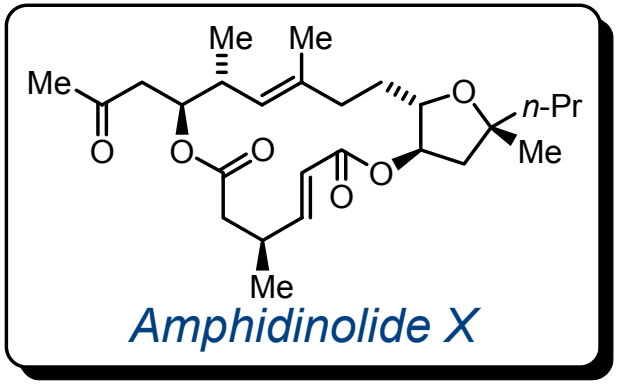
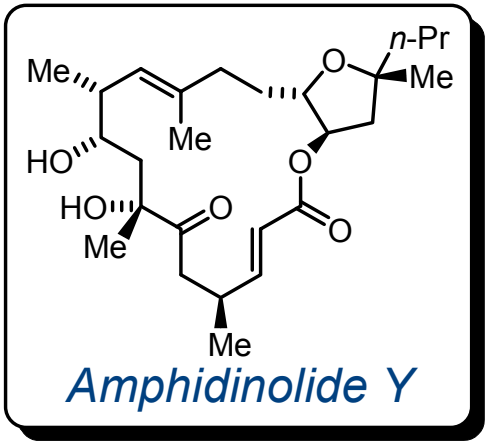
Current Literature Meeting
July 1st, 2006

Total Syntheses of Amphidinolide X and Y



Amphidinolide X



Amphidinolide Y

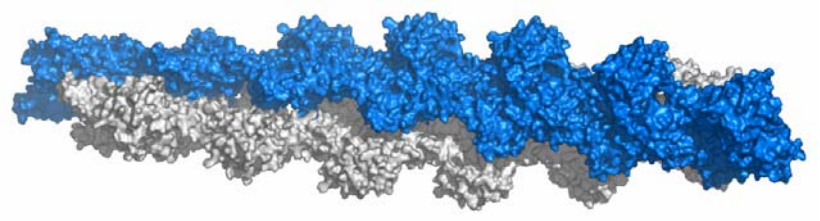
A. Fürstner, E. Kattnig, O. Lepage
J. Am. Chem. Soc. **2006**, ASAP (06/24/2006, ja061918e)

Amphidinolides

- Amphidinolides are secondary metabolites isolated from *Amphidinium sp.* collected from Okinawa Island (Kobayashi). Marine dinoflagellates from the genus *Amphdinium* are found in the inner tissue of symbiotic flatworm *Amphiscolops.*
- The family of amphidinolides consists of more than 30 members characterized by macrocyclic highly oxygenated lactone ring.
- Amphidinolides B, H and N show potent cytotoxic activity against murine Lymphoma L1210 cells and human epidermoid carcinoma KB cells. Amph H is F-actin stabilizer covalently binding to Tyr200 of actin subdomain 4. For comparison, other actin inhibitors such as mycalolide B, swinholide A, aplyronine A and misakinolide A destabilize actin cytoskeleton, while jasplakinolide, a cyclodepsipeptide, binds F-actin and promotes polymerization.

Amphidinium

www.mbl.edu



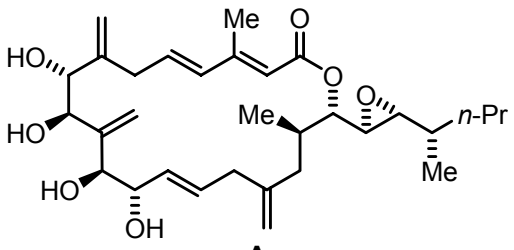
F-actin

www.wikipedia.com

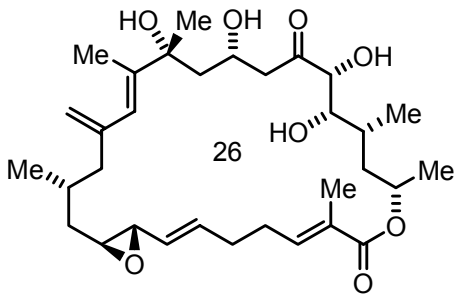
Representative Articles:

Nat. Prod. Rep. **2004**, *21*, 77; *Curr. Med. Chem.: Anti-Cancer Agents* **2001**,*1*,131; *Comprehensive Natural Products Chemistry* **1999**, 619 *Org. Biomol. Chem.* **2005**, *3*, 2675; *Chem. & Biol.* **2004**, *11*, 1269

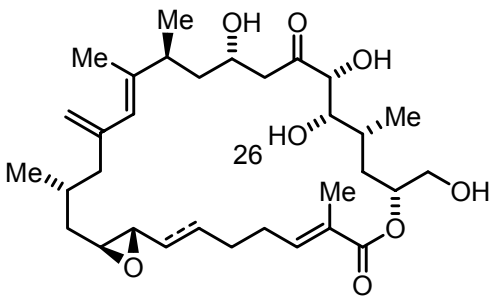
Amphidinolides – Some Representative Examples



