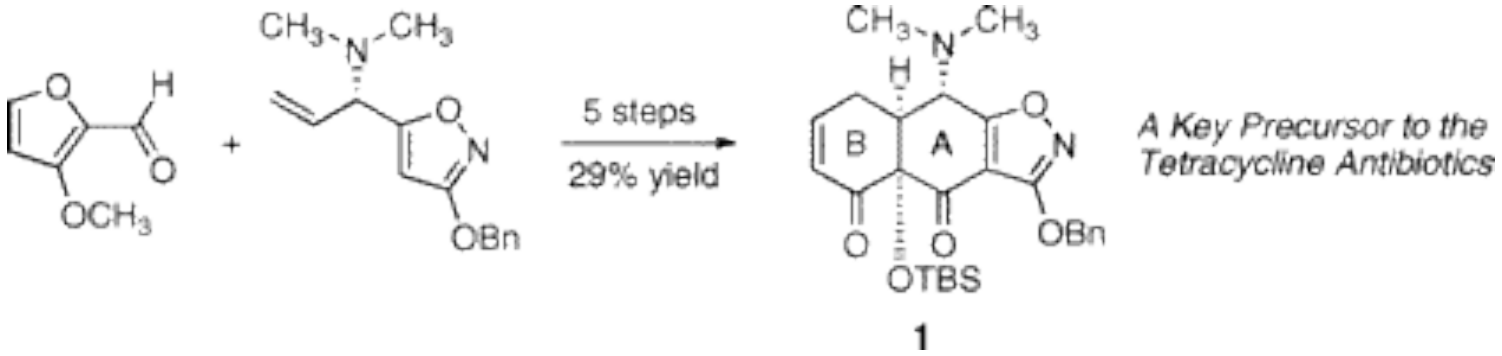
A Practical, Enantioselective Synthetic Route to a Key Precursor to the Tetracycline Antibiotics

Brubaker, J. D; Myers, A. G. *Org. Lett.* **2007**, *9*, 3523.



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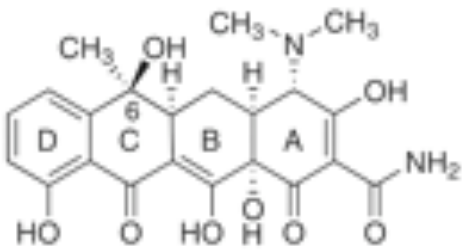
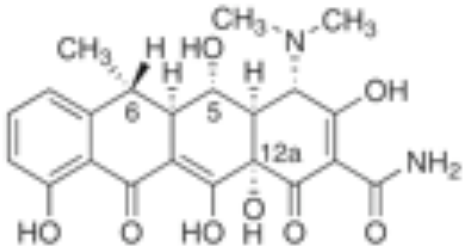
Wipf Group
Current Literature Presentation
September 15th, 2007

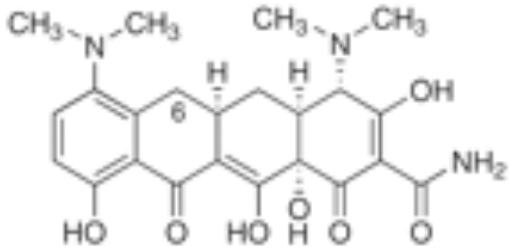
Tetracycline Antibiotics



(–)-Tetracycline (**1**)



