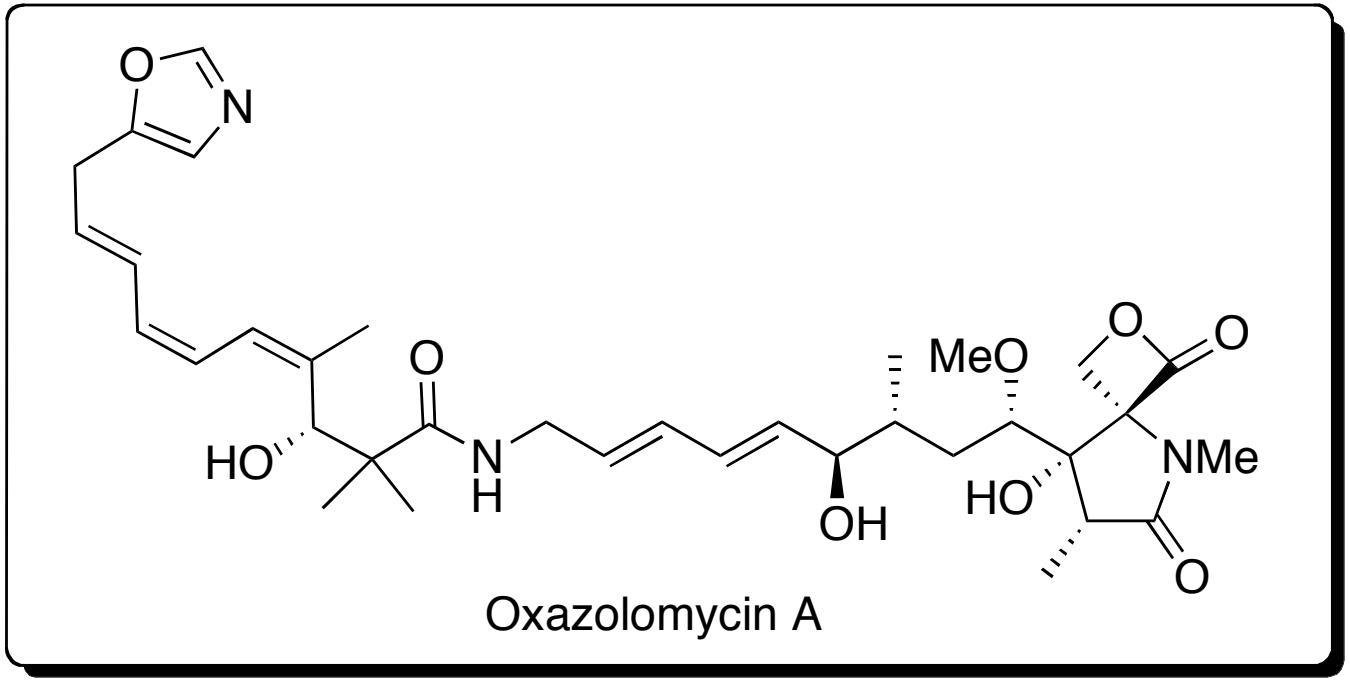
Total Synthesis of Oxazolomycin A



Oxazolomycin A

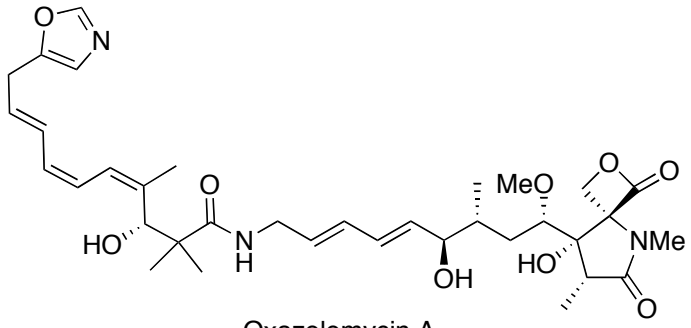
Eto, K.; Yoshino, M.; Takahashi K.; Ishihara, J.; Hatakeyama S.
Org. Lett. **2011**, *13*, 5398

Dimas Paz
Wipf group- Current Literature
October 8, 2011

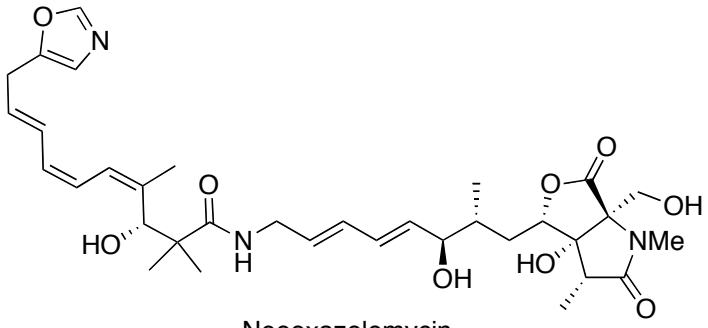
Oxazolomycin A - Isolation and Biological Active

• Oxazolomycin A was isolated from a strain *Streptomyces* together with Neooxazolomycin in 1985 by Uemura at al.

• Oxazole polyene lactam-lactone



Oxazolomycin A



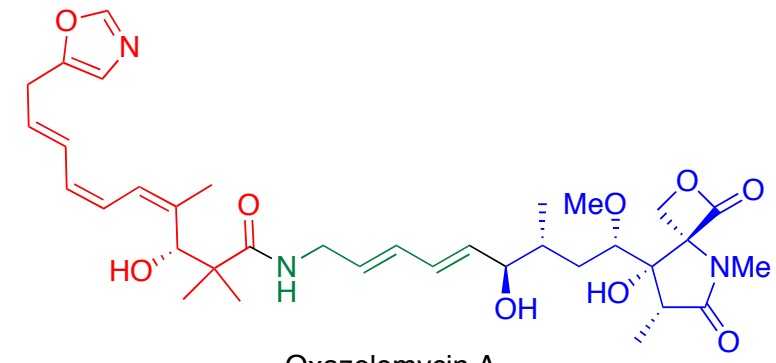
Neooxazolomycin

• They exhibit wide ranging and potent antibacterial and activities as well as in vivo antitumor activity.

