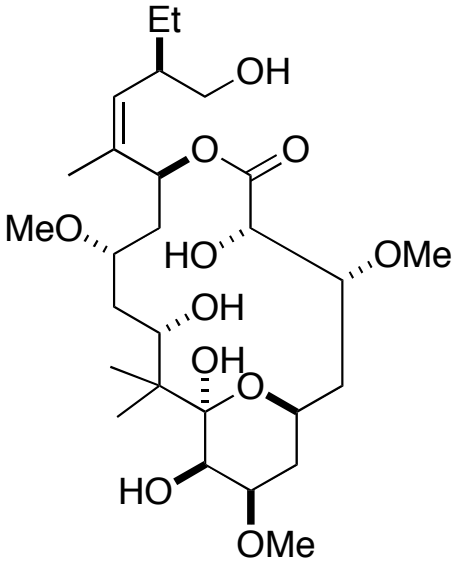
Total Synthesis of Peloruside A Through Kinetic Lactonization and Relay Ring-Closing Metathesis Cyclization Reactions

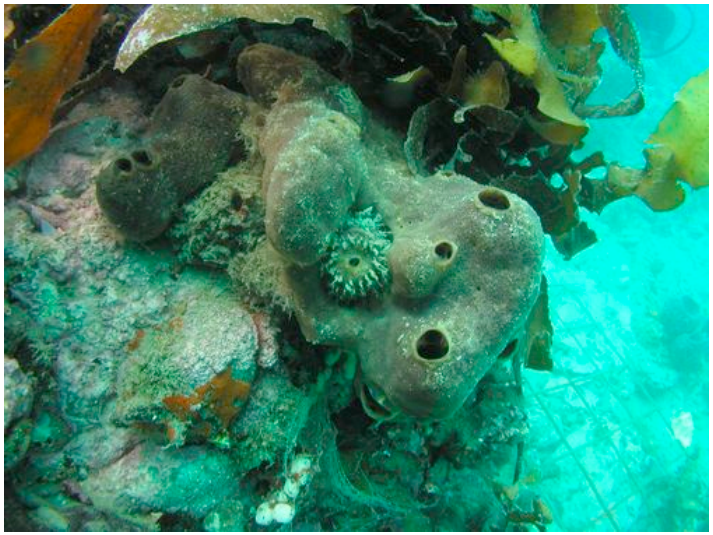
Thomas R. Hoye, Junha Jeon, Lucas C. Kopel, Troy D. Ryba, Manomi A. Tennakoon, and Yini Wang. *Angew. Chem. Int. Ed.* **2010**, 6151-6155



Peloruside A

Eric E. Buck
Current Literature
August 28, 2010

Isolation and Background



• Peloruside A was Isolated from the marine sponge *Mycale hentscheli* (pictured left) by Northcote in 2000.

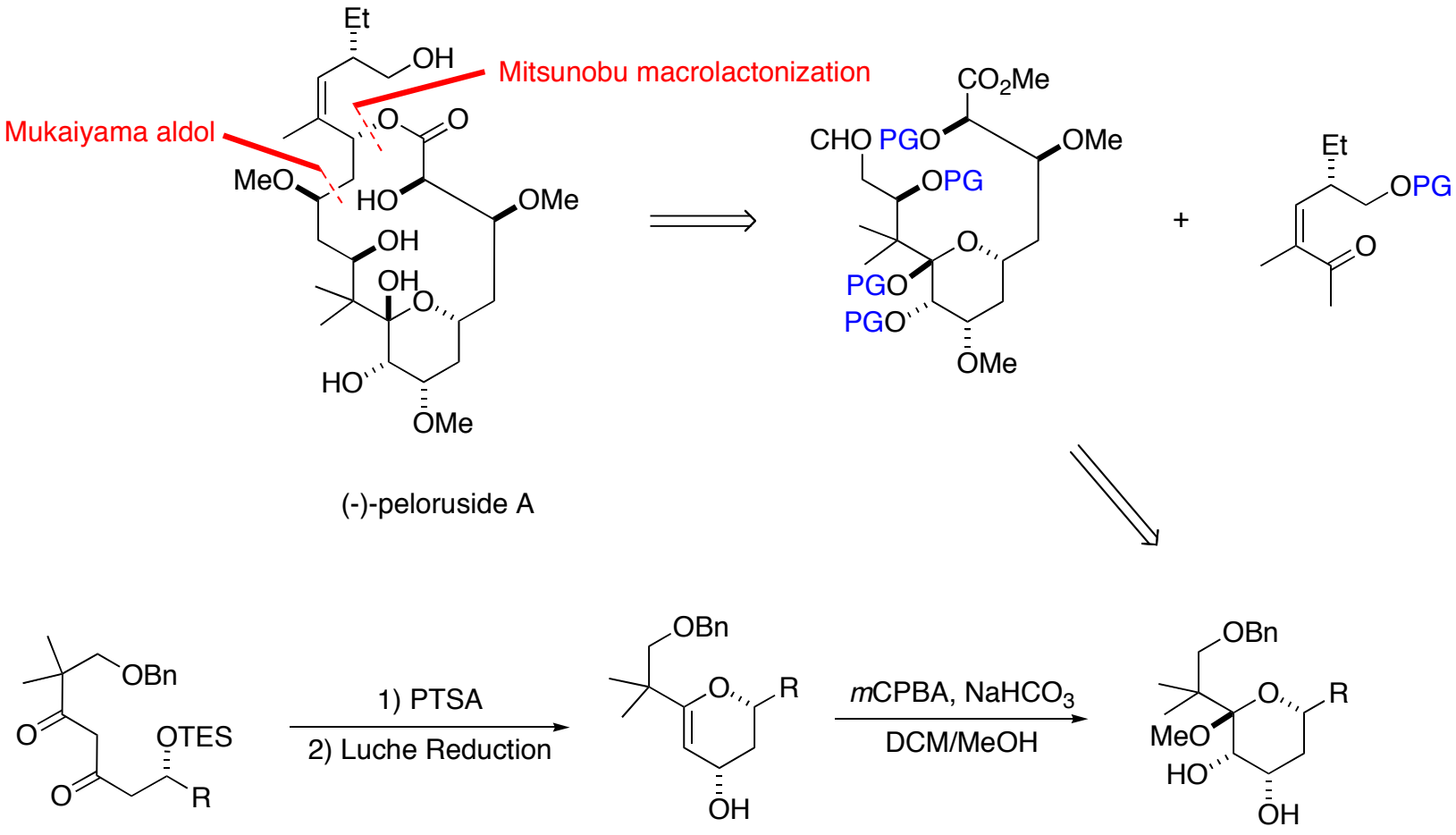
• The marine sponge *Mycale hentscheli*, located in Pelorus Sound (pictured below), is also responsible for the production of mycalamide A and pateamine.

