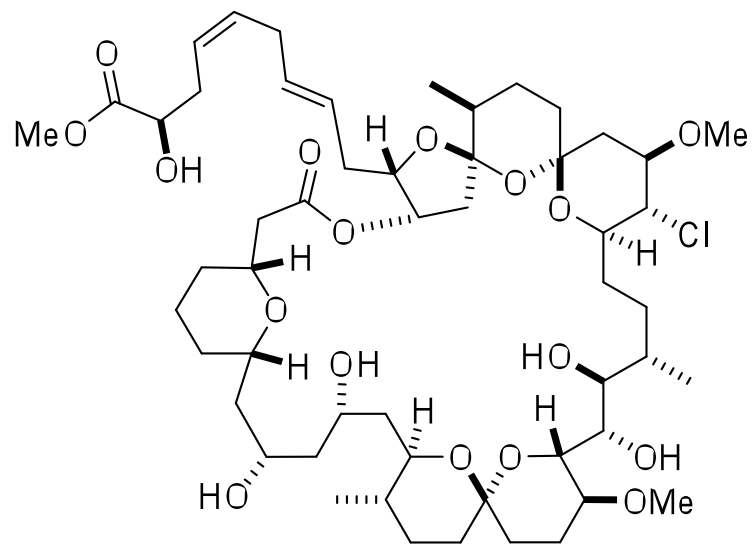


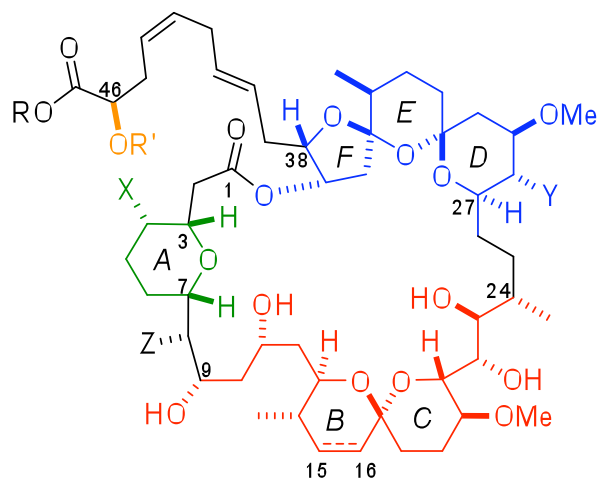
# Total Synthesis of Spirastrellolide F Methyl Ester

Fürstner *et al.* *ACIE* **2009**, *48*, 9940 and 9946.



Marija Manojlović  
Wipf Group Current Literature Meeting  
12-26-2009

# Spirastrellolides



Spirastrellolides A-G

- A:  $R = R' = X = Z = H$ ,  
 $Y = Cl, \Delta^{15,16}$   
 B:  $R = R' = X = Y = Z = H$   
 C:  $R = R' = X = Y = H$ ,  
 $Z = OH$   
 D:  $R = R' = Z = H$ ,  
 $X = Y = Cl, \Delta^{15,16}$   
 E:  $R = R' = X = Y = Z = H$ ,  
 $\Delta^{15,16}$   
 F:  $R = R' = X = Z = H$ ,  
 $Y = Cl$   
 G:  $R = X = Z = H, Y = Cl$ ,  
 $R' = Me, \Delta^{15,16}$

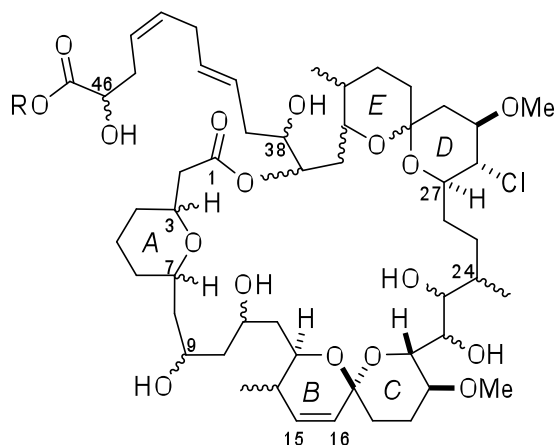


*Spirastrella coccinea*

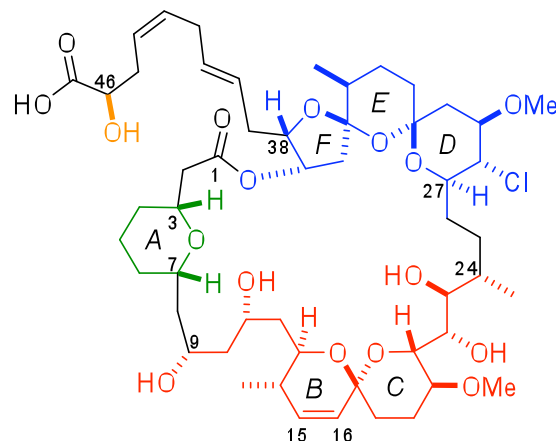
- Spirastrellolide A was isolated from the marine sponge *Spirastrella coccinea* in 2003, followed by B-G in 2007
- Methyl esters showed uniformly strong activity and an unusual phenotypic response in a cell-based antimitotic assay (against breast cancer MDF-7 cells).
- Potent ( $IC_{50} = 1$  nM) and selective inhibitors of Ser/Thr protein phosphatase 2A causing premature cell entry into mitosis from the S-phase
- Other PP2A inhibitors: fostriecin, calyculin A, okadaic acid.

*JACS* **2003**, 125, 5296. *JACS* **2007**, 129, 508.  
*Nat. Prod. Rep.* **2009**, 26, 865.  
*Curr. Med. Chem.* **2002**, 9, 2055.

