Temporary Restraints to Overcome Steric Obstacles: An Efficient Strategy for the Synthesis of Mycalamide B

John C. Jewett and Viresh H. Rawal
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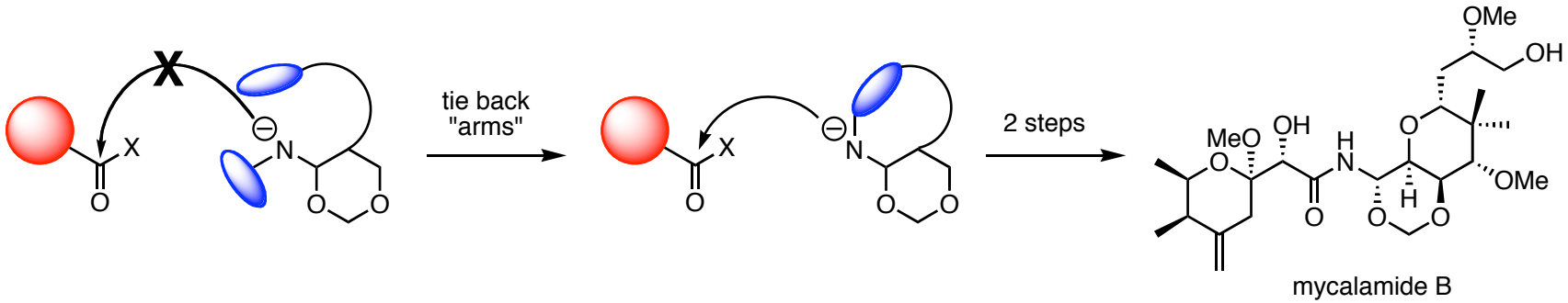
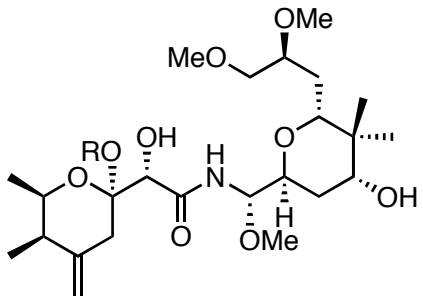
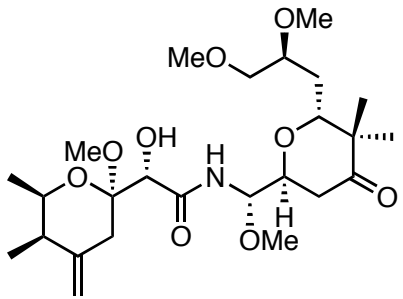


Christopher Rosenker
Wipf Group - Current Literature
October 23, 2010

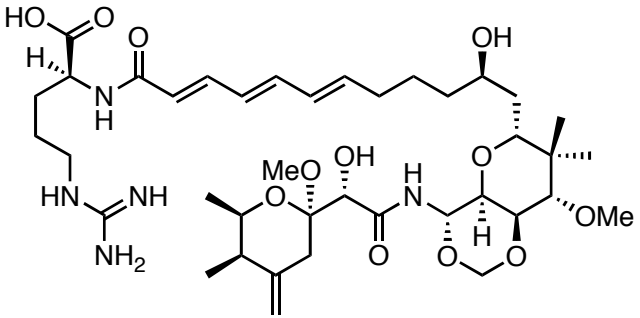
Pederin Family of Natural Products



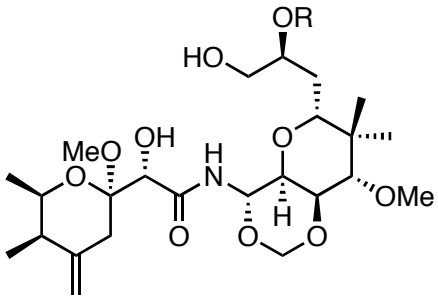
pederin (R = Me)
pseudopederin (R = H)



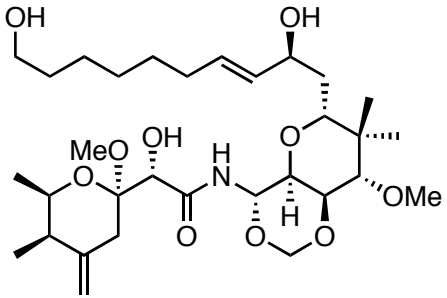
pederone



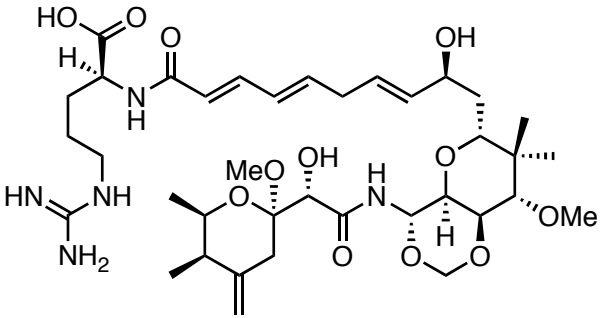
Onnamide A



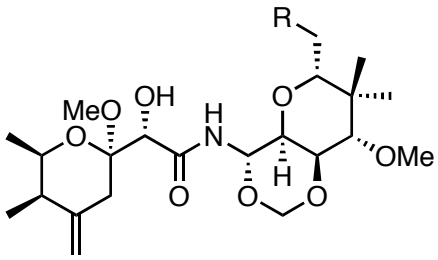
mycalamide A (R = H)
mycalamide B (R = Me)



