

Strategies for the Total Syntheses of Dimeric Natural Products

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27Apr2021

Symmetry of Dimeric Natural Products

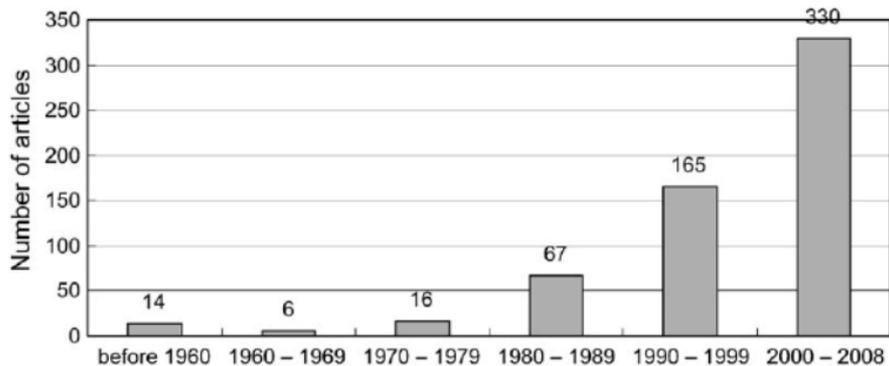
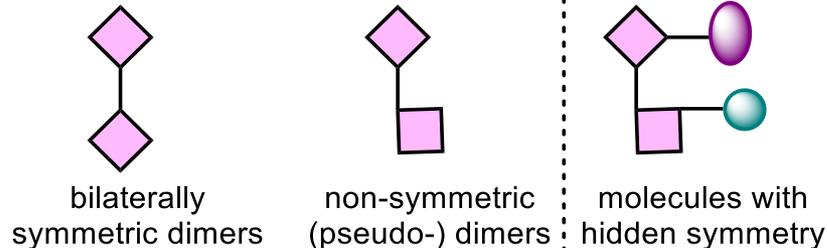


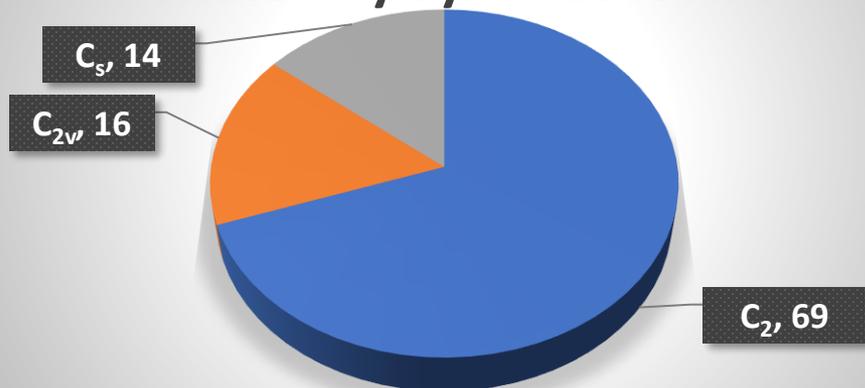
Figure. Histogram of relevant articles on dimeric natural products



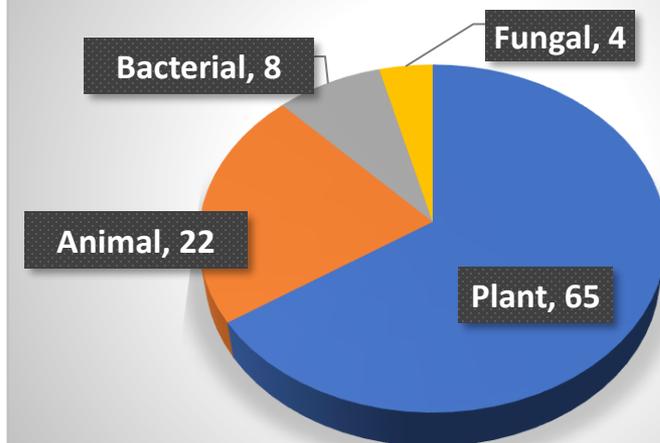
Molecular bilateral symmetry: molecules that contain a C_2 (sigma plane or axis), C_s or C_{2v} point groups

- Survey of ~3,000 (1996-2004) articles found bilateral symmetry in ~7% of natural products
- An additional 10% of the 3,000 articles included molecules regarded as “derivatized dimers”

% Symmetry Types of Bilaterally Symmetric NPs



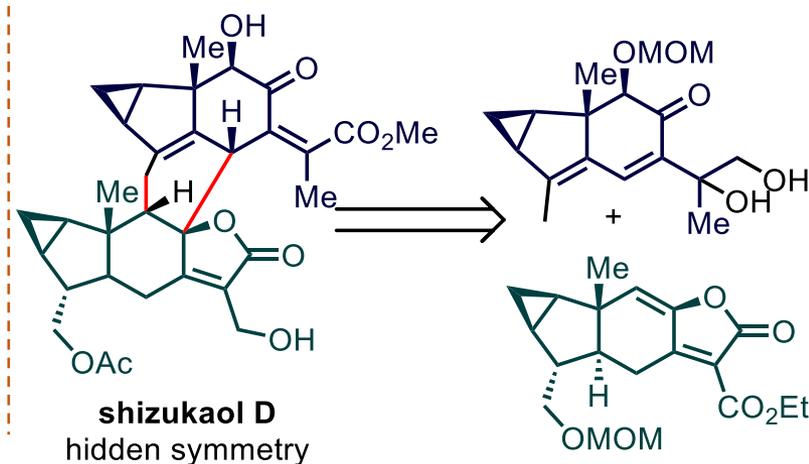
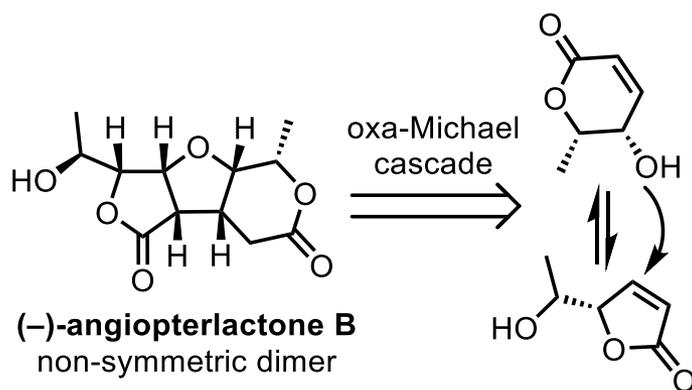
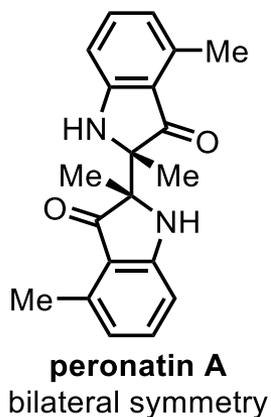
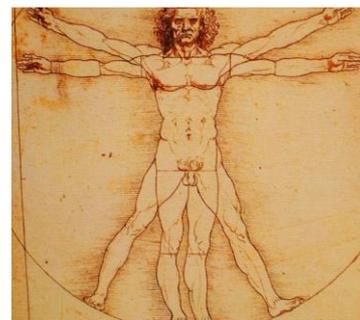
% Source of NP



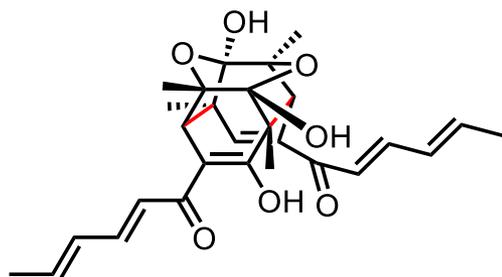
Nature's Impetus for Dimeric Natural Products

Why do dimeric NPs form?

- Bind 2 distinct sites
- Increased potency & selectivity
- Post-dimerization functionalization may facilitate niche function
- Balances enthalpic cost (oligomers) with potency

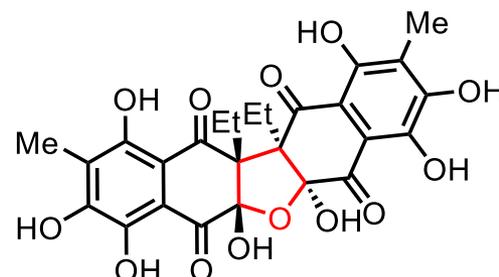


Dimeric Natural Products as Pharmaceuticals



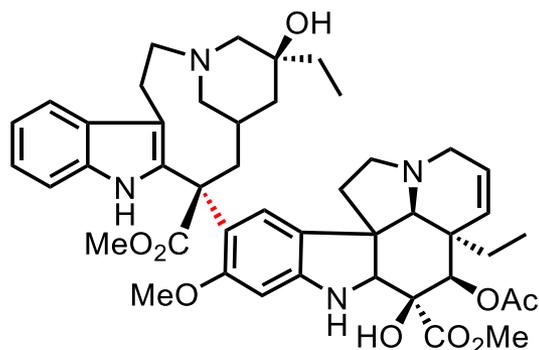
trichodimerol

Lead for treatment of septic shock.



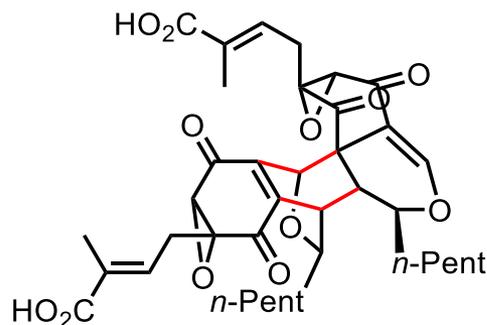
hybocarpone

Cytotoxic against murine mastocytoma with an IC_{50} of 150 ng/mL.



