Total Synthesis of Callipeltoside A

Denmark Group Meeting

Aaron Bailey

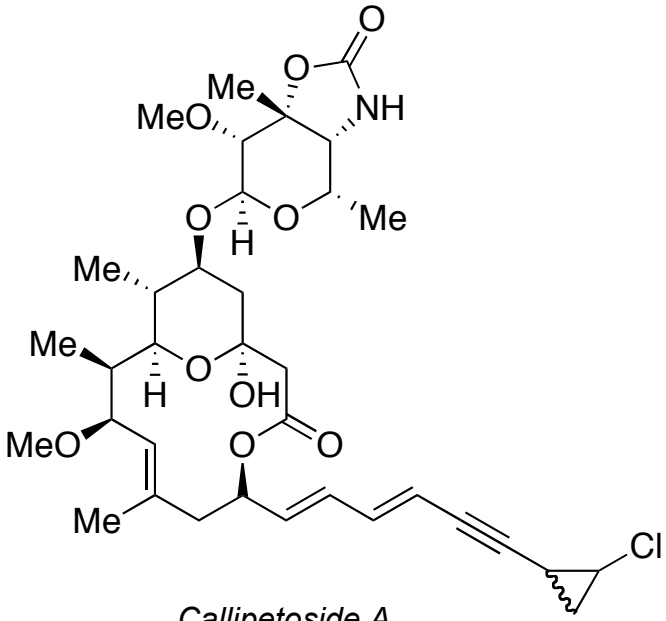
September 23, 2008

Callipeltoside A

- First isolated from Lithistid sponge in 1996

- Exhibits moderate cytotoxicity against human bronchopulmonary non-small-cell lung carcinoma

- Extensive NMR experiments were used to assign the relative stereochemical relationships in macrolactone and sugar regions

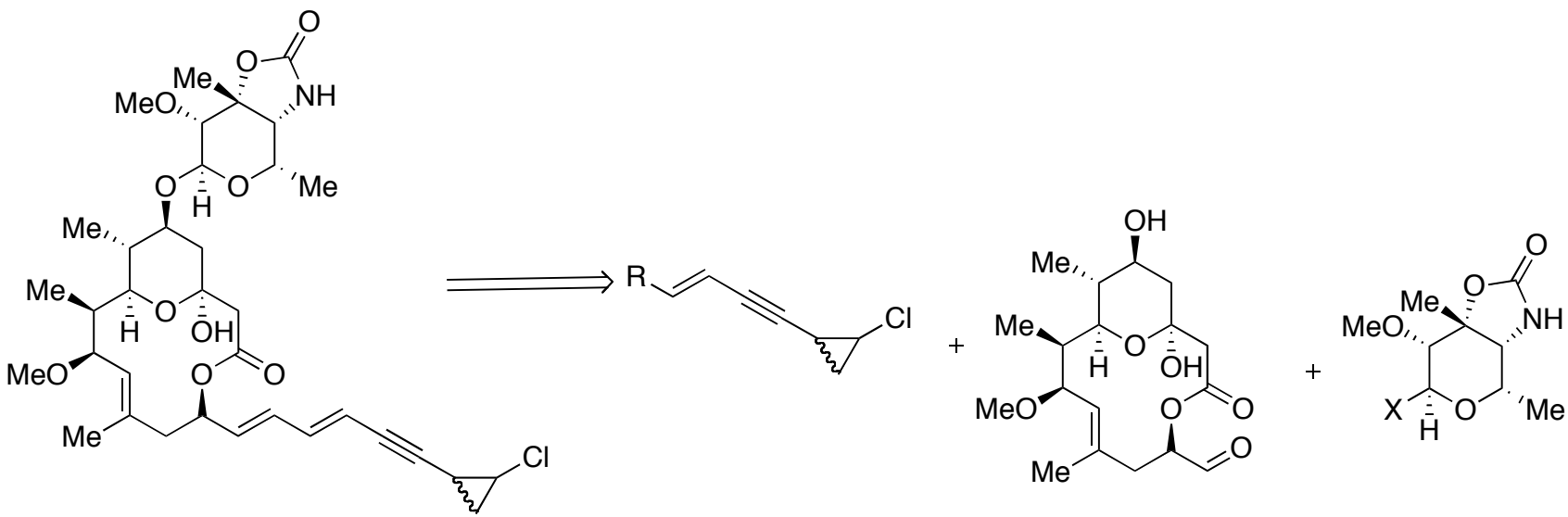


Callipetoside A

Synthetic Rationale

- Only able to isolate from sponge in small quantities (~35 mg total studied since first isolation)
- Relative stereochemistry of cyclopropyl moiety unclear from NMR experiments
- SAR studies from diastereomers
- Four total syntheses reported to date: Evans (02), Trost (02), Patterson (03), Panek (04)

Common Retrons

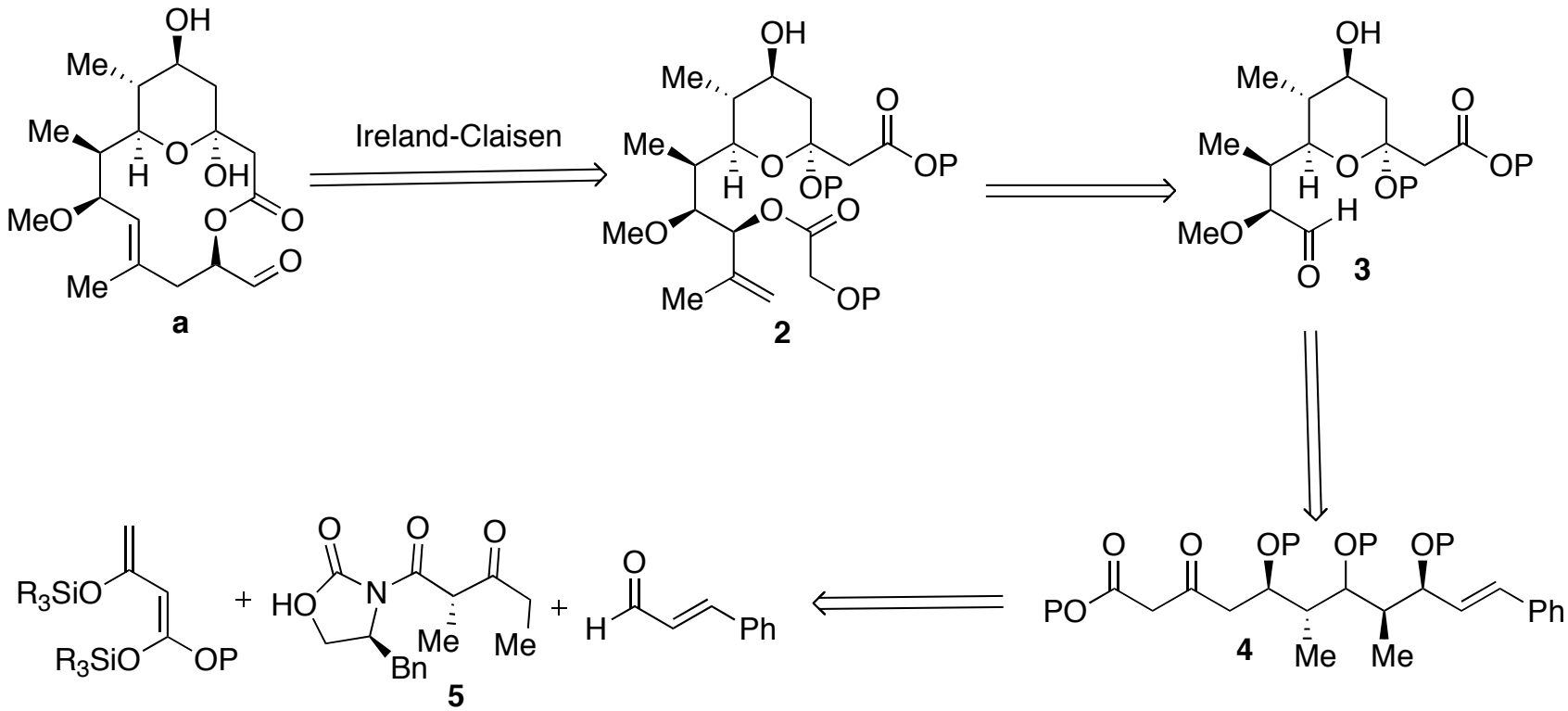


Same disconnects proposed in each total synthesis: Horner-Wadsworth Emmons Olefination, and glycosylation to append the sugar

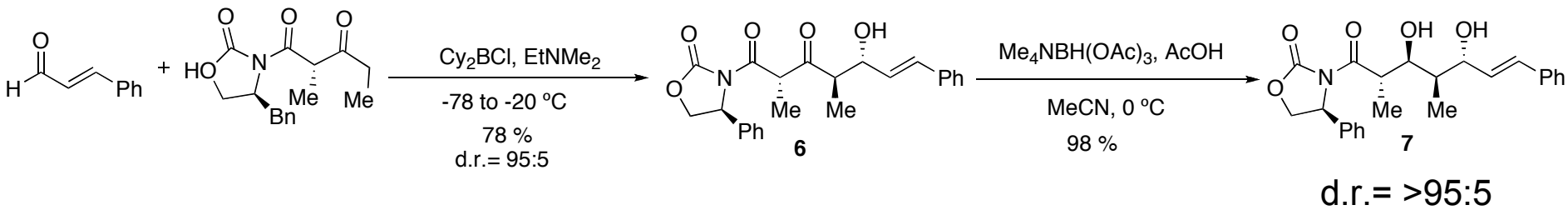
Each total synthesis demonstrates a unique method of preparing each structure utilizing a variety of different known synthetic transformations

Evans total synthesis

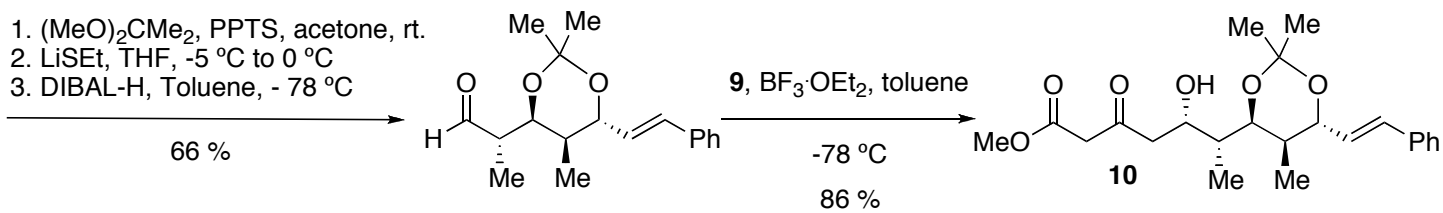
Retrosynthetic Analysis for macrolactone **a**



