

An eight-step synthesis of epicolactone reveals its biosynthetic origin

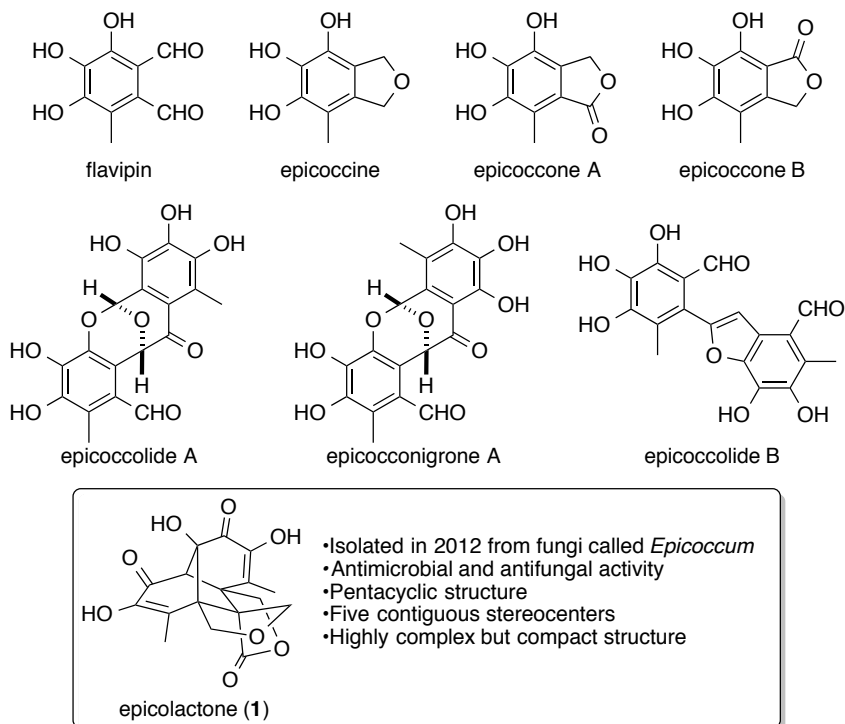
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1. Introduction

1-1 Epicolactone

- The endophytic fungus *Epicoccum* sp. is known to produce a variety of bioactive metabolites, the best known of which is flavipin. Several heterocyclic derivatives of flavipin as well as dimeric congeners have also been described. (Fig. 1)
- Epicolactone was isolated in 2012 and displays both antimicrobial and antifungal activity, but the biological mechanism of its action is still unknown.
- Epicolactone has a pentacyclic structure with five contiguous stereocenters, three of which are quaternary. Despite its highly complex structure, it is compact.

Figure 1 Fungal pyrogallols of *Epicoccum*

2. Results and Discussion

2-1 The authors' analysis of epicolactone

- The drawing of epicolactone (1) on the top right in Fig. 2 reveals the pseudosymmetric structure of epicolactone and its C_2 -symmetric skeleton (2).
- This suggests that a dimerization with the loss of a carbon is involved in its biosynthesis.
- The drawing of 1 on the bottom right in Fig. 2 displays a connectivity pattern that can be recognized in purpurogallin (3), which is formed via oxidative dimerization of pyrogallol.

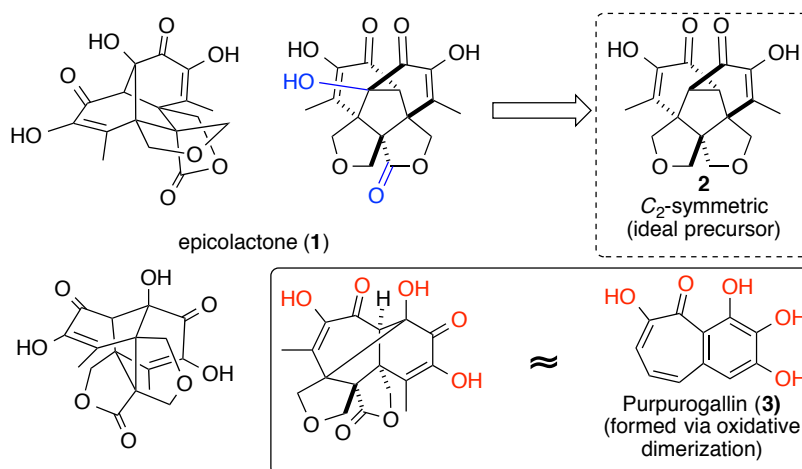
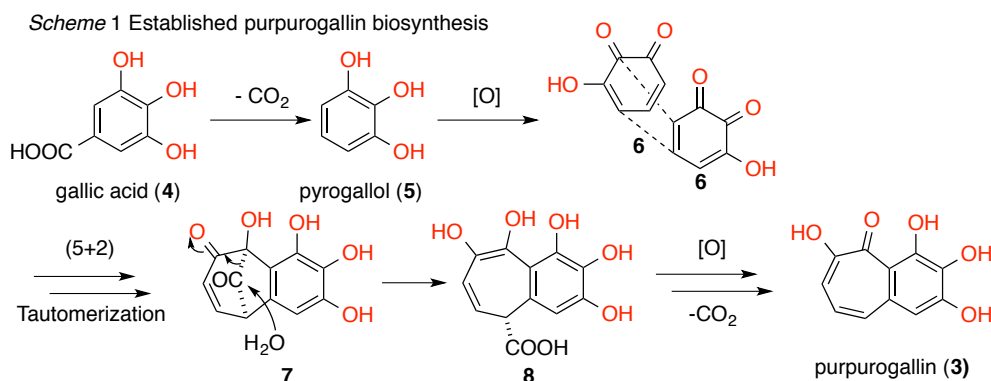


