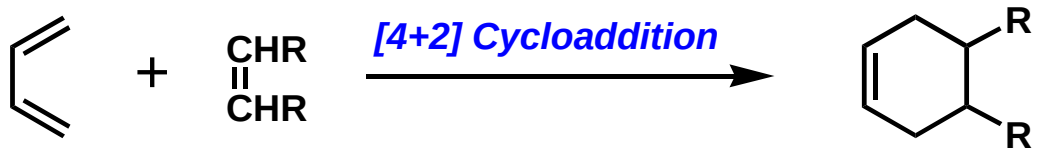
The Intramolecular Diels–Alder Reaction as Part of Multi-step Reactions in Total Syntheses of Complex Natural Products

Christoph Zapf

Supergroup Meeting

Princeton University
6/1/2005

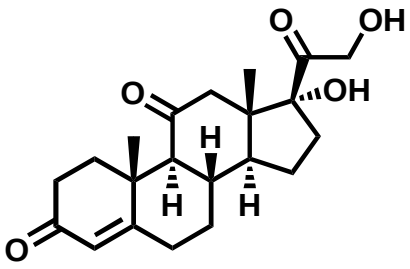
The Diels-Alder Reaction



"Syntheses in the Hydroaromatic Series"
O. Diels, K. Alder, *Annalen* **1928**, *460*, 98.

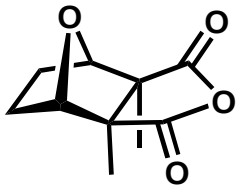
Otto Diels **Kurt Alder**

1950 Nobel Prize in Chemistry: *"For their discovery and development of the diene synthesis"*



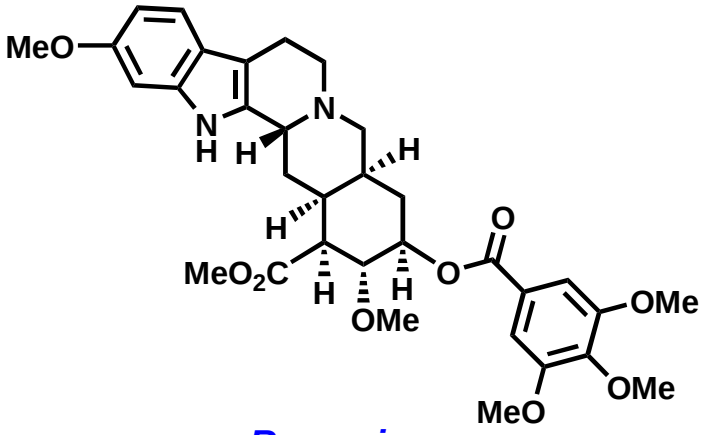
Cortisone

R. B. Woodward and coworkers,
J. Am. Chem. Soc. **1951**, *73*, 2403.



Cantharidin

G. Stork and coworkers,
J. Am. Chem. Soc. **1951**, *73*, 4501.

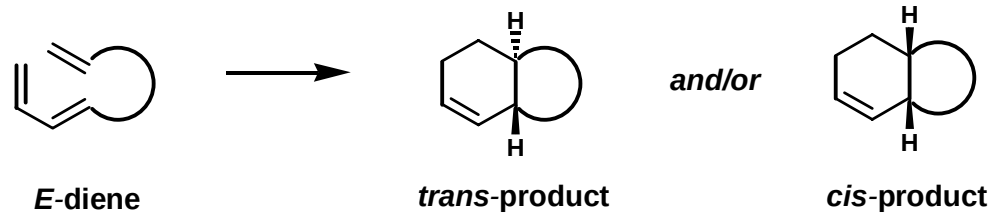


Reserpine

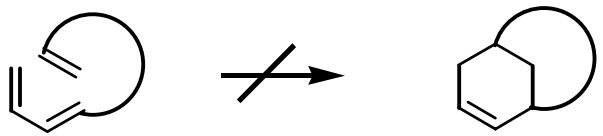
R. B. Woodward and coworkers,
J. Am. Chem. Soc. **1956**, *78*, 2023, 2657.

Intramolecular Diels–Alder – Fundamentals

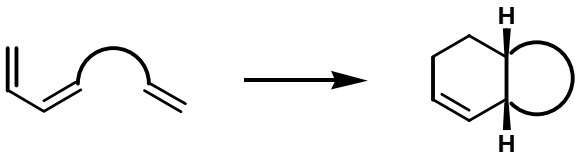
Type I Dienes



E*-diene** ***trans*-product** ***and/or ***cis*-product**



E*-diene** **bridged product** ***too strained for short tethers

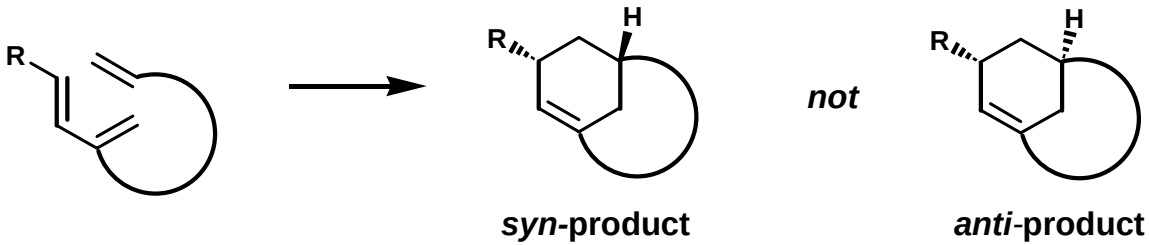


Z*-diene** ***cis*-product** ***not ***trans*-product** ***too strained for short tethers***

Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 513-550.

Intramolecular Diels–Alder – Fundamentals

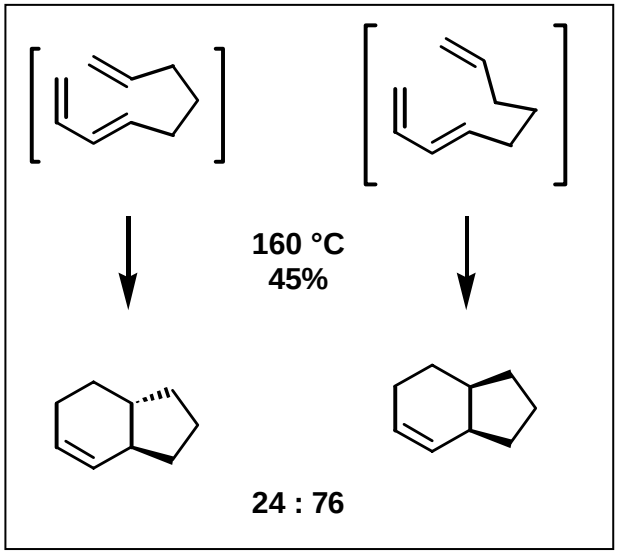
Type II Dienes

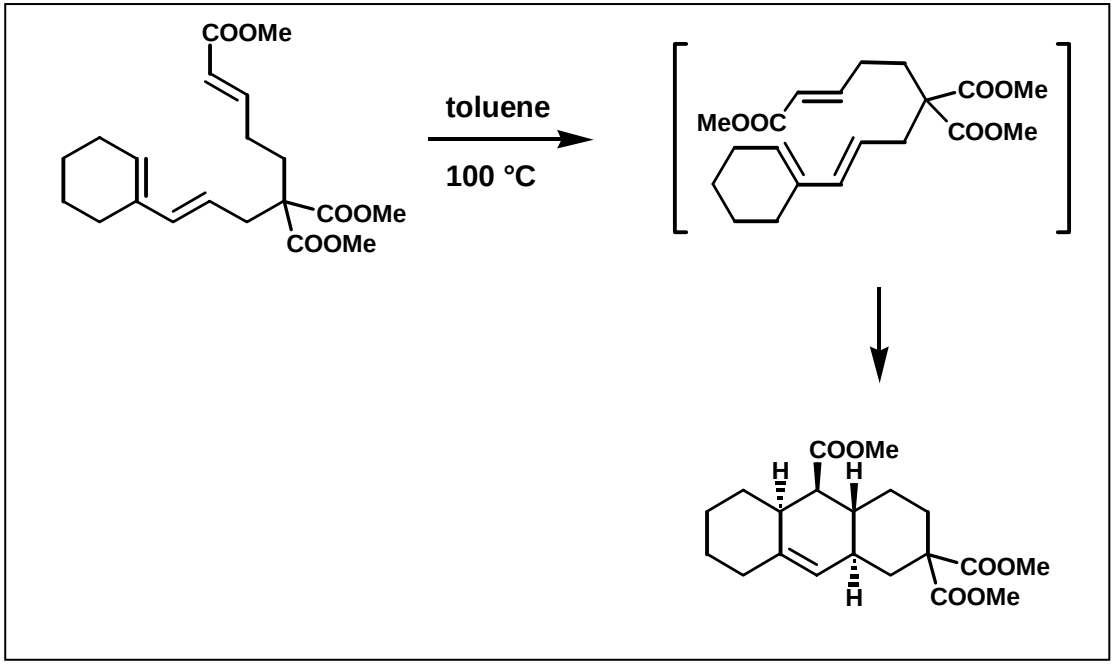


Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 513-550.

Intramolecular Diels–Alder – Fundamentals

Predicting relative Stereochemistry





Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 513-550.

Outline

- Introduction
- Definition
- Examples of Heteroatom Dienes/Dienophiles
- Examples of all Carbon Dienes/Dienophiles
- Conclusion

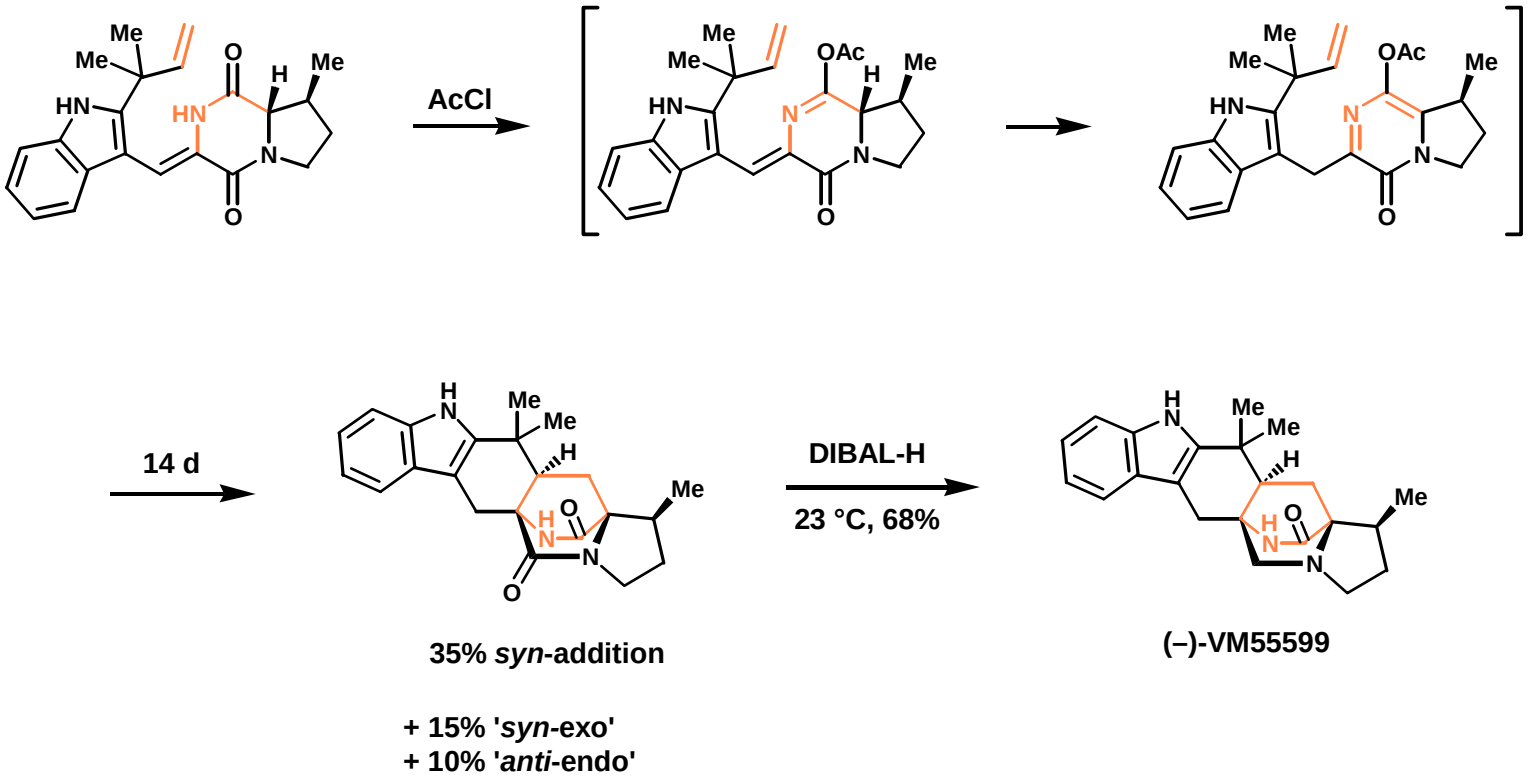
Outline

Examples of IMDA Triggered by:

- Heat
- Activating Reagents (Acetylation, Sulfonylation)
- Fragment Couplings
- Elimination
- Oxidation

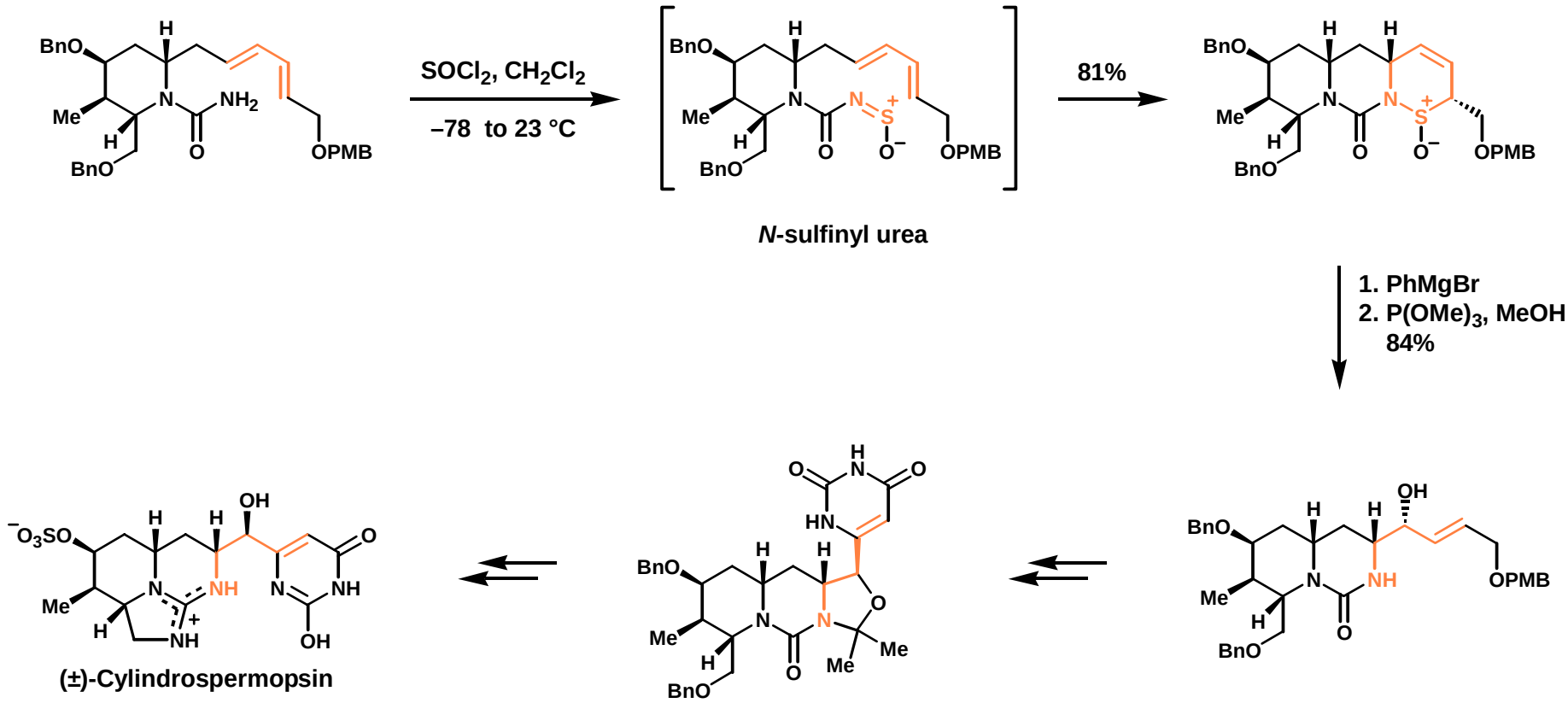
Examples of Heteroatom Dienes/Dienophiles

Total Synthesis of VM55599. Utilization of an Intramolecular Diels–Alder Cycloaddition of Potential Biogenetic Relevance



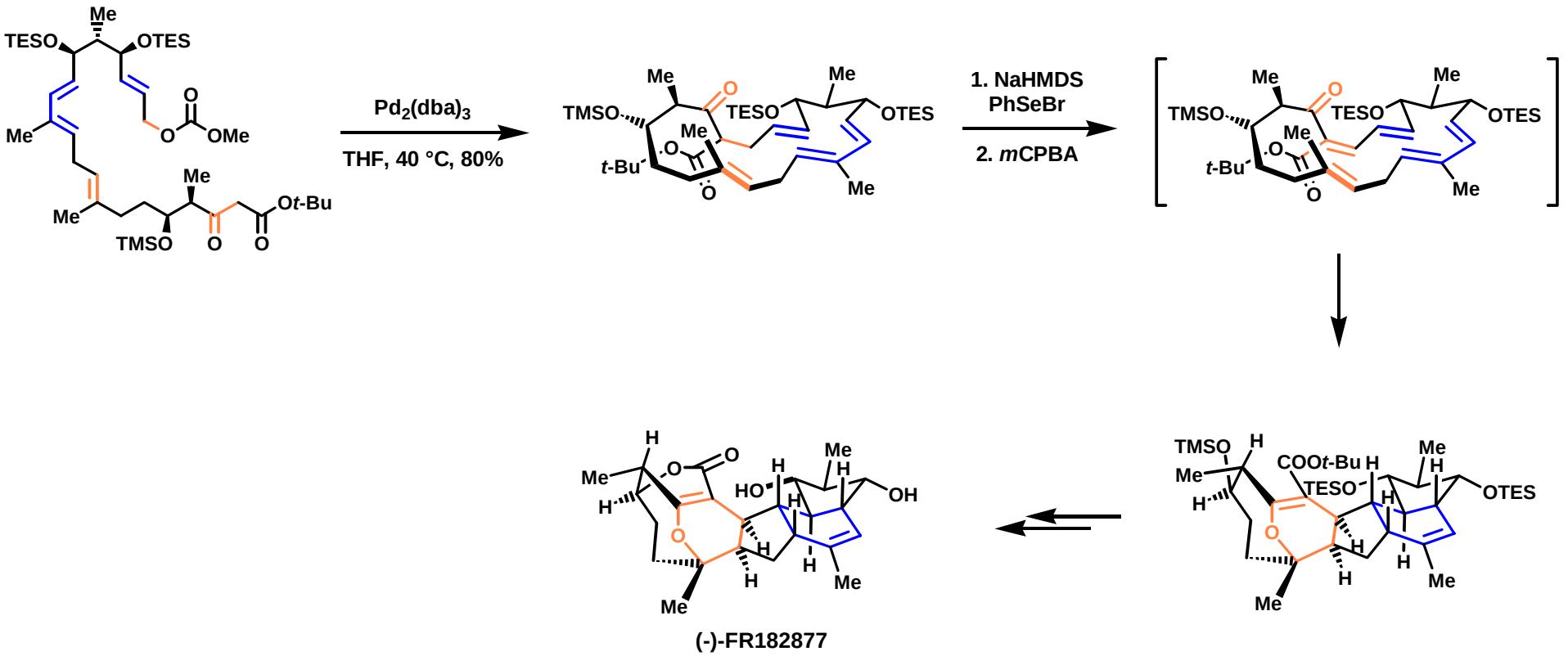
(a) Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 1675-1683. (b) Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 2556-2559.

Stereoselective Total Syntheses and Reassignment of Stereochemistry of Cylindrospermopsin



Heintzelman, G. R.; Fang, W.-K.; Keen, S. P.; Wallace, G. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 3939-3945.

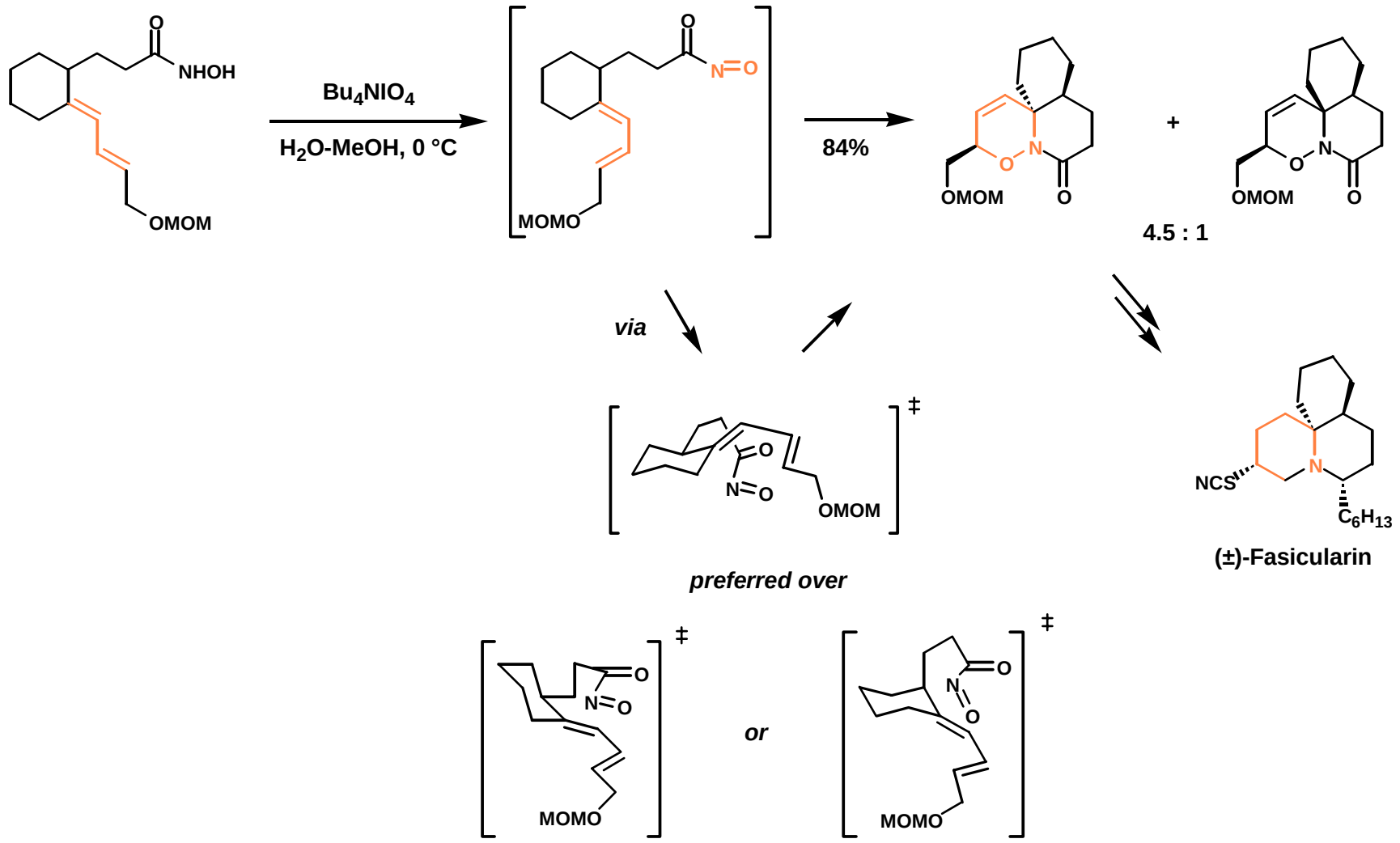
An enantioselective synthesis of (–)-FR182877 provides a chemical rationalization of its structure



(-)-FR182877

Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393-5407.

