

Feb. 2020



The Art and Science of Synthesis

Hugh Nakamura, Ph. D.

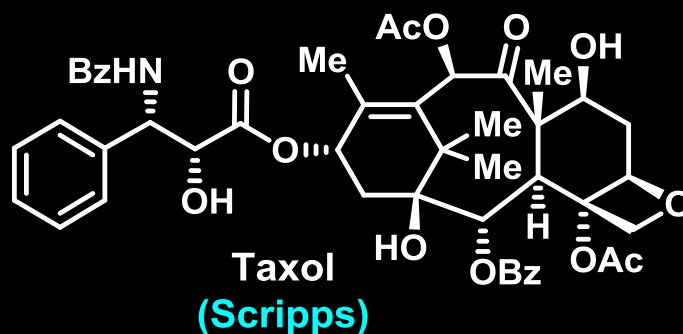
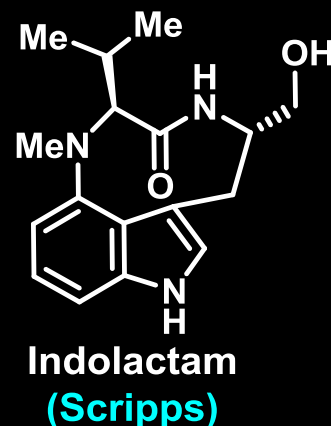
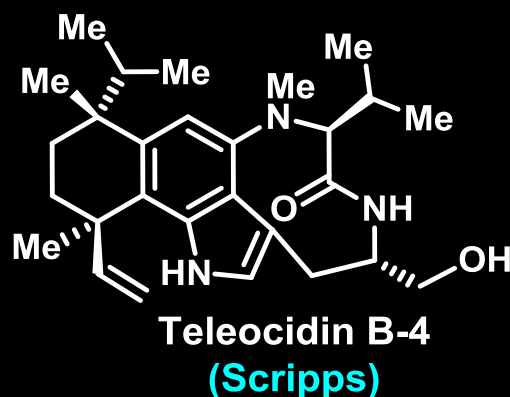
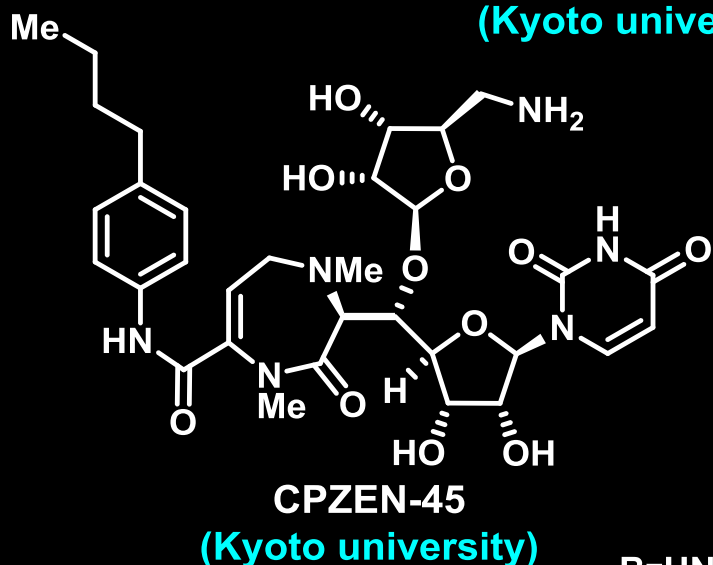
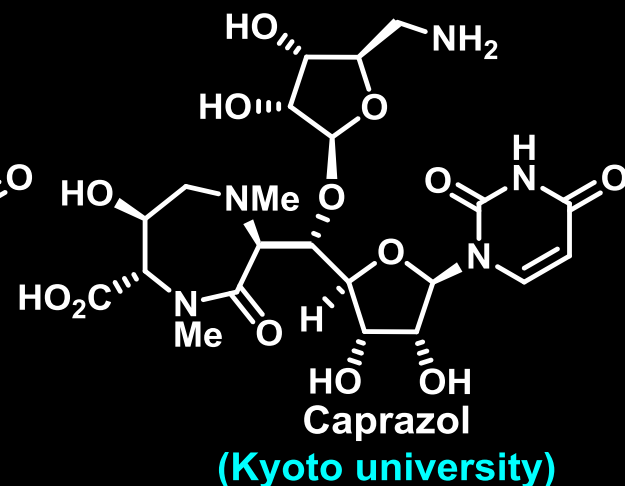
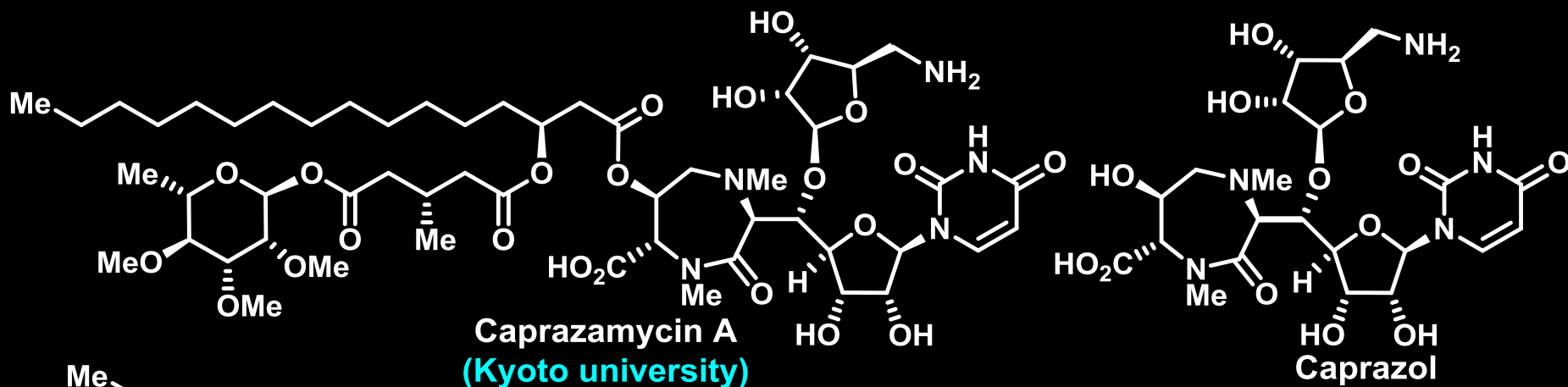
(Prof. Phil. S. Baran)

Scripps Research, Department of Chemistry, USA

Outline

- 1. Total synthesis of caprazamicins
(Ph.D. study) 2012-2017
Takemoto group, Kyoto university*
- 2. Total synthesis of teleocidins B
(Post-doc study) 2017-2020
Baran group, Scripps Research*

