Concise Total Synthesis of Variocolortides A and B through an Unusual Hetero-Diels-Alder Reaction

Christian A. Kuttruff, Hendrik Zipse, and Dirk Trauner

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Marija Manojlović

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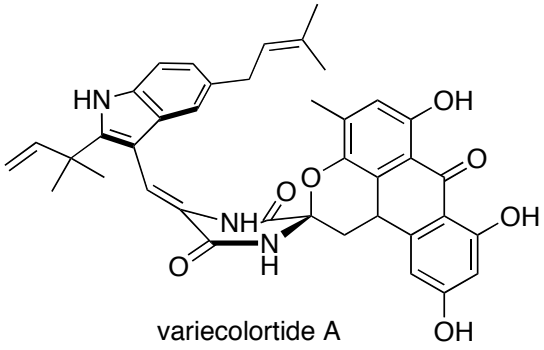
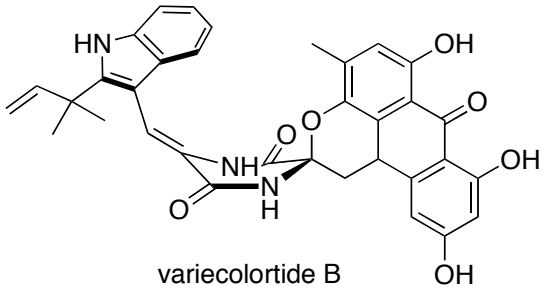
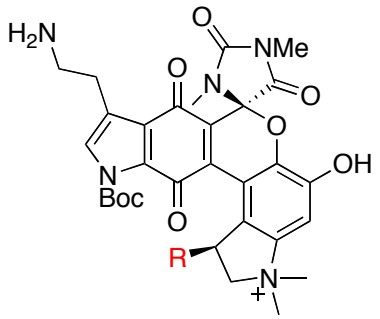
Variecolortides A and B



variecolortide A



variecolortide B



R = H Exiguamine A
R = OH Exiguamine B

- Isolated in 2007 from black mold, *Aspergillus variecolor*

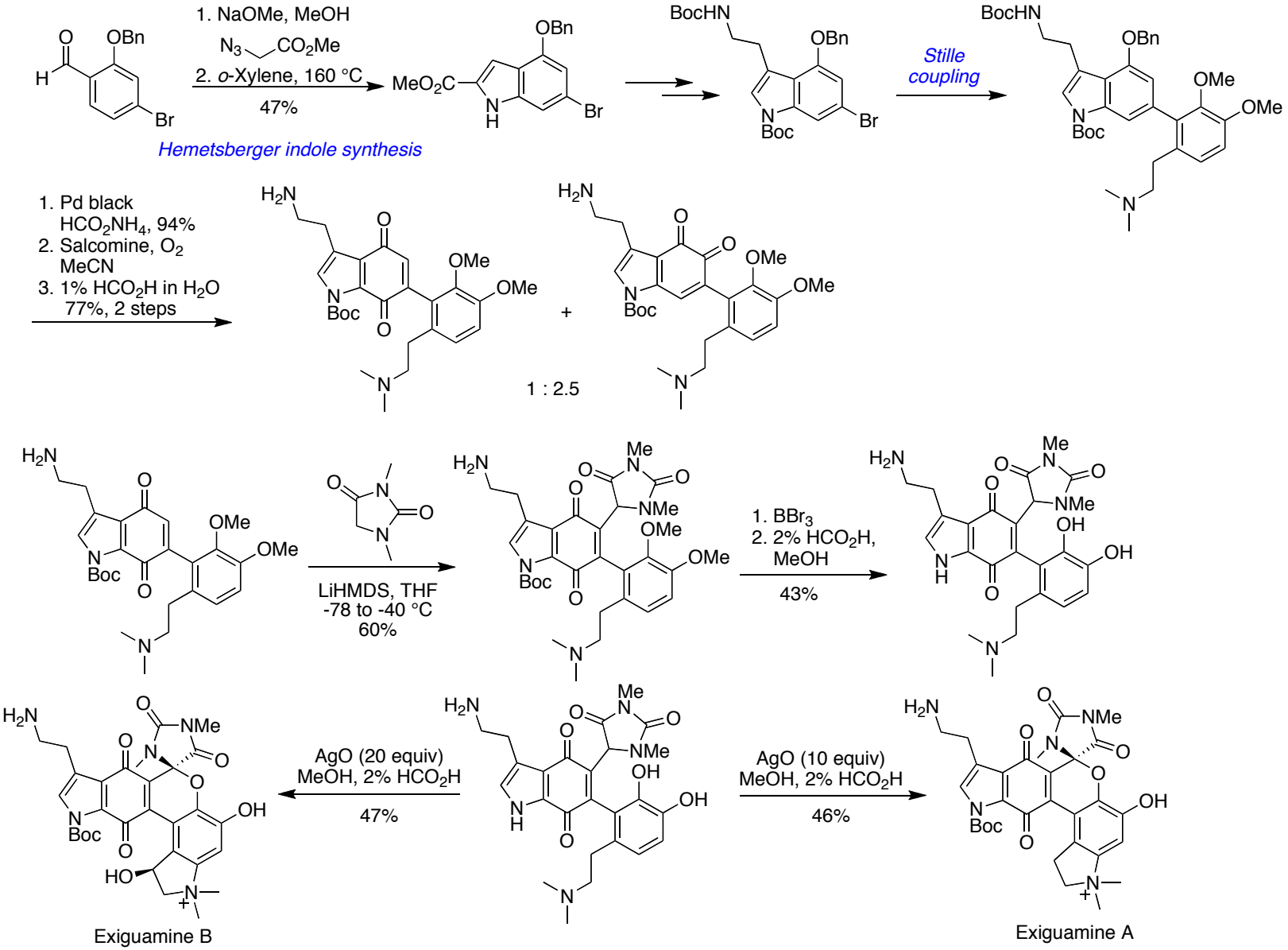
- Modest cytotoxic and oxygen scavenging activity (μM range)

