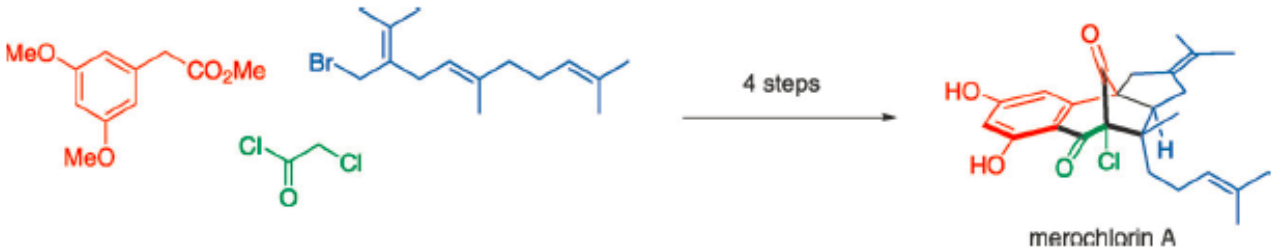
Biomimetic Synthesis | **Hot Paper**



Biomimetic total synthesis of (±)-merochlorin A

Pepper, H.P.; George, J.H. *Angew. Chem. Int. Ed.* ASAP

I. Gorokhovik – 31.10.2013

Isolation, activity, structure

- Meroterpenoid = mixed polyketide and terpenoid.

4 members.

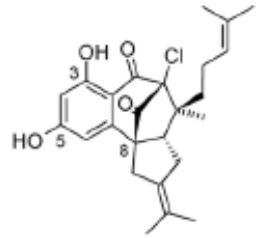
- Isolated from marine bacterium strain *Streptomyces* near California.

- Antibiotic activity against methicilline-resistant

Staphylococcus aureus MIC = 2-4 µg/mL

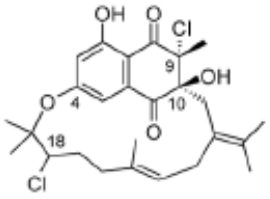
Clostridium difficile MIC = 0.15 µg/mL

- Mechanism of action unknown.

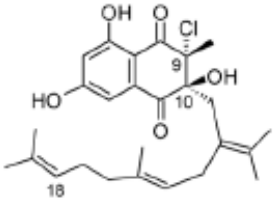


merochlorin A (**1**)

merochlorin B (**2**)



merochlorin C (**3**)

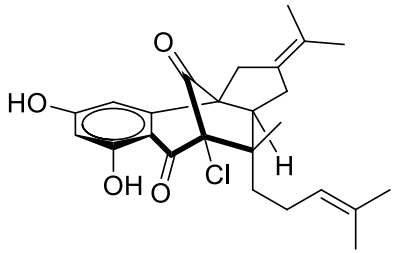


merochlorin D (**4**)

Kaysser, L.; Bernhardt, P.; Nam, S.-J.; Loesgen, S.; Ruby, J.G.; Skewes-Cox, P.; Jensen, P.R.; Fenical, W.; Moore, B.S. *J. Am. Chem. Soc.* **2012**, *134,* 11988-11991.

Isolation, activity, structure

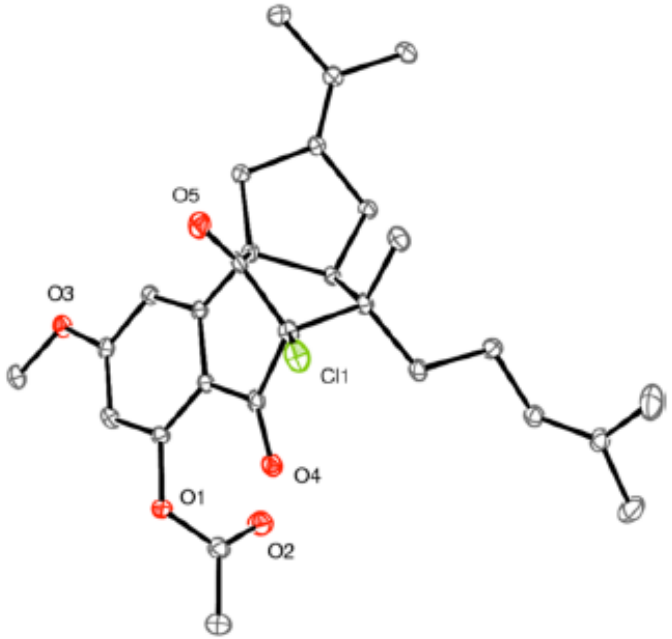
- Novel chemical skeleton unrelated to known bacterial agents.

