Literature Report I

Total Syntheses of Xiamycins A, C, F, H and Oridamycin A

Reporter: Yu-Qing Bai
Checker: Xiao-Qing Wang
Date: 2019-12-16

Sarpong, R. *et al. Angew. Chem. Int. Ed.* **2019**, *58*, 15304−15308.

CV of Professor Sarpong, R.

Sarpong, R.

Background:

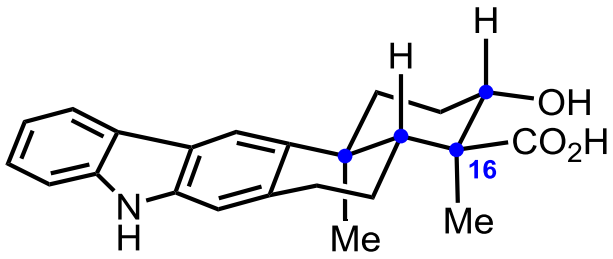
- **1991-1995** B.S., Macalester College;
- **1995-2000** Ph.D., Princeton University;
- **2000-2004** Postdoctoral Fellow, Caltech;
- **2004-2010** Assistant Professor, UC, Berkeley;
- **2010-2014** Associate Professor, UC, Berkeley;
- **2014-now** Full Professor, UC, Berkeley.

Research:

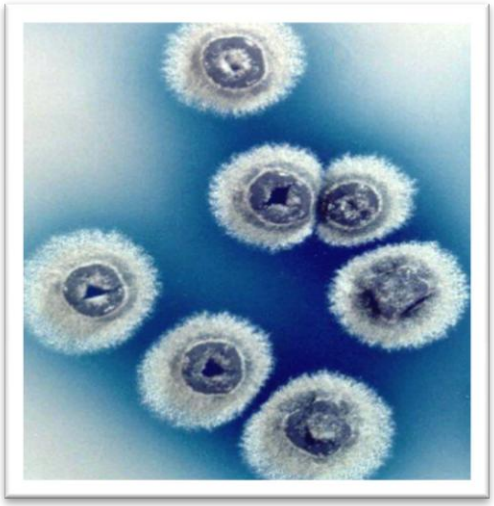
Total synthesis of biologically active and architecturally complex natural products as a platform for the development of new synthetic methods and strategies.

Contents

Introduction



Xiamycin A

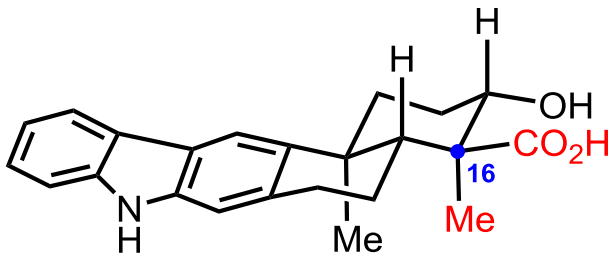


Streptomyces

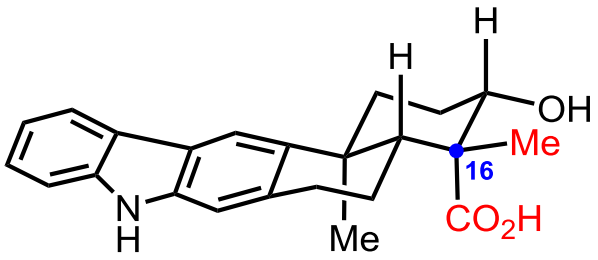
- It was first isolated from a range of Streptomyces species in 2010;
- It is composed of a challenging pentacyclic framework that bears four contiguous stereocenters;
- It displays antibiotic and anti-HIV activity.

Hertweck, C. *et al. Bioorg. Med. Chem. Lett.* **2010**, *20*, 6685-6687.