# Spirastrellolide structural uncertainties



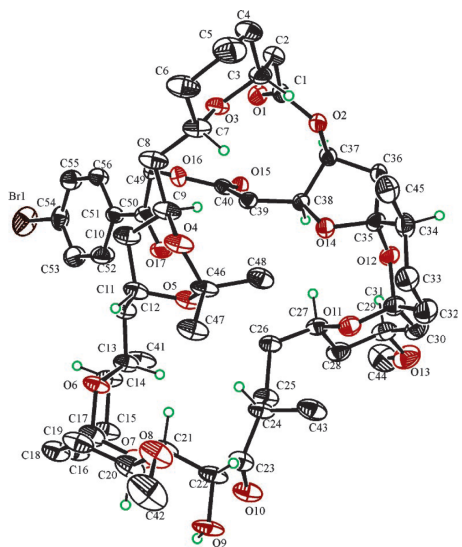
Spirastrellolide A (2003)  
Originally proposed structure



Spirastrellolide A (2004)  
Revised structure (ROESY)

Regions of unknown  
relative  
stereochemistry:

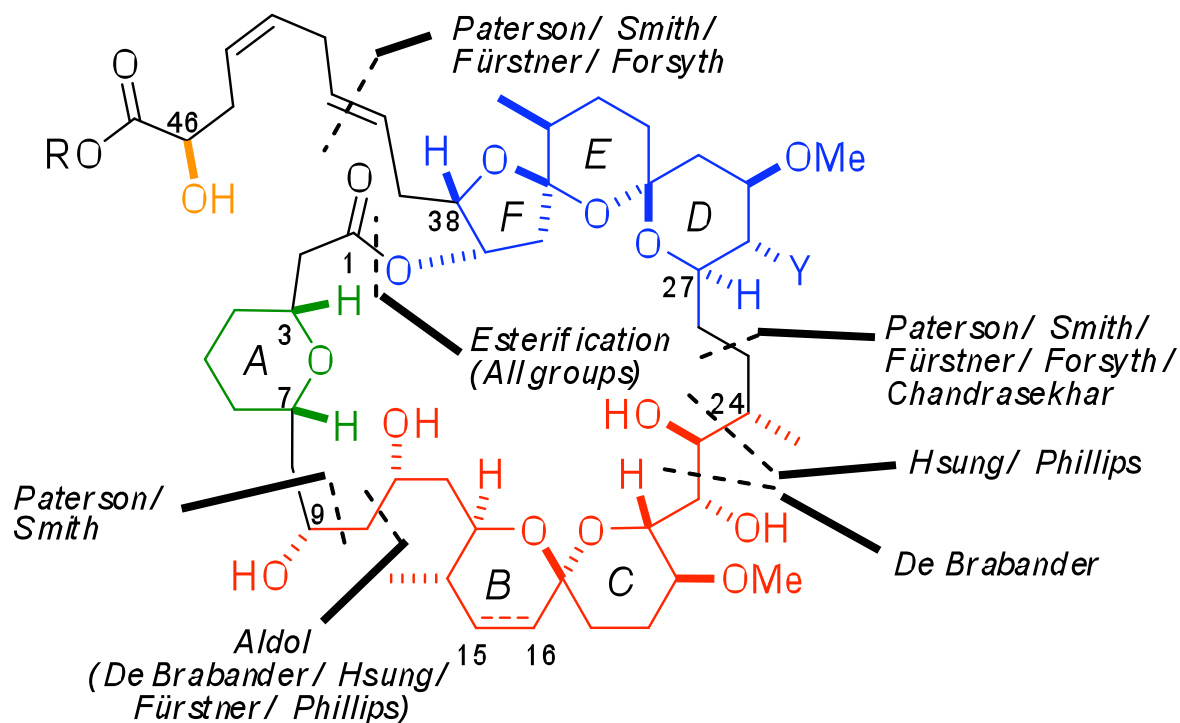
C3-C7 (A)  
C9-C24 (BC)  
C27-C36 (DEF)  
C46



- Possible 16 diastereoisomers were synthetic targets until the X-ray of the Spirastrellolide B derivative was obtained (2006)
- The stereochemistry of C46 was determined in 2007 by the isolation of the cleaved side-chain fragment and its transformation to dimethylmalate.

*JACS* **2003**, 125, 5296.  
*OL* **2004**, 6, 2607.  
*JACS* **2007**, 129, 508.  
*JOC* **2007**, 72, 9842.

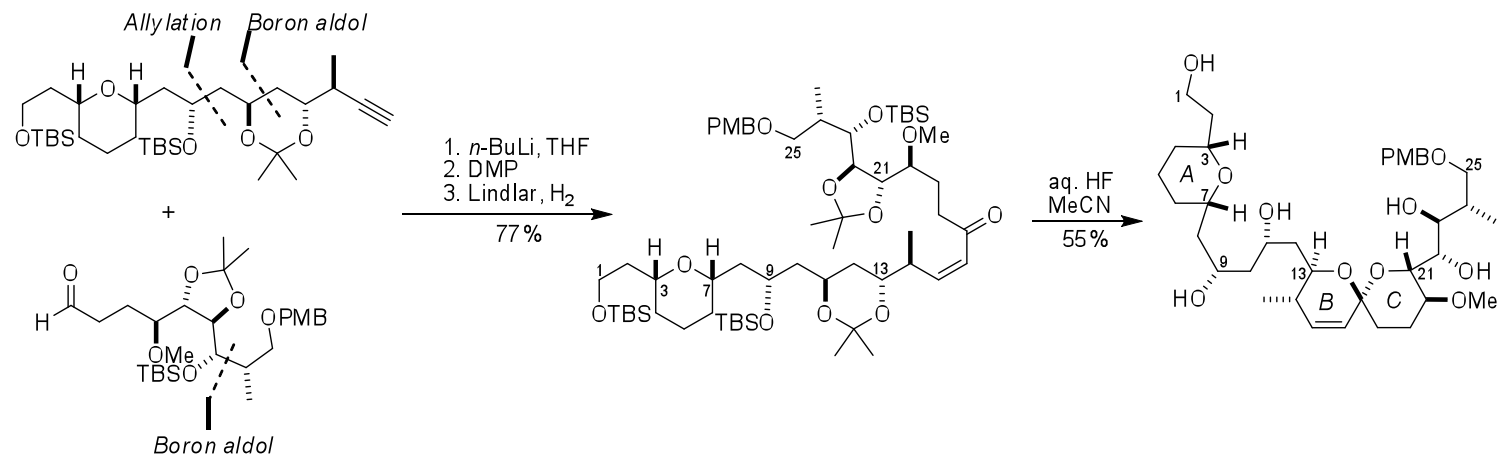
# Spirastrellolide Synthetic Considerations



