

# Literature Report IX

## Total Syntheses of Polyhydroxylated Steroids by an Unsaturation-Functionalization Strategy

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**Checker: Gao-Wei Wang**

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Tang, W. *et al. Angew. Chem. Int. Ed.* **2023**, 62, e202303639

# CV of Professor Wenjun Tang

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## Research:

- ◆ Design and development of efficient, practical, and industrially viable catalytic reactions;
- ◆ Total synthesis of complex and biologically active natural products;
- ◆ Development of efficient, economical, and green chemical processes for pharmaceutically important molecules.

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## Background:

- **1991-1995** B. Eng., East China University of Sciences and Technology;
- **1995-1998** M. S., Shanghai Institute of Organic Chemistry, CAS;
- **1998-2003** Ph. D., The Pennsylvania State University;
- **2003-2005** Postdoc., The Scripps Research Institute;
- **2005-2011** Senior Scientist, Principal Scientist, Boehringer Ingelheim Pharmaceuticals, Inc.;
- **2011-Now** Professor, Shanghai Institute of Organic Chemistry, CAS.

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**Introduction**

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**Pd-catalyzed Enantioselective Dearomative Cyclization**

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**Total Synthesis of Polyhydroxylated Steroids**

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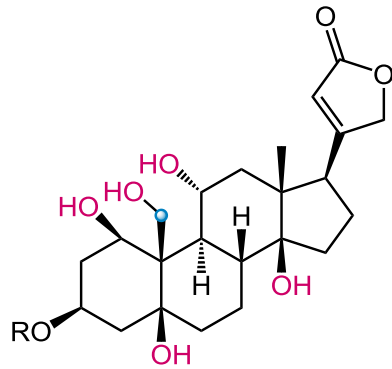
4

**Summary**

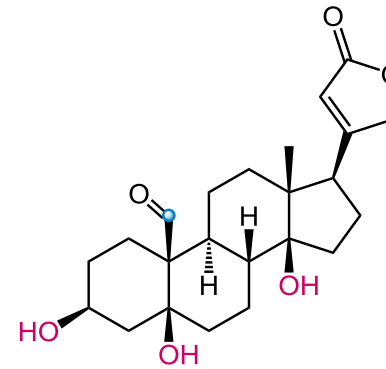
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# Introduction

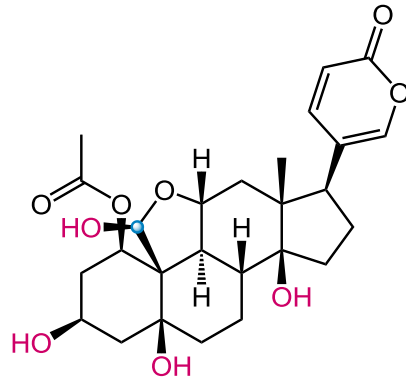
## Selected C19-oxygenated polyhydroxylated steroids



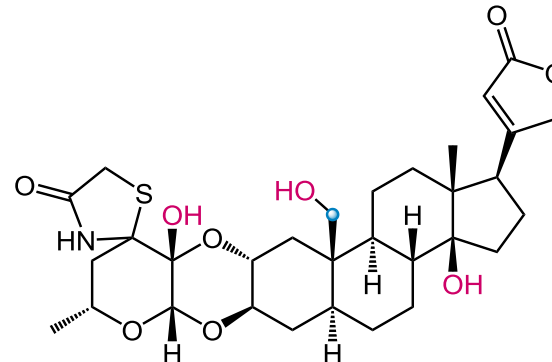
**Ouabain (1):** R =  $\alpha$ -L-rhamnoside  
**Ouabagenin (2):** R = H



**Strophanthidin**



**Bryophyllin B**

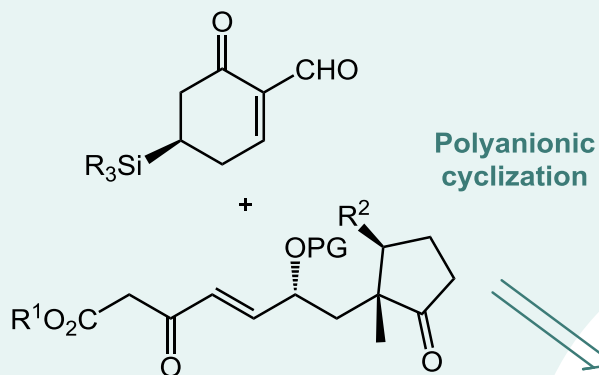


**UNBS 1450**

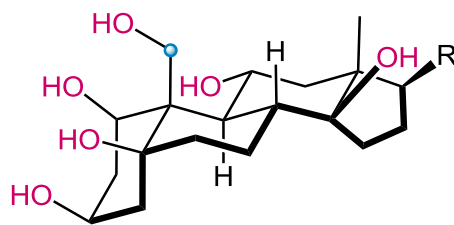
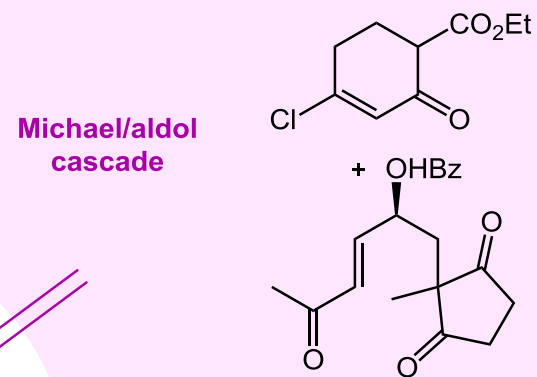
# Introduction

## Synthetic approaches to ouabagenin

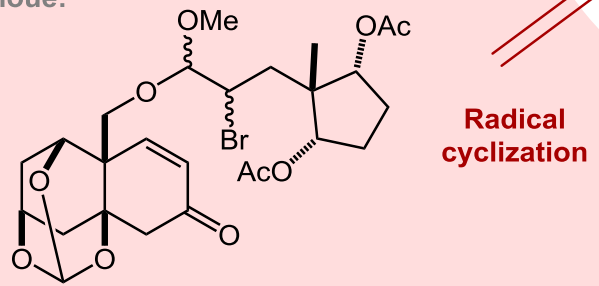
Deslongchamps:



Nagorny:



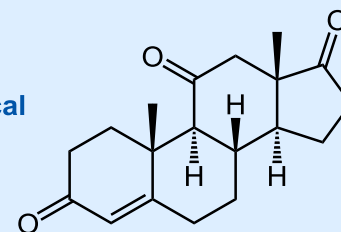
Inoue:



Ouabagenin

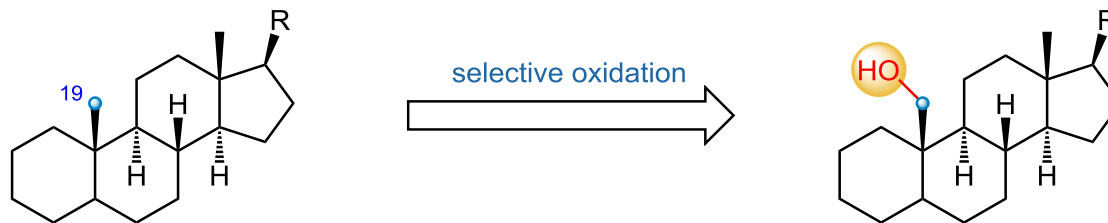
Baran:

Redox and stereochemical relays

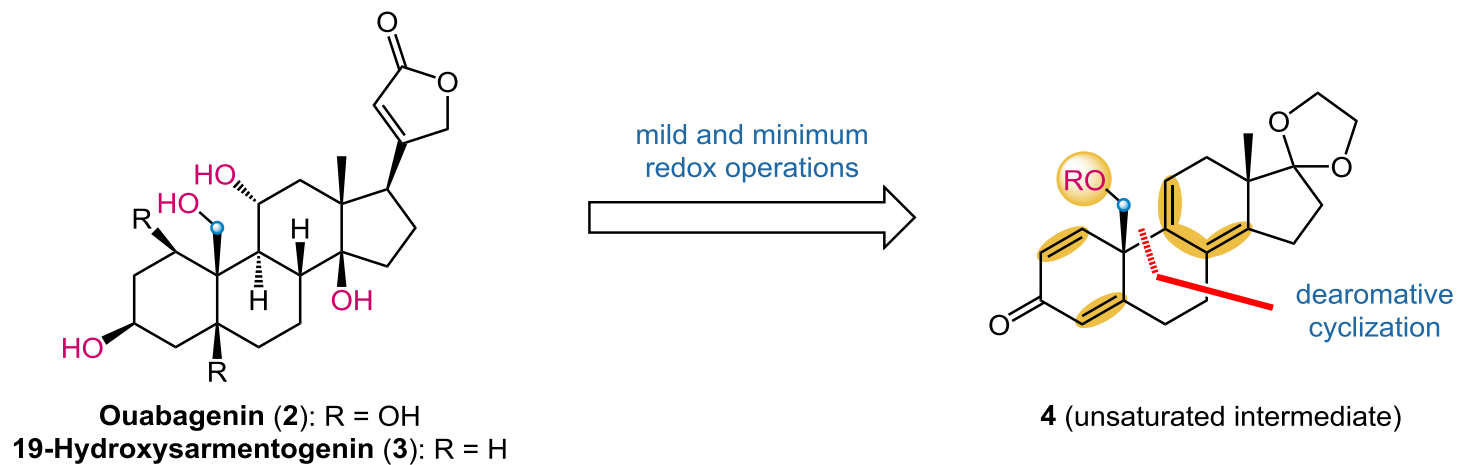


# Introduction

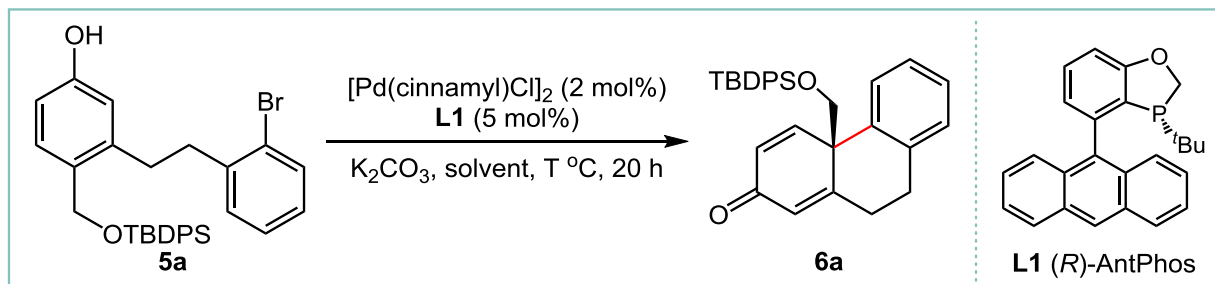
## Oxidation of the C19 methyl group



## Retrosynthetic analysis of polyhydroxylated steroids (this work)



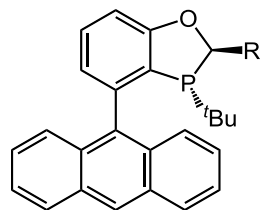
# Optimization of the Reaction Conditions



entry	solvent	T (°C)	yield (%)	e.r. (%) <sup>b</sup>
1	dioxane	80	56	95:5
2	THF	80	46	95:5
3	DCE	80	49	95:5
4	DMF	80	0	-
5	toluene	80	37	96:4
6	toluene	90	95	95:5
7	toluene	70	14	95:5

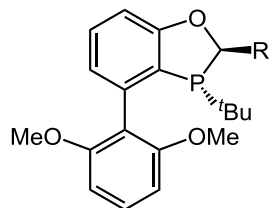
<sup>a</sup>Reaction Conditions: **5a** (0.10 mmol),  $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$  (2 mol%), **L1** (5 mol%),  $\text{K}_2\text{CO}_3$  (1.5 equiv), solvent (1 mL),  $T$  °C, 20 h. <sup>b</sup>Determined by chiral HPLC analysis.

