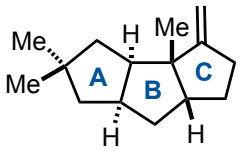
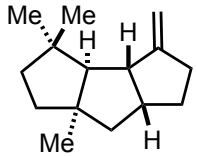
Hirsutene: an Exercise in Construction of 5-membered Rings

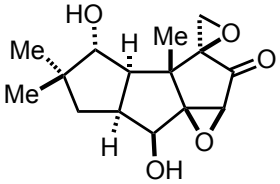
Tricyclopentanoids (triquinanes)
cis,anti,cis-tricyclo[6.3.0.0]undecane



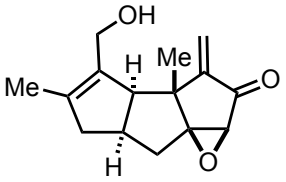
hirsutene



capnellene



coriolin



pleurotellol

Fungal Sesquiterpenes isolated from mold *Stereum hirsutum*

Possess antitumor and antibiotic activity

Reaction Classification & Strategy Evaluation

C–C bond formation		forms C–C bond present in the target
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		oxidation state is altered away from the oxidation state present in the target
protecting group manipulations		protection or deprotection of functional groups
	(14)	# of carbon atoms in intermediate (excluding carbons of protecting groups

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

Covered Syntheses

Kuniaki Tatsuta *J. Am. Chem. Soc.* **1979**, *101*, 6116

Andrew Greene *Tetrahedron Lett.* **1980**, *21*, 3059

Tomas Hudlicky *J. Am. Chem. Soc.* **1980**, *102*, 6353

Daniel Little *J. Am. Chem. Soc.* **1981**, *103*, 2744

Goverdhan Mehta *Chem. Comm.* **1981**, 756

Paul Wender *Tetrahedron Lett.* **1982**, *23*, 3983

Steven Ley *Chem. Comm.* **1982**, 1252

Raymond Funk *J. Org. Chem.* **1984**, *49*, 5021

Dennis Curran *J. Am. Chem. Soc* **1985**, *107*, 1449

Philip Magnus *J. Org. Chem.* **1985**, *50*, 1621

Alan Weedon *J. Org. Chem.* **1987**, *52*, 2905

Janine Cossy *Tetrahedron Lett*. **1987**, *28*, 4547

Benjamin List *J. Am. Chem. Soc.* **2008**, *130*, 6737

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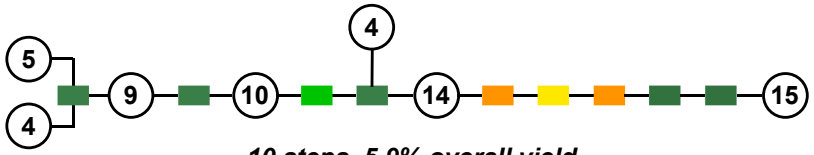
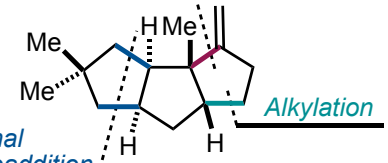
J. Cossy
Tetrahedron Lett. **1987**, *28*, 4547



