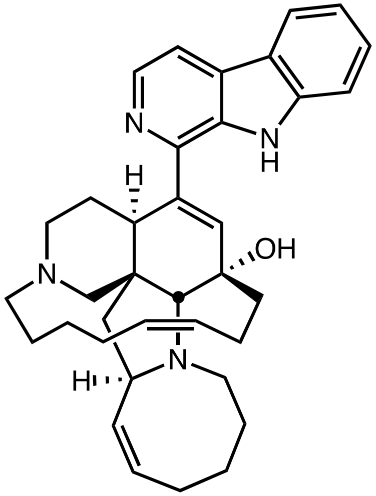
Total Syntheses of Manzamine A



MacMillan Group Meeting
July 8, 2009
Spencer Jones

Key References

Isolation: (a) Sakai, R.; Higa, T. *J. Am. Chem. Soc.* **1986**, *108*, 6404. (b) Nakamura, H.; Deng, S.; Kobayashi, J.; Ohizumi, Y. *Tet. Lett.* **1987**, *28*, 621.

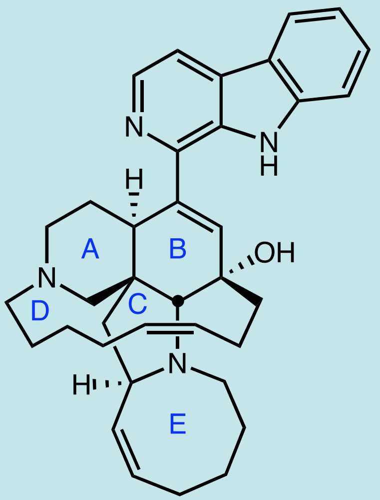
Biosynthesis: (a) Baldwin, J. E.; Whitehead, R. C. *Tet. Lett.* **1992**, *33*, 2059. (b) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2661. (c) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C. *Chem. Eur. J.* **1999**, *5*, 3154.

Winkler Synthesis: (a) Winkler, J. D.; Siegel, M. G.; Stelmach, J. E. *Tet. Lett.* **1993**, *34*, 6509. (b) Winkler, J. D.; Stelmach, J. E.; Siegel, M. G.; Haddad, N.; Axten, J.; Daileyl, W. P. *Isr. J. Chem.* **1997**, *37*, 47. (c) Winkler, J. D.; Axten, J.; Hammach, A. H.; Kwak, Y. S.; Lengweiler, U.; Lucero, M. J.; Houk, K. N. *Tetrahedron* **1998**, *54*, 7045. (d) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425.

Martin Synthesis: (a) Martin, S. F.; Rein, T.; Liao, Y. *Tet. Lett.* **1991**, *32*, 6481. (b) Martin, S. F.; Liao, Y. Wong, Y.; Rein, T. *Tet. Lett.* **1994**, *35*, 691. (c) Martin, S. F.; Chen, H. J.; Courtney, A. K.; Liao, Y.; Patzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251. (d) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. (e) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y. L.; Chen, H. J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584.

Manzamine A: Polycyclic Marine Alkaloid

> "It's provenance is problematical as there appears to be no obvious biogenetic path."
> -Higa



manzamine A

Isolated independently by Higa and Nakamura

Isolated from the sponge *Haliclona sp.* near Okinawa

735 g sponge yielded 100 mg manzamine A (0.014%).

Inhibits growth of P388 leukemia cell with IC_{50} of 70 ng/mL.

Related manzamines possess insecticidal, antibacterial and antimalarial activity (being less toxic and showing higher *in vivo* activity than current antimalarials arteminsinin and chloroquine).

Synthetic Challenges

Densely functionalized pyrrolo[2,3-*i*]isoquinoline core

Four vicinal stereocenters, two of which are fully substituted

pentacyclic core contains 5,6,8, and 13 membered rings

Completed Syntheses

Winkler 1998

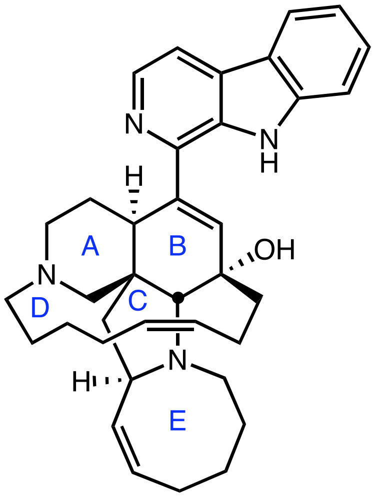
vs.

Martin 1999

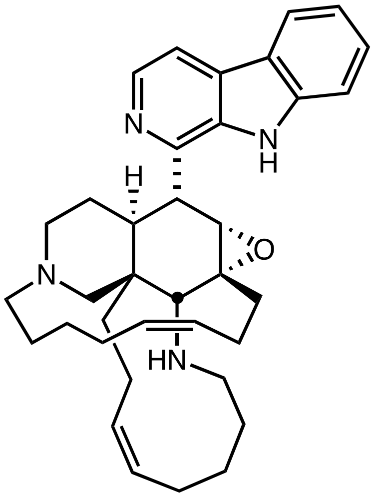
Ongoing or Abandoned Efforts

Fukuyama 2008
Nishida 2006
Coldham 2005
Magnus 2002
Marazano 2002
Clark 2001
Hart 1999
Nakagawa 1998
Langlois 1998
Yamamura 1998
Brands 1998
Pandit 1996
Overman 1994
Simpkins 1991

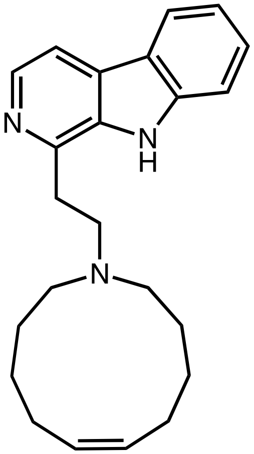
Representative Members of the Manzamine Alkaloids



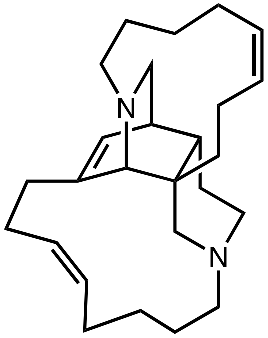
manzamine A



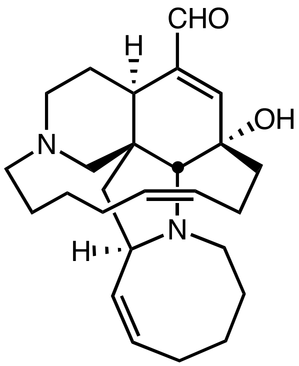
manzamine B



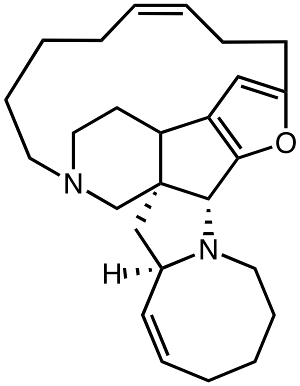
manzamine C



kermaphidin B

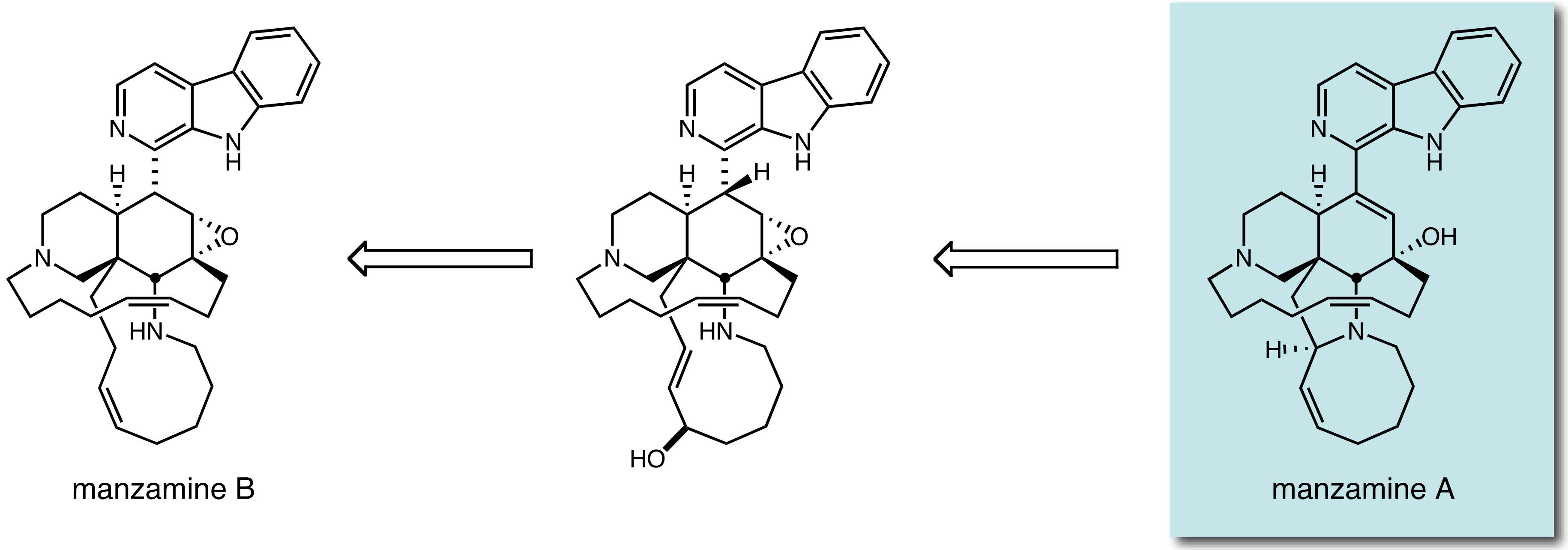


ircinal A

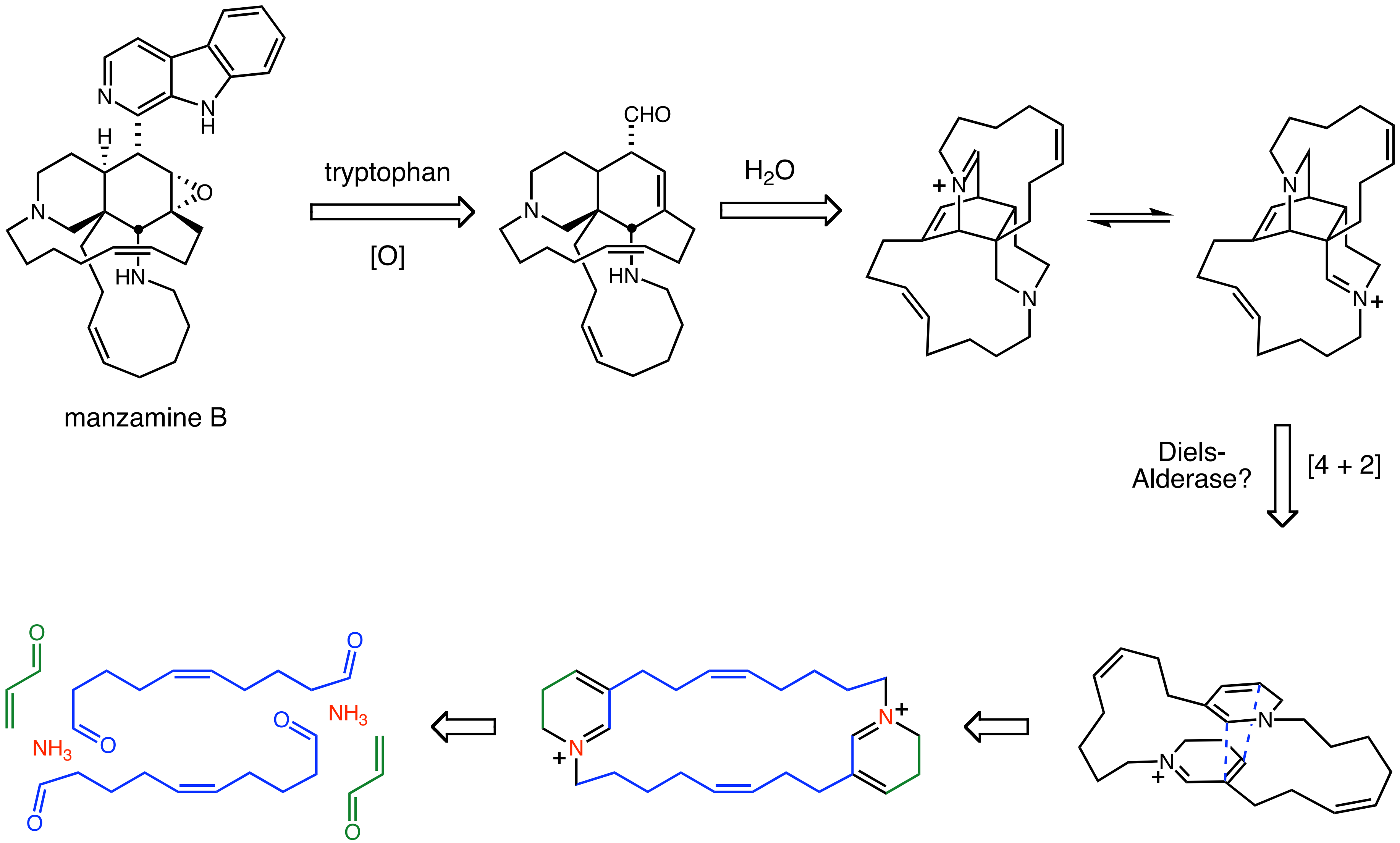


nakadomarin A

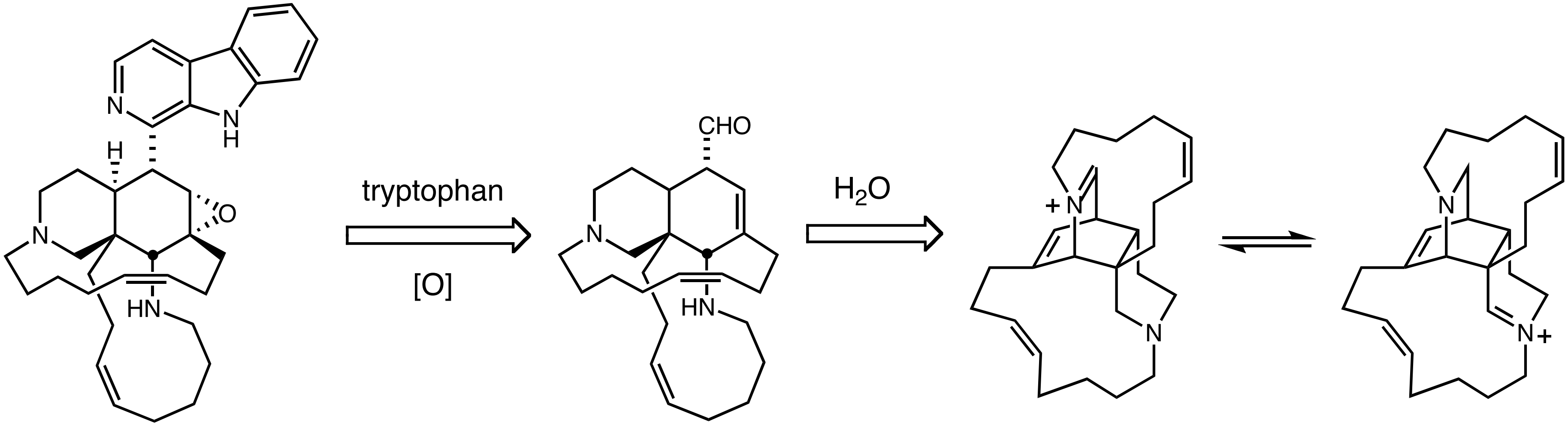
The Baldwin-Whitehead Hypothesis for Manzamine Alkaloid Biosynthesis



The Baldwin-Whitehead Hypothesis for Manzamine Alkaloid Biosynthesis

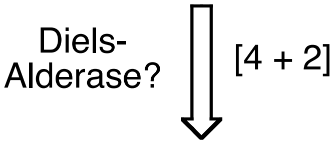


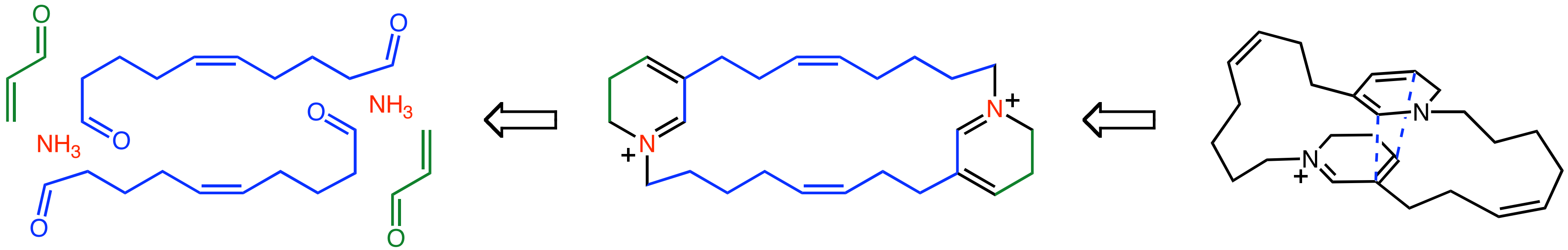
The Baldwin-Whitehead Hypothesis for Manzamine Alkaloid Biosynthesis



