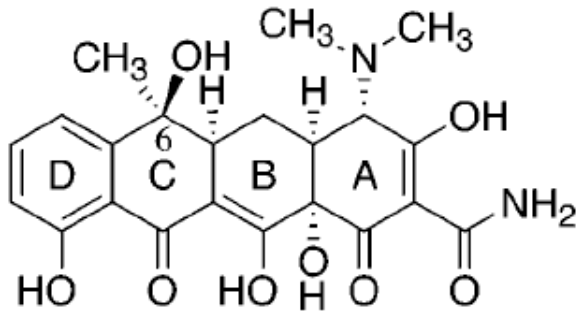
A Convergent Enantioselective Route to Structurally Diverse Tetracyclines



(–)-Tetracycline (**1**)

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

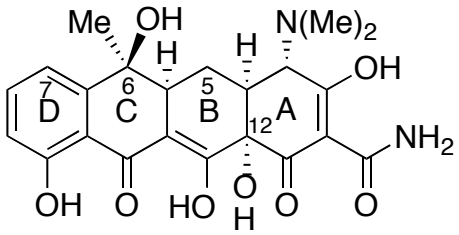
2. Charest, M. G.; Siegel, D. R.; Myers, A. G. *J. Am. Chem. Soc*. **2005**, *127*, 8292.

Literature Presentation

Zhenjie Lu

Apr 21, 2006

Introduction



(-)-Tetracycline **1**

- Isolation: First announced by Duggar in 1948.
  X-ray and NMR analysis were done in 1960 and 1965.

- Bioactivity: Used to treat bacterial infections by preventing the growth and spread of bacteria; and as an alternative to other medications for the treatment of Lyme disease and prevention of anthrax.

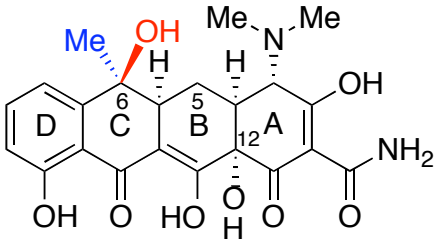
- Structural: Four linearly fused six-membered carbon rings with five chiral-centers.

- Synthesis :
  - ♦ Semisynthesis or biosynthetic pathways.
    Such as Fermentation of certain strains of *Streptomyces aureofaciens.*
  - ♦ Woodward's 6-demethyl-6-deoxytetracycline synthesis in 1962. (*J.A.C.S*, **1962**, 3222)
    Muxfeldt's terramycin synthesis in 1968. (*J.A.C.S*, **1968**, 6534)
    Stork's 12a-deoxytetracycline in 1996. (*J.A.C.S*, **1996**, 5304) (16 steps, 18~25%)
    First synthesis of tetracycline by Tatsuta. (*C.L*, **2000**, 646)
    (asymmetric, 34 steps, 0.002%)

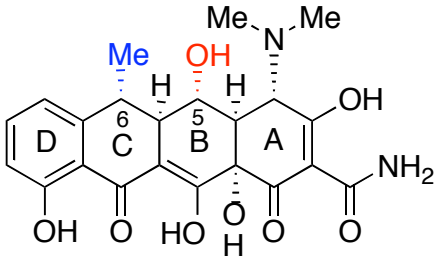
Duggar, B. M. *Ann, N, Y, Acad. Sci.* **1948**, *51*, 177.

Takeuchi, Y.; Buerger, M. J. *Proc. Natl. Acad. Sci. U. S.* **1960**, *46*, 1366.