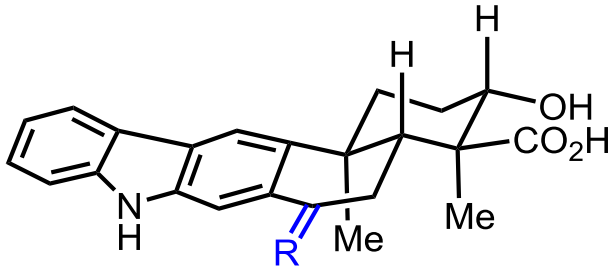
Introduction



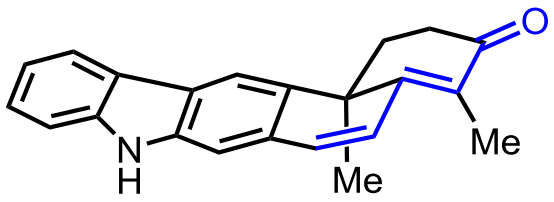
Xiamycin A



Oridamycin A

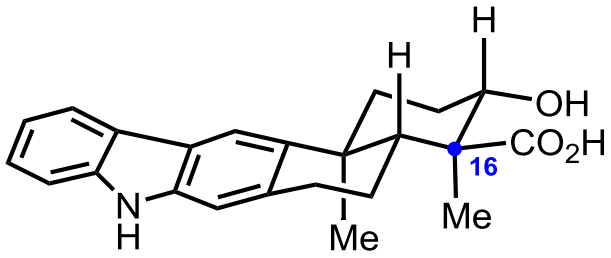


Xiamycin C, R = OH (eq.), H
Xiamycin F, R = O

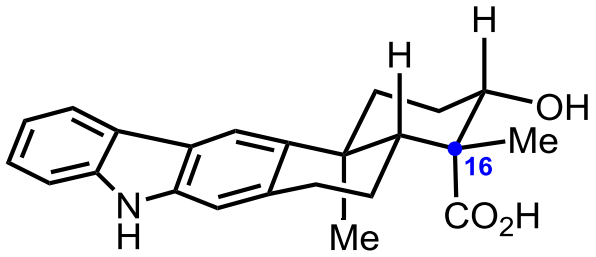


Xiamycin H

Total Syntheses of Xiamycin A and Oridamycin A

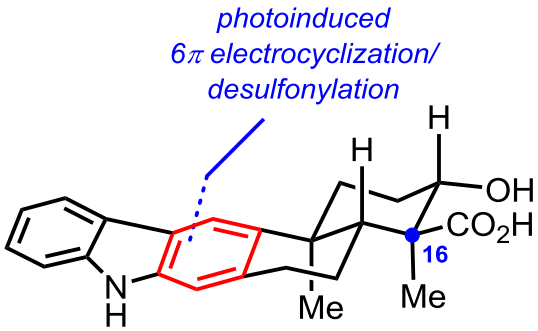


Xiamycin A

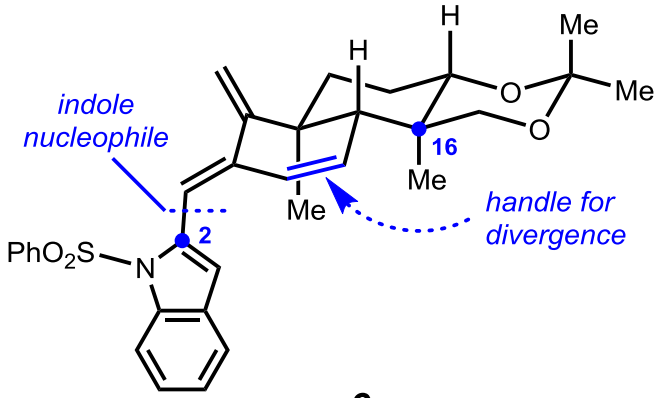


Oridamycin A

Retrosynthetic Analysis of Xiamycin A



Xiamycin A



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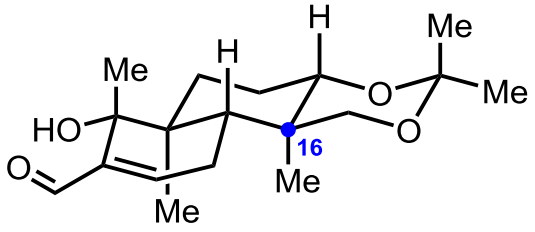

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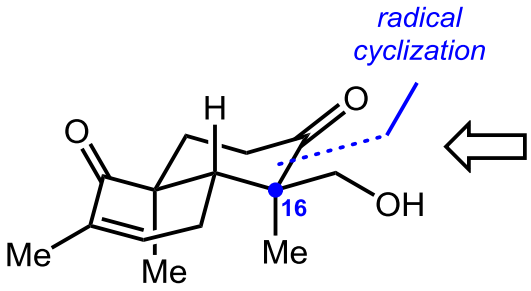
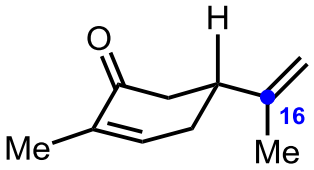
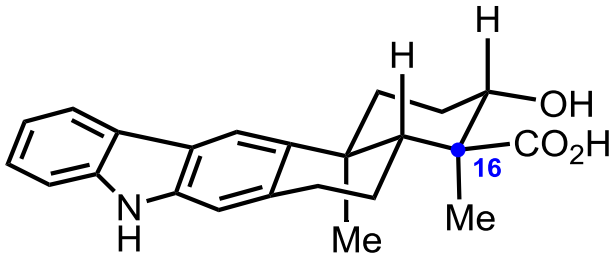


8a

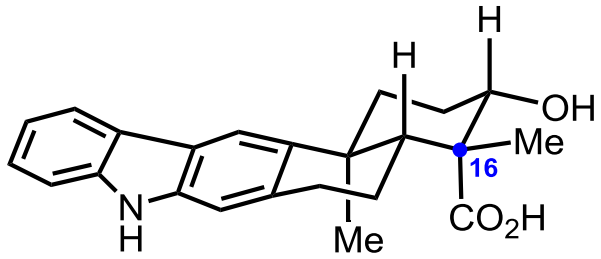


(*R*)-carvone (9)

