

Synthesis of Nonclassical Taxane

Literature Seminar

2022/12/10

Wentao Wang

Contents

- 1. Introduction**
- 2. Total Synthesis of canataxpropellane
by Prof. Gaich's Group¹⁾**
- 3. Synthetic Approach to Diverse Taxane
Cores by Prof. Sarpong's Group²⁾**
- 4. Summary**

Contents

1. Introduction

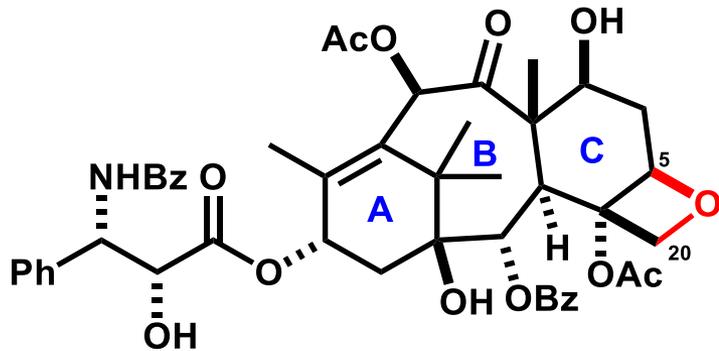
2. Total Synthesis of canataxpropellane
by Prof. Gaich's Group¹⁾

3. Synthetic Approach to Diverse Taxane
Cores by Prof. Sarpong's Group²⁾

4. Summary

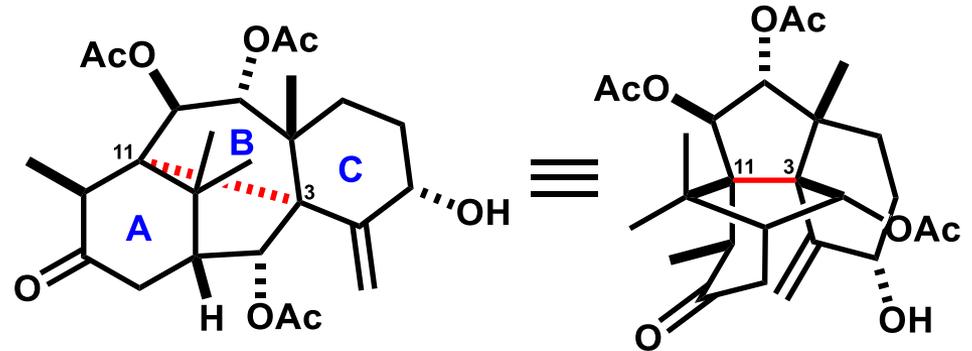
1. Introduction: Taxane Natural Products

Classical:

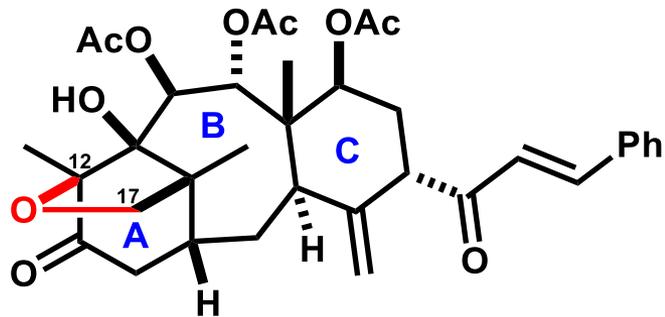


taxol (paclitaxel, 1)

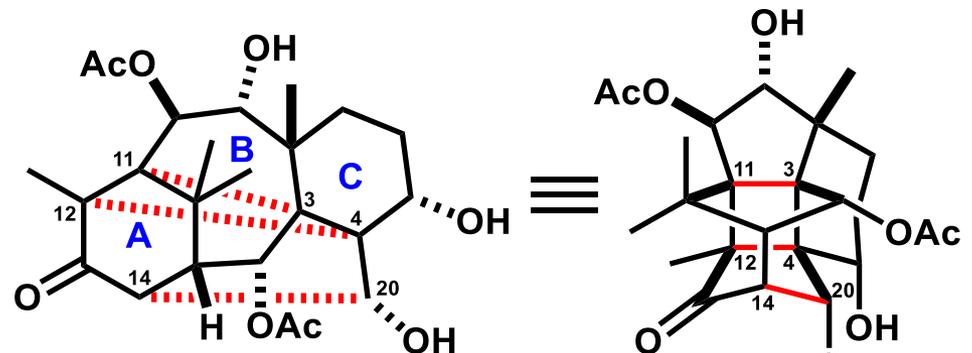
Nonclassical:



taxinine K (3)



taxagifine (2)



canataxpropellane (4)

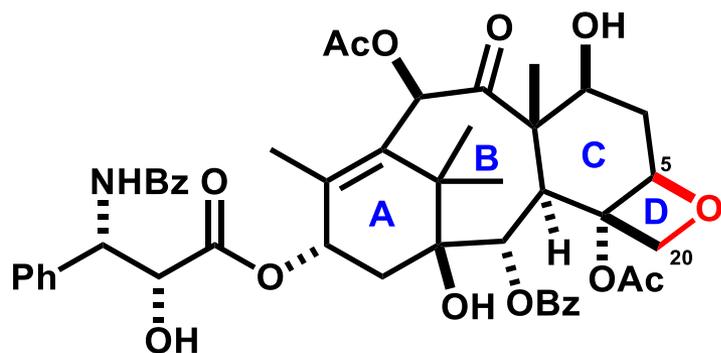
Isolation: genus *Taxus*

Biological activities:

taxol (1): anti-cancer (the most prominent anticancer drug)

canataxpropellane (4): unknown (due to inefficient sourcing from its natural producer)

1. Introduction: Taxane Natural Products



taxol (1)

Structural features:

- 6/8/6/4 (A/B/C/D) tetracyclic core
- bridgehead double bond
- oxetane ring (D-ring)
- 11 stereocenters, 9 on the core

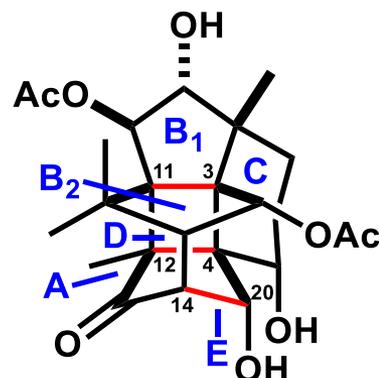
Total syntheses: (12 examples³⁻¹⁴)

- a) Holton, R. A. et al. *J. Am. Chem. Soc.* **1994**, *116*, 1597. b) Holton, R. A. et al. *J. Am. Chem. Soc.* **1994**, *116*, 1599.
- Nicolaou, K. C. et al. *Nature* **1994**, *367*, 630.
- Danishefsky, S. J. et al. *J. Am. Chem. Soc.* **1996**, *118*, 2843.

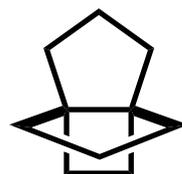
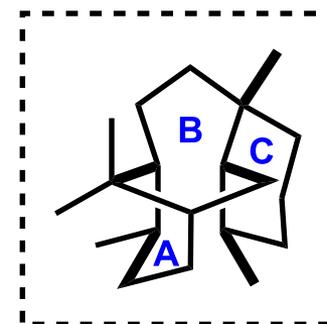
.....

- Hu, Y.-J. et al. *J. Am. Chem. Soc.* **2021**, *143*, 17862.
- Iiyama, S. et al. *Org. Lett.* **2022**, *24*, 202.

Also refer to: 201031_LS_Yusuke_Imamura



canataxpropellane (4)



[3.3.2]propellane



[4.4.2]propellane

Structural features:

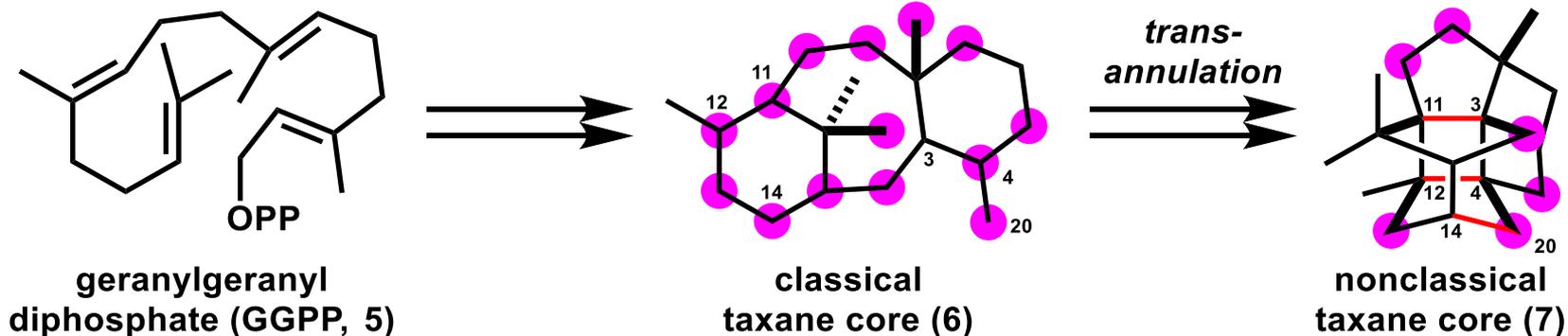
- 6/5/5/6/4/5 (A/B₁/B₂/C/D/E) hexacyclic core
- 2 highly strained propellane structures
- 12 contiguous stereocenters
- cyclobutane ring (D-ring) with all quaternary stereocenters

Total syntheses: (only 1 example¹) among the nonclassical taxane natural products)

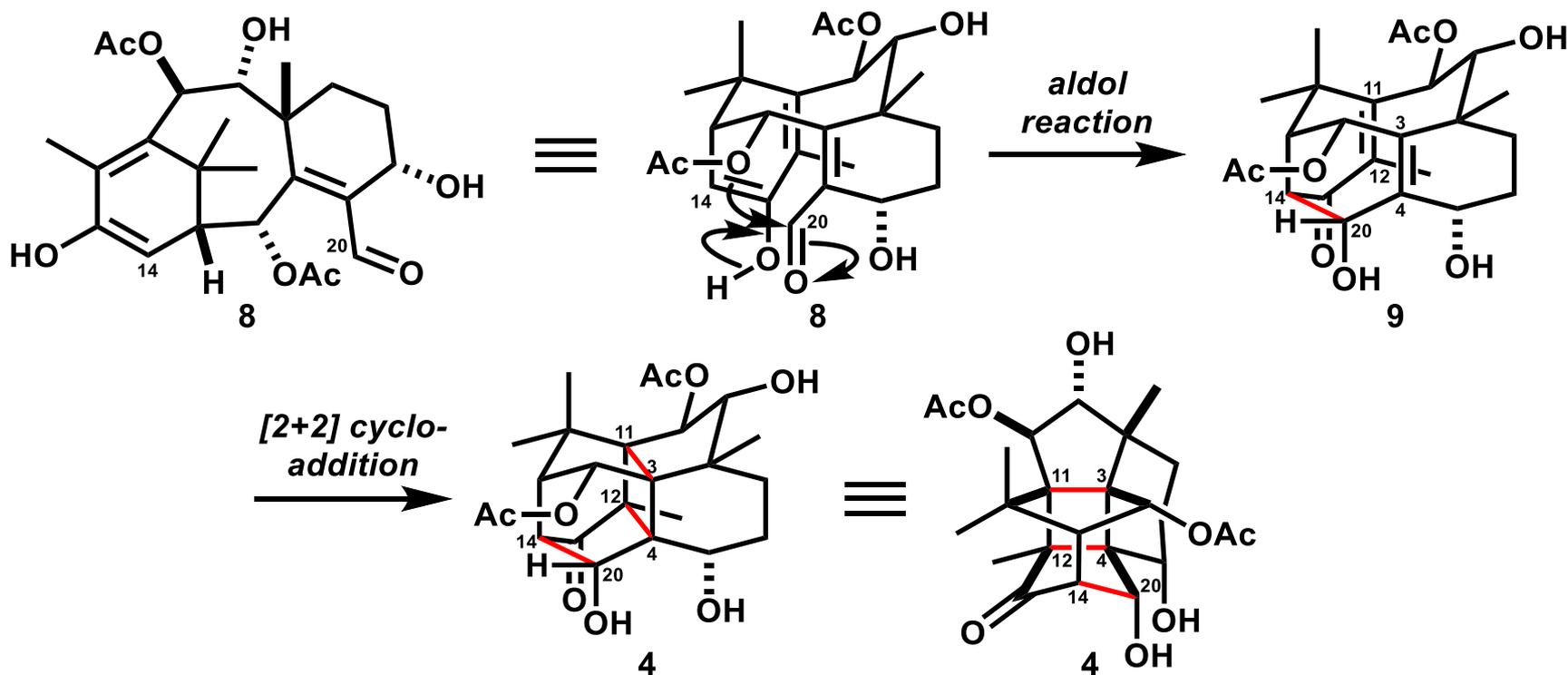
- Schneider, F. et al. *Science* **2020**, *367*, 676.

1. Introduction: Proposed Biosynthesis¹⁵⁾

● potential oxidations



Proposed biosynthesis of canataxpropellane (4):



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by Prof. Gaich's Group¹⁾**
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2. Introduction of Prof. Tanja Gaich



Education & Academic Career:

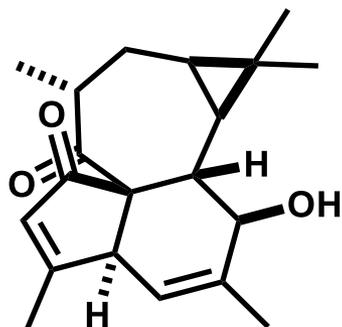
2005-2009: Ph.D. @ University of Vienna (Prof. J. Mulzer)

2009-2010: Postdoctoral Fellow @ Scripps Research Institute (Prof. P. S. Baran)

2010-2015: Independent Researcher @ Leibniz University Hannover (Prof. M. Kalesse)

2015-present: Full Professor @ University of Konstanz

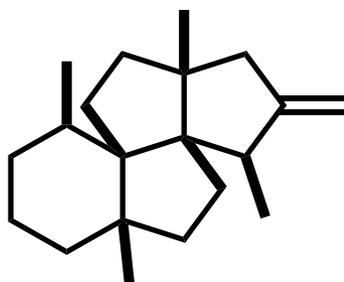
Research: Natural Product Synthesis and Synthetic Methodology



(+)-pepluanol A¹⁶

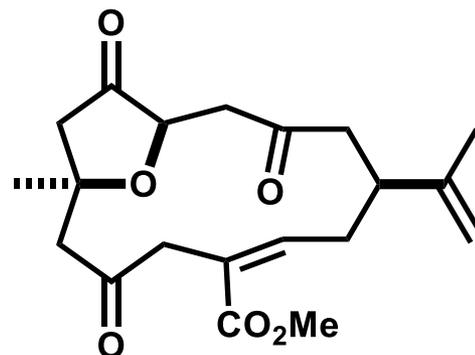
J. Am. Chem. Soc. **2021**,
143, 11934.

Org. Lett. **2022**, 24, 4717.



(+)-waihoensene¹⁷

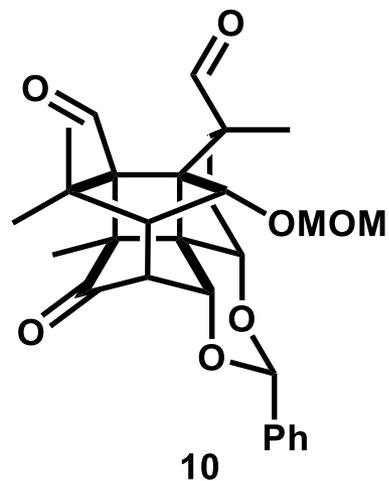
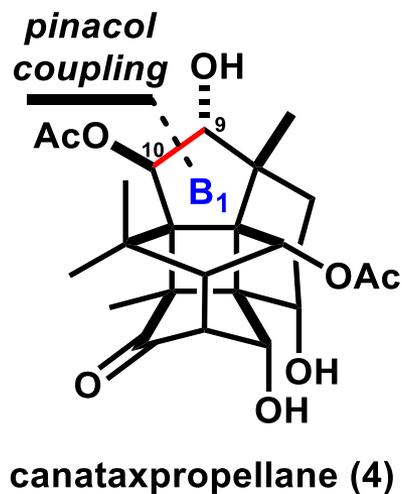
Angew. Chem. Int. Ed. **2020**,
60, 2939.



