Toward More "Ideal" Polyketide Natural Product Synthesis: A Step-Economical Synthesis of Zincophorin Methyl Ester

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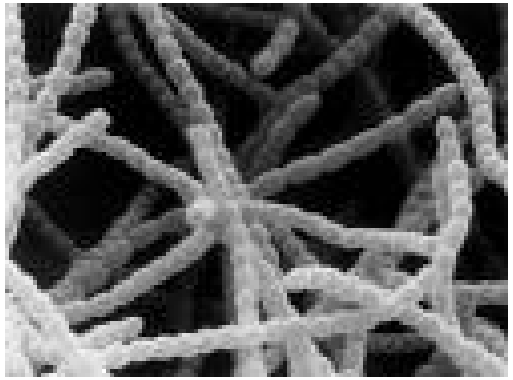
J. Am. Chem. Soc., **2011**, *133*, 7308

Ki Bum Hong

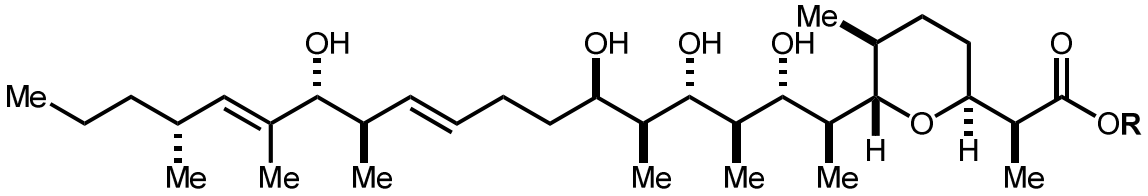
Current Literature

May 21, 2011

Isolation, Background



Streptomyces griseus

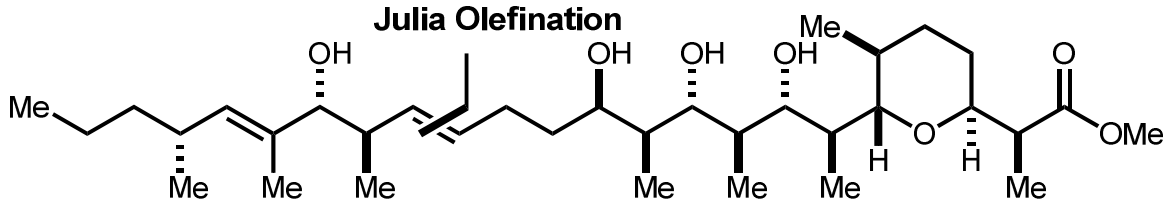


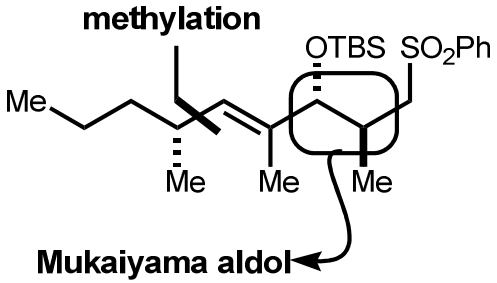
R = H Zincophorin
R = Me Zincophorin methyl ester

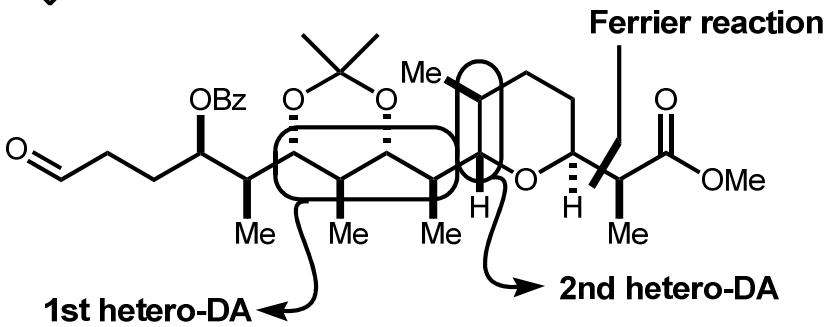
- Isolated in 1984 from cultures of strains of *Streptomyces griseus*
- Zincophorin and its calcium salt: in vitro antibiotic activities against Gram-positive bacteria
  Ammonium and sodium salts: anticoccidal activity
- Zincophorin methyl ester: antiviral activity with reduced host cell toxicity compared to the free acid
- First total synthesis completed in 1987 by Danishefsky (36 steps),
  two additional by Cossy (28 steps) and Miyashita (37 steps)

Grafe, U.; Schade, W.; Roth, M.; Radics, L.; Incze, M.; Ujszaszy, K. *J. Antibiot*. **1984**, *37*, 836
Brooks, H. A.; Gardner, D.; Poyser, J. P.; King, T. J. *J. Antibiot.* **1984**, *37*, 1501