• Peloruside A demonstrated LD_{50} vaulues in the 6-18 nM range towards several cancer cell lines.

• Peloruside A is a microtubule stabilizer that binds to a different site than paclitaxel.

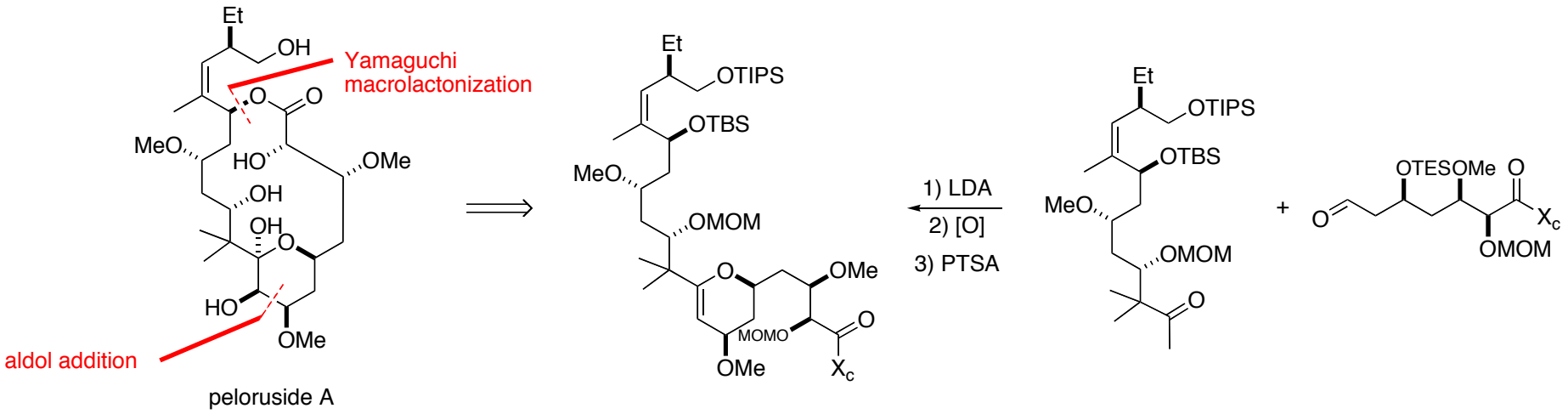
West, L. M.; Northcote, P. T. *J. Org. Chem.* **2000**, 65, 445-449
Hood, K. A.; West, L. M.; Rouwé, B.; Northcote, P. T.; Berridfe, M.V.; Wakefield, St. J.; Miller, J. H. *Cancer Res.* **2002**, 64, 3356-3360
Teesdale-Spittle, p.; Andreu, J. M.; Miller, J. H. *Cancer Res.* **2004**, 64, 5063-5067

First Synthesis and the Confirmation of Absolute Configuration

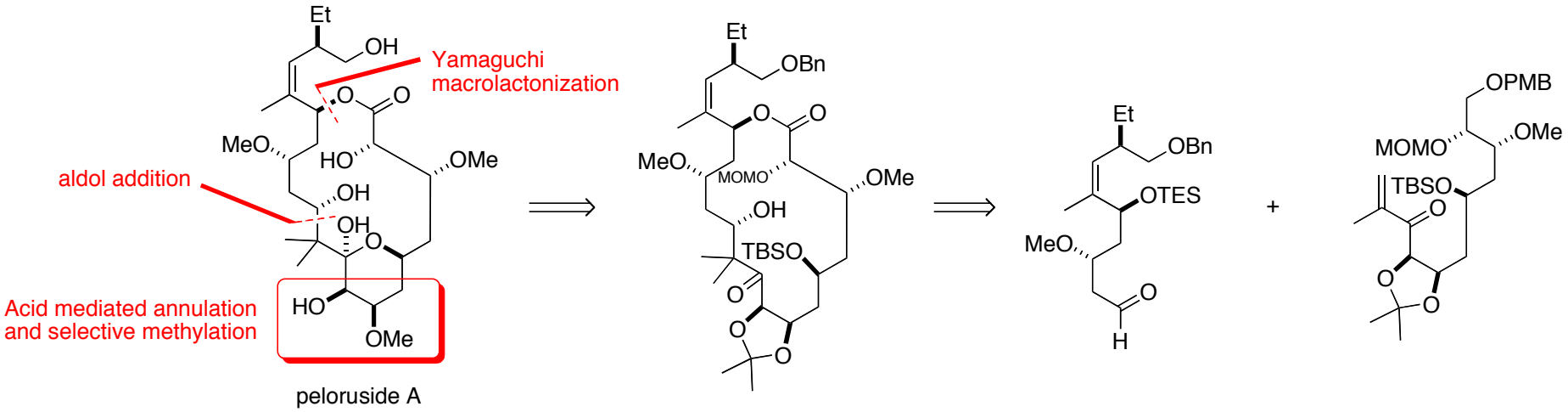


Liao, X.; Wu, Y. De Brabander, J. K. *Angew. Chem. Int. Ed.* **2003**, 42, 1648-1652