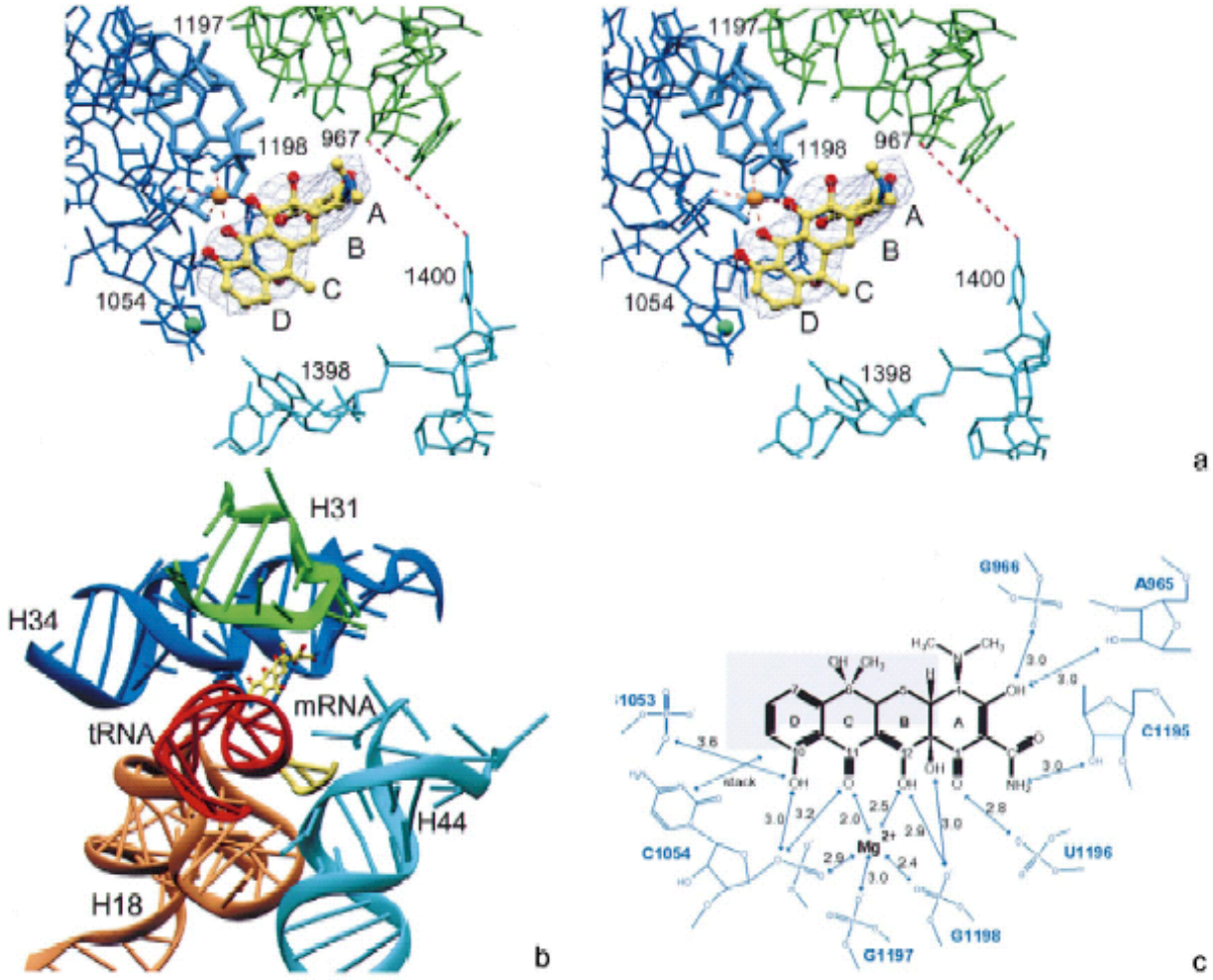
(–)-Doxycycline (**2**)



(–)-Minocycline (**3**)