# Optimization of the Reaction Conditions



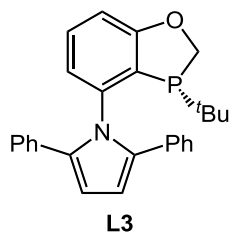
**L1:** R = H [(*R*)-AntPhos]

**L4:** R = *i*Pr [(*R,R*)-*i*Pr-AntPhos]

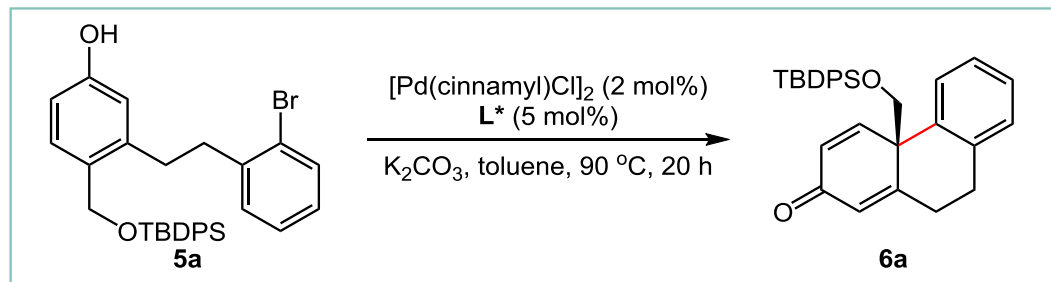


**L2:** R = H [(*R*)-BI-DIME]

**L5:** R = Me [(*R,R*)-Me-BI-DIME]



**L3**

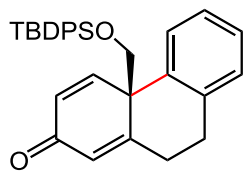
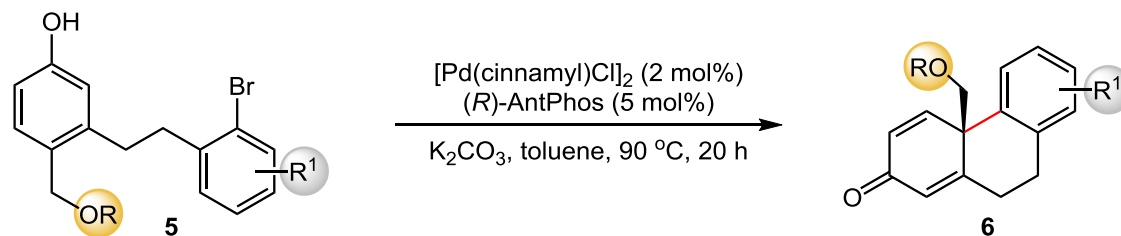


entry	L*	yield (%)	e.r. (%) <sup>b</sup>
1	<b>L1</b>	95	95:5
2	<b>L2</b>	85	91:9
3	<b>L3</b>	62	93:7
4	<b>L4</b>	62	62:38
5	<b>L5</b>	93	76:24

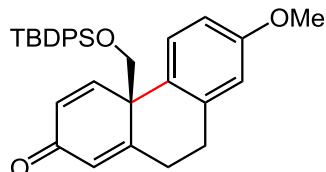
<sup>a</sup>Reaction Conditions: **5a** (0.10 mmol), [Pd(cinnamyl)Cl]<sub>2</sub> (2 mol%), **L\*** (5 mol%), K<sub>2</sub>CO<sub>3</sub> (1.5 equiv), toluene(1 mL), 90 °C, 20 h. <sup>b</sup>Determined by chiral HPLC analysis.



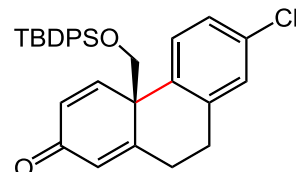
# Substrate Scope



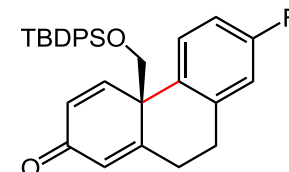
**6a**, 95%, 95:5 e.r.



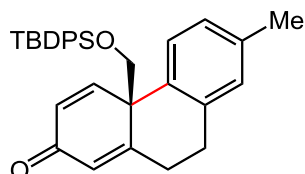
**6b**, 87%, 91:9 e.r.



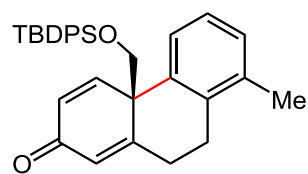
**6c**, 93%, 92:8 e.r.



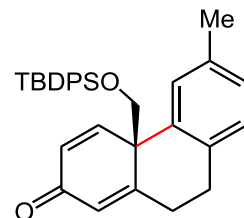
**6d**, 86%, 94:6 e.r.



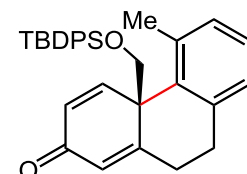
**6e**, 92%, 93:7 e.r.



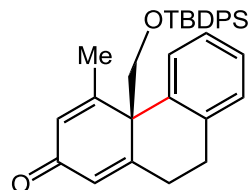
**6f**, 87%, 92:8 e.r.



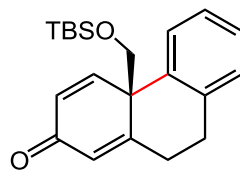
**6g**, 92%, 93:7 e.r.



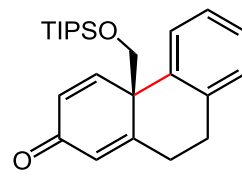
**6h**, 60%, 77:23 e.r. [ $100\text{ }^\circ\text{C}$ ]



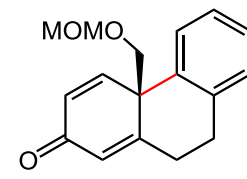
**6i**, 73%, 90:10 e.r.



**6j**, 82%, 92:8 e.r.

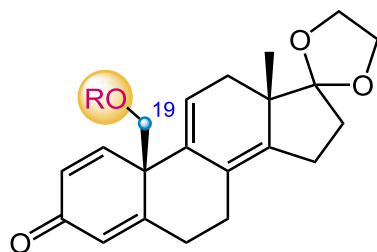


**6k**, 87%, 92:8 e.r.



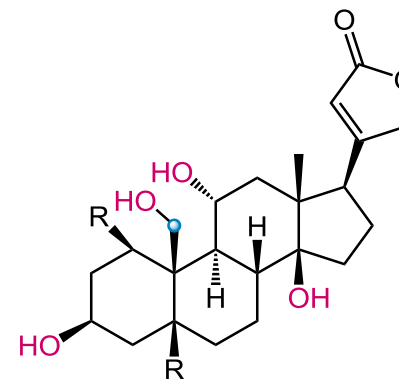
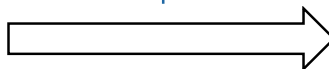
**6l**, 80%, 94:6 e.r.