Synthesis of Macrolactone



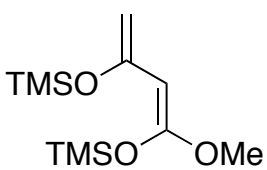
d.r.= >95:5



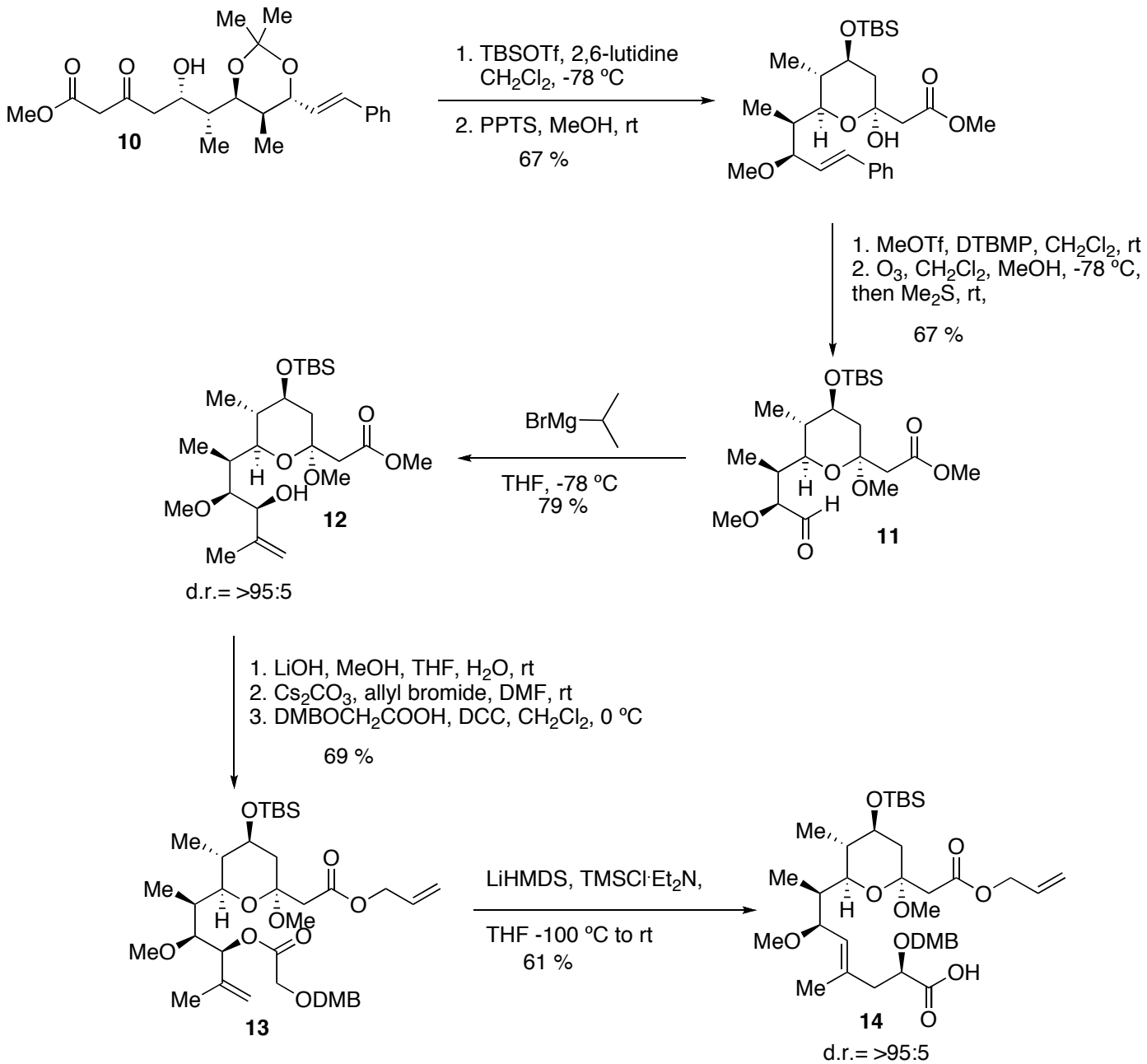
d.r.= >95:5

Chan's diene utilized to synthesize **10**, under Felkin control

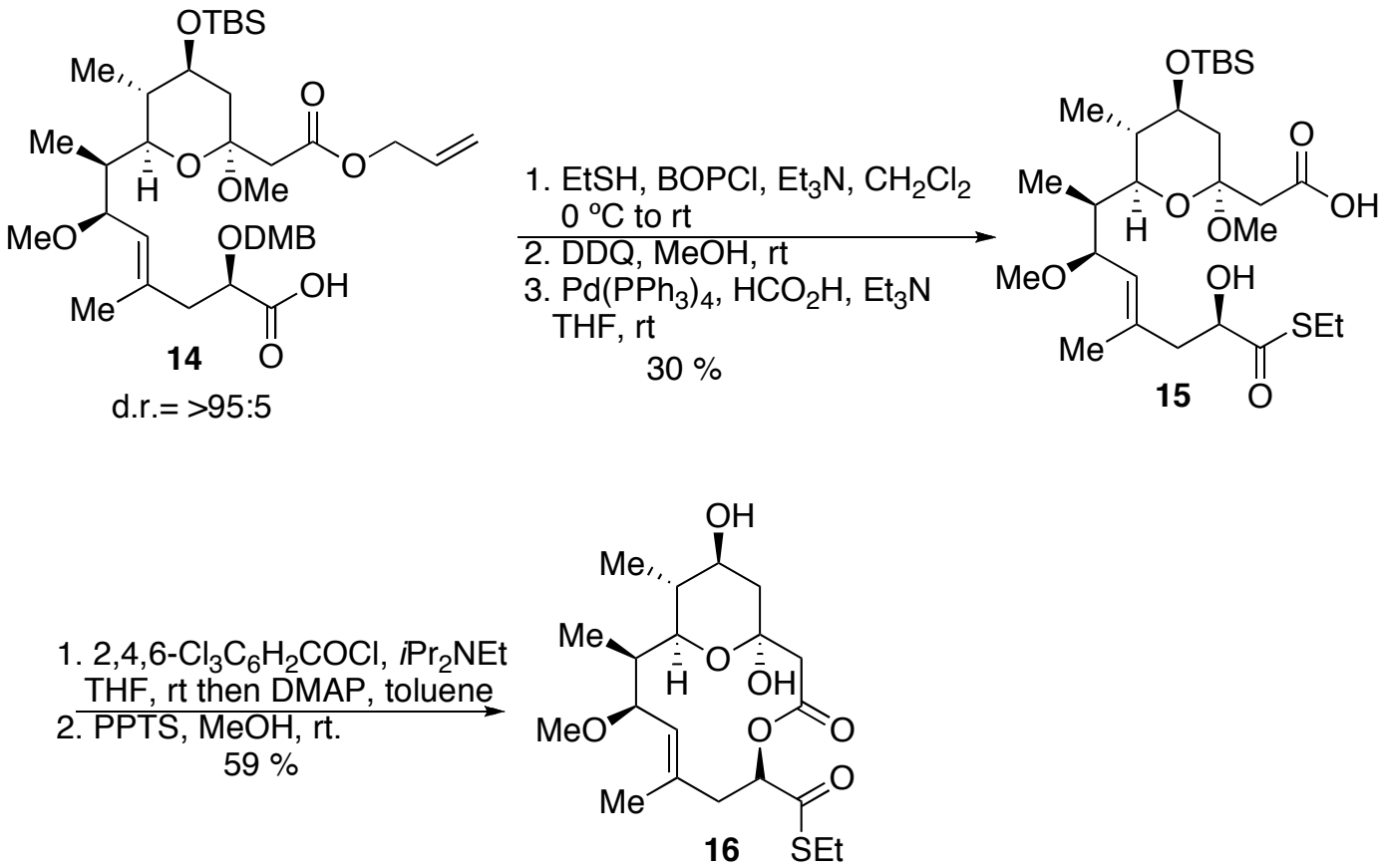
9=



Ireland-Claisen Rearrangement



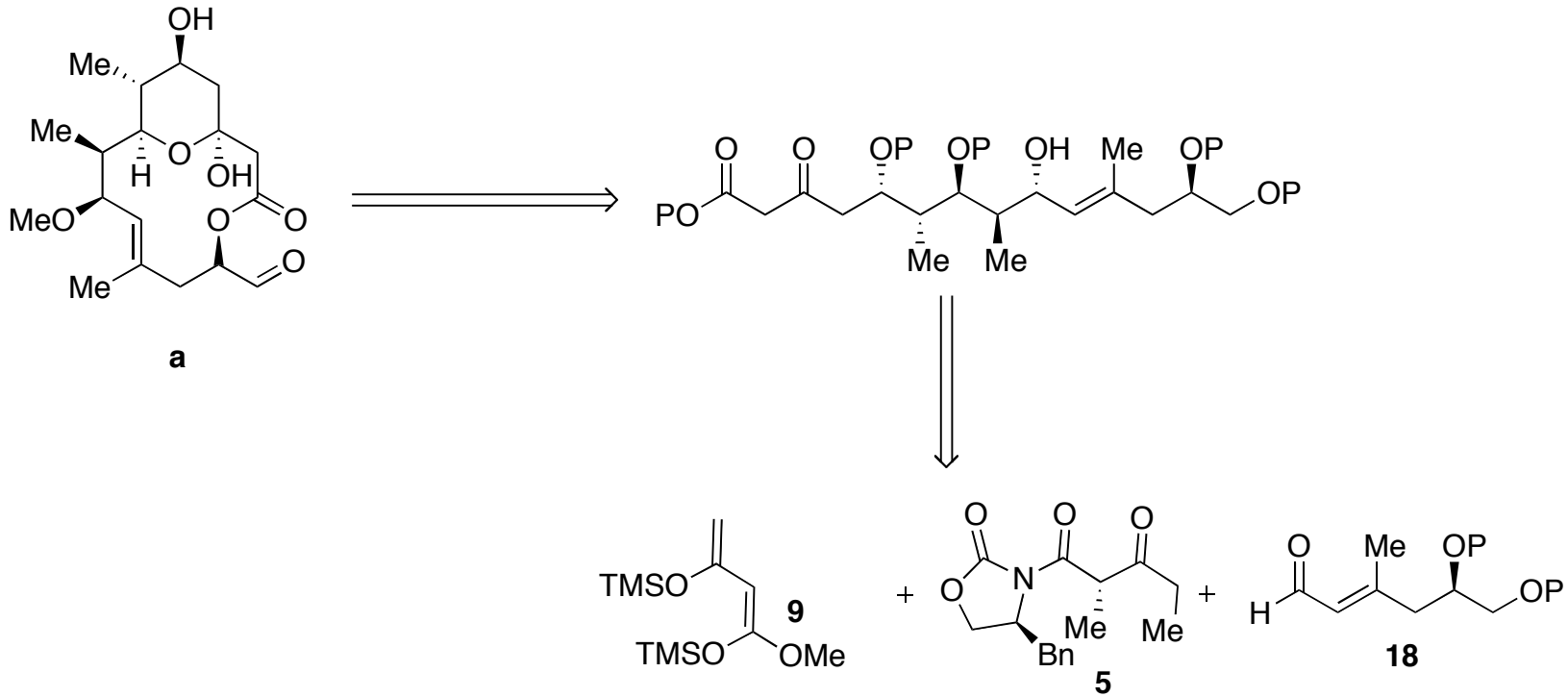
Completion of Macrolactone



20 steps to obtain desired macrolactone

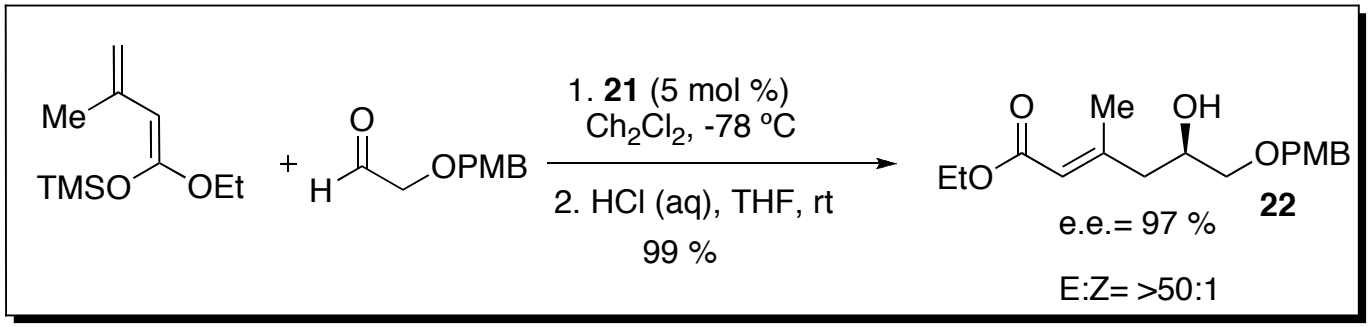
Abundance of functional group manipulations

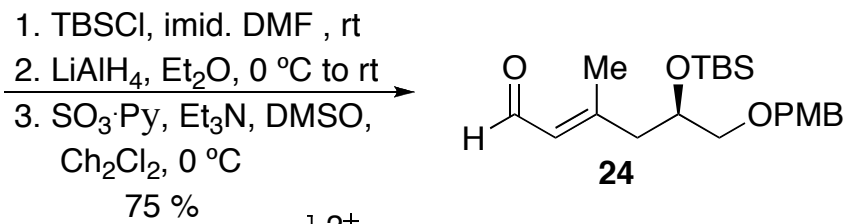
Second Synthesis of Macrolactone



- First route required many functional group manipulations
- Revised route eliminates requirement of protecting group manipulations

Second Synthesis of Macrolactone





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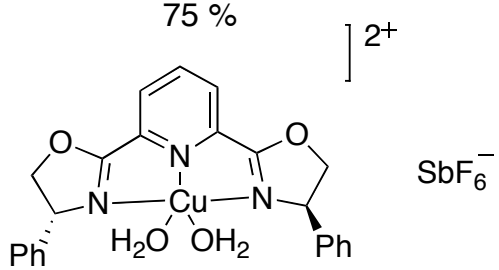
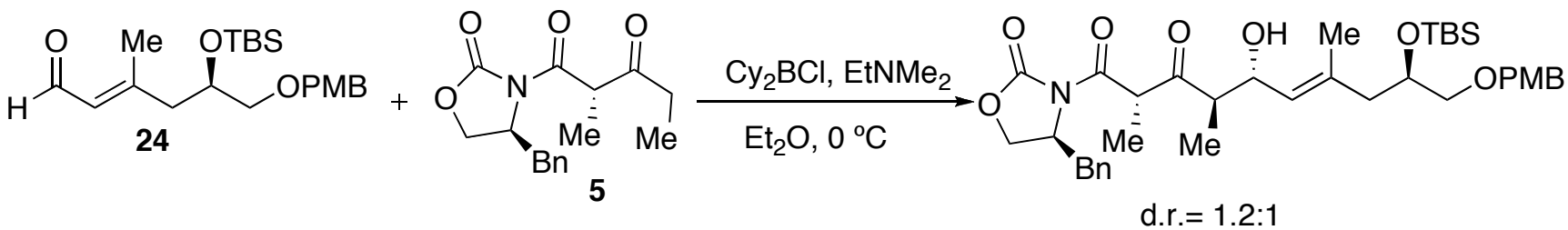
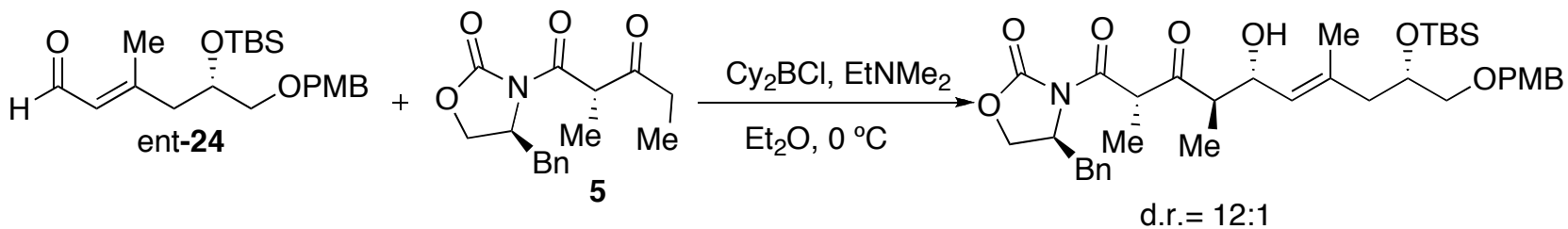


- Initial reactions conditions provided low yields and poor olefin selectivity (27 % yield, 80 % ee, 11:1 E/Z rapid addition)
- Optimal reaction conditions were achieved by the slow addition of both reagents.

Stereochemical Complications in Aldol Reaction

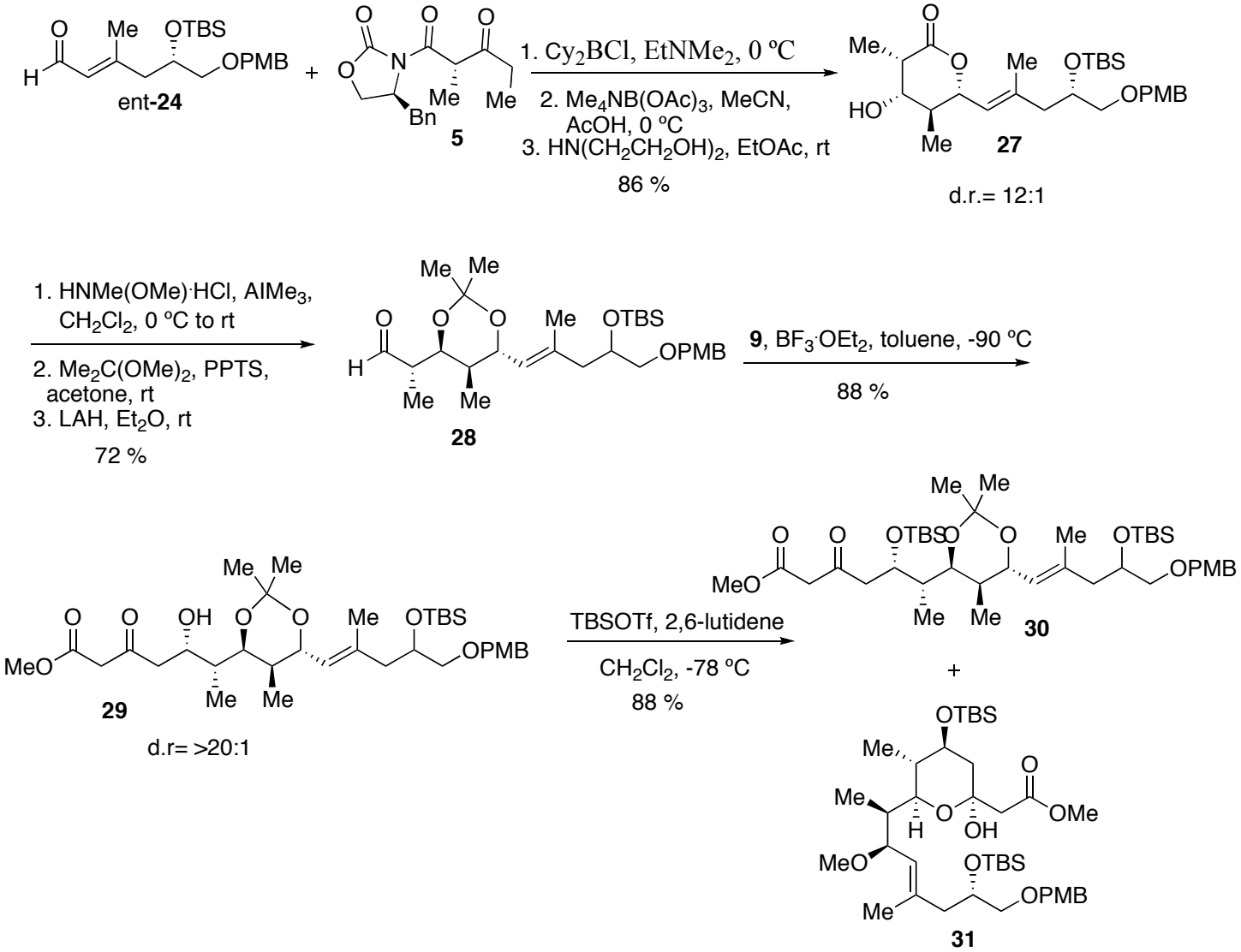




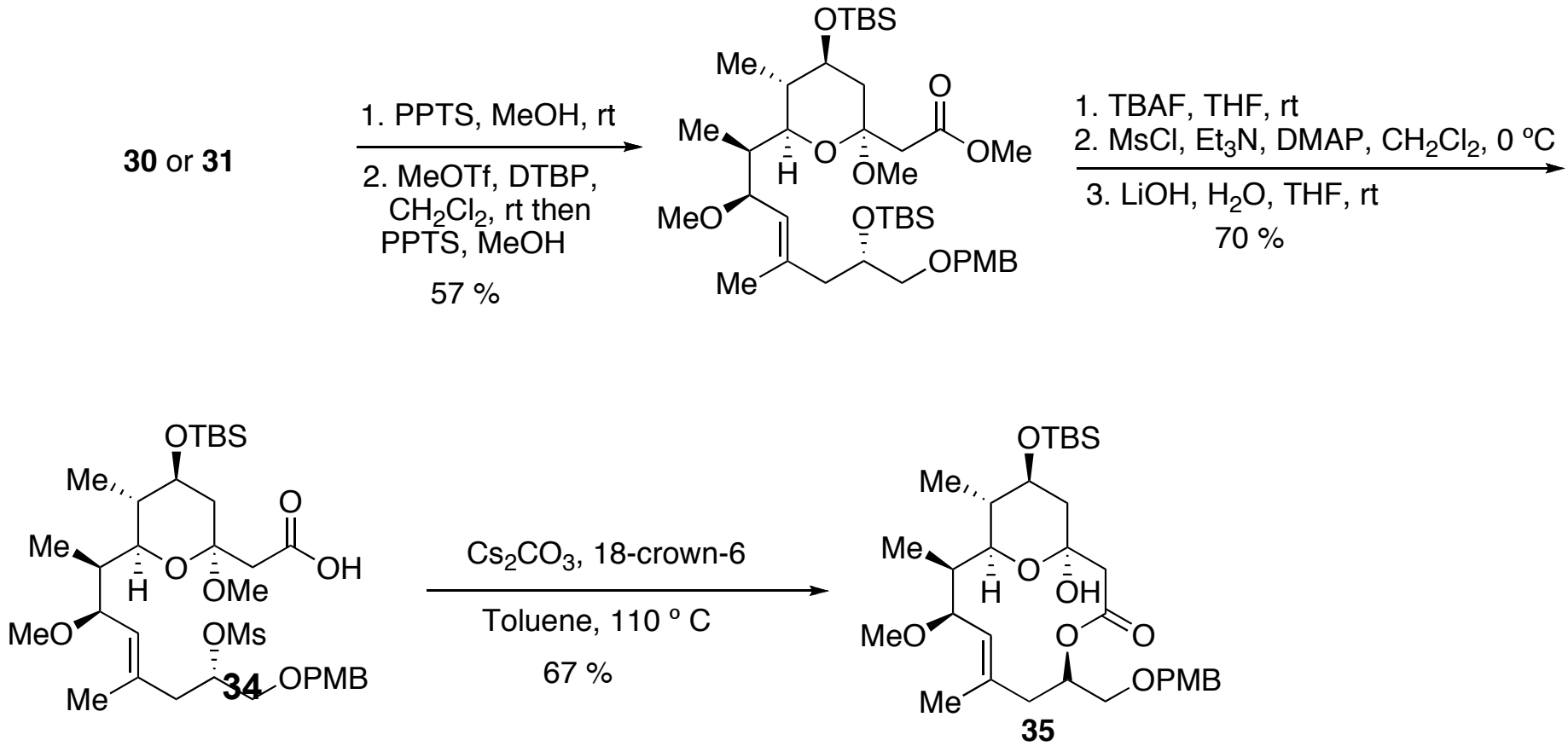
•Using the enantiomer of **24** leads to 10 fold improvement in diastereoselectivity.