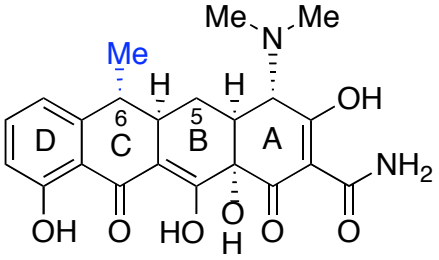
A Few Family Members



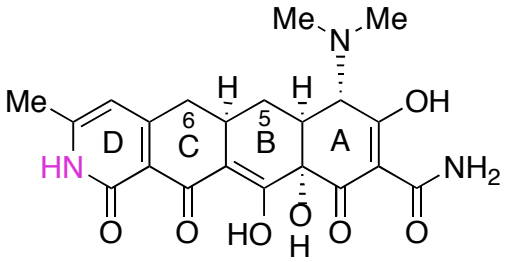
(-)-Tetracycline **1**



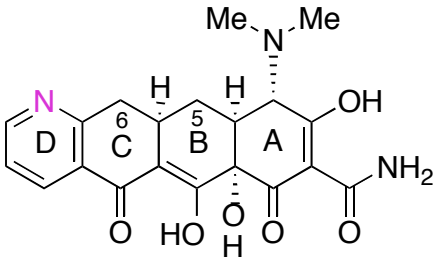
(-)-Doxycycline **2**



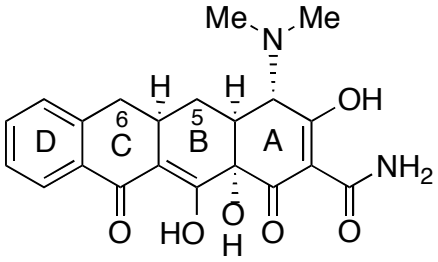
(-)-6-Deoxytetracycline **6**



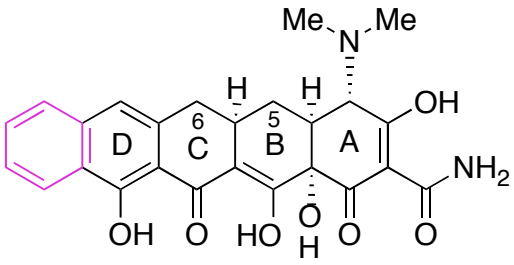
Pyridone Derivative **7**



Pyridine Derivative **8**



10-Deoxysancycline **9**

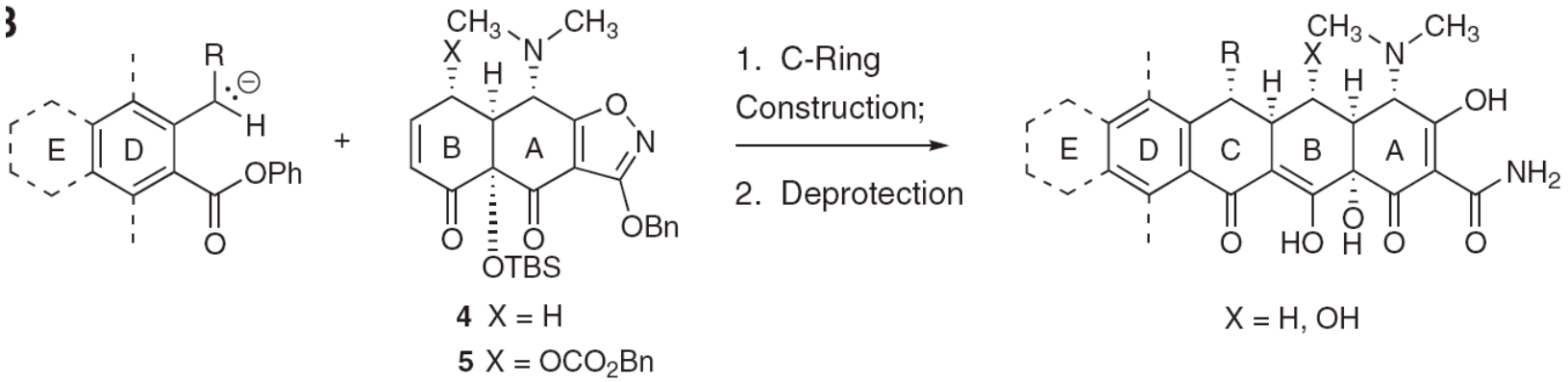


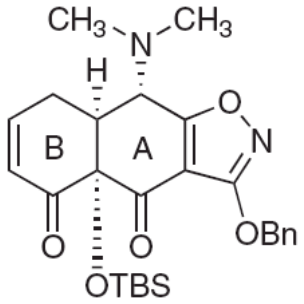
Pentacycline Derivative **10**

- Late-stage, diastereoselective C-ring construction was used.
- Compound **2** to **10** were coupled via Michael-Dieckmann rxn.
- Compound **1** was coupled via Diels-Alder rxn.

1. Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D. R.; Myers, A. G. *Science*. **2005**, 395.
2. Charest, M. G.; Siegel, D. R.; Myers, A. G. *J. Am. Chem. Soc.* **2005**,*127*, 8292.

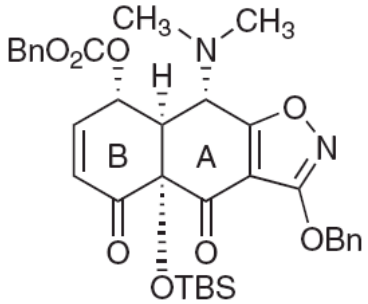
C-ring Formation from Varied Carbanionic D-ring Precursors with AB-ring Precursors





