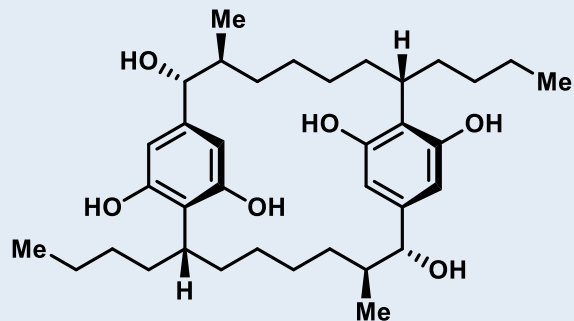

Cyclophane Natural Products

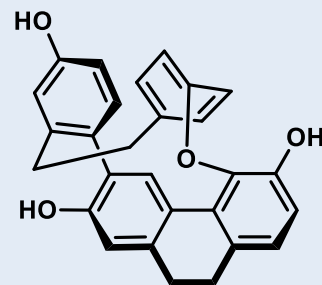
Magnus Pfaffenbach
Gaich Group Seminar
October 16, 2014

Overview

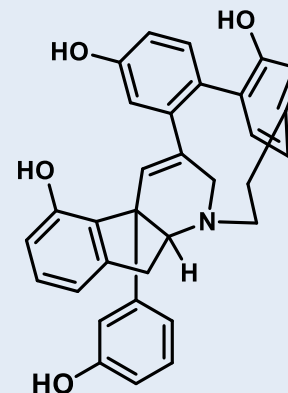


Cylindrocyclophane A

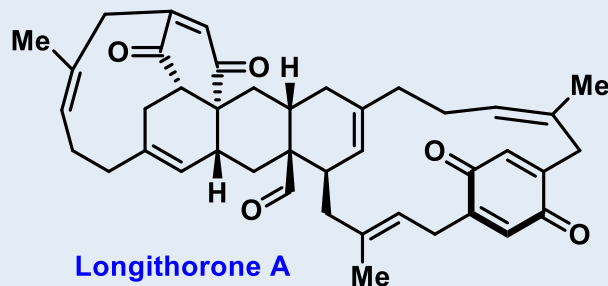
Cylindrocyclophanes



Cavicularin



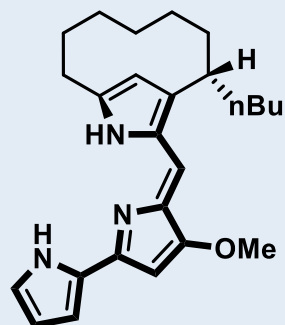
Haouamine A



Longithorone A

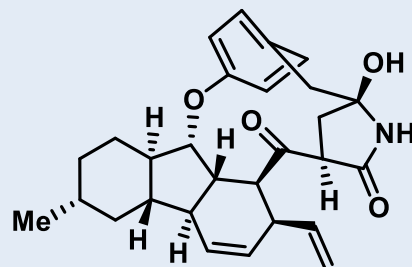
Longithorones

*Natural cyclophanes
with bent benzene rings*

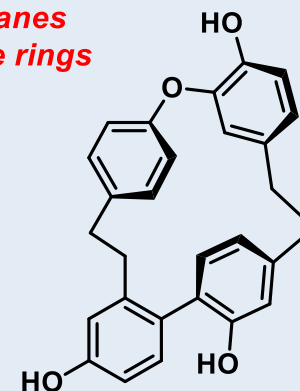


Streptorubin B

Pyrrolophanes



Hirsutellone B

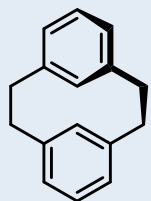


Riccardin C

Cyclic bisbibenzyl

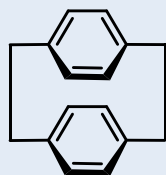
General Information

- **Cyclophane** = *cyclo*, *phenyl*, and *alkane*
- **Original definition** (1951) = Two phenylene moieties held together face-to-face by an aliphatic chain
- **IUPAC** = Substrates bearing (1) a cyclic or a system of cyclic units having (formally) the maximum number of noncumulative double bonds and (2) atoms and/or saturated or unsaturated chains, with or without heteroatoms, as alternate components of a macrocycle.
- **Characteristics:**
 - Macrocyclic structures with immense strain
 - Bent and battered benzene rings
 - Restricted conformational flexibility
- **Main synthetic challenge:**
 - Merging both ends of a linear precursor while introducing strain and in many cases chirality into the macrocycle



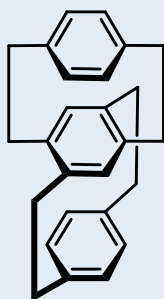
[2.2]metacyclophane

1899: first synthesized
cyclophane

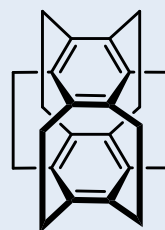


[2.2]paracyclophane

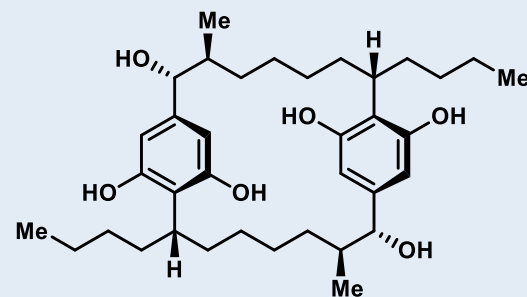
1949: discovered
1951: synthesized



multiple
layered phane
(1972)



superphane
(1979)



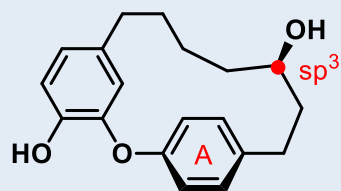
Cylindrocyclophane A

1990: first natural cyclophane isolated

Rigidity of Cyclophanes

Constitution of the handle

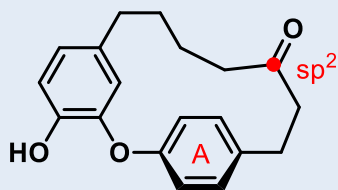
rotationally restricted



Acerogenin A

A protons: 4x dd

rotationally flexible



Acerogenin C

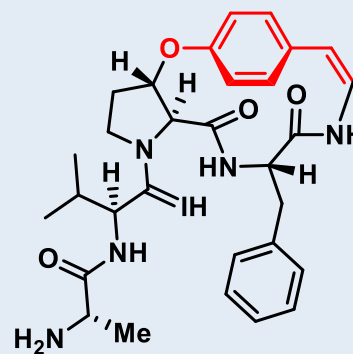
A protons: AB q

Smaller bond angle ($sp^3 < sp^2$)

- ➔ Angle strain + van-der-Waals H–H interactions increased
- ➔ Rotationally more restricted ring system in Acerogenin A

Point of attachment

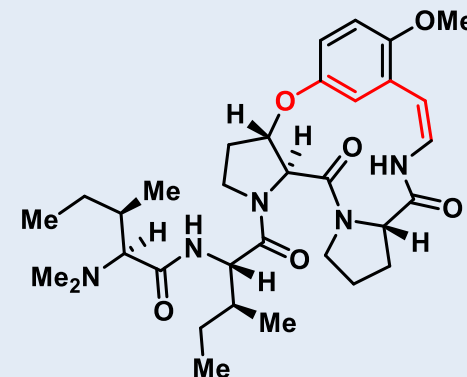
rotationally restricted



Mauritine A

- Bent benzene ring
- Distorted styrylamide system

rotationally flexible



Zizyphine A

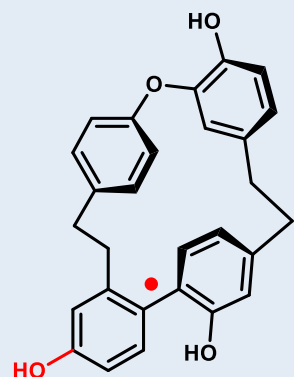
- (a) A. Kirfel, G. Will, R. Tschesche and H. Wilhelm, *Z. Naturforsch.*, B, **1976**, 31b, 279–280.
 (b) G. Islas-Gonzalez and J. Zhu, *J. Org. Chem.*, **1999**, 64, 914–924.
 (c) T. Gulder and Phil S. Baran *Nat. Prod. Rep.*, **2012**, 29, 899.

