

Literature Report 6

Total Synthesis of Isorosthin L and Isoadenolin I

Reporter: Wen-Jun Huang

Checker: Li-Xia Liu

Date: 2022-05-30

Ao, J.; Liang, G.* *et al. Angew. Chem. Int. Ed.* **2022**, 61, e202114489

Lv, Z.; Liang, G.* *et al. Chem. Eur. J.* **2018**, 24, 9773

CV of Prof. Guangxin Liang



Background:

- **1993-1997** B.S., School of Chemistry, Nankai University
 - **2000-2002** M.S., The Ohio State University
 - **2002-2007** Ph.D., University of California, Berkeley
 - **2007-2009** Abbott Laboratories
 - **2009-2019** Nankai University
 - **2019-Now** Professor, Shanghai Tech University
-

Research:

- Total synthesis of complex natural products with important biological activities or physiological functions;
- Research on synthesis technology of drugs and fine chemicals.

Contents

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Introduction

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Total Synthesis of Isorosthin L and Isoadenolin I

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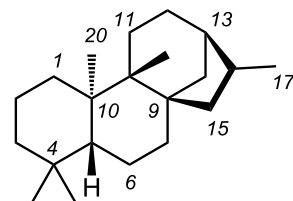
Total Synthesis of Trichorabdal A and Maoecrystal Z

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Summary

Introduction

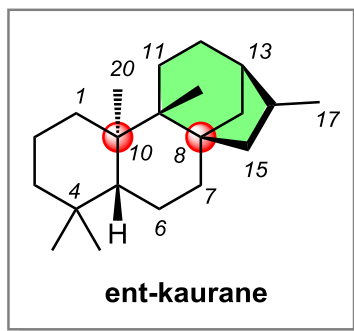
唇形科 (*Lamiaceae*) 香茶菜属 (*Isodon*) 植物是我国民间广泛使用的草药，具有清热解毒、抗菌消炎、舒筋活血、抗肿瘤等功效。全世界共分布约150余种，我国有90余种，变种20余种。



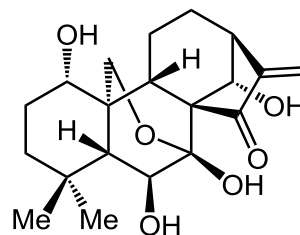
ent-kaurane

研究的部分
香茶菜属植物

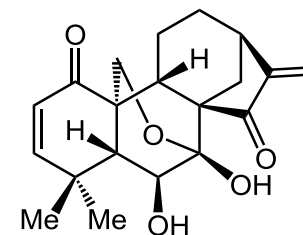
Introduction



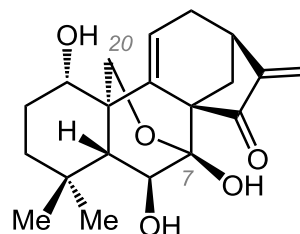
- ♥ Antibacterial
- ♥ Antineoplastic
- ♥ Anti-inflammatory



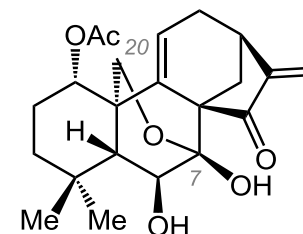
Oridonin (1)



Eriocalyxin B (2)

