



中国科学院大连化学物理研究所

DALIAN INSTITUTE OF CHEMICAL PHYSICS, CHINESE ACADEMY OF SCIENCES

Literature Report 8

Unified Total Syntheses of Rhamnofolane, Tigliane, and Daphnane Diterpenoids

Reporter: Xiang Li

Checker: Gao-Wei Wang

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Hirose, A. Watanabe, A. Ogino, K. Nagatomo, M. **Inoue, M.**

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CV of Prof. Masayuki Inoue



Research Interests:

- Total synthesis and functional analysis of biologically active natural products

Education:

- **1989-1993** B.S., The University of Tokyo
- **1993-1998** Ph.D., The University of Tokyo
- **1998-2000** Postdoc., Sloan-Kettering Institute for Cancer Research
- **2000-2007** Assistant Professor, Lecturer, Associate Professor, Tohoku University
- **2007-Present** Professor, The University of Tokyo

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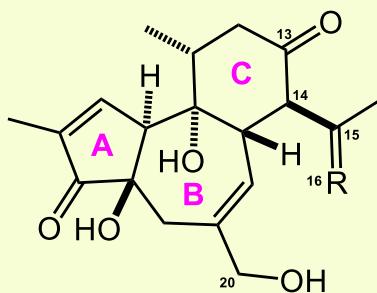
1 Introduction

2 Unified Total Syntheses of Rhamnofolane, Tigliane, and Daphnane Diterpenoids

3 Summary

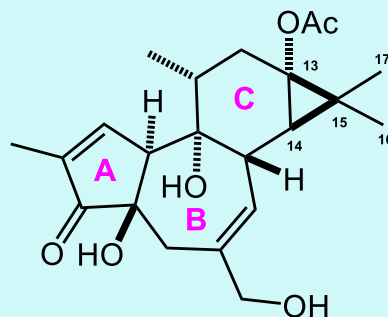
Introduction

Rhamnfolane



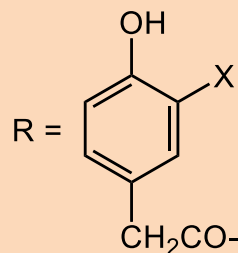
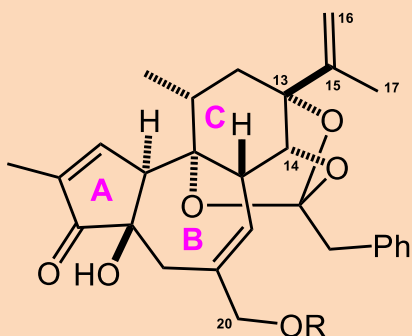
Crotophorbolone (1): R = CH₂
Langduin A (2): R = CH₃, H

Tigliane



Prostratin (3)

