Literature Report 1

Divergent Total Syntheses of Elisapterane Assisted by *In Silico* Structure Reassignment

Reporter: Chang Chen
Checker: Xin-Yu Zhan
Date: 2025.11.10

Liu, C.; Gong, H.; Sheng, Y.; Wang, W.; Xia, Q.*; Ding, H.* *J. Am. Chem. Soc.* **2025**, *147*, 33136

CV of Prof. Han-Feng Ding (丁寒锋)

Background:

- **1999-2003** B.S., in Chemistry, Zhejiang University
- **2003-2008** Ph.D., in Organic Chemistry, Zhejiang University
- **2008-2011** Research Fellow, ICES, A*STAR
- **2011-2016** Tenure-Track Associate Prof., Zhejiang University
- **2016-present** Prof., Zhejiang University

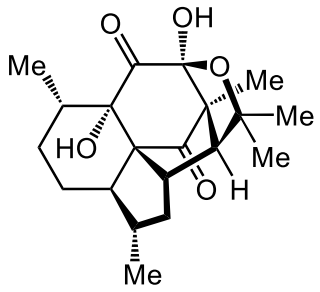
Research:

- ✓ **Natural Product Total Synthesis**
- ✓ **Design of New Synthetic Methodologies Inspired by Nature**
- ✓ **Medicinal Chemistry**

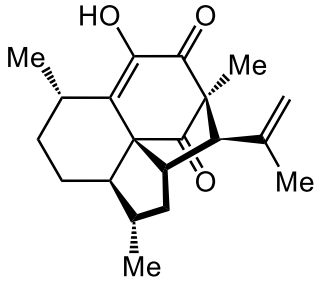
Contents

Introduction

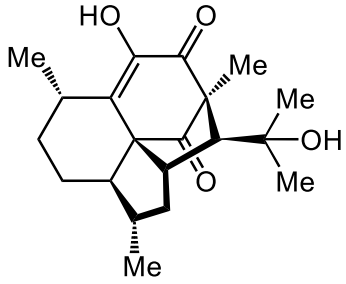
Elisapterosins A–F



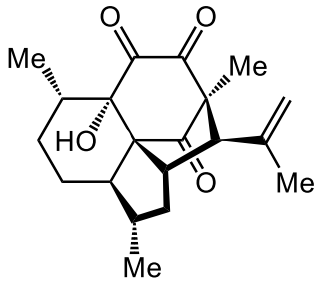
Elisapterosin A (**1**)



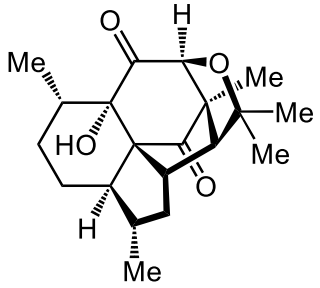
Elisapterosin B (**2**)



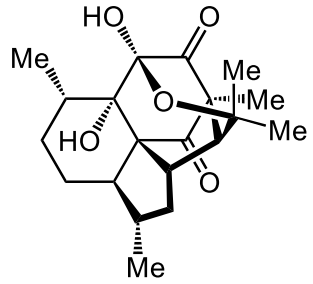
Elisapterosin C (**3**)



Elisapterosin D (**4**)

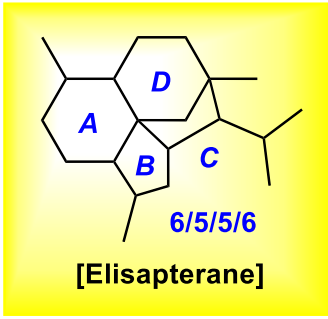


Elisapterosin E (**5**)



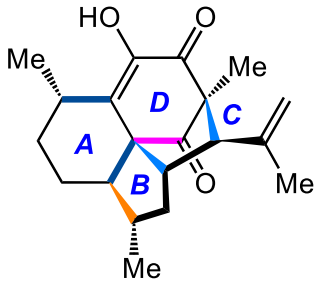
Elisapterosin F (**6**)

Pseudopterogorgia elisabethae



Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I.; Barnes, C. L. *J. Org. Chem.* **2000**, *65*, 1390.

Synthetic Strategy 1: Late-stage D-ring Formation



Elisapterosin B (**2**)

Potent inhibitory activity against *Mycobacterium tuberculosis* H37Rv

- ***D-ring first strategy***
  well studied
- ***late-stage D-ring formation***
  underexplored

Previous Approaches

Rychnovsky (2003)
D→AD→ABCD
[4+2]-cycloaddition
[5+2]-cycloaddition

Rawal (2003)
D→ABD→ABCD
[4+2]-cycloaddition
oxidative cyclization

Harrowven (2005)
A→AD→ABCD
Moore rearrangement
[5+2]-cycloaddition

Jacobsen (2005)
D→AD→ABCD
[4+2]-cycloaddition
[5+2]-cycloaddition

Davies (2006)
D→AD→ABCD
[4+2]-cycloaddition
[5+2]-cycloaddition

Mulzer (2014)
D→AD→ABD (formal)
[4+2]-cycloaddition
Heck reaction

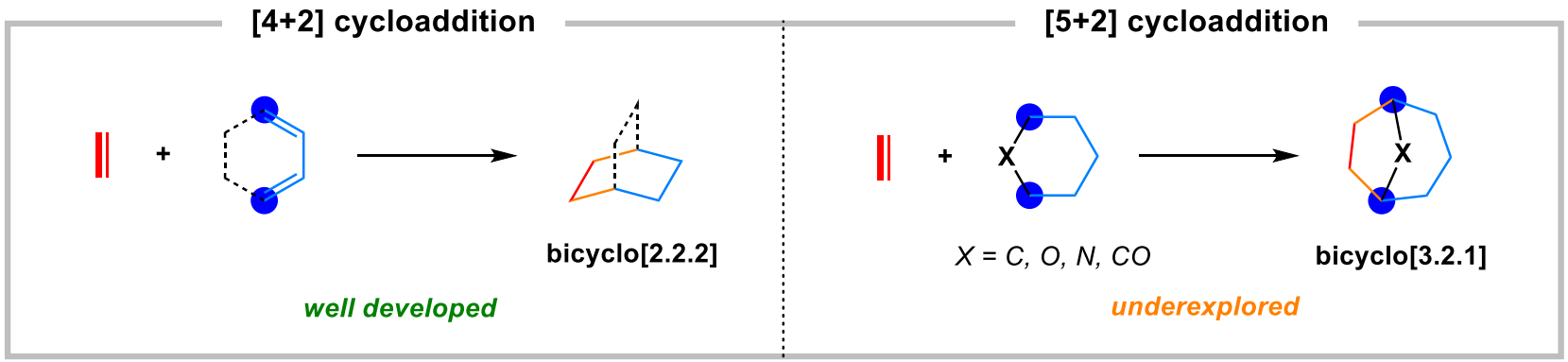
RajanBabu (2018)
D→AD (formal)
Friedel-Crafts reaction

