Mitsunobu Reaction

(1934-2003)

Outline

- General Information:
  - Who discovered this? What is the basic reaction?
- The Mechanism:
  - What exactly happens and how?
- Applications:

i) Variations of the method- where are certain conditions used and why?

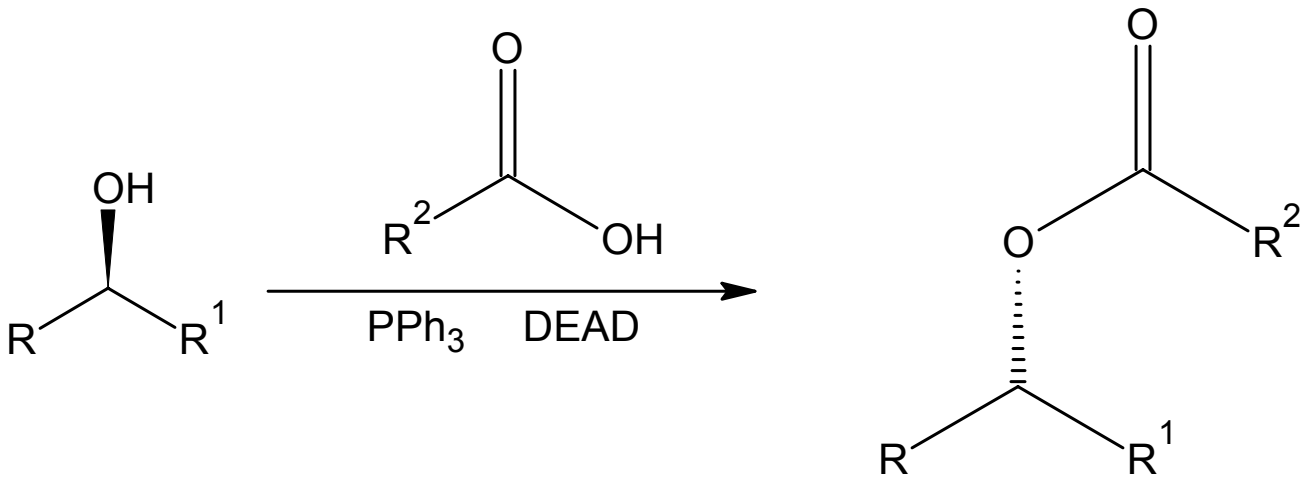
ii) What problem is solved by the reaction? What are the competing methods?

iii) What are some examples of this reaction in total synthesis?

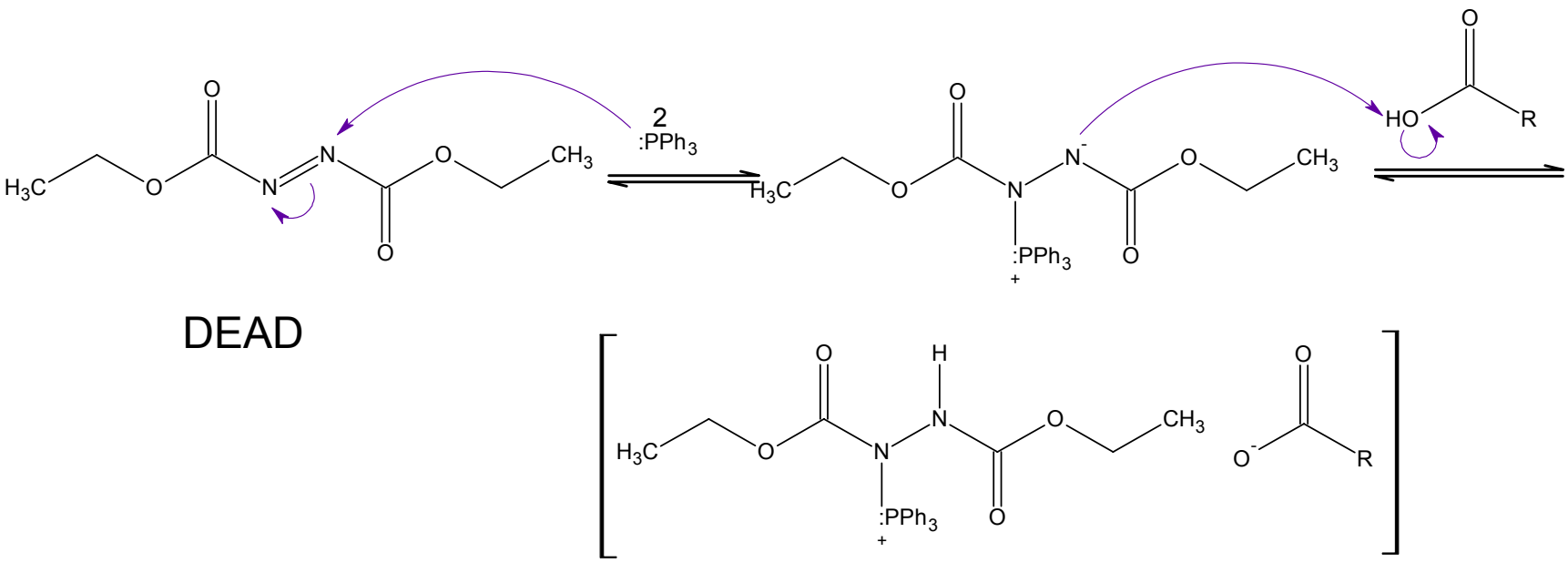
Oyo Mitsunobu

One of Japan's eminent scientists

- Gained importance due to it's ability to invert the stereochemistry of the –OH functional group
- Allows for facile change of functionality via a nucleophilic displacement