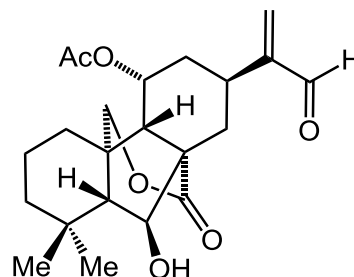


Isorosthin L

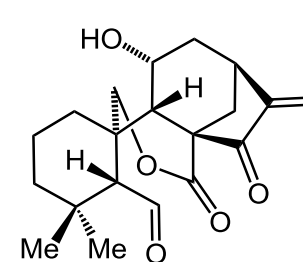


Isoadenolin I

Liang, G.* *et al.* 2022



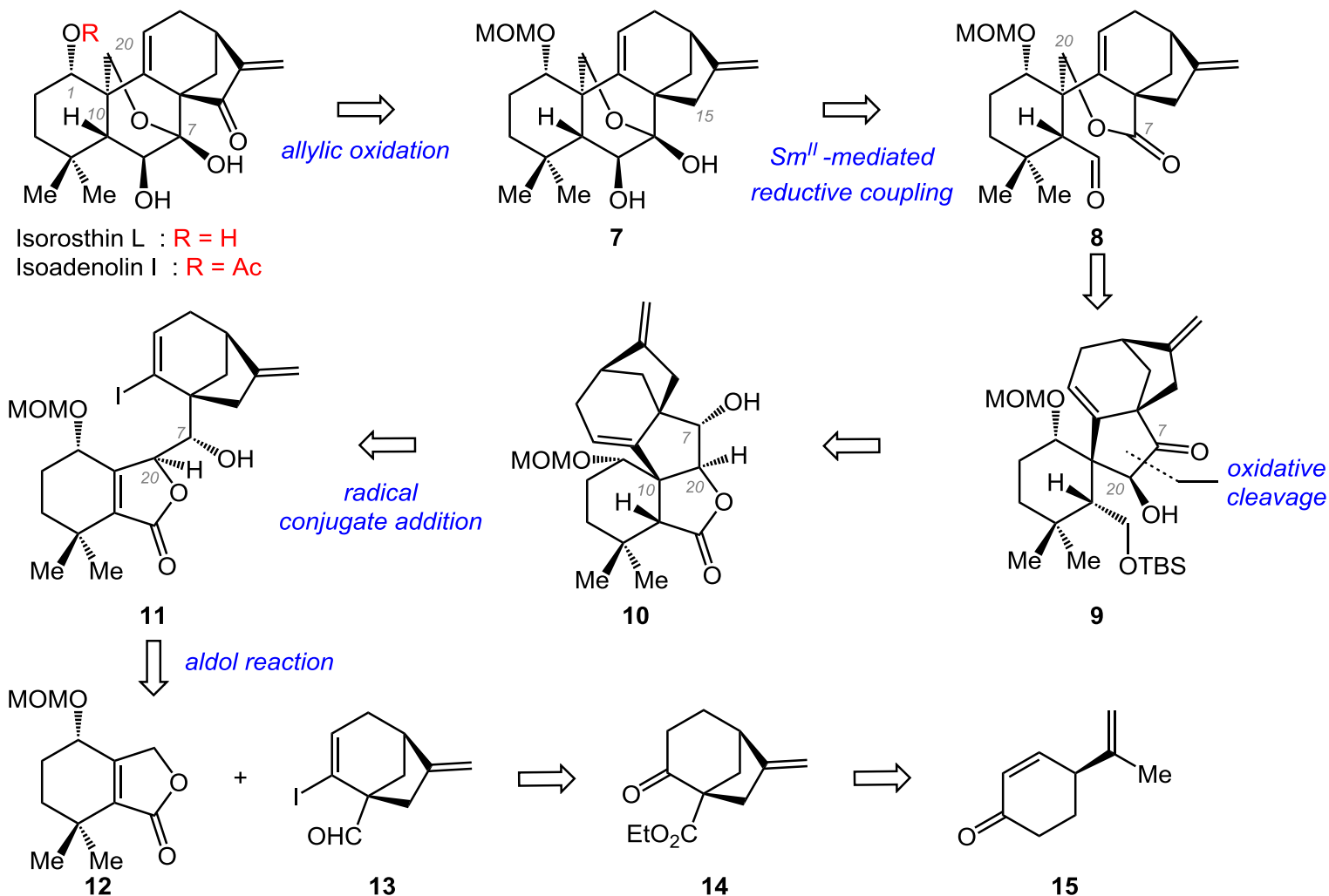
Maoecrystal Z



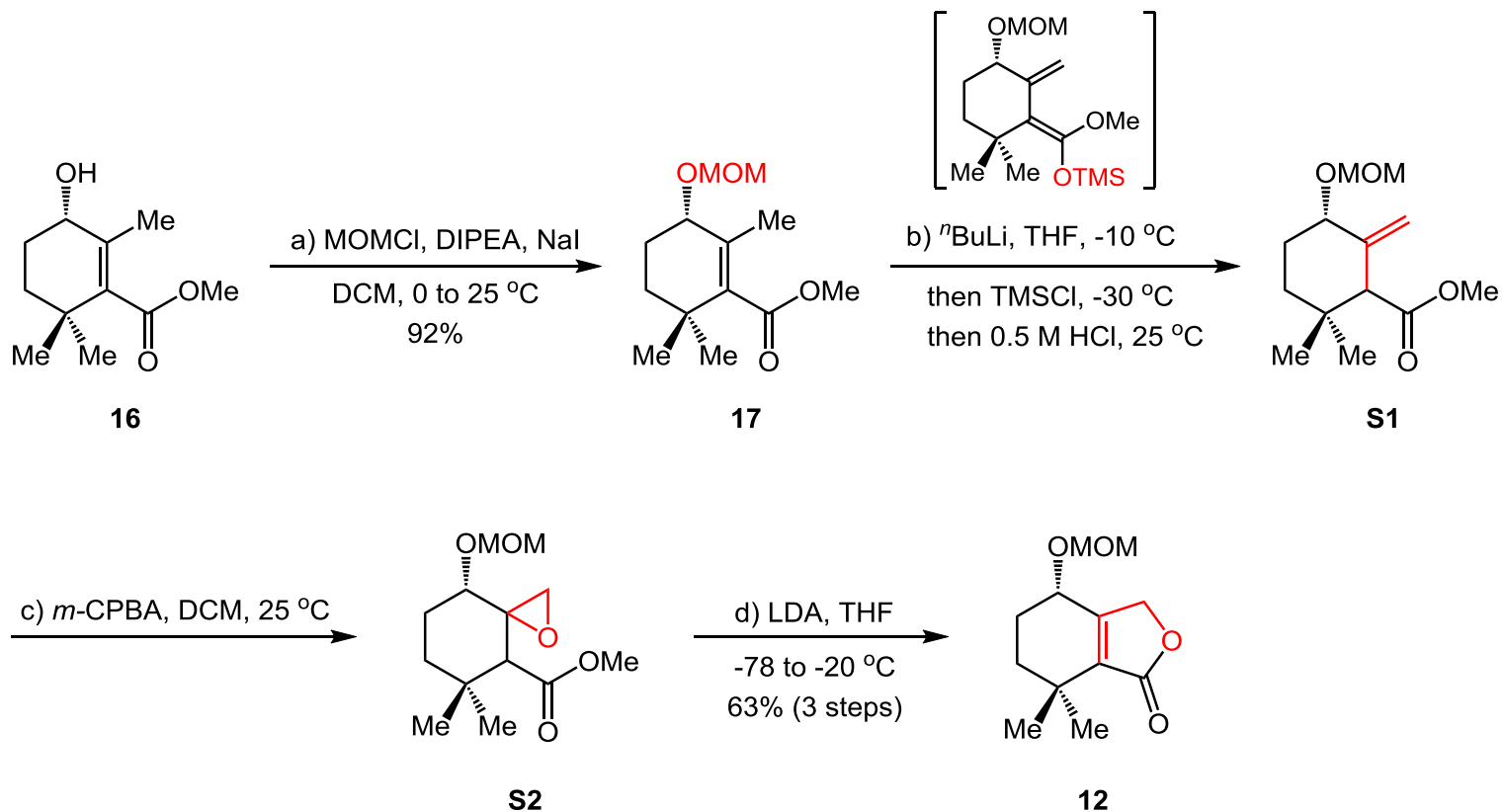
Trichorabdal A

Liang, G.* *et al.* 2018

