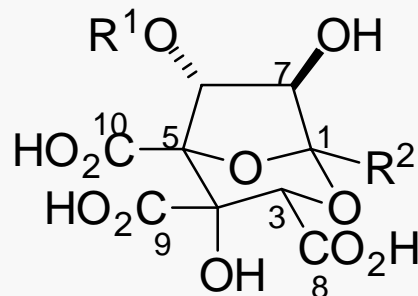
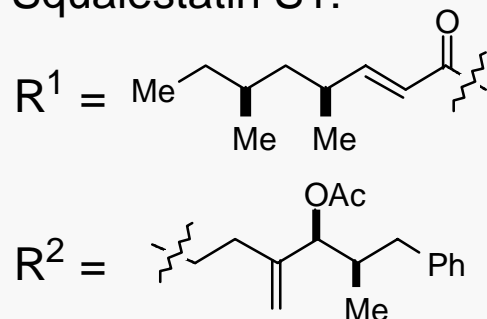

Zaragozic Acids: Strategy and Discovery in Total Synthesis

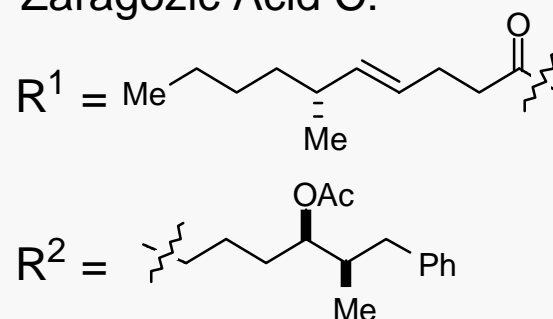
Eric A. Voight
February 28th, 2002

Introduction

Zaragozic Acid A/
Squalestatin S1:



Zaragozic Acid C:



- In 1991 and 1992, research groups at Merck,¹ Glaxo,² and Tokyo Noko University/Mitsubishi Kasei Corporation³ independently reported isolation of the zaragozic acids (squalestatins).
- All but five of the >40 known zaragozic acids (squalestatins) differ only in R^1 or R^2 , containing a common 4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid core.

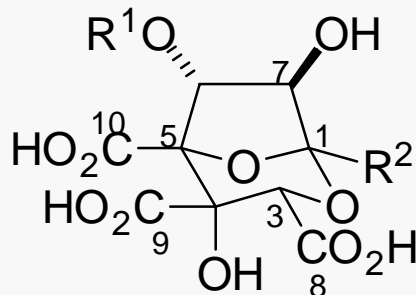
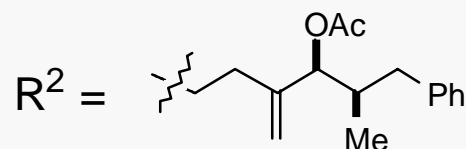
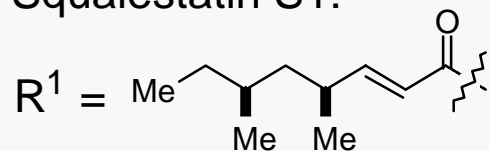
1) (a) Bergstrom, J.D.; Kurtz, M.M.; et. al. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 80. (b) Hensens, O.D.; Dufresne, C.; et. al. *Tetrahedron Lett.* **1993**, *34*, 399.

2) (a) Dawson, M.J.; Farthing, J.E.; et. al. *J. Antibiot.* **1992**, *45*, 639. (b) Sidebottom, P.J.; Highcock, R.M.; et. al. *J. Antibiot.* **1992**, *45*, 648.

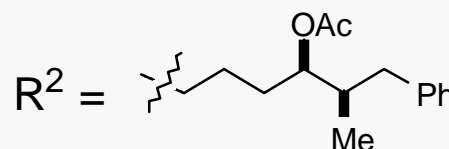
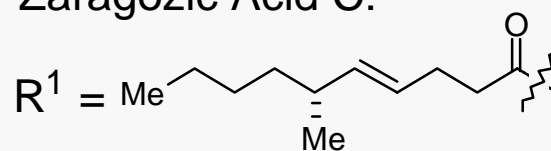
3) Hasumi, K.; Tachikawa, K.; et. al. *J. Antibiot.* **1993**, *46*, 689.

Introduction

Zaragozic Acid A/
Squalestatin S1:



Zaragozic Acid C:



- The zaragozic acids are potent and novel cholesterol biosynthesis inhibitors in that they act as presqualene pyrophosphate mimics to inhibit squalene synthase.
- This potential for treatment of hypercholesterolemia combined with promising antifungal and antitumor activities have led to intense interest in the total synthesis of the zaragozic acids and simplified analogs.

1) Koert, U. *Angew. Chem. Int. Ed.* **1995**, *34*, 773-778.

2) Nadin, A.; Nicolaou, K.C. *Angew. Chem. Int. Ed.* **1996**, *35*, 1622-1656.

3) Jotterand, N.; Vogel, P. *Curr. Org. Chem.* **2001**, *5*, 637-661.

Outline

- Dihydroxylation Strategy

- » Nicolaou

- » Anderson

- Carbonyl Addition Strategy

- » Carreira

- » Heathcock

- Tartrate-Derived Aldol Strategy

- » Evans

- » Hashimoto

- Acetal [1,2] Wittig Rearrangement Strategy

- » Tomooka

Outline

- **Dihydroxylation Strategy**

- » Nicolaou

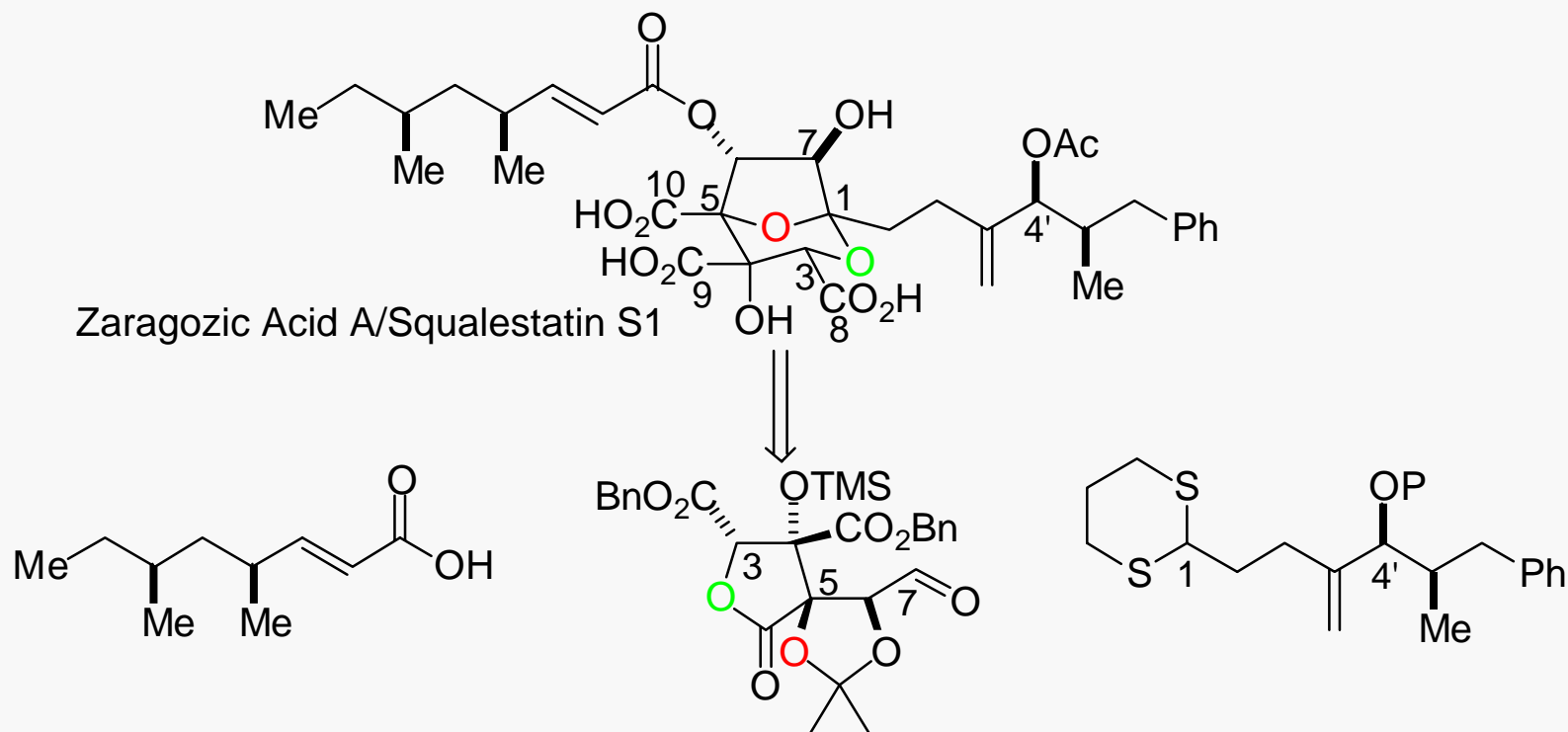
- » Anderson

- **Carbonyl Addition Strategy**

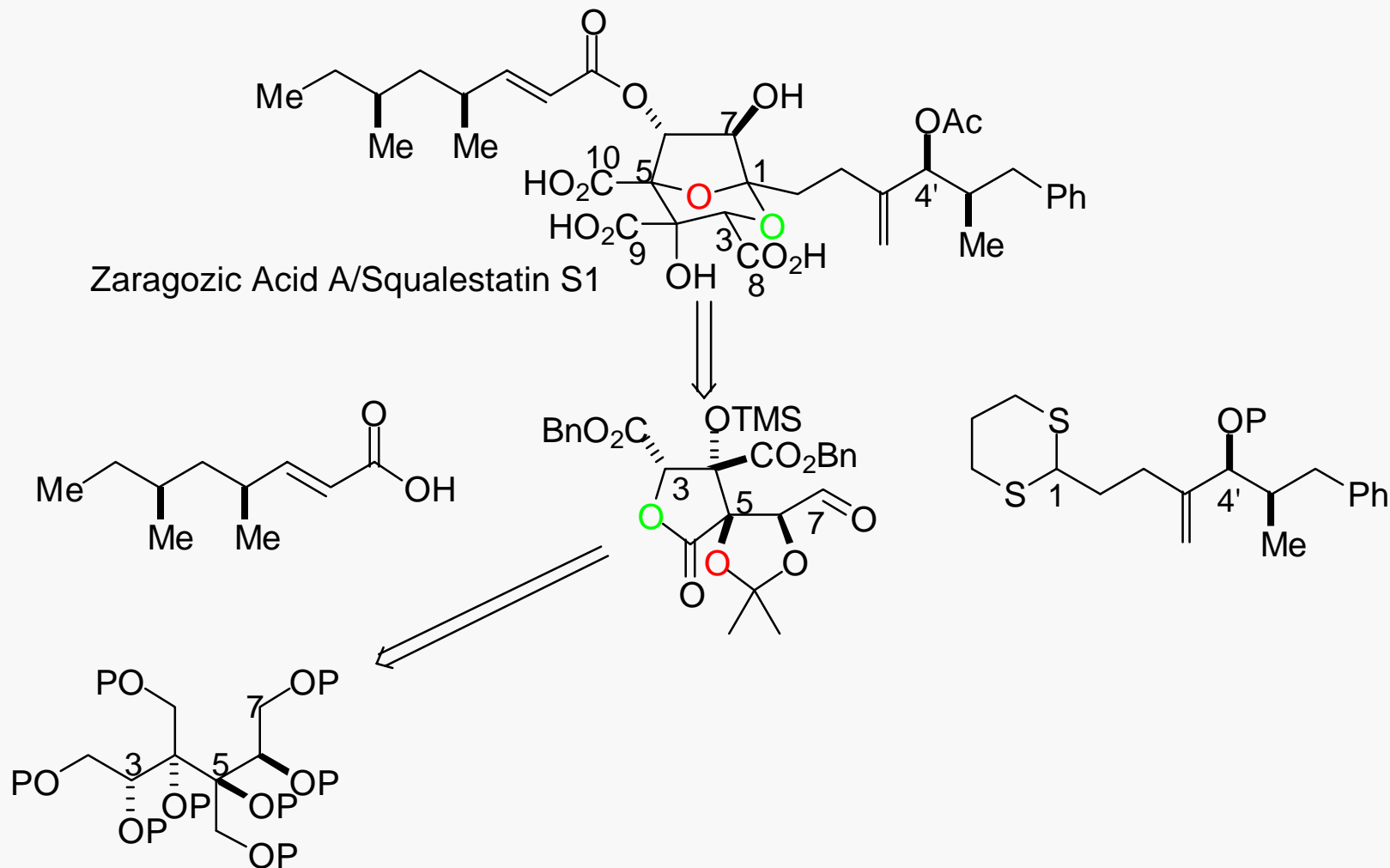
- **Tartrate-Derived Aldol Strategy**

- **Acetal [1,2] Wittig Rearrangement Strategy**

Nicolaou's Retrosynthetic Analysis

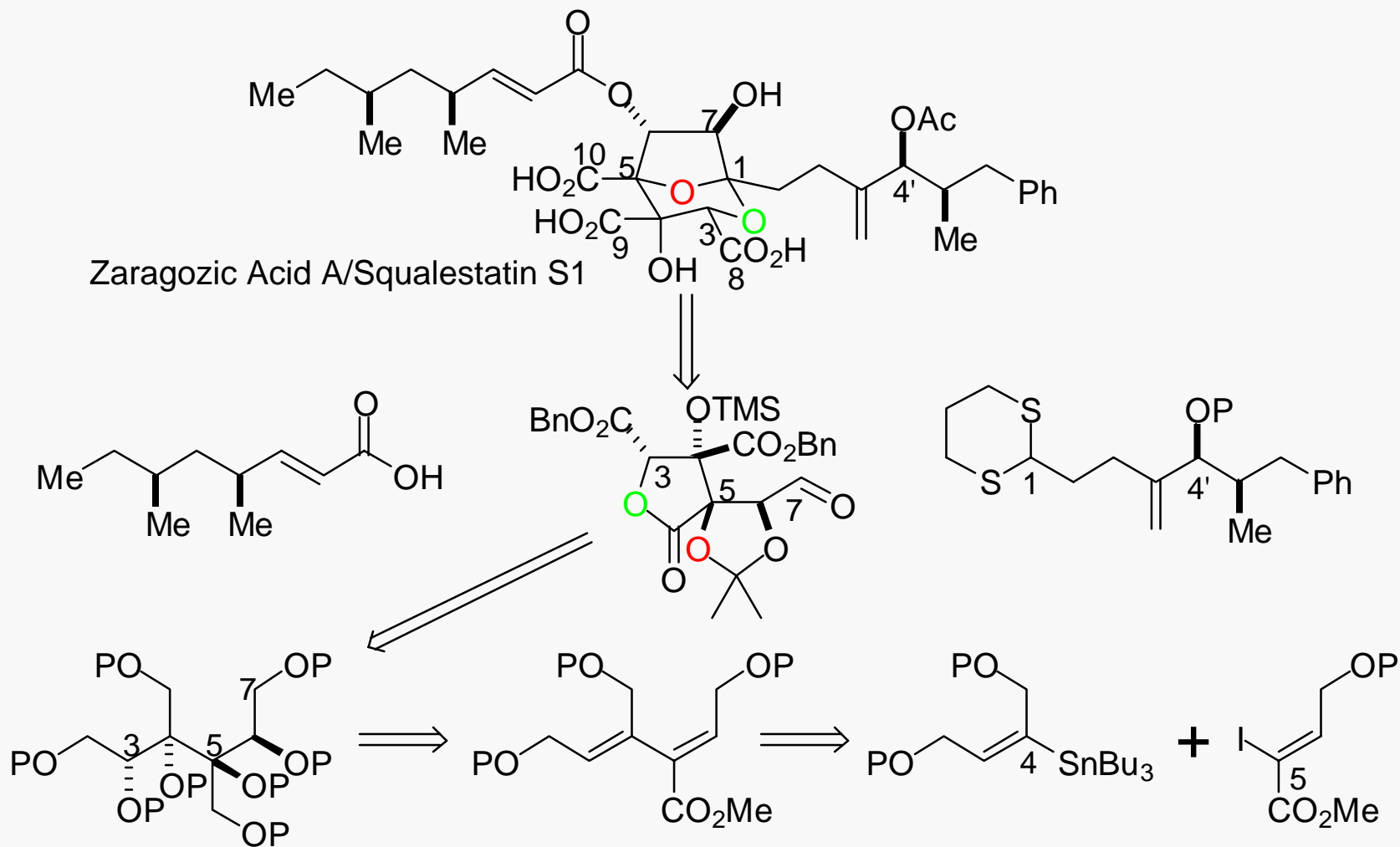


Nicolaou's Retrosynthetic Analysis

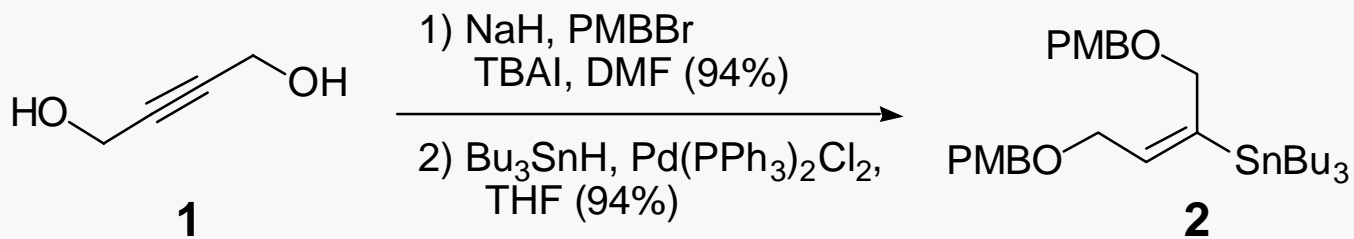


Nicolaou, K.C.; Yue, E.W.; Greca, S.L.; Nadin, A.; Yang, Z.; Leresche, J.E.; Tsurii, T.; Naniwa, Y.; Riccardis, F.D. *Chem. Eur. J.* **1995**, *1*, 467-494.

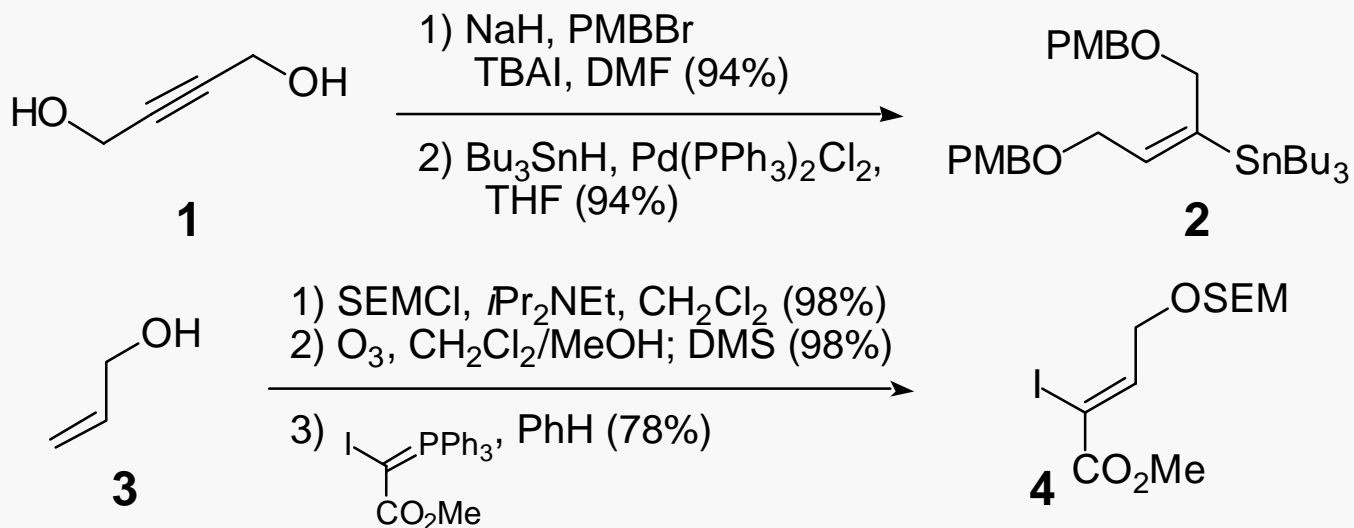
Nicolaou's Retrosynthetic Analysis



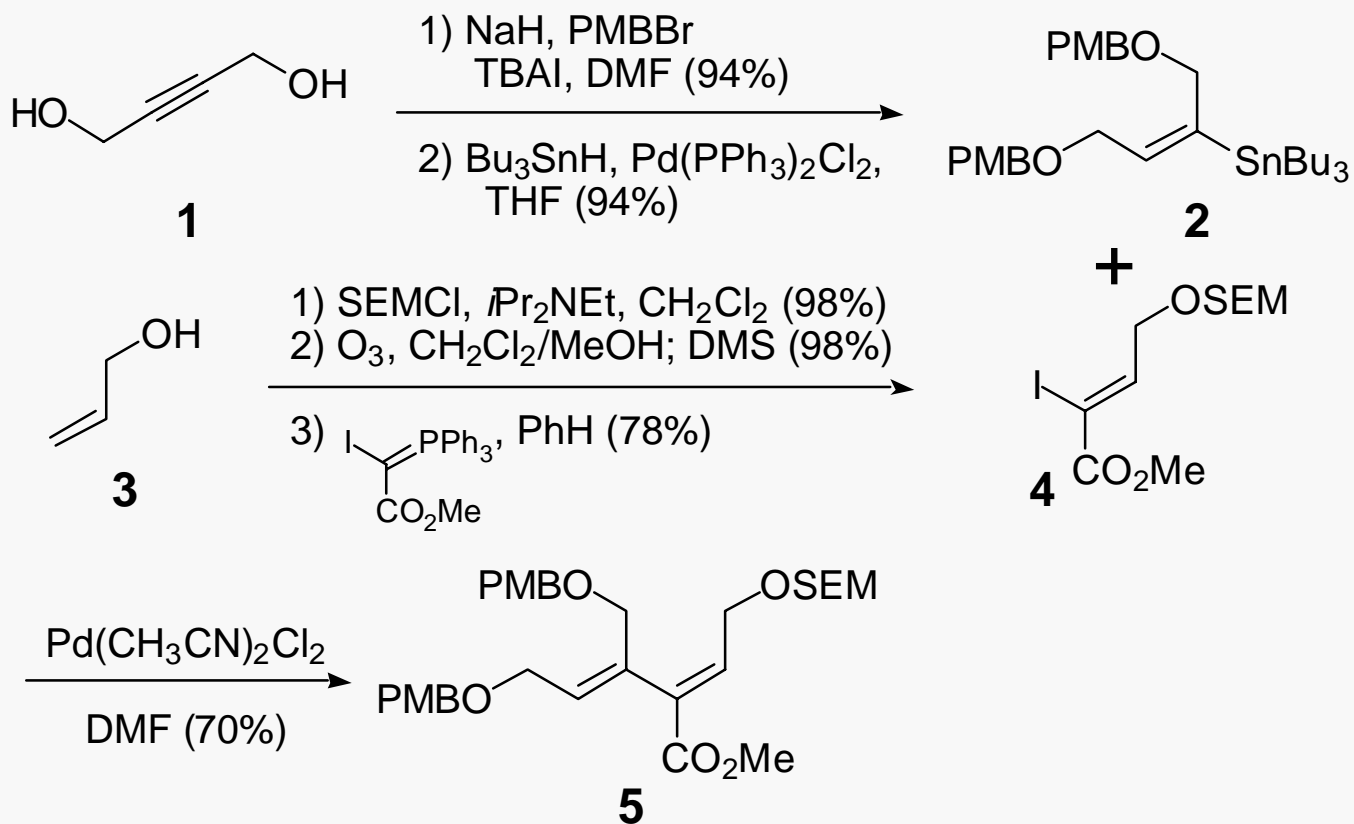
Stille Coupling



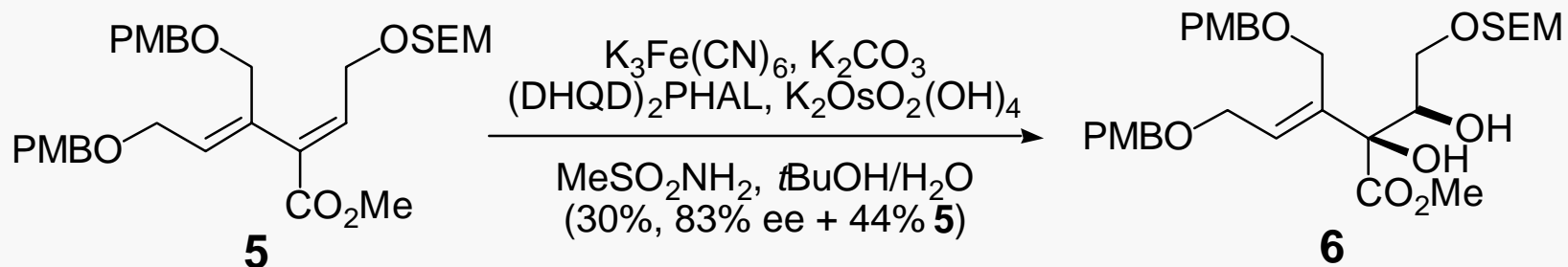
Stille Coupling



Stille Coupling

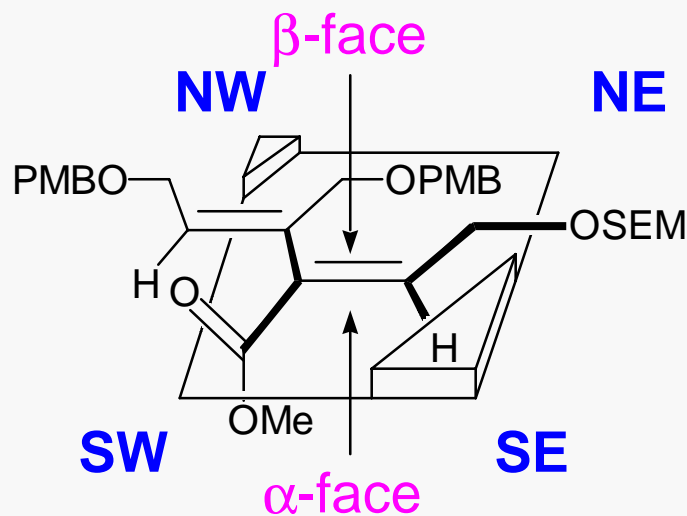
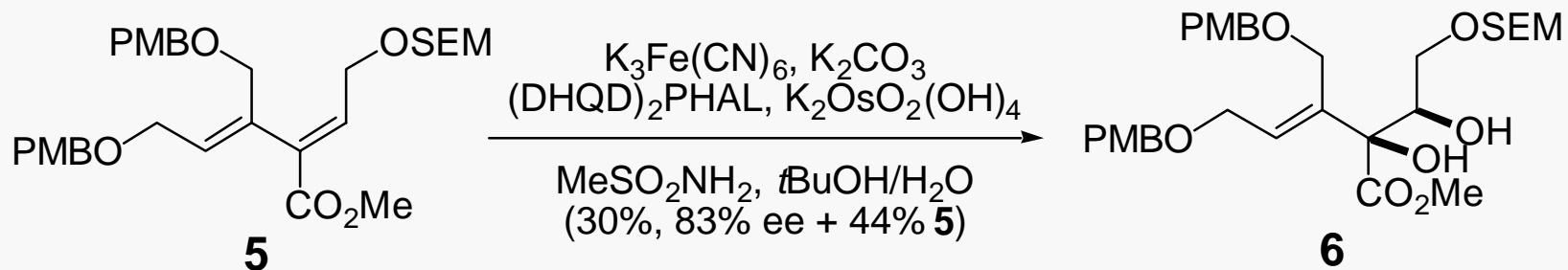


Asymmetric Dihydroxylation



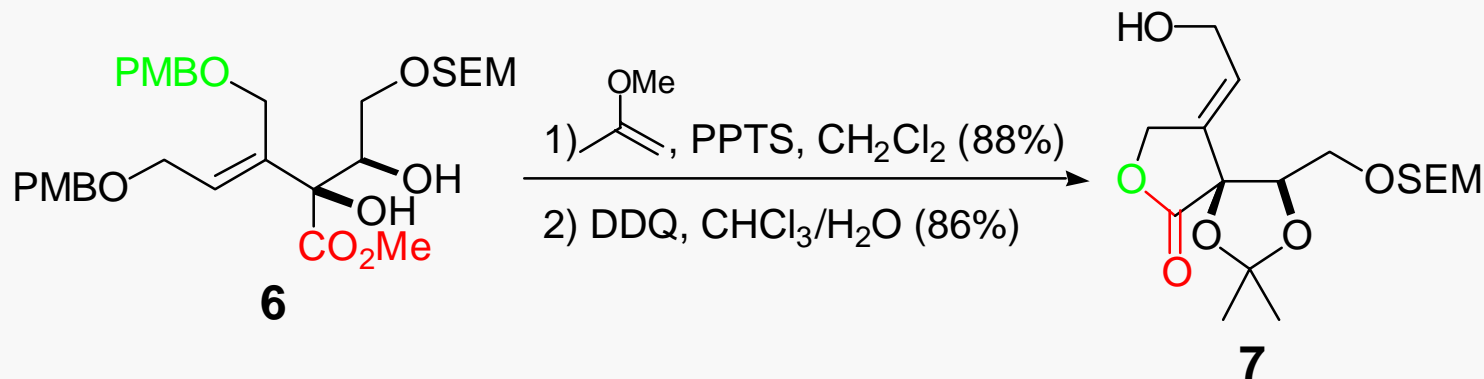
Nicolaou, K.C.; Yue, E.W.; Greca, S.L.; Nadin, A.; Yang, Z.; Leresche, J.E.; Tsurii, T.; Naniwa, Y.; Riccardis, F.D. *Chem. Eur. J.* **1995**, *1*, 467-494.

Asymmetric Dihydroxylation



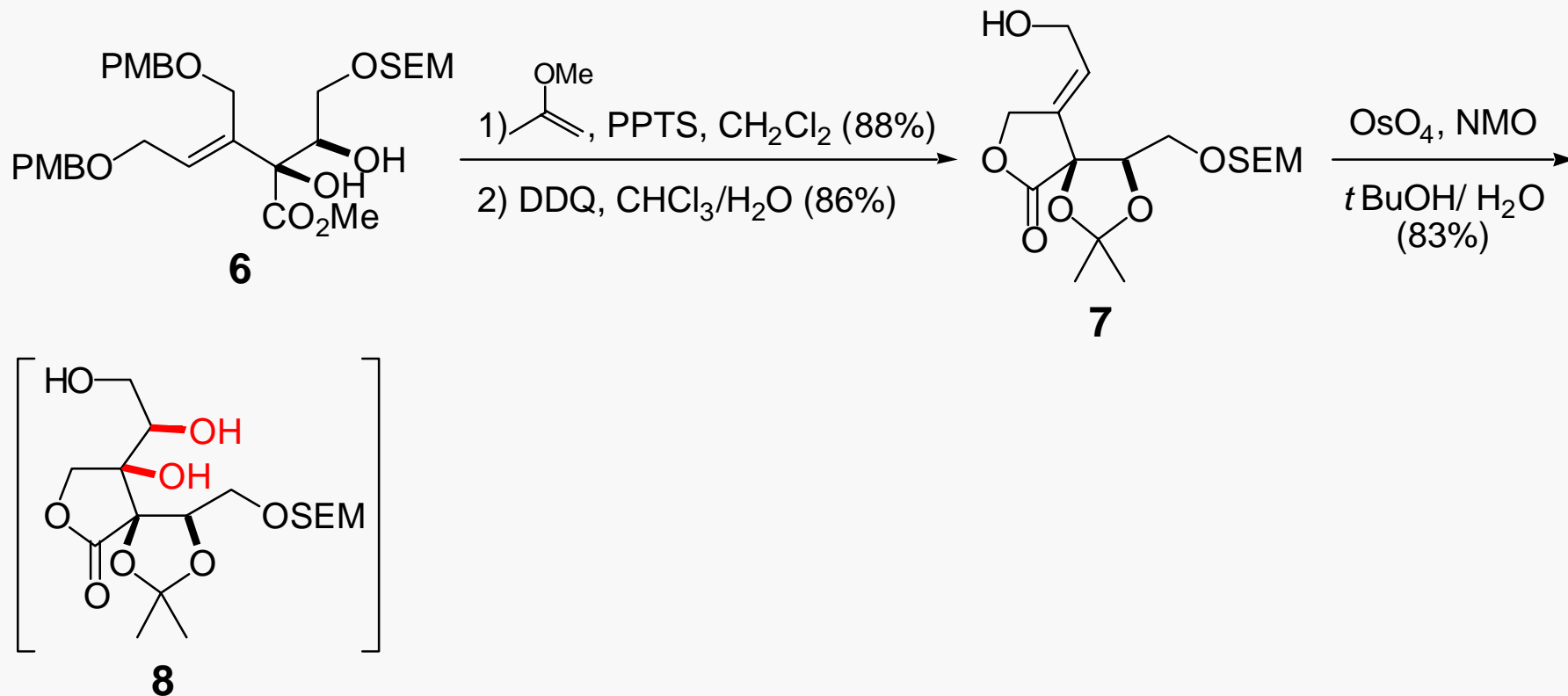
Nicolaou, K.C.; Yue, E.W.; Greca, S.L.; Nadin, A.; Yang, Z.; Leresche, J.E.; Tsurii, T.; Naniwa, Y.; Riccardis, F.D. *Chem. Eur. J.* **1995**, *1*, 467-494.