10 steps, 5.9% overall yield

Radical Cyclization

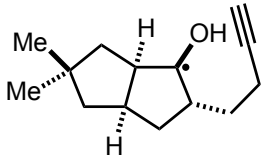


Alkylation

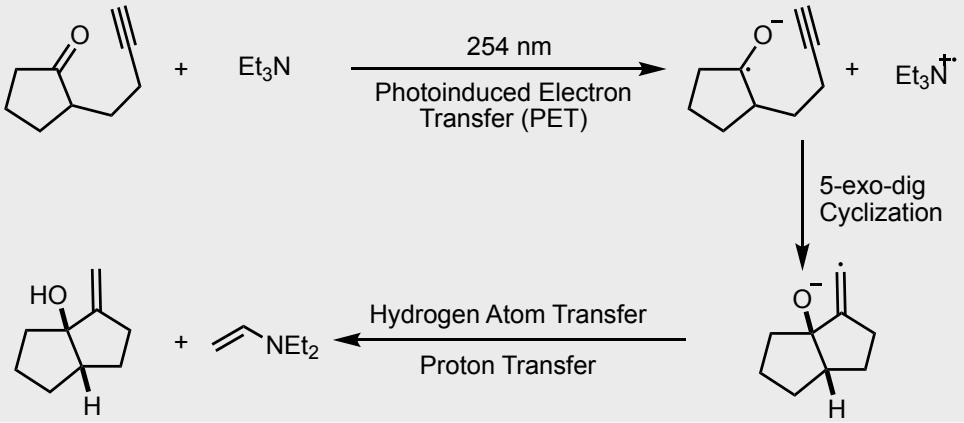
Formal [3+2]-Cycloaddition

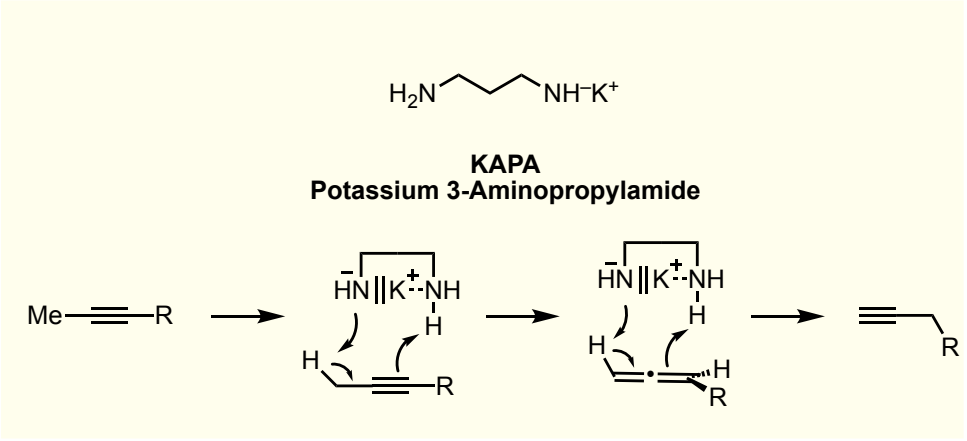
B → AB → ABC

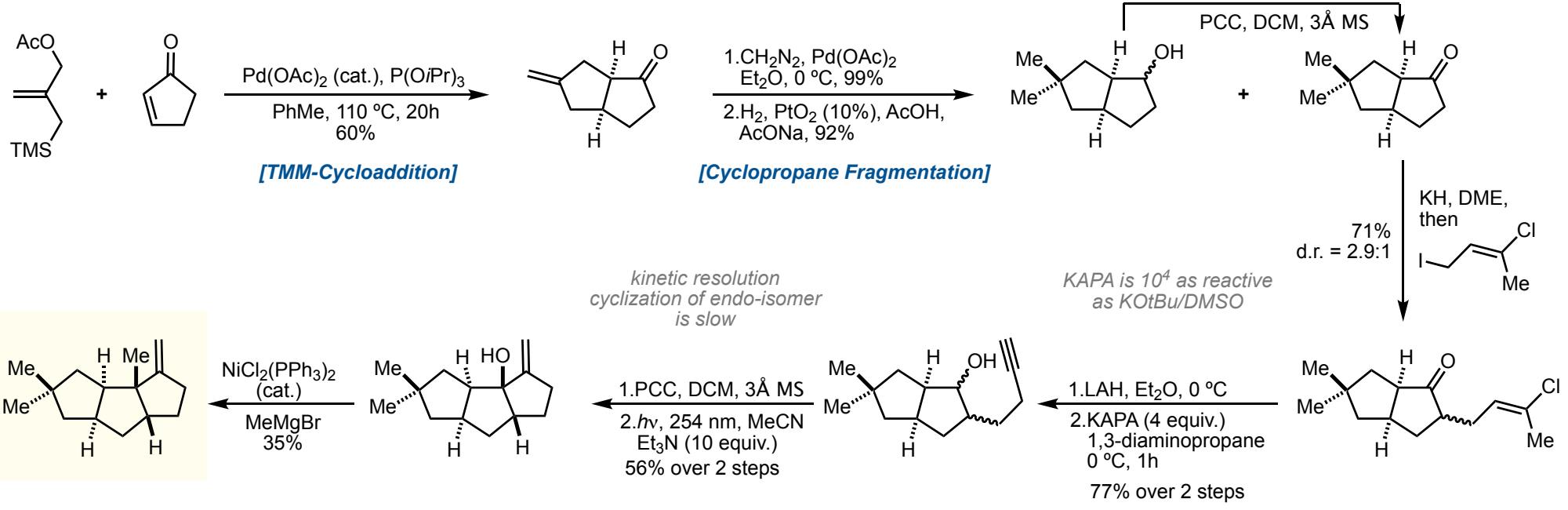
Stepwise Annelation Approach



Key intermediate accessed *via* PET

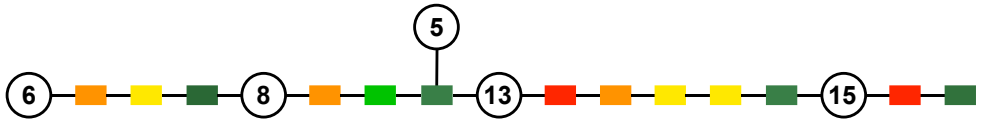




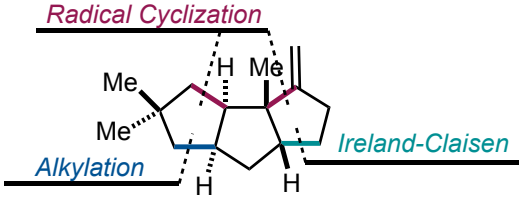


Hirsutene: an Exercise in Construction of 5-membered Rings

D. Curran
J. Am. Chem. Soc **1985**, *107*, 1449

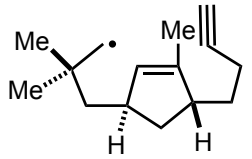


14 steps, 7.8% overall yield

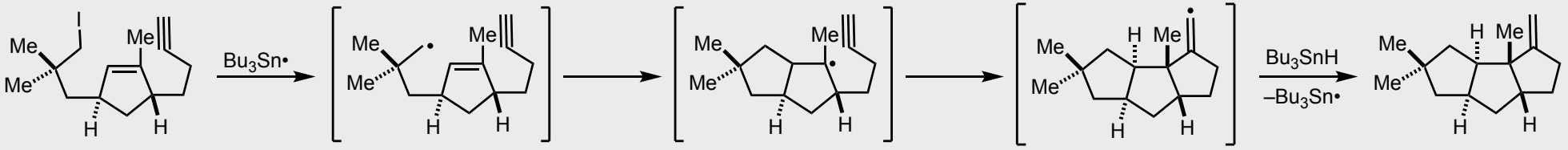


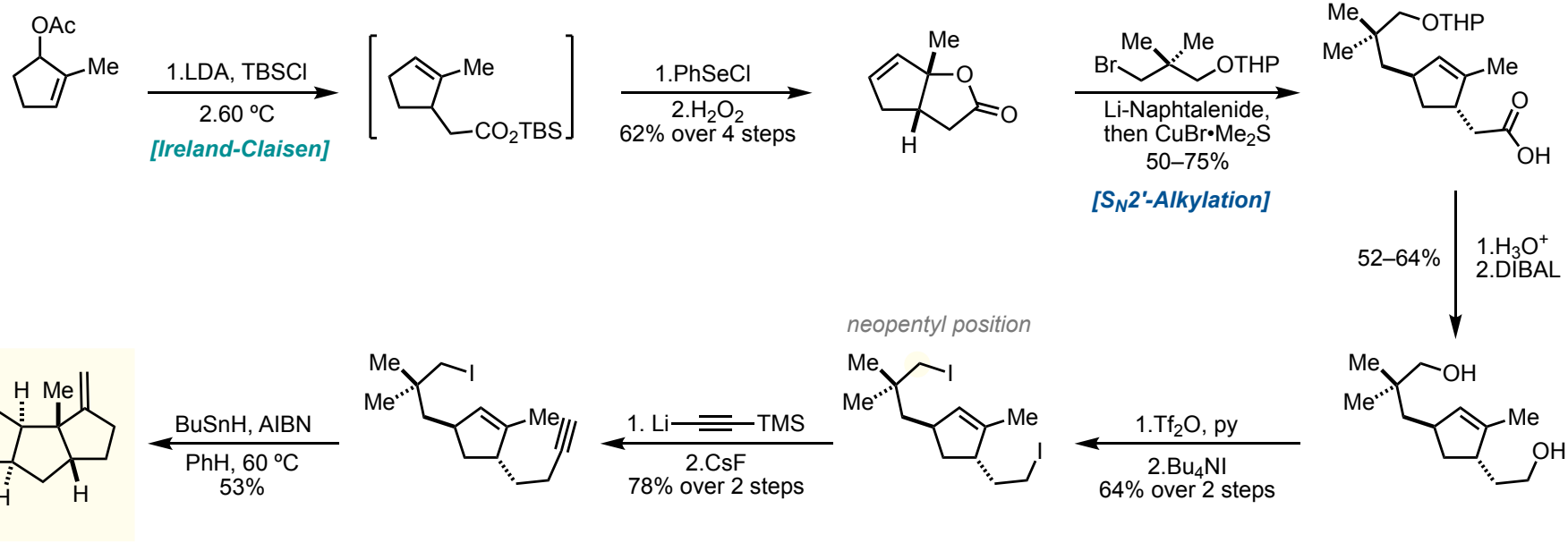
B → ABC

Tandem Radical Cyclization



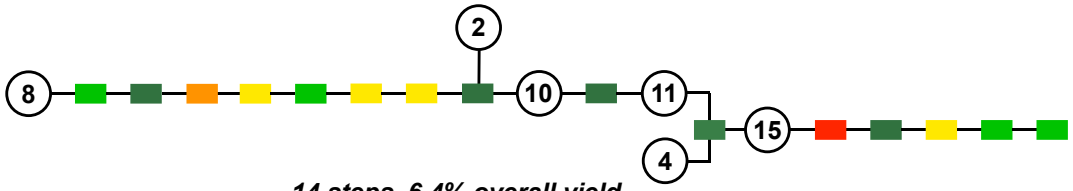
Key intermediate accessed *via* halogen atom abstraction



