Literature Report 3

Enantioselective Total Synthesis of Berkeleyone A and Preaustinoids

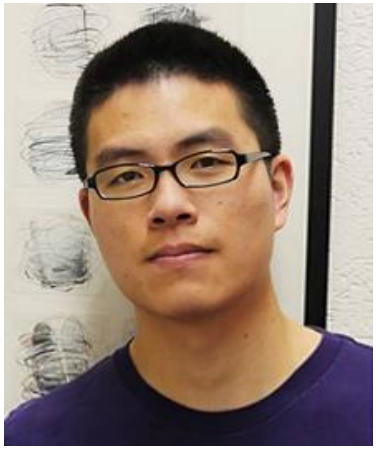
Reporter: Tong Niu

Checker: Shanshan Xun

Ting, C. P.; Xu, G.; Maimone, T. J. *J. Am. Chem. Soc.* **2016**, *138*, 14868
Zhang, Y.; Ji, Y.; Li, H. *Angew. Chem. Int. Ed.* **2021**, *60*, 14869

2022.01.10

CV of Prof. Houhua Li (黎后华)



Research:

- Total Synthesis of Bioactive Natural Products
- Cellular Targets Identification and Elucidation of the Mechanism of Action of Natural Products
- Natural Product Research for Translational Medicine and Therapeutics

Education & Professional Experience:

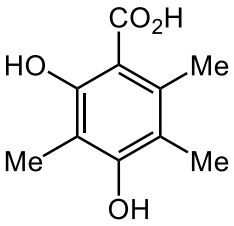
- **2002-2006** B.S. in Pharmaceutical Sciences, Peking University
- **2006-2009** M.S. in Chemical Biology, Peking University
- **2009-2011** Research Assistant, National Institute of Biological Sciences
- **2011-2016** Ph.D. in Organic Chemistry, University of Geneva
- **2016-2019** Postdoc, Max Planck Institute of Molecular Physiology
- **2019-Present** Tenure-Track Assistant Professor, Peking University

Contents

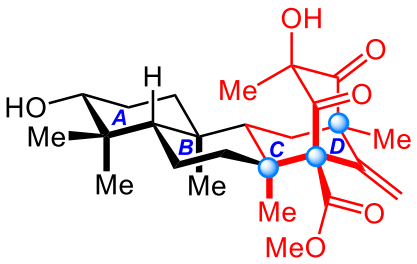
Introduction

Isolation of their first congener—1976

terpenoids ⟹ (*metabolized*) meroterpenoids ⟹ fungal meroterpenoids derived from DMOA



3,5-dimethyl-orsellinic acid (DMOA)

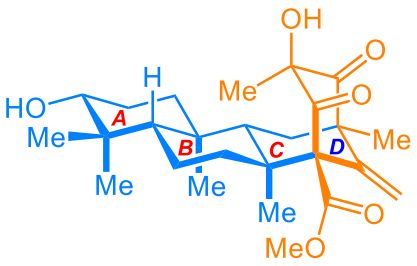


(–)-berkeleyone A (**1**)

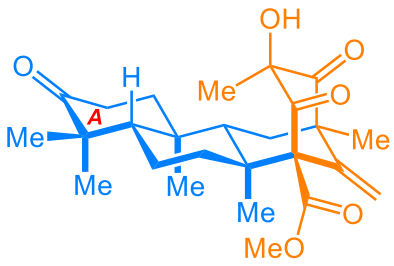
- Dense (稠密的) tetracyclic framework
  - Bicyclo[3.3.1]nonane core
- Three quaternary carbon within C-ring
- Highly oxidized D-ring without any hydrogen-atom substituents

Introduction

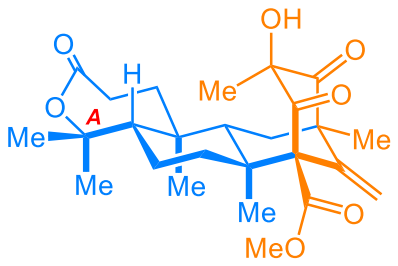
☐ Representative Structures



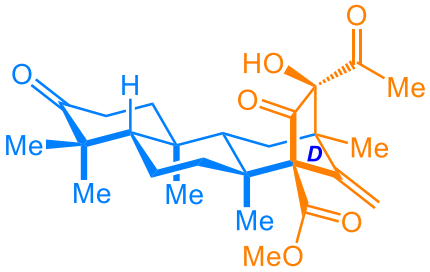
(–)-berkeleyone A (**1**)
anti-inflammatory



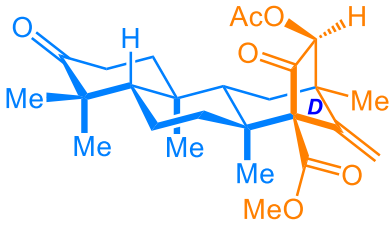
(–)-preaustinoid A (**2**)
caspase-1 inhibitor



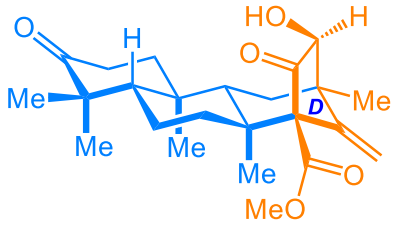
(–)-preaustinoid A1 (**3**)
caspase-1 inhibitor



(–)-preaustinoid B (**4**)

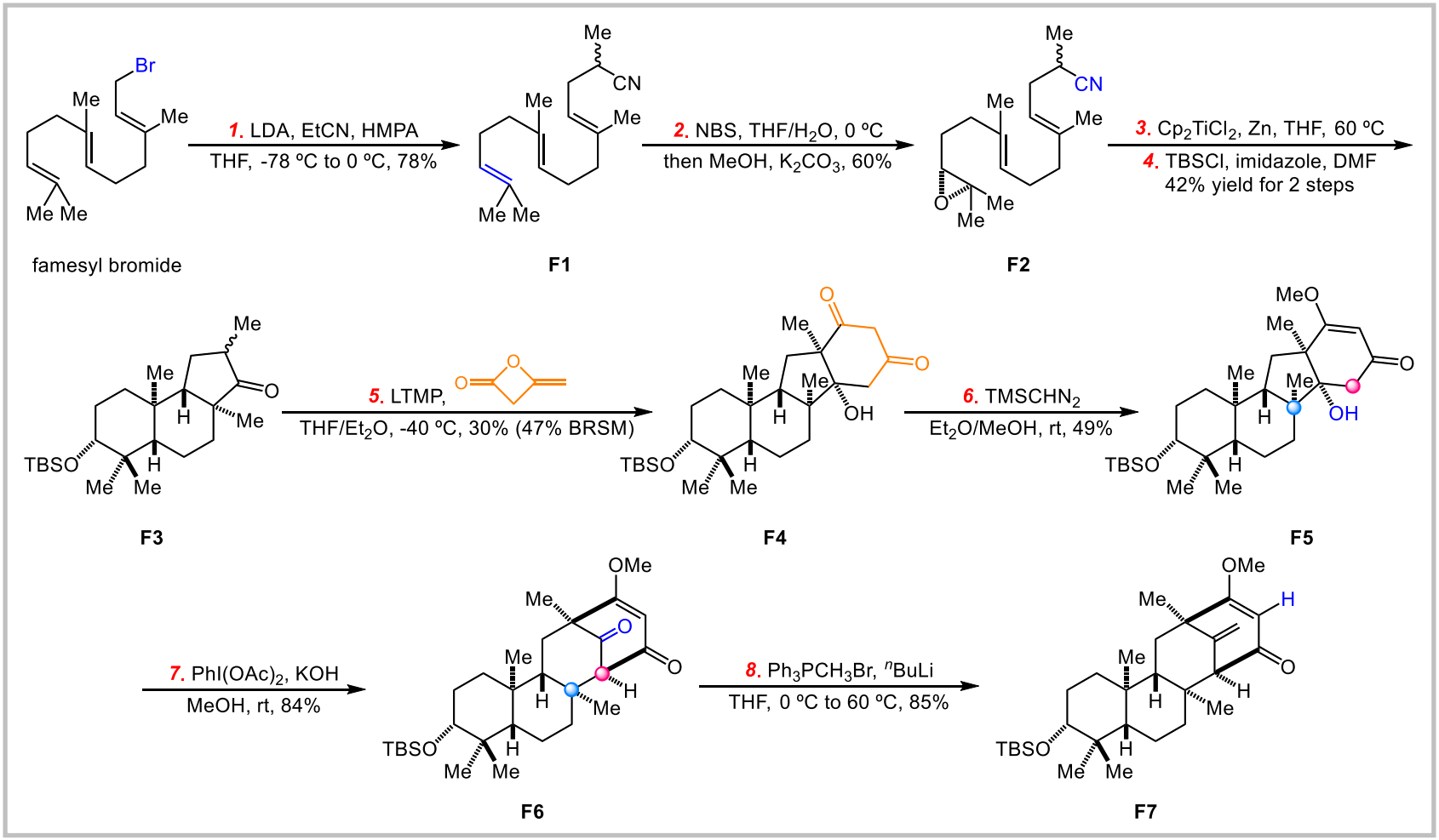


(–)-preaustinoid B1 (**5**)

