Literature Report I

Total Synthesis of (+/–)-Rubriflordilactone A

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Checker: Qing-Xian Xie

Zheng, X.-D.; Guo, X.-L.; Wang, H.-Y.; Chen, X.-M. *J. Am. Chem. Soc.* **2024**, *146*, 7198-7203

2024-11-25

CV of Prof. Xiao-Ming Chen

Background:

- **2003-2007** B. S., Northwest University
- **2009-2015** Ph. D., Lanzhou University
- **2015-2017** Postdoctor, Peking University Shenzhen Graduate School
- **2017-2019** Research Assistant, Peking University Shenzhen Graduate School
- **2019-Now** Professor, Lanzhou University

Research Field:

- **Total Synthesis of Natural Products**
- **Organic Synthesis Methodology**

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2 Total Synthesis of (+/–)-Rubriflordilactone A

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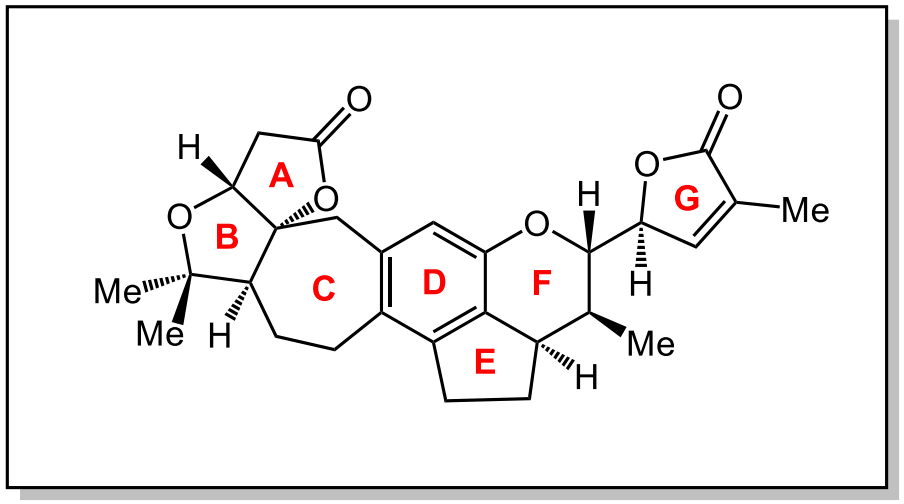
Introduction



