

Biomimetic Syntheses of Dibefurin and Epicolactone

1. Ellerbrok, P.; Armanino, N.; Trauner, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 13414.
2. Ellerbrok, P.; Armanino, N.; Ilg, M. K.; Webster, R.; Trauner, D. *Nat. Chem.* **2015**, *7*, 879.
3. Ellerbrok, P. *Ph. D. Thesis. Ludwig-Maximilians-Universität München* **2015**.

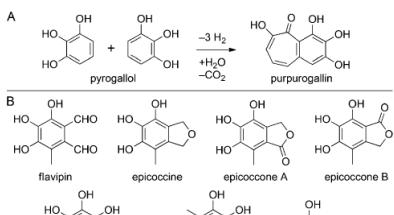
Angewandte
Communications

Total Synthesis

Biomimetic Synthesis of the Calcineurin Phosphatase Inhibitor Dibefurin**

Pascal Ellerbrock, Nicolas Armanino, and Dirk Trauner*

Abstract: Dibefurin is a C_2 -symmetric natural product that acts as an inhibitor of calcineurin phosphatase. A six-step synthesis of this compound is reported, which features an oxidative dimerization of the aromatic polyketide epicoccine as the key step. Dibefurin is proposed to be related to epicolactone, a complex yet racemic fungal metabolite that has recently been discovered. Attempts to access epicolactone from epicoccine and epicoccone B resulted in an unusual dimer that is formed through a hetero-Diels-Alder reaction of a para-quinone methide with an ortho-quinone.



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An eight-step synthesis of epicolactone reveals its biosynthetic origin

Pascal Ellerbrock¹, Nicolas Armanino¹, Marina K. Ilg, Robert Webster and Dirk Trauner*

Epicolactone is a recently isolated fungal metabolite that is highly complex for its size, and yet racemic. With its array of quaternary stereocentres, high degree of functionalization and intricate polycyclic structure, it poses a considerable challenge to synthesis, a challenge that can be met by understanding its biosynthetic origin. If drawn in a certain way, epicolactone reveals a pattern that resembles purpurogallin, the archetype of ubiquitous natural colourants formed via oxidative dimerization. Based on this insight, we designed a biomimetic synthesis of epicolactone that proceeds in only eight steps from vanillyl alcohol. We have isolated a key intermediate that supports our biosynthetic hypothesis and anticipate that an isomer of epicolactone stemming from our synthetic efforts could also be found as a natural product.

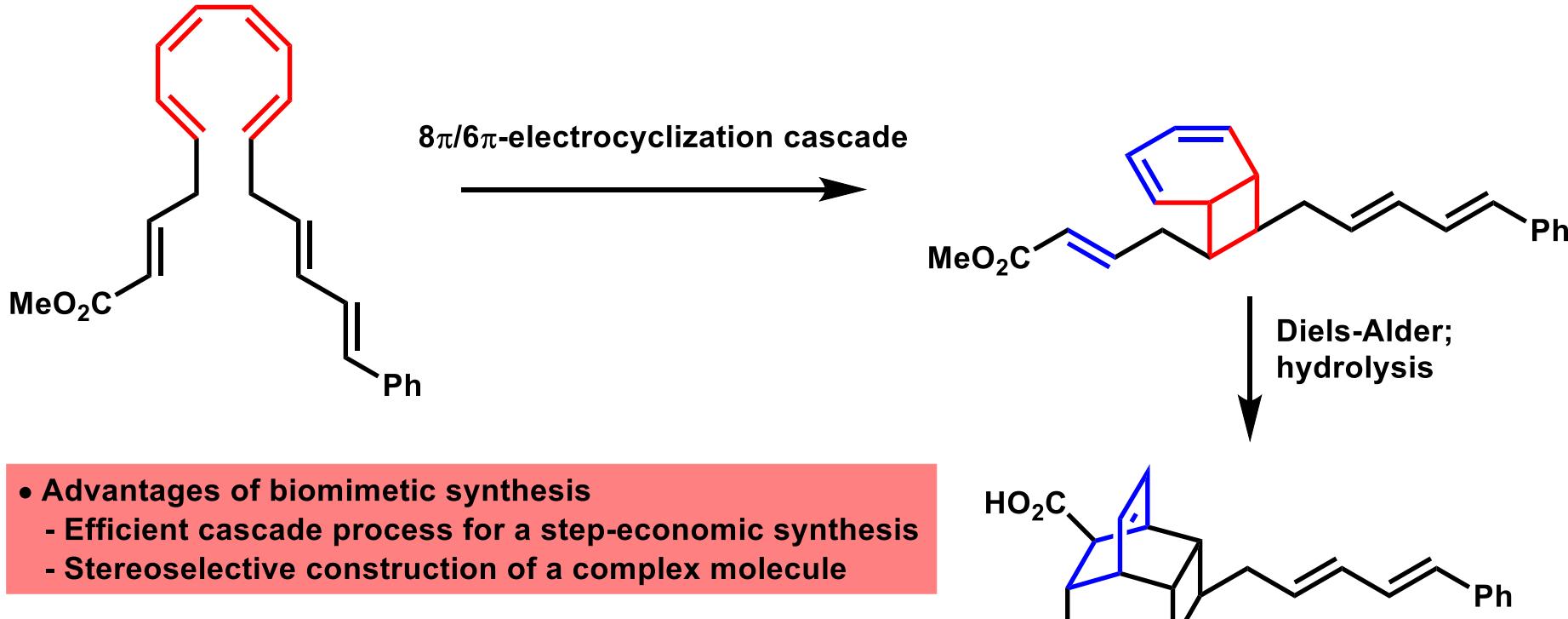
16/09/03
D3 Komei Sakata

Biomimetic Synthesis

"a transformation or a sequence of reactions that mimics the proposed biosynthesis of natural product"

Biomimetic synthesis of endiandric acid C

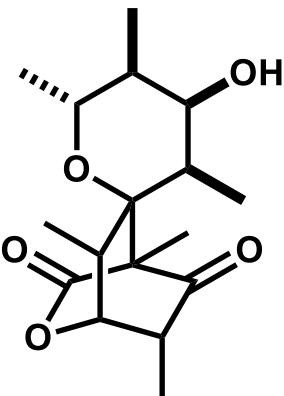
(Nicolaou, K. C.; Petasis, N. A.; Uenishi, J.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5557.)



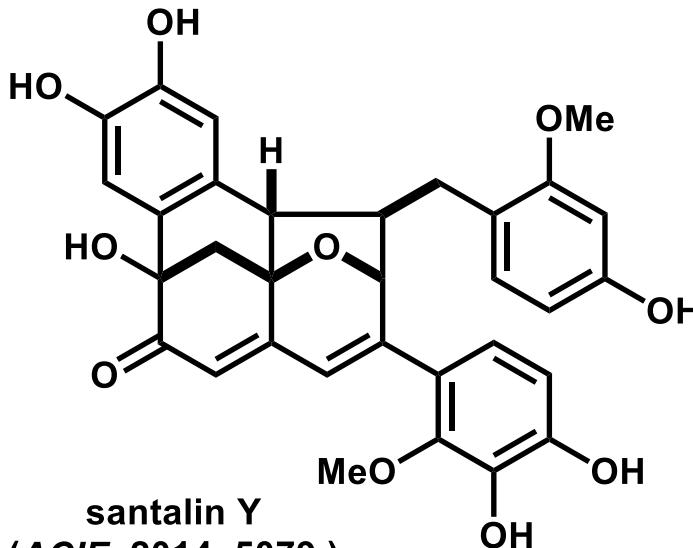
- Advantages of biomimetic synthesis
 - Efficient cascade process for a step-economic synthesis
 - Stereoselective construction of a complex molecule

- Challenges in biomimetic synthesis
 - Realistic proposal of a biosynthesis
 - Experimental realization in the Lab.
(Nature has optimised biosyntheses by utilizing enzymes)

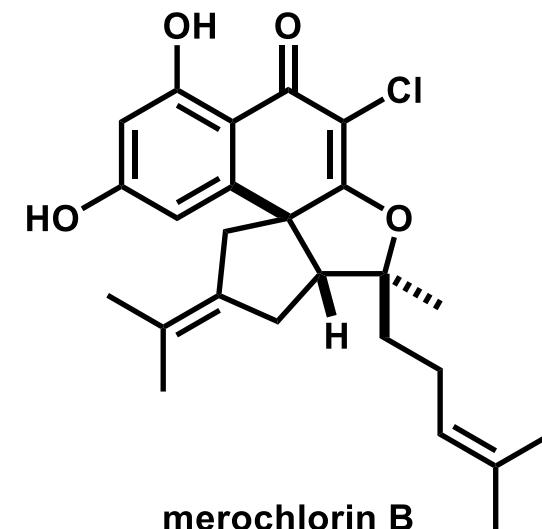
Biomimetic Syntheses by Trauner Group (2013-)



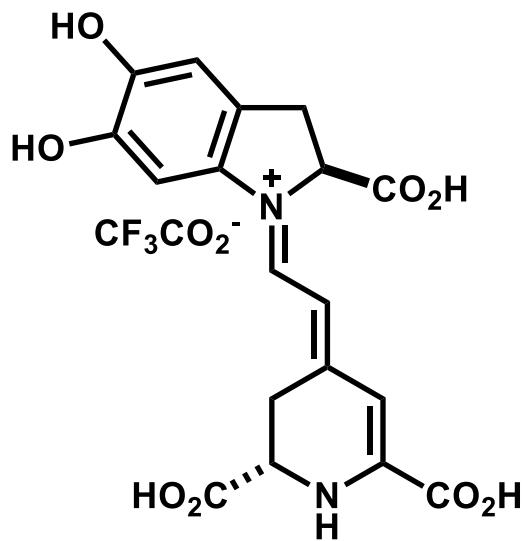
portntol
(JACS, 2015, 13800.)



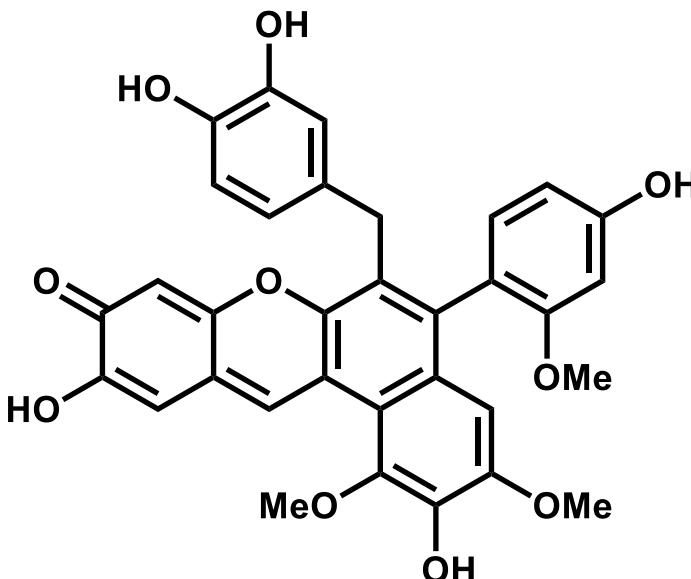
santalin Y
(ACIE, 2014, 5079.)



merochlorin B (OL, 2014, 2634.)



