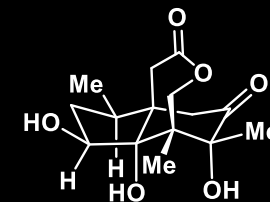
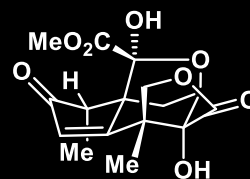
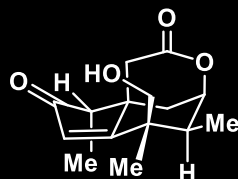
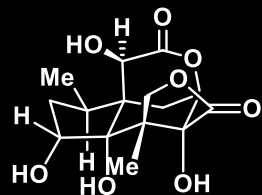
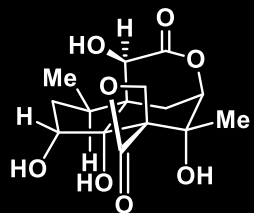


Modern Synthesis of *Illicium* Natural Products

Aaron Roth

October 22nd 2019



Outline

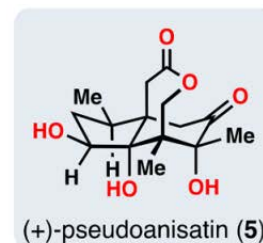
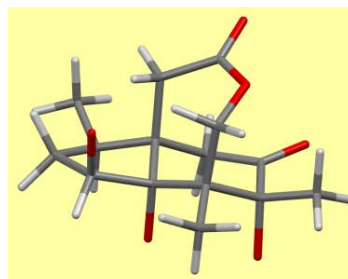
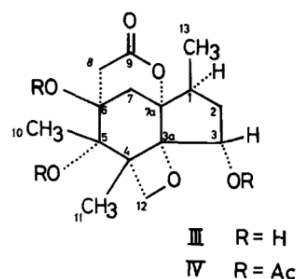
- **1950's** - Isolation, activity and structure elucidation
- Previous Total Synthesis
- **2015** - Shenvi's 8-step total synthesis of (-)-jiadifenolide
- Biosynthesis of *illicium* terpenes
- **2016, 2017** - Maimones strategy and synthesis of *Illicium* natural products

Origin of *Illicium* Sesquiterpenoids

- Genus *Illicium* is an evergreen shrub or tree encompassing ~40 species
 - Essential oils have been the primary motivation for research
- Some fruits have been known to be toxic for several centuries
- 1952 – isolation of anisatin by Lane et. al.
 - Complete Structure later established by Yamada and Hirata (1968)
 - Done through degradation studies and NMR spectroscopy
- Pseudoanisatin was originally mischaracterized by spectroscopic methods (1971)



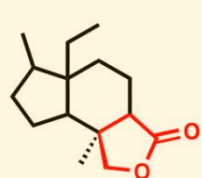
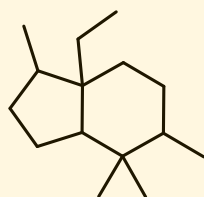
I. anisatum
Japanese star anise



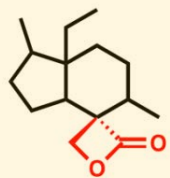
- Later characterized by X-ray crystallography (1983) and the structure revised

Classification of *Illicium* terpenoids – Carbon Skeleton

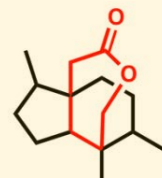
Seco-Prezizaane-Type



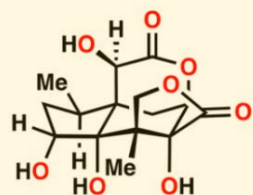
majucinoids
>25 members



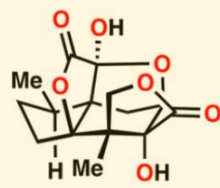
anisatinoids
ca. 15 members



pseudoanisatinoids
>50 members



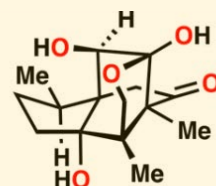
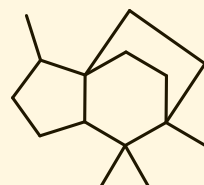
majucin (1)



jiadifenolide (2)

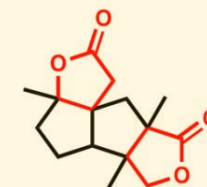
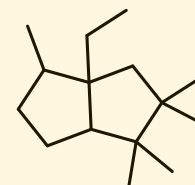
[seco-prezizaane sesquiterpenes]

Allo-cedrane-type

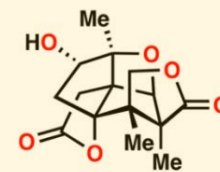


11-O-debenzoyl-
tashironin (4)

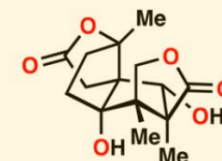
Anisactone-Type



anisactone-type
ca. 10 members



merrillactone A (14)



anisactone A (13)

[anisactone sesquiterpenes]

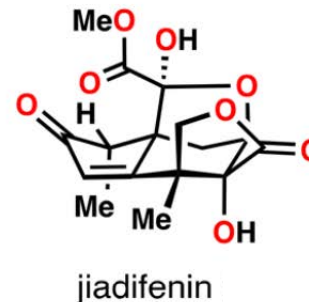
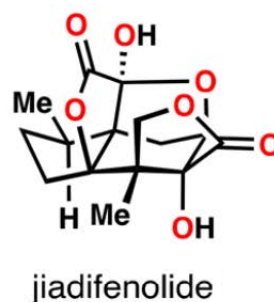
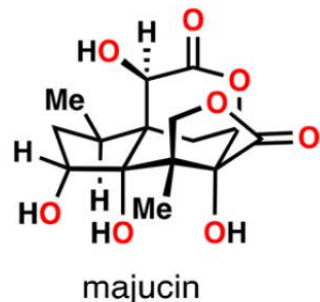
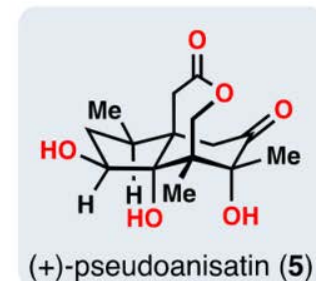
Over 100 sesquiterpene lactones have been isolated from the *Illicium* genus

Biological Activity

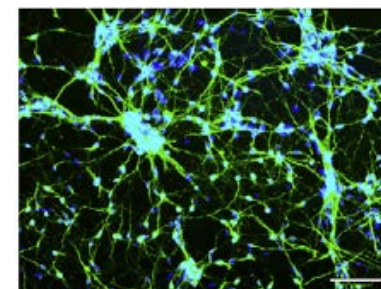
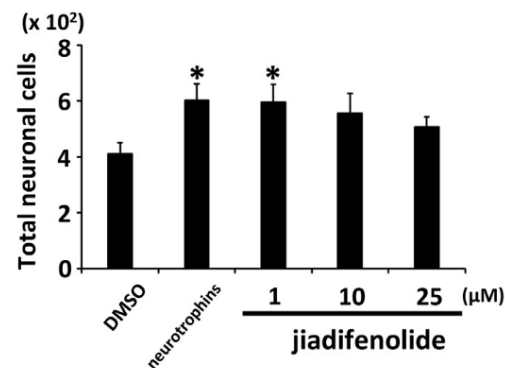
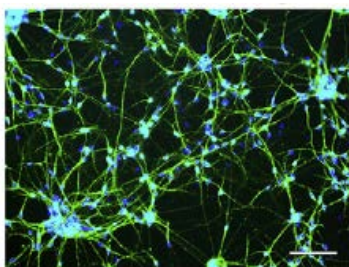


A strong convulsant by acting as a noncompetitive inhibitor of GABA_AR (LD₅₀ < 1mg/kg)

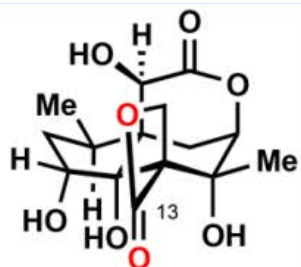
Highly selective for insect GABA_AR over mammalian GABA_AR suggesting a possible role as an insecticide



Many of these compounds have shown “neurotrophic” activity



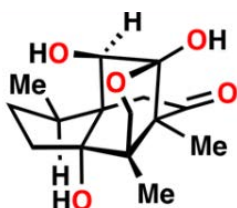
Previous Synthesis



anisatin

Anisatin

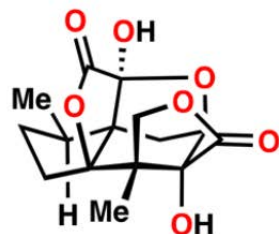
Woodward, 1982
Chen, 1985
Yamada, 1990
Yamada, 2001
Fukuyama, 2012



11-O-debenzoyl-
tashironin

11-O-debenzoyltashironin

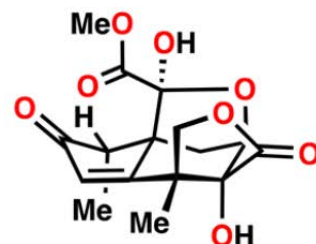
Danishefsky, 2006
Danishefsky, 2008
Mehta, 2011



jiadifenolide

jiadifenolide

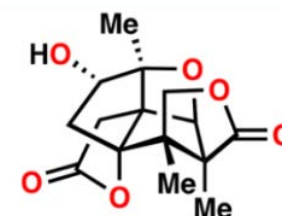
Theodorakis, 2011
Sorenson, 2014
Dalby, 2014
Shenvi, 2015
Zhang, 2015
Gademann, 2016



jiadifenin

Jiadifenin or ODNM

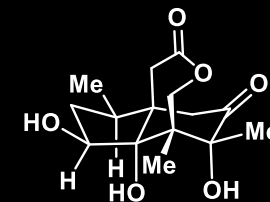
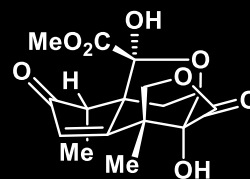
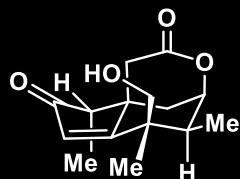
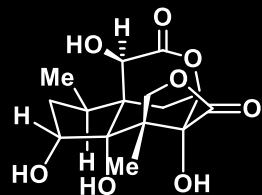
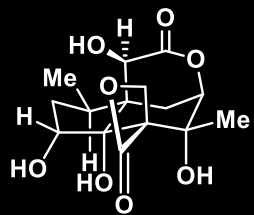
Danishefsky, 2004
Danishefsky, 2006
Fukuyama, 2009
Theodorakis, 2013
Fukuyama, 2015
Micalizio, 2016



merrilactone A

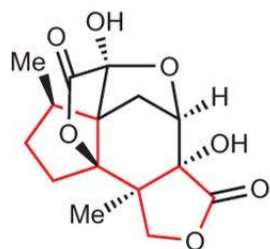
Merrilactone A

Danishefsky, 2002
Inoue, 2003
Greaney, 2005
Fukuyama, 2005
Danishefsky, 2005
Mehta, 2006
Fukuyama, 2007
Frontier, 2007
Frontier, 2008
Greaney, 2010
Zhai, 2012
Greaney, 2012

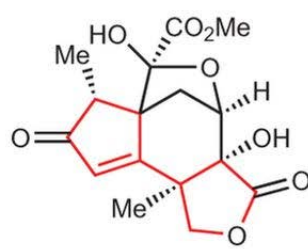


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(-)-jiadifenolide (1)

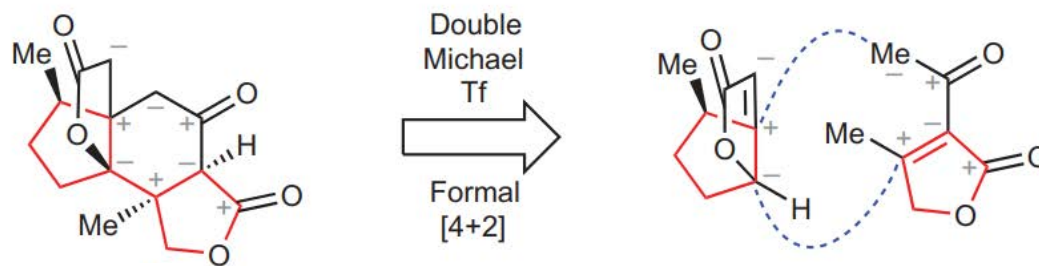
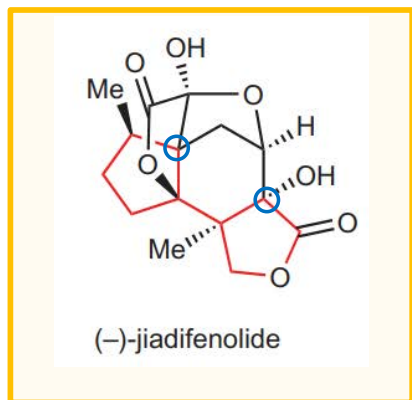


(-)-jiadifenin (2)

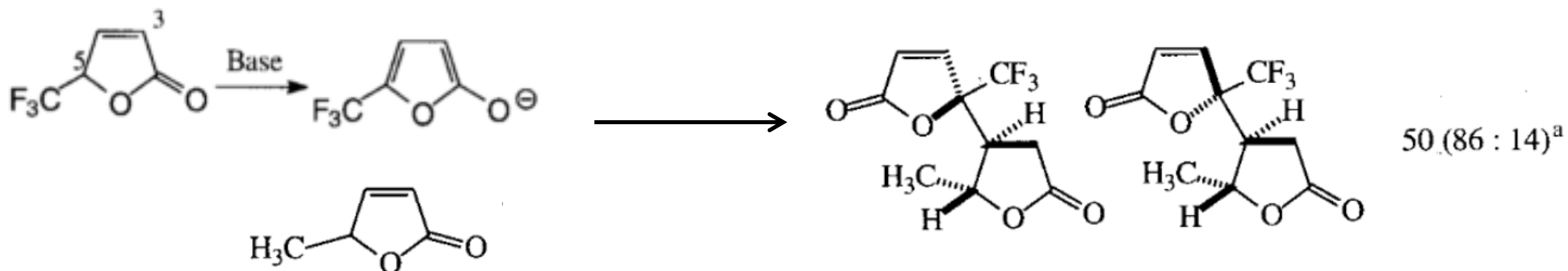


(-)-jiadifenoxolane A (3)

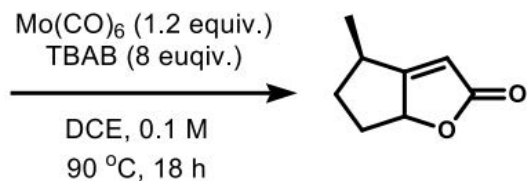
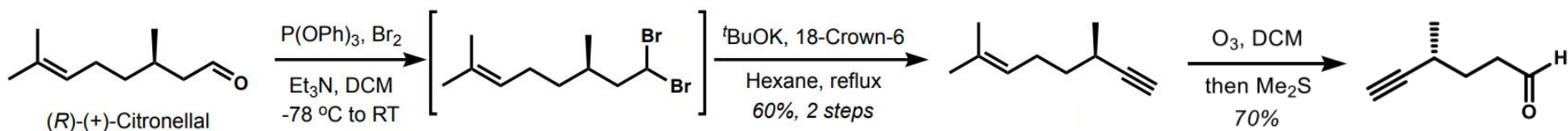
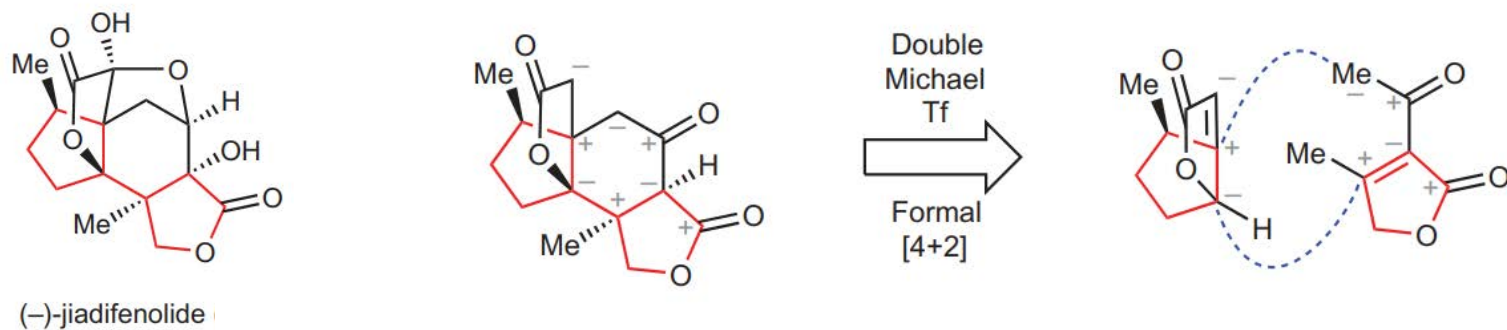
Shenvi's Retrosynthetic Strategy



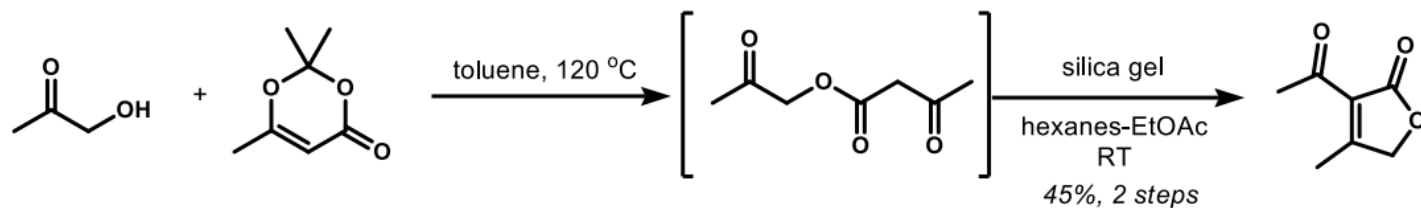
behave as γ -nucleophiles in Michael and aldol reactions²¹. The stereoselectivity in this process²² was left to chance. Thus, division of **7** in half via two Michael transforms would deliver two butenolides, **8** and **9**.