Second Dihydroxylation

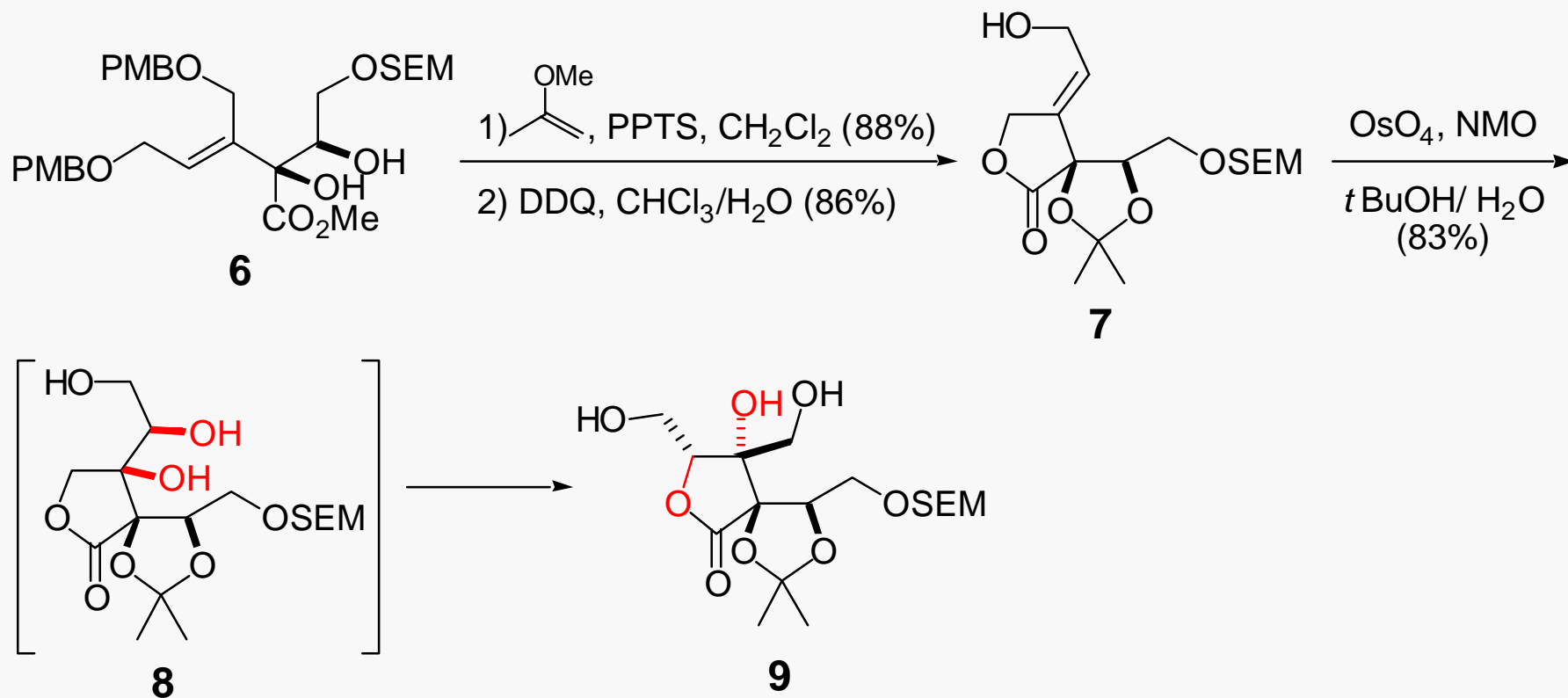


Nicolaou, K.C.; Yue, E.W.; Greca, S.L.; Nadin, A.; Yang, Z.; Leresche, J.E.; Tsurii, T.; Naniwa, Y.; Riccardis, F.D. *Chem. Eur. J.* **1995**, *1*, 467-494.

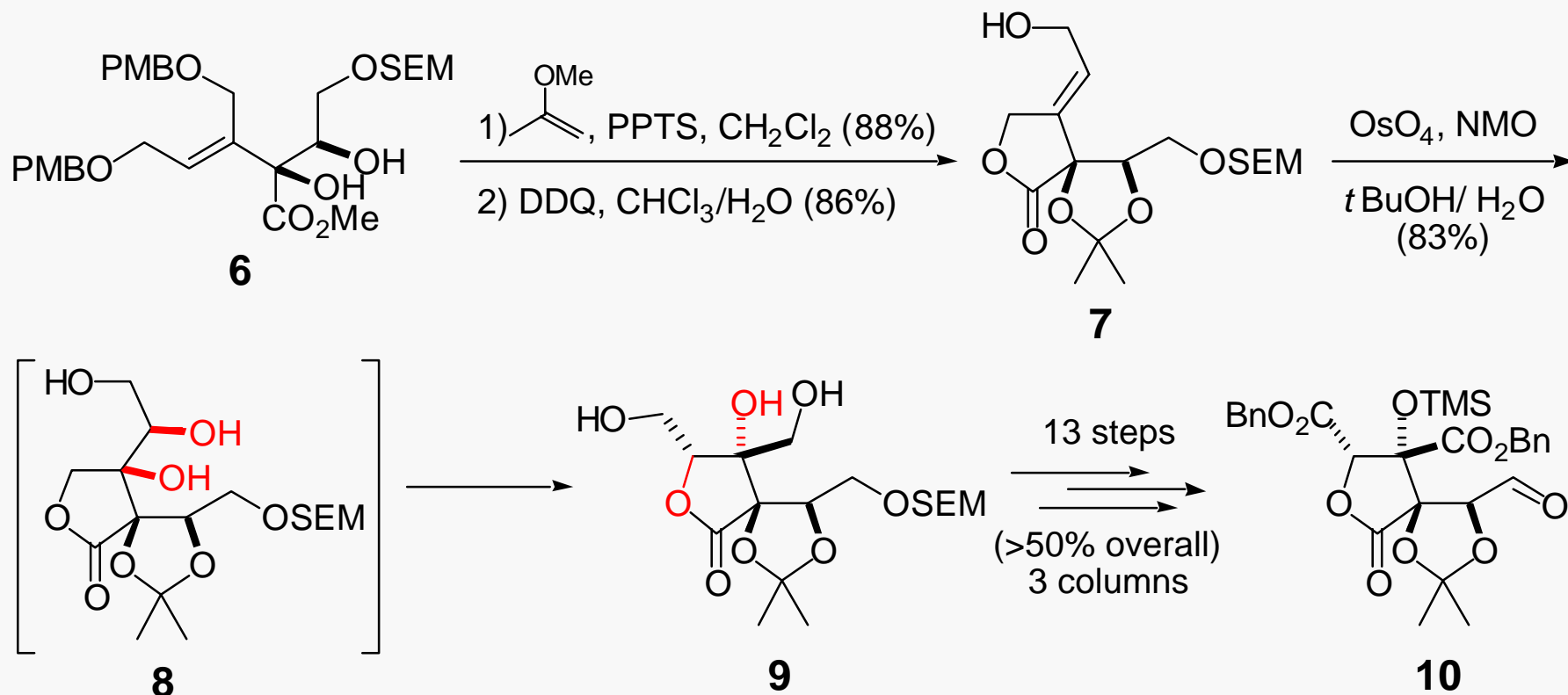
Second Dihydroxylation



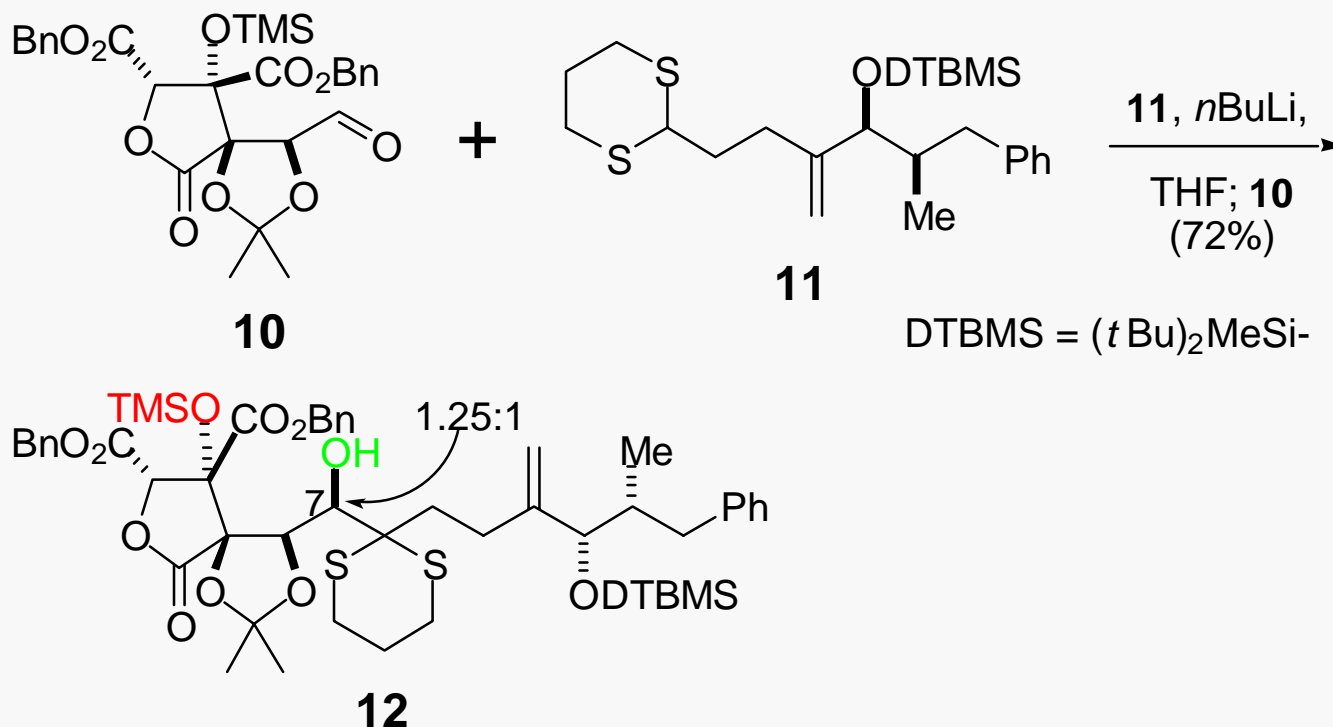
Second Dihydroxylation



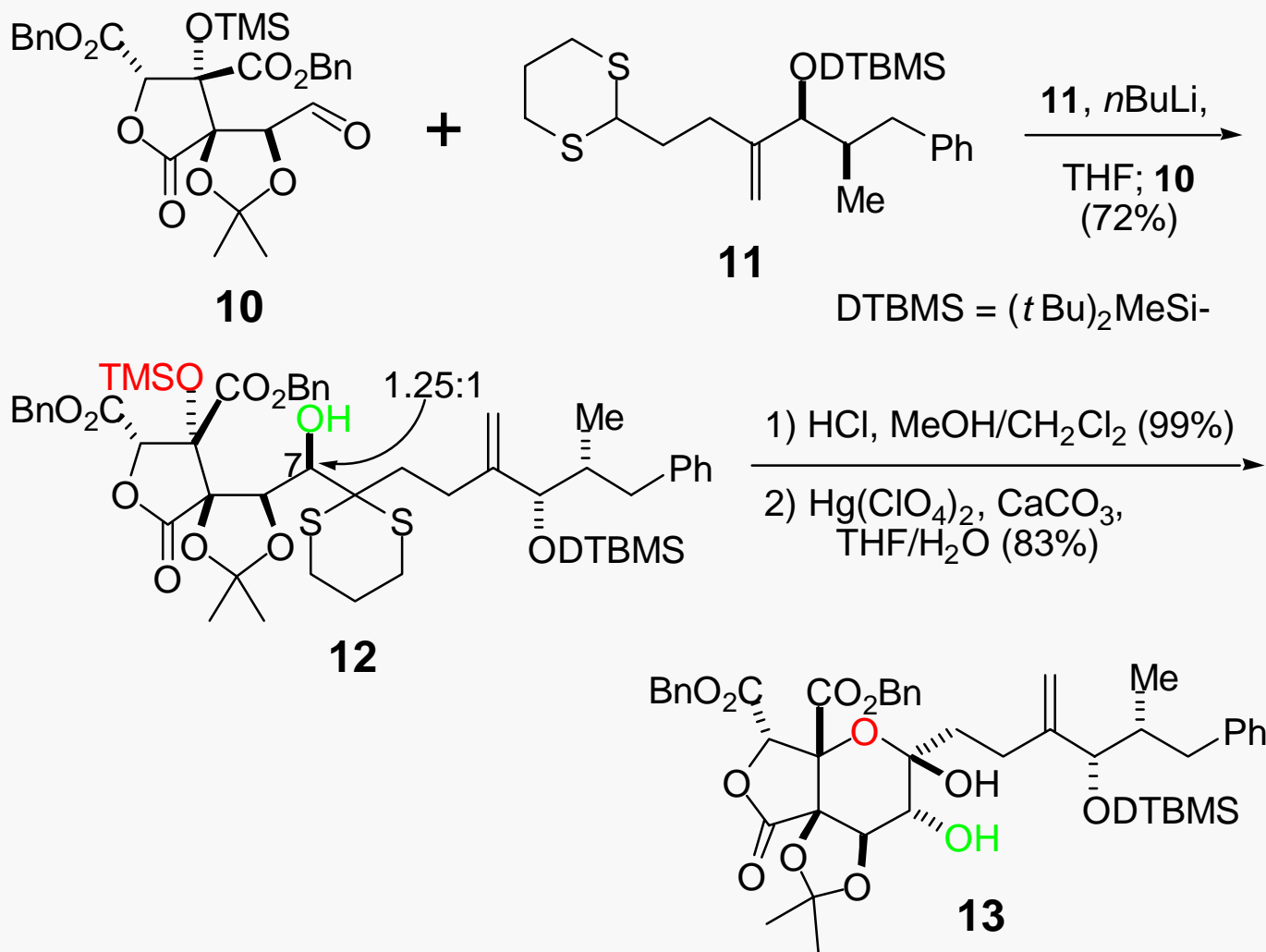
Second Dihydroxylation



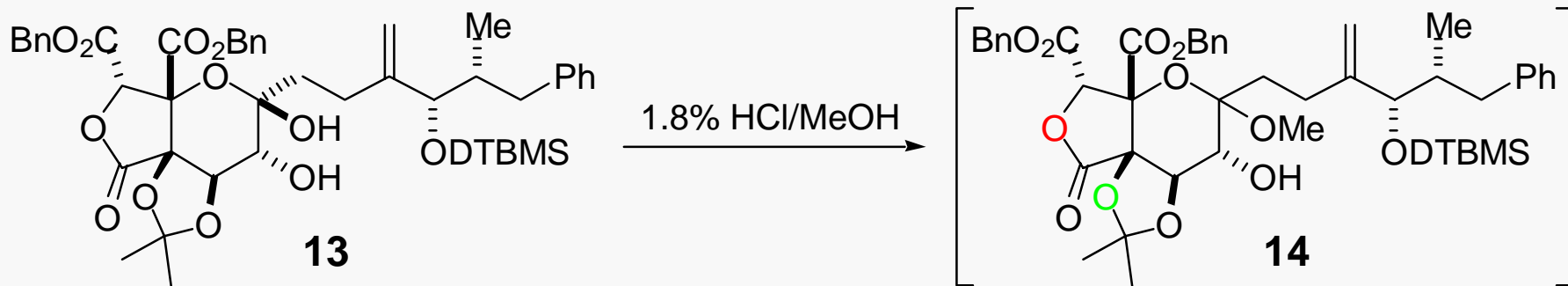
Dithiane Addition



Dithiane Addition

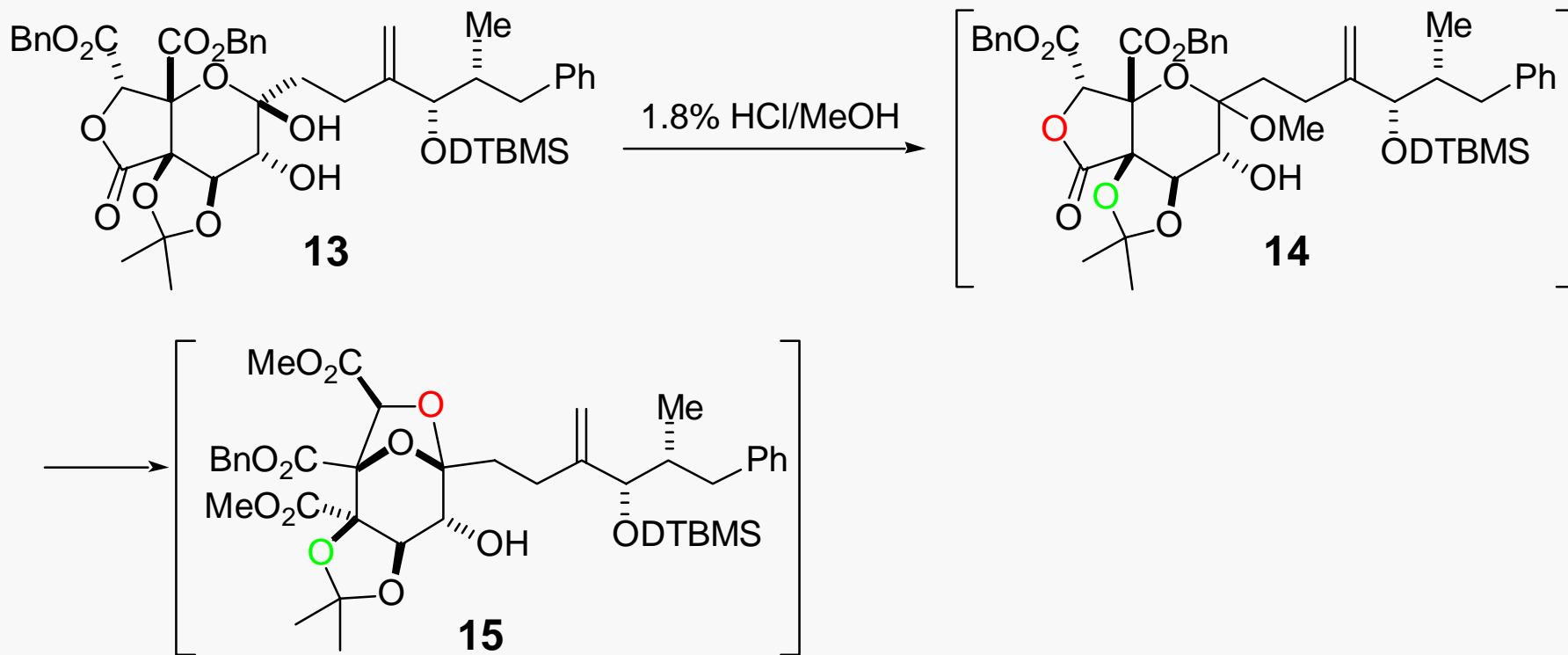


Rearrangement Cascade

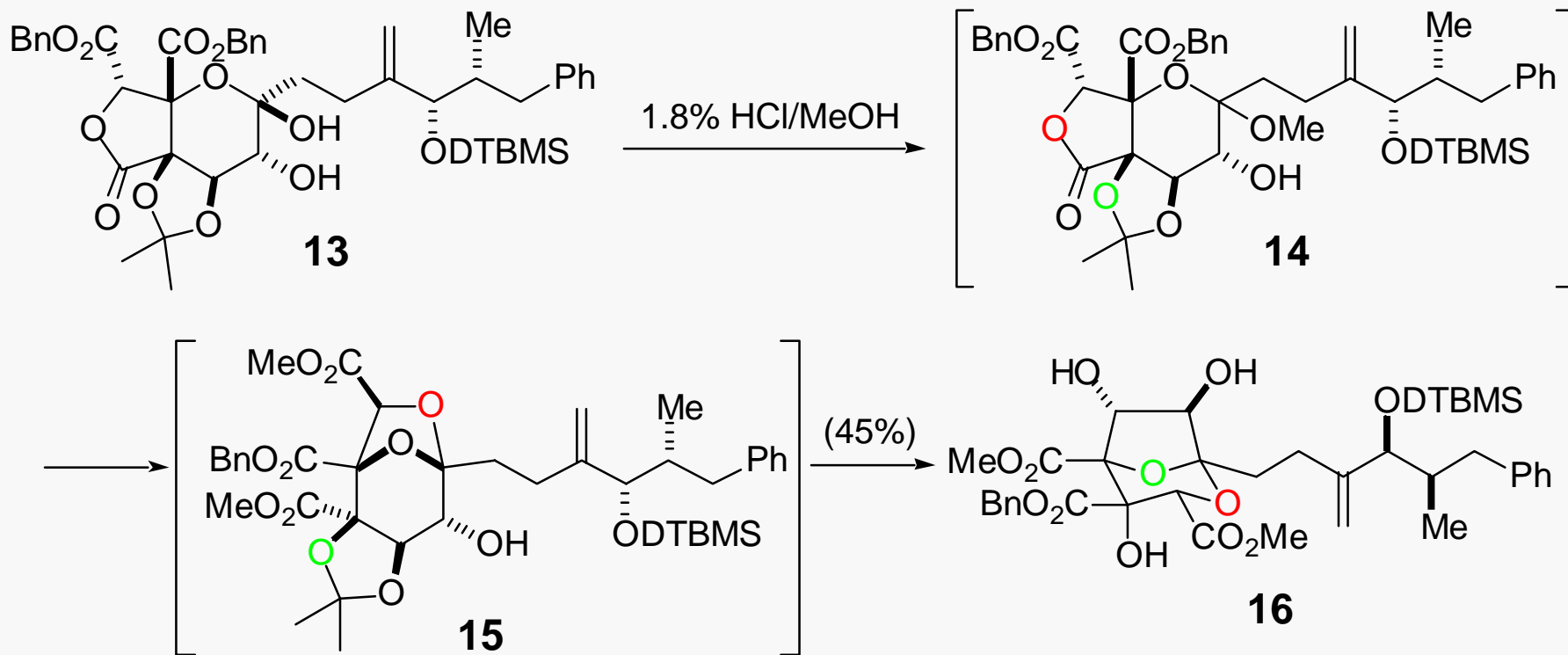


Nicolaou, K.C.; Yue, E.W.; Greca, S.L.; Nadin, A.; Yang, Z.; Leresche, J.E.; Tsuru, T.; Naniwa, Y.; Riccardis, F.D. *Chem. Eur. J.* **1995**, *1*, 467-494.

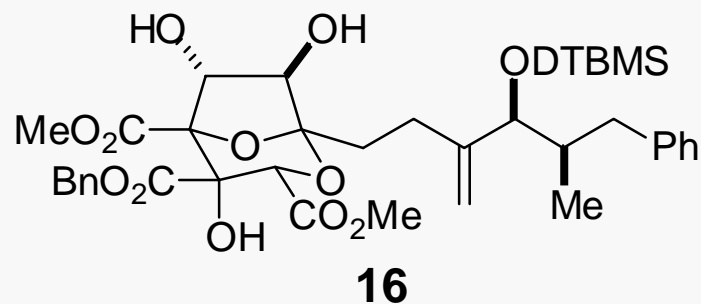
Rearrangement Cascade



Rearrangement Cascade

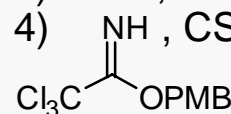


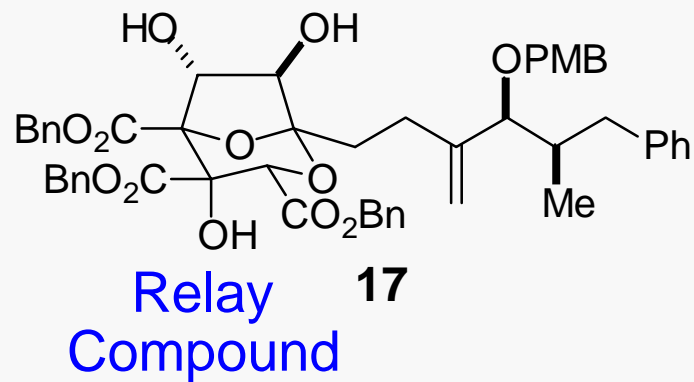
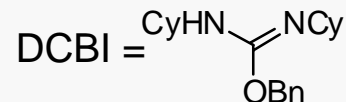
Completion of the Total Synthesis



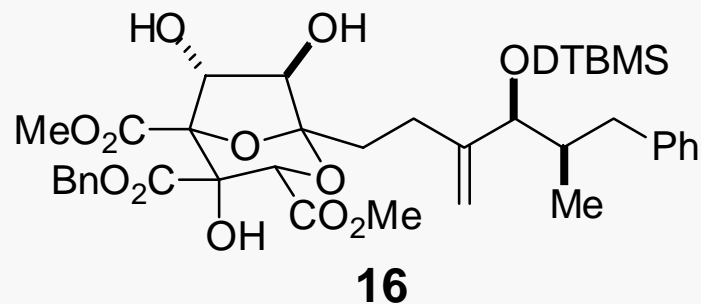
- 1) aq. HF/MeNO₂ (30%)
- 2) LiOH•H₂O, THF/H₂O

3) DCBI, THF (68% overall)

- 4)  , CSA (21% + 36%
rec. SM)

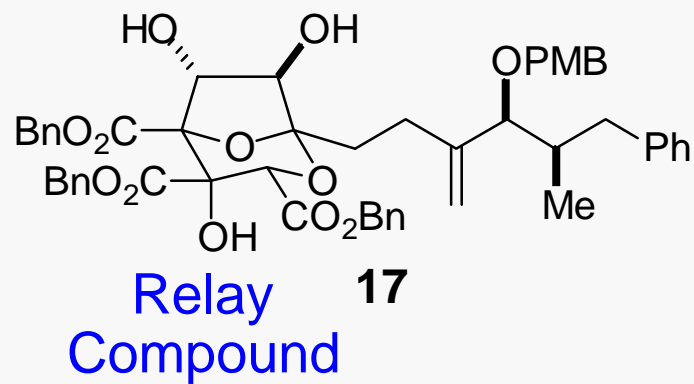
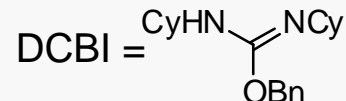


Completion of the Total Synthesis



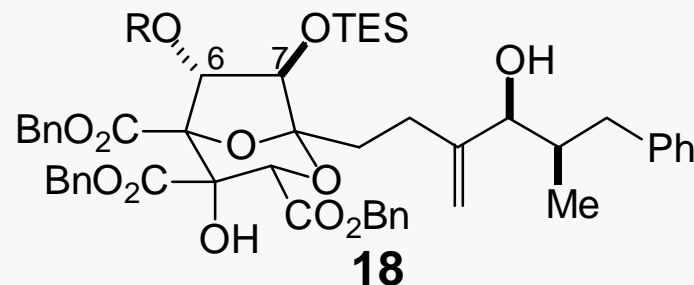
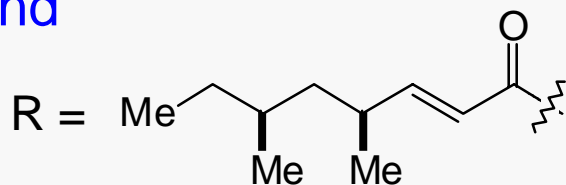
- 1) aq. HF/MeNO₂ (30%)
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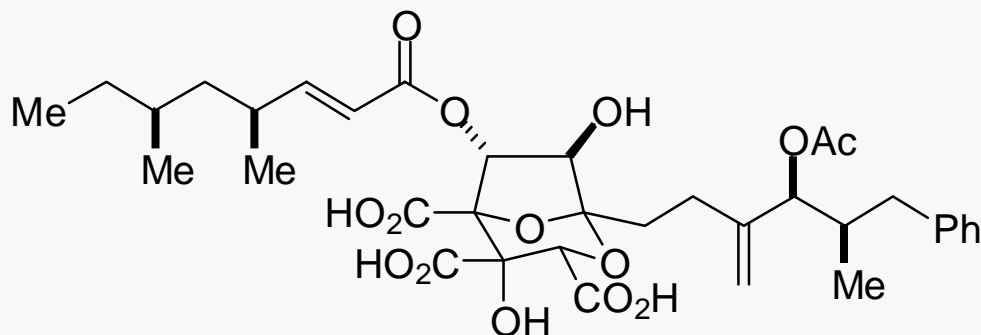
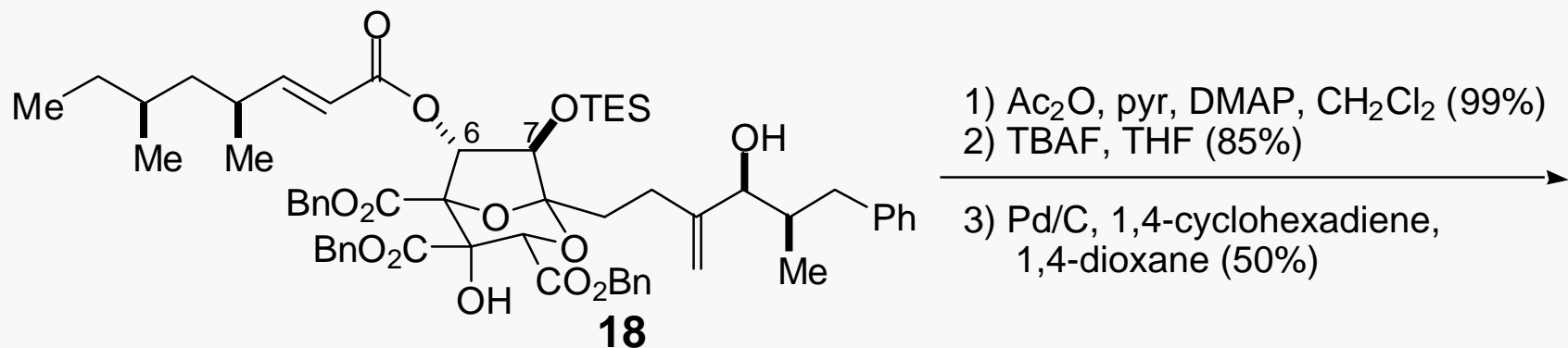


- 1) ROH, EDC, DMAP, CH₂Cl₂
(28% C6, 19% C7, 20% **17**)

- 2) TESOTf, pyr, CH₂Cl₂ (79%)
- 3) DDQ, CH₂Cl₂/H₂O (98%)

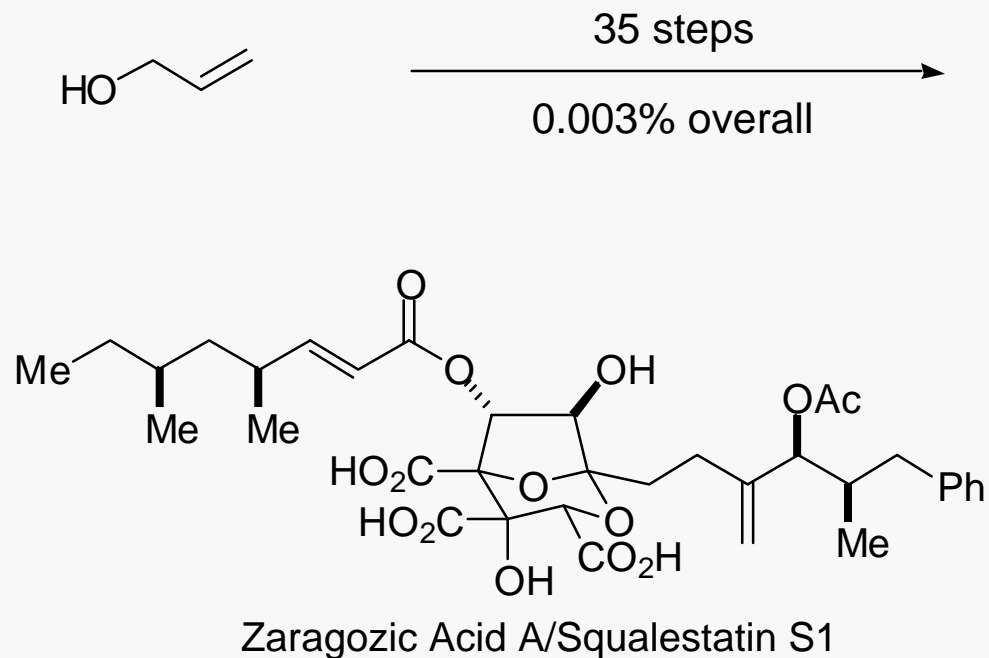


Completion of the Total Synthesis



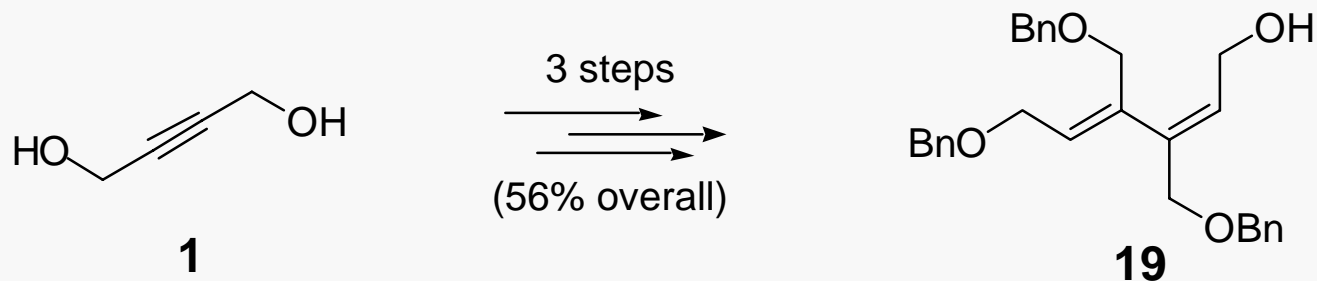
Zaragozic Acid A/Squalestatin S1

Total Synthesis Summary

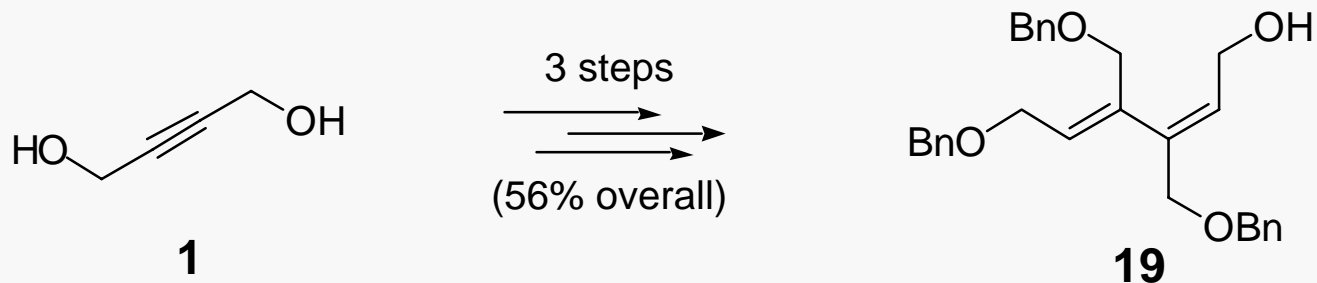


Nicolaou, K.C.; Yue, E.W.; Greca, S.L.; Nadin, A.; Yang, Z.; Leresche, J.E.; Tsuru, T.; Naniwa, Y.; Riccardis, F.D. *Chem. Eur. J.* **1995**, *1*, 467-494.