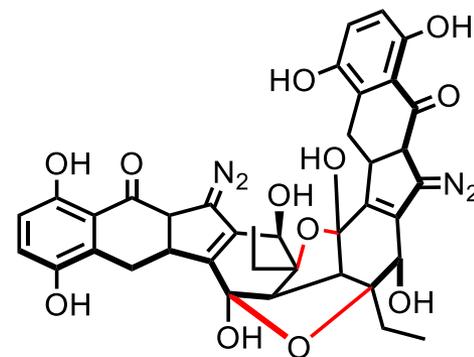
(+)-vinblastine

Clinical treatment of Hodgkin's disease, testicular, ovarian, breast, head, & neck cancer, and non-Hodgkin's lymphoma.



(+)-torreyanic acid

5-10x more potent against cell lines sensitive to protein kinase C agonist 12-*o*-tetradecanoyl phorbol-13-acetate.



(-)-lomaiviticin aglycon

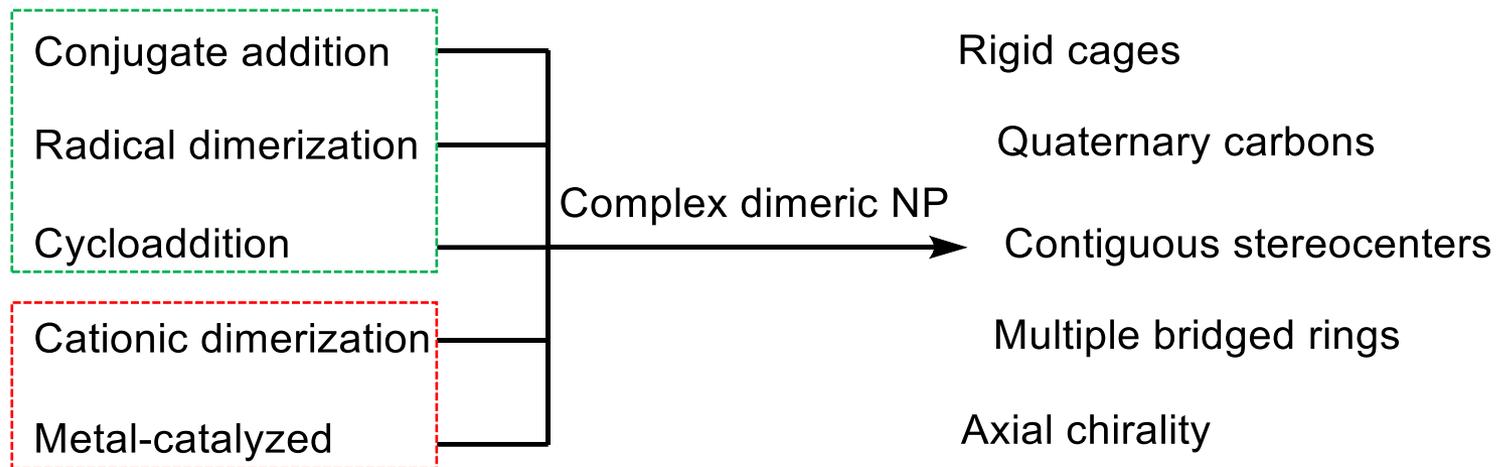
Inhibits the growth of 25 cancer cell lines at low nanomolar to picomolar concentrations.

