Literature Report 2

Total Synthesis of Hybridaphniphylline B

Reporter: Xin-Wei Wang
Checker: Xiao-Yong Zhai
Date: 2018-4-16

Zhang, W.; Ding, M.; Li, J.; Guo, Z.; Lu, M.; Chen, Y.; Li, Ang.
J. Am. Chem. Soc. **2018**, *140*, 4227−4231.

CV of Professor Ang Li

Ang Li

Background:

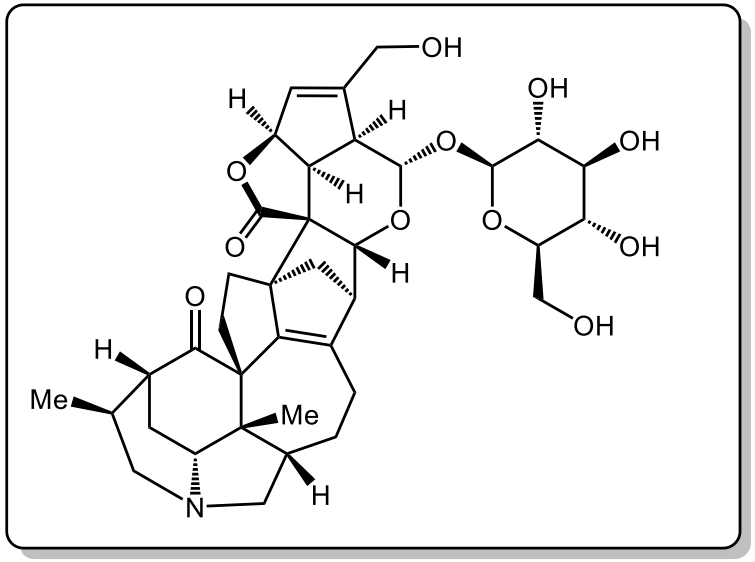
- **2000-2004** B.S. Peking University (Zhen Yang)
- **2004-2009** Ph.D. The Scripps Research Institute (K. C. Nicolaou)
- **2009-2010** Postdoc. The Scripps Research Institute (K. C. Nicolaou)
- **2010-** Shanghai Institute of Organic Chemistry

Research:

Total synthesis of structually and biologically interesting natural products

Contents

Introduction



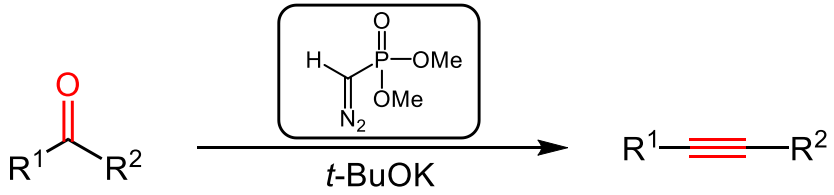
Hybridaphniphylline B

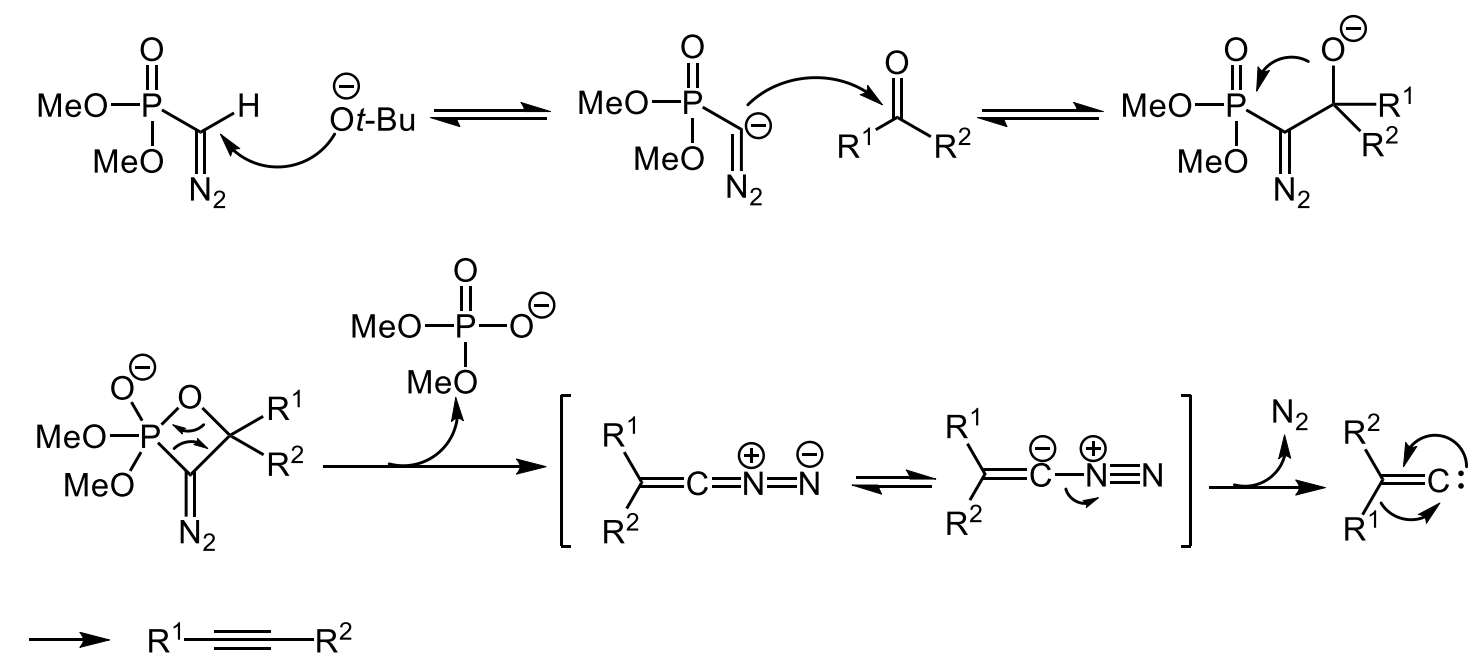
Daphniphyllum longeracemosum
长序虎皮楠

- Hybridaphniphylline B was isolated in 2013;
- The Daphniphyllum alkaloid family comprise more than 320 members with fascinating molecular architectures and diverse biological activities;
- It possesses 11 rings and 19 stereocenters.

Wang, F.; Mao, M.-F.; Wei, G.-Z.; Gao, Y.; Ren, F.-C.; Liu, J.-K. *Phytochemistry* **2013**, *95*, 428-435.