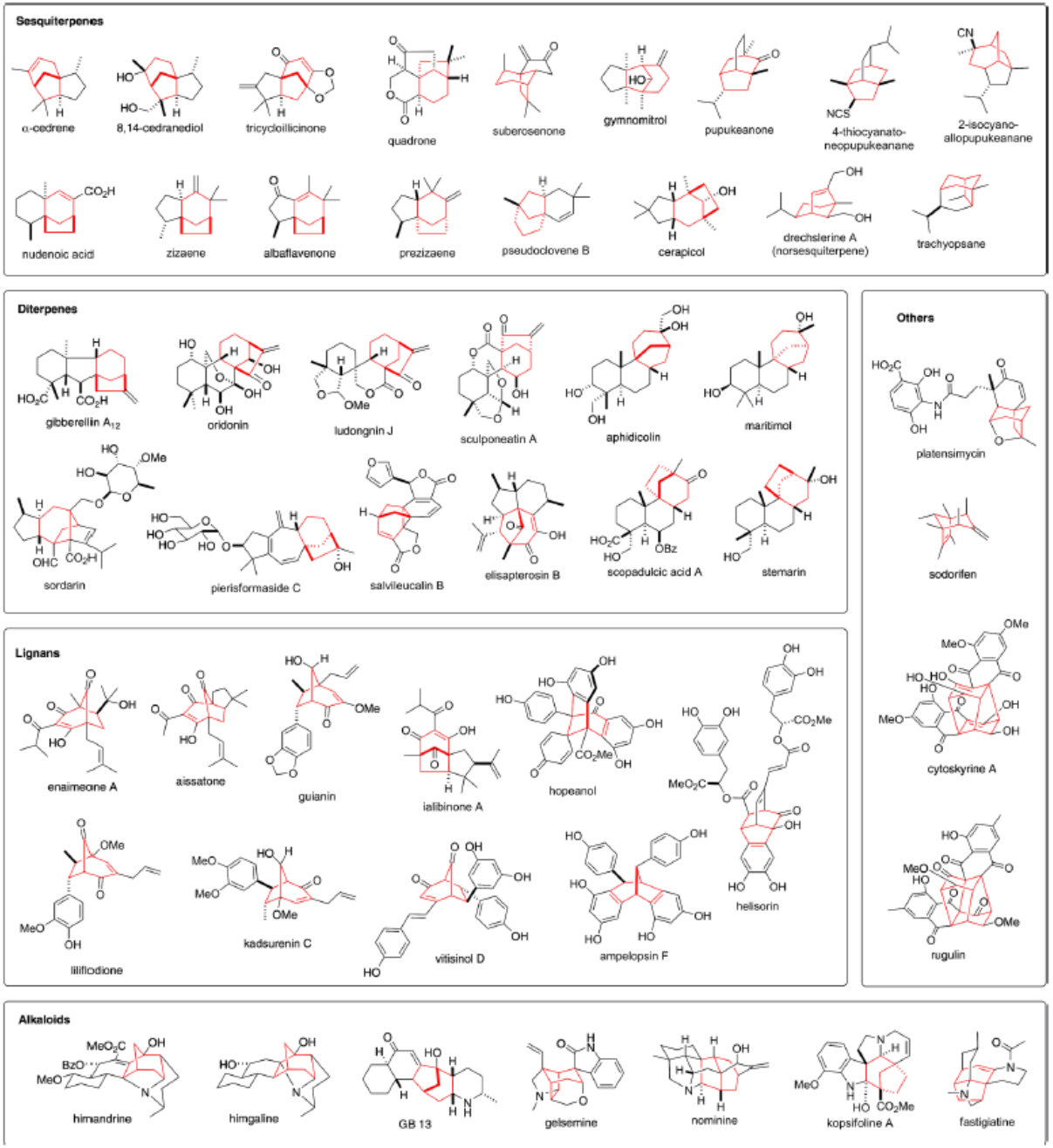


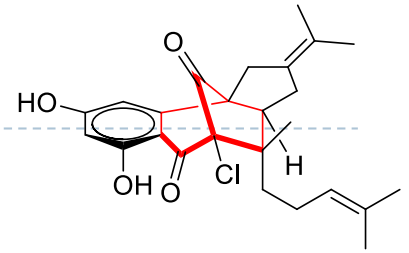
- Structure determined by NMR experiments, but 2 centers' configuration corrected by X-ray.

- Bicyclo[3.2.1]octanone core with

4 contiguous centers, 3 of which are quaternary.