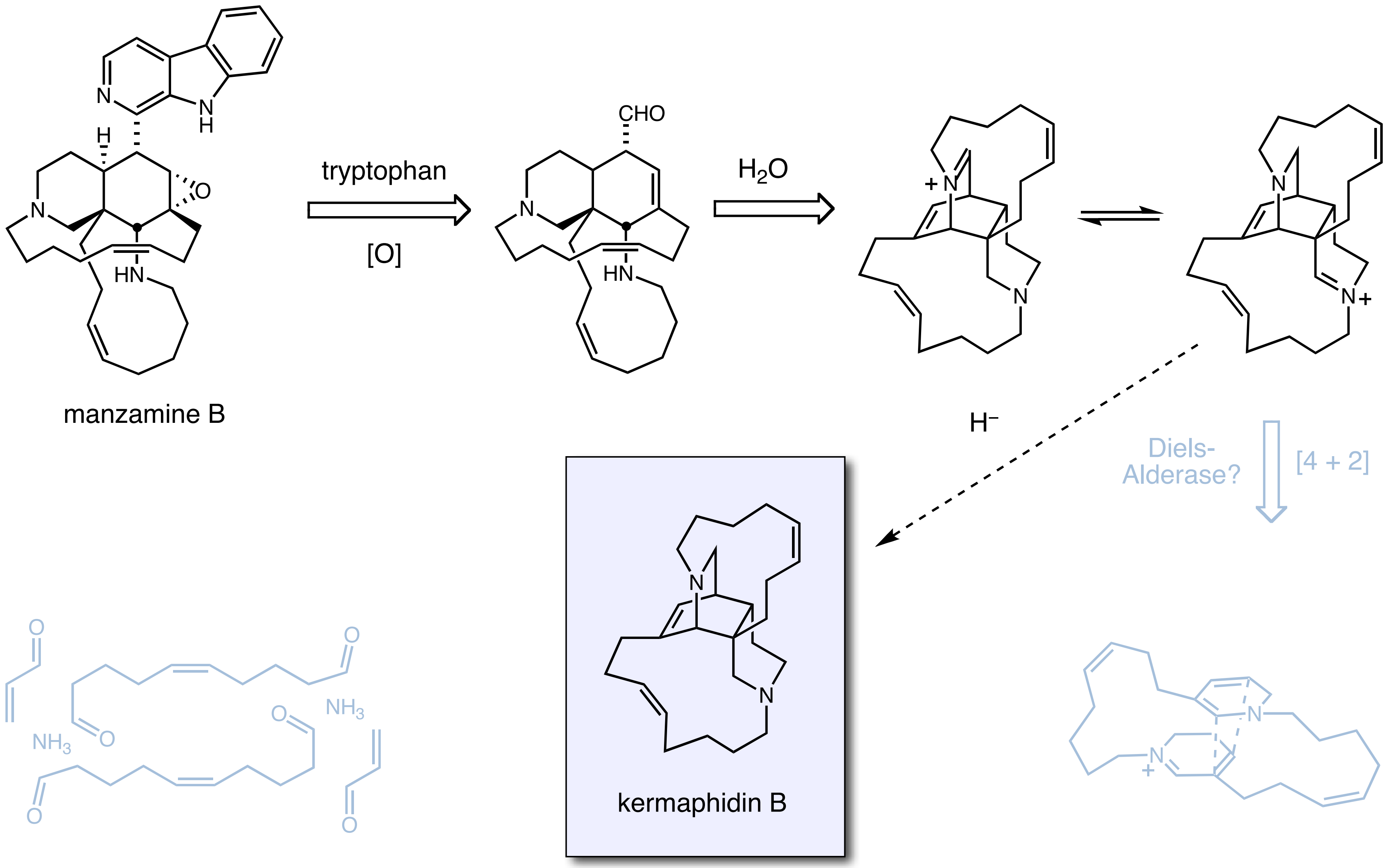
manzamine B

> "If I was God, I would have made it this way."
>
> -Baldwin





The Baldwin-Whitehead Hypothesis for Manzamine Alkaloid Biosynthesis



manzamine B

tryptophan

[O]

H_2O

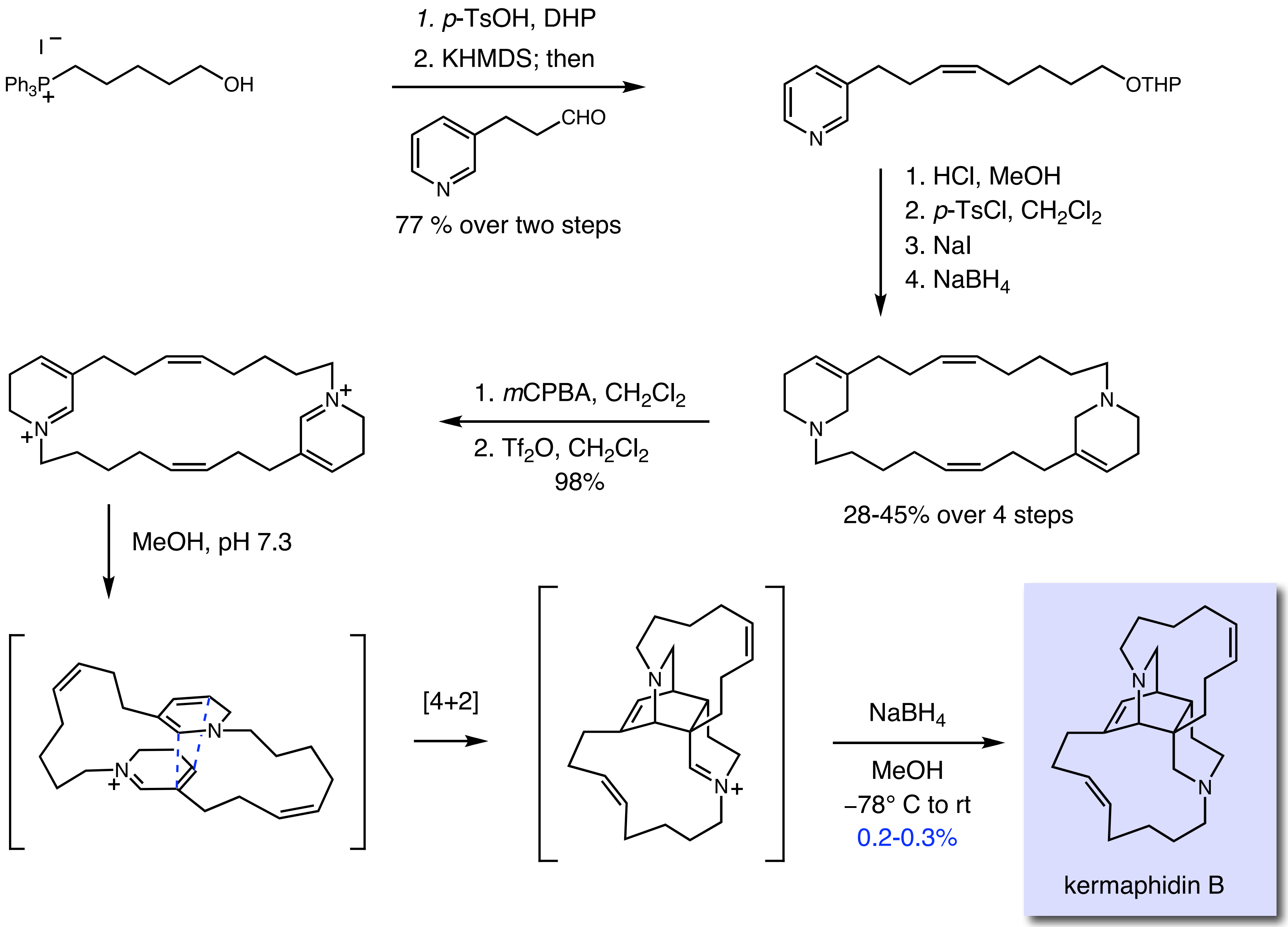
H^-

Diels-Alderase?

[4 + 2]

kermaphidin B

Baldwin's Biomimetic Synthesis of Kermaphidin B



1. p-TsOH, DHP

2. KHMDS; then

77 % over two steps

1. HCl, MeOH
2. *p*-TsCl, CH_2Cl_2
3. NaI
4. $NaBH_4$

28-45% over 4 steps

1. *m*CPBA, CH_2Cl_2

2. Tf_2O, CH_2Cl_2

98%

MeOH, pH 7.3

[4+2]

$NaBH_4$

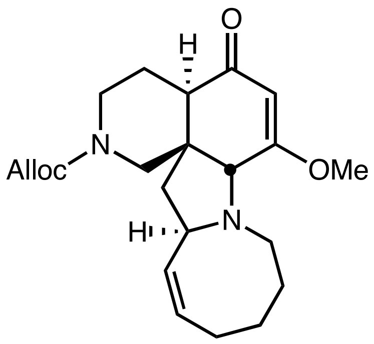
MeOH

–78° C to rt

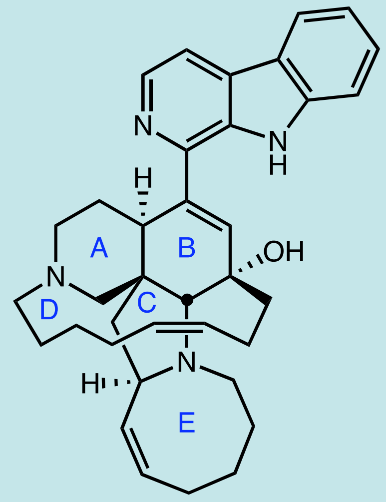
0.2-0.3%

kermaphidin B

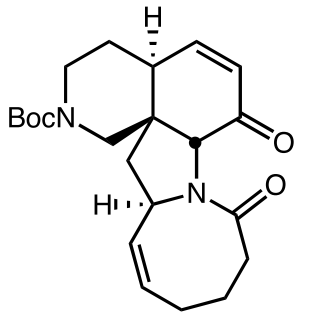
Ongoing or Failed Attempts Toward Manzamine A



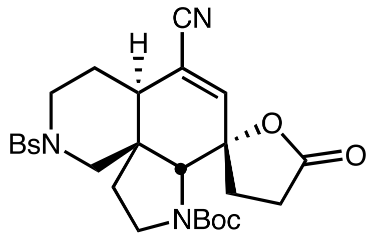
Fukuyama 2008
24 steps



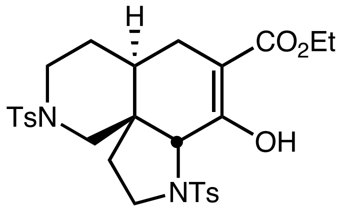
manzamine A



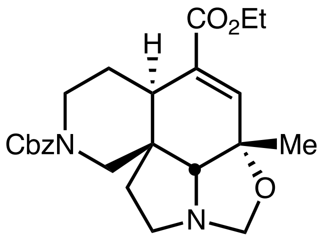
Coldham 2005
21 Steps



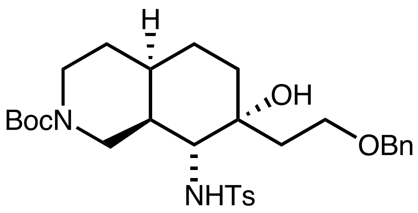
Nishida 2006
25 steps



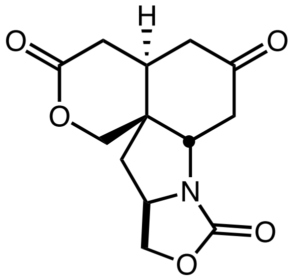
magnus 2002
10 steps



marazano 2002
18 steps

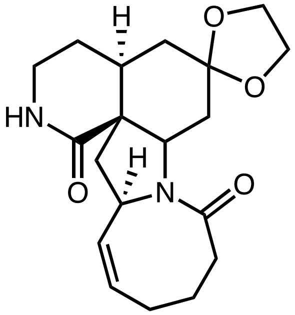


Clark 2001
10 steps

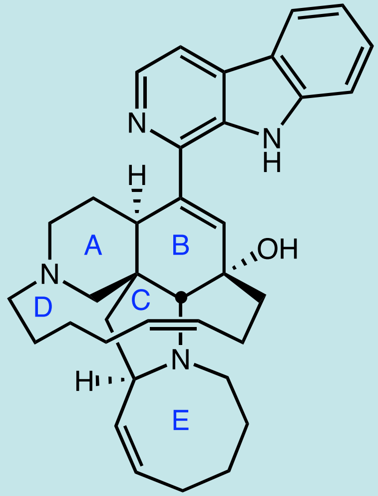


Hart 1999
14 steps

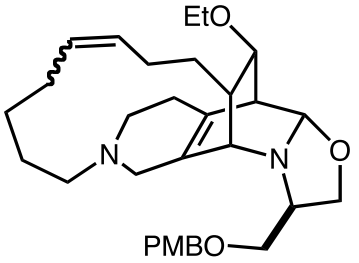
Ongoing or Failed Attempts Toward Manzamine A