Daphnane



Resiniferatoxin (4): X = OMe
Tinyatoxin (5): X = H

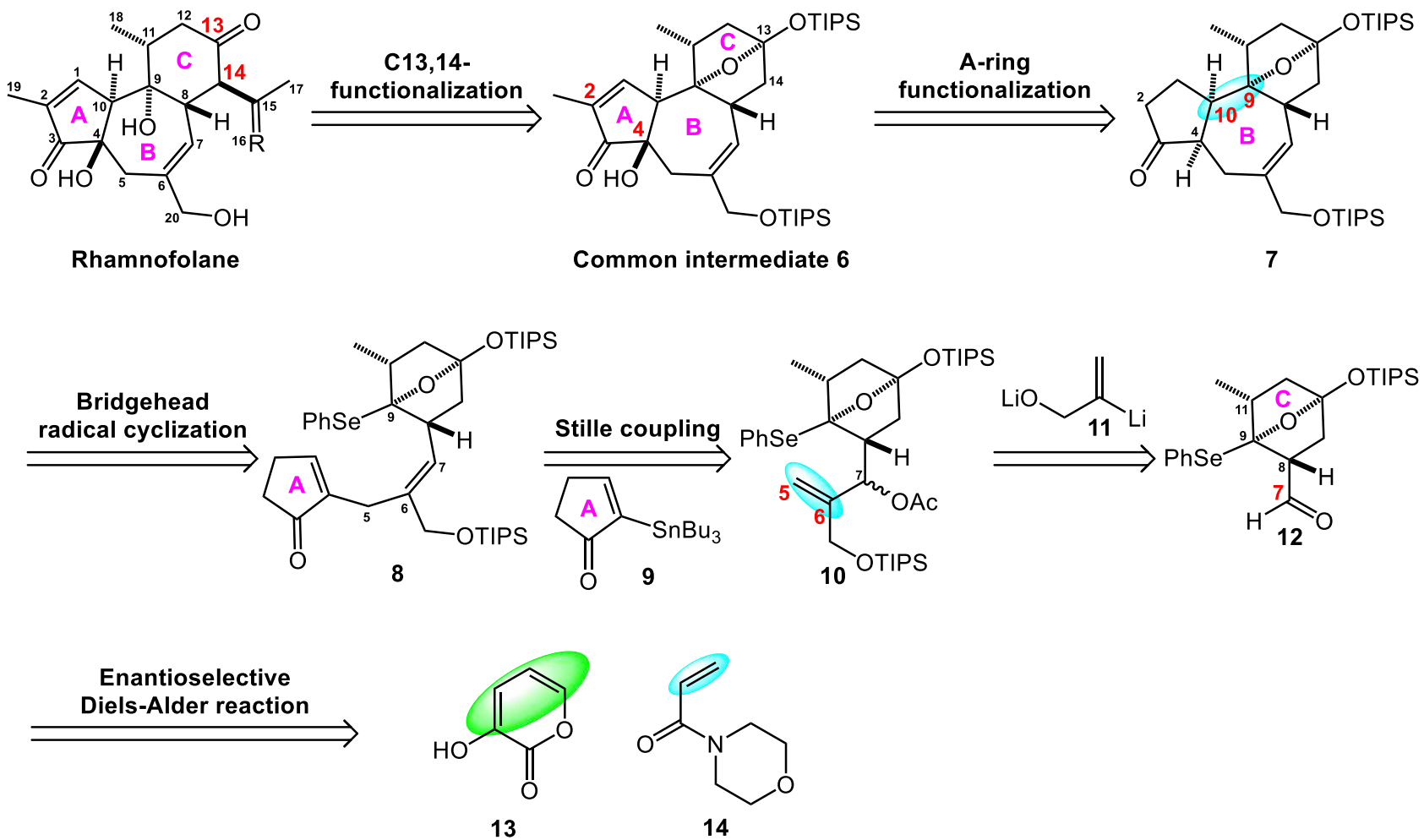


Euphorbiaceae

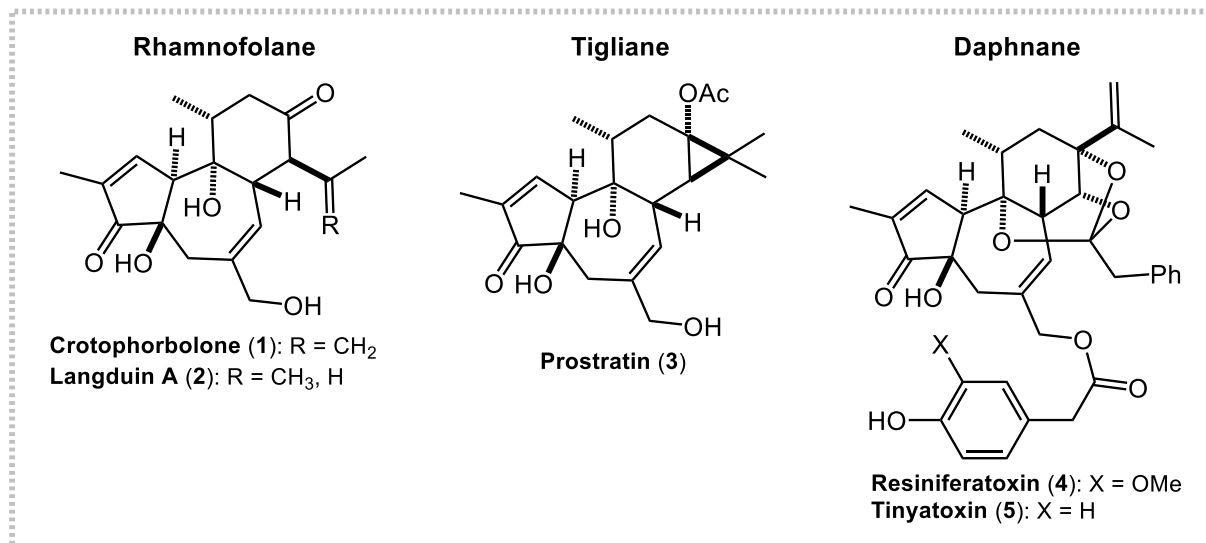
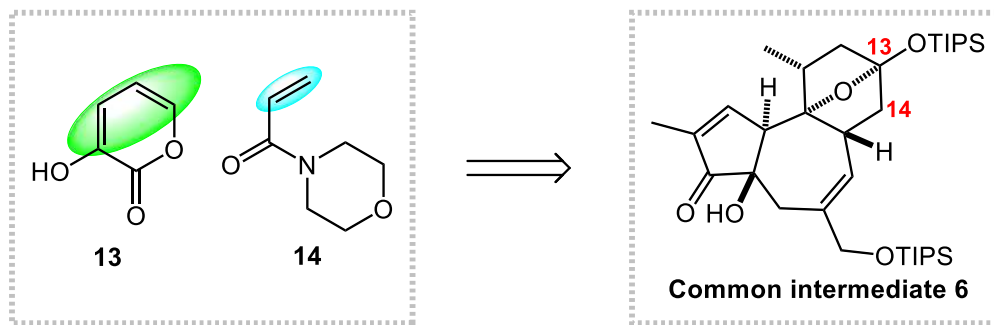
Thymelaeaceae

- They have been identified from plants of the **Euphorbiaceae** and **Thymelaeaceae** species.
- Many of these molecules display a wide range of properties, such as **antiviral, anticancer, analgesic, immunomodulatory, neurotrophic, and tumor promotional activities.**