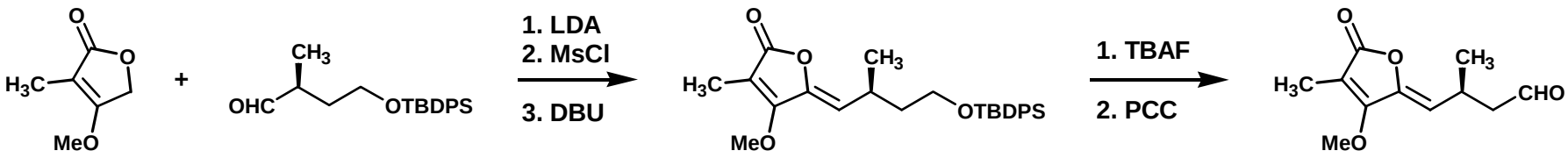
Total Synthesis of (±)-Fasicularin Based on Stereocontrolled Intramolecular Acylnitroso-Diels–Alder Reaction



Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583-4592.

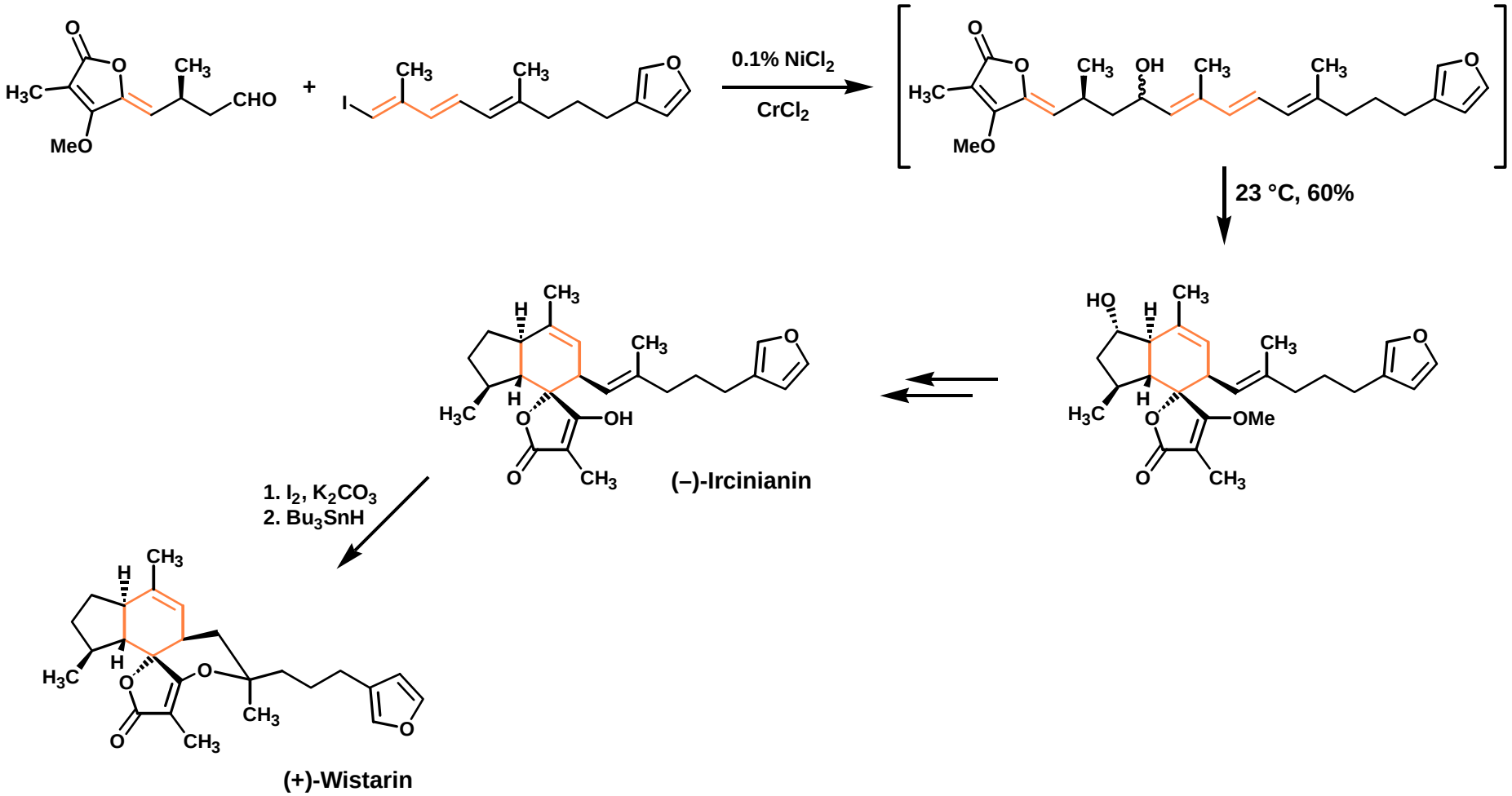
Examples of all Carbon Dienes/Dienophiles

Total Synthesis of (–)-Ircinianin and (+)-Wistarin



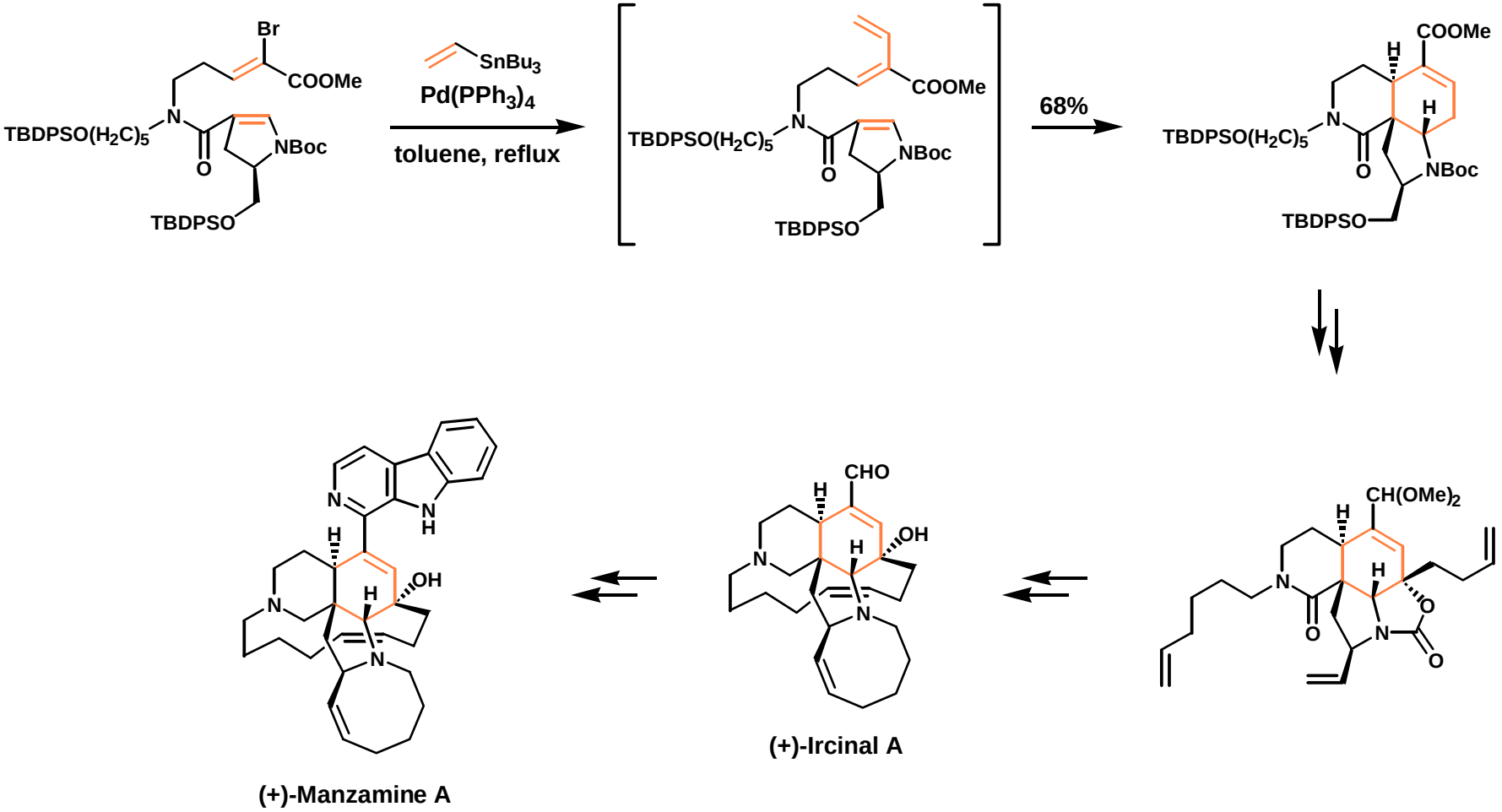
Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1997**, *62*, 1691-1701.

Total Synthesis of (–)-Ircinianin and (+)-Wistarin



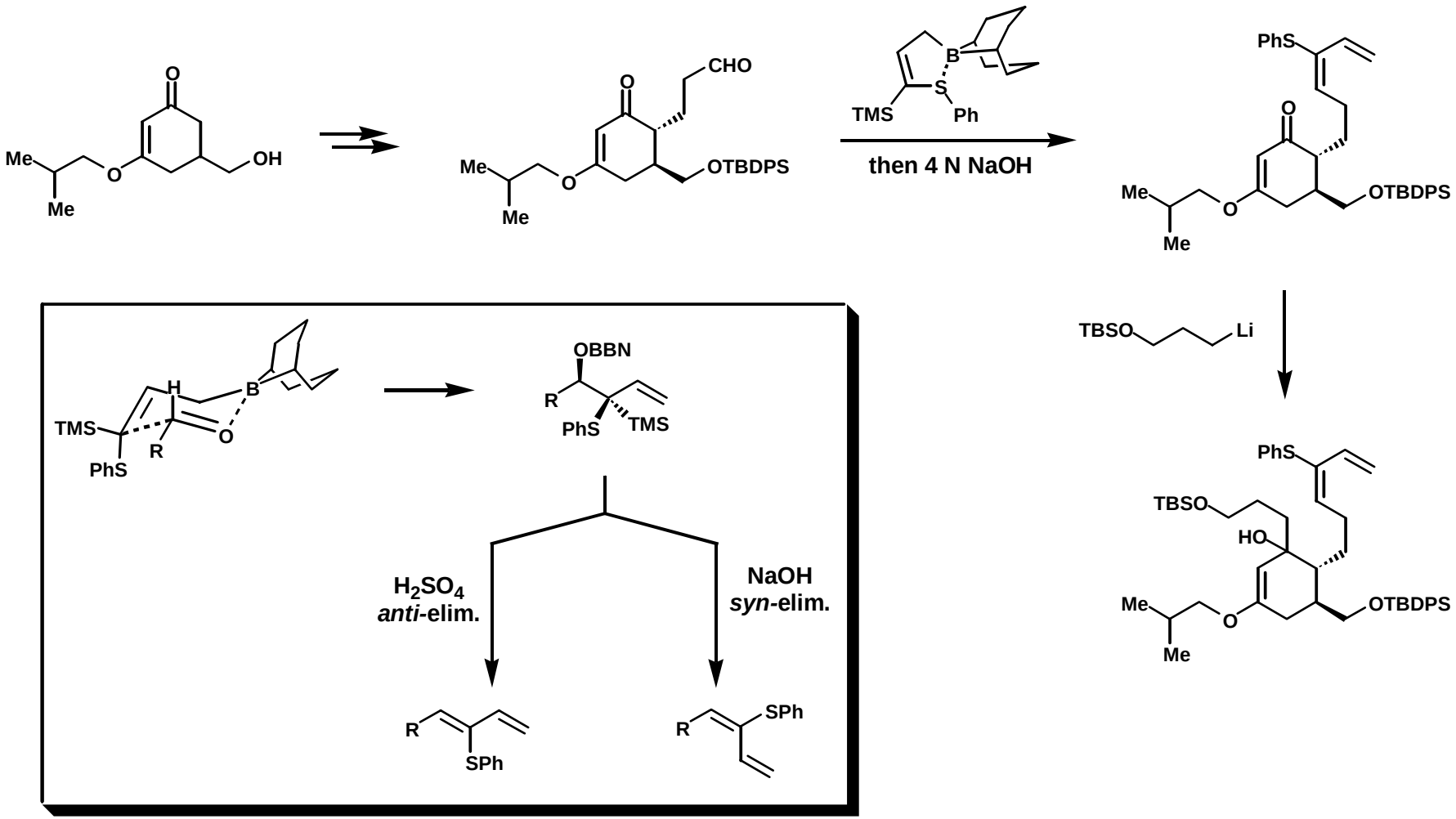
Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1997**, *62*, 1691-1701.

