Literature Report 7

Total Synthesis of Ginkgolide C and Formal Syntheses of Ginkgolides A and B

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Checker: Shan-Shan Xun
Date: 2022.11.02

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CV of Dr. Louis Barriault

Background:

- **1989-1993** B.S., University of Sherbrooke
- **1993-1997** Ph.D., University of Sherbrooke
- **1997-1999** Postdoc., Ohio State University
- **1999-2010** Assistant Prof., University of Ottawa
- **2010-now** Full Professor, University of Ottawa

Research:

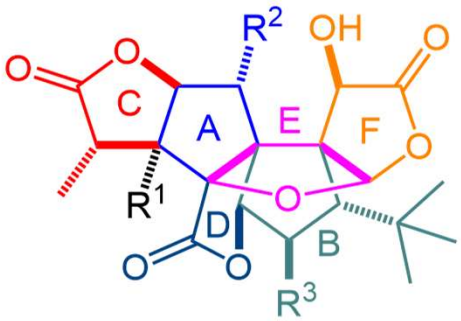
- ✓ **Asymmetric methodology;**
- ✓ **Development of new synthetic methods;**
- ✓ **Total synthesis of complex natural products**.

Contents

Introduction

Ginkgolide Family

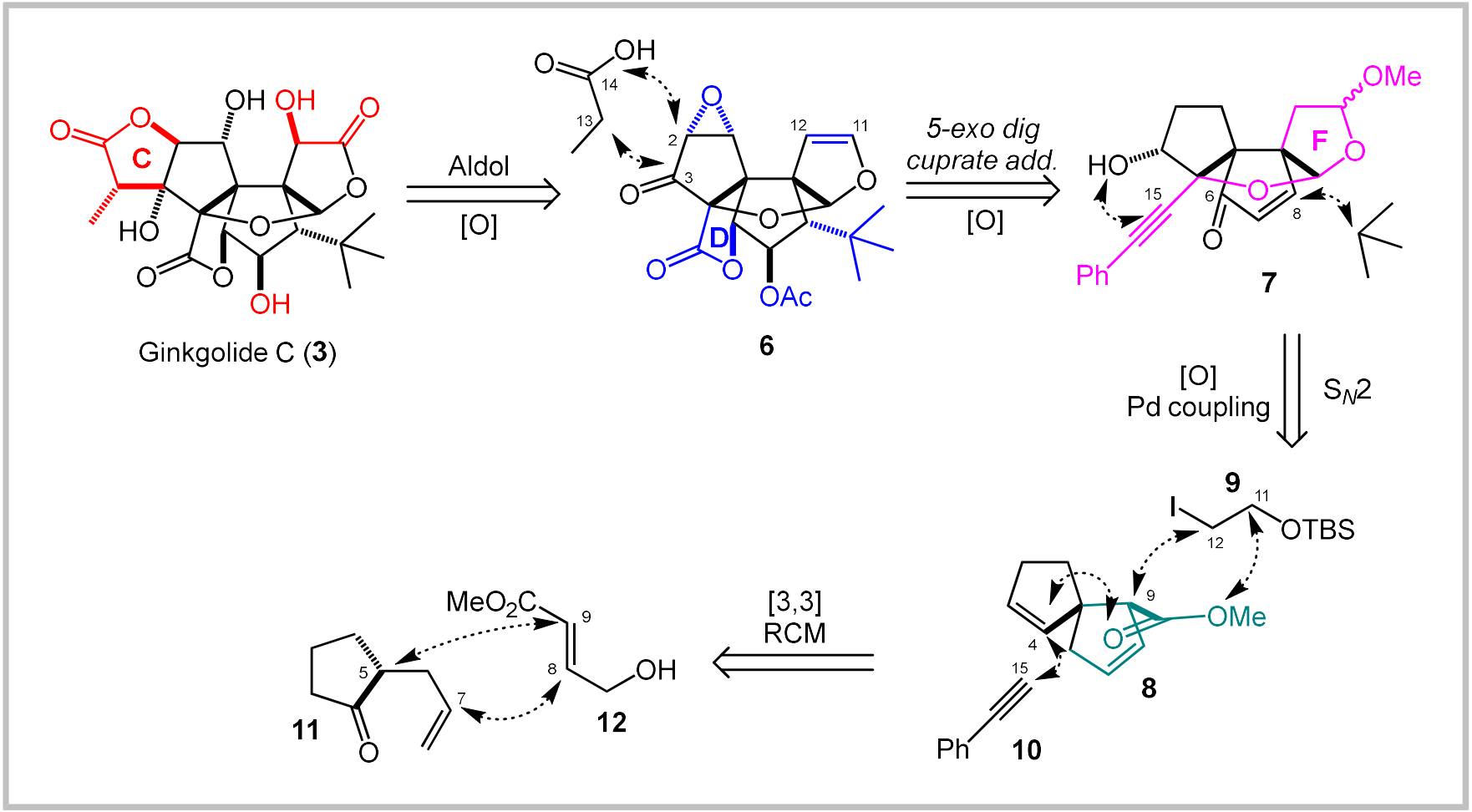
- ♣ Ginkgolides were firstly isolated by Furukawa in 1932
- ♣ Strong antagonists to the platelet-aggregating receptor
- ♣ Effective against central nervous system illnesses (Alzheimer's and Parkinson's disease; Multiple sclerosis)



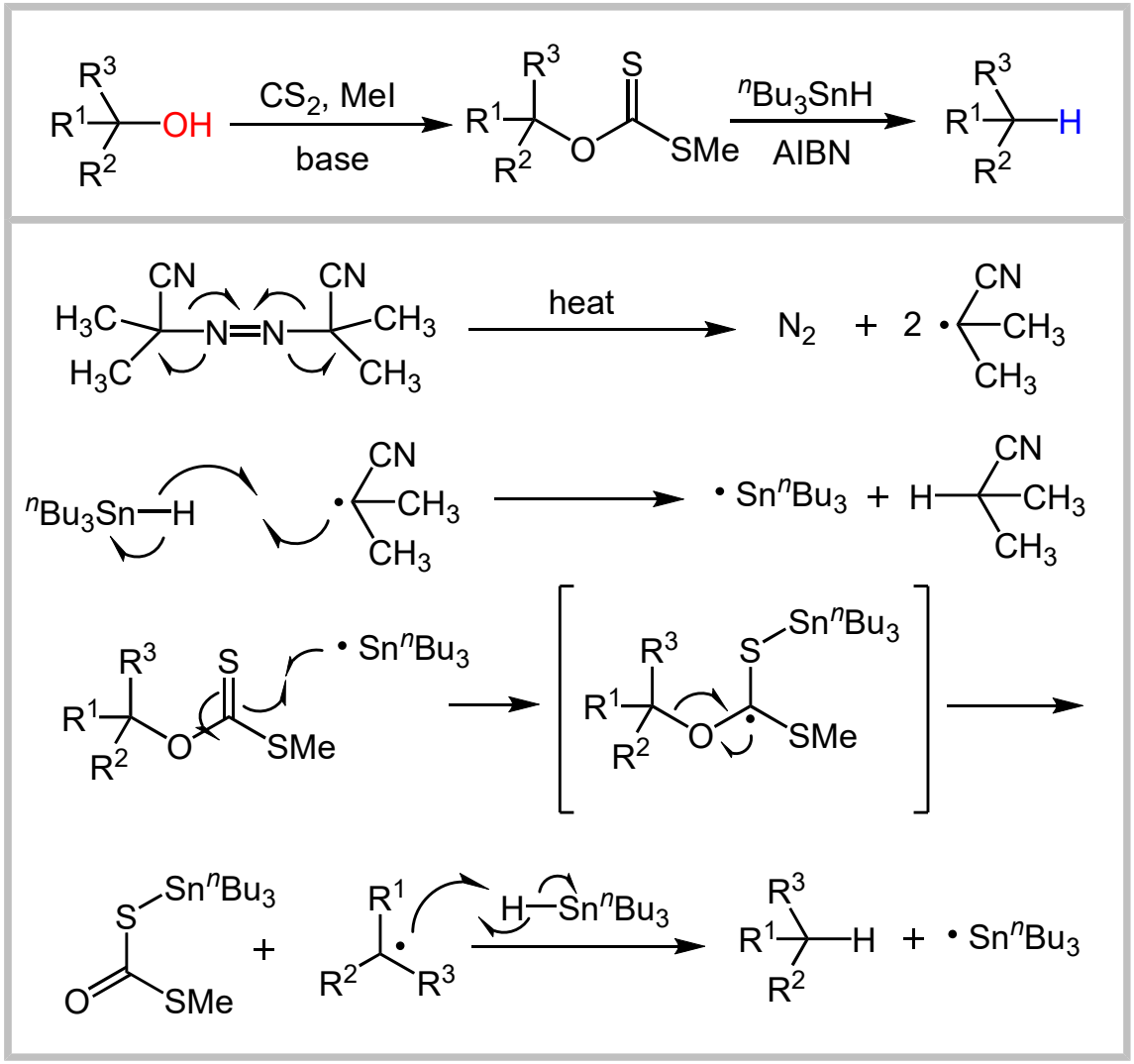
Ginkgolide A (**1**)	R^1 = OH, R^2 = R^3 = H
Ginkgolide B (**2**)	R^1 = OH, R^2 = OH, R^3 = H
Ginkgolide C (**3**)	R^1 = OH, R^2 = OH, R^3 = OH
Ginkgolide M (**4**)	R^1 = OH, R^2 = H, R^3 = OH
Ginkgolide J (**5**)	R^1 = H, R^2 = OH, R^3 = OH

Furukawa, S. *Sci. Pap. Inst. Phys. Chem. Res.* **1932**, *19*, 27.
Cai, J. *et al. Mol. Neurobiol.* **2017**, *54*, 5563.

