The Tetracycline Antibiotics

Leading Articles:

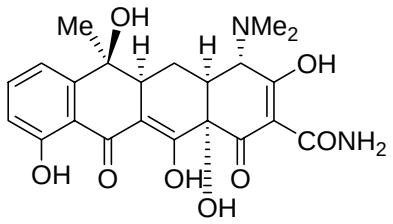
Myers *et al. J. Am. Chem. Soc*. **2005**, *ASAP* (ja052151d)

Myers *et al. Science* **2005**, *308*, 395

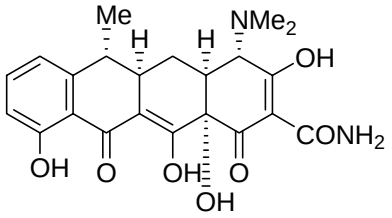
Tetracyclines

- First members discovered in 1940s
- Teracyclines show antibacterial activity against gram-positive and gram-negative bacteria but also against protozoan parasites, chlamydiae and others

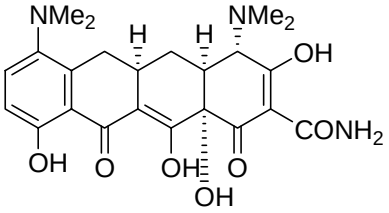
Generic Name	Trade Name	Year of Discovery
Chlortetracycline	Auromycin	1948
Oxytetracycline	Terramycin	1948
Limecycline	Tetralysal	1961
Doxycyline	Vibramycin	1967
Minocycline	Minocin	1972
t-Butyglycylamidominocycline	Trigilcycline	1993 (phase II)



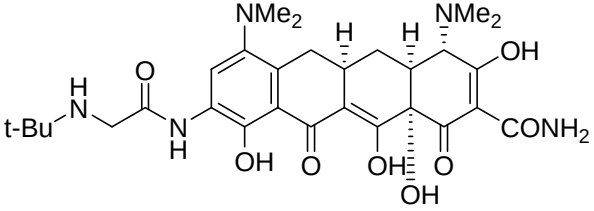
Tetracycline



Doxycyline



Minocycline



9-(t-Butylglycylamido)-minocycline

Mechanism of Action

- Tetracyclines traverse the outer membrane as magnesium complexes *via* the porin channels
- In the cytosol tetracyclines probably become chelated by divalent cations
- Tetracycline-metal complexes bind to the ribosomal 30S unit reversibly and block binding of aminoacyl-tRNA to the A-site
- Tetracyclines show weak antieukariotic activity (small inhibition of 80S ribosomes but interact with 70S ribosomes present in mitochondria)

Mechanism of Resistance

- The resistance to tetracycline antibiotics is transmitted *via* mobile genetic elements
- Over 30 genes have been identified that are responsible for tetracycline (*tet*) or oxytetracycline (*otr*) resistance
- Three main methods of tetracycline resistance
  - Synthesis of efflux proteins
  - Synthesis of ribosomal protection proteins – homologous to EF-Tu and may allow for aminoacyl-tRNA binding
  - Enzymatic inactivation of tetracyclines

Chopra, Roberts *Microbiol. Mol. Biol. Rev.* **2001**, *61*, 232
Saenger *at al. Angew. Chem. Int. Ed.* **2000**, *39*, 2042

The Total Syntheses of Tetracyclines

6-Demethyl-6-deoxytetracycline
Conover *et al. J. Am. Chem. Soc.* **1962**, *84*, 3222
Woodward *Pure Appl. Chem.* **1963**, *6*, 561
Korst *et al. J. Am. Chem. Soc.* **1968**, *90*, 439

Muxfeldt, Rogalski. *J.Am. Chem. Soc.* **1965**, *87*, 933

(±)-12a-Deoxy-5a,6-anhydrotetracycline
Gurevich *et al. Tetrahedron Lett.* **1967**, 132

(±)-Terramycin
Muxfeld *et al. J. Am. Chem. Soc.* **1979**, *101*, 689

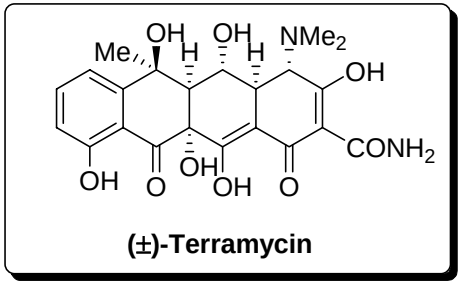
(±)-12a-Deoxytetracycline
Stork *et al. J. Am. Chem. Soc.* **1996,** *118,* 5304

(-)-Tetracycline
Tatsuta *et al. Chem. Lett.* **2000**, 646
Myers *et al. J. Am. Chem. Soc*. **2005**, *ASAP* (ja052151d)

