

# Literature Report IV

## Concise Synthesis of 9,11-Secosteroids Pinnigorgiols B and E

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Reporter: Zi-Qi Hu

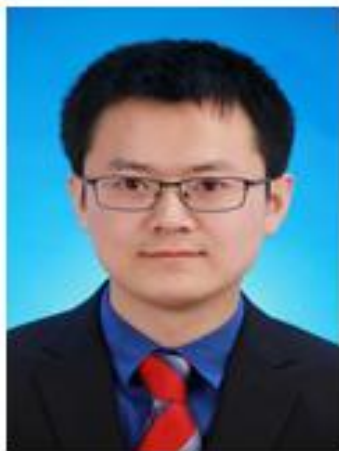
Checker: Xiang Li

Date: 2021-5-17

Gui, J. *et al. J. Am. Chem. Soc.* **2021**, 143, 4886

# CV of Prof. Jinghan Gui

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## Research:

- Efficient synthesis of complex steroids and triterpenoid natural products;
  - Research on new practical synthetic methodology for constructing carbon-carbon and carbon-heteroatom bonds.
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## Background:

- **2003-2007** B.S., Anhui Normal University
- **2007-2012** Ph.D., SIOC
- **2012-2013** Research assistant, SIOC
- **2013-2016** Postdoc., The Scripps Research Institute
- **2016-Now** Professor, SIOC

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**Total Synthesis of Pinnigorgiol B and E**

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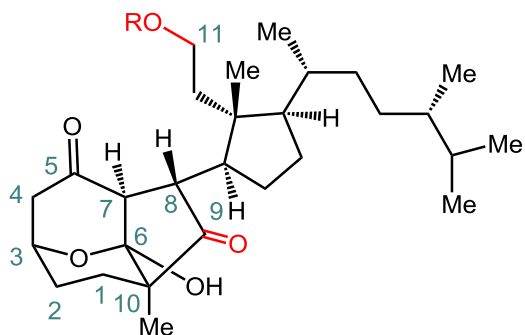
**3**

**Summary**

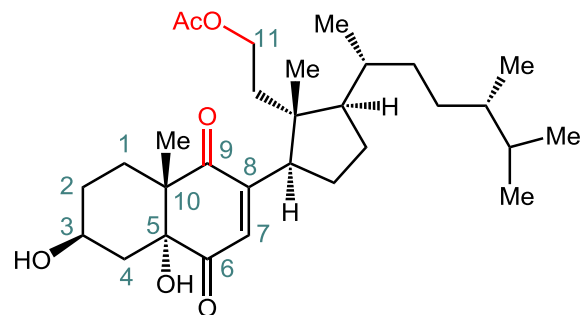
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# Introduction

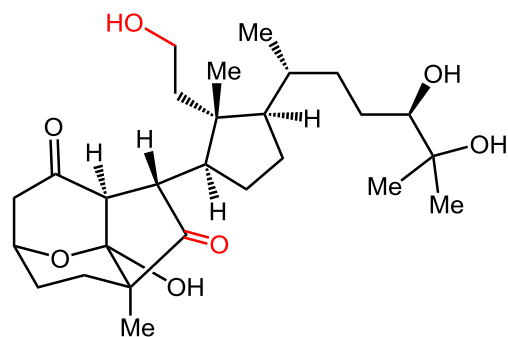
## Structures of 9,11-Secosteroids



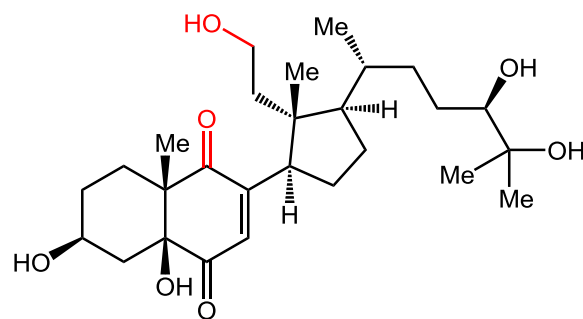
R = H, pinnigorgiol B (1)  
R = Ac, pinnigorgiol E (2)



pinnisterol E (3)

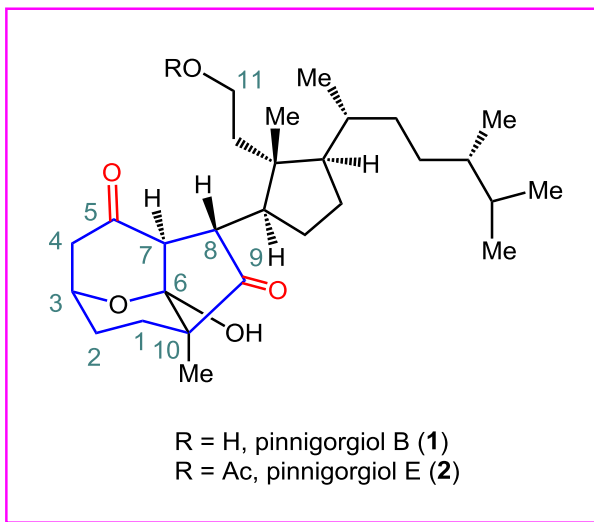


aplysiasecosterol A (4)



aplysiasecosterol B (5)

