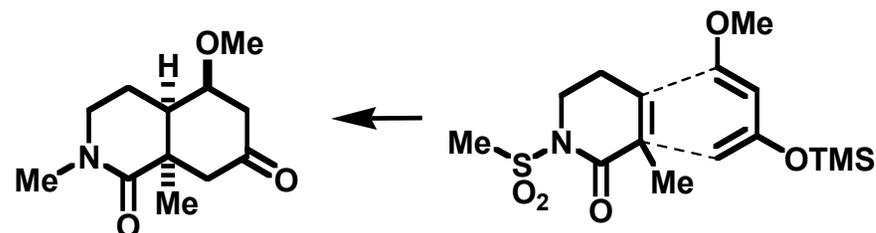
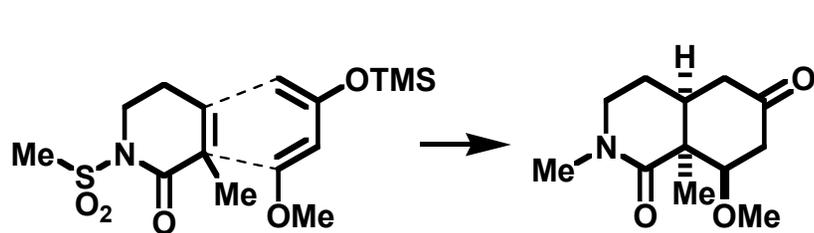


Nakagawa, M. J. *Heterocyclic Chem.*,
2000, 37, 567

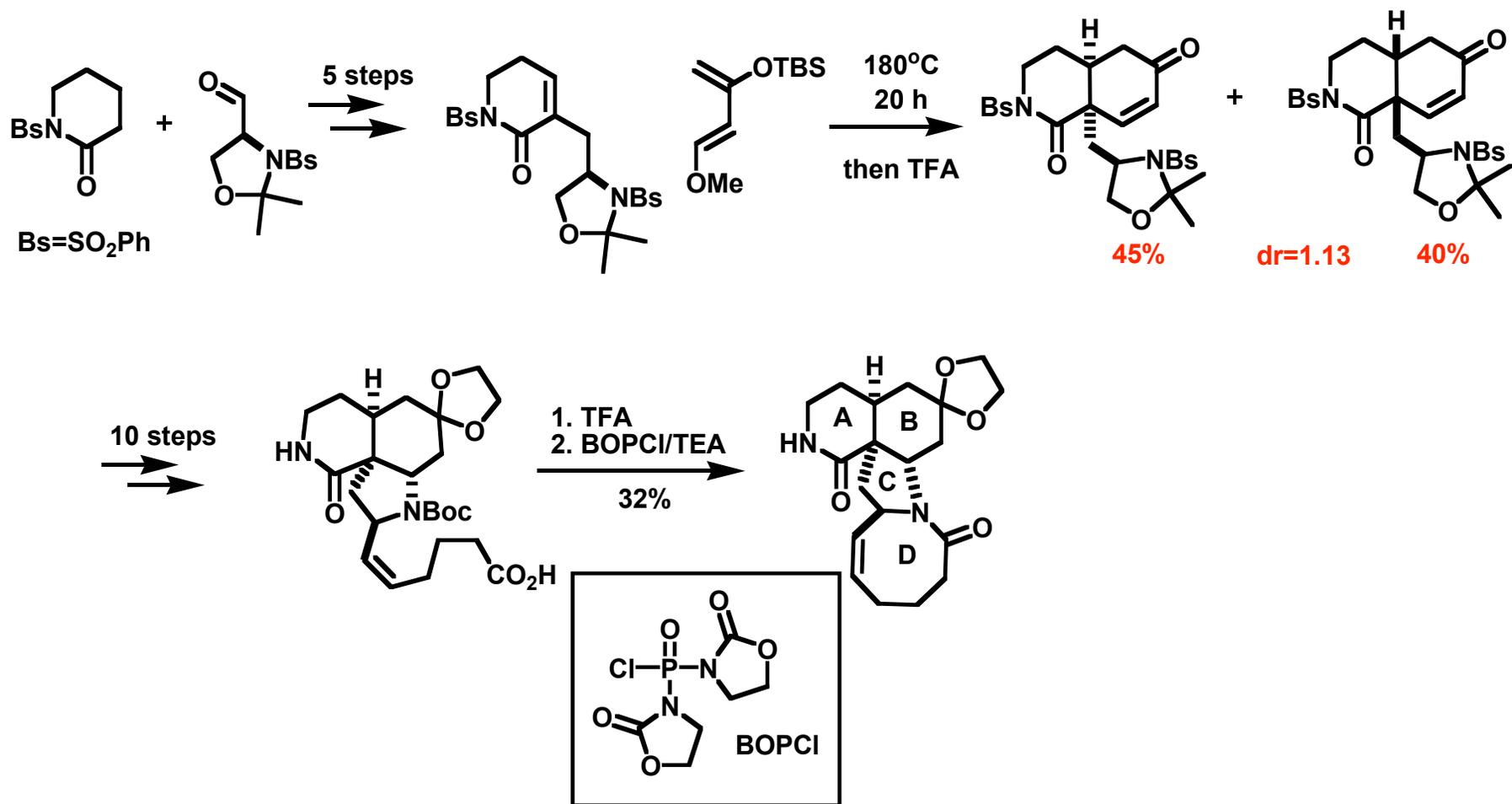
Nakagawa. Regioselectivity.



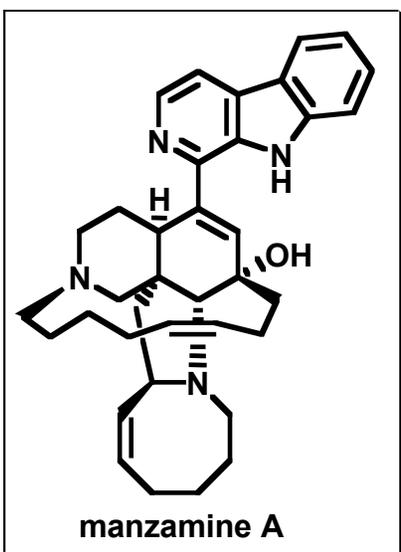
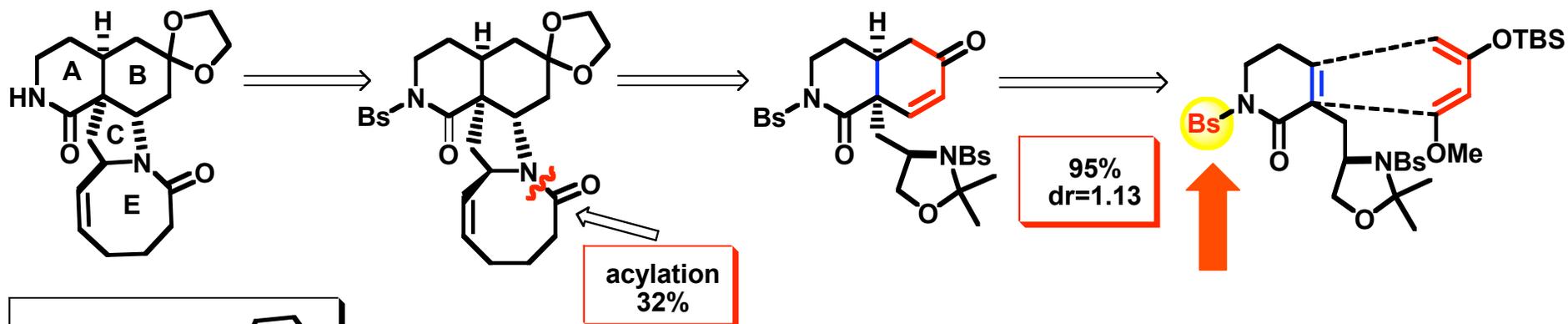
Nakagawa. Regioselectivity.