Retrosynthetic Analysis

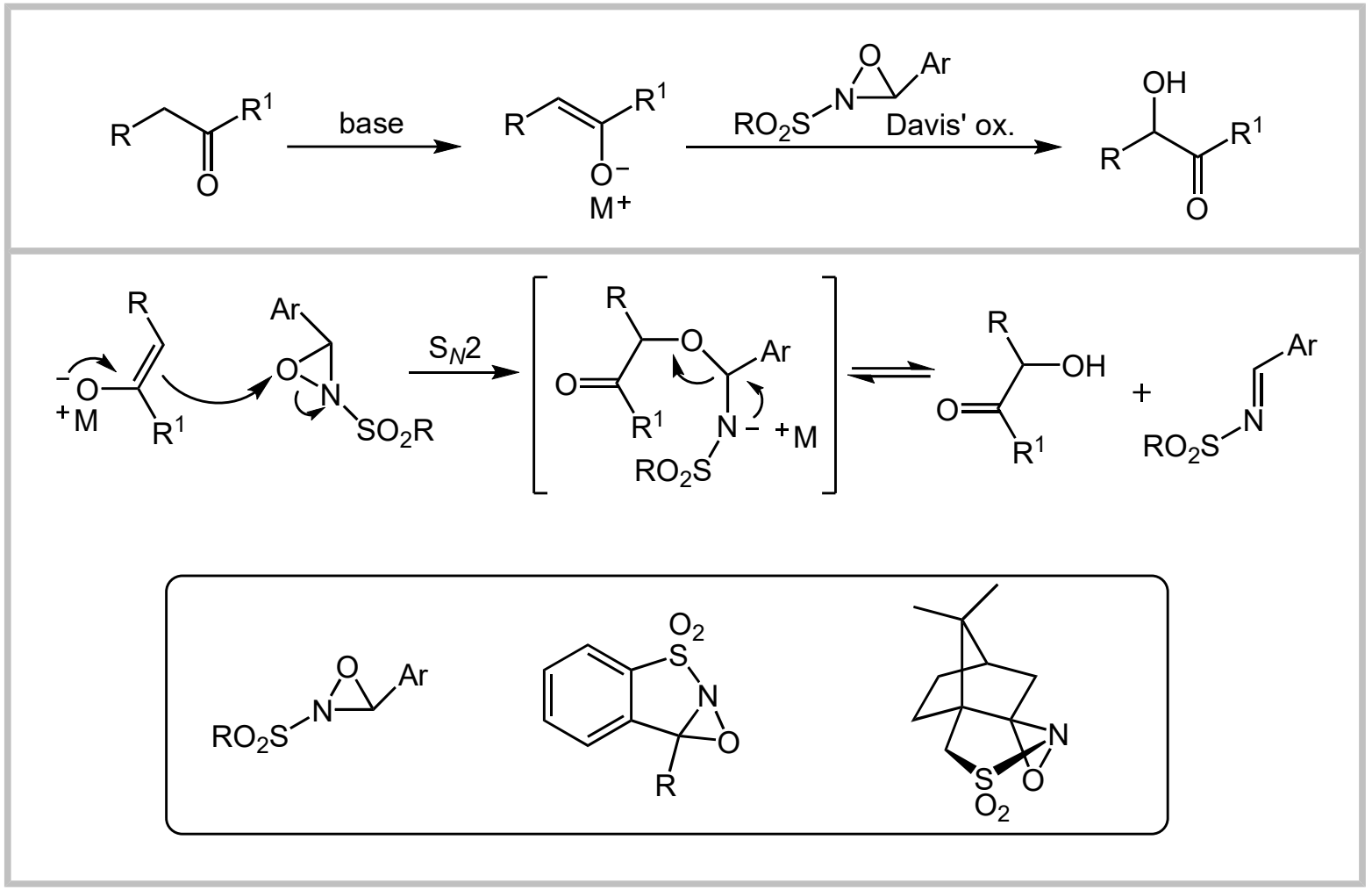


Barton-McCombie Deoxygenation



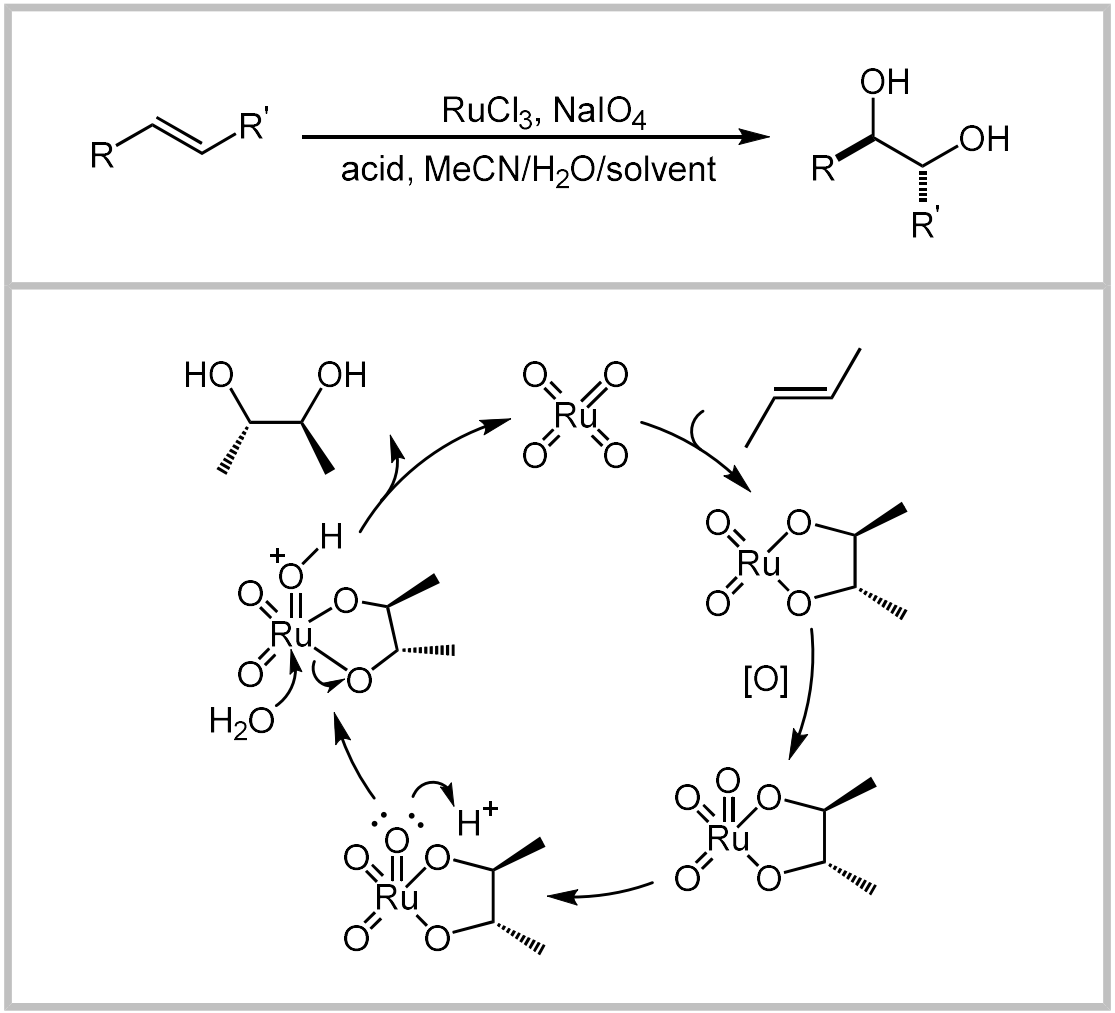
From Name Reaction

Davis' Oxidation



From Name Reaction

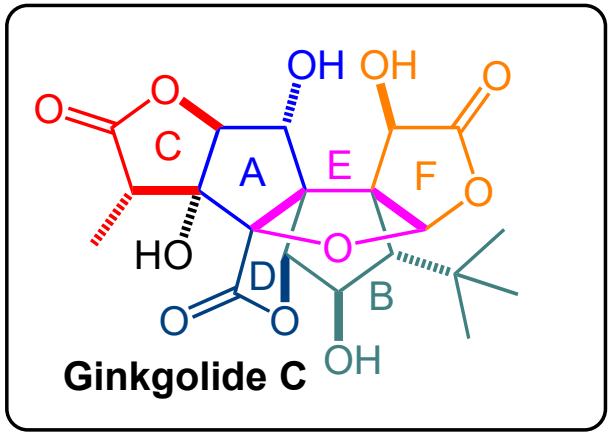
Shing-Plietker Dihydroxylation



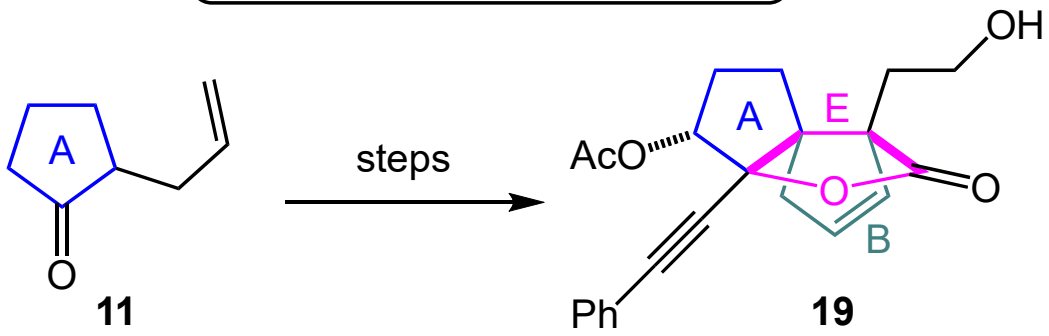
Shing, T. K. M. *et al. Angew. Chem. Int. Ed.* **1994**, *33*, 2312.
Plietker, B. *et al. Org. Lett.* **2003**, *5*, 3353.

