

Historically, how has the study of biosynthesis benefitted synthetic chemistry?

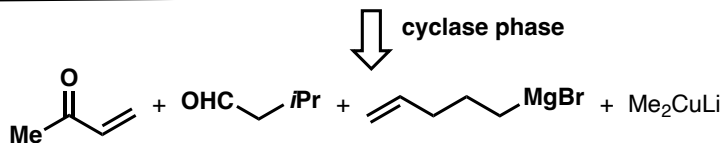
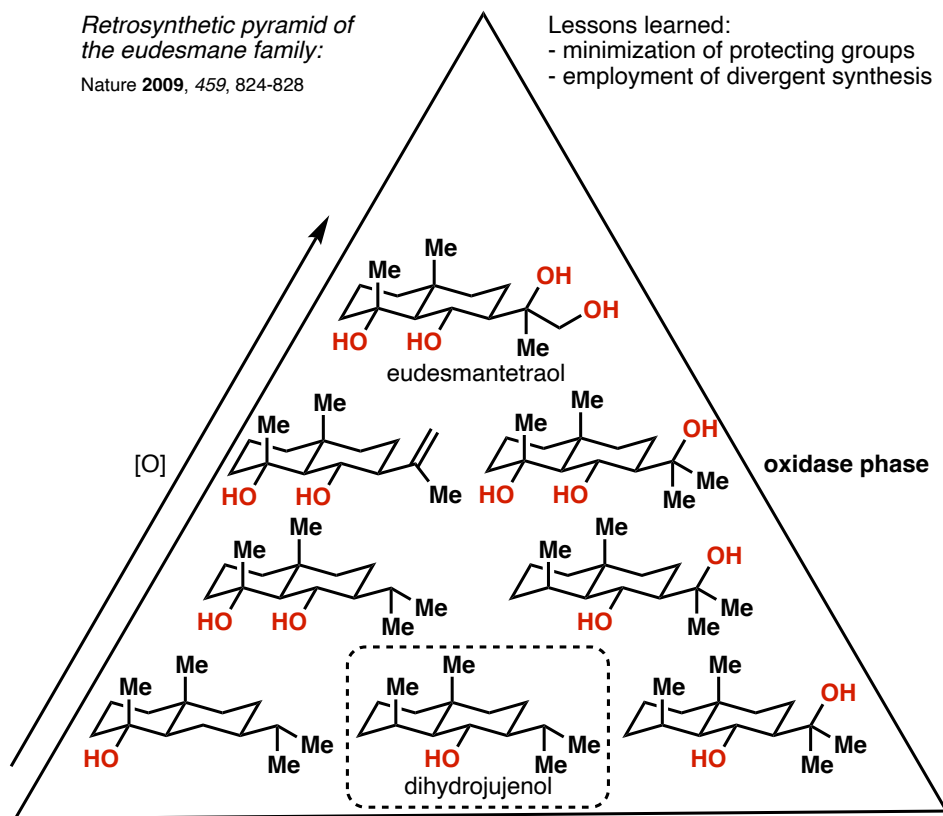
1. Driving innovation in chemical synthesis

Two-phase biosynthesis of terpenoids

- **Cyclase phase** (via cascade polyene cyclizations)
- **Oxidase phase** (late-stage, selective oxidations via oxidases)
- mimicked by C-H activation

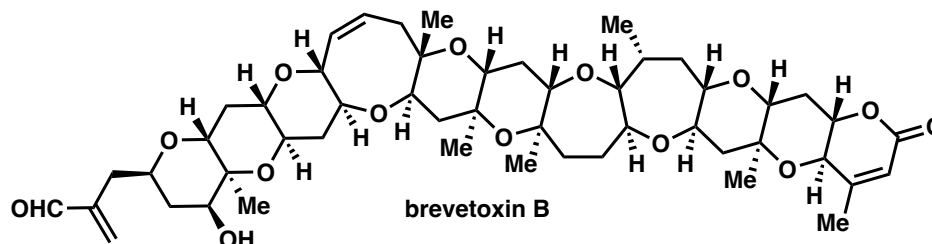
Retrosynthetic pyramid of the eudesmane family:

Nature **2009**, *459*, 824-828

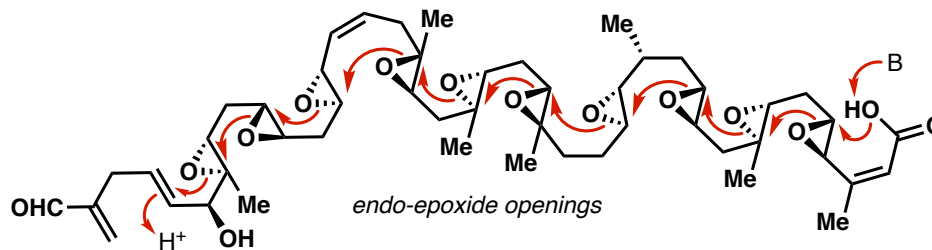


2. Overturning chemical "rules"

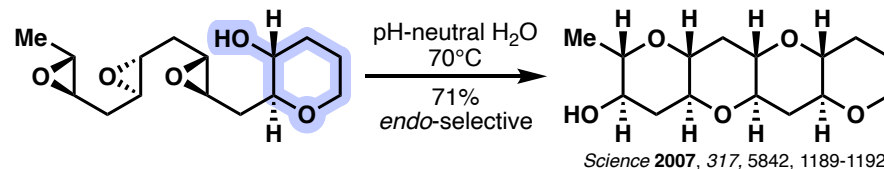
JACS **1989**, *111*, 6234-6241



proposed biosynthesis



- **Baldwin rules:** *exo* epoxide-opening products are kinetically favored
- The first biomimetic, contra-Baldwin cascade without the use of directing groups was developed by Jamison (template THF & neutral water promote *endo*-selectivity)



What to expect from this GM:

- Strategies for bond formation & cleavage
- Oxidative rearrangements
- General biosynthetic strategies (divergent synthesis)
- Miscellaneous structures (metal-containing NPs)
- Unresolved biosyntheses of curious structures

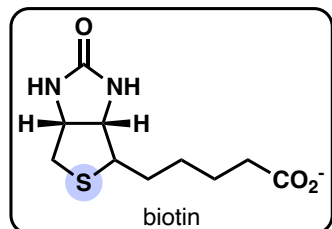
Relevant Baran GMs:

- Biocatalysis (Gulder, 2009)
- Nature's Catalysts: A Search for Synthetic Equivalents I (Rodriguez, 2010)

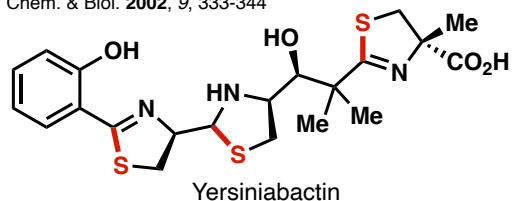
Useful resources:

- Natural Product Biosynthesis: Chemical Logic and Enzymatic Machinery, **2017**

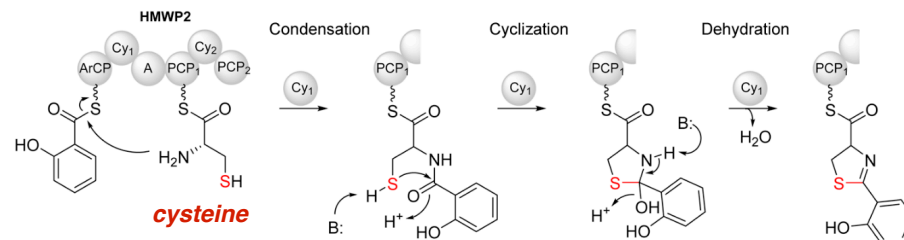
Bond formation: Sulfur insertion in biotin



Sulfur-incorporation often arises from amino acids
Chem. & Biol. 2002, 9, 333-344

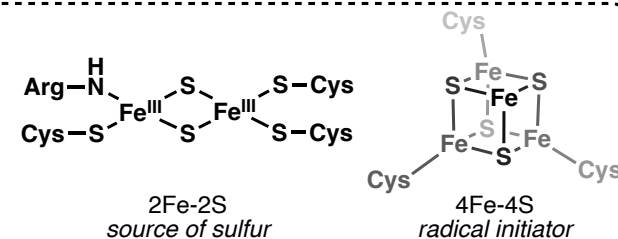


Mechanism of thiazoline biosynthesis (via NRPS assembly line): Chem. & Biol. 2002, 9, 333-344

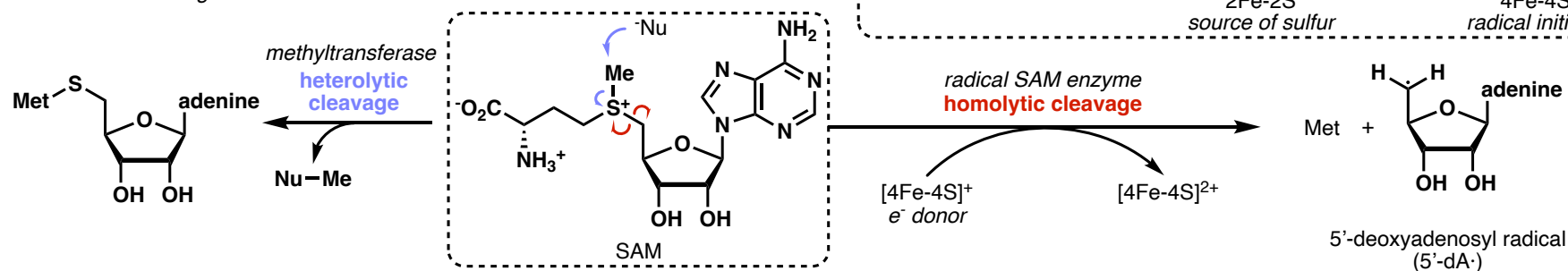


Biotin synthase is a radical S-adenosylmethionine (SAM) enzyme that performs sulfur insertion via iron-sulfur clusters

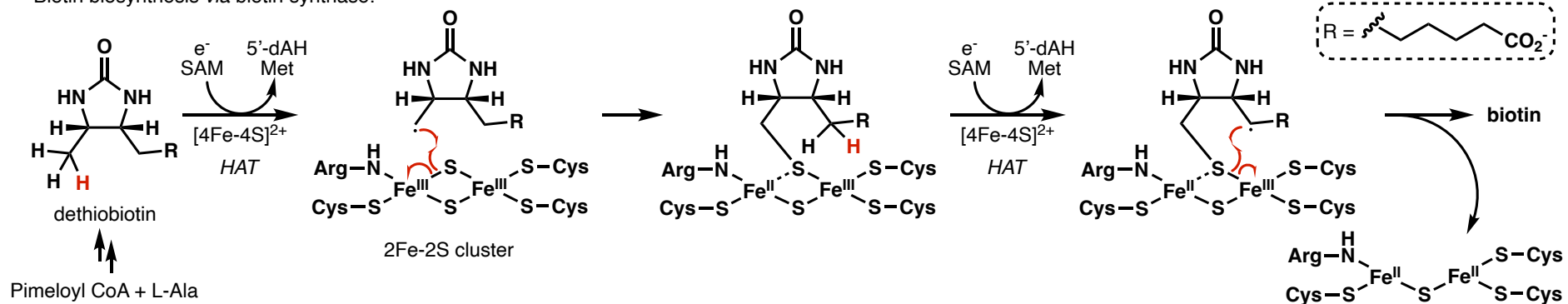
Iron-sulfur clusters are cofactors that commonly mediate electron transfer



Two modes of cleavage of SAM:



Biotin biosynthesis via biotin synthase:



Bond Formation: Nature's Strategies Towards N-N Bonds

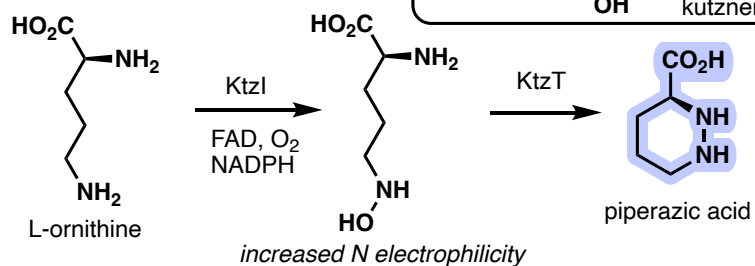
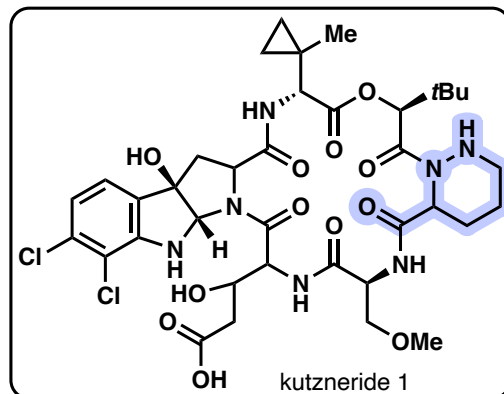
ACS Chem. Biol. 2021, 16, 559-570

Strategies:

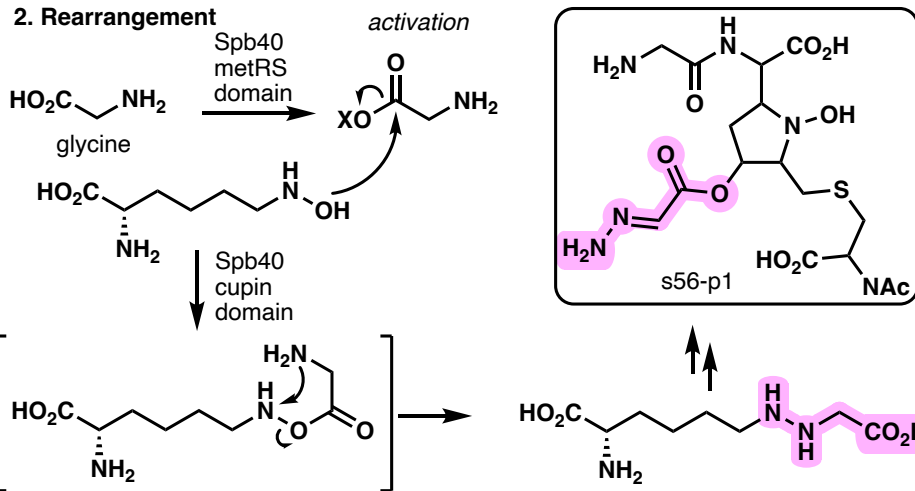
1. Comproportionation
2. Rearrangement
3. Radical Recombination

1. Comproportionation

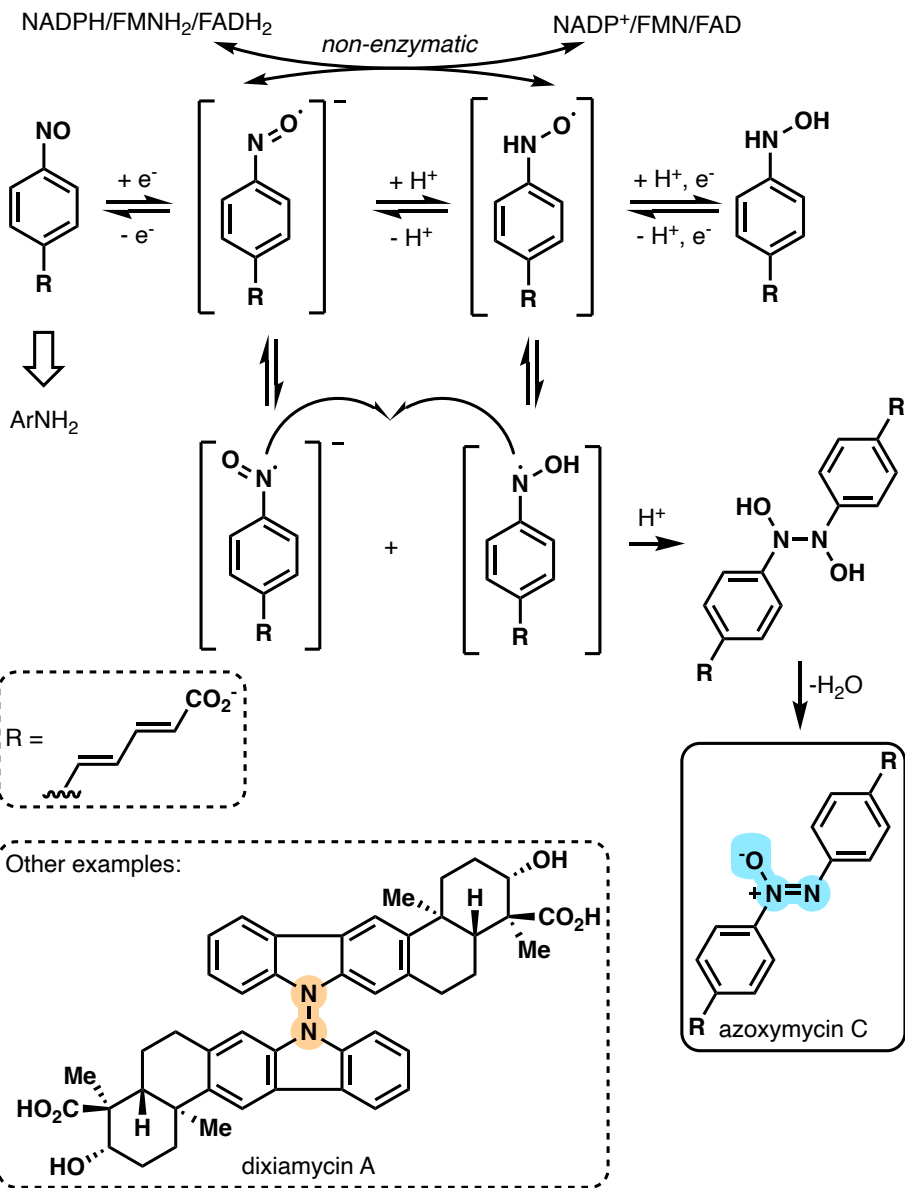
Kutzneride 1 biosynthesis
 - nonribosomal peptide synthase (NRPS) assembly line
 - piperazic acid (non-proteinogenic amino acid) as a building block