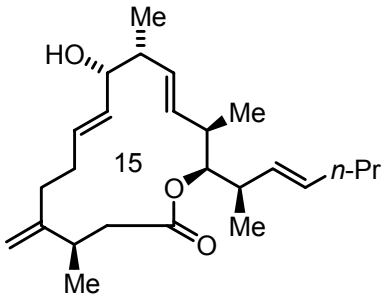
A
2.0
5.7



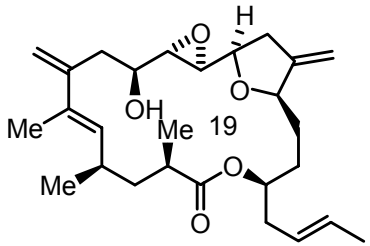
B
0.00014
0.0042



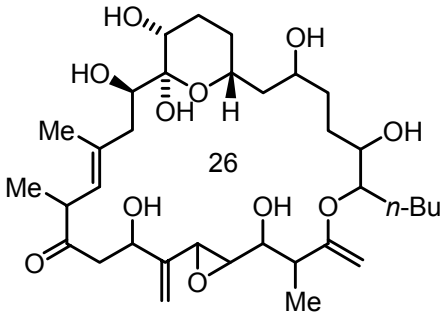
H
0.00048
0.00052



J
2.7
3.9



K
1.65
2.9



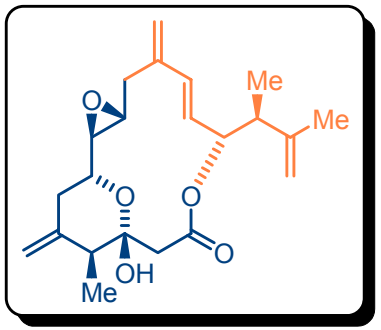
N
0.00005
0.00006

IC_{50} μg/mL
L1210
KB

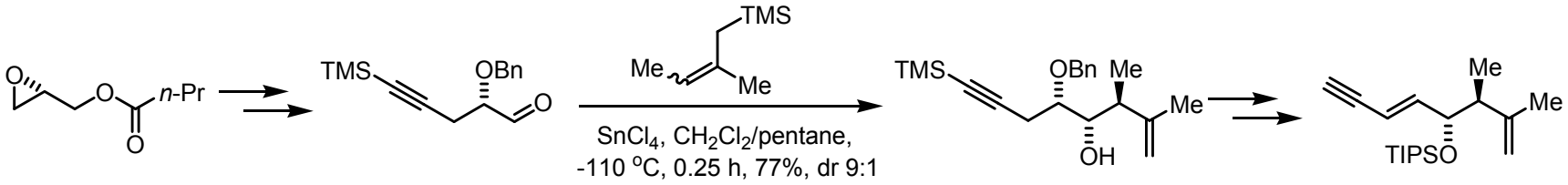
Total syntheses: **A**: Trost *J. Am. Chem. Soc.* **2005**, *127*, 13598; Trost *J. Am. Chem. Soc.* **2005**, *127*, 13589; Trost *J. Am. Chem. Soc.* **2004**, *126*, 5028; Trost *J. Am. Chem. Soc.* **2002**, *124*, 12420; Maleczka *Org. Lett.* **2002**, *4*, 2841; Pattenden *Angew. Chem., Int. Ed.* **2002**, *41*, 508. **J**: Williams *J. Am. Chem. Soc.* **1998**, *120*, 11198. **K**: Williams *J. Am. Chem. Soc.* **2001**, *123*, 765. **P**: Trost *J. Am. Chem. Soc.* **2005**, *127*, 17921; Trost *J. Am. Chem. Soc.* **2004**, *126*, 13618; Williams *Org. Lett*. **2000**, *2*, 945. **T:** Jamison *J. Am. Chem. Soc.* **2005**, *127*, 4297; Jamison *J. Am. Chem. Soc.* **2004**, *126*, 998; Fürstner *J. Am. Chem. Soc.* **2003**, *125*, 15512; Ghosh *J. Am. Chem. Soc.* **2003**, *125*, 2374; Fürstner *Angew. Chem., Int. Ed.*, **2002**, *41*, 4763. **W:** Ghosh *J. Am. Chem. Soc.* **2004**, *126*, 3704.

Partial syntheses: Nicolaou *Org. Biomol. Chem.* **2006**, *4*, 2119 and references therein

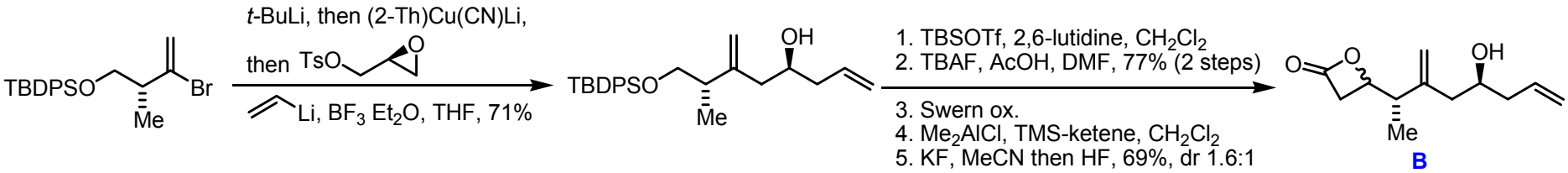
Amphidinolide P
Alkene-Alkyne Coupling as a Linchpin –Trost