Construction of Ring E and B

Stage I

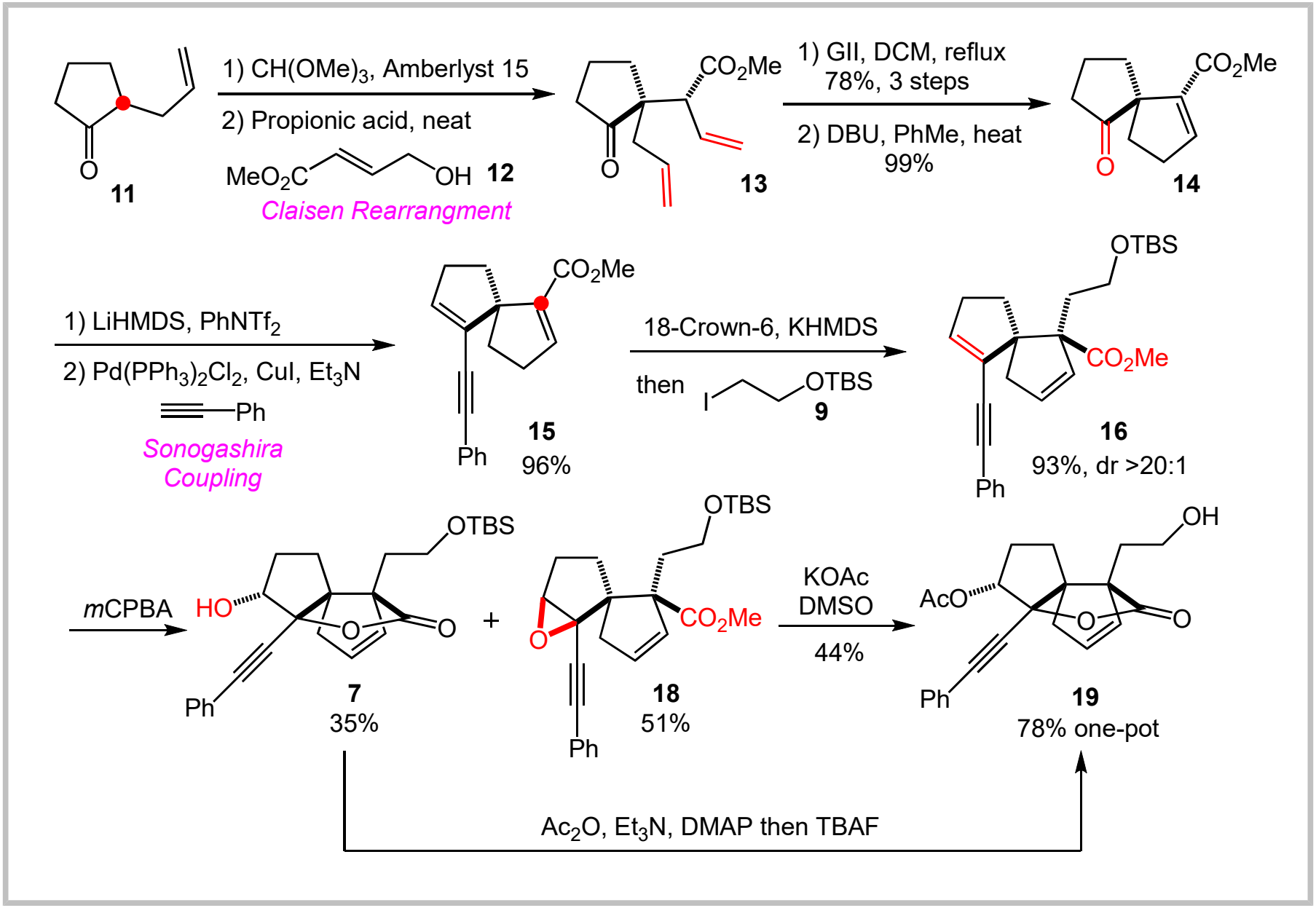


Ginkgolide C



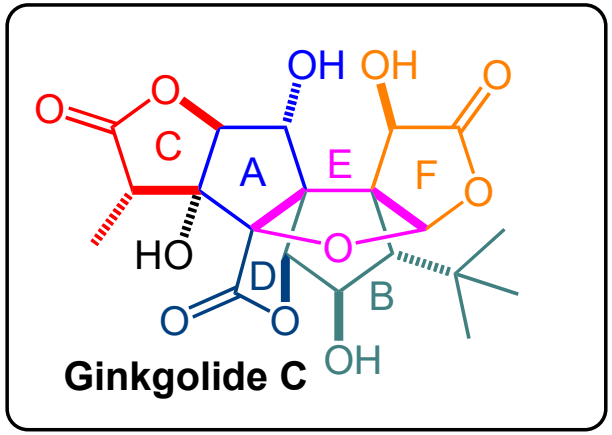
11 **19**

Construction of Ring E and B

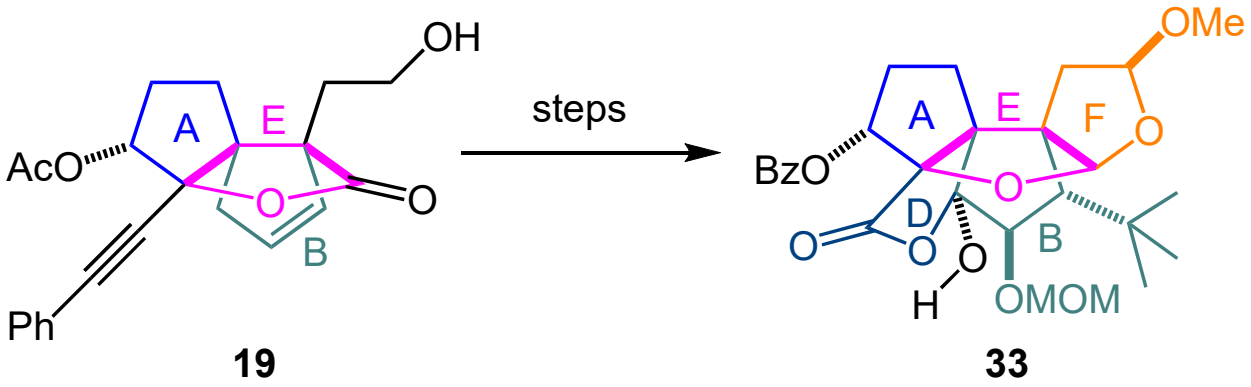


Construction of Ring F and D

