Literature Report IV

Enantioselective Synthesis of (+)-Auriculatol A

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Checker: Hao-Dong Chen

Thompson, J. K.; Youngblood, K. C.; Teh, Y. H. S.; Reisman, S. E.* *J. Am. Chem. Soc.* **2025**, *147*, 42170.

2025-11-24

CV of Prof. Sarah E. Reisman

Background:

- ☐ **1997-2001** B.S., Connecticut College
- ☐ **2001-2006** Ph.D., Yale University
- ☐ **2006-2008** Postdoctor, Harvard University
- ☐ **2008-2014** Assistant Professor, California Institute of Technology
- ☐ **2014-now** Professor, California Institute of Technology

Research Field:

- ➢ Total Synthesis of Complex Natural Product

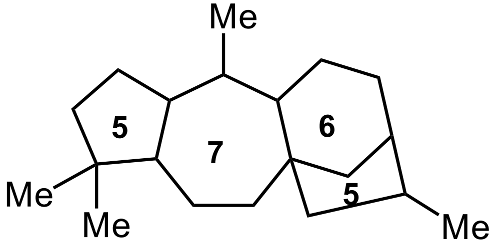
Contents

1 Introduction

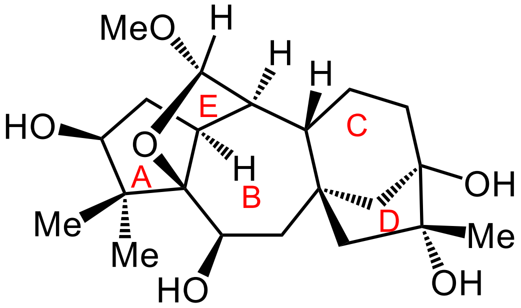
2 Enantioselective Total Synthesis of (+)-Auriculatol A

3 Summary

Introduction



Grayanane



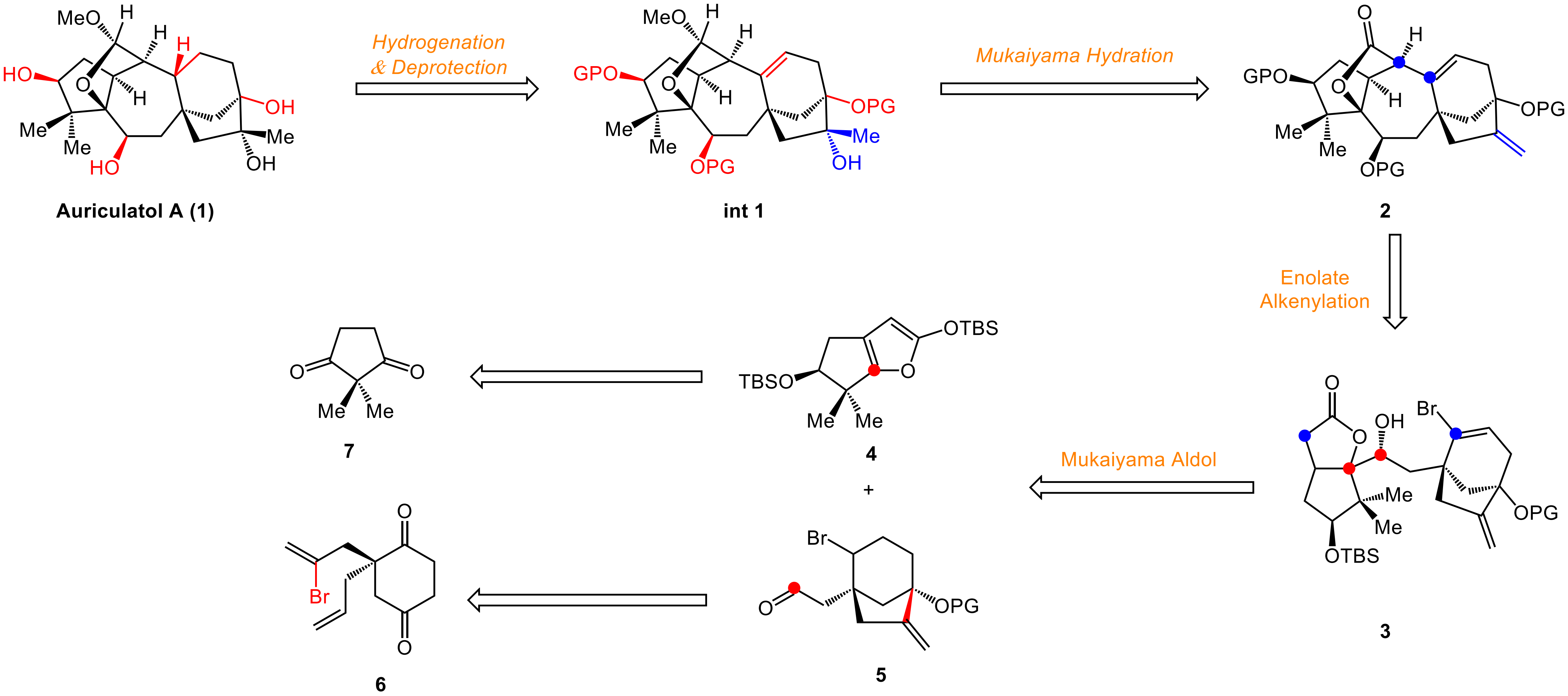
Auriculatol A (1)