# Introduction

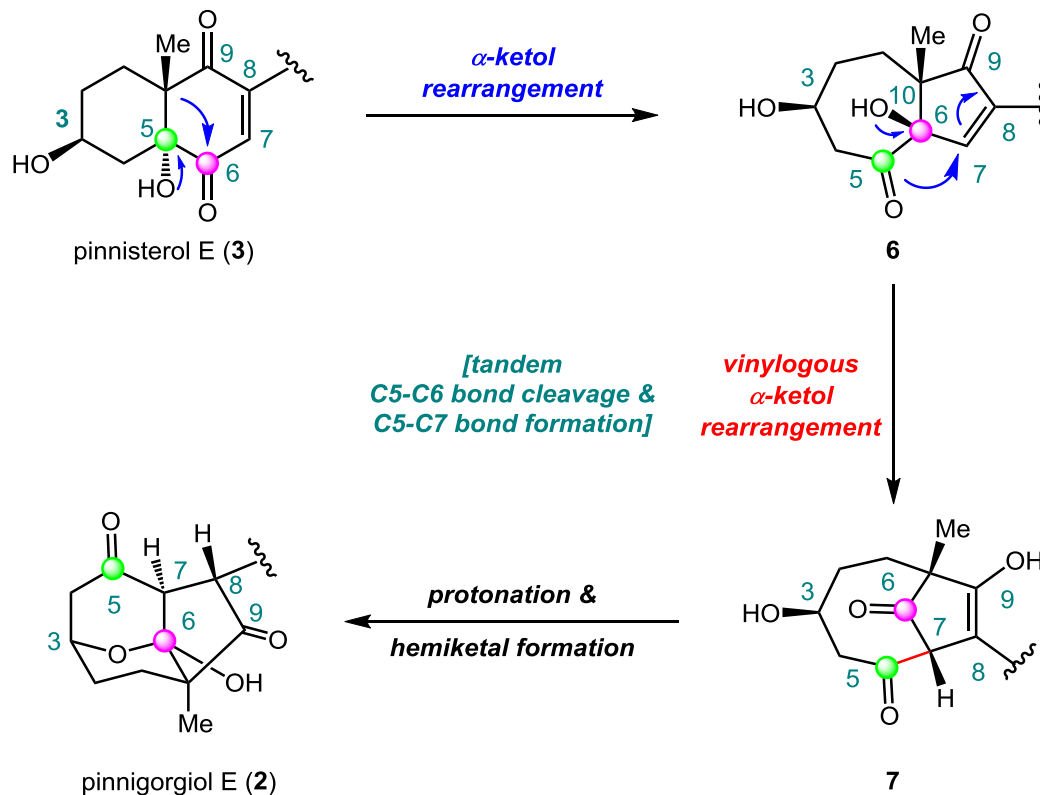


- Isolated from a Pinnigorgia coral species;
- Unique tricyclo [5,2,1,1] decane framework;
- Embedded  $\gamma$ -diketone moiety;
- First total synthesis reported.

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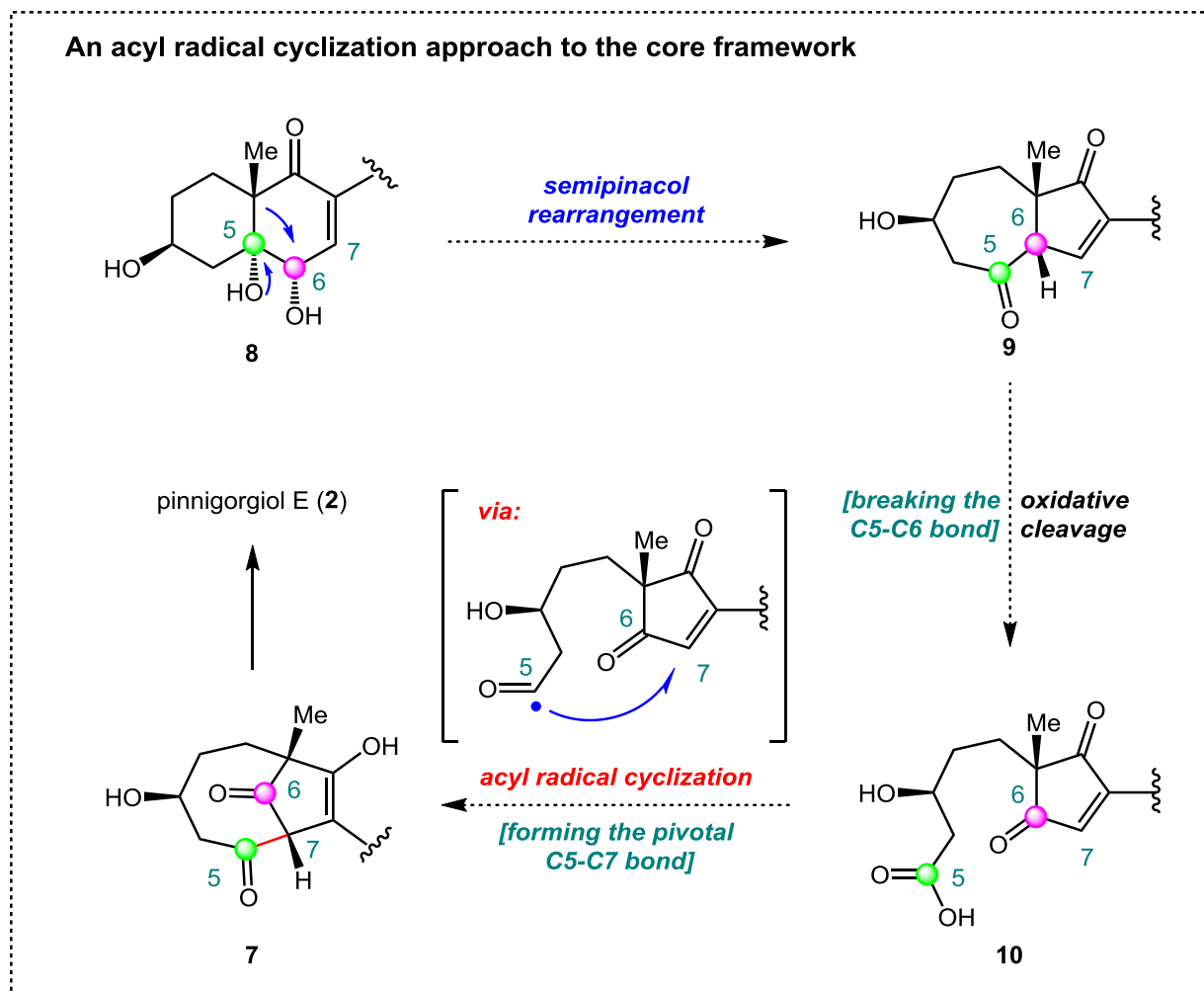
# Proposed Biosynthetic Pathway

