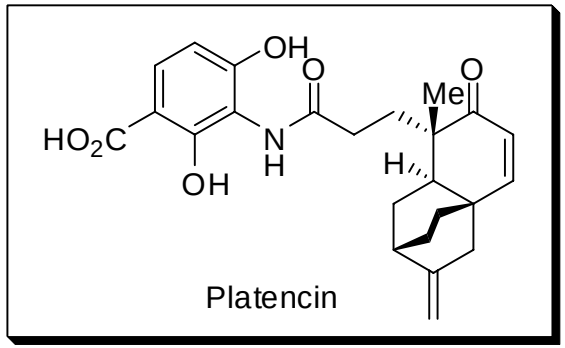
Total Synthesis of Platencin



Platencin

K. C. Nicolaou,* G. Scott Tria, David J. Edmonds
***Angew. Chem. Int. Ed.* 2008, *47*, 1780-1783.**

Shuli Mao
Current Literature Presentation
02-16-2008

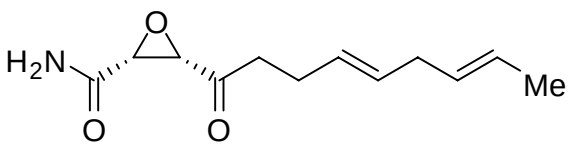
Background

Emergence of bacterial resistance to all known classes of antibiotics made discovery of new antibiotics critical

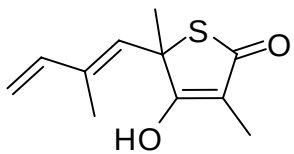
New discovery should emphasize on novel mode of action

Fatty acids are required for bacterial survival and their biosynthesis is catalyzed by condensing enzyme **FabF**

Two poor inhibitors (**cerulenin** and **thiolactomycin**) were reported toward **FabF** (IC50=1.5-13 μg/mL) with poor antibacterial activity (***Staphylococcus aureus*** MIC 64 μg/mL)

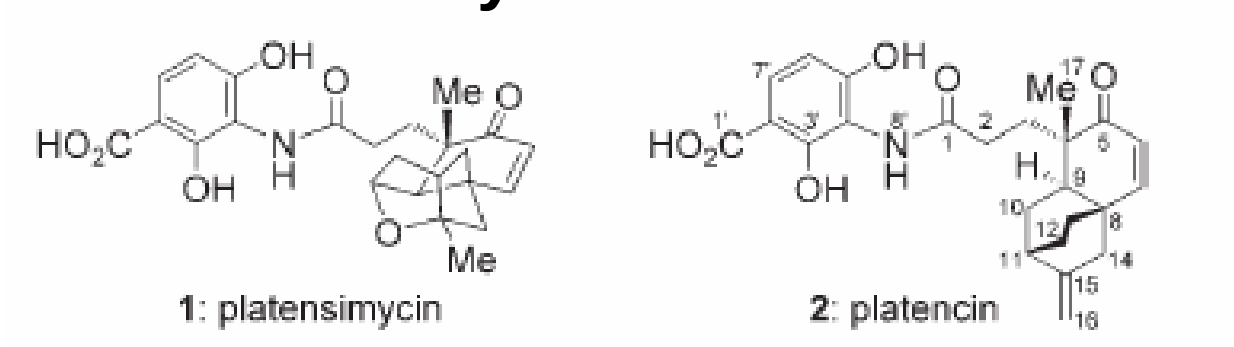


Cerulenin



Thiolactomycin

Platensimycin and Platencin



Merck scientists discovered **1** inhibits **FabF (IC50=0.29μM) [FabH (IC50=247μM)]** while **2** inhibits both **FabF (IC50=4.6μM)** and **FabH (IC50=9.2μM)** through a target-based, whole-cell, high throughput screening assay of 250,000 compounds

Both were isolated from strains of *Streptomyces platensis*

Both has an amide linker, but **1** has a pentacyclic core with a cyclic ether ring while **2** has a tetracyclic core

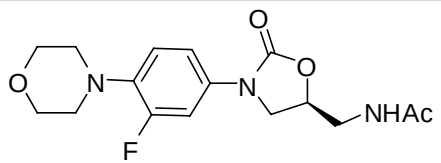
Both exhibits broad-spectrum antibacterial activity but **2** is more potent

Nature **2006**, *441*, 358-361.
PNAS **2007**, *104*, 7612-7616.

in vitro Gram-positive Activity

Organism and genotype	Platensimycin*	Platencin	Linezolid*†
	MIC, μg/ml		
S. aureus (MSSA)	0.5	0.5	4
S. aureus plus serum	2	8	4
S. aureus (MRSA)	0.5	1	2
S. aureus (MRSA, macrolide^R)	0.5	1	2
S. aureus (MRSA, linezolid^R)	1	1	32
S. aureus (VISA, vancomycin^I)	0.5	0.5	2
E. faecalis (macrolide^R)	1	2	1
E. faecium (vancomycin^R)	0.1	<0.06	2
S. pneumoniae‡	1	4	1
E. coli (WT)	>64	>64	>64
E. coli (*tolC*)	16	2	32
S. aureus (*AS-fabF*) (MDC,§ μg)	0.004	0.002	ND
	Toxicity, μg/ml		
HeLa MTT (IC_{50})	>1,000	>100	>100
RBC lysis (MLC)¶	>67	>67	>67
C. albicans (MIC)	>64	>64	>64
	Whole-cell activity, IC_{50}, μg/ml		
Fatty acid synthesis (*S. aureus*)	0.1	0.19	ND
Fatty acid synthesis (*S. pneumoniae*)	0.8	2.7	ND