•Different conditions tested determined effects of remote directing groups.
O-silyl group necessary, but PMB protecting group not required

Completion of Macrolactone



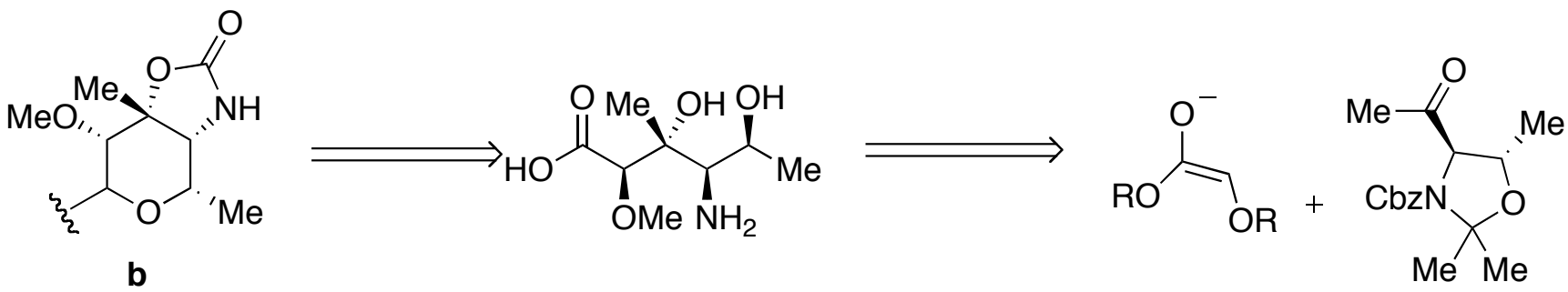
Mitsunobu to the Rescue



- Modified Mitsunobu conditions afforded desired stereochemistry
- No isolation of product **35** when starting from alcohol derivative of **34**

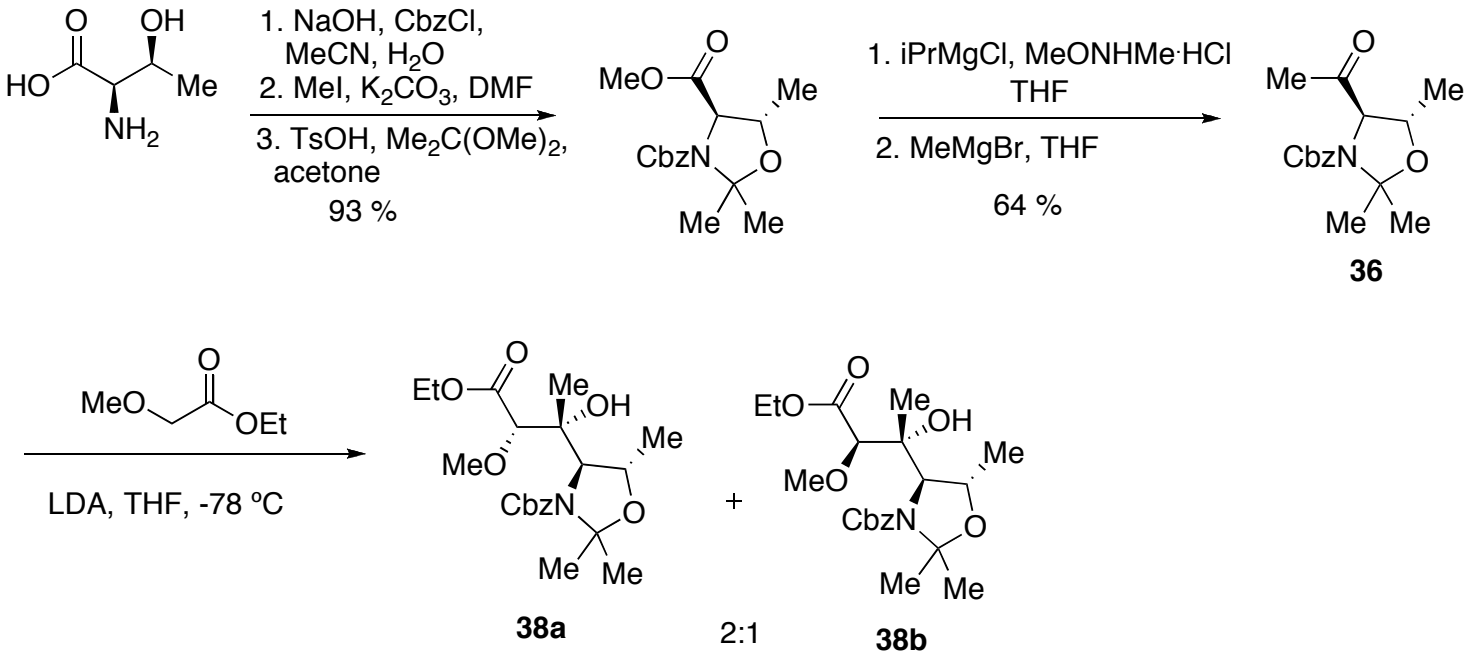
Evans Total Synthesis

Retrosynthetic analysis for callipeltose sugar



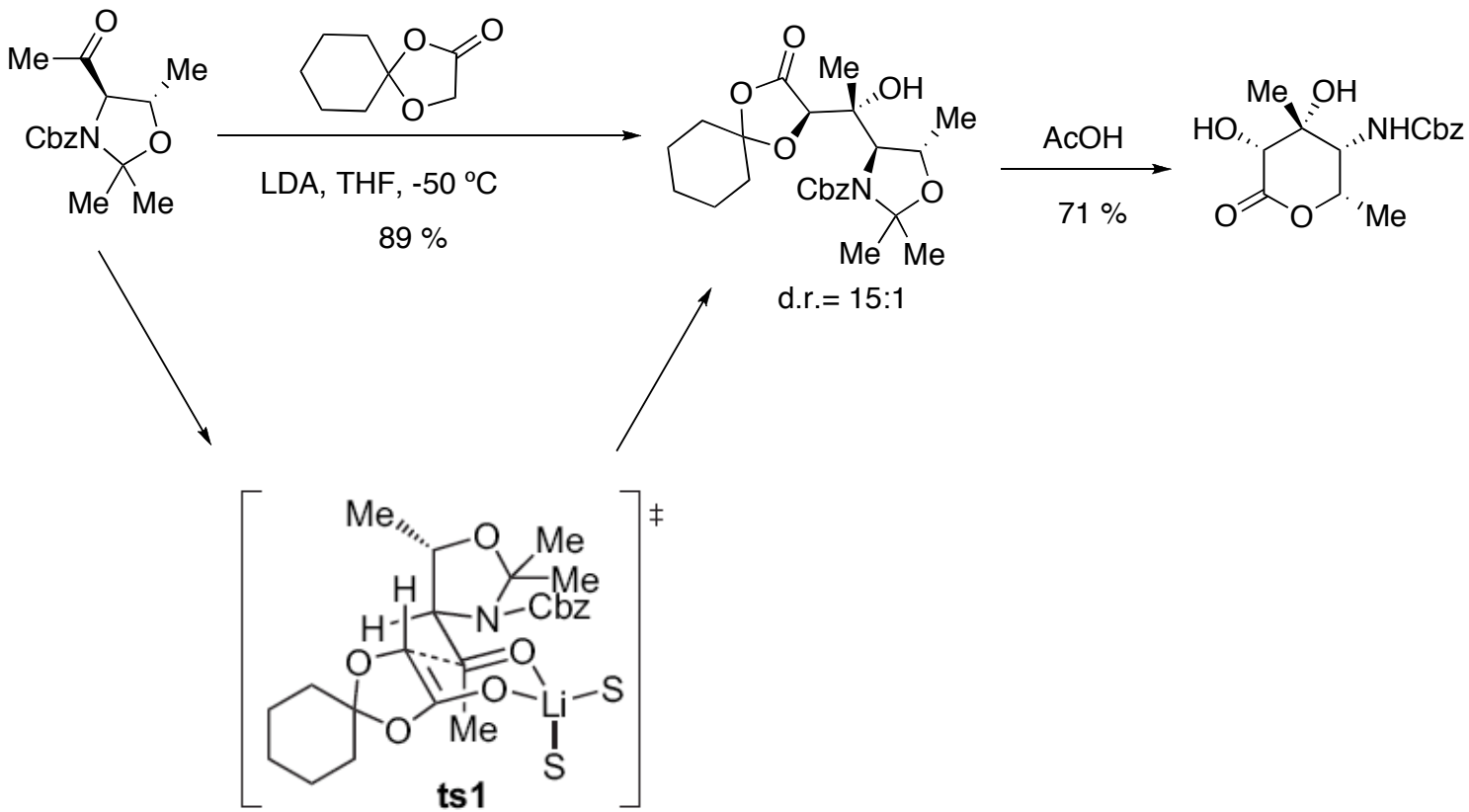
- Synthetic challenges: installation of stereocenters
- Enolate chemistry can be used to obtain high diastereoselectivity

Callipeltose from D-Threonine



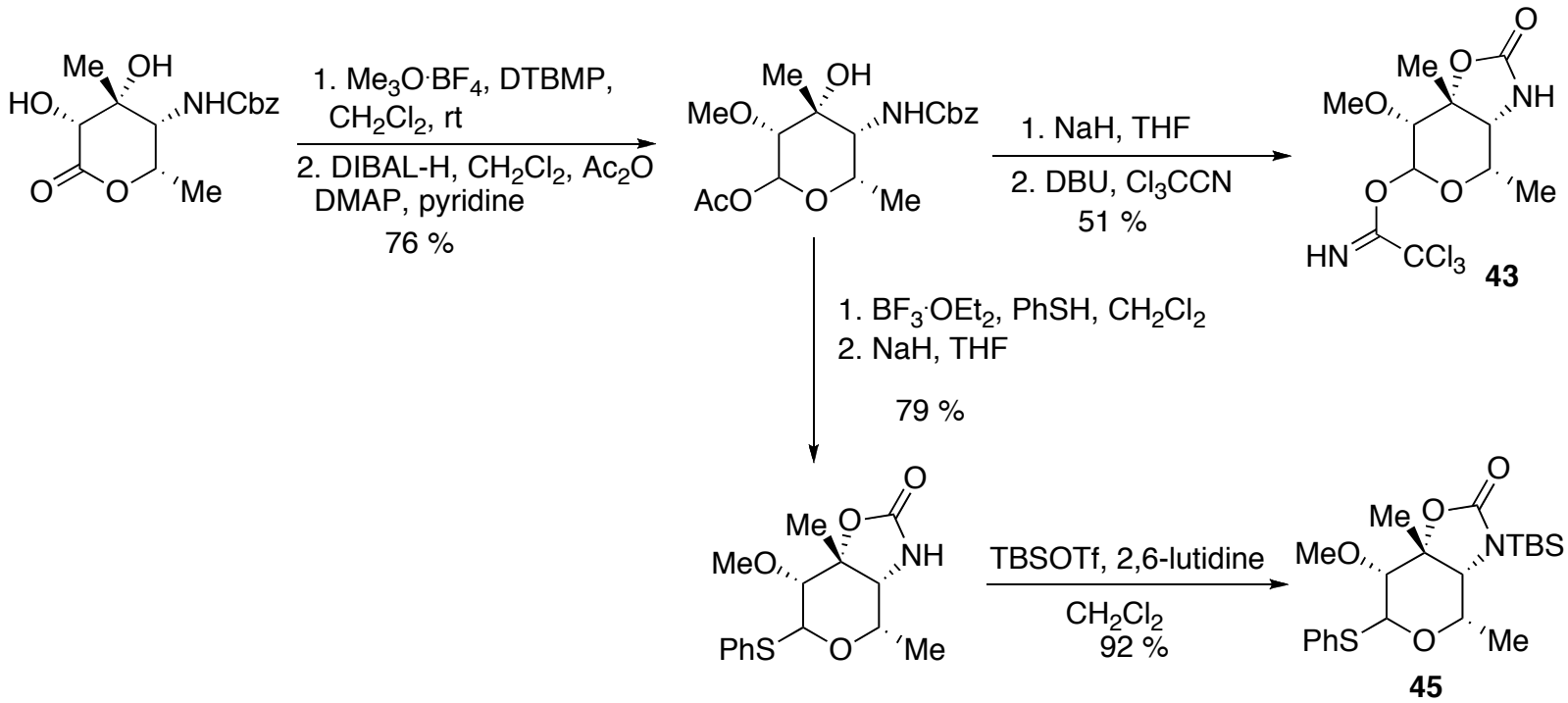
- Obtained poor d.r. due to formation of undesired enolate
- Unfortunately, the selectivity could not be improved upon by using alternative bases

Formation of Desired Diastereomer



By utilizing a cyclic ester as the starting material the desired product was obtained in good yield and high selectivity

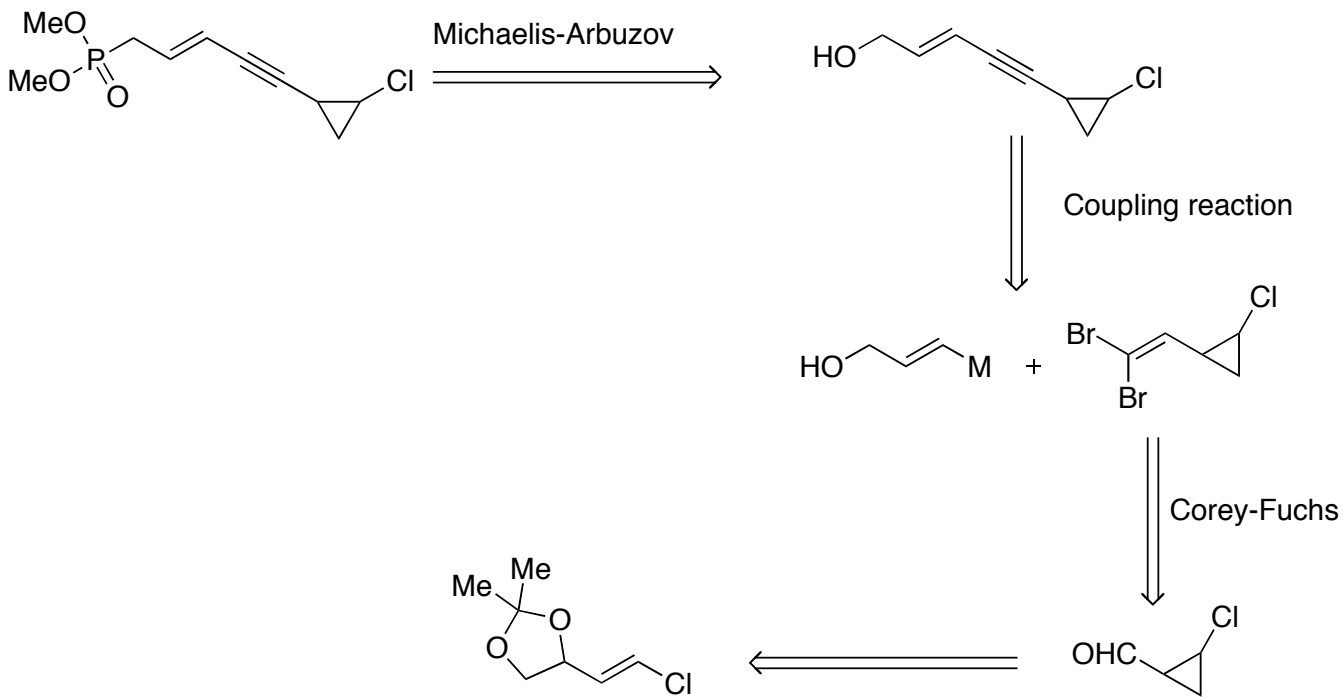
Completion of the Sugar Ring



Synthesized two different sugar moieties to test in the glycosylation step

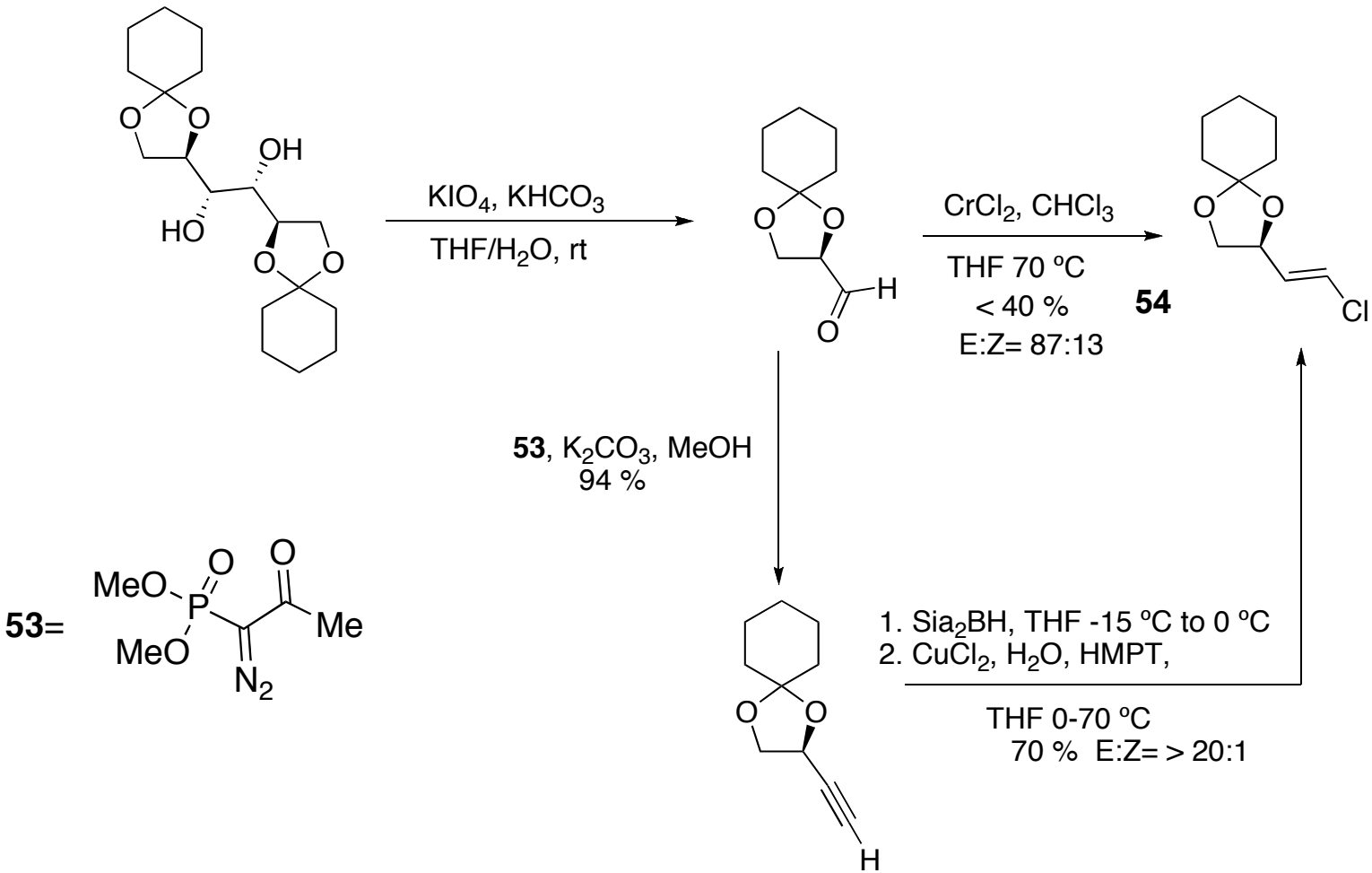
Evans Total Synthesis

Retrosynthetic Analysis of Side Chain



Needed to prepare both enantiomers to determine absolute stereochemistry of cyclopropane moiety