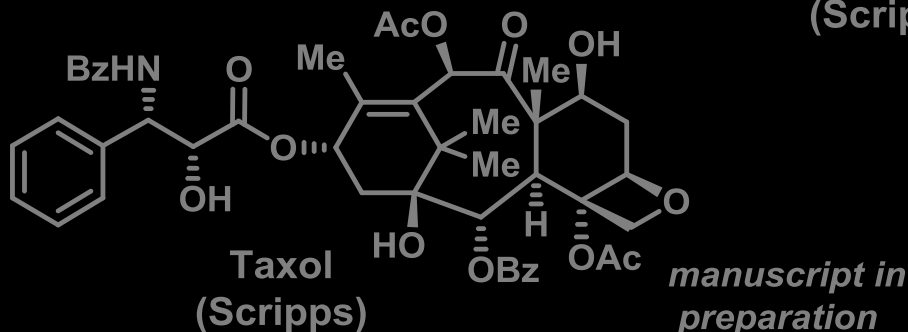
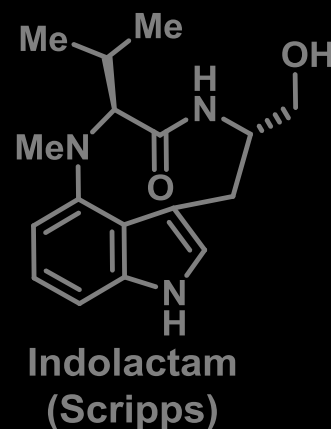
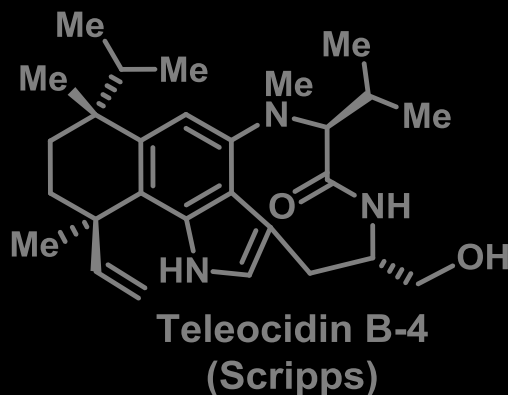
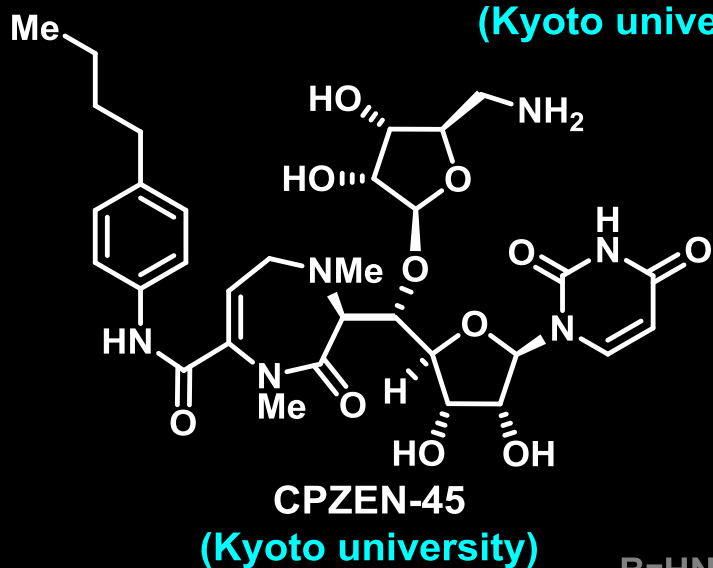
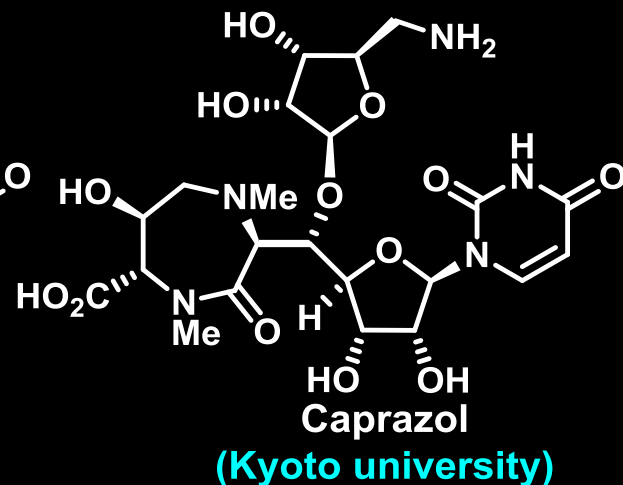
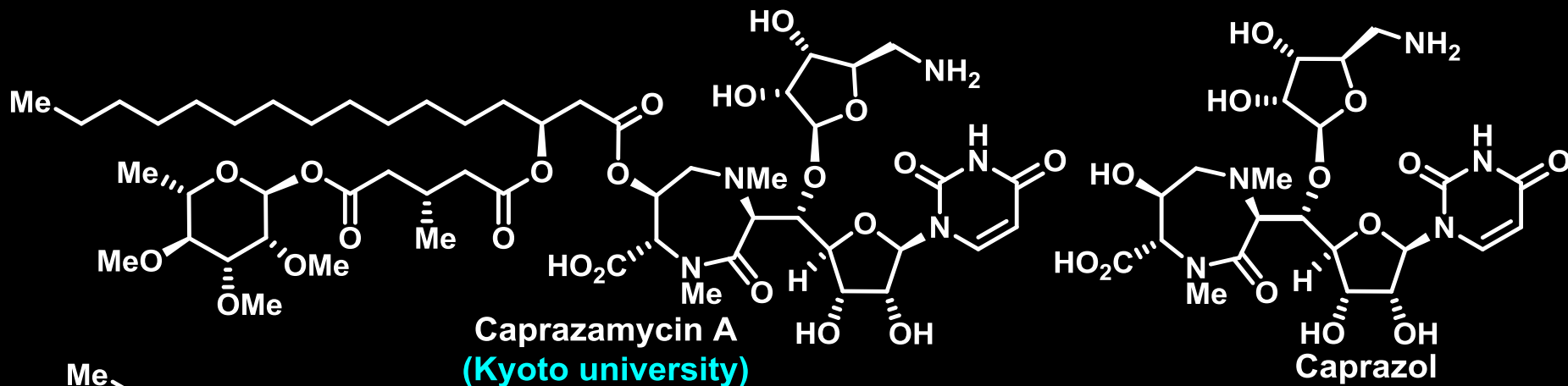
Completed total synthesis of natural products



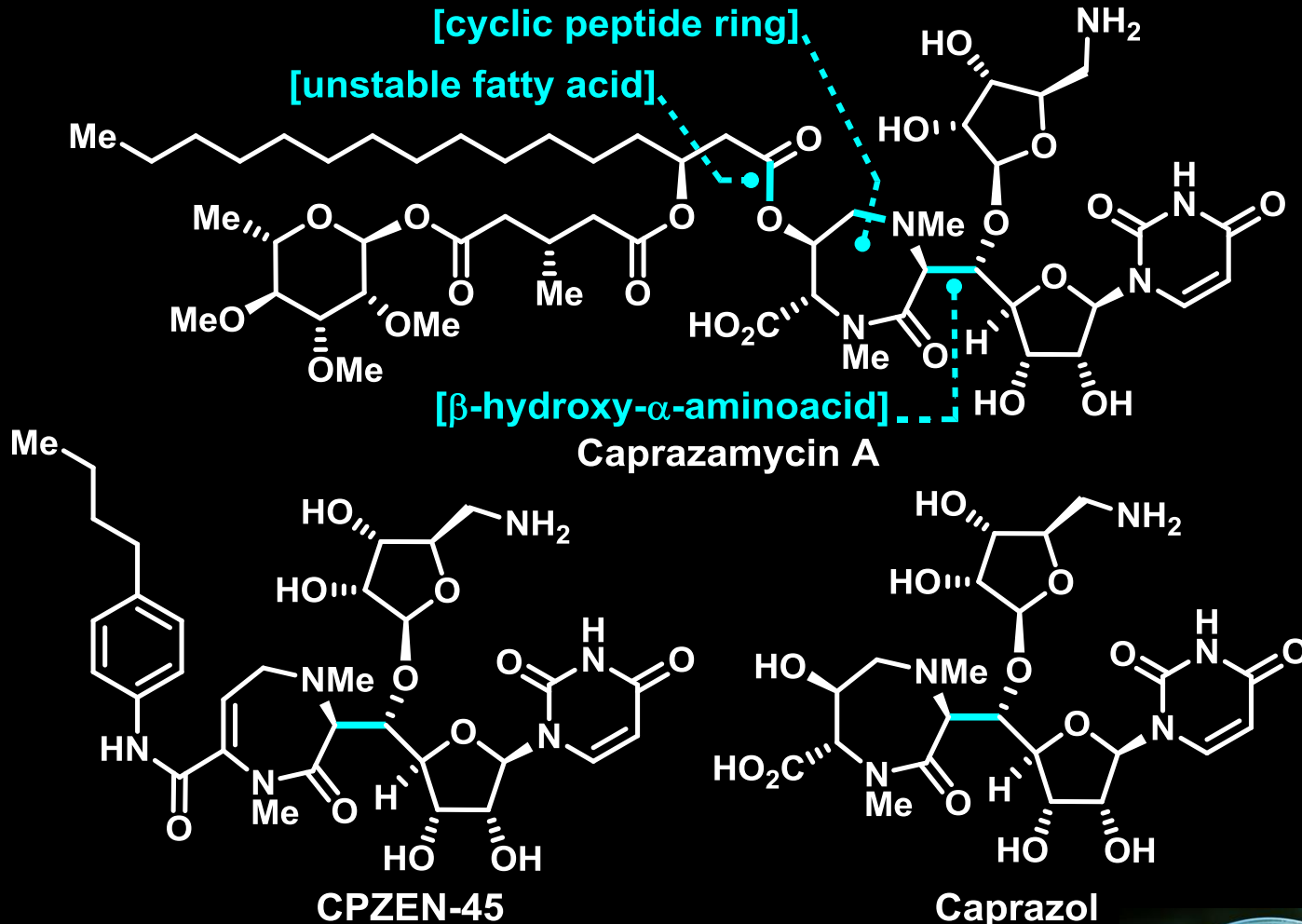
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Completed total synthesis of natural products