Rhododendron auriculatum

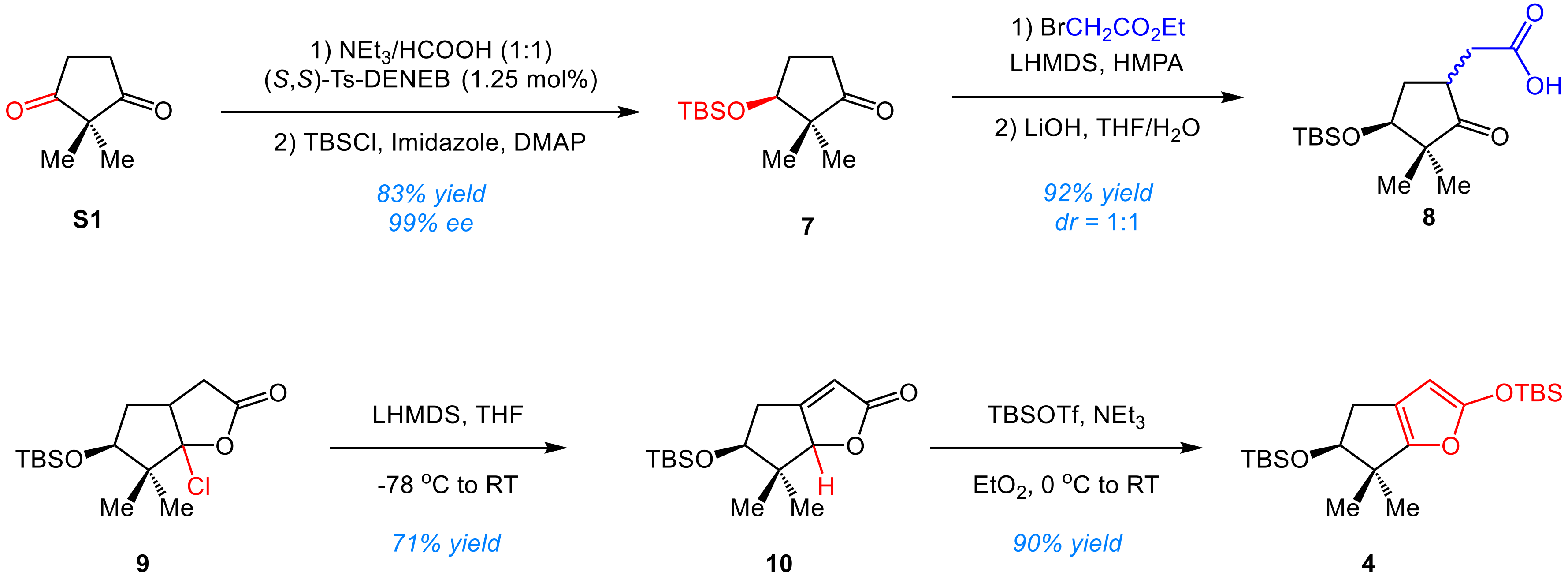
- ➢ Grayanane family of natural products have a common 5/7/6/5 carbon framework;
- ➢ Auriculatol A is a pentacyclic grayanane that was first isolated by Yao group from the leaves of *Rhododendron auriculatum* and shown to possess antinociceptive properties;
- ➢ There have been no prior syntheses of Auriculatol A or grayananes containing an E-ring acetal.

Sun, N.; Zheng, G.; He, M.; Feng, Y.; Liu, J.; Wang, M.; Yao, G.* *J. Nat. Prod.* **2019**, *82*, 1849.

Retrosynthetic Analysis



Synthesis of Compound 4



S1

1) NEt_3/HCOOH (1:1)
(*S*,*S*)-Ts-DENEB (1.25 mol%)