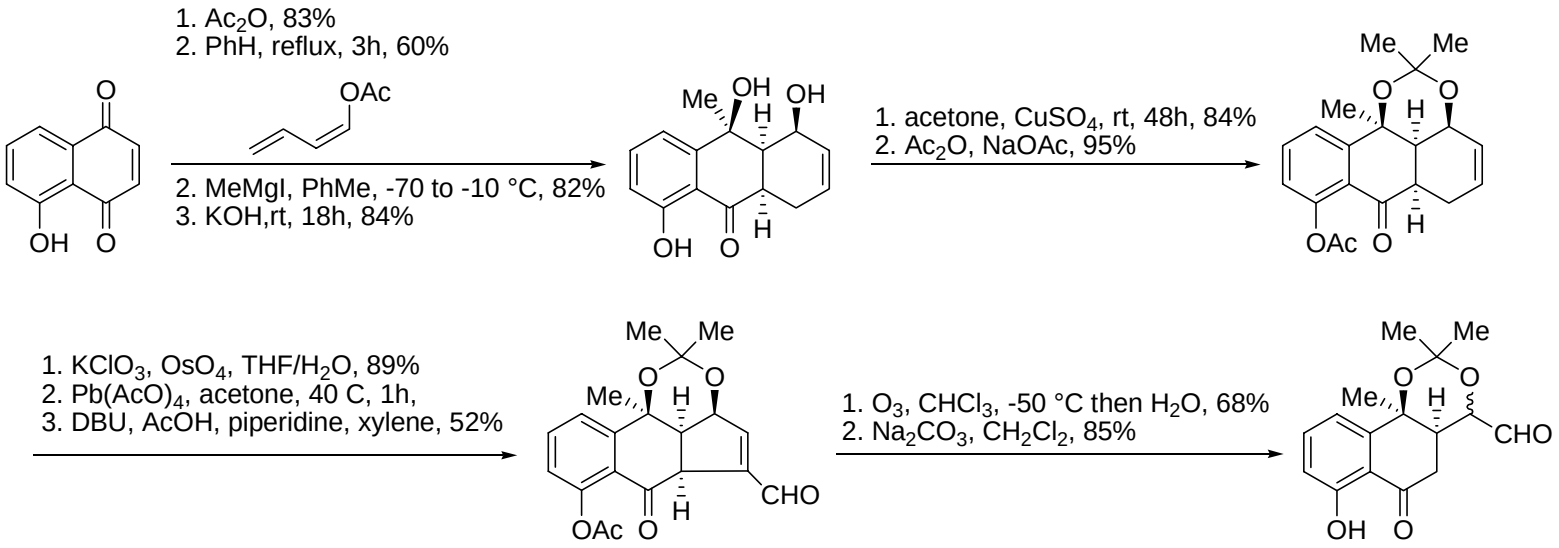
(-)-Doxycycline
Myers *et al. Science* **2005**, *308*, 395