Synthetic Strategy 1: Bioinspired Late-stage D-ring Formation

Proposed Biosynthetic Relationship

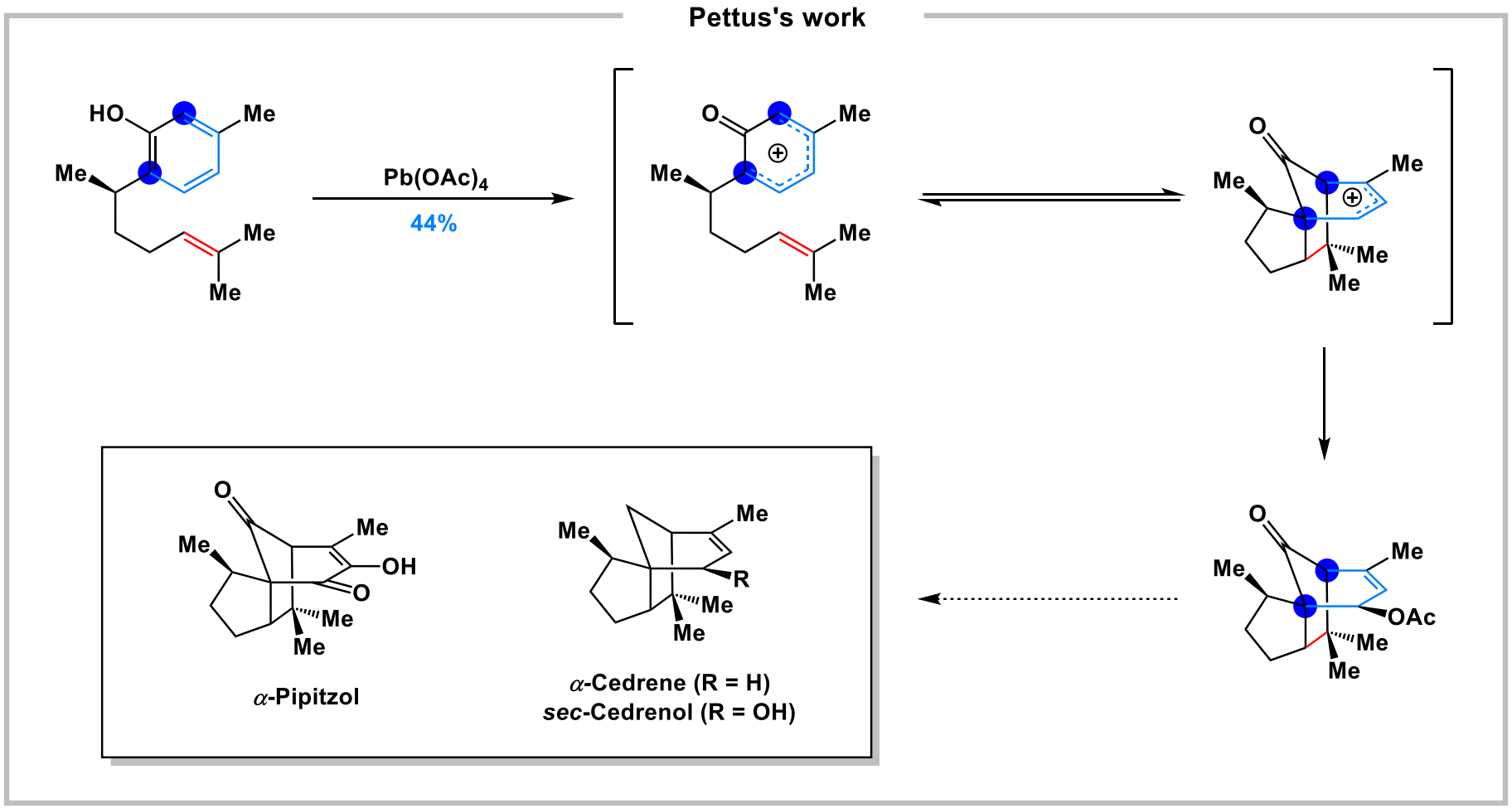
[Neoelisabane] [Elisapterane]

