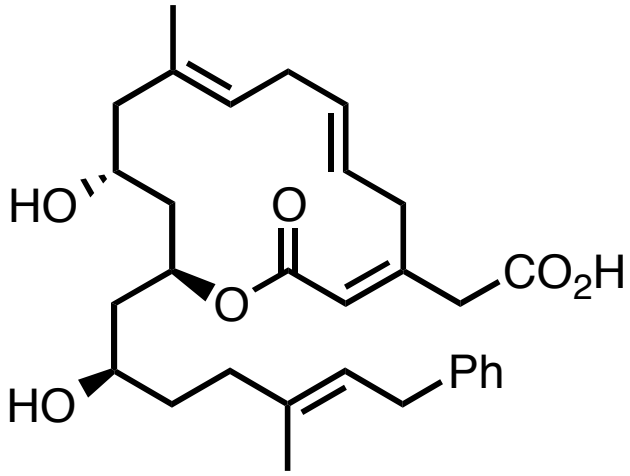
Total Synthesis of RNA Polymerase Inhibitor Ripostatin B



Brandon Parks

Wipf Group Current Literature

April 28th, 2012

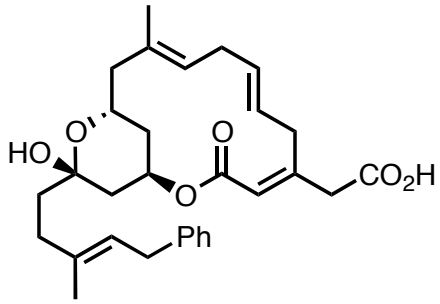
Bacterial RNA Polymerase (RNAP)

- Multi-drug-resistant bacterial strains present an emerging problem
- Bacterial RNAP subunit sequences are highly conserved
- Rifamycins are currently the only approved class of RNAP inhibitors

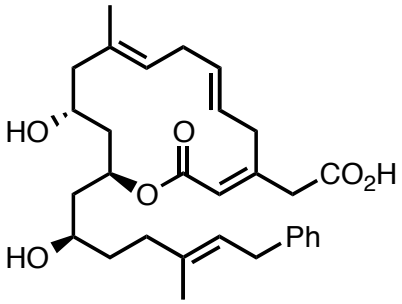
Irschik, H.; Augustiniak, H.; Gerth, K.; Höfle, G.; Reichenbach, H.; *J. Antibiot.*, **1995**, *48*, 787.
Mukhopadhyay, J.; Das, K.; Ismail, S.; Koppstein, D.; Jang, M.; Hudson, B.; Sarafianos, S.; Tuske, S.; Patel, J.; Jansen, R.; Irshik, H.; Arnold, E.; Ebright, R. H.; *Cell*, **2008**, *135*, 295.
Haebich, D.; Nussbaum, F.; *Angew. Chem. Int. Ed.*, **2009**, *48*, 3397.
Arias, C. A.; Murrary, B. E.; *N. Eng. J. Med.*, **2009**, *360*, 439.

Meet the Ripostatins

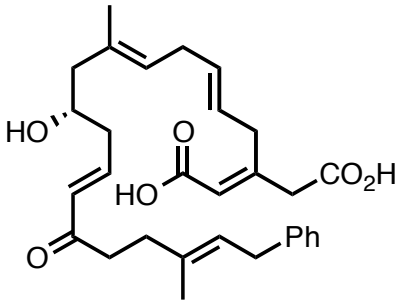
- Isolated in 1995 from *S. cellulosum*
- Display narrow antibiotic activity
  - Interacts with RNAP, no cross-resistance with rifampin