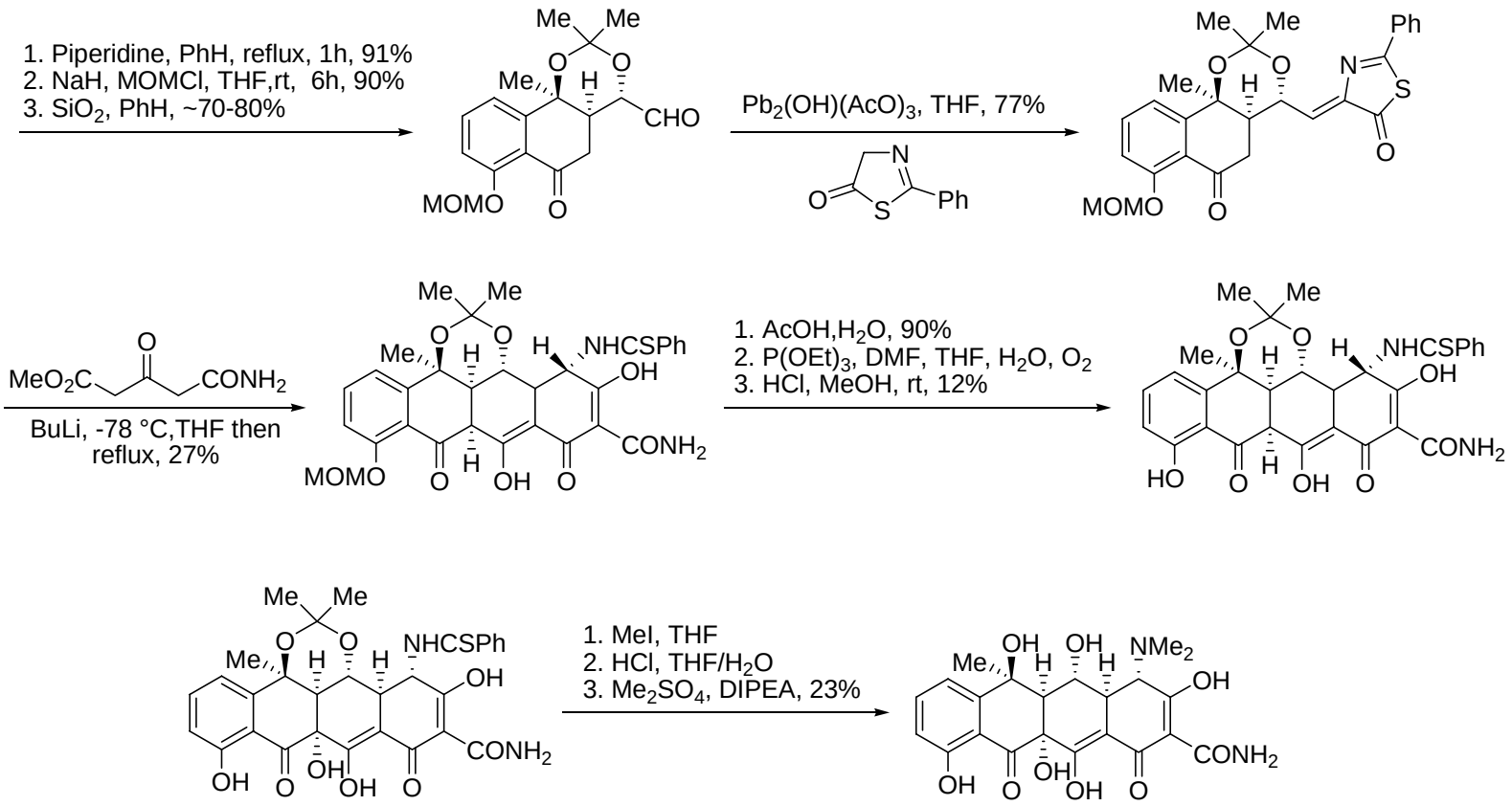
The Total Synthesis of Terramycin

Muxfeld *et al. J. Am. Chem. Soc.* **1979**, *101*, 689



(±)-Terramycin





Summary:

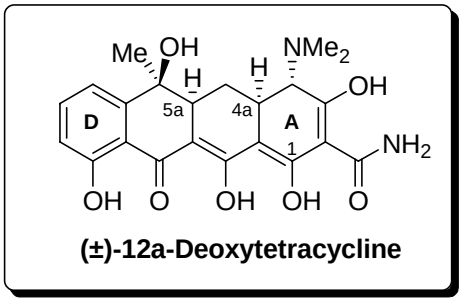
22 steps, 0.06%

Key Transformations:

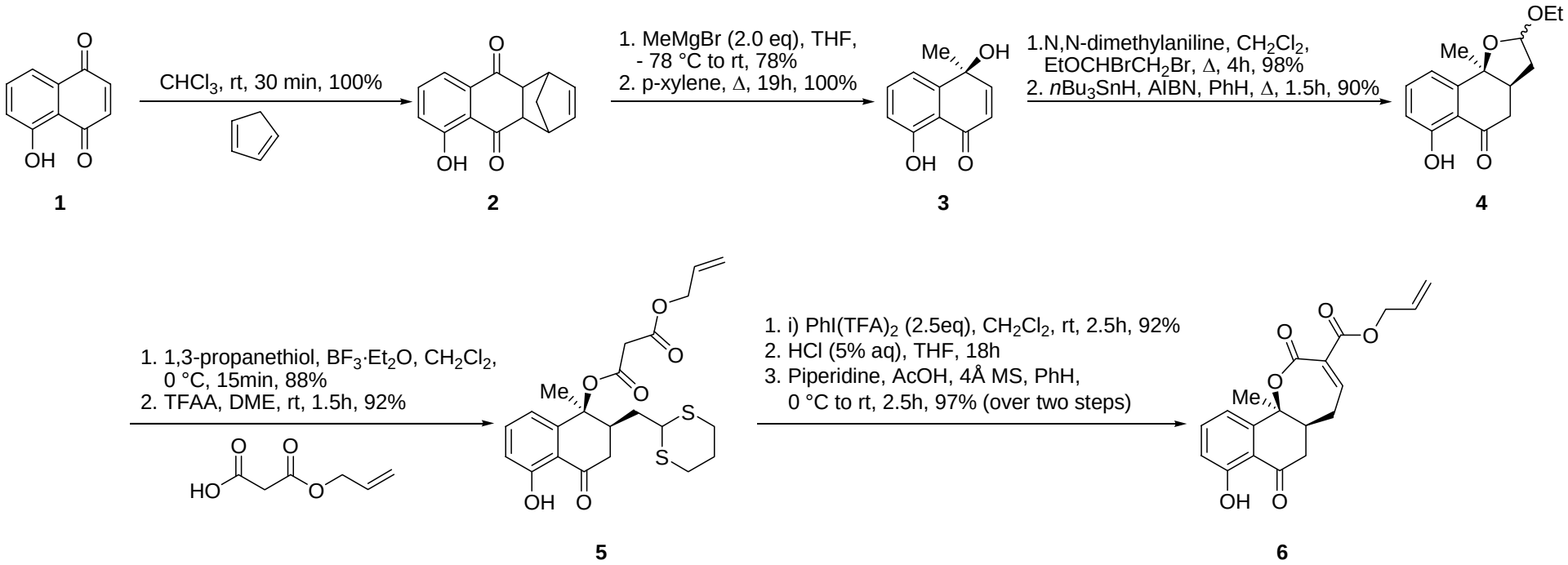
- DA reaction to construct C ring
- Cascade condensation to construct rings A and B

