

Literature Report I

Total Syntheses of (-)-Conidiogenone B, (-)-Conidiogenone and (-)-Conidiogenol

Reporter: Kun Wang
Checker: Xiao-Qing Wang
Date: 2021-01-04

Zhai, H. *et al. Angew. Chem. Int. Ed.* **2020**, *59*, 16475–16479

CV of Prof. Hongbin Zhai



Hongbin Zhai

Background:

- 1981-1985 B.S., Peking University
- 1985-1988 M.S., Peking Union Medical College
- 1989-1997 Ph.D. & Postdoctor, The Ohio State University
- 1998-2000 Postdoctor, University of California, Berkeley
- 2000-2010 Professor, Shanghai Institute of Organic Chemistry
- 2010-2015 Professor, Lanzhou University
- 2015-now Professor, Peking University (Shenzhen)

Research:

1. Total synthesis of natural products
2. Heterocyclic chemistry/medicinal chemistry
3. Synthetic methodology development

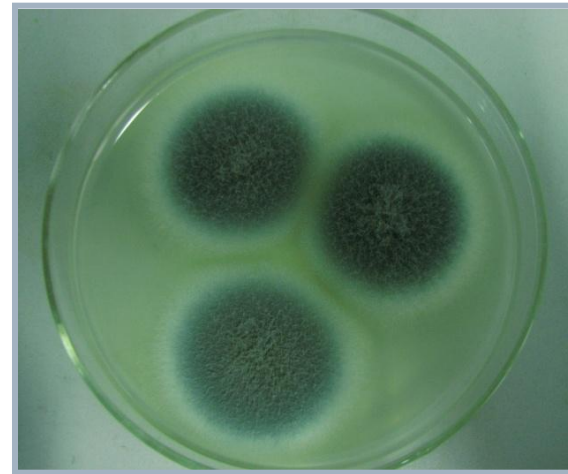
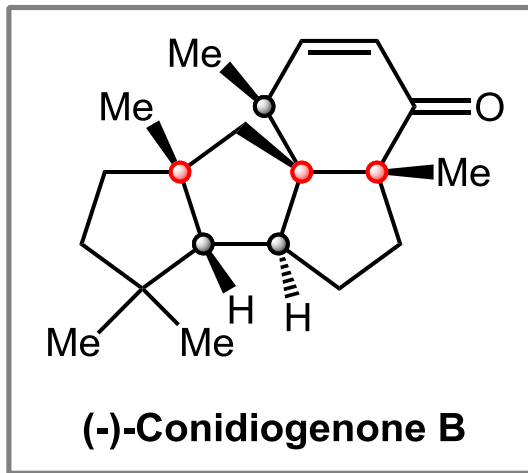
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2 Total Synthesis of (-)-Conidiogenone B

3 Summary

Introduction

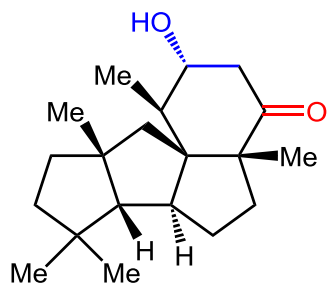


Penicillium

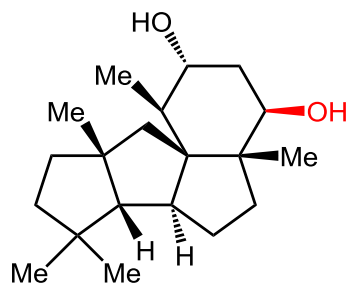
- It features a highly strained 6/5/5/5 tetracyclic core embedded with 6 consecutive stereocenters;
- It shows antibacterial activity against methicillin-resistant *Staphylococcus aureus*.

Gao, S.-S.; Li, X.-M.; Zhang, Y.; Li, C.-S.; Wang, B.-G. *Chem. Biodiversity* **2011**, 8, 1748–1753

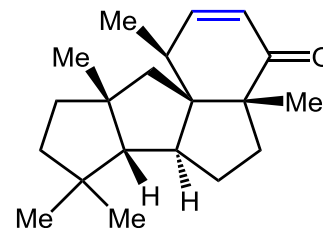
Introduction



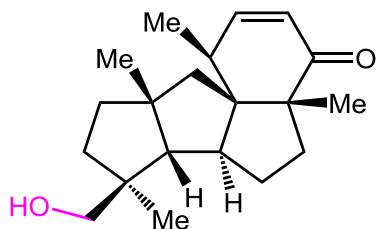
Conidiogenone (1)



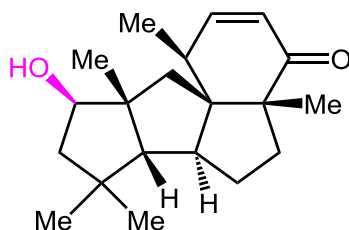
Conidiogenol (2)



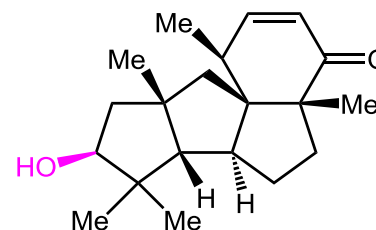
Conidiogenone B (3)



Conidiogenone C (4)

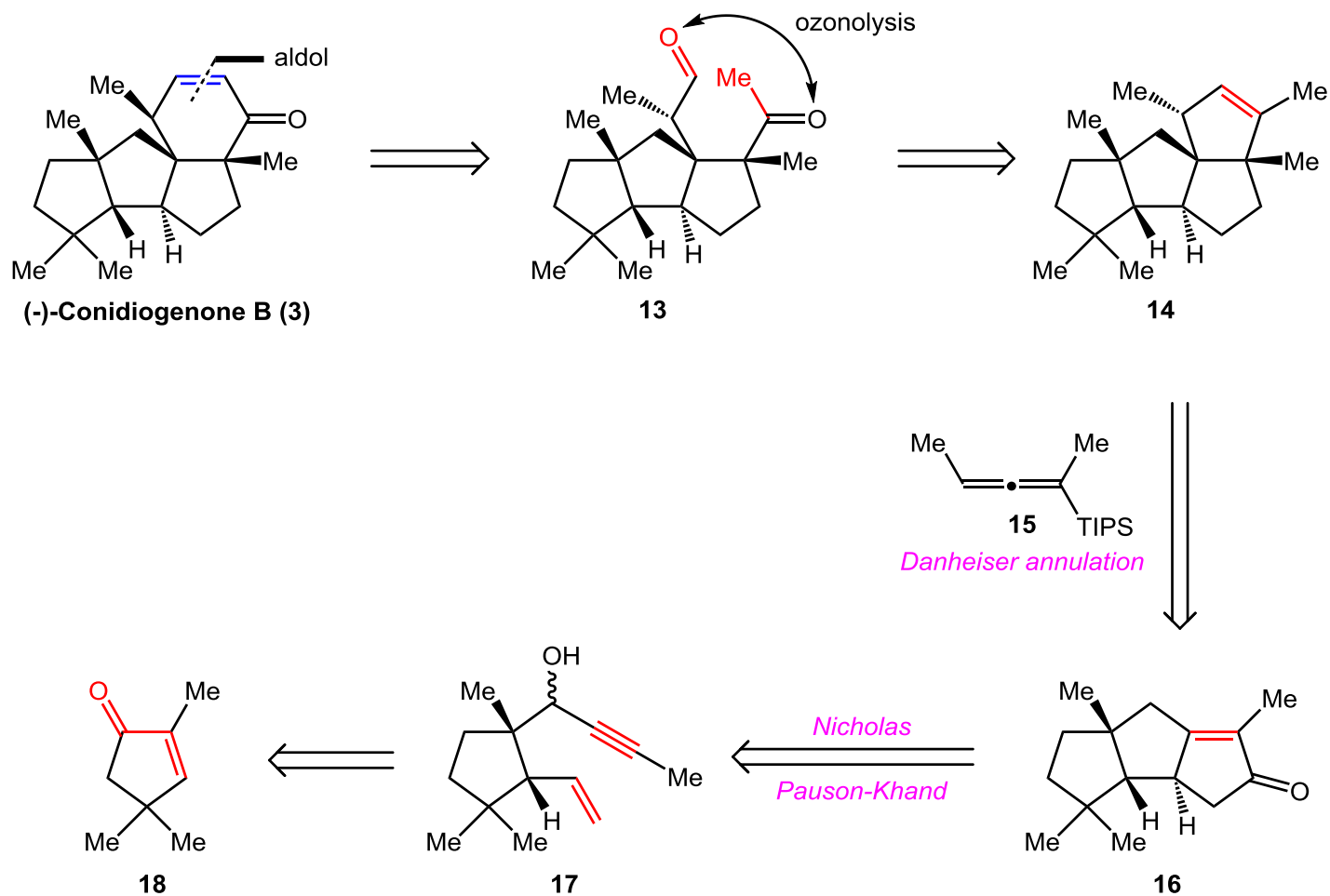


Conidiogenone E (5)

