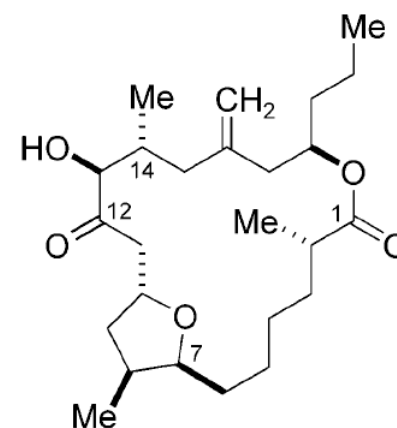


Total Syntheses of Amphidinolides T1 and T4 via Catalytic, Stereoselective, Reductive Macrocyclizations

1. Colby, E. A.; O'Brien, K. C.; Jamison*, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297.
2. Colby, E. A.; O'Brien, K. C.; Jamison*, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998.
3. Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342.



1 amphidinolide T1

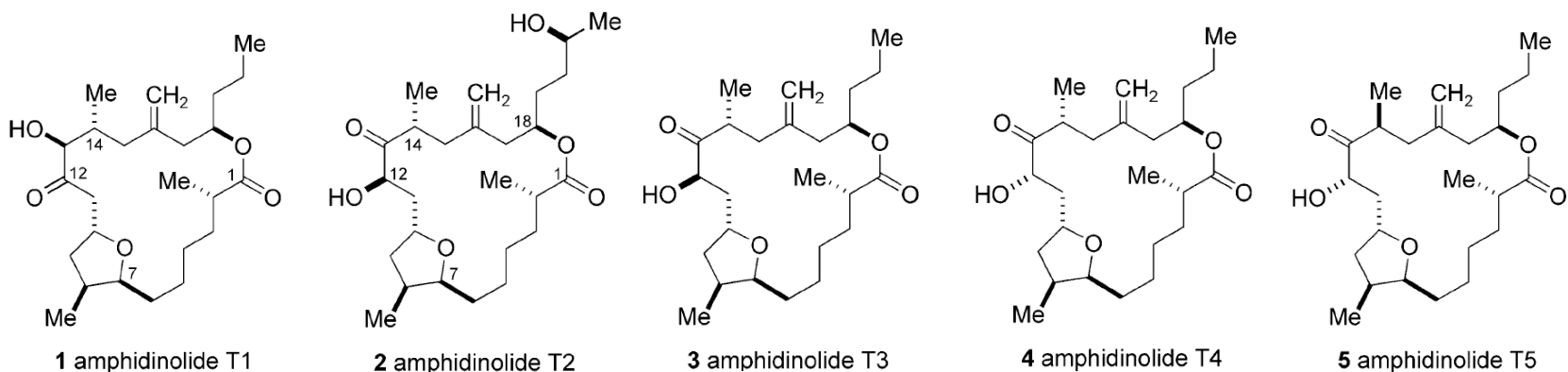
Literature Presentation

Zhenjie Lu

Mar 31, 2005

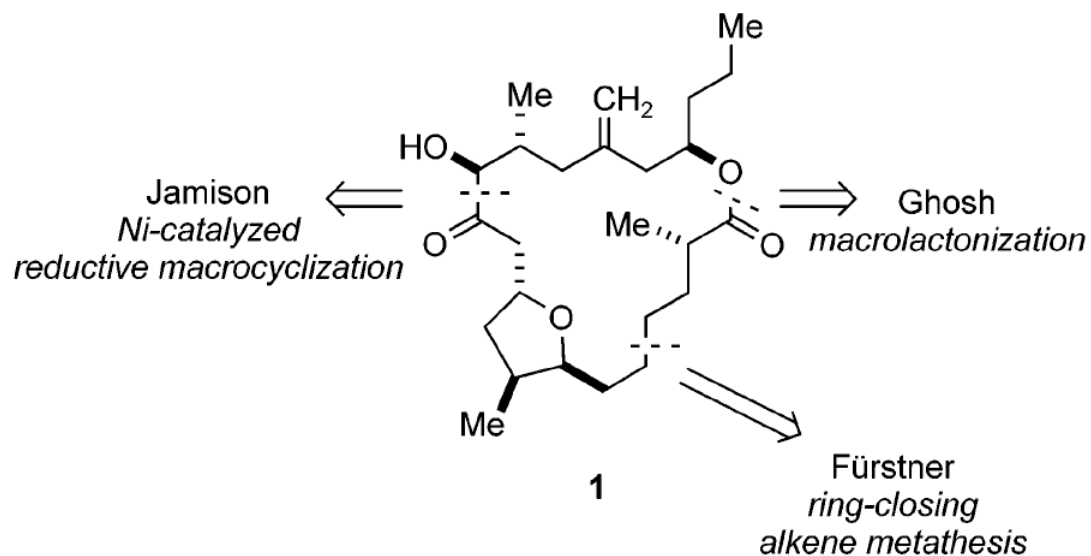
About Amphidinolide T family

- Amphidinolide T1 is a cytotoxic macrolides isolated from the marine flatworm *Amphiscolops* sp, it was characterized by Kobayashi, J. in 2000, the T2 to T5 members were isolated later by the same group in 2001.
- Amphidinolides T1-T5 exhibit modest cytotoxicity against L1210 cells *in vitro* with IC_{50} values of 18, 10, 7.0, 11, and 12 $\mu\text{g mL}^{-1}$, respectively.



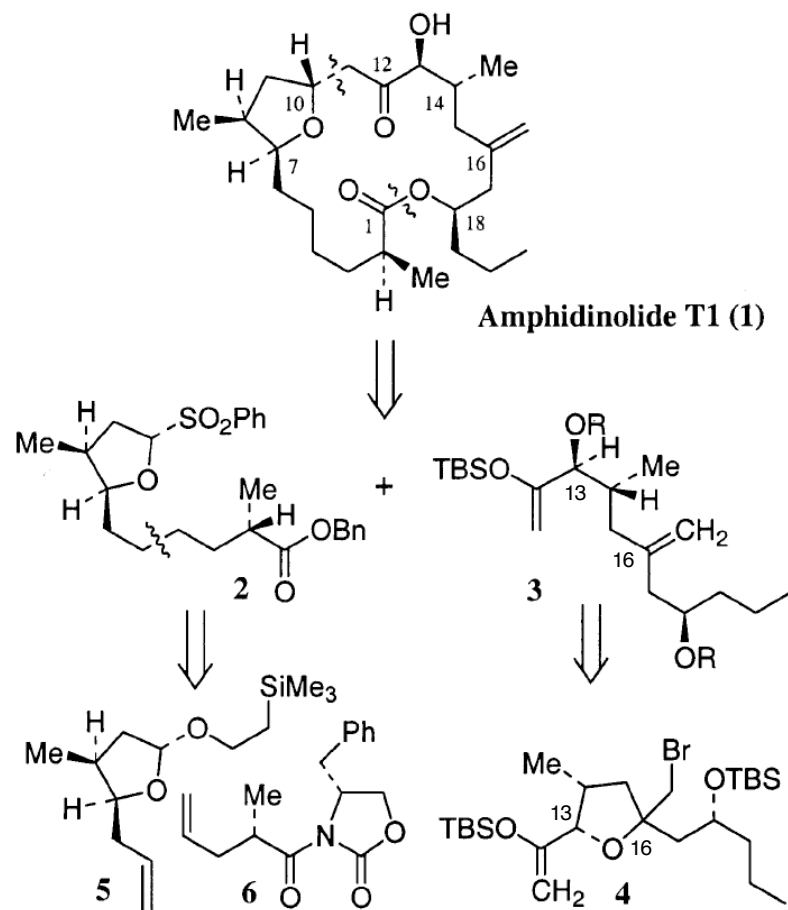
- Similarity on the structures in class T family:
19-member macrocycle ; trisubstituted tetrahydrofuran moiety
a -hydroxy ketone; exocyclic methylene; homoallylic ester

Different Synthesis to the Amphidinolide T Macrocycle



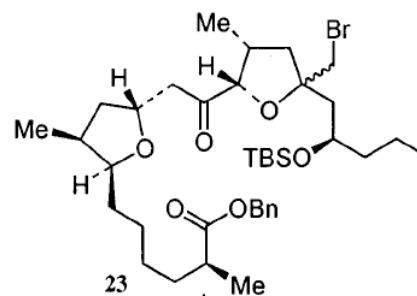
1. Fürstner, A.; Aissa, C.; Riveiros, R.; Ragot, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 4763.
2. Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374.
3. Aissa, C.; Riveiros, R.; Ragot, J.; Fürstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512.
4. Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998.