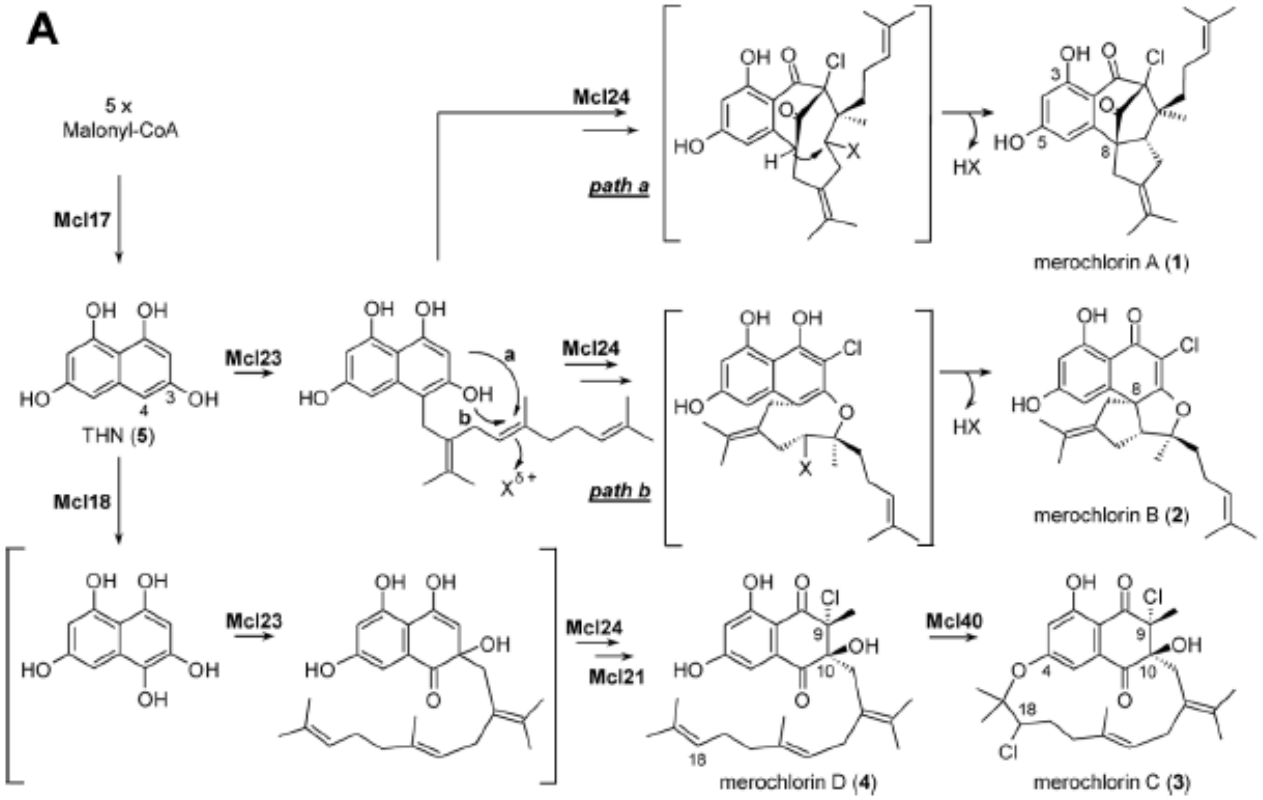




Presset, M.; Coquerel, Y.; Rodriguez, *J. Chem. Rev.*, **2013**, *113*, 525-595.

Biosynthesis by Fenical and Moore

DNA sequencing and mutations to identify genes/enzymes involved in the biosynthesis.



Mcl23: prenyl trasferase
Mcl24: vanadium-dependent haloperoxidase

Path a,b:
2 divergent cyclizations

Mcl18: oxidase

«Highly speculative»

1 gene cluster : 4 metabolites

Kaysser, L.; Bernhardt, P.; Nam, S.-J.; Loesgen, S.; Ruby, J.G.; Skewes-Cox, P.; Jensen, P.R.; Fenical, W.; Moore, B.S. *J. Am. Chem. Soc.* **2012**, *134,* 11988-11991.

Biosynthesis by George

- Same strating point

prenylation by **Mcl23**

- Then chlorination by **Mcl24**

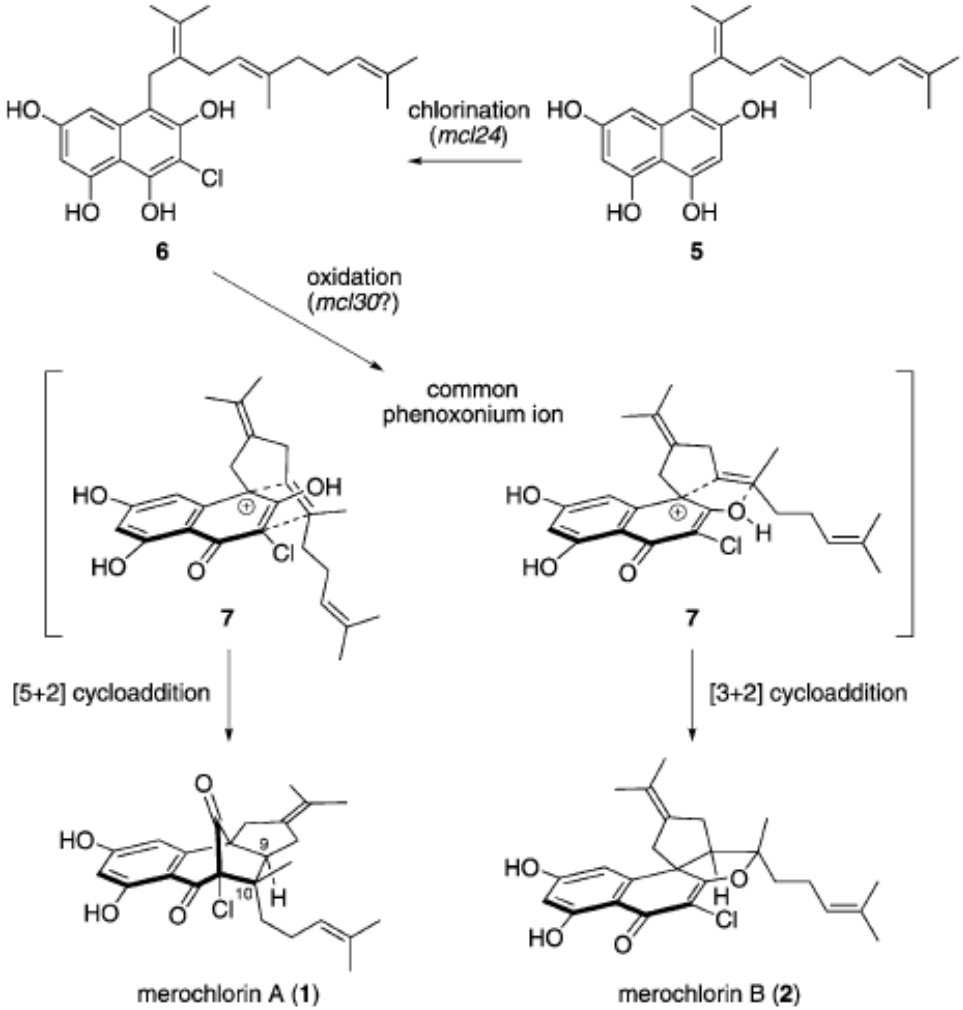
⟹ Common intermediate

- Oxidative dearromatization by **Mcl3**

(protein containing Fe-S cluster)

- 2 possible cycloadditions initiated,

probable stepwise mechanism.