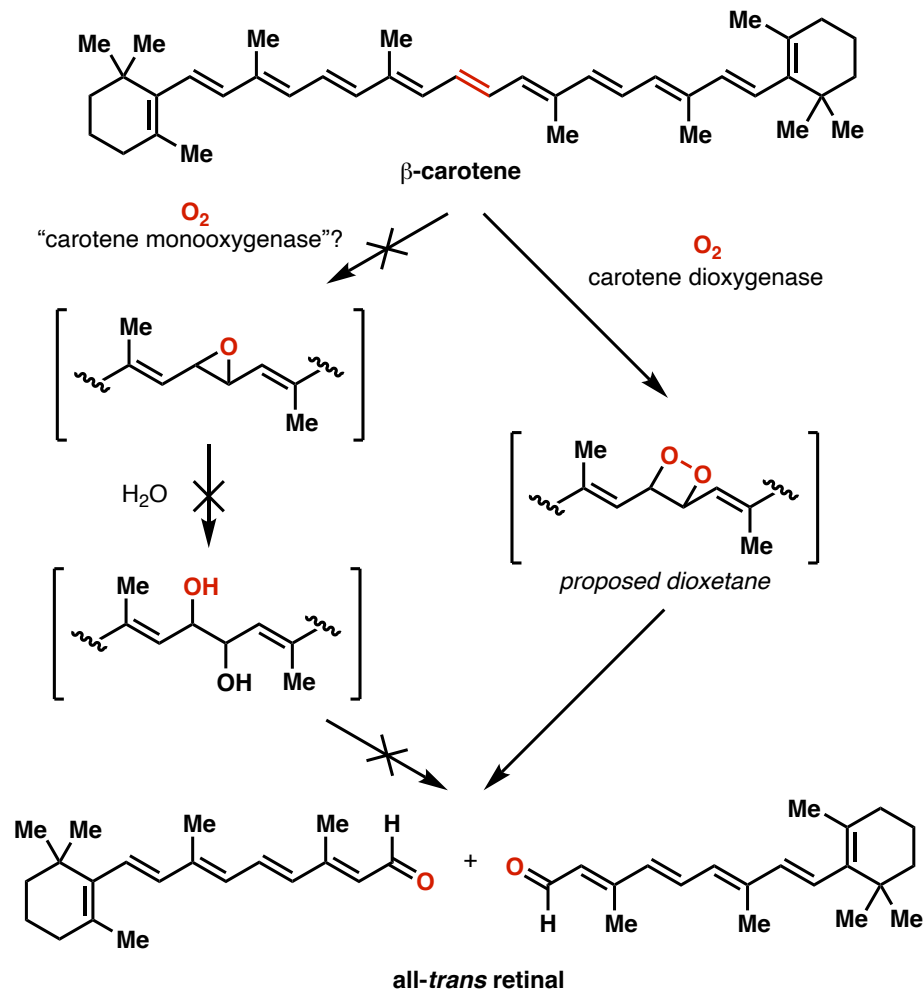
2. Rearrangement



3. Radical Recombination

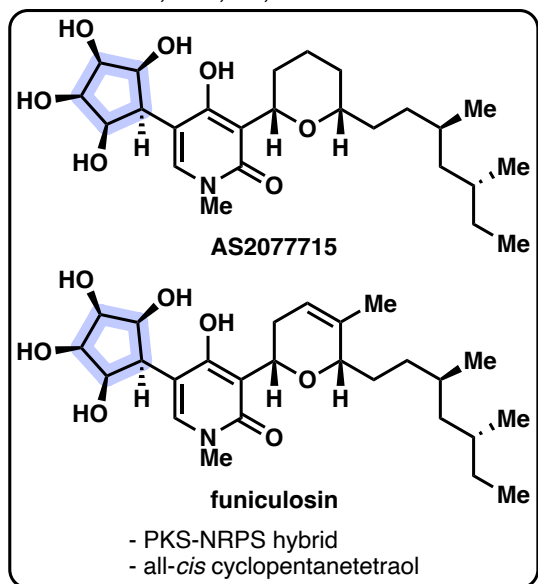
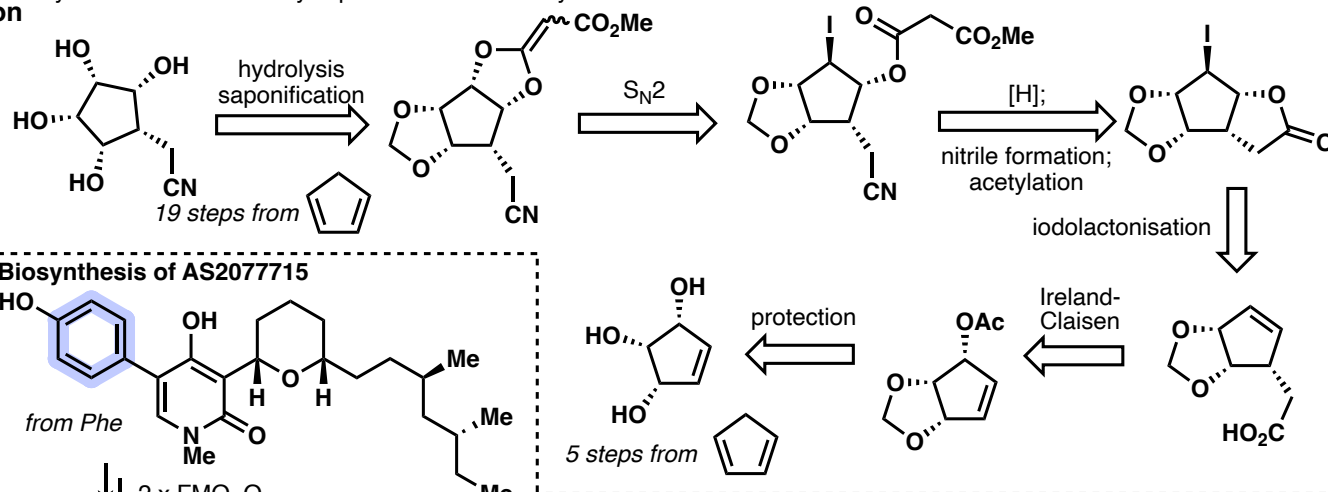


