Terpene Ring Construction - Case Studies

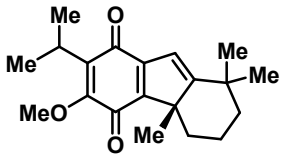
Jieyu Gu

Baran Group Meeting
04/06/20

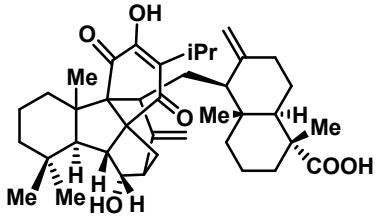
General Strategies

*Selected syntheses from past 10 years utilizing each strategy are summarized here
*Each molecule including its family members have at least been synthesized twice

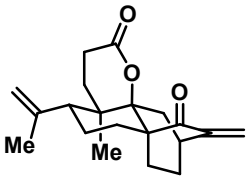
Form 1 C-C bond



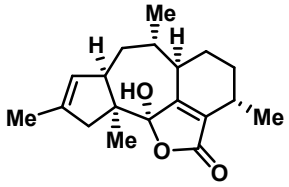
taiwaniaquinone H



taiwaniadduct D



Crotogoudin



Caribenol A

Organotransition metal chemistry:

- **RCM, RCEM:** Atropurpuran, Lancifodilactone, Ryanodol, Chinensiolide B, Cortistatins
- **Cross Coupling:** Presilphiperfolan-8-ol, Maoecrystal V, Cephanolides
- **C-H functionalization:** Longikaurin E, Taiwaniaquinone H
- **Carbene Chemistry:** Maoecrystal V

Radical cyclization:

- **Oxidative cyclization:** Berkeleyone A
- **Reductive cyclization:**
  - **Barton-McCombie:** Resiniferatoxin
  - **R-SePh:** Seco-prezizaane, Maoecrystal V
  - **Carbonyl:** Principinol D, Pleuromutilin, Longikaurin E, Maoecrystal Z
  - **Alkene:** Ophiobolin

Pericyclic Rxns:

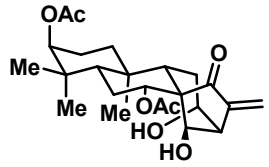
- **6π electrocyclization:** Crotogoudin, Rubriflordilactone A
- **4π electrocyclization:** Oridonin
- **Carbonyl-ene:** Taiwaniadducts

Miscellaneous ways

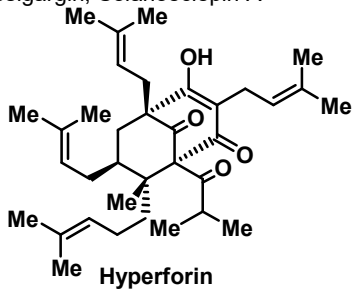
- **Friedel-Crafts:** Wortmannin, Cyrneines A, Caribenol
- **Oxidative dearomatization:** Maoecrystal V
- **Pinacol Coupling:** Thapsigargin, Echinopines
- **LA promoted Epoxide opening:** Hyperforin

Classic Carbonyl Chemistry:

- **1,2 addition:** Guaianolide, Periconianone A, Lungshengenin D, Pallambins C, Taiwaniaquinone H
- **1,4 addition:** Lungshengenin D, Andirolide N, Salvinorin A, Arisandilactone A, Caribenol A, Bilobalide(Giese)
- **Ketone α alkylation:** Wickerol A, Thapsigargin, Solanoeclepin A



Pharicin A



Hyperforin

Break + Form C-C bond(aka ring expansion/contraction)

- **Cyclopropane fragmentation:** Cyclocitrinol, Pavidolide B
- **Pinacol/Semipinacol:** Illisimonin A, Pharicin A, Maoecrystal V, Ingenol
- **Oxidative ring expansion**: Berkeleyone A, Hyperforin, Garsubellin A

Form multiple C-C bonds

Polyene cyclization

- **See GM**: Polyene Cyclizations (Harwood, 2018)

Cycloaddition/ formal cycloaddition

- **[5+2]**: Cerorubenic Acid, Vinigrol, Cyclocitrinol, Hainanolidol, Englerin A
- **[4+2]**: Vinigrol, Illisimonin A, Wickerol A, Maoecrystal V, Crotogoudin, Rippertenol, Caribenol A, Shizukaols A, Taxadiene, Solanoeclepin A, Bolivianine(DA+heteroDA cascade)
- **[3+2]**: Crinipellin A, Lingzhiol
- **[4+3]**: Frondosin
- **[2+2]**: Canataxpropellane
- **[2+2+1]**: Lancifodilactone, Propindilactone G, Ingenol, Phorbol, Ryanodol
- **[2+2+2]**: seco-prezizaane
- **Cyclopropanation**: Echinopines, Salvileucalin B, Arisandilactone A, Bolivianine

Miscellaneous ways

- **Cycloisomerization**: Pre-schisanartanin C, Drimane, Salvileucalin B
- **Oxidative dearomatization**: Atropurpuran, Pharicin A[5+2]
- **Diketene annulation**: Berkeleyone A, Hyperforin, Garsubellin A