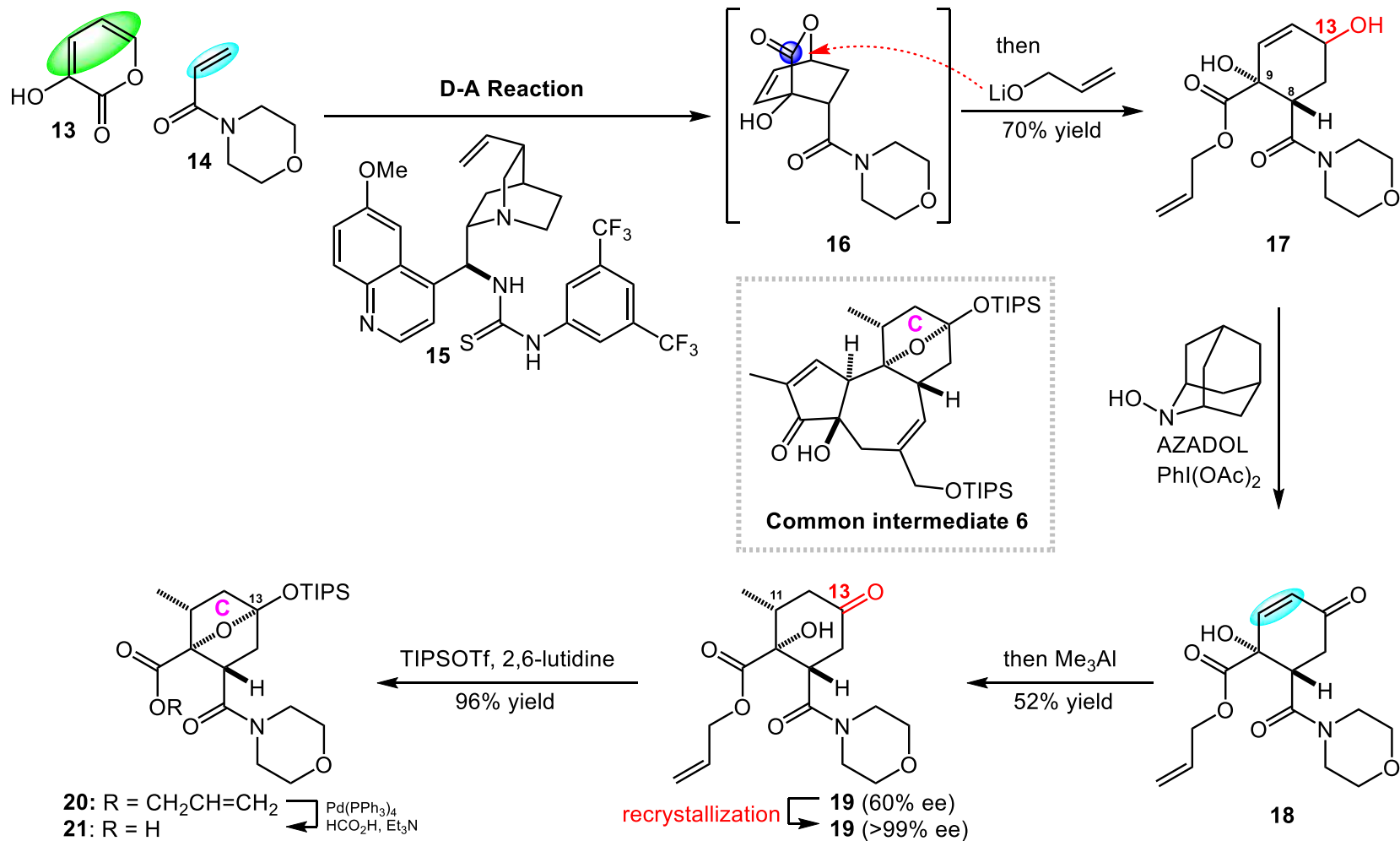
Retrosynthetic Analysis



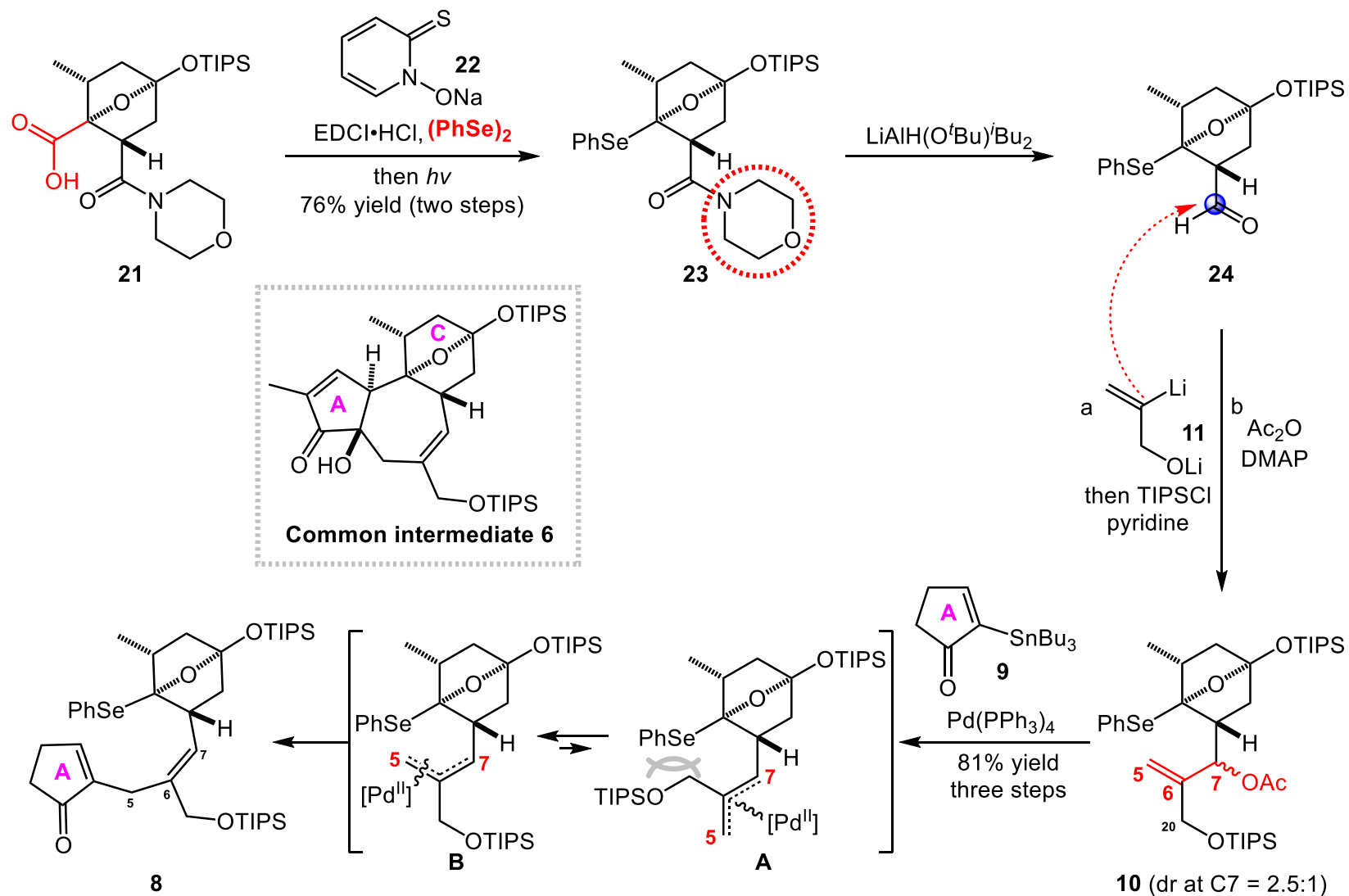
Synthesis of Diterpenoids



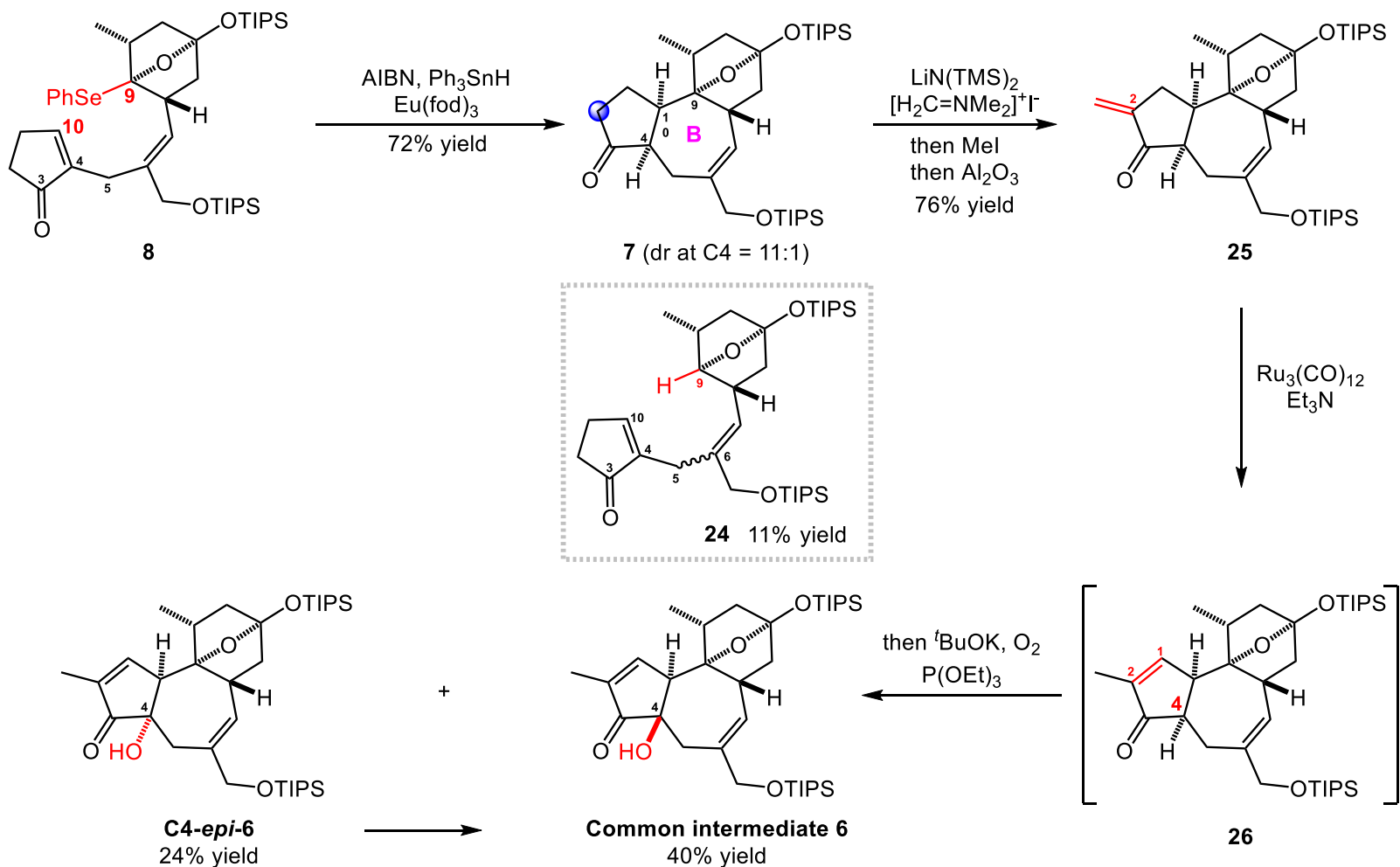
Synthesis of Common Intermediate 6



Synthesis of Common Intermediate 6