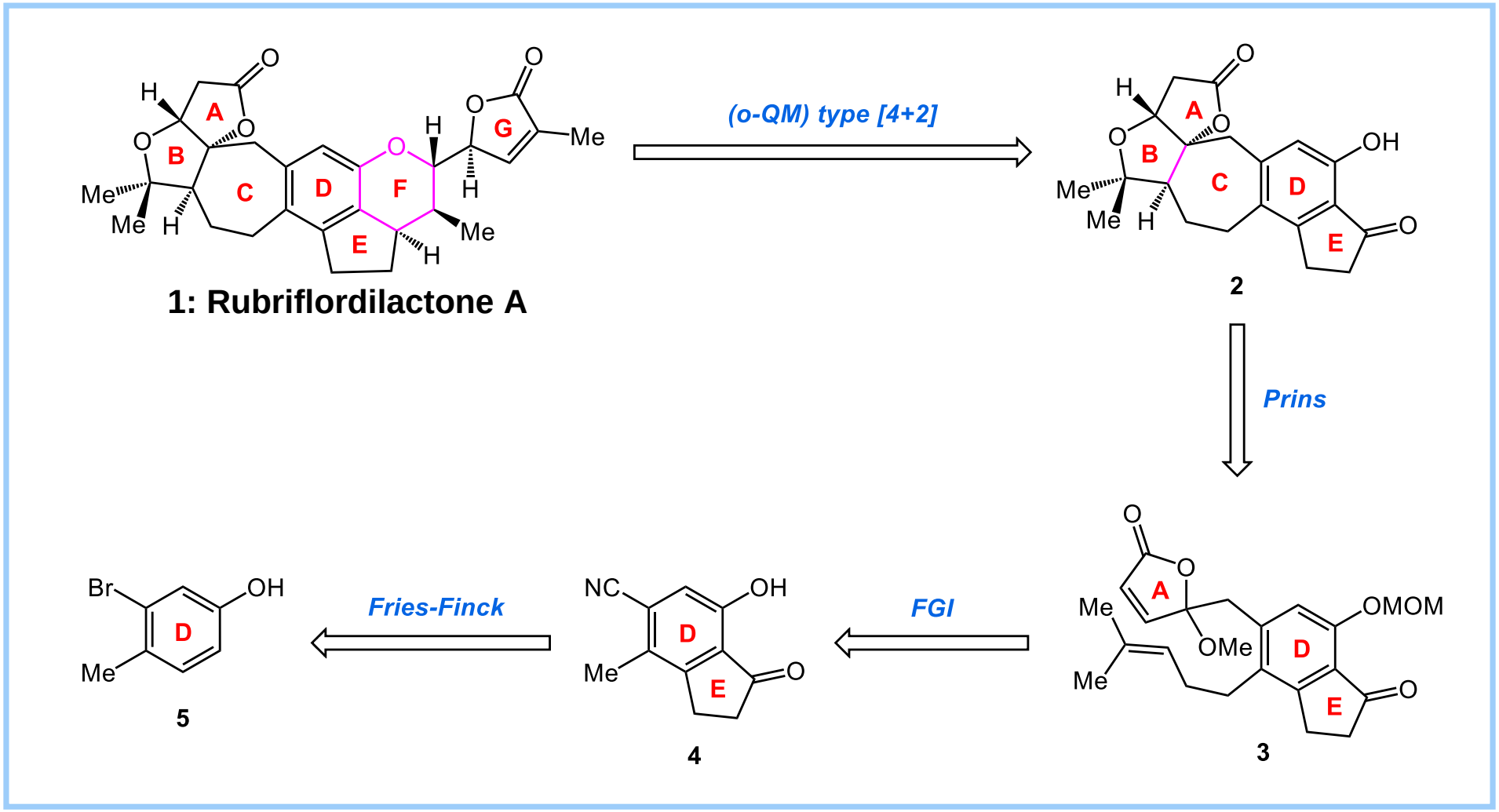
Rubriflordilactone *A*

Schisandra Chinensis

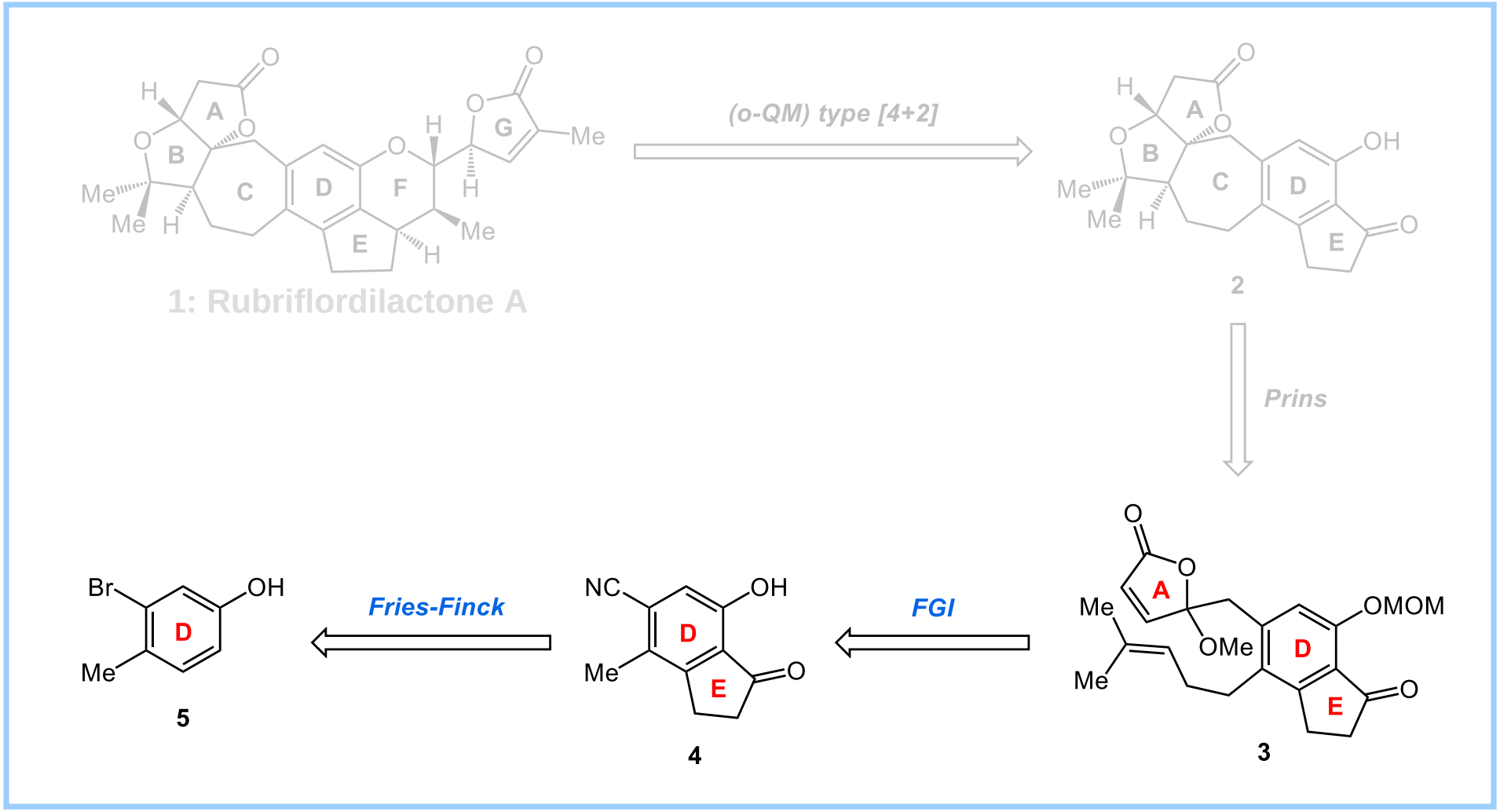
- It was isolated from the leaves of Schisandra Chinensis in 2006;
- It is stereochemically dense and highly oxygenated polycyclic triterpenoids;
- Bioassays showed that it possessed anti-inflammatory and anti-HIV-1 activities.

Xiao, W.-L.; Yang, L.-M.; Gong, N.-B.; Wu, L.; Sun, H.-D. *Org. Lett.* **2006**, *8*, 991−994