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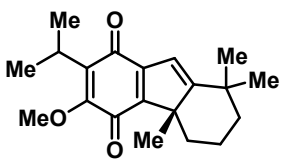
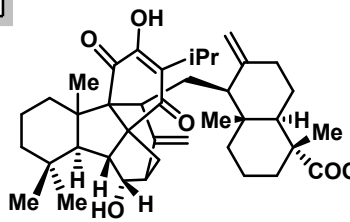
Case 1: Taiwaniaquinoid



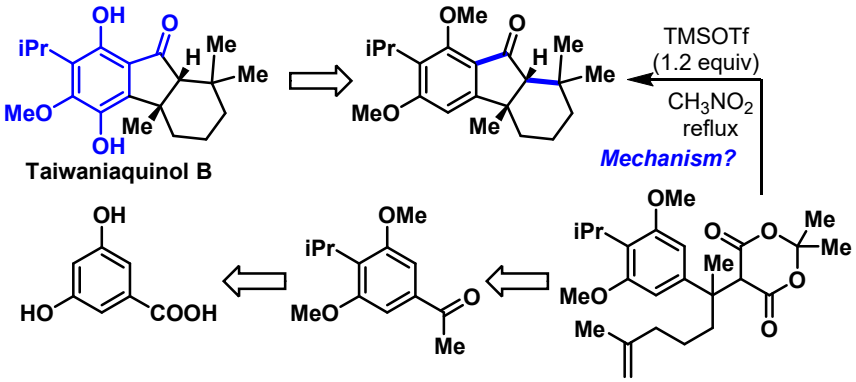
(–)-taiwaniaquinone H



taiwaniadduct D

Strategies discussed:
- Friedel-Crafts
- 4π electrocylization
- Ring contraction
- C-H funtionalization
- ene reaction

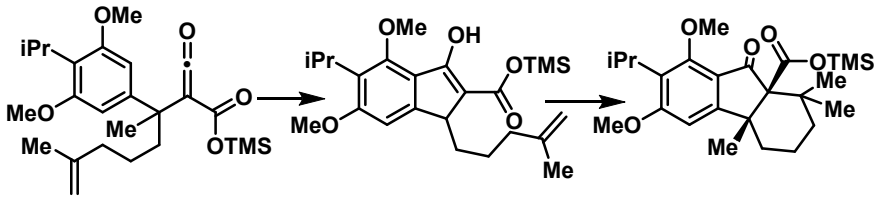
Racemic synthesis - Friedel-Crafts Acylation/α-alkylation domino reaction



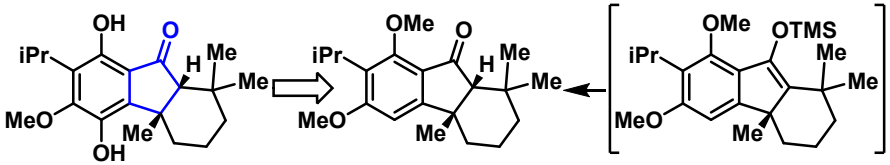
Taiwaniaquinol B

Fillion. *JACS*. **2005**, 13144

Mechanism

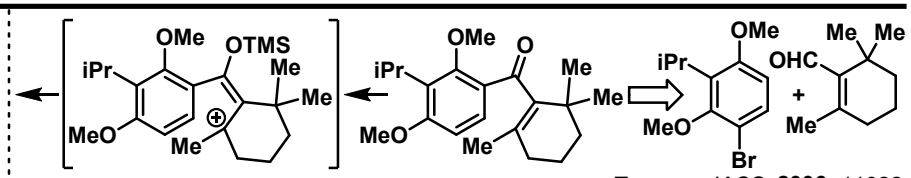


Nazarov Triflation



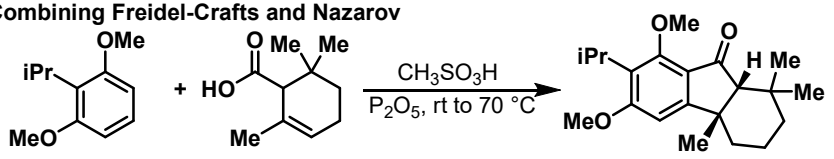
Taiwaniaquinol B

interrupted Nazarov see: Oridonin - Luo. *JACS*, **2019**, 20048



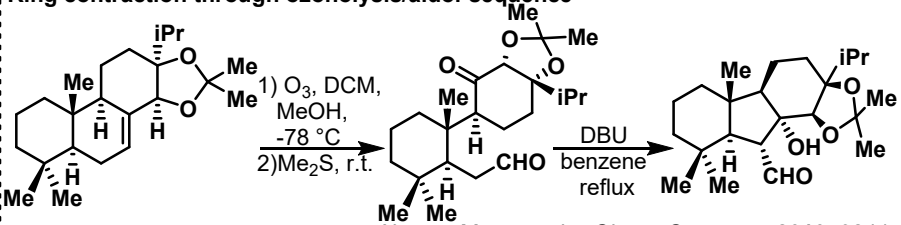
Trauner. *JACS*, **2006**, 11022

Combining Freidel-Crafts and Nazarov



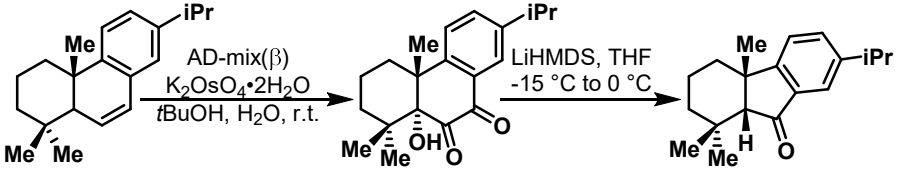
She. *OL*, **2008**, 1855
also: *Tetrahedron Lett.* **2008**, 1741