Nakagawa. Use of "Optically Pure" Dienophile.



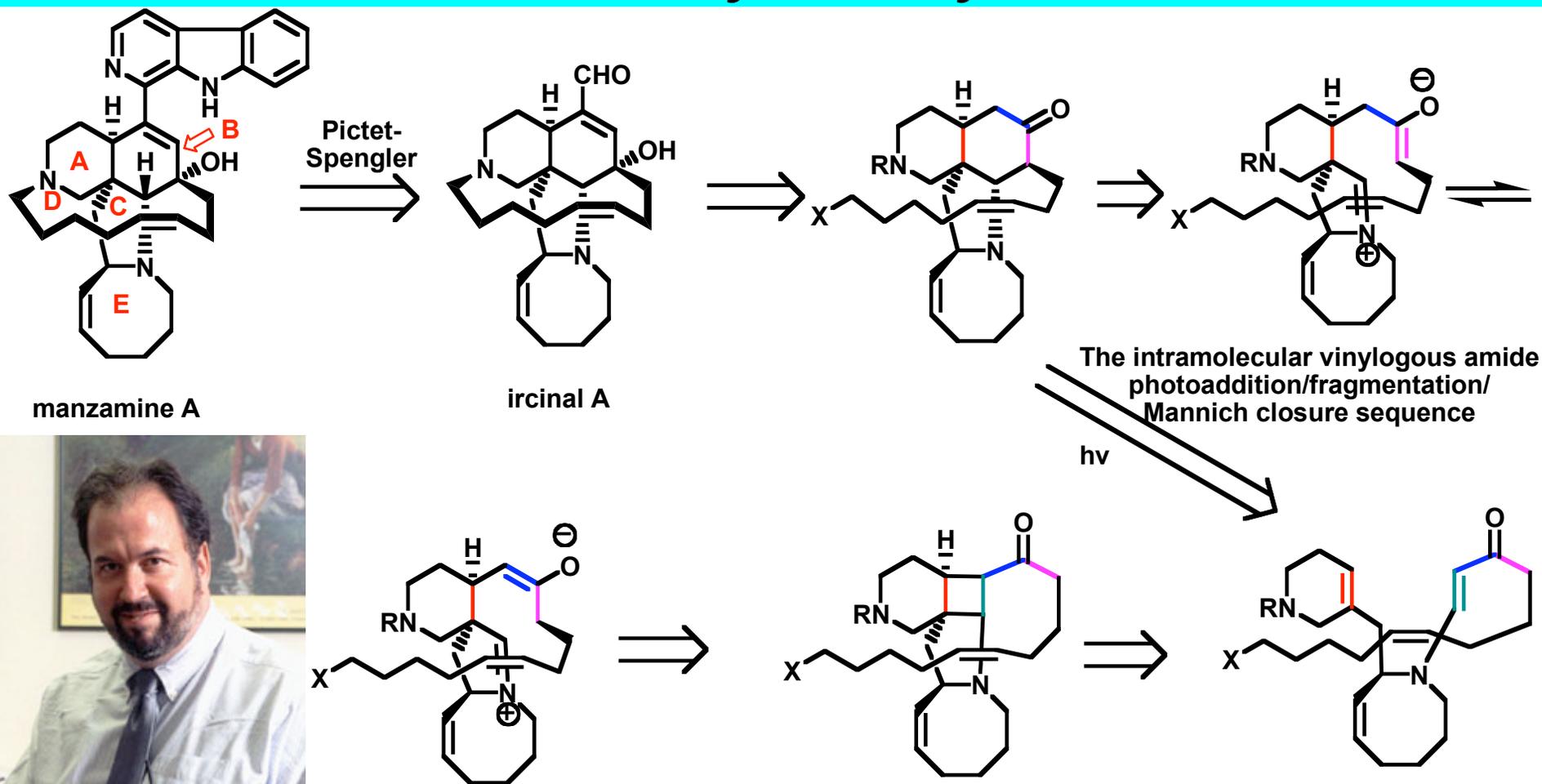
Nakagawa's ABCE Synthesis. Summary.



e-withdrawing protective group (**sulfamide**)
on the lactam is necessary to activate the dienophile

very poor diastereoselectivity

Winkler's Total Synthesis of Manzamine A. Retrosynthesis.