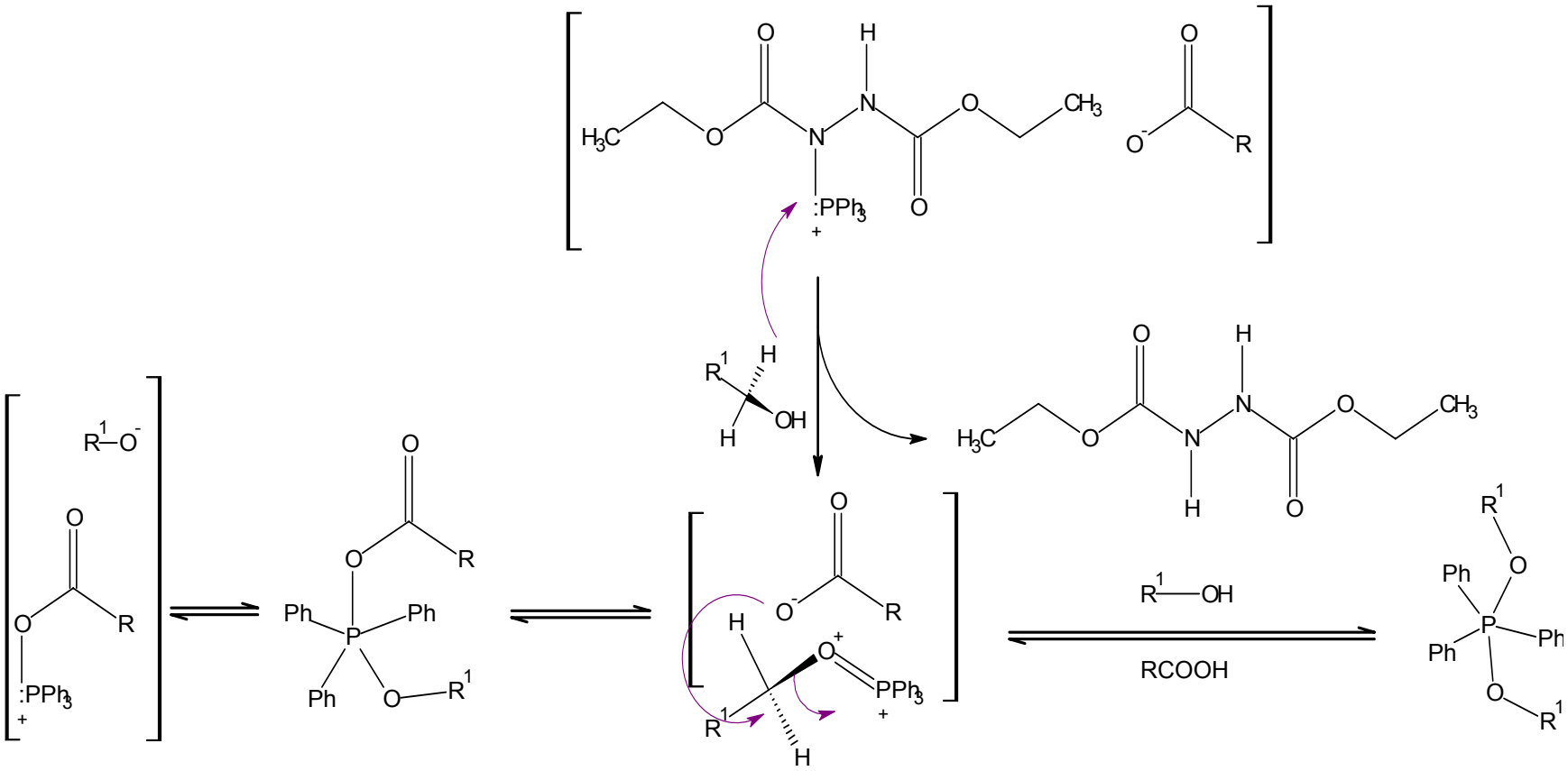
The Mechanism



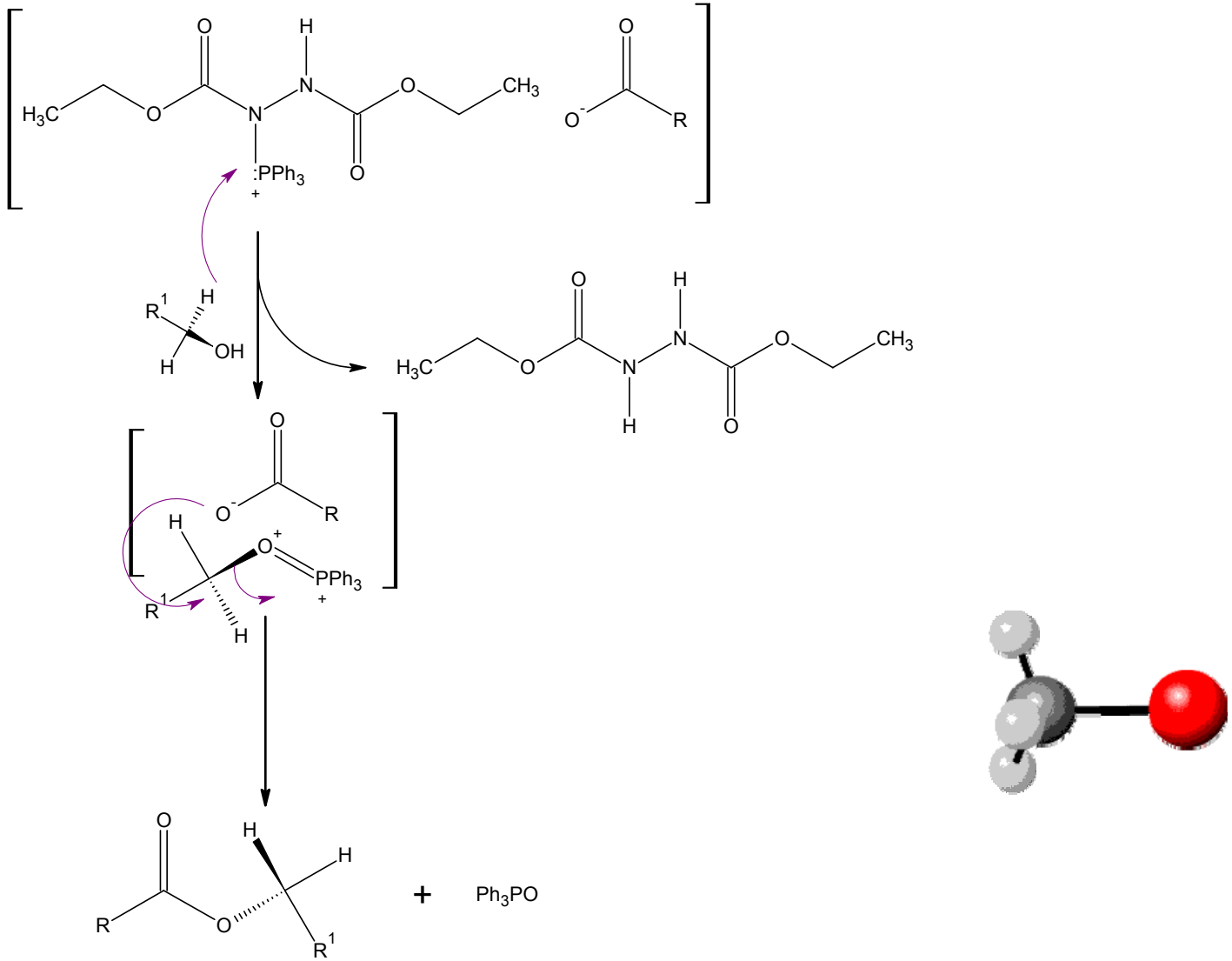
DEAD

- Diethyl azodicarboxylate (DEAD)
- Triphenylphosphine

The Mechanism: Part II

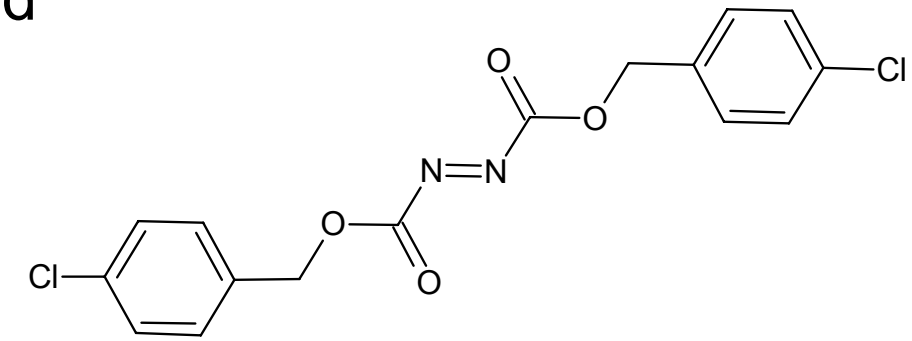


The Mechanism: Part III



i) (a) Variations of the Method

- Any nucleophile with pK_a under 15
