Literature Report 1

Total Synthesis of (+)-Aberrarone

Reporter: Yan-Xin Sun
Checker: Sheng-Mei Lu
Date: 2023-10-30

Wang, Y.; Su, Y.; Jia, Y.* *J. Am. Chem. Soc.* **2023**, *145*, 9459-9463

CV of Prof. Yan-Xing Jia

Research:

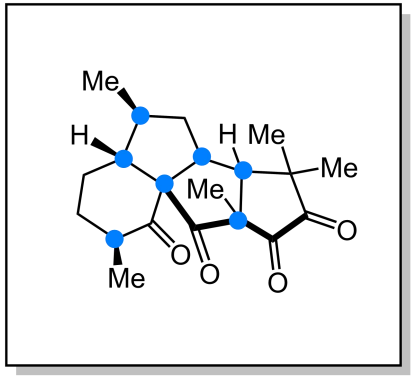
- Total Synthesis and Biomimetic Synthesis of Natural Products
- Drug Synthesis and Structure-Activity Relationship Studies
- New Methods for Organic Synthesis
- Discovery of Small Molecule Probes

Background:

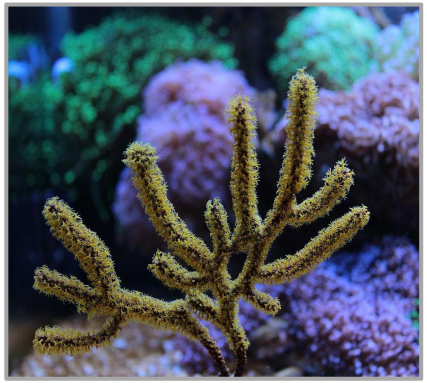
- **1997-2002** Ph.D., Lanzhou University (Prof. Yong-Qiang Tu)
- **2002-2007** Postdoc., Centre National de la Recherche Scientifique (Prof. Jie-Ping Zhu)
- **2007-2011** Associate Professor, Peking University, School of Pharmaceutical Sciences
- **2011-** Professor, Peking University, School of Pharmaceutical Sciences