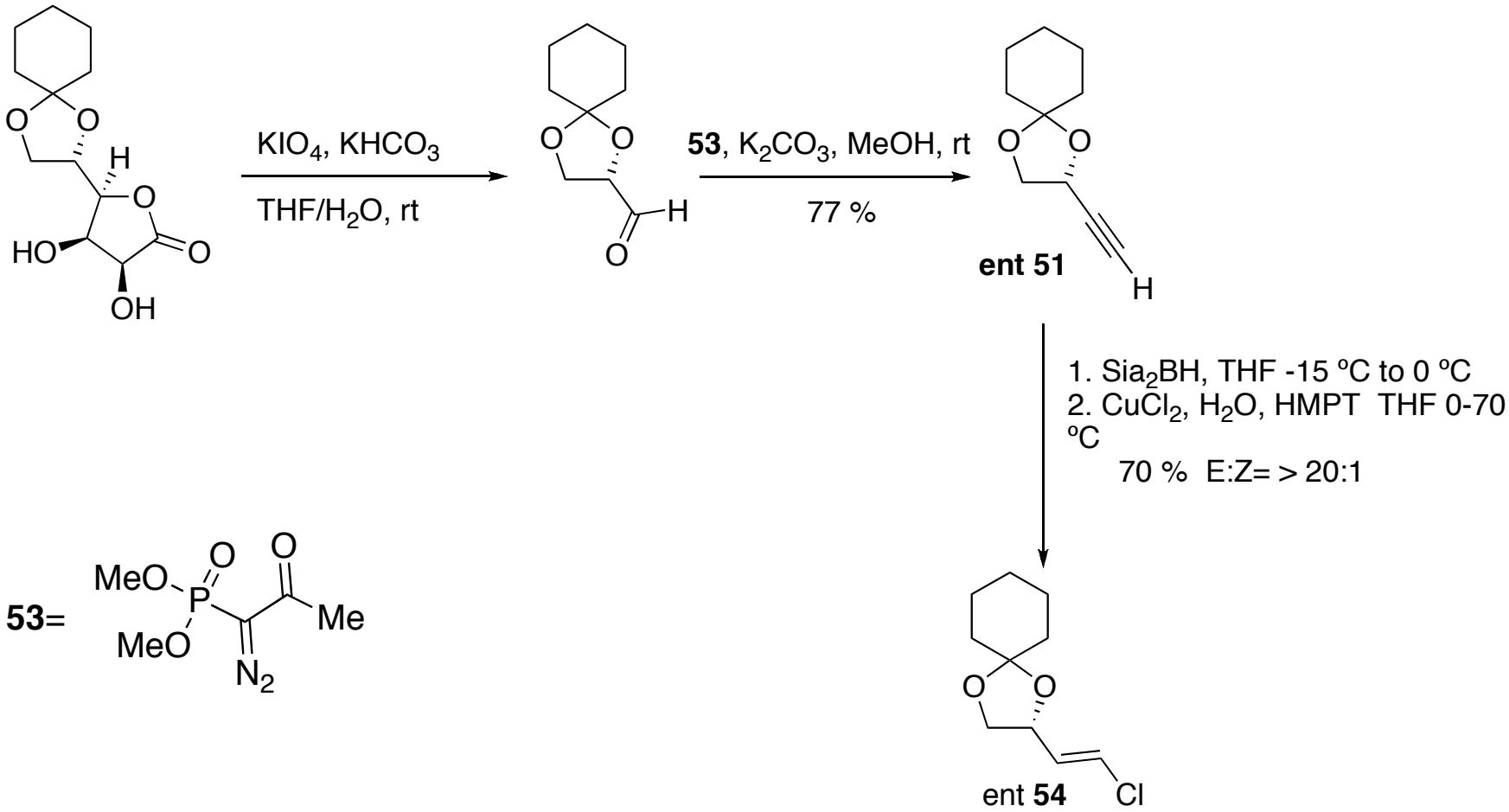
Synthesis of Side Chain From D-Mannitol



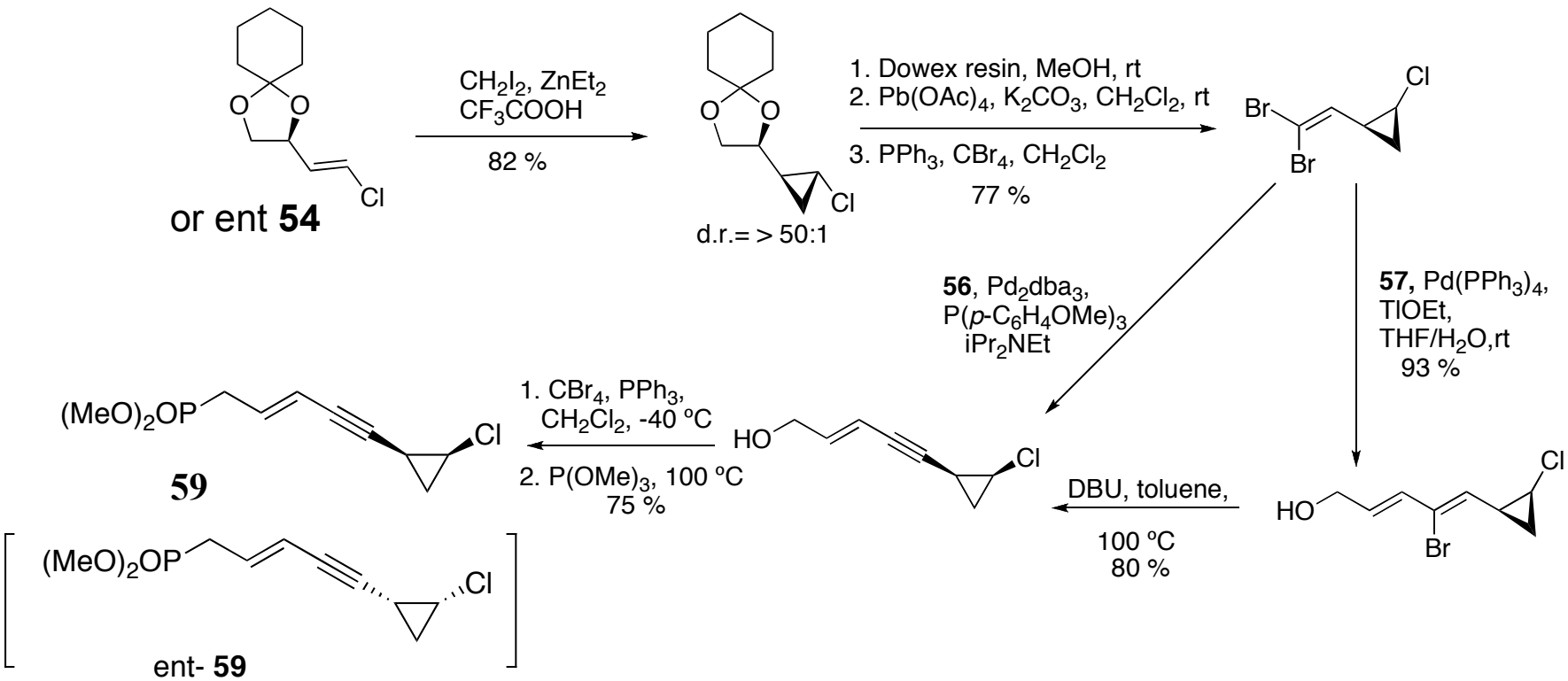
Takai olefination provided low yields and moderate selectivity

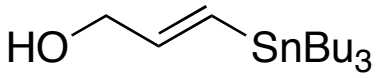
Modifying conditions based on Masuda's work the desired product was formed in high yield and selectivity

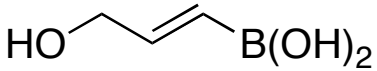
Synthesis of Side Chain Enantiomer



Competion of Side Chain

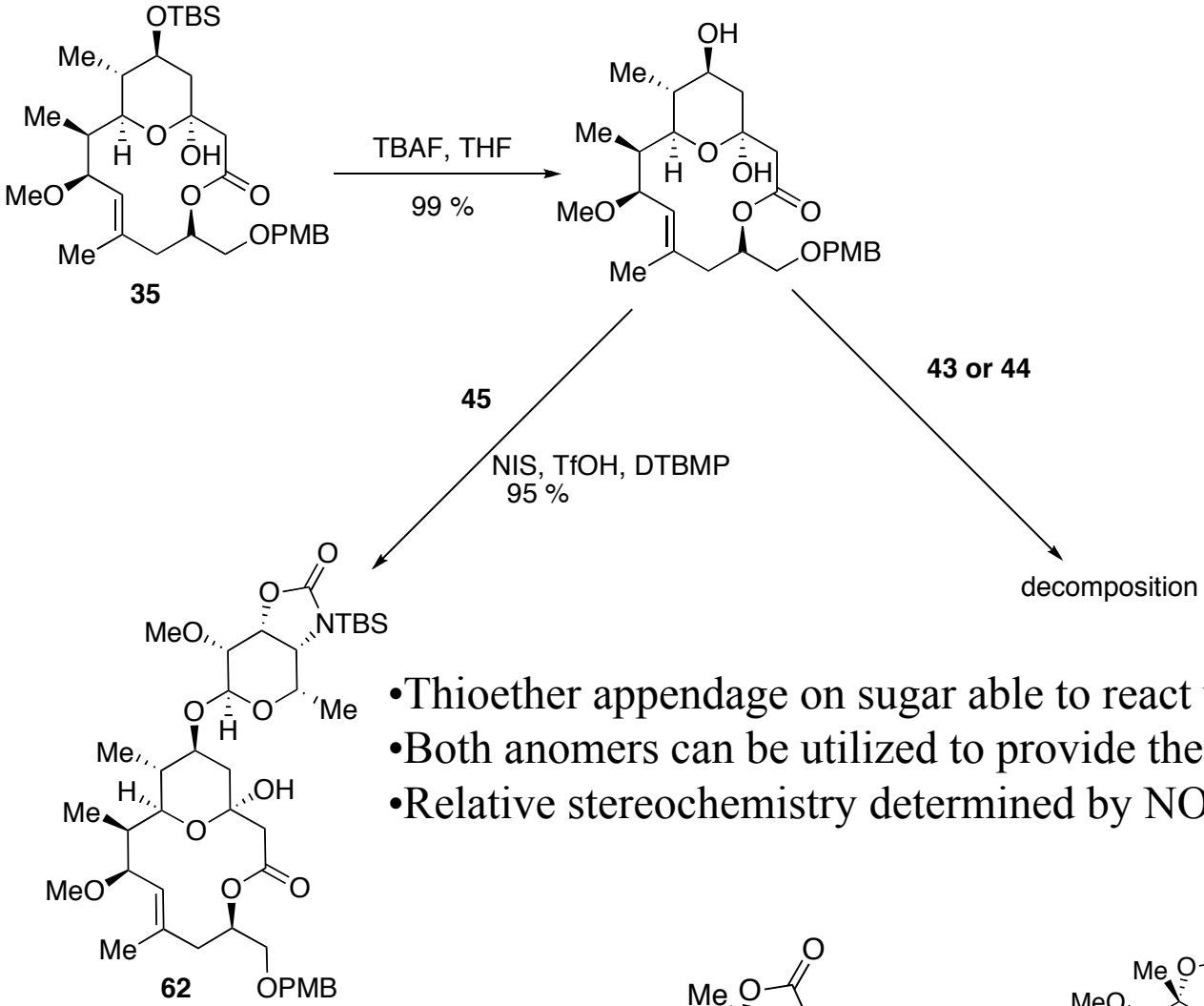


56= 

57= 

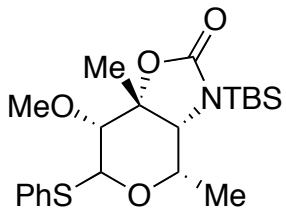
Shen's modified Stille conditions could not be applied to the dibromo-olelfin.
Instead the coupling reaction was carried out prior to elimination to provide the enyne in good yield

Fragment Assembly



- Thioether appendage on sugar able to react without decomposition of SM
- Both anomers can be utilized to provide the desired product
- Relative stereochemistry determined by NOESY

45=



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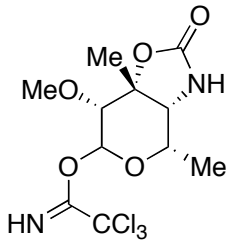

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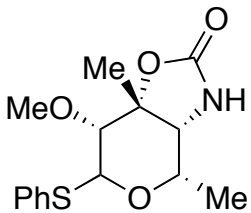
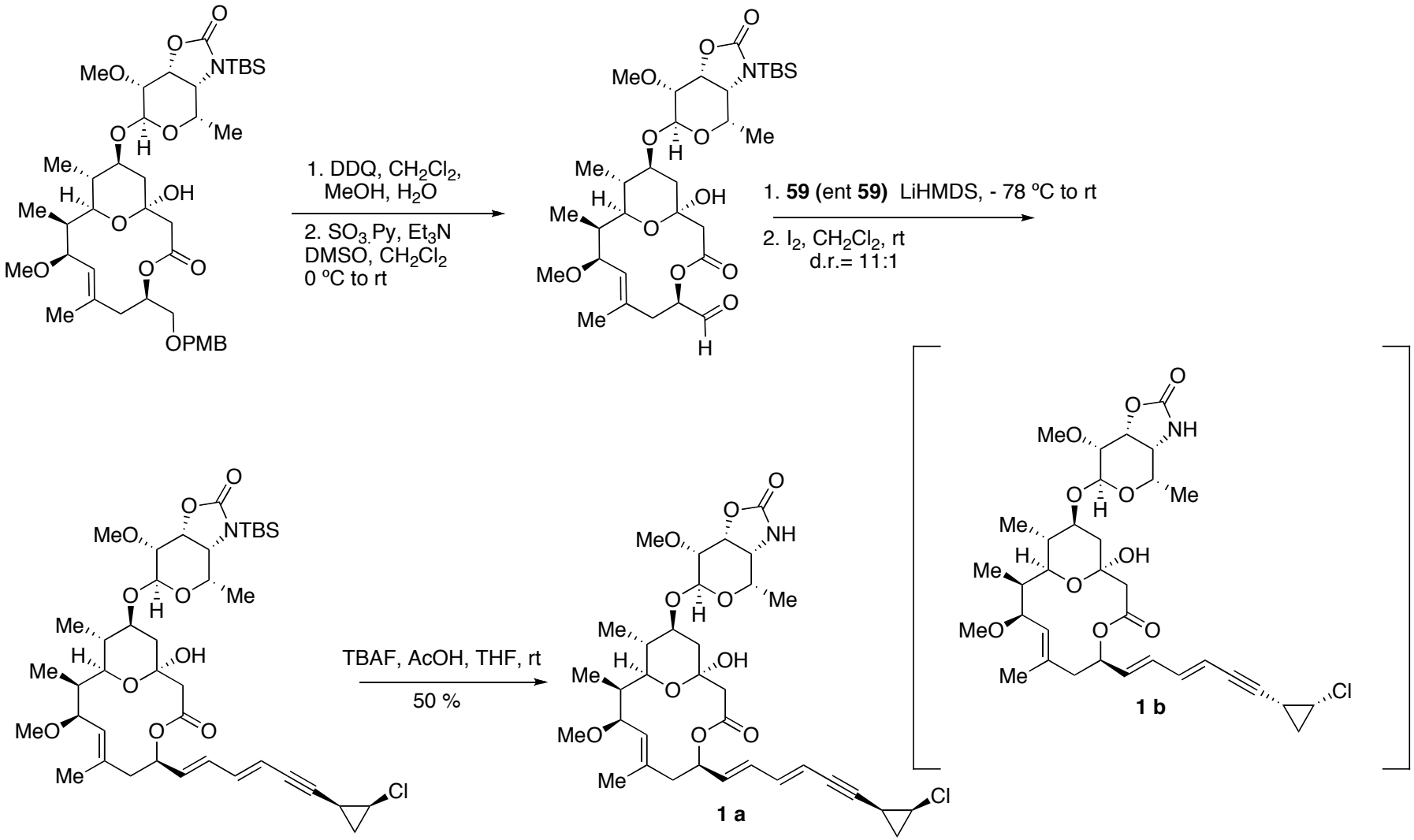