Stage II

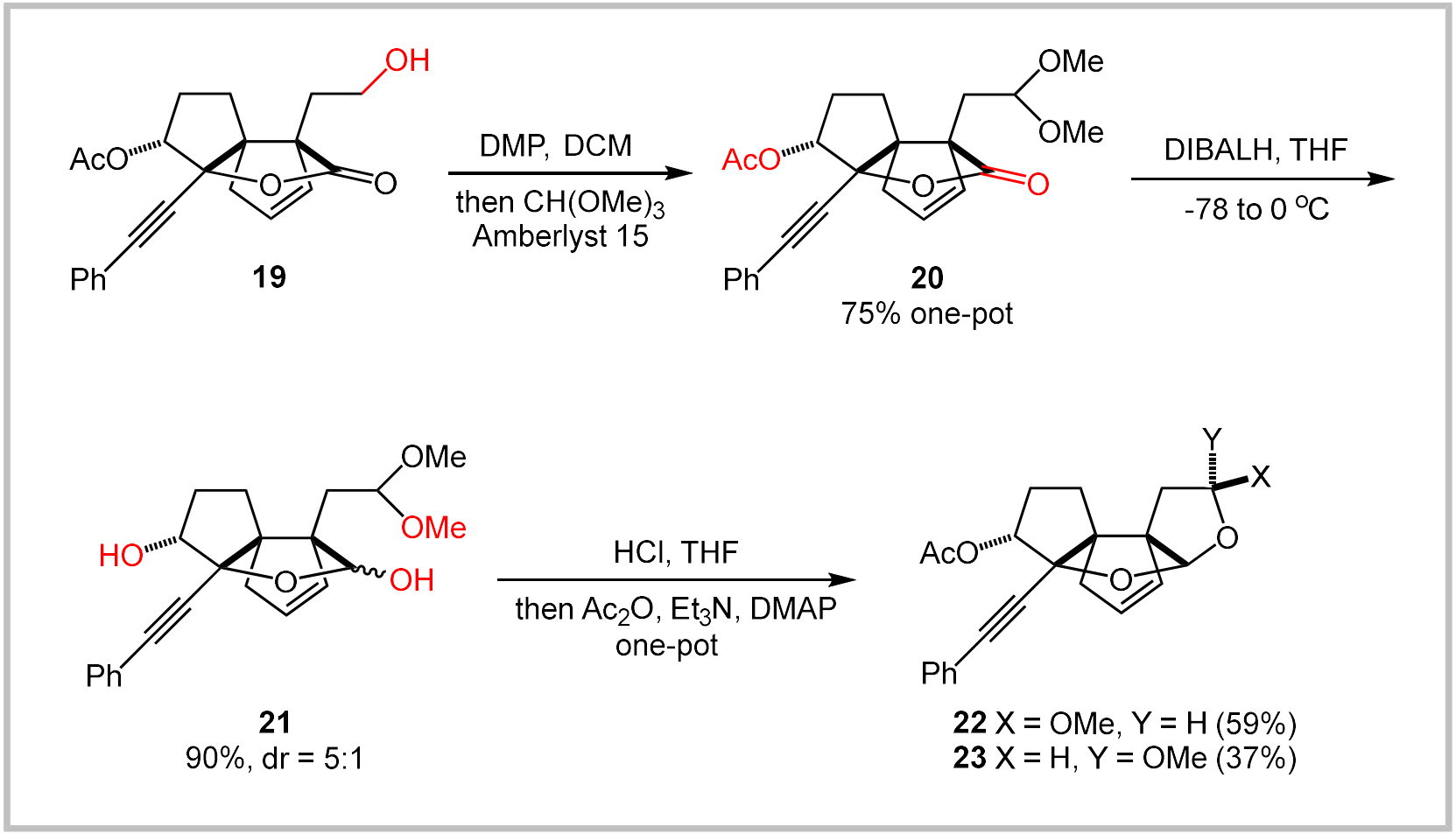


Ginkgolide C

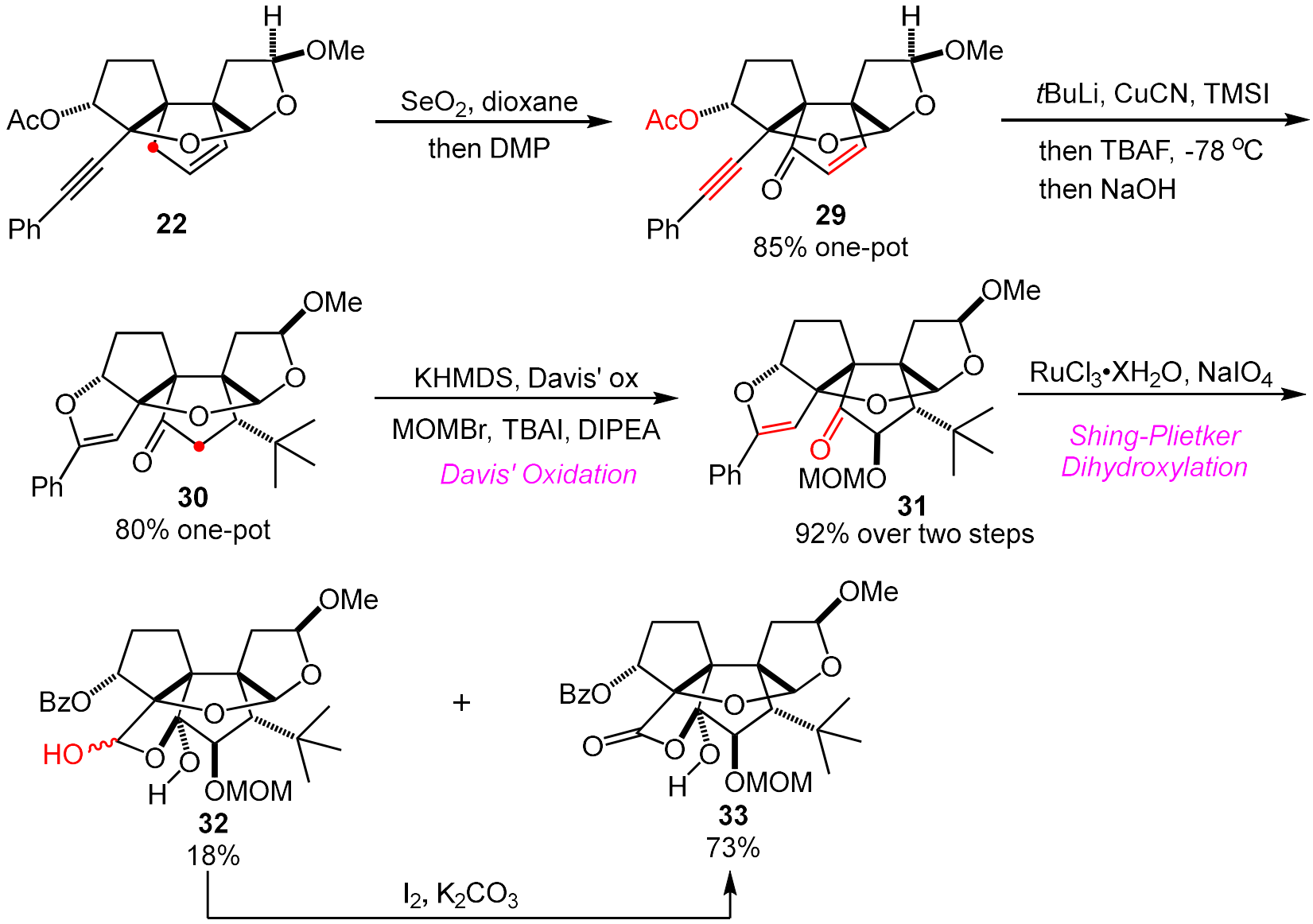


19 **33**

Construction of Ring F and D

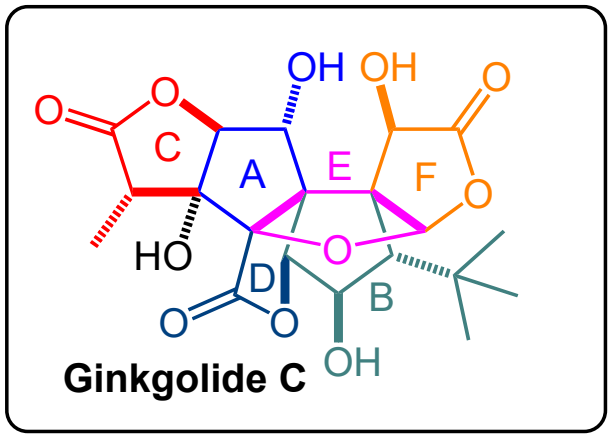


Construction of Ring F and D