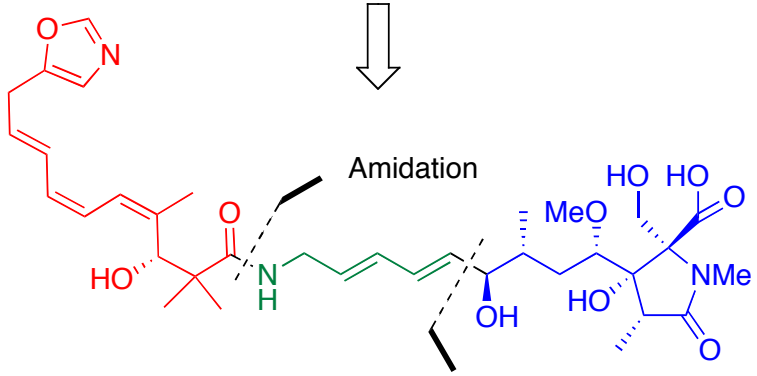
a) Mori, T.; Takahashi, K.; Kashiwabara, M.; Uemura, D.; Katayama, C.; Iwadare, S.; Shizuri, Y.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1073. b) Takahashi, K.; Kawabata, M.; Uemura, D.; Iwadare, S.; Mitomo,R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1077.

Moloney, M. G.; Trippier, P. C.; Yaqoob, M.; Wang, Z. *Curr. Drug. Discovery Technol.* **2004**, *1*, 181