Strategies for Late-Stage Dimerization

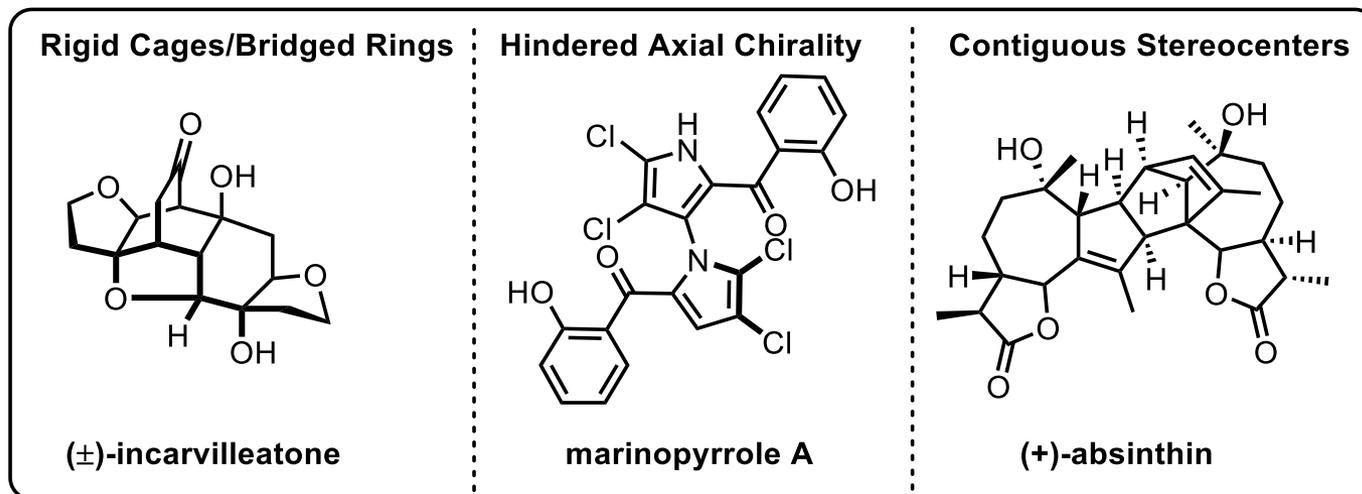
Strategy

Result

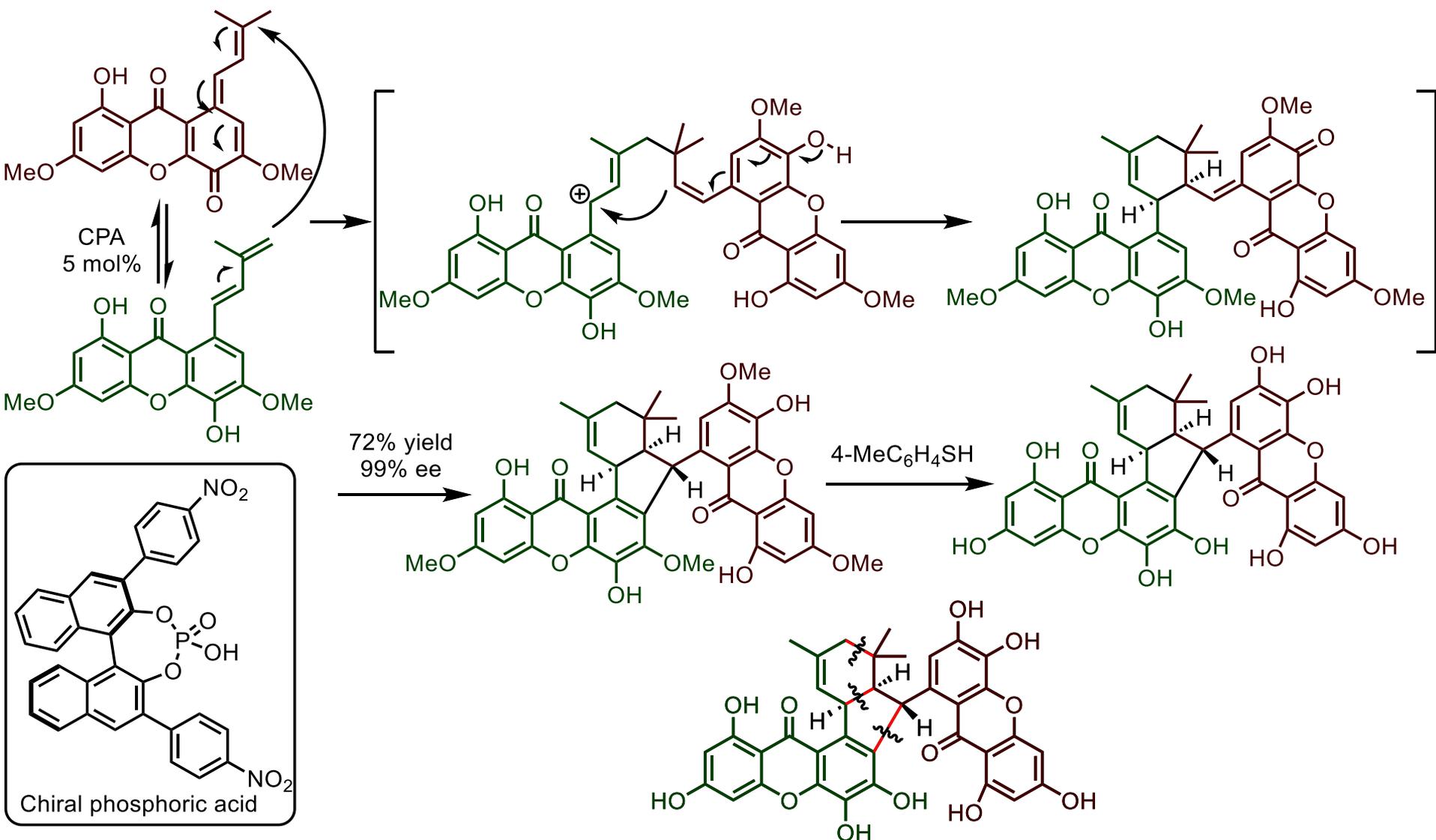
Rapidly formed complexity



Synthetically useful reactions but relatively limited in complexity generation

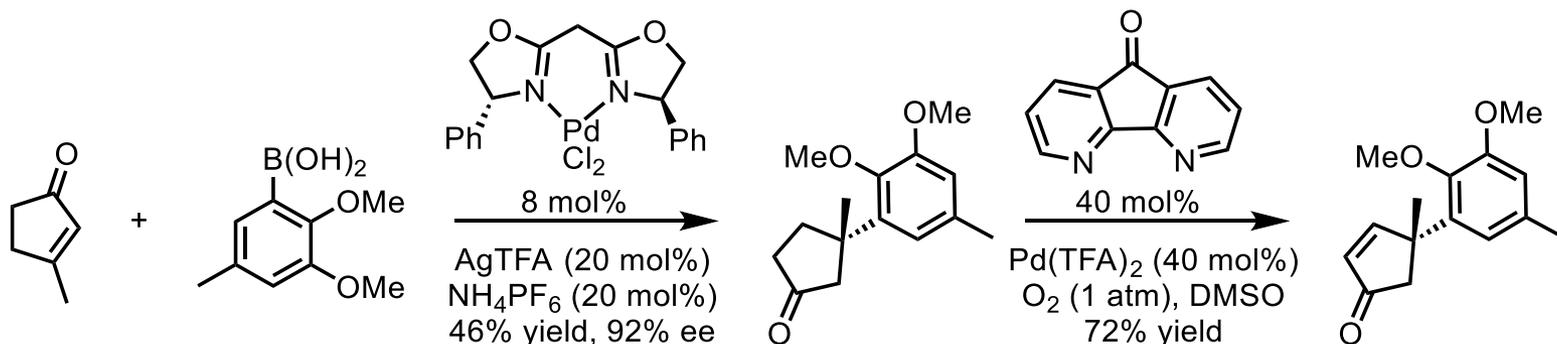


Brief Examples of Cationic & TM-Dimerizations



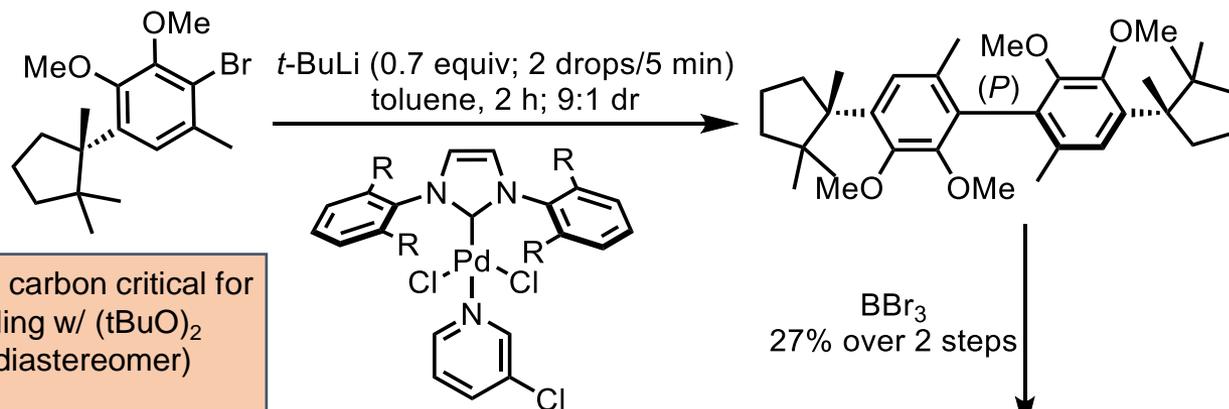
Imidodiphosphoric acids and N-triflyl phosphorimides also surveyed. **griffipavixanthone**

Brief Examples of Cationic & TM-Dimerizations



1. Methylation
2. Deoxygenation
+ Hydrogenation
3. Bromination

54% yield over 4 steps



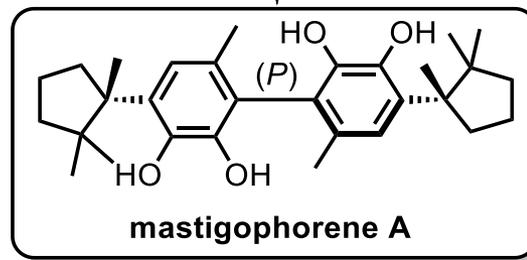
Remote quaternary benzylic carbon critical for *P* selectivity (oxidative coupling w/ (tBuO)₂ affords 40:60 dr favoring *M* diastereomer)

Natural isolate is 40:60 mixture of *P*:*M*

Point-to-axial chirality transfer

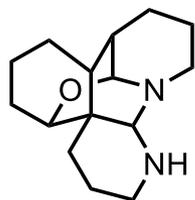
Tetra-*ortho*-substituted biaryl coupling

PEPPSI: pyridine-enhanced precatalyst preparation stabilization and initiation

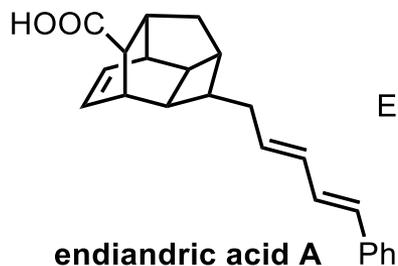


Cycloaddition: Preisolactone A

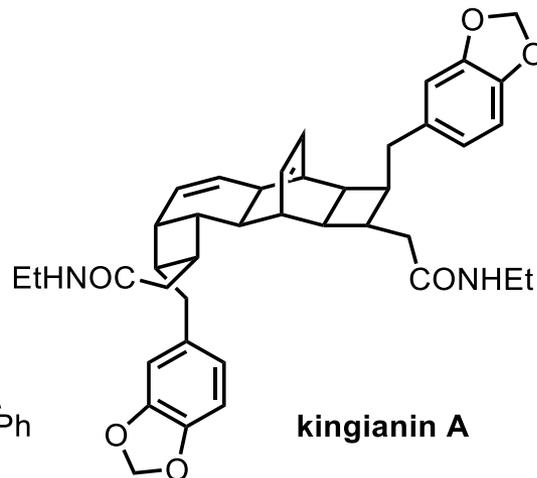
Isolated as racemates:



nitramine

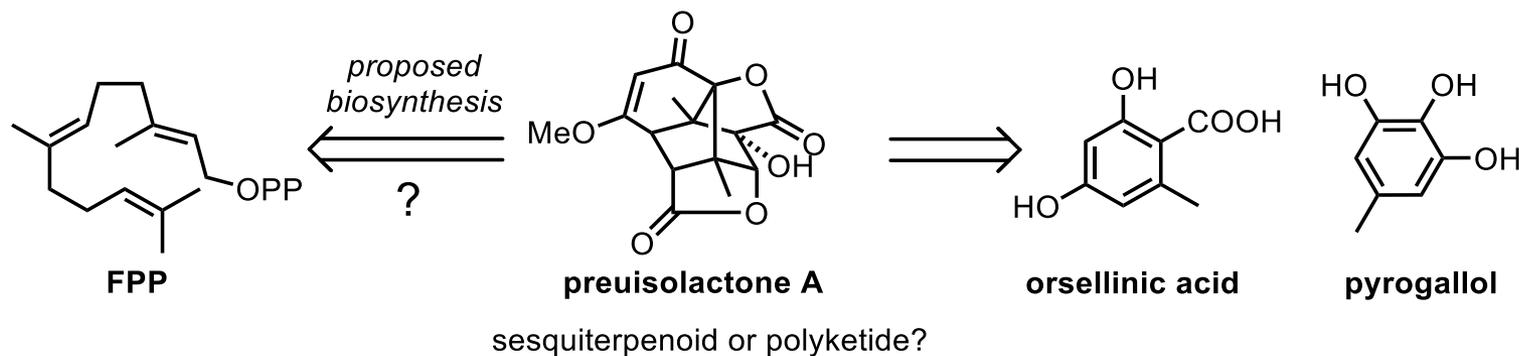


endiandric acid A

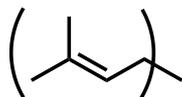


kingianin A

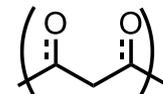
The isolation of natural products that feature multiple stereocenters and complex topologies and yet are racemates is unusual in Nature.