Strain-Induced Chirality

● configurationally unstable

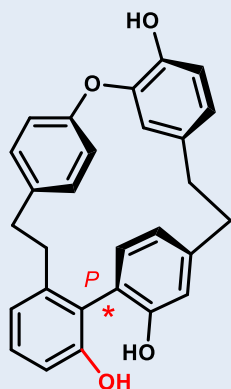
* configurationally stable

increase in molecular strain



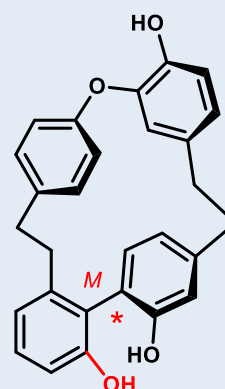
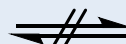
Riccardin C

configurationally unstable
achiral molecule at rt

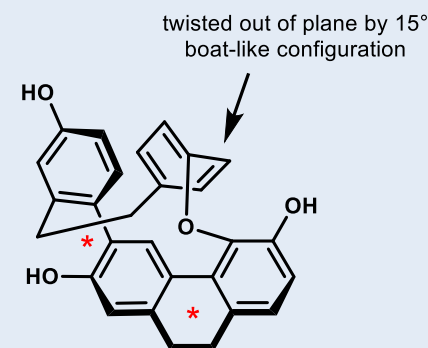


P-Riccardin D

configurationally stable
separable atropenantiomers



M-Riccardin D

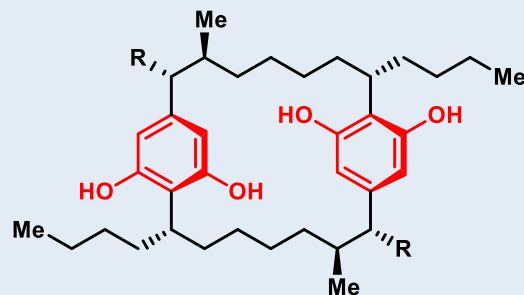


Cavicularin

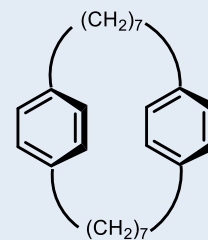
high atropisomerization barrier
locked configuration
obtained as single enantiomer

Cylindrocyclophanes - Smith III

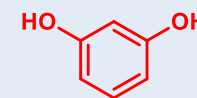
- First cyclophanes isolated from a natural source (1990)
- C₂ symmetric structure
- High *in-vitro* cytotoxicity
- First total synthesis 1999



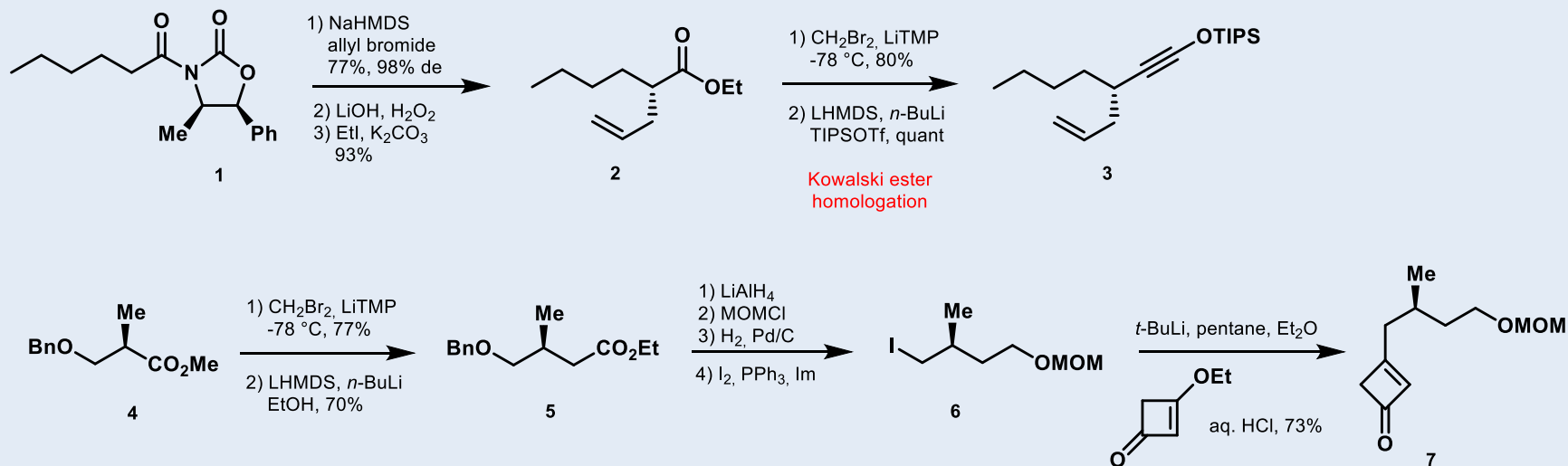
Cylindrocyclophane A, R = OH
Cylindrocyclophane F, R = H