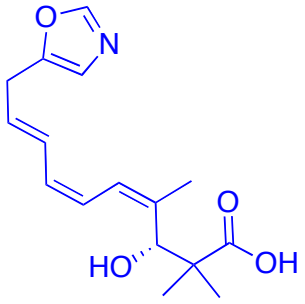
Retrosynthesis

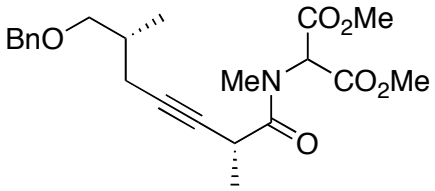


Oxazolomycin A

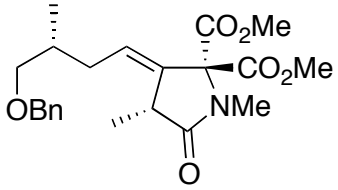


Nozaki-Hiyama-Kishi

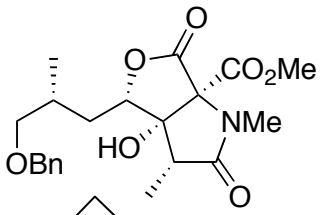


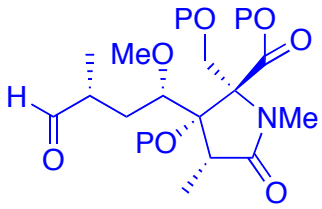


Conia-ene type cyclization

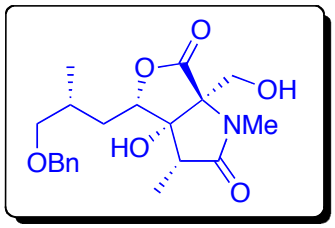


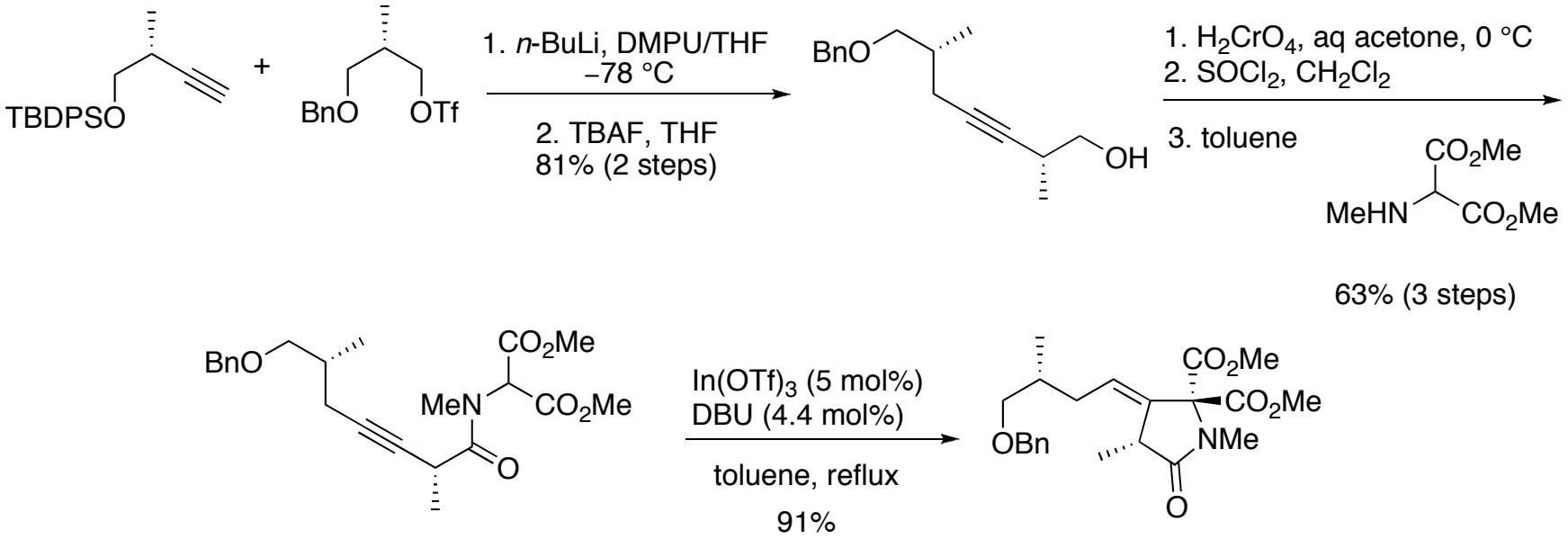
Dihydroxylation





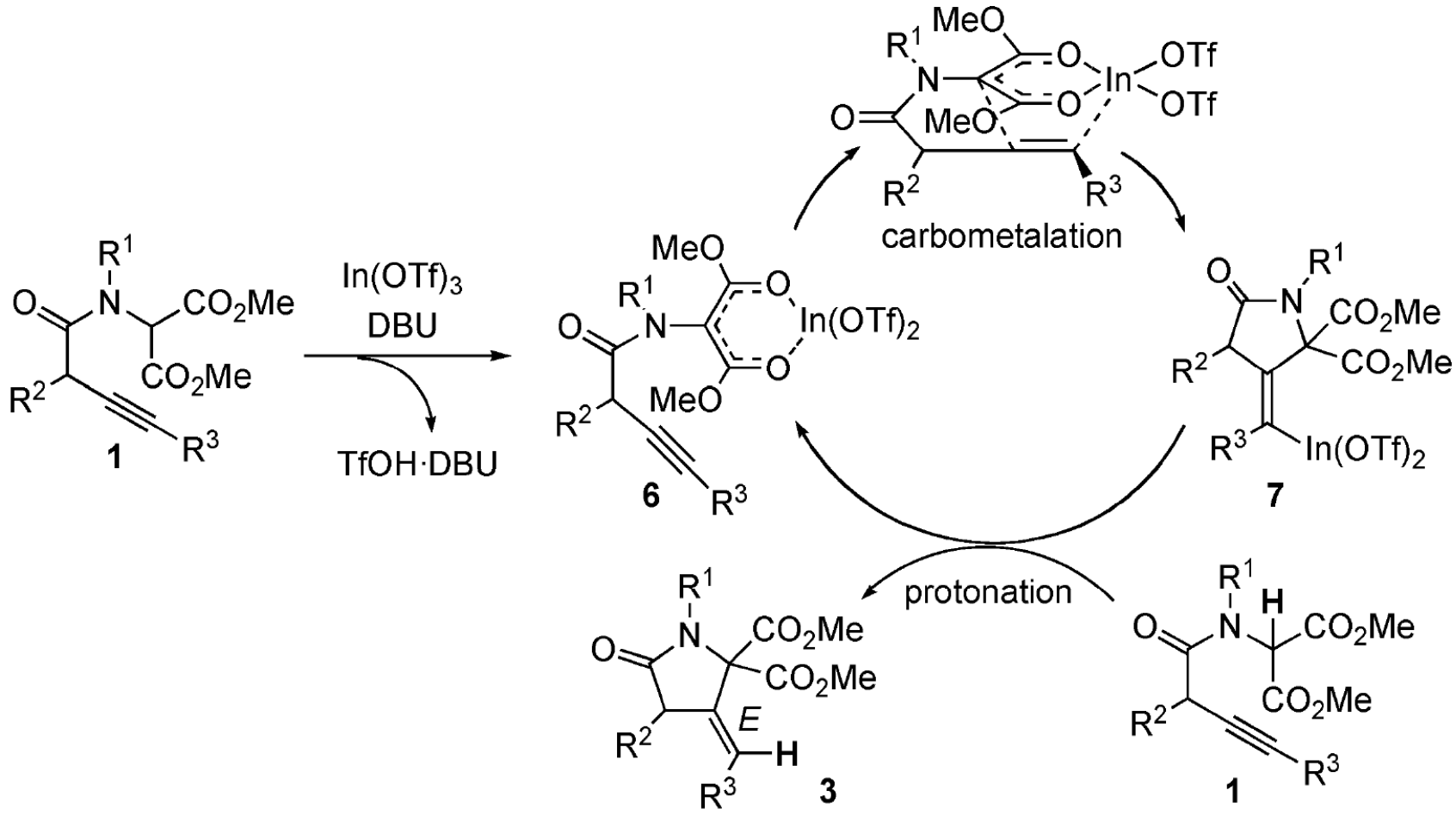
Synthesis of the γ-Lactone





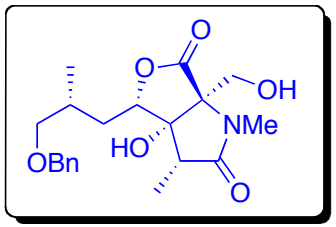
Onyango, E. O.; Tsurumoto, J.; Imai, N.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 6703.

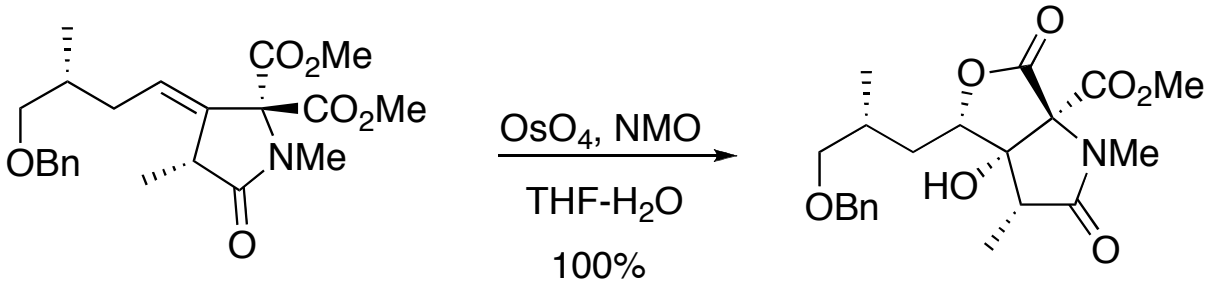
Plausible mechanism - In(III)-catalyzed Conie-ene type cyclization