(±)-12a-Deoxytetracycline

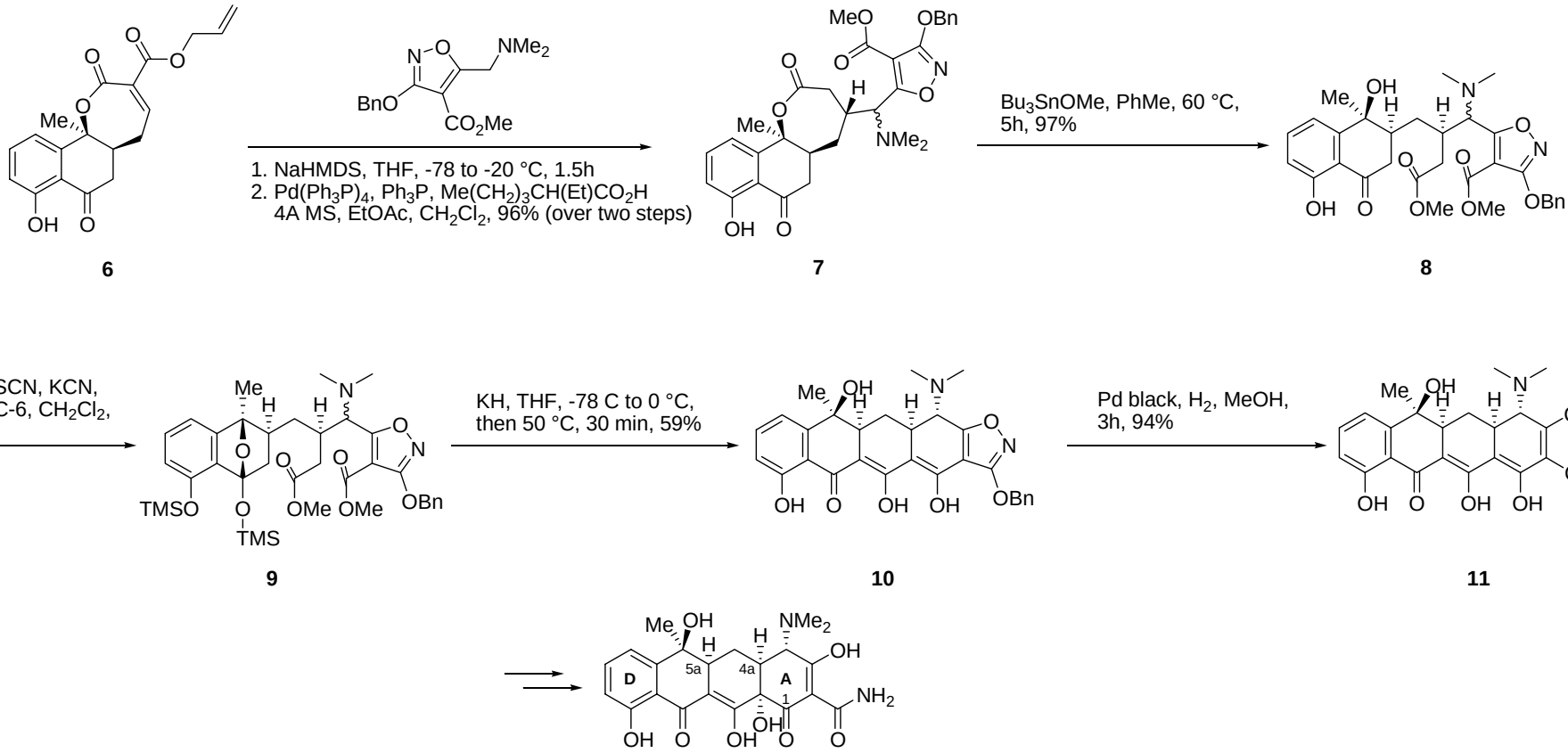
Stork *et al. J. Am. Chem. Soc.* **1996,** *118,* 5304



(±)-12a-Deoxytetracycline



Completion of the Synthesis



6 **7** **8** **9** **10** **11**

Summary:

15 steps, 25% overall yield

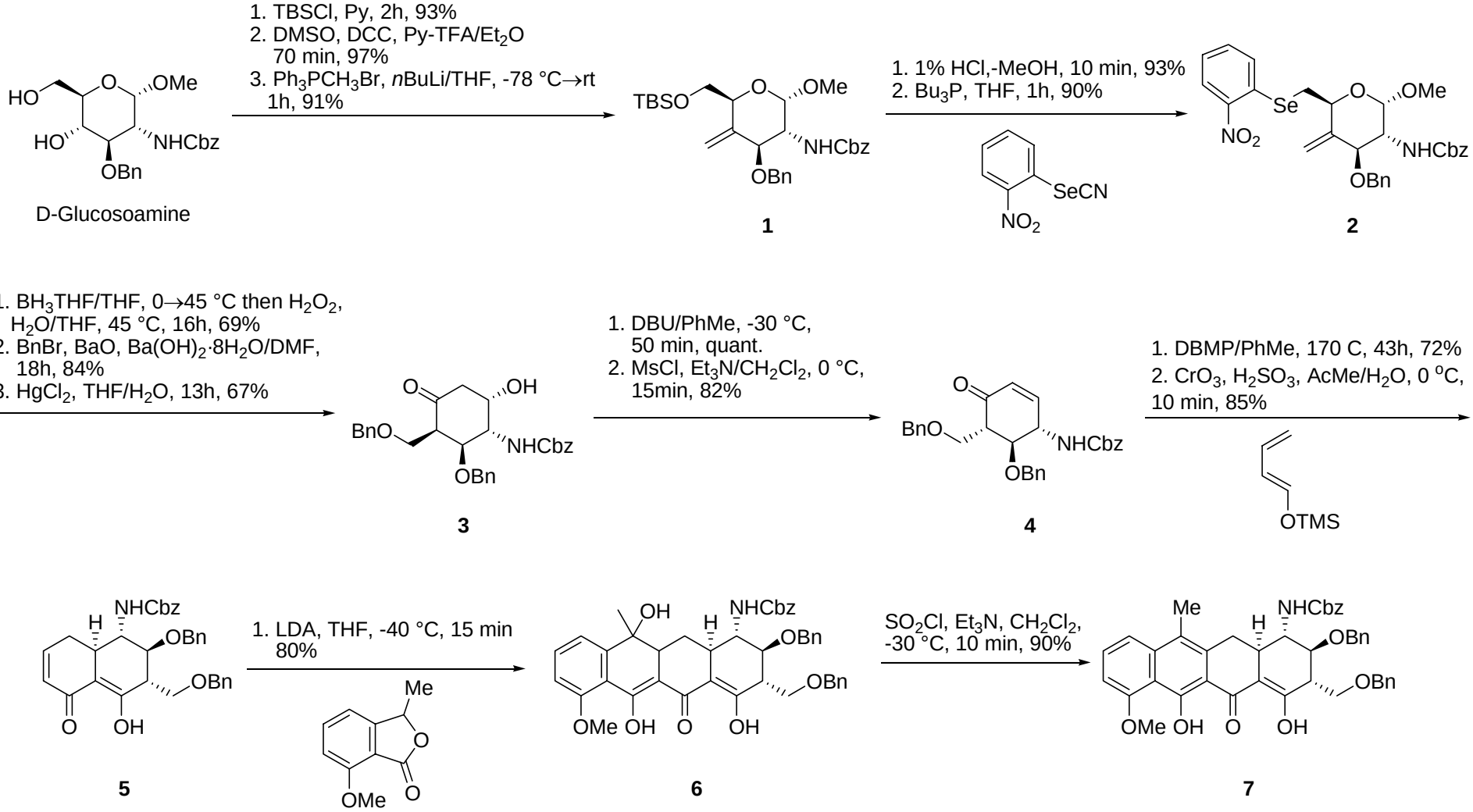
Key Transformations:

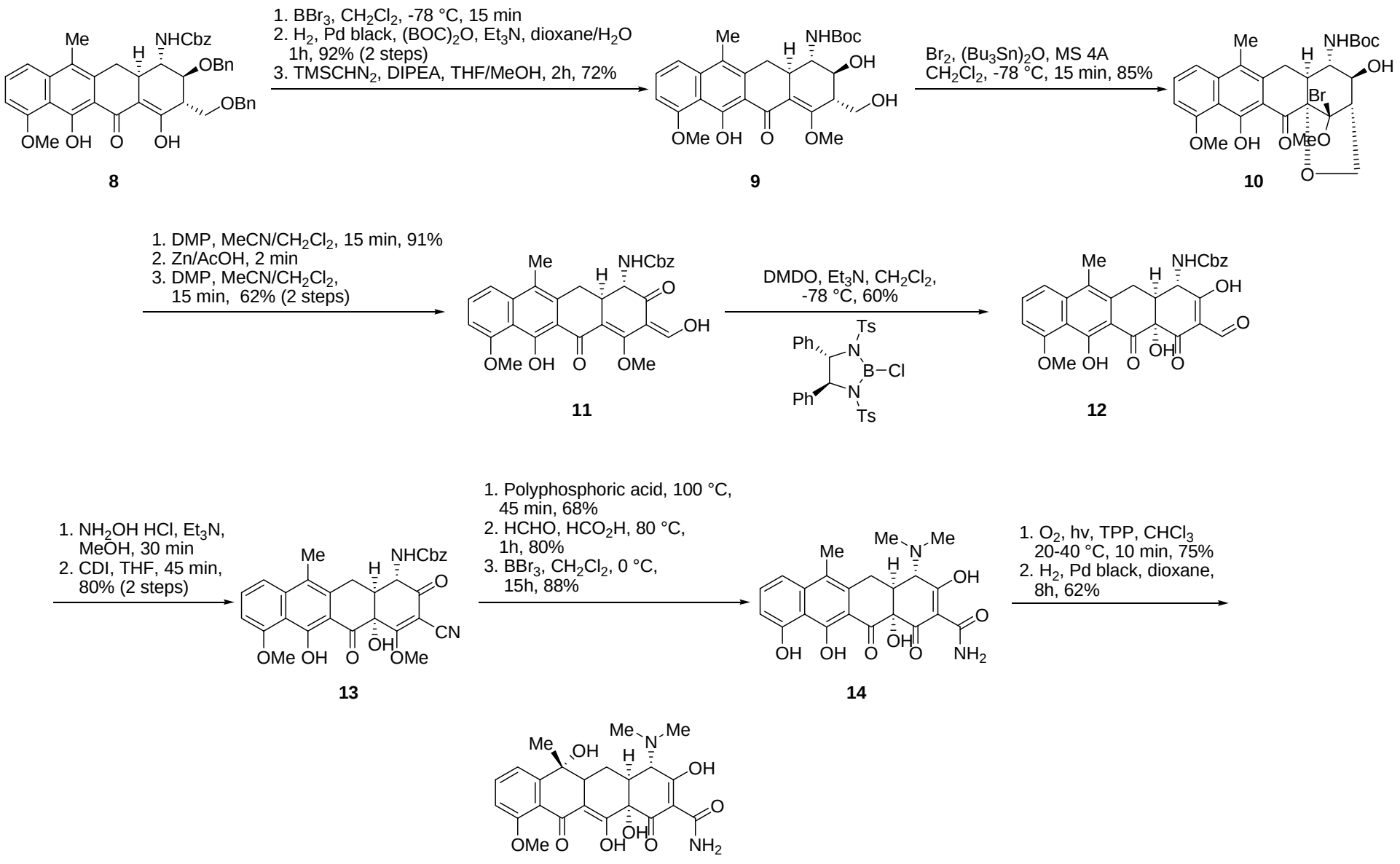
- Double Claisen condensation
- Functionalized oxazole as a masked β-ketoamide

