Literature Report 5

Three-Component Assembly and Structure-Function Relationships of (–)-Gukulenin A

Reporter: Xin-Yu Zhan
Checker: Yu-Yang Shi

Gupta, V.; Wang, Z.; Combs, J. B.; Wright, T.; Herzon, S. B*. *et al*. *Science* **2025**, *390*, aea9310

2026-02-02

CV of Prof. Seth Herzon

Background:

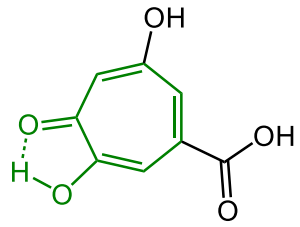
- **1998-2002** B.S., Temple University
- **2002-2006** Ph.D., Harvard University (Prof. Andrew G. Myers)
- **2006-2008** Postdoctoral fellow, UIUC (Prof. John Hartwig)
- **2008-now** Professor, Yale University

Research:

- Synthesis of Natural Products
- Structure–Function Studies of Anticancer and Microbiome-Derived Natural Products

Contents

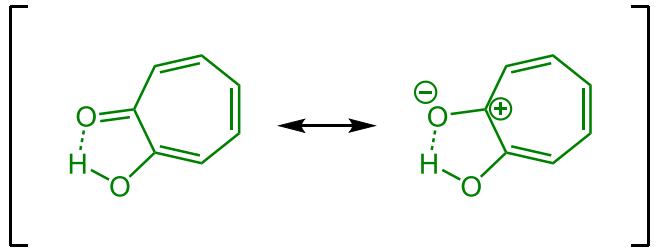
Introduction



Stipitatic Acid (**1**)

Aromaticity

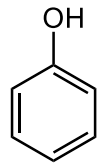
Dipole



α-Tropolone (**2**)

47 kcal/mol

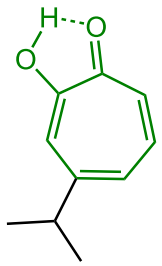
3.71 *D*



Phenol (**3**)

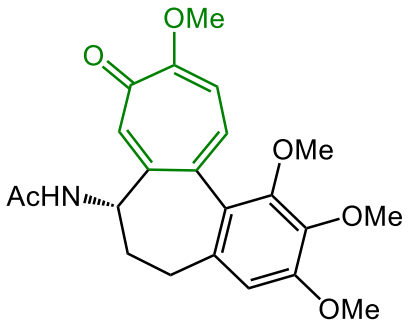
36 kcal/mol

1.56 *D*



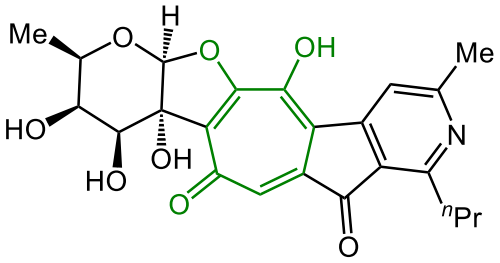
Hinokitiol (**4**)

Fe Transpoter



Colchicine (**5**)

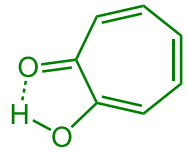
Tubulin Binding Agent

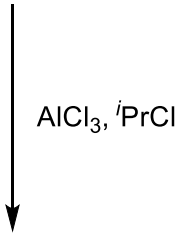


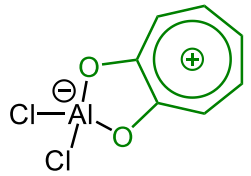
Rubrolone A (**6**)

Bacterial Defense

No F.C. Alkylation

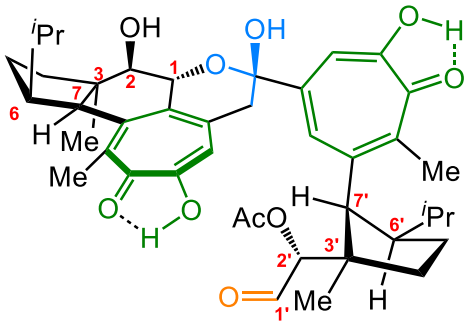






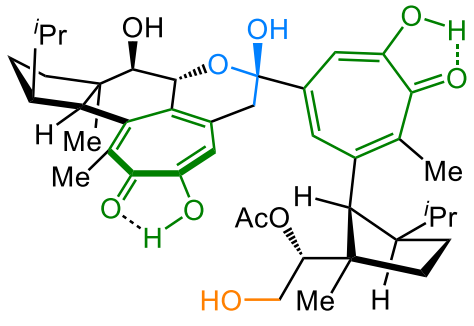
Tropolonate

Introduction



(–)-Gukulenin A (**7**)

No Reported Synthesis



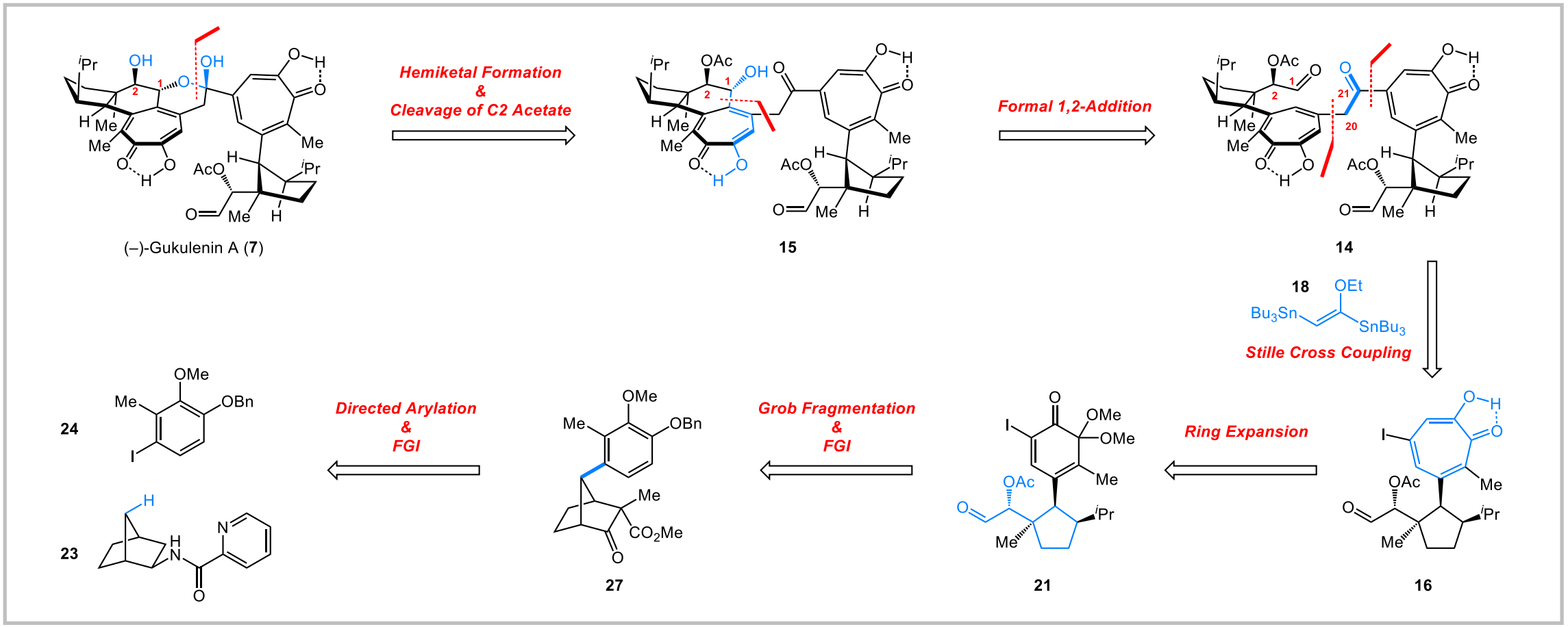
(–)-Gukulenin B (**8**)

Nicolaou (2022)

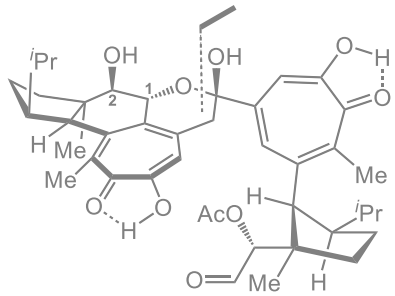
Phorbas gukulensis

- Two α-Tropolone Residues and 10 Asymmetric Stereocenters
- The Most Structurally Complex Tropolone Natural Products
- Efficacious and Well-Tolerated in Murine Models of Ovarian Cancer