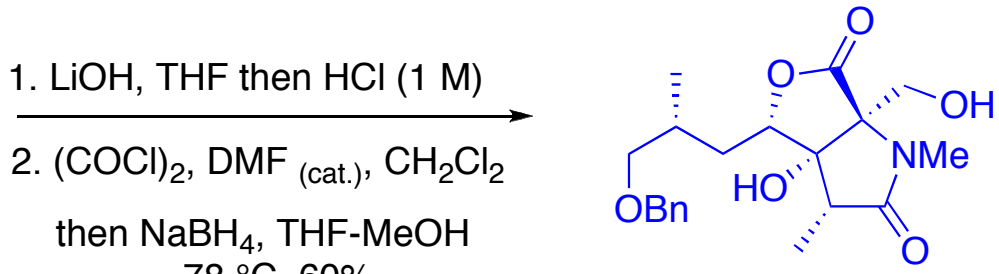


Endo, K.; Hatakeyama, T; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc*. **2007**, *129*, 5264

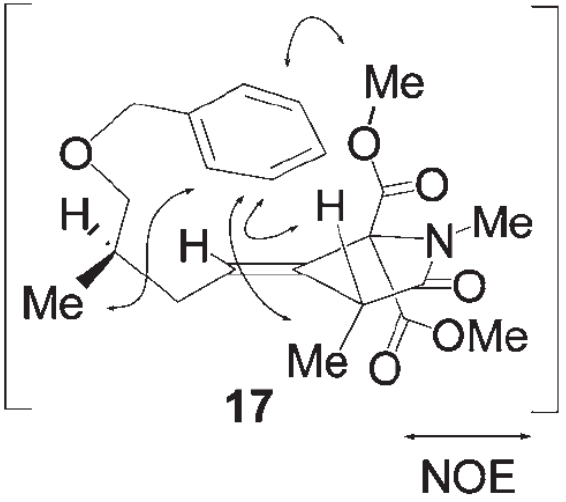
Synthesis of the γ-Lactone



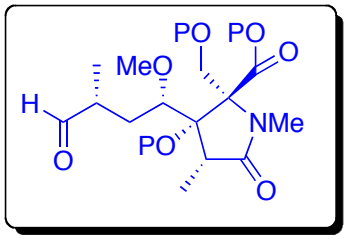


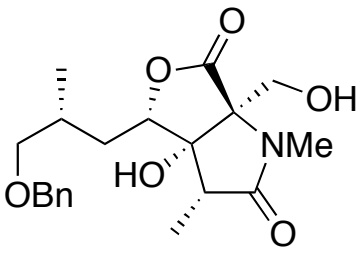


17 was supported by NOESY spectrum in [D_8]THF/D_2O and also suggested to be energetically most stable by Molecular mechanics calculation.



Synthesis of the right-hand segment

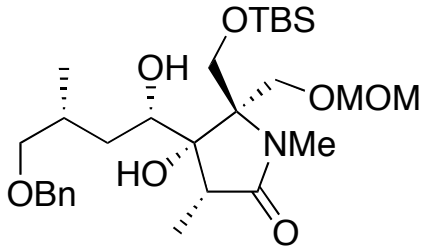




1. MOMCl, *i*-Pr_2EtN, CH_2Cl_2

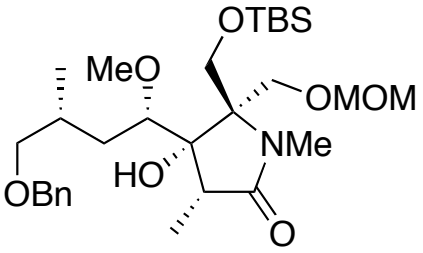
2. $NaBH_4$, THF-EtOH

3. TBSOTf, 2,6-lutidine
CH_2Cl_2, –78 °C
93% (3 steps)



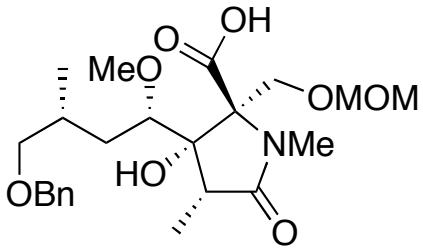
$Me_3O^+BF_4^-$
proton sponge

4 Å MS, CH_2Cl_2
95%



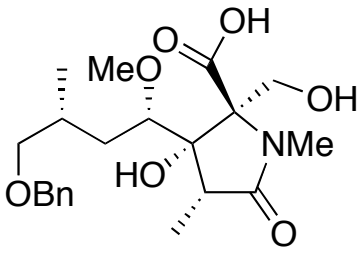
1. TBAF, THF
2. H_2CrO_4, acetone, 0 °C

3. $NaClO_2$, NaH_2PO_4
2-methyl-2-butene
t-BuOH-H_2O



$ZrCl_4$, *i*-PrOH

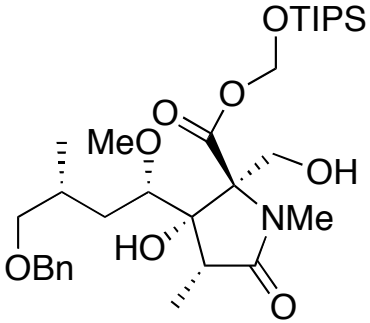
reflux



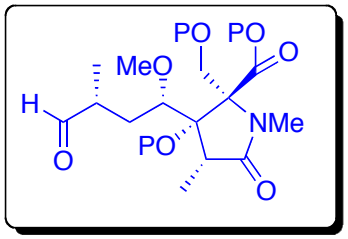
n-$C_{12}H_{25}SCH_2OTIPS$
$CuBr_2$, *n*-Bu_4NBr