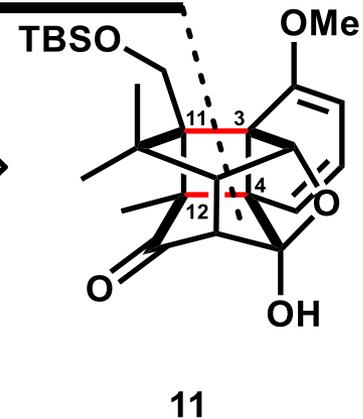
(+)-norcembrene¹⁸

Angew. Chem. Int. Ed. **2020**,
59, 5521.

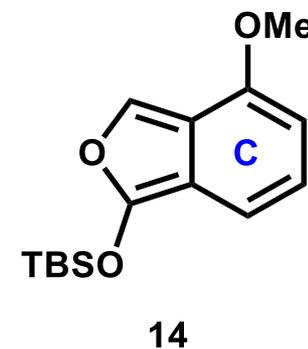
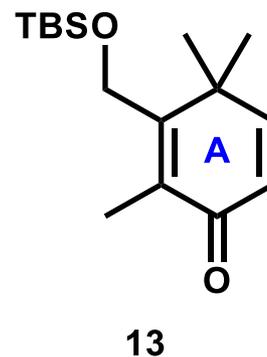
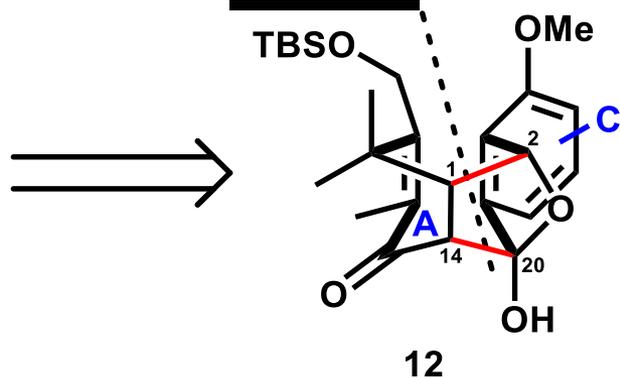
2. Retrosynthetic Analysis



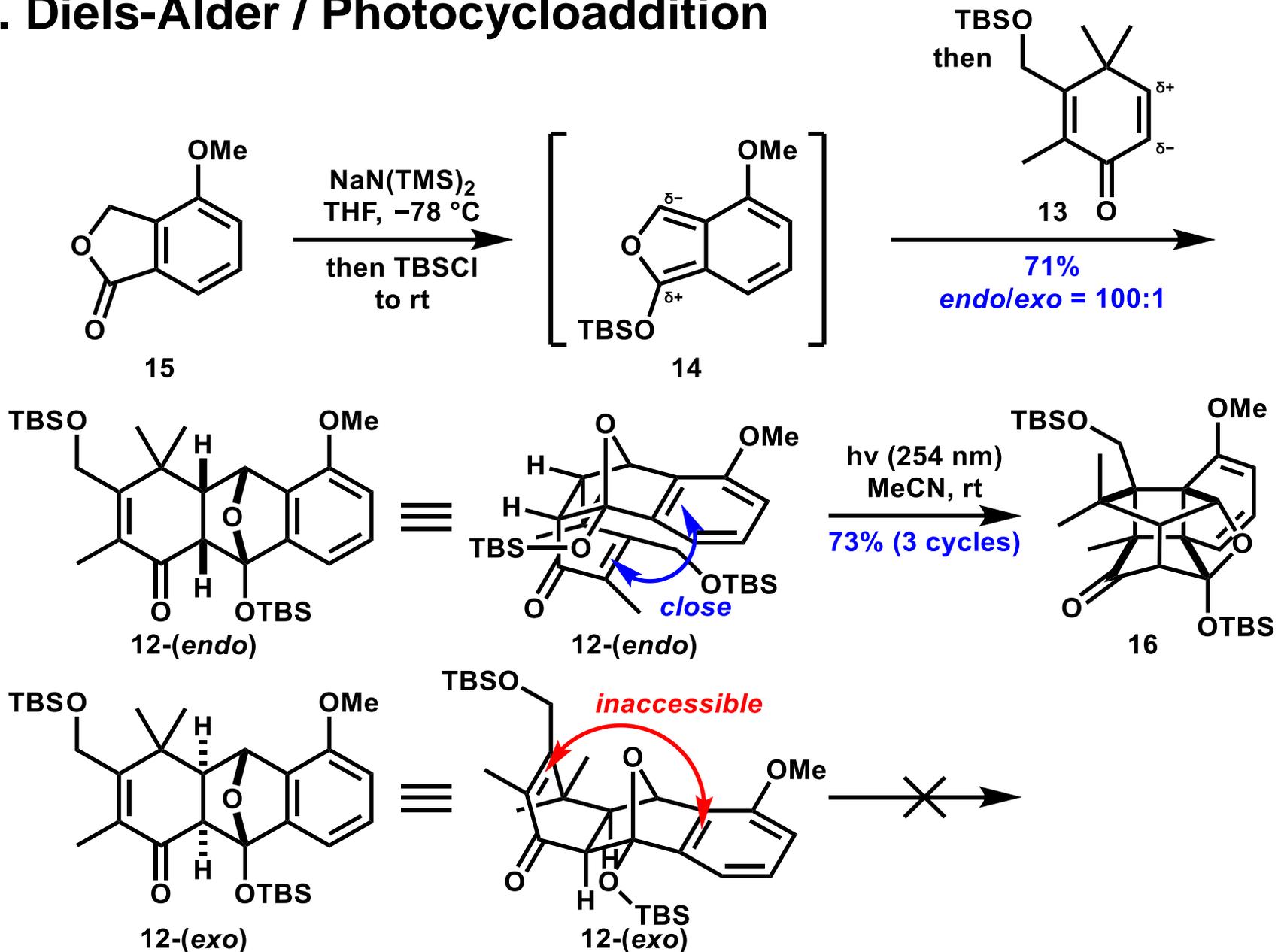
alkene-arene-ortho-photo-cycloaddition



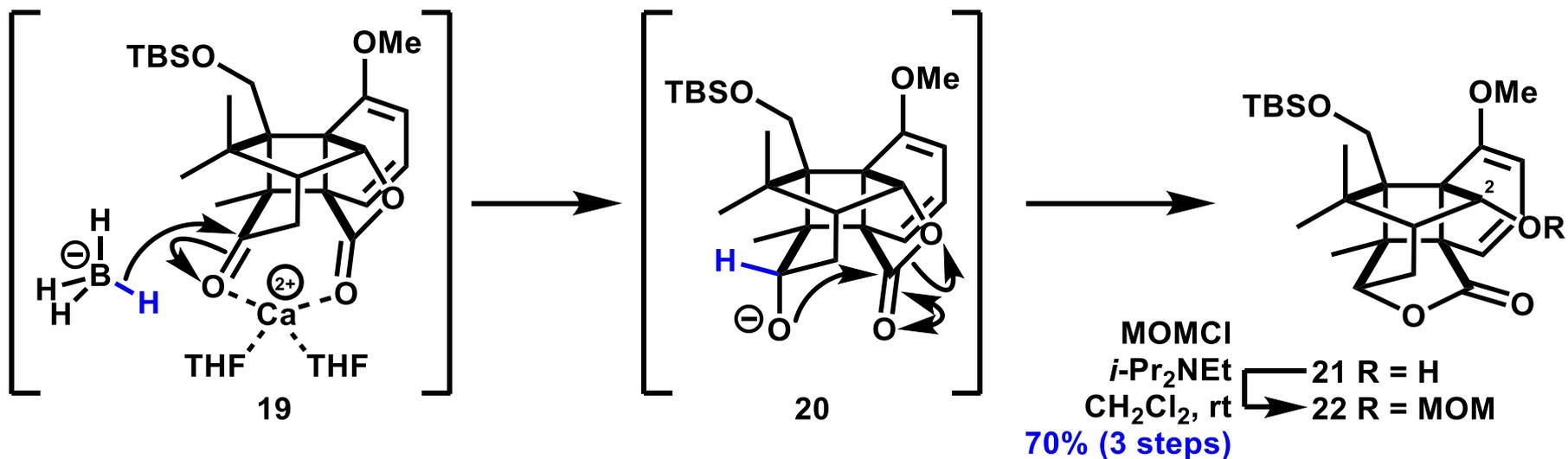
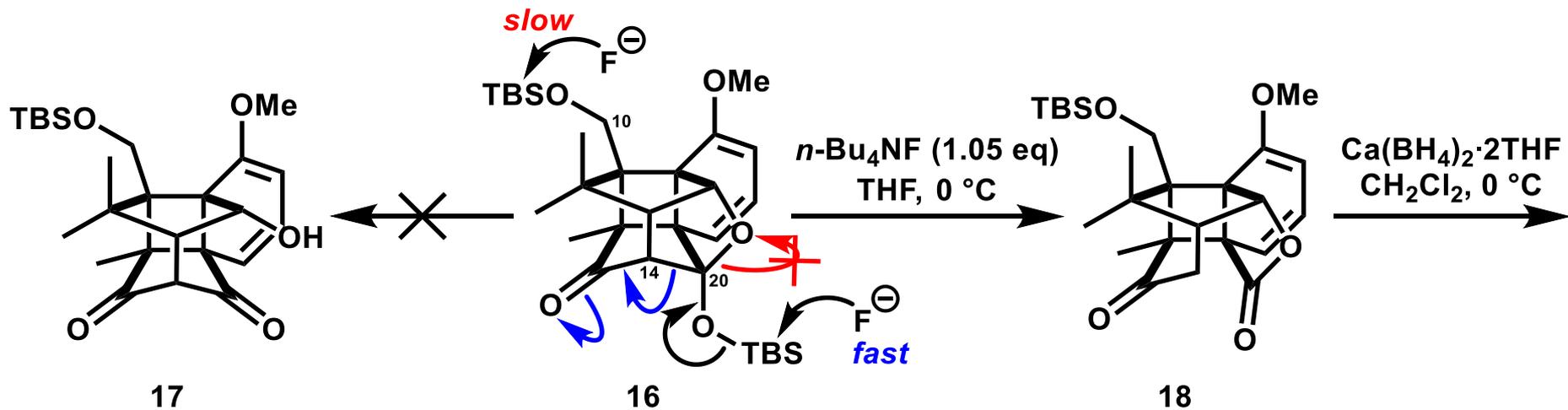
Diels-Alder reaction



