Scott A. Snyder

Shenvi Lab Group Meeting

4/27/2024

Kevin Zong

Scott. A. Snyder

1999: B.A. with highest honours in Chemistry,
Summa Cum Laude, valedictorian
Advisor: Professor J. Hodge Markgraf
Williams College

1999 - 2004: NSF, Pfizer, and BMS Doctoral Fellow in Chemistry
Advisor: Professor K. C. Nicolaou
The Scripps Research Institute

2004 - 2006: NIH Postdoctoral Associate
Advisor: Professor E. J. Corey
Harvard University

2006 - 2011: Columbia University, Assistant Professor of Chemistry

2011 - 2013: Columbia University, Associate Professor of Chemistry, untenured

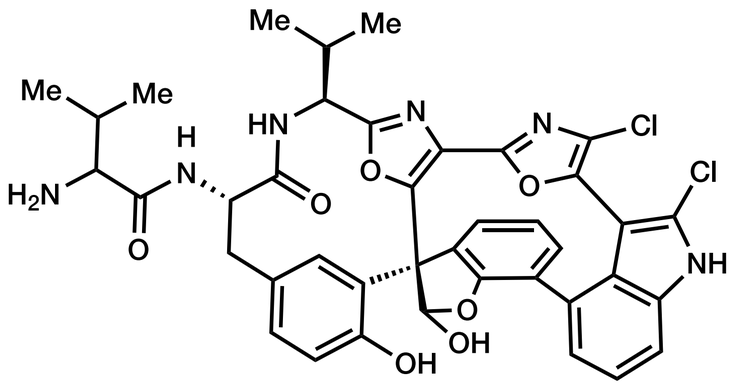
2013 - 2015: The Scripps Research Institute, Associate Professor of Chemistry, tenured

2015 - present: The University of Chicago, Professor of Chemistry
Associate Chair, Deputy Dean of Professional Programs

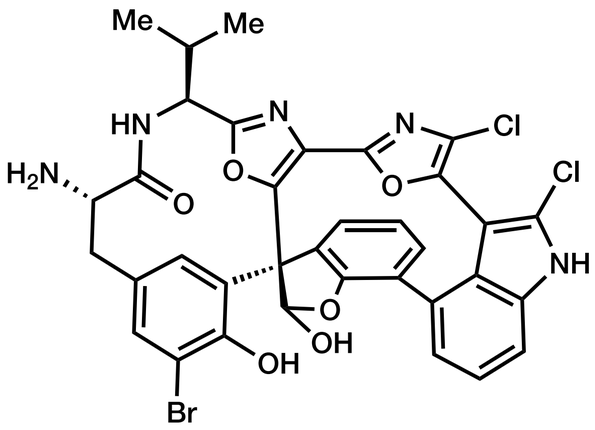
PhD Work - Diazonamide A

Synthesis and Structural Revision/Confirmation

Determined by William Fenical (Scripps Institution of Oceanography) and Jon Clardy (Cornell University)



Diazonamide A



Diazonamide B

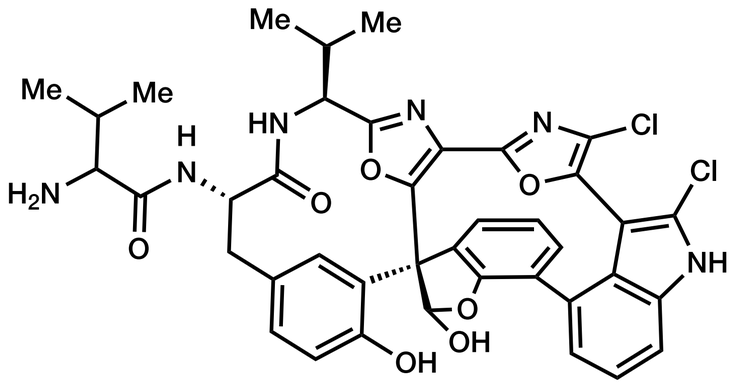
- Two 12 membered macrocyclic rings
- Single atropisomer
- Reported cytotoxicity against several tumour cell lanes with IC_{50} values of < 15 ng/mL
- First synthesised by Patrick Haran, in 2001
  - But spectroscopic data for the synthetic products is inconsistent with initial reports.

J. Am. Chem. Soc. 1991, 113, 6, 2303–2304
Angew. Chem. Int. Ed., 40: 4765-4769
Angew. Chem. Int. Ed., 40: 4770-4773;

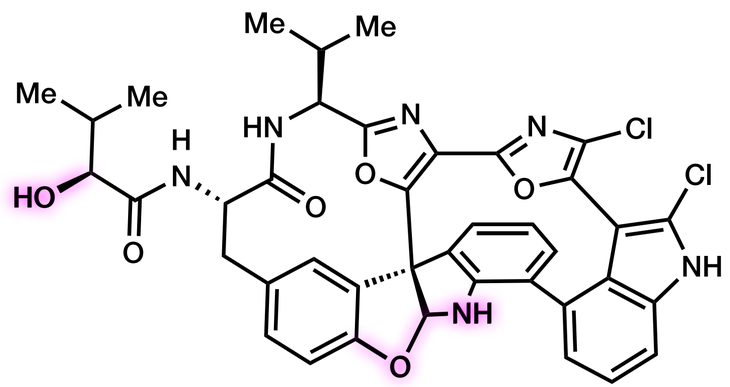
PhD Work - Diazonamide A

Structures of Diazonamide A and B

Determined by William Fenical (Scripps Institution of Oceanography) and Jon Clardy (Cornell University)



Diazonamide A
Original



Diazonamide A
Revised

- Two 12 membered macrocyclic rings
- Single atropisomer
- Reported cytotoxicity against several tumour cell lanes with IC_{50} values of < 15 ng/mL
- First synthesised by Patrick Haran, in 2001
  - But spectroscopic data for the synthetic products is inconsistent with initial reports.

J. Am. Chem. Soc. 1991, 113, 6, 2303–2304
Angew. Chem. Int. Ed., 40: 4765-4769
Angew. Chem. Int. Ed., 40: 4770-4773;

Post Doctoral Work - Regioselective Aldol

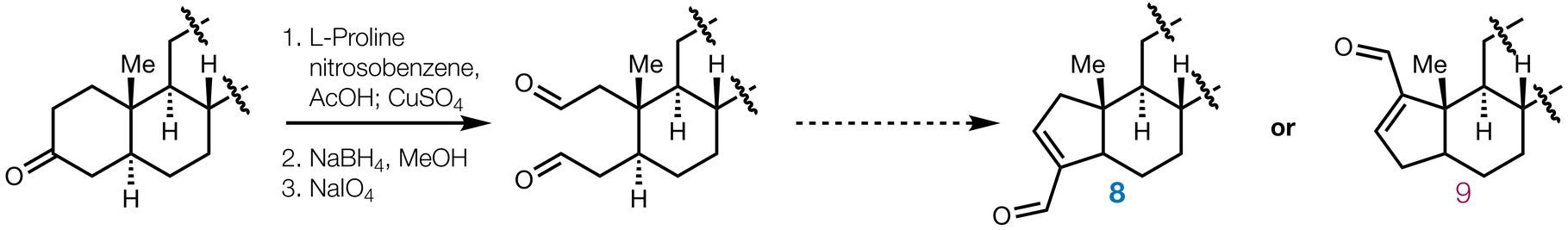


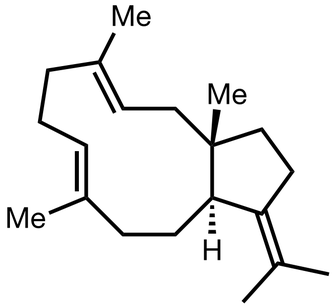
Table 1. Aldol cyclization/dehydration reactions of dialdehyde **7**[a]

Entry	Conditions	Ratio of **8**:**9**	Yield (%)
1	Piperidine (cat.), AcOH (cat.), benzene, 25 °C, 15 min; 55 °C, 75 min	4:1	61
2	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), benzene, 25 °C, 12 h	6:1	68
3	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), CH_2Cl_2, 25 °C, 12 h	4:1	57
4	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), DME, 25 °C, 12 h	3:1	59
5	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), THF, 25 °C, 12 h	2:1	59
6	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), DME/HMPA (1:1), 25 °C, 12 h	2:1	66
7	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), THF/HMPA (1:1), 25 °C, 12 h	2:1	62
8	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), HMPA, 25 °C, 12 h	1.3:1	59
9	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), DMSO, 25 °C, 12 h	1.1:1	60
10	$PhBnNH_2^{+-}OCOCF_3$ (5.0 equiv), benzene, 25 °C, 30 min; 50 °C, 1 h	5:1	56
11	$(Cyclohexyl)_2NH_2^{+-}OCOCF_3$ (5.0 equiv), benzene, 25 °C, 30 min; 50 °C, 5 h	2:1	24
12	Morpholine (6.0 equiv), octanoic acid (7.0 equiv), HMPA (1.5 equiv), Et_2O, 0 °C, 20 h	50:1	44
13	D-Proline (5.0 equiv), DMSO, 25 °C, 10 h	1:2	48
14	L-Proline (5.0 equiv), DMSO, 25 °C, 10 h	1:2	52
15	(*S*)-Indoline-2-carboxylic acid (5.0 equiv), $MeCN/CH_2Cl_2$ (1:1), 25 °C, 10 h	1:50	47
16	D-Proline (5.0 equiv), $MeCN/CH_2Cl_2$ (1:1), 25 °C, 10 h	8:1	17
17	L-Proline (5.0 equiv), $MeCN/CH_2Cl_2$ (1:1), 25 °C, 10 h	1:2	16

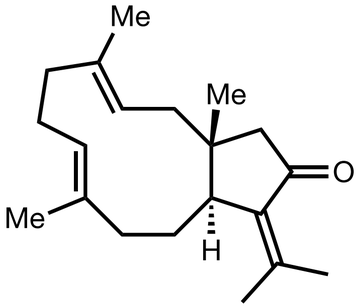
[a] Substrate concentration was 0.01–0.02 M in each case.

Tetrahedron Lett. 2006, 47, 2083.

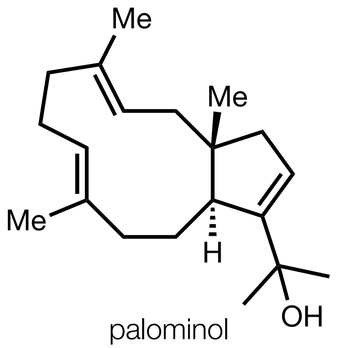
Post Doctoral Work - Dolabellane Diterpenoids



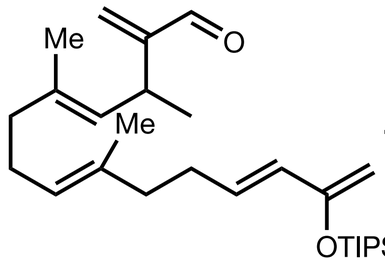
β-araneosene



dolabellatrienone

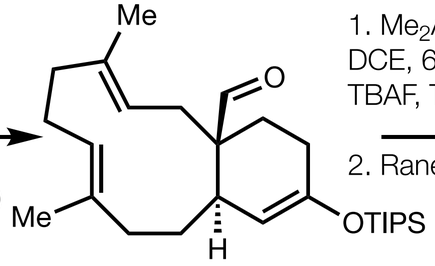


palominol



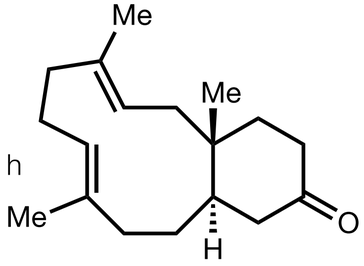
cat. (0.2 eq),
toluene,
-93°C, 3 h;

-78°C, 10 h
(74%, 90% e. e.)



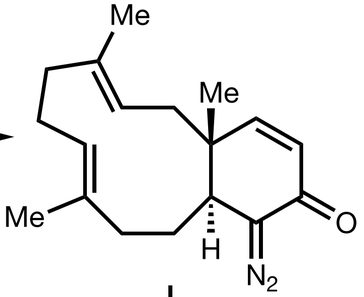
1. $Me_2AlSCH_2CH_2SAlMe_2$,
DCE, 60°C 12 h;
TBAF, THF

2. Raney Ni, THF, 25°C, 10 h
(65% overall)

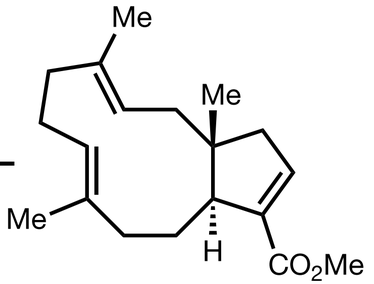


1. NaHMDS, TMSCl;
IBX-MPO, DMSO

2. Trisyl Azide
18-C-6,
$BnEt_3NCl$. aq. KOH/
benzene, 40°C
(62% overall)

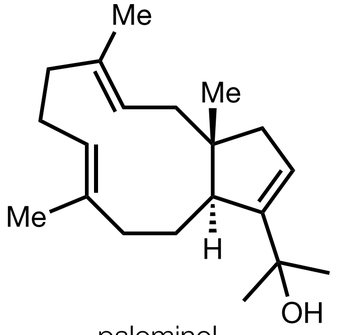


1. hv, MeOH
25°C, 2h;
DBU, 115°C, 18 h
(68%)



MeLi, THF

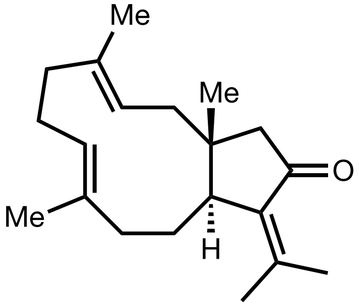
-20°C, 1h
(92%)