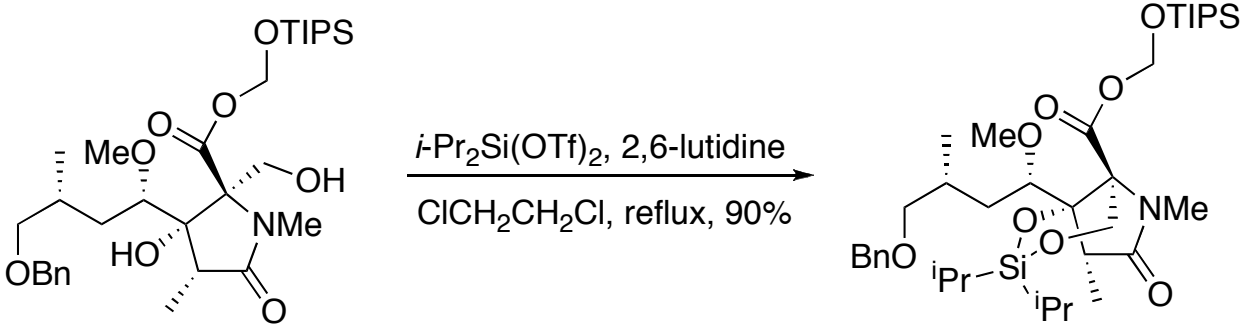
Et_3N, 4 Å MS, CH_2Cl_2

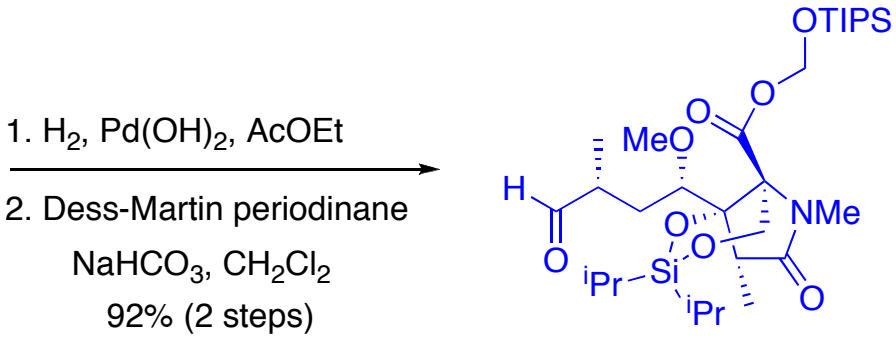
67% (5 steps)



