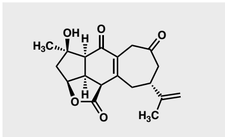
The Stoltz Group: Total Synthesis Projects

Caltech

stoltz

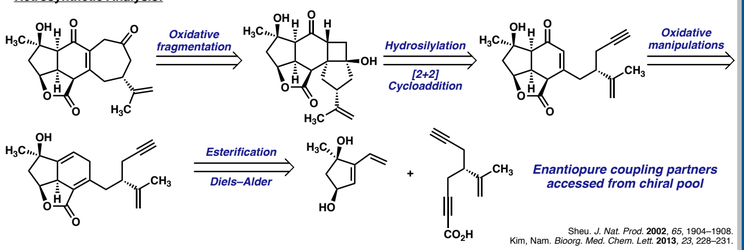
Scabrolide A



Sinularia soft coral

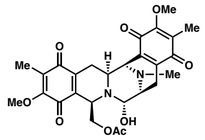
- Isolated from Taiwanese soft coral *Sinularia scabra*
- Member of the norcembranoid diterpenoid family
- Exhibits promising anti-inflammatory activity via inhibition of IL-6 and IL-12 production

Retrosynthetic Analysis:



Sheu. *J. Nat. Prod.* **2002**, *65*, 1904–1908.
Kim, Nam. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 228–231.

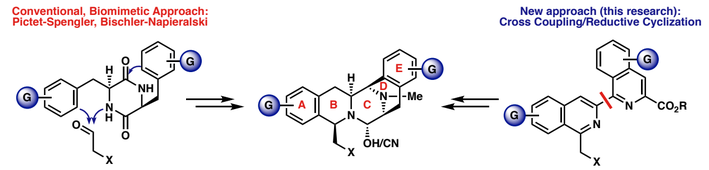
(–)-Jorumycin: an Anticancer bis-THIQ Natural Product



Isolated in 2000 from *Jorunna Funebris*, aka the spotted nudibranch

cell line	cancer type	IC_{50} (nM)
A549	lung	0.24
HCT116	colon	0.57
QG56	lung	0.76
DU145	prostate	0.49
BGC-823	adenocarcinoma	3.25
BEL-7402	liver	1.22
HeLa	cervical	2.11
HELF	embryonic lung	3.64
KB	oral	2.56

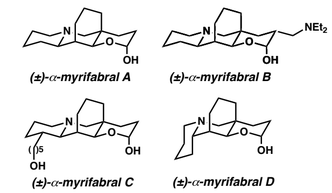
- Typical bis-THIQ syntheses employ sequential Pictet–Spengler reactions for THIQ construction (biomimetic)

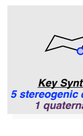


- Goal: Complementary, Non-Biomimetic Syntheses

Fontana, *Tetrahedron.* **2000**, *56*, 7305–7308 Williams, *Chem. Rev.* **2002**, *102*, 1669–1630

Myrioneuron Alkaloids — Myrifabrals A–D





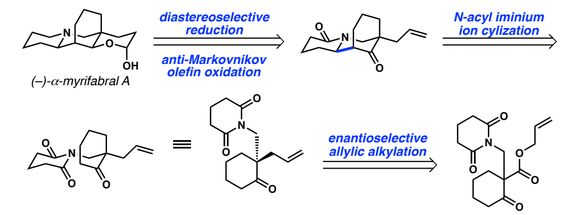
Key Synthetic Challenges
5 stereogenic centers (4 contiguous)
1 quaternary carbon center