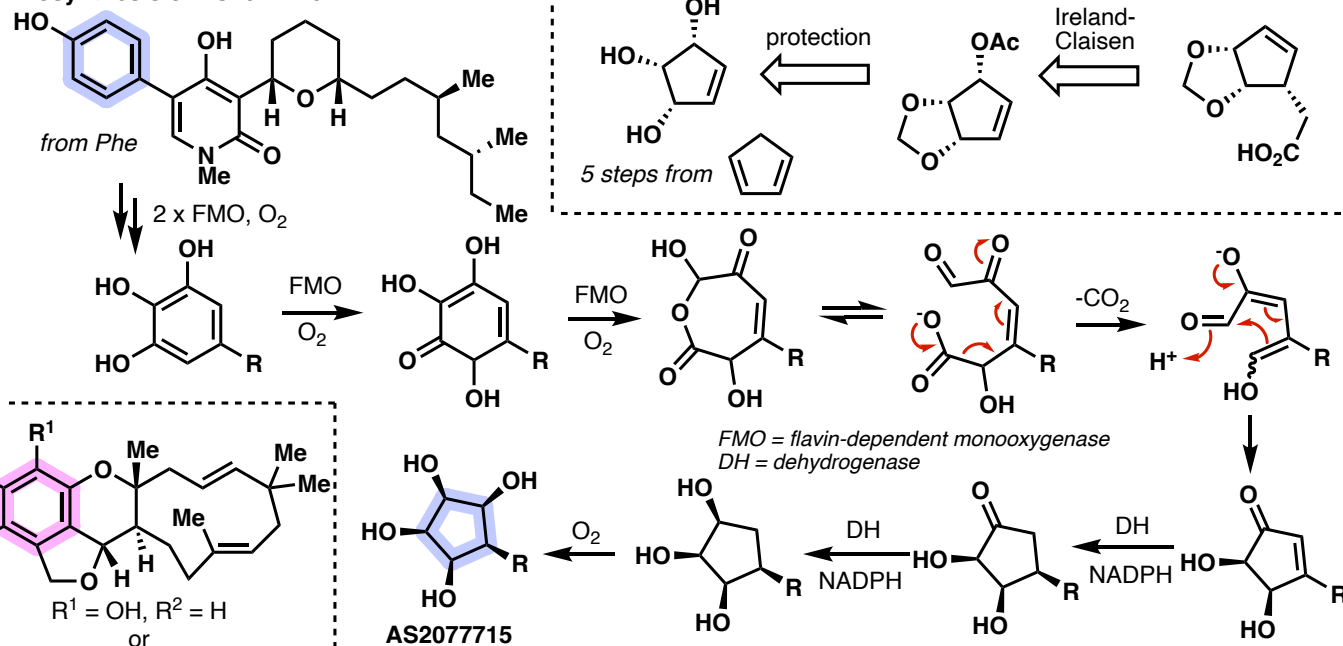
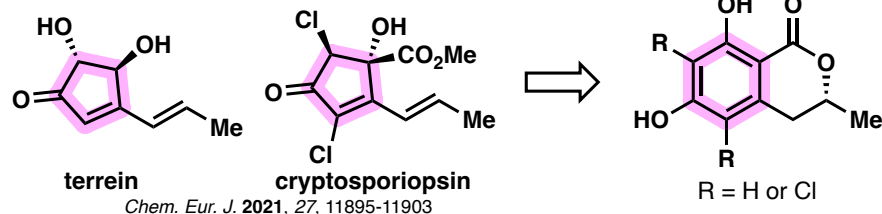
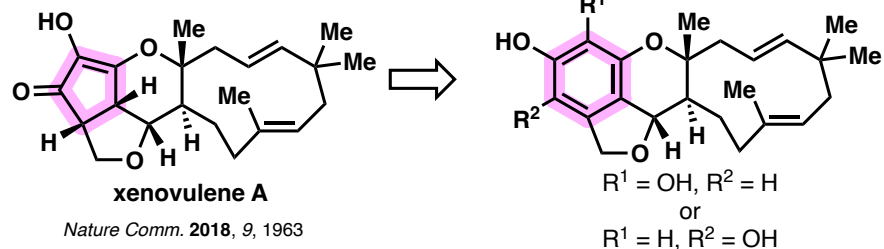
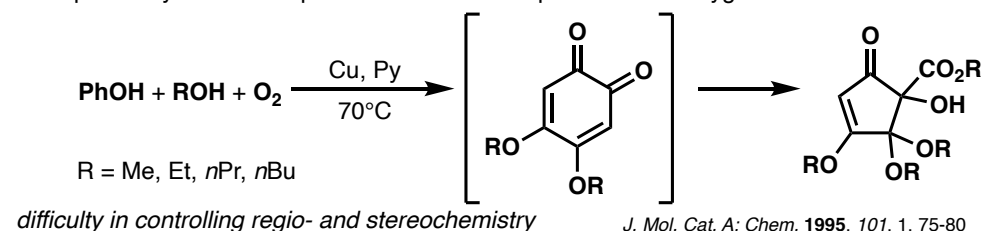
Oxidative Cleavage

J. Biol. Chem. 2014, 289, 19, 13661-13666

This section is intentionally left blank.

- carotene oxygenase was previously falsely named as a monooxygenase
- ^{18}O labelling studies: aldehydic oxygens in the retinal product pair derive from the same molecule of substrate O_2
- oxidative cleavage *via* dioxygenase logic
- methods in synthesis: $\text{OsO}_4/\text{NaIO}_4$, O_3 , photoexcited nitroarenes

Oxidative Dearomatization/Ring Contraction
JACS 2023, 145, 12, 6643–6647

Synthesis of the all-*cis* cyclopentanetetraol moiety

J. Chem. Soc., Perkin. Trans. 1 1992, 57-65

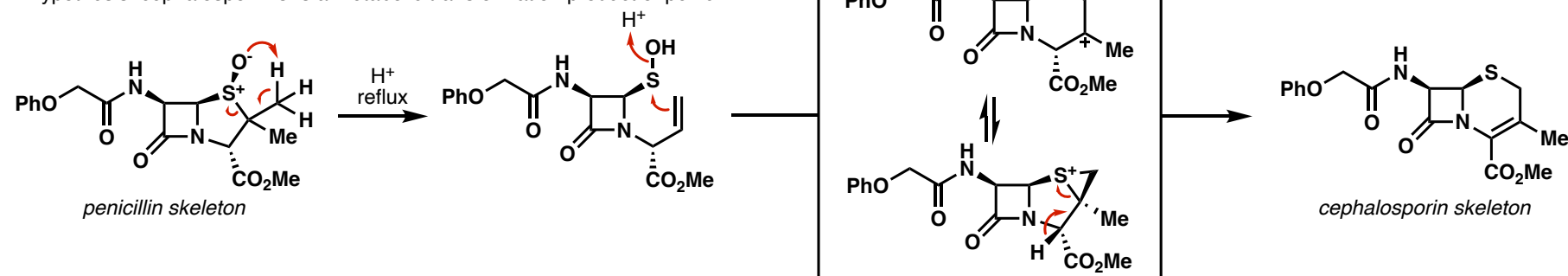
Biosynthesis of AS2077715

Examples in natural product biosynthesis

Examples in synthesis: Cu promoted oxidation of phenol with dioxygen


Oxidative Rearrangements: Ring Expansion in Cephalosporin C

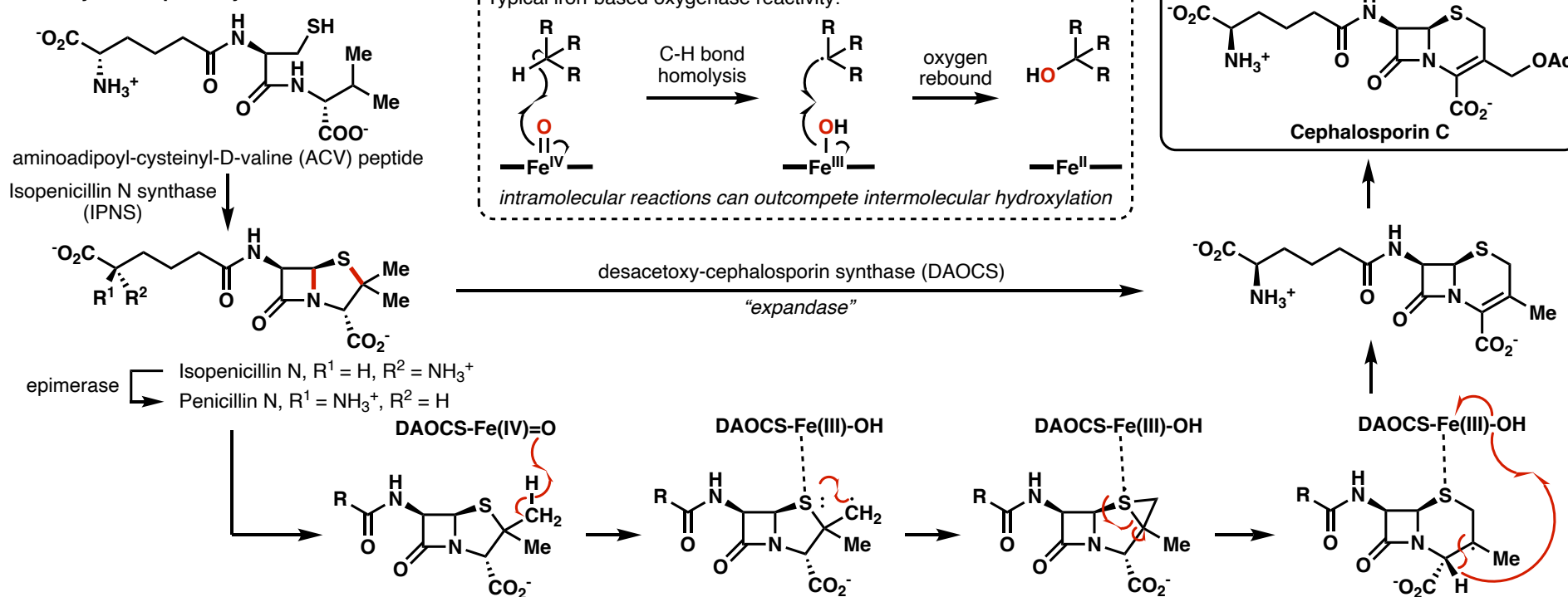
JACS 1963, 85, 12, 1896-1897
JACS 1969, 91, 6, 1401-1407