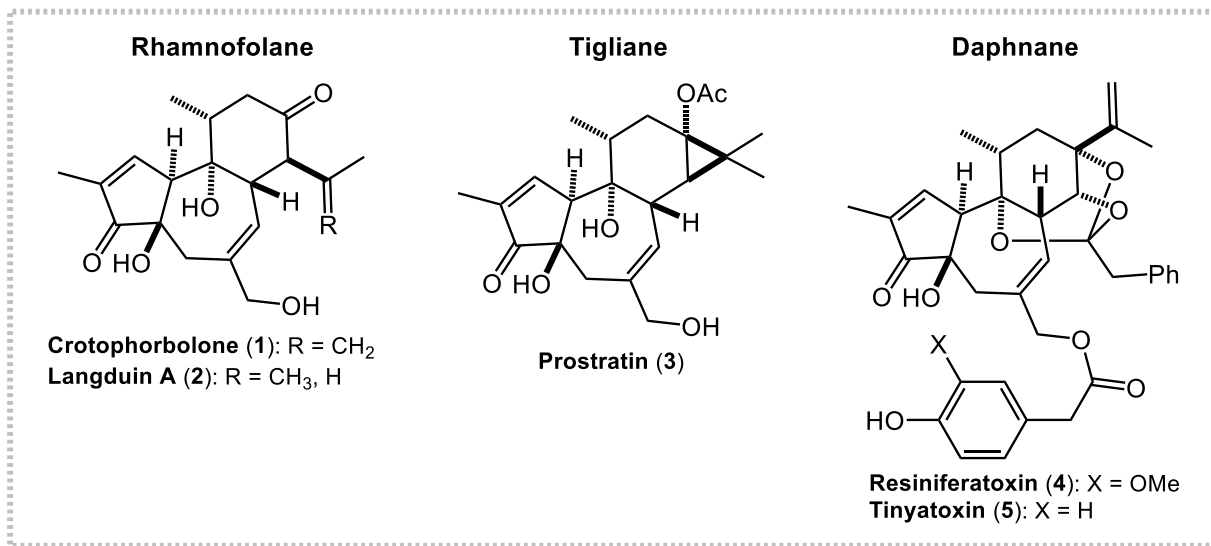
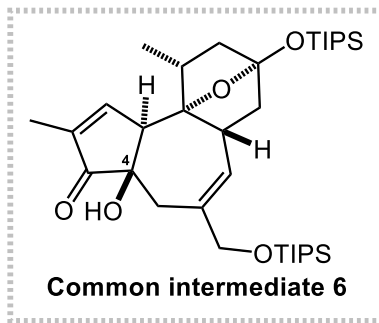
Synthesis of Common Intermediate 6



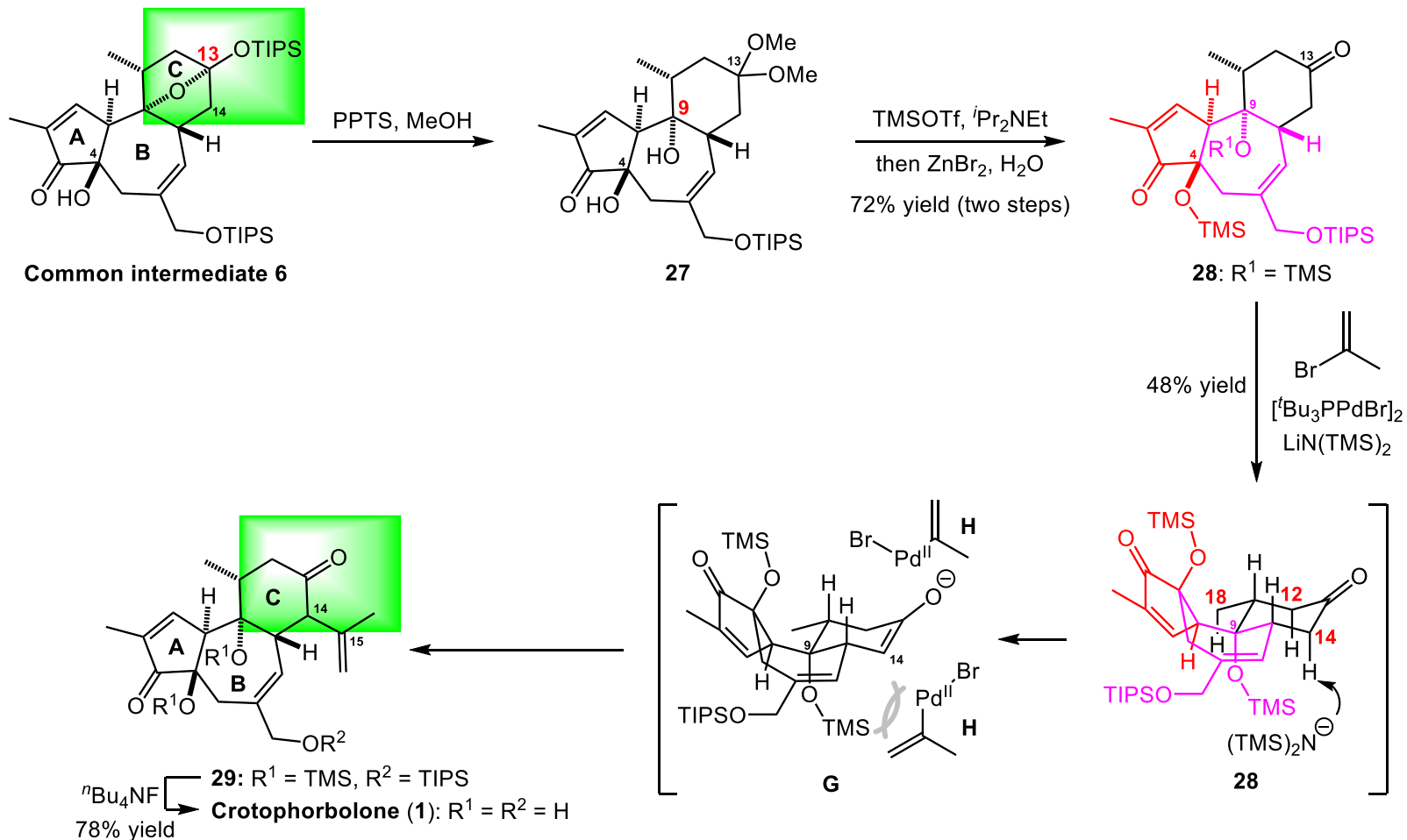
a. Sml_2 , 79% yield (brsm 88% yield, **26**:**C4-epi-26** = 1:2).