  - Eg. Esters, alcohols, aryl ethers, amine and thioethers
- Alternative azodicarboxylate
- CH_2Cl_2 solvent
- Advantages to DEAD, DIAD
  - Solid
  - Polarity of byproduct significantly different

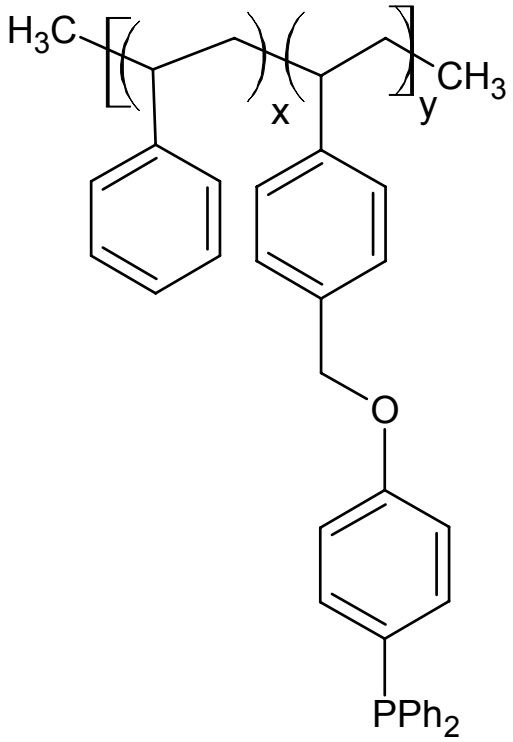


DCAD

Lipshutz, B. H. et. al. *Organic Letters*. **2006**, *8 No.22*, 5069-5072

i) (b) Where are certain conditions used and why?

