Literature Report 7

A chiral pool approach for asymmetric syntheses of (-)-antrocin, (+)-asperolide C, and (-)-*trans*-ozic acid

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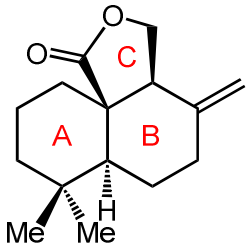
Checker: Lei Shi
Date: 2017-03-06

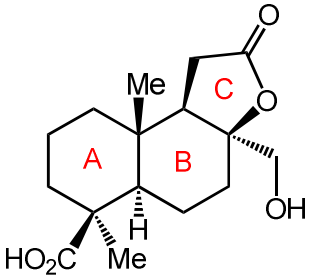
Yang, Z. et al
Chem. Commun. **2016**, *52*, 12426.

Contents

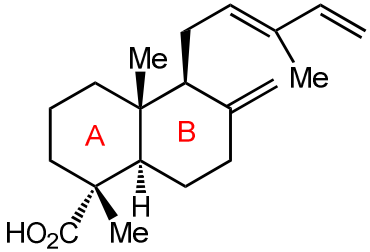
Introduction



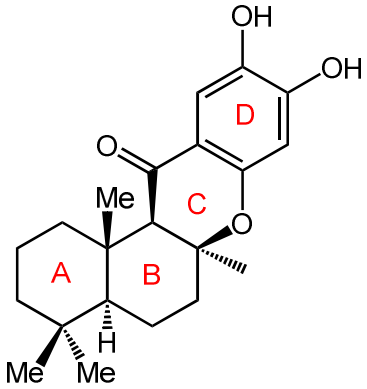
(-)-antrocin (1)
anticancer agent



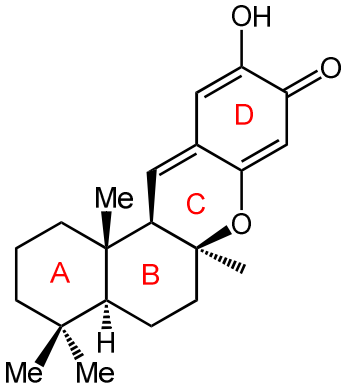
(+)-asperolide C (2)
antibacterial activity



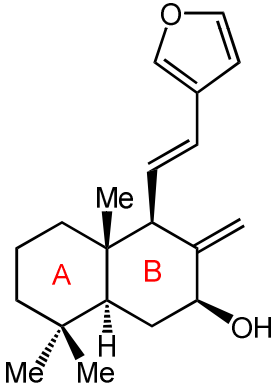
(-)-*trans*-ozic acid (3)
analgesic activity



(-)-15-oxopuupehenol
antimalarial activity



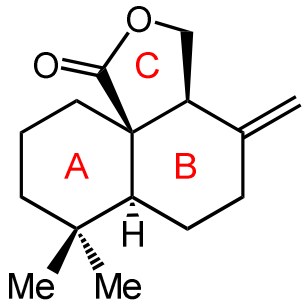
(+)-puupehenone
antituberculosis activity



(+)-coranarian
antiangiogenic activity

Afonso, C. A. M. et al *Chem. Rev.***2011**, *111*, 4418.

Introduction



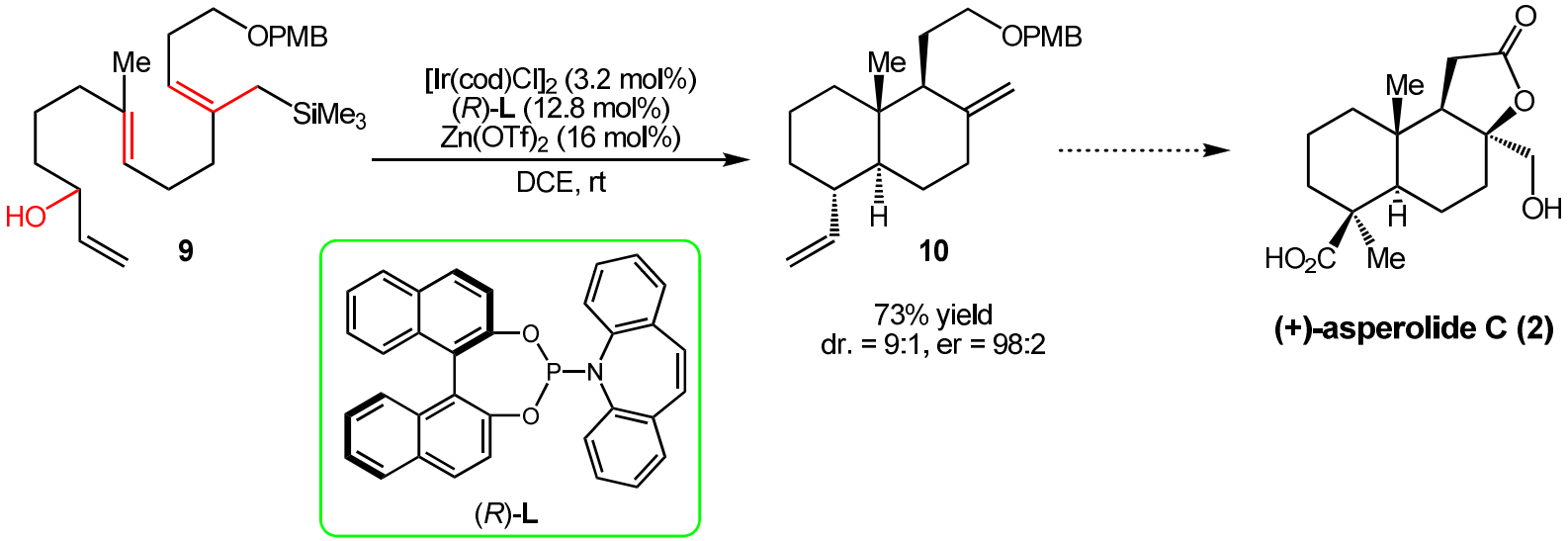
(-)-antrocin (**1**)

Antrodia camphorata
(牛樟芝)

牛樟芝胶囊

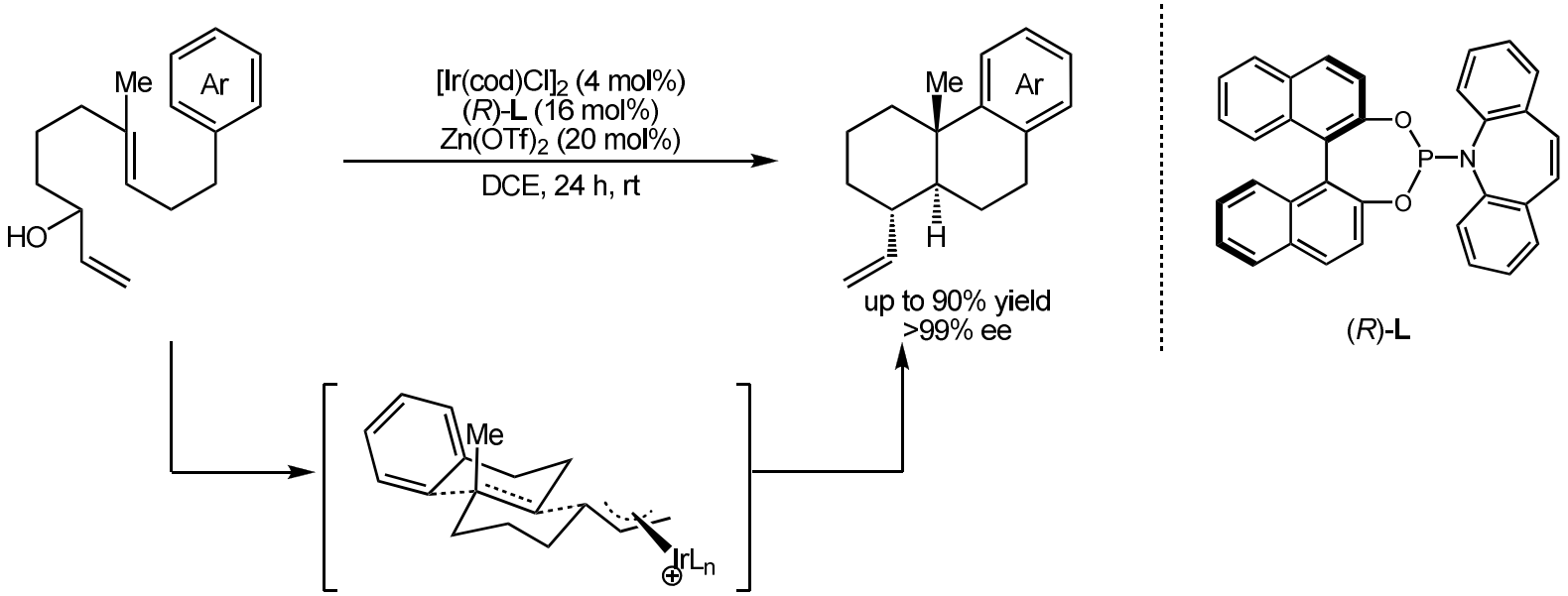
- (-)-Antrocin can be found in an expensive medicinal mushroom Antrodia camphorata in Taiwan.
- (-)-Antrocin can be used as a dietary supplement for cancer prevention and hepatoprotection.
- It is a potent antagonist in various cancer cells and can affect lung cancer cells through inhibition of the JAK/STAT3 signaling pathway.