Caprazamycins



Isolation:

Streptomyces sp. MK730-62F2 (Igarashi et al. *J. Antibiot.* **2003**, 56, 58)

Bioactivity :

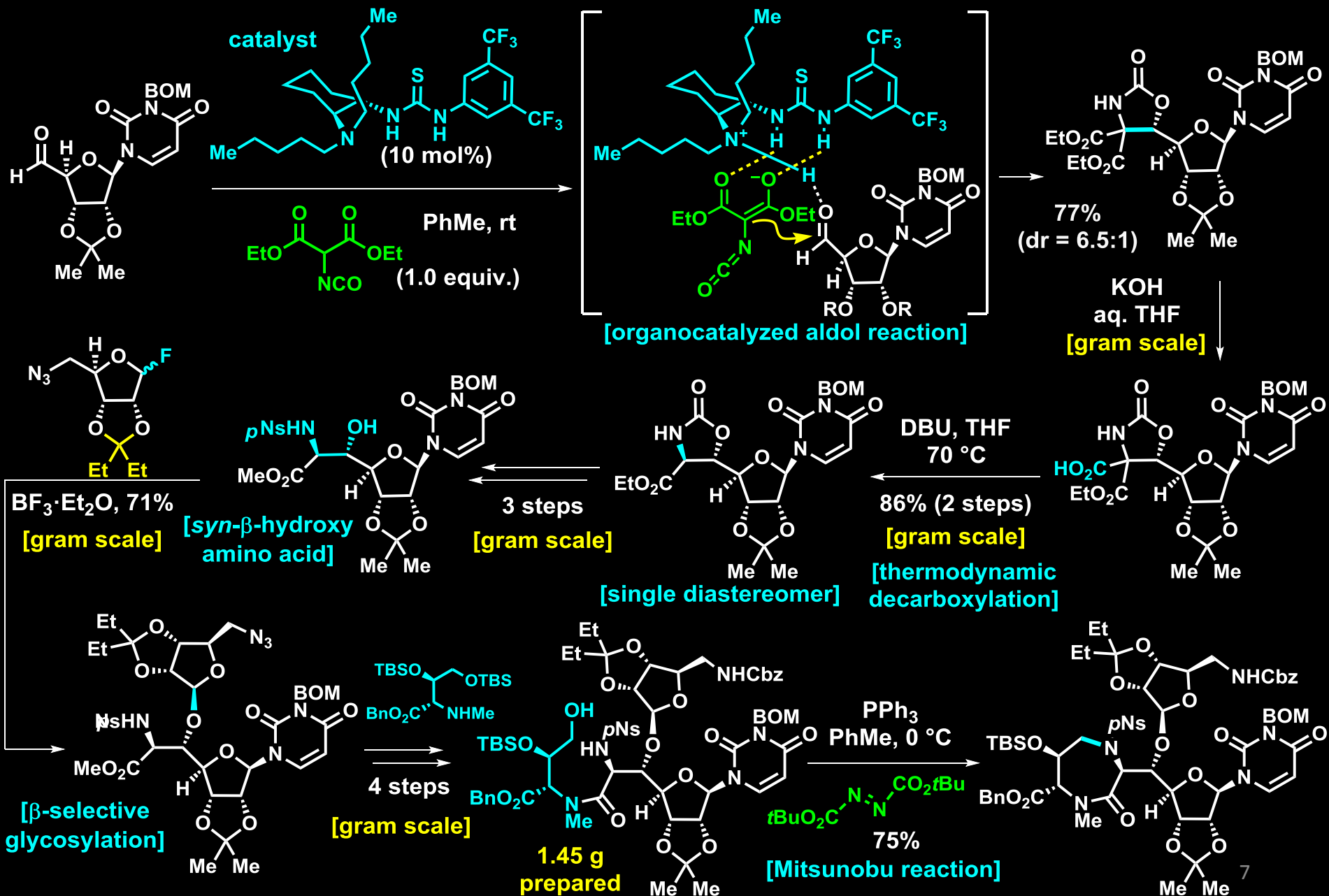
anti-mycobacterial activity against *Mycobacterium tuberculosis* (MIC =