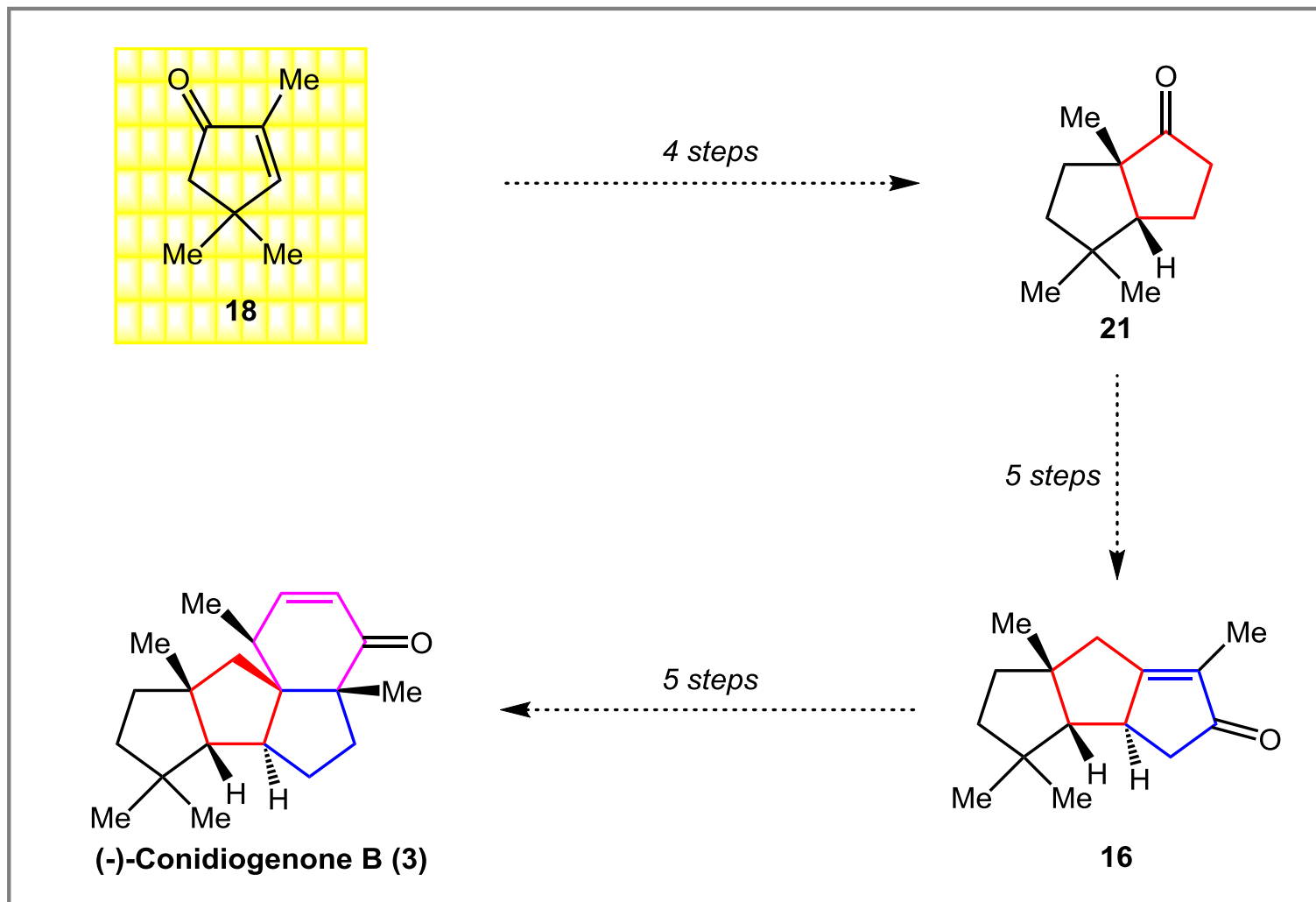


Conidiogenone F (6)

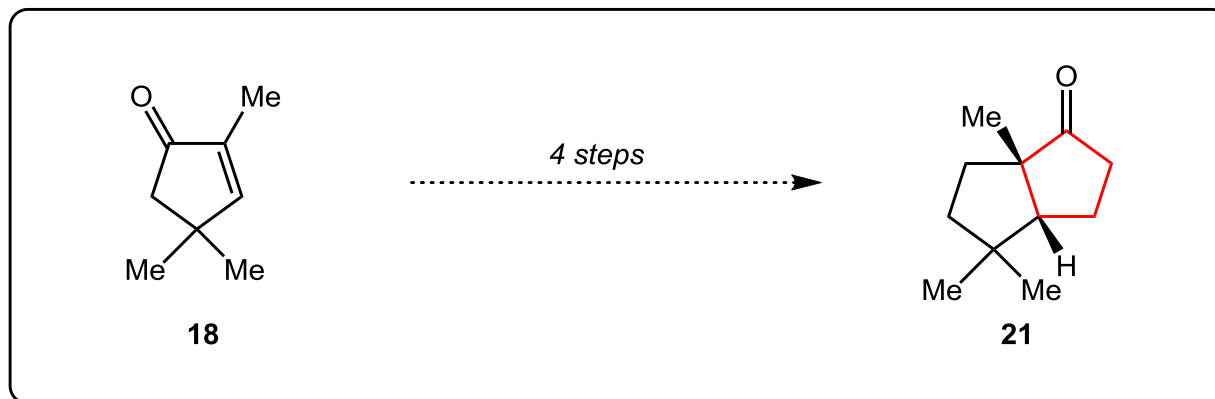
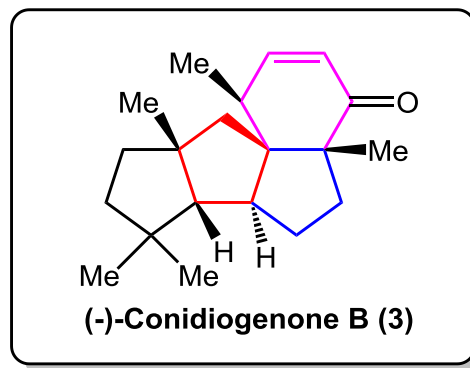
Retrosynthetic Analysis



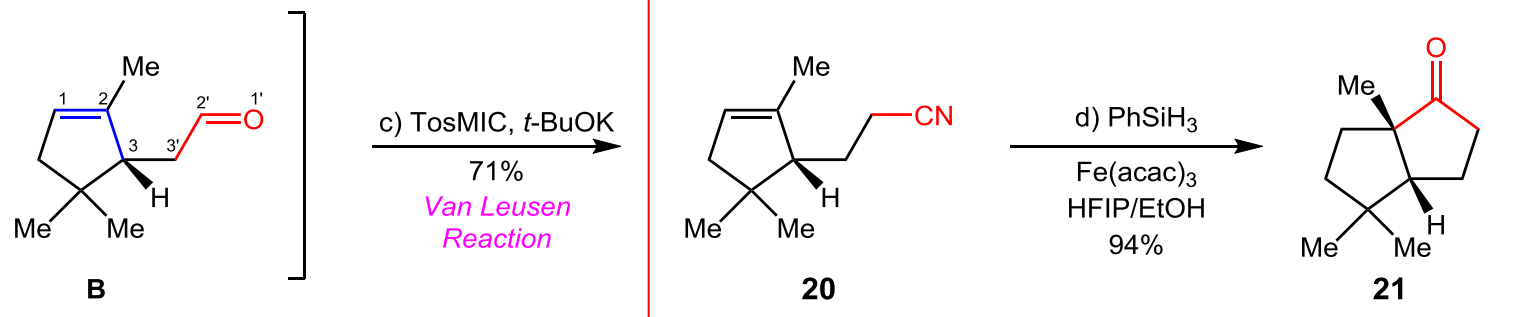
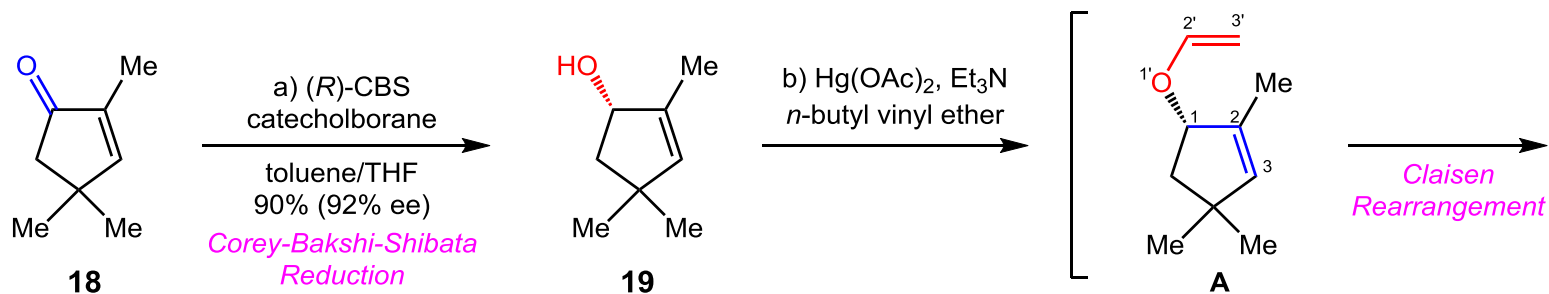
Synthesis of (-)-Conidiogenone B