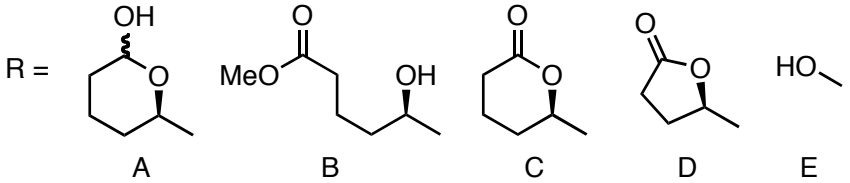
icadamide A



icadamide B



theopederin A-E

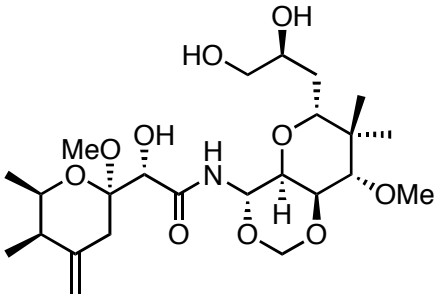


A B C D E

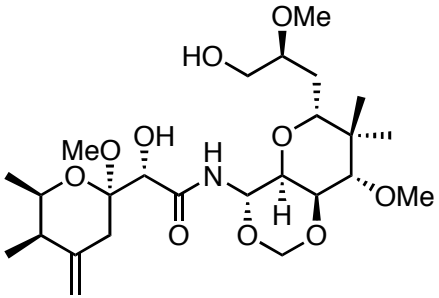
Narquizian, R.; Kocienski, P. J. In *The Role of Natural Products in Drug Discovery*, Mulzer, J.; Bohlmann, R., Eds. Springer: Berlin, **2000**; pp.25-56.

Isolation and Biological activity

- Isolated from a marine sponge of the genus *Mycale* off the coast of New Zealand.
  - Pederin was isolated from a black beetle (*Paederus*)
  - Pederin family of compounds show antiviral and antitumor properties
  - Pederin family of natural products could come from uncultivated symbiotic bacteria
- Exhibit >1.5 nM activity towards human promyelocytic leukemia, lung, and colon cancer cells
  - Biological activity attributed to ability to arrest protein synthesis by binding to 80S ribosome and preventing transfer of new peptide from the A site to the P site
  - Capable of changing morphology of *ras*-transformed Normal Rat Kidney cells to normal cells by inhibiting the biosynthesis of p21



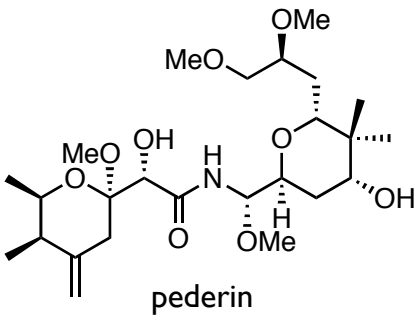
mycalamide A



mycalamide B

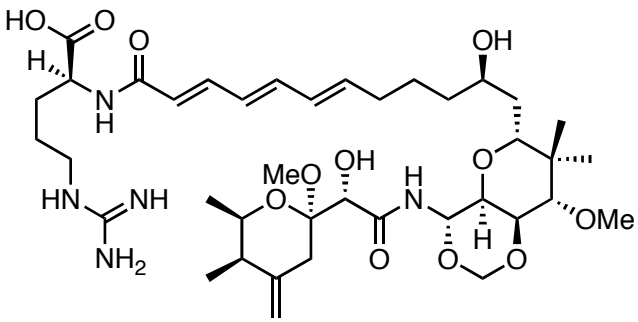
Perry, N. B.; Blunt, J.; Munro, M.; Pannell, L. *J. Am. Chem. Soc.* **1988**, *110*, 4850.
Burres, N.; Clement, J. *Cancer Res.* **1989**, *49*, 2935.
Perry, N. B.; Blunt, J.; Munro, M.; Thompson, A. *J. Org. Chem.* **1990**, *55*, 223.
Ogawara, H.; Higashi, K.; Uchino, K.; Perry, N. B. *Chem. Pharm. Bull.* **1991**, *39*, 2152.
Piel, J.; Butzke, D.; Fusetani, N.; Hui, D.; Platzer, M.; Wen, G.; Matsunaga, S. *J. Nat. Prod.* **2005**, *68*, 472.
Narquizian, R.; Kocienski, P. J. In *The Role of Natural Products in Drug Discovery*, Mulzer, J.; Bohlmann, R., Eds. Springer: Berlin, **2000**; pp.25-56.

Syntheses of the Pederin Family of Natural Products



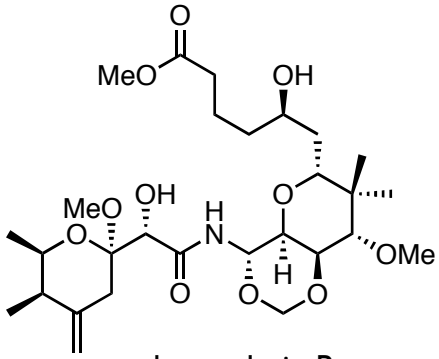
pederin

Matsuda **1988**
Kocienski **2000**
Nakata **2002**
Rawal **2007**



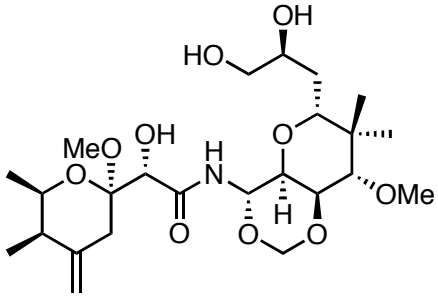
onnamide A

Kishi **1991**



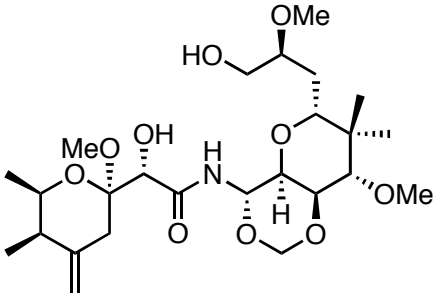
theopederin B

Nakata **2009**



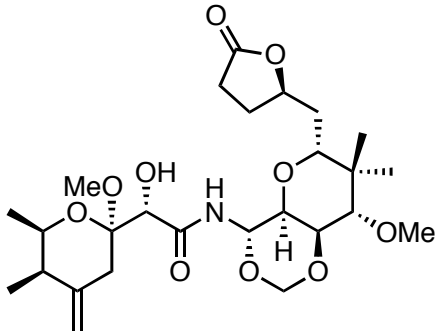
mycalamide A

Kishi **1990**
Nakata **1996**
Roush **2000**
Trost **2004**
Rawal **2005**
Toyota **2006**