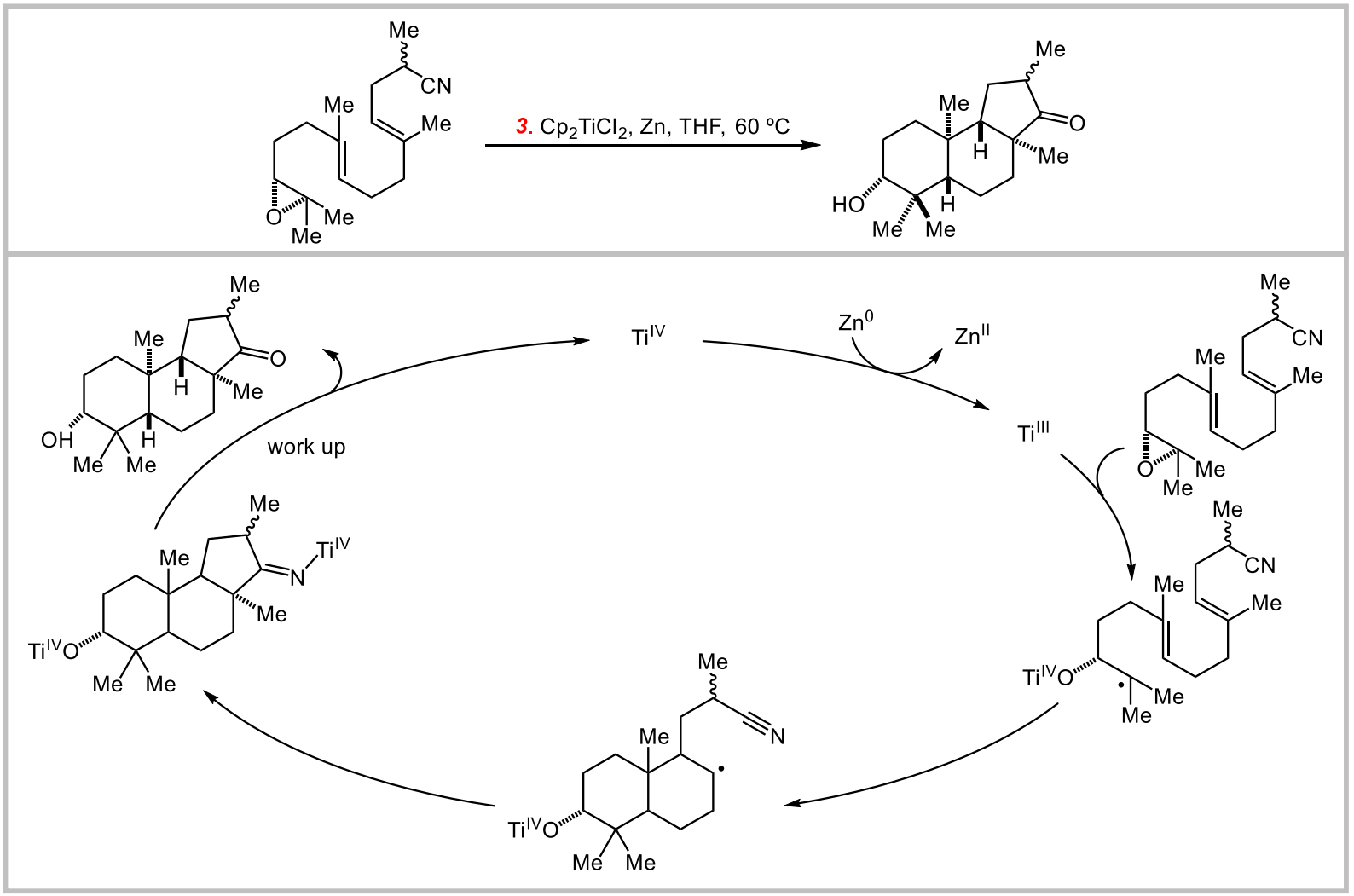


(+)-preaustinoid B2 (**6**)

Synthesis of (±)-Berkeleyone A

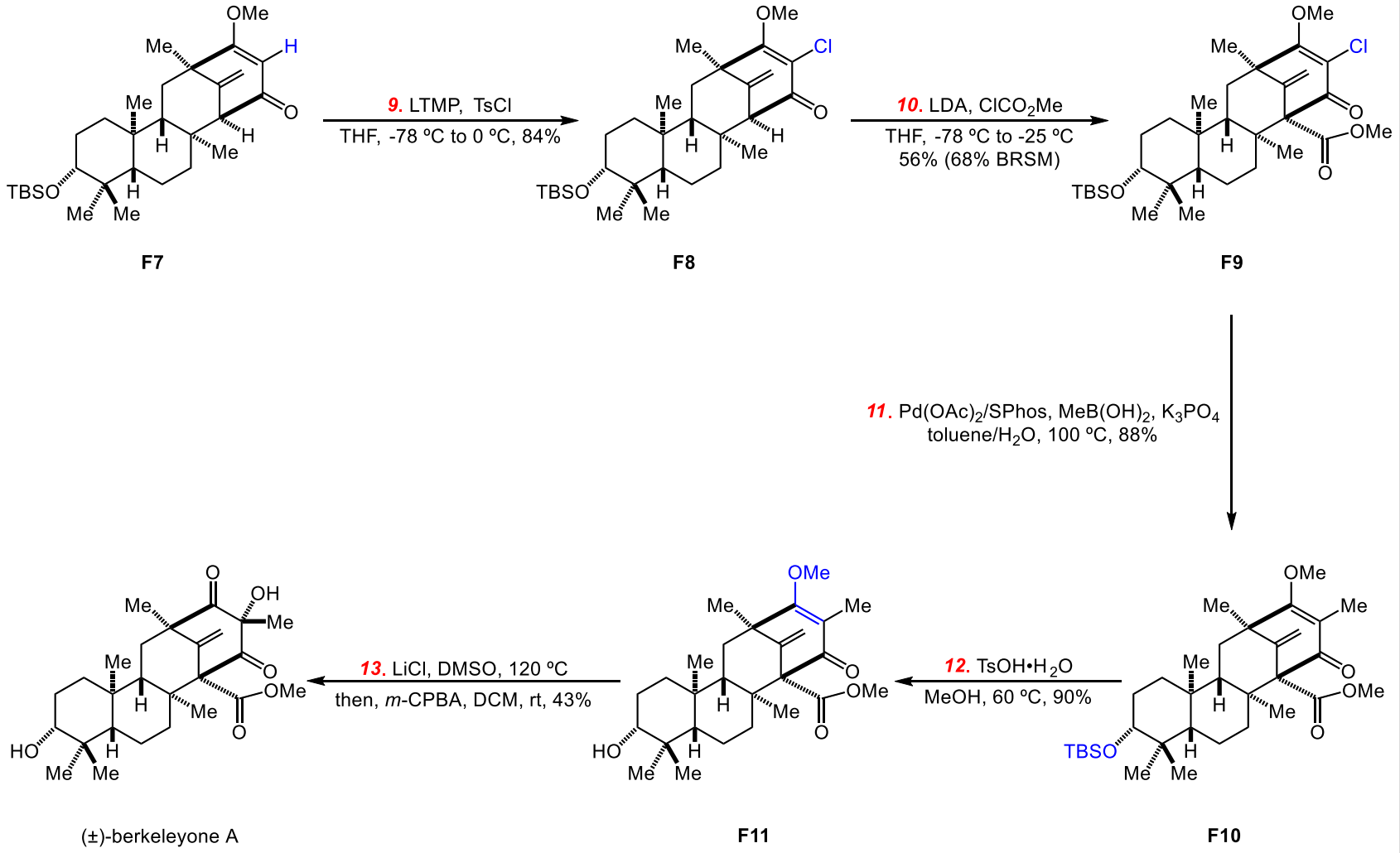


Ti(III)-Mediated Radical Cyclization

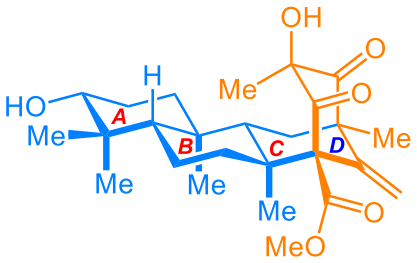


Justicia, J.; Rosales, A.; Cuerva, J. M. *Chem. Eur. J.* **2004**, *10*, 1778

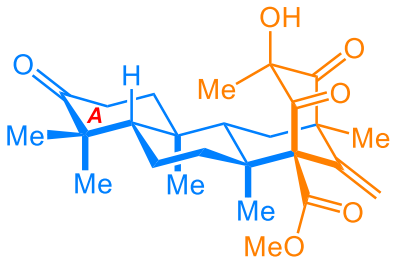
Synthesis of (±)-Berkeleyone A



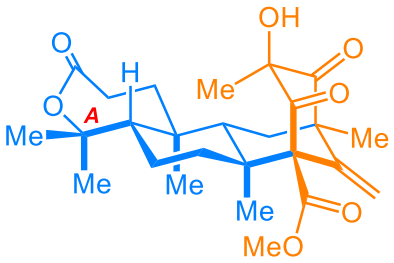
Enantioselective Synthesis of Berkeleyone A and Preaustinoids



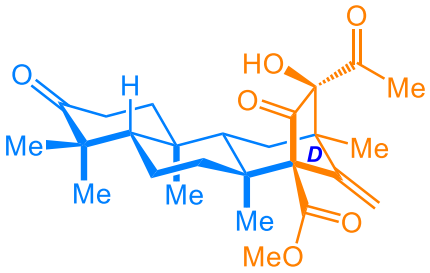
(–)-berkeleyone A (**1**)
anti-inflammatory