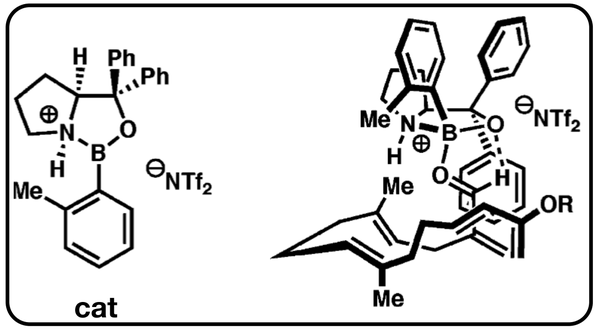
palominol

PDC, 4Å M. S
CH_2Cl_2, 25°C, 5 h

(67%)



dolabellatrienone



J. Am. Chem. Soc. 2006, 128, 740

Independent Career

Outline of Presentation

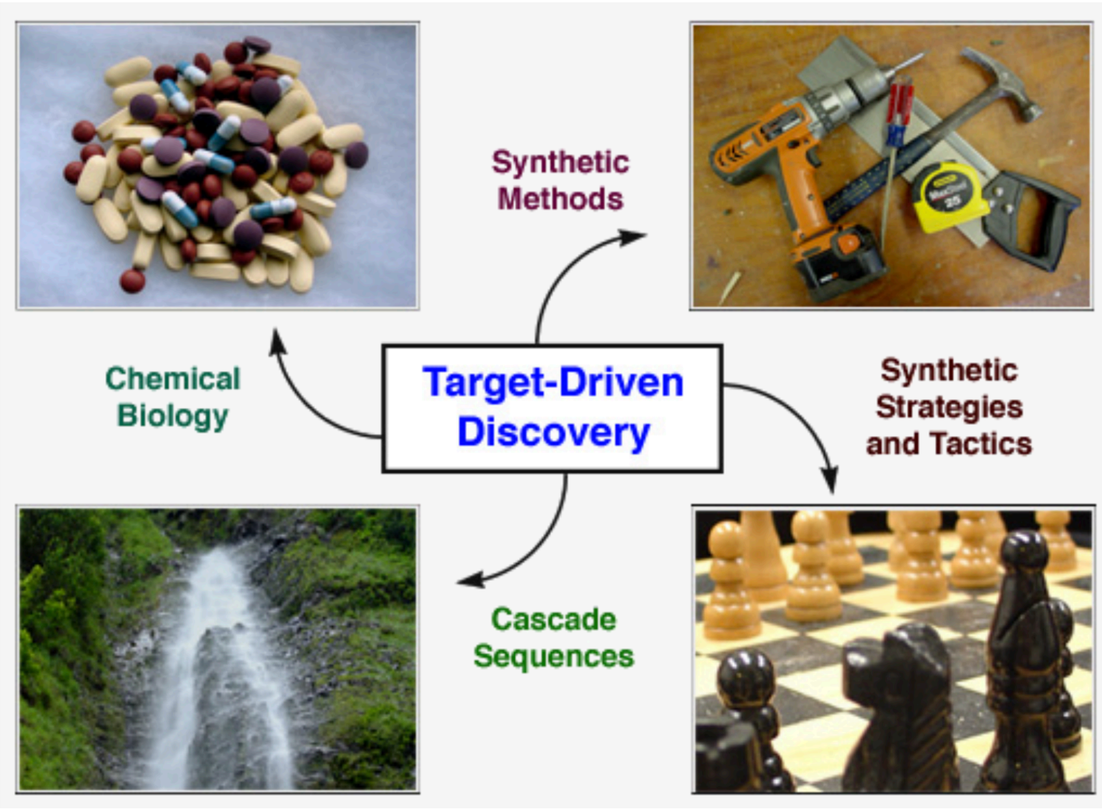
1. Nature: An Inspiration, but not the Answer Key
    a) Phenylpropanoid/Polyketide Synthesis
2. Efficient and Controlled Skeleton Formation
    a) Polyene Cyclizations
    b) Akuamalline Alkaloids
    c) Metal and LA Catalysed Cyclizations
3. Quaternary Center Guided Synthesis Design
    a) Terpene/Terpenoid Synthesis

"Natural Products: Divine Inspiration for Chemistry"

COLUMBIA UNIVERSITY

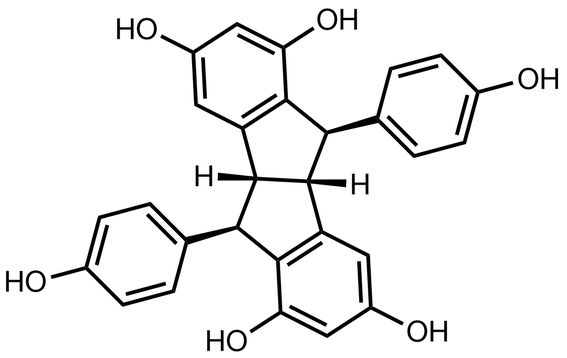
IN LVMINE TVO VIDEBIMVS LVMEN

THE SCRIPPS RESEARCH INSTITUTE

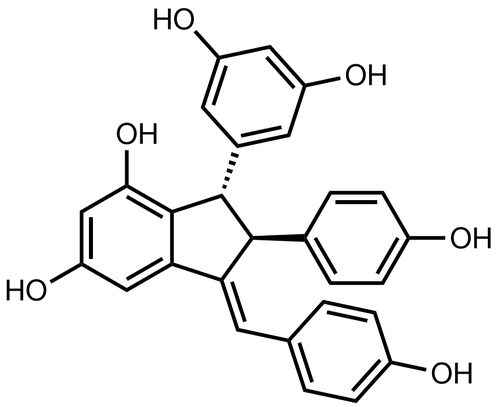


Nature: An Inspiration, not the Answer Key

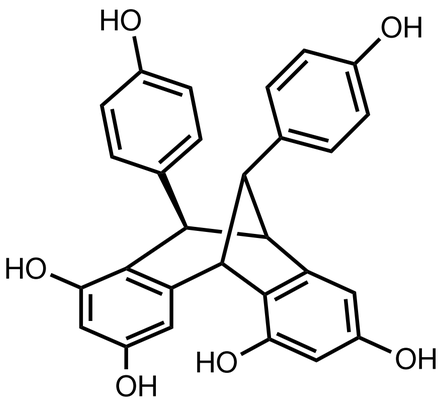
Resveratrol Oligomers



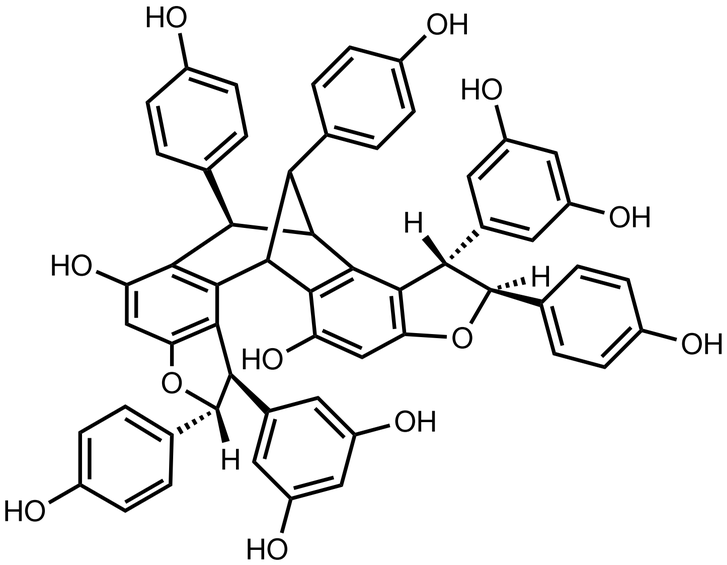
pallidol (C_{28})



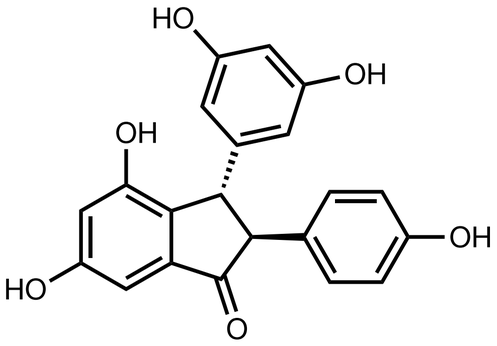
ampelopsin D (C_{28})



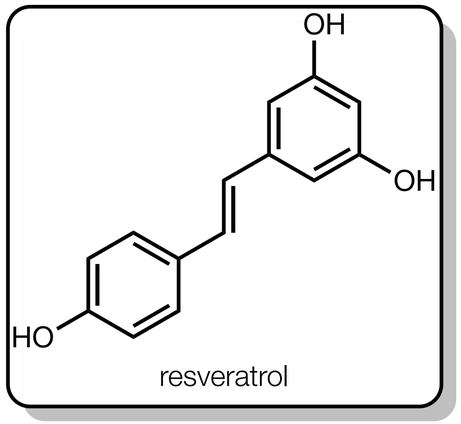
ampelopsin F (C_{28})



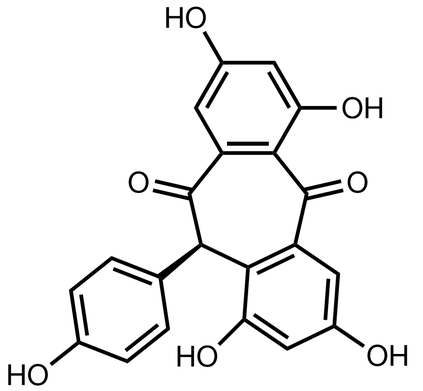
vaticanol C (C_{56})



paucifloral F (C_{21})



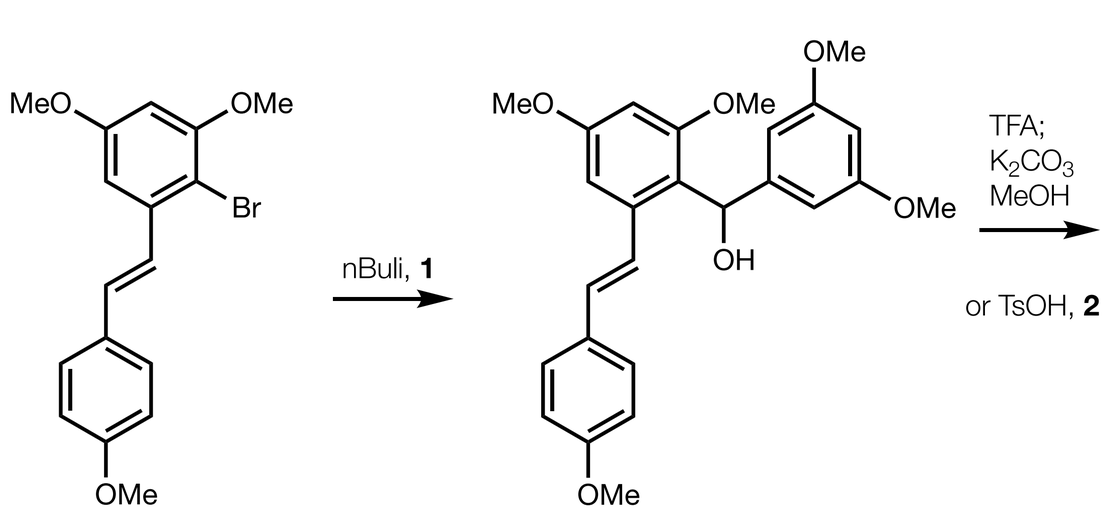
resveratrol

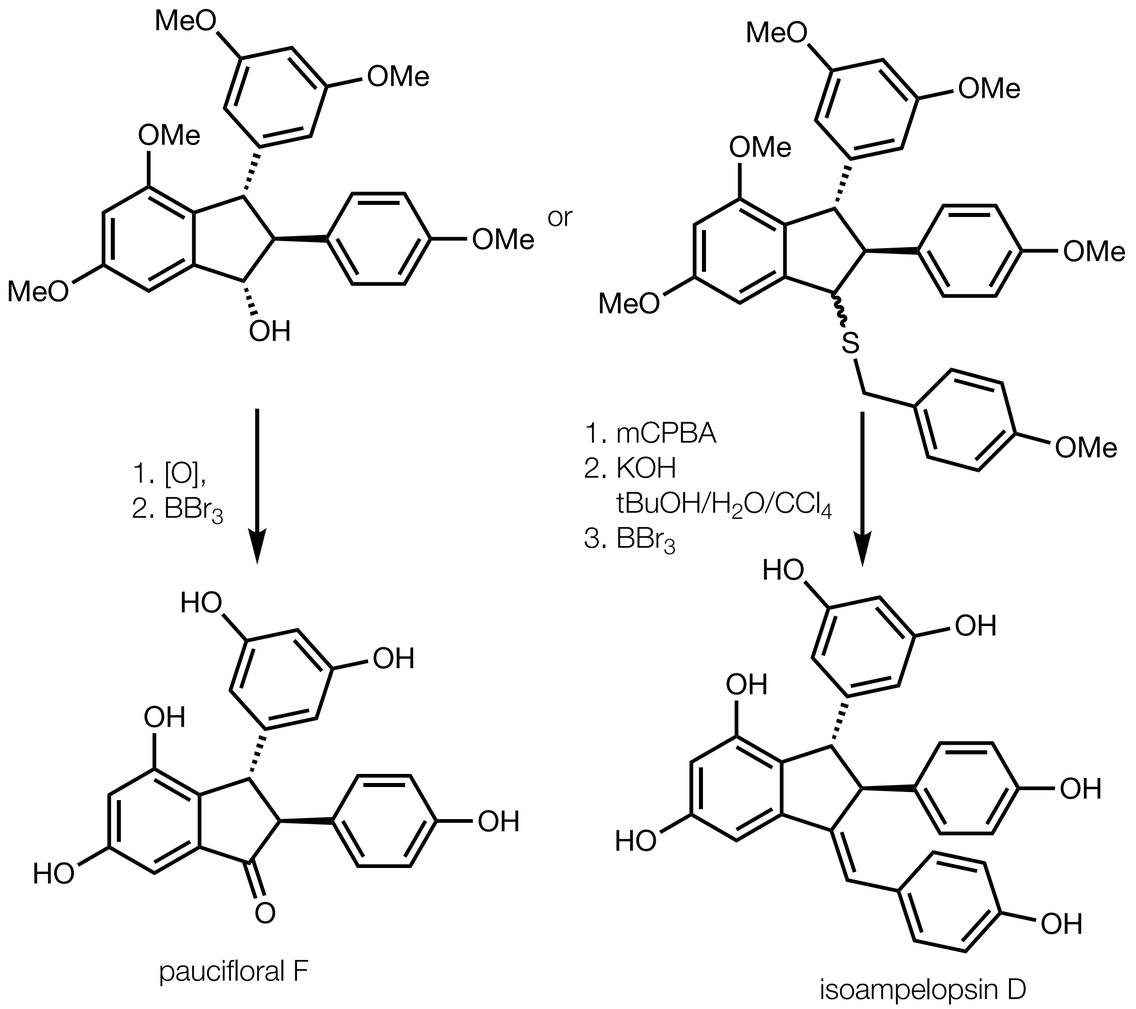


diptoindonesin A (C_{21})

Angew. Chem. Int.Ed. 2007, 46, 8186 –8191
J. Am. Chem. Soc. 2009, 131, 1745.
Angew. Chem. Int. Ed. 2010, 49, 5146.