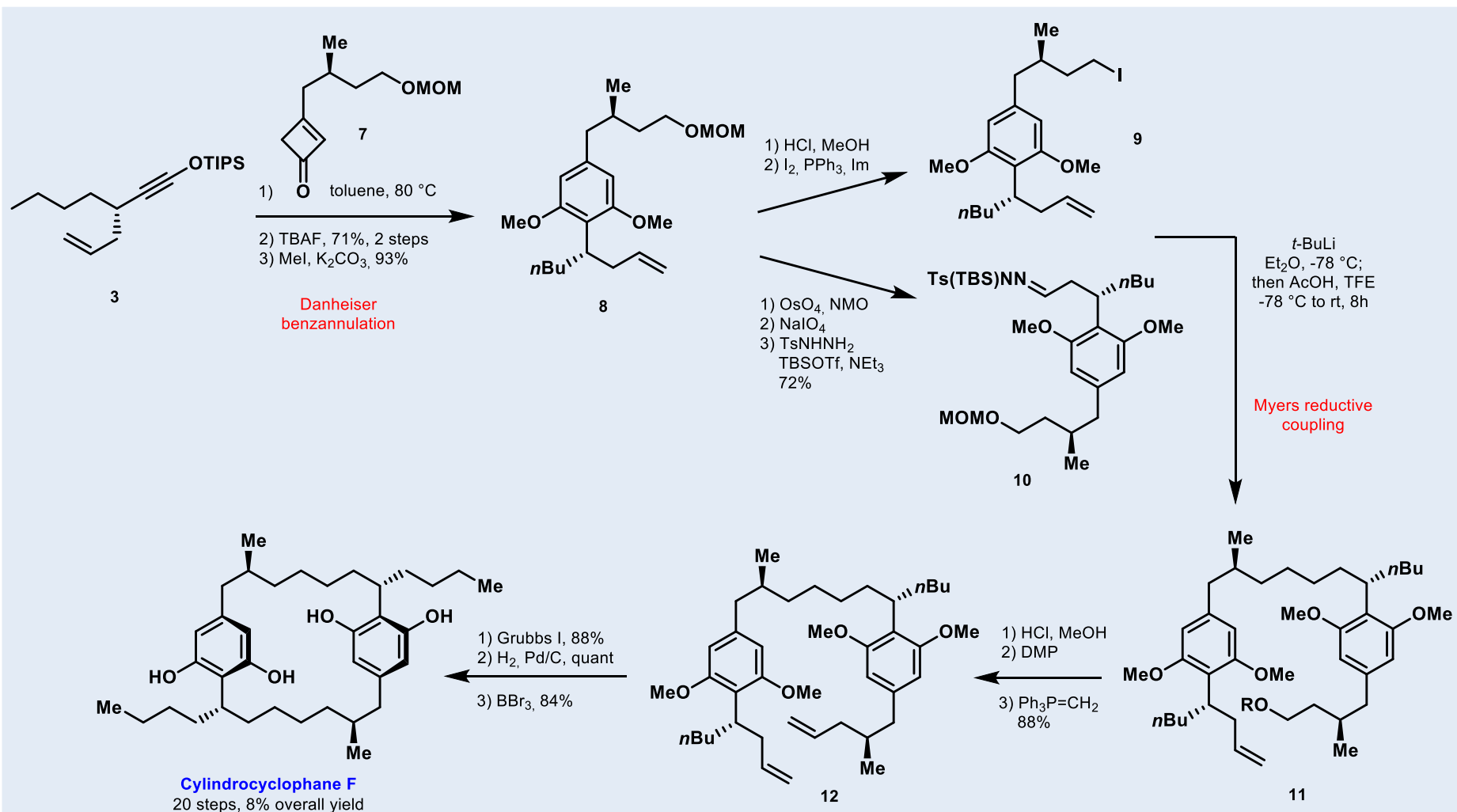
[7.7]paracyclophane



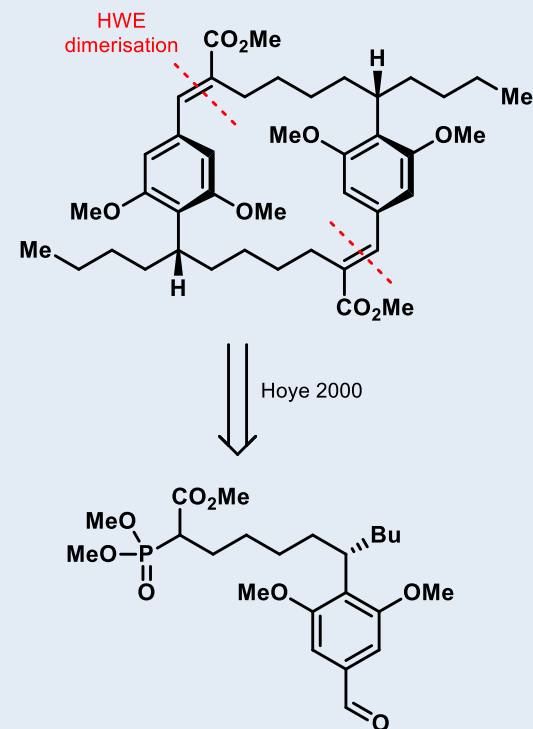
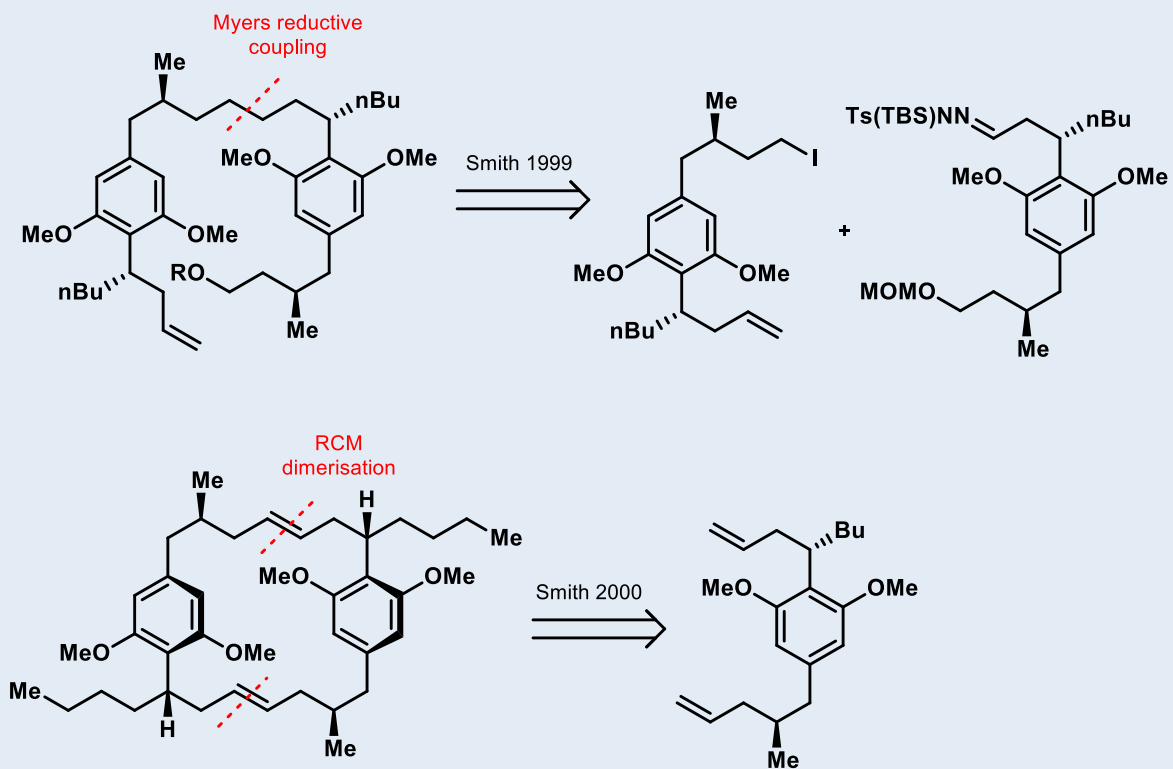
Resorcinol