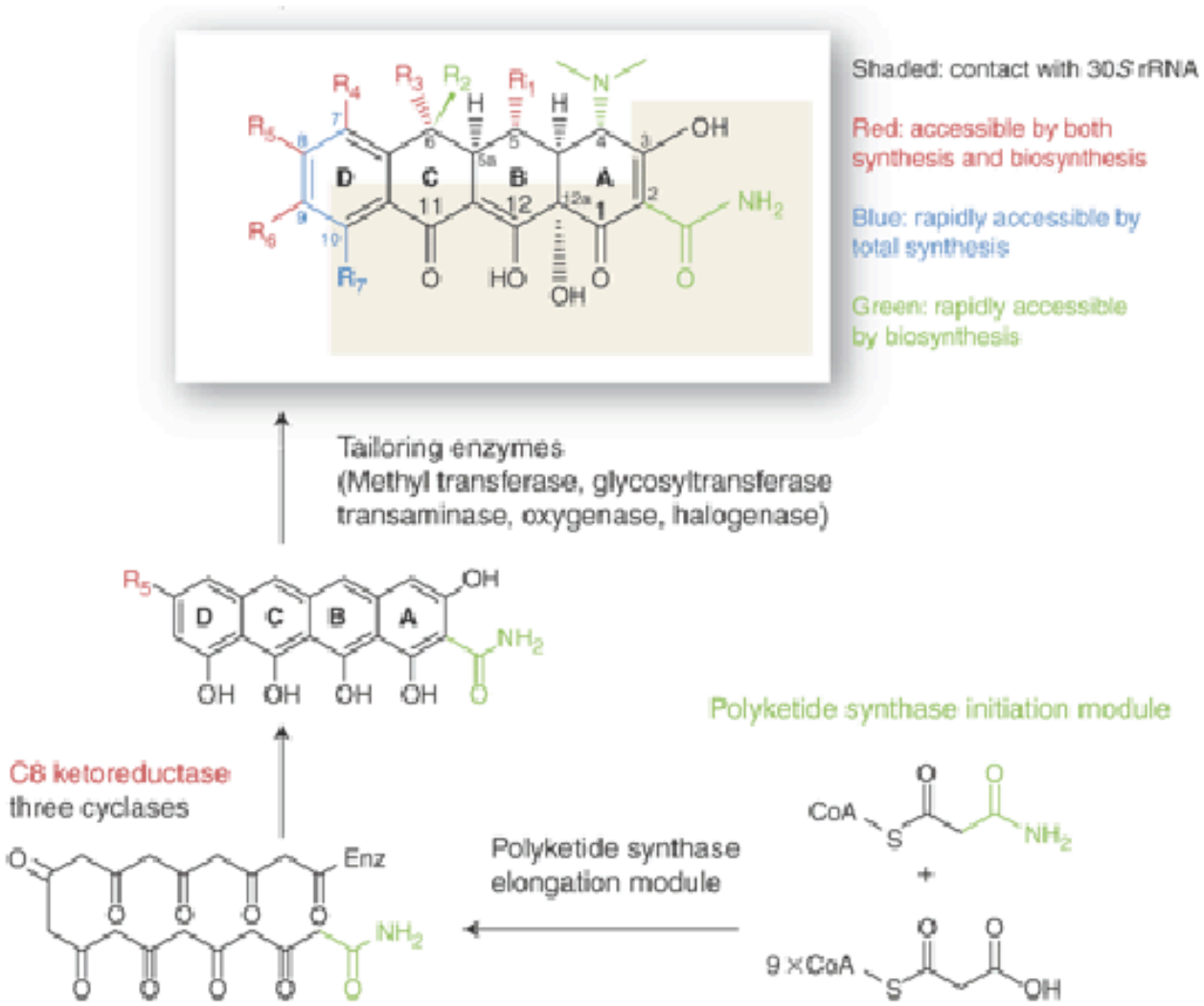
- Discovered in late 1940's by fermentation methods
- The four fused ring system binds to the 30S subunit of the bacterial ribosome
- Used widely as broad-spectrum antibiotics for human and animals
- Extensive use over the past half century has led to widespread bacterial resistance by two major mechanisms: direct cleaning from the ribosome (TetM protein) or pumping out of the cell (TetA protein)

Crystal Structure of the Tetracycline-bound 30S



Brodersen, D. E. et al. *Cell* **2000**, *103*, 1143-1154.

Biosynthesis of Tetracycline Antibiotics



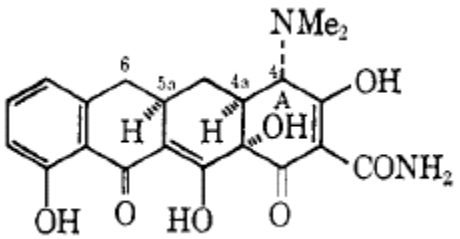
➢**Much of the polar functionality important for binding lies in the AB fragment.**

➢**D ring is tolerant to diverse modifications-important site to generate analogs to overcome bacterial resistance.**

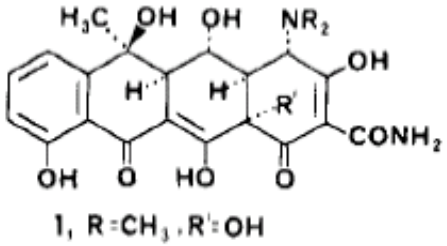
➢**Analogs without hydroxyl at C-6 are more resistant to degradation.**

Khosla, C.; Tang, Y. *Science* **2005**, *308*, 367-368.

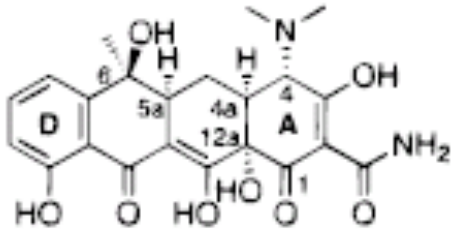
Past Synthetic Endeavors



Sancycline
25 steps, ~0.002% yield
Woodward et al. *JACS* **1968**, *90*, 439.

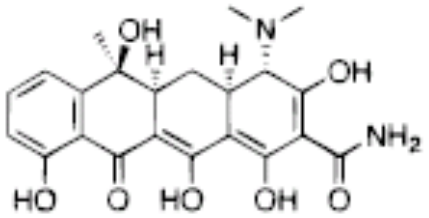


Terramycin
22 steps, 0.06% yield
Muxfeldt et al. *JACS* **1979**, *101*, 689.



tetracycline (**1**)

34 steps, 0.002%
Tatsuta et al. *Chem. Lett.* **2000**, *2000*, 646.