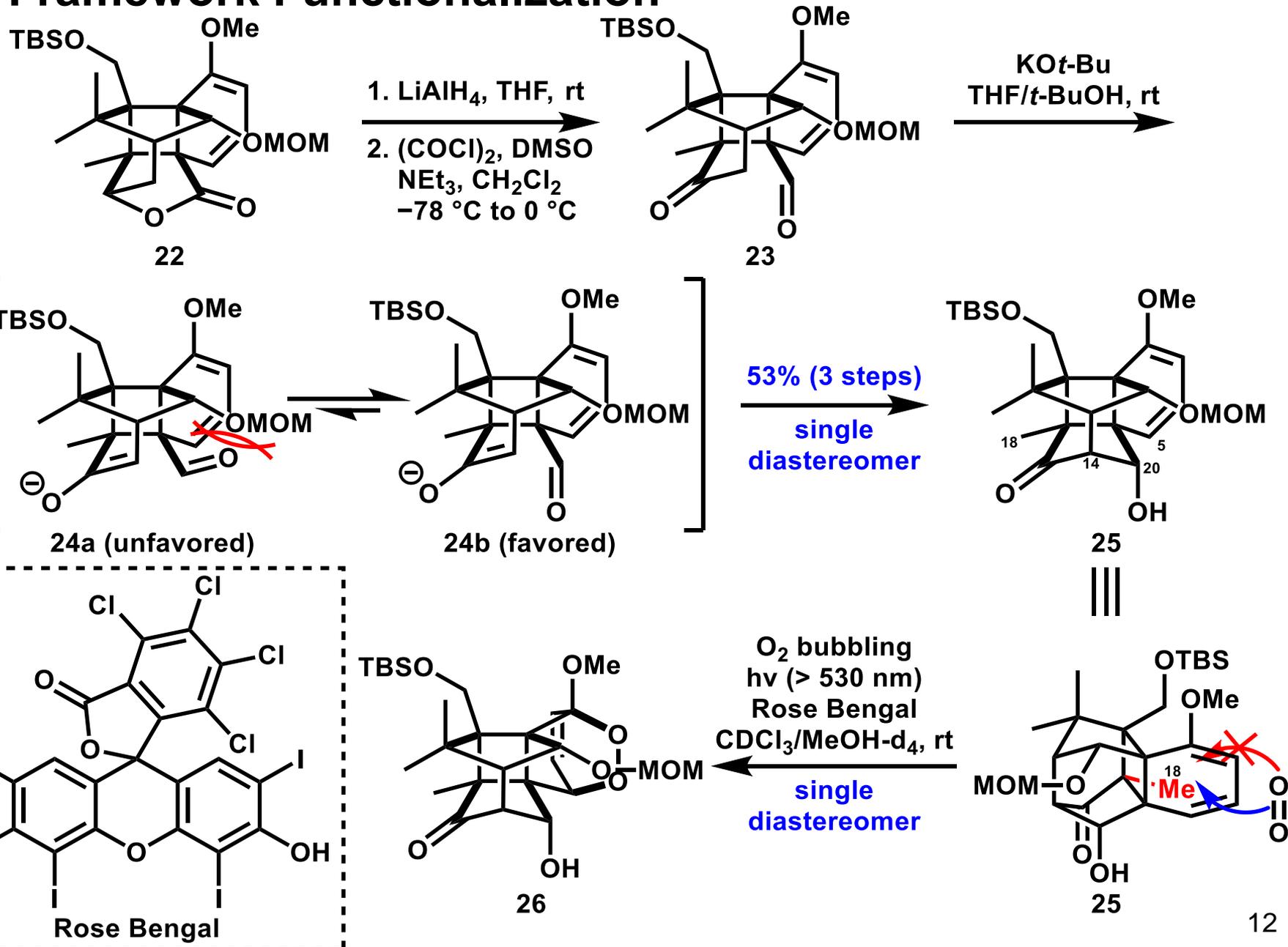
2. Diels-Alder / Photocycloaddition



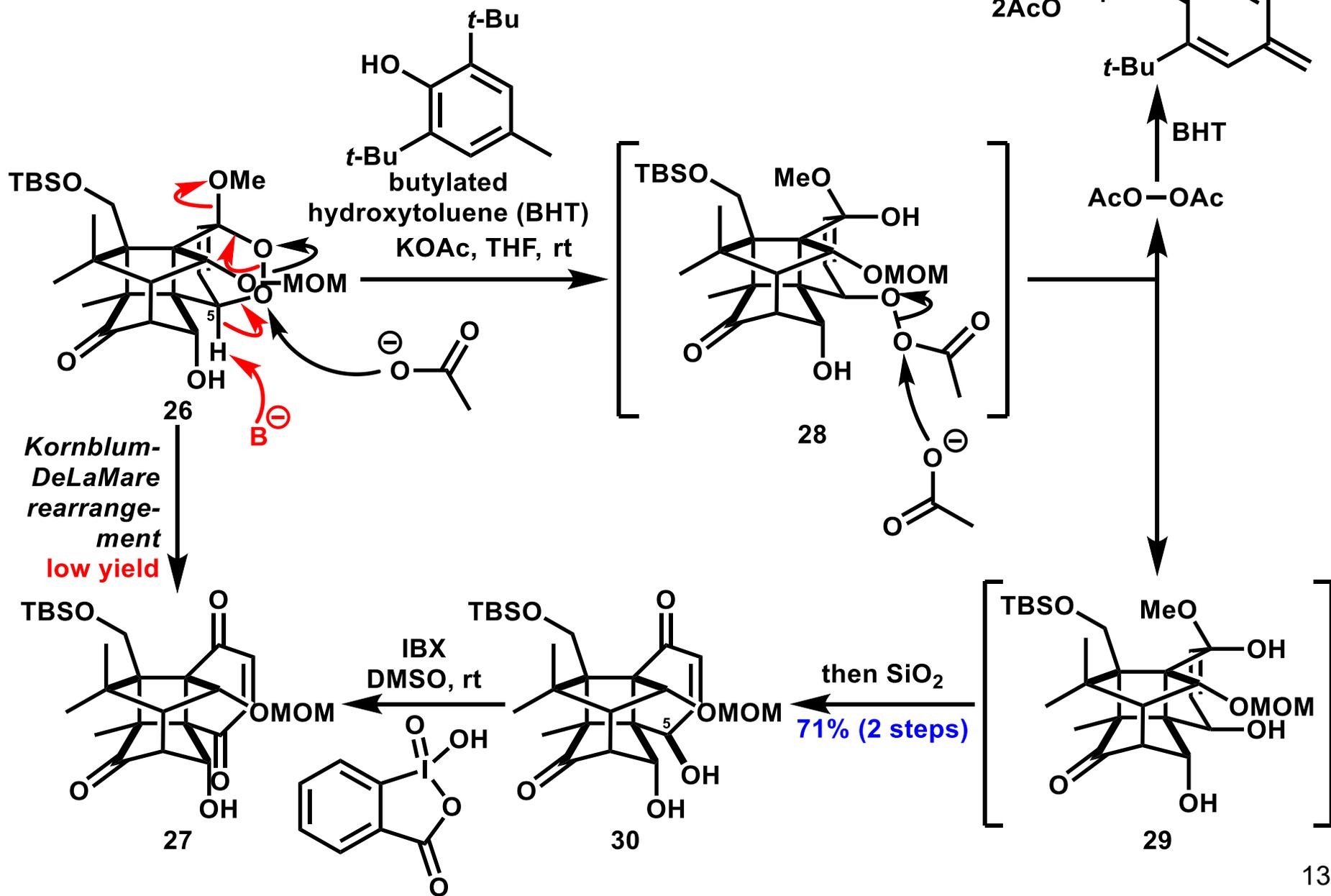
2. Framework Functionalization



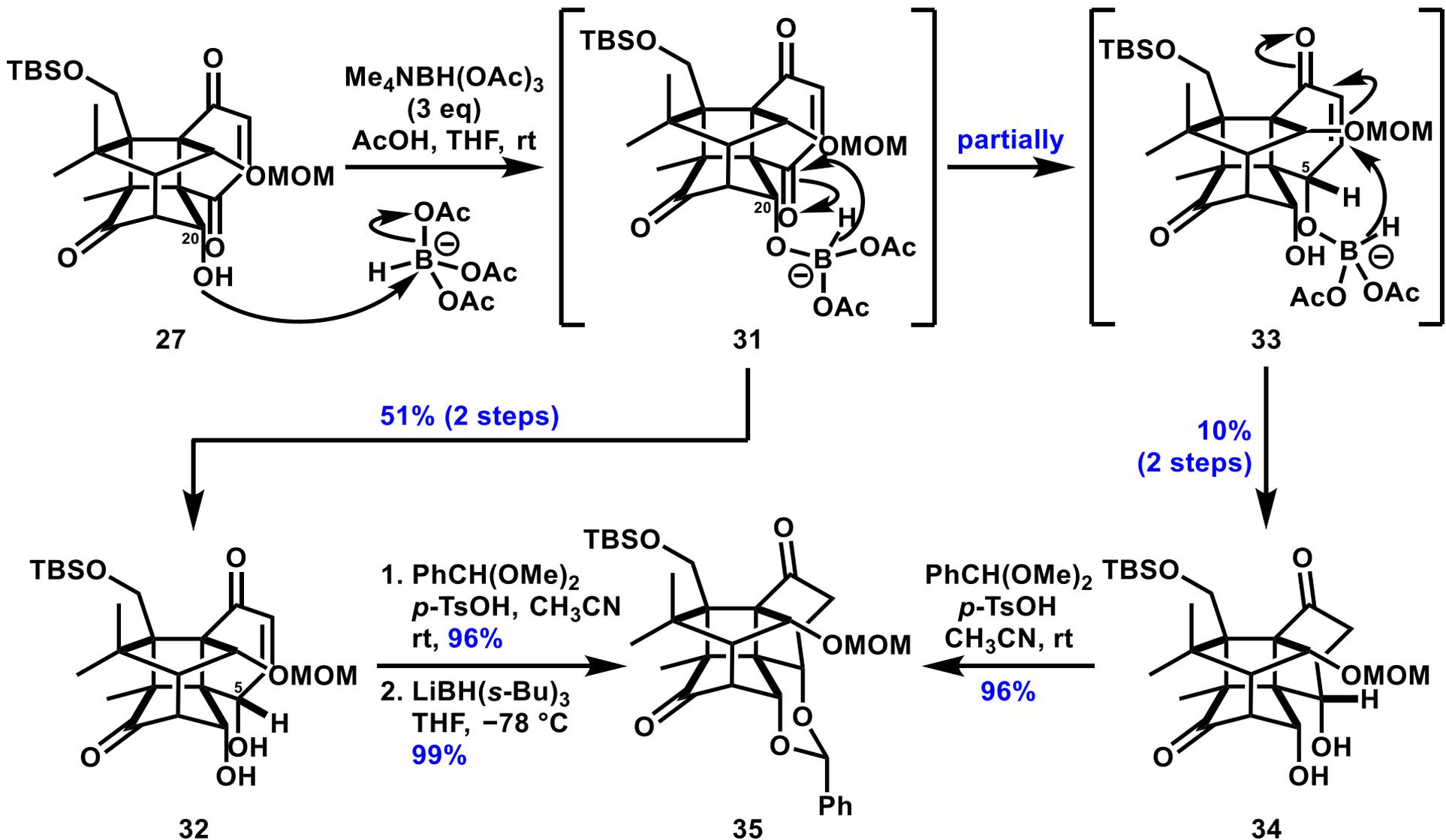
2. Framework Functionalization



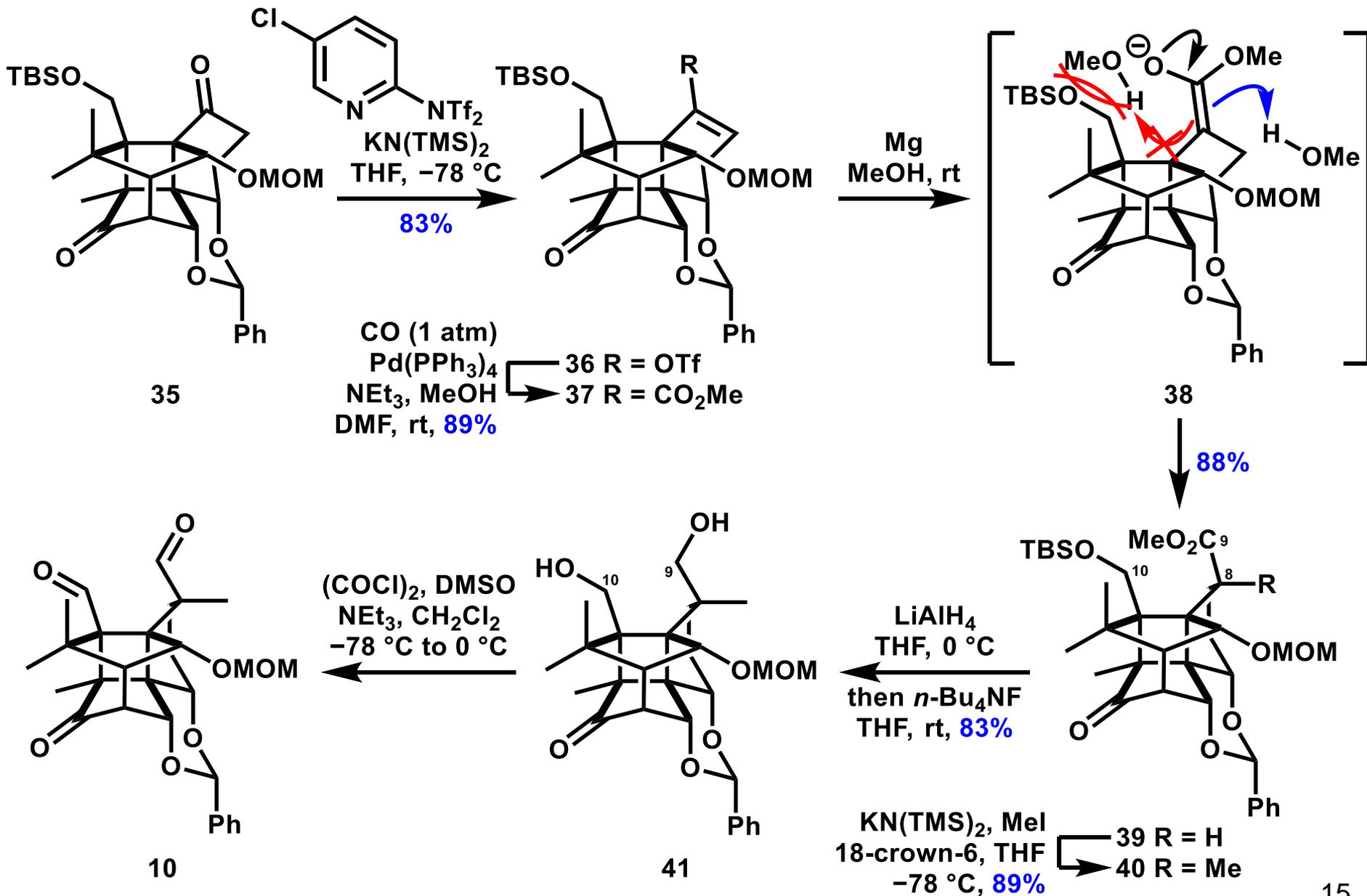
2. Framework Functionalization



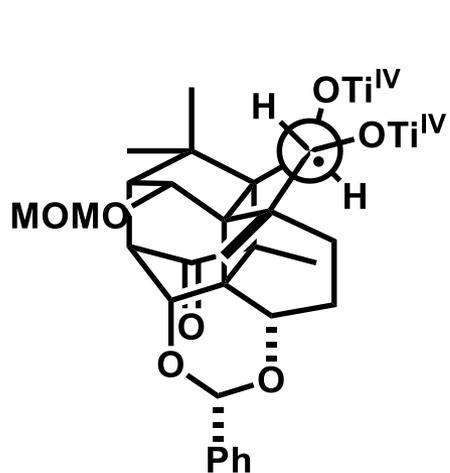
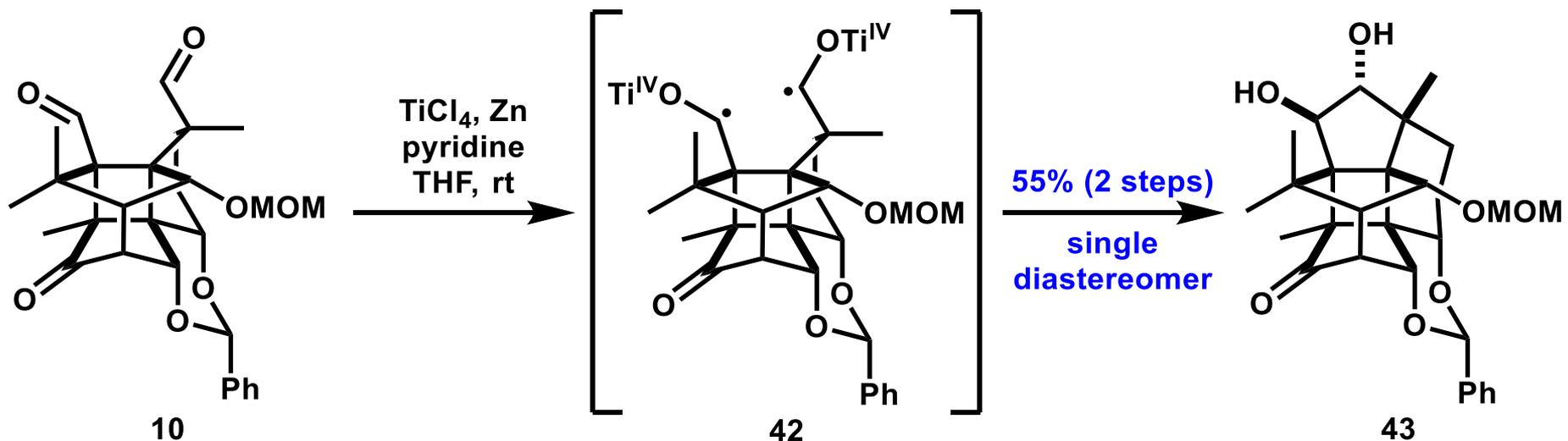
2. Framework Functionalization



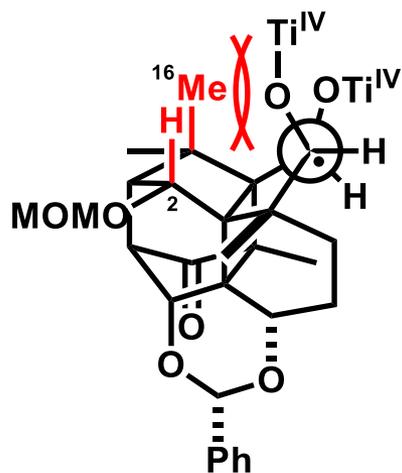
2. Framework Functionalization



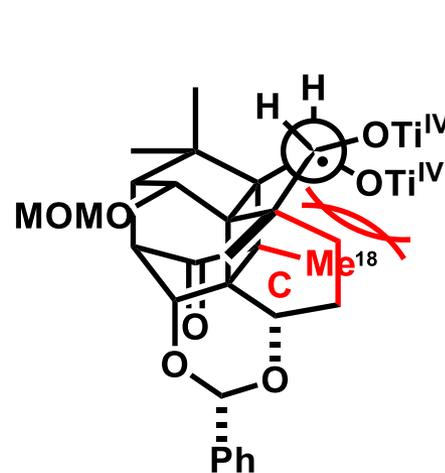
2. Pinacol Coupling



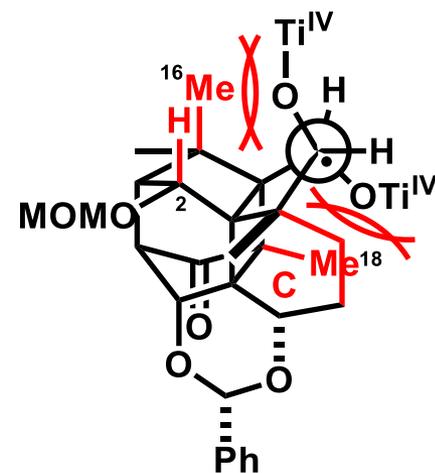
42a (favored)



42b (unfavored)