Ring contraction through ozonolysis/aldol sequence



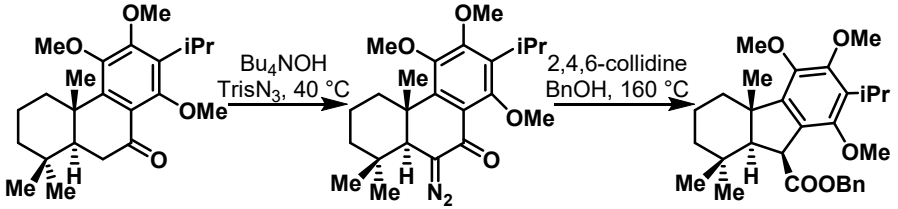
Alvarez-Manzaneda, *Chem. Commun.*, **2010**, 9244
also: *Org. Biomol. Chem.*, **2009**, 5146; *Chem. Commun.*, **2009**, 592

Ring contraction through benzilic acid rearrangement



Gademann. *Chem. Eur. J.* **2010**, 7692

Ring contraction through benzilic acid rearrangement



8 steps

Li. *OL*, **2013**, 2022
also: *JACS*. **2014**, 8185

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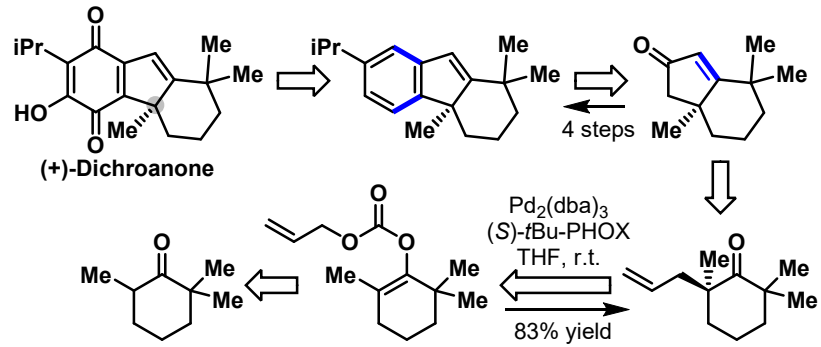
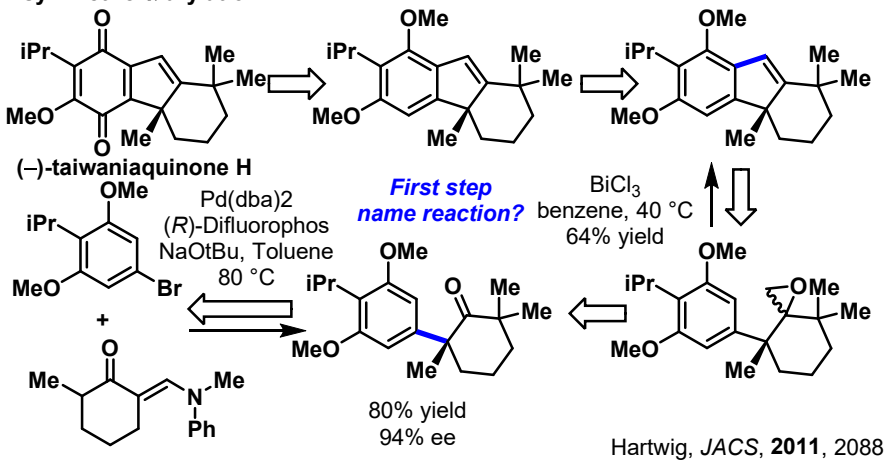
Asymmetric Tsuji allylation