Total synthesis by George

Biomimetic approach :

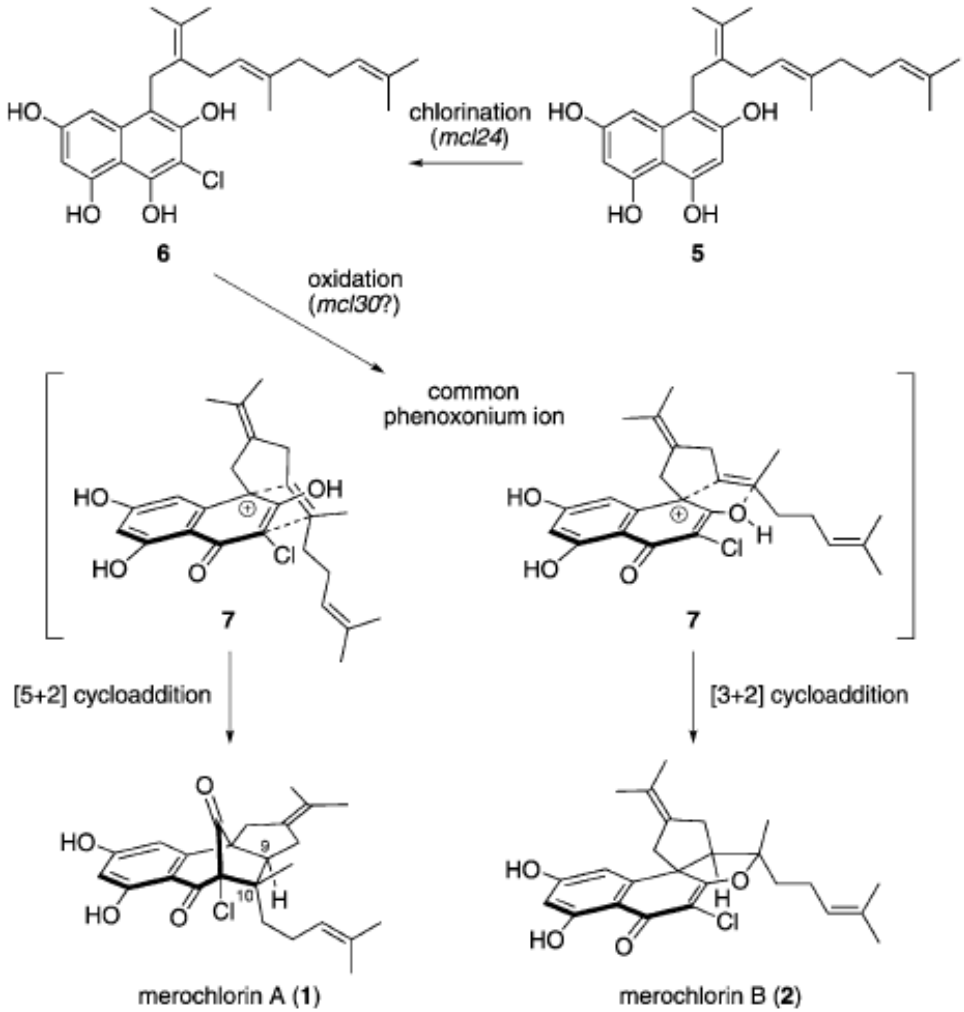
- Rapid installation of molecular

architecture

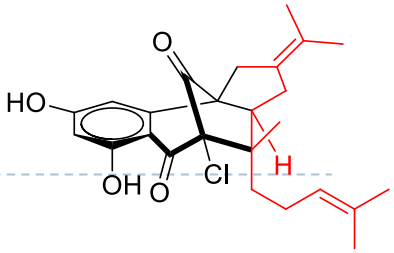
- Minimal protecting group manipulations
- Minimal functional group interconversions

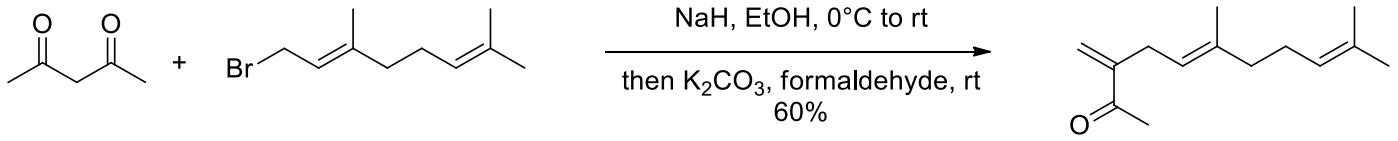
Retrosynthesis :

Alkylation, chlorination and oxidative cyclization.