Total synthesis of (+)-asperolide C by Carreira



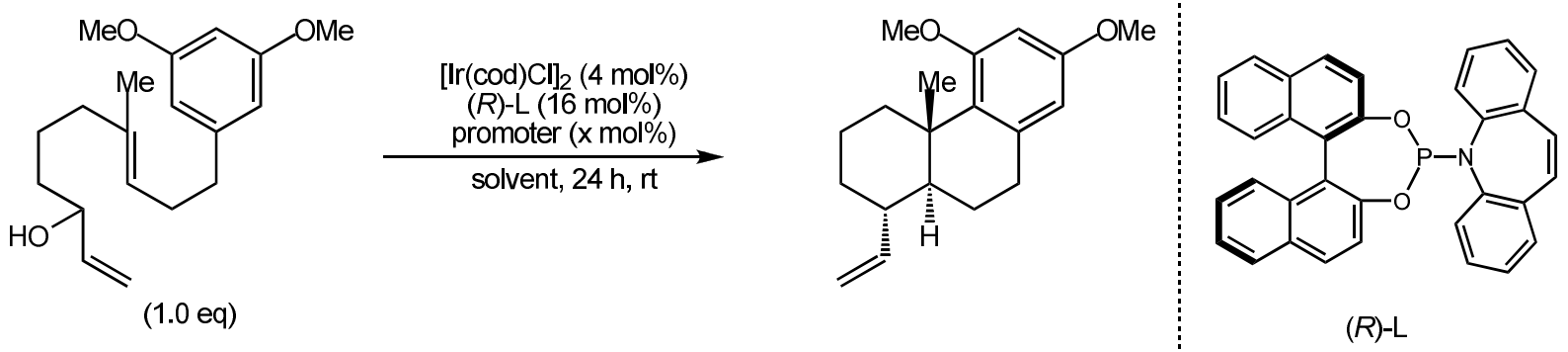
Carreira, E. M. et al *Angew. Chem. Int. Ed*. **2013**, *52*, 12166.

Iridium-catalyzed enantioselective cyclization



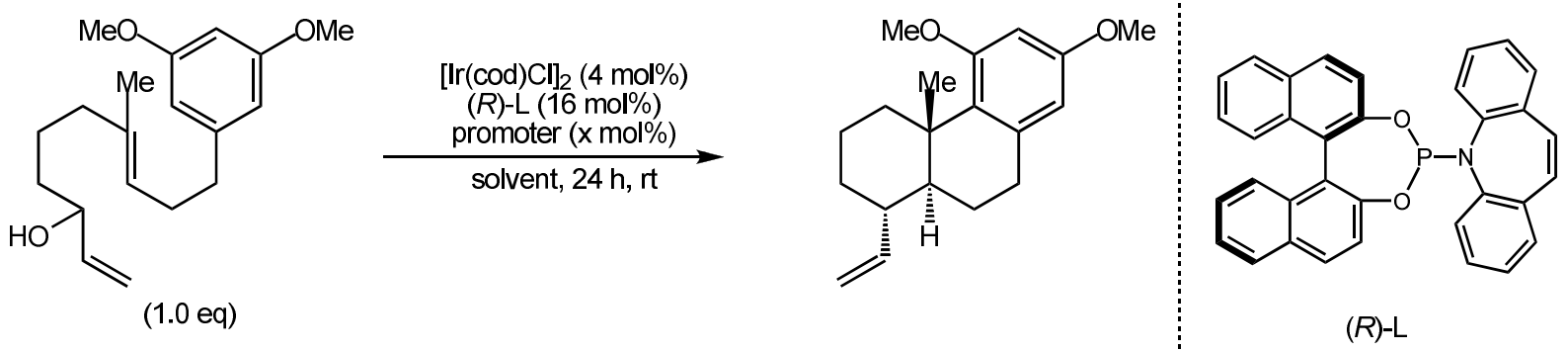
Carreira, E. M. et al *J. Am. Chem. Soc*. **2012**, *134*, 20276.

Optimization of the reaction condition



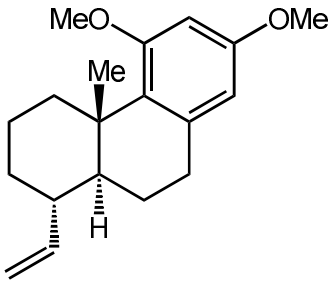
entry	promoter	x (mol%)	solvent	yield (%)	ee (%)
1	$P(O)(OBu)_2OH$	50	DCE	42	89
2	$Bi(OTf)_3$	10	DCE	71	96
3	$Sc(OTf)_3$	10	DCE	91	80
4	$In(OTf)_3$	10	DCE	84	88
5	$Yb(OTf)_3$	10	DCE	79	94
6	$Zn(OTf)_2$	10	DCE	72	>99.5

Optimization of the reaction condition

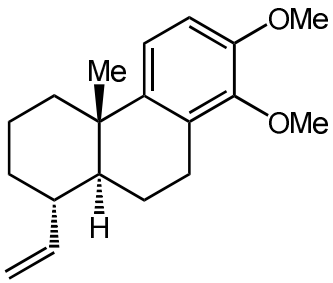


entry	promoter	x (mol%)	solvent	yield (%)	ee (%)
7	$Zn(OTf)_2$	10	Dioxane	8	>99.5
8	$Zn(OTf)_2$	10	DMF	NR	--
9	$Zn(OTf)_2$	20	DCE	90	>99.5
10	$Zn(OTf)_2$	50	DCE	83	99
11	TfOH	20	DCE	12	81

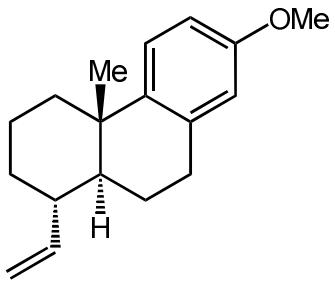
Scope of the Ir-catalyzed cyclization reaction



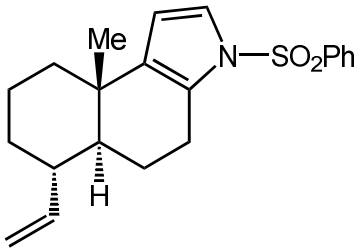
90% yield, >99.5% ee
(1.0 mmol scale)



