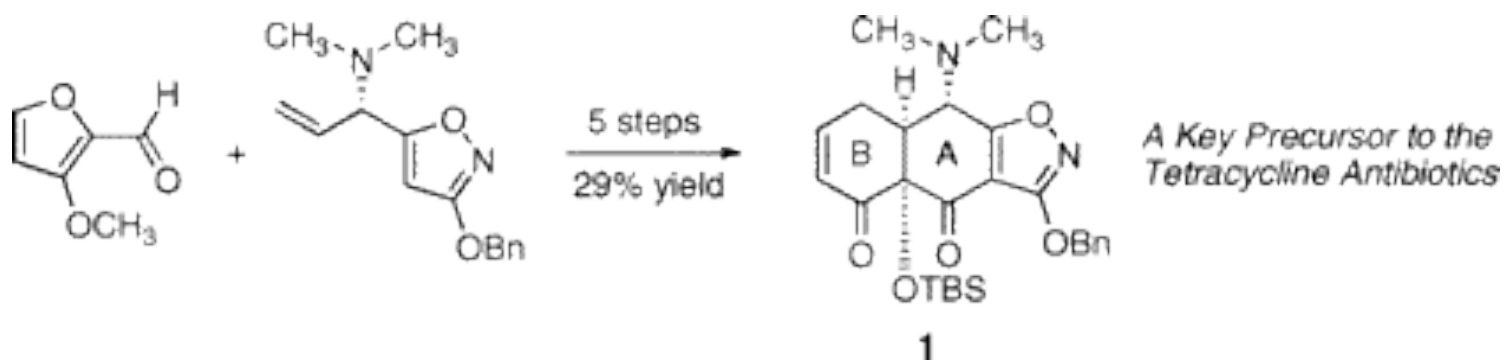


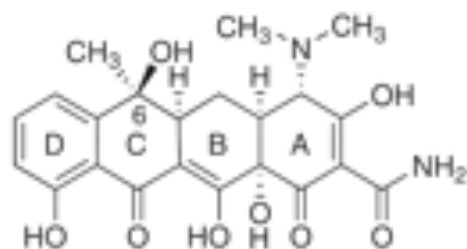
A Practical, Enantioselective Synthetic Route to a Key Precursor to the Tetracycline Antibiotics

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

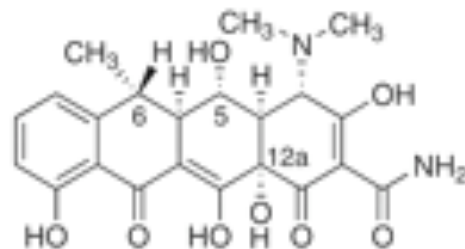


Zhiyong Wang
Wipf Group
Current Literature Presentation
September 15th, 2007

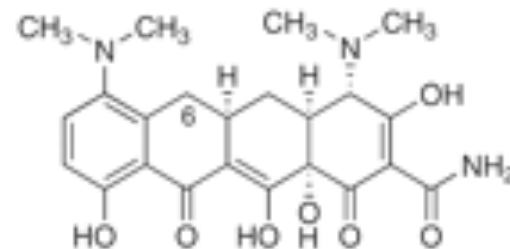
Tetracycline Antibiotics



(-)-Tetracycline (1)