Synthetic Strategy 2: ODI-[5+2]cycloaddition



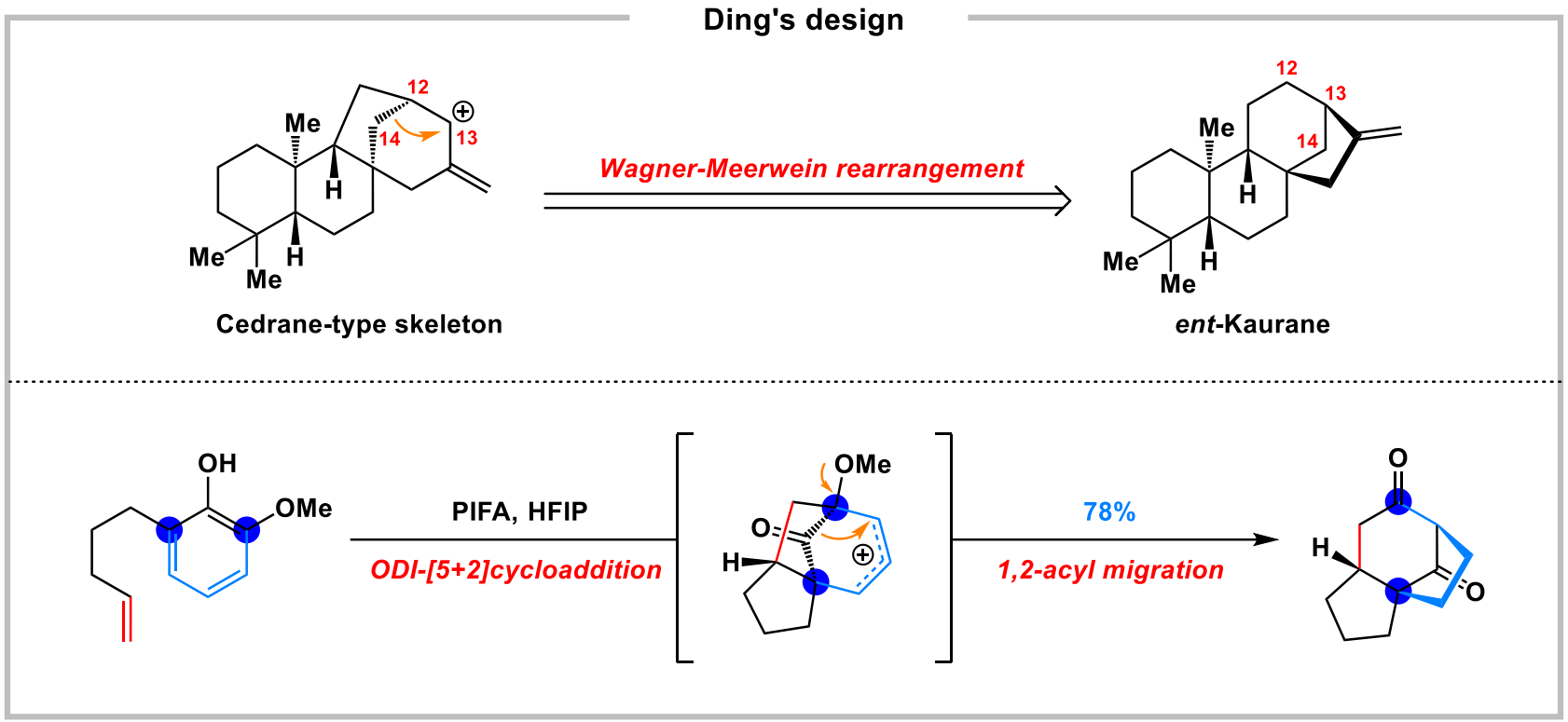
- ***Similar Mechanism: Pericyclic reactions involving π-electron reorganization***
- ***Similar Selectivity: Dienophile configuration retained; endo rule***
- ***One-step formation of polycyclic frameworks and continuous stereocenters***

Synthetic Strategy 2: ODI-[5+2]cycloaddition



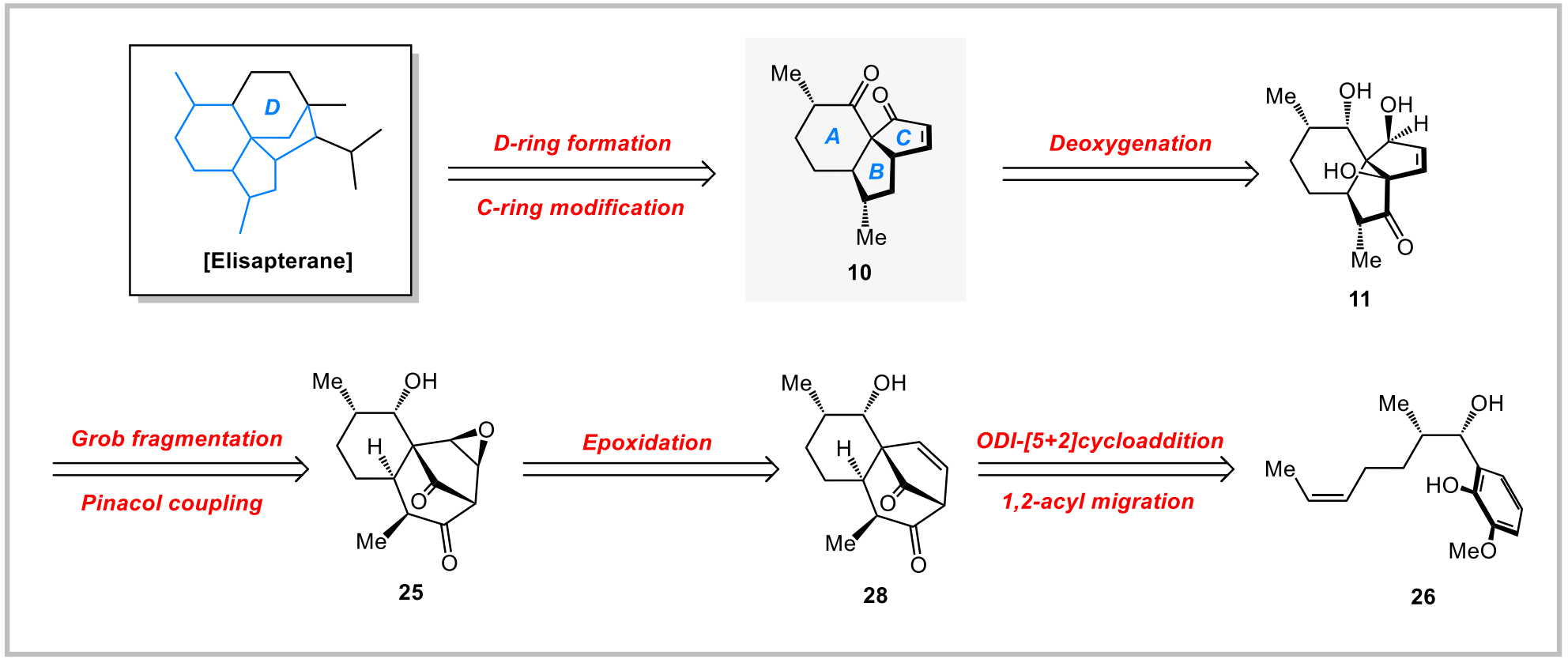
Green, J. C.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2011**, *133*, 1603

