Literature Report 6

Total Synthesis of Thapsigargin

Reporter : Fan-Jie Meng
Checker : Lei Shi
Date : 2018-06-19

Chu, H.; Smith, J. M.; Felding, J.; **Baran, P. S.** *ACS Cent. Sci.* **2017**, *3*, 47

Curriculum Vitae of Phil S. Baran

Research:

- Total Synthesis of Natural Products

Education:

- **1995-1997** B.S., New York University
- **1997-2001** Ph.D., The Scripps Research Institute
- **2001-2003** Postdoctoral Associate, Harvard University
- **2003-2006** Assistant Professor, The Scripps Research Institute
- **2006-2008** Associate Professor, The Scripps Research Institute
- **2008-Now** Professor, The Scripps Research Institute

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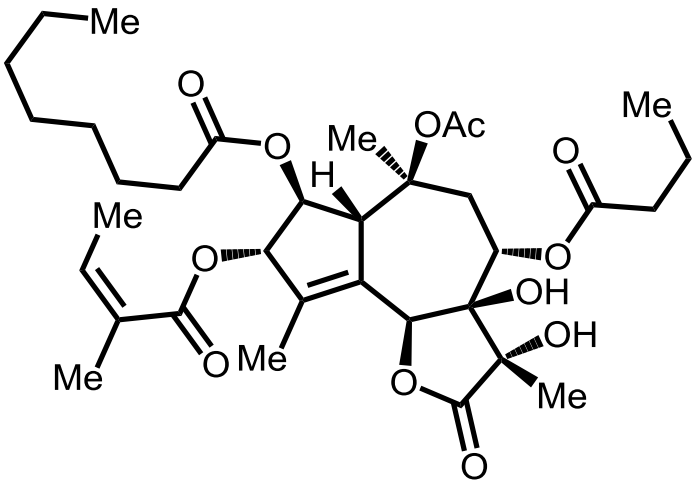
Introduction