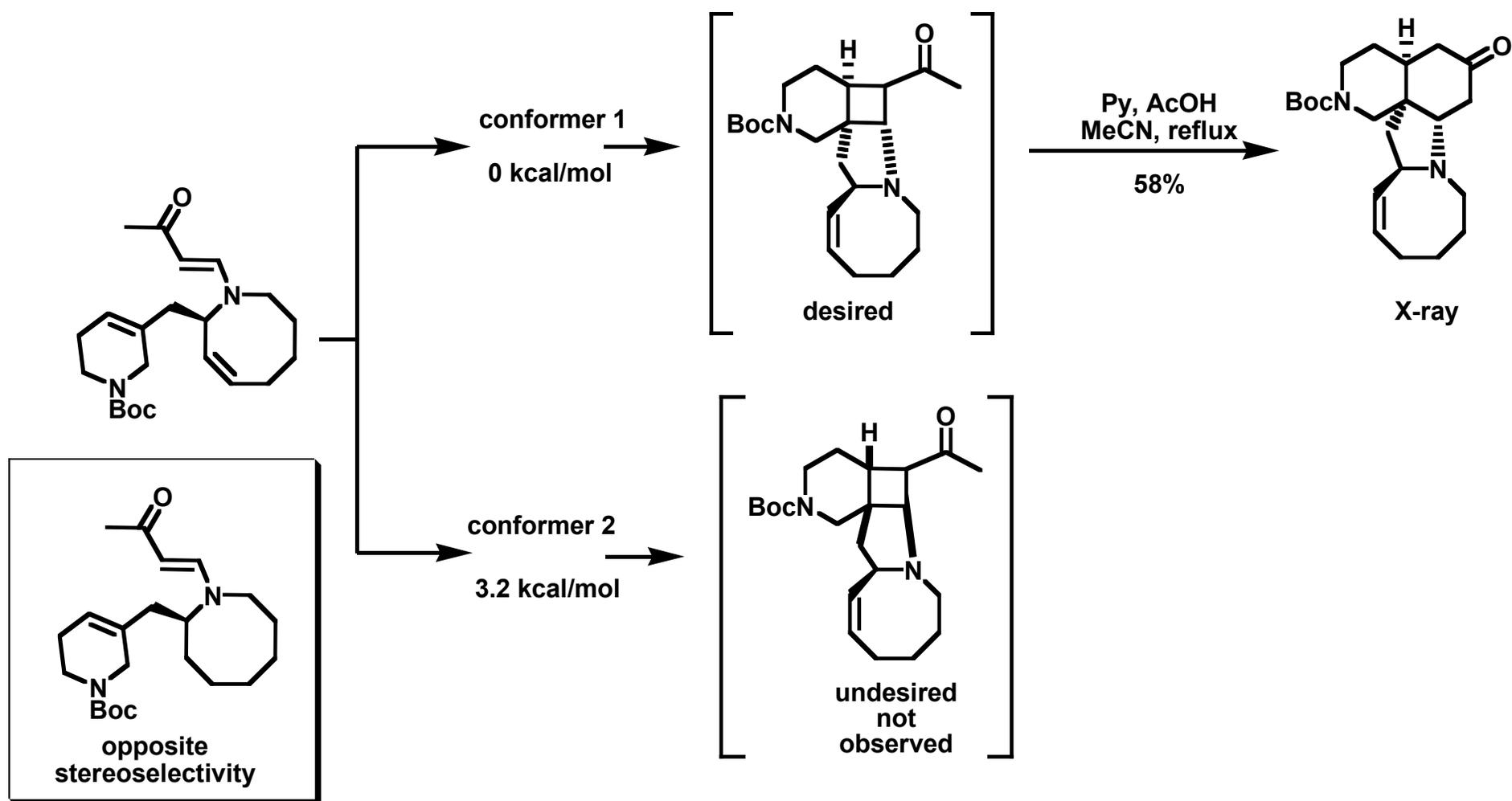


Prof. Jeffrey D. Winkler

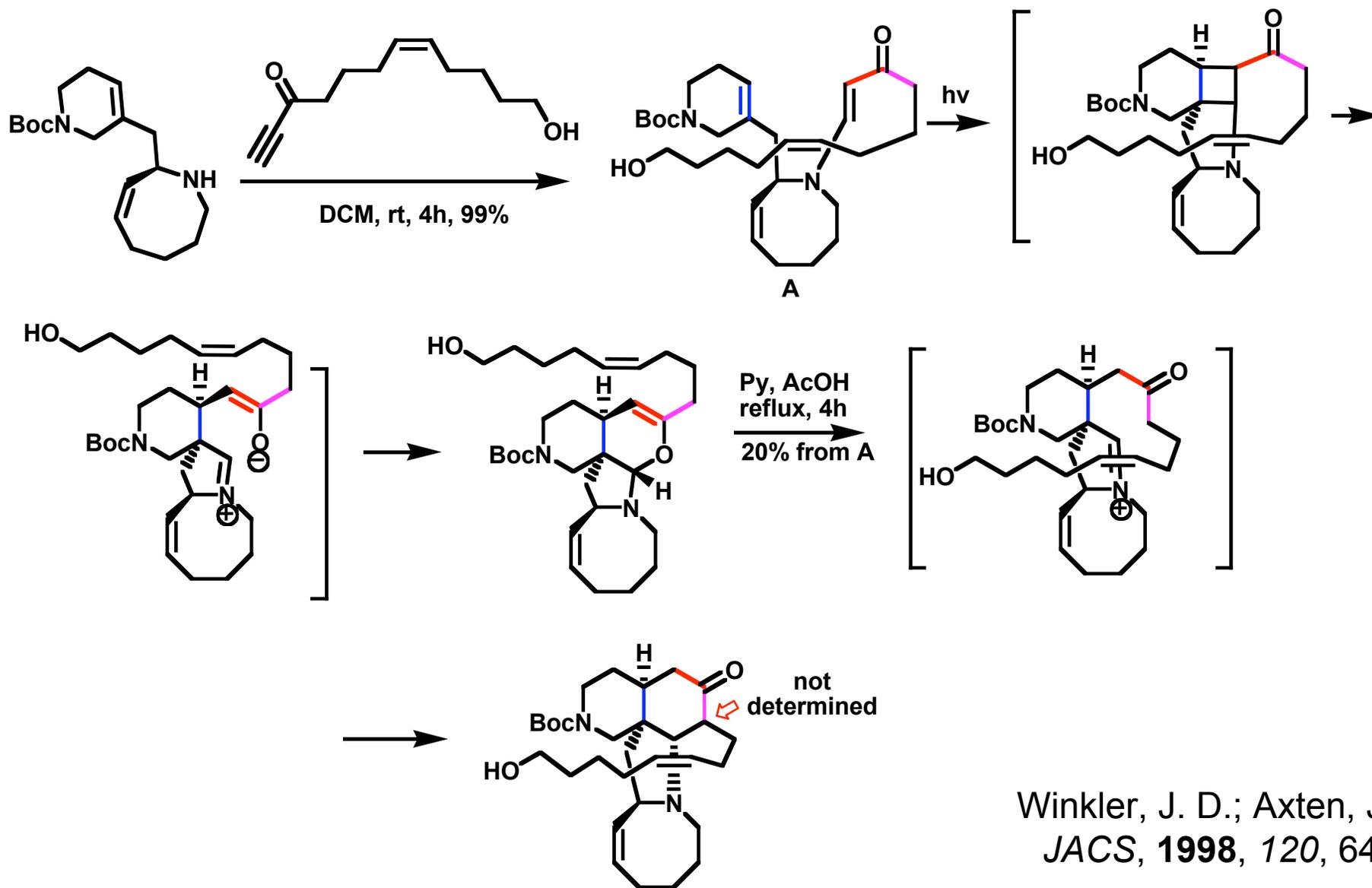
University of Pennsylvania, Philadelphia

Winkler, J. D.; Axten, J. M. *JACS*, **1998**, *120*, 6425

Photoaddition/fragmentation/Mannich closure sequence. Model Study.