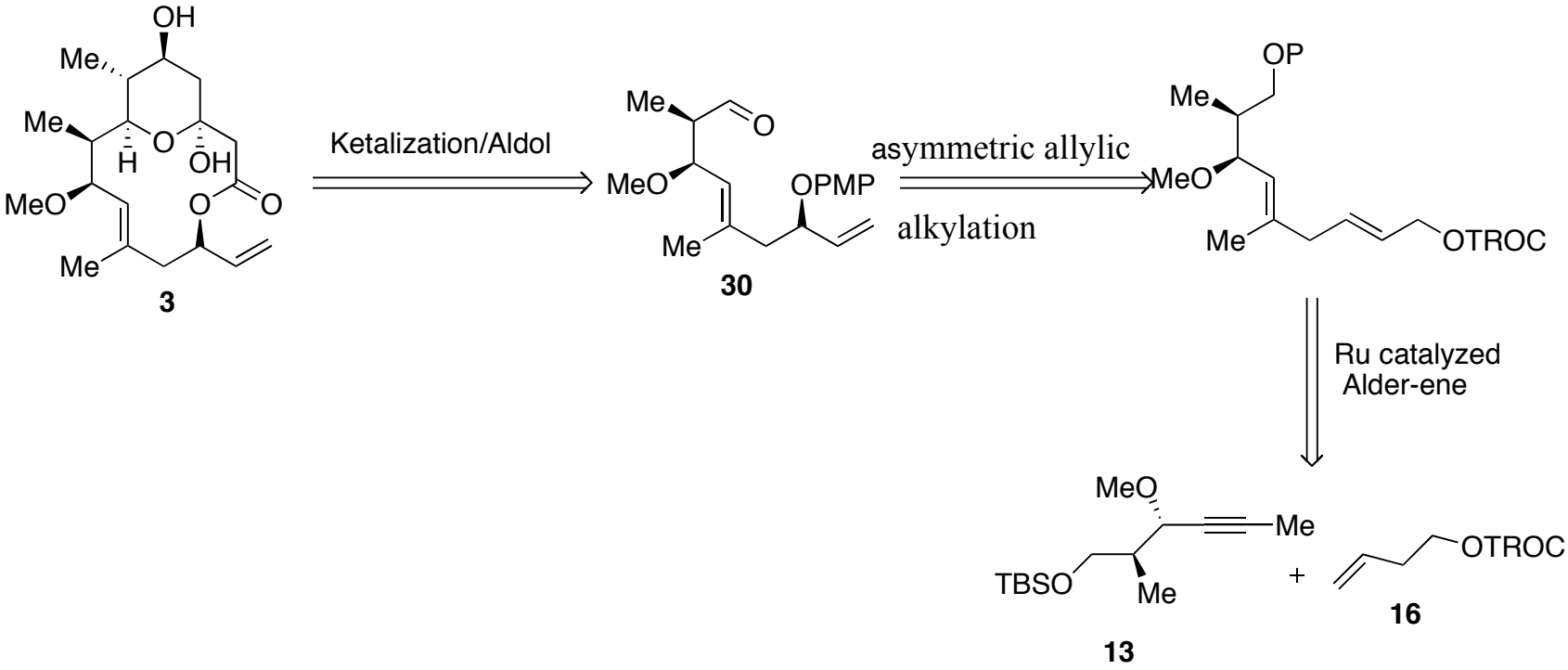
Fragment Completion



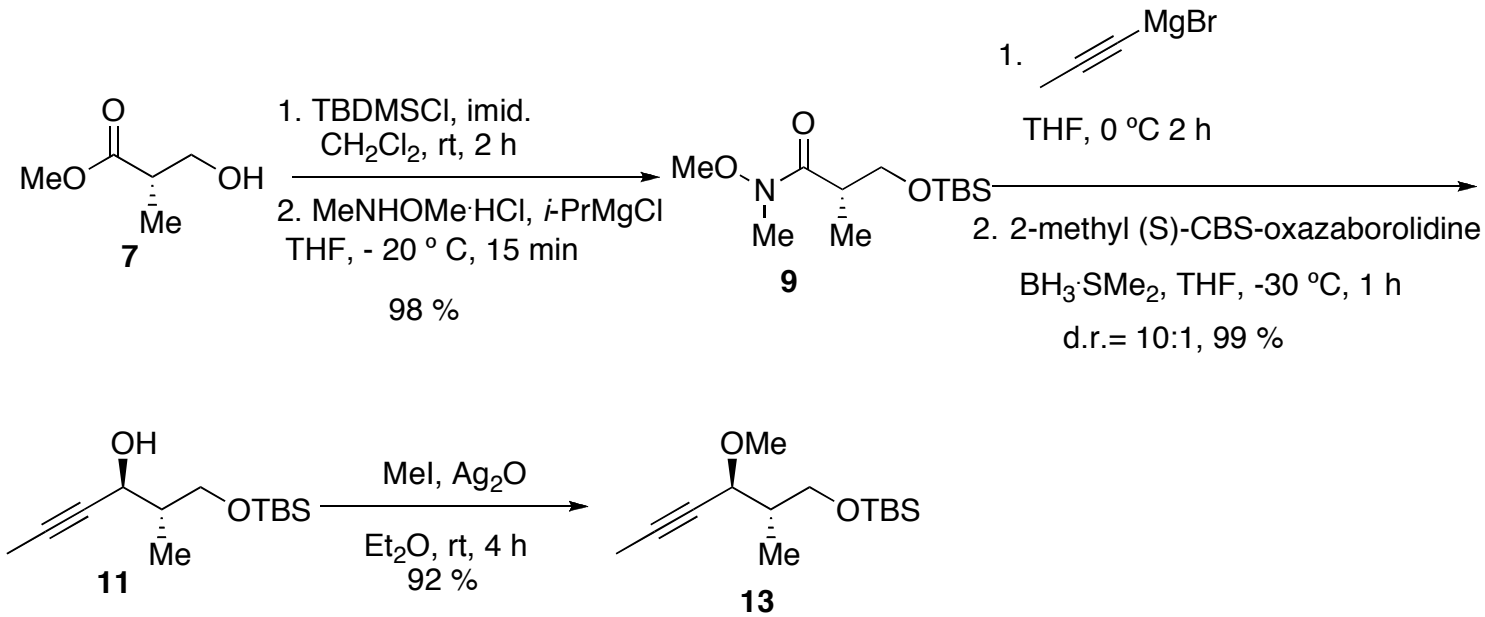
- Accomplished in 25 linear steps and a 4 % overall yield.
- NMR data confirms cyclopropyl moiety too remote for determination
- Optical rotation confirms natural product to have relative configuration matching that of **1 a**

Trost's Total Synthesis

Retrosynthetic Analysis from macrolactone **3**

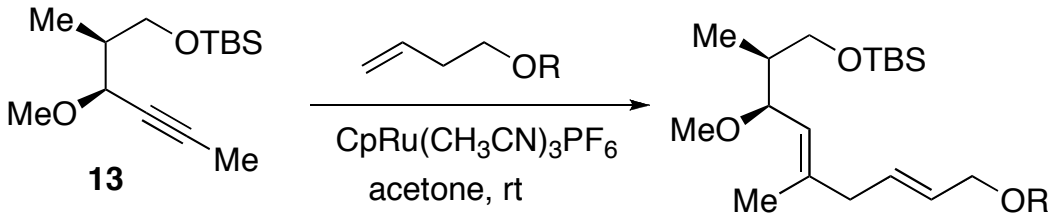


Preparation of Macrolactone



Reduction required 2.0 equivalents of 2-methyl (S)-CBS-oxazaborolidine for moderate selectivity

Synthesis of Macrolactone-Alder-Ene Reaction



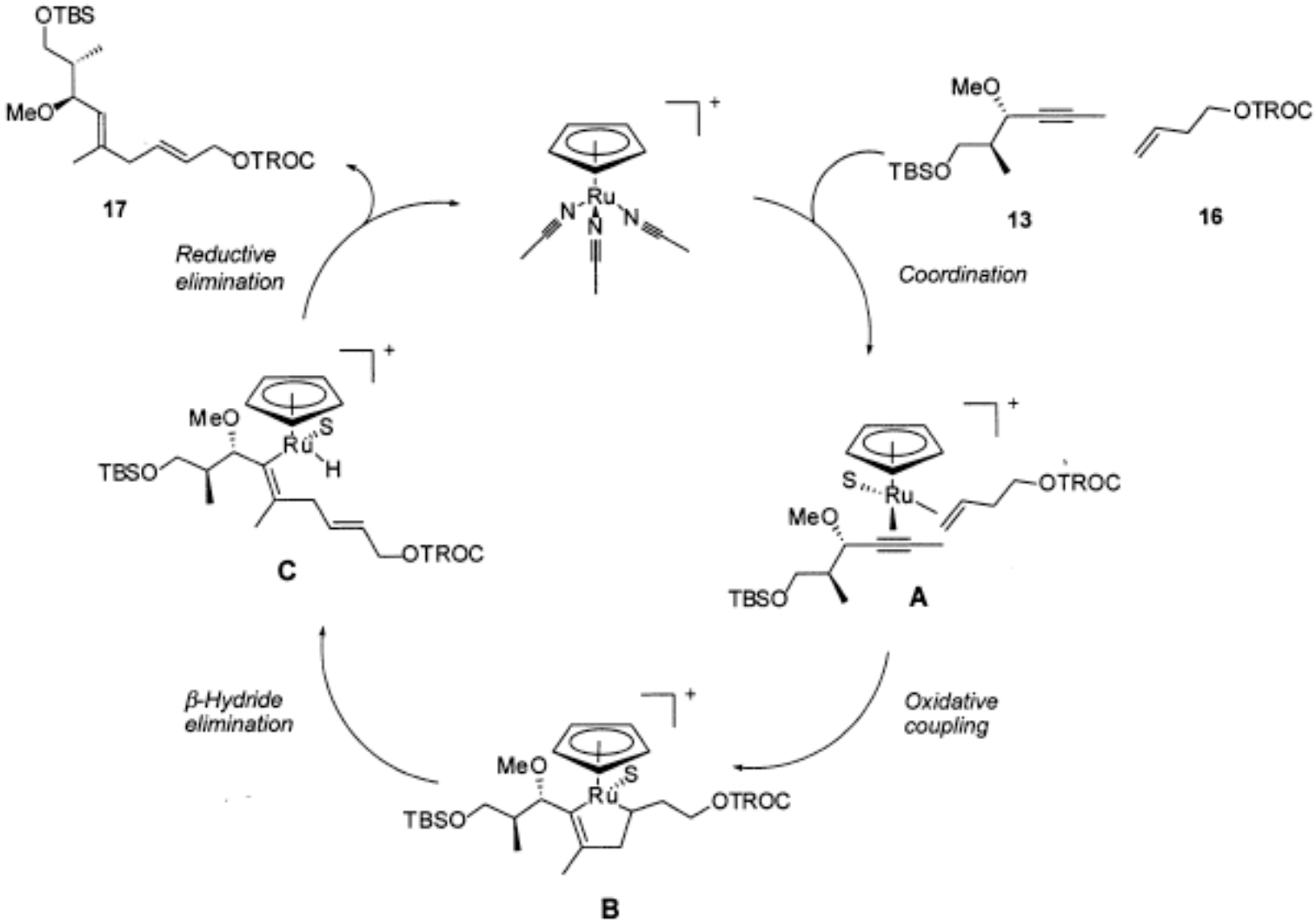
Entry	R	Mol % Ru	Time	Yield
A	H	10	2 h	62 %
B	TROC	5	0.5 h	85 %

•Product obtained exclusively as linear chain

•One of few examples of ruthenium catalyzed Alder-ene reaction to give exclusively linear products

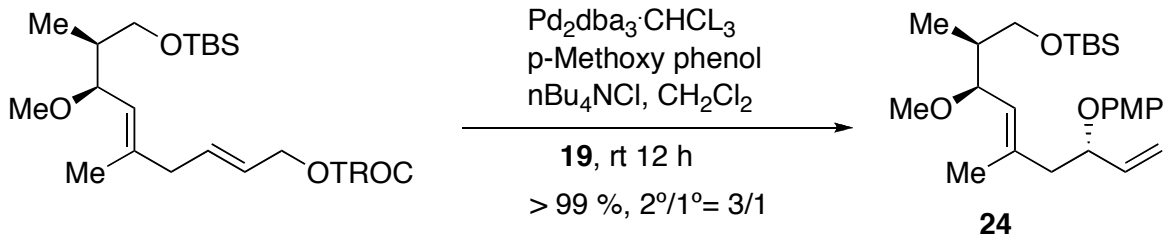
•Selectivity attributed to coordination of propargylic methyl ether in ruthenacycle and inductive effect of homoallylic oxygen

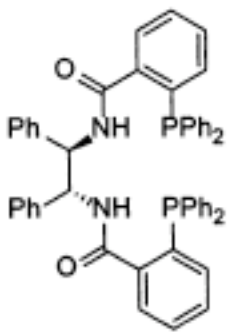
Proposed Mechanism of Alder-ene Reaction



Trost, B. M., et. al. *J. Am. Chem. Soc.* **2002,** *124,* 10396

Asymmetric Allylic Alkylation (AAA)



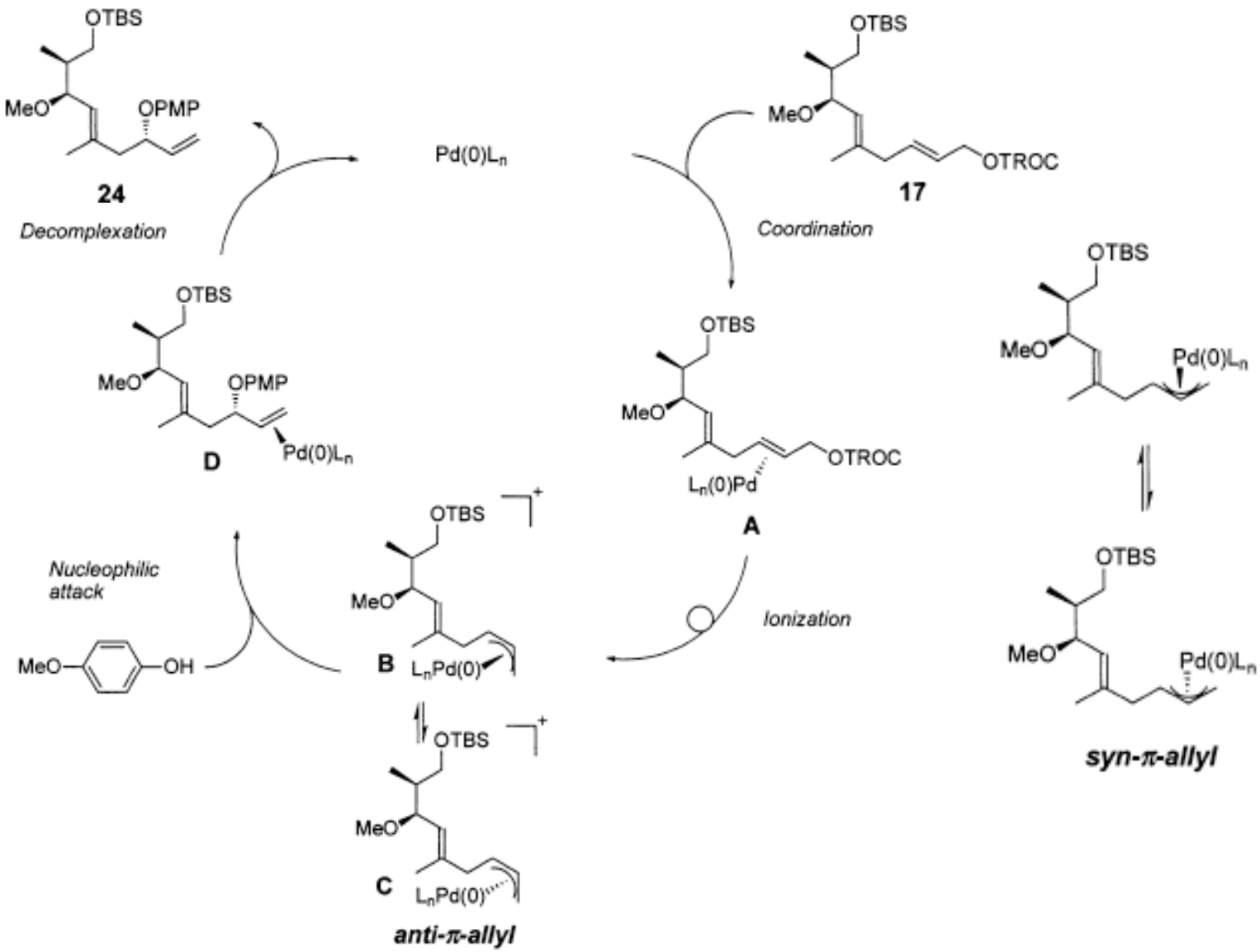


(*R*,*R*)-diphenyl

19

- Opposite stereocenter observed from expected configuration
- Selectivity arises from Pd ability to switch from η^1 to η^3 which allows syn to anti interconversion
- Chloride ion helps facilitate equilibrium by coordinating to Pd