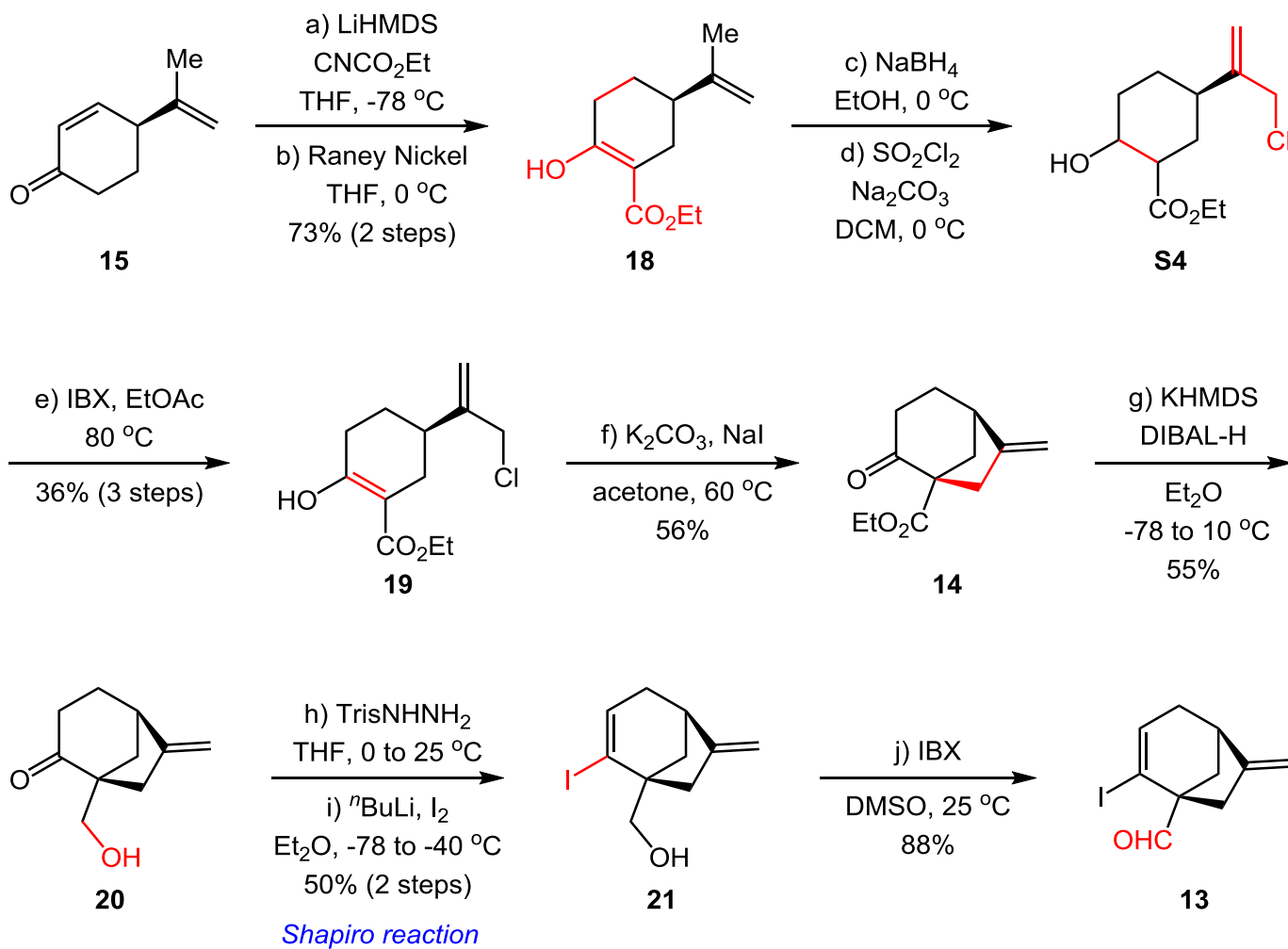
Retrosynthetic analysis



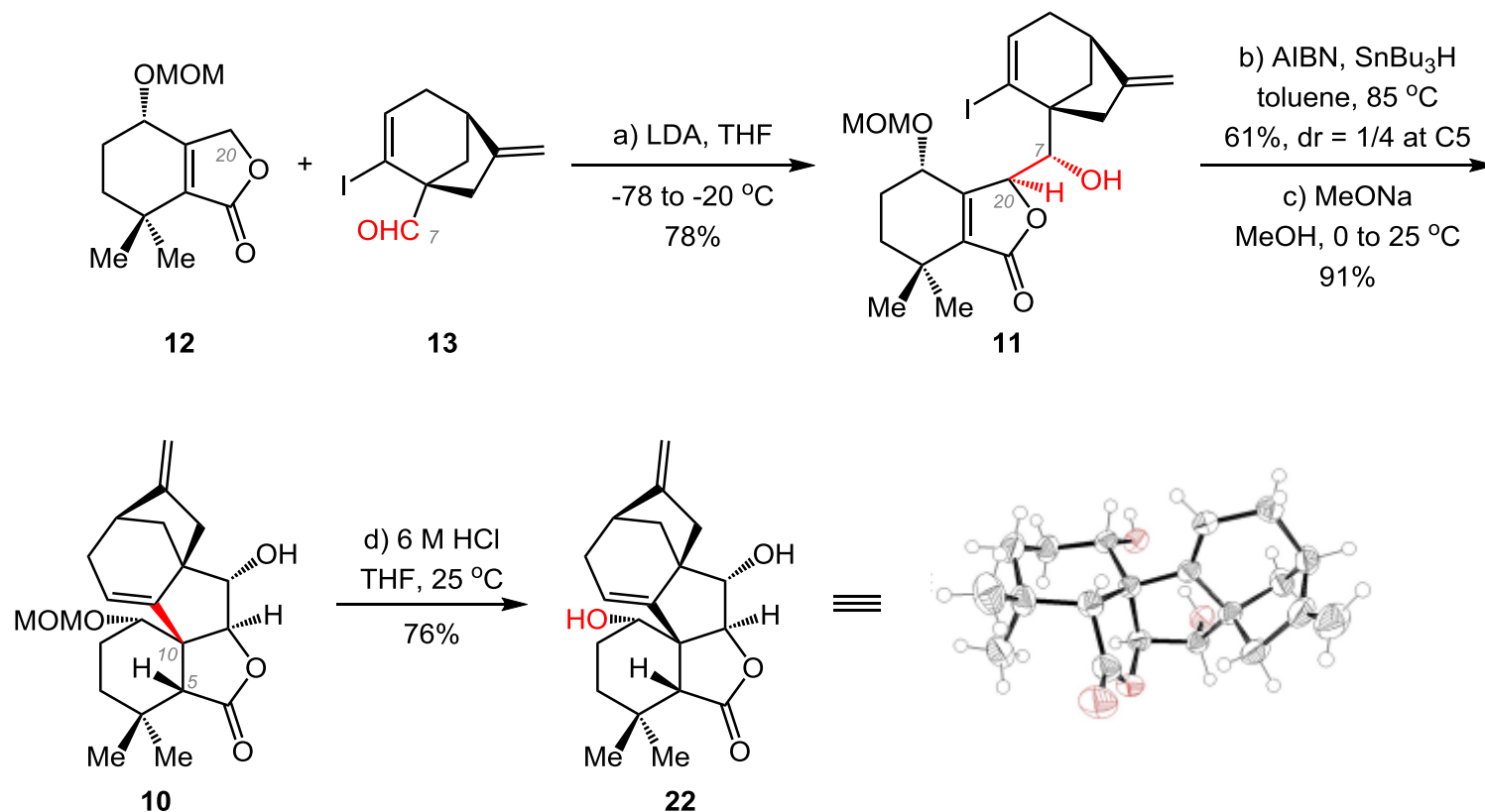
Preparation of the building block 12



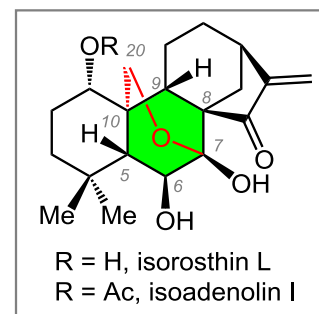
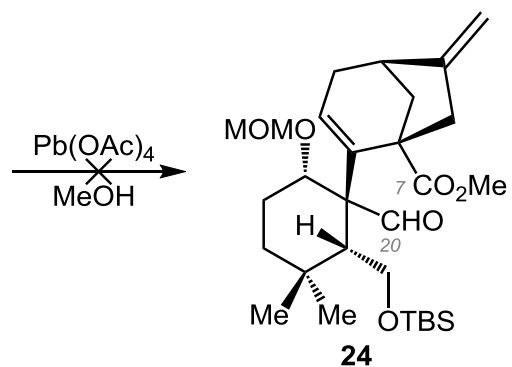
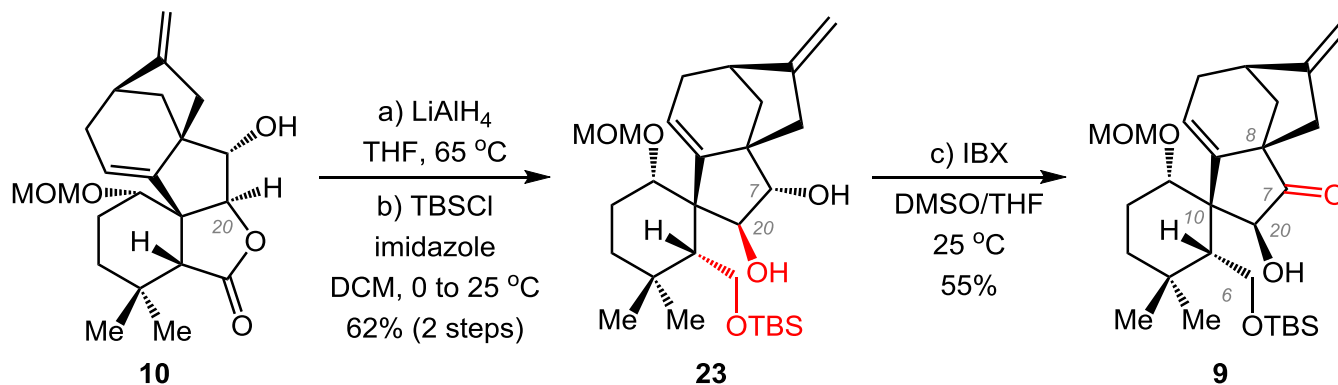
Preparation of the building block 13