Total synthesis

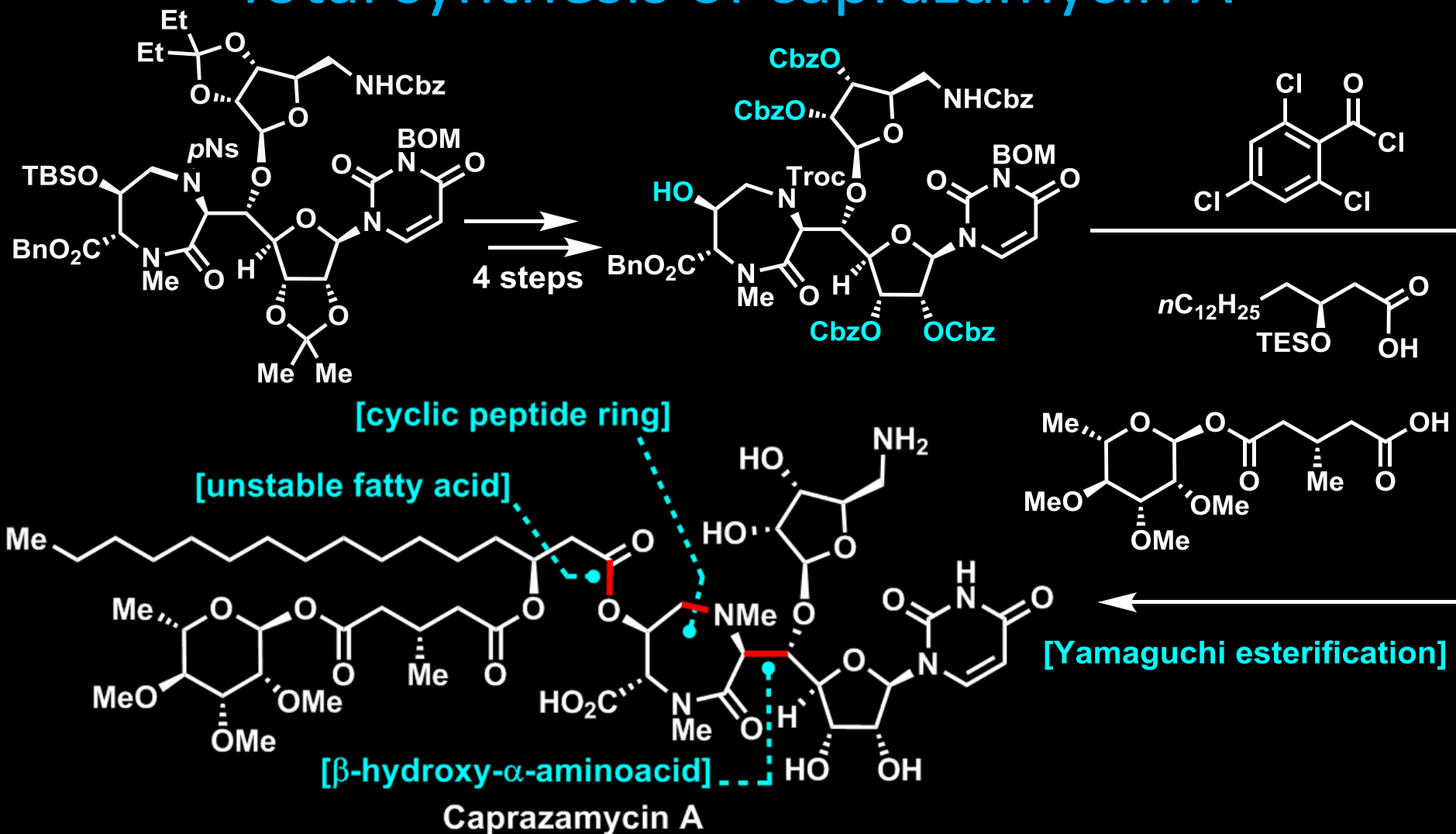
caprazamycin : **no report**



Organocatalyzed aldol reaction



Total synthesis of caprazamycin A

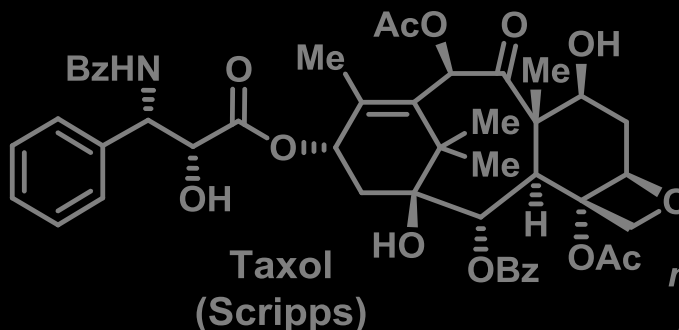
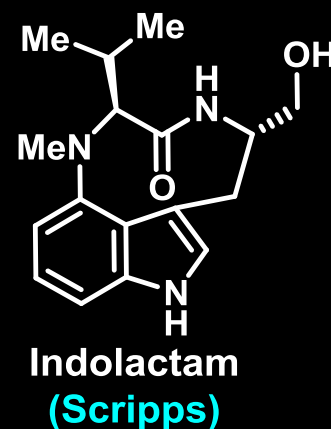
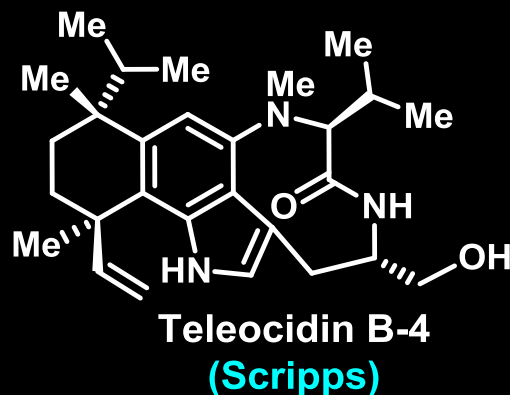
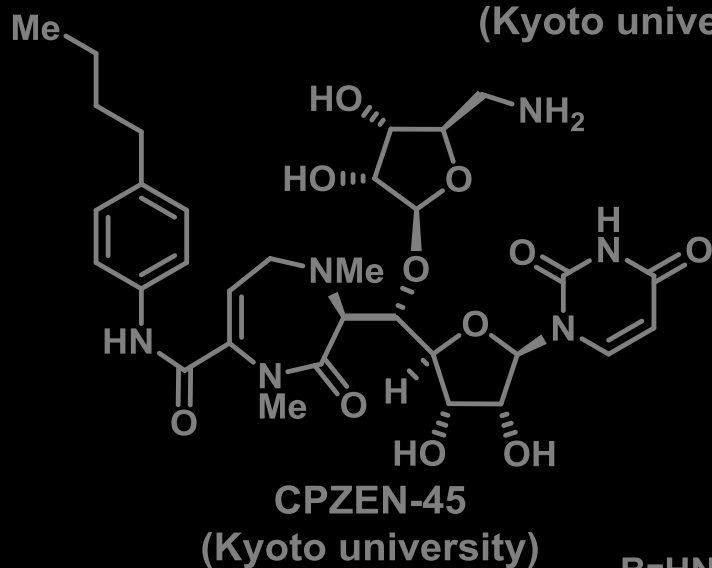
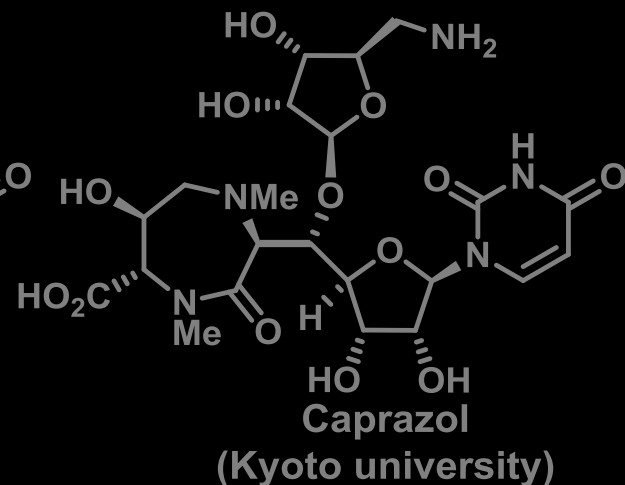
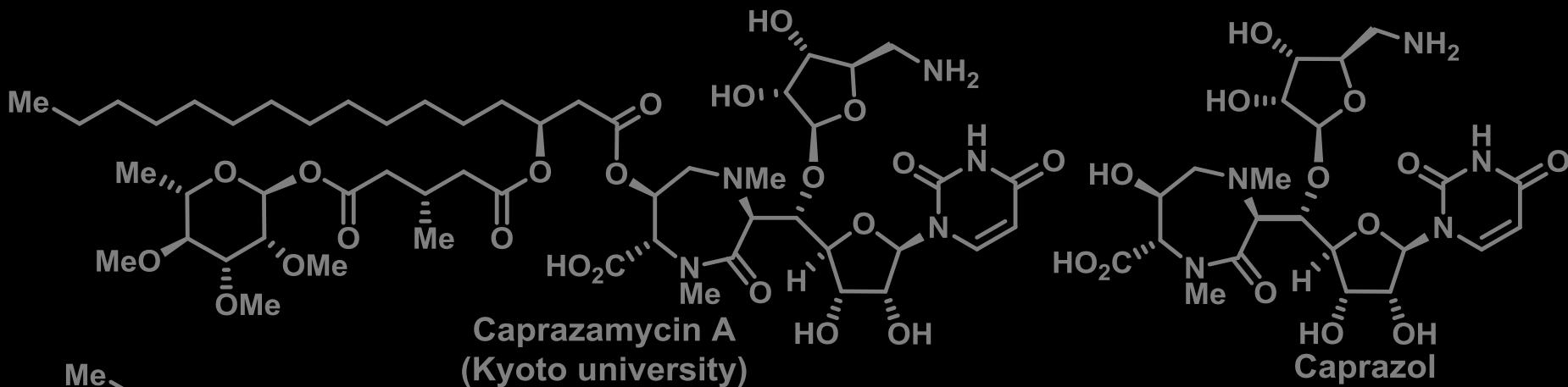


1. H. Nakamura, C. Tsukano, T. Yoshida, M. Yasui, S. Yokouchi, Y. Kobayashi, M. Igarashi, Y. Takemoto *J. Am. Chem. Soc.* 2019, **141**, 8527.
2. H. Nakamura, C. Tsukano, M. Yasui, S. Yokouchi, M. Igarashi, Y. Takemoto *Angew. Chem. Int. Ed.* 2015, **54**, 3136.