Proposed biosynthetic pathway: tandem  $\alpha$ -ketol rearrangement



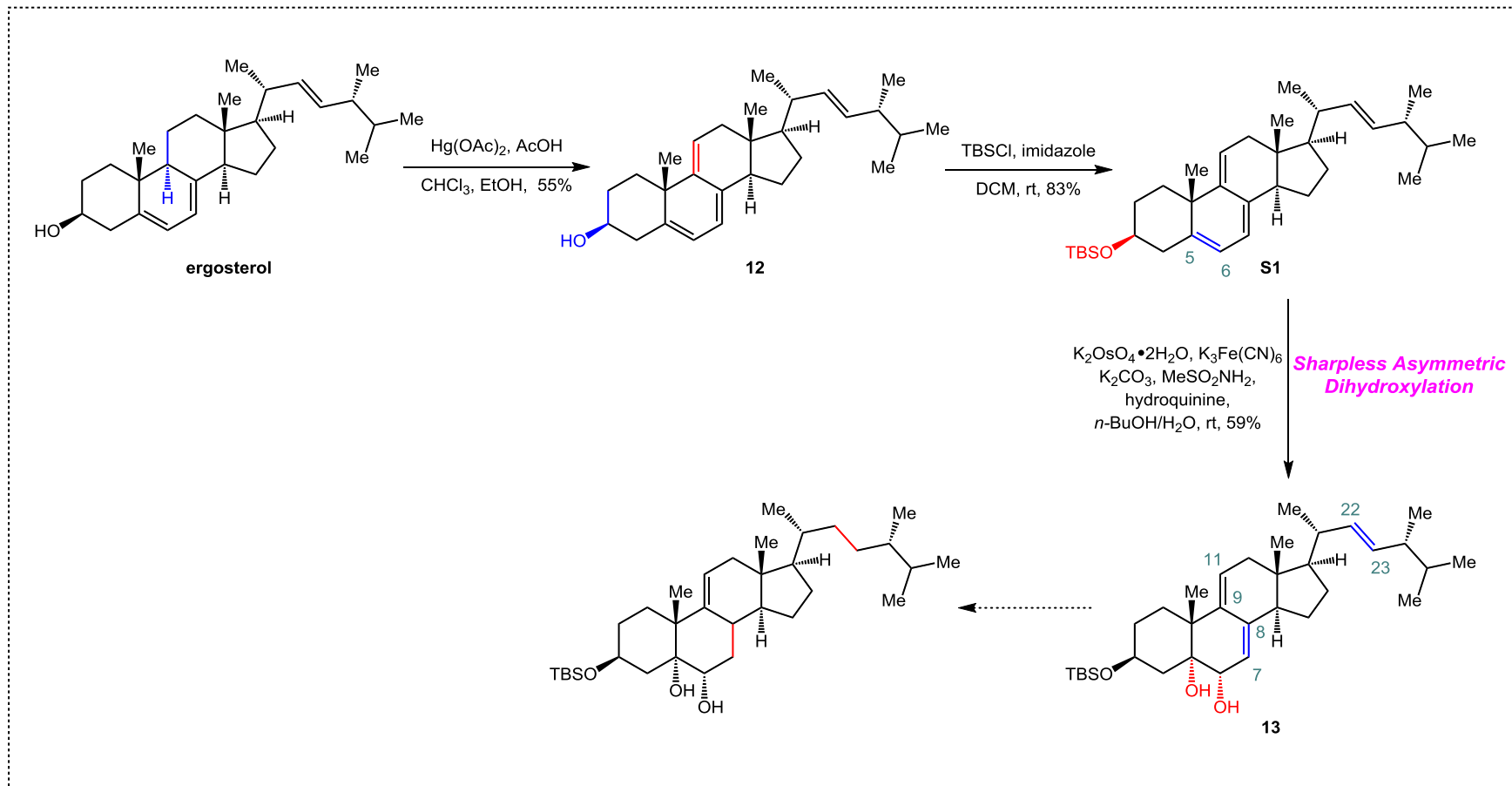
Kigoshi, H. *et al. Angew. Chem. Int. Ed.* **2015**, 54, 7073  
 Kigoshi, H. *et al. Tetrahedron Lett.* **2016**, 57, 858

# Retrosynthetic Analysis



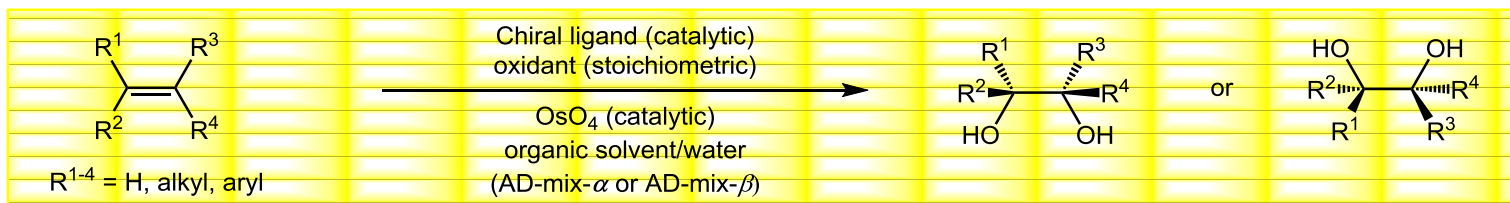
Gui, J. et al. *J. Am. Chem. Soc.* **2021**, 143, 4886

# Synthesis of Compound 13



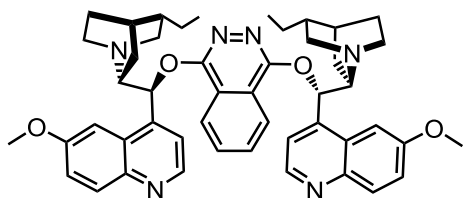


# Sharpless Asymmetric Dihydroxylation



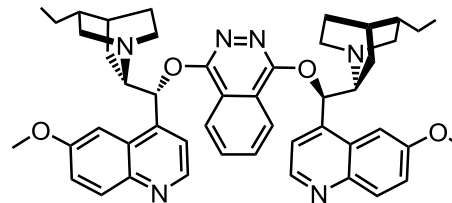
## AD-mix- $\beta$ :

$K_2OsO_2(OH)_4$  (cat.),  $K_2CO_3$ ,  $K_3Fe(CN)_6$ ,  $(DHQD)_2PHAL$  (cat.):

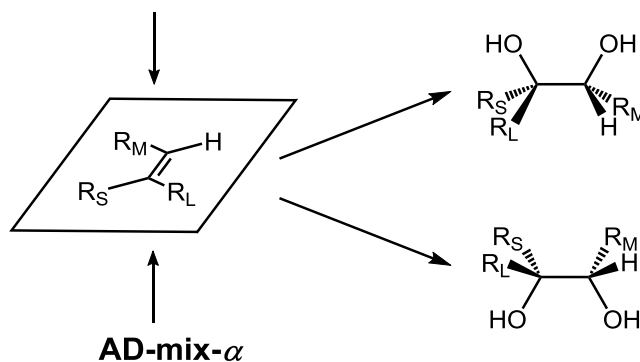


## AD-mix- $\alpha$ :

$K_2OsO_2(OH)_4$  (cat.),  $K_2CO_3$ ,  $K_3Fe(CN)_6$ ,  $(DHQ)_2PHAL$  (cat.):