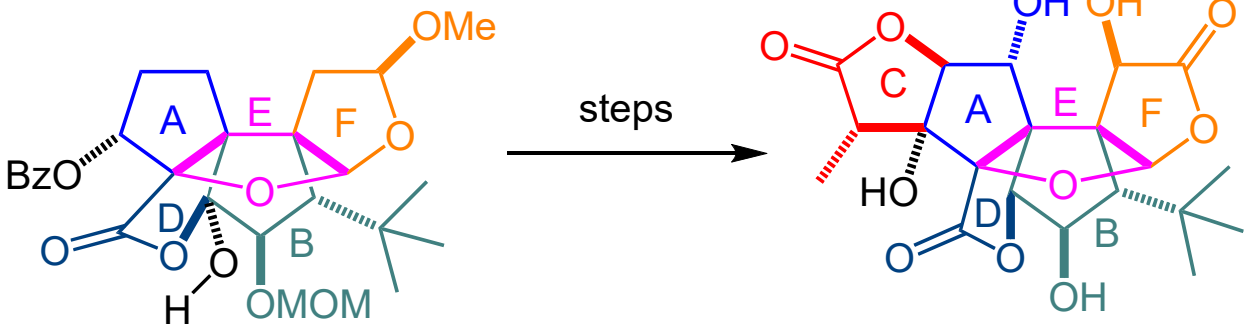


Construction of Ring C

Stage III

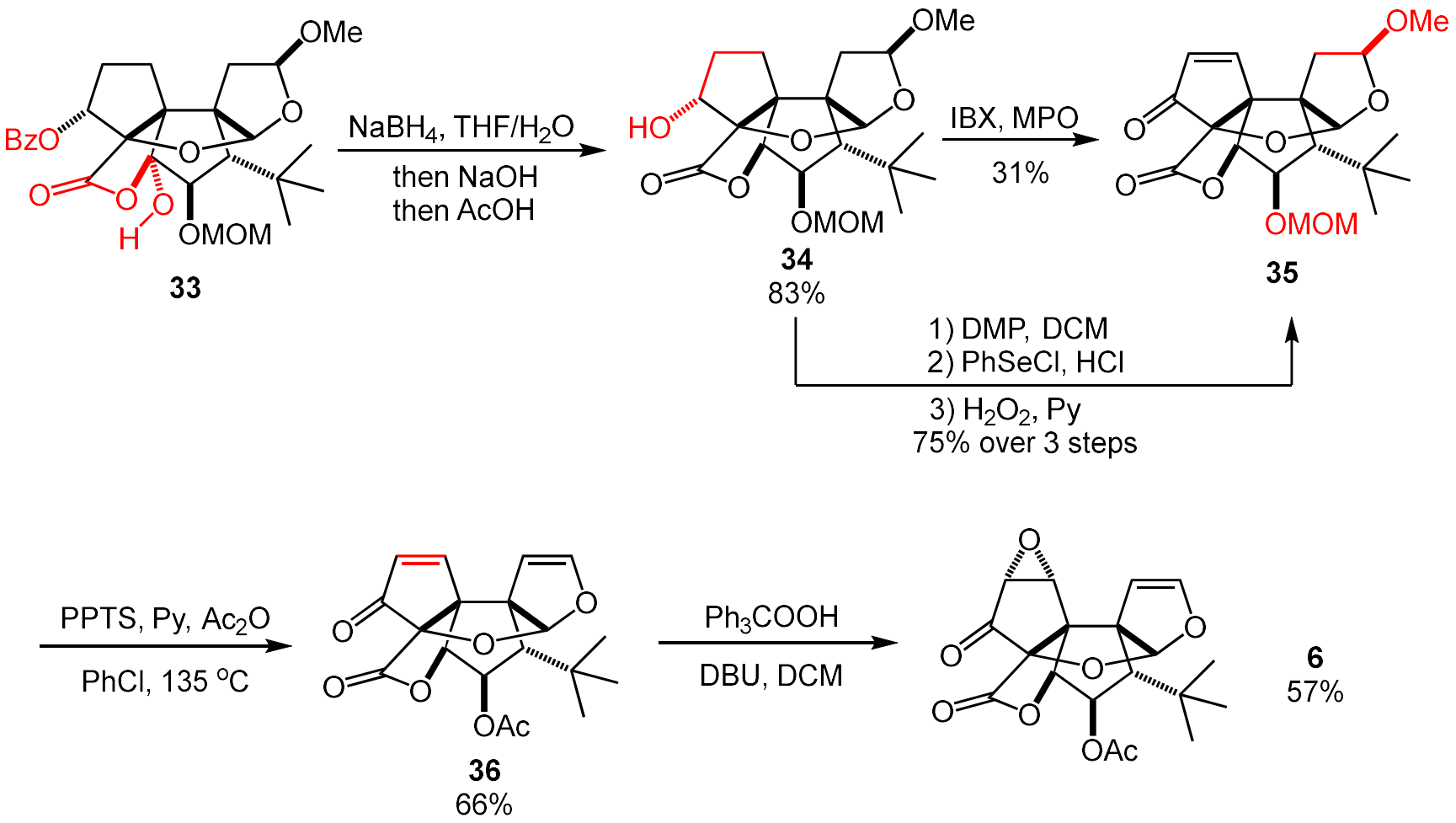


Ginkgolide C

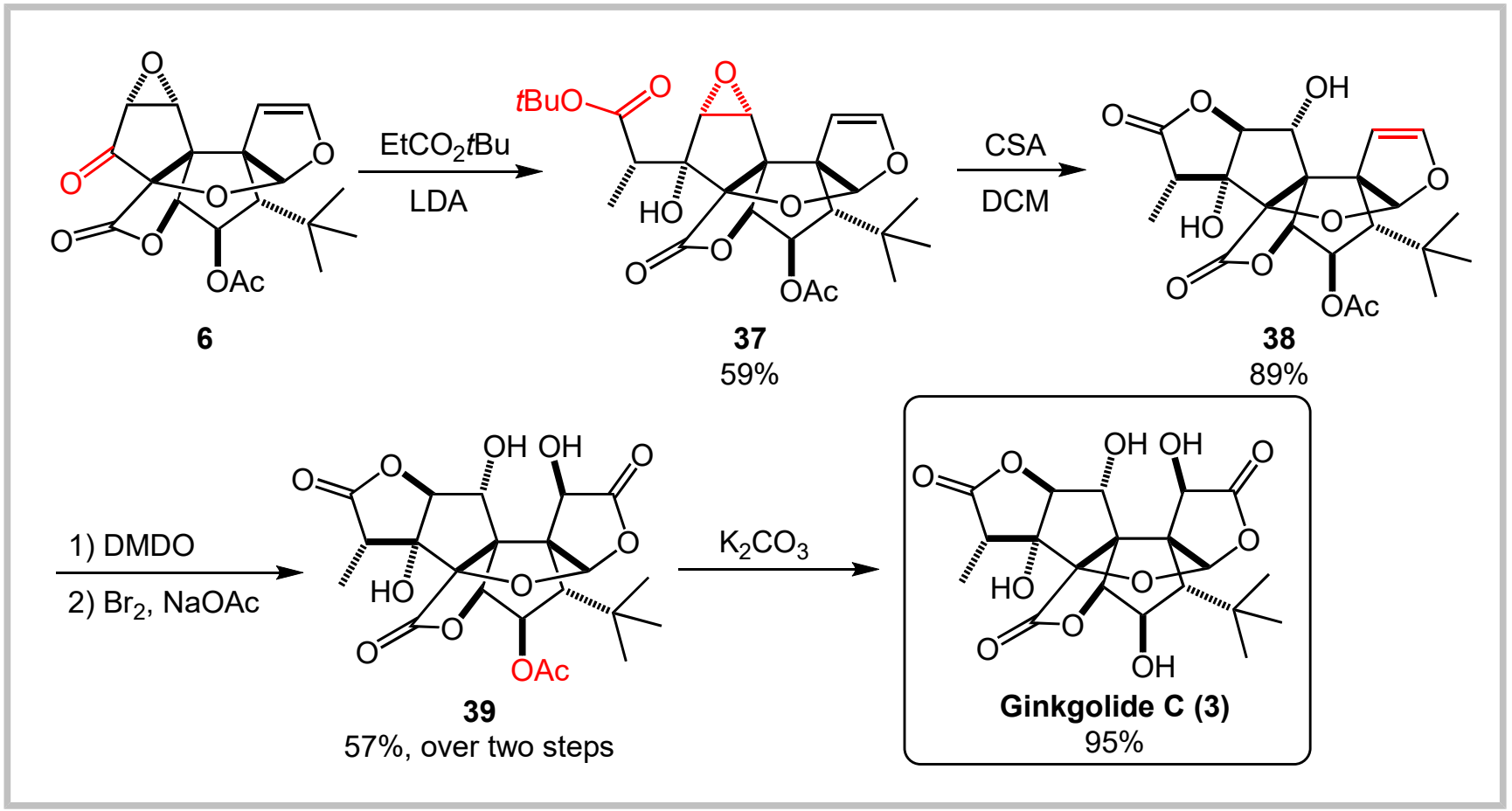


33 **Ginkgolide C**

Synthesis of Ginkgolide C

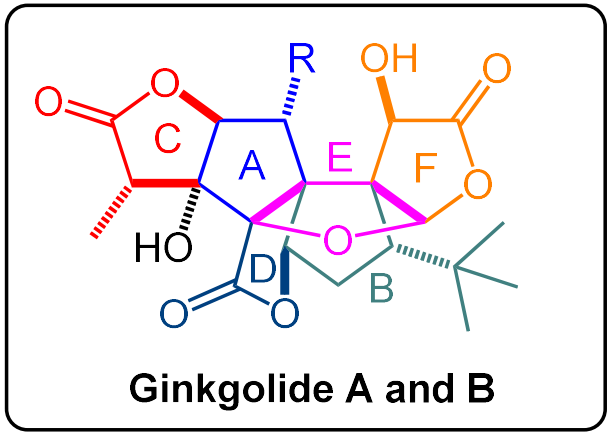