Ripostatin A



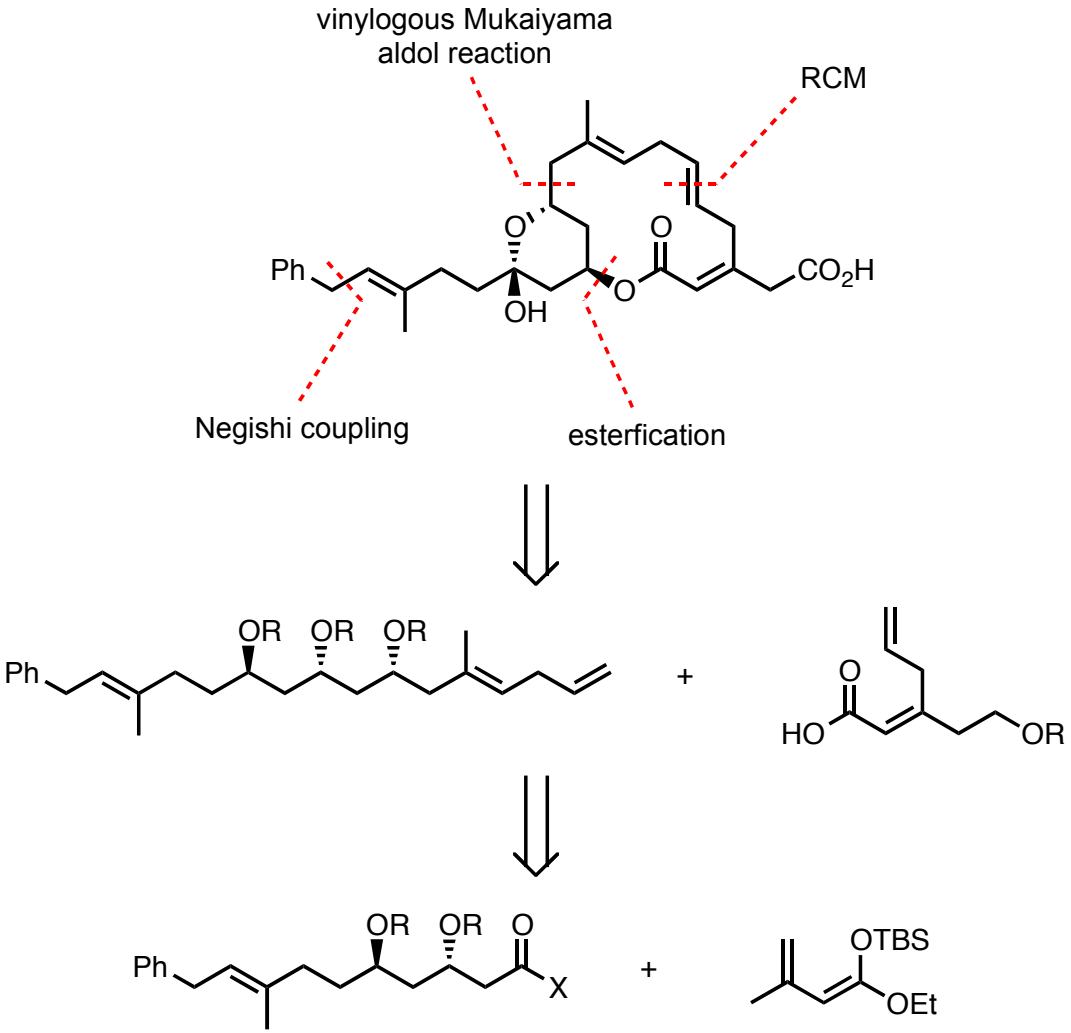
Ripostatin B



Ripostatin C

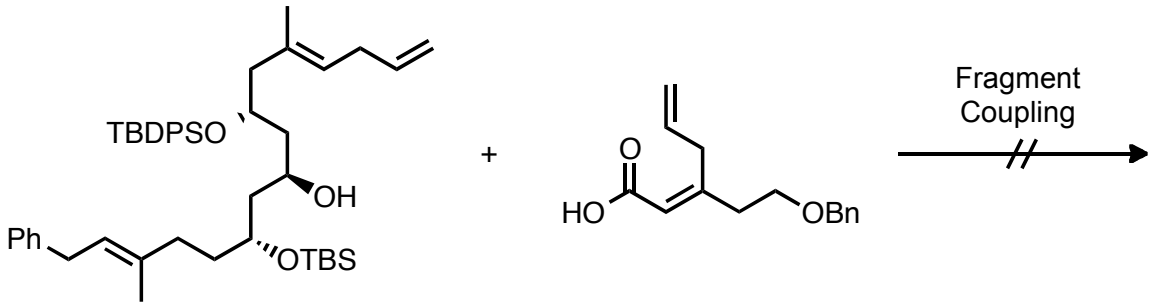
Irschik, H.; Augustiniak, H.; Gerth, K.; Höfle, G.; Reichenbach, H.; *J. Antibiot.*, **1995**, *48*, 787.
Winter, P.; Hiller, W.; Christmann, M.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 3396.

Previous Work



Kujat, C.; Bock, M.; Kirschning, A.; *Synlett*, **2006**, *3*, 419.

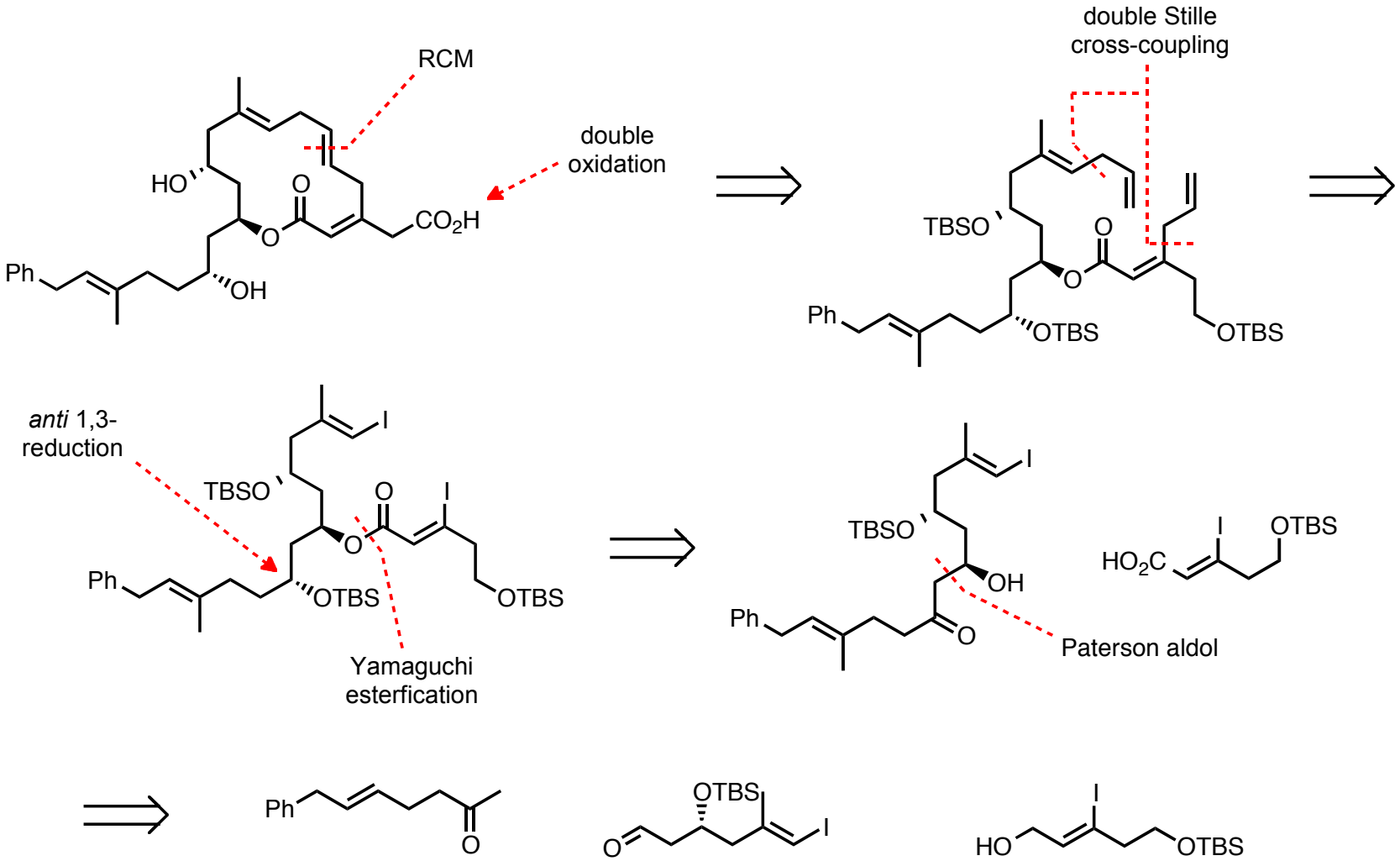
So Close, Yet So Far Away:



- Sterically demanding protecting groups
- Double bond isomerization and migration