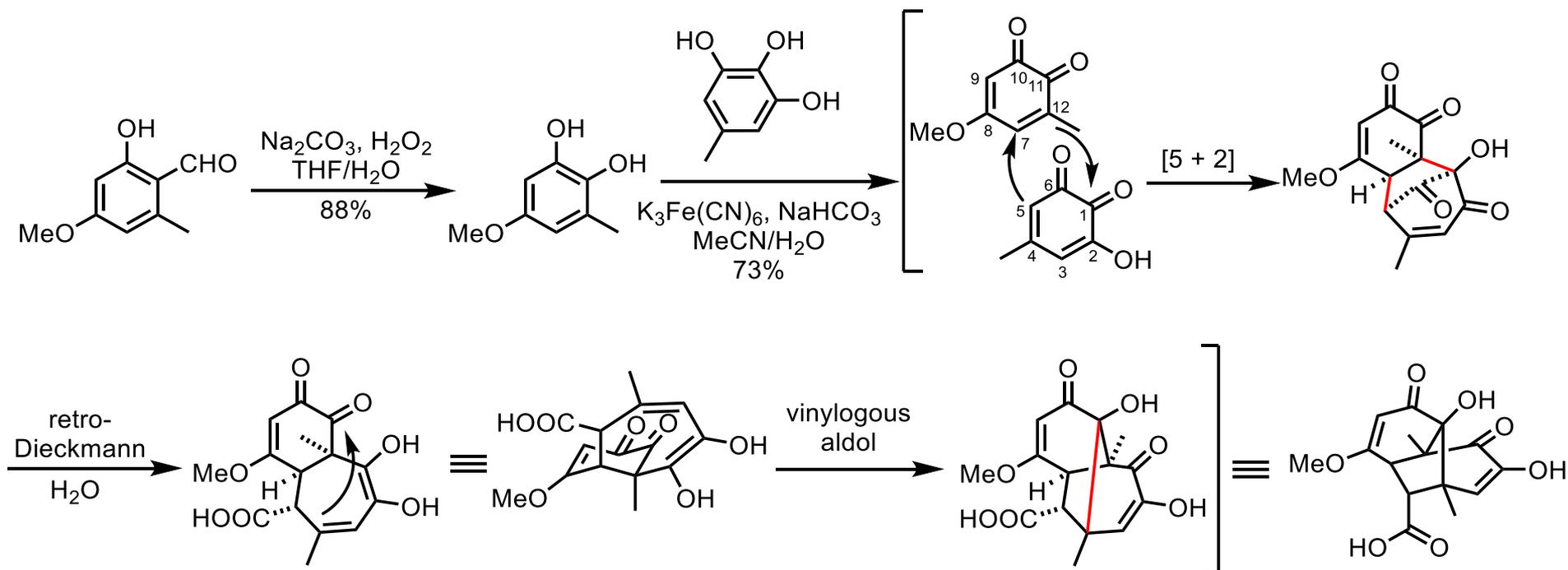
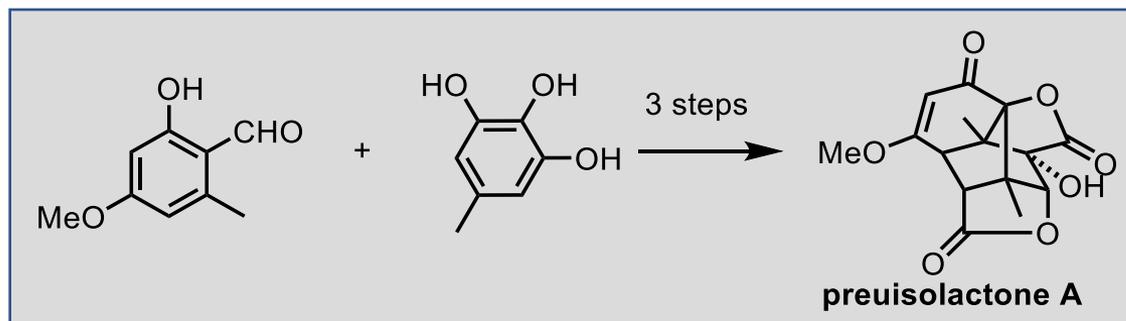
terpenoids



polyketides



Cycloaddition: Preisolactone A

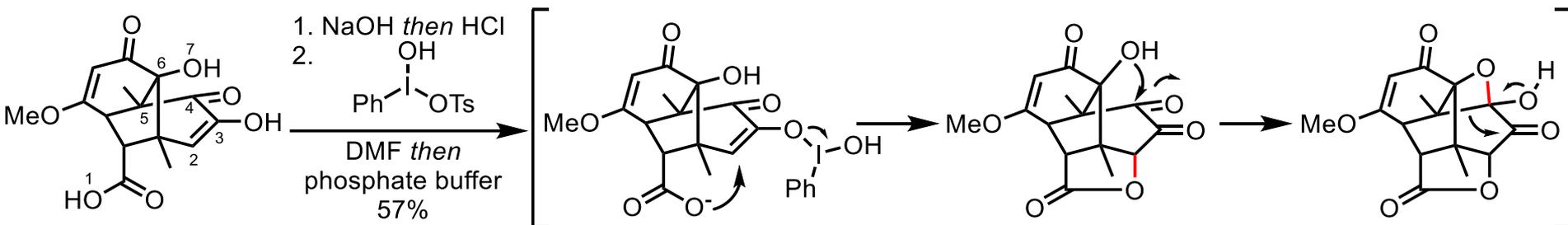


Step 1: [5+2]

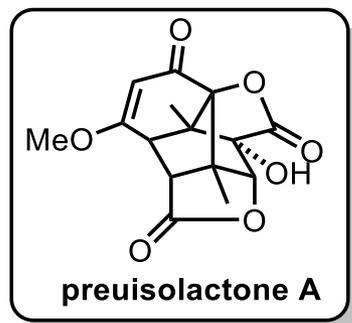
Step 2: retro-Dieckmann (H_2O)

Step 3: Vinylogous aldol

Cycloaddition: Preisolactone A



benzylic acid
rearrangement



3 oxidative steps; 37% overall yield from Me-orsellinaldehyde

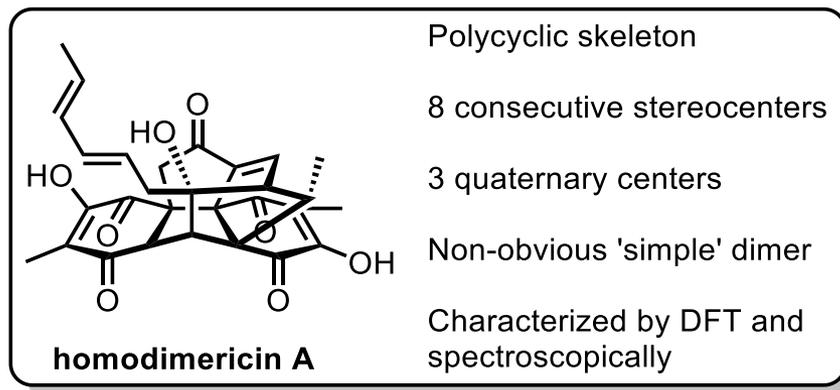
Biomimetic synthesis contributes to elucidation of biosynthetic pathways

Remaining questions: Attempts to oxidize intermediate with horseradish peroxidase, H_2O_2 , or O_2 failed to produce any preisolactone A. Which oxidant might nature use and is there a dedicated oxidizing enzyme for each phase of the pathway?

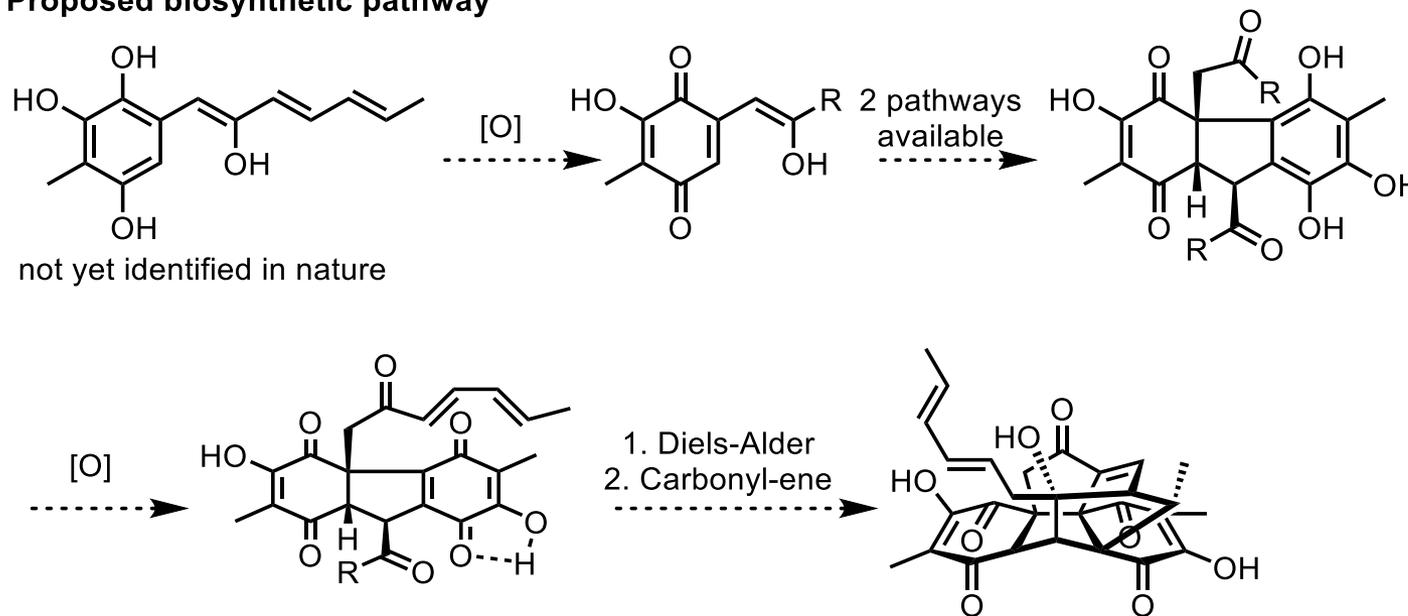
How did a cycloaddition strategy facilitate this synthesis?