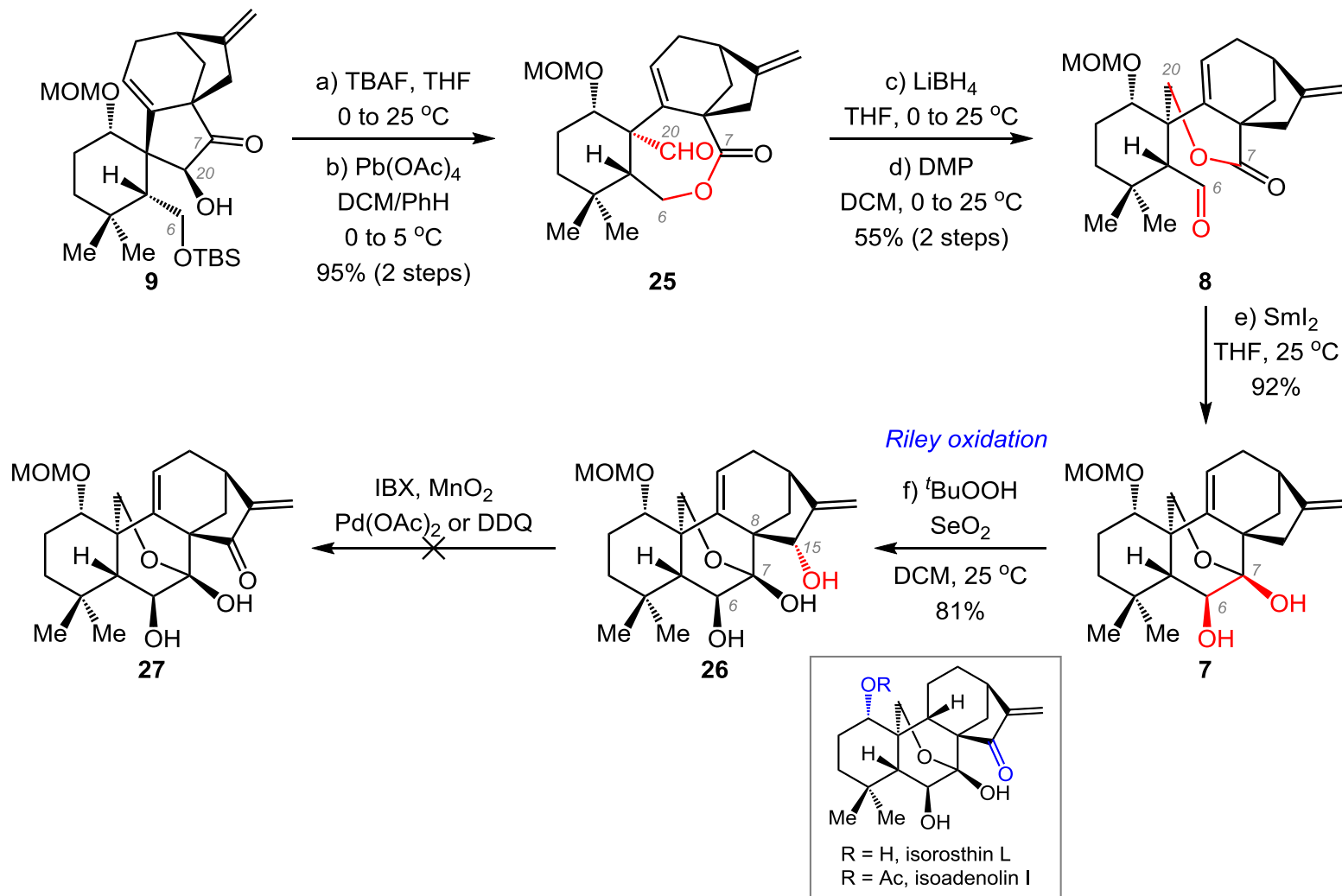
Preparation of the intermediate 22



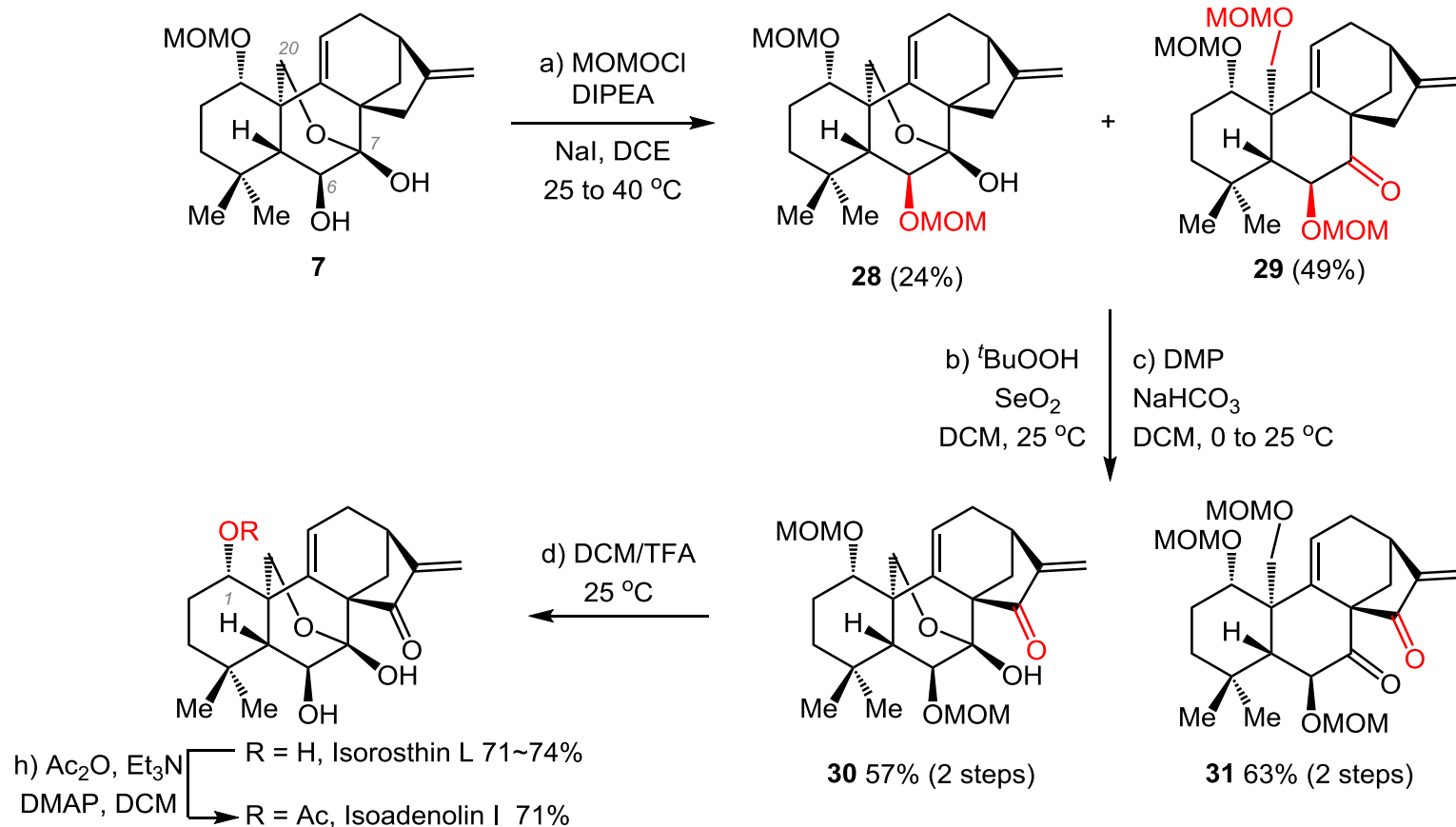
Preparation of the intermediate 9



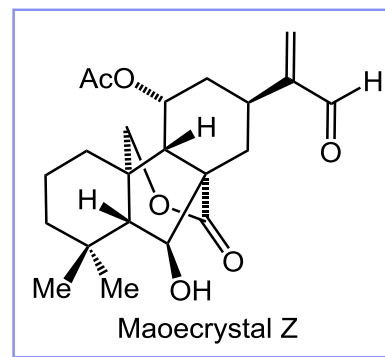
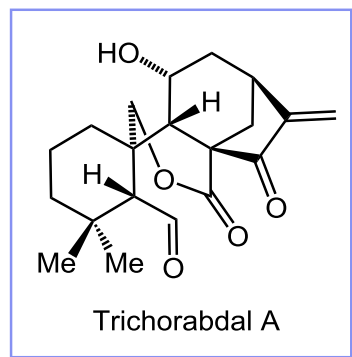
Preparation of the advanced intermediate 26