Armstrong's Improvements

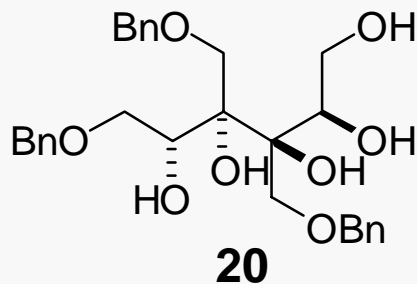


Armstrong's Improvements

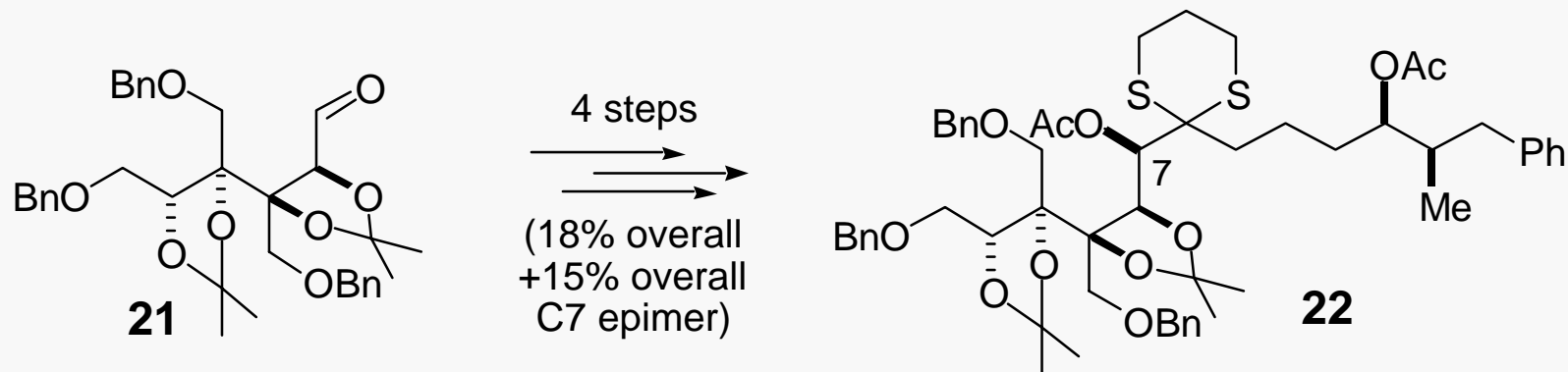
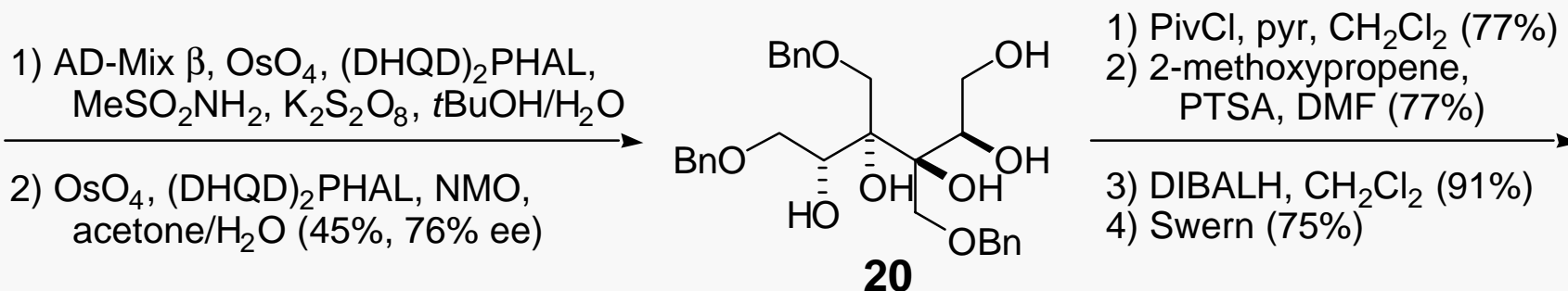
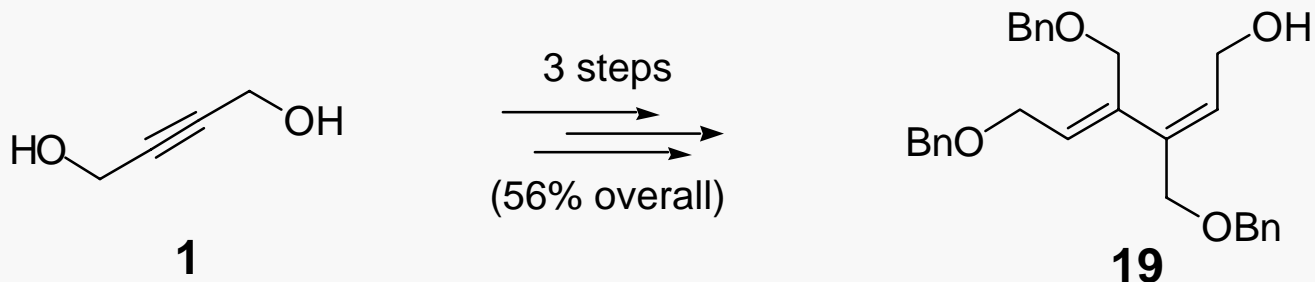


1) AD-Mix β , OsO₄, (DHQD)₂PHAL,
MeSO₂NH₂, K₂S₂O₈, *t*BuOH/H₂O

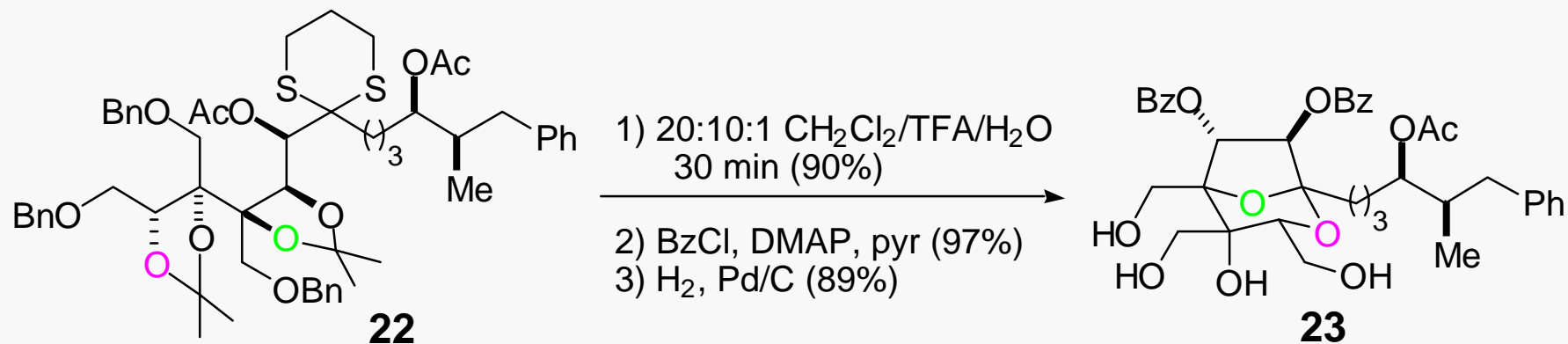
2) OsO₄, (DHQD)₂PHAL, NMO,
acetone/H₂O (45%, 76% ee)



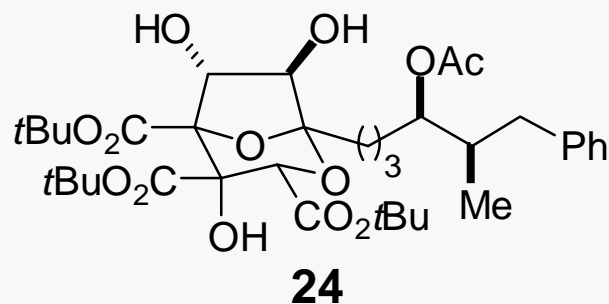
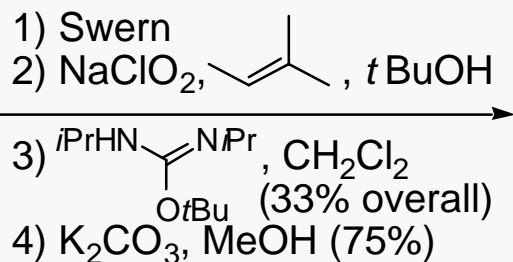
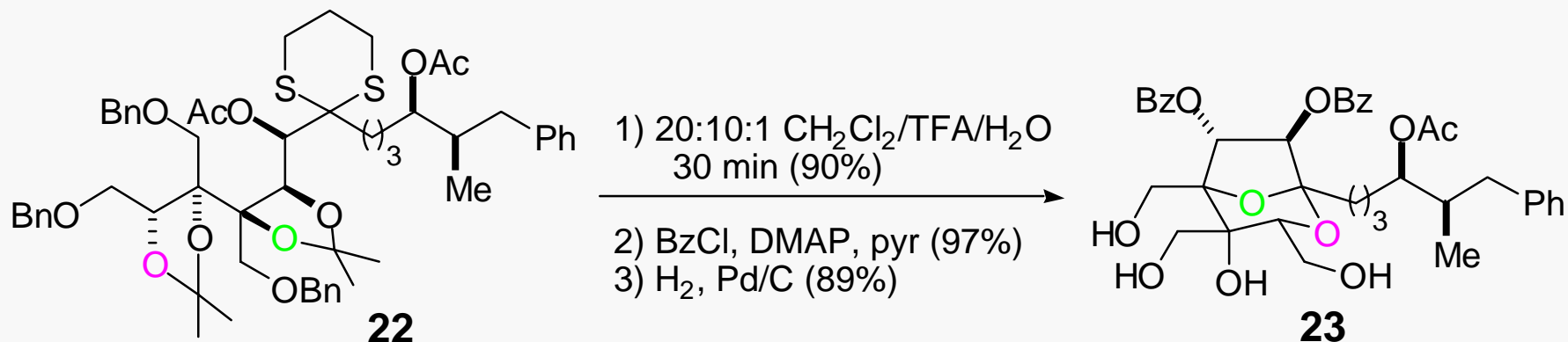
Armstrong's Improvements



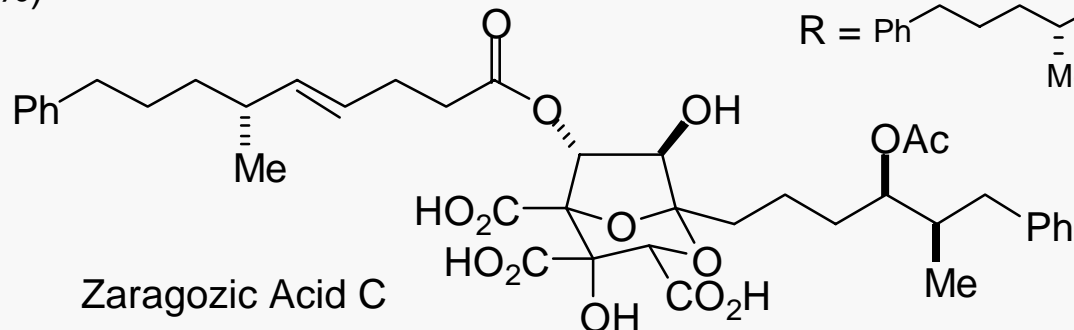
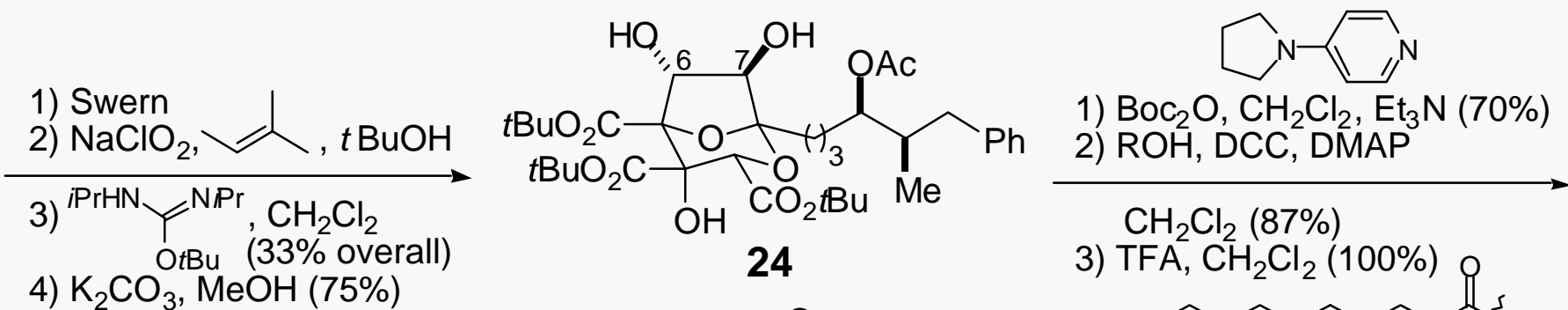
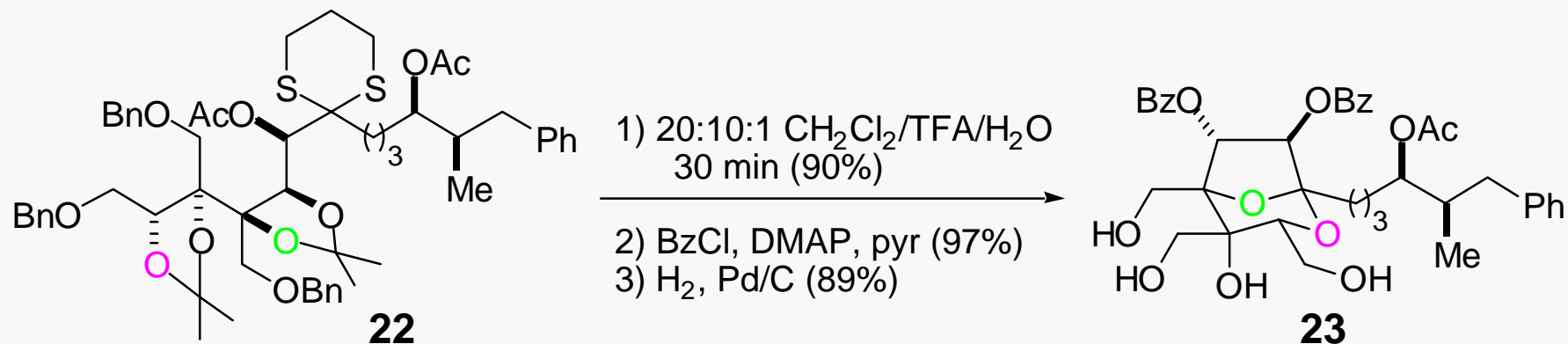
Armstrong's Improvements



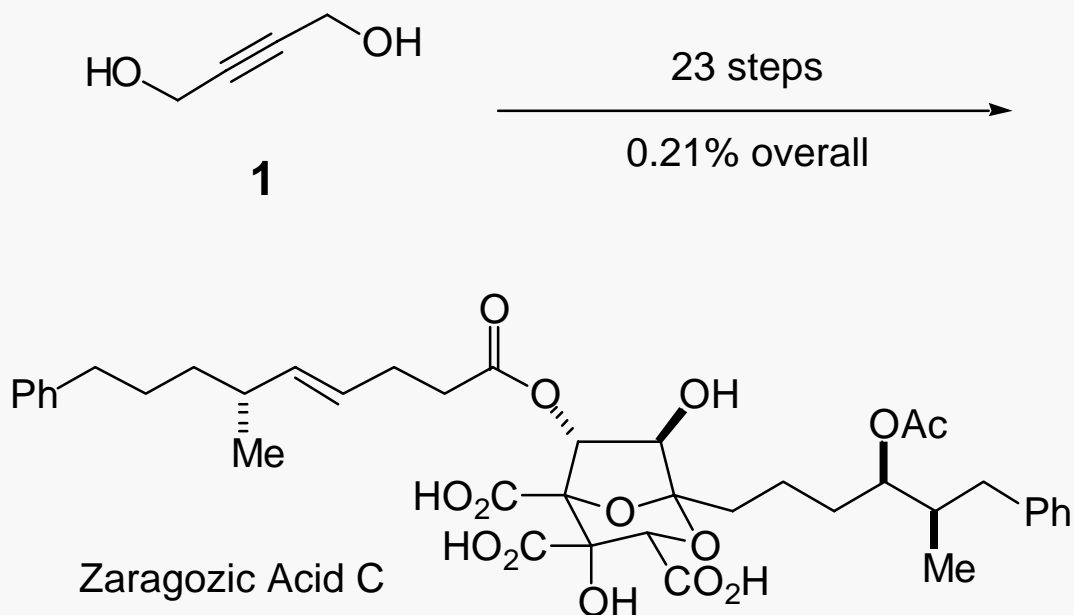
Armstrong's Improvements



Armstrong's Improvements



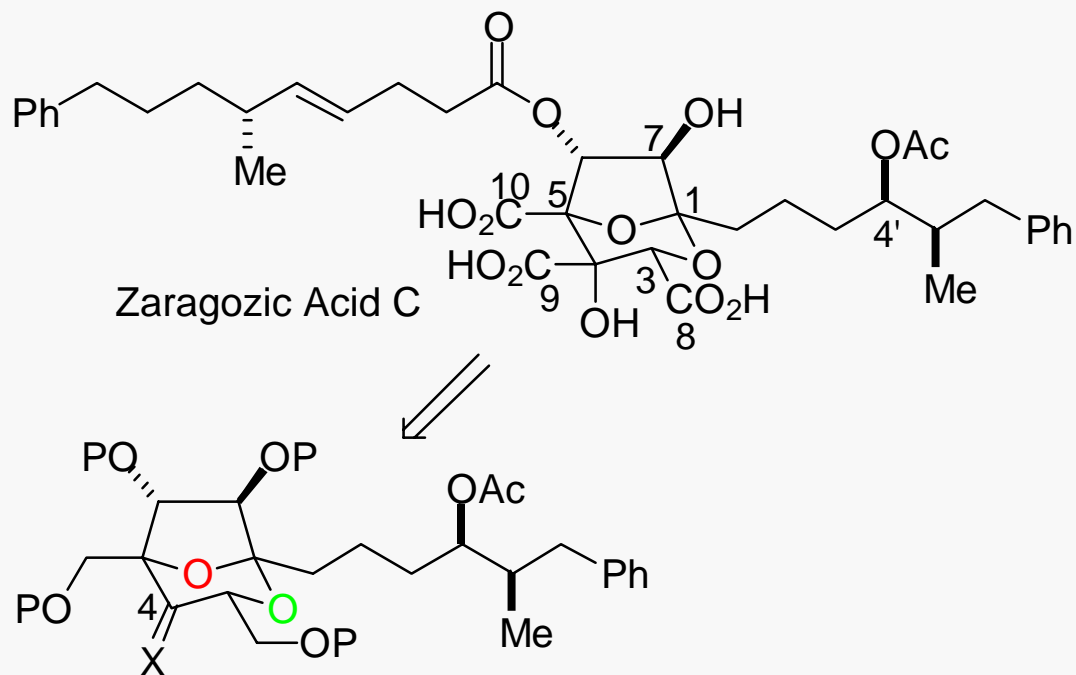
Total Synthesis Summary



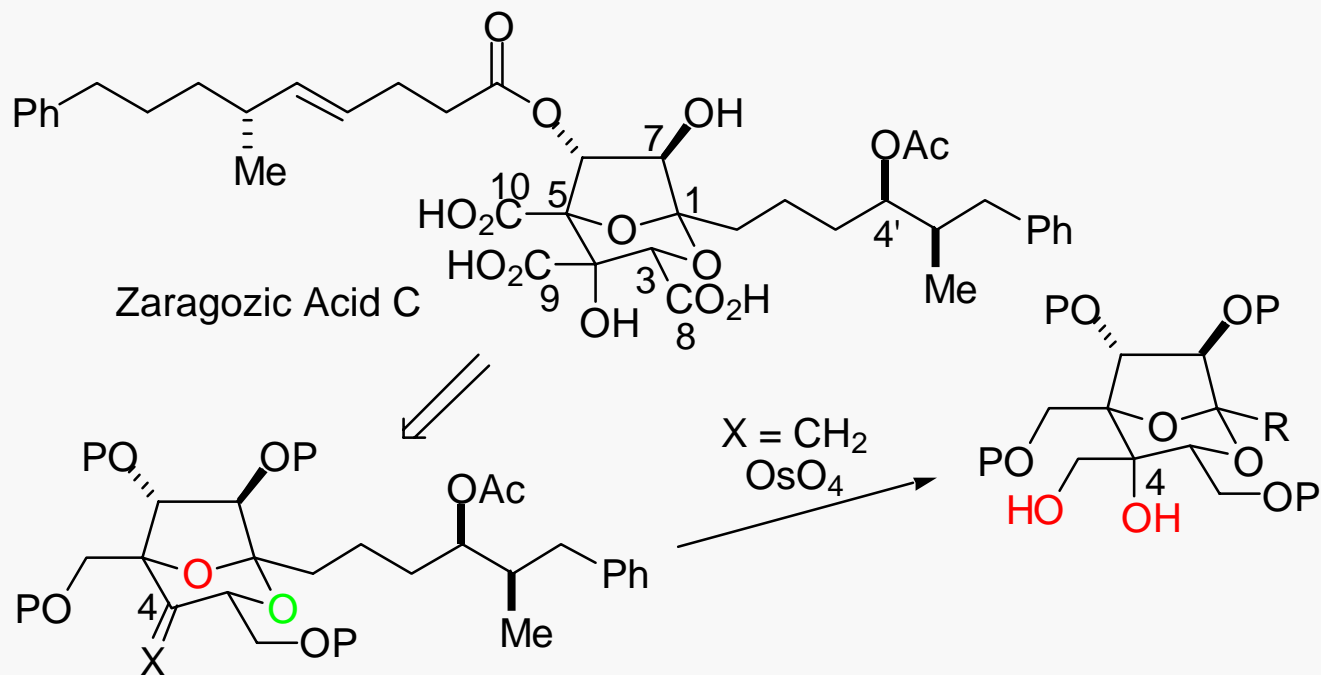
Outline

- Dihydroxylation Strategy
- **Carbonyl Addition Strategy**
 - » Carreira
 - » Heathcock
- Tartrate-Derived Aldol Strategy
- Acetal [1,2] Wittig Rearrangement Strategy