Retrosynthetic Analysis

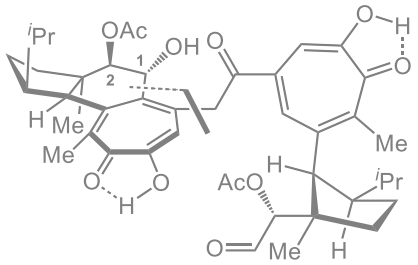


Retrosynthetic Analysis



(–)-Gukulenin A (**7**)

Hemiketal Formation
&
Cleavage of C2 Acetate



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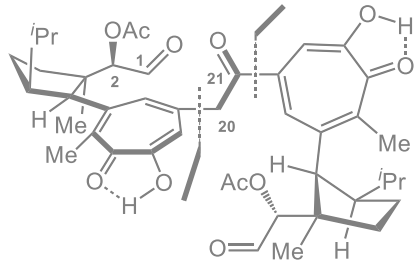
Formal 1,2-Addition



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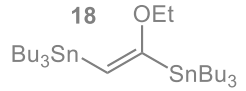
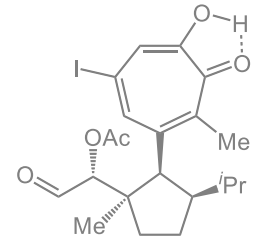


Stille Cross Coupling

Ring Expansion



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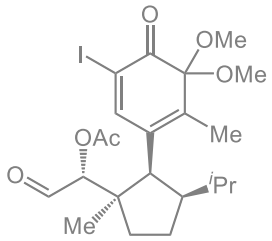

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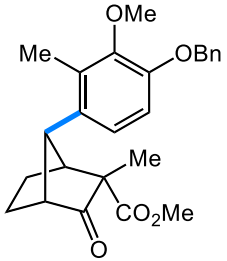
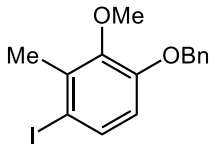
Grob Fragmentation
&
FGI



27

Directed Arylation
&
FGI

24



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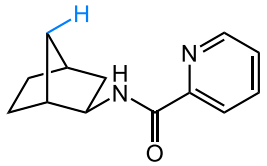
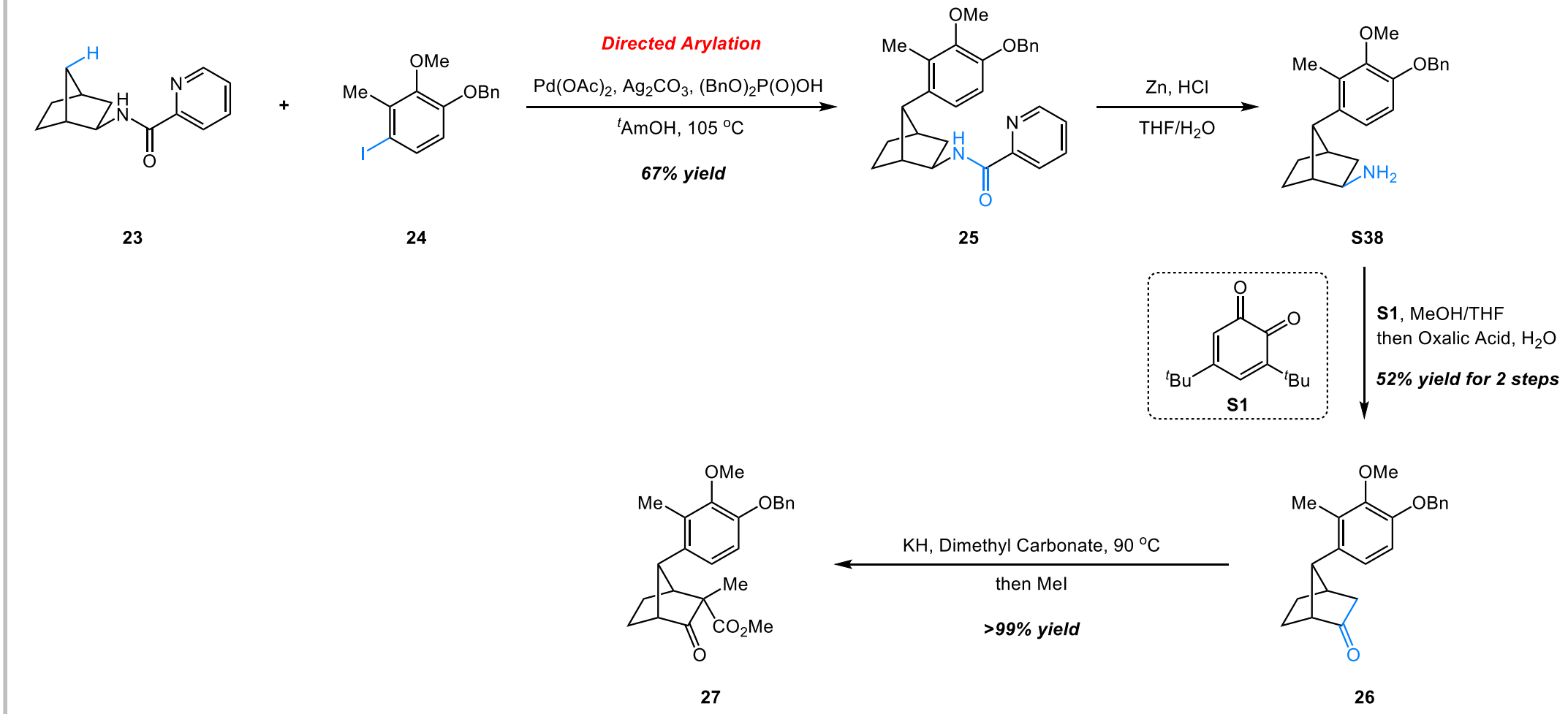
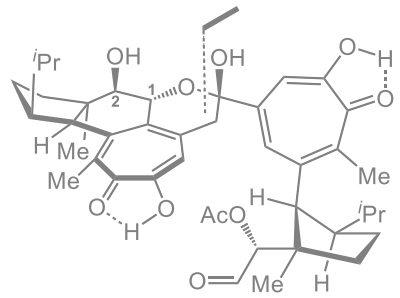


Synthesis of Compound 27

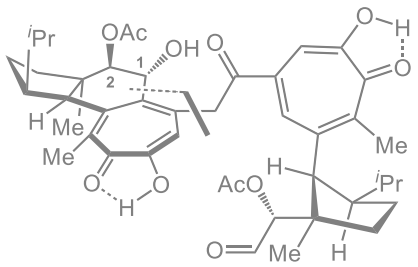


Retrosynthetic Analysis



(–)-Gukulenin A (**7**)

Hemiketal Formation
&
Cleavage of C2 Acetate



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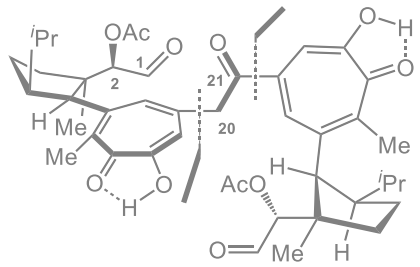
Formal 1,2-Addition



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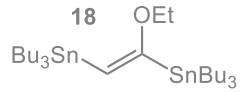
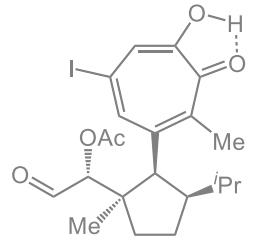


Stille Cross Coupling

Ring Expansion



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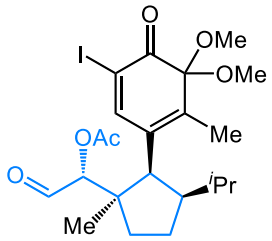

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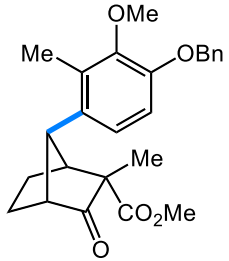
Grob Fragmentation
&
FGI



27

Directed Arylation
&
FGI

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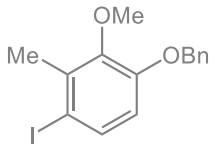