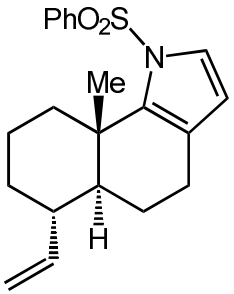
71% yield, >99.5% ee



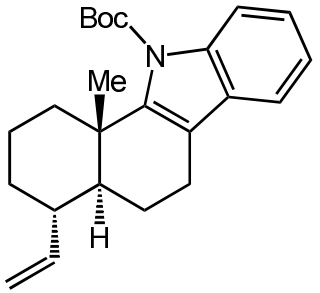
69% yield, >99.5% ee



90% yield, >99.5% ee

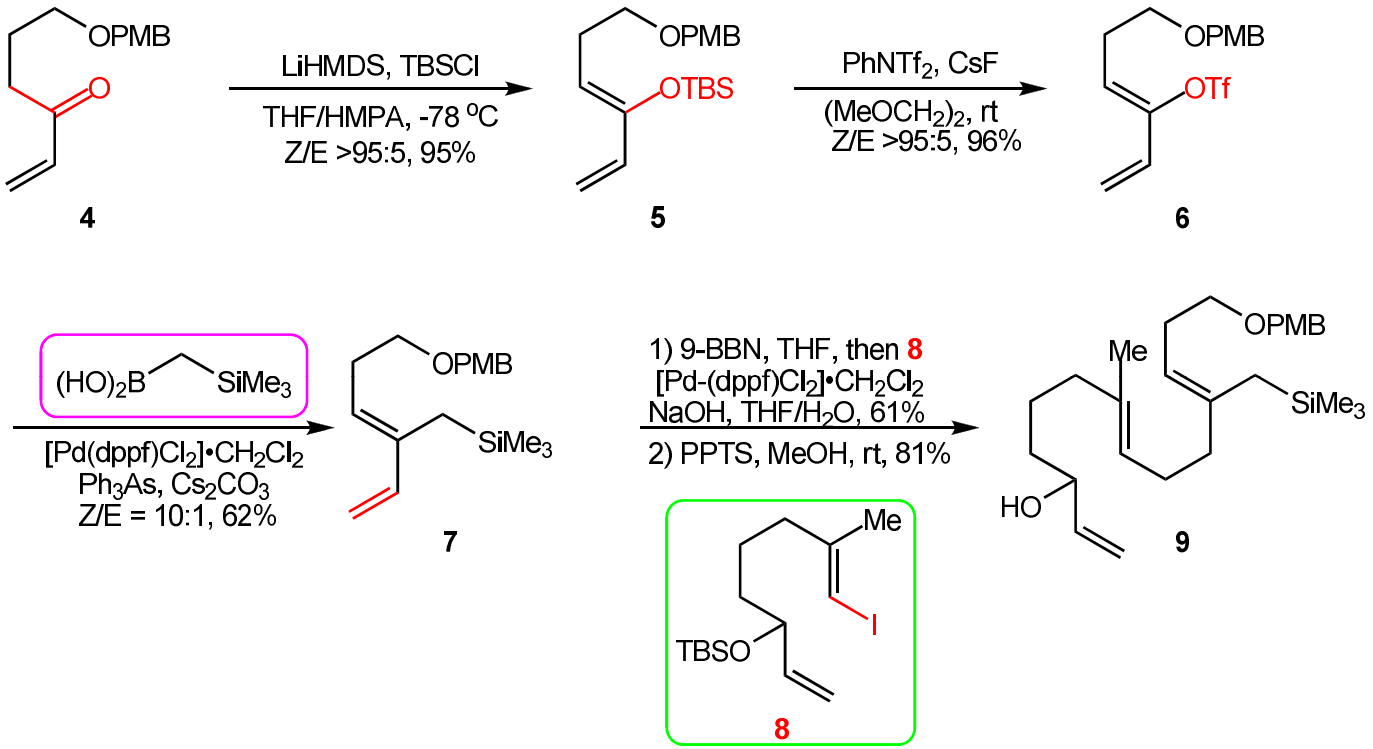


93% yield, >99.5% ee



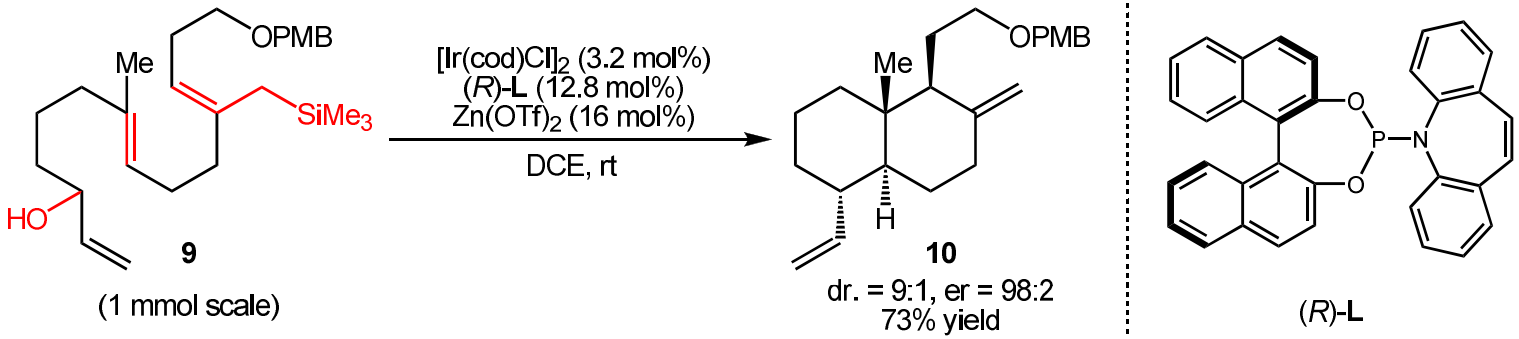
86% yield, >99.5% ee

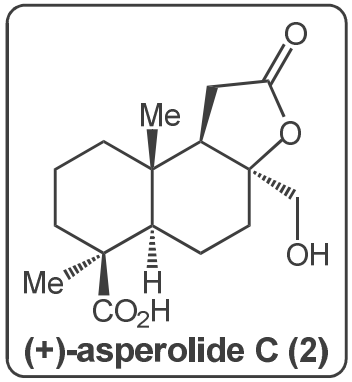
Total synthesis of (+)-asperolide C by Carreira



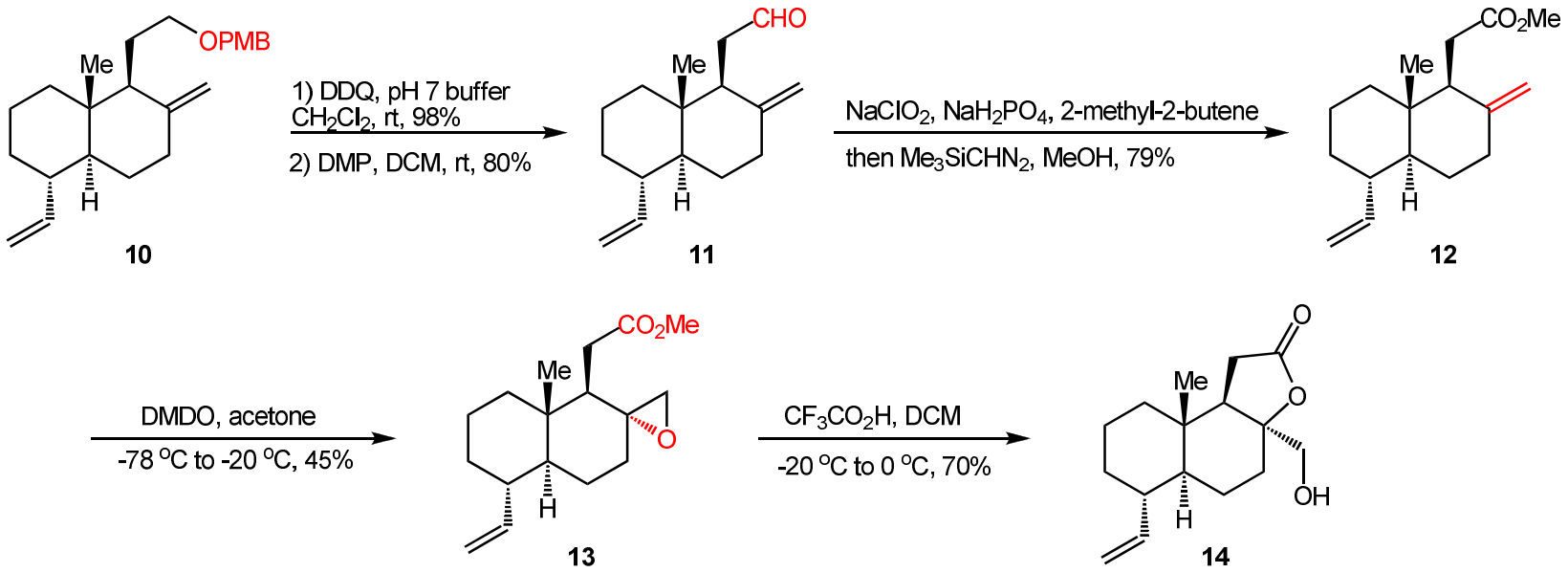
Carreira, E. M. et al *Angew. Chem. Int. Ed*. **2013**, *52*, 12166.

Total synthesis of (+)-asperolide C by Carreira

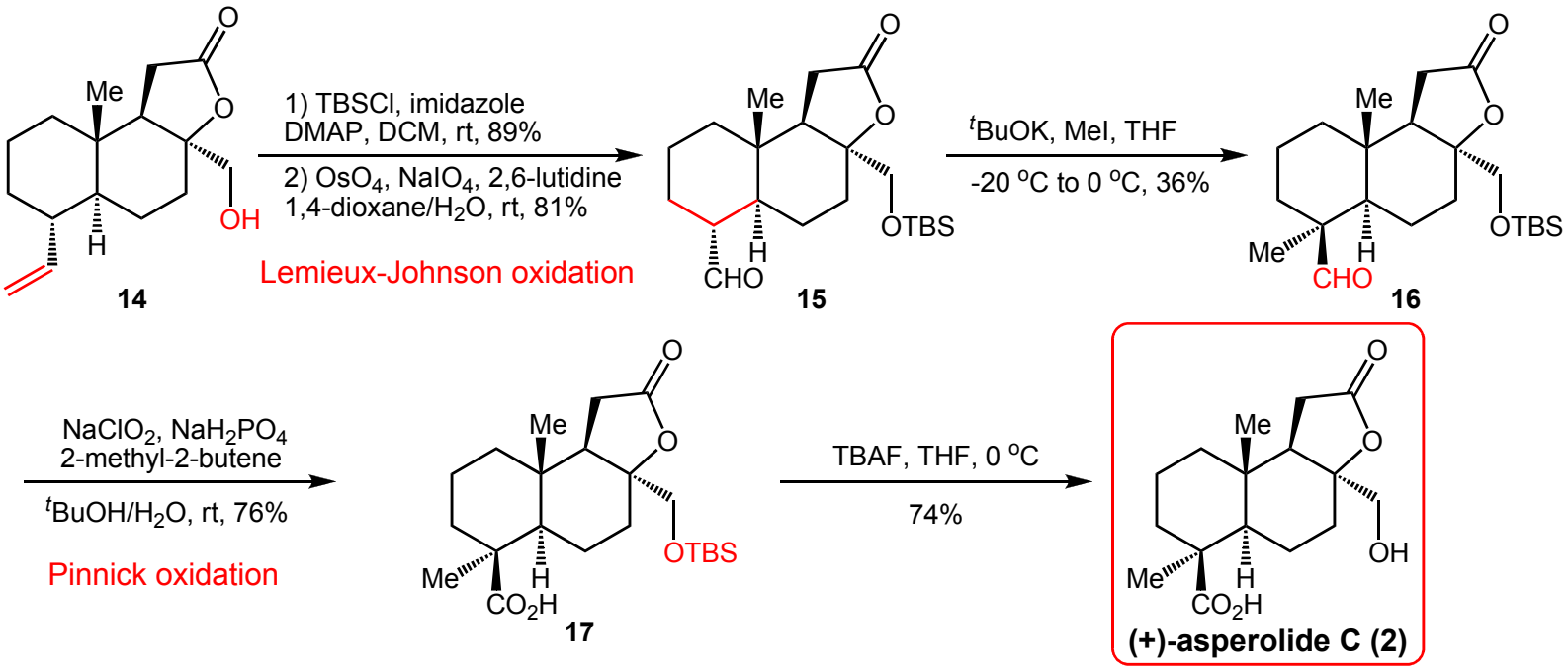




Total synthesis of (+)-asperolide C by Carreira



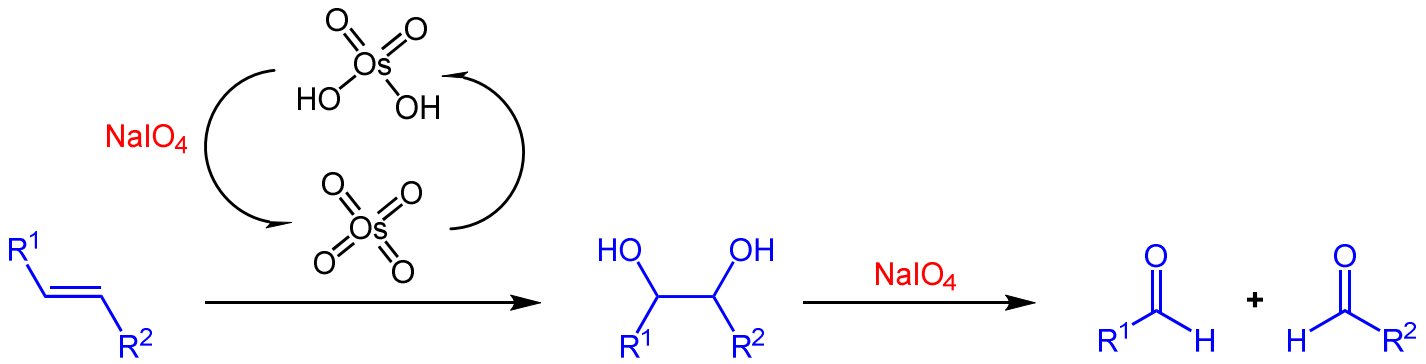
Total synthesis of (+)-asperolide C by Carreira



Lemieux–Johnson oxidation

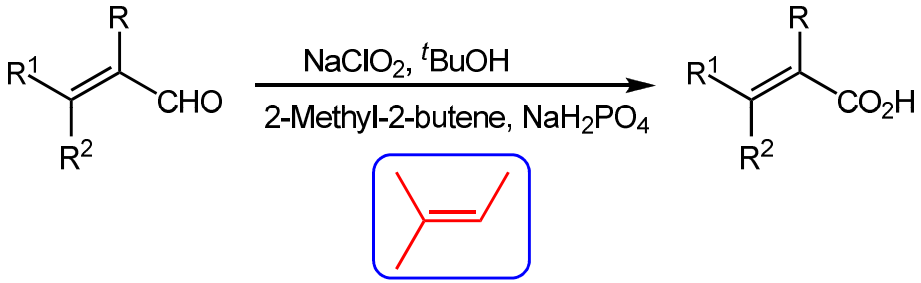
◆ The Lemieux–Johnson oxidation is a chemical reaction in which an olefin undergoes oxidative cleavage to form two aldehyde or ketone units.

