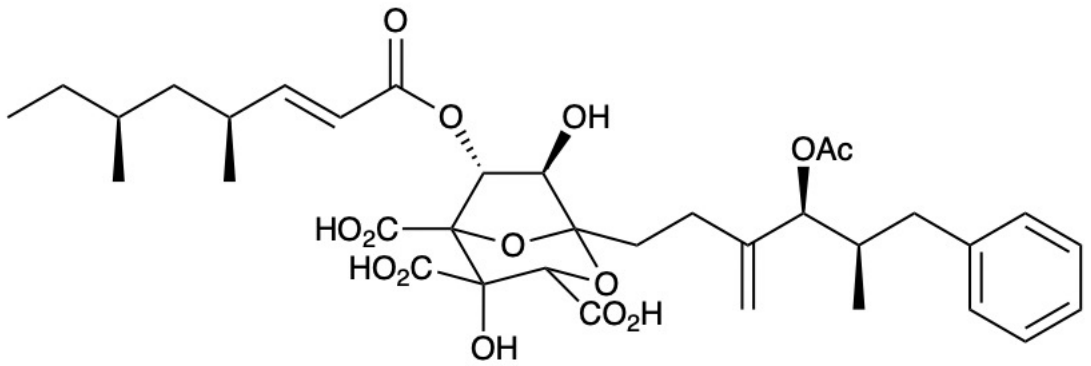
Zaragozic Acid A/Squalestatin S1

Sydney Cobb



Background

- This natural product class was discovered at approximately the same time in 1992 by two different companies from two different fungi
- Bergstrom et al. at Merck called the class “zaragozic acids”
- Dawson et al. at Glaxo (now GSK) called the class “squalestatins”

1. Nicolaou, K. C.; Sorenson E. J. *Classics in Total Synthesis*; VHC, 1996
2. Bergstrom, et al. *Annu. Rev. Microbio.*, **1995**, *49*, 607-39
3. Dawson, et al. *J. Antibiot. (Tokyo)*, **1992**, *45* (5), 639-47

Background

- Zaragozic acid A showed promise as it targeted squalene synthase and lowered the cholesterol levels *in vivo* of marmosets
- This presentation focuses on the Nicolaou synthesis
- The Sharpless asymmetric dihydroxylation is the reaction of note for the forward synthesis

1. Nicolaou, K. C.; Sorenson E. J. *Classics in Total Synthesis*; VHC, 1996
2. Nicolaou, K. C., et al. *Chem. Eur. J.* **1995**, *1* (7), 467-94
3. Kolb, H. C., et al. *Chem. Rev.* **1994**, *94* (8), 2483-2547

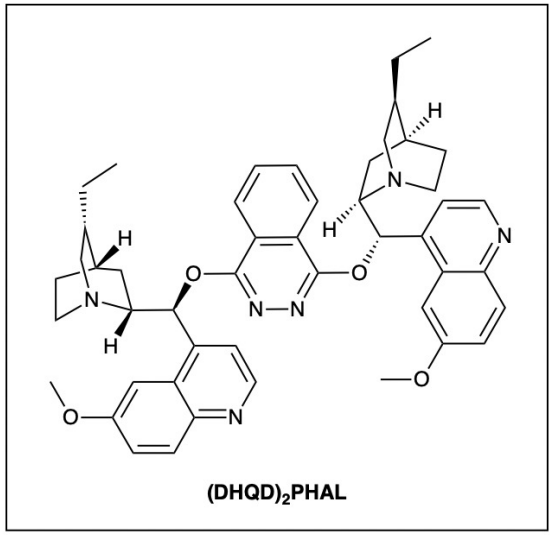
Sharpless Asymmetric Dihydroxylation

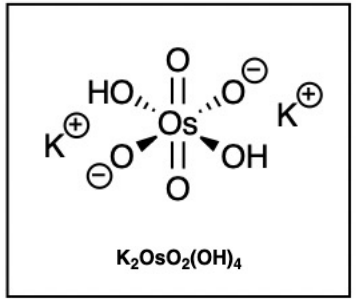
- A *cis* dihydroxylation was first reported in 1908 by Makaowaka and used osmium tetroxide to convert olefins into vicinal diols
  - Problems: Osmium tetroxide is expensive, volatile, toxic, and inconvenient on small scales
- Solution: Osmium tetroxide would be more advantageous if used catalytically
  - Problem: The co-oxidant method was less reliable than the stoichiometric one
- Solution: Incorporating a catalyst-ligand system