- Structural features: unprecedent anthraquinone methide moiety, diketopiperazine, spirocyclic N,O-acetal

Black mold, *Aspergillus variecolor*

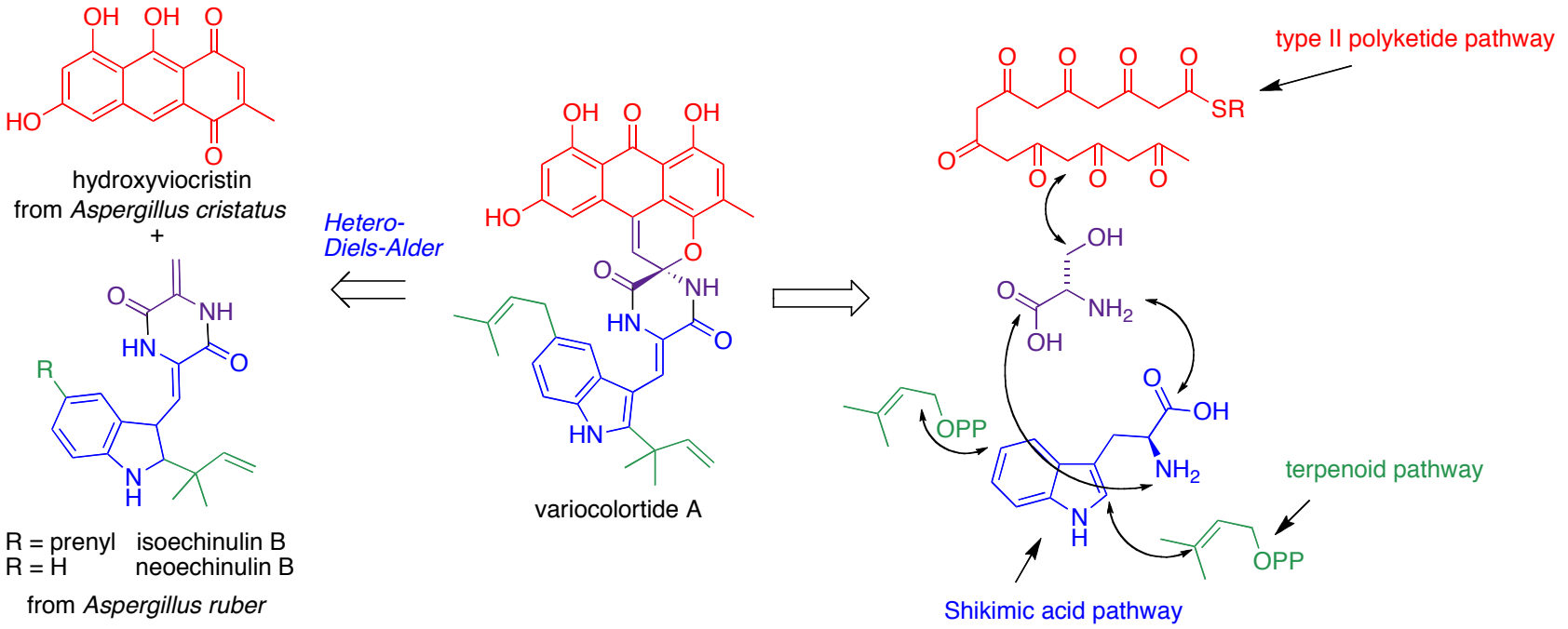
Zhu *et al. Chem. Biodiversity* **2007**, *4*, 2913.