2) TBSCl, Imidazole, DMAP

83% yield
99% ee

7

1) $BrCH_2CO_2Et$
LHMDS, HMPA

2) LiOH, THF/H_2O

92% yield
dr = 1:1

8

$SOCl_2$, DCM

RT to 40 ^oC

77% yield

9

LHMDS, THF

-78 ^oC to RT

71% yield

10

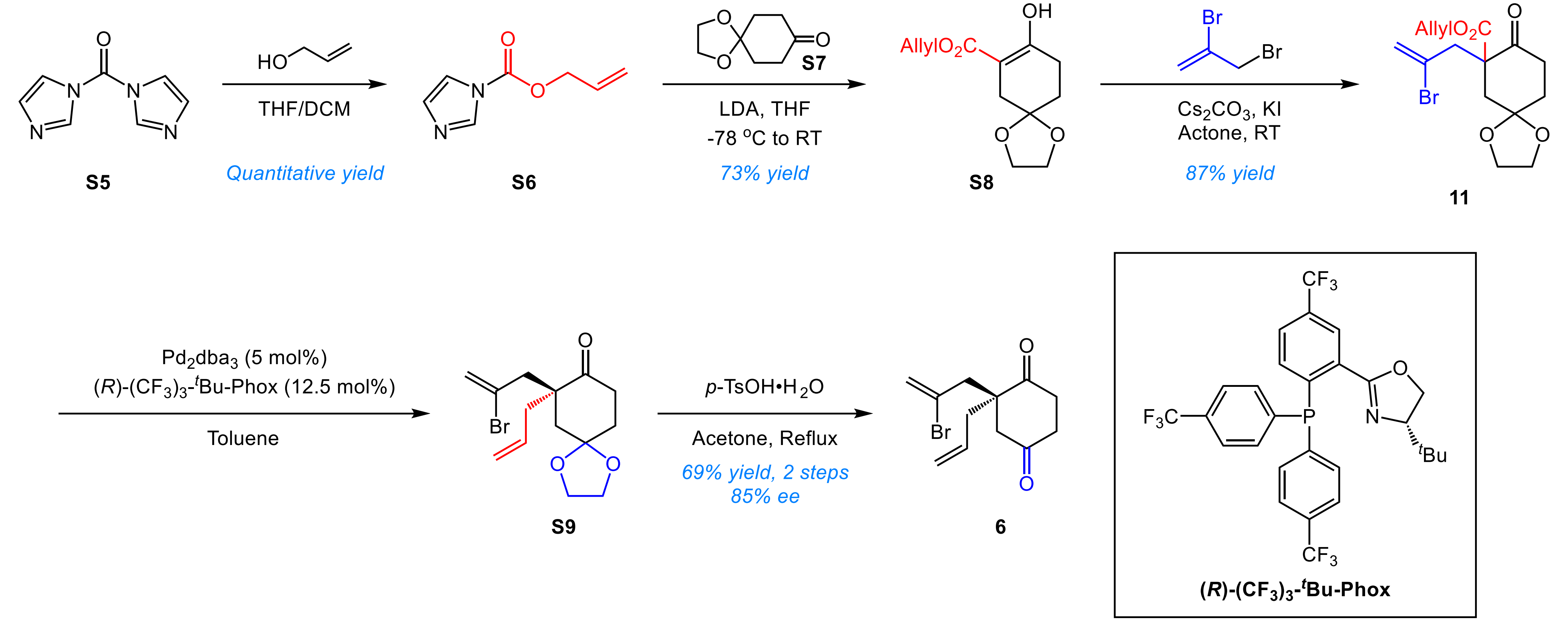
TBSOTf, NEt_3

EtO_2, 0 ^oC to RT

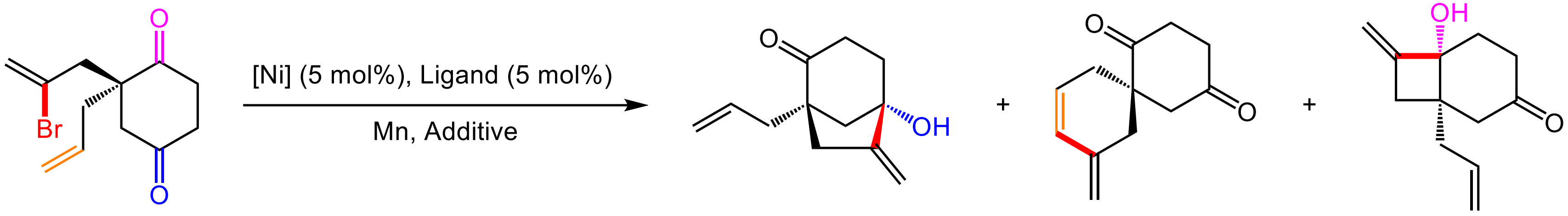
90% yield

4

Synthesis of Compound 6



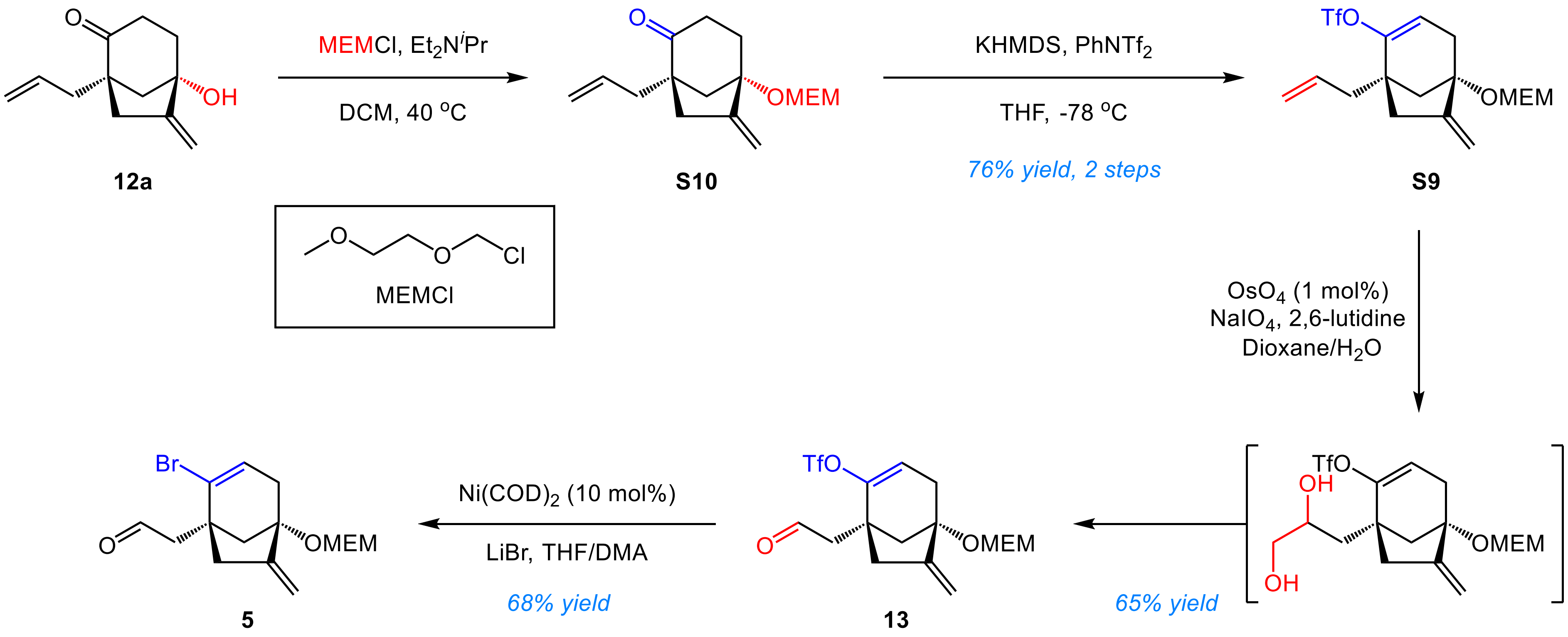
Synthesis of Compound 12a



6 12a 12b 12c

Entry	Conditions	Yield of **12a** (%)	Yield of **12b** (%)	Yield of **12c** (%)
1	Ni(COD)$_2$, Bpy, Mn, MgCl$_2$	<3	17	---
2	Ni(COD)$_2$, Bphen, Mn, MgCl$_2$	<3	25	---
3	Ni(COD)$_2$, Terpy, Mn, MgCl$_2$	43	---	---
4	NiBr$_2$•DME, Terpy, Mn, MgI$_2$	56	---	--
5	NiBr$_2$•DME, Terpy, Mn	68	---	---