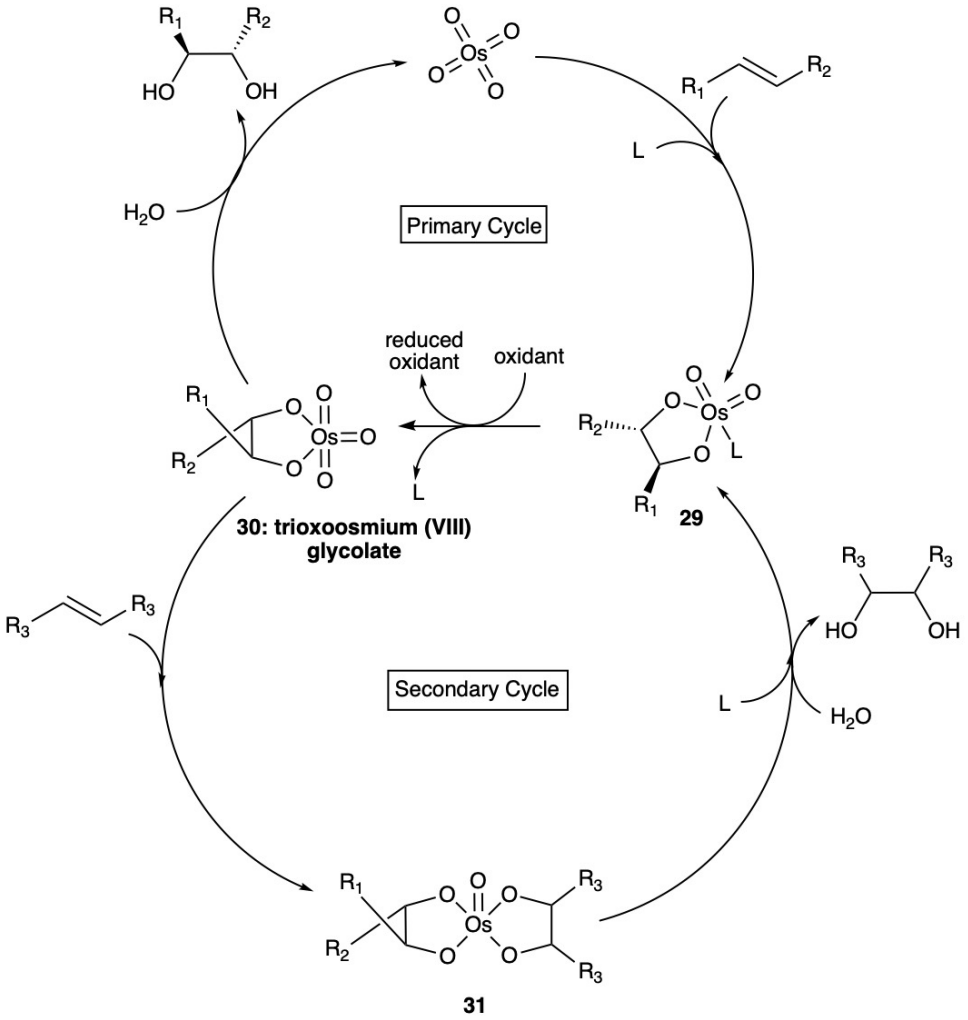
1. Nicolaou, K. C.; Sorenson E. J. *Classics in Total Synthesis*; VHC, 1996
2. Kolb, H. C., et al. *Chem. Rev.* **1994**, *94* (8), 2483-2547

The Mechanism

- In the Nicolaou Synthesis:
  - The osmium source: $K_2OsO_2(OH)_4$
  - The oxidants: $K_3Fe(CN)_6$ and K_2CO_3
  - The ligand (L): $(DHQD)_2PHAL$