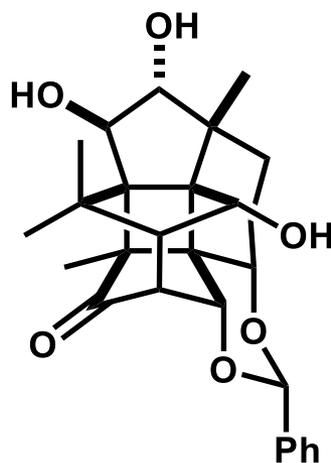
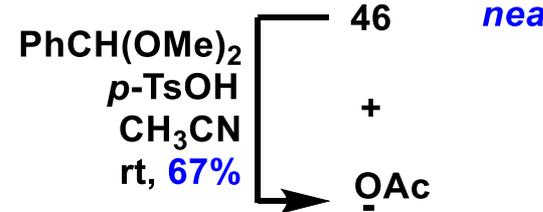
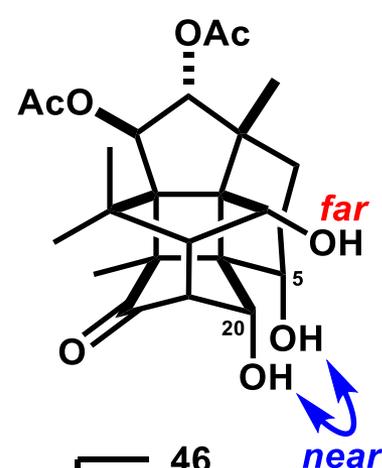
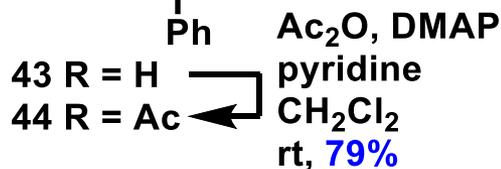
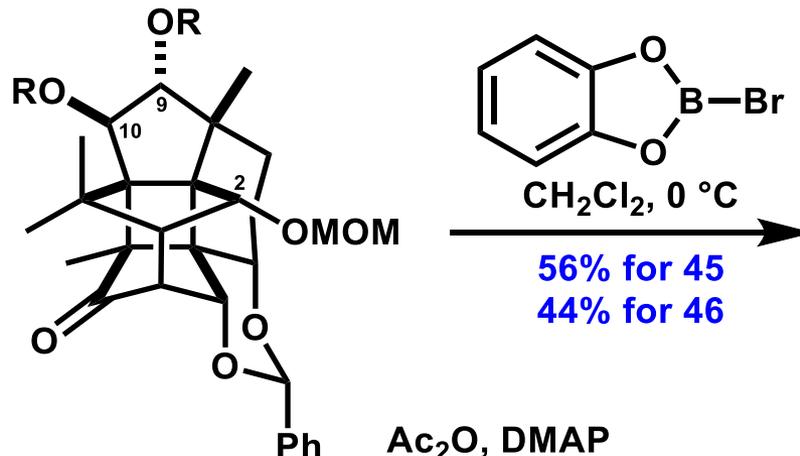
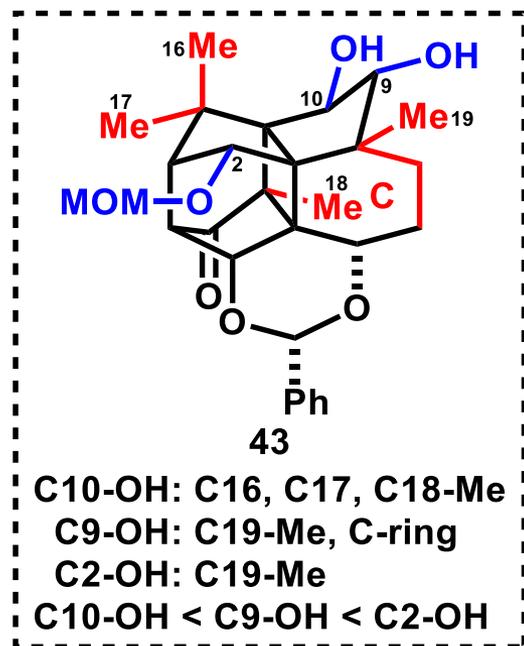


42c (unfavored)



42d (unfavored)

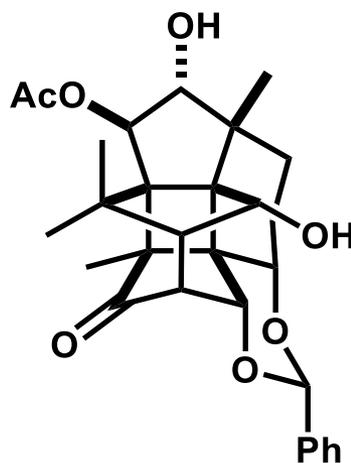
2. Completion of the Total Synthesis



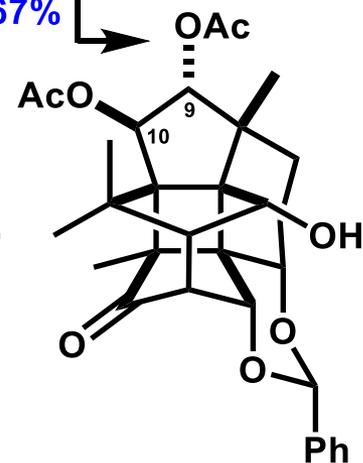
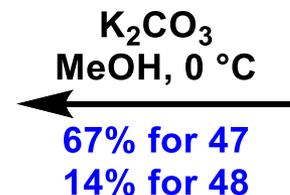
48

slowly decomposed
in MeOH-d₄

+

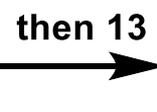
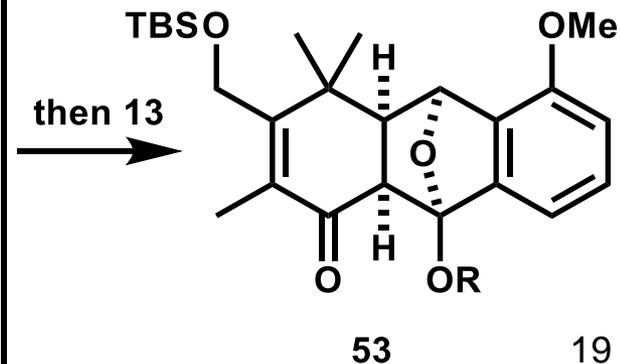
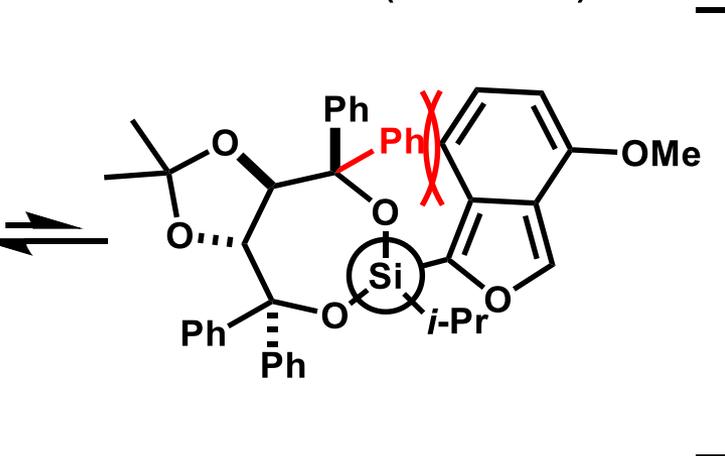
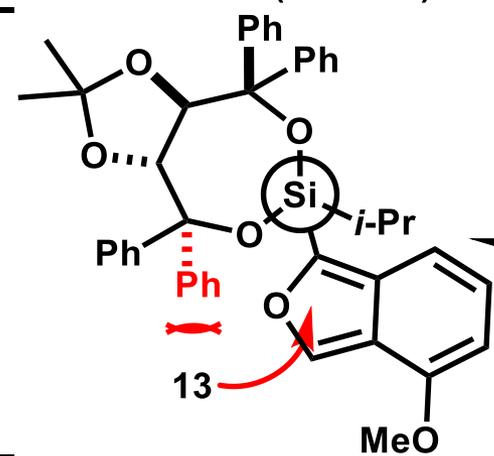
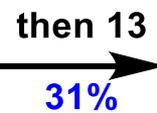
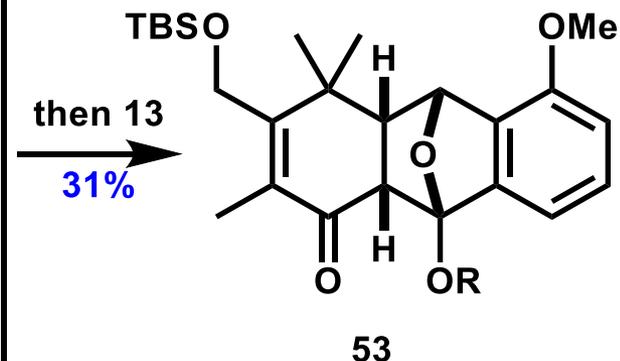
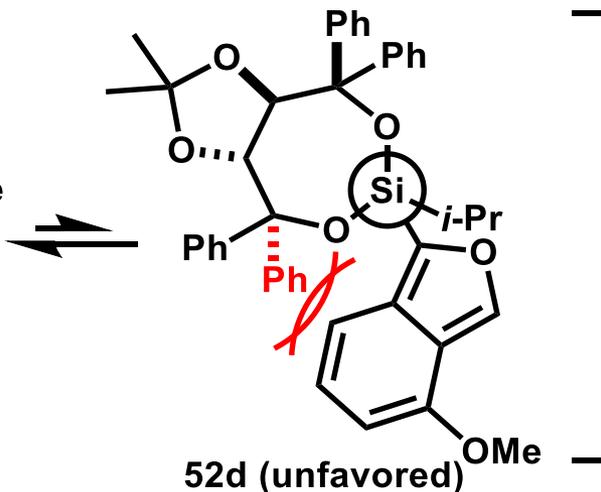
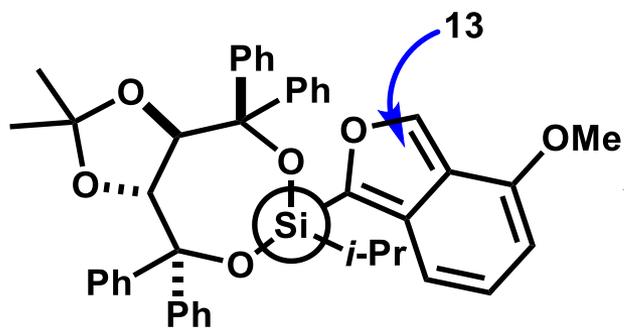
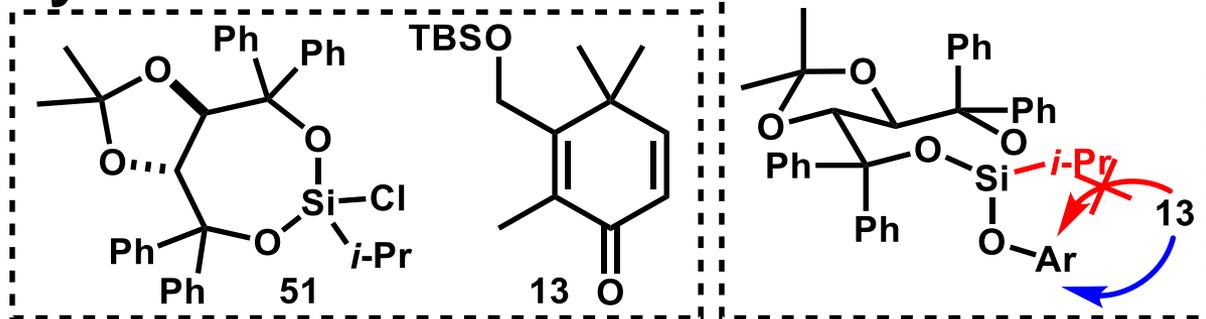
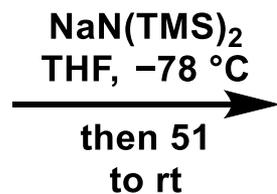
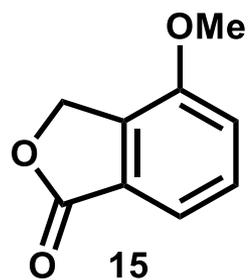


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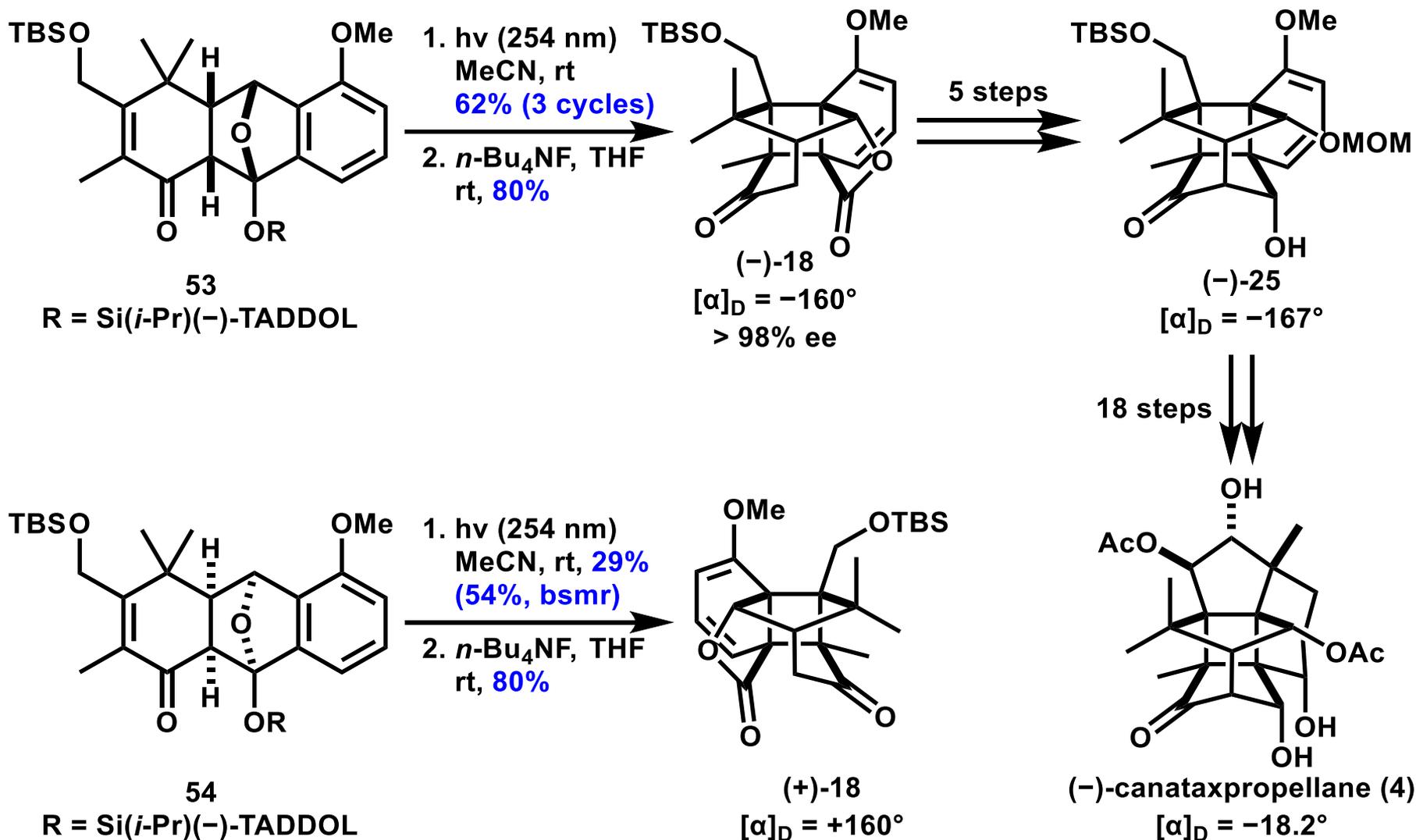
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2. Asymmetric Total Synthesis



53/54 = 1.5:1

2. Asymmetric Total Synthesis



Contents

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2. Total Synthesis of canataxpropellane by Prof. Gaich's Group¹⁾
- 3. Synthetic Approach to Diverse Taxane Cores by Prof. Sarpong's Group²⁾**
4. Summary

3. Introduction of Prof. Richmond Sarpong



Education & Academic Career:

1995: B.A. @ Macalester College (Prof. Rebecca C. Hoye)

2001: Ph.D. @ Princeton University (Prof. Martin F. Semmelhack)