Synthesis of Compound 5



12a

MEMCl, Et_2N^iPr

DCM, 40 ^oC

S10

KHMDS, $PhNTf_2$

THF, -78 ^oC

76% yield, 2 steps

S9

MEMCl

OsO_4 (1 mol%)
$NaIO_4$, 2,6-lutidine
Dioxane/H_2O

65% yield

13

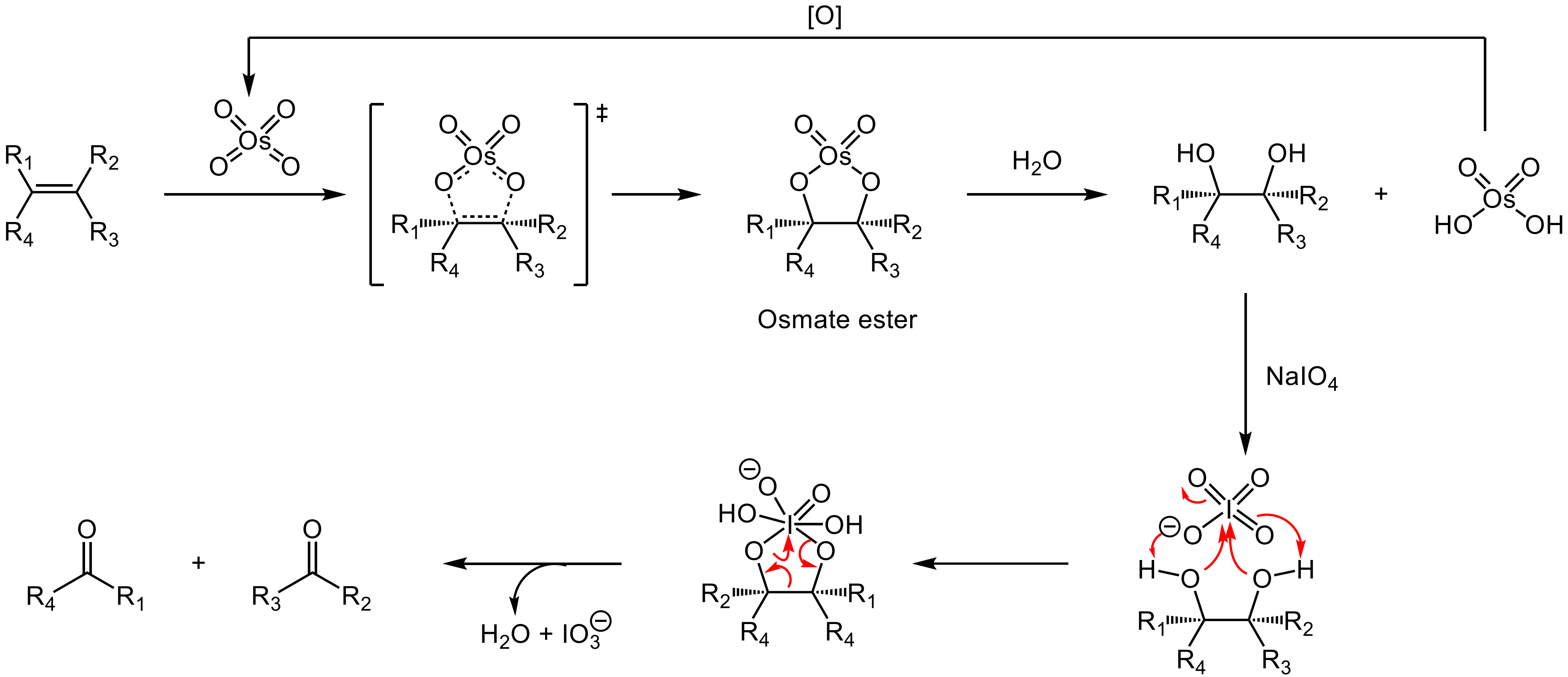
$Ni(COD)_2$ (10 mol%)