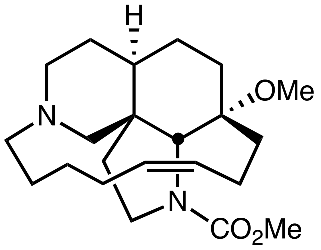
Nakagawa 1998
18 steps



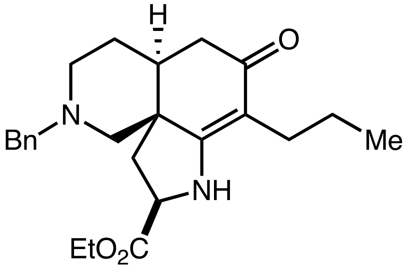
manzamine A



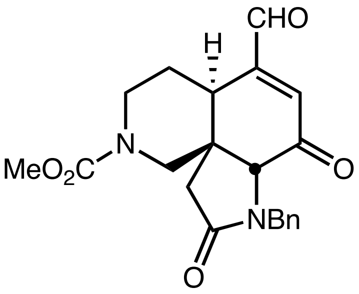
Langlois 1998
6 steps



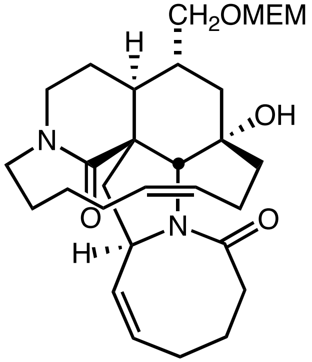
Yamamura 1998
37 steps



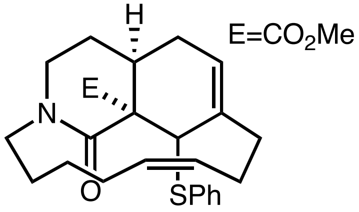
Brands 1998
10 steps



Overman 1994
15 steps

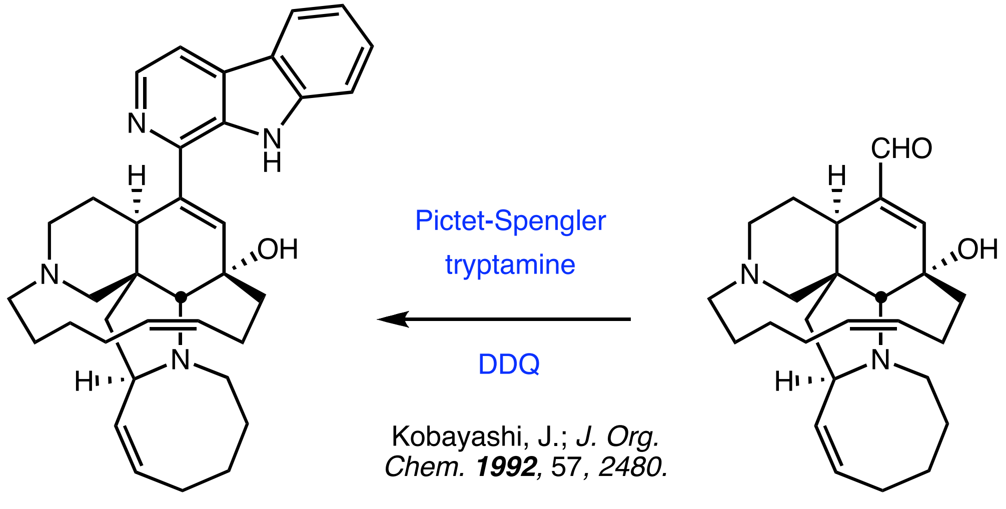


Pandit 1996
27 steps



Simpkins 1991
11 steps

Winkler: Photocycloaddition/Retro-Mannich/Mannich Cyclization Approach



Pictet-Spengler
tryptamine

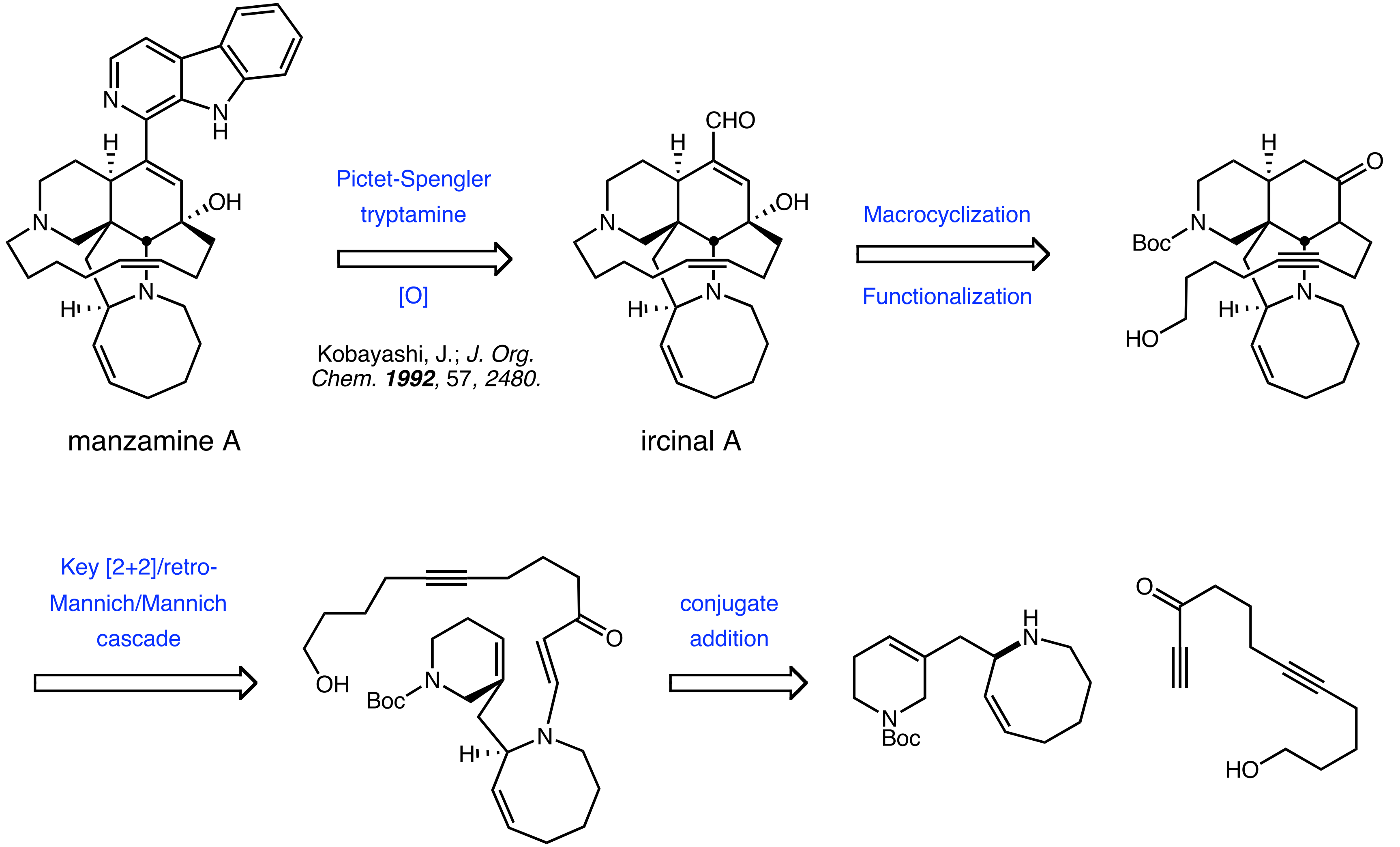
DDQ

Kobayashi, J.; *J. Org. Chem.* ***1992***, 57, *2480.*

manzamine A

ircinal A

Winkler: Photocycloaddition/Retro-Mannich/Mannich Cyclization Approach

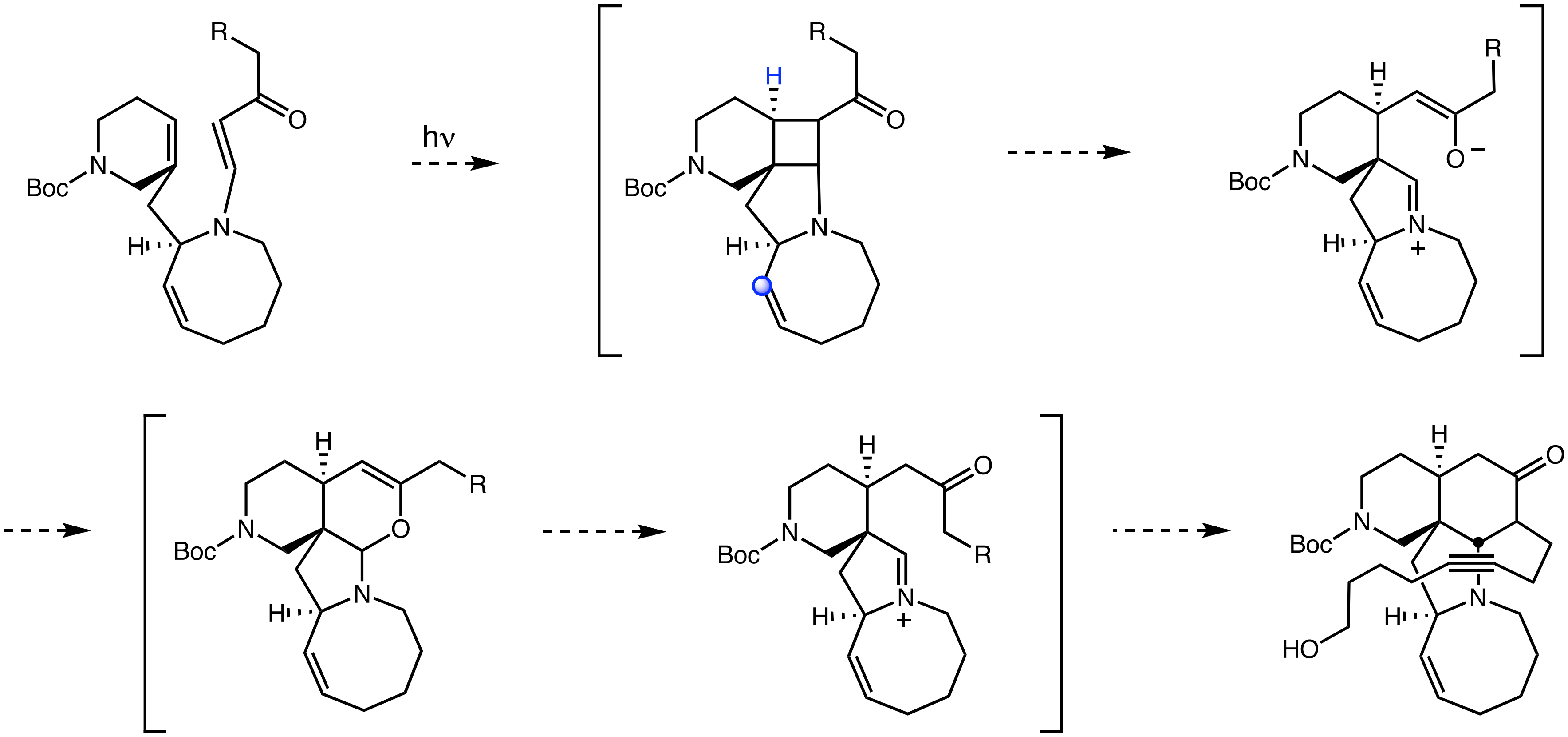


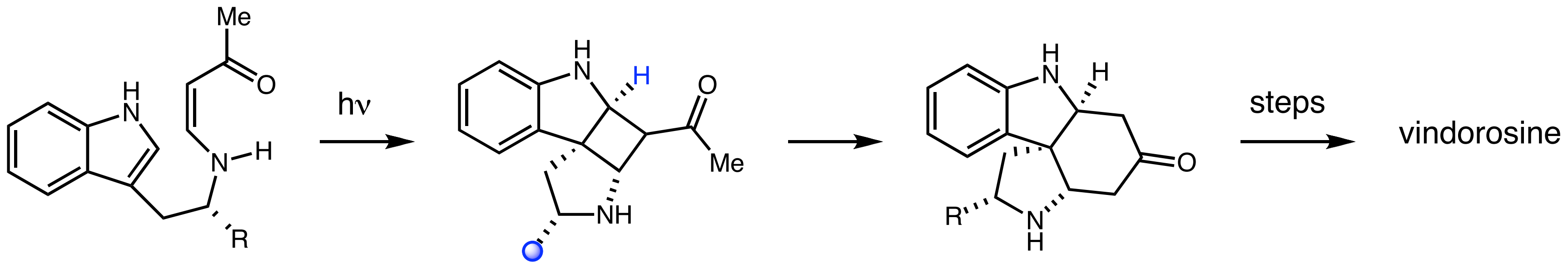
manzamine A

ircinal A

Kobayashi, J.; *J. Org. Chem.* ***1992***, 57*, 2480.*

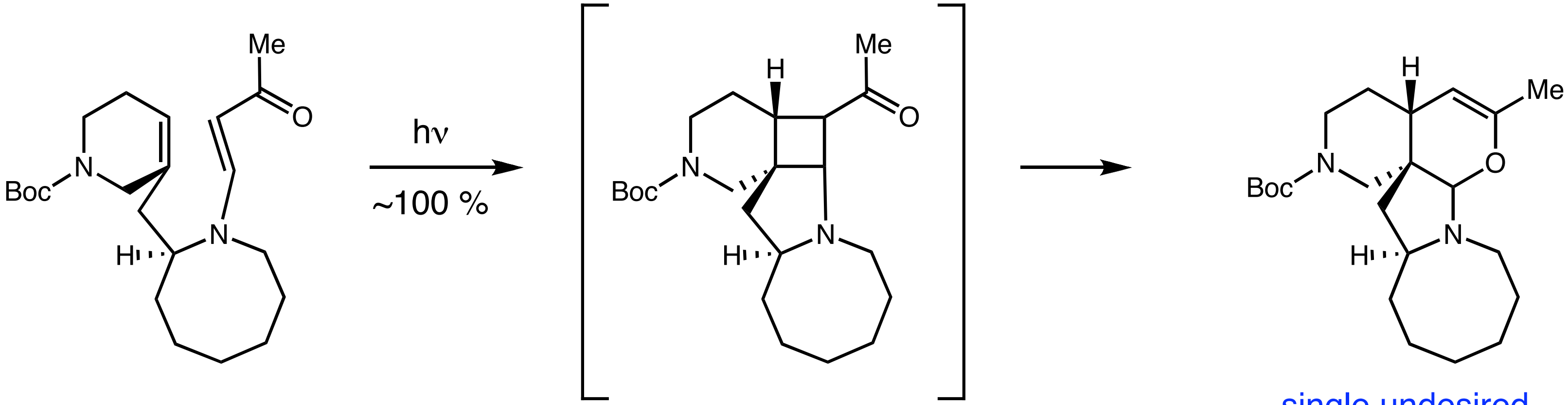
Key Step: [2+2]/Retro-Mannich/Mannich Cascade



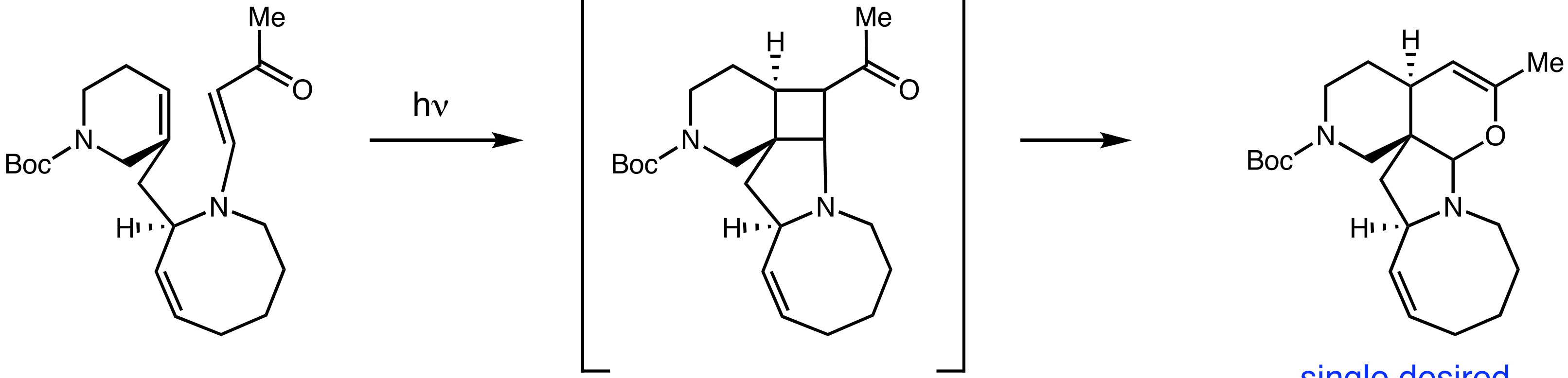


Winkler, J. D.; Scott, R. D.; Williard, P. G.; *J. Am. Chem. Soc.* **1990**, *112*, 8971.

[2+2]/Retro-Mannich/Mannich Cascade: Model Systems

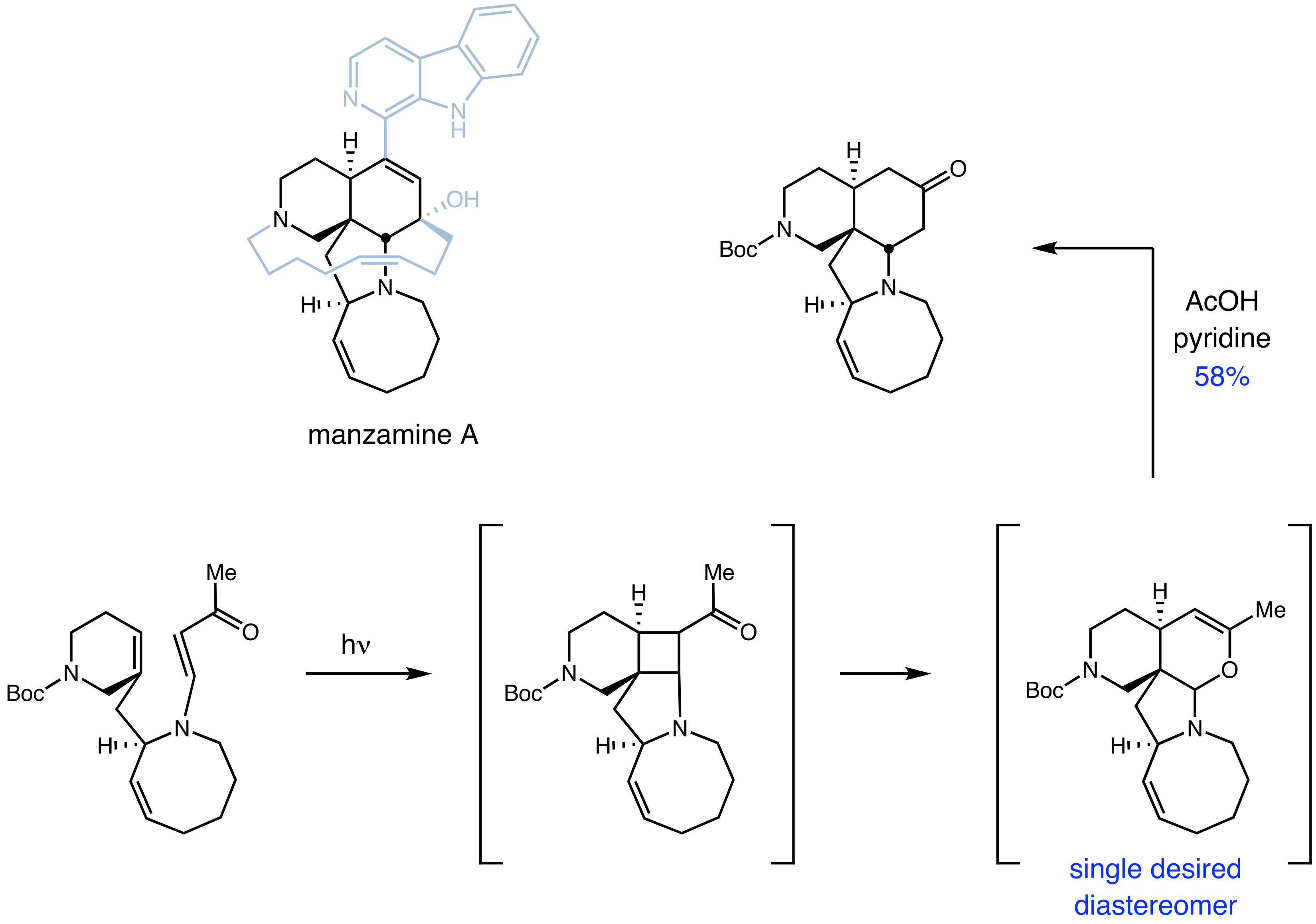


single undesired
diastereomer



single desired
diastereomer

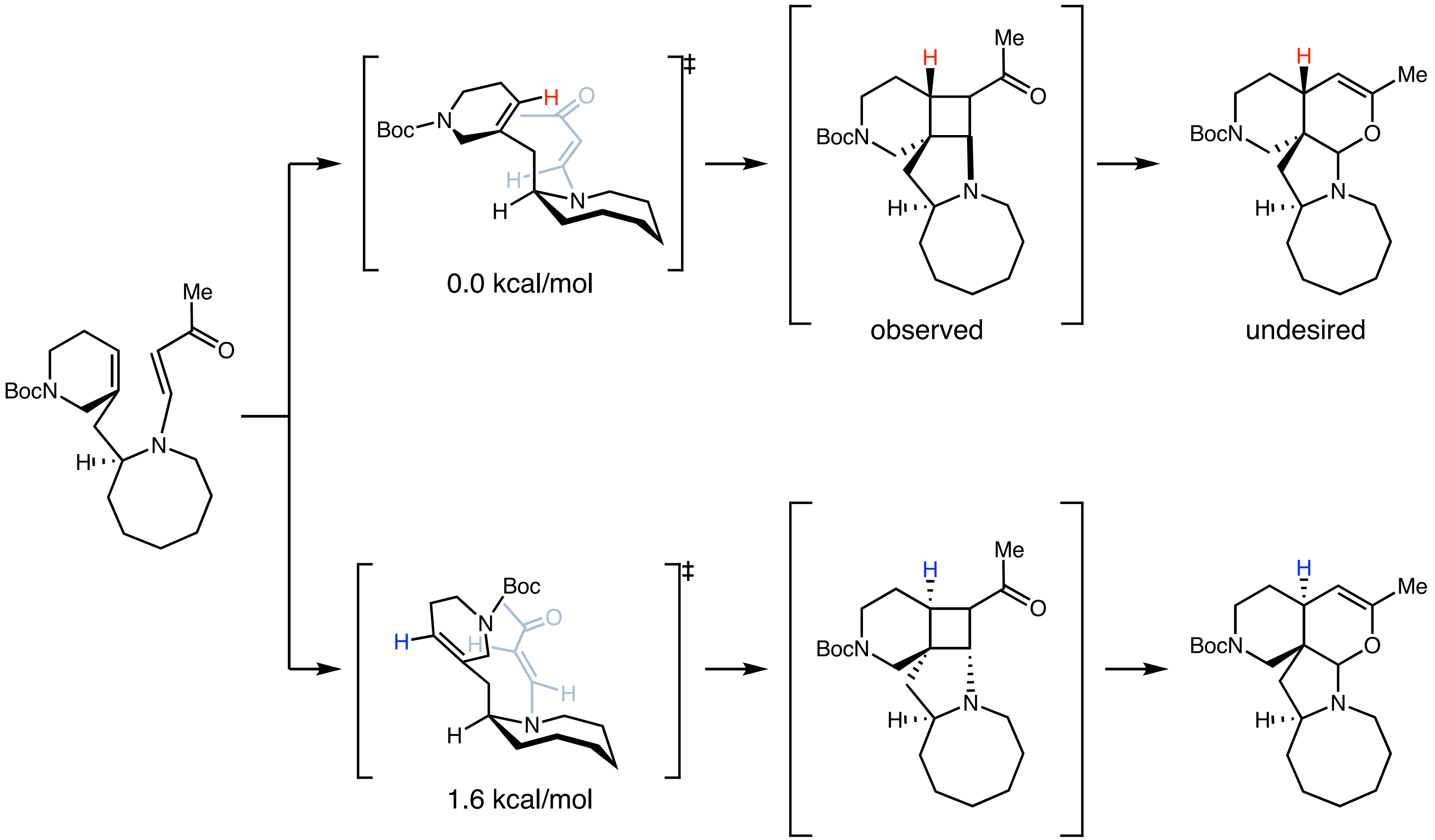
[2+2]/Retro-Mannich/Mannich Cascade: Model Systems