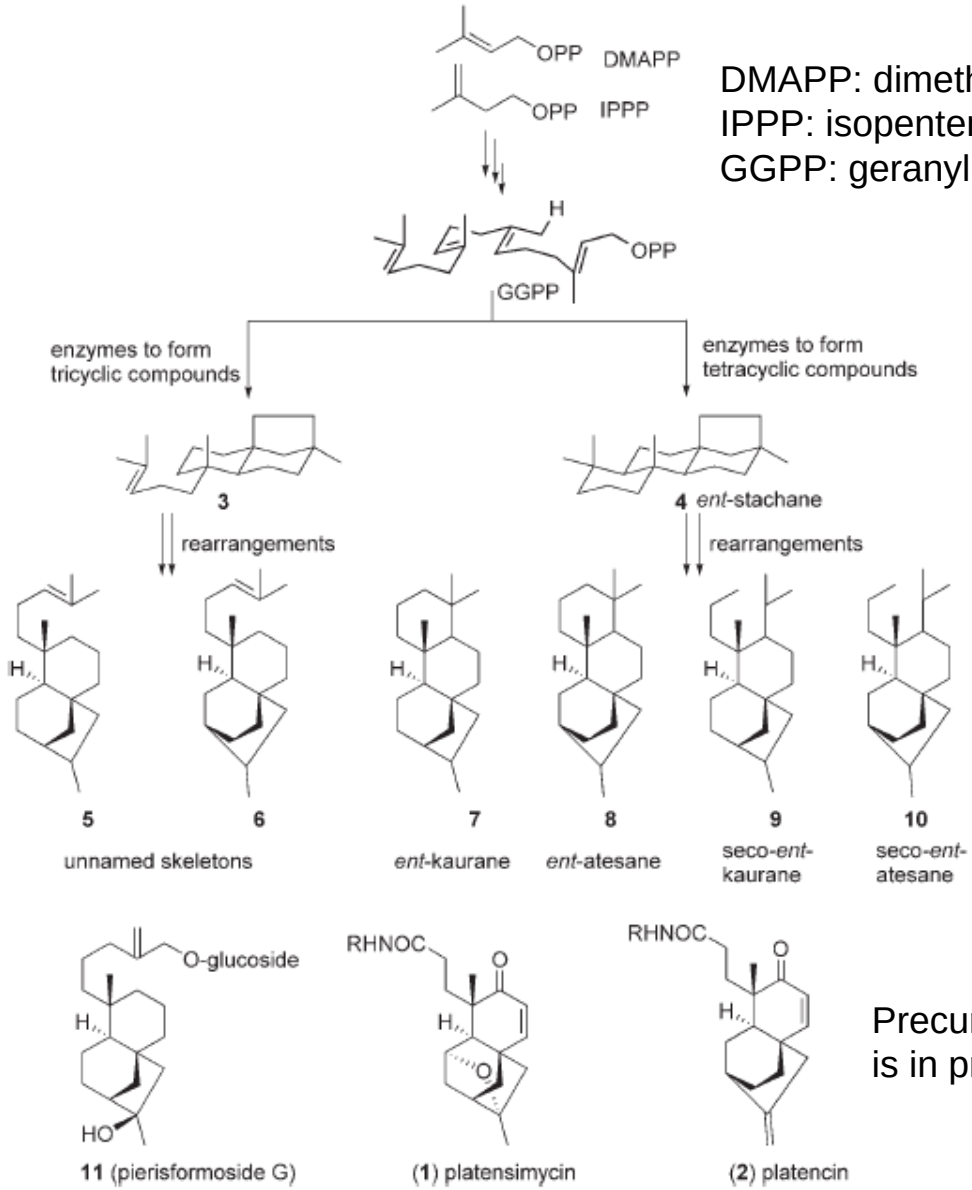
Linezolid: synthetically derived agent in clinical use since 2000



linezolid (Zyvox^{TM})

PNAS **2007**, *104*, 7612-7616.

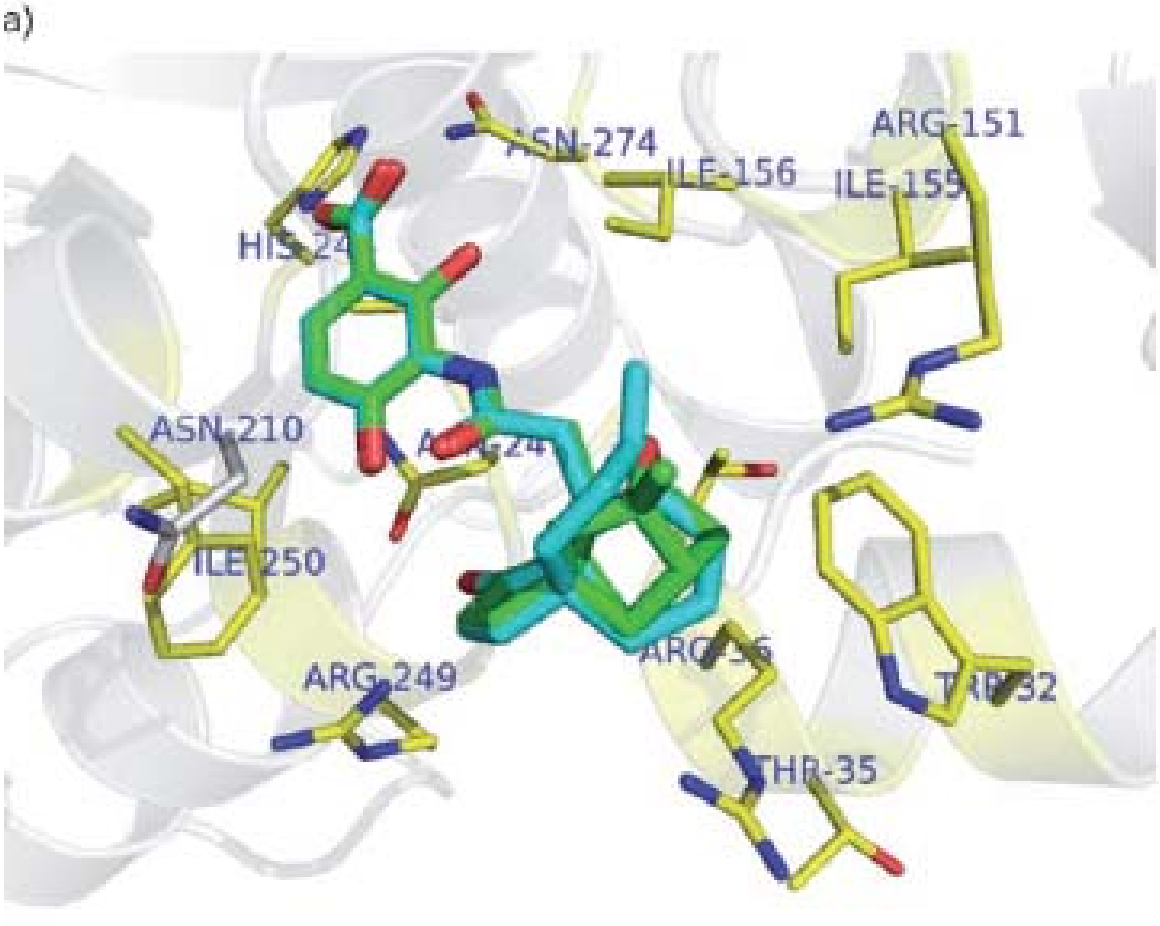
Plausible Biogenesis from Isoprenoid Precursors