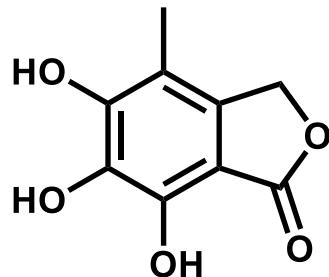
betanidin *(ChemEurJ, 2014, 9519.)*



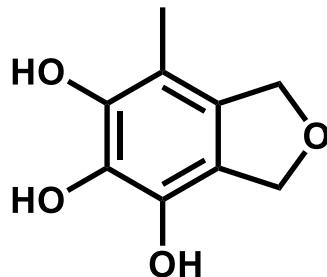
**santalil A
(*ACIE*, 2014, 9509.)**

*Introduction of
Dibefurin and Epicolactone*

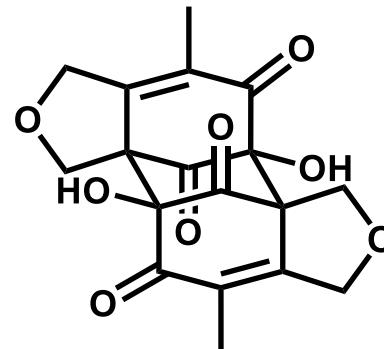
Fungal Poliketides



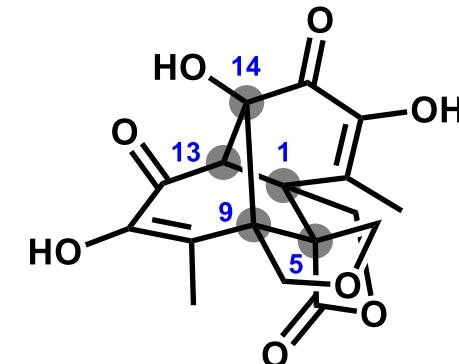
epicoccone B



epicoccine



dibefurin¹



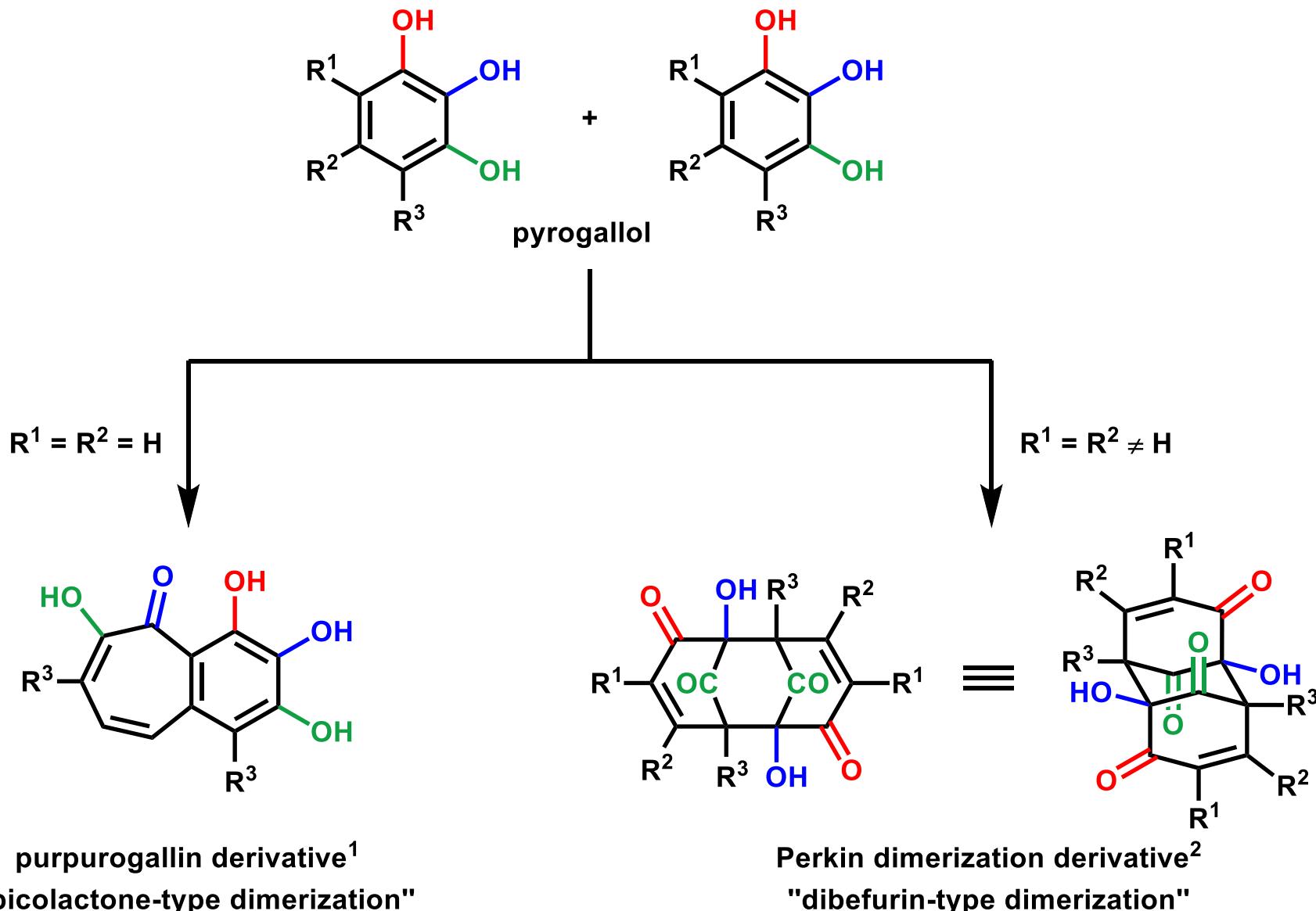
epicolactone²

- Epicoccone B, epicoccine and **epicolactone** were isolated from *Epicoccum nigrum*, which was an *endophytic fungus* (内生真菌) of phylum Ascomycota (子囊菌門).
- **Dibefurin** was isolated from a fungus of phylum Basidiomycota (担子菌門).
- Bioactivity
 - dibefurin**: calcineurin phosphatase inhibition
 - epicolactone**: antimicrobial and antifungal activity
- Structure:
 - dibefurin**: C₁-symmetric ($C_{18}H_{16}O_8$)
 - epicolactone**: unprecedent pentacyclic ($C_{17}H_{16}O_8$), 5 contiguous stereocenters

1. Brill, G. M. et al *J. Antibiot.* **1996**, 49, 124.

2. Marsaioli, A. J. et al *Eur. J.Org. Chem.* **2012**, 5225.

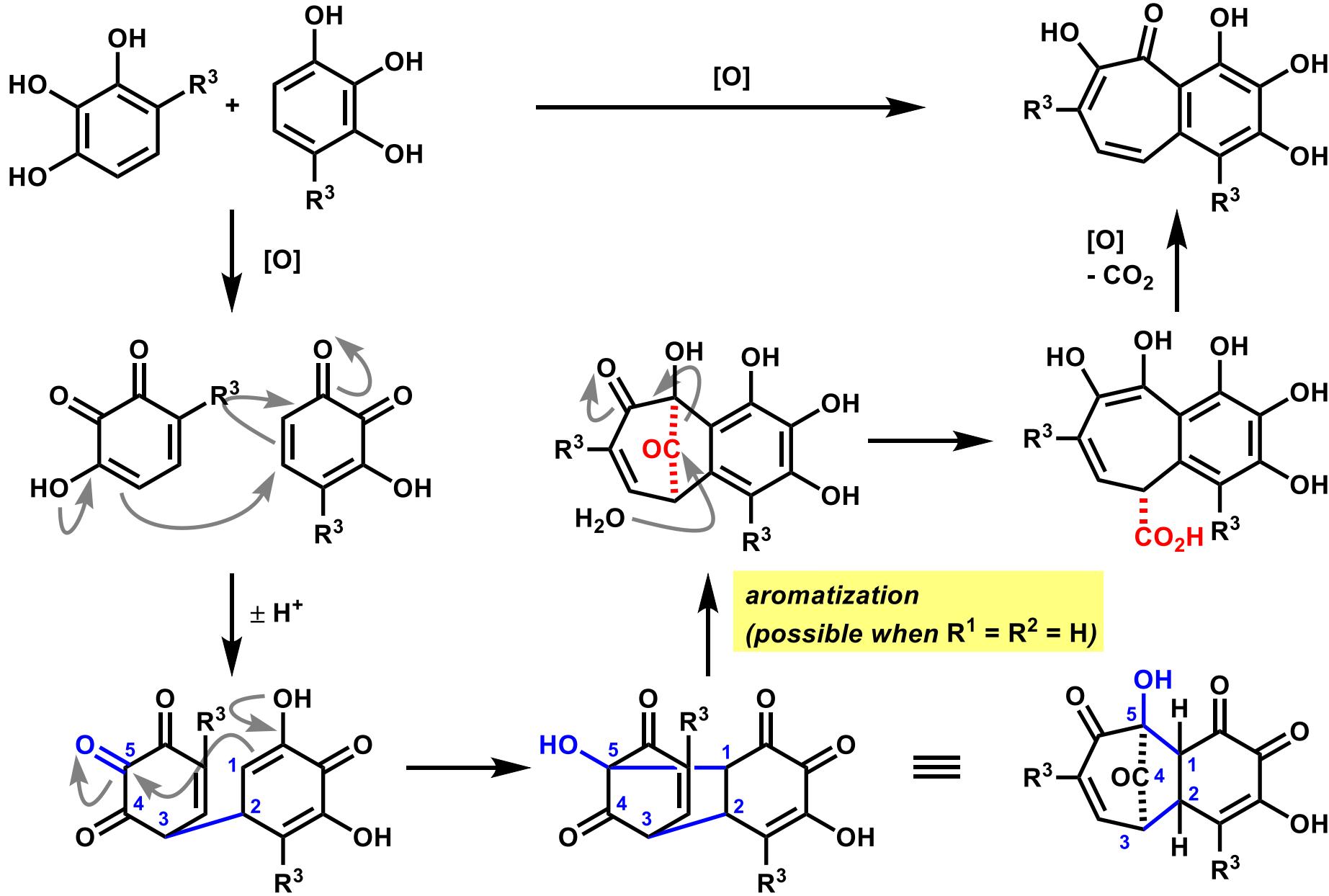
Oxidative Dimerization of Pyrogallols



1. Salfeld, J.-C. *Angew. Chem.* **1957**, *69*, 723.

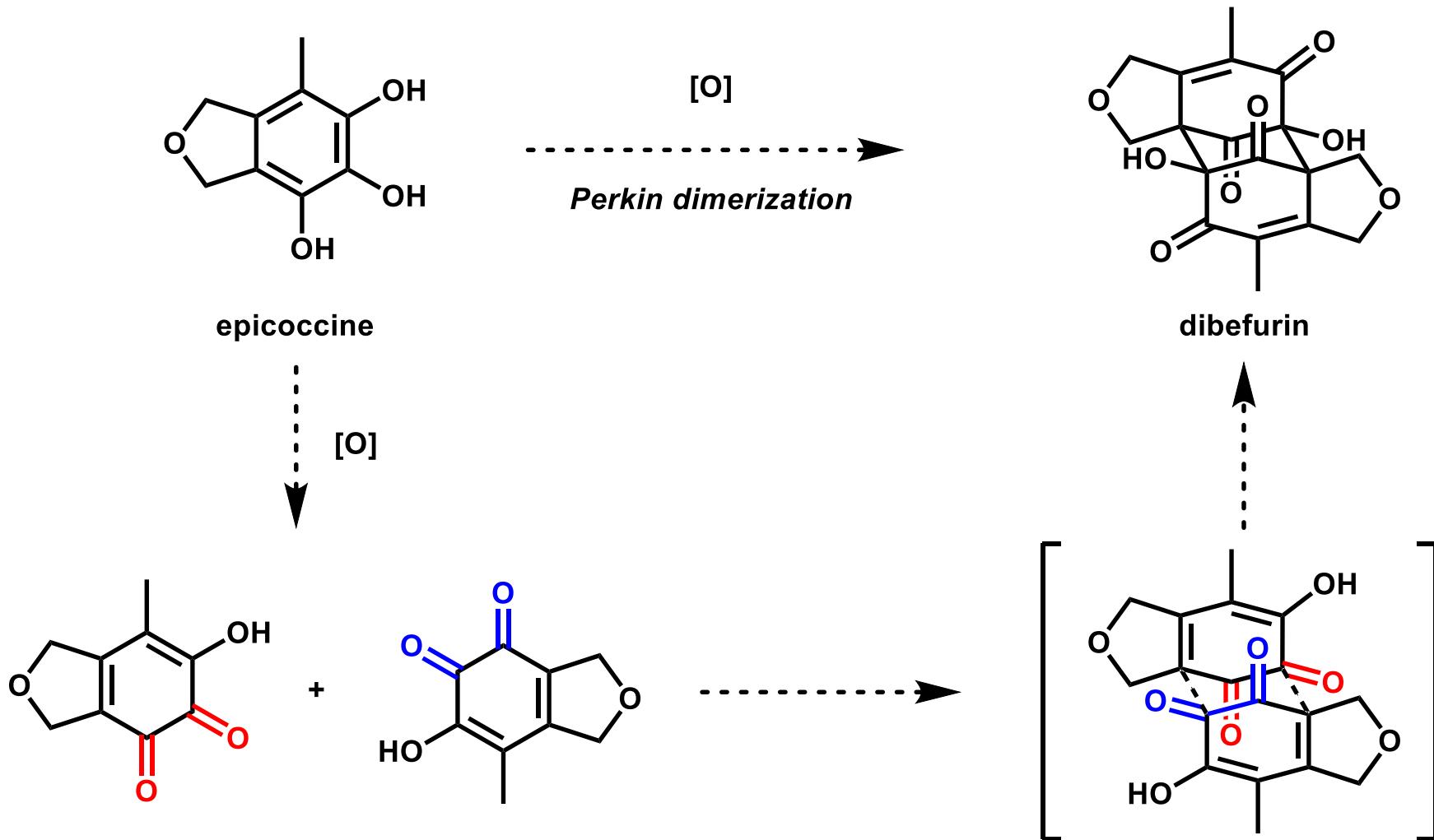
2. Teuber, H.-J.; Dietrich, M.; *Chem. Ber.* **1967**, *100*, 2908.

Purpurogallin Formation Reaction



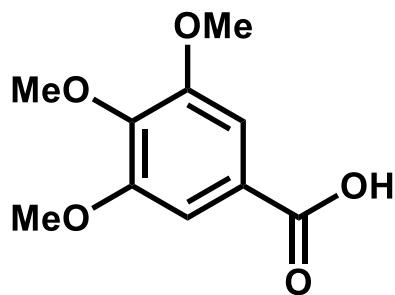
*Biomimetic Synthesis of
Dibefurin*

Proposed Biosynthesis of Dibefurin

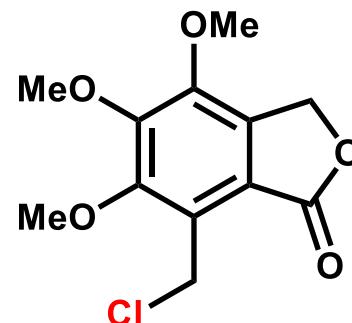


Perkin dimerization would be favored compared to purpurogallin formation because the aromatization would not occur in purpurogallin formation reaction.

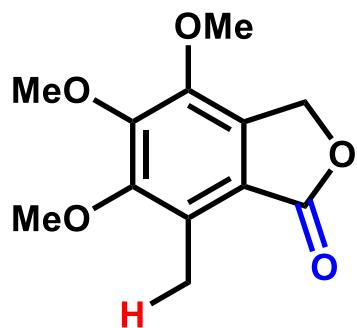
Synthesis of Epicoccine



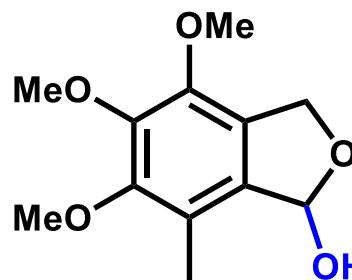
HCl, HCHO
94%



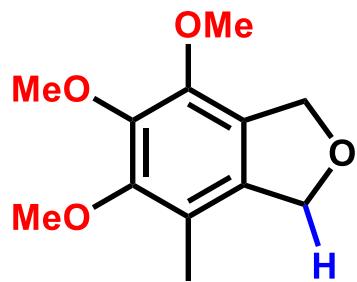
Zn
85%



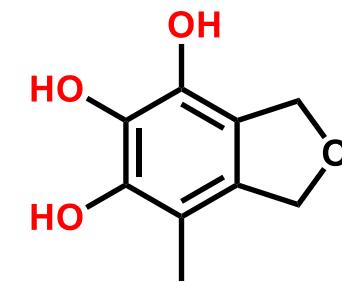
DIBAL-H



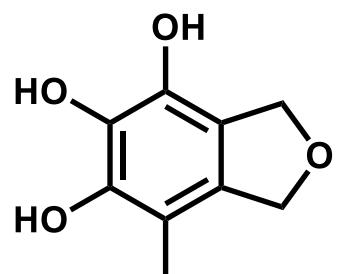
Et₃SiH, TFA
58% (2 steps)



BBr₃
80%

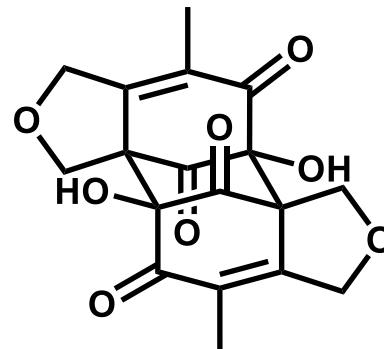


Biomimetic Synthesis of Dibefurin (1)