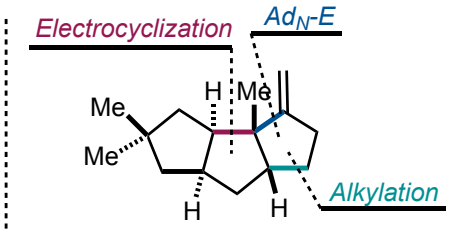


Hirsutene: an Exercise in Construction of 5-membered Rings

P. Magnus
J. Org. Chem. **1985**, *50*, 1621

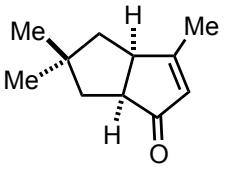


14 steps, 6.4% overall yield

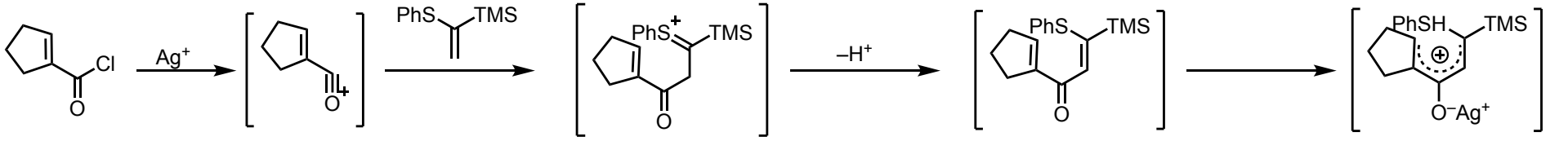


A → AB → ABC

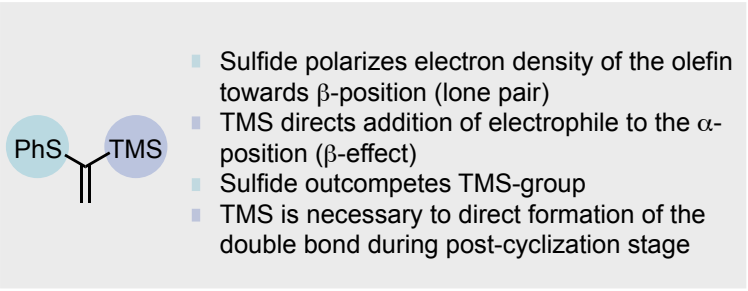
Tandem Polar Annelation



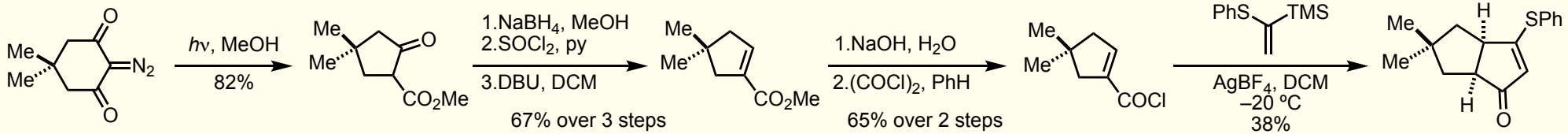
Key intermediate accessed *via* Nazarov electrocyclization



4π-electrocyclization

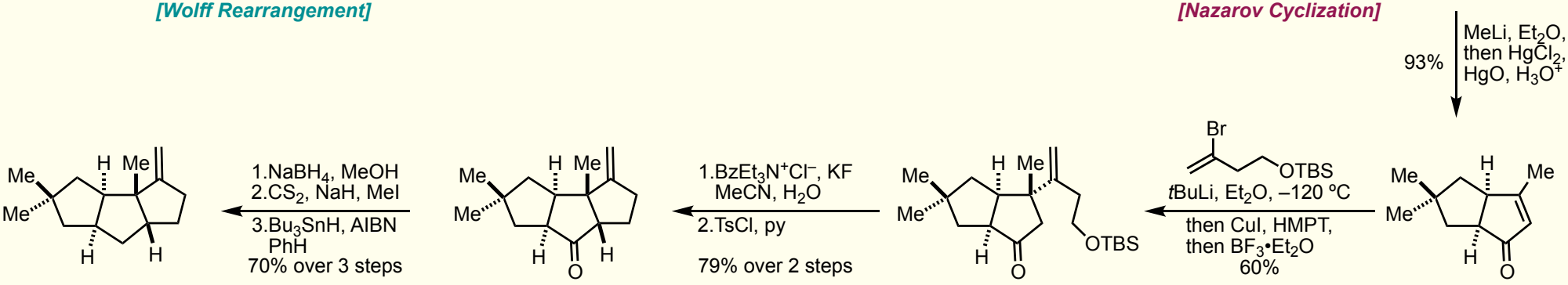


- Sulfide polarizes electron density of the olefin towards β-position (lone pair)
- TMS directs addition of electrophile to the α-position (β-effect)
- Sulfide outcompetes TMS-group
- TMS is necessary to direct formation of the double bond during post-cyclization stage



[Wolff Rearrangement]

[Nazarov Cyclization]



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R. Funk
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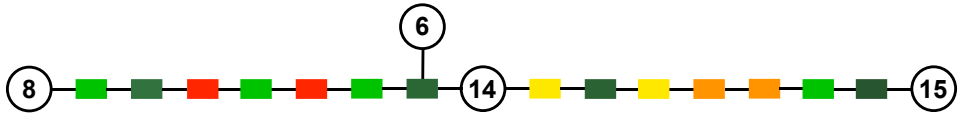
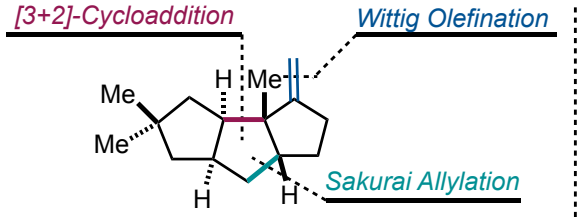
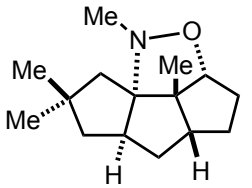