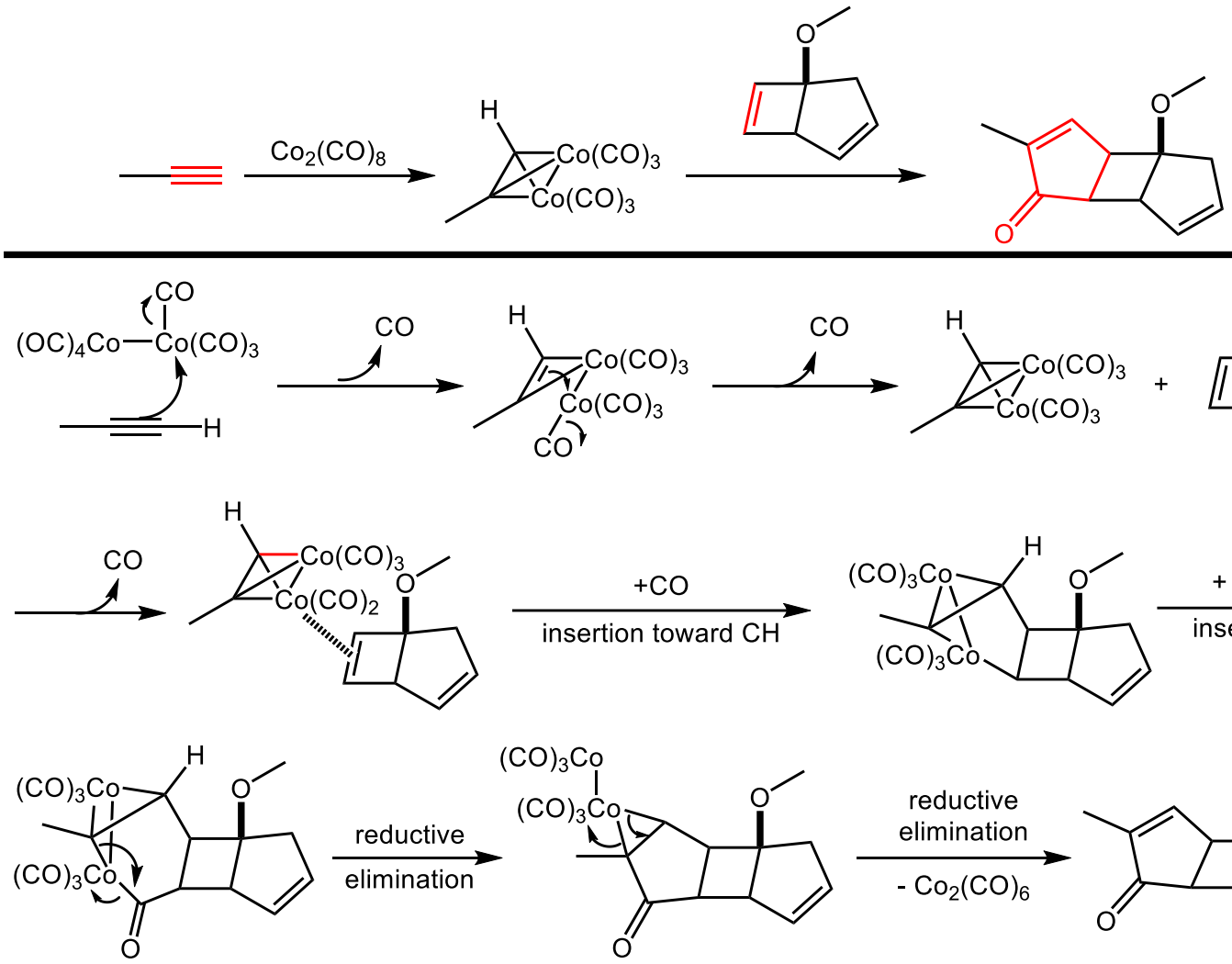
Seyferth–Gilbert Homologation





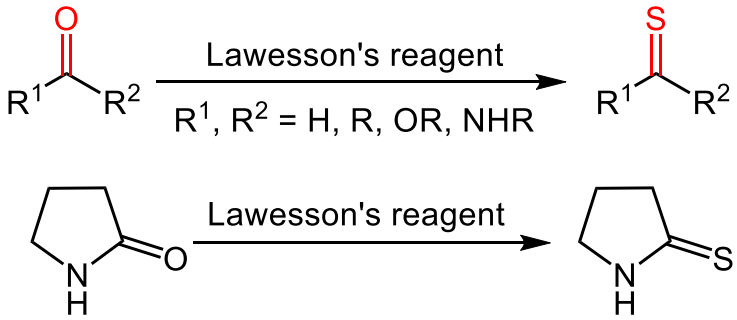
From Wikipedia

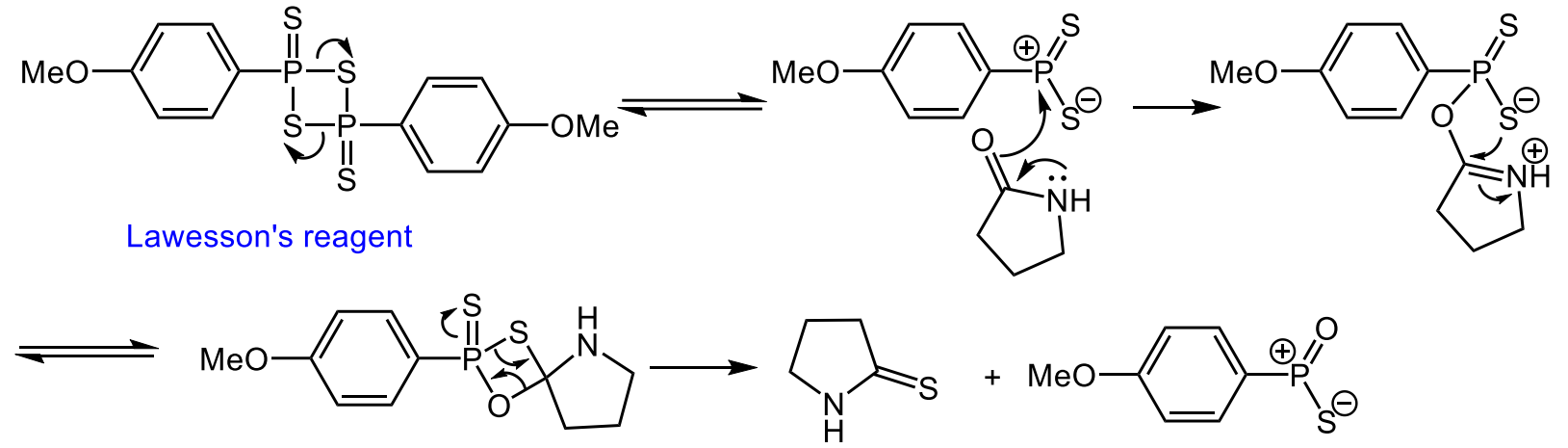
Pauson–Khand Reaction



From Name Reactions by Jie Jack Li

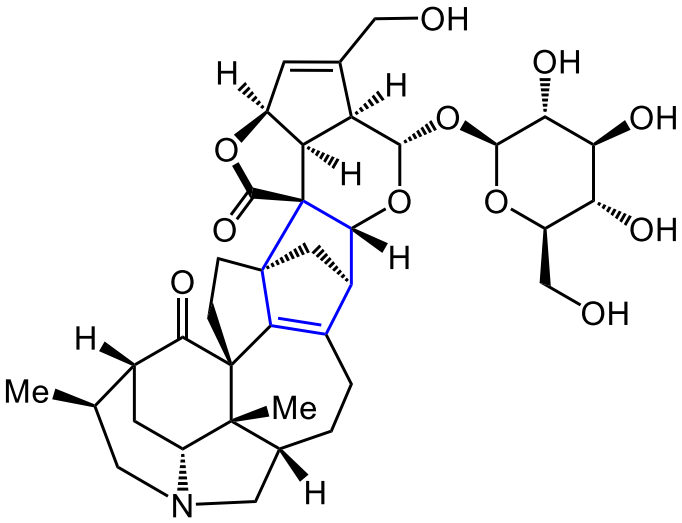
Lawesson's reagent





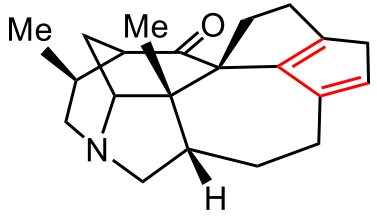
From Name Reactions by Jie Jack Li

Retrosynthetic Analysis



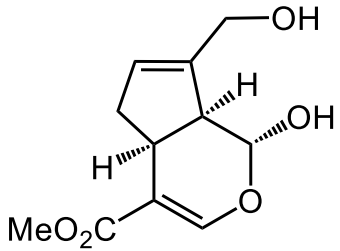
1: Hybridaphniphylline B

Diels-Alder

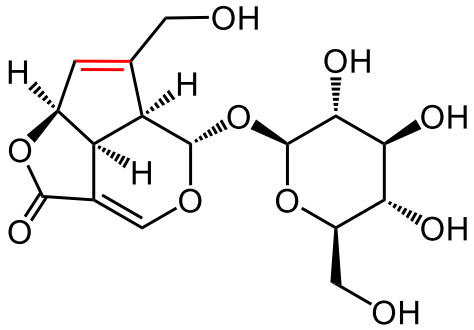


3

+

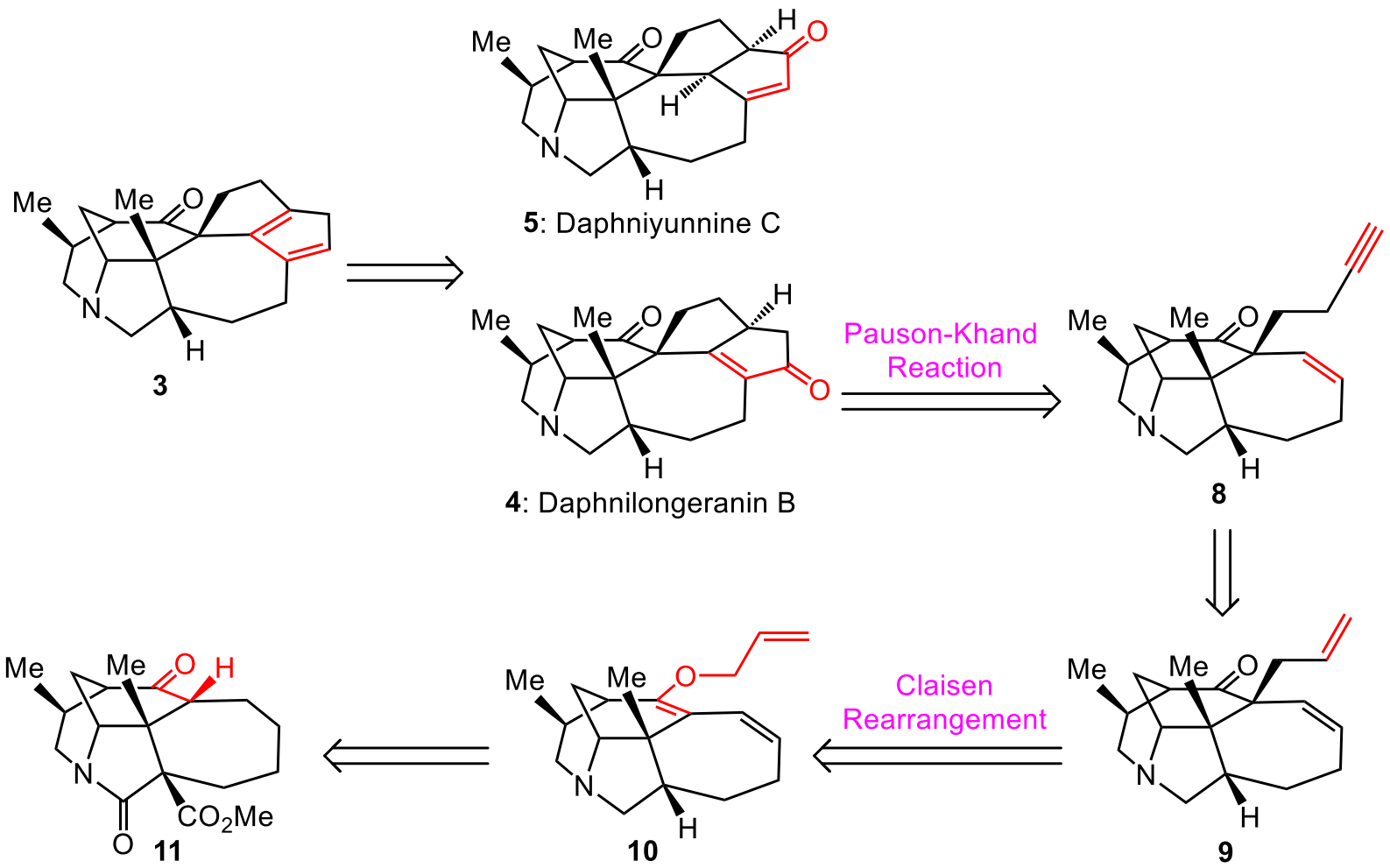


12: (+)-Genipin

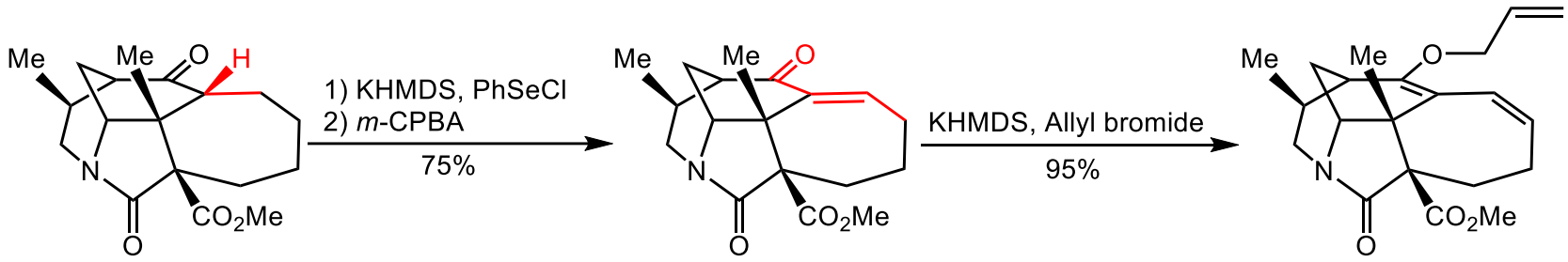


2: Deacetylasperuloside

Retrosynthetic Analysis

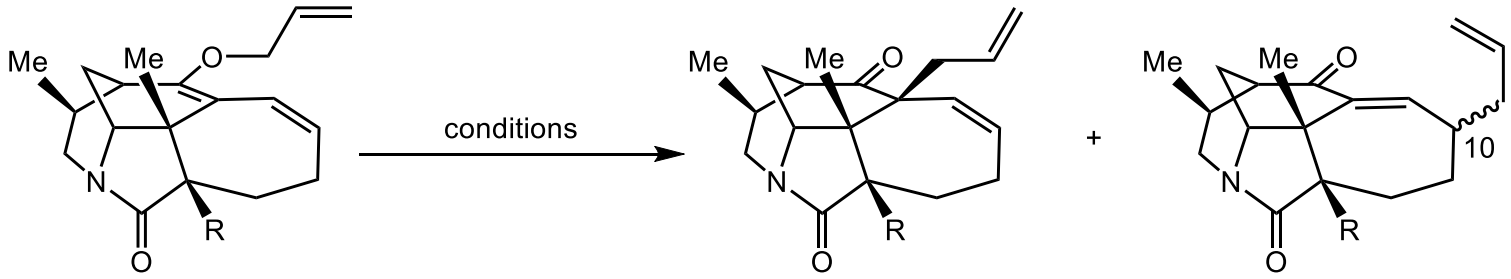


Synthesis of Allyl Dienol Ether 13



11 **11a** **13**

Claisen Rearrangement of Allyl Dienol Ethers