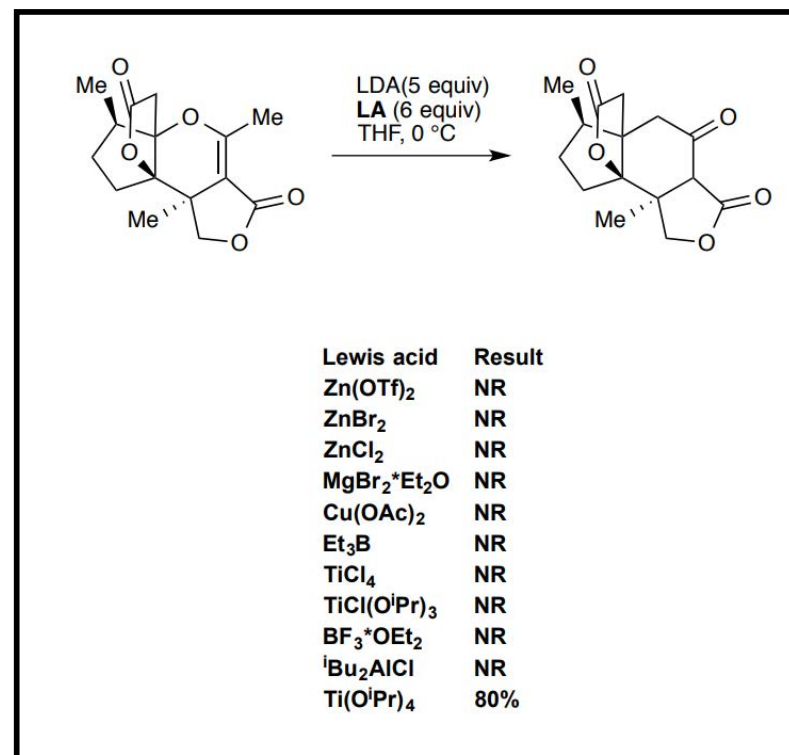
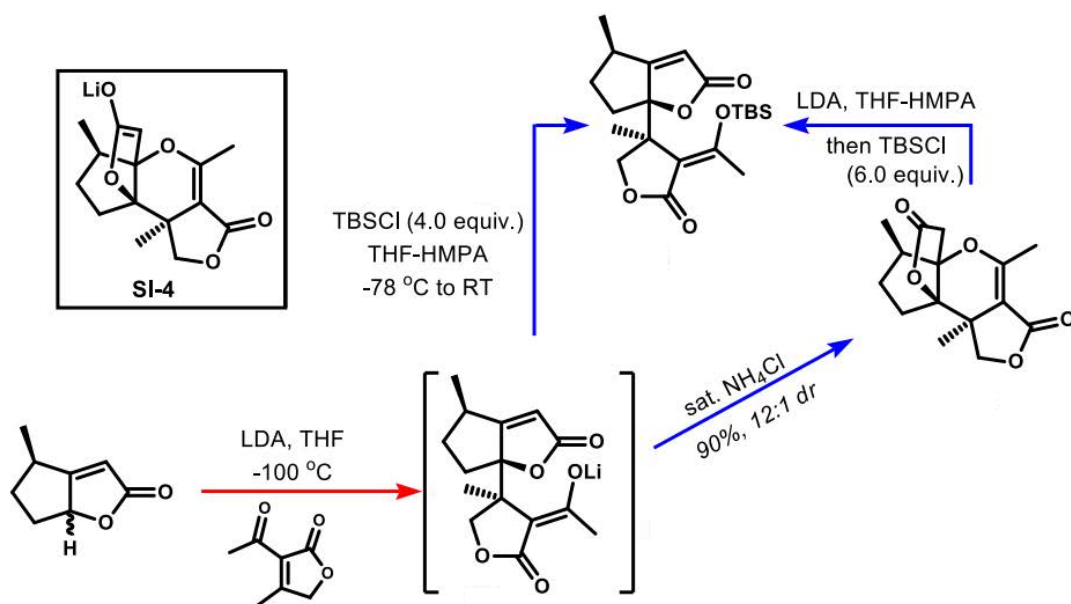
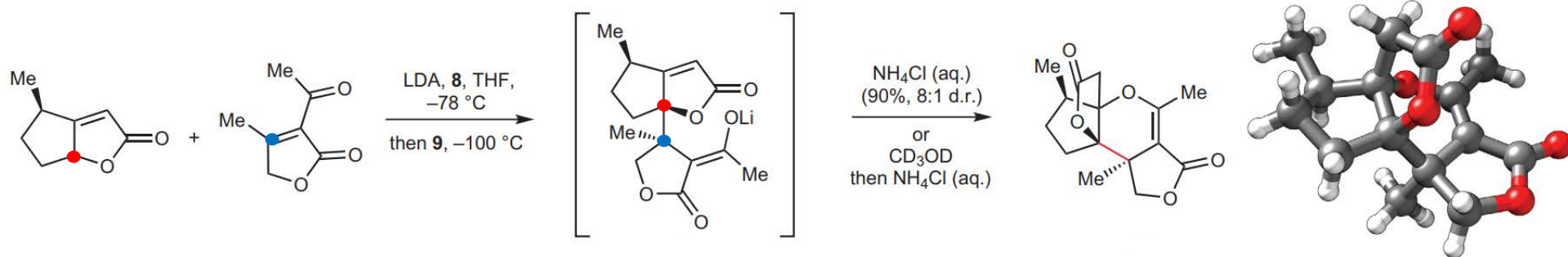
Starting material synthesis



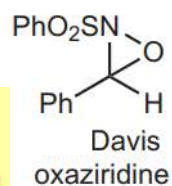
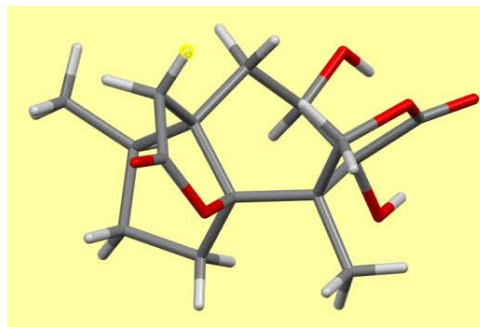
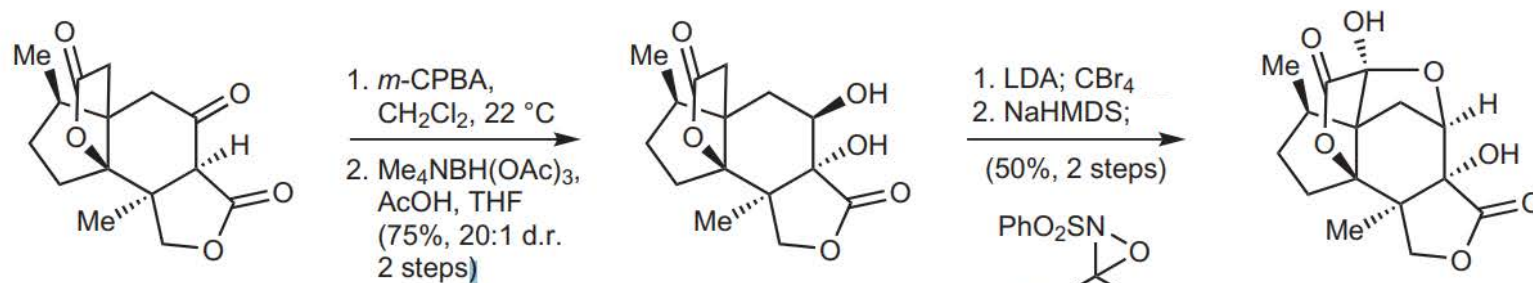
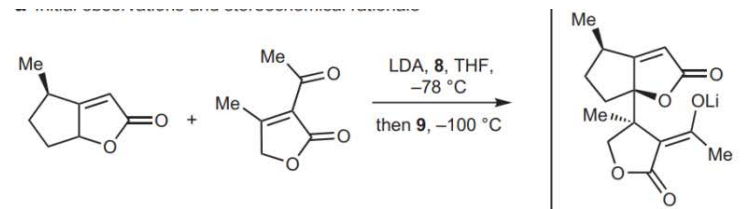
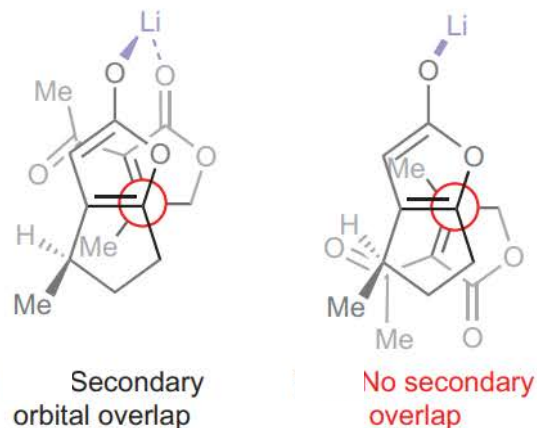
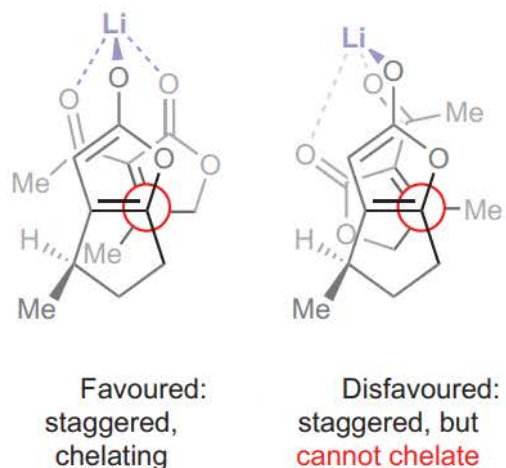
1 gram scale: 50% yield
 4 gram scale: 56% yield



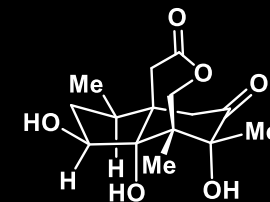
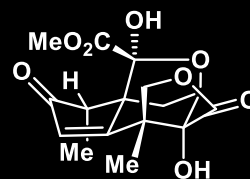
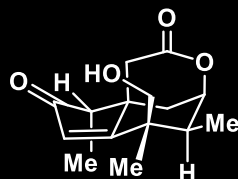
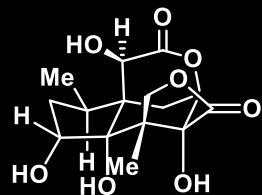
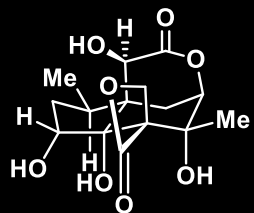
Key Disconnection and Mechanistic Understanding



Rationalization of Stereochemistry and End Game



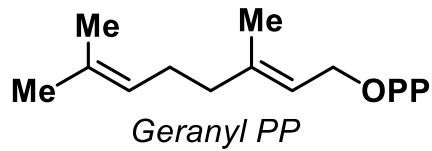
1 gram produced by total synthesis which would have required 117 kilograms of *I. jiadifengpi*



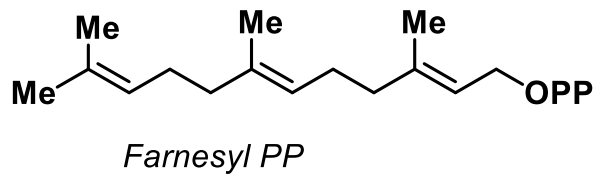
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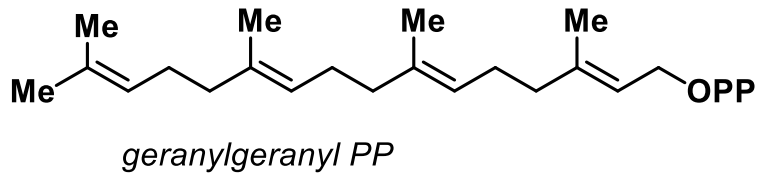
Terpene Biosynthesis



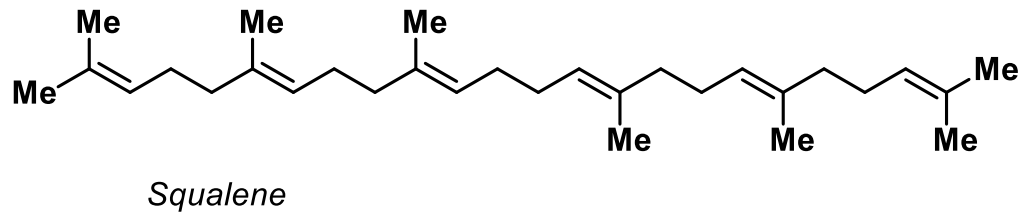
Monoterpenes



Sesquiterpenes



Diterpenes

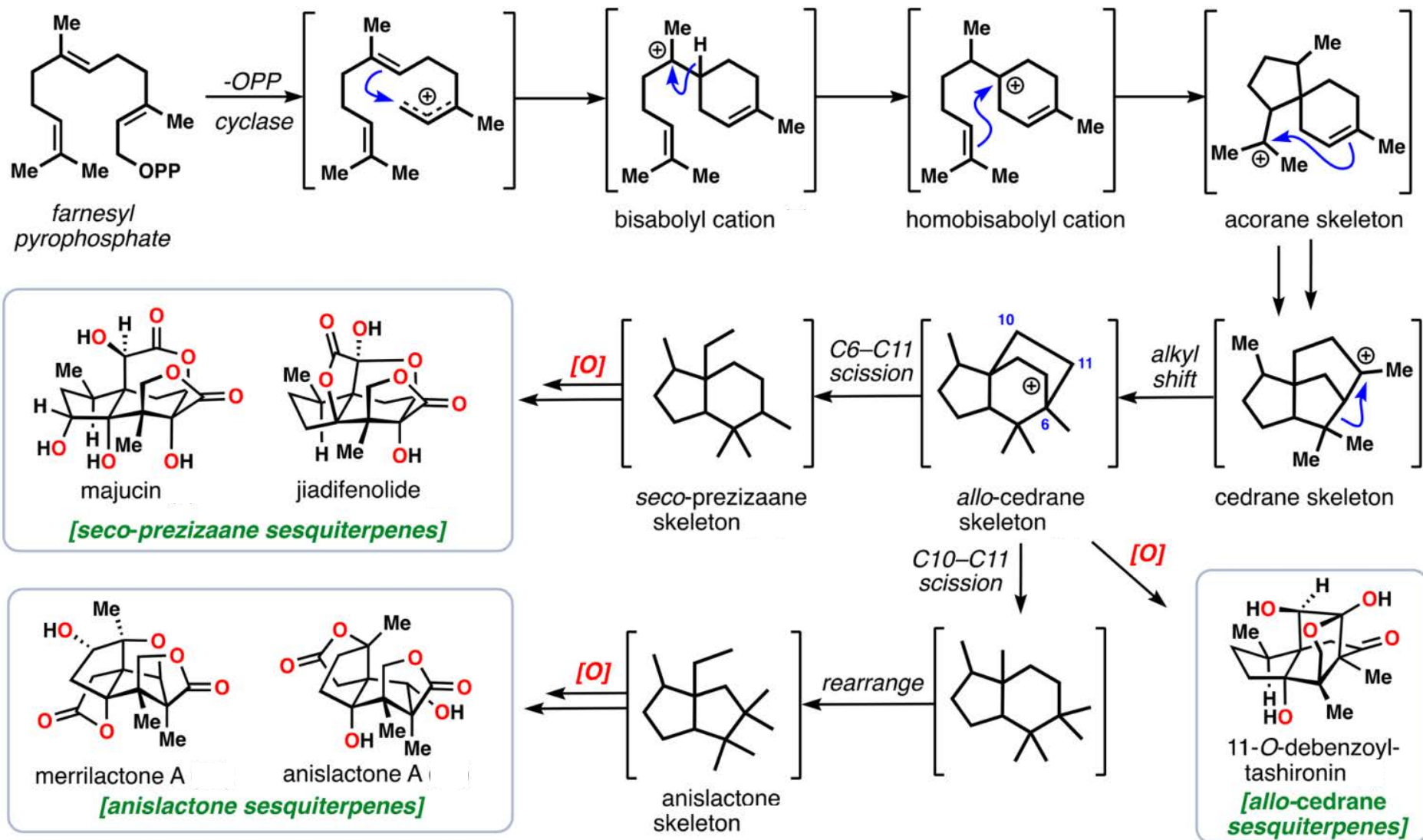


Triterpenes (steroids)