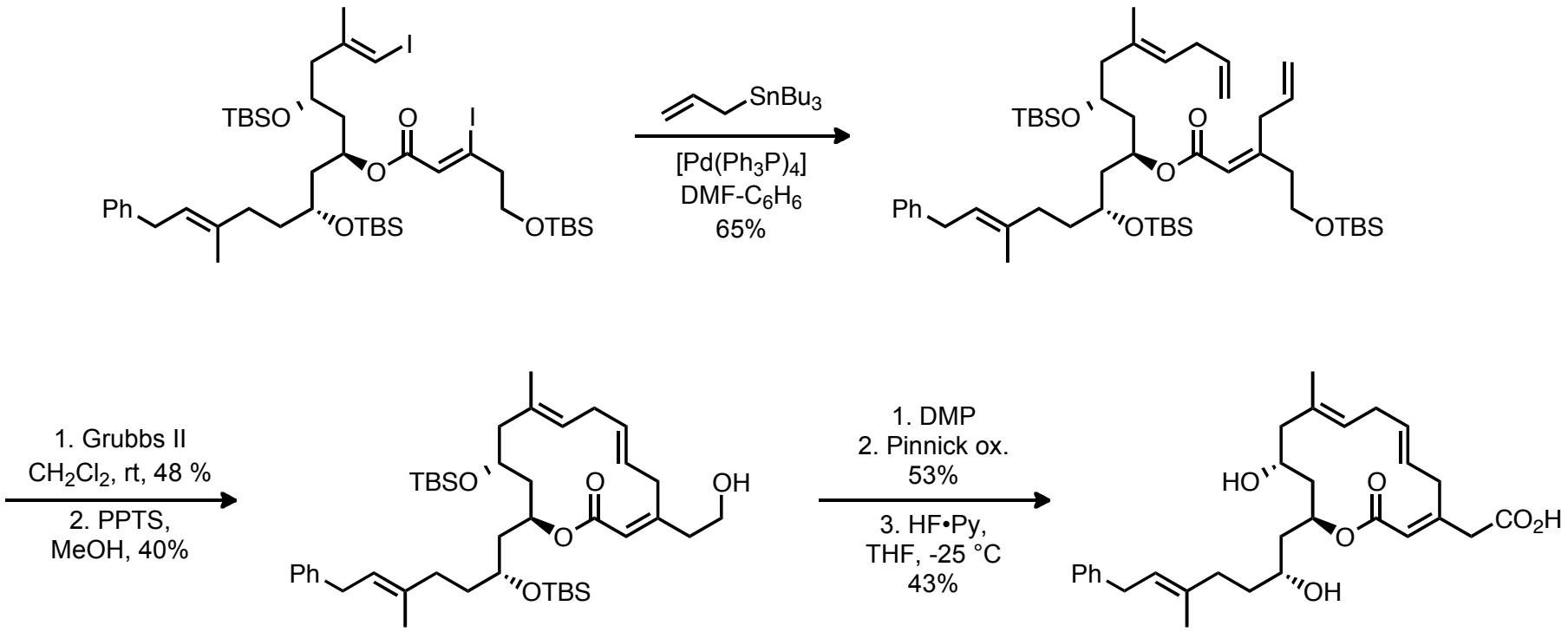
Kujat, C.; Bock, M.; Kirchning, A.; *Synlett*, **2006**, *3*, 419.

Prusov Retrosynthesis



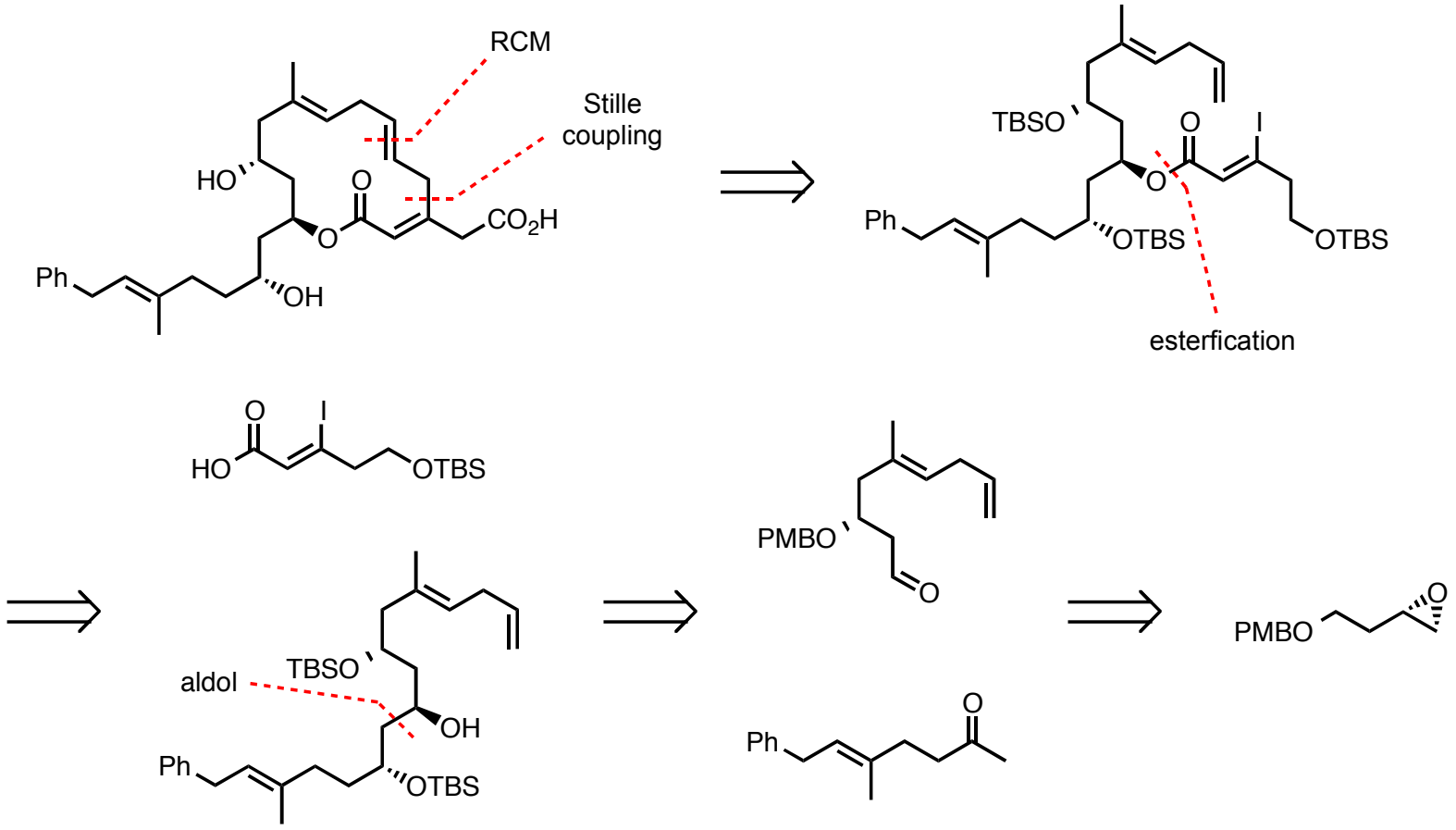
Tang, W.; Prusov, E. V.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 3401.