# Synthesis of Polyhydroxylated Steroids



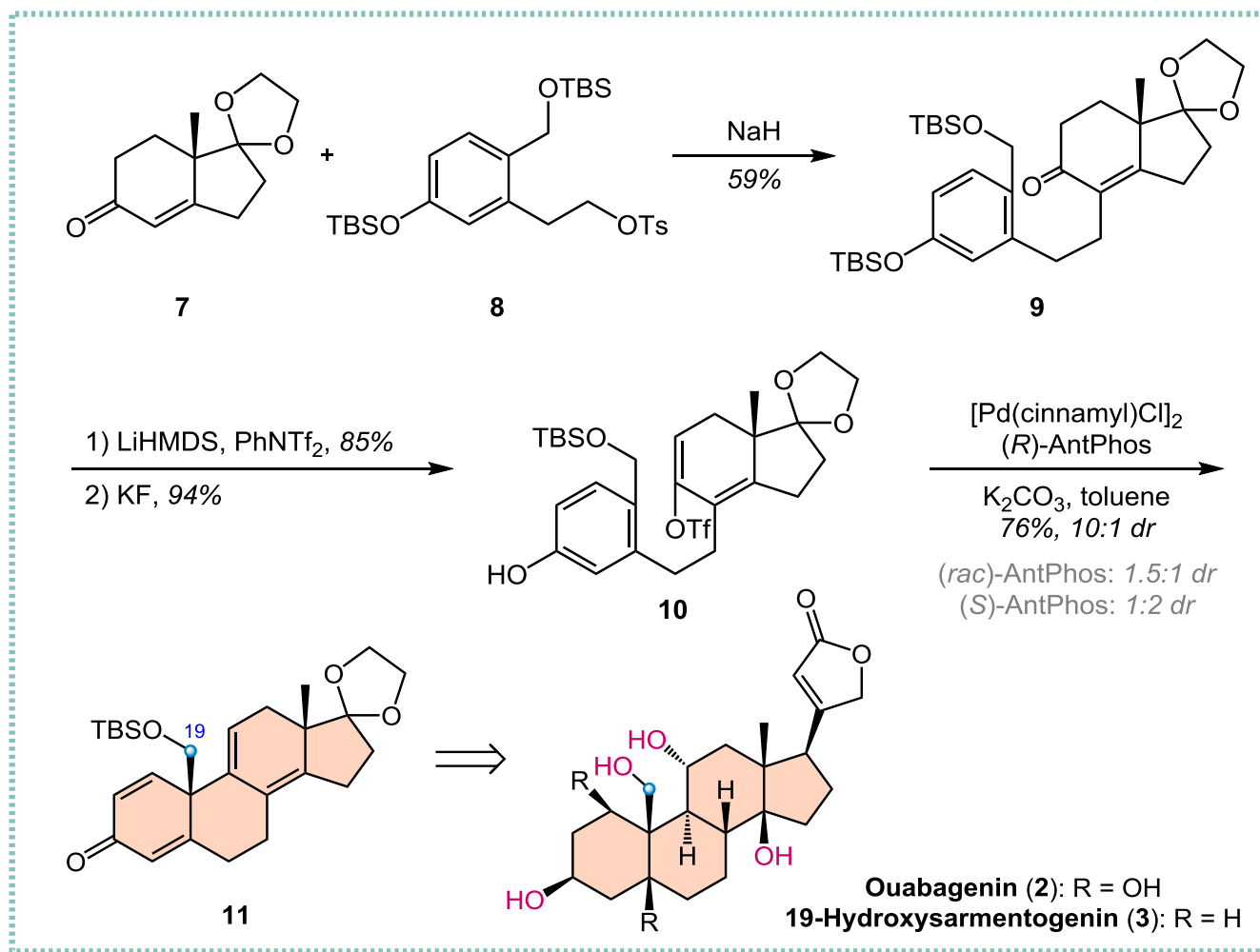
4 (unsaturated intermediate)