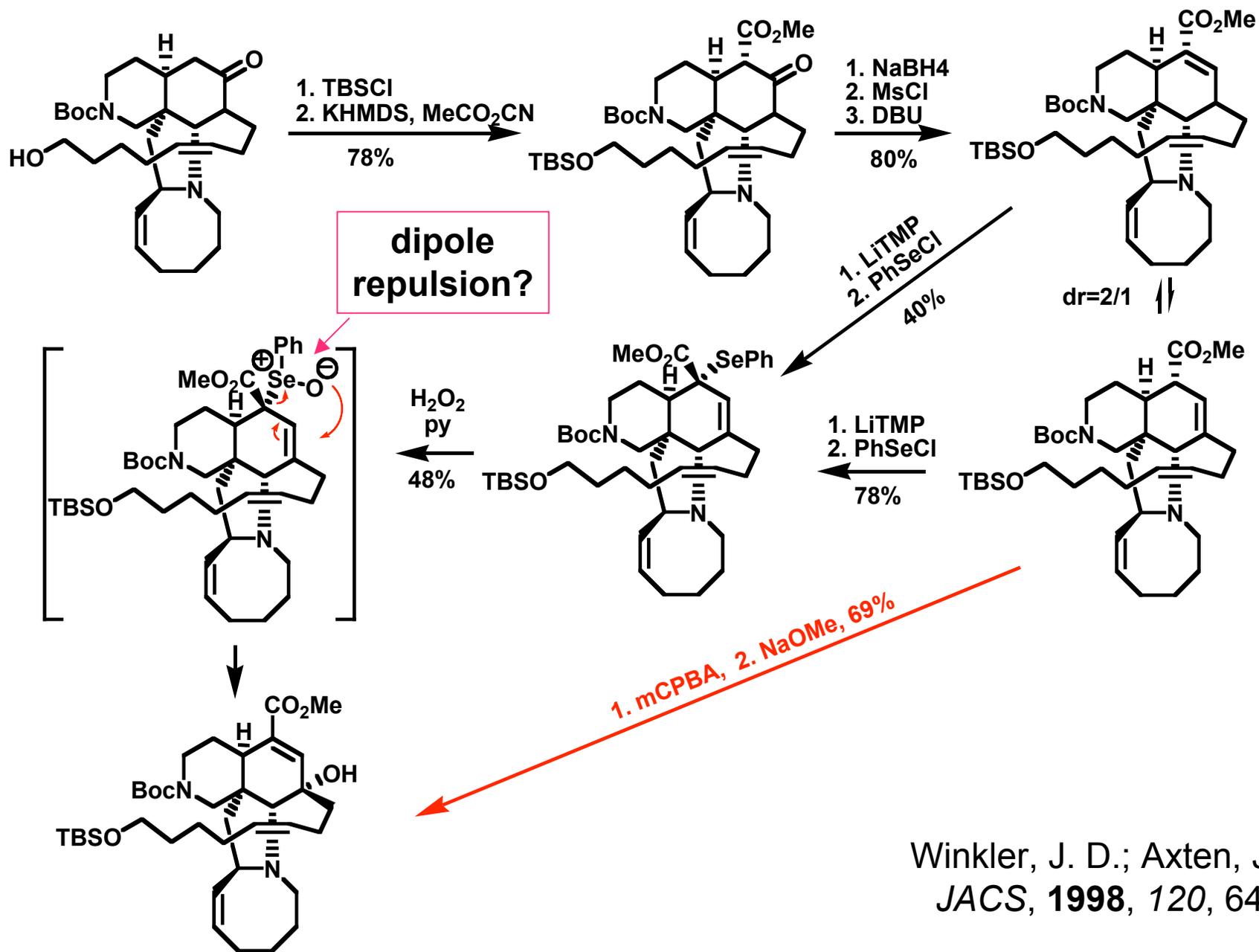


Photoaddition/fragmentation/Mannich closure sequence



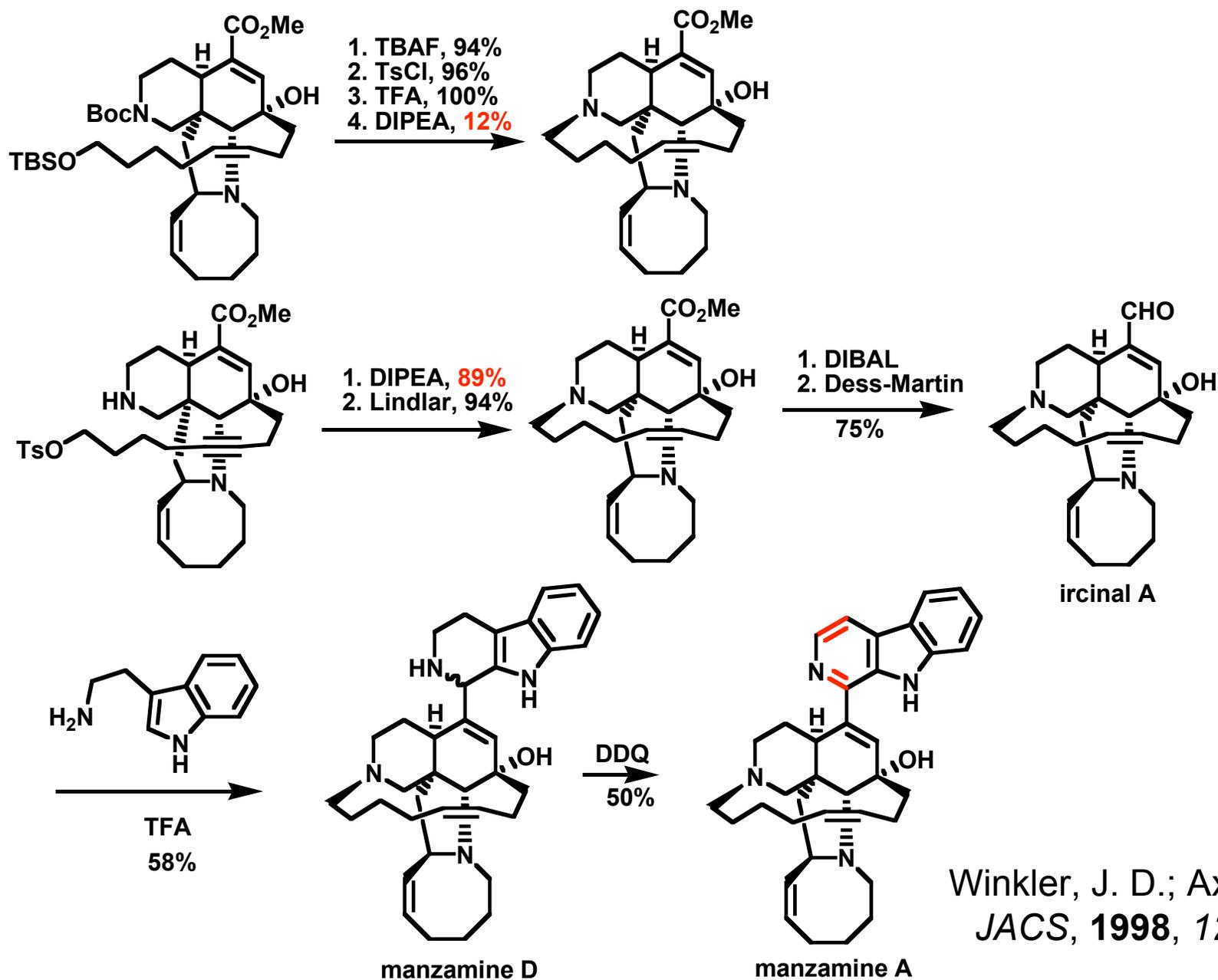
Winkler, J. D.; Axten, J. M.
JACS, **1998**, *120*, 6425

Winkler's Total Synthesis



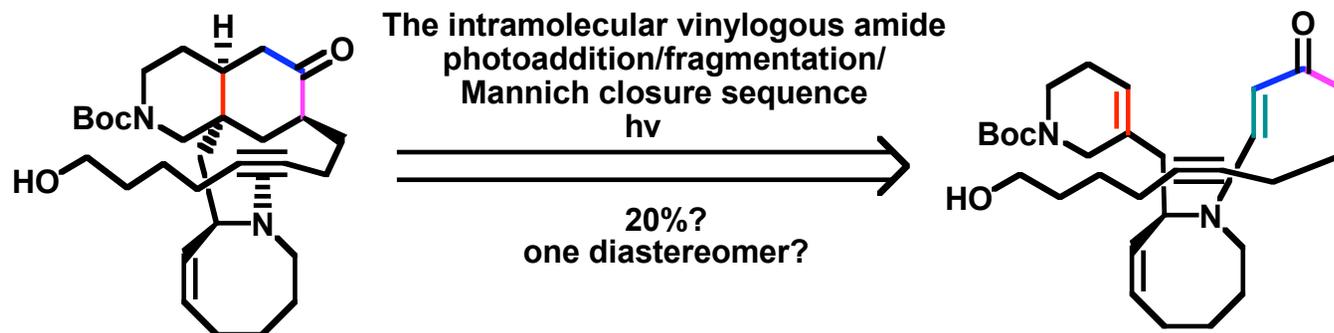
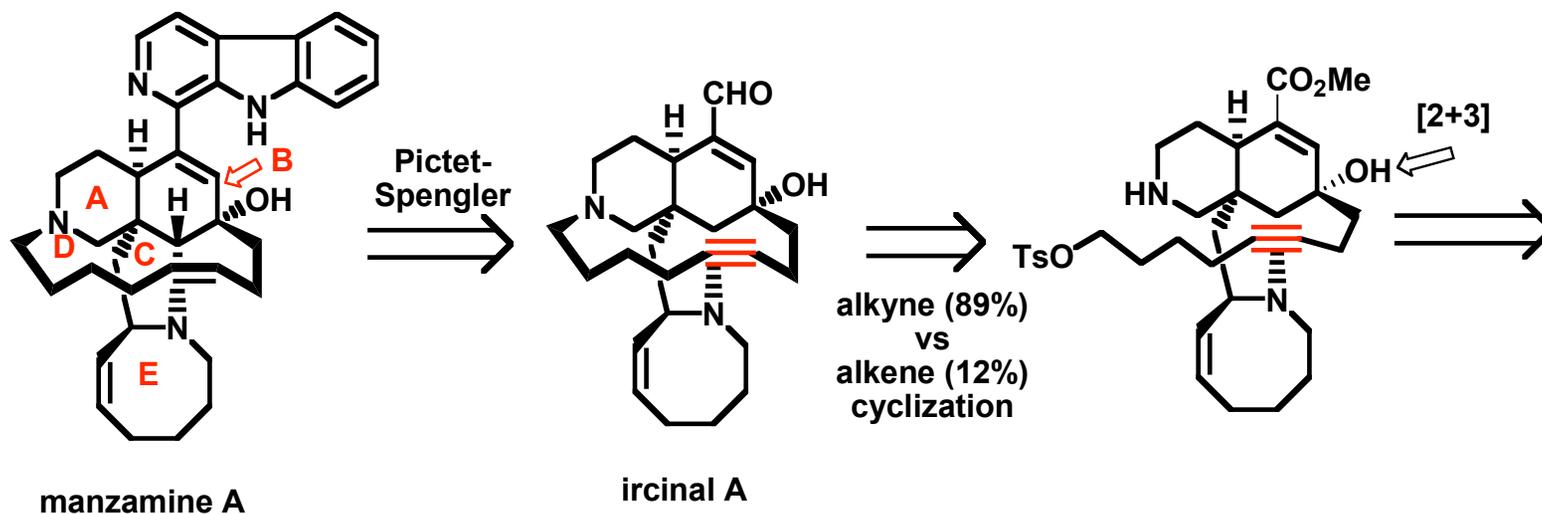
Winkler, J. D.; Axten, J. M.
JACS, **1998**, *120*, 6425

