

Literature Report I

C-C Activation Application in Total Synthesis of Xishacorene B

Reporter: Xiao-Qing Wang

Checker: Zhou-Hao Zhu

Date: 2018-12-3

Sarpong, R. *et al. J. Am. Chem. Soc.* **2015**, *137*, 6327.

Sarpong, R. *et al. J. Am. Chem. Soc.* **2018**, *140*, 9810.

CV of Prof. Richmond Sarpong

Background:



Richmond
Sarpong

- 1991-1995 B.S., Macalester College (St. Paul, MN)
- 1995-2000 Ph.D., Princeton University
- 2000-2004 Postdoctoral, California Institute of Technology
- 2004-2010 Assistant Professor, UC, Berkeley
- 2010-2014 Associate Professor, UC, Berkeley
- 2014-now Full Professor, UC, Berkeley

Research Interests:

- Organic and Organometallic Chemistry — Total synthesis of biologically active and architecturally complex natural products as a platform for the development of new synthetic methods and strategies.
-

Contents

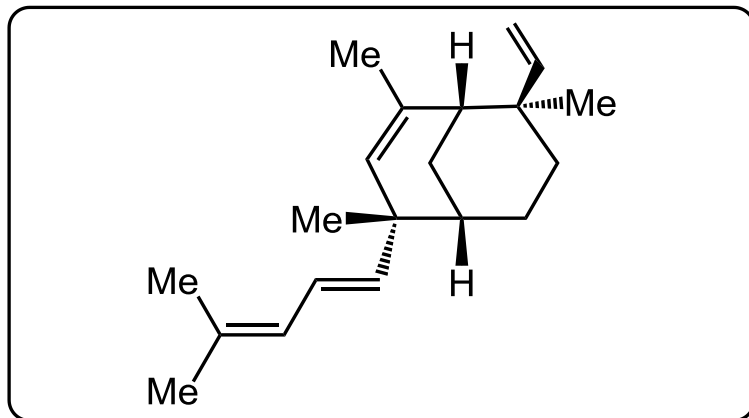
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2 C-C Activation Strategy

3 Total Synthesis of Xishacorene B

4 Summary

Introduction



Xishacorene B

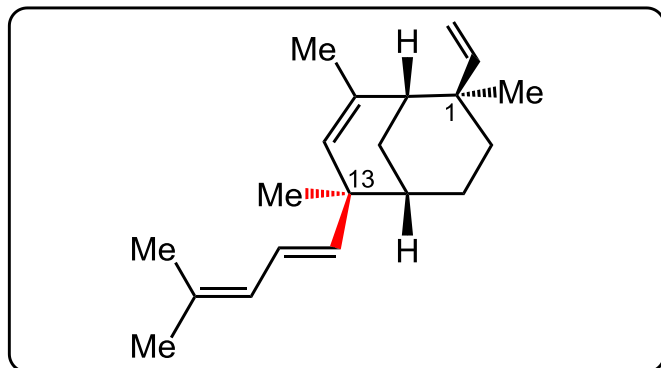


Xisha Coral

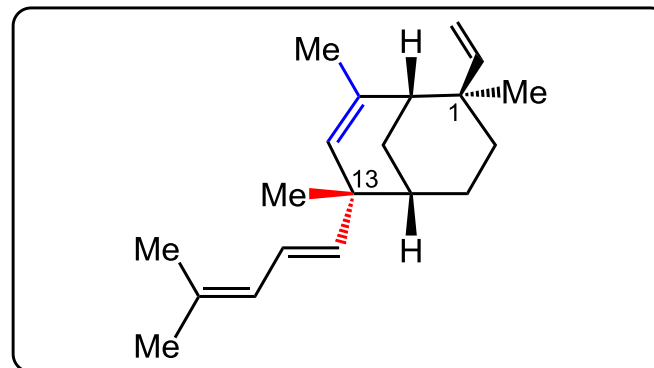
- A new member of diterpenes;
- Isolated from the soft coral *Sinularia polydactyla* off the coast of the Xisha Islands in China;
- As promoters of concanavalin A-induced T-lymphocyte proliferation.

Guo, Y.-W. *et al. Org. Lett.* **2017**, *19*, 4183.

Introduction



Xishacorene A

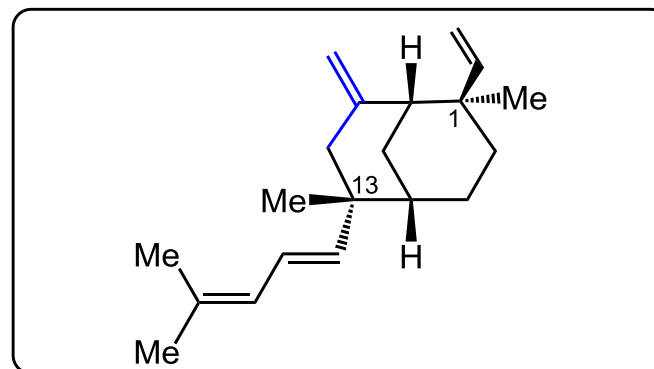


Xishacorene B

Xisha + Coral + Terpene



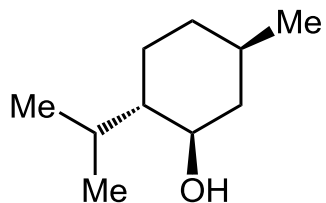
Xishacorene



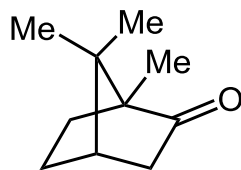
Xishacorene C

Introduction

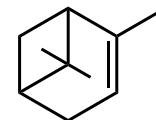
单萜
(10个碳)



薄荷醇
Menthol

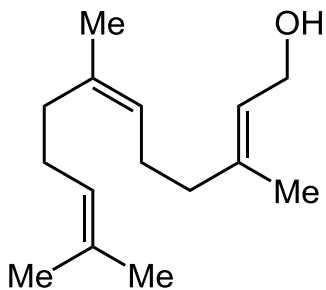


樟脑
Camphor

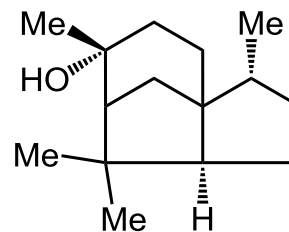


蒎烯
Pinene

倍半萜
(15个碳)

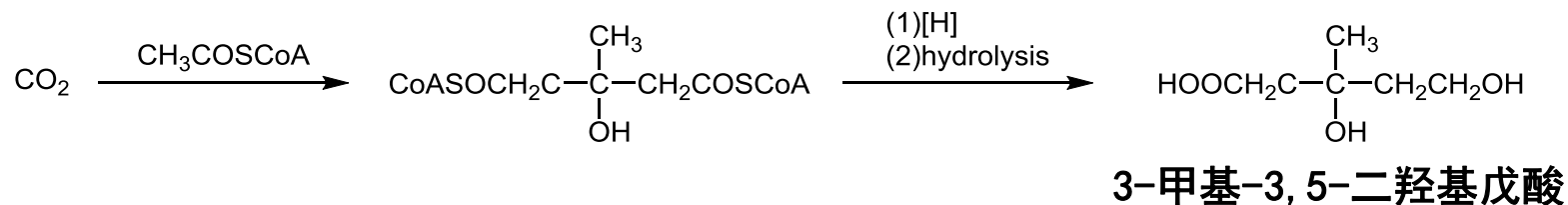


金合欢醇
Farnesol

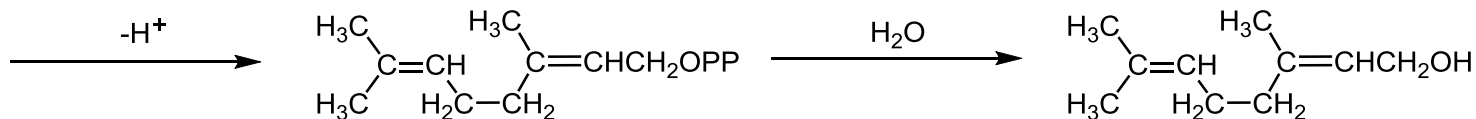


柏木醇
Cedrol

Introduction

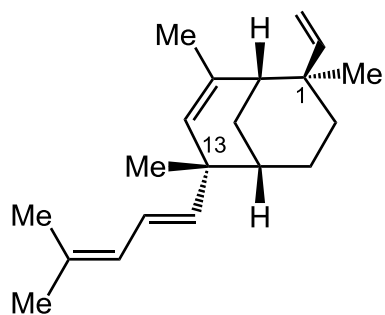


焦磷酸异戊烯酯

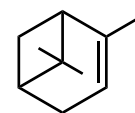
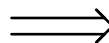