Ghosh's Approach to Amphidinolide T1



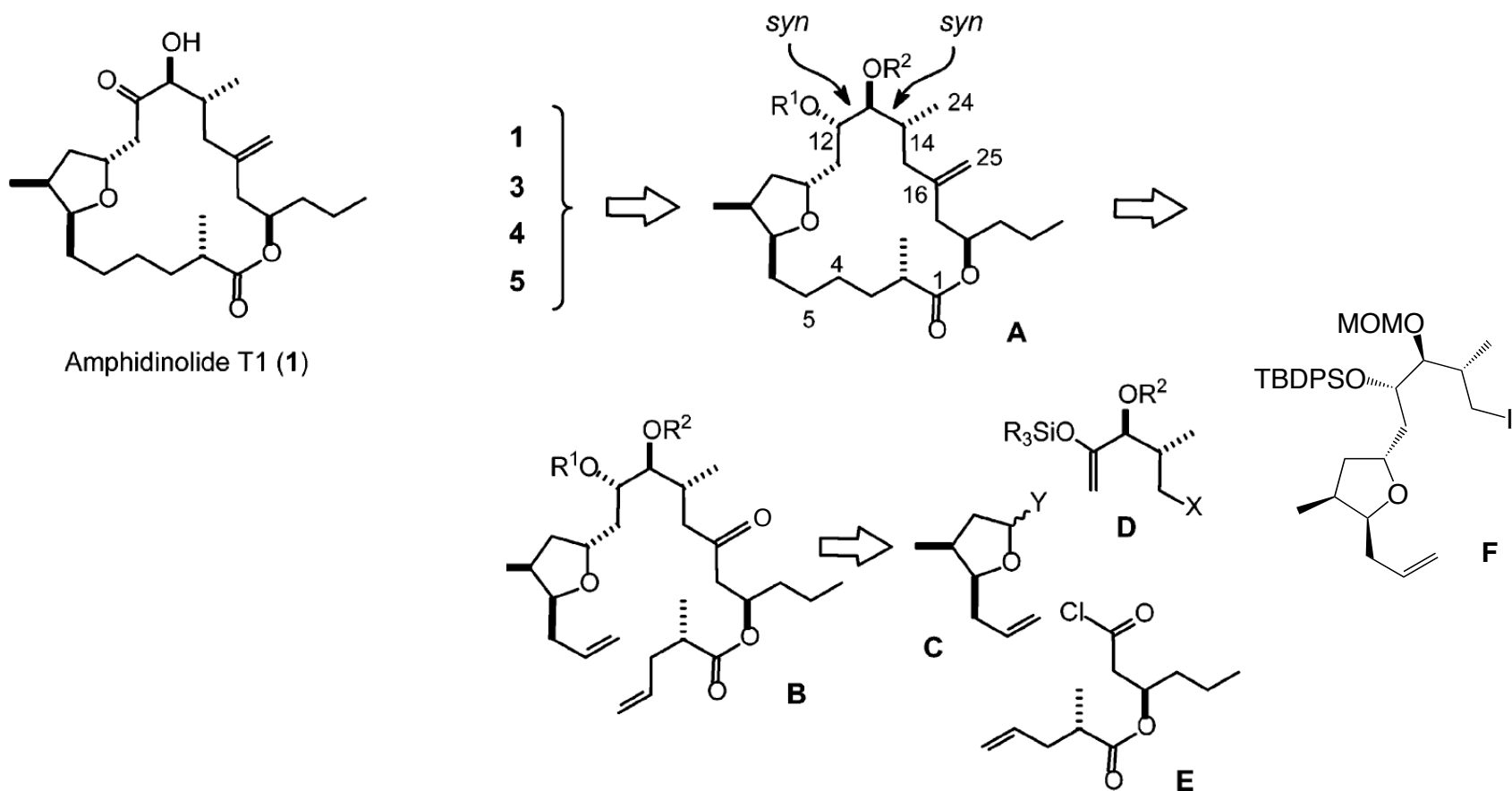
5 + 6 \rightarrow 2: Grubb's cross metathesis, 96% yield.

2 + 4 \rightarrow 1: (4 is the surrogate of the 3 to protect the C16 methylene and C13 hydroxy.)
a. Oxocarbenium ion-mediated alkylation.



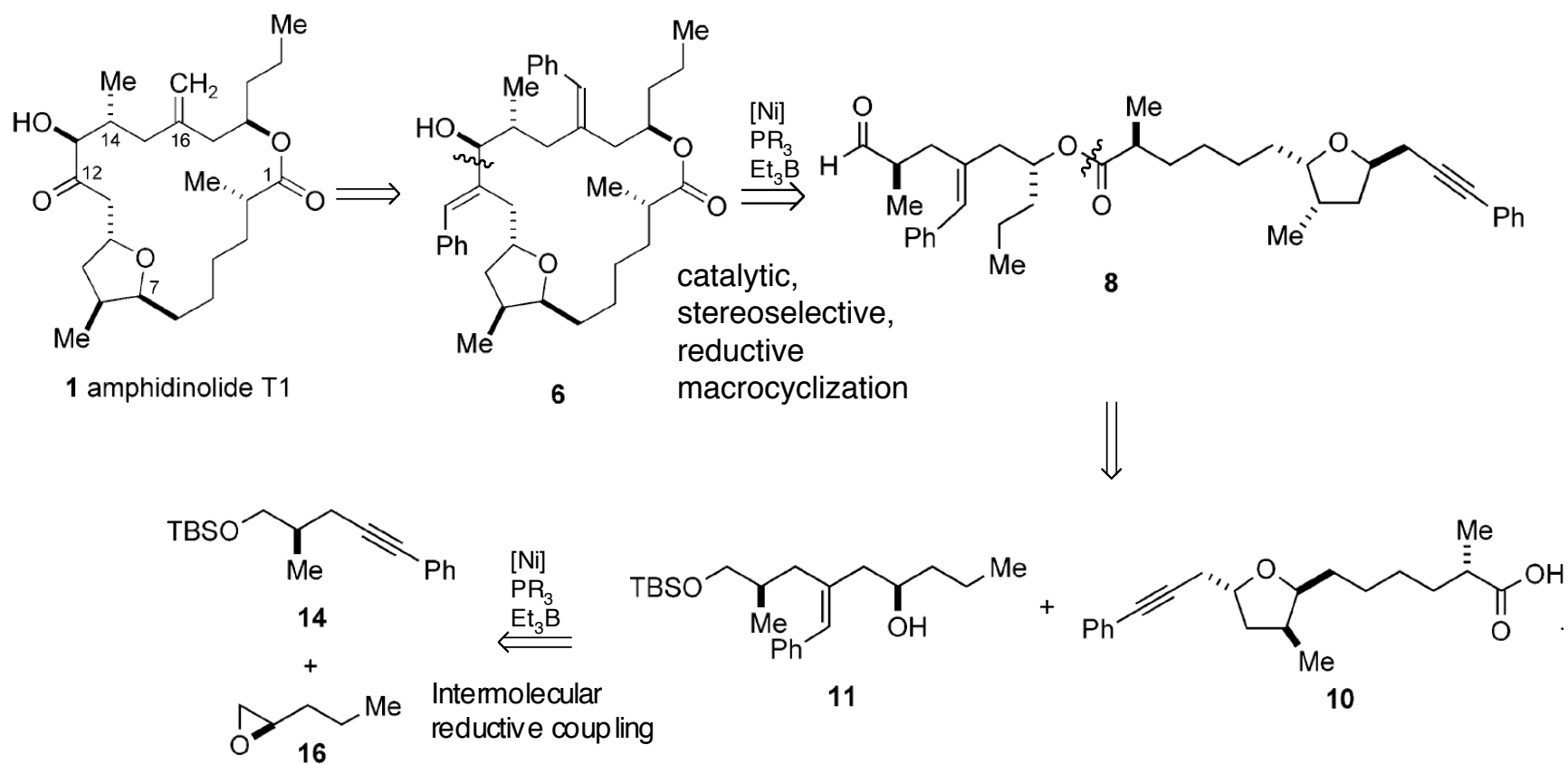
b. Yamaguchi lactonization.