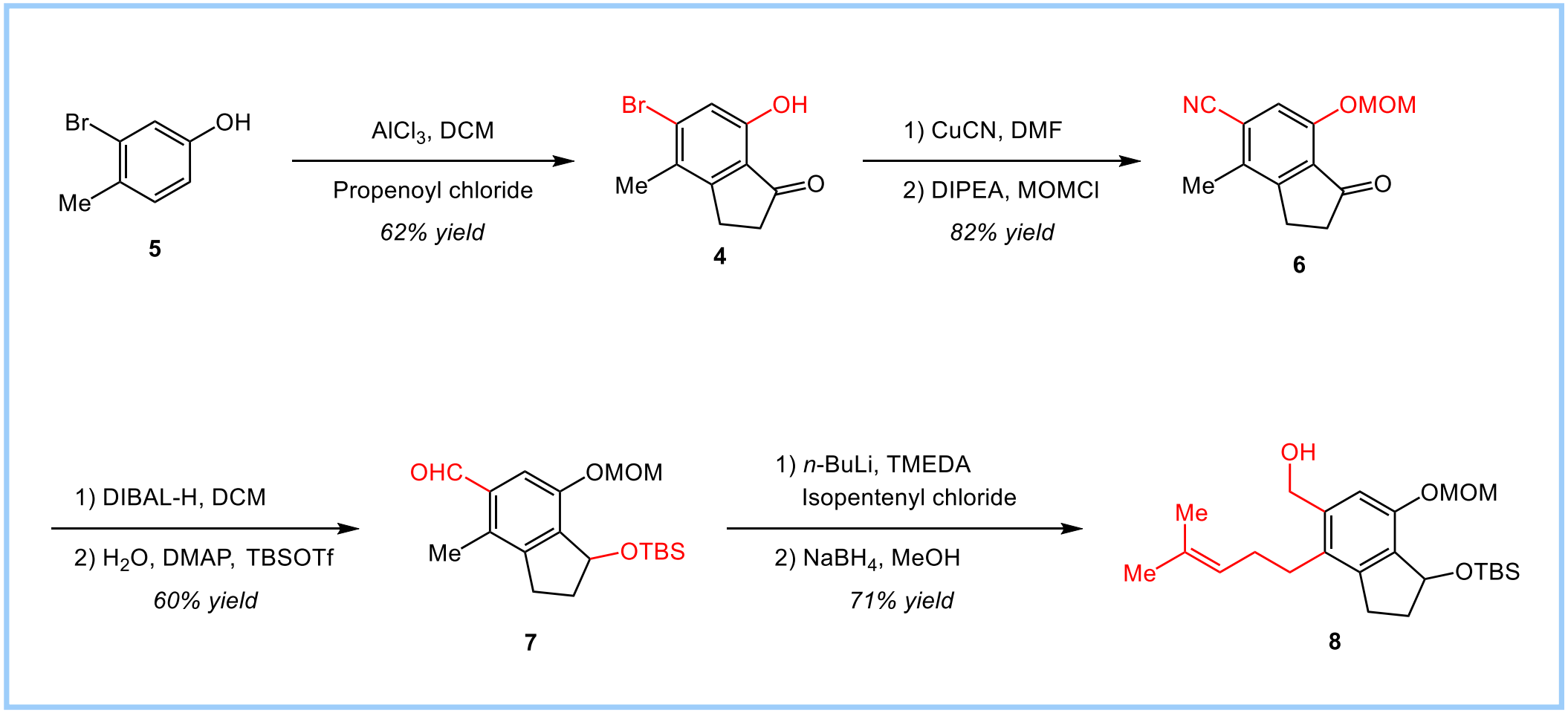
Retrosynthetic Analysis



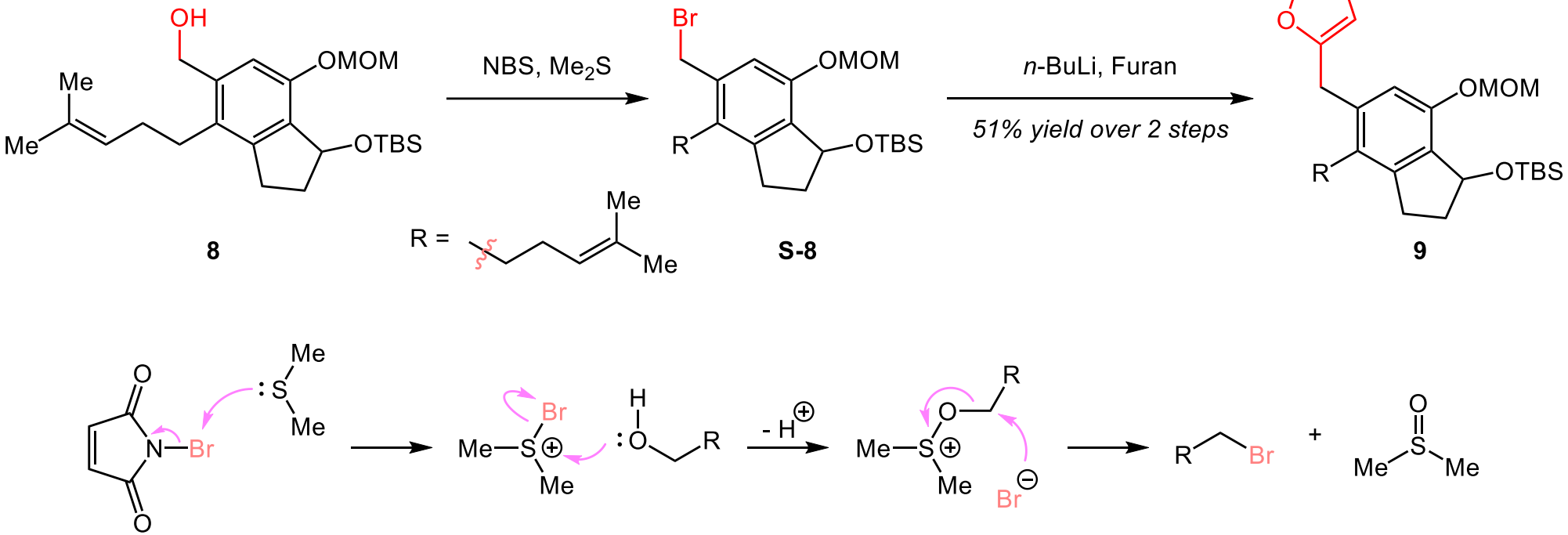
Retrosynthetic Analysis



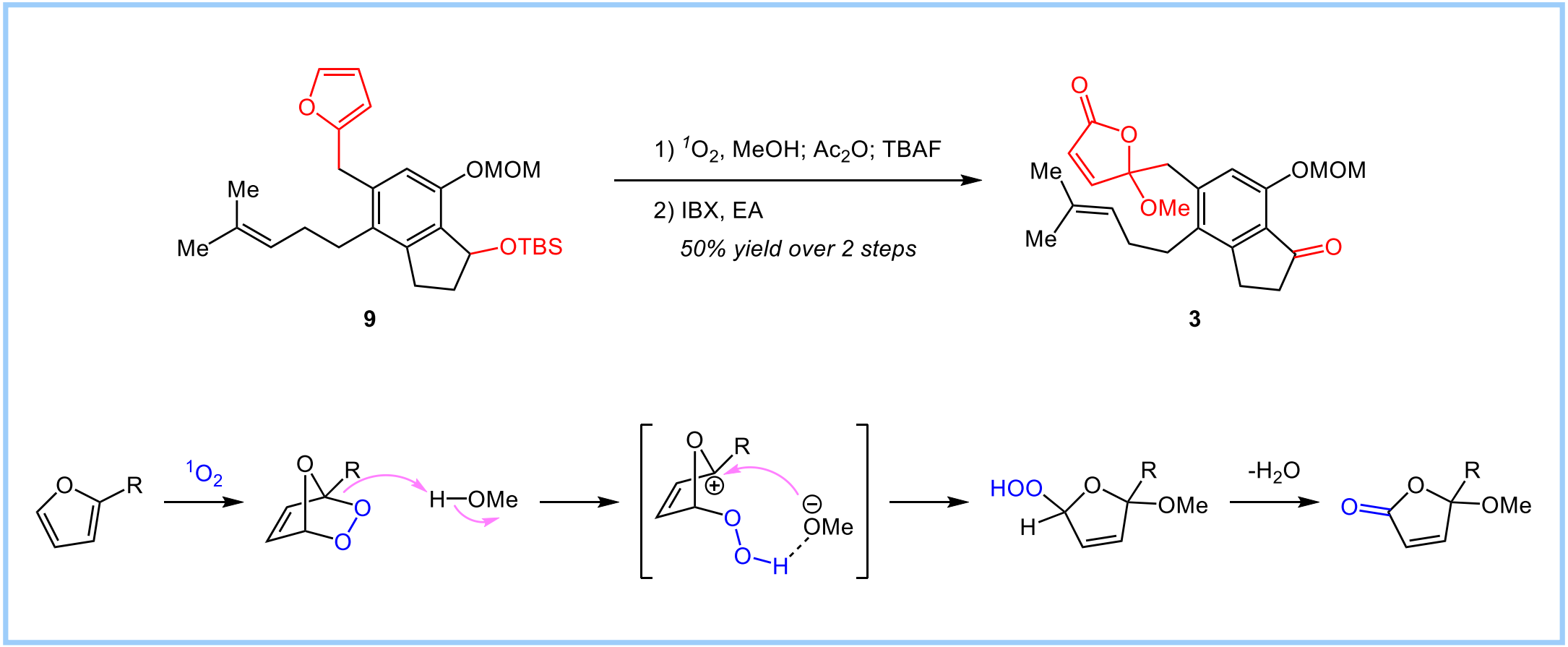
Synthesis of Compound 8



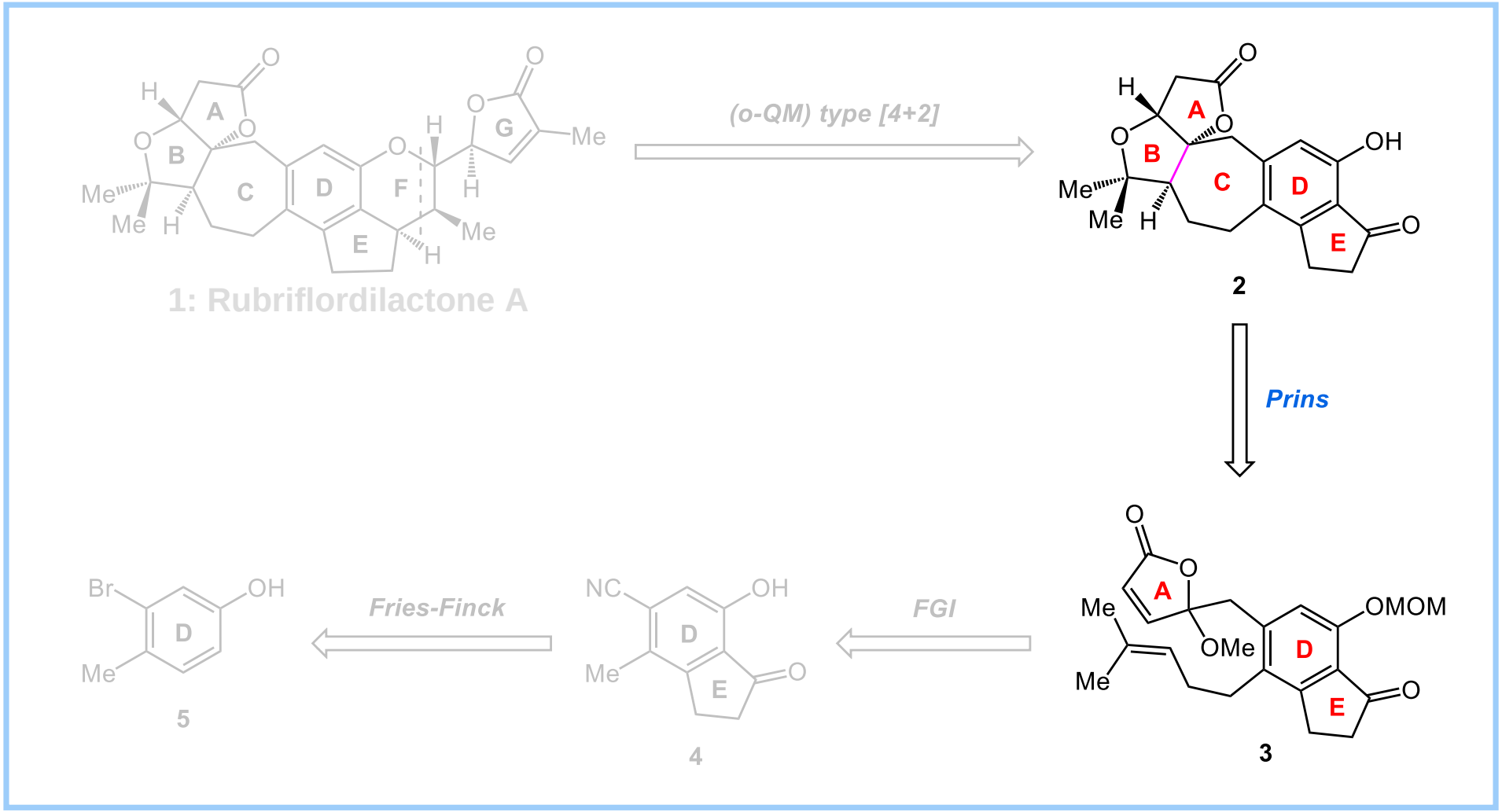