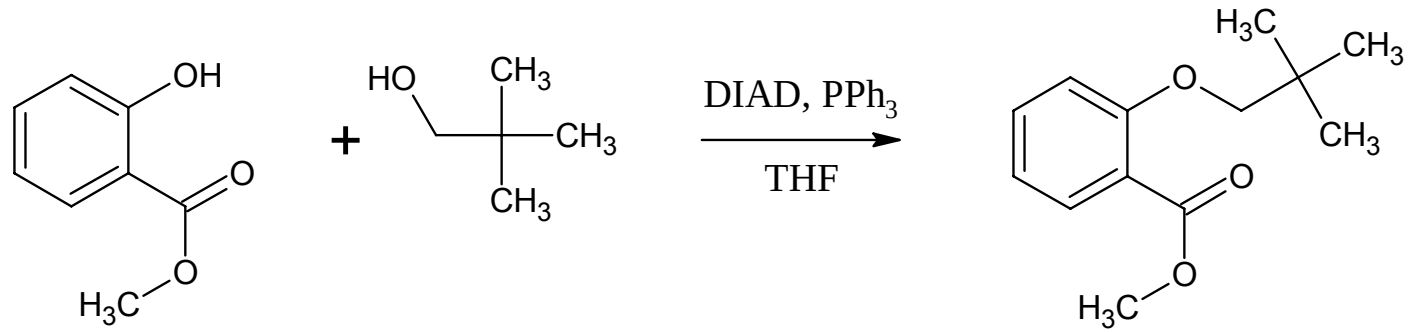
- Solid supported reagents for better product isolation
- Solution: non-crosslinked polystyrene with triphenylphosphine
- Successful Mitsunobu reaction with menthol, 2-(S)-octanol, ethyl-(S)-lactate



Charette, A. B. et. al. *J. Org. Chem*. **2001**, *66*, 2178-2180

i) (b) continued…

- Sterically hindered alcohol and phenol
- Reaction time reduced from 7 days to 15 minutes
- Concentration 0.1M->3M
- Sonic waves better mixing, generate free radicals

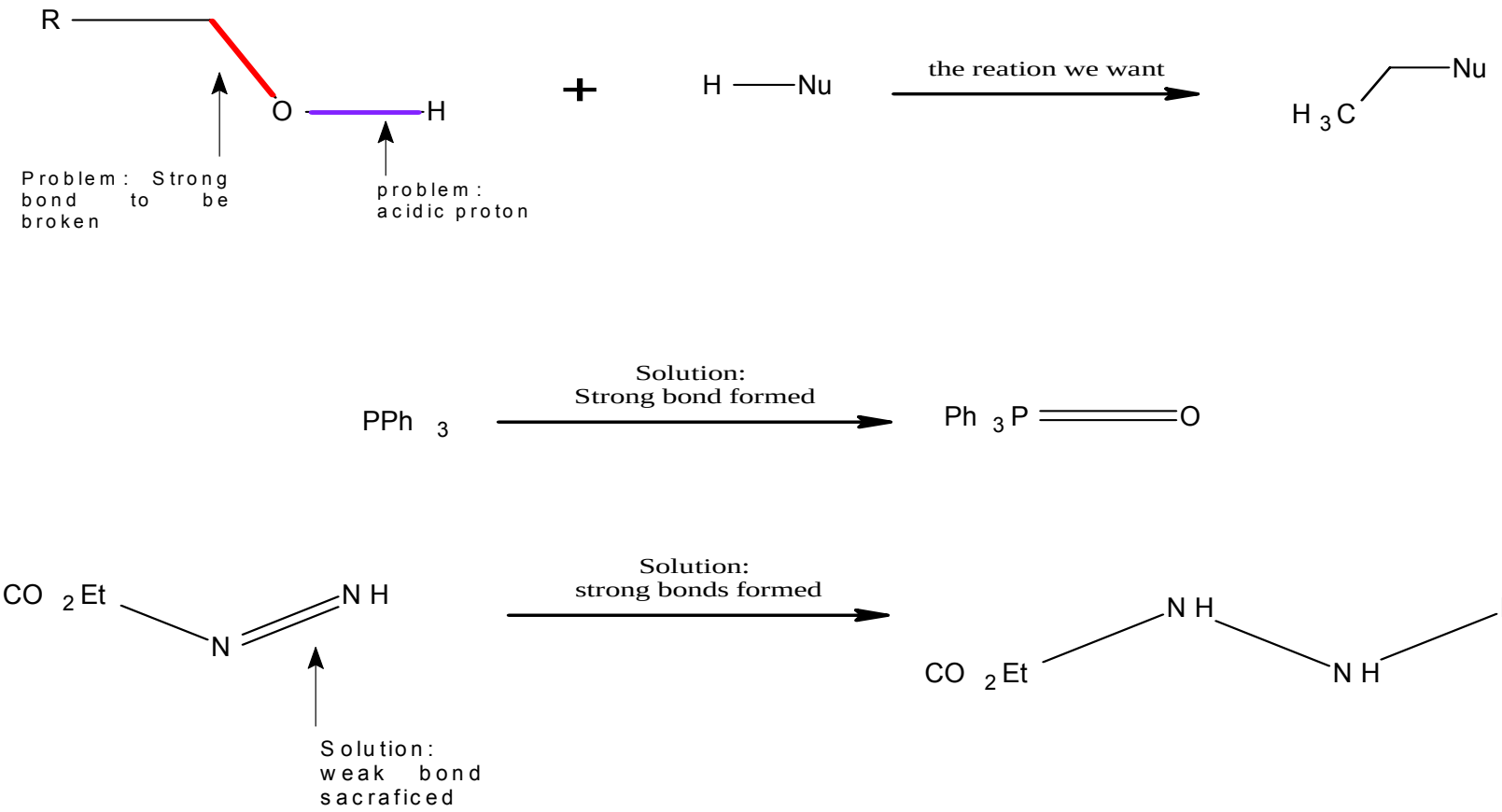


70-75% yield

Lepore, S. D.; He, Y.. *J. Org. Chem*. **2003**, *68*, 8261-8263

ii) (a) Problems solved

- The Mitsunobu reaction is used to replace –OH by another group with inversion of configuration.