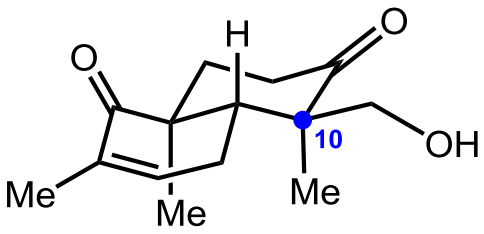
Syntheses of Compounds 8a and 8b



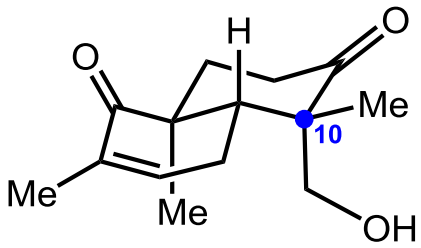
Xiamycin A



Oridamycin A

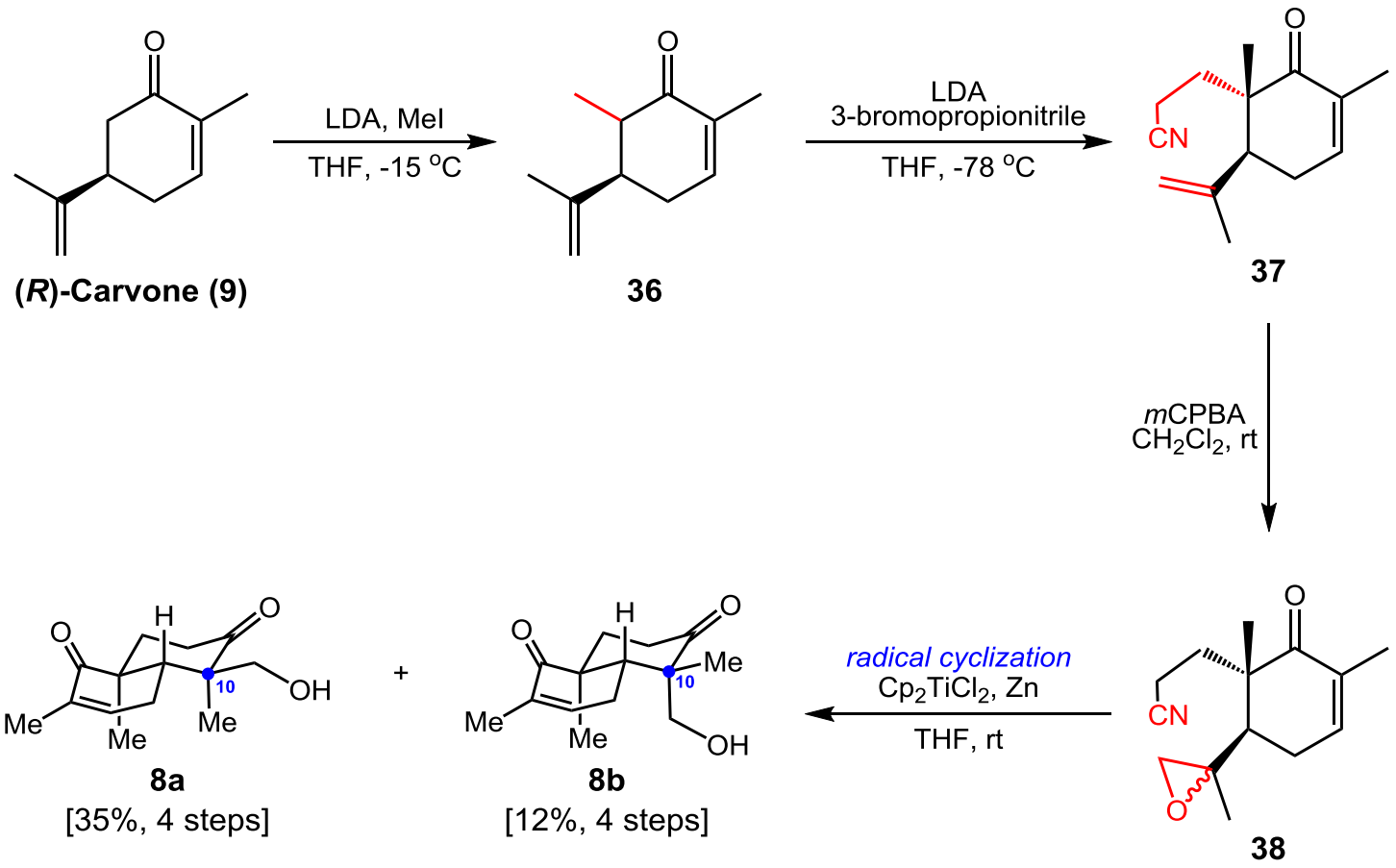


8a



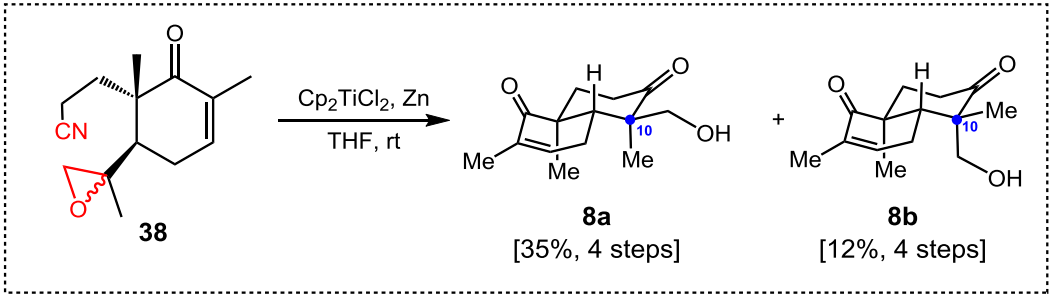
8b

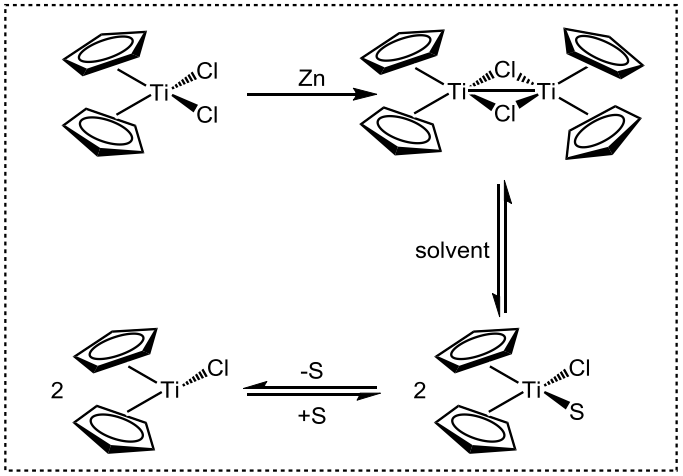
Syntheses of Compounds 8a and 8b

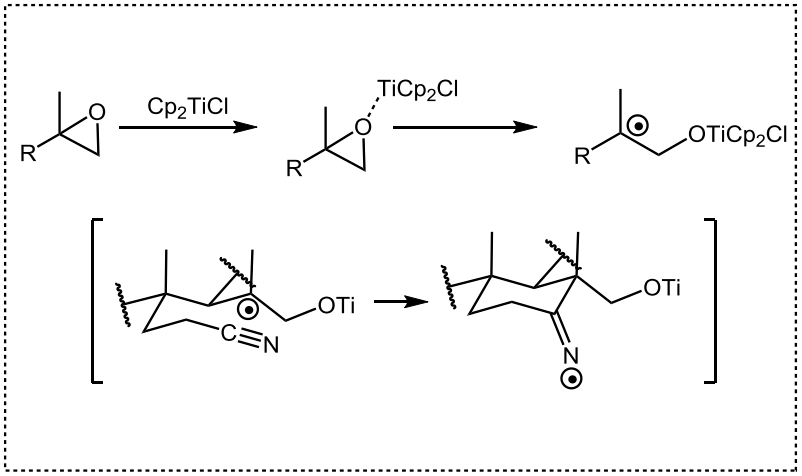


Nagamitsu, T. *et al. Tetrahedron* **2011**, *67*, 8195-8203.