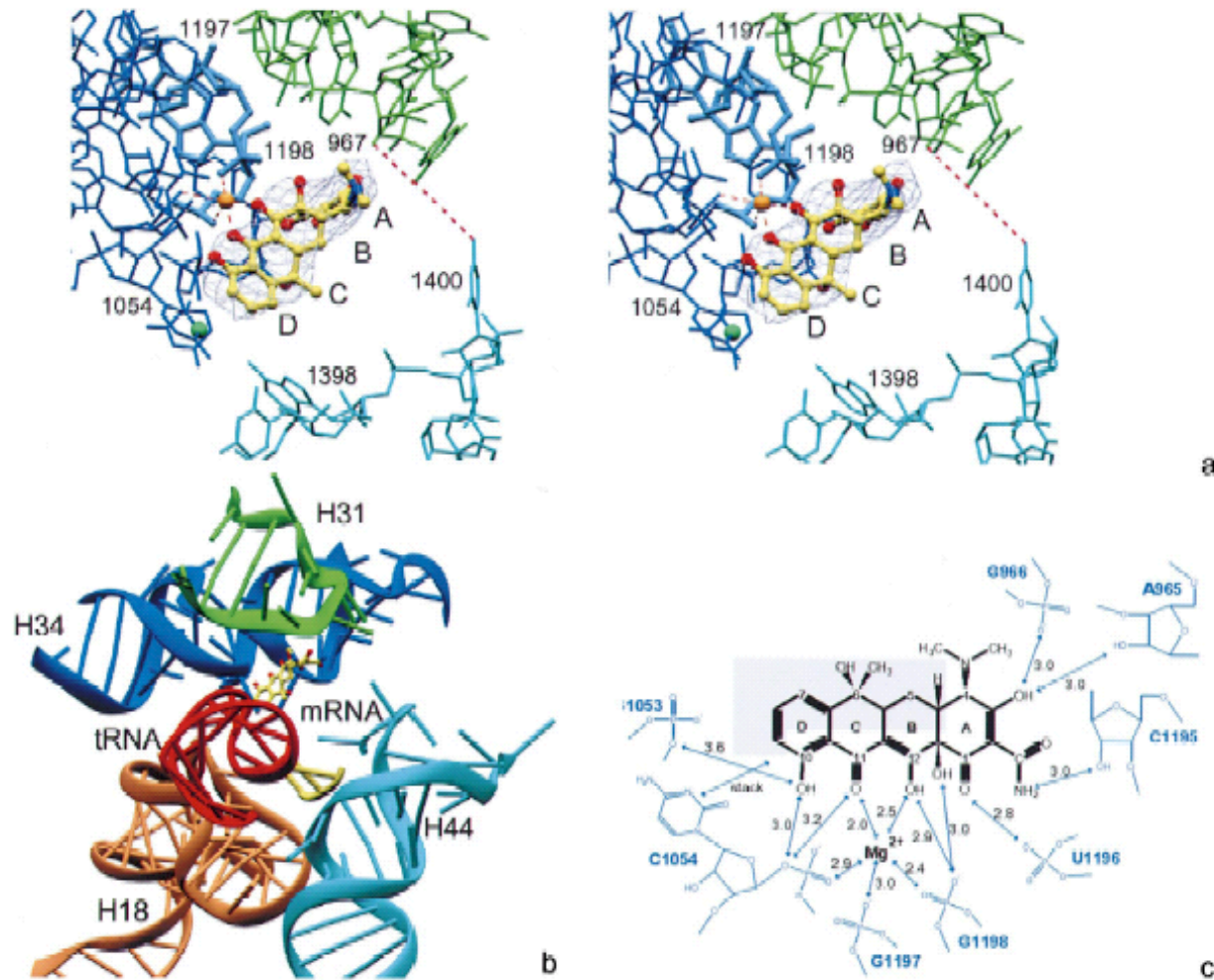
(-)-Doxycycline (2)



(-)-Minocycline (3)

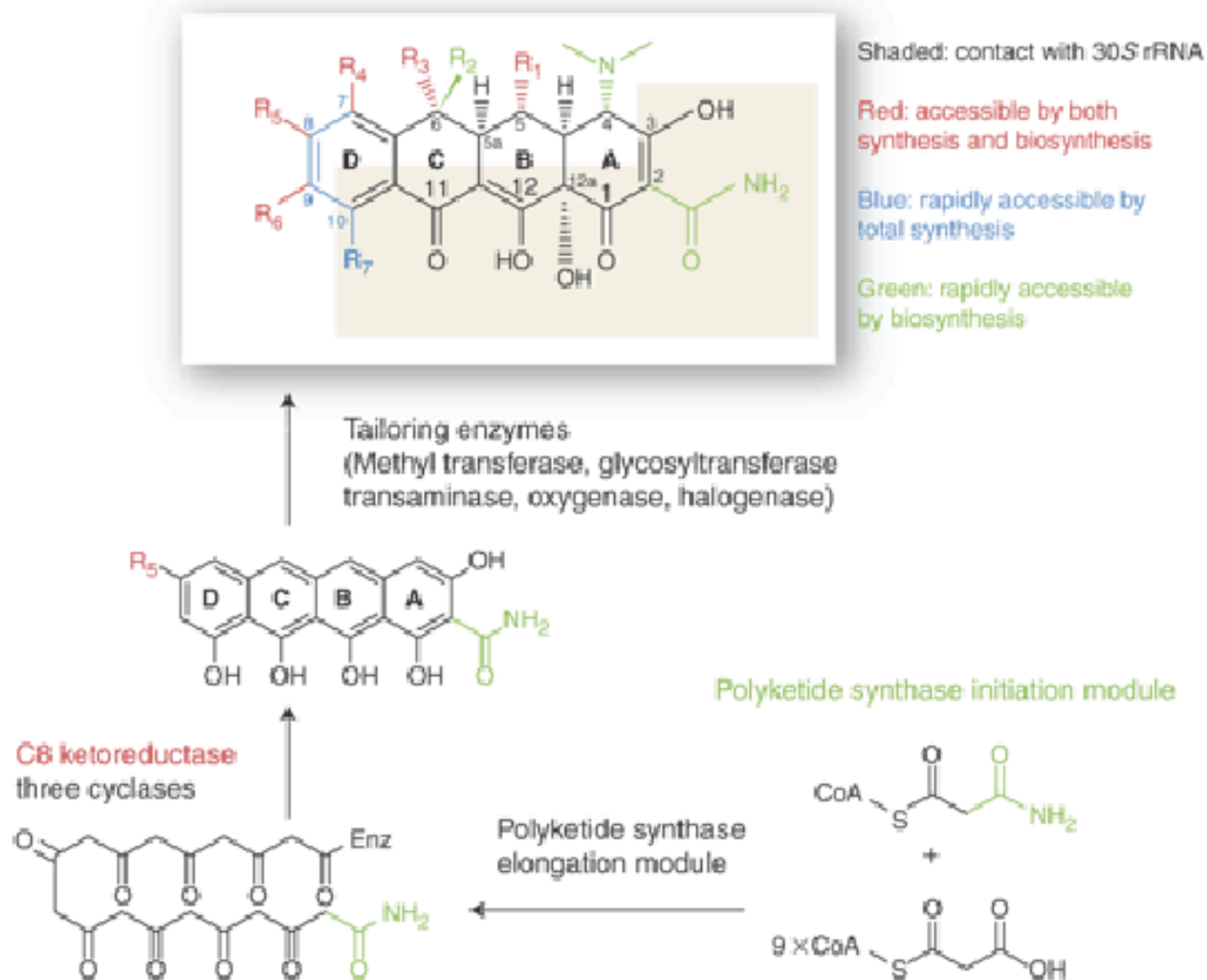
- Discovered in late 1940's by fermentation methods
- The four fused ring system binds to the 30S subunit of the bacterial ribosome
- Used widely as broad-spectrum antibiotics for human and animals
- Extensive use over the past half century has led to widespread bacterial resistance by two major mechanisms: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