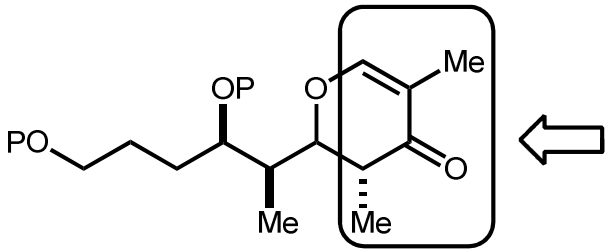
First Total Synthesis of Zincophorin Methyl Ester (Danishefsky)

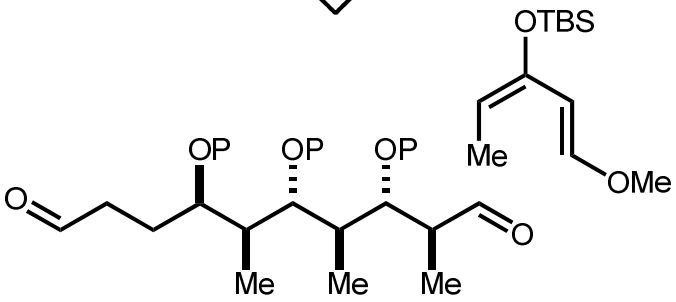






J. Org. Chem. **1986**, *51*, 5032

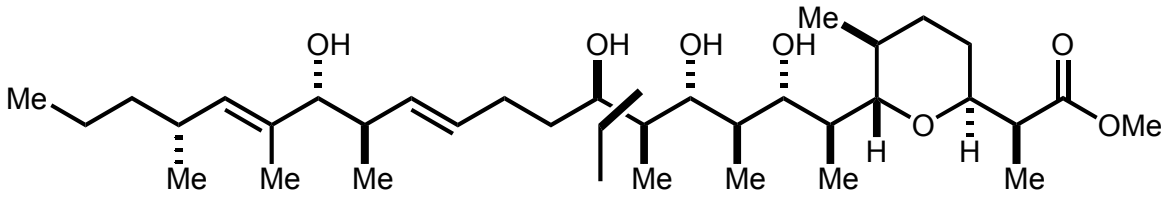




J. Am. Chem. Soc., **1987**, *109*, 1572

J. Am. Chem. Soc., **1988**, *110*, 4368

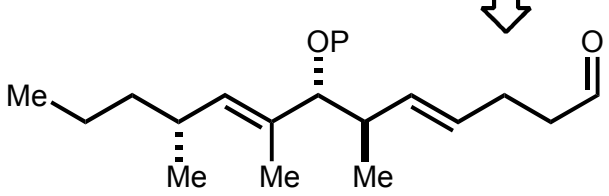
Cossy's Total Synthesis of Zincophorin Methyl Ester

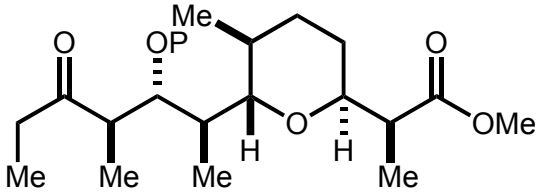


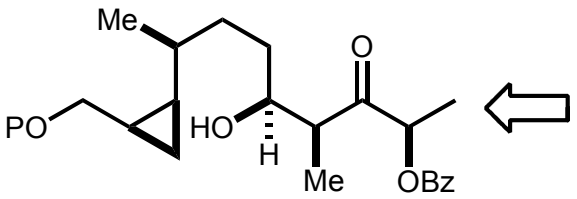
Aldol condensation

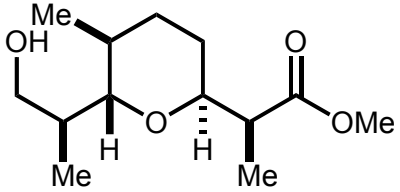
Org. Lett. **2003**, *5*, 4037

28 steps

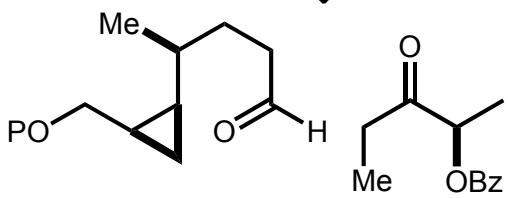




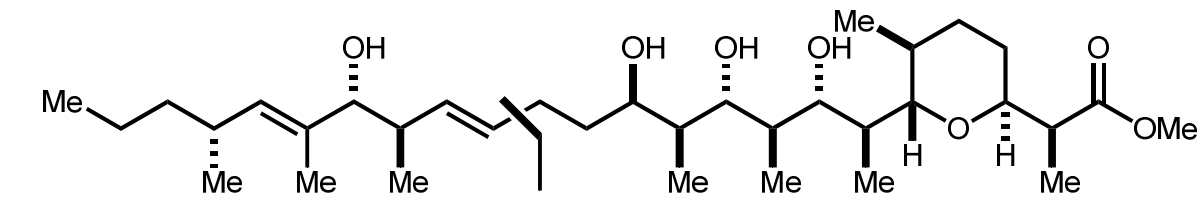




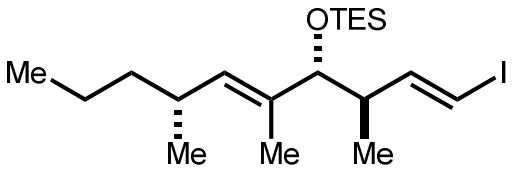
Angew. Chem. Int. Ed. **2002**, *41*, 2144