1. Established key C–C bonds in a stereospecific manner
2. Aligned reactive functionality for cascade processes (increased propinquity)

Conjugate Addition: Homodimericin A

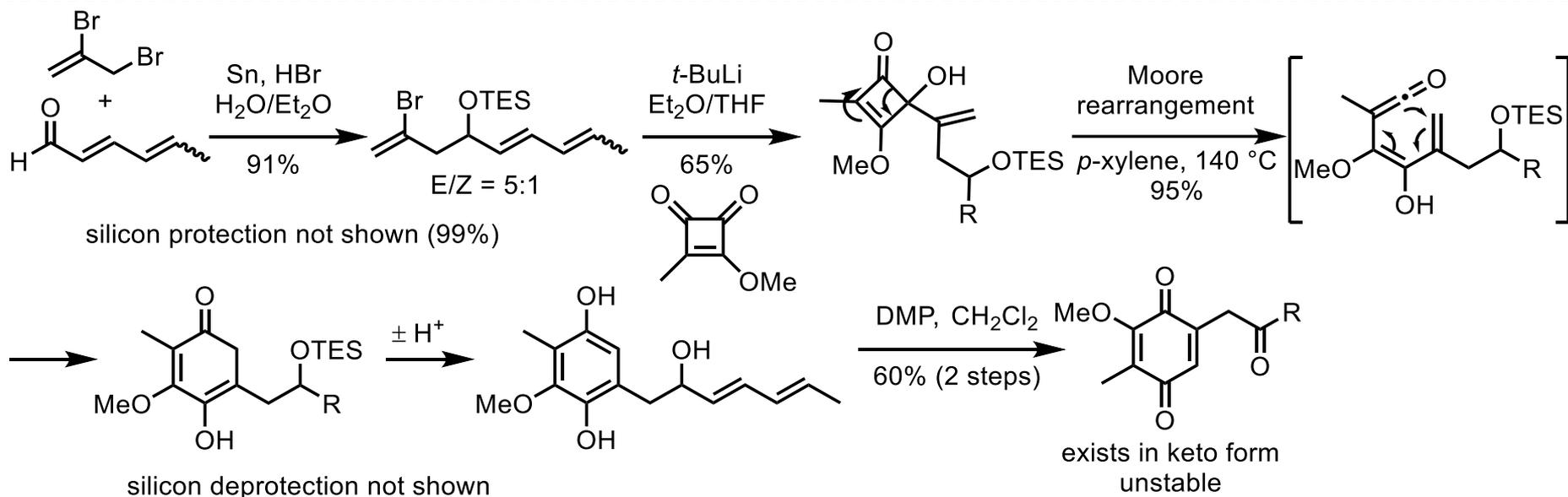
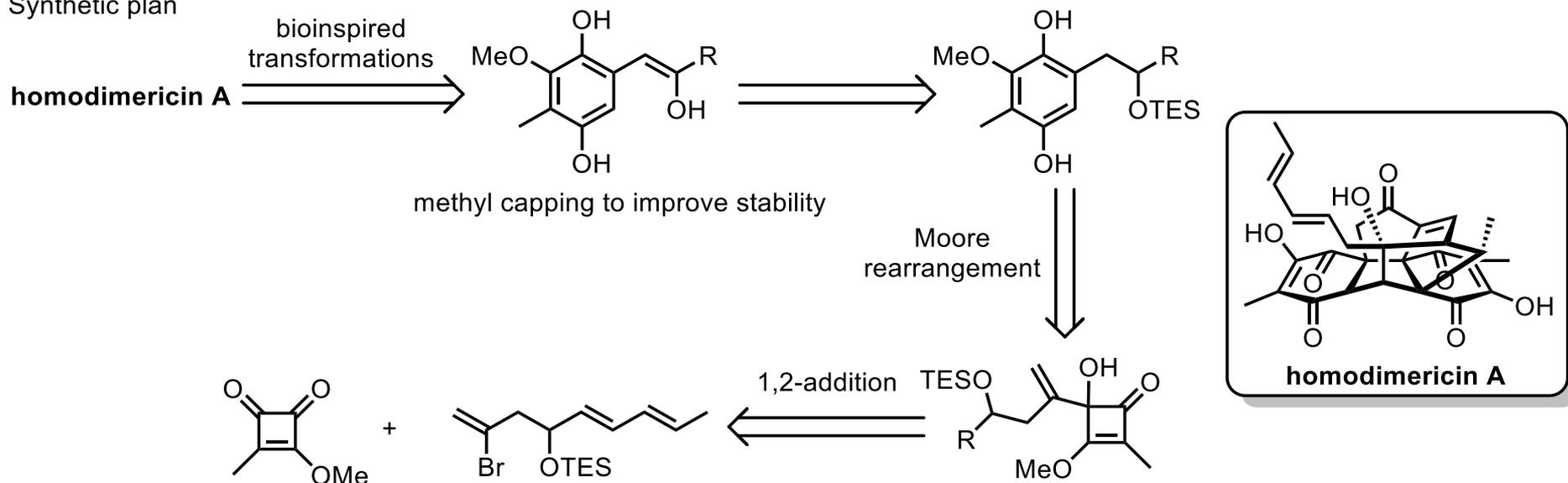


Proposed biosynthetic pathway

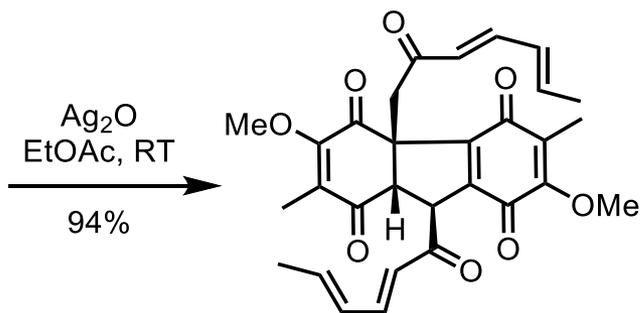
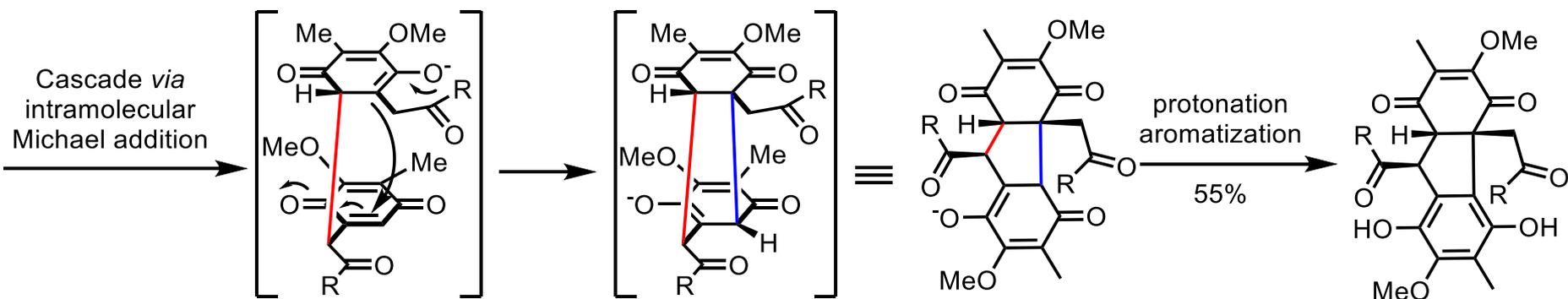
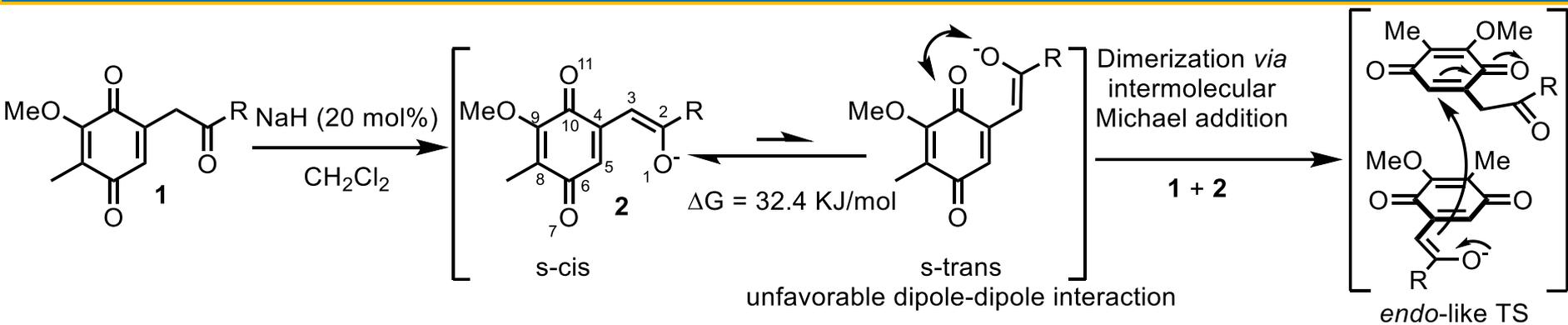