◆ Excess periodate is used to regenerate the osmium tetroxide, allowing it to be used in catalytic amounts.

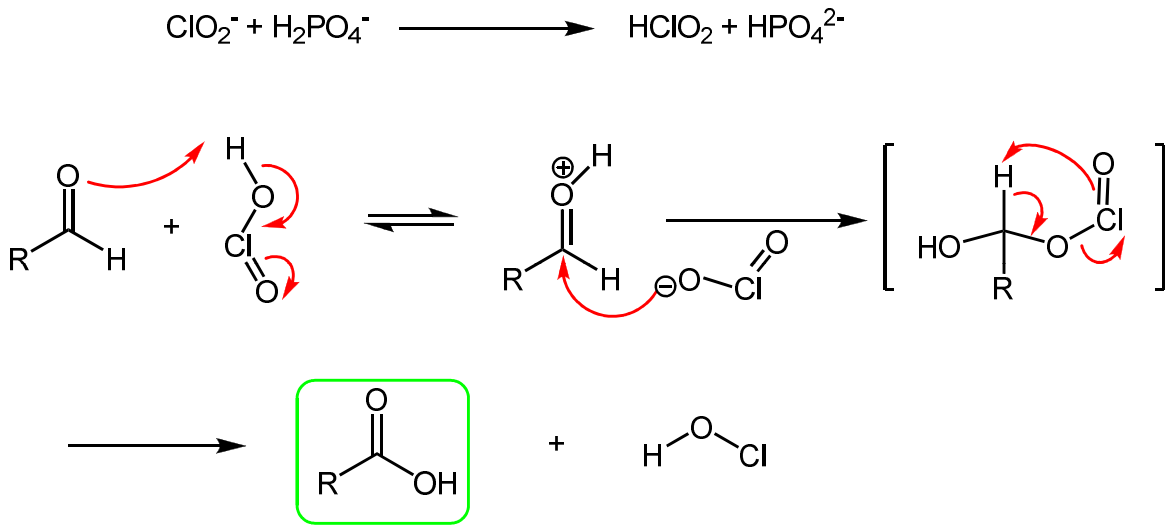


Pinnick oxidation

The Pinnick oxidation is an organic reaction by which aldehydes can be oxidized into their corresponding carboxylic acids using sodium chlorite ($NaClO_2$) under mild acidic conditions.

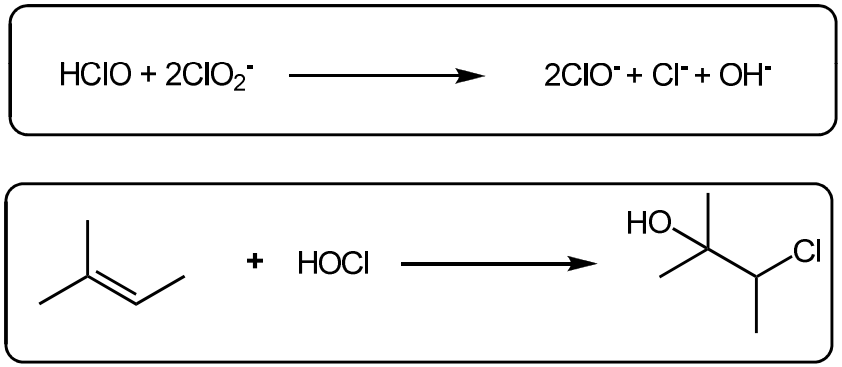


The mechanism of Pinnick oxidation

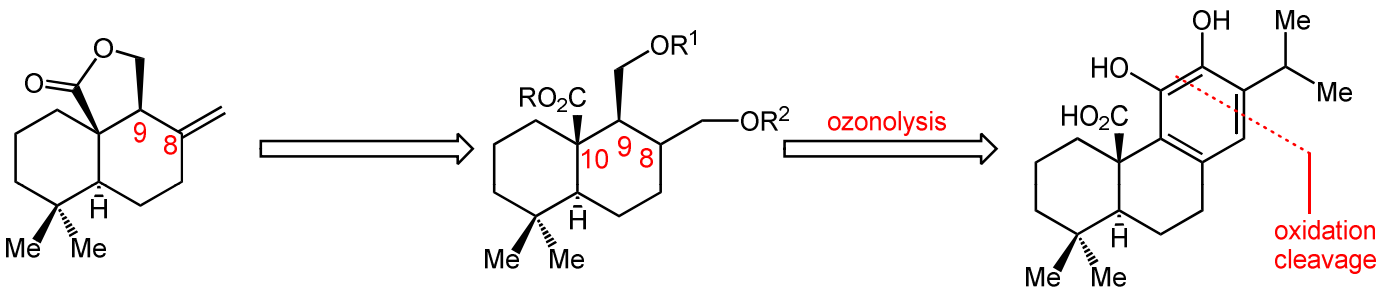


Side reactions and scavengers

- The HClO byproduct is itself a reactive chemical that can destroy the $NaClO_2$ reactant or cause other undesired reactions with the organic materials.
- To prevent this interference, various scavengers are usually added to the reaction to consume the HClO as it is formed.



Retrosynthetic analysis of (-)-antrocin



(-)-antrocin (1) **intermediate** **(+)-carnosic acid (18)**

1.1 $/g

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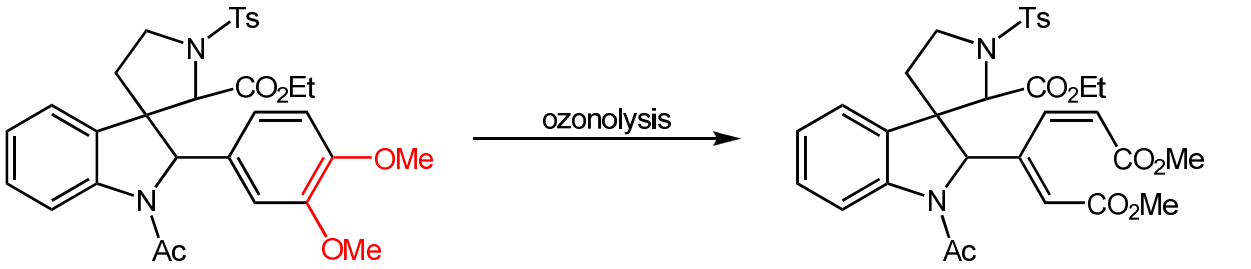
Ozonolysis reactions of phenol derivatives