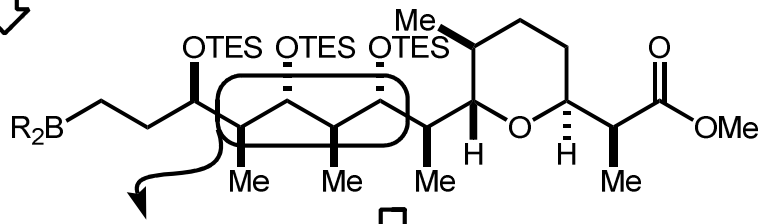


Miyashita's Total Synthesis of Zincophorin

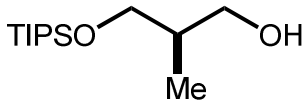


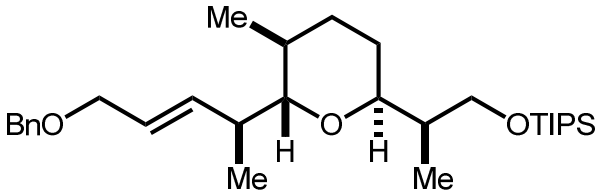
Suzuki coupling

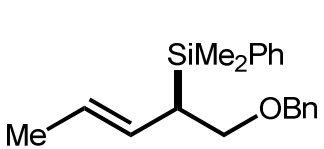


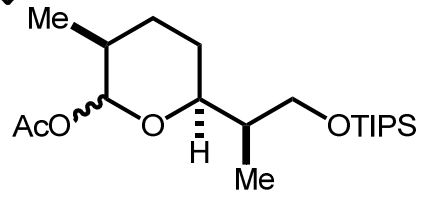


Methylation of epoxide







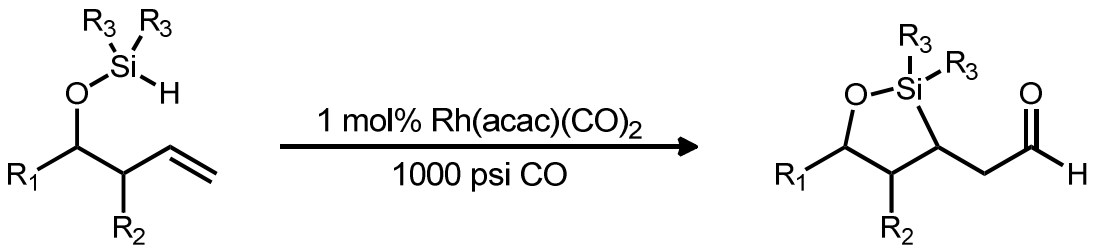


Angew. Chem. Int. Ed. **2004**, *43*, 4341

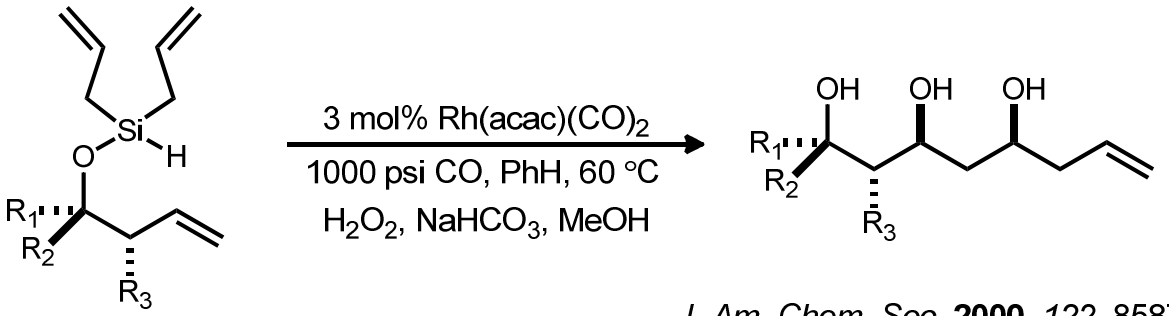
37 steps

Leighton's Methodology Developments

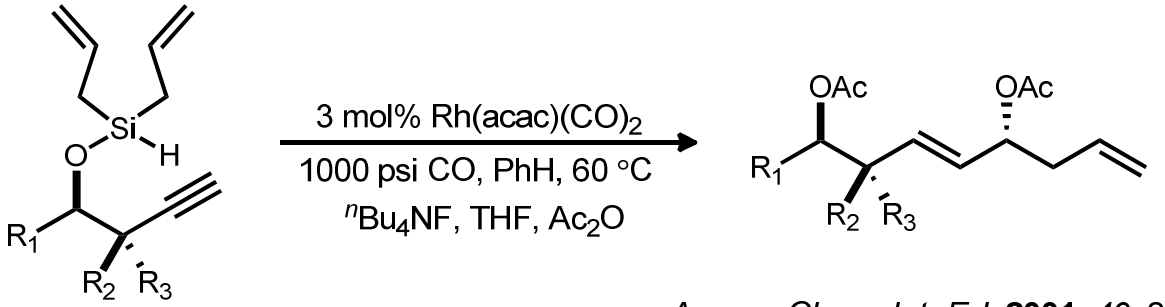
- Intramolecular Silylformylation of Alkenes and Alkynes