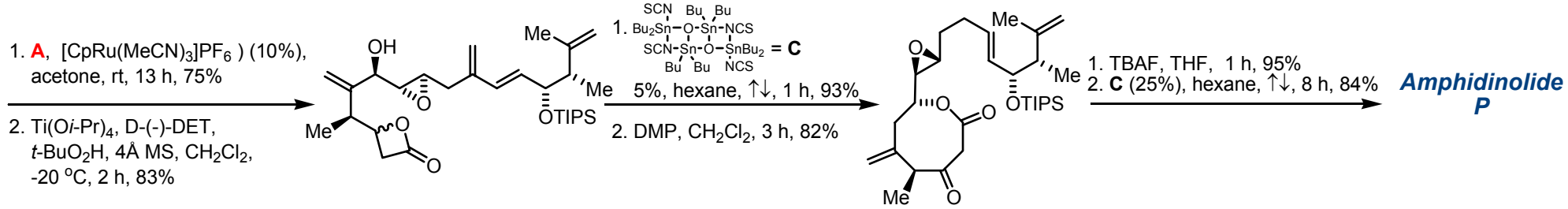
J. Am. Chem. Soc. **2004**, *126*, 13618
J. Am. Chem. Soc. **2005**, *127*, 17921



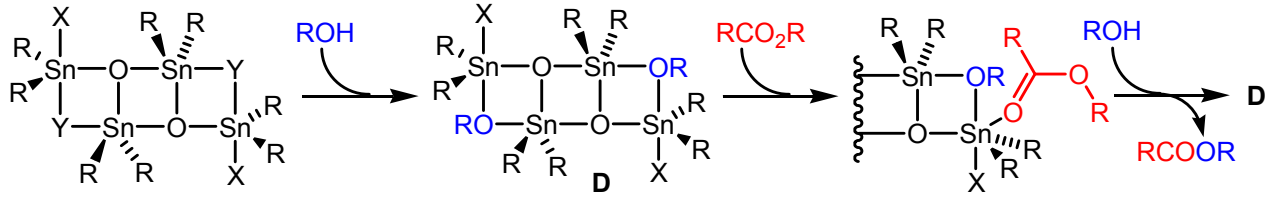
A



B

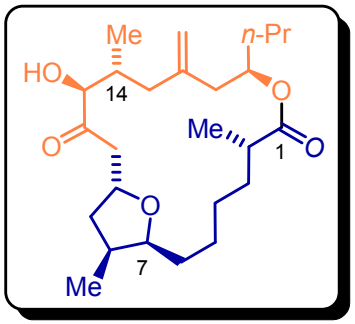


Otera's Catalyst: X, Y = OH, Cl, NCS; R = Bu, Me; ca. 100x faster in hydro(halo)carbons