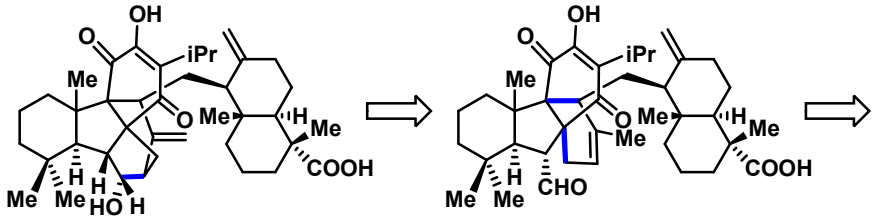
Stoltz. *JACS*, **2006**, 7738

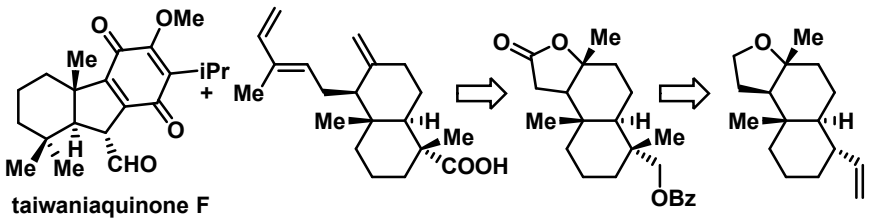
Asymmetric α-arylation



Hartwig, *JACS*, **2011**, 2088

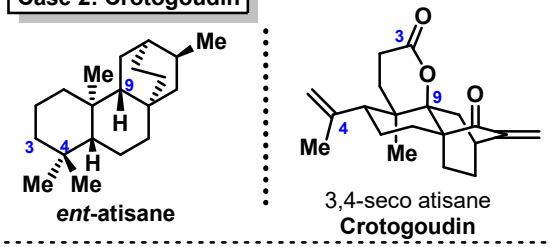
Bonus! - Carbonyl ene reaction





Li. *JACS*. **2014**, 8185

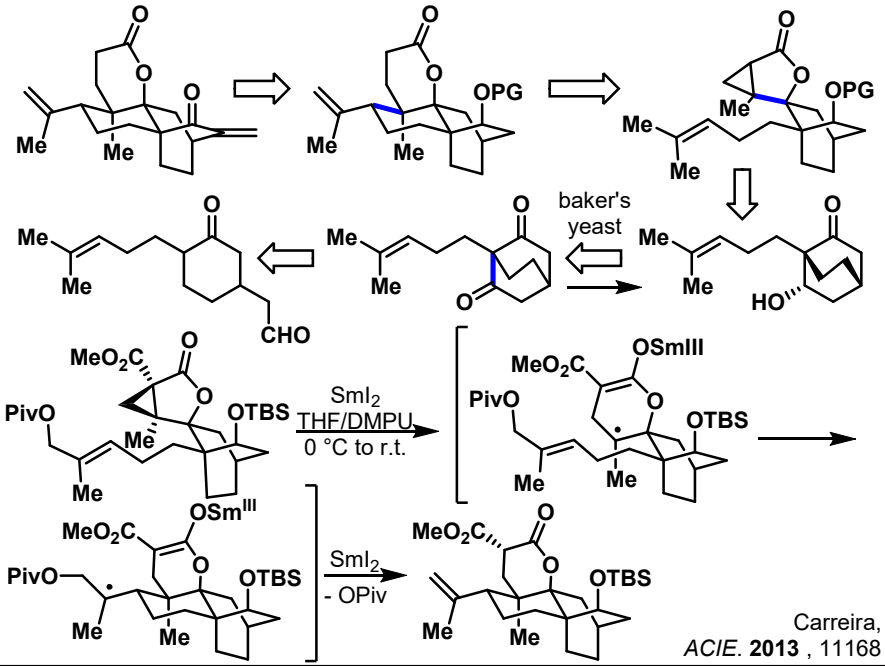
Case 2: Crotogoudin



Strategies discussed:

- 6π electrocyclization
- Diels-Alder cycloaddition
- Reductive radical cyclization
- Ring expansion
- Cycloisomerization

Ring expansion and Radical annulation



Carreira, *ACIE*. **2013** , 11168

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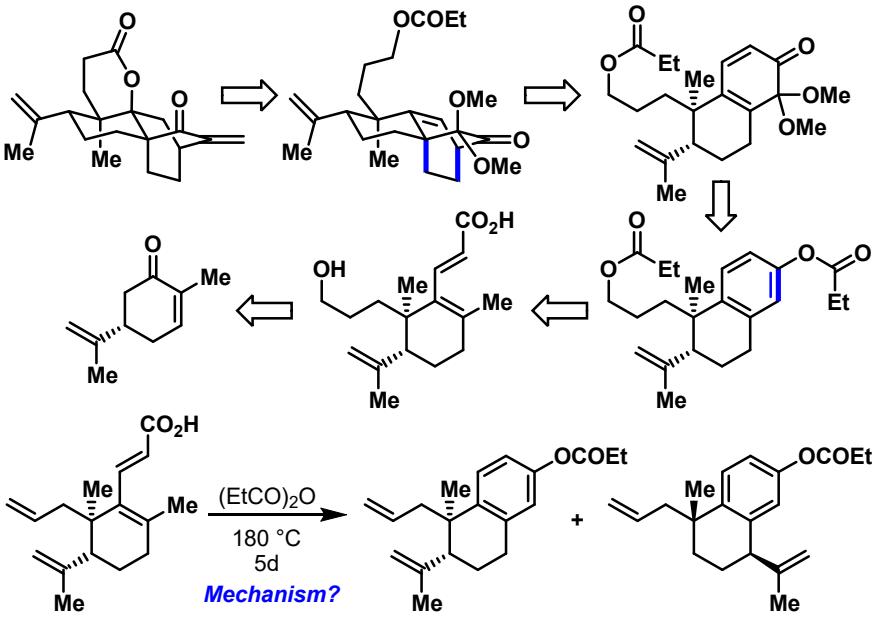
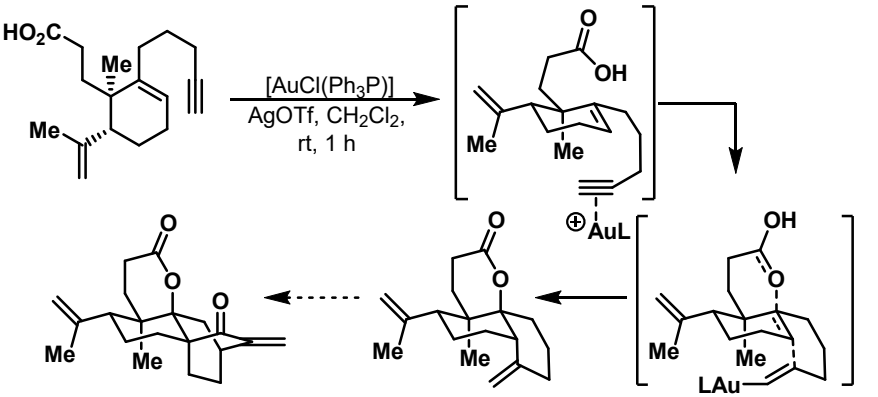
Diels-Alder and 6π electrocyclization



