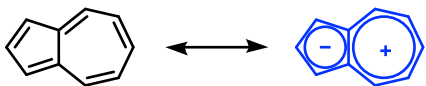


## Hydroazulene Sesquiterpenes

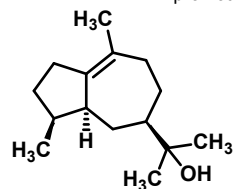


Hydroazulenes are a large family of sesquiterpenes named for their relationship with the intense blue pigment azulene. Many of these compounds were first identified by their rapid conversion into "blue hydrocarbons" upon treatment with sulfuric acid or strong oxidants.



Lactarius indigo

Many of the more complex members of this family have potent cytotoxic properties (such as guanacastapenes) or tumor-promoting properties (such as thapsigargin or phorbol).

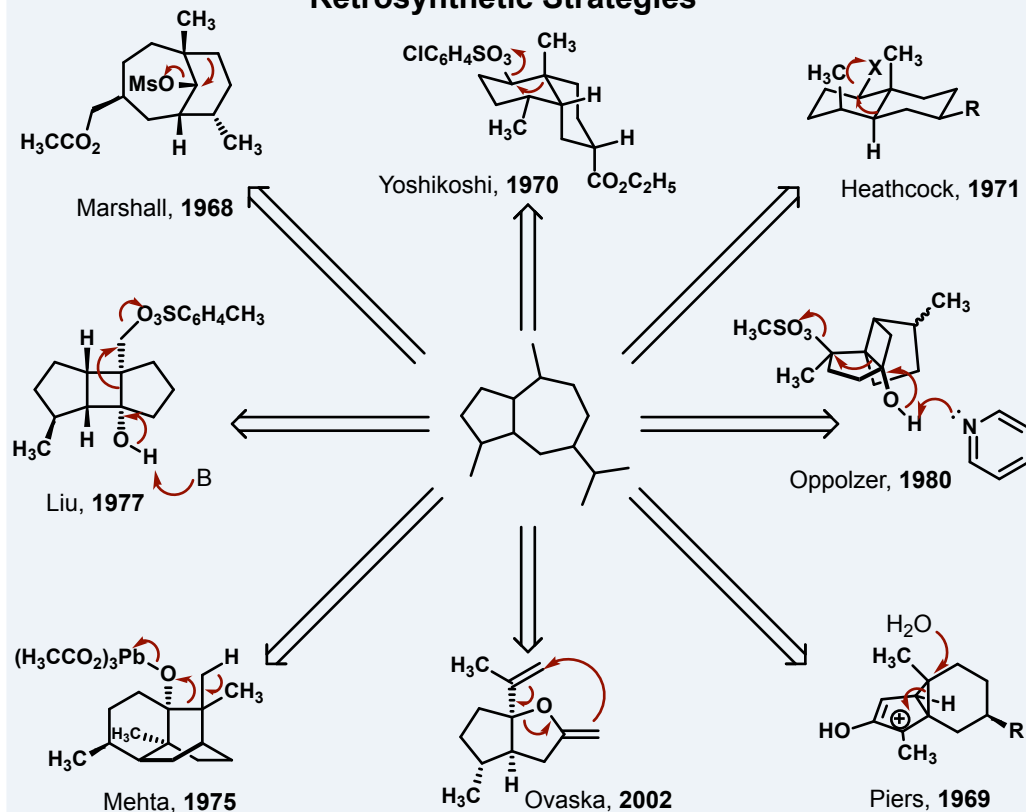


bulnesol

For a review on guanacastapene synthesis, see: "Classics in Guanacastapene Synthesis" (<https://www.sarlahgroup.com/topics>)

This review will focus on simpler guaiane-type hydroazulenes, centered around the parent molecule bulnesol, with an emphasis on strategy and efficiency in total synthesis

## Retrosynthetic Strategies



## Evaluation of efficiency in total synthesis

Christmann Flow Chart: see Christmann, *Chem. Soc. Rev.* **2018**, DOI:10.1039/c8cs00399h

C—C bond manipulation		forms C—C bond present in the target, or cleaves C—C bond of overbred intermediate
C—Het bond formation/strategic redox reactions		forms C—Het bond present in the target / oxidation state is altered towards oxidation state present in the target
isomerization/functional group interconversion		one functional group is converted to another - not present in the target, includes isomerizations
non-strategic redox reactions/defunctionalization		oxidation state is altered away from the oxidation state present in the target or C—Het bond replaced with C—H
protecting group manipulations		protection or deprotection of functional groups
		# of carbon atoms in intermediate or reagent that are present in the target

Baran's % Ideality Formula: see *J. Org. Chem.* **2010**, 75, 4657–4673

$$\% \text{ ideality} = \frac{[(\# \text{ of construction rxns}) + (\# \text{ of strategic redox rxns})]}{(\text{total } \# \text{ of steps})} \times 100 = \frac{\sum(\text{Green, Light Green})}{\sum(\text{Green, Light Green, Yellow, Orange, Red})} \times 100$$