13: R = CO_2Me
16: R = H

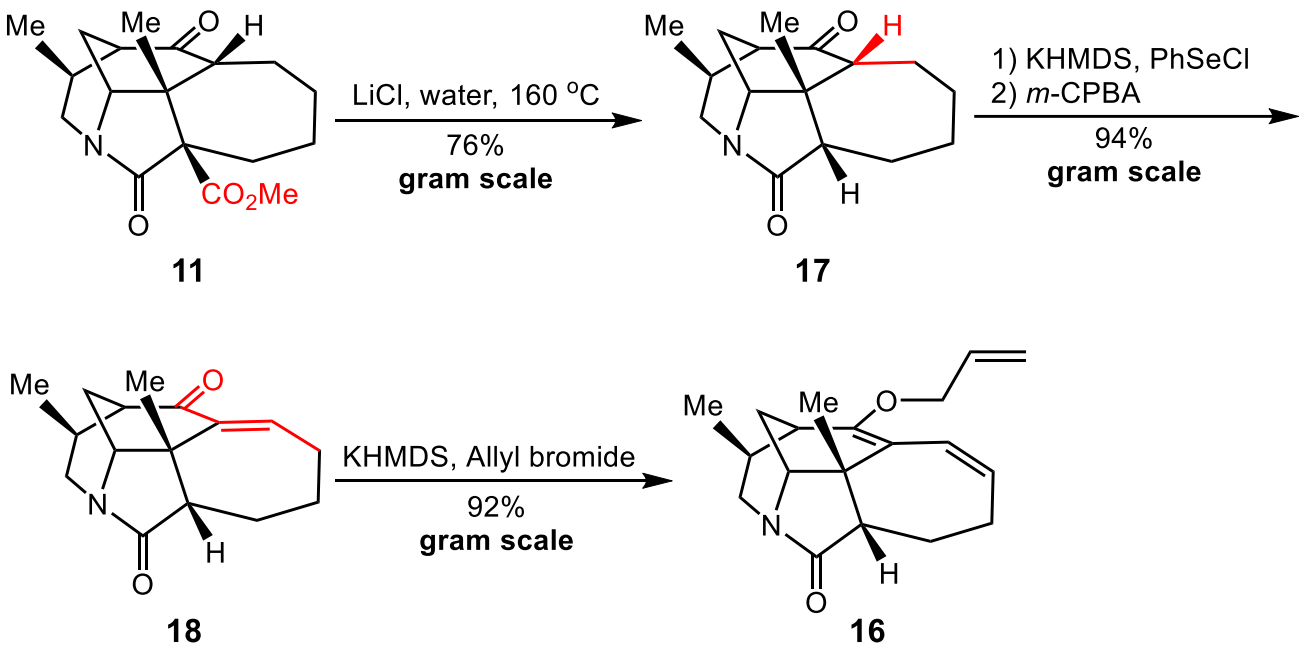
14: R = CO_2Me
19: R = H

15: R = CO_2Me
20: R = H

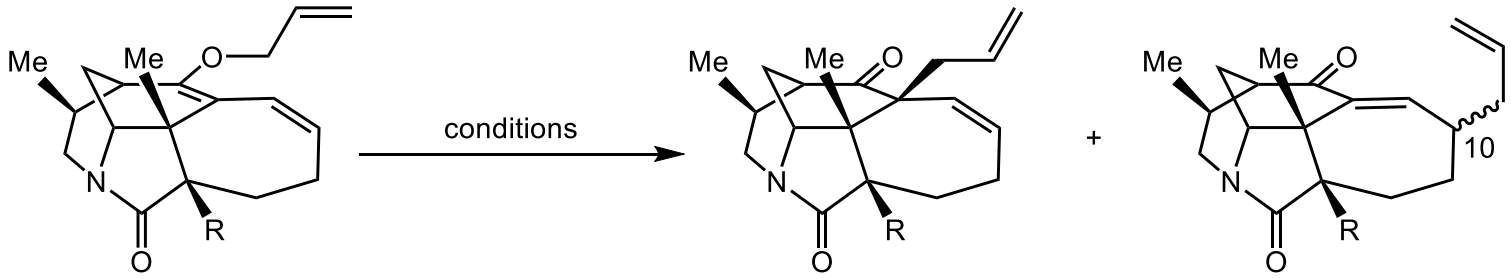
Entry	S	Conditions	Products (yield %)	
1[a,b]	**13**	*o*-DCB, 140 °C, 3 h	**14** (< 2)	**15**[c] (31)
2[d]	**13**	$TiCl_4$, $AlMe_3$, 0 °C	**14** (< 5)	**15**[c] (47)
3[a,f]	**16**	*o*-DCB, 120 °C, 12 h	**19** (48)	**20**[e] (5)
4[a,g]	**16**	*o*-DCB, 120 °C, 24 h	**19** (46)	**20**[h] (27)
5[i]	**16**	aq. NaOH/MeOH, 80 °C, 3 d	**19** (94)	**20**[e] (0)

[a] 47 mol % *i*-Pr_2NEt. [b] 53% recovery of **13**. [c] 10*R*: 10*S* = 1.7: 1. [d] 3.2 equiv [Ti], 3.2 equiv [Al], 100 wt % 4 Å MS, CH_2Cl_2. [e] 10*R* only. [f] 38% recovery of **16**. [g] 9% recovery of **16**. [h] 10*R*: 10*S* = 20: 1. [i] v [aq. NaOH (0.010 M)]: v (MeOH) = 5: 2.