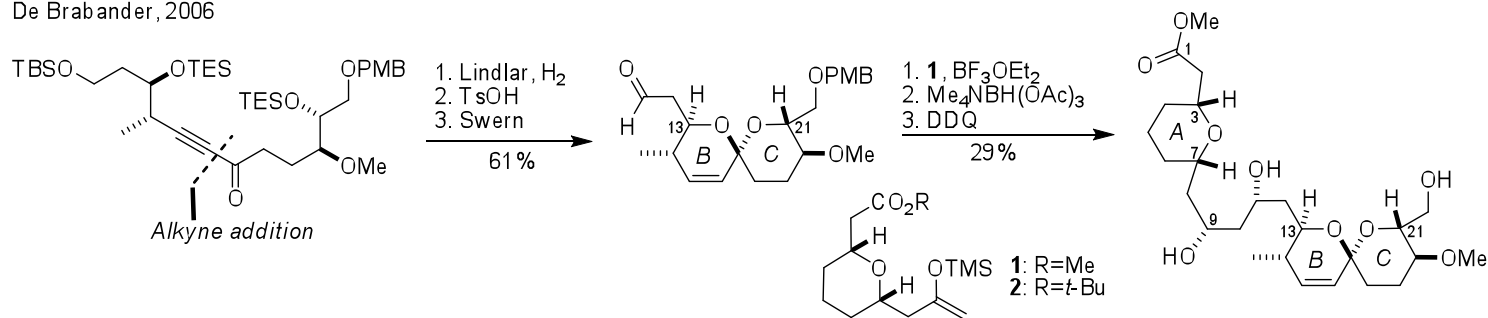
- Retrosynthetic analyses are highly dictated by previous structural uncertainties
- ABC “southern hemisphere” fragments were synthesized first by several groups
- Following final structure assignment two total synthesis were published so far: Paterson’s Spirastrellolide A (2008) and Fürstner’s Spirastrellolide F (2009)