12a-deoxytetracycline (**2**)

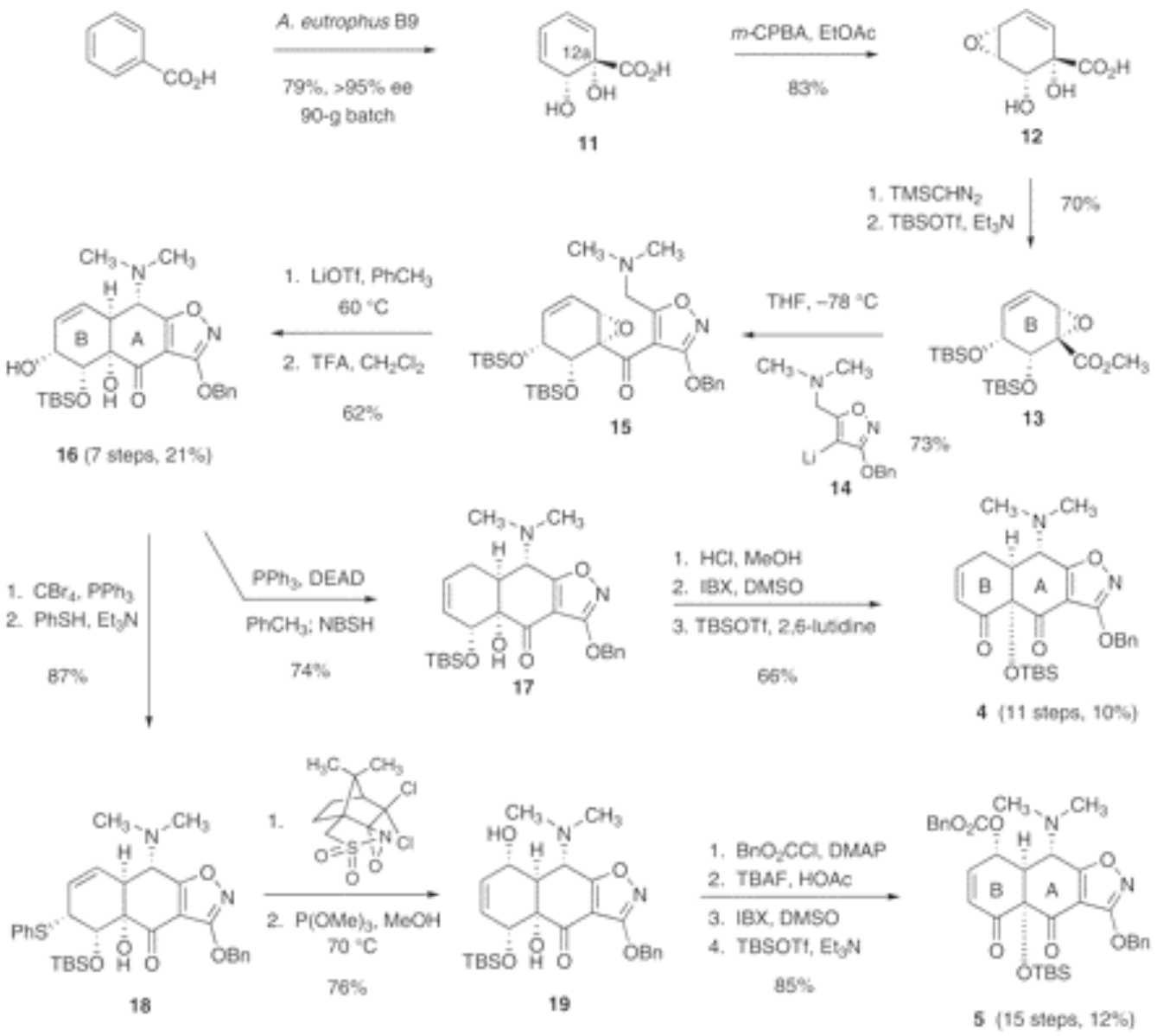
16 steps, 18-25% yield
Stork et al. *JACS* **1996**, *118*, 5304.