Taylor's and Ghosh's Synthesis of Peloruside A

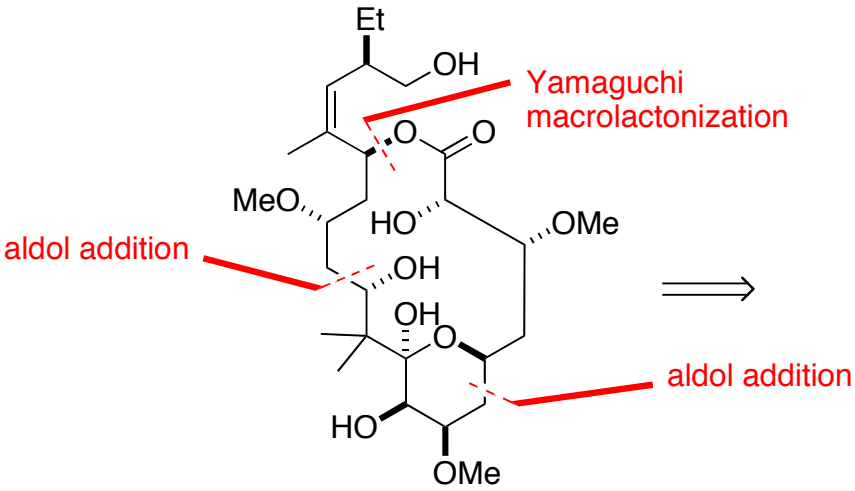


Jin, M.; Taylor, R. *Org. Lett.* **2005**, 7, 1303-1305

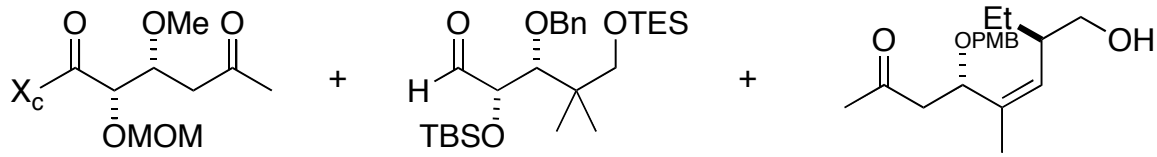


Gosh, A. K.; Xu, X.; Kim, J.; Xu, C. *Org. Lett.* **2008**, 10, 1001-1004

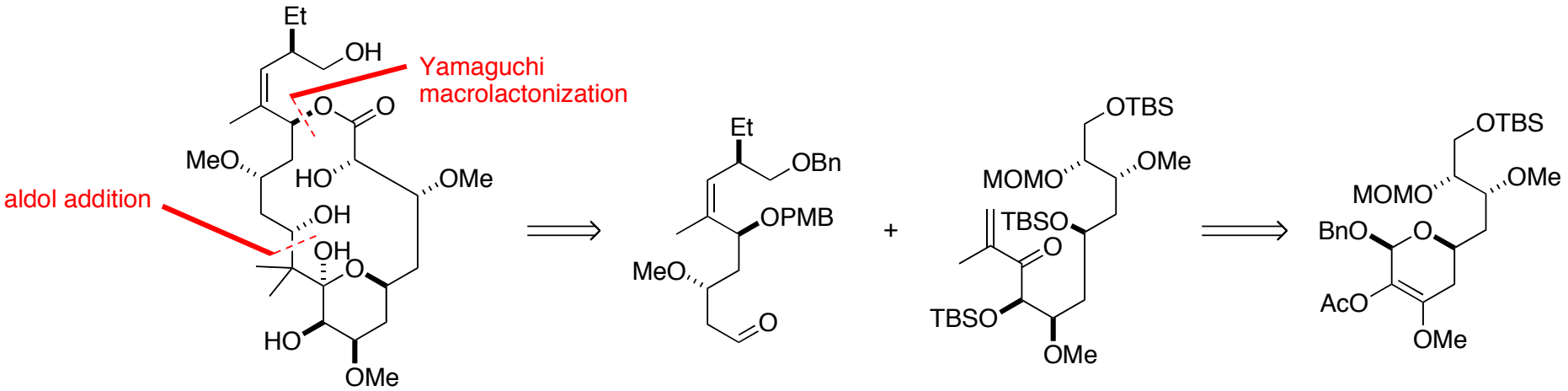
Evan's and Jacobsen's Synthesis of Peloruside A



peloruside A



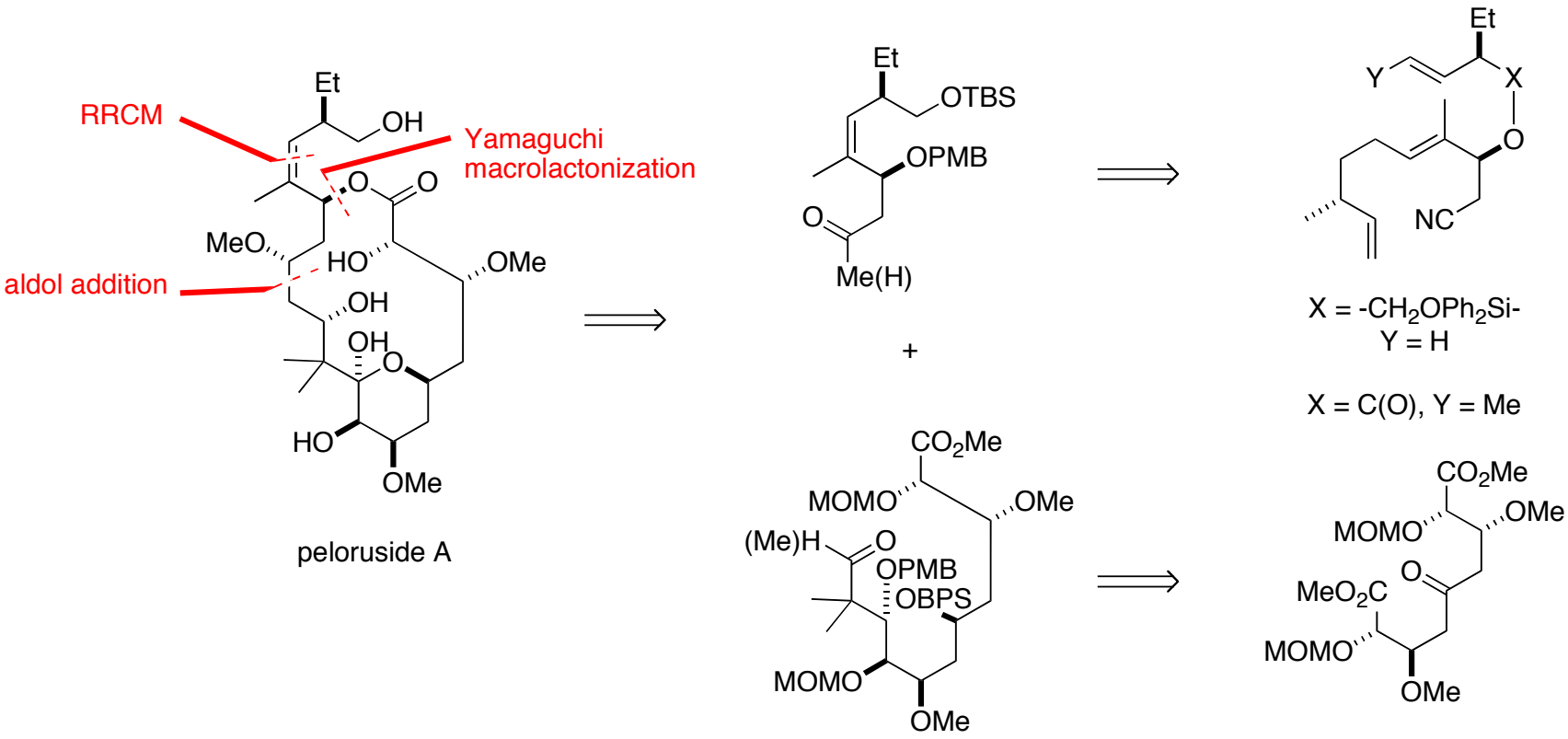
Evans, D. A.; Welch, D. S.; Speed, A. W. H.; Moniz, G. A.; Reichelt, A.; Ho, S. *J. Am. Chem. Soc.* **2009**, 131, 3840-3841