Mechanism of AAA



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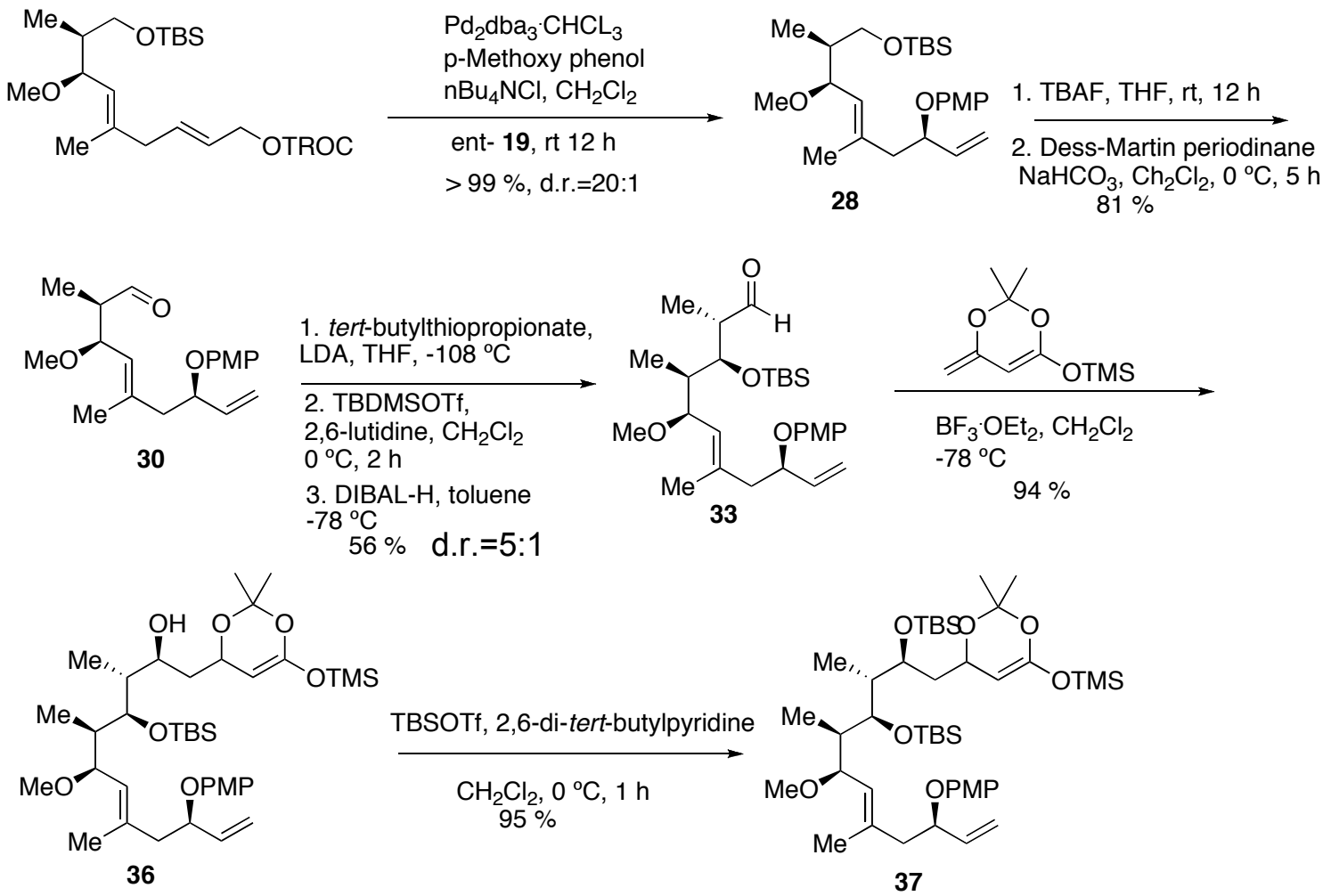
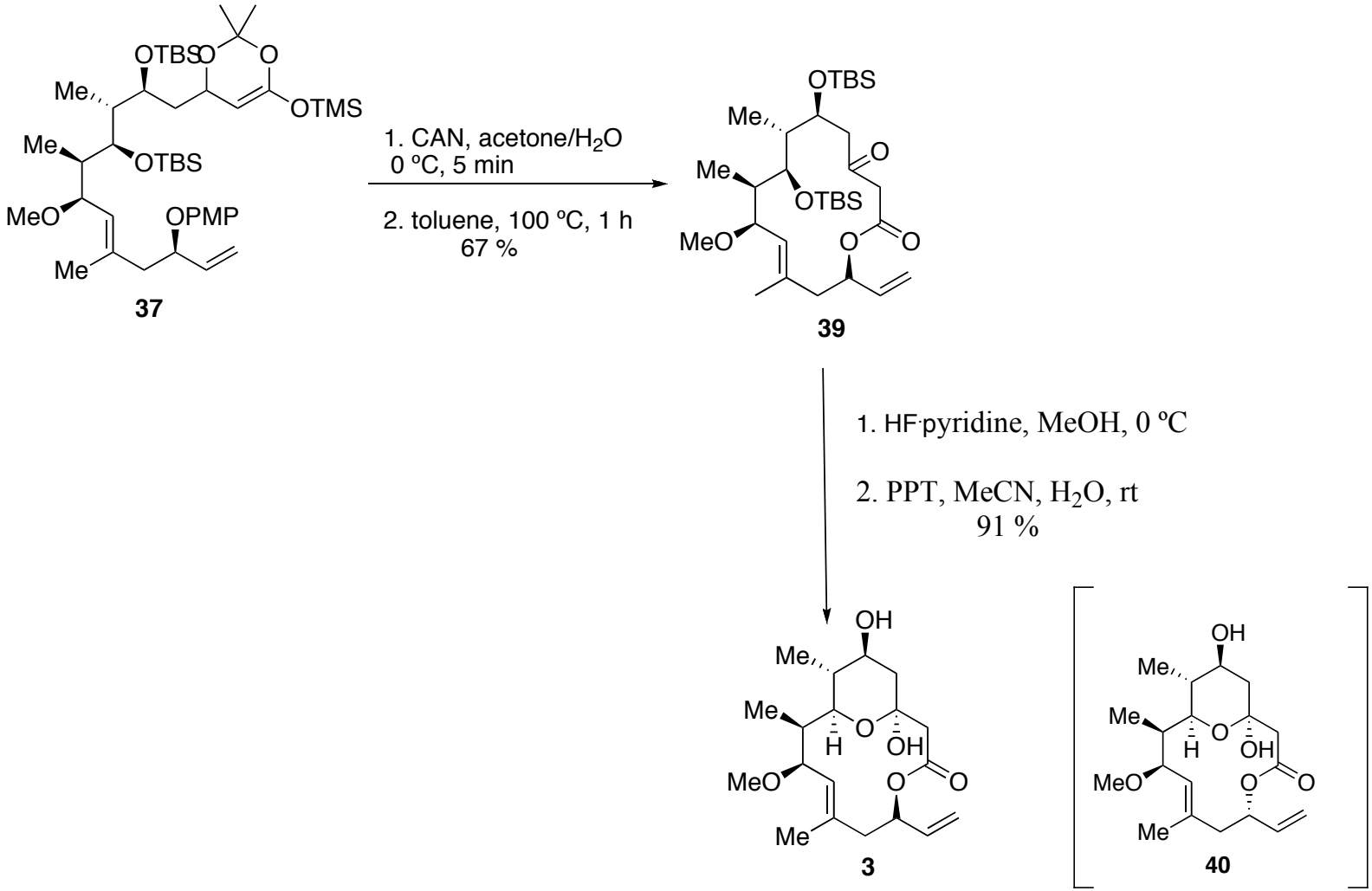
Aplication of AAA to Macrolactone



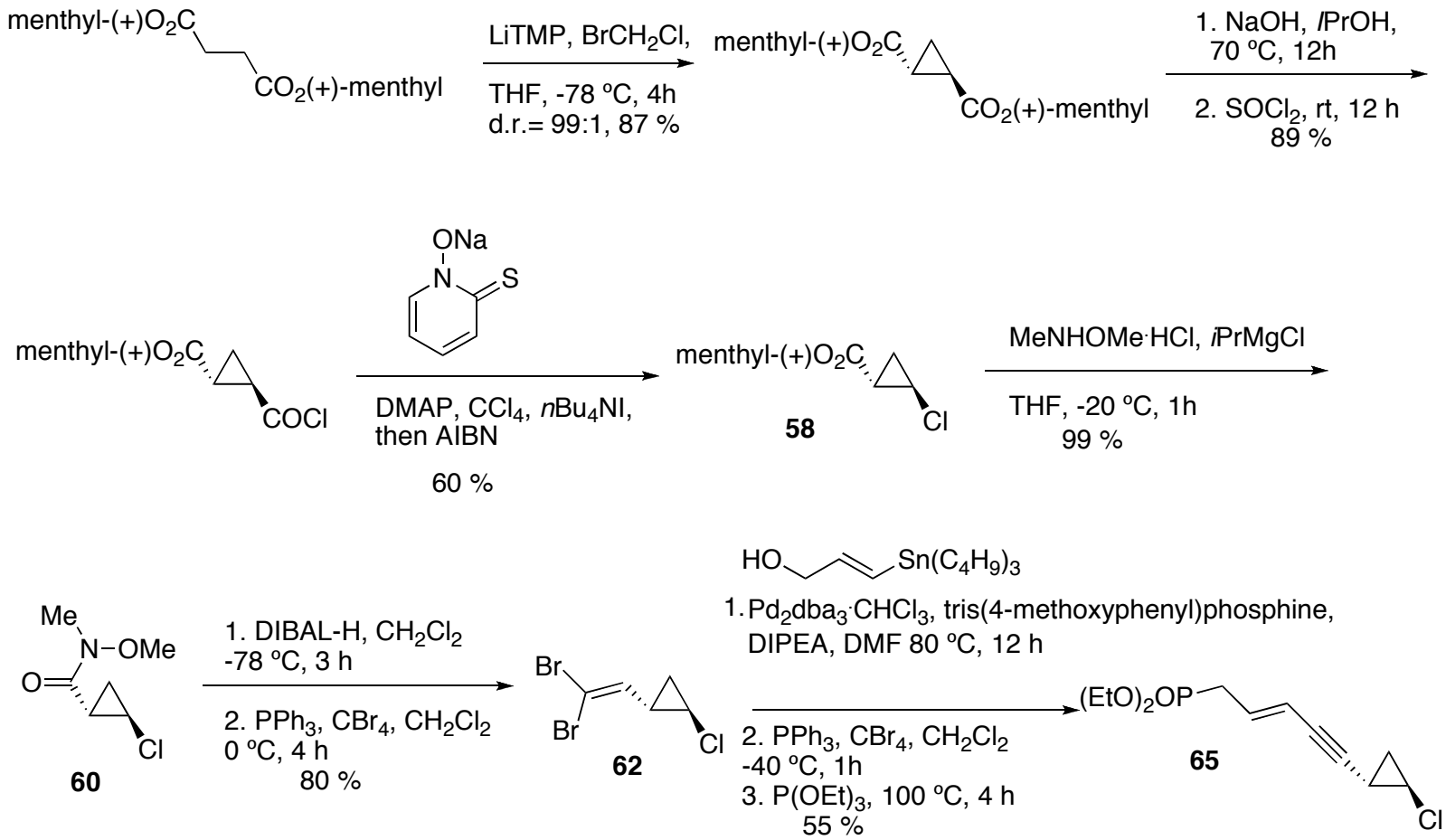
Completion of Macrolactone Fragments



Same steps carried out starting from diasteromer **24** to provide **40**
nOe studies confirmed stereochemistry of lactones

Appending Cyclopropyl Moiety

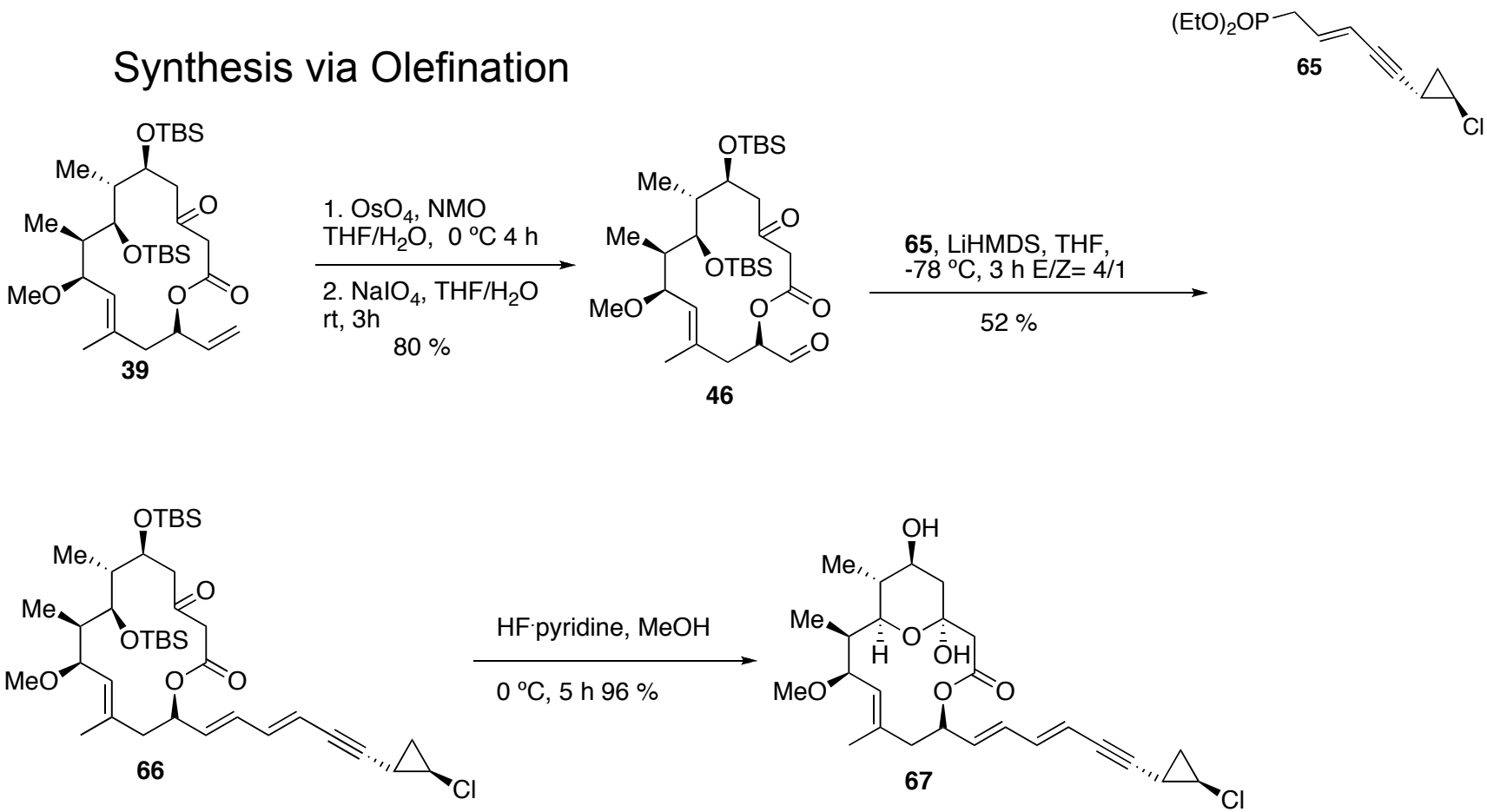
To determine absolute configuration need to synthesize and append both enantiomers of cyclopropyl moiety