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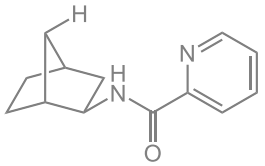
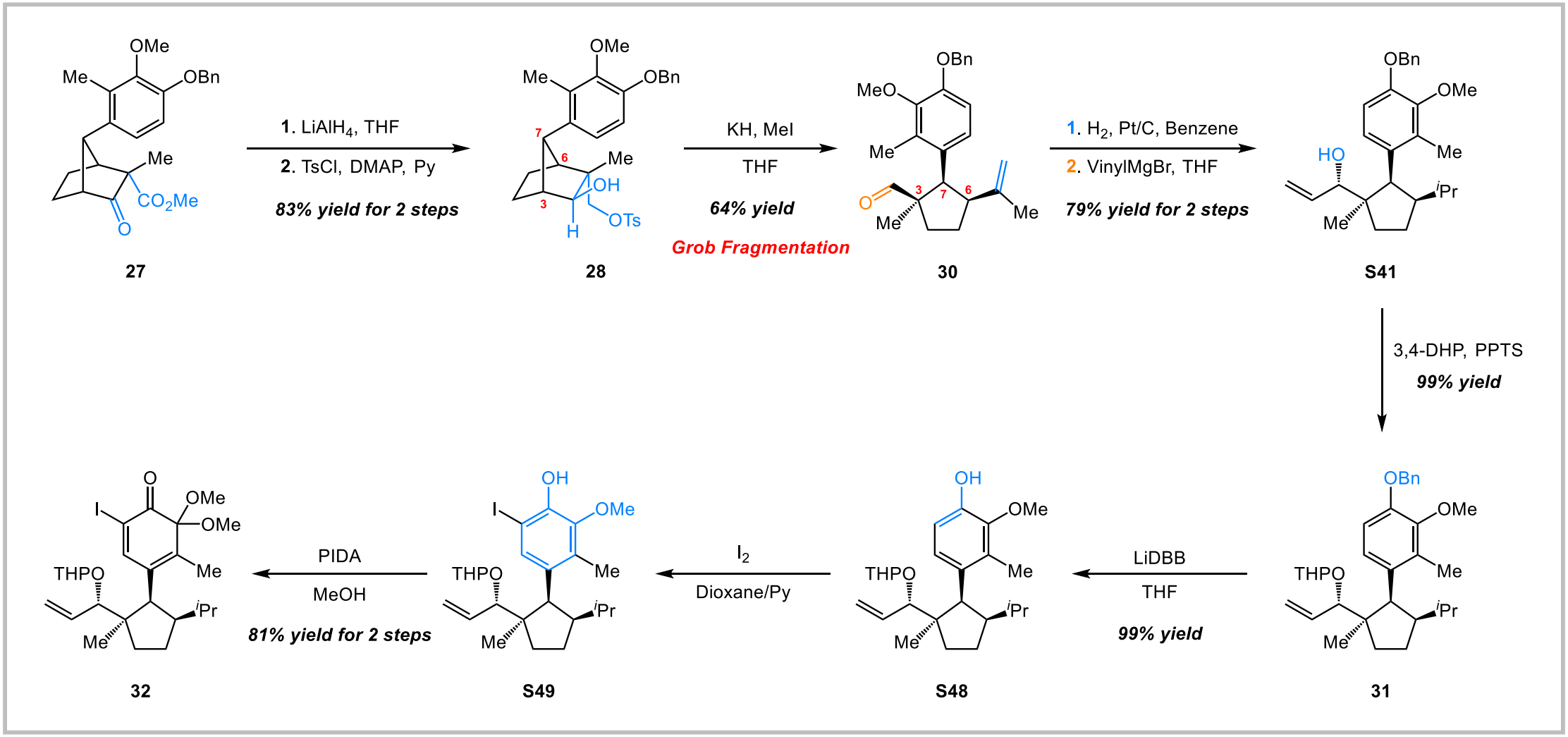
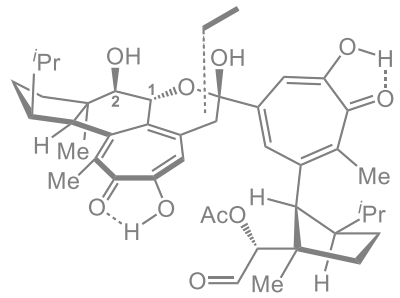


Synthesis of Compound 32

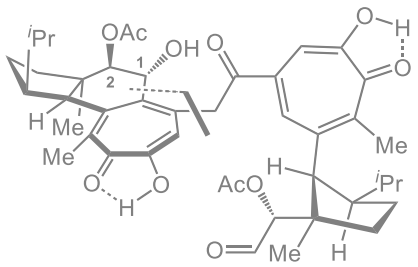


Retrosynthetic Analysis



(–)-Gukulenin A (**7**)

Hemiketal Formation
&
Cleavage of C2 Acetate



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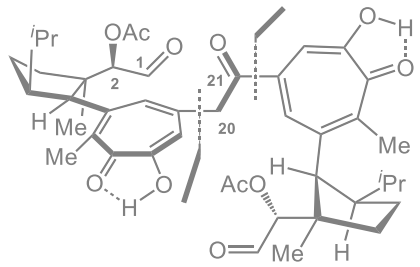
Formal 1,2-Addition



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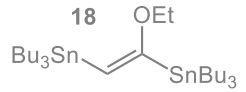
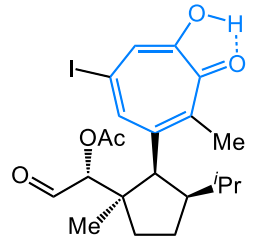


Stille Cross Coupling

Ring Expansion



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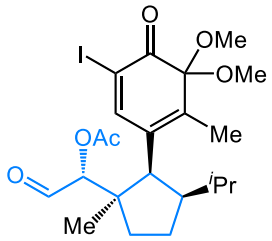
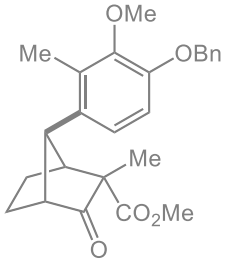


21

Grob Fragmentation
&
FGI



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Directed Arylation
&
FGI

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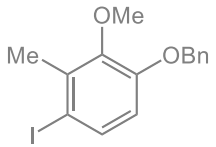

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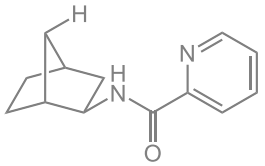
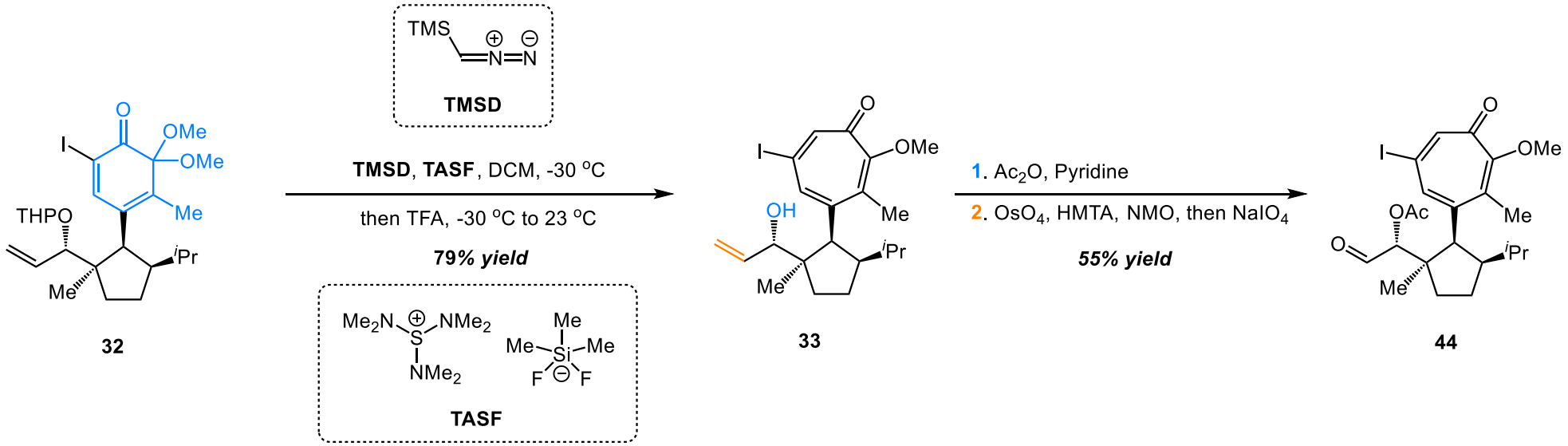
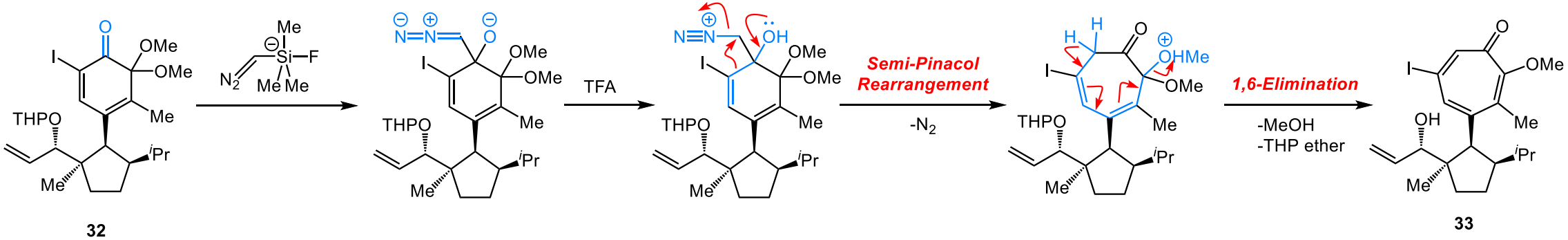