Synthesis of Ginkgolide C

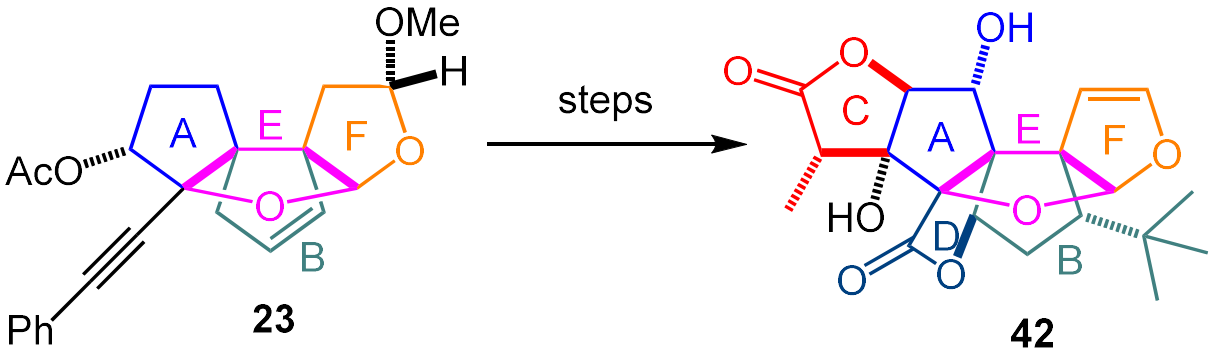


Construction of Intermediate 42

Stage IV

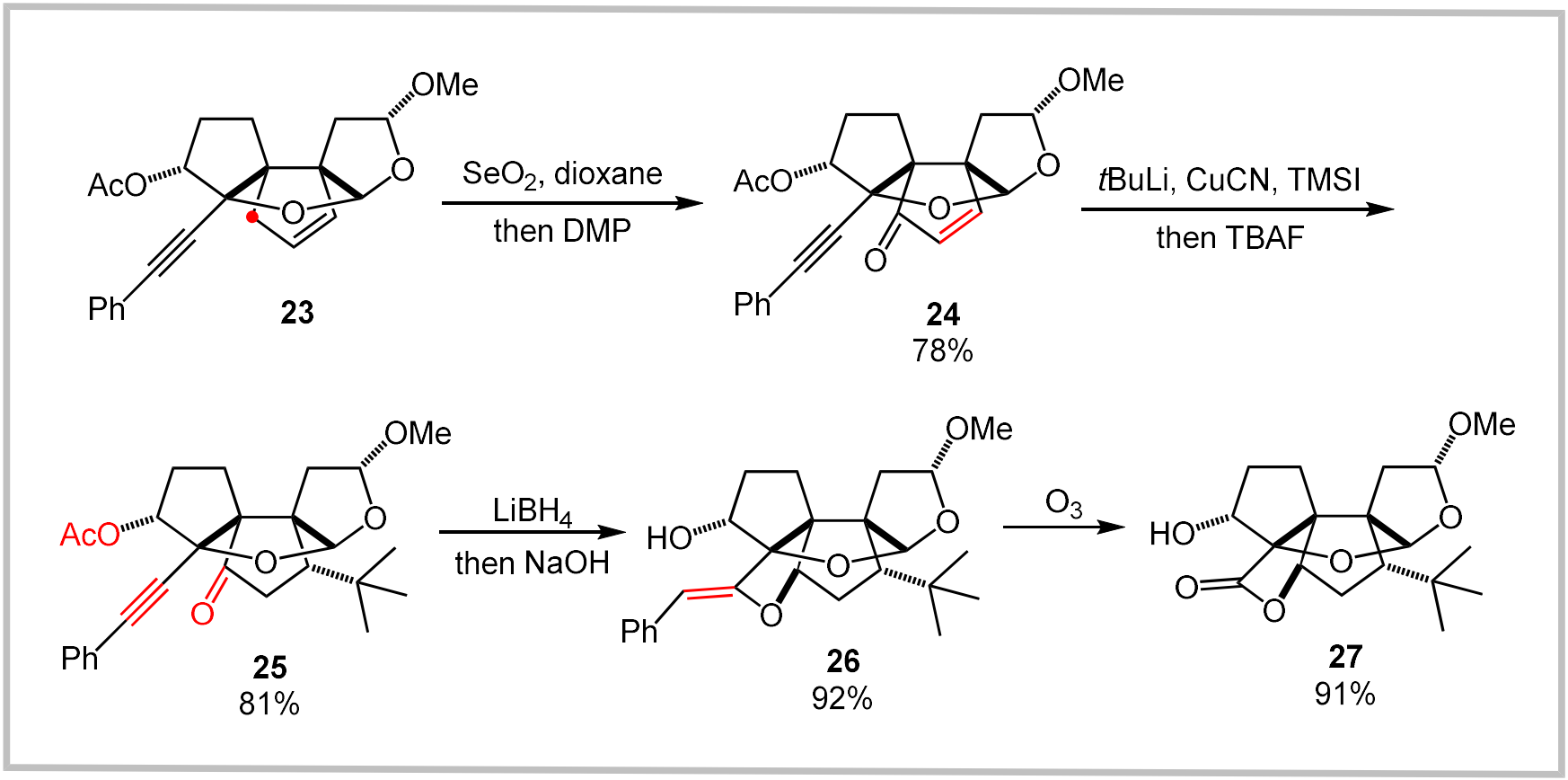


Ginkgolide A and B

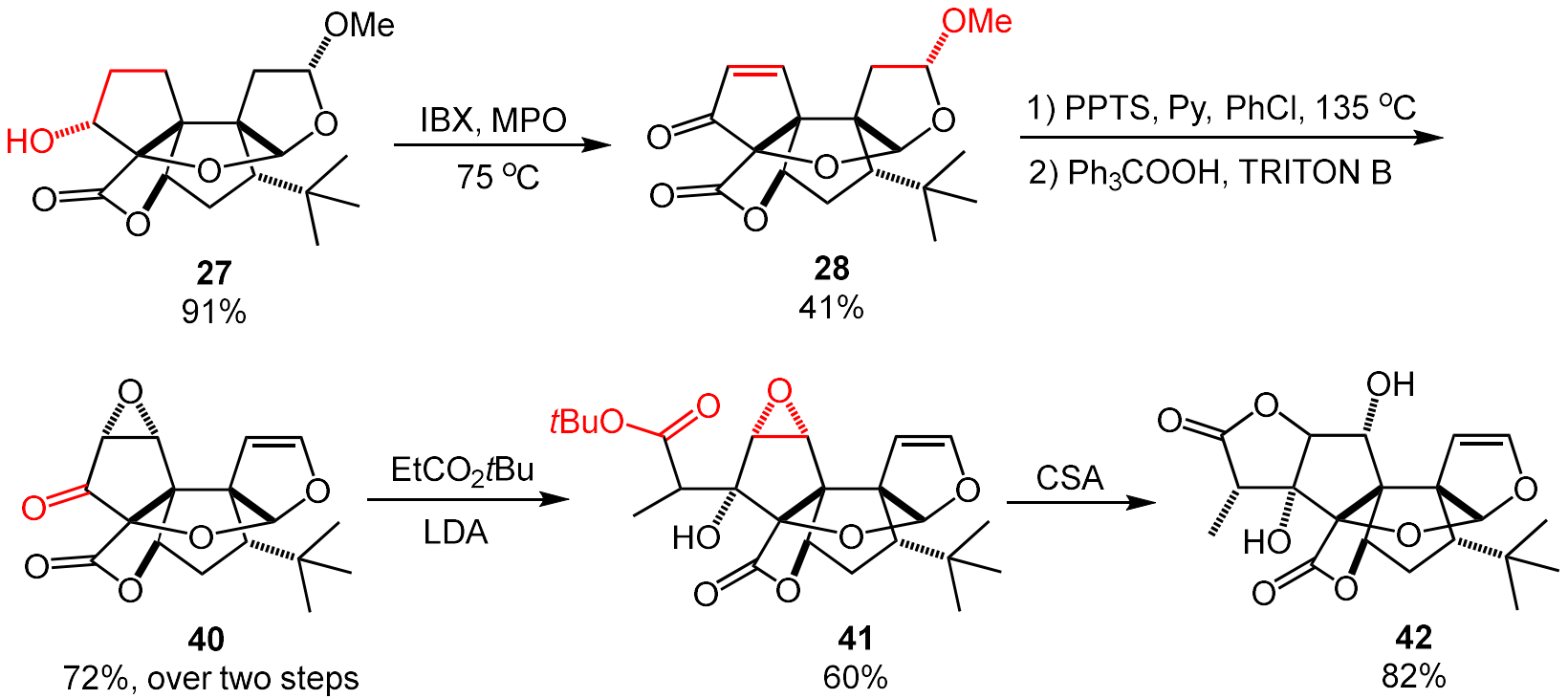


23 **42**