Winkler's Total Synthesis



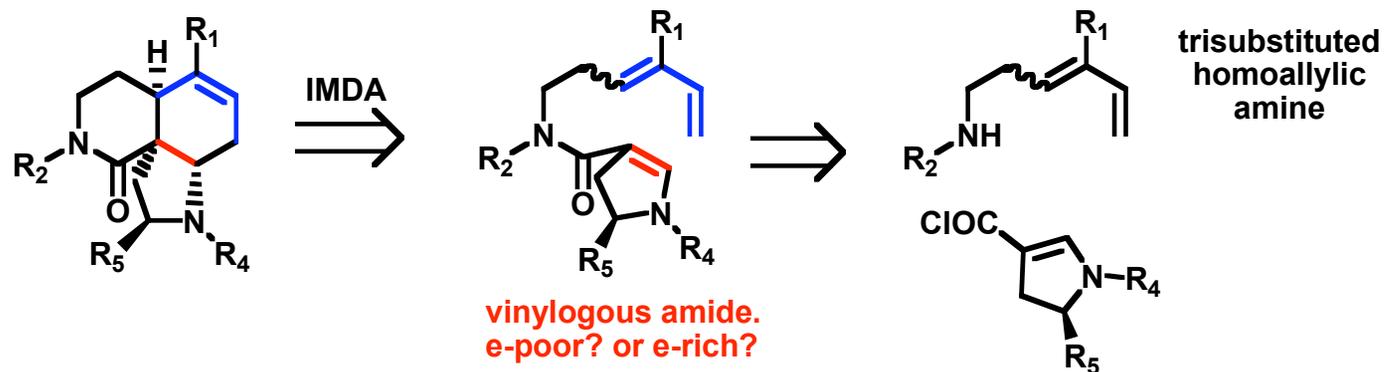
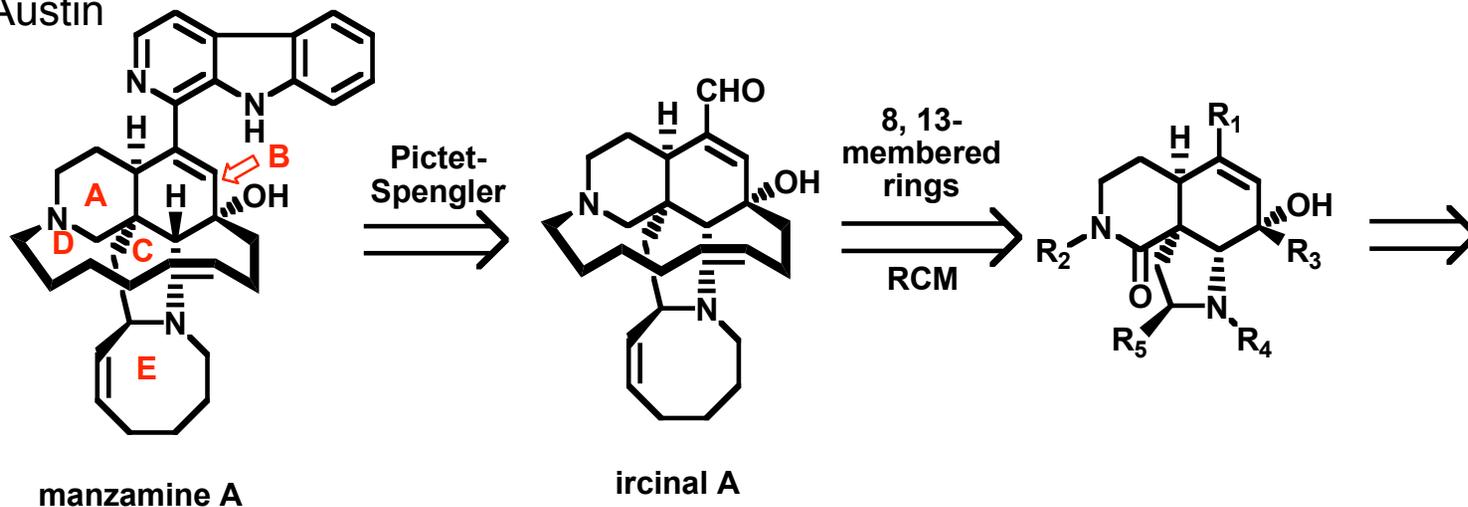
Winkler, J. D.; Axten, J. M.
JACS, 1998, 120, 6425

Winkler's Total Synthesis of Manzamine A. Summary.