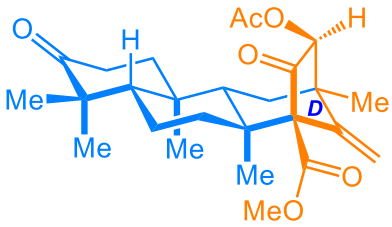
(–)-preaustinoid A (**2**)
caspase-1 inhibitor



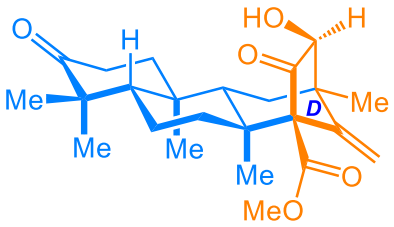
(–)-preaustinoid A1 (**3**)
caspase-1 inhibitor



(–)-preaustinoid B (**4**)



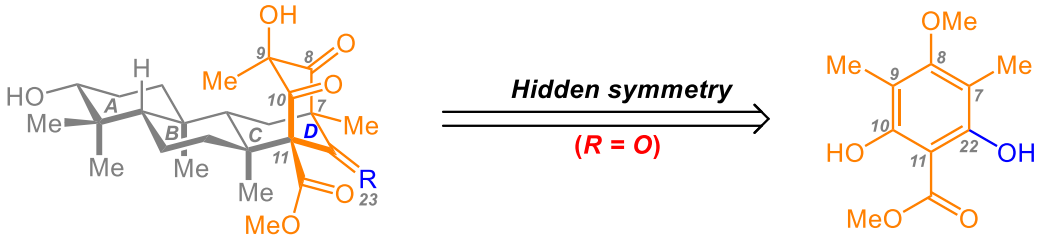
(–)-preaustinoid B1 (**5**)



(+)-preaustinoid B2 (**6**)

Retrosynthetic Analysis

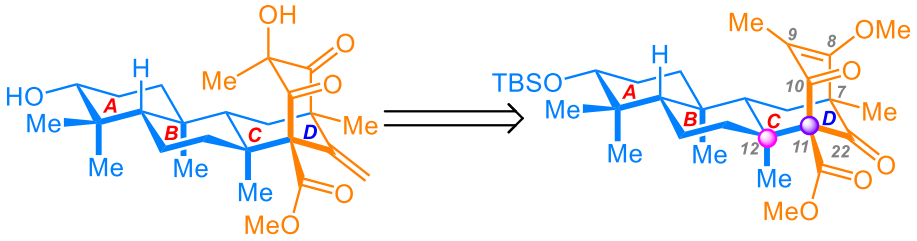
♣*Hidden symmetry recognition within the D-ring*



1, $R = CH_2$ **7**

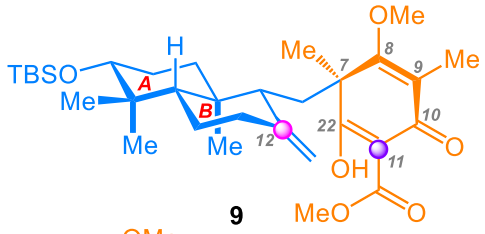
(–)-preaustinoid A (**2**)
(–)-preaustinoid A1 (**3**)
(–)-preaustinoid B (**4**)
(–)-preaustinoid B1 (**5**)
(+)-preaustinoid B2 (**6**)

Biomimetic diversification



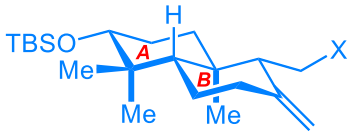
1 **8**

Carbonyl α-tert-alkylation (C_{11}-C_{12})