Synthesis of Allyl Dienol Ether 16



Claisen Rearrangement of Allyl Dienol Ethers



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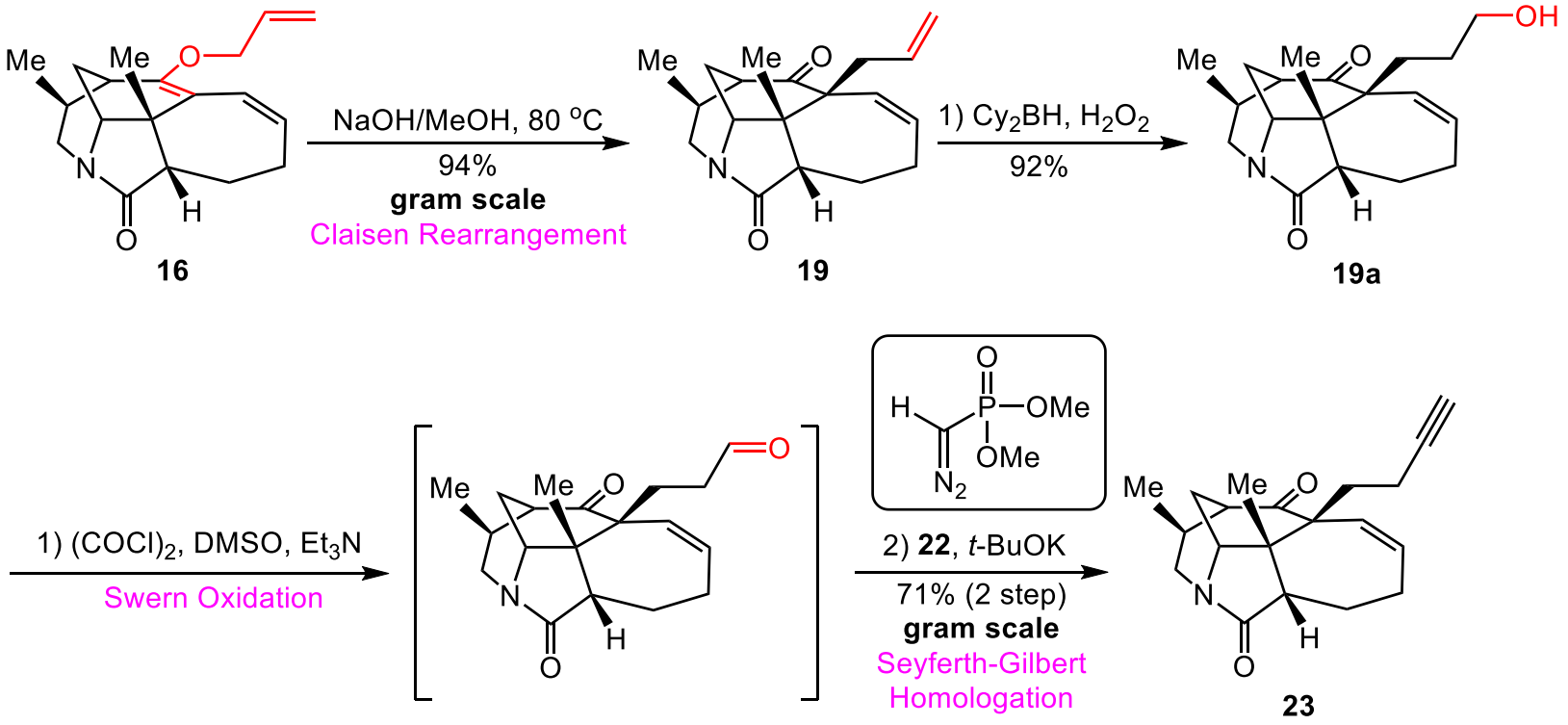
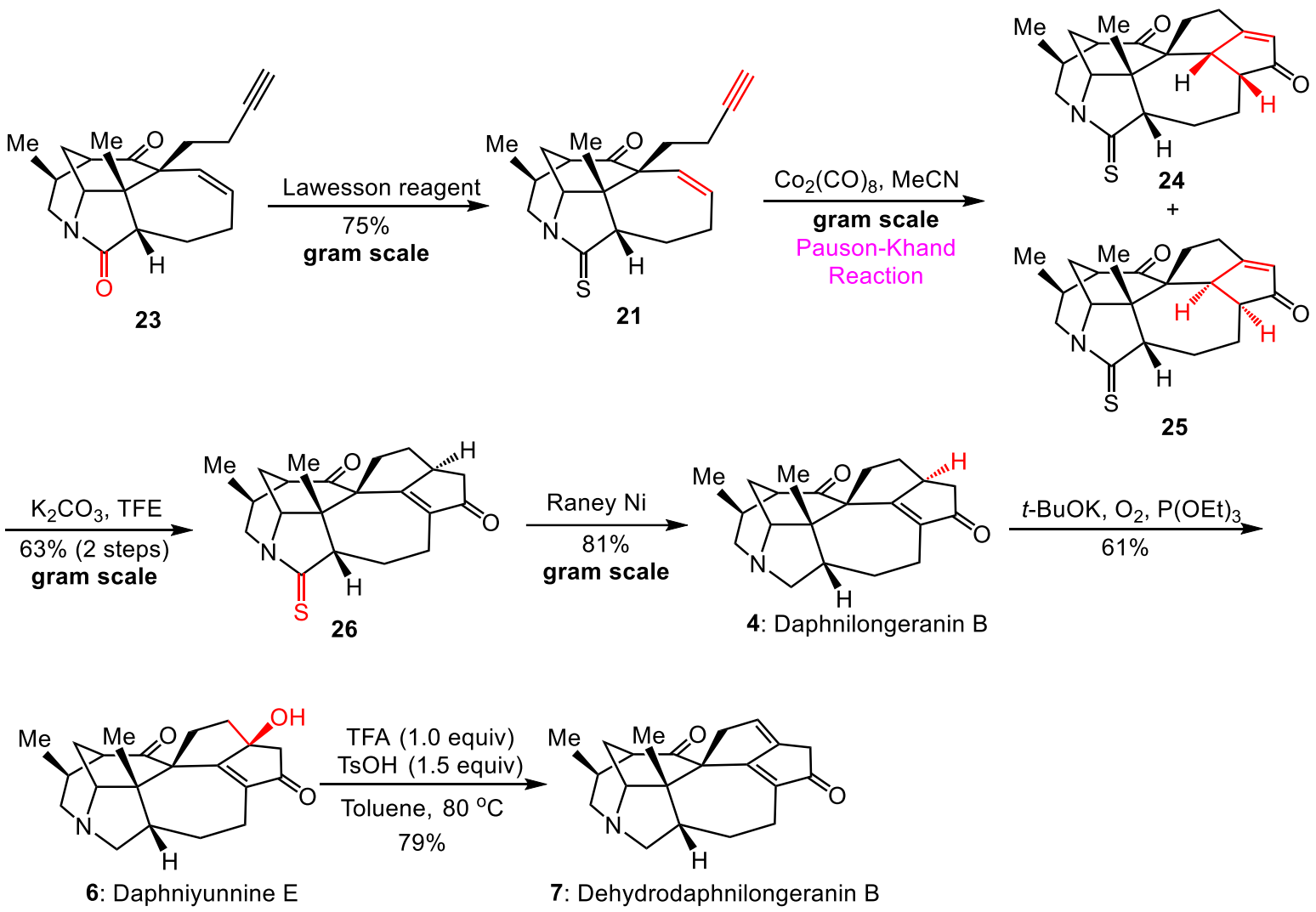
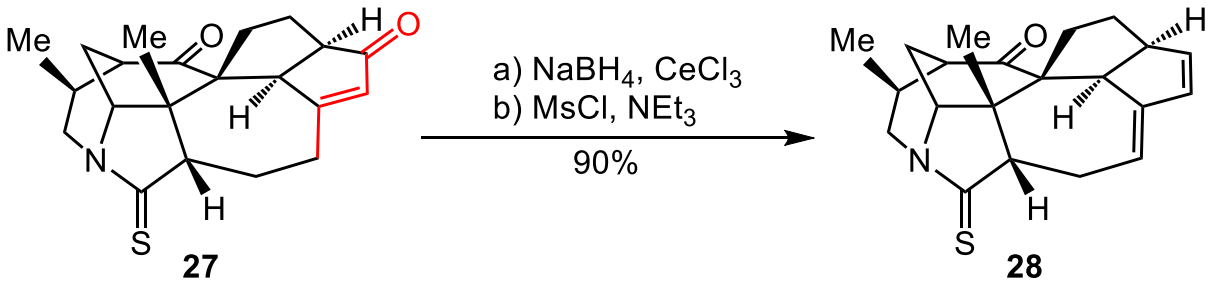
Synthesis of Alkyne 23



Synthesis of Daphniphyllum alkaloid 4, 6, 7

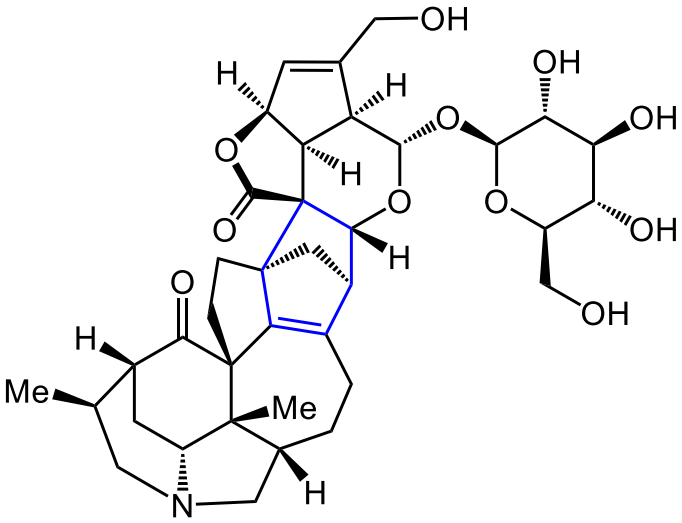


Preparation of the Diene



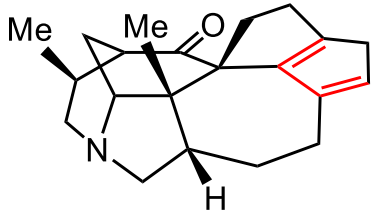
27 **28**

Retrosynthetic Analysis



1: Hybridaphniphylline B

Diels-Alder



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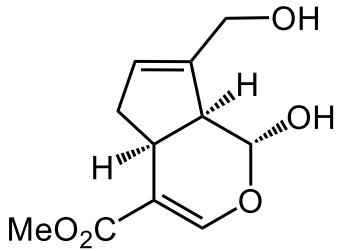