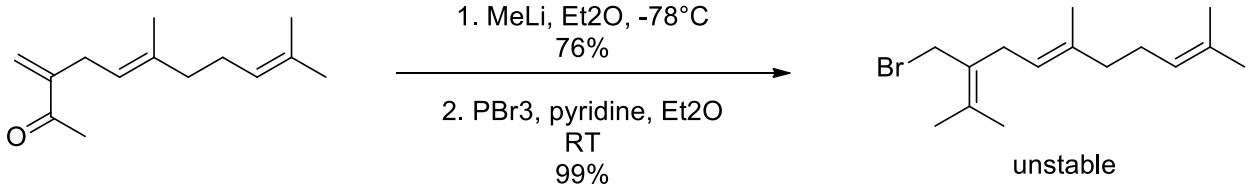


Total synthesis by George



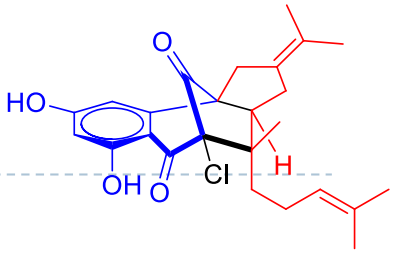


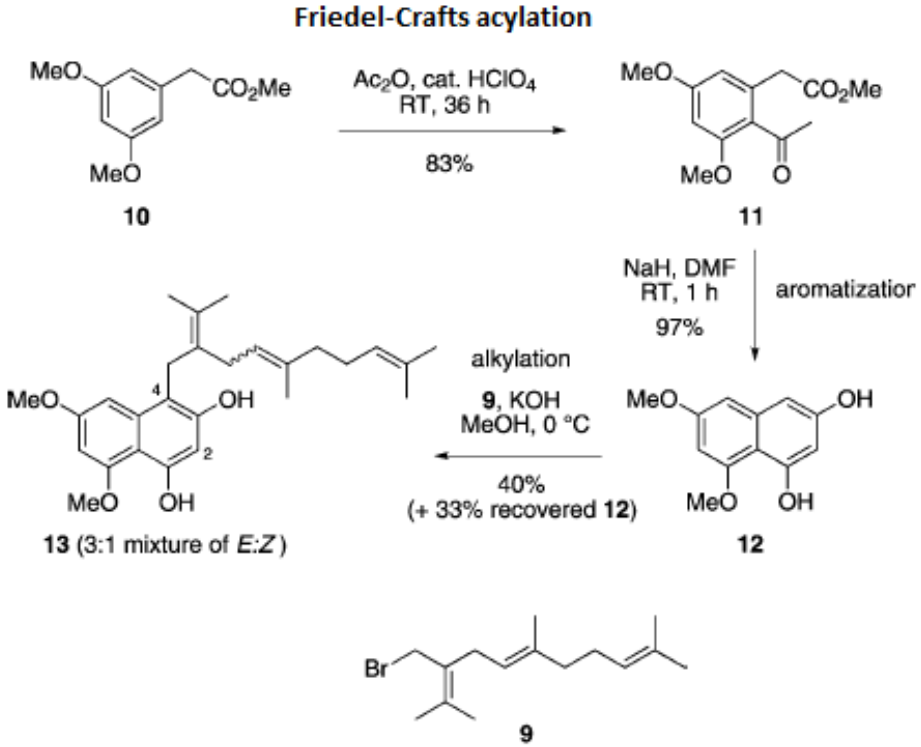
"alkylation-deacetylating aldol-type methylenation"



Biber, N.; Möws, K.; Plietker, B. *Nat. Chem.* **2011**, *3*, 938-942. Qi, J.; Beeler, A.B.; Zhang, Q.; Porco, Jr. J.A. *J. Am. Chem. Soc.* **2010**, *132*, 13642-13644.

Total synthesis by George

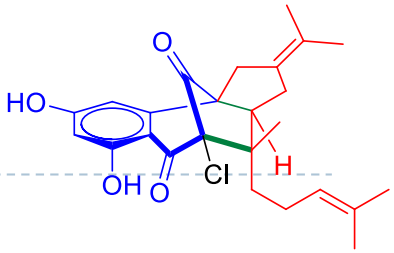


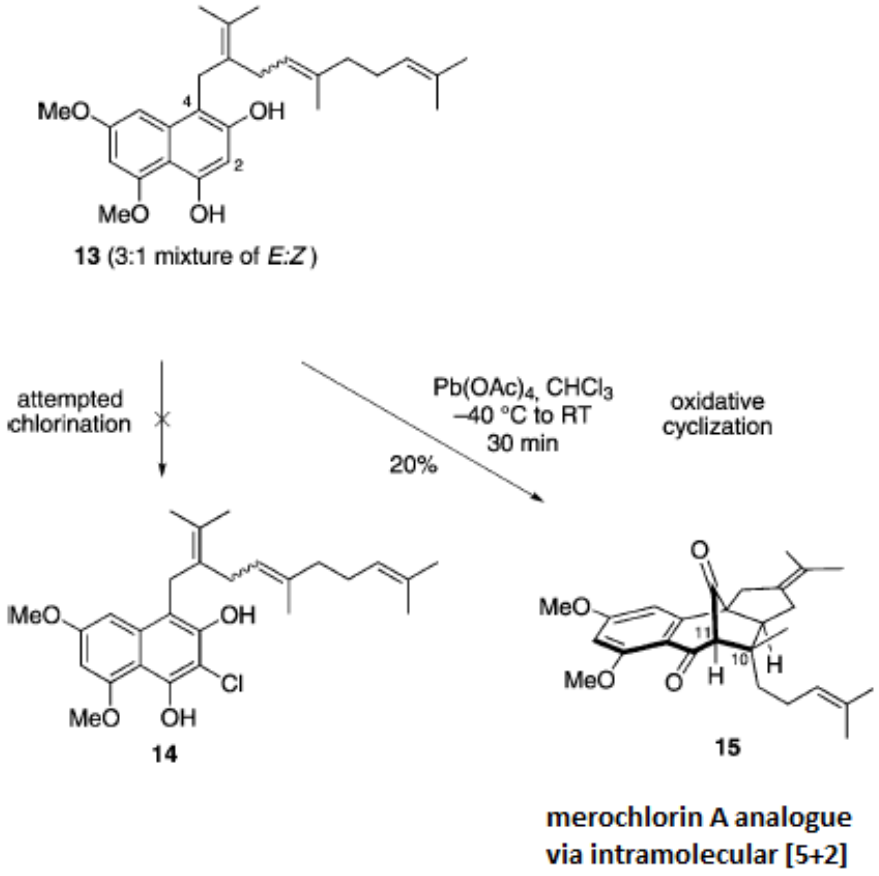


Alkylation

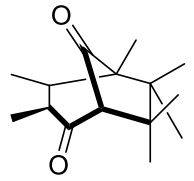
- Good 4-selectivity
- Efforts to drive the reaction further delivered 2-alkylated side product.
- «unusual partial isomerization» delivered 3:1 mixture