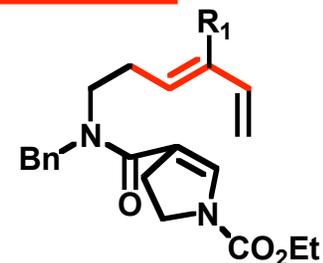
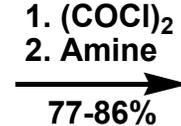
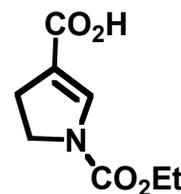
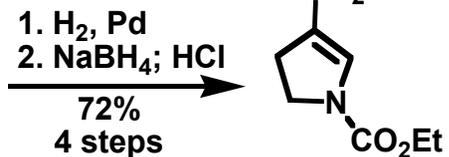
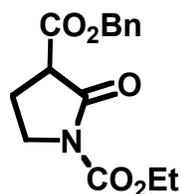
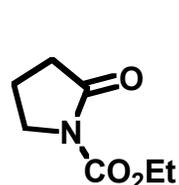
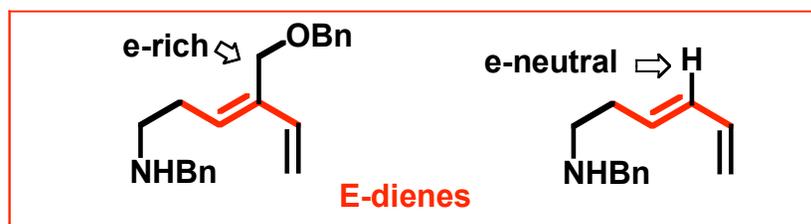
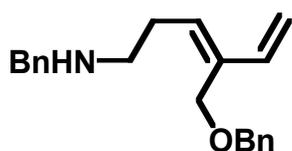
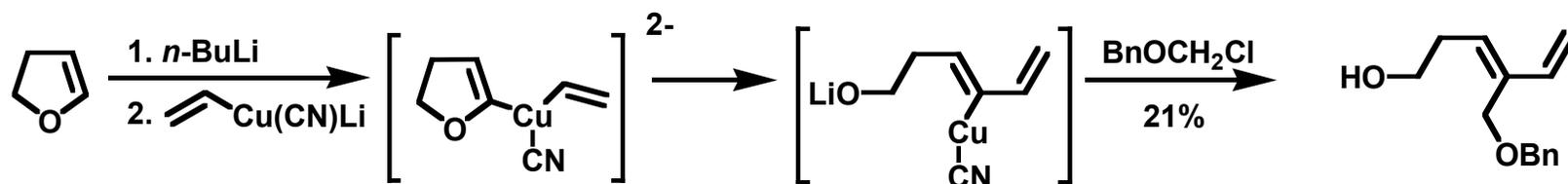
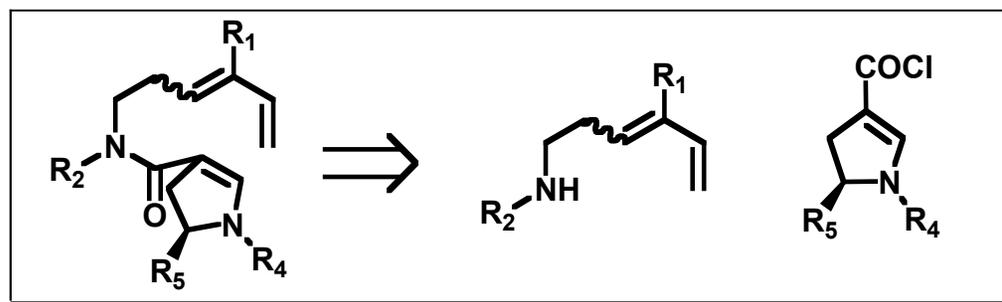
Martin's Total Synthesis. Retrosynthesis.

Prof. Stephen F. Martin
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Is the dienophile e-poor or e-rich?

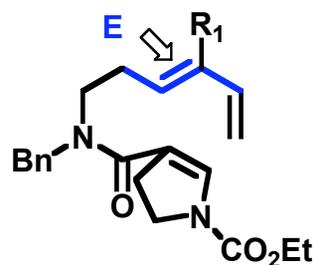
Martin's Total Synthesis. Model. SM.



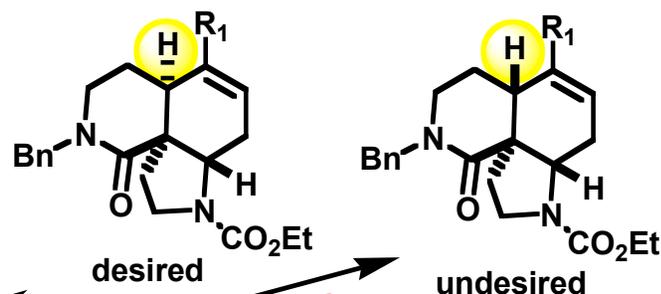
Martin, S. F. et al *JACS*, **2002**, *124*, 8584

Kocienski, P.; Wadman, S. *JACS*, **1989**, *111*, 2363

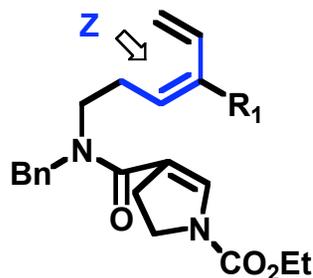
Martin's Total Synthesis. E-Rich Dienes.



1. $R_1 = H$ (e-neutral diene), a. 180°C , 81%, d/u=2/1; b. EtAlCl_2 , 110°C , 17 h: 71%, d/u=6/1
2. $R_1 = \text{CH}_2\text{OBn}$ (e-rich diene), a. Thermal: d/u=2/3; b. EtAlCl_2 : d/u=3/2



impossible?

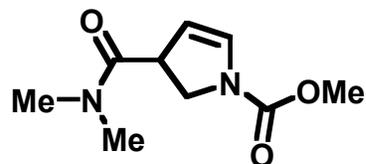


1. $R_1 = H$ (e-neutral diene), EtAlCl_2 (1.5 eq), 120°C , 100h, 70%, d/u=8/1; thermally- less pure
2. $R_1 = \text{CH}_2\text{OBn}$ (e-rich diene), a. Thermal: stable at $<150^\circ\text{C}$, undesired at 200°C ; slightly better with EtAlCl_2

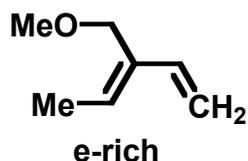
Is the dienophile e-rich?

Martin. Electronics of the Diene.

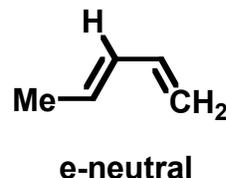
LUMO: -0.332 eV
HOMO: -9.200 eV



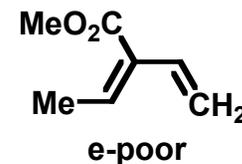
LUMO: 0.341 eV (9.541)
HOMO: -9.032 eV (8.700)



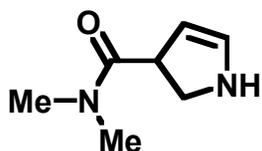
LUMO: 0.245 eV (9.445)
HOMO: -9.167 eV (8.835)



LUMO: -0.387 eV (8.813)
HOMO: -9.543 eV (9.211)