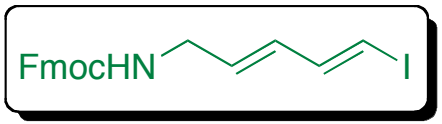
Synthesis of the right-hand segment

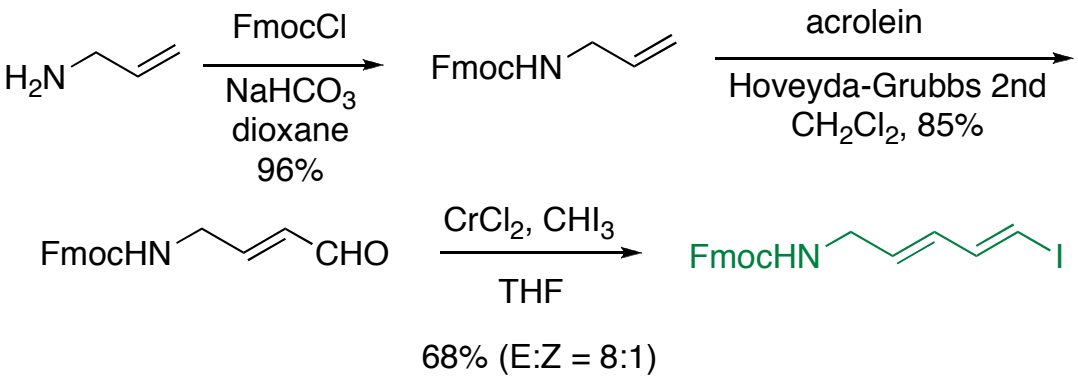




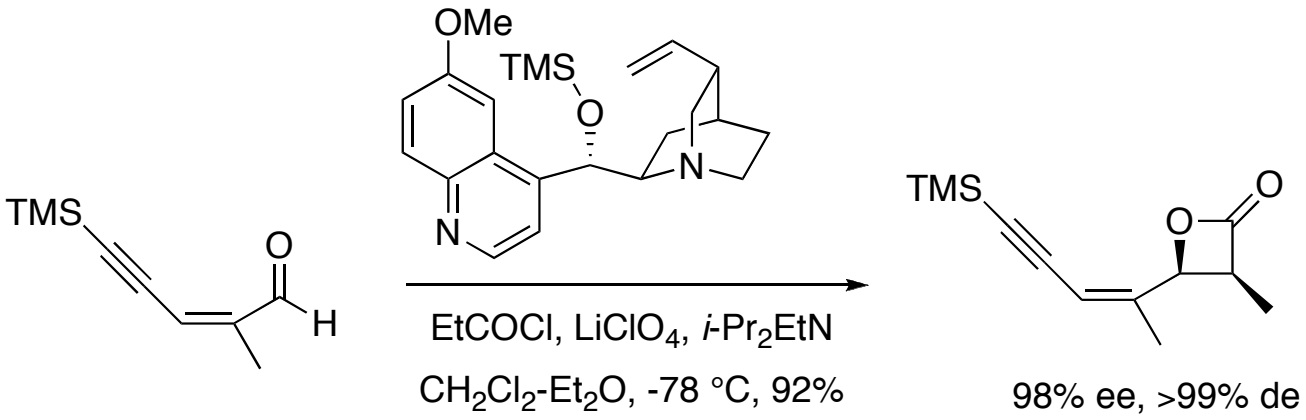


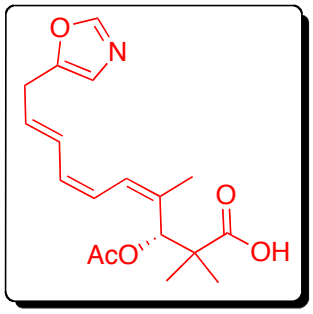
Synthesis of the middle segment



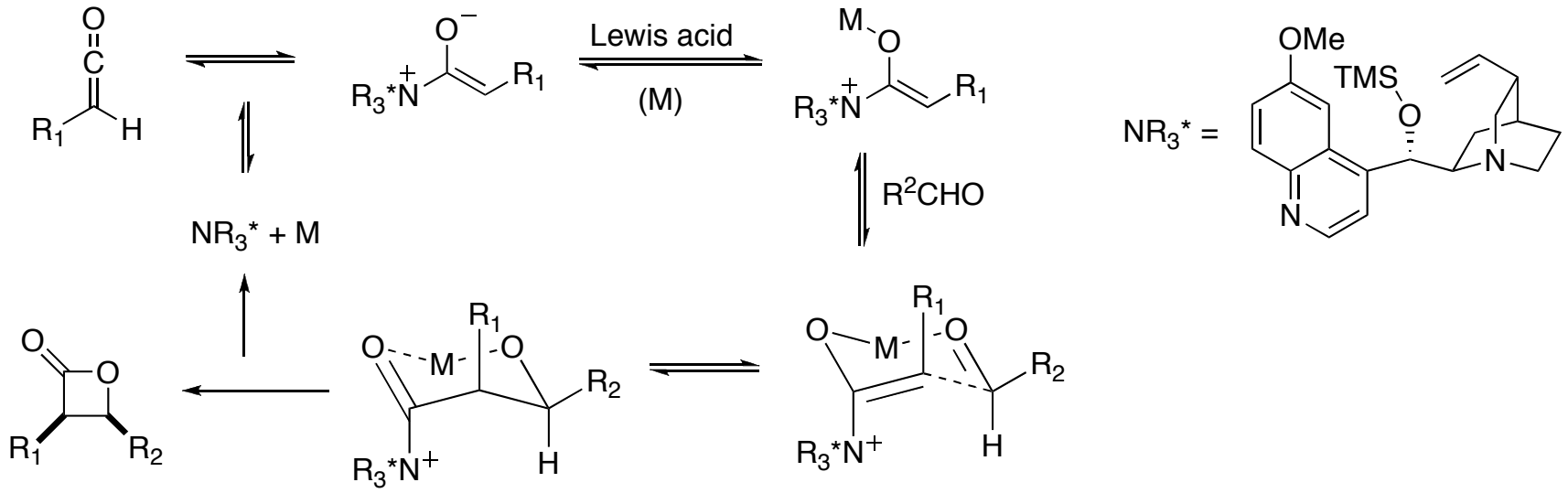