牻牛儿醇
Geraniol

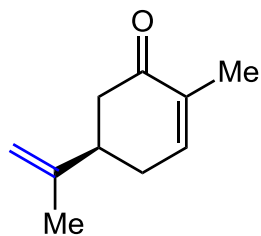
Introduction



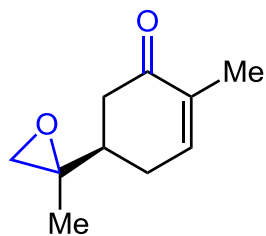
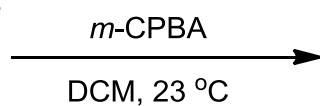
Xishacorene B



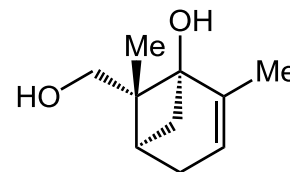
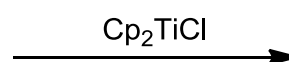
蒎烯
Pinene



(R)-Carvone 1

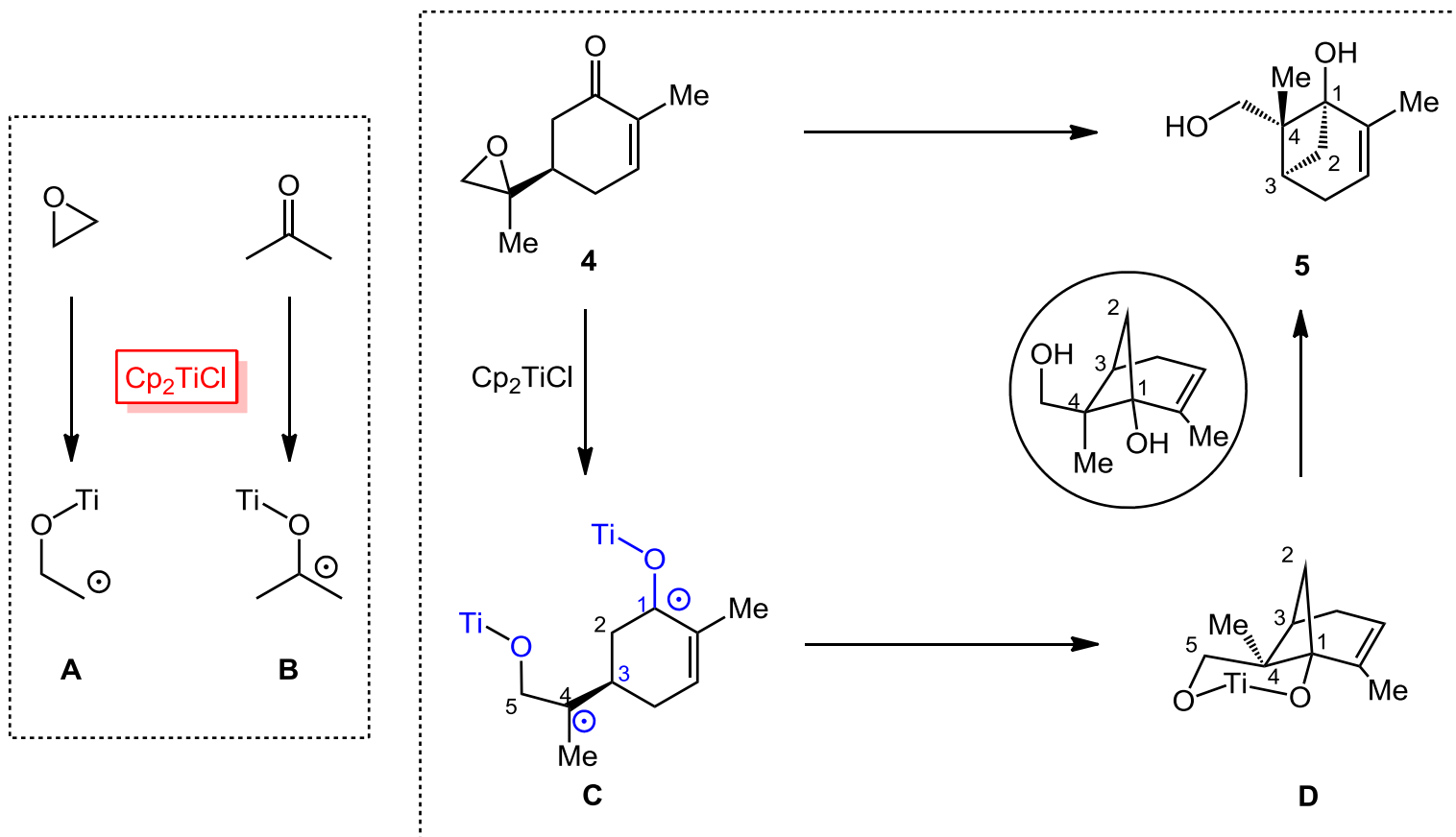


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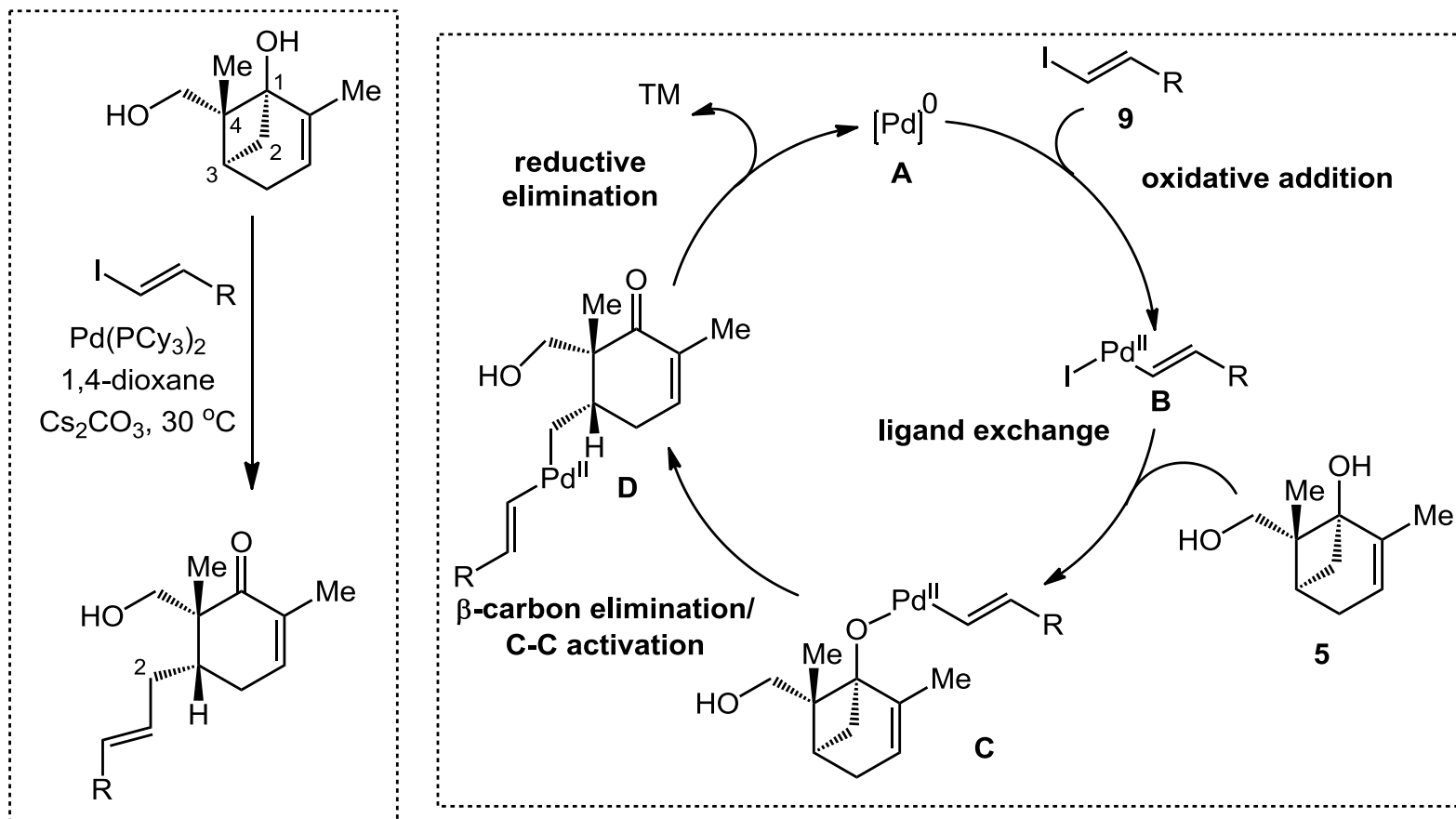
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C-C Activation Reaction