13 steps, 7.9% overall yield

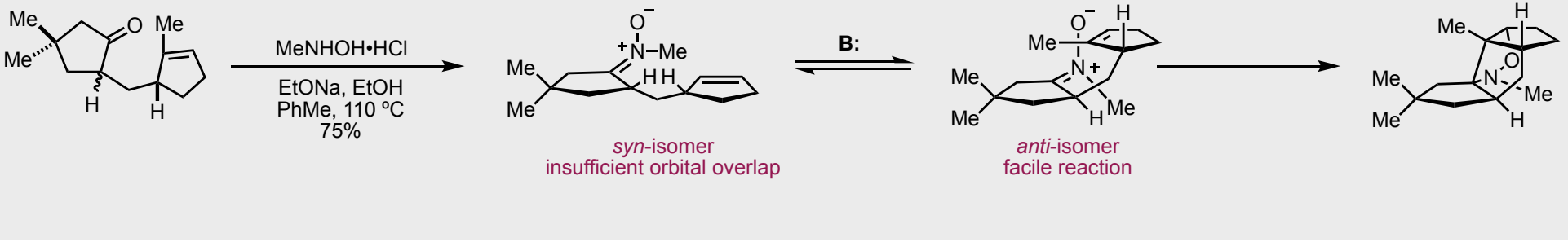


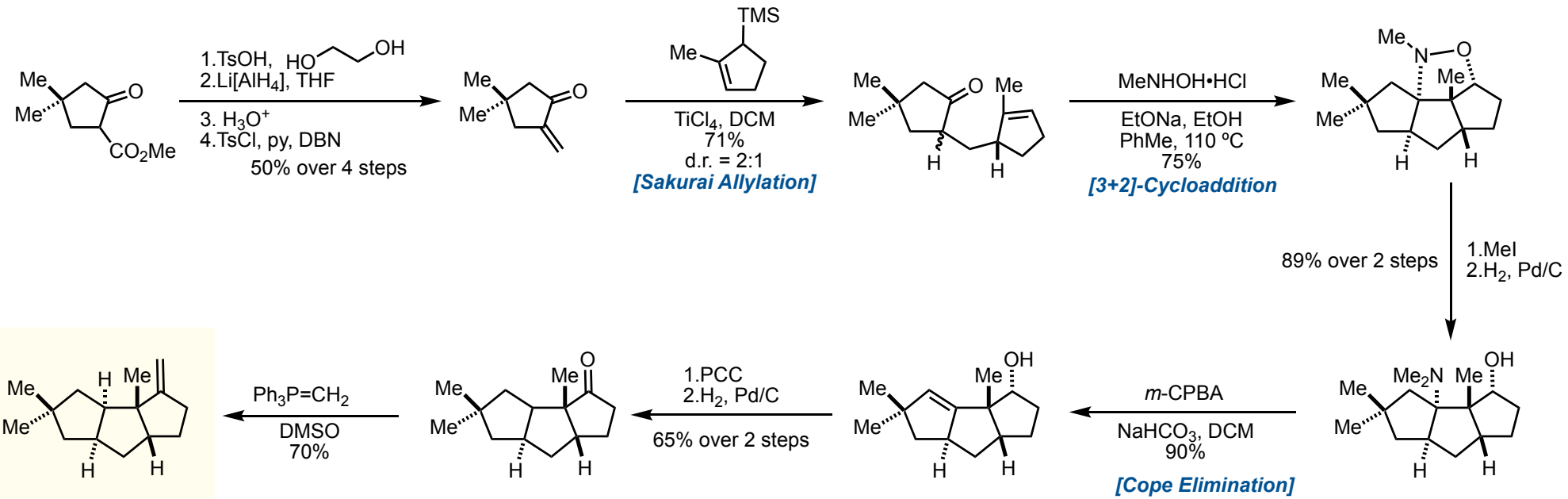
A → AC → ABC

Convergent Approach



Key intermediate accessed *via* sequentional Sakurai/Nitrone-olefin cycloaddition





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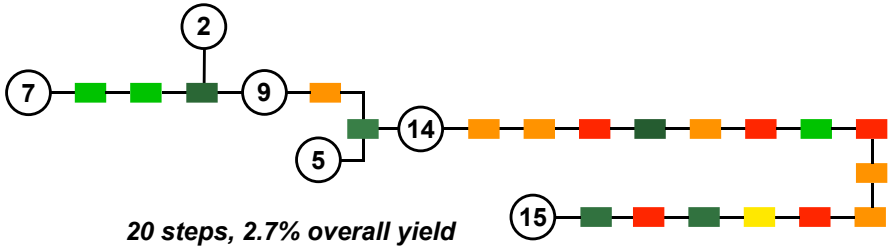
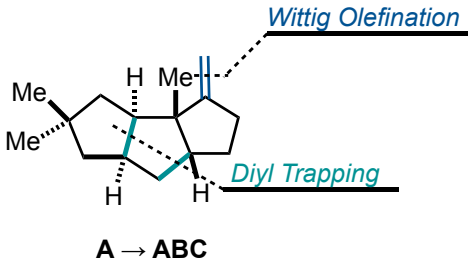
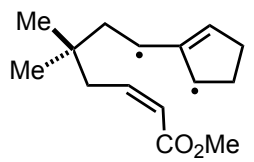


20 steps, 2.7% overall yield

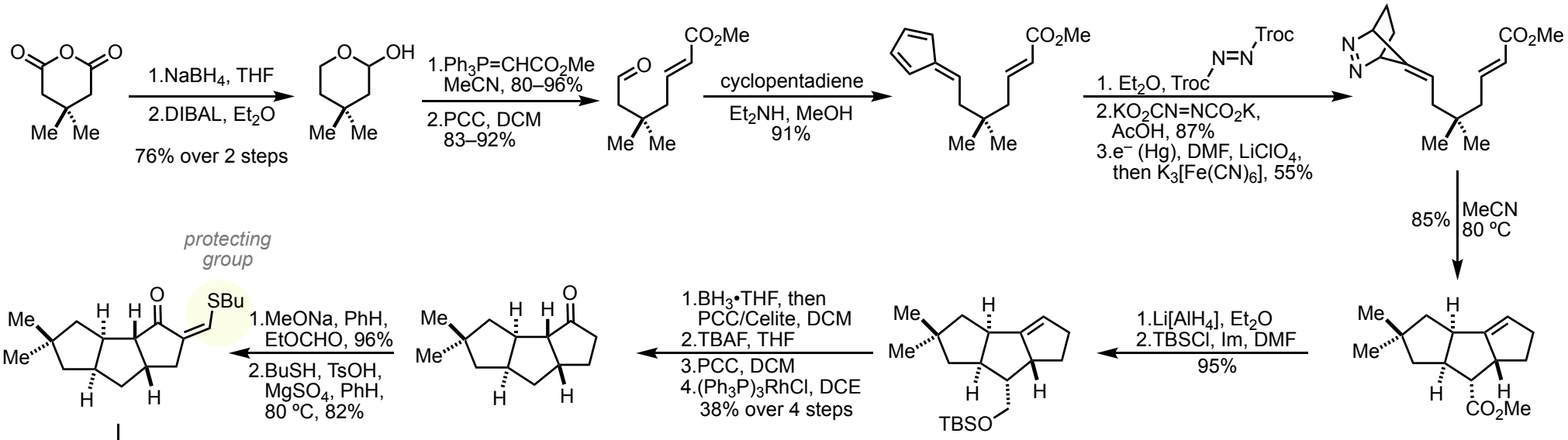


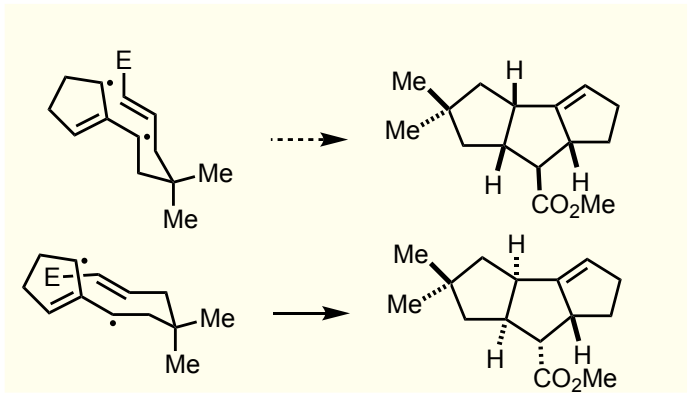
A → ABC

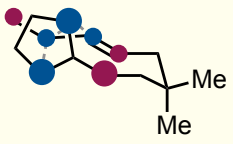
Convergent Approach



Key intermediate accessed *via* thermal decomposition of aza-bicycle







HOMO diyl
LUMO diylophile

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A. Weedon
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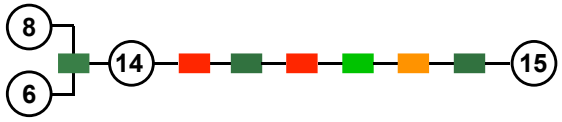
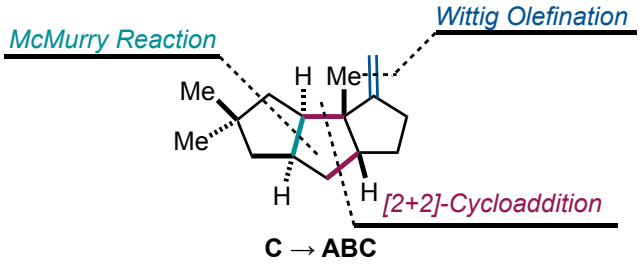
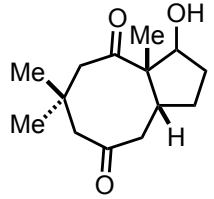