Synthesis of the left-hand segment



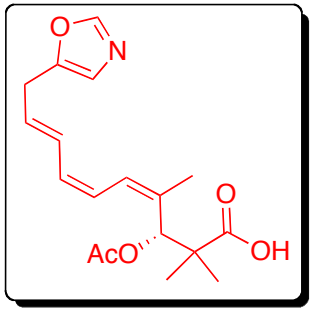


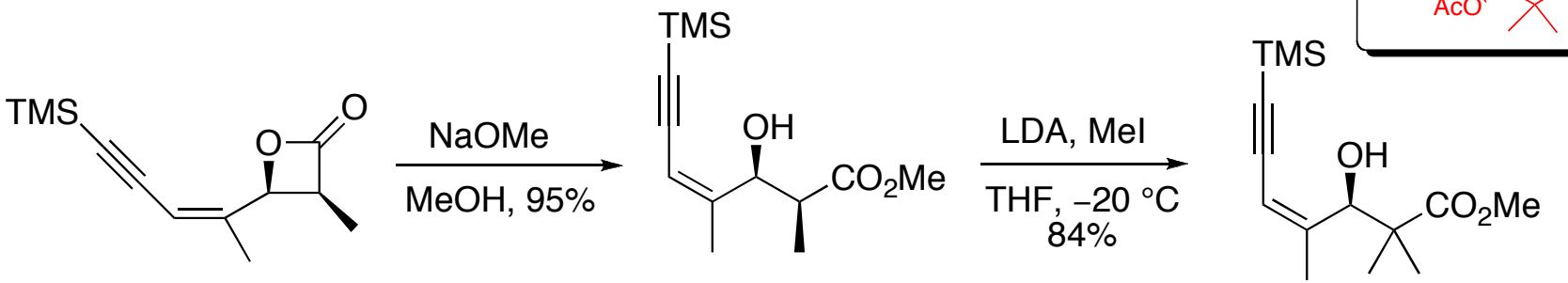
Plausible mechanism

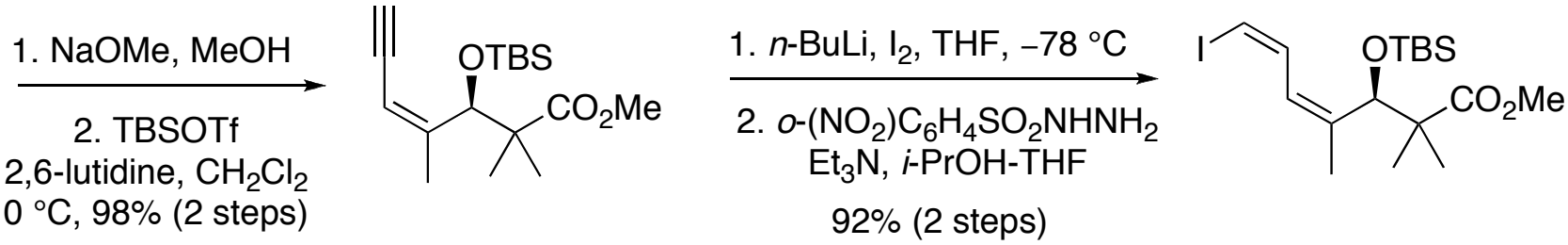


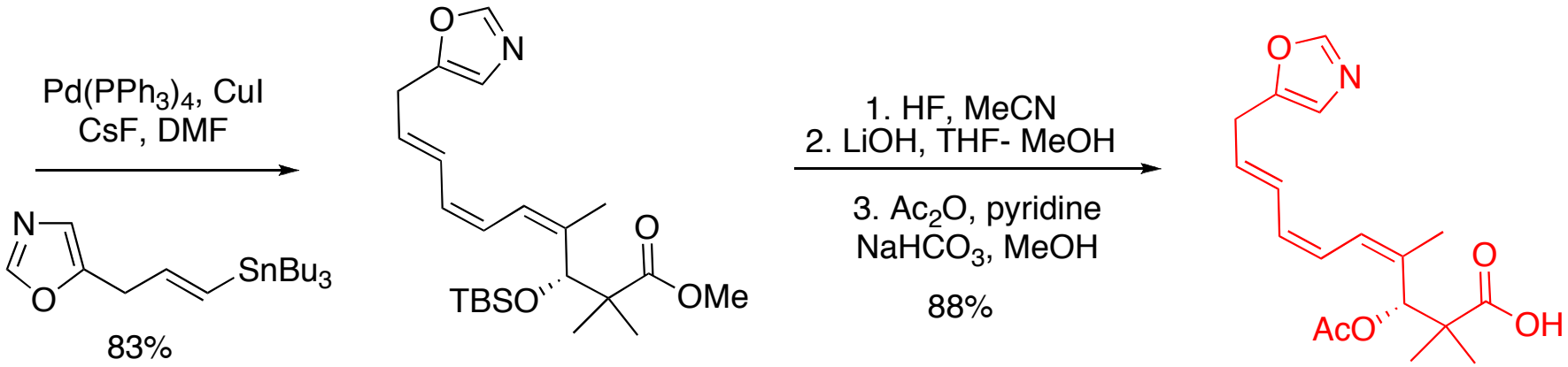
Zhu, C.; Shen, X.; Nelson, S. C. *J. Am. Chem. Soc*. **2004**, *126*, 5352