4

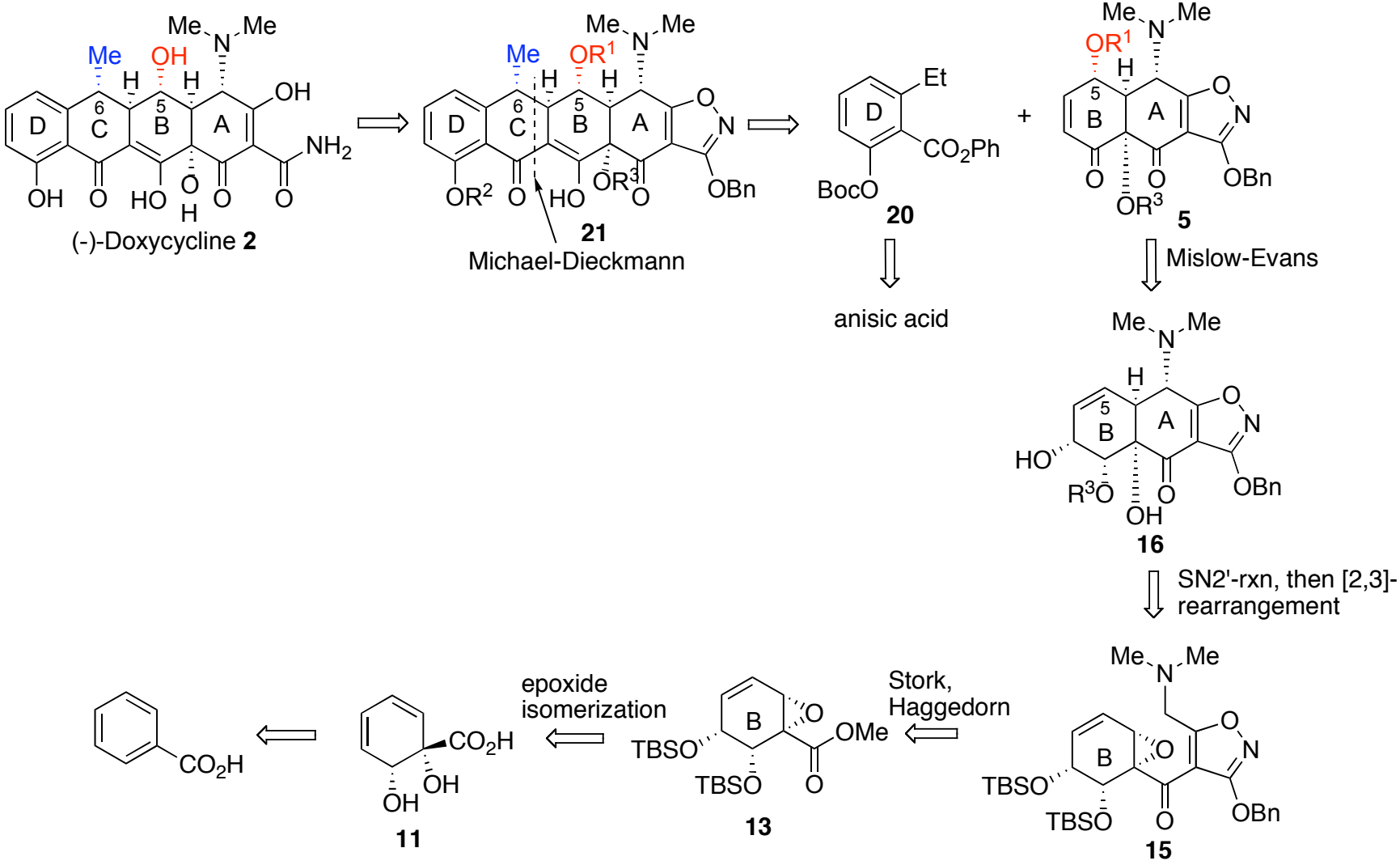
Precursor for products: **1**, **6**, **7**, **8**, **9**, **10**