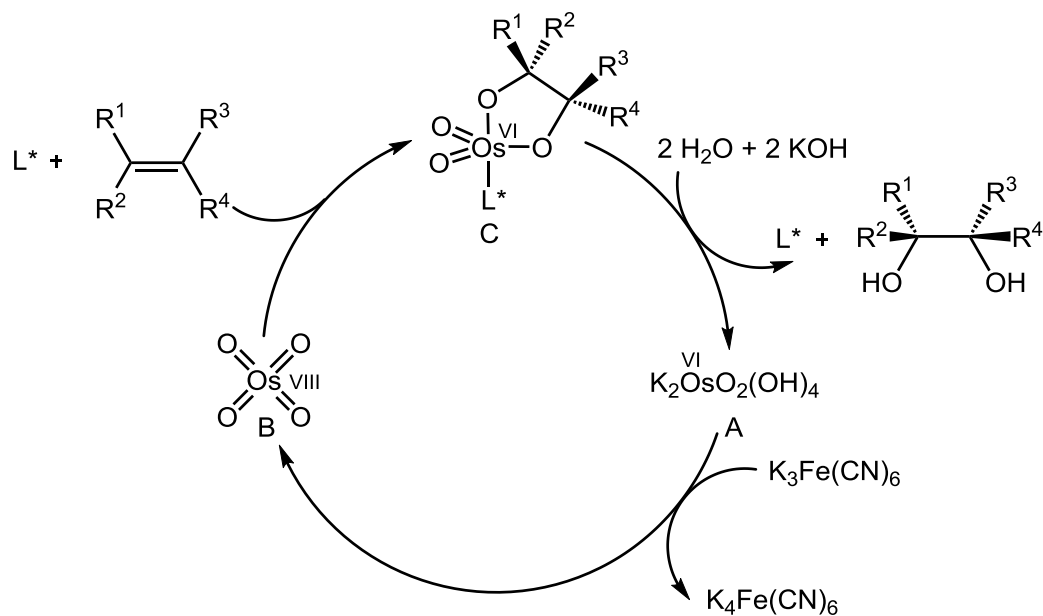
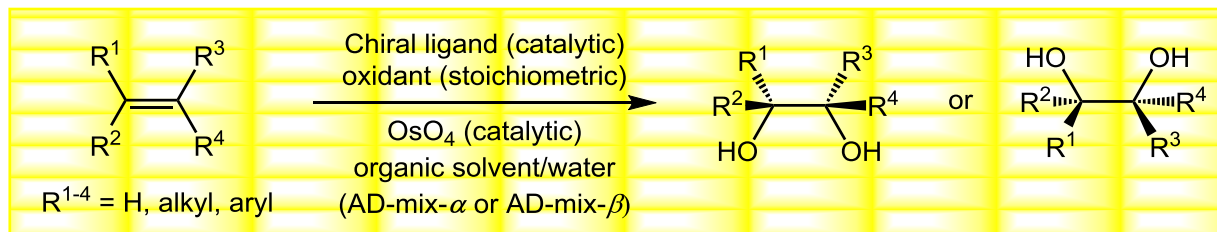