Biomimetic Synthesis of Exiguamines A and B

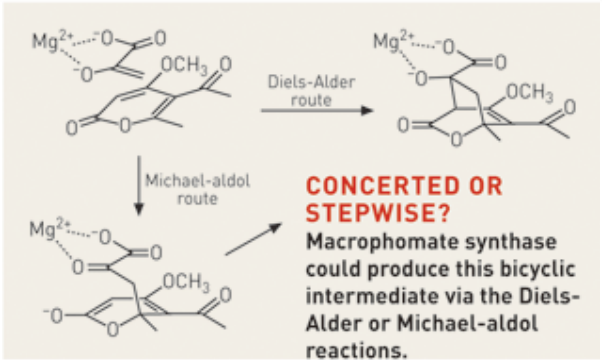


Trauner *et al. Nat. Chem. Biol.* **2008**, *4*, 535.

Biosynthetic Analysis of Variecolortides – Is Diels-Alderase involved?

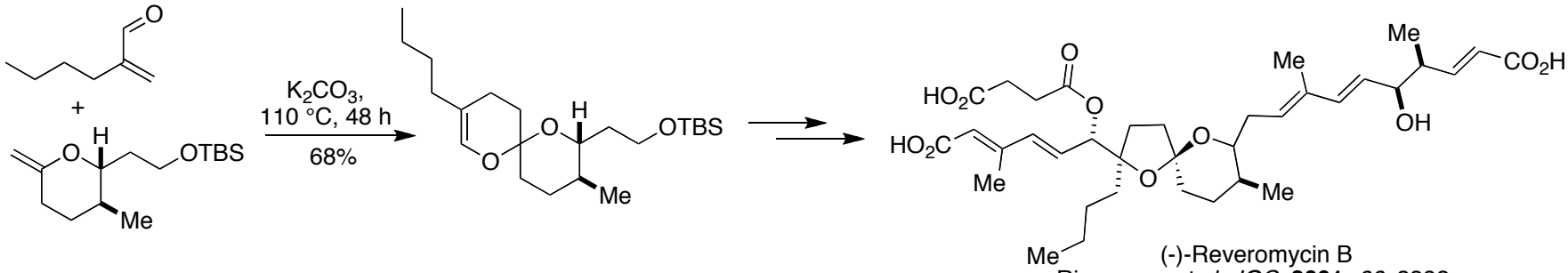


- 1989 – Monoclonal antibodies that catalyze Diels-Alder (DA) reaction
- 1999 – RNA (ribozymes) can catalyze DA reaction
- 2000 - 2003 – potential Diels-Alderases isolated from fungi: lovastatin nonaketide synthase, solanapyrone synthase, and macrophomate synthase
- 2005 – Theoretical study of macrophomate synthase – stepwise process (Michael then aldol reaction) has more probable energetic profile then concerted process
- 2008 – Macrophomate synthase is a very efficient aldolase
- Existence of real Diels-Alderases still elusive

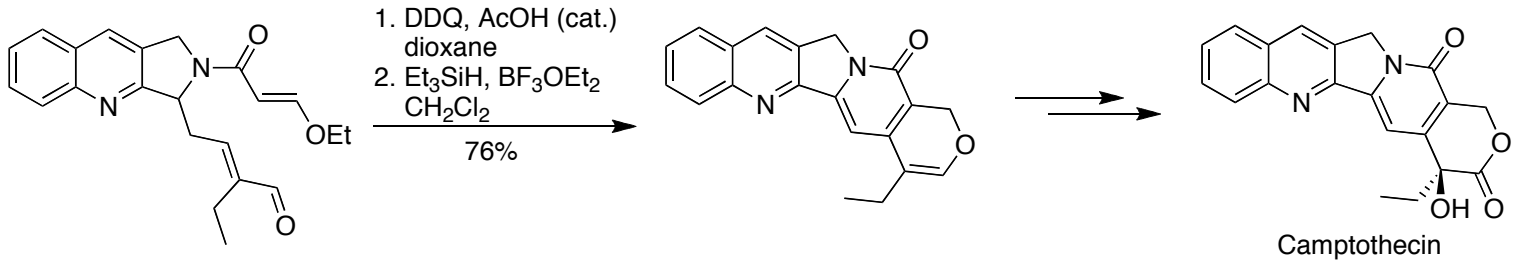


ACIE **2003**, *42*, 3078.
OBC **2008**, *6*, 4483.
JACS **2005**, *130*, 7789.
C&EN News, May 4, 2005.