Total syntheses of Isorosthin L and Isoadenolin I

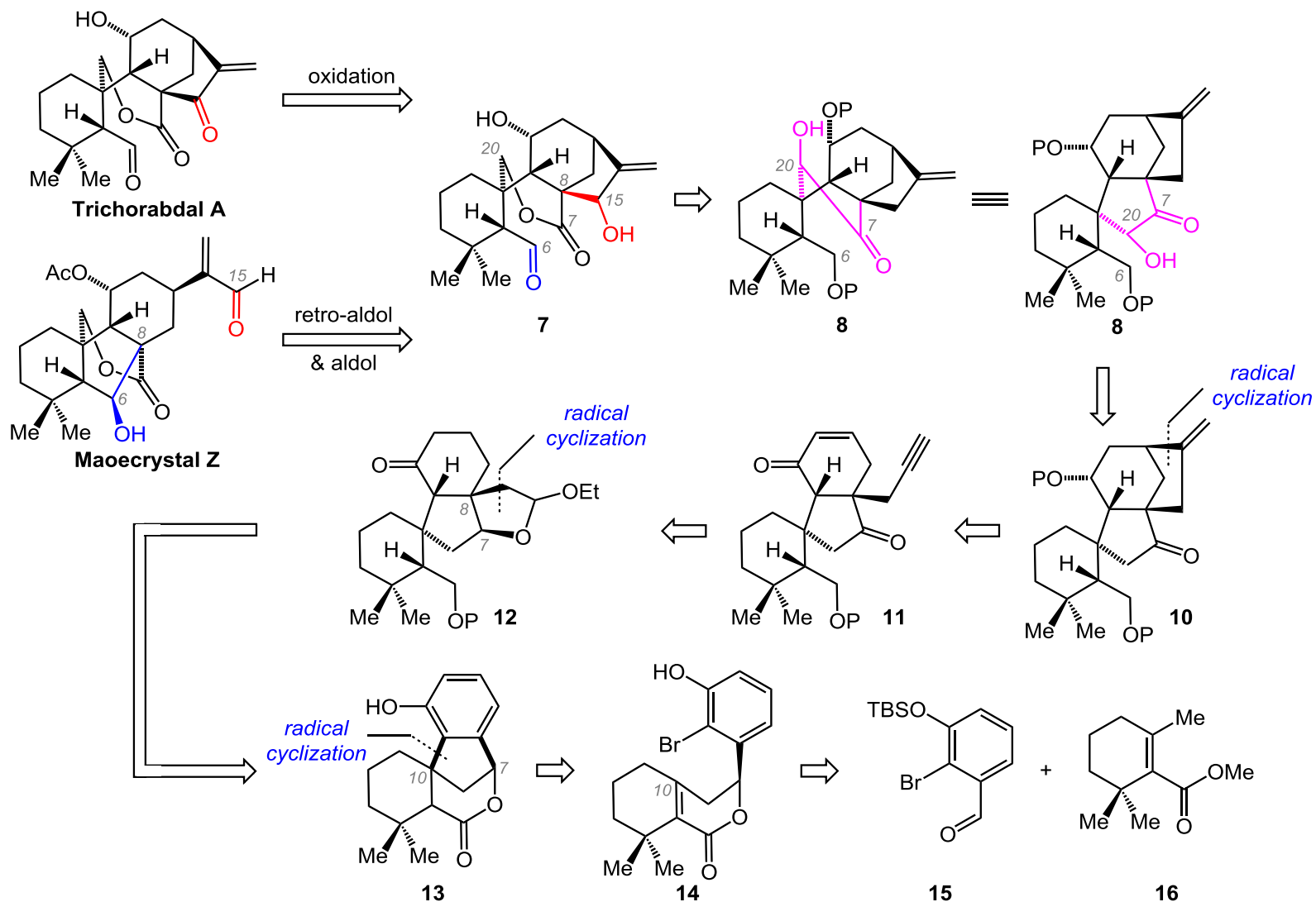


Total syntheses of Trichorabdal A and Maoecrystal Z

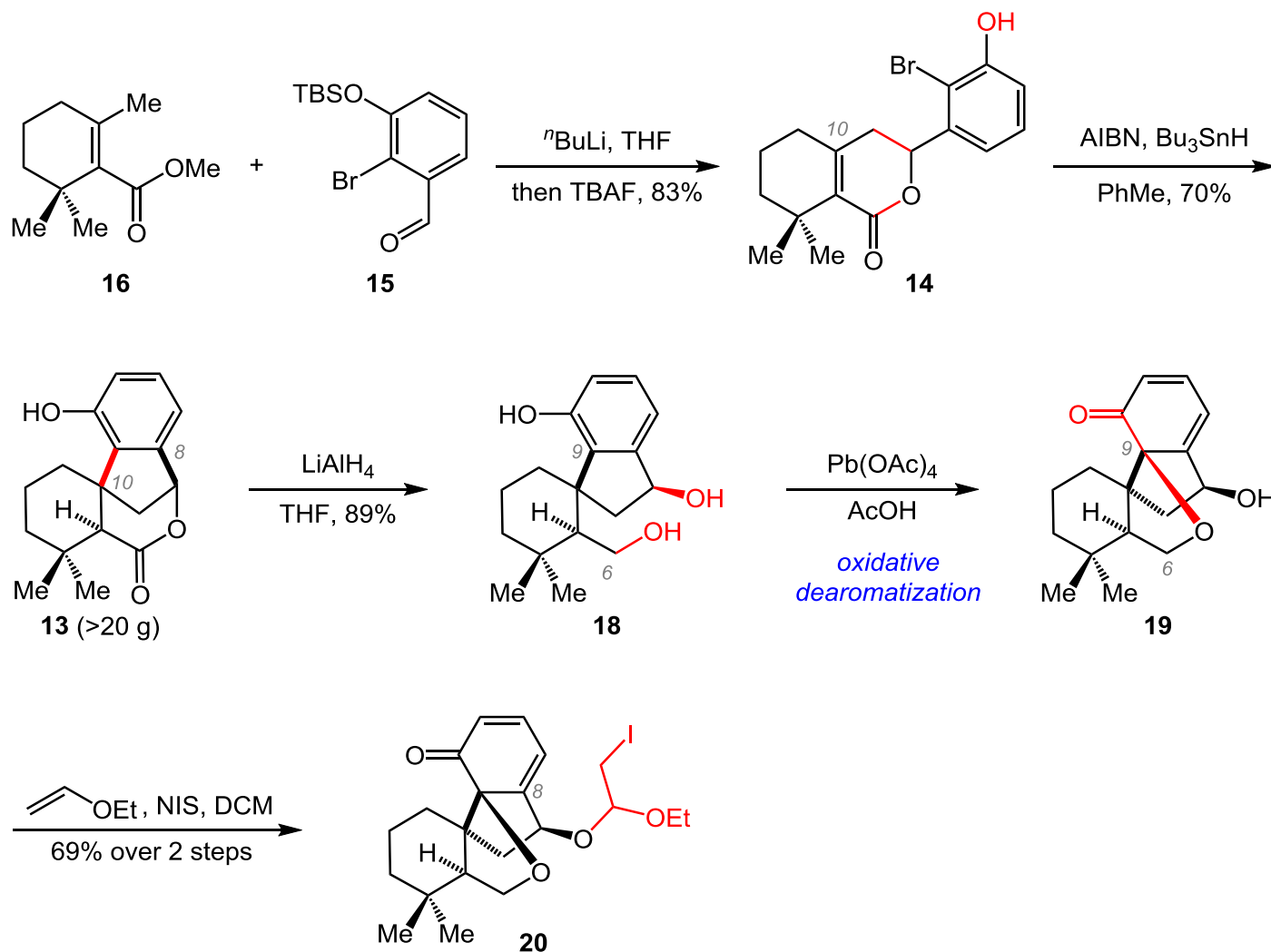


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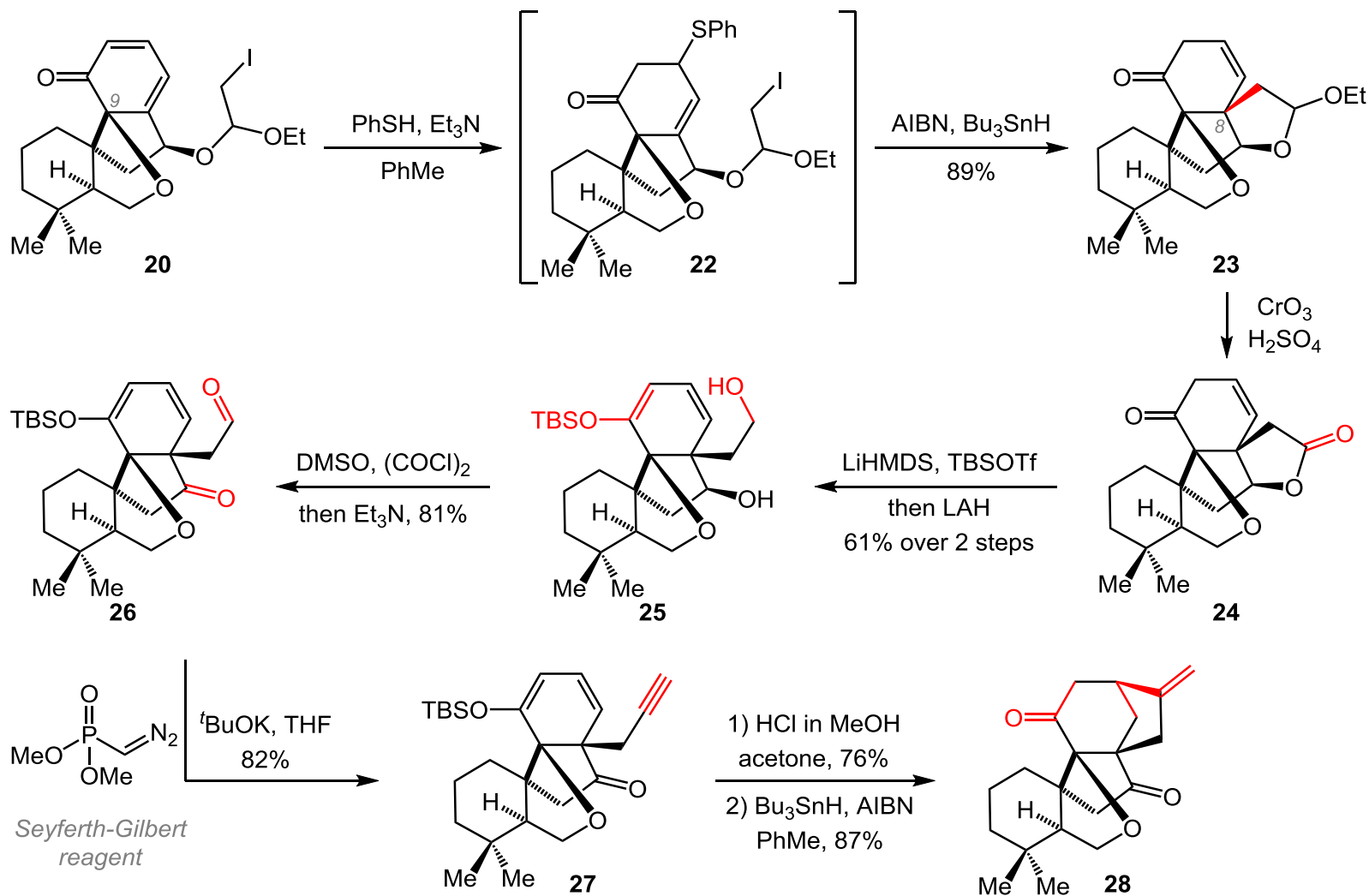
Retrosynthetic analysis