mycalamide B

Kishi **1990**
Kocienski **1998**
Rawal **2010**

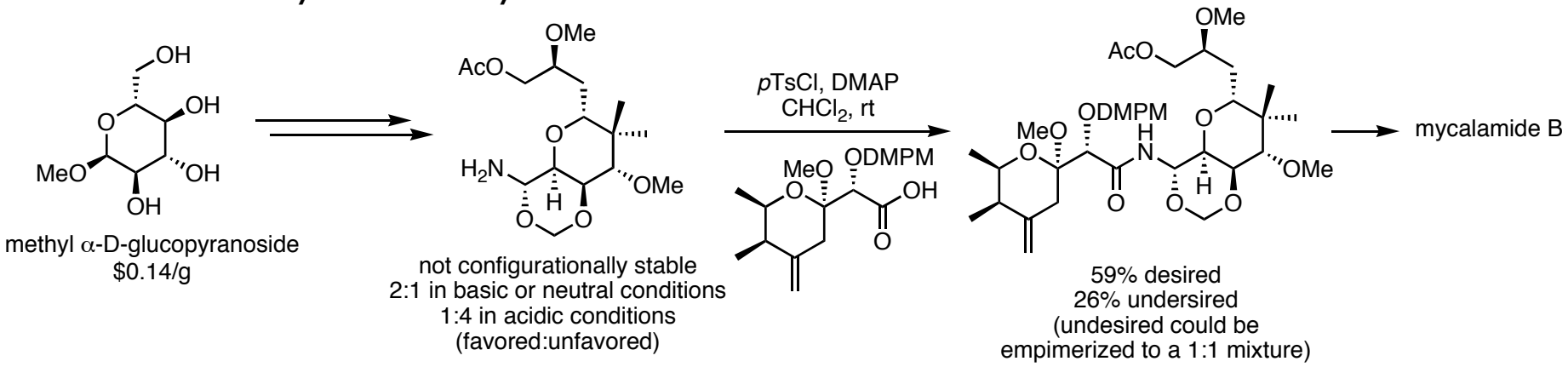


theopederin D

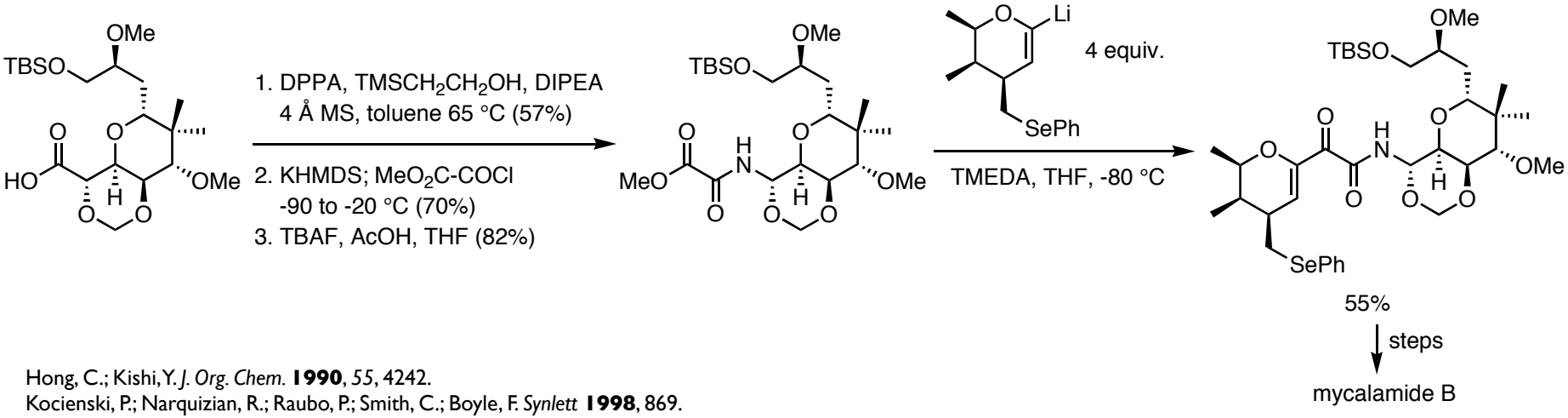
Kocienski **2000**
Floreancig **2008**

Highlights from Previous Synthetic Work in the Pederin Family

Kishi: First total synthesis of mycalamide B