Conjugate Addition: Homodimericin A

Synthetic plan

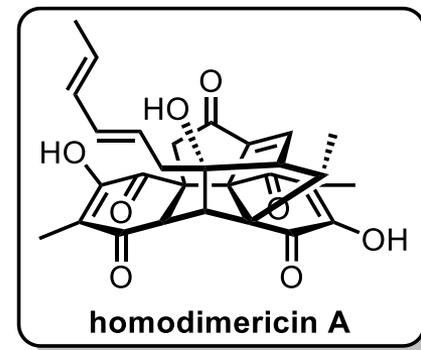


Conjugate Addition: Homodimericin A

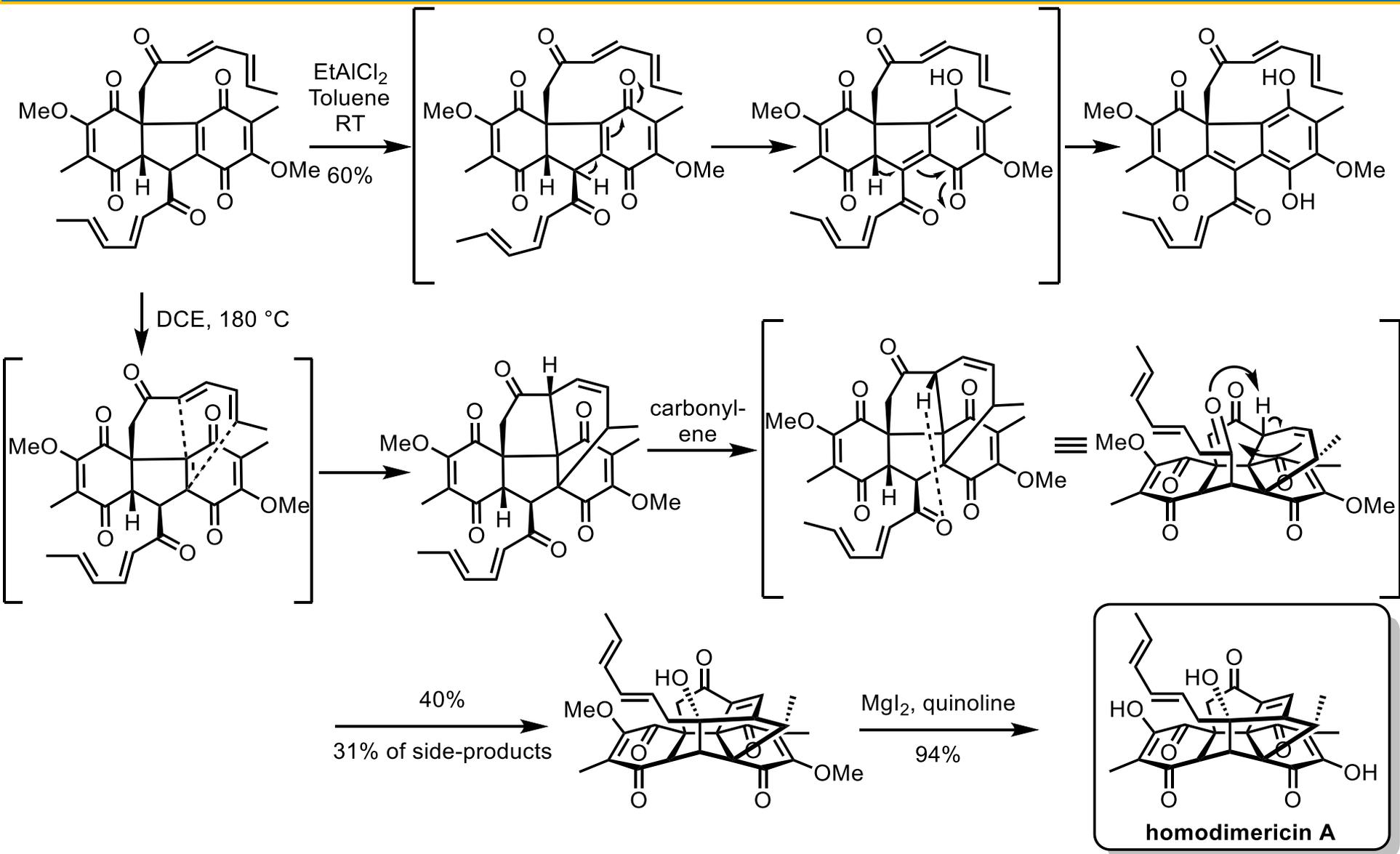


Cascade conjugate addition established:

- 1 new ring
- 3 stereocenters (racemically)
- Functional handles



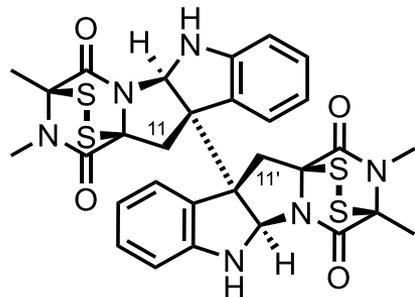
Conjugate Addition: Homodimericin A



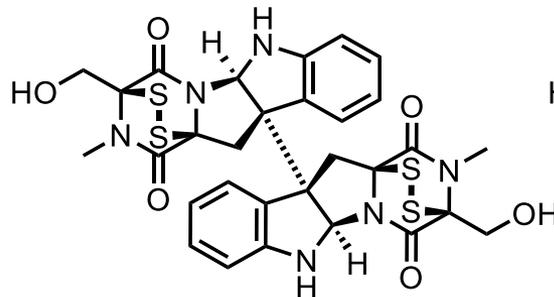
Radical Dimerization: Dideoxyverticillin A

Family of epidthiodiketopiperazine alkaloids

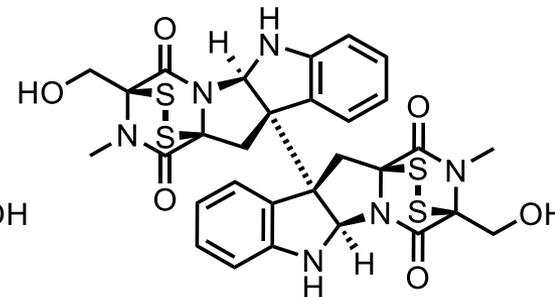
As of 2009, no members of the family had been synthesized