J. Am. Chem. Soc. **1997**, *119*, 12416



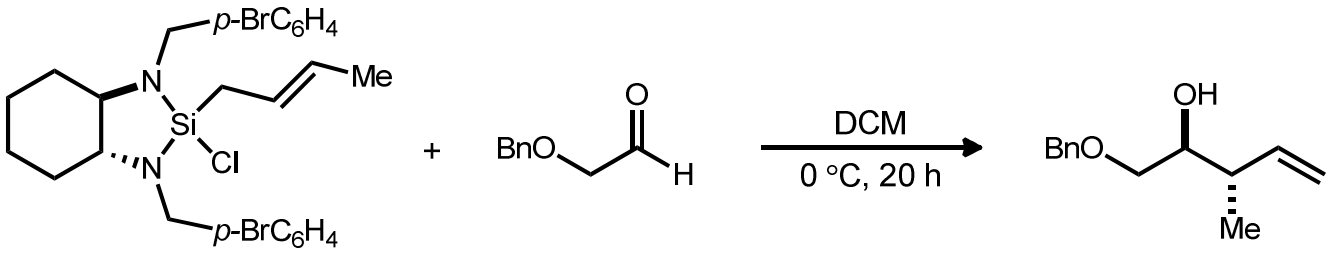
J. Am. Chem. Soc. **2000**, *122*, 8587



Angew. Chem. Int. Ed. **2001**, *40*, 2915

Leighton's Methodology Developments

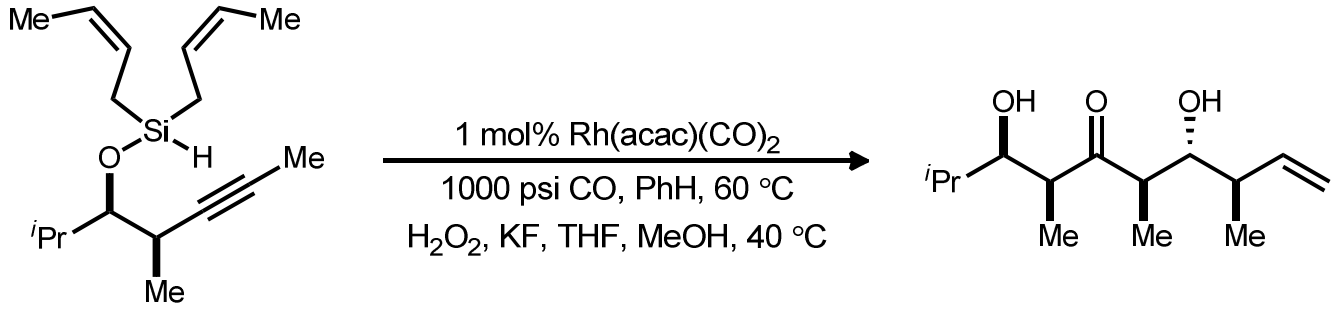
- Aldehyde Crotylation



83%; 99% ee

Org. Lett. **2004**, *6*, 4375

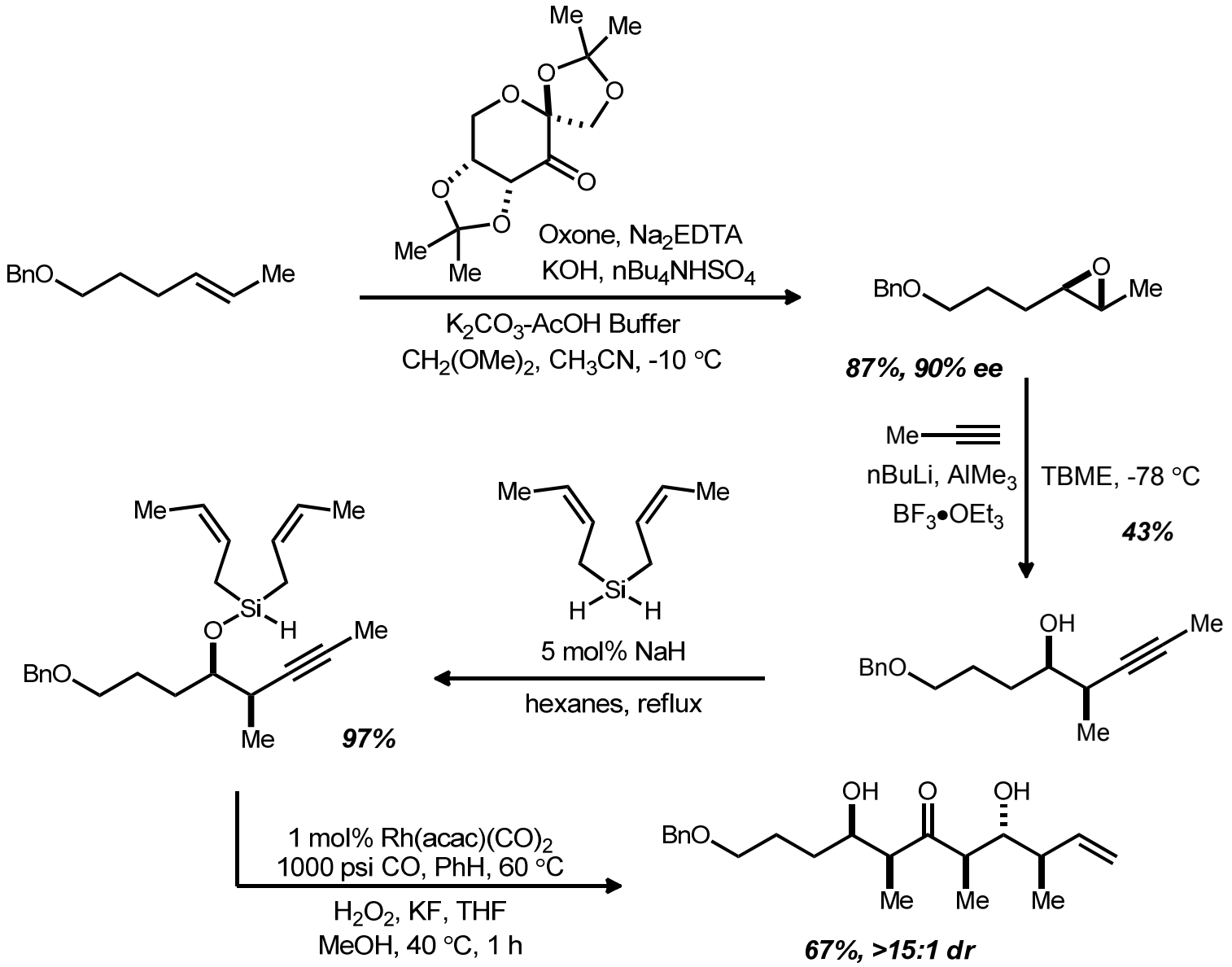
- Intramolecular Silylformylation - Crotylsilylation