Outline

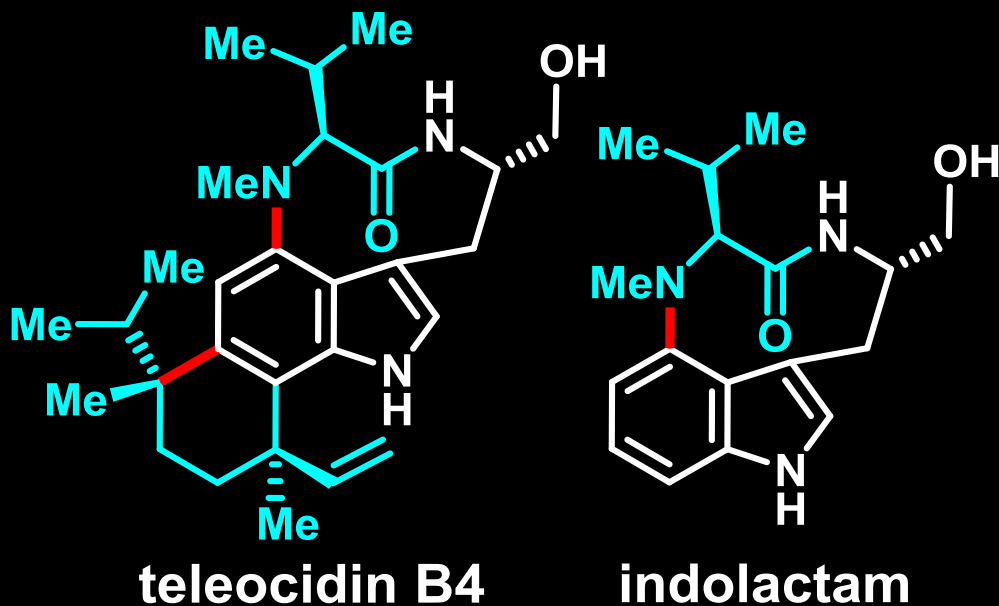
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Completed total synthesis of natural products



manuscript in preparation

Teleocidins



Bioactivity :

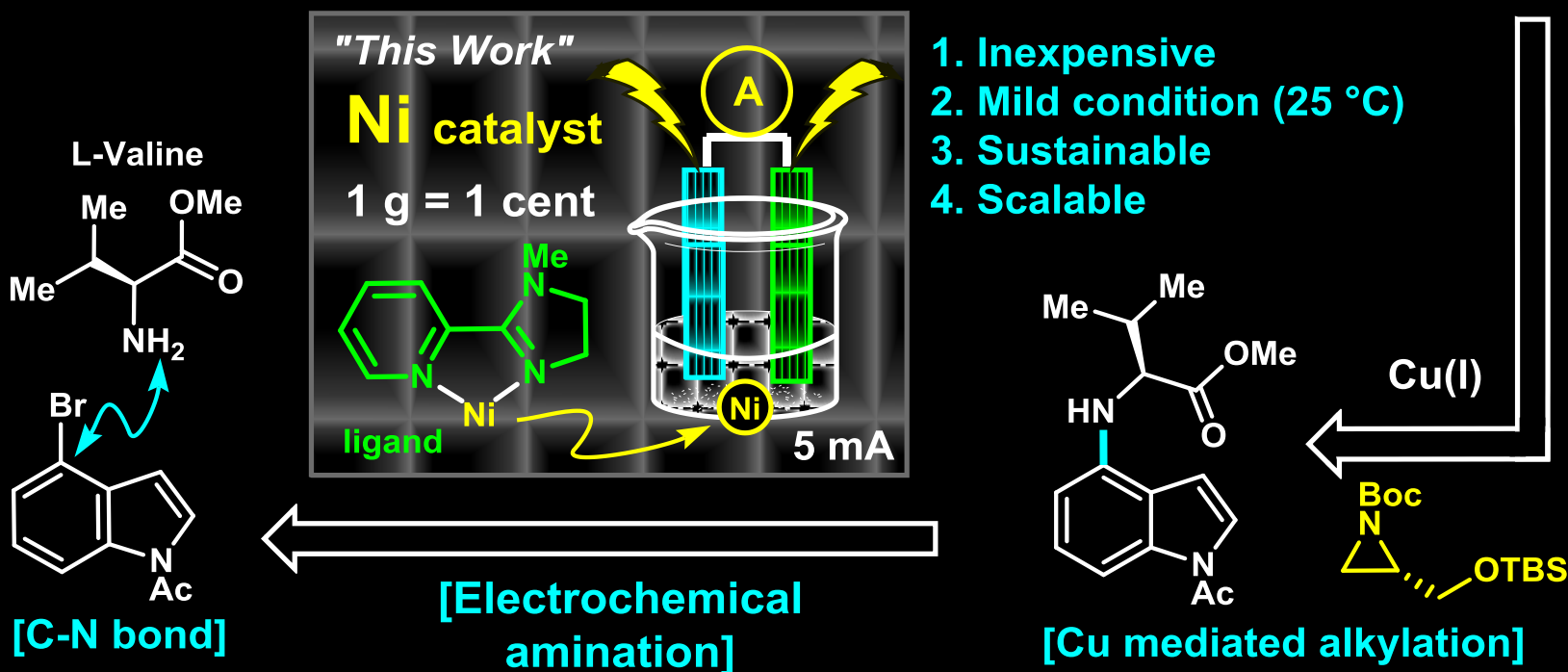
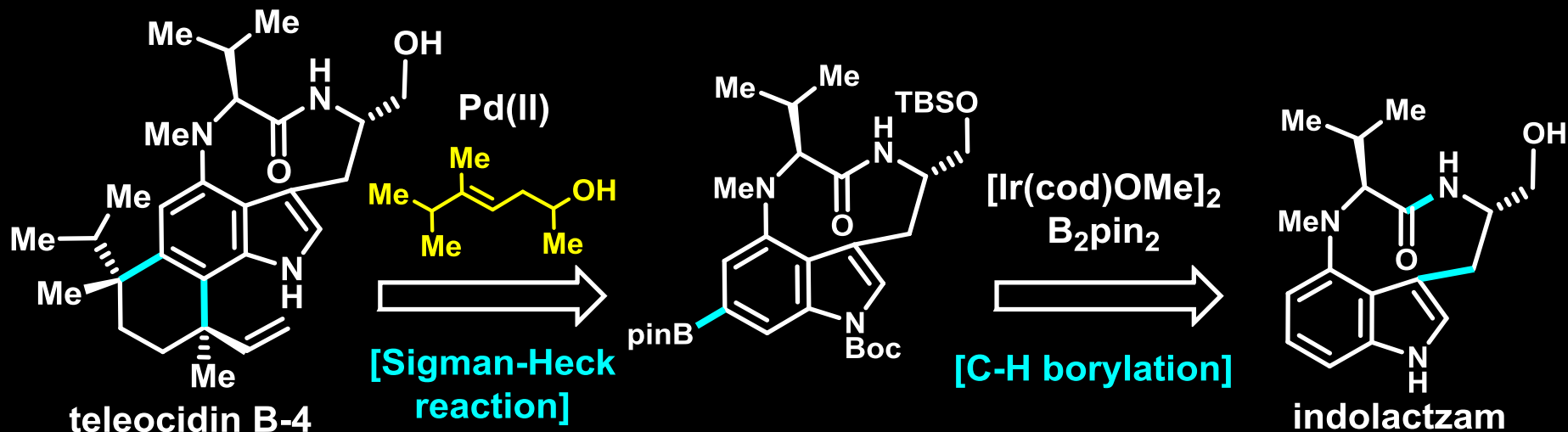
Potent protein kinase-C (PKC) activation

Total synthesis :