Furstner's Approach to Amphidinolides



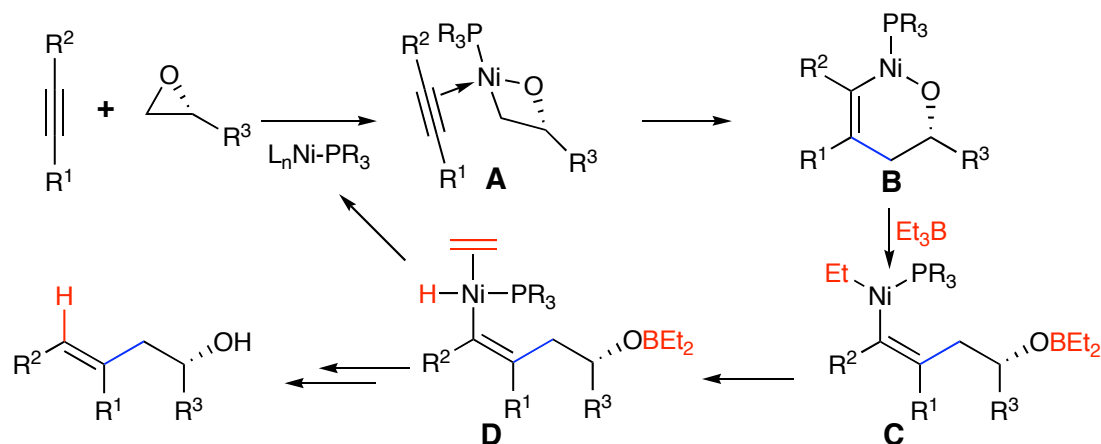
1. $C + D \rightarrow F'$: Oxocarbenium ion alkylation. Reduction using L-Selectride gave (12*S*), LAH gave (12*R*) configuration.
2. $F + E \rightarrow B'$: Pd catalyzed Negishi cross coupling.
3. $B \rightarrow A$: RCM.

Jamison's Approach to Amphidinolide T1

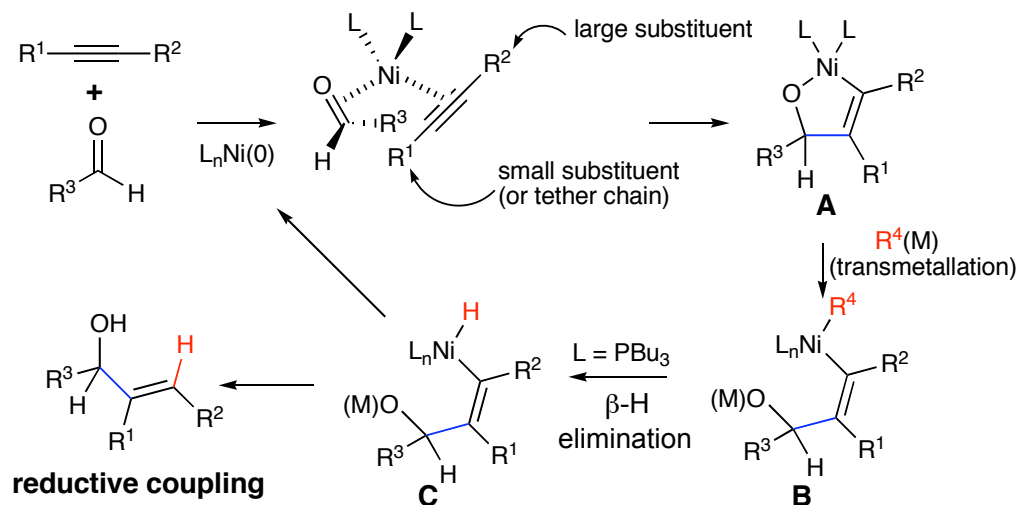


Ni-Catalyzed Alkyne Electrophile Reductive Coupling

◆ Coupling of alkyne with epoxide:



◆ Coupling of alkyne with aldehyde:

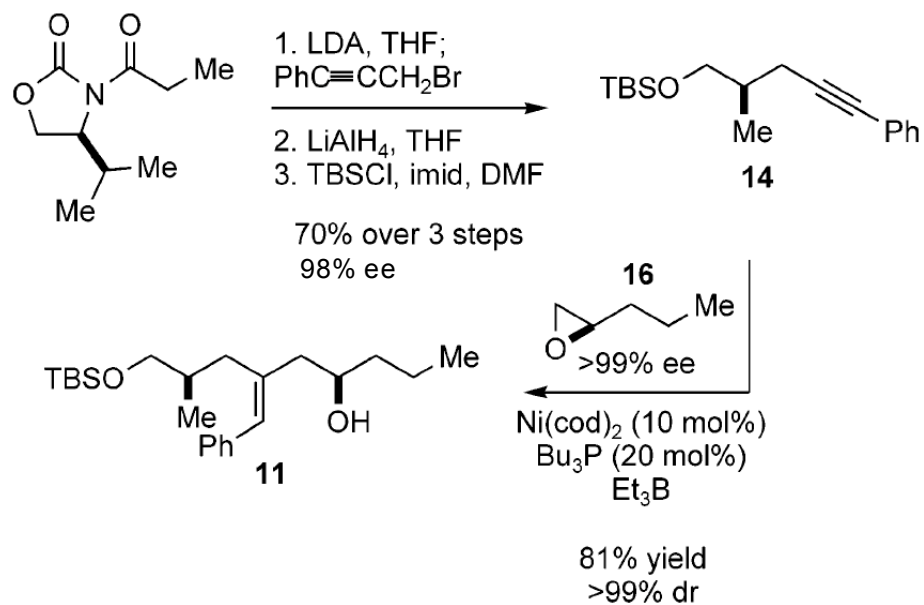
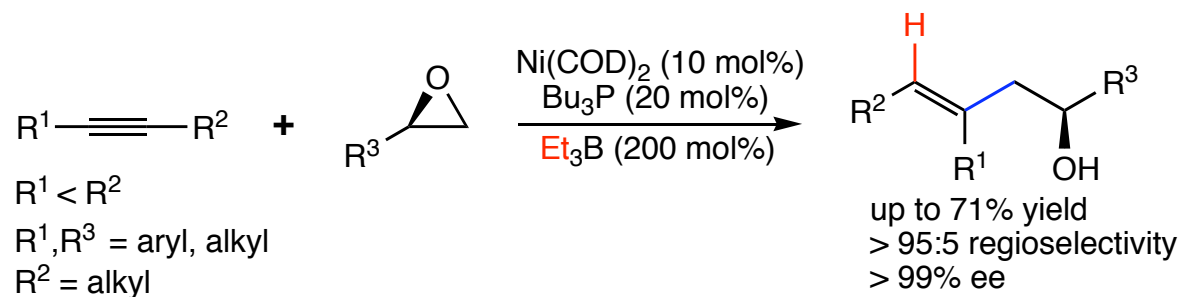


1. Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076.

2. Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065.