(+)-11,11'-dideoxyverticillin A

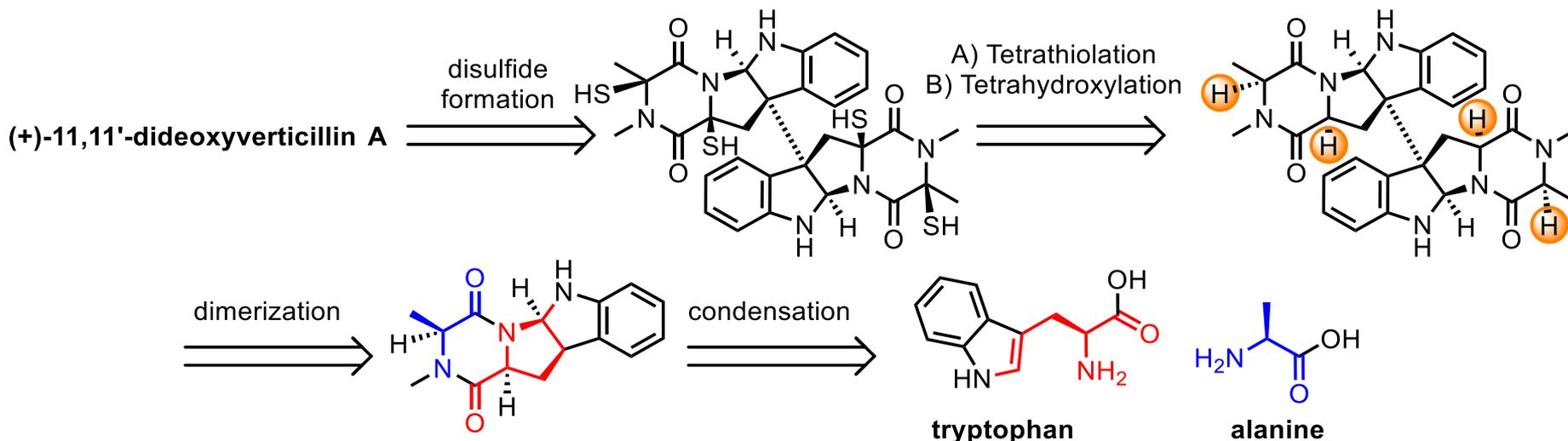


(+)-chaetocin A

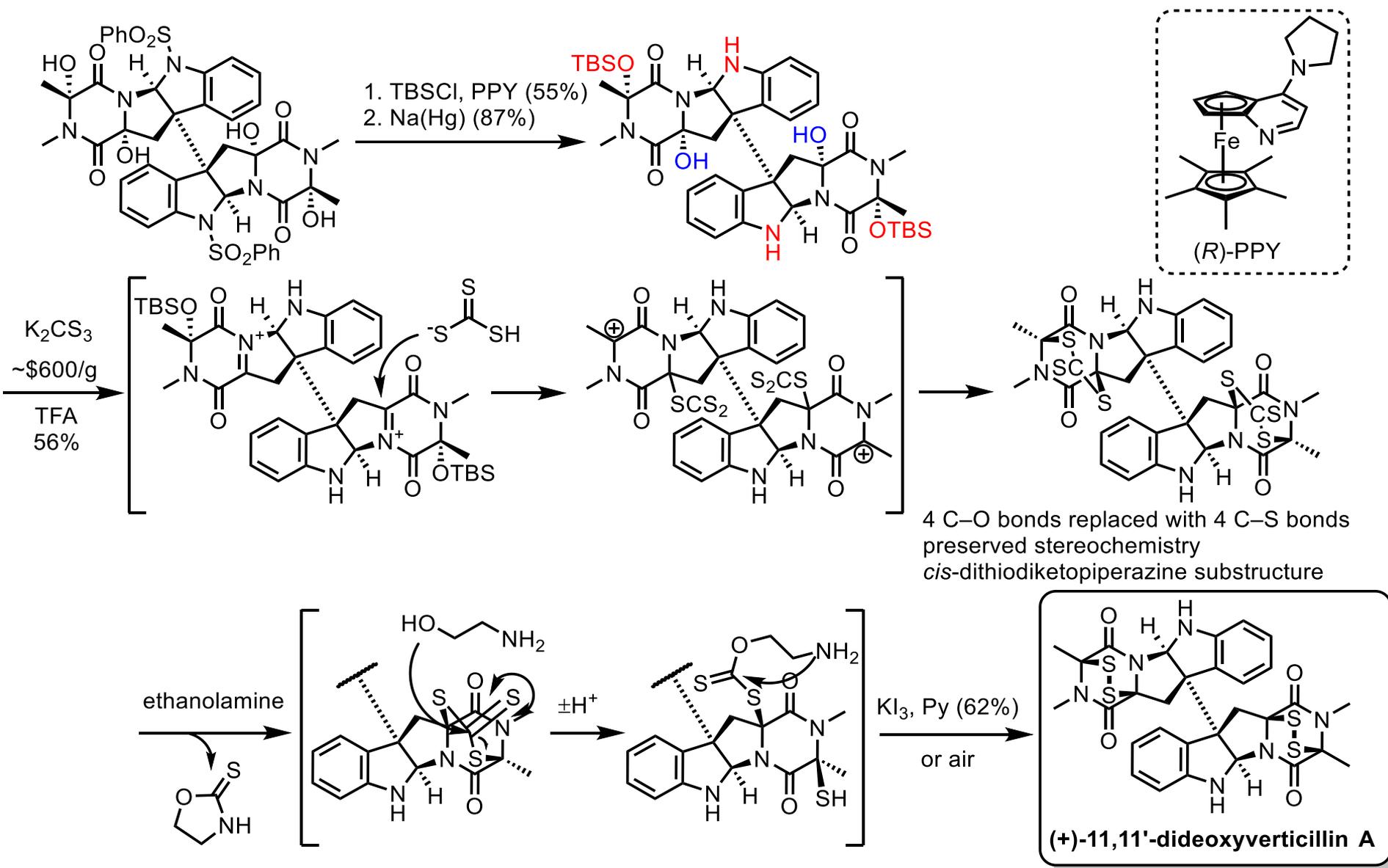


(+)-leptosin K

6 tetrasubstituted carbons (3 per monomer)
Post-dimerization functionalization strategy

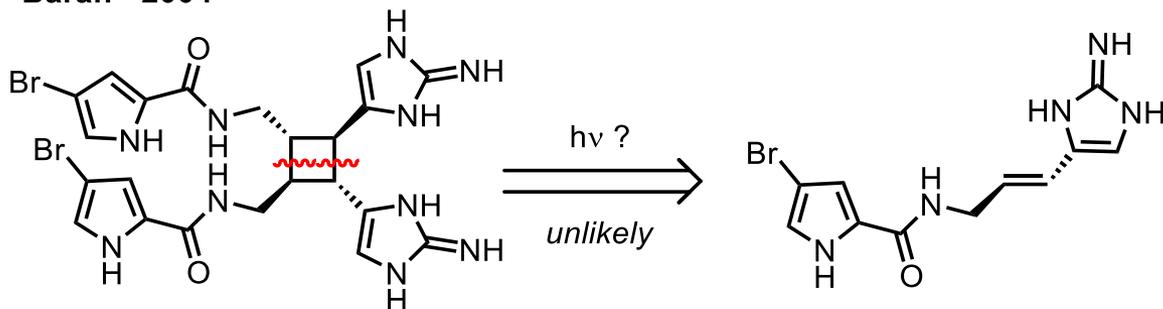


Radical Dimerization: Dideoxyverticillin A



When Dimerization Strategies Fail: Sceptrin

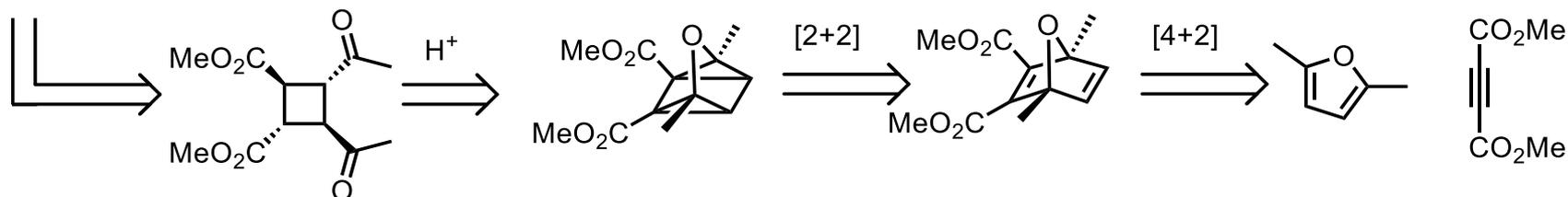
Baran - 2004



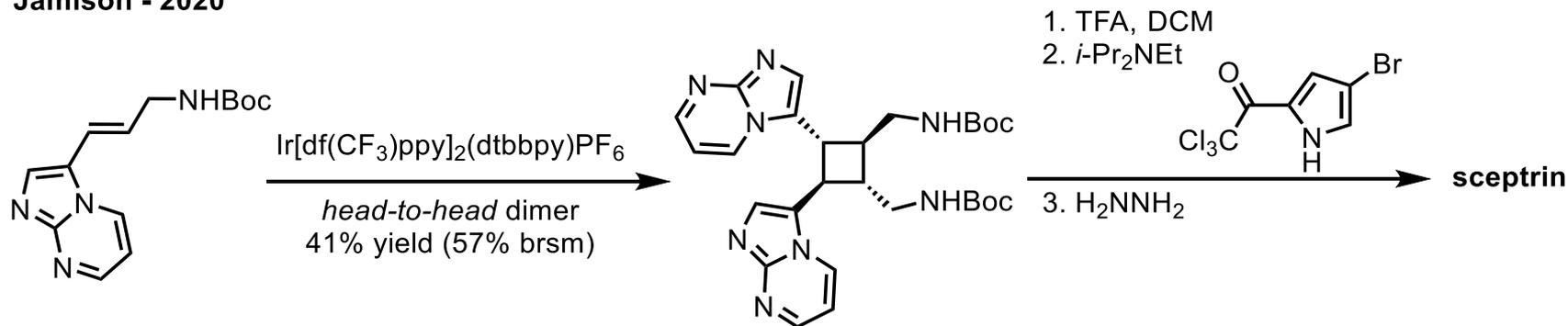
sceptrin ($[\alpha]_D -7.4$)