First Synthesis from the Myers Group

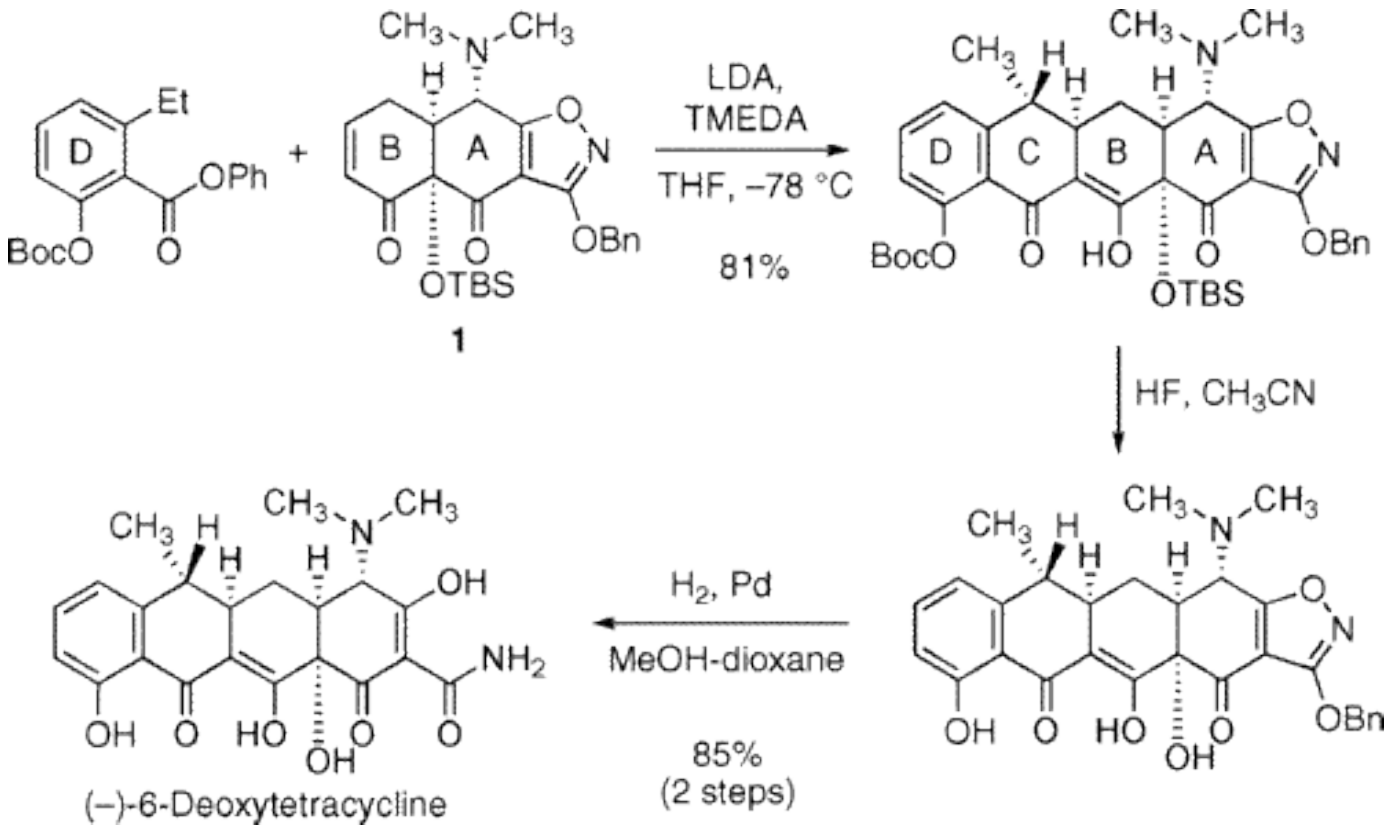
*Key step: a generalized Michael-Dieckmann reaction sequence that forms the C ring of tetracyclines from the coupling of structurally varied carbanionic D-ring precursors with either of the AB precursors **4** or **5**.*

Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D. R.; Myers, A. G. *Science* **2005**, *308*, 395.