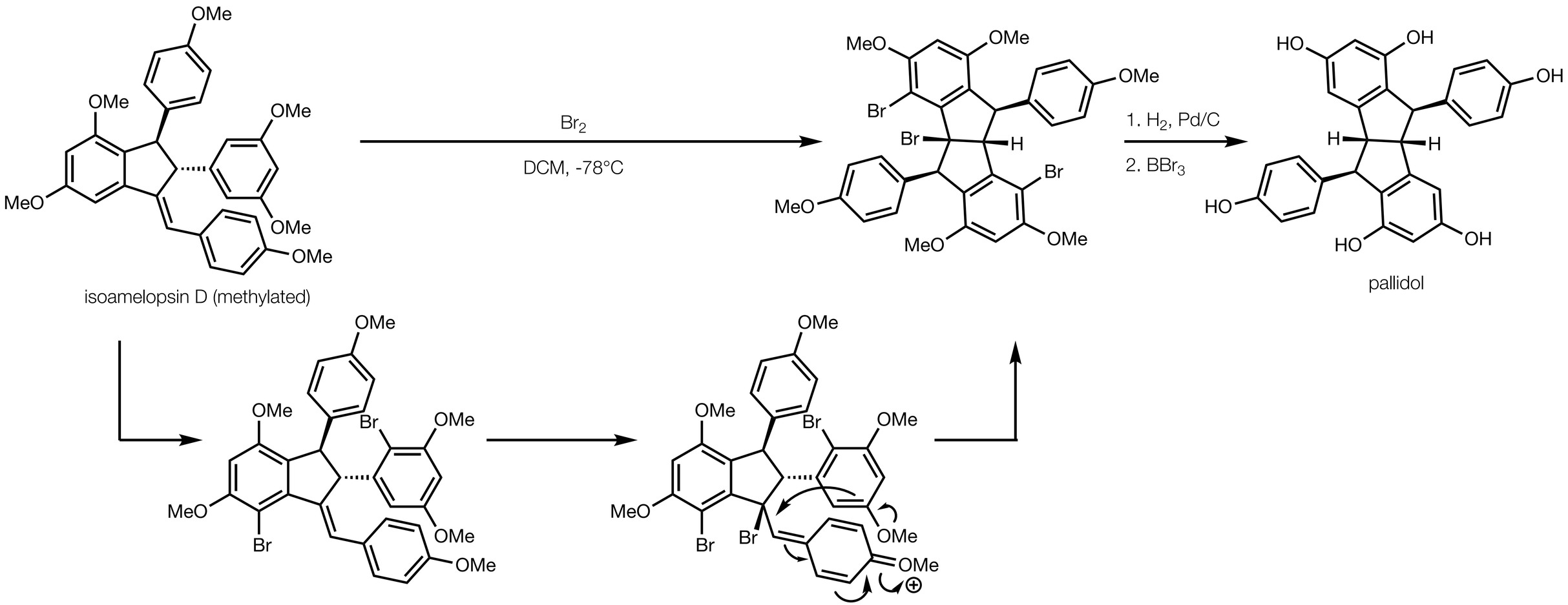
Resveratrol Oligomers





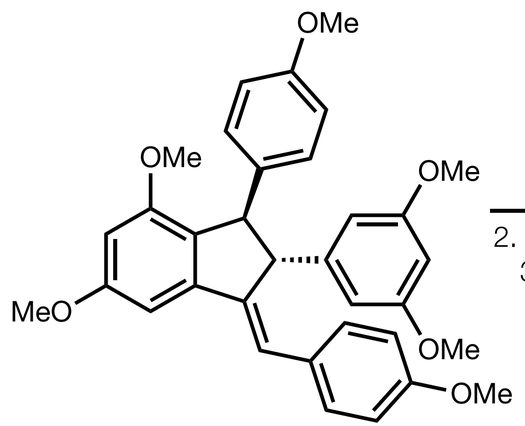
Angew. Chem. Int.Ed. 2007, 46, 8186 –8191

Resveratrol Oligomers

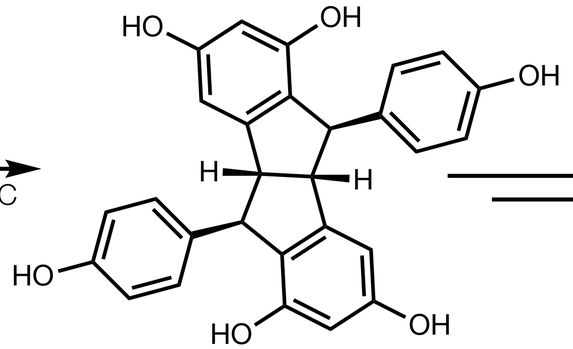


Angew. Chem. Int.Ed. 2007, 46, 8186 –8191

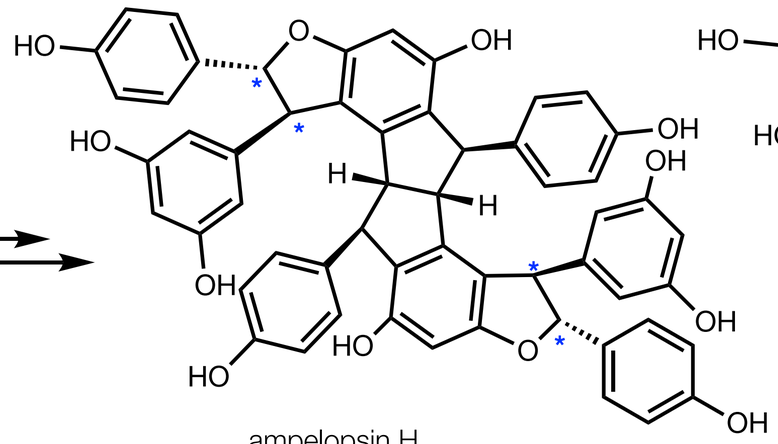
Resveratrol Oligomers



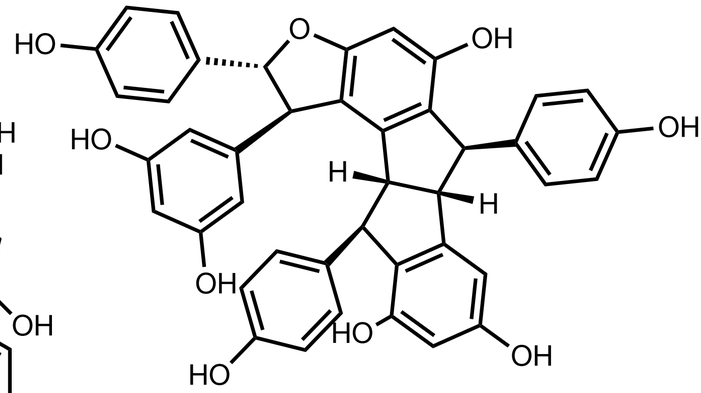
1. Br_2
2. H_2, Pd/C
3. BBr_3



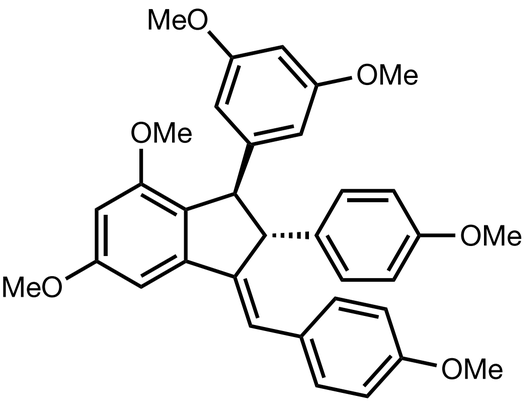
pallidol



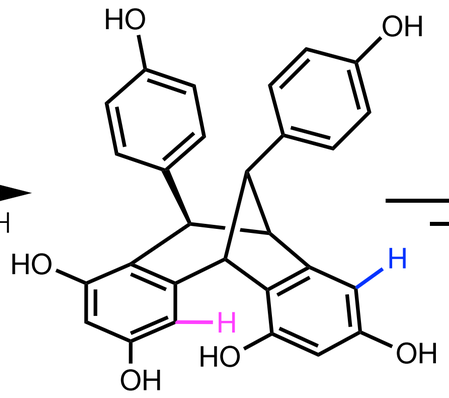
ampelopsin H
nepalensinol B (epimer)



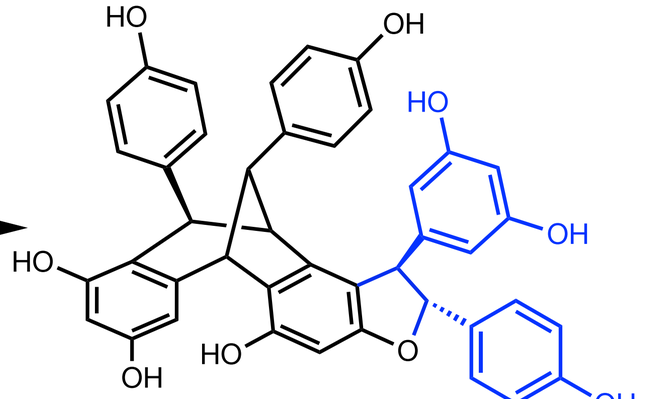
carasiphenol C



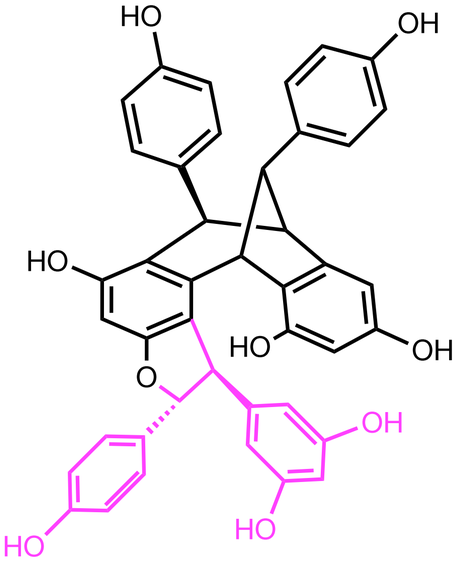
1. Br_2
2. $(TMS)_3SiH$
   AIBN
3. BBr_3



ampelopsin F



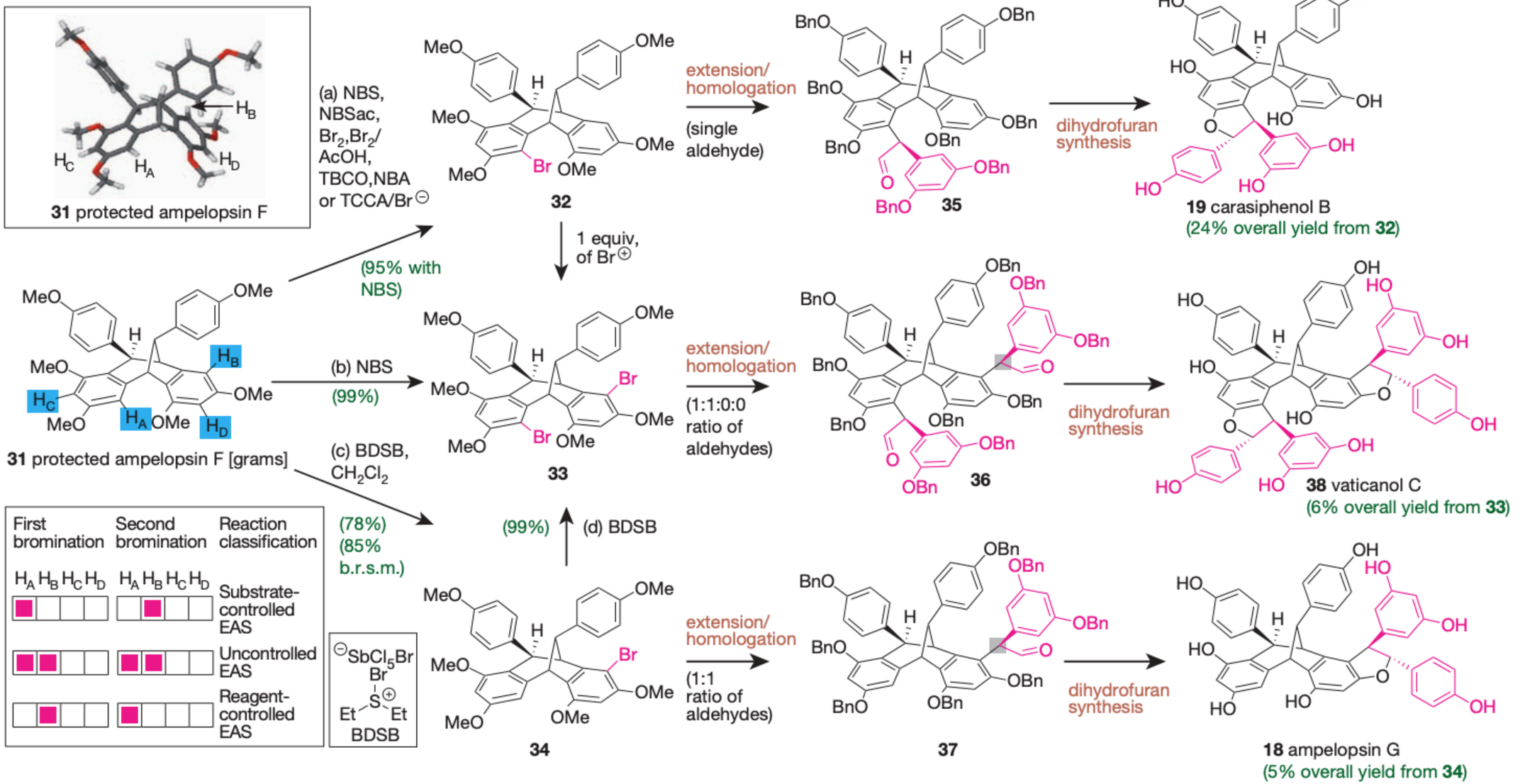
ampelopsin G



carasiphenol B

Nature 2011, 474, 461.

Controlled Bromination to Access Additional Congeners

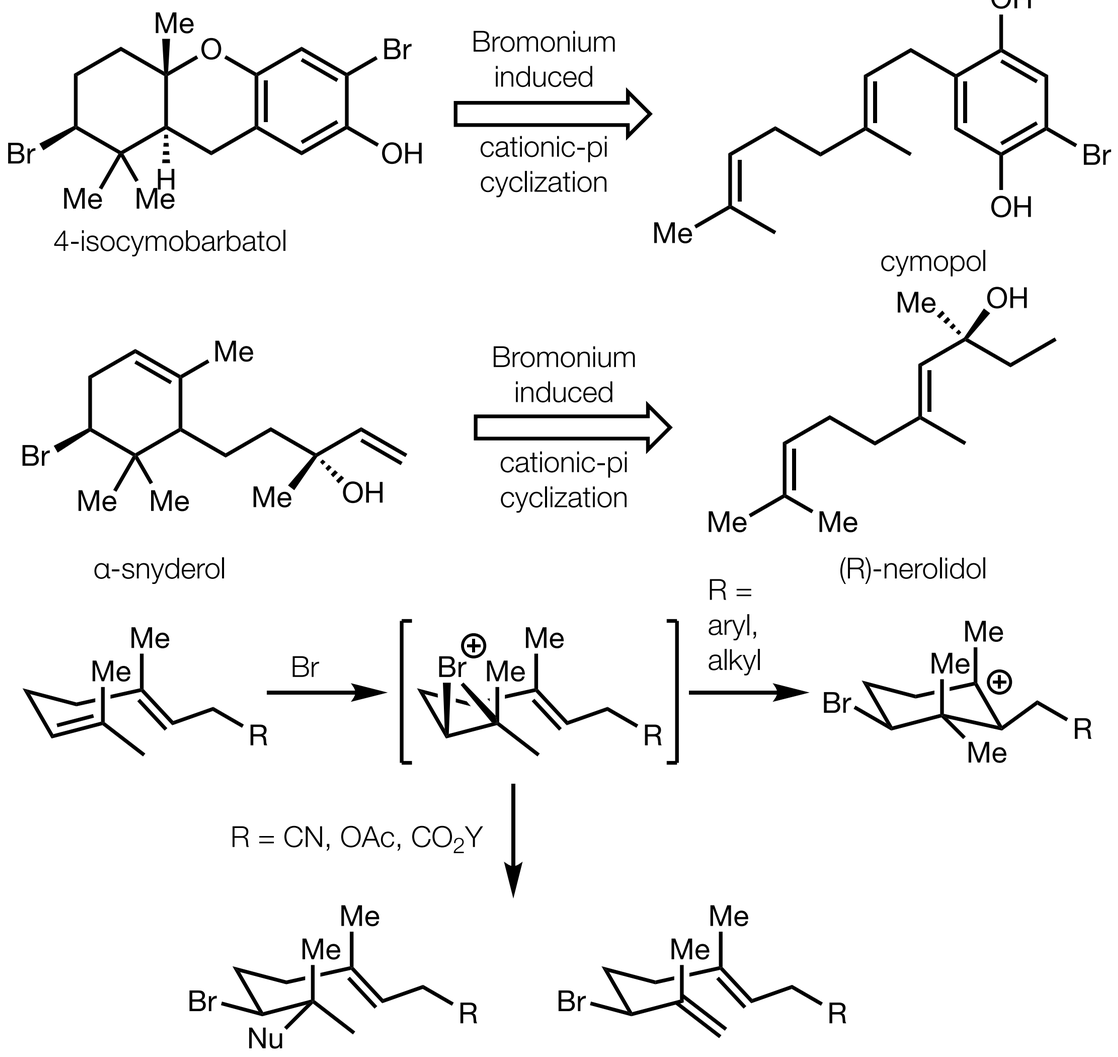


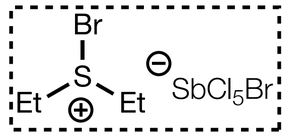
Nature 2011, 474, 461.