Low Valence Titanium: Single Electron Transfer (SET) Reagent (Ti(III)---Ti(IV) one electron transfer)

C1-C2 Activation

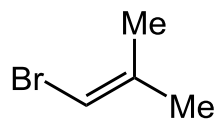
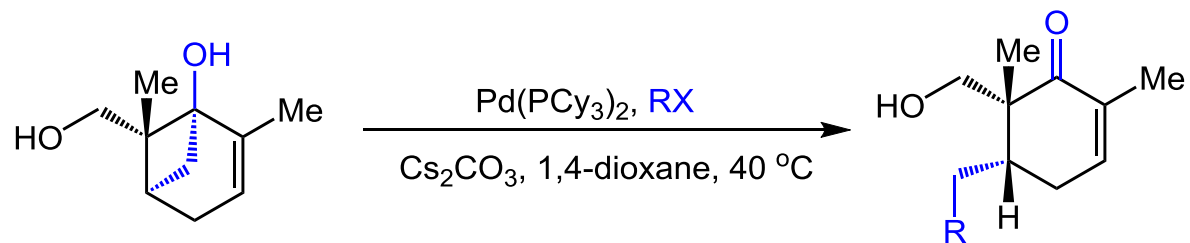


Pd-Catalyzed C-C Activation/Coupling Sequence

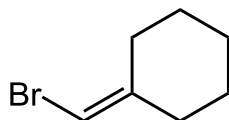
| Entry | Pd-complex | 9 | Temperature | Solvent | Conversion ^a | Yield ^a |
|-------|--|-----------|-------------|-------------|-------------------------|--------------------|
| 1 | Pd(PCy ₃) ₂ | 1.5 equiv | 30 °C | 1,4-dioxane | >98% | 85% |
| 2 | Pd(PCy ₃) ₂ | 1.1 equiv | 30 °C | 1,4-dioxane | >98% | 74% |
| 3 | Pd(PCy ₃) ₂ | 1.5 equiv | 18 °C | 1,4-dioxane | 67% | 49% |
| 4 | Pd(PPh ₃) ₄ | 1.5 equiv | 30 °C | 1,4-dioxane | 81% | 63% |
| 5 | Pd[P(^t Bu) ₂ Ph] ₂ | 1.5 equiv | 30 °C | 1,4-dioxane | 73% | 56% |
| 6 | Pd(PCy ₃) ₂ | 1.5 equiv | 30 °C | benzene | 92% | 63% |

^a Determined by ¹H NMR analysis using benzyl benzoate as an internal standard

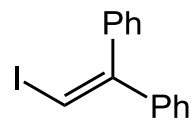
Substrate Scope



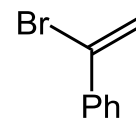
89%



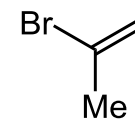
53%



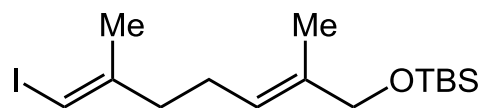
69%



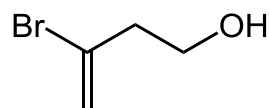
78%



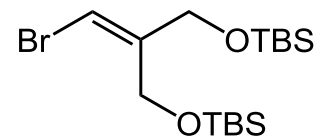
68%



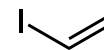
77%



53%

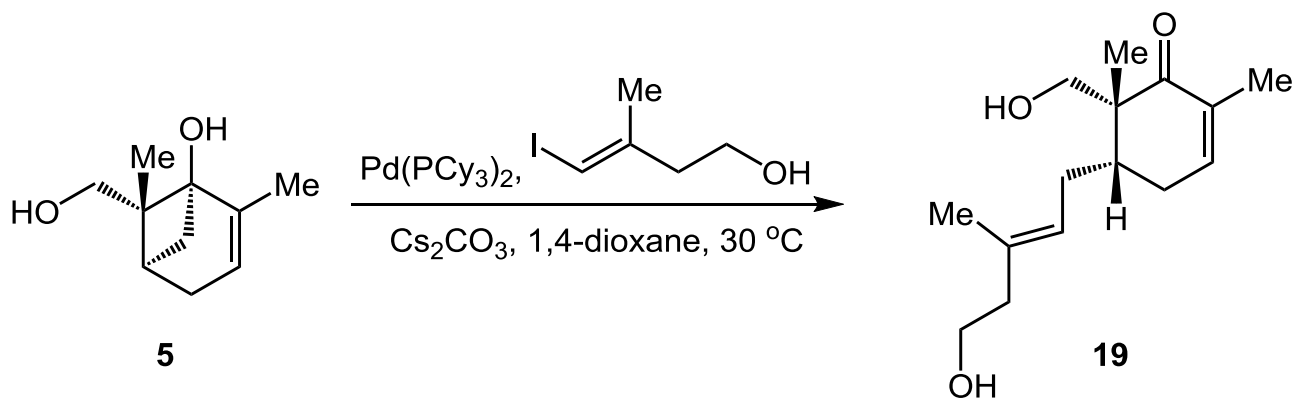


50%

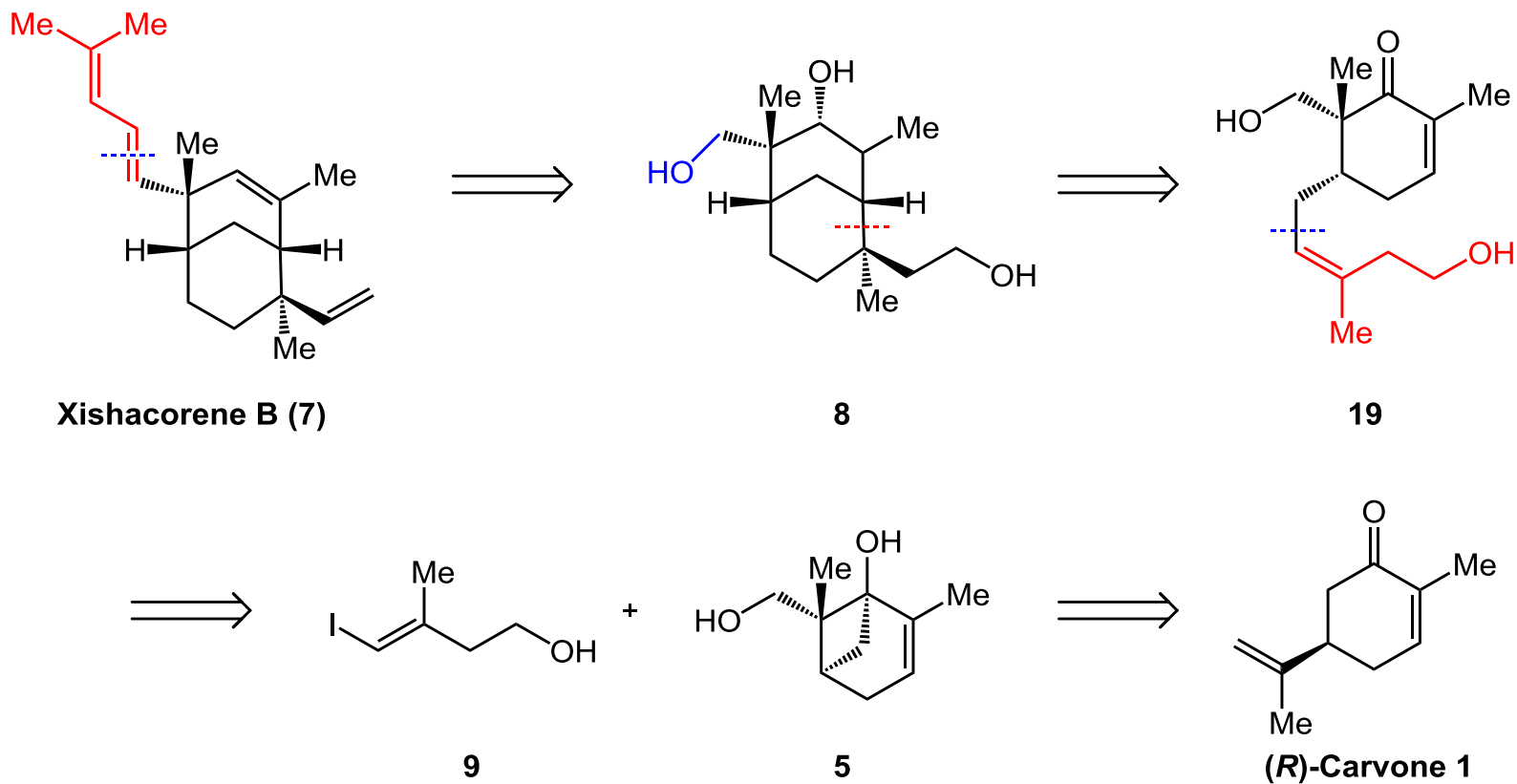


38%

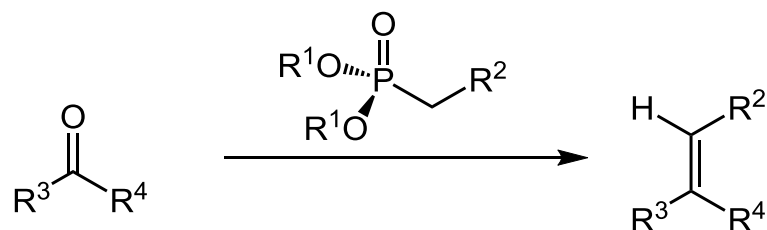
Pd-Catalyzed C-C Activation/Coupling Sequence