Sarpong, *JACS*. **2017**, 11349
also: Liu, *JACS*. **2015**, 13706

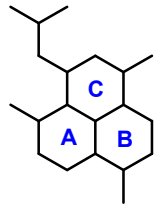
Side bar: attempted synthesis through cycloisomerization



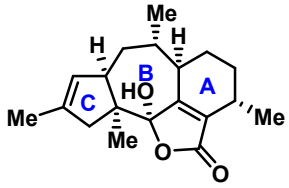
69% yield

Chem. Commun., **2015**, 889

Case 3: Caribenol A



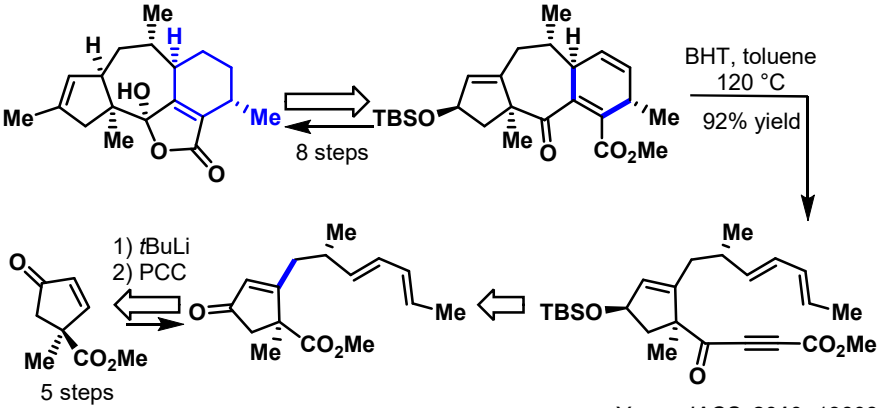
amphilectane skeleton



amphilectane diterpenoid Caribenol A

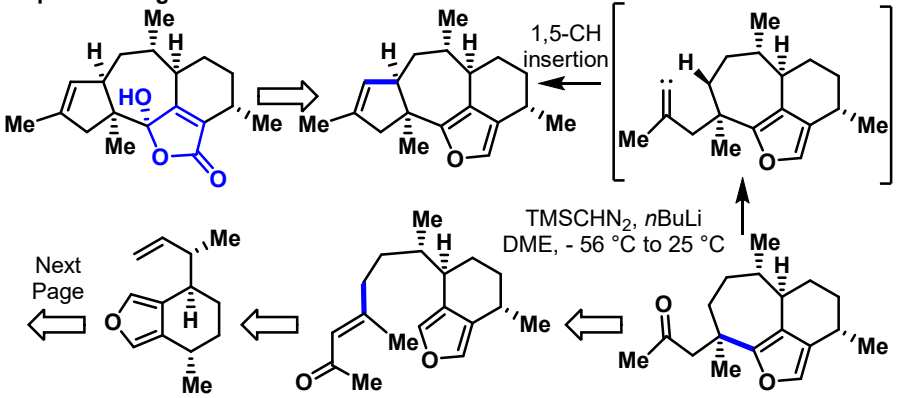
Strategies discussed:
- Intramolecular Diels Alder
- Cope rearrangement
- Michael Addition
- Friedel-Crafts

Intramolecular Diels Alder reaction



Yang, *JACS*, **2010**, 13608
also: *JOC*, **2013**, 5492; *Chem. Asian J.* **2013**, 1972