Enantioselective Total Syntheses of Manzamine A and Related Alkaloids



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*, 8584-8592.

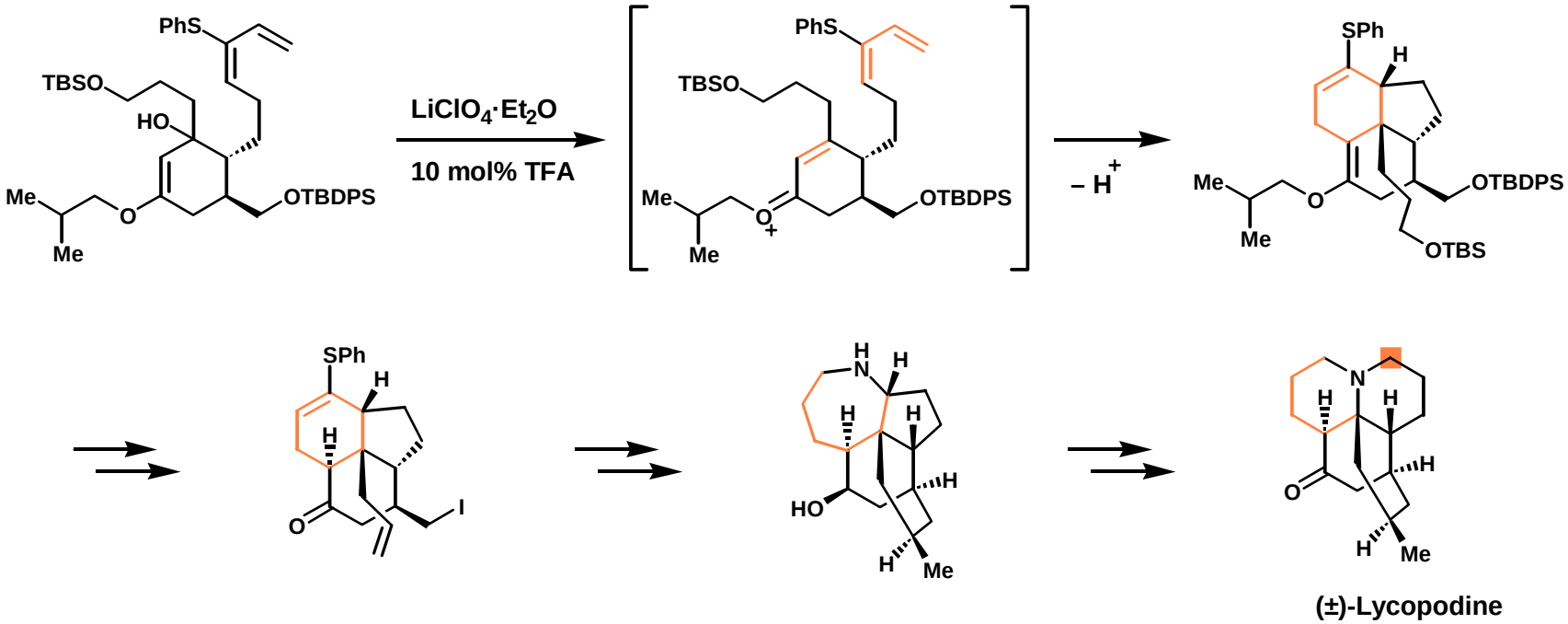
IMDA Reaction of an in Situ-Generated, Heteroatom-Stabilized Allyl Cation: Total Synthesis of (±)-Lycopodine



Grieco, P. A.; Dai, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5128-5129.

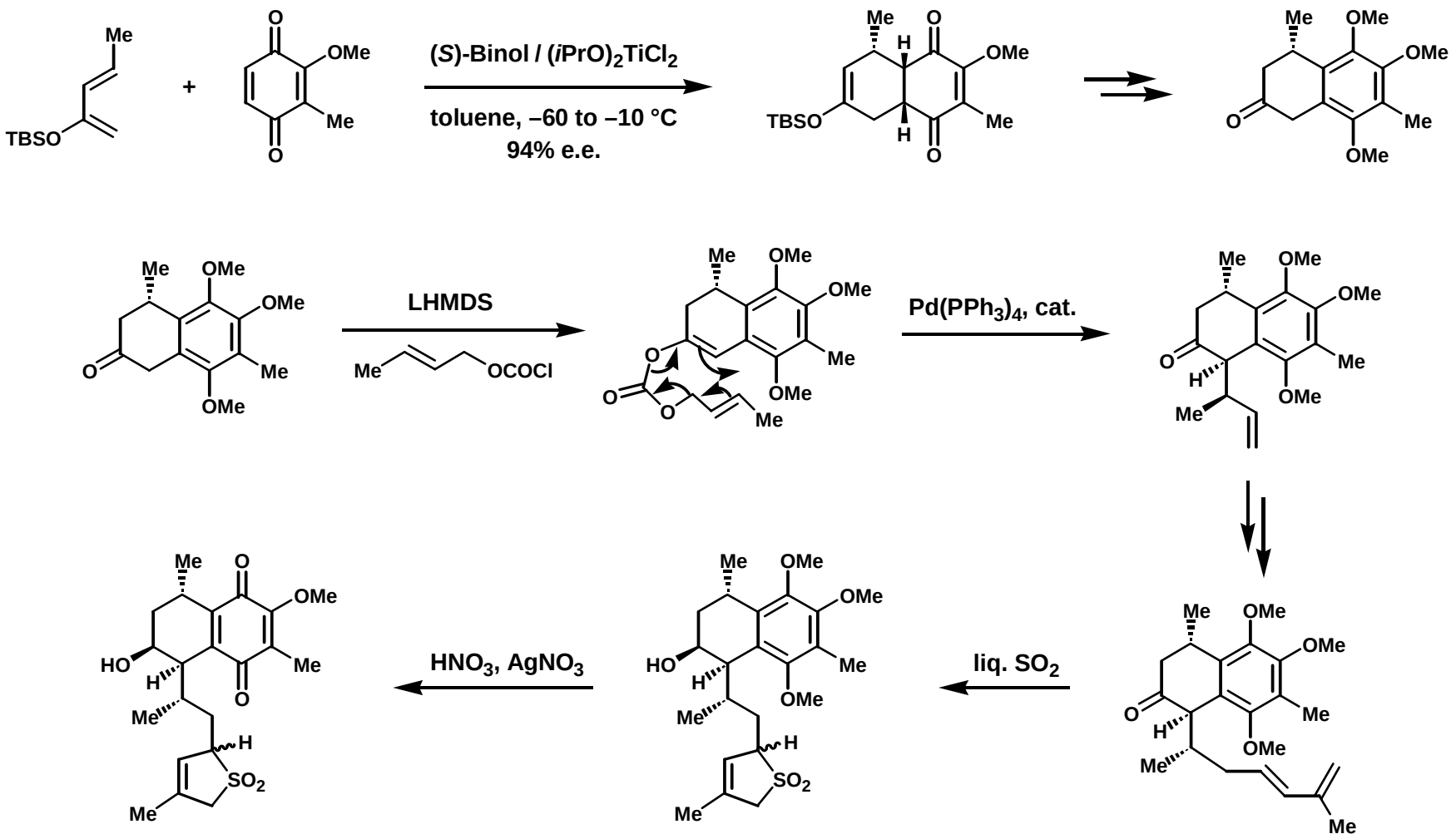
Pearson, W. H.; Lin, K.-C.; Poon, Y.-F. *J. Org. Chem.* **1989**, *54*, 5814-5819.

IMDA Reaction of an in Situ-Generated, Heteroatom-Stabilized Allyl Cation: Total Synthesis of (±)-Lycopodine



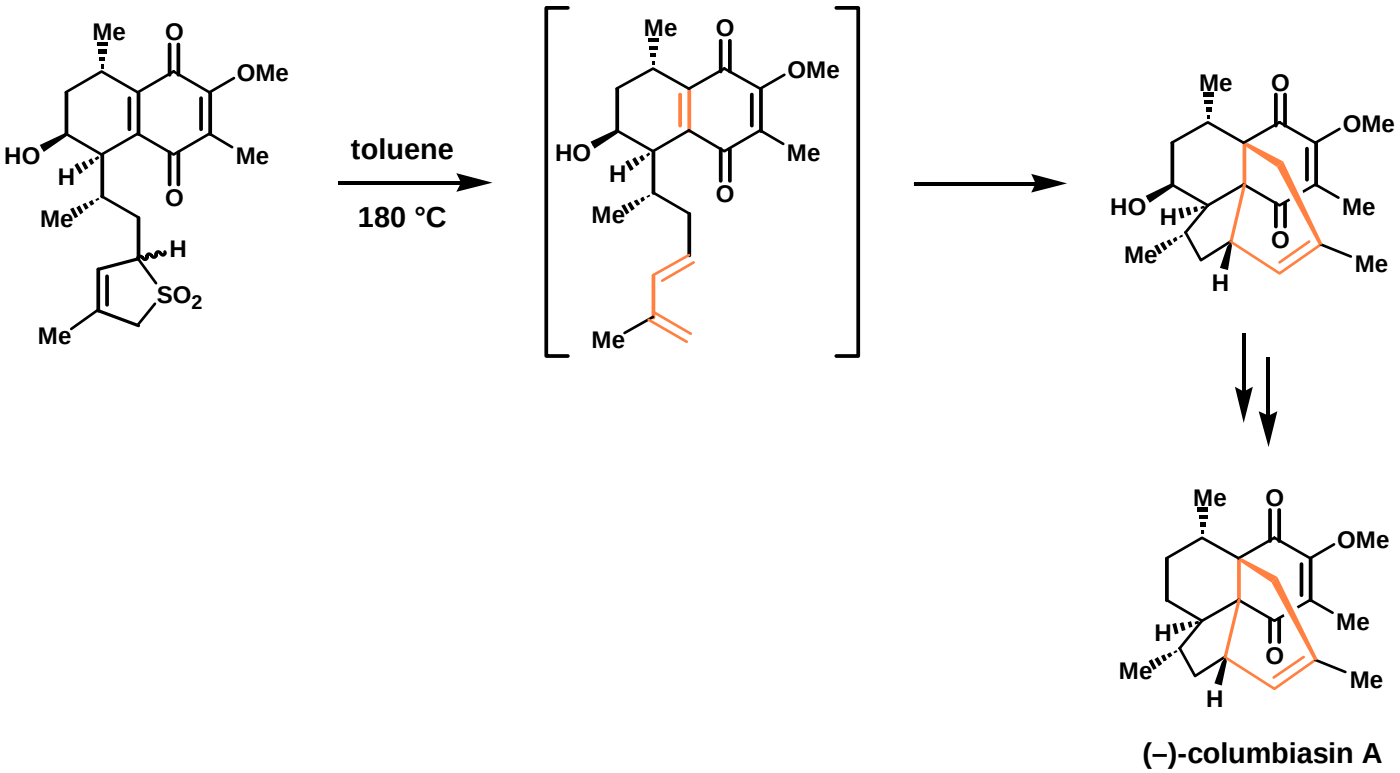
Grieco, P. A.; Dai, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5128-5129.