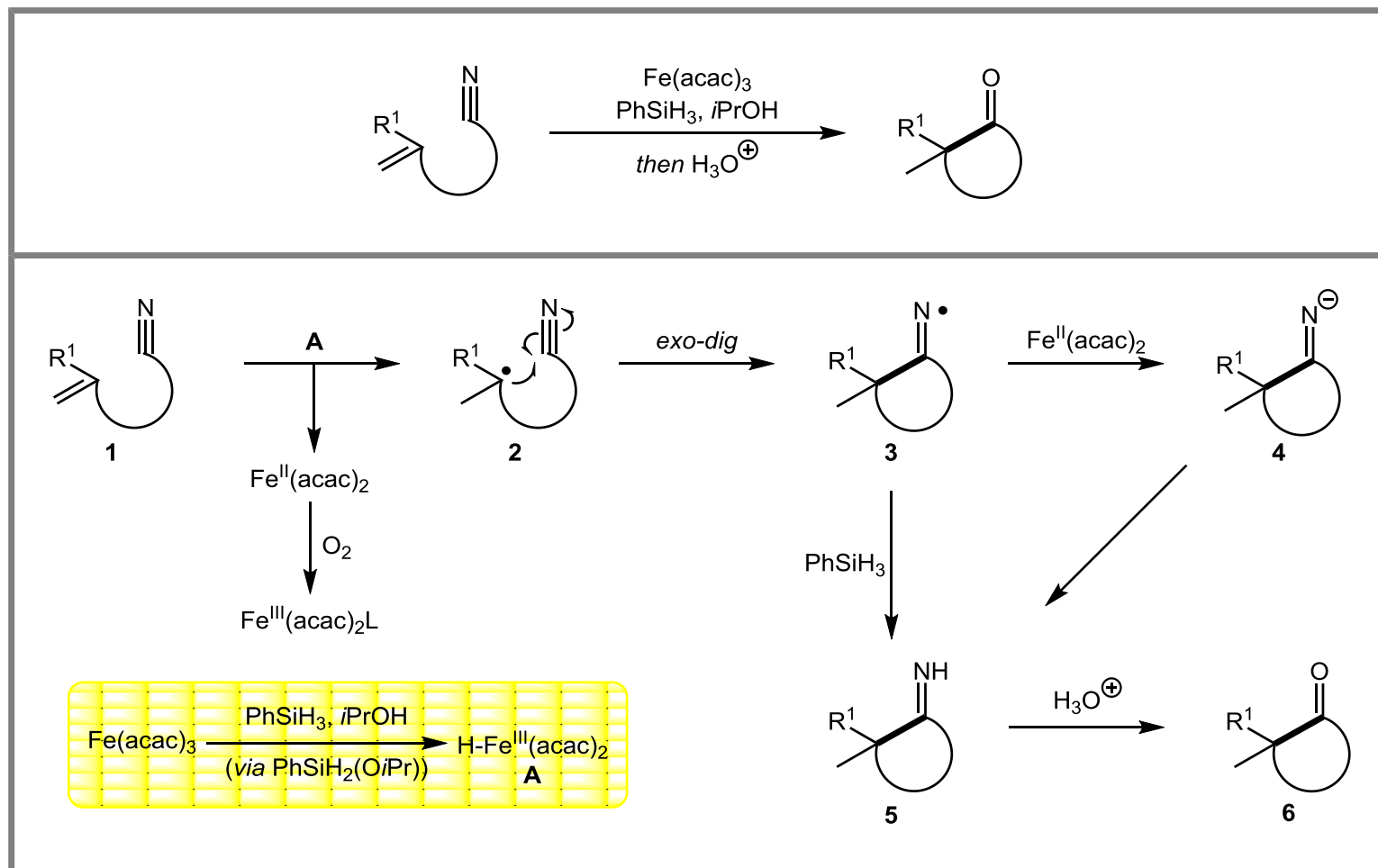
Stage 1: Synthesis of 21



Stage 1: Synthesis of 21

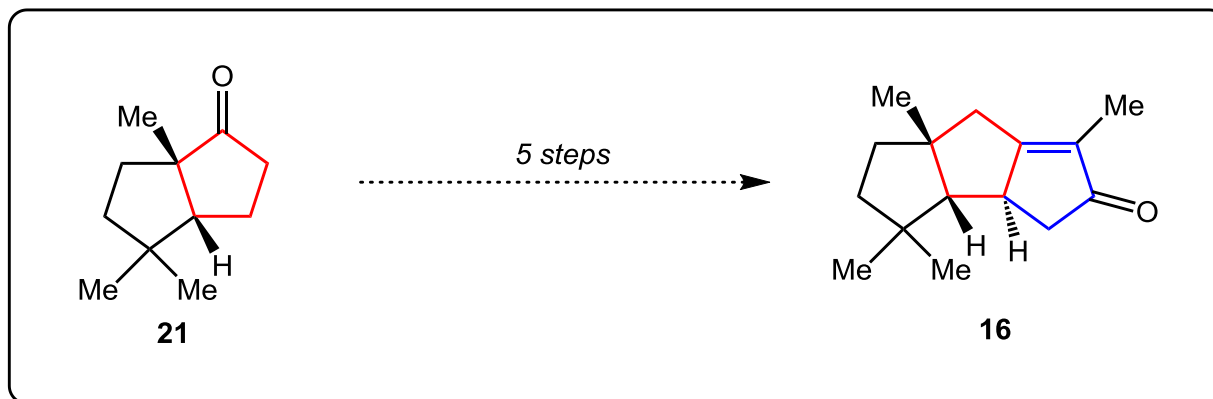
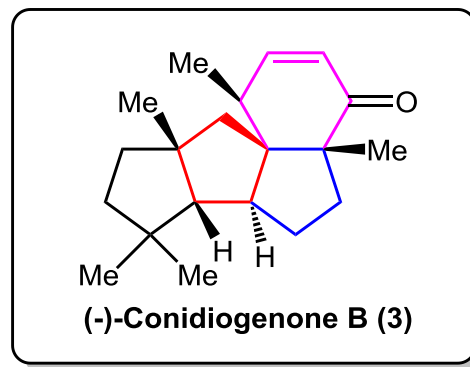