ii) (a) Problems solved

- Presents a method of inverting stereochemistry by an S_N2 displacement
  - Beneficial for making sterically active compounds in the pharmaceutical industry
- New method for easily changing the functionality of the hydroxyl group
  - Converts primary or secondary alcohols
  - New functional groups include esters, phenyl ethers, thioethers etc.
- Other functional groups beside carboxylic acids may also be used so long as their pK_a is less than 15.

ii) (a) Problems solved

Mitsunubu vs. Ts for allowing oxygen to be a better leaving group

Mitsunubu Reaction

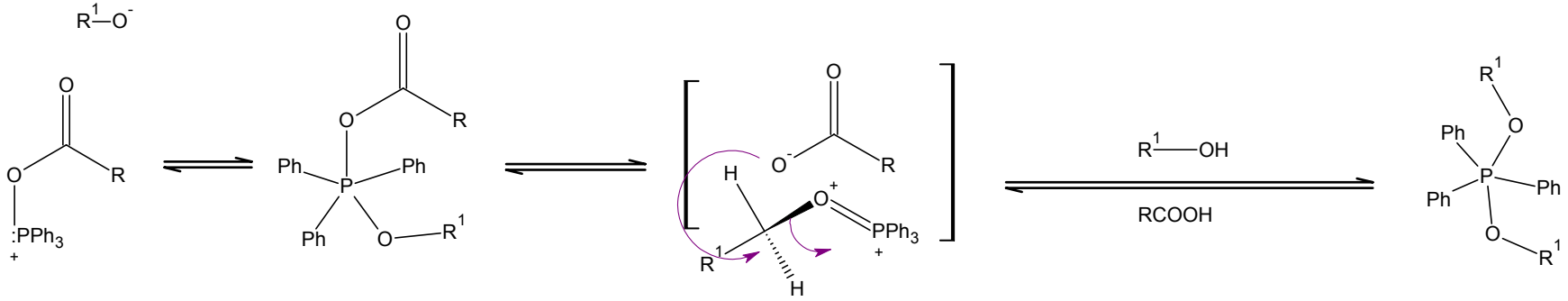
- Better controlled
- The exact product is known
- Can control the stereochemistry

Ts

- Not as easily controlled
- Several products possible (elimination, inversion etc.)
- Stereochemistry not controlled

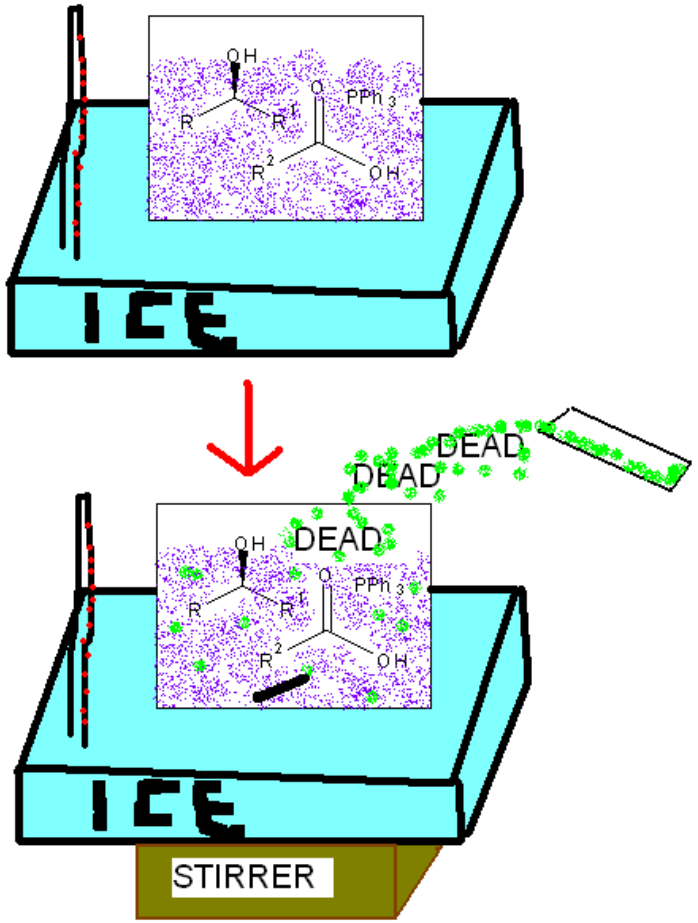
ii) (b) Competing Methods

- The ratio of interconversion of intermediates depend on the carboxylic acid pK_a (or other nucleophile used) and the solvent polarity
- The rate of reaction is controlled by carboxylate (or other nucleophile) basicity and solvation.
- The order of addition of reagents is very important for limiting side reactions and achieving an appreciable amount of wanted product