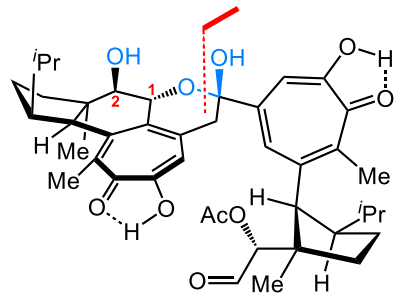
Synthesis of Compound 44



Mechanism of 32 to 33

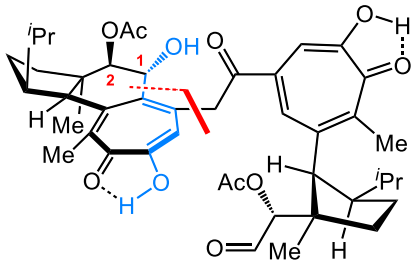


Retrosynthetic Analysis



(–)-Gukulenin A (**7**)

Hemiketal Formation & Cleavage of C2 Acetate



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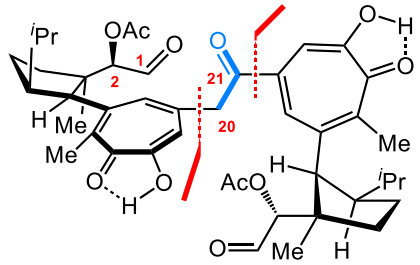
Formal 1,2-Addition



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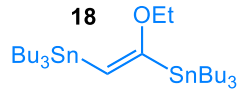

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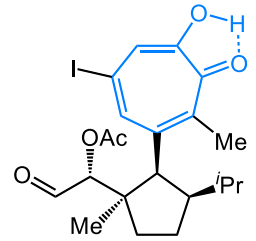
Stille Cross Coupling



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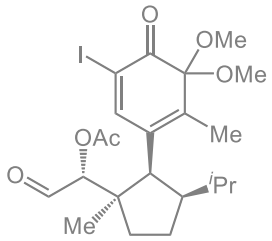
Ring Expansion



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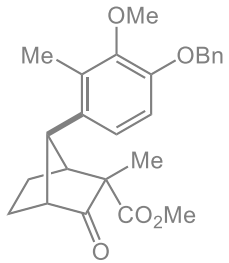
Grob Fragmentation & FGI



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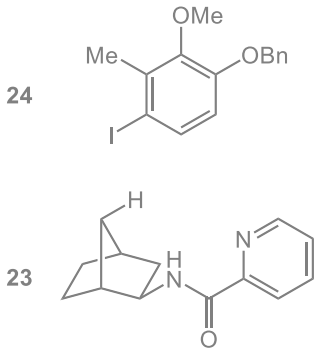
Directed Arylation & FGI



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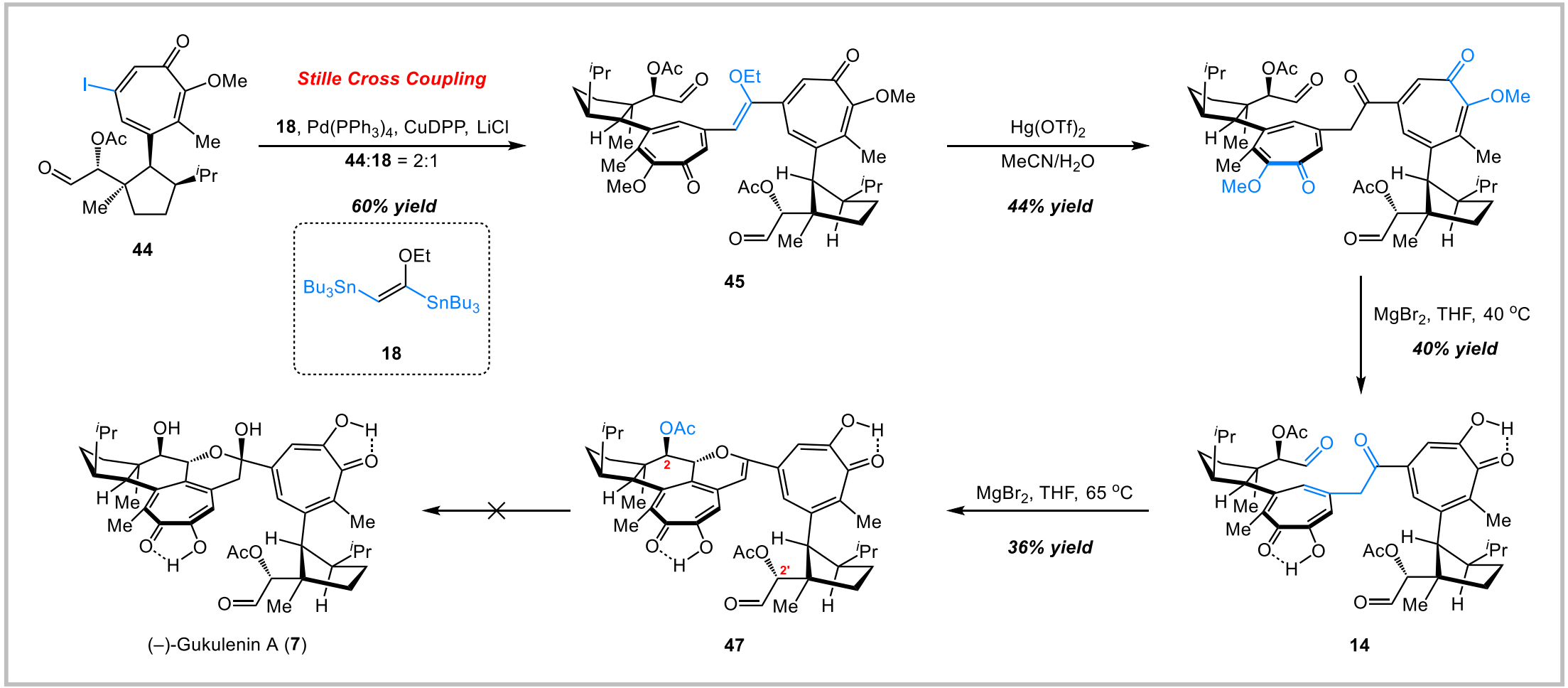
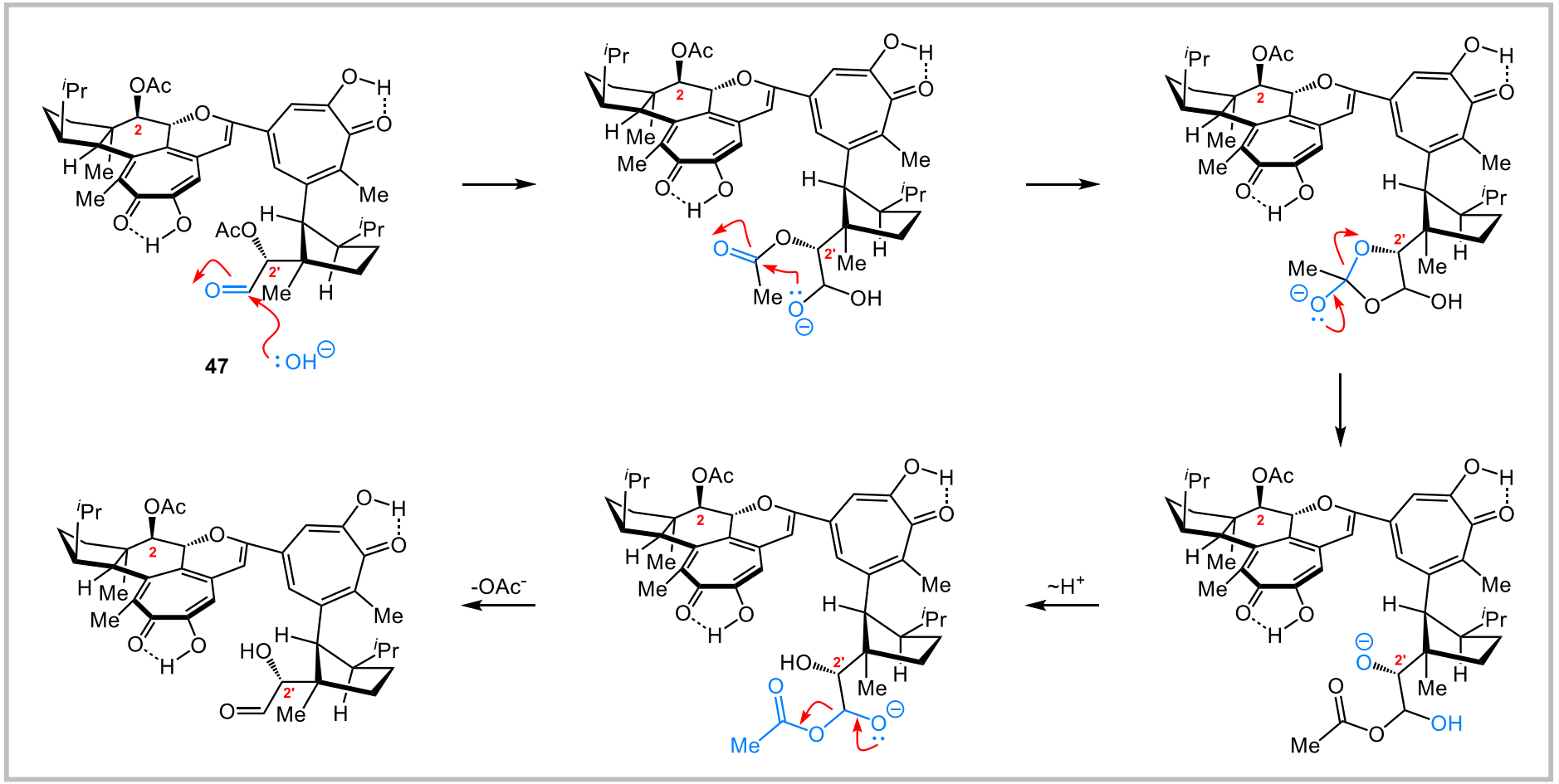
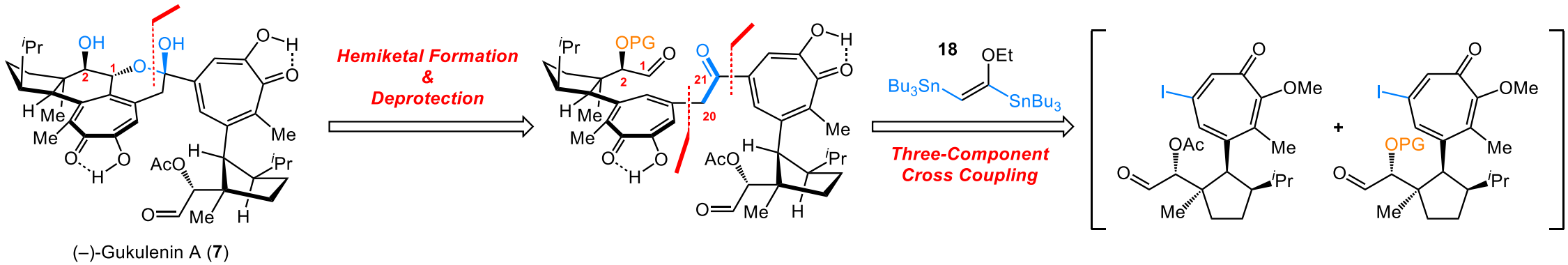
Synthesis of Compound 7