HAT-Mediated Alkene-Nitrile Cyclization

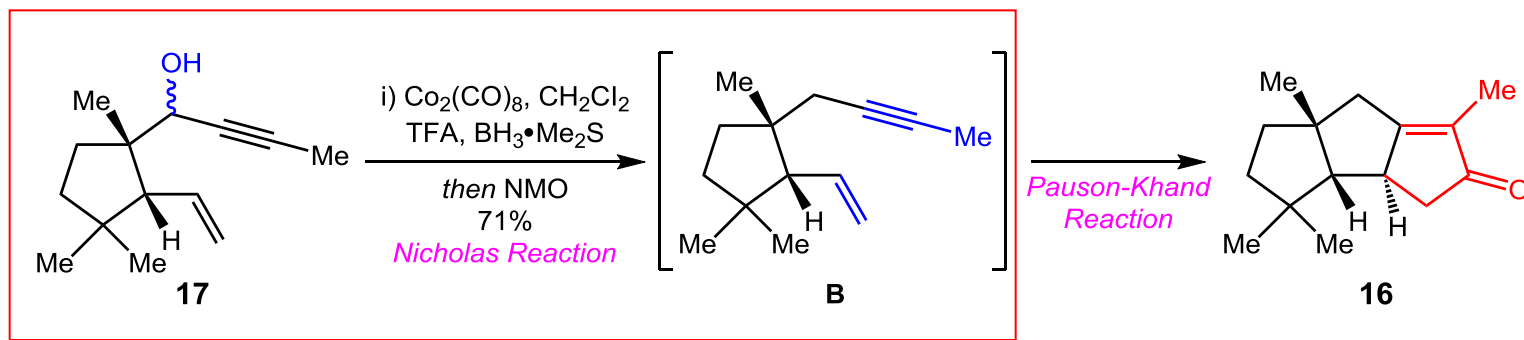
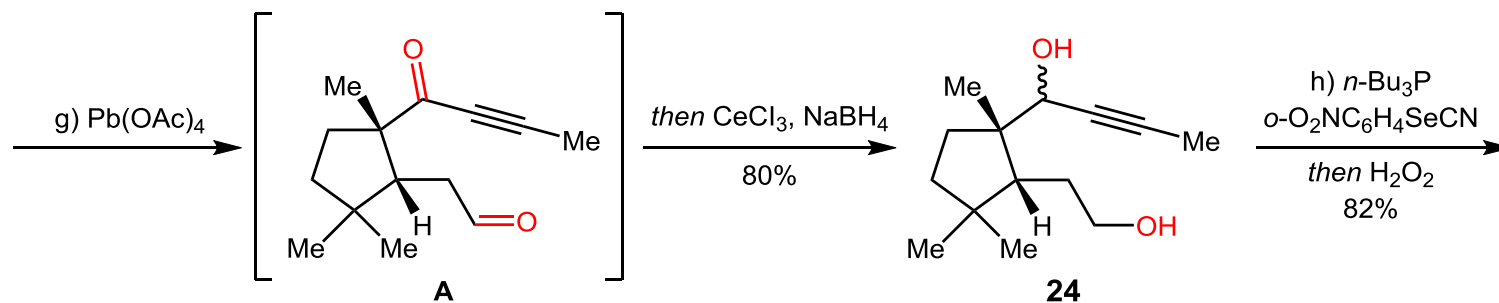
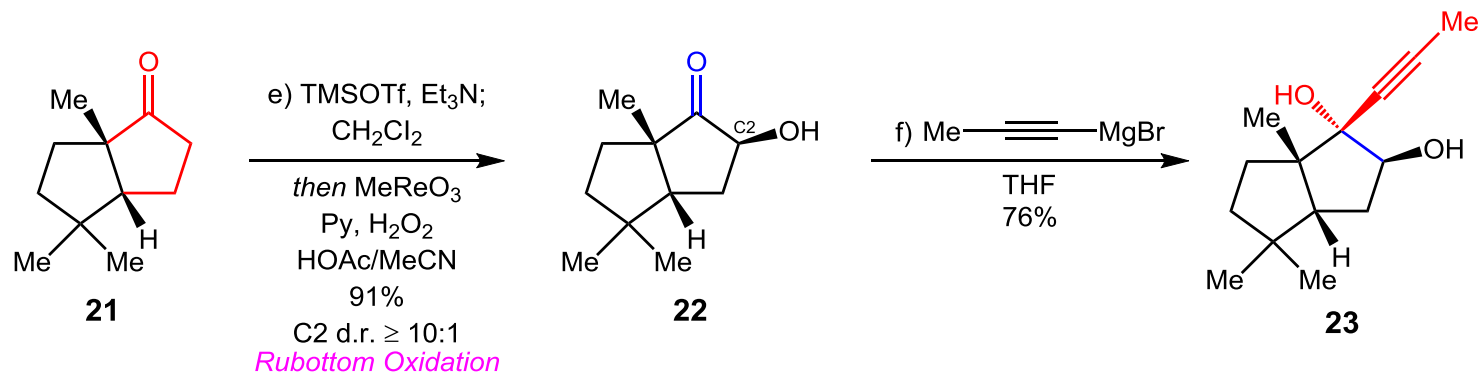


Turner, O. J.; Murphy, J. A.; Hirst, D. J.; Talbot, E. P. A. *Chem. Eur. J.* **2018**, *24*, 18658–18662