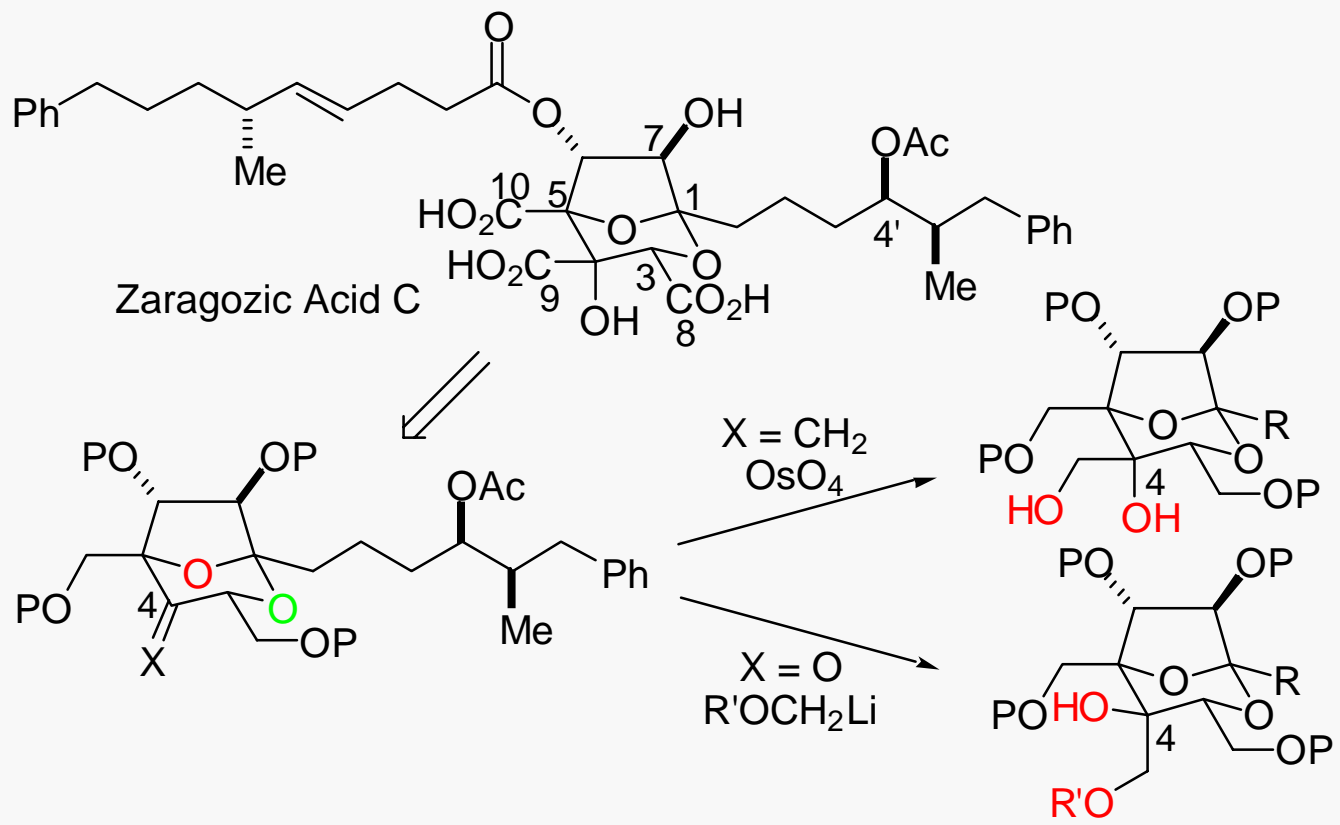
Carreira's Retrosynthetic Analysis



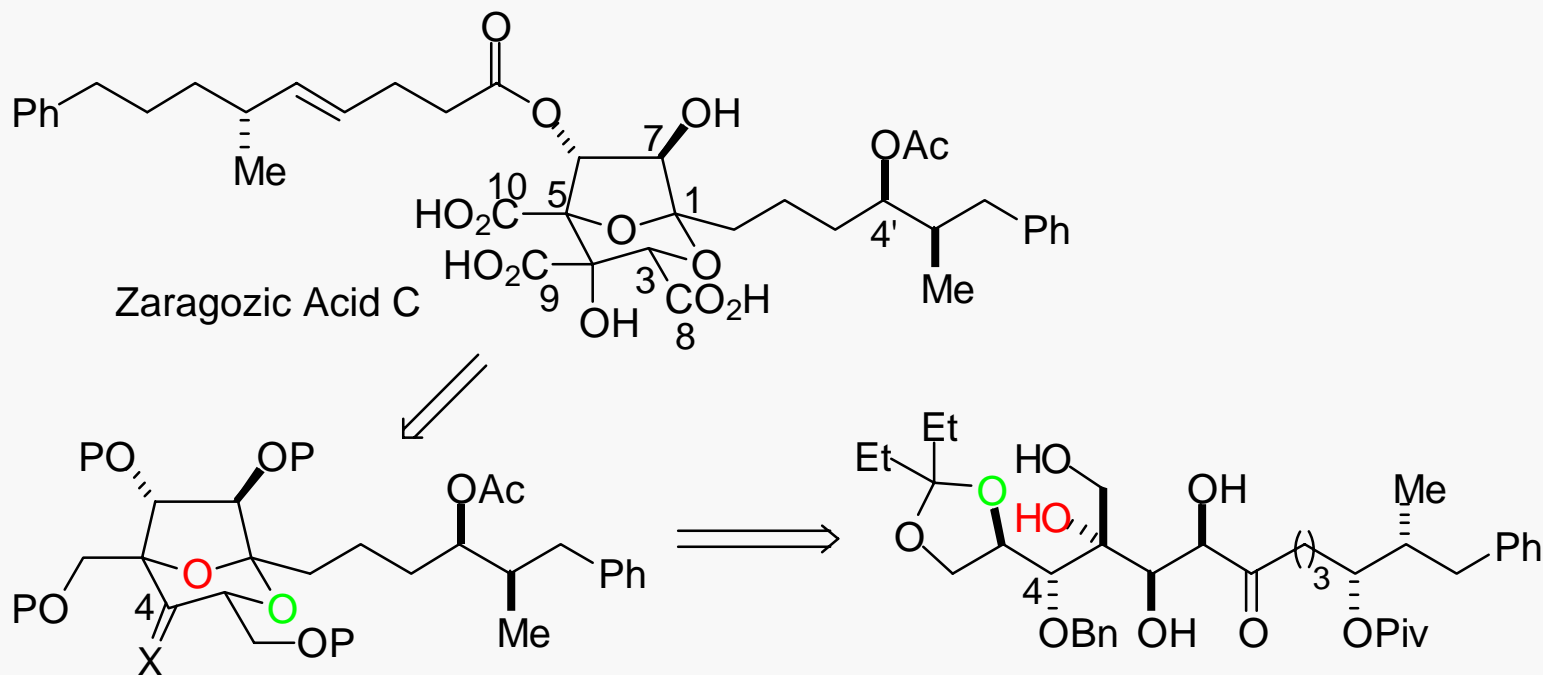
Carreira's Retrosynthetic Analysis



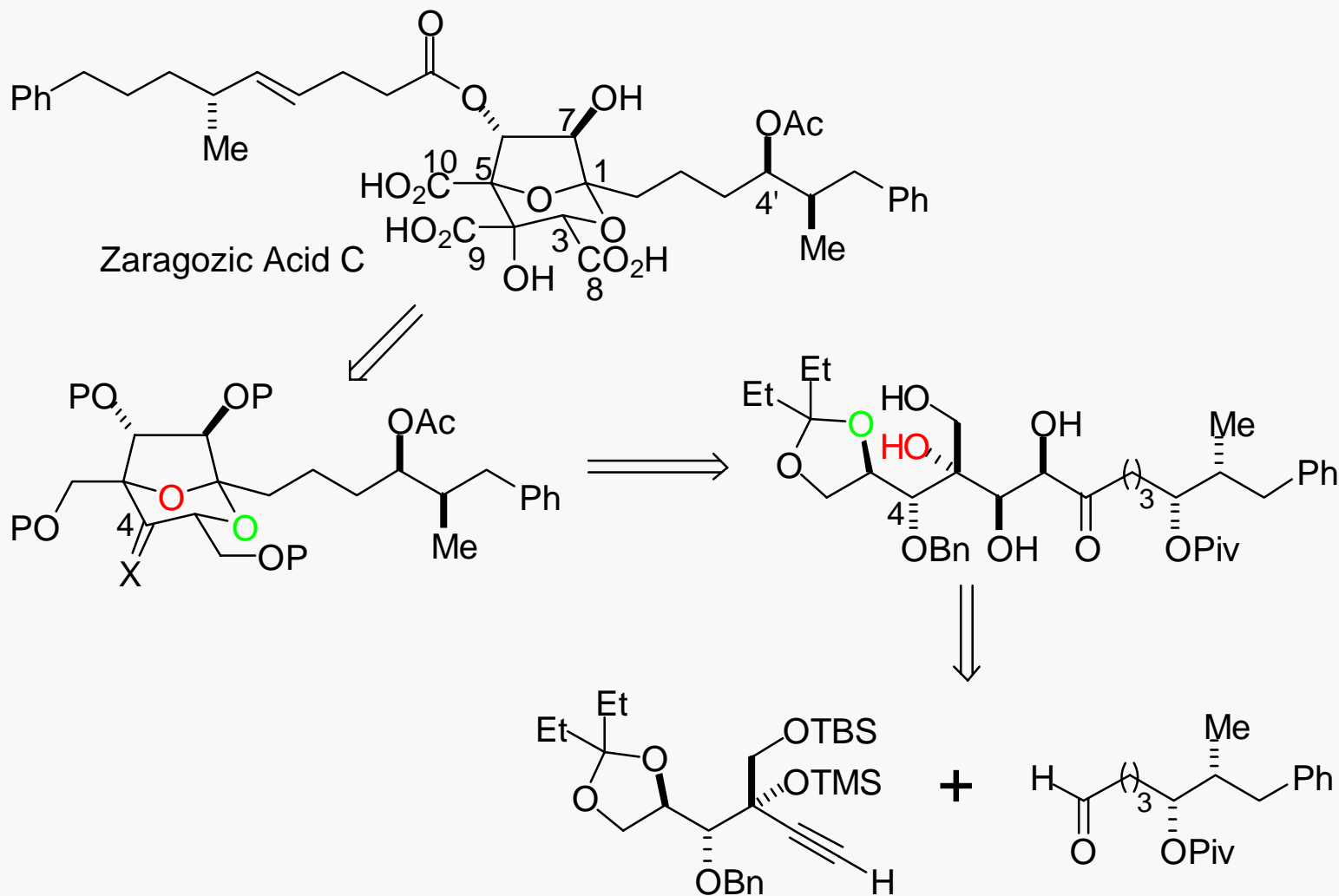
Carreira's Retrosynthetic Analysis



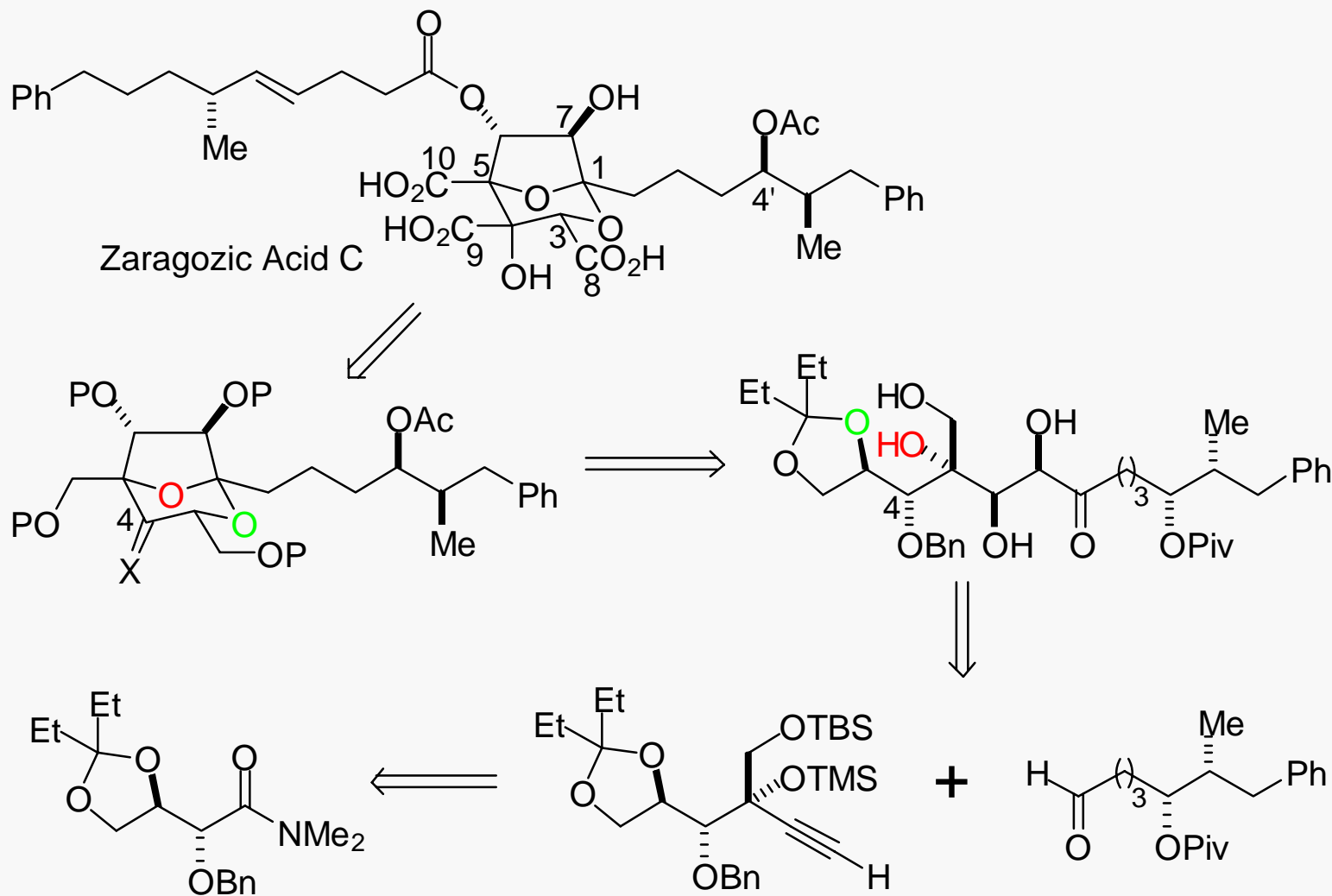
Carreira's Retrosynthetic Analysis



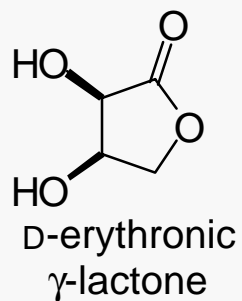
Carreira's Retrosynthetic Analysis



Carreira's Retrosynthetic Analysis

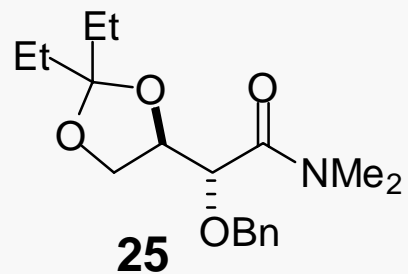


Carbonyl Addition

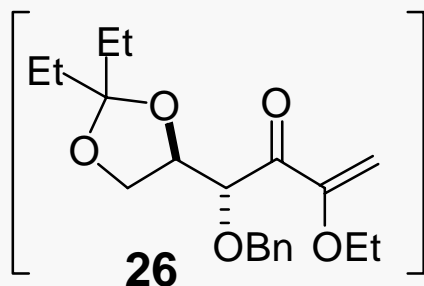
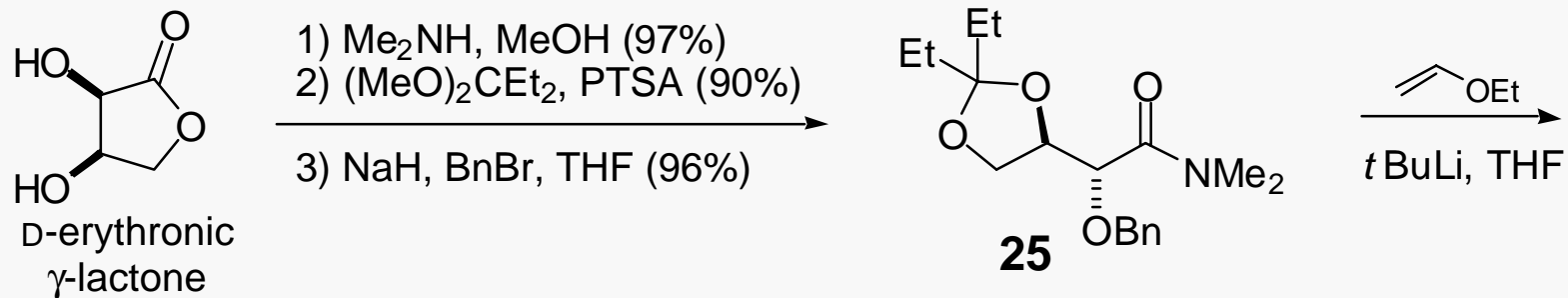


1) Me_2NH , MeOH (97%)
2) $(\text{MeO})_2\text{CEt}_2$, PTSA (90%)

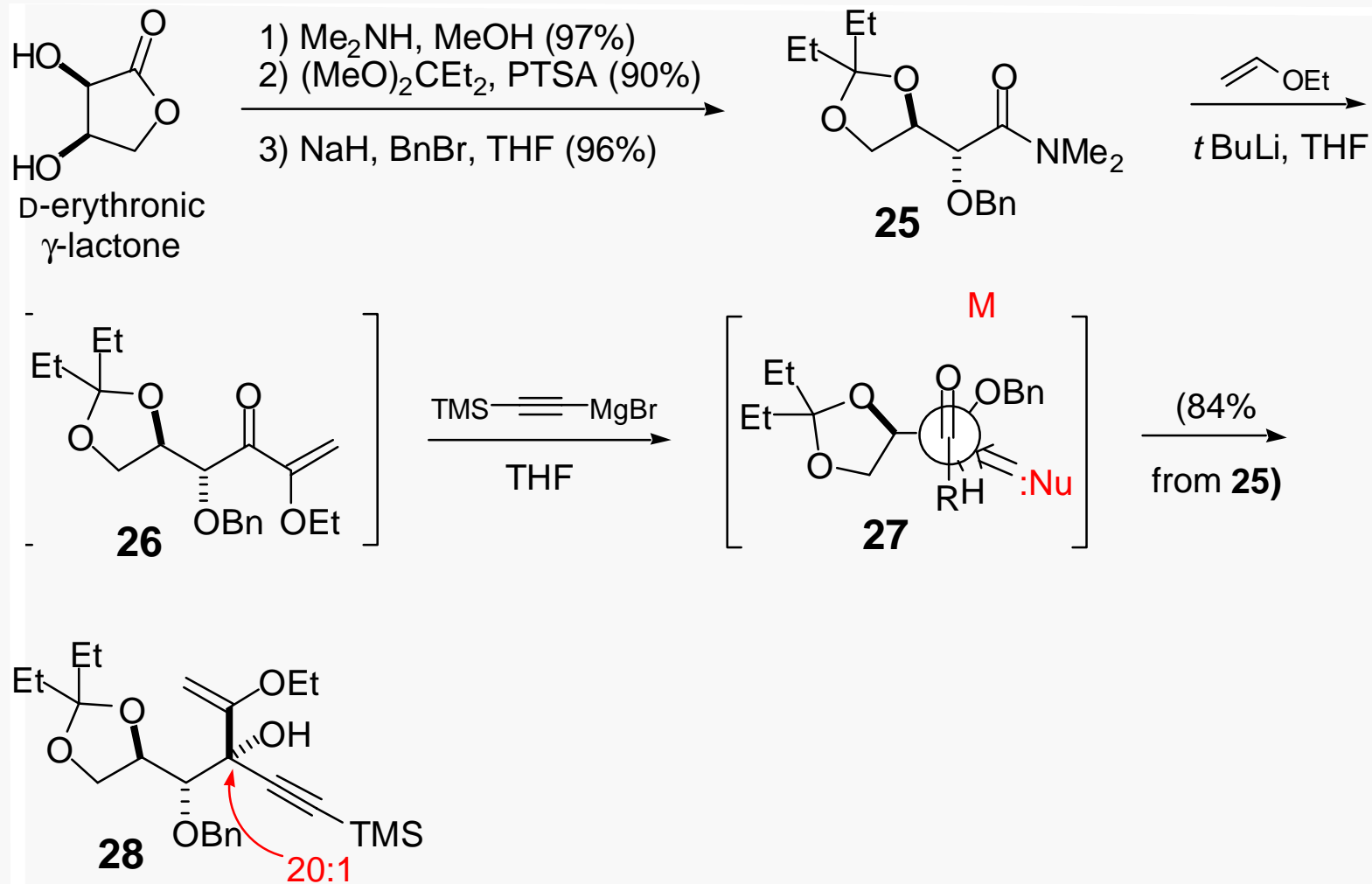
3) NaH , BnBr , THF (96%)



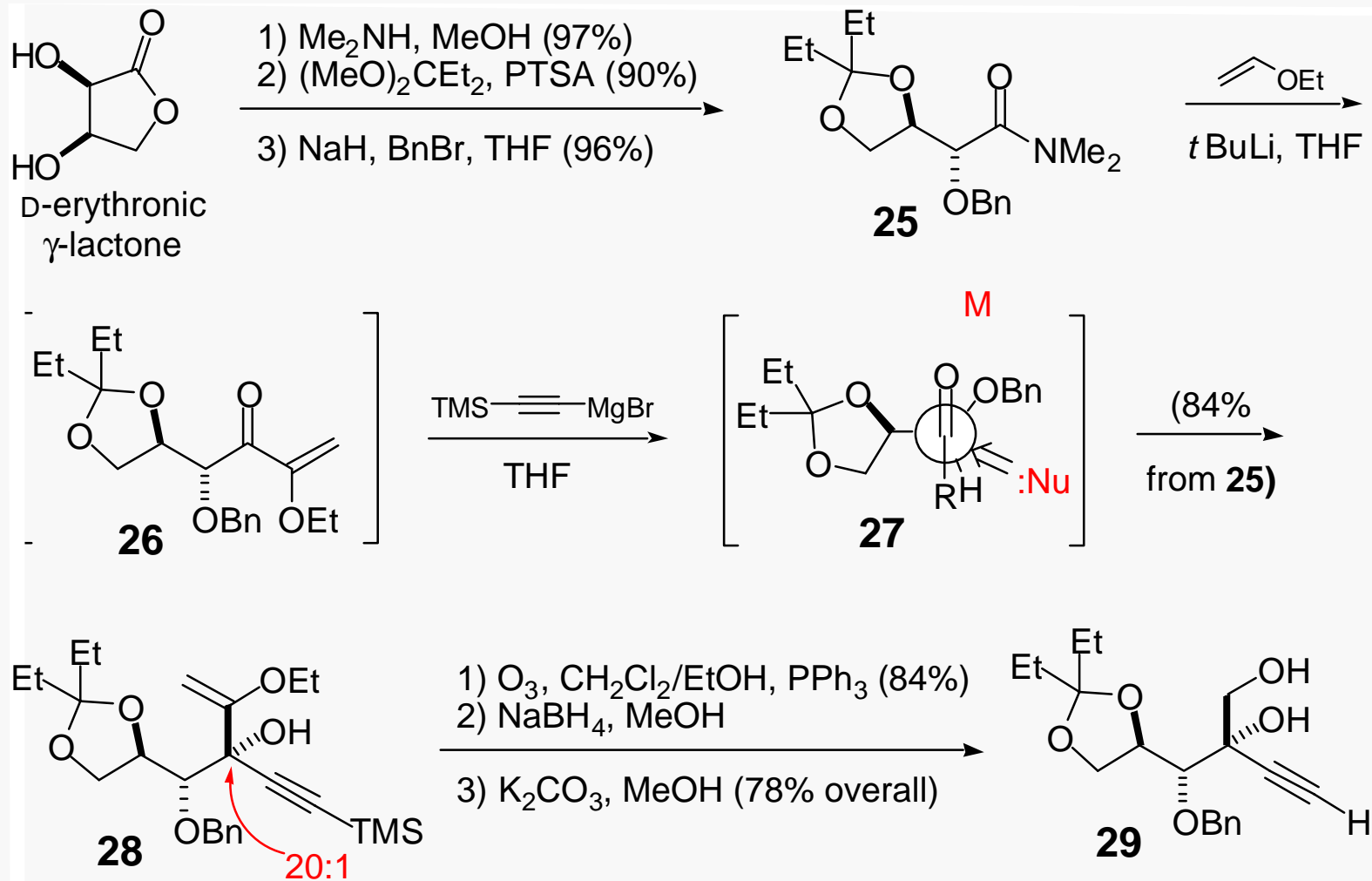
Carbonyl Addition



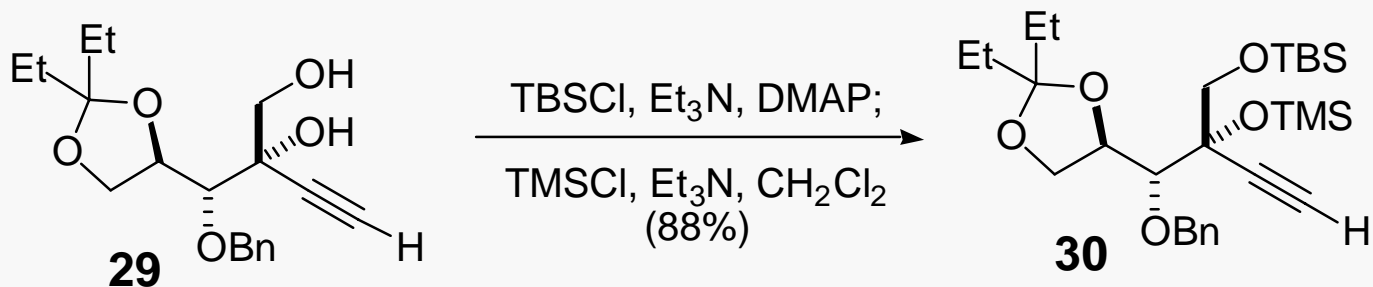
Carbonyl Addition



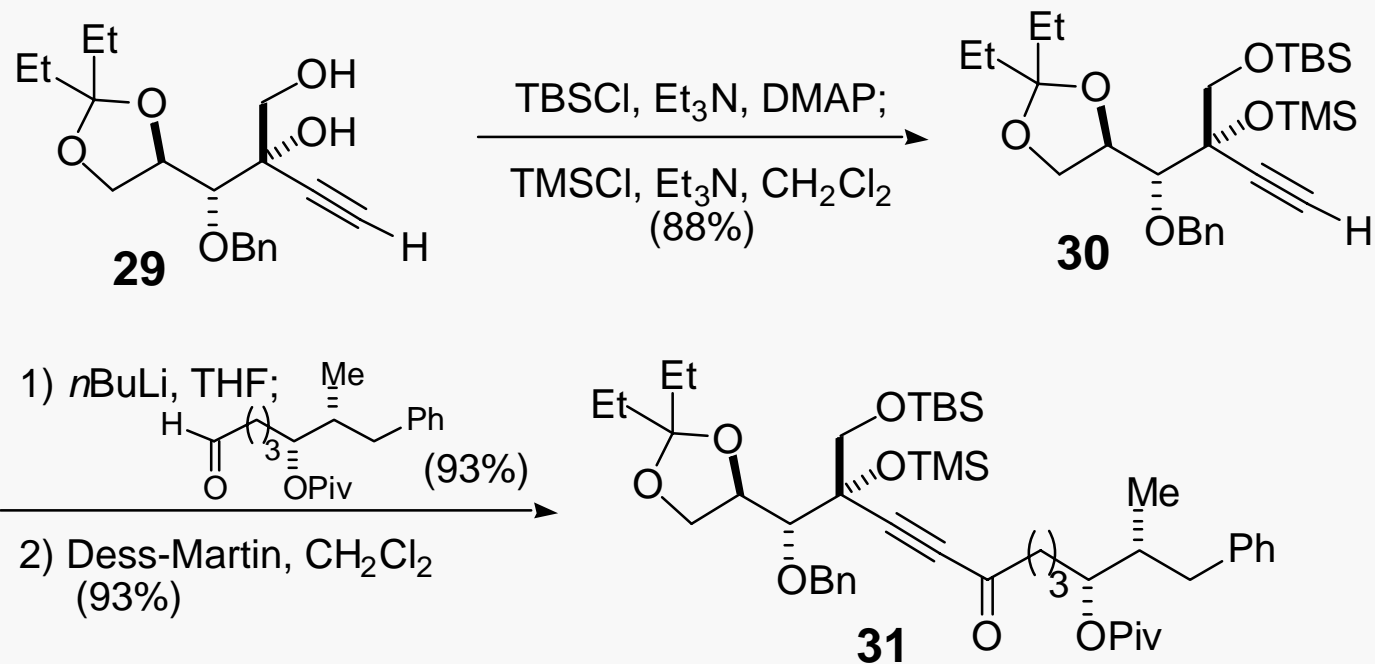
Carbonyl Addition



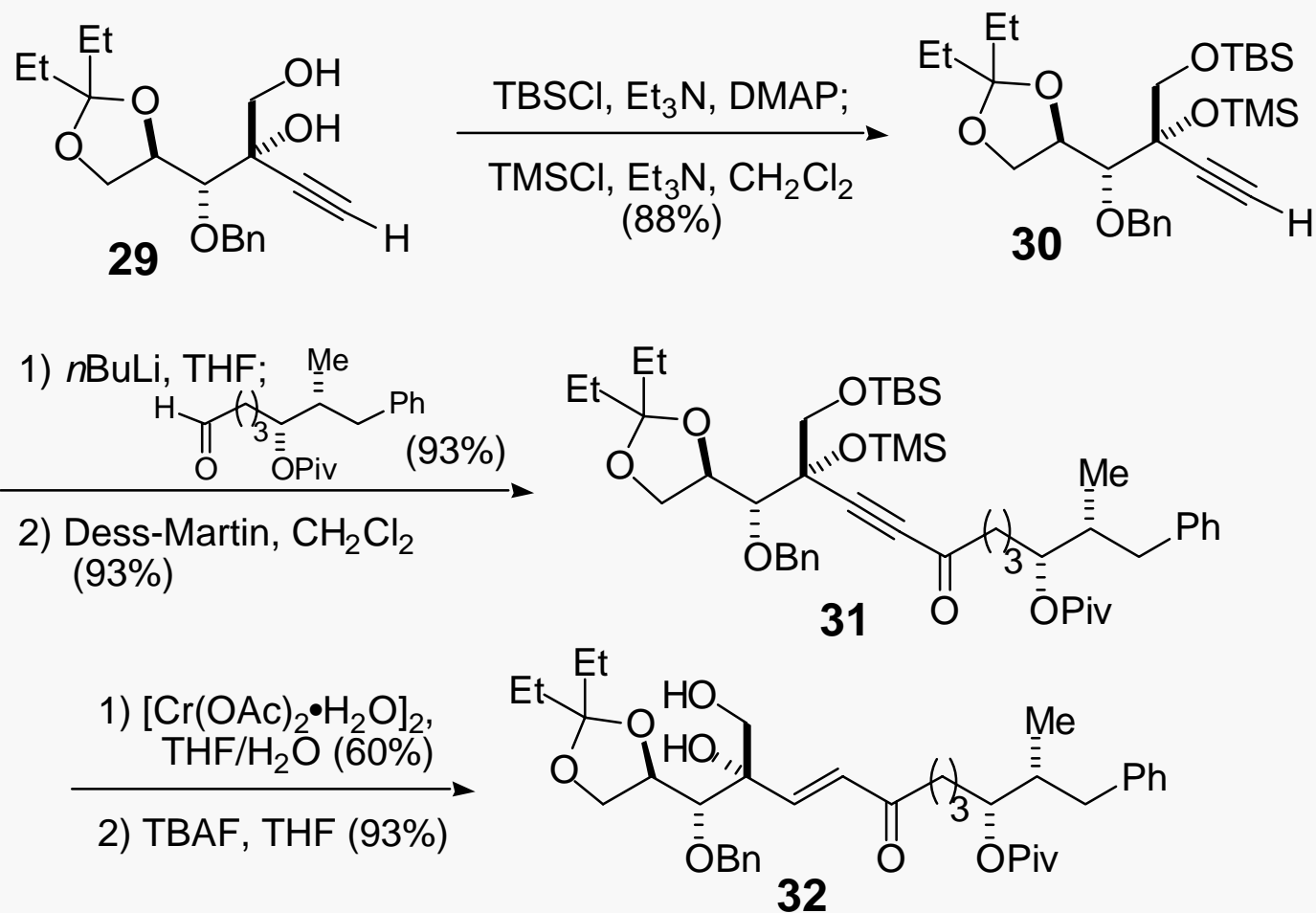
Chain Extension



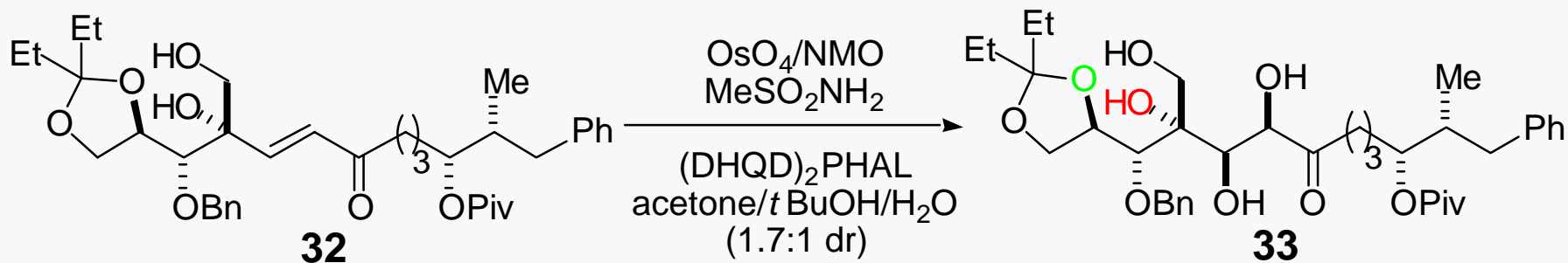
Chain Extension



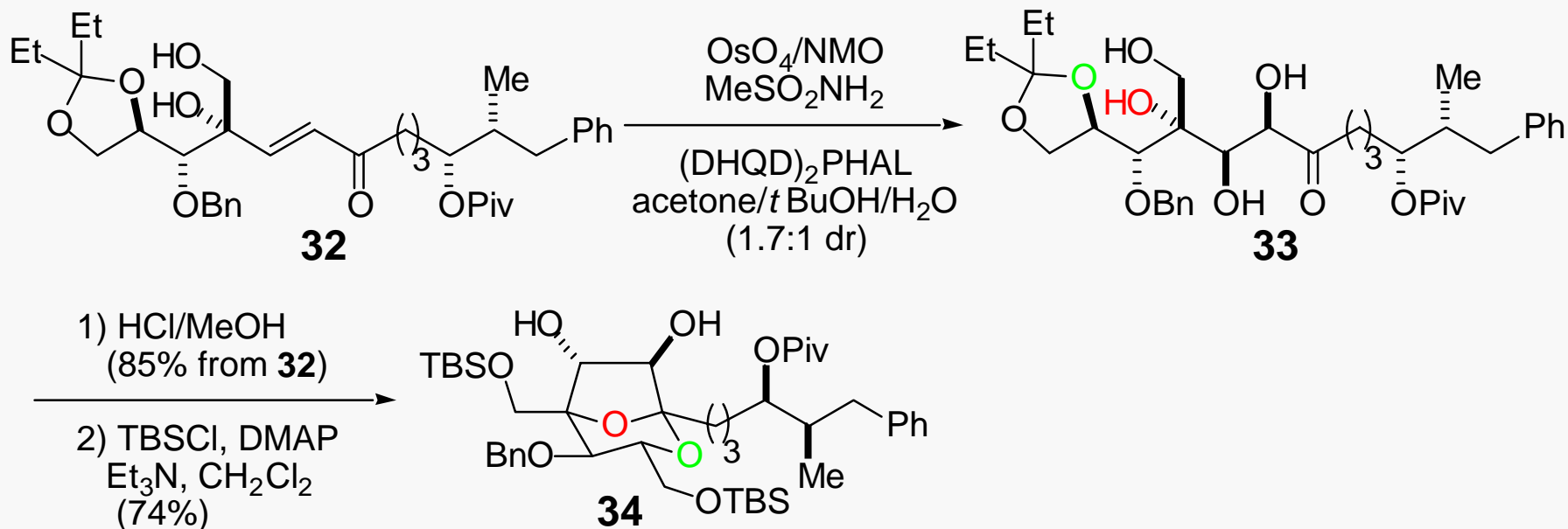
Chain Extension



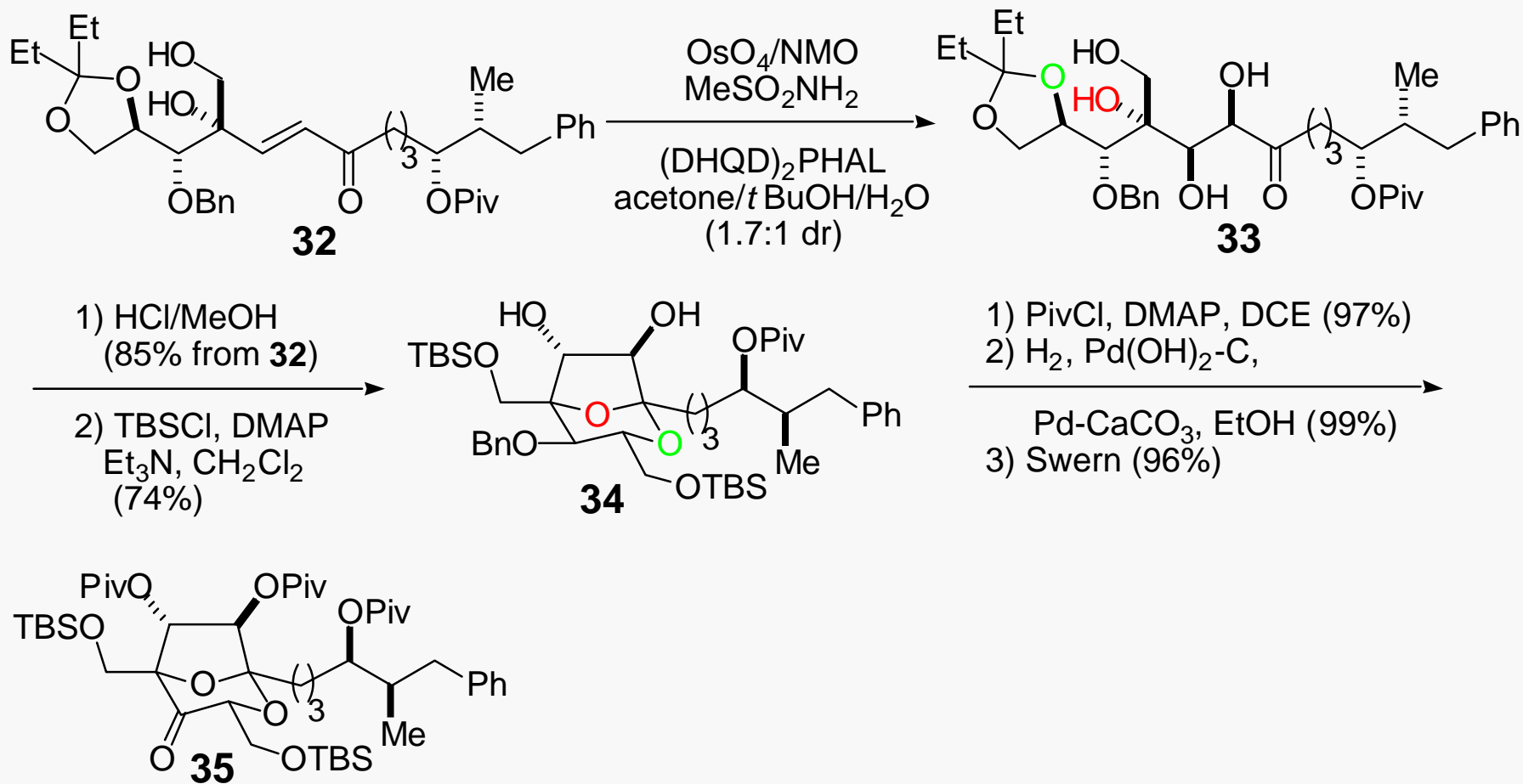
Ketalization/Functionalization



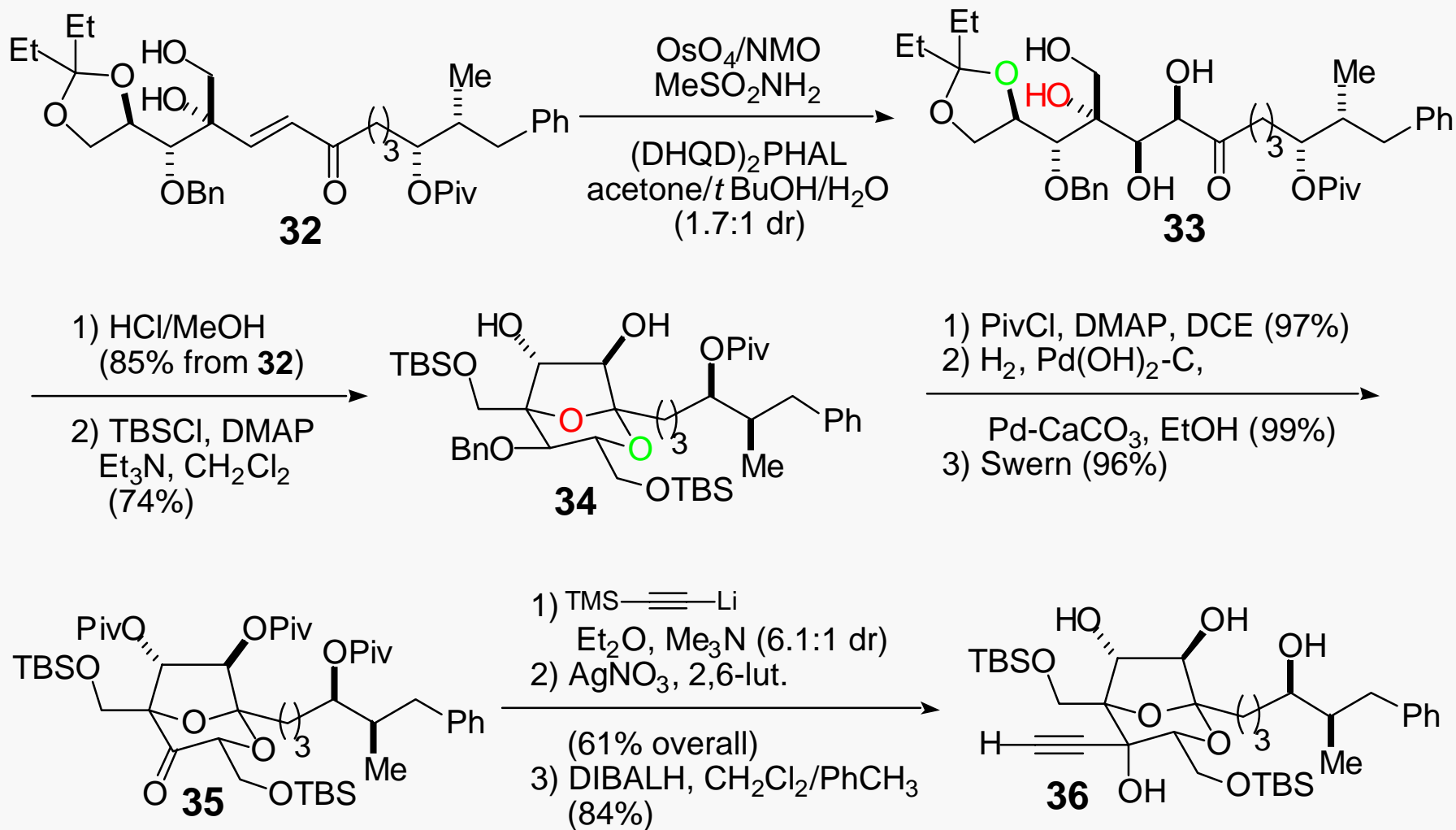
Ketalization/Functionalization



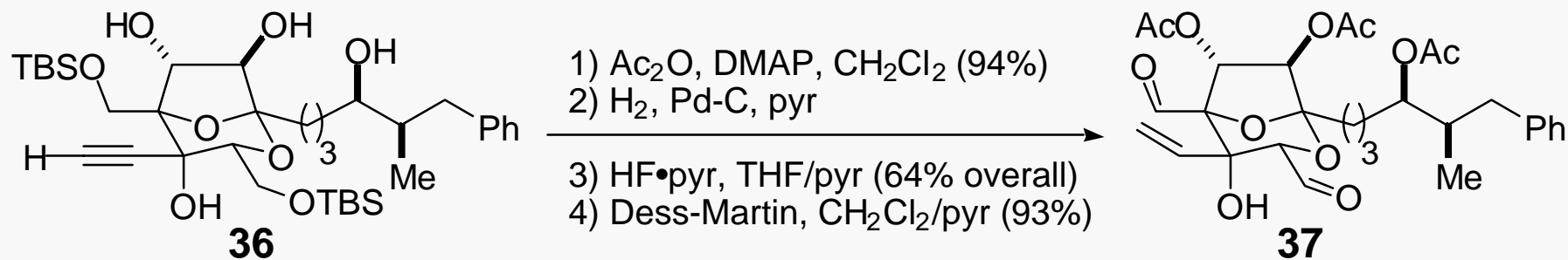
Ketalization/Functionalization



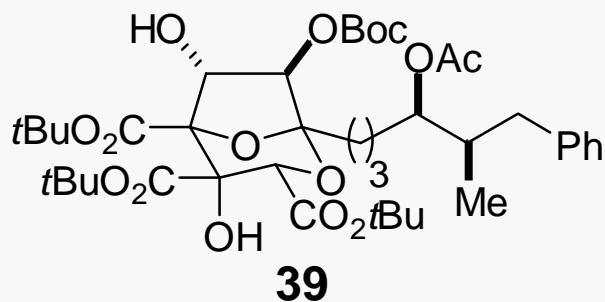
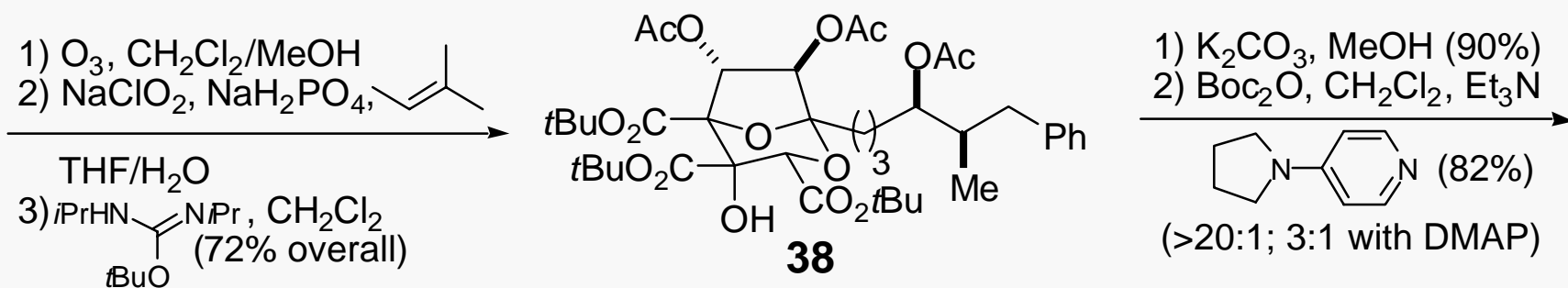
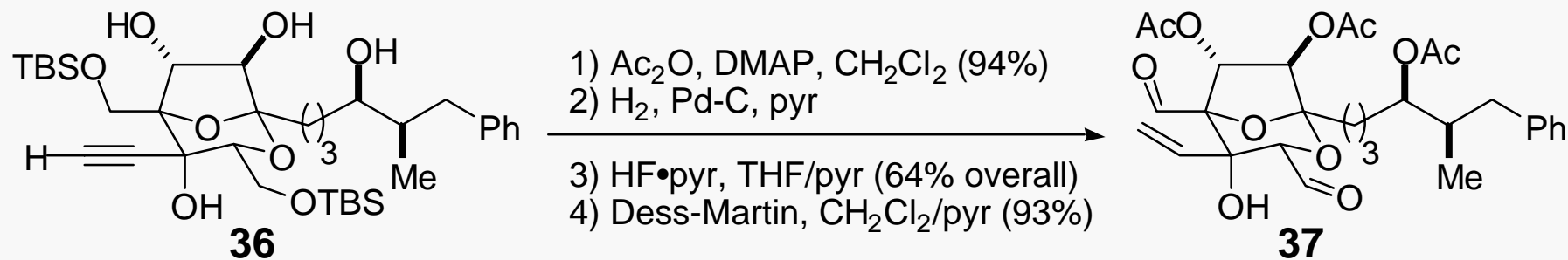
Ketalization/Functionalization