Mechanism for Hydrolysis of C2’ Acetate

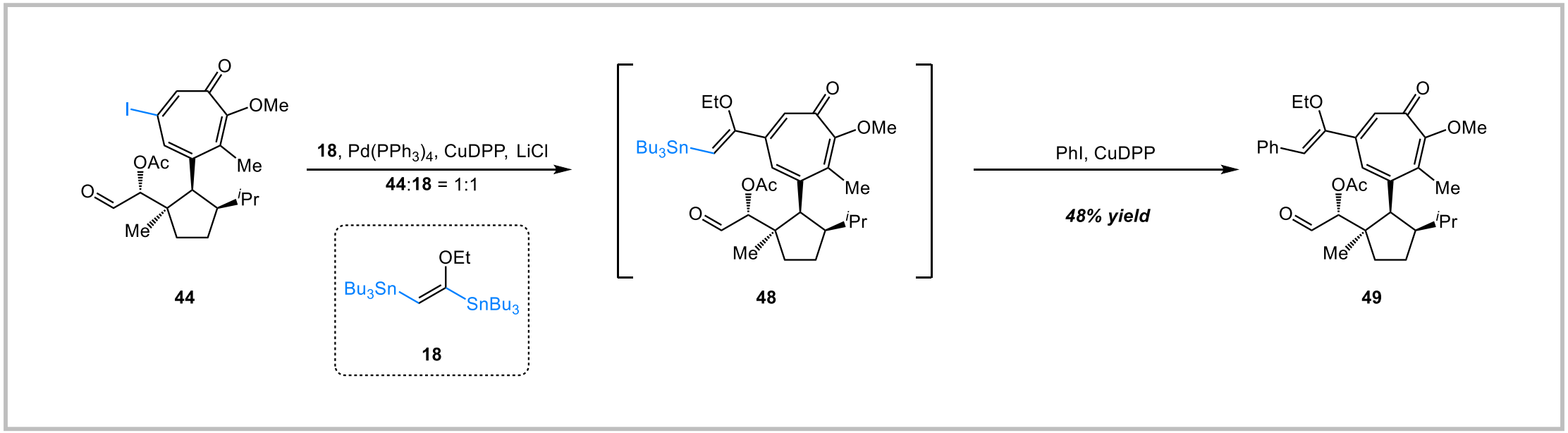


Retrosynthetic Analysis

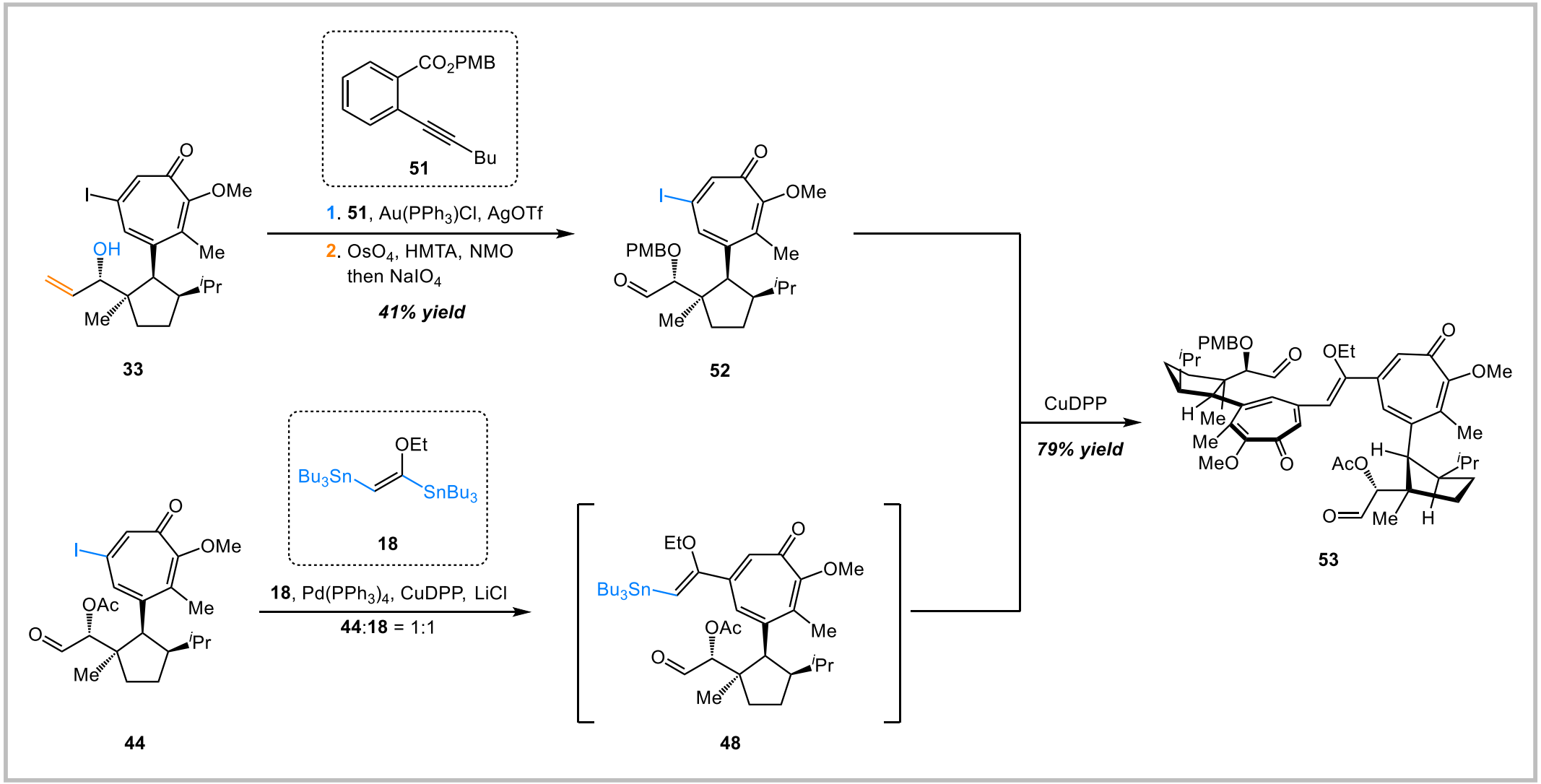


(–)-Gukulenin A (**7**)