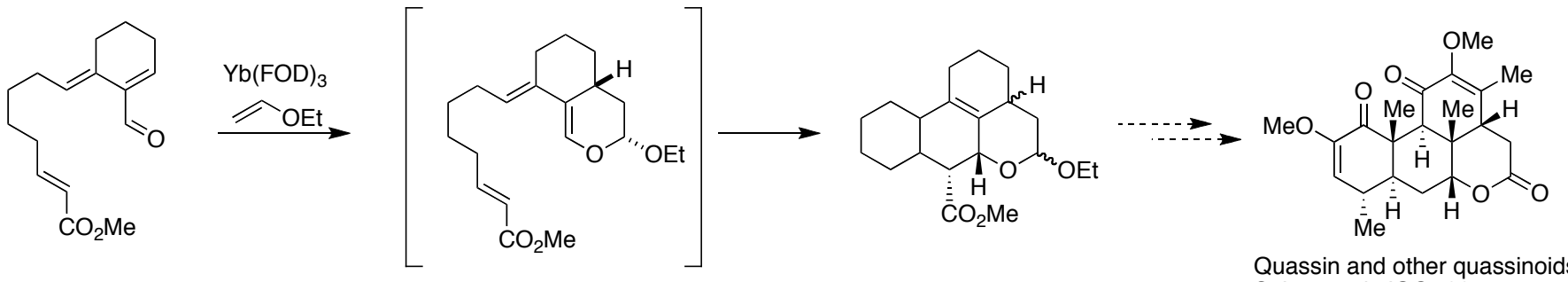
Hetero Diels-Alder Reactions of 1-oxa-1,3-butadiene



(-)-Reveromycin B
Rizzacasa *et al. JOC* **2001**, *66*, 2382.

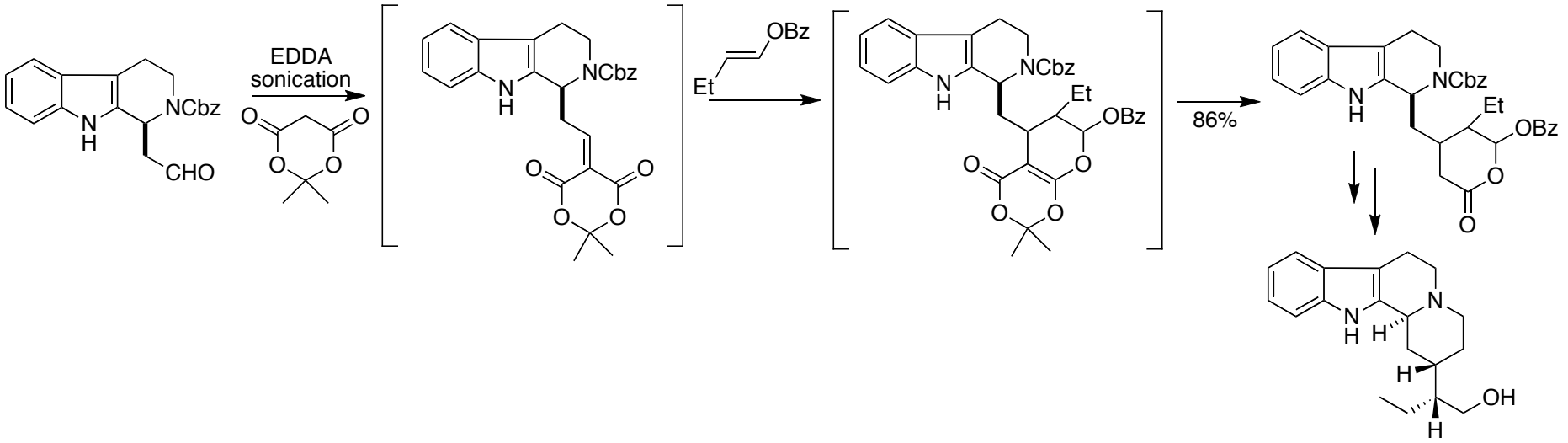


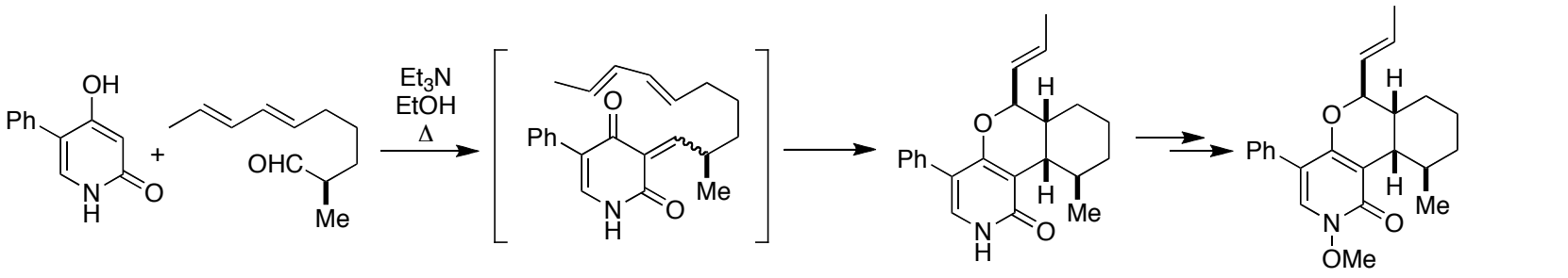
Camptothecin
Yao *et al. OL* **2008**, *10*, 5393.