1. Nicolaou, K. C.; Sorenson E. J. *Classics in Total Synthesis*; VHC, 1996
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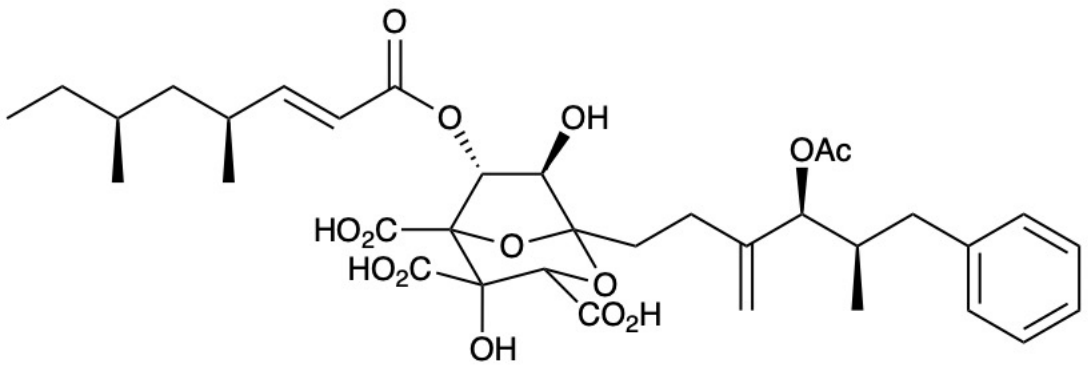
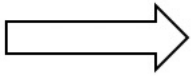
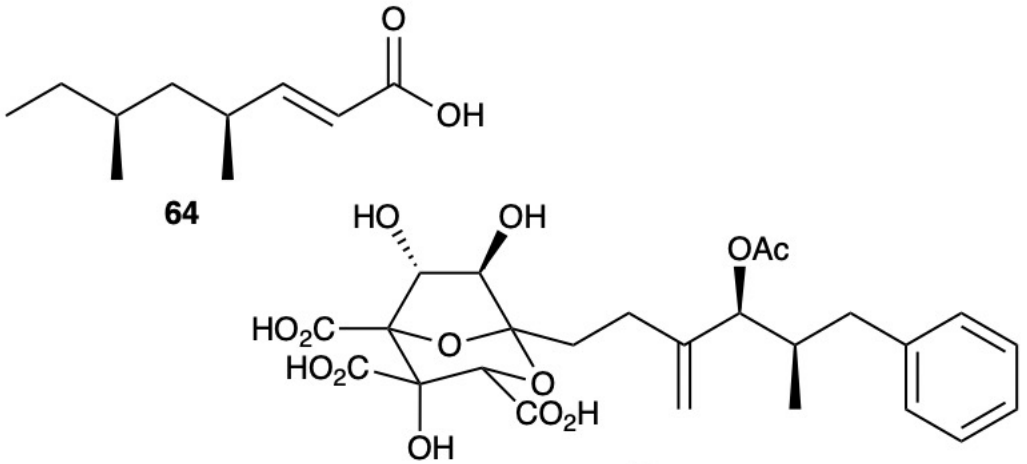
Retrosynthesis



1: zaragozic acid A





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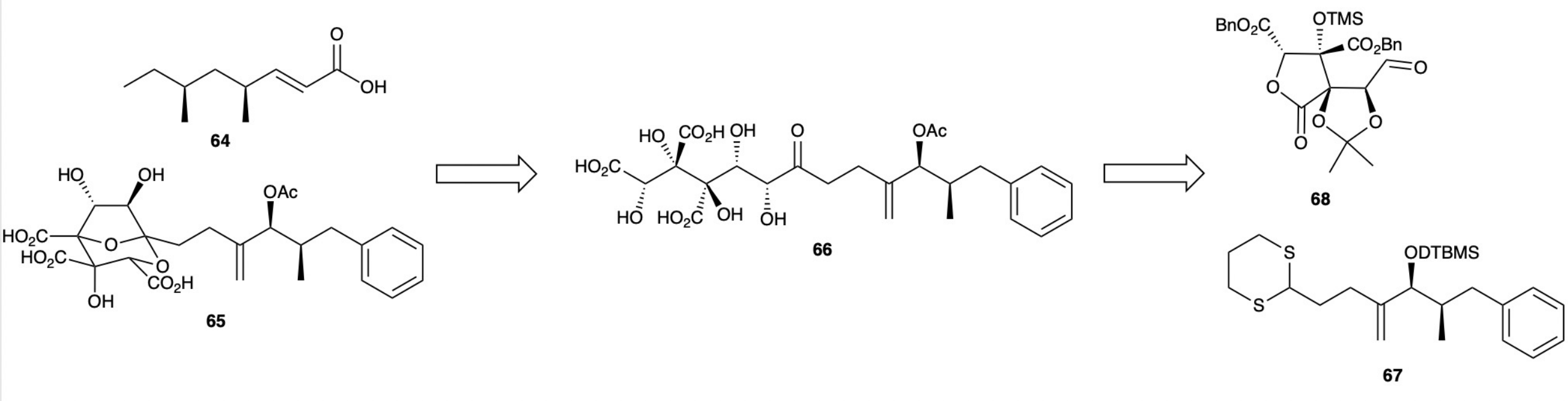