peloruside A

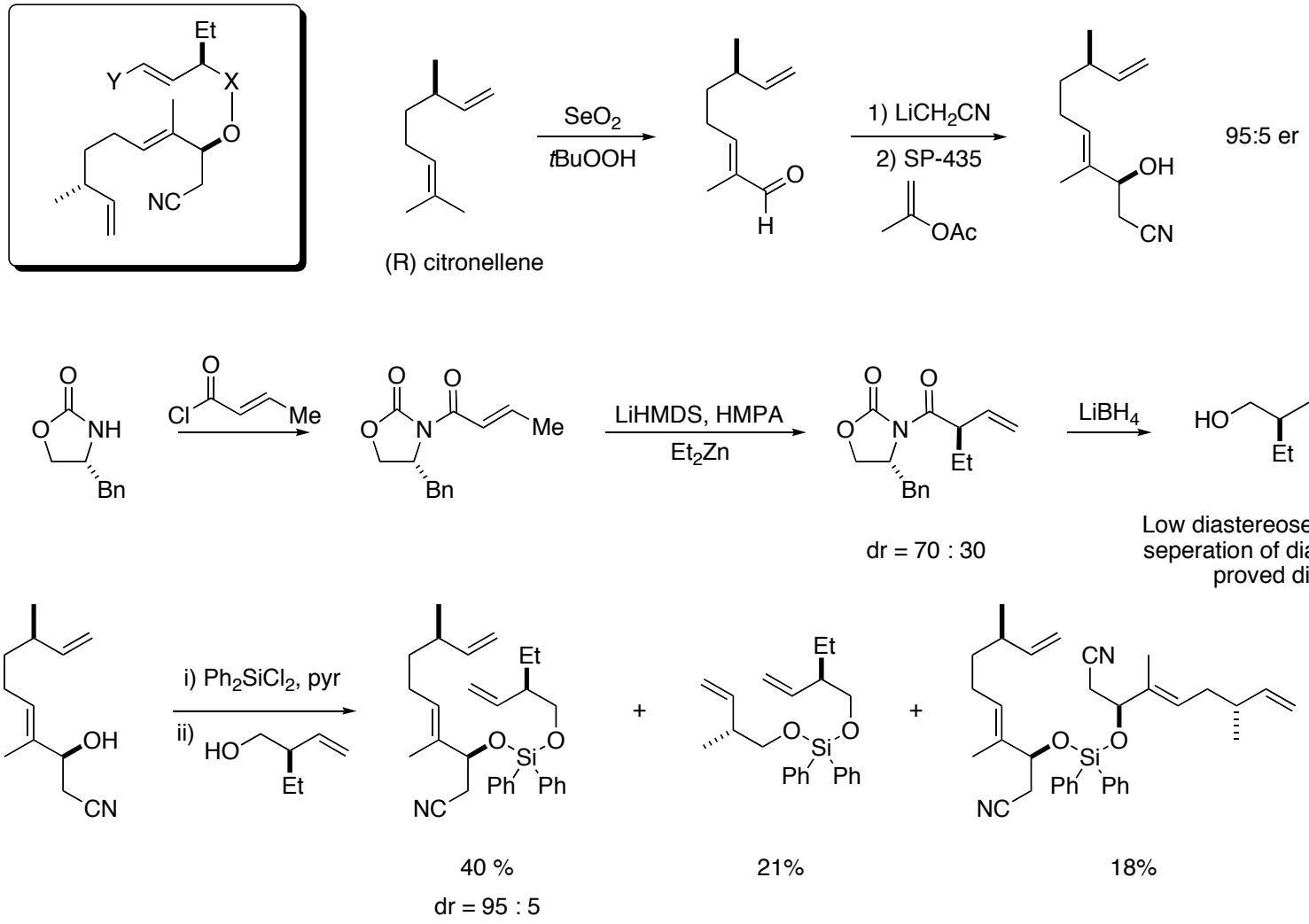
McGrown, M. A.; Stevenson, P. C.; Schiffler, M. A.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2010**, 49, 6147-6150

Title Paper: Retro Synthesis



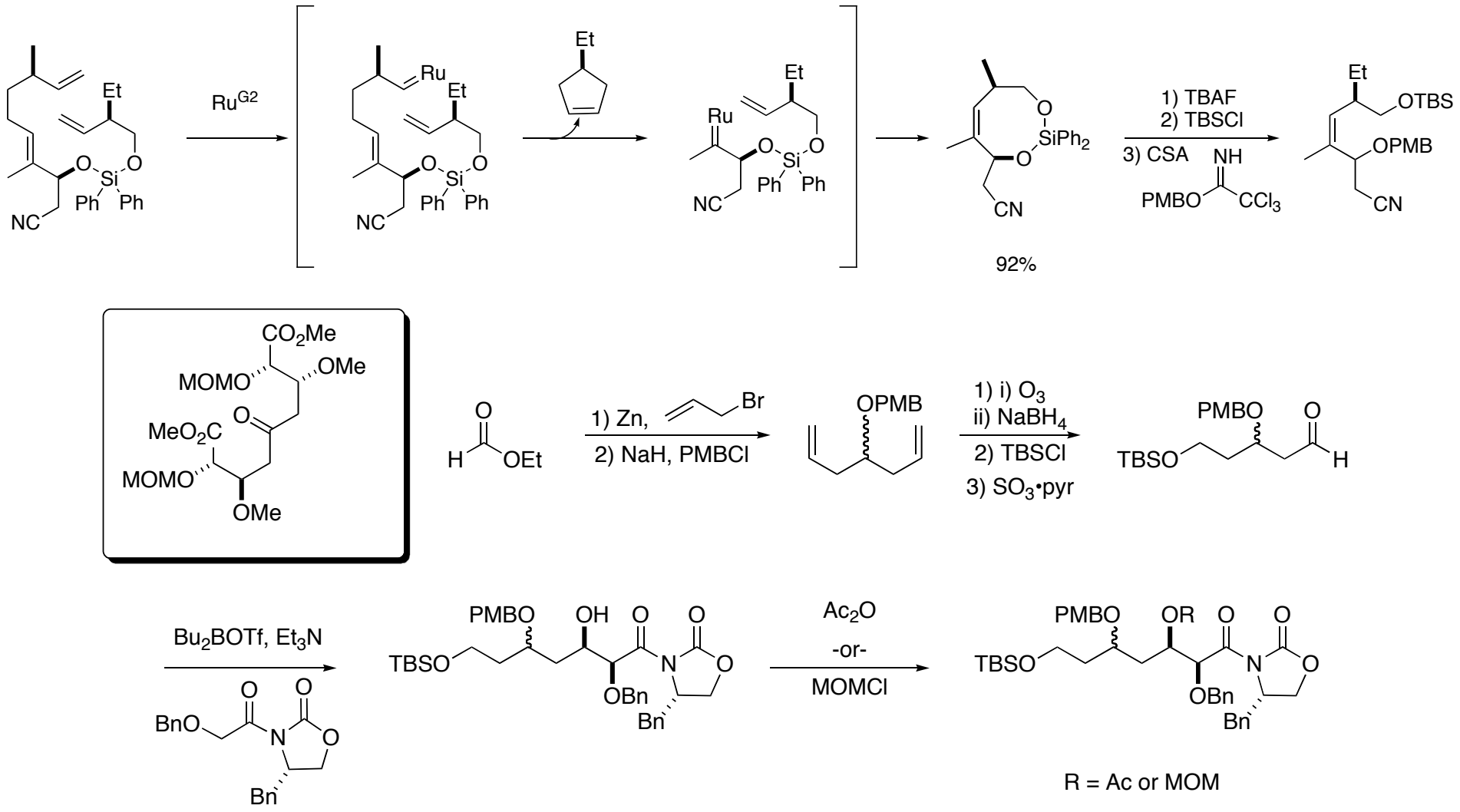
Thomas R. Hoye, Junha Jeon, Lucas C. Kopel, Troy D. Ryba, Manomi A. Tennakoon, and Yini Wang. *Angew. Chem. Int. Ed.* **2010**, 6151-6155