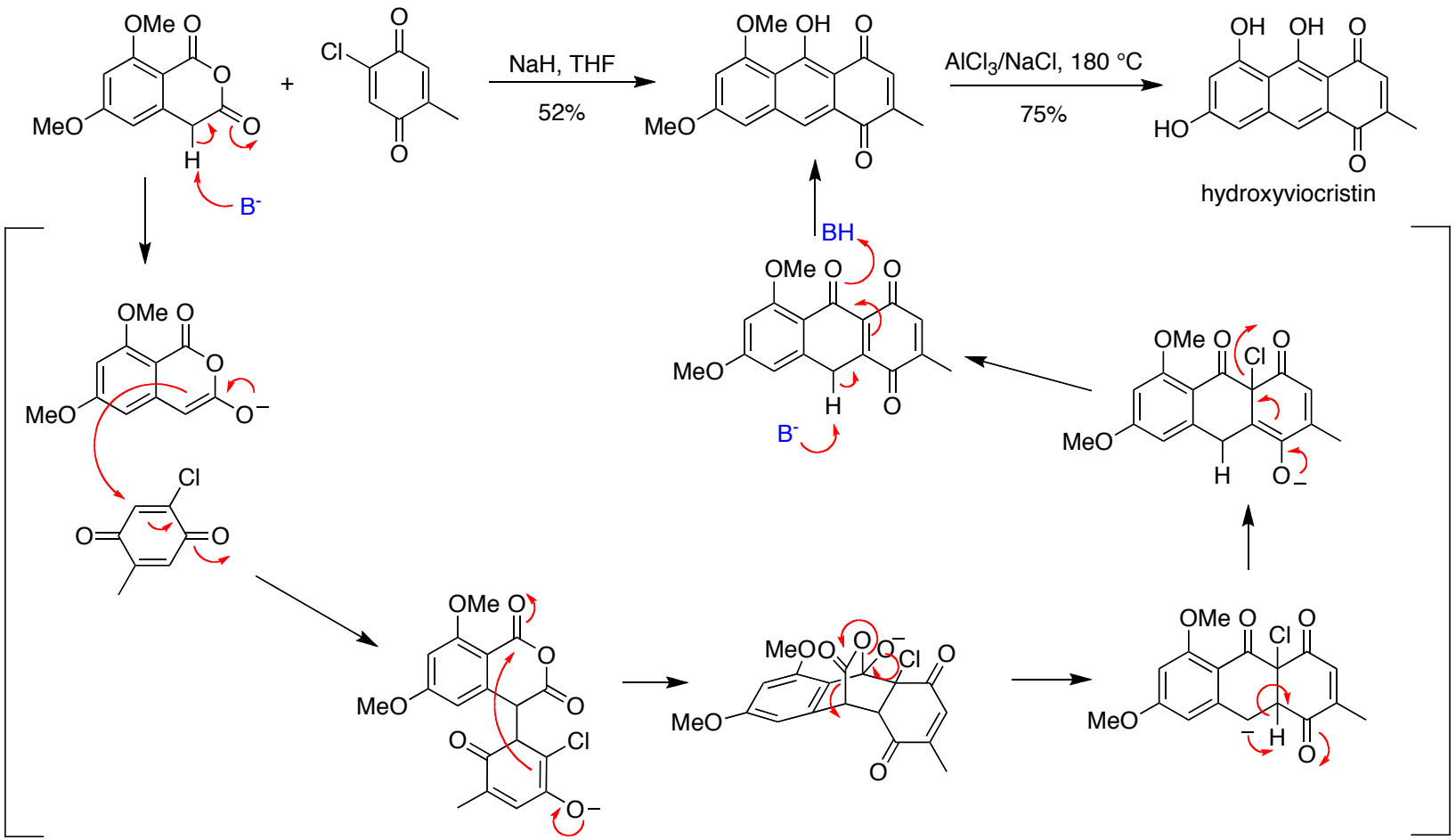
Quassin and other quassinoids
Spino *et al. JOC* **1994**, *59*, 5596.