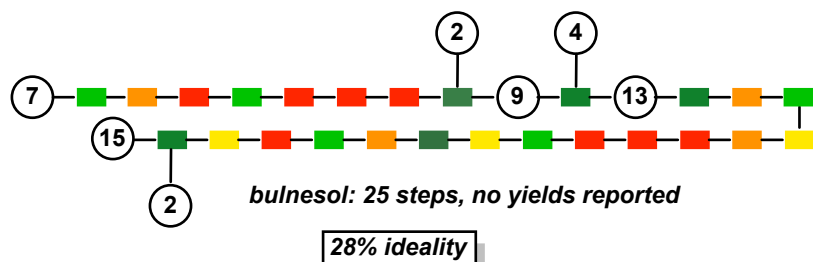
Regarding step economy:

For the purposes of this presentation, reported starting materials that were not commercially available at the time of publication have been extrapolated back to commercial materials through the references cited within the articles

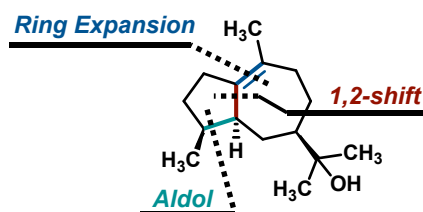
## References

- Marshall, *J. Am. Chem. Soc.* **1968**, 90, 1090-1091
- Piers, *J. Chem. Soc. D*, **1969**, 0, 562-563
- Yoshikoshi, *J. Chem. Soc. D*, **1970**, 0, 185-186
- Heathcock, *J. Am. Chem. Soc.* **1971**, 93, 1746-1757
- Mehta, *Tetrahedron Letters*, **1975**, 16, 4495-4498
- Liu, *Tetrahedron Letters*, **1977**, 18, 3699-3702
- Oppolzer, *Helv. Chim. Acta* **1980**, 63, 1198-1203
- Ovaska, *Tetrahedron Letters*, **2002**, 43, 1939-1941

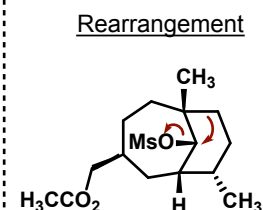
### Sequence Analysis:



**Key Disconnections:**



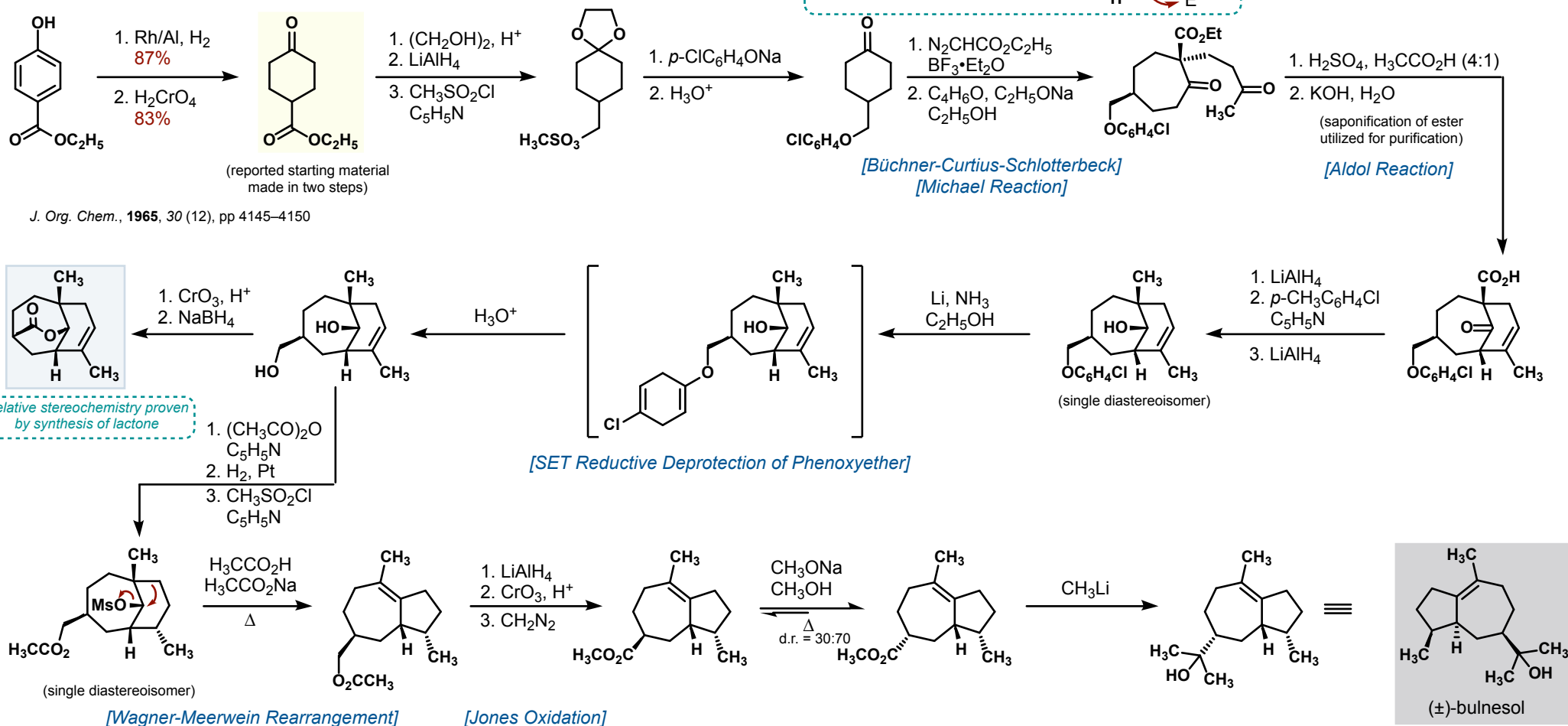
### Strategic Maneuver:



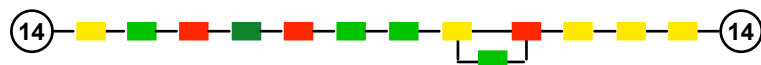
### Notable Features:

- First reported synthesis
- Total synthesis provided first structural confirmation
- Hydrogenation to set stereocenter at C<sub>4</sub> planned as a means to synthesize both epimers

**Synthetic Sequence:** Marshall, *J. Am. Chem. Soc.* **1968**, 90, 1090-1091



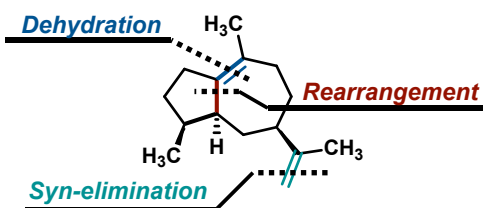
## Sequence Analysis:



**bulnesene:**  
12 steps, overall yield >4.1%  
or  
13 steps, overall yield >9.5%

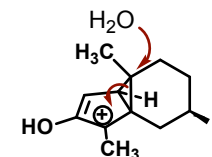
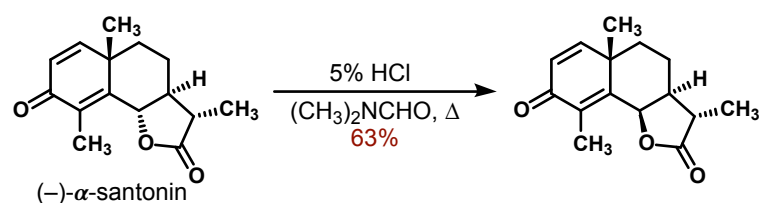
**33.33% ideality**

## Key Disconnections:

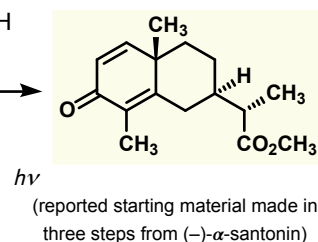


## Strategic Maneuver:

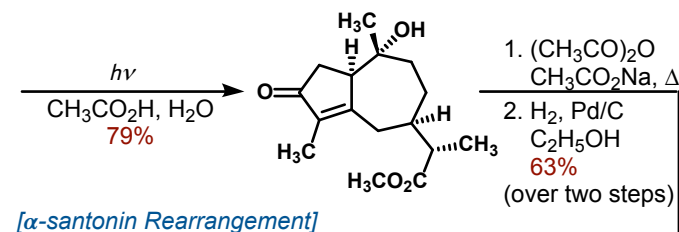
## Photochemical Rearrangement

Synthetic Sequence: Piers, *J. Chem. Soc. D*, 1969, 0, 562-563

*Canad. J. Chem.*, 1968, 46, 377-383

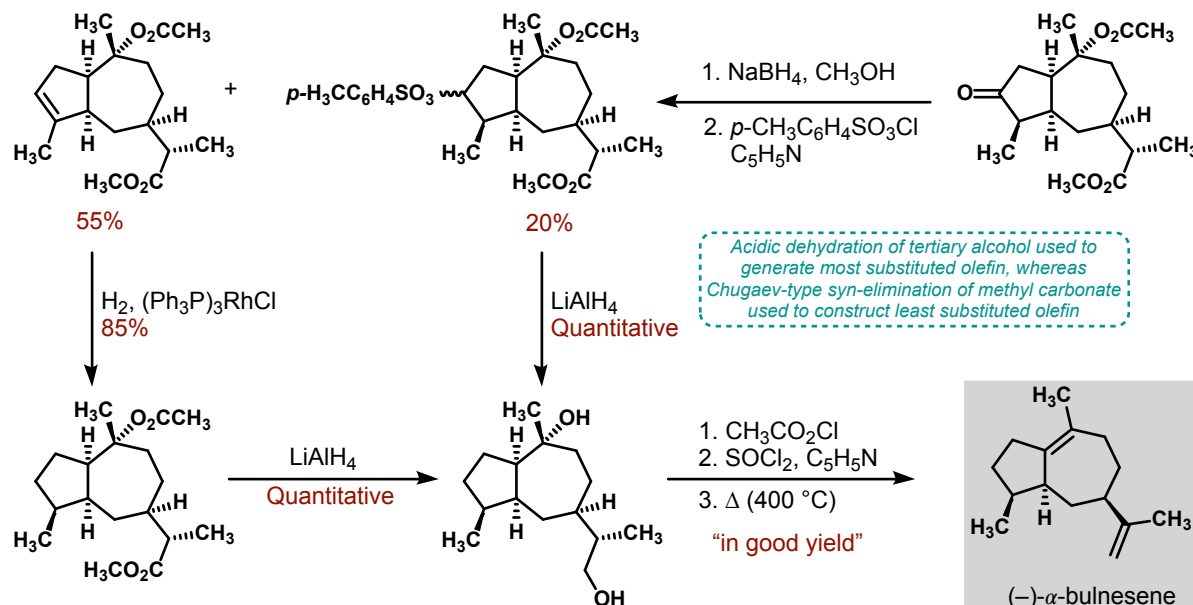
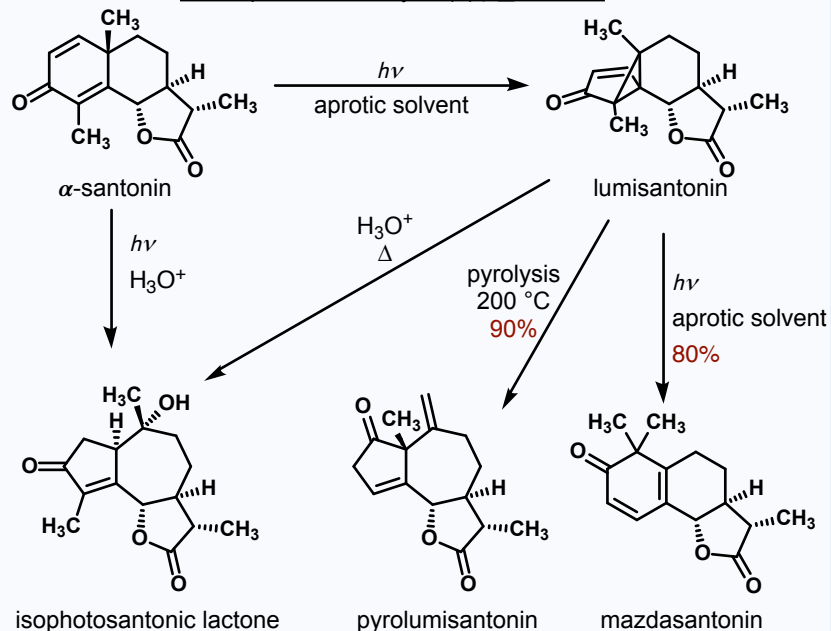