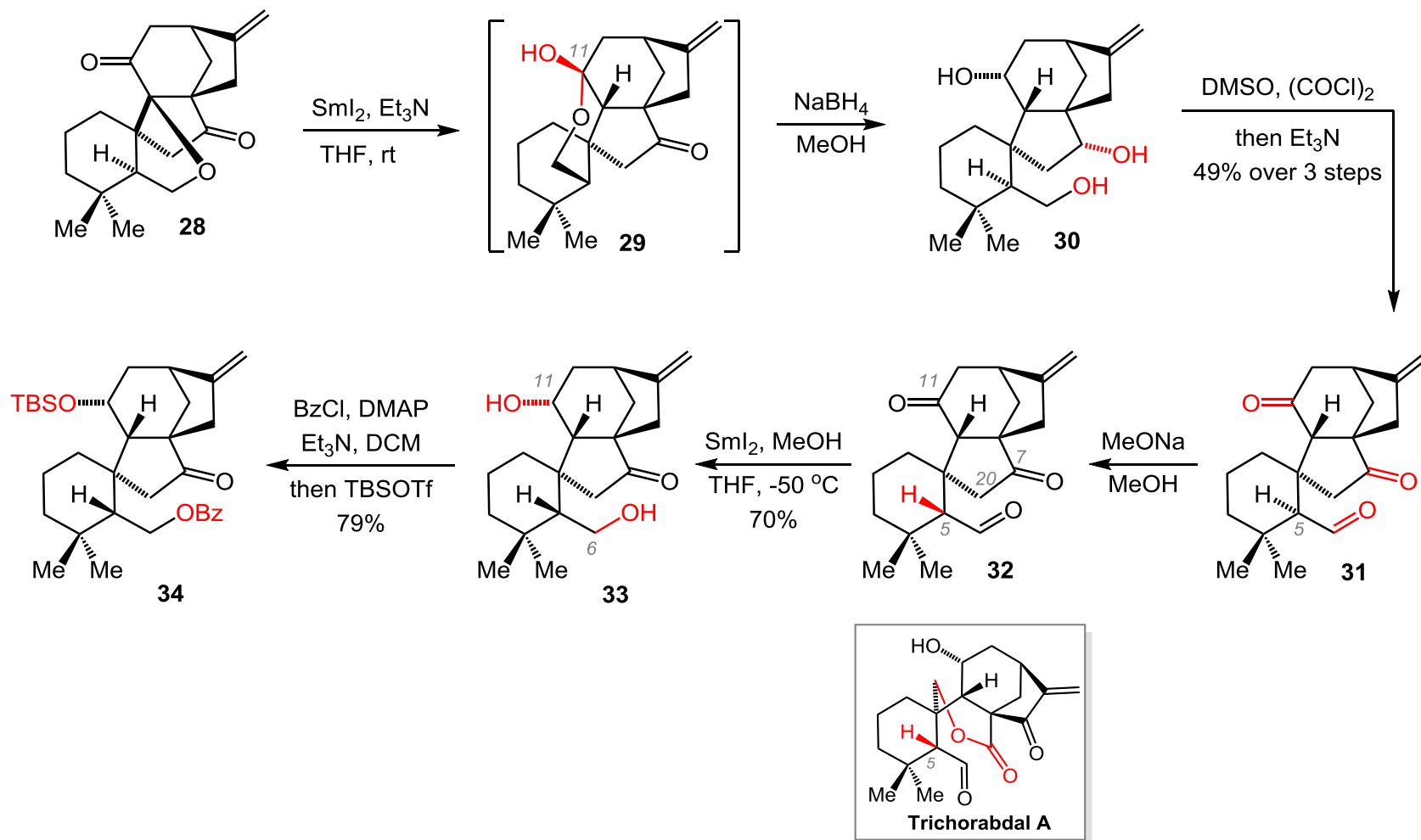
Rapid construction of 20



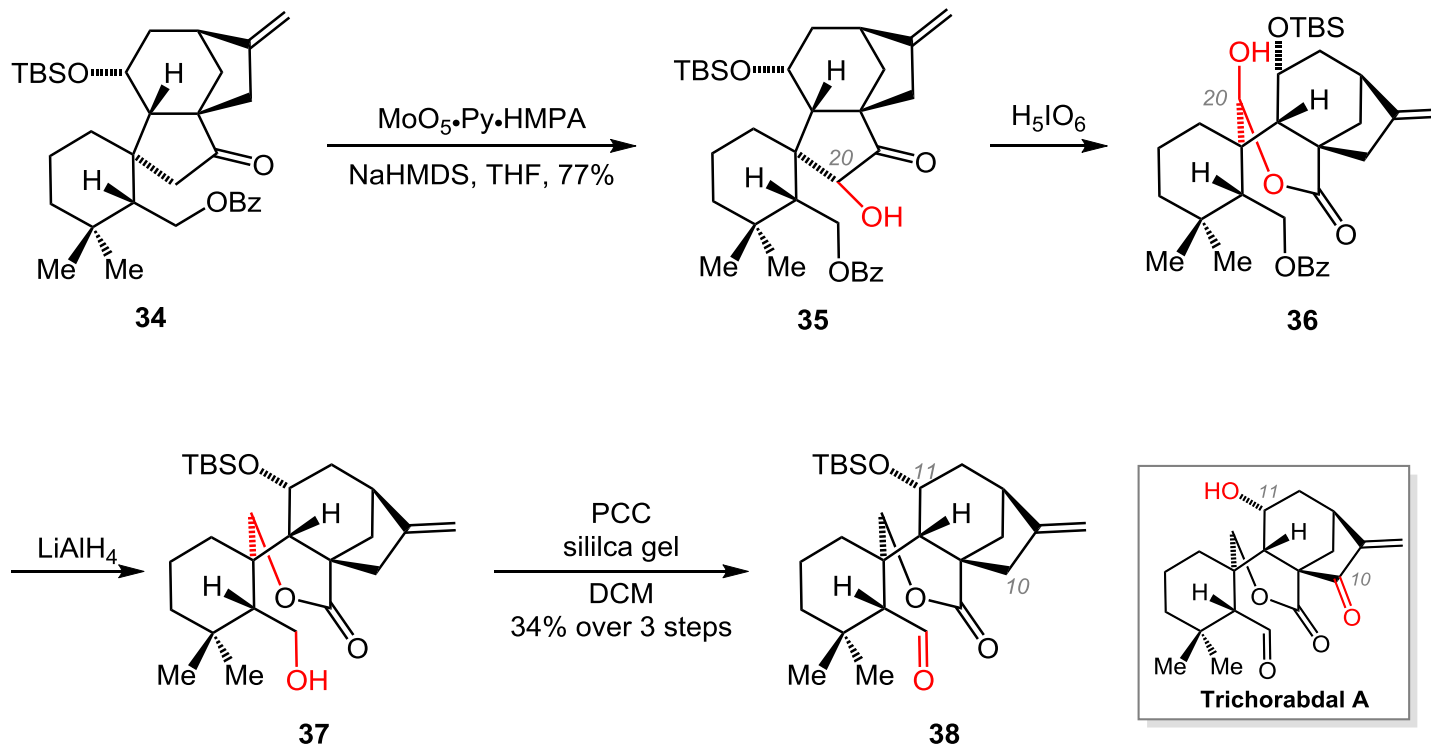
The construction of 28



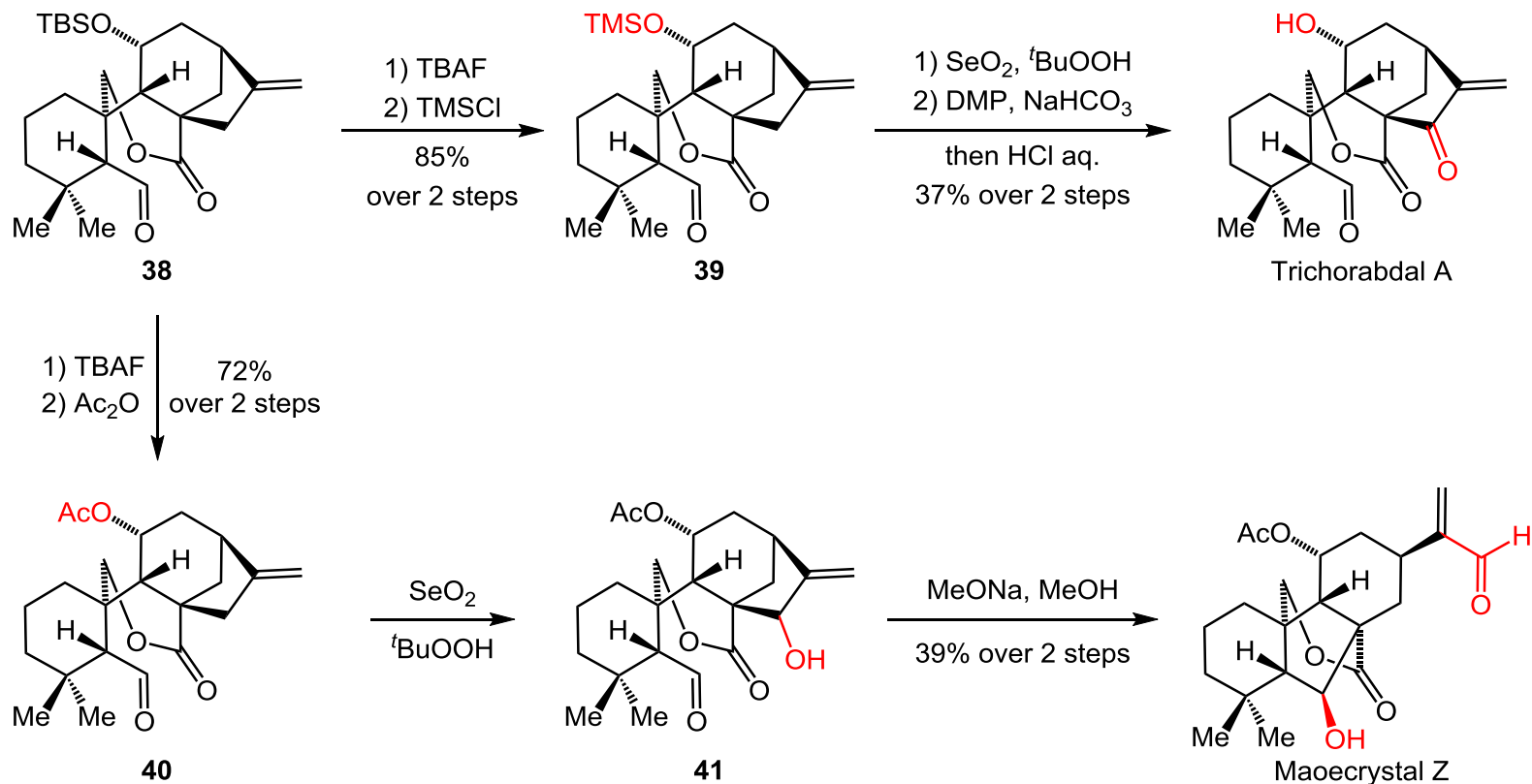
Synthesis of 34



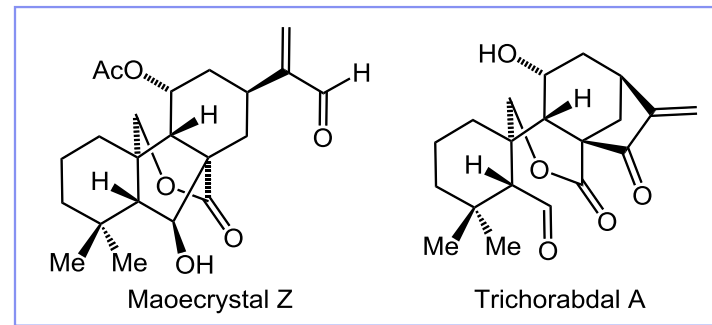
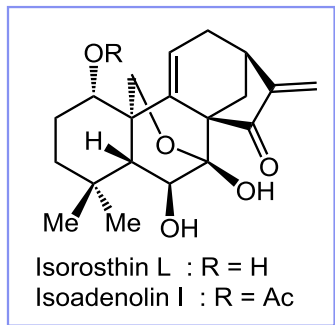
Synthesis of the advanced intermediate 38



