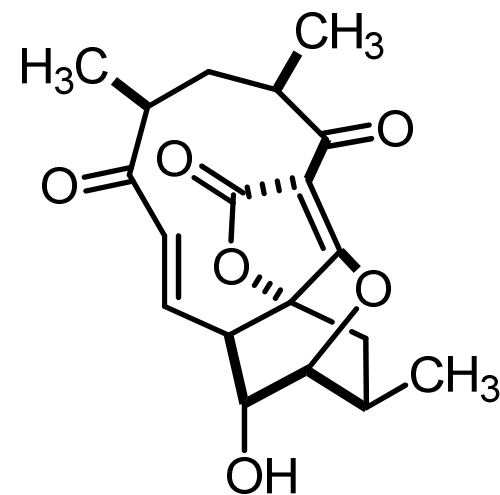


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# Synthesis of Abyssomicin C

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Marie-Caroline Cordonnier  
Literature Review  
23/01/2009



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# Isolation

- Isolated in 2004 from the actinomycete *Verrucosispora* strain collected from a sediment at a depth of 289m in the Japanese sea. (name: abyss)
- Discovered as a whole family but only abyssomicin C shows antibiotic activity.

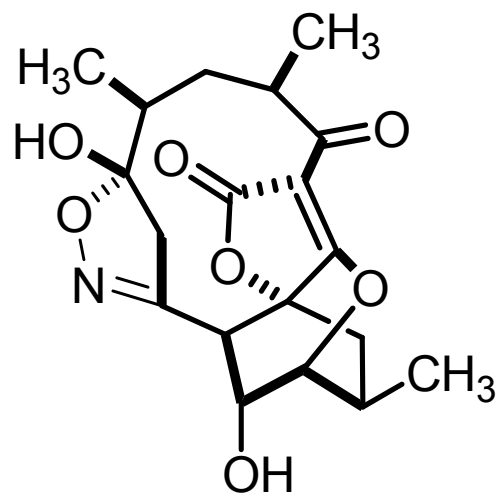
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# Biological activity

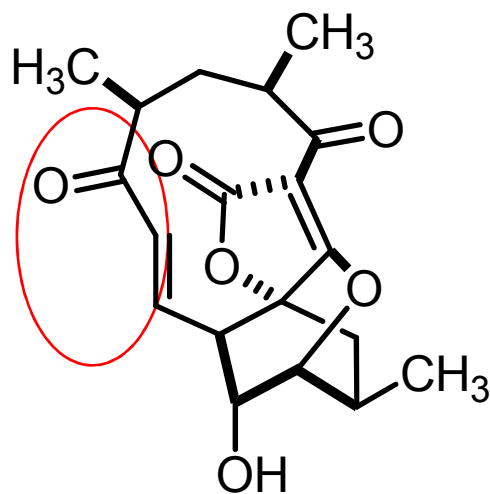
- Antibiotic activity against Gram-positive bacteria including methicilin - resistant (MRSA, MIC = 4  $\mu\text{g}/\text{mL}$ ) and vancomycin - resistant (VRSA, MIC = 13  $\mu\text{g}/\text{mL}$ ) *Staphylococcus aureus* strains.
- Inhibitor of the enzyme responsible for the conversion of chorismate to para-aminobenzoic acid as such it is a potential antibacterial drug.

# Biological activity

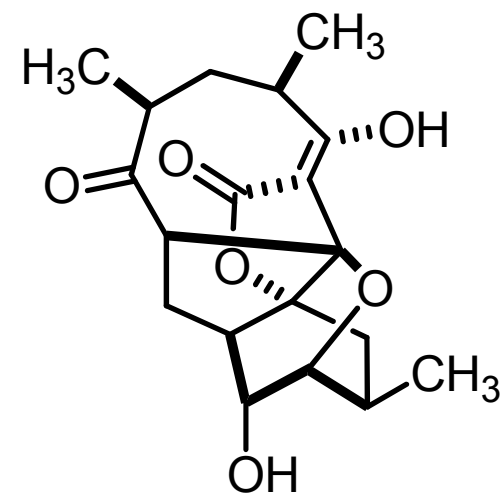
- Could be explained by the Michael system missing in the inactive compounds



Abyssomicin B



Abyssomicin C



Abyssomicin D

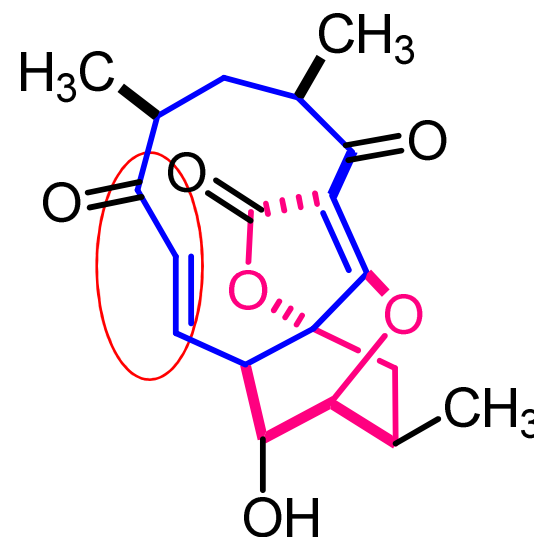
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# Total Syntheses

- Because of this intriguing system and of the biological activity several groups attempted the total synthesis of Abyssomicin C.
    - B. B. Snider  
*Org. Lett.* **2005**, 7, 4939.
    - E. J. Sorensen  
*Angew. Chem. Int. Ed.* **2005**, 44, 6533.
    - K. C. Nicolaou  
*Angew. Chem. Int. Ed.* **2006**, 45, 3256, and *J. Am. Chem. Soc.* **2007**, 129, 429.
-

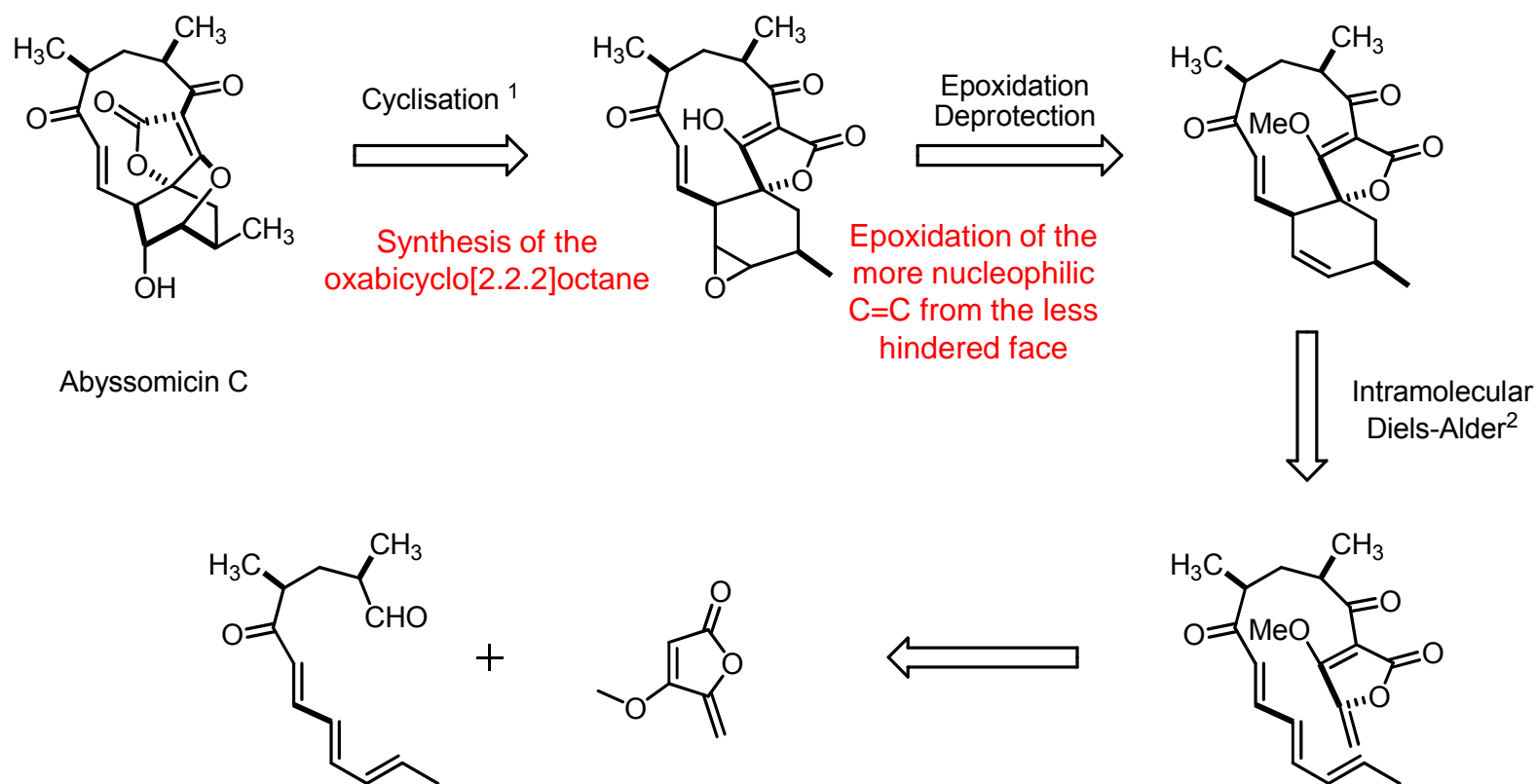
# Challenging structural elements

- Strained 11-membered macrocyclic ring
- 7 stereogenic centers
- Potentially reactive  $\alpha$ ,  $\beta$  unsaturated ketone
- Novel fused tetronate oxabicyclo[2,2,2]octane core



# Snider's Approach: Retrosynthesis

## ■ Biomimetic route



1. Maier *et al.* *Synlett* **2005**, 314 and Maier *et al.* *Org. Lett.* **2005**, 7, 3089.
2. Yoshii *et al.* *J. Org. Chem.* **1987**, 52, 4135.