Total synthesis by George

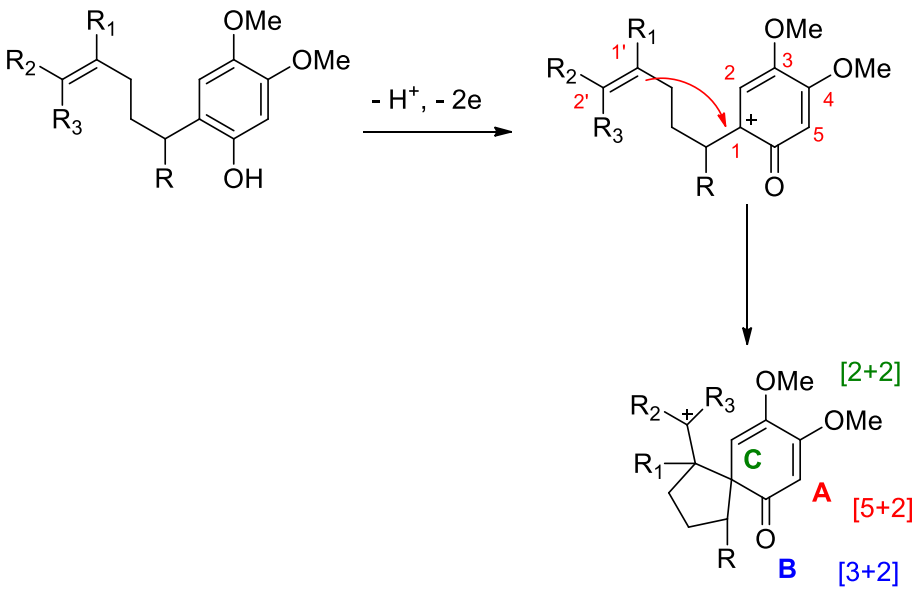


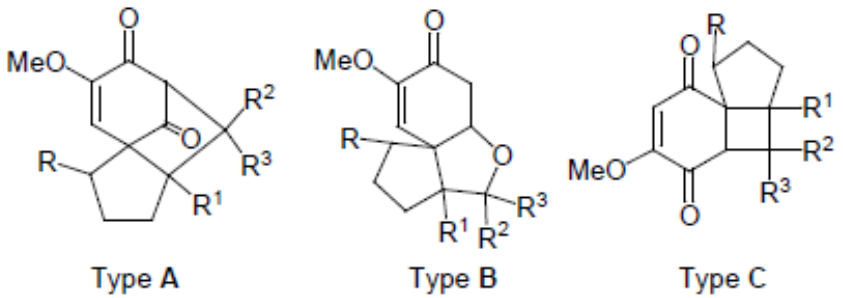


Oxidative dearomatization – [5+2] cycloaddition



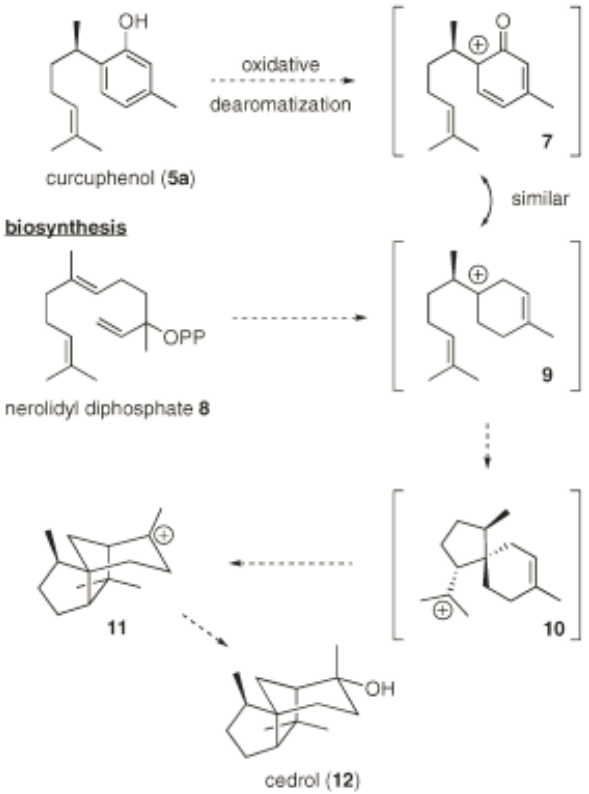
- Method commonly used for bicyclo-[3.2.1]octanone core.





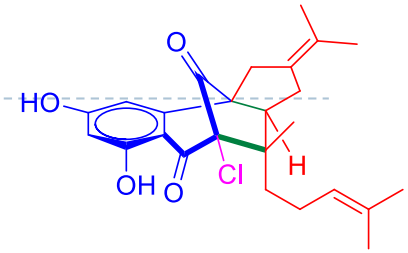
- $Pb(OAc)_4$ already used by Pettus et al.

Scheme 1. Biosynthetically Inspired [5 + 2] Cycloaddition

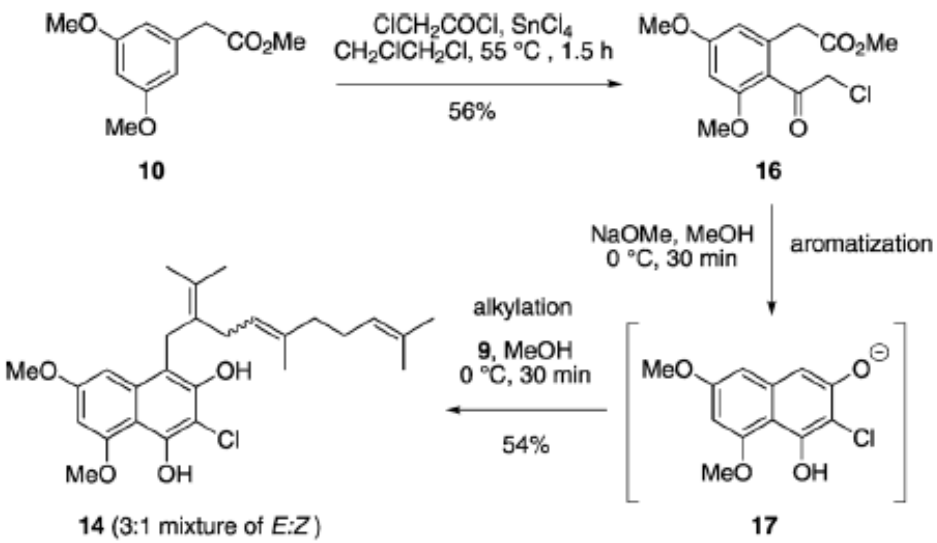


Green, J.C.; Pettus, T.R.R. *J. Am. Chem. Soc.* **2011**, *133*, 1603-1608. Yamamura, S.; Nishiyama, S. *Synlett,* **2002**, 533.