## AD-mix- $\beta$



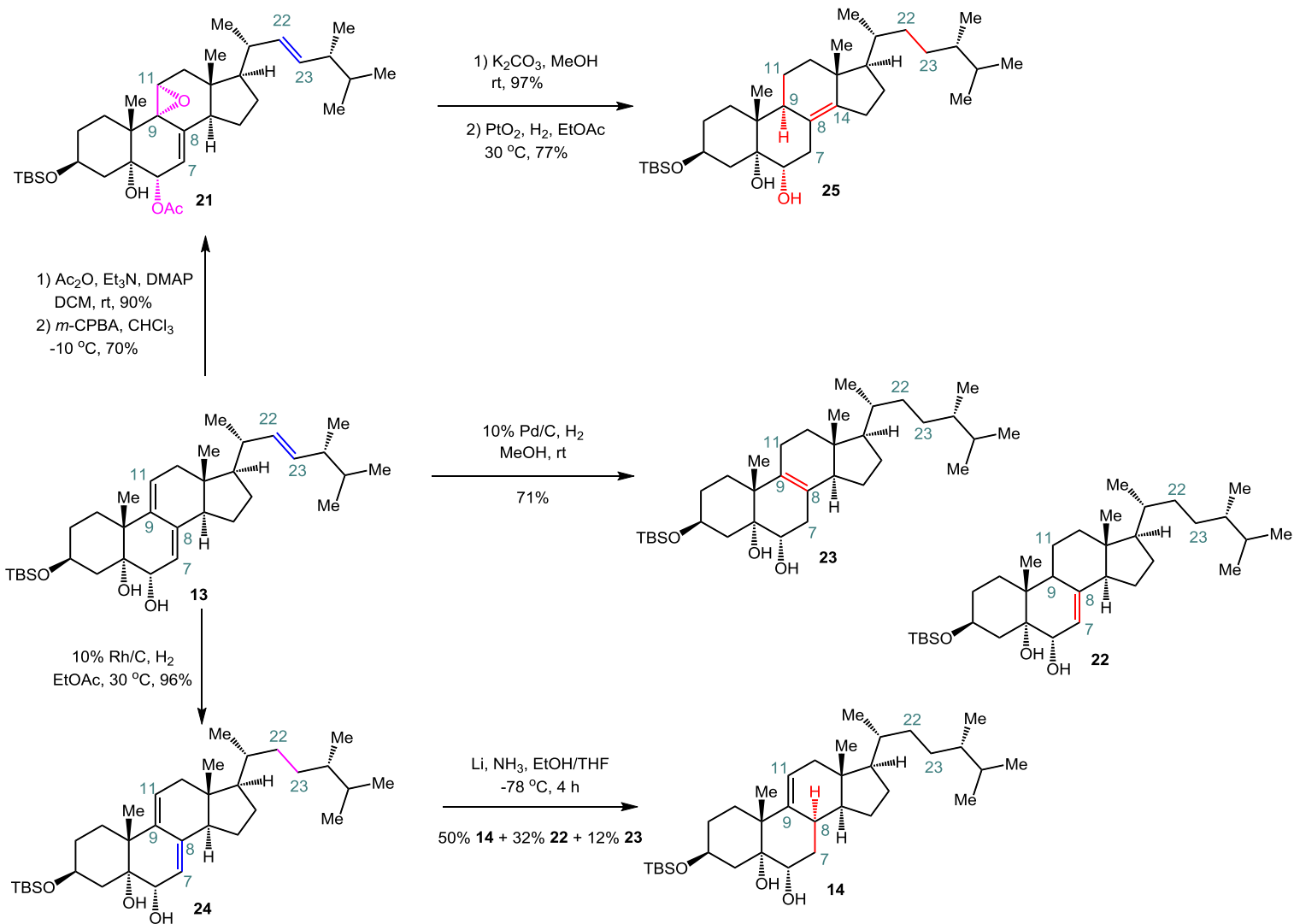
From Name Reaction

# Sharpless Asymmetric Dihydroxylation

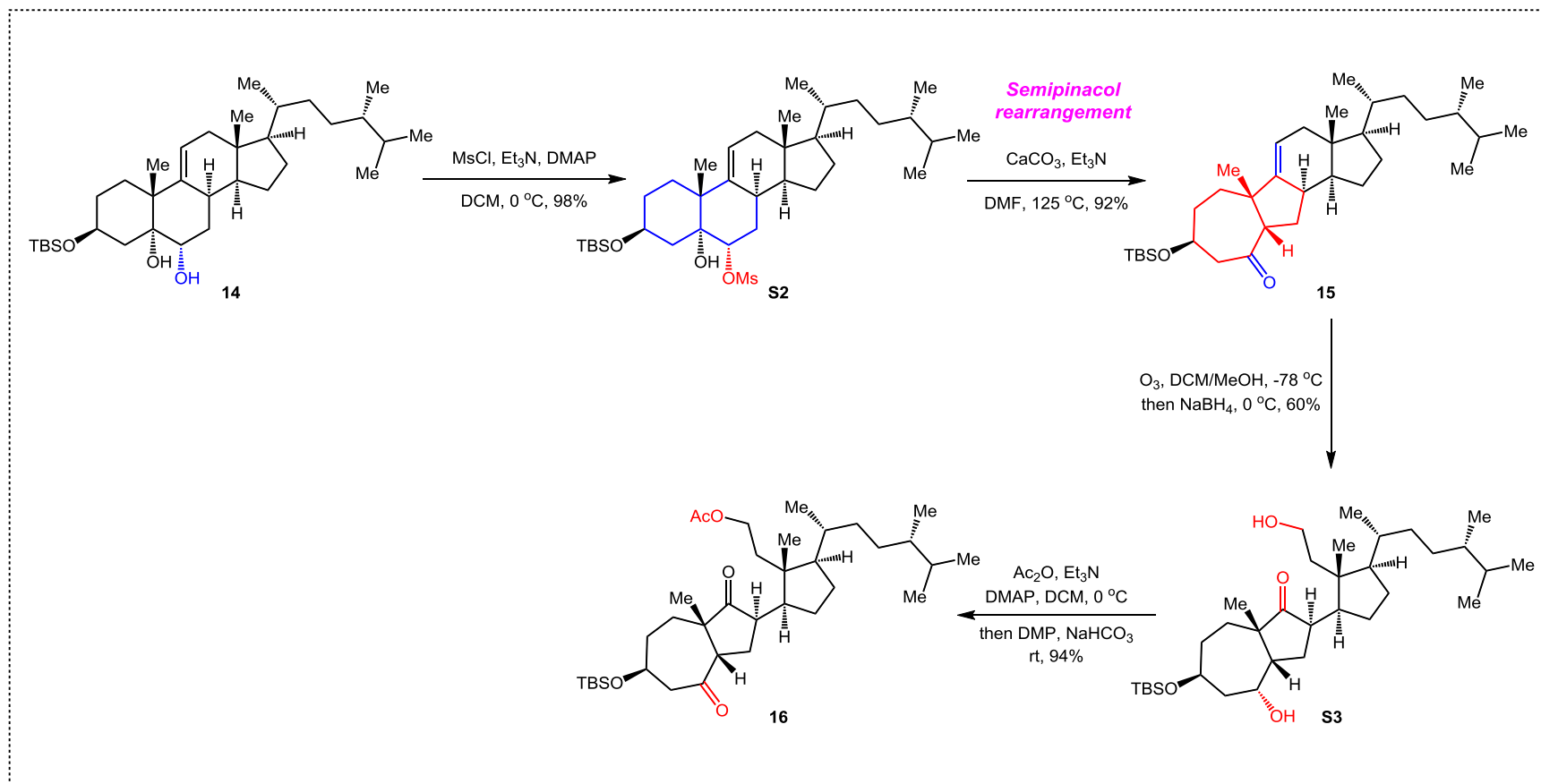


From Name Reaction

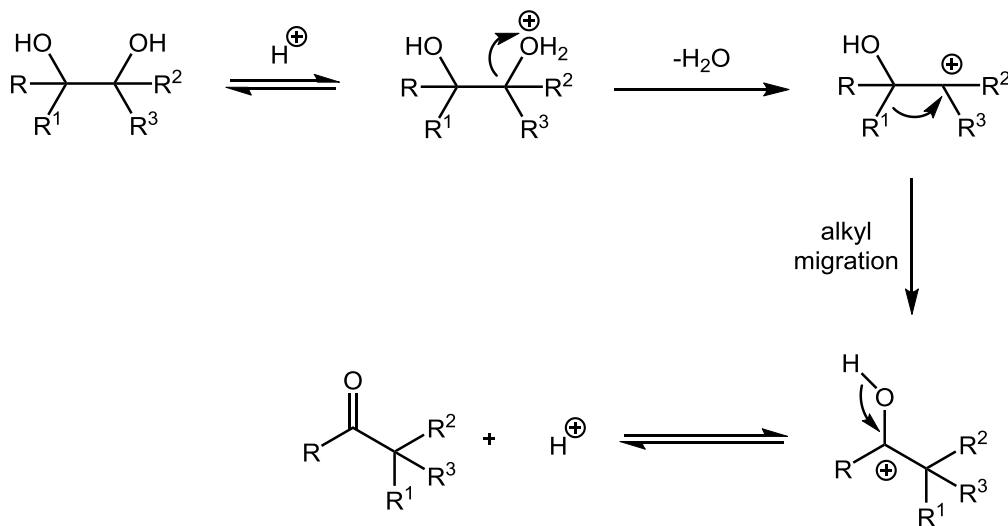
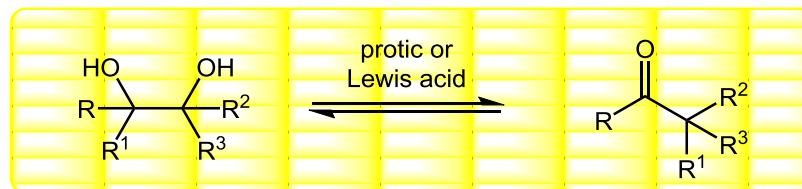
# Synthesis of Compound 14