Titanocene-Mediated Radical Cyclization

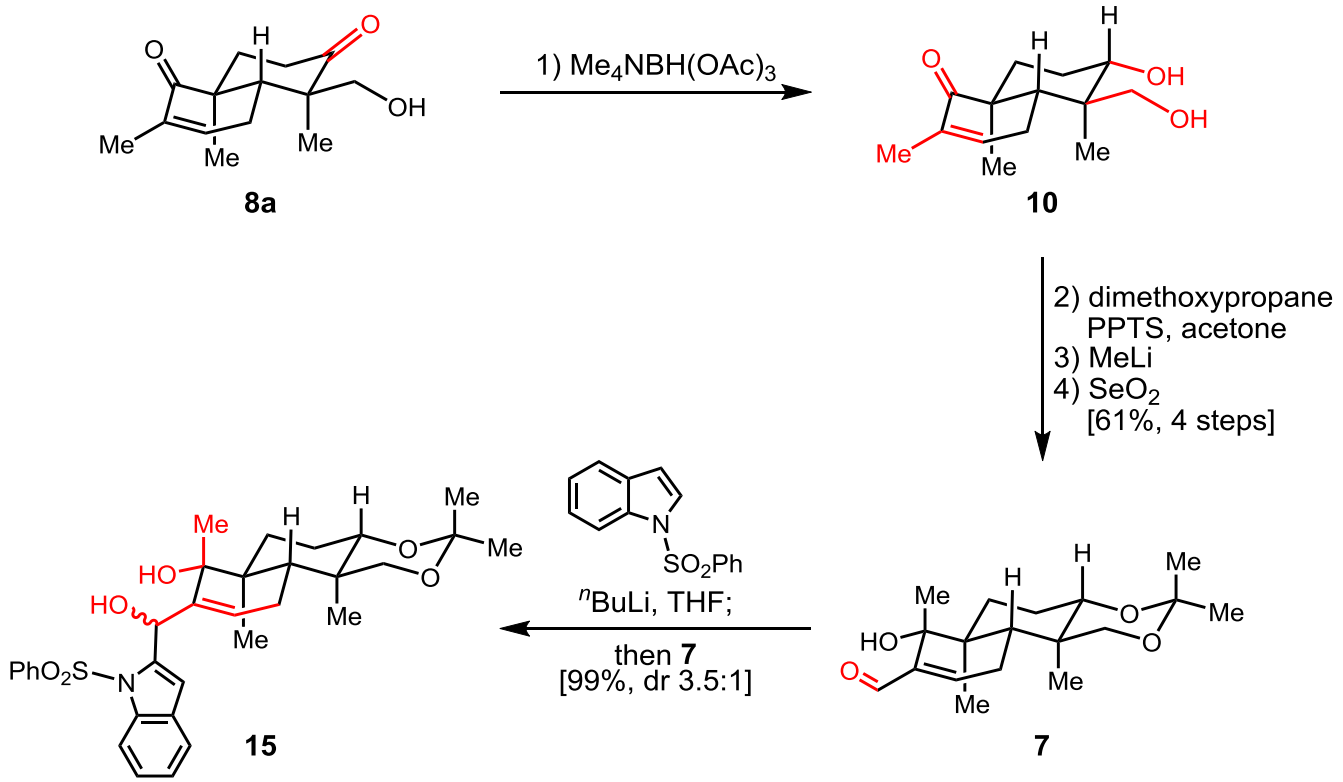




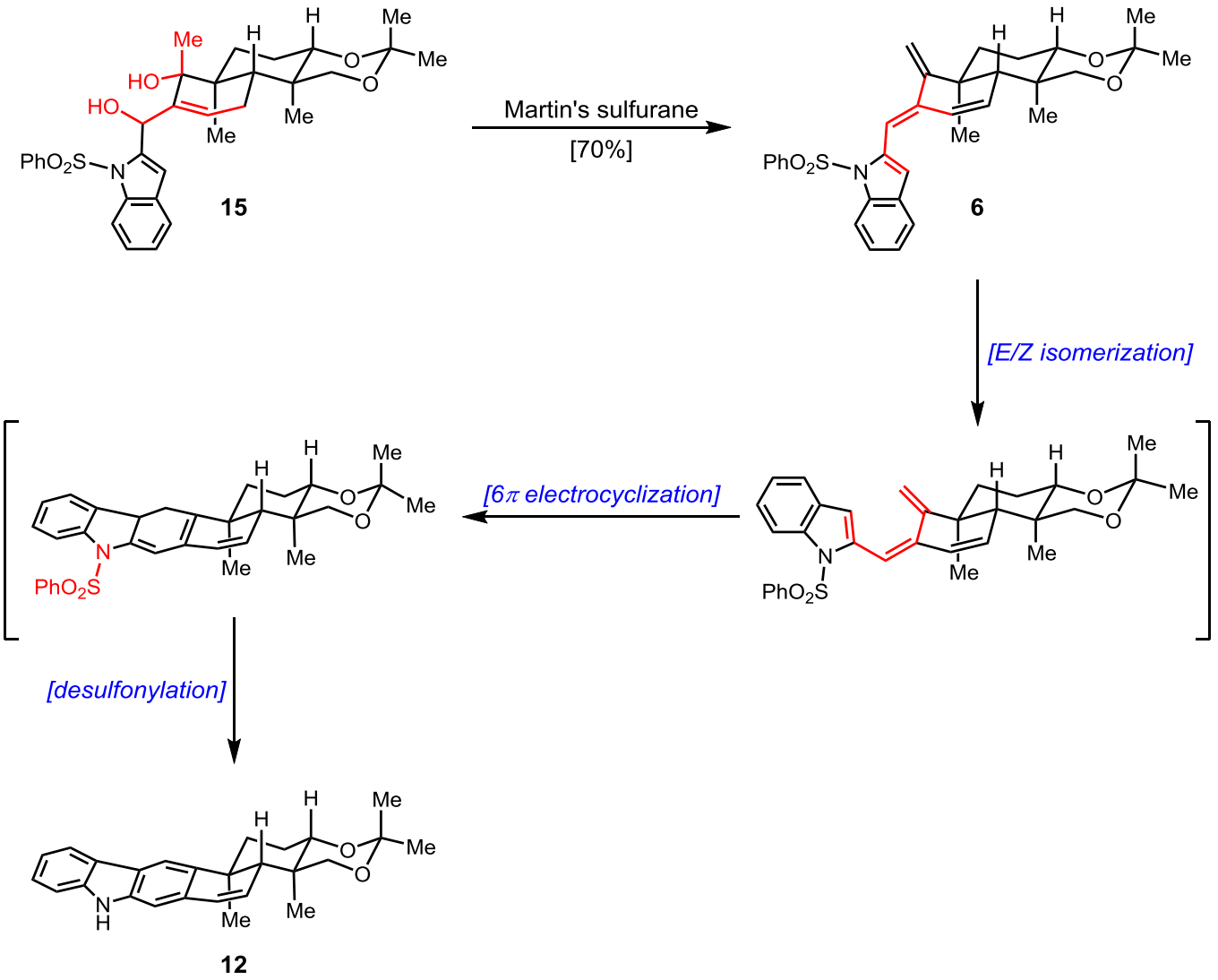


Arteaga, J. F. *et al. Eur. J. Org. Chem.* **2006**, *7*, 1627-1641.

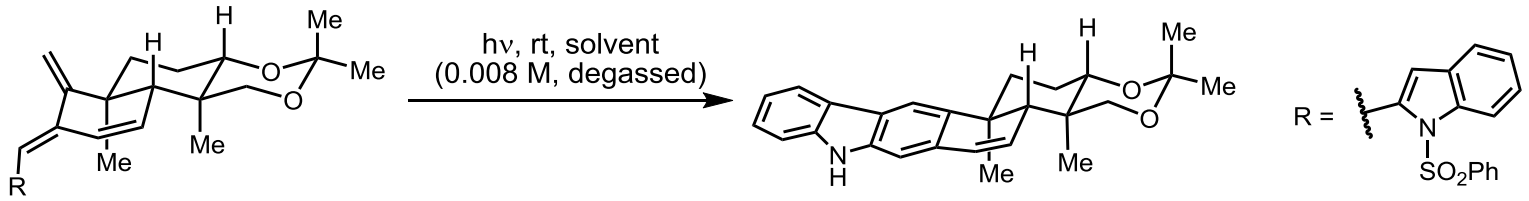
Synthesis of the Compound 15



Synthesis of the Compound 12



Optimization of the Photocyclization Reaction



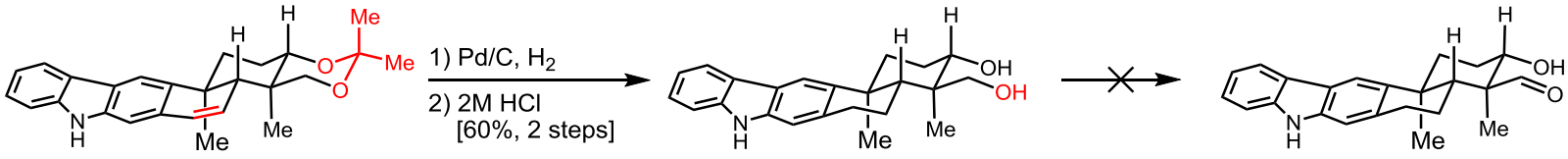
6 **12**

Entry	Wavelength (nm)[a]	Conditions[d]	Yield[e]
1	310/350	PhH, 1 h	28%/33%
2	310/350	5% aq. EtOH, 1 h	30%/44%
3	400[b]	5% aq. EtOH, 1.5 h	30%
4	500-800[c]	5% aq. EtOH, 40 °C, 1.5 h	no reaction
5	350	10% aq. EtOH/THF, 1 h	46%
6	350	MeCN, 1 h	< 5%
7	310	50% aq. MeCN, 0.5 h	23%
8	350	PhH, 1,4-CHD, 0.2 h	30%
9	350	5% aq. EtOH, Na_2CO_3, 0.5 h	< 5%
10	350	5% aq. MeOH, DABCO, 0.5 h	< 5%
11	350	NEt_3, $^nBu_3SnH$, MeCN, 0.5 h	< 5%
12	350	5% aq. EtOH, anisole, $NaBH_4$, 1.5 h	33%

[a] Luzchem photobox. [b] Kessil blue LED. [c] Sunlite tungsten lamp. [d] Reactions were performed in pyrex glass tubes; 5% aq. EtOH refers to technical grade (95%); [e] Yield of isolated product.