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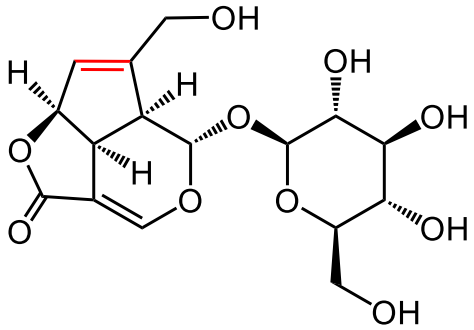
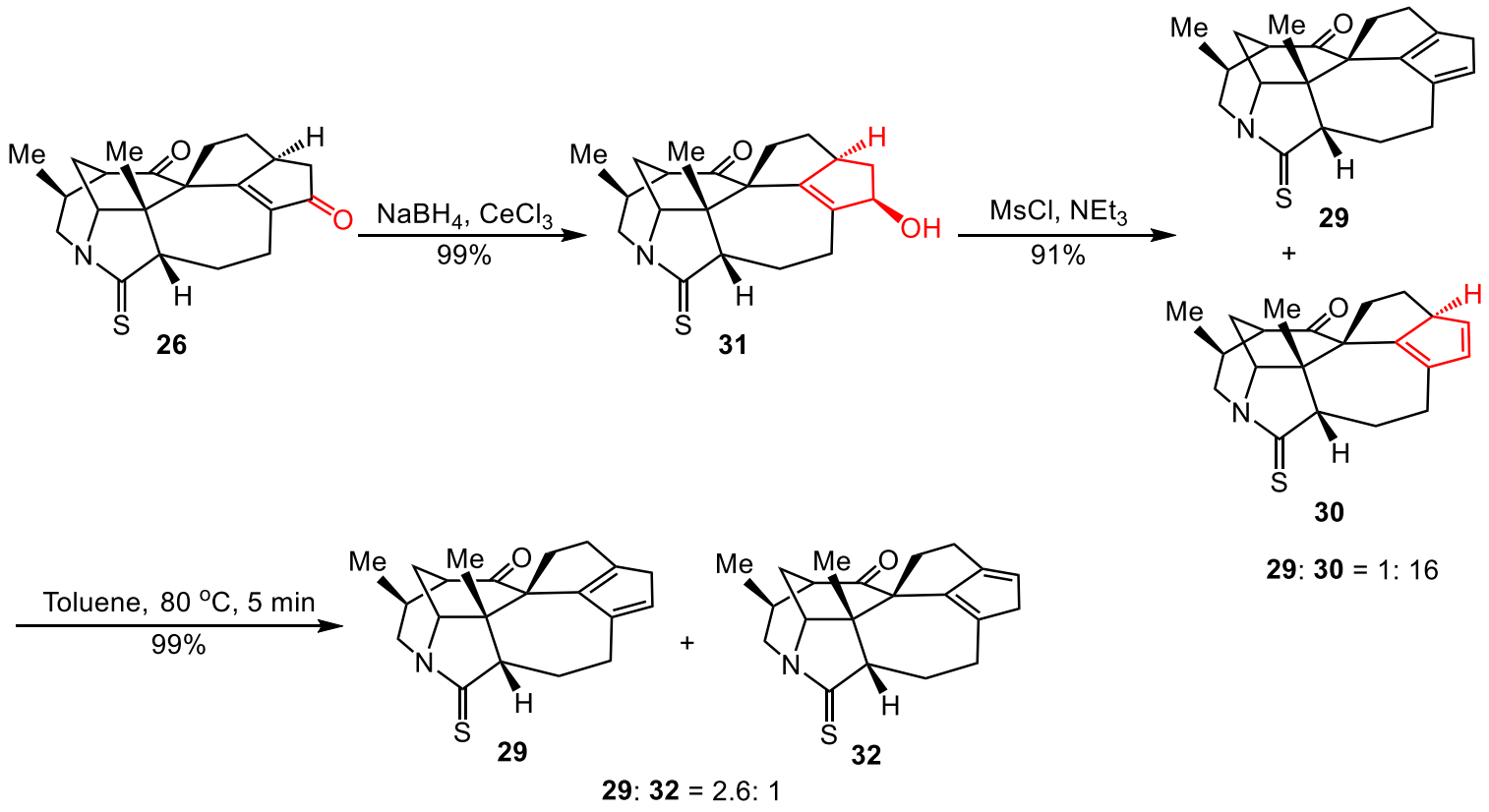
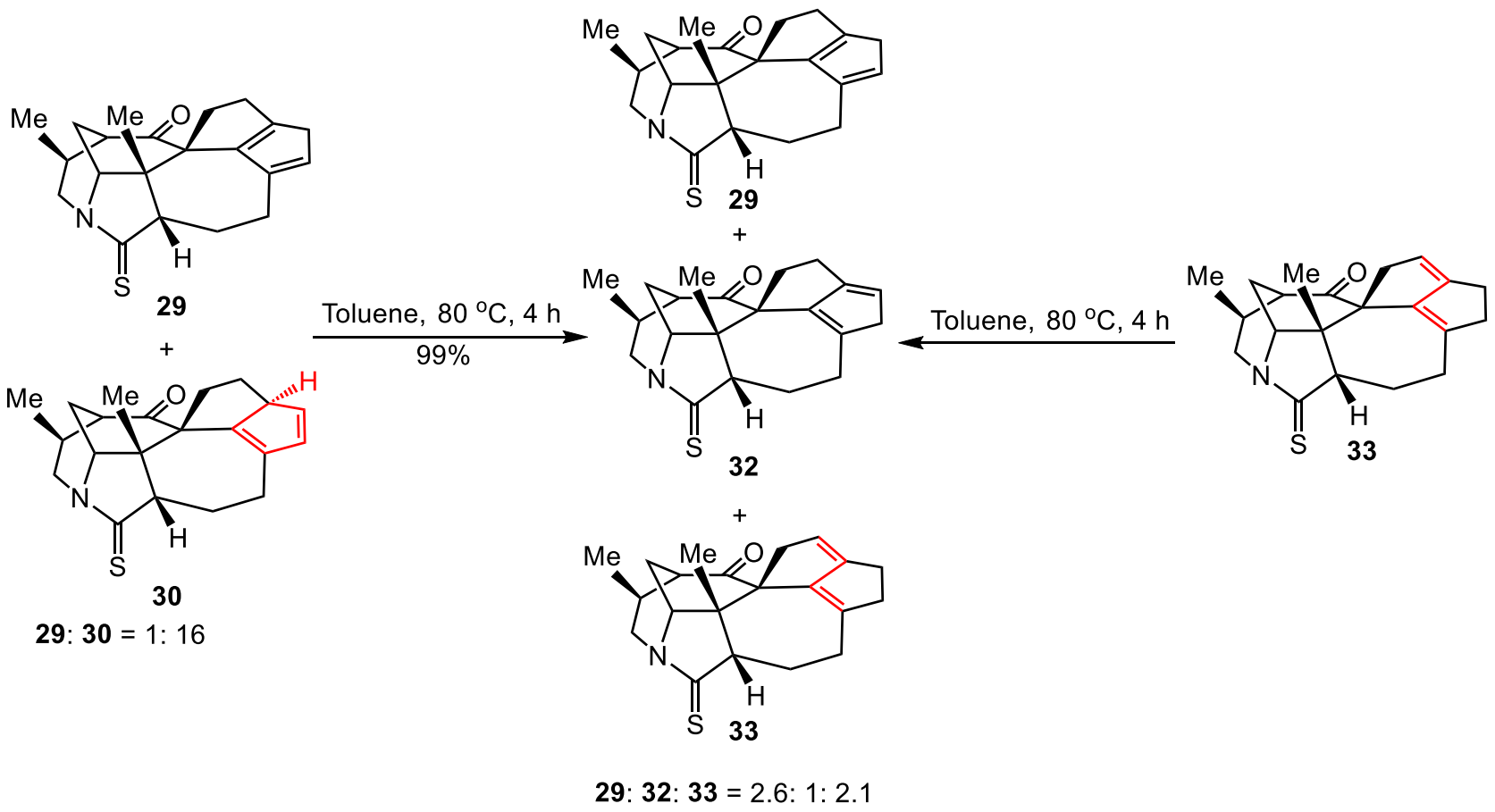