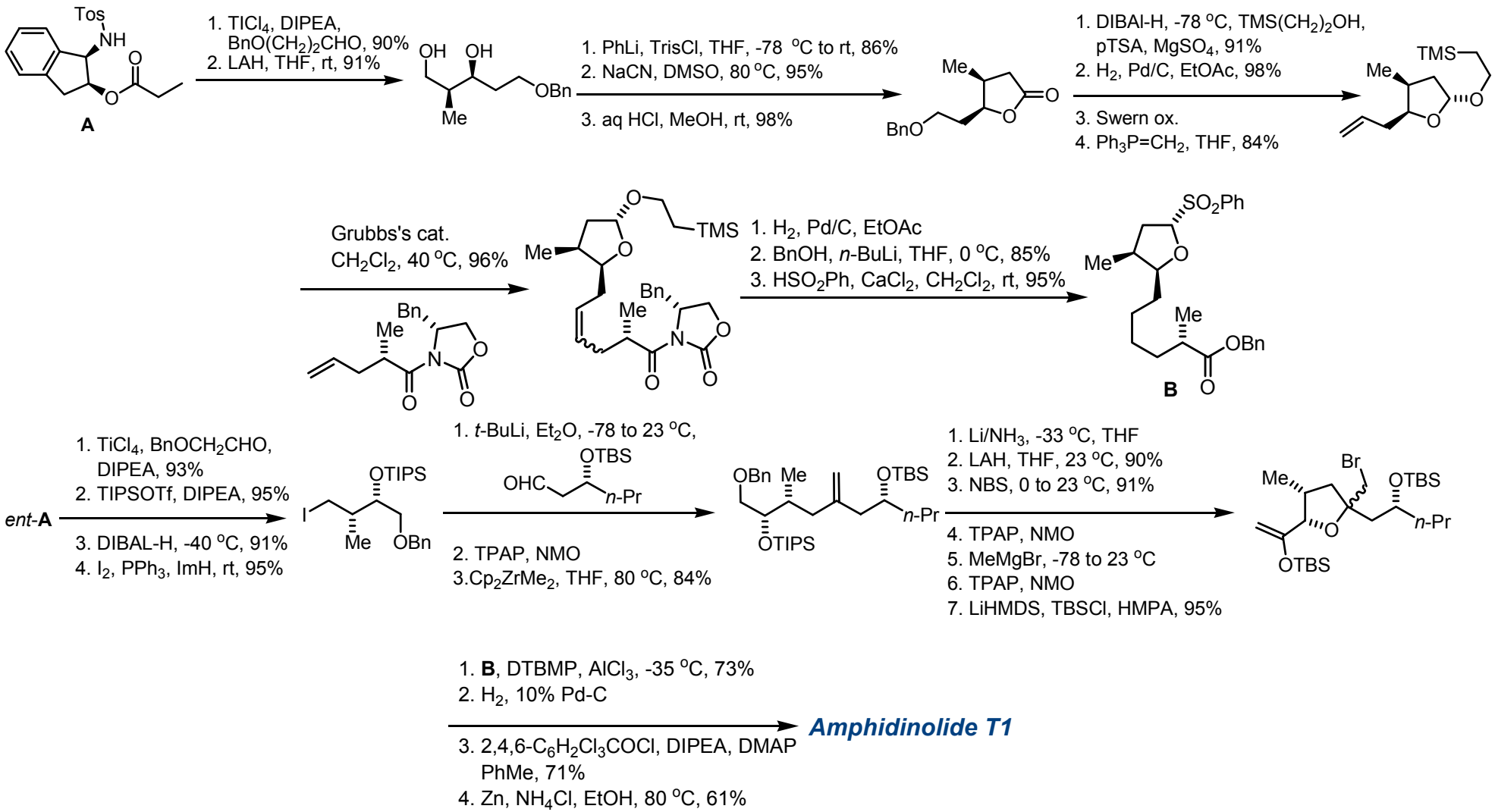


J. Org. Chem. **1989**, *54*, 4013; *J. Org. Chem.* **1991**, *56*, 5307

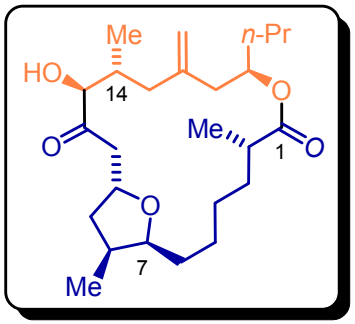
Amphidinolide T1
Ghosh



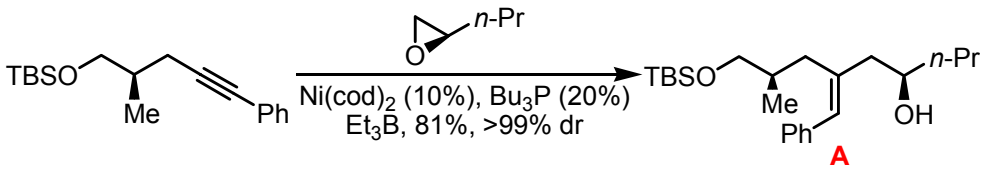
J. Am. Chem. Soc. **2003**, 125, 2374

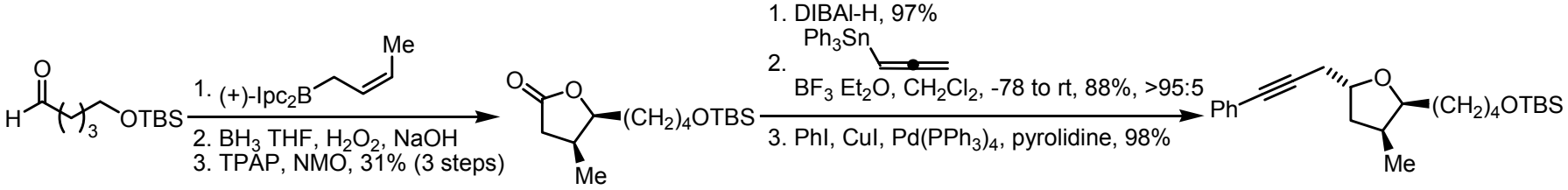


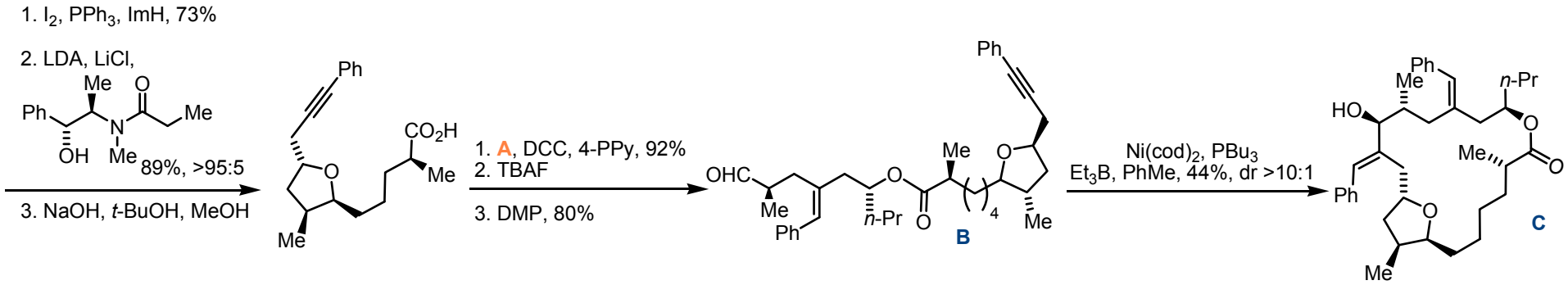
Amphidinolide T1
Ni-catalyzed Reductive Macrocyclization – Jamison