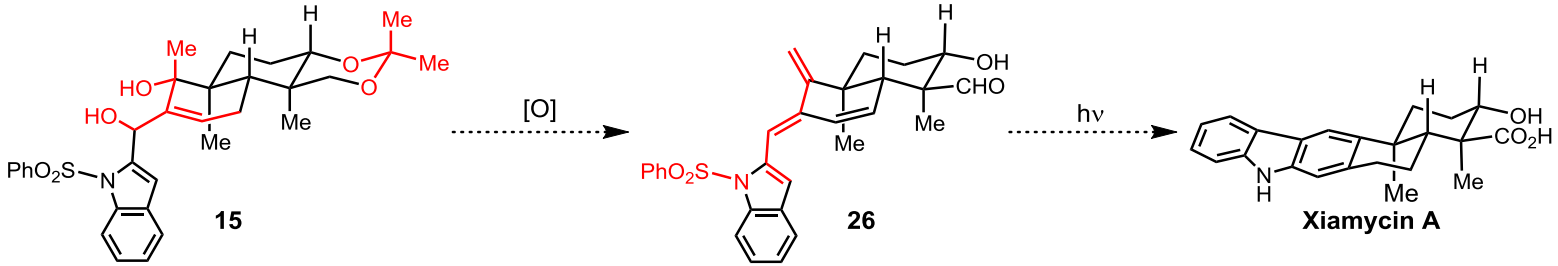
Synthesis of Xiamycin A

a. First approach toward finishing the synthesis of **Xiamycin A**



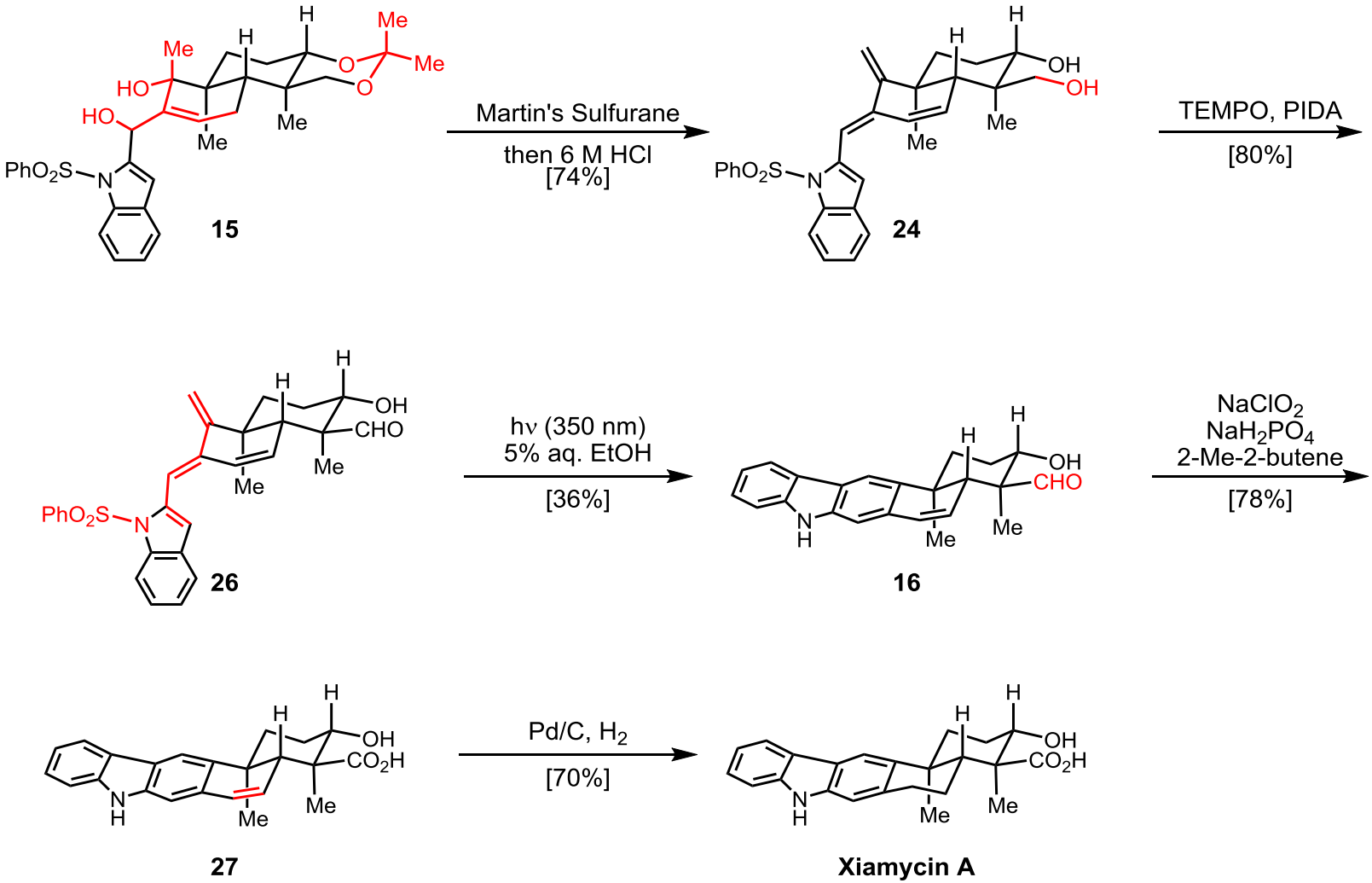
12 **13** **14**

b. Second approach toward finishing the synthesis of **Xiamycin A**

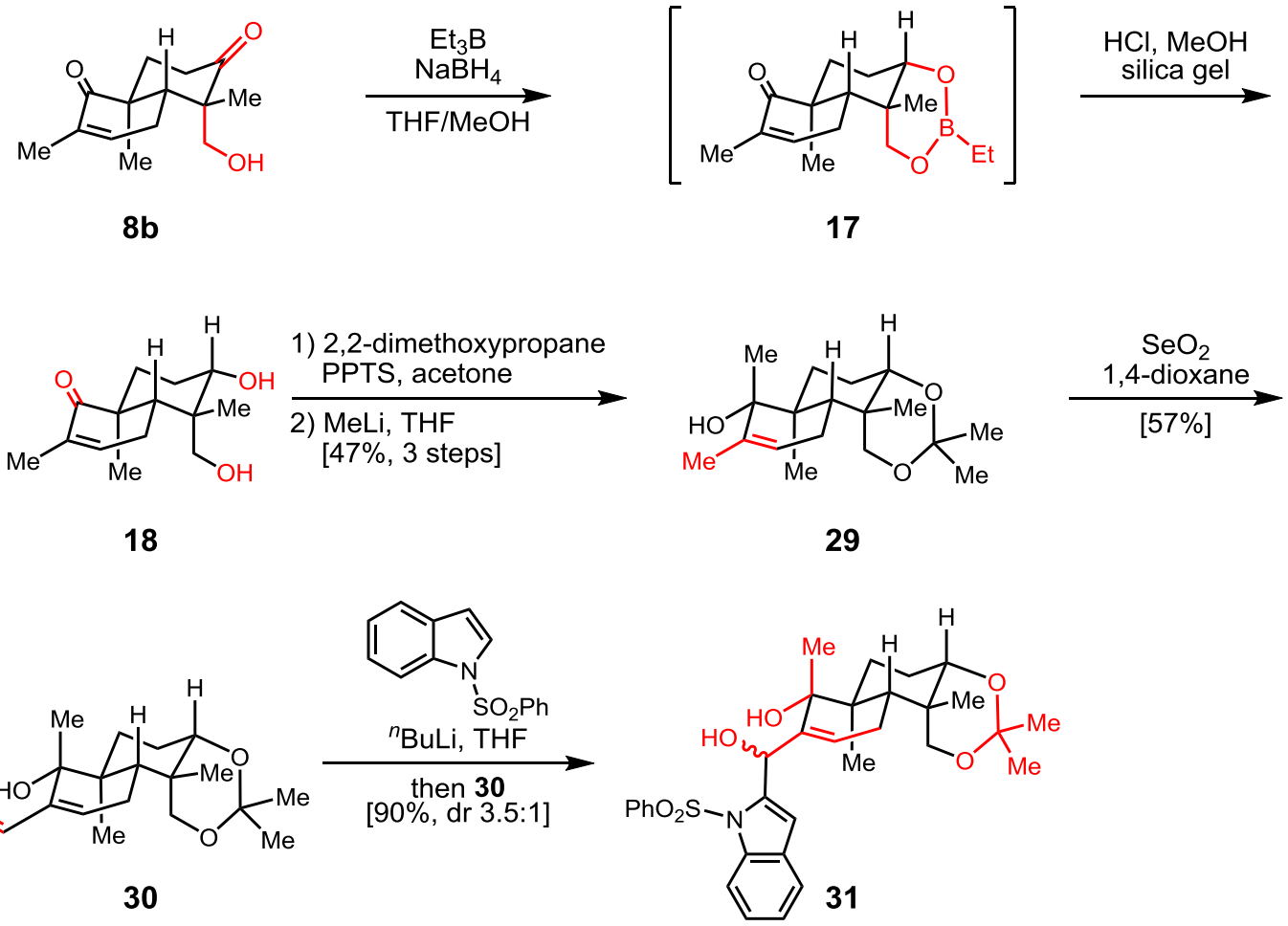


15 **26** **Xiamycin A**

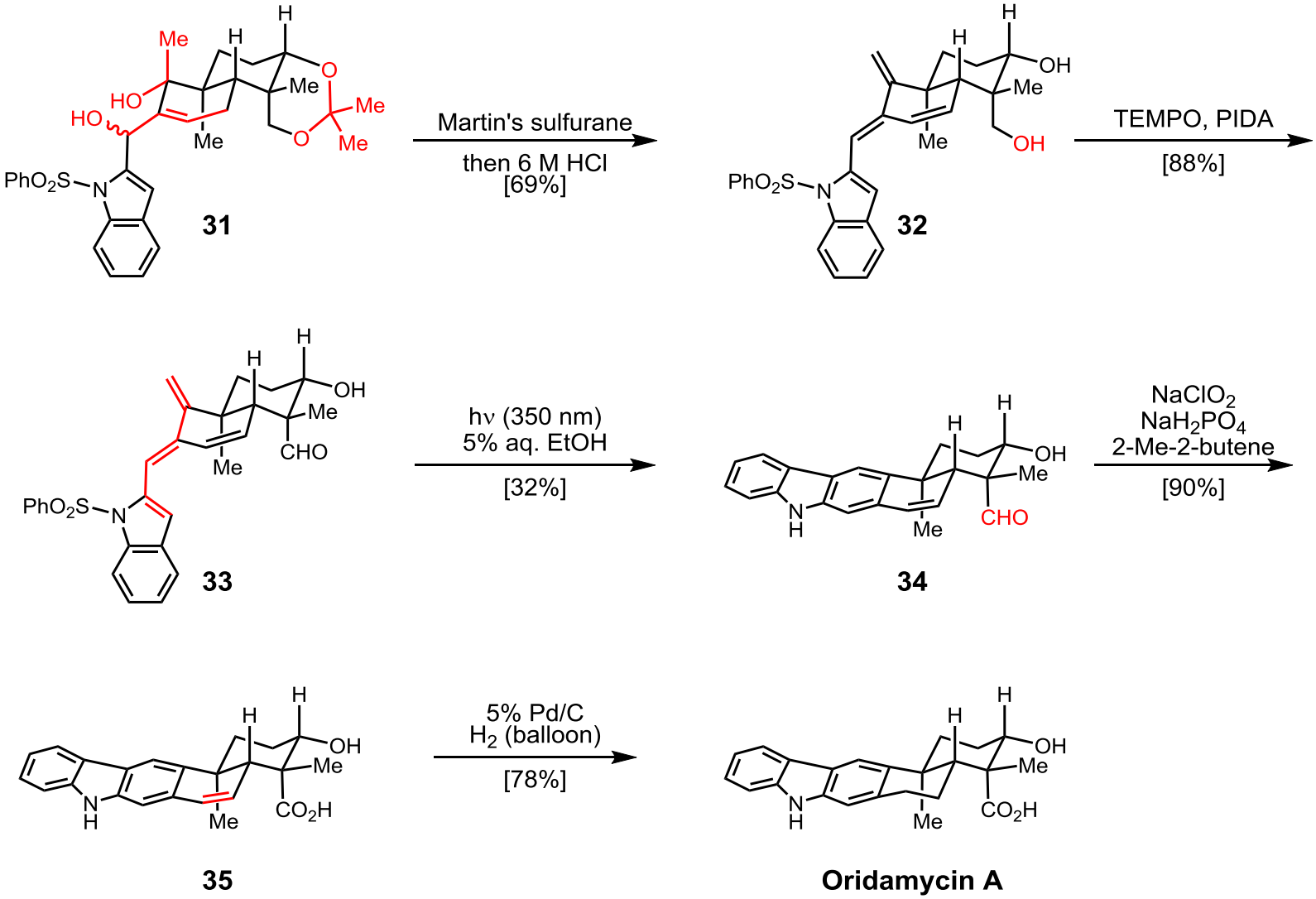