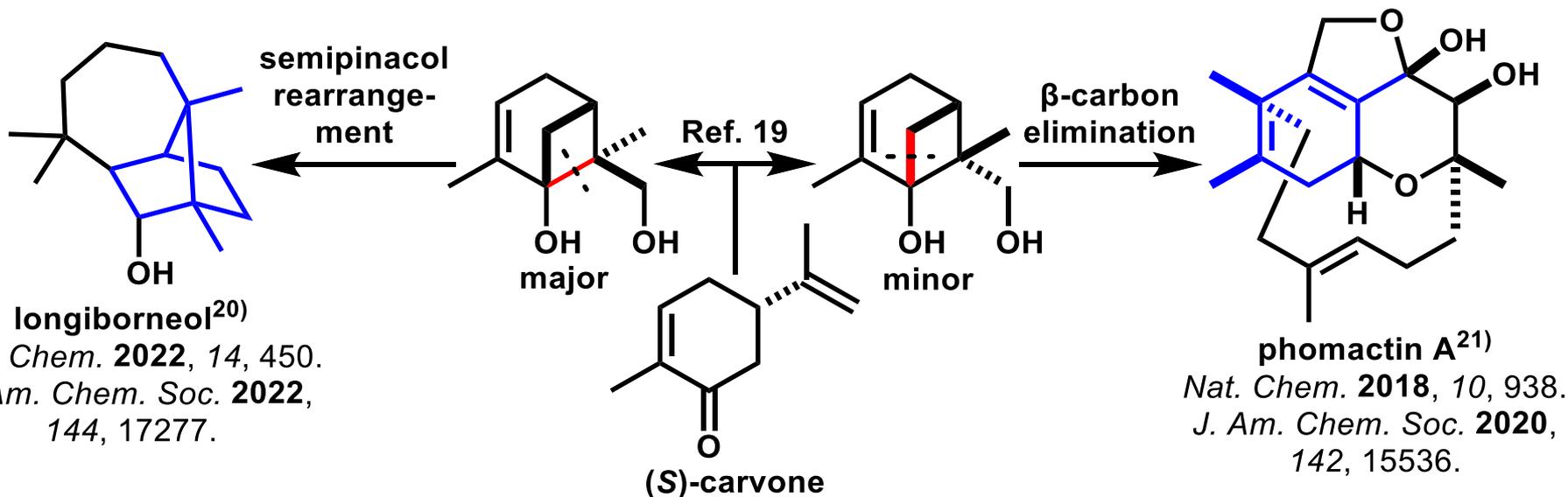
2001-2004: Postdoctoral Fellow @ California Institute of Technology (Prof. Brian M. Stoltz)

2004-2010: Assistant Professor @ University of California, Berkeley

2010-2014: Associate Professor @ S/A

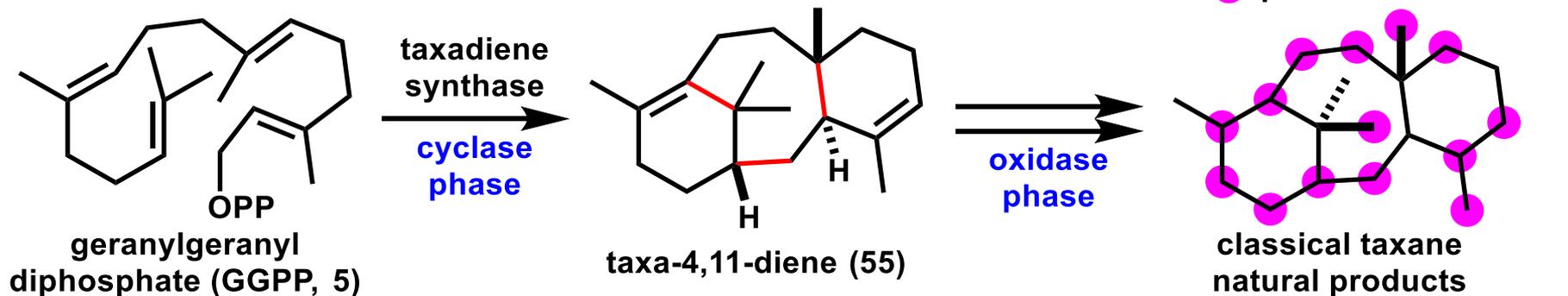
2014-present: Full Professor @ S/A

Research: Total Synthesis of Complex Molecules, Development of Synthetic Methods

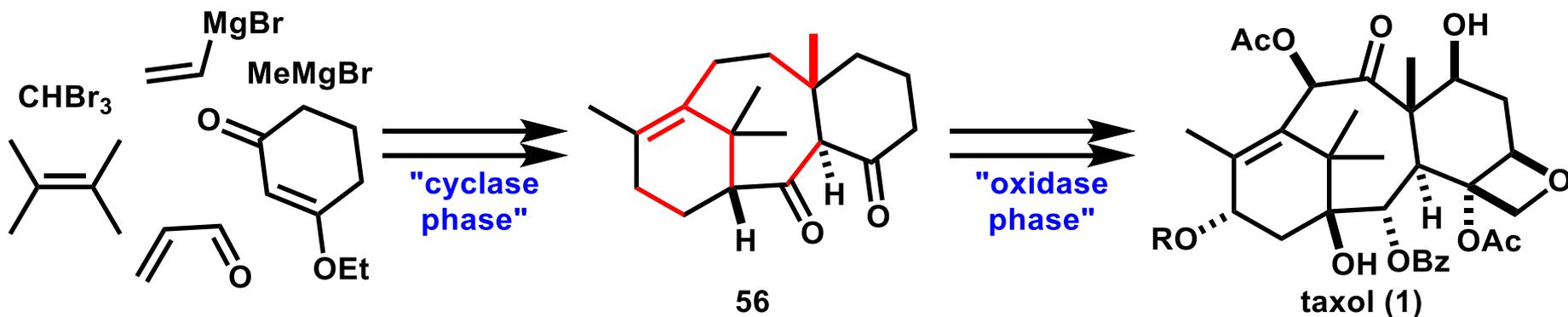


3. Background

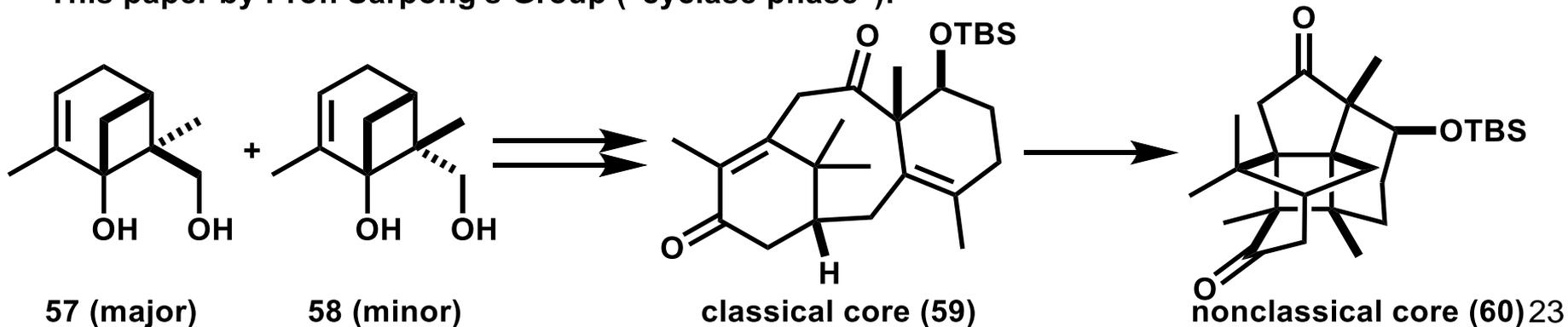
Proposed biosynthesis of classical taxane natural products¹⁵⁾:



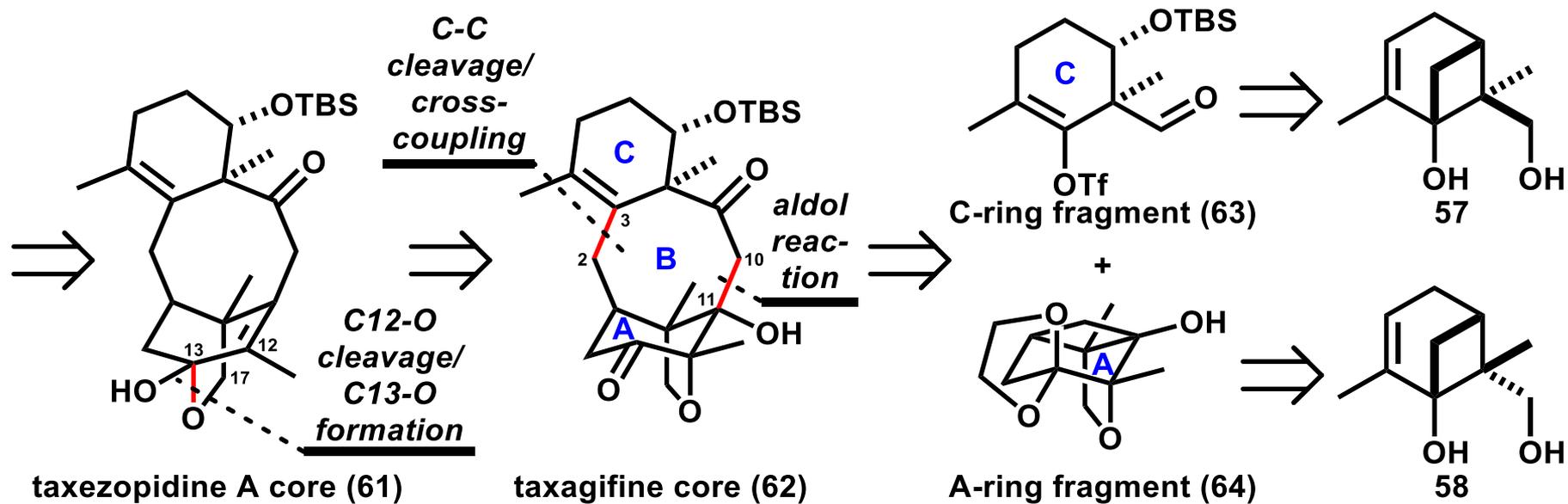
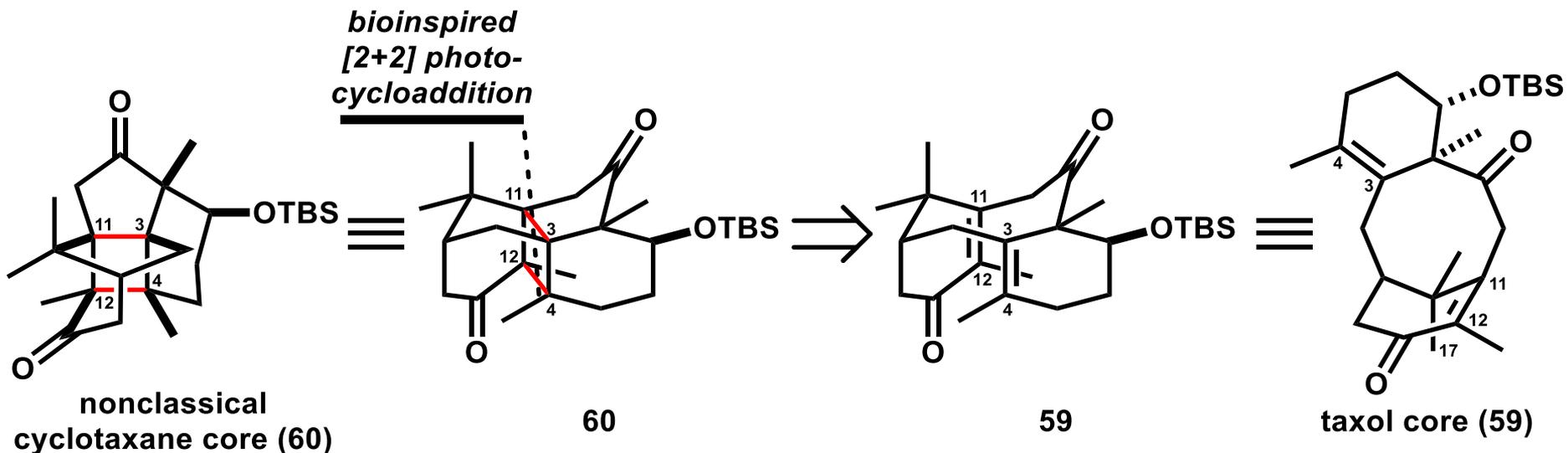
Two-phase synthesis of taxol (1) by Prof. Baran's Group¹²⁾:



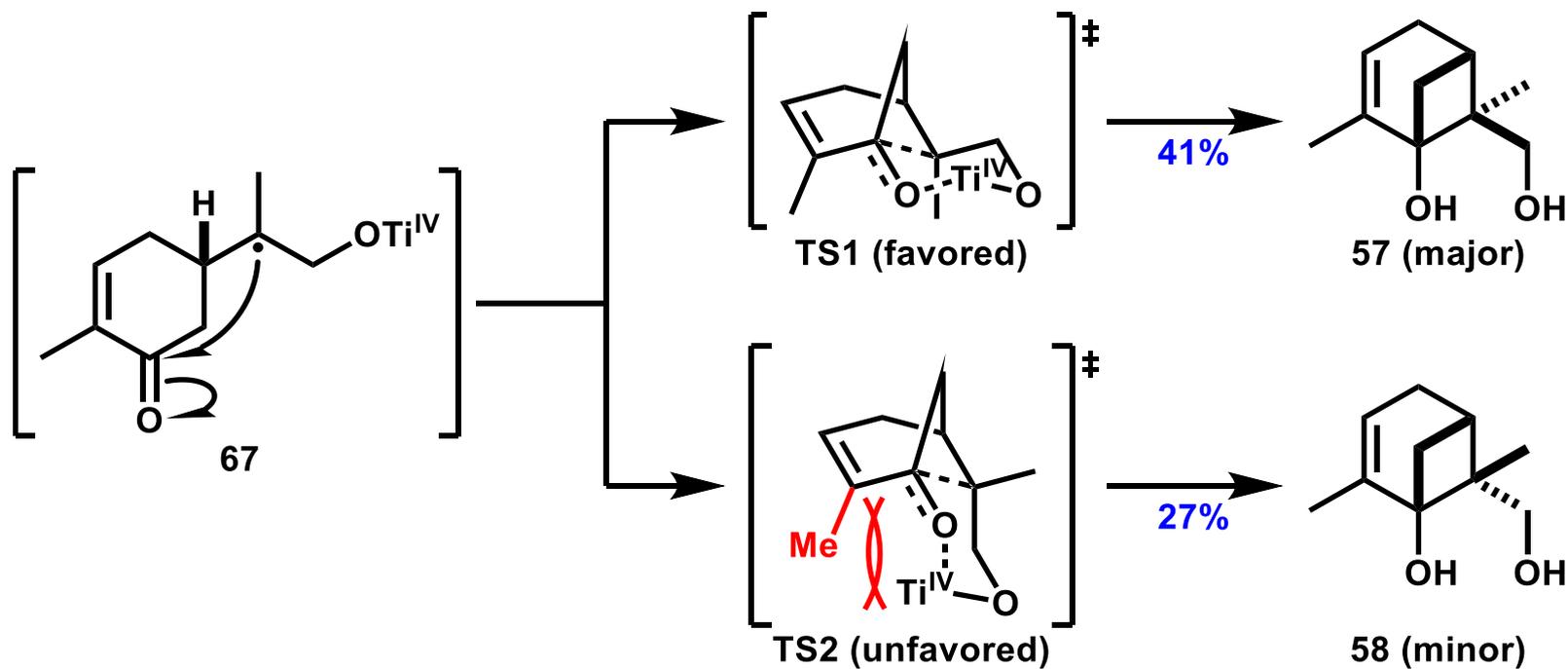
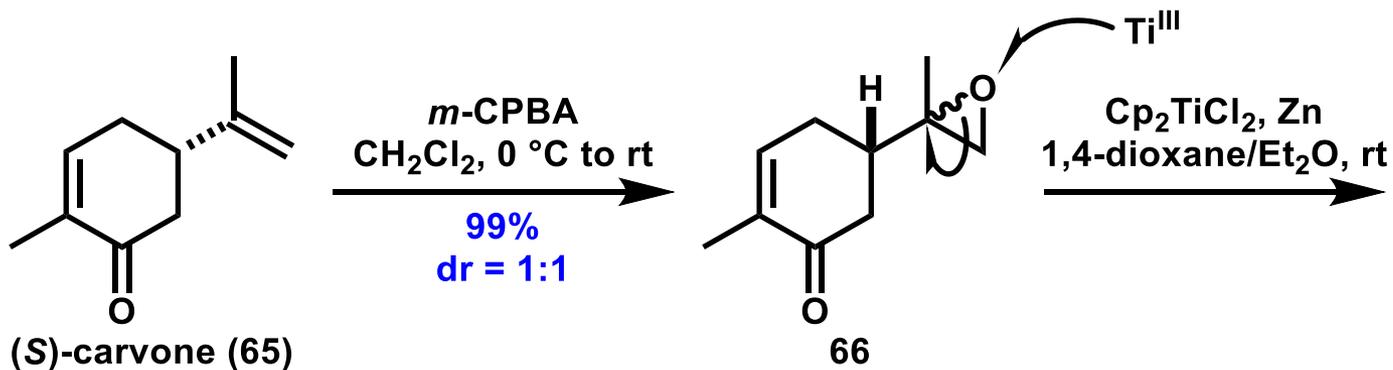
This paper by Prof. Sarpong's Group ("cyclase phase"):