manzamine A

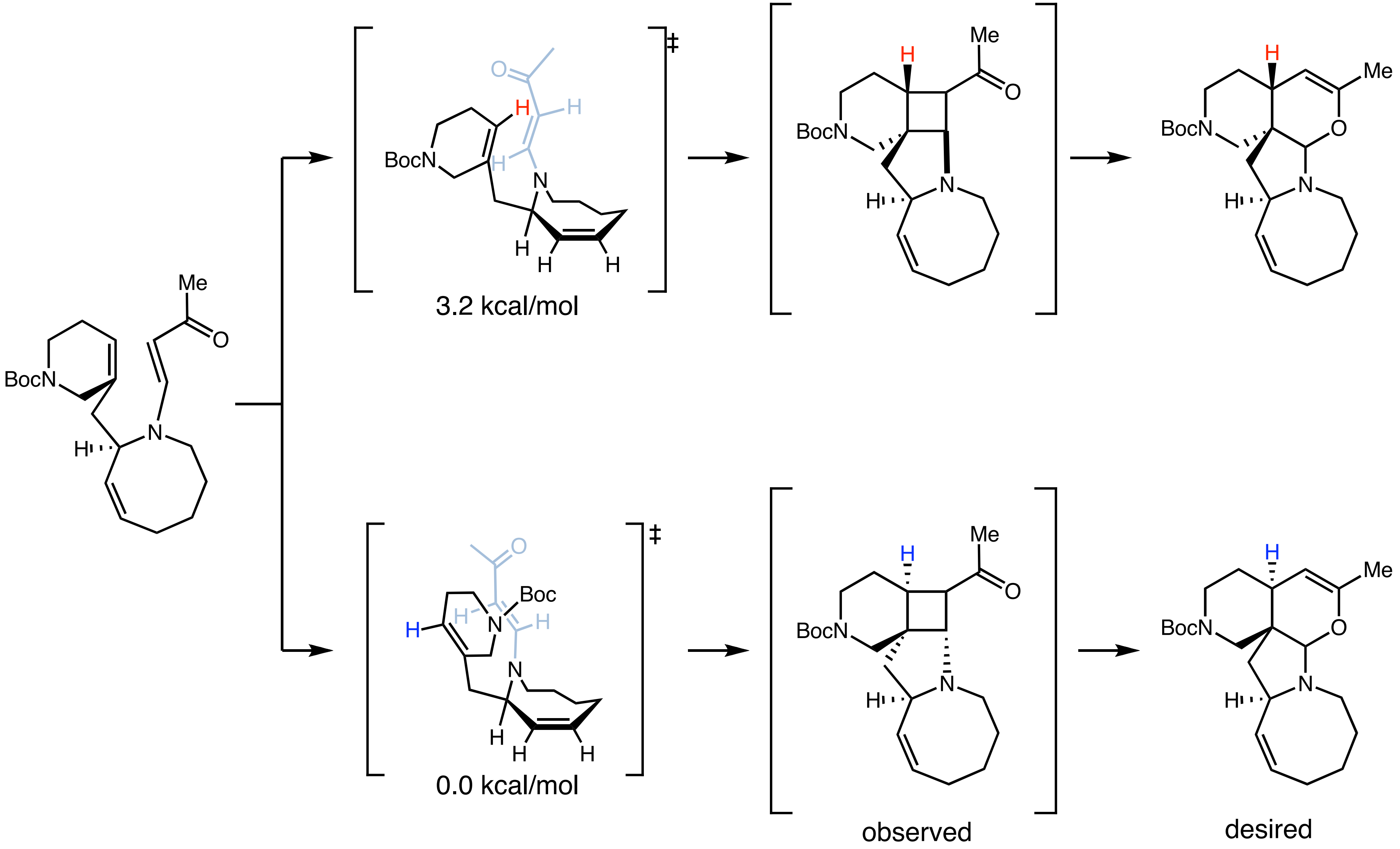
single desired diastereomer

[2+2]/Retro-Mannich/Mannich Cascade: Model Systems



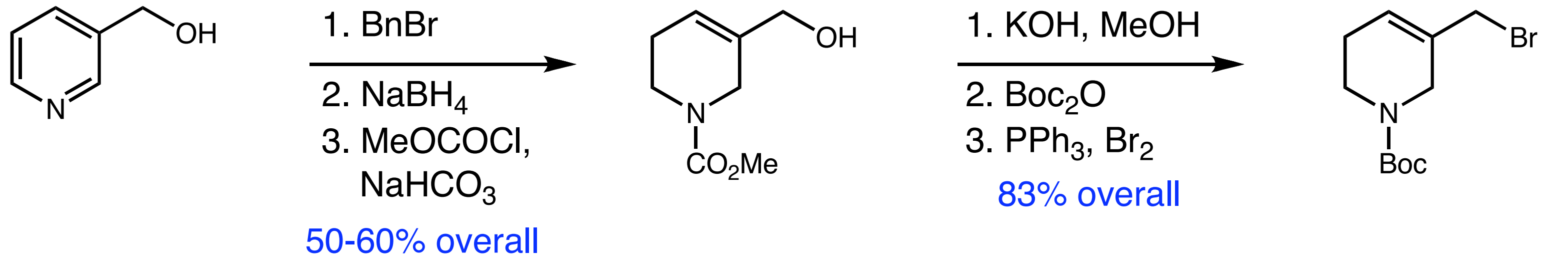
- Calculations performed using the MM2* AMBER force field on Macromodel 4.0 with K. Houk

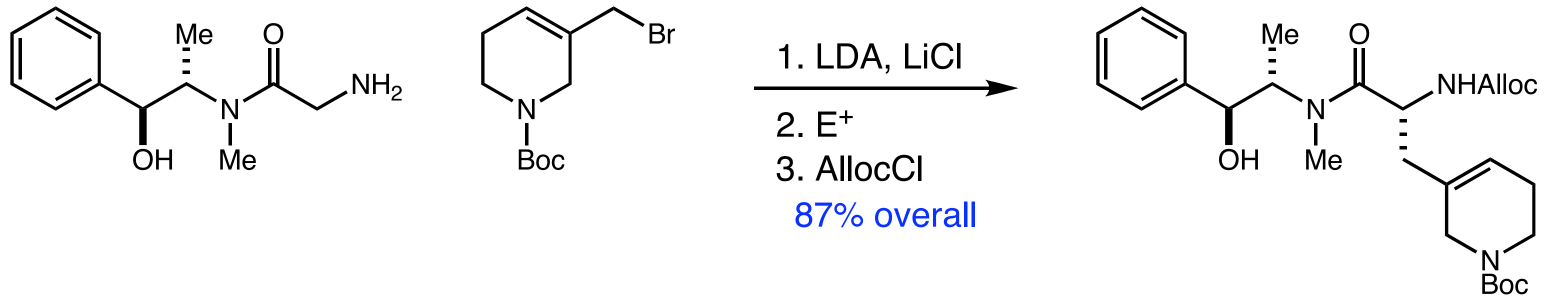
[2+2]/Retro-Mannich/Mannich Cascade: Model Systems

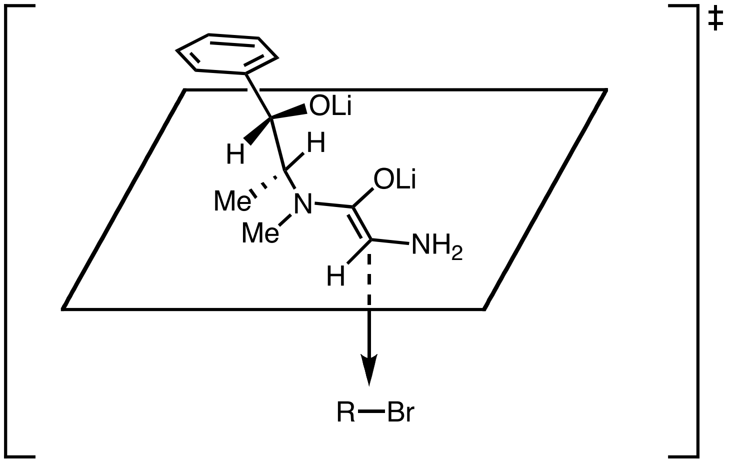


- Calculations performed using the MM2* AMBER force field on Macromodel 4.0 with K. Houk

Preparation of the Azocine Fragment

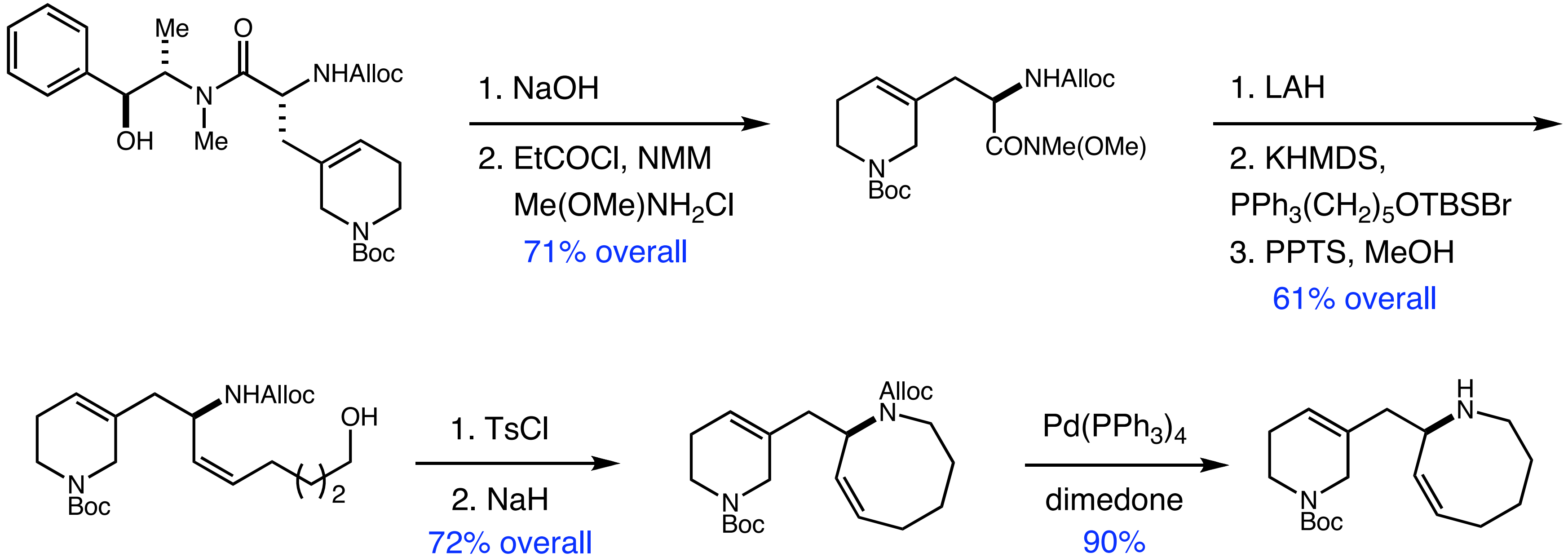




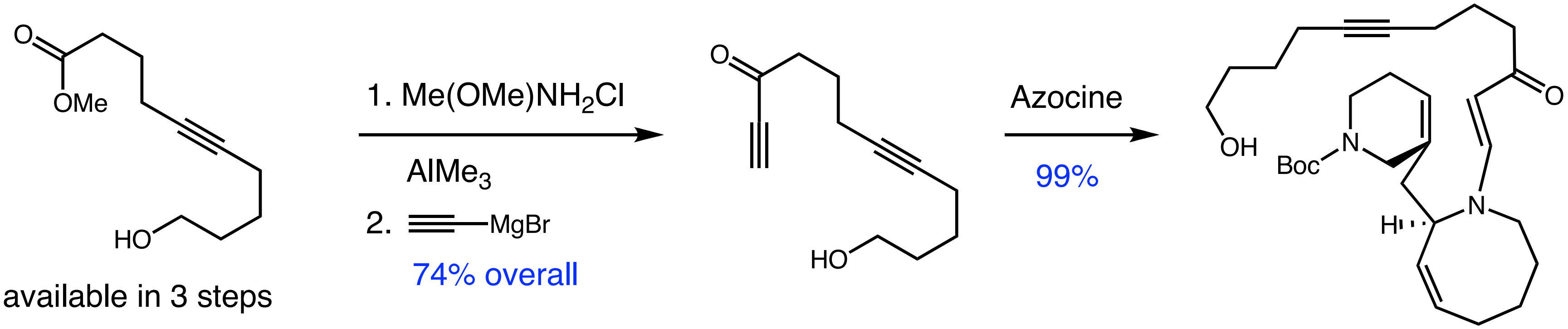


- Myer's alkylation sets the sole stereocenter in the synthesis from which all others will be induced
- Initial treatment with LDA results in deprotonation of the amine. Subsequent warming results in C to N proton exchange

Preparation of the Azocine Fragment/Photocyclization Precursor



14 steps
11% overall

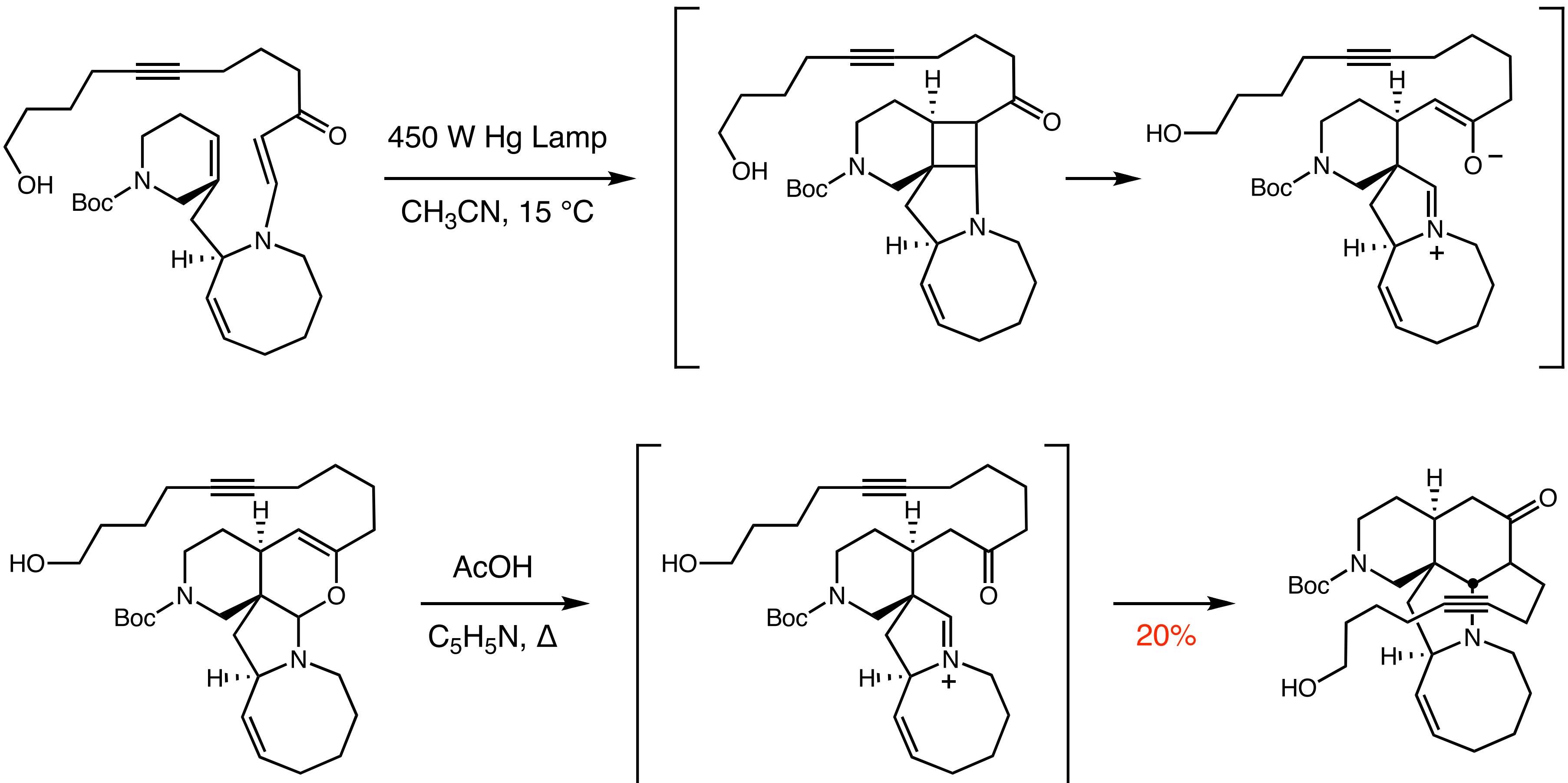


available in 3 steps

Liebigs Ann. Chem. ***1993***, *153.*

photocyclization precursor

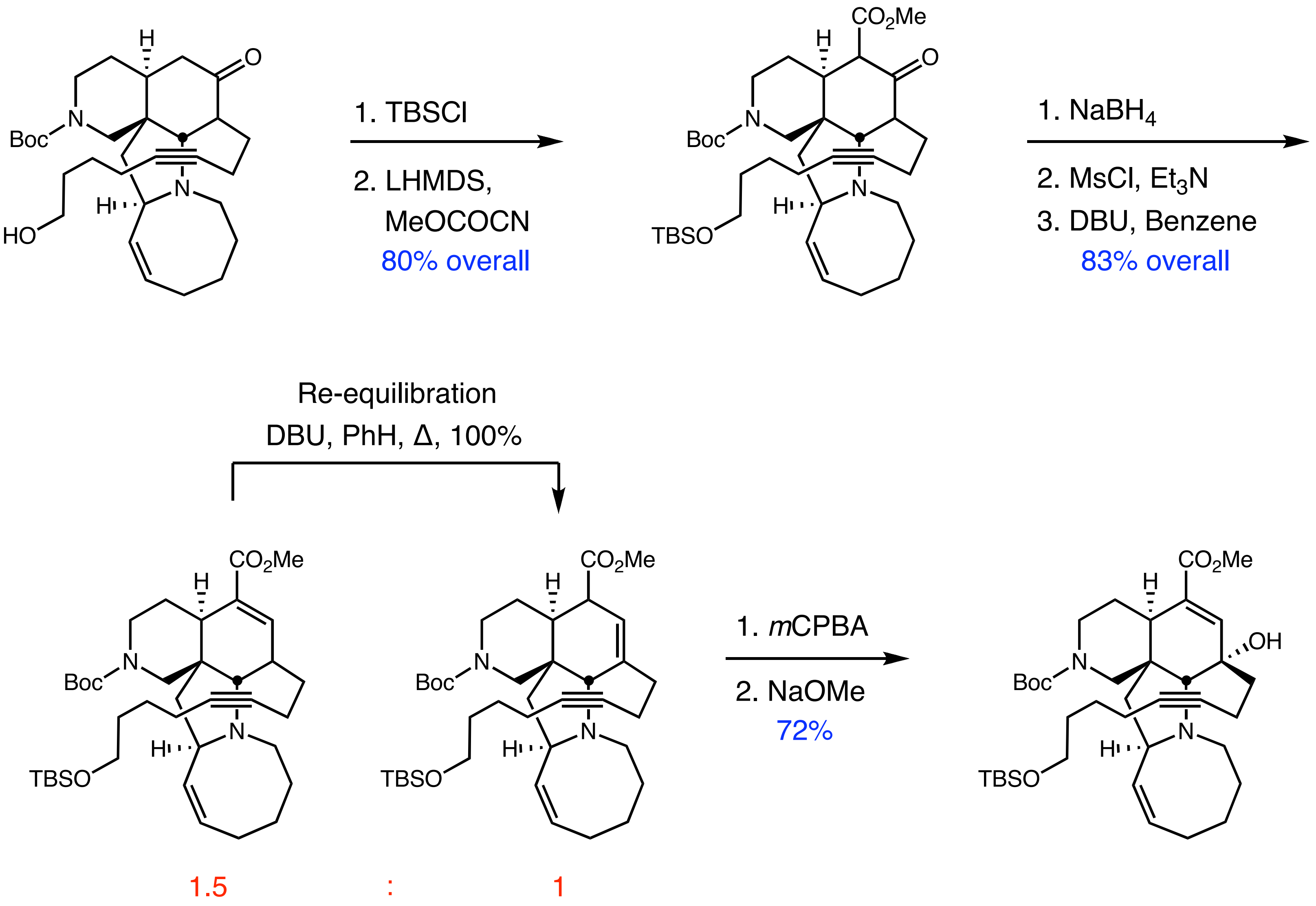
[2+2]-Retro-Mannich-Mannich Cascade: For Real



single isomer

- Real system undergoes photocycloaddition-retro-Mannich-Mannich cascade albeit with reduced yield as compared to the model system
- 20% yield corresponds to roughly 60% for each step in the cascade