Key Transformations



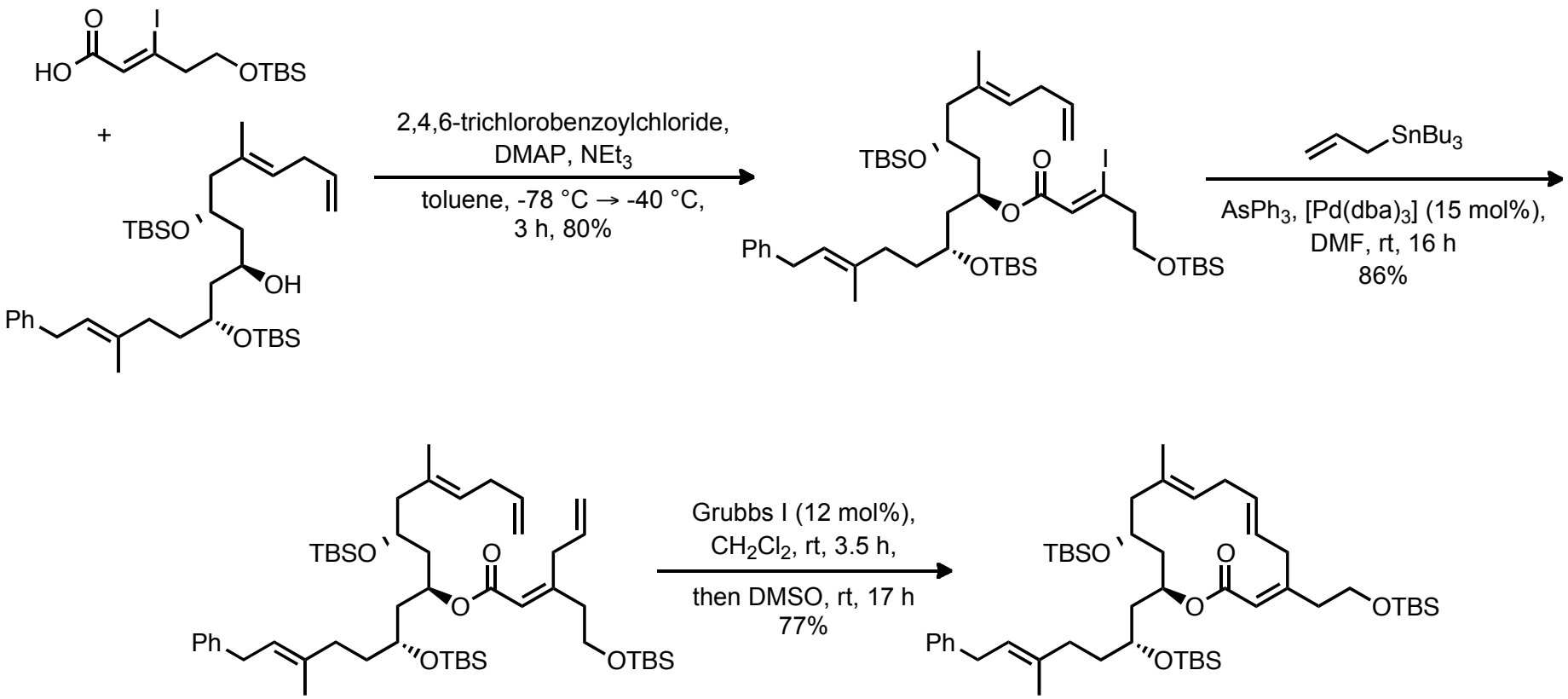
Tang, W.; Prusov, E. V.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 3401.

Altmann Retrosynthesis



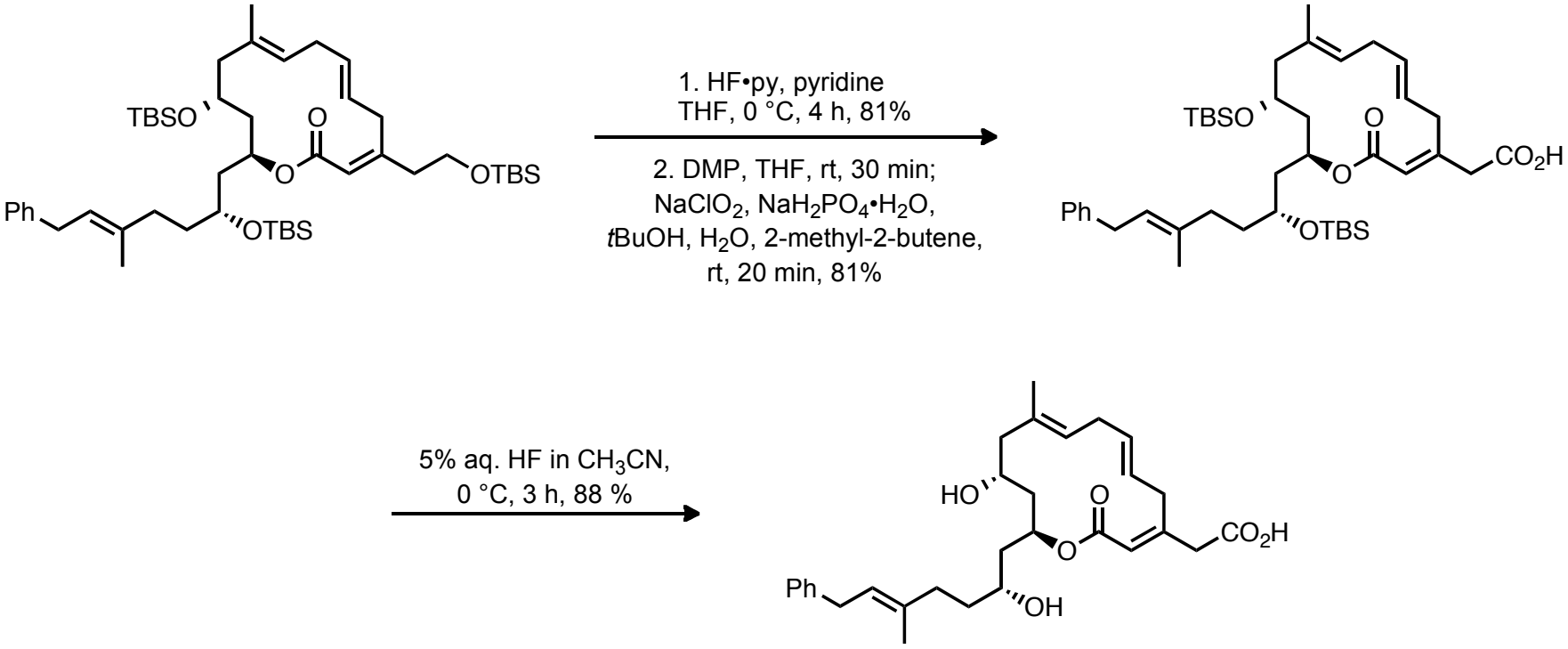
Glaus, F.; Altmann, K-H.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 3405.