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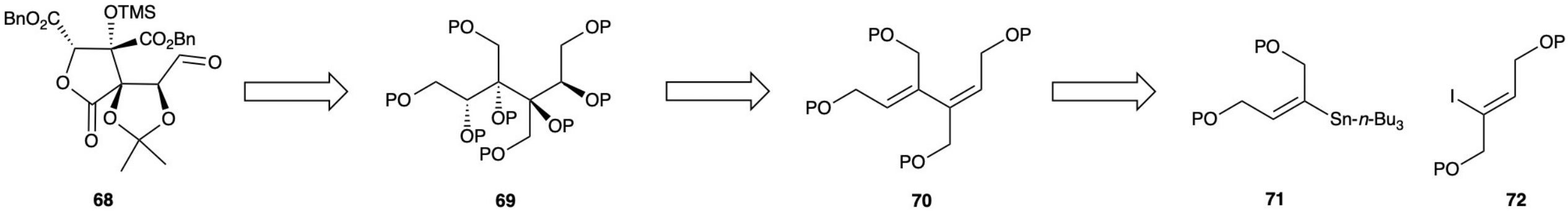

68 **69** **70** **71** **72**

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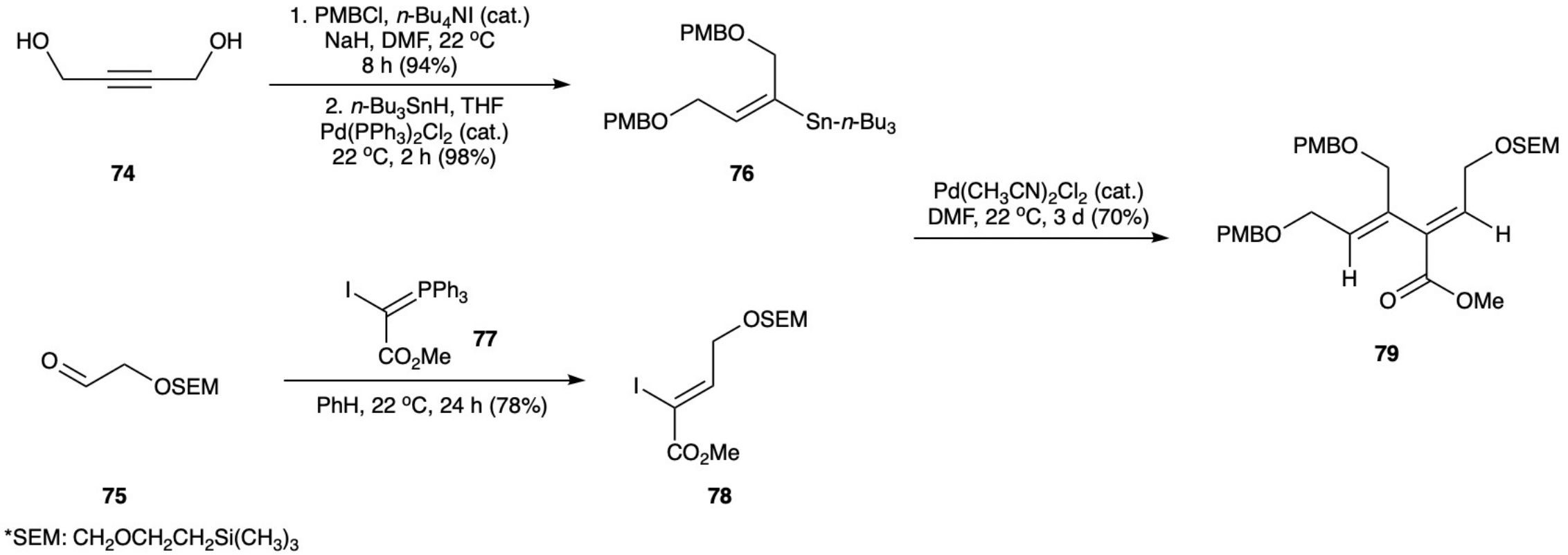
2. Nicolaou, K. C., et al. *Chem. Eur. J.* **1995**, *1* (7), 467-94

Forward Synthesis (Intermediate 68)