Total Synthesis of Colombiasin A



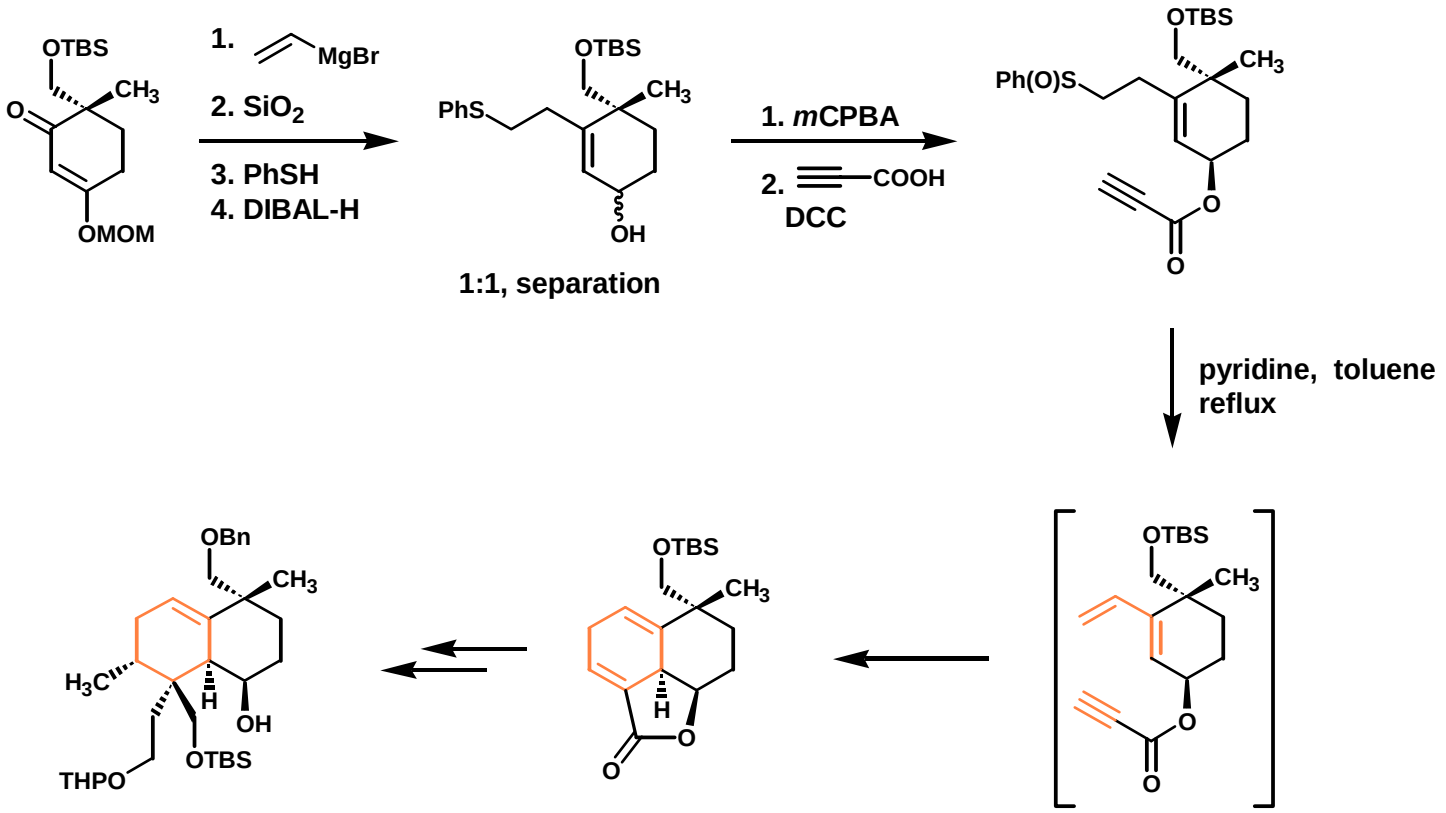
Nicolaou, K. C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 2482-2486.
Nicolaou, K. C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Chem. Eur. J.* **2001**, *7*, 5359-5371.

Total Synthesis of Colombiasin A



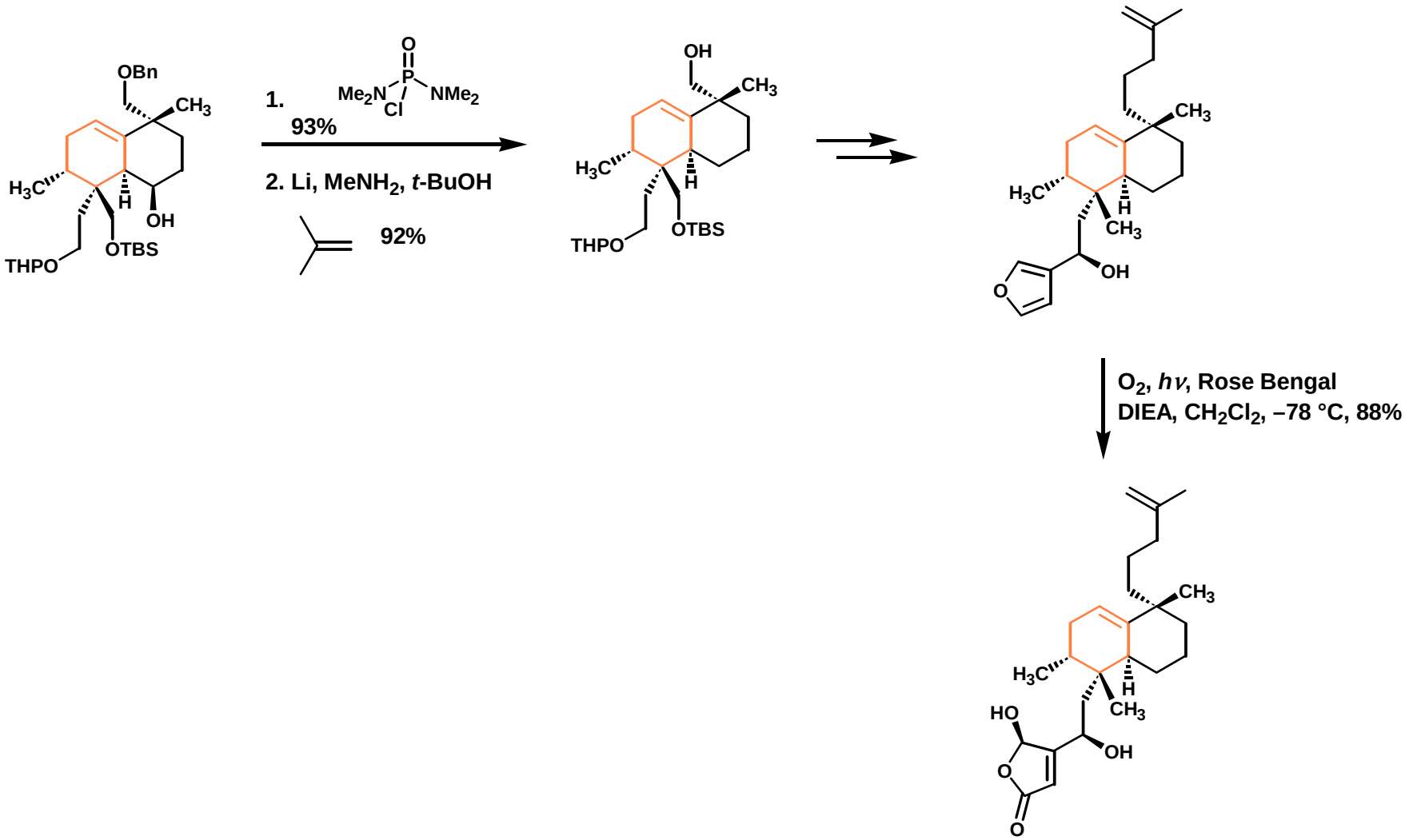
Nicolaou, K. C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 2482-2486.
Nicolaou, K. C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Chem. Eur. J.* **2001**, *7*, 5359-5371.

Total Synthesis of Natural Dysidiolide



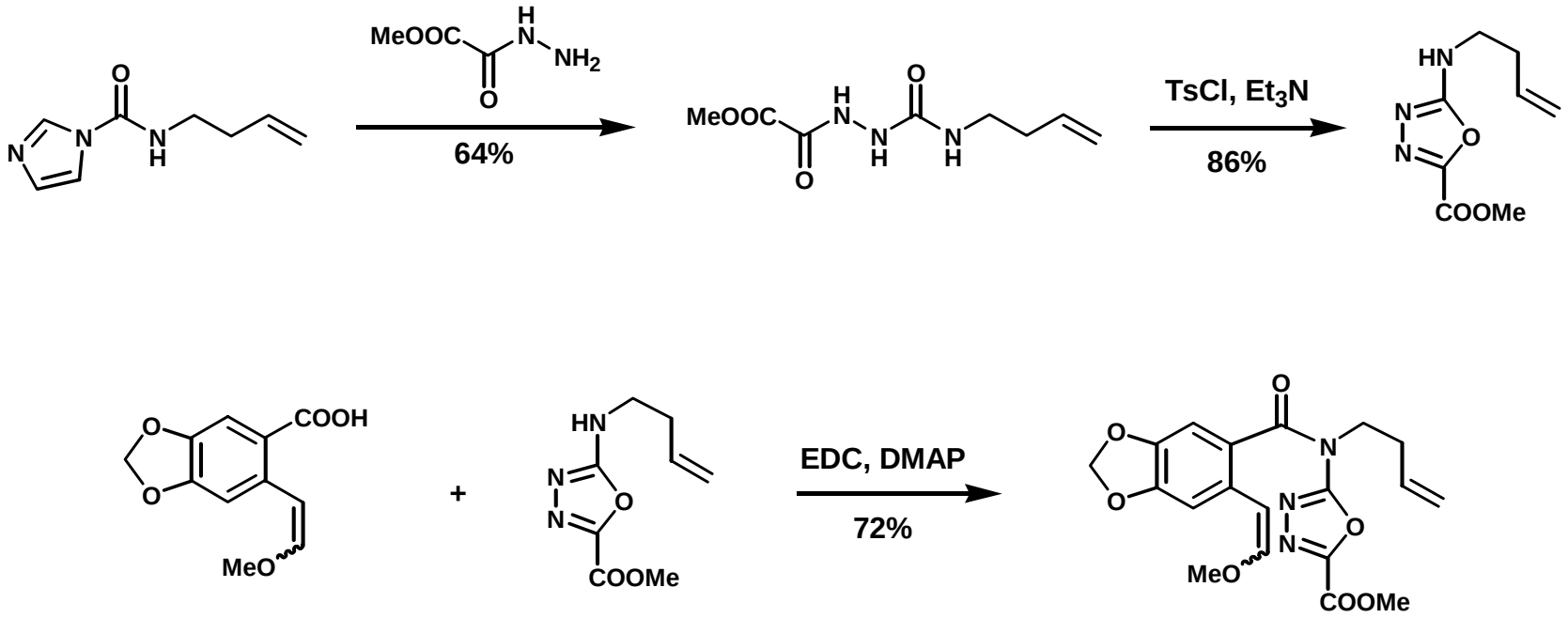
Miyaoka, H.; Kajiwara, Y.; Hara, Y.; Yamada, Y. *J. Org. Chem.* **2001**, *66*, 1429-1435.

Total Synthesis of Natural Dysidiolide



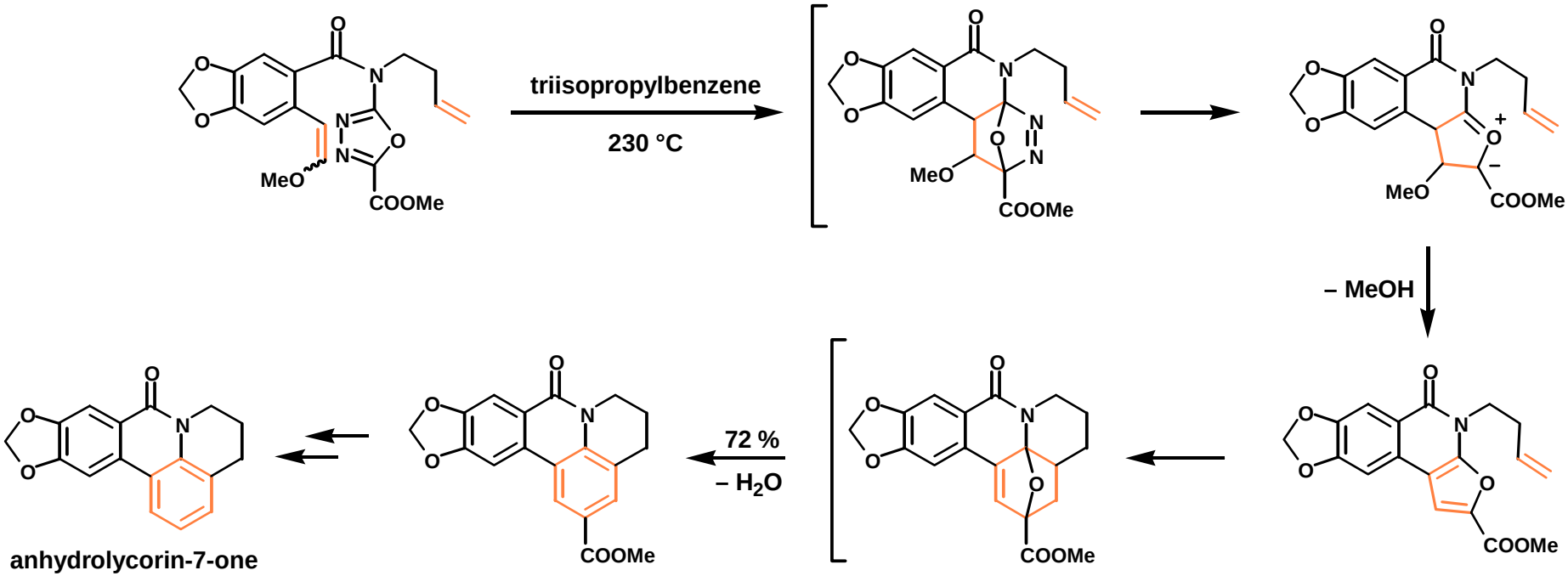
Miyaoka, H.; Kajiwara, Y.; Hara, Y.; Yamada, Y. *J. Org. Chem.* **2001**, *66*, 1429-1435.