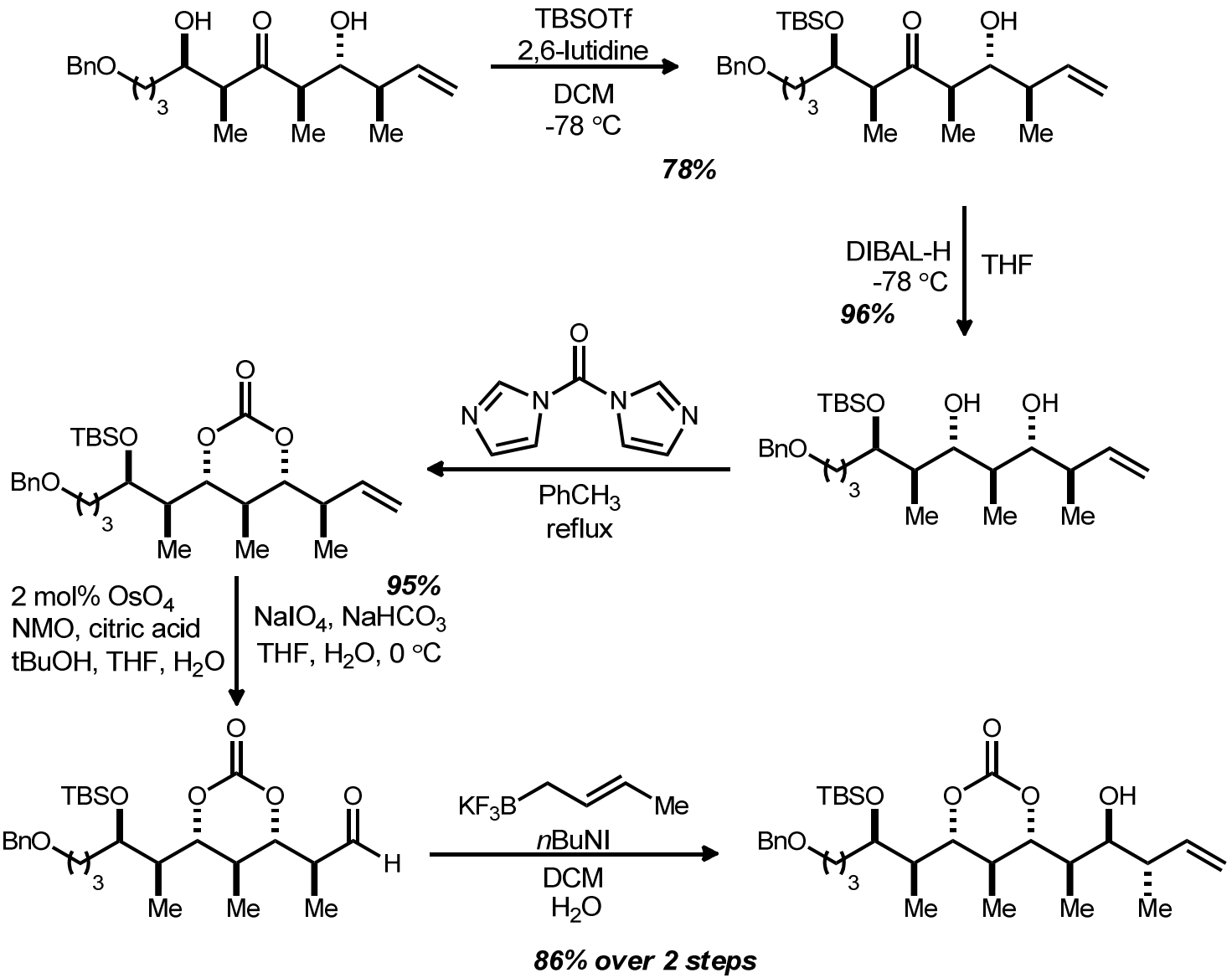
60%; 13:1 dr

Org. Lett. **2008**, *10*, 5593