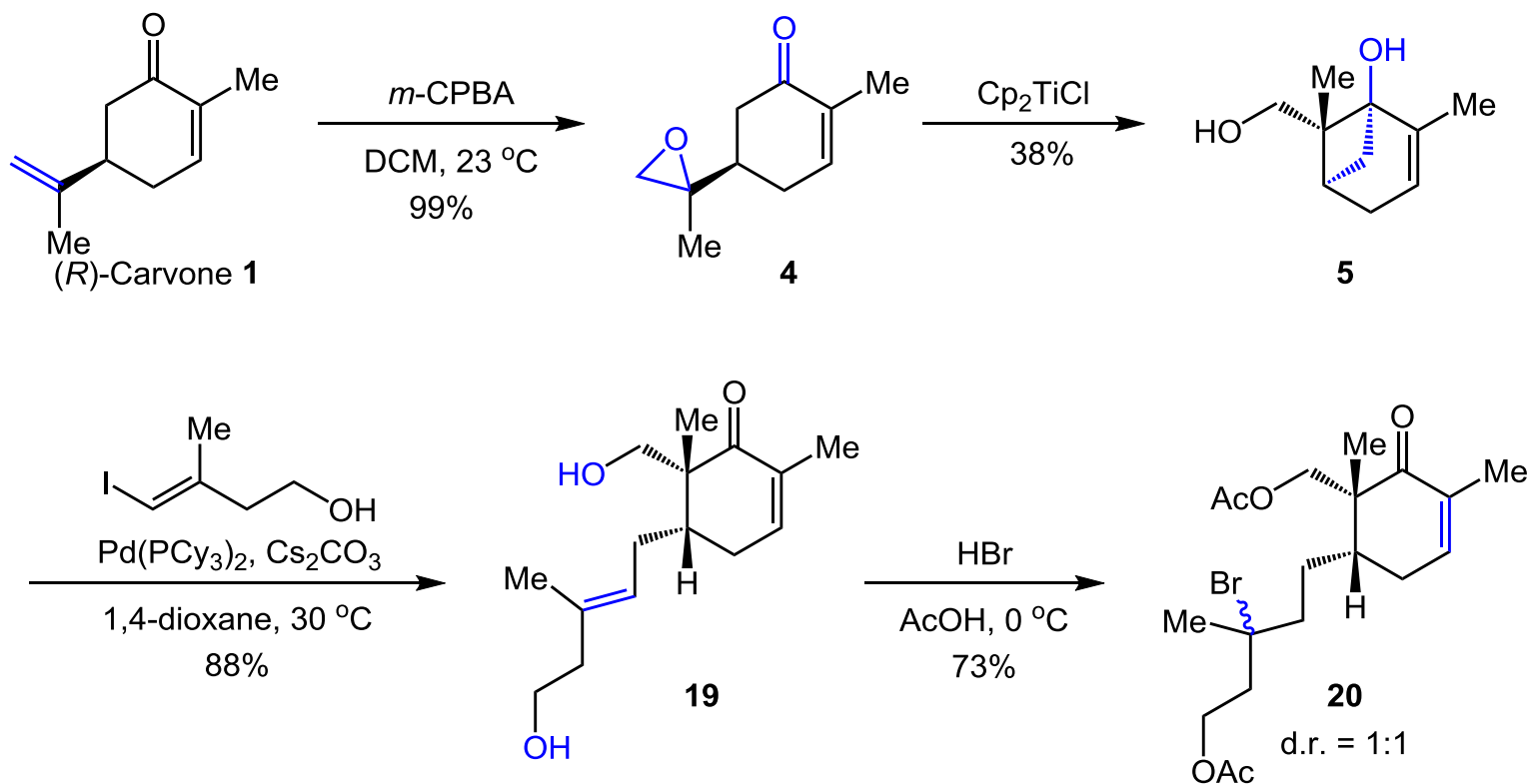
Retrosynthetic Analysis



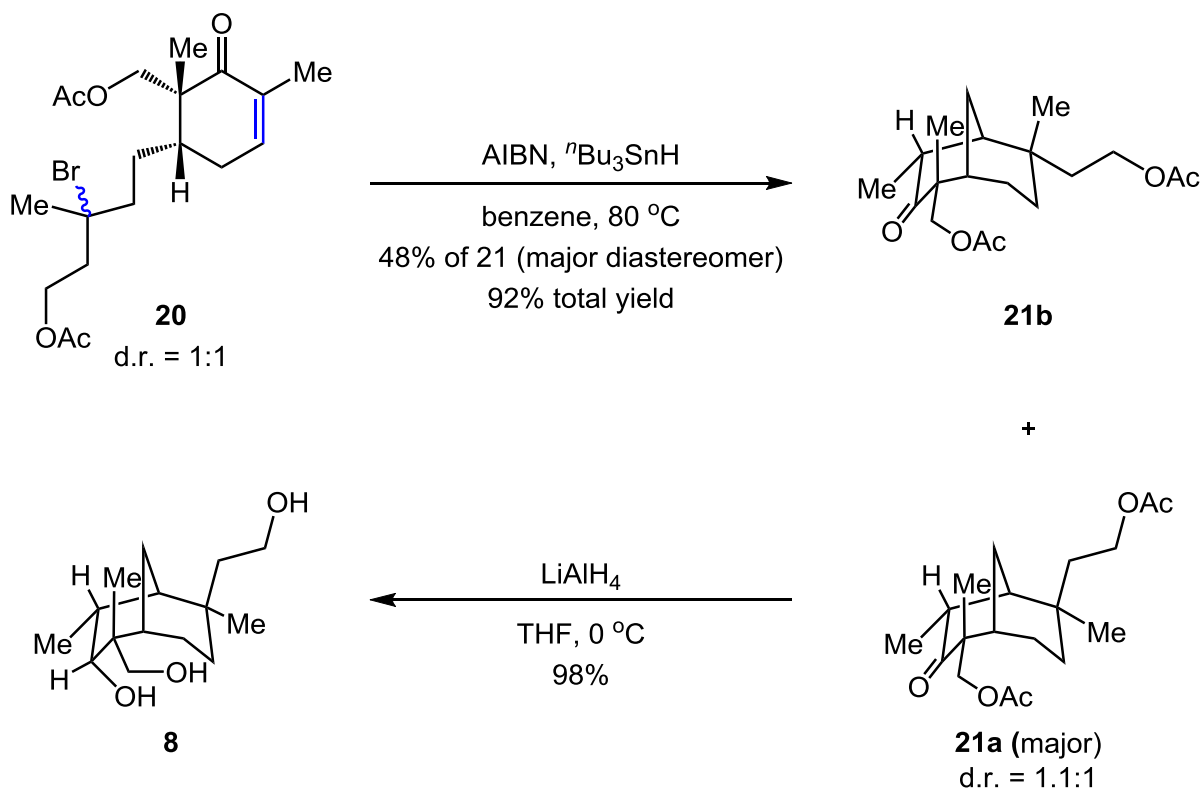
Horner-Wadsworth-Emmons Olefination



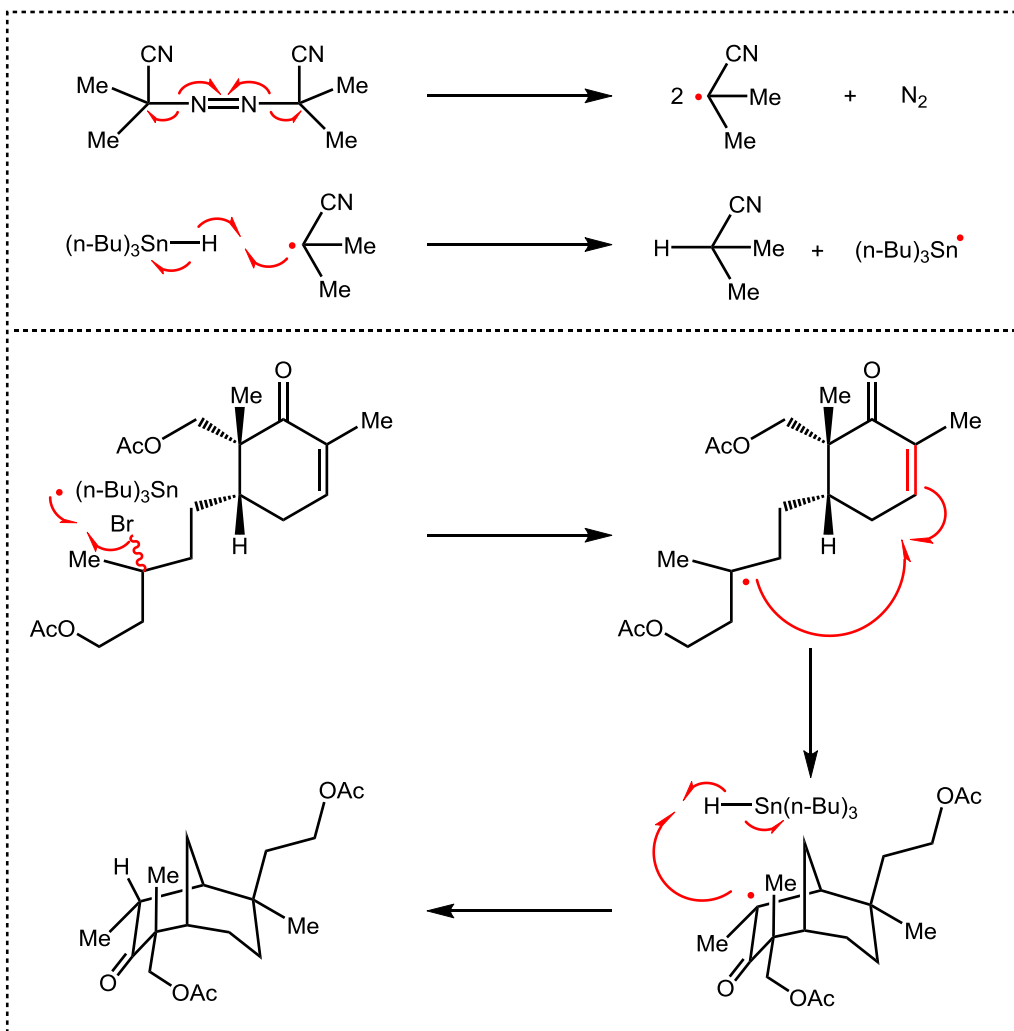
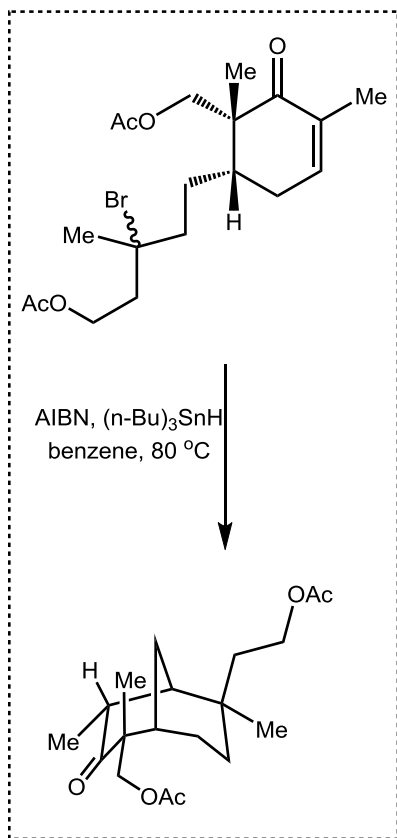
The Synthesis of 20