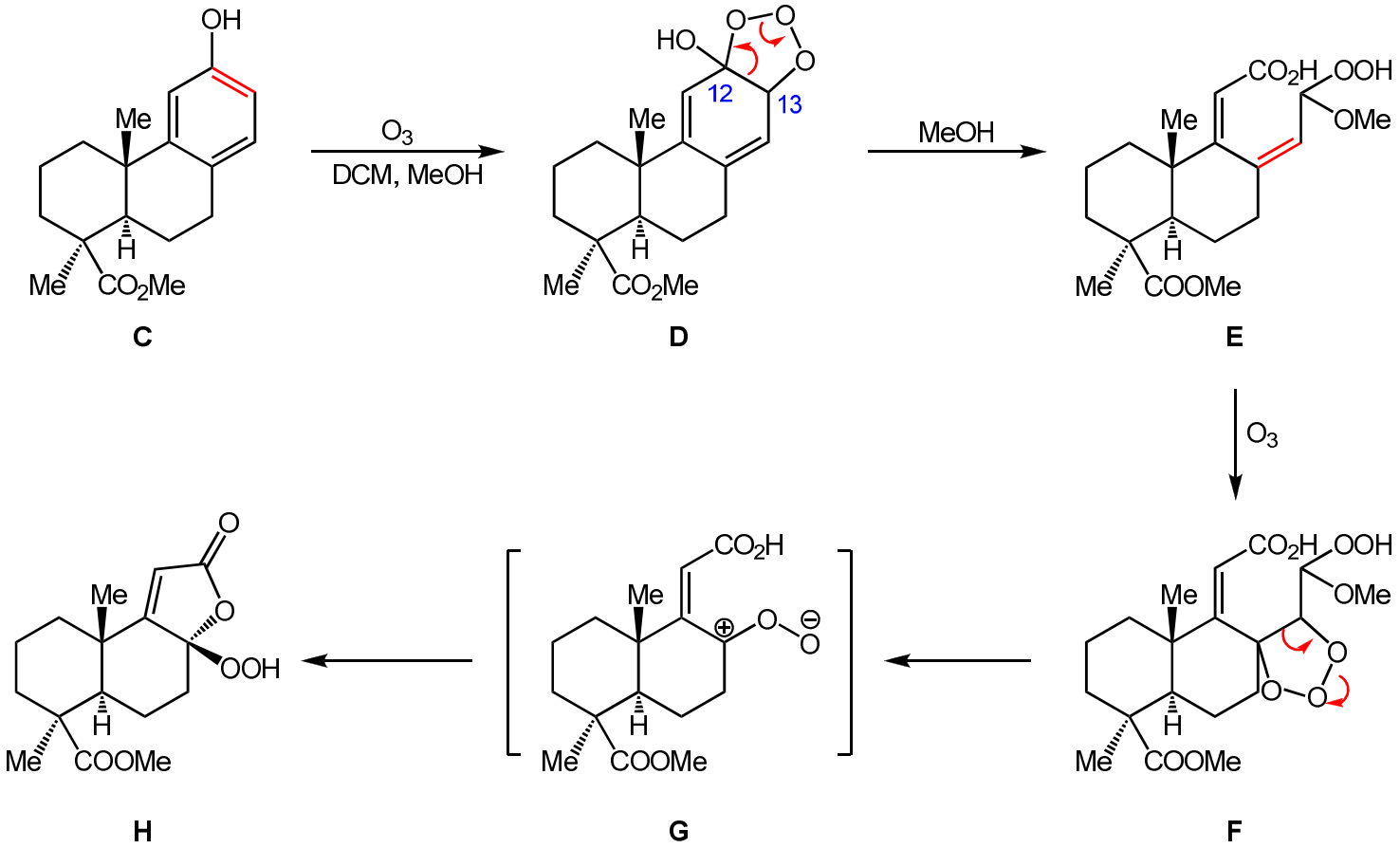


1,2-dimethoxybenzene (A) **dimethyl hexa-2,4-dienedioate (B)**

Ozonolysis of the electron-rich 1,2-dimethoxybenzene moiety in substrate **A** to intermediate **B** in the first total synthesis of strychnine by Woodward.

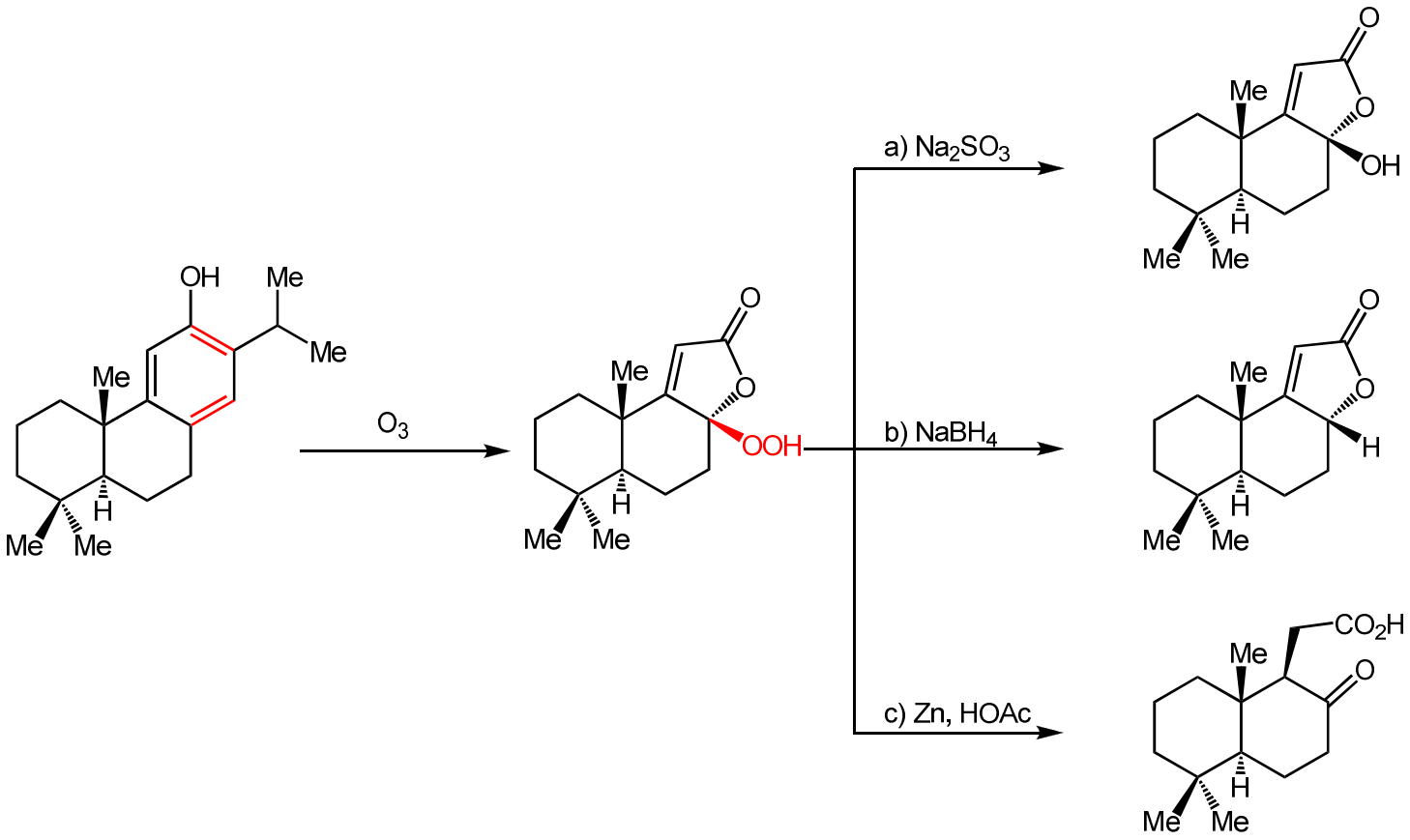
Woodward, R. B. et al *J. Am. Chem. Soc.* **1954**, *76*, 4749.

Ozonolysis reactions of phenols



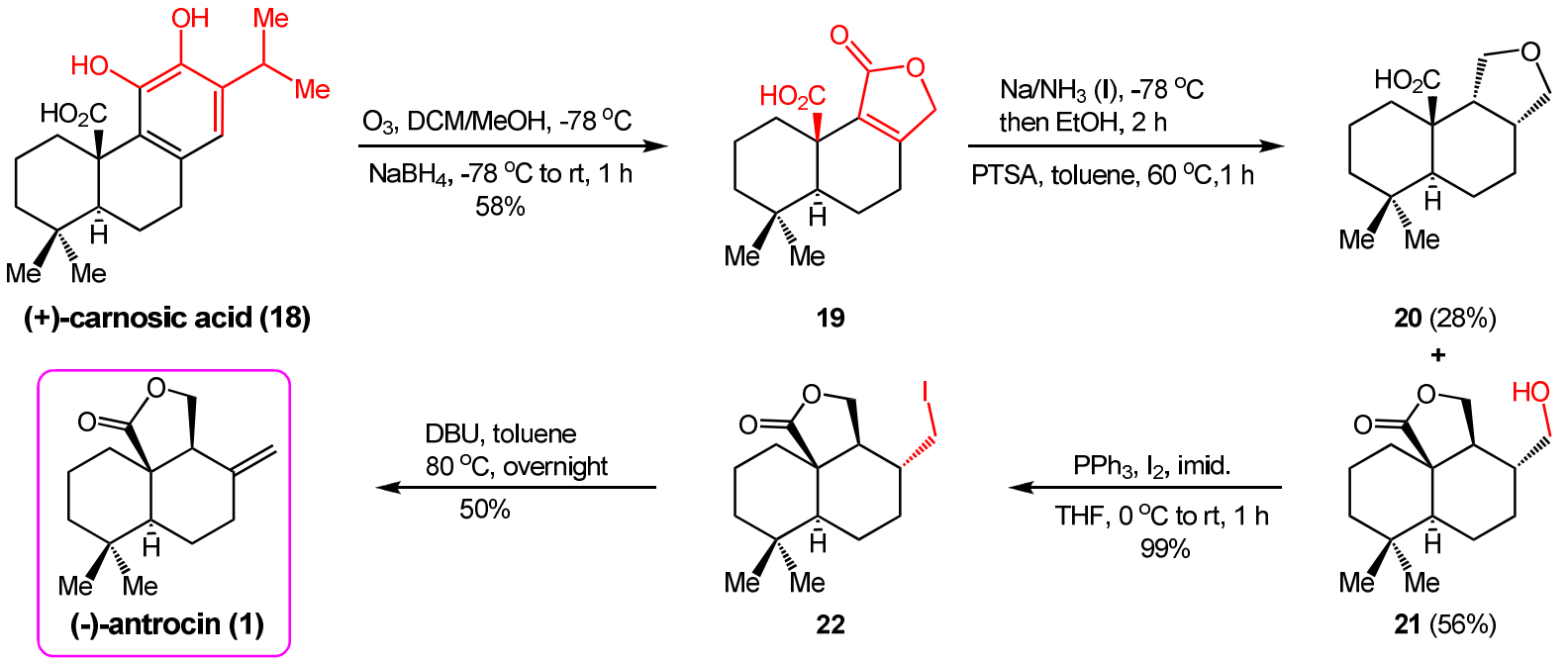
Bell, R. A.; Gravestock, M. B. *Can. J. Chem.* **1970**, *48*, 1105.