Hemiterpenes (C₅)
Monoterpenes (C₁₀)
Sesquiterpenes (C₁₅)
Diterpenes (C₂₀)
Triterpenes (C₃₀)
Tetraterpenes (C₄₀)

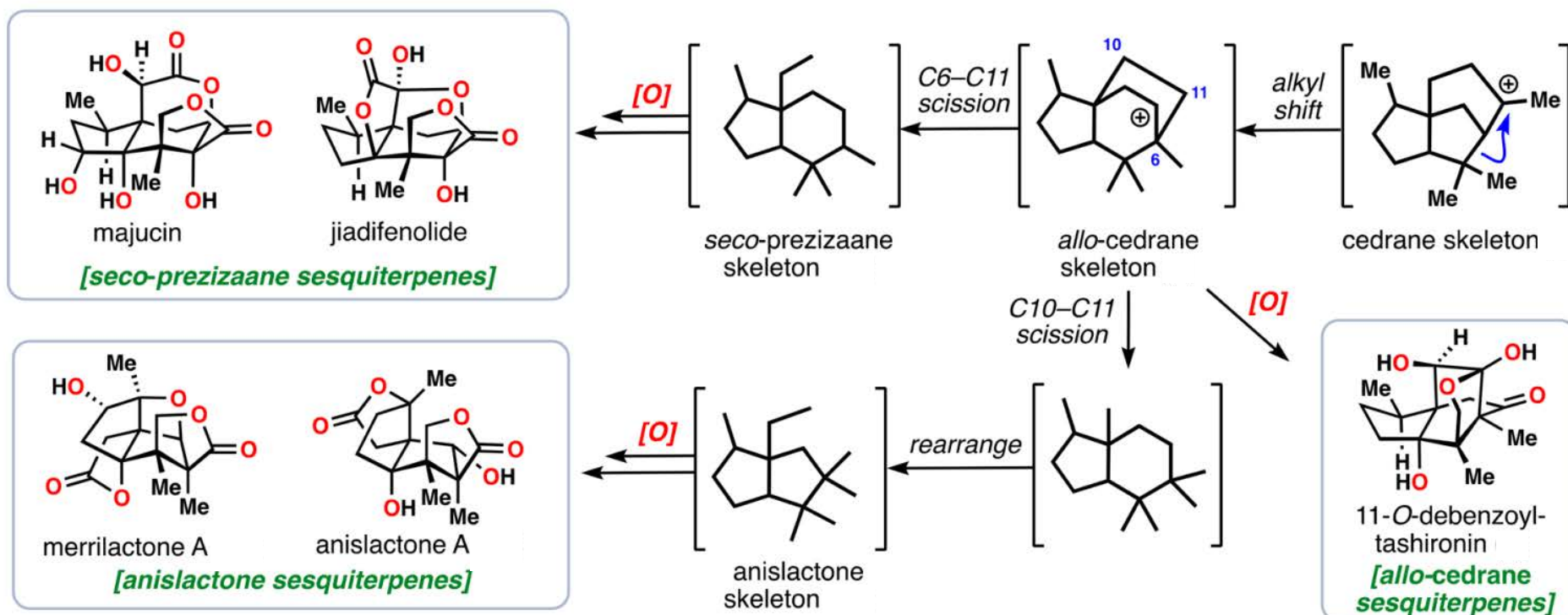
What biosynthetic steps remain to access *Illicium* sesquiterpenes?

Terpene Biosynthesis – Access to Core Scaffolds

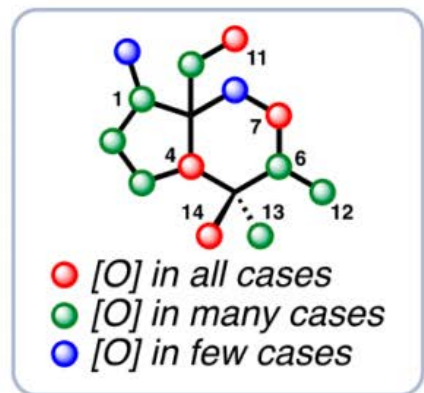
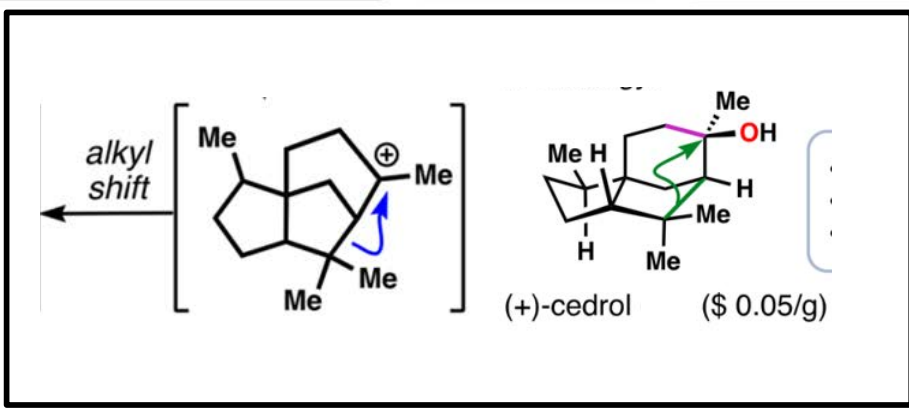
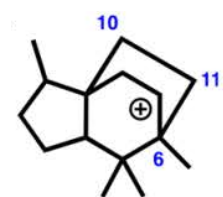
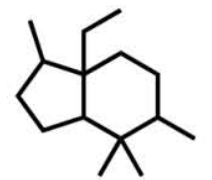
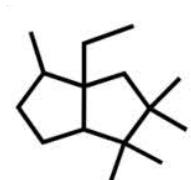
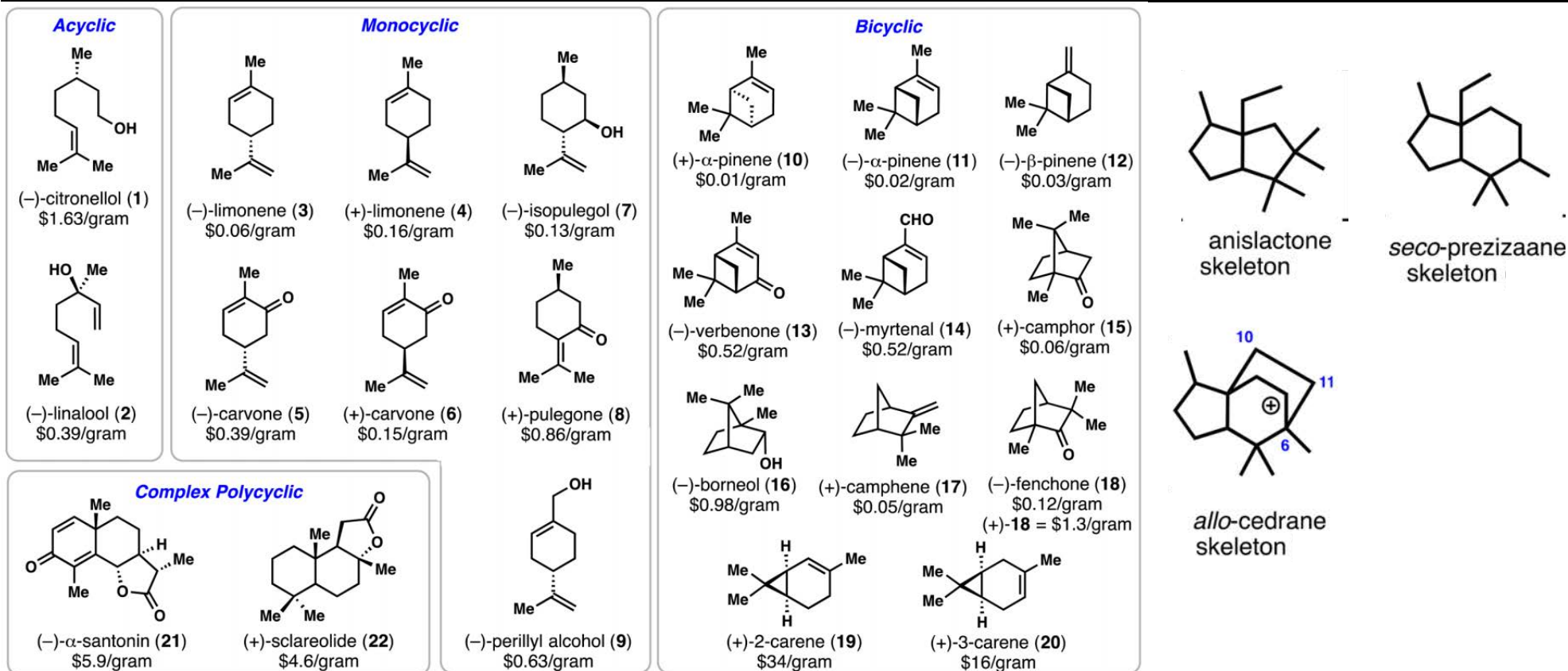


Maimone Retrosynthetic Strategy

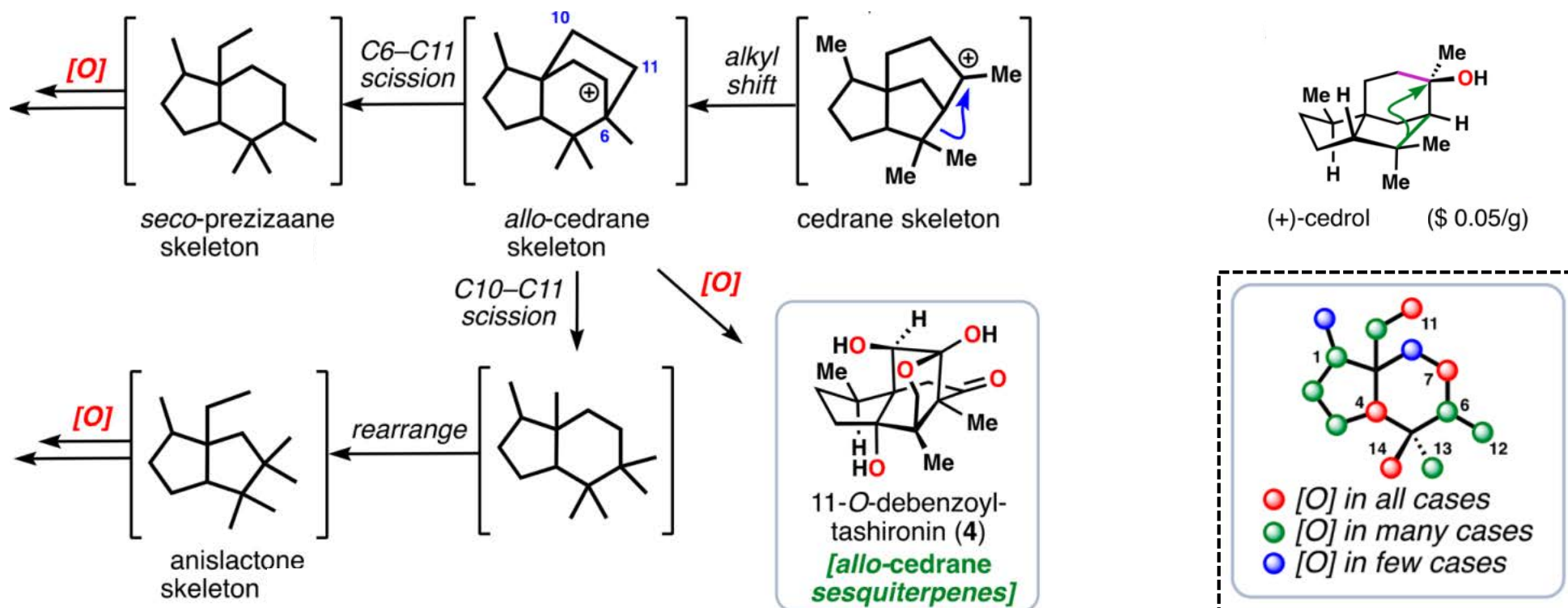
A biomimetic strategy through a common core in the biosynthesis could give rapid access to a large number of *Illicium* terpeneoids



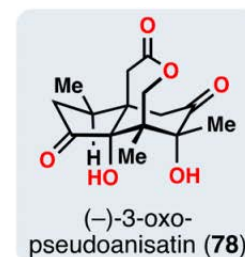
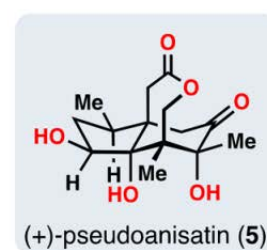
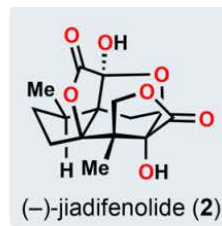
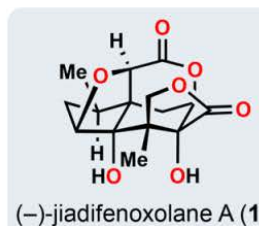
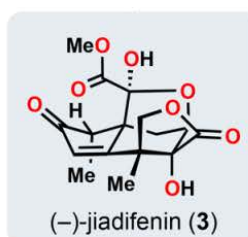
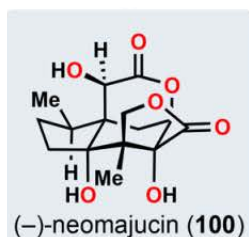
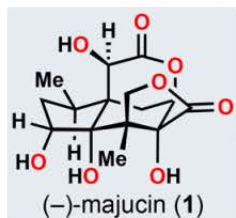
Maimone Retrosynthetic Strategy



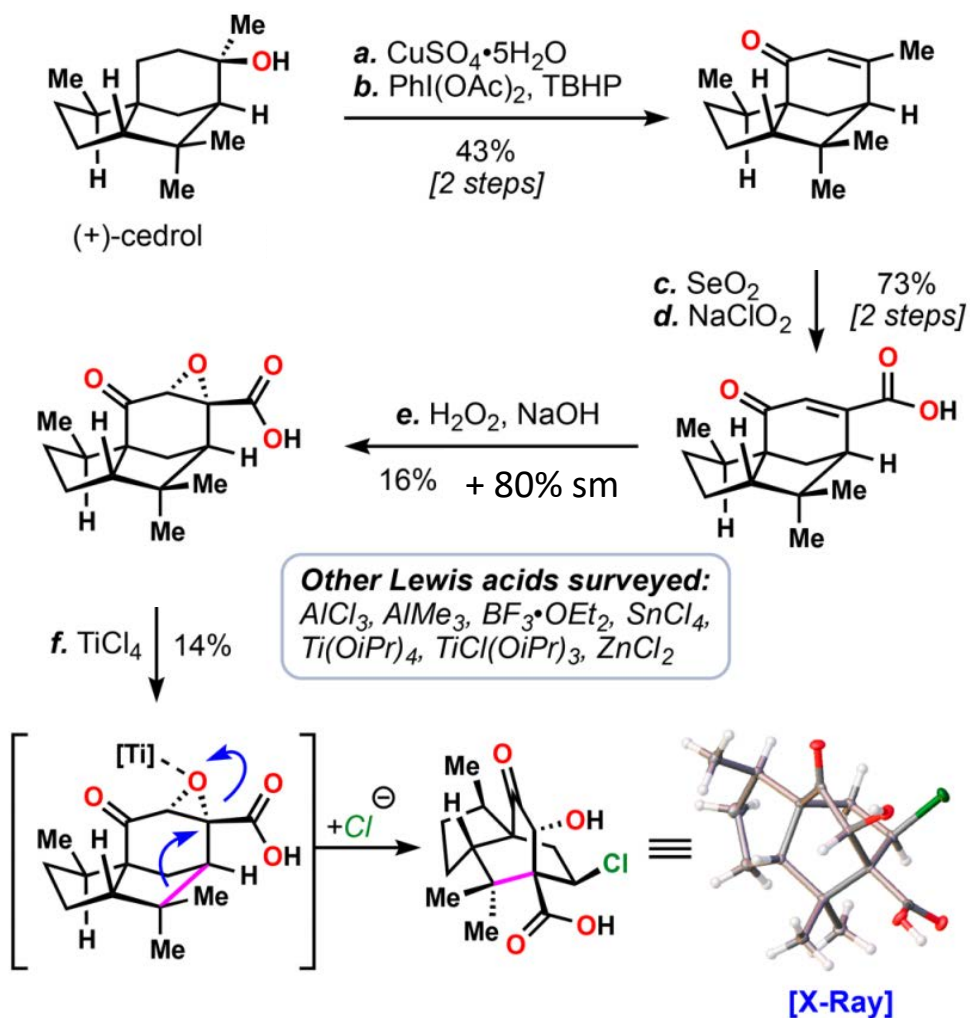
Maimone Retrosynthetic Strategy



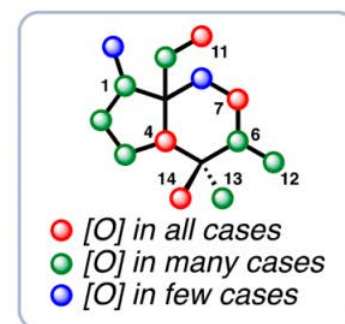
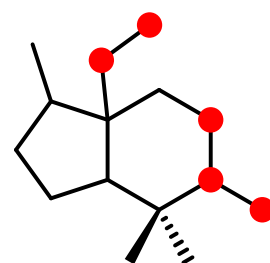
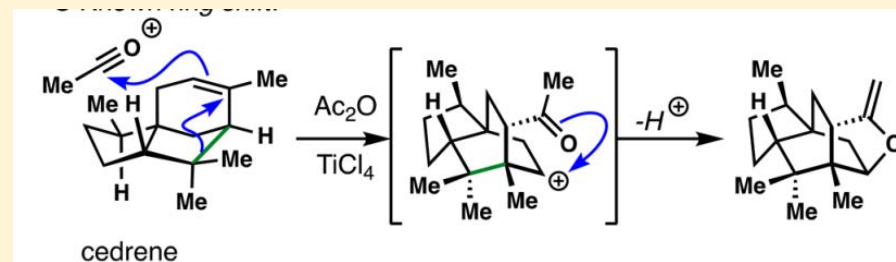
From cedrol effect a C-C bond Shift, a C-C bond cleavage and 6-12 net oxidations