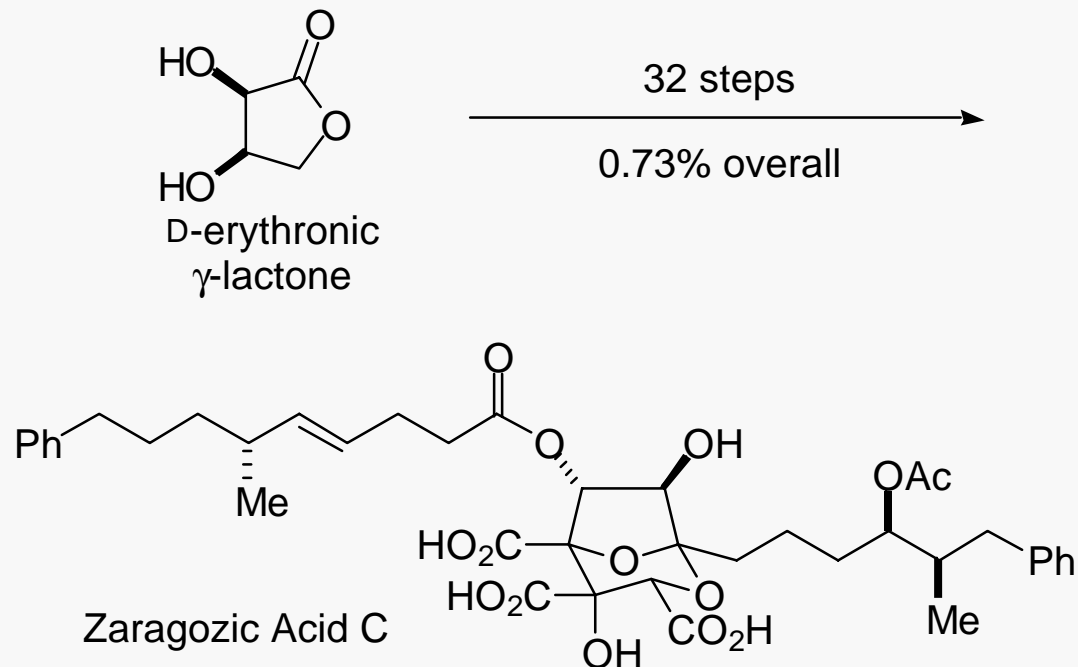
Completion of the Total Synthesis



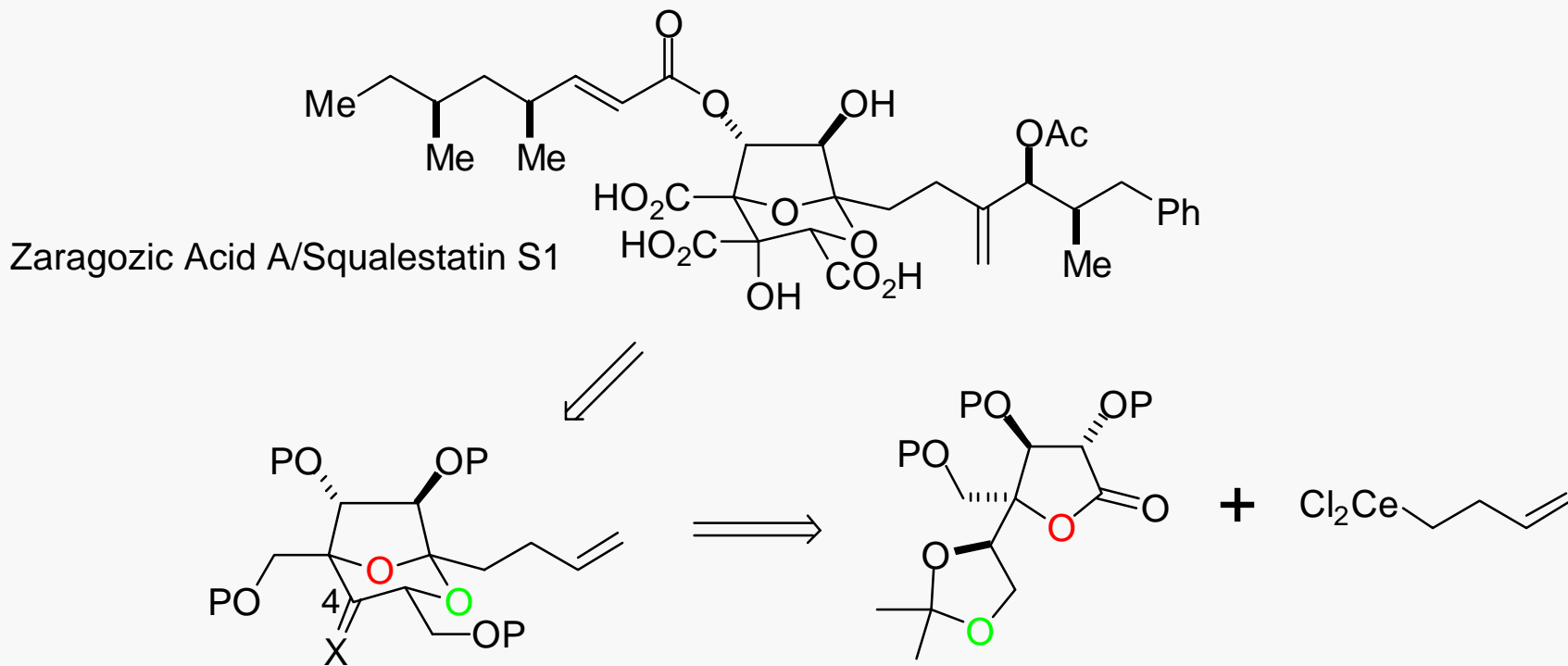
Completion of the Total Synthesis



Total Synthesis Summary

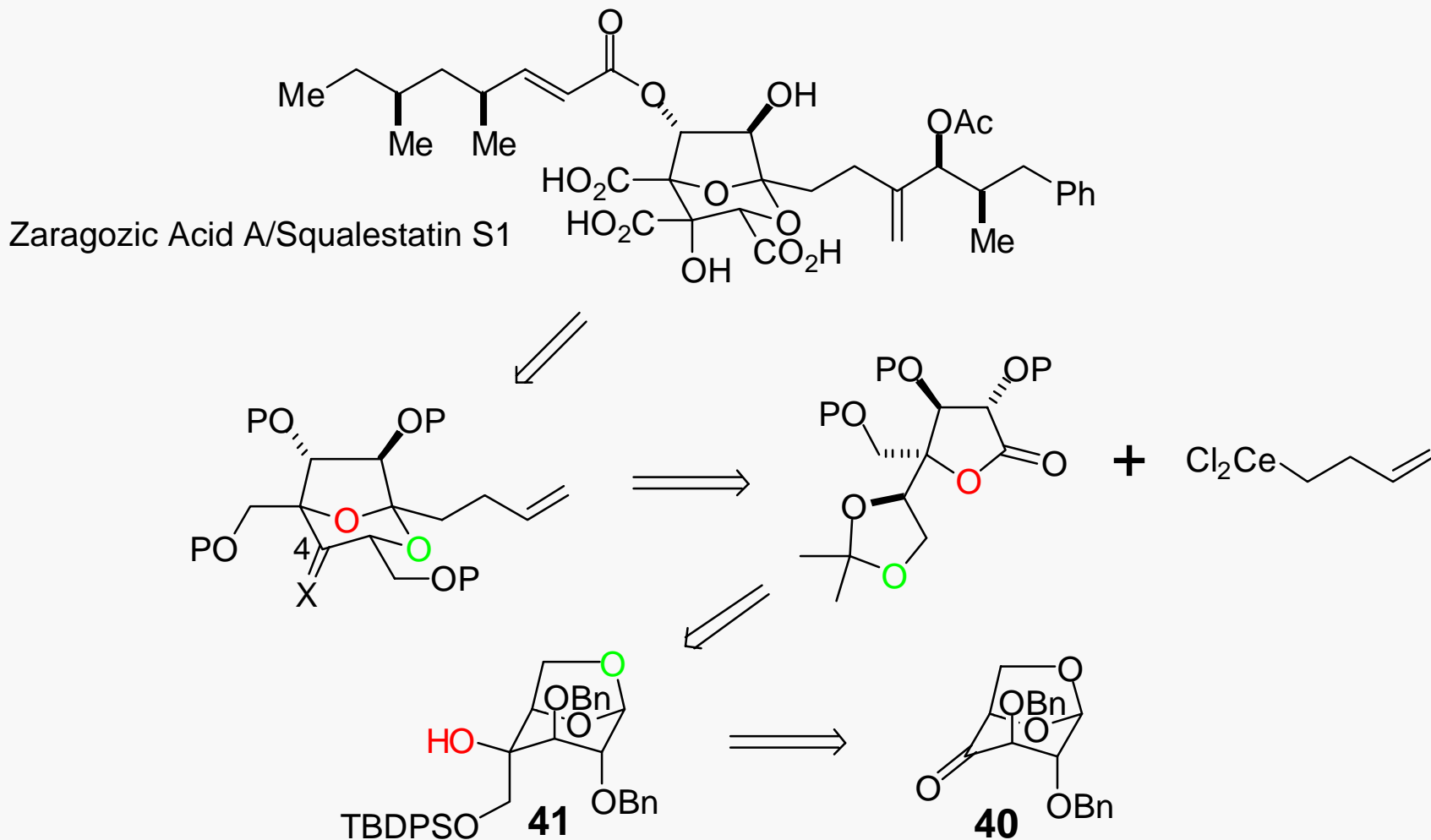


Heathcock's Retrosynthetic Analysis



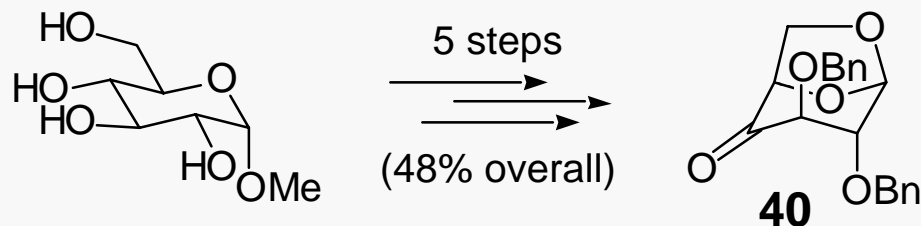
- 1) Stoermer, D.; Caron, S.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 9115-9125.
- 2) Caron, S.; Stoermer, D.; Mapp, A.K.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 9126-9134.

Heathcock's Retrosynthetic Analysis



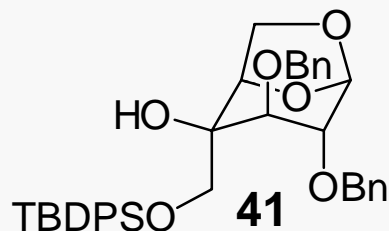
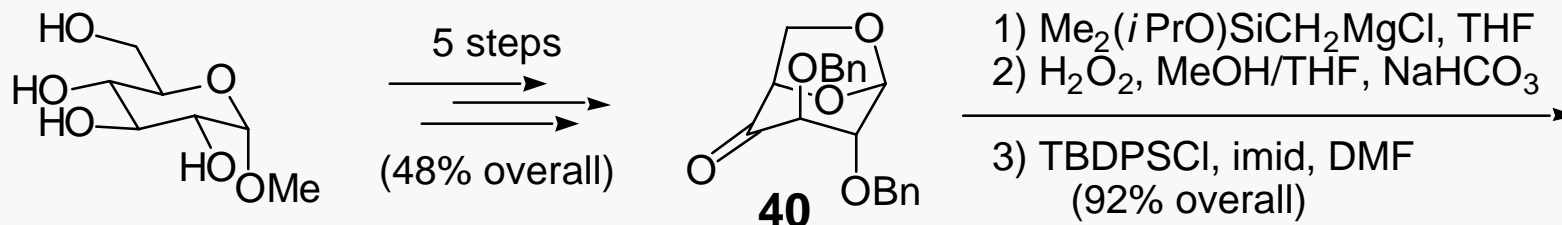
- 1) Stoermer, D.; Caron, S.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 9115-9125.
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Heathcock's Approach



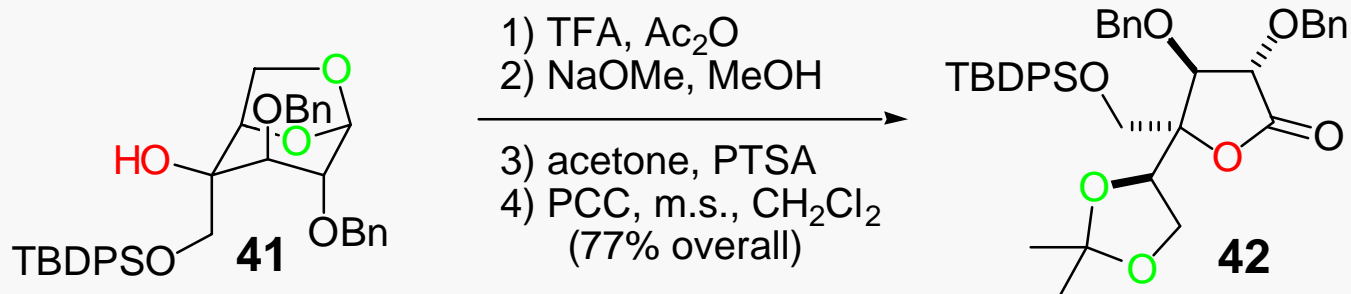
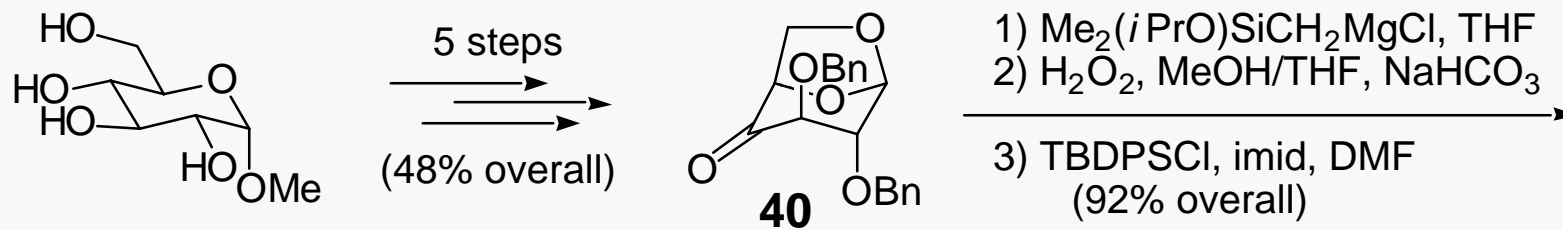
- 1) Stoermer, D.; Caron, S.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 9115-9125.
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First Carbonyl Addition



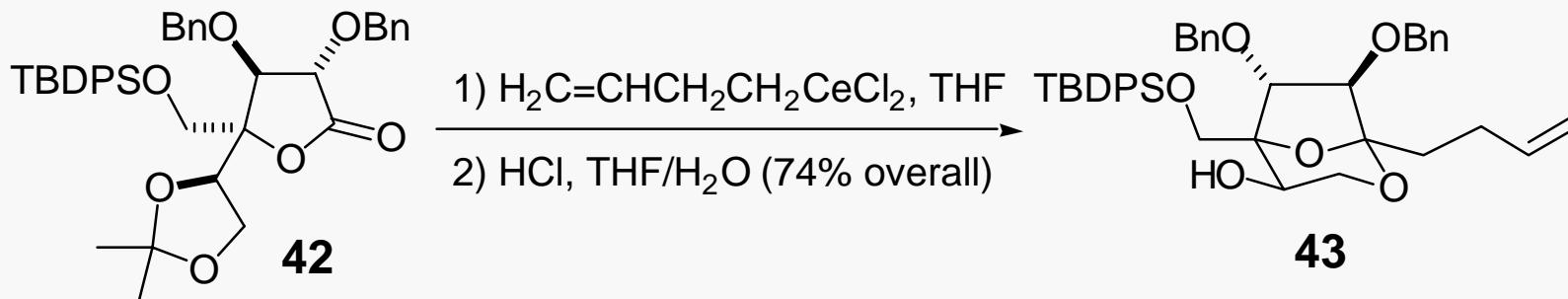
- 1) Stoermer, D.; Caron, S.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 9115-9125.
- 2) Caron, S.; Stoermer, D.; Mapp, A.K.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 9126-9134.

First Carbonyl Addition



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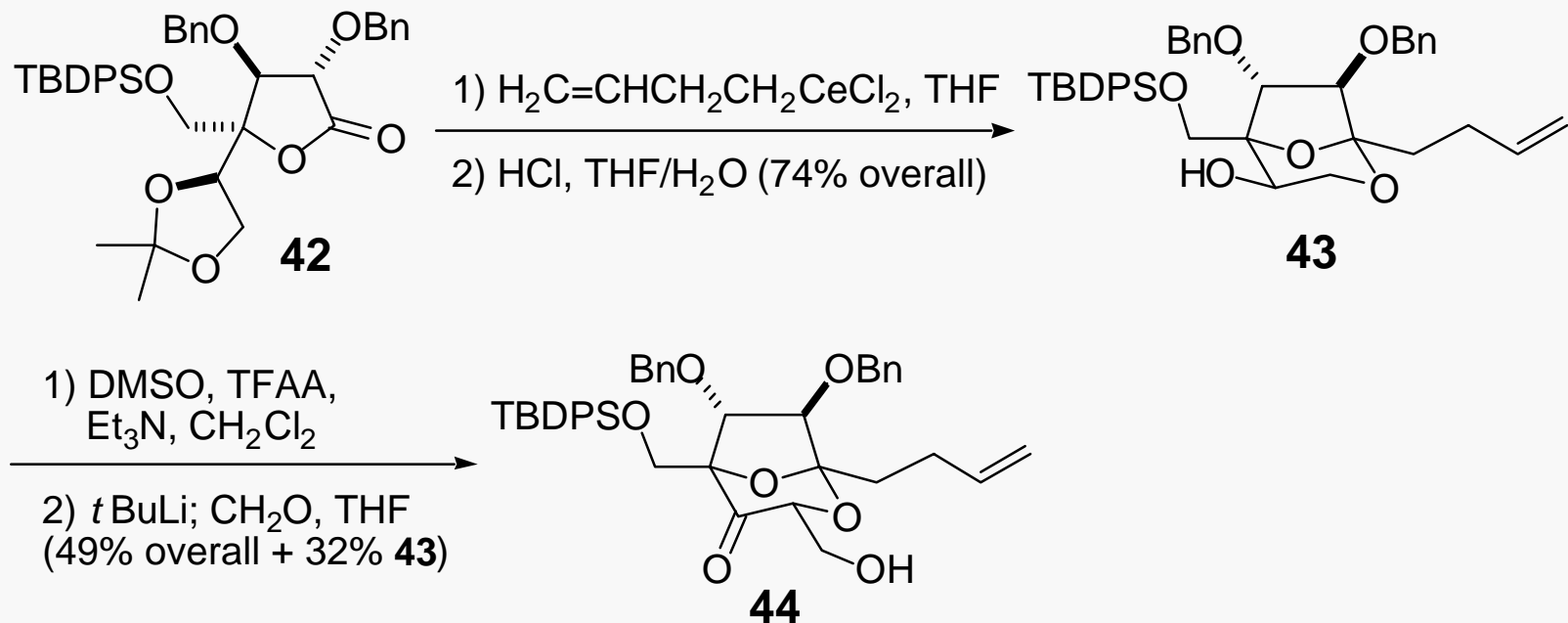
Second Carbonyl Addition



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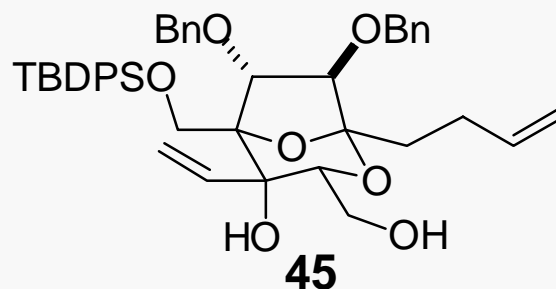
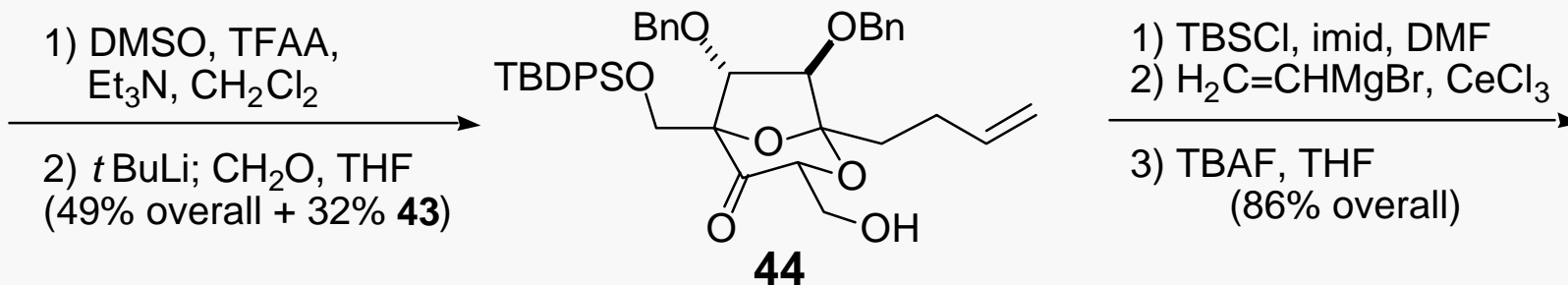
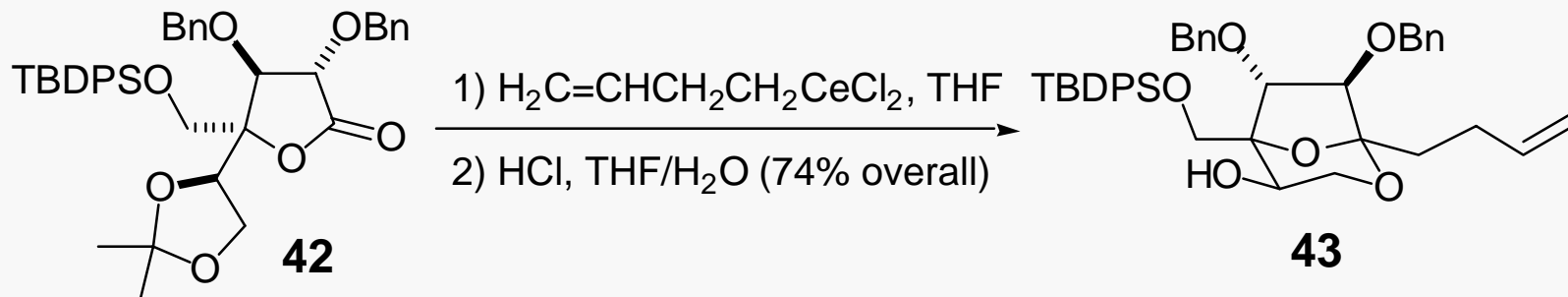
Second Carbonyl Addition



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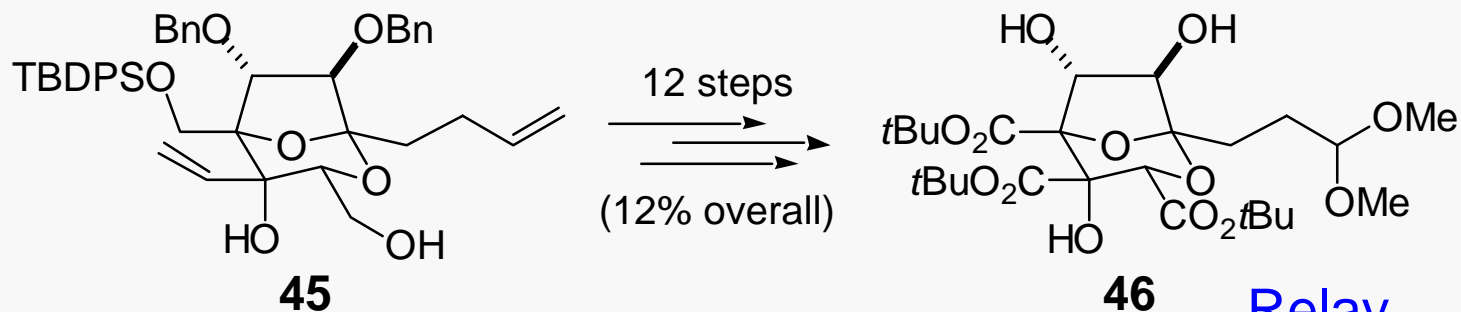
2) Caron, S.; Stoermer, D.; Mapp, A.K.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 9126-9134.

Second Carbonyl Addition

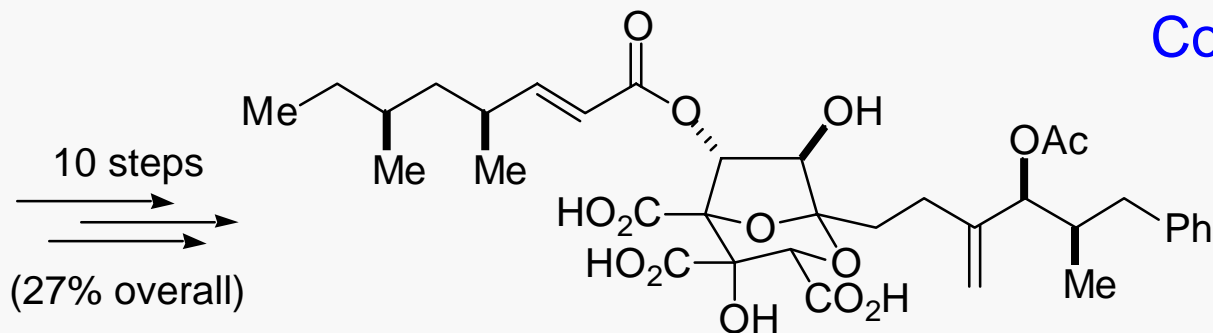


- 1) Stoermer, D.; Caron, S.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 9115-9125.
- 2) Caron, S.; Stoermer, D.; Mapp, A.K.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 9126-9134.

Completion of the Total Synthesis



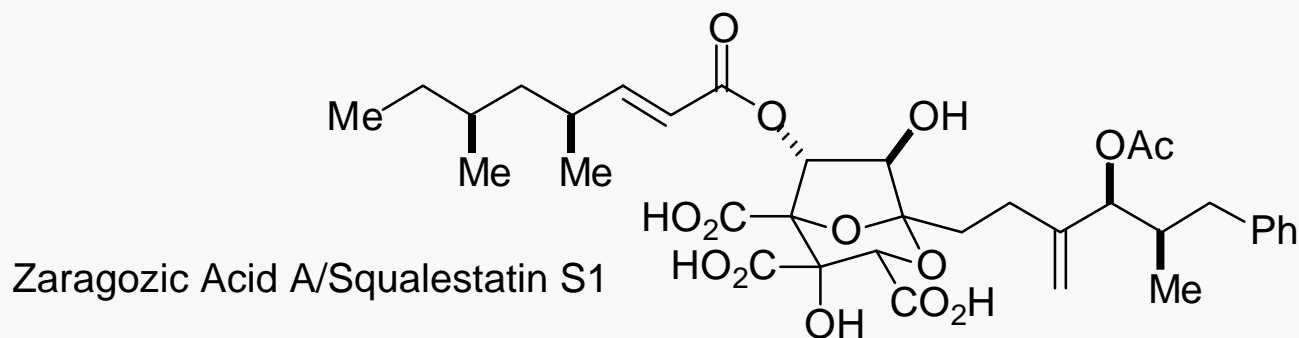
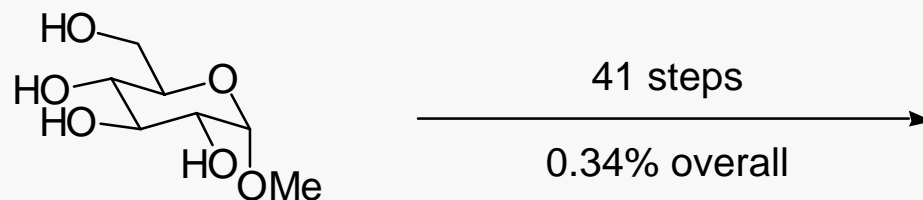
Relay
Compound



Zaragozic Acid A/Squalestatin S1

- 1) Stoermer, D.; Caron, S.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 9115-9125.
- 2) Caron, S.; Stoermer, D.; Mapp, A.K.; Heathcock, C.H. *J. Org. Chem.* **1996**, *61*, 9126-9134.