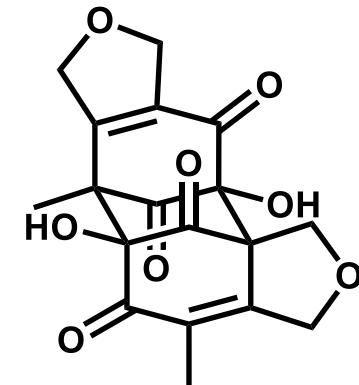
epicoccine

$\text{K}_3\text{Fe}(\text{CN})_5$
 NaHCO_3
 $\text{MeCN}/\text{H}_2\text{O}$



dibefurin

NMR yield: 62%
isolated: 49%

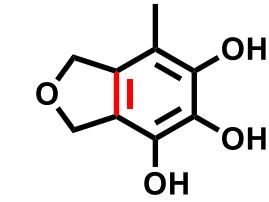
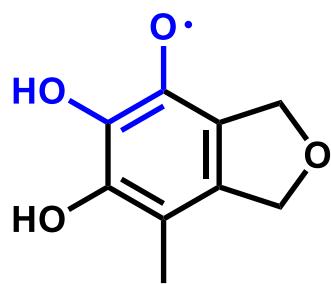


regioisomer

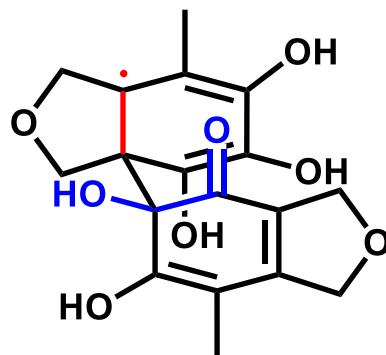
NMR yield: 36%



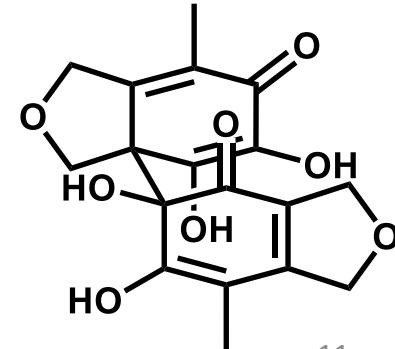
Radical pathway



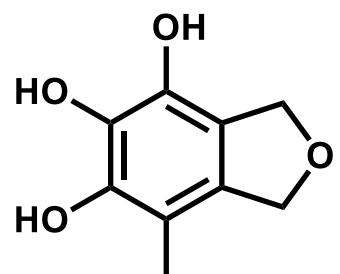
radical coupling



- H^+
- e^-

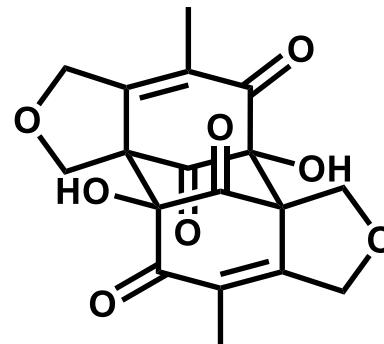


Biomimetic Synthesis of Dibefurin (2)

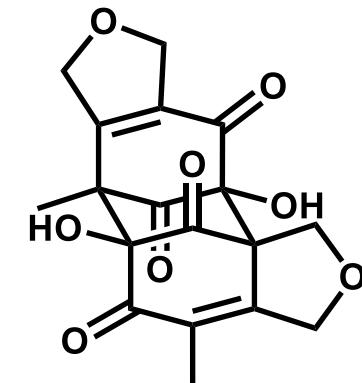


epicoccine

$\text{K}_3\text{Fe}(\text{CN})_5$
 NaHCO_3
 $\text{MeCN}/\text{H}_2\text{O}$



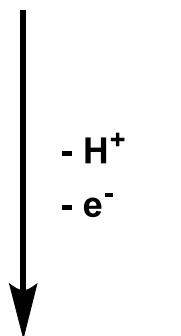
dibefurin



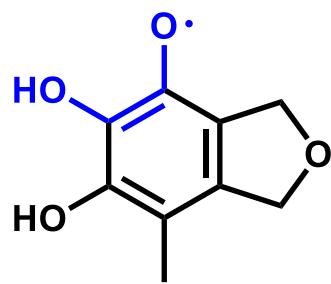
regiosomer

NMR yield: 62%
isolated: 49%

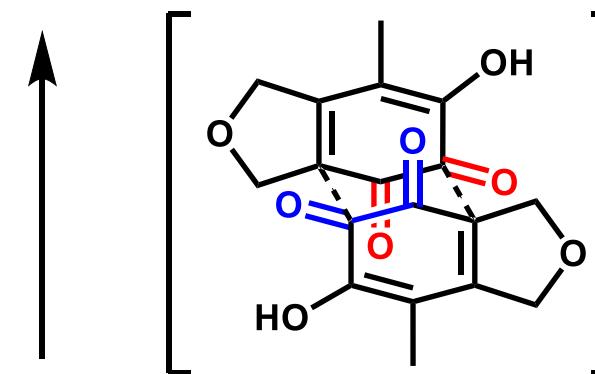
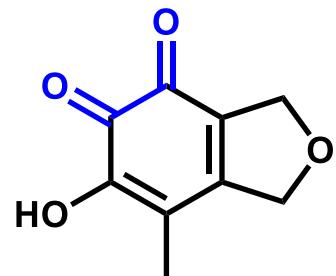
NMR yield: 36%