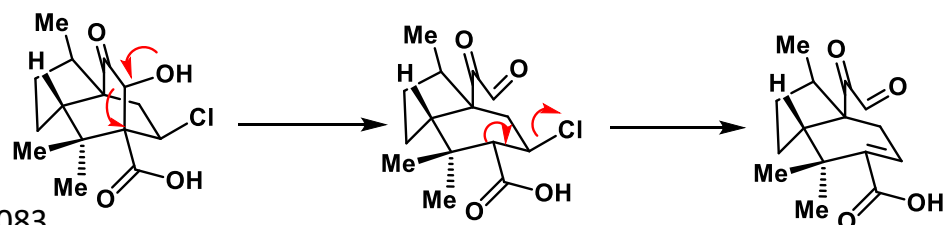
Biomimetic C-C Shift Strategy – Forward Direction



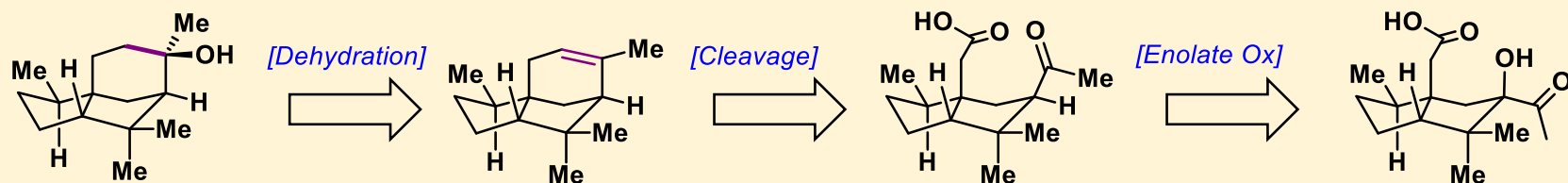
Known ring shift:



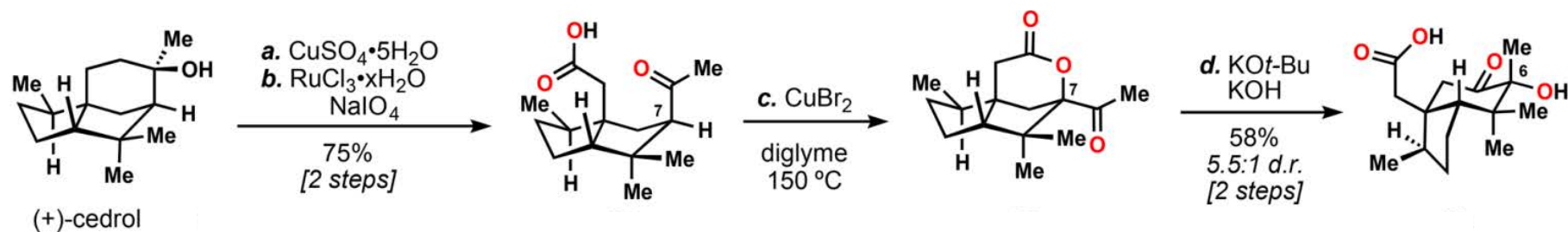
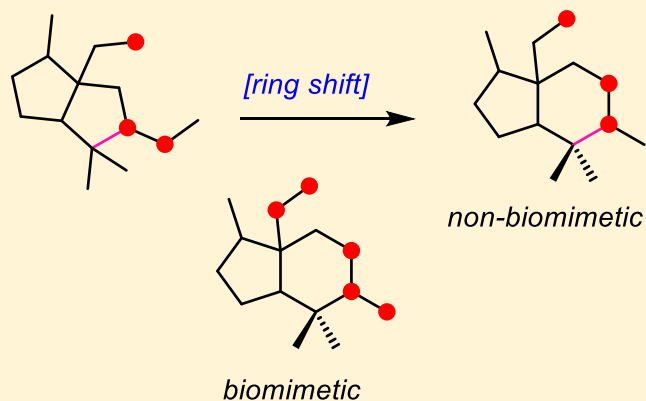
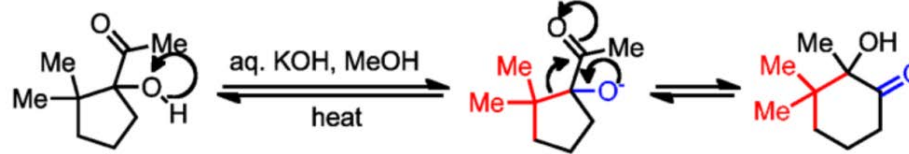
Anticipated retro-aldol:



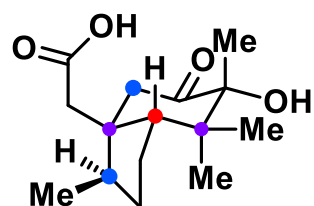
Breaking the C₆-C₁₁ Bond Reassessed



α -ketol rearrangement

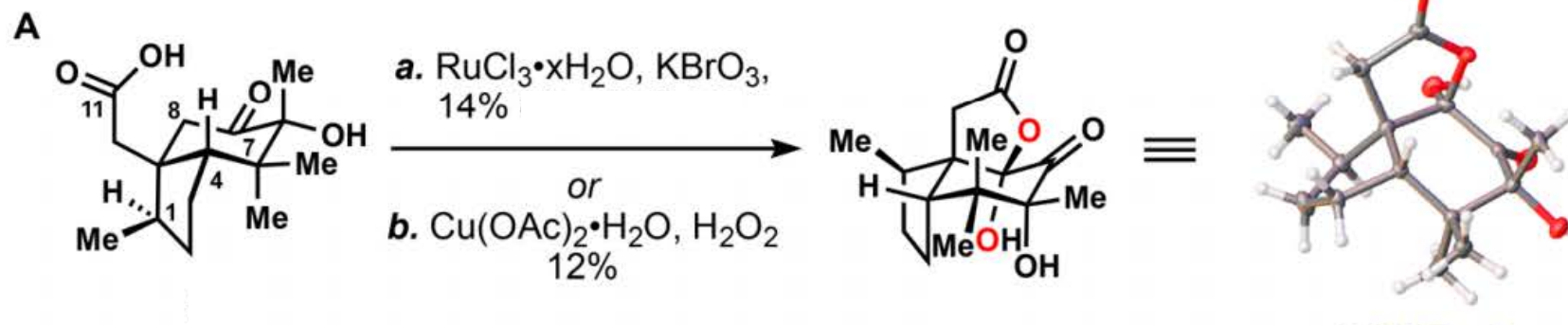
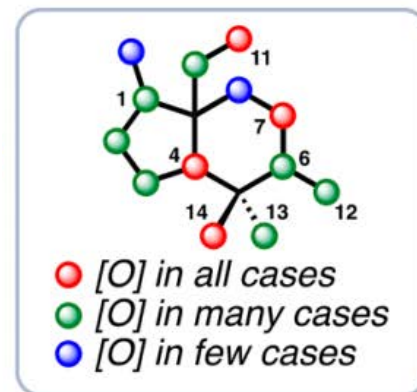


Undirected Oxidation of C4 Methyne

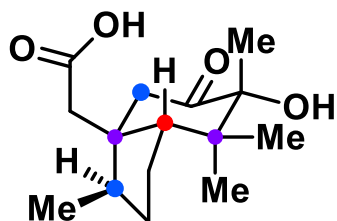


Undirected attempts

- Challenges:
1. Flanked by 2 quaternary centers
 2. Multiple other positions of oxidation



Copper-Mediated Oxidation of C4 Methyne

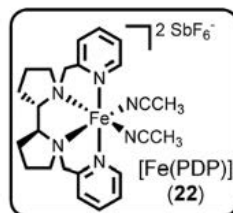
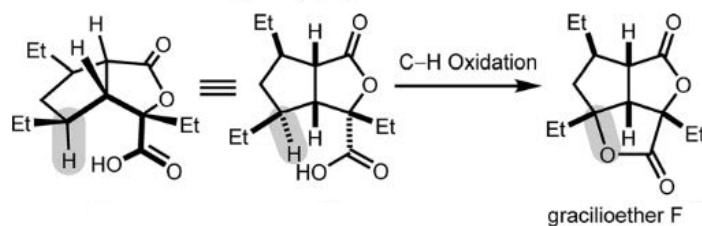


Challenges:

1. Flanked by 2 quaternary centers
2. Multiple other positions of oxidation

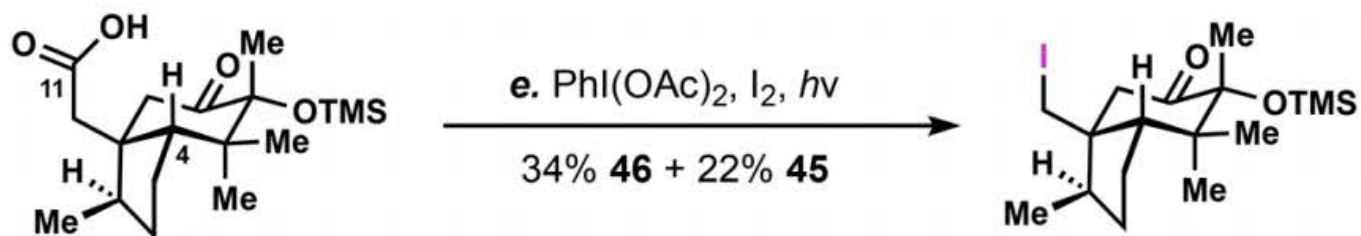
Cu-Mediated Directed attempts

Table 1: Late-stage C(sp³)-H oxidation.

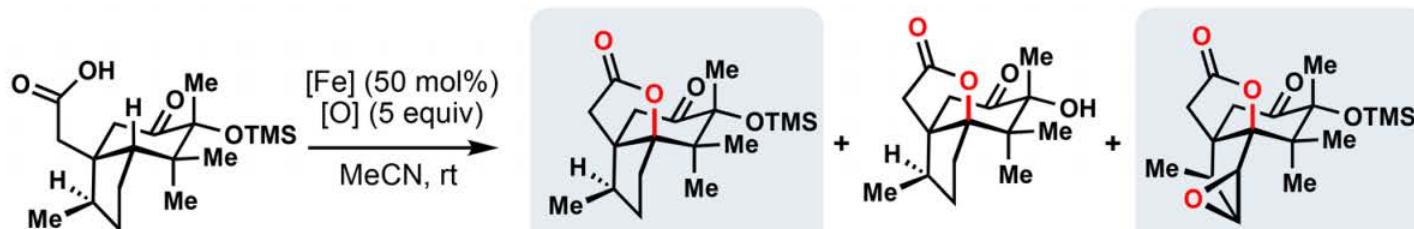


Conditions ^[a]	Yield ^[b] [%]	RSM ^[b] [%]
Cu(OAc) ₂ (1 equiv), H ₂ O ₂ , MeCN, 22 °C	15 (15)	51
Cu(OAc) ₂ (1 equiv), H ₂ O ₂ , MeCN, 0 °C	10	88
Cu(OAc) ₂ (1 equiv), H ₂ O ₂ , MeCN, 22 °C	<2	>90

Photolysis conditions

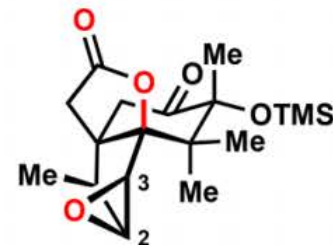
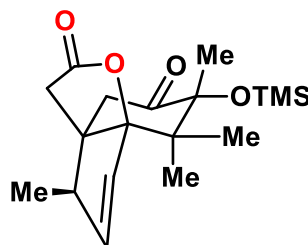
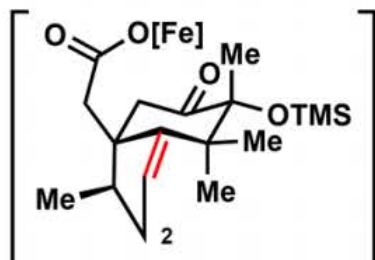
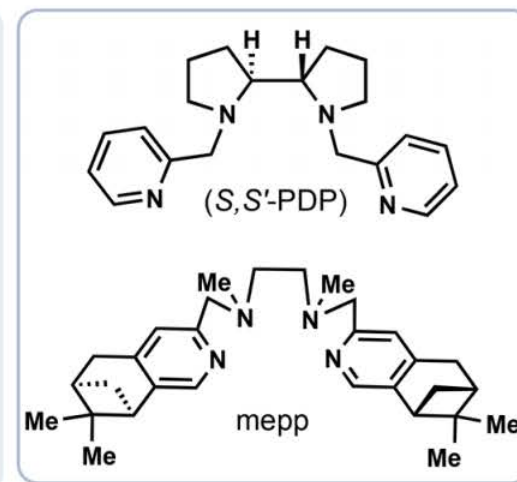


Iron-Mediated Oxidation of C₄ Methyne



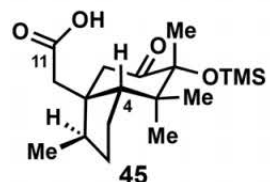
Entry	Conditions
1	Fe(mep)(MeCN) ₂ (SbF ₆) ₂ , H ₂ O ₂
2	Fe(<i>S,S'</i> -PDP)(MeCN) ₂ (SbF ₆) ₂ , H ₂ O ₂
3	Fe(mep)(MeCN) ₂ (SbF ₆) ₂ , TBHP
4	Fe(<i>R,R'</i> -PDP)(MeCN) ₂ (SbF ₆) ₂ , H ₂ O ₂
5	Fe(mepp)(MeCN) ₂ (SbF ₆) ₂ , H ₂ O ₂

22%	30%	4%
25%	0%	0%
21%	10%	4% (17% RSM)
16%	0%	0% (46% RSM)
26%	0%	0% (30% RSM)

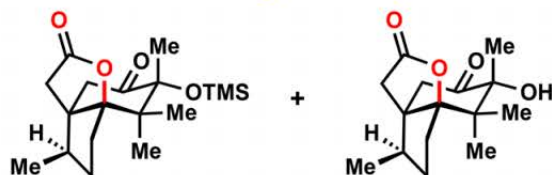


Possible that ligand architecture lowers reactivity of Iron center to prevent over oxidation