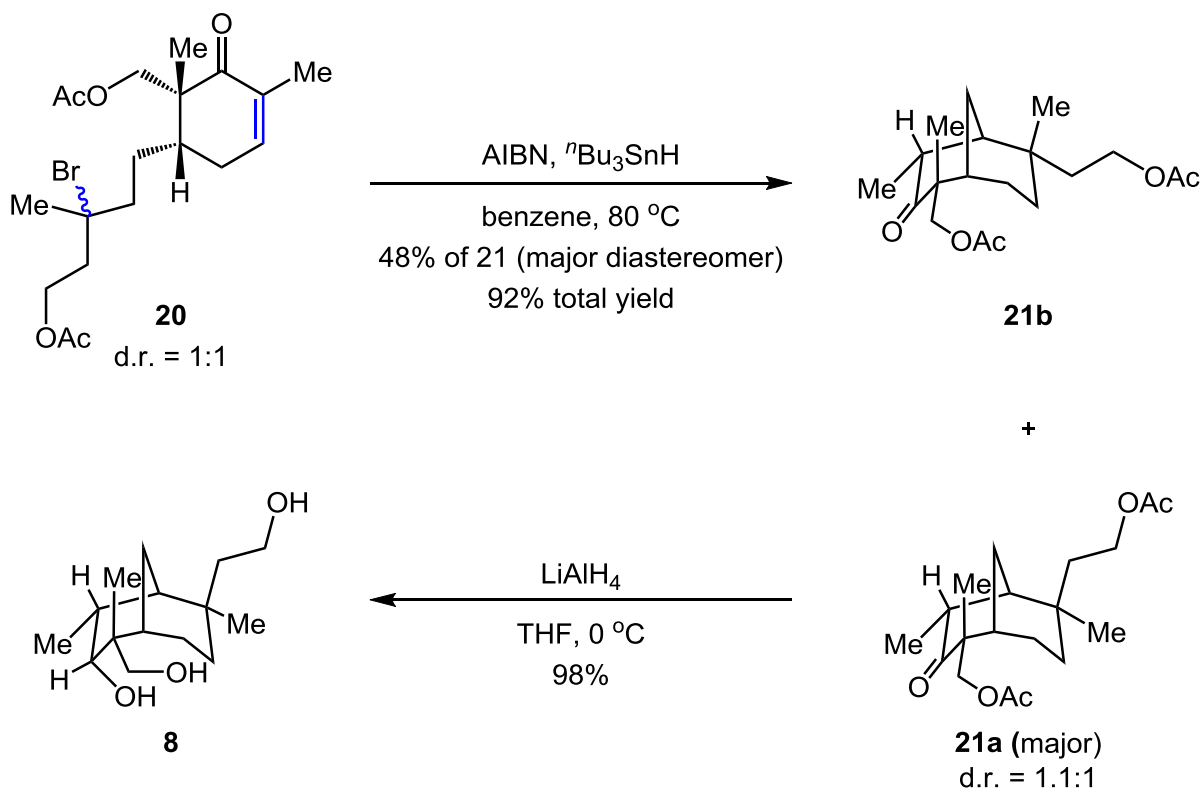
The Synthesis of 8



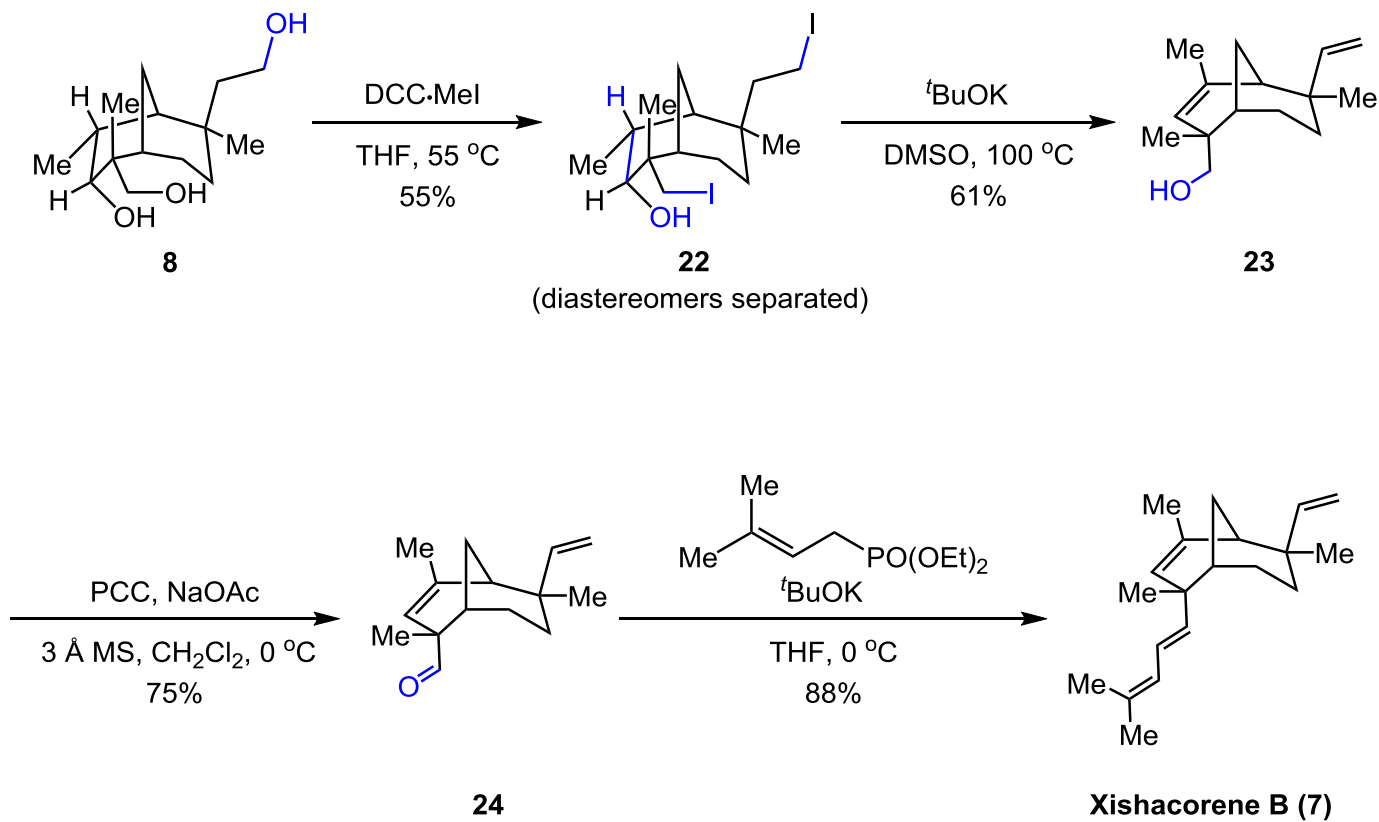
The Synthesis of 21