# Synthesis of Southern Hemisphere Domain

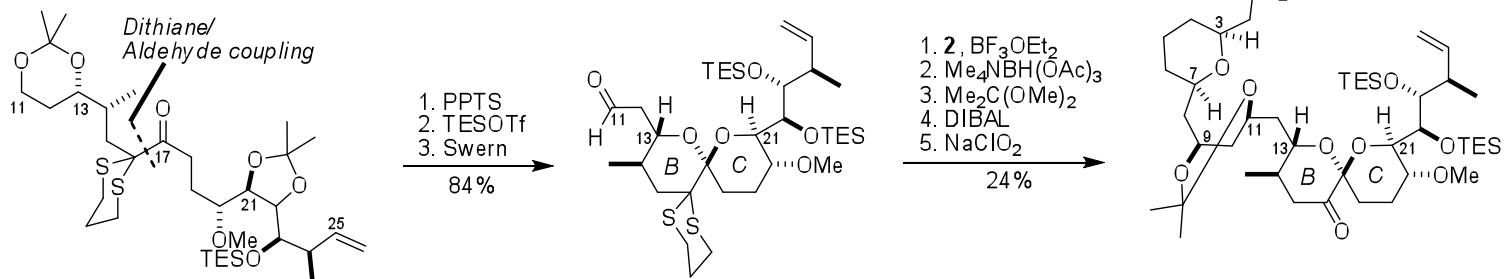
Paterson, 2005



De Brabander, 2006

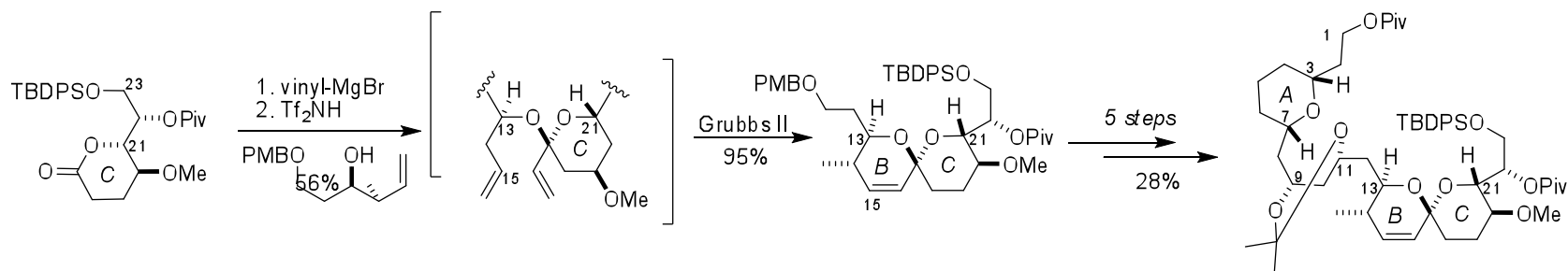


Fürstner, 2006

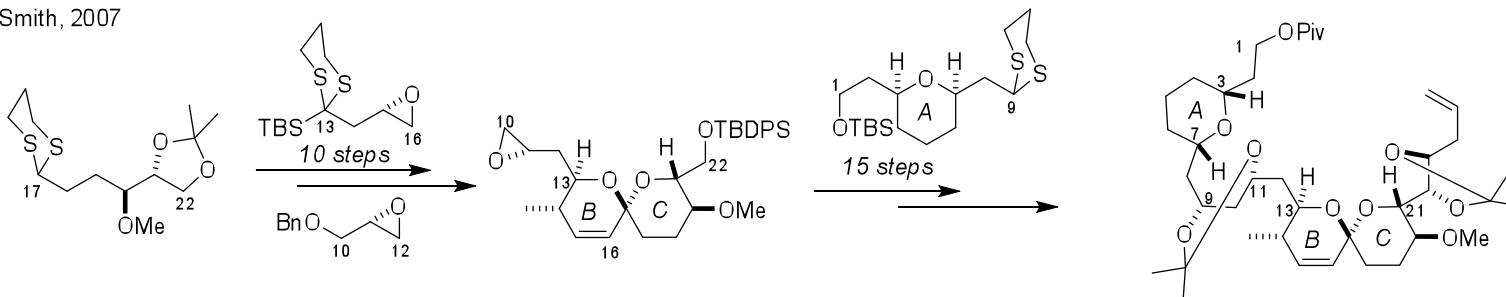


# Synthesis of Southern Hemisphere Domain

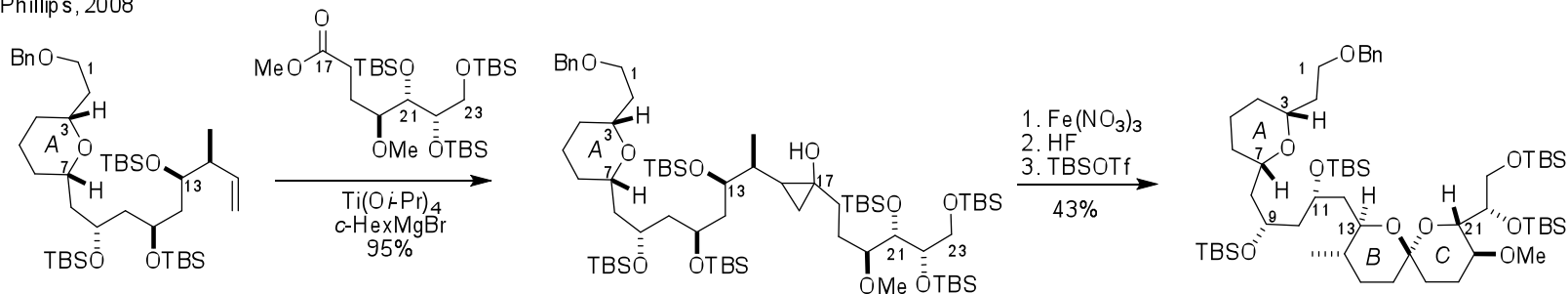
Hsung, 2008



Smith, 2007

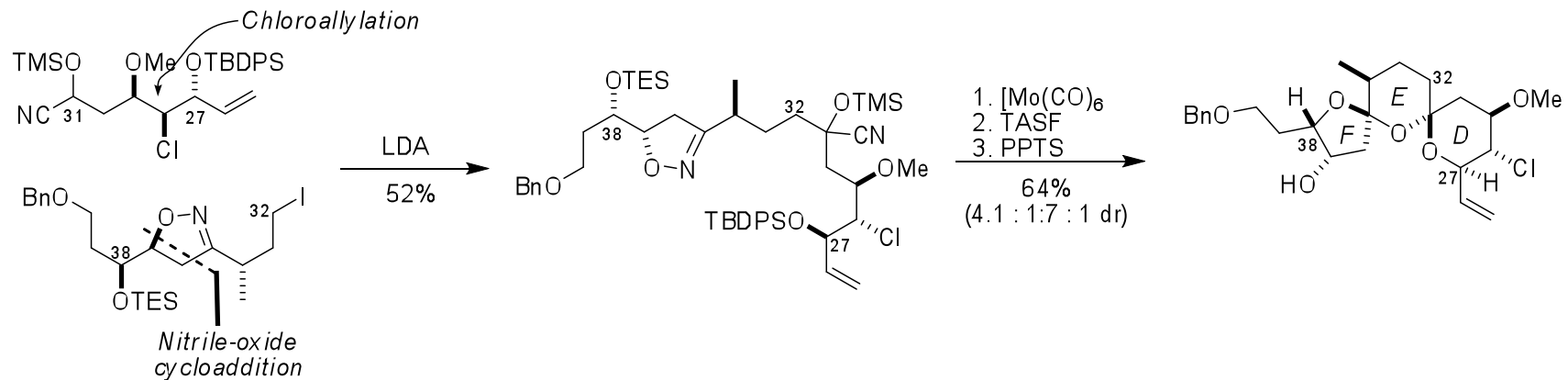


Phillips, 2008

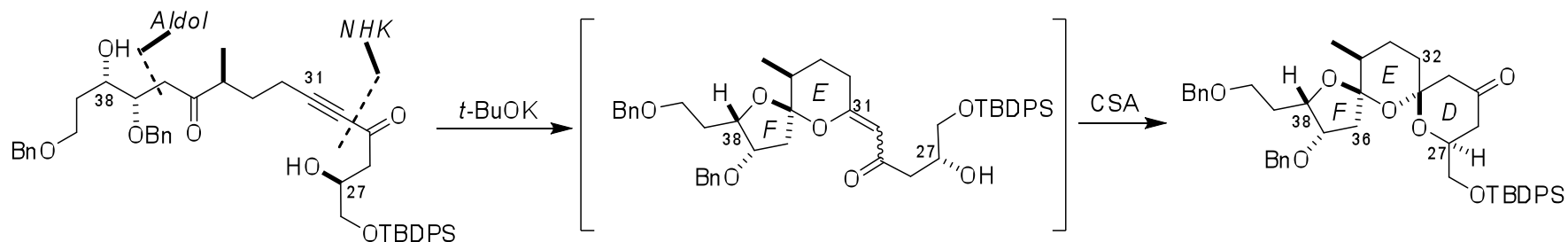


# Synthesis of Northern Hemisphere Domain

Fürstner, 2006

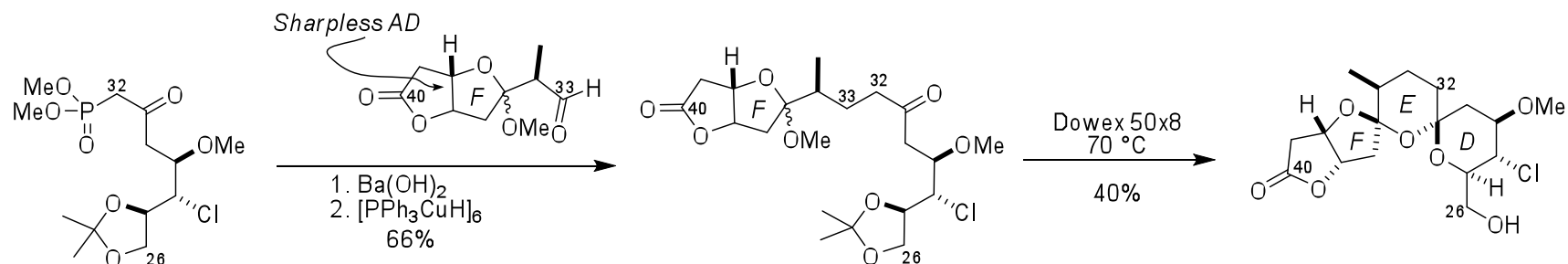


Forsyth, 2006

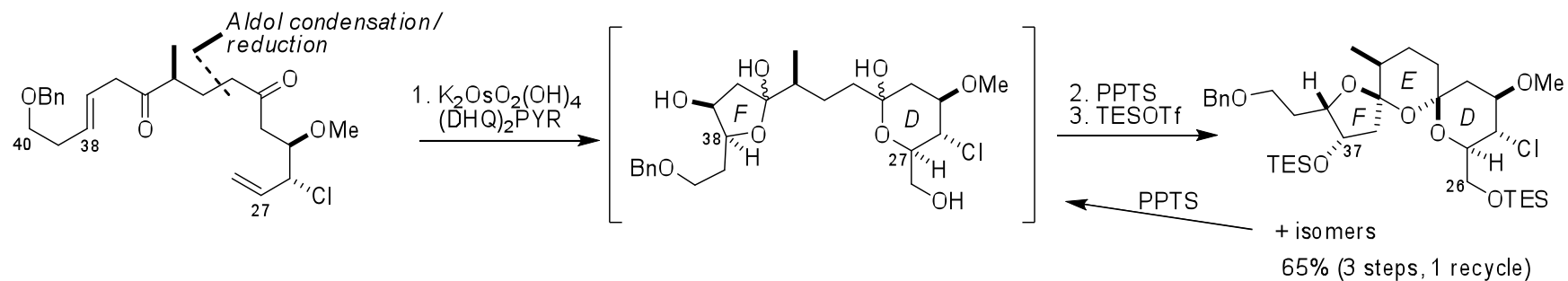