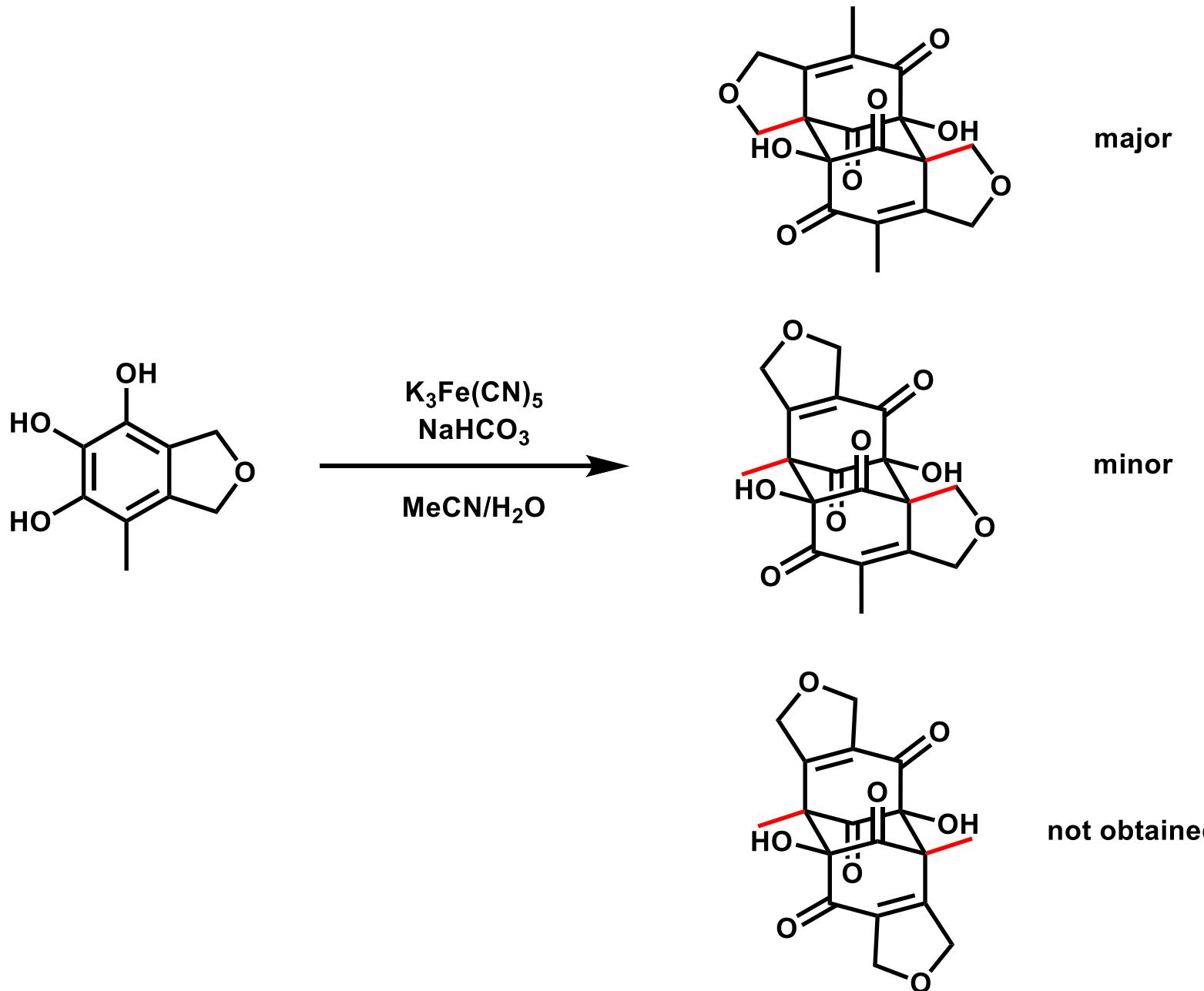
Quinone pathway



$- \text{H}^+$
 $- \text{e}^-$



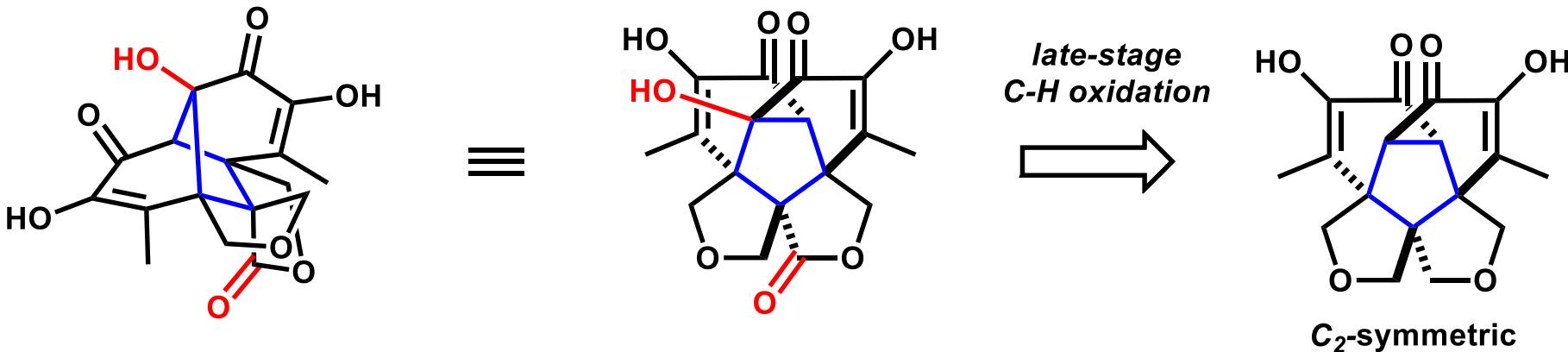
Regioselectivity in Homodimerization



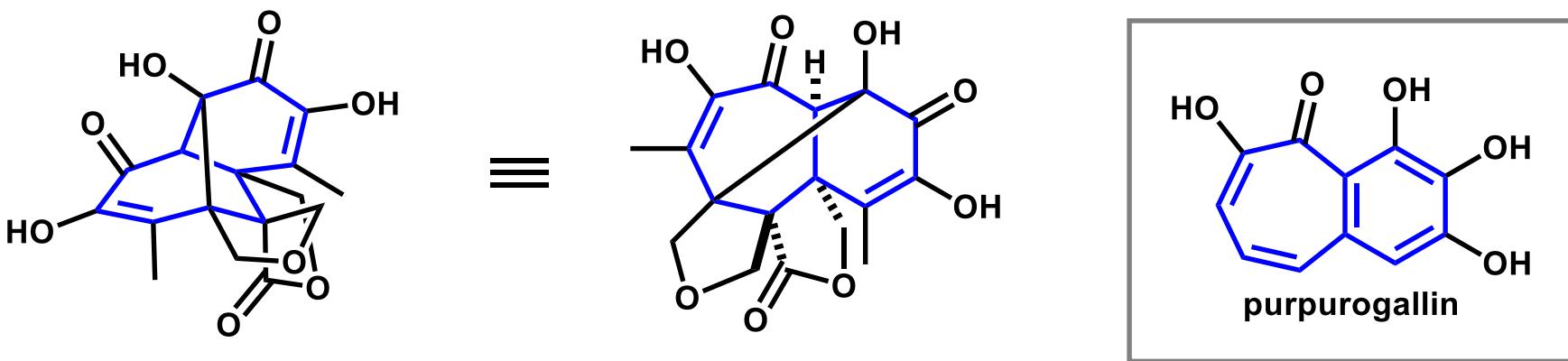
Biomimetic Synthesis of Epicolactone

Retrosynthetic Analysis of Epicolactone

Pattern A

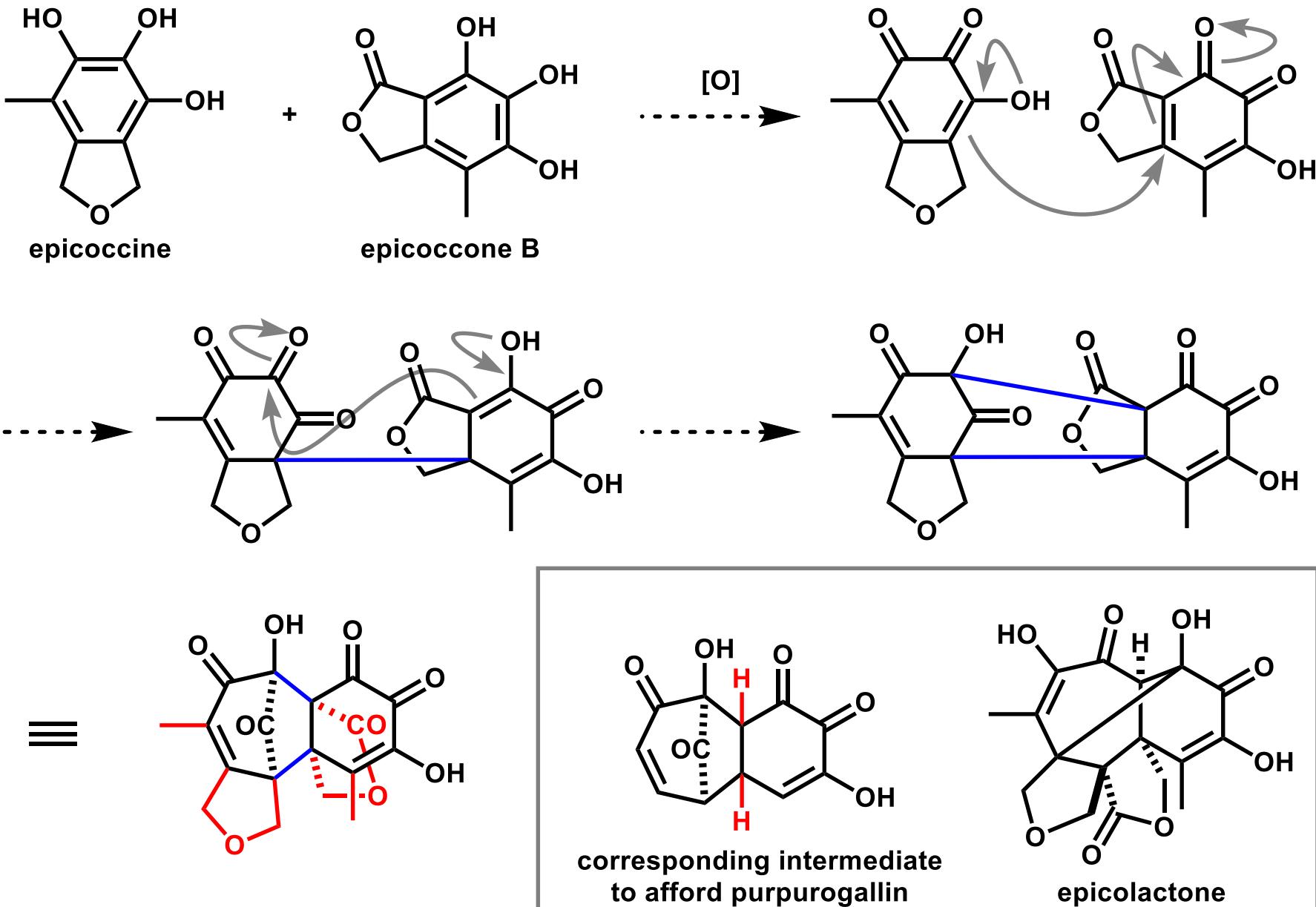


Pattern B

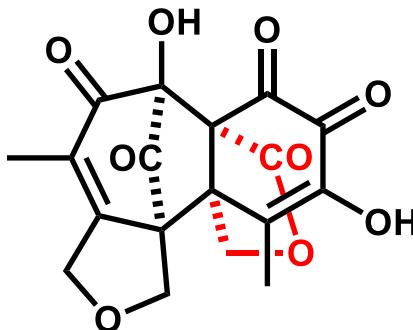


In pattern B, Prof. Trauner realized that epicolactone had purpurogallin-like structure. He proposed a biosynthetic pathway of epicolactone based on that of purpurogallin.

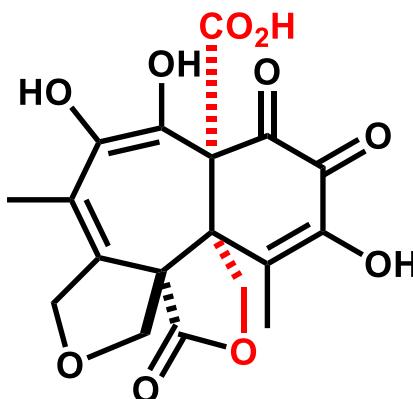
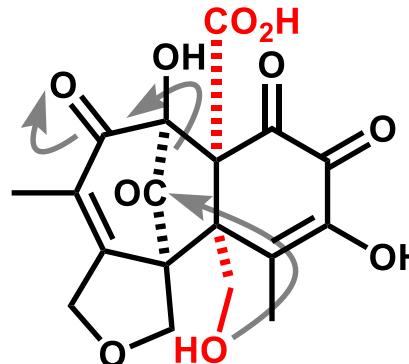
Proposed Biosynthesis of Epicolactone (1)



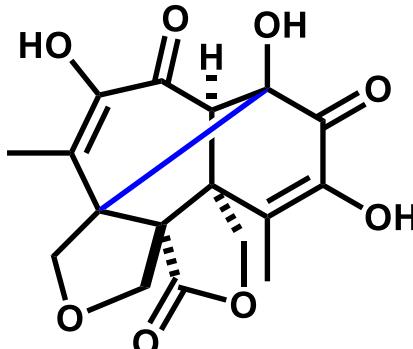
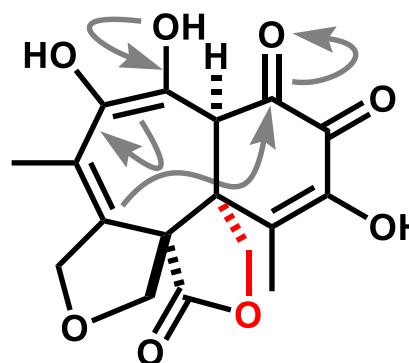
Proposed Biosynthesis of Epicolactone (2)



hydrolysis of lactone



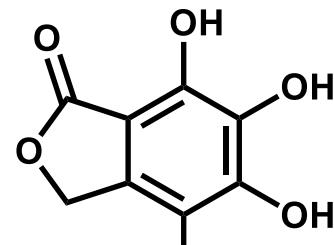
- CO₂



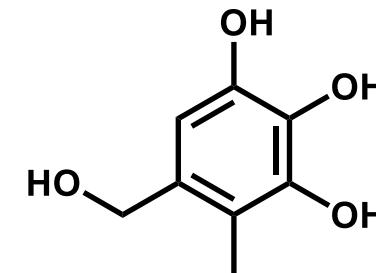
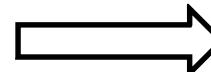
epicolactone

* Order of the reactions is not set.

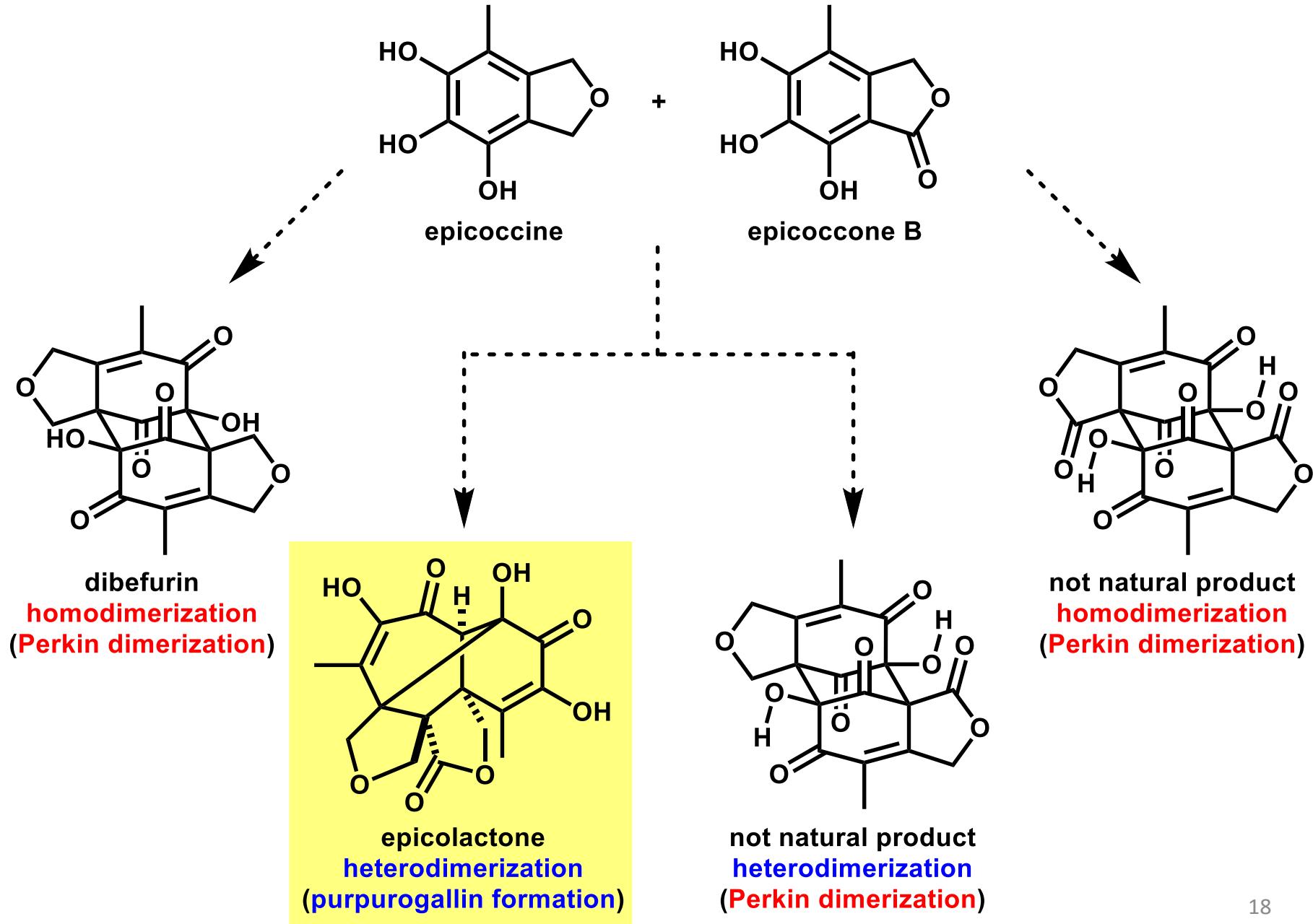
* Epicoccone B can be replaced with the compound shown below. However, such a natural product has not been isolated yet.



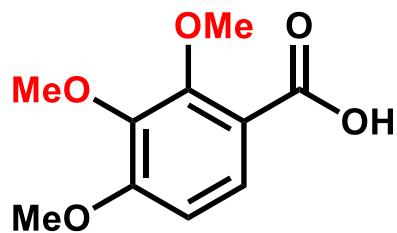
epicoccone B



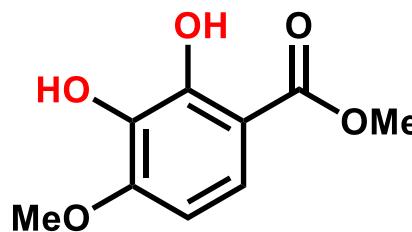
Potential Challenges in Epicolactone Synthesis



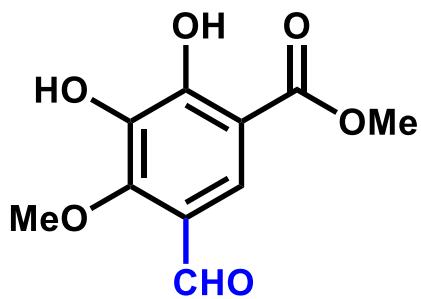
Synthesis of Epicocone B



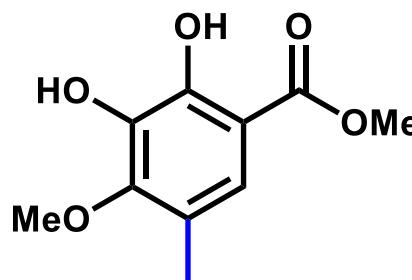
1. BCl_3 , 76%
2. H_2SO_4
MeOH, 98%



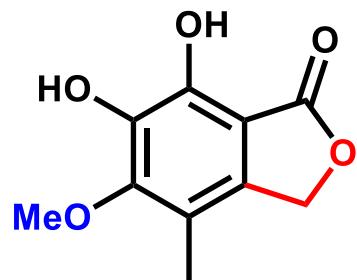
, TFA
94%



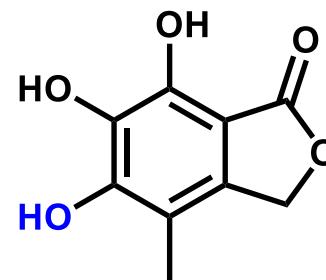
Pd/C, H_2
HCl
92%



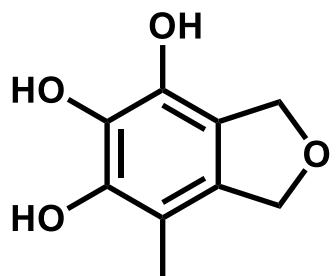
$(\text{HCHO})_n$
 H_2SO_4
99%



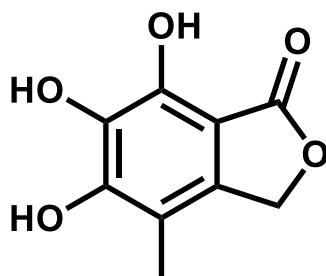
BBr_3
72%



Attempted Heterodimerization (1)