Cope Rearrangement and intramolecular Michael



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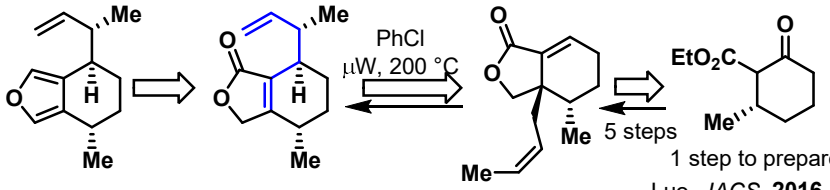
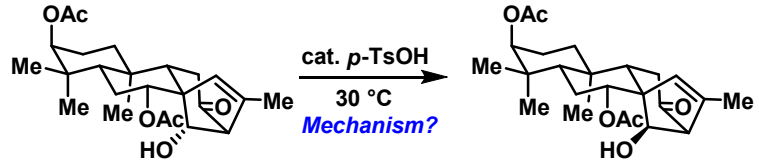
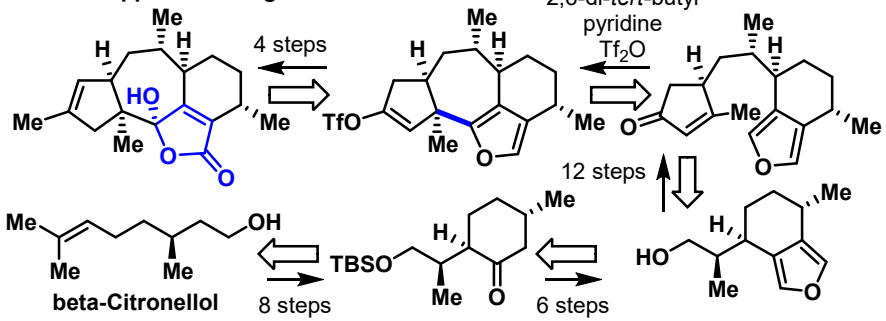


Luo, *JACS*. **2016**, 6261



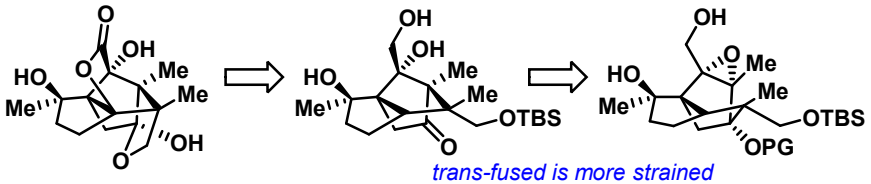
Ding, *JACS*. **2017**, 6098

A similar approach using Friedel-Crafts triflation



Trauner. *JACS*. **2017**, 4117

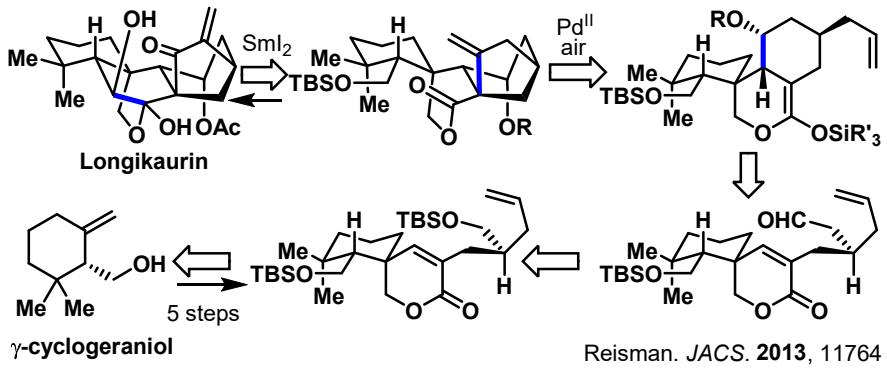
Side bar: Can you find the semipinacol disconnection



trans-fused is more strained

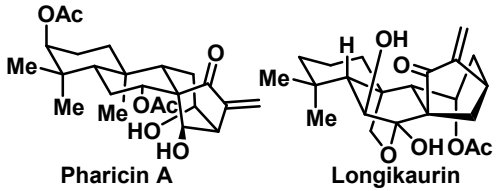
Rychnovsky, *JACS*. **2019**, 13295

Oxidative and reductive cyclization



Reisman. *JACS*. **2013**, 11764

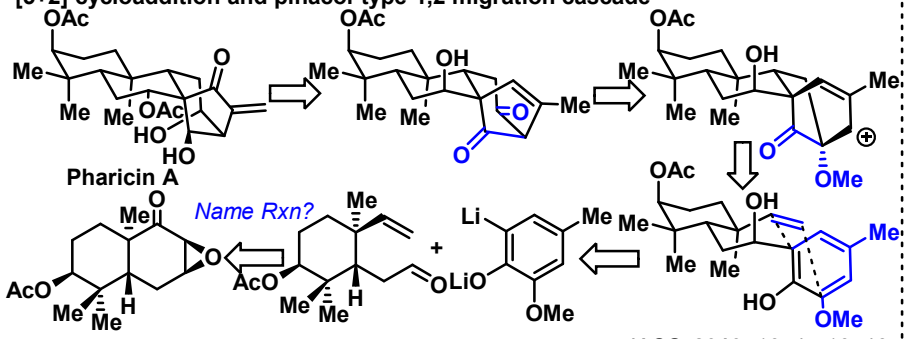
Case 4: *ent*-Kaurenoids



Pharicin A Longikaurin

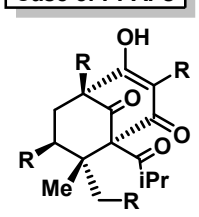
Strategies discussed:
- **Semipinacol rearrangement**
- **Oxidative dearomatization [5+2]**
- **Pd mediated oxidative cyclization**
- **Sm mediated reductive cyclization**