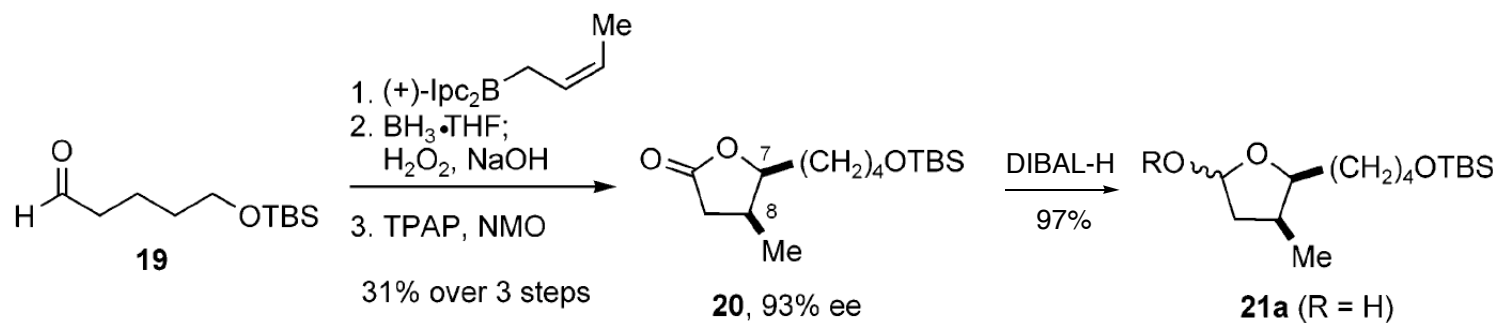
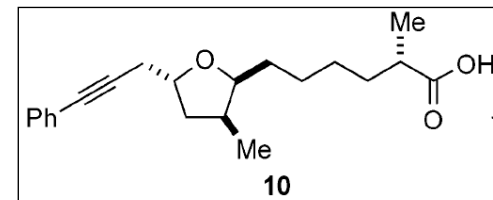
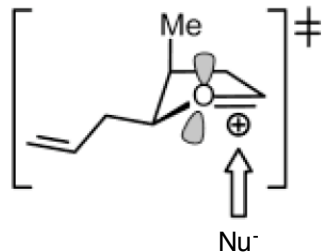
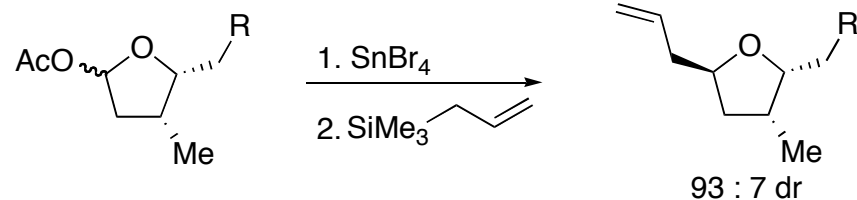
Construction of Fragment 11

Construction of fragment **11** via intermolecular alkyne-epoxide reductive coupling

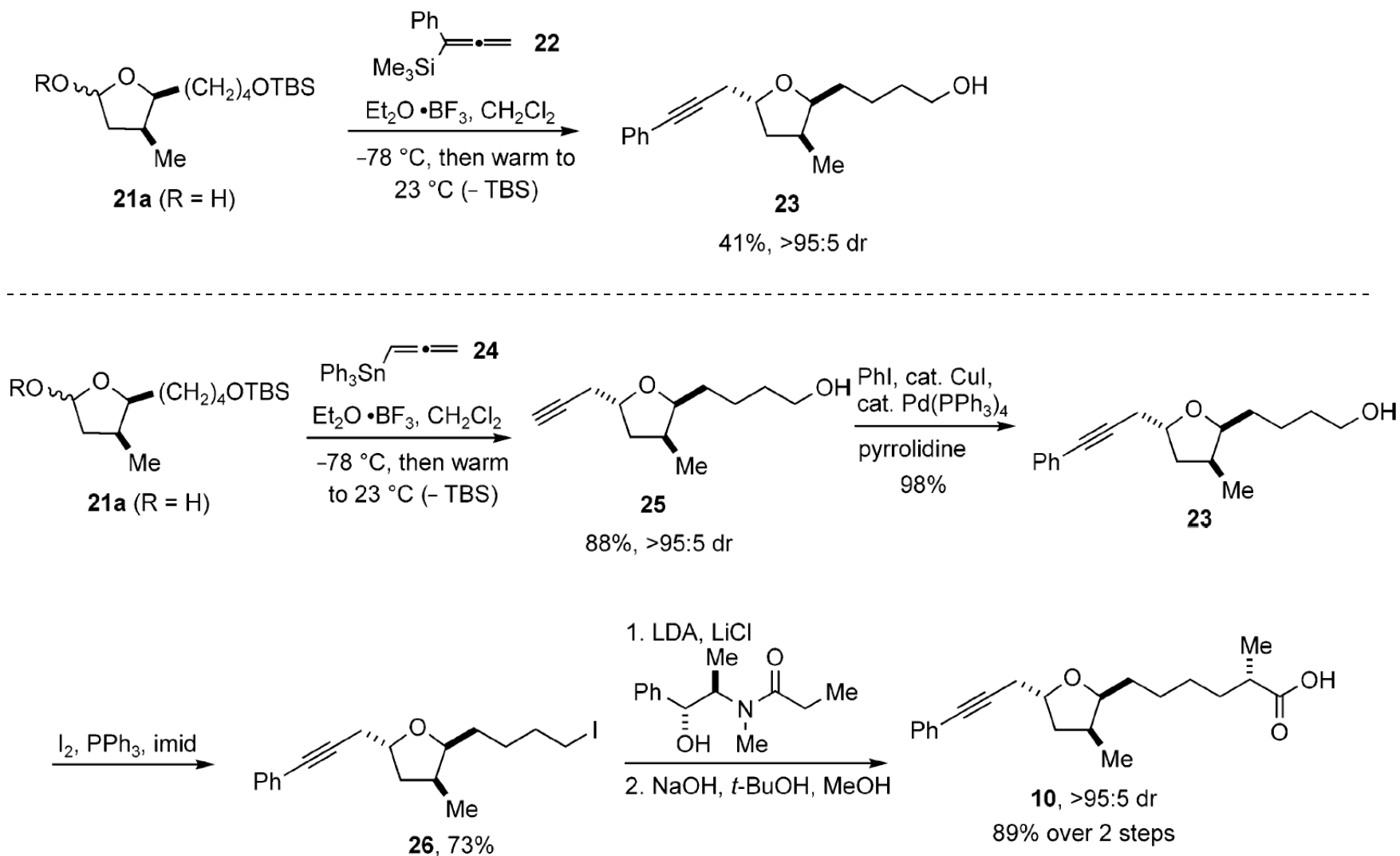


Assembly of Fragment 10

Woerpel's study of addition to oxocarbenium ion:



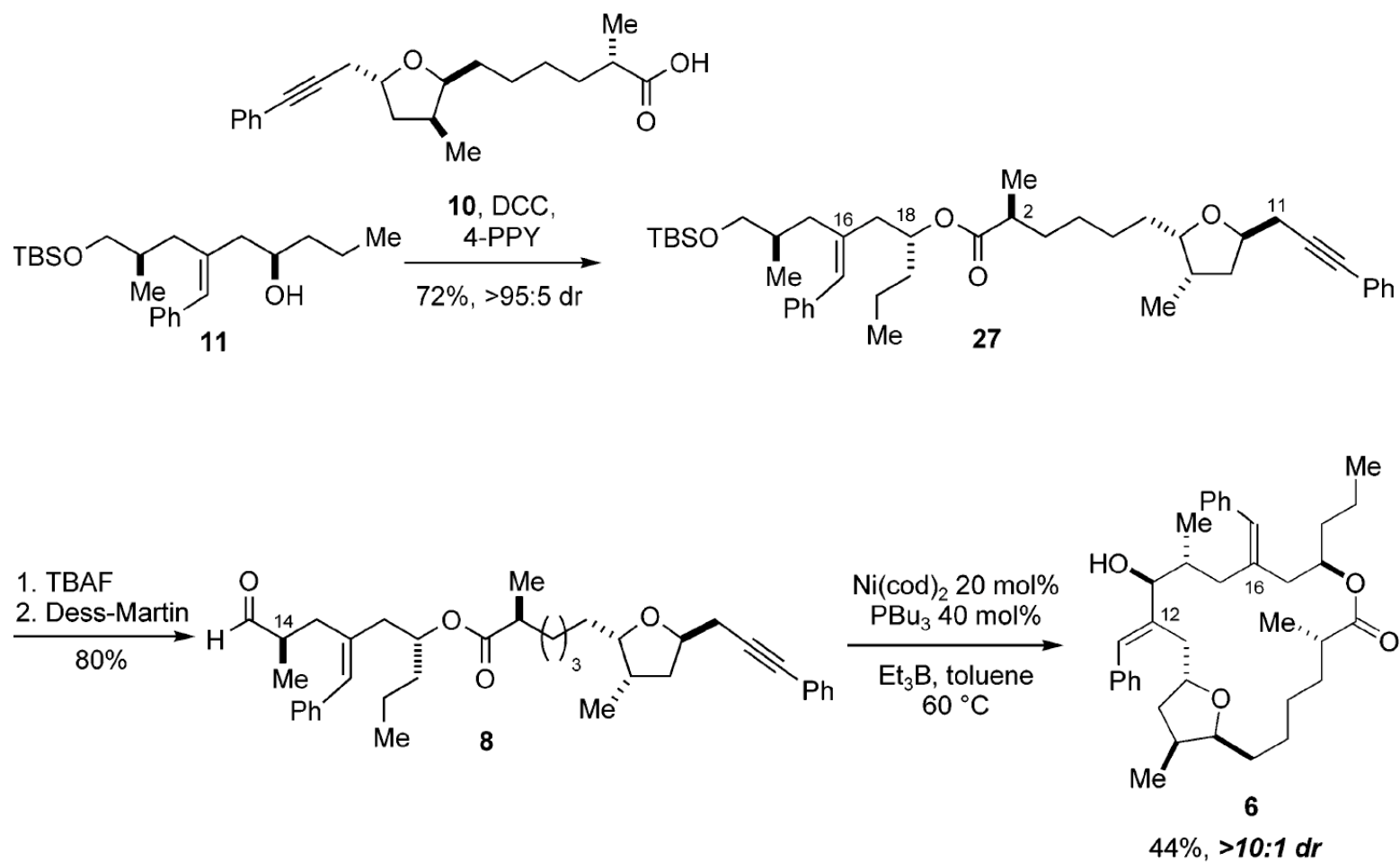
Synthesis of Alkynyl Acid 10



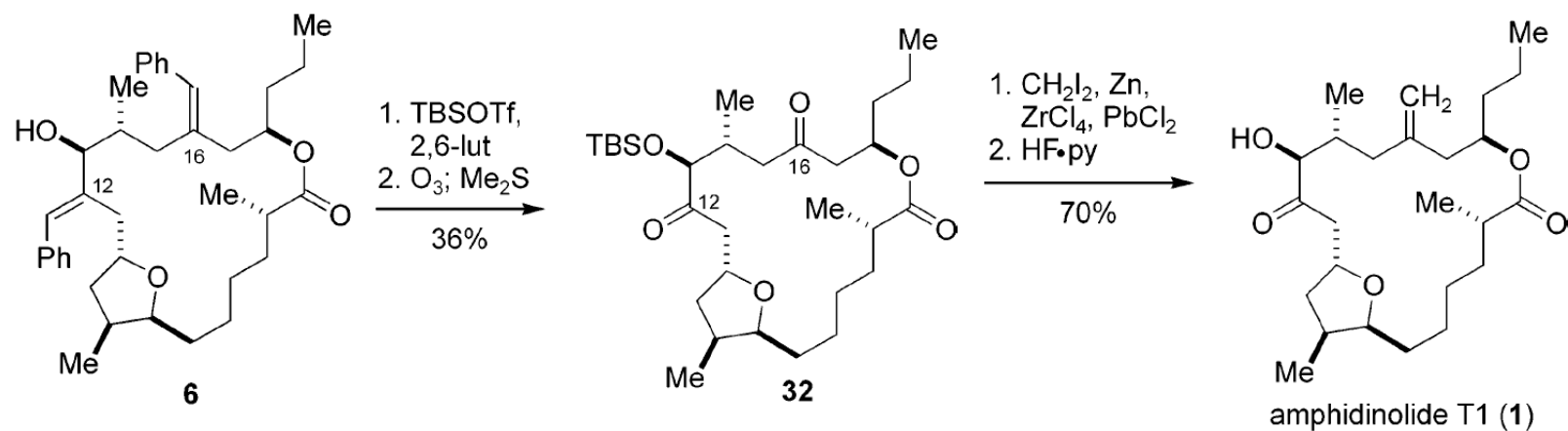
1. Colby, E. A.; O'Brien, K. C.; Jamison*, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998.

2. Myers, A. G.; Yang, B.H.; Chen, H.; Mckinsty, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

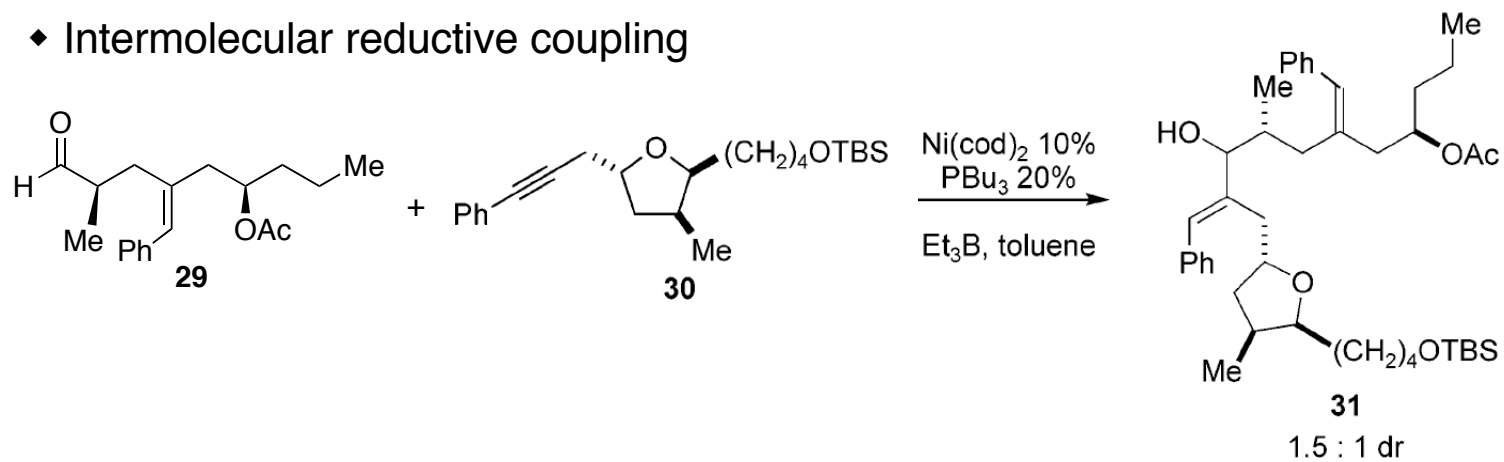
Ni-Catalyzed Macrocyclization

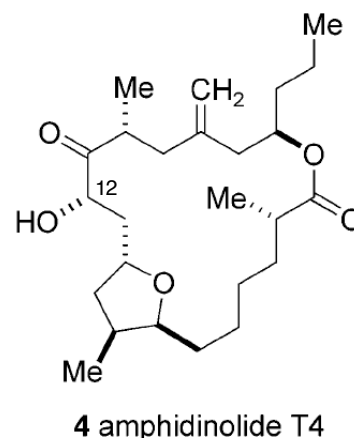
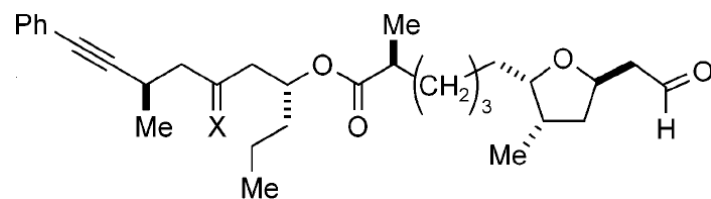
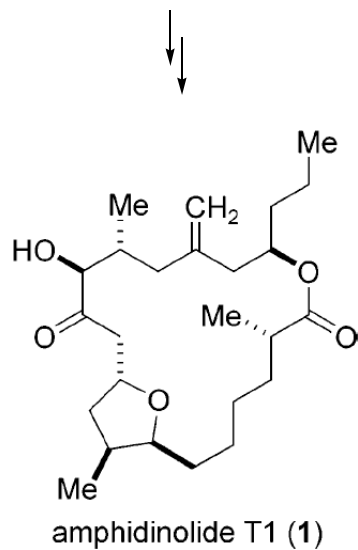
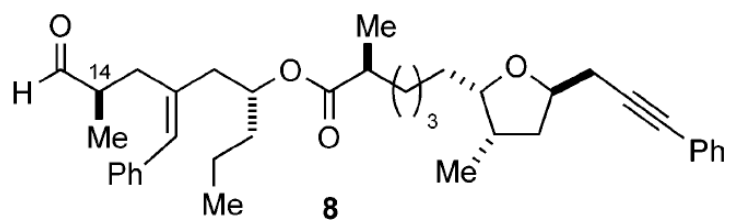