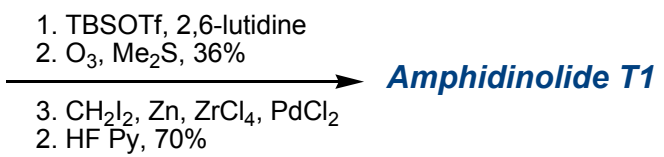


J. Am. Chem. Soc. **2004**, *126*, 998
J. Am. Chem. Soc. **2005**, *127*, 4297

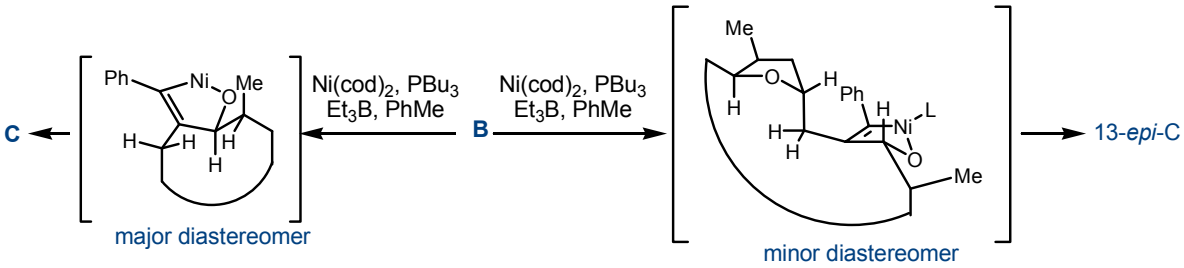




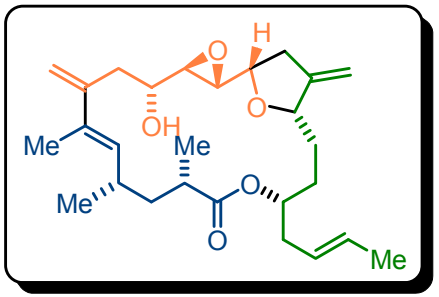




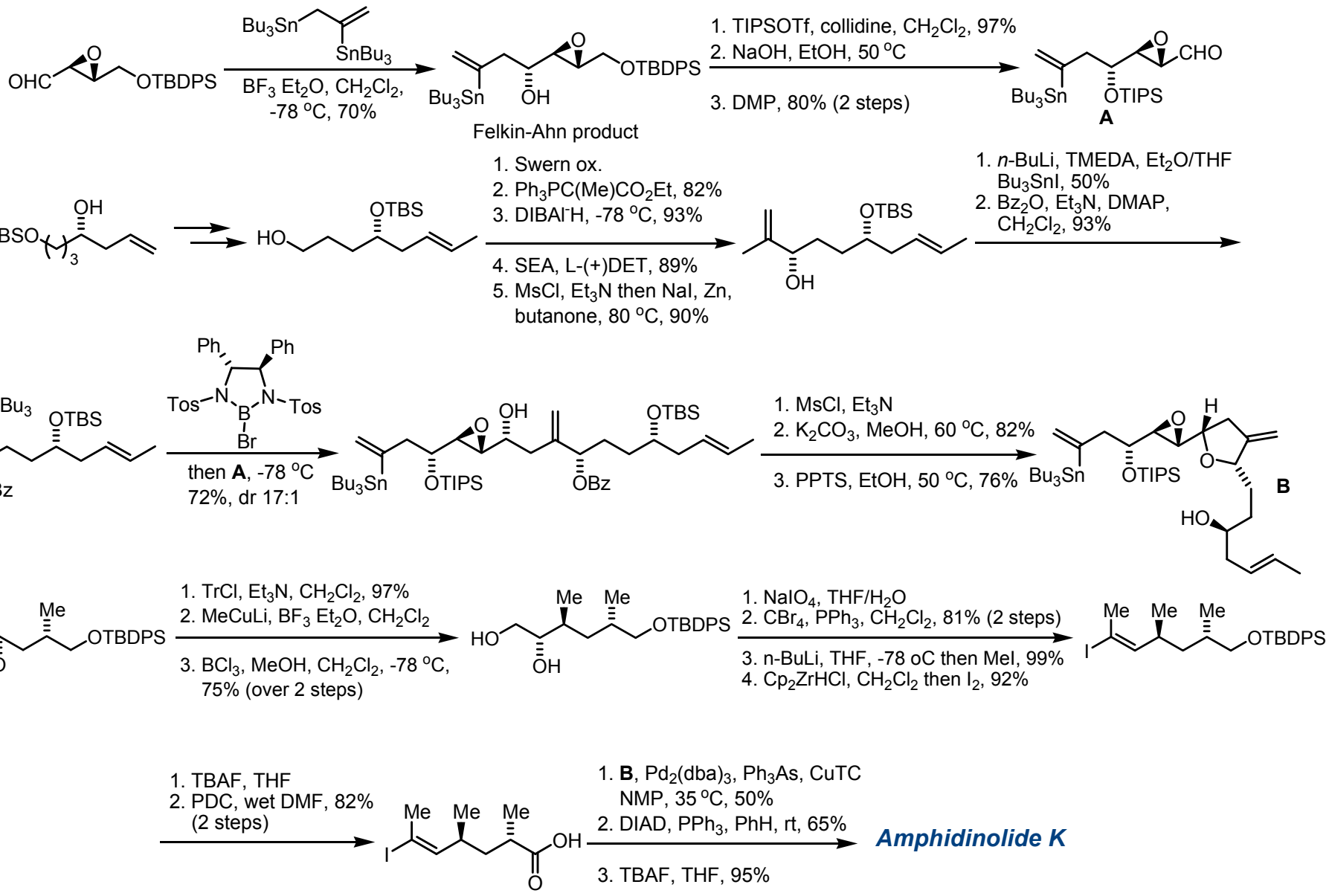
Stereochemical Model for Substrate-Controlled Cyclization:



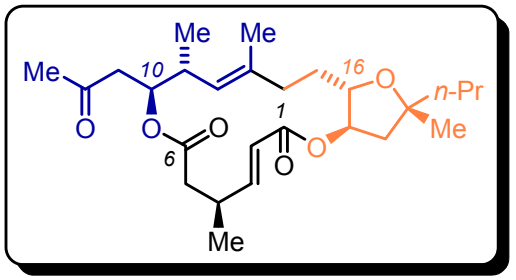
Amphidinolide K
Revision of Absolute Stereochemistry – Williams

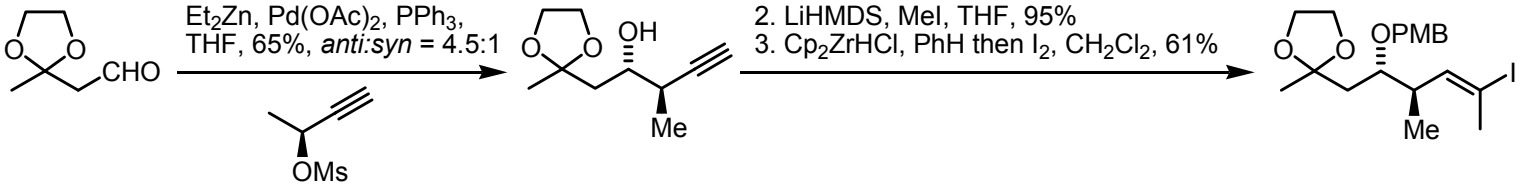


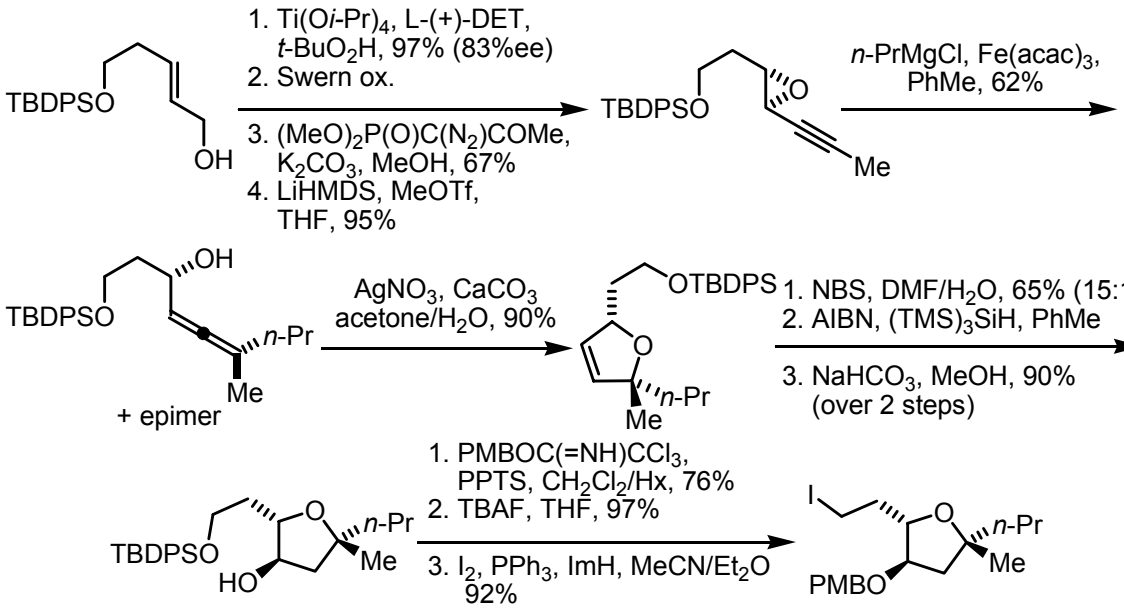
J. Am. Chem. Soc. **2001**, *123*, 765



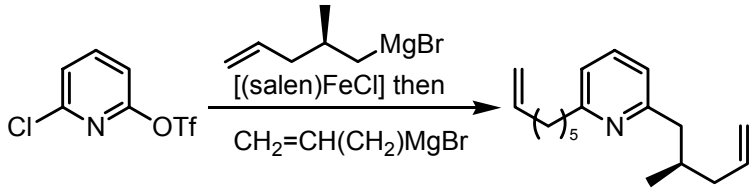
Amphidinolide X
Synthesis of Coupling Fragments – Fürstner