Efficient and Controlled Skeleton Formation: BDSB

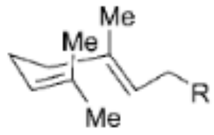
BDSB - Polyene Cyclization

BDSB (2009)



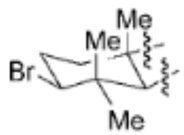


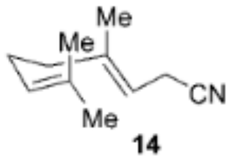
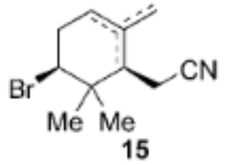
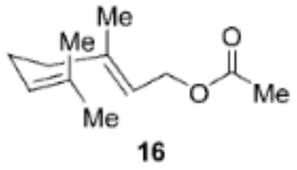
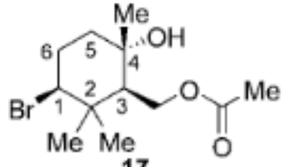
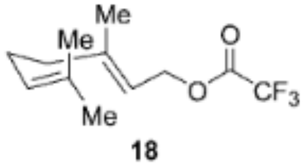
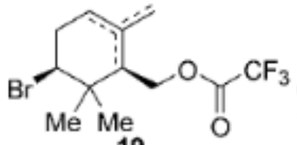
Bromodiethylsulfoniumbromopentachloroantimonate(V)



Halogen source (1.0-1.2 equiv), solvent (~0.1 M)

optimized conditions for each substrate and reagent

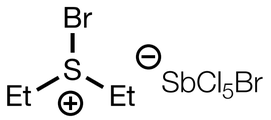


	Starting material	Product	Yield [%] (reaction temperature) (time)			
			13 (BDSB), CH_3NO_2	Br_2/ $AgBF_4$, CH_3NO_2	TBCO, CH_3CN	NBS/ Ph_3P, CH_2Cl_2
1	 **14**	 **15**	73[a] (25 °C) (5 min)	8[b] (25 °C) (5 min)	< 5[b] (25 °C) (15 min)	< 5[b] (–40 °C) (6 h)
2	 **16**	 **17**	80[c] (0 °C) (5 min)	22 (0 °C) (5 min)	< 5 (0 °C) (15 min)	< 5 (–40 °C) (6 h)
3	 **18**	 **19**	56[a] (25 °C) (5 min)	< 5 (25 °C) (5 min)	< 5 (25 °C) (15 min)	< 5 (–40 °C) (6 h)

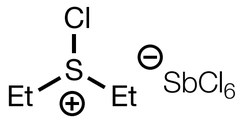
Angew. Chem. Int. Ed. 2009, 48, 7899.

BDSB… and friends

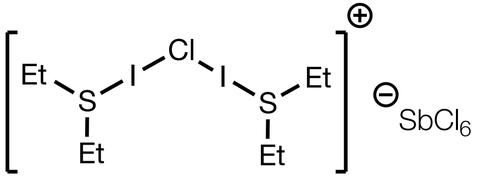
XDSX Reagents



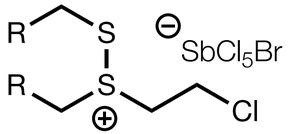
BDSB



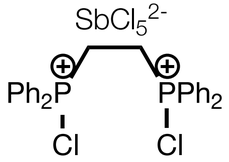
CDSC



IDSI

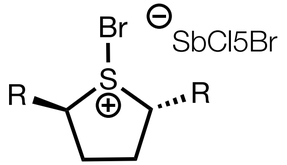


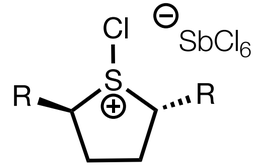
Electrophilic Sulfur

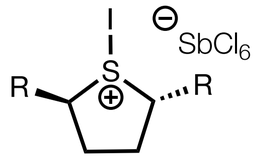


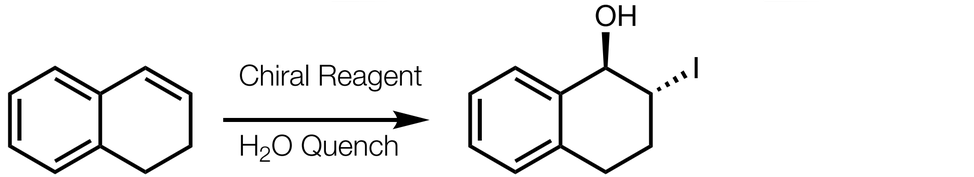
Hydrohalogenating Reagent

Attempt at Chiral Variants



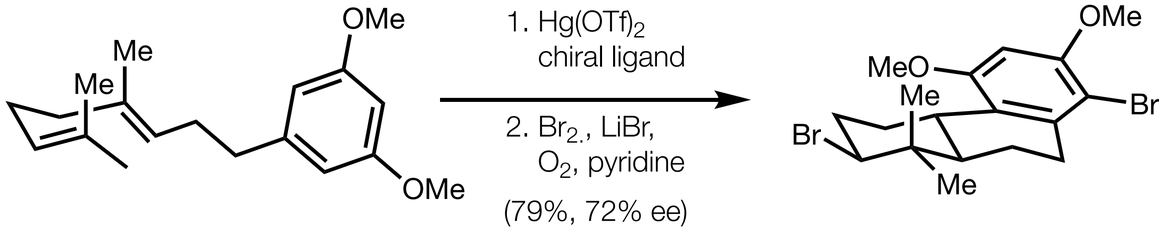


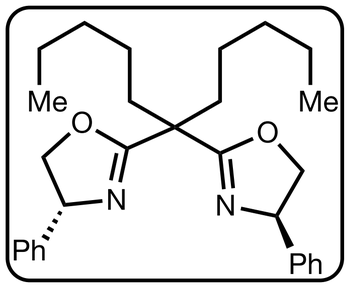




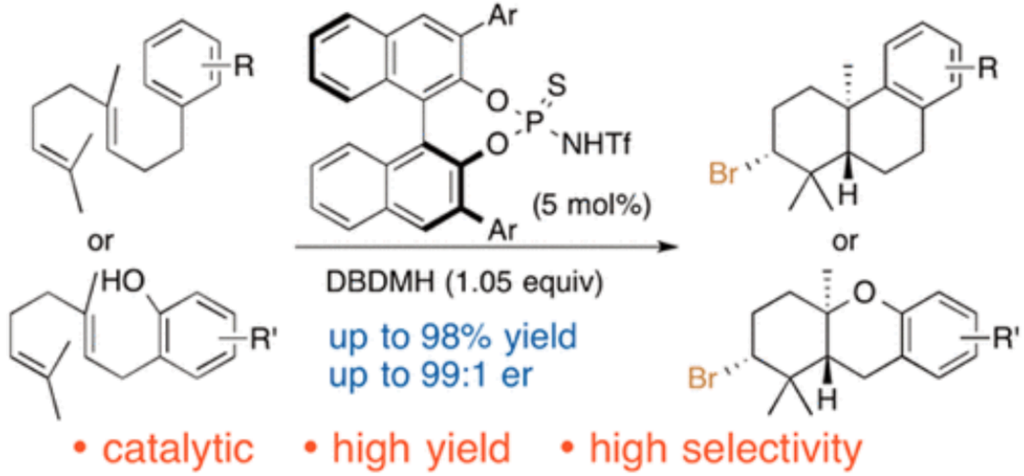
Best result: R = Et (67%, 63% ee)

Asymmetric Polyene Cyclization





Samanta and Yamamoto (2017)

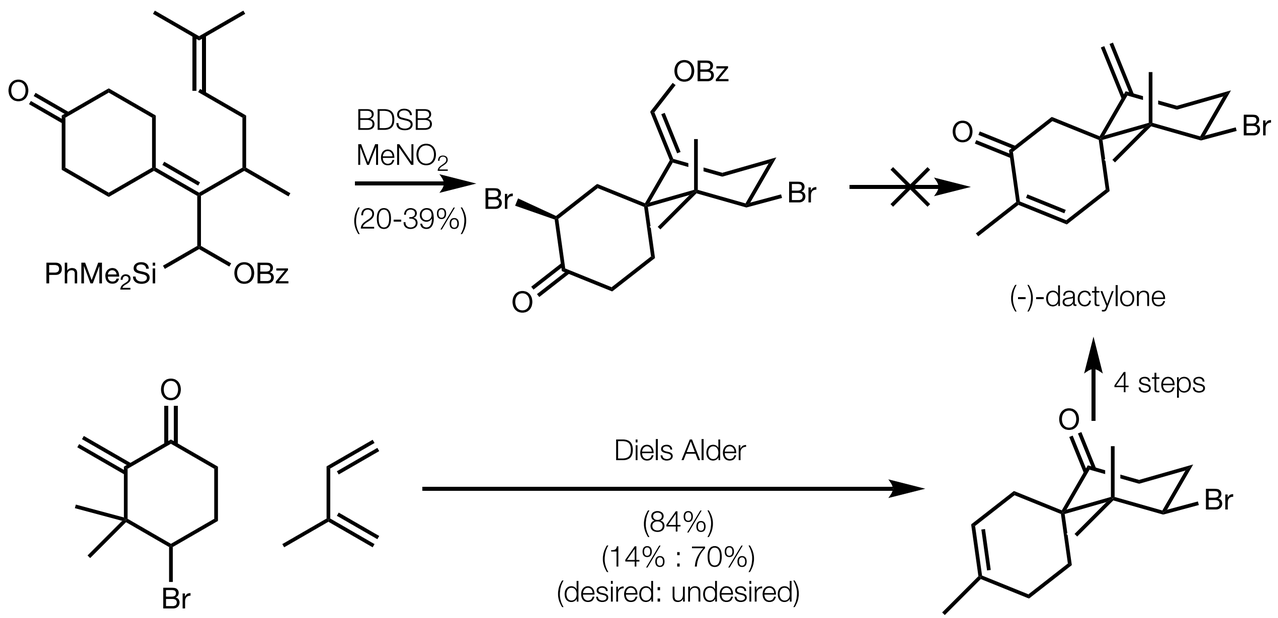


Synthesis 2013, 45, 1886.
J. Am. Chem. Soc. 2017, 139, 4, 1460–1463

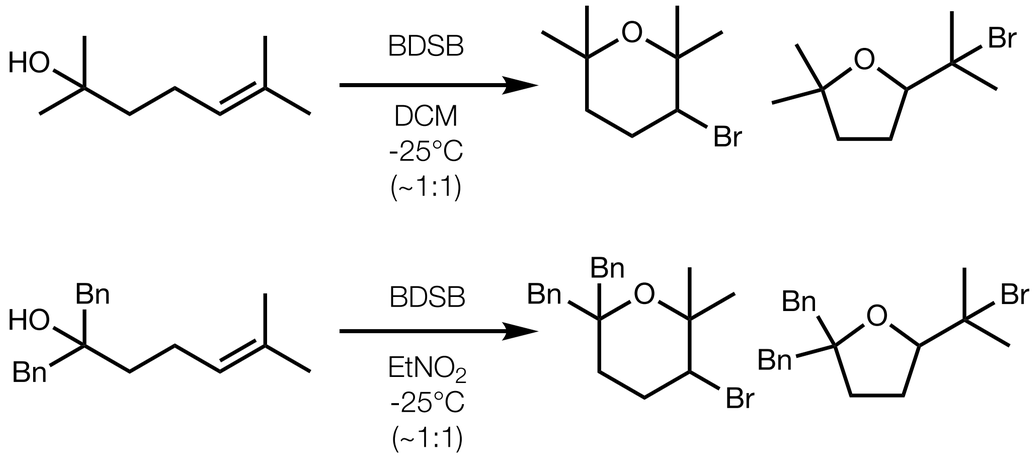
Org.Lett. 2017,19, 2.
J. Am. Chem. Soc. 2017,139, 6329.