Contents

Introduction



(+)-Aberrarone

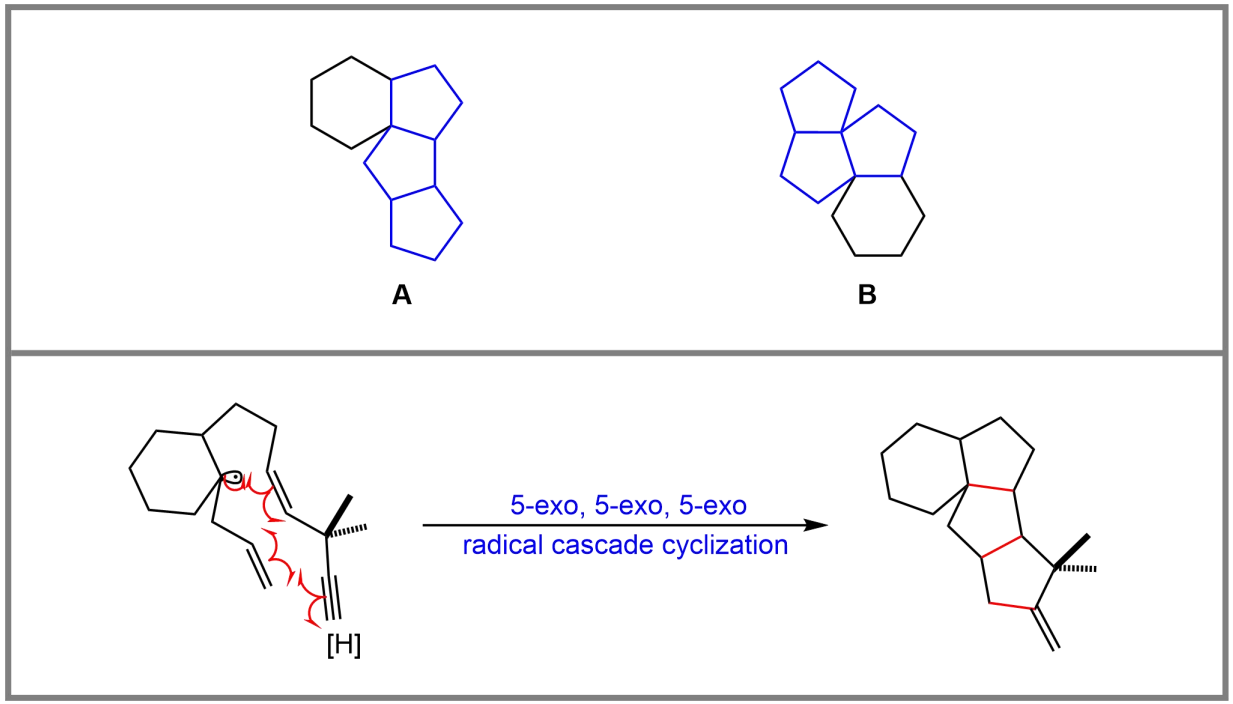


Gorgoniidae

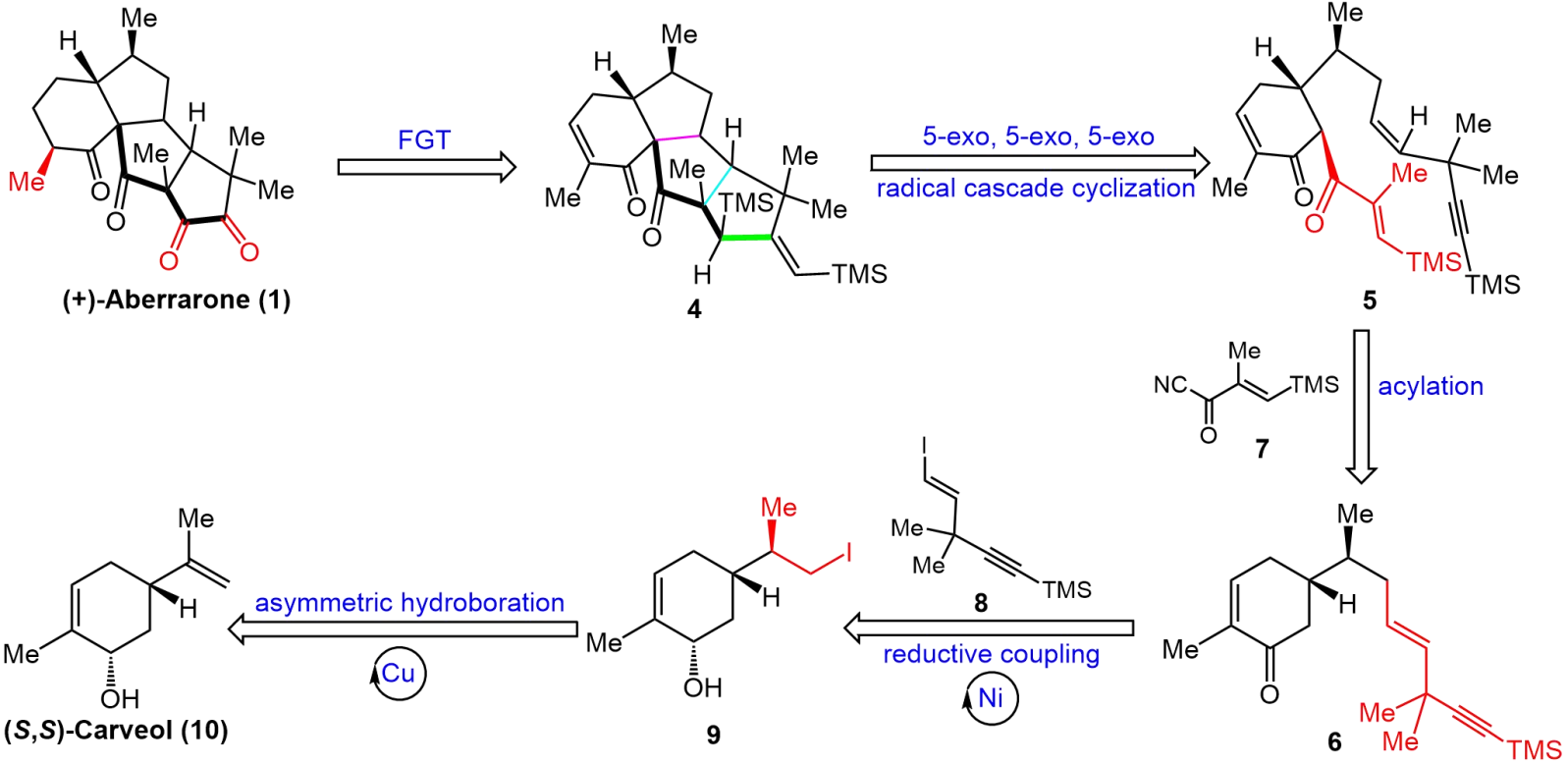
- **Aberrarone** was isolated from the West Indian gorgonian octocoral Pseudopterogorgia elisabethae by Rodríguez and co-workers in 2009.
- This compound showed in vitro activity against malaria parasite (疟疾).
- **Aberrarone** bears a unique 6/5/5/5 tetracyclic ring system, four ketones, seven stereocenters, and three quaternary carbon centers.

Rodríguez, I. I.; Rodríguez, A. D.; Zhao, H. *J. Org. Chem.* **2009**, *74*, 7581-7584