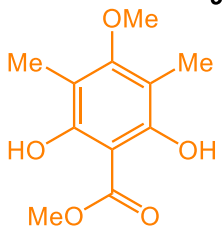
9

Diastereoselective dearomative alkylation

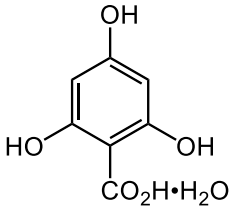


10, X = OH
10a-c, X = I, Br, OTf

\+

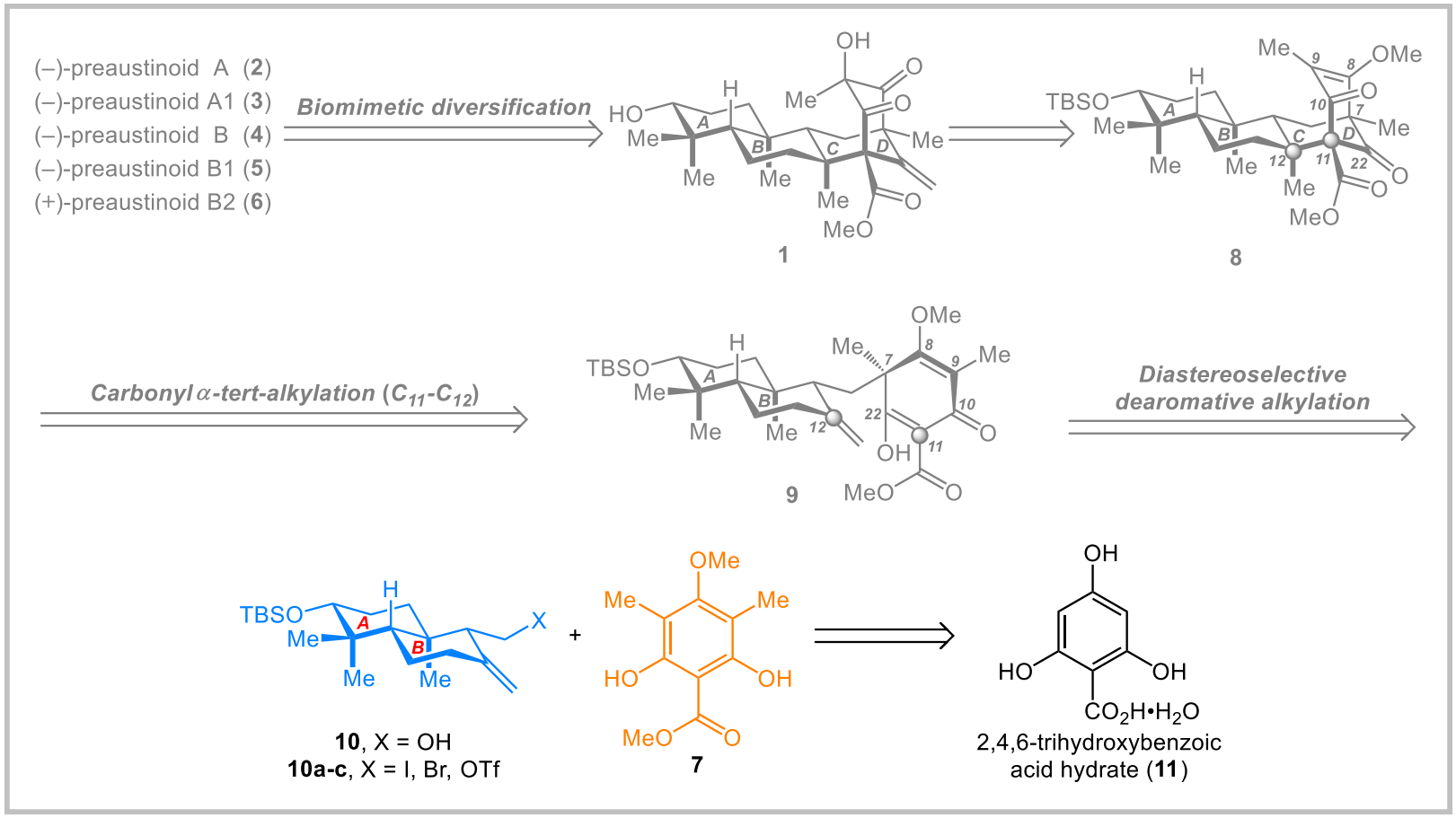


7



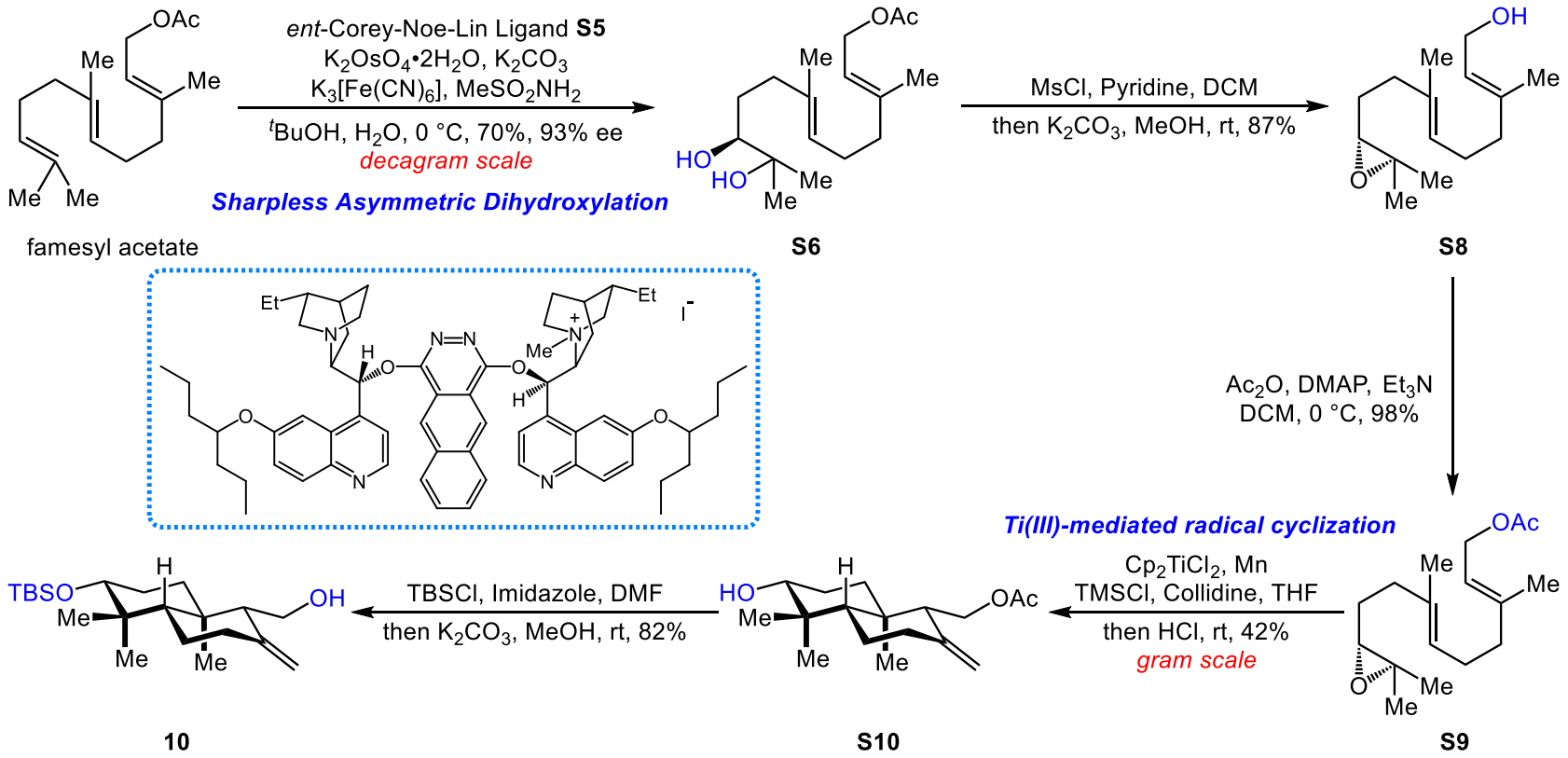
2,4,6-trihydroxybenzoic acid hydrate (**11**)