Cylindrocyclophanes - Smith III

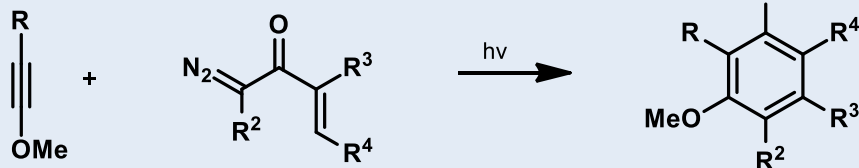


Cylindrocyclophanes – Alternative Approaches

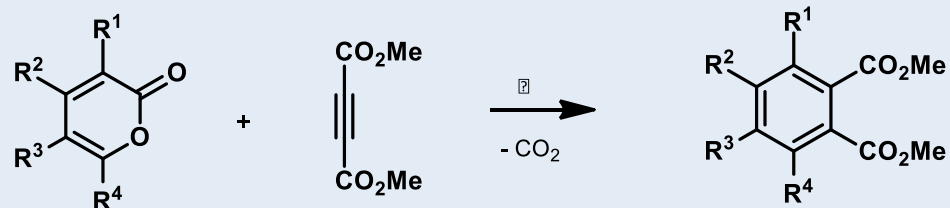


Highly Functionalized Benzene Rings

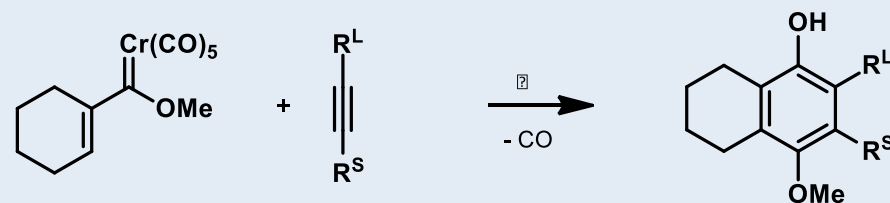
Photochemical Wolff
Rearrangement



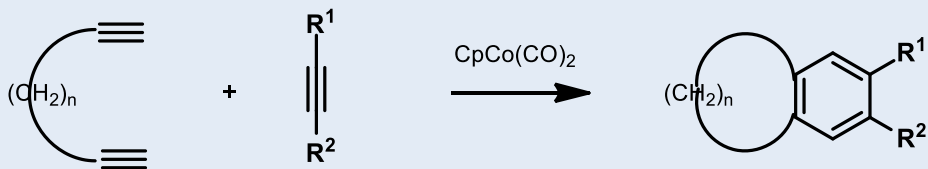
Diels-Alder



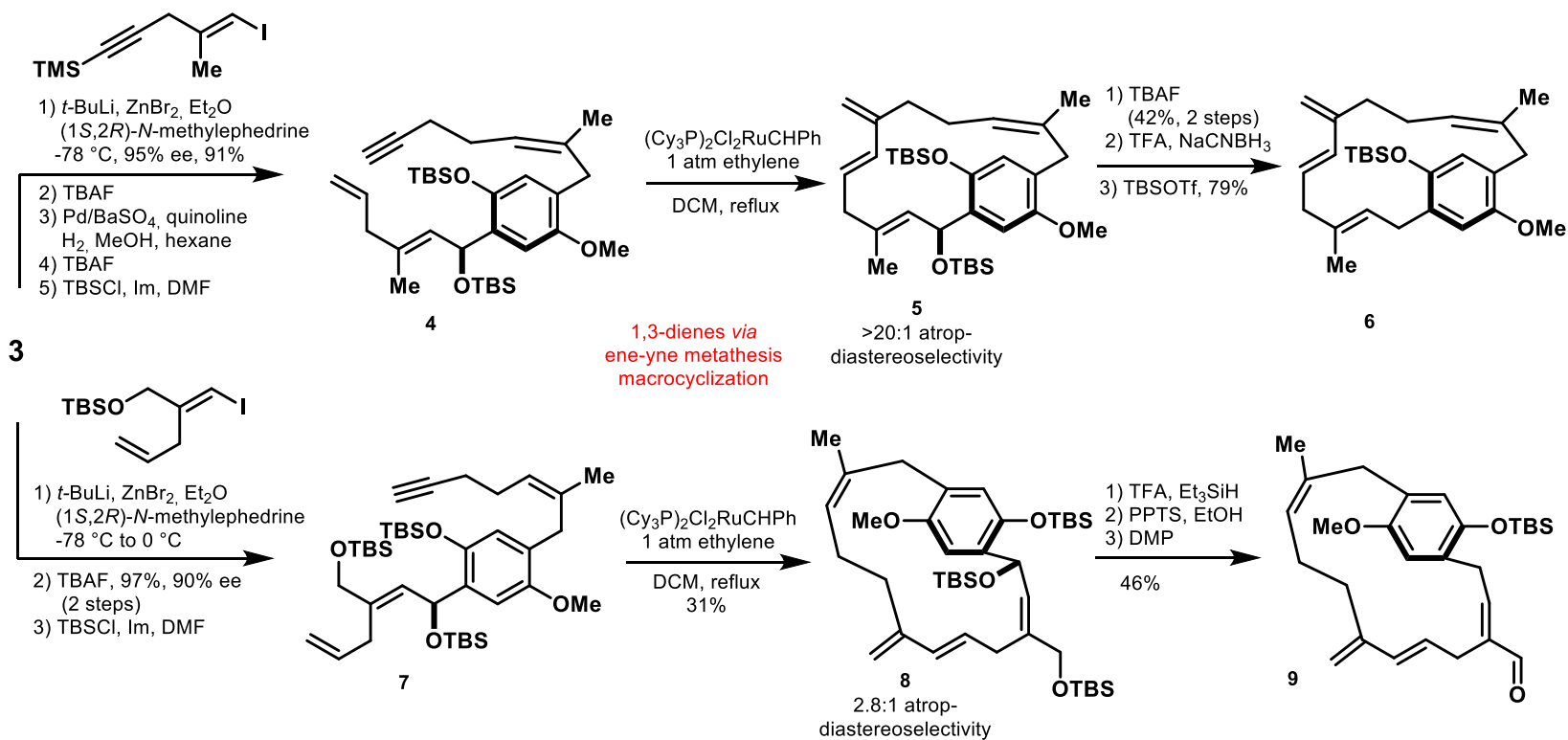
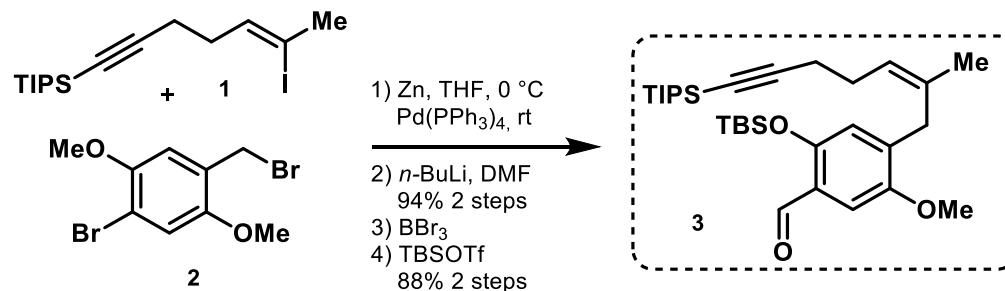
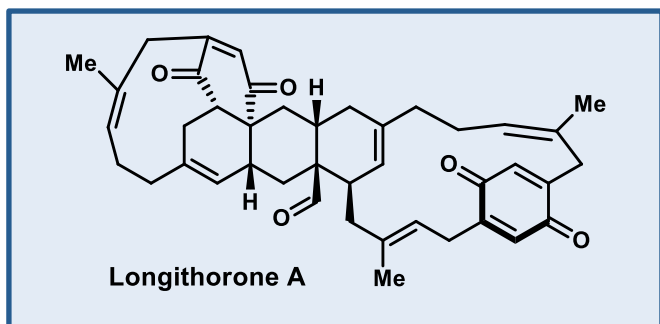
Dötz Reaktion