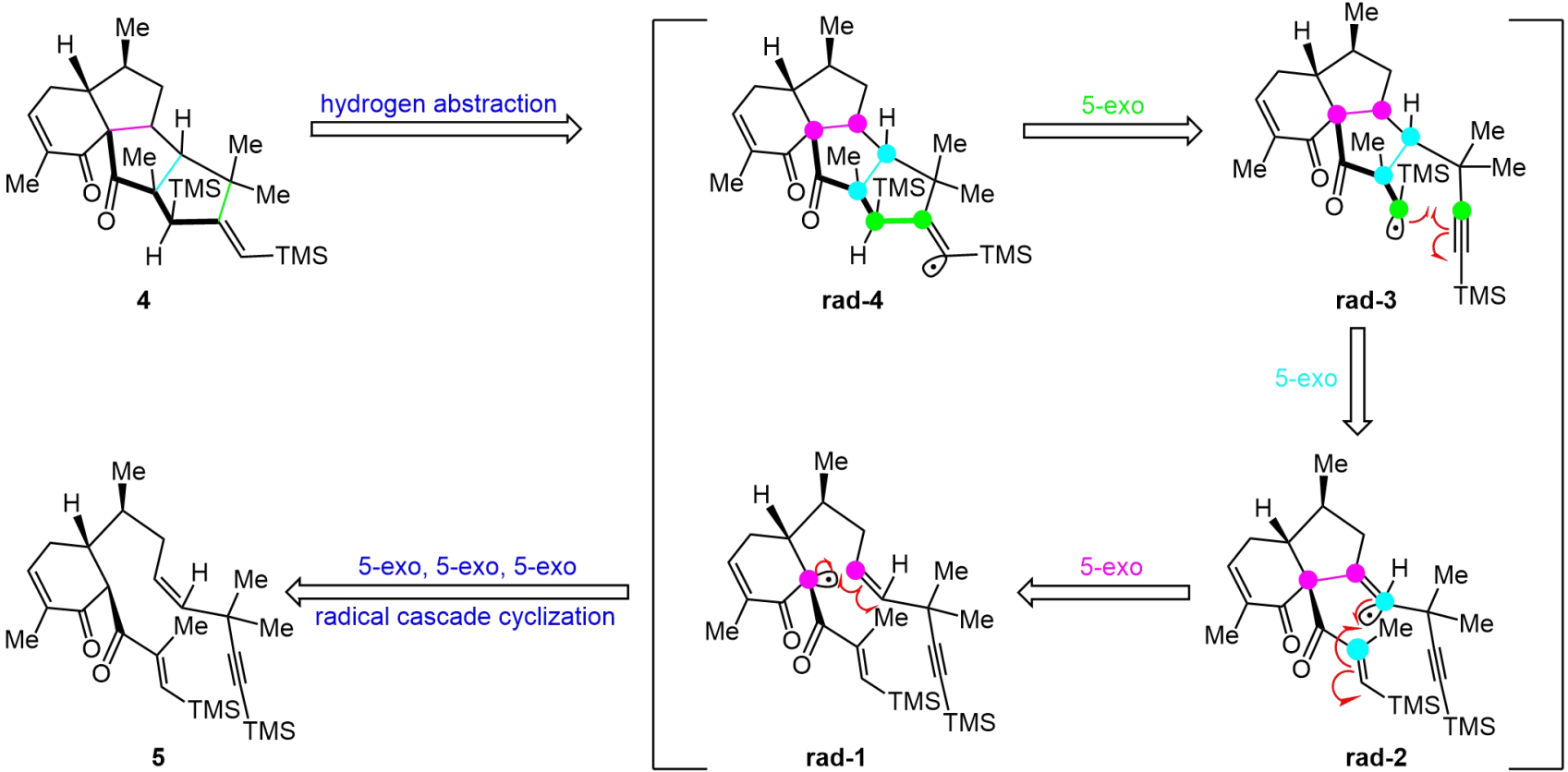
Introduction



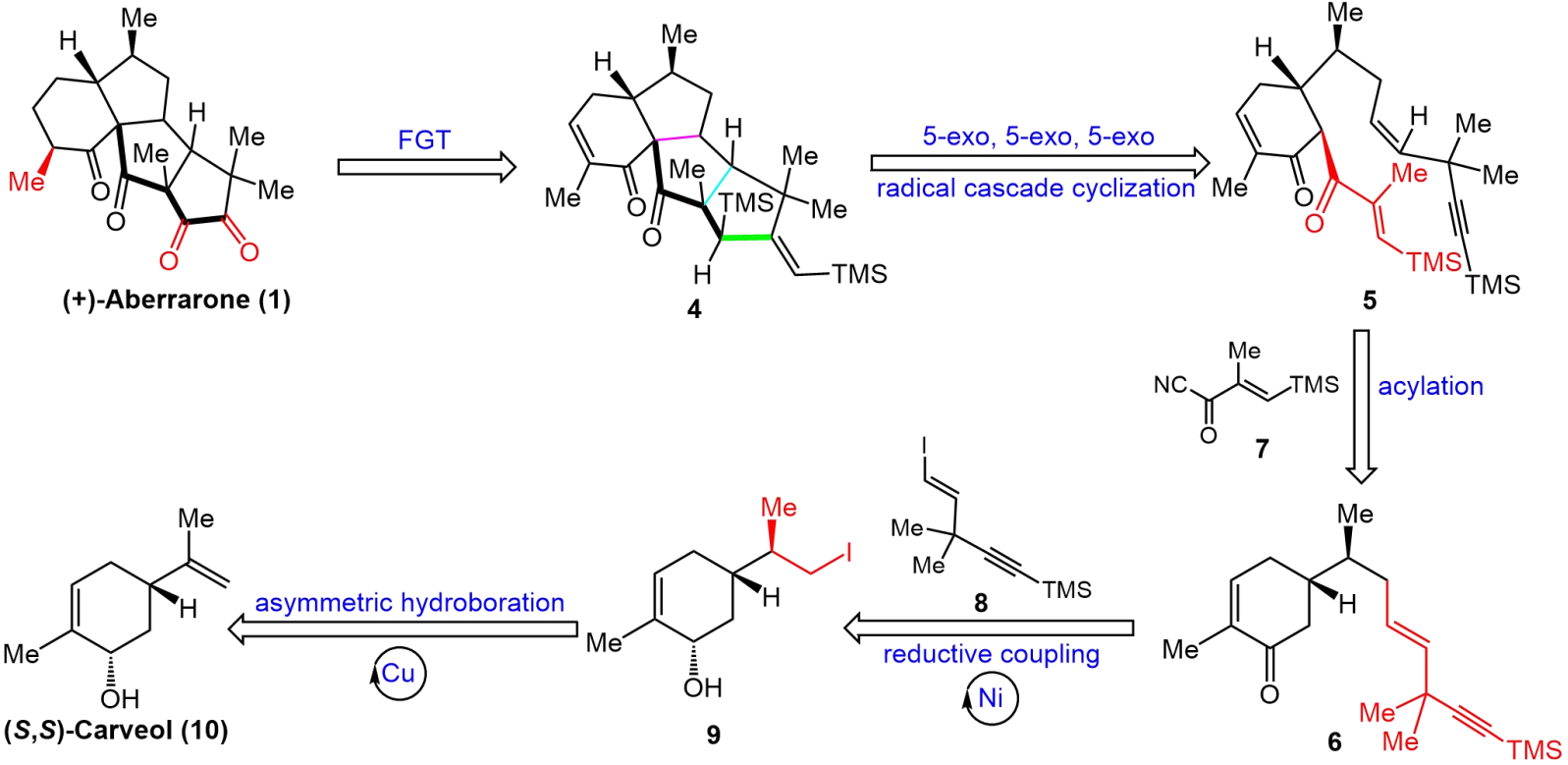
Retrosynthetic Analysis



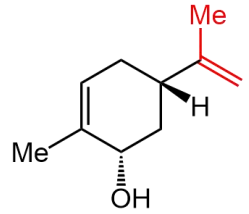
Retrosynthetic Analysis



Retrosynthetic Analysis

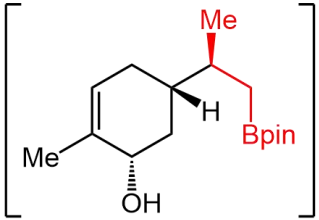


Stage 1: Synthesis of Iodoalkyl Compound 9



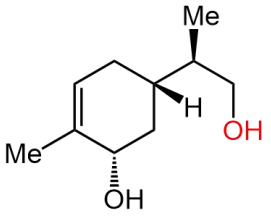
(*S*,*S*)-Carveol (10)

CuCl, **L$_1$**, *t*-BuOK
HBpin, PhMe

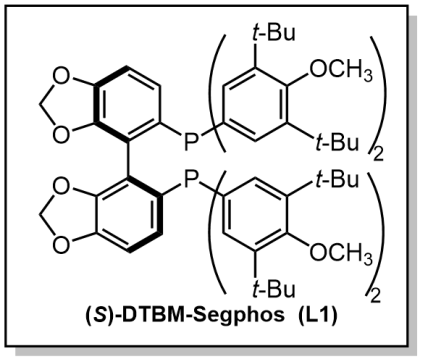


13

then $NaBO_3$
96% yield
(dr >20:1)