# Synthesis of Northern Hemisphere Domain

Paterson 1<sup>st</sup> Generation Approach, 2005

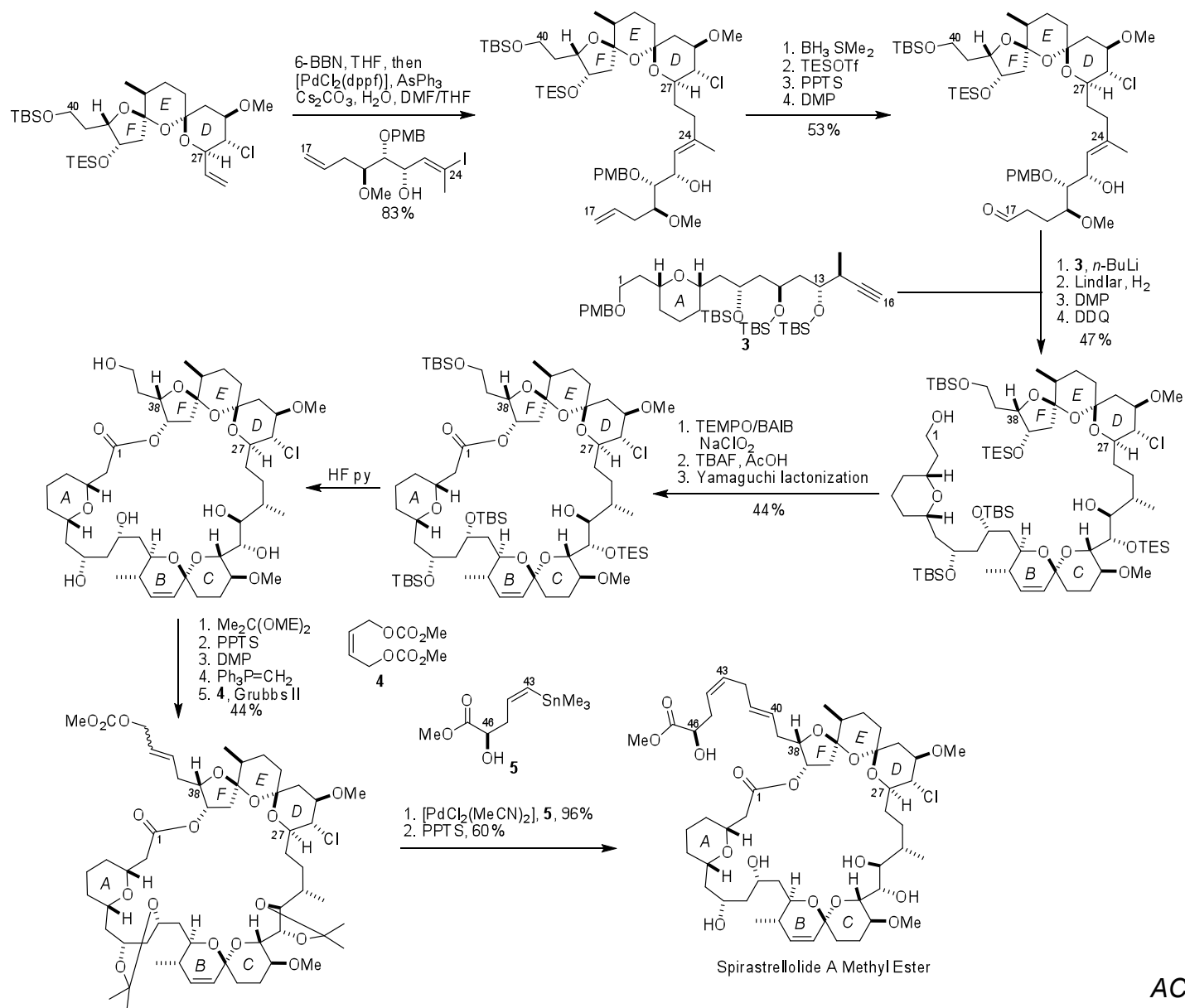


Paterson Final Approach, 2006, 2008

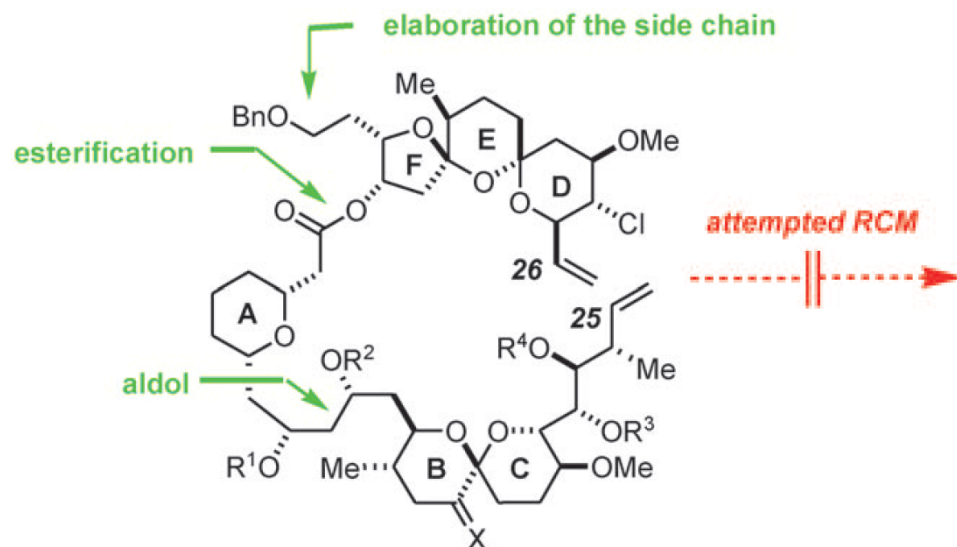




# Paterson's Synthesis of Spirastrellolide A



# Fürstner's Synthesis of Spirastrellolide F



**Scheme 1.** Summary of our “first-generation” approach to the spirastrellolides.<sup>[10-13]</sup> The formation of the C25–C26 bond was not only attempted by ring-closing metathesis (RCM) but also in an intermolecular setting through olefin cross-metathesis. Bn = benzyl.