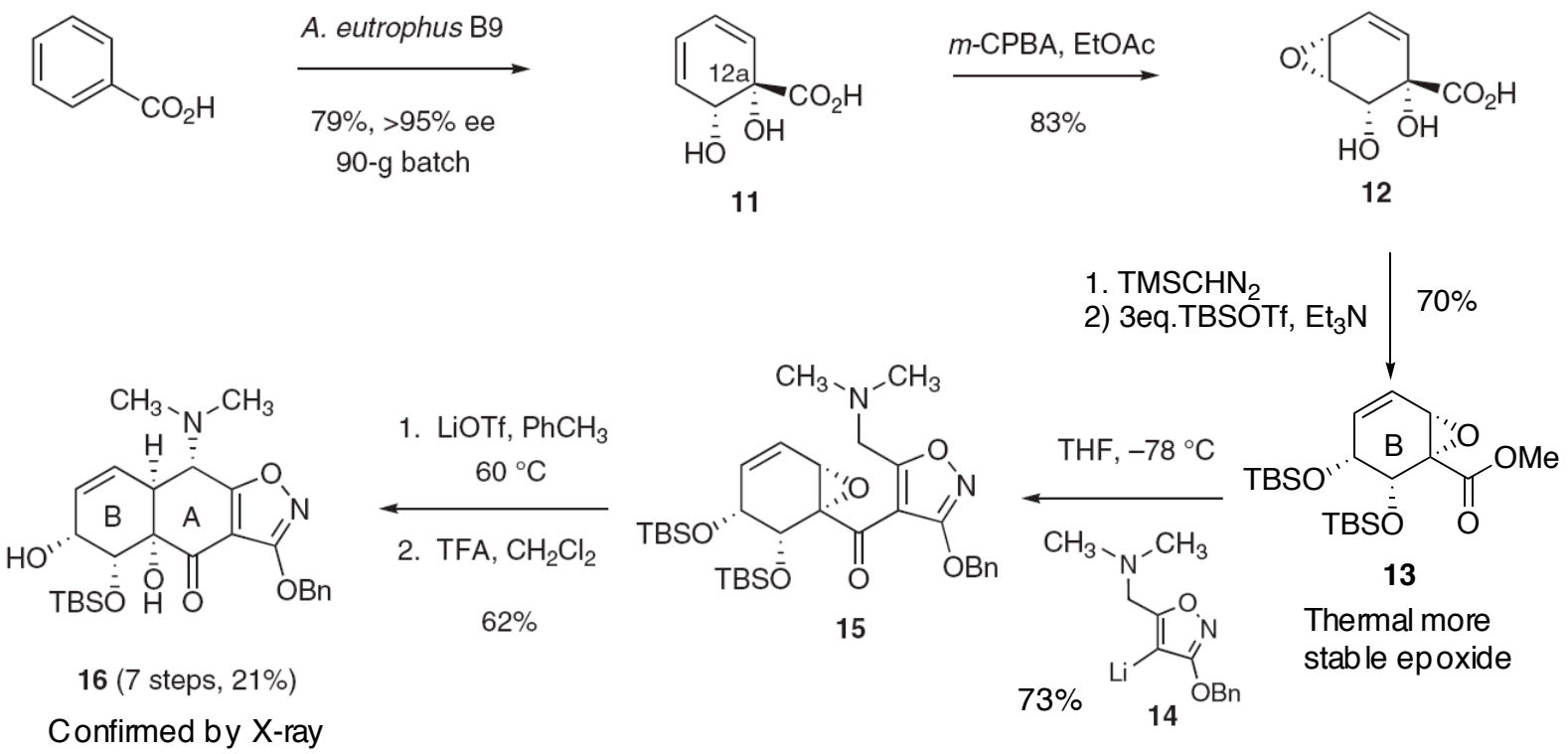
5

Precursor for product: **2**

Retrosynthetic Analysis of Deoxycycline
- via Michael-Dieckmann Reaction

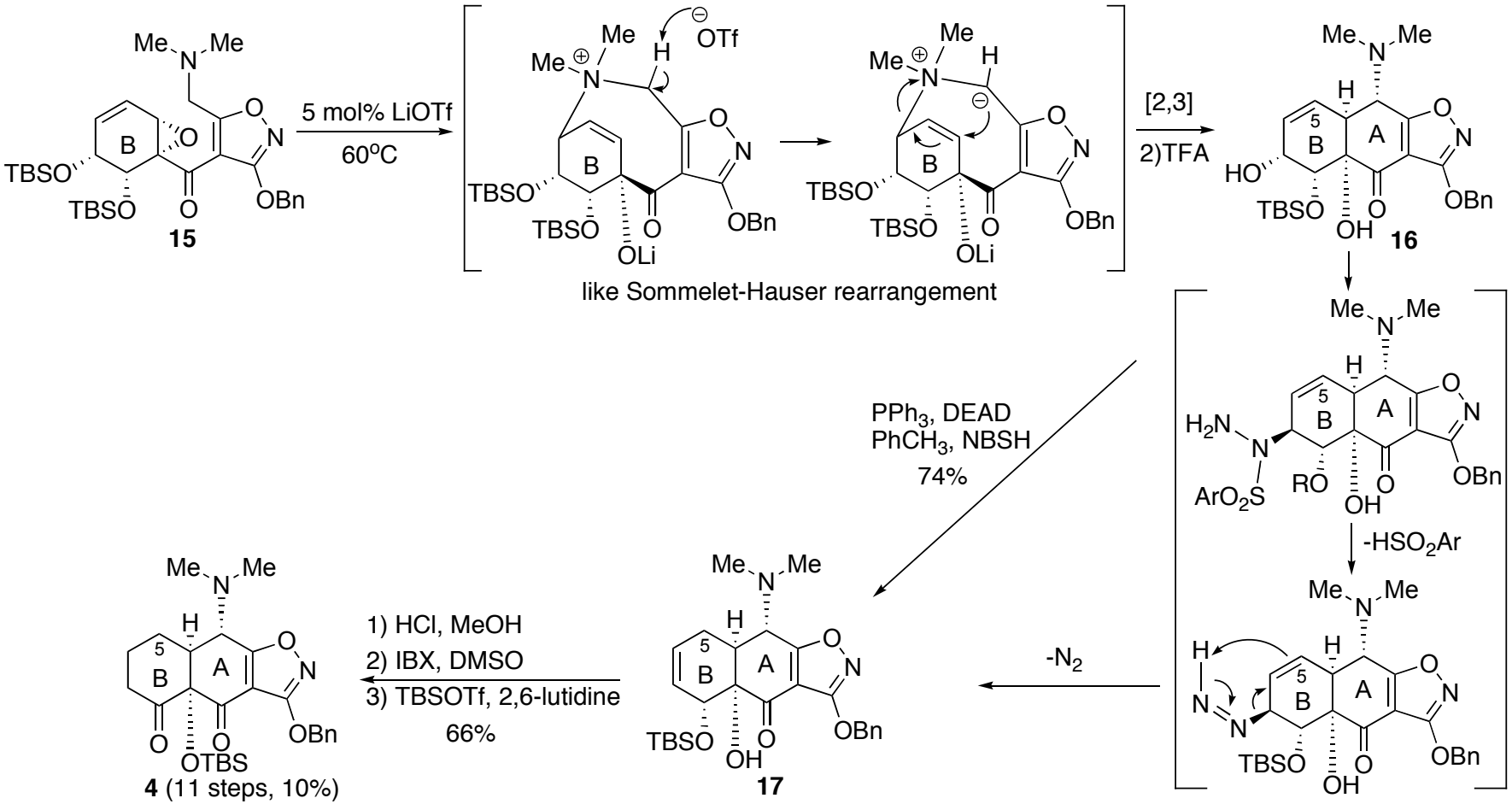


Constuction of Fragment 16



1) Myers, A. G.; Siegel, D, R.; Buzard, D, J.; Charest, M. G. *Org. Lett.* **2001**,*3*, 2923.