7 steps, 4.2% overall yield

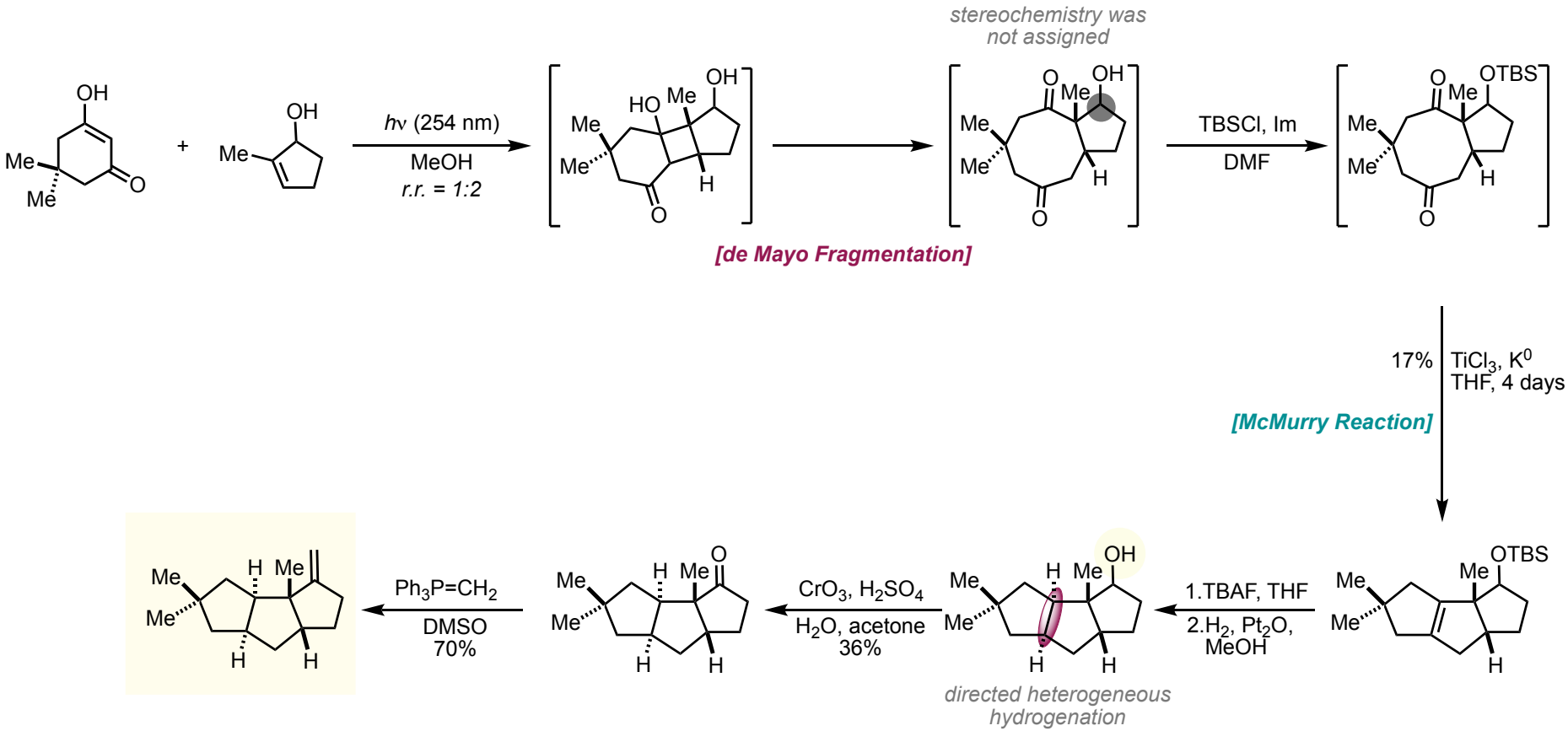


C → ABC

Transannular Approach



key intermediate accessed *via* de Mayo fragmentation



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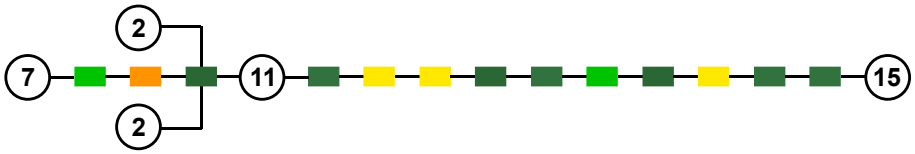
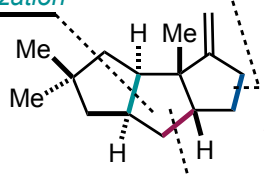
B. List
J. Am. Chem. Soc. **2008**, *130*, 6737



13 steps, 6.5% overall yield

Coupling of Diazo Compound

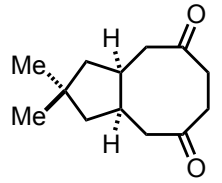
Radical Cyclization



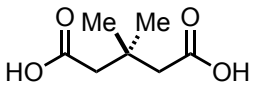
Transannular Aldolization

A → ABC

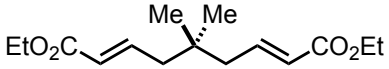
Transannular Approach



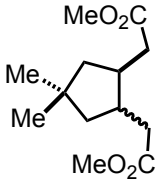
key intermediate accessed *via* dimerization of diazo compound



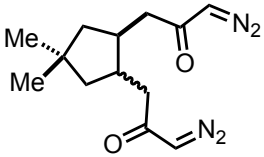
1.BH_3•THF
2.$(COCl)_2$, Et_3N, DMSO
3. Ph_3P=$CHCO_2Et$
DCM
70% over 2 steps



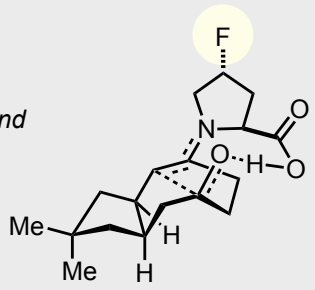
Mg^0
MeOH
88%
d.r. = 1.1:1



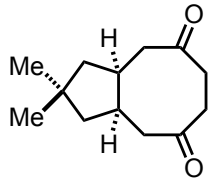
1.$KOH_{(aq)}$, EtOH
2.$(COCl)_2$, DCM
3.$TMSCHN_2$, THF
41% over 2 steps

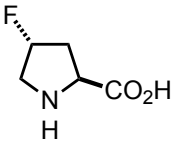


Substitution at C-4 has a profound effect on enantioselectivity in proline-derivative-catalyzed reactions

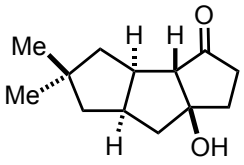


1.$RuCl(\eta^5\text{-}C_5H_5)(PPh_3)_2$
(3 mol %), DCM, 52%
2. H_2, Pd/C, EtOAc, 91%



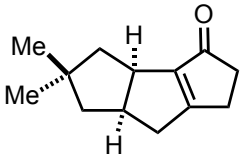


(10 mol %)
DMSO
84%
e.r. = 98:2

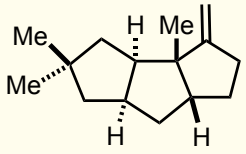


[Transannular Aldolization]

$NaOH_{(aq)}$
Et_2O
99%



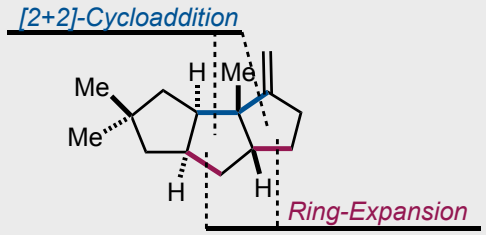
1.Li, NH_3, THF,
then MeI
2.Ph_3P=CH_2,
PhMe, 115 °C
65% over 2 steps



Hirsutene: an Exercise in Construction of 5-membered Rings

A. Greene
Tetrahedron Lett.. **1980**, *21*, 3059

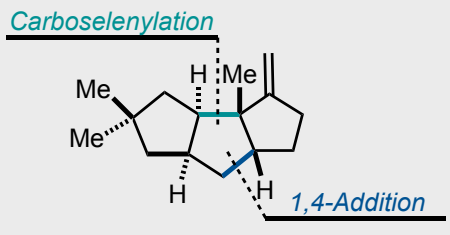
sequential annelation approach
via
cycloaddition/ring-expansion