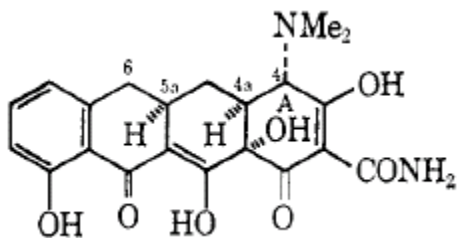
➤ Much of the polar functionality important for binding lies in the AB fragment.

➤ 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.

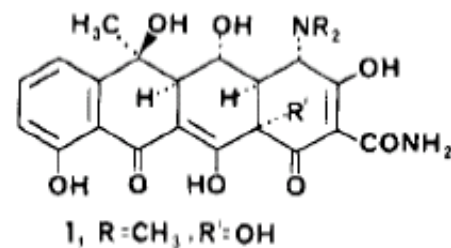
Khosla, C.; Tang, Y. *Science* **2005**, *308*, 367-368.

Past Synthetic Endeavors



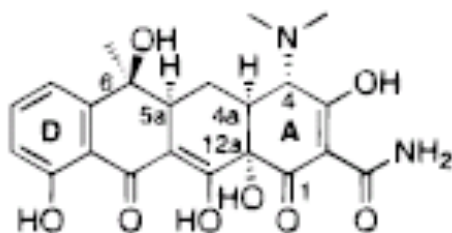
Sancycline

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



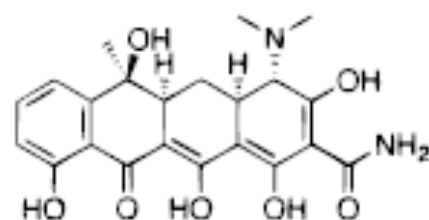
Terramycin

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



tetracycline (1)