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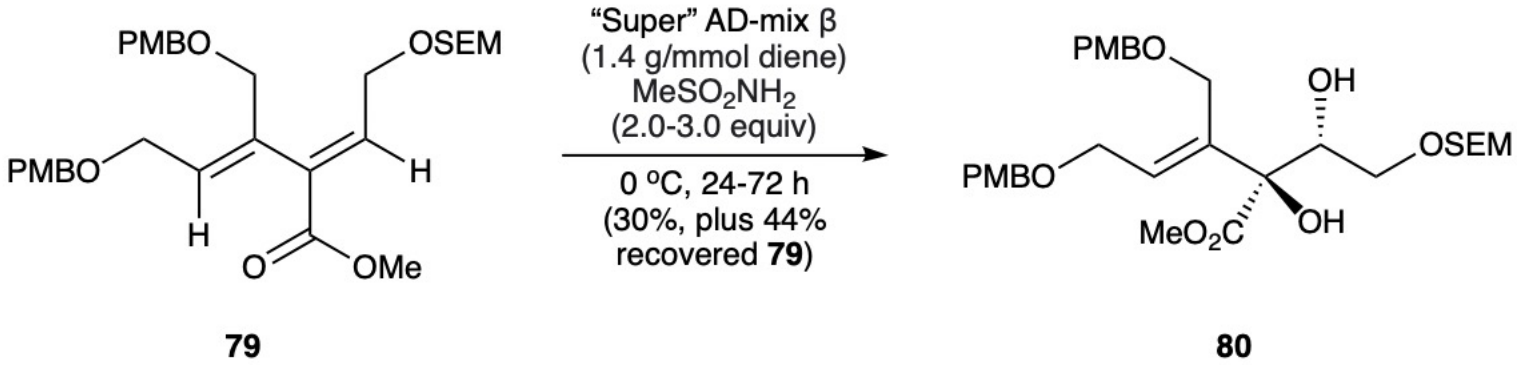
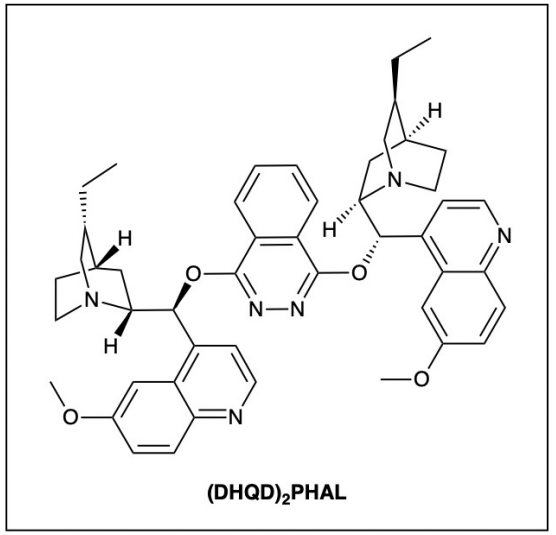


79 **80**

"Super" AD-mix β
$K_3Fe(CN)_6$: K_2CO_3 : $(DHQD)_2PHAL$: $K_2OsO_2(OH)_4$
3.0 : 3.0 : 0.10 : 0.01 molar ratio

Oxidants: $K_3Fe(CN)_6$ and K_2CO_3
Ligand: $(DHQD)_2PHAL$
Osmium Source: $K_2OsO_2(OH)_4$



1. Nicolaou, K. C.; Sorenson E. J. *Classics in Total Synthesis*; VHC, 1996
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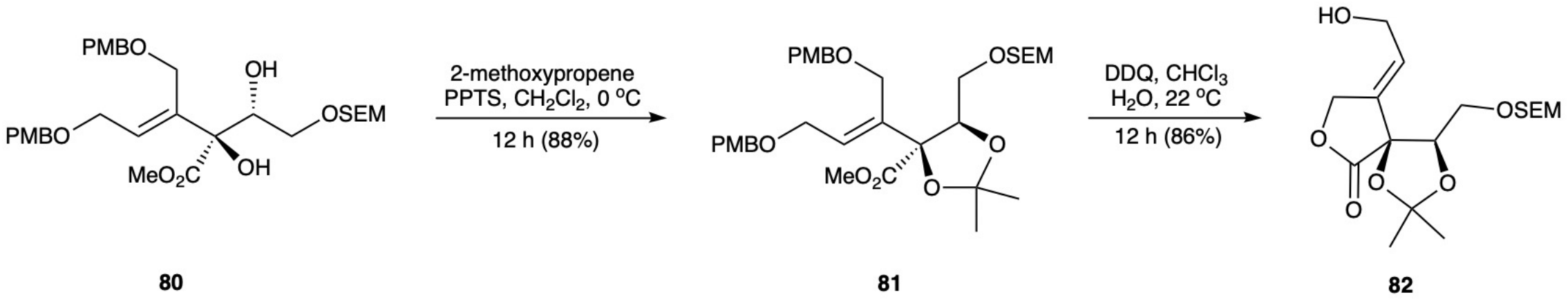