2: Deacetylasperuloside

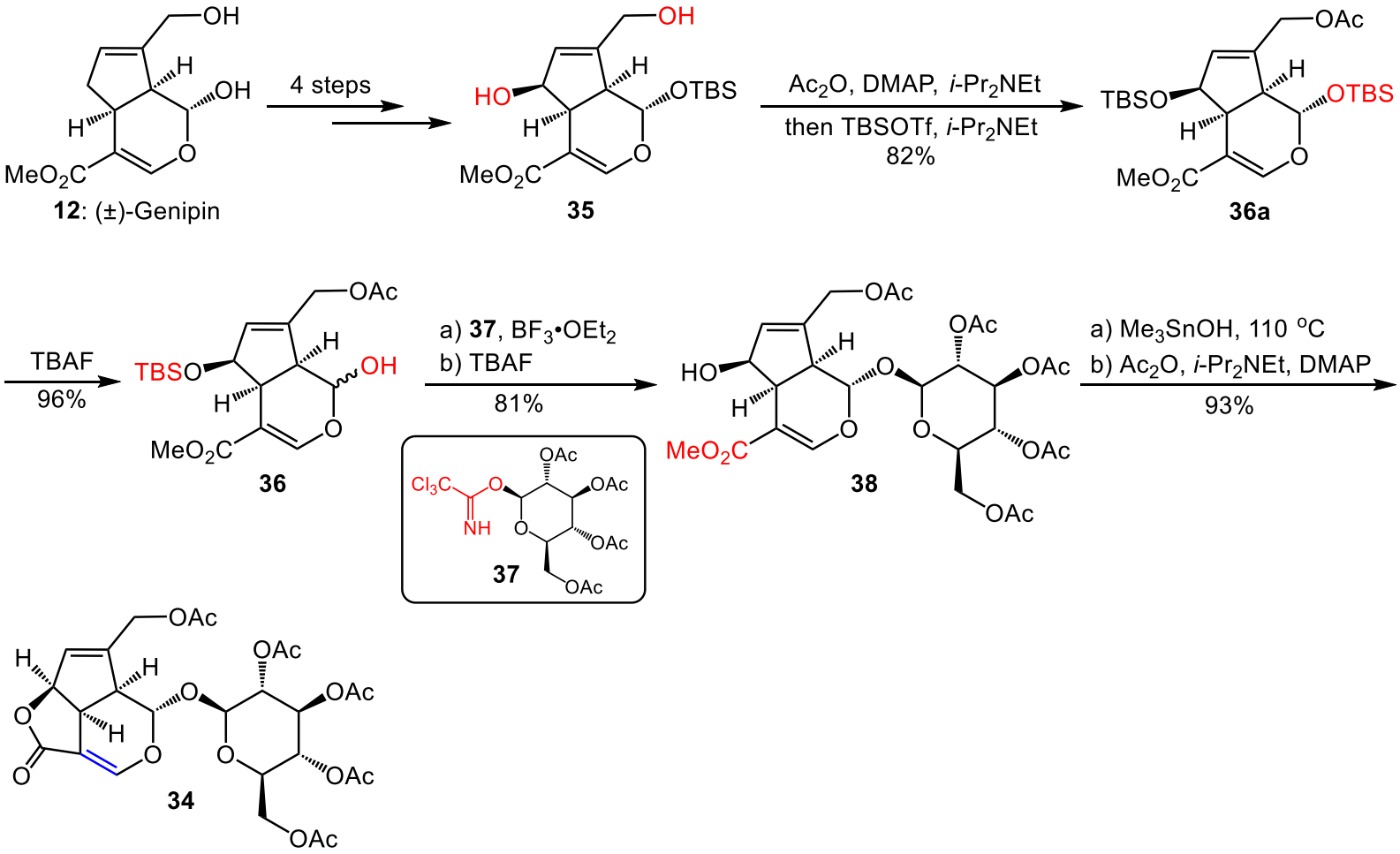
Preparation of the Diene



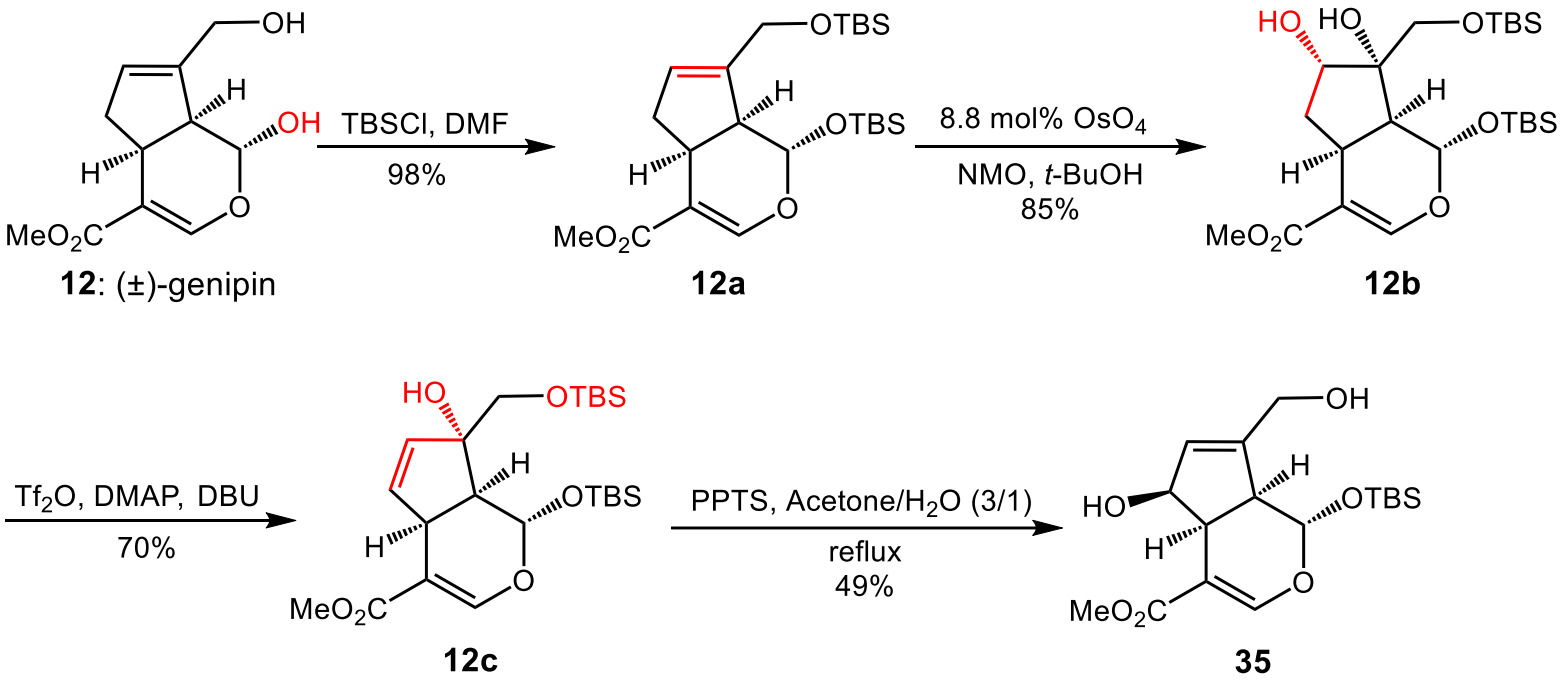
Preparation of the Diene



Preparation of the Dienophile



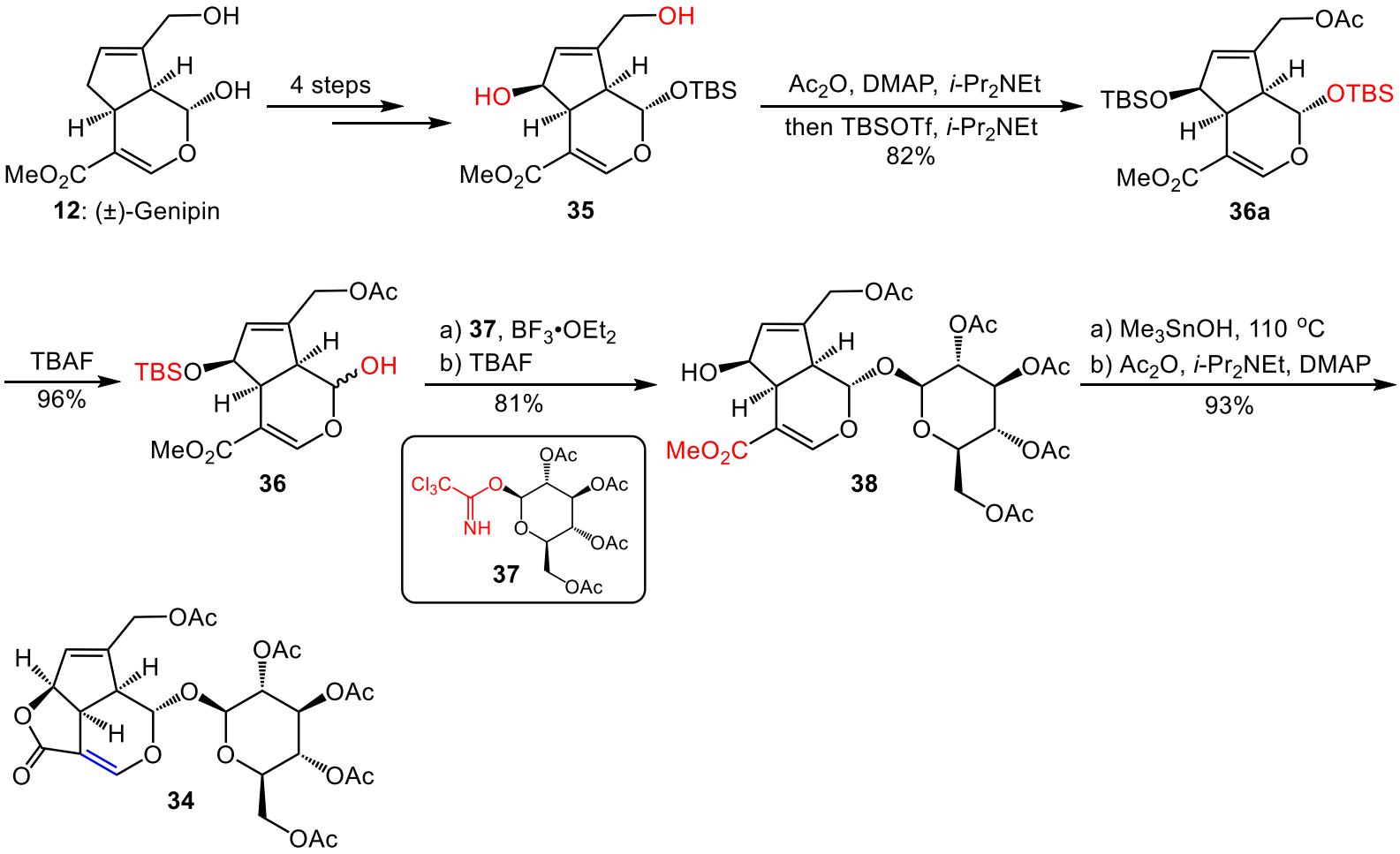