Altmann Key Transformations



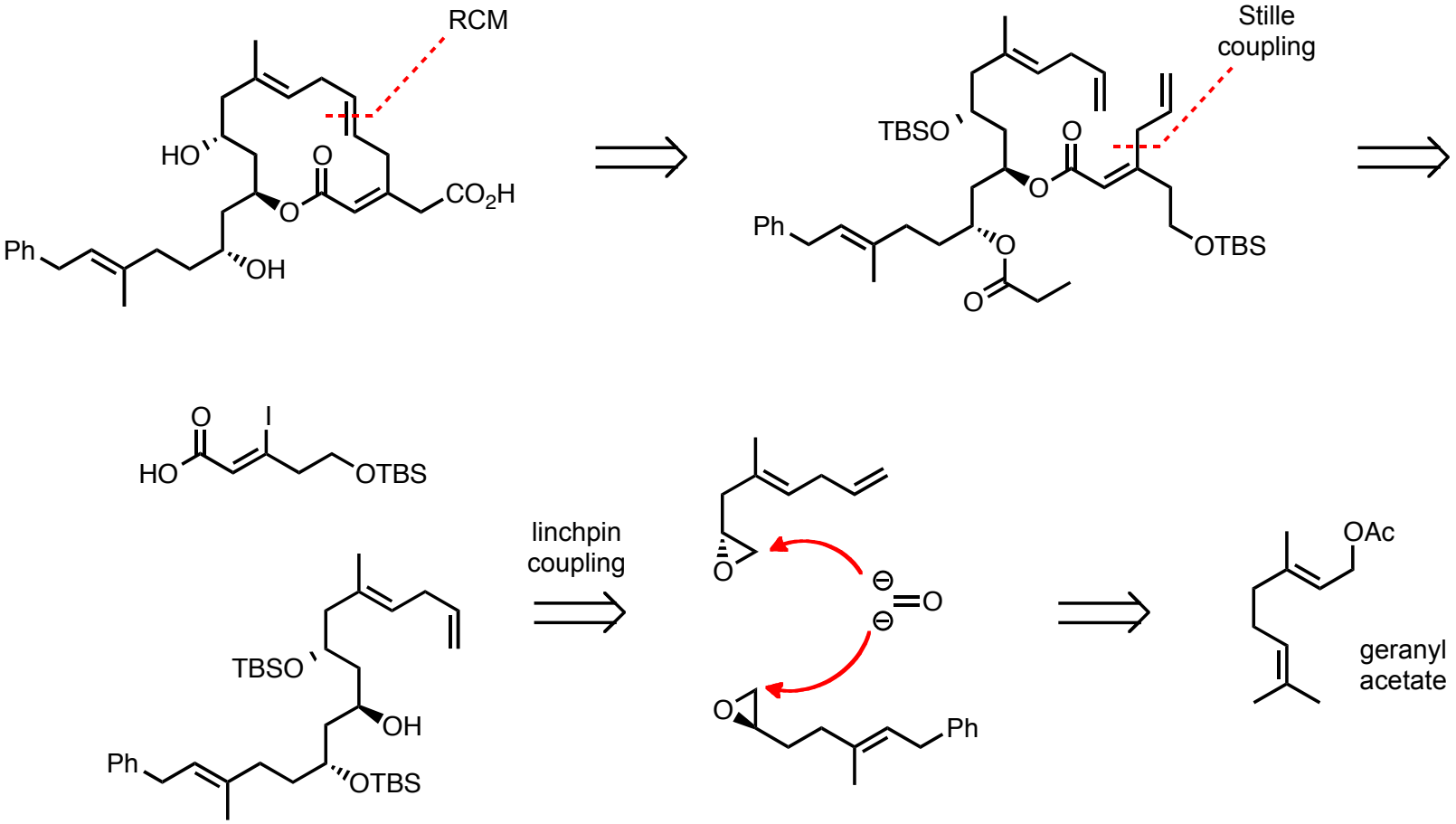
Glaus, F.; Altmann, K-H.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 3405.