Synthesis of Xiamycin A



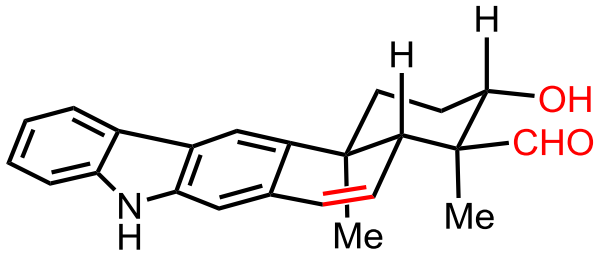
Synthesis of Oridamycin A



Synthesis of Oridamycin A



Total Syntheses of Xiamycins C, F, H



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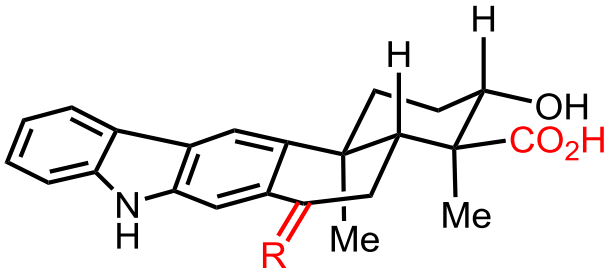
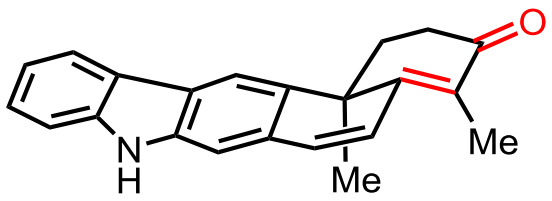
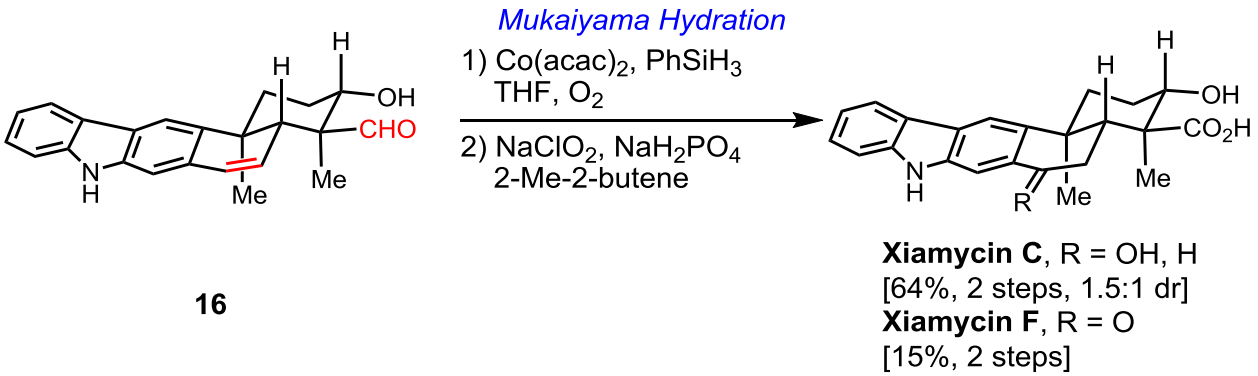


Xiamycin C, R = OH (eq.), H
Xiamycin F, R = O