b. $t\text{BuOK}$, O_2 , P(OEt)_3 (**6**:**C4-epi-6** = 1.5:1), **6**: 51% yield, **C4-epi-6**: 33%.

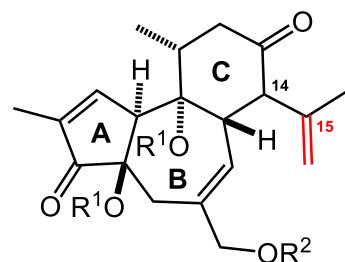
Synthesis of Diterpenoids



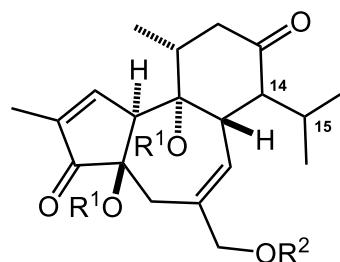
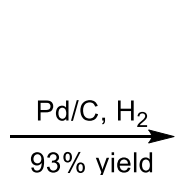
Synthesis of Crotophorbolone (1)



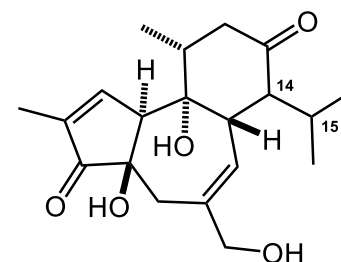
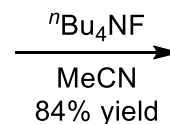
Synthesis of Langduin A (2) and Prostratin (3)



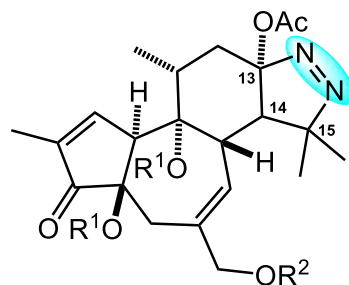
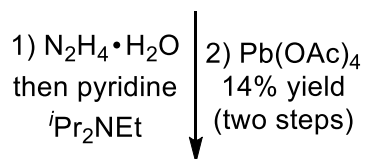
29: R¹ = TMS, R² = TIPS



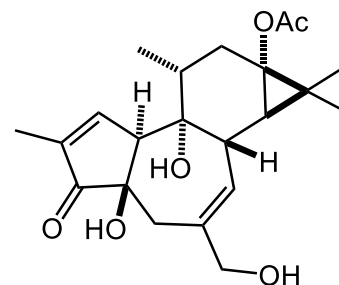
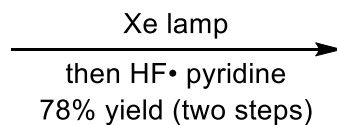
30



Langduin A (2)