Vollhardt [2+2+2]
Acetylene Cycloaddition



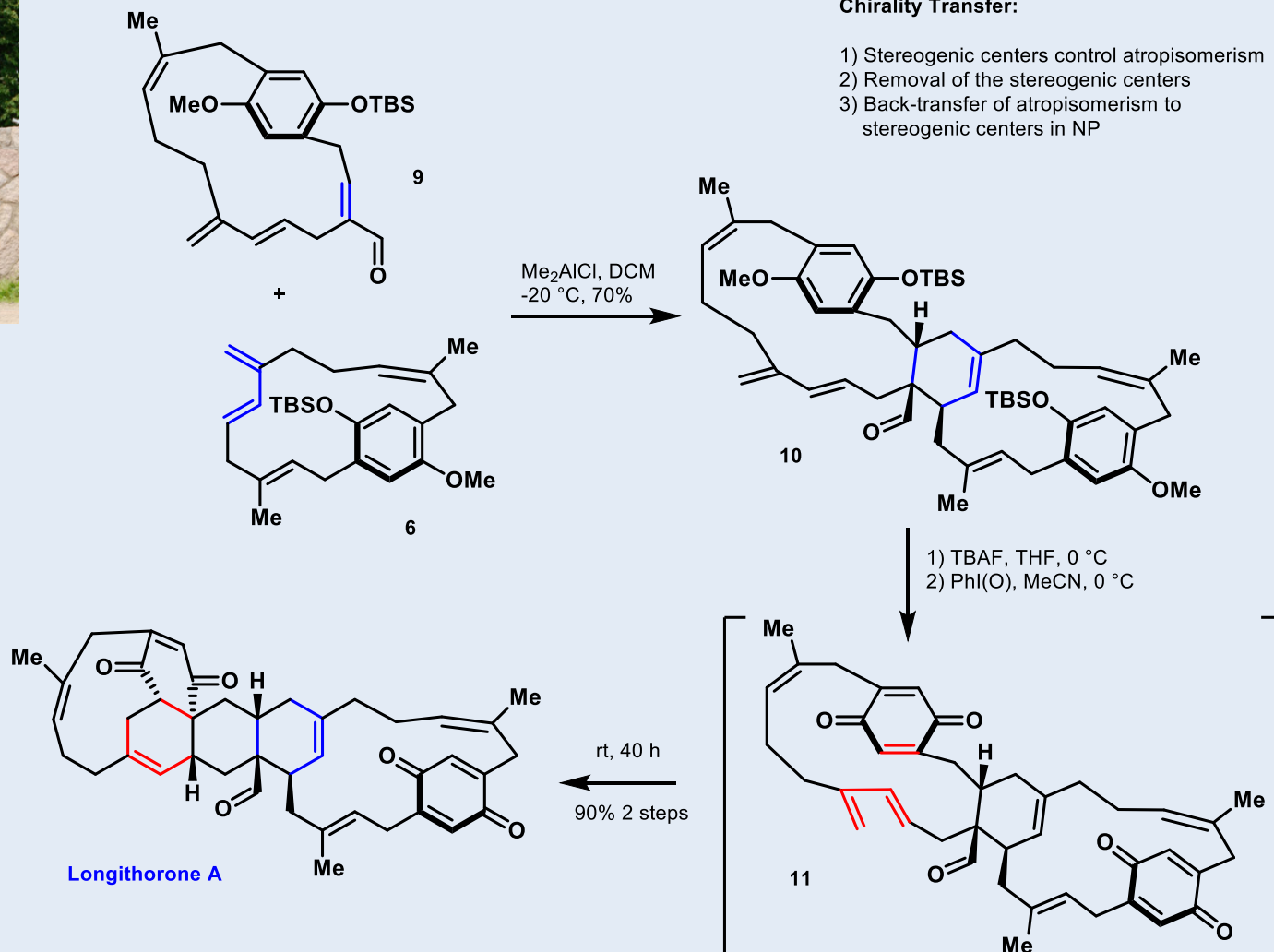
Longithorone A - Shair



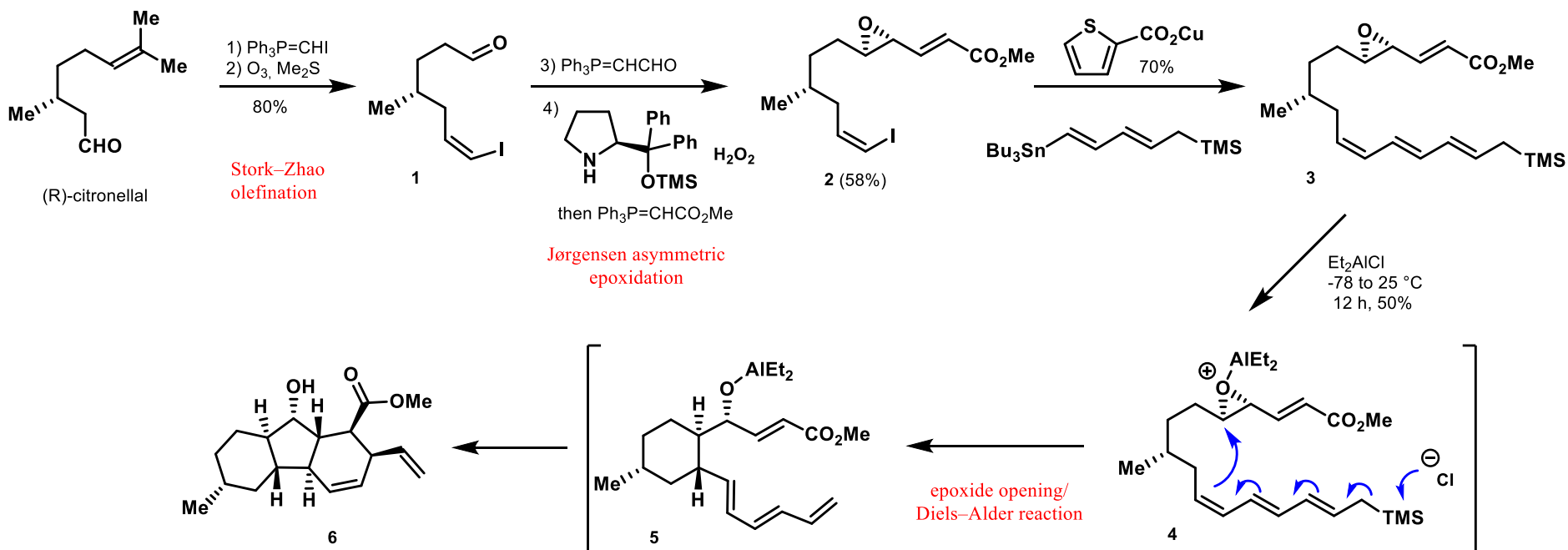
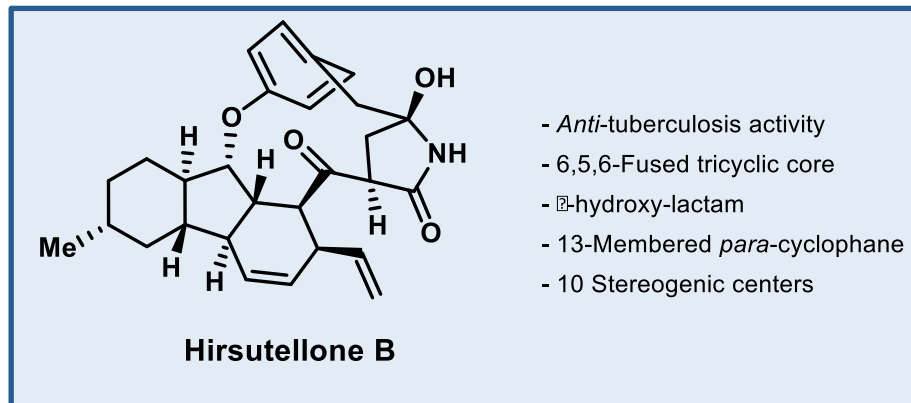
Longithorone A - Shair



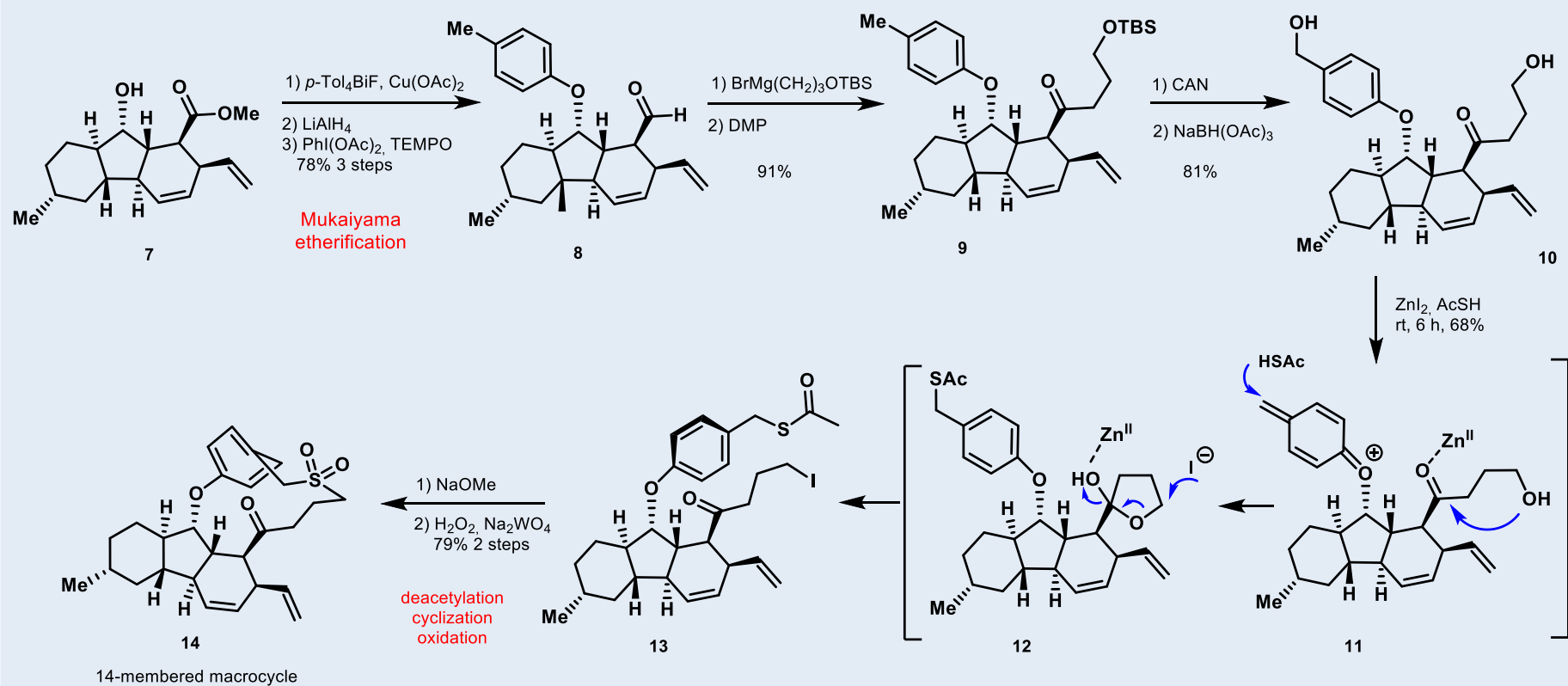
Matthew D. Shair
(Harvard University)