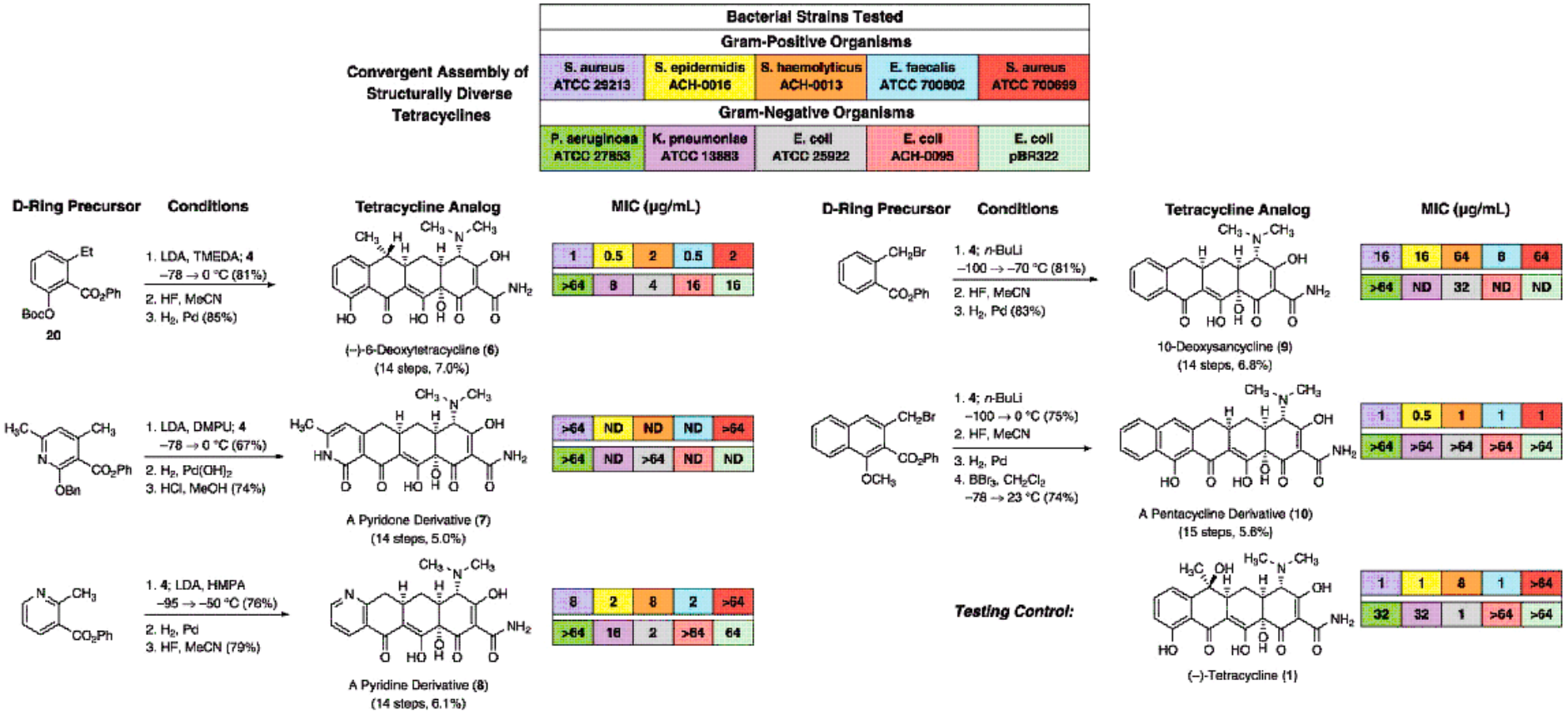
Synthesis of **4** and 5



Michael-Dieckmann Cyclization

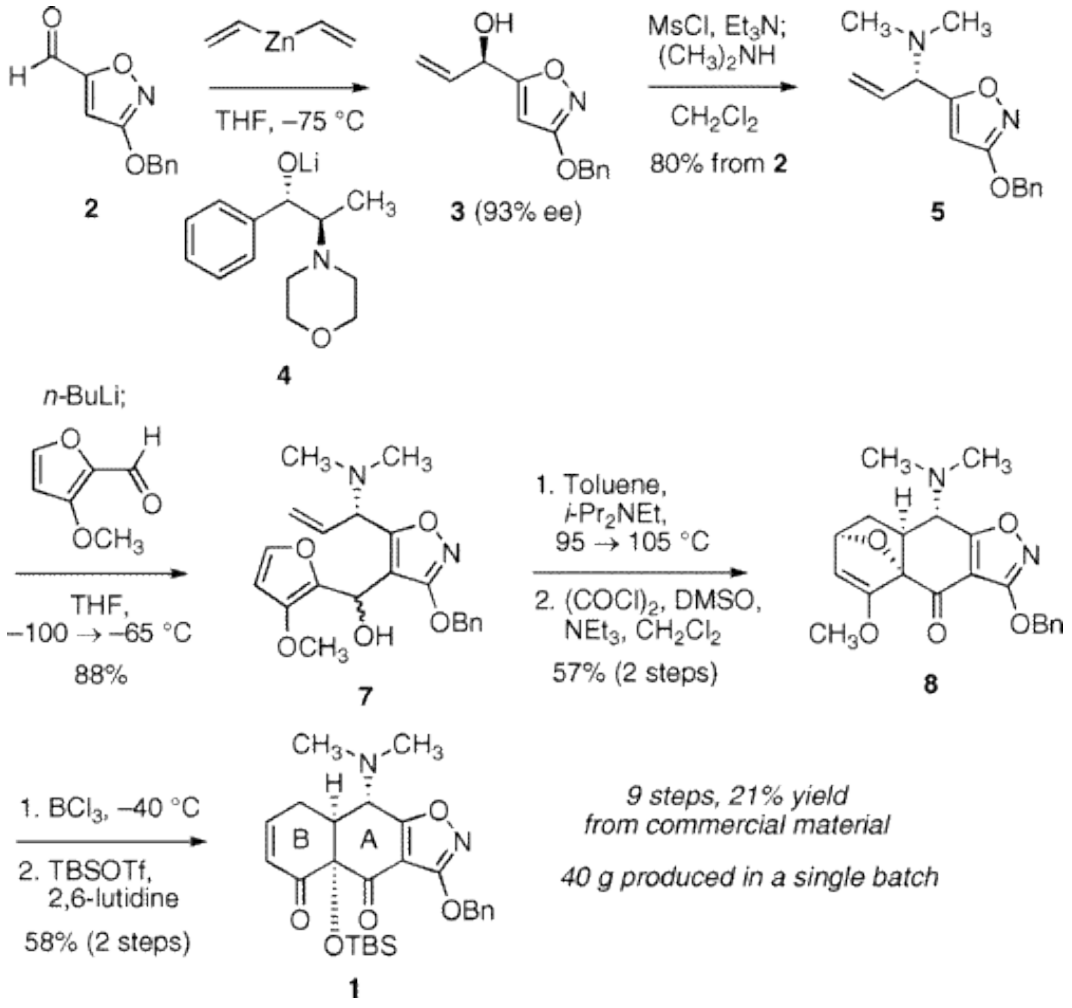


Synthesis of Analogs



➢Compound **10** showed activity equal to or greater than tetracycline including strains with resistance to tetracycline, methicillin, and vancomycin.