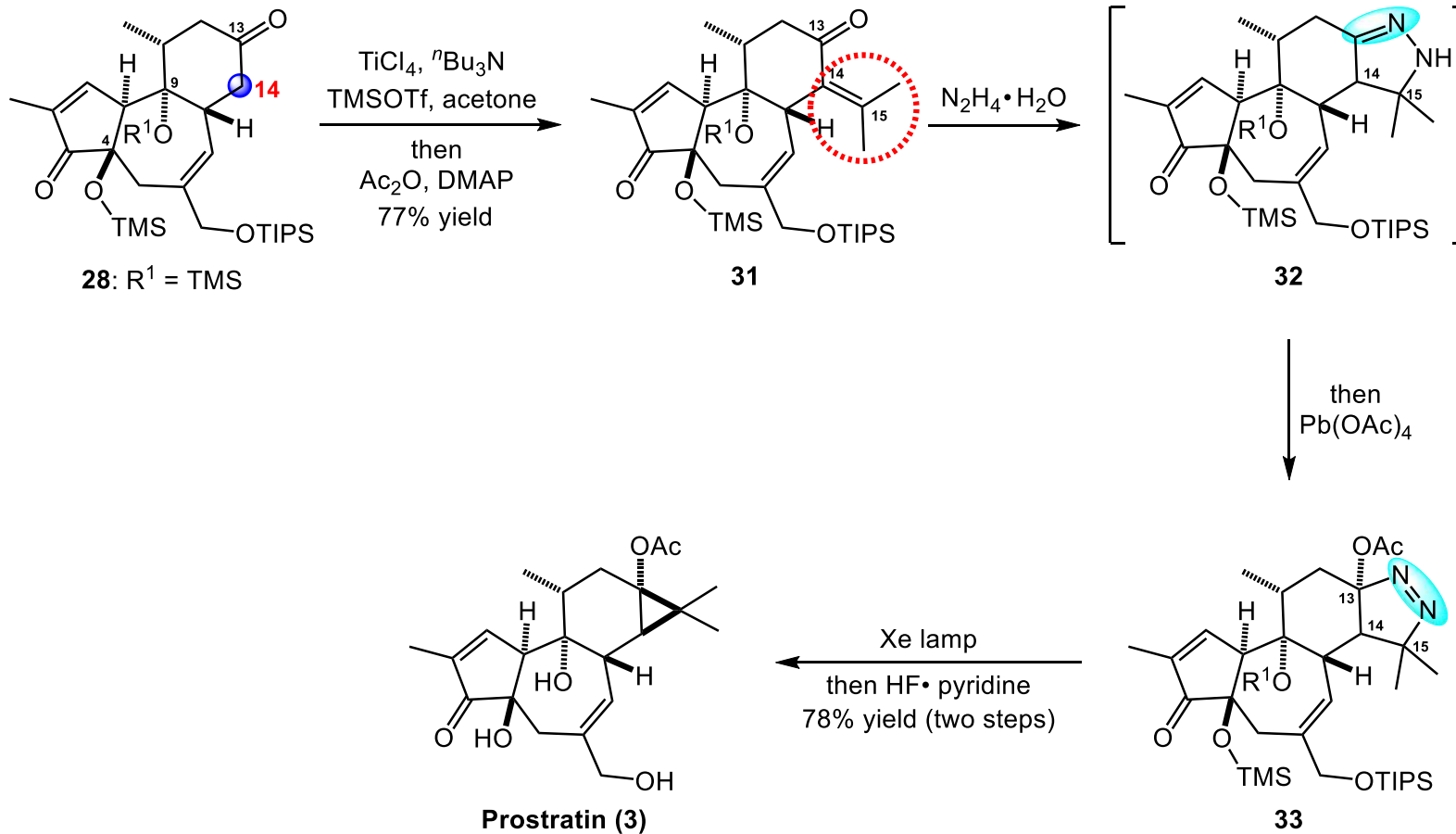


33

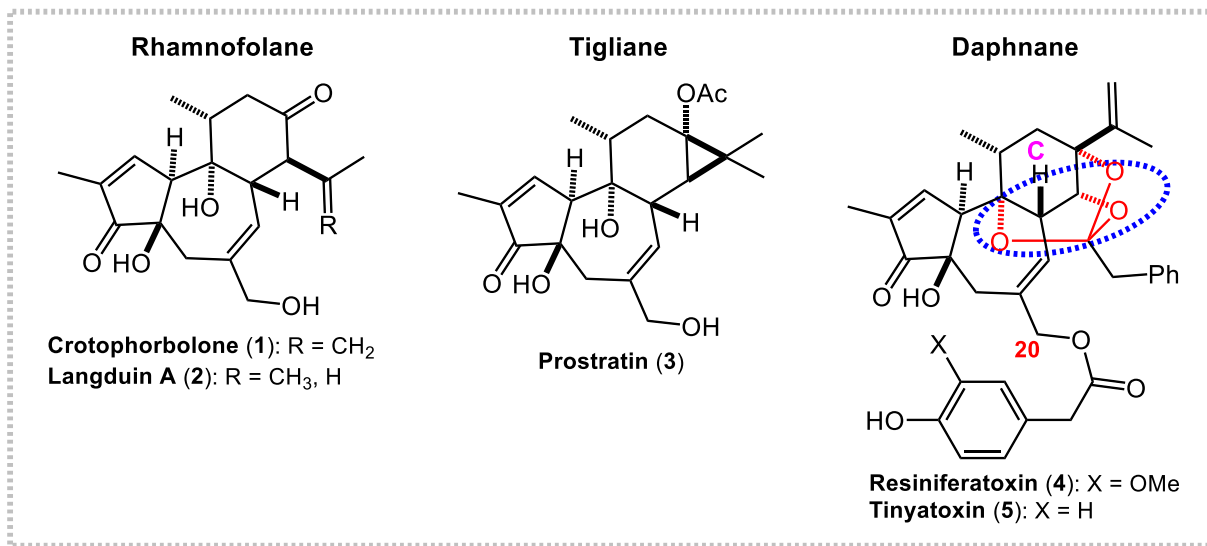
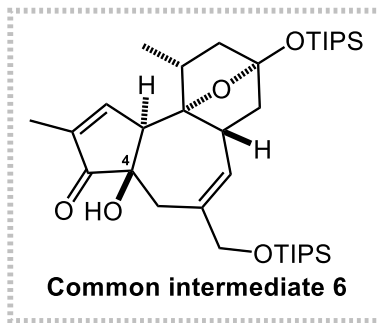


Prostratin (3)

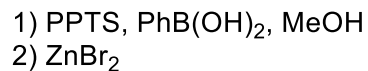
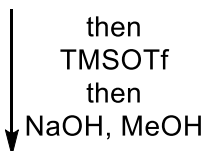
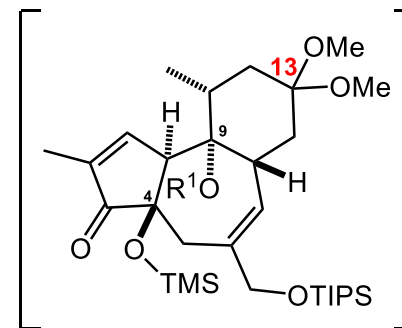
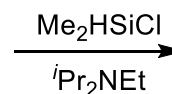
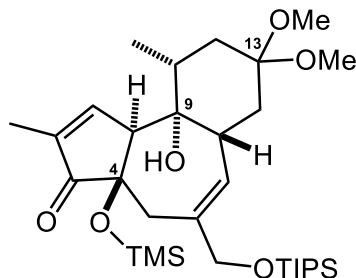
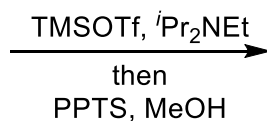
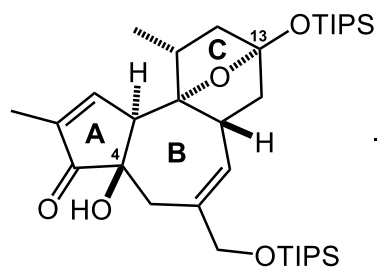
Synthesis of Prostratin (3)



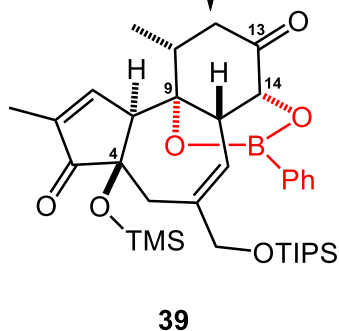
Synthesis of Diterpenoids



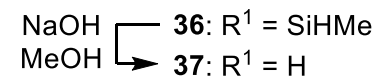
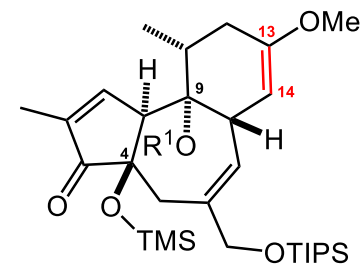
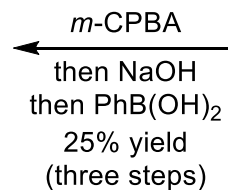
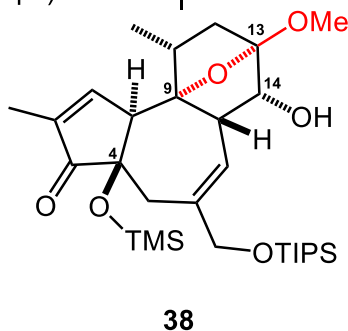
Synthesis of Daphnane