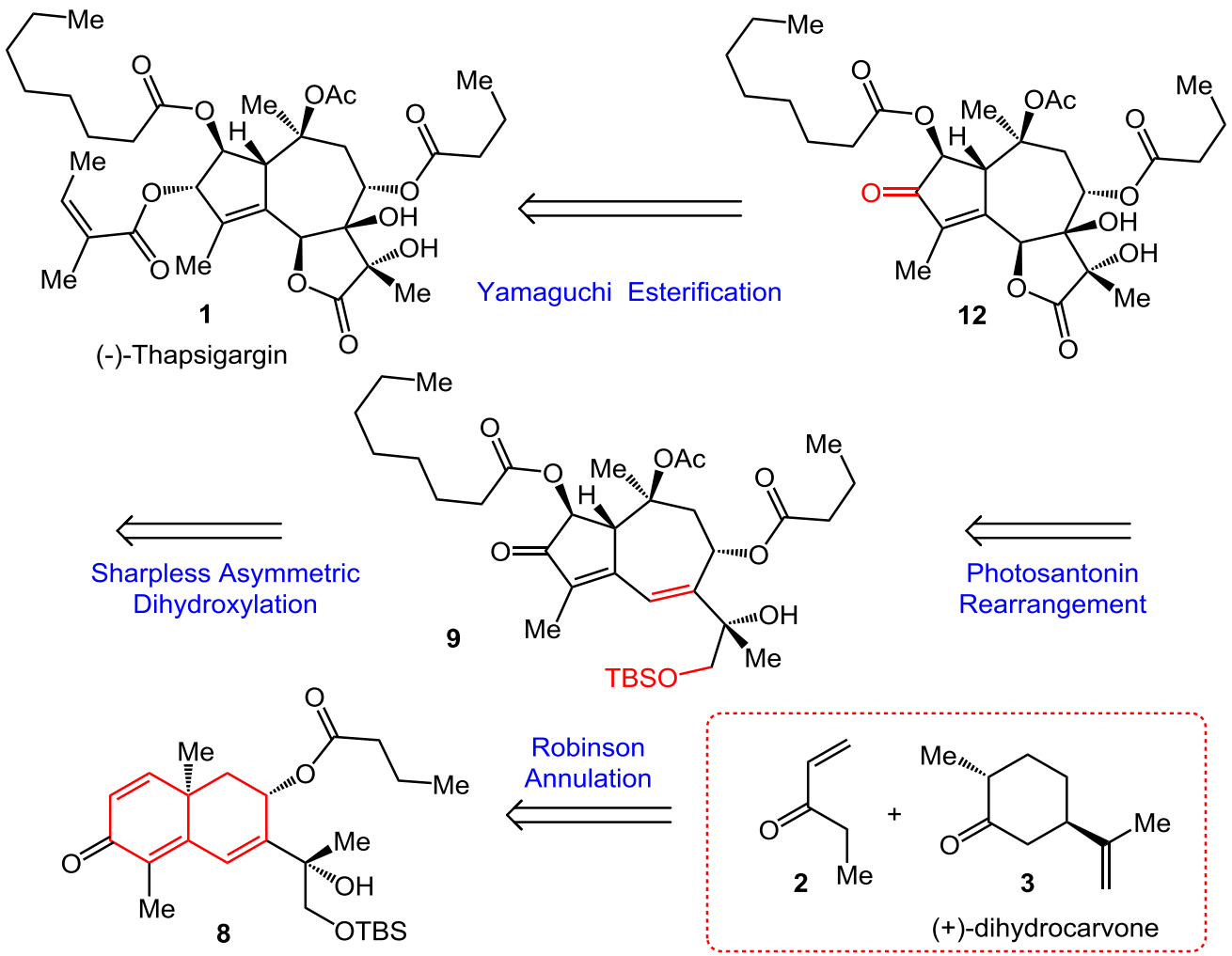


(-)-Thapsigargin

毒胡萝卜

- A efficient and scalable synthesis of thapsigargin from commercially available (*R*)-(−)-carvone;
- The classic photosantonin rearrangement and precisely choreographed installation of the multiple oxygenations.