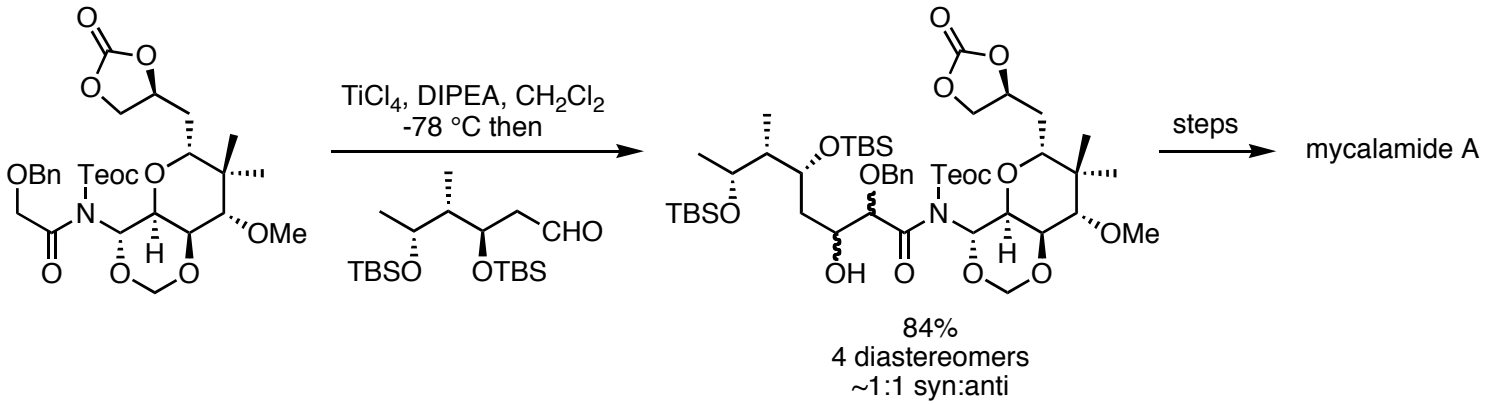
Kocienski: Vinyl lithium addition to ester joins two fragments in mycalamide B



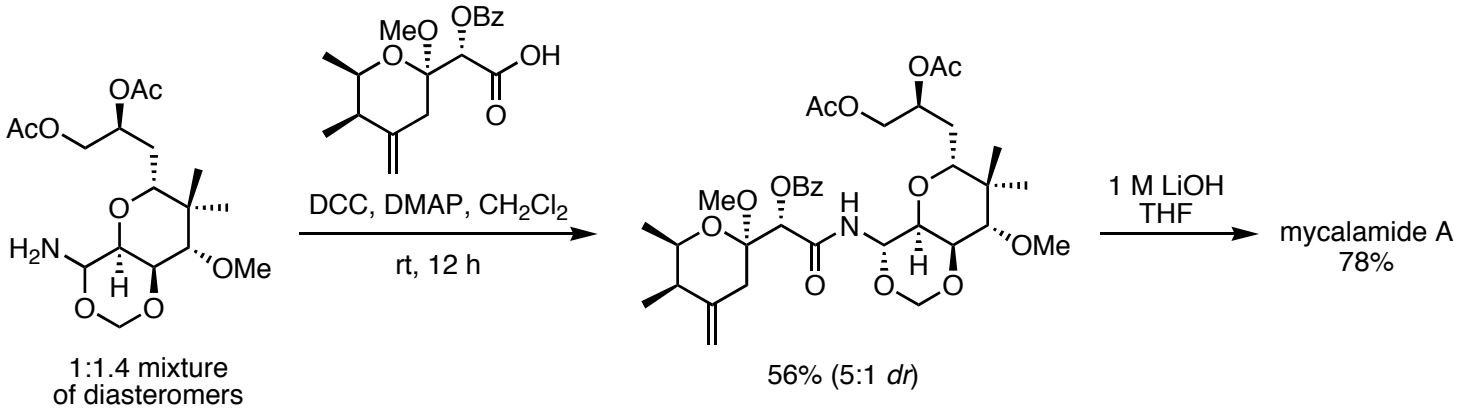
Hong, C.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242.
Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. *Synlett* **1998**, 869.