Synthesis of Amphidinolide T1

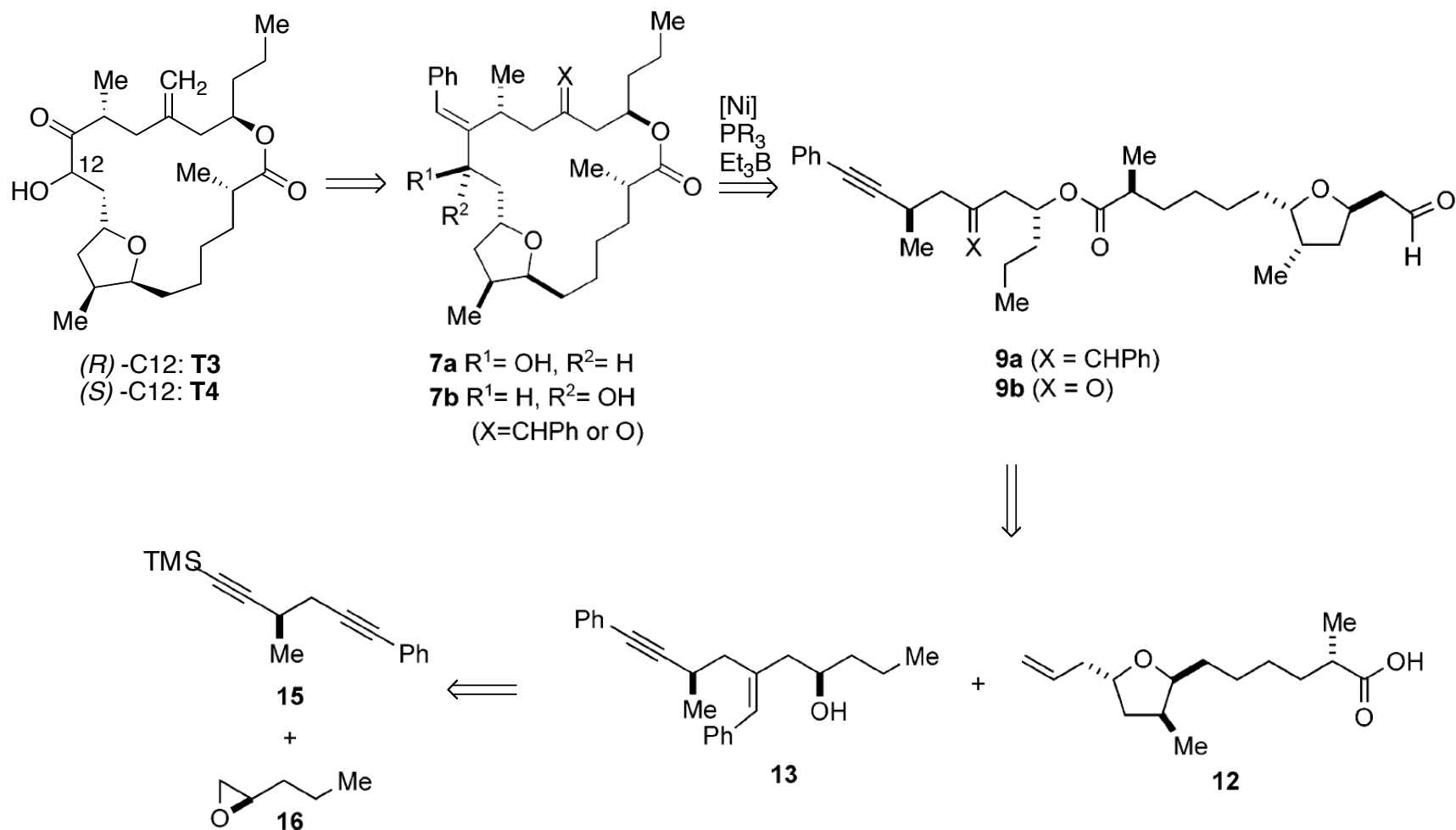


◆ Intermolecular reductive coupling

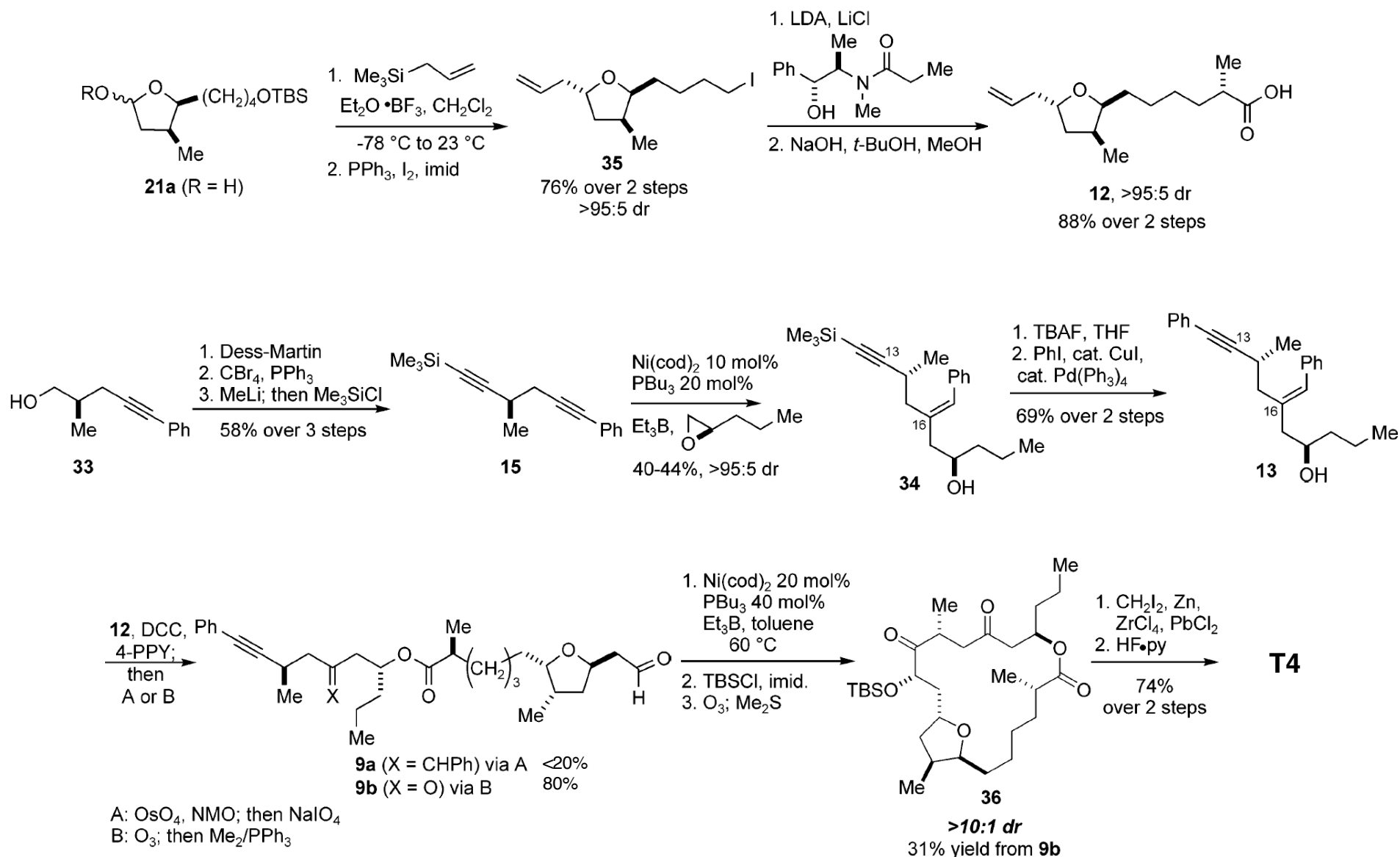




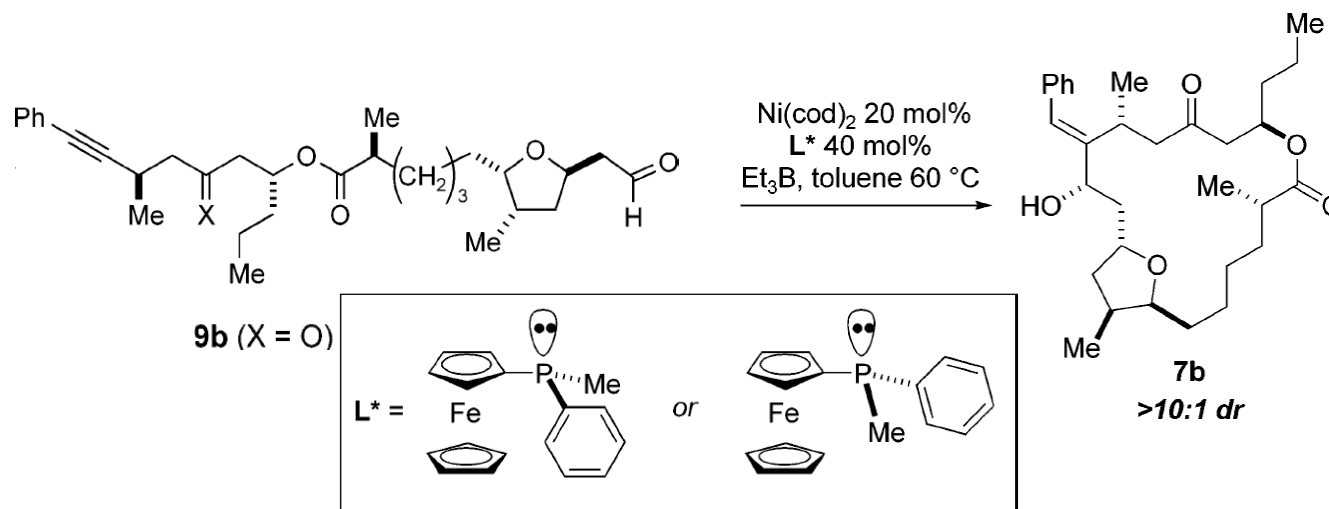
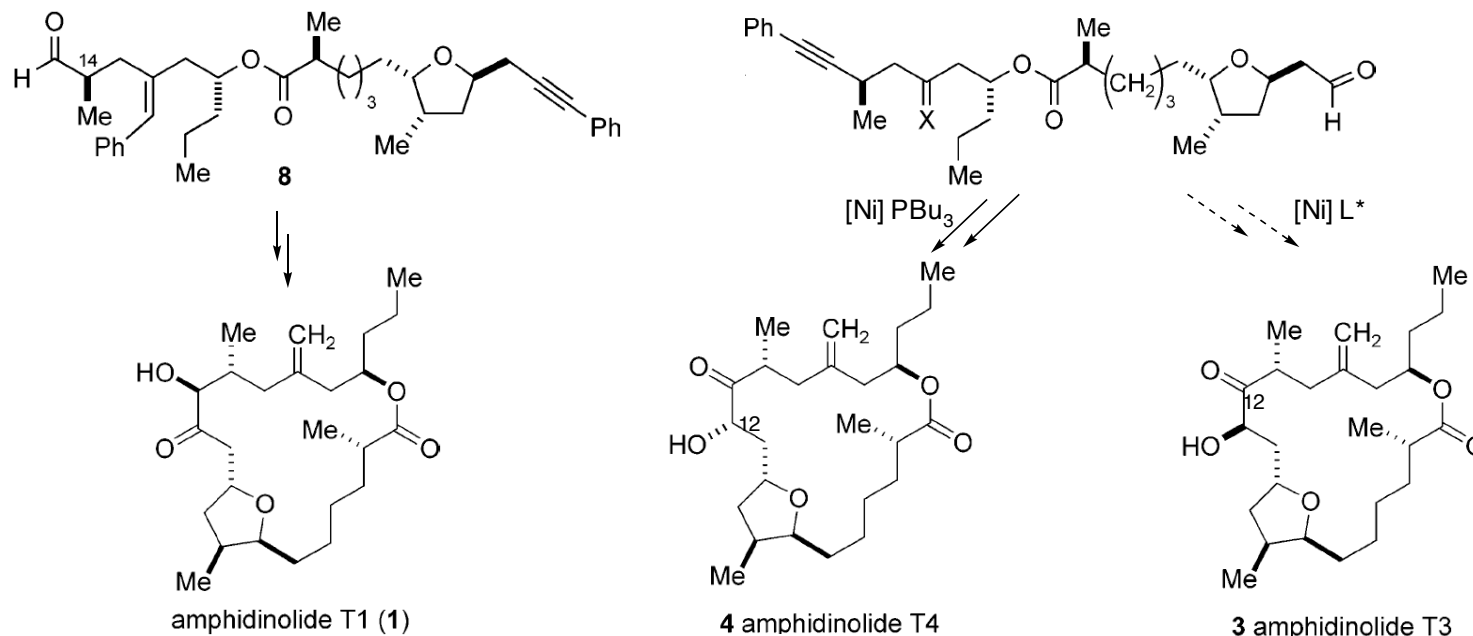
Retrosynthetic Analysis of Amphidinolide T4



Synthesis of Amphidinolide T4

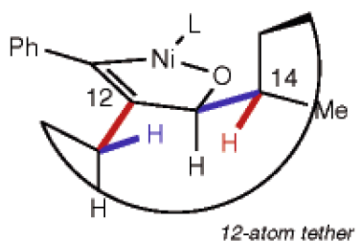
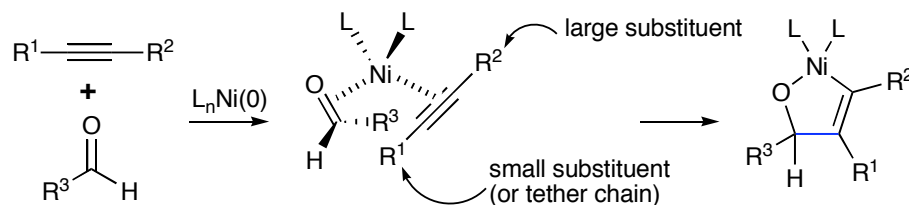


Possibility of the Synthesis of Amphidinolide T3 via Using Chiral Ligand

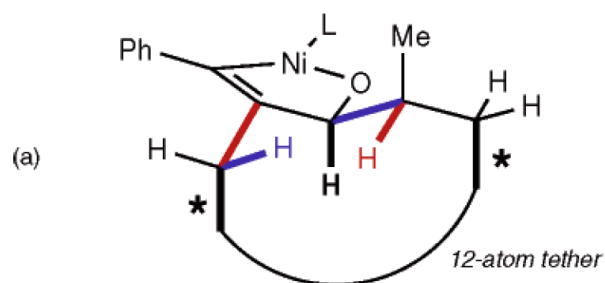