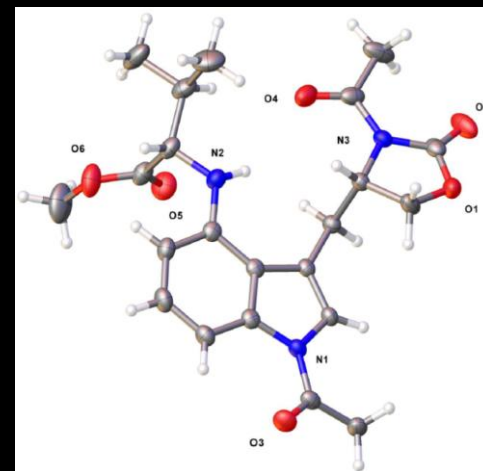
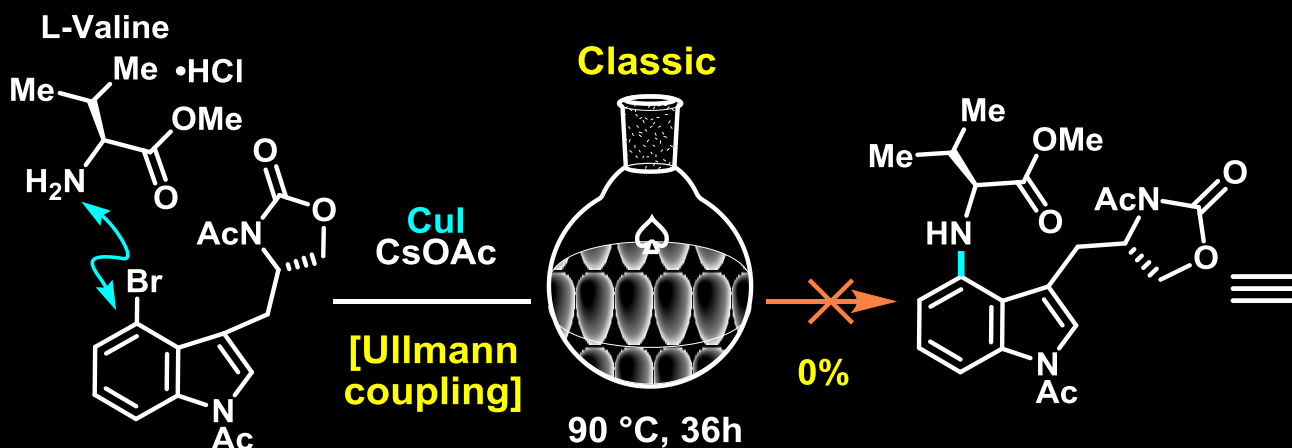
Nakatsuka and co-workers, *Tet. Lett.* **1986**, 27, 6245. **(28 chemical steps)**

Natsume co-workers, *Tet. Lett.* **1987**, 28, 2265. **(17 chemical steps)**

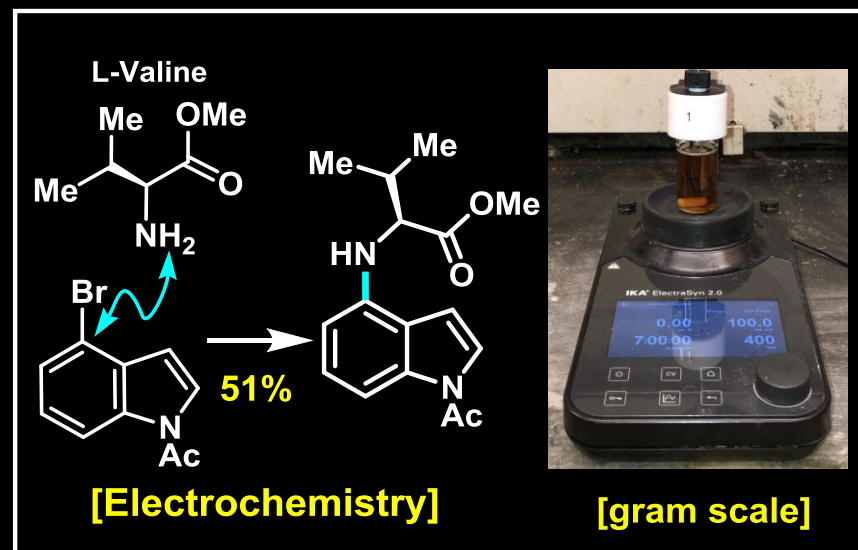
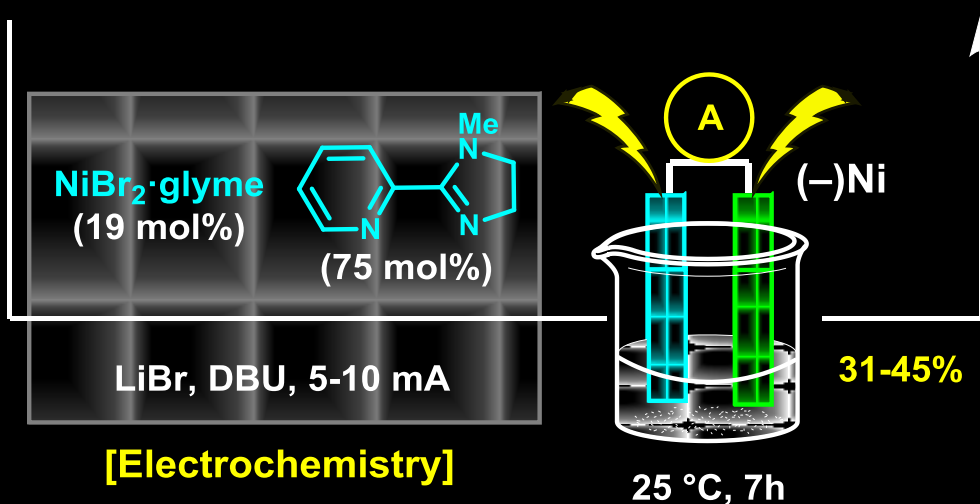
Retrosynthetic Analysis of Teleocidins B



Electrochemical amination

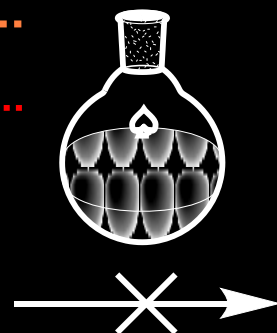
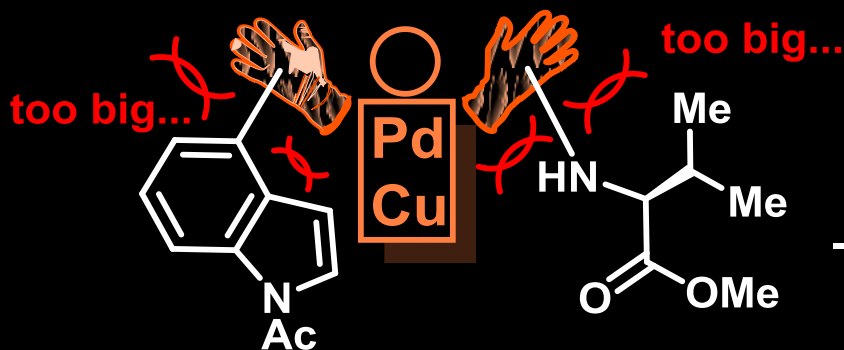


X-ray crystallographic analysis

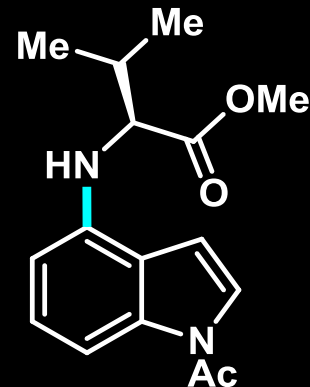


Electrochemical amination

I don't want to work with them...

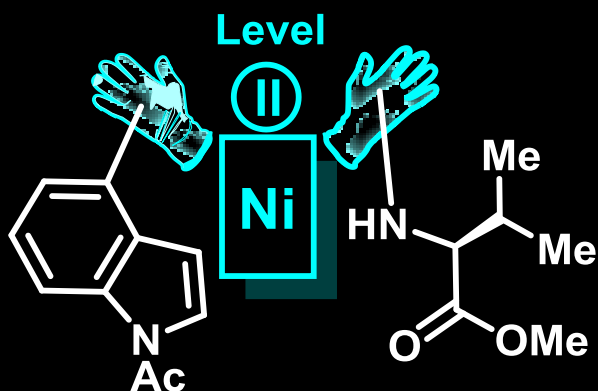


Classic
0%

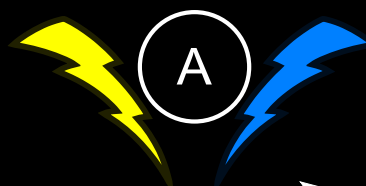


51%

I'm still sleepy...