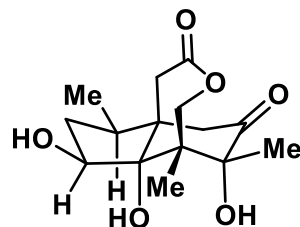
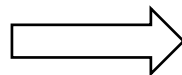
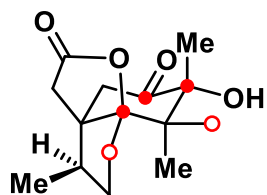
Iron-Mediated Oxidation of C4 Methylene



f. $[\text{Fe}(\text{mep})(\text{MeCN})_2][(\text{SbF}_6)_2]$
 H_2O_2 , slow addition
 22% + 30%
 [gram scale]



g. TMSCl, imid.,
 DMF, 67%

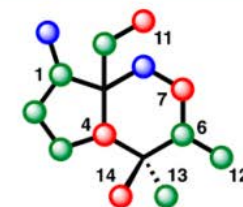
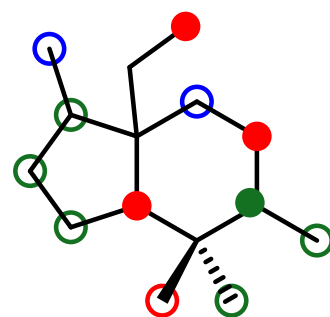


Pseudoanisatin

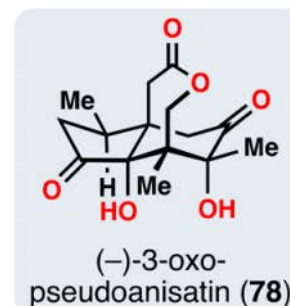
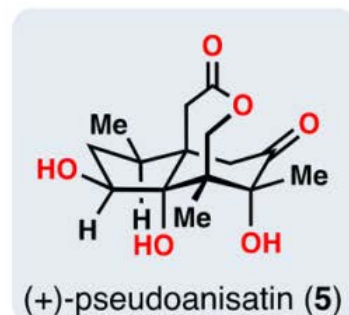


[X-Ray]

Oxidation summary



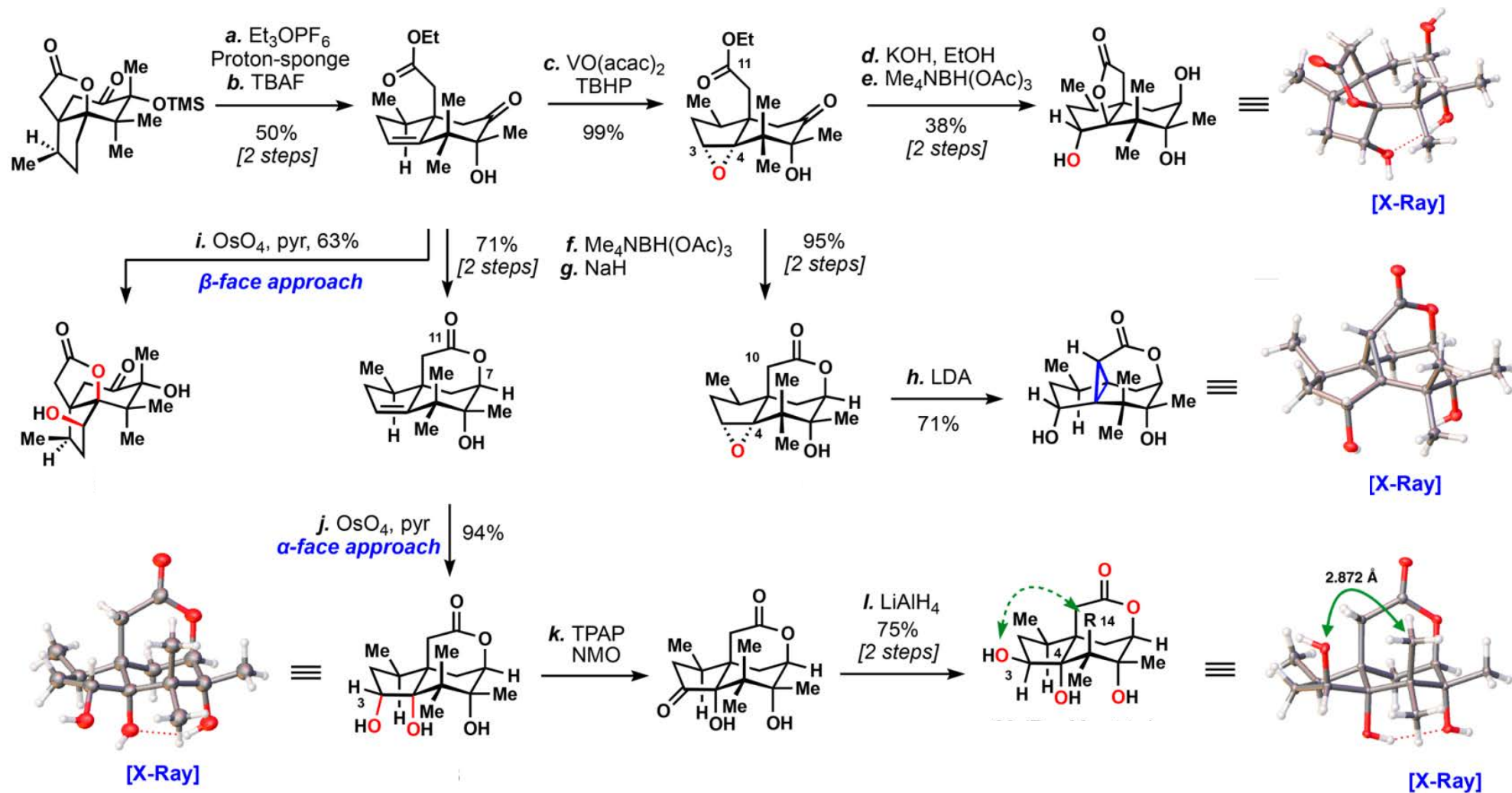
● [O] in all cases
 ● [O] in many cases
 ● [O] in few cases



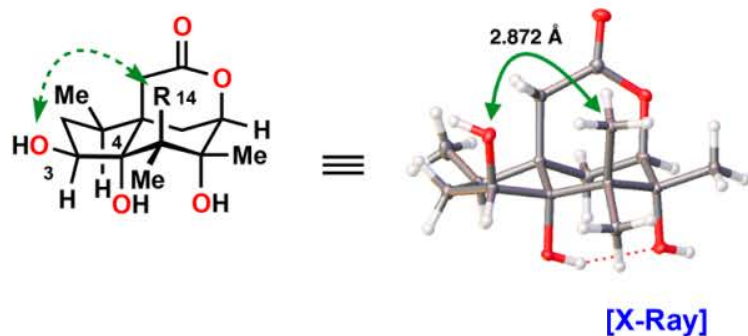
Required Manipulations:

1. Oxidation at C_{14}
2. inversion of stereochemistry at C_4
3. Oxidation at C_3
4. Form δ -lactone

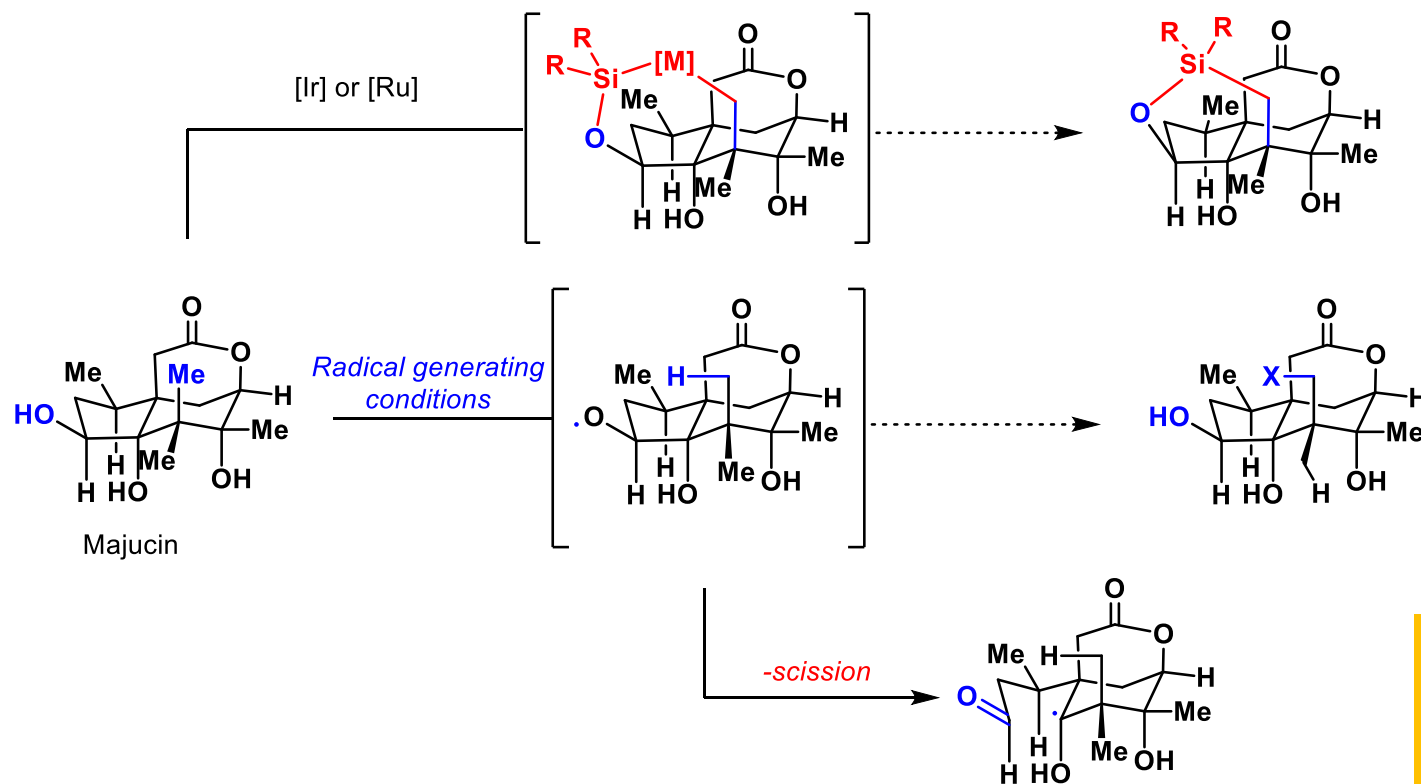
Late Stage C₄ Oxidation – Access to pseudoanisatin family



C₁₄ Oxidation – A revised Approach

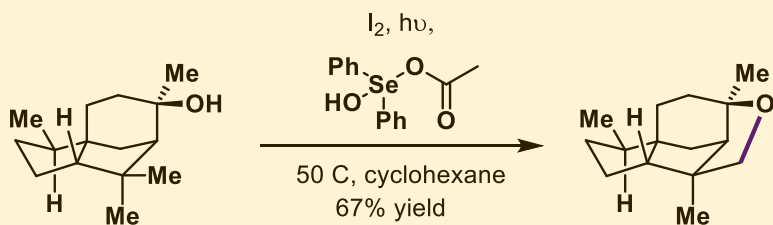


Previously proposed that of <3 Å is necessary for highly efficient CH abstractions

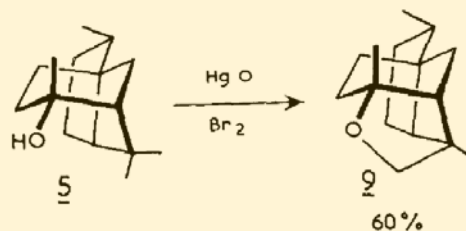


Given these challenges a revised strategy was needed

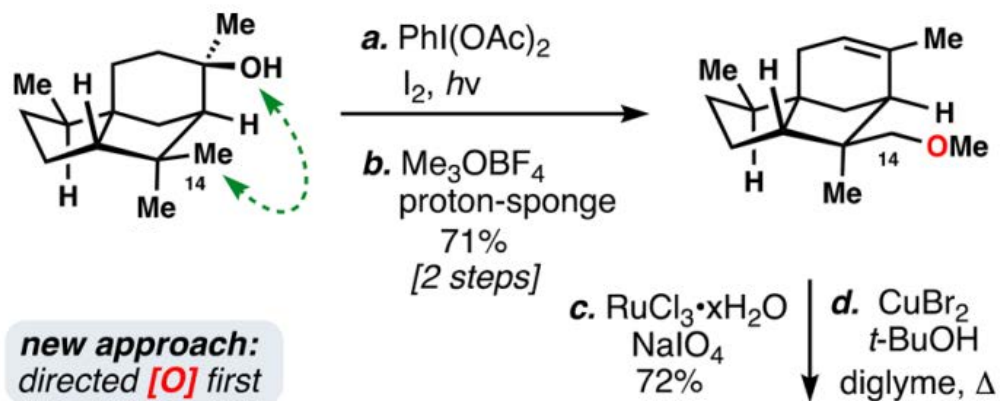
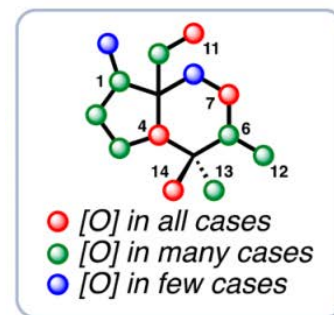
C₁₄ Oxidation – A revised Approach



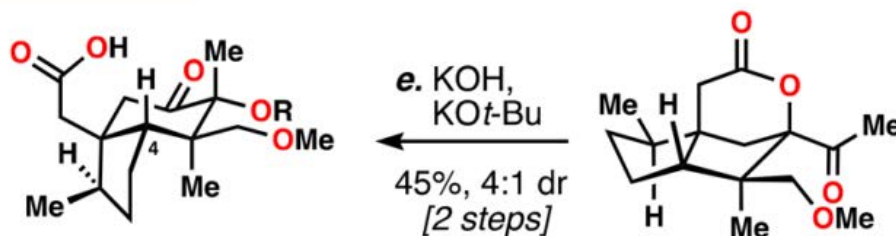
Tetrahedron 1988 29 5429



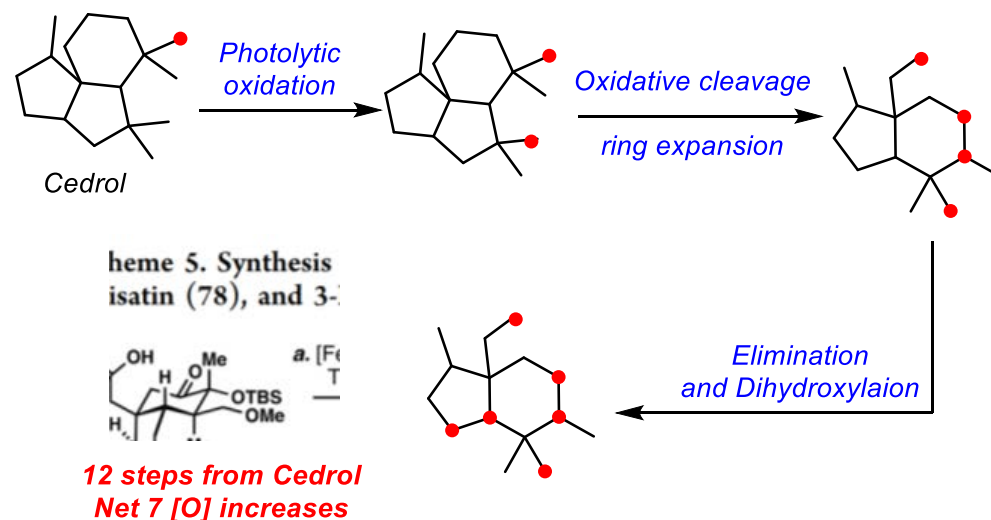
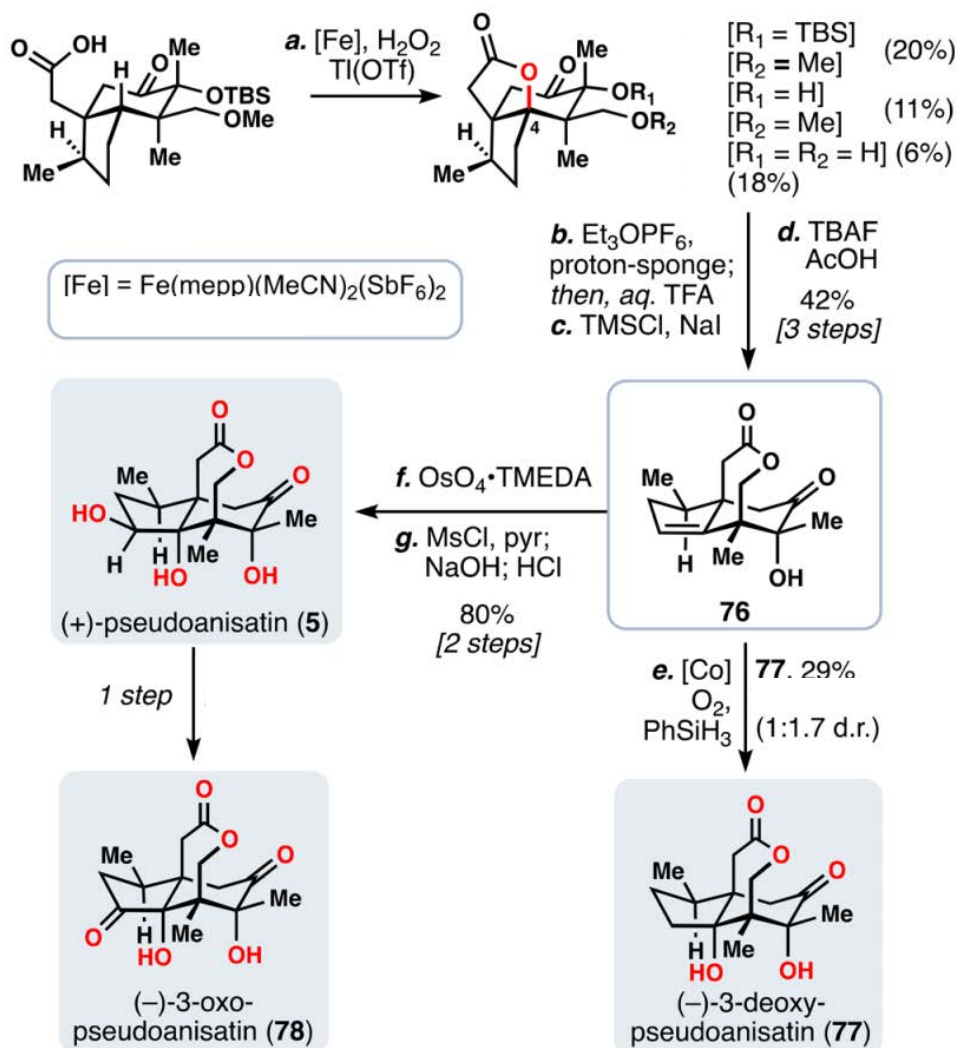
Tetrahedron 1976 32 1137