DMAPP: dimethylallyl pyrophosphate
IPPP: isopentenyl pyrophosphate
GGPP: geranyl geranyl phrophosphate

Precursor feeding experiment is in progress.

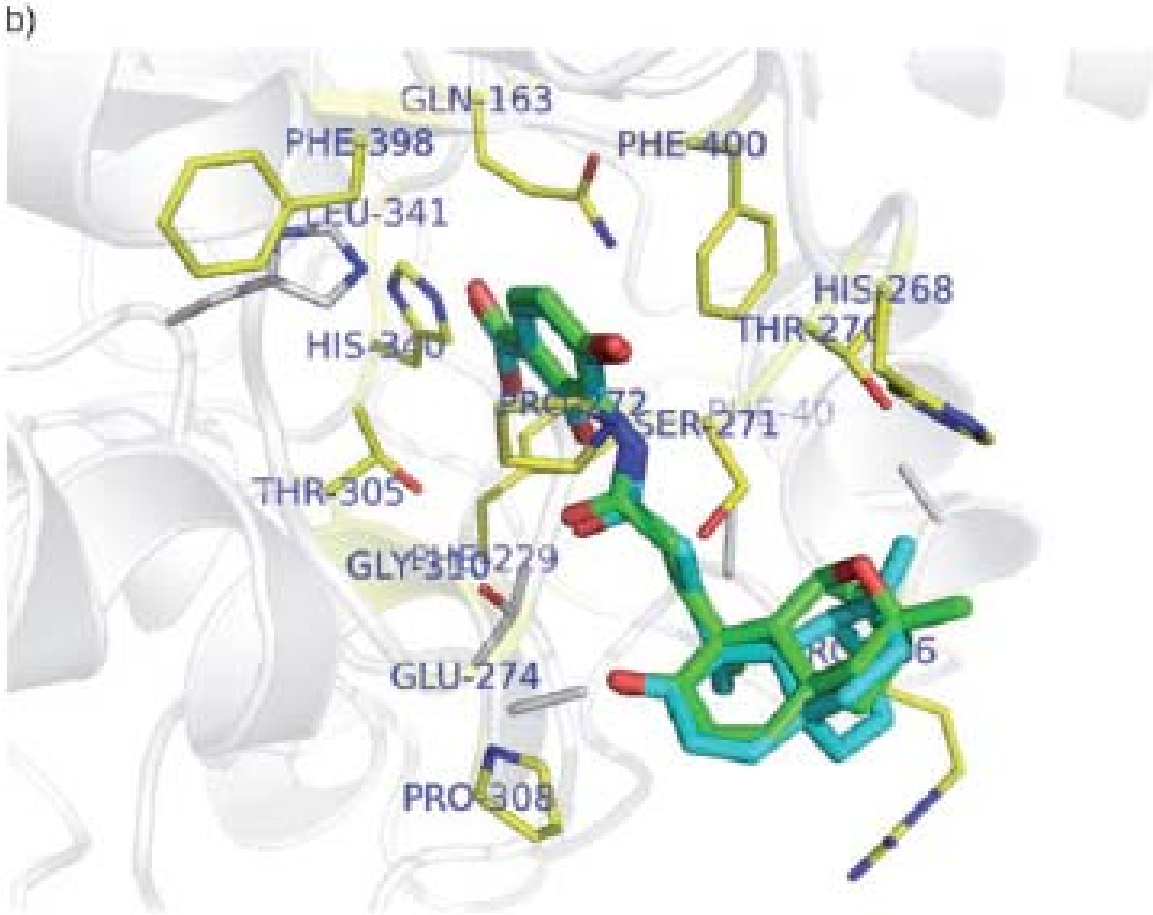
Docking Experiment



E. Coli condensing enzyme active site of **FabH** with docked platensimycin (green) and platencin (cyan).

ACIE **2007**, *46*, 4684-4688.