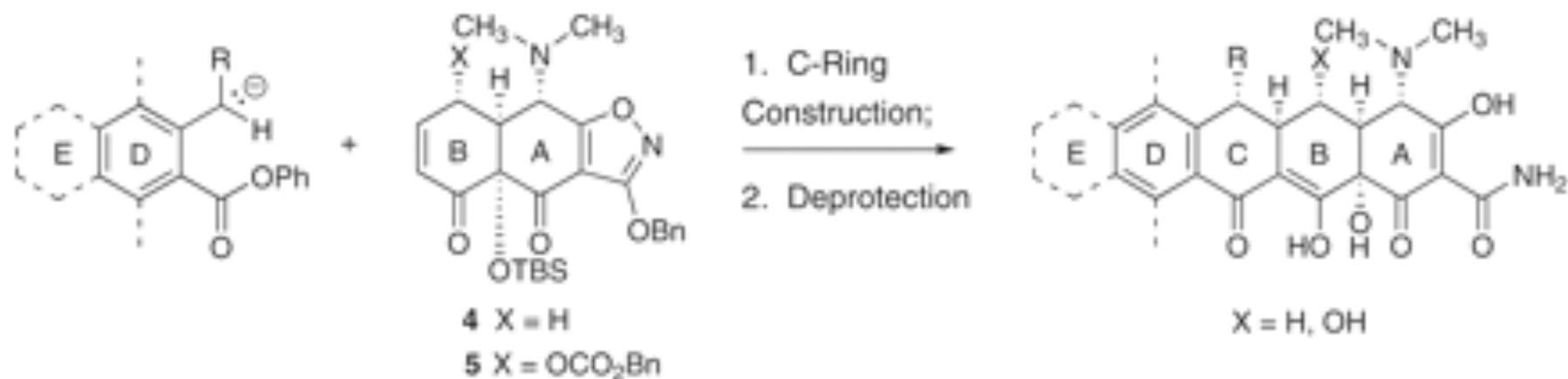
34 steps, 0.002%
Tatsuta et al. *Chem. Lett.* **2000**, *2000*, 646.



12a-deoxytetracycline (2)