new approach:
directed [O] first

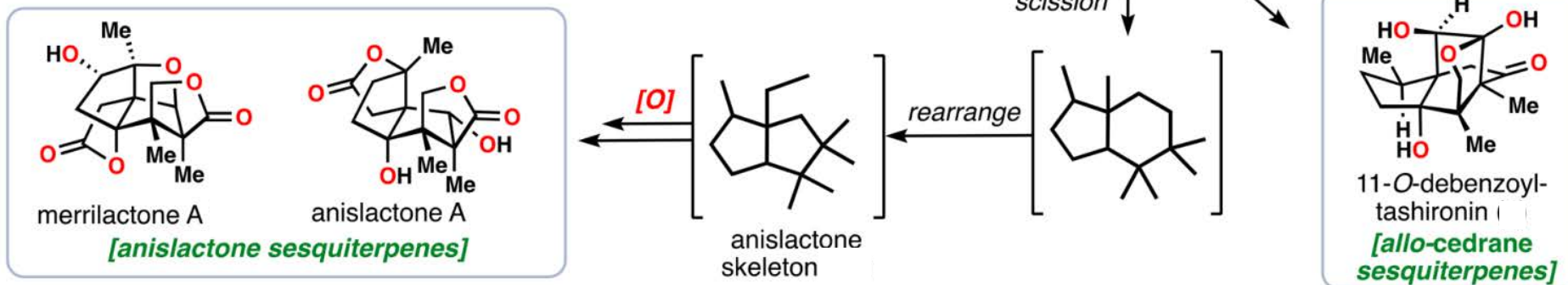
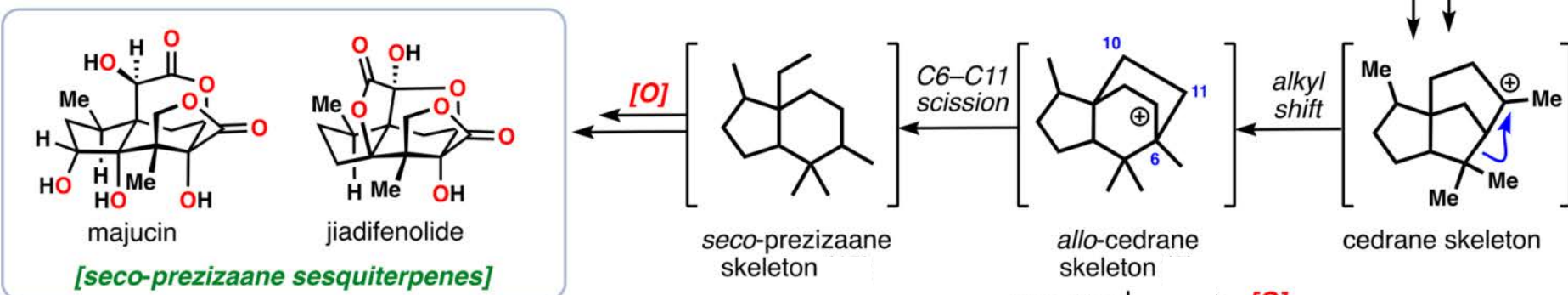
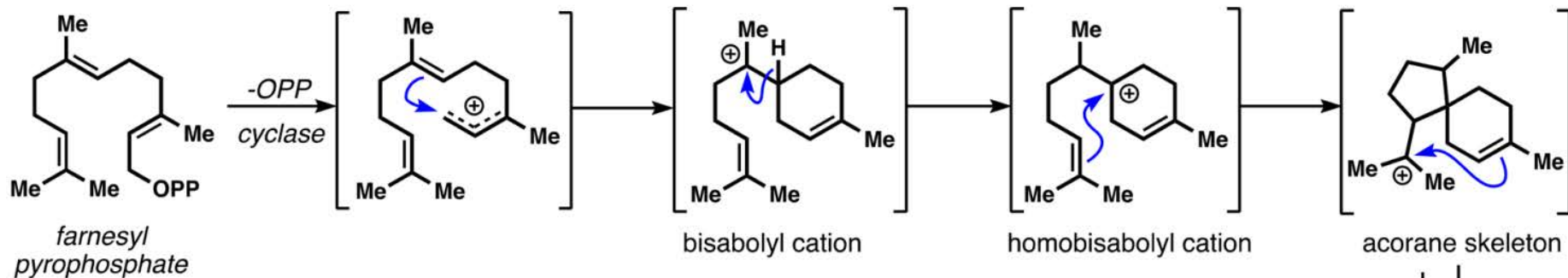
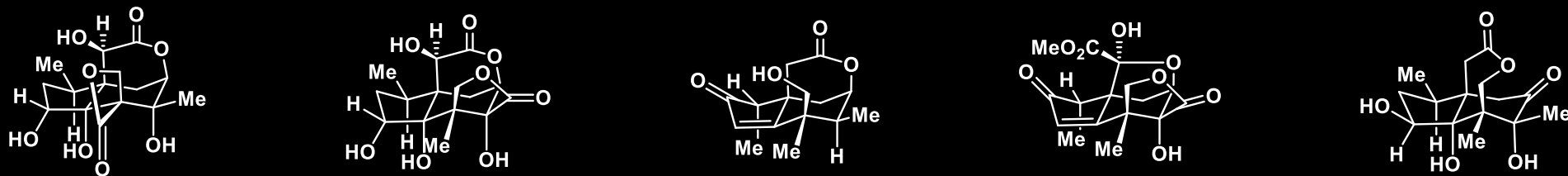


Access to pseudoanisatin family – The Final Stages

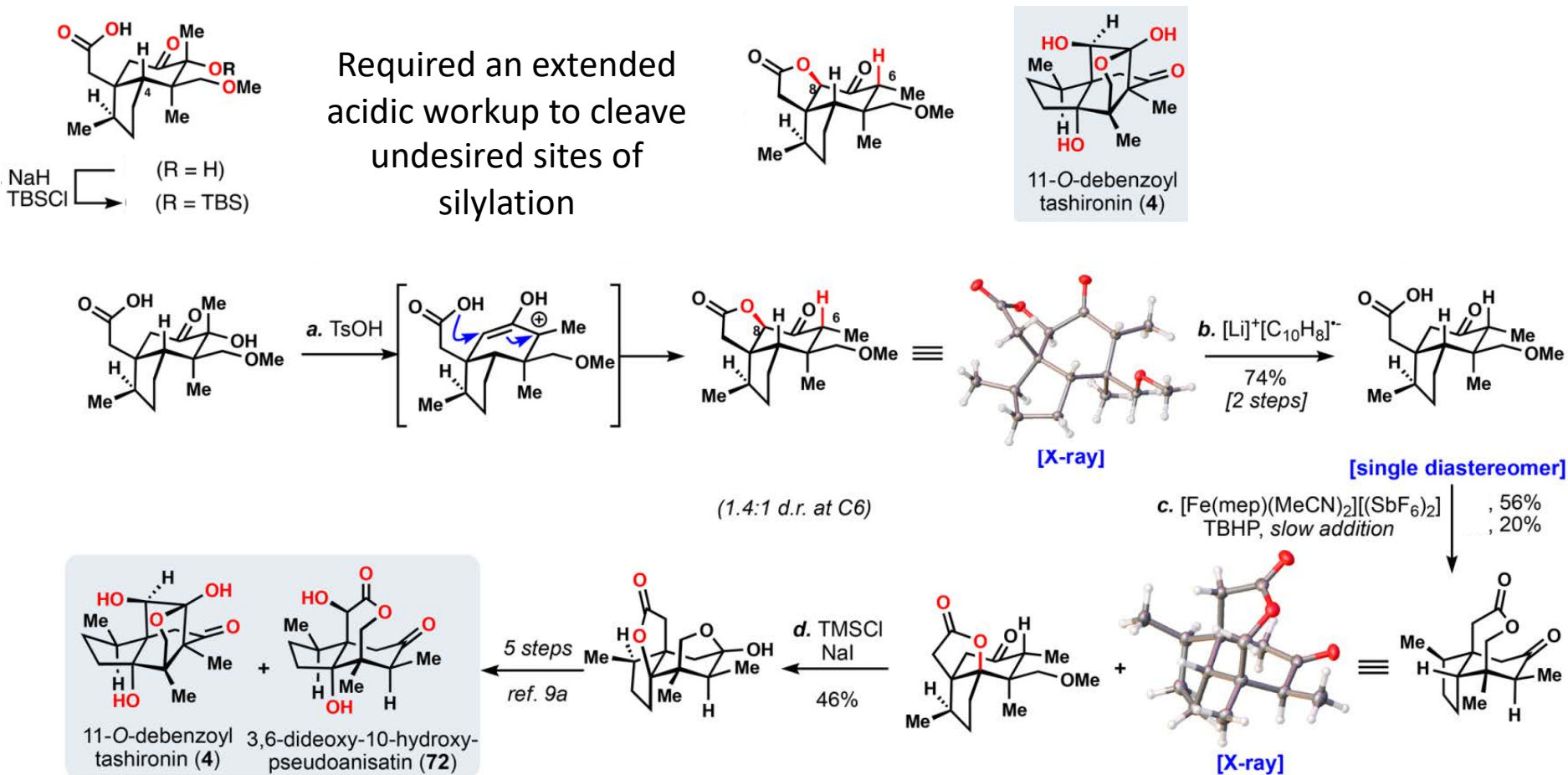


Remaining Challenges

- C14 oxidation left room for improvement
- Goal to target “majucinoids” which are more heavily oxidized
- Access allo-cedrane scaffold

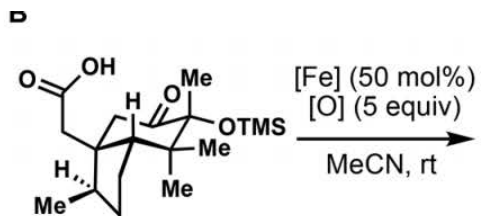


A fortuitous discovery – Access to 11-O-debenzoyltashironin



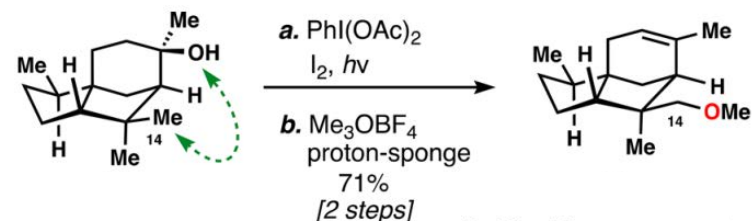
A New Synthetic Strategy for C₄ Oxidation

Gen-1 C₄ Oxidation

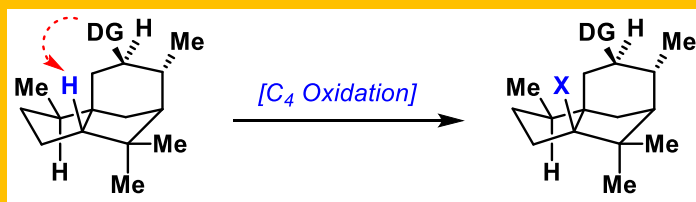


Entry	Conditions	22%	30%
1	Fe(mep)(MeCN) ₂ (SbF ₆) ₂ , H ₂ O ₂	22%	30%
2	Fe(S,S'-PDP)(MeCN) ₂ (SbF ₆) ₂ , H ₂ O ₂	25%	0%
3	Fe(mep)(MeCN) ₂ (SbF ₆) ₂ , TBHP	21%	10%
4	Fe(R,R'-PDP)(MeCN) ₂ (SbF ₆) ₂ , H ₂ O ₂	16%	0%
5	Fe(mepp)(MeCN) ₂ (SbF ₆) ₂ , H ₂ O ₂	26%	0%

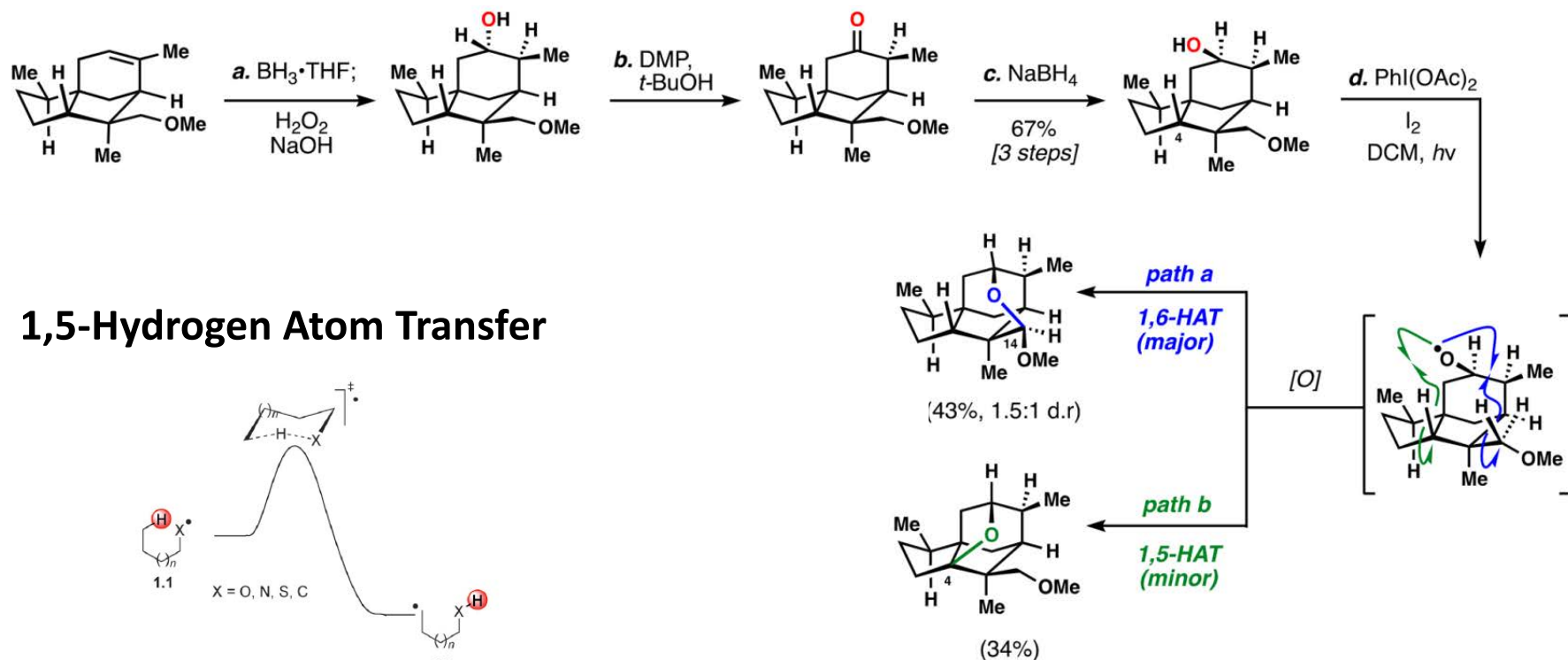
C₁₄ Oxidation



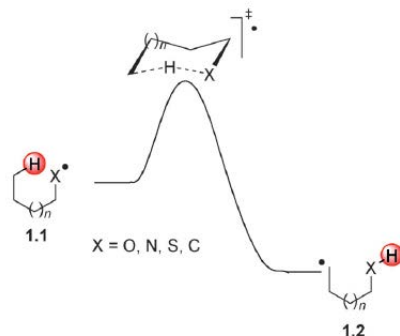
Could a similar approach to C₁₄ oxidation be taken for C₄ oxidation?