Hetero Diels-Alder Reactions of 1-oxa-1,3-butadiene





Title Paper – Synthesis of Precursors



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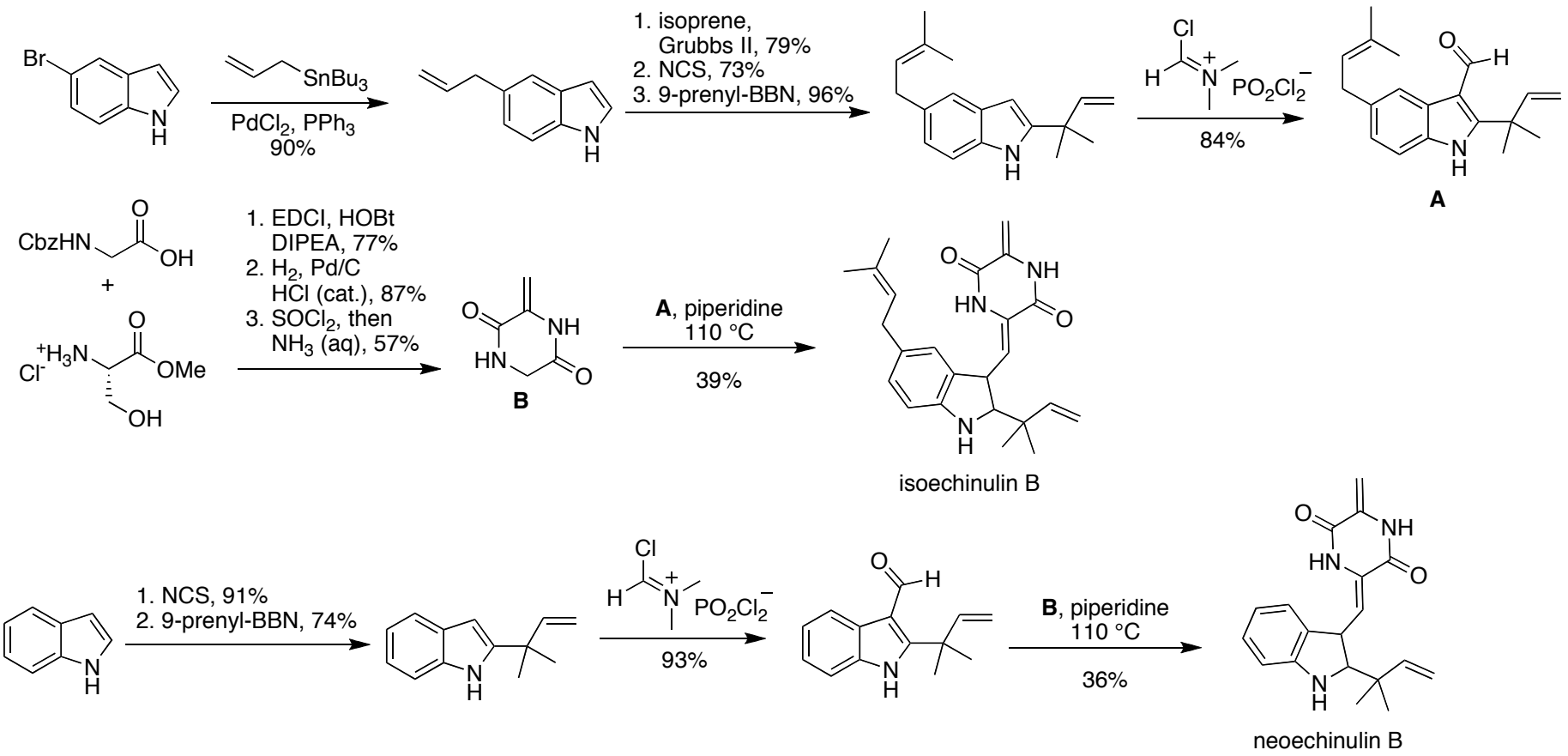
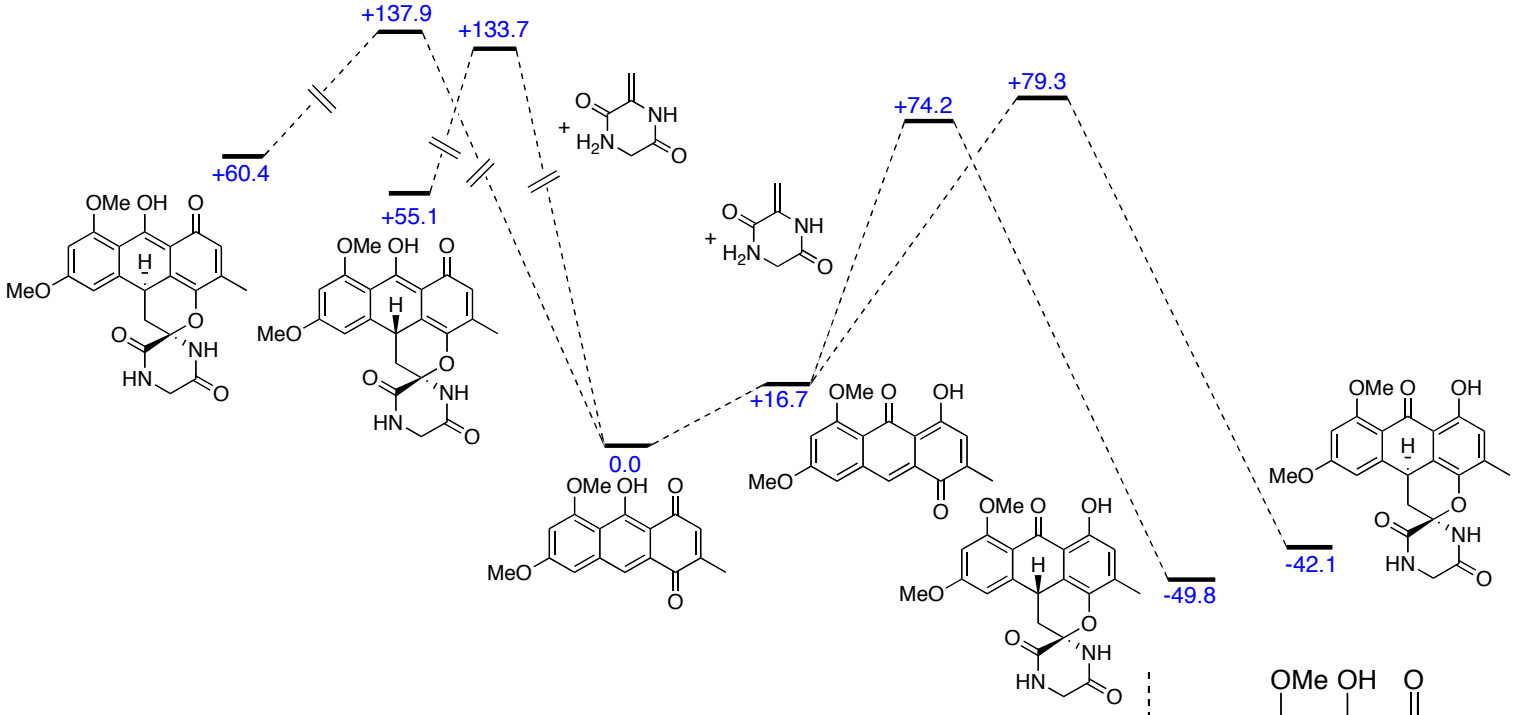
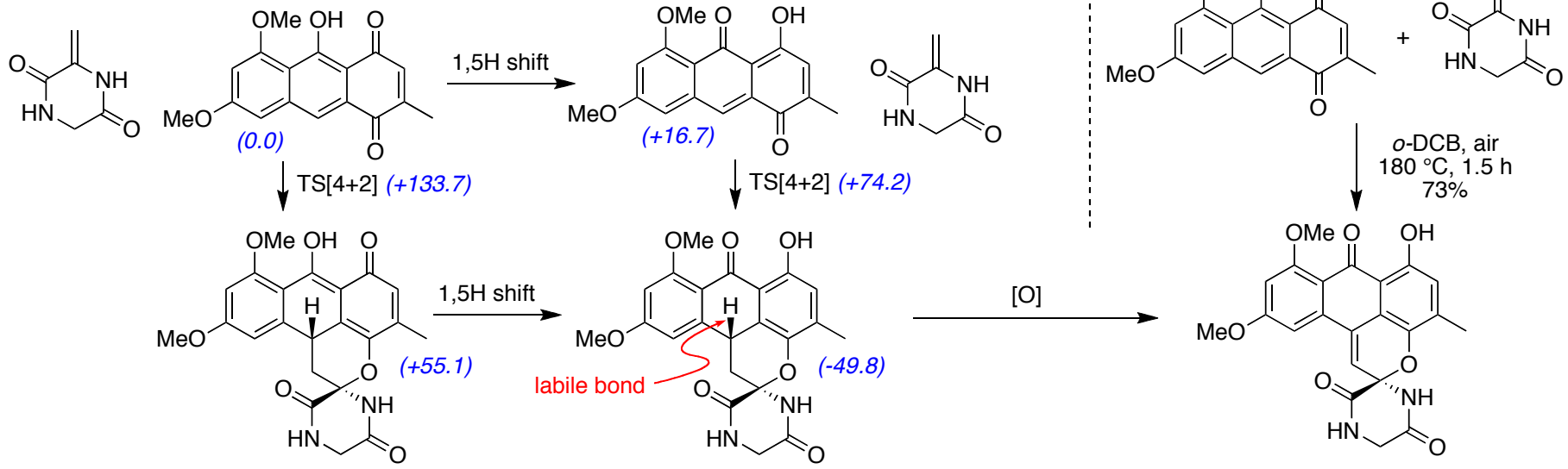
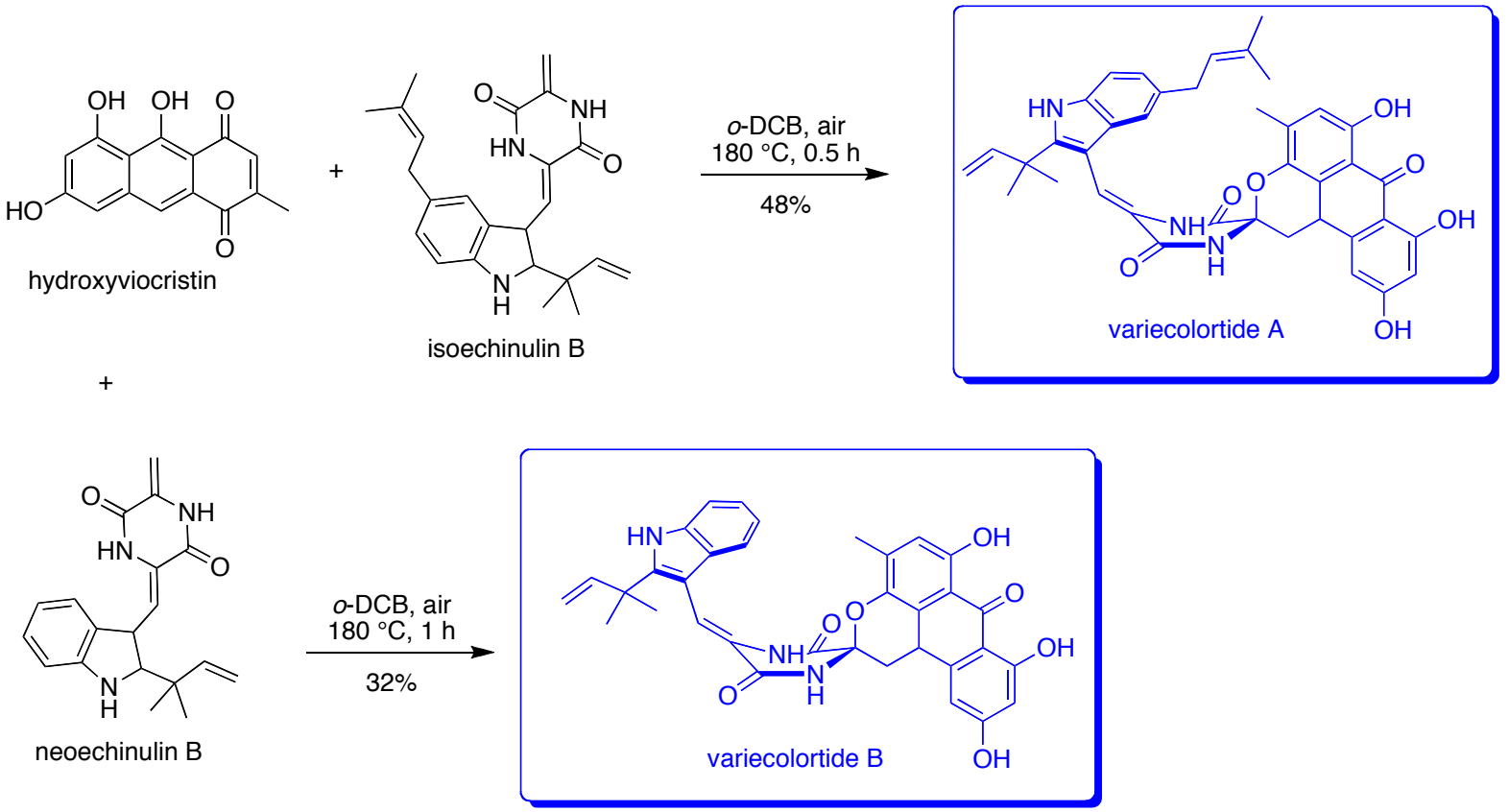


Computational Studies on Model System





Title Paper – End Game



• There is no reaction under more biological conditions (aqueous phosphate buffer at room temperature) => catalyst is needed in nature, possibly Diels-Alderase

Conclusions

- Variecolortides A and B were synthesized in concise manner (7 and 5 steps, respectively)
- Synthesis is mostly protecting group free (except for amide coupling reaction to form dipeptide)
- Unprecedented hetero-Diels-Alder reaction is used in a key step, and the concerted mechanism is strongly supported by DFT calculations
- The question of whether similar reaction occurs in nature is yet to be answered
- Further biological exploration of these natural product is ongoing.