Total syntheses of Trichorabdal A and Maoecrystal Z



Summary



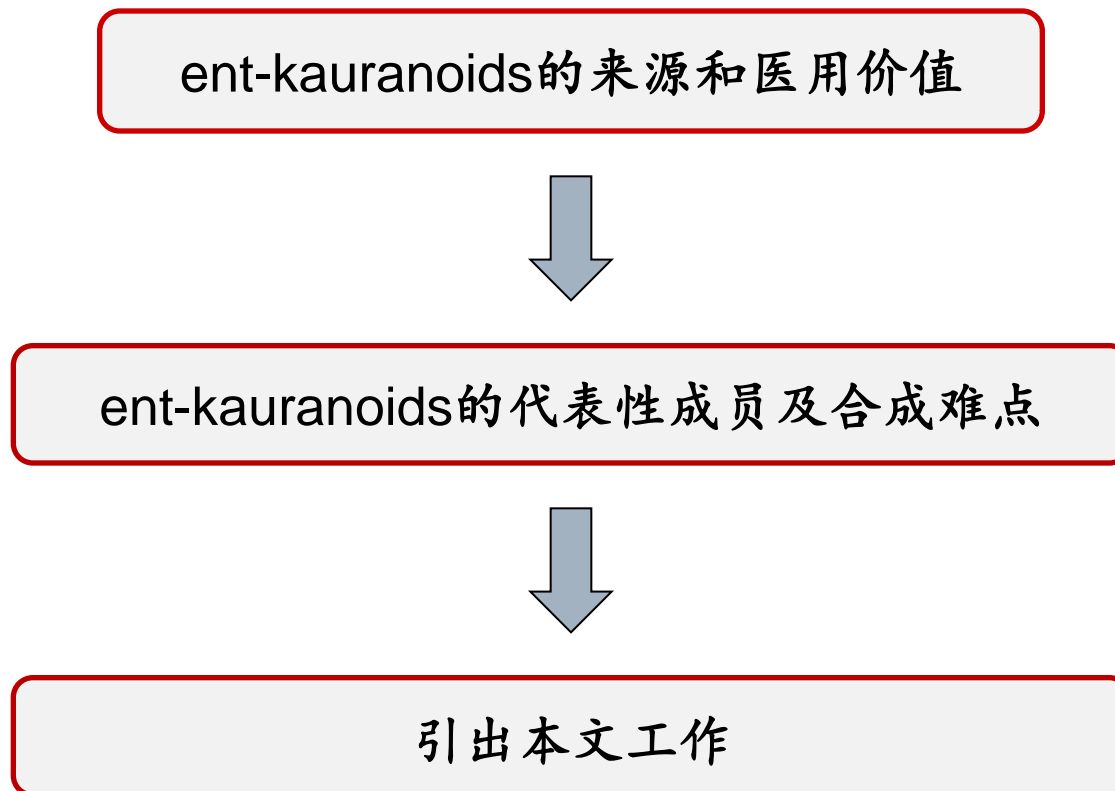
- Isorosthin L : 15 steps, 1.56% overall yield
- Isoadenolin I : 16 steps, 1.10% overall yield
- Intermolecular aldol reaction
- Radical cyclization
- Oxidative cleavage of the C-C bond