Competing C₄ and C₁₄ Oxidation



1,5-Hydrogen Atom Transfer

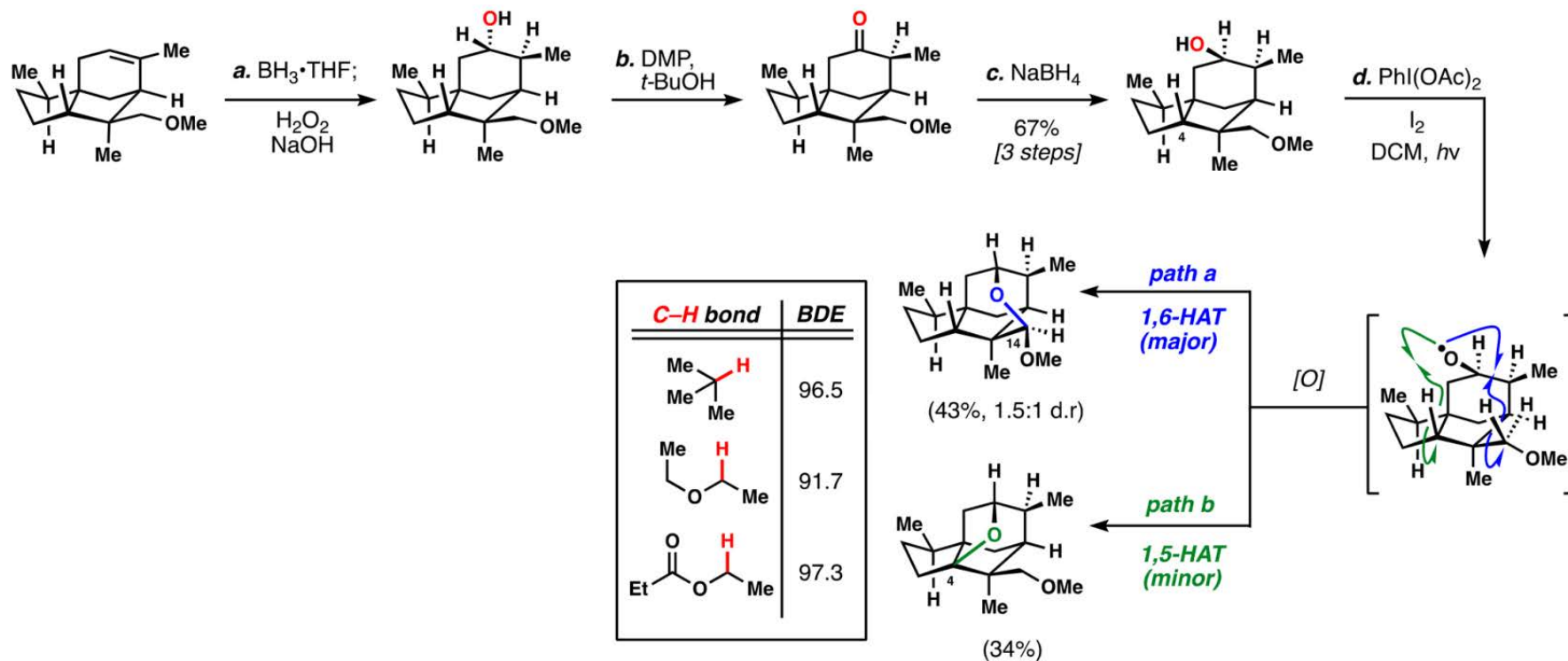


Generally favored due to a lack of entropic penalty in the transition state

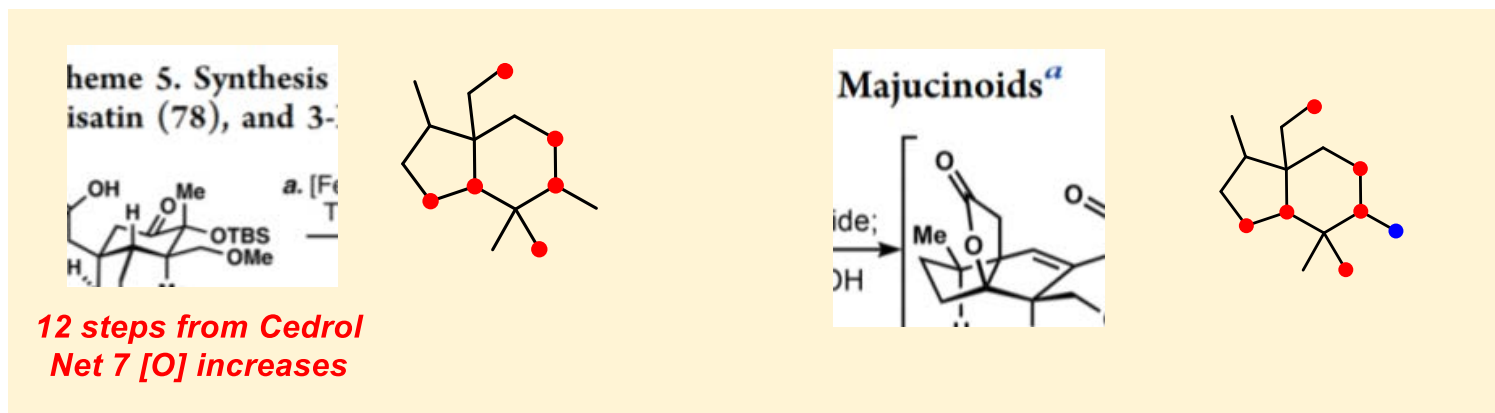
Rigidity of the system in combination with weak C₁₄-H bond led to competing 1,6-HAT

Protecting Group Change Enables C₄ Oxidation

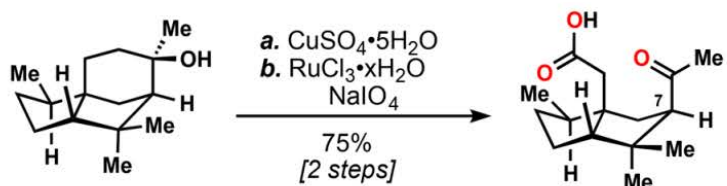
Can the strength of the C₁₄-H bond be strengthened to favor 1,5-HAT?



Strategy to access the Majucinoids

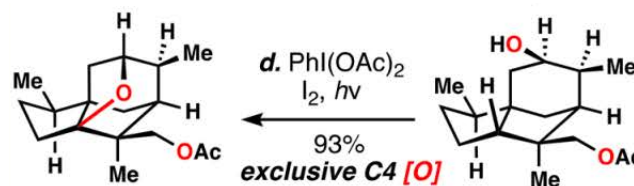


Fe-Mediated C4 Oxidation

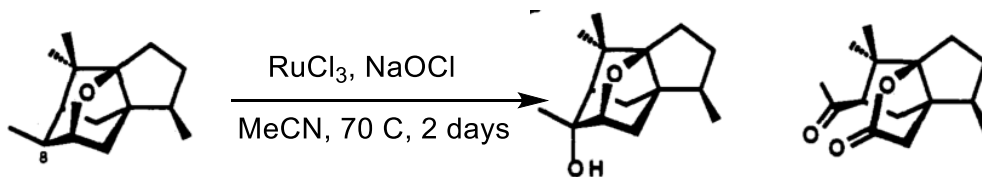


Double bond cleaved under oxidative conditions

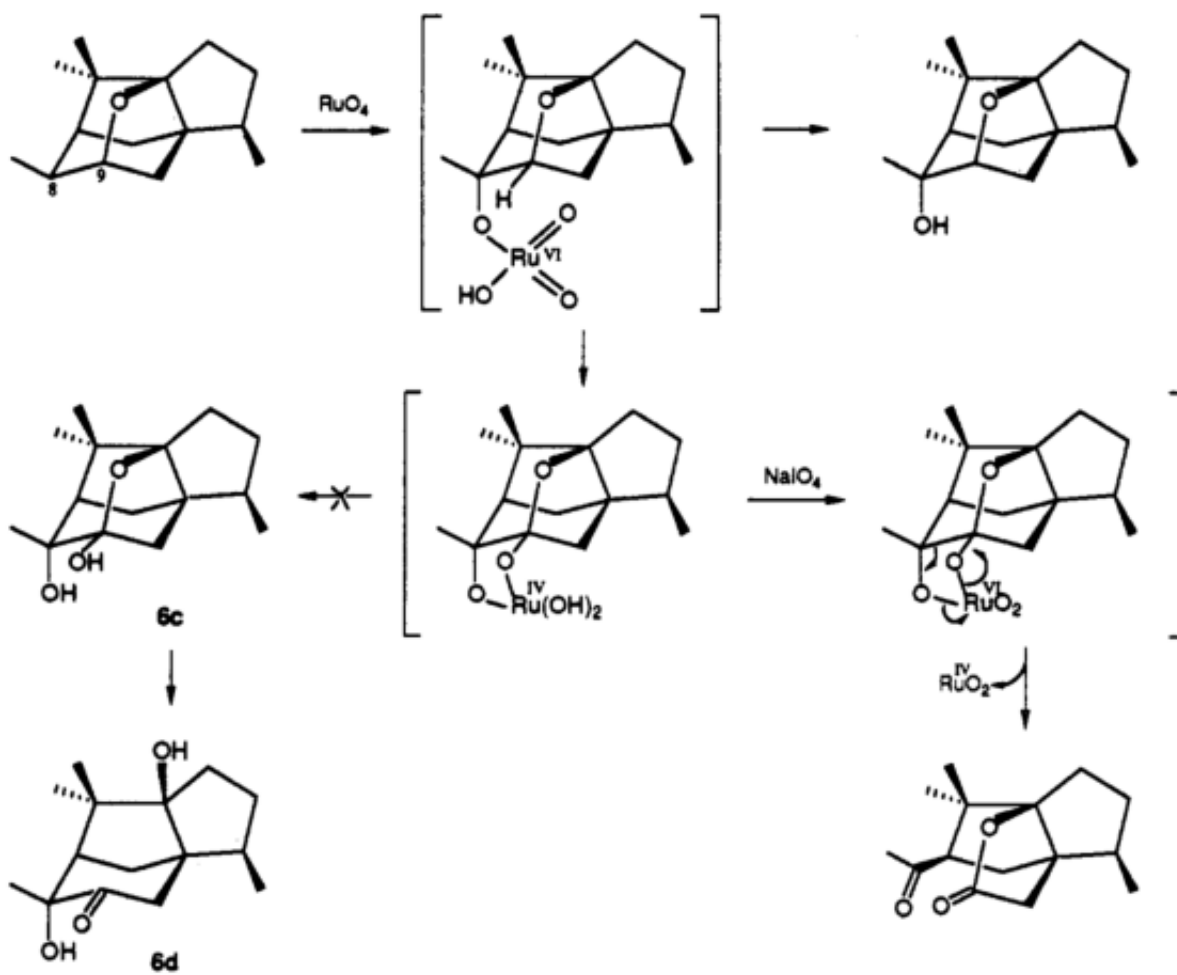
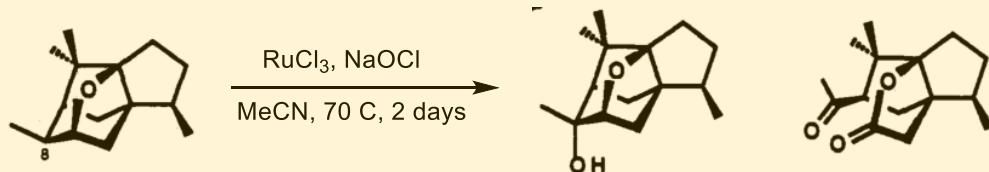
1,5-HAT strategy for C4 oxidation



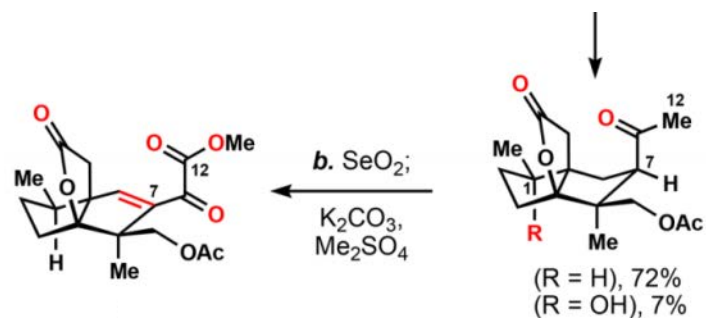
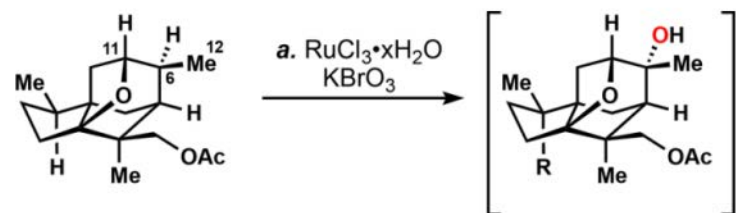
Double bond use to install a directing group



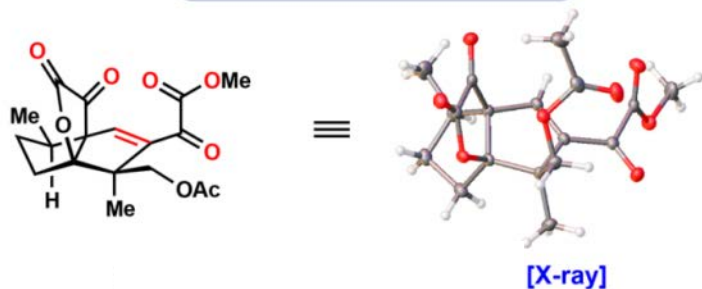
Mechanism of RuO₄ mediated bond cleavage



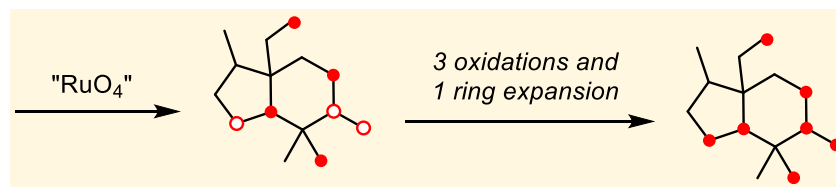
2 Pots, 9 Oxidations



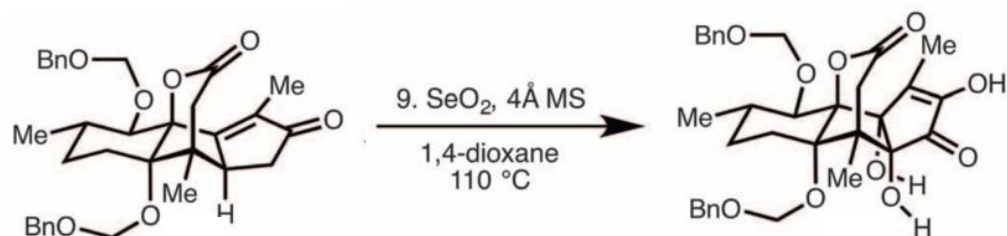
+ with 4 Å MS: 55% **91**, 0% **92**
without 4 Å MS: 43% **91**, 15% **92**



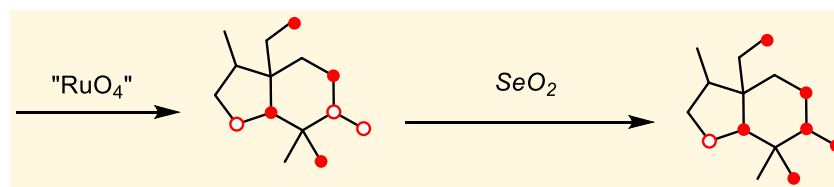
Other common reagents such as KMnO_4 and cat. SeO_2 were tried but were not successful



En route to Ryanodol



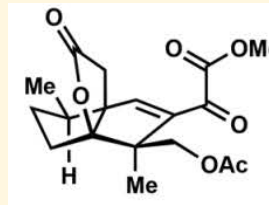
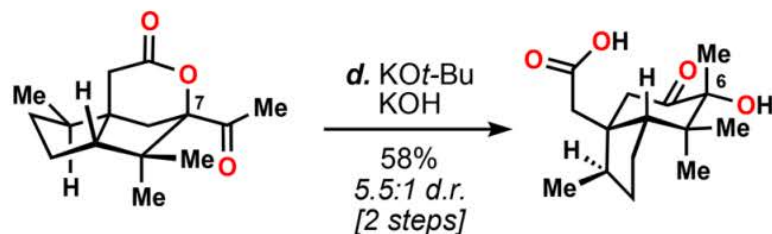
Reisman and coworkers
Science **2016** 353 912