Synthesis of the left-hand segment

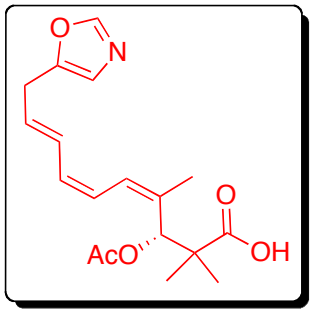


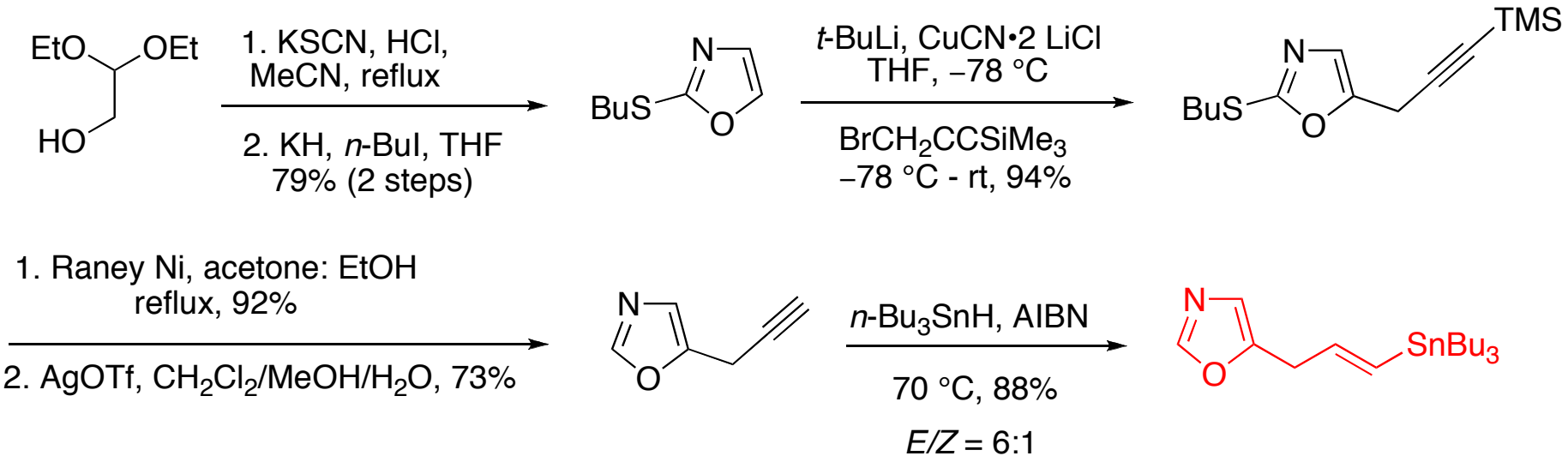




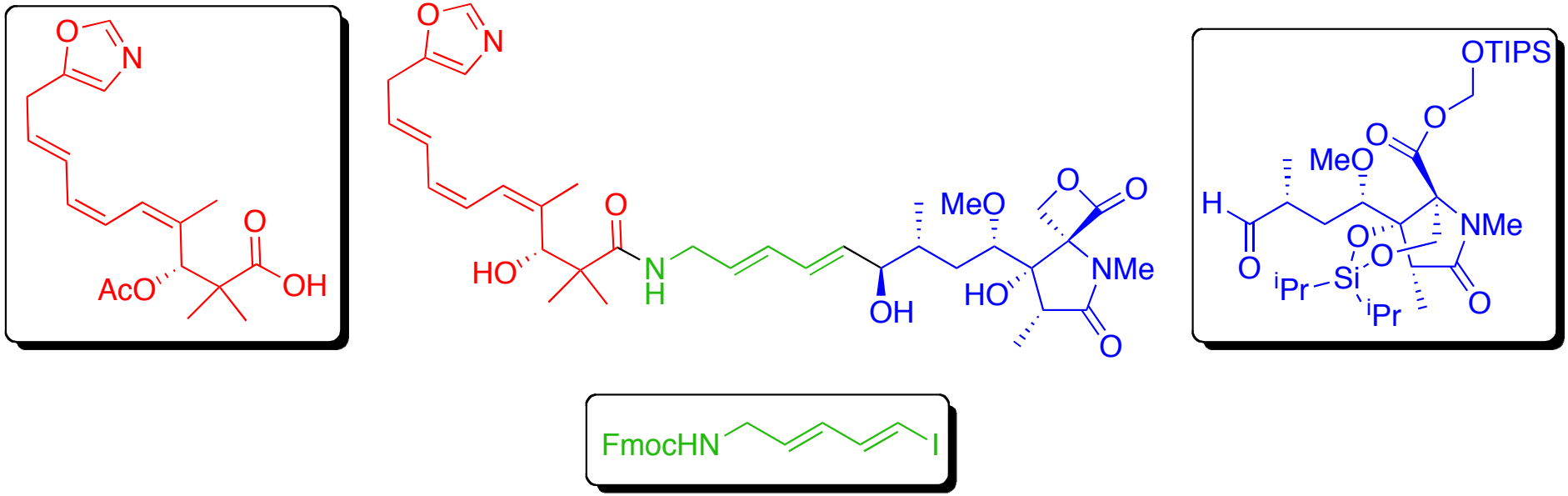


Synthesis of the left-hand segment

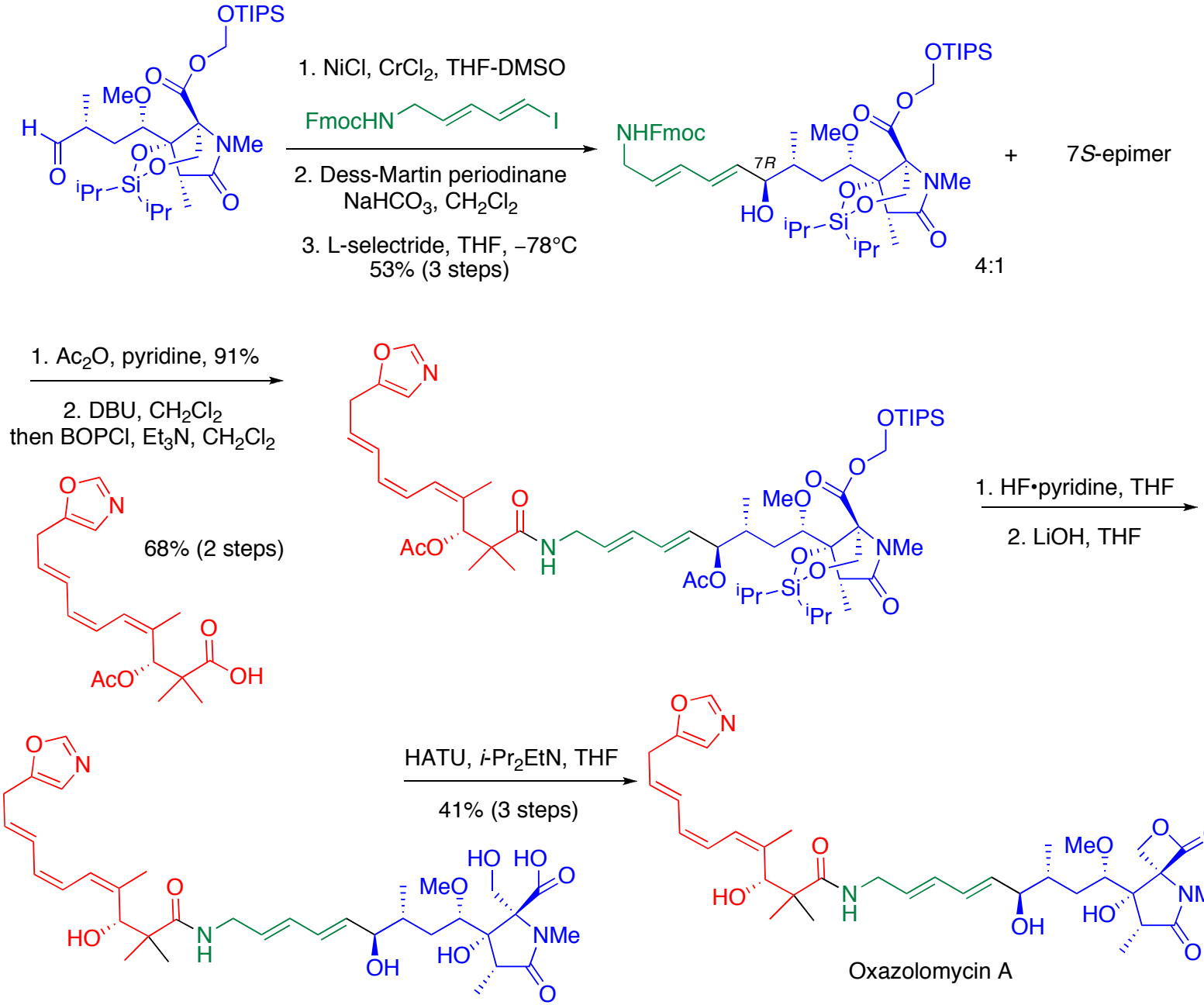




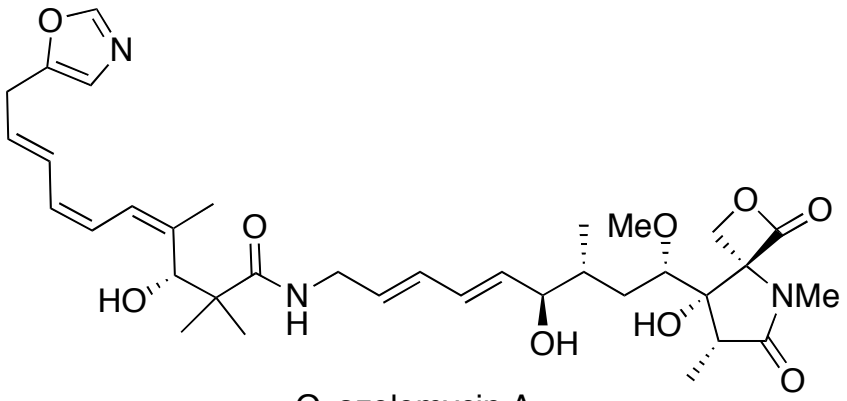
Synthesis of Oxazolomycin A



Synthesis of Oxazolomycin A



Summary and Outlook



Oxazolomycin A

Oxazolomycin A was synthesized in 34 steps of the longest linear sequence in 1.4% overall yield from methyl (*S*)-3-hydroxy-2-methylproprionate.

Key transformation include In(III)-catalyzed Conia-ene type cyclization, *Cinchona* alkaloid-catalyzed cyclocondensation and asymmetric dihydroxylation.