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

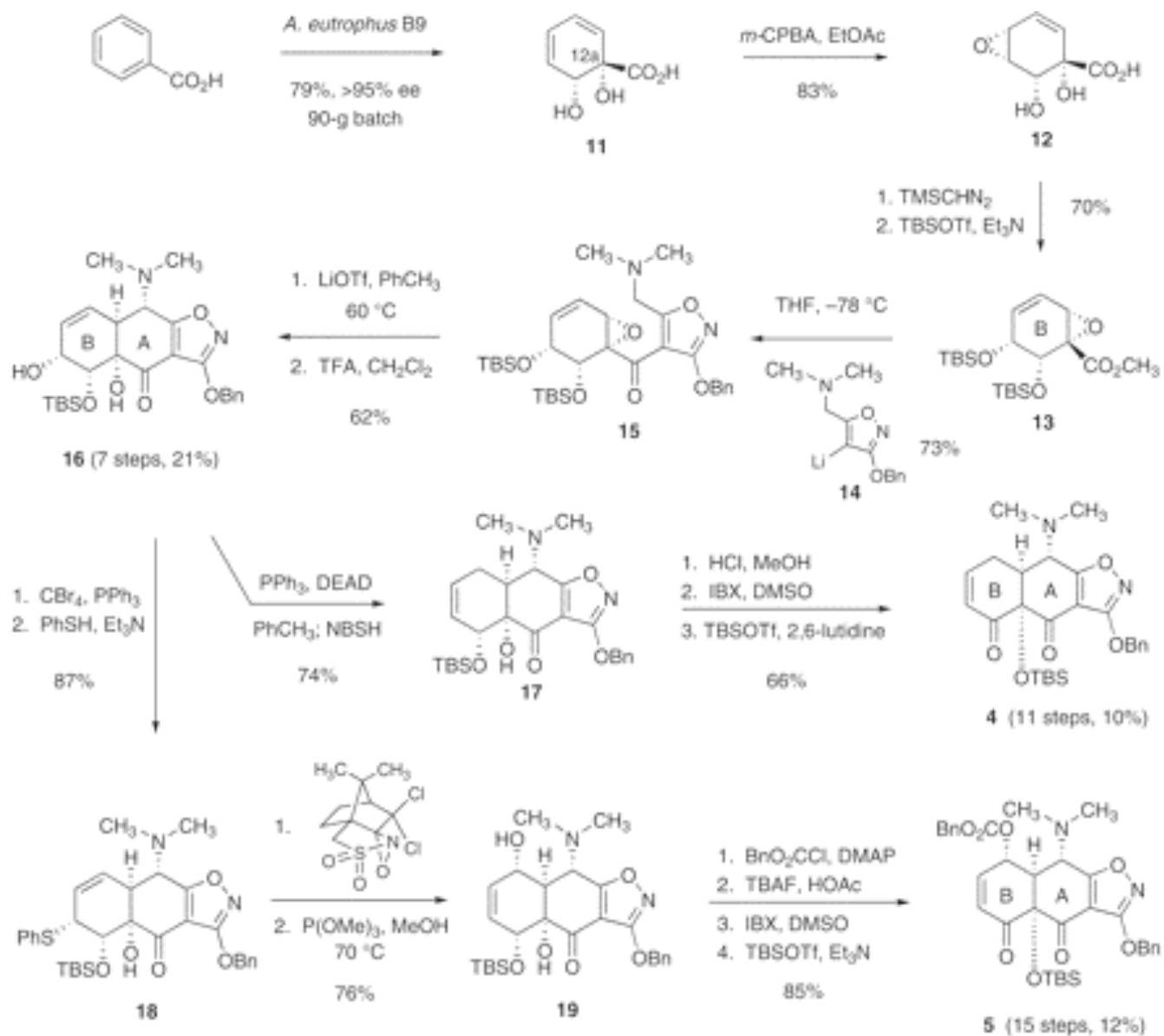
First Synthesis from the Myers Group



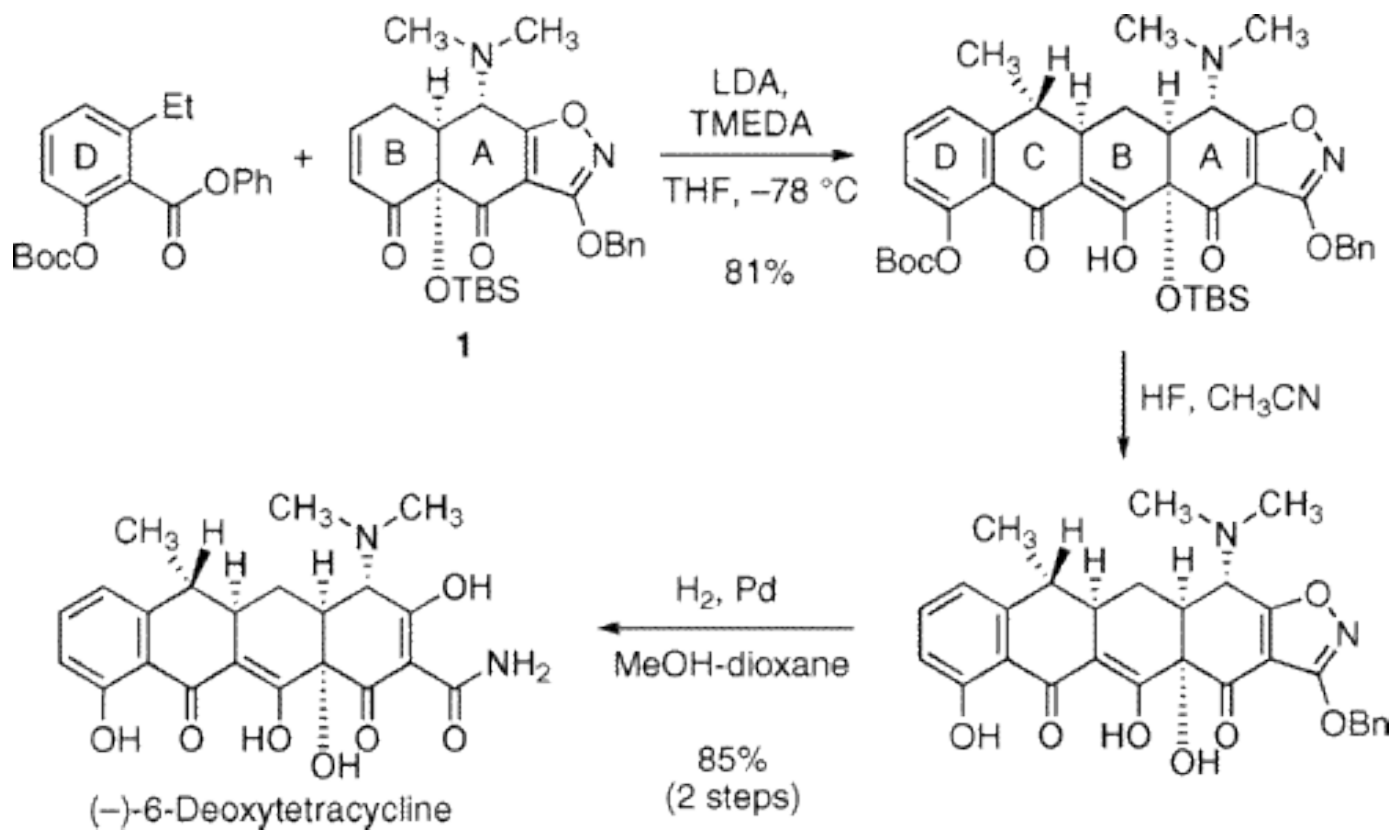
Key step: a generalized Michael-Dieckmann reaction sequence that forms the C ring of tetracyclines from the coupling of structurally varied carbanionic D-ring precursors with either of the AB precursors 4 or 5.