Total Synthesis of Anhydrolycorinone Utilizing Sequential Intramolecular Diels-Alder Reactions of a 1,3,4-Oxadiazole



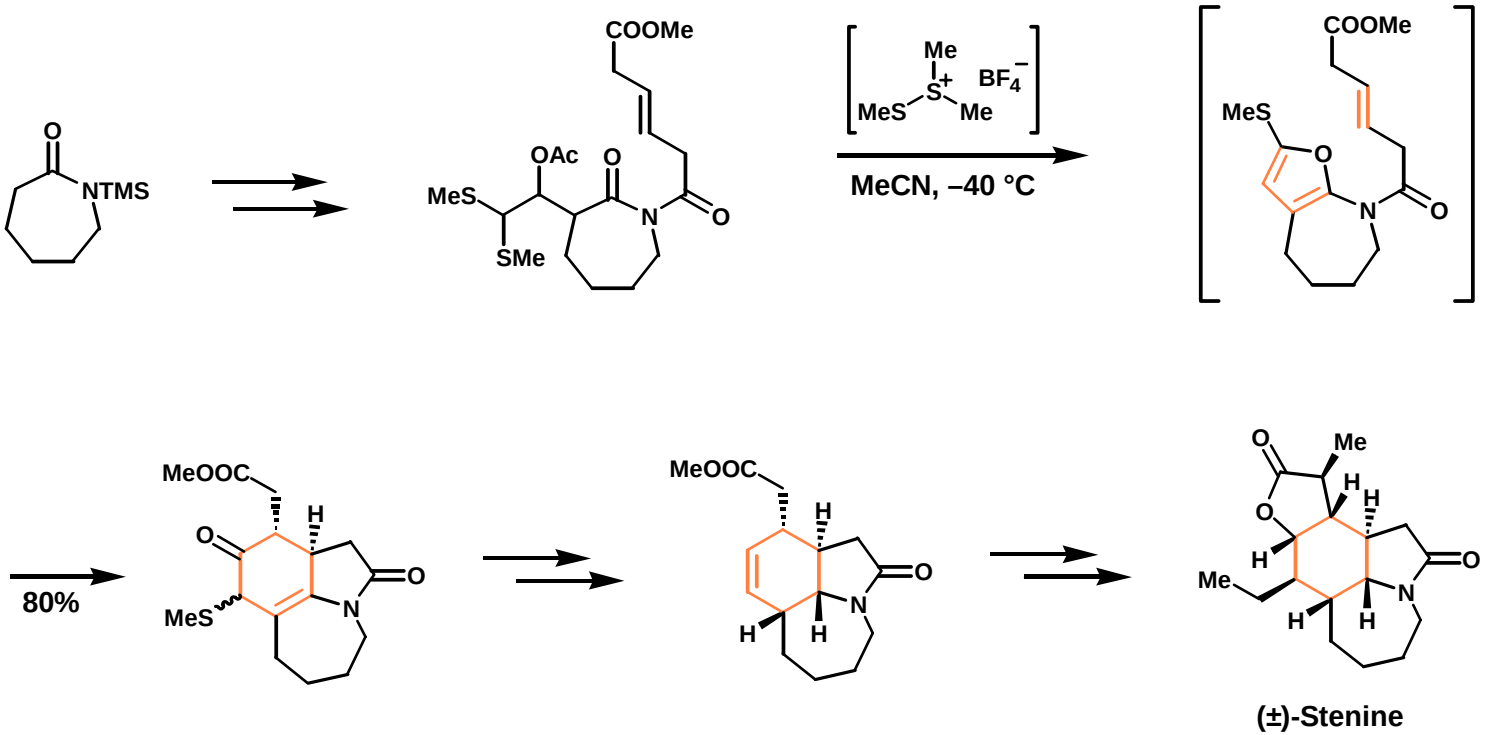
(a) Wilkie, G. D.; Elliott, G. I.; Blagg, B. S. J.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 11292-11294. (b) Wolkenberg, S. E.; Boger, D. L. *J. Org. Chem.* **2002**, *67*, 7361-7364.

Total Synthesis of Anhydrolycorinone Utilizing Sequential Intramolecular Diels-Alder Reactions of a 1,3,4-Oxadiazole



(a) Wilkie, G. D.; Elliott, G. I.; Blagg, B. S. J.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 11292-11294. (b) Wolkenberg, S. E.; Boger, D. L. *J. Org. Chem.* **2002**, *67*, 7361-7364.

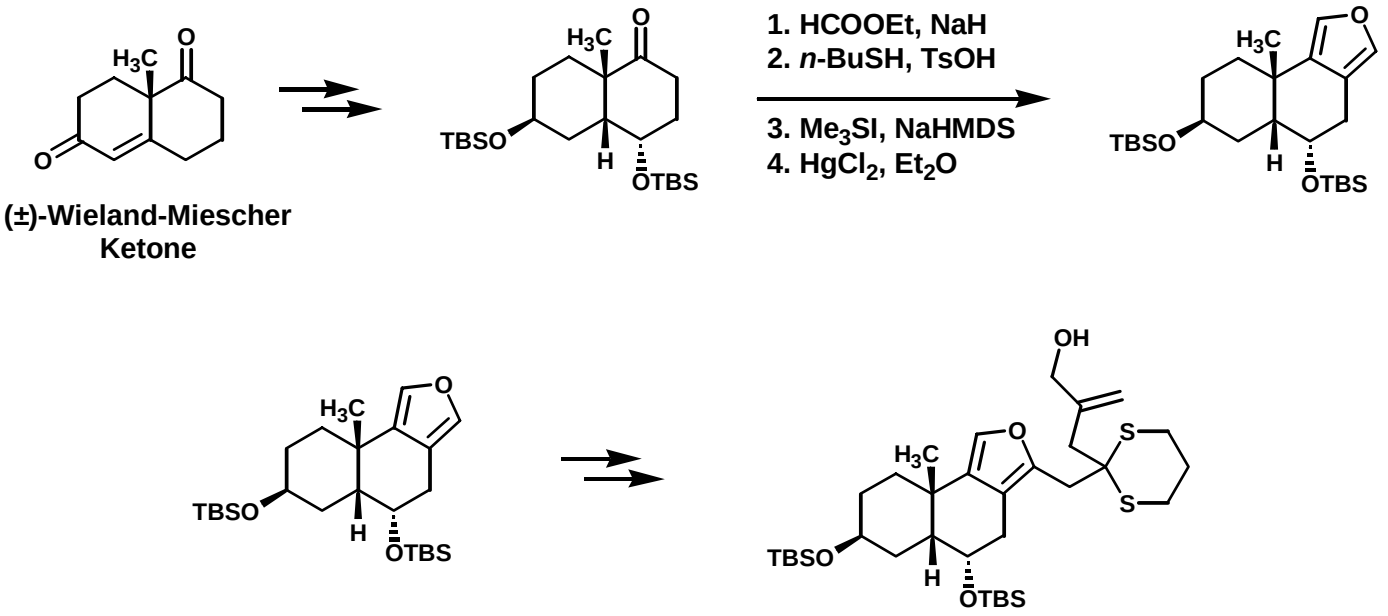
Total Synthesis of (±)-Stenine Using the IMDA Cycloaddition of a 2-Methylthio-5-amido-substituted Furan



Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515.

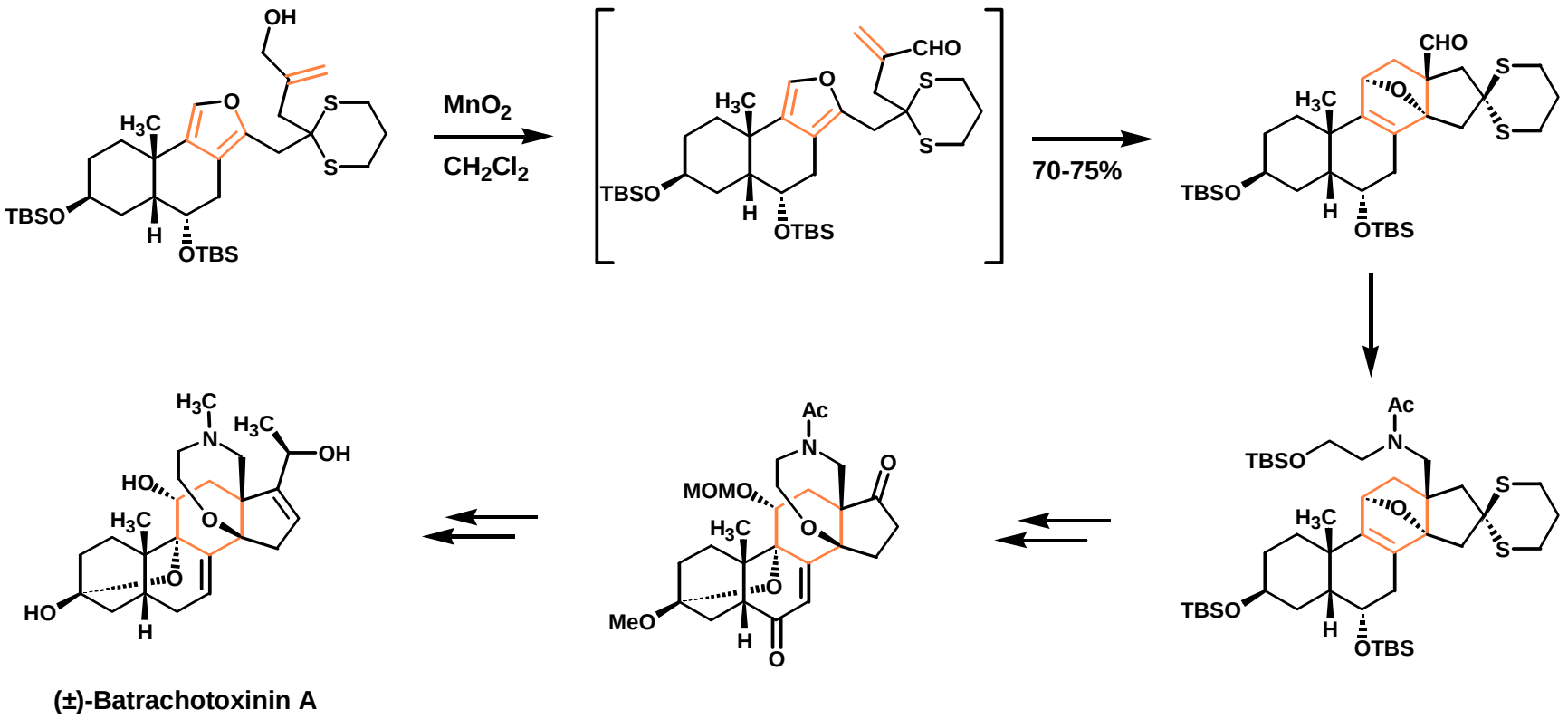
Padwa, A.; Ginn, J. D. *J. Org. Chem.* **2005**, *asap*.