BDSB - Applications

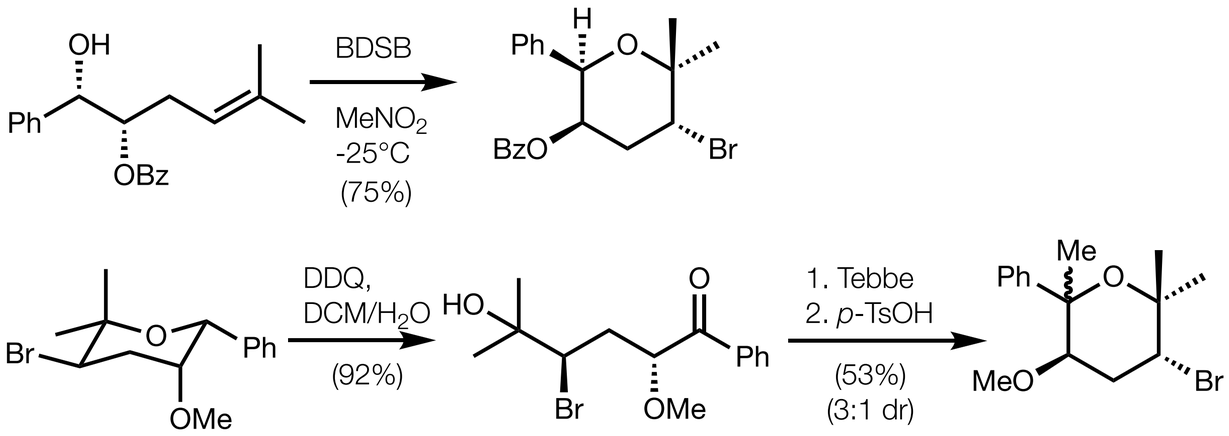
Bromo-Chamigrenes



Initial Attempts at 6-endo cyclization



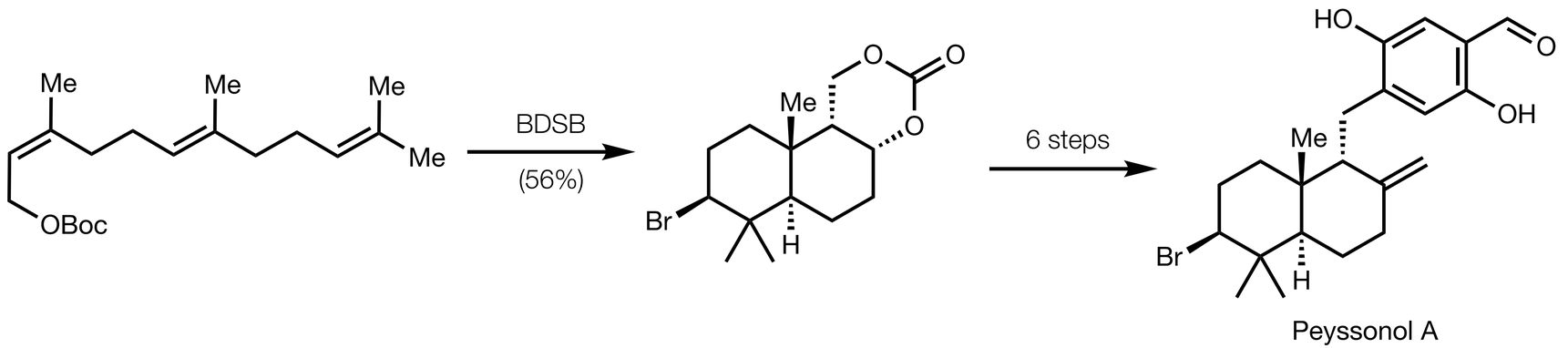
Secondary Alcohols (removal of $A_{1,3}$-strain)



Org.Lett. 2016, 18, 5018.
Tetrahedron Lett. 2015, 56, 3553.

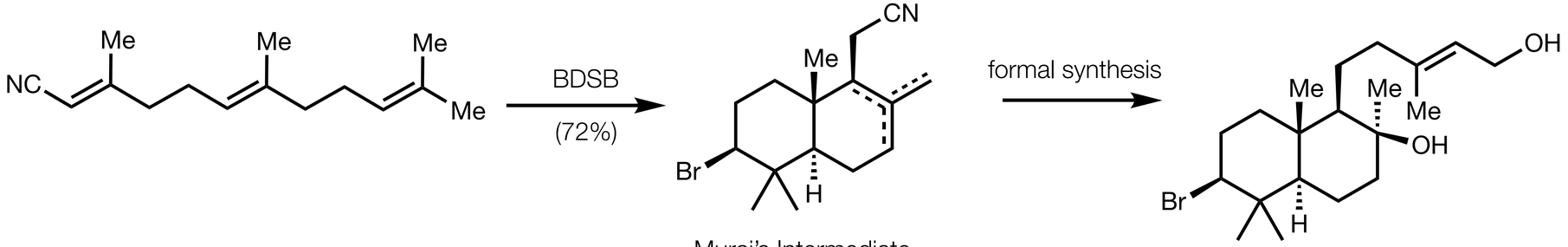
BDSB - Applications

Peyssonol A



Peyssonol A

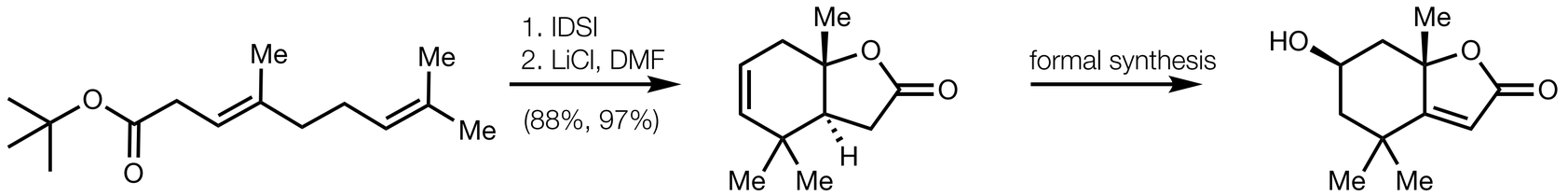
Aplysin-20



Murai's Intermediate

Aplysin-20

Ioliolide

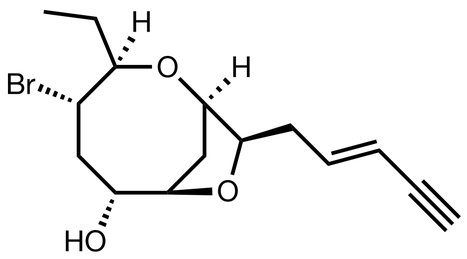


Rouessac's Intermediate

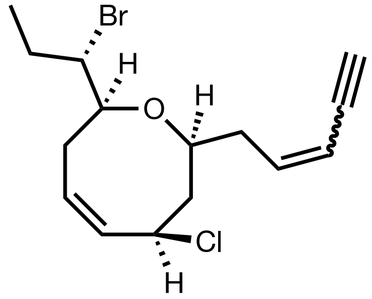
Ioliolide

J. Am. Chem. Soc. 2010, 132, 40, 14303–14314

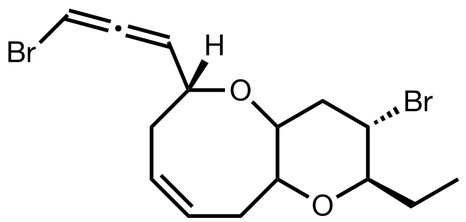
BDSB - Laurencia C15 Acetogenins



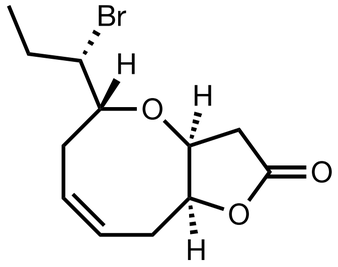
Laurefucin



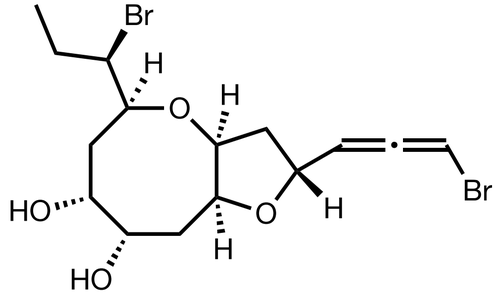
E/Z - pinnatifidenyne



microladallene A

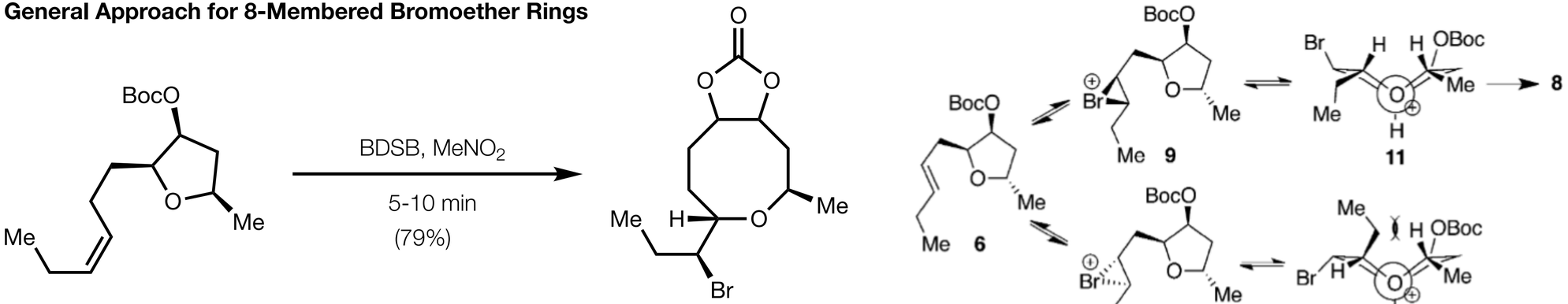


desepilaurallene

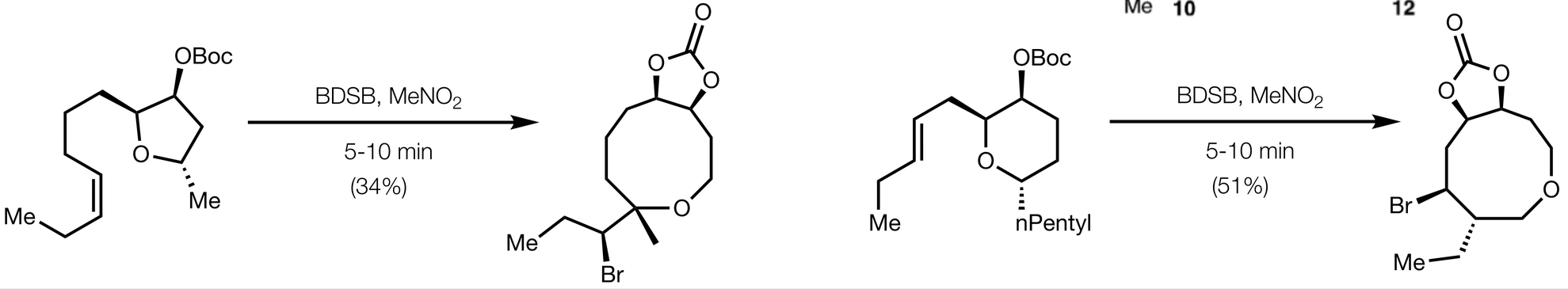


laurendecumallene B

General Approach for 8-Membered Bromoether Rings

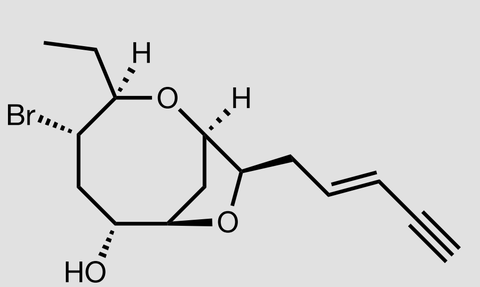


Application to 9-membered Ring Systems

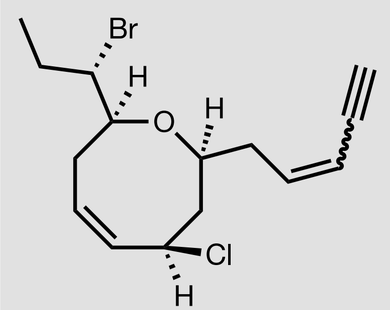


J. Am. Chem. Soc. 2011, 133, 15898.

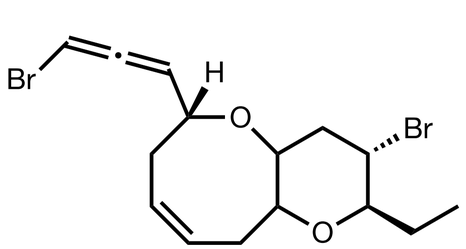
Formal Syntheses to Laurafucin and E/Z-Pinnatifidenyne



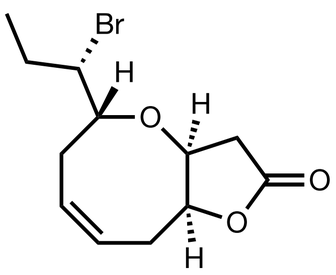
Laurefucin



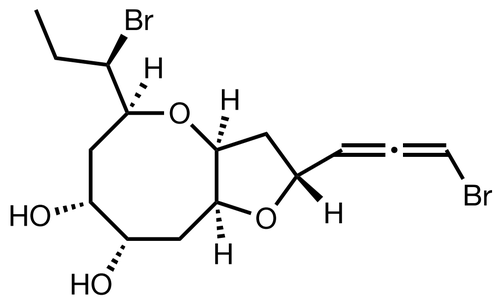
E/Z - pinnatifidenyne



microladallene A

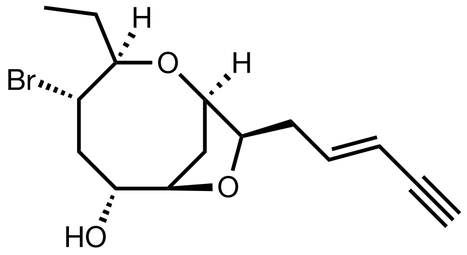


desepilaurallene

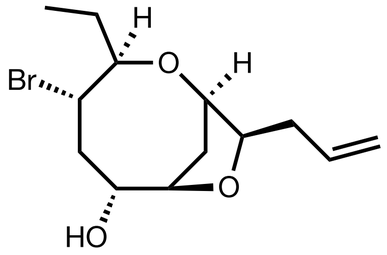


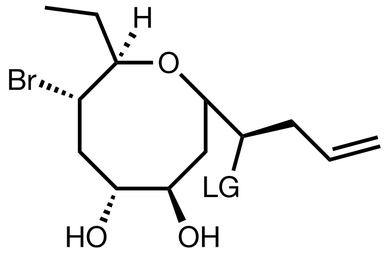
laurendecumallene B

Laurefucin

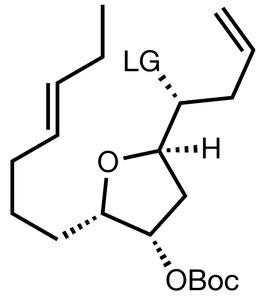


Kim, 2008

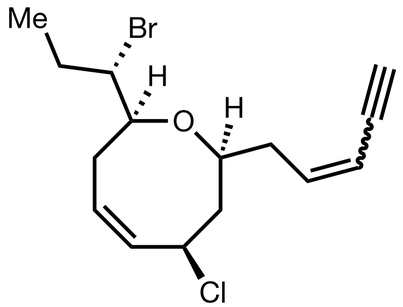




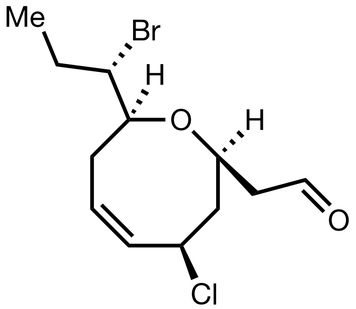
BDSB



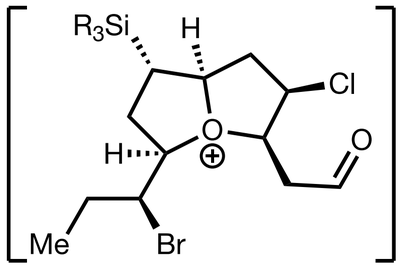
E/Z - pinnatifidenyne

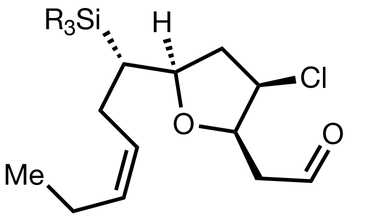


Kim, 2008



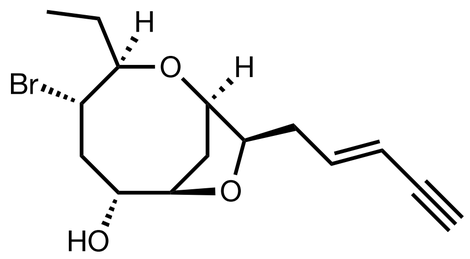
BDSB



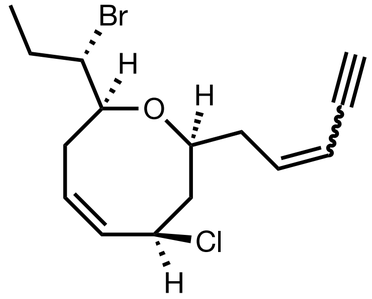


J. Am. Chem. Soc 2012, 134, 17714.

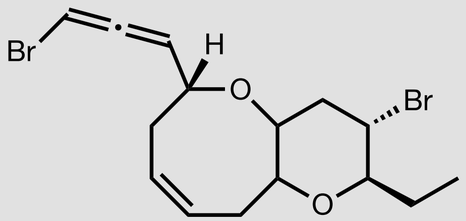
Microadallene A and Desepilaurallene: Modified Strategy