Total Synthesis Summary

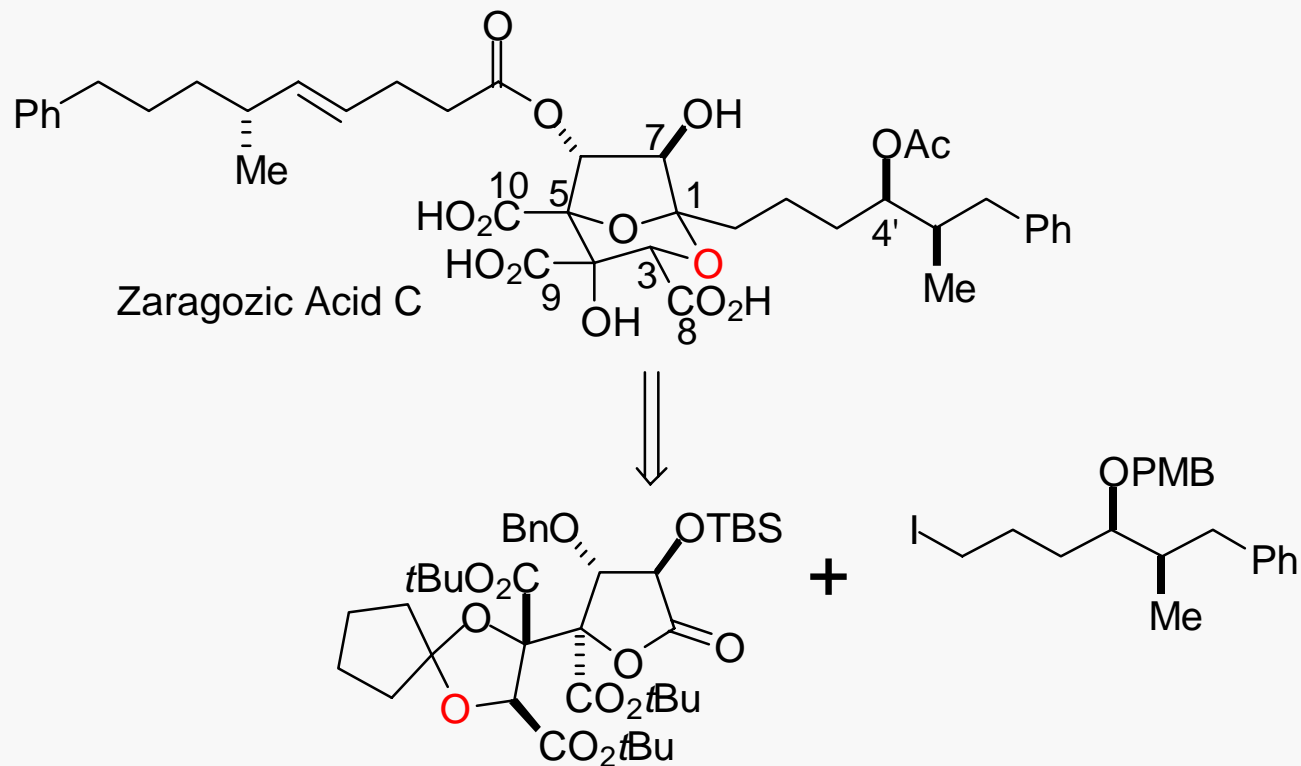


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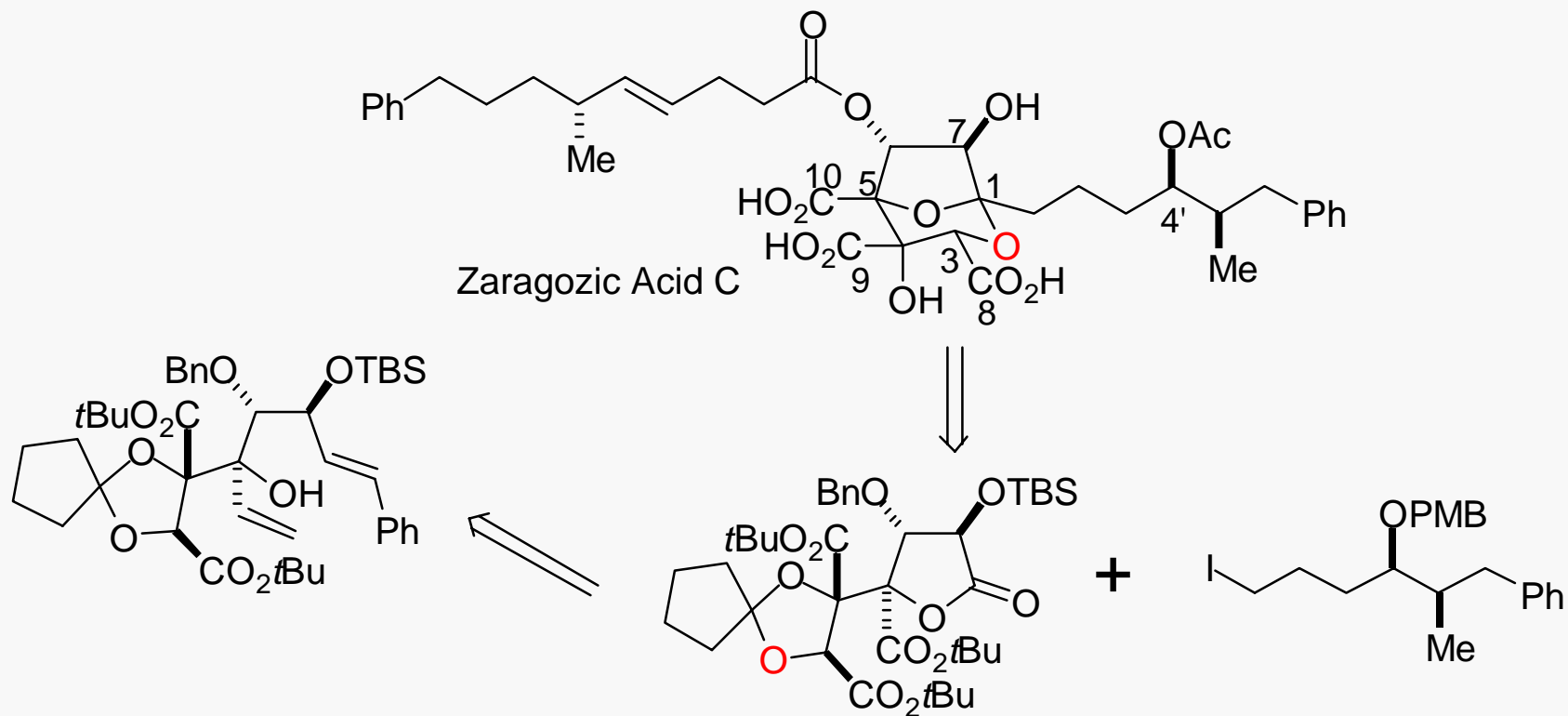
Outline

- Dihydroxylation Strategy
- Carbonyl Addition Strategy
- **Tartrate-Derived Aldol Strategy**
 - » Evans
 - » Hoshimoto
- Acetal [1,2] Wittig Rearrangement Strategy

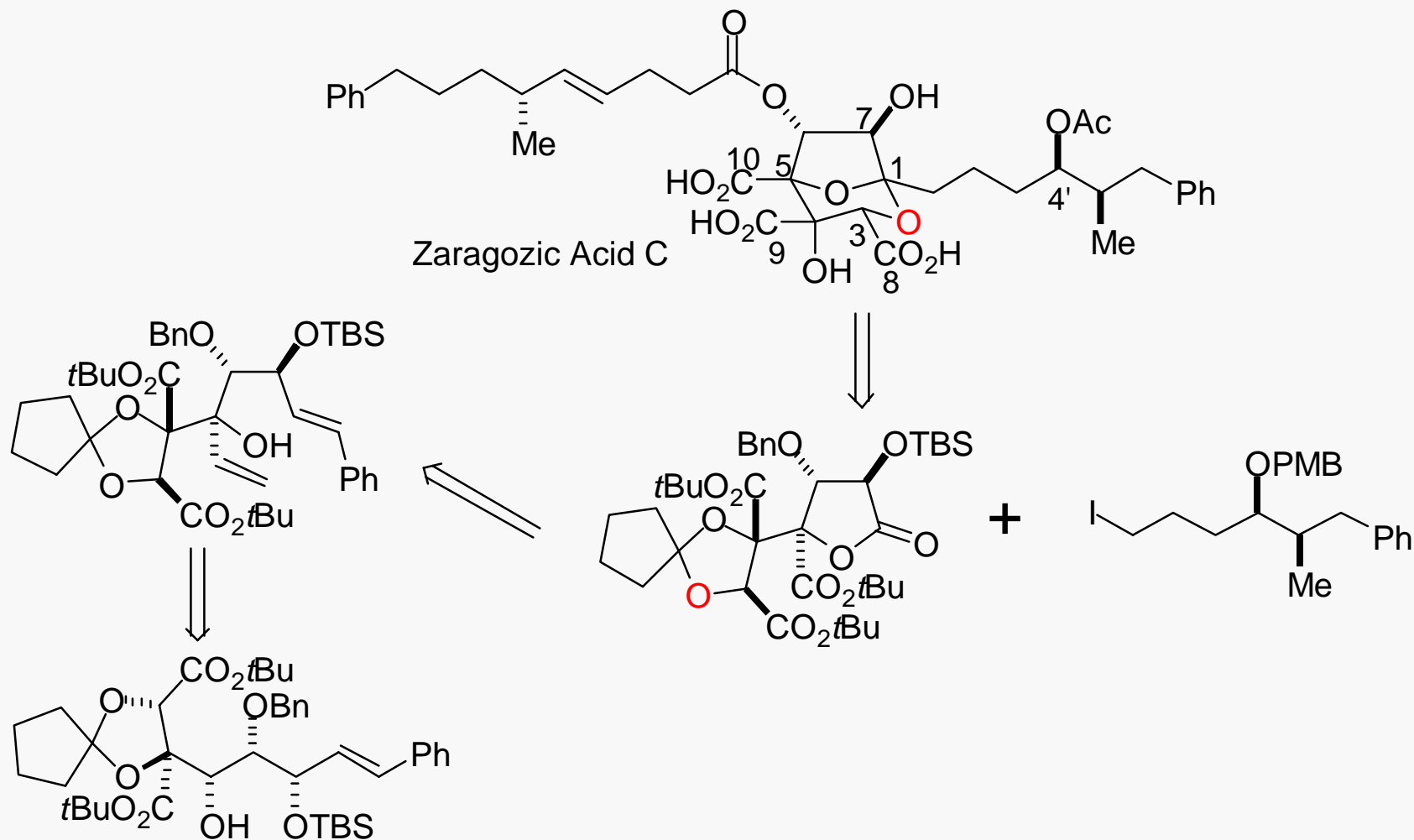
Evans' Retrosynthetic Analysis



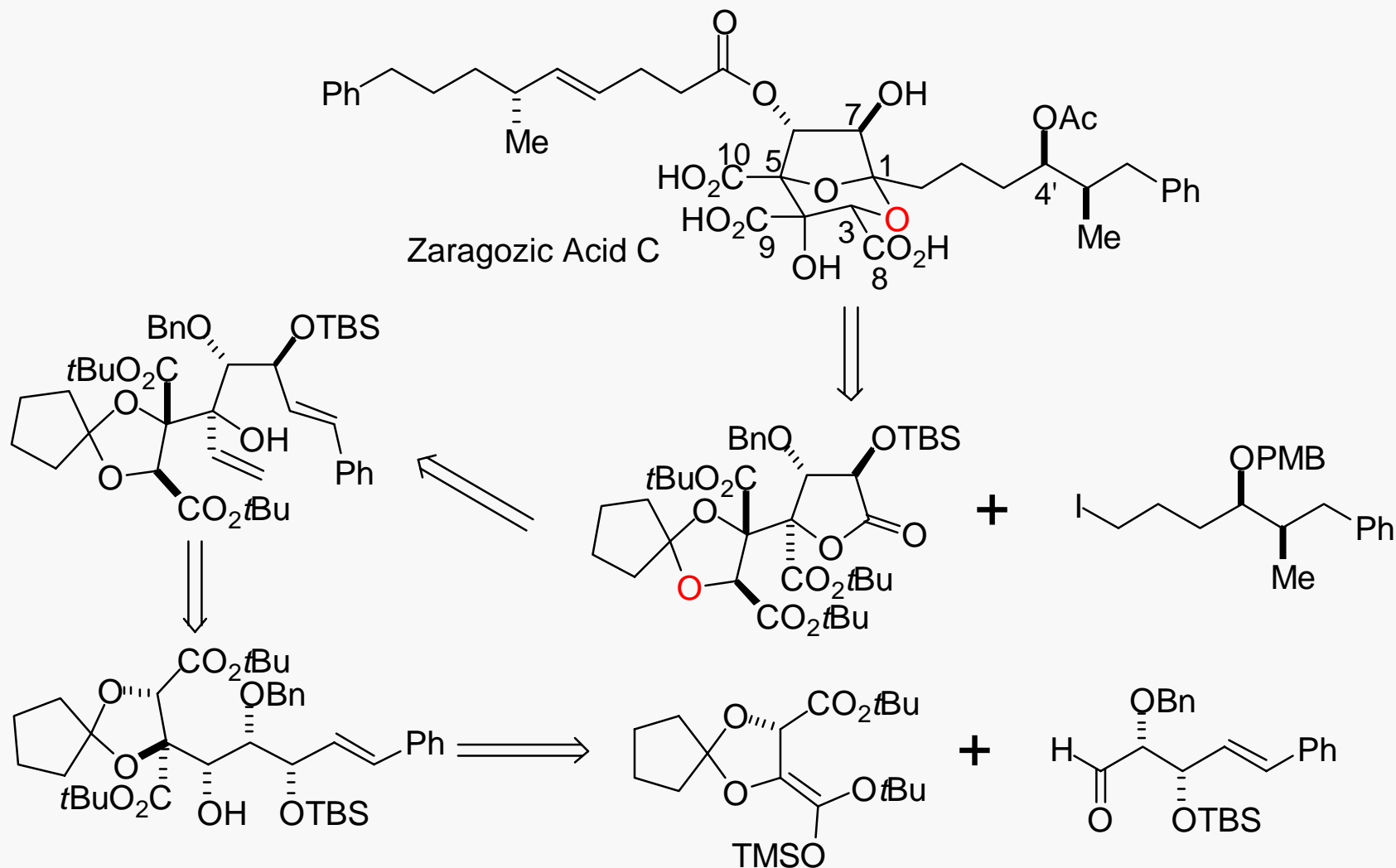
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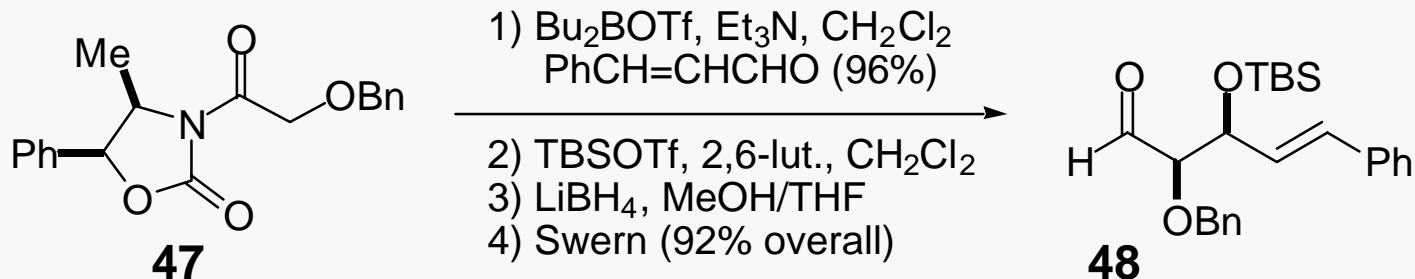
Evans' Retrosynthetic Analysis



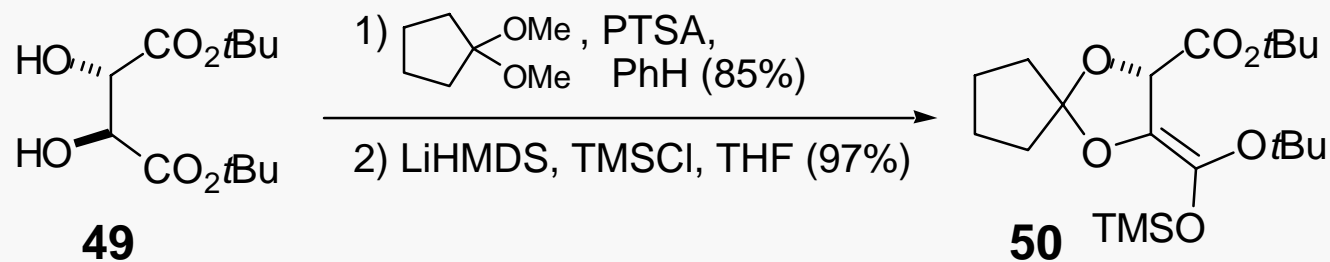
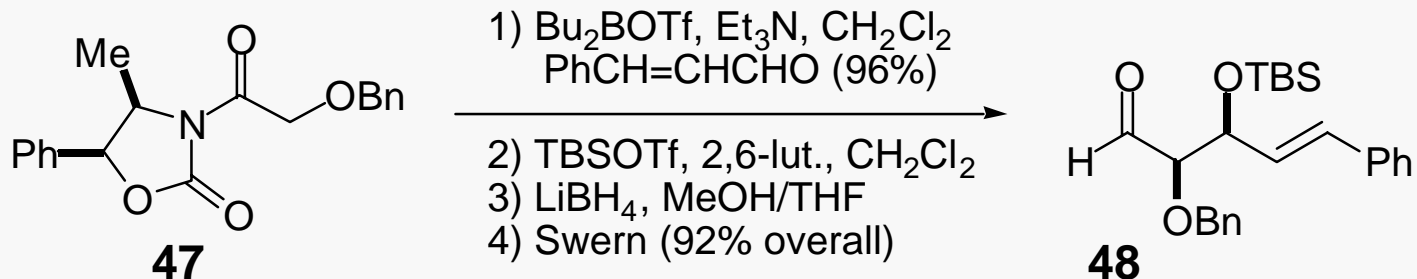
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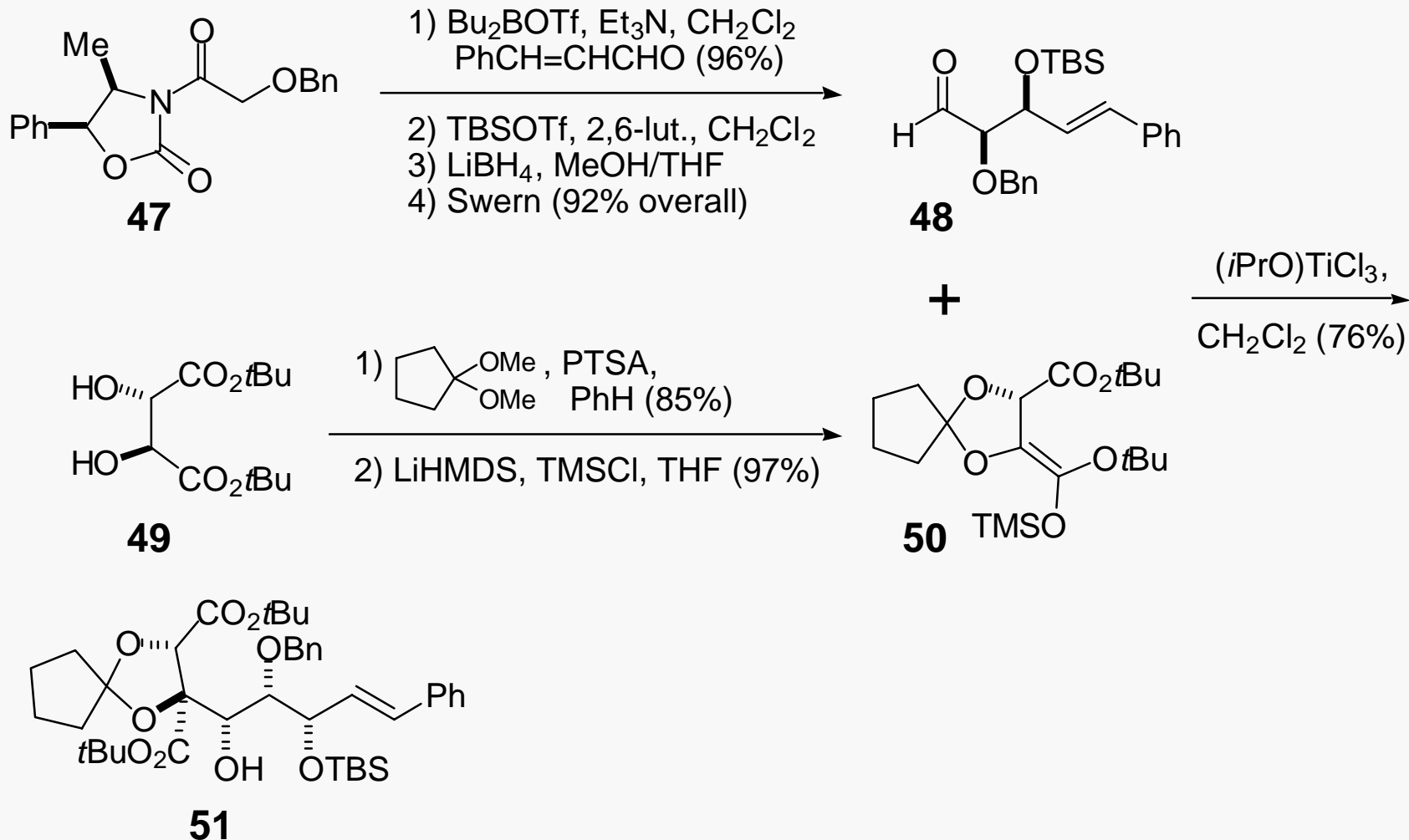
Tartrate-Derived Aldol



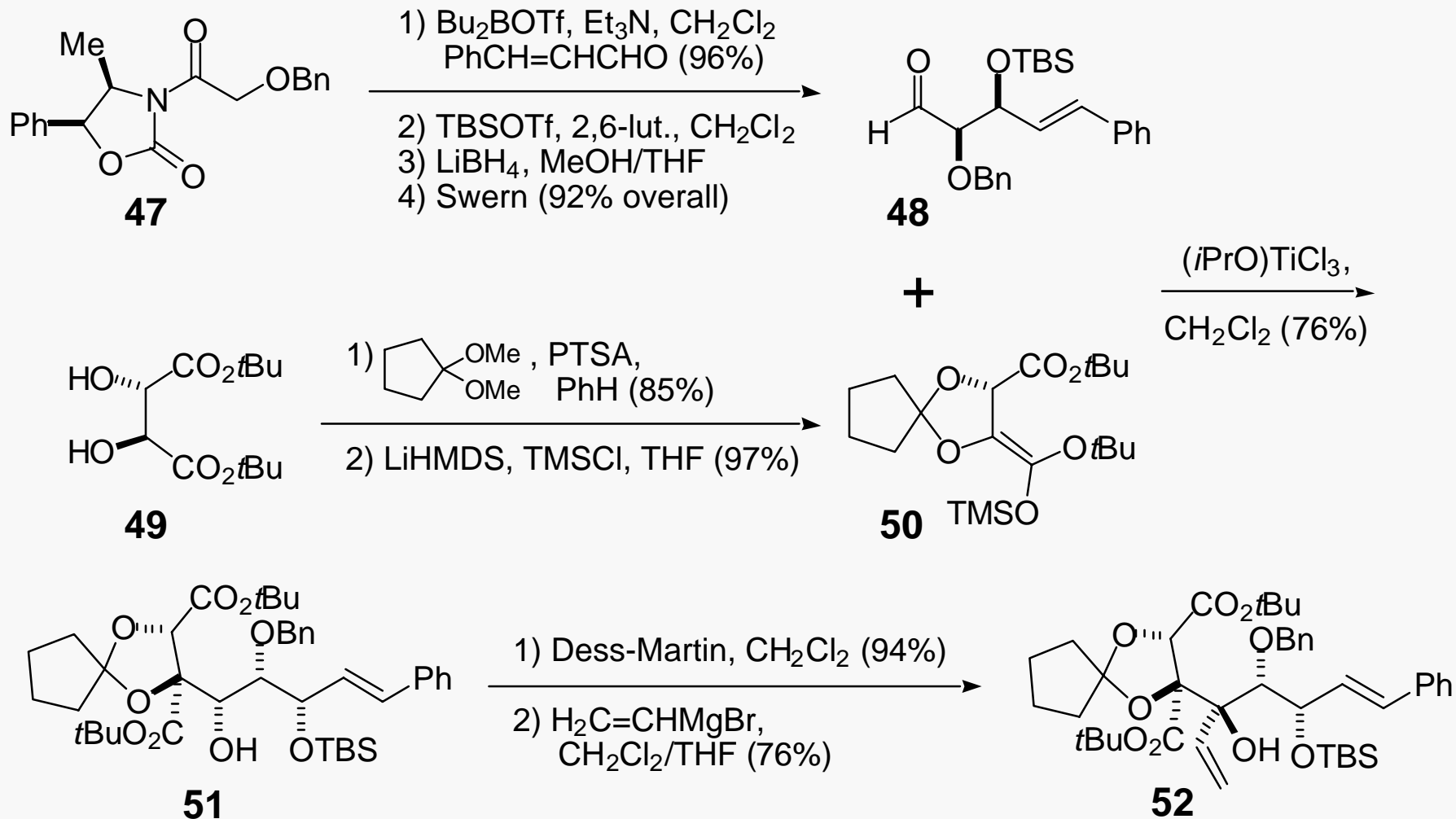
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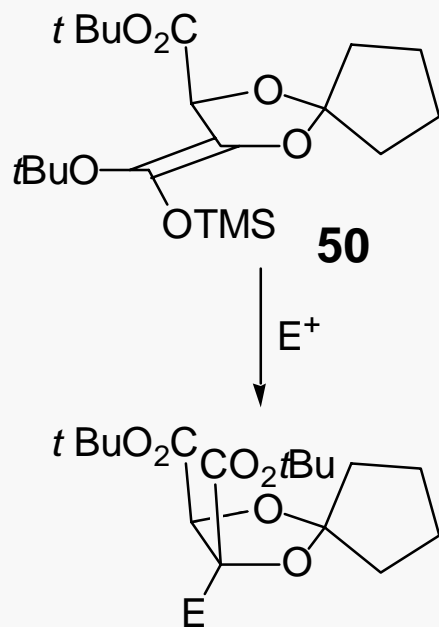
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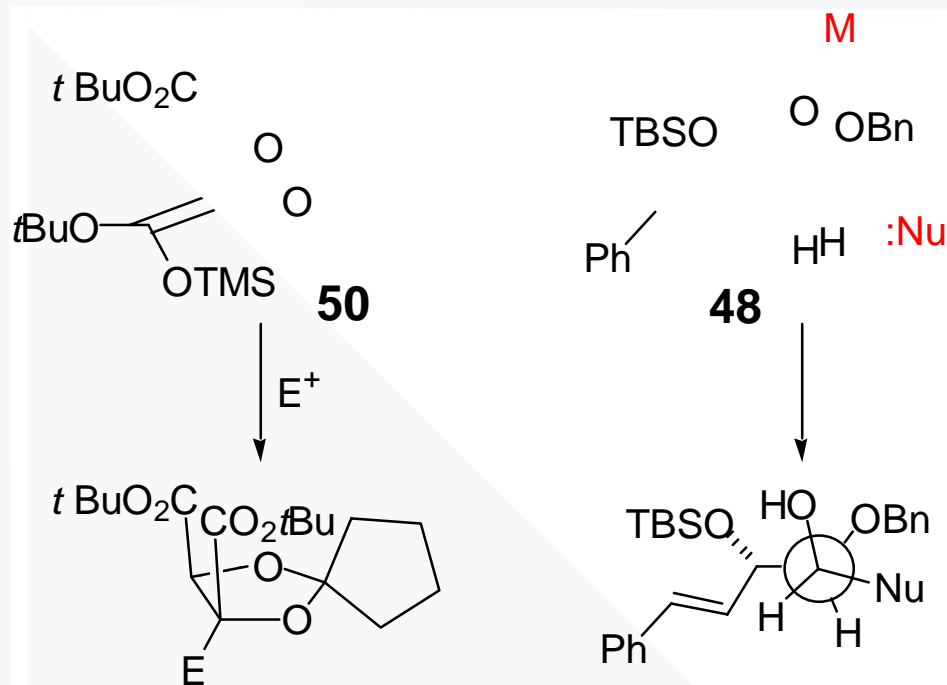
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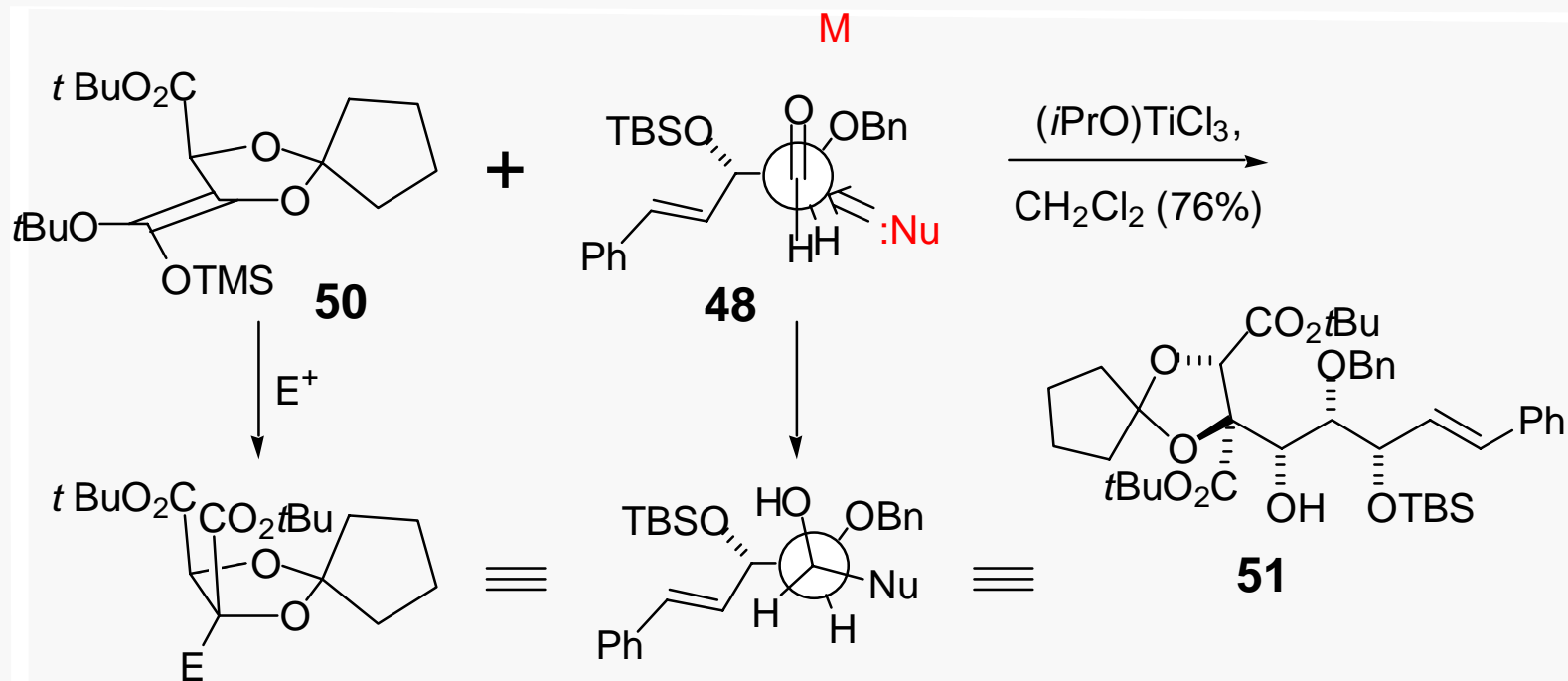
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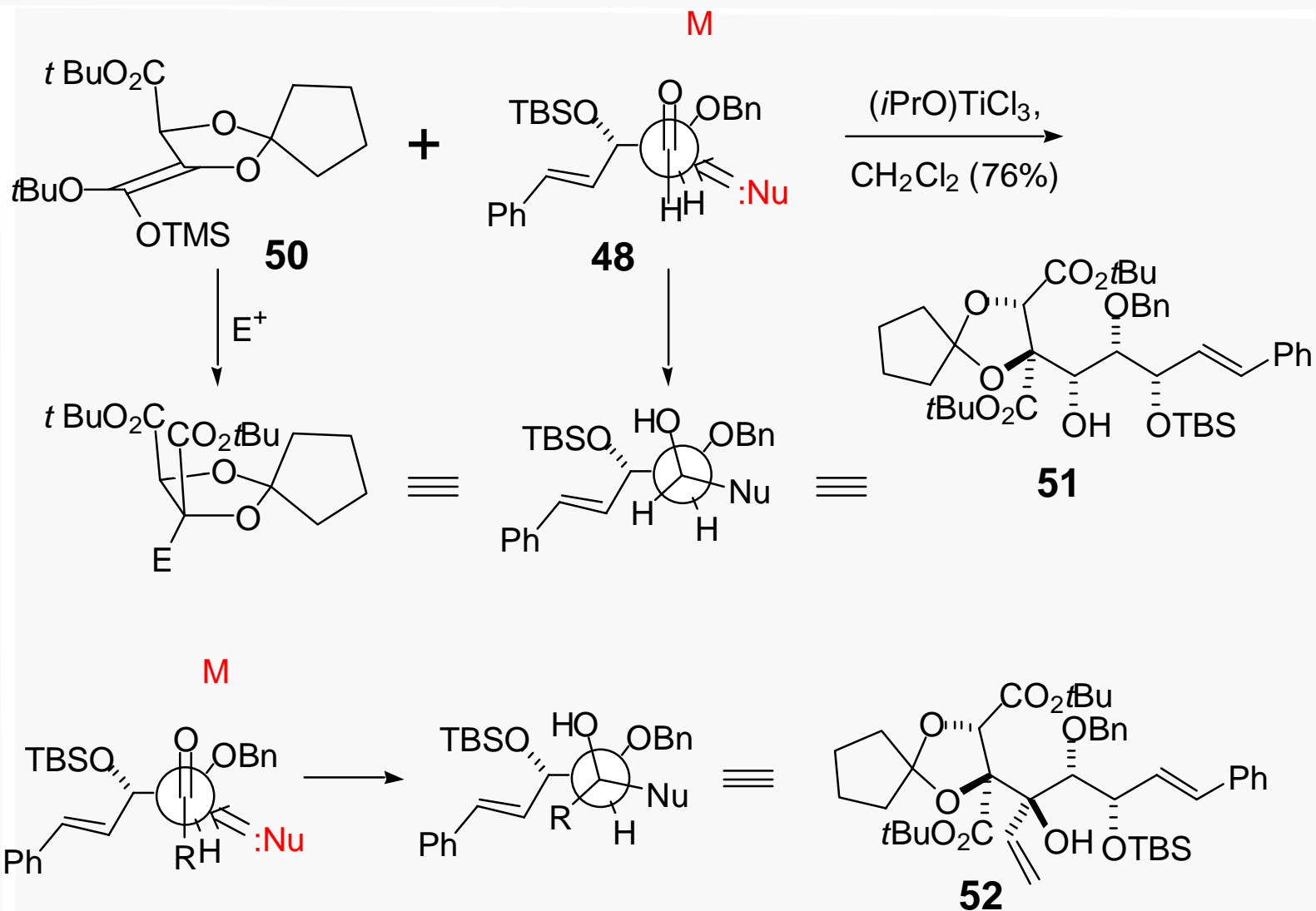
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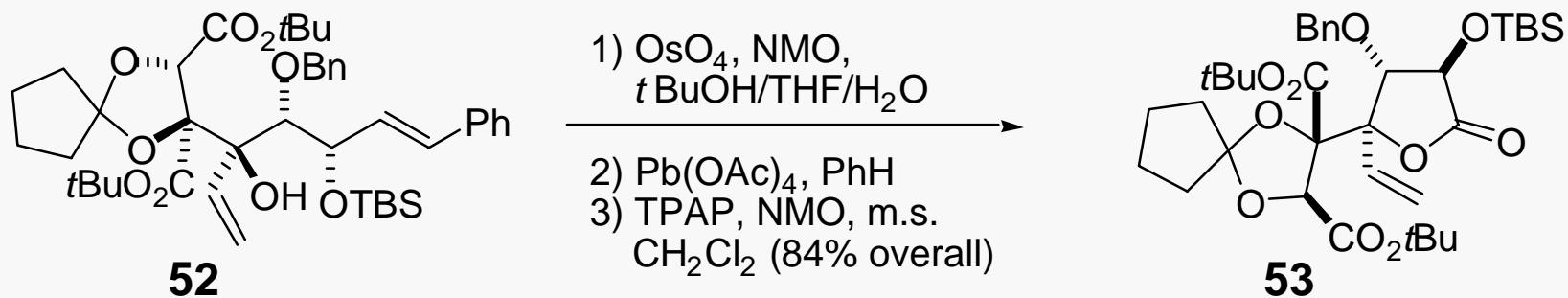
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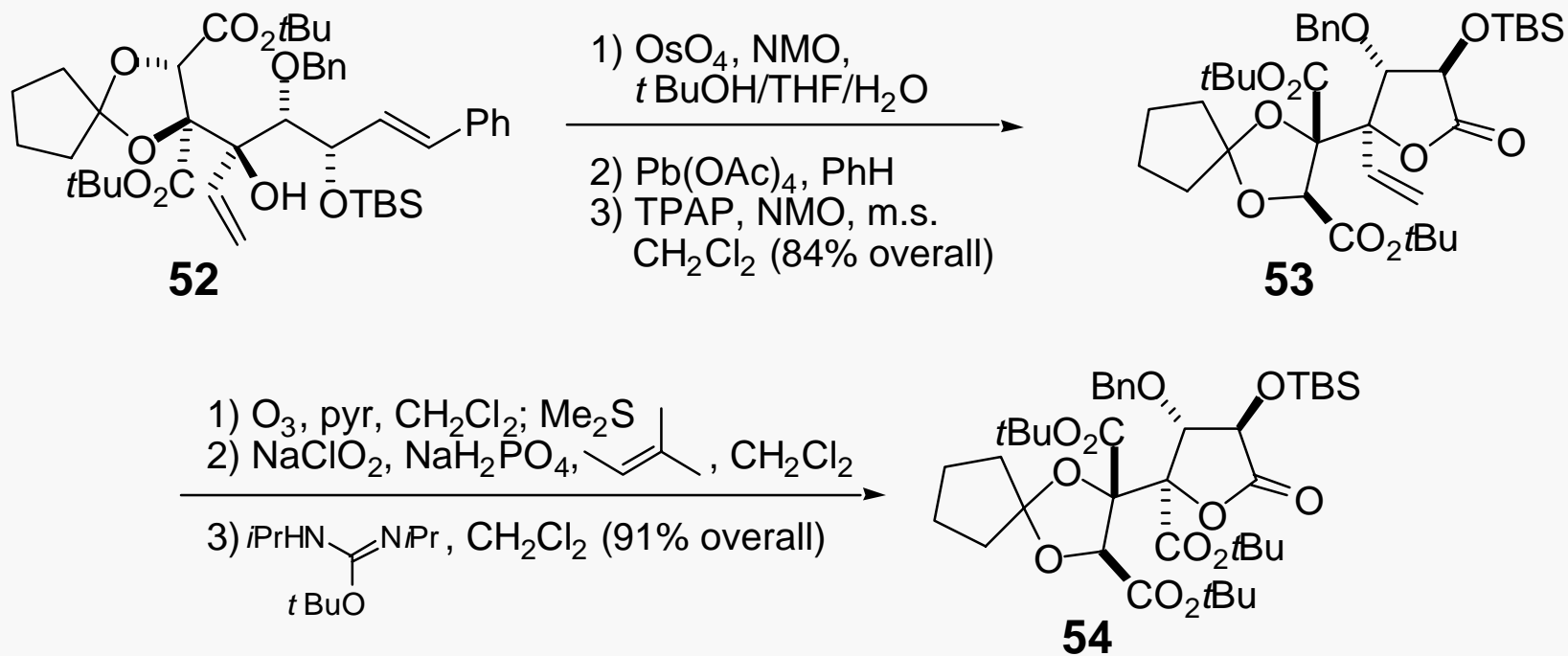
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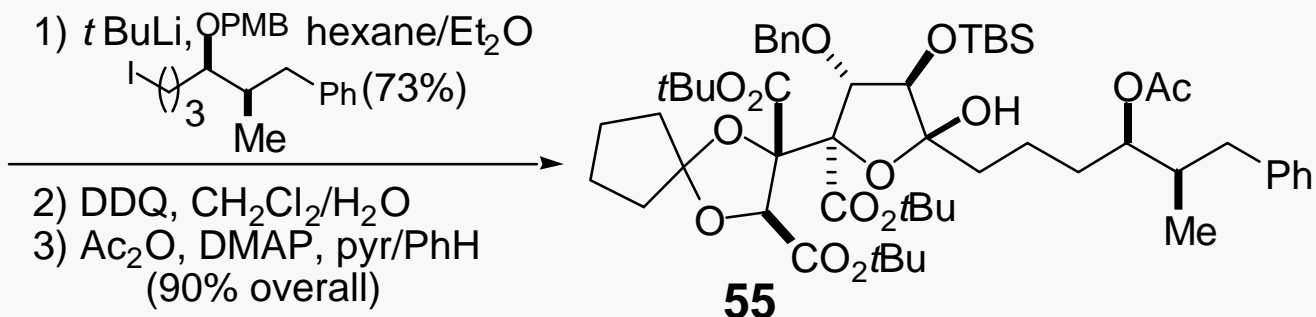
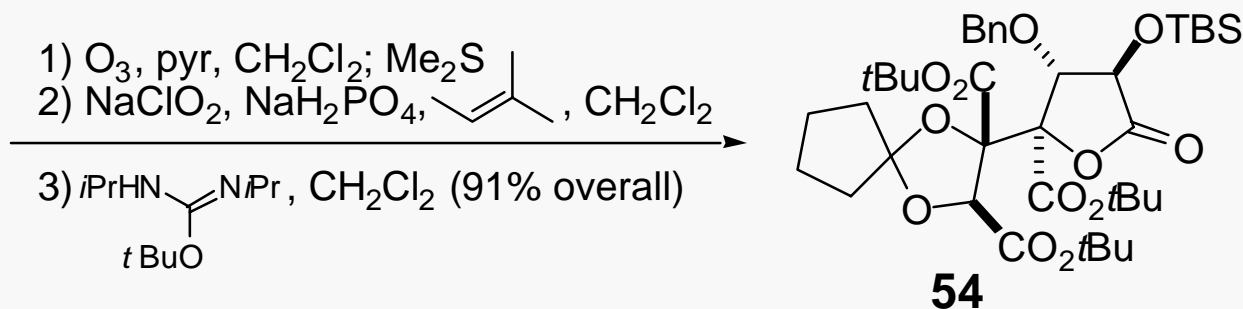
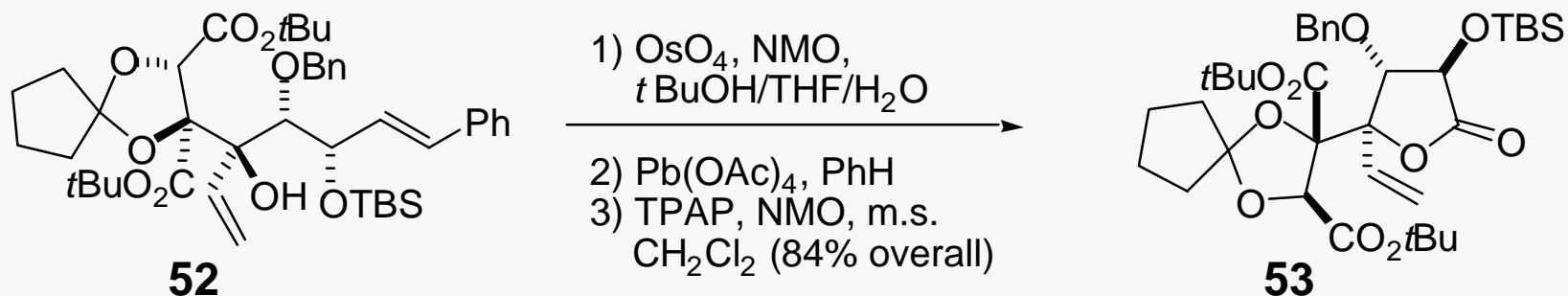
Functionalization