80 **81** **82**

1. Nicolaou, K. C.; Sorenson E. J. *Classics in Total Synthesis*; VHC, 1996
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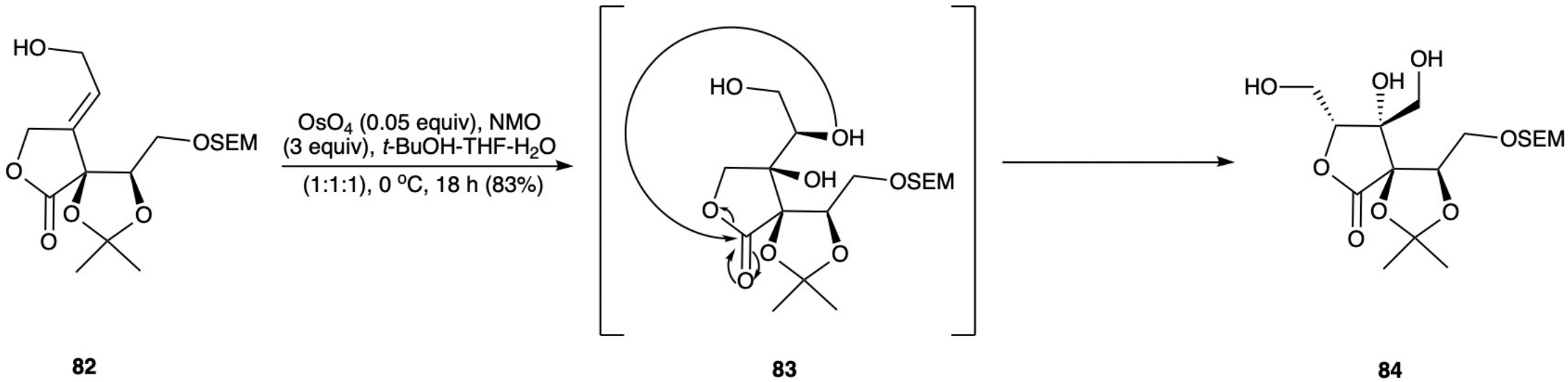

82 **83** **84**

*The resulting stereochemistry is substrate controlled – not reagent controlled

1. Nicolaou, K. C.; Sorenson E. J. *Classics in Total Synthesis*; VHC, 1996
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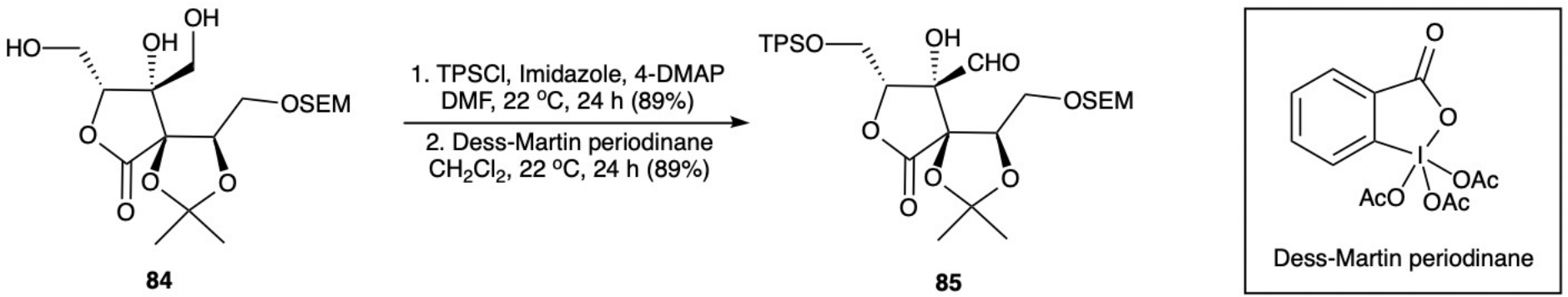
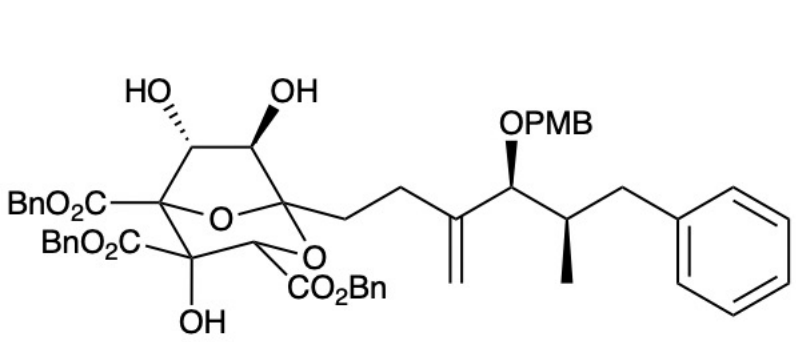