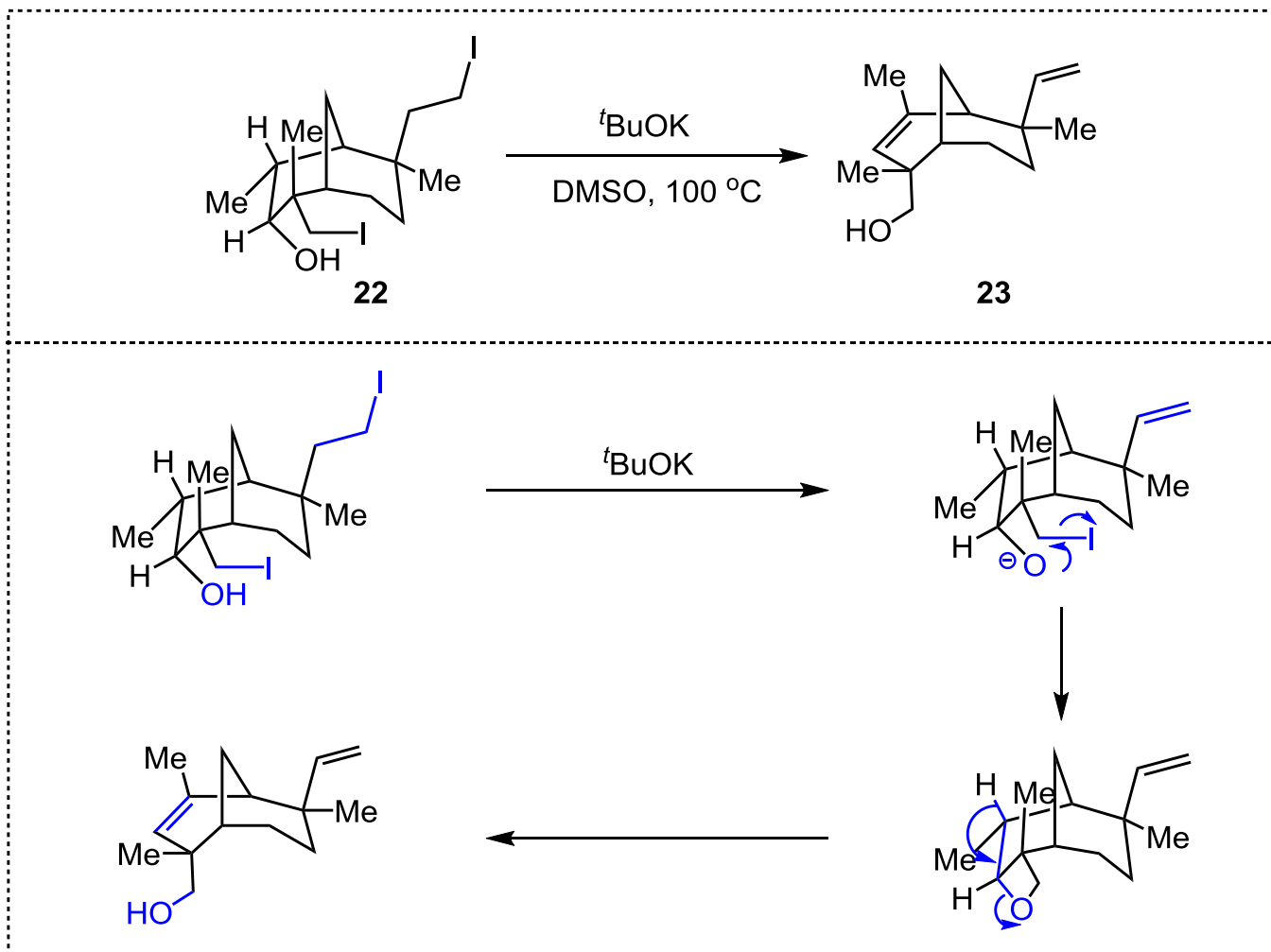
The Synthesis of 8



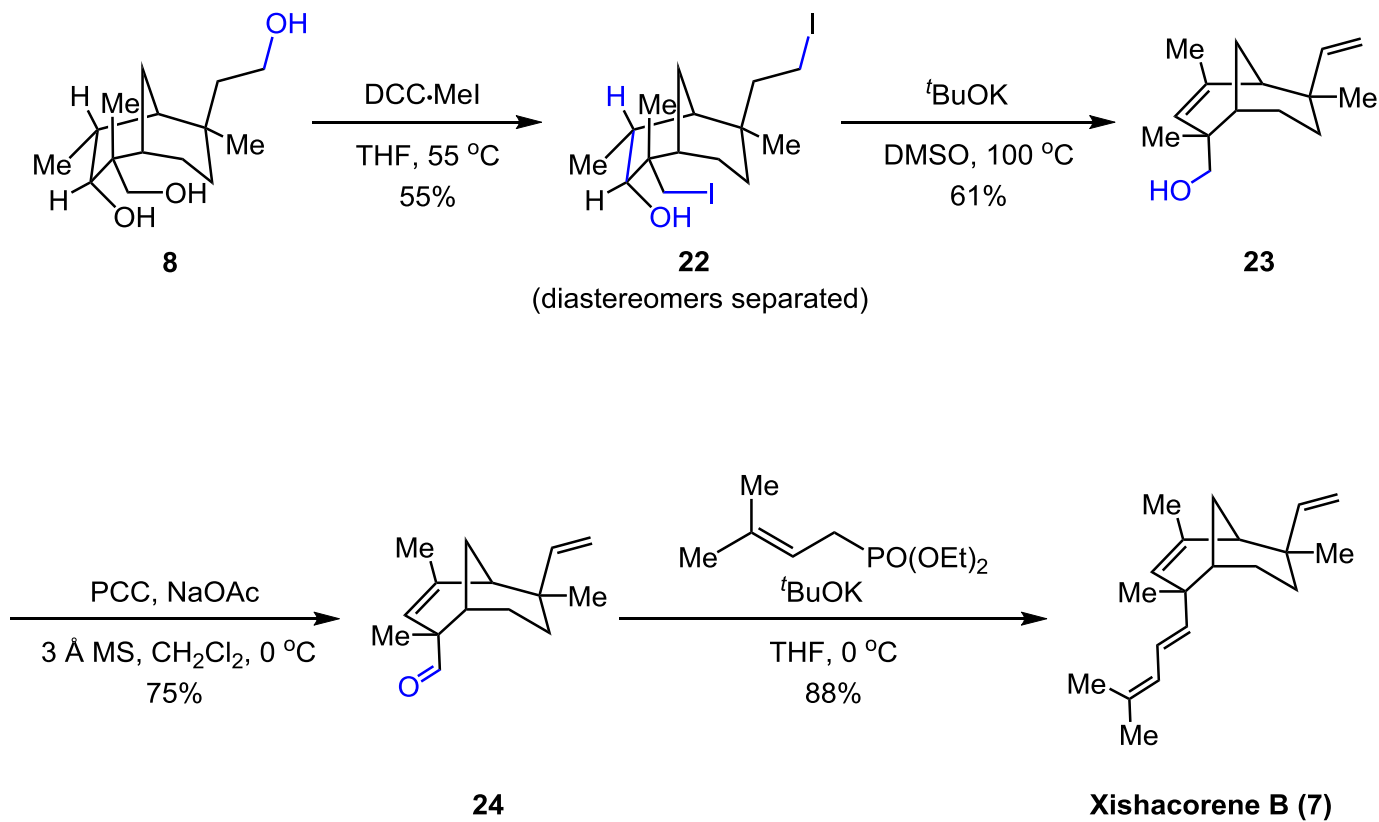
The Synthesis of Xishacorene B (7)