Stage 1—Preparation of two Fragments



Stage 1—Preparation of two Fragments

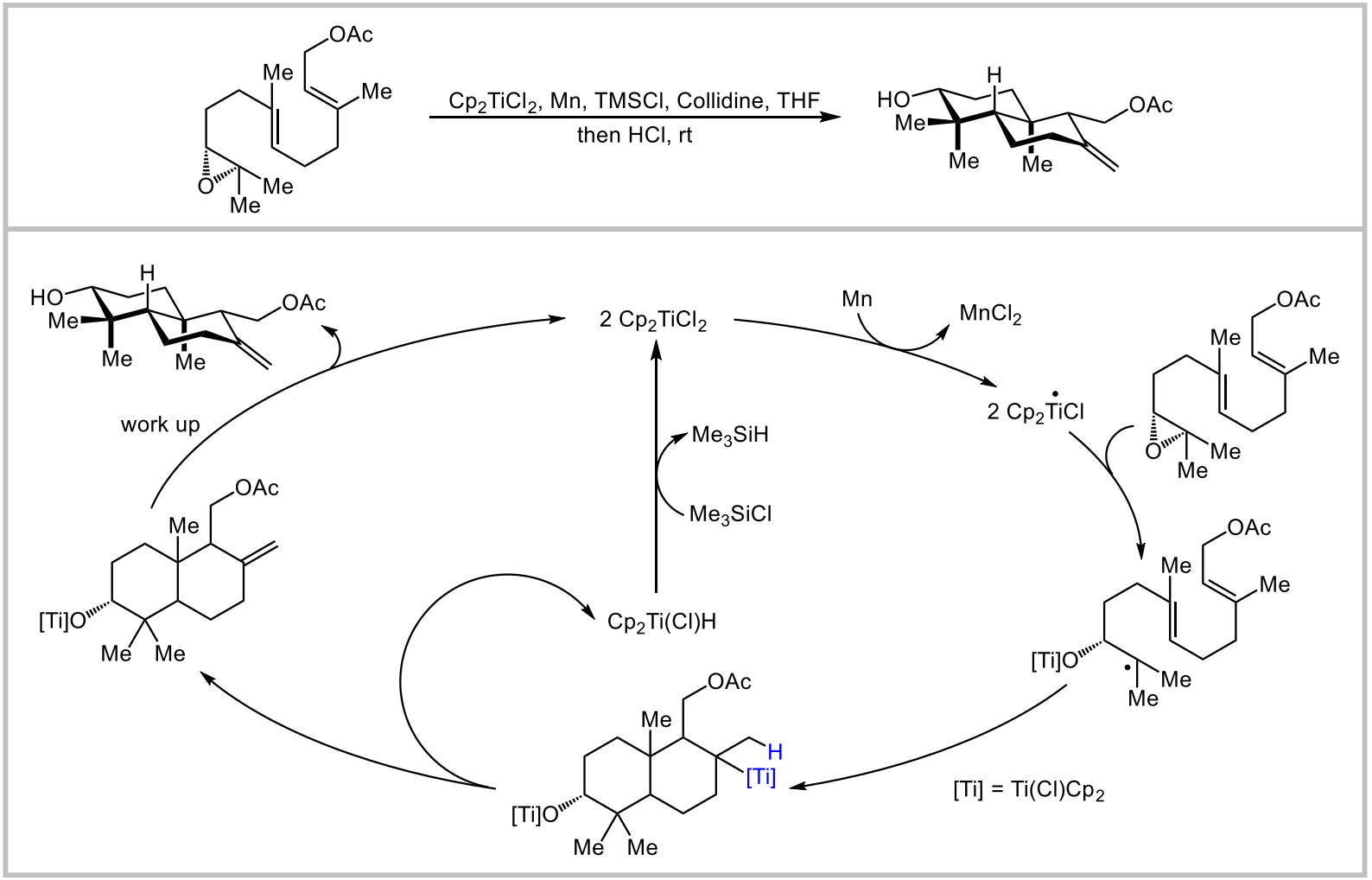
☐ Synthesis of 10



Barrero, A. F.; Herrador, M. M.; Sánchez, E. M. *Org. Lett.* **2005**, *7*, 2301

Domingo, V.; Silva, L.; Barrero, A. F. *J. Org. Chem.* **2009**, *74*, 6151

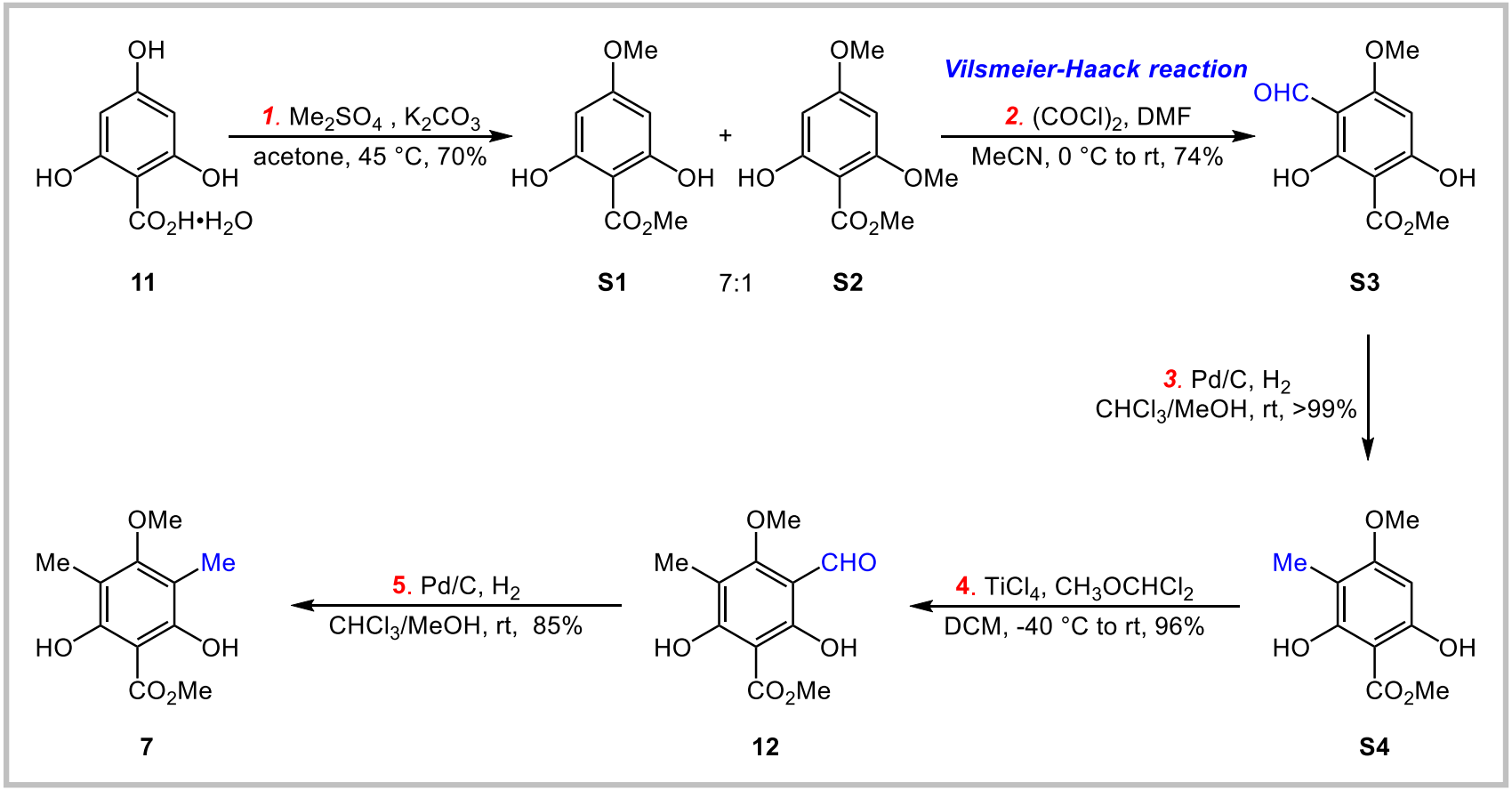
Ti(III)-Mediated Radical Cyclization



Justicia, J.; Rosales, A.; Cuerva, J. M. *Chem. Eur. J.* **2004**, *10*, 1778

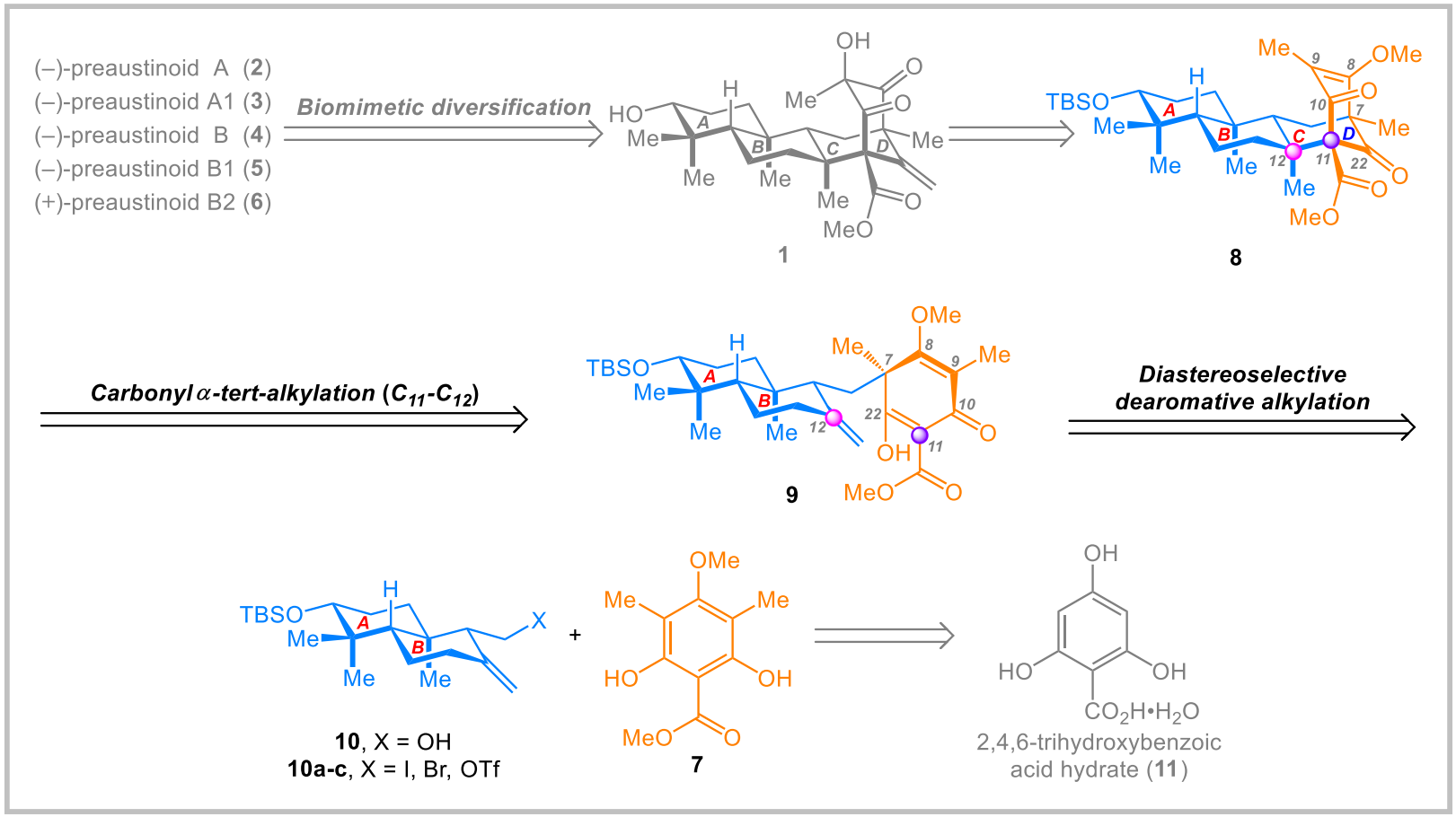
Stage 1—Preparation of two Fragments

☐ Synthesis of 7

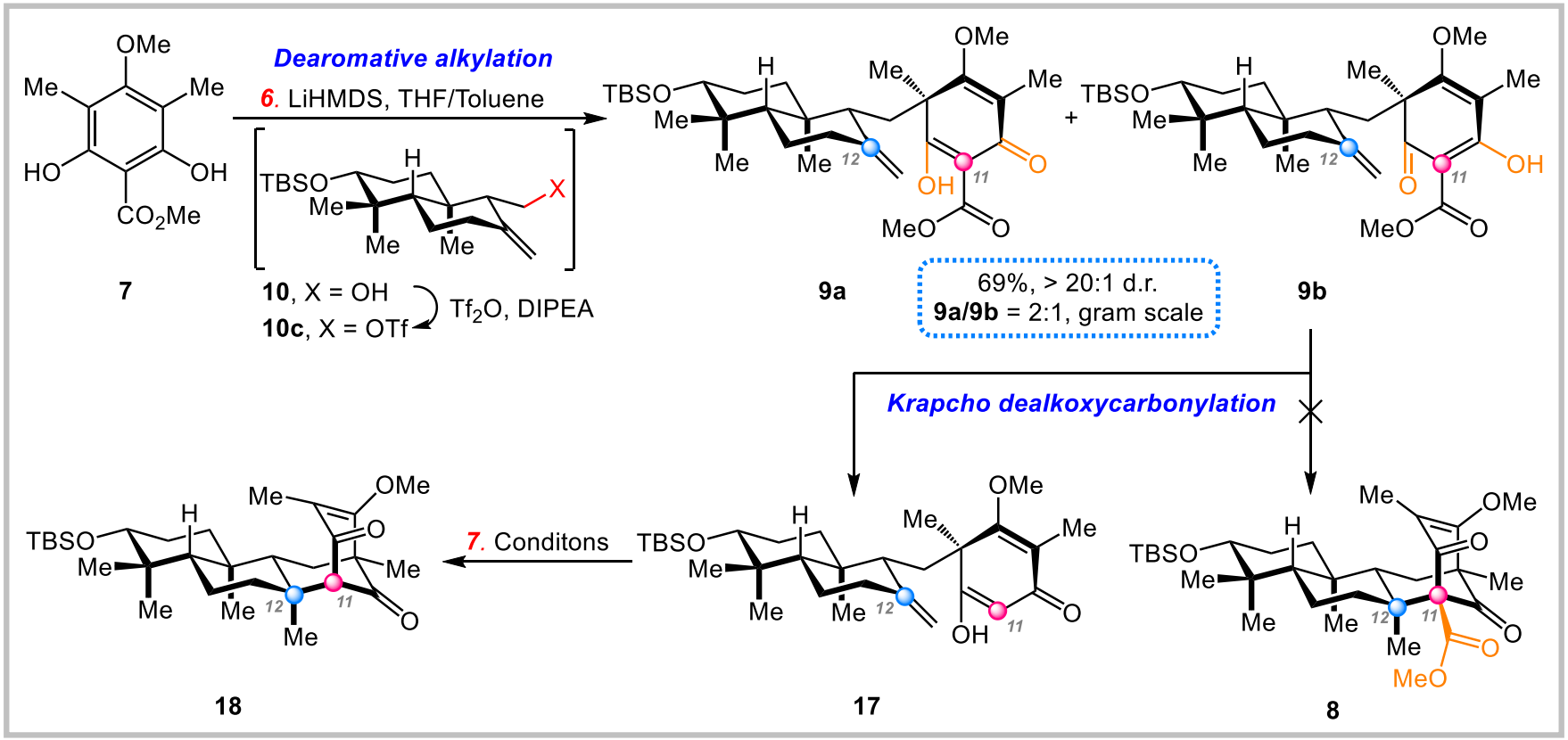