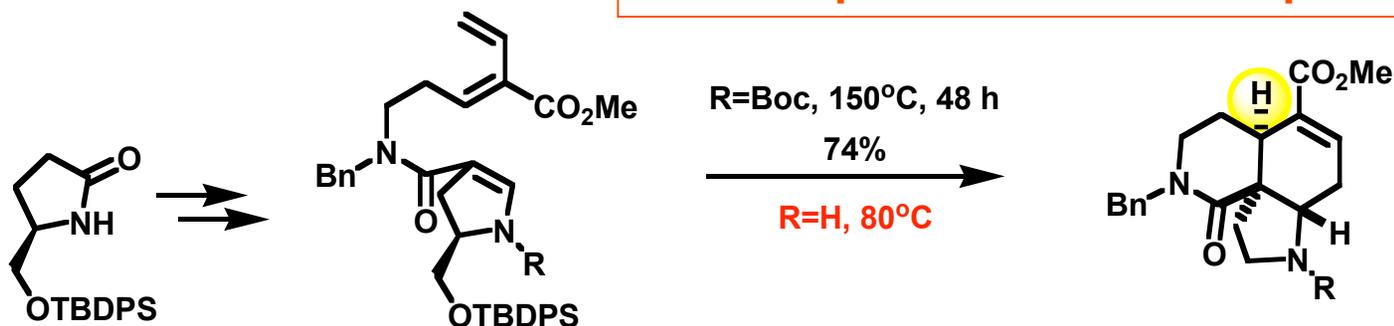


LUMO: -0.034 eV
HOMO: -8.879 eV

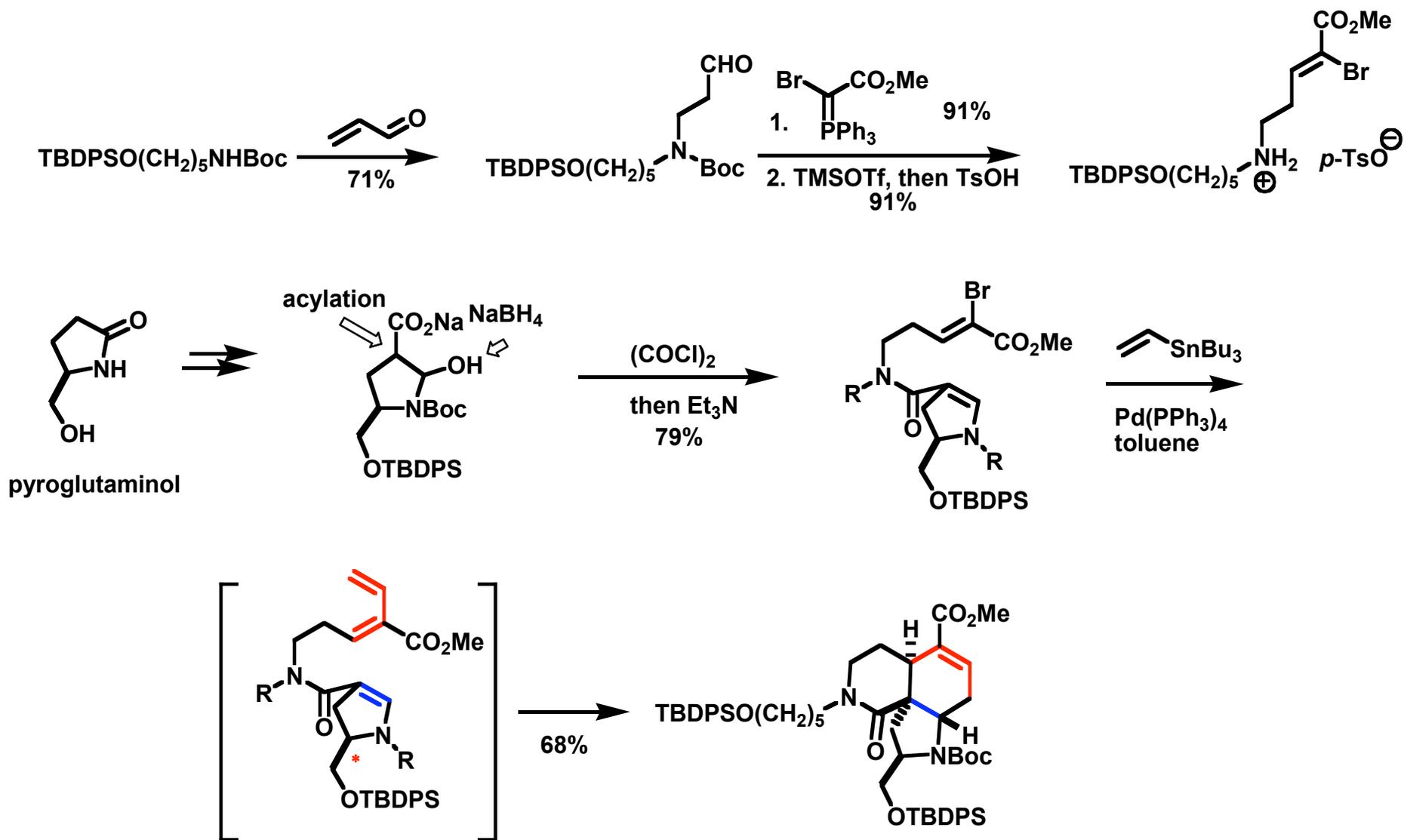


even more e-rich
dienophile

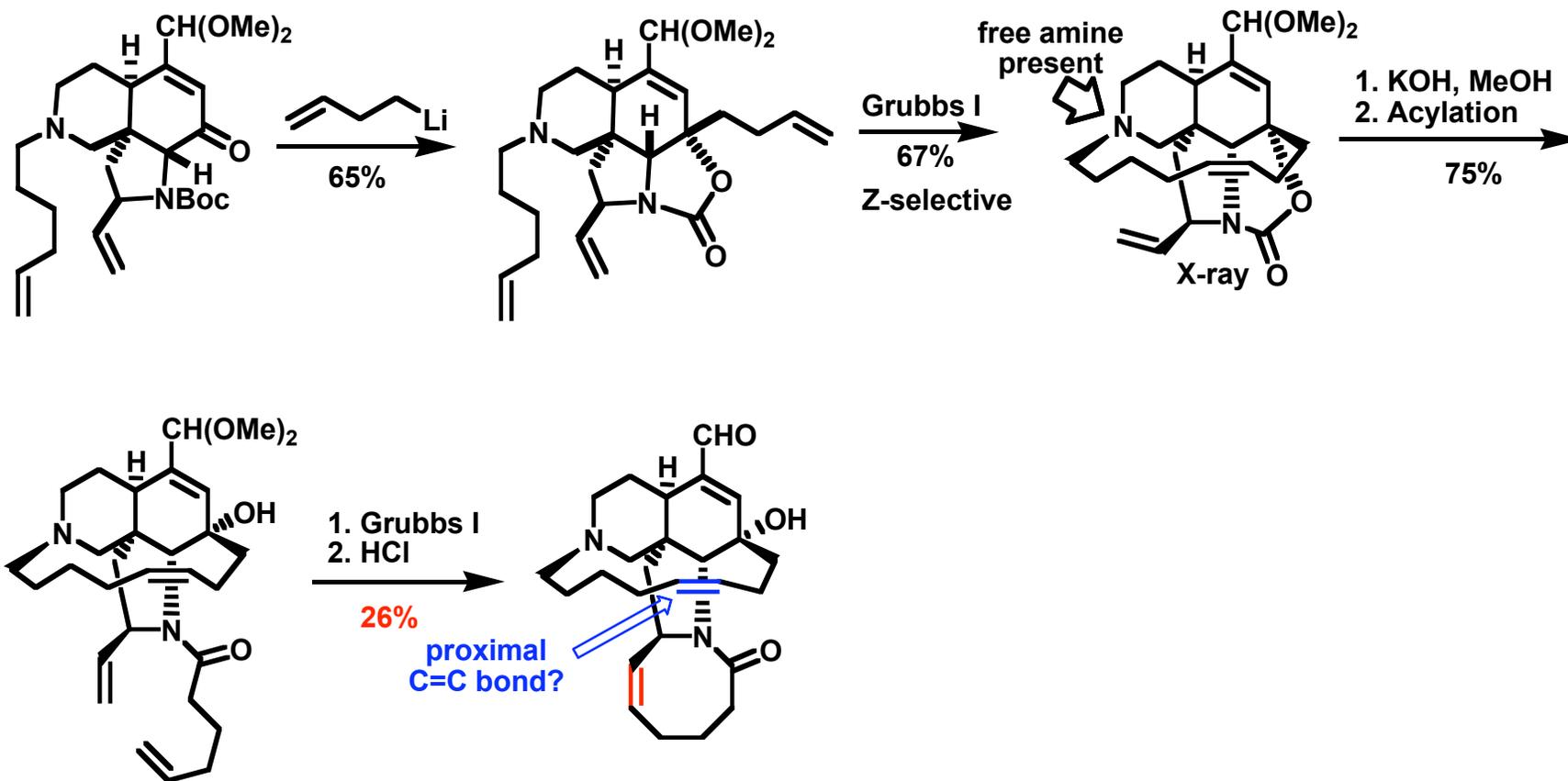
Another proof that the dienophile IS e-rich