*hν*  
(reported starting material made in three steps from (-)-α-santonin)



[α-santonin Rearrangement]

## Some photochemistry of (-)-α-santonin:

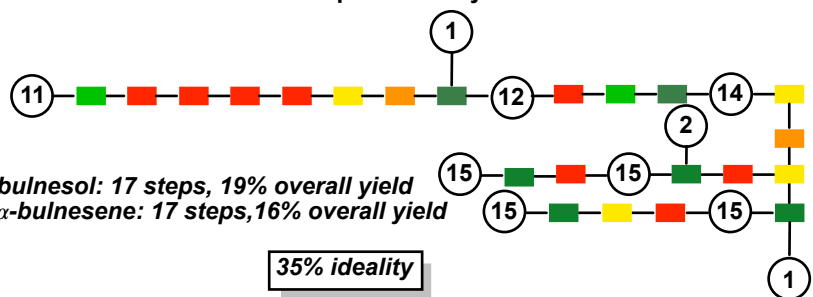


Use of Wilkinson's catalyst was essential for high stereoselectivity; with Adam's catalyst, mixtures were observed

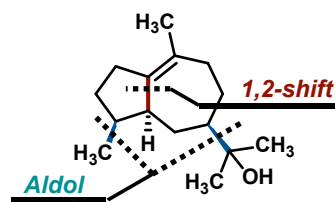
(-)-α-bulnesene



## Sequence Analysis:

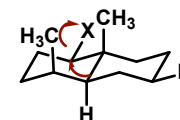


## Key Disconnections:

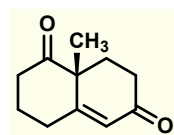
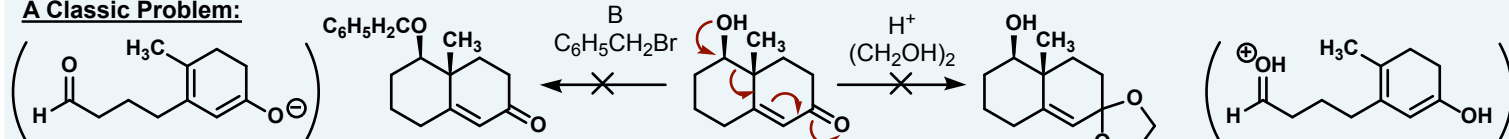


## Strategic Maneuver:

## Rearrangement



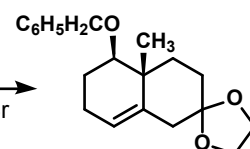
## A Classic Problem:



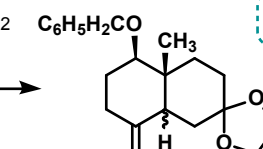
1.  $\text{NaBH}_4$ ,  $\text{C}_2\text{H}_5\text{OH}$   
92%
2.  $(\text{CH}_3\text{CO})_2\text{O}$ ,  $\text{C}_5\text{H}_5\text{N}$   
Quantitative



1.  $(\text{CH}_2\text{OH})_2$ ,  $\text{H}^+$   
68%
2.  $\text{LiAlH}_4$   
95%
3.  $\text{NaH}$ ,  $\text{C}_6\text{H}_5\text{CH}_2\text{Br}$   
80%