Ozonolysis of phenolic dehydroabietic acid derivatives

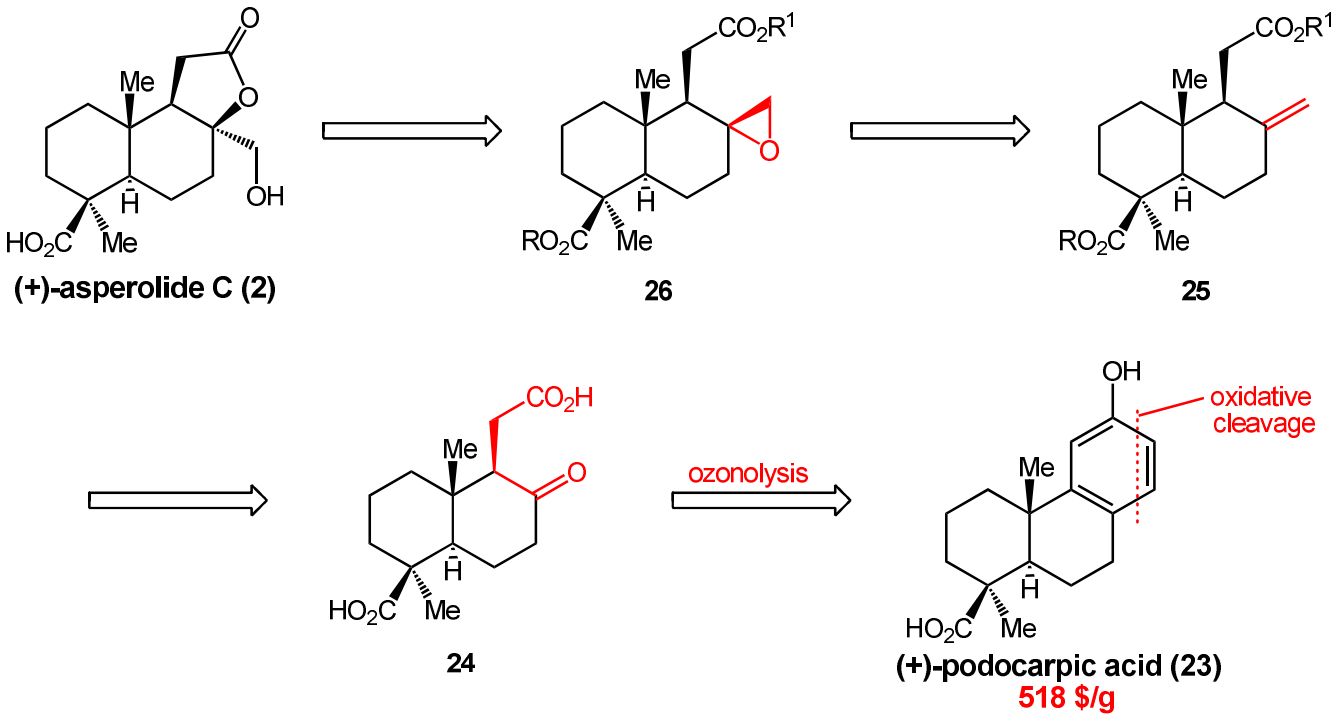


Oishi, T. et al T*etrahedron Lett.* **1978**, *39*, 3733.

Synthesis of (-)-antrocin from (+)-carnosic acid



Retrosynthetic analysis of (+)-asperolide C



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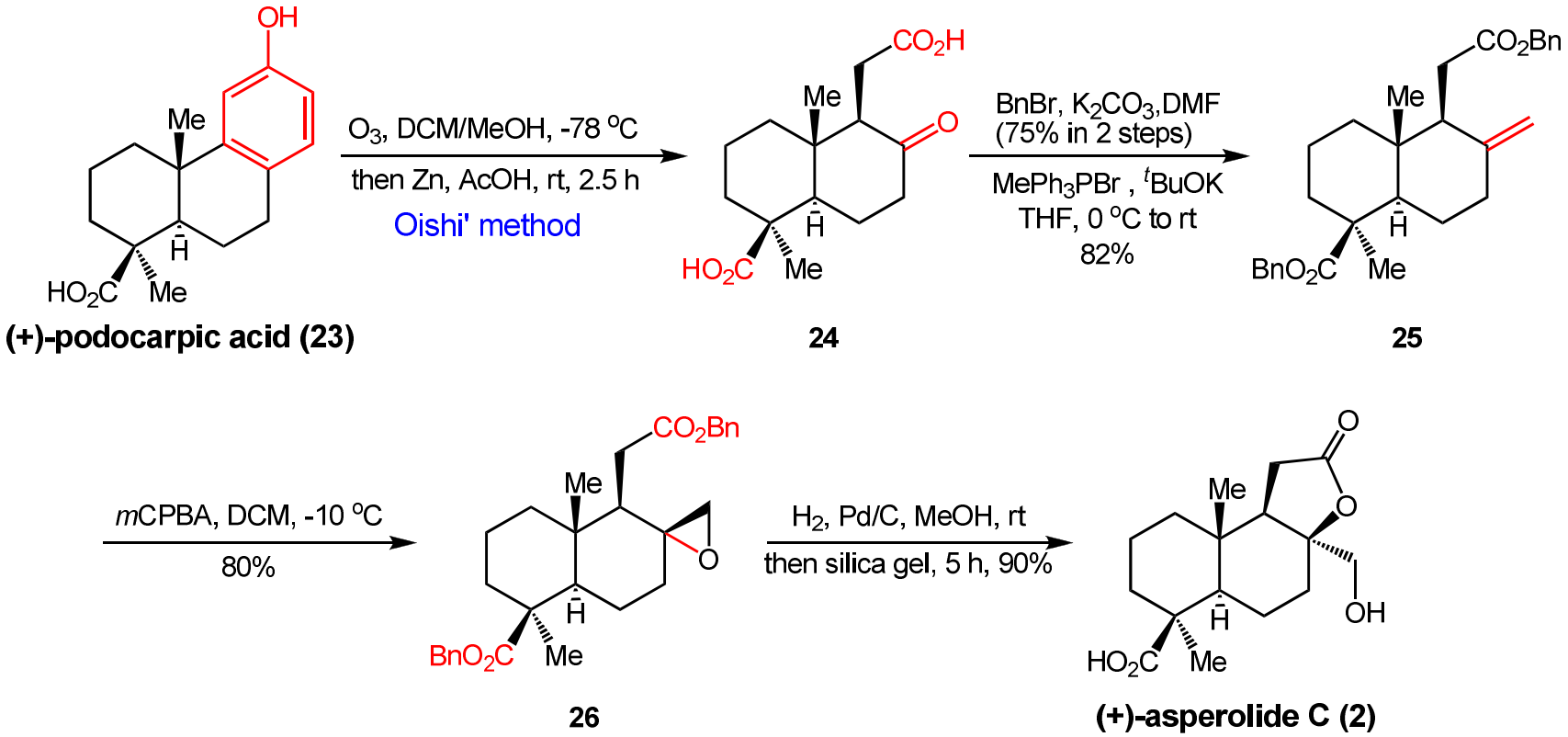
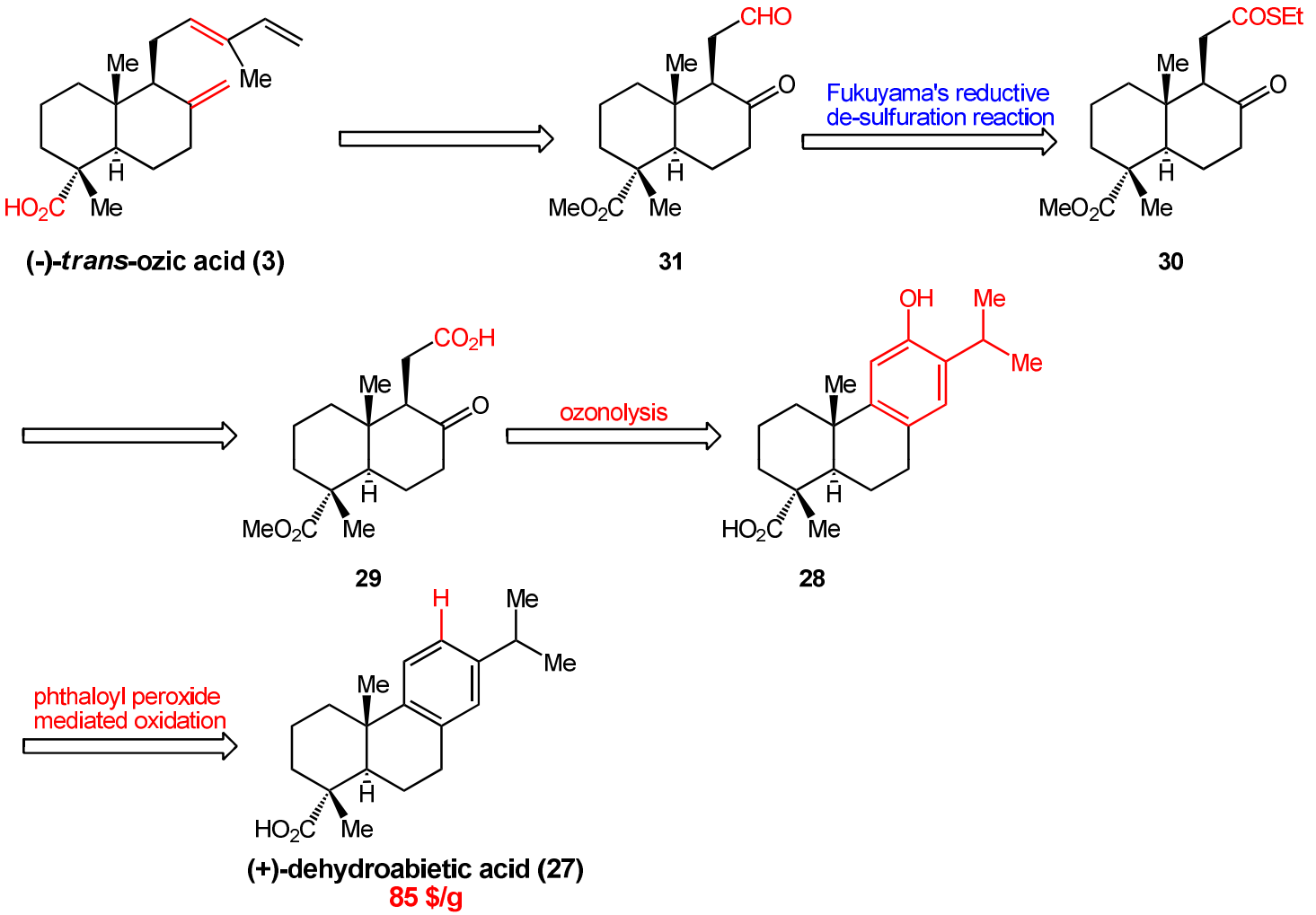
Synthesis of (+)-asperolide C from (+)-podocarpic acid