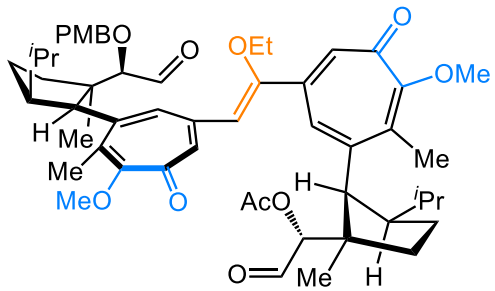
Synthesis Attempt



Synthesis of Compound 53



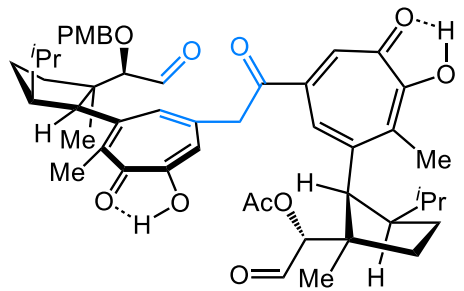
Synthesis of Compound 7



53

1. $MgBr_2$
2. $Hg(OTf)_2$

***91% yield* (NMR)**

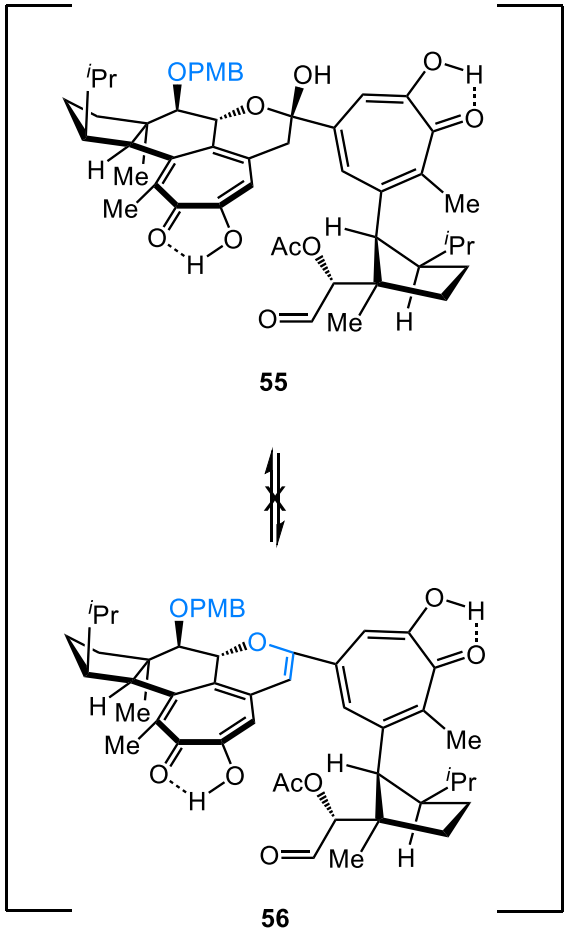


54

DMSO-d_6

120 °C

55:**56** = 14:1

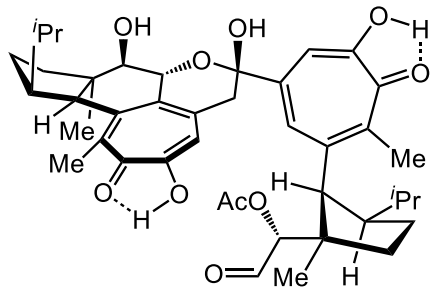


55

56

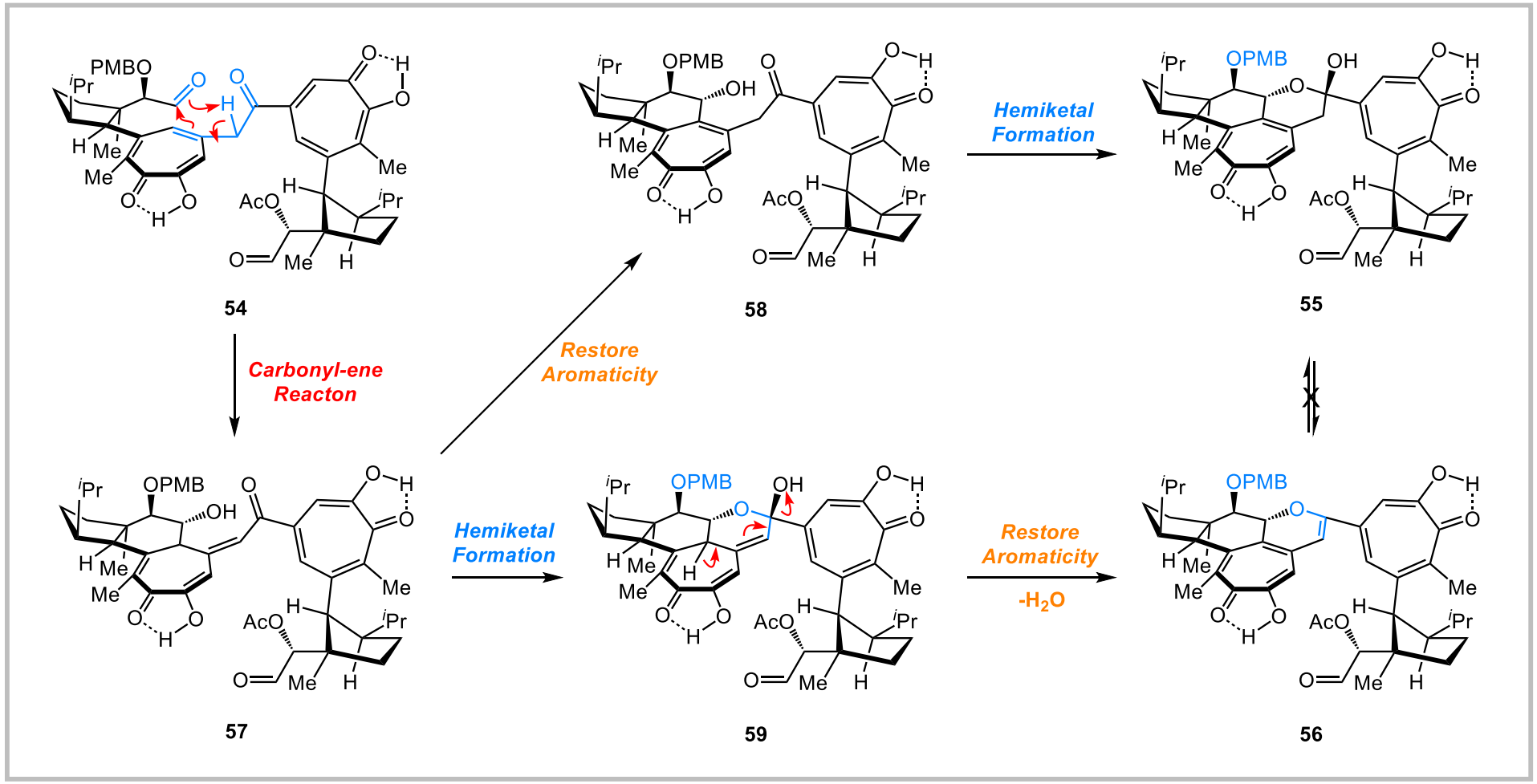
DDQ

***86% yield* (NMR)**
***28% yield* (Isolated)**

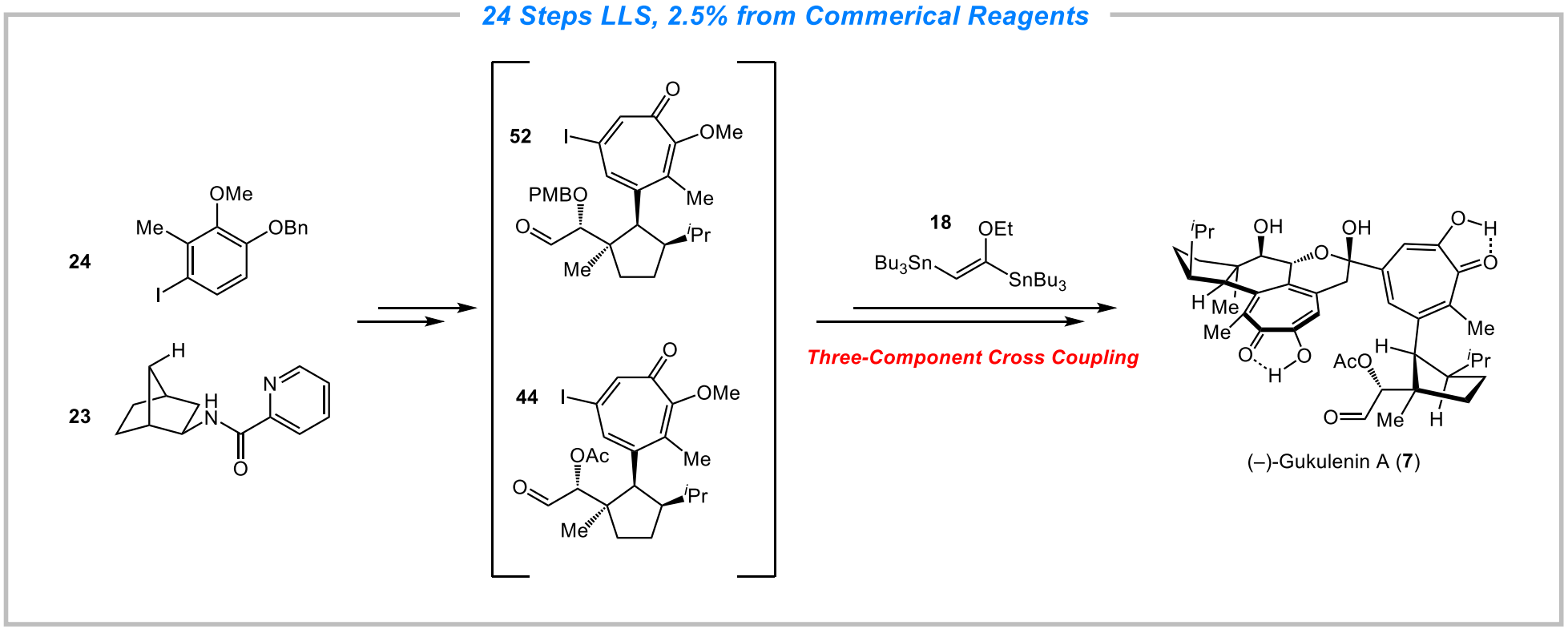


(–)-Gukulenin A (**7**)

Mechanism of 54 to 55 & 56



Summary



- First Total Synthesis of (–)-Gukulenin A
- Three-Component Cross Coupling; Thermal Carbonyl-ene Reaction

Gupta, V.; Wang, Z.; Combs, J. B.; Wright, T.; Herzon, S. B. et al. *Science* **2025**, *390*, aea9310

Writing Strategy

➢ **First paragraph**

Tropolone

↓

Species and Structure

- The existence of a seven-membered aromatic ring was first posited by Dewar in 1950 to account for the physical properties of the natural product stipitatic acid Dewar named this unconventional ring an α-tropolone and estimated its aromatic stabilization energy to be ~47 kcal/mol, which is considerably greater than that of benzenoid systems, such as phenol. This aromatic character is enhanced by separation of charge in the carbon-oxygen π bond. Consequently, α-tropolones present a strong molecular dipole and…
- (–)-Gukulenins A and B were first isolated from a sample of the marine sponge Phorbas gukulensis found off the coast of Gageodo Island, South Korea, and are the most structurally complex tropolone natural products discovered to date. The pseudodimeric structure of (–)-gukulenin A comprises two α-tropolone residues, 10 asymmetric stereocenters, and an electrophilic α-acetoxy aldehyde. (–)-Gukulenin B is identical to (–)-gukulenin A save for the presence of a primary alcohol in place of the aldehyde substituent.