Electrochemistry

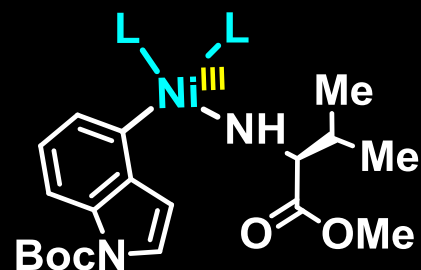
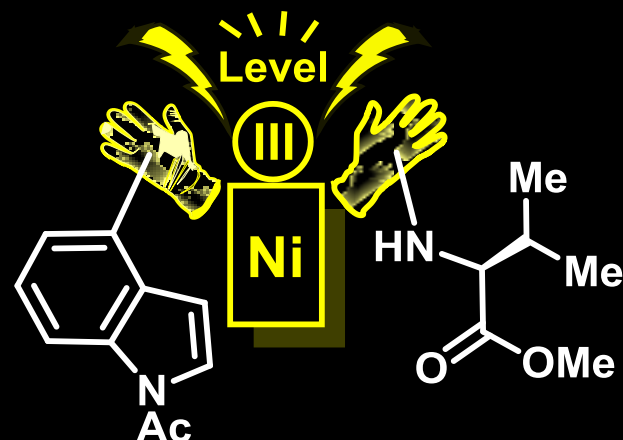


This work

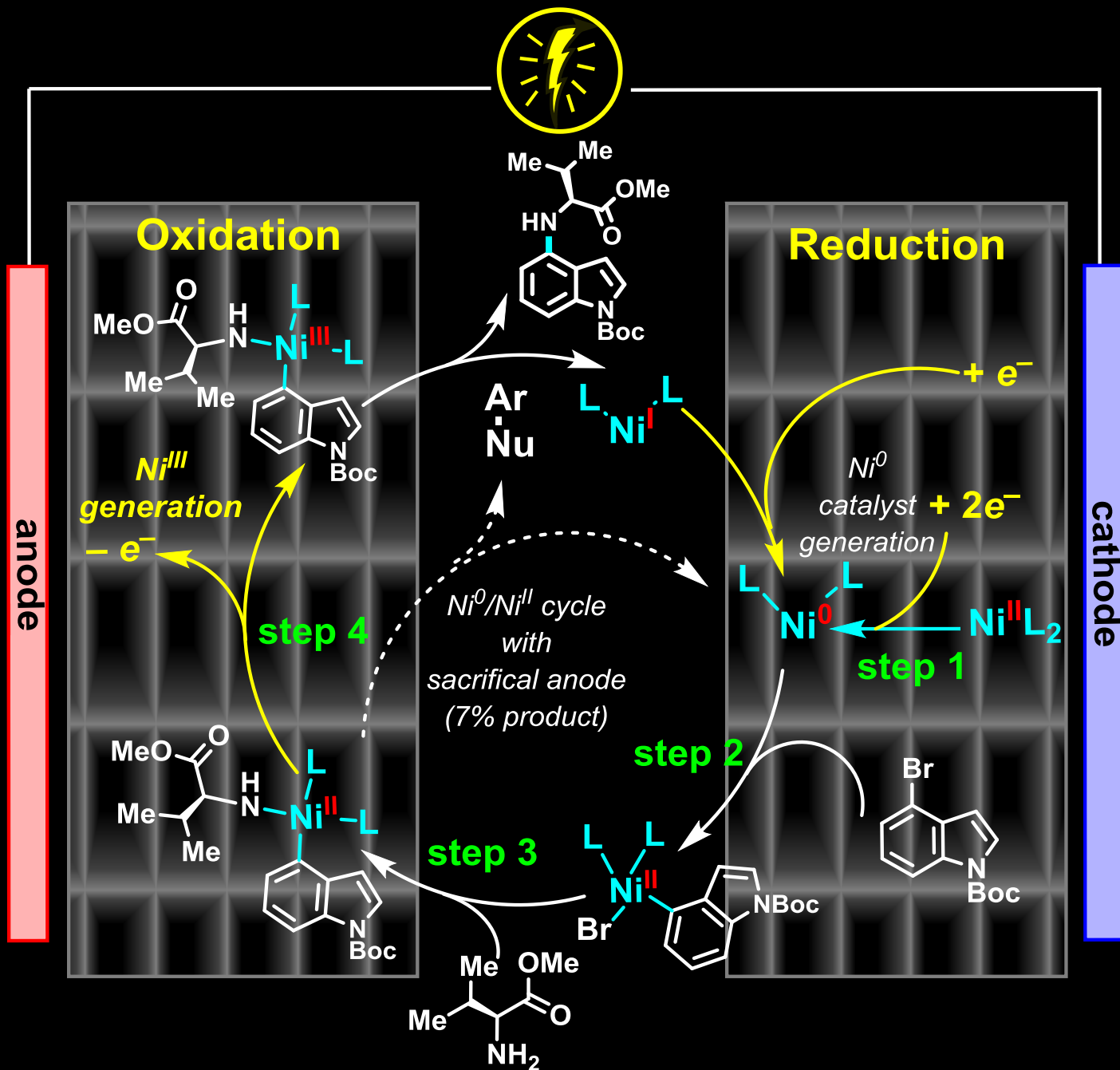


Oxidation

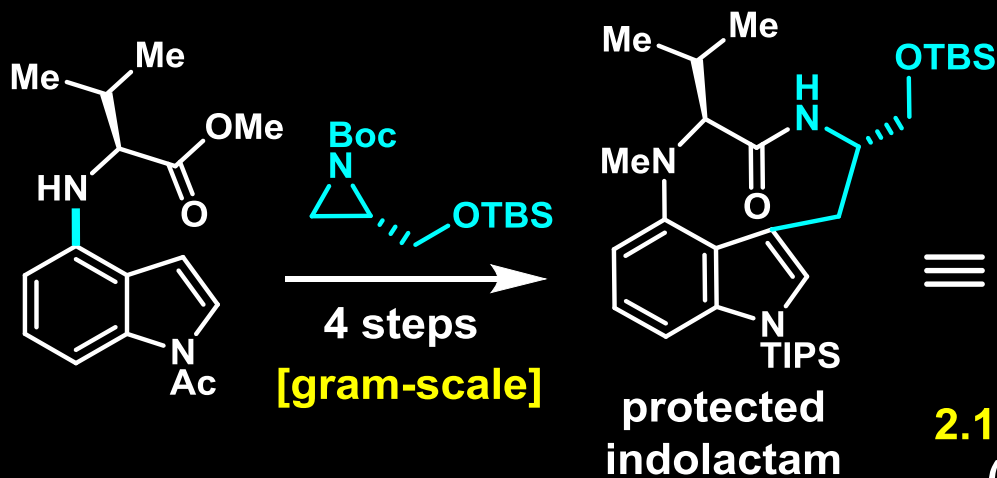
Let's do it!!!