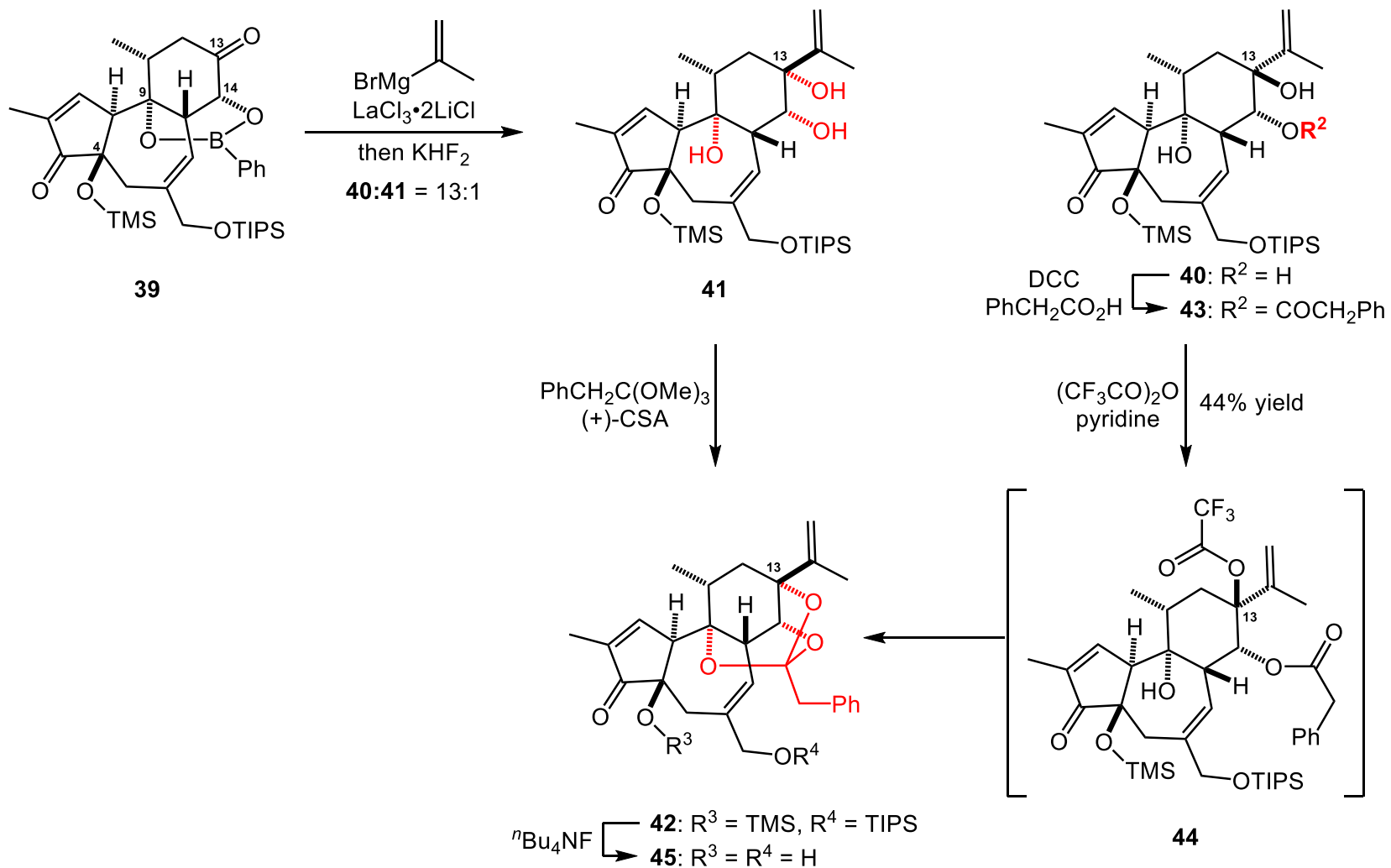
87% yield (two steps)



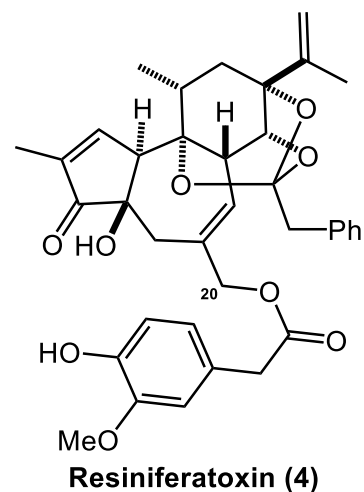
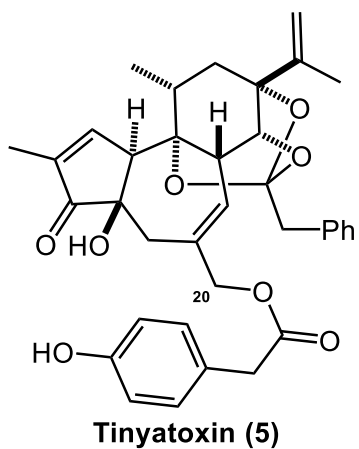
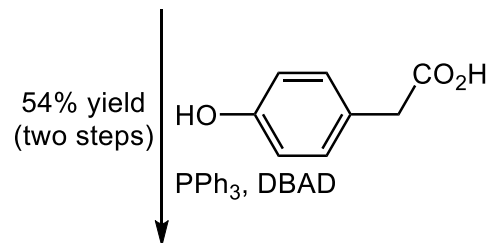
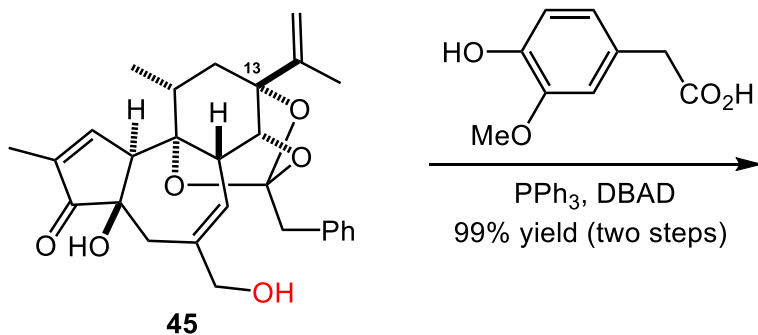
39:38 = 1.7:1