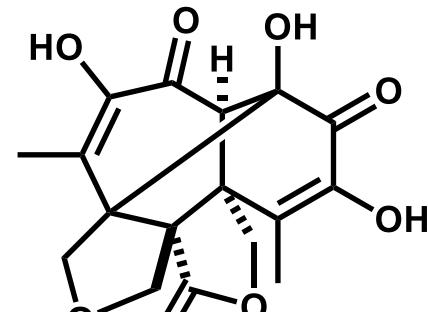


epicoccine



epicoccone B

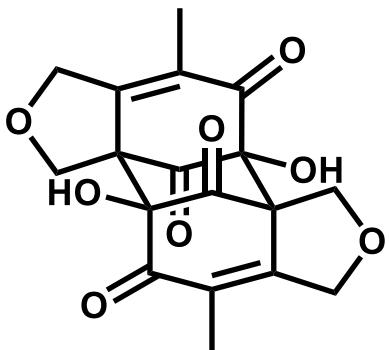
$K_3[Fe(CN)_6]$
 $NaHCO_3$
MeCN/H₂O



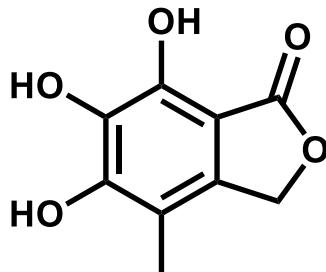
epicolactone



$K_3[Fe(CN)_6]$
 $NaHCO_3$
MeCN/H₂O



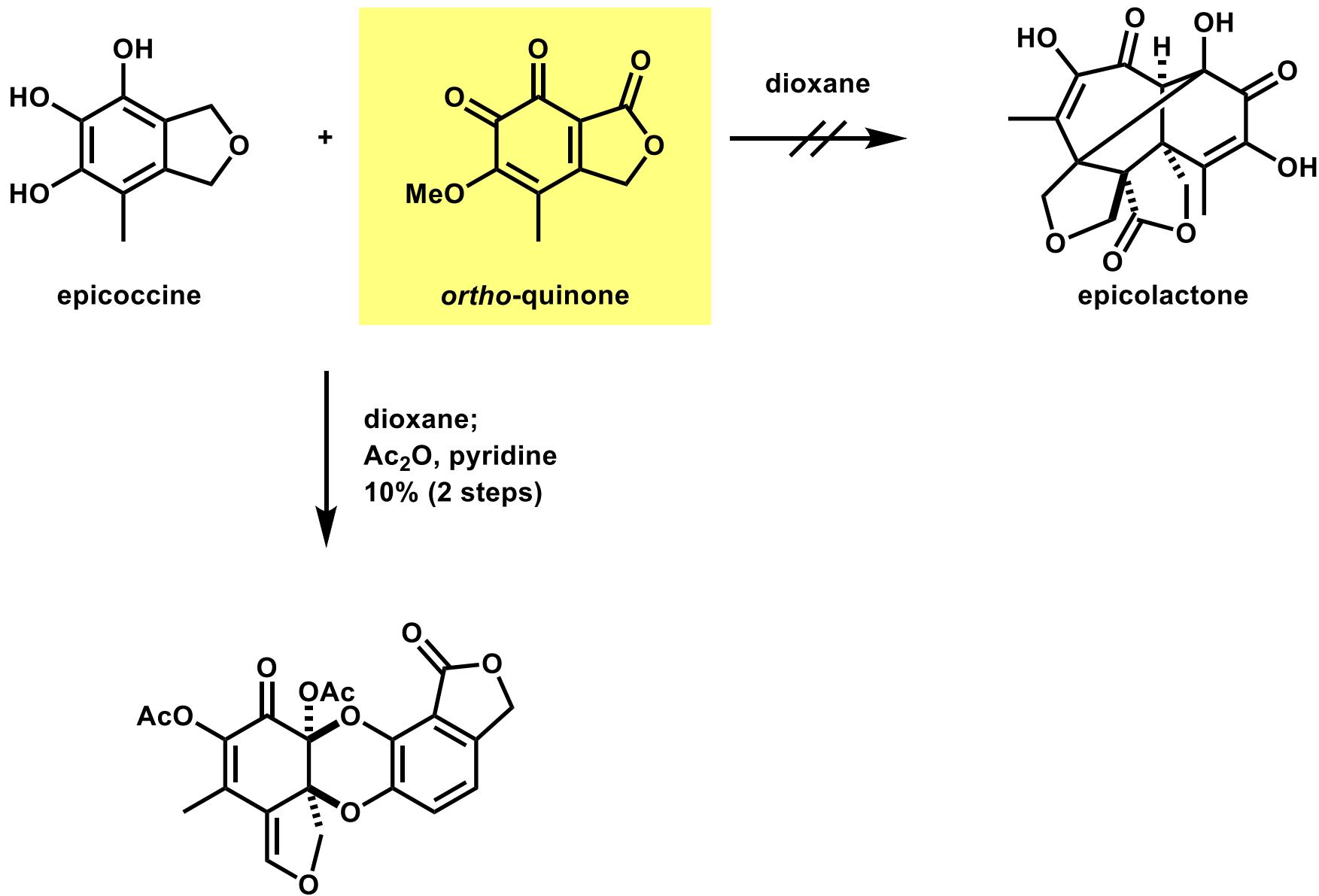
dibefurin



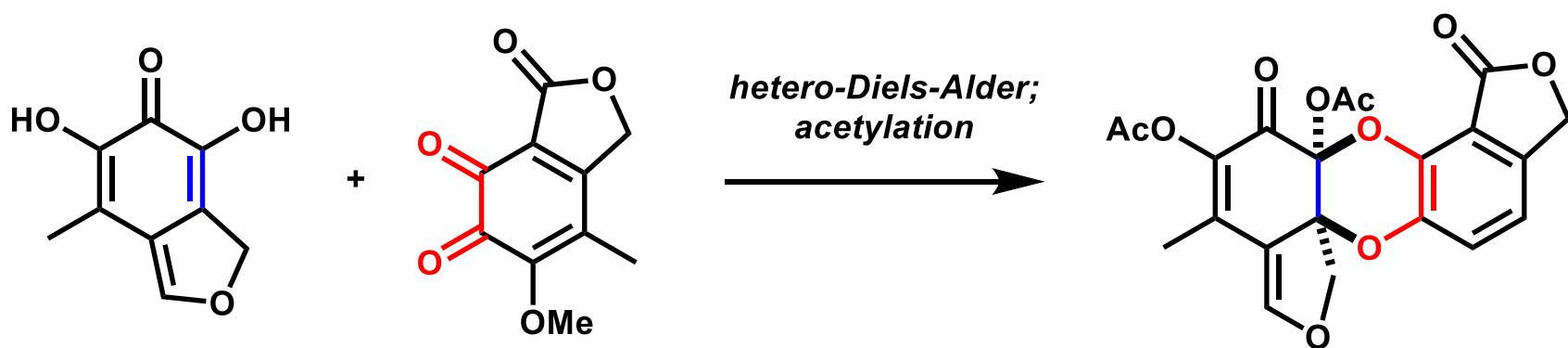
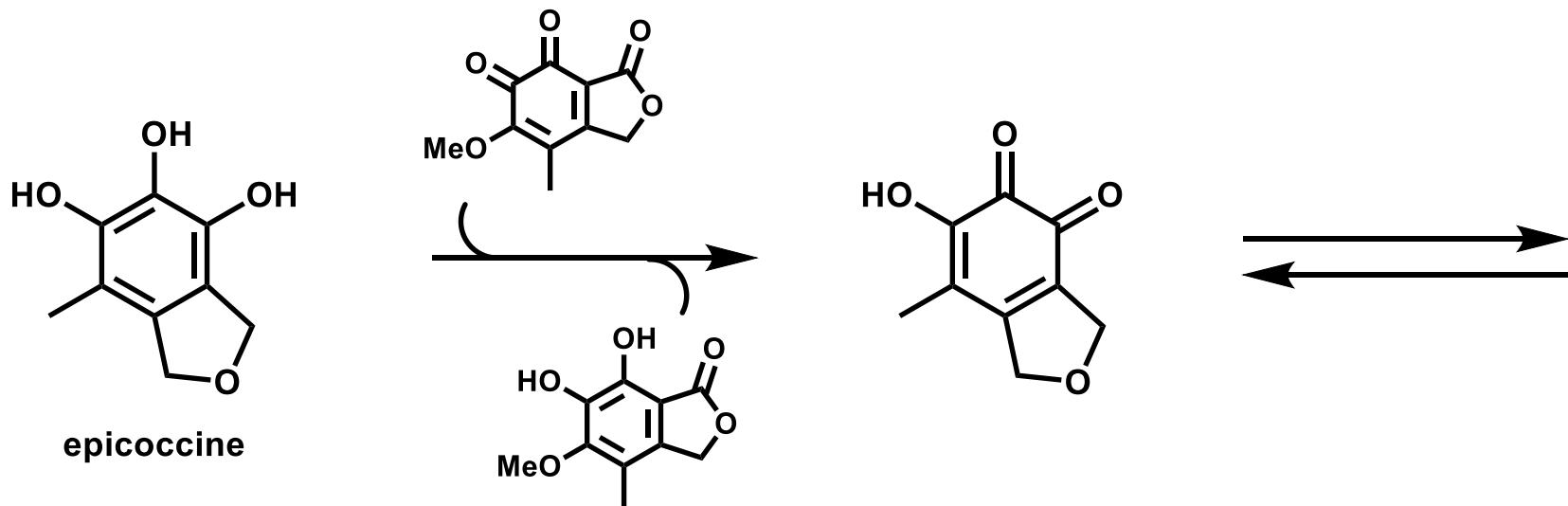
epicoccone B
(unreacted)

◆ Problem ◆
More facile oxidation of epicoccine
compared to epicoccone B
(Epicoccine B is more electron deficient
due to the additional carbonyl group.)

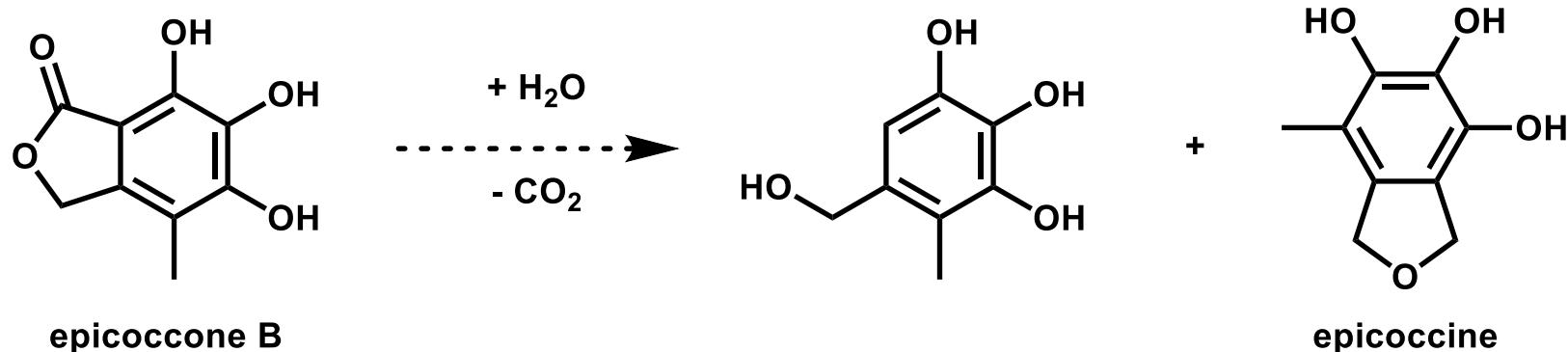
Attempted Heterodimerization (2)



Proposed Mechanism



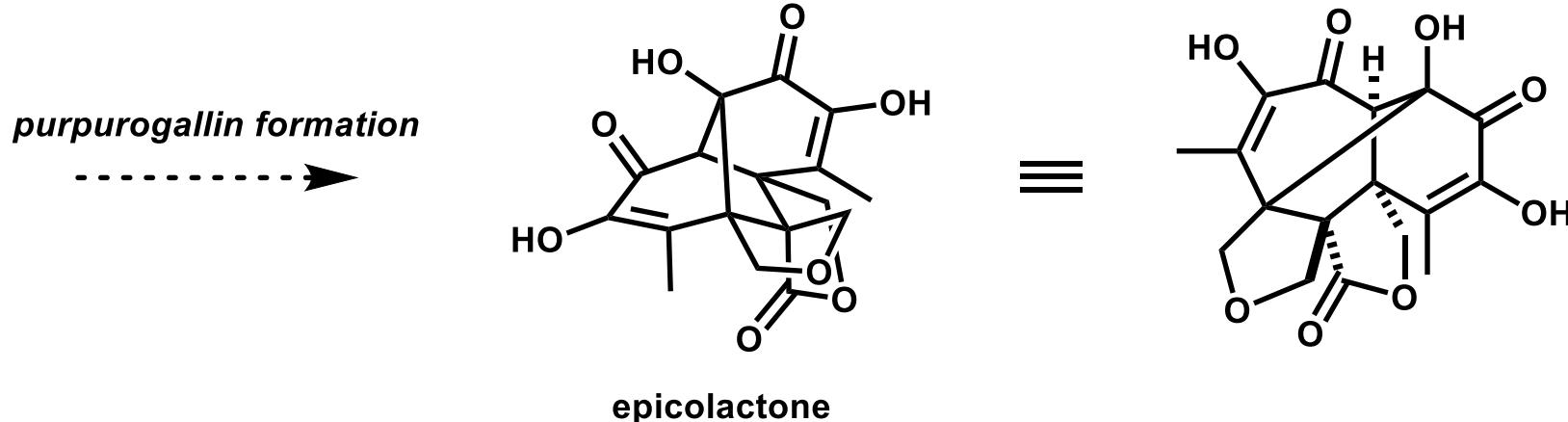
Modified Proposed Biosynthesis of Epicolactone



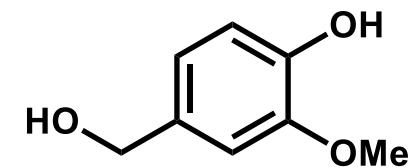
◆ Hypothesis ◆

Hexasubstituted epicoccone B structure is too sterically encumbered to allow for a purpurogallin-type coupling reaction.

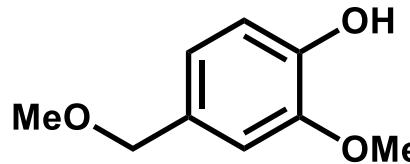
Hydrolysis of lactone and the following decarboxylation would occur before the coupling reaction.