Figure 2 The structure of epicolactone (1) from several different perspective

2-2 Biosynthetic analogy between purpurogallin and epicolactone

*Established biosynthesis of purpurogallin(3)¹*

4→5: decarboxylation of gallic acid (4) gives pyrogallol (5).

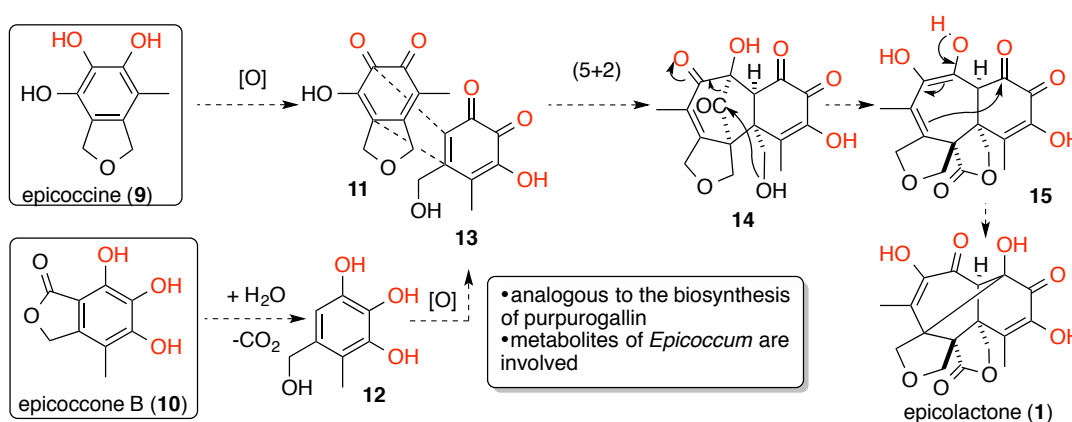
5→6: oxidation of pyrogallol (5) gives corresponding *o*-quinone 6.

6→7: homodimerization of 6 via (5+2) cycloaddition followed by tautomerization gives carbonyl-bridged intermediate 7.

7→8: intermolecular nucleophilic attack by water to the carbonyl bridge of 7 gives 6/7 fused bicyclic compound 8.

8→3: oxidation and decarboxylation of 8 gives purpurogallin (3).

Scheme 2 Proposed biosynthesis of epicolactone

*Proposed biosynthesis of epicolactone*

9,10: both are known metabolites of *Epicoccum*, the same fungus that produces epicolactone.

10→12: hydrolysis and decarboxylation of epicoccone B (10) gives pyrogallol 12.

9→11, 12→13: oxidation of 9 and 12 gives corresponding quinone 11 and 13 respectively.