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# Snider's Approach: Retrosynthesis

## The Key Step

- Diels-Alder very risky
  - Creation of three stereocenters  $\Rightarrow$  4 possible products
  - Endo and Exo products are possible
  - Facial selectivity is also an issue
  - Reactivity of the methylene butenolide as dienophile?
    - Yoshii reported that reaction of a ten-atom tether proceeded under forcing conditions (180°C in *o*-dichlorobenzene) with a low yield and as a mixture of 4 cycloadducts.



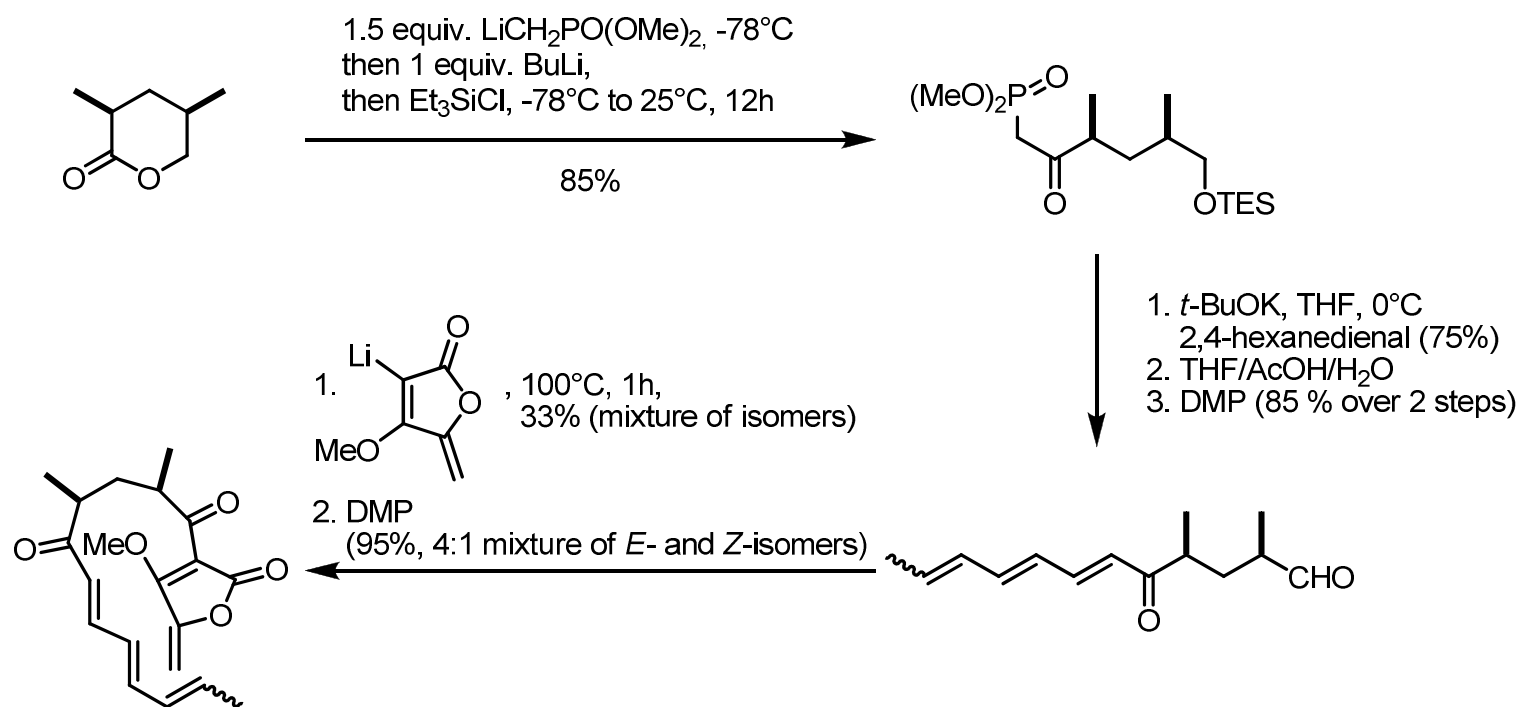
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# Snider's Approach: Retrosynthesis

## The Key Step

- Two encouraging factors
    - Presence of an acyl group in the tether  $\Rightarrow$  dienophile more electron deficient
    - Biosynthesis probably involves a similar Diels-Alder reaction under physiological conditions in which the stereochemistry of the product is controlled by the substrate rather than an enzyme.
-

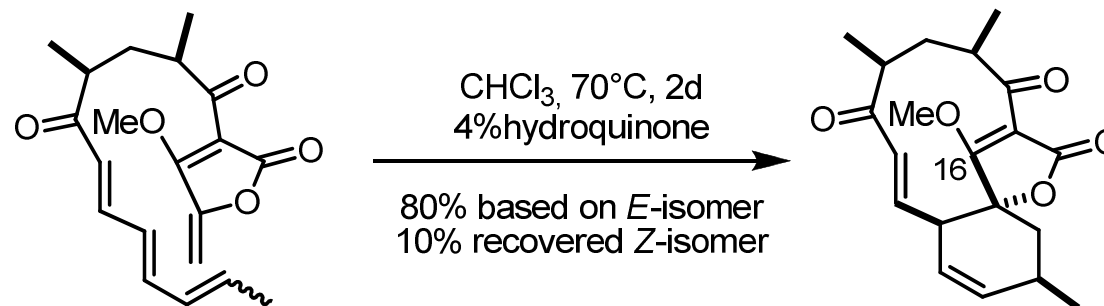
# Snider's Approach: Synthesis of the Diels-Alder Substrate



Hoffmann *et al.* *Tet. Lett.* **1985**, 26, 6325.  
Paintner *et al.* *Tet. Lett.* **2000**, 41, 9977.

Yoshii *et al.* *E. J. Chem. Soc.* **1989**, 712.

# Diels-Alder reaction



- One single cycloadduct isolated
- Desired cycloadduct formed showed by NOE in which C-16 is in endo position
- Novel and mild stereospecific Diels-Alder  $\Rightarrow$  facile access to the carboxylic skeleton of Abyssomicin C

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# End of the synthesis

- Hydrolysis of the vinylogous carbonate with LiCl in DMSO: 88% yield<sup>1</sup>
- Epoxidation of the cyclohexene double bond afforded complex mixture in which enone double bond had reacted
  - m-CPBA
  - DMDO
- Not surprising considering that this is probably the reason for Abyssomicin C's biological activity