Synthesis of Compound 9



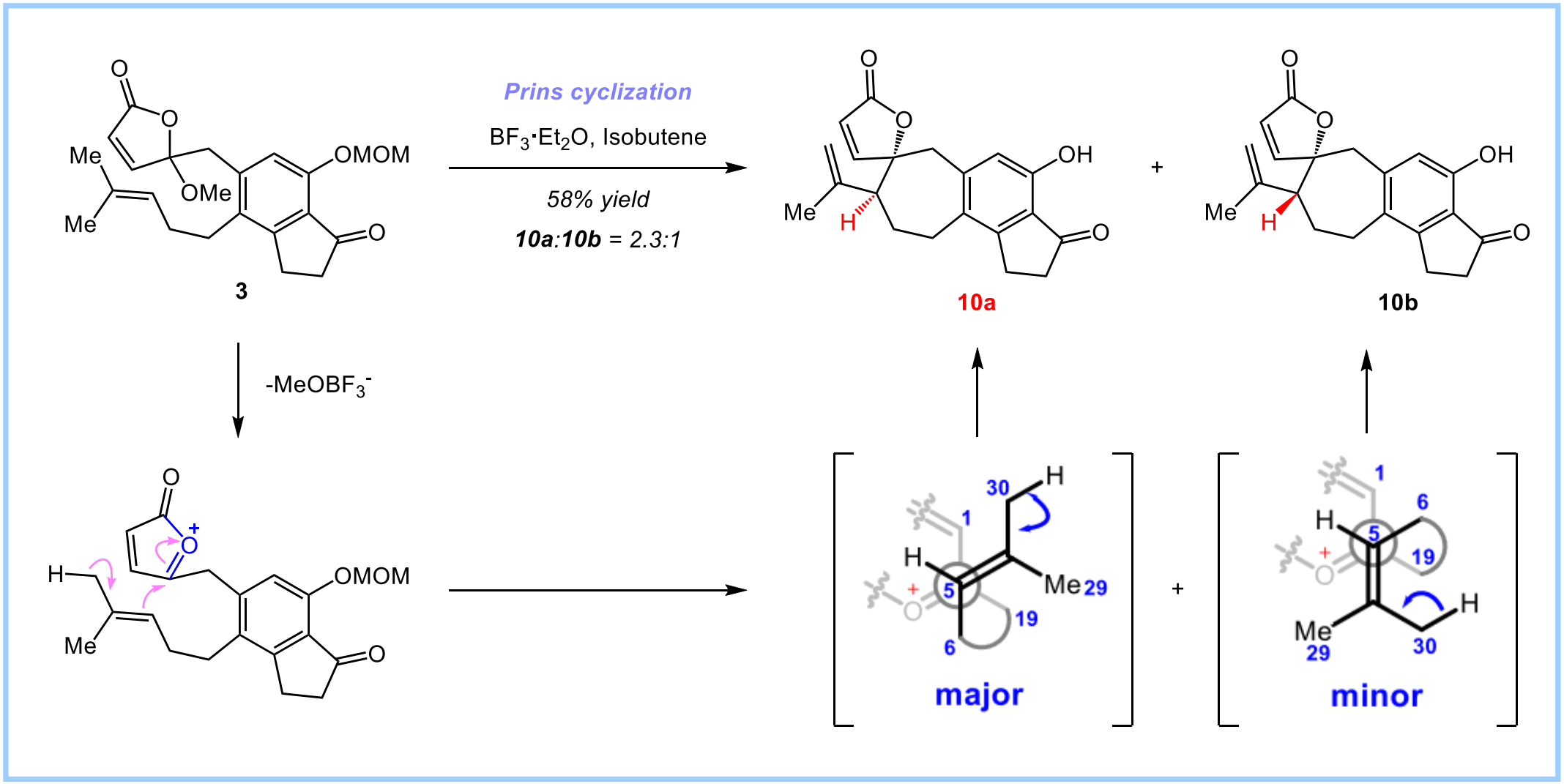
Synthesis of Critical Intermediate 3



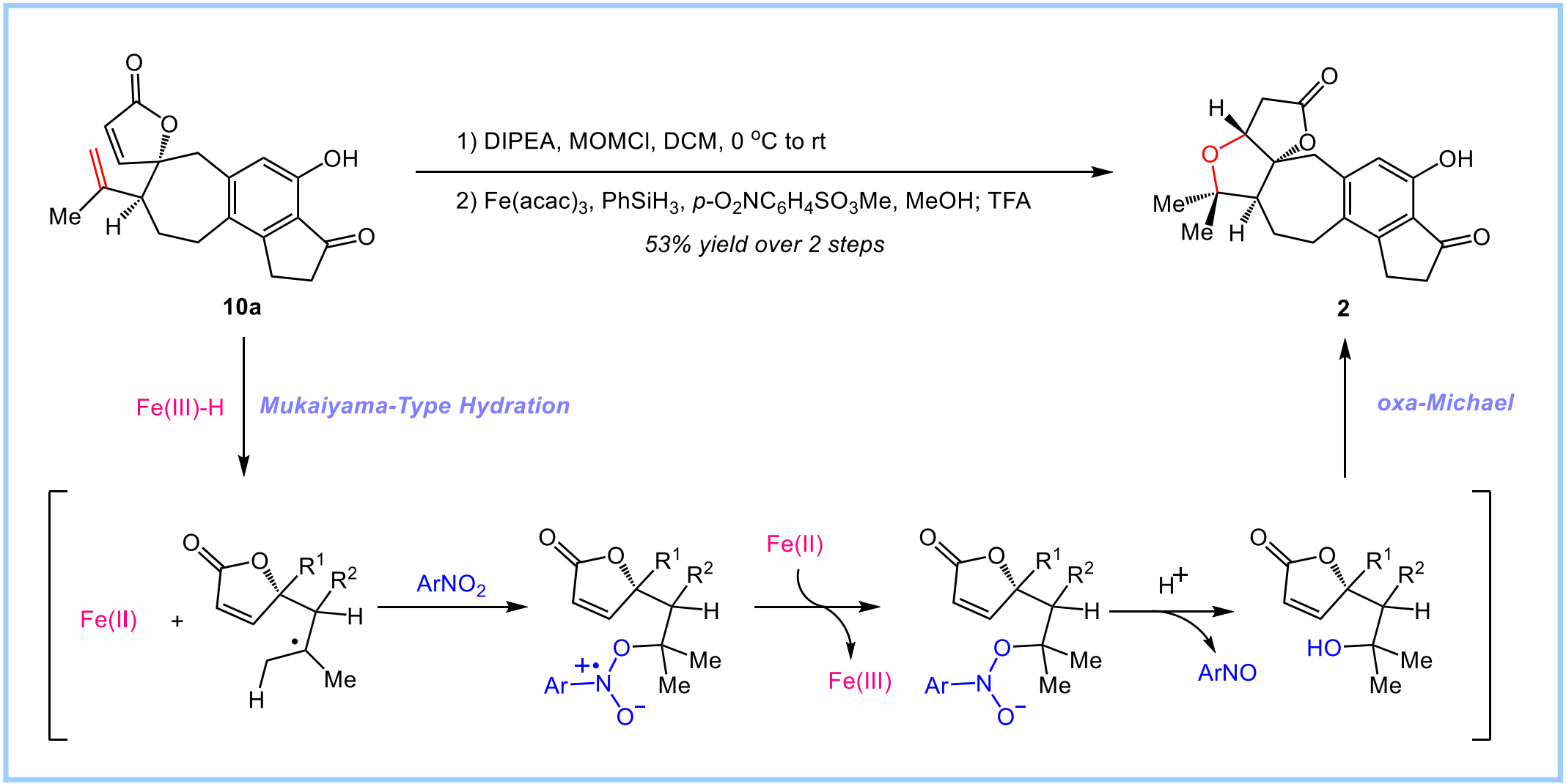
Retrosynthetic Analysis



Synthesis of Compound 10



Synthesis of Critical Intermediate 2