Schmid, M.; Trauner, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 12332

Stage 2—Construction of C-ring

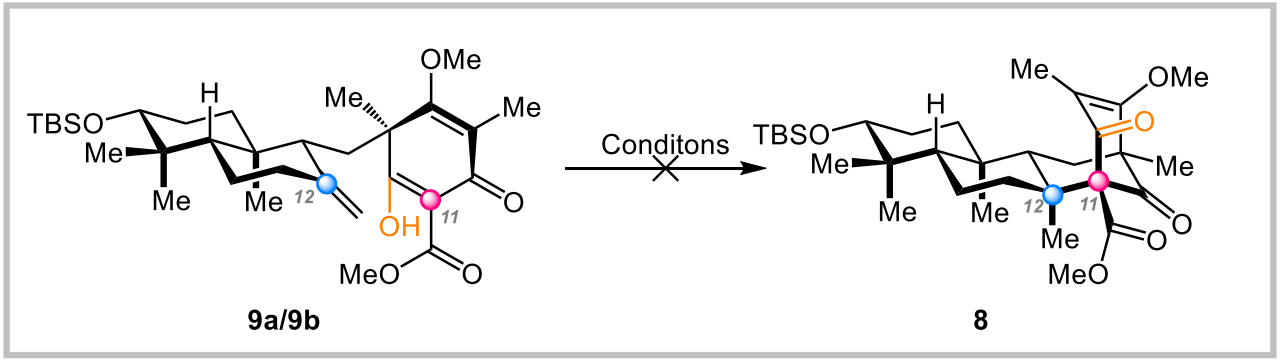


Stage 2—Construction of C-ring



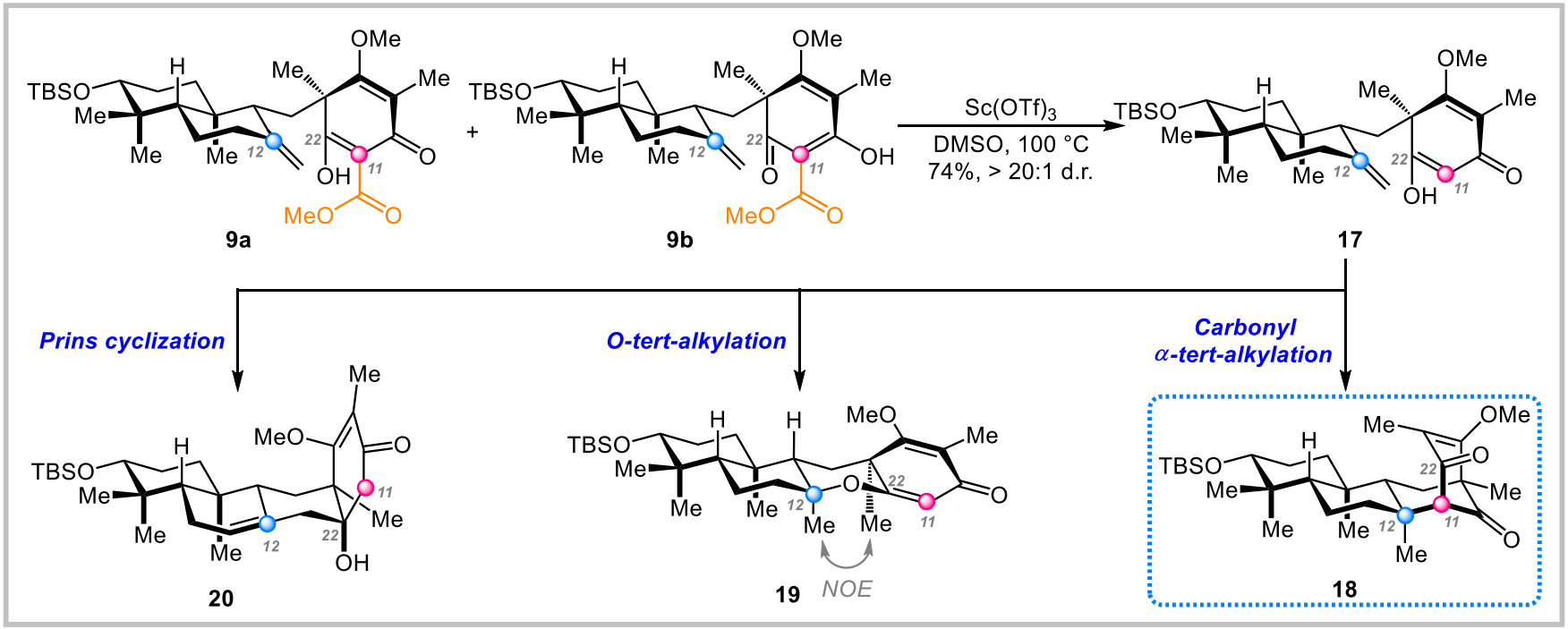
Stage 2—Construction of C-ring

☐ Carbonyl *α-tert*-Alkylation



Entry	Tactics	Conditions	results
1	Brønsted acid-mediated cationic cyclization	formic acid, TFA, TsOH, etc.	100% cons. unidentified decomposed side products
2	Lewis acid-mediated cationic cyclization	$SnCl_4$, Et_2AlCl, BF_3•Et_2O, etc.	
3	Photocatalyzed radical cylization	LED 390 nm, MeCN	
4	$Mn(OAc)_3$-mediated oxidative cyclization	$Mn(OAc)_3$, $Cu(OAc)_2$, AcOH	