Tennakoon and Yini: Initial Work on Peloruside A



Tennakoon, M. A., Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2001**

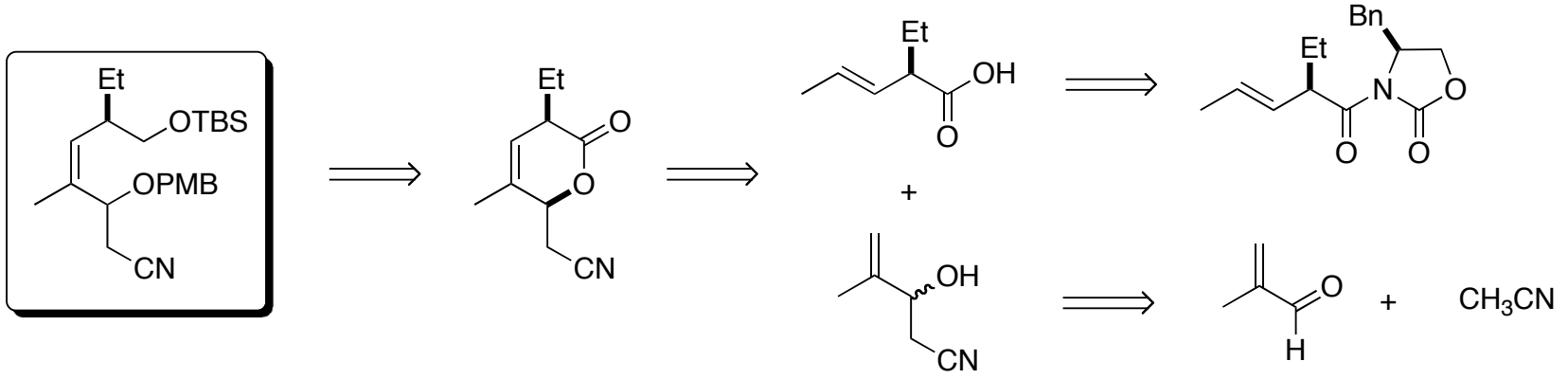
Tennakoon and Yini: Initial Work on Peloruside A