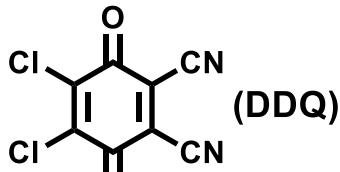
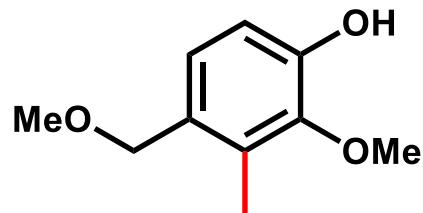
Synthesis of Epicoccone B Derivative



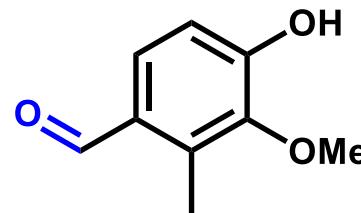
p-TsOH, MeOH



n-BuLi;
MeI

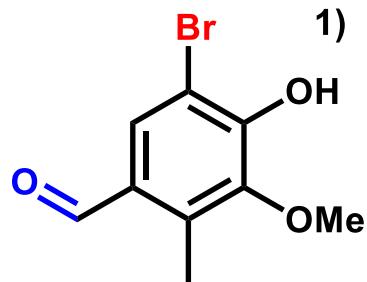


54% (3 steps)



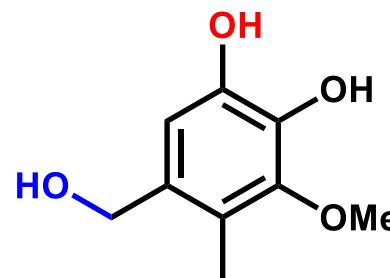
Br₂, AcOH

72%

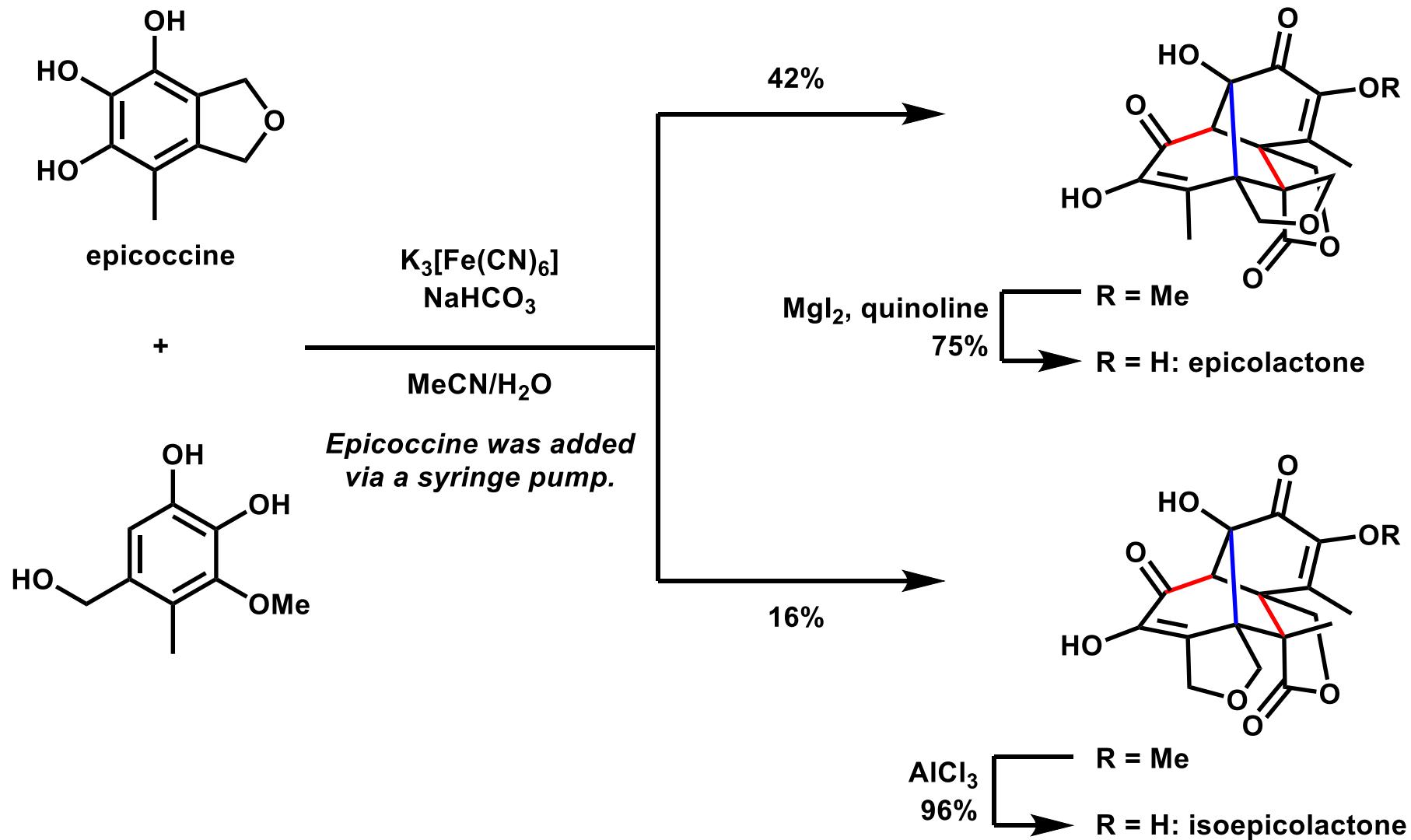


1) 1. CuSO₄ (2 mol%)
aq. NaOH, 75%

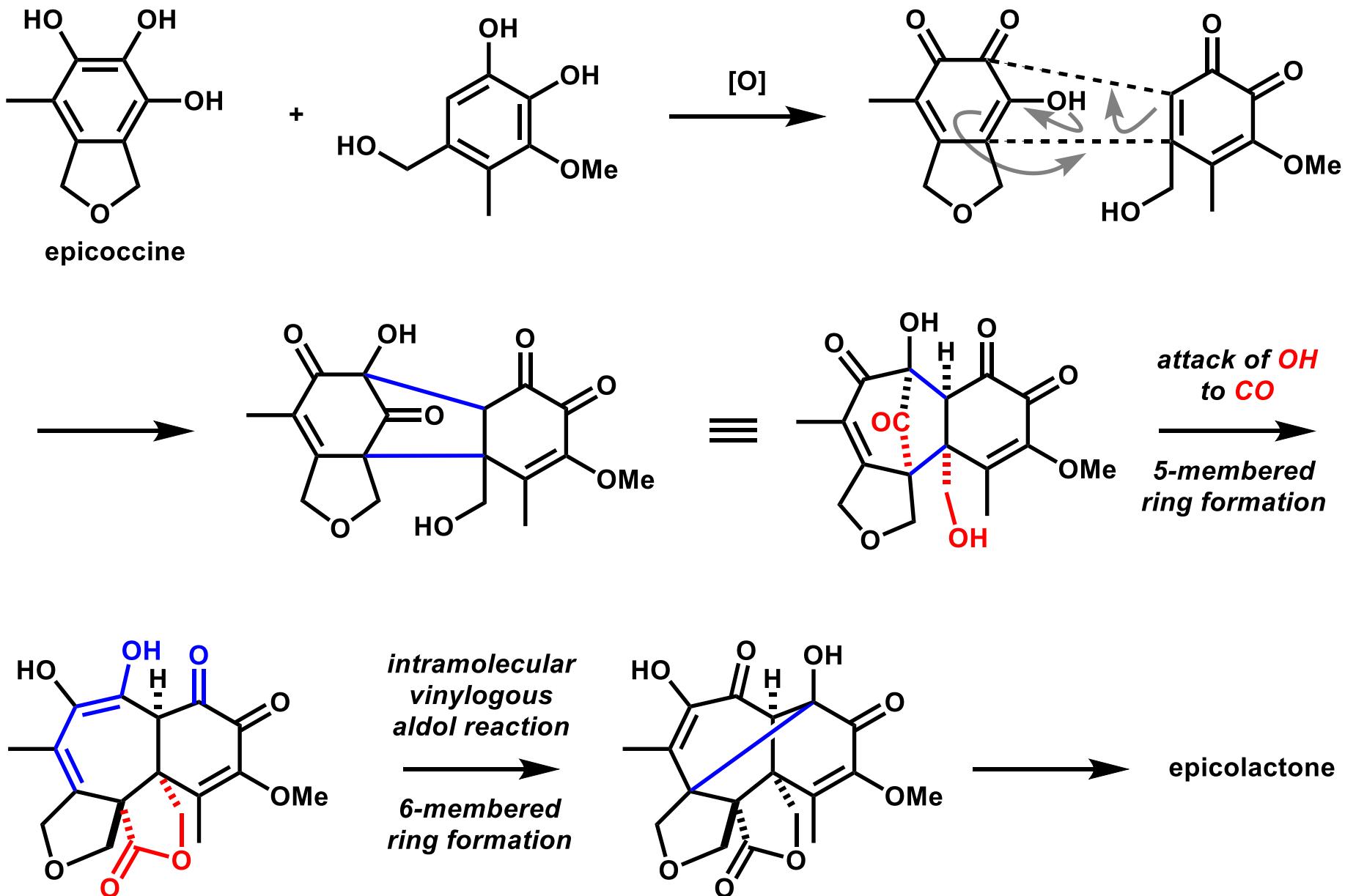
2. NaBH₄, 79%



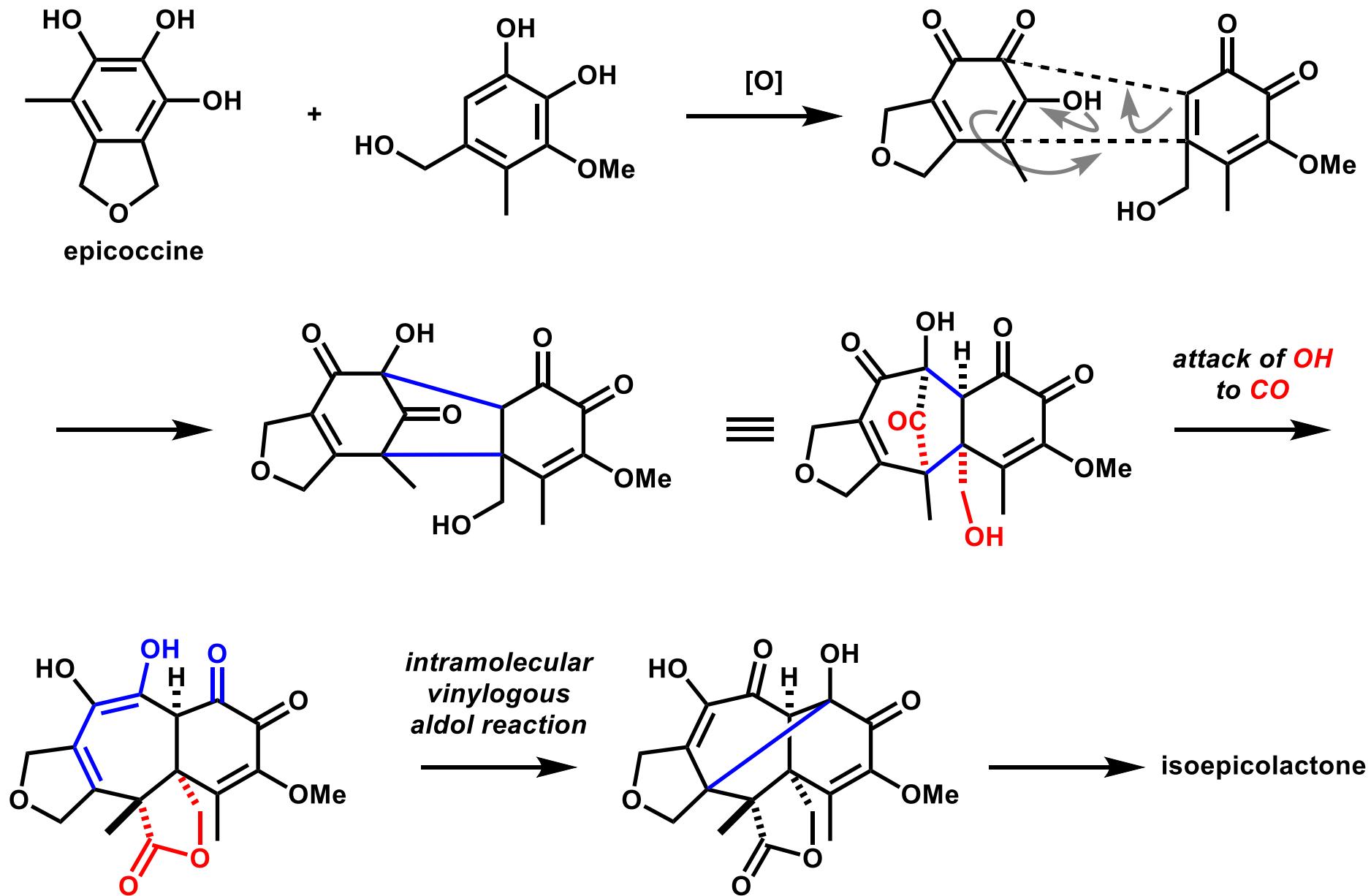
Successful Synthesis of Epicolactone



Proposed Mechanism to give Epicolactone



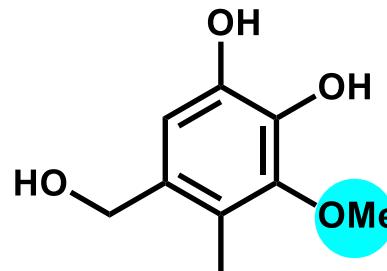
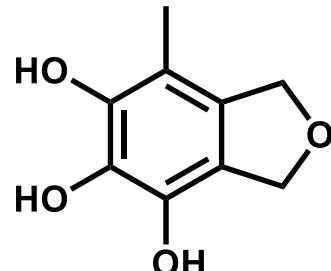
Proposed Mechanism to give Isoepicollactone