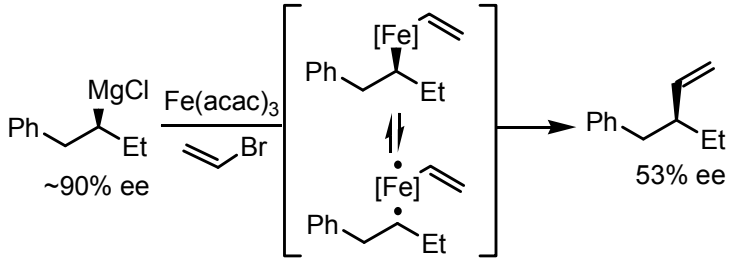




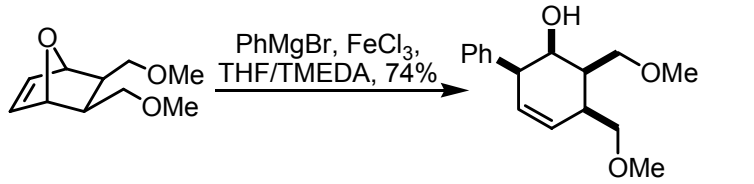
Related Applications of Iron (III):



Fürstner *Angew. Chem. Int. Ed.* **2003**, *42*, 308

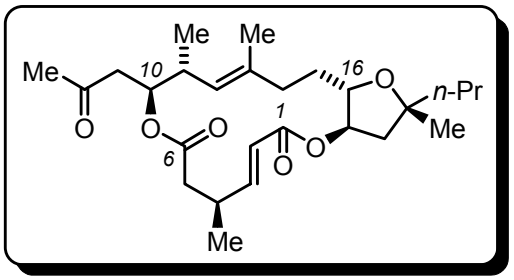


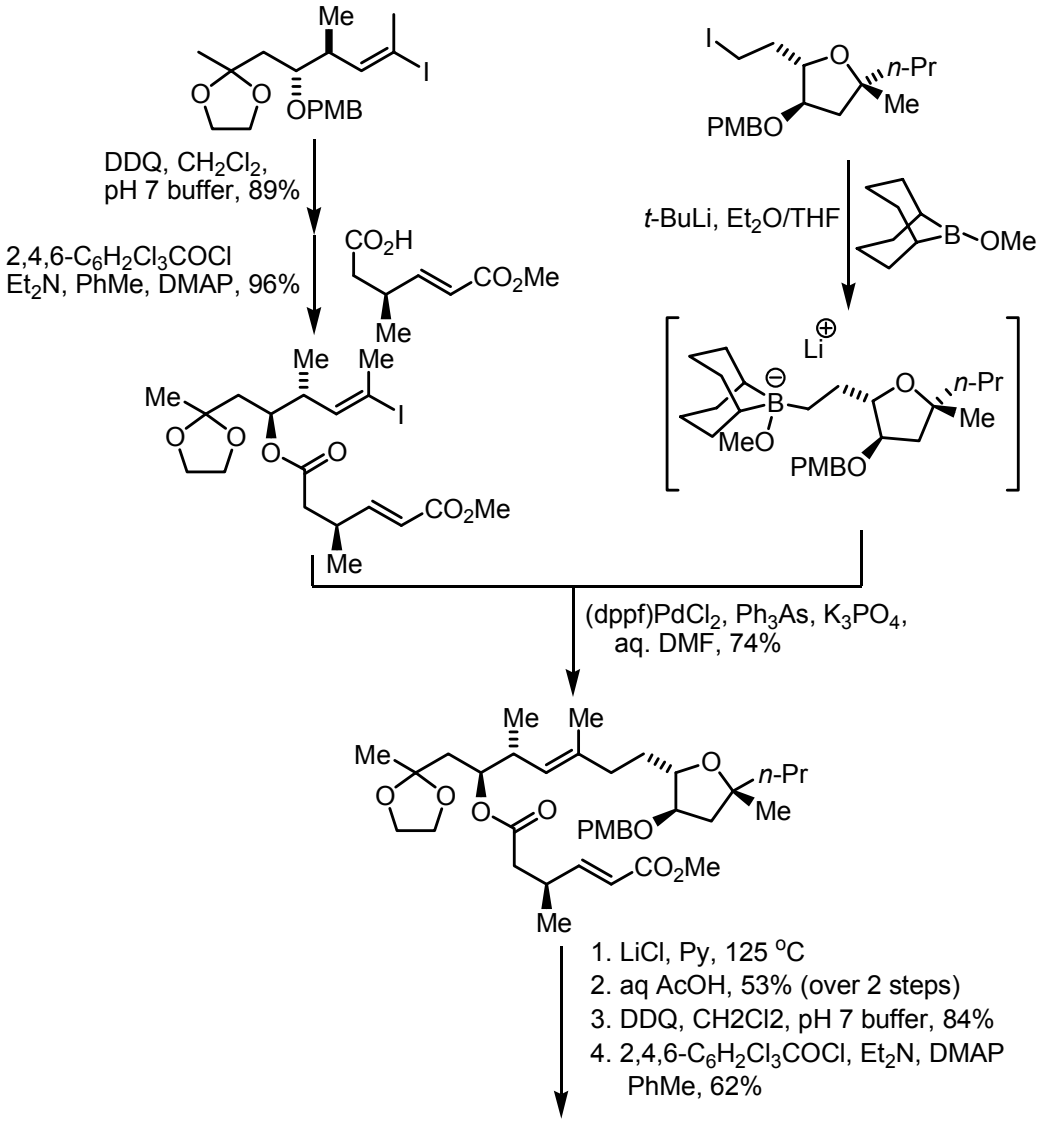
Hoffmann *Chem. Comm.* **2003**, 732



Nakamura *Org. Lett.* **2003**, *5*, 5507

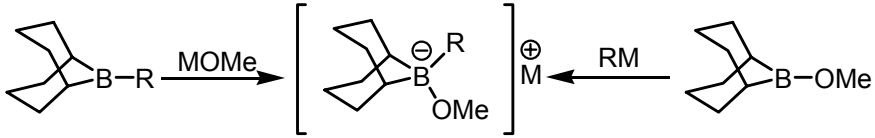
Amphidinolide X
Completion of Synthesis – Fürstner