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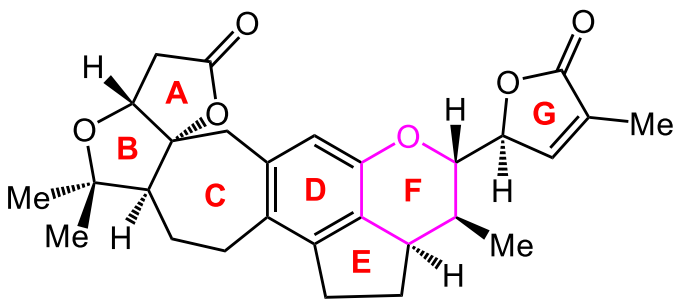
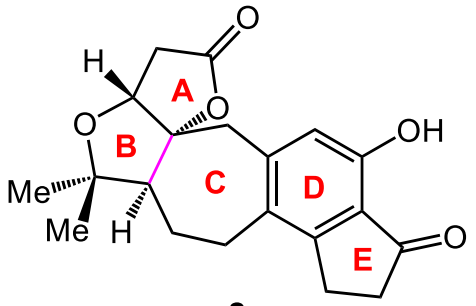


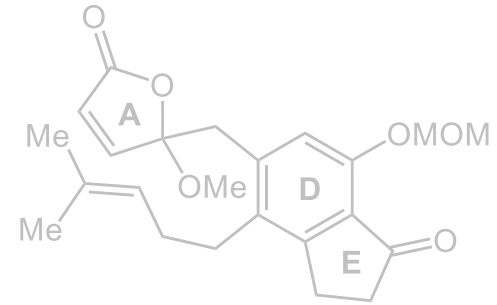
1: Rubriflordilactone A

(o-QM) type [4+2]