Writing Strategy

➢ **Last paragraph**

Summary

↓

Challenges and Committed Steps

↓

Prospect

■ The synthetic strategy we developed has provided an enantioselective route to (–)-gukulenin A. Our approach was inspired by a bio synthetic hypothesis and implemented experimentally by a three-component assembly, using the linchpin reagent (*E*)-1,2-di(tributylstannyl)-1-ethoxyethylene. Although this route maximized convergence, it also presented challenges because the C2 acetate substituent in anhydrogukulenin A C2-acetate could not be successfully removed in the presence of the C2′ acetate residue. To circumvent this, we exploited the relative rates of transmetalation of the α- and β-tributylstannyl substituents in 18 to achieve a high-yielding, three-component coupling reaction that provides the dimeric methyl-tropolone ether, which contains differentially protected C2/C2′ oxygen substituents.

■ The development of three methods for the synthesis of methyl tropolone ethers from ortho- benzophenone monoketals, a strategy for the synthesis of highly substituted cyclopentanes, and the discovery of a thermal carbonyl-ene reaction formed the foundation of our successful approach and may find use in other contexts.

Representative Examples

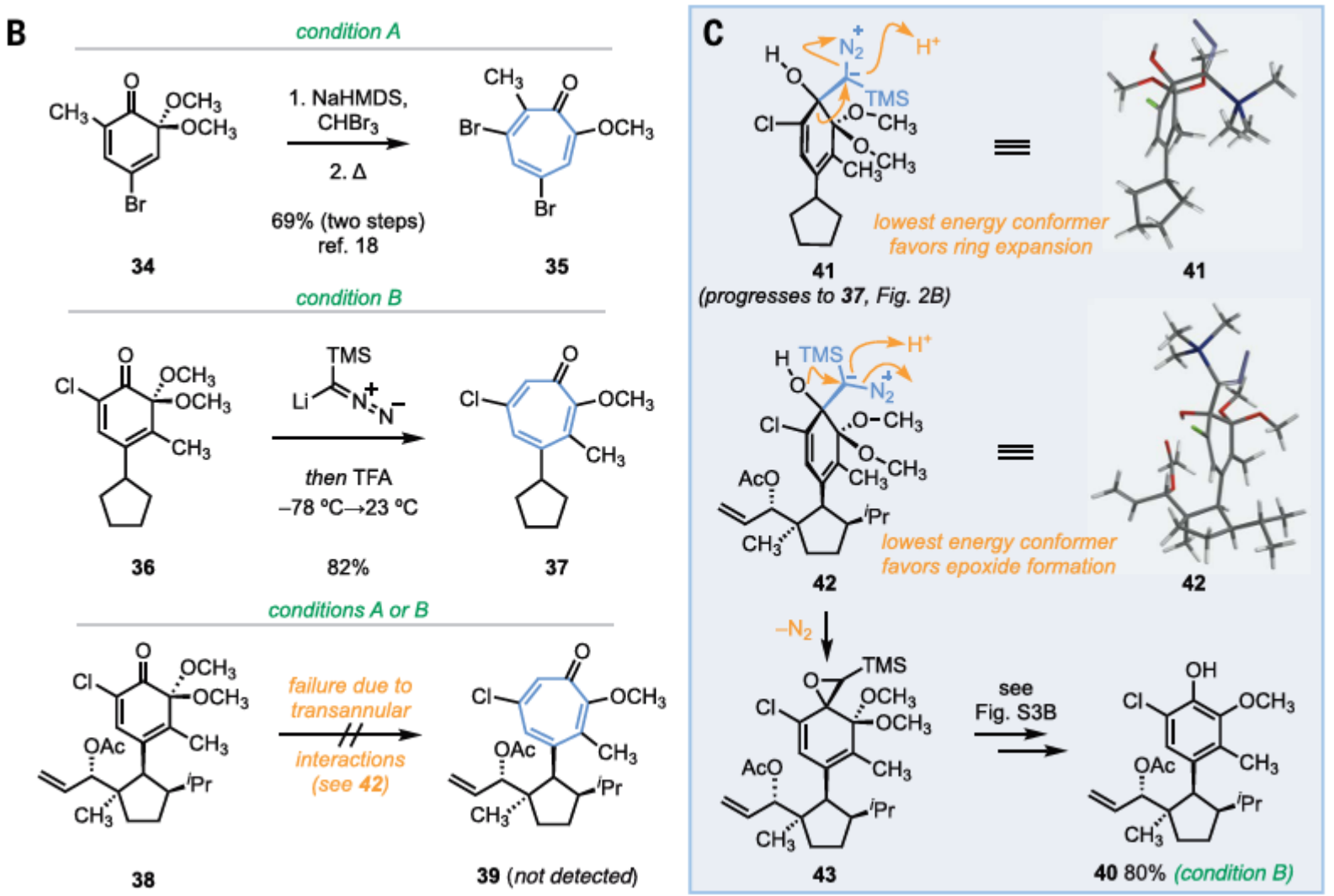
- Given the established affinity of α- tropolones toward divalent metals this finding raises the intriguing possibility that (–)-gukulenin A may bind two discrete metalloproteins… (*adj*. 有趣的；引人入胜的)