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

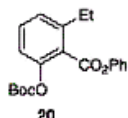


Synthesis of Analogs

Convergent Assembly of Structurally Diverse Tetracyclines

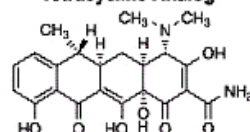
Bacterial Strains Tested				
Gram-Positive Organisms				
<i>S. aureus</i> ATCC 29213	<i>S. epidermidis</i> ACH-0016	<i>S. haemolyticus</i> ACH-0013	<i>E. faecalis</i> ATCC 700902	<i>S. aureus</i> ATCC 700699
Gram-Negative Organisms				
<i>P. aeruginosa</i> ATCC 27853	<i>K. pneumoniae</i> ATCC 13883	<i>E. coli</i> ATCC 25922	<i>E. coli</i> ACH-0095	<i>E. coli</i> pBR322

D-Ring Precursor Conditions



1. LDA, TMEDA; 4
-78 → 0 °C (81%)
2. HF, MeCN
3. H₂, Pd (85%)

Tetracycline Analog

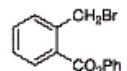


(-)-6-Deoxytetracycline (6)
(14 steps, 7.0%)

MIC (µg/mL)

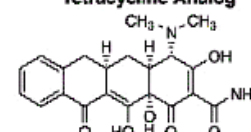
1	0.5	2	0.5	2
>64	8	4	16	16

D-Ring Precursor Conditions



1. 4; *n*-BuLi
-100 → -70 °C (81%)
2. HF, MeCN
3. H₂, Pd (83%)

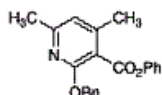
Tetracycline Analog



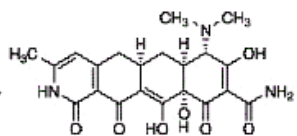
10-Deoxysancycline (9)
(14 steps, 6.8%)

MIC (µg/mL)

16	16	64	8	64
>64	ND	32	ND	ND

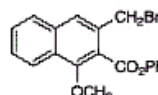


1. LDA, DMPU; 4
-78 → 0 °C (67%)
2. H₂, Pd(OH)₂
3. HCl, MeOH (74%)

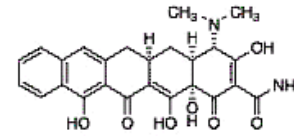


A Pyridone Derivative (7)
(14 steps, 5.0%)

>64	ND	ND	ND	>64
>64	ND	>64	ND	ND

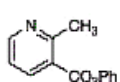


1. 4; *n*-BuLi
-100 → 0 °C (75%)
2. HF, MeCN
3. H₂, Pd
4. BBr₃, CH₂Cl₂
-78 → 23 °C (74%)

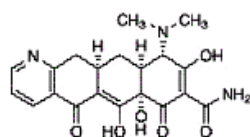


A Pentacycline Derivative (10)
(15 steps, 5.8%)

1	0.5	1	1	1
>64	>64	>64	>64	>64



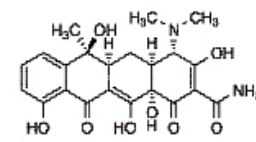
1. 4; LDA, HMPA
-95 → -50 °C (78%)
2. H₂, Pd
3. HF, MeCN (79%)



A Pyridine Derivative (8)
(14 steps, 6.1%)

8	2	8	2	>64
>64	16	2	>64	64

Testing Control:

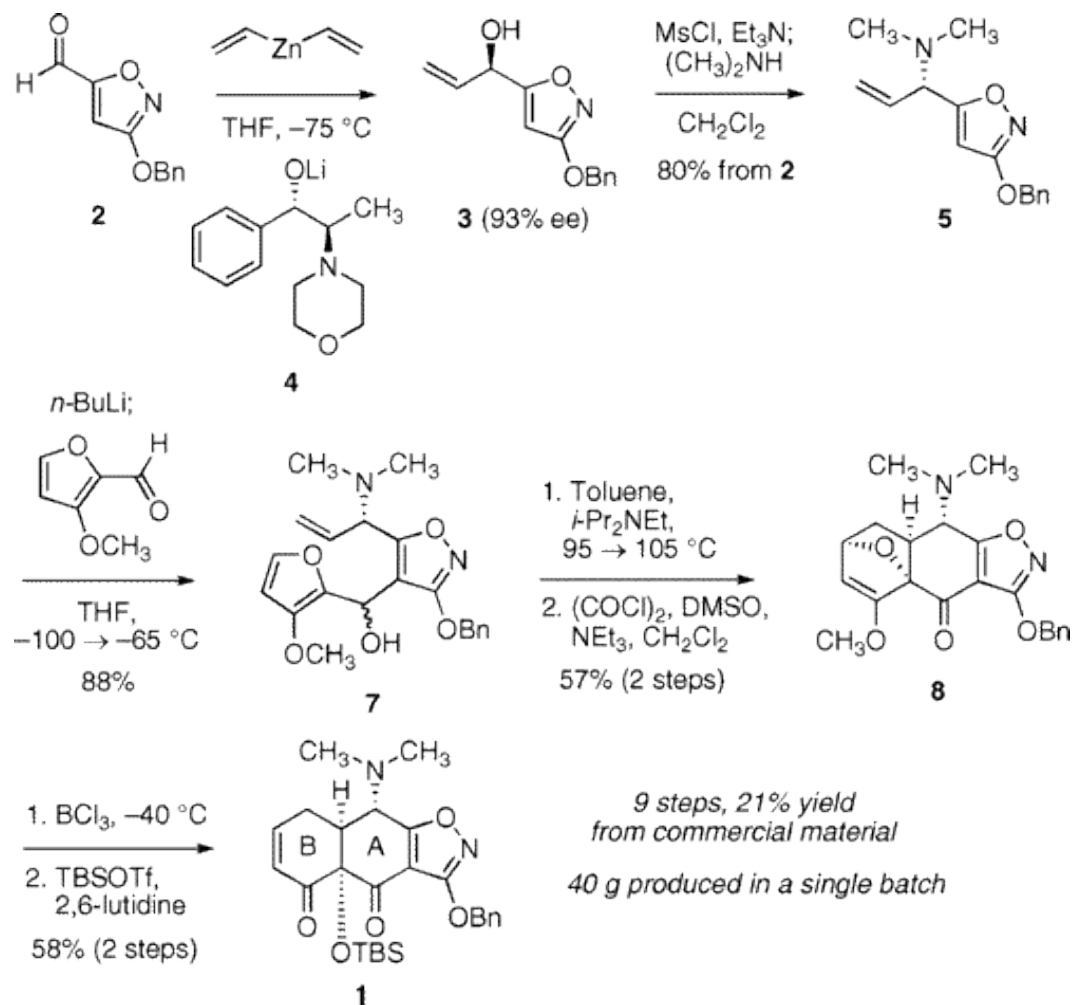


(-)-Tetracycline (1)

1	1	8	1	>64
32	32	1	>64	>64

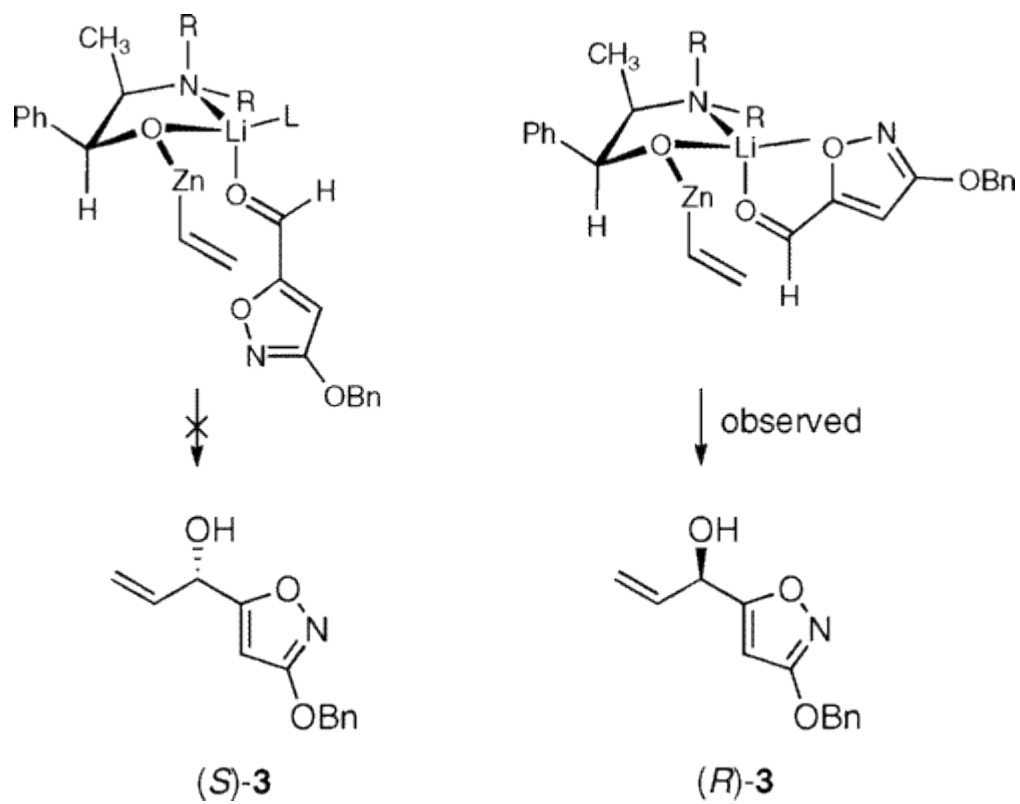
➤ Compound **10** showed activity equal to or greater than tetracycline including strains with resistance to tetracycline, methicillin, and vancomycin.