Synthetic Strategy 2: ODI-[5+2]cycloaddition

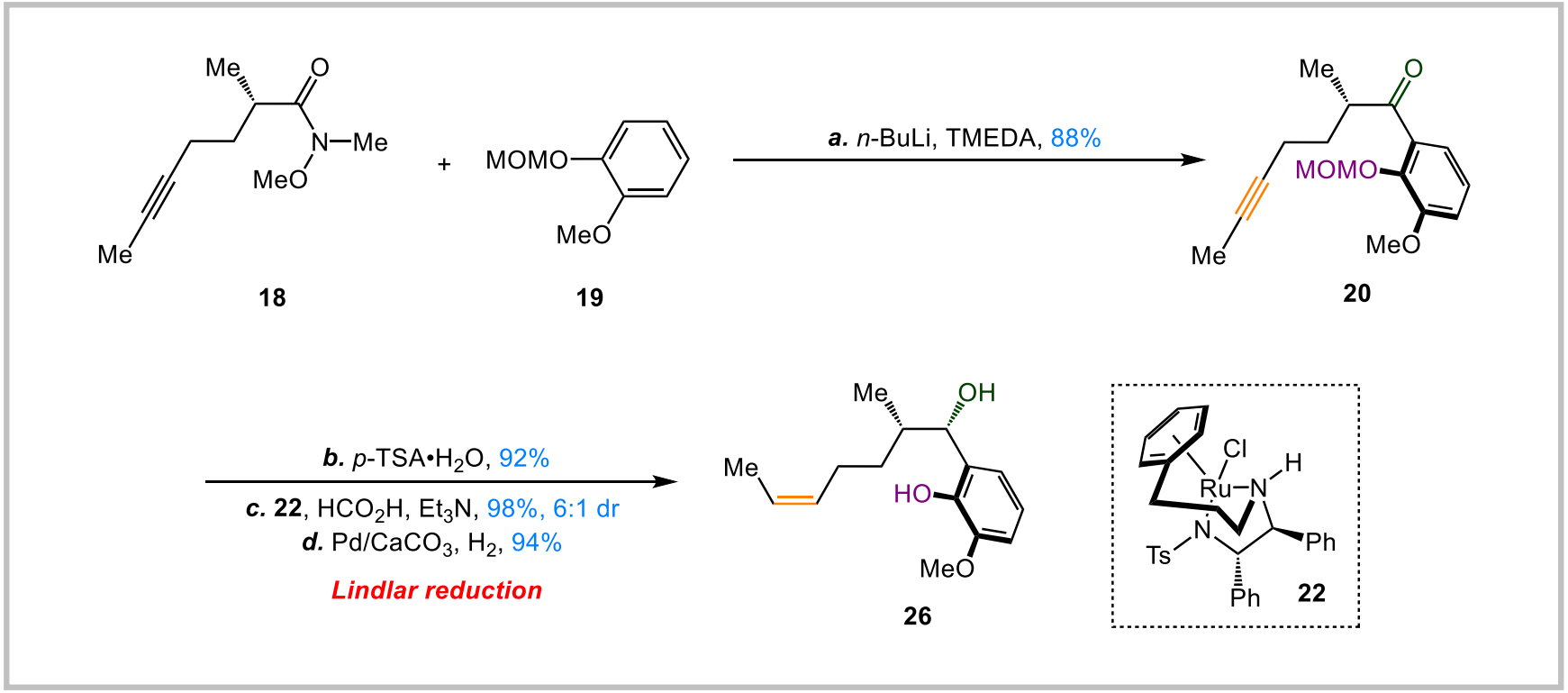


He, C.; Hu, J.; Wu, Y.; Ding, H. *J. Am. Chem. Soc.* **2017**, *139*, 6908

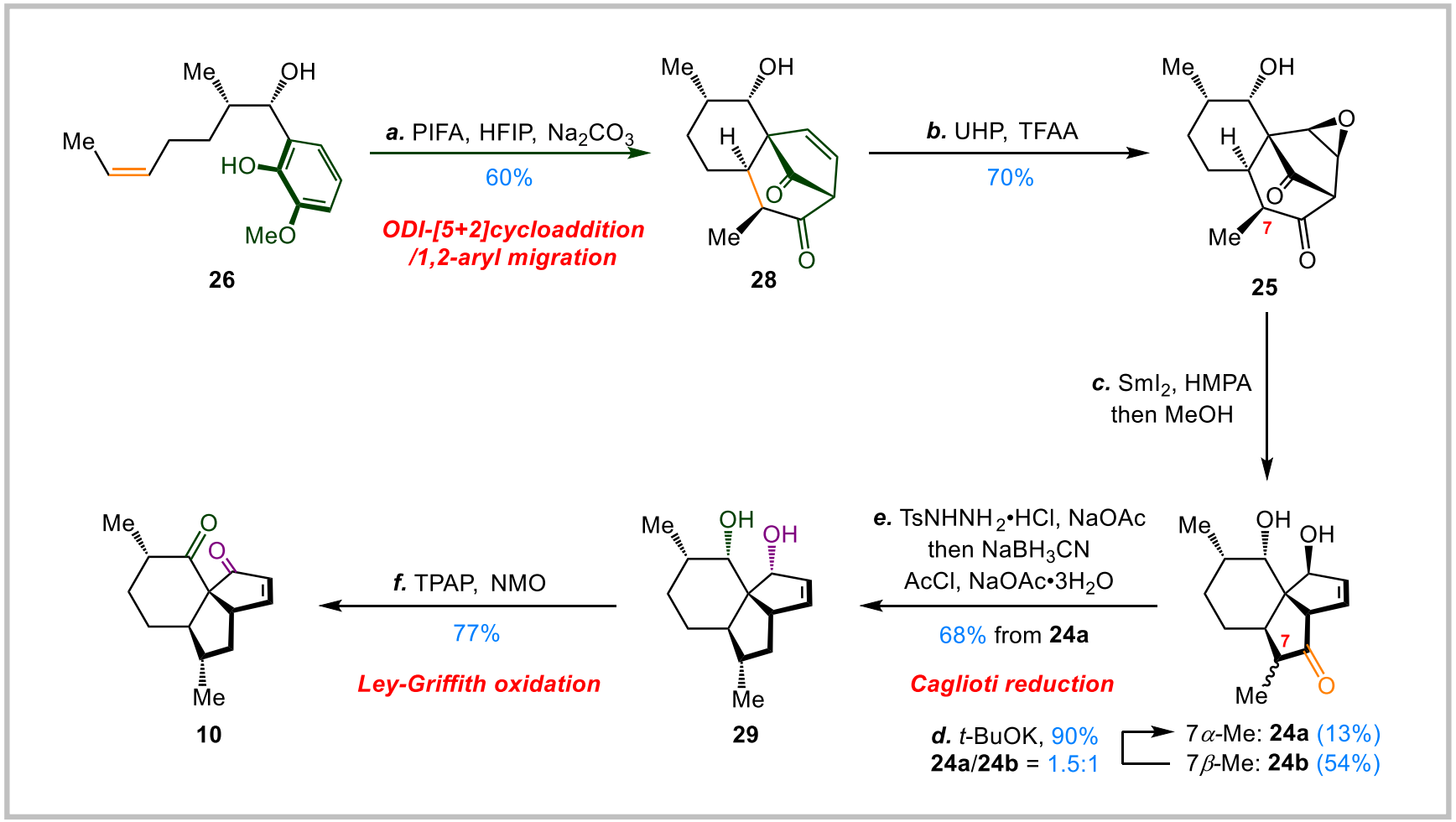
Retrosynthetic Analysis



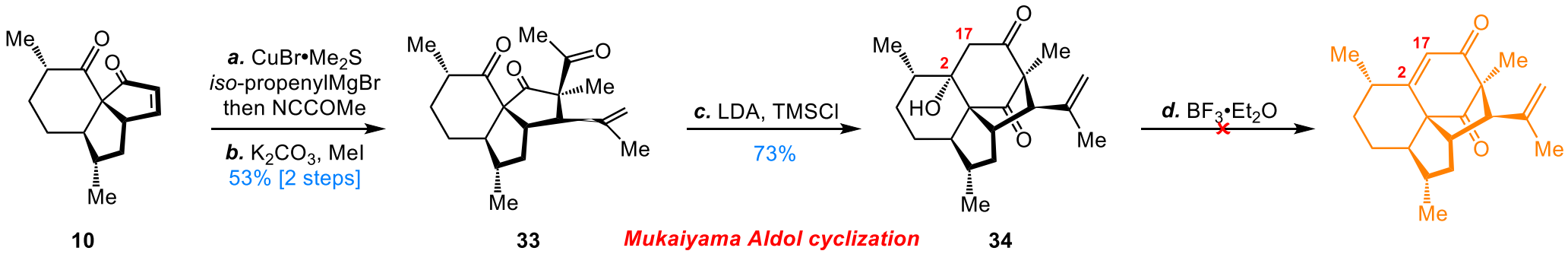