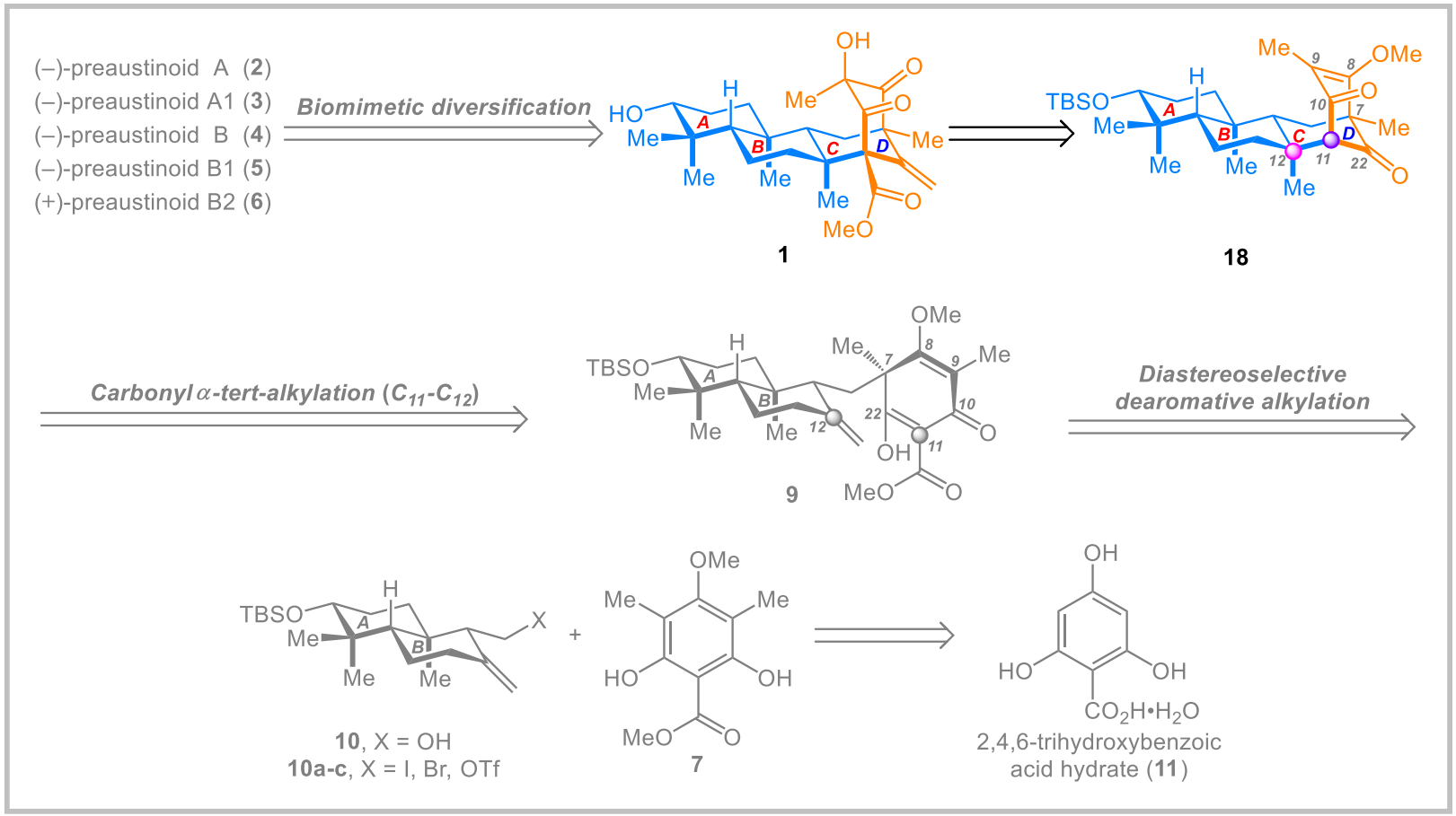
Stage 2—Construction of C-ring



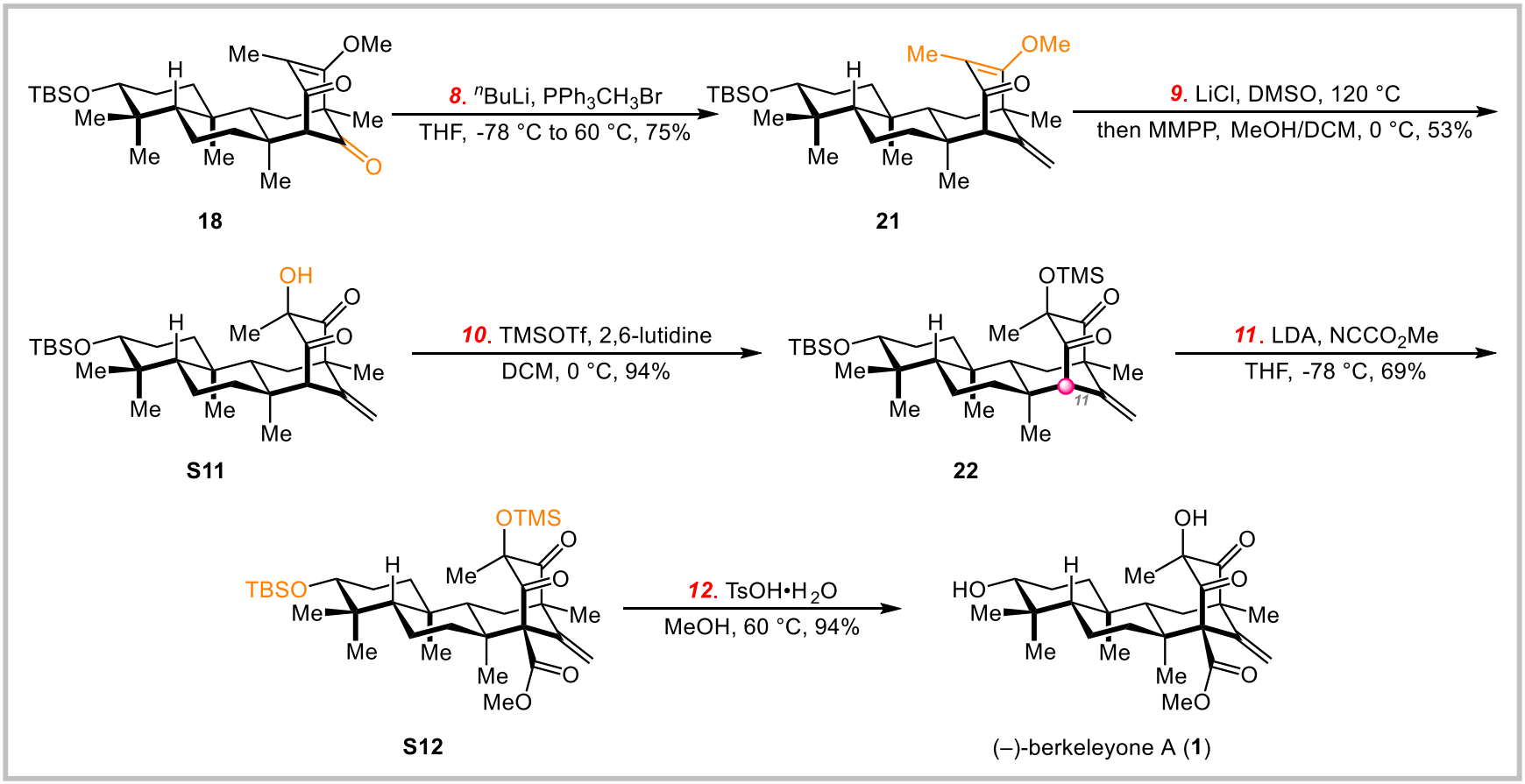
Entry	Conditions[a]	**18**[b] (desired product)	**19**[b]	**20**[b]
1	**17**, $Sc(OTf)_3$, DCM, 23 ºC	50	13	23
2	**9a/9b**, $Sc(OTf)_3$, DMSO, 100 ºC, then DCM, 23 ºC	41	6	9

[a] All reactions were performed on a 0.01 mmol scale in 1.0 mL solvent. [b] Isolated yield.

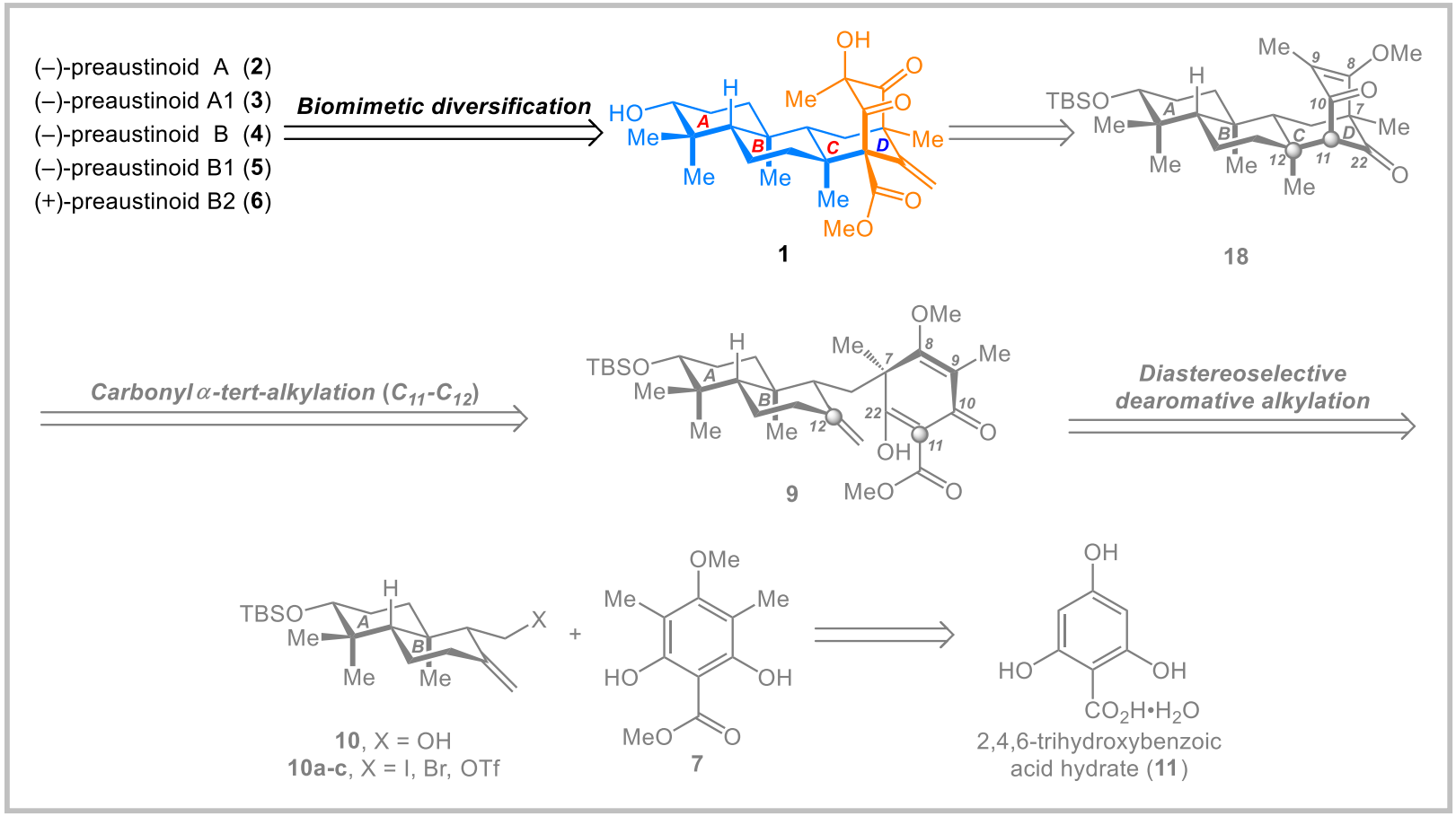
Stage 3—Elaboration of Highly Oxidized D-ring



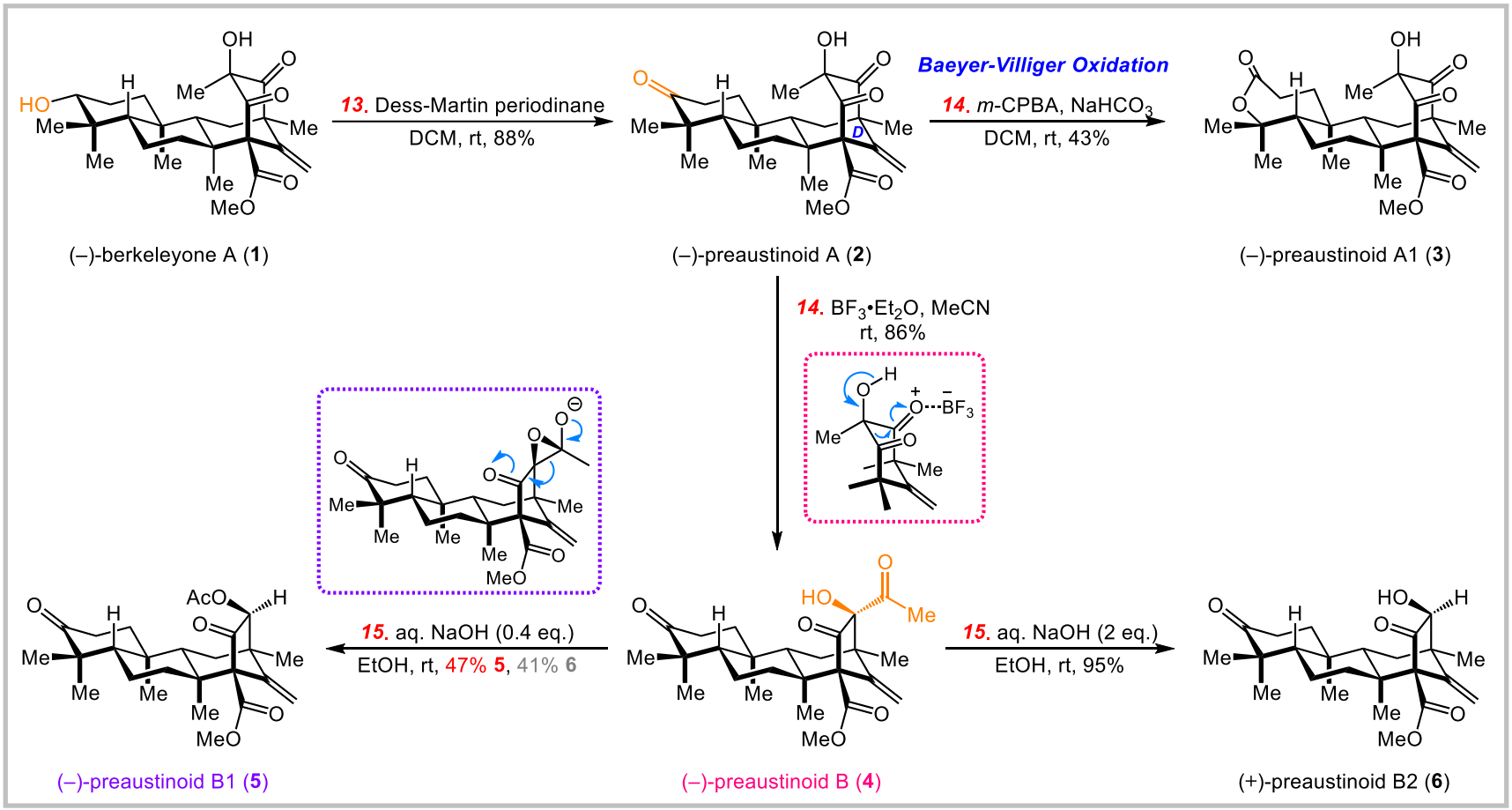
Stage 3—Elaboration of Highly Oxidized D-ring