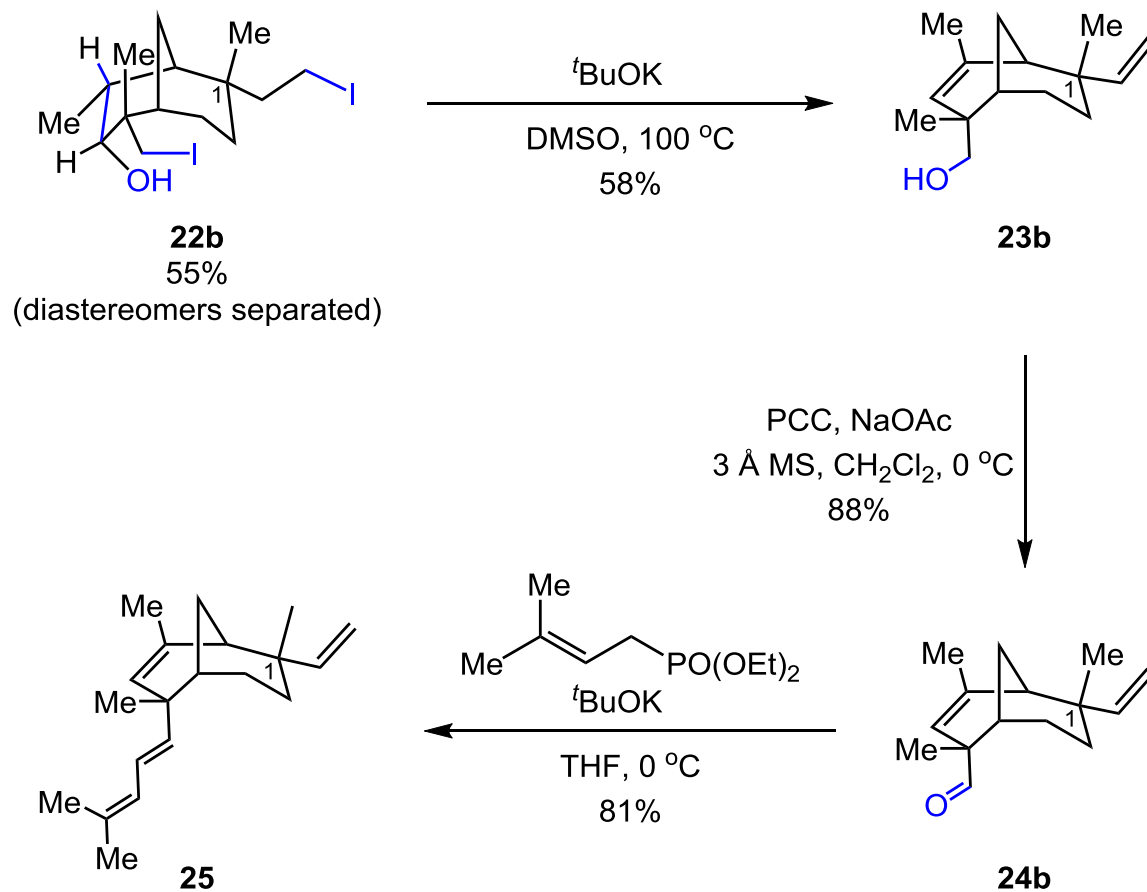
The Synthesis of 23



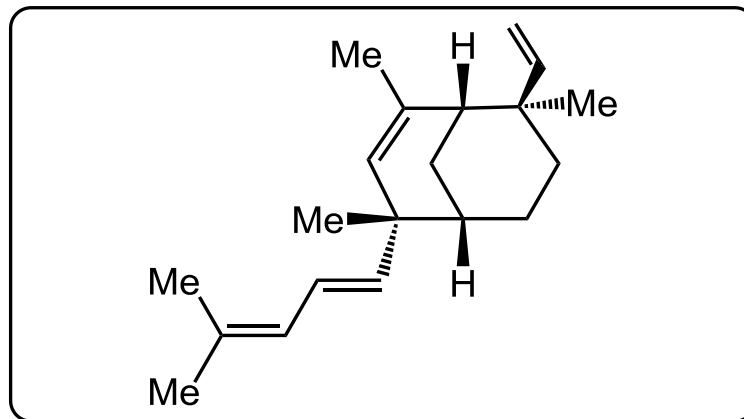
The Synthesis of Xishacorene B (7)



The Synthesis of 25



Summary



Xishacorene B

- The first total synthesis of Xishacorene B: 10 Steps;
 - Pd-catalyzed cyclobutanol C-C cleavage/coupling;
 - Radical-mediated C-C bond construction;
 - Minimal protecting group manipulation.
-

The First Paragraph

The formation of carbon-carbon (C-C) bonds is paramount to the synthesis of complex organic molecules such as terpenoid natural products, which consist primarily of a carbon skeleton. Therefore, in developing strategies for the total synthesis of terpenoids, significant emphasis is often placed on methods that form new C-C bonds. As part of a program to exploit readily available, “chiral pool” reagents for terpene syntheses, we recognized that C-C activation of carvone, when coupled with new C-C bond forming processes, would yield novel structural frameworks that significantly expand the scope of complex molecules conventionally accessible from carvone.

The First Paragraph

We have shown previously that this type of transformation can be realized by converting epoxy carvone to bis-hydroxylated pinene derivatives using a method by Bermejo, followed by Pd(0)-catalyzed cross coupling with vinyl or aryl halides to provide access to structures such as 6, which form the core of myriad natural products.

The Last Paragraph

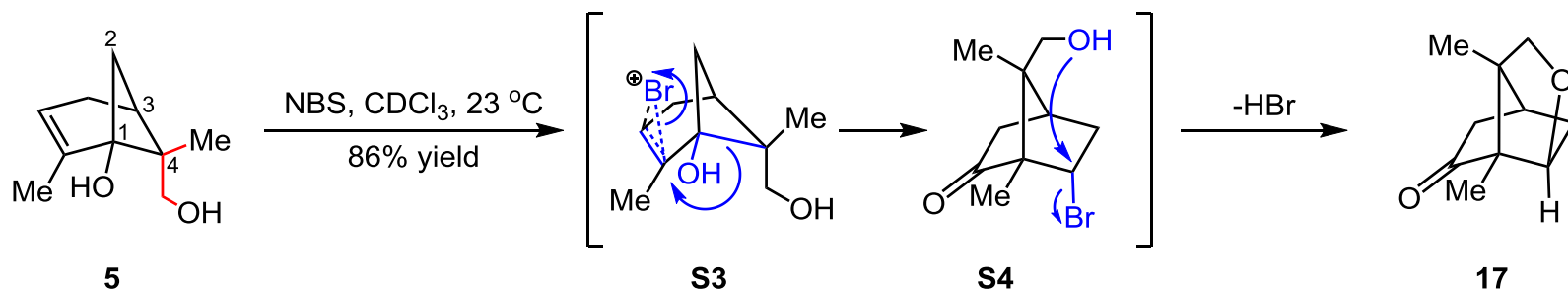
In conclusion, we have demonstrated the utility of a C–C activation/cross-coupling sequence for the construction of complex molecular frameworks. Specifically, carvone can be converted in two steps to a hydroxylated pinene derivative to set the stage for a key cross-coupling. A Pd-catalyzed cyclobutanol C–C cleavage/coupling with vinyl halides followed by radical-mediated C–C bond construction provided rapid access to a variety of [3.3.1] bicycles. Using this approach, the first total synthesis of the marine diterpene xishacorene B has been achieved in 10 steps from carvone minimal protecting group manipulation.