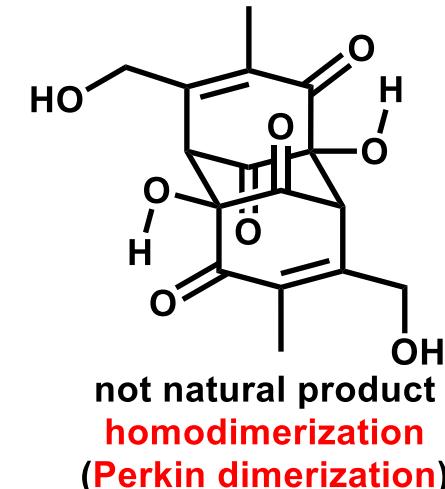
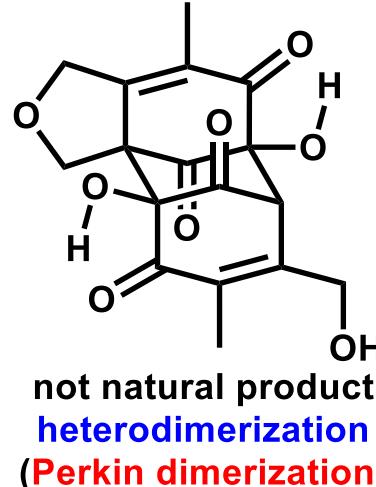
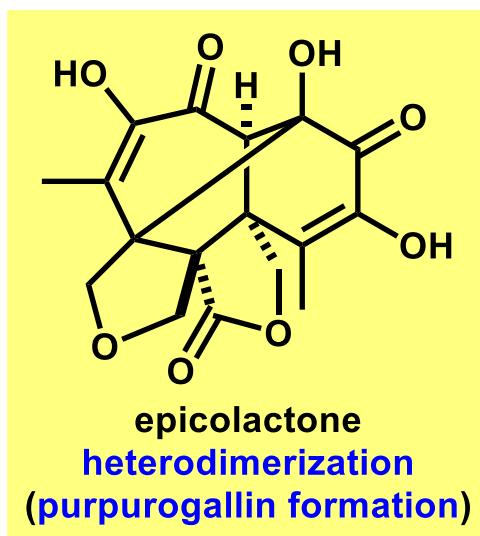
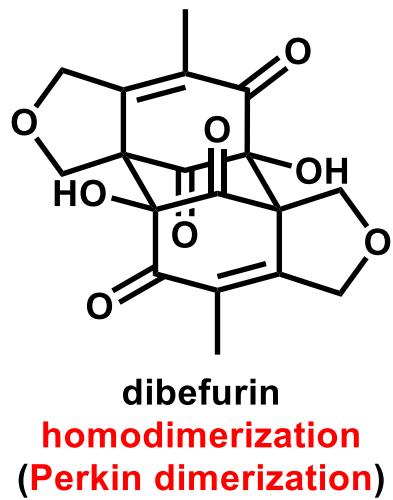
Key to Success (*My Opinion*)

1. Use of syringe pump

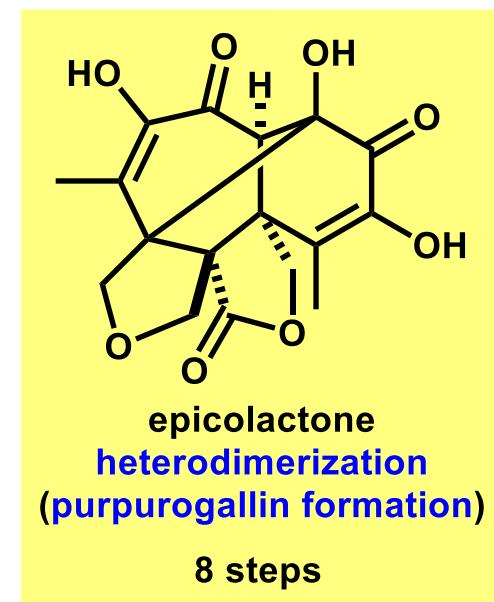
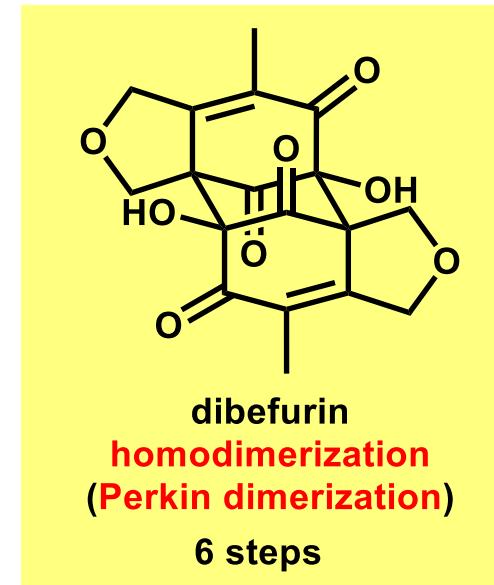
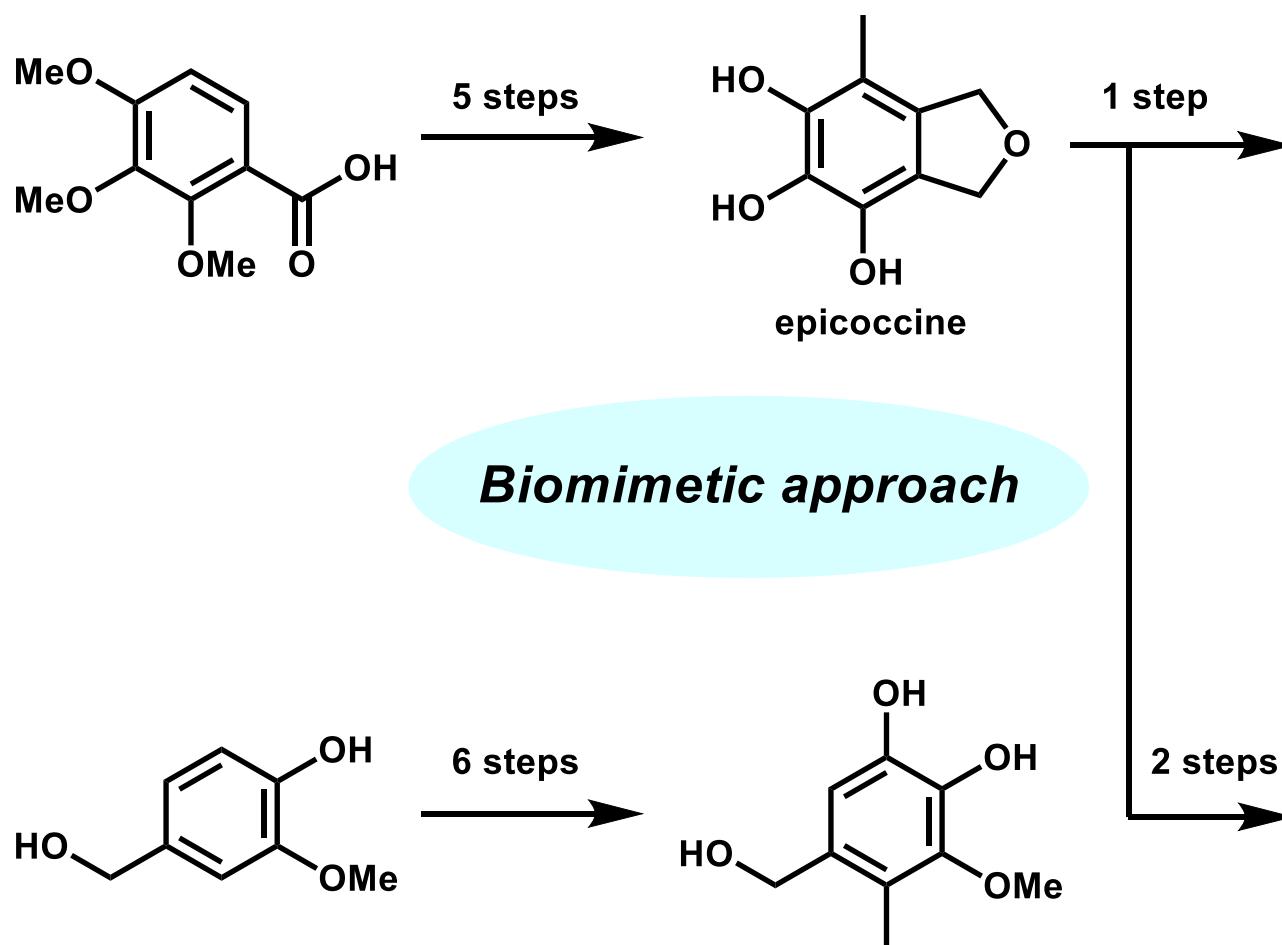
Low concentration



2. Use of OMe

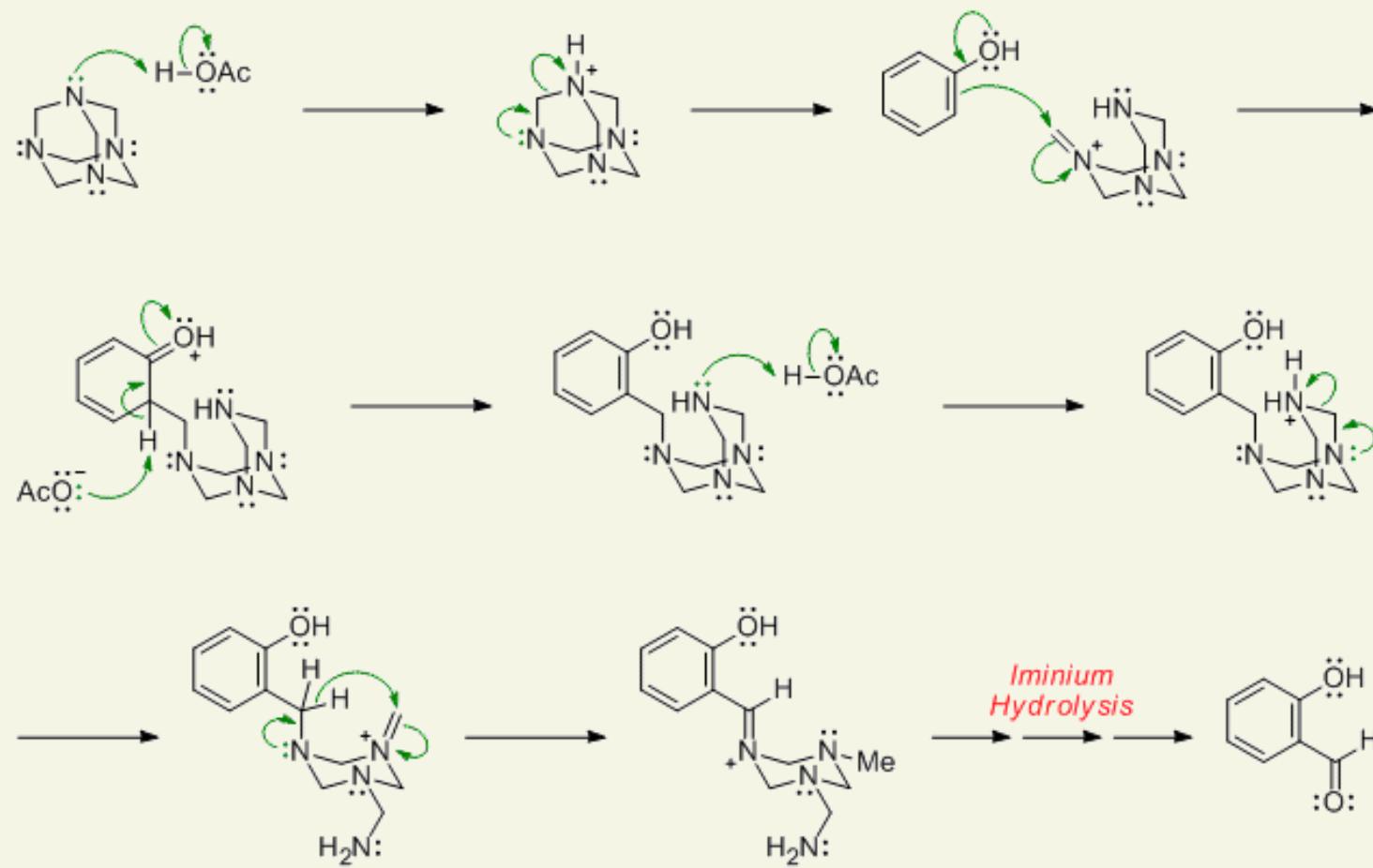


Summary



Appendix

Mechanism of the Duff Reaction



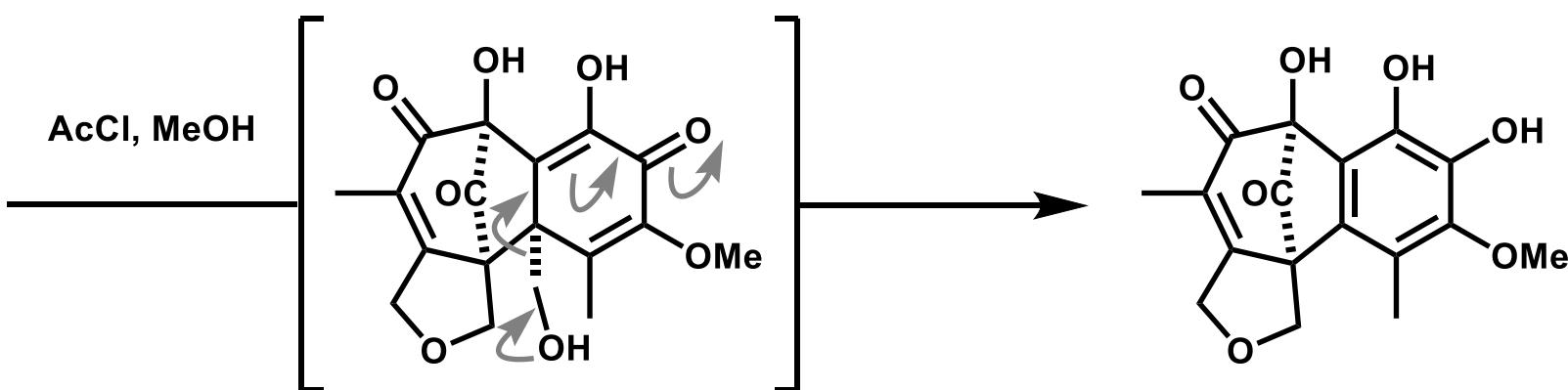
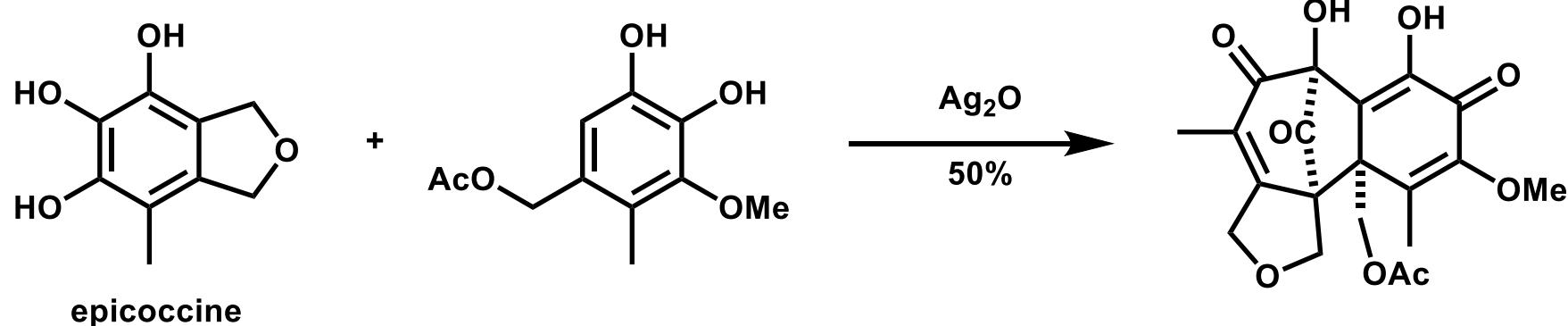
[Report an error](#)