* Both ligands gave the same configuration at C12. Completely substrate control macrocyclization

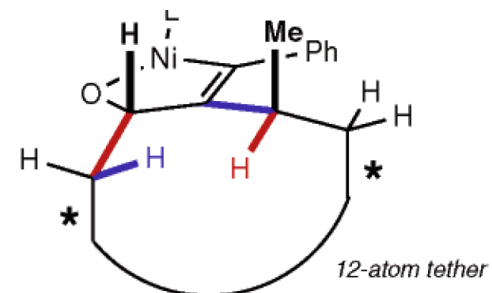
Macrocyclization study



14-epi-T1 series
major diastereomer



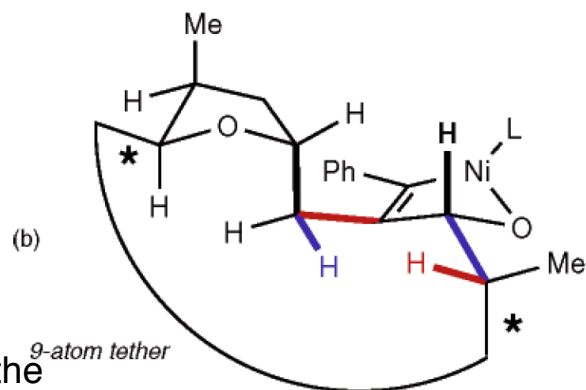
T1 series
major diastereomer



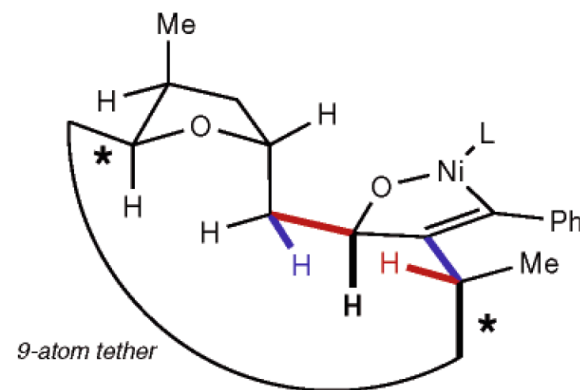
T4 series
major diastereomer

sp^2 hybridization at C12 eliminates **syn-pentane-like** interaction with any of the substituents at C14 in macrocyclizations leading to both T1 and 14-epi-T1.