1.  $\text{BH}_3 \cdot \text{C}_4\text{H}_8\text{O}$ ;  $\text{H}_2\text{O}_2$   
96%
2.  $\text{CrO}_3 \cdot 2\text{C}_5\text{H}_5\text{N}$ ,  $\text{CH}_2\text{Cl}_2$   
94%



Complete epimerization to trans-decalin observed during Wittig Reaction

- $(\text{C}_6\text{H}_5)_3\text{P}=\text{CH}_2$   
 $(\text{CH}_3)_2\text{SO}$   
93%

[Wittig Reaction]

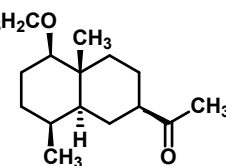
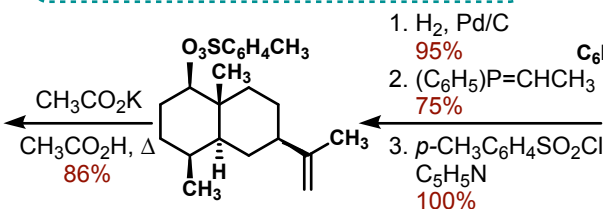
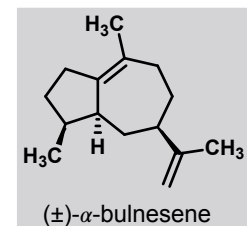
Wieland-Miescher Ketone

The electron-withdrawing acetate protecting group is used to destabilize the fragmented intermediate and push the equilibrium towards desired decalinic products

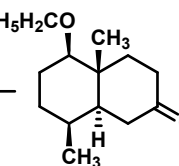
Ketalization occurs with concomitant olefin isomerization

[Collins Oxidation]

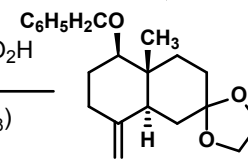
[Wittig Reaction]



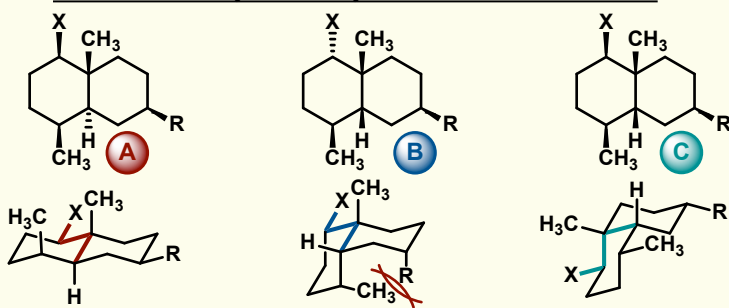
1.  $(\text{C}_6\text{H}_5)\text{P}=\text{CHCH}_3$   
94%
2.  $\text{BH}_3 \cdot \text{C}_4\text{H}_8\text{O}$ ;  $\text{H}_2\text{O}_2$
3.  $\text{CrO}_3 \cdot 2\text{C}_5\text{H}_5\text{N}$   
99% (two steps)
4.  $\text{HCl}$ ,  $\text{CH}_3\text{OH}$   
Quantitative



1.  $\text{H}_2\text{O}$ ,  $\text{CH}_3\text{CO}_2\text{H}$   
93%
2.  $\text{H}_2$ ,  $\text{Rh}(\text{Al}_2\text{O}_3)$   
76%  
d.r. = 7:1

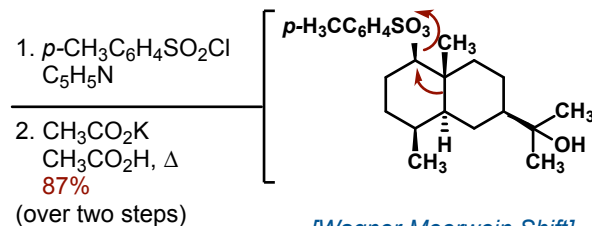
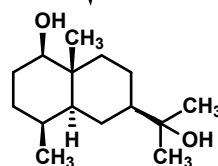


## Conformational analysis of solvolysis reaction in the decalin series:

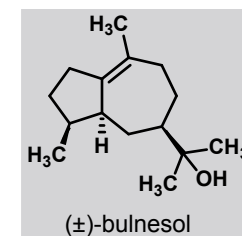


The leaving group and angular methyl must be cis (**A**, **C**) in both the trans- and cis-decalin systems to achieve the requisite antiperiplanar geometry for successful Wagner-Meerwein shift. Although an antiperiplanar alignment can still be achieved when they are trans in the cis decalin system (**B**), the conformation required suffers from severe steric clashing.

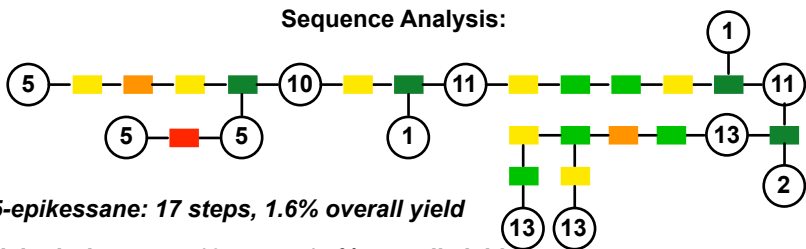
1.  $\text{CH}_3\text{Li}$   
98%
2.  $\text{H}_2$ ,  $\text{Pd/C}$   
98%



[Wagner-Meerwein Shift]