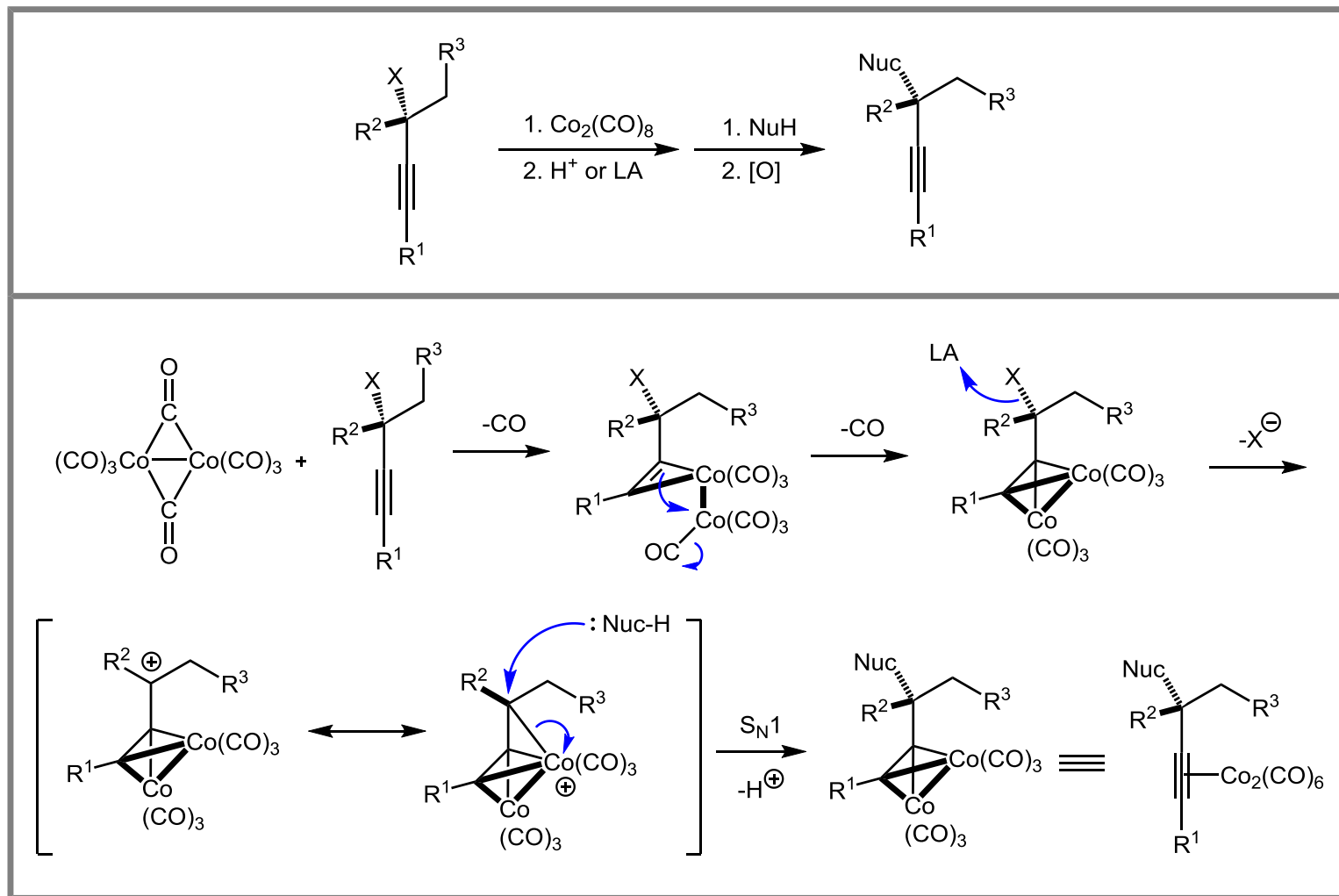
Stage 2: Synthesis of 16



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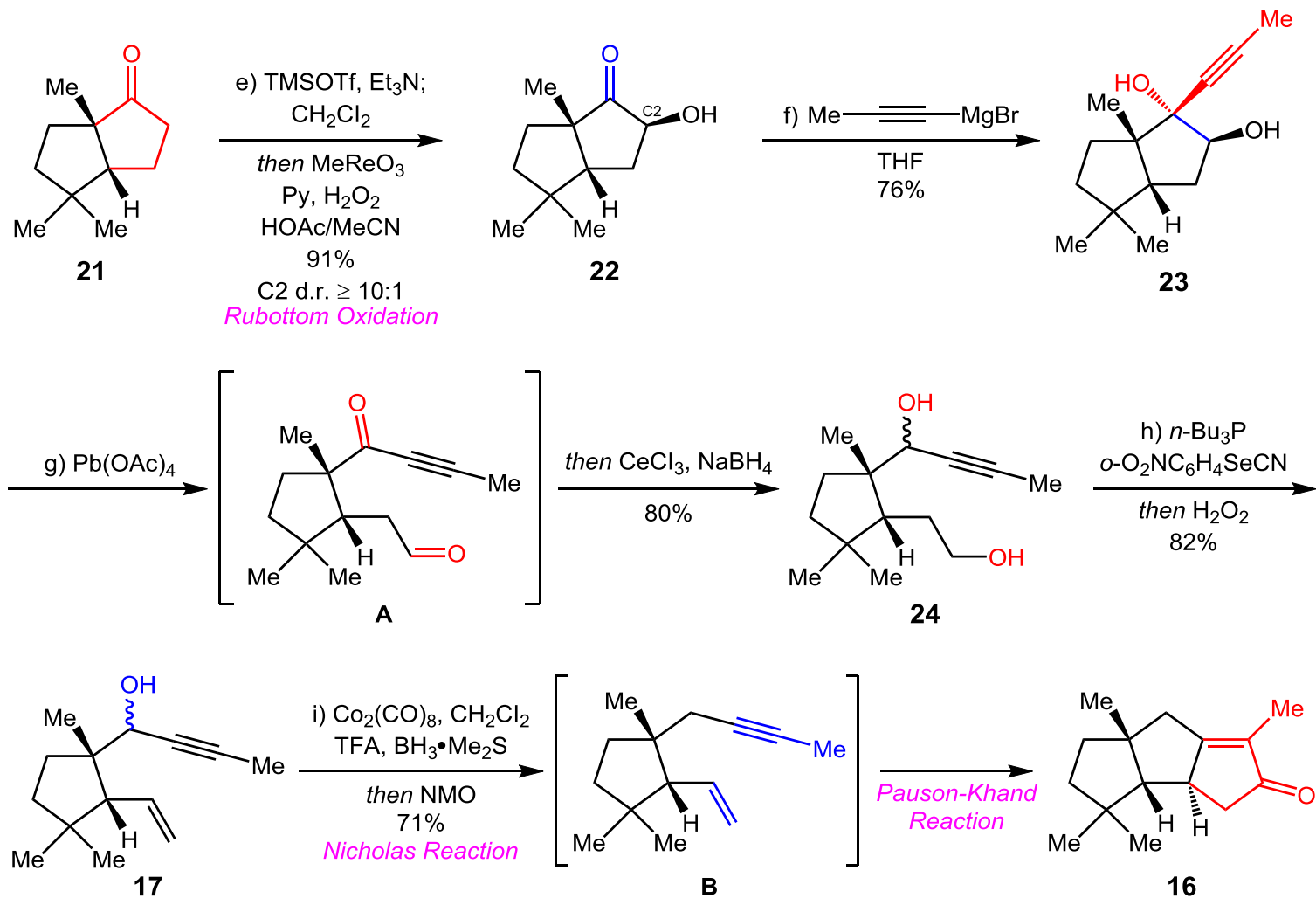


Nicholas Reaction

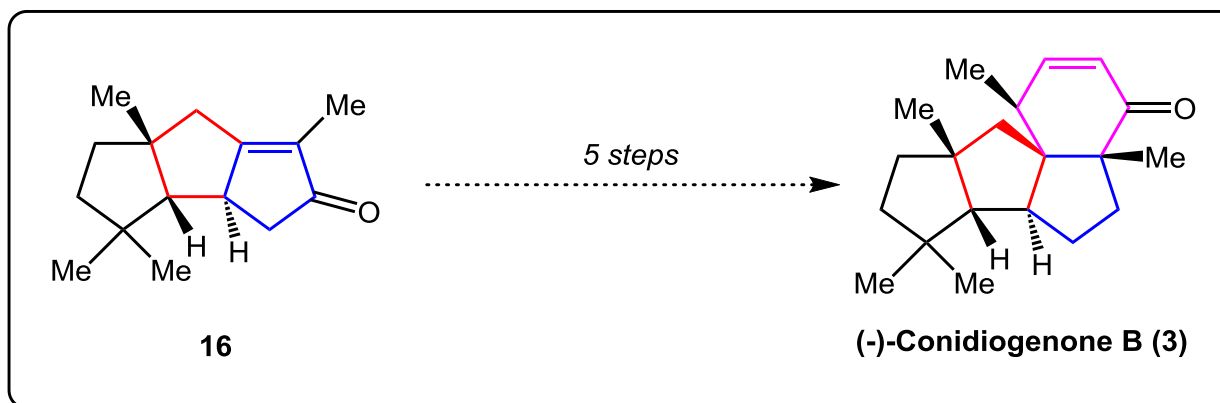
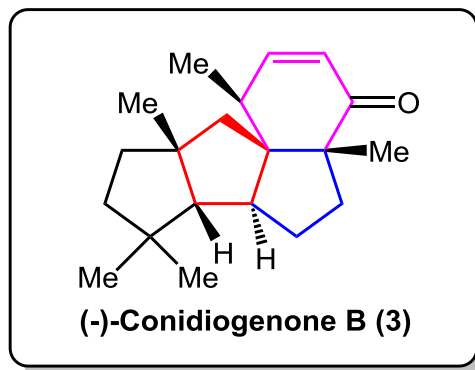