Highlights from Previous Synthetic Work in the Pederin Family

Roush: Application of the aldol reaction to the synthesis of mycalamide A

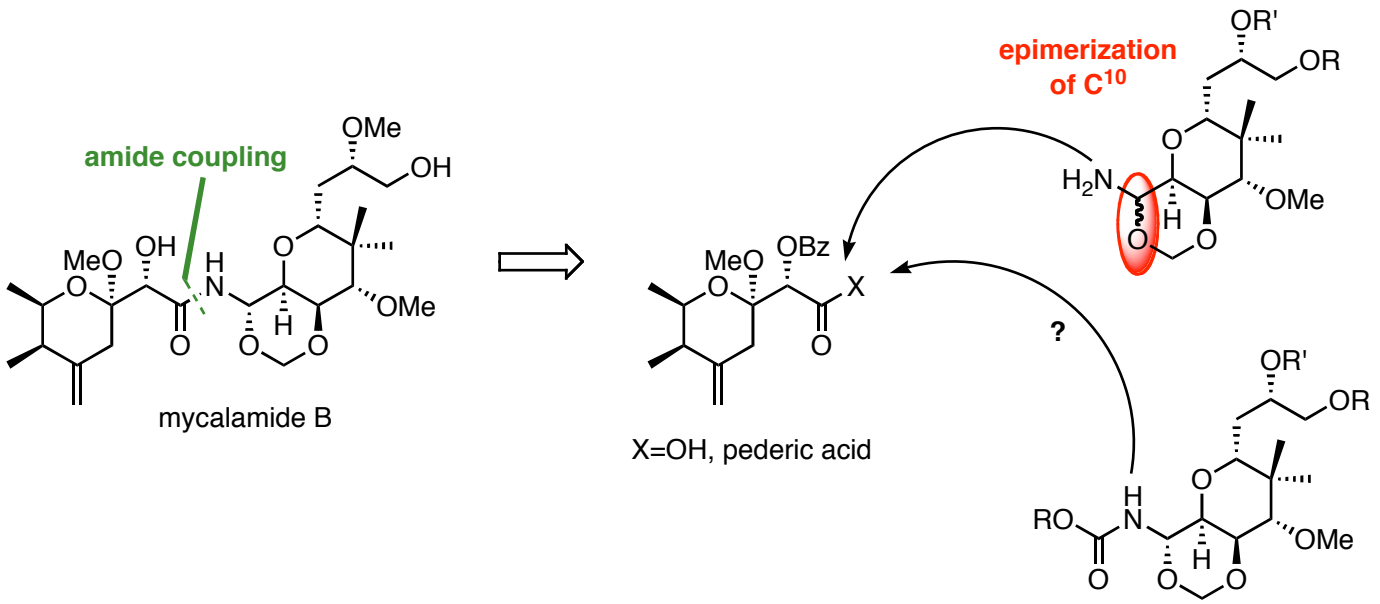


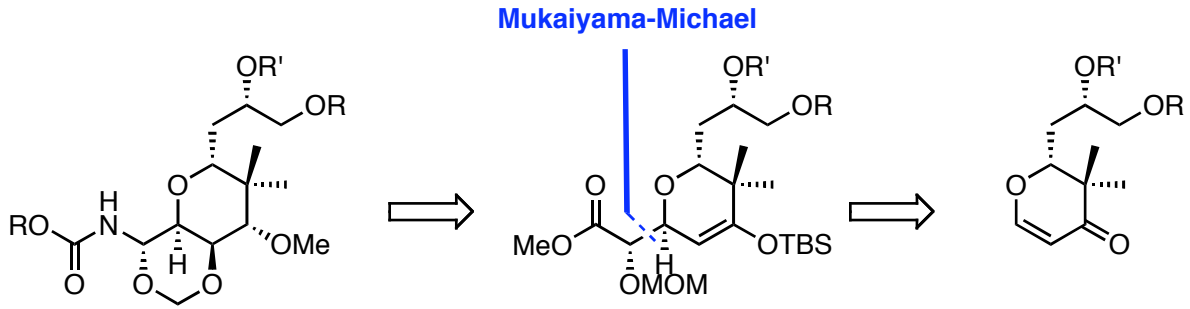
Rawal: Improved coupling of amine and acid fragments of mycalamide A



Roush, W.; Pfeifer, L. *Org. Lett.* **2000**, *2*, 859.
Sohn, J.-H.; Waizumi, N.; Zhong, H.; Rawal, V. *J. Am. Chem. Soc.* **2005**, *127*, 7290.

Retrosynthetic Analysis





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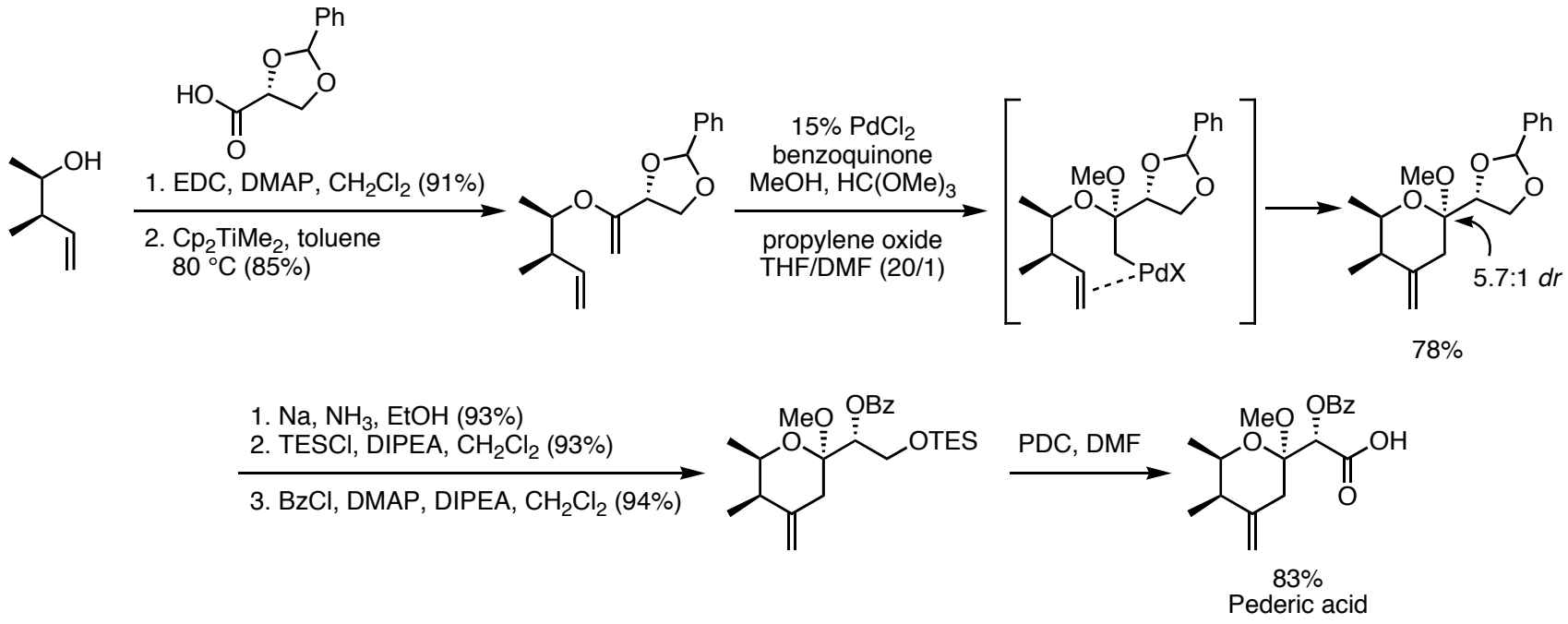
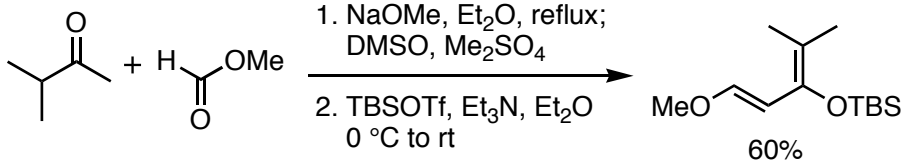
Synthesis of Mycalamide B