## Sequence Analysis:

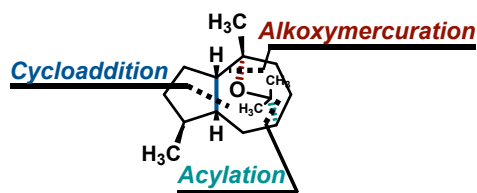


5-epikessane: 17 steps, 1.6% overall yield

dehydrokessane: 16 steps, 1.7% overall yield

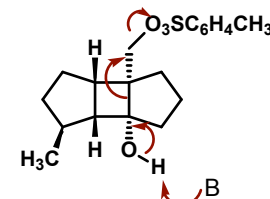
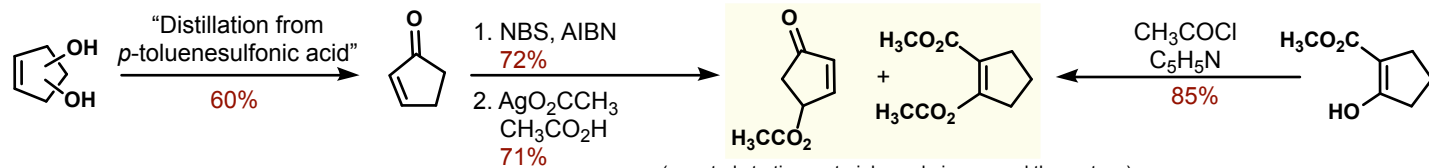
59% ideality

## Key Disconnections:



## Strategic Maneuver:

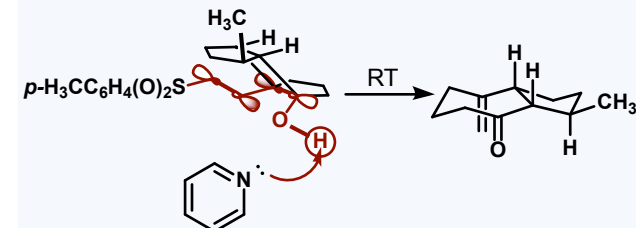
## Fragmentation

Synthetic Sequence: Liu, *Tetrahedron Letters*, 1977, 18, 3699-3702*J. Org. Chem.*, 1959, 24 (9), pp 1380-1381*J. Org. Chem.*, 1964, 29 (12), pp 3503-3507

(reported starting materials made in one and three steps)

1.  $h\nu$ , Pyrex  
450 W Hg  
2.  $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H}$   
 $\text{C}_6\text{H}_6$   
80%  
(over two steps)

## Henbest-Wharton Fragmentation:



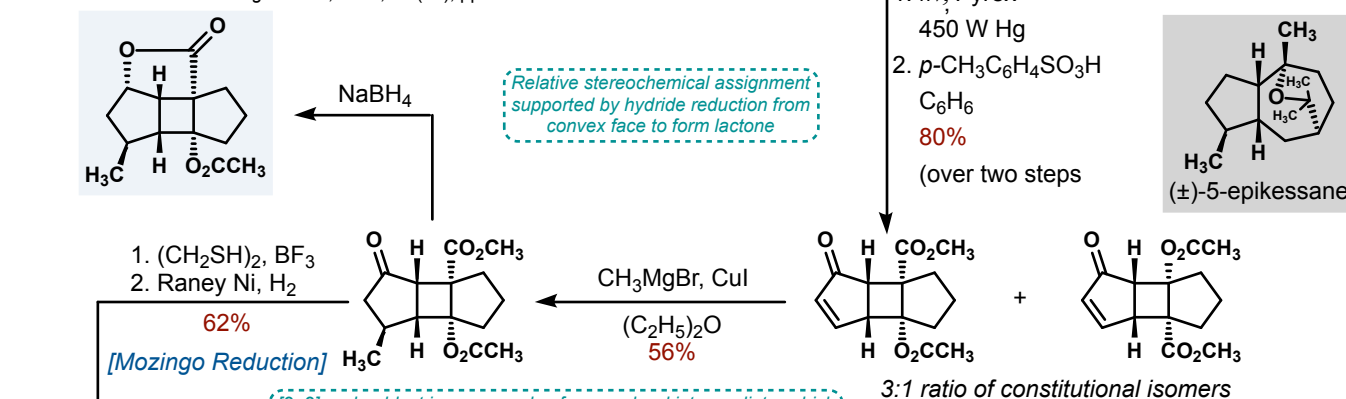
Fragmentation is facile at ambient temperature due to favorable orbital alignment and rigid structure

1.  $\text{Cl}_2\text{P}(\text{O})\text{N}(\text{CH}_3)_2$   
then,  $(\text{CH}_3)_2\text{NH}$   
2.  $\text{Li}$ ,  $\text{C}_2\text{H}_5\text{NH}_2$   
71%  
(over two steps)

[Ireland Deoxygenation]