Completion of Manzamine A



1. TBSCl
2. LHMDS, MeOCOCN

80% overall

1. NaBH$_4$
2. MsCl, Et$_3$N
3. DBU, Benzene

83% overall

Re-equilibration

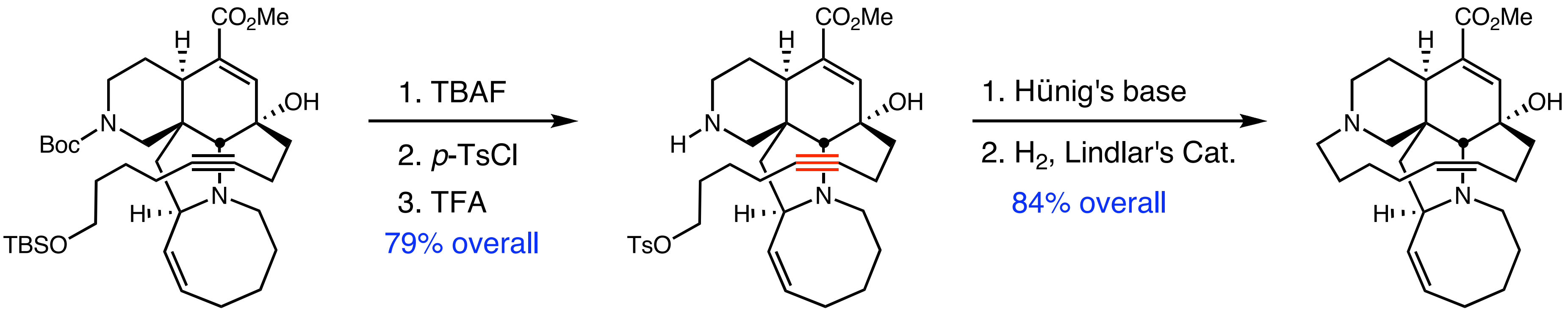
DBU, PhH, Δ, 100%

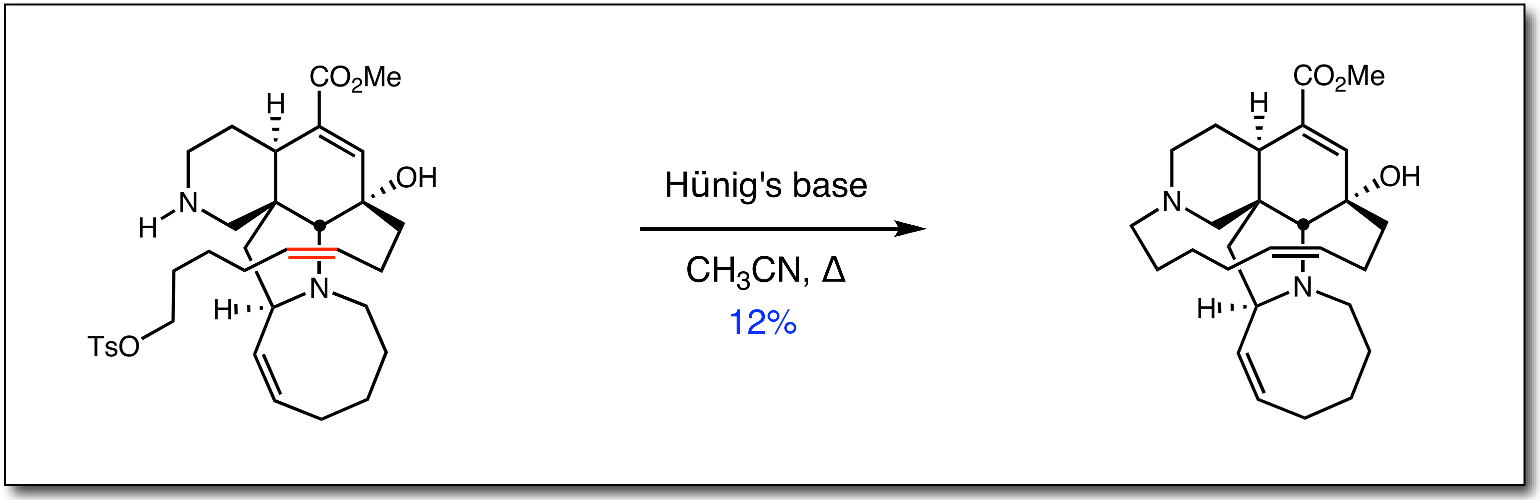
1.5 : 1

1. *m*CPBA
2. NaOMe

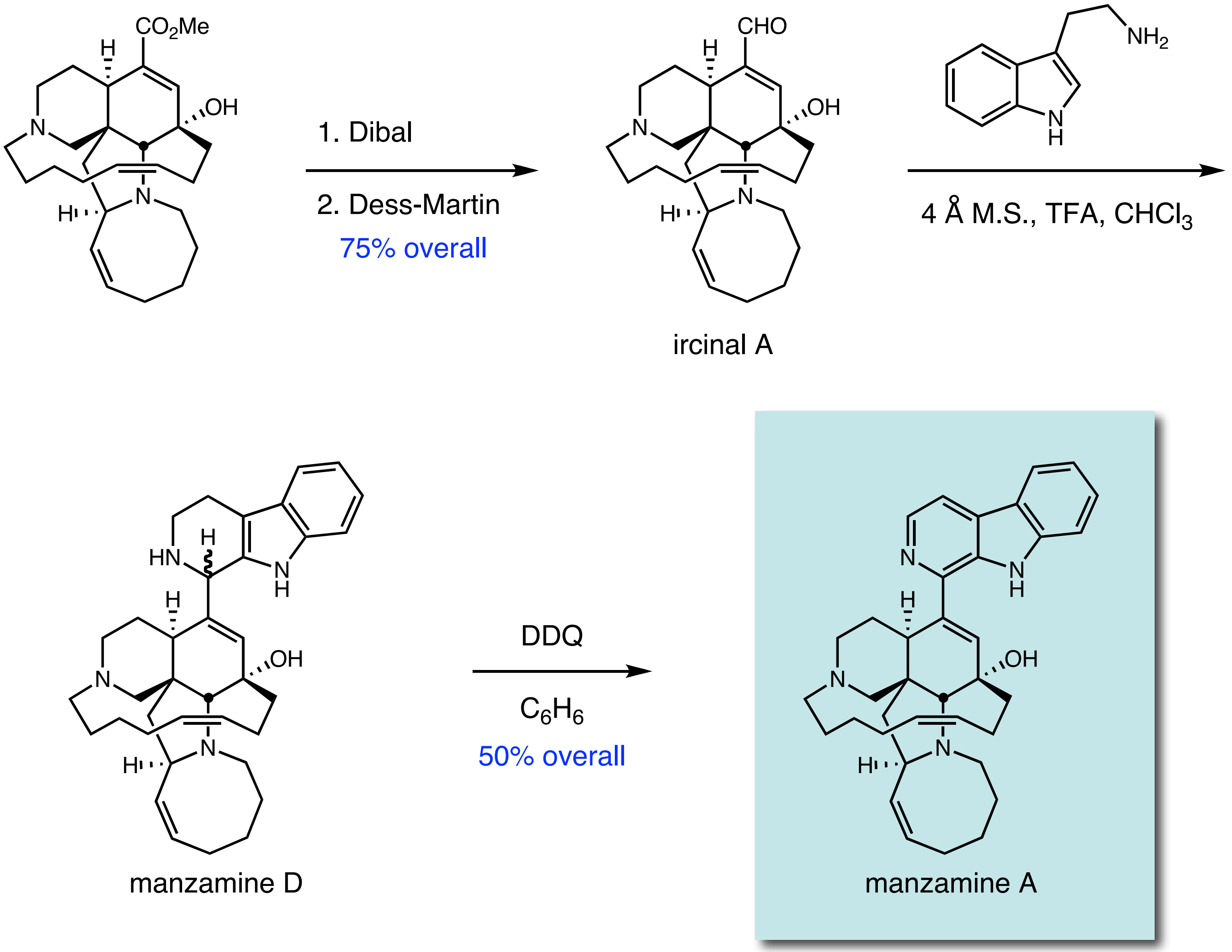
72%

Completion of Manzamine A





Completion of Manzamine A



1. Dibal

2. Dess-Martin

75% overall

ircinal A

4 Å M.S., TFA, $CHCl_3$

manzamine D

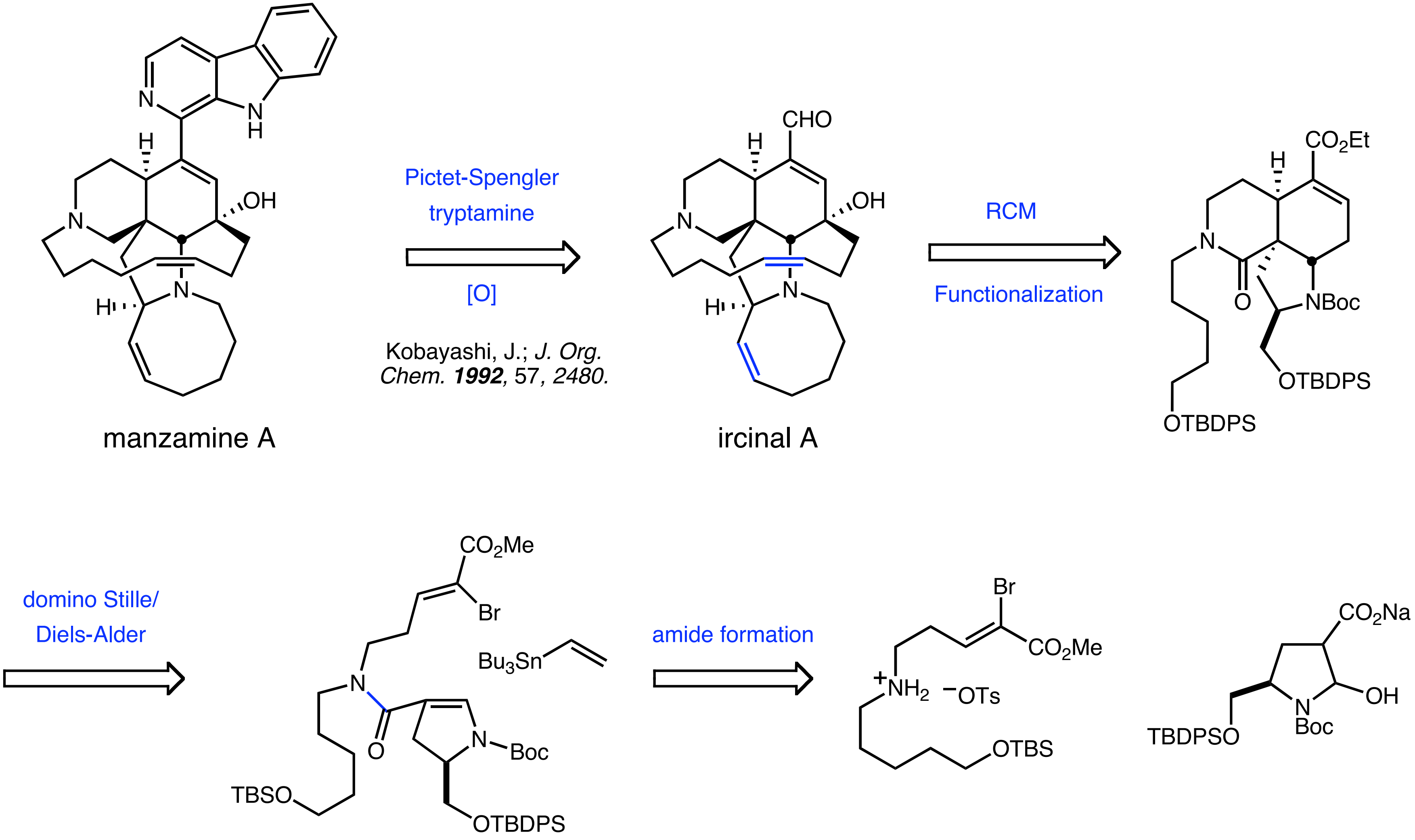
DDQ

C_6H_6

50% overall

manzamine A

Martin: Domino Stille/Diels-Alder Approach Toward Manzamine A

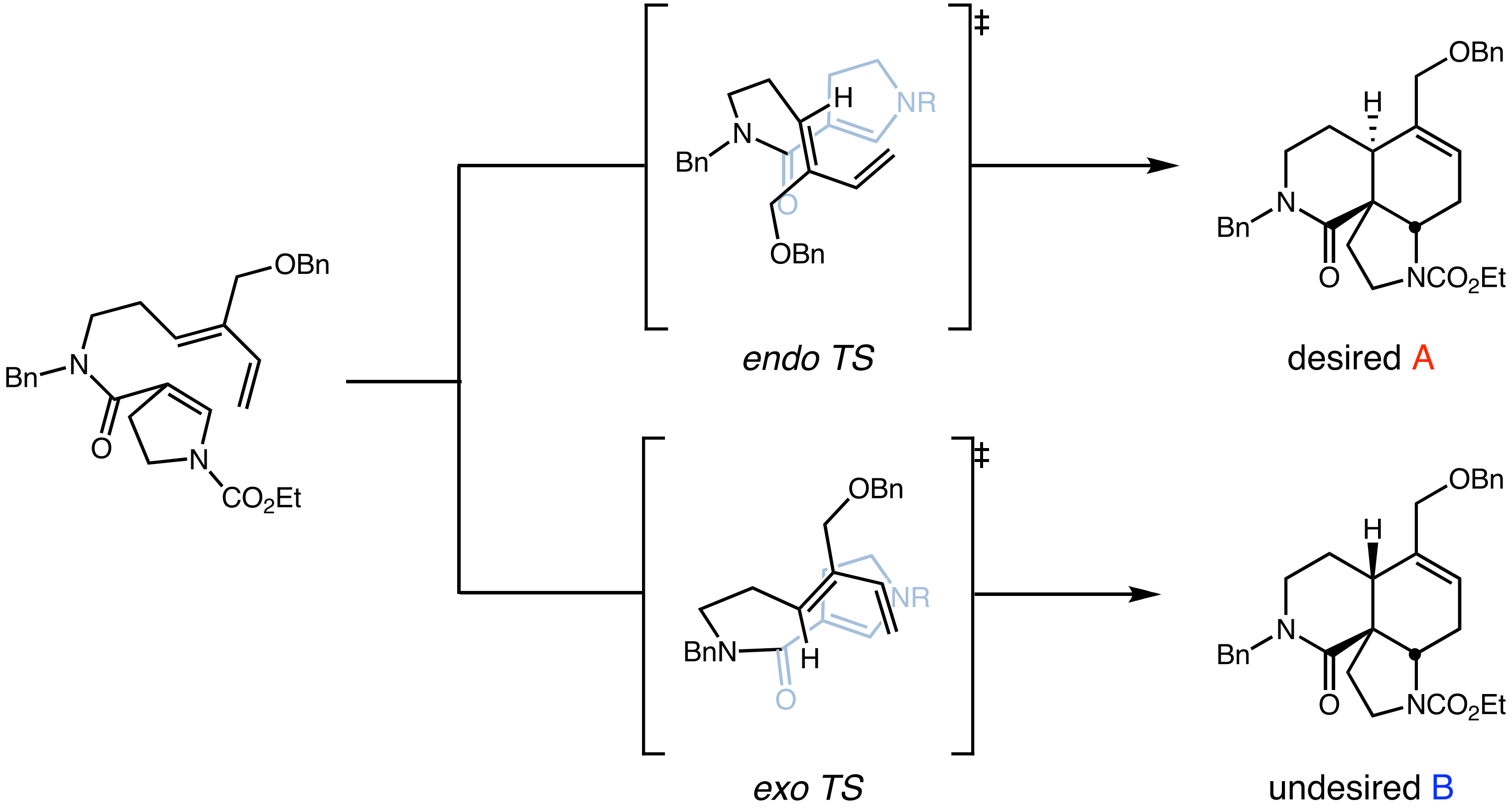


manzamine A

Kobayashi, J.; *J. Org. Chem.* ***1992***, 57, *2480.*

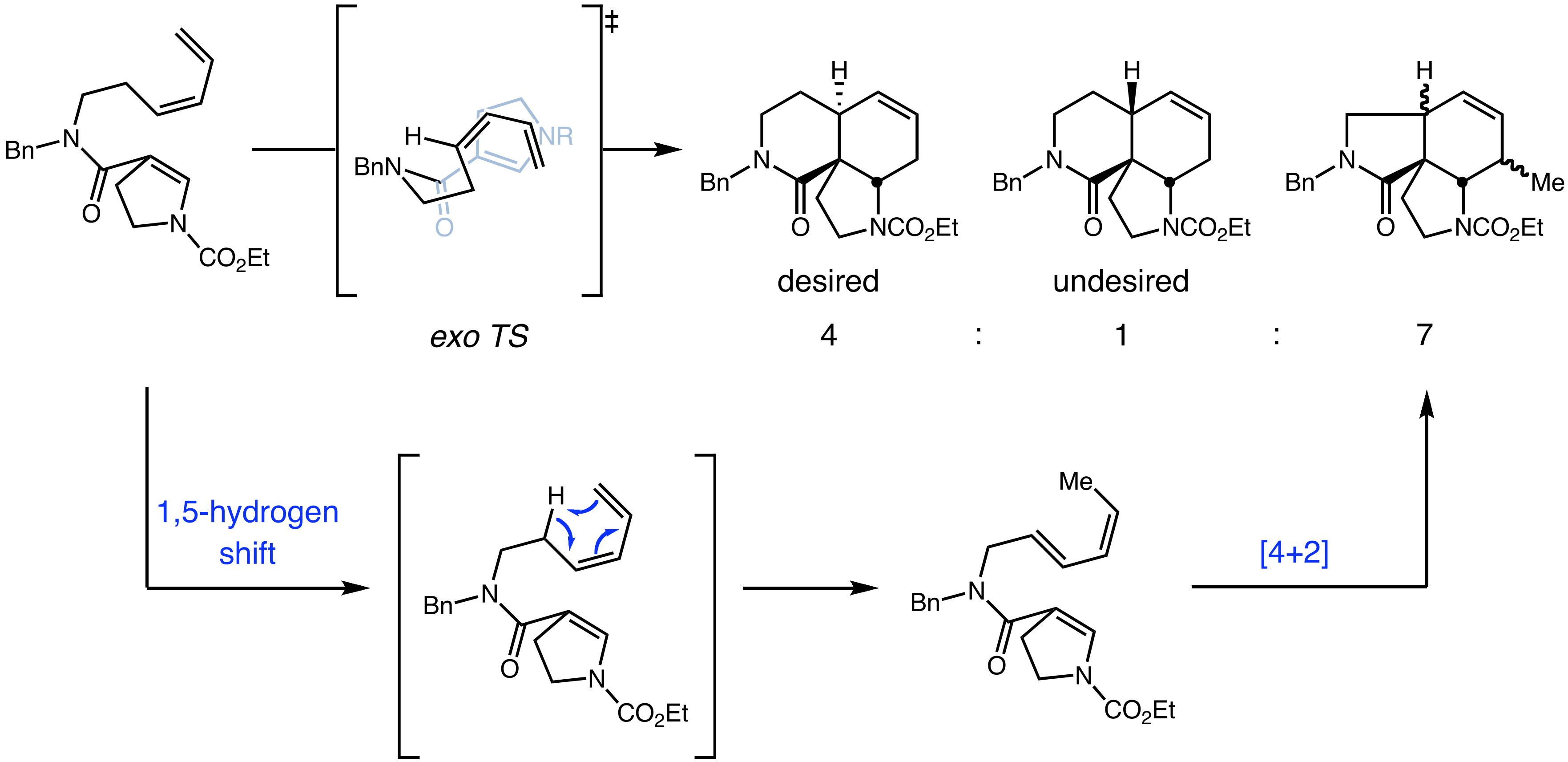
ircinal A

Model Systems to Probe Key Diels-Alder Cyclization