LiBr, THF/DMA

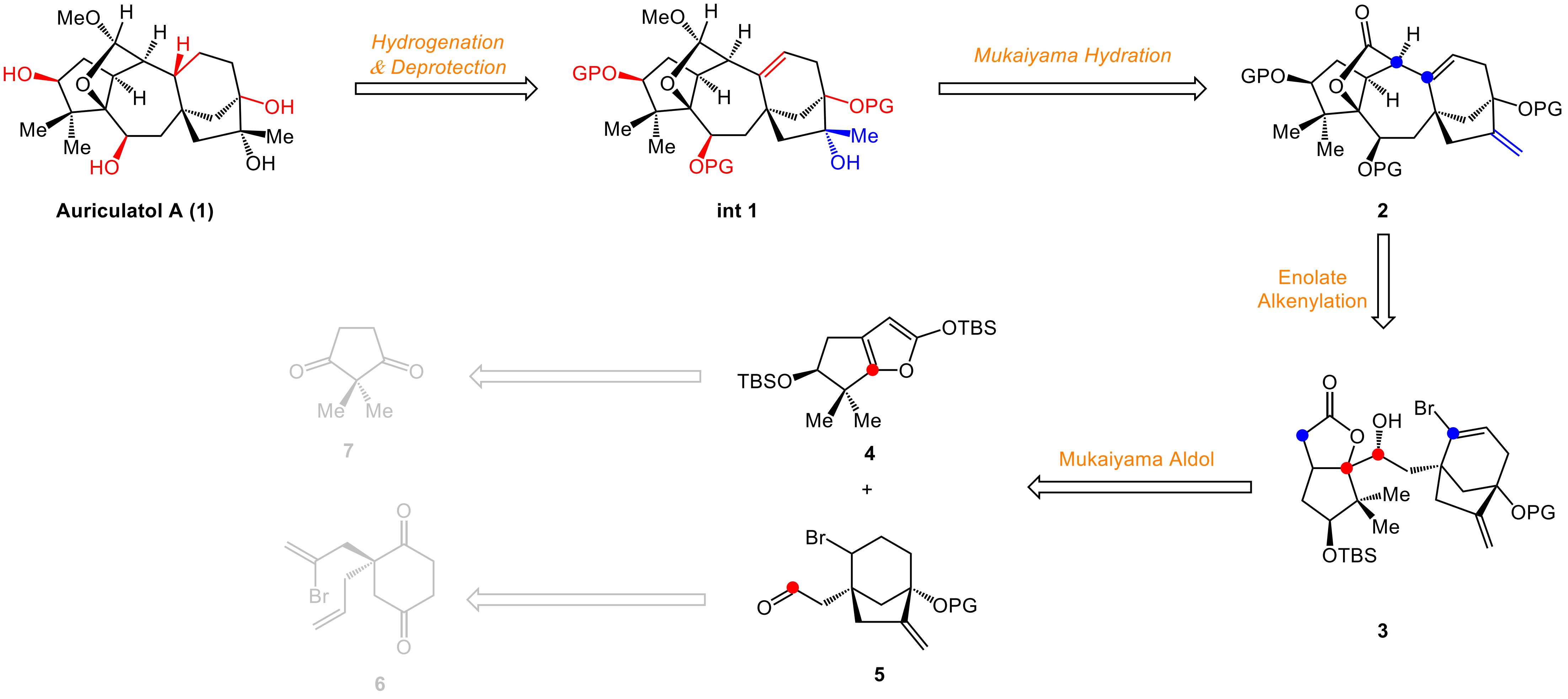
68% yield

5

Lemieux-Johnson Oxidation



Retrosynthetic Analysis



Auriculatol A (1)

Hydrogenation & Deprotection

int 1

Mukaiyama Hydration

2

Enolate Alkenylation

3

Mukaiyama Aldol

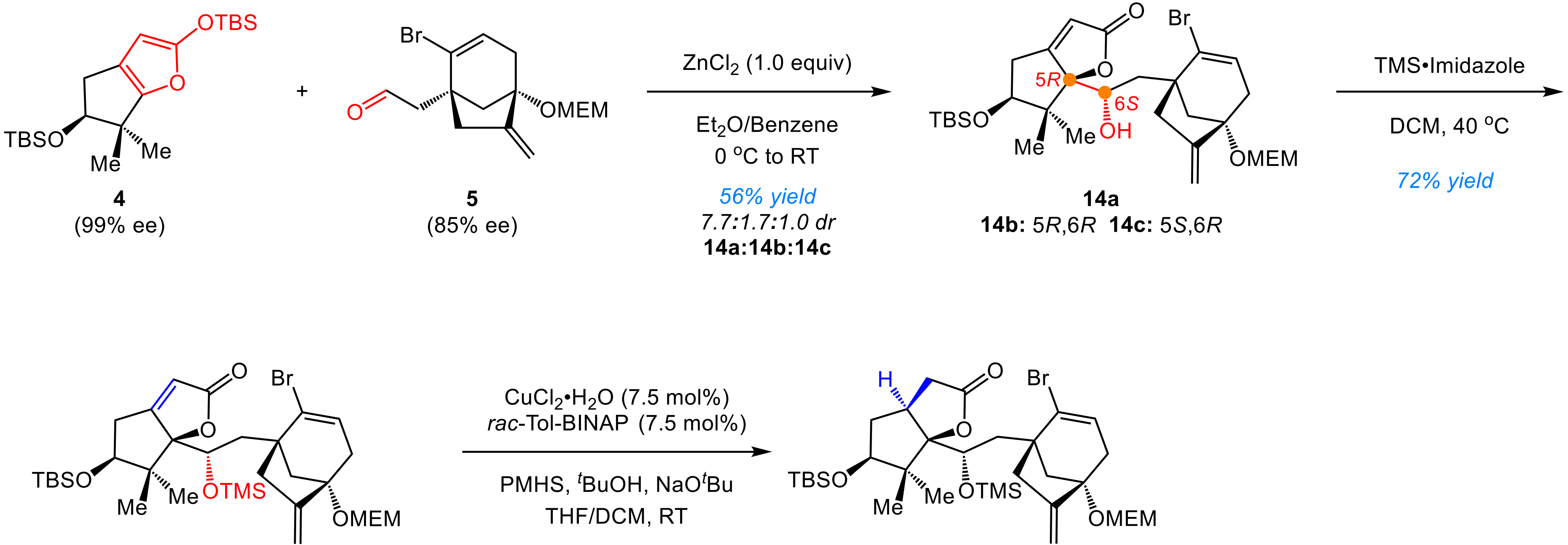
4

5

7

6

Synthesis of Compound 16



4
(99% ee)

+

5
(85% ee)

$ZnCl_2$ (1.0 equiv)
Et_2O/Benzene
0 ^oC to RT
56% yield
7.7:1.7:1.0 dr
14a:14b:14c

14a
14b: 5*R*,6*R* **14c:** 5*S*,6*R*

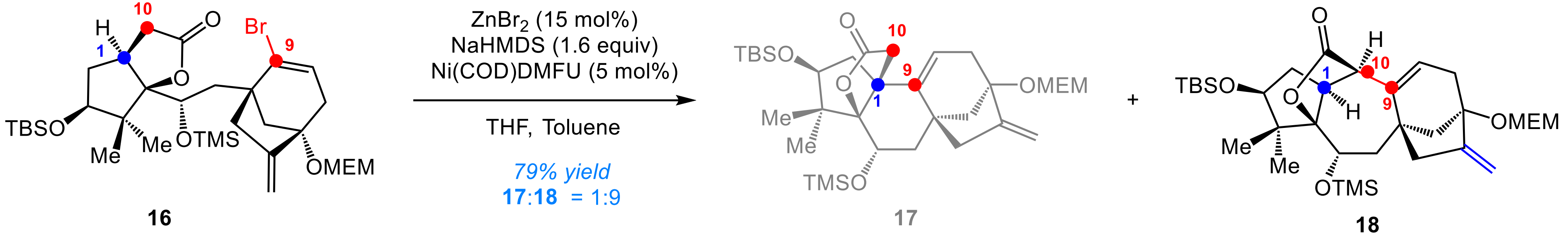
TMS•Imidazole
DCM, 40 ^oC
72% yield

15

$CuCl_2$•H_2O (7.5 mol%)
rac-Tol-BINAP (7.5 mol%)
PMHS, ^{t}BuOH, NaO^{t}Bu
THF/DCM, RT
>20:1 dr, 85% yield