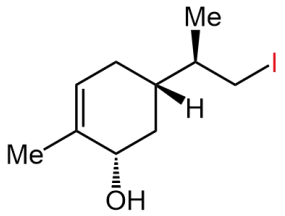


14



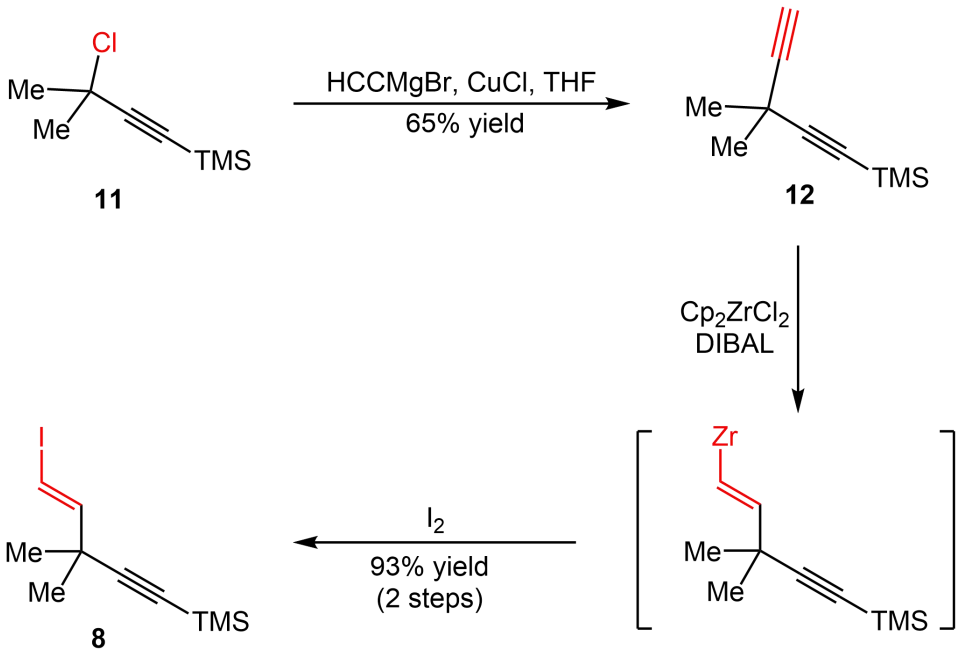
(*S*)-DTBM-Segphos (L1)