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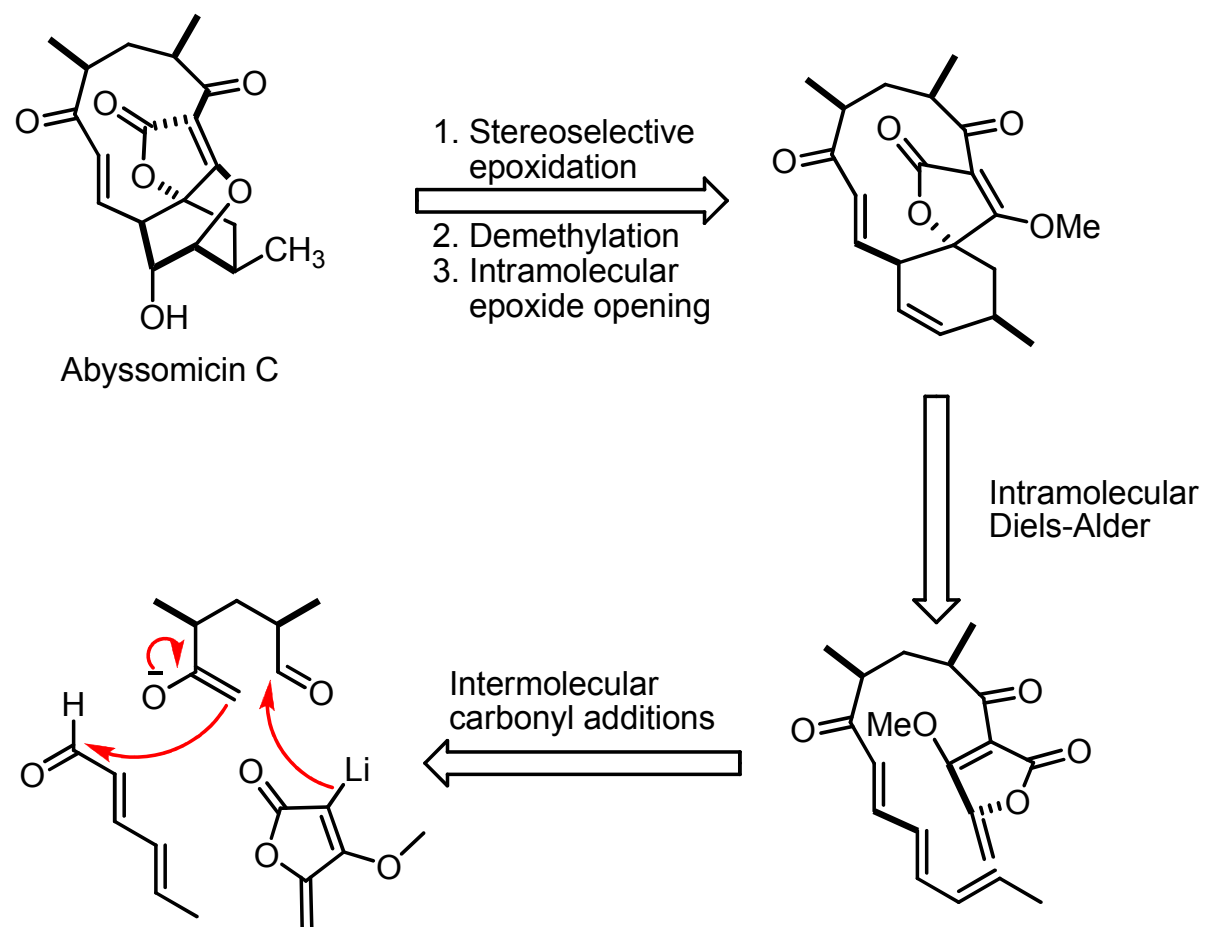
# End of the synthesis

- Never completed because Sorensen published at the same time a full synthesis of Abyssomicin C...



# Sorensen's Approach: Retrosynthesis

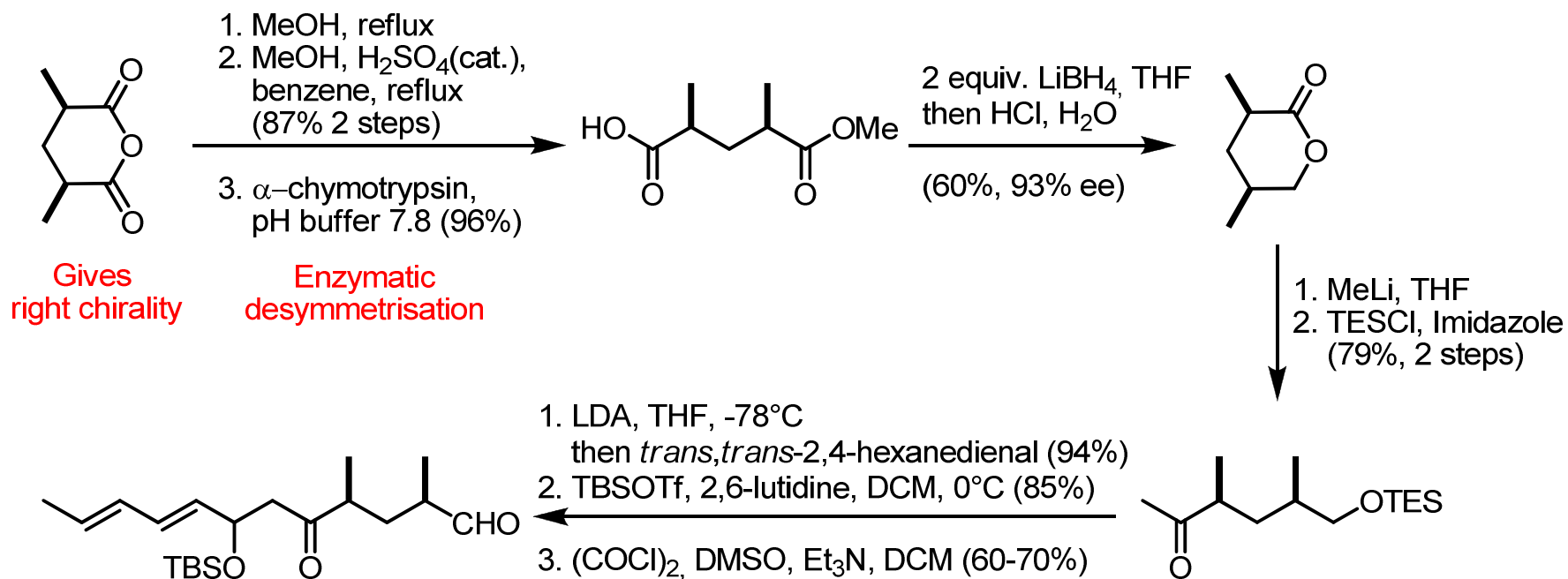
## ■ Convergent asymmetric synthesis



Yoshii *et al.* *Tet. Lett.* **1986**, 27, 3903.

Yoshii *et al.* *J. Org. Chem.* **1990**, 55, 3431.

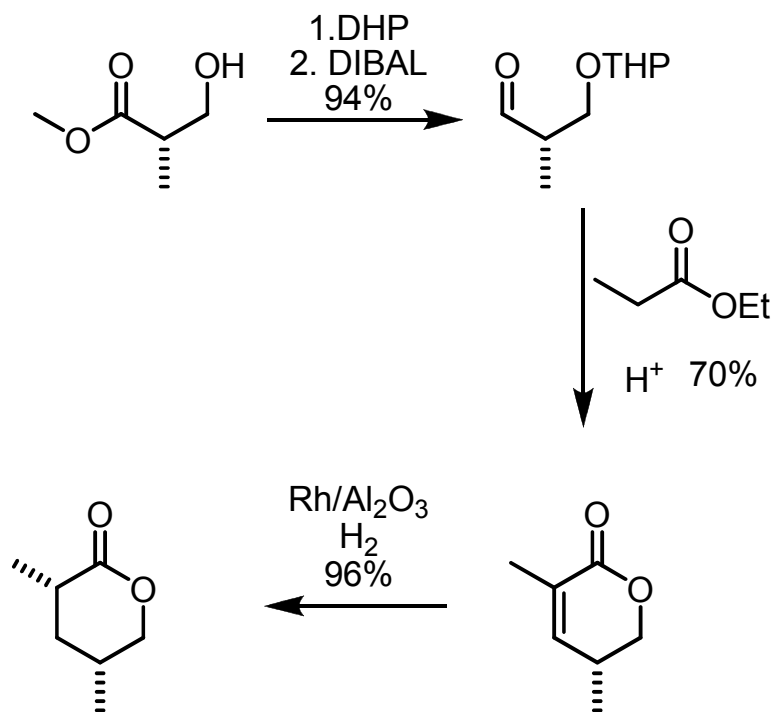
# Synthesis of the Diels-Alder substrate



Lautens *et al.* *Org. Lett.* **2002**, 4, 1879.

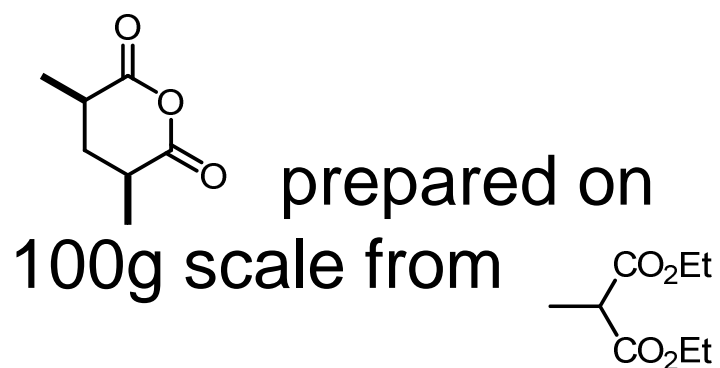
Schick *et al.* *Tetrahedron: Asymmetry.* **1993**, 4, 695.