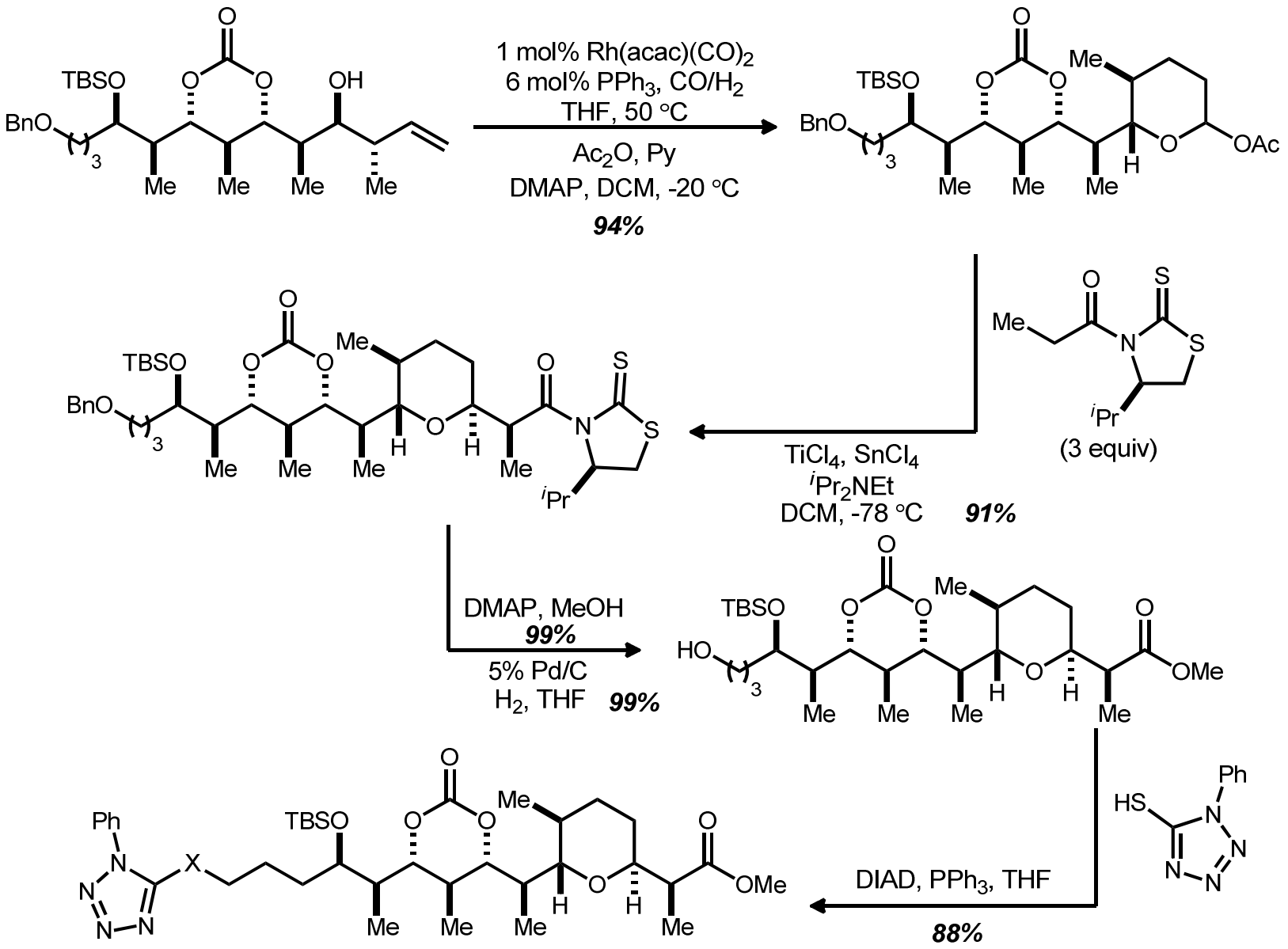
Silylformylation-Crotylsilylation/Tamao Oxidation-Tautomerization