mild and minimum  
redox operations

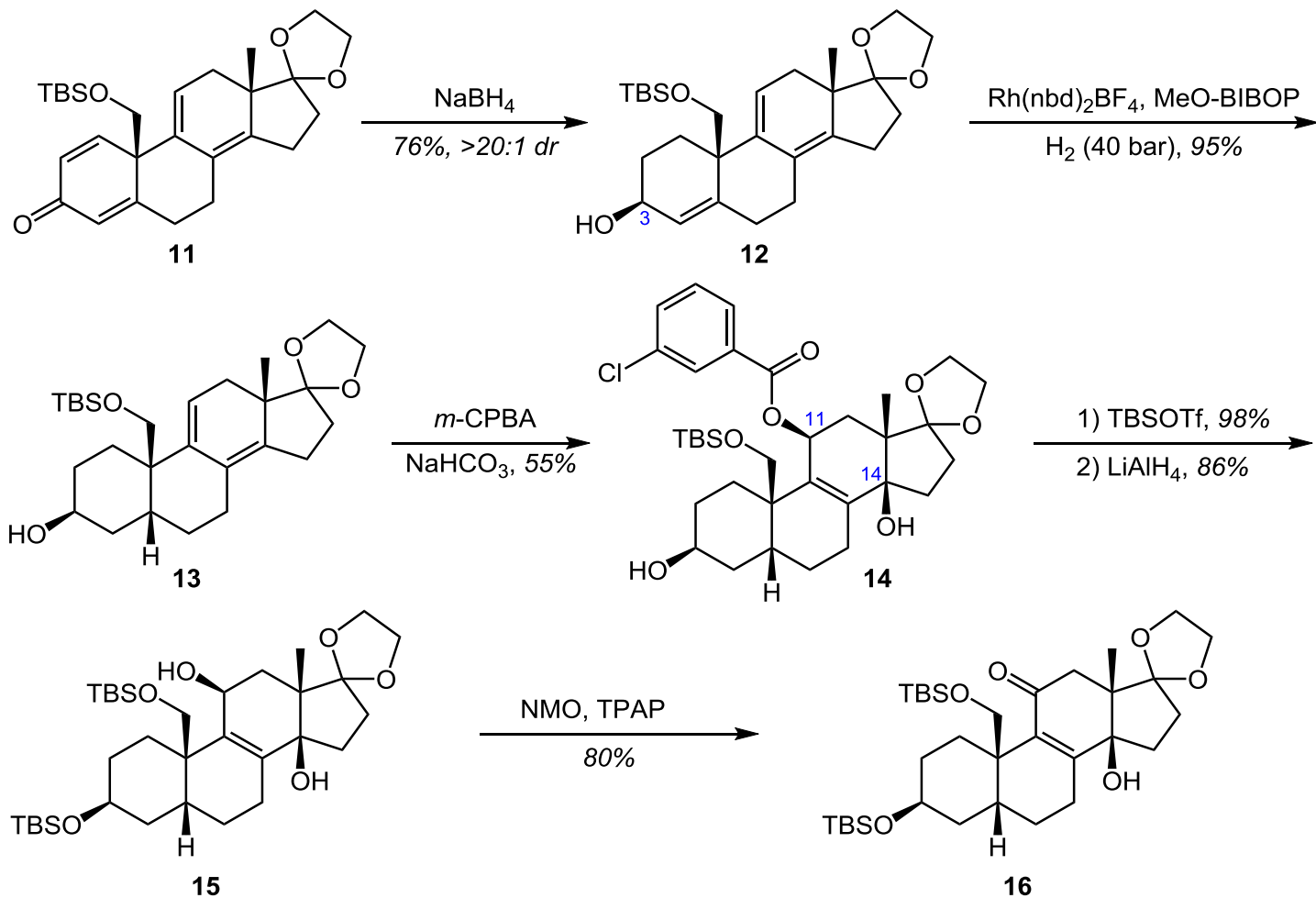


**Ouabagenin (2): R = OH**  
**19-Hydroxysarmentogenin (3): R = H**

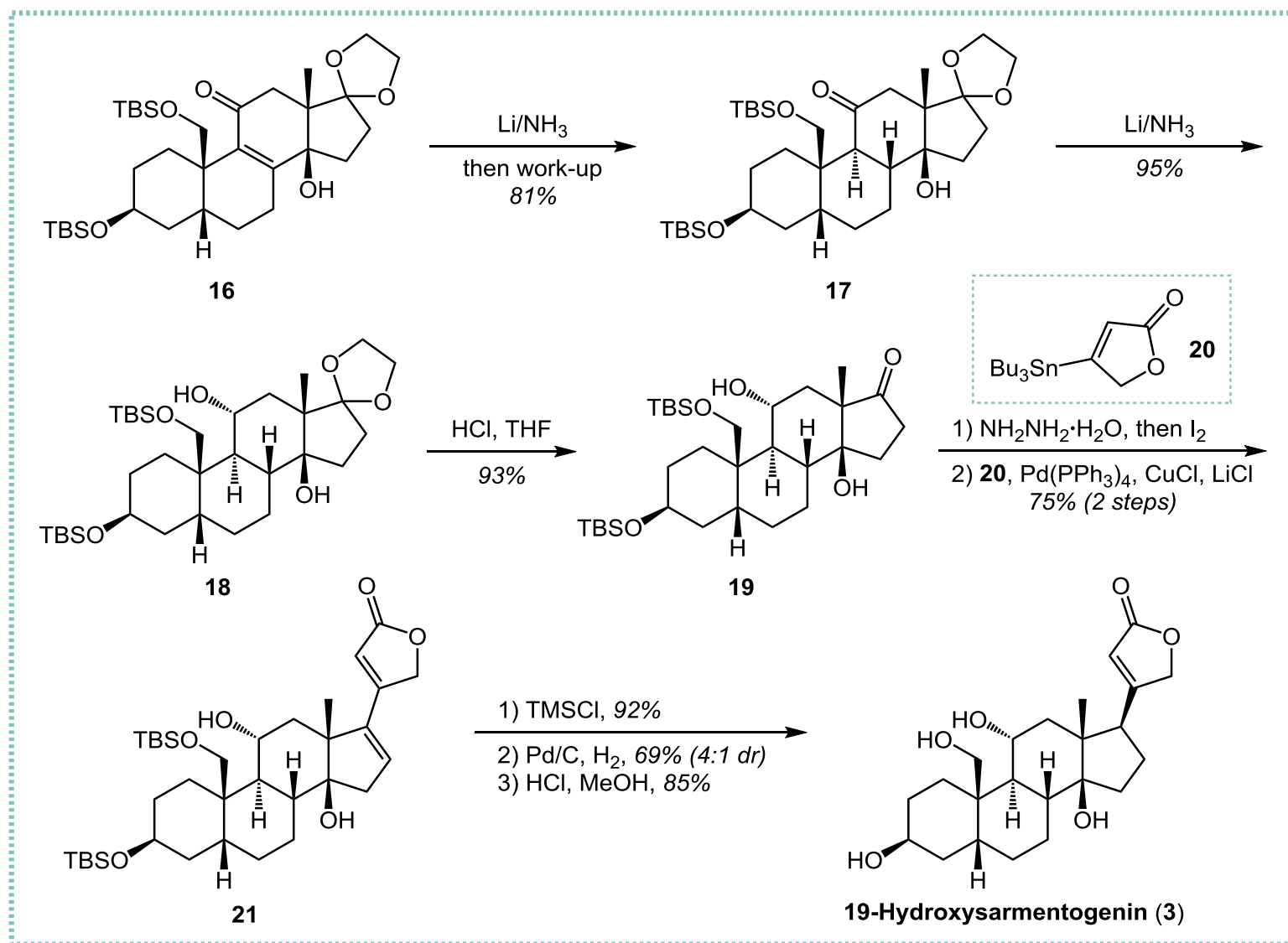
# Synthesis of Key Unsaturated Intermediate 11