From Name Reaction P314

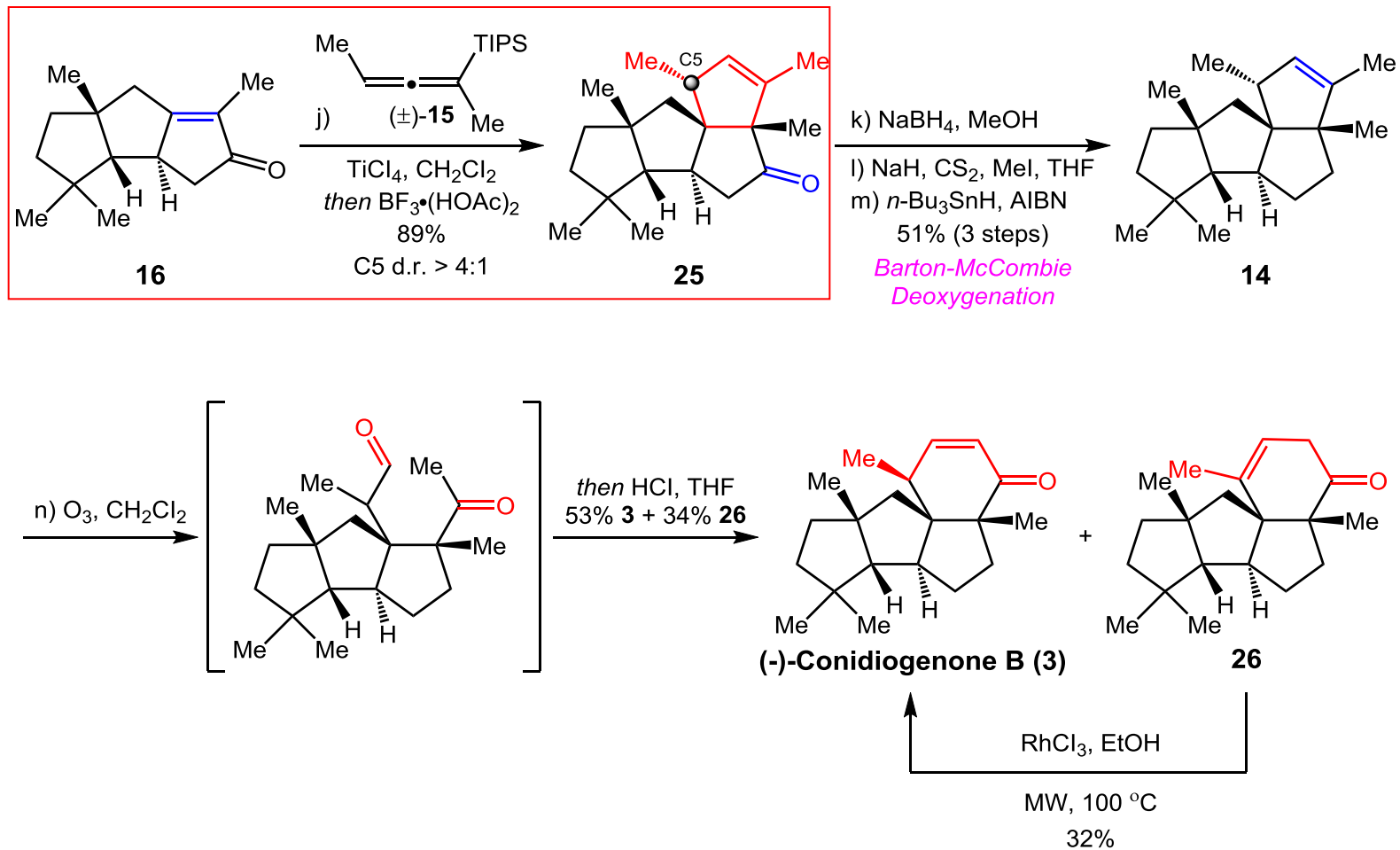
Stage 2: Synthesis of 16



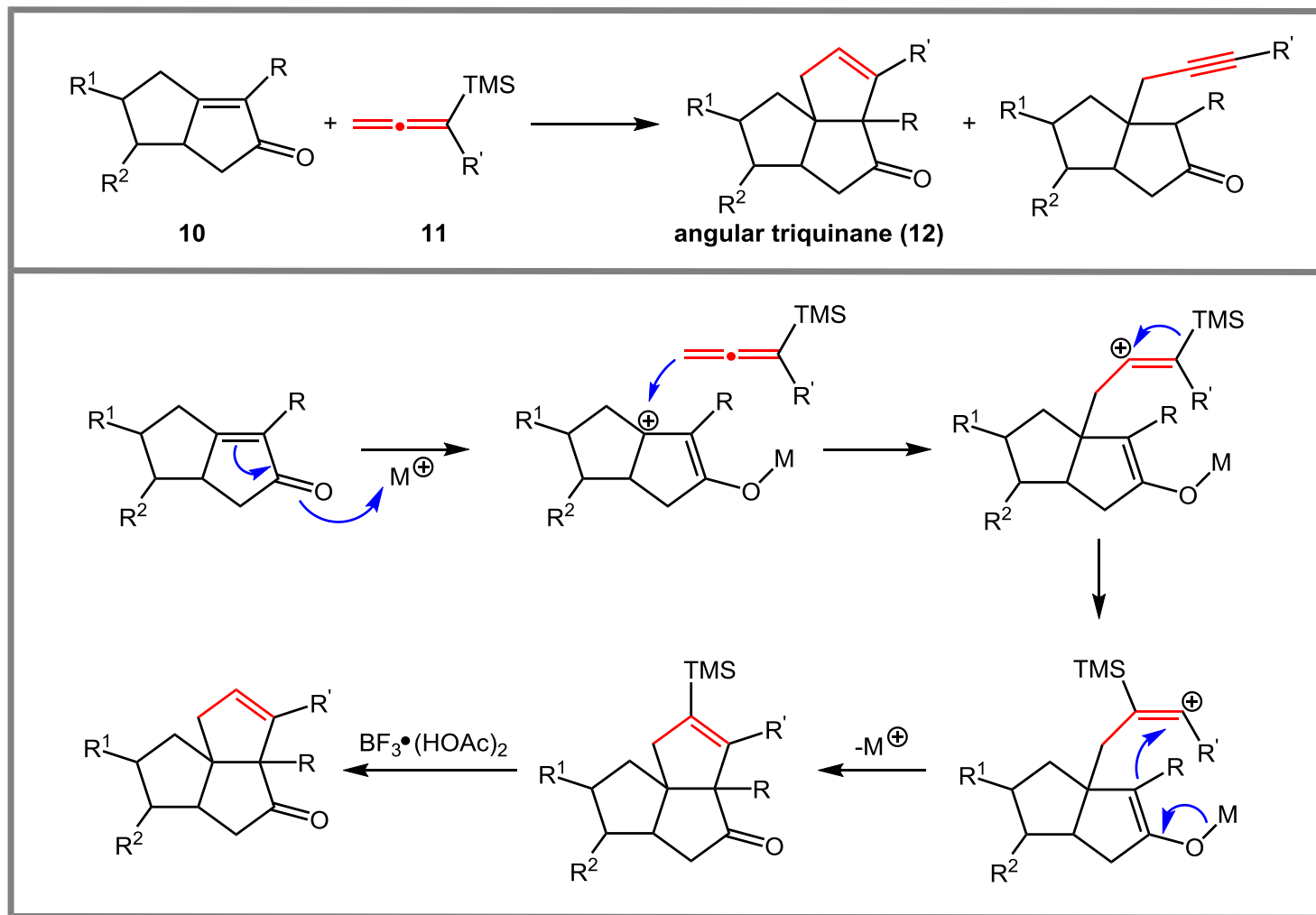
Stage 3: Synthesis of (-)-Conidiogenone B



Stage 3: Synthesis of (-)-Conidiogenone B

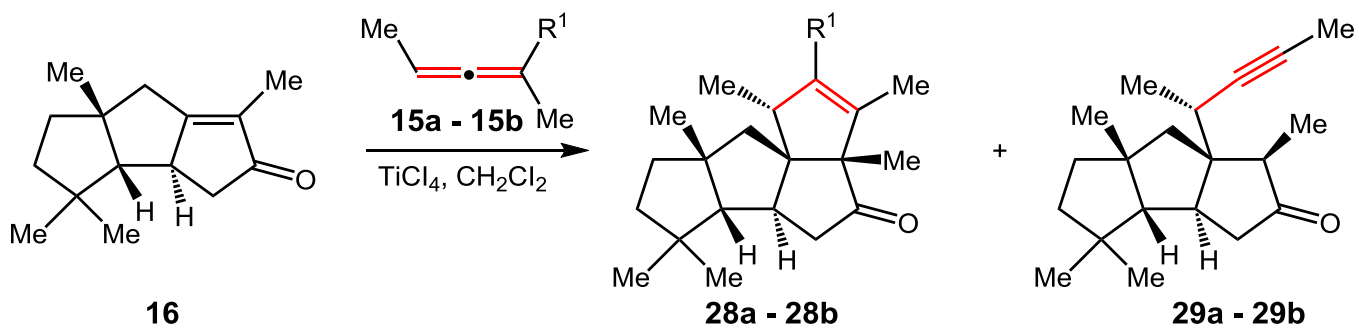


Danheiser Annulation



Becker, R. L.; Danheiser, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 389–391