Preparation of the Dienophile



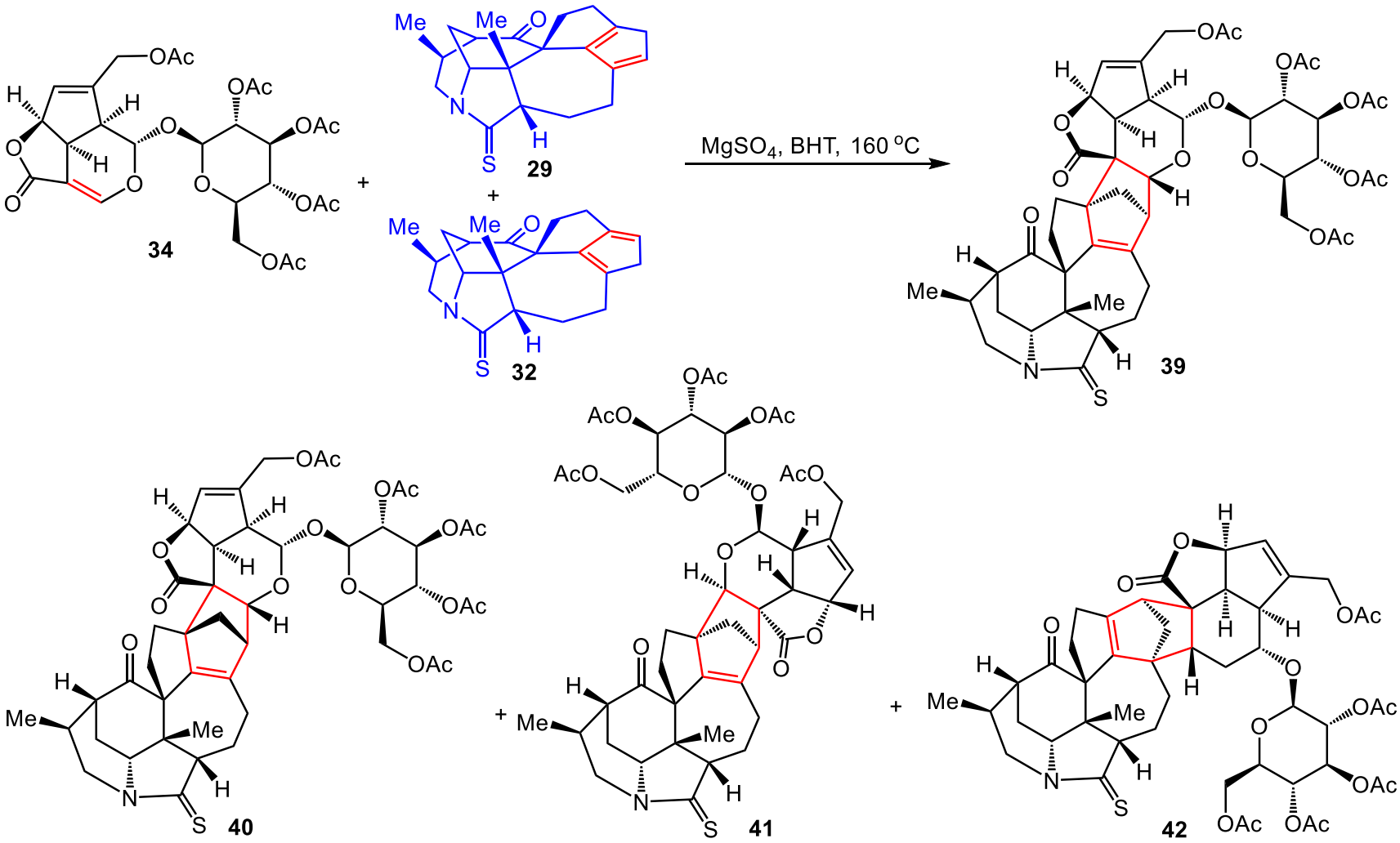
12: (±)-genipin **12a** **12b** **12c** **35**

Nakatani, K.; Shimano, K.; Isoe, S. *Bull.Chem. Soc. Jpn.* **1993**, *66*, 2646-2652.