Current Paper: Scalable Synthesis of the AB Core Intermediate



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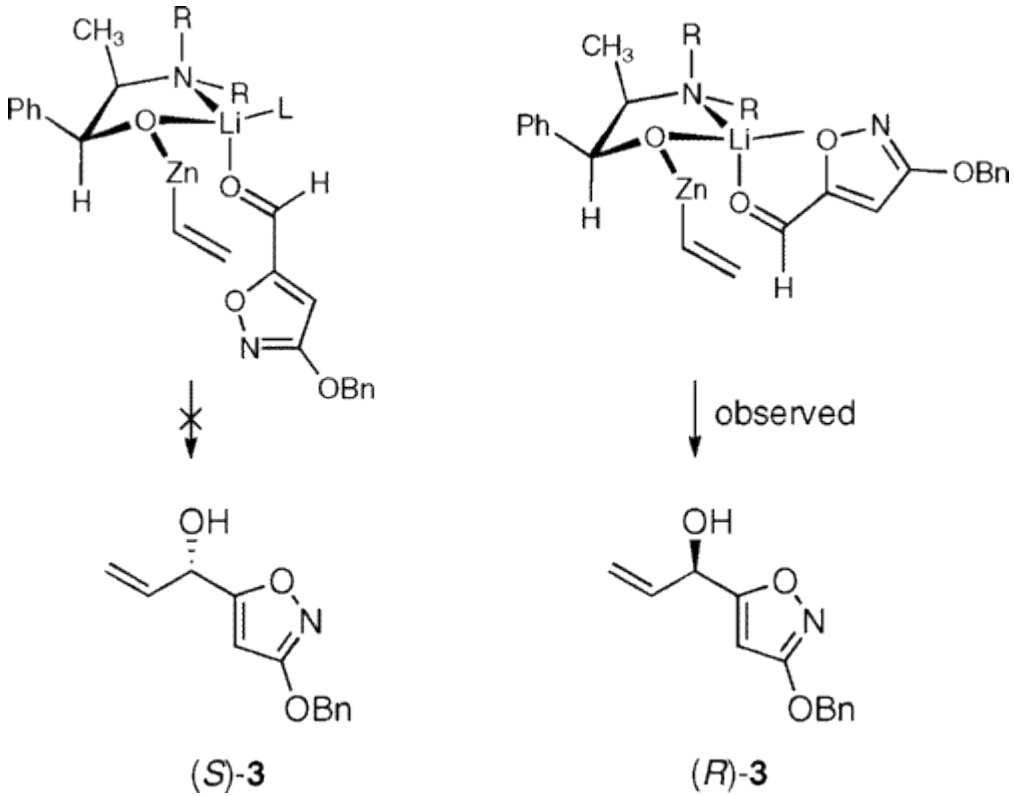
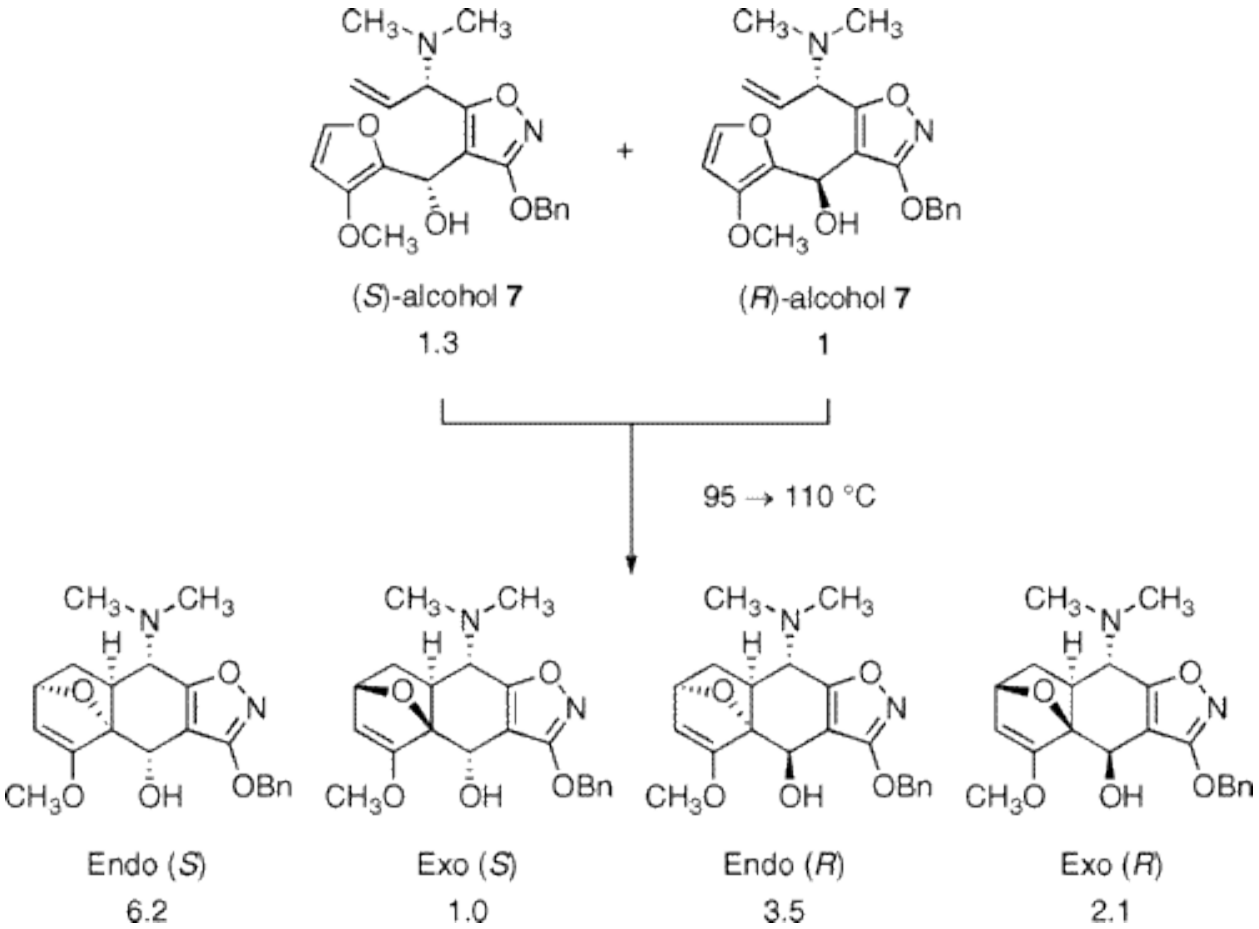
Transition State



(*S*)-**3** (*R*)-**3**

Intramolecular Diels-Alder Reaction



Summary

- A highly efficient route to produce a common AB core intermediate in 9 steps and 21% overall yield from commercially available starting material for tetracycline antibiotics synthesis has been developed. The material has been produced in 40 g scale with 93% ee in a single batch after chromatography purification.

- The readily availability of this core intermediate would make possible the synthesis of a large number of tetracycline analogs to find more potent antibiotics for drug-resistant bacterium.

- The synthesis might be scaled up to multi-kilogram amounts.

- More Crystalline derivatives of the core intermediate should be studied to increase its optical purity.