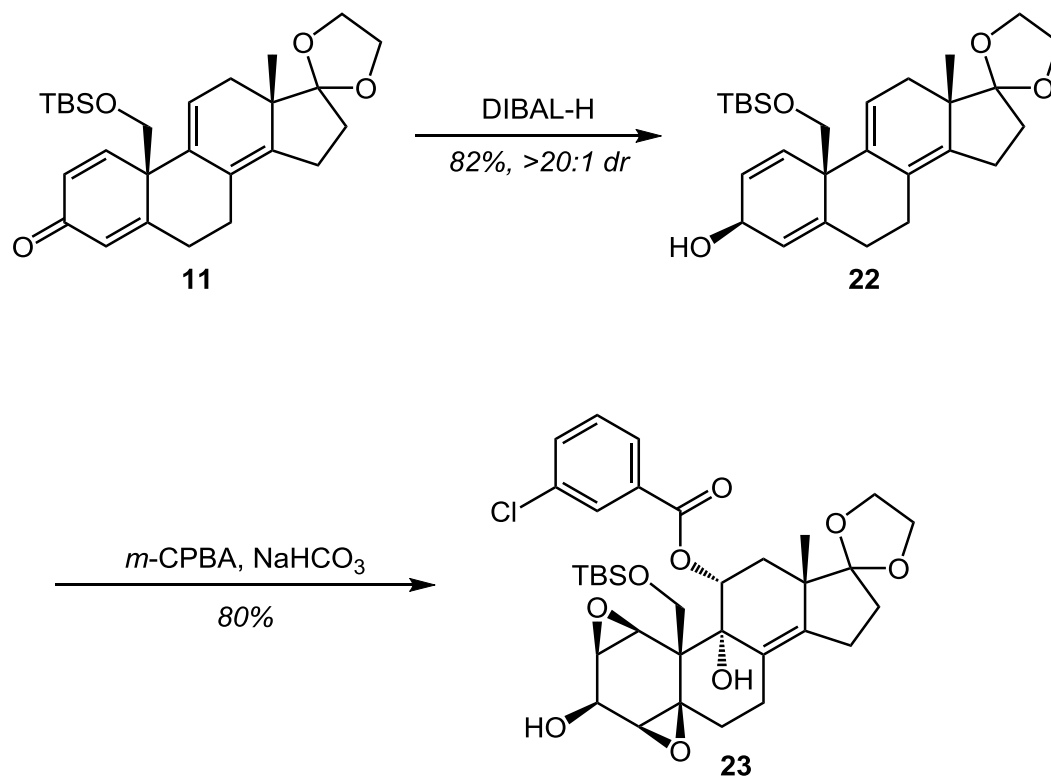
# Synthesis of Intermediate 16



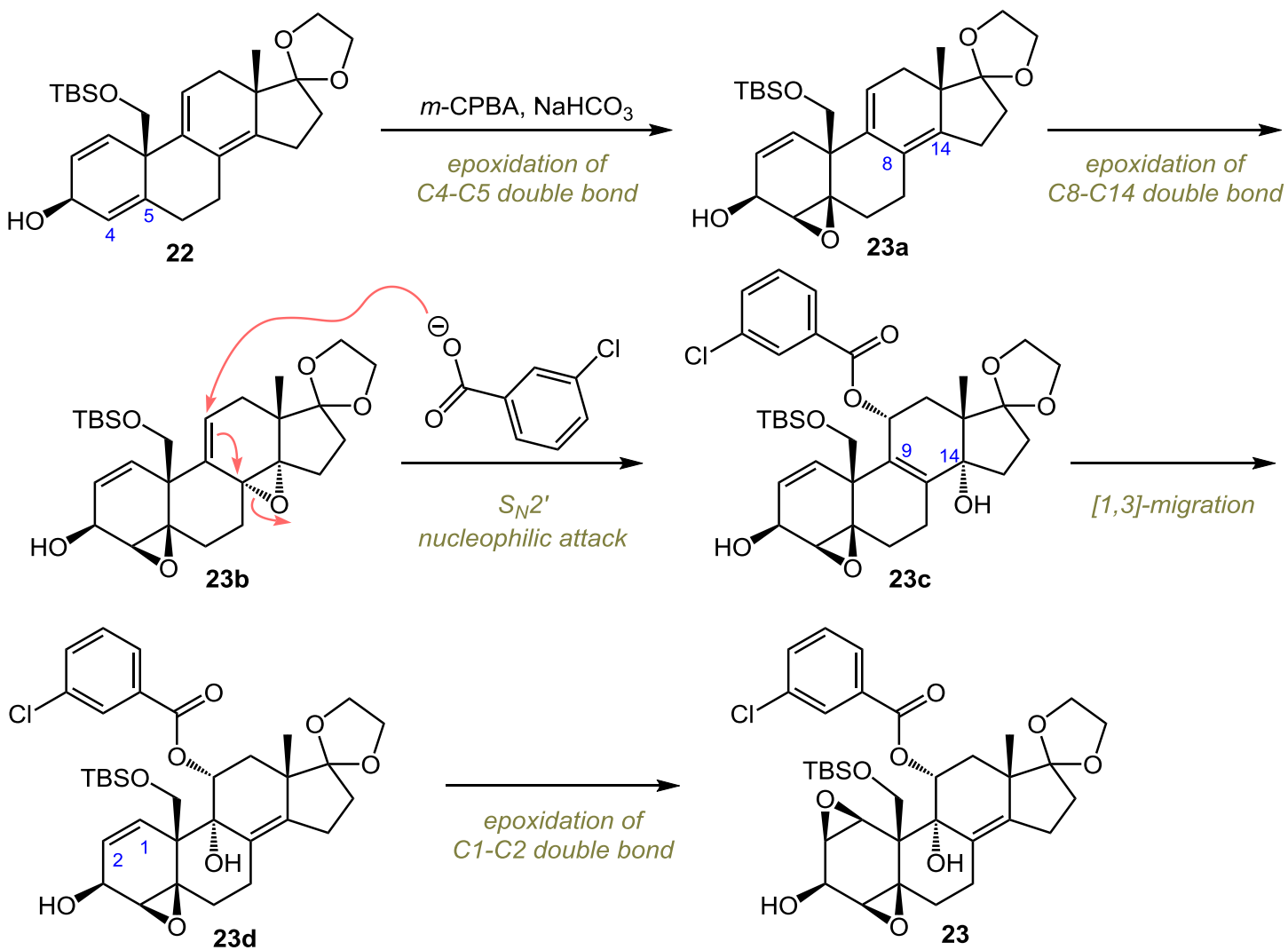
# Synthesis of 19-Hydroxysarmentogenin



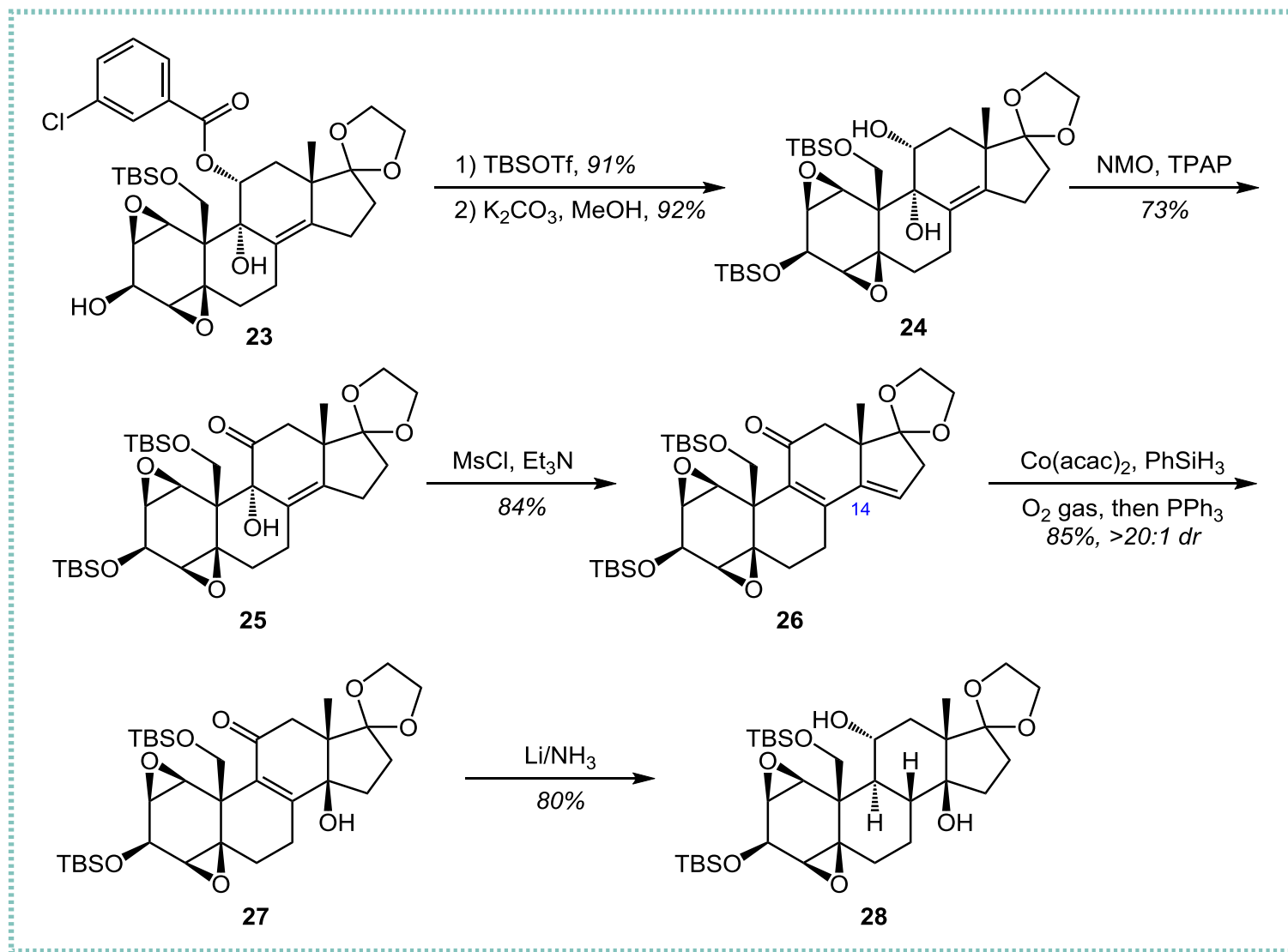
# Synthesis of Intermediate 23



# Synthesis of Intermediate 23

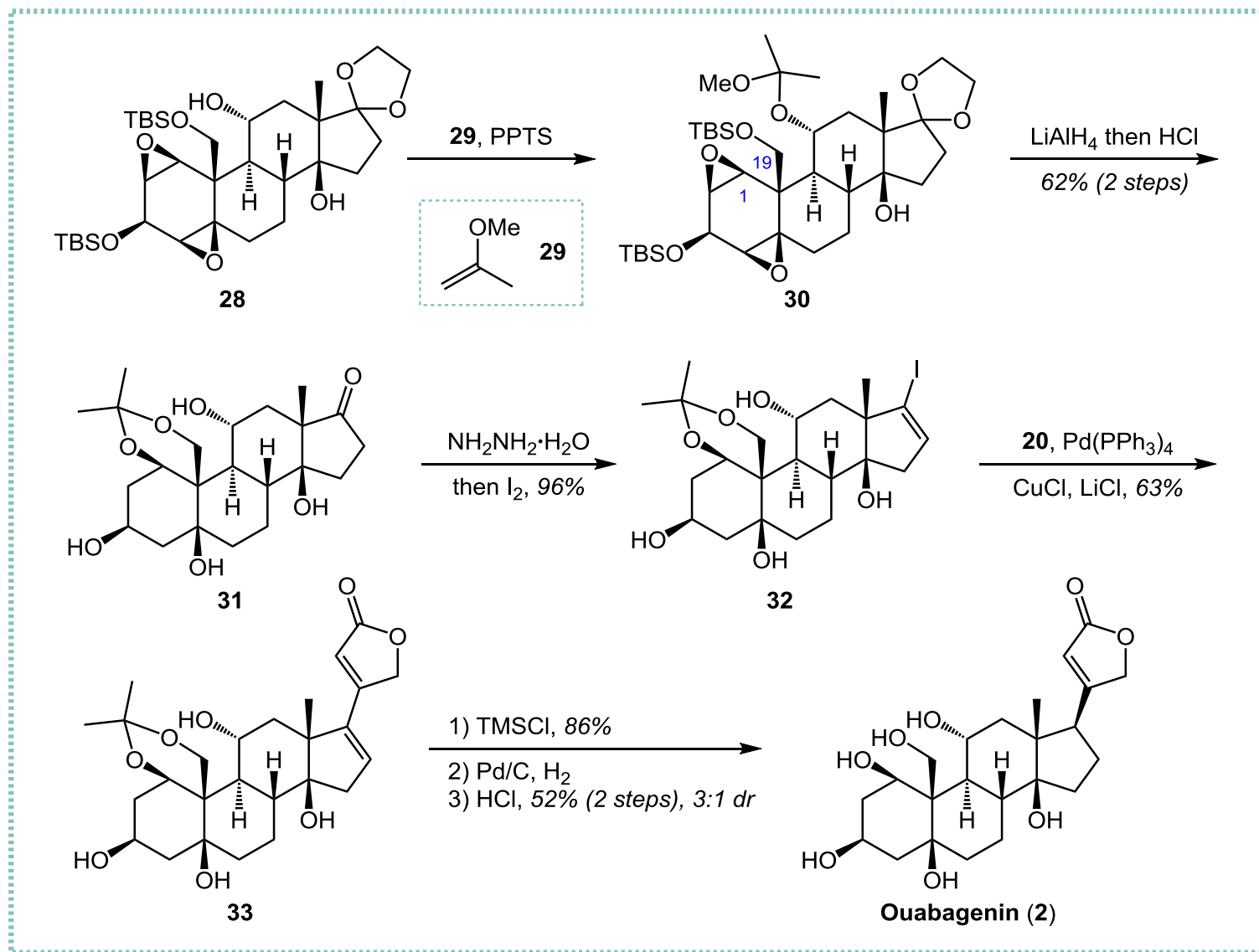


# Synthesis of Intermediate 28



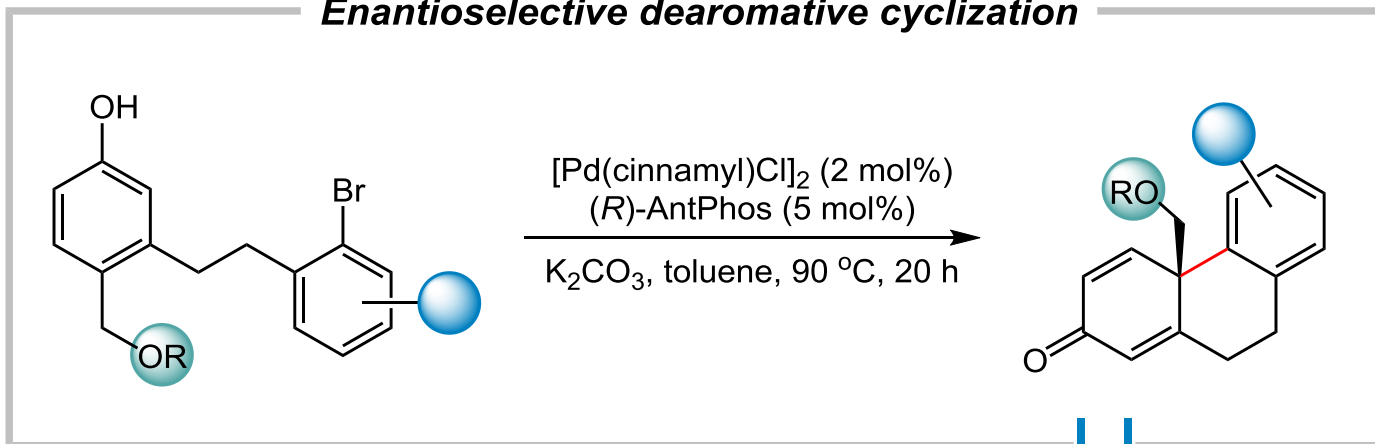


# Synthesis of Ouabagenin

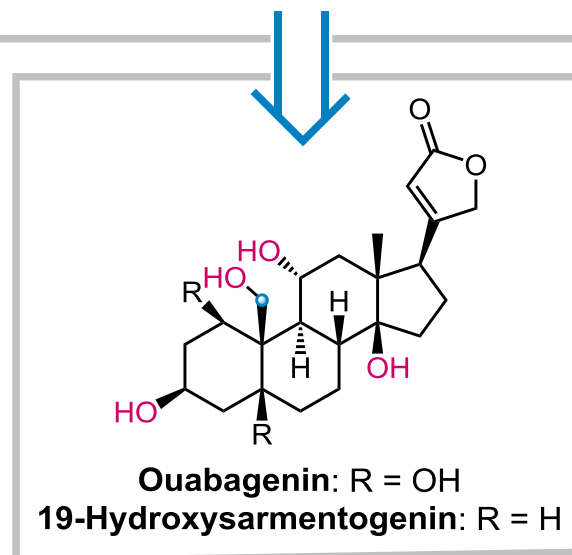


# Summary

## Enantioselective dearomative cyclization



- enantioselective
- 12 examples
- up to 95% yield, up to 95:5 e.r.
- applied in synthesis of natural products



# Writing Strategy

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## ➤ Introduction

The importance  
of total synthesis  
of natural products



The importance  
of Cardiotonic  
steroids



Several impressive  
synthetic strategies of  
total synthesis of  
ouabagenin


- ♪ The total synthesis of natural products has long served as the driving force for developing new synthetic strategies and methods to access important and intriguing molecules.