Myrioneuron faberi

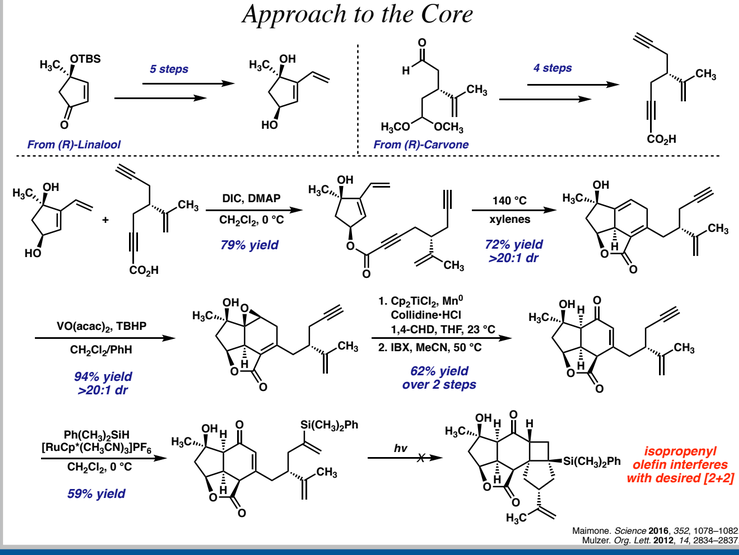
- Unique cyclohexane fused octahydroquinolizine skeleton
- Inhibition of Hepatitis C virus replication (HCV, IC50 0.9 to 4.7 μM with racemates)
- Isolated as racemic mixtures of α and β-OH epimers

Hao, *J. Org. Chem.* **2014**, *79*, 7945–7950.
Hao, *J. Nat. Prod.* **2015**, *78*, 2609–2616.
Hao, *Tetrahedron. Lett.* **2016**, *57*, 5632–5635.

Retrosynthetic Analysis of (–)-Myrifabral A



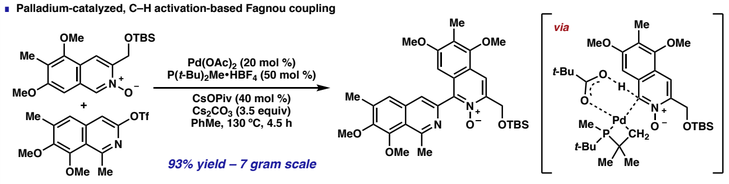
Approach to the Core



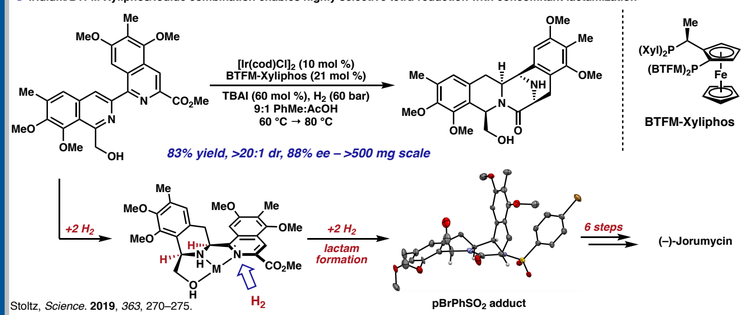
Maimone. *Science* **2016**, *352*, 1078–1082.
Mulzer. *Org. Lett.* **2012**, *14*, 2834–2837.

Total Syntheses of (–)-Jorumycin

- Palladium-catalyzed, C–H activation-based Fagnou coupling

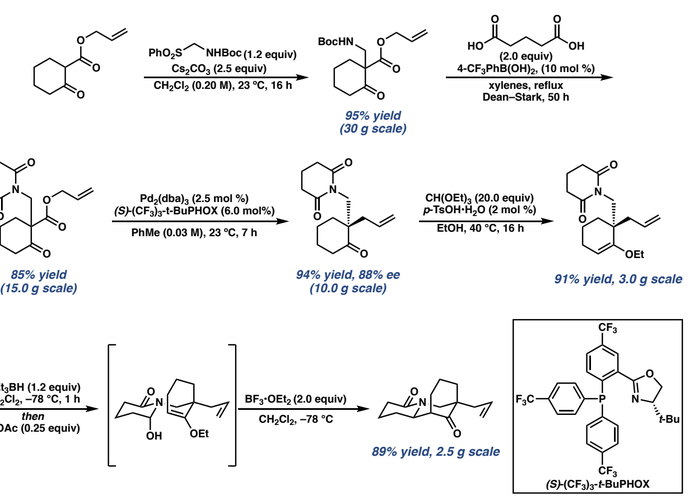


- Iridium/BTFM-Xyliphos/Iodide combination enables highly selective tetra-reduction with concomitant lactamization