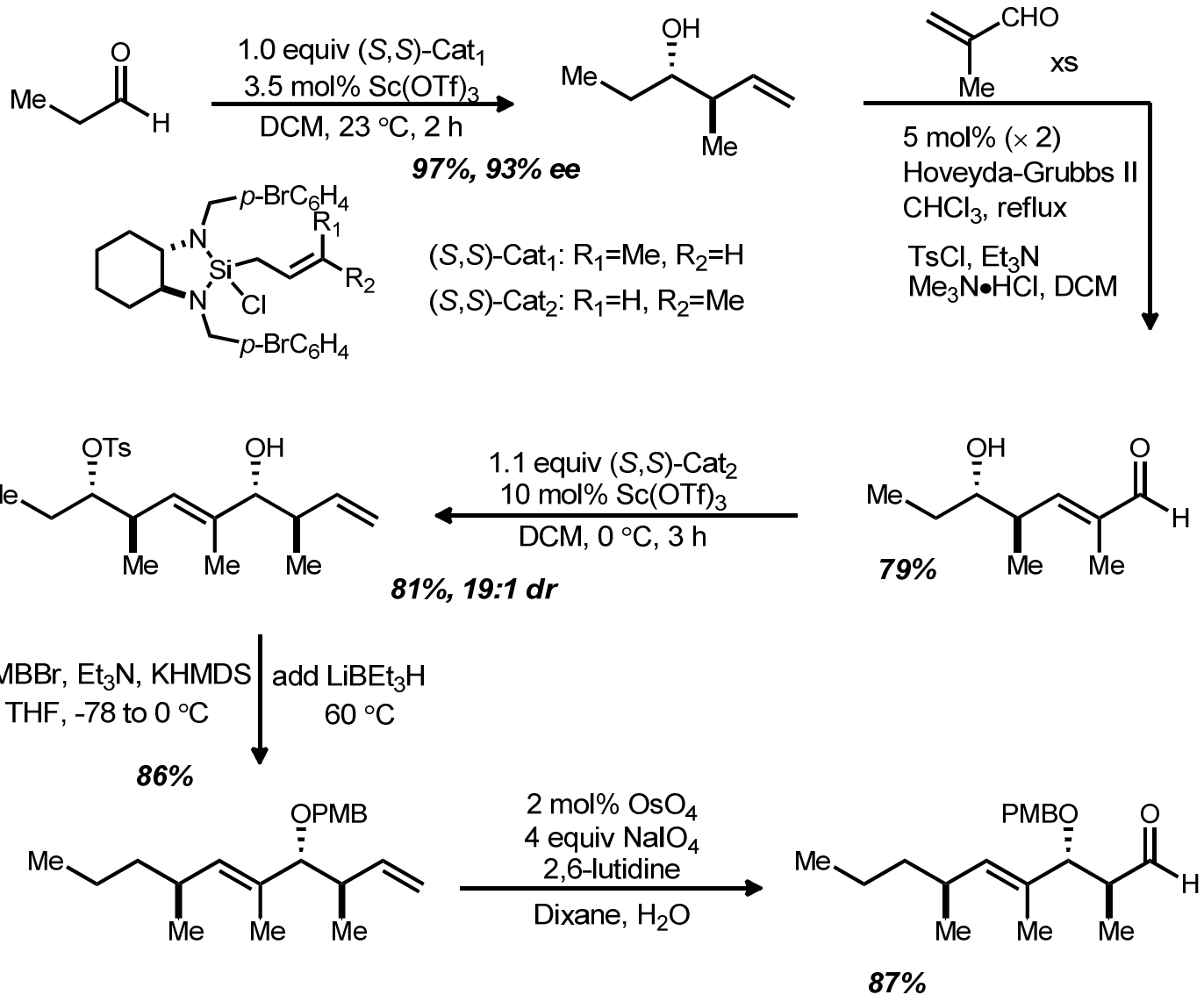
Synthesis of the C(11), C(7), and C(6) Stereocenters