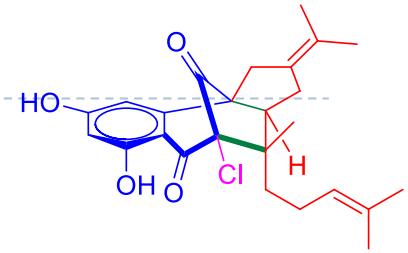
Total synthesis by George



Chlorine introduced earlier. Same strategy.

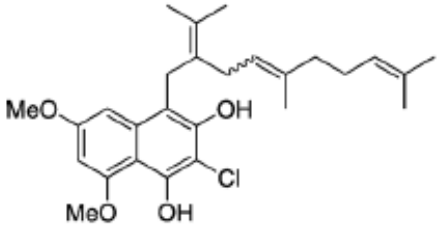


Total synthesis by George

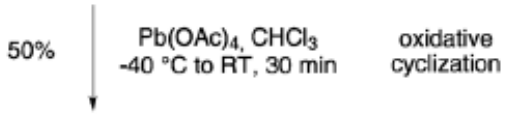


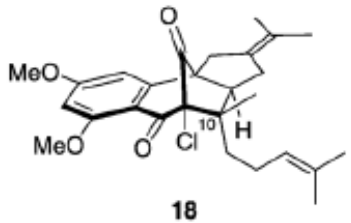
- Oxidation-cycloaddition cascade :
- 2 C-C bonds formation (green)
- 2 rings formation
- 4 contiguous stereocenters formation.
- 2 all-carbon stereocenters formation.

Biosynthesis ?



14 (3:1 mixture of *E*:*Z*)





18

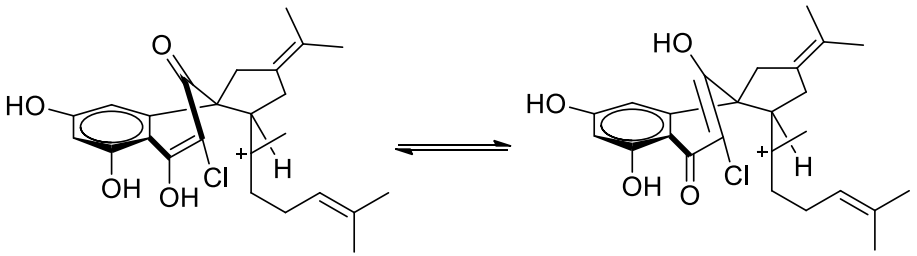
- I diastereoisomer formed from mixture

Nonconcerted [5+2] – tertiary carbocation intermediate.

Formation of sterically favored – most stable diastereisomer.

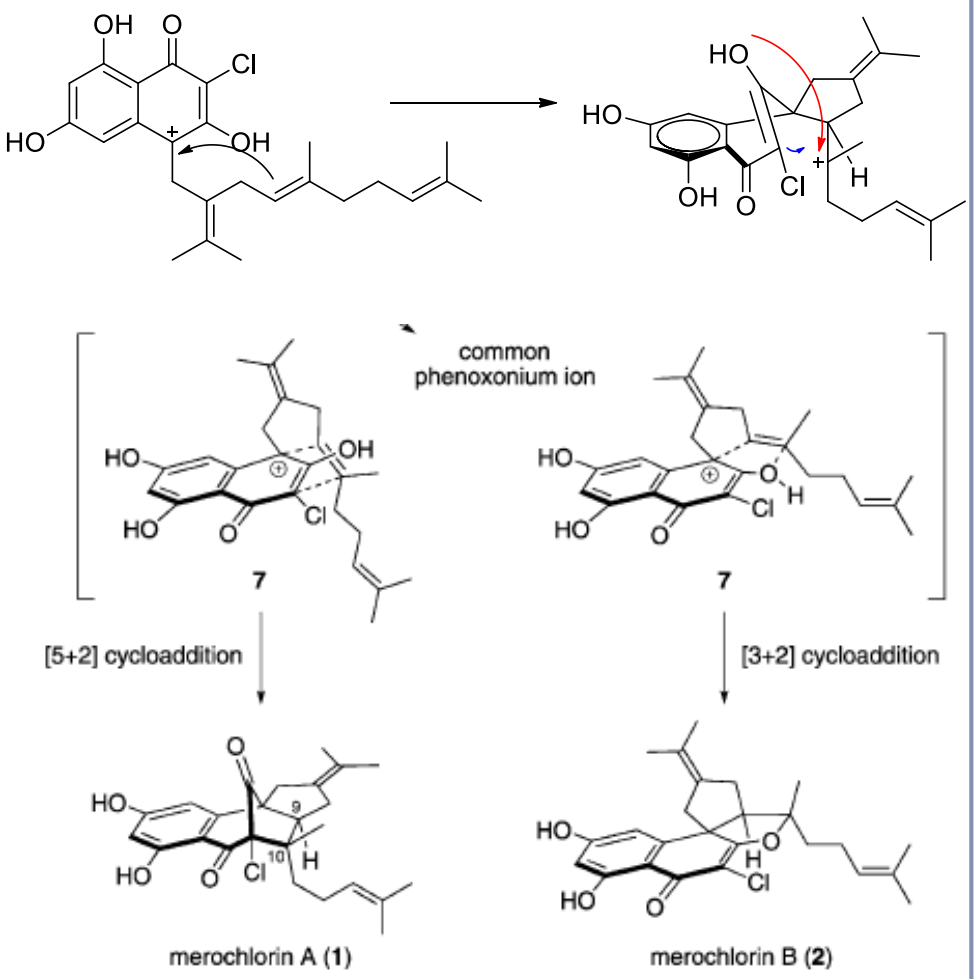
- Yield better than without Cl (20%).
- No merochlorin B formed by [3+2]