# Snider's Approach: Synthesis of the Starting Material



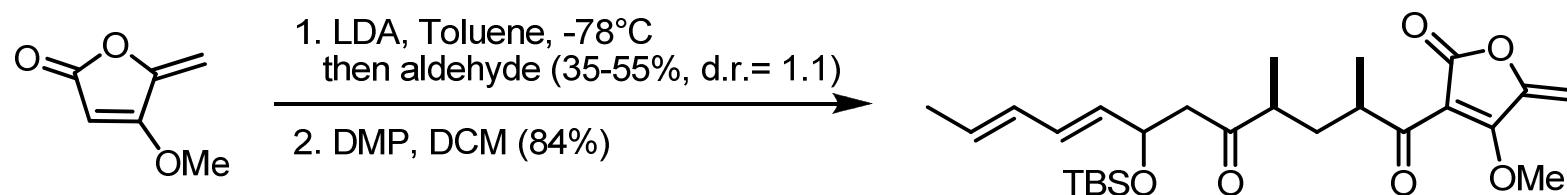
Snider's preparation of the starting material is 63% yield

Sorensen's preparation is 50% yield



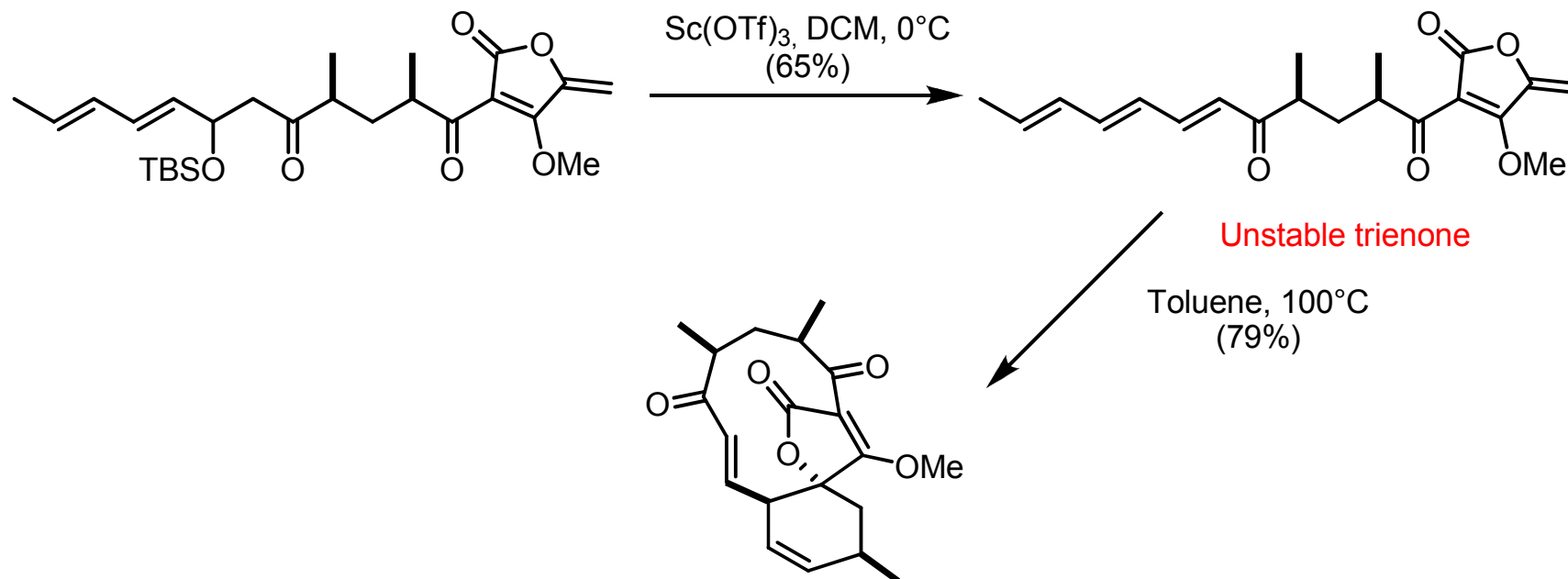


# Synthesis of the Diels-Alder adduct



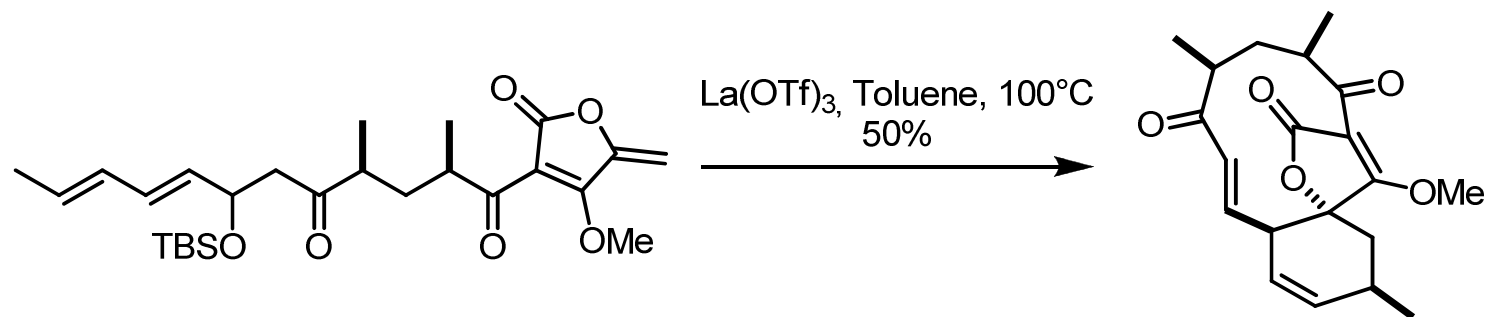
- Contains all carbons of Abyssomicin C
  - But yields modest and variable
  - Mixture of diastereomers

# Cyclisation Step



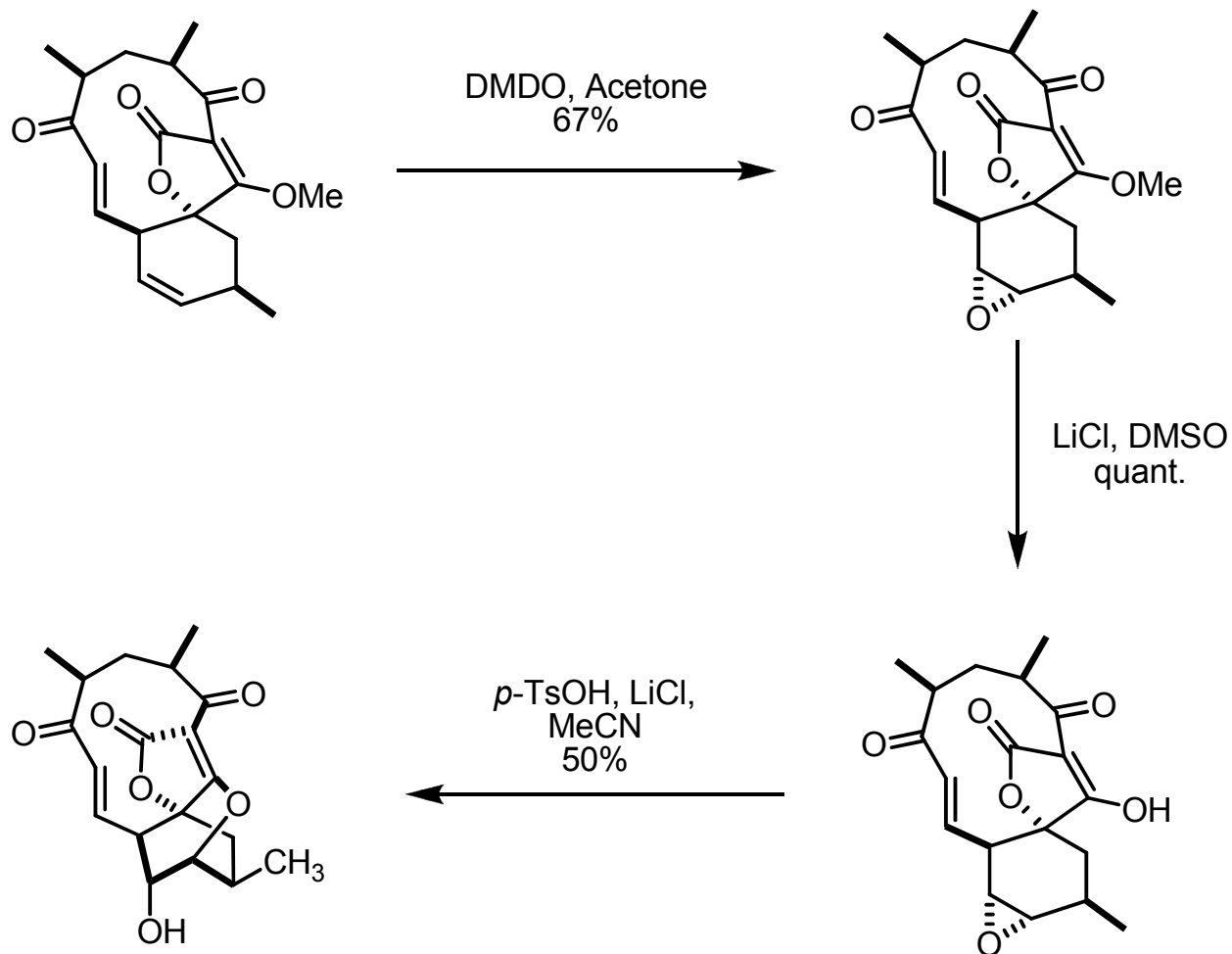
- OTBS used as precursor of the trienone
- Trienone is an unstable compound  $\Rightarrow$  one pot synthesis required