Docking Experiment

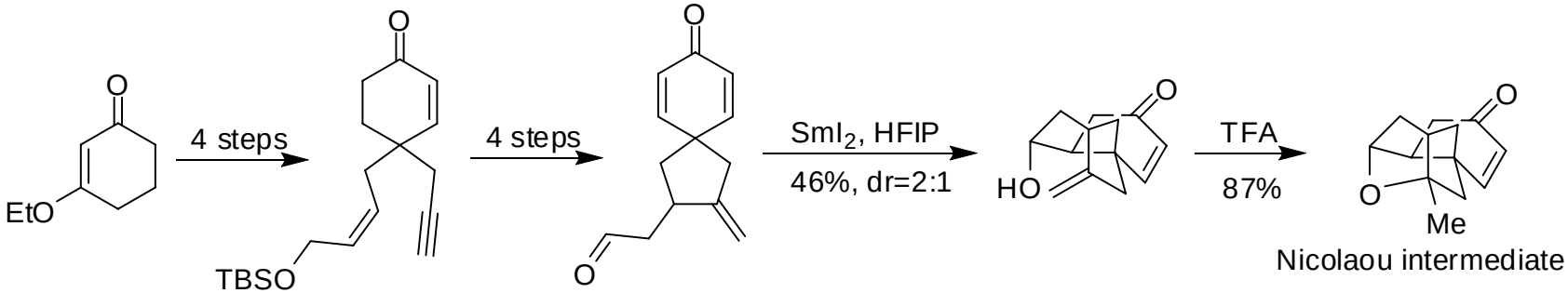


E. Coli condensing enzyme active site of **FabF** with docked platensimycin (green) and platencin (cyan).

ACIE **2007**, *46*, 4684-4688.

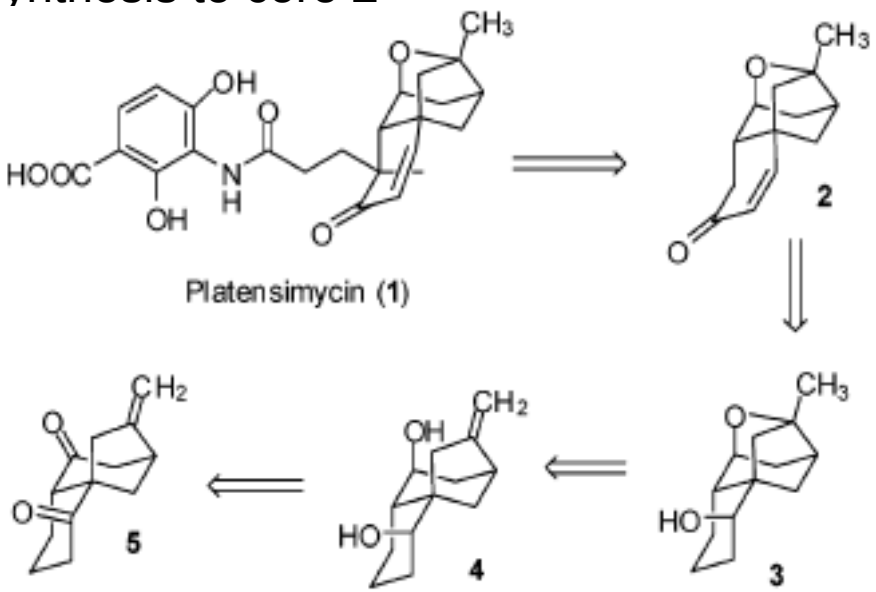
Synthesis of Platensimycin

K.C.Nicolaou: 1st racemic; 1st asymmetric; chiral pool based synthesis



ACIE **2006**, *45*, 7086-7090.; *ACIE* **2007**, *46*, 3942.; *ACIE* **2008**, *47*, 944-946.

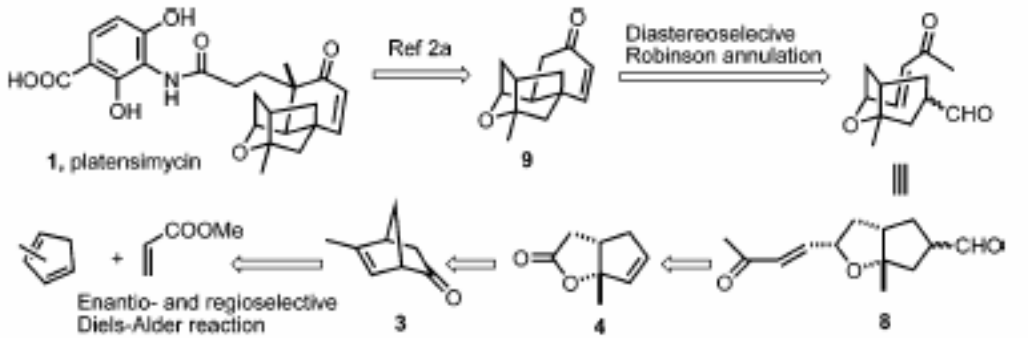
Barry B. Snider: formal synthesis to core **2**



OL **2007**, *9*, 1825-1828.

Synthesis of Platensimycin

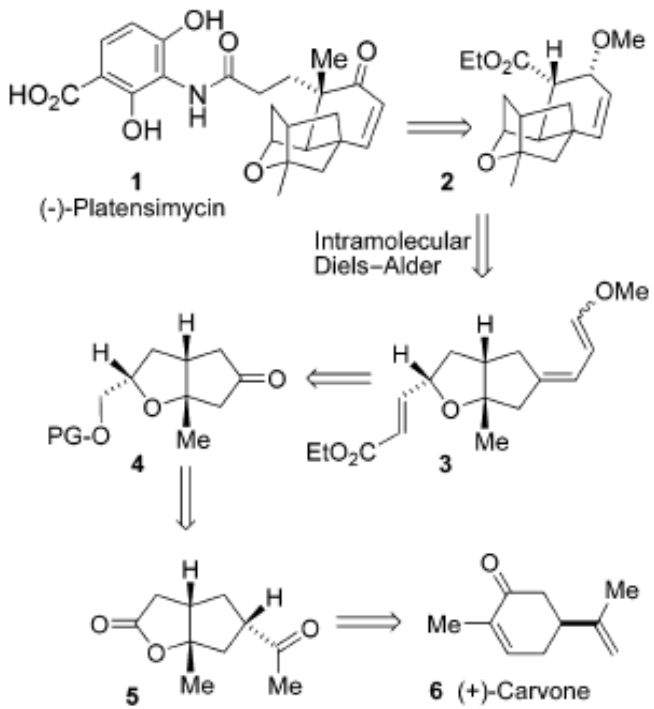
Hisashi Yamamoto: enantioselective synthesis to core **9**



JACS **2007**, *129*, 9534-9535.