Current Paper: Scalable Synthesis of the AB Core Intermediate

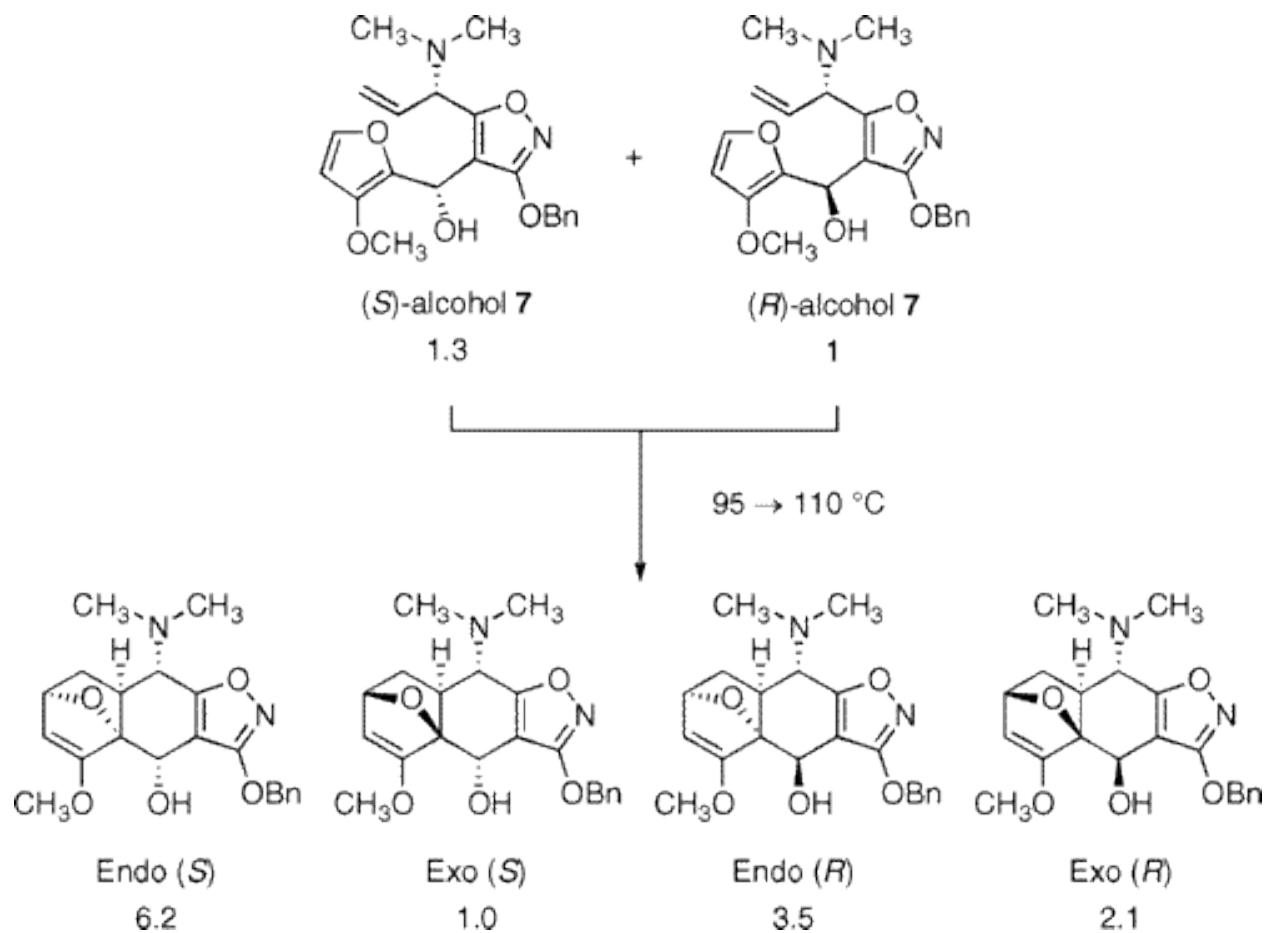


Brubaker, J. D; Myers, A. G. *Org. Lett.* **2007**, *9*, 3523.

Transition State



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.