Stage 1: Synthesis of Compound 10

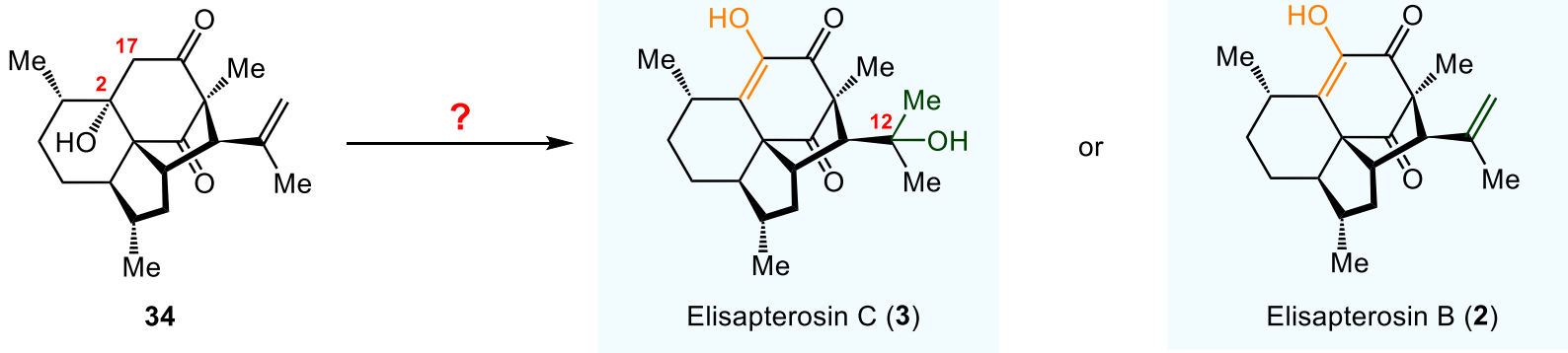


Stage 1: Synthesis of Compound 10



Stage 2: Syntheses of Elisapterosins B and C





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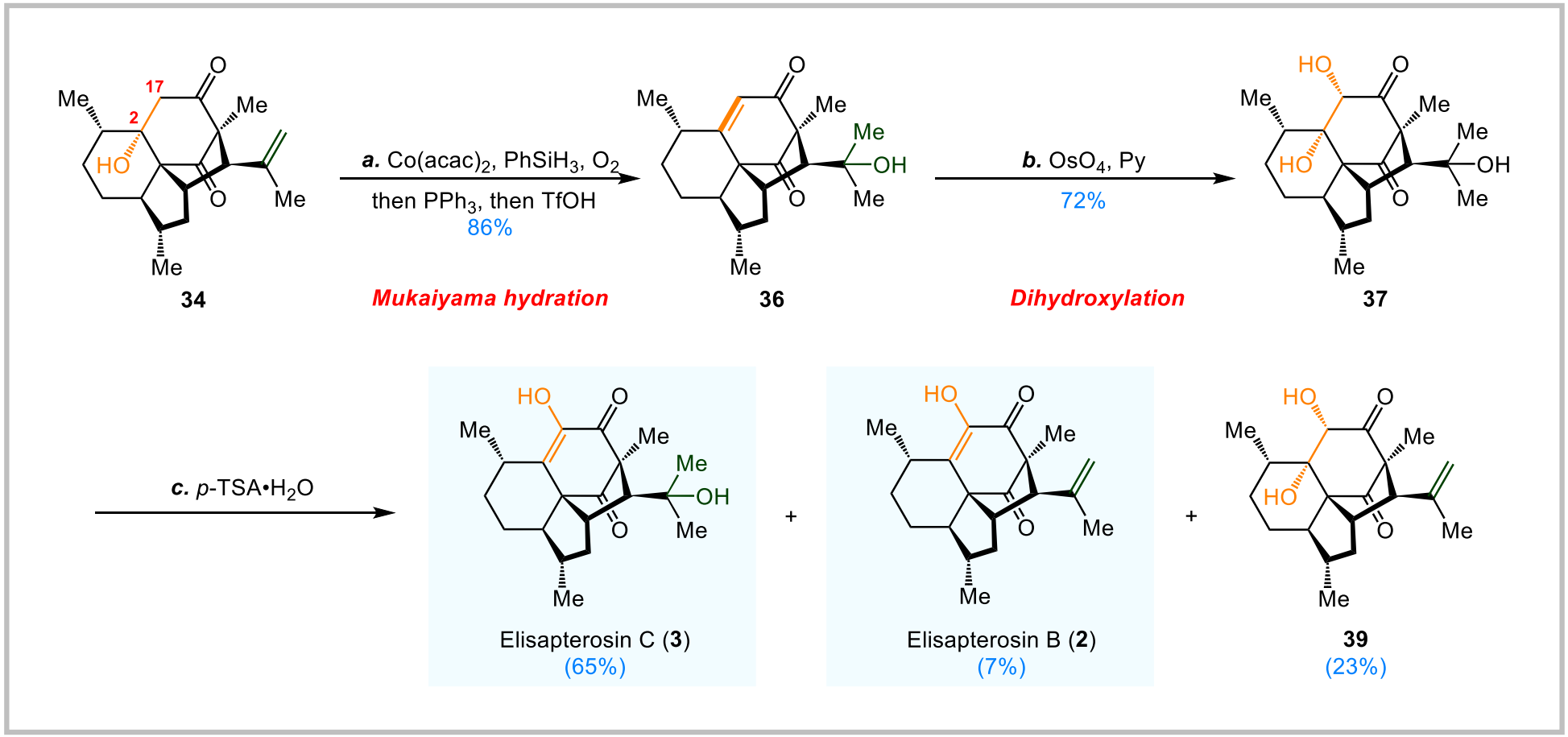