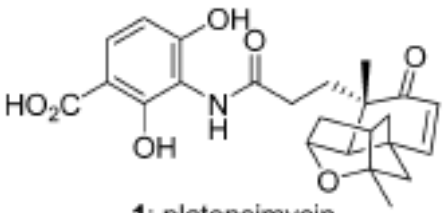
Arun K. Ghosh: enantioselective synthesis to core **2**

OL **2007**, *9*, 4013-4016.

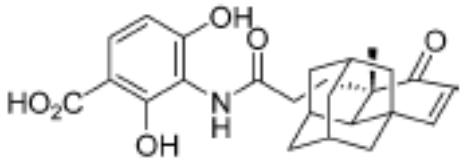


Others:
E.J.Corey: *OL* **2007**, *9*, 4921-4923.
Johann Mulzer: *ACIE* **2007**, *46*, 8074-8075.
Krishna P. kaliappan: *OL* **2007**, *9*, 2417-2419.

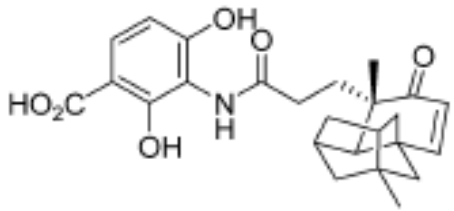
Two Isosteres of Platensimycin: Synthesized by Nicolaou Group



1: platensimycin



2: adamantaplatensimycin



3: carbaplatensimycin

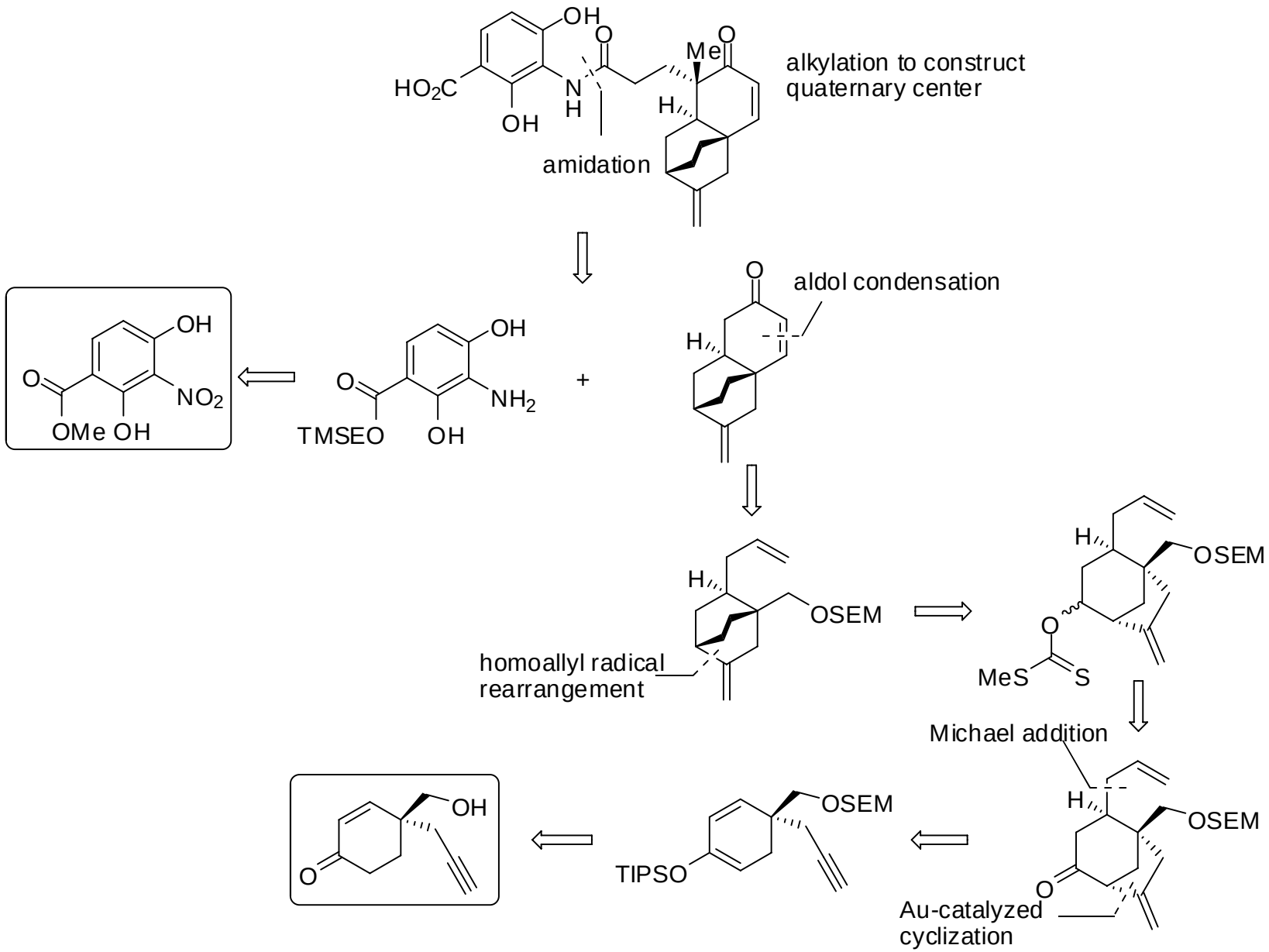
Table 1. Minimum Inhibitory Concentration (MIC) Values (μg mL^{-1}) of **1**, **2**, and 3 against a Variety of Bacterial Strains[a]