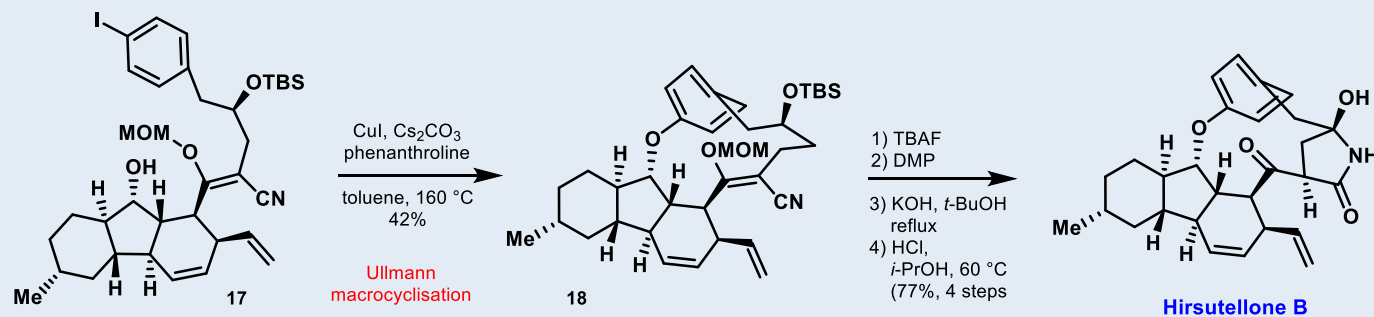
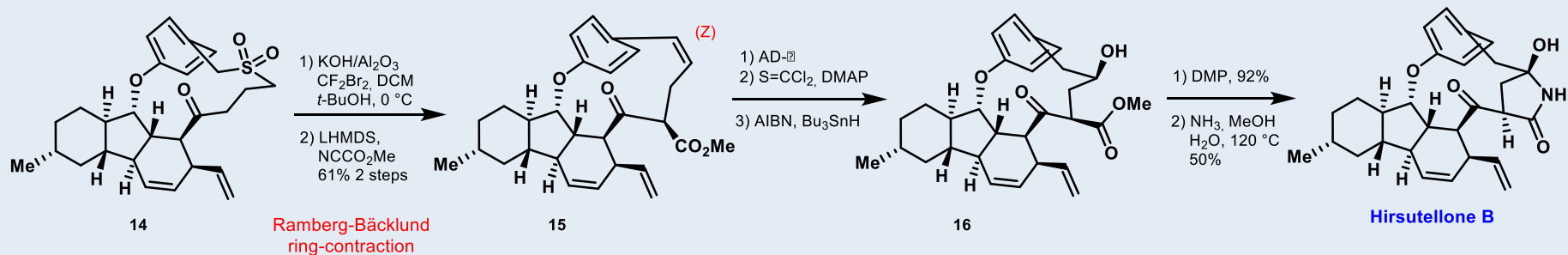
Hirsutellone B - Nicolaou



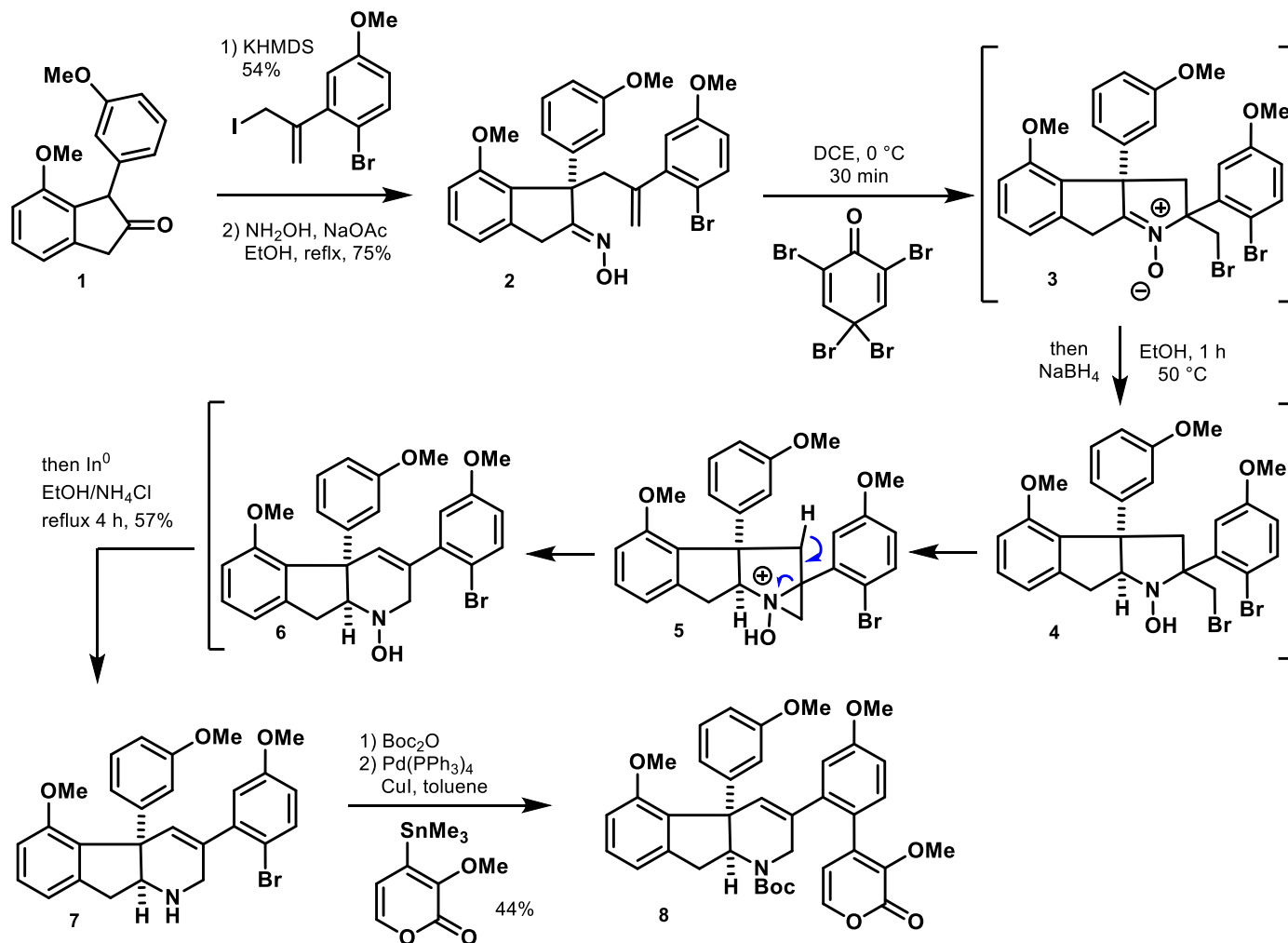
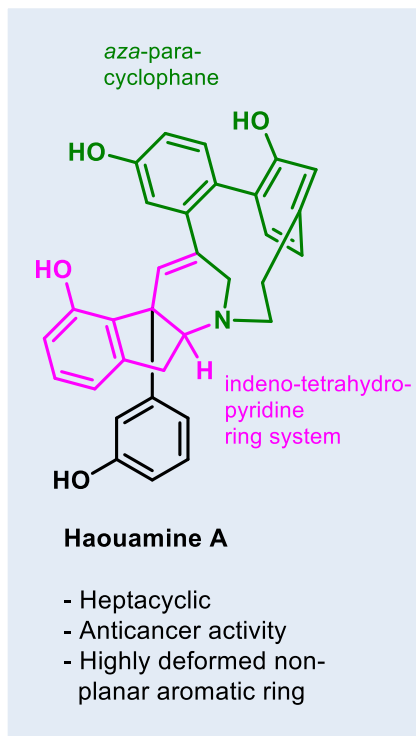
Hirsutellone B - Nicolaou