# Optimised cyclisation step

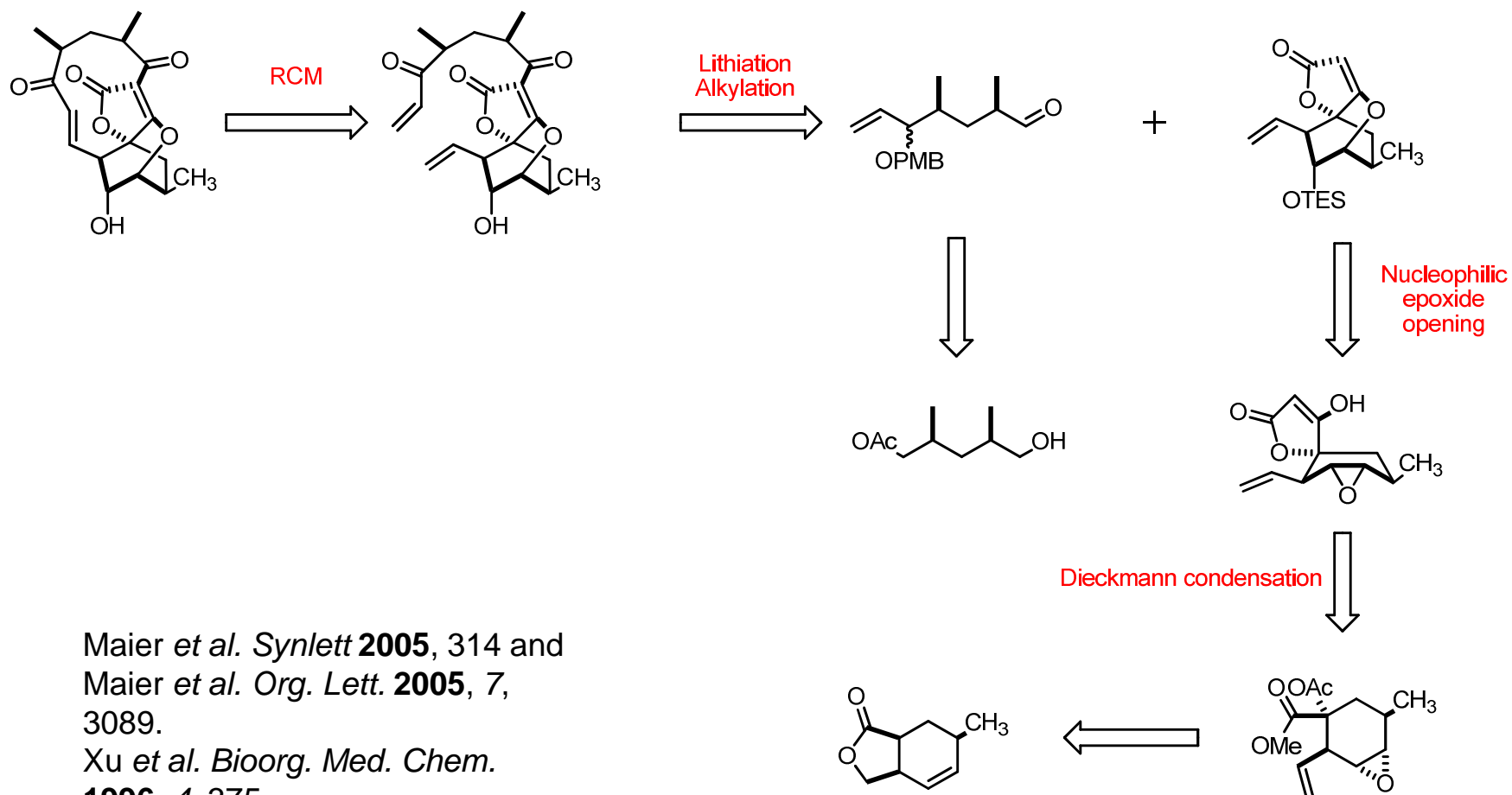


- Is it really interesting? As the overall yield of the 2 steps is 51%...

# Completion of the synthesis



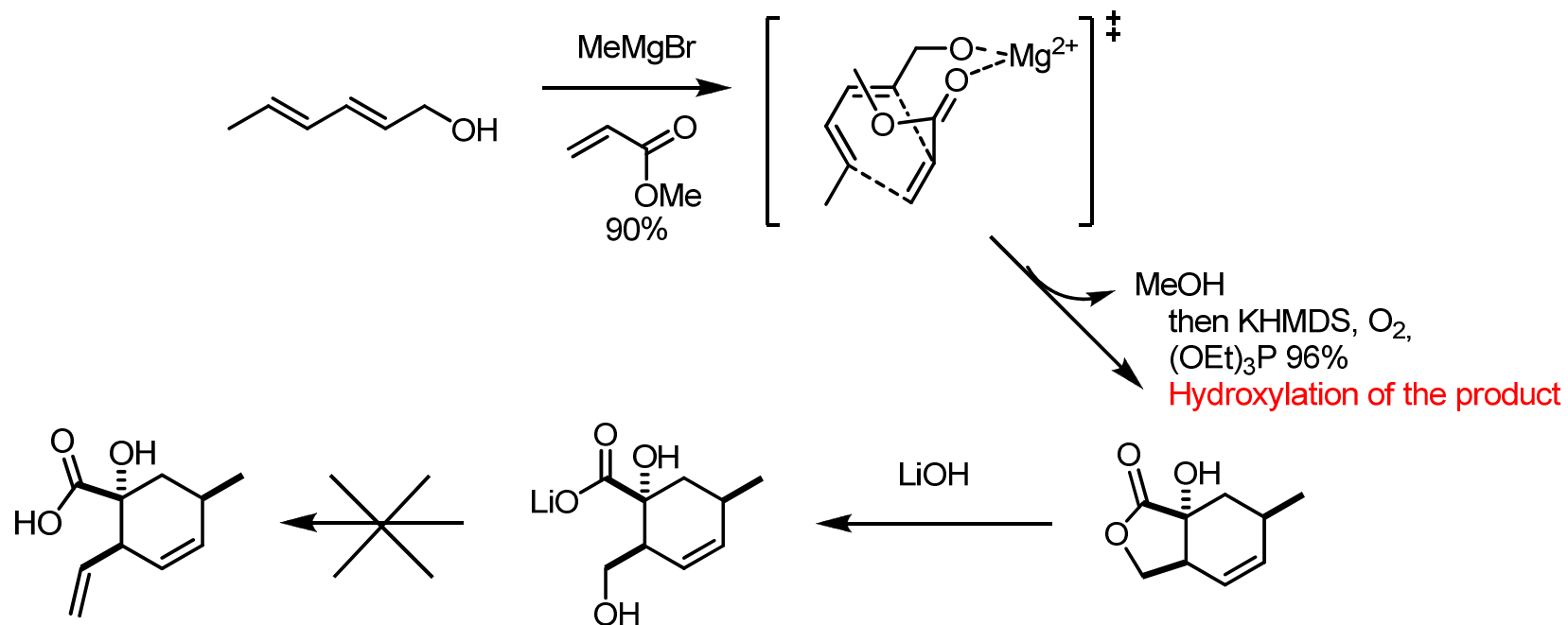
# Nicolaou's Approach: Retrosynthesis



Maier *et al.* *Synlett* **2005**, 314 and  
Maier *et al.* *Org. Lett.* **2005**, 7,  
3089.