	1	2	3
MRSA	0.2−0.4	1.3−1.8	1.1−2.2
VREF	0.4−0.8	1.3−1.8	1.1−2.2
Staphylococcus aureus	0.2−0.6	1.1−2.2	0.4−1.1
Staphylococcus epidermidis	<0.2	0.5−1.1	0.2−0.5
Bacillus cereus	2.2−4.4	8.8−11.1	17.6−22.0
Lysteria monocytogenes	<0.2	3.3−4.4	1.1−2.2

[a] The antibacterial activity was determined by National Committee for Clinical Laboratory Standards (NCCLS) broth microdilution methods.

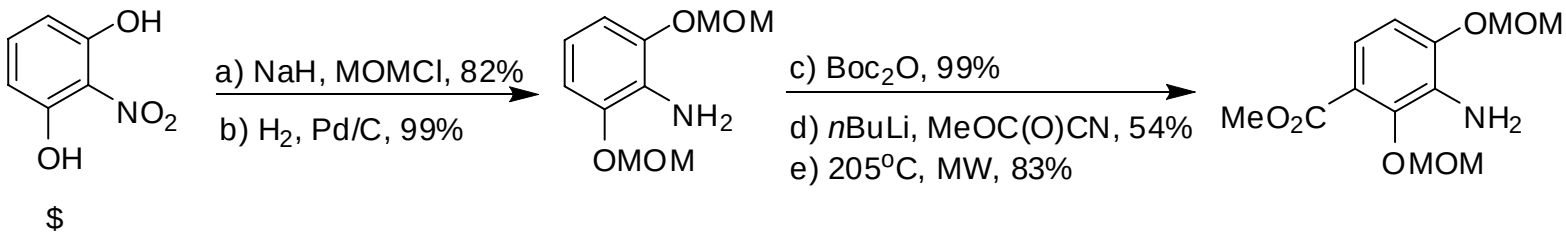
ACIE **2007**, *46*, 4712-4714.; *JACS* **2007**, *129*, 14850-14851.

Retrosynthetic Analysis of Platencin



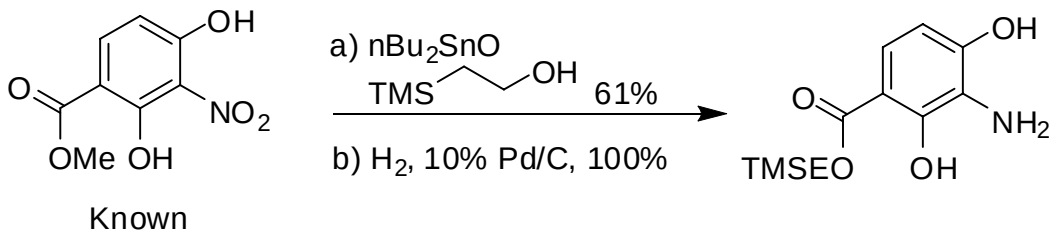
Synthesis of Aniline Derivative

Previous synthesis: 5 steps, 36% from commercially available compound



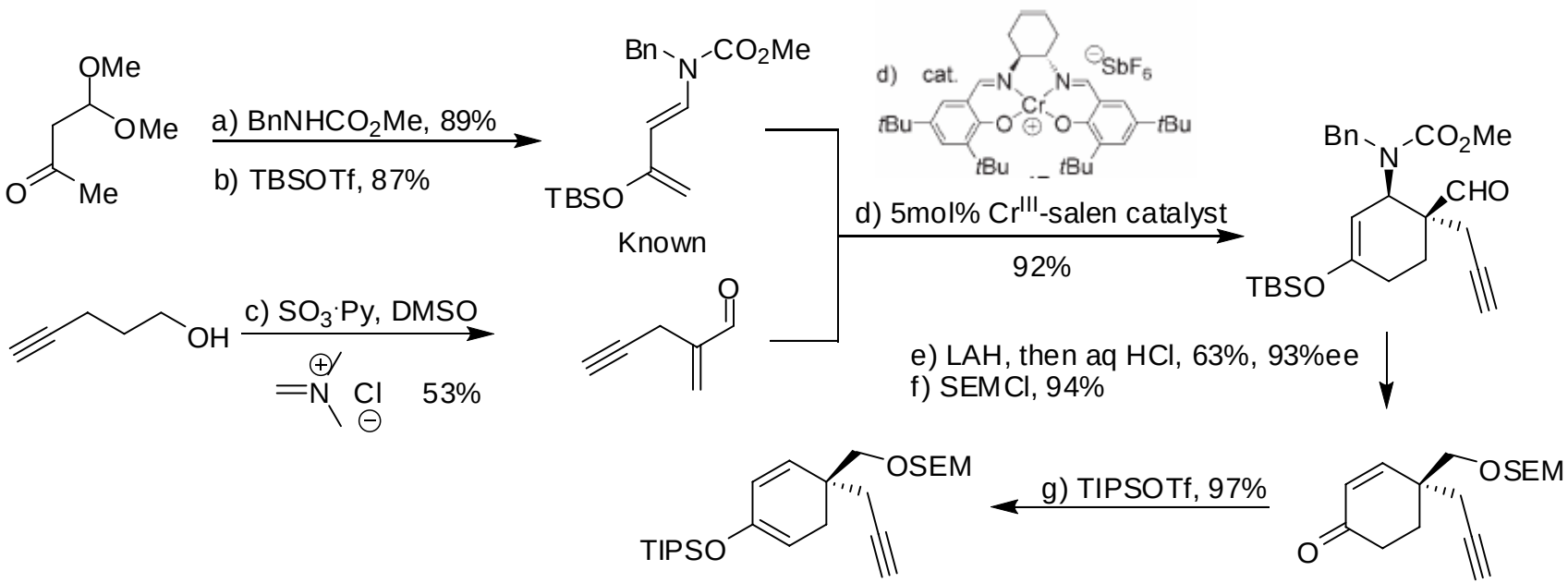
ACIE **2006**, *45*, 7086-7090.