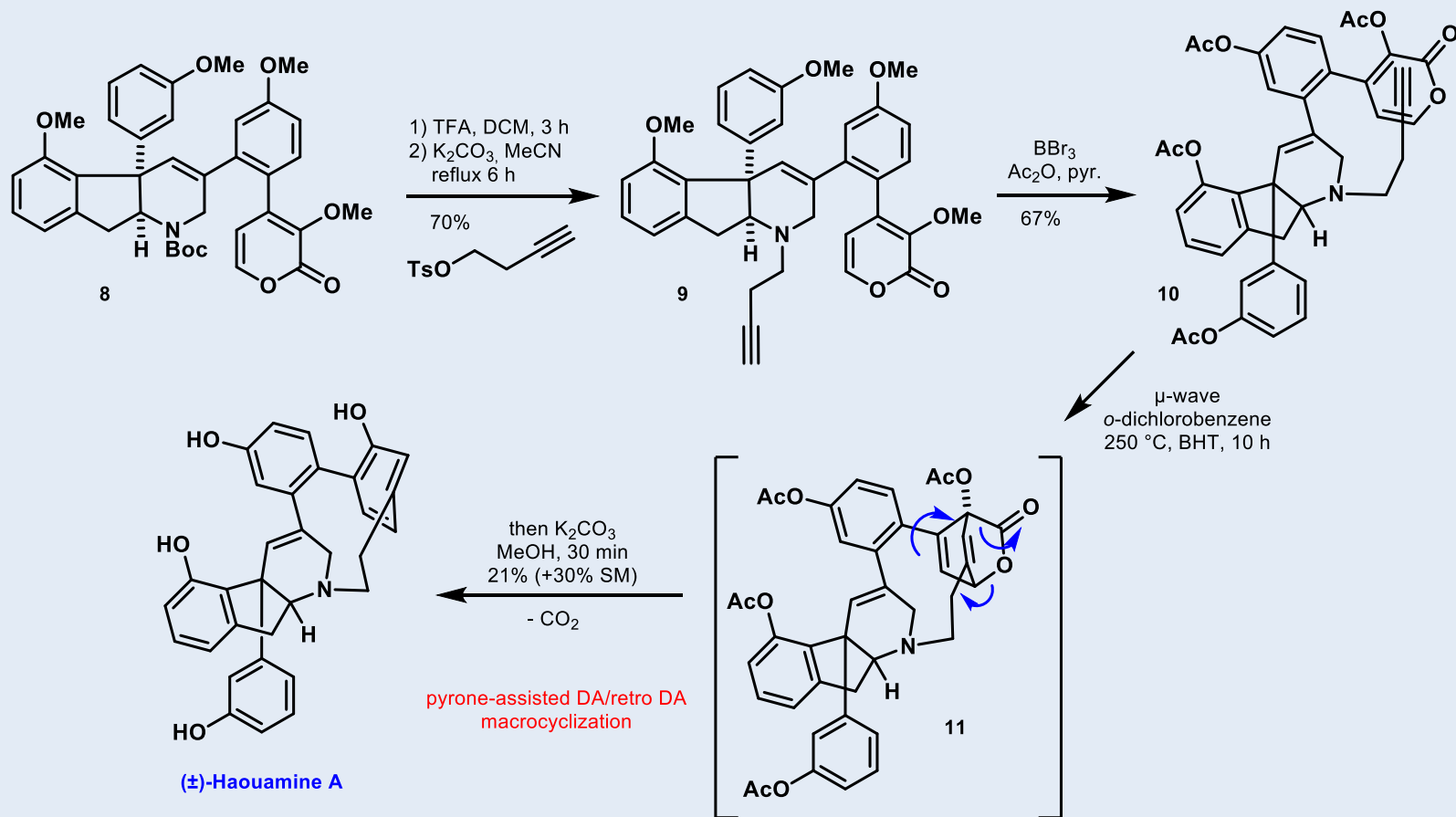
Hirsutellone B – Nicolaou / Uchiro



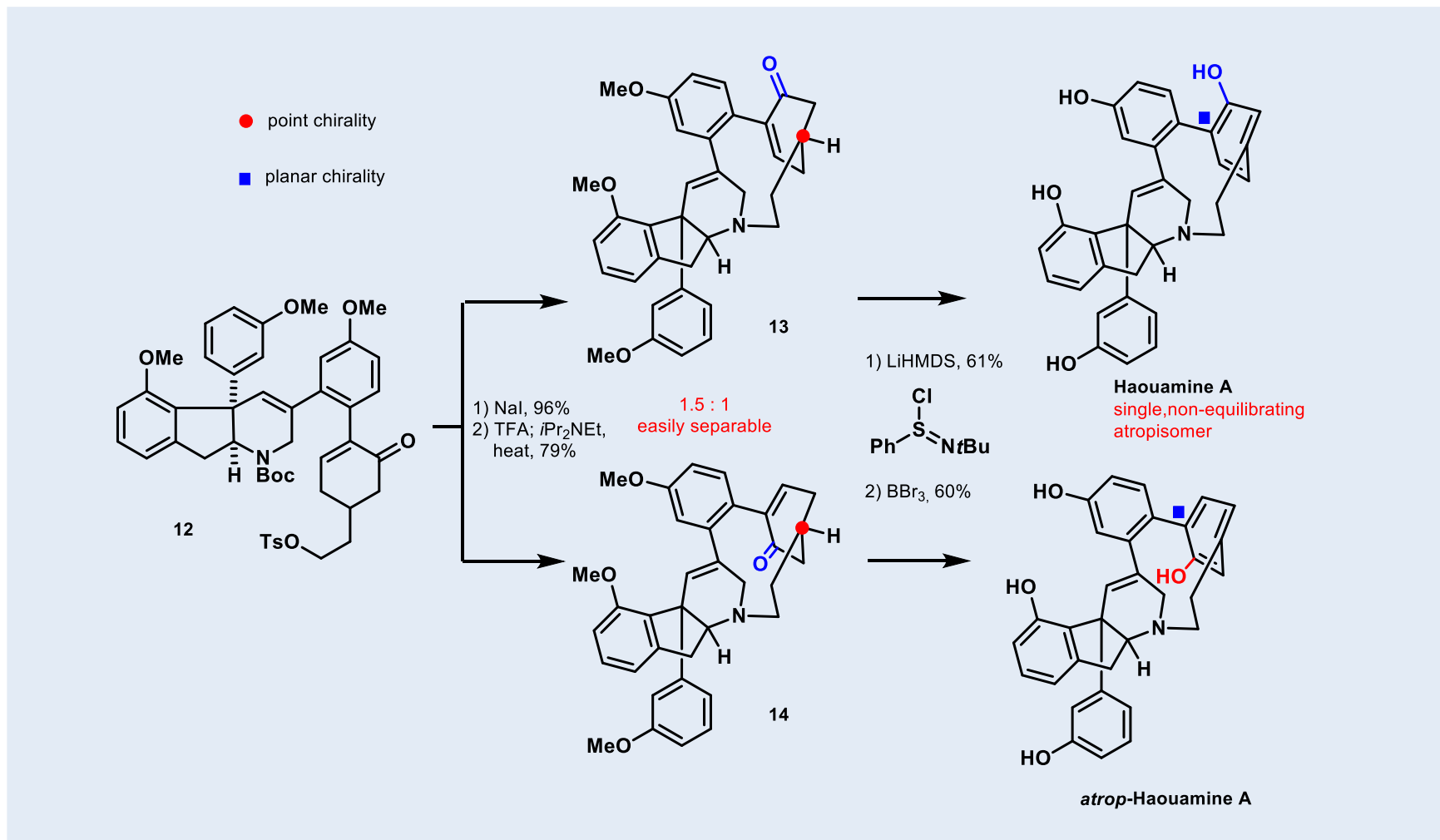
Haouamine A - Baran



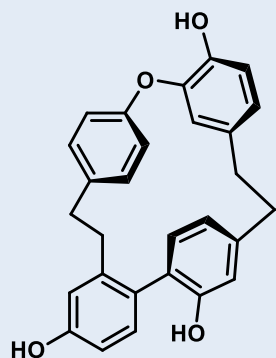
Houamine A - Baran



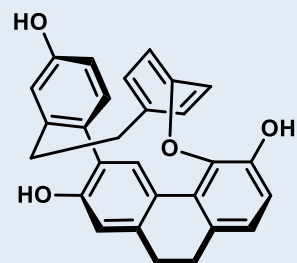
Houamine A - Baran



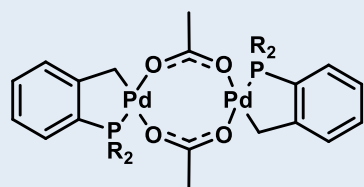
Riccardin C and Cavicularin - Harrowven



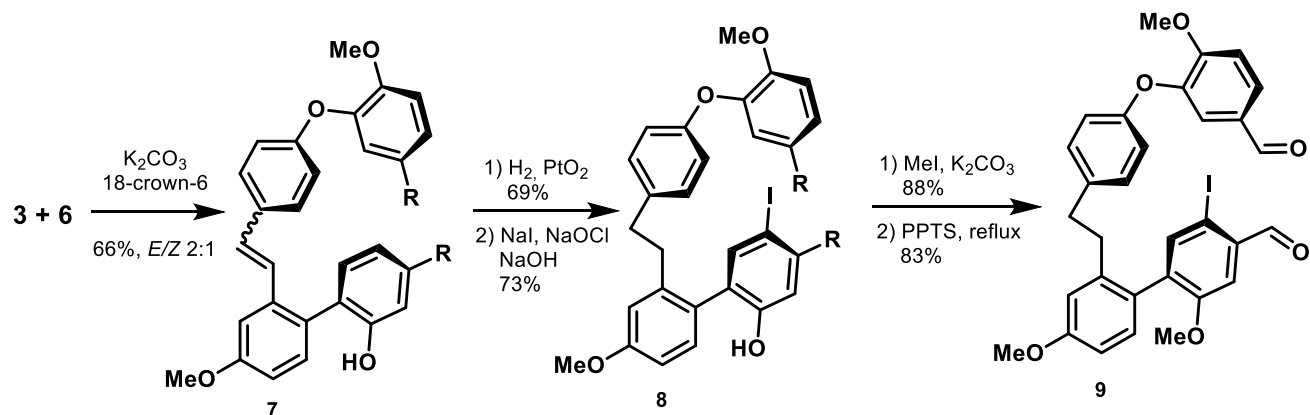