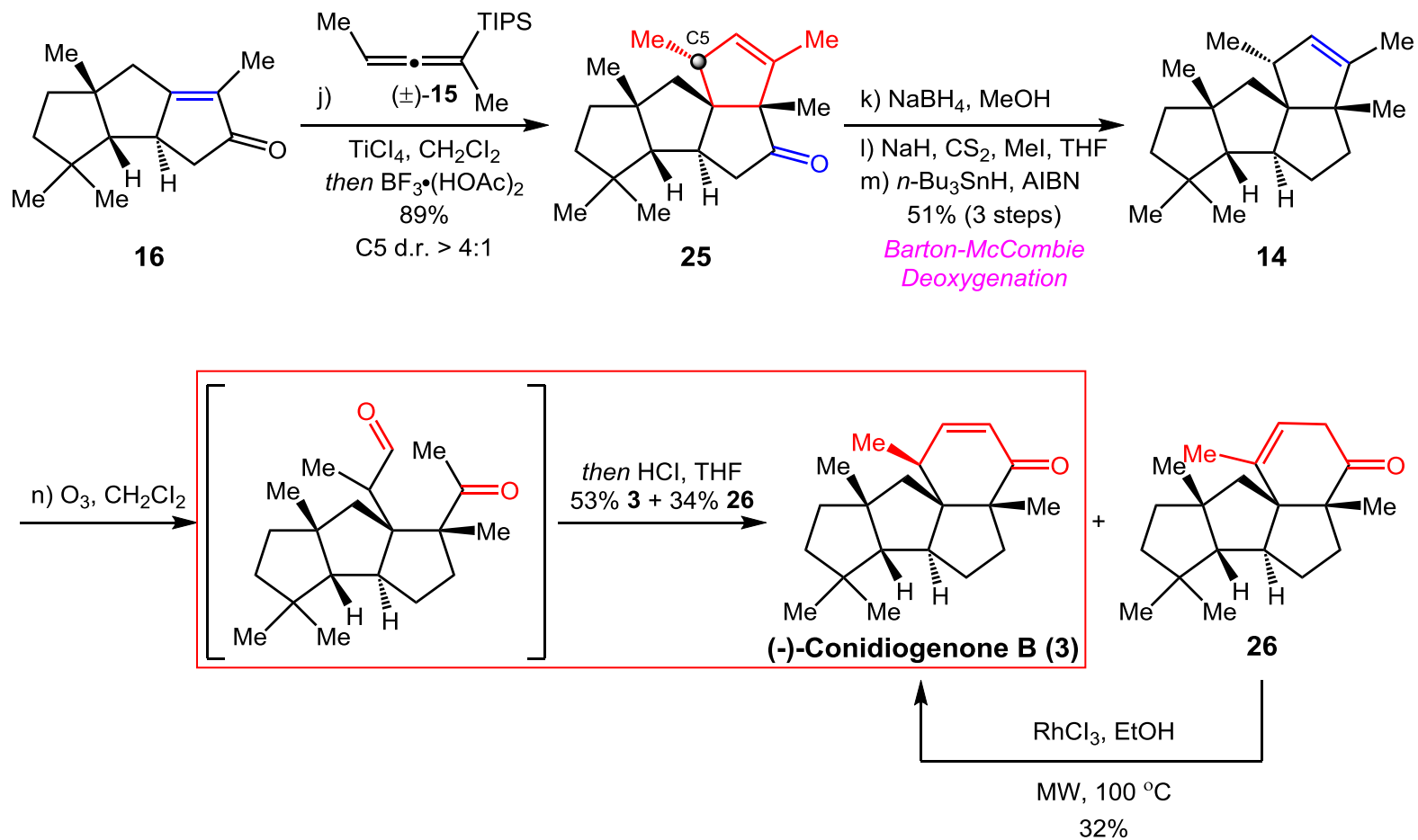
Danheiser Annulation



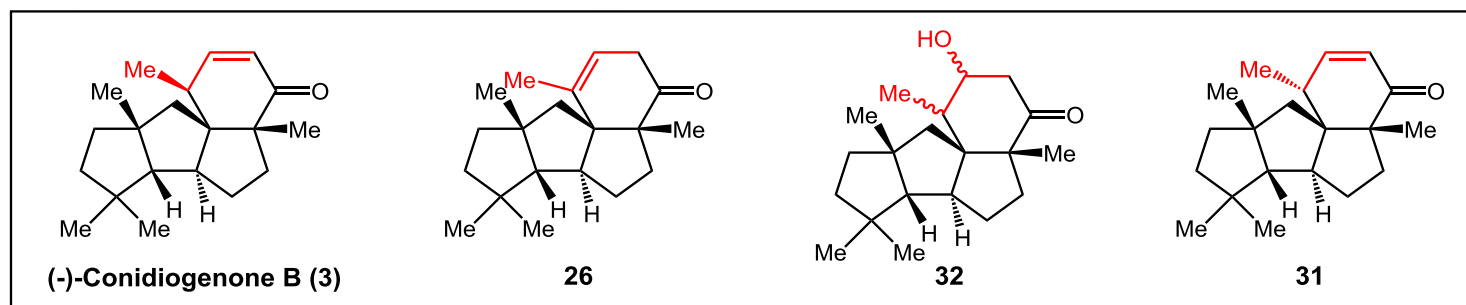
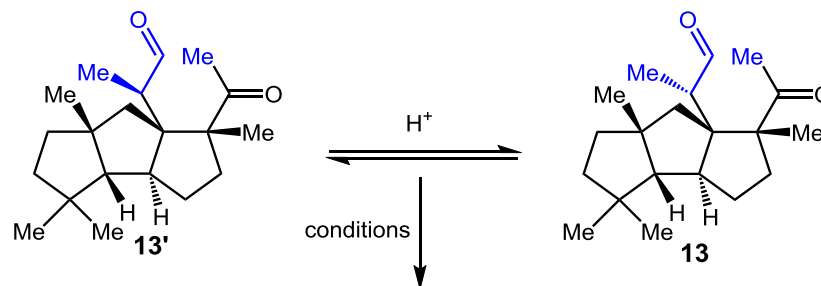
15a: R¹ = TMS: **28a** (33%), **29a** (46%)

15b: R¹ = TIPS: **28b** (89%), **29b** (< 5%)

Stage 3: Synthesis of (-)-Conidiogenone B

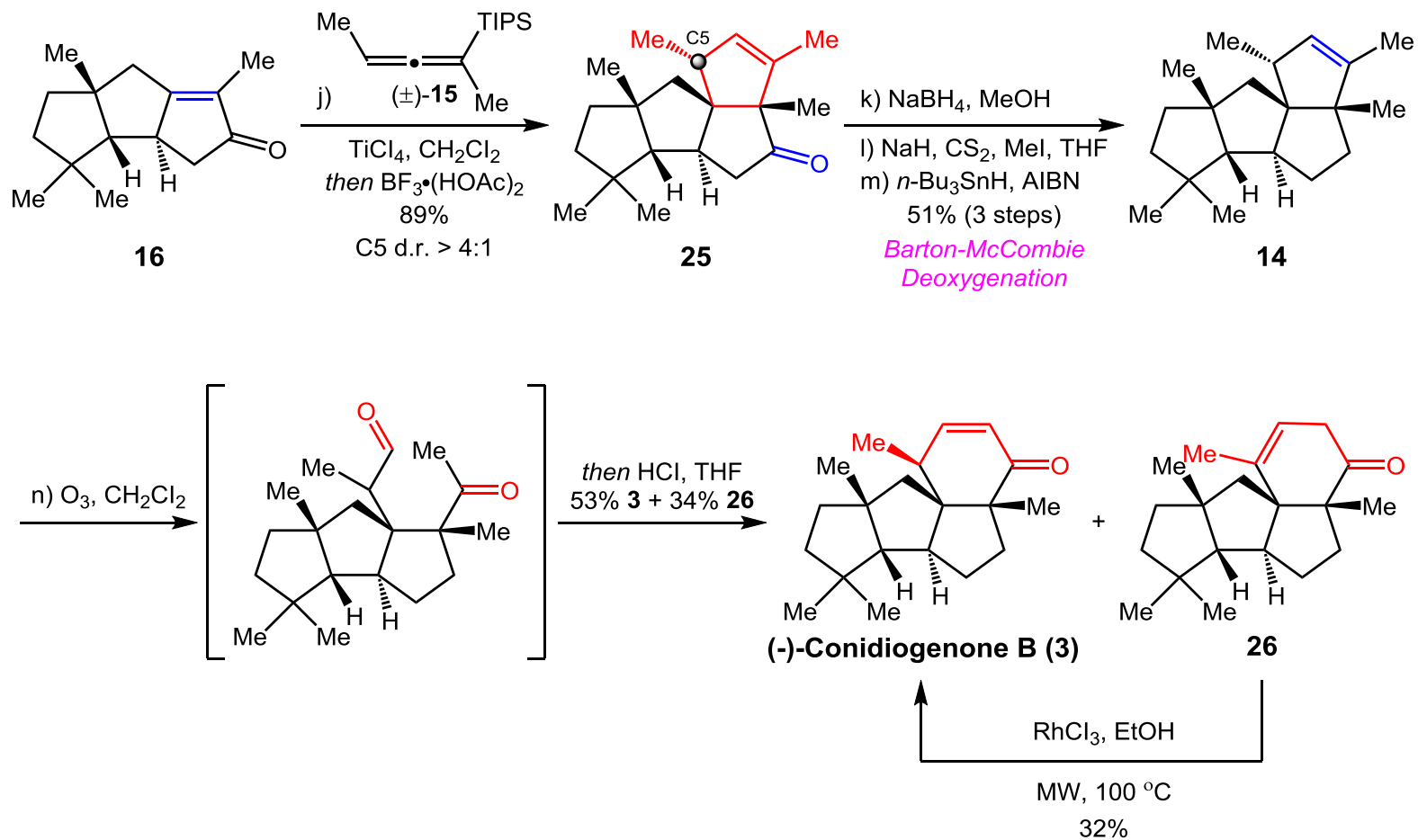


Aldol Condensation

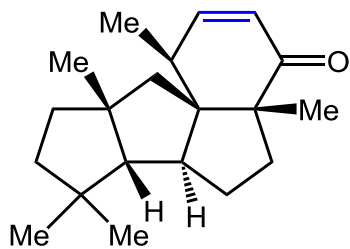


Entry	Conditions	Yield [%]				rsm
		3	31	26	32	
1	LiOH, <i>i</i> PrOH, rt, 48 h	—	46	—	32	—
2	DBU, CH ₂ Cl ₂ , 24 h	—	—	—	42	24
3	L-proline, DMSO, rt to 80 °C	—	—	—	—	35
4	(±)-BNPPA, CH ₂ Cl ₂ , rt	—	—	—	—	32
5	<i>p</i> -TsOH, toluene, 80 °C	—	—	78	—	—
6	1 M HCl, reflux	37	31	—	—	—
7	3 M HCl, reflux	53	—	34	—	—

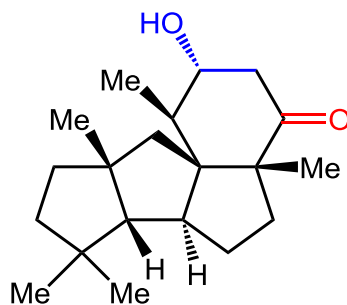
Stage 3: Synthesis of (-)-Conidiogenone B



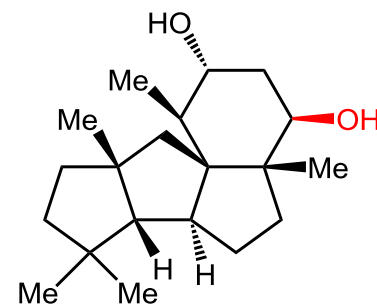
Syntheses of 1 and 2



(-)-Conidiogenone B (3)