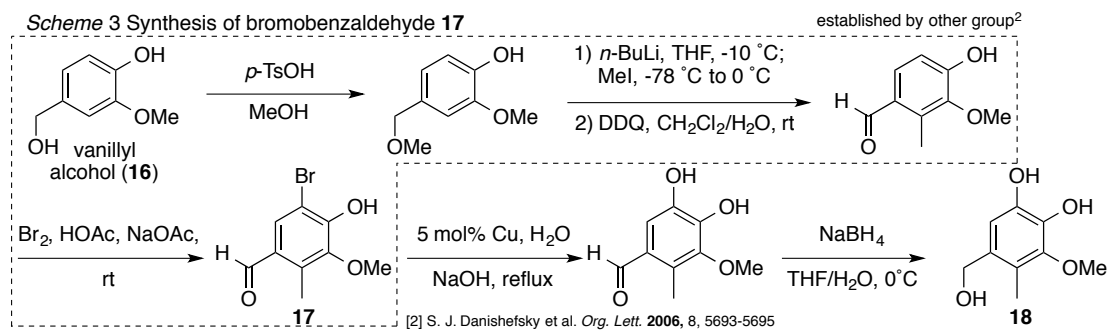
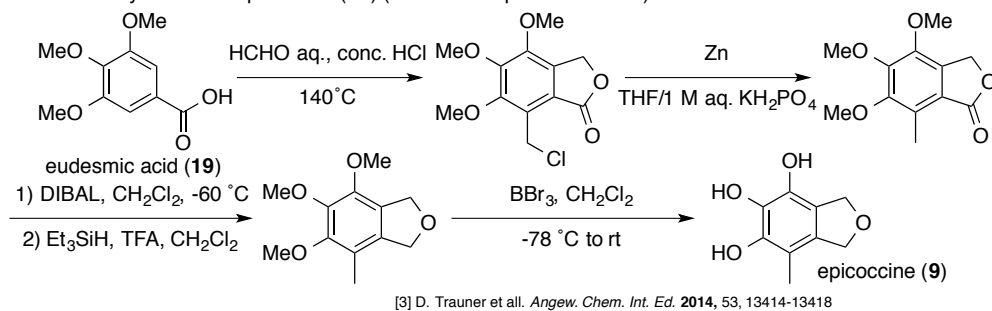
12,13→14: heterodimerization of 12 with 13 via (5+2) cycloaddition gives carbonyl-bridged intermediate 14.

14→15: intramolecular nucleophilic attack by the primary alcohol forms lactone 15.

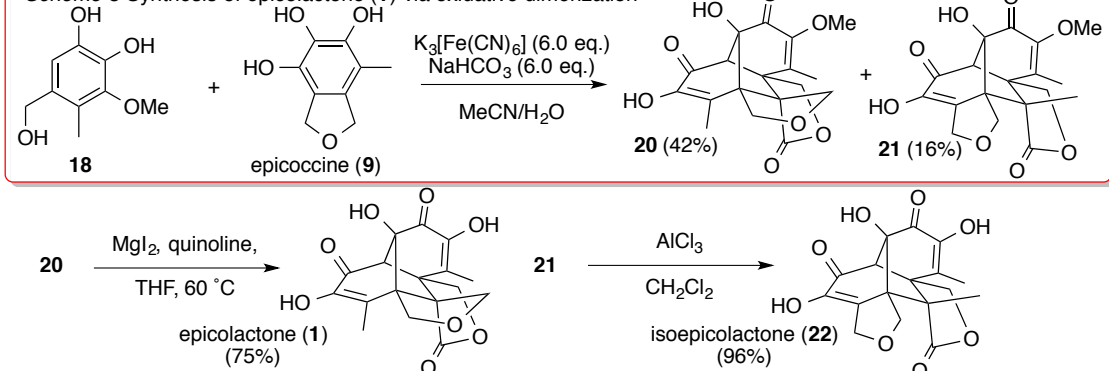
15→1: another intramolecular step completes the cascade to give epicolactone (1).

¹ S. M. Armstrong, T. R. Patel, *J. Basic Microbiol.* **1994**, *34*, 123-135.

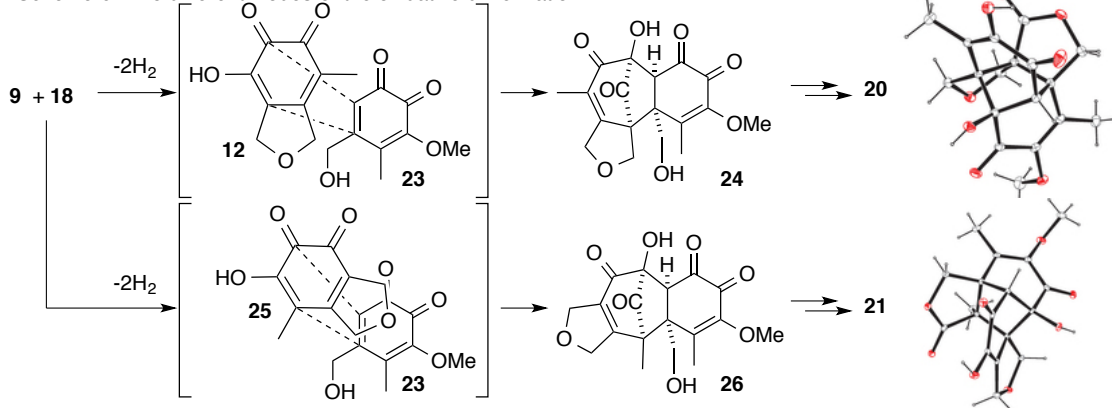
2-3 Synthesis of epicolactone

Scheme 4 Synthesis of epicoccine (10) (the authors' previous work³)