Retrosynthetic Analysis of (-)-Thapsigargin



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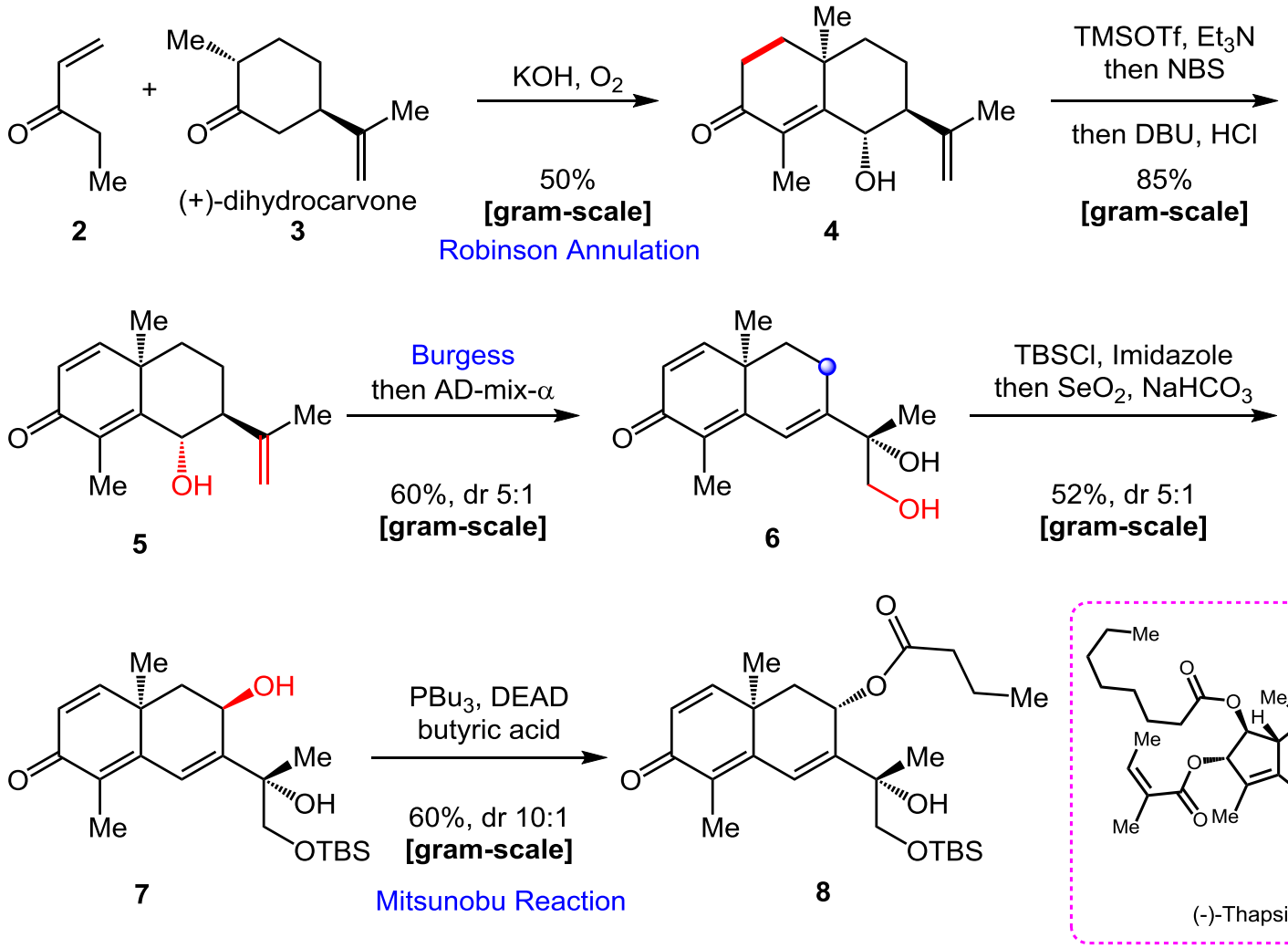
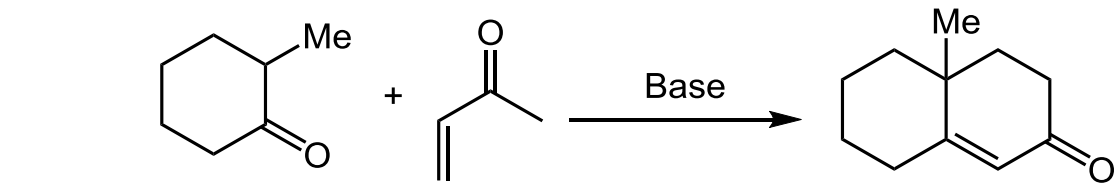
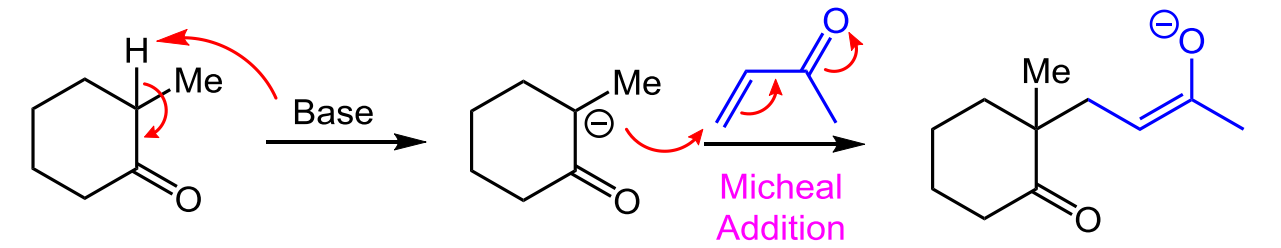
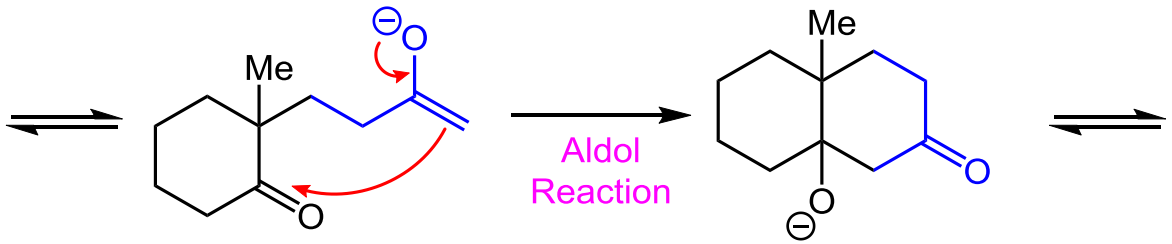
Scalable Synthesis of (−)-Thapsigargin by Baran

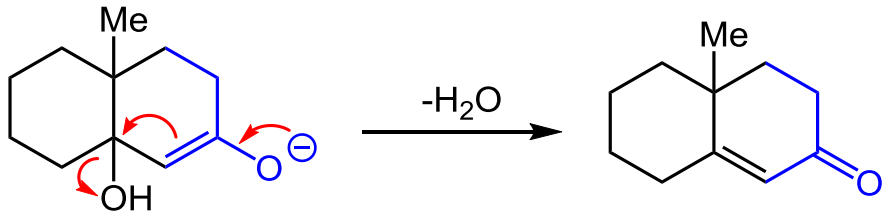


Robinson Annulation