hymenidin

Isolated at ocean depths which do not promote photochemical reactions

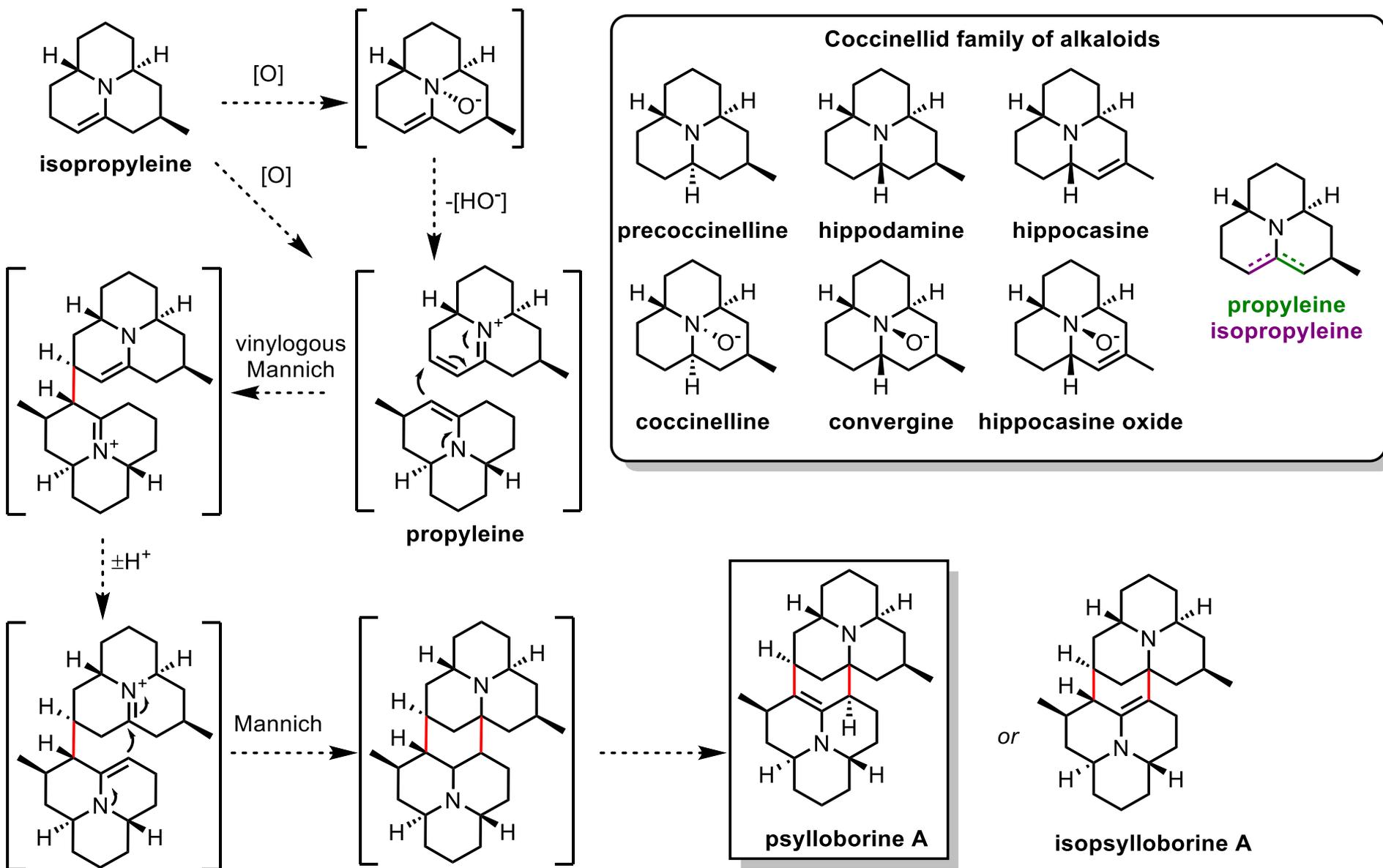


Jamison - 2020

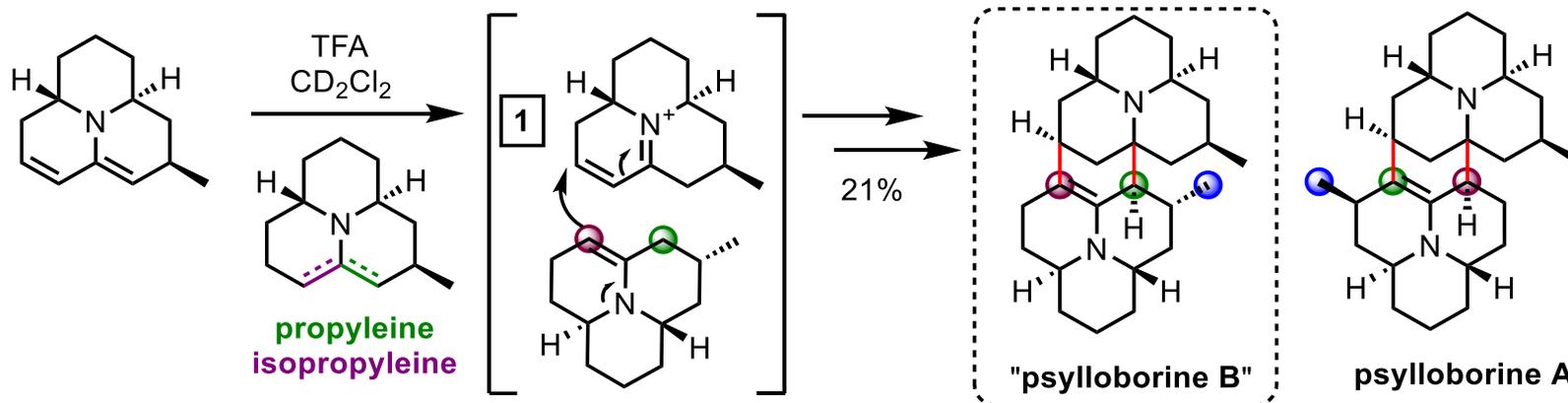


<5% yield at 390 nm irradiation w/o photocatalyst indicating TTET

Psyloborine Class and Biogenesis

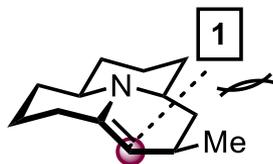


Attempted Dimerization Strategy



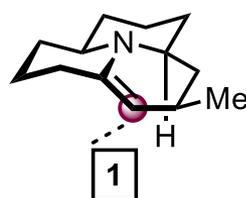
"We have elected to give this new dimeric material [sic] the name "psylloborine B", should it ever prove to be a natural isolate."

Top-side approach



direct steric clash

Bottom-side approach

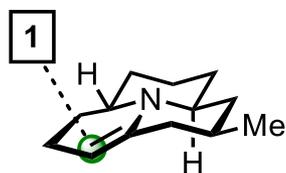


flagpole interactions

Neither approach
observed

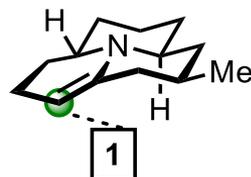


Top-side approach



pseudoboat
flagpole interactions

Bottom-side approach

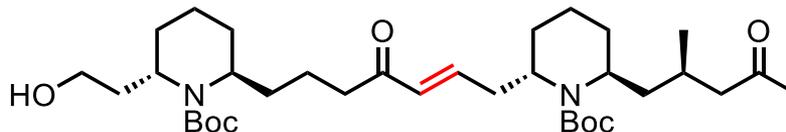
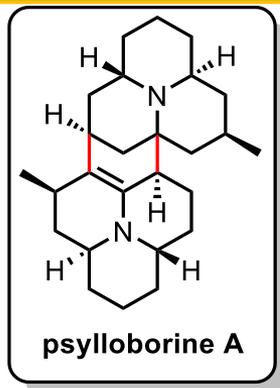


pseudochair
minimal steric effects

Observed reactivity

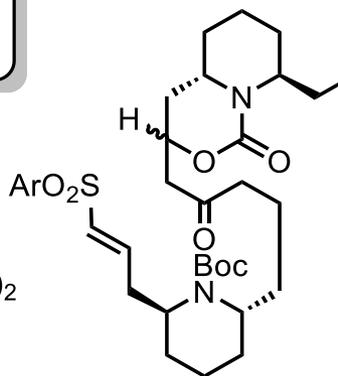


“Intramolecular Dimerization” Strategy

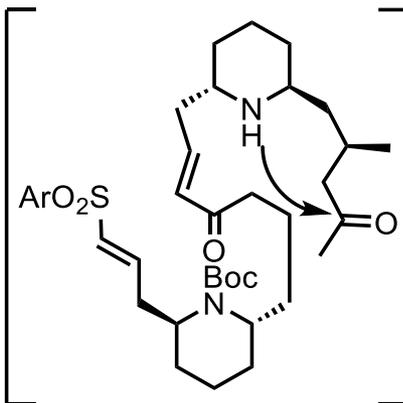


"...this approach appears contrary to the general tenets of retrosynthetic analysis, since an arguably more complex precursor and set of terminating events are required than those needed for the two dimerization strategies..."

1. TFA, -78 °C
2. Swern
3. LiCl, *i*-Pr₂NEt

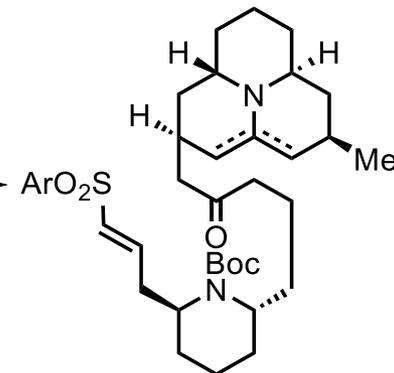


TMG



Cascade #1

Condensation +
Michael addition

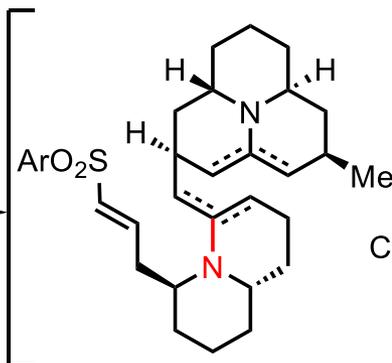


60% over 3 steps

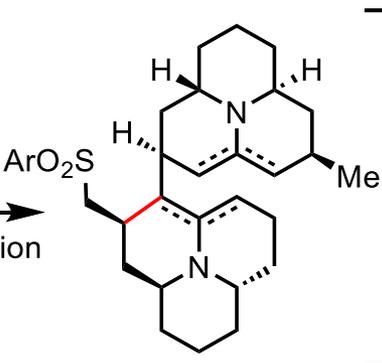
1.2:1 dr favoring undesired
desired is drawn

1. TFA, 0 °C
2. C₆D₆ (monitor)

Deprotection +
condensation



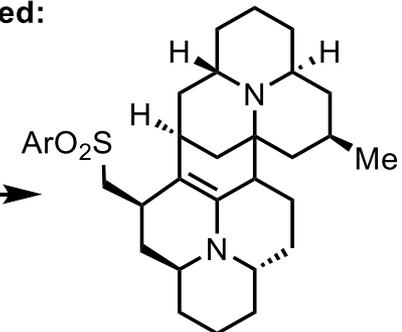
Cascade #2
Conjugate addition



Cascades generated:

- 3 C-C bonds
- 2 C-N bonds
- 5 rings
- 4 stereocenters

Mannich
Ar = 3,5-CF₃Ph
4-NO₂Ph



15% over 3 steps
79% per transformation

Conclusions for Dimeric Natural Products

Exploiting symmetry leads to:

- Strategic disconnections
- Facilitate elucidation of a biosynthetic pathway
- Shorten step count/atom economy
- Aid in biological studies
- Establish absolute configuration and structural assignments

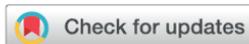
Relevant Literature



Chem Soc Rev

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Recent advances in total syntheses of complex dimeric natural products

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Jiawei Sun,^a He Yang^{*a} and Wenjun Tang ^{*ab}

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REVIEW

Naturally Occurring Dimers from Chemical Perspective

by Gaoyan Lian and Biao Yu*

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REVIEW

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Appreciation of symmetry in natural product synthesis

Cite this: *Nat. Prod. Rep.*, 2017, 34, 1345

Wen-Ju Bai ^{*a} and Xiqing Wang ^{*b}