Total Synthesis of (±)-Batrachotoxinin A



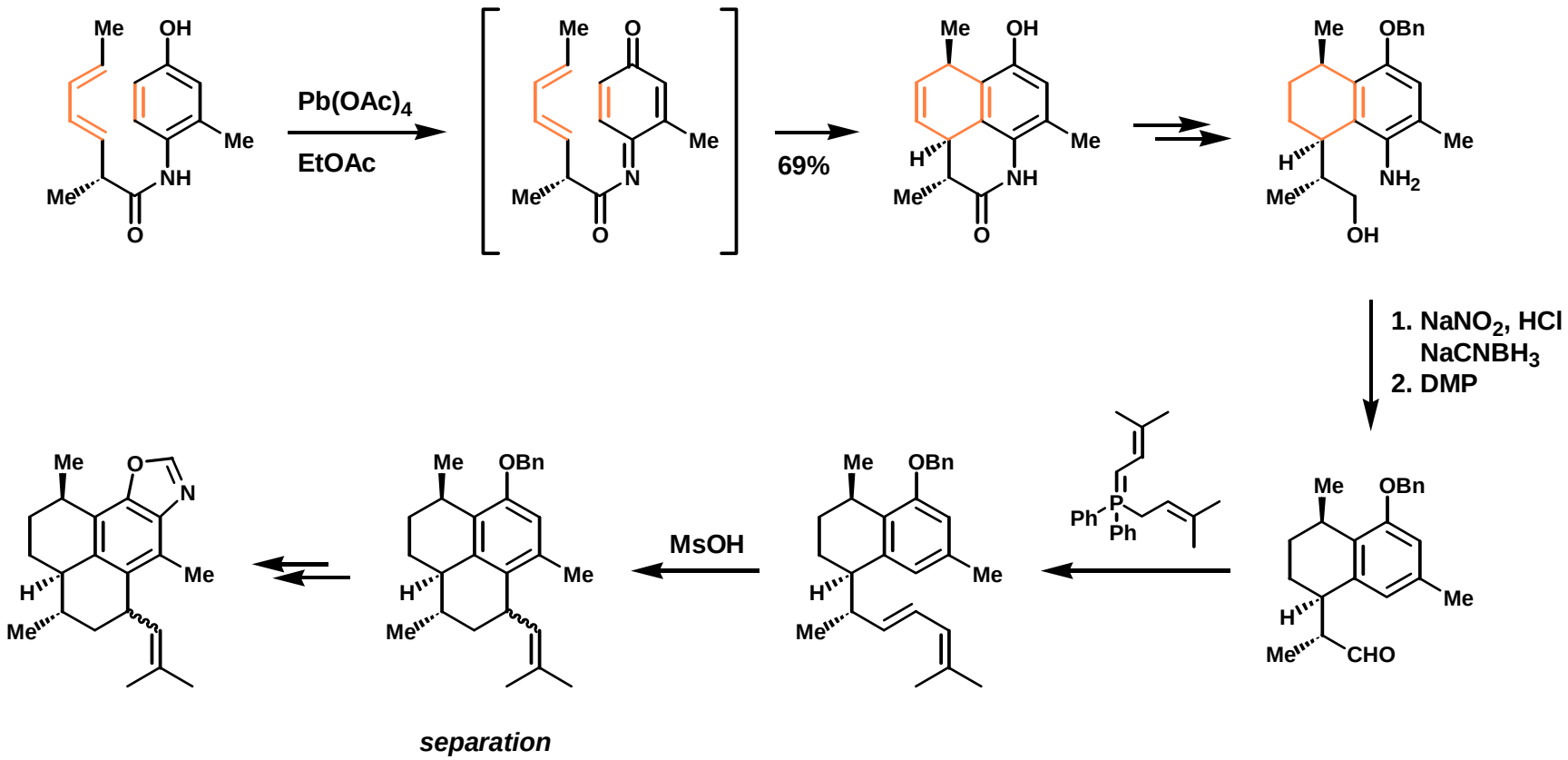
Kurosu, M.; Marcin, L. R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6627-6628.

Total Synthesis of (±)-Batrachotoxinin A



Kurosu, M.; Marcin, L. R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6627-6628.

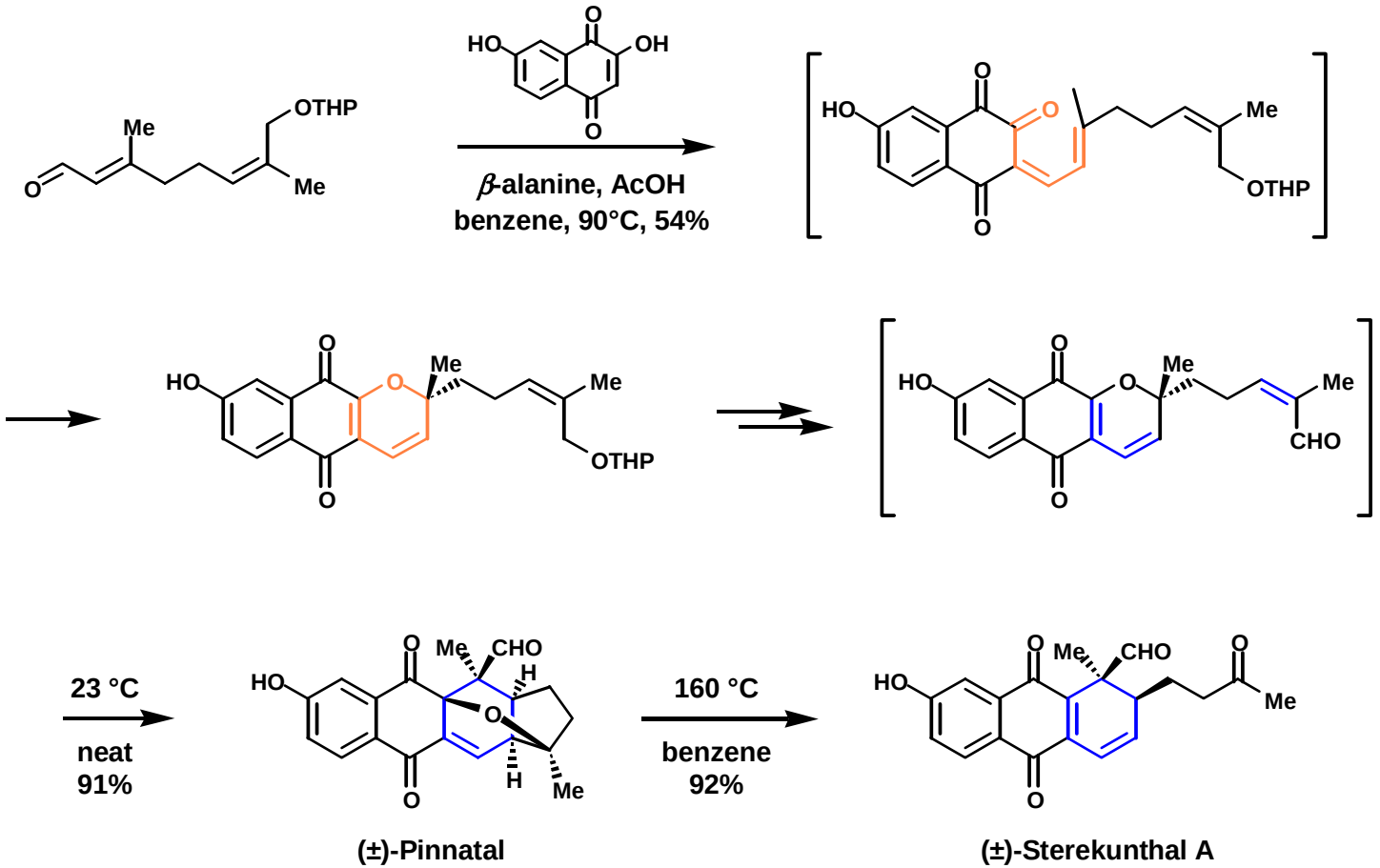
Enantiospecific Synthesis of the Proposed Structure of Diterpenoid Pseudopteroxazole



Johnson, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2001**, *123*, 4475-4479.

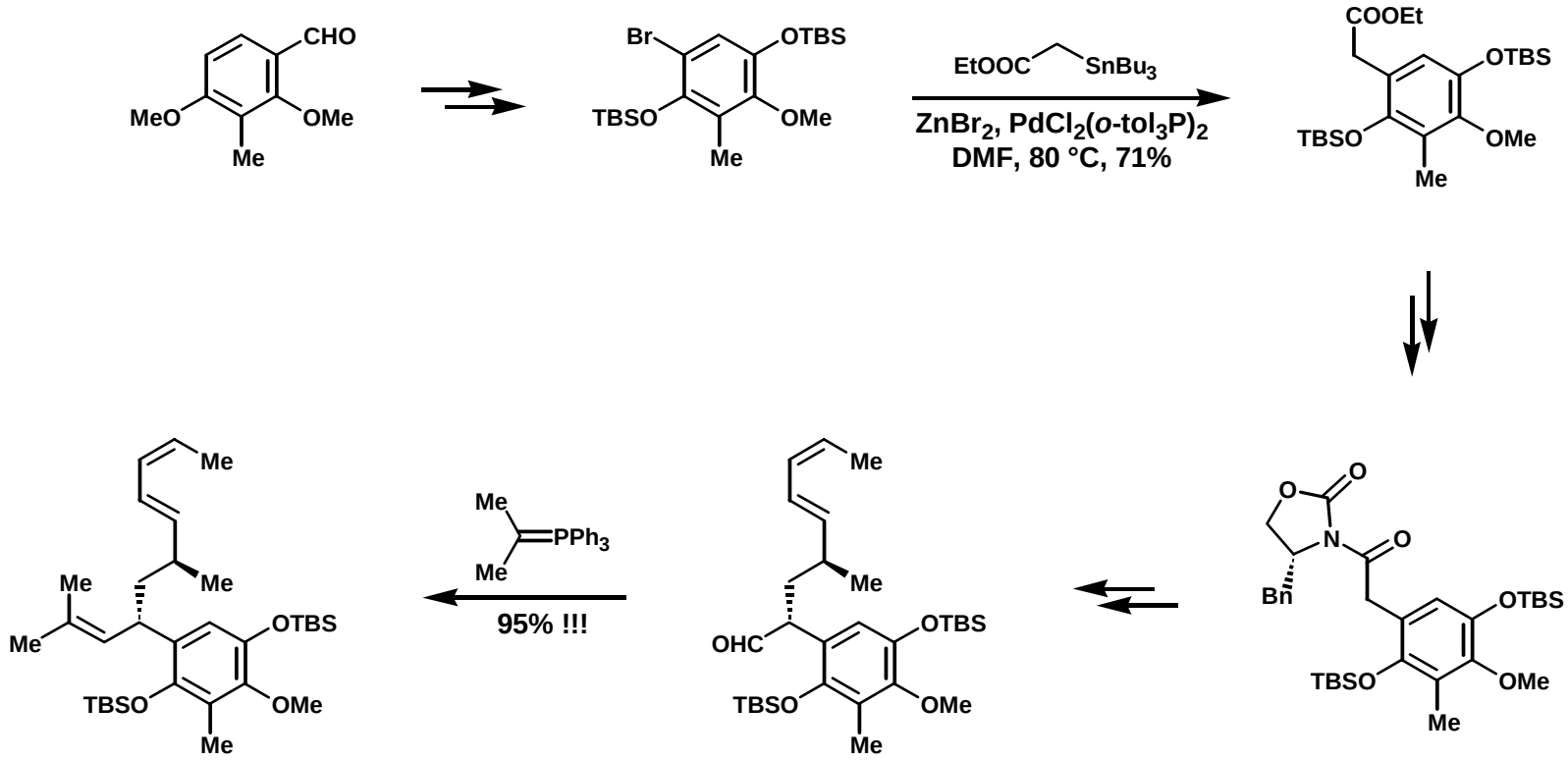
Davidson, J. P.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 13486-13489.

Biomimetic Synthesis of (±)-Pinnatal and (±)-Sterekunthal A



Malerich, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2003**, *125*, 9554-9555.