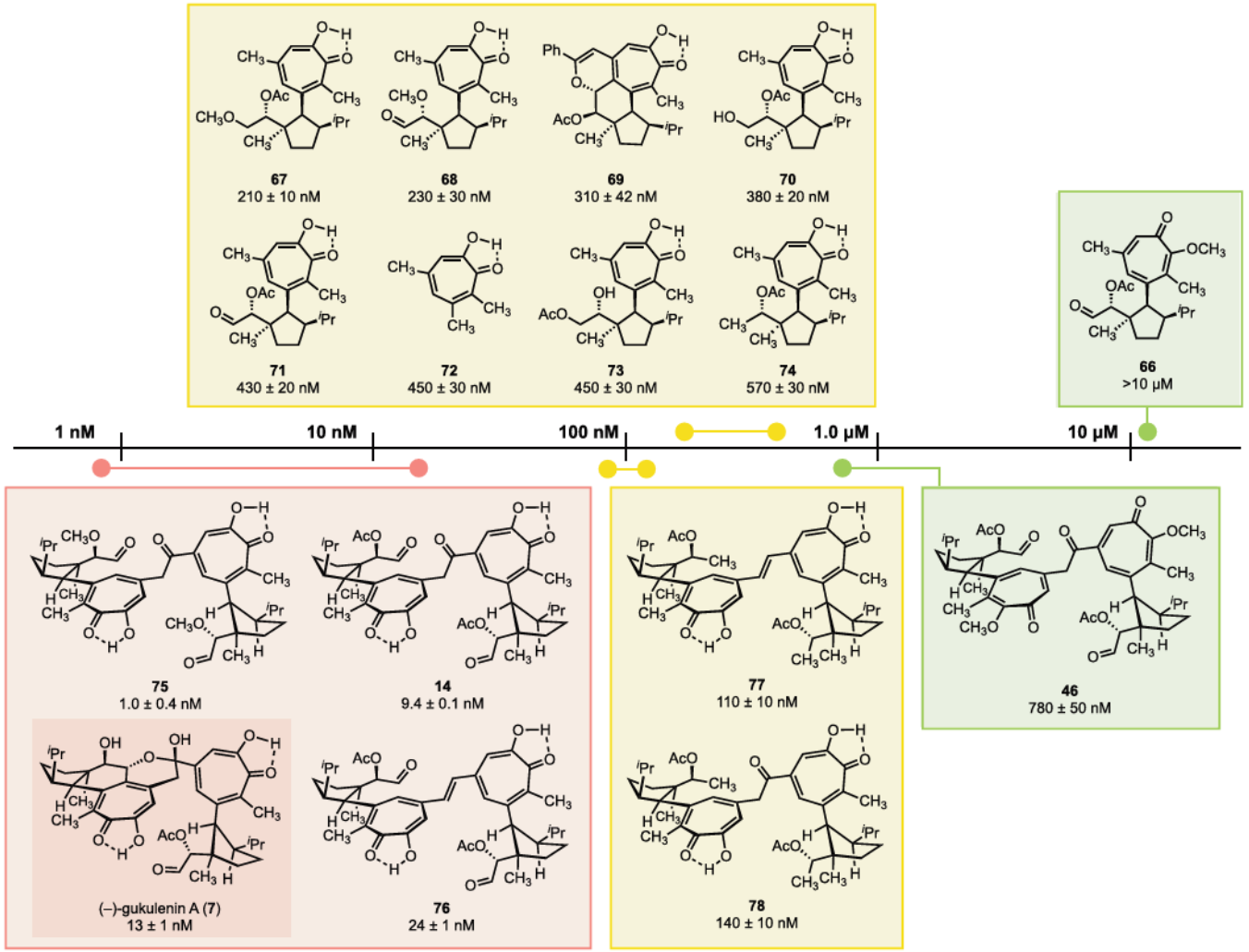
- Although this residue is fully dispensable in the monomeric series, dimeric tropolones lacking this residue displayed decreased potency relative to (–)-gukulenin A... (*adj*. 可有可无的，不必要的)

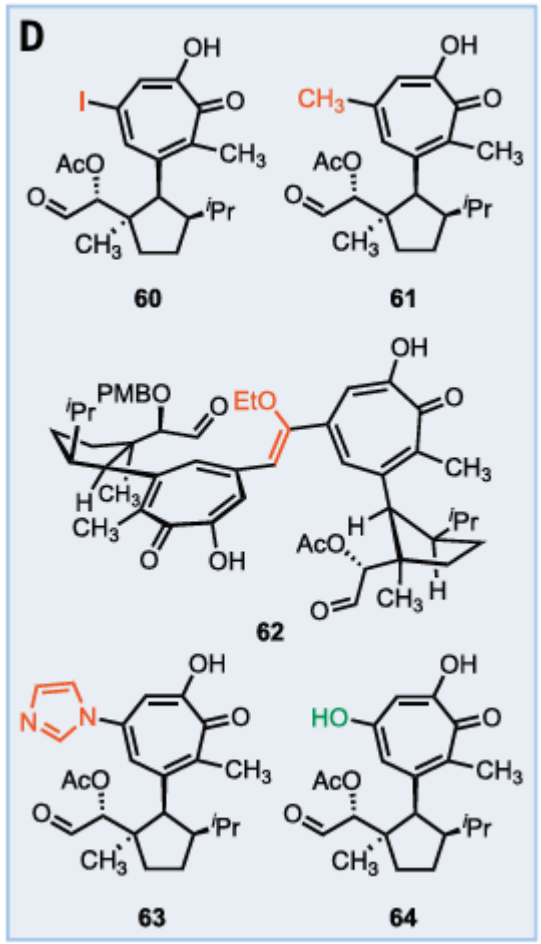
- Fifteen discrete monomeric and dimeric gukulenin derivatives were designed and synthesized to evaluate the effects of dimerization, the α- tropolone residues. (*adj.* 离散的; 分离的)

Acknowledgement

Thank You for Your Attention!


B
condition A
1. NaHMDS, CHBr3
2. Δ
69% (two steps)
ref. 18
34
35
condition B
TMS
Li
then TFA
–78 °C→23 °C
36
82%
37
conditions A or B
failure due to transannular interactions (see 42)
38
39 (not detected)
C
lowest energy conformer favors ring expansion
41
(progresses to 37, Fig. 2B)
41
lowest energy conformer favors epoxide formation
42
42
–N2
see Fig. S3B
43
40 80% (condition B)


67
210 ± 10 nM
68
230 ± 30 nM
69
310 ± 42 nM
70
380 ± 20 nM
71
430 ± 20 nM
72
450 ± 30 nM
73
450 ± 30 nM
74
570 ± 30 nM
66
>10 μM
1 nM
10 nM
100 nM
1.0 μM
10 μM
75
1.0 ± 0.4 nM
14
9.4 ± 0.1 nM
(–)-gukulenin A (7)
13 ± 1 nM
76
24 ± 1 nM
77
110 ± 10 nM
78
140 ± 10 nM
46
780 ± 50 nM


D
OH
I
O
CH3
AcO
O
iPr
CH3
60
OH
CH3
O
CH3
AcO
O
iPr
CH3
61
OH
iPr
PMBO
O
EtO
O
CH3
H
CH3
CH3
O
OH
H
AcO
iPr
O
CH3
H
62
OH
N
N
O
CH3
AcO
O
iPr
CH3
63
OH
HO
O
CH3
AcO
O
iPr
CH3
64