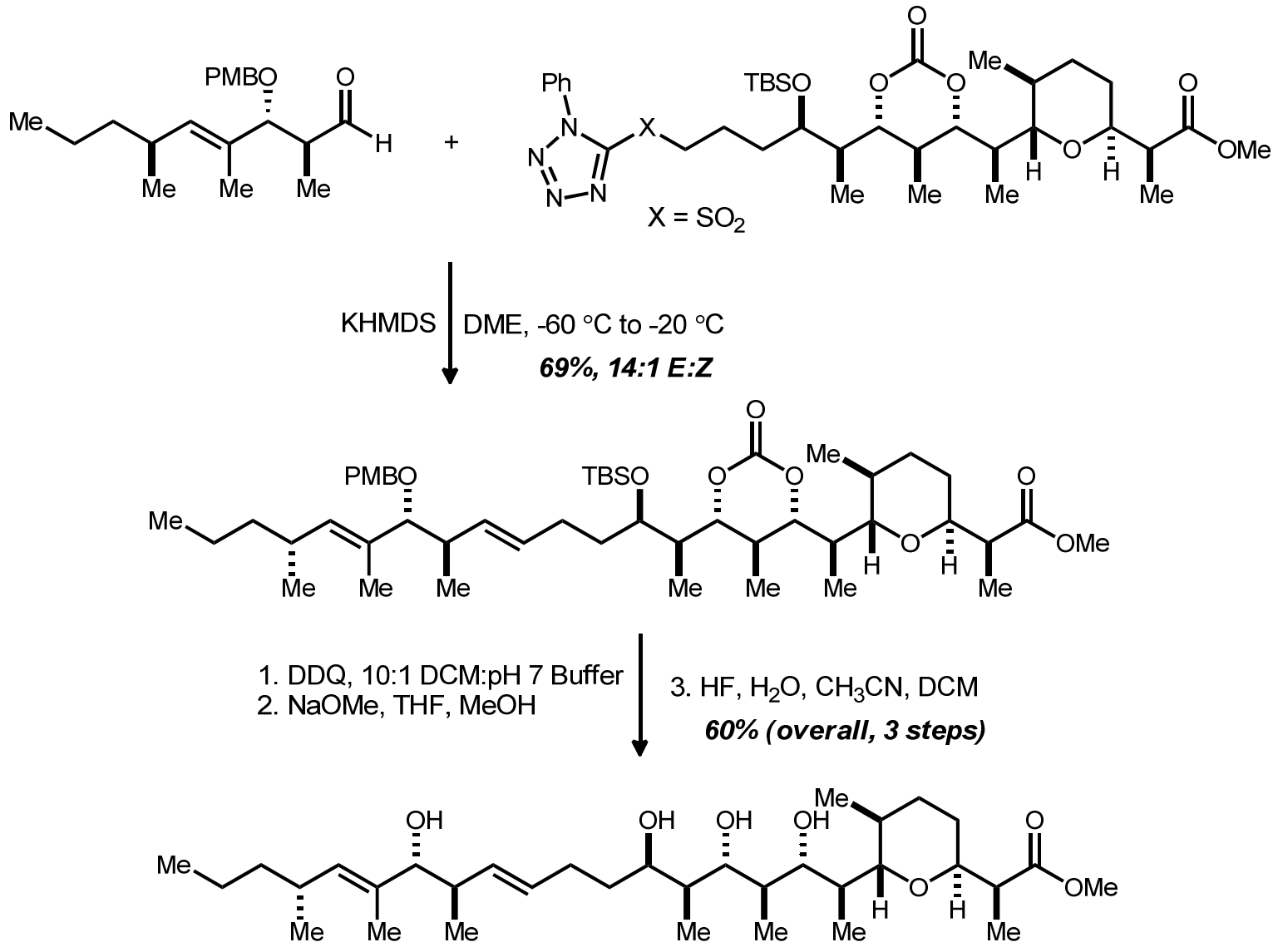
Completion of the C(1)-C(16) Fragments



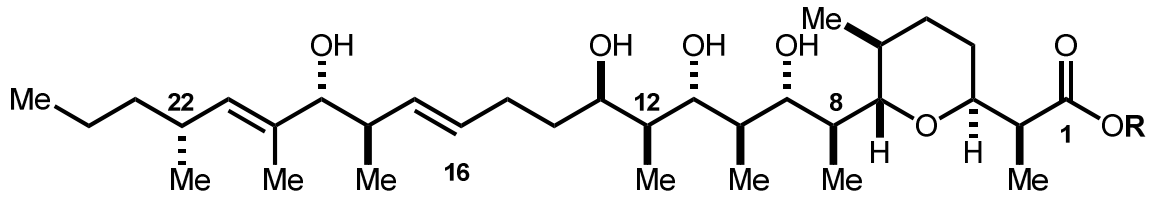
Synthesis of the C(17)-C(25) Fragments



Completion of the Synthesis



Conclusions



R = H Zincophorin
R = Me Zincophorin methyl ester

- The synthesis of zincophorin methyl ester : a longest linear sequence of 22 steps
  from commercially available 4-hexen-1-ol in 4.2% overall yield

- C(1)-C(16) fragment : five of 10 stereocenter was accessed in just four steps
  no protection group, nonstrategic redox reactions, chiral auxiliaries

- C(6)-C(23) fragment : five steps and 46% overall yield
  rely on two applications of the $Sc(OTf)_3$-catalyzed crotylation