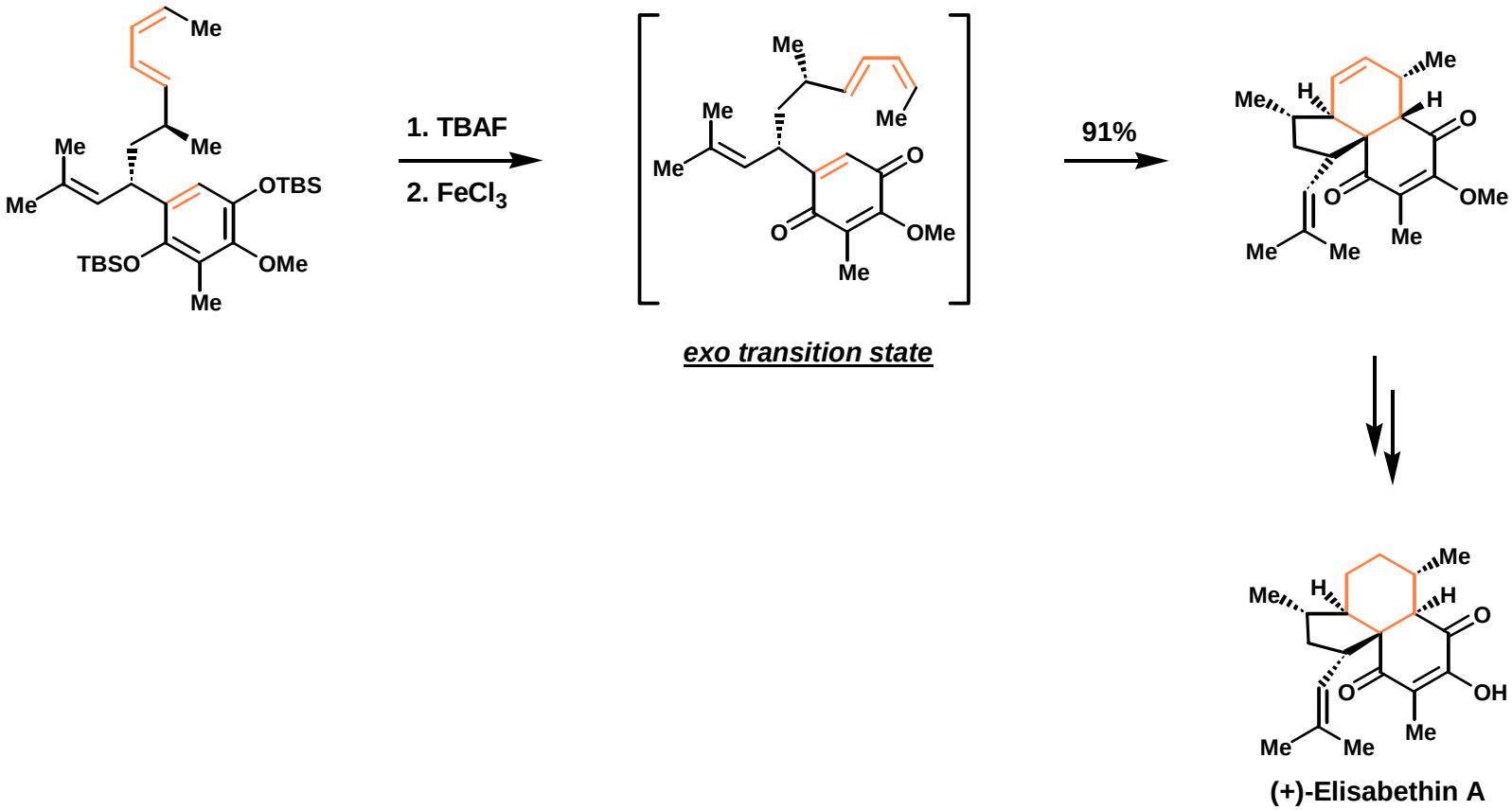
Total Synthesis of (+)-Elisabethin A



Heckrodt, T. J.; Mulzer, J. *J. Am. Chem. Soc.* **2003**, *125*, 4680-4681.

Heckrodt, T. J.; Mulzer, J. *J. Am. Chem. Soc.* **2003**, *125*, 9538 (addition correction).

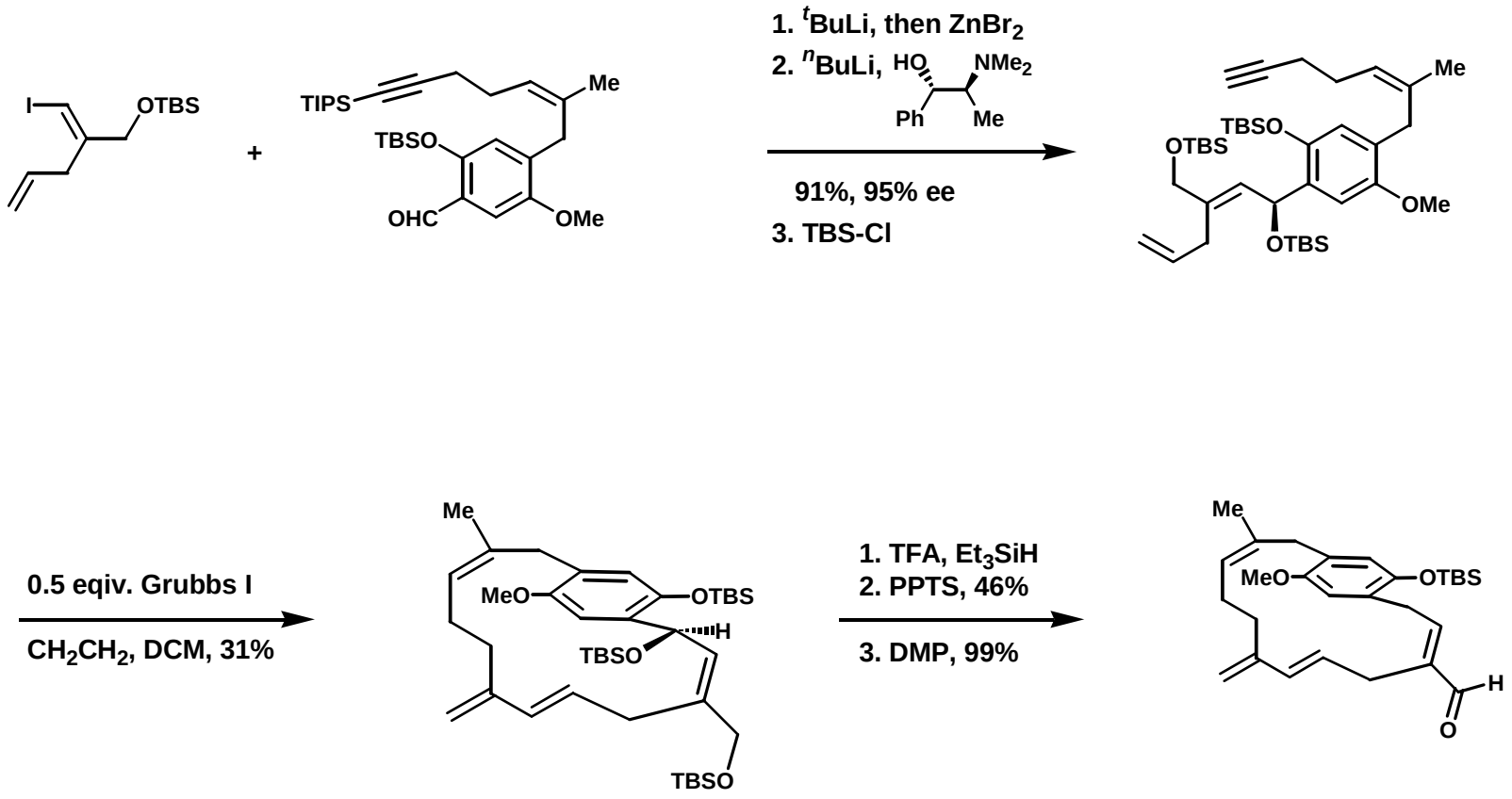
Total Synthesis of (+)-Elisabethin A



Heckrodt, T. J.; Mulzer, J. *J. Am. Chem. Soc.* **2003**, *125*, 4680-4681.

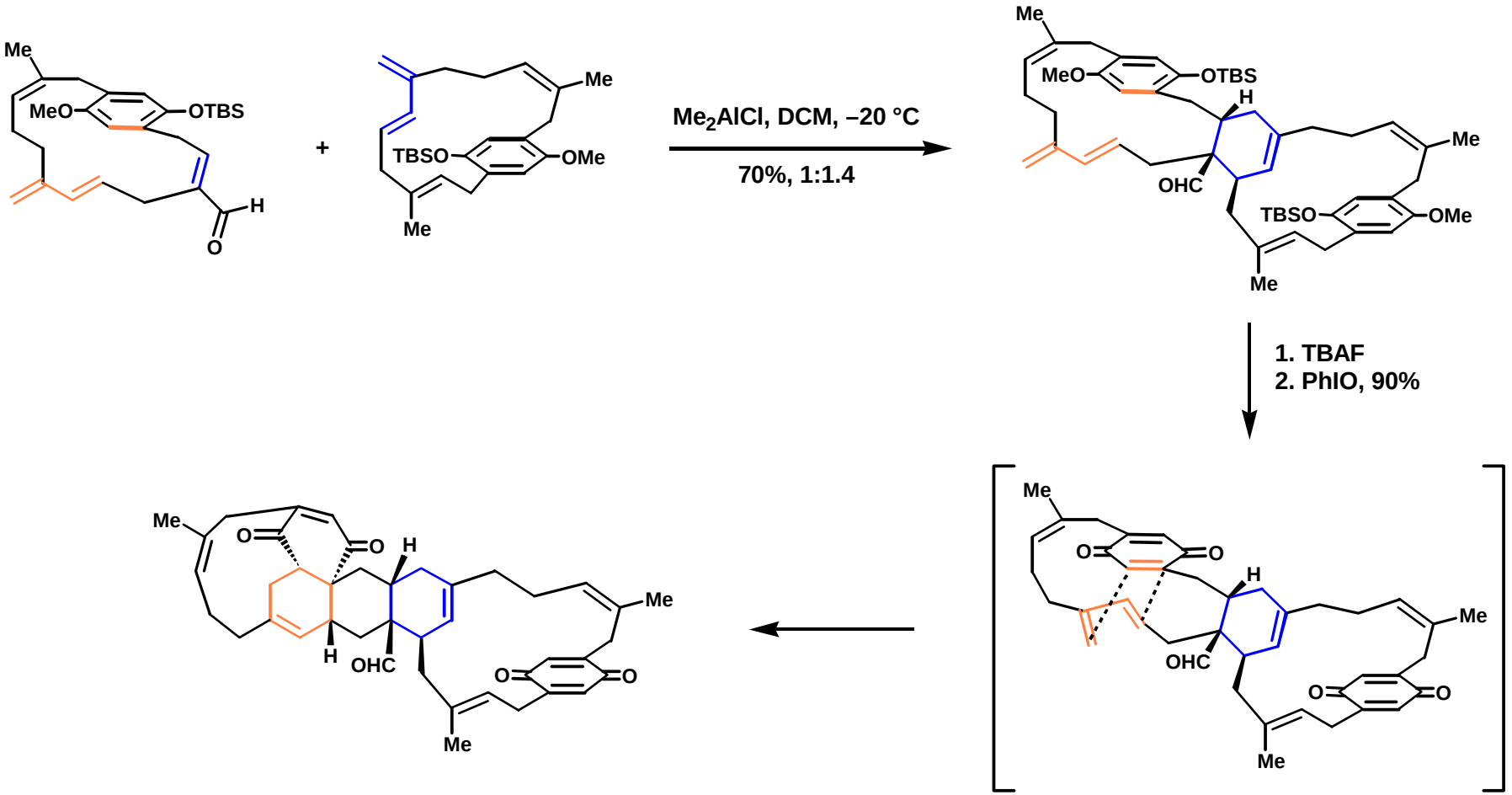
Heckrodt, T. J.; Mulzer, J. *J. Am. Chem. Soc.* **2003**, *125*, 9538 (addition correction).

Biomimetic Synthesis of (–)-Longithorone A



Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *125*, 773-775.

Biomimetic Synthesis of (–)-Longithorone A



Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *125*, 773-774.

Conclusions

- **Seek the intramolecular Diels–Alder reaction in your natural product synthesis even though it might not be obvious!**
- **Many intramolecular Diels–Alder reactions can be initiated by simple activation**
- **It is difficult to imagine that Nature would not take advantage of IMDA.**