16

Synthesis of Compound 19



$ZnBr_2$ (15 mol%)
NaHMDS (1.6 equiv)
Ni(COD)DMFU (5 mol%)

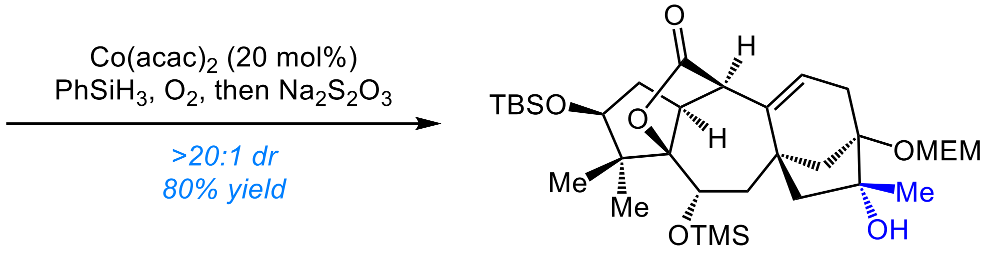
THF, Toluene

79% yield
17:**18** = 1:9

16

17

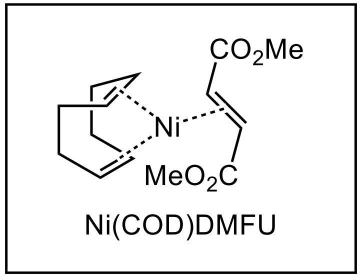
18



$Co(acac)_2$ (20 mol%)
$PhSiH_3$, O_2, then $Na_2S_2O_3$

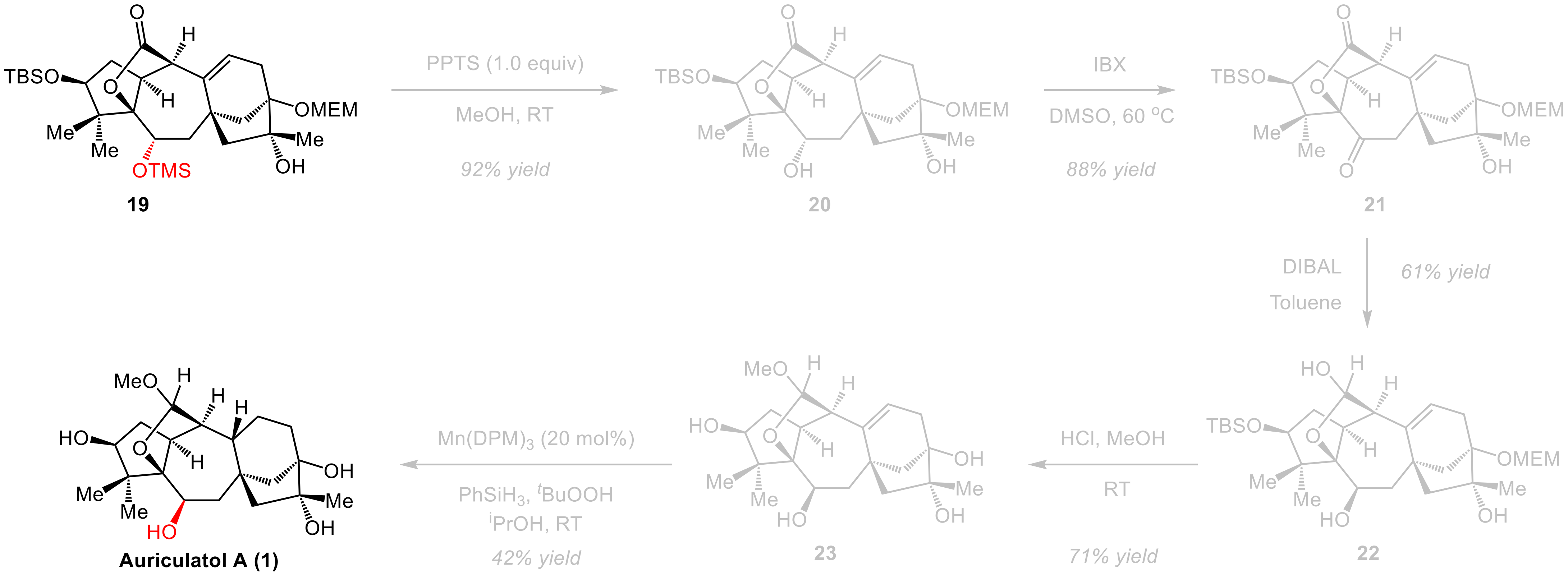
>20:1 dr
80% yield

19



Ni(COD)DMFU

Synthesis of Compound Auriculatol A



19

PPTS (1.0 equiv)

MeOH, RT

92% yield

20

IBX

DMSO, 60 °C

88% yield

21

DIBAL

Toluene

61% yield

22

HCl, MeOH

RT

71% yield

23

$Mn(DPM)_3$ (20 mol%)