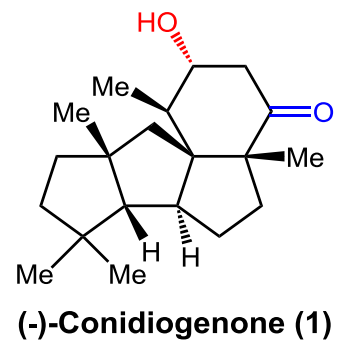
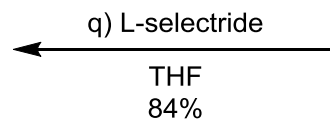
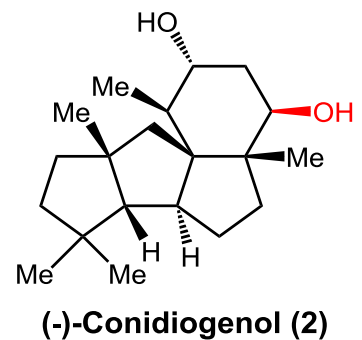
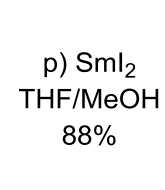
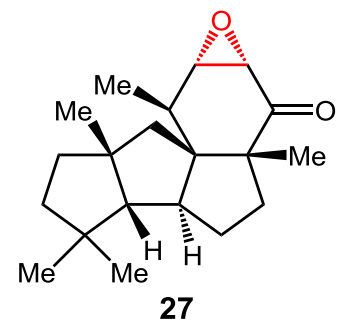
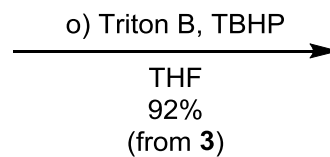
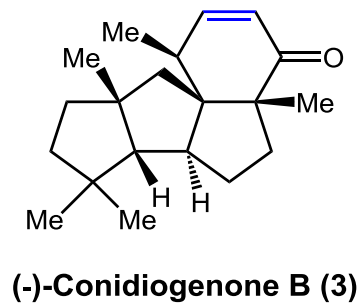


(-)-Conidiogenone (1)

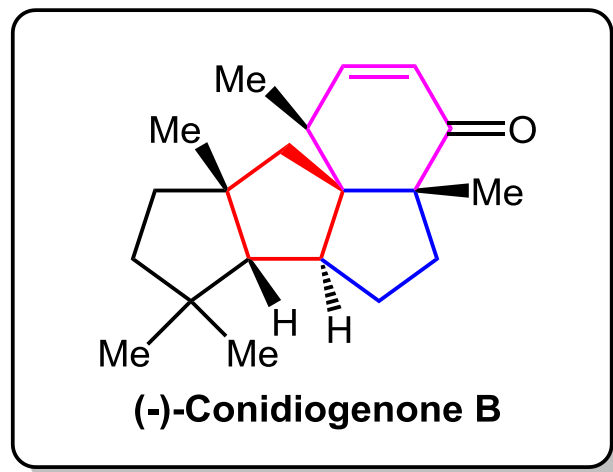


(-)-Conidiogenol (2)

Syntheses of 1 and 2



Summary

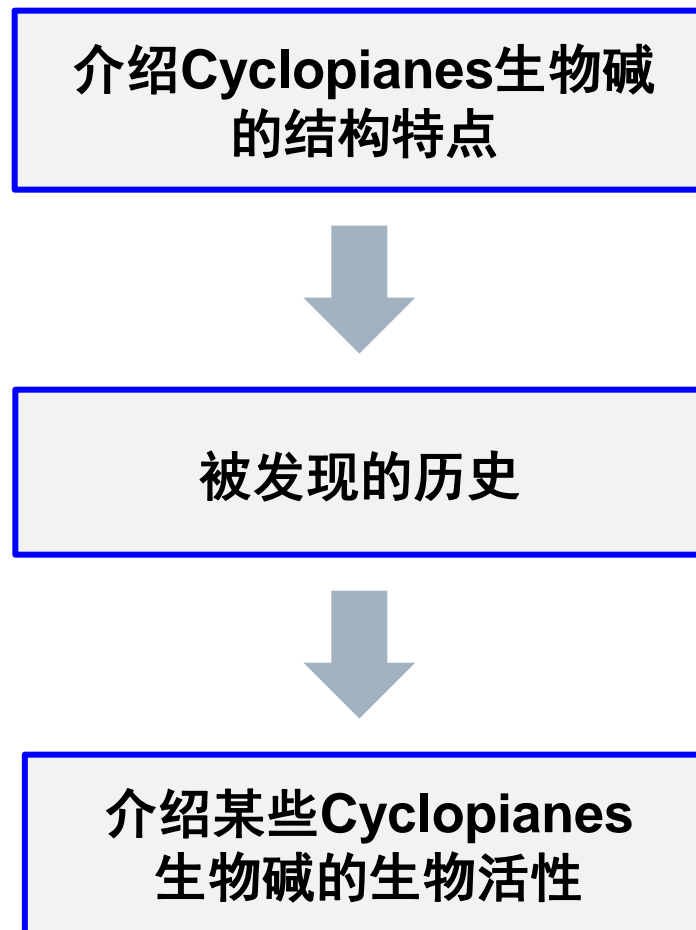


- 14 steps, 4.7% overall yield;
- HAT-mediated alkene–nitrile cyclization;
- Sequential Nicholas/Pauson–Khand reactions;
- Danheiser annulation;
- A combined ozonolysis/Aldol reaction.

Xu, B.; Xun, W.; Su, S.; Zhai, H. *Angew. Chem. Int. Ed.* **2020**, *59*, 16475-16479

The First Paragraph

写作思路



The First Paragraph

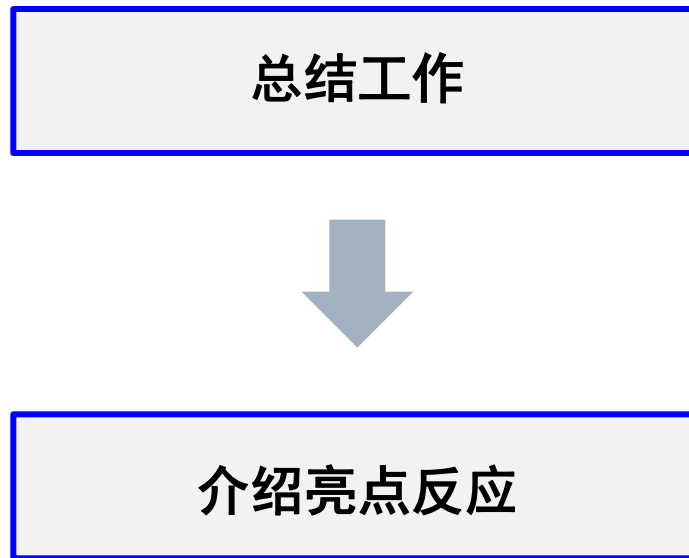
Cyclophanes are novel diterpenes featuring a highly strained 6/5/5/5 tetracyclic core embedded with 6–8 consecutive stereocenters, four of which are quaternary carbon centers. The structural variations of cyclophanes are mainly manifested as differences in the oxidation state of certain carbon atoms within the skeleton. Since the first isolation of conidiogenone (**1**) and conidiogenol (**2**) by Sterner and coworkers in 2002, more than 20 compounds of this family have been isolated from the genus *Penicillium*.

The First Paragraph

Interestingly, cyclopiane diterpenes display a range of biological activities. Conidiogenone (1) and conidiogenol (2) as inducers of conidogenesis in *P. cyclopium* may become new tool compounds for the study of the morphogenetic event. Conidiogenone B (3) shows significant antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA; MIC = 8 $\mu\text{g mL}^{-1}$). Conidiogenone C (4) exhibits potent cytotoxicity against HL60 cells (IC₅₀ = 38 nM).

The Last Paragraph

写作思路



The Last Paragraph

In summary, a concise total synthesis of (-)-conidiogenone B has been achieved in 14 steps and with 4.7% overall yield from readily available trimethylcyclopentenone **18**. Moreover, (-)-conidiogenone and (-)-conidiogenol were also realized through a modified Tu protocol. The synthesis features a HAT-mediated alkene–nitrile cyclization to access the *cis*-biquinane, a sequential Nicholas/Pauson–Khand reactions for the construction of the linear triquinane, a Danheiser annulation to forge the congested angular triquinane portion, and a combined ozonolysis/aldol reaction to assemble the α,β -unsaturated cyclohexenone skeleton. The current work may facilitate larger-scale preparation and further biological studies of various cyclopiane natural products.

Representative Examples

We next **turned our attention to** the key Danheiser annulation to forge a five-membered ring **with concomitant establishment of** two all carbon quaternary carbon centers. (把注意力转移到; 同时建立)

The synthesis **features** a HAT-mediated alkene–nitrile cyclization **to access** the *cis*-biquinane, a sequential Nicholas/Pauson–Khand reactions **for the construction of** the linear triquinane, a Danheiser annulation **to forge** the congested angular triquinane portion, and a combined ozonolysis/aldol reaction **to assemble** the α,β -unsaturated cyclohexenone skeleton. (具有……的特点; 构建)

Acknowledgement

***Thanks
for your attention***