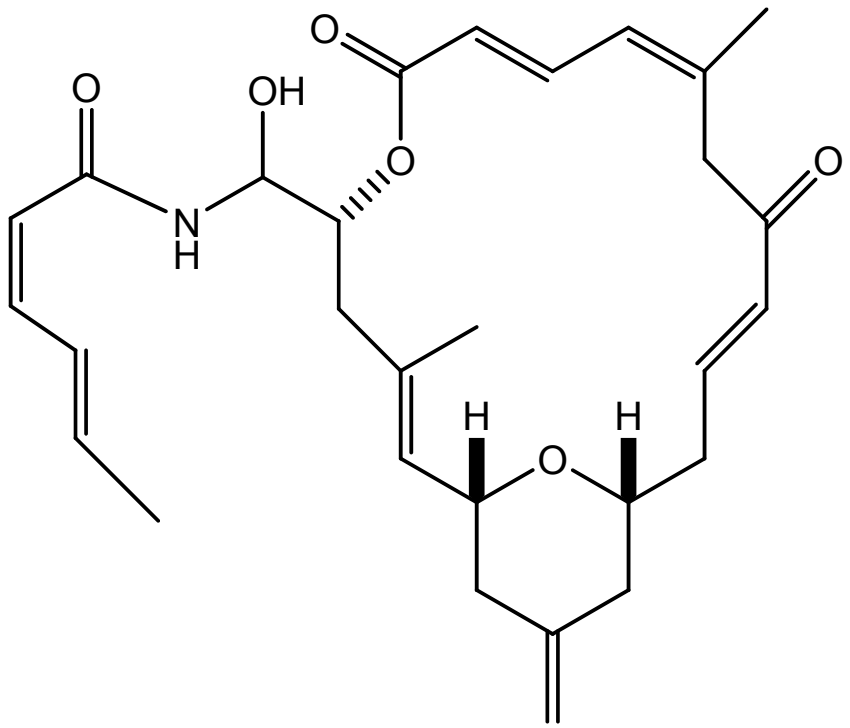
Ideal Order of Addition To Limit Byproduct Formation:

- Dissolve the alcohol, the carboxylic acid (or other nucleophile) and triphenlyphosphine in THF (or other suitable solvent ex. Et_2O)
- Cool to 0 °C using an ice bath
- Slowly add the DEAD dissolved in THF
- Stir at room temperature for several hours.
- If unsuccessful performing the betaine may give better results
  - Add DEAD to triphenylphosphine in THF at 0 °C
  - Add the alcohol and finally the acid



iii) Examples in total synthesis

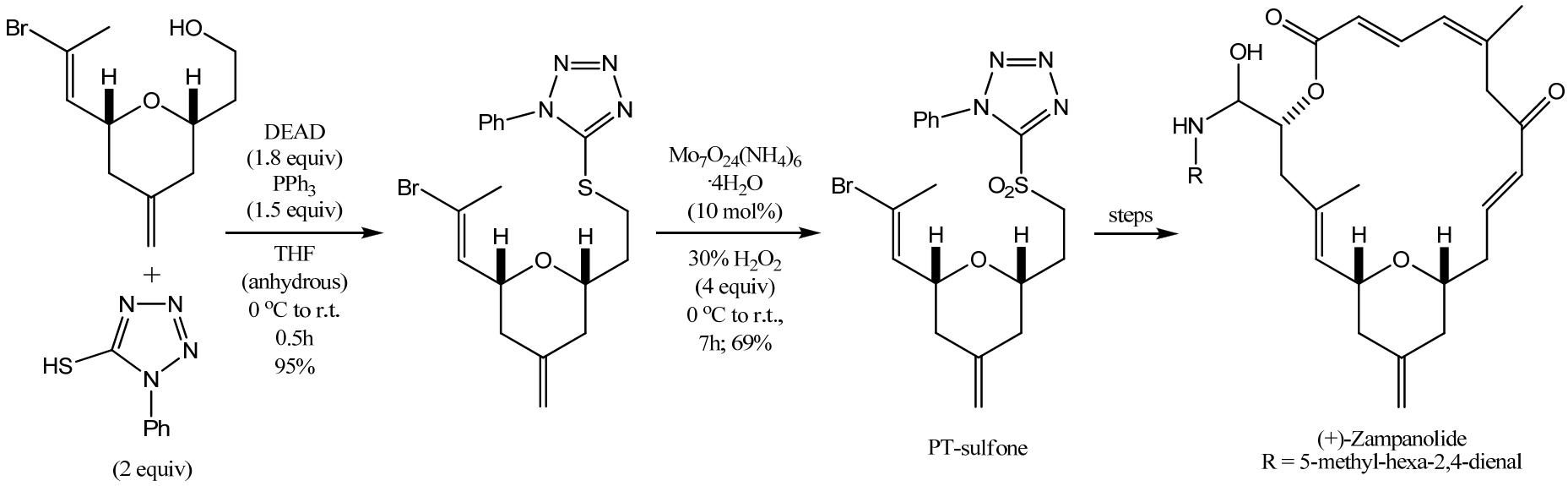
- (+)-zampanolide synthesized in laboratory of A.B. Smith
- Tanaka and Higa reported isolation, partial structure elucidation, and biological activity of (-)-zampanolide
- Key structural elements include highly unsaturated framework and uncommon N-acyl hemiaminal side chain
- (-)-zampanolide shows impressive cytotoxicity against P388, HT29, A549, and MEL28 cell lines (IC_{50} 1-5 ng/mL)