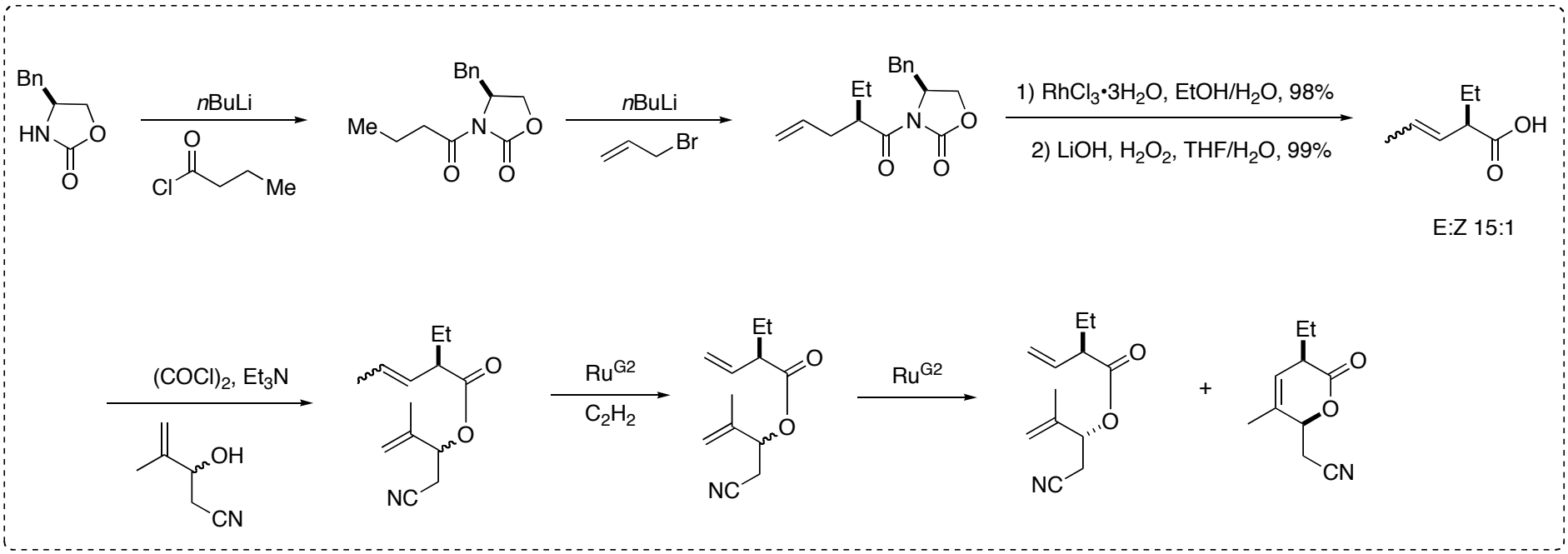


Tennakoon, M. A., Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2001**

Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, 126, 10210-10211

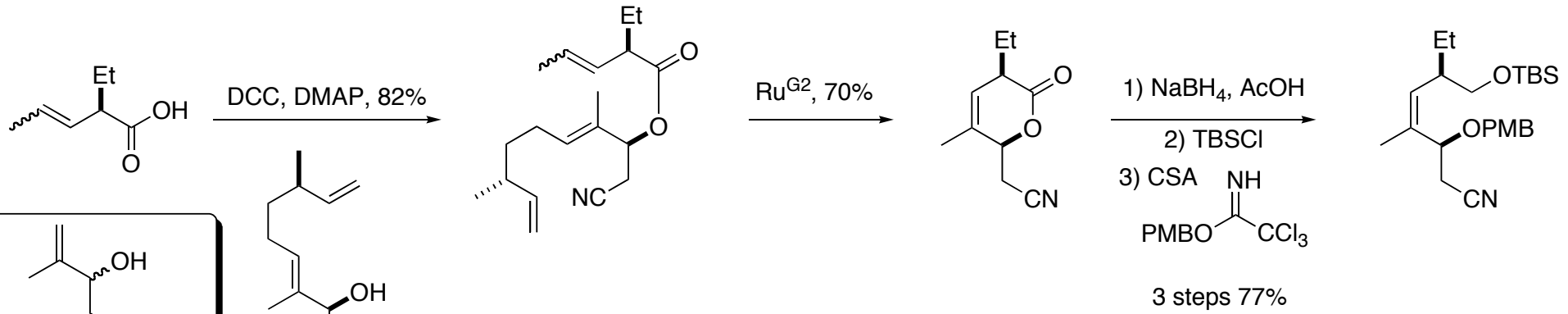
Troy : The Issue of Scalability



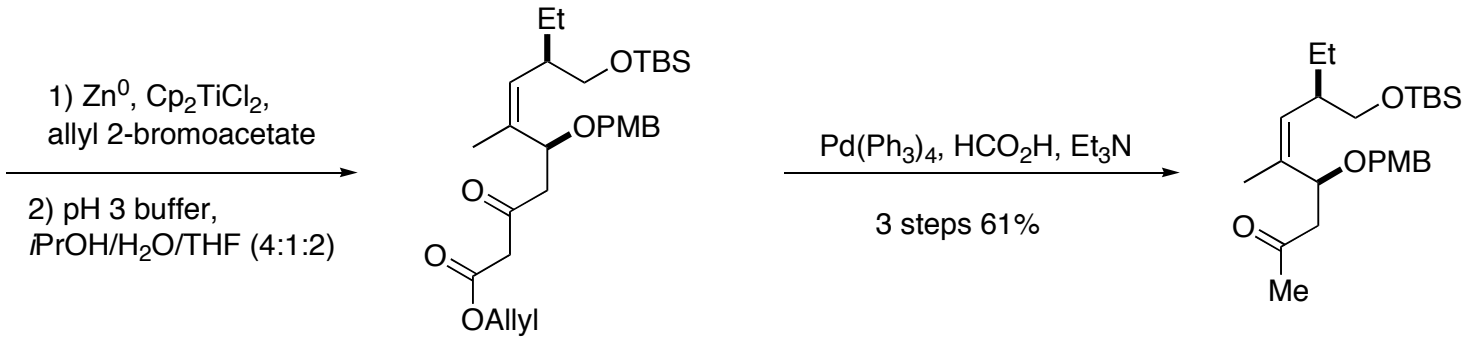


Ryba, T. D., Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2005**
Roulland, E.; Ermolenko, M. S. *Org. Lett.* **2005**, 7, 2225-228

Junha : Completion of a Scalable Route to the Northern Fragment

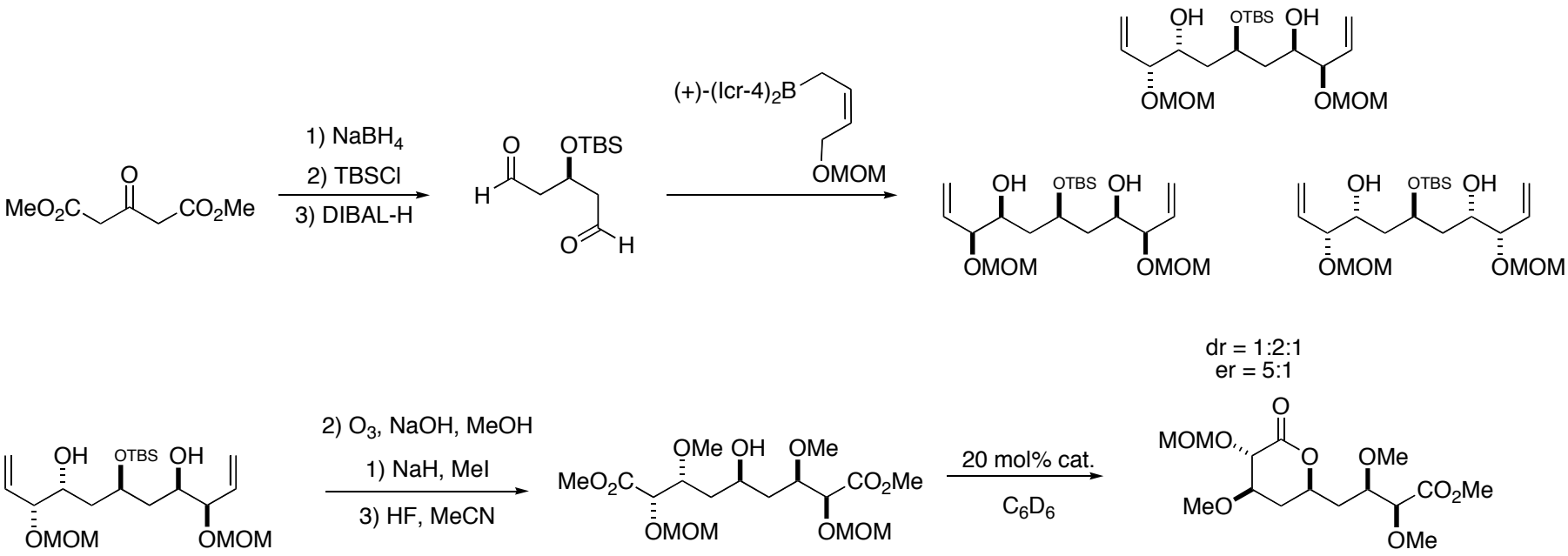


"… although Troy's diastereoselective RRCM was a great reaction, I thought it was not scalable."



"Nitrile to ketone or to complementary aldehyde was not easy. The nitrile was extremely base sensitive."