Stage 4—Biomimetic Diversification of 1

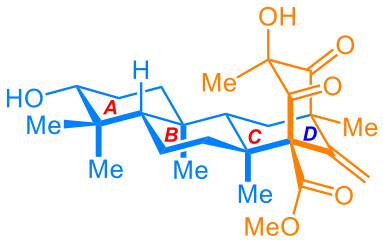


Stage 4—Biomimetic Diversification of 1

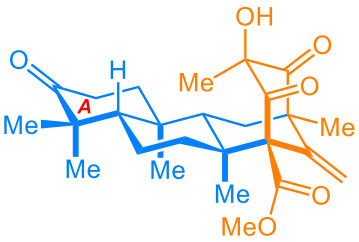


$[\alpha]_D^{25}$ = +90.0 (*c* 1.0, $CHCl_3$, *Ref.*)
$[\alpha]_D^{25}$ = −54.0 (*c* 0.1, $CHCl_3$, *revised*)

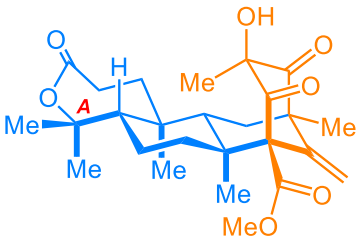
Summary



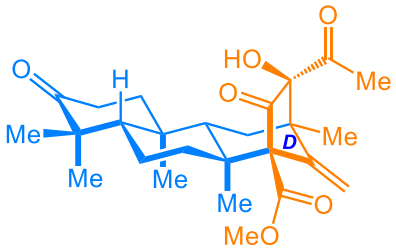
(–)-berkeleyone A (**1**)
anti-inflammatory



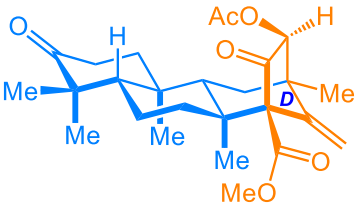
(–)-preaustinoid A (**2**)
caspase-1 inhibitor



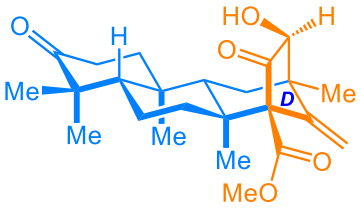
(–)-preaustinoid A1 (**3**)
caspase-1 inhibitor



(–)-preaustinoid B (**4**)



(–)-preaustinoid B1 (**5**)



(+)-preaustinoid B2 (**6**)

- Recognition of a hidden symmetry
- Total synthesis of **1-6** in 12-15 steps
- Diastereoselective dearomative alkylation
- $Sc(OTf)_3$-mediated sequential Krapcho dealkoxycarbonylation/carbonyl *α-tert*-alkylation

Writing Strategies

☐ The First Paragraph

The importance of fungal meroterpenoids (especially for berkeleyone A)

↓

The challenge of synthesis and previous work (racemic)

↓

Main content of this work— enantioselective synthesis of 1-6

The First Paragraph

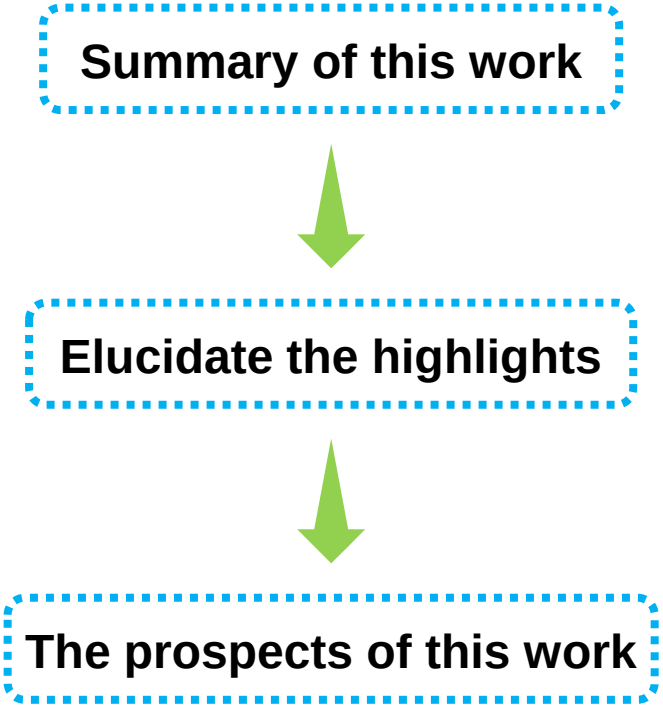
Fungal meroterpenoids derived from a simple aromatic polyketide 3,5-dimethylorsellinic acid (DMOA) are a large series of hybrid natural products with huge structural diversity and impressive bioactivities. Since the isolation of their first congener in 1976, over 100 compounds have been described. From a biosynthetic point of view, (–)-berkeleyone A (**1**) stands as a potential gateway compound through the union of a polyketide fragment DMOA with farnesyl pyrophosphate. Thereon, diversification at A-ring generates (–)-preaustinoid A (**2**) and (–)-preaustinoid A1 (**3**), where contraction of D-ring produces (–)-preaustinoid B (**4**), (–)-preaustinoid B1 (**5**), and (+)-preaustinoid B2 (**6**). Interestingly, **1–3** also possess anti-inflammatory properties by inhibiting the signaling enzyme caspase-1. To further unveil the biological function and therapeutic potential of DOMA-derived meroterpenoids, both biological and chemical synthetic studies have been done extensively in the past decade.

The First Paragraph

From a chemical synthesis perspective, DMOA-derived meroterpenoids present an exceedingly challenge, as exemplified by (–)-berkeleyone A (**1**), which possesses a dense tetracyclic framework with a hallmark bicyclo-[3.3.1]nonane core, three quaternary carbon centers within C-ring, and a highly oxidized D-ring without any hydrogen atom substituents. Hitherto two elegant racemic total synthesis of **1** have been reported by Maimone and Newhouse groups, where oxidative ring expansion and an isomerization-cyclization cascade have been independently applied for the installation of bicyclo[3.3.1]nonane core. En route to polycyclic terpenoids and terpenoid hybrids, we also initiated our investigations into DMOA-derived meroterpenoids. Herein we report our synthetic endeavors, which ultimately accumulate into the first enantioselective total synthesis of **1–6** in 12–15 steps, respectively.

Writing Strategies

☐ The Last Paragraph



The Last Paragraph

To conclude, benefited from the recognition of a hidden symmetry within the D-ring, we have accomplished the first enantioselective total synthesis of **1–6** in 12–15 steps, respectively, starting from commercially available 2,4,6-trihydroxybenzoic acid hydrate. In the course of our synthetic studies, we devised a highly convergent route relied upon a diastereoselective dearomative alkylation. Meanwhile, a $Sc(OTf)_3$-mediated sequential Krapcho dealkoxycarbonylation/carbonyl *α-tert*-alkylation have been developed to forge bicyclo[3.3.1]nonane core. At last, we also disclosed our preliminary biomimetic investigations, which generated five additional preaustinoid congeners through a series of rearrangements (*α*-ketol rearrangement, *α*-hydroxyl-*β*-diketone rearrangement, etc).

The Last Paragraph

Overall, our convergent route is highly modular, thereby should be amenable to access structurally diverse DMOA-derived meroterpenoids, as well as other bicyclo[3.3.1]nonane-containing meroterpenoids, which are currently underway and will be reported in due course.

Representative Examples

- With five-step access to tetracycle **16**, we proceeded to evaluate the second **pivotal**（**关键的**）transformation in the synthetic pathway: conversion of the 5,6-fused ring system into the **hallmark**（**标志的**）bicyclo[3.3.1]nonane skeleton.

- **En route**（**在途中、从头开始**）to polycyclic terpenoids and terpenoid hybrids, we also initiated our investigations into DMOA-derived meroterpenoids.

- As has already been constantly recognized in many landmark total syntheses, the recognition of **latent**（**潜在的**）symmetry in a target molecule would drastically simplify the task at hand. (**表现某种策略、方法的优越性**)

Acknowledgement

Thanks for your attentions!