(+)-Zampanolide

J. Am. Chem. Soc. 123 (2001) 12426-12427

iii) Example 1 continued…

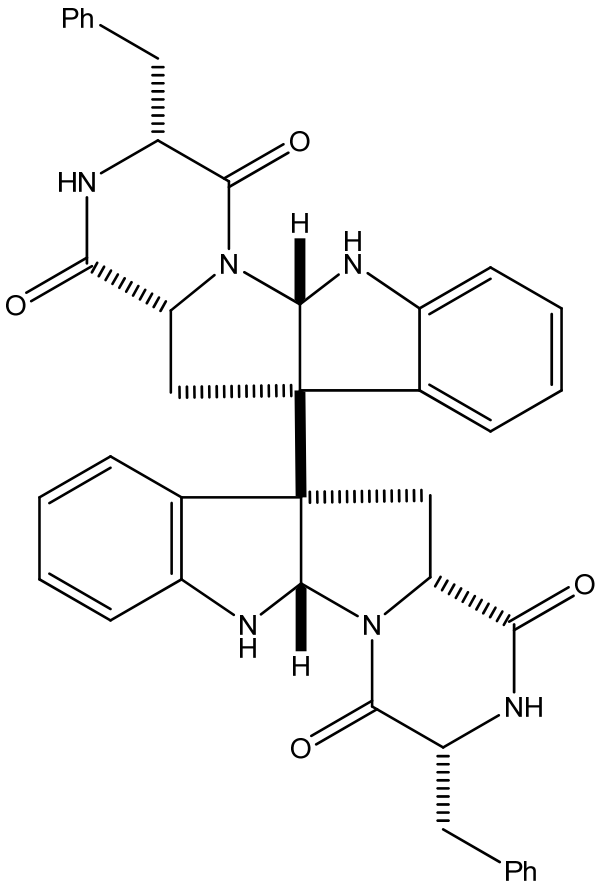


- C8-9 (*E*)-olefin moiety constructed using *Kocienski-modified Julia olefination*
- required PT-sulfone prepared from corresponding primary alcohol *via* two-step protocol employing sequential *Mitsunobou reaction* and sulfide-sulfone oxidation

J. Am. Chem. Soc. 123 (2001) 12426-12427

iii) Example 2

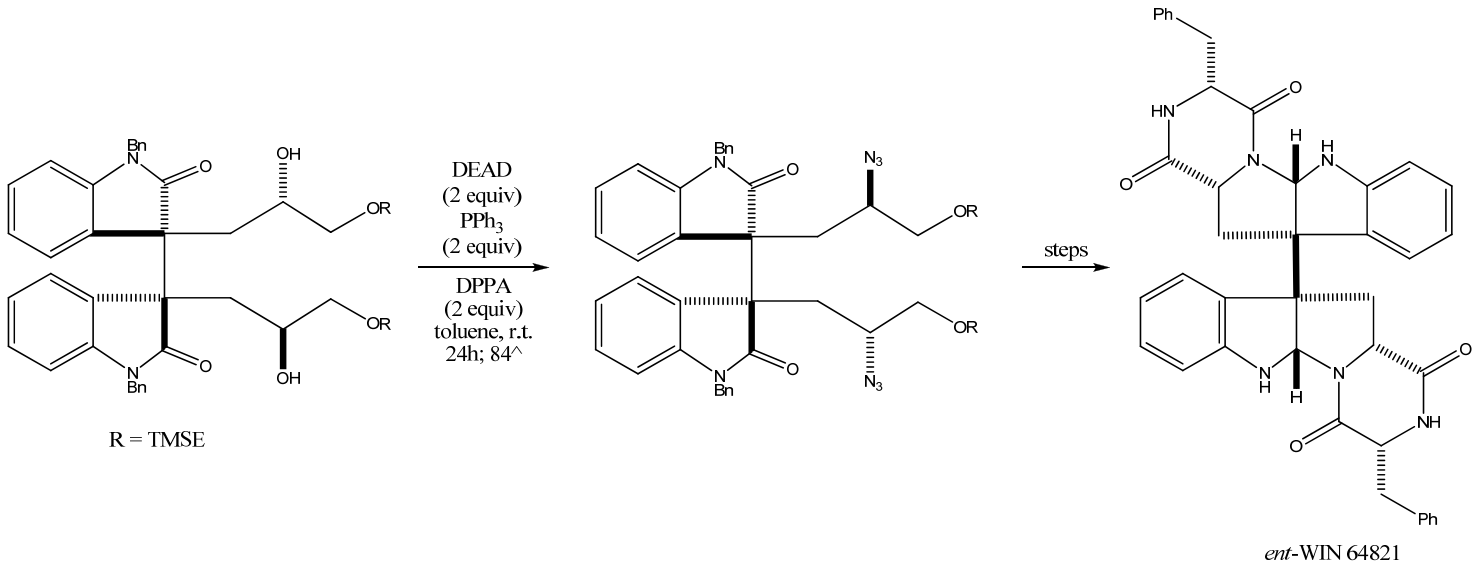
- enantioselective total synthesis of *ent*-WIN 64821 accomplished by L.E. Overman and co-workers
- compound representative member of family of *C2*-symmetric bispyrrolidinoindoline diketopiperazine alkaloids
- WIN 64821 a competitive substance P antagonist with submicromolar potency against human NK1 receptor and also an antagonist of the cholecystokinin type-B receptor



ent-WIN 64821

J. Am. Chem. Soc. 123 (2001) 9465-9467

iii) Example 2 continued…



R = TMSE

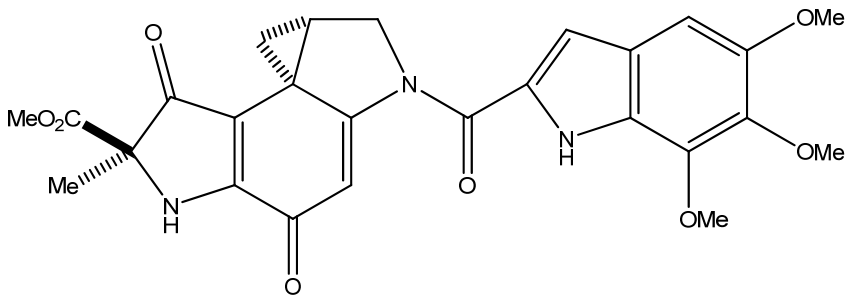
ent-WIN 64821

- stereospecific incorporation of two C-N bonds achieved using *Mitsunobu reaction* to convert two secondary alcohol functionalities to corresponding alkyl azides with inversion of configuration
- azides subsequently reduced to primary amines and cyclized to desired *bis*-amidine functionality