Scheme 5 Synthesis of epicolactone (1) via oxidative dimerization

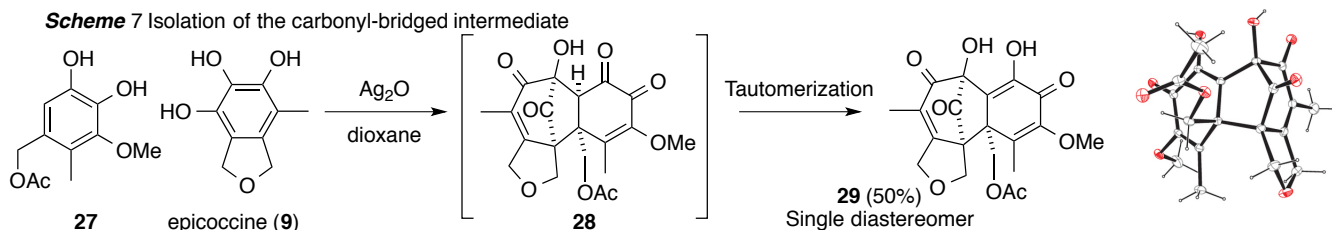


Scheme 6 Two different modes of the oxidative dimerization



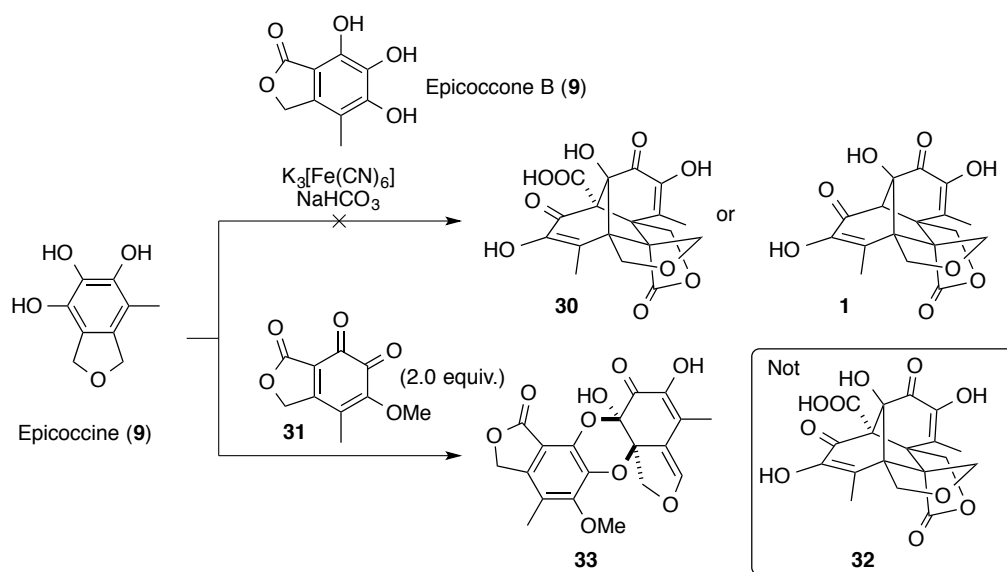
- Ether group was introduced to catechol **18**, which reduced the modes of dimerization.
- Two simple aromatic starting materials (**18**, **9**) were prepared via established protocol.
- Caged compound with five condensed rings and three contiguous quaternary carbons and a tertiary alcohol (**20**, **21**) was formed in a single chemical operation.
- Once the cycloaddition has taken place and carbonyl-bridged intermediate **24** was formed, all subsequent steps are all intramolecular, which overcomes enormous steric hinderance.

2-4 Isolation of the carbonyl-bridged intermediate



- When the primary alcohol was protected as an acetate (**27**), the intramolecular lactone formation was prevented and the carbonyl-bridged intermediate was obtained.
- Only one diastereomer was observed. This shows that the initial (5+2) cycloaddition is highly diastereoselective.

2-5 Failed approaches to the synthesis of epicolactone



Scheme 8 Failed approaches to the synthesis of epicolactone

- The addition of epicoccine (**10**) to epicoccone B (**9**) did not yield the anticipated product **30** or epicolactone (**1**).
- When epicoccine (**10**) was exposed to 2 equivalents of *o*-quinone **31**, partially methylated and oxidized version of epicoccone B (**9**), the intended adduct **32** was not obtained, but the hetero-Diels-Alder adduct **33** was observed.

3. Conclusion

- Epicolactone was synthesized in 8 steps from vanillyl alcohol via a biomimetic synthesis route.
- A key intermediate **29** that supports the authors' biosynthetic hypothesis was isolated.

4. Appendix

DDQ: 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, DIBAL: diisobutylaluminium hydride ,
TFA: trifluoroacetic acid