Troy : The Issue of Scalability

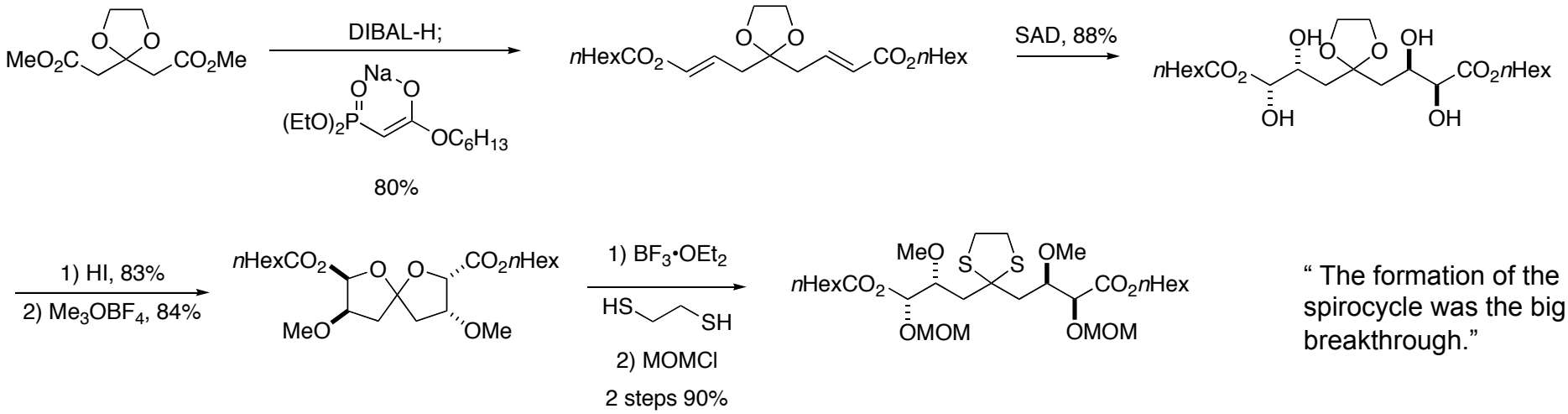


Catalyst	time	Lactone Ratio
DBU	15	10:1
TMG	40	13:1
DBN	40	10:1

"…from a total synthesis perspective it was a total nightmare. From a training exercise it was a blessing."

Ryba, T. D., Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2005**

Troy : The Issue of Scalability

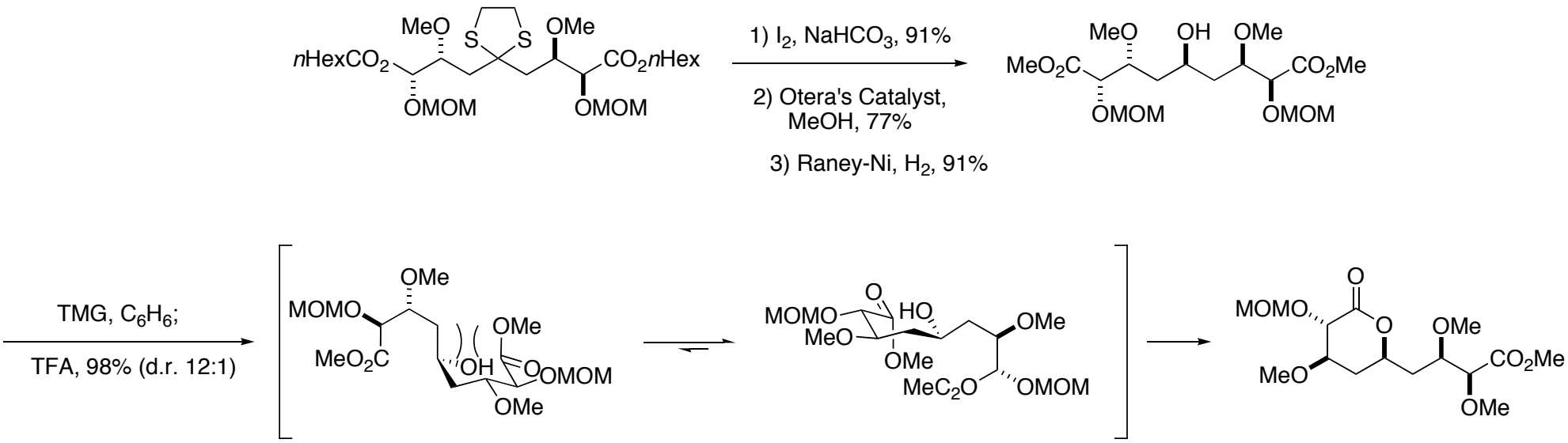


" The formation of the spirocycle was the big breakthrough."

Catalyst	% Conv.	Time (h)	Lactone Ratio
DBU	100	15	10:1
TMG	<10	40	13:1
DBN	70	40	10:1

Ryba, T. D., Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2005**

Lucas: Optimization of the Kinetic Lactonization



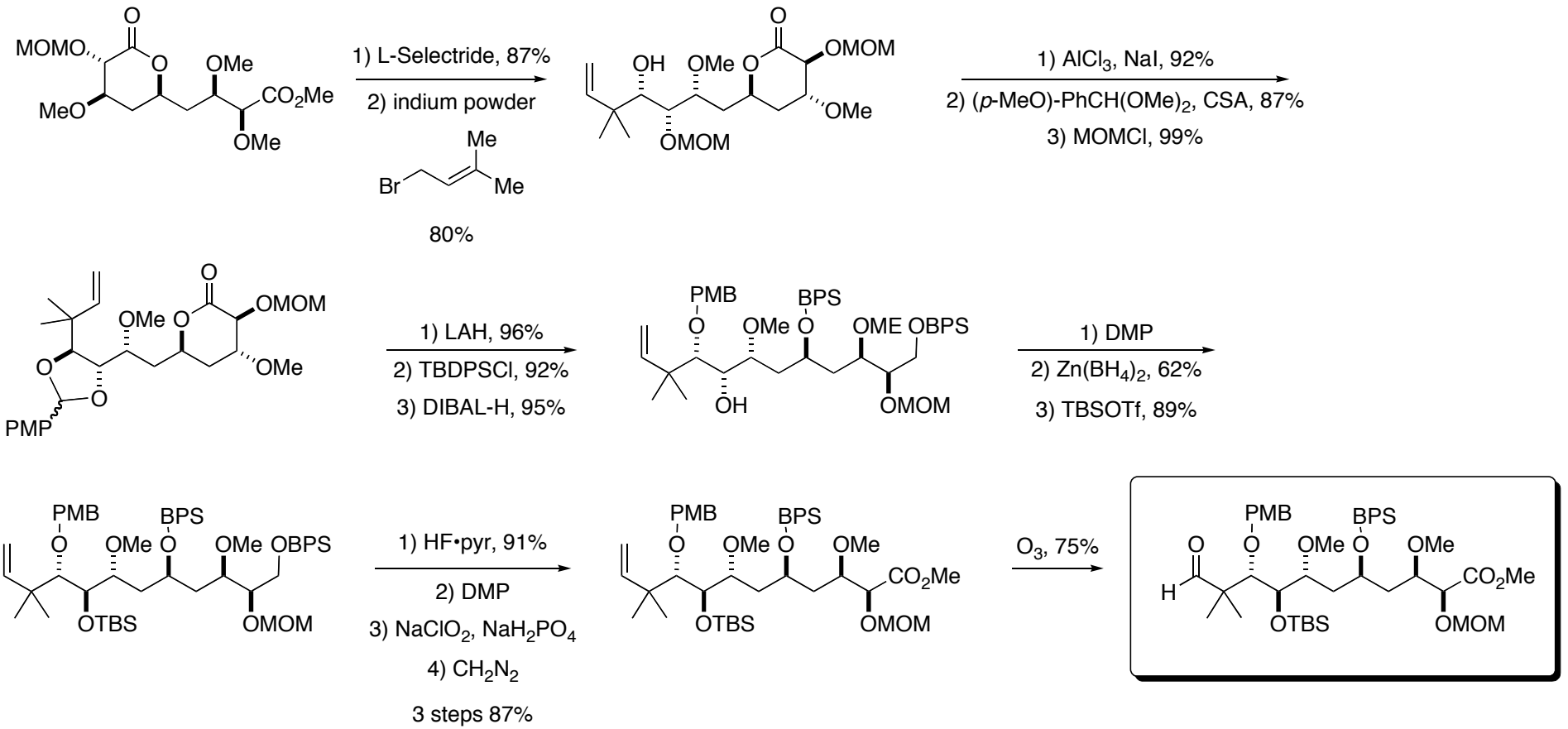
"… I observed that as the ratio of DBN increased, so too did the peaks that I initially assigned as being associated with by-products.