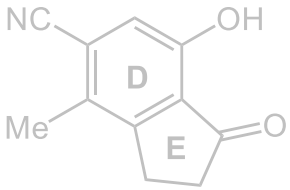
2

Prins



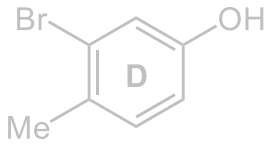
3

FGI



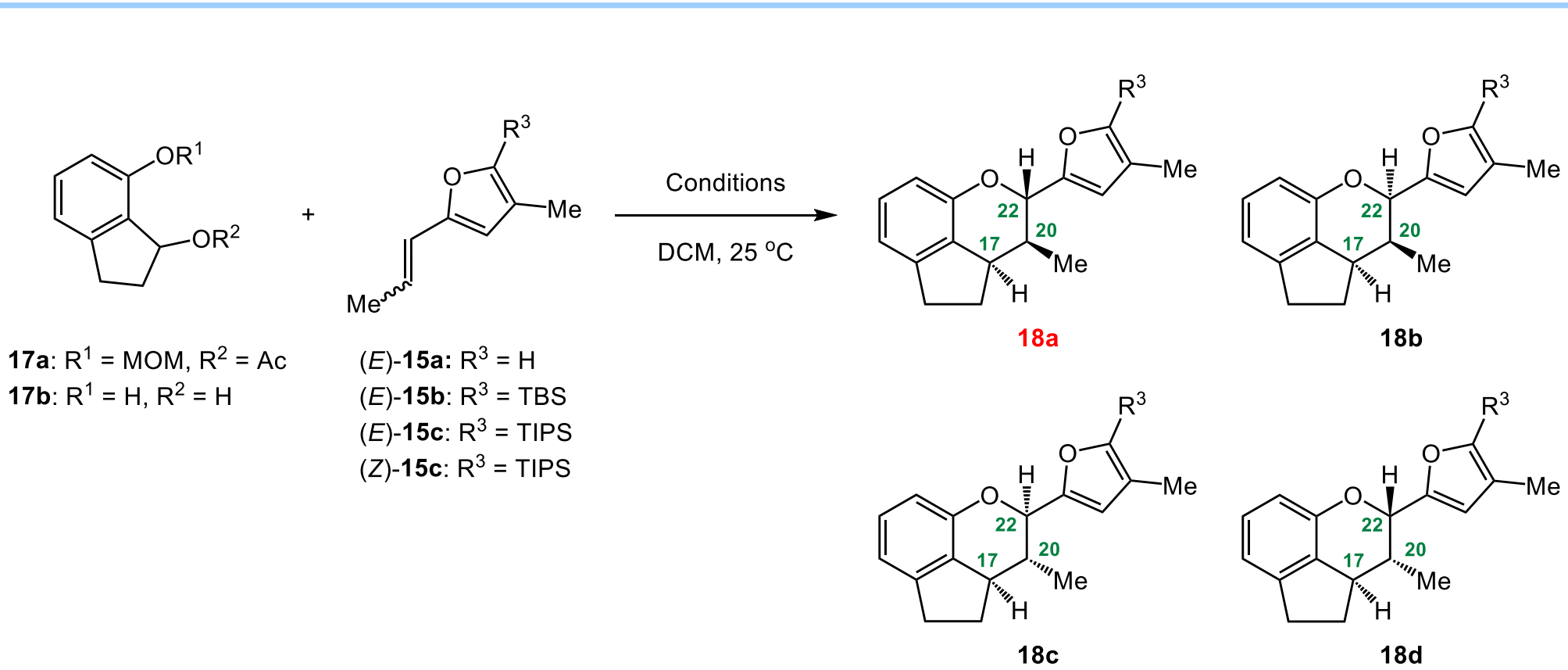
4

Fries-Finck



5

Optimization of *o*-QM Type [4+2]-Cycloaddition



17a: R^1 = MOM, R^2 = Ac
17b: R^1 = H, R^2 = H

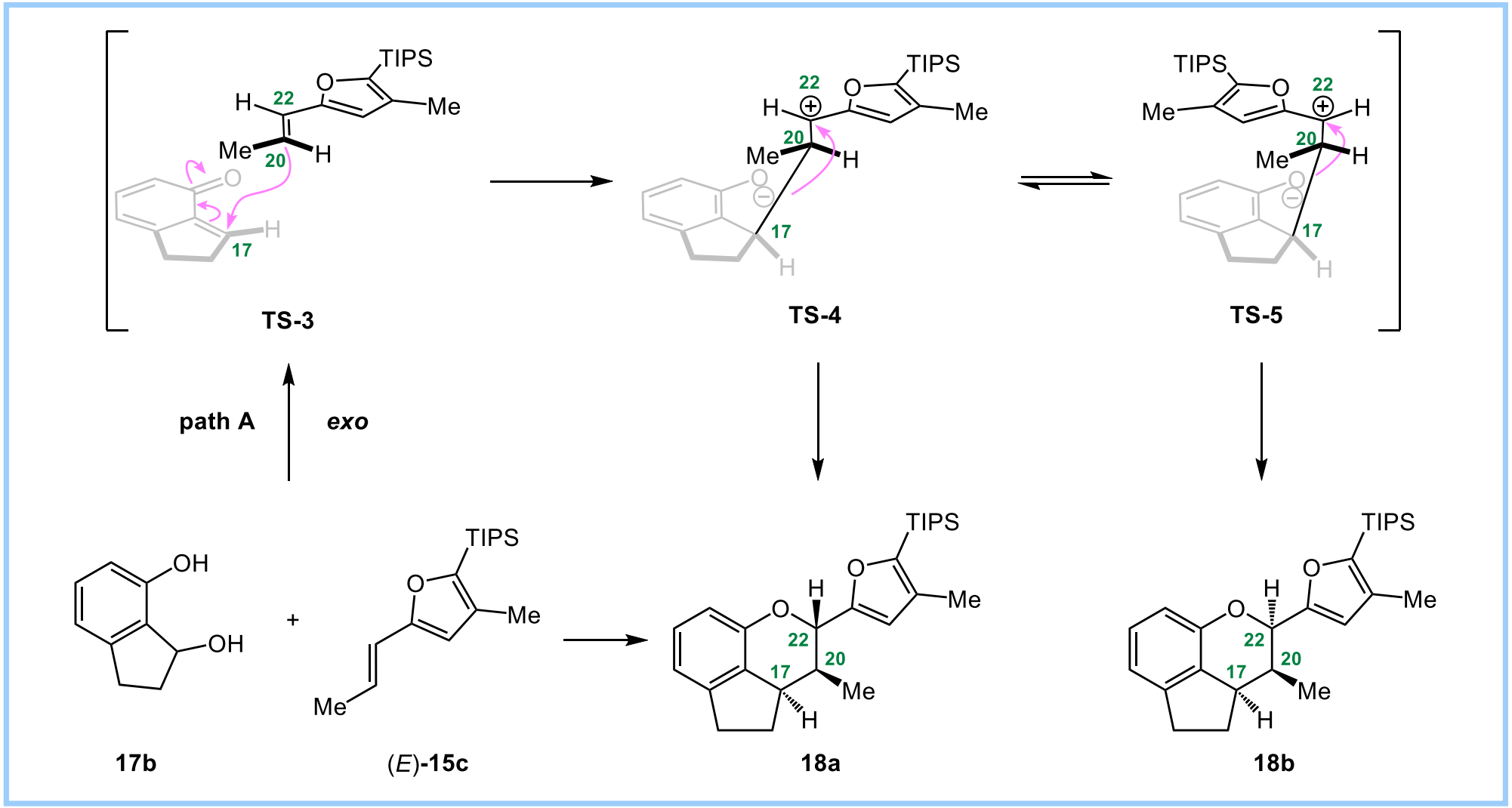
(*E*)-**15a:** R^3 = H
(*E*)-**15b**: R^3 = TBS
(*E*)-**15c**: R^3 = TIPS
(*Z*)-**15c**: R^3 = TIPS

Optimization of *o*-QM Type [4+2]-Cycloaddition

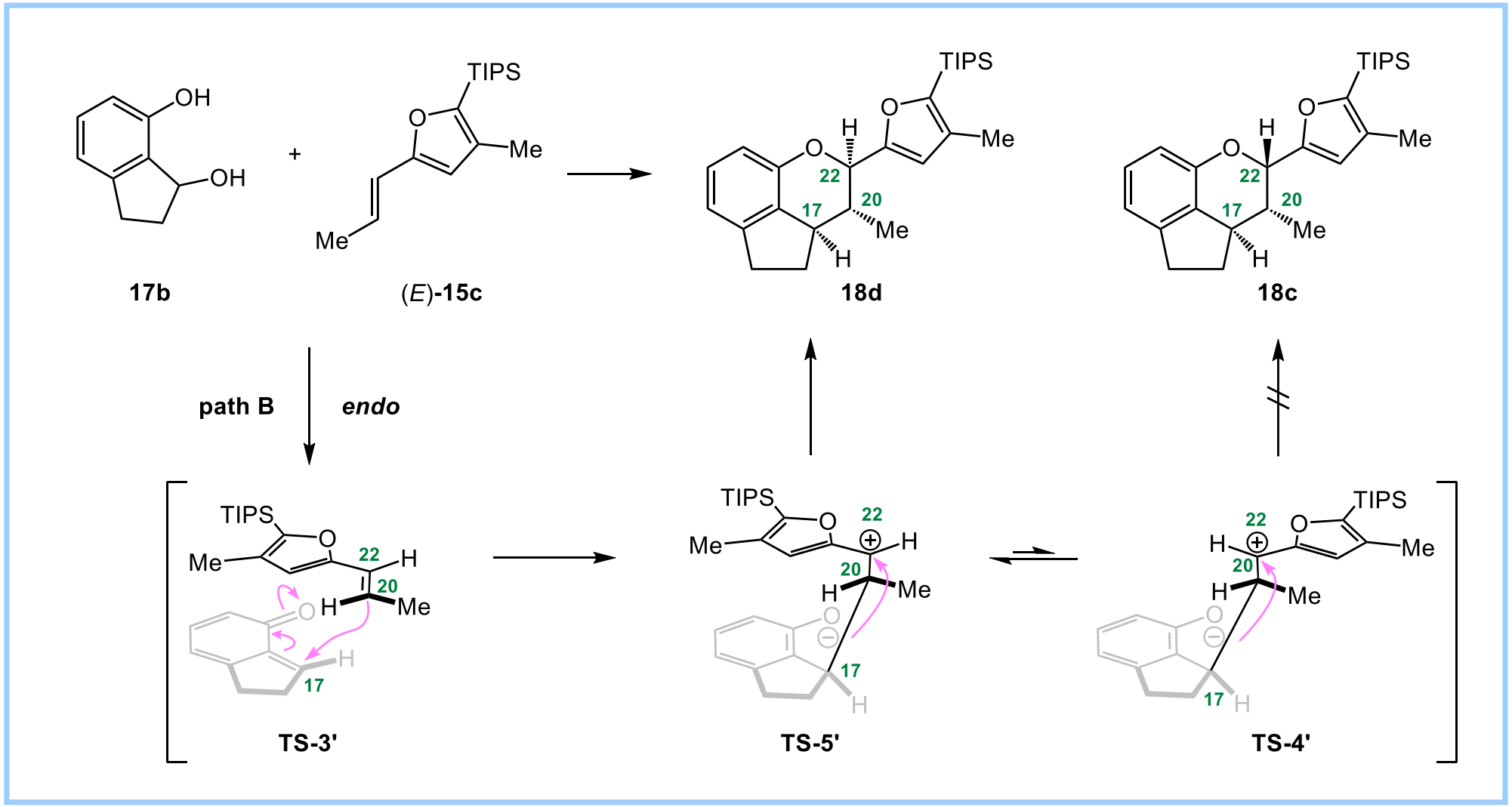
Entry[a]	Substrates	Catalysts (10 mol%)	4 Å MS	Yield (%)[b]	18a:18b
1	**17a**, (*E*)-**15a**	$PtCl_4$	——	NA	——
2	**17a**, (*E*)-**15b**	$PtCl_4$	——	NA	——
3	**17a**, (*E*)-**15c**	$PtCl_4$	——	3	1.5:1.0
4	**17b**, (*E*)-**15c**	$PtCl_4$	——	6	1.5:1.0
5	**17b**, (*E*)-**15c**	$PtCl_4$	50 mg	14	1.5:1.0
6	**17b**, (*E*)-**15c**	CSA	50 mg	23	3.7:1.0
7	**17b**, (*E*)-**15c**	$Zn(OTf)_2$	50 mg	28	3.2:1.0
8	**17b**, (*E*)-**15c**	$In(OTf)_3$	50 mg	31	2.2:1.0
9	**17b**, (*E*)-**15c**	$Sc(OTf)_3$	50 mg	33	1.1:1.0
10	**17b**, (*E*)-**15c**	$Bi(OTf)_3$	50 mg	57	3.0:1.0
11	**17b**, (*Z*)-**15c**	$Sc(OTf)_3$	50 mg	63	2.1:1.0
12	**17b**, **15c**[c]	$Sc(OTf)_3$	50 mg	30	1.5:1.0