2) Stork, G.; Hagedorn III, A. A. *J. Am. Chem. Soc.* **1978**, *100*, 3609.
3) Pine, S. H. *Org. React.* **1970**,*18*, 403.

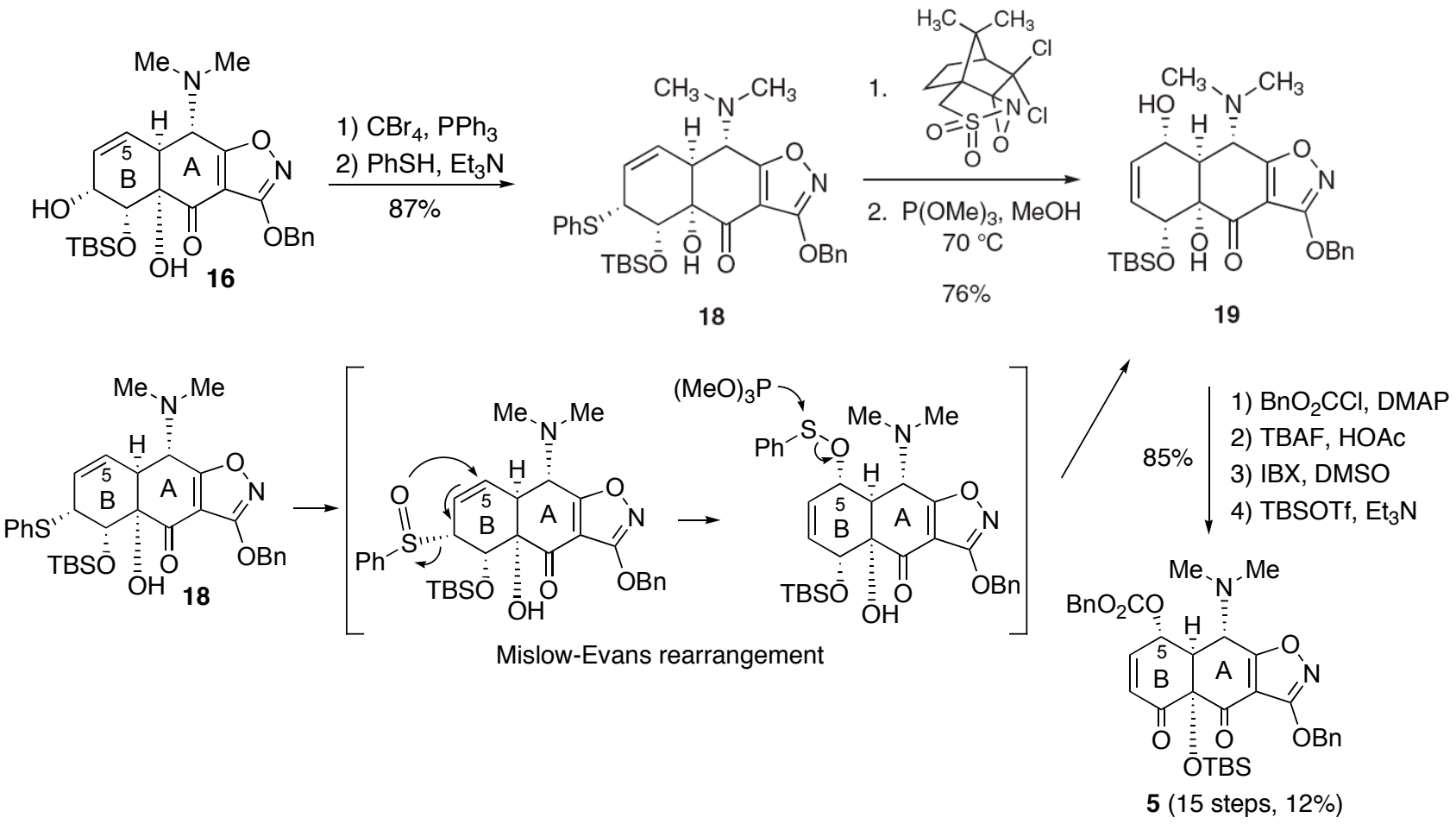
Constuction of Fragment 4



1) Myers, A. G. Zheng, B. *Tetrahedron, Lett.* **1996**, *37*, 4841.