Sohn, J.-H.; Waizumi, N.; Zhong, H.; Rawal, V. *J. Am. Chem. Soc.* **2005**, *127*, 7290.
Jewett, J. C.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6502.
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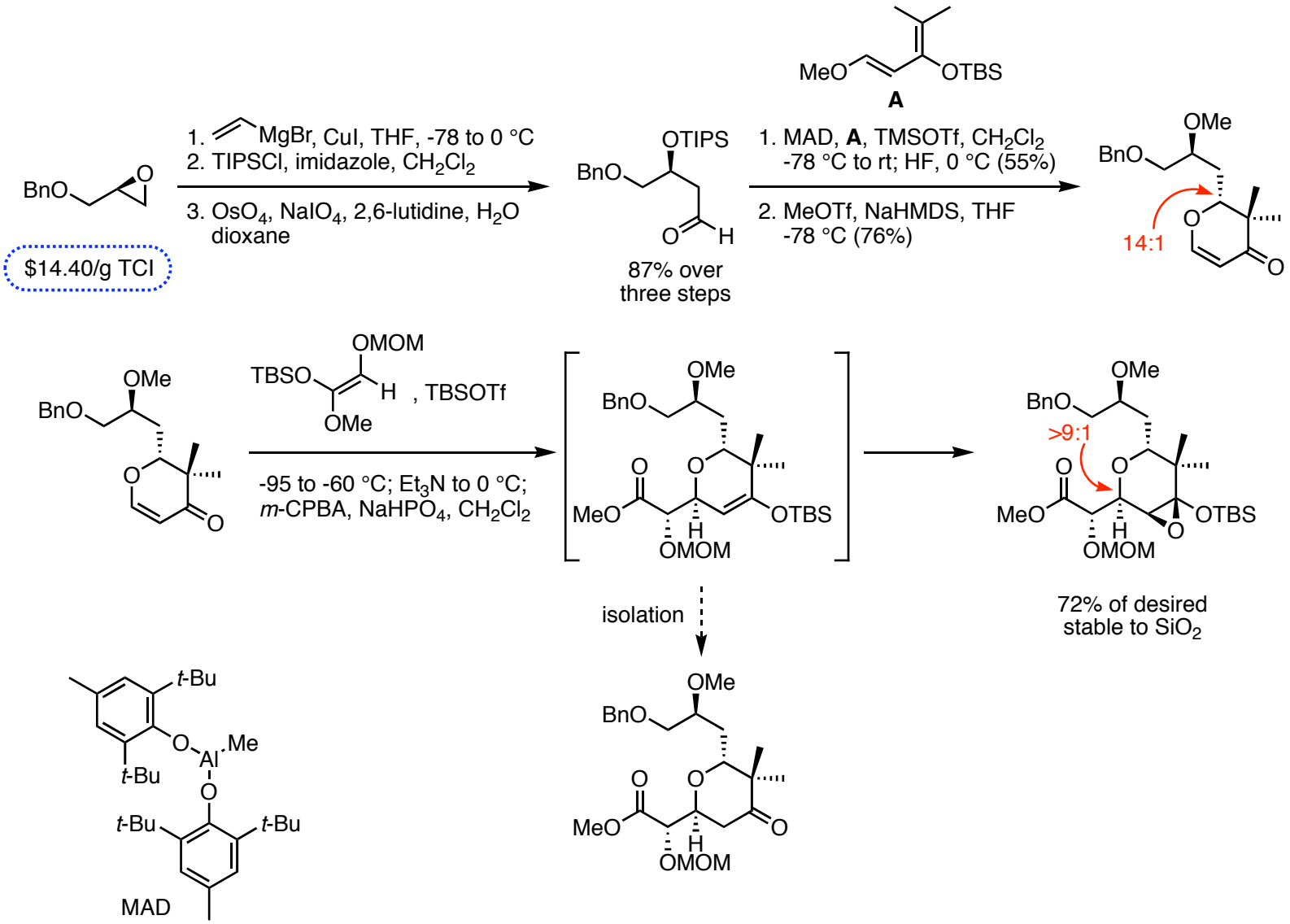

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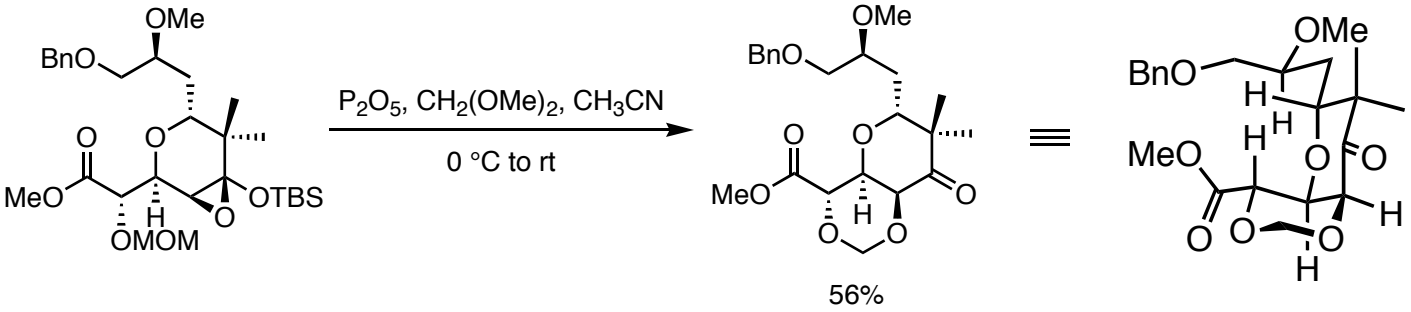