The Last Paragraph

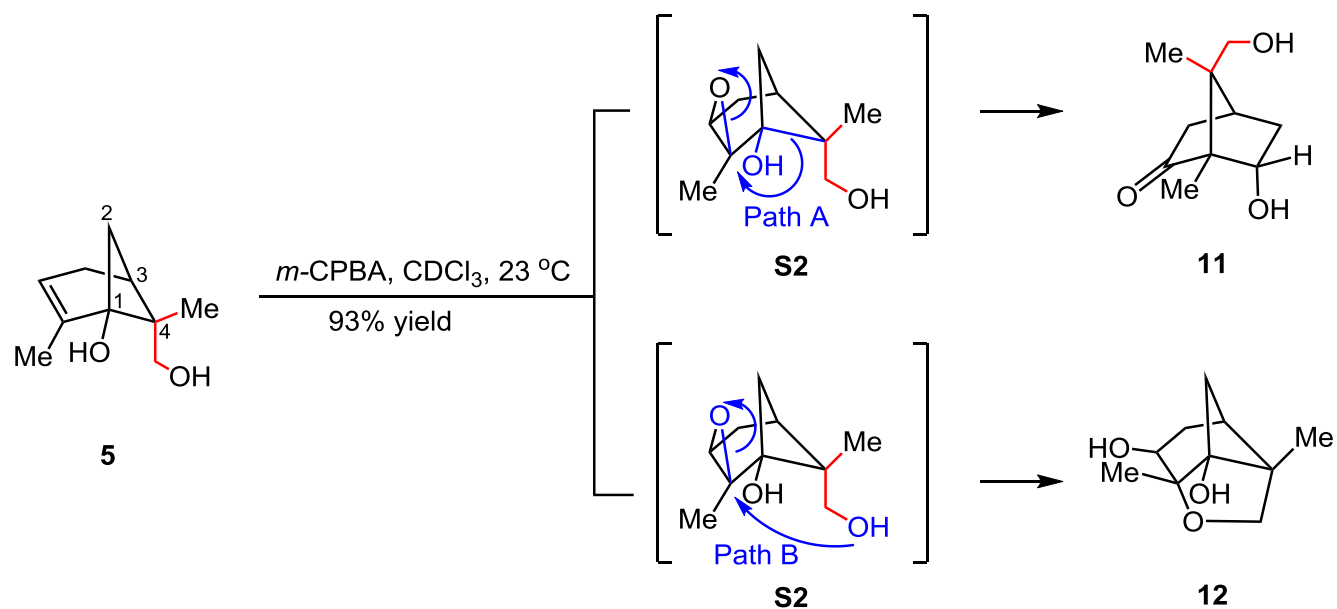
Future studies will focus on applying this strategy to the synthesis of xishacorene congeners and their derivatives as well as the investigation of their bioactivity.

***Thanks
for your attention***

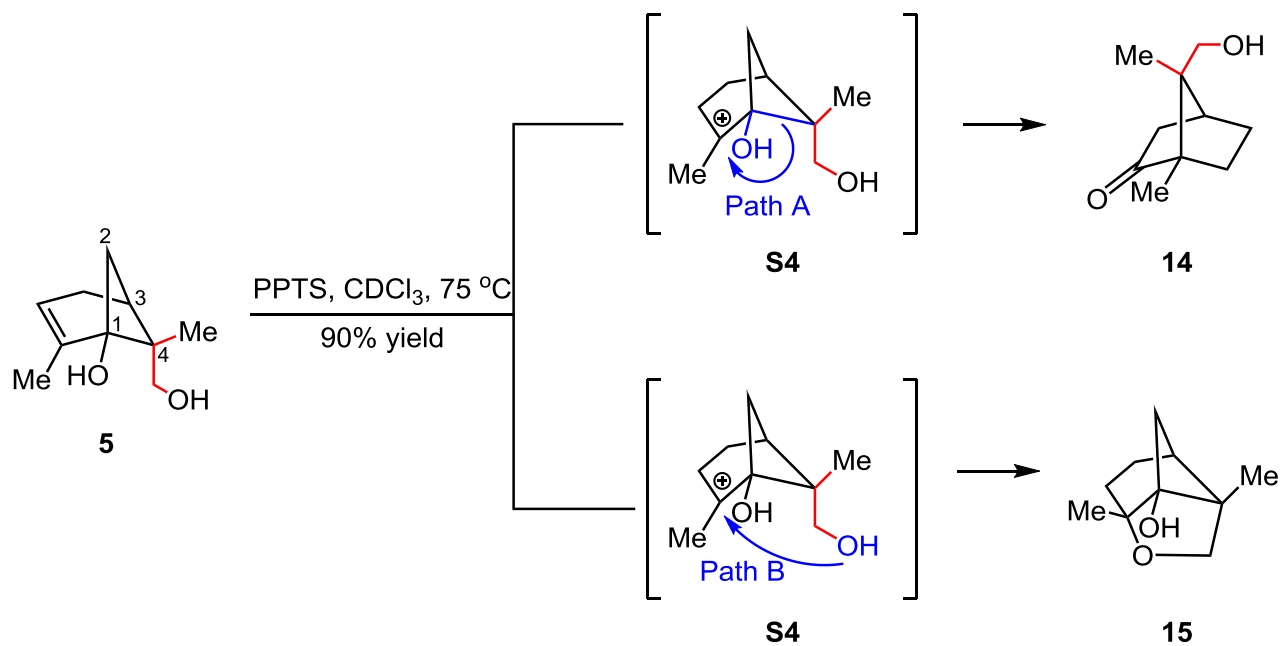
C1-C4 Activation



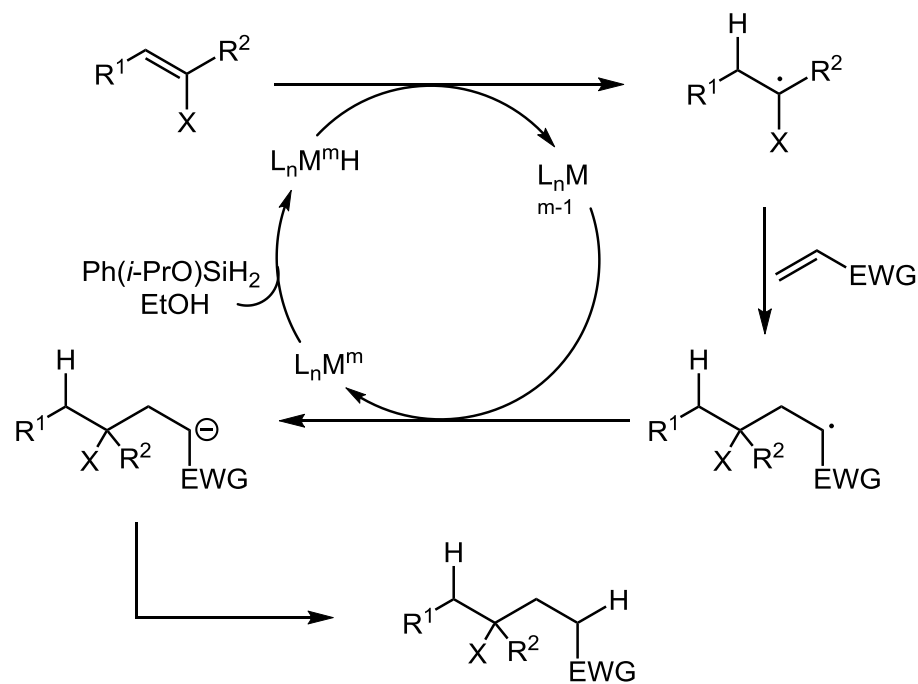
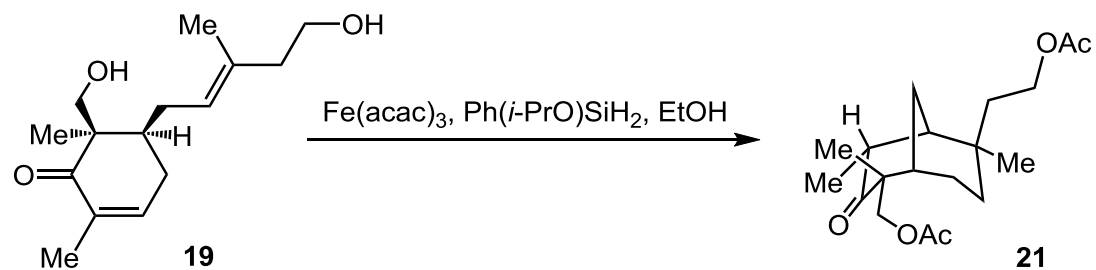
C1-C4 Activation



C1-C4 Activation



Mukaiyama-type Reactions



Williamson-Etherification Reaction