Altmann Key Transformations



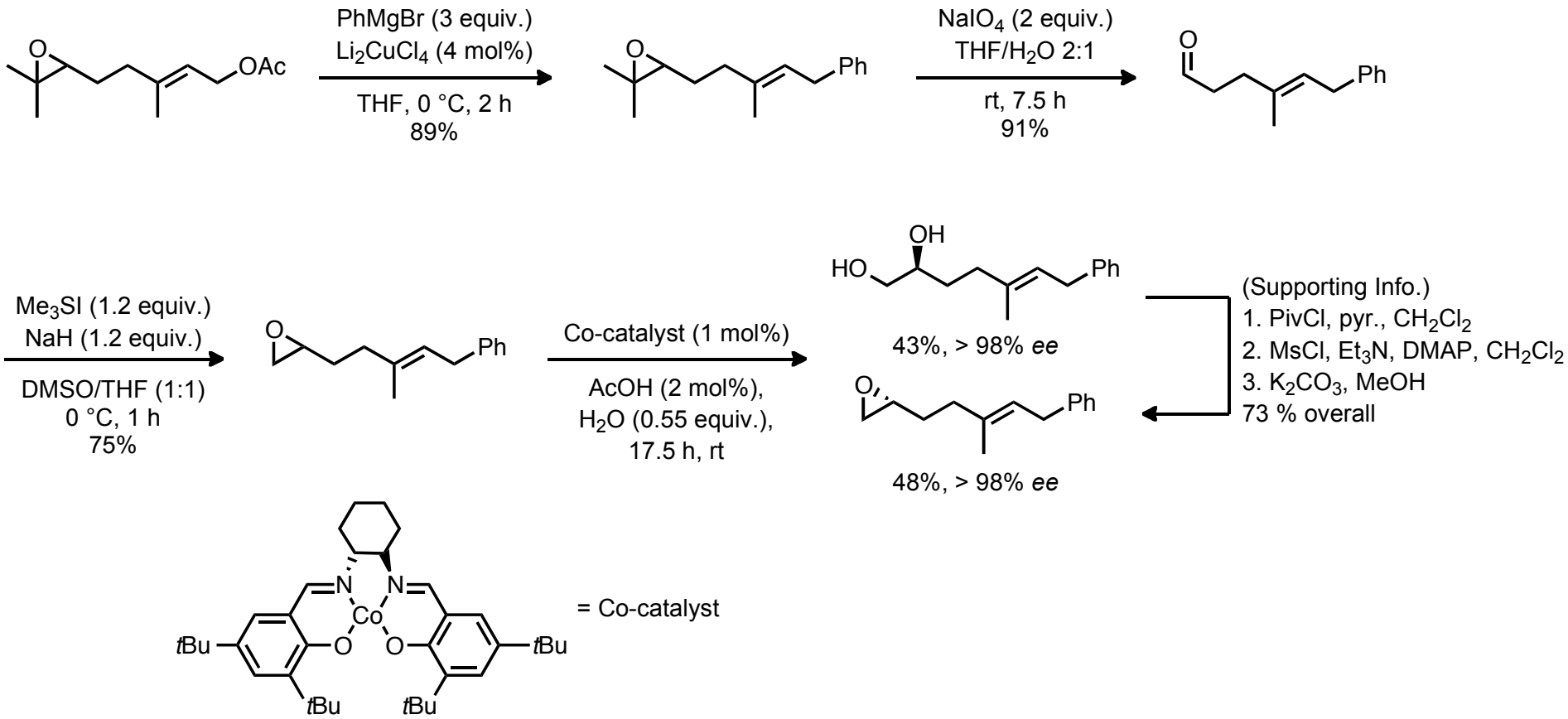
Glaus, F.; Altmann, K-H.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 3405.

Christmann Retrosynthesis



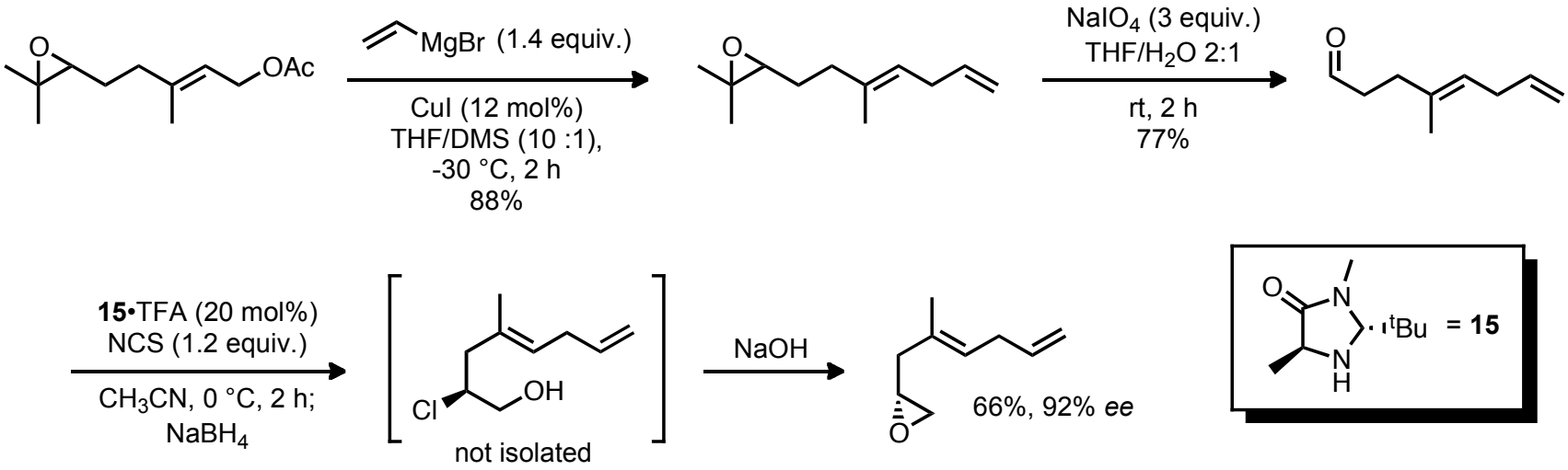
Winter, P.; Hiller, W.; Christmann, M.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 3396.

Fragment Synthesis



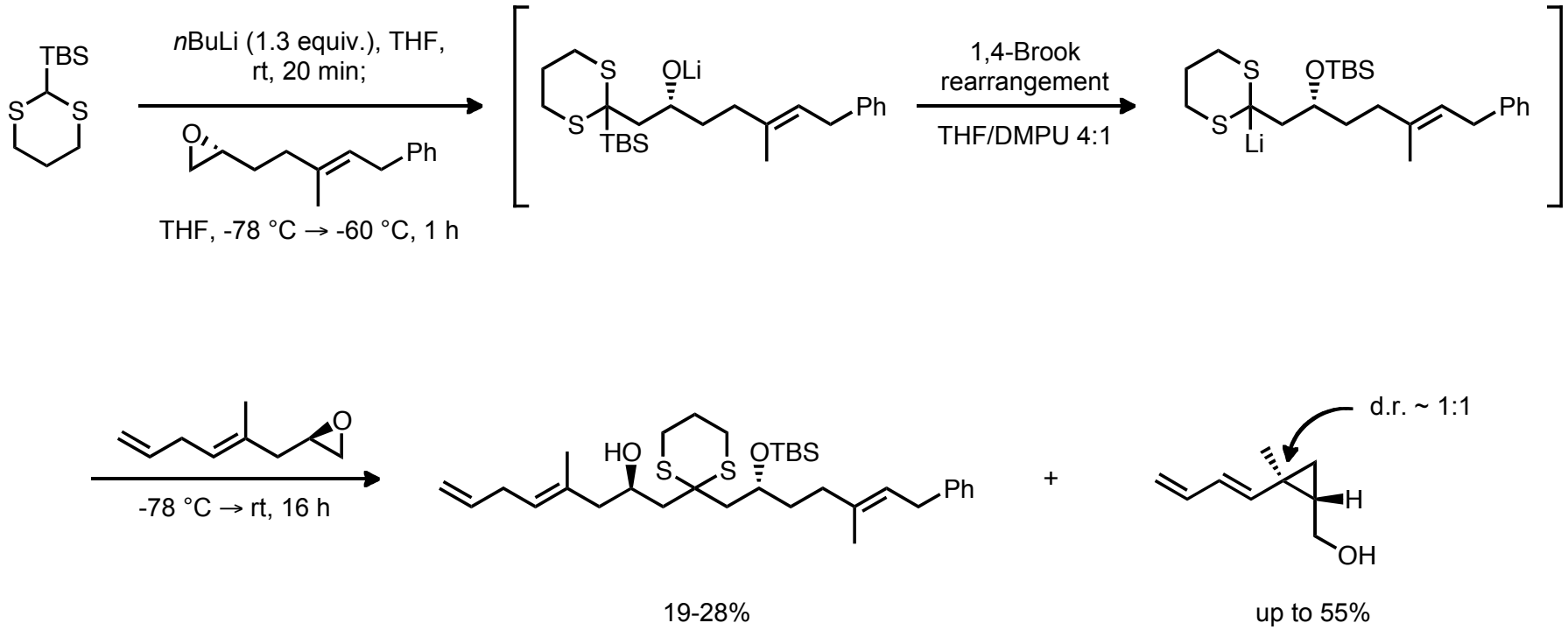
Winter, P.; Hiller, W.; Christmann, M.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 3396.
Gansäuer, A.; Justicia, J.; Rosales, A.; Rinker, B.; *Synlett*, **2005**, *12*, 1954.
Persson, E.S.M.; Bäckvall, J-E.; *Acta Chemica Scand.*, **1995**, *49*, 899.
Smith, A. B.; Kim, D-S.; *Org. Lett.*, **2004**, *6*, 1493.