[a]Conditions: **17** (0.07 mmol), **15** (0.2 mmol), **Cat.** (10 mol%), DCM (5 mL), 25 °C. [b]Isolated yield. [c]**15c**: (*E*)-***15c***:(*Z*)-***15c*** = 1:1

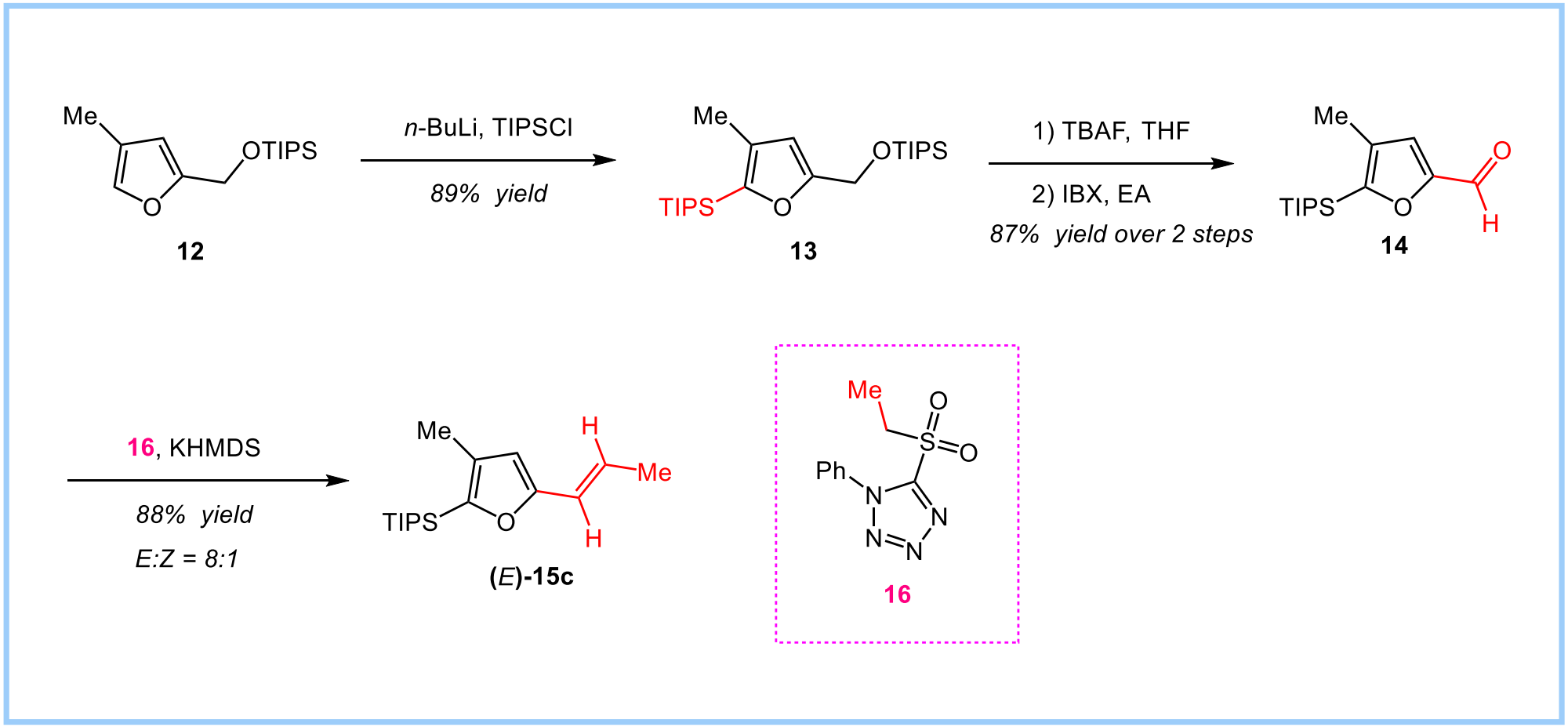
Mechanism of *o*-QM Type [4+2]-Cycloaddition



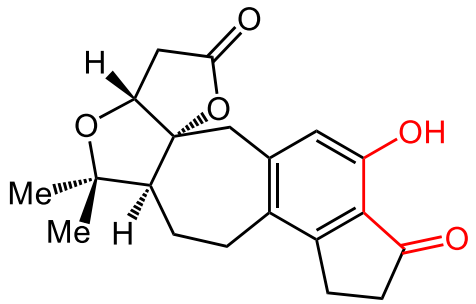
Mechanism of *o*-QM Type [4+2]-Cycloaddition



Synthesis of Critical Intermediate 15



Synthesis of Compound 11



2

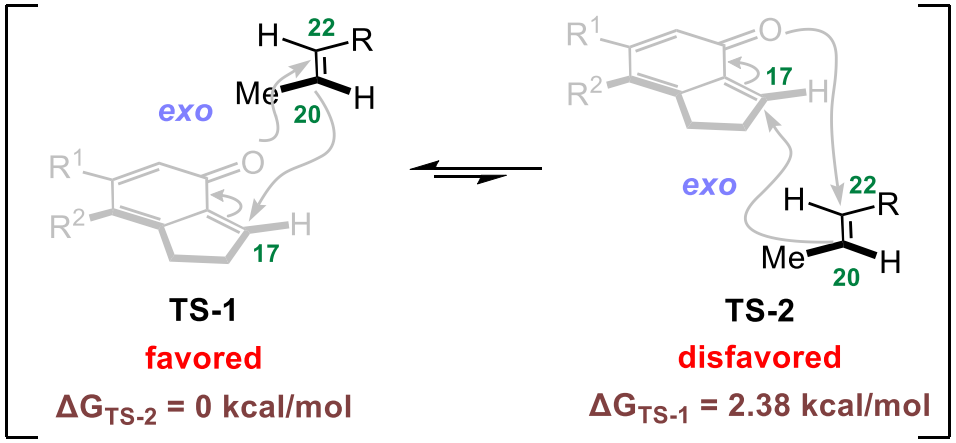
1) $NaBH_4$, MeOH

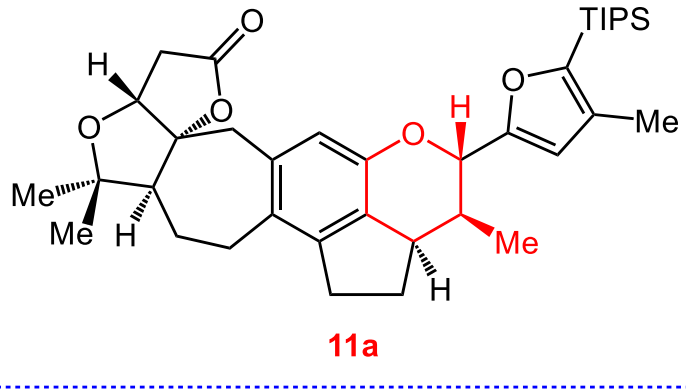
2) $Sc(OTf)_3$, (*E*)-**15c**, 4 Å MS

40% yield over 2 steps

***exo*: 11a:11b** = 4.5:1

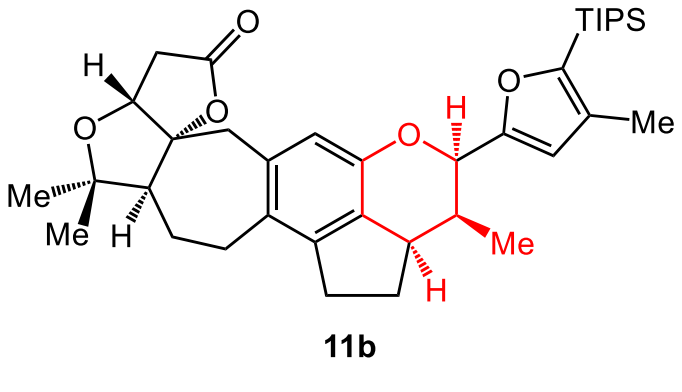
***endo*: 11c and 11d were not observed**