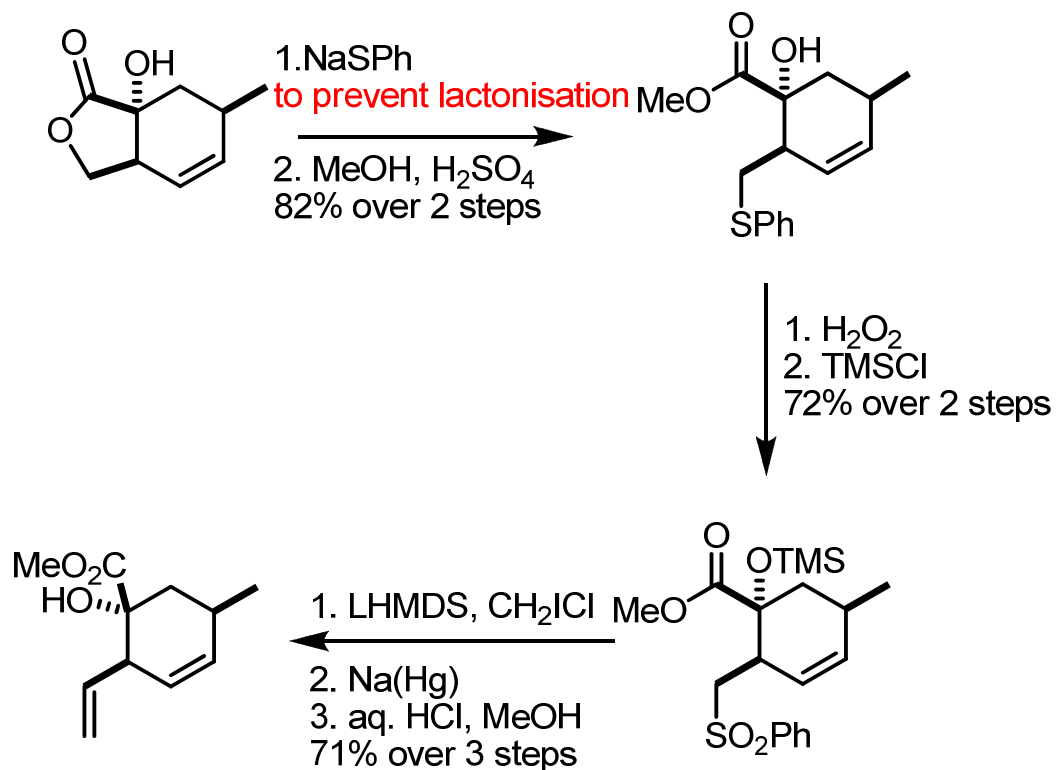
Xu *et al.* *Bioorg. Med. Chem.*  
**1996**, 4, 375.

# Nicolaou's Synthesis: Studies toward the oxabicyclic core



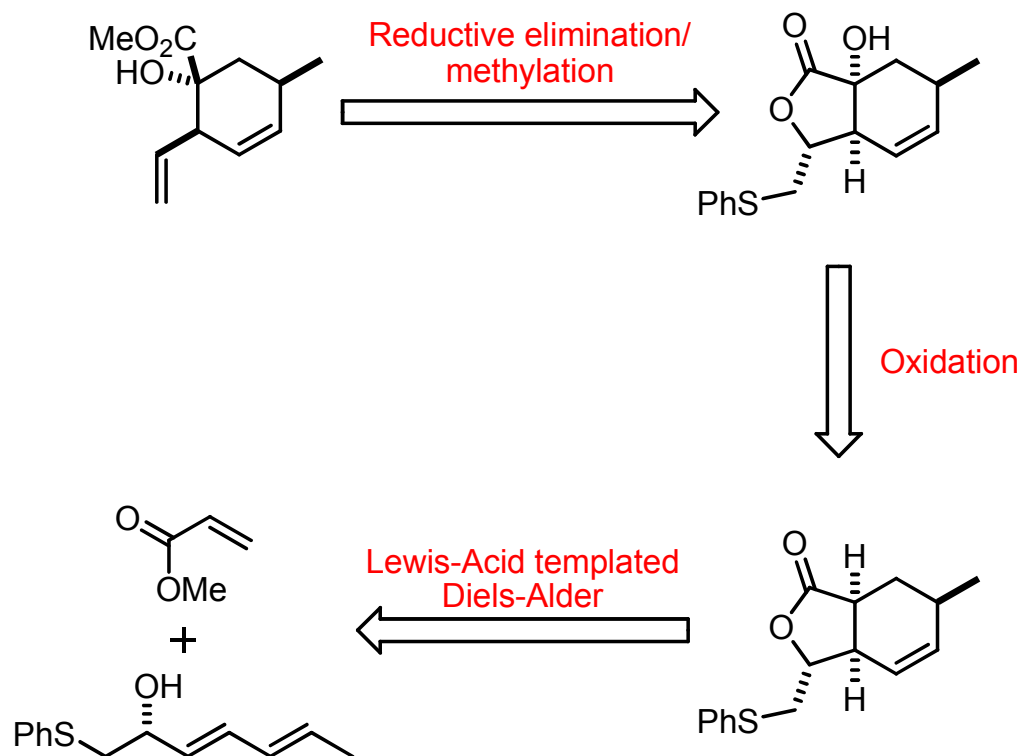
Abae *et al.* *Org. Lett.* **2000**, 2, 3937.  
Maier *et al.* *Org. Lett.* **2005**, 7, 3089.

# Nicolaou's Synthesis: Studies toward the oxabicyclic core



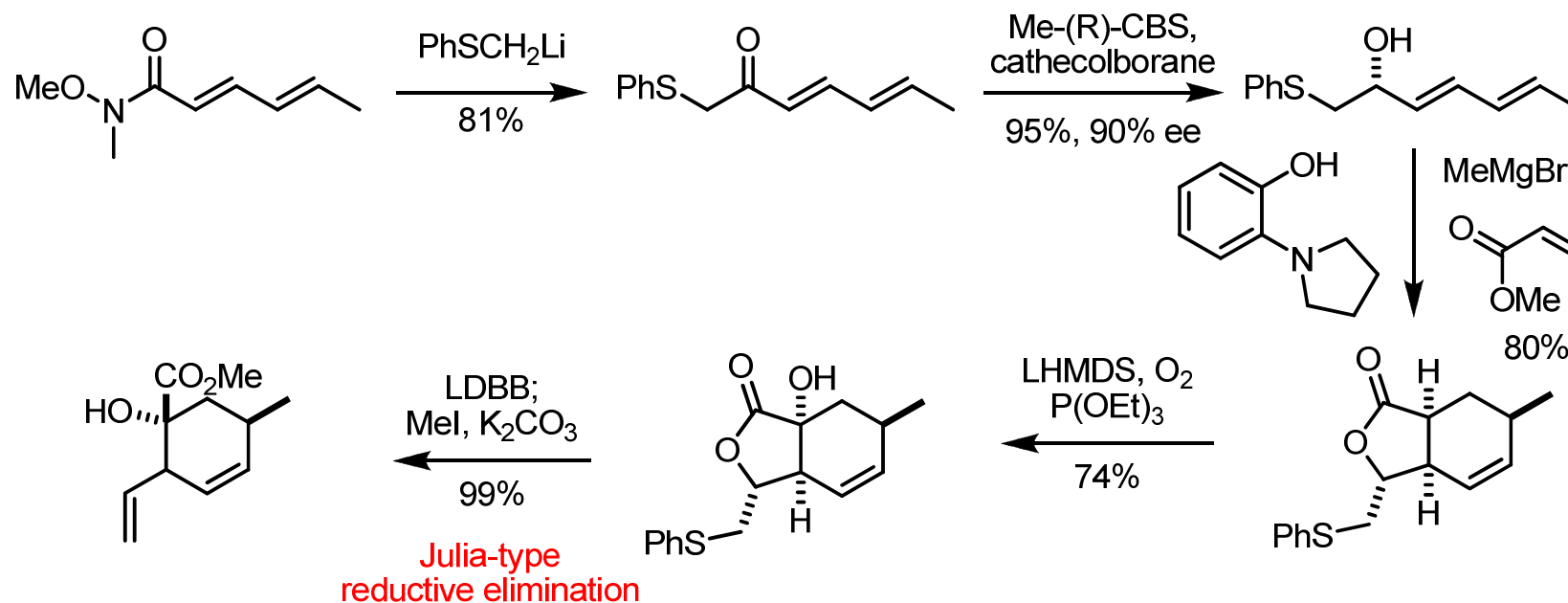
# Nicolaou's synthesis: improved approach