PPh_3, I_2, imd.
94% yield

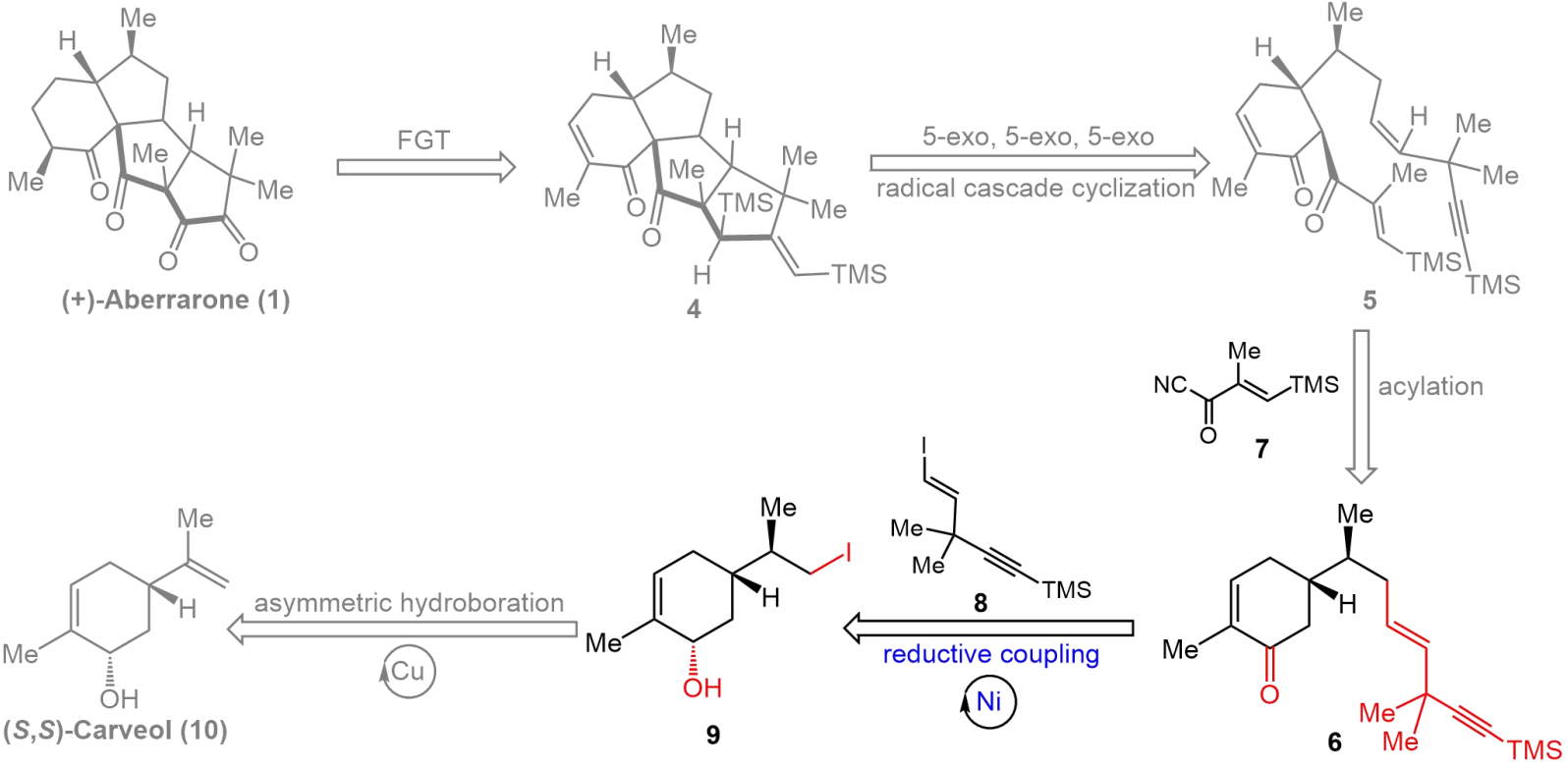


9

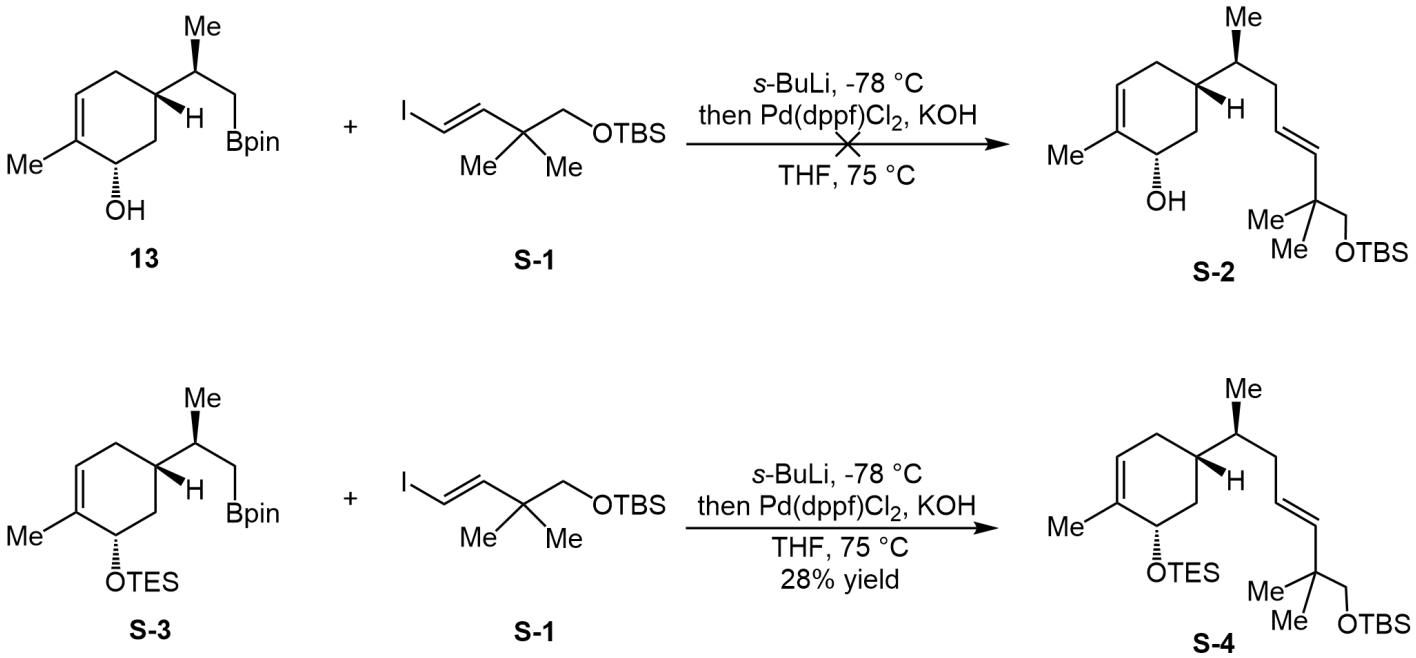
Stage 2: Synthesis of Iodoalkenyl Compound 8



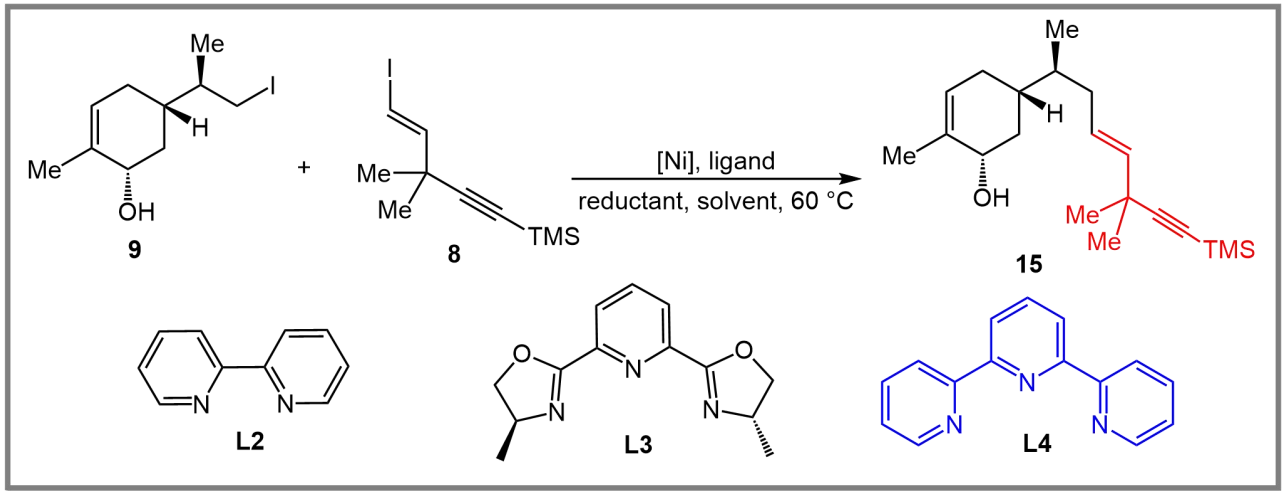
Stage 3: Synthesis of Ketone 6



Stage 3: Synthesis of Ketone 6



Stage 3: Synthesis of Ketone 6



Entry	[Ni]	Ligand	Reductant	Solvent	Yield
1	NiI_2	**L2**	Mn	DMF	40%
2	NiI_2	**L3**	Mn	DMF	54%
3	NiI_2	**L4**	Mn	DMF	68%

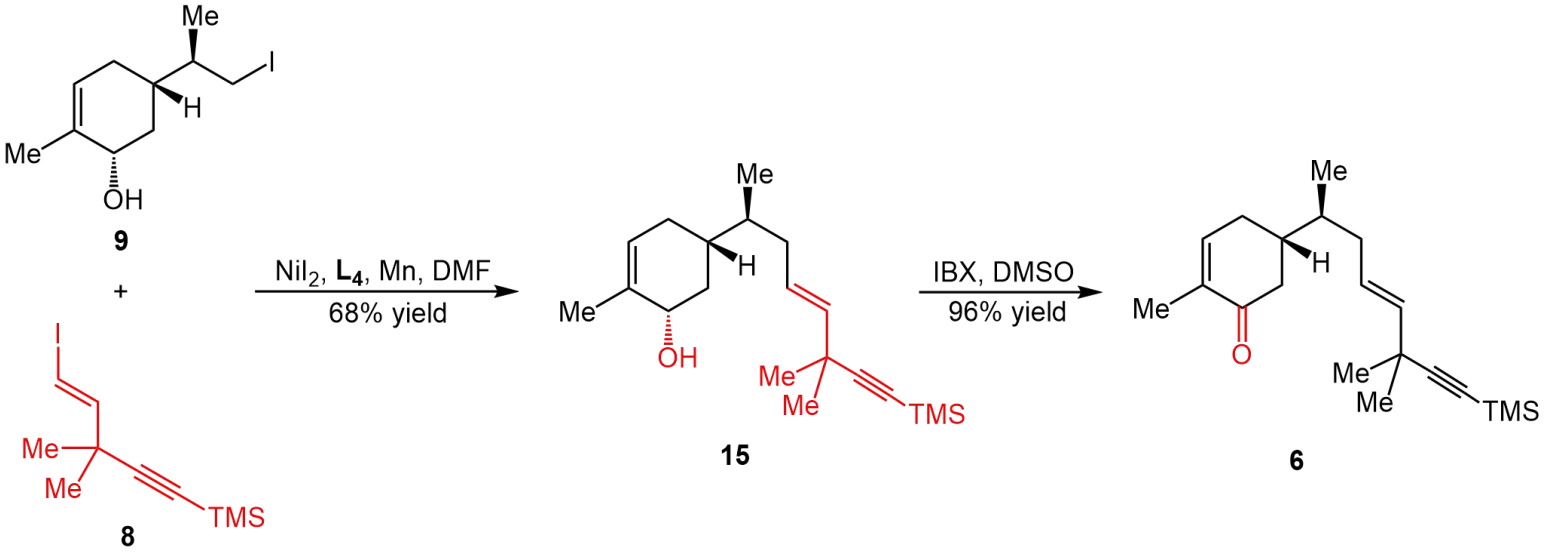
Reaction conditions: **9** (2.0 equiv), **8** (1.0 equiv), NiX_2 (10 mol %), ligand (12 mol %), reductant (2.0 equiv), and solvent (0.1 M).