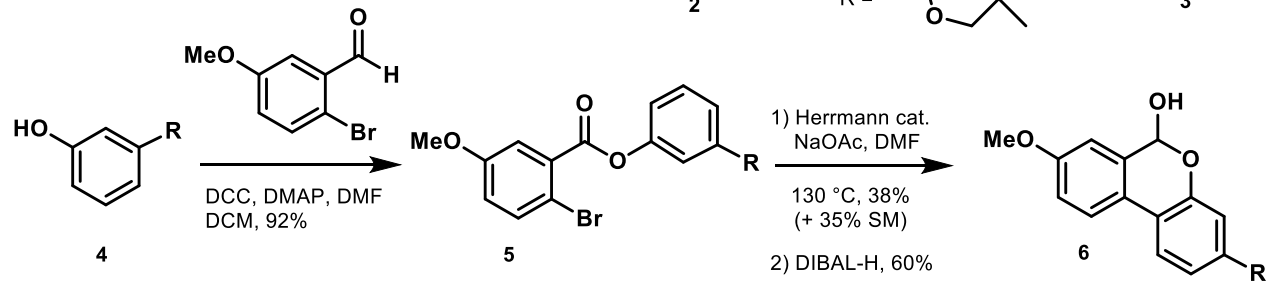
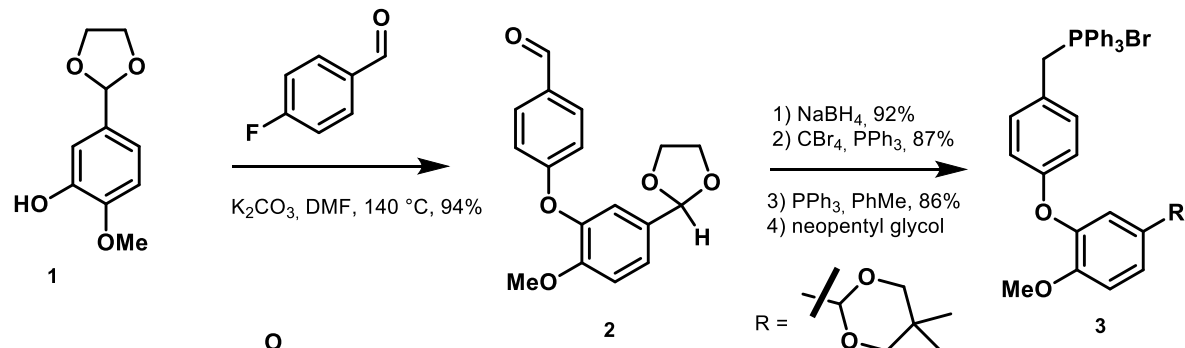
Riccardin C



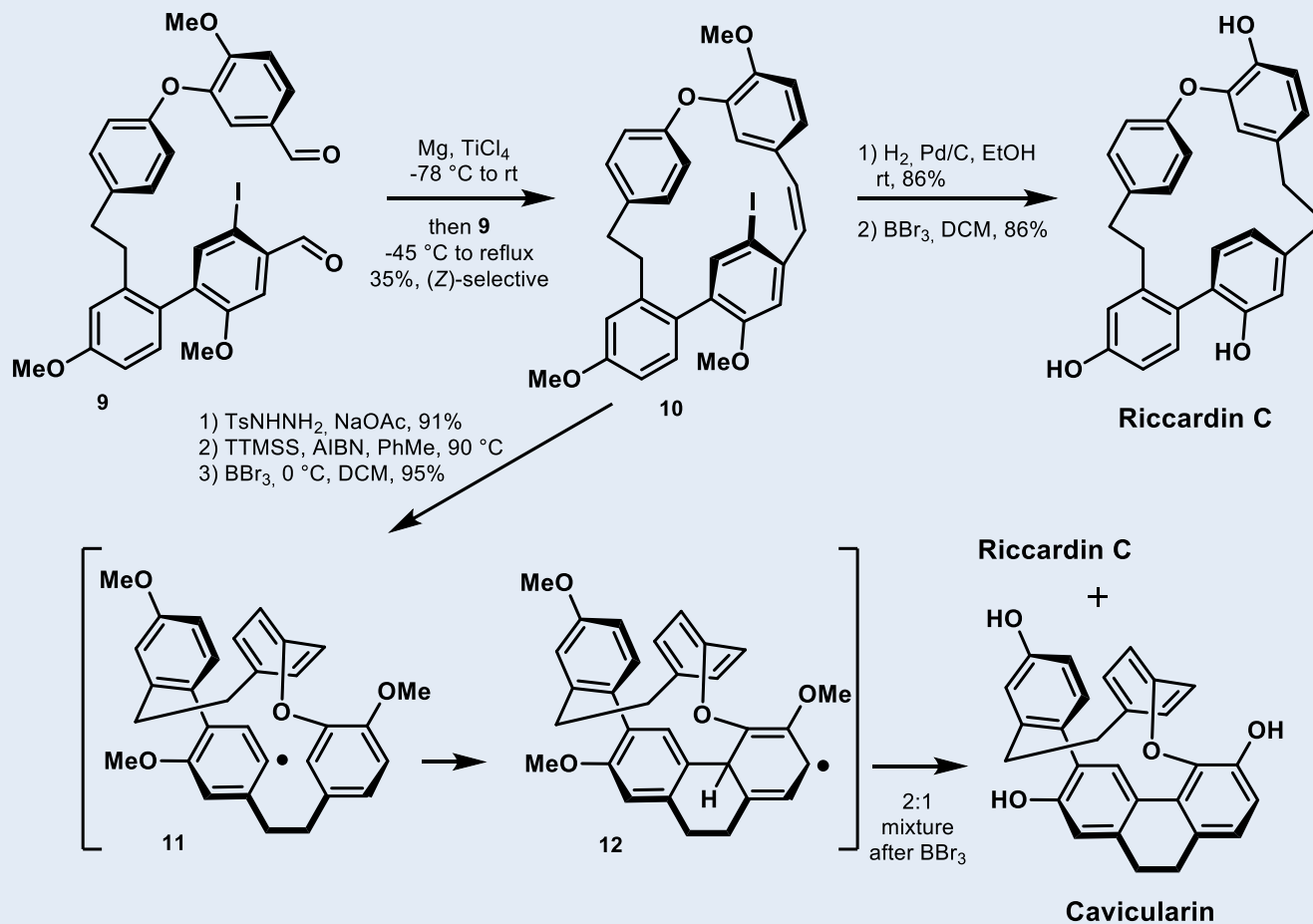
Cavicularin



Herrmann cat.



Riccardin C and Cavicularin - Harrowven



TTMSS = tris(trimethylsilyl)silane
(reagent of the choice for the reduction of functional groups after a radical mechanism)

Thank you for your attention!

Questions?