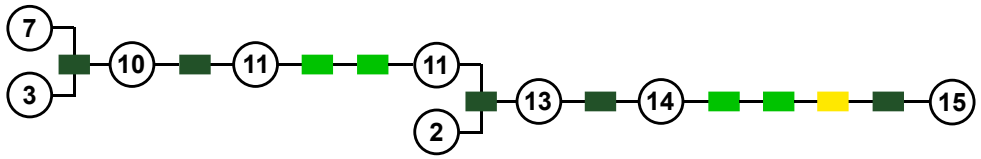
A → AB → ABC

S. Ley
Chem. Comm. **1982**, 1252

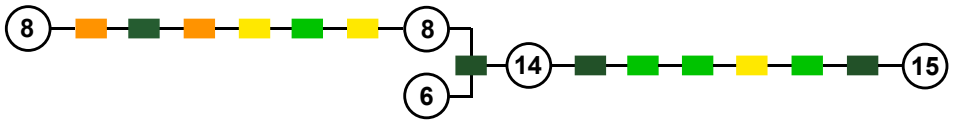
convergent approach
via
intramolecular cyclization



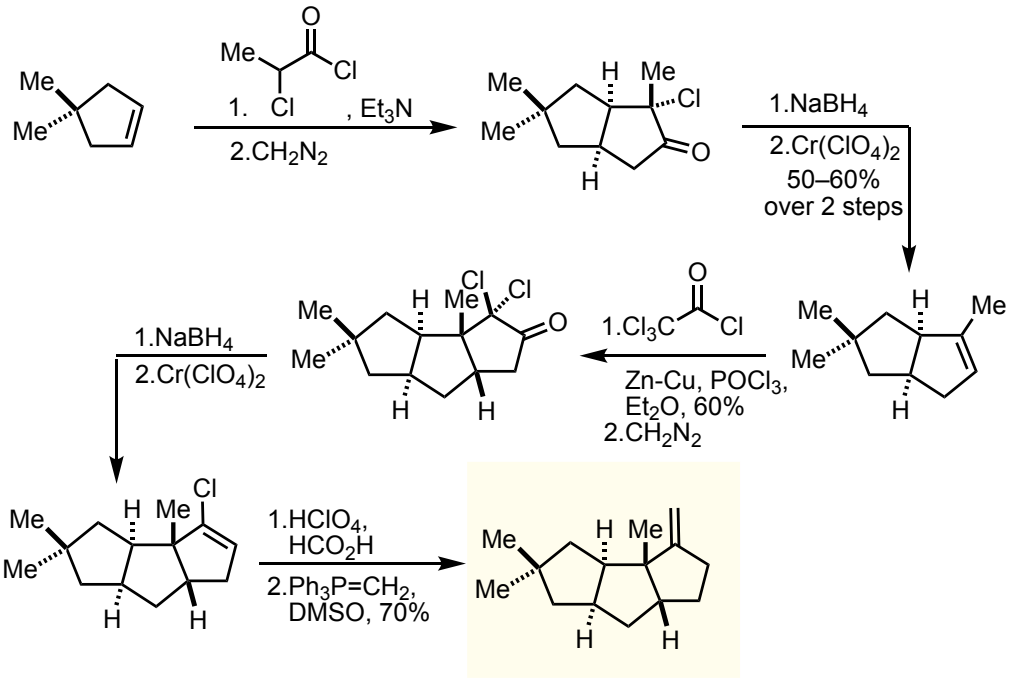
A → AC → ABC

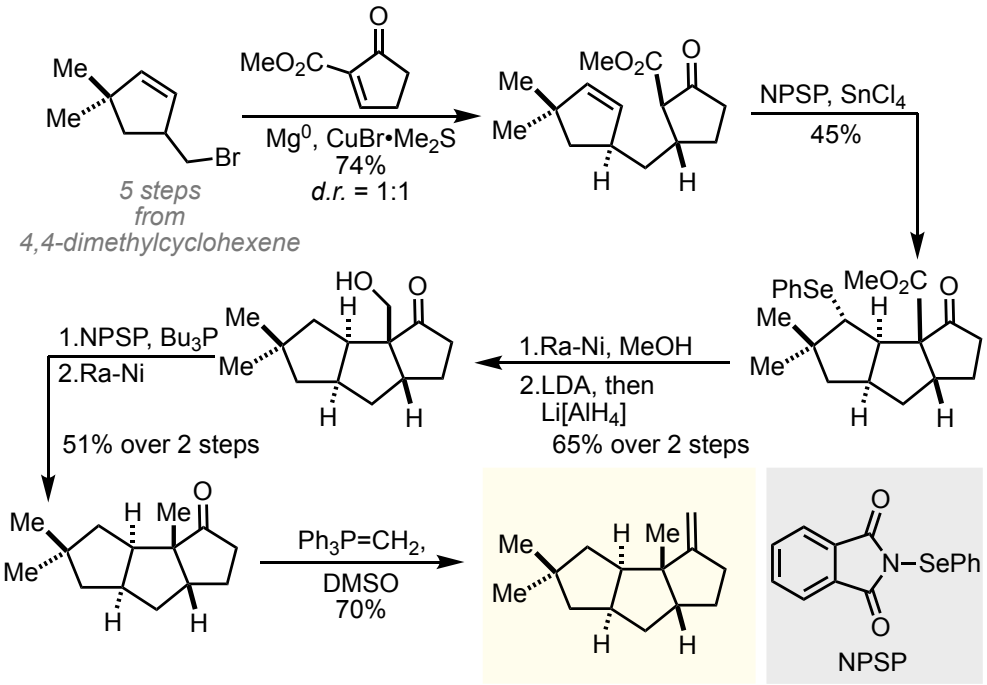


10 steps



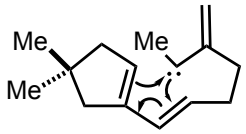
12 steps, 3.8% overall yield from bromide



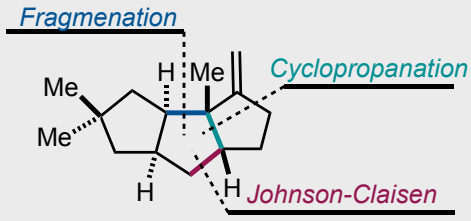


Hirsutene: an Exercise in Construction of 5-membered Rings

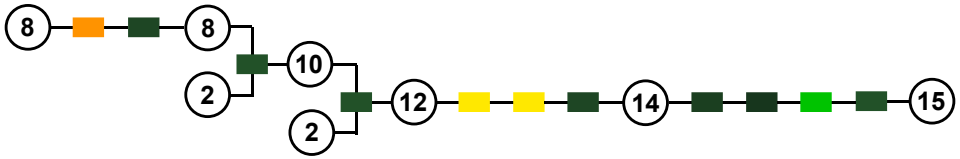
T. Hudlicky
J. Am. Chem. Soc. **1980**, *102*, 6353