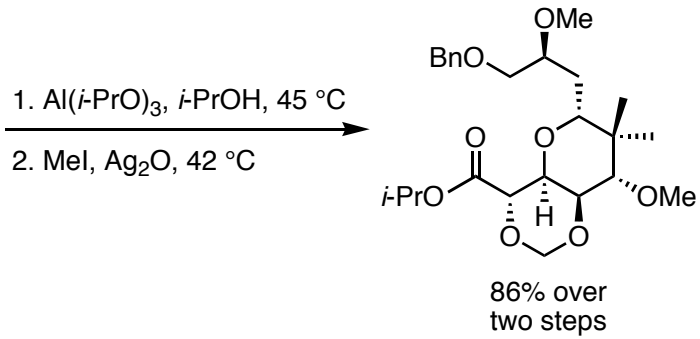

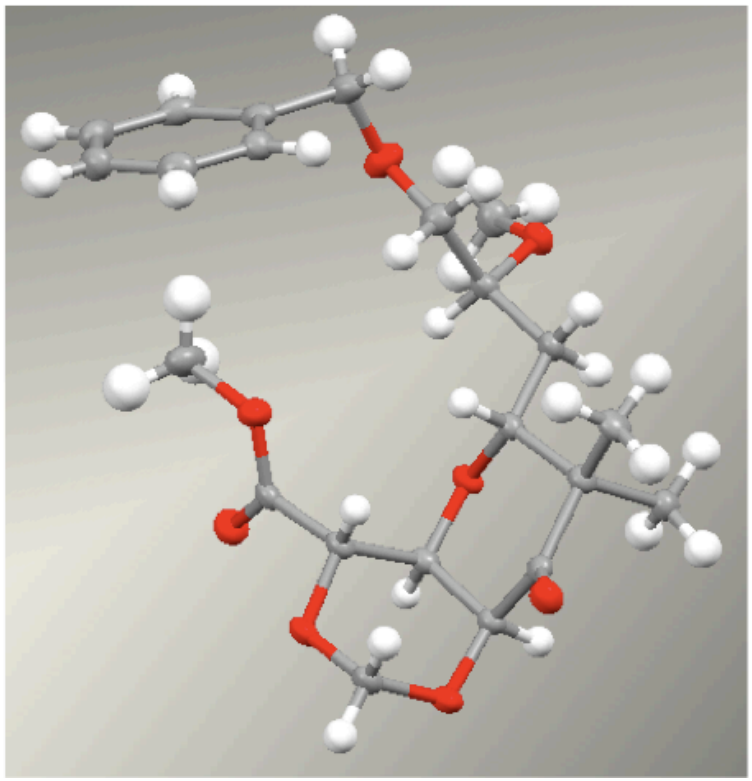

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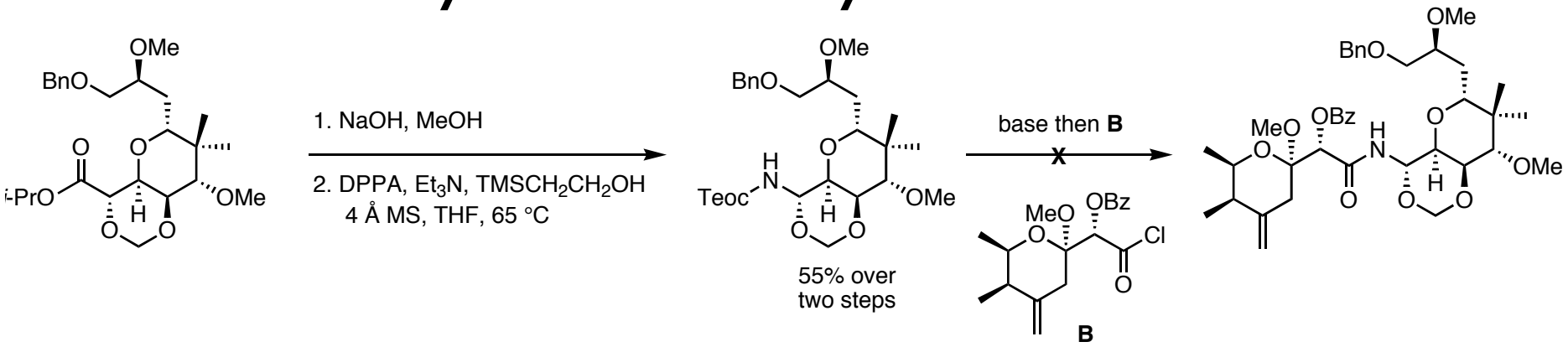