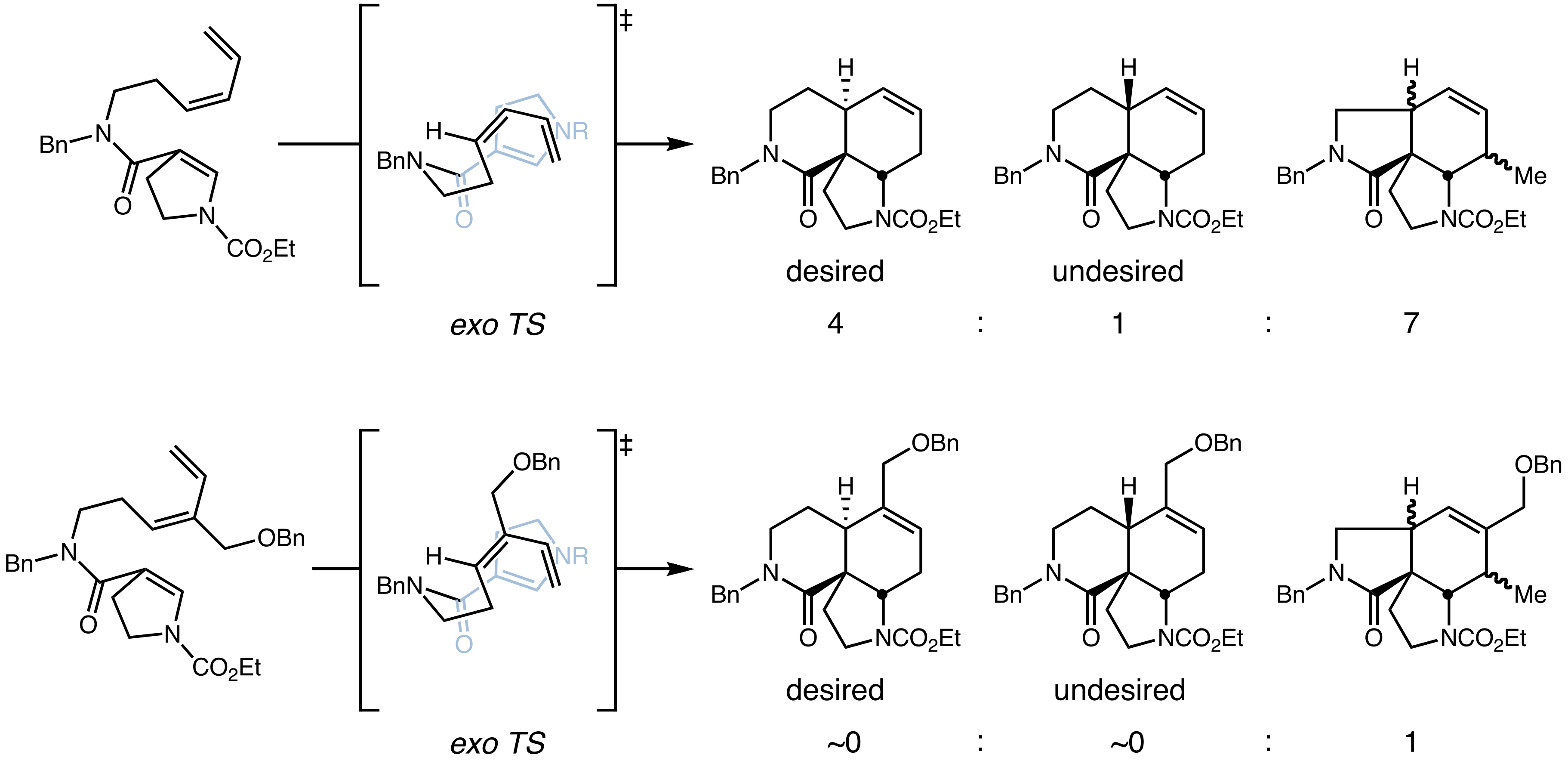


conditions	yield	ratio A:B
Δ	~80%	2:3
$EtAlCl_2$	~80%	3:2

Model Systems to Probe Key Diels-Alder Cyclization

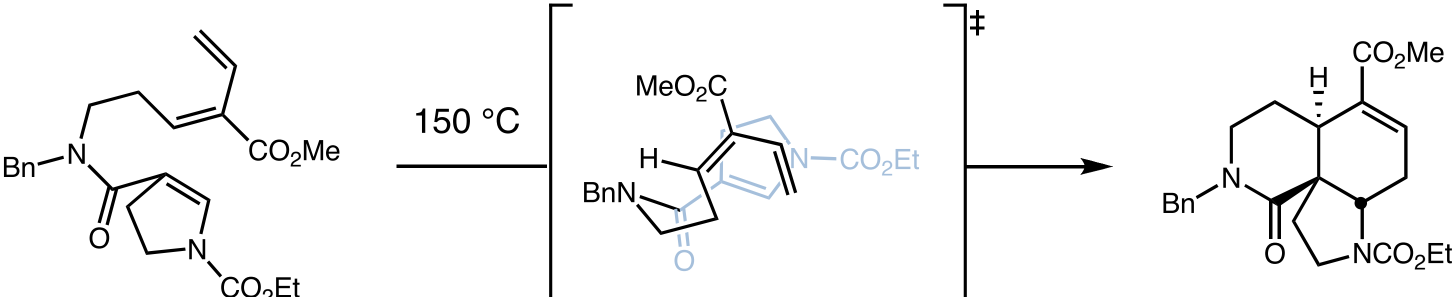


Model Systems to Probe Key Diels-Alder Cyclization



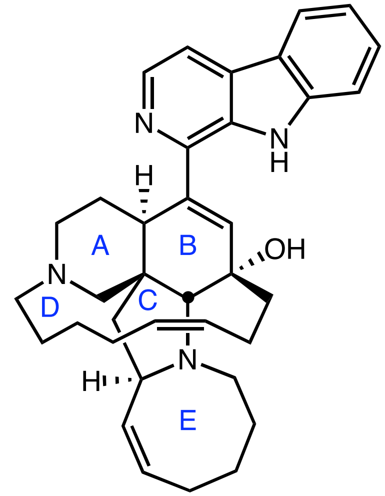
"It then occurred to us that the vinylogous imide might behave as an electron-rich dienophile, and therefore the presence of an electron-withdrawing group on the diene might both facilitate the key cycloaddition and render it more stereoselective."

Model Systems to Probe Key Diels-Alder Cyclization



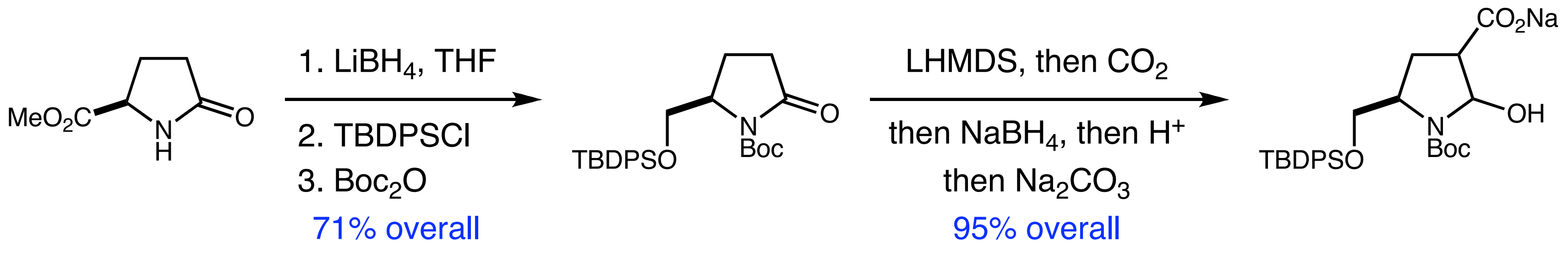
exo TS

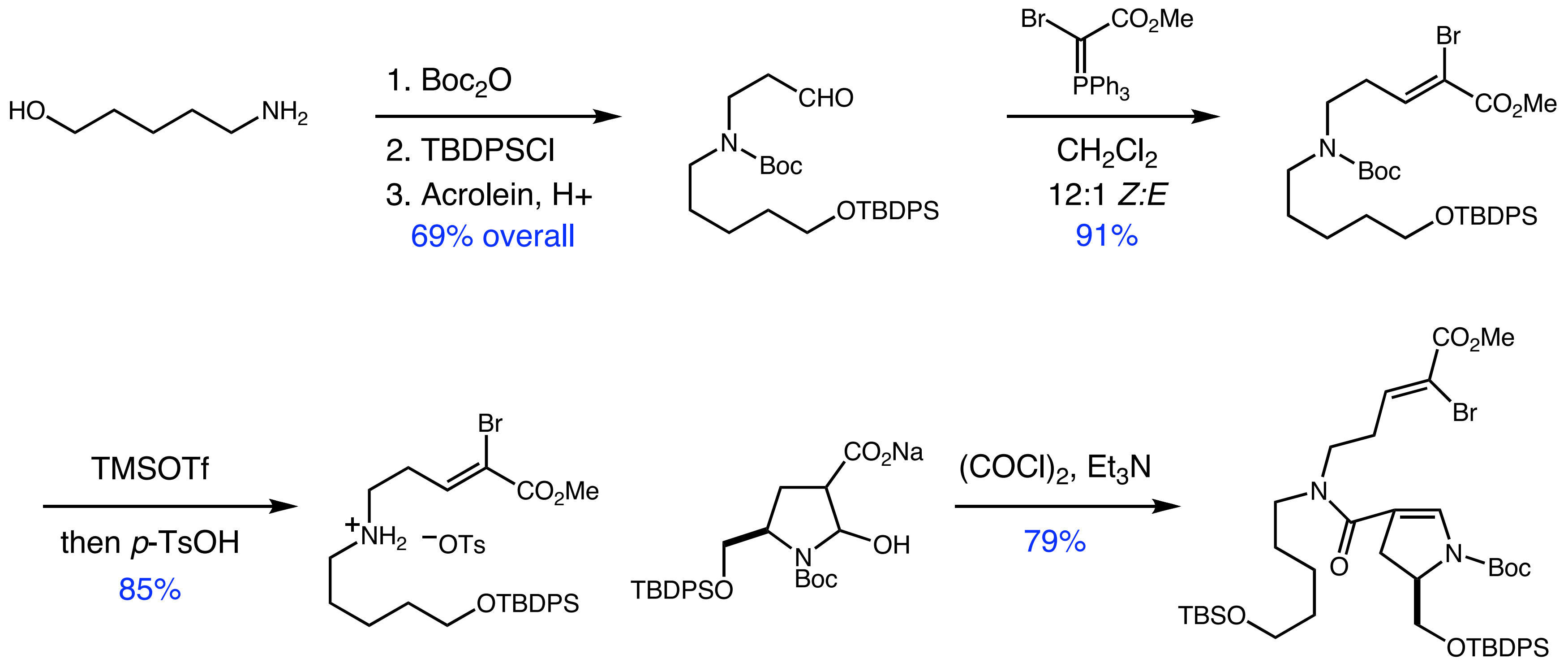
93% yield
single isomer



manzamine A

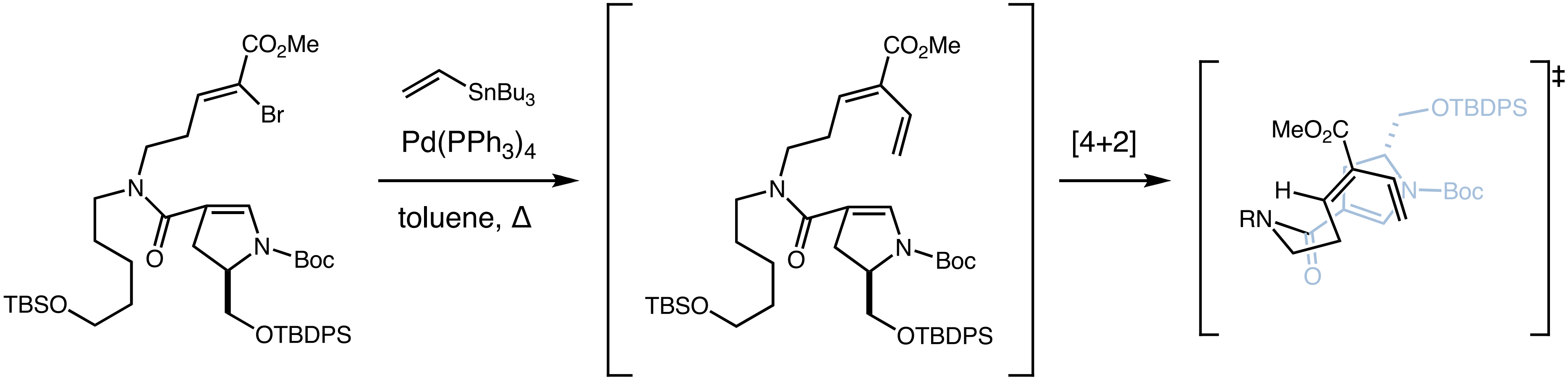
Preparation of Stille/Diels-Alder Reaction Precursor