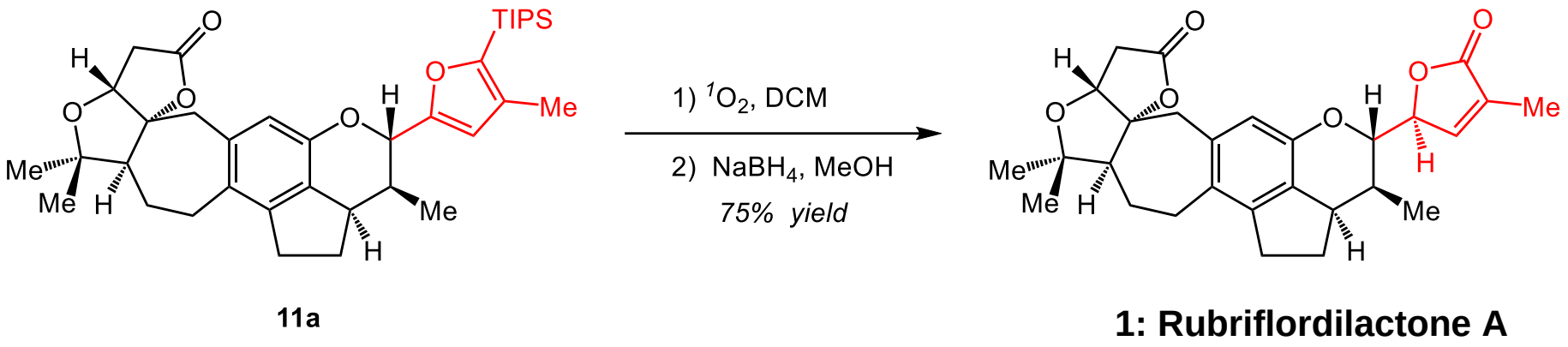
11a

+



11b

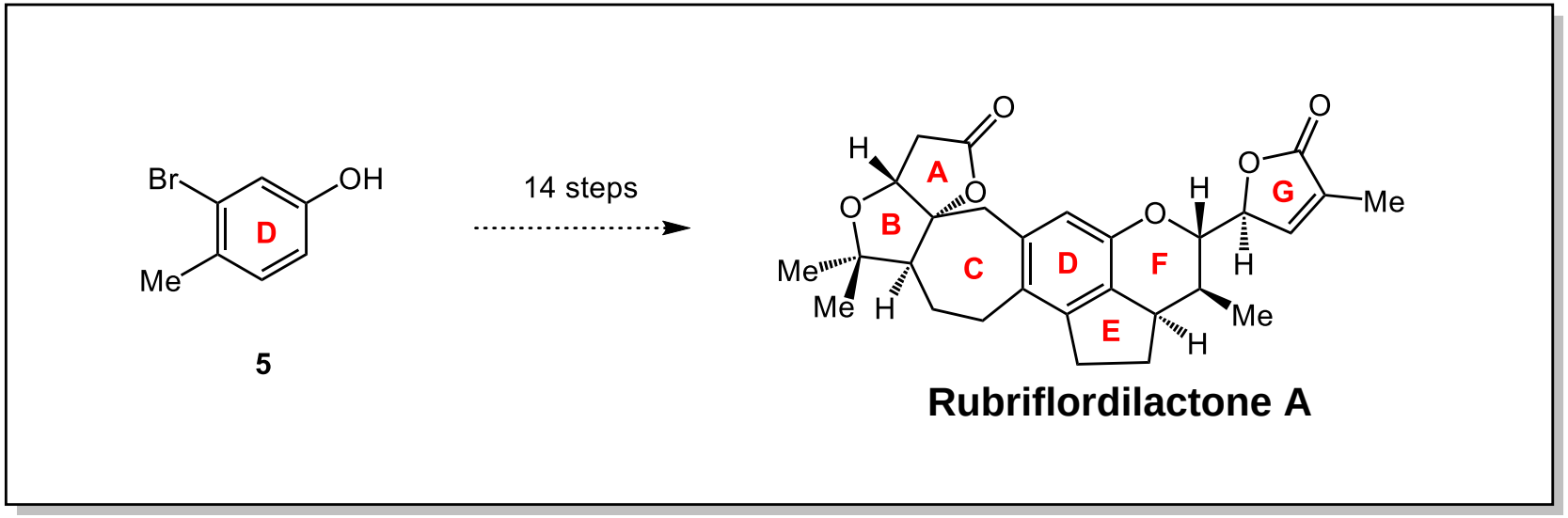
Synthesis of Compound 1



11a

1: Rubriflordilactone A

Summary



- Prins Cyclization to Access the Seven-membered C-ring;
- Mukaiyama Hydration/Oxa-Michael Cascade to Forge the B-ring;
- Intermolecular *O*-QM Type [4+2]-Cycloaddition to Rapidly Assemble Rubriflordilactone A.

Writing Strategy

First paragraph

Structure

↓

Origin and History

↓

This Work

- A range of bioactive natural products, especially structurally diverse, stereo-chemically dense, and highly oxygenated polycyclic triterpenoids have been isolated from these plants…
- Among them, isolated by Sun and co-workers from the Chinese herbal medicine Schisandra rubriflora in 2006, Rubriflordilactone A and Rubricflor-diactone B incurporated a rare polysubstituted arene motif, and both exhi-bited anti-HIV activities, especially B (EC_{50} = 9.75 μg/mL) …
- In this communication, we disclose an alternative approach to (+/–)-Rubri-flordilactone A.

Writing Strategy

Last paragraph

Summary

Committed Steps

Prospect

- In summary, a linear convergent total synthesis of the nortriterpenoid Rubriflordilactone A was achieved from commercially available phenol .
- During the course of this study, a Prins cyclization to access the seven-membered C-ring and a Mukaiyama hydration/oxa-Michael cascade to forge the B-ring have been investigated in detail. More importantly, an unprecedented late-stage long-range stereocontrolled intermolecular *o*-QM type [4+2]-cycloaddition to rapidly assemble the core structure of Rubriflordilactone A has been established, which has substantially increased the synthetic efficiency.
- In addition, the current strategy would enable flexible access to the AB-ring backbone embedded in numerous Schisandra triterpenoid natural products.

Representative Examples

- Since formaldehyde could be consumed by addition of exogenous olefins, addition of isobutene should be helpful in the transformation. (*adj*. 外源的，外生的)

- During the reaction optimization investigation, utilization of an appropriate furyl propene derivative was found to be crucial. (*v*. 调查，科学研究，尤指为了发现问题的真相)

- More importantly, an unprecedented late-stage long-range stereocontrolled intermolecular *o*-QM type [4+2]-cycloaddition to rapidly assemble the core structure of Rubriflordilactone A has been established, which has substantially increased the synthetic efficiency. (*adj*. 立体控制的)

Acknowledgment

Thanks for your attention!

Julia–Kocienski Olefination