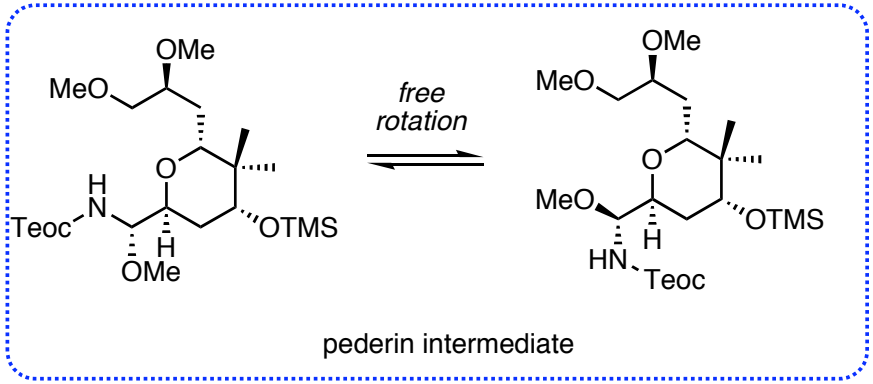

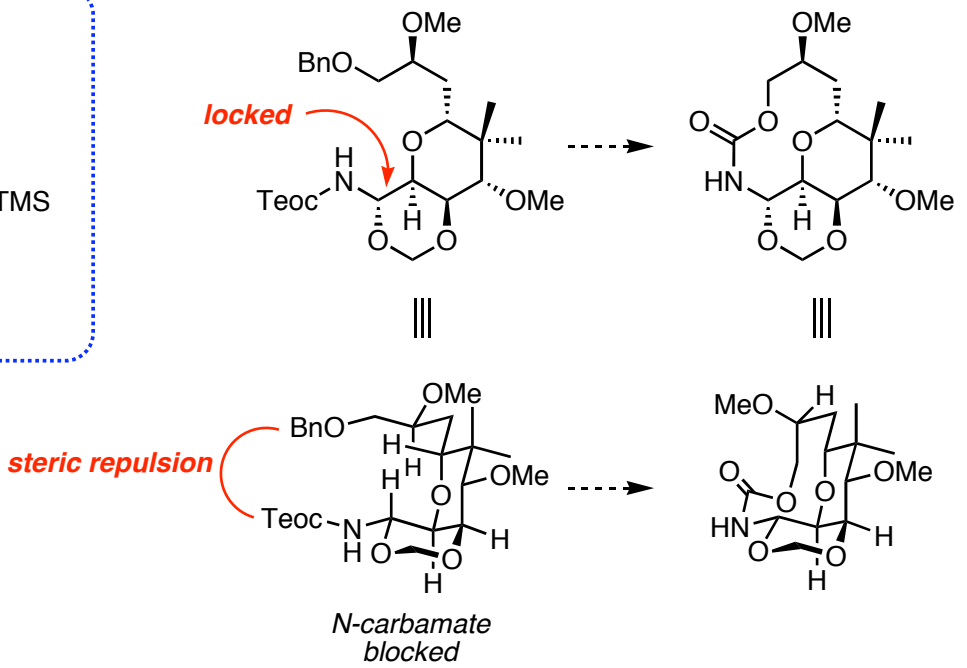

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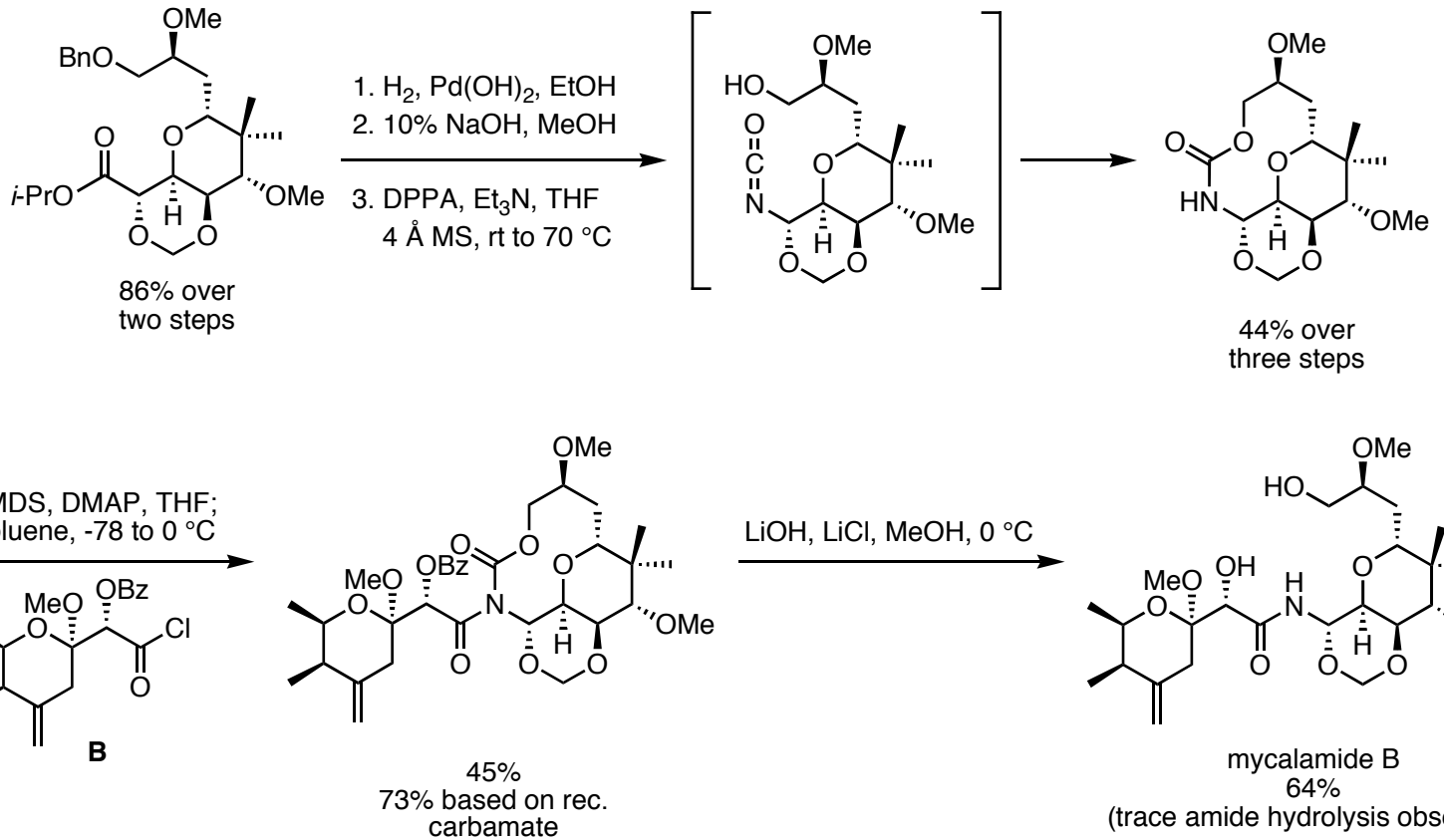
Synthesis of Mycalamide B



2.6% yield and 14 steps from commercially available materials

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Conclusions

- Key steps include:
  - one-pot Mukaiyama-Michael/epoxidation sequence introducing three contiguous stereocenters
  - intramolecular trapping of an isocyanate, resulting from a Curtius rearrangement, to provide a cyclic carbamate, which allowed for the key coupling reaction to occur with no loss of stereochemical information
  - selective carbamate hydrolysis in the presence of an amide
- Synthesis of mycalamide B in 14 steps from commercial material (longest linear sequence) with a 2.6% overall yield.
- Interesting solution to overcome the difficulty of a convergent stereocontrolled coupling of two fully functionalized halves of pederin-like natural products.