"… the additional peaks are in fact coming from an amine-product complex and unpon treatment with TFA, this adduct collapses to regenerate the desired lactone product."

"… it was decided to use TMG as the catalyst in C_6D_6 because of its high selectivity for forming the desired product. TMG was also reported not to have the problems associated with decomposition of product."

Kopel, L. C., Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2009**

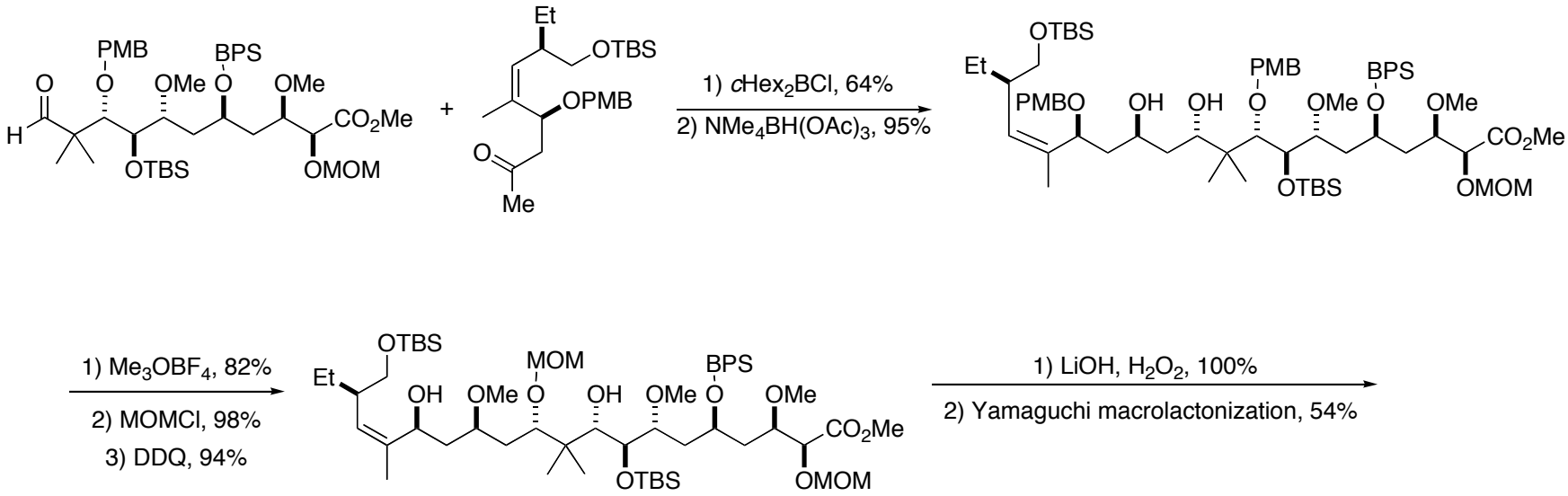
Lucas: Finishing the Southern Fragment



" The C8 stereocenter was previously inverted by a lengthy intramolecular inversion strategy: mesylation, ozonolysis, oxidation to the acid, cyclization to invert, DIBAL-H reduction, and wittig to reveal the inverted C8 hydroxyl."

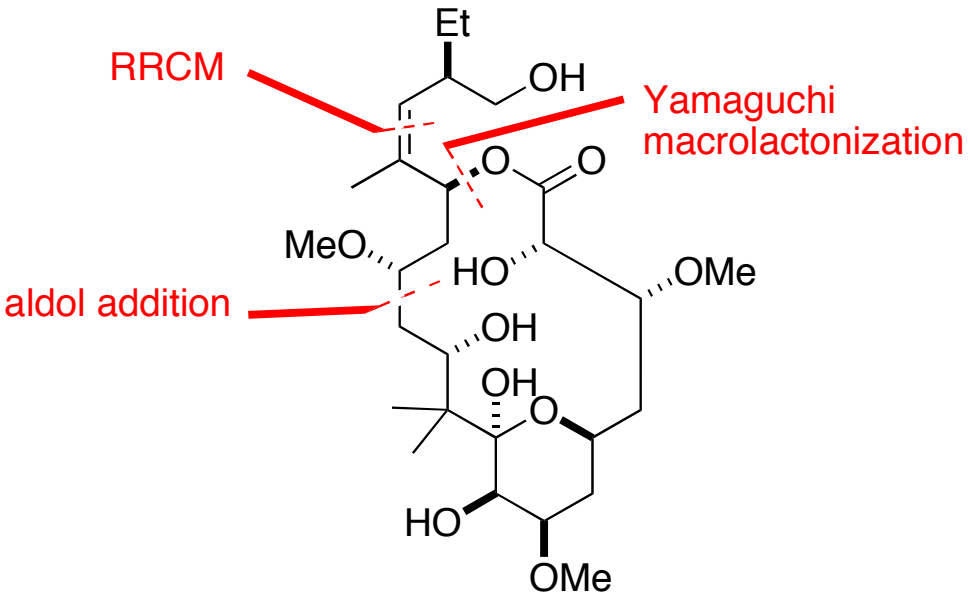
Kopel, L. C., Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2009**

Junha and Lucas: End Game



" After a final removal of 5 protecting groups, on TLC I saw two spots, which correspond to peloruside A and isopeloruside. I don't understand why others didn't see the this because virtually all the synthesis used almost identical deprotection conditions."

Summary



peloruside A

- A detailed look into the synthesis of peloruside A from an author perspective.

- Highlights from the synthesis include a RRCM strategy to set the z-olefin and desymmetrizing kinetic lactonization to assemble the southern fragment.

- The final synthesis yielded 6.9 mg followed by another 5 mg. There remains enough addition material to produce ca 100 mg.

- A Special thanks to Lucas, Junha, and Troy.