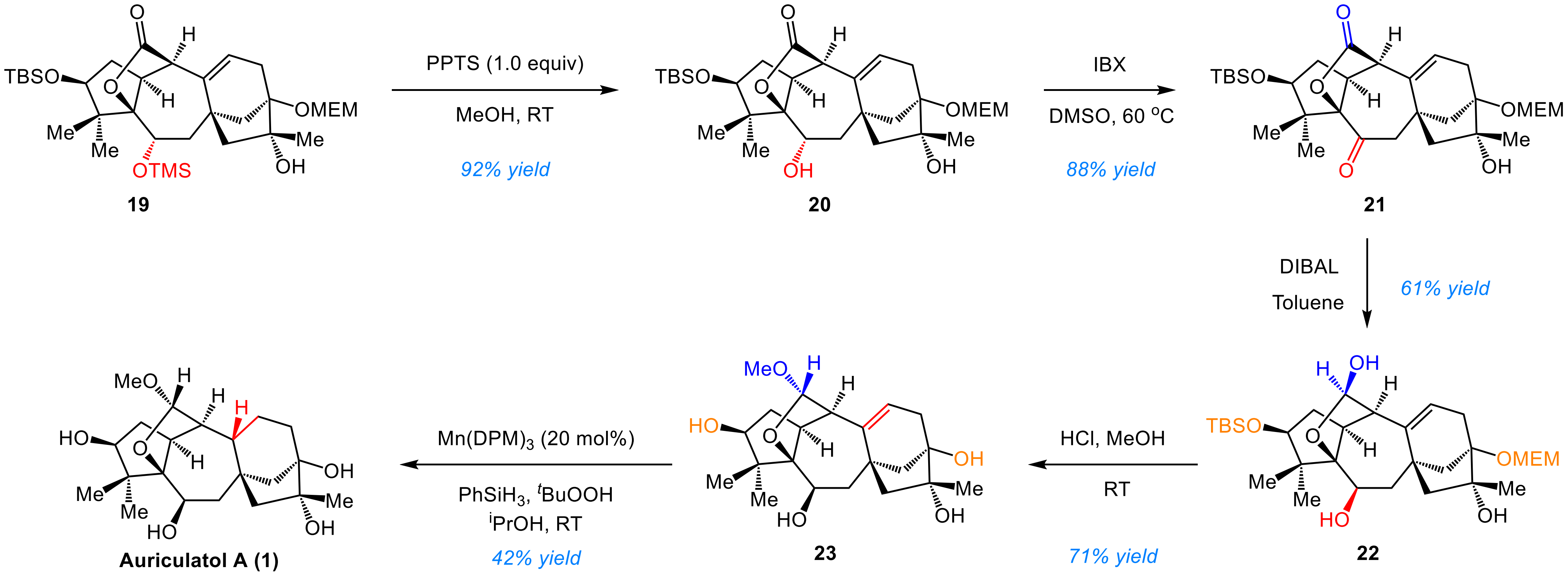
$PhSiH_3$, ${}^tBuOOH$

${}^iPrOH$, RT

42% yield

Auriculatol A (1)

Synthesis of Compound Auriculatol A



19 → **20**: PPTS (1.0 equiv), MeOH, RT, *92% yield*

20 → **21**: IBX, DMSO, 60 °C, *88% yield*

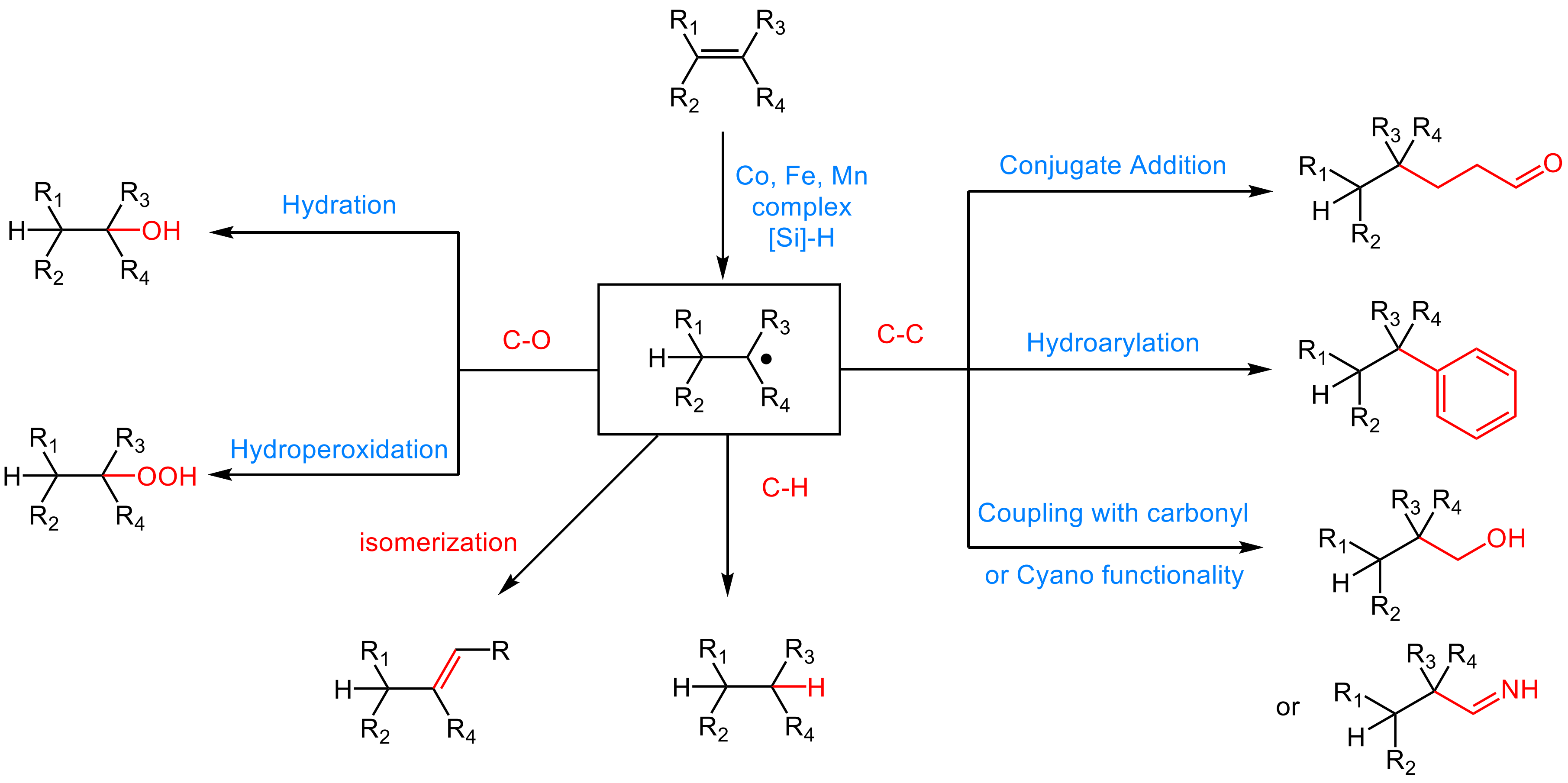
21 → **22**: DIBAL, Toluene, *61% yield*