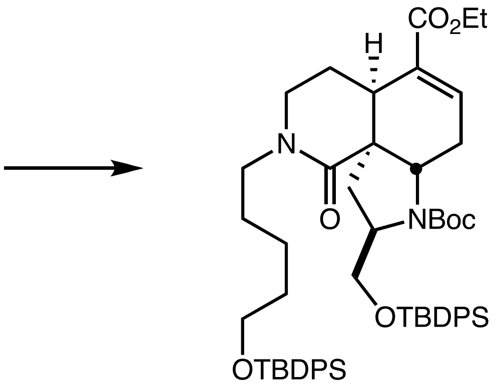




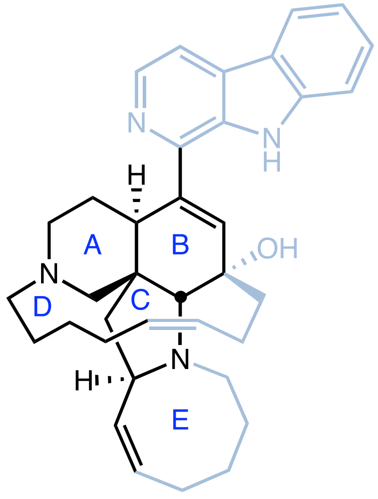
Domino Stille/D.A. Precursor

Key Domino Stille/Diels-Alder Reaction



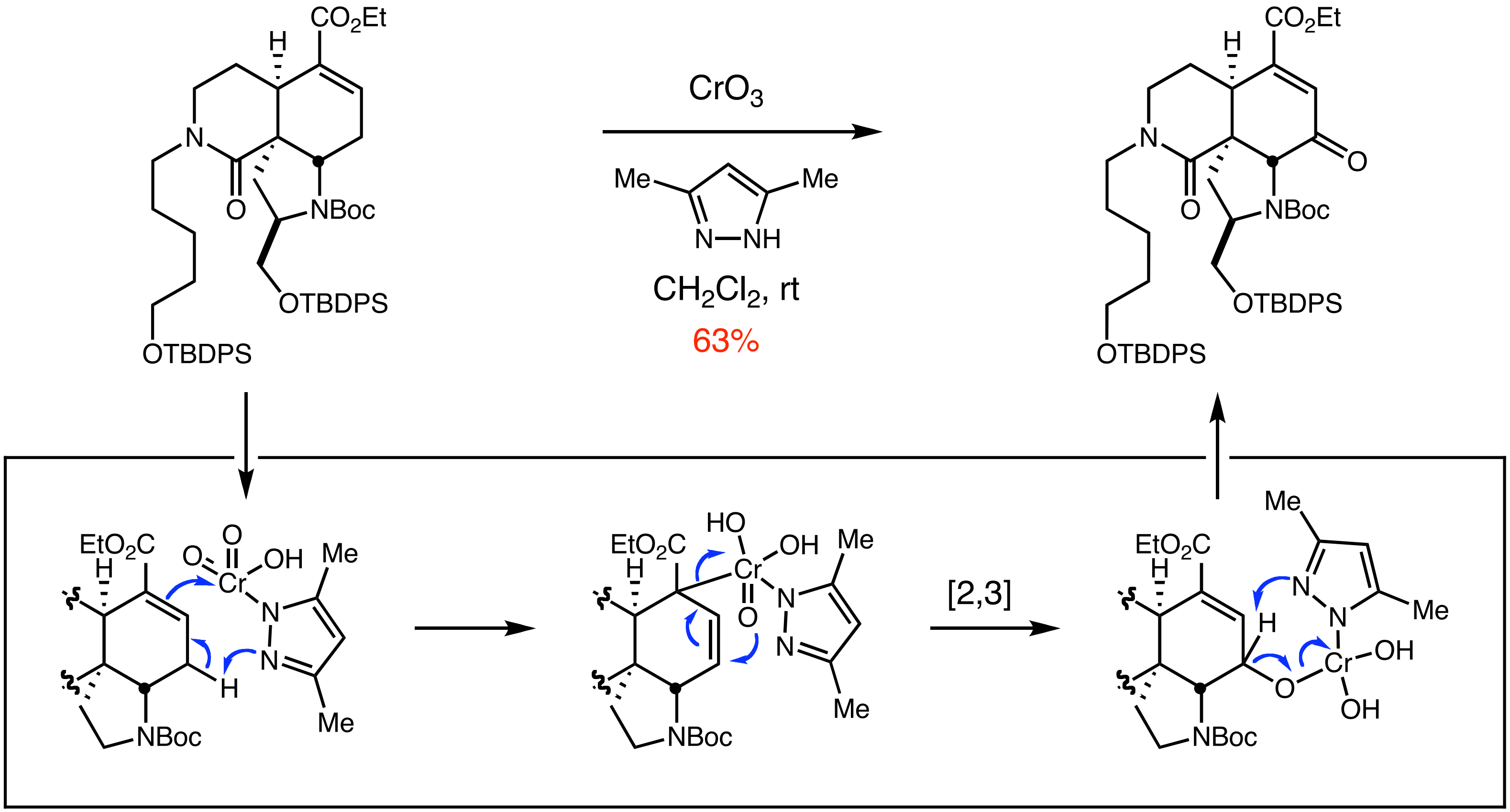


68%
single isomer
7 steps



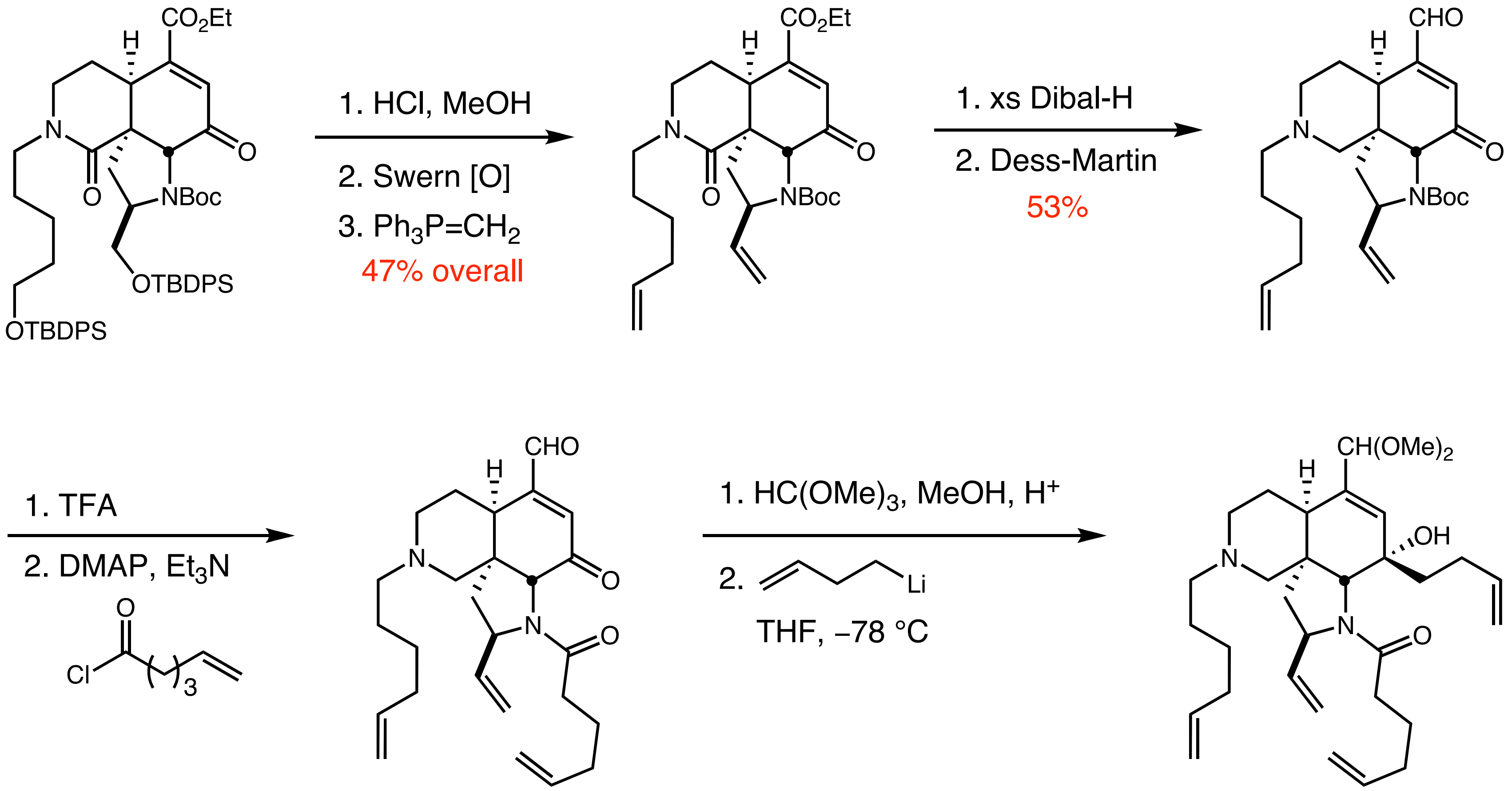
manzamine A

Allylic Oxidation of B-Ring



Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057

Application of Ring Closing Metathesis to Forge the D and E Rings



1. HCl, MeOH
2. Swern [O]
3. $Ph_3P{=}CH_2$
47% overall

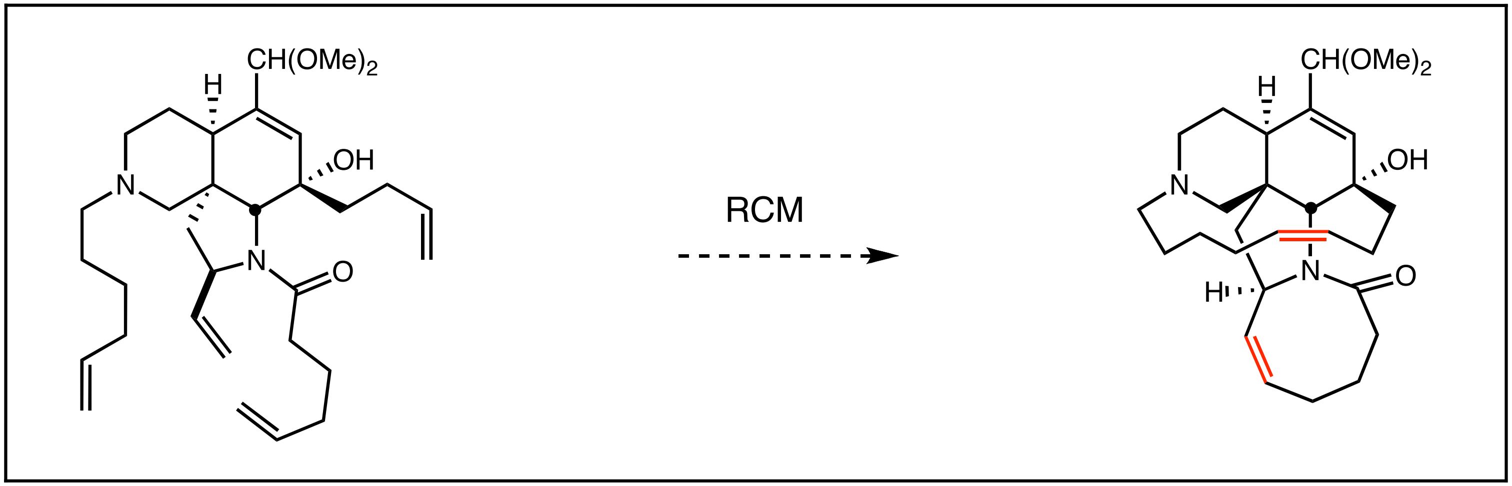
1. xs Dibal-H
2. Dess-Martin
53%

1. TFA
2. DMAP, Et_3N

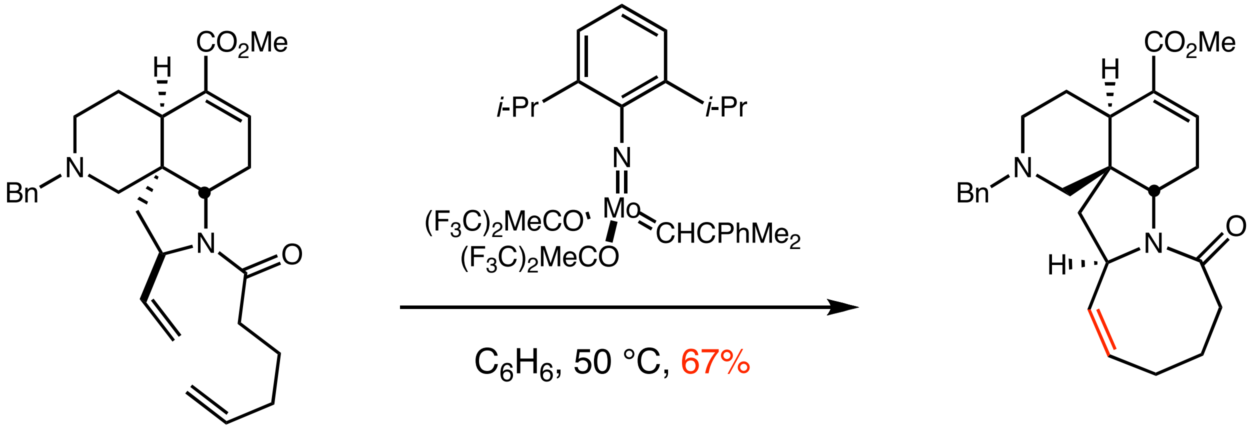
1. $HC(OMe)_3$, MeOH, H^+
2.
THF, −78 °C

Double RCM Precursor

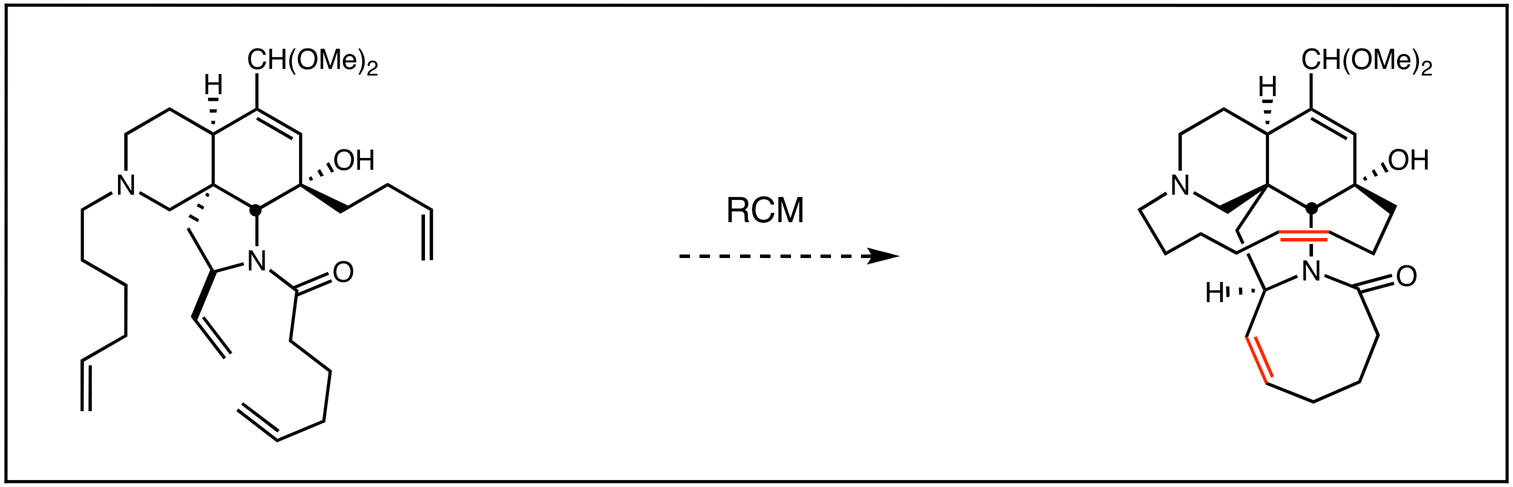
Application of Ring Closing Metathesis to Forge the D and E Rings



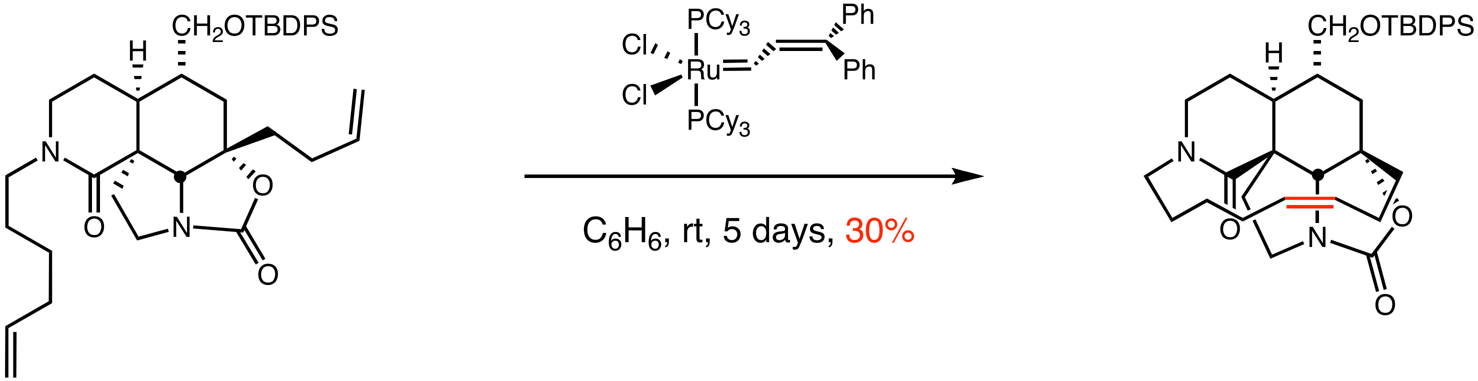
■ Precedent for Azocine Formation



Application of Ring Closing Metathesis to Forge the D and E Rings



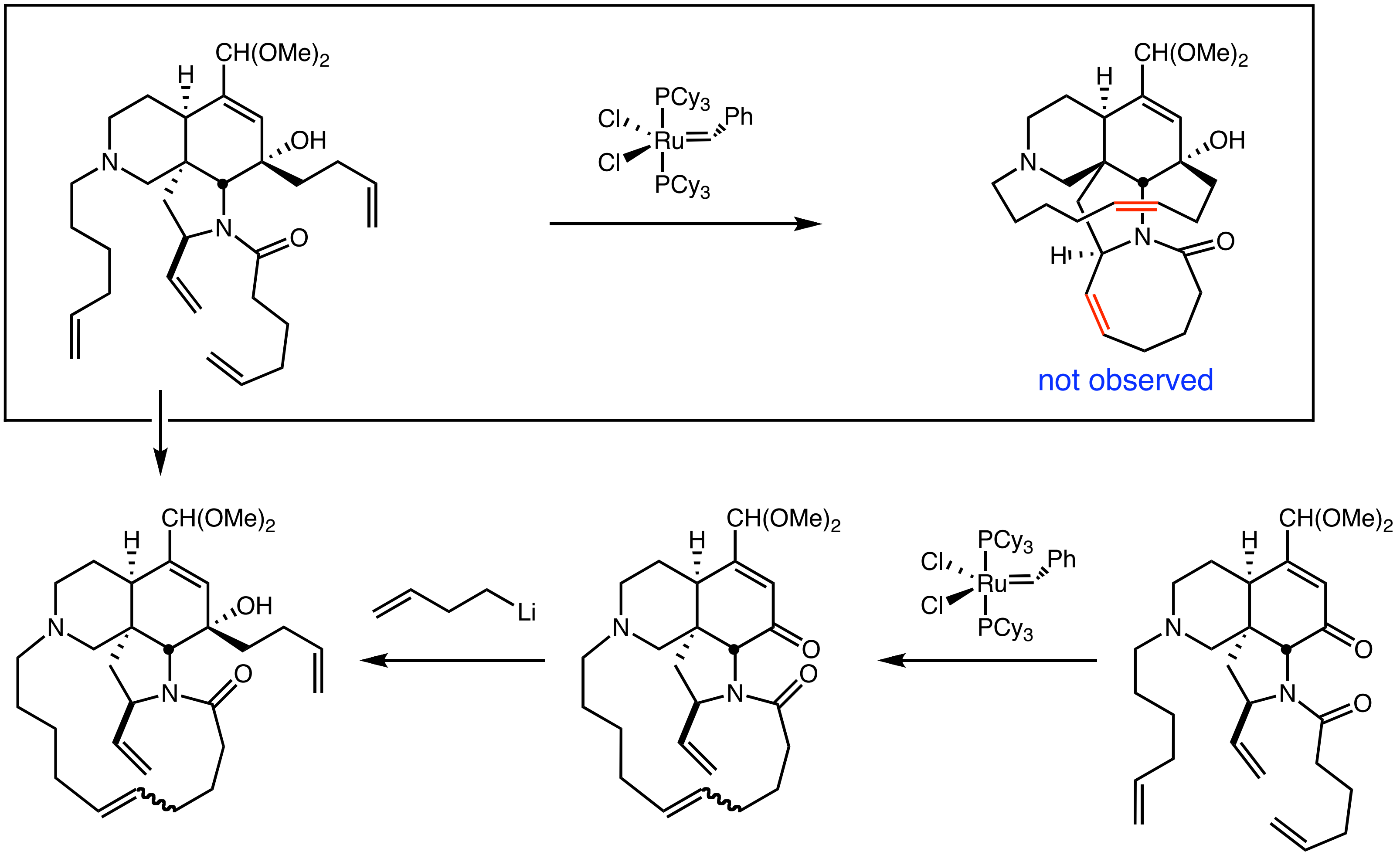
- Precedent for 13 membered ring formation by RCM



C_6H_6, rt, 5 days, 30%

Borer, B. C.; Deerenberg, S.; Bieraugel, H.; Pandit, U. K. *Tet. Lett.* **1994**, *35*, 3191.

Application of Ring Closing Metathesis to Forge the D and E Rings

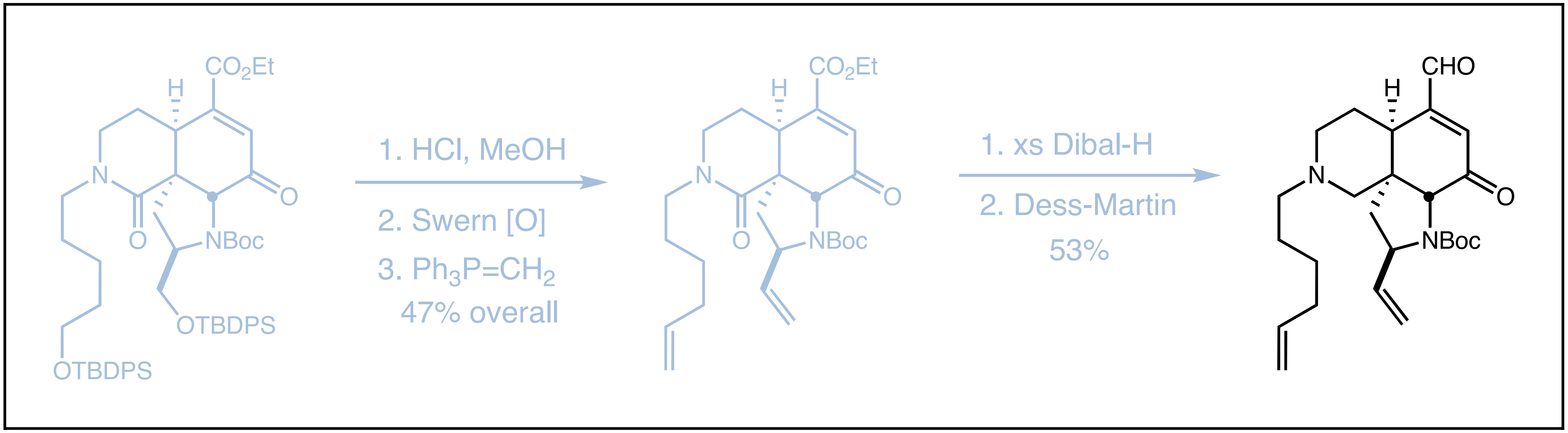


not observed

Major Product

15 membered ring

Application of Ring Closing Metathesis to Forge the D and E Rings

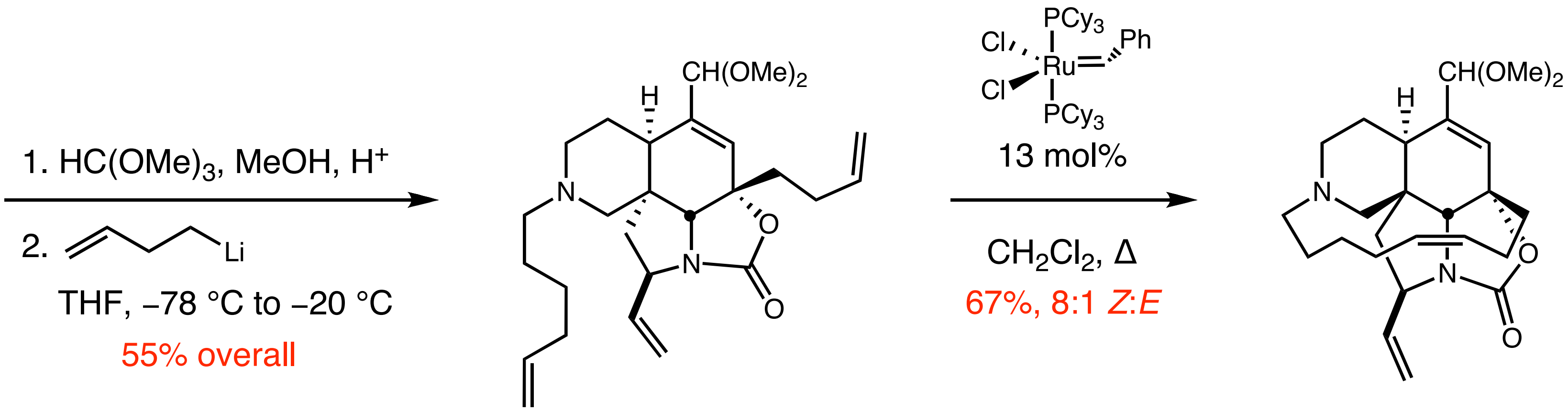


1. HCl, MeOH
2. Swern [O]
3. $Ph_3P{=}CH_2$

47% overall

1. xs Dibal-H
2. Dess-Martin

53%



1. $HC(OMe)_3$, MeOH, H^+
2.