Stage 3: Synthesis of Ketone 6

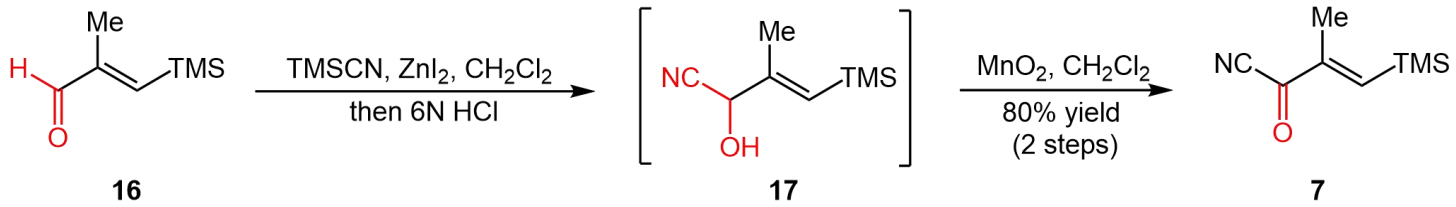
Entry	[Ni]	Ligand	Reductant	Solvent	Yield
3	NiI_2	**L4**	Mn	DMF	68%
4	$NiBr_2$	**L4**	Mn	DMF	46%
5	$NiCl_2$	**L4**	Mn	DMF	32%
6	NiI_2	**L4**	Mn	DMPU	21%
7	NiI_2	**L4**	Mn	DMA	46%
8	NiI_2	**L4**	Zn	DMF	22%

Reaction conditions: **9** (2.0 equiv), **8** (1.0 equiv), NiX_2 (10 mol %), ligand (12 mol %), reductant (2.0 equiv), and solvent (0.1 M).