via

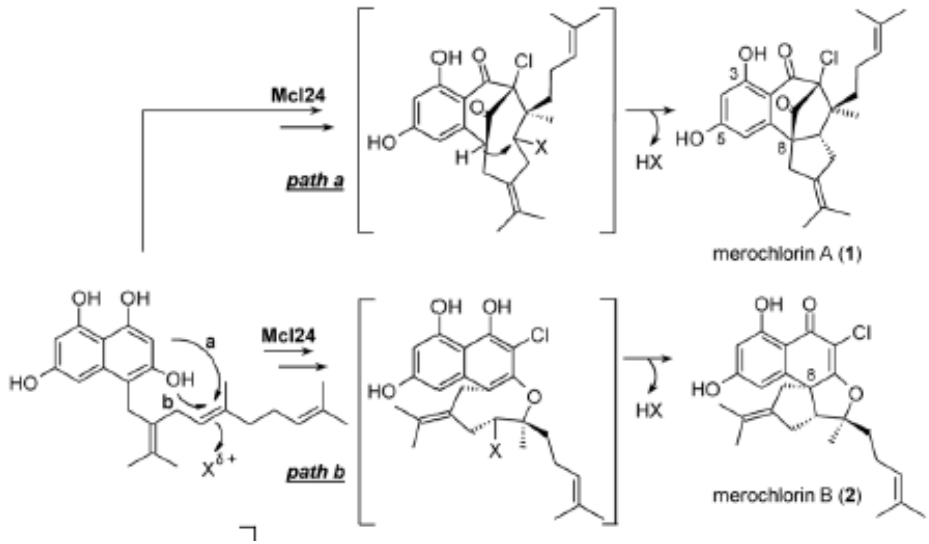


Proposed biosyntheses

- George

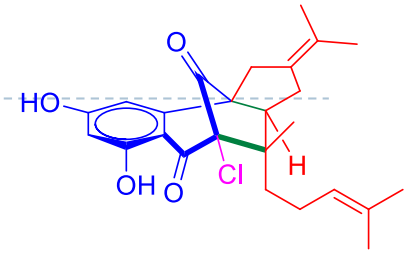


- Fenical and Moore

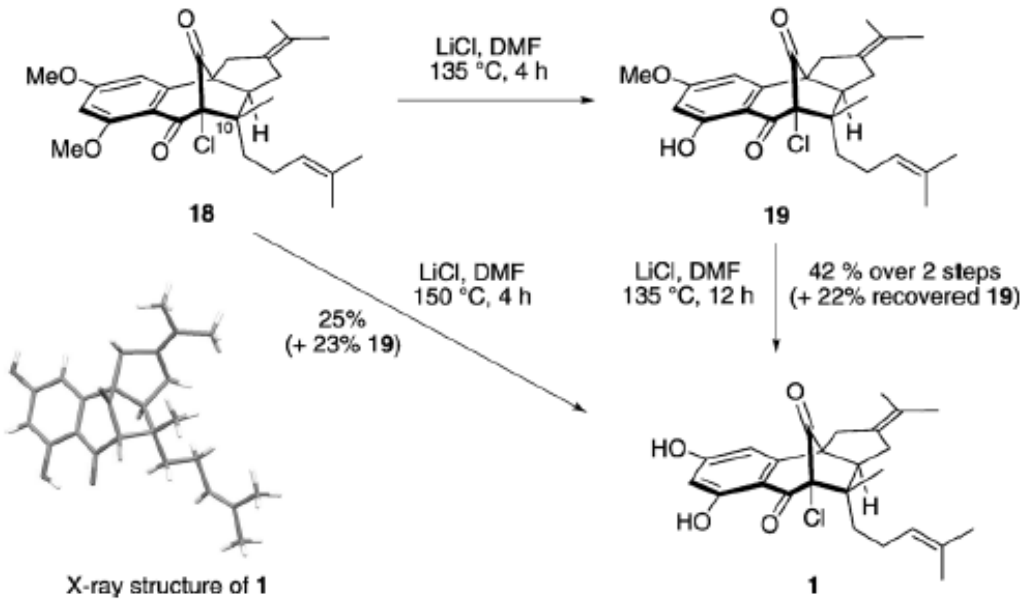


Kaysser, L.; Bernhardt, P.; Nam, S.-J.; Loesgen, S.; Ruby, J.G.; Skewes-Cox, P.; Jensen, P.R.; Fenical, W.; Moore, B.S. *J. Am. Chem. Soc.* **2012**, *134,* 11988-11991.

Total synthesis by George

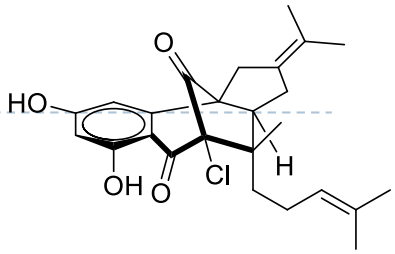


Methoxy deprotection. Compound unstable to Lewis acids.



Second demethylation hindered by phenolate :
Inetermediate workup.

Conclusion



Racemic synthesis.
Rapid generation of analogues possible
Scalable synthesis : 1g of merochlorin A obtained.

4-step synthesis.
Key steps : aromatozation, alkylation, oxidative cyclization, based on biosynthesis proposal.