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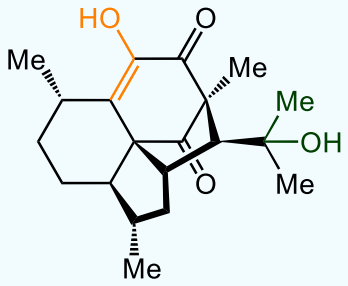
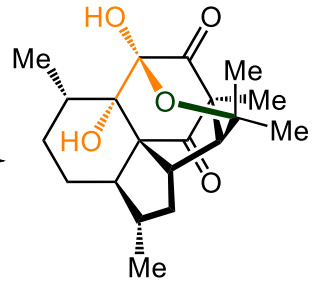


Elisapterosin C (**3**)
(65%)

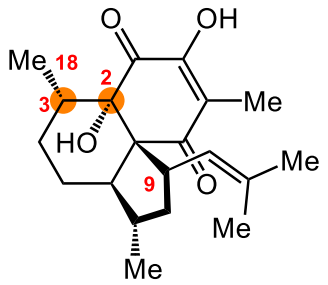
OsO_4, Py

86%



Elisapterosin F (**6**)
[proposed structure]

Questionable Configurations at C2/C3

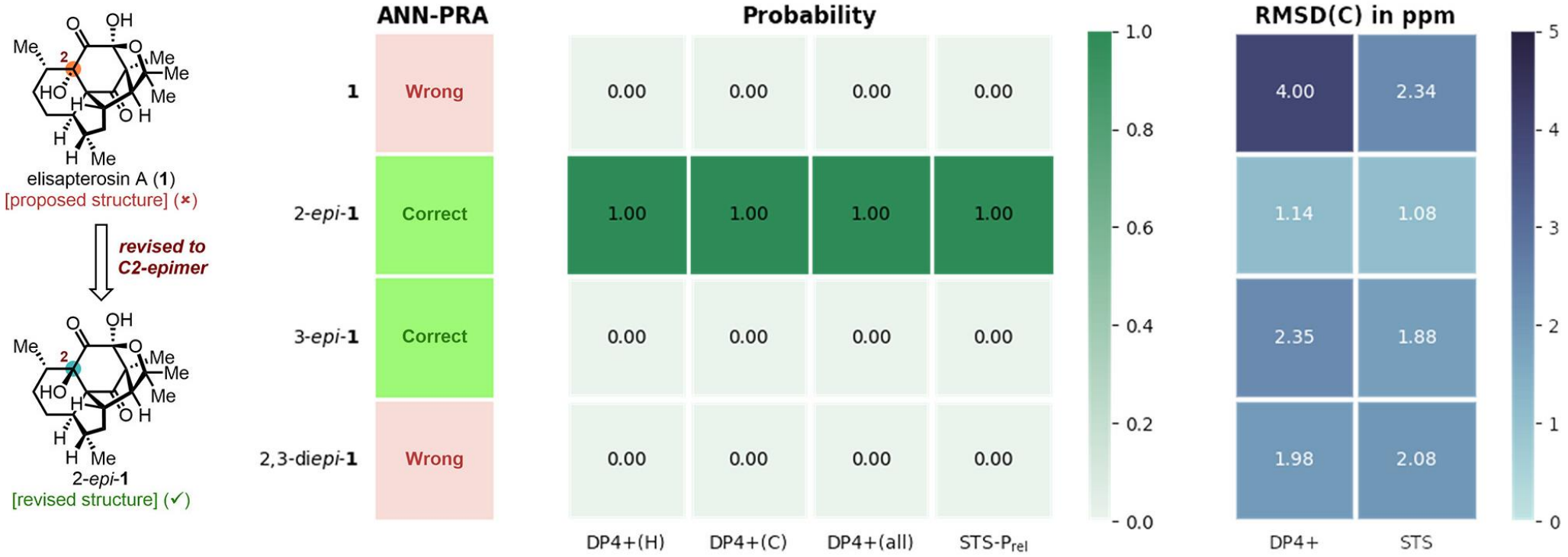


Elisabethin D
[X-ray]

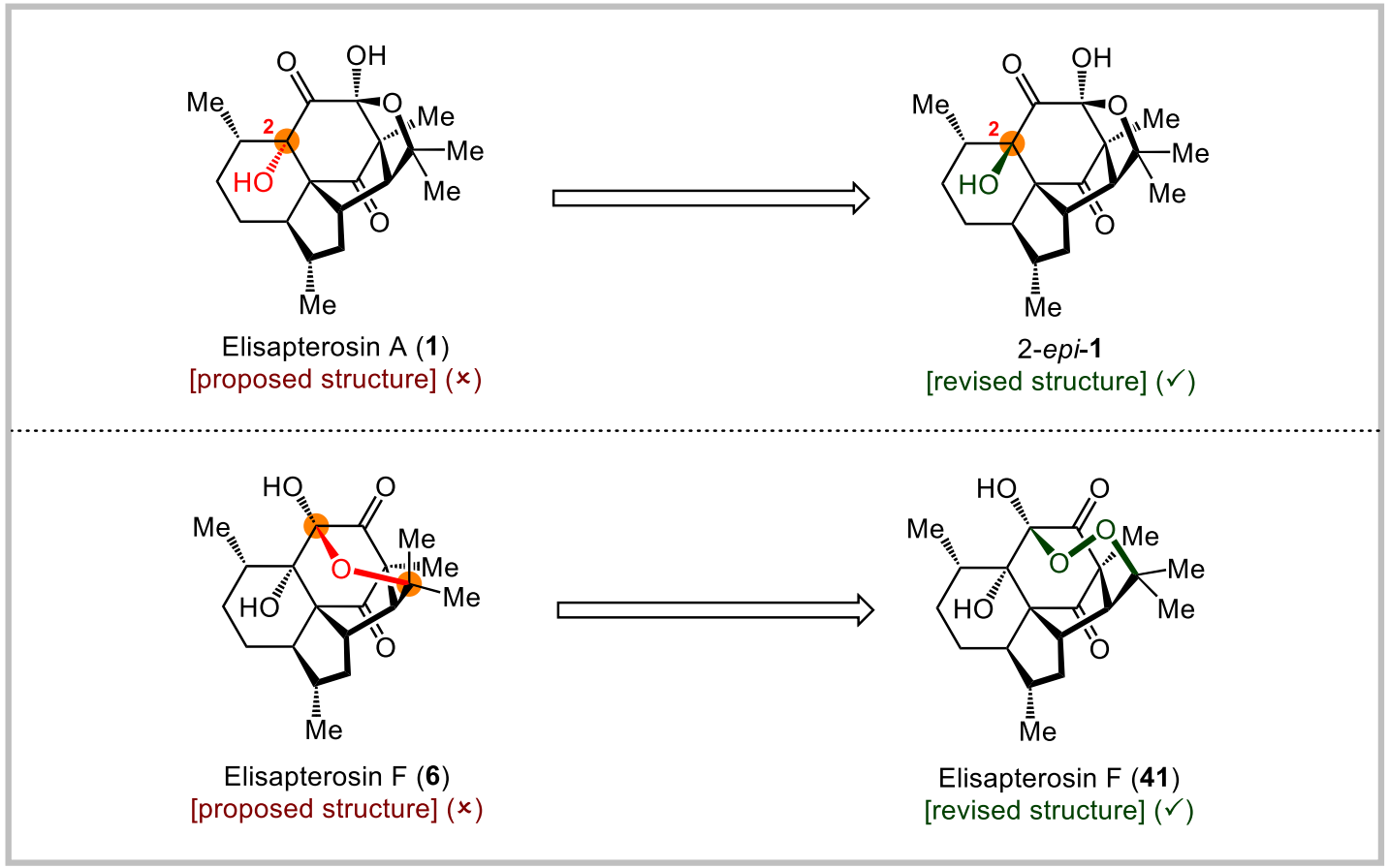
Elisapterosin A
[analogy to Elisabethin D]
[no C18(H)-C9(H) NOE]
[2D-NMR not available]

Elisapterosin F
[C3(H)-C9(H) NOE]
[2D-NMR available]

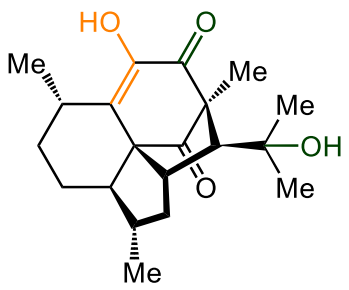
Stage 3: *In Silico* Structure Revision-Elisapterosin A



Stage 3: *In Silico* Structure Revision-Elisapterosin A and F



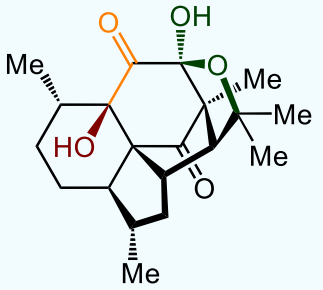
Stage 4: Syntheses of the Revised Structures-Elisapterosin A



Elisapterosin C (**3**)

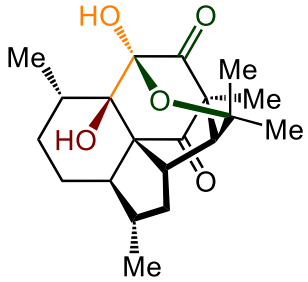
a. $(PhSeO)_2O$, 88%

2-*epi*-**1**/2-*epi*-**6** = 11:1
(inseparable mixture)

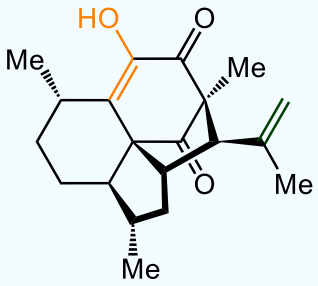


Elisapterosin A (2-*epi*-**1**)
[revised structure]

+

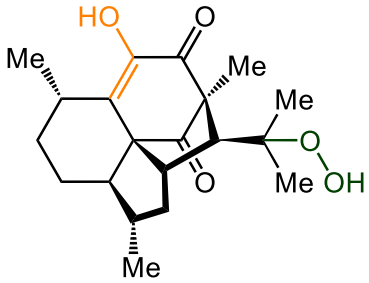


2-*epi*-**6**



Elisapterosin B (**2**)

b. $Co(pic)_2$, TBHP
O_2, TMDSO, 87%



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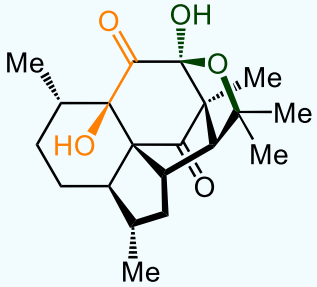
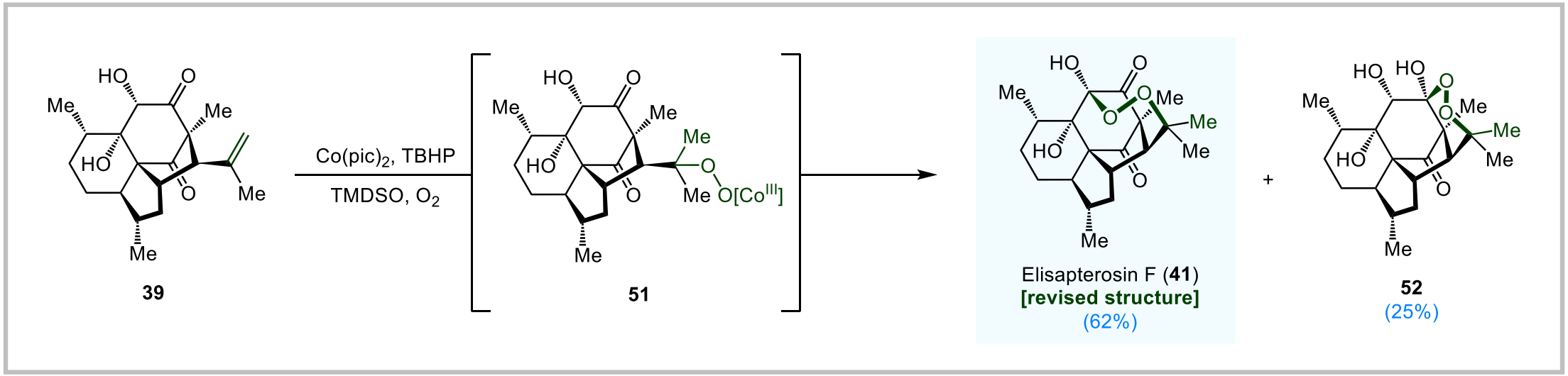
c. $Co(pic)_2$, O_2
20% (25% brsm)



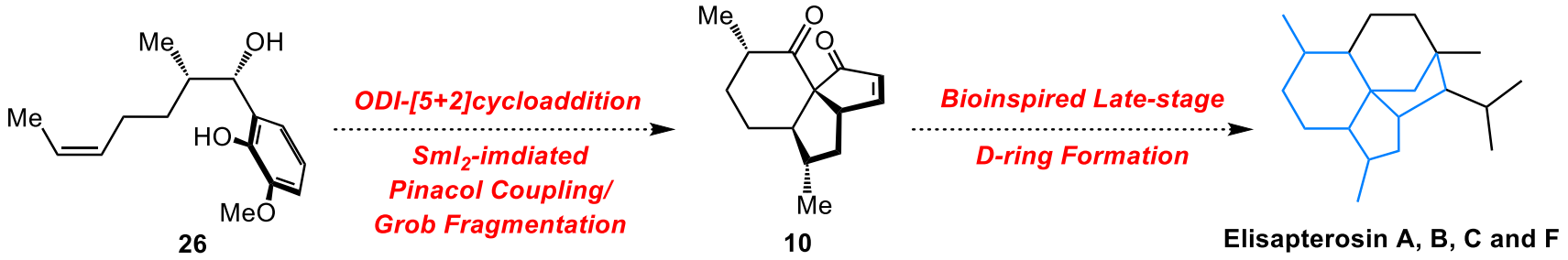
Elisapterosin A (2-*epi*-**1**)
[revised structure]

Stage 4: Syntheses of the Revised Structures-Elisapterosin F

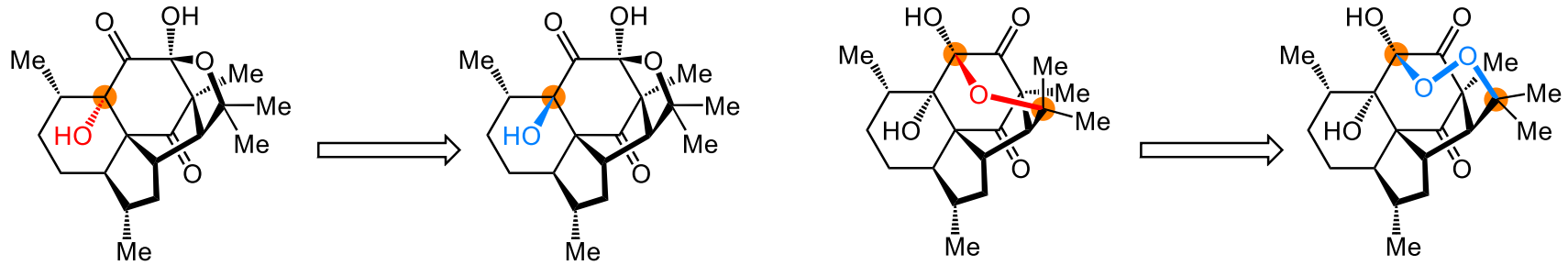


Summary

Divergent Total Syntheses of 4 Numbers



Structure Revision of 2 Numbers



- ***Bioinspired divergent approach***
- ***4 Members from 1 subtype***
- ***Structure revision by NMR calculation***
- ***Validation by total synthesis***

Writing Strategy

➢The First Paragraph

海洋天然产物具有引人入胜的复杂结构

↓

指出结构确证具有挑战性

↓

由全合成的劣势引出计算机辅助的结构解析方法

♣ The ocean has given rise to a plethora of secondary metabolites with structurally diverse and ingenious designs. The elegant architectures of complex **marine natural products (MNPs)** have attracted the broad interest of organic chemists for a long time.

♣ Occasionally, the **scarcity, inaccessibility, and intrinsic complexity** of these MNPs make **deciphering their structures particularly challenging.** For synthetic chemists, **"chasing the molecules that were never there"** is undoubtedly one of the most frustrating issues.

♣ Although total synthesis **serves as the unequivocal benchmark for structure validation**, **its laborextensive nature restricted the efficiency of structure revision.** The development of **modern computer-assisted structure elucidation (CASE)** approaches, however, remarkably changed this situation.

Writing Strategy

➢The Last Paragraph

总结本文
全合成工作

↓

总结本文
结构修正工作

↓

指出本工作的
启示与警示

♣ We have developed **a distinctive bioinspired late-stage D-ring formation strategy for divergent syntheses of elisapterane and relevant diterpenoids**, leading to the enantioselective total syntheses of **elisapterosins A−F, aberrarone, elisabanolide, and 3-*epi*-elisabanolide**.

♣ Leveraging the power of these state-of-the-art computational tools, we have **corrected elisapterosins A, D and elisapterosin F**. These unexpected structural mutations were completely **verified by total syntheses**.

♣ Synergy between our *in silico* prediction and experimental validation **exemplifies a case of computer-guided total synthesis**, effectively minimizing “chasing the molecules that were never there”. We further cautioned against **the error-prone approach to elucidate the organic structures by analogy and comparison**, as the notion of similarity is subjectively defined.

Representative Examples

- The key tricyclic intermediate bearing a norneoelisabane skeleton could be efficiently prepared via an ODI-(5 + 2) cycloaddition/1,2-acyl migration cascade and a SmI_2-mediated pinacol coupling/Grob fragmentation/deoxygenation **orchestration**. (*n.* 管弦乐编曲，此处强调反应序列性)

- **Mechanistically**, a 1,5-hydrogen atom transfer (HAT) process of primary radical intermediate **48** occurred to generate more stable ketyl radical **49**. (*adv.* 机理上地)

- The unambiguous NOE correlations observed in the reported spectrum of elisapterosin F also **ruled out** these stereochemical interrogations. (排除)

Acknowledgement

Thanks for Your Attention!