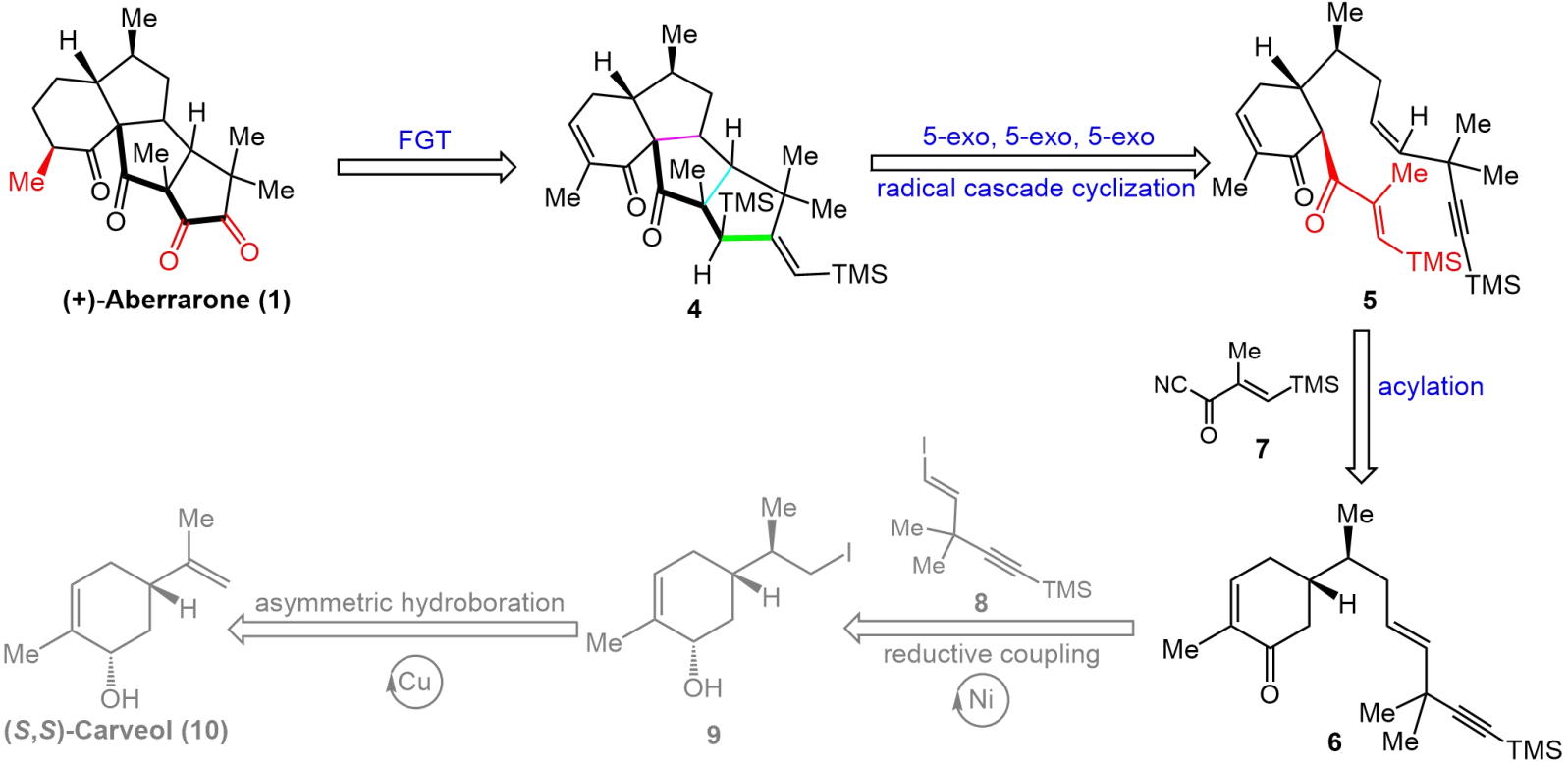
Stage 3: Synthesis of Ketone 6



Stage 4: Synthesis of Acyl Cyanide 7



Stage 5: Synthesis of the Key Tetracyclic Compound 4



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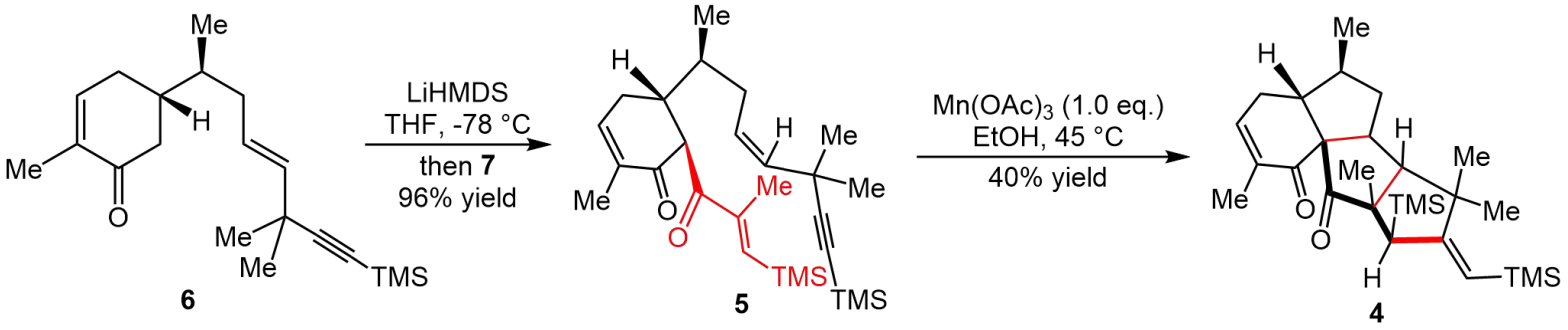
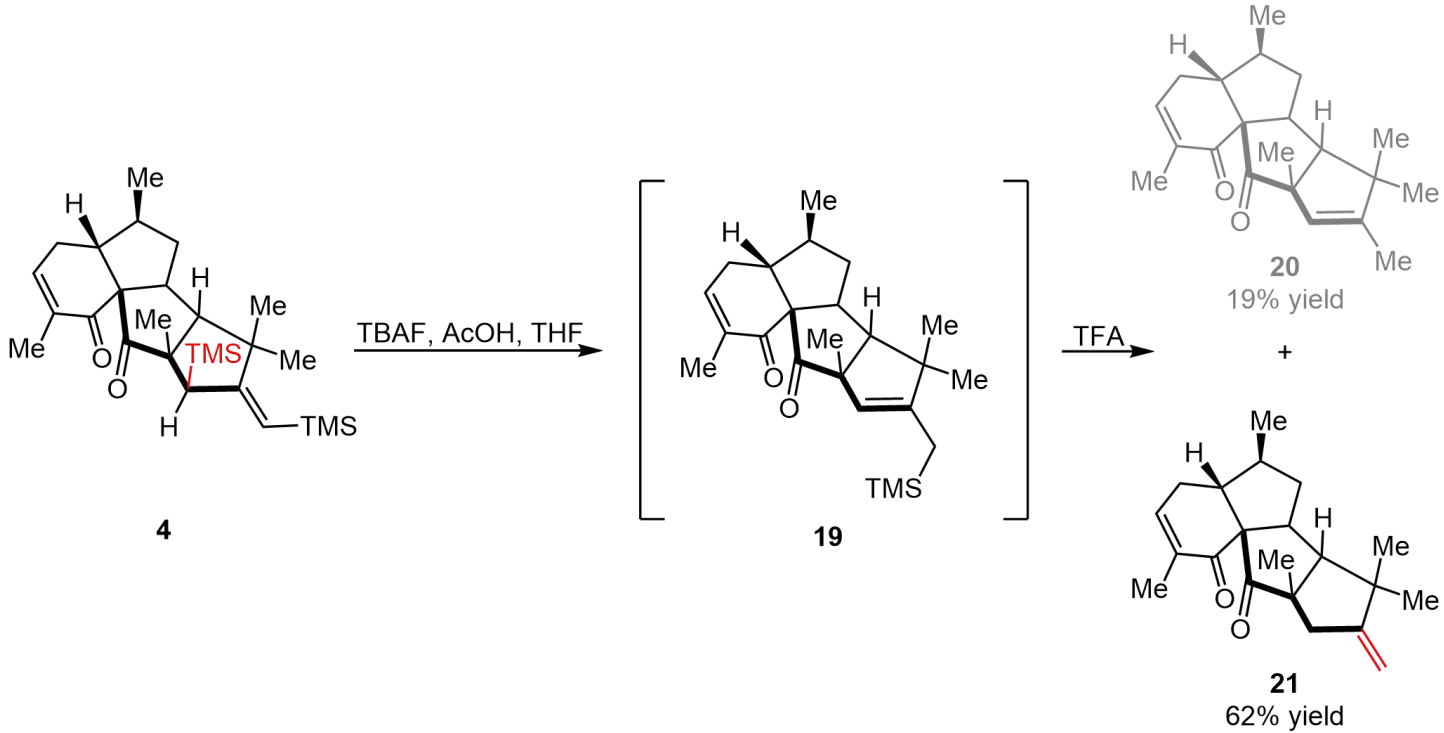
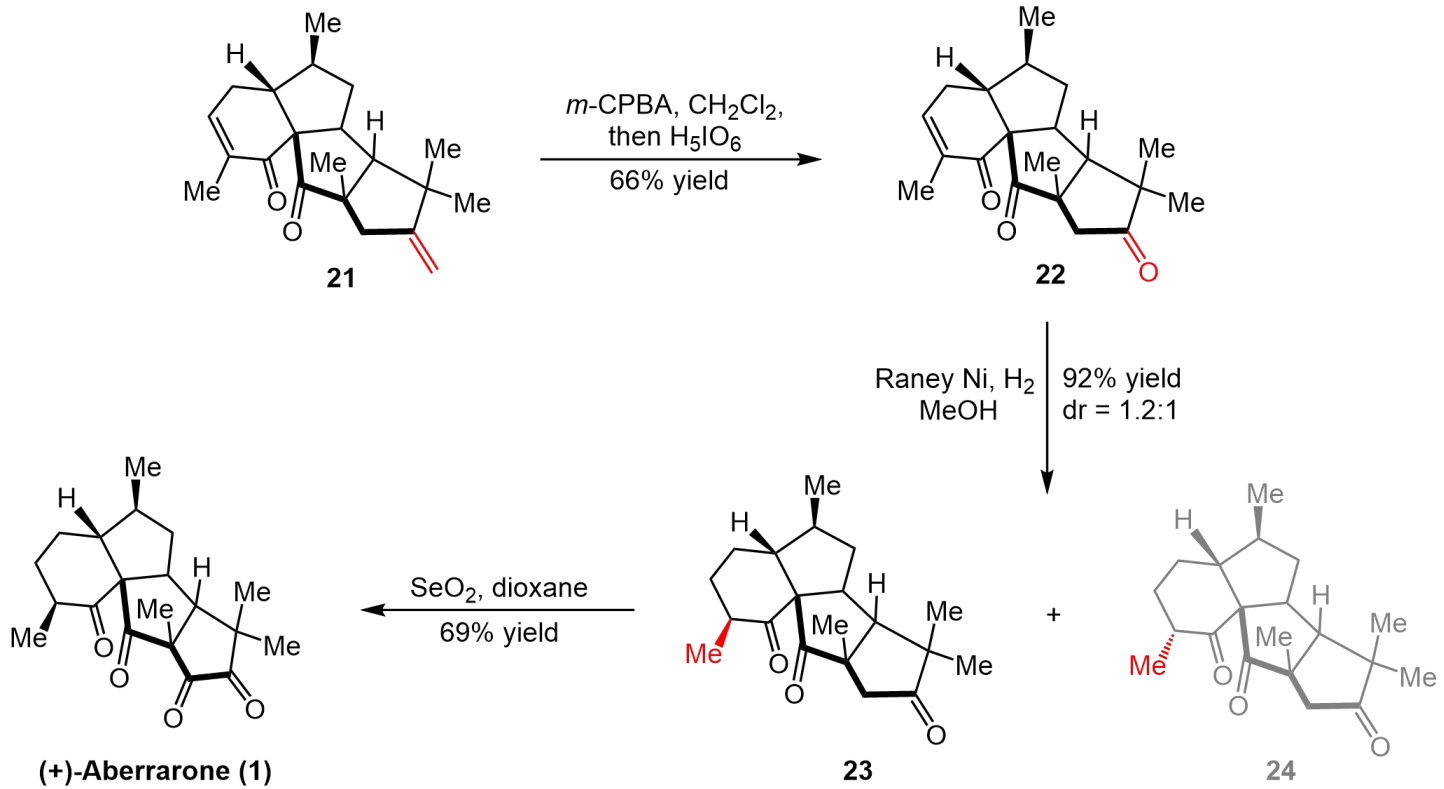