- Trichorabdal A : 24 steps, 0.25% overall yield
- Maoecrystal Z : 25 steps, 0.22% overall yield
- Retro-aldol/aldol reaction cascade
- Cross-ring radical cyclization
- Ueno–Stork cyclization

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The first paragraph

写作思路



The first paragraph

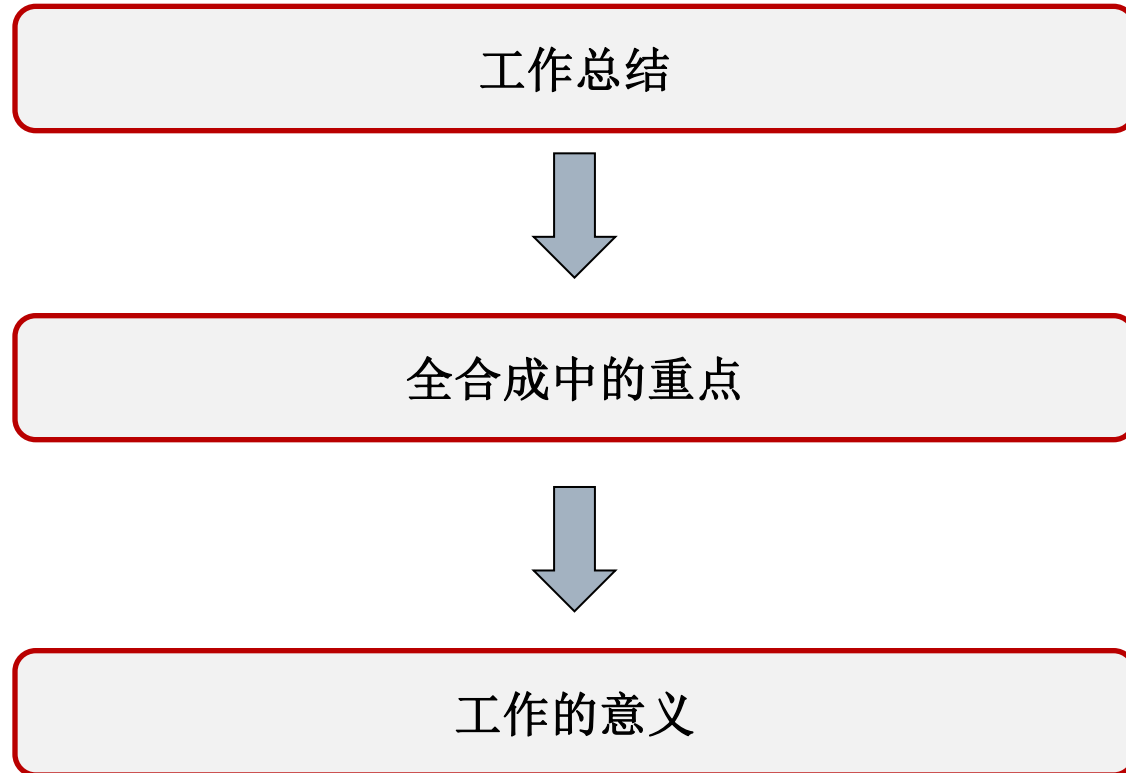
Isodon species are widely distributed plants, many of which have been used in Chinese folk medicine with a long history. Phytochemical research has disclosed that this genus is an abundant source of ent-kauranoids exhibiting a variety of bioactivities. For example, oridonin (1), ericalyxin B (2), pharicin A (3), and longikaurin A (4) all have promising therapeutic properties and have been used as lead compounds in antineoplastic drug development. The intriguing structures as well as important biological activities of ent-kaurane diterpenoids have attracted considerable attention from the synthetic community. These synthetic efforts culminated in many elegant syntheses of this family of molecules.

The first paragraph

Our group has also worked on these fascinating targets and achieved the total syntheses of trichorabdal A and maoecrystal Z in 2018. The oxidative dearomatization and late-stage construction of the [3.2.1] bicyclic motif in this previous synthesis have significantly increased the overall synthetic steps, which damaged the overall synthetic efficiency. This problem prompted us to develop a more efficient synthetic strategy for ent-kaurane diterpenoids by introducing the [3.2.1] bicyclic unit at the early stage of the synthesis. Herein, we report our total syntheses of isorosthin L and isoadenolin I, two unique cytotoxic 7,20-epoxy-ent-kauranoids bearing a distinctive double bond, based on such a strategy.

The last paragraph

写作思路



The last paragraph

In conclusion, a building-block-welding strategy has enabled the first total syntheses of isorosthin L and isoadenolin I from two simple building blocks 12 and 13. A substrate controlled diastereoselective aldol addition and a vinyl radical cyclization efficiently “welded” 12 and 13 together to assemble a rather complex intermediate bearing the critical quaternary center featured in ent-kaurane diterpenoids. Such a strategy also set the stage for easy cleavage of the C-C bond in the newly formed cyclopentane unit to create a lactone commonly seen in many ent-kaurane diterpenoids. The early-stage convergent and late-stage divergent nature of the strategy would accelerate the synthesis of many other members of this class of fascinating natural products and allow further exploration of their biological functions.

Representative examples

我们设想.....

We envisioned that... (预期; 展望)

We anticipated that... (预期, 预料; 期待, 盼望)

We conceived that... (构思; 设想)

We assumed that... (假定, 假设, 认为)

We reasoned that... (说服; 推断)

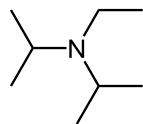
Oxidation of the allylic hydroxyl group in 7 gives 2, whereas a retro-aldol/aldol reaction sequence in 7 would fulfill the **nontrivial** C8-C15 bond cleavage and C6-C8 bond formation to provide 1. (adj. 重要的, 显要的)

The key cross-ring radical cyclization of 14 under standard conditions **furnished** 13 in 70% yield. (v. 供应; 装备; furnish 的过去分词)

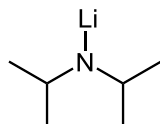
Acknowledgement

***Thanks
for your attention***

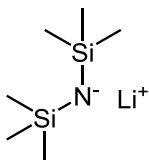
Reagent



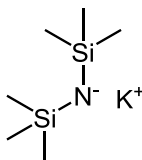
DIPEA



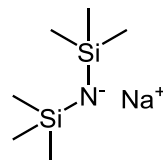
LDA



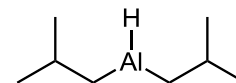
LHMDS



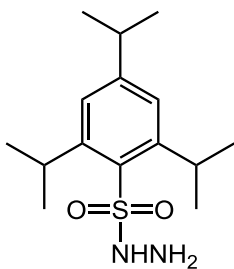
KHMDS



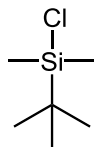
NaHMDS



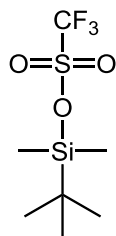
DIBAL-H



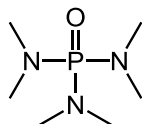
TrisNHNH₂



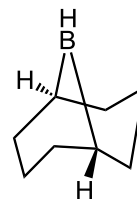
TBSCl



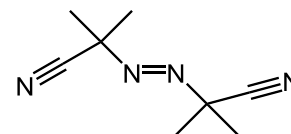
TBSOTf



HMPA



9-BBN



AIBN