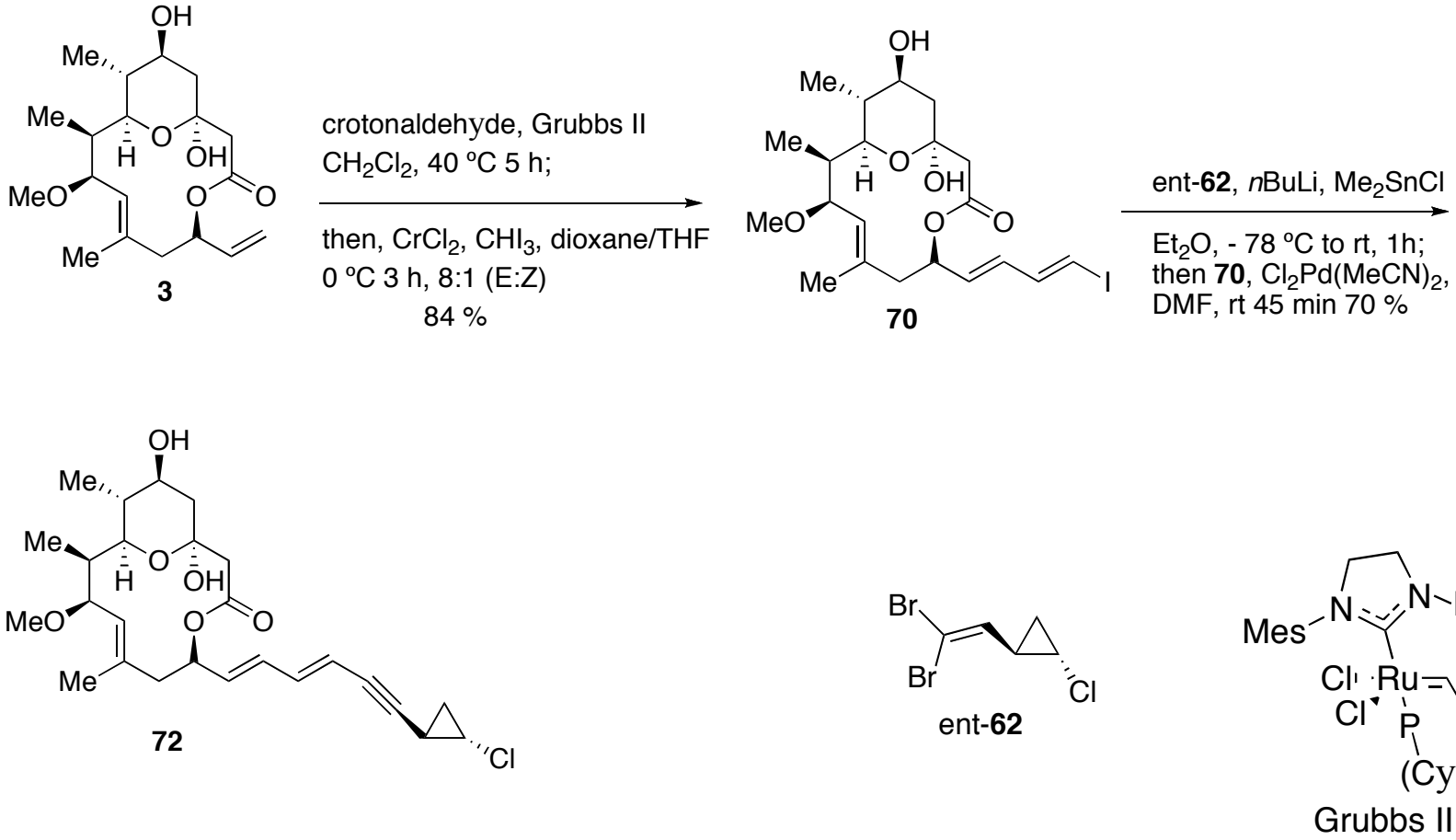
Two Methods for Appending Dienyne

Model studies based on deschlorocallipeltoside

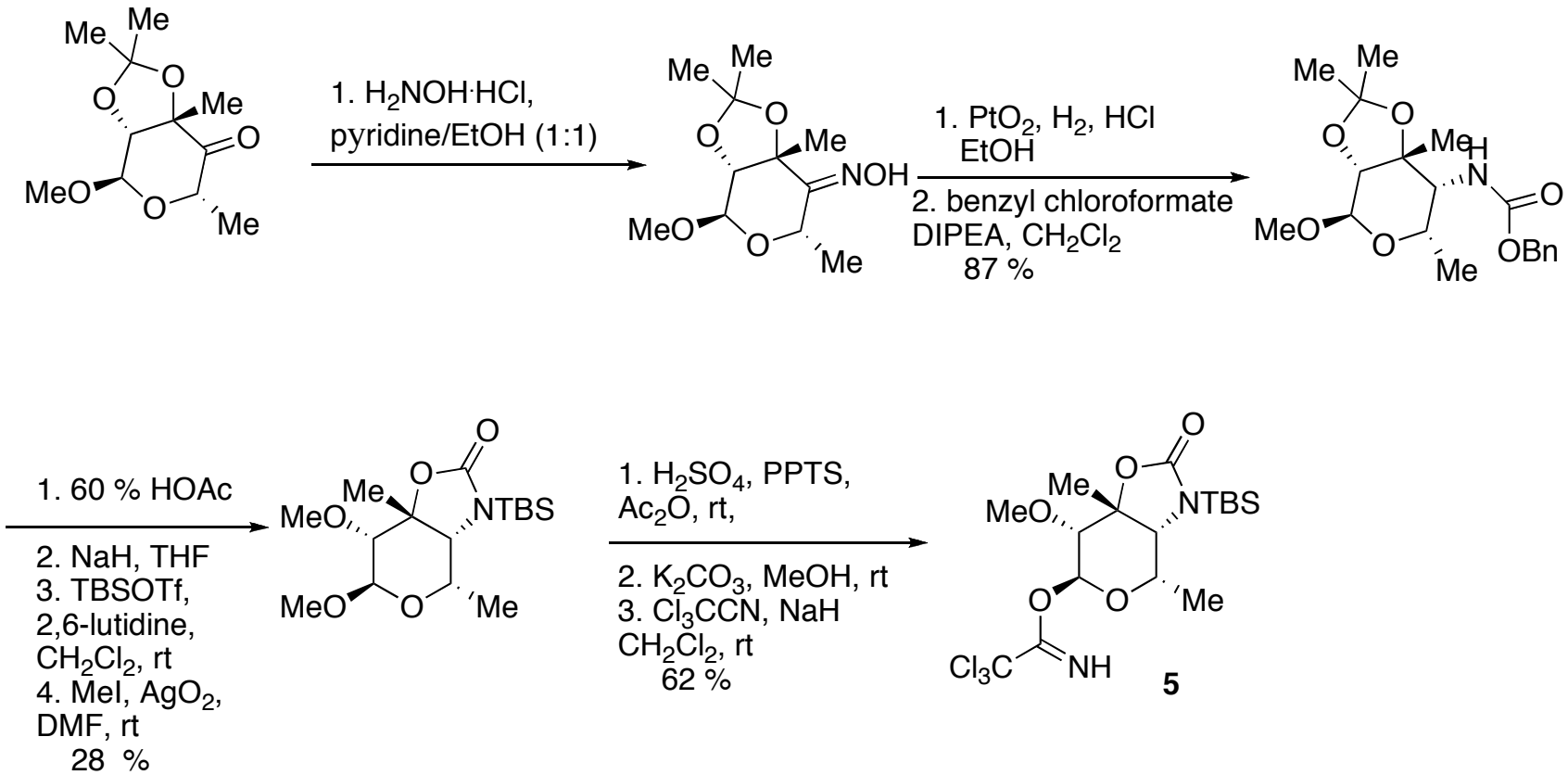
Synthesis via Olefination



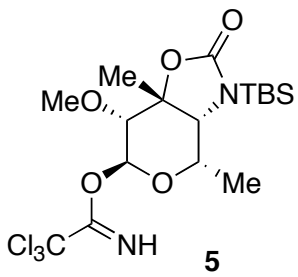
Method 2: Metathasis



Synthesis of Sugar

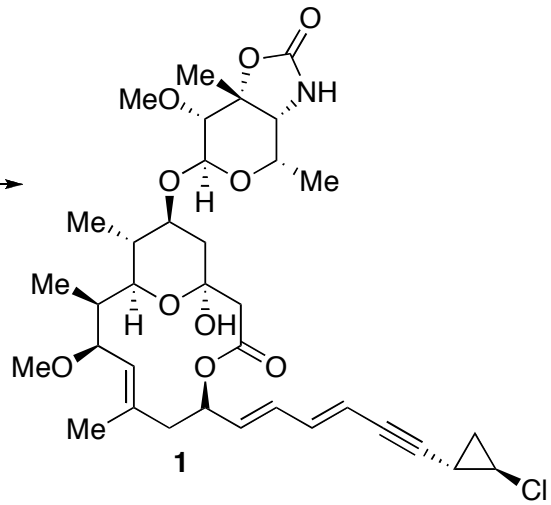


End Game Strategy

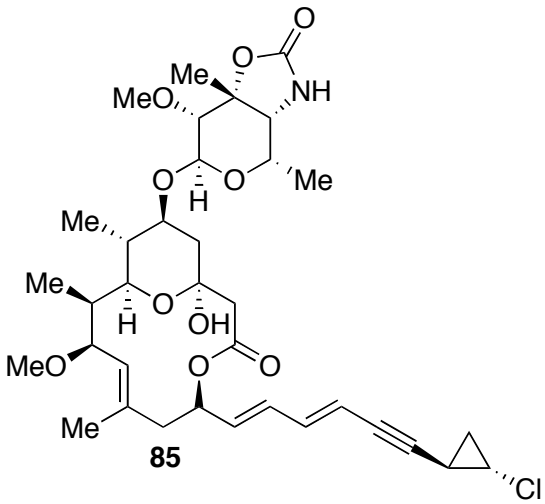


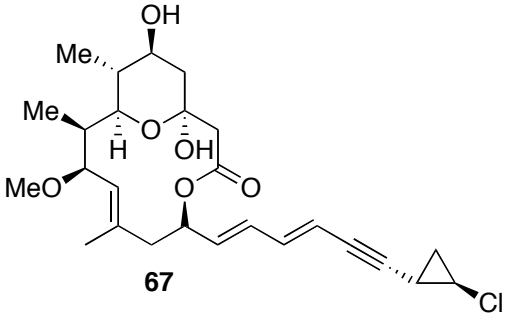
1. **67 (72)** TMSOTf, dichloroethane, 4 Å MS, - 30 ºC