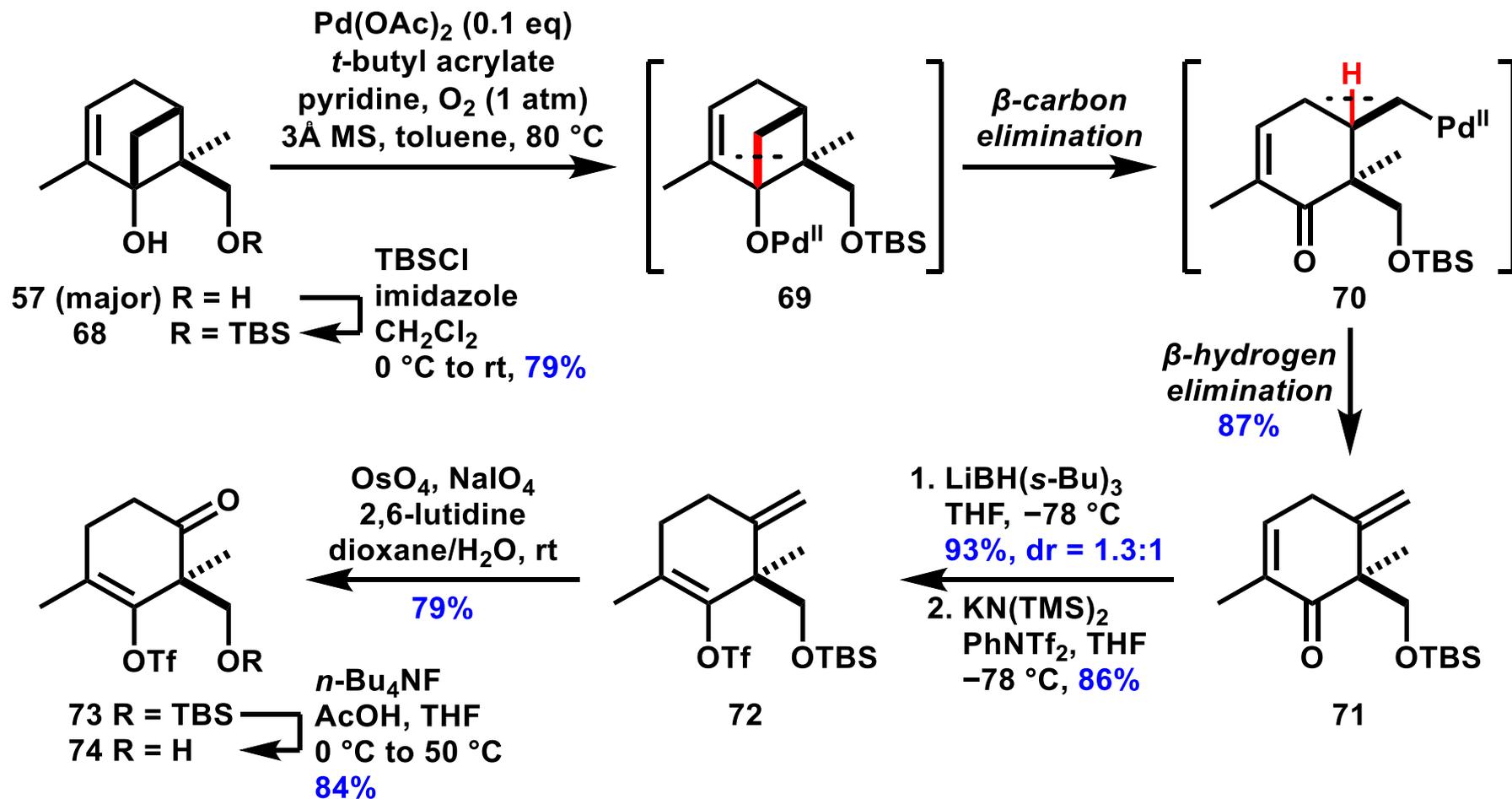
3. Retrosynthetic Analysis



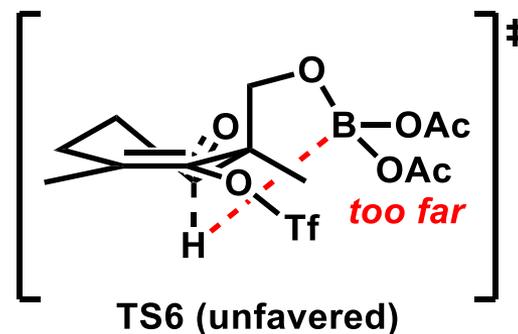
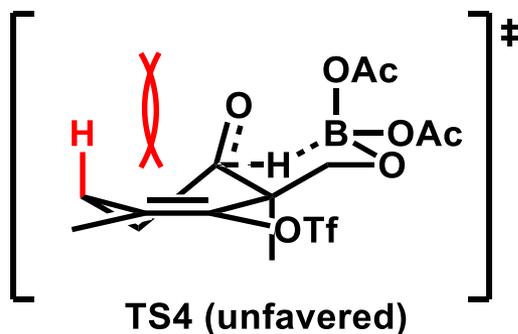
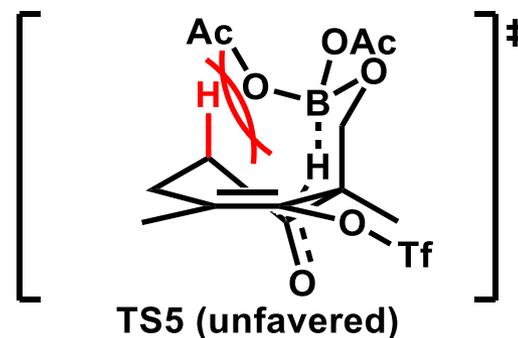
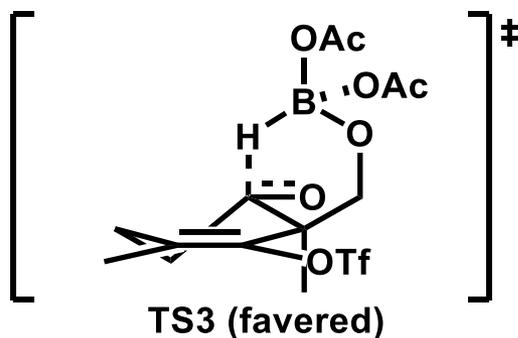
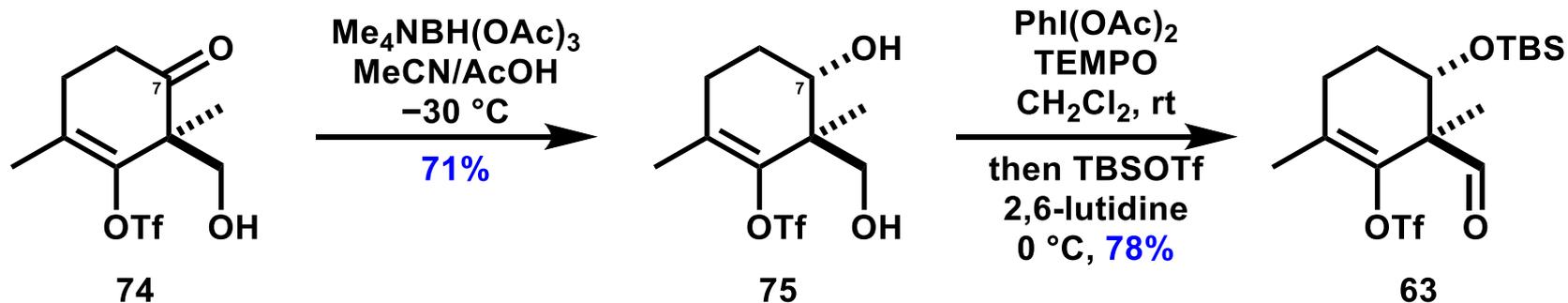
3. Preparation of Cyclobutanols