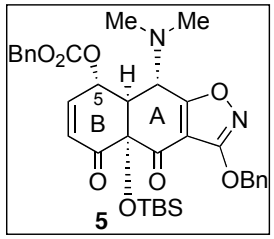
2) Frigerio, M.; Santagostino, M. *Tetrahedron, Lett.* **1994**, *35*, 8019.

Constuction of Fragment 5



Davis, F. A.; Weismiller, M. C.; Murphy, C. K.; Reddy, R. T.; Chen, B. -C. *J. Org. Chem.* **1996**, *57*, 7274.

Total synthesis of (-)-Doxycycline



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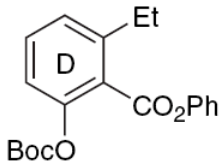
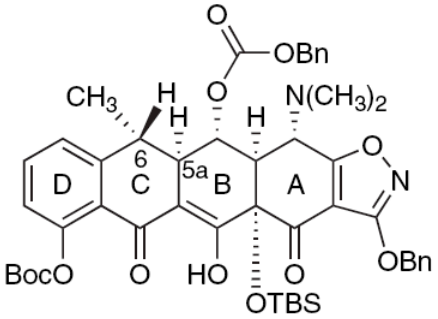


20

5 steps,
42% from anisic acid.

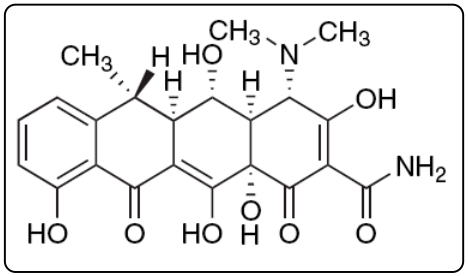
LDA, TMEDA
THF, –78 °C;
5, –78 → 0 °C
79%



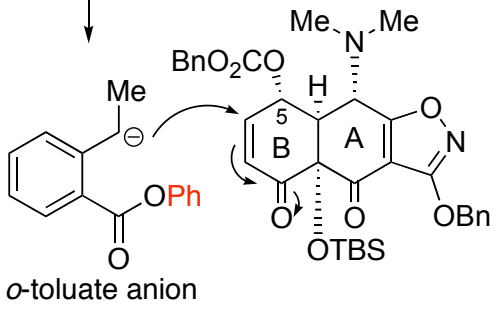
21

Single diastereomer isolated

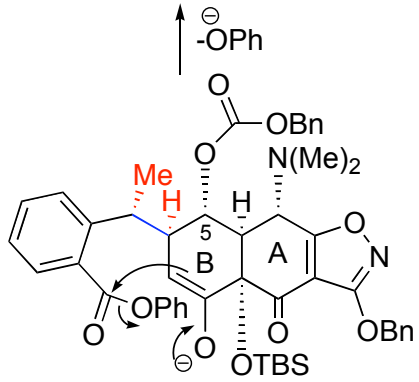
1. HF, MeCN
2. H_2, Pd, THF
MeOH
90%



(–)-Doxycycline (**2**)
(18 steps, 8.3%)



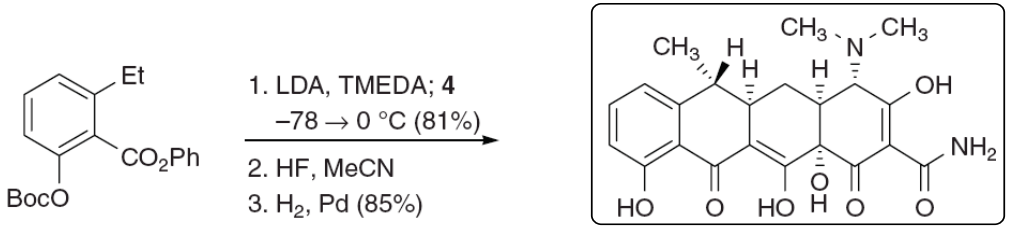
o-toluate anion



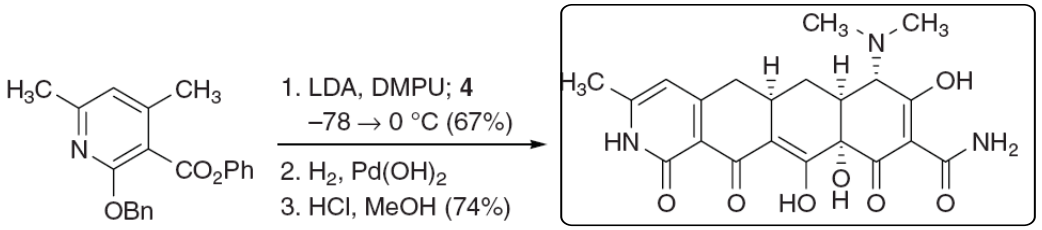
Dodd, J. H.; Weinreb, S. M. *Tetrahedron, Lett.* **1979**, *20*, 3593.