Fragment Synthesis



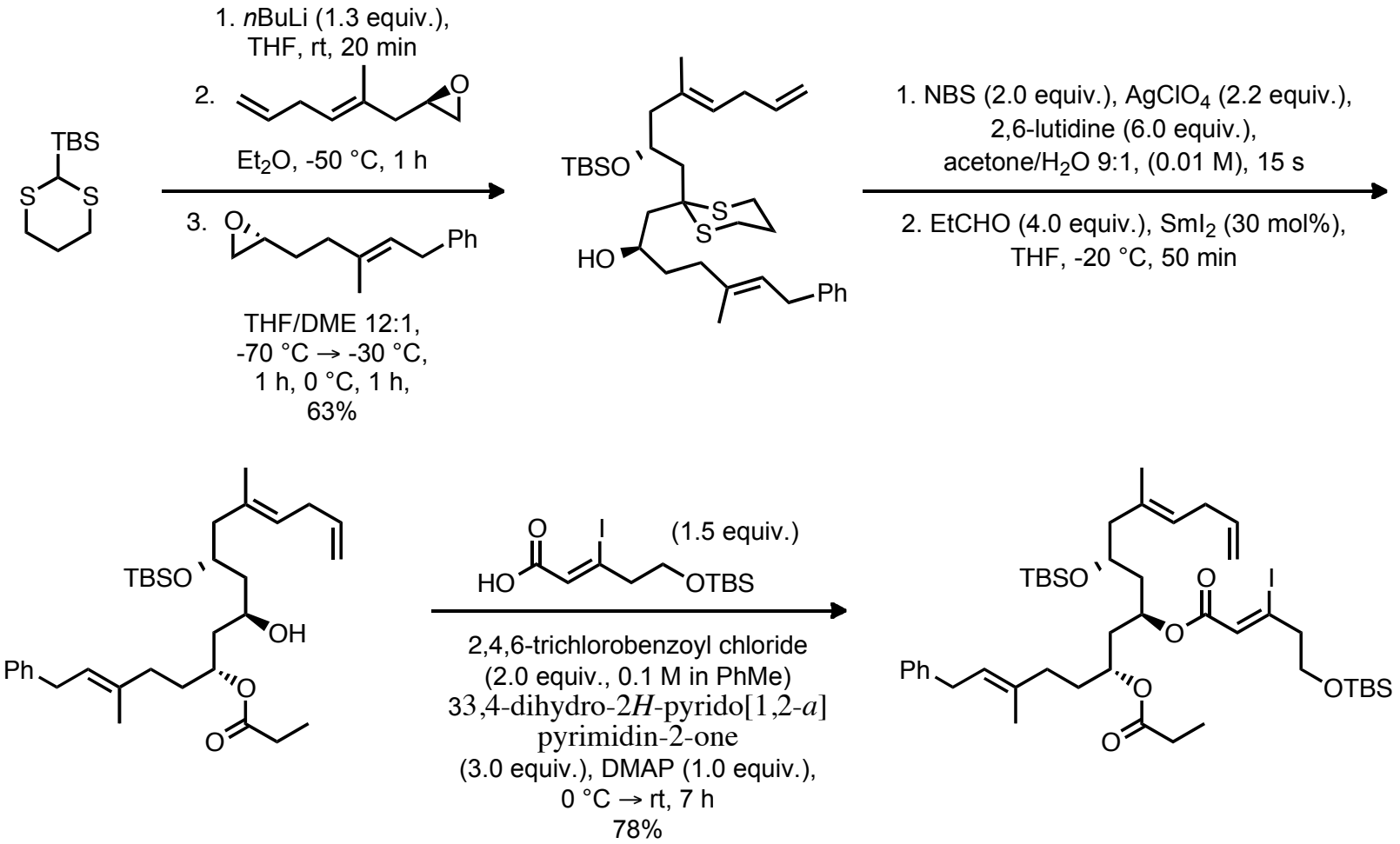
Winter, P.; Hiller, W.; Christmann, M.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 3396.
Persson, E.S.M.; Bäckvall, J-E.; *Acta Chemica Scand.*, **1995**, *49*, 899.
Winter, P.; Swatschek, J.; Willot, M.; Radtke, L.; Olbrisch, T.; Schäfer, A.; Christmann, M.; *Chem. Commun*, **2011**, *47*, 12200.
Winter, P.; Vaxelaire, C.; Heinz, C.; Christmann, M.; *Chem. Commun.*, **2011**, *47*, 394.