1. Nicolaou, K. C.; Sorenson E. J. *Classics in Total Synthesis*; VHC, 1996
2. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48* (22), 4155-4156.

Forward Synthesis (Final Steps)

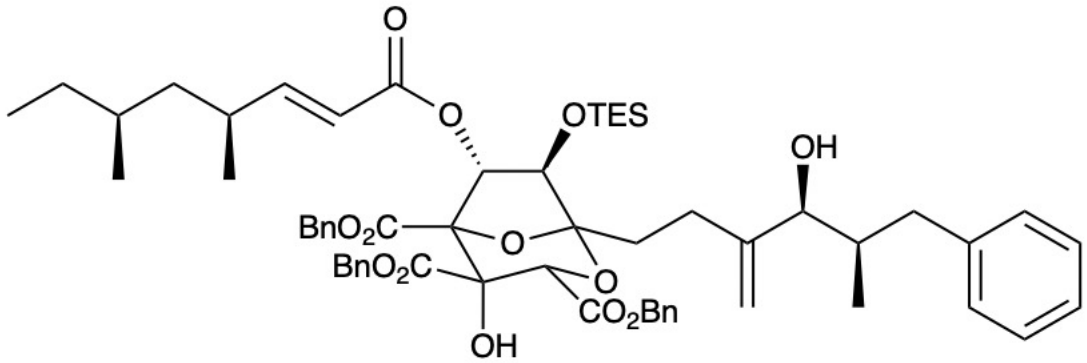


73

1. EDC, **64**, 4-DMAP, CH_2Cl_2
22 °C, 10.5 h (47%, 3:2 mixure of C-6/C-7 esters)

2. TESOTf, pyr., CH_2Cl_2
22 °C, 20 min (79%)

3. DDQ, CH_2Cl_2-H_2O (20:1)
22 °C, 1 h (98%)



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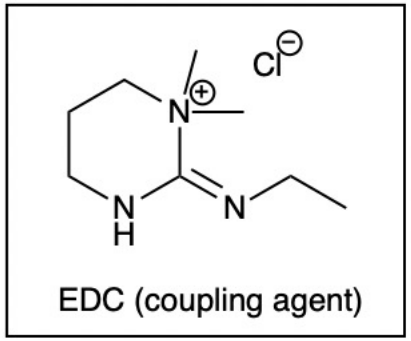
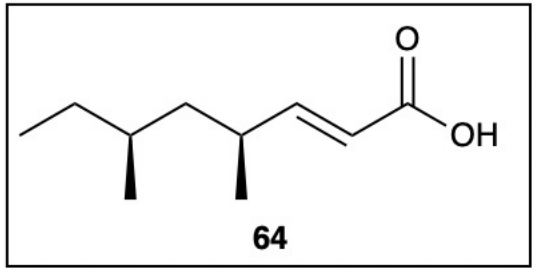


EDC (coupling agent)



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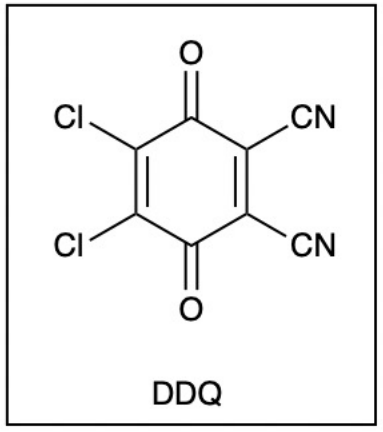