Synthesis of Other Tetracycline Analogs- 6 to 10

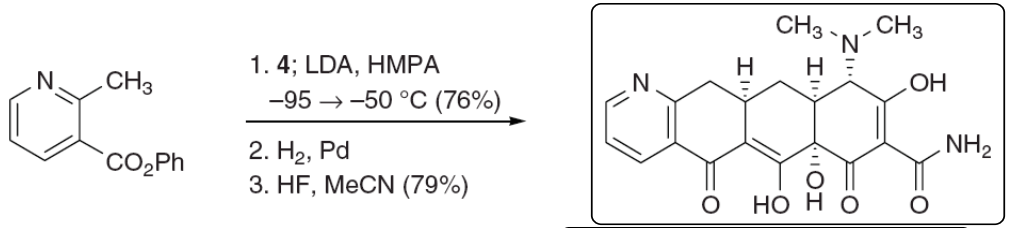
- (-)-6-Deoxytetracycline **6**
  (14 steps, 7.0% yield)



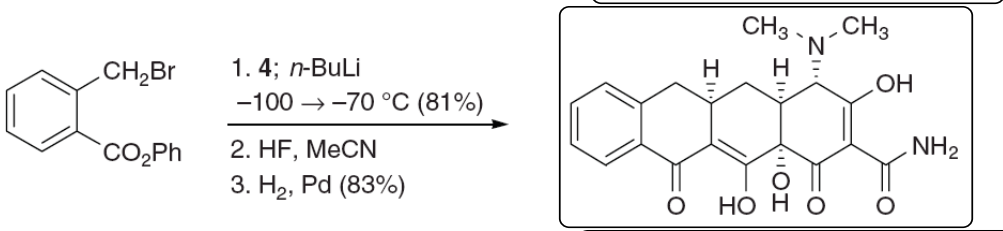
- Pyridone Derivative **7**
  (14 steps, 5.0% yield)



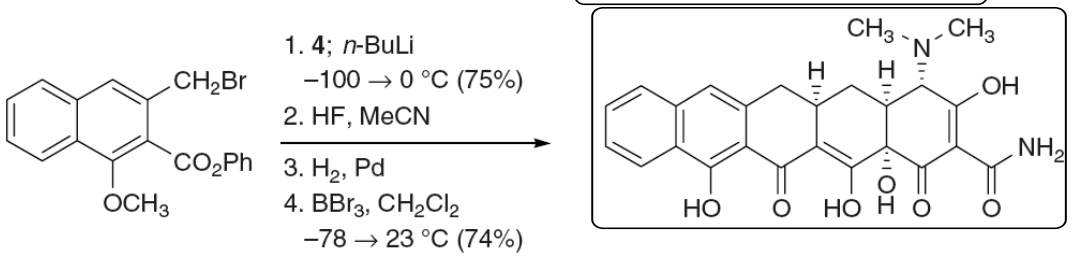
- Pyridine Derivative **8**
  (14 steps, 6.1% yield)



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



- Pentacycline Derivative **10**
  (15 steps, 5.6% yield)