J. Am. Chem. Soc. 123 (2001) 9465-9467

iii) Example 3

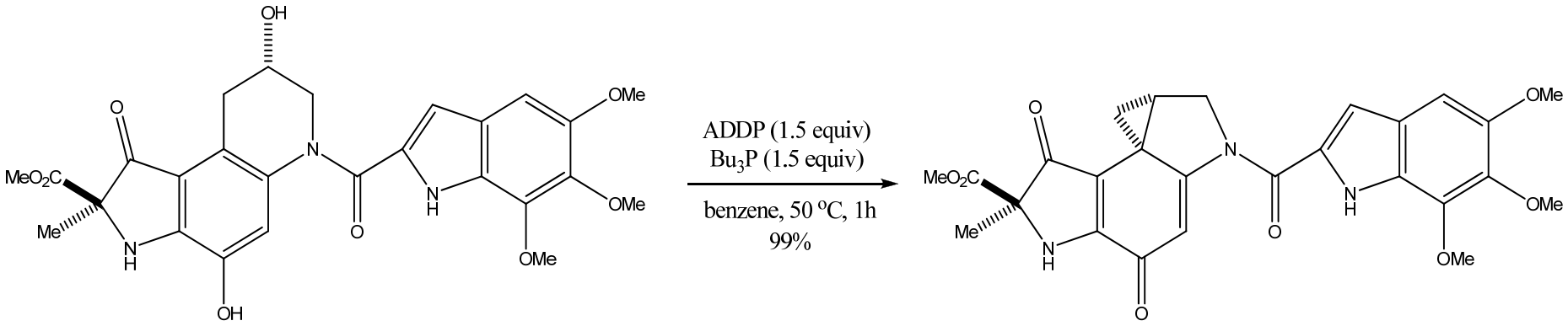
- naturally occurring potent antitumor antibiotic (+)-duocarmycin A, its epimer and unnatural enantiomers prepared by D.L. Boger et al.
- Represents most challenging member of class
- Properties derived through sequence-selective alklyation of duplex DNA



(+)-Duocarmycin A

J. Am. Chem. Soc. 118 (1996) 2301-2302

Example 3

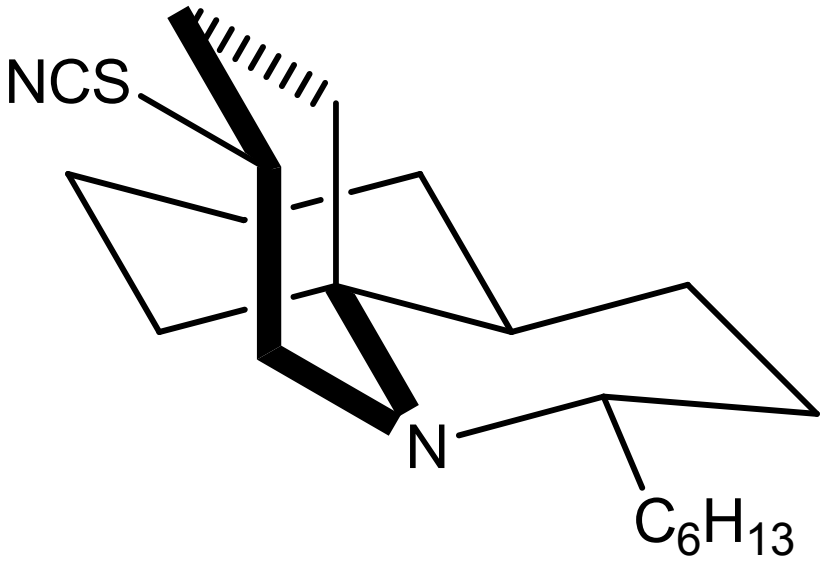


- last step of synthesis was elaboration of reactive cyclopropane moiety carried out *via* a *transannular spirocyclization* using Mitsunobu conditions
- special case where *Mitsunobu reaction* used to create new C-C bonds

J. Am. Chem. Soc. 118 (1996) 2301-2302

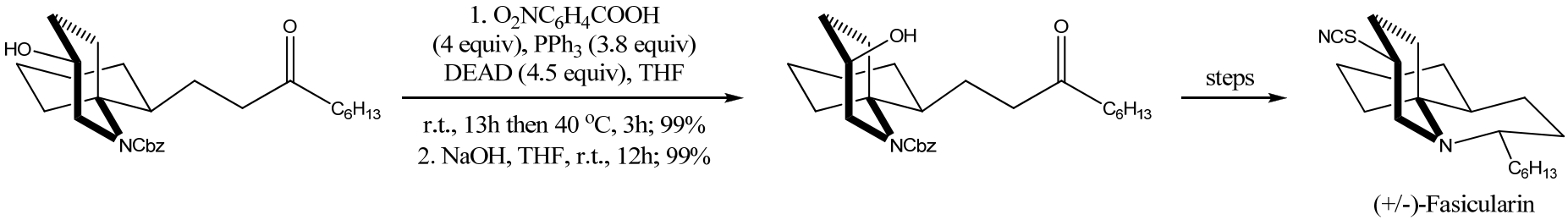
iii) Example 4

- first total synthesis of tricyclic marine alkaloid (±)-fasicularin completed by team of C. Kibayashi
- Discovered by Patil and co-workers from Micronesian ascidian
- Selective activity against DNA repair-deficient organism and cytotoxic to Vero cells (IC_{50} = 14 µg/mL)



(+/-)-Fasicularin

Example 4



(+/-)-Fasicularin

- secondary alcohol functionality inverted using Mitsunobu protocol
- resulting *p*-nitro benzoate readily hydrolyzed under basic conditions

J. Am. Chem. Soc. 122 (2000) 4583-4592