THF, –78 °C to –20 °C

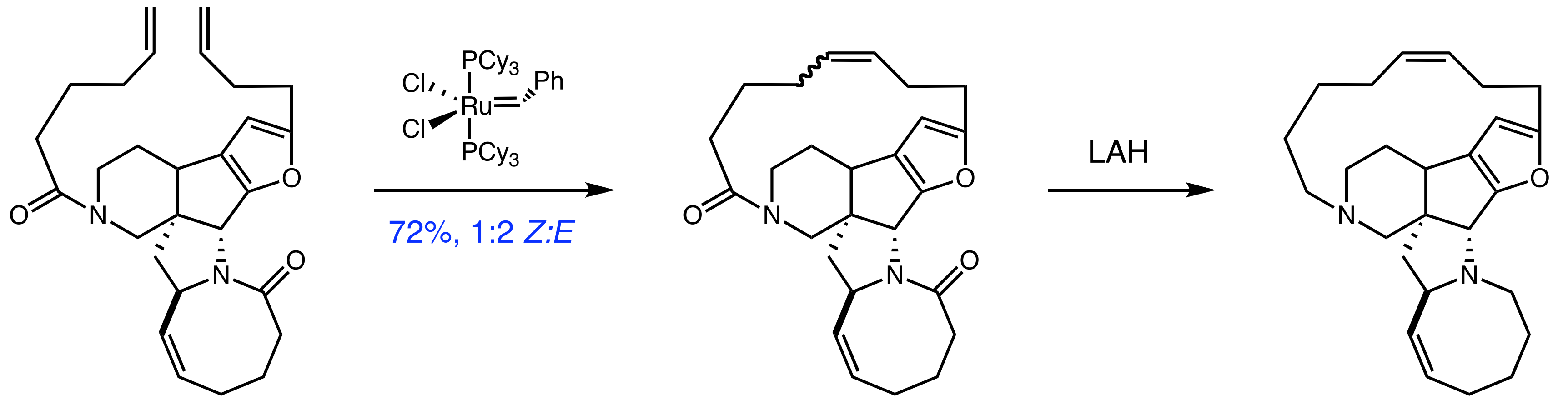
55% overall

13 mol%

CH_2Cl_2, Δ

67%, 8:1 *Z*:*E*

Application of Ring Closing Metathesis to Forge the D and E Rings

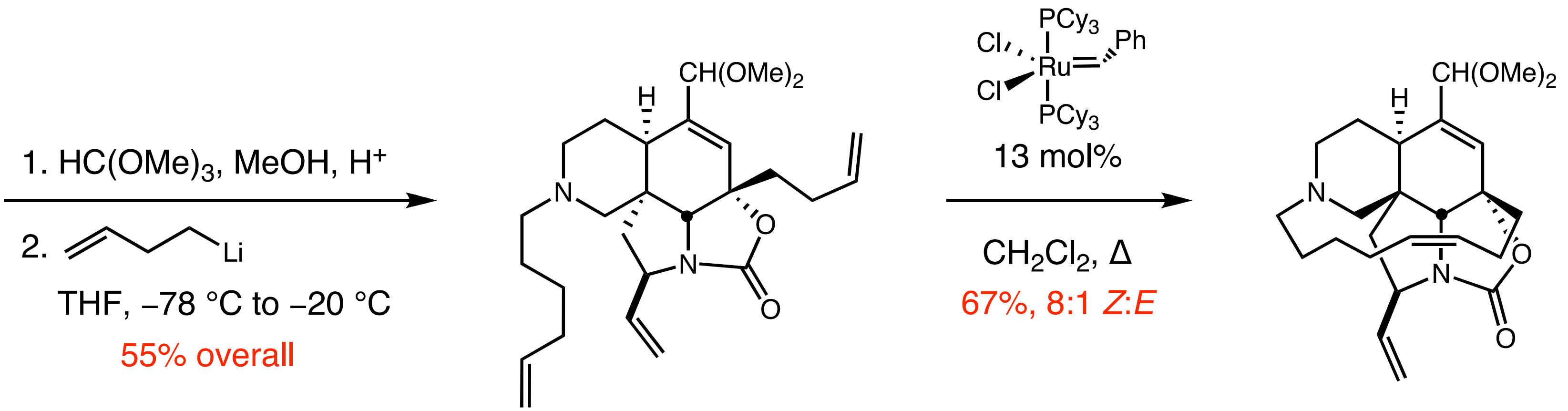


72%, 1:2 *Z:E*

LAH

nakadomarin A

Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2020



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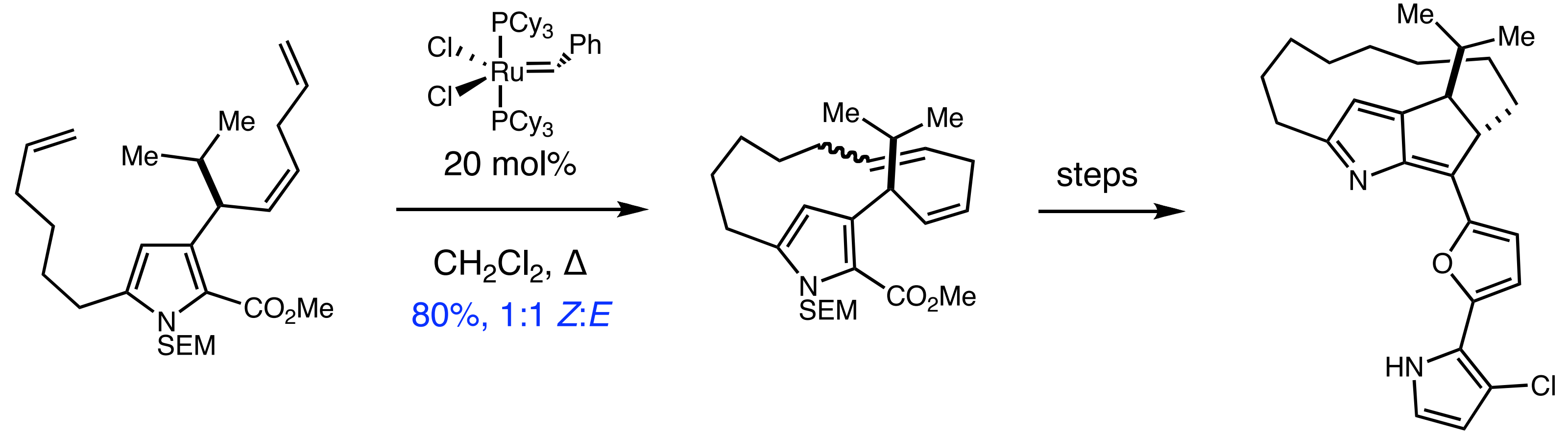
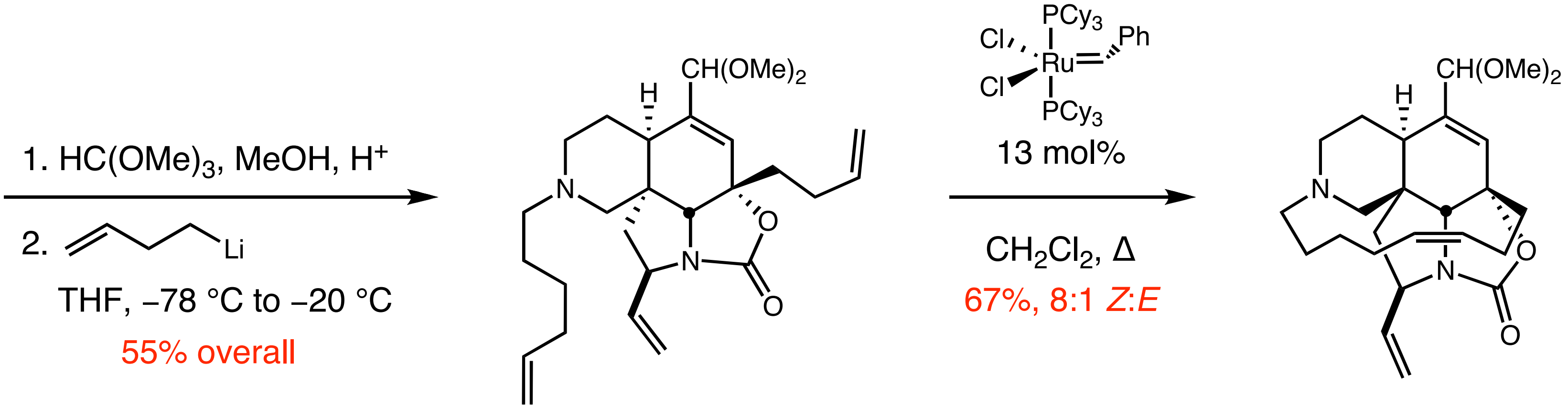
Application of Ring Closing Metathesis to Forge the D and E Rings

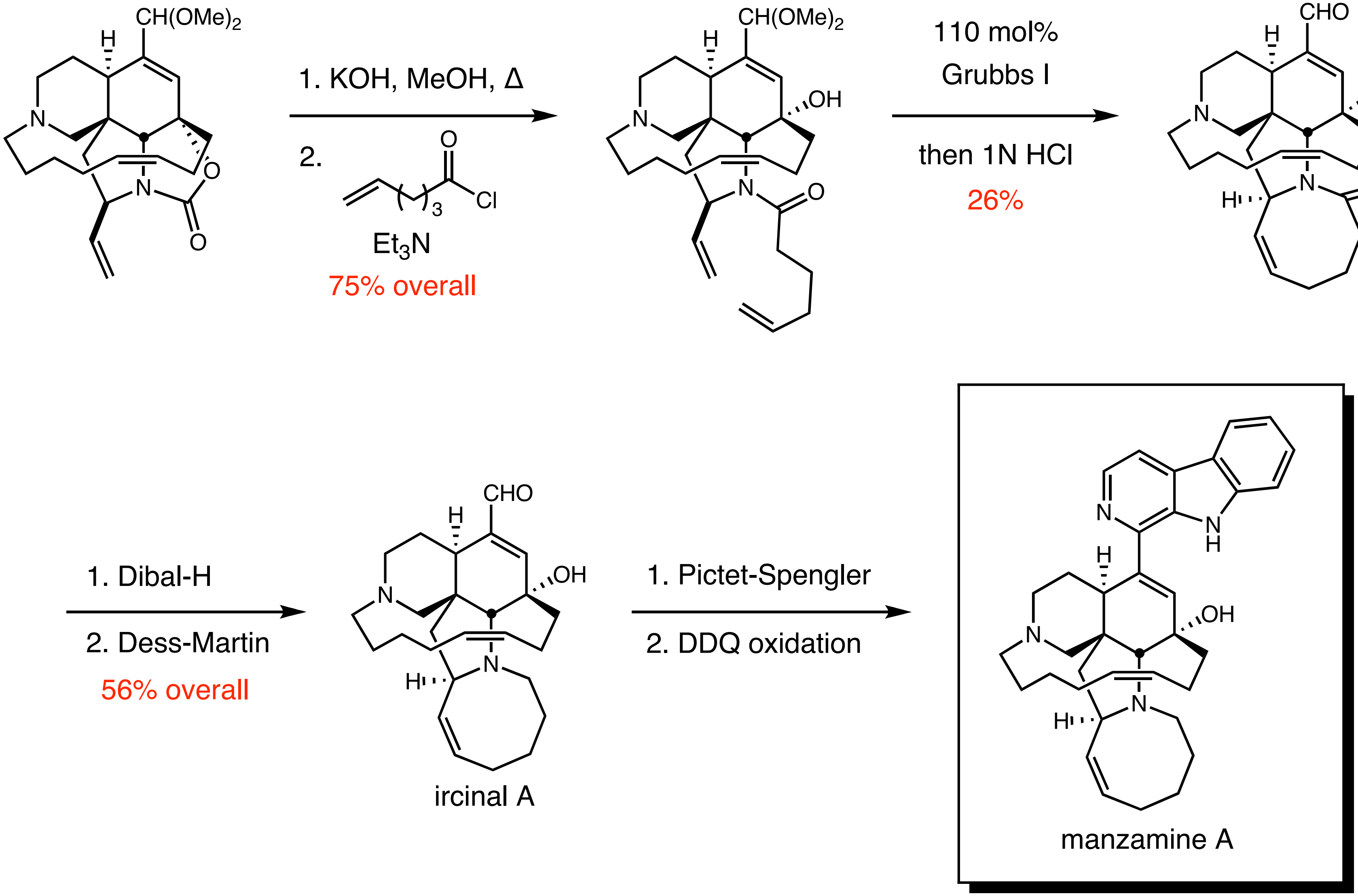


Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* ***2001****, 123*, 8515

ent-roseophilin

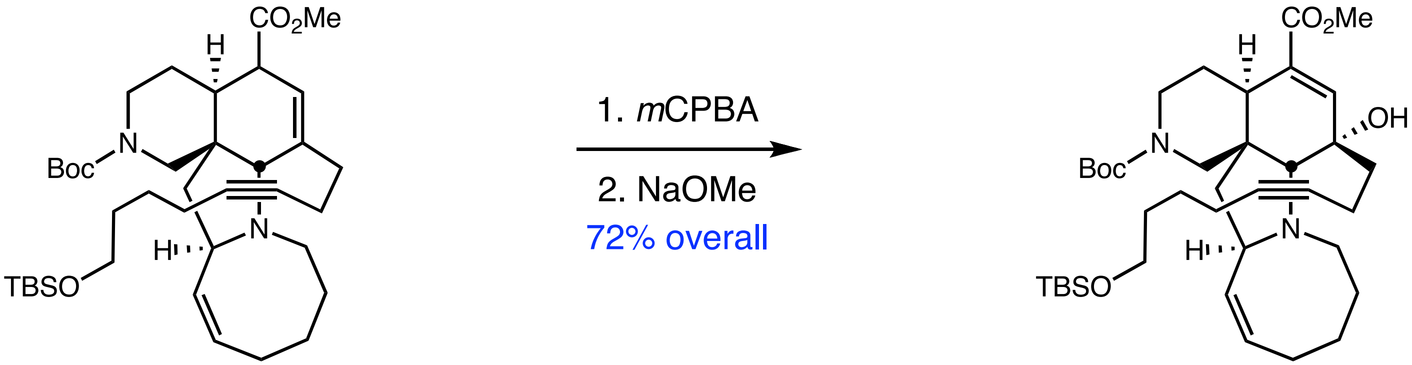


Ring Closing Metathesis and Finishing Touches



Differing Facial Selectivity Based on Nucleophilic or Electrophilic Substitution

- In Winkler's synthesis, epoxidation occurs selectively from the back face

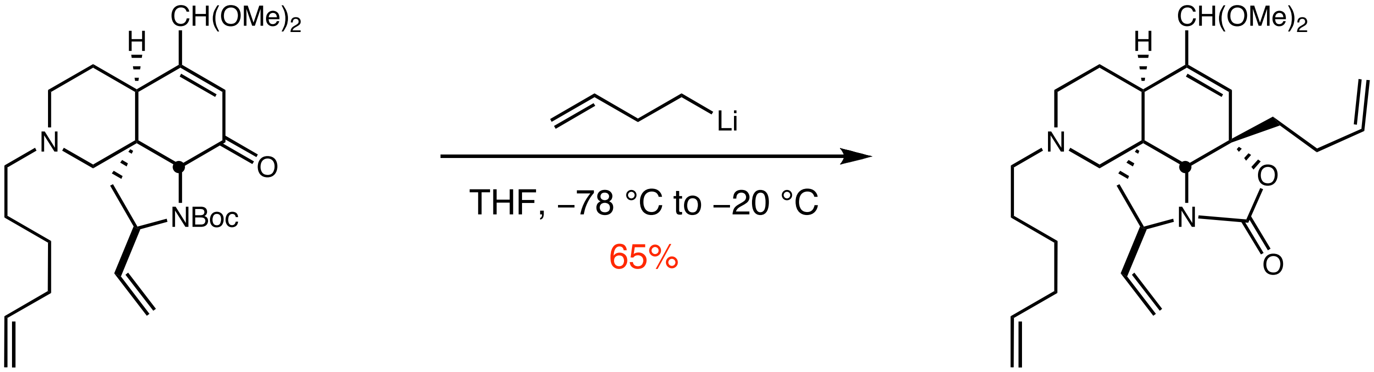


1. *m*CPBA

2. NaOMe

72% overall

- In Martin's synthesis, organolithium addition proceeds onto the top face



THF, –78 °C to –20 °C

65%

Overview of Winkler and Martin's Syntheses

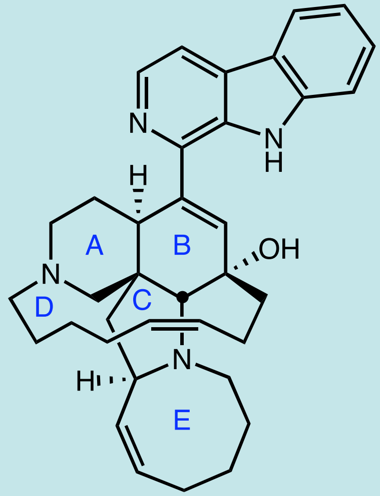
- Winkler and Martin executed syntheses of manzamine A that were completely different from one another based on novel tandem reaction sequences
- While both syntheses were stereoselective, both had critical steps proceed in ~20% yield

Winkler 1998

29 linear steps to ircinal A

0.54% overall yield

83.5% ave. yield/step



manzamine A

Martin 1999

21 linear steps to ircinal A

0.15% overall yield

73.4 % ave. yield/step