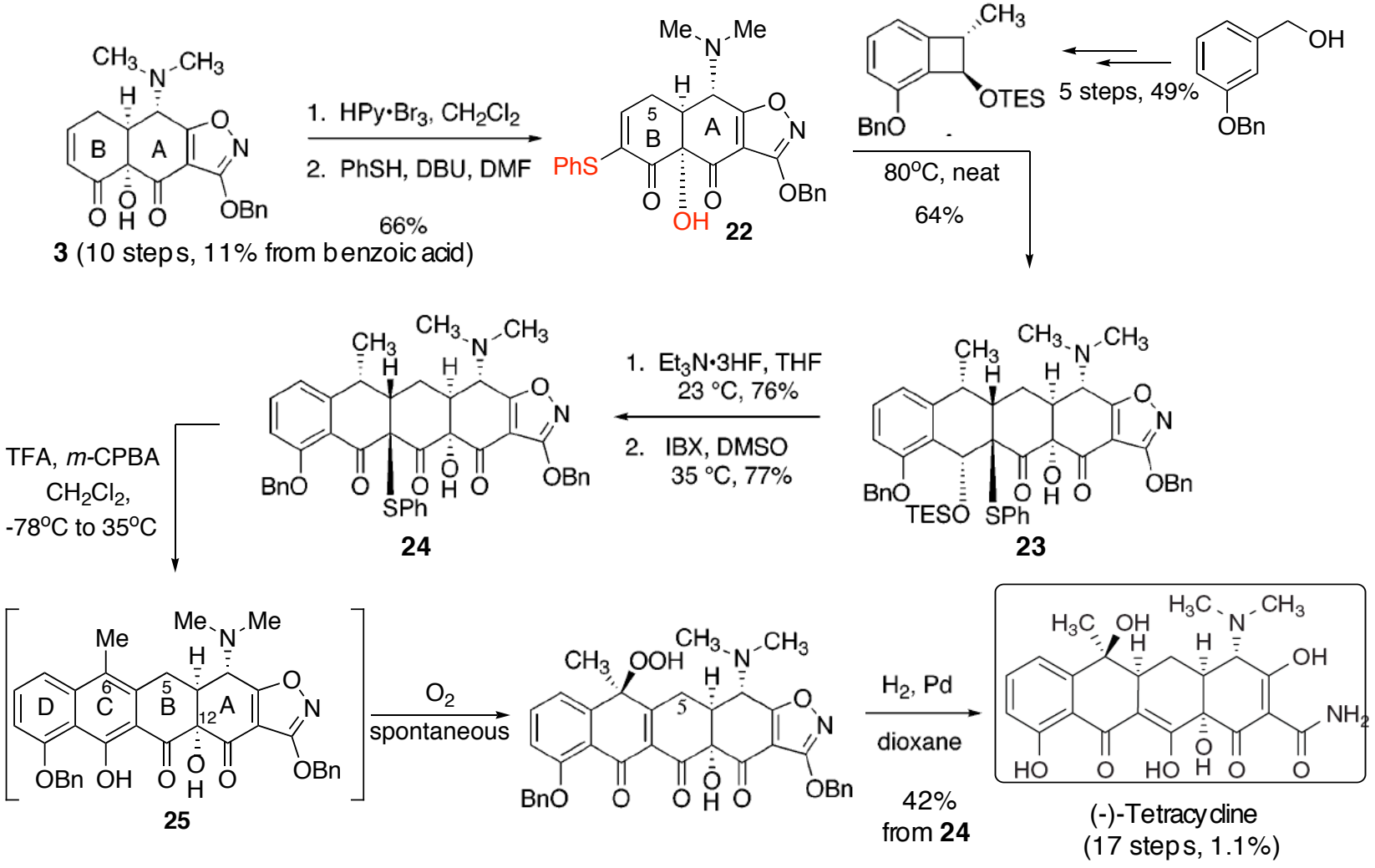
Antibacterial Testing

Bacterial Strains Tested				
Gram-Positive Organisms				
S. aureus ATCC 29213	S. epidermidis ACH-0016	S. haemolyticus ACH-0013	E. faecalis ATCC 700802	S. aureus ATCC 700699
Gram-Negative Organisms				
P. aeruginosa ATCC 27853	K. pneumoniae ATCC 13883	E. coli ATCC 25922	E. coli ACH-0095	E. coli pBR322

	MIC (µg/mL)				
Tetracycline **1**	1	1	8	1	>64
	32	32	1	>64	>64
6-Deoxytetracycline **6**	1	0.5	2	0.5	2
	>64	8	4	16	16
Pyridone Derivative **7**	>64	ND	ND	ND	>64
	>64	ND	>64	ND	ND

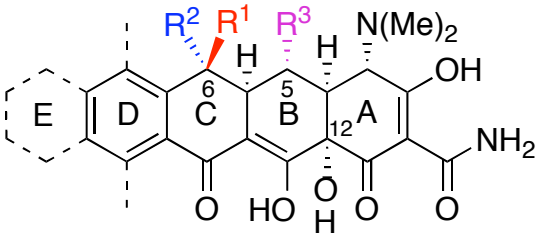
	MIC (µg/mL)				
Pyridine Derivative **8**	8	2	8	2	>64
	>64	16	2	>64	64
10-Deoxysancycline **9**	16	16	64	8	64
	>64	ND	32	ND	ND
Pentacycline Derivative **10**	1	0.5	1	1	1
	>64	>64	>64	>64	>64

Total Synthesis of Tetracycline



1) Charest, M. G.; Siegel, D. R.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 8292.
2) Allen, J. G.; Hentemann, M. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 571.
3) Wasserman, H. H.; Lu, T.-J.; Scott, A. I. *J. Am. Chem. Soc.* **1986**, *108*, 4237.

Conclusion



Tetracycline antibiotics

❖ Convergent enantioselective routes the synthesis of diverse tetracycline antibiotics.

❖ Diastereoselective C-ring construction:

a. Michael-Dieckmann reaction
(Tetracycline derivatives **2** to **10**, 14 ~ 18 steps in 5.0% ~ 8.3% yield)

b. Diels-Alder reaction
Tetracycline, 17 steps in 1.1% yield.
Compared with the first synthesis: 34 steps in 0.002% yield.