Synthesis of Intermediate 40

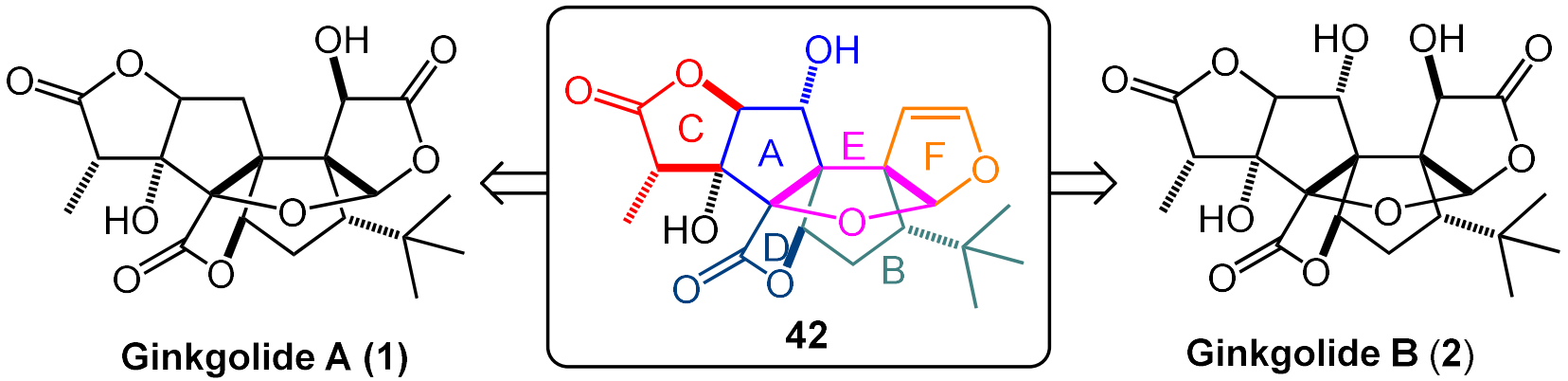


Synthesis of Intermediate 40



Construction of Ginkgolide A and B

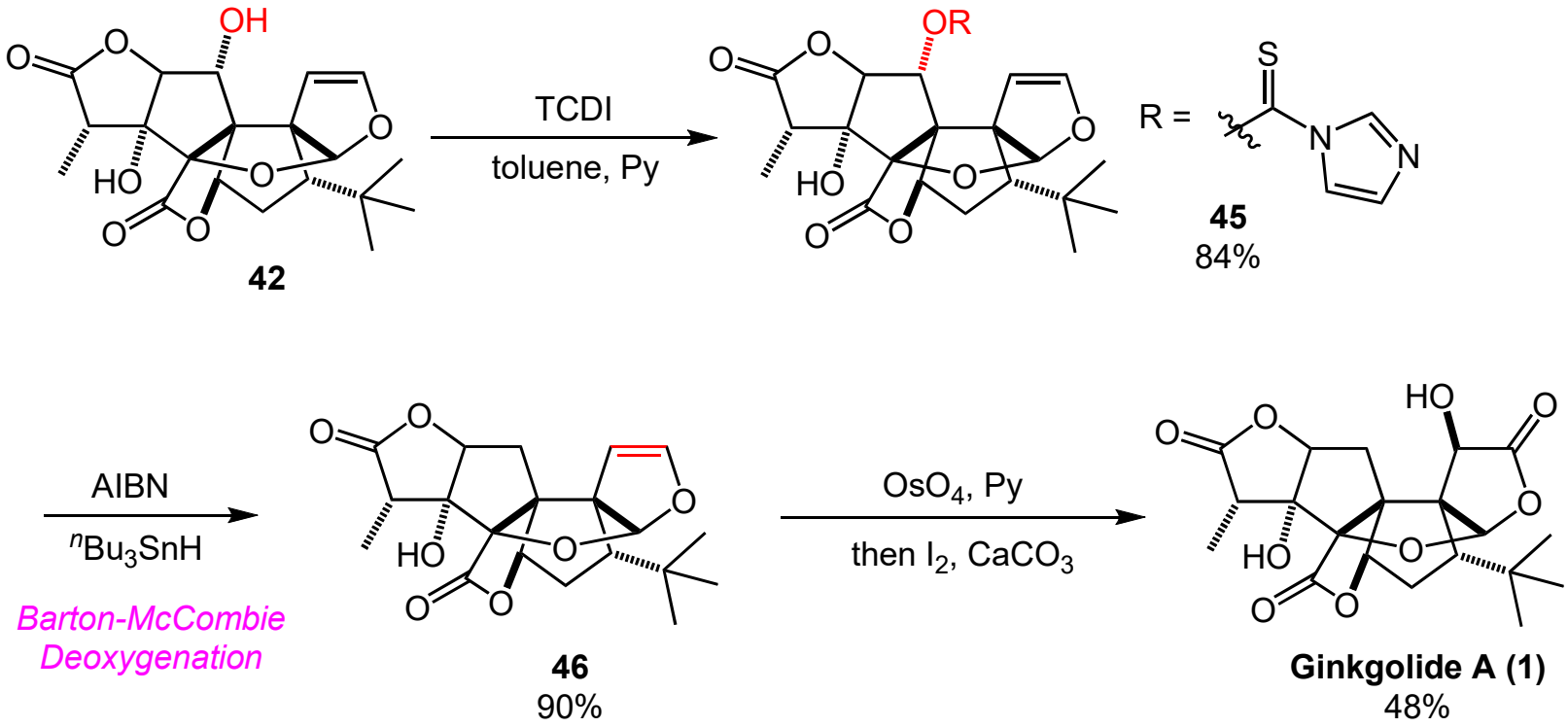
Stage V



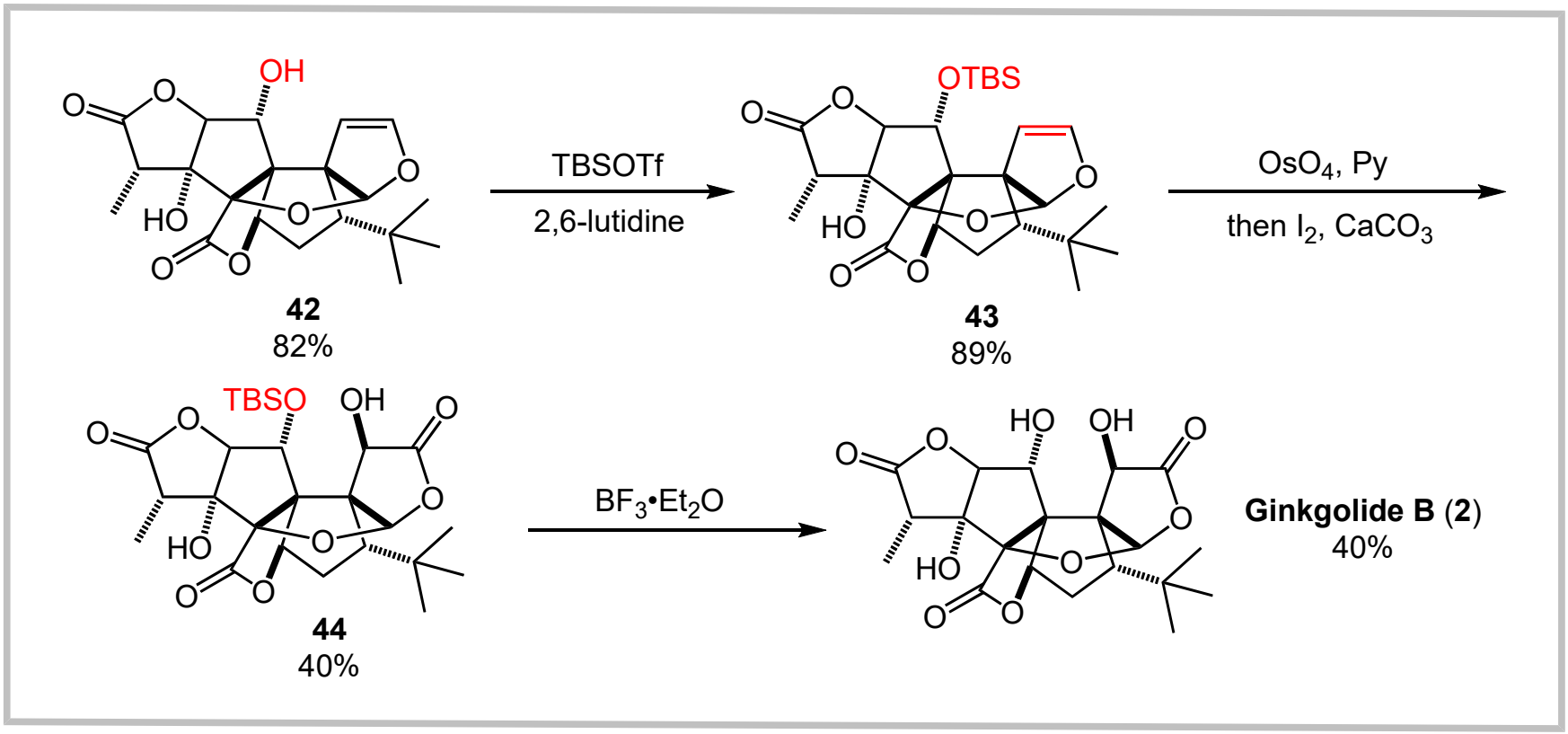
Ginkgolide A (1)