DDQ

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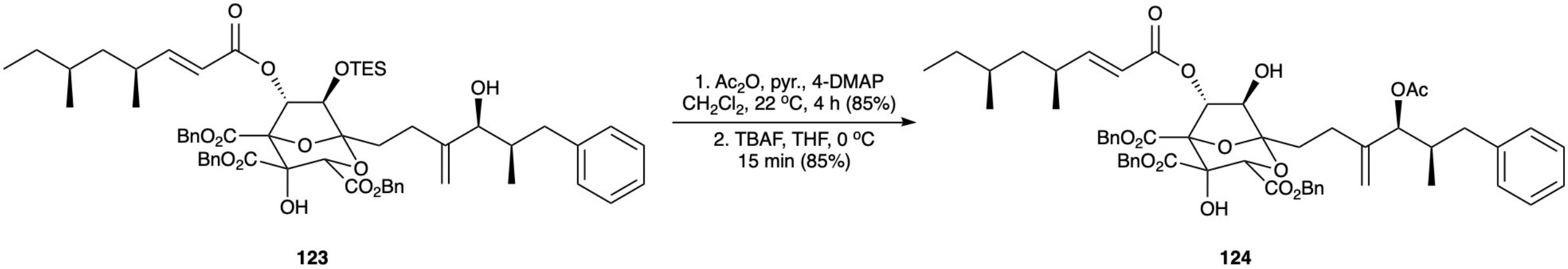
Forward Synthesis (Final Steps)



123 **124**

1. Nicolaou, K. C.; Sorenson E. J. *Classics in Total Synthesis*; VHC, 1996
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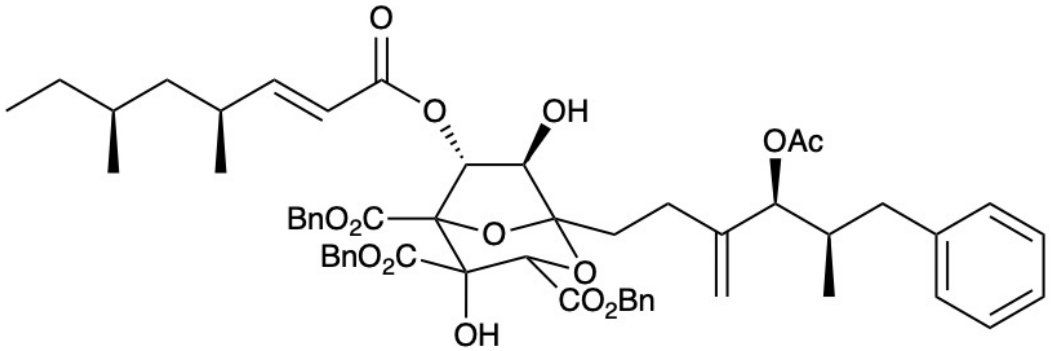
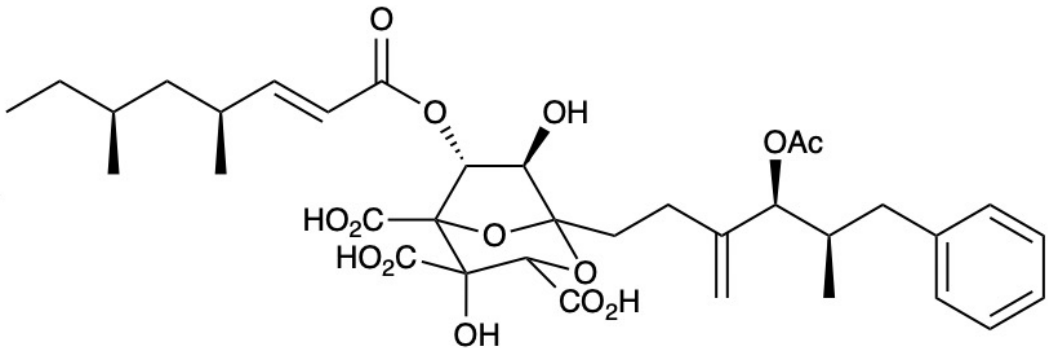


124

10% Pd-C
1,4-cyclohexadiene

1,4-dioxane, 110 °C
2 h (50%)



1: (+)-zaragozic acid A

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Conclusion

- This class of natural products bears two names due to the circumstances surrounding its original discovery
- It was discovered from two fungi species
- The Sharpless asymmetric dihydroxylation was key in Nicolaou's forward synthesis of (+)-zaragozic acid A

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