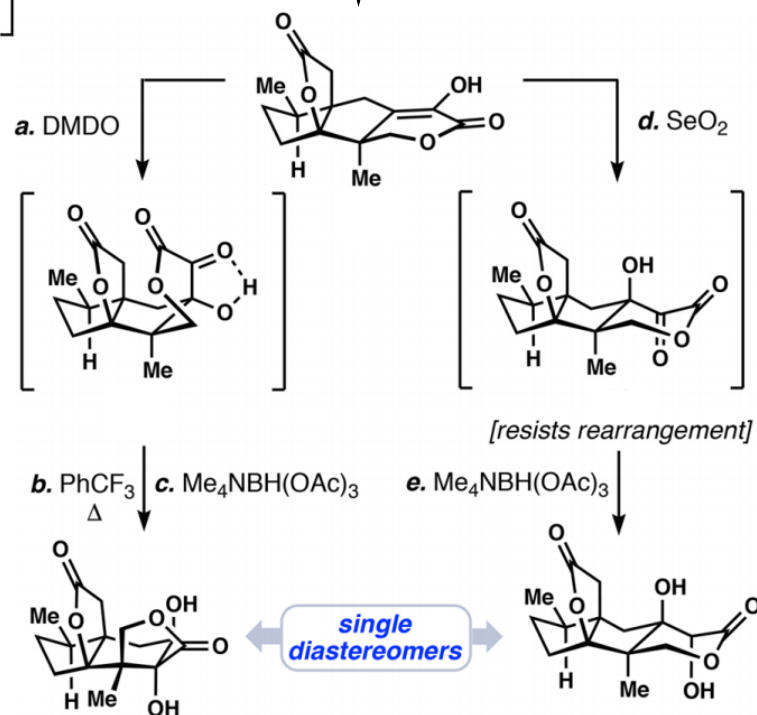
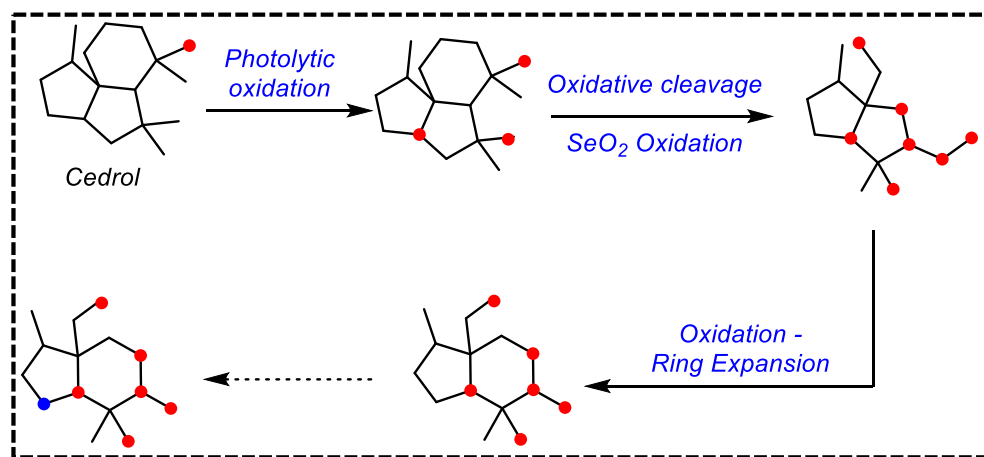
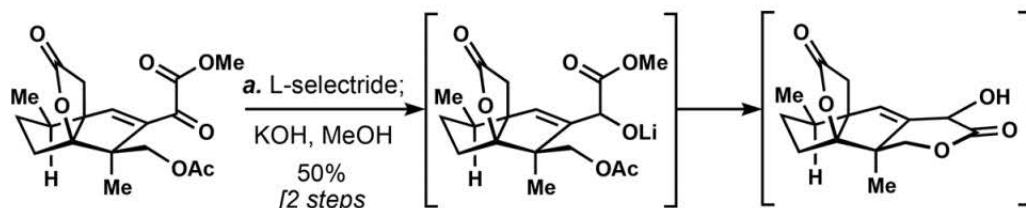
How to access the required ring shift?

SeO₂ Mediated Exhaustive Oxygenation

Recall:

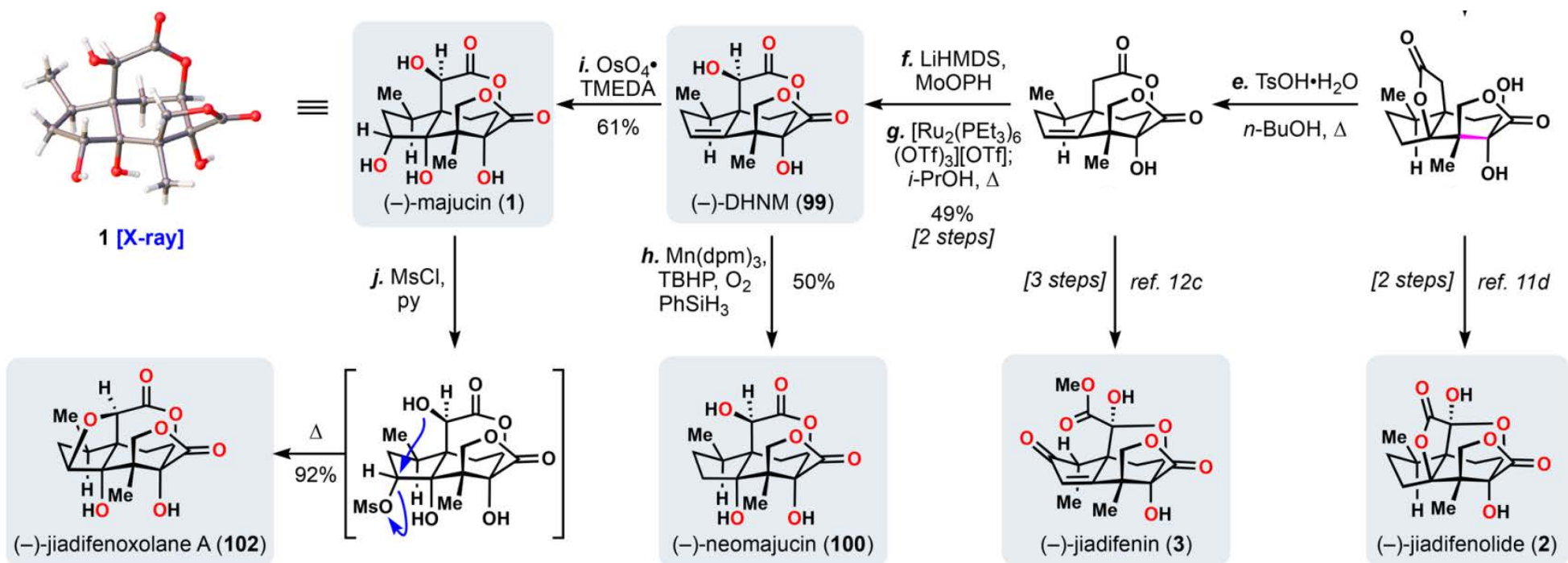
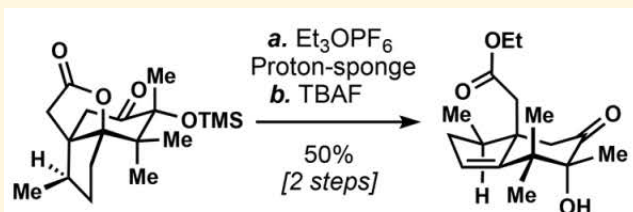


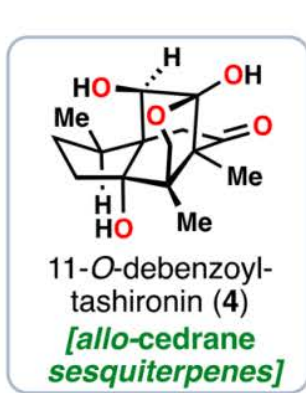
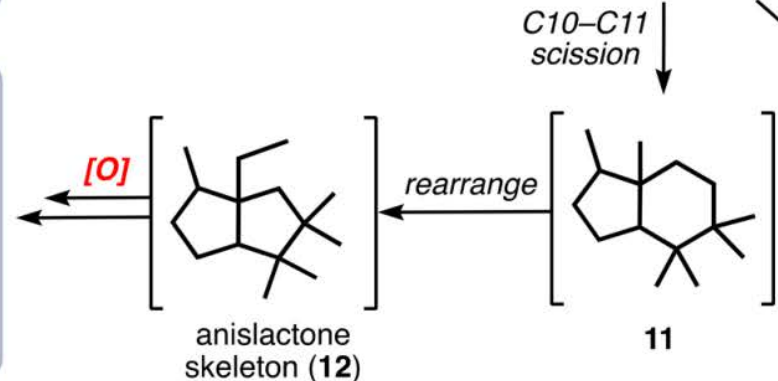
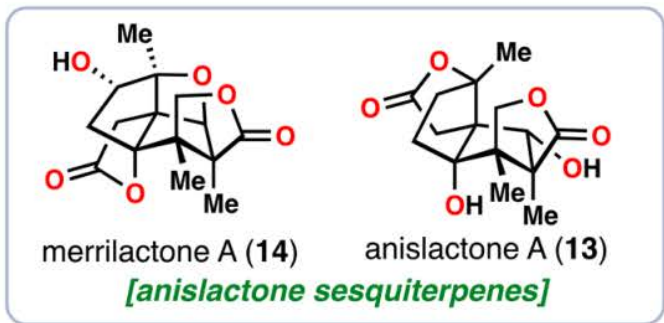
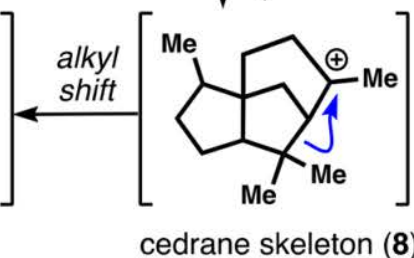
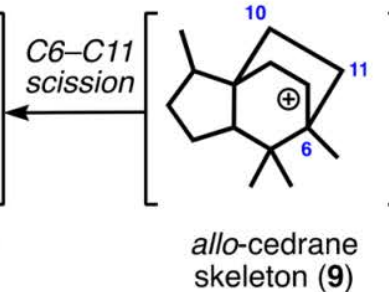
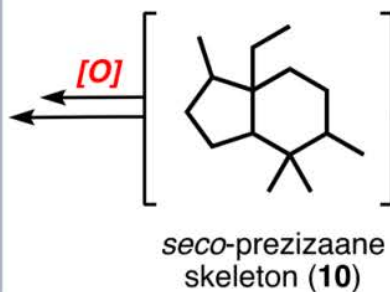
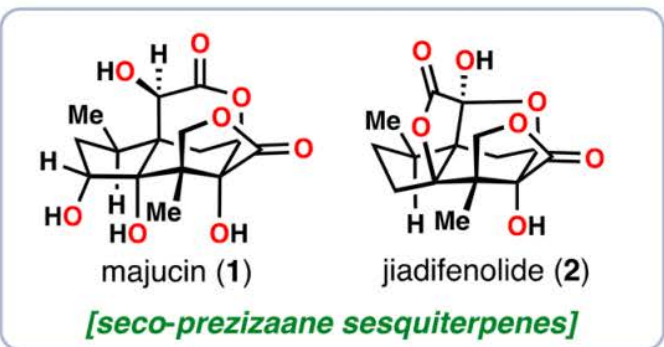
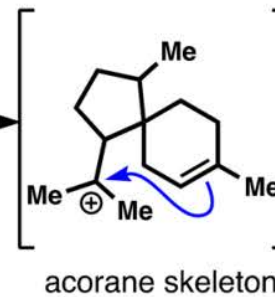
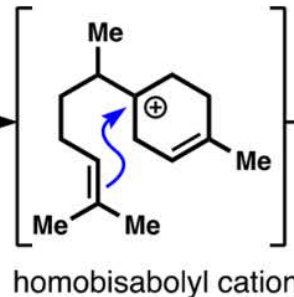
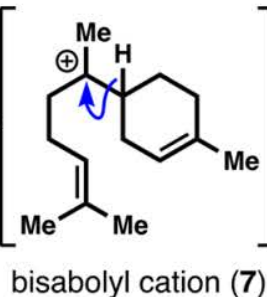
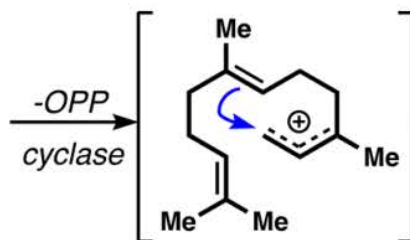
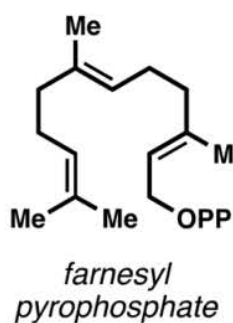
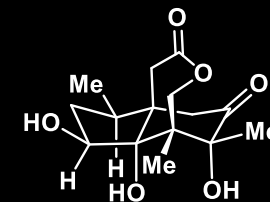
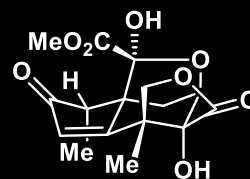
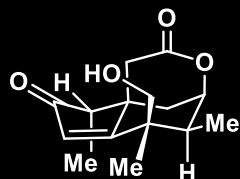
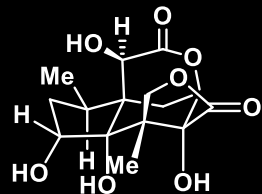
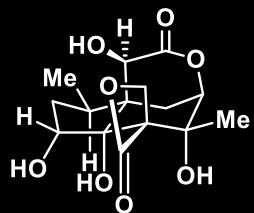
α -hydroxy ketone needs to be installed to facilitate the requisite ring shift

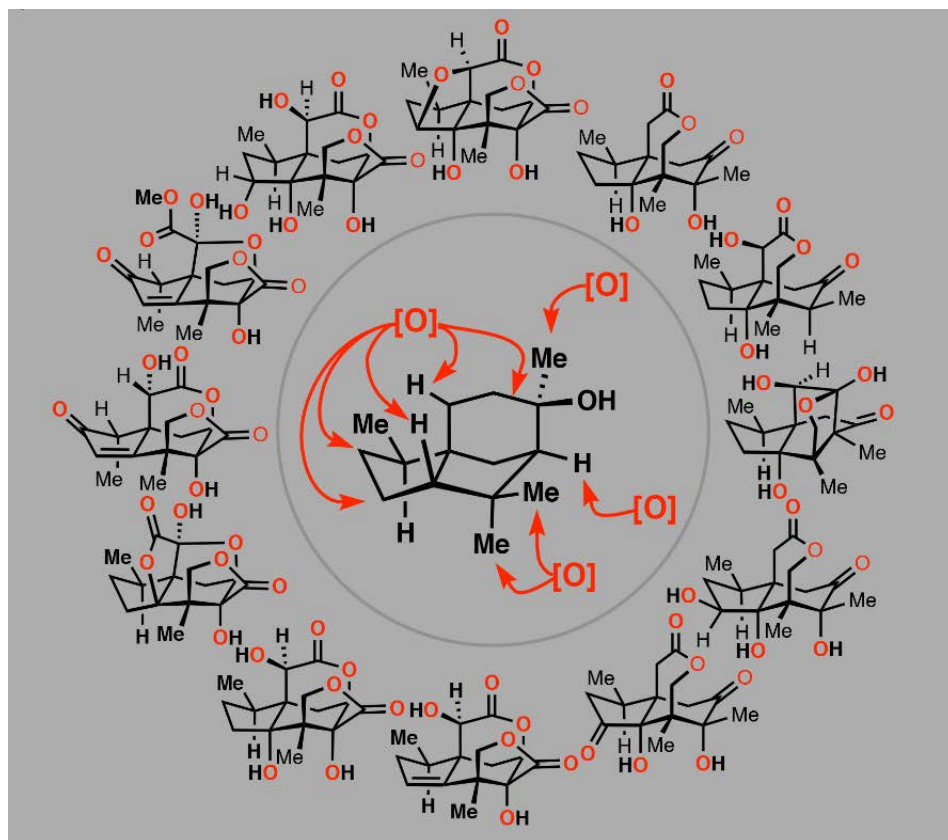
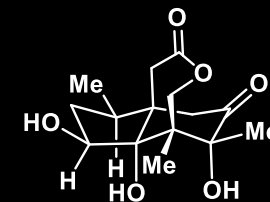
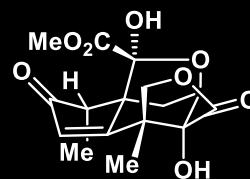
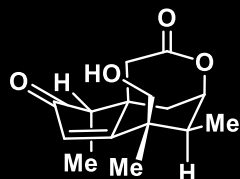
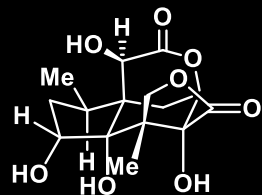
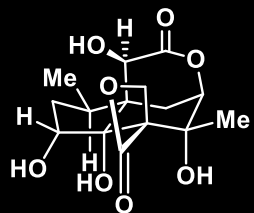


Majucinoids End Game

Recall:







Questions?