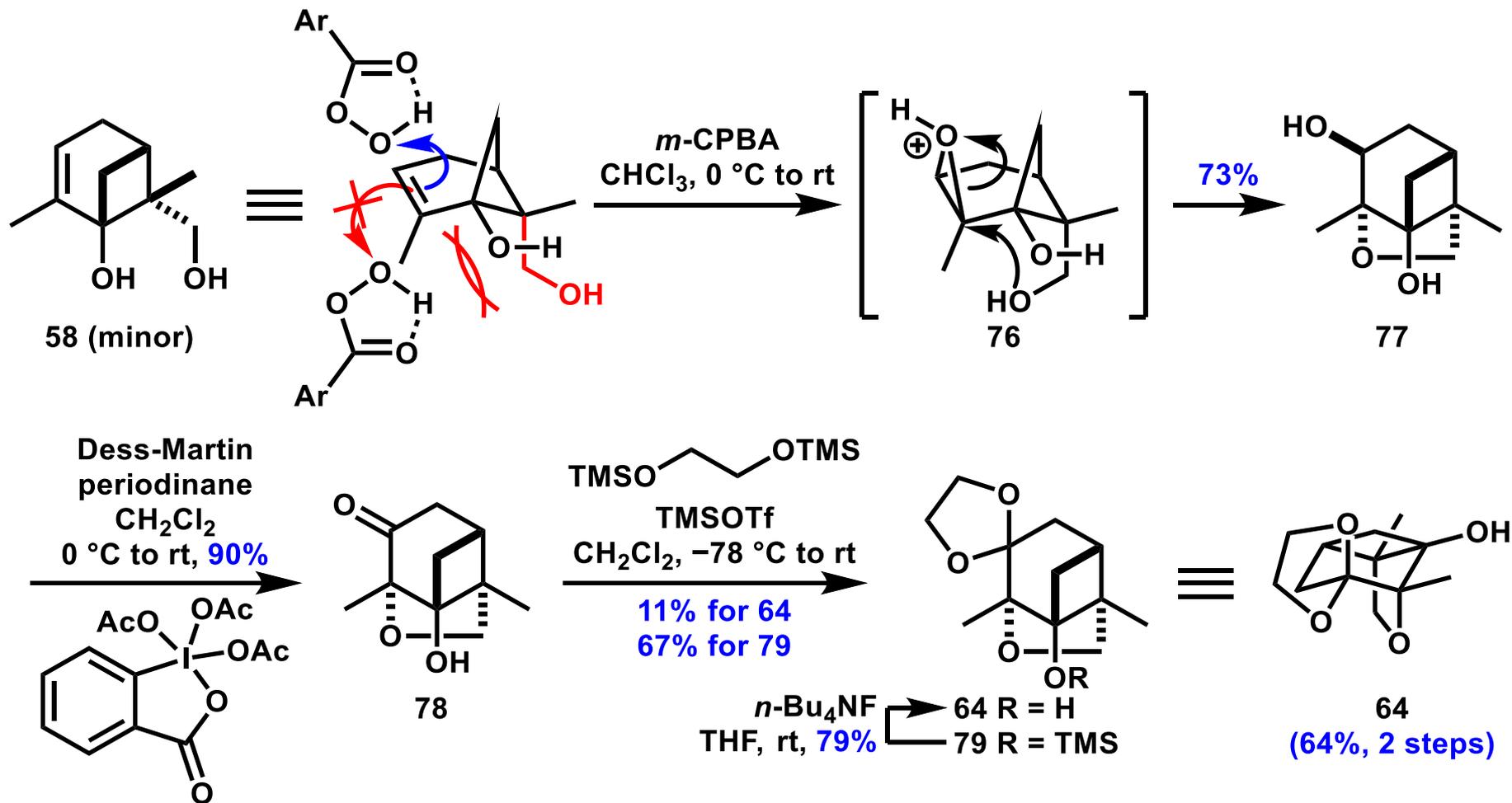
3. Synthesis of C-Ring Fragment



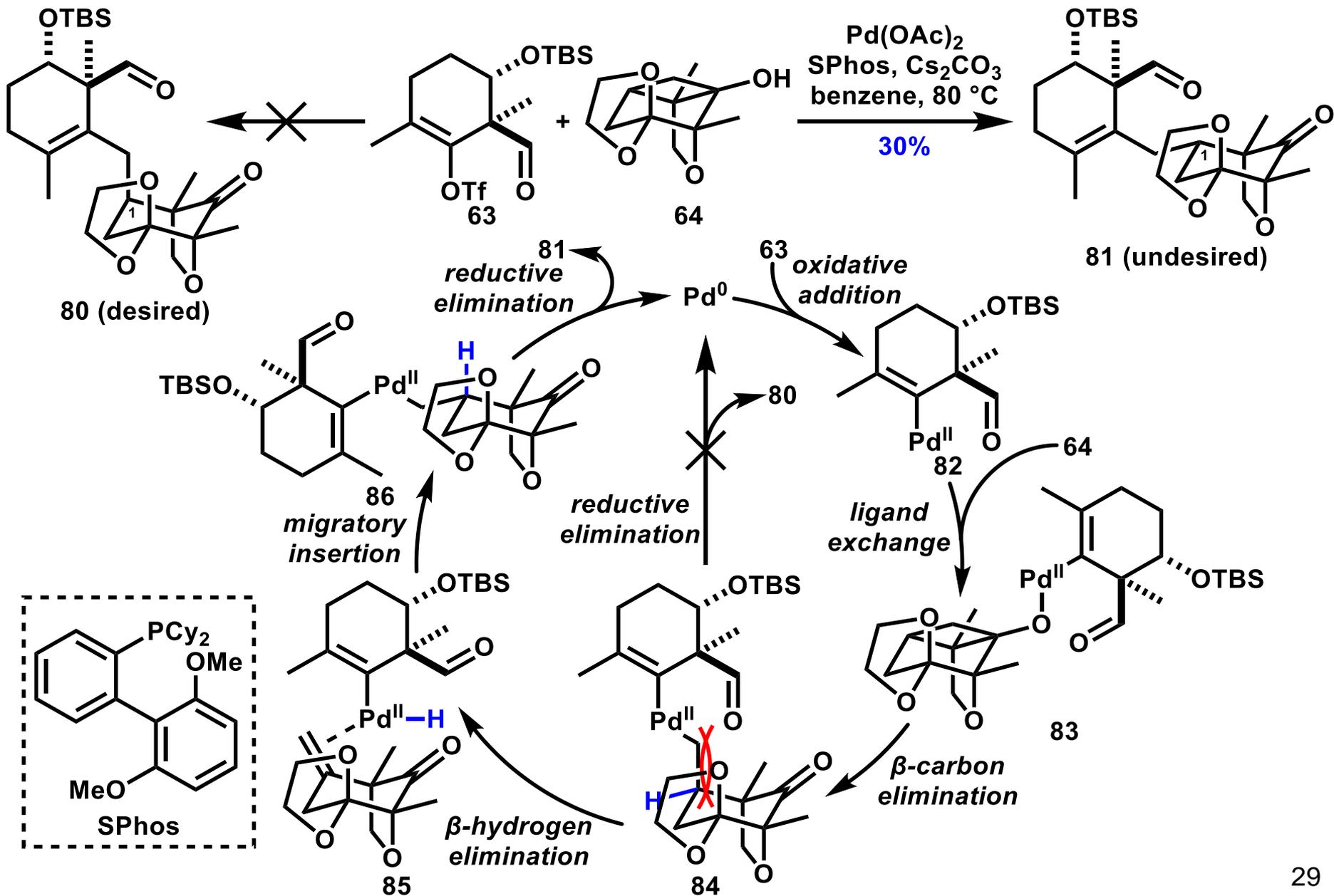
3. Synthesis of C-Ring Fragment



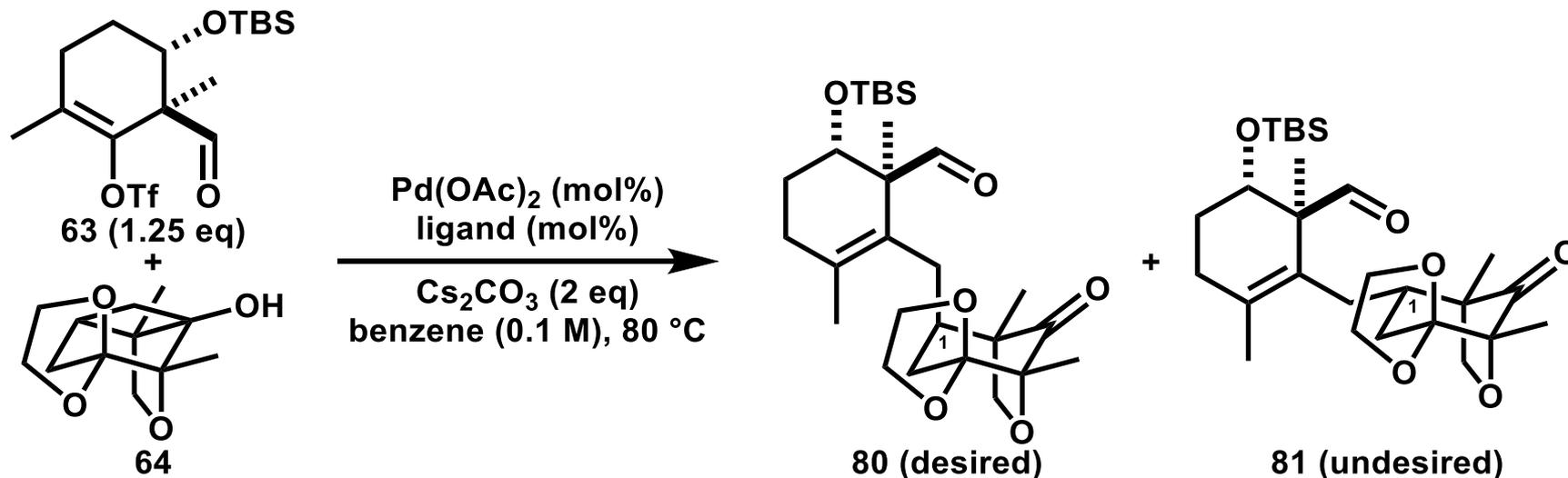
3. Synthesis of A-Ring Fragment



3. C-C Bond Cleavage/Cross-Coupling

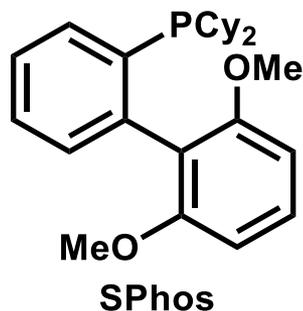


3. C-C Bond Cleavage/Cross-Coupling

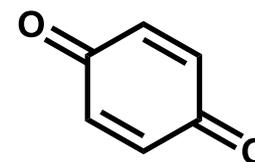
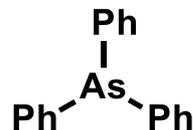


entry	Pd mol%	ligand (mol%)	additive (mol%)	80	81	dr
1 ^a	10%	SPhos (20%)	none	0%	30%	0:100
2 ^a	10%	AsPh ₃ (20%)	none	8%	21%	27:73
3 ^a	20%	AsPh ₃ (50%)	none	20%	45%	31:69
4 ^a	20%	AsPh ₃ (50%)	1,4-benzoquinone (20%)	67%	5%	94:6
5 ^b	20%	AsPh ₃ (50%)	1,4-benzoquinone (20%)	(68%) ^c	/	/

a) ca. 0.02 mmol scale, 21 h; b) 2.9 mmol scale, 27 h; c) Isolated yield.

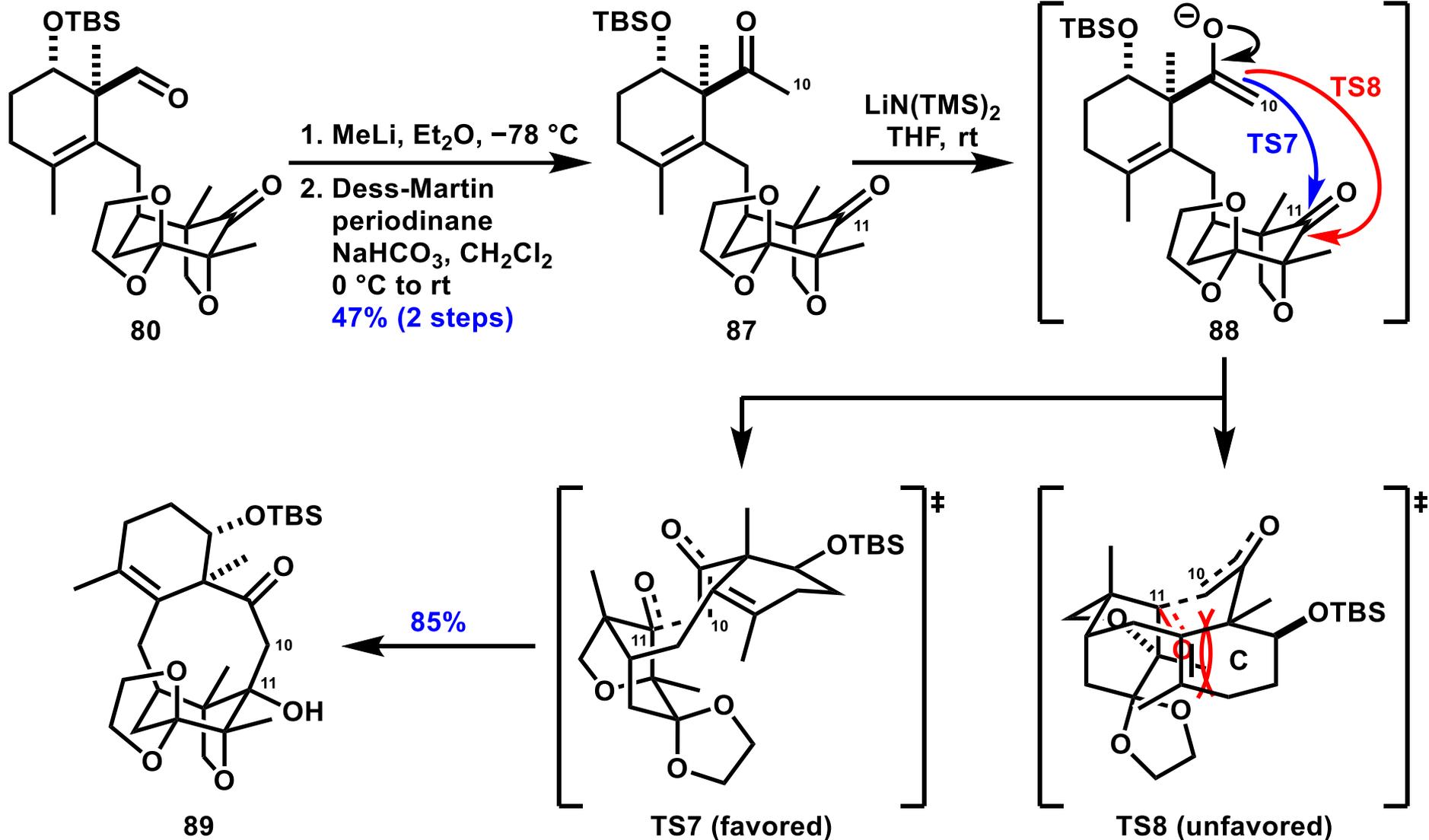


sigma donor
ability
>

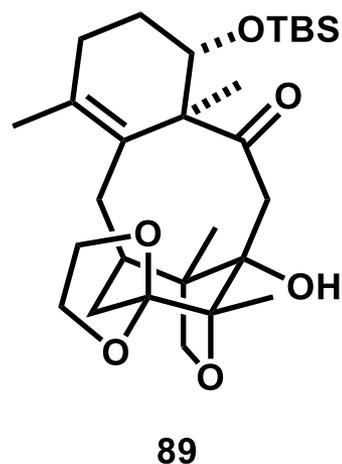


1,4-benzoquinone
(electron-deficient)

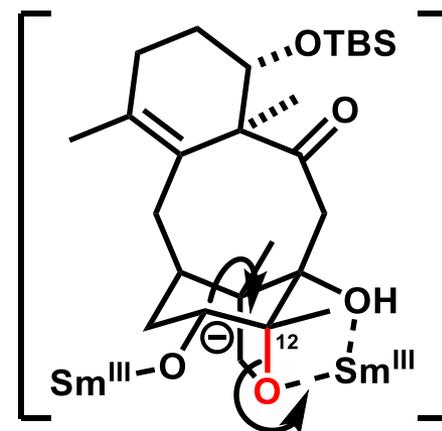
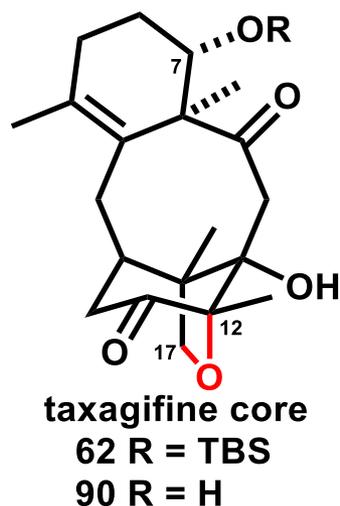
3. Synthesis of Diverse Taxane Cores



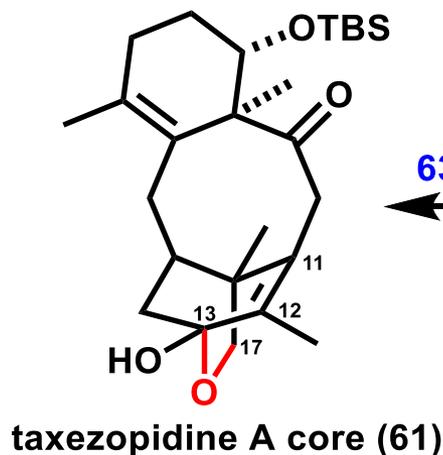
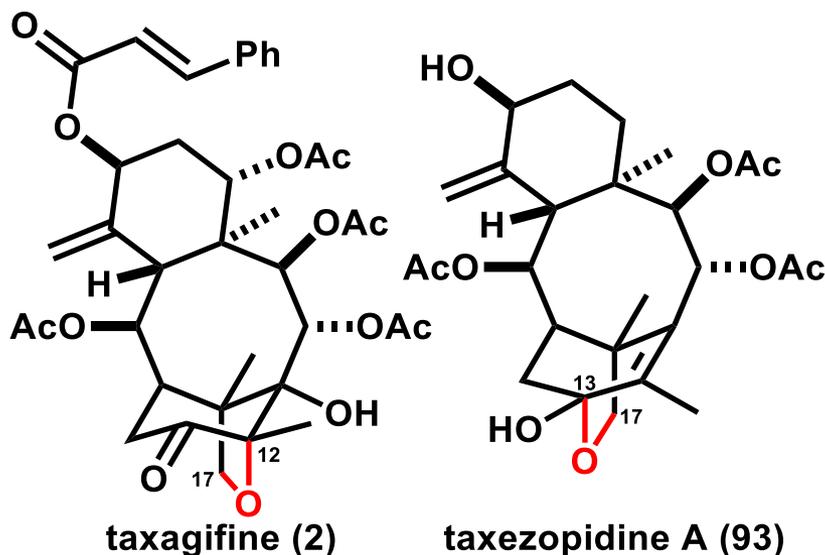
3. Synthesis of Diverse Taxane Cores



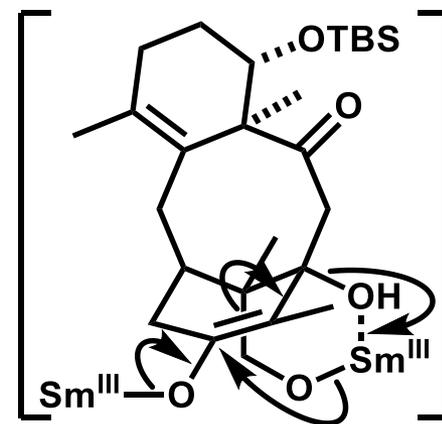
1 d, 33% for 62
65% for 89
3 d, 48% for 62
14% for 90
12% for 89



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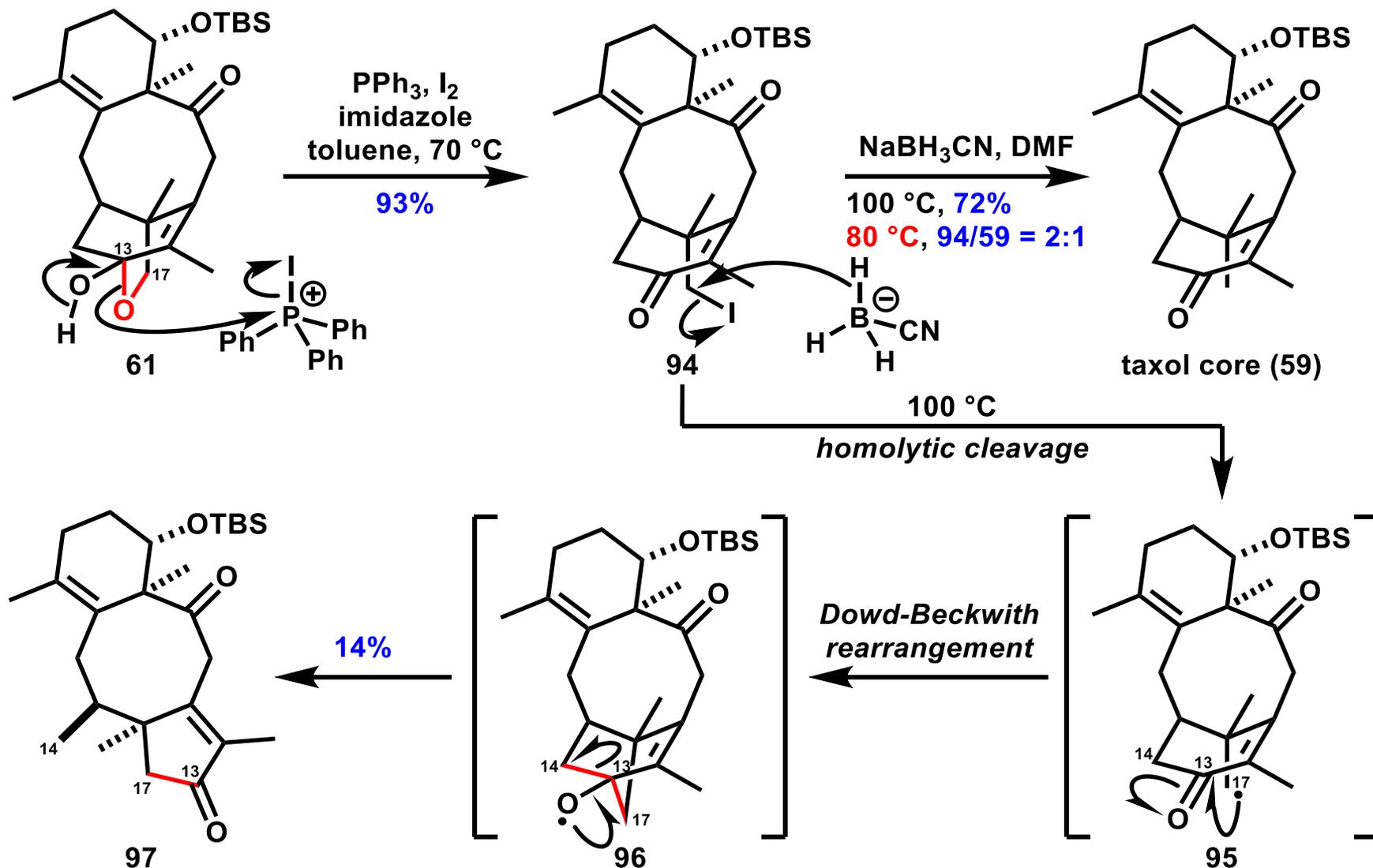