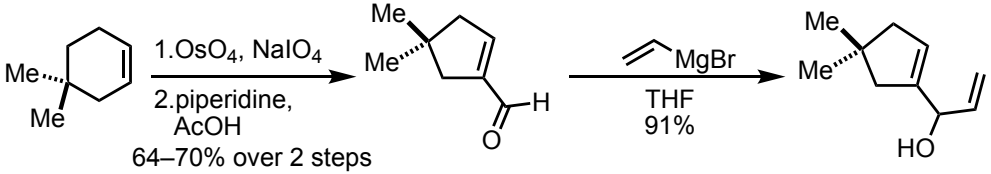
concept of formal
[4+1]-cycloaddition



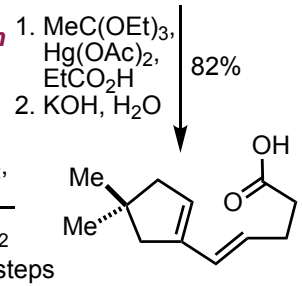
A → AC → ABC

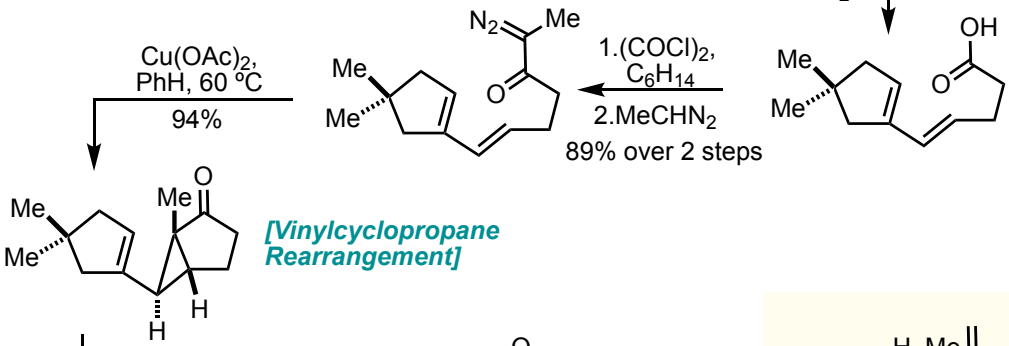


11 steps, 23% overall yield



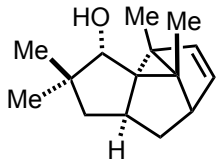
[Johnson-Claisen Rearrangement]



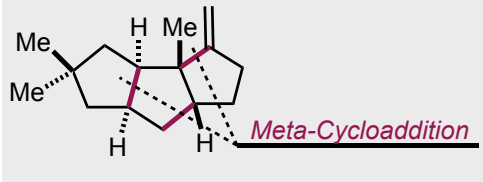


[Vinylcyclopropane Rearrangement]

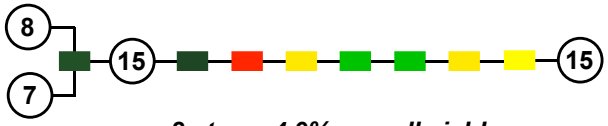
P. Wender
Tetrahedron Lett. **1982**, *23*, 3983



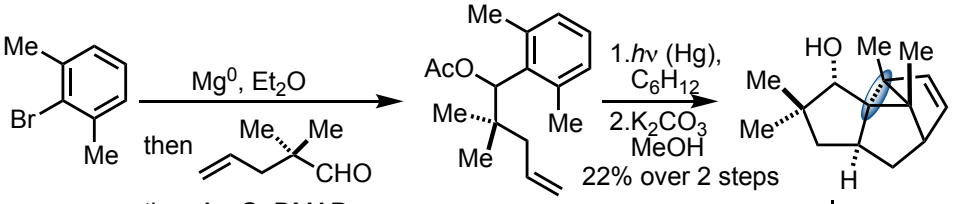
key overbred intermediate
via
photochemical cycloaddition



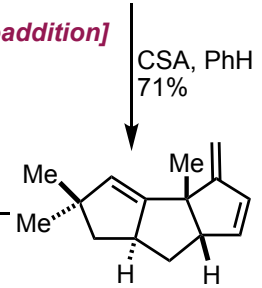
x → ABC



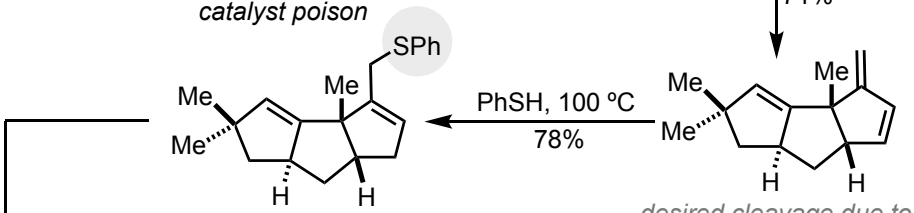
8 steps, 4.9% overall yield



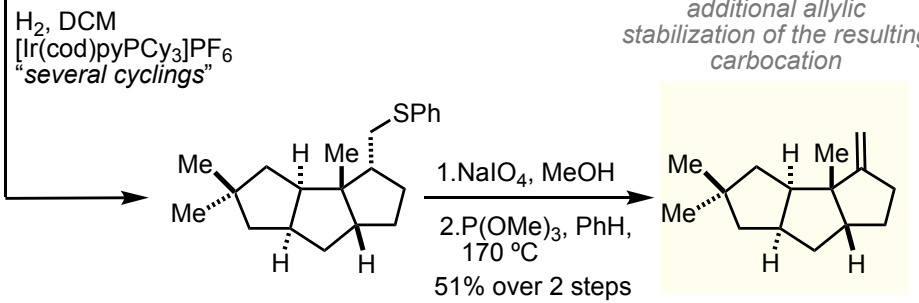
[Meta-Cycloaddition]



catalyst poison

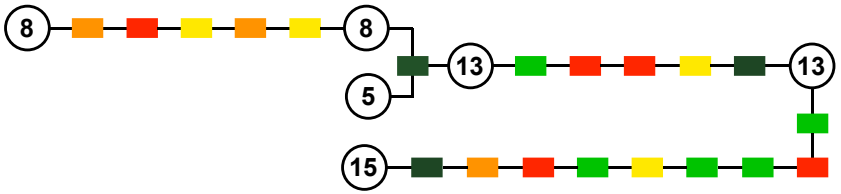


desired cleavage due to additional allylic stabilization of the resulting carbocation

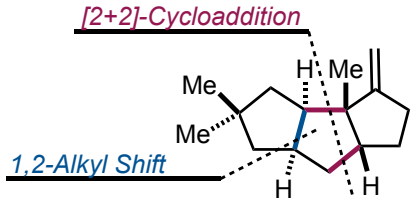


Hirsutene: an Exercise in Construction of 5-membered Rings

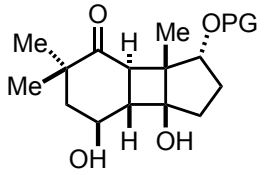
K. Tatsuta
J. Am. Chem. Soc. **1979**, *101*, 6116