# Synthesis of Compound 16

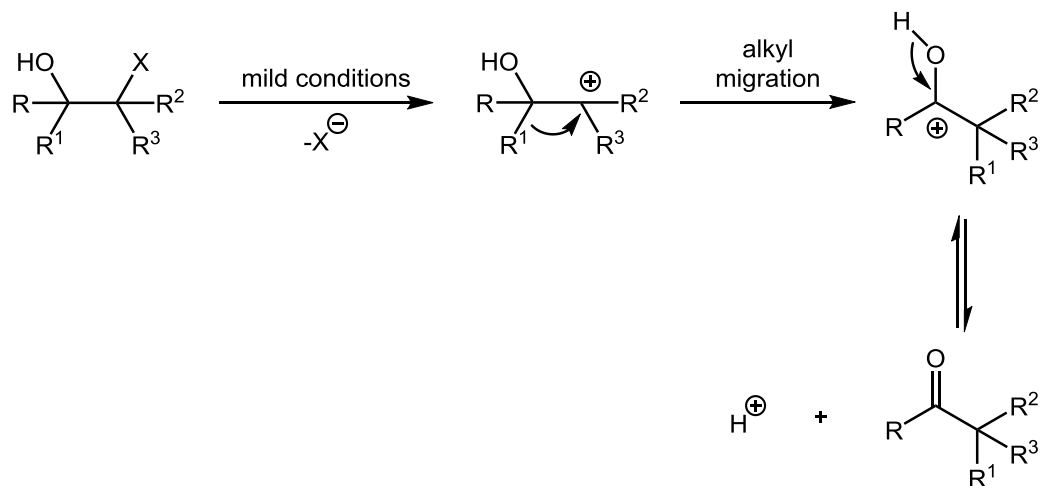
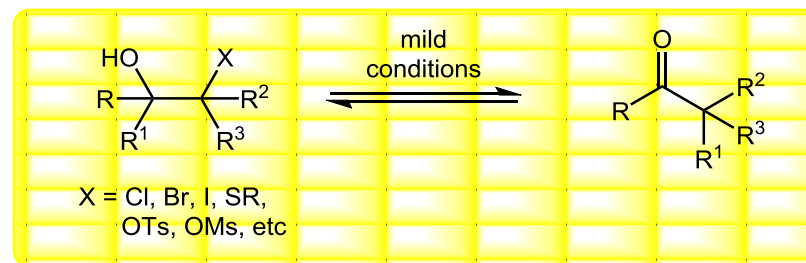