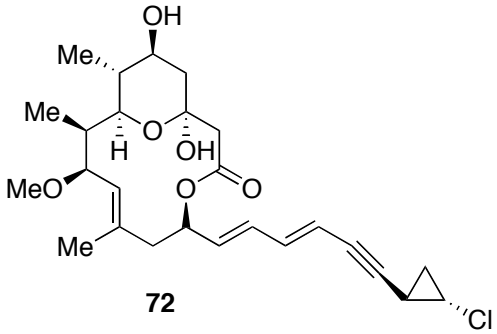
2. TBAF, AcOH, THF, rt 69 %



or

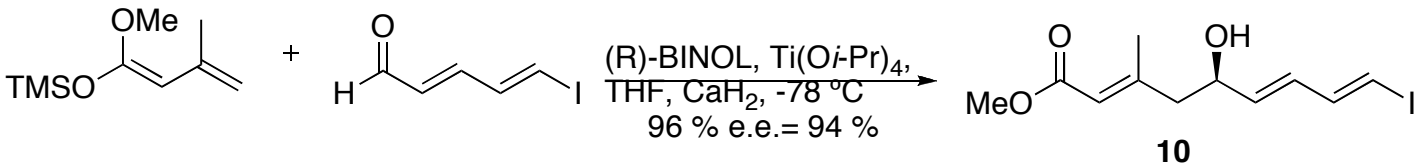


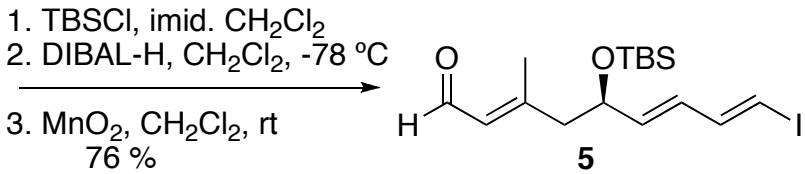


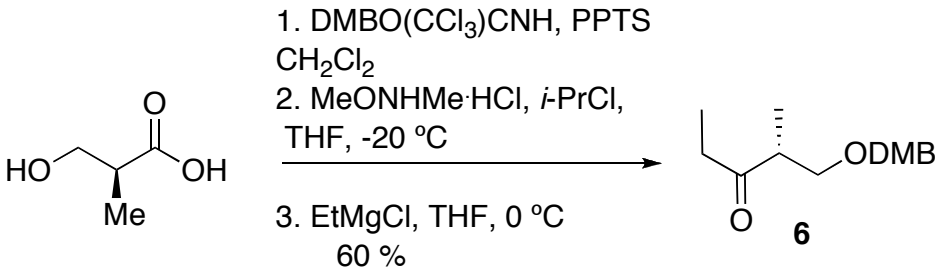


Completion of molecule in 46 total steps (22 linear) for 0.05 % overall yield

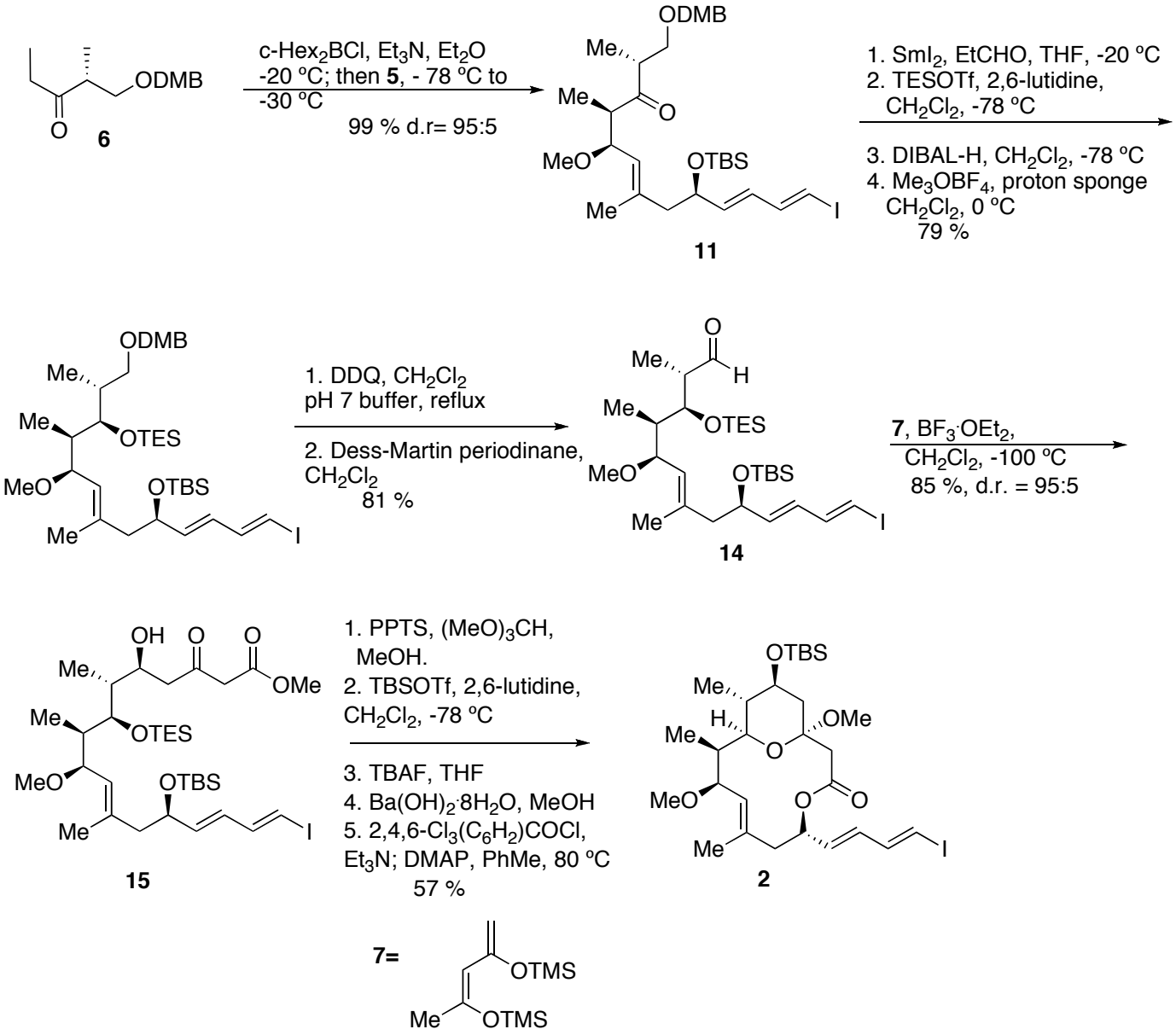
Paterson's Synthesis of Macrolactone



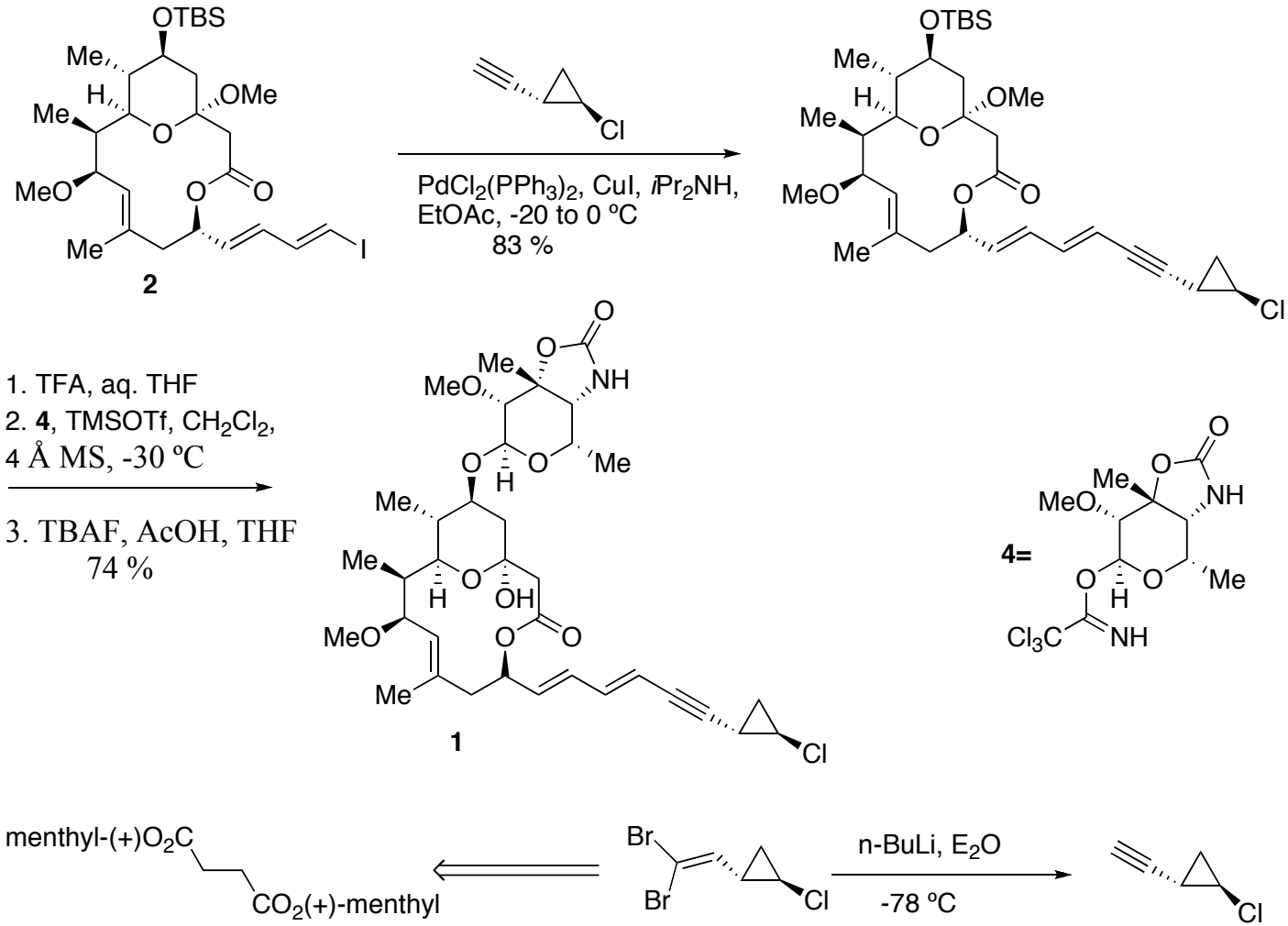




Completion of Macrolactone

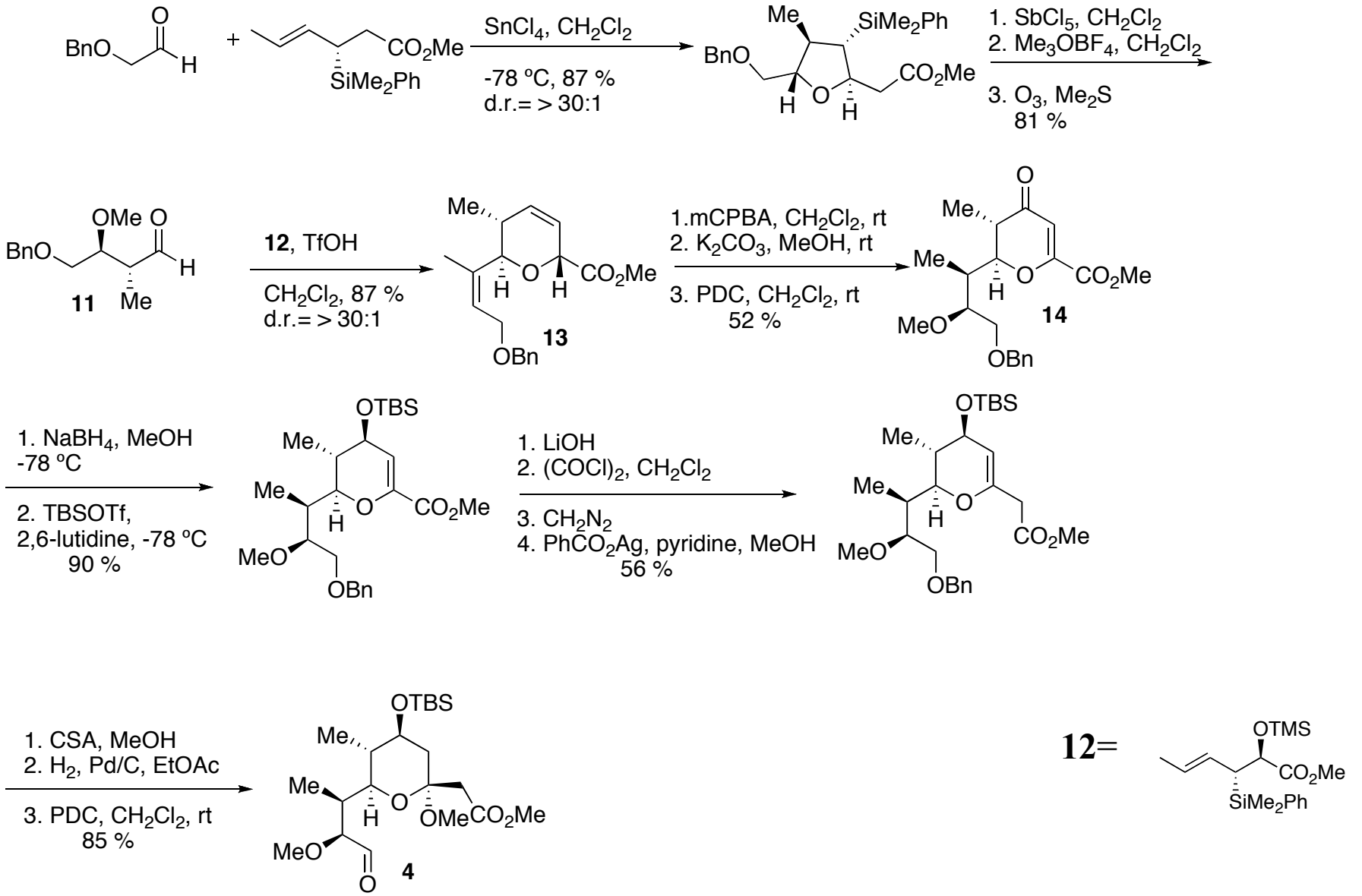


Completion of Callipeltoside A

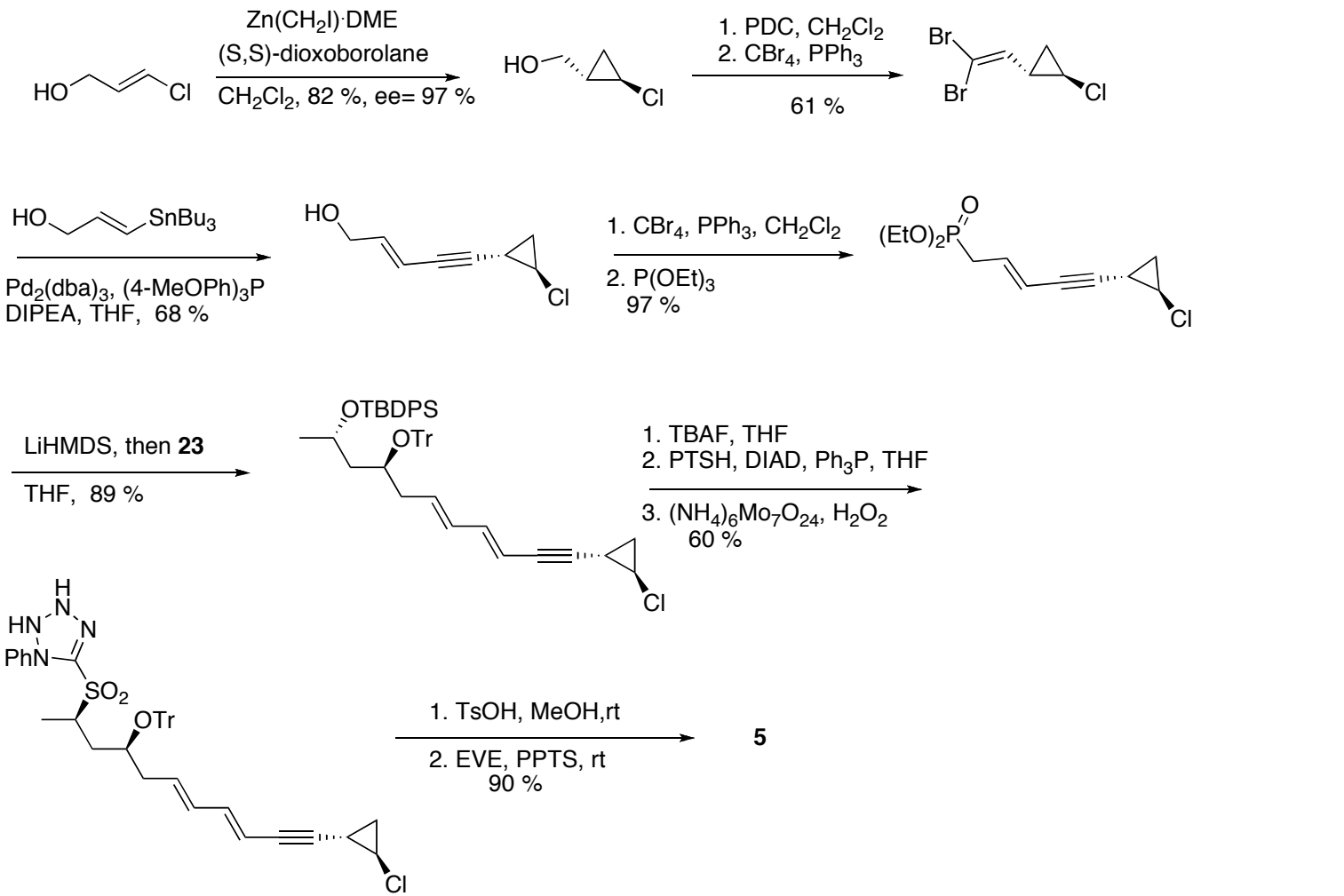


Synthesized in 4.8 % overall yield (23 steps- longest linear sequence)
Sugar and cyclopropyl appendages synthesized by previously reported methods

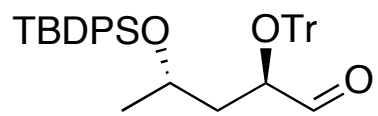
Panek's Total Synthesis



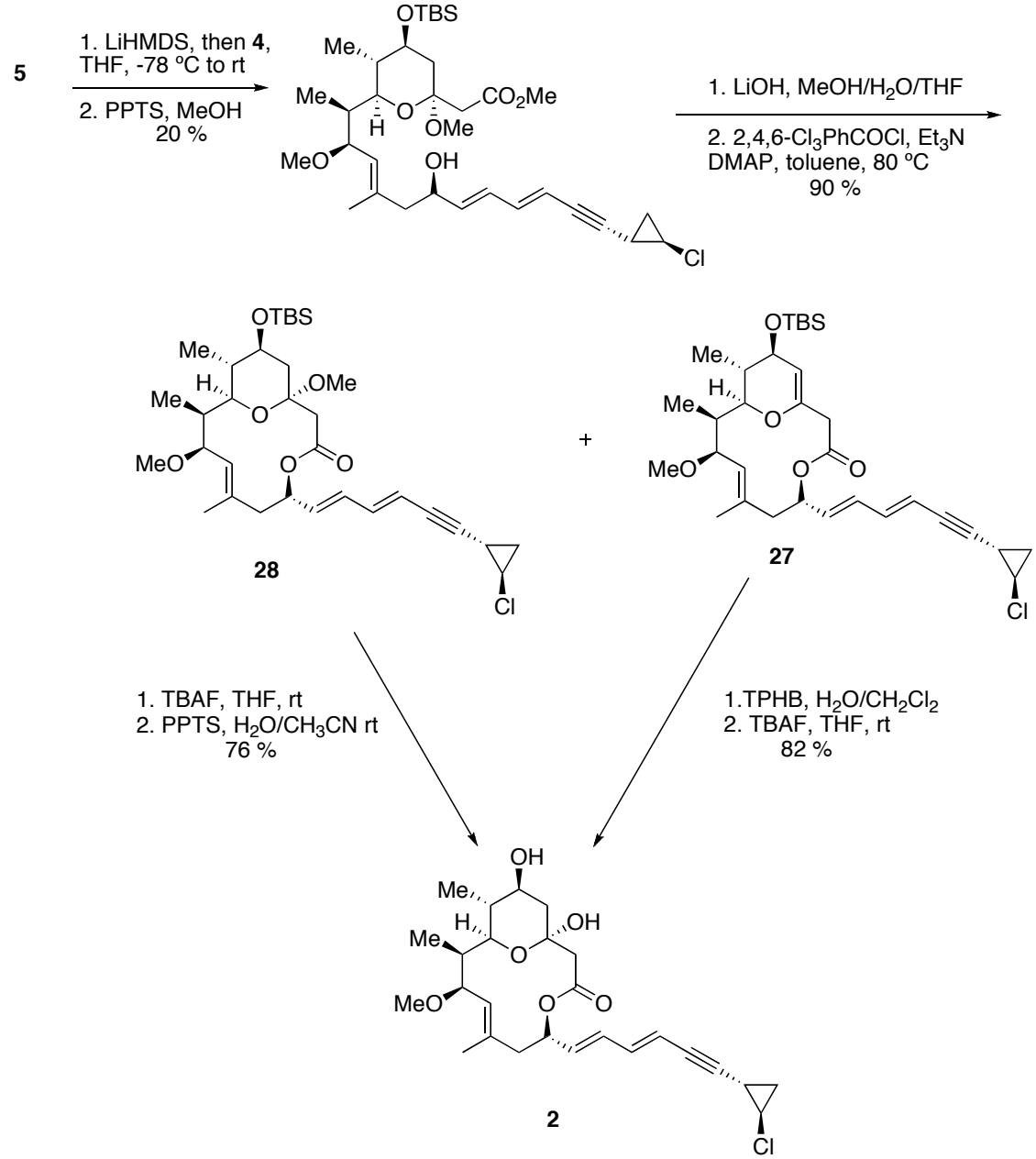
Synthesis of Cyclopropyl Dienyne



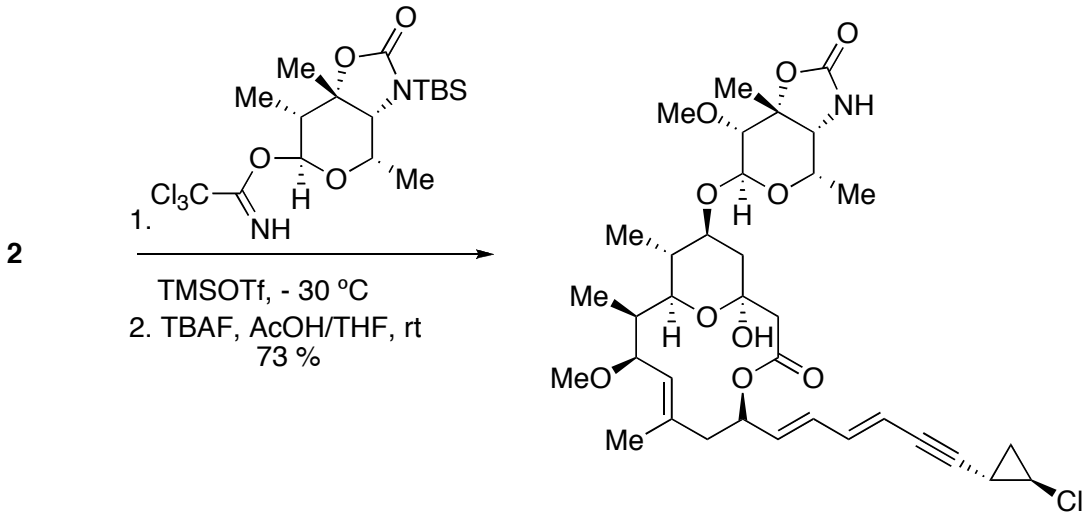
23=



Completion of Callipeltoside A



Glycosylation of Macrolactone



Sugar fragment prepared as described by Trost

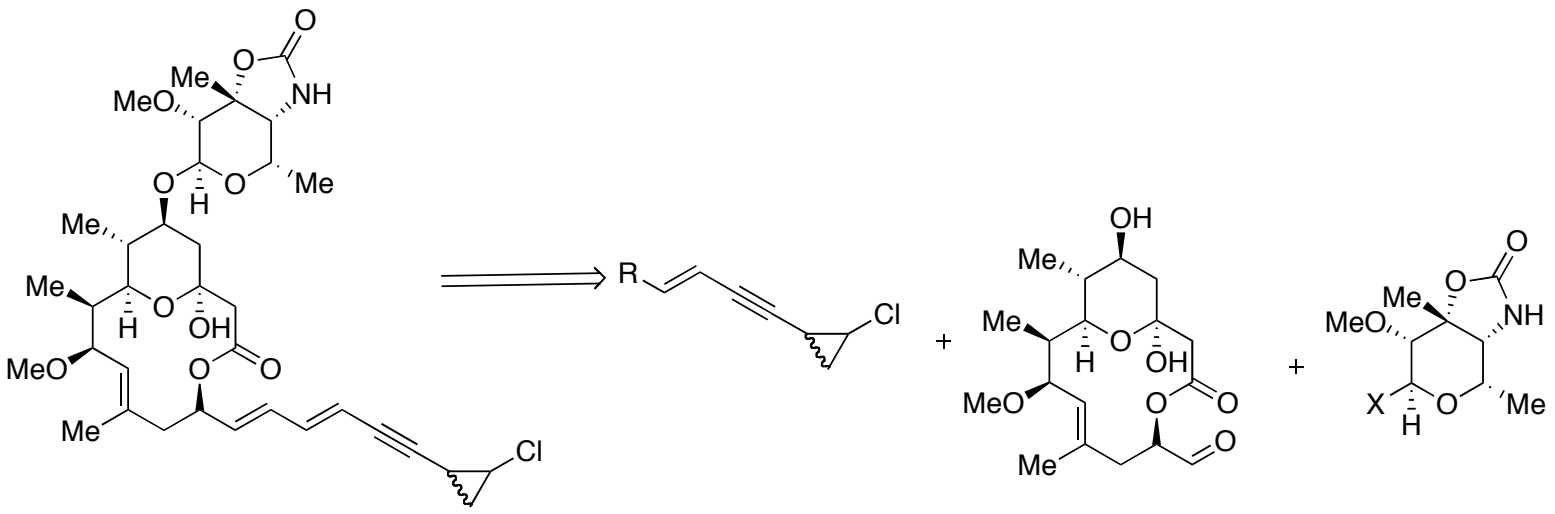
Formal synthesis accomplished with longest linear sequence of 25 steps

Conclusions

•Four Total Syntheses of Callipeltoside A have been reported to date

•Trost and Evans both synthesized a diastereomer; changing the configuration about the cyclopropyl moiety

•The absolute and relative configurations have been assigned based on independent syntheses



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