See also: Stork, Hagedorn *J. Am. Chem. Soc.* **1978**, *100*, 3611

The First Total Synthesis of Natural (-)-Tetracycline

Tatsuta *et al. Chem. Lett.* **2000**, 646



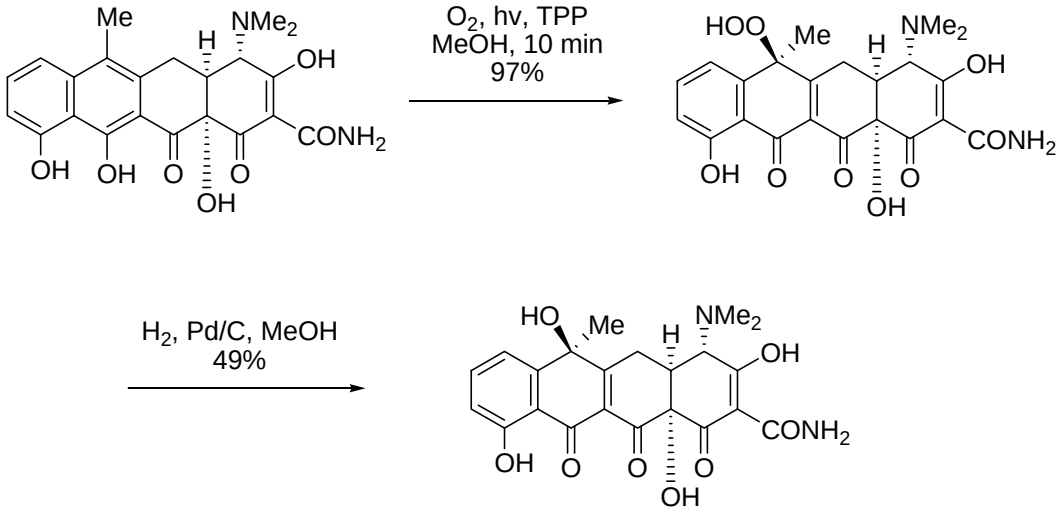


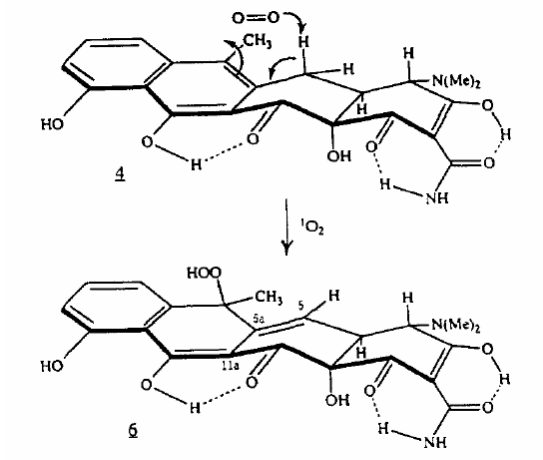
Summary:

34steps, 0.002%

Highly Selective Oxidation of Deoxytetracycline

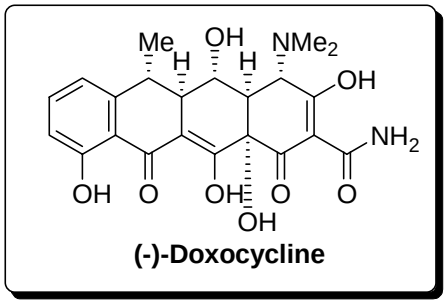
Wasserman, Lu *J. Am. Chem. Soc.* **1986,** *108,* 4237