22 → **23**: HCl, MeOH, RT, *71% yield*

23 → **Auriculatol A (1)**: Mn(DPM)$_3$ (20 mol%), PhSiH$_3$, ^{t}BuOOH, ^{i}PrOH, RT, *42% yield*

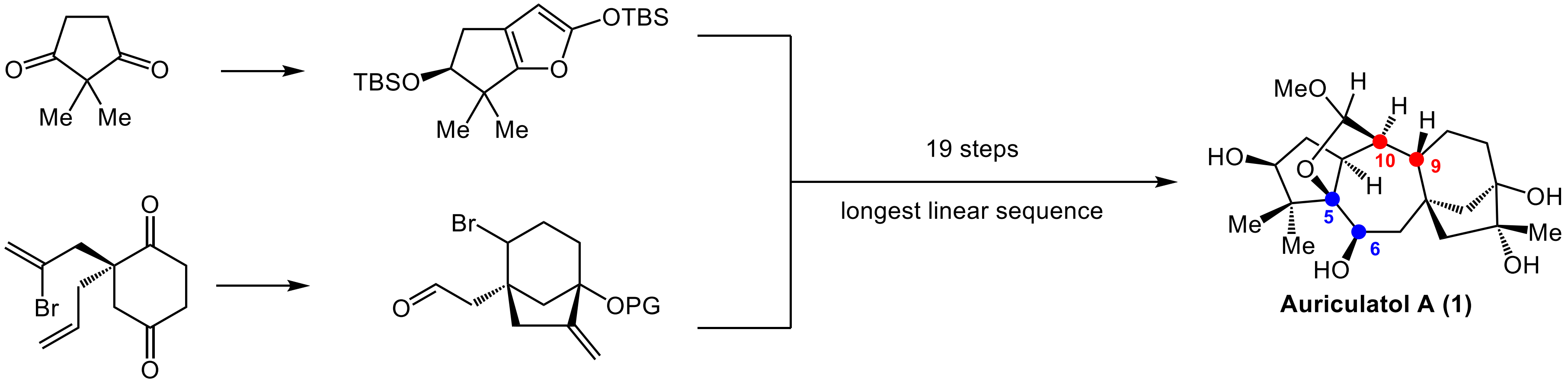
Metal-Hydride Hydrogen Atom Transfer (MHAT) Reactions

MHAT-based reactions of olefins



Wu, J.; Ma, Z. *Org. Chem. Front.*, **2021**, *8*, 7050.

Summary



Auriculatol A (1)

- The first enantioselective total synthesis of (+)-Auriculatol A was completed in 19 steps;
- An intramolecular Ni-catalyzed 1,2-addition was developed to get the bicyclo[3.2.1] octane fragment;
- The synthesis forged the C5−C6 bond through a vinylogous Mukaiyama-aldol reaction;
- An intramolecular Ni-catalyzed enolate alkenylation was used to construct the central 7-membered ring.

Writing Strategy

- **First paragraph**

Introduction

Biological activity

The grayananes comprise more than 400 oxidized diterpenes isolated from the *Ericaceae* family of plants.

These diterpenoids are best known for their activity as modulators of voltage-gated sodium ion channels and are the molecular constituents associated with poisoning from honey produced during the pollination of rhododendrons. Although toxic when ingested in large amounts, in lower doses, grayananes can induce antinociception in mice. In addition, grayananes and related compounds have been reported to inhibit PTP1B and carbonic anhydrase.

Writing Strategy

- **Last paragraph**

Summary

Key Steps

In conclusion, the first total synthesis of (+)-auriculatol A was completed in 19 steps from 1,4-dioxaspiro[4.5]decan-8 one.

The synthesis forged the C5−C6 bond through a vinylogous Mukaiyama-aldol reaction, leveraging the intrinsic reactivity of siloxyfurans for γ-functionalization. An intra molecular Ni-catalyzed enolate alkenylation was used to construct the central 7-membered ring, providing access to the grayanane scaffold in a modular fashion. These studies identified Ni(COD)DMFU as an effective catalyst for butyrolactone enolate alkenylation. Finally, an intramolecular Ni-catalyzed 1,2-addition was developed to access the bicyclo[3.2.1]octane fragment, a method that may be useful for the synthesis of other diterpenoid natural products.

Representative Examples

- Structurally, auriculatol A has a 5/7/6/5 carbon framework common to the larger grayanane family of natural products but is differentiated by the presence of a bridging E-ring acetal. (differentiate *v*. 区分，区别，辨别；区别对待)

- A key discovery was the use of Ni(COD)DMFU as the catalyst for this transformation, which has not previously been deployed for enolate alkenylation. (deploy, *vt*. 使展开；部署；施展)

- Cleavage of the TMS ether with PPTS furnished alcohol **20**, which was oxidized with IBX to ketone **21**. (furnish *vt*. 陈设，布置；提供)

Acknowledgement

Thank You for Your Attention!