Xiamycin H

Syntheses of Xiamycins C, F, H



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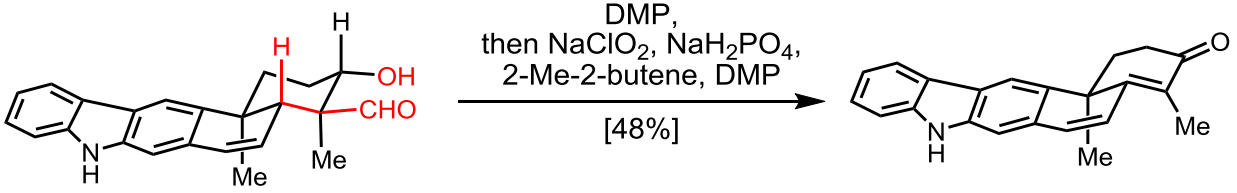
Xiamycin C, R = OH, H
[64%, 2 steps, 1.5:1 dr]
Xiamycin F, R = O
[15%, 2 steps]



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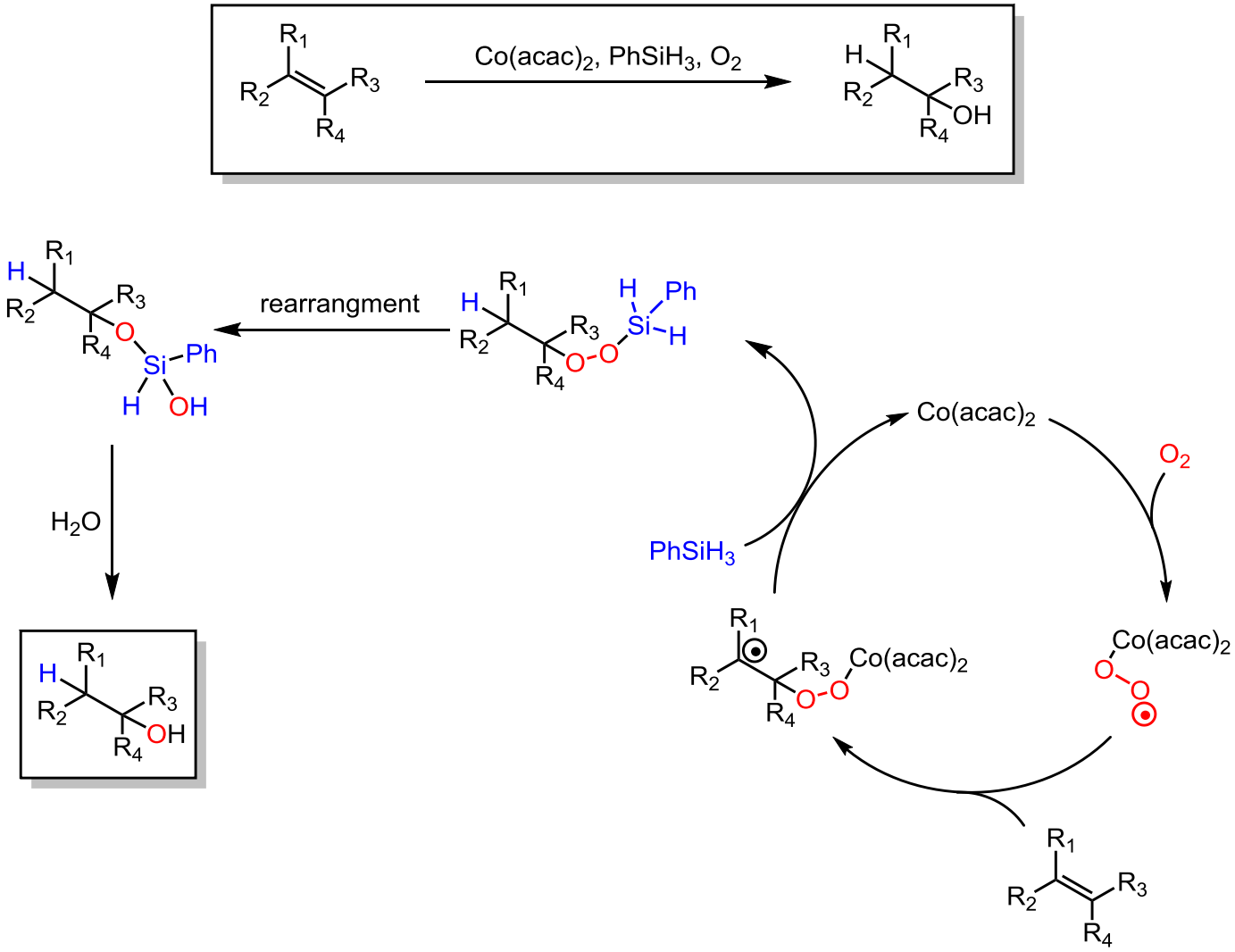
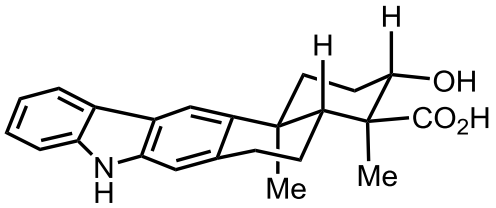
Xiamycin H