Preparation of the Dienophile

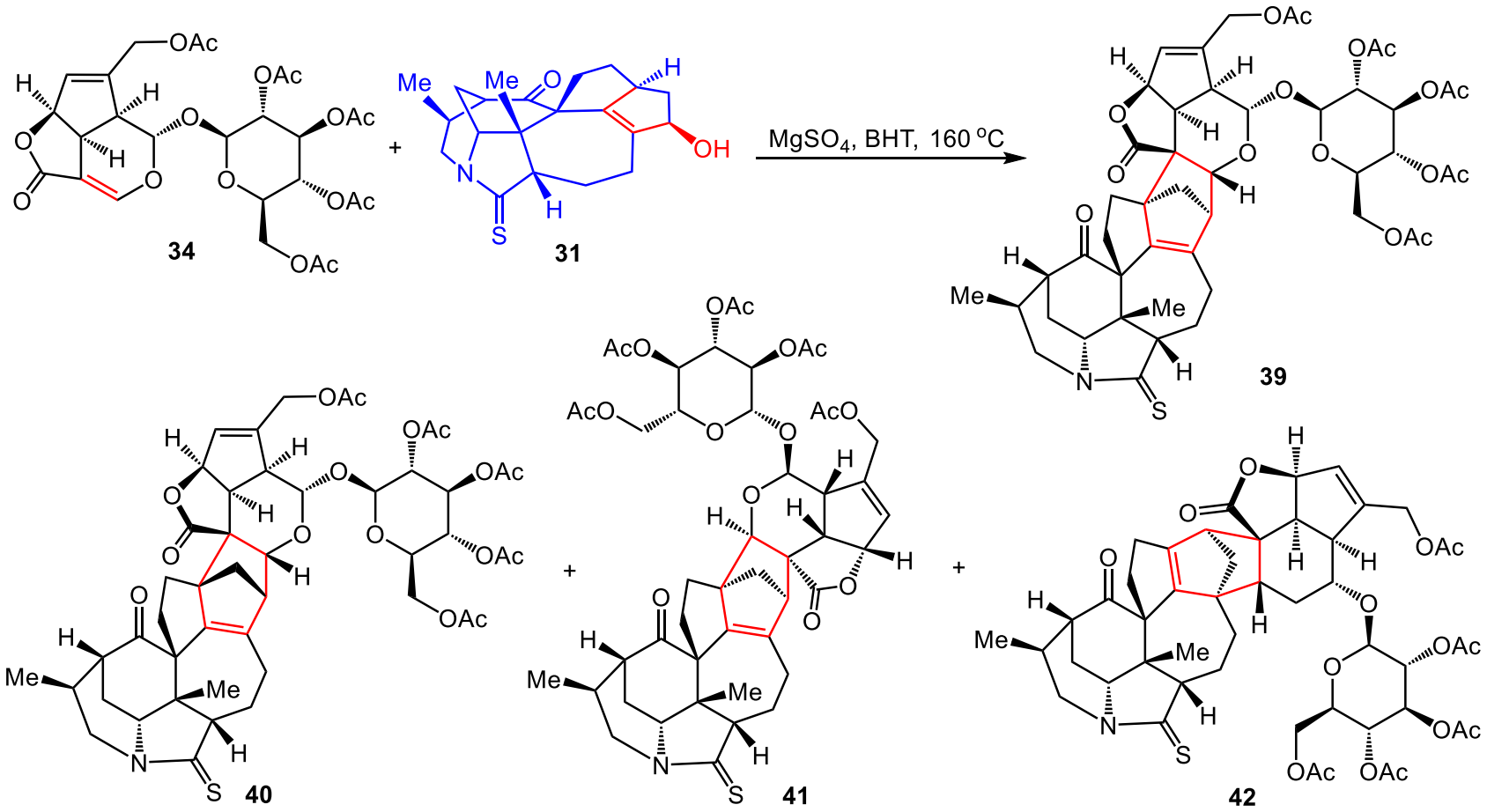


Synthesis of Hybridaphniphylline B



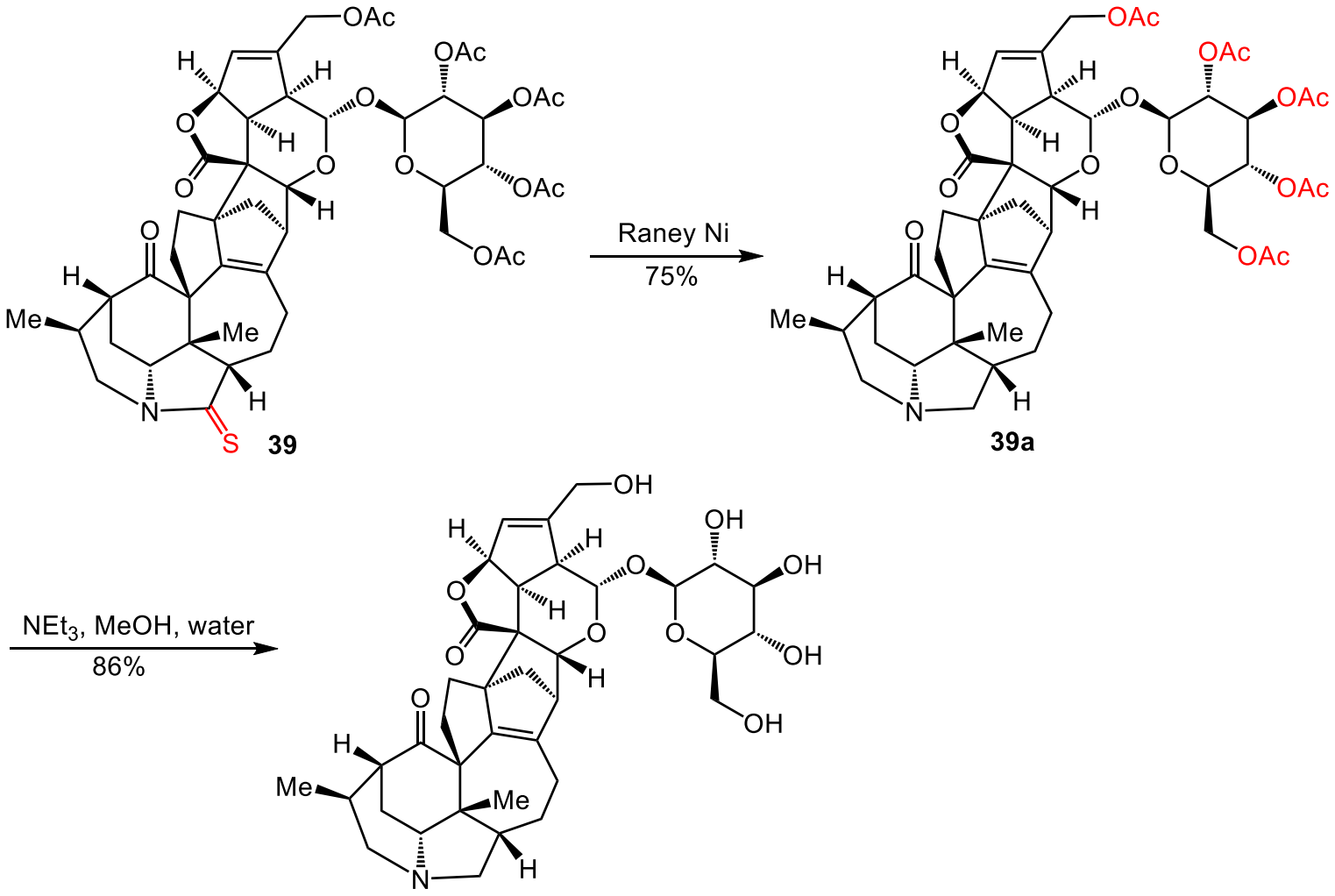
39: **40**: **41**: **42** = 3.9: 1.7: 2.7: 1, 58% yield in total

Synthesis of Hybridaphniphylline B

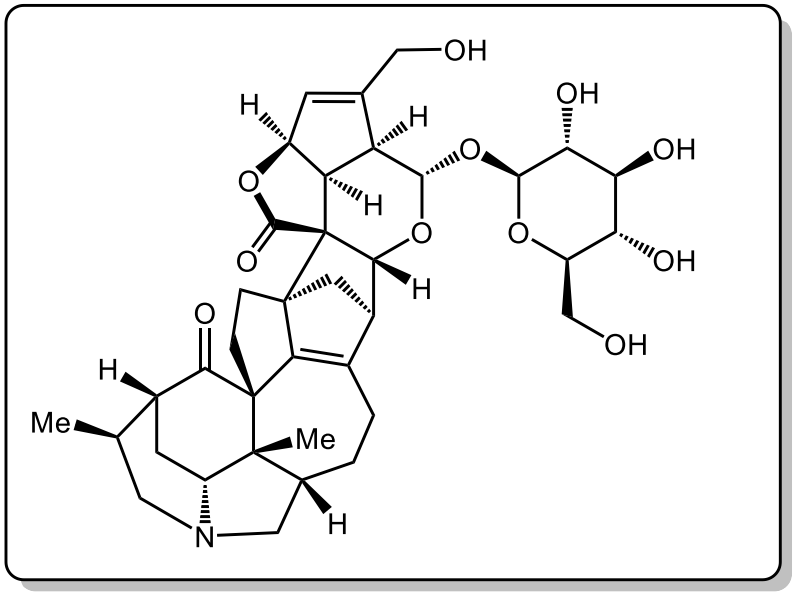


39: **40**: **41**: **42** = 3.9: 1.7: 2.7: 1, 79% yield in total

Synthesis of Hybridaphniphylline B



Summary



Hybridaphniphylline B

- The first total synthesis Hybridaphniphylline B;
- 15 steps (the longest linear sequence), 2.9% overall yield;
- Bioinspired Diels-Alder reaction;
- To prepare the diene, achieve the first syntheses of **4**, **6** and **7**;
- Claisen rearrangement of an allyl dienol ether as a key step.

The First Paragraph

The Daphniphyllum alkaloid family comprise more than 320 members with fascinating molecular architectures and diverse biological activities. Synthetic chemists have been intrigued by the challenges posed by these molecules. The groups of Heathcock, Smith, Zhai, and Dixon accomplished elegant syntheses of a dozen of Daphniphyllum alkaloids. Our endeavors in this area also resulted in the syntheses of several members of this family. During the studies, we developed strategies such as 6π electrocyclization/aromatization for constructing multisubstituted benzenes and alkyne cyclization for assembling azabicyclo [3.3.1] nonanes, which found further use in the syntheses of other natural products.

The First Paragraph

Hybridaphniphylline B is a complex Daphniphyllum alkaloids containing 11 rings and 19 stereogenic centers, which was isolated by Liu and co-workers from Daphniphyllum longeracemosum. Biogenetically, **1** may result from an intermolecular Diels-Alder reaction of naturally occurring deacetylasperuloside (**2**) and a putative cyclopentadiene (**3**). Our experience with bioinspired Diels-Alder cycloaddtion and Daphniphyllum alkaloid synthesis suggested an opportunity for an expedient route to the undecacyclic scaffold of **1**. Here we report the first total synthesis of **1** as well as the syntheses of **4**, **6** and **7**.

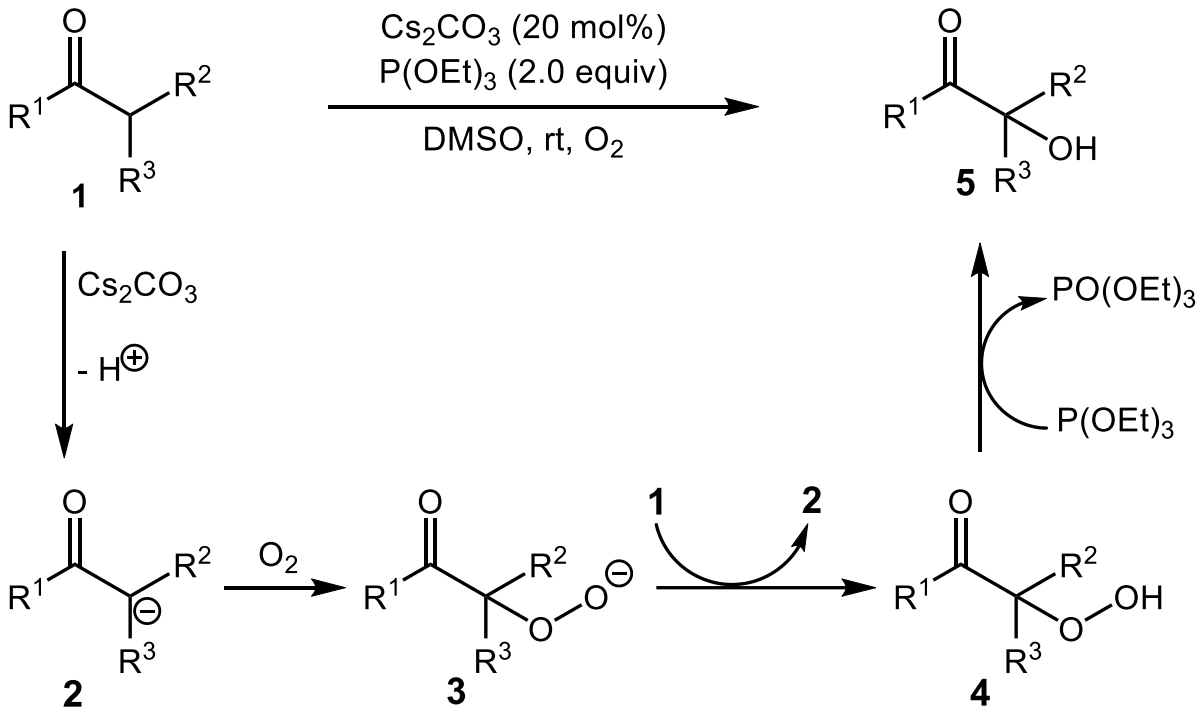
The Last Paragraph

In summary, we have accomplished the first total synthesis of **1** exploiting an bioinspired Diels-Alder strategy. To prepare the diene, we developed a scalable route to **4** and achieved the first syntheses of **6** and **7**. The late stage cycloaddition of dienophile **34** and the in situ generated diene forged the highly congested norbornene domain of **1**.

Acknowledgement

Thanks
for your attention

C-H Hydroxylation of Carbonyl Compounds



Jiao, N.; Liang, Y.-F. *Angew. Chem. Int. Ed.* **2014**, *53*, 548–552.