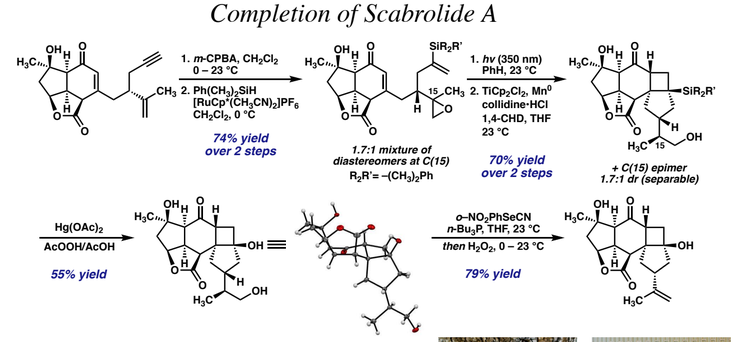


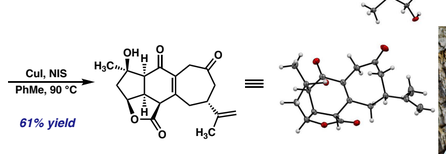
Stoltz, *Science.* **2019**, *363*, 270–275.

Synthesis of the Tricyclic Core



Completion of Scabrolide A





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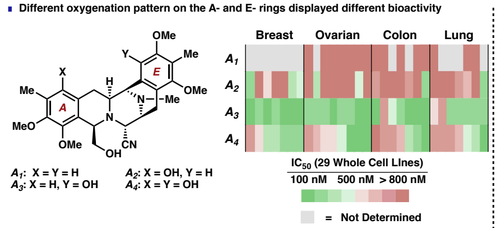
Stoltz. *ChemRxiv preprint.* 2020. DOI: 10.26434/chemrxiv.11923632.v1

Syntheses and Biological Evaluation of bis-THIQ Analogs

- Different oxygenation pattern on the A- and E- rings displayed different bioactivity



A_1: X = Y = H
A_2: X = OH, Y = H
A_3: X = H, Y = OH
A_4: X = Y = OH

In collaboration with with Dr. Dennis Slamon at UCLA Translational Oncology Research Laboratories

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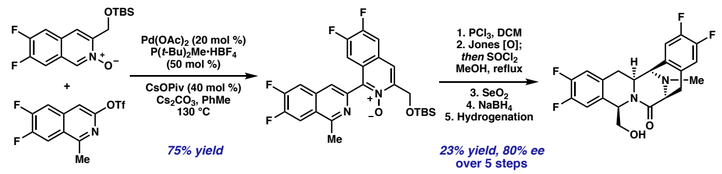
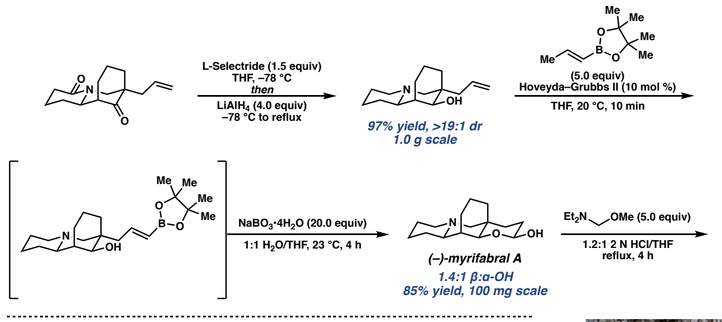
- Syntheses of other non-natural bis-THIQ analogs for medicinal chemistry studies



Goals: improve/maintain potency, simplify the structure, and improve metabolic stability

End Game of (–)-Myrifabral A and B



Tyler Fulton (G4)

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