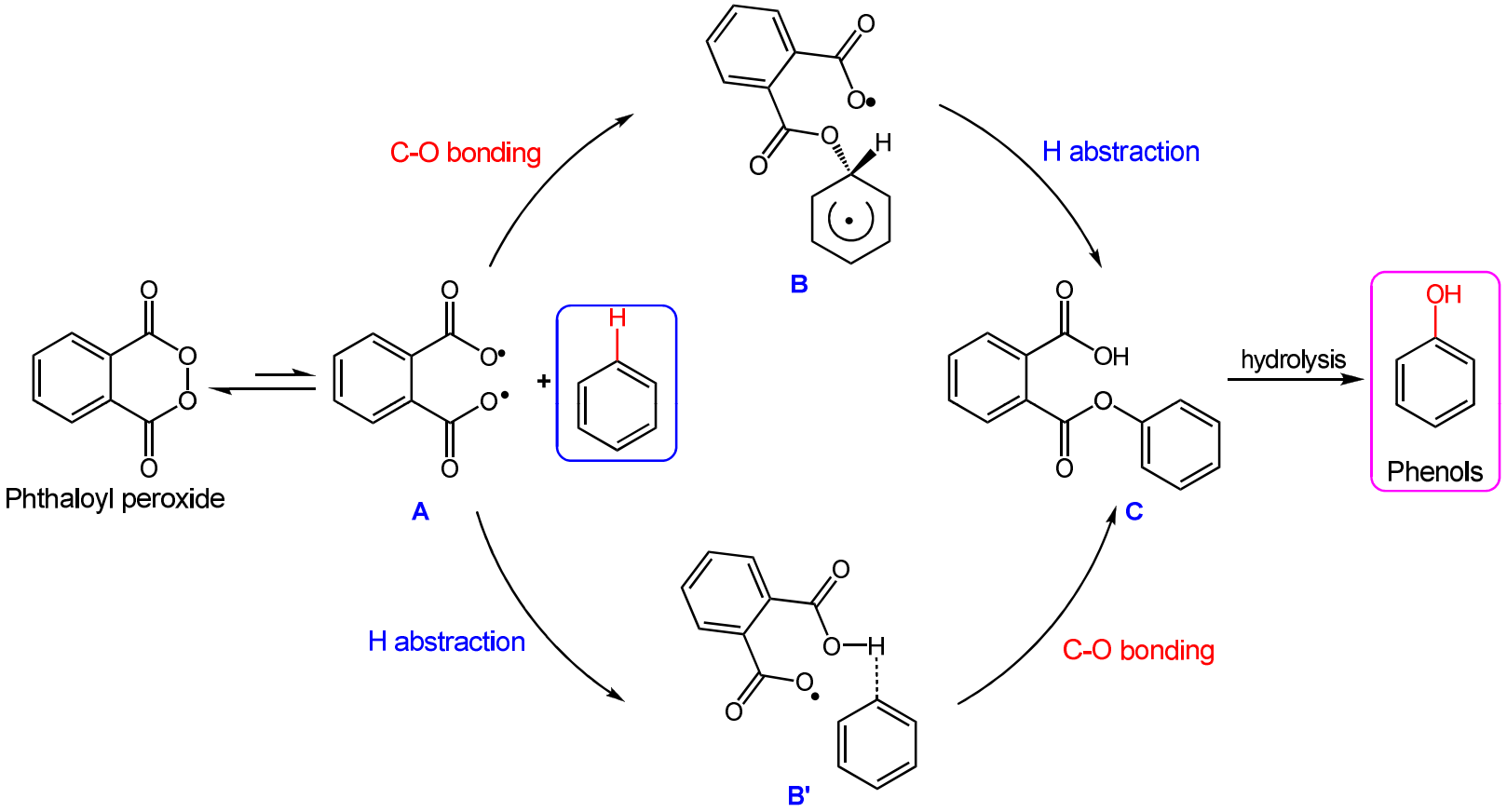


Retrosynthetic analysis



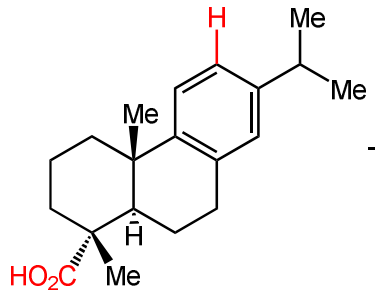
Yang, Z. et al *Chem. Commun.* **2016**, *52*, 12426.

Proposed diradical activation leading to aryl C–H oxidation



Siegel, D. et al *Nature* **2013**, *499*, 192.

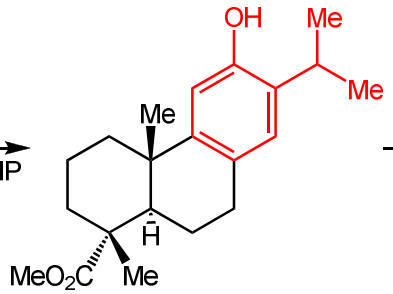
Synthesis of (-)-trans-ozic acid from (+)-dehydroabietic acid



(+)-dehydroabietic acid (27)

1) MeI, K_2CO_3, acetone
rt, overnight, 86%

2) phthaloyl peroxide, HFIP
76%



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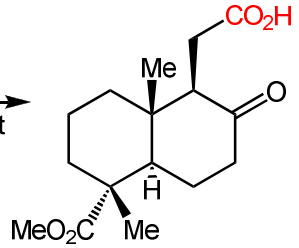
O_3, DCM/MeOH

then Zn, AcOH, rt



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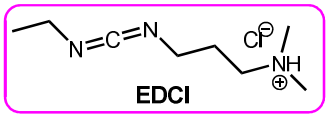
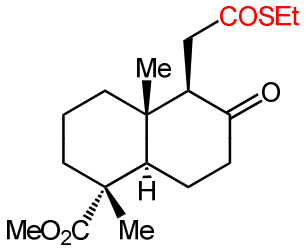
EtSH, EDCI, DMAP

67% in 2 steps



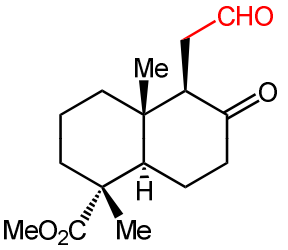


30

Pd/C, Et_3SiH, THF

95%

Fukuyama's reductive de-sulfuration reaction



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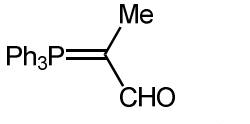
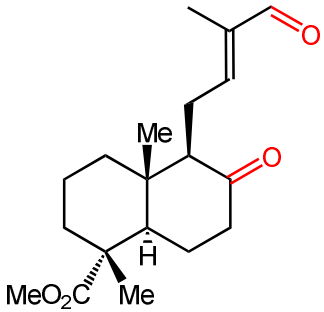


toluene, 110 °C, 24 h
71%



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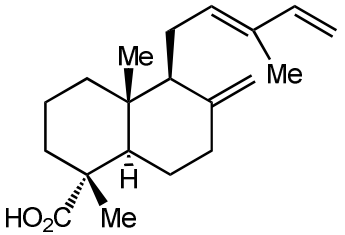
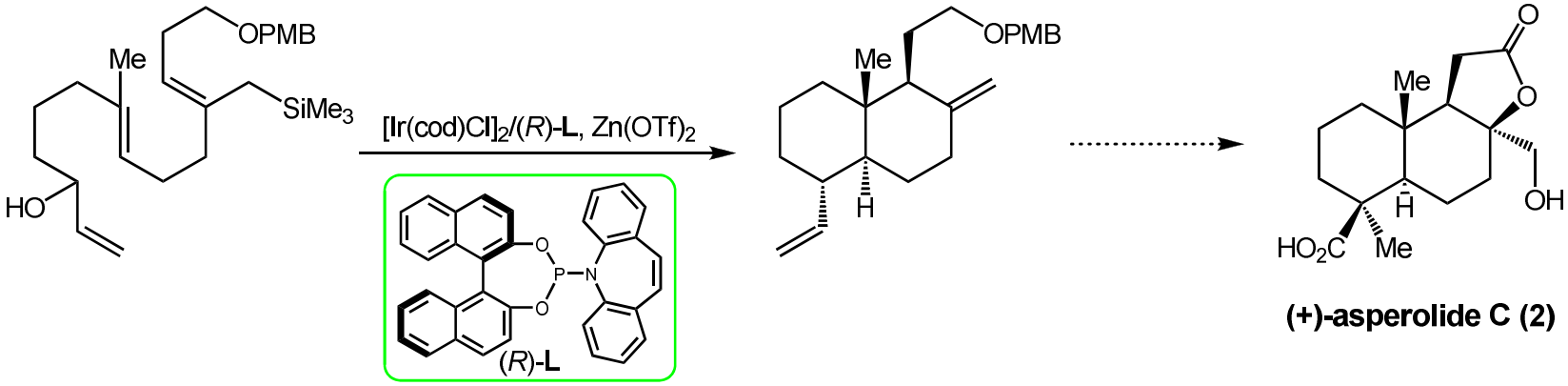
1) $MePPh_3Br$, ^tBuOK
THF, 0 °C to rt, 3 h

2) $LiOH{\bullet}H_2O$, KOH, MeOH
reflux (83% in two steps)



(-)-*trans*-ozic acid (3)