[5+2] cycloaddition and pinacol-type 1,2 migration cascade

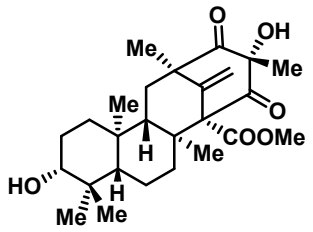


see *JACS*. **2010**, 16745-16746

Case 5: PPAPs



Hyperforin
R = prenyl



Berkeleyone A

PPAP: polycyclic polyprenylated acylphloroglucinol

Strategies discussed:
- **Oxidative radical cyclization**
- **Oxidative ring expansion**
- **Diketene annulation**
- **Claisen rearrangement**
- **Ring expansion**
- **Epoxide opening cyclization cascade**

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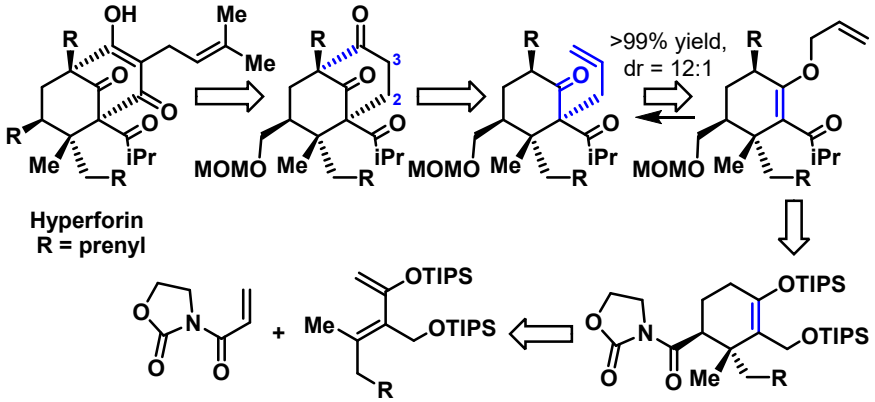
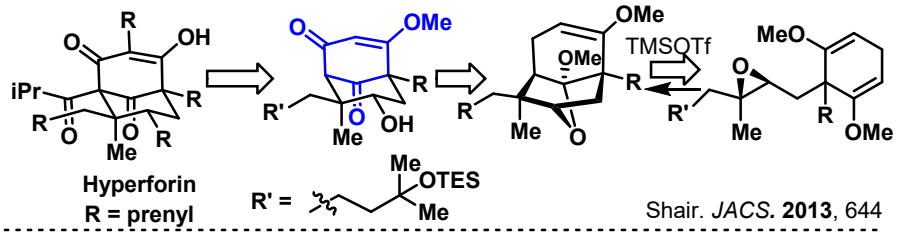
Claisen rearrangement

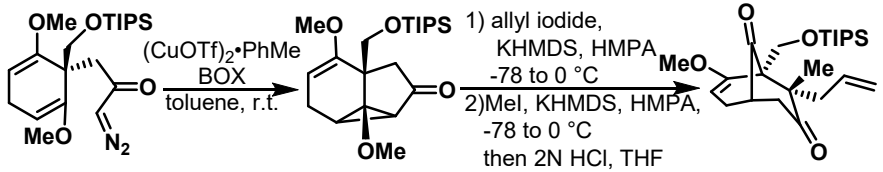


Epoxide opening cyclization cascade



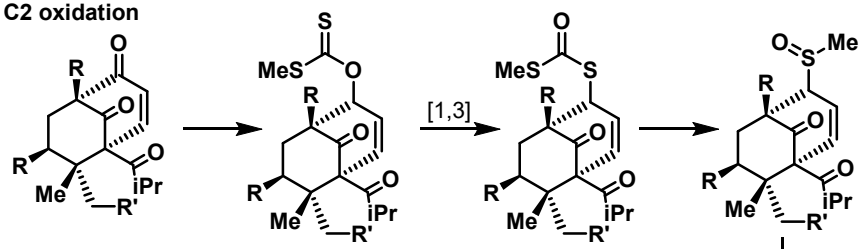
Shair. *JACS*. **2013**, 644

Cyclopropanation and Ring expansion (racemic)