- More efficient approach





# Nicolaou's synthesis: Improved synthesis

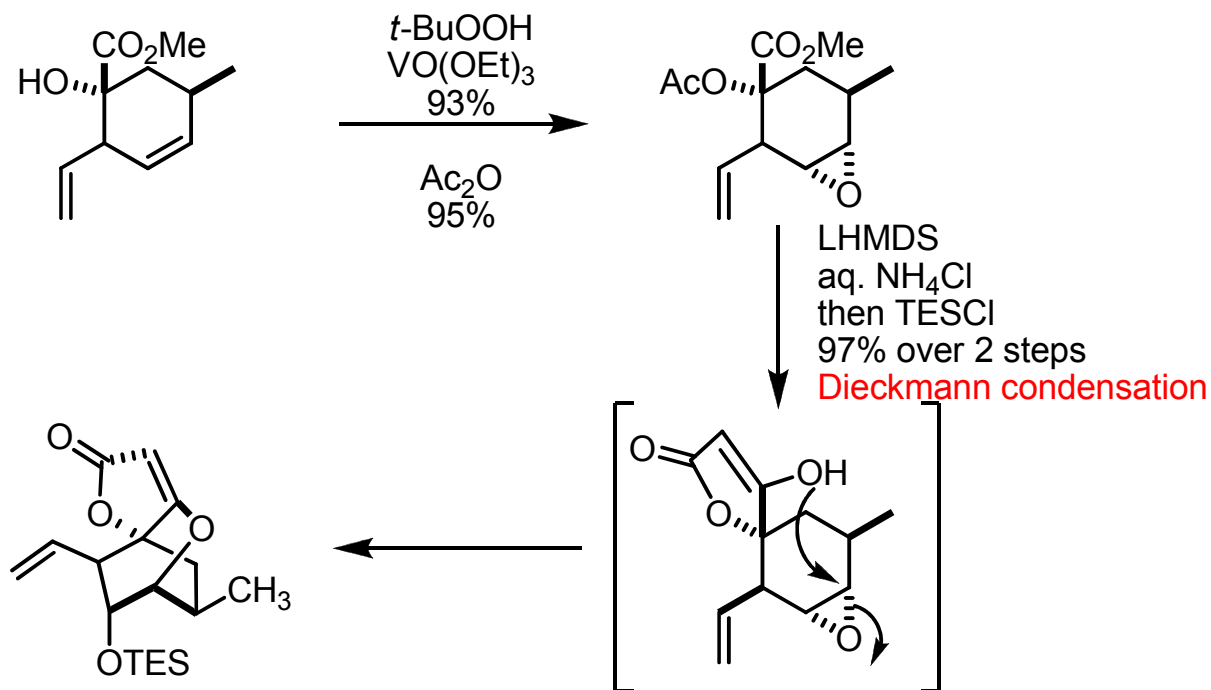


CBS = 2-methyl-CBS-oxazabolrolidine  
LDBB = Li, 4,4'-di-*tert*-butylbiphenyl

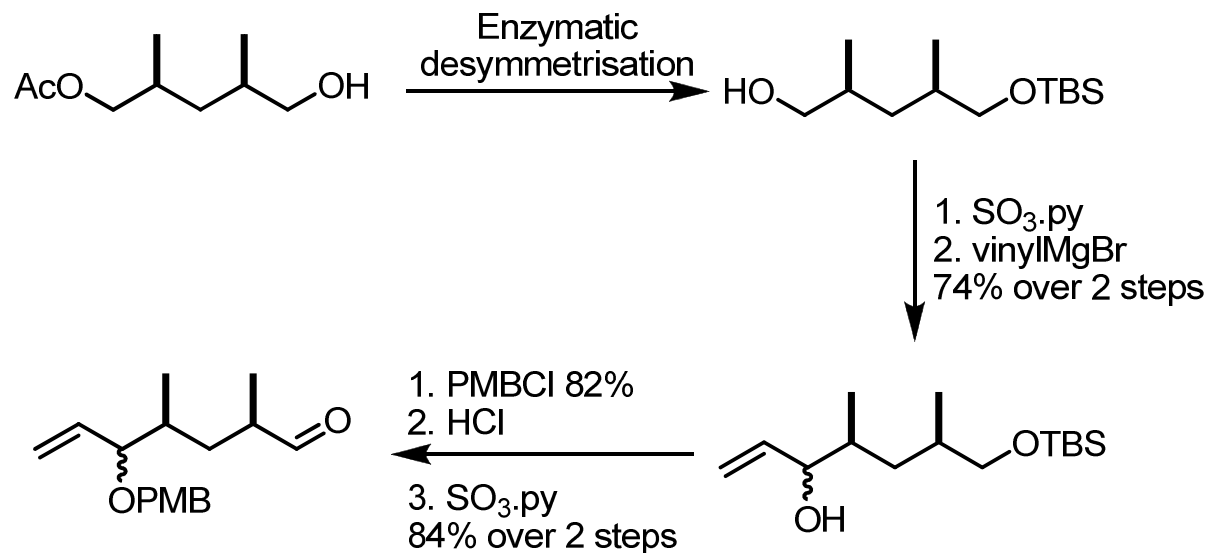
Corey et al. *J. Org. Chem.* **1966**, 31, 4097.  
Cohen et al. *Acc. Chem. Res.* **1989**, 22, 152.

Corey et al. *Angew. Chem. Int. Ed.* **1998**, 37, 1986.

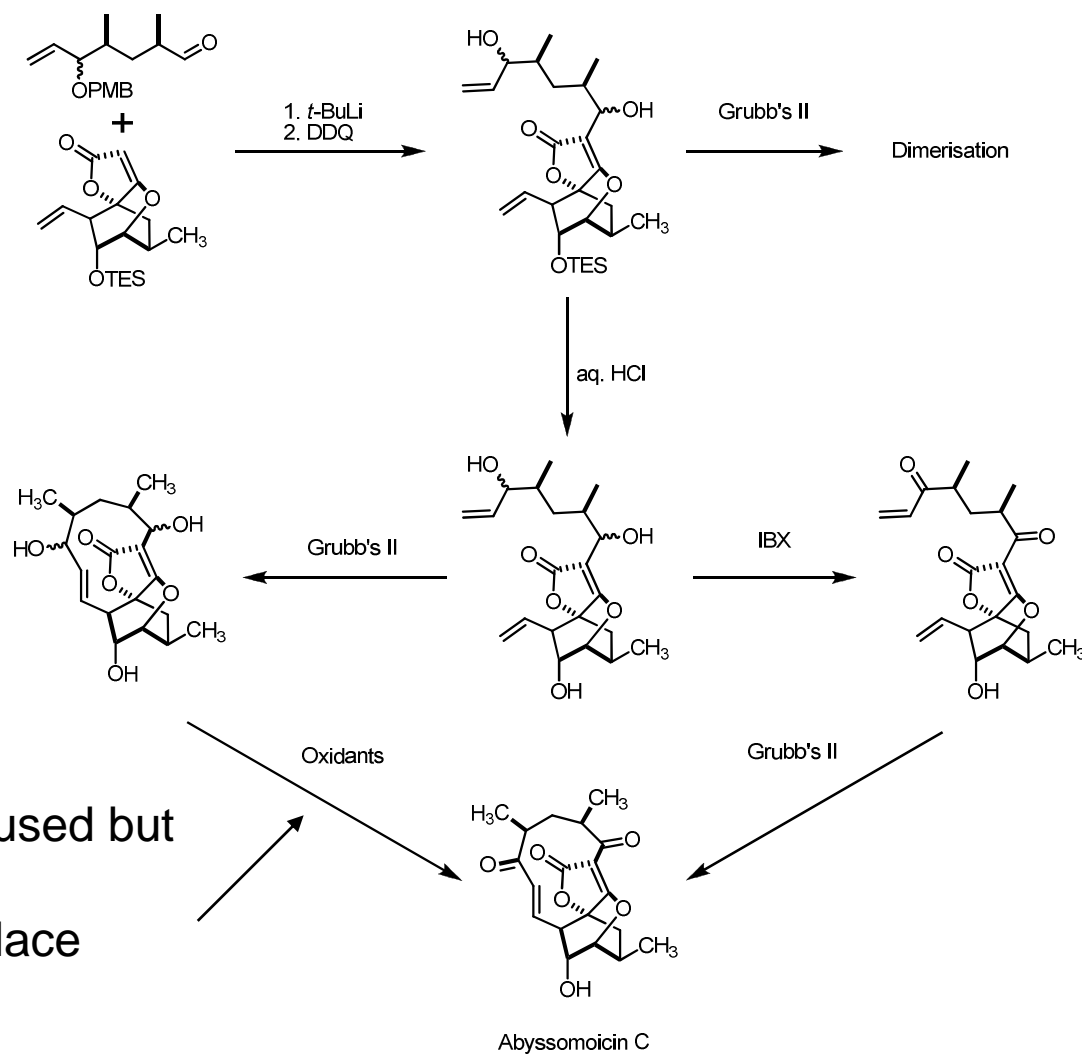
# Nicolaou's synthesis: Synthesis of the oxabicyclic [2,2,2]octane core