# Pinacol Rearrangement



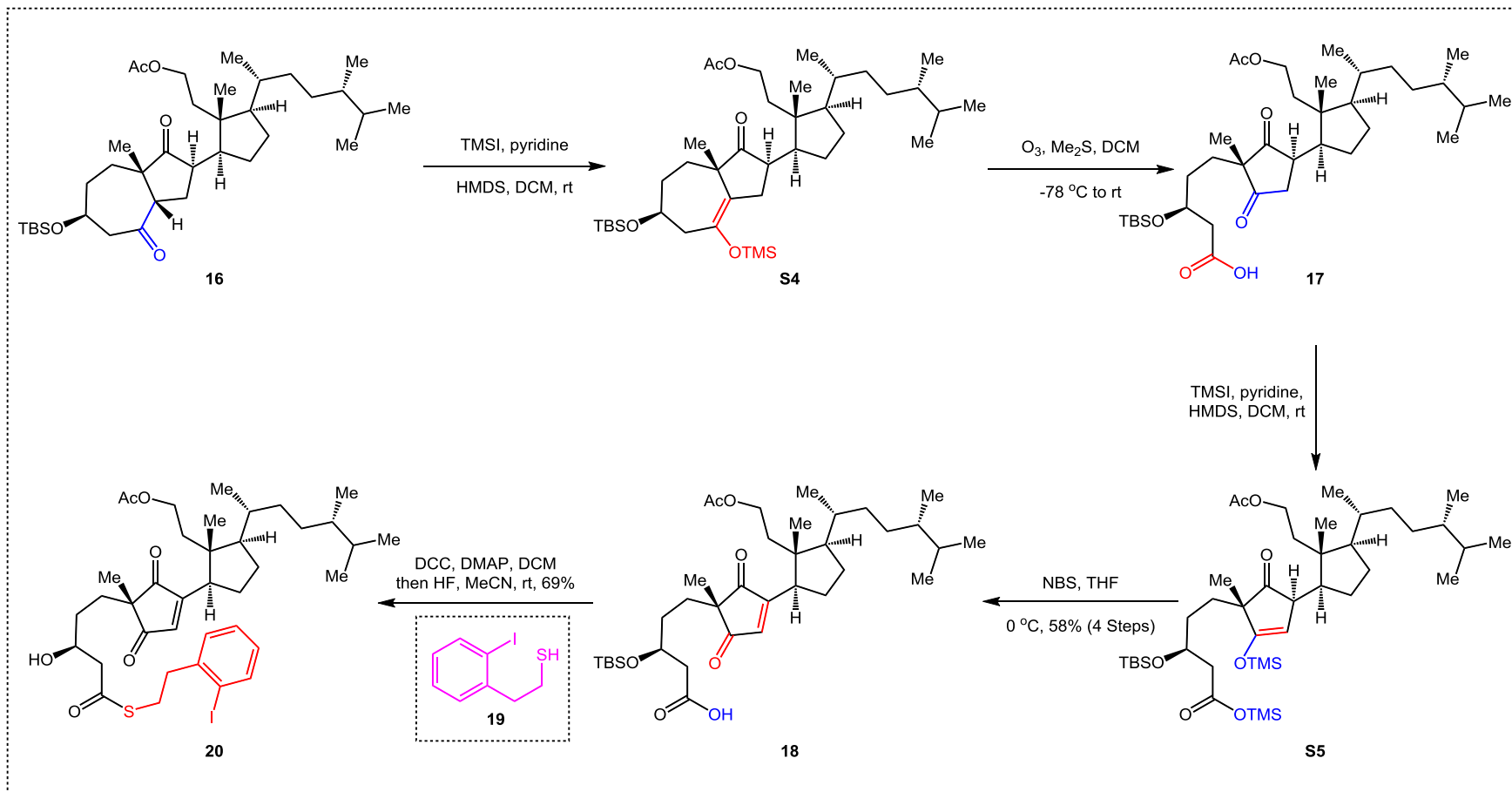
From Name Reaction

# Semipinacol Rearrangement

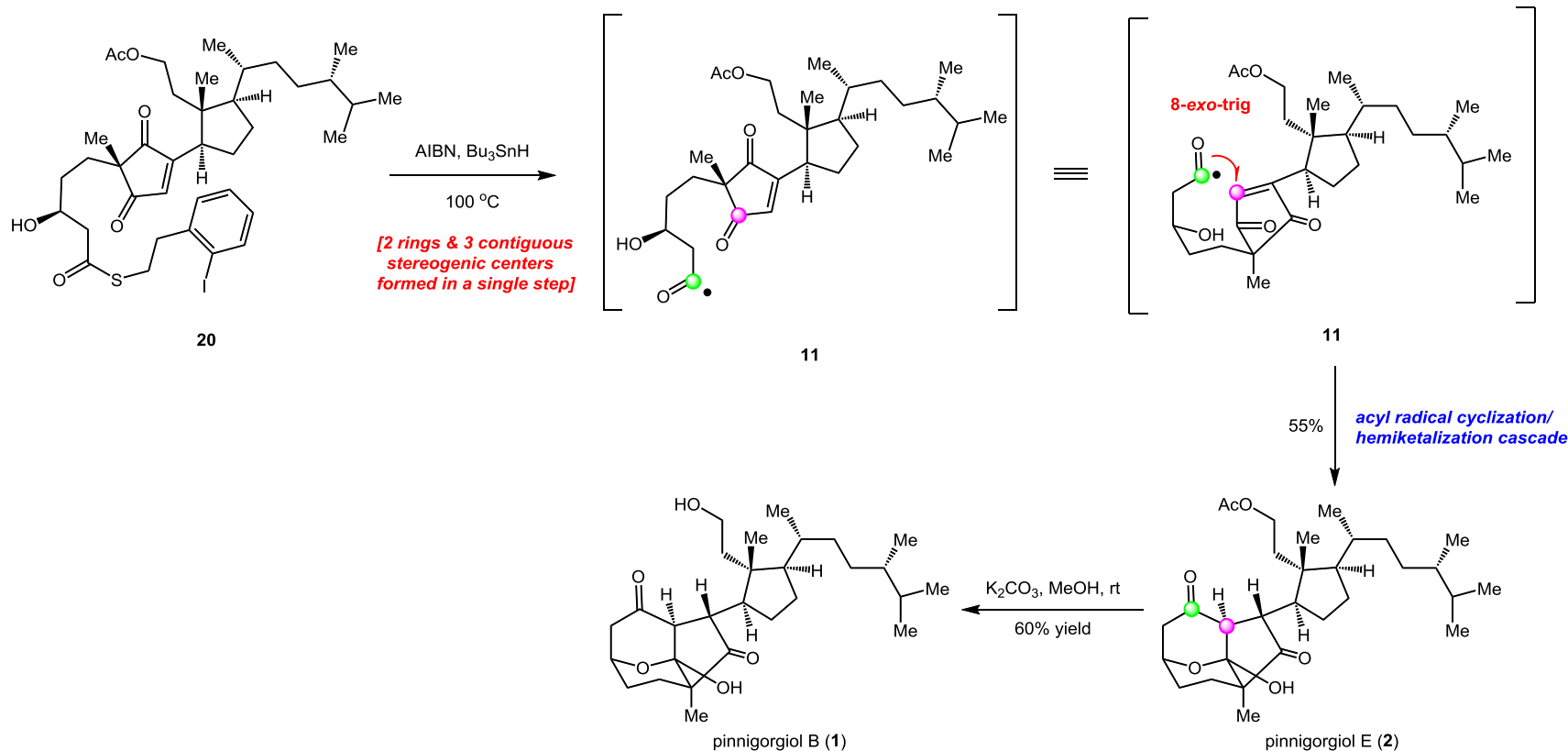


From Name Reaction

# Synthesis of Compound 20



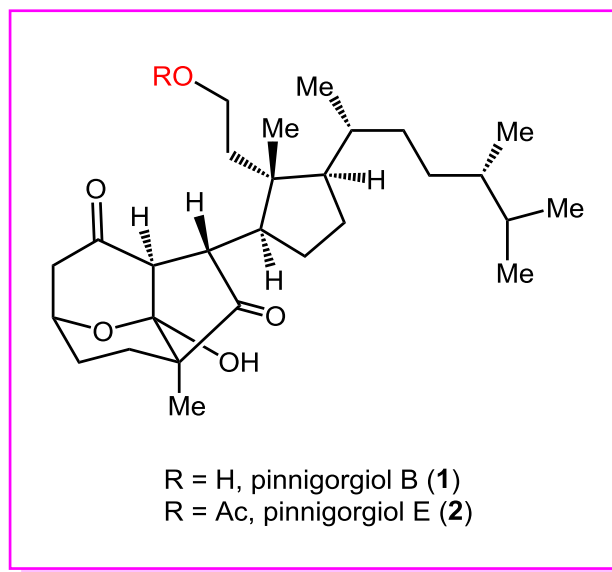
# Synthesis of Compound Pinnigorgiols B and E