- ♪ Cardiotonic steroids are a unique class of polyoxygenated steroids of both plant and animal origin for the treatment of heart failure as  $\text{Na}^+/\text{K}^+$ -ATPase inhibitors. They have been increasingly applied as antitumor, antiviral, neuroprotection, and immune regulation agents through a multimolecular mechanism. Ouabain, and its aglycone ouabagenin, are...
- ♪ The densely functionalized core structure and unique stereochemical configurations, mostly represented by ouabagenin, pose a formidable synthetic challenge and have attracted synthetic efforts, leading to several impressive synthetic strategies. Deslongchamps and co-workers employed a key...

# Writing Strategy


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## ➤ The Last Paragraph

Summary of  
the work



Significant steps  
in total synthesis



The outlook of  
this work

- ♪ In summary, by employing an unsaturation-functionalization strategy and developing an efficient method for constructing the C19-hydroxy steroidal skeleton, total syntheses of polyhydroxylated steroids were accomplished with brevity.
- ♪ The high effectiveness of an asymmetric dearomative cyclization in accessing a series of polycyclic compounds bearing stereogenic quaternary stereocenters with a protected hydroxymethyl functionality led to the preparation of the C19-hydroxy unsaturated steroidal skeleton in only four steps from the Hajos-Parrish ketone ketal 7. ...
- ♪ Finally, efficient total synthesis by the unsaturation-functionalization strategy offers versatility in exploring analogues of these complex cardiotonic steroids in the search for new anticancer drugs with an appreciable therapeutic index.

# Representative Examples

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- Strophanthidin, the aglycone of convallatoxin isolated from lily-of-the-valley, **attenuates** the MAPK, PI3K/AKT/mTOR, and Wnt/ $\beta$ -catenin signaling pathways as a **promising** anticancer agent. (attenuate: 使减轻, 使减弱, 使削弱; promising: 有希望的, 有前途的, 有出息的)
- The densely functionalized core structure and unique stereochemical configurations, mostly represented by ouabagenin, **pose a formidable synthetic challenge** and have attracted synthetic efforts, leading to several impressive synthetic strategies. (formidable: 可怕的, 令人敬畏的, 难对付的)
- To demonstrate the synthetic **relevance** of highly functionalized intermediate 11 for cardiotonic steroids, synthesis toward 19-hydroxy-sarmentogenin was **pursued**. (relevance: 相关性, 意义, 重要性; pursue: 执行, 致力于, 追逐)

# Acknowledgement

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*Thanks for your attention !*