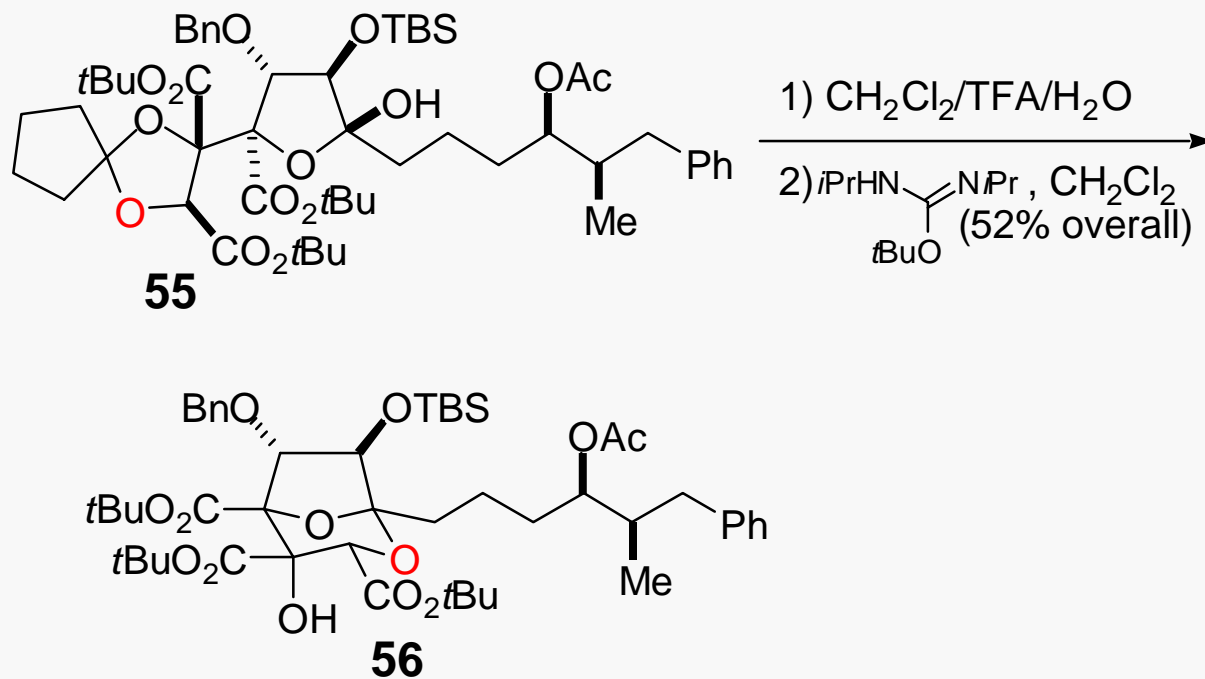
Functionalization



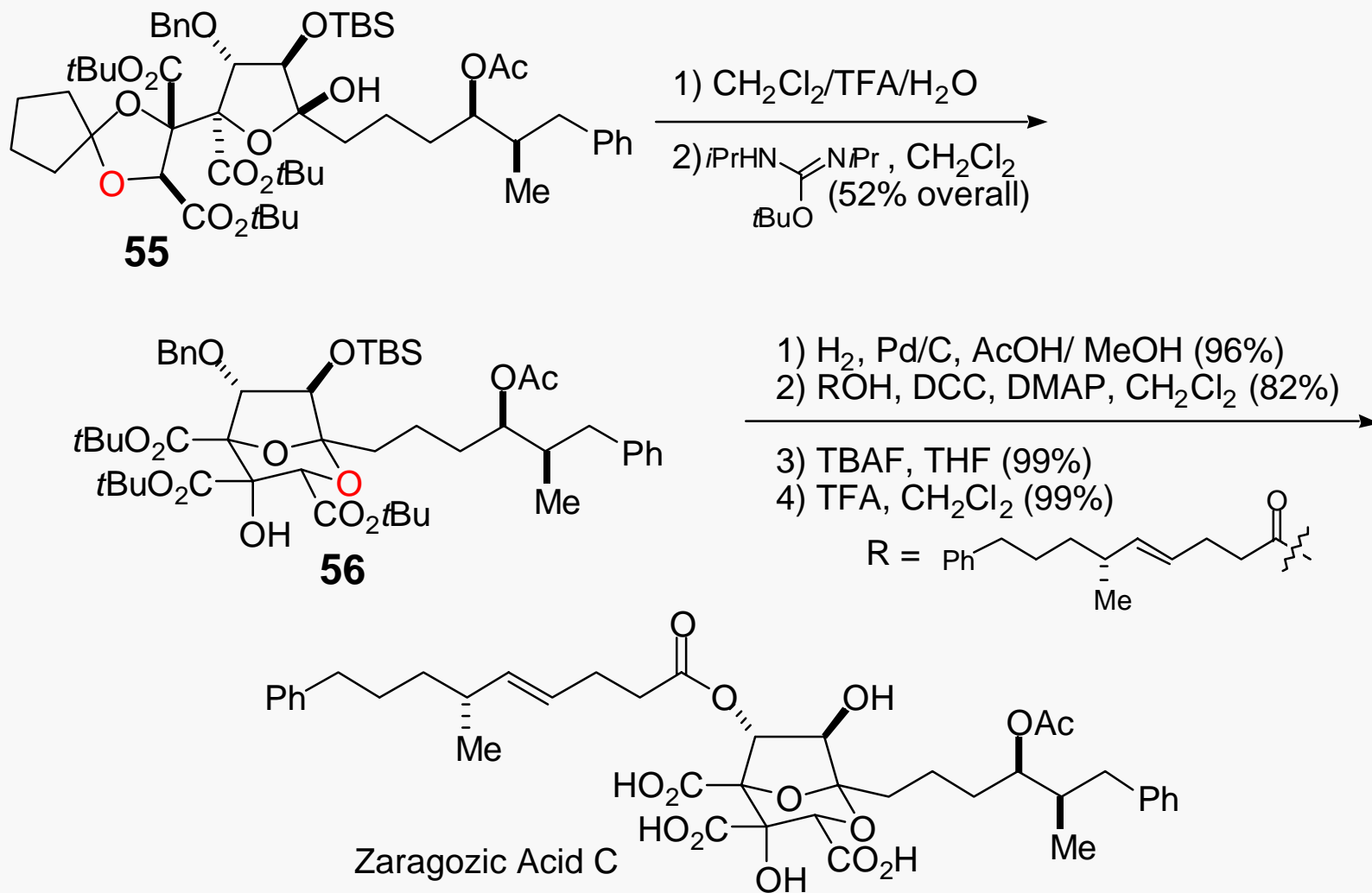
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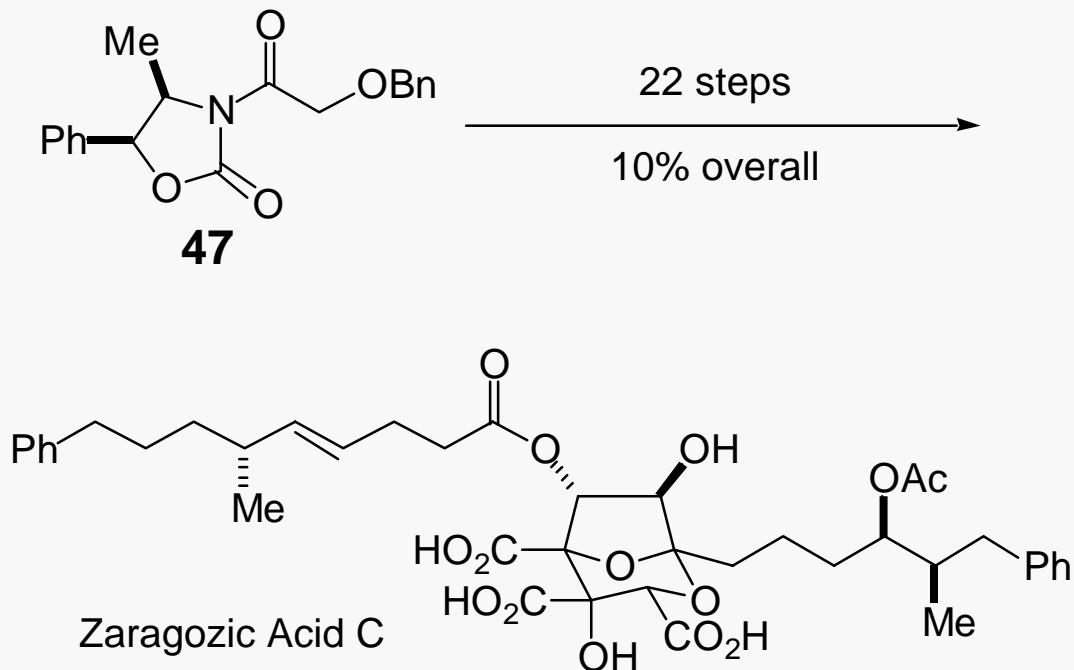
Completion of the Total Synthesis



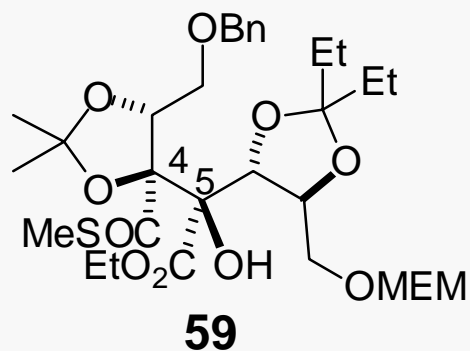
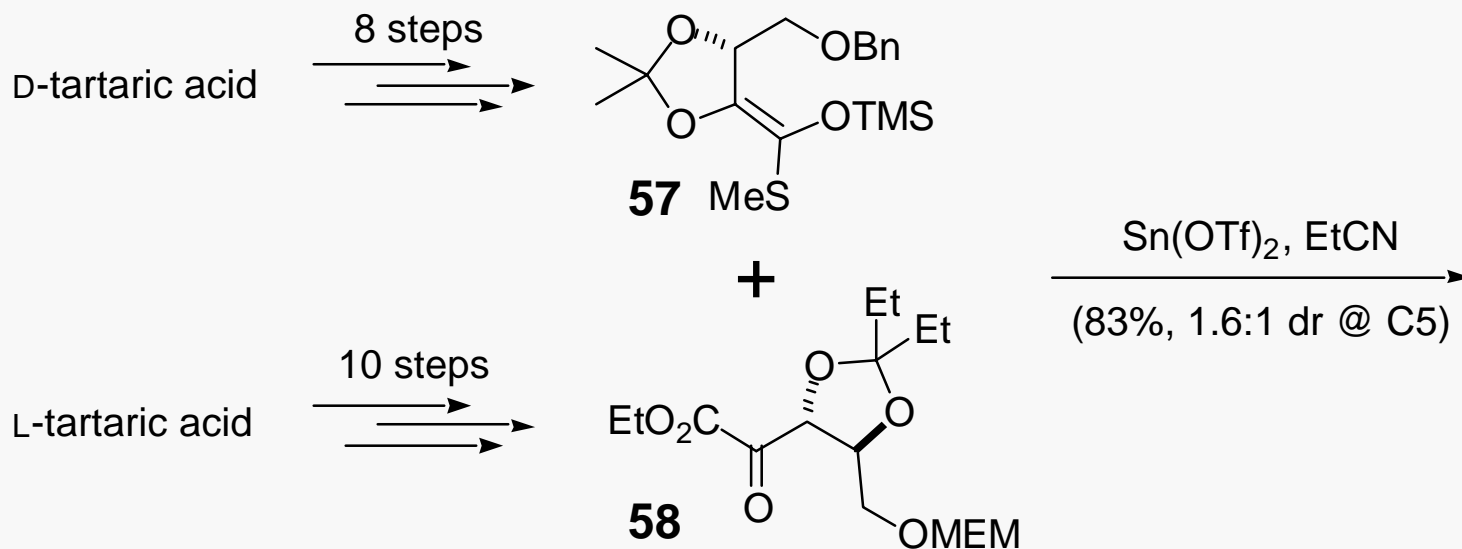
Completion of the Total Synthesis



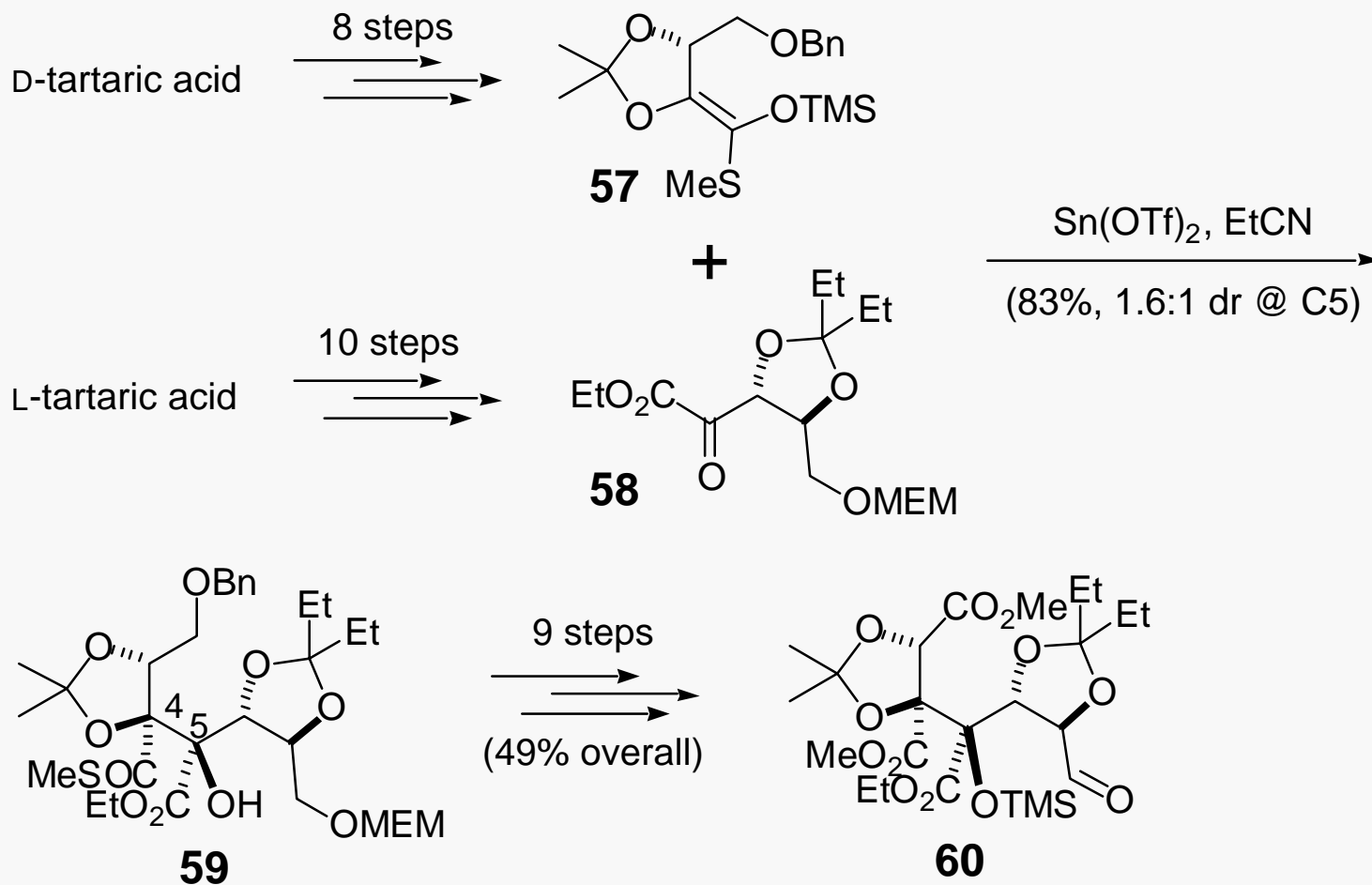
Total Synthesis Summary



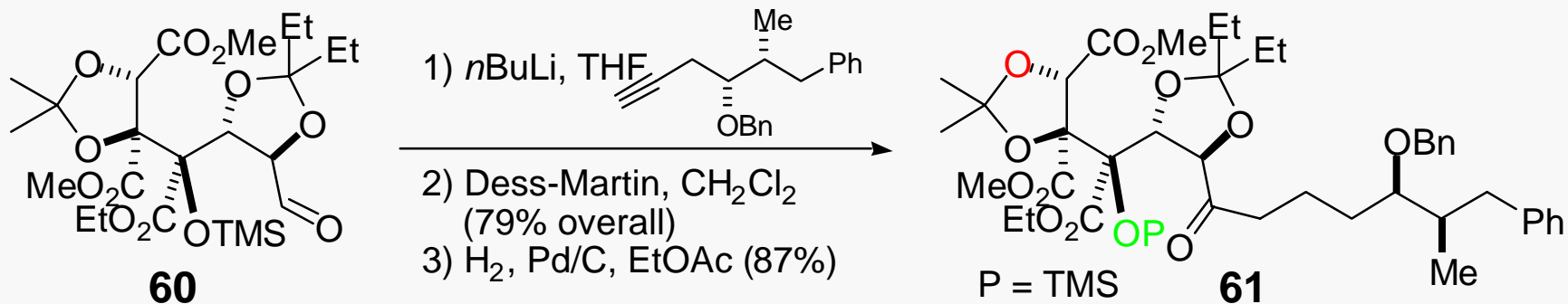
Hashimoto's Tartrate-Derived Aldol



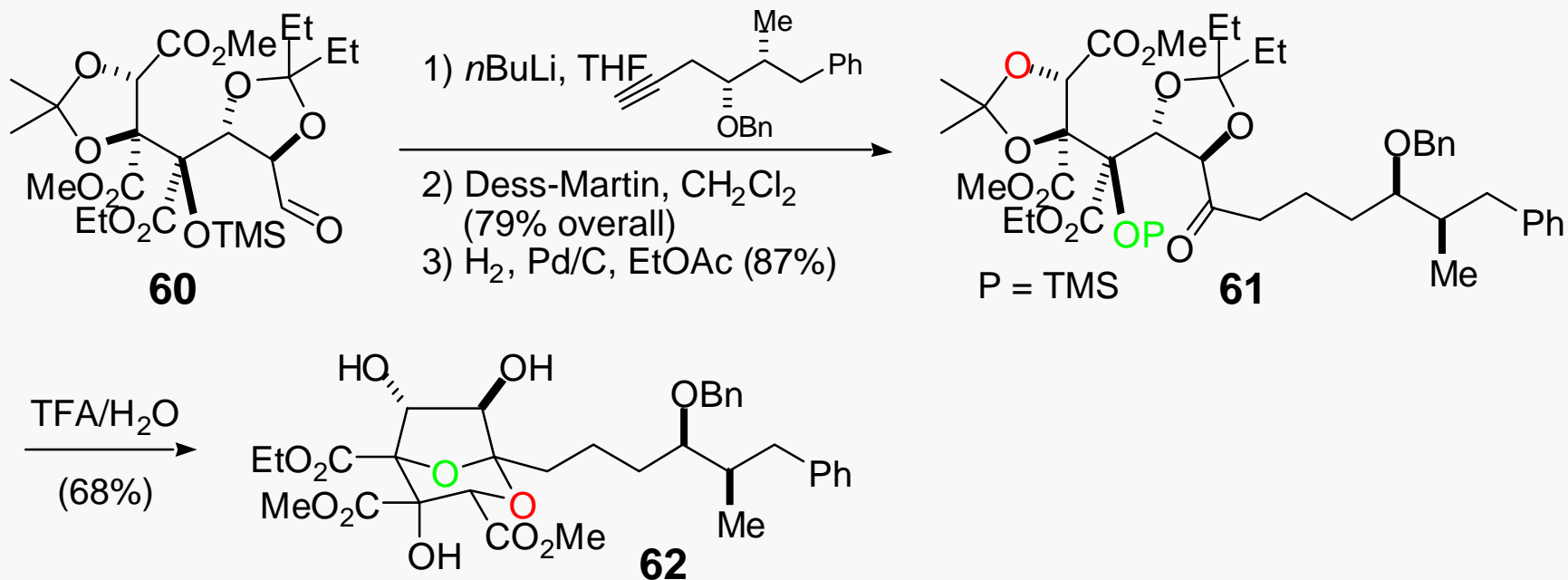
Hashimoto's Tartrate-Derived Aldol



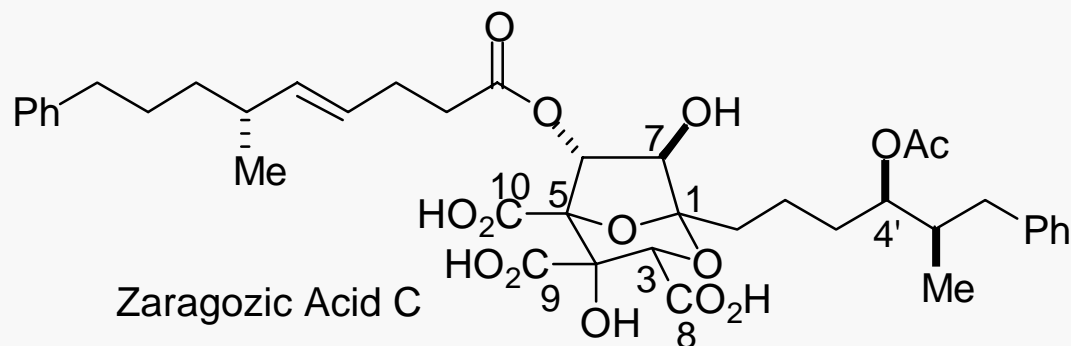
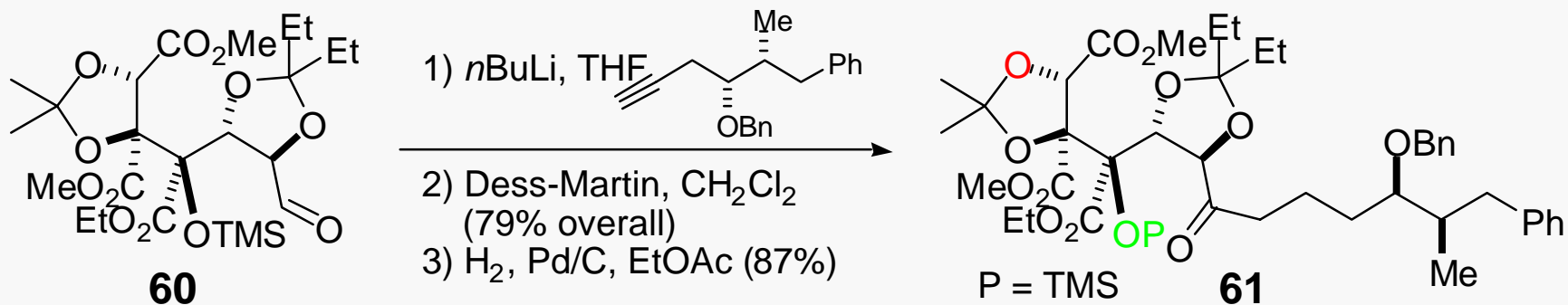
Chain Extension/Ketalization



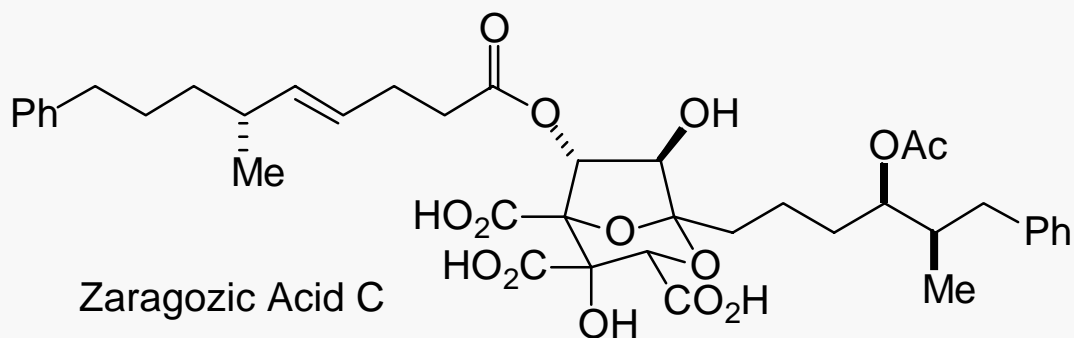
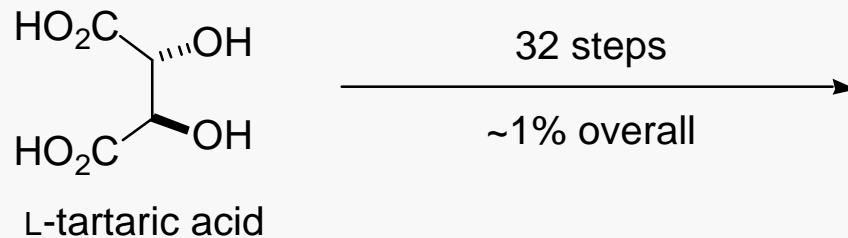
Chain Extension/Ketalization