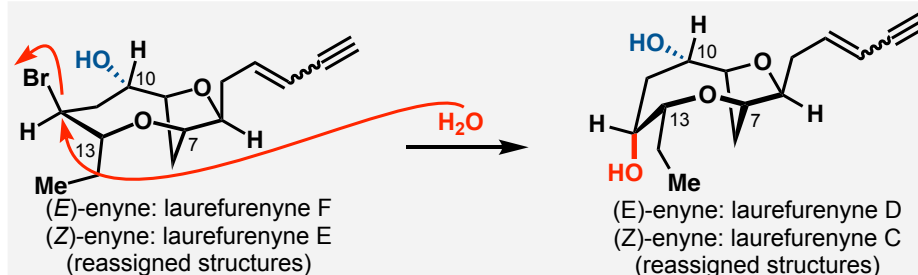
Synthesis of Cephalosporin skeleton (Lilly)

- Hypothesis: cephalosporin C is a metabolic transformation product of penicillin N

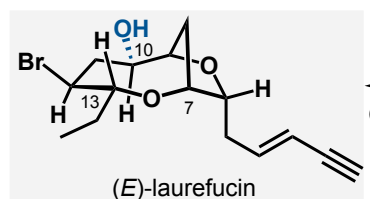
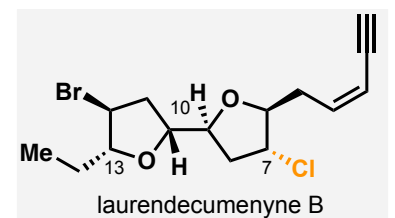
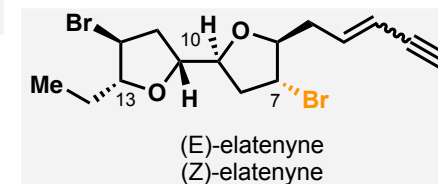
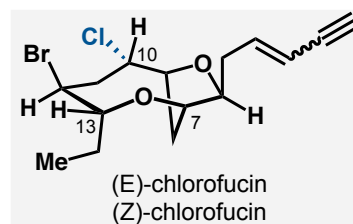
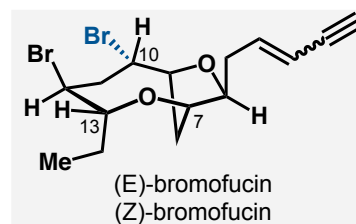
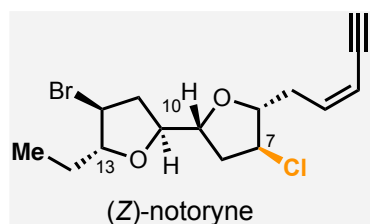


Biosynthetic pathway

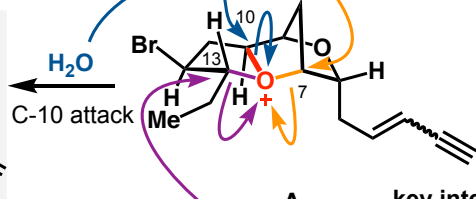


Divergent Biosynthesis: Oxonium Ions as Key Intermediates in *Laurencia* Natural Products

C₁₅ halogenated ether acetogenins
 - polyketide origin, isolated from red algae of the genus *Laurencia*
 - trialkyloxonium ions proposed with chemical evidence as key intermediates
 - trialkyloxonium ions are susceptible to rapid hydrolysis and typically do not participate in biological processes, in contrast to trialkylsulfonium ions

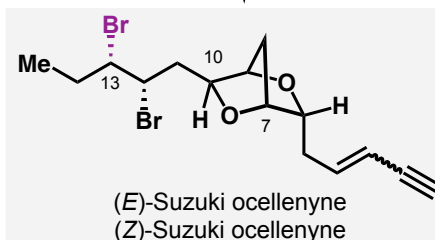


C-7 attack
C-10 attack

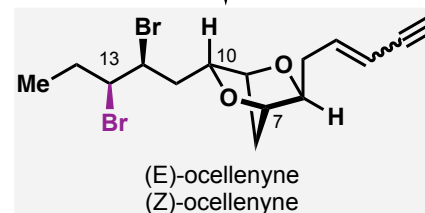


key intermediates

C-13 attack

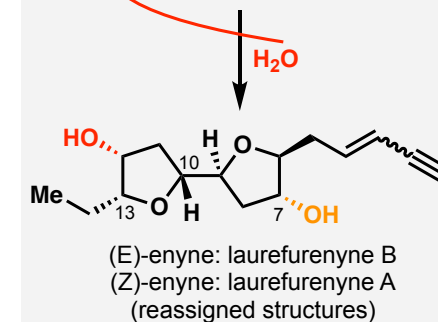
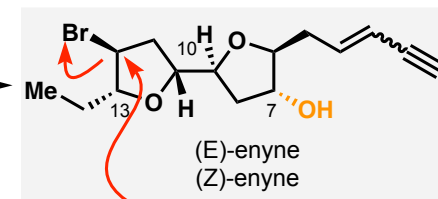