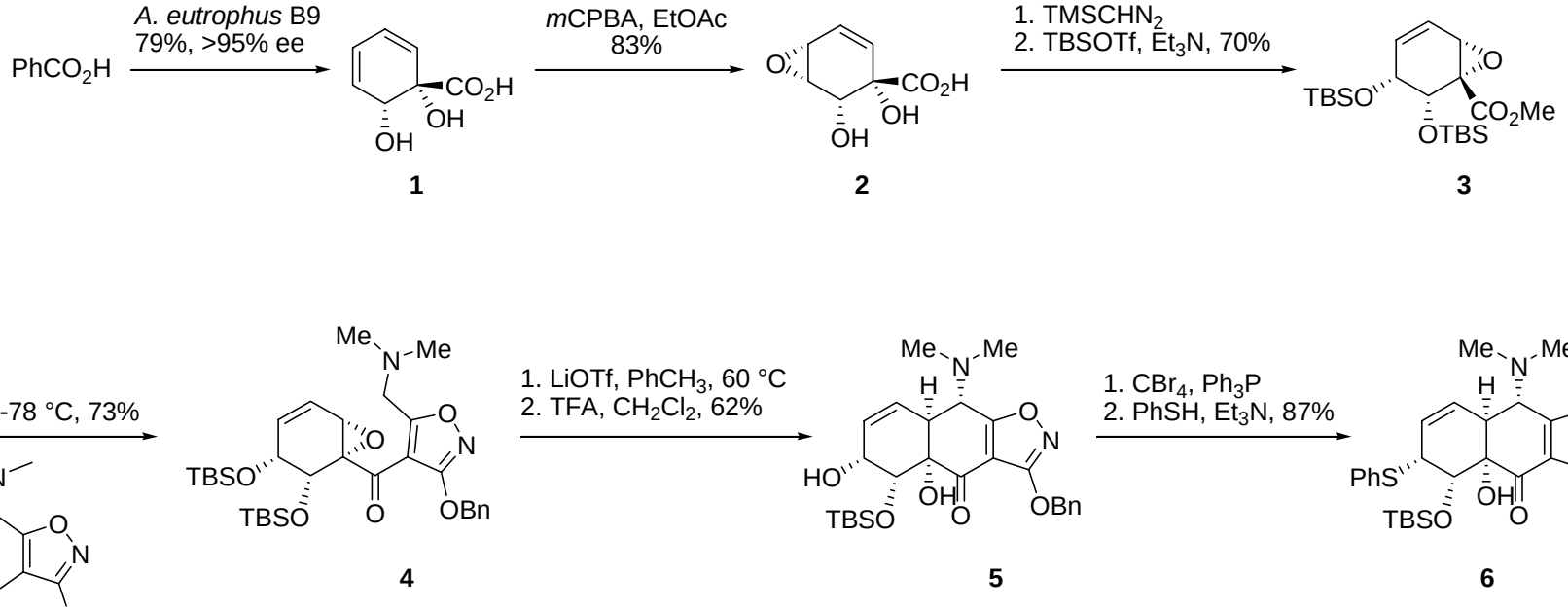


Synthesis of (-)-Doxycycline – Assembly of AB Rings

Myers *et al. Science* **2005**, *308*, 395

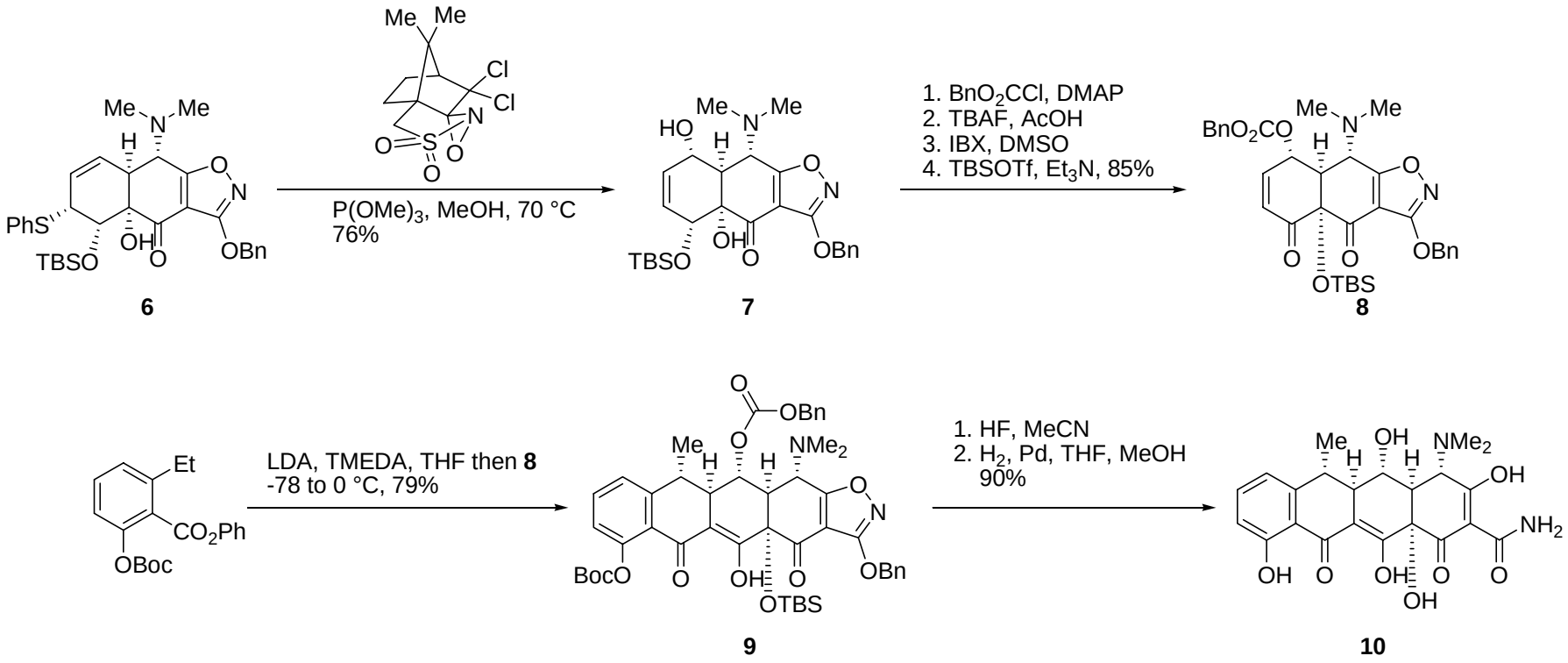


(-)-Doxocycline



Myers *et al. Org. Lett.* **2001**, *3*, 2923

Synthesis of (-)-Doxycycline



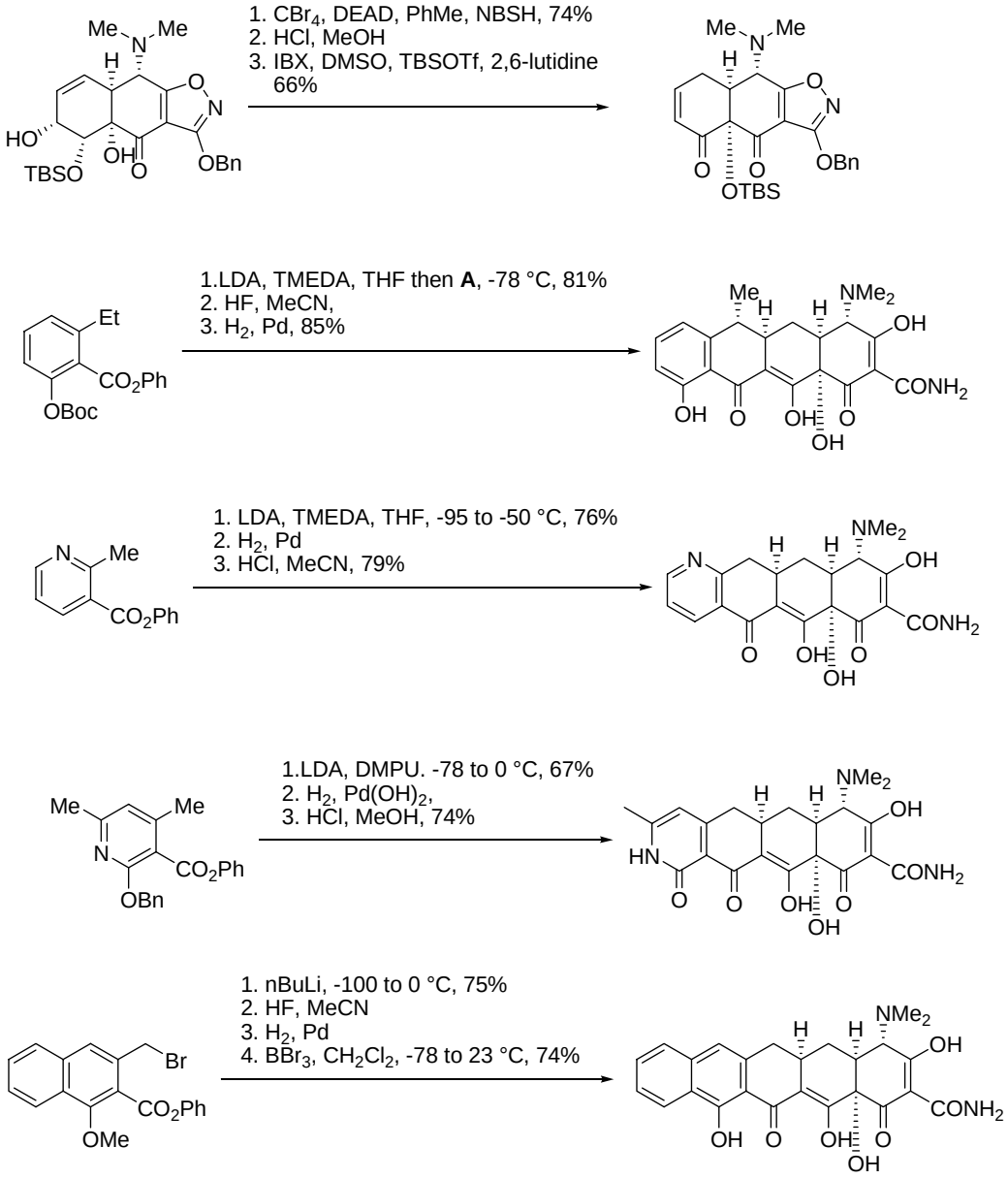
Summary:

18 linear steps, overall yield 8.3%

Key Transformations:

- microbial dihydroxylation of benzoic acid
- LiOTf-catalyzed opening of epoxide
- Michael-Dieckmann condensation to assemble C ring

Synthesis of the Tetracycline Derivatives



The Total Synthesis of (-)-Tetracycline

Myers *et al. J. Am. Chem. Soc*. **2005**, *ASAP* (ja052151d)