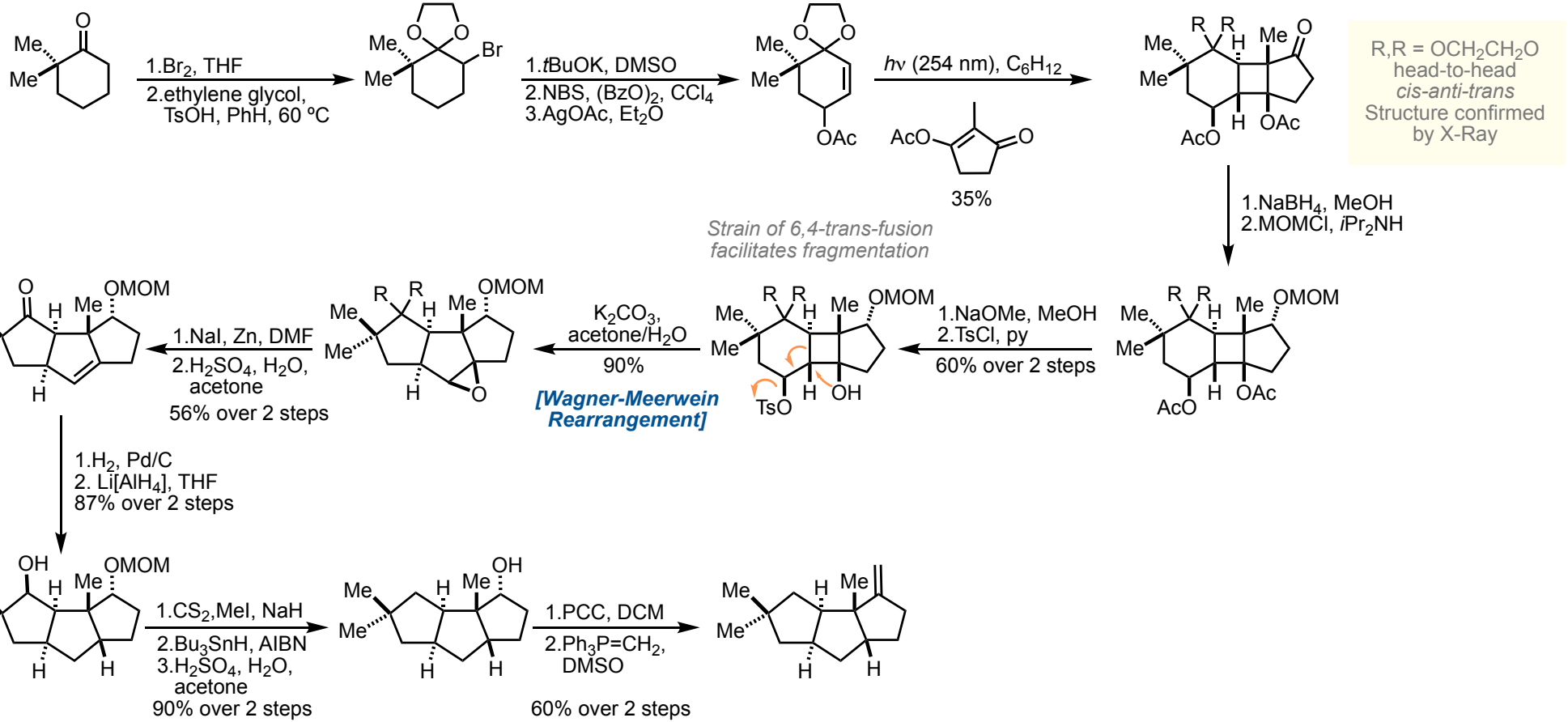
20 steps



C → ABC

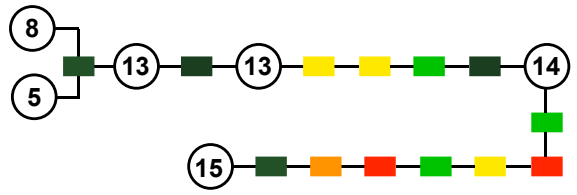


key intermediate
via
photochemical cycloaddition

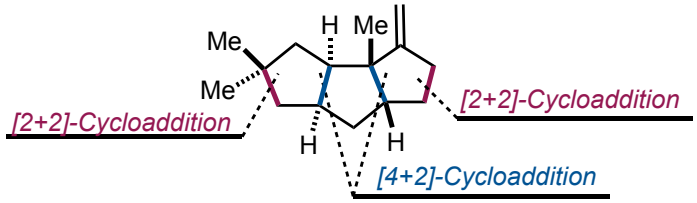


Hirsutene: an Exercise in Construction of 5-membered Rings

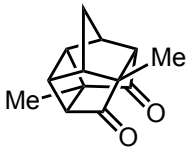
G. Mehta
Chem. Comm. **1981**, 756



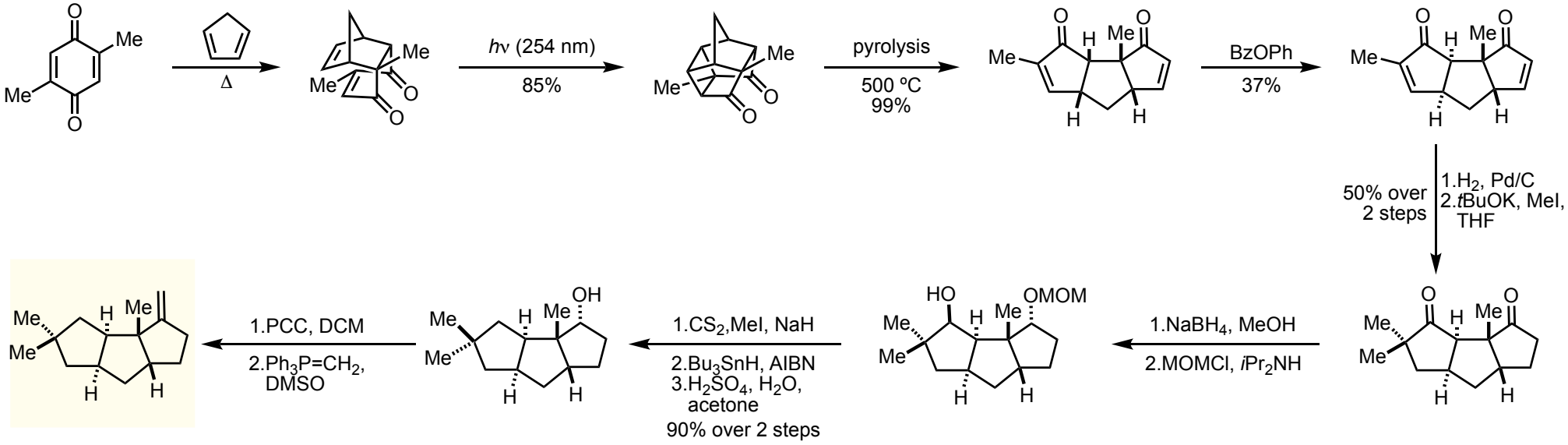
13 steps



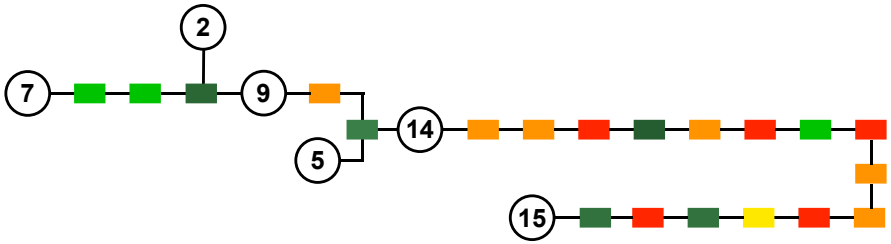
x → ABC



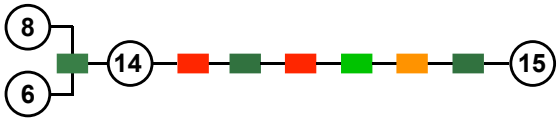
key overbred intermediate
via
tandem [4+2]/[2+2]-cycloaddition



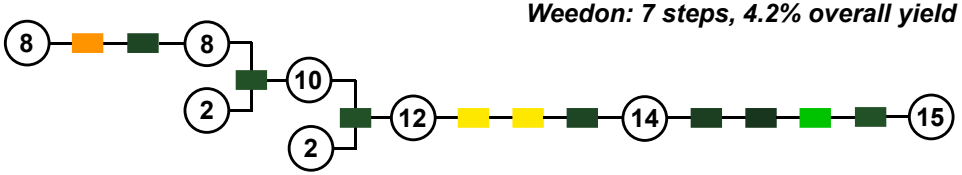
Ideal Recipe?



Little: 20 steps, 2.7% overall yield



Weedon: 7 steps, 4.2% overall yield



Hudlicky: 11 steps, 23% overall yield