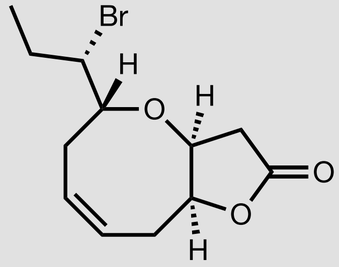
Laurefucin



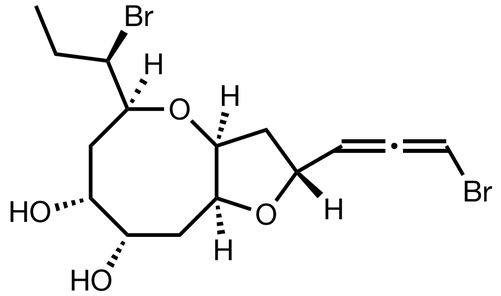
E/Z - pinnatifidenyne



microladallene A

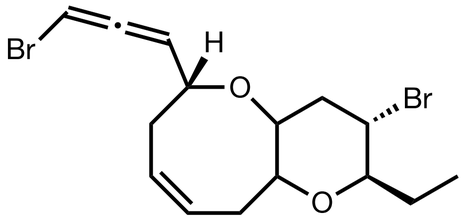


desepilaurallene

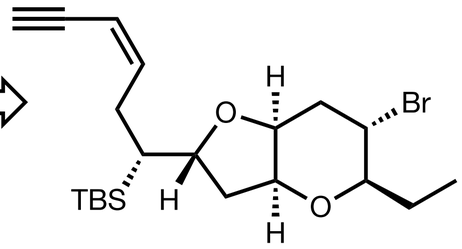


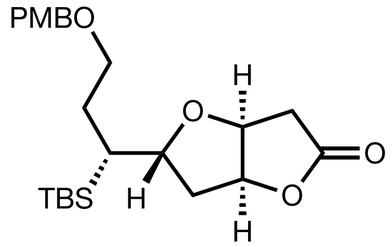
laurendecumallene B

microladallene A

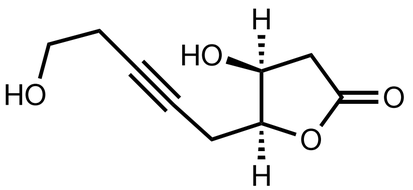


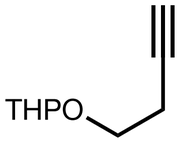
BDSB



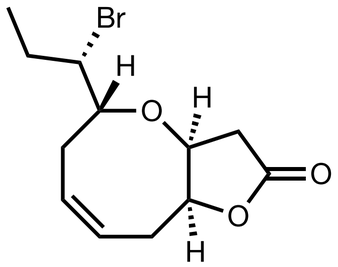


diversifiable intermediate

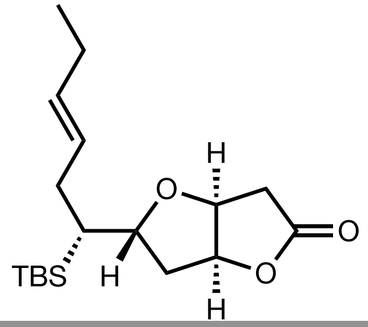




desepilaurallene

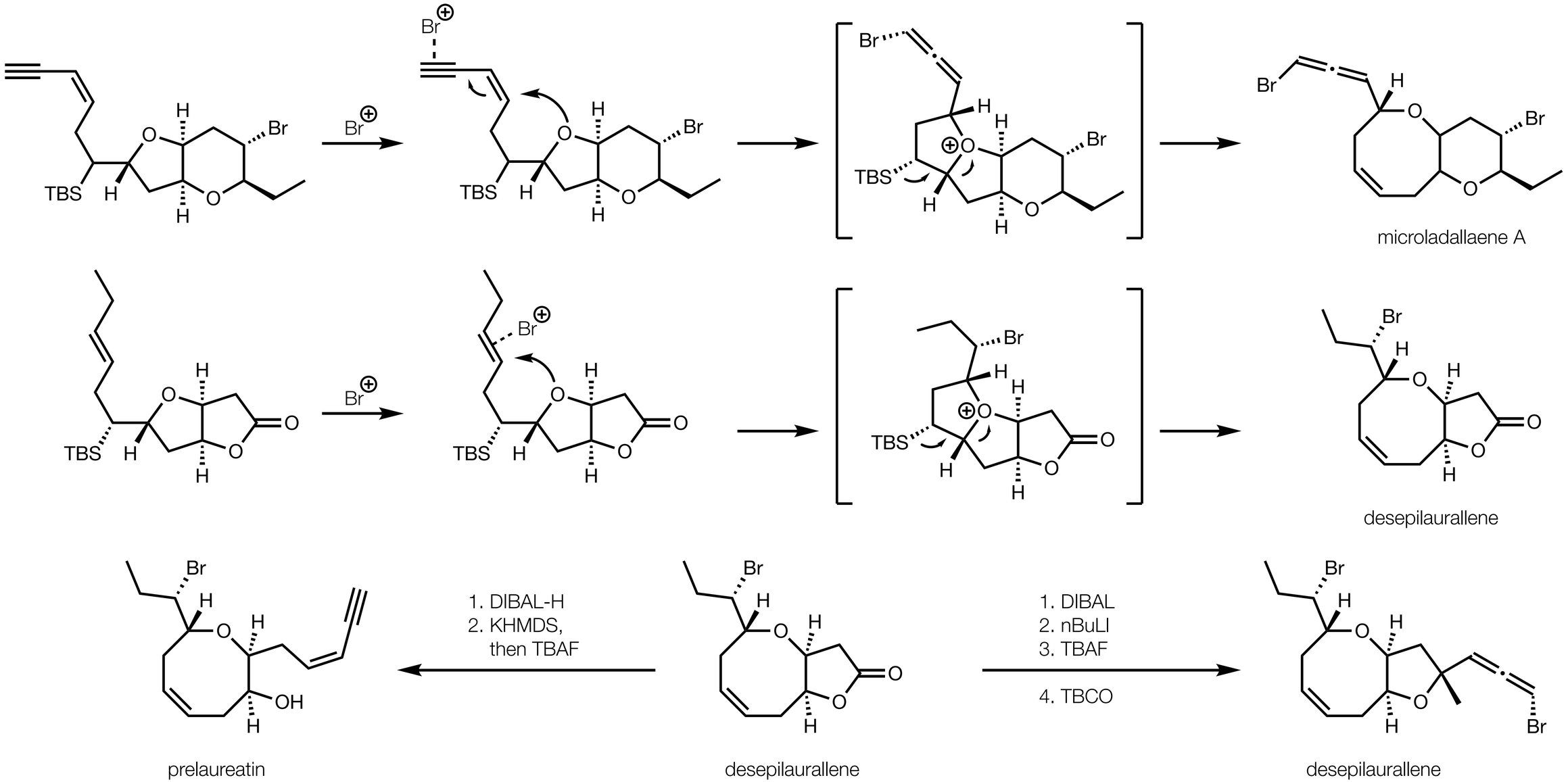


BDSB



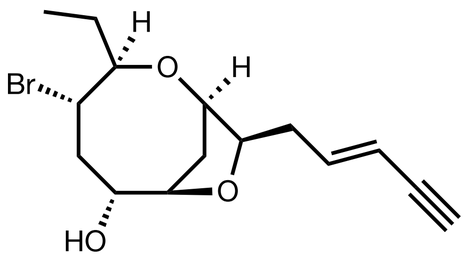
J. Am. Chem. Soc. 2019, 141, 7776.

Microadallene A and Desepilaurallene: Modified Strategy

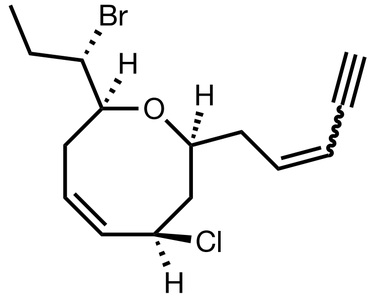


J. Am. Chem. Soc. 2019, 141, 7776.

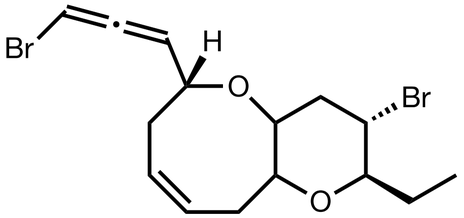
Laurendecumallene B: Double Bromonium Induced Cyclization



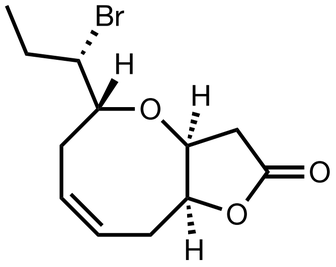
Laurefucin



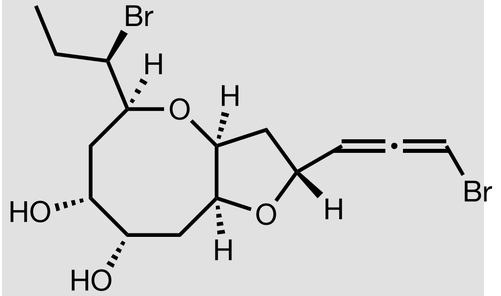
E/Z - pinnatifidenyne



microladallene A

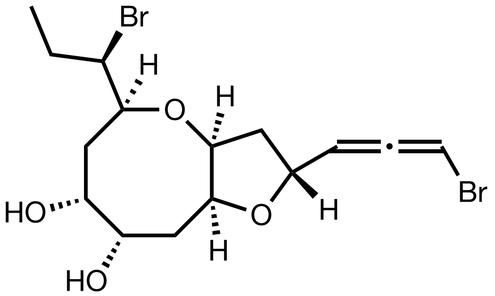


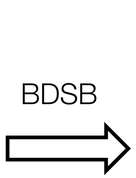
desepilaurallene



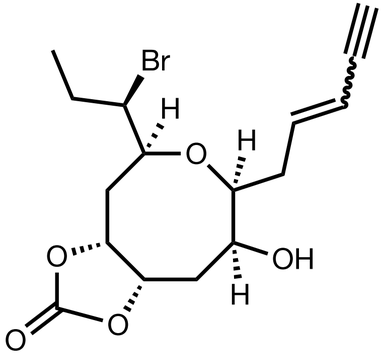
laurendecumallene B

laurendecumallene B



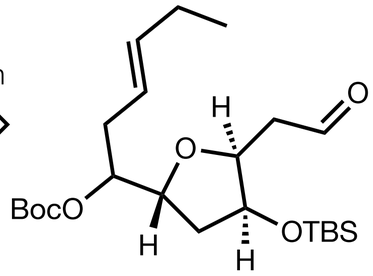


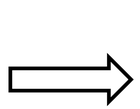
BDSB

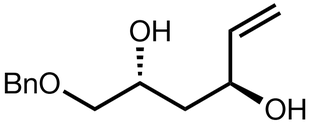


Olefiniation

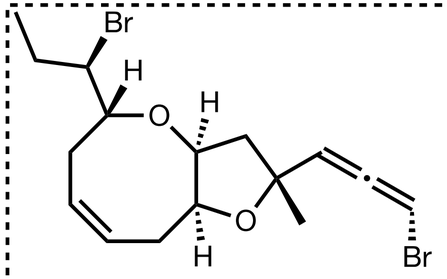
BDSB







5 steps from
(-)-glycidol

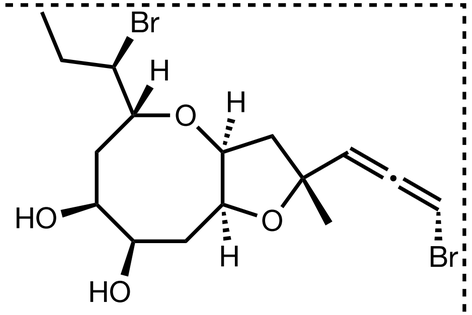


iso-desepilaurallene

OsO_4, NMO

(60%)

Undesired Stereochemistry



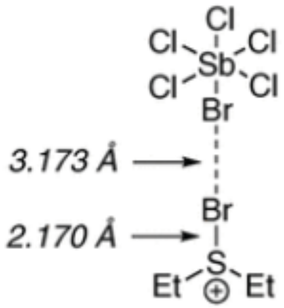
Chem. Sci. 2020, 11, 3036.