The key tetracyclic compound **4** was successfully obtained with 40%

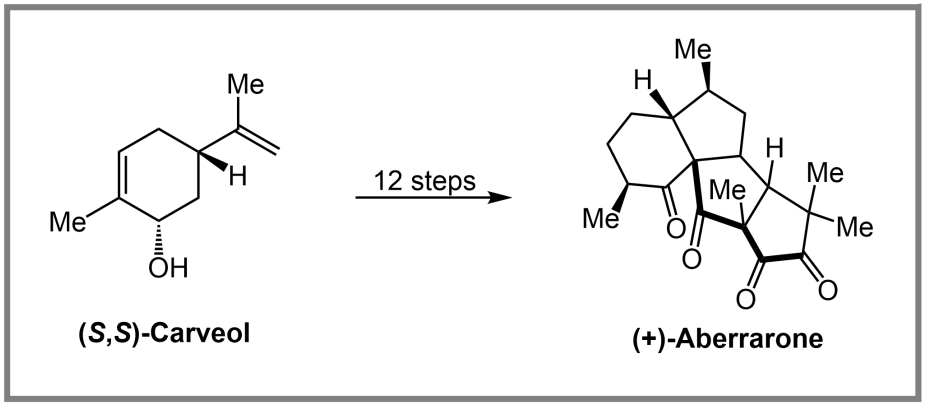
Stage 6: Synthesis of (+)-Aberrarone



Stage 6: Synthesis of (+)-Aberrarone



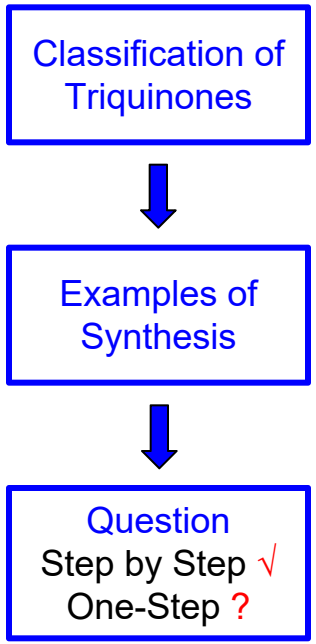
Summary



- Total synthesis of **(+)-Aberrarone** in 12 linear steps, 5.8% overall yield
- The key step was an intramolecular $Mn(OAc)_3$-mediated radical tandem cyclization to construct the 6/5/5/5 tetracyclic skeleton

The First Paragraph

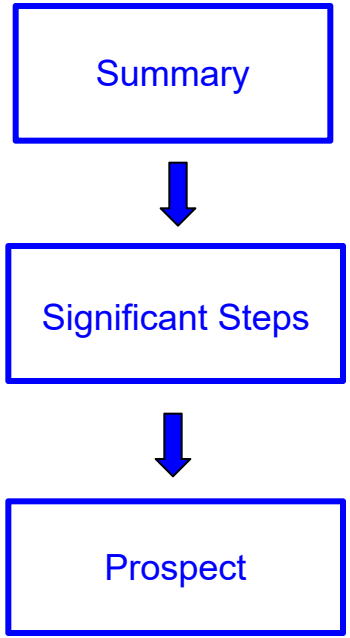
Writing Strategy



- Cyclohexane-angularly-fused triquinane natural products can be categorized into two classes on the basis of the structure of triquinanes: linear triquinanes **A**, and angular triquinanes **B.**
- These natural products have attracted widespread attention of the synthetic community...and many novel methodologies have been developed for the synthesis of these tetracyclic scaffolds.
- However, the triquinane units are constructed step by step, and a one-step method for the formation of triquinane has not yet been reported.

The Last Paragraph

Writing Strategy



- In summary, we have successfully achieved a concise total synthesis of (+)-aberrarone in 12 steps from the commercially available (*S*,*S*)-carveol .
- The most key step in the synthesis was an intramolecular $Mn(OAc)_3$-mediated radical tandem cyclization to construct the 6/5/5/5 tetracyclic skeleton.
- The application of such radical cascade cyclization in the total syntheses of other cyclohexane-angularly-fused triquinane natural products is in progress in our laboratory and will be reported in due course.

Representative Examples

- If successful, three C−C bonds, three rings, and four stereocenters would be formed in one step with high chemo-, regio-, and stereo selectivity, thus dramatically reducing the number of synthetic steps. (adj. 显著地)

- We envisioned that (+)-aberrarone (1) could be generated from the tetracycle 4 through functional group transformations. (v. 想象，展望)

- It is worth noting that both the TMS groups at the alkene and alkyne terminus play a pivotal role in the regioselectivity of this radical cascade reaction and favor 5-exo cyclization. (发挥关键作用)

Acknowledgement

Thanks for Your Attention