$\text{POCl}_3$   
73%

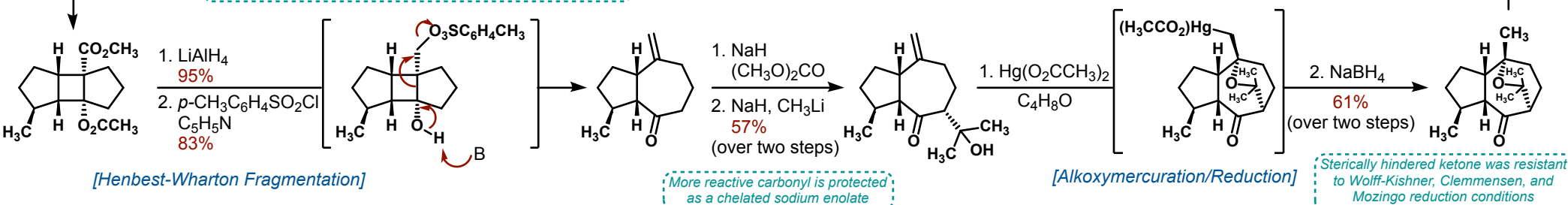
$\text{LiAlH}_4$   
Quantitative



Relative stereochemical assignment  
supported by hydride reduction from  
convex face to form lactone

[2+2] cycloaddition is an example of an overbred intermediate, which  
contains one or more carbon-carbon bonds than are present in the  
target, and which will have to be cleaved at a later stage

3:1 ratio of constitutional isomers



[Henbest-Wharton Fragmentation]

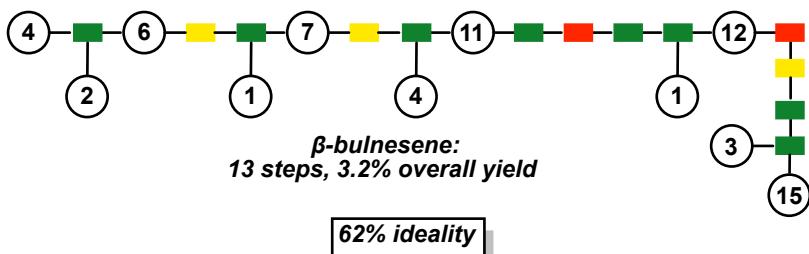
More reactive carbonyl is protected  
as a chelated sodium enolate

[Alkoxymercuration/Reduction]

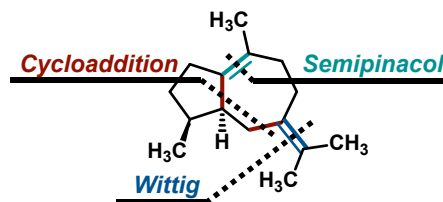
Sterically hindered ketone was resistant  
to Wolff-Kishner, Clemmensen, and  
Mozingo reduction conditions



## Sequence Analysis:

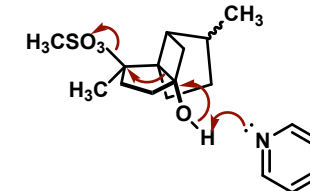


## Key Disconnections:



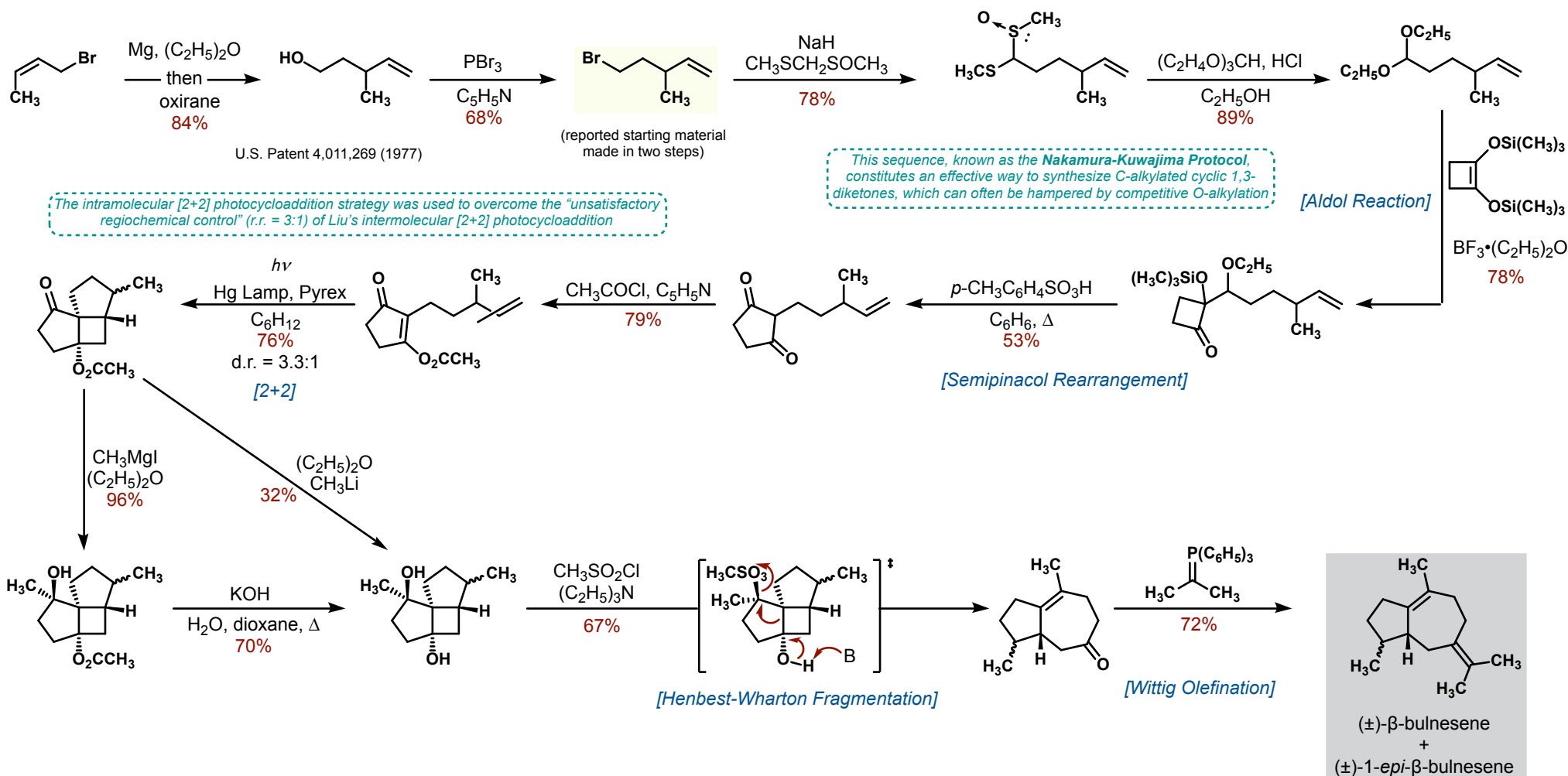
## Strategic Maneuver:

## Cycloaddition/Fragmentation

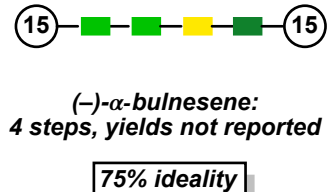


**Synthetic Sequence:** Oppolzer, *Helv. Chim. Acta* **1980**, 63, 1198-1203

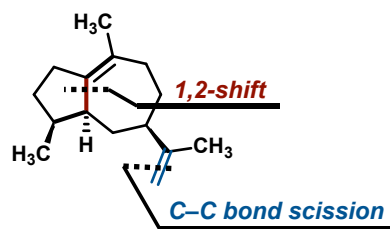
alkylation with methylthiomethyl sulfoxide provides a method to oxidatively homologate alkyl halides to protected aldehydes



## Sequence Analysis:

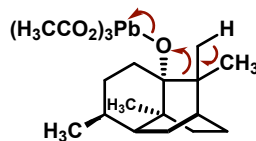


## Key Disconnections:



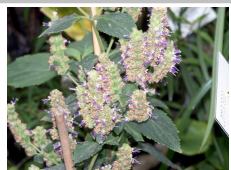
## Strategic Maneuver:

## C-C Bond Scission



"...we had no access to an NMR machine and importing chemicals for research was a Herculean task. However, what we had was access to highly motivated and ambitious graduate students and availability of some 'exotic' natural products of indigenous origin, particularly terpenes that came as free gifts!"

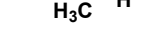
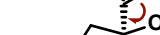
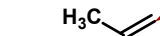
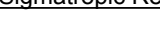
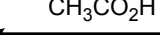
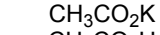
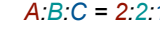
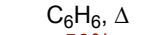
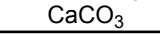
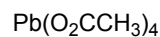
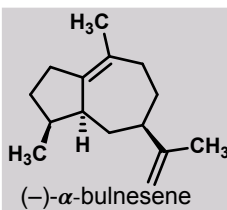
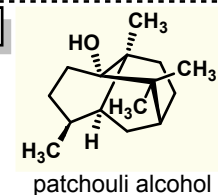
– Goverdhan Mehta

Synthetic Sequence: Mehta, *Tetrahedron Letters*, 1975, 16, 4495-4498

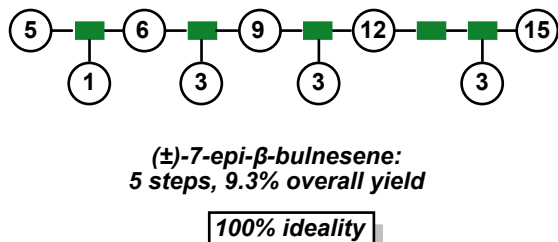
*Pogostemon cablin*

Patchouli alcohol is the chief component responsible for the fragrance of patchouli, an important essential oil in perfumery. It can be easily extracted from the essential oil and purified by chromatography for use in synthesis.

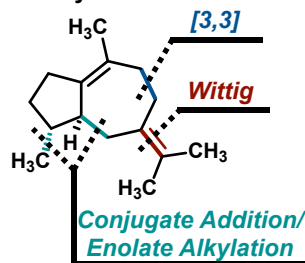
"Its characteristic odor pervaded the corridors. While we thought we were doing some interesting chemistry, others on the floor, under the influence of the lingering patchouli odor, thought that we had run out of research ideas and were doing a development project for the perfumery industry."



## Sequence Analysis:

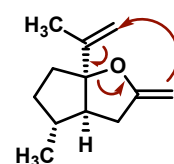


## Key Disconnections:



## Strategic Maneuver:

## Sigmatropic Rearrangement



"This work was done entirely at Connecticut College. Perhaps the synthesis of *epi*-bulnesene is a good example of the fact that a lot of good synthetic work can be done with dedicated undergraduate students!"

– Timo Ovaska

Synthetic Sequence: Ovaska, *Tetrahedron Letters*, 2002, 43, 1939-1941