Mukaiyama Hydration

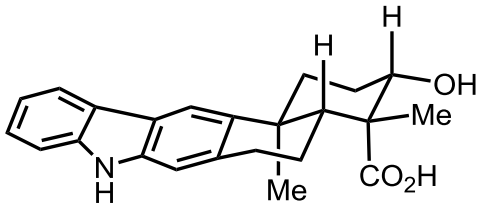


From *Name Reaction*

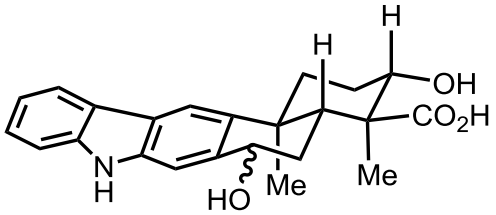
Summary



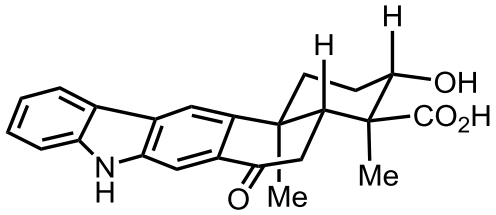
Xiamycin A
18 steps, 0.29 % overall yield



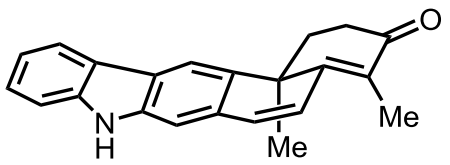
Oridamycin A
14 steps, 0.39 % overall yield



Xiamycin C
18 steps, 0.34 % overall yield



Xiamycin F
18 steps, 0.08 % overall yield



Xiamycin H
17 steps, 0.26 % overall yield

- Titanocene-mediated radical cyclization;
- Martin's sulfurane-double dehydration;
- A photochemical benzannulation-6π electrocyclization;
- Mukaiyama hydration.

The First Paragraph

Writing Strategy

Describing the source of the "Xiamycin-type" secondary metabolites

↓

Introducing the biological activity of such compounds

↓

Envisaging based on the biological activity of such compounds

The First Paragraph

The “Xiamycin-type” secondary metabolites were first isolated from a range of *Streptomyces* species in 2010. These molecules represent the first examples of indolosesquiterpenoids from bacterial sources, and new members continue to be discovered to this day. The emerging biological activity of these indolosesquiterpenoids has sparked interest in employing them as a starting point for the development of pharmaceuticals and agrochemicals. For example, xiamycin A displays antibiotic and anti-HIV activity, whereas its C-16 epimer, oridamycin A, exhibits modest activity against the water mold *Saprolegnia parasitica*. On the basis of this latter bioactivity, we have become especially interested in profiling the potential of the xiamycins as fungicides against a broad range of fungal pathogens that significantly impact crop yields.

The First Paragraph

Notably, we sought to identify new chemotypes active against wheat leaf blotch which has been known to cause up to 50% crop yield loss in the European Union (EU). While there are known fungicides to combat this fungus, newer compounds that possess novel modes of action are critical to addressing the resistance shifts that continue to emerge for many damage-causing fungi.

The Last Paragraph

Writing Strategy

Summarizing this work and pointing out the characteristic reaction

Summarizing the fungicidal activity of these compounds and prospecting its function

The Last Paragraph

In summary, we have accomplished the divergent, enantiospecific total synthesis of the indolosesquiterpenoids xiamycin A, xiamycin C, xiamycin F, oridamycin A, as well as xiamycin H in a maximum of ten steps from known compound 8. A key feature in the formation of the characteristic carbazole moiety is a photoinduced 6π-electrocyclization with concomitant desulfonylation, which represents a rare example of this type of transformation. These syntheses proceed in a total of 13–14 steps from carvone and are highly scalable, providing enough material for a preliminary bioactivity screen. Evaluation of the fungicidal activity of these compounds revealed that xiamycin H and some of the synthetic intermediates display notable inhibition of agriculturally relevant pathogens that could set the stage for the identification of new small molecules for crop protection.

Representative Examples

The emerging biological activity of these indolosesquiterpenoids has sparked interest in employing them as a starting point for the development of pharmaceuticals and agrochemicals. **这些吲哚倍半萜类化合物的新兴生物活性激发了人们将它们用作药物和农用化学品开发的起点的兴趣。**

For example, xiamycin A displays antibiotic and anti-HIV activity, whereas its C-16 epimer, oridamycin A, exhibits modest activity against the water mold Saprolegnia parasitica. **例如，厦霉素A表现出抗细菌和抗HIV活性，而其C-16差向异构体，奥达霉素A表现出对抗水霉菌寄生的中等活性。**

While there are known fungicides to combat this fungus, newer compounds that possess novel modes of action are critical to addressing…… **尽管有已知的杀真菌剂可以对抗这种真菌，但是具有新颖作用方式的新型化合物对于解决……至关重要。**

Acknowledgement

Thanks
for your attention