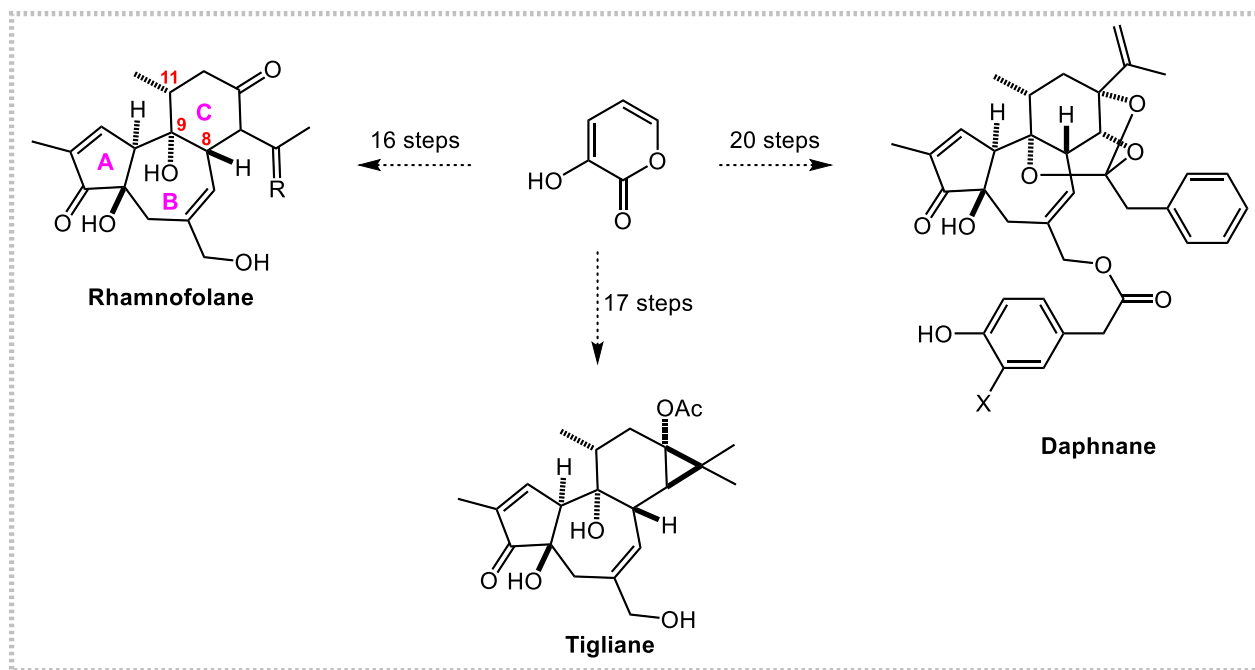
Synthesis of Daphnane



Synthesis of Daphnane



Summary



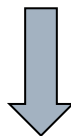
The synthetic route features:

- ❑ Asymmetric Diels–Alder reaction to install the C8,9-stereocenters
- ❑ 1,4-Addition to introduce the C11-stereocenter
- ❑ PhSe-introduction to form the bicyclic bis-acetal;
- ❑ Pd(0)-catalyzed π -allyl Stille coupling to append the A-ring and fix the *E*-olefin
- ❑ Eu(fod)₃-mediated C9-bridgehead radical cyclization.

The First Paragraph

写作思路

化合物的结构特征



指出化合物的重要性

The First Paragraph

Rhamnofolane, tigliane, and daphnane are three families of diterpenoids with closely related biosynthetic origins and are classified according to their carbon frameworks. To date, more than 400 family members have been identified from plants of the Euphorbiaceae and Thymelaeaceae species. Many of these molecules display a wide range of properties, such as antiviral, anticancer, analgesic, immunomodulatory, neurotrophic, and tumor promotional activities, making them pharmacologically useful leads. The carbon skeletons of these diterpenoids comprise the same 5/7/6-*trans*-fused ring system (ABC-ring), but the three-carbon substitutions attached at the C13- and C14-positions of the C-ring differ among them. Their structures are further diversified by various oxygen functional groups. Scheme 1 shows five representative examples of these natural products 1–5.

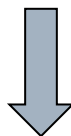
The First Paragraph

Crotophorbolone (1)/langduin A (2), prostratin (3), and resiniferatoxin (4) /tinyatoxin (5) belong to the rhamnfolane, tigliane, and daphnane families, respectively. Although their core carbon skeletons differ only with respect to the C13- and C14-substituents, 1–5 display very disparate activities. Compounds 1 and 2 have noncytotoxic and weakly cytotoxic effects, respectively, against cancer cells. Compound 3 strongly activates HIV replication in latently infected cells, thereby potentially eradicating latent HIV in combination with current antiretroviral therapy. Compounds 4 and 5 are potent activators of transient receptor potential vanilloid 1 (TRPV1), a sensory neuron ion channel protein. As 4 and 5 strongly desensitize transduction of painful stimuli, they hold great promise for the treatment of chronic pain.

The Last Paragraph

写作思路

总结工作



指出合成路线中所用方法的特点

The Last Paragraph

In conclusion, we developed a new, unified strategy for expeditious total syntheses of five representative members of the rhamnofolane, tigliane, and daphnane diterpenoid families: crotophorbolone (**1**), langduin A (**2**), prostratin (**3**), resiniferatoxin (**4**), and tinyatoxin (**5**). The syntheses were divided in two stages: preparation of the common 5/7/6-membered ABC-ring **6**, followed by introduction of the C13,14-substituents and the appending groups at the oxygen functionalities from **6**. The key transformations enroute to **6** were (i) the **15**-catalyzed asymmetric Diels–Alder reaction to install the C8,9-stereocenters of the C-ring; (ii) Me₃Al promoted 1,4-addition to introduce the C11-stereocenter; (iii) PhSe-introduction to form the bicyclic bis-acetal; (iv) Pd(0)-catalyzed π -allyl Stille coupling to append the A-ring and fix the *E*-olefin; and (v) Eu(fod)₃-mediated C9-bridgehead radical cyclization of the 7-membered B-ring to forge the hindered C9–C10 bond.

The Last Paragraph

The synthesis of **6** especially highlighted the reliability of the stereochemically predestined and highly reactive bridgehead radical for assembly of a densely functionalized compound. Then, derivatization of **6** to **1–5** was realized by controlling the order of the reactions and exploiting the three-dimensional shapes of the intermediates. The Pd(0)-catalyzed attachment of the C14- β -isopropenyl group was utilized for the synthesis of **1** and **2**. The C13,14- β -dimethylcyclopropane of **3** was in turn fused to the tricycle through acetone condensation and photoirradiation of the cyclic diazene. Finally, the α -oriented caged orthoester of **4** and **5** was constructed by C14- α -hydroxylation, C13- α -vinylation, and C13-stereochemical inversion. Consequently, **1**, **2**, **3**, **4**, and **5** were synthesized from 3-hydroxy-2*H*-pyran-2-one (**13**) in 16, 17, 17, 20, and 20 steps, respectively.

Representative Examples

1. Many of these molecules **display a wide range of** properties, **such as** antiviral, anticancer, analgesic, immunomodulatory, neurotrophic, and tumor promotional activities, making them pharmacologically useful leads. (.....显示出广泛的....., 例如.....)
2. Although their core carbon skeletons **differ** only with respect to the C13- and C14-substituents, **1-5** display very disparate activities. (不同, 差异)
3. In conclusion, we developed a new, **unified** strategy for expeditious total syntheses of five representative members..... (统一, 使成一体)

Acknowledgement

Thanks for your attention