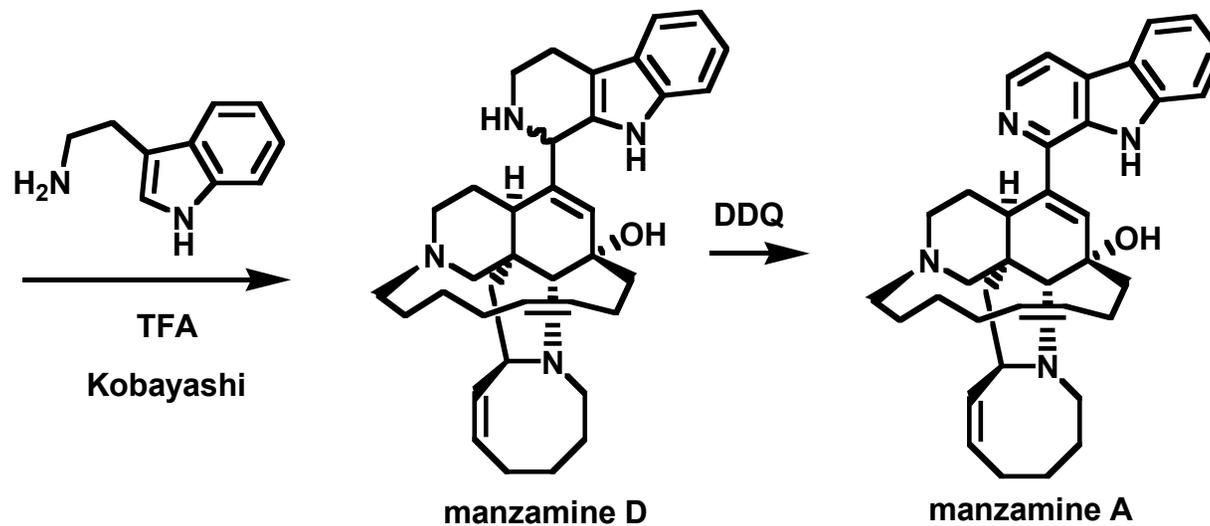
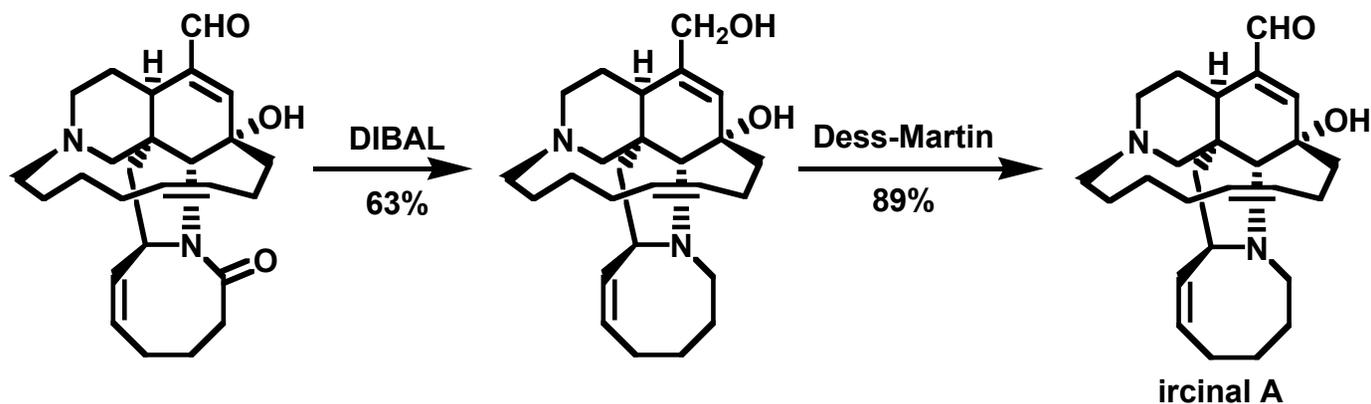
Martin's Total Synthesis. *E*-Poor Diene.



Martin's Total Synthesis. Stepwise RCM.

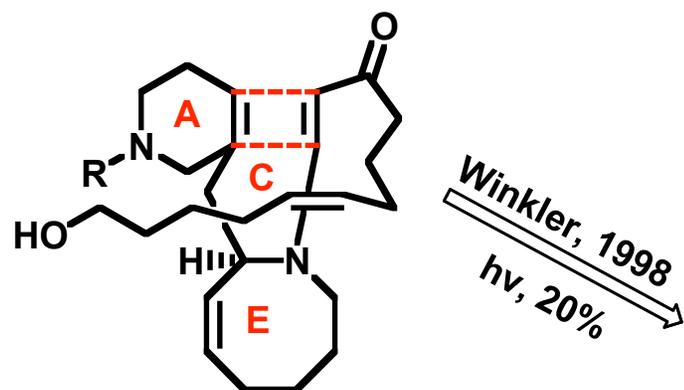


Martin's Total Synthesis. Completion.

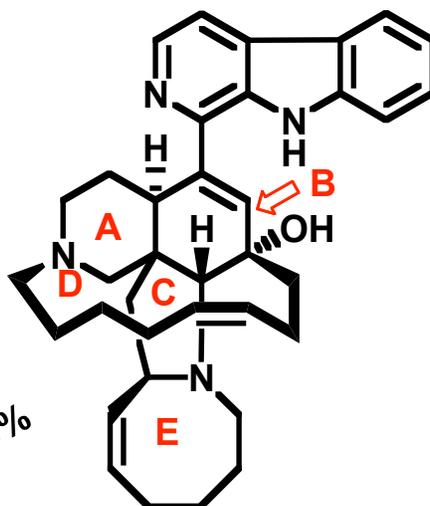


Summary.

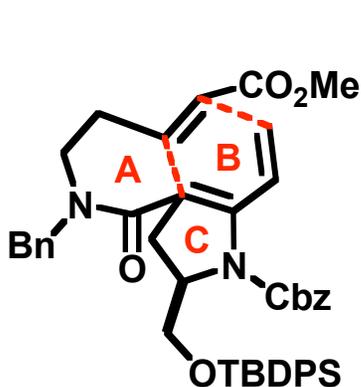
1. First total synthesis
2. [2+2] then rearrangements



Winkler, 1998
 $h\nu$, 20%



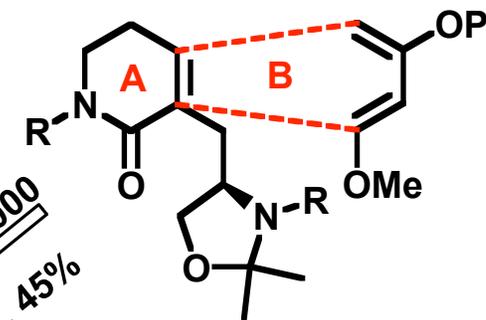
manzamine A



Pandit, 1991
 [4+2], 69%

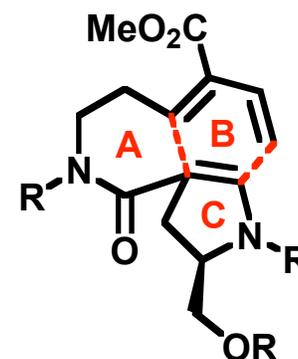
1. The first synthesis of ABCDE
2. Use of Z-diene for [4+2]

1. ABCE fragment
2. Poor diastereoselectivity
3. Influence of the substitution on the nitrogen studied



Nakagawa, 2000
 [4+2], 45%

Martin, 1999
 [4+2], 68%



1. Second and last total synthesis
2. Vinylogous amide is an e-poor dienophile
3. RCM, 13: 67%, 8: 26%

by RCM 8-membered ring was more difficult to form than the 13-membered