Chain Extension/Ketalization



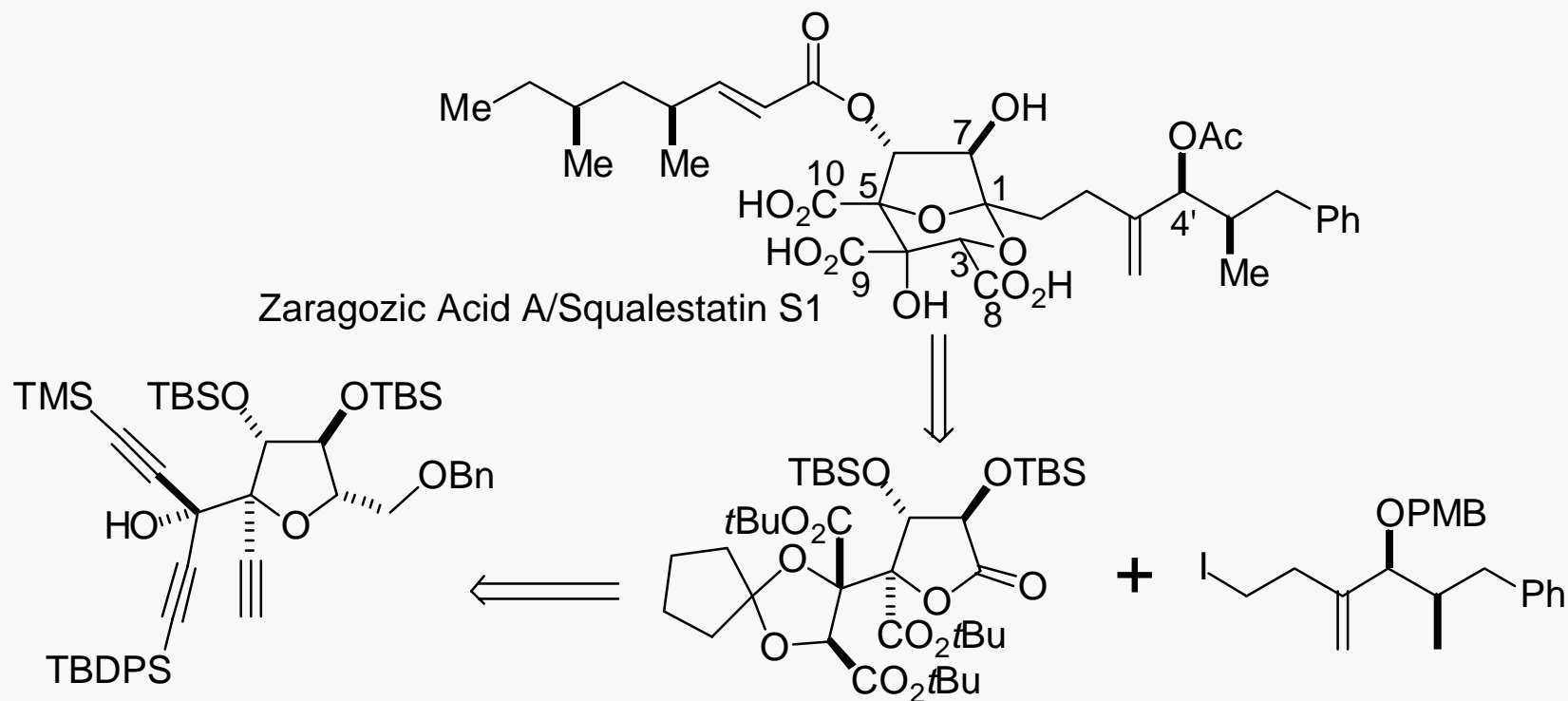
Total Synthesis Summary



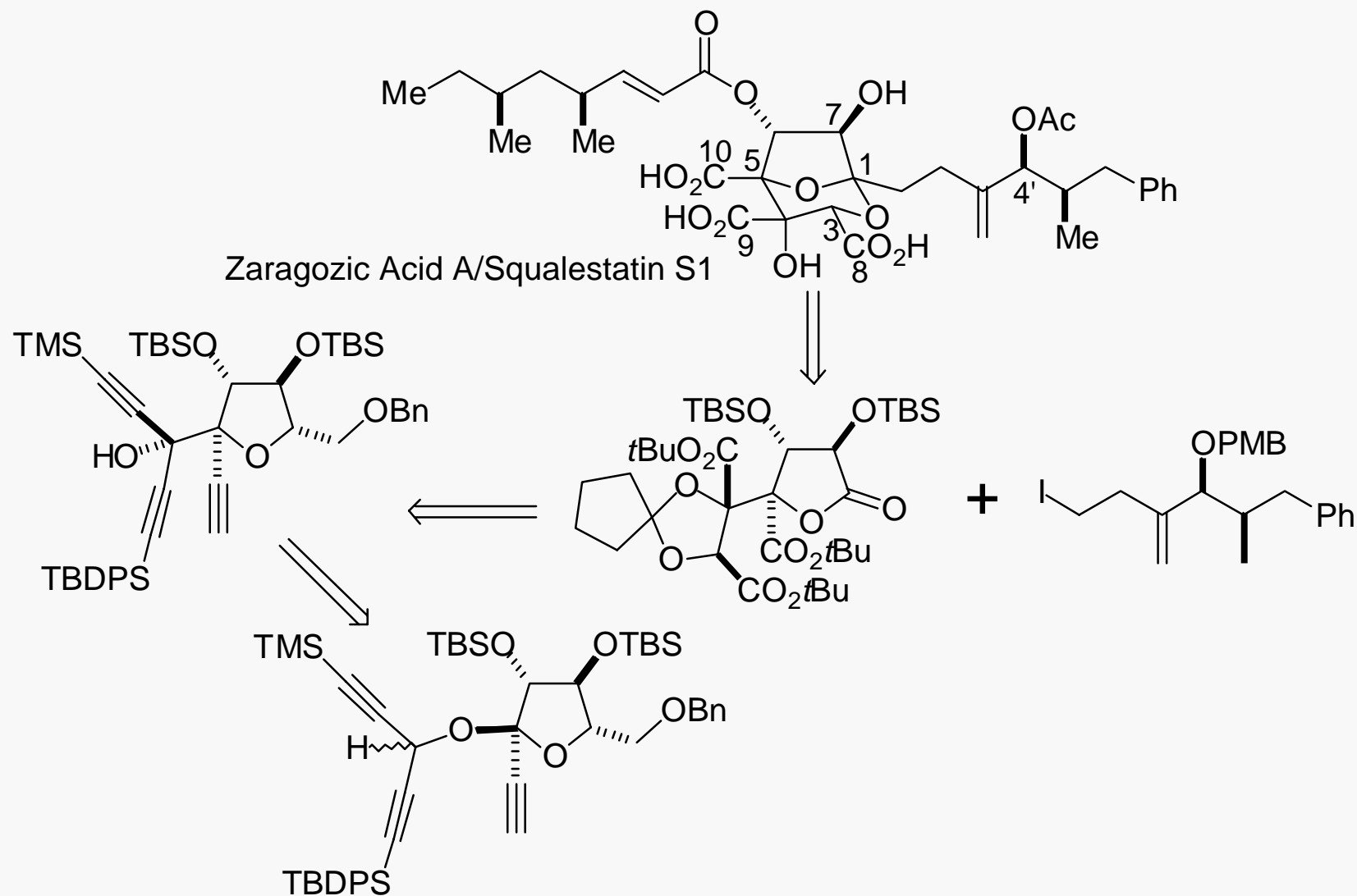
Outline

- Dihydroxylation Strategy
- Carbonyl Addition Strategy
- Tartrate-Derived Aldol Strategy
- **Acetal [1,2] Wittig Rearrangement Strategy**
 - » Tomooka

Tomooka's Retrosynthetic Analysis

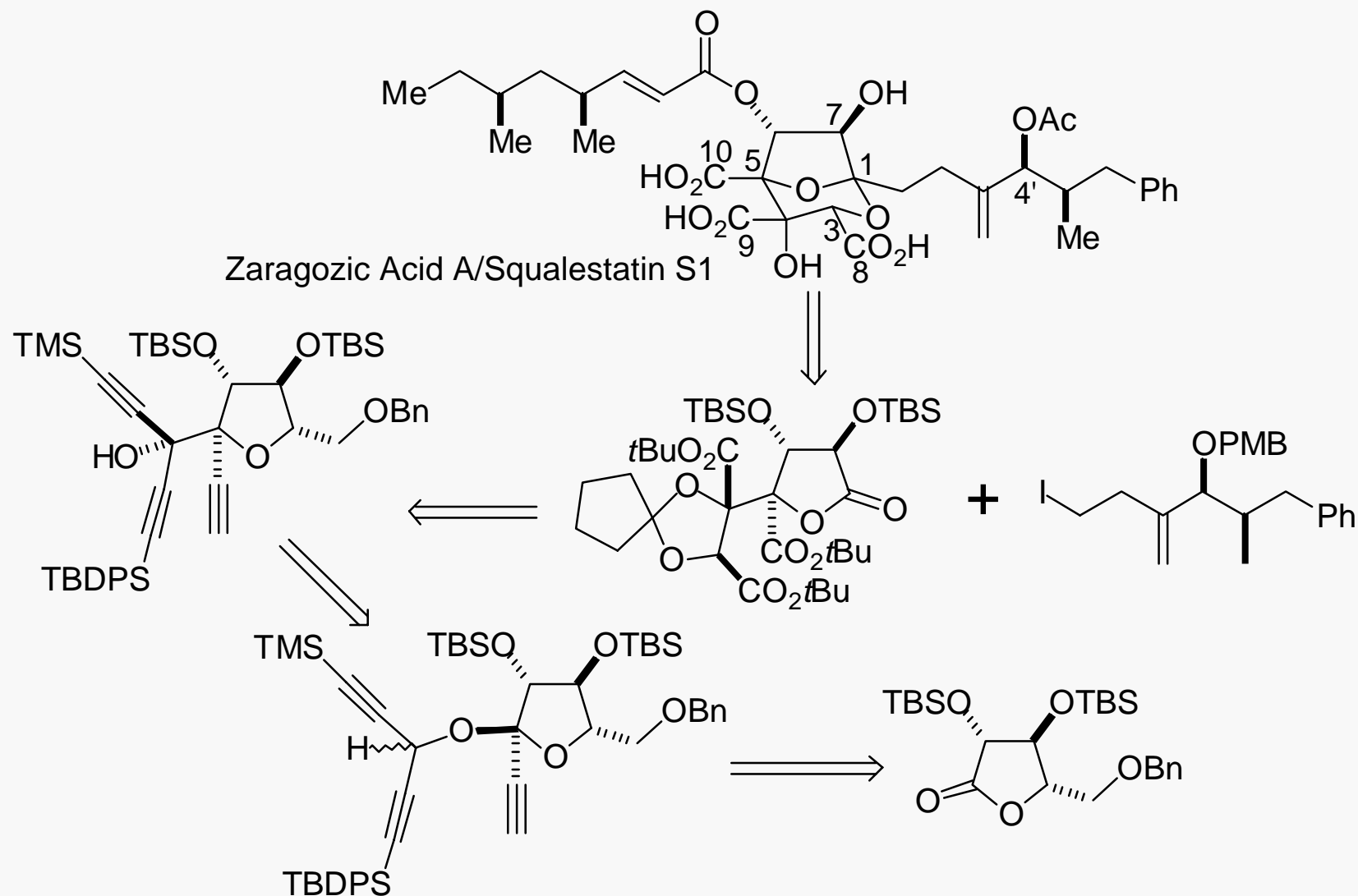


Tomooka's Retrosynthetic Analysis



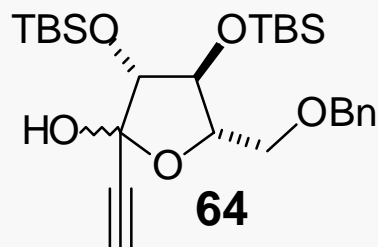
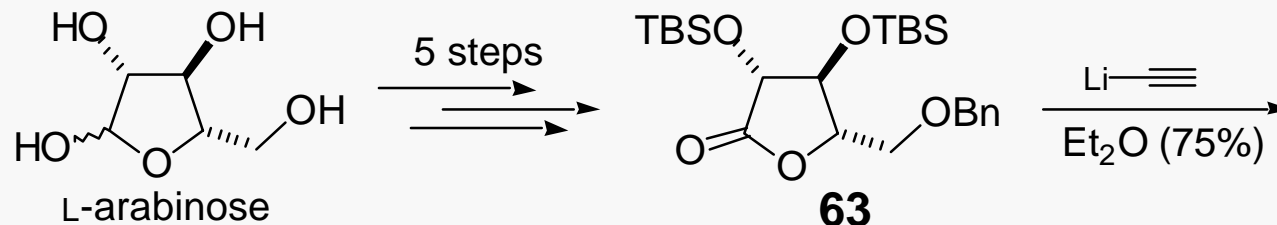
Tomooka, K.; Kikuchi, M.; Igawa, K.; Suzuki, M.; Keong, P.-H.; Nadai, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 4502-4505.

Tomooka's Retrosynthetic Analysis

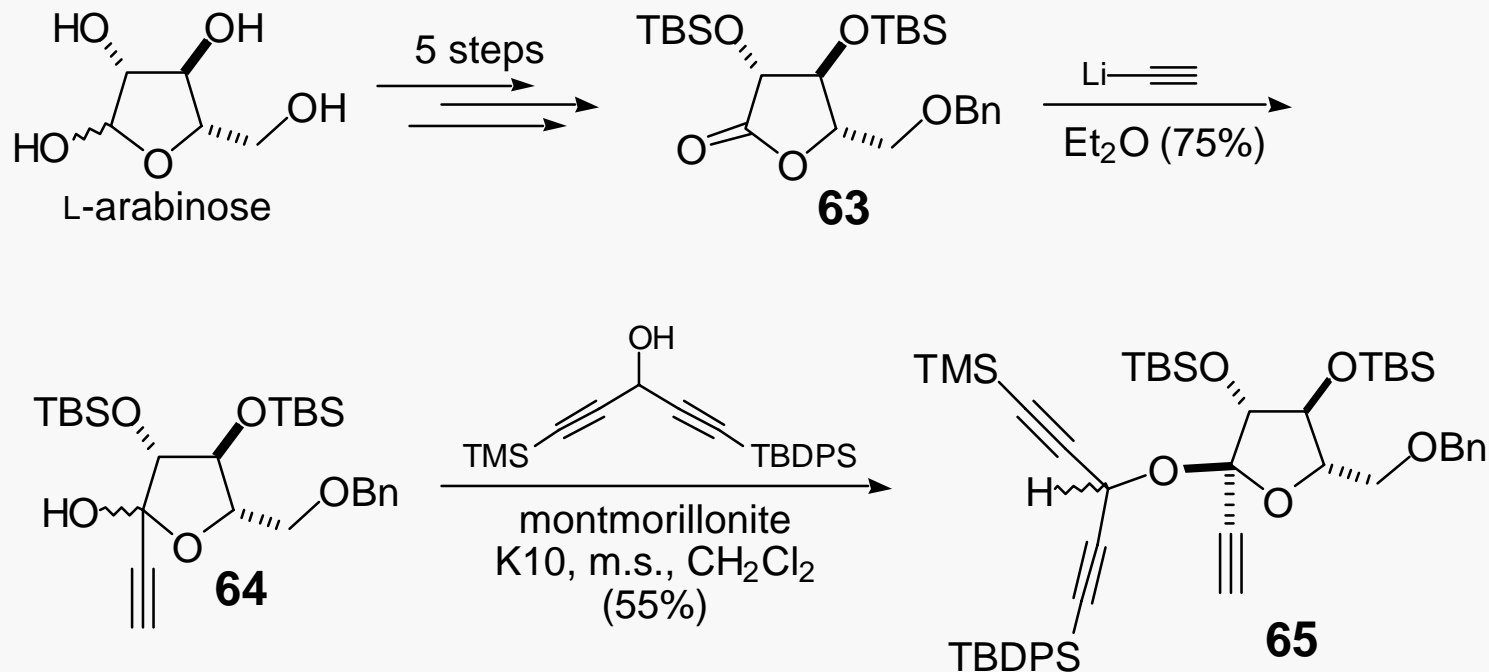


Tomooka, K.; Kikuchi, M.; Igawa, K.; Suzuki, M.; Keong, P.-H.; Nadai, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 4502-4505.

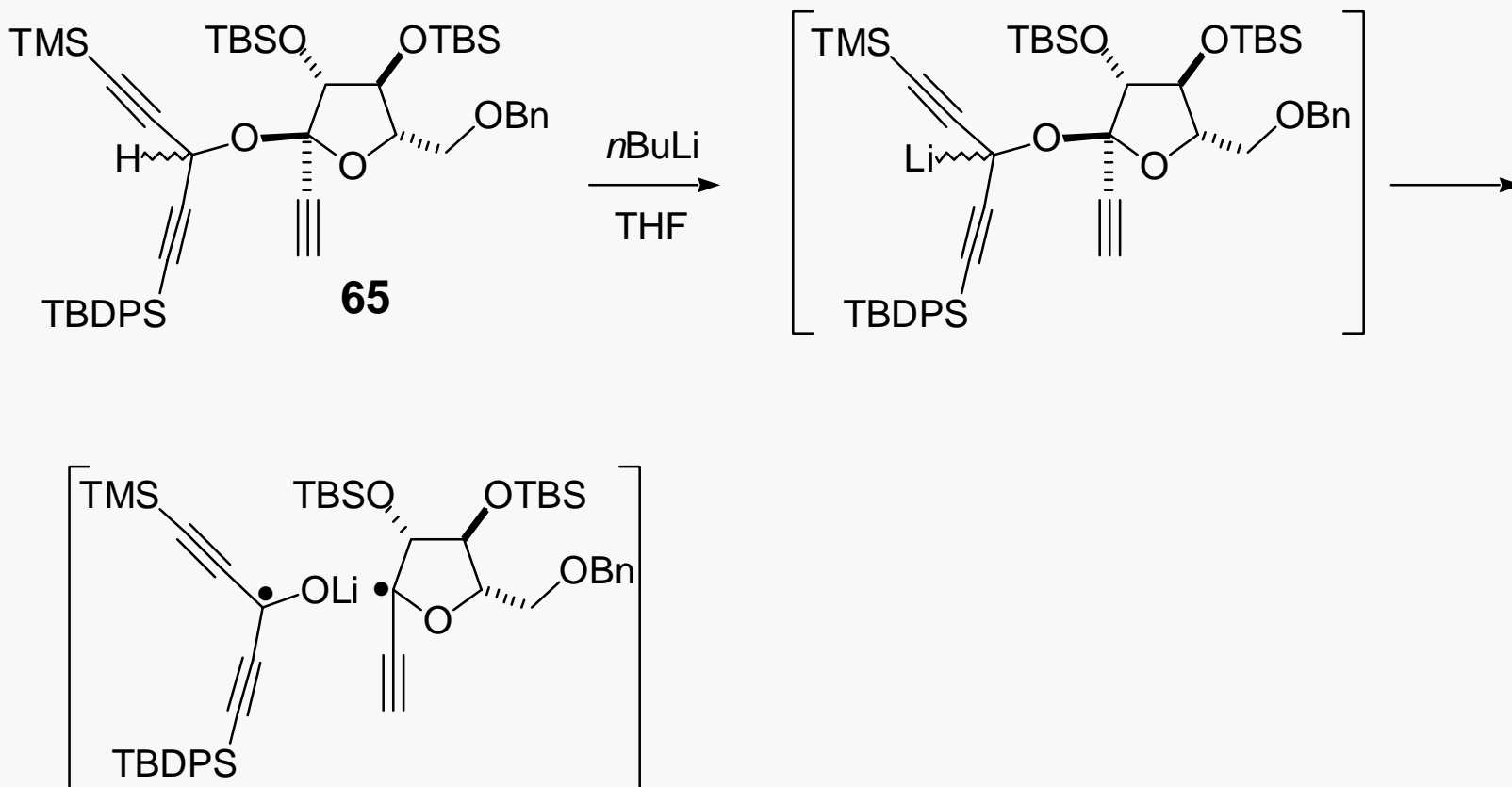
Zaragozic Acid A Total Synthesis



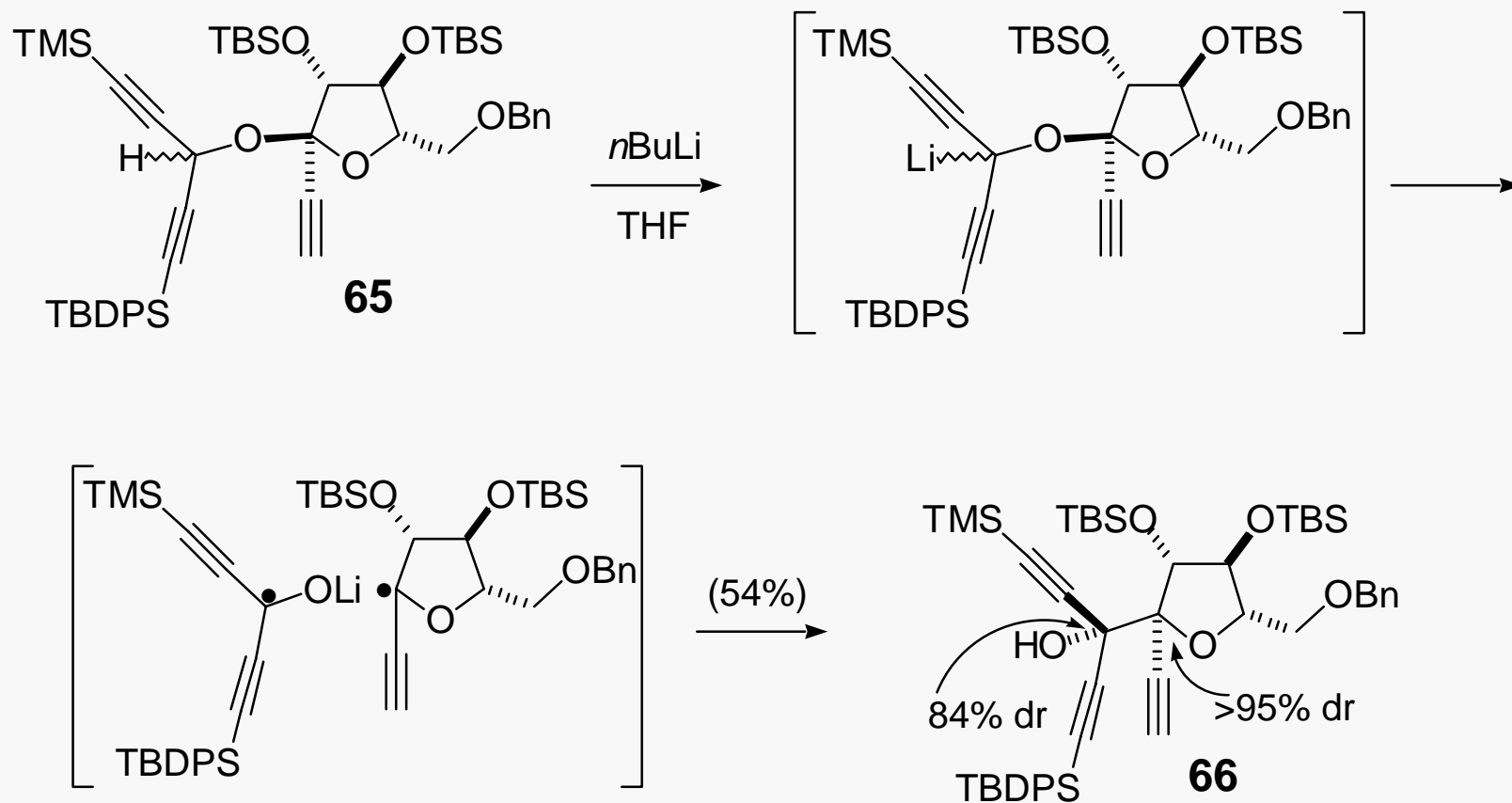
Zaragozic Acid A Total Synthesis



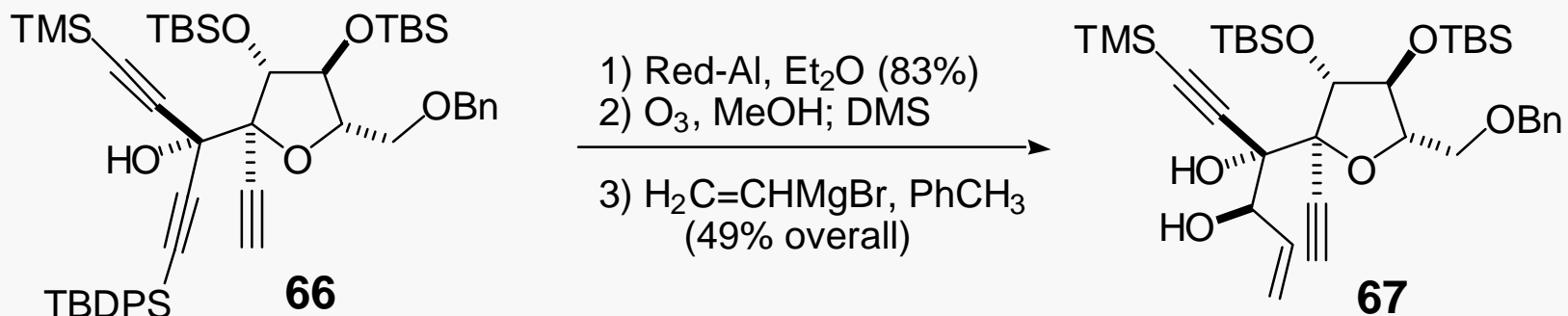
Zaragozic Acid A Total Synthesis



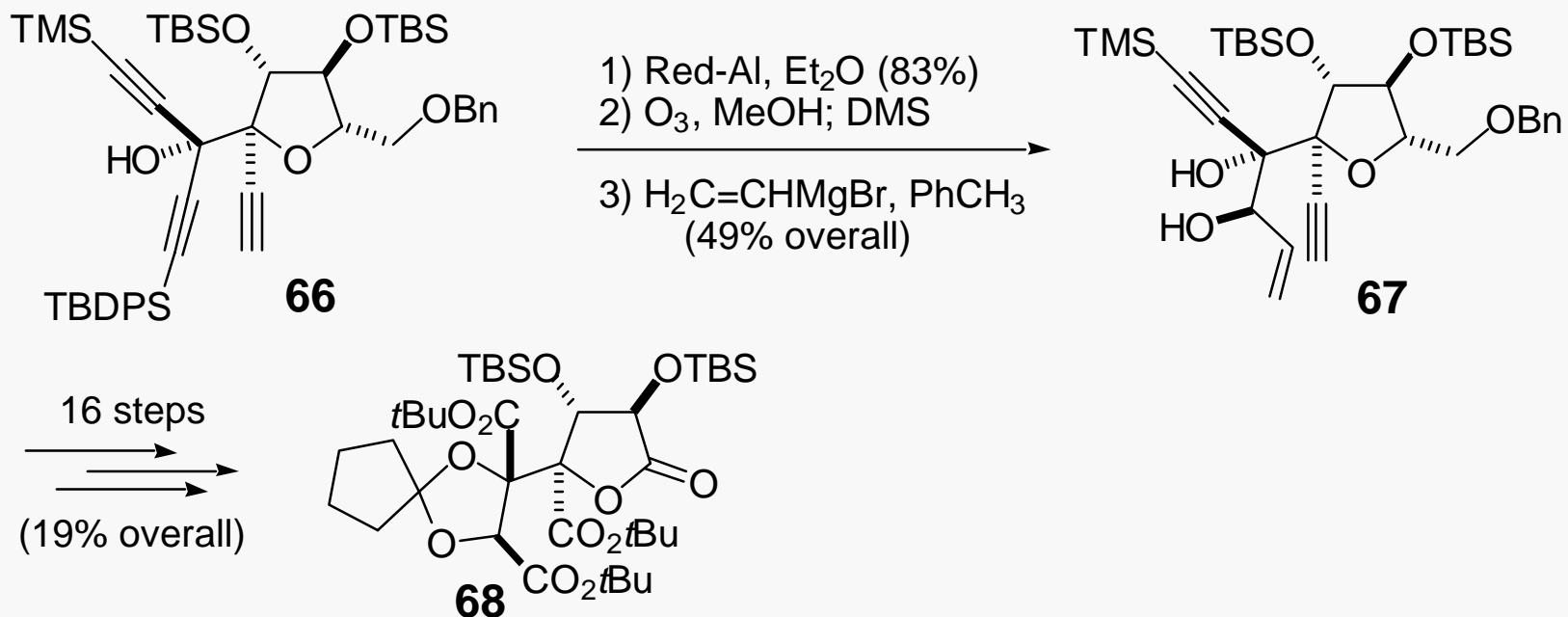
Zaragozic Acid A Total Synthesis



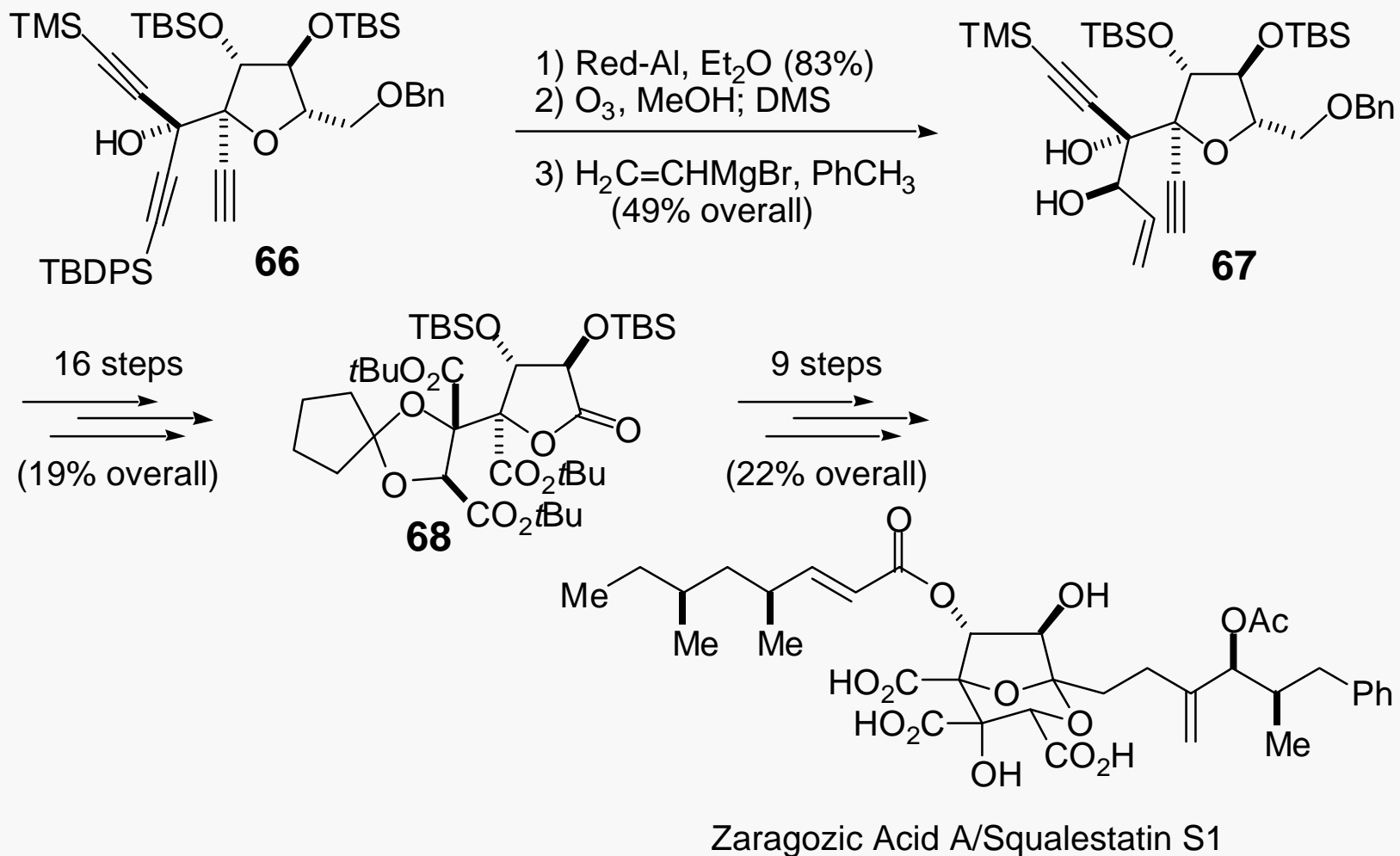
Zaragozic Acid A Total Synthesis



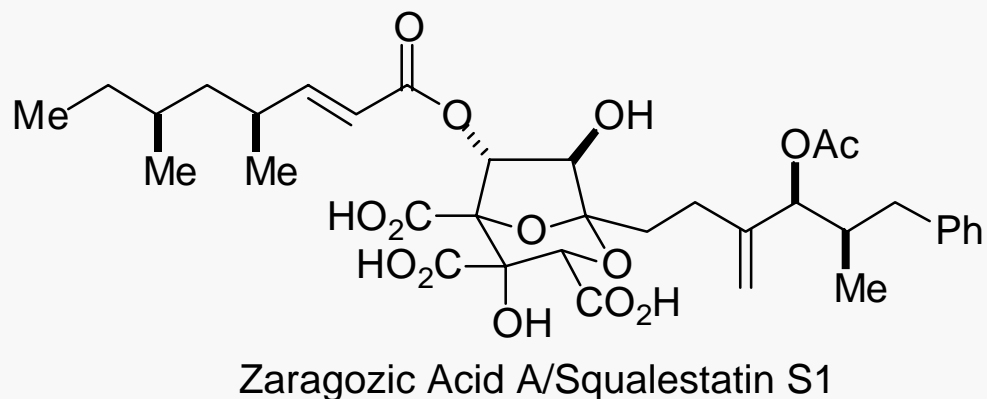
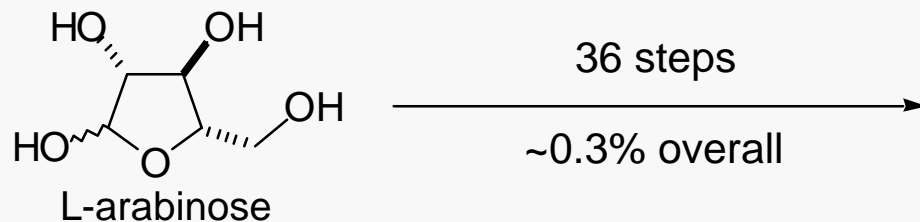
Zaragozic Acid A Total Synthesis



Zaragozic Acid A Total Synthesis



Total Synthesis Summary



Summary of Total Syntheses

- Dihydroxylation Strategy

- » Nicolaou (35 steps, 0.003%)

- » Anderson (23 steps, 0.21%)

- Carbonyl Addition Strategy

- » Carreira (32 steps, 0.73%)

- » Heathcock (41 steps, 0.34%)

- Tartrate-Derived Aldol Strategy

- » Evans (22 steps, 10%)

- » Hashimoto (32 steps, ~0.1%)

- Acetal [1,2] Wittig Rearrangement Strategy

- » Tomooka (36 steps, ~0.3%)

Conclusions

- Several distinct synthetic strategies have provided access to the densely oxygenated Zaragozaic Acid natural products.
- Only the syntheses of Evans, Heathcock, and Tomooka produced each new stereocenter with high selectivity.
- Evans' total synthesis of Zaragozaic Acid C has proved the most efficient to date (22 steps, 10% overall yield).

Acknowledgements

- God
- Professor Steve Burke
- Andy Hawk
- Lei Jiang
- John Campbell
- Bill Lambert
- Valerie Keller
- Melissa Feenstra
- Greg Hanson
- Khun-Ho Kim
- Brian Lucas
- Katie Voight