Present synthesis: 2 steps, 61% from known compound



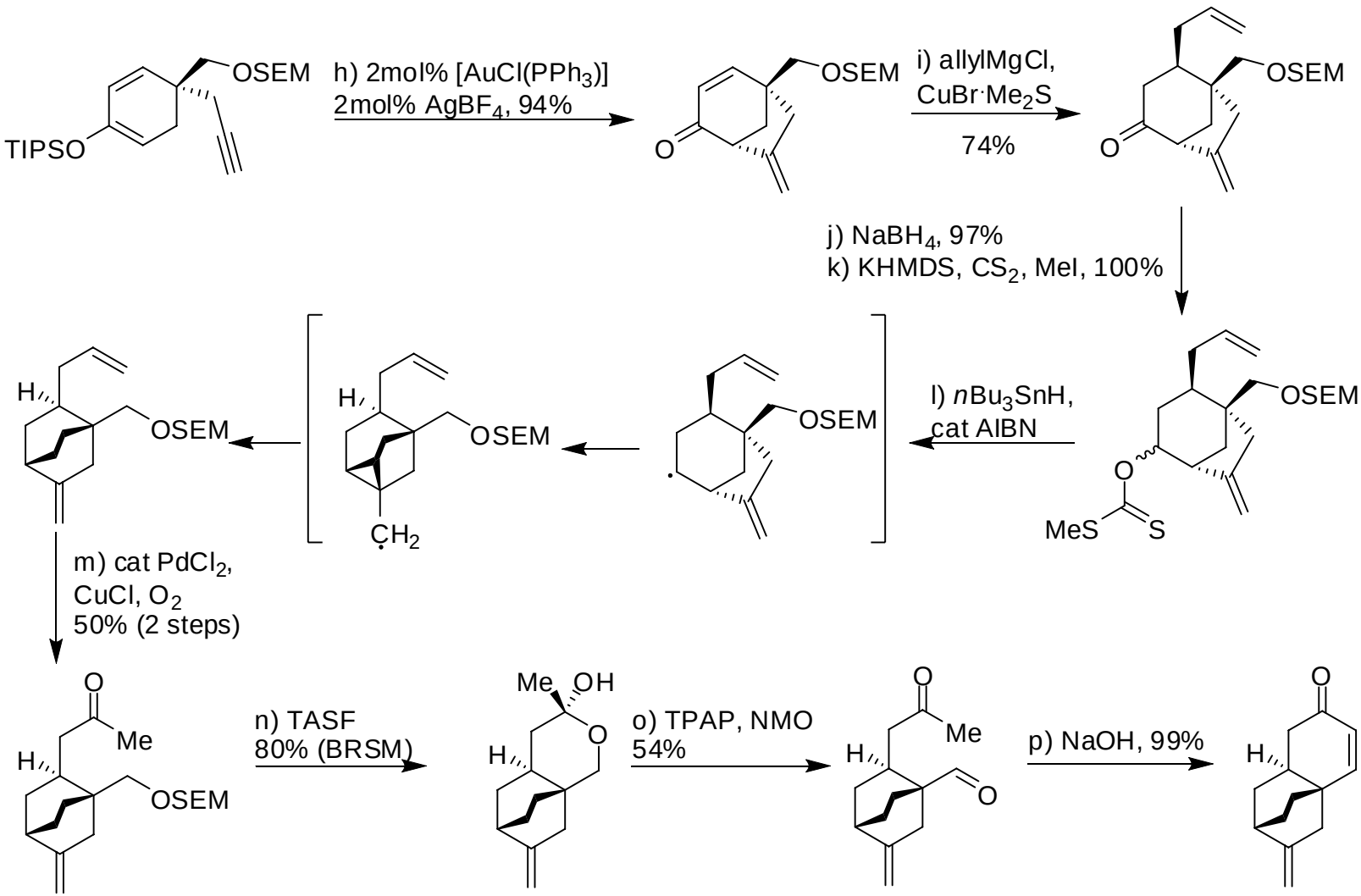
P. Heretsch, A. Giannis *Synthesis* **2007**, *17*, 2614-2616.