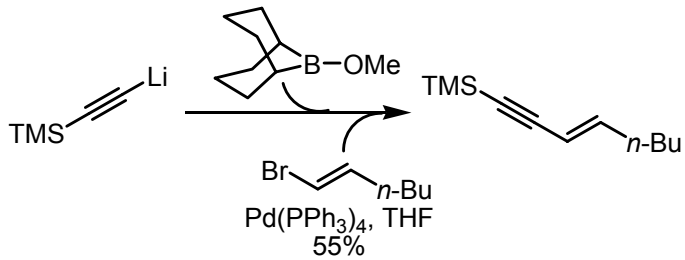




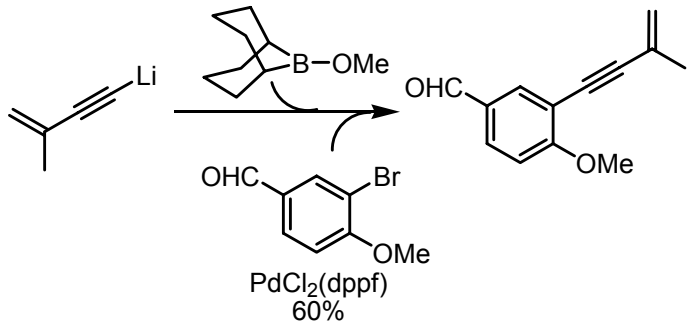
Amphidinolide X

Suzuki Cross-Coupling - "9-MeO-9-BBN" Variant



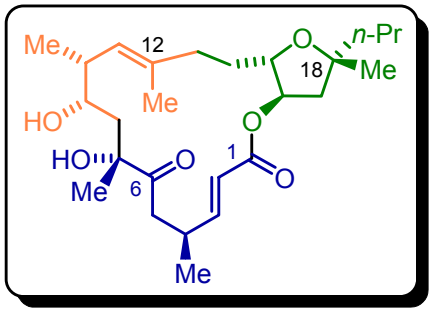


Soderquist *Tetrahedron Lett.* **1995**, *36*, 2401



Fürstner *Tetrahedron* **1995**, *51*, 11165

Amphidinolide Y
Remote Stereochemical Relay – Fürstner



1. NaOMe, MeOH, -40 °C, 86%
2. $[((S)\text{-BINAP})_2Ru_2Cl_5]^-[Et_2NH_2]^+$, HCl (cat.), H_2, MeOH, 92%, dr >23:1

1. $PMBOC(=NH)CCl_3$, $BF_3\ Et_2O$, CH_2Cl_2/cyclohexane (1:2), 0 °C, 84%
2. LiOH, MeOH/THF/H_2O, (4:1:1)
3. HN(OMe)Me HCl, DCC, DIPEA, DMAP, CH_2Cl_2, 0 °C to rt, 86% (over 2 steps)
4. MeMgBr, THF, 0 °C, 91%

1,4-*anti*

Et_2BOTf, DIPEA, PhMe
-90 °C, 84%, dr 4:1

1. TESCl, ImH, CH_2Cl_2, 0 °C to rt, 91%
2. MeMgBr, Et_2O, -78 °C, 96%, dr 15:26:1
3. TESOTf, 2,6-lutidine, -78 °C to rt, 92%

1,3-syn dipolar model

1,2-anti chelate-Cram model

1. DDQ, CH_2Cl_2/ pH 7 buffer, 0 °C, 92%
2. DMP, 93%
3. CSA (cat.), MeOH/THF (5:1), 0 °C, 65%, α:β 3:1

1. NIS, MeCN, 0 °C
2. TBAF, THF, 72% (over 2 steps)
3. TMSCl, ImH, CH_2Cl_2, 0 °C ro rt (94%
4. Swern ox.
5. LiHMDS, $(EtO)_2P(=O)CH_2CO_2Me$, THF -78 °C to 0 °C, 76 % (over 2 steps)

1. *t*-BuLi, Et_2O,/THF, then 9-MeO-9-BBN
2. $(dppf)PdCl_2$, Ph_3As, K_3PO_4, aq. DMF, 79%

1. DDQ, CH_2Cl_2/pH 7 buffer (1:1), 0 °C, 51-75%
2. LiOH, MeOH/THF/H_2O (4:1:1) then Et_3N
3. 2,4,6-$C_6H_2Cl_3COCl$, Et_3N, THF then DMAP, PhMe
4. AcOH/THF/H_2O (4:1:1), 56% (over 3 steps)

Amphidinolide Y

Summary

- **Fürstner successfully accomplished convergent total syntheses of amphidinolide X and Y**

- **Fe(III) was used to catalyze opening of propargylic epoxides to form allenic alcohols under mild conditions**

- **Future extensions may involve application to the synthesis of other members of the amphidinolide family leading to complete elucidation of their structure**