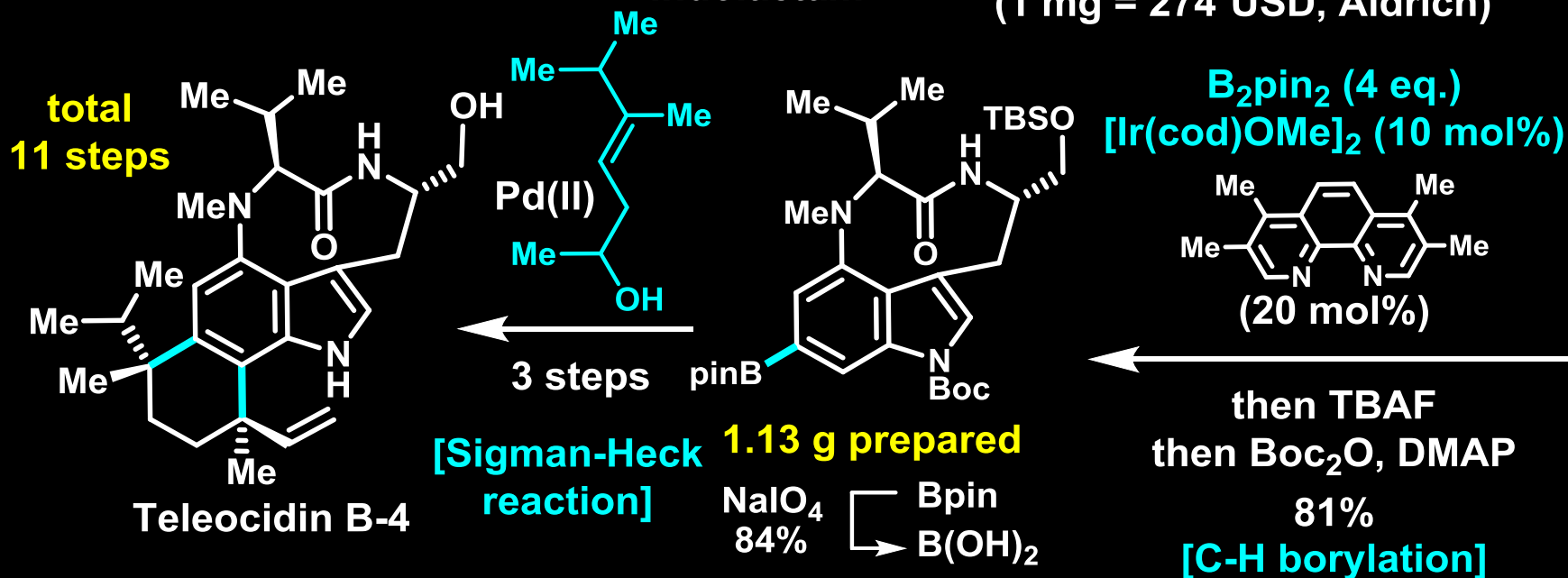
Electrochemical amination



11-step total synthesis of teleocidin B4

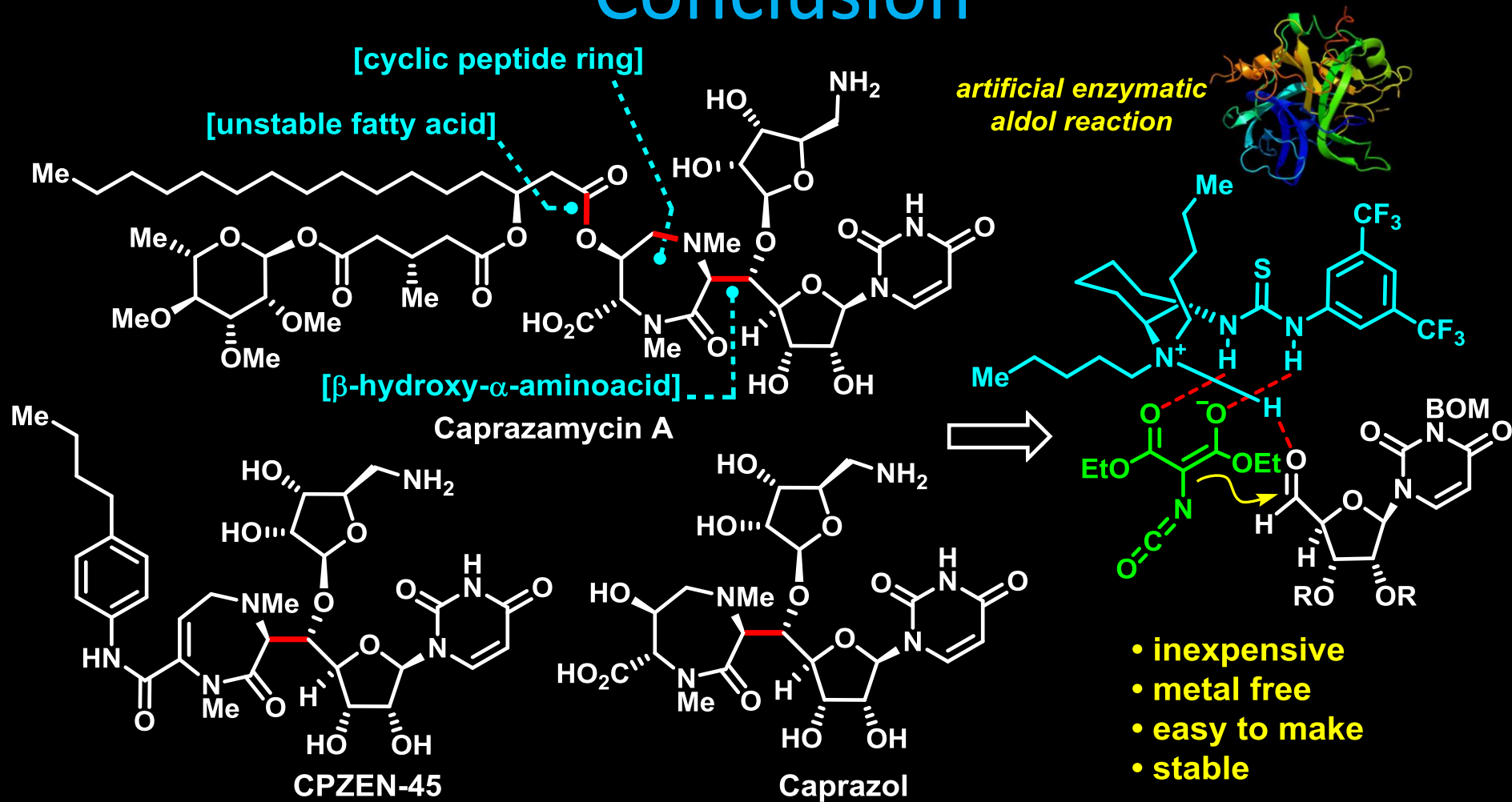


2.1 g prepared = 575,400 USD
 (1 mg = 274 USD, Aldrich)



Hugh Nakamura, Kosuke Yasui, Yuzuru Kanda, Phil S. Baran
J. Am. Chem. Soc. 2019, 141, 1494.

Conclusion

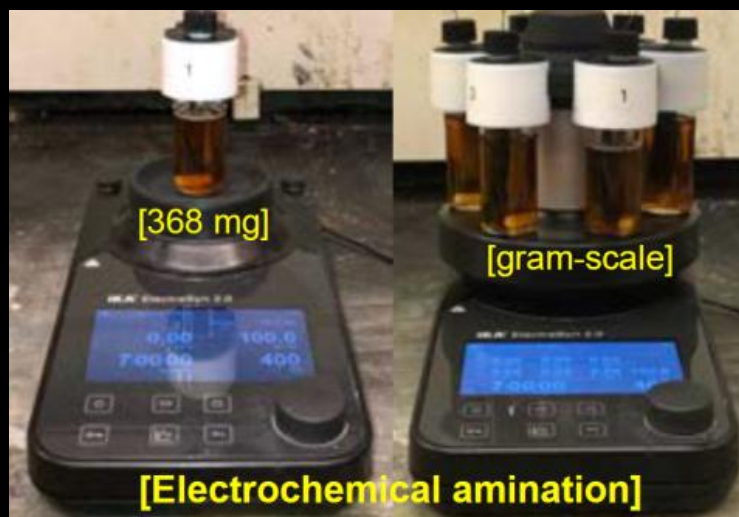


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3. H. Nakamura, T. Yoshida, C. Tsukano, Y. Takemoto *Org. Lett.* 2016, **18**, 2300.

Conclusion

"11-Step Total Synthesis of Teleocidins B-1-B-4"

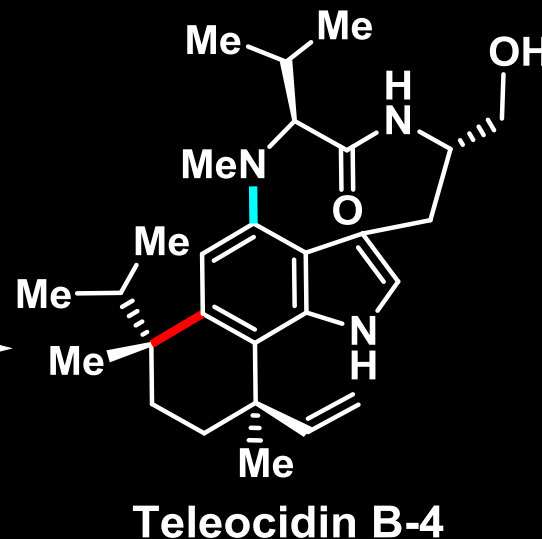
Electrochemistry



This work
11 steps

- inexpensive
- sustainable
- short steps

Prior work
17-28 steps



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