Synthesis of Tetracyclic Core

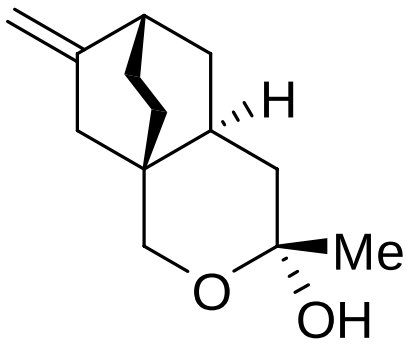


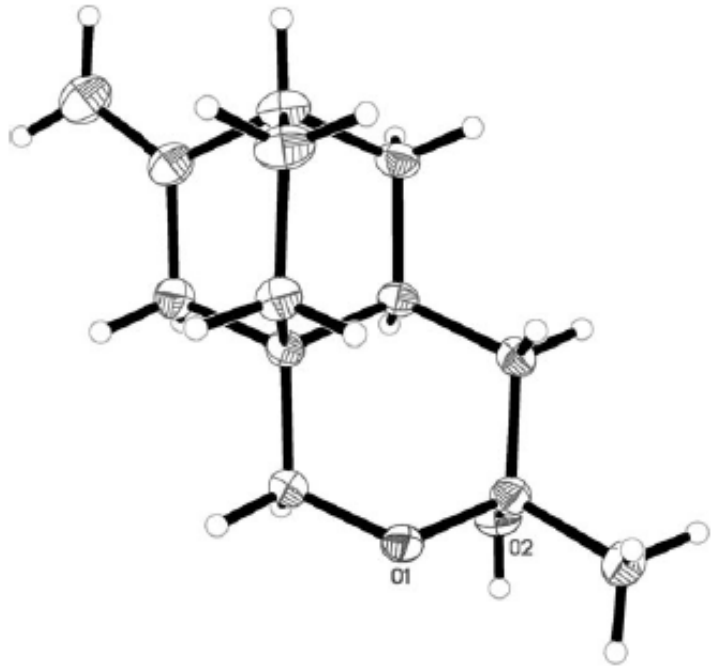
K. C. Nicolaou, G. Scott Tria, David J. Edmonds
Angew. Chem. Int. Ed. **2008**, *47*, 1780-1783.

Synthesis of Tetracyclic Core (Cont'd)

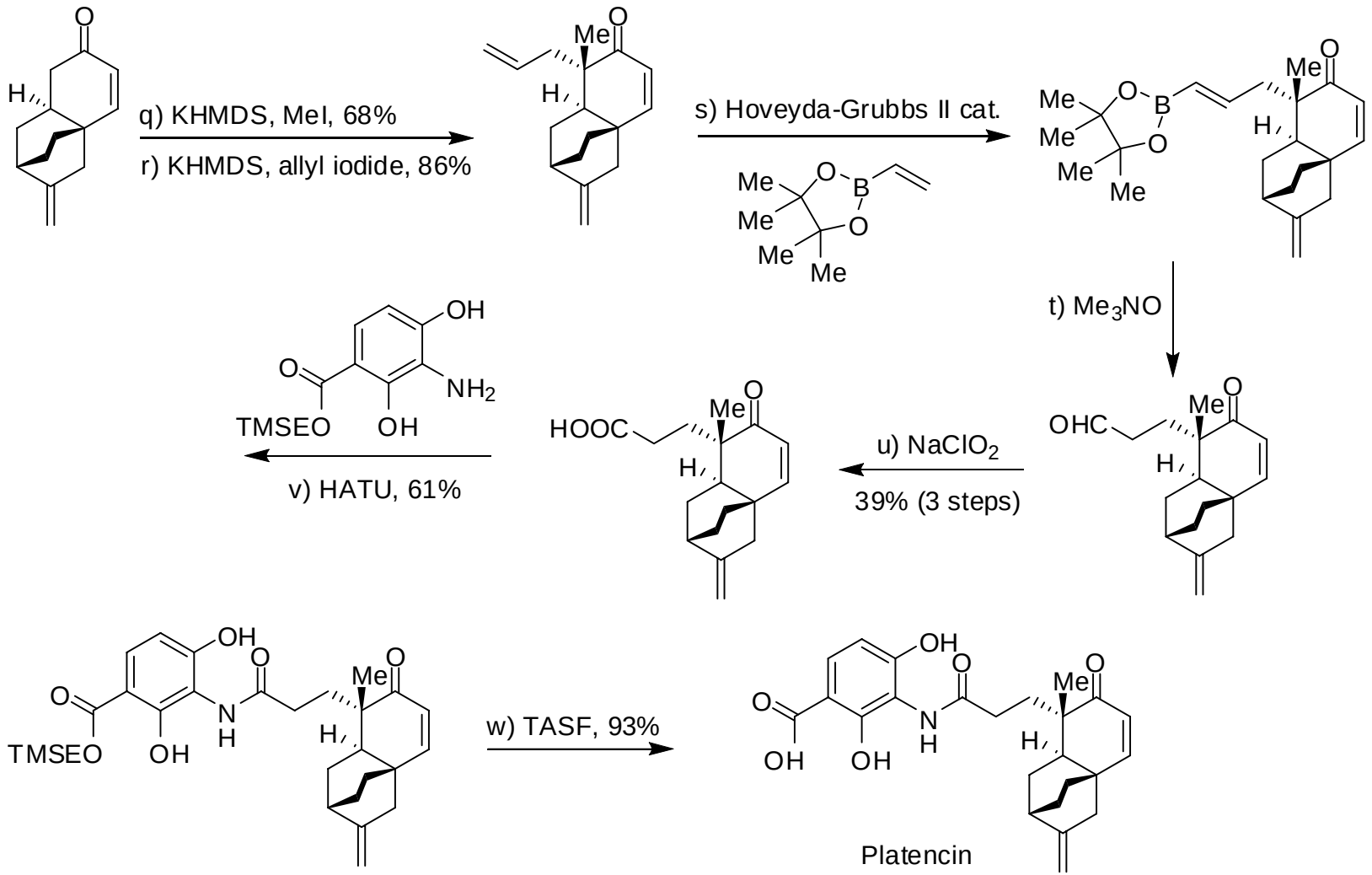


X-ray of Hemiacetal Intermediate





Completion of the Synthesis



Summary

- First enantioselective synthesis of platencin was achieved in 22 steps (longest linear sequence) with a yield of 0.76%

- Key transformations are: homoallyl radical rearrangement and Au-catalyzed cyclization

- Platencin is a potent and dual inhibitor of FabH and FabF; it exhibits broad-spectrum antibacterial activity against many Gram-positive pathogens that show resistance to current antibiotics

- Future work will involve the synthesis of platencin analogs and the exploration of other synthetic routes toward platencin