Screening of Oxidative Dimerization

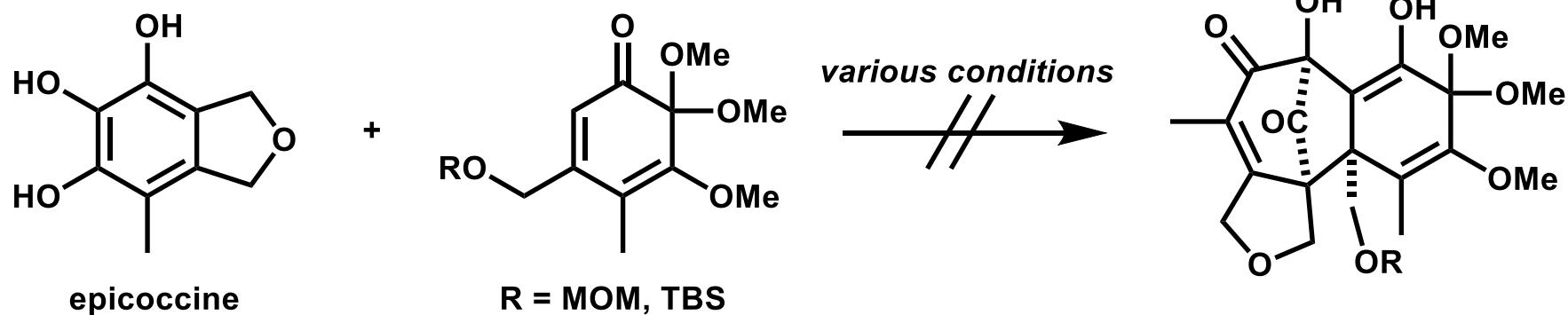


Entry	Oxidant	Additive (equiv)	Yield by ¹ H NMR [%] ^[a]	Yield ^[b] [%]	
1	<i>o</i> -chloranil	—	decomp.	—	
2	DDQ	—	—	—	(<i>o</i> -chloranil)
3	Frémy's salt	—	42	25	
4	MnO ₂	—	decomp.	—	K ₂ [NO(NO ₃) ₂] (Frémy's salt)
5	Ag ₂ O	—	30	n.d. ^[c]	
6	AgO	aq HNO ₃	decomp.	—	
7	CAN	—	decomp.	—	
8	FeCl ₃ ·6 H ₂ O	NaHCO ₃ (2.0)	—	—	(NH ₄) ₂ Ce(NO ₃) ₆ (CAN)
9	K ₃ [Fe(CN) ₆]	NaHCO ₃ (2.0)	62	49	
10	O ₂ (balloon)	FeSO ₄ ·7 H ₂ O (0.1)	31	23	

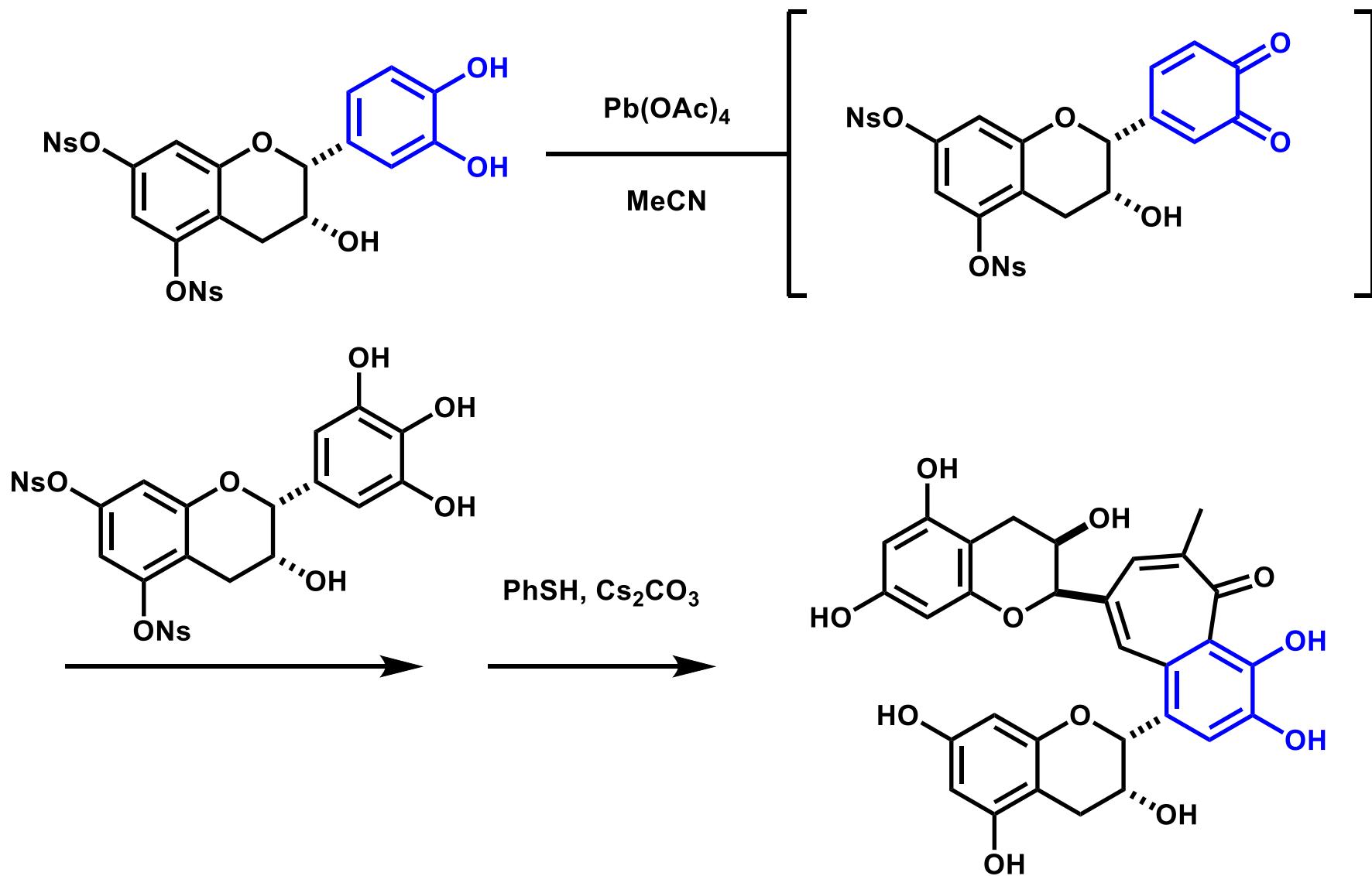
Observation of Intermediate



Attempted Heterodimerization (My Work)



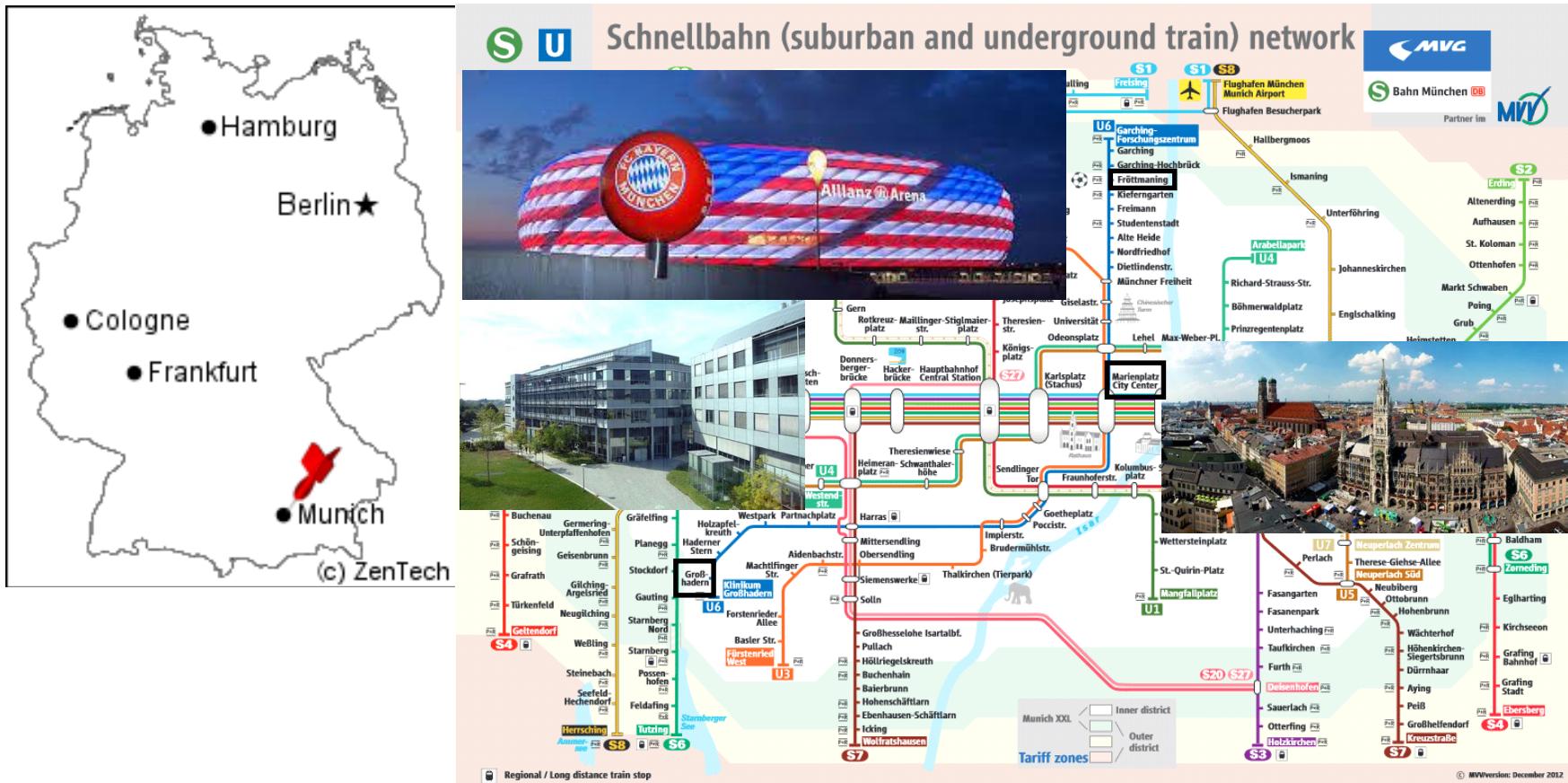
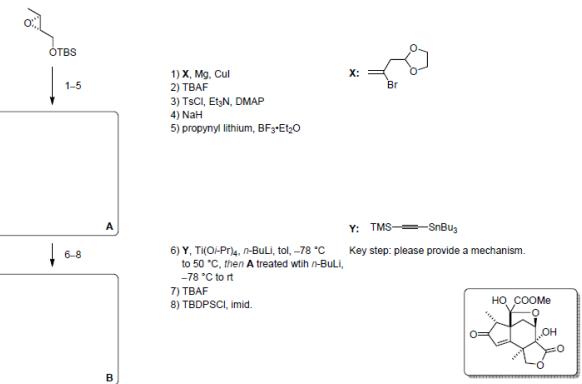
Biomimetic Synthesis of Theaflavin

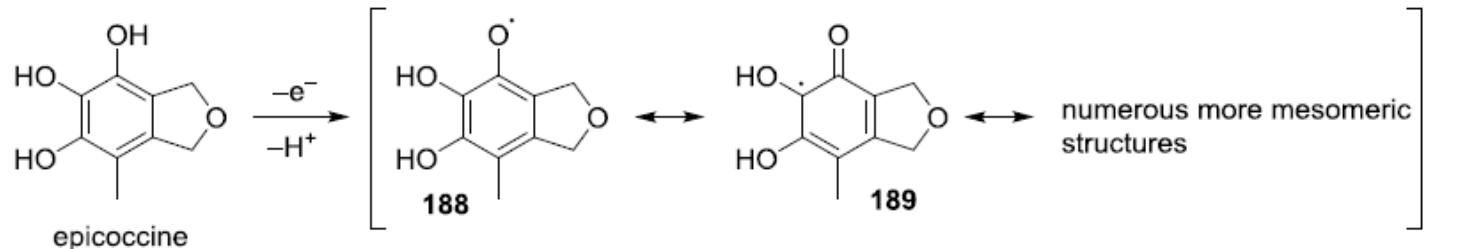


Trauner Group

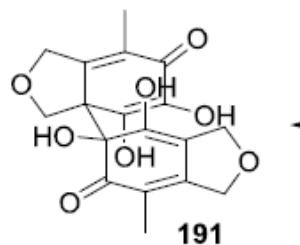
X. Cheng, G. C. Micalizio, J. Am. Chem. Soc. 2015, 138, 1150–1153.

- From Monday to Friday, Saturday or Sunday
- Monday: Group meeting
- Tuesday: Denksport (see right figure)
- PhD students and posdocs from all over the world
- Not so good university cafeteria
- 15 min from Marienplatz (City center of Munich)
- 30 min to Allianz Arena



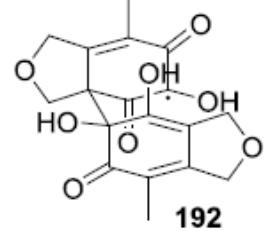


RADICAL PATHWAY



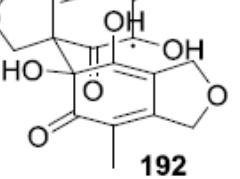
$-e^-$

$-H^+$



$-e^-$

$-H^+$



$-e^-$

$-H^+$

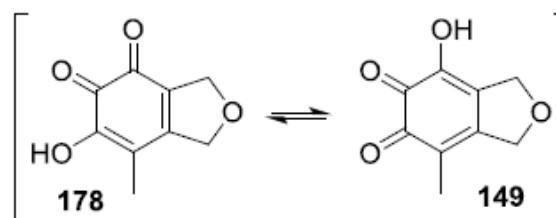
selectivity-determining
step

epicoccine

$-e^-$

$-H^+$

QUINONE PATHWAY



$2x$

selectivity-determining
step