★ The strongest effect on the sense of induction is minimization of 1,3-interactions. Branching on C14 has no effect.



T1 series
minor diastereomer
(not observed)



T4 series
minor diastereomer
(not observed)

Conclusion

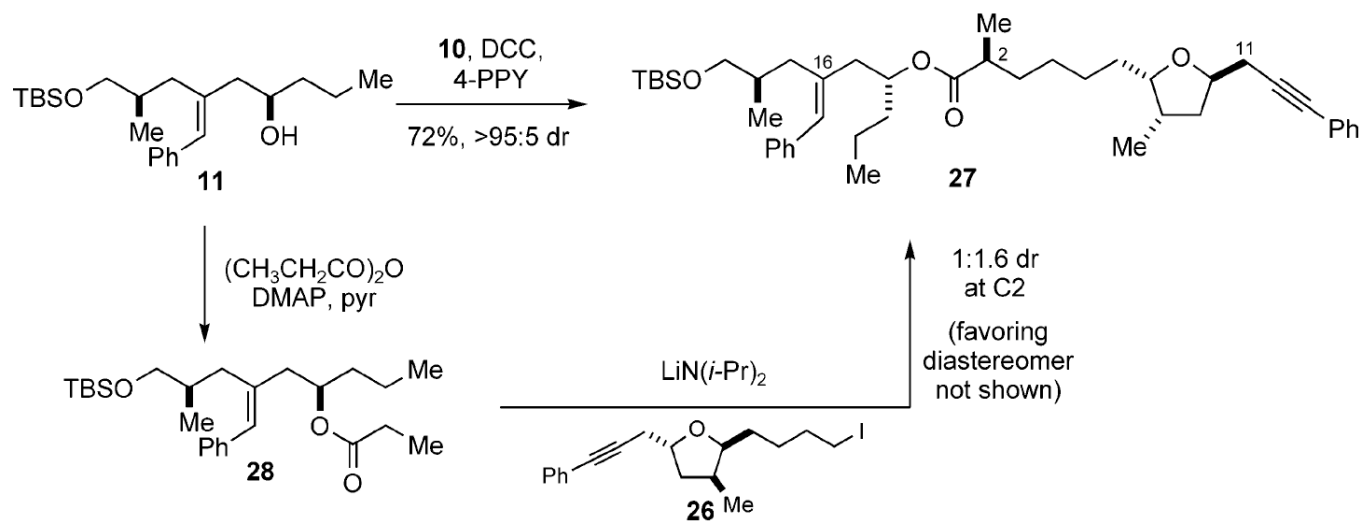
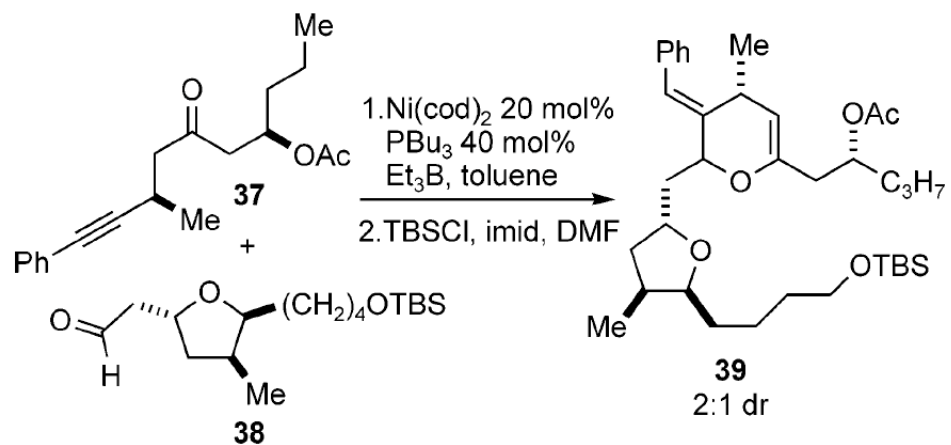
Synthesis of Amphidinolide T1 and T4:

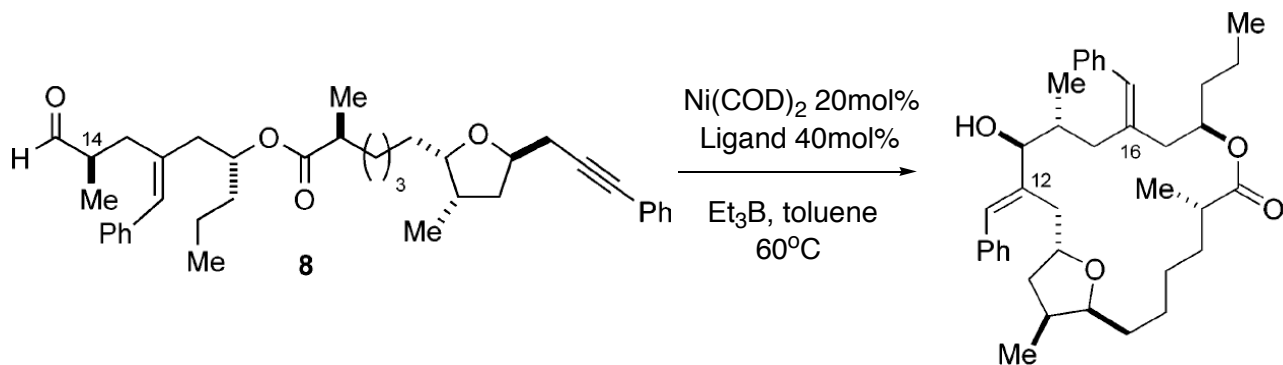
1. Ni catalyzed macrocyclization not only closed the 19-membered ring but also concurrently install a stereogenic center.
2. Intermolecular Ni-catalyzed coupling gave the desired homoallylic alcohol.
3. Construction of the trisubstituted tetrahydrofuran via addition of oxocarbenium ion.
4. Jamison's synthesis of Amphidinolide T1: 15 longest linear steps.
T4: 14 longest linear steps.

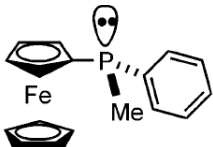
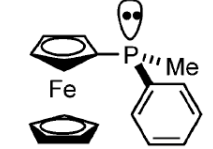
Ghosh's synthesis of T1: 18 longest linear steps.

Furstner's synthesis of T1 and T4: 21 longest linear steps.

Intermolecular coupling





entry	macrocyclization experiment	ligand	dr	configuration of major diastereomer
1	T1 (8 , Scheme 11)	PBu_3	>10:1	(S) C13
2	14- <i>epi</i> -T1 (40 , Scheme 20)	PBu_3	8:1	(S) C13
3	T4 (9a , Scheme 17)	PBu_3	>10:1	(S) C12
4	T4 (9b , Scheme 17)	PBu_3	>10:1	(S) C12
5	T4 (9b , Scheme 19)		>10:1	(S) C12
6	T4 (9b , Scheme 19)		>10:1	(S) C12
7	14- <i>epi</i> -T4 (41 , Scheme 20)	PBu_3	n.a.	(macrocyclization not observed)