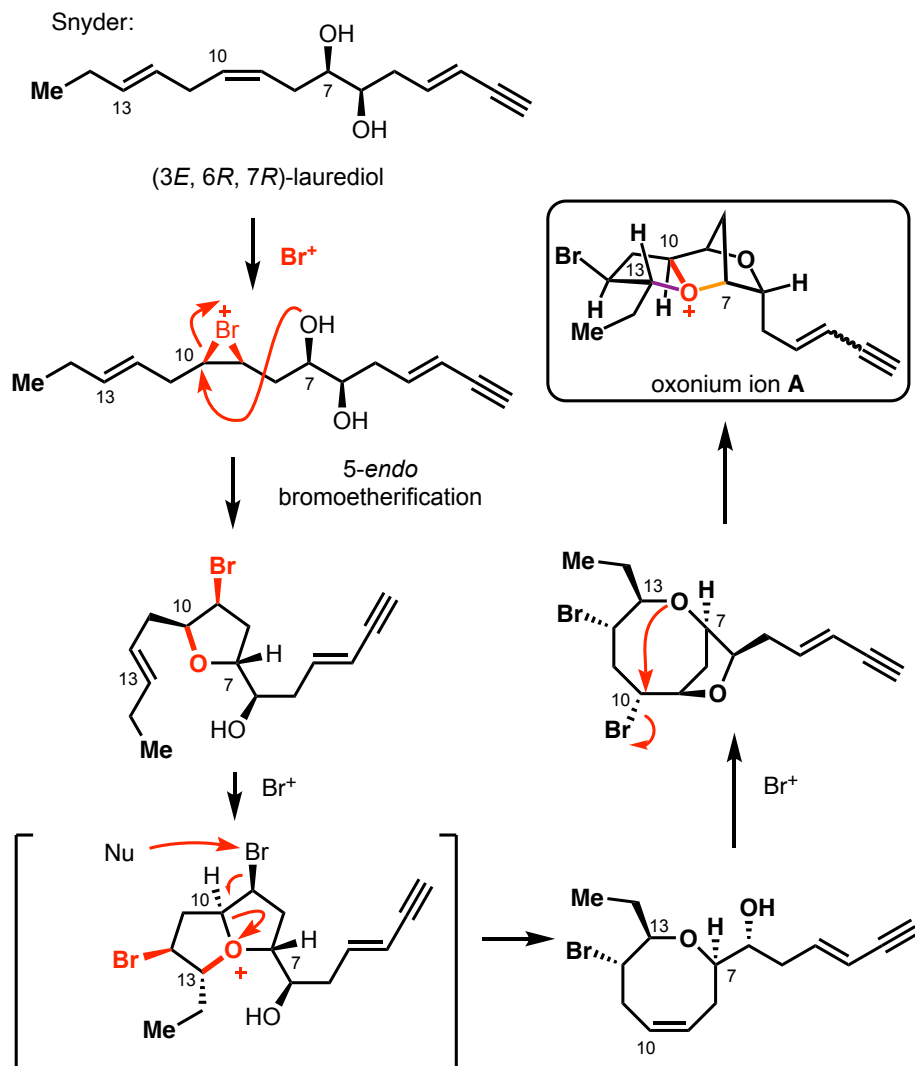
C-13 attack



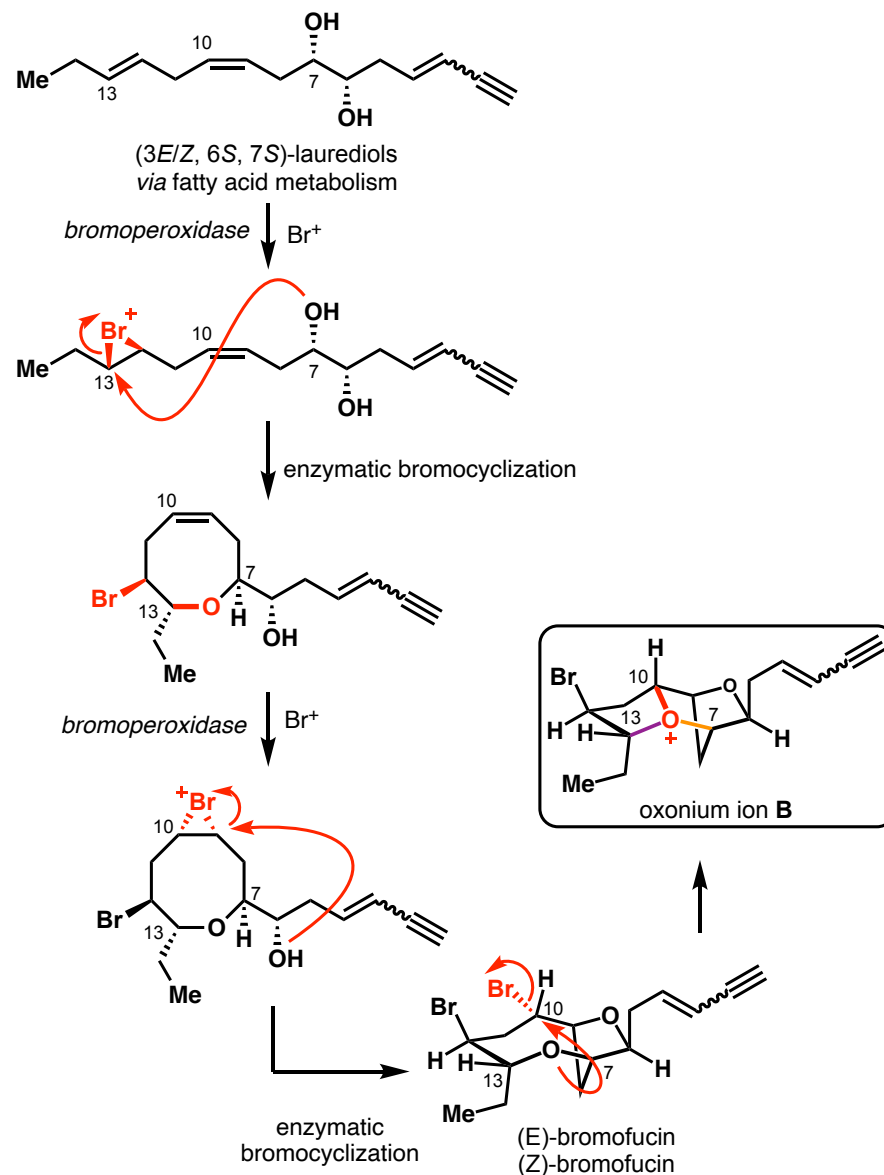
H₂O, Cl⁻, Br⁻

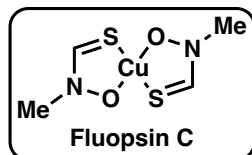
H₂O, Cl⁻, Br⁻
C-7 attack



Biosynthetic Proposals Towards Key Oxonium Ion Intermediates in *Laurencia* Natural Products

Murai & Suzuki:

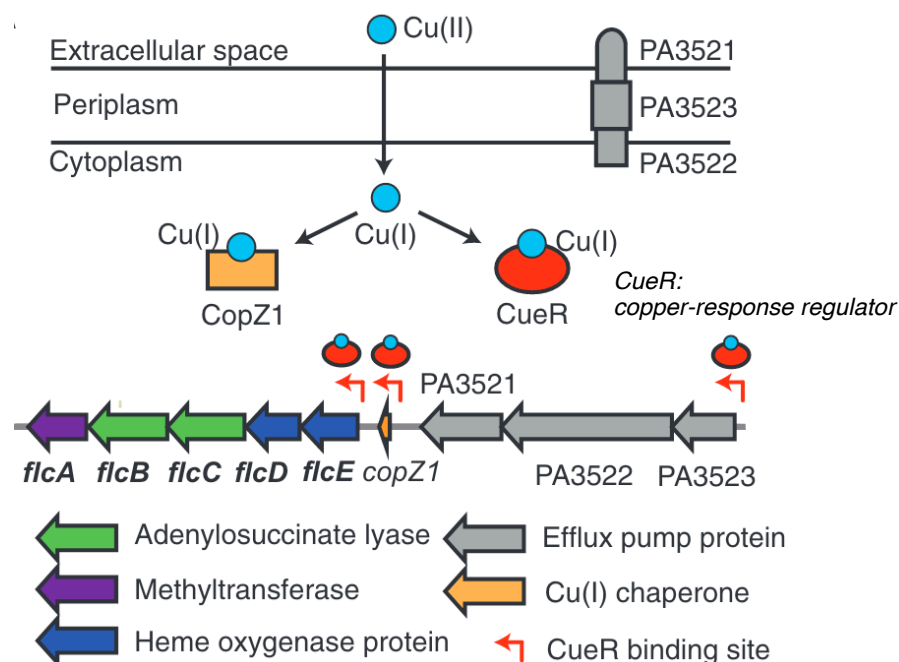
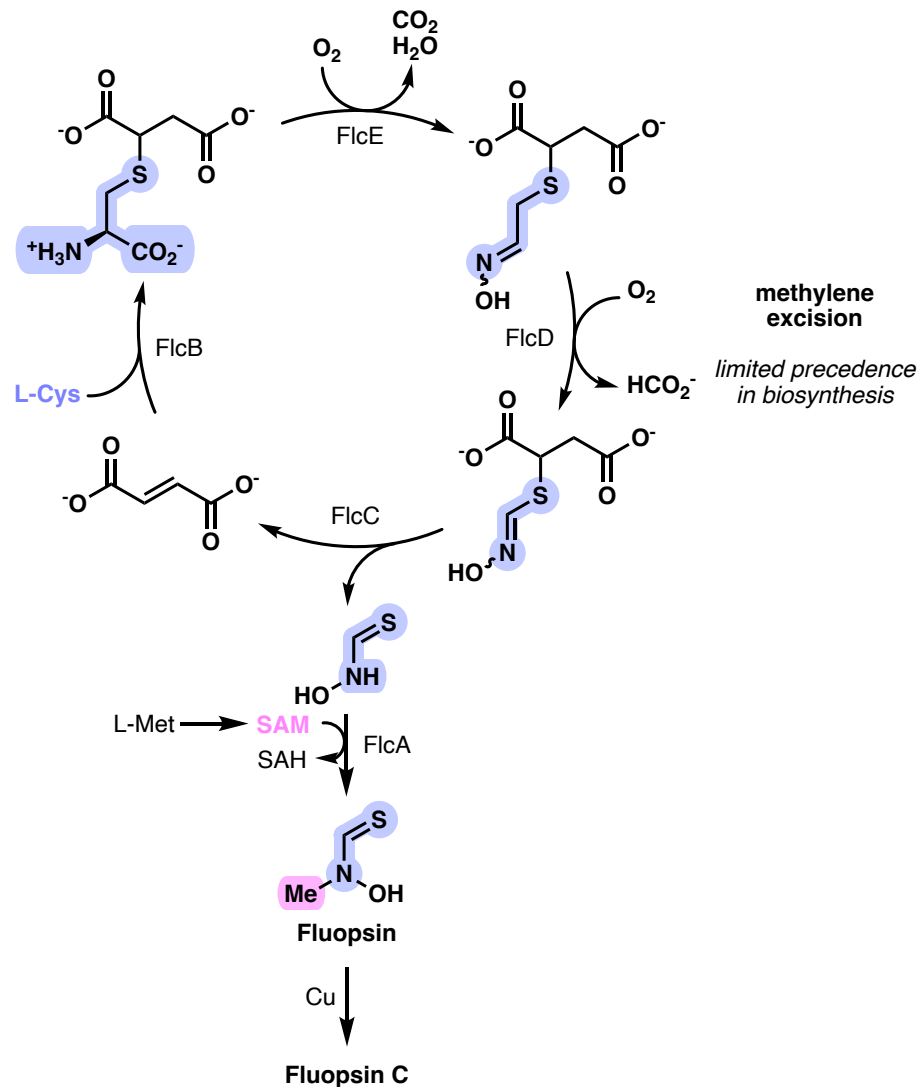


Metal-containing Antibiotics*Science* 2021, 374, 1005-1009**Fluopsin C**

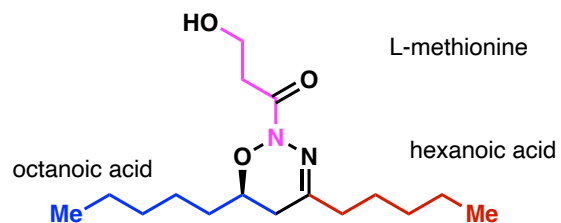
- Cu(II) complex containing 2 N-methylthiohydroxamate ligands
- Discovered in bacterium *Pseudomonas aeruginosa*
 - found in soil, water & on human skin
 - responsible for many dangerous infections for the immunocompromised
- Antimicrobial activity & cytotoxicity against mammalian cells & whole animals

Biological background

- Cu is utilized by bacterial immune cells as a bactericide to poison invading microbes
- Copper resistance and detoxification is essential for the bacteria
- Cu-chelating compounds facilitate Cu import or detoxification in the cytoplasm

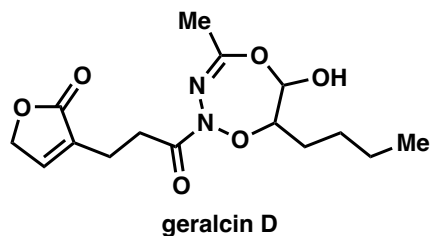
**Biosynthesis of Fluopsin C:**

Unresolved Biosyntheses



nocuolin A *ACS Chem. Biol.* **2022**, *17*, 2528-2537

- 1,2,3-oxadiazine (yet to be accessed synthetically)
- 1,3,4- and 1,2,4-oxadiazines have been prepared by chemical synthesis



geralcin D

J. Nat. Prod. **2013**, *76*, 2, 142-149

This section is intentionally left blank.