Ginkgolide B (2)

Synthesis of Ginkgolide A



Synthesis of Ginkgolide B

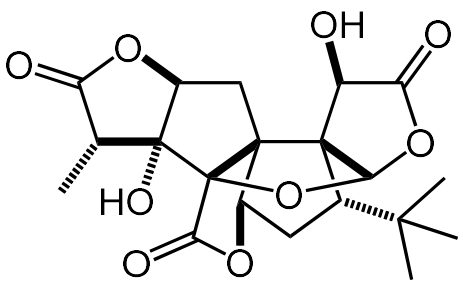


42
82%

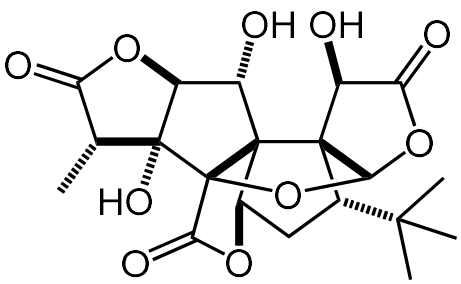
43
89%

44
40%

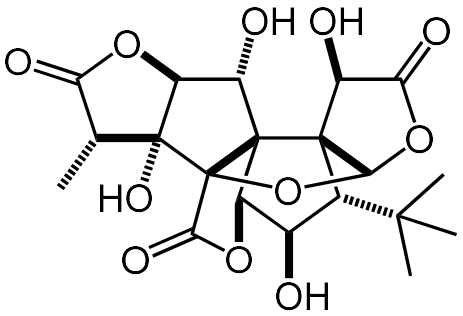
Summary



Ginkgolide A (**1**)



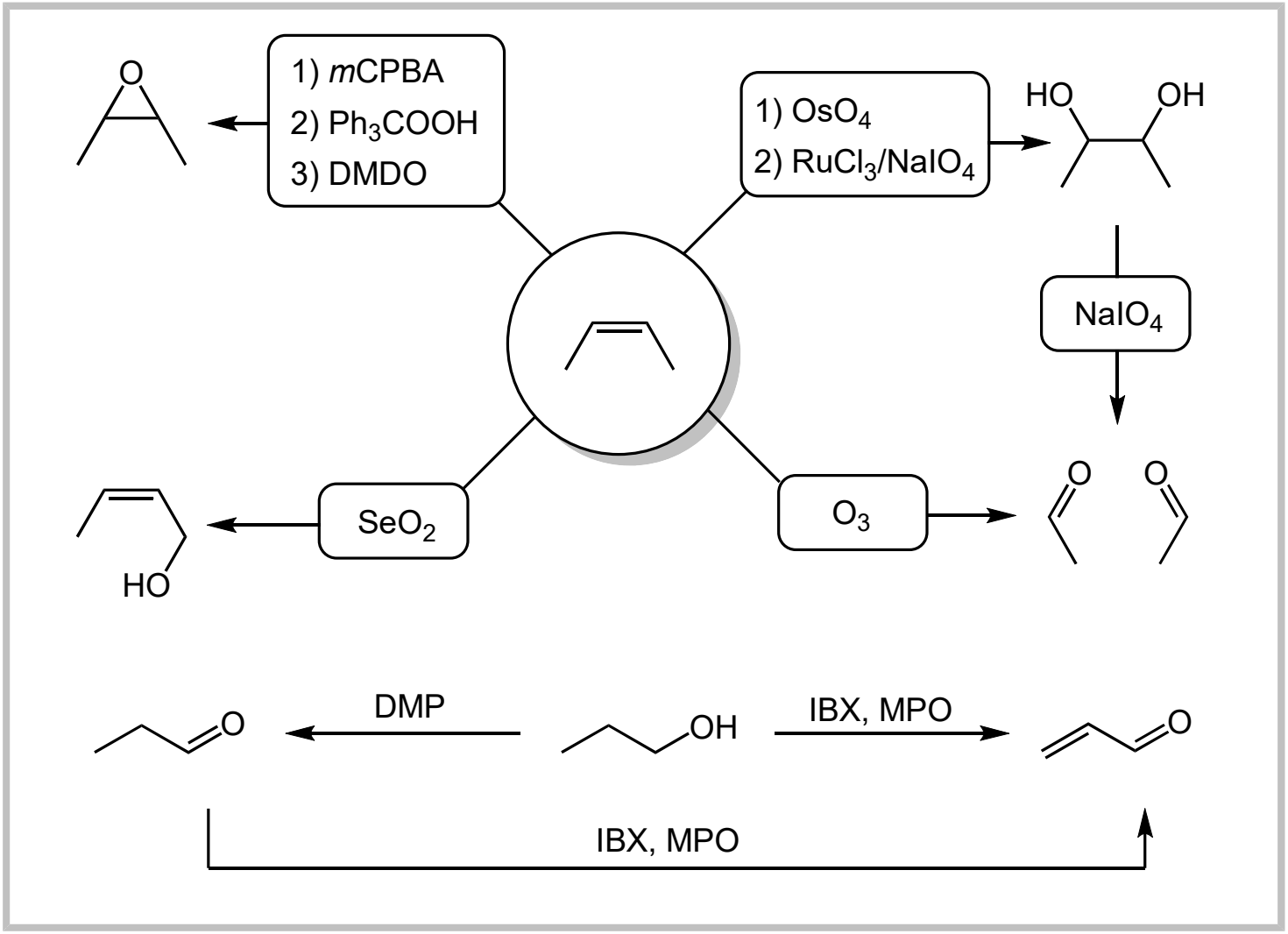
Ginkgolide B (**2**)



Ginkgolide C (**3**)

- ✓ **First total synthesis of Ginkgolide C: 26 steps, 1.5% overall yield;**
- ✓ **Orchestrate a series of C-C formations and oxidations;**
- ✓ **Provide an unique platform for the total synthesis of Ginkgolides.**

Oxidation in This Work



The First Paragraph

写作思路

Ginkgolide A、B、C的来源

↓

Ginkgolide化合物的应用

↓

合成Ginkgolide化合物的方法

The First Paragraph

- ✓ Ginkgolides are complex polyoxygenated diterpenoids isolated from the leaves and root bark of the Ginkgo biloba tree, also known as the maidenhair tree or as the “living fossil”, as its fossils date back to the Jurassic period.
- ✓ Ginkgolides, especially ginkgolide B, are strong antagonists to the platelet-aggregating receptor (PAFR), which is known as a potent inflammatory factor that plays a role in acute and chronic inflammation.
- ✓ Although their therapeutic profile is remarkable, their daunting structures present a significant challenge for chemical synthesis, for which only a handful of synthetic studies of these molecules have been performed.

The Last Paragraph

写作思路

总结工作：完成Ginkgolide C的首次全合成

⇩

阐述特点：通过合成关键中间体构建Ginkgolide化合物的合成平台

⇩

进行展望：构建更多天然产物

The Last Paragraph

In summary, the first total synthesis of ginkgolide C was achieved in 26 steps from commercially available starting material, concluding a journey that began more than 10 years ago. Along the way, we also completed the formal syntheses of ginkgolides A and B by intercepting intermediate 28 in 17 steps, which is the shortest synthesis of these ginkgolides to date. This work serves as a platform for further synthetic and biological studies of these complex and unique natural products.

Representative Examples

At the outset, ketone **6** would arise from a *5-exo-dig* cyclization on the alkyne at C15 preceded by a stereoselective cuprate addition of a *tert*-butyl group at C8 on enone **7**. (开始，*adv,* 可替换firstly)

The synthesis commenced by the conversion of ketone 11 to the corresponding dimethyl ketal, which underwent a Claisen rearrangement with allylic alcohol **12** to generate ketone **13**. (开始，*verb*，可替换start)

To our dismay, no expected enol product was isolated; only several side products were observed, resulting from the deprotection of the MOM group. (令我们沮丧的是)

Acknowledgement

Thanks
for your attention