BDSB: Summary

Highly electrophilic bromonium (and others!) source

Has been employed in:

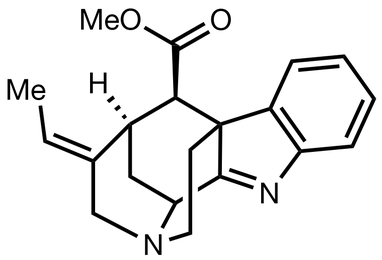
1. *Controlled* Bromonium-induced polyene cyclizations
2. *Controlled* Electrophilic bromination of aromatic rings
3. Bromoetherification



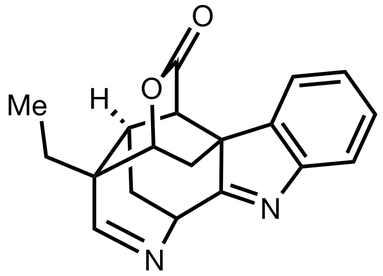
Overall, a good alternative to consider for electrophilic bromination

Efficient and Controlled Skeleton Formation: Akuammiline Alkaloids

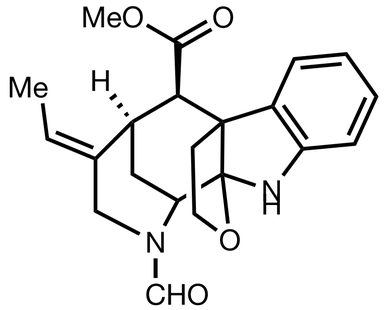
Akuammiline Alkaloids



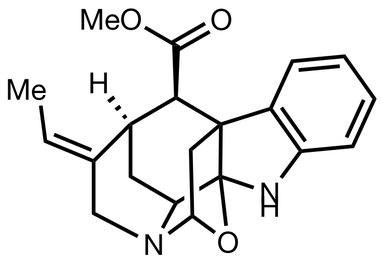
Strictamine



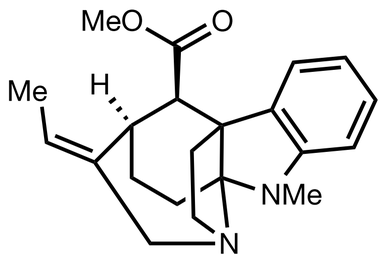
Scholarisine A



aspidophylline A

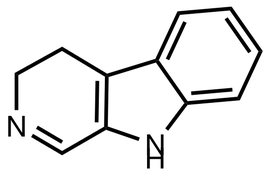


picrinine



vincorine

Strictamine (2017)

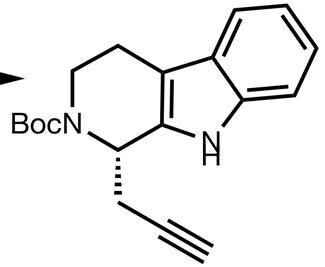


1 step from tryptamine

1. Asymmetric Propargylation

2. Boc_2O, Et_3N DCM, 10h

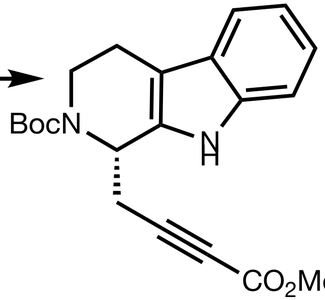
(62%, 89% ee)



$Pd(OAc)_2$
Ph_3P
CO/O_2

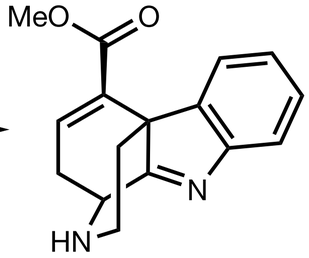
DMF/MeOH
23°C, 16 h

(80%)



1. TFA/DCM; evaporate
2. Ph_3PAuCl $AgSbF_6$

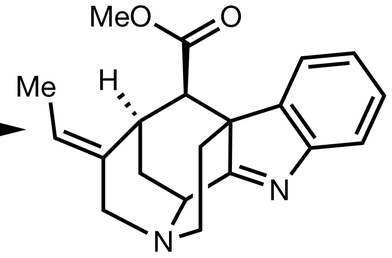
MsOH
DCE, 23°C, 24h
(65%)



"Zhu Approach"

1. alkylation

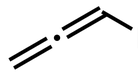
2. $Ni(cod)_2$ Et_3SiH



Strictamine

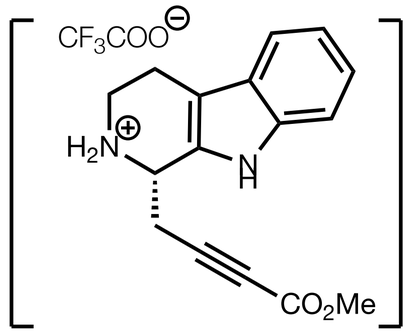
Asymmetric Propargylation Conditions:

(R)-DTBM-SEGPHOS
CuCl
tBuONa



THF/MeOH, -78°C to 30°C, 48h

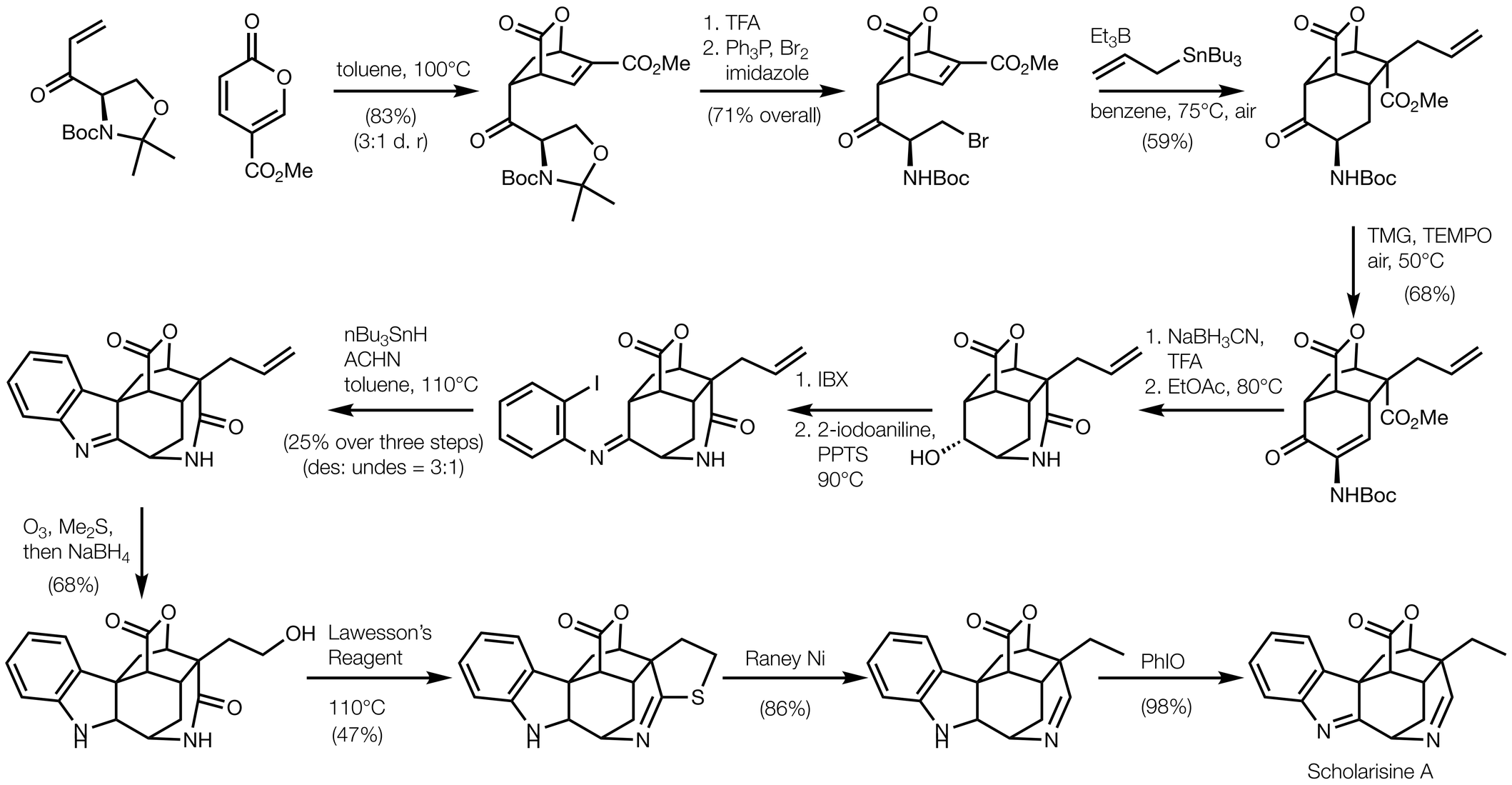
via



Org. Lett. 2017, 19, 5, 1004–1007

Akuammiline Alkaloids

Scholarisine A (2013)



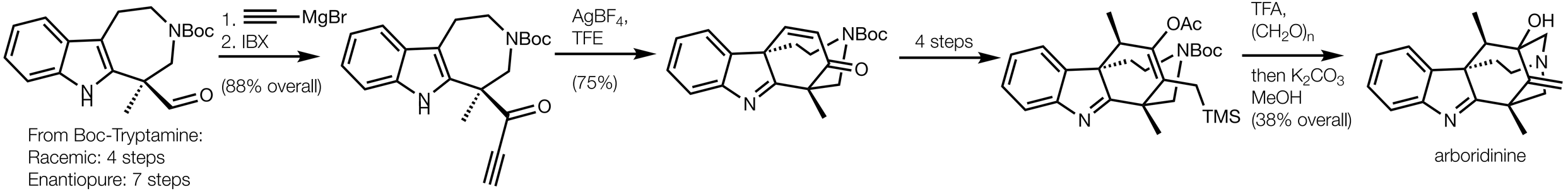
J. Am. Chem. Soc. 2013, 135, 35, 12964–12967

Efficient and Controlled Skeleton Formation:

Metal and LA Catalysed Cyclizations

Rapid Skeletal Building

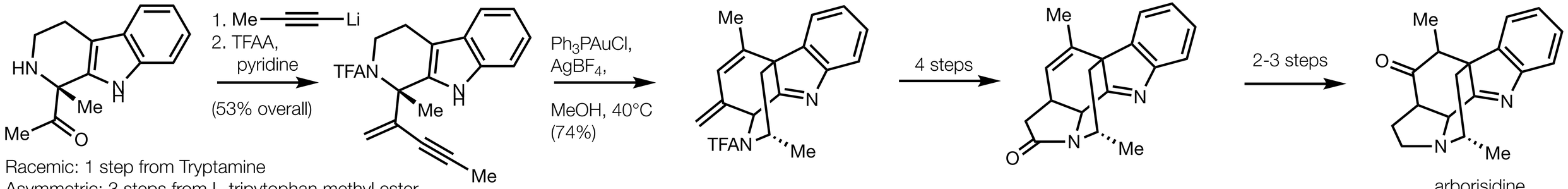
Arboridinine (2018)



From Boc-Tryptamine:
Racemic: 4 steps
Enantiopure: 7 steps

arboridinine

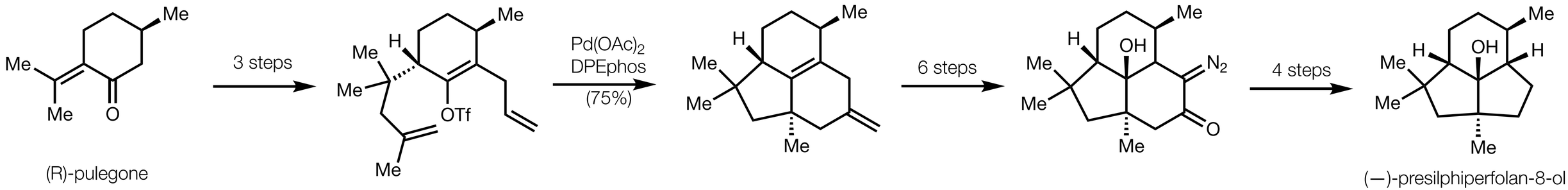
Aborisidine (2019)



Racemic: 1 step from Tryptamine
Asymmetric: 3 steps from L-tripytophan methyl ester

arborisidine

(—)-presilphiperfolan-8-ol (2017)