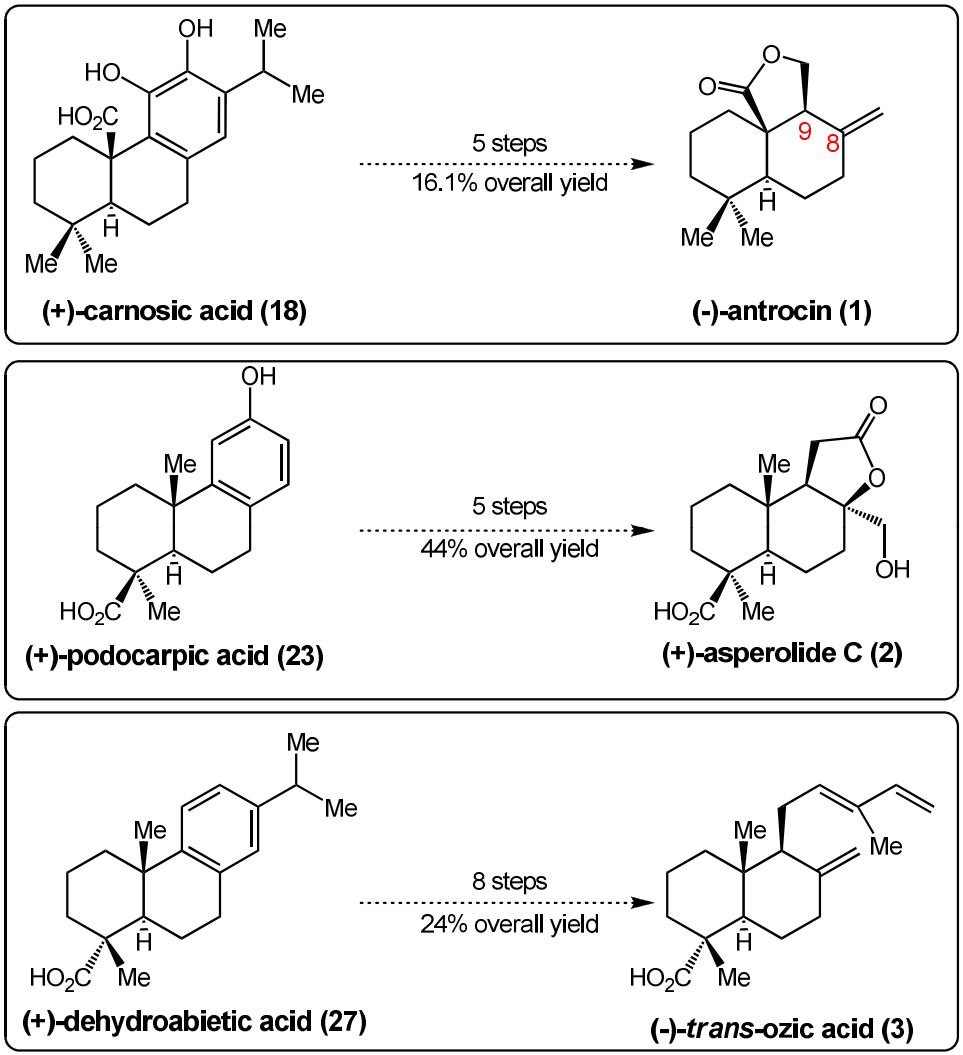
Summary



- **The first total synthesis of (-)-asperolide C.**
- **The asymmetric synthesis of (+)-asperolide C was achieved in 16 steps with 0.6% overall yield.**
- **Iridium-catalyzed asymmetric polyene cyclization as a key step.**

Carreira, E. M. et al *Angew. Chem. Int. Ed.* **2013**, *52*, 12166.

Summary



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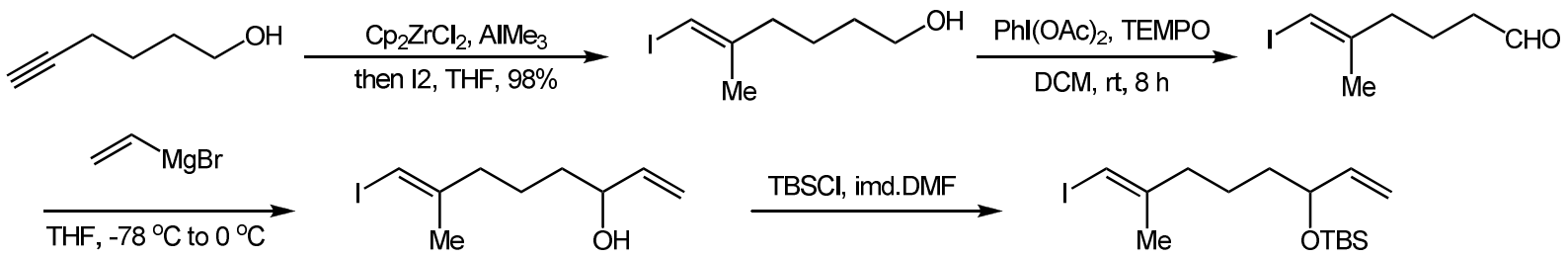
The first paragraph

(-)-Antrocin, (+)-asperolide C, and (-)-*trans*-ozic acid are naturally occurring terpenoids and have been the subject of synthetic interest because of their biological activities. Antrocin (**1**) has been synthesized by us as a racemic mixture *via* a gold-catalyzed tandem reaction of diynes as a key step to construct its drimane core; this total synthesis was achieved in 11 steps with 7.3% overall yield. The total synthesis of asperolide C (**2**) and *trans*-ozic acid (**3**) has been asymmetrically achieved using iridium-catalyzed asymmetric polyene cyclization as a key step.

The last paragraph

In summary, we have developed a unified strategy for the asymmetric syntheses of terpenoids based on a chiral pool strategy from naturally occurring aromatic abietanes using ozonolysis as a key step. This strategy not only achieves the syntheses of (-)-antrocin (**1**), (+)-asperolide C (**2**), and (-)-*trans*-ozic acid (**3**) but also provides an efficient approach to access analogs of these biologically active terpenoids.

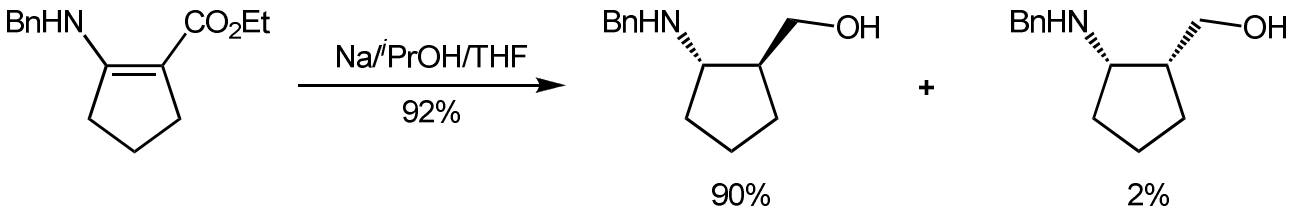
Synthesis of 8



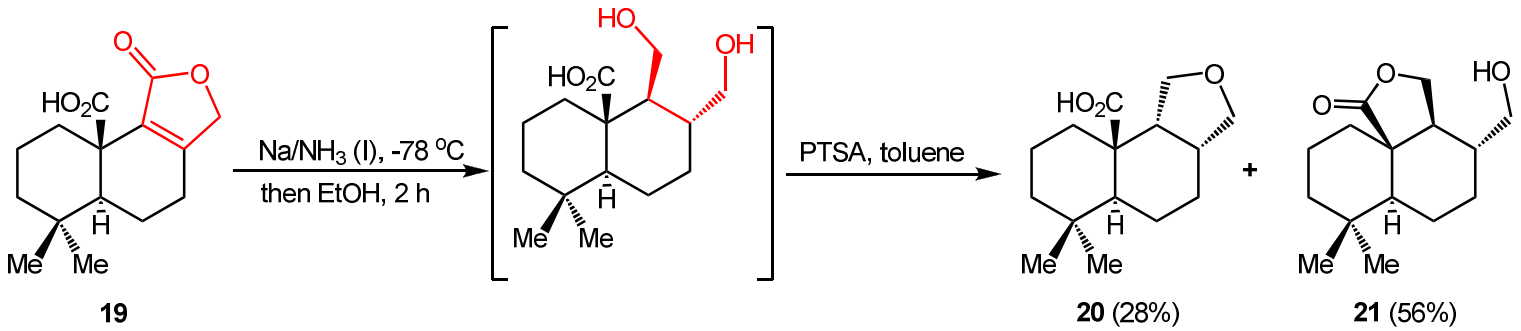
Roush, W. R. et al *J. Am. Chem. Soc*. **2005**, *127*, 16778.

Carreira, E. M. et al *J. Am. Chem. Soc*. **2012**, *134*, 20276.

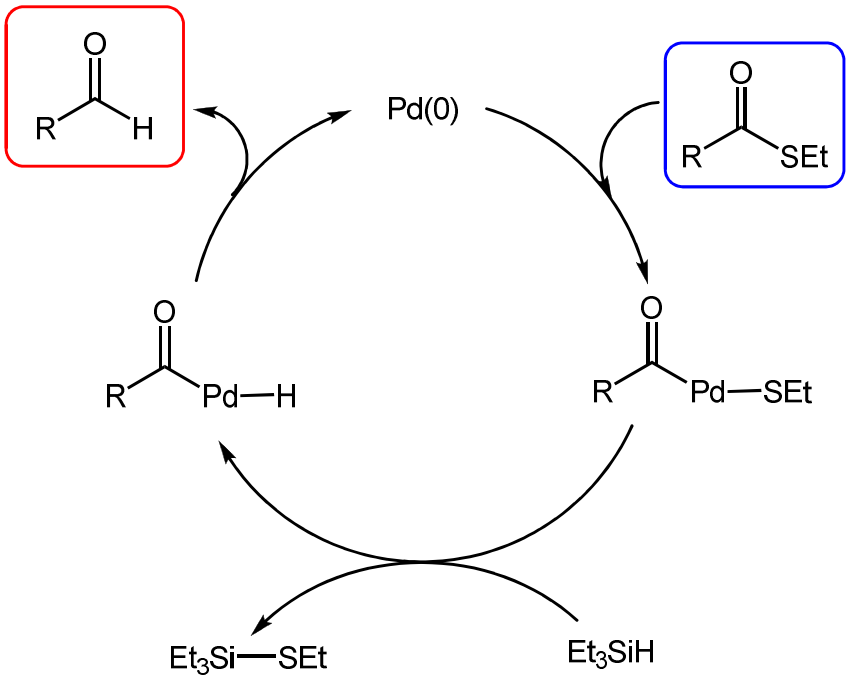
Synthesis of 21



Gellman, S. H. et al *J. Org. Chem.* **2001**, *66*, 5629.



Fukuyama's reductive de-sulfuration reaction



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