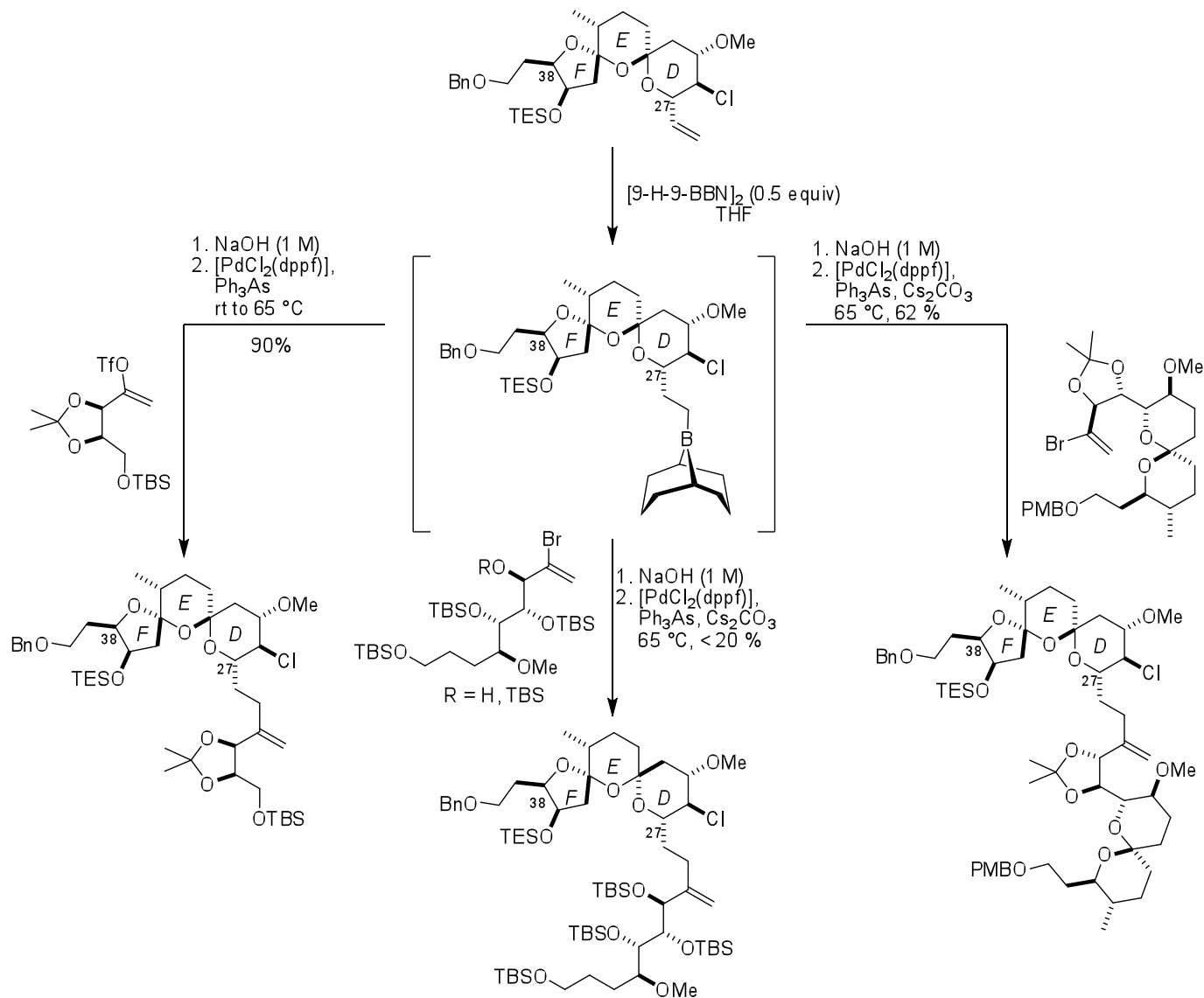
-RCM has been attempted on >30 different precursors!!!  
⇒ Chlorinated bis(spiroketal) is too bulky

-DEF fragment is sensitive and poised to furan formation  
⇒ Southern half should be modified

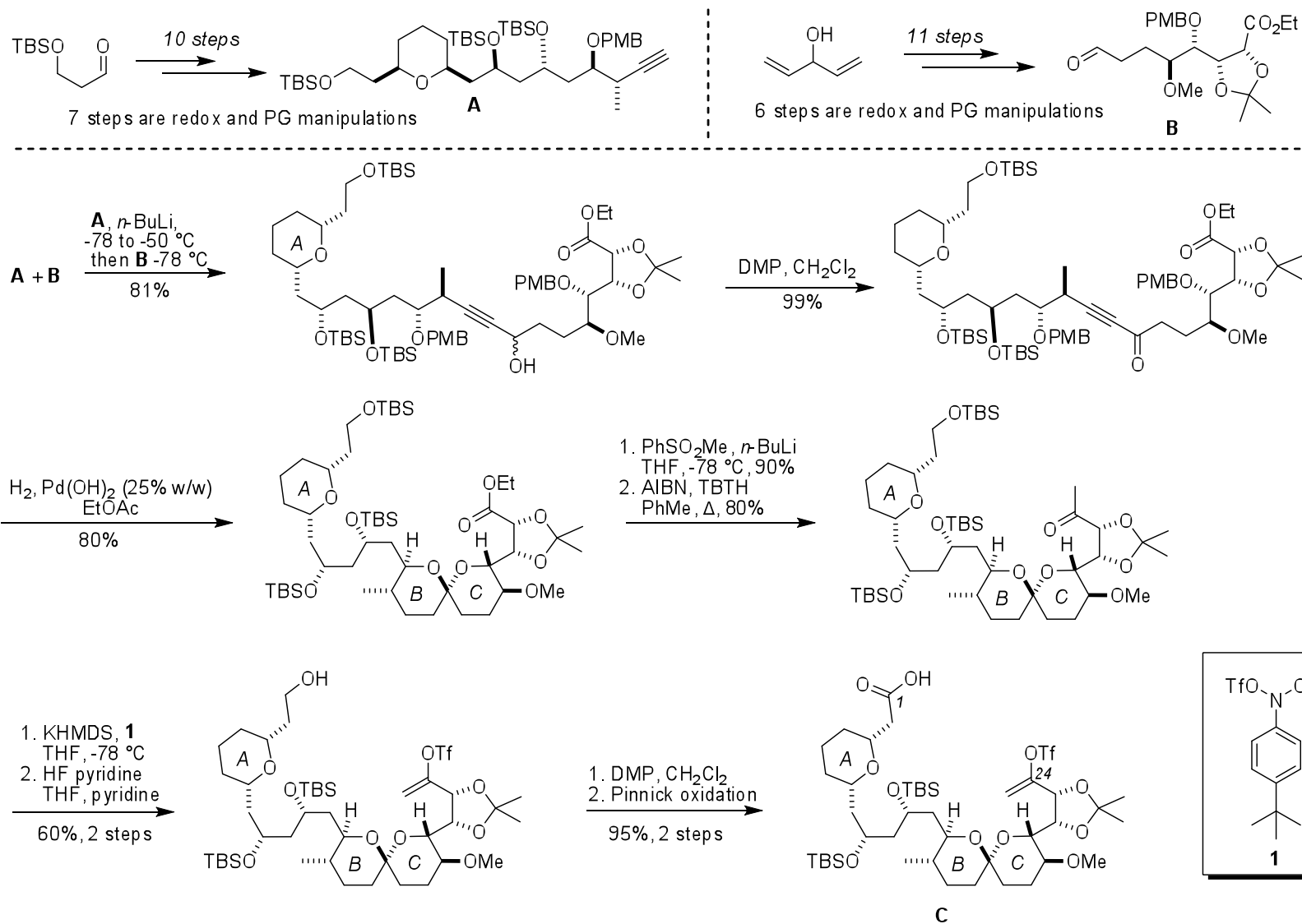
- Model system for the alkyl-Suzuki reaction needs to be investigated.