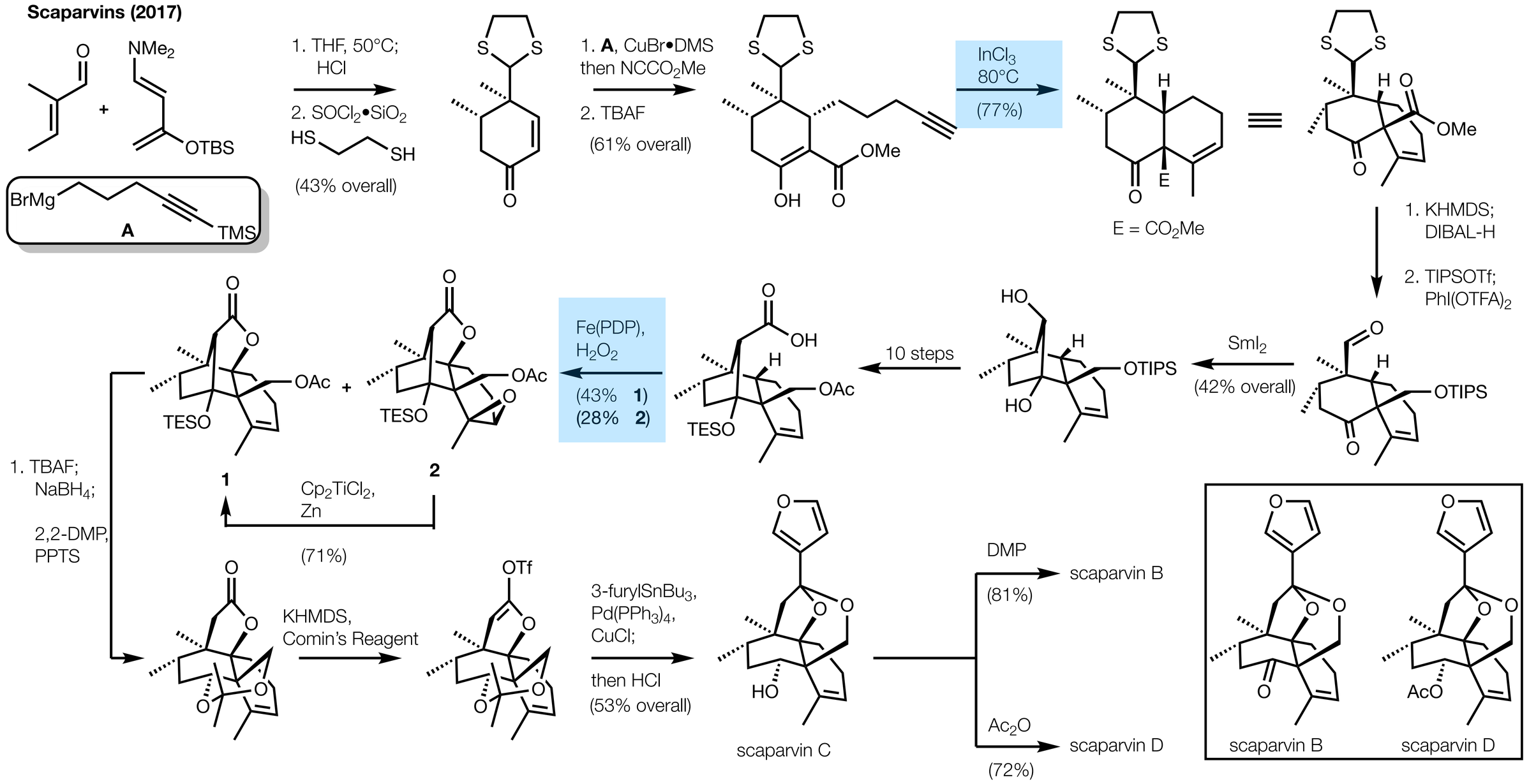


(R)-pulegone

(—)-presilphiperfolan-8-ol

J. Am. Chem. Soc. 2018,140, 919.
J. Am. Chem. Soc. 2019, 141, 7715.
J. Am. Chem. Soc. 2017,139, 5007.

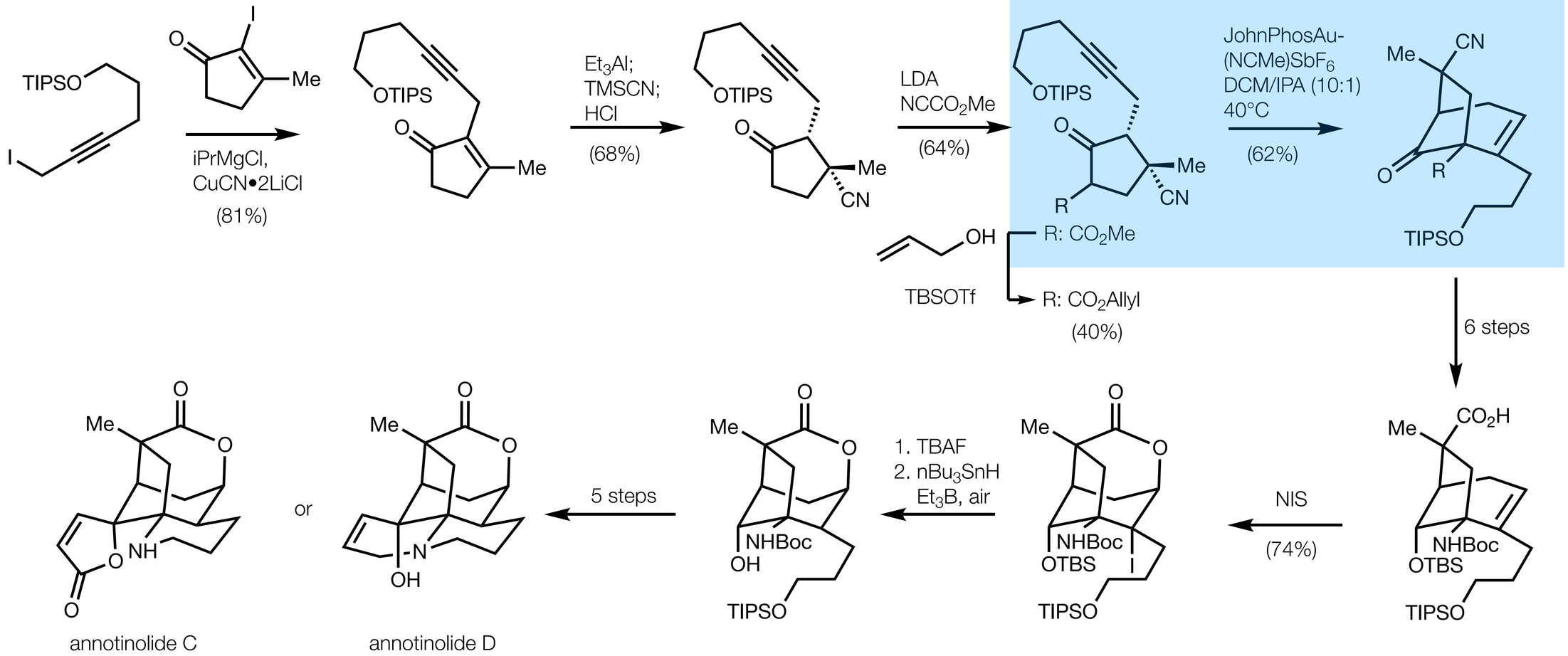
Harnessing Conia-ene: Scaparvins



J. Am. Chem. Soc. 2017,139, 18428.

Harnessing Conia-ene: Annotinolides

Annotinolides (2021)



J. Am. Chem. Soc. 2021, 143, 11951.

Quaternary Center Guided Synthesis Design

Quaternary-Center-Guided Synthesis

Goal: Identifying the optimal order of quaternary-center construction

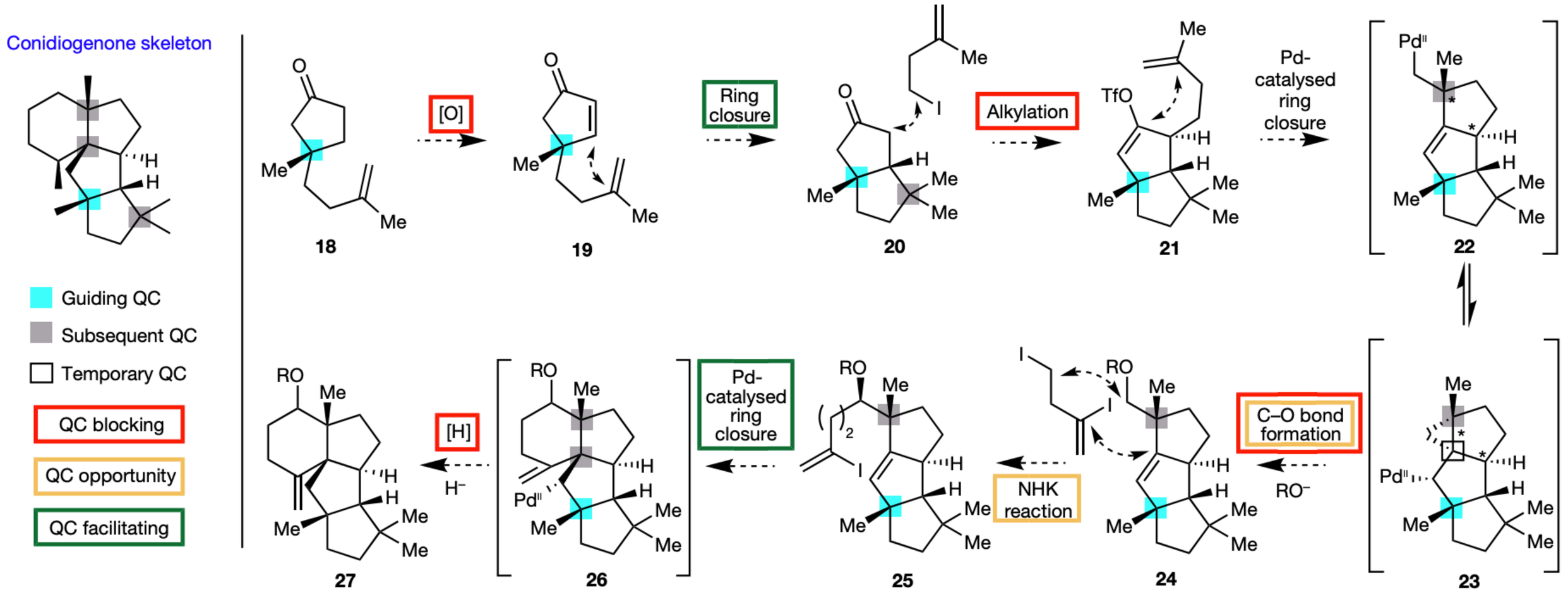
Method: Individually evaluate the “benefits” of each quaternary carbon as the initial guiding quaternary carbon

“Benefits”
1) QC Blocking - Blocking undesired reactivity and/or enforcing site selectivity
2) QC Facilitating - Facilitating a reaction through rate acceleration
3) QC Opportunity - An opportunity for reaction development

In other words, design a synthesis that sets quaternary carbon or stereocenter (preferably enantioselectively) early on, then utilizing substrate control to set the remaining quaternary carbons or stereocenters.

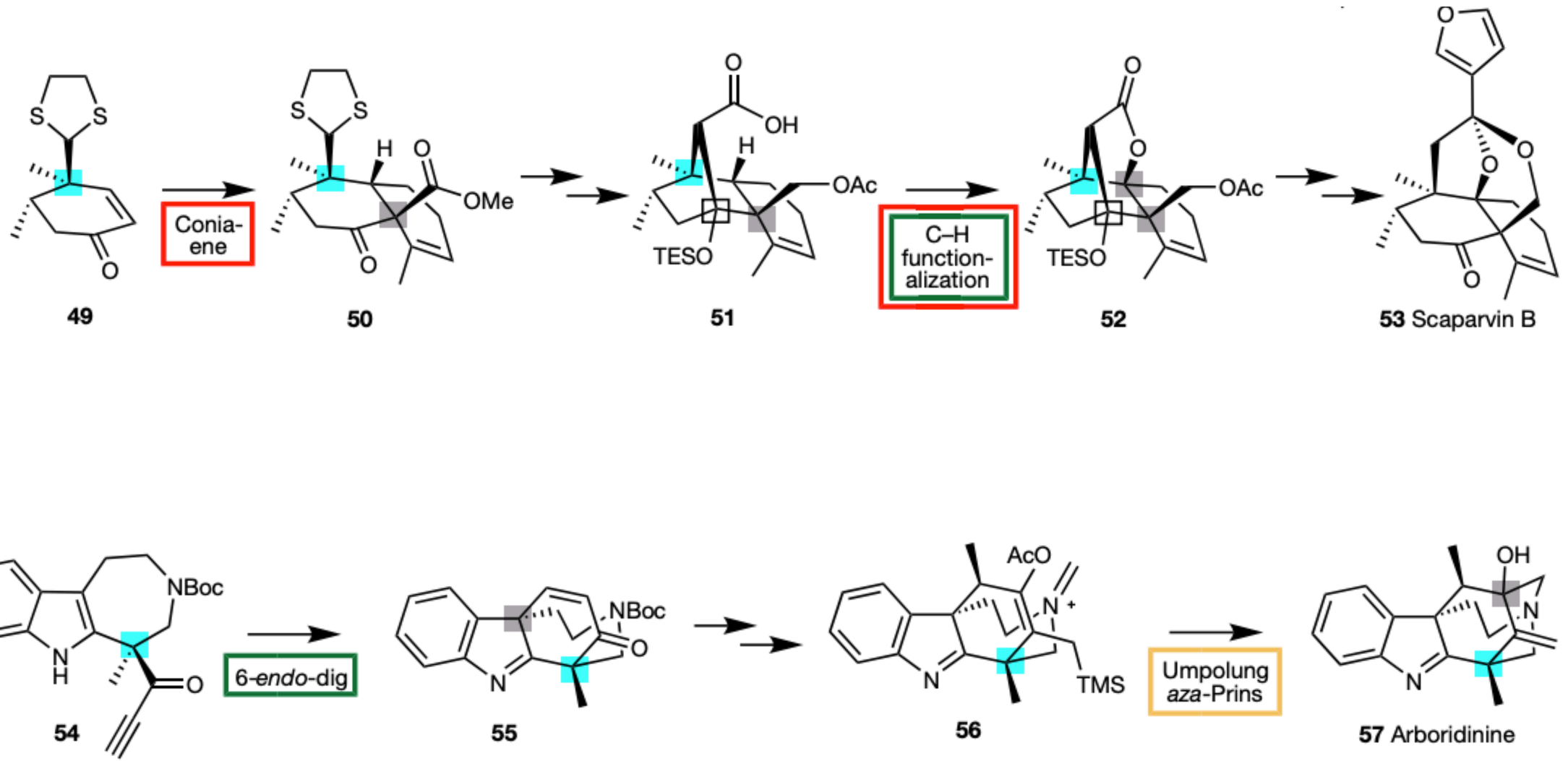
Nature 2019, 569, 703.

Quaternary-Center-Guided Synthesis



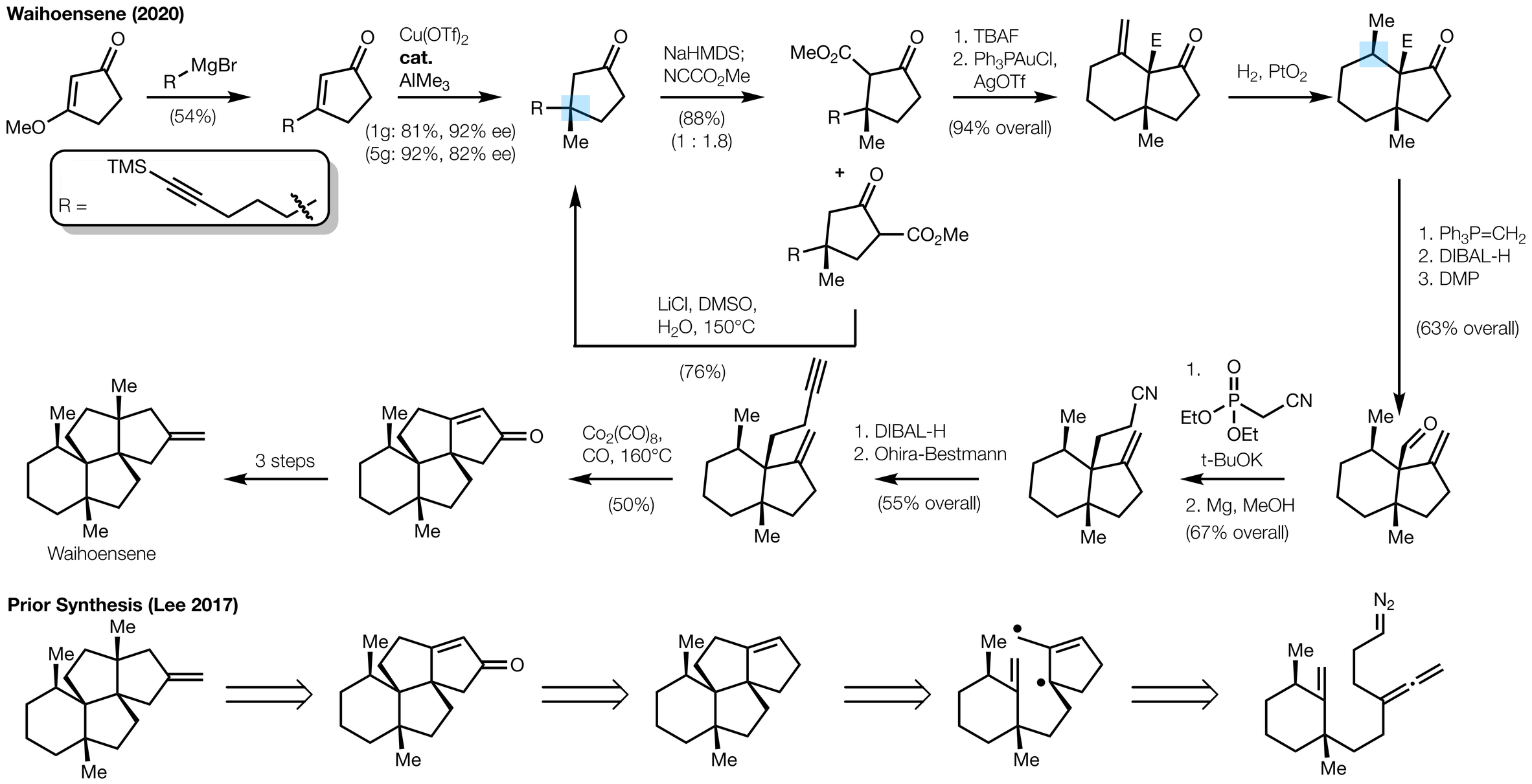
Nature 2019, 569, 703.

Quaternary-Center-Guided Synthesis



Nature 2019, 569, 703.

QS Guided Synthesis Case Study: Waihoensene



Angew. Chem. Int. Ed. 2020, 59, 13521.
Angew. Chem.2017,129, 8366 – 8369.

Scott Snyder - Conclusion

- **Notable contributions towards:**
  - Phenylpropanoid synthesis
  - Bromonium Induced Cationic Polyene Cyclisation
  - Bromo ether ring expansion
  - Complex terpene and alkaloid synthesis
- **General strategy in synthesis:**
  - Nature as a source of inspiration
  - Facile formation of natural product core
    - Cascades
  - Quaternary Center Guided Analysis
  - Total synthesis is an opportunity to identify, develop, optimize unprecedented reactions

** Only a selection of work was represented in this presentation

** Scott also has made enormous contributions towards mentorship and chemical education at UChicago and beyond

** Excellent mentor, PI, scientist and person!

Thank you for your attention!