# Summary

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- 15 Total steps, 1.44 % overall yield (Pinnigorgiol B (2))
- 16 Total steps, 0.87 % overall yield (Pinnigorgiol E (1))
- Sharpless asymmetric dihydroxylation
- Semipinacol rearrangement
- Acyl radical cyclization/Hemiketalization cascade

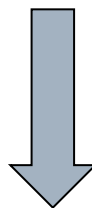
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# The First Paragraph

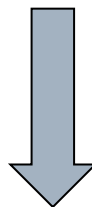
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## Writing Strategy

9,11-甾类固醇的共同结构特点



代表的天然产物



来源和性质

# The First Paragraph

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Rearranged steroid natural products, including secosteroids (in which at least one ring is cleaved) and *abeo*-steroids (in which there is at least one migrated C–C bond within the classic tetracyclic framework), have recently received considerable attention from synthetic chemists owing to the structural diversity and biological importance of these compounds. Representative naturally occurring rearranged steroids include cyclopamine, glaucogenins, cortistatins, nakiterpiosin, strophasterol A, cyclocitrinols, pleurocins, swinhoeisterol, bufospirostenin A, dankasterones, and periconiastone A. Two particularly challenging examples of such natural products are the 9,11-secosteroids pinnigorgiol B (**1**) and pinnigorgiol E (**2**), which possess a unique tricyclo [5,2,1,1] decane framework with an embedded  $\gamma$ -diketone moiety.

# The First Paragraph

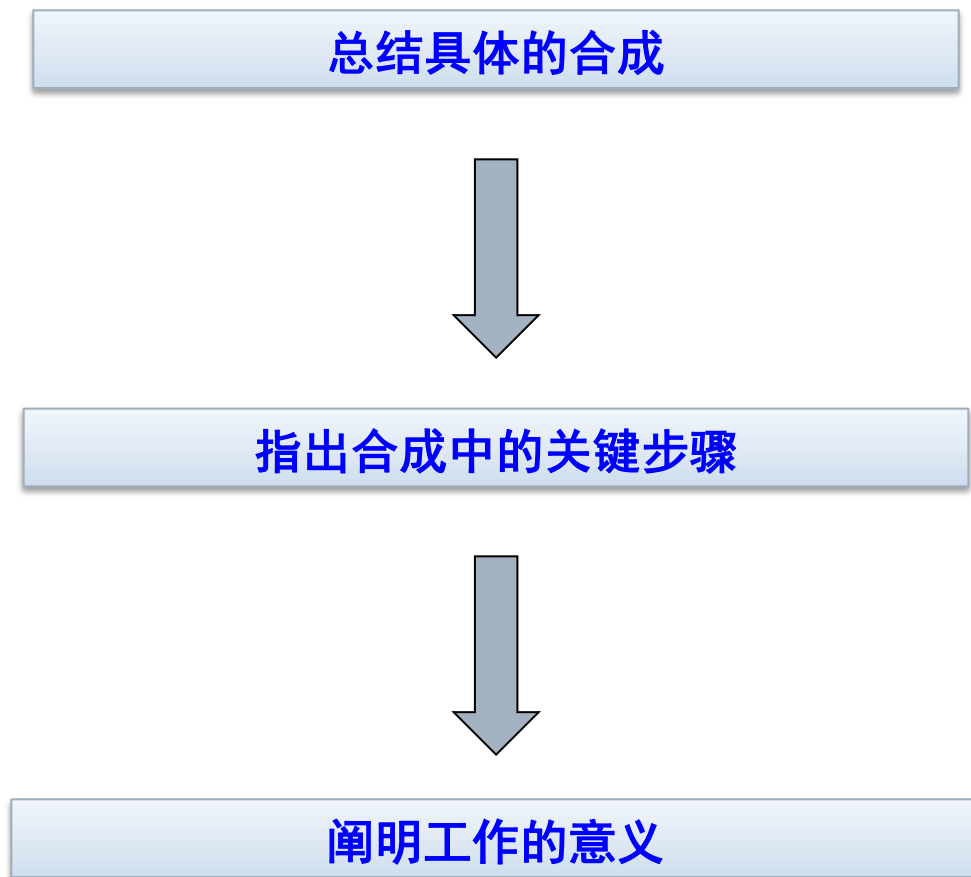
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These compounds were isolated by Sung and co-workers from a *Pinnigorgia* coral species in 2016, along with a biogenetic precursor, pinnisterol E (**3**). Pinnisterol E is a typical secosteroid with one cleaved C–C bond, whereas pinnigorgiol B is both a secosteroid (the C9–C11 bond is cleaved) and an *abeo*-steroid (several bonds of the A/B bicyclic skeleton are migrated) and is among the most heavily rearranged steroid natural products reported so far. Notably, aplysiasecosterol A (**4**) and aplysiasecosterol B (**5**), which share the same core skeleton as **1** and **3**, were isolated by Kigoshi and co-workers from the sea hare *Agplysia kurodai*. Importantly, pinnigorgiols have been shown to induce apoptosis of hepatic stellate cells, and aplysiasecosterol A is moderately cytotoxic to human myelocytic leukemia cells (HL-60).

# The Last Paragraph

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## Writing Strategy



# The Last Paragraph

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In conclusion, we have achieved the first synthesis of the 9,11-secosteroids pinnigorgiols B and E from inexpensive ergosterol. Our synthesis of the pinnigorgiols features a semipinacol rearrangement and an acyl radical cyclization/hemiketalization cascade, which converts a biogenetic tandempolar rearrangement into a stepwise hybrid combination of polar and radical reactions. Our work also demonstrates how inspiration from a putative biosynthesis pathway can be strategically used to develop a practical synthetic approach.

# Representative Examples

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Because the ketol intermediate structurally similar to **6** was reported to undergo facile C10 migration from C6 to C5, and achieving the desired vinylogous  $\alpha$ -ketol rearrangement was challenging, we **opted to** design an alternative, stepwise strategy for accessing **2**. (选择了.....)

Interestingly, acetylation of the C6 hydroxyl group of **13** enabled regioselective epoxidation of the C9–C11 double bond, **giving rise to** epoxide **24**. (生成了.....)

Having established a reliable method for preparing **14**, we **were poised to** attempt the first bond migration within the decalin A/B ring system to generate the 7,5-bicyclic scaffold by means of the semipinacol rearrangement.. (准备好去做.....)

# Acknowledgement

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***Thanks  
for your attention***