Nakada, *Tet. Lett.* **2013**, 2022

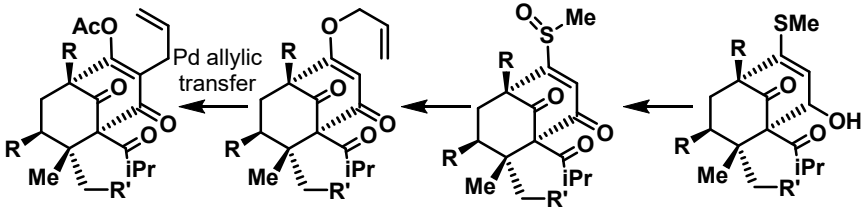
C2 oxidation



Conjugate addition with heteronuclephiles failed

[3,3] sigmatropic rearrangement failed

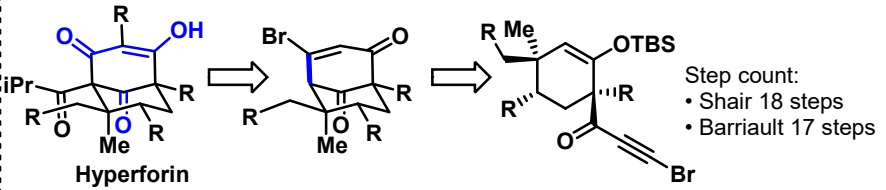
Pummerer



Claisen only gave trace product

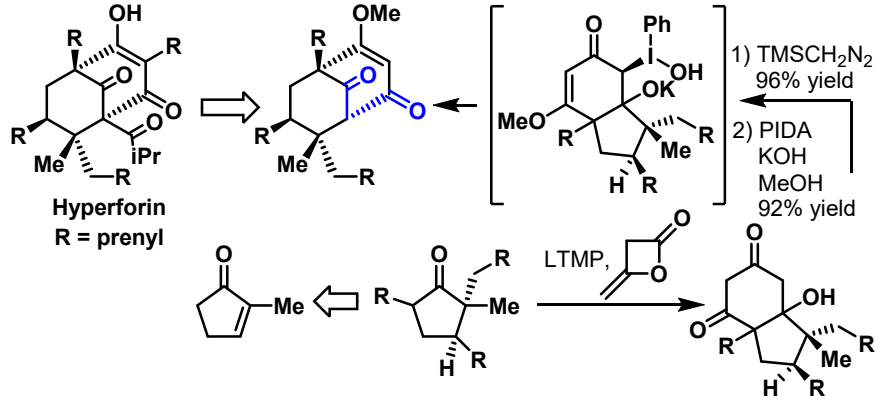
Shibasaki, *ACIE*. **2010**, 1103

Gold carbocyclization (racemic)



Barriault, *ACIE*. **2014**, 6701

Diketene annulation and oxidative fragmentation (racemic)



Maimone, *JACS*. **2015**, 10516

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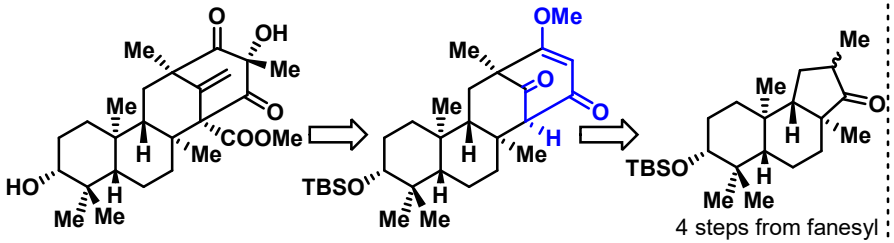
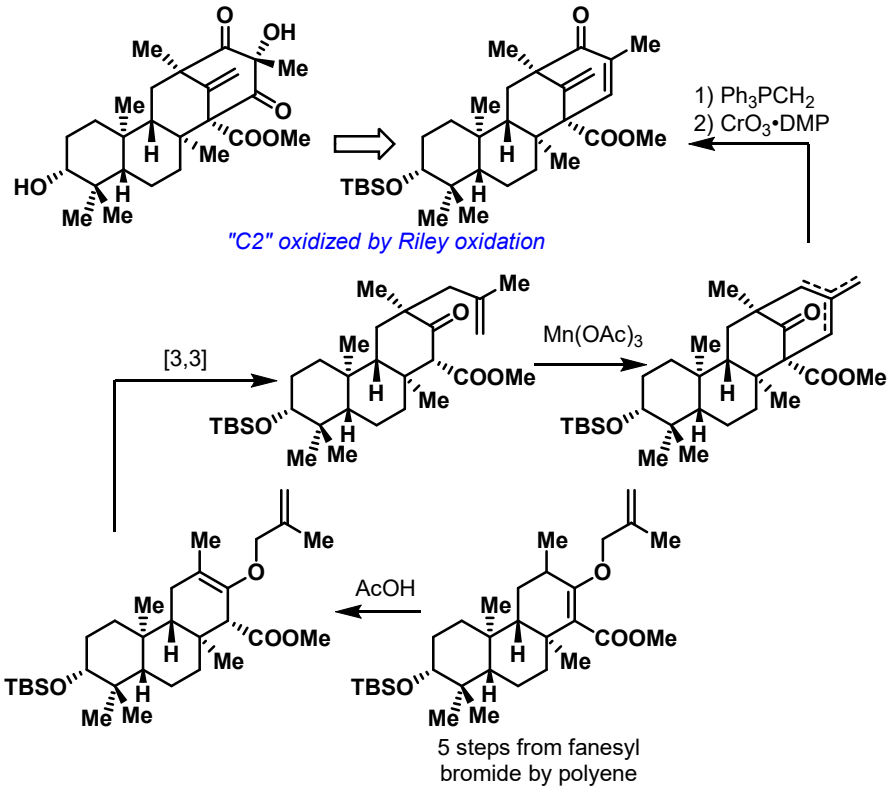
Baran Group Meeting
04/06/20



Maimone, *JACS*. **2017**, 1790

Oxidative radical cyclization



Newhouse, *JACS*. **2017**, 1790