# Nicolaou's synthesis

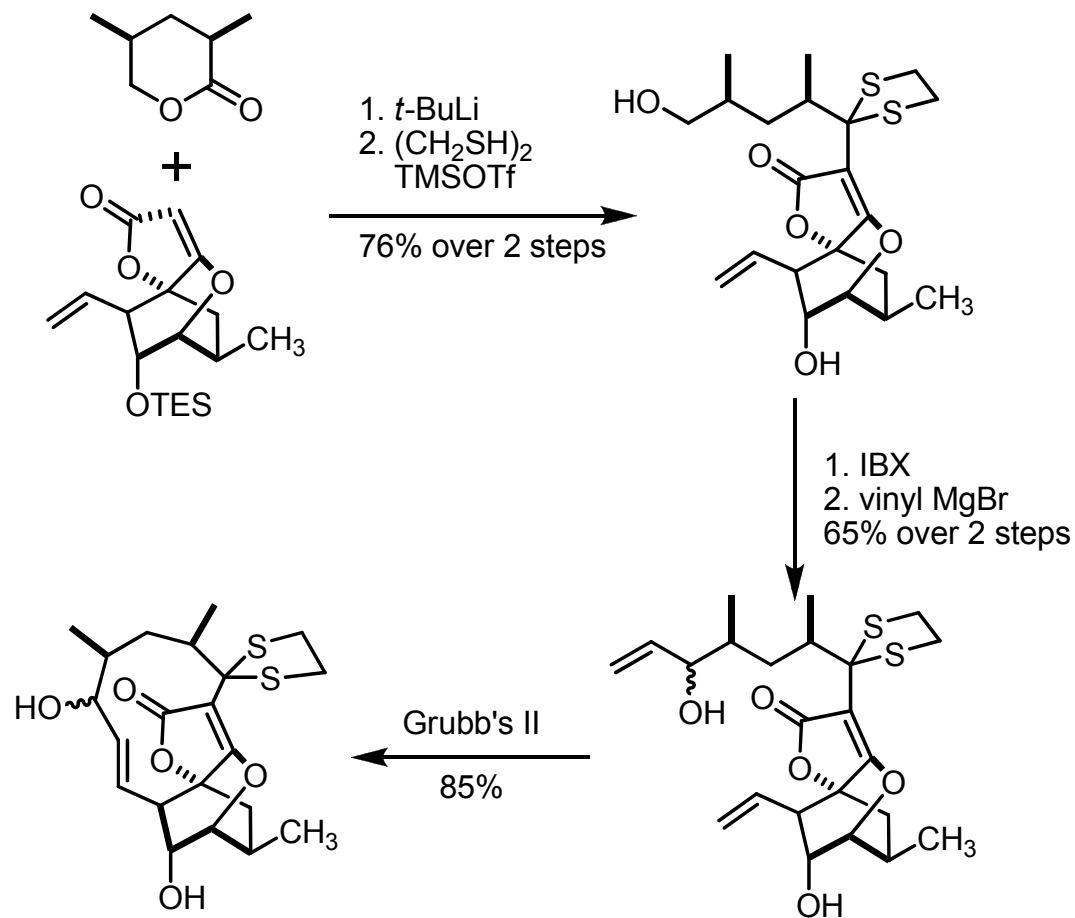


# Nicolaou's synthesis: fragment coupling

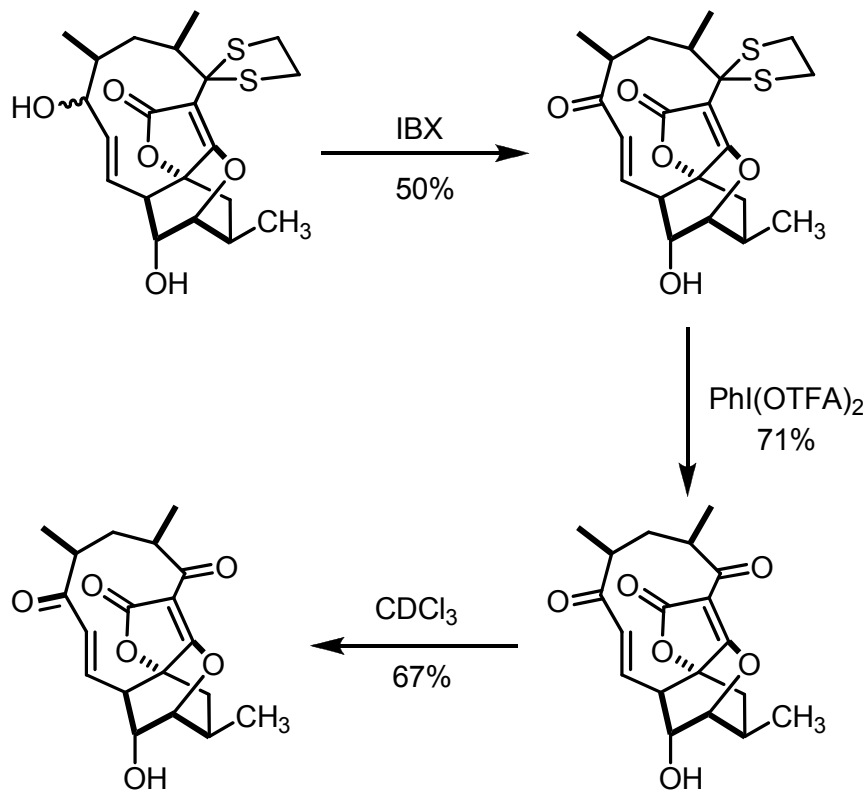


Several oxidants were used but after 1st oxidation hemiketalization took place

# Nicolaou's synthesis: synthesis of Abyssomicin C framework



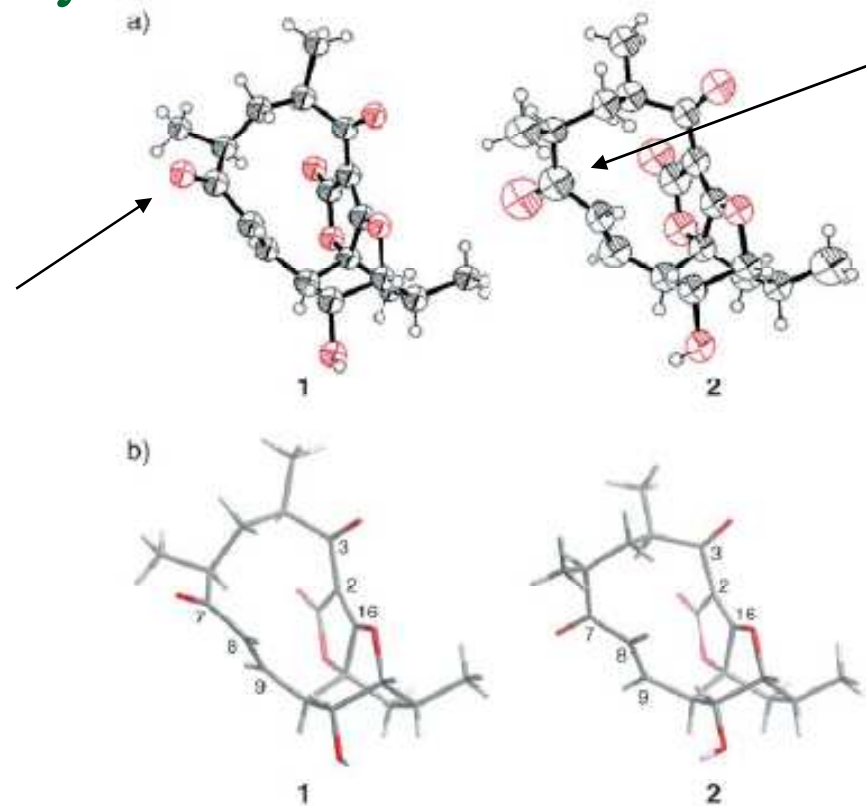
# Nicolaou's synthesis: completion of the synthesis



Abyssomicin C

atrop-Abyssomicin C

# Abyssomicin C and atrop-Abyssomicin C



**Figure 2.** a) ORTEP drawings of abyssomicin C (1)<sup>[1]</sup> and atrop-abyssomicin C (2)<sup>[15]</sup> generated from X-ray crystallographic analysis. Spheres are drawn at a 50% probability level. b) Computer-generated stick models of 1 and 2 based on X-ray crystallographic data.

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# Comparison of Sorensen's and Nicolaou's total syntheses

- Highlight the power of the Diels-Alder reaction
    - Either intramolecular to form a strained macrocyclic system
    - Or intermolecular via a Lewis mediated templated transition state
  - Both well-suited to synthesize new analogues to enable further studies of the structure-activity relationship
-



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## Comparison in numbers

	Sorensen's synthesis	Nicolaou's synthesis
Number of linear steps	15	16
Overall yield	2 %	4 %

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