# Fürstner's Synthesis of Spirastrellolide F

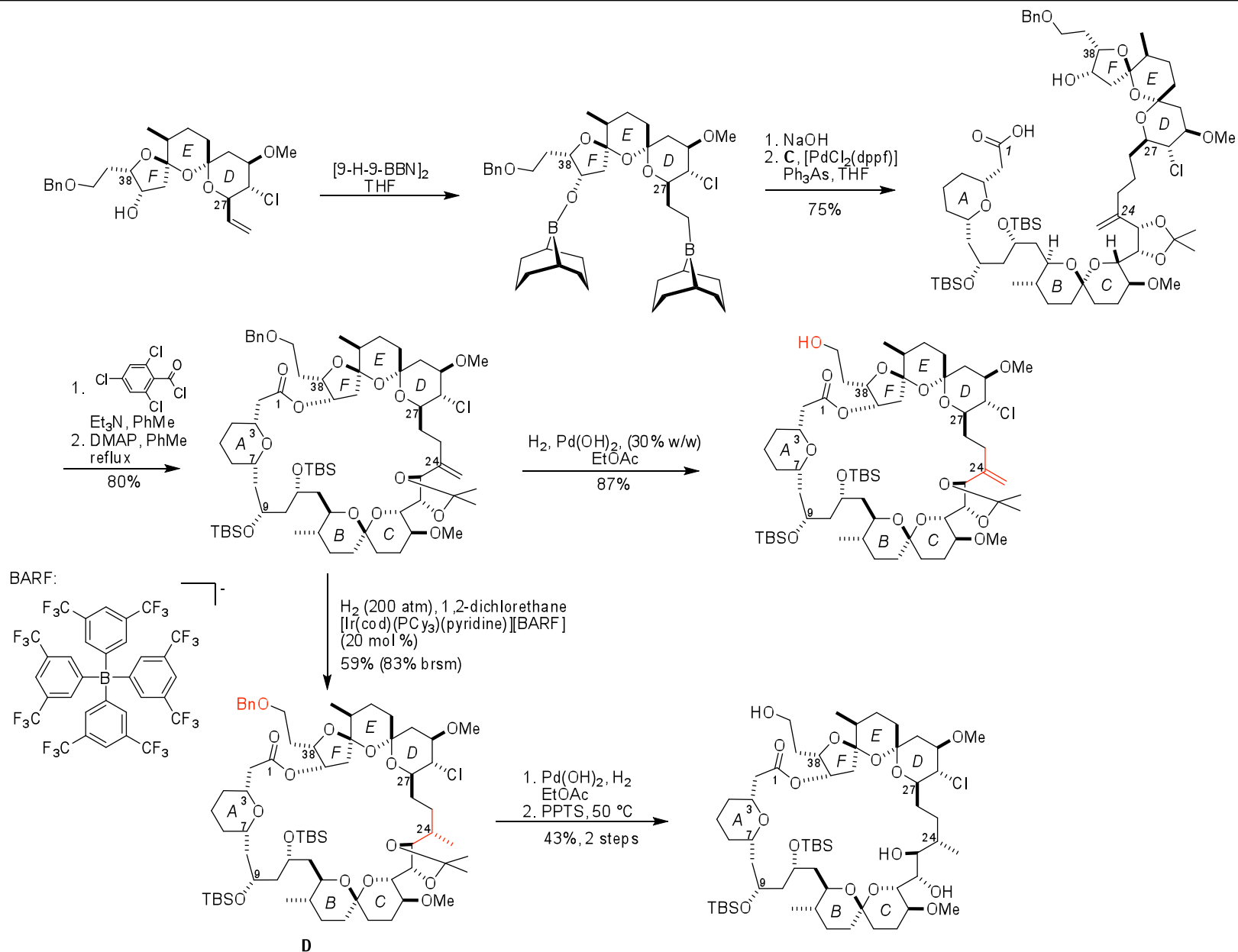
## Model Studies on Suzuki Coupling



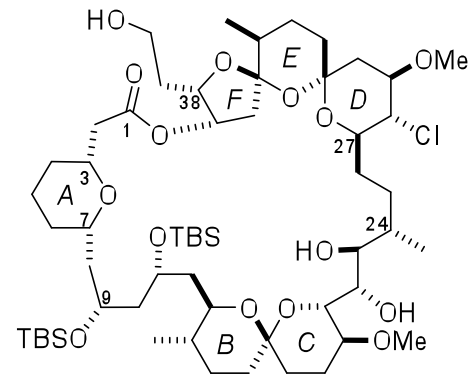
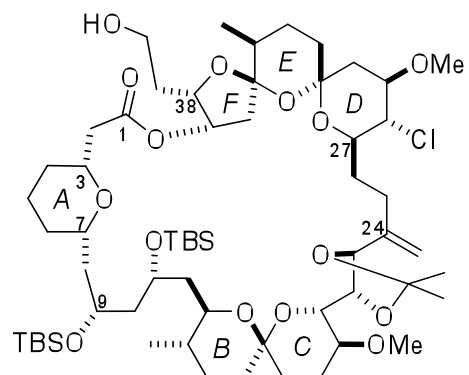
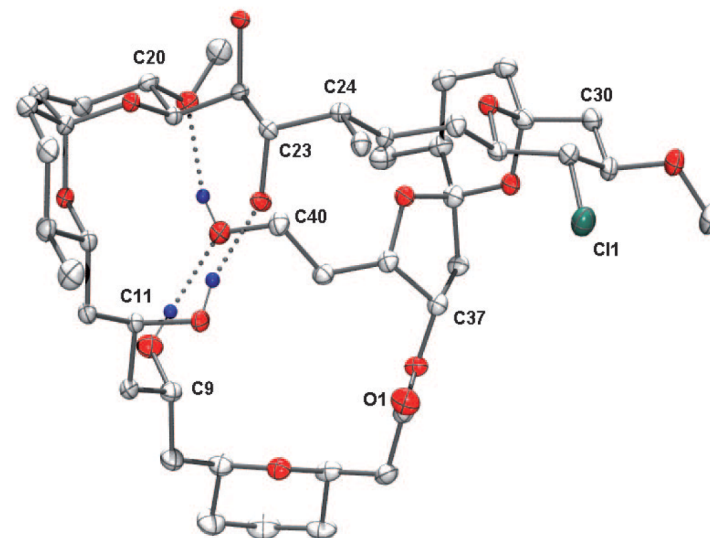
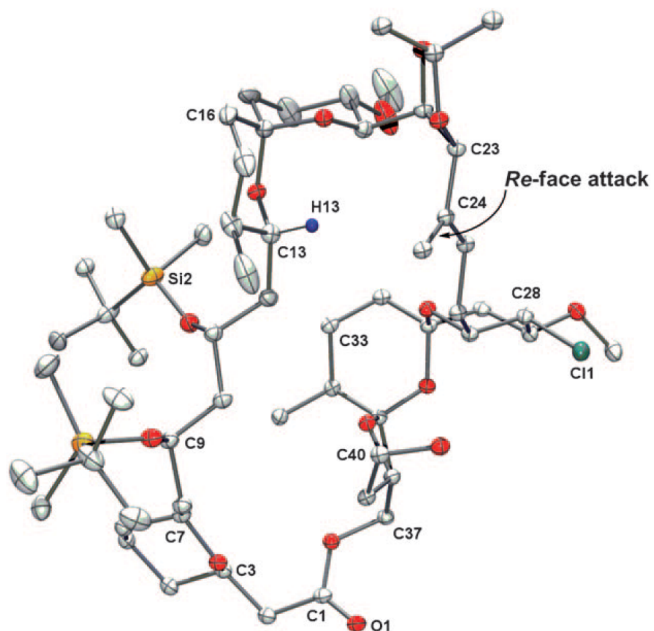
# Fürstner's Synthesis of Spirastrellolide F



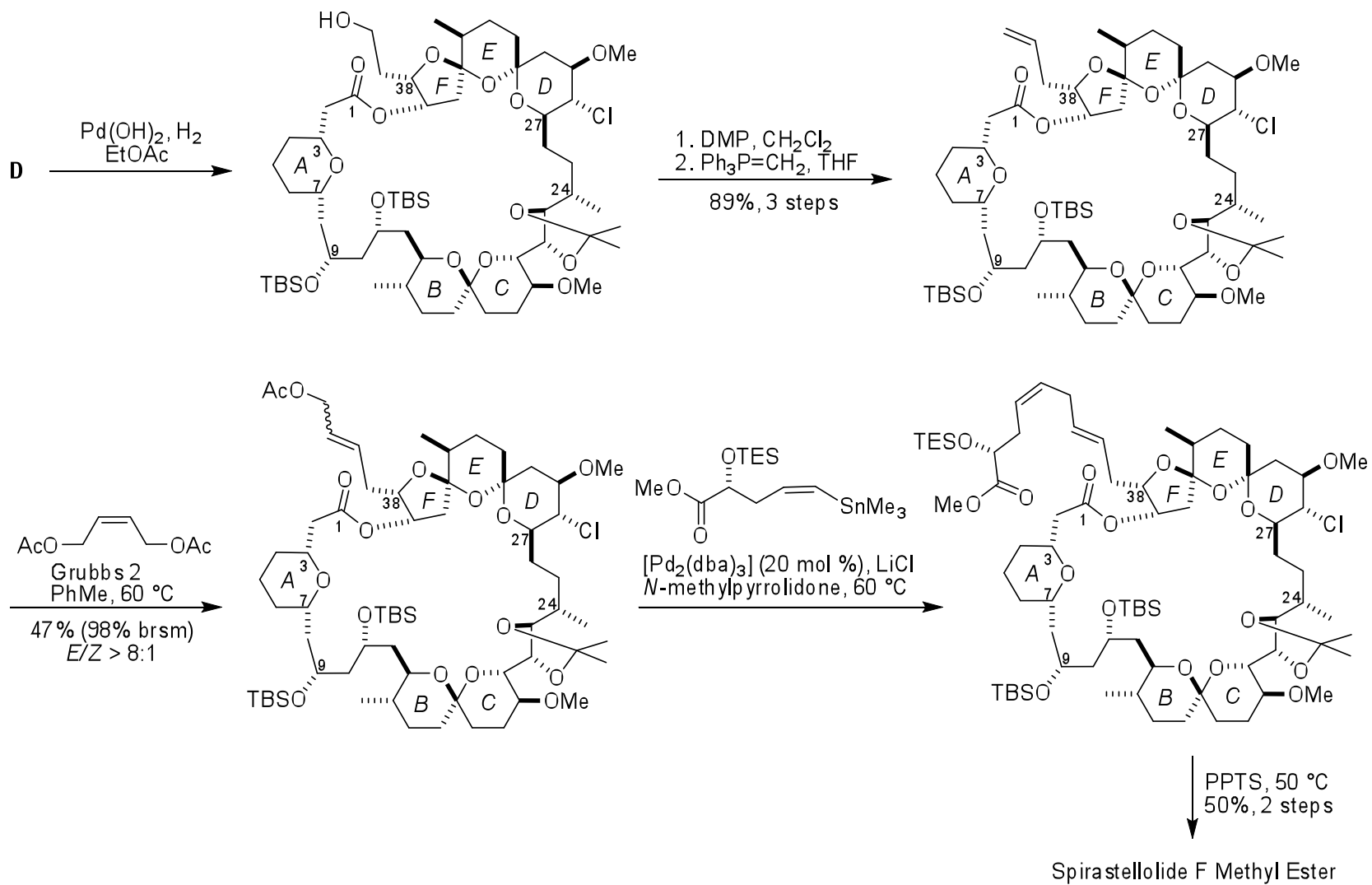
# Fürstner's Synthesis of Spirastrellolide F



# Fürstner's Synthesis of Spirastrellolide F



# Fürstner's Synthesis of Spirastrellolide F



# Conclusions

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-The first total synthesis of the potent mitotic inhibitor spirastrellolide F methyl ester has been accomplished in a highly convergent manner.

-Alkyl-suzuki coupling and Yamaguchi lactonization were used to stitch north and south hemisphere fragments together after numerous RCM attempts failed.

-The synthesis include numerous highly diastereoselective steps, including substrate controlled late stage hydrogenization to install C24 stereocenter.

-Further chemical and biological studies of this molecule are underway in the Fürstner group.