“Linchpin” Coupling: Take I



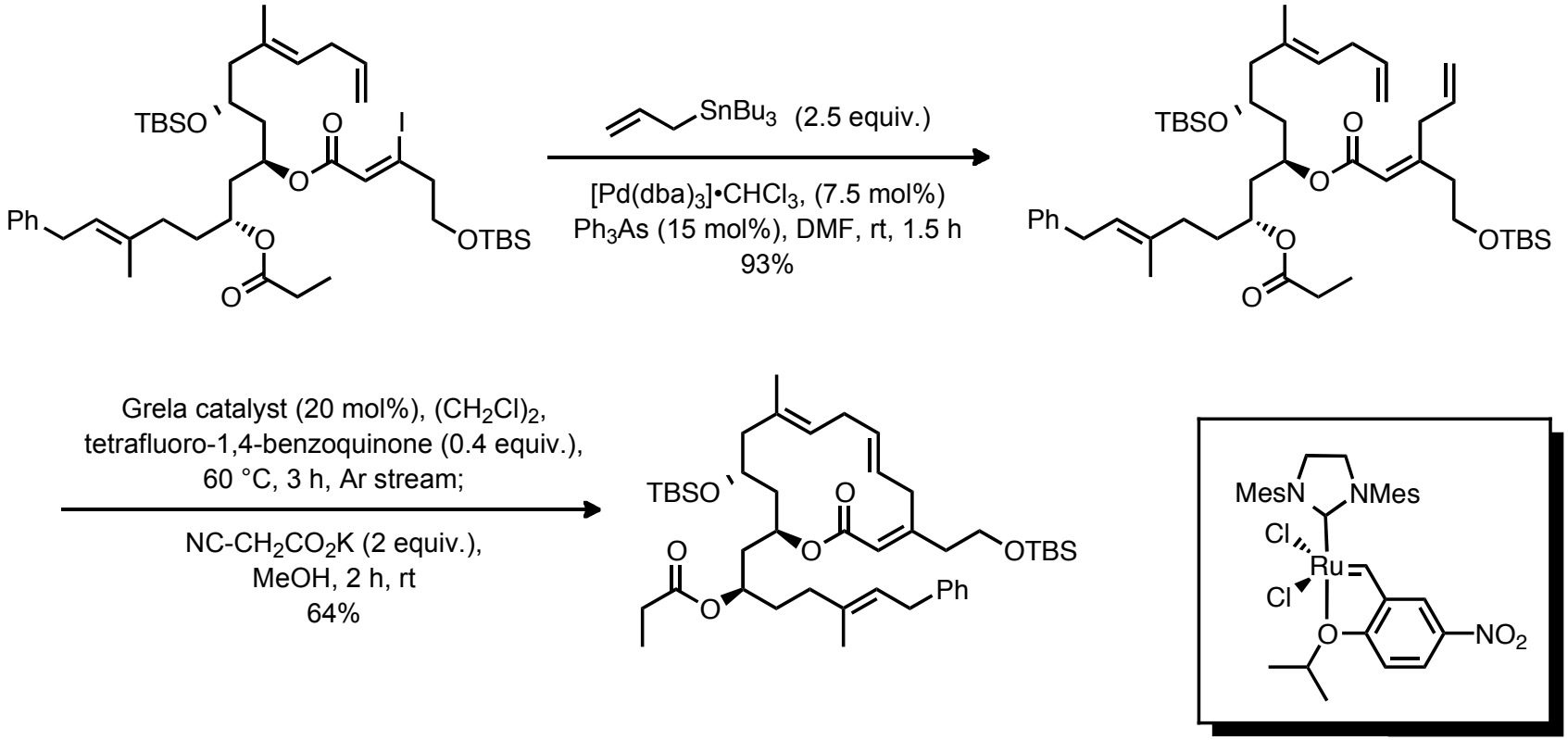
Winter, P.; Hiller, W.; Christmann, M.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 3396.
Smith, A.B.; Xian, M.; *J. Am. Chem. Soc.*, **2006**, *128*, 66.

“Linchpin” Coupling: Take II



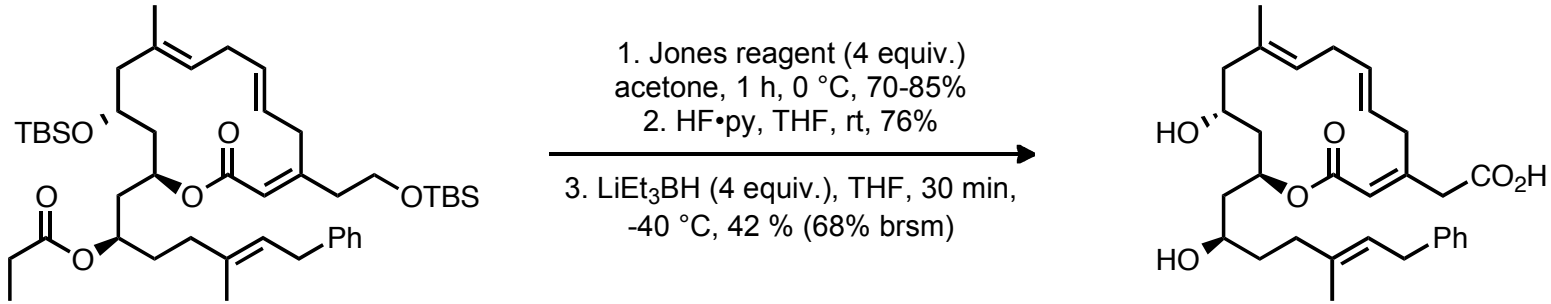
Winter, P.; Hiller, W.; Christmann, M.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 3396.
Smith, A.B.; Xian, M.; *J. Am. Chem. Soc.*, **2006**, *128*, 66.

End Game Synthesis



Winter, P.; Hiller, W.; Christmann, M.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 3396.
Galan, B. R.; Kalbarczyk, K. P.; Szczepankiewicz, S.; Keister, J. B.; Diver, S. T.; *Org. Lett.*, **2007**, *9*, 1203.
Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubss, R. H.; *J. Am. Chem. Soc.*, **2005**, *127*, 17160.
Michrowska, A.; Bujok, R.; Harutyunyna, S.; Sashuk, V.; Dolgonos, G.; Grela, K.; *J. Am. Chem. Soc*, **2004**, *126*, 9318..

End Game Synthesis



- 14 steps (longest linear sequence) from geranyl acetate
- 4% overall yield

Winter, P.; Hiller, W.; Christmann, M.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 3396.

Conclusions

- One-pot “linchpin” epoxide coupling
- Assembly of sensitive 14-membered macrolactone
- 14 steps, 4% overall yield
  - Prusov: 18 steps, 0.22 % overall yield
  - Altmann: 21 steps, 3.6 % overall yield
- New opportunities for SAR studies