63%

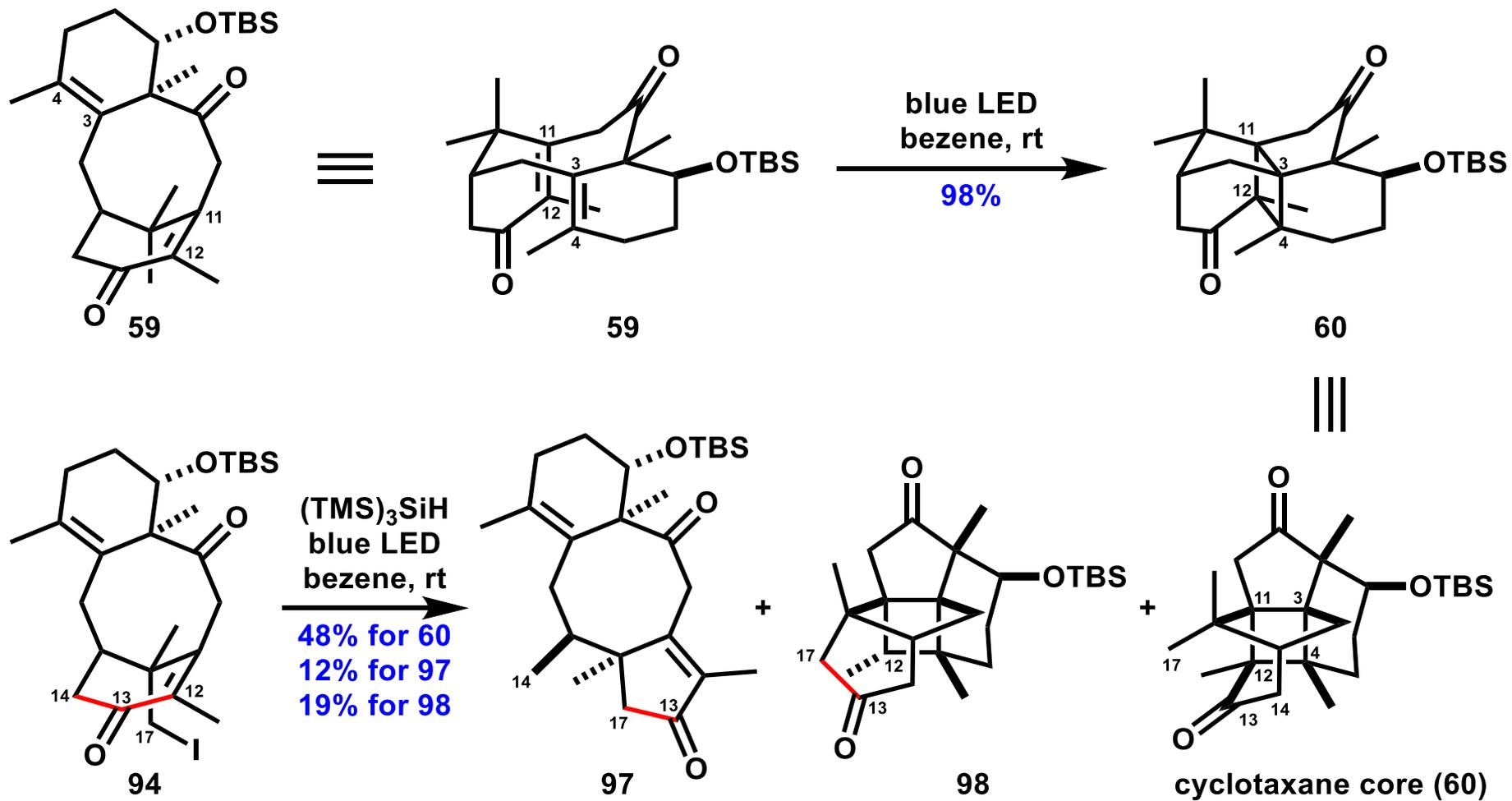


92

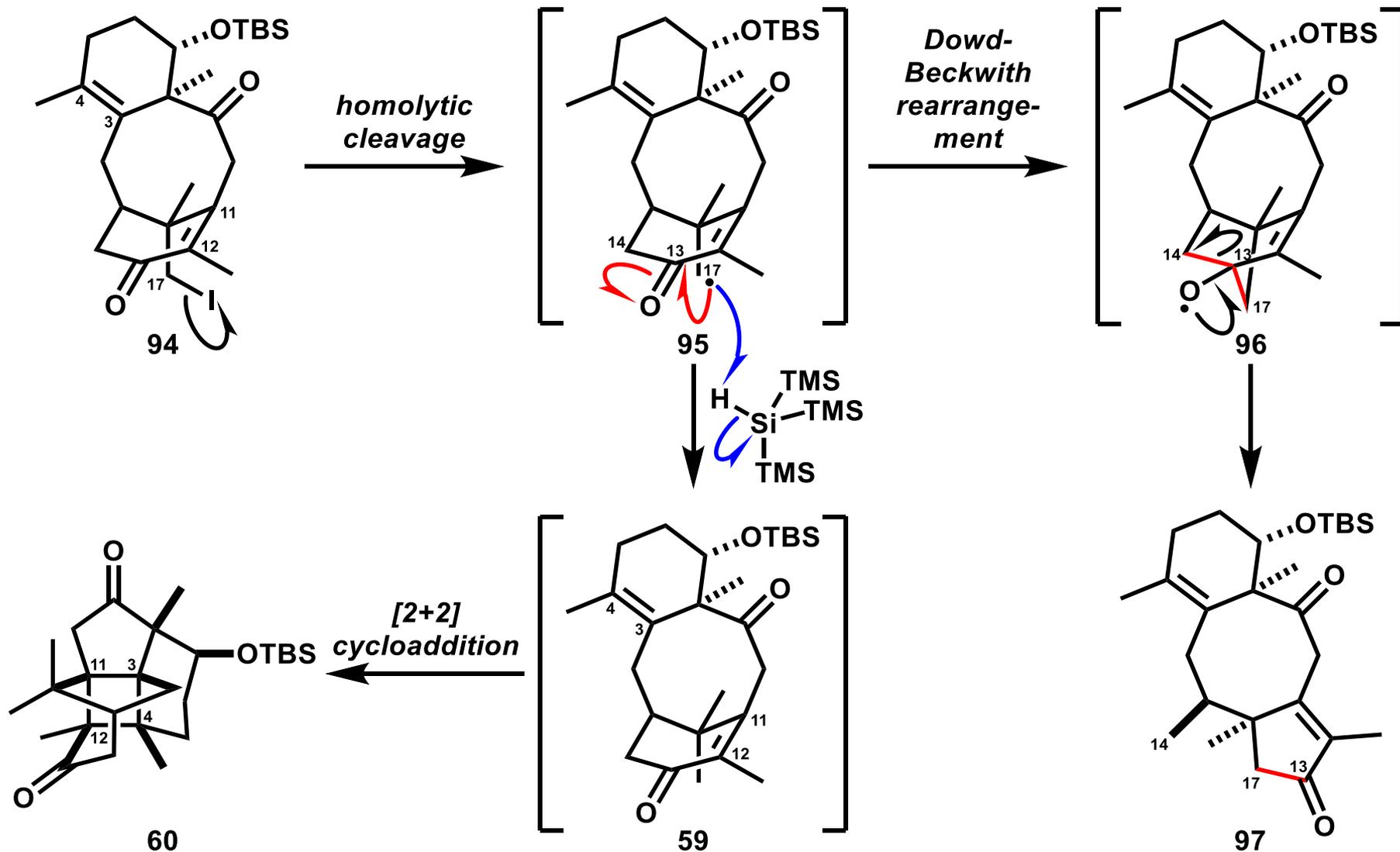
3. Synthesis of Diverse Taxane Cores



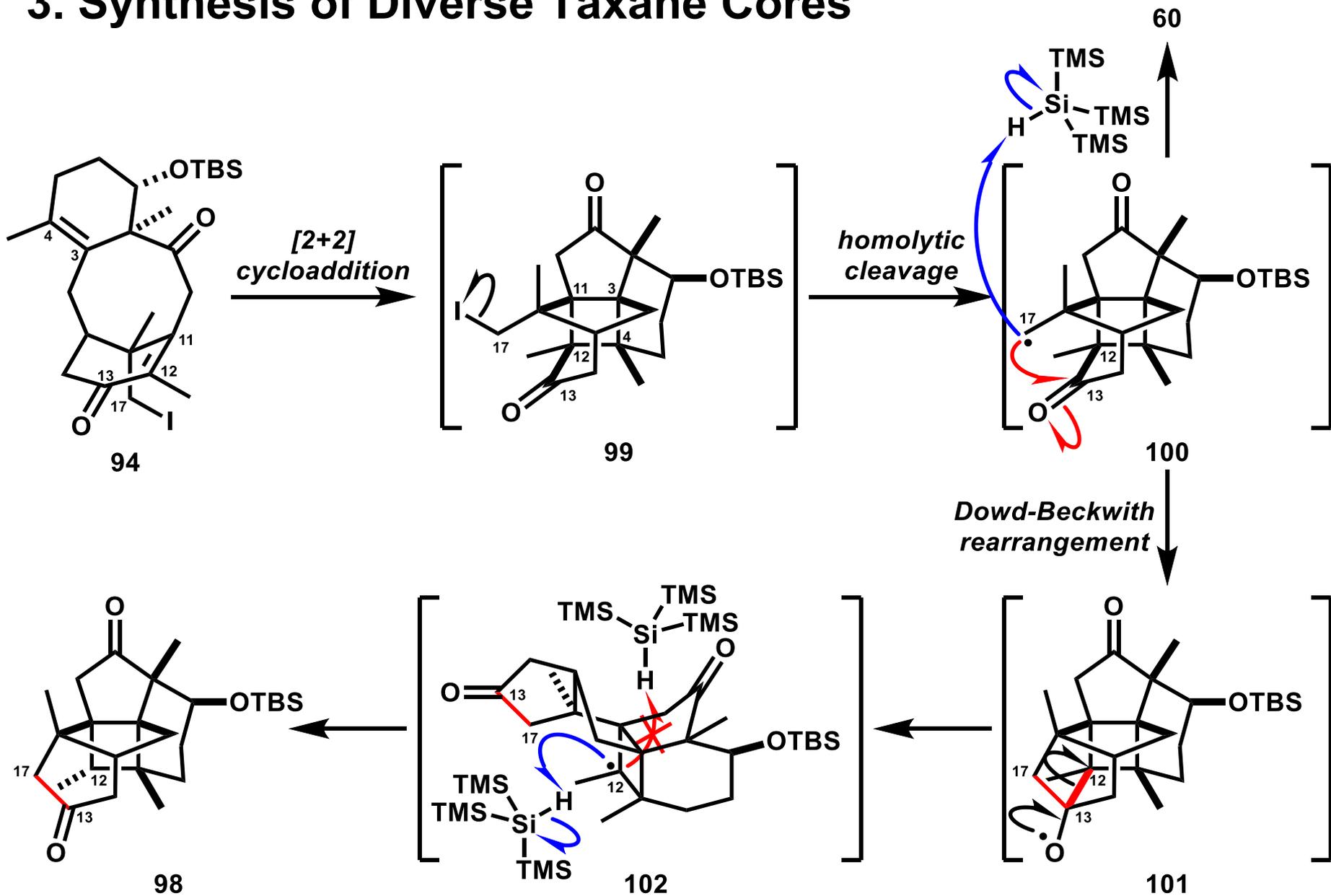
3. Synthesis of Diverse Taxane Cores



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3. Synthesis of Diverse Taxane Cores



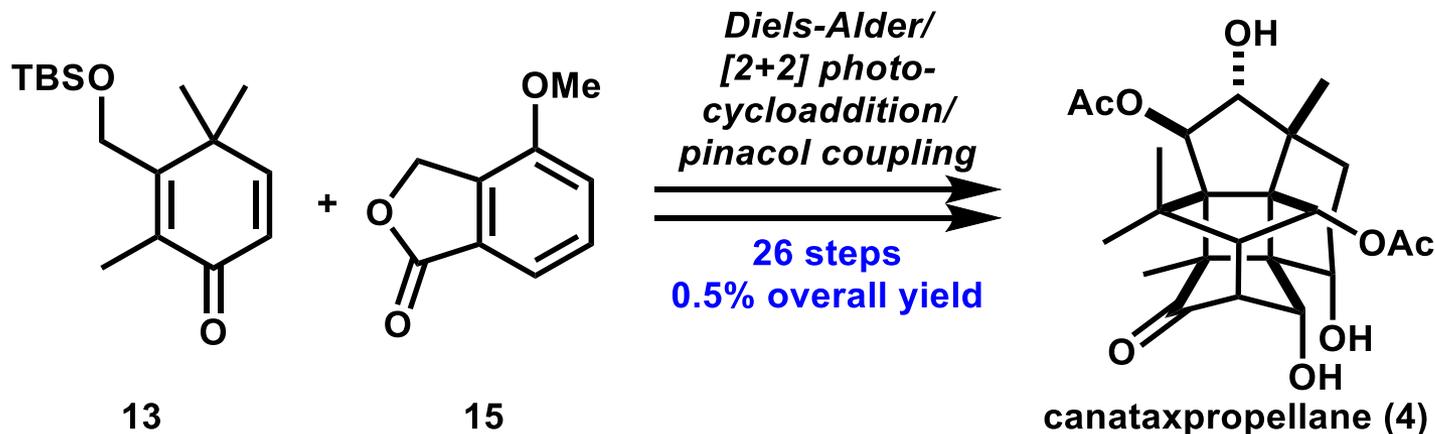
Contents

1. Introduction
2. Total Synthesis of canataxpropellane by Prof. Gaich's Group¹⁾
3. Synthetic Approach to Diverse Taxane Cores by Prof. Sarpong's Group²⁾
- 4. Summary**

4. Summary

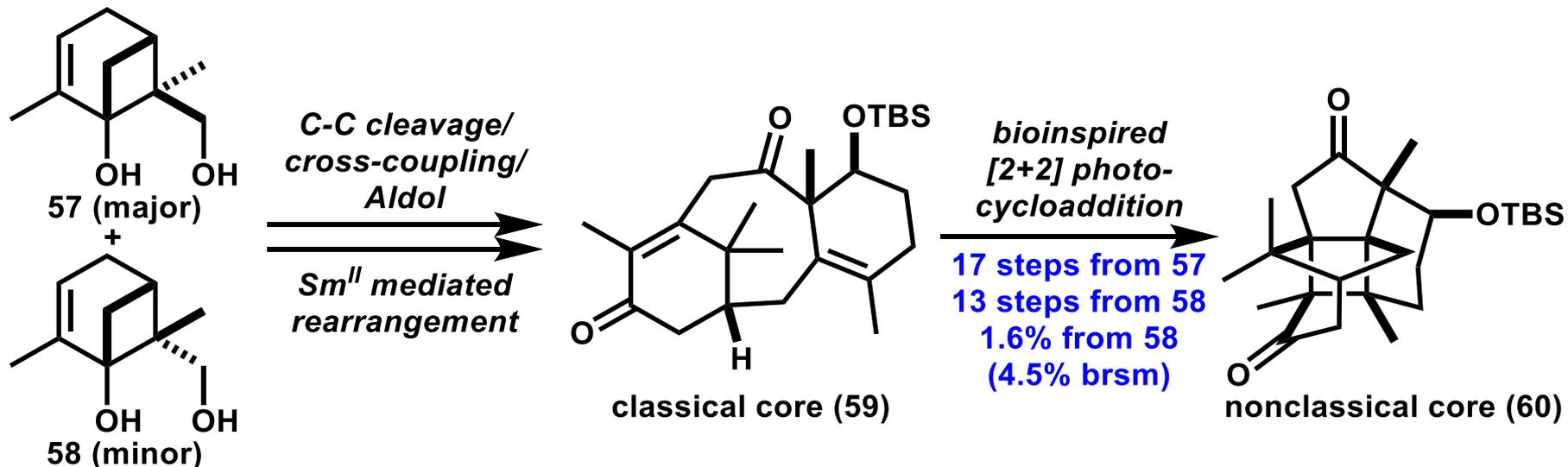
Prof. Gaich's group:

Achieved the first total synthesis of a nonclassical taxane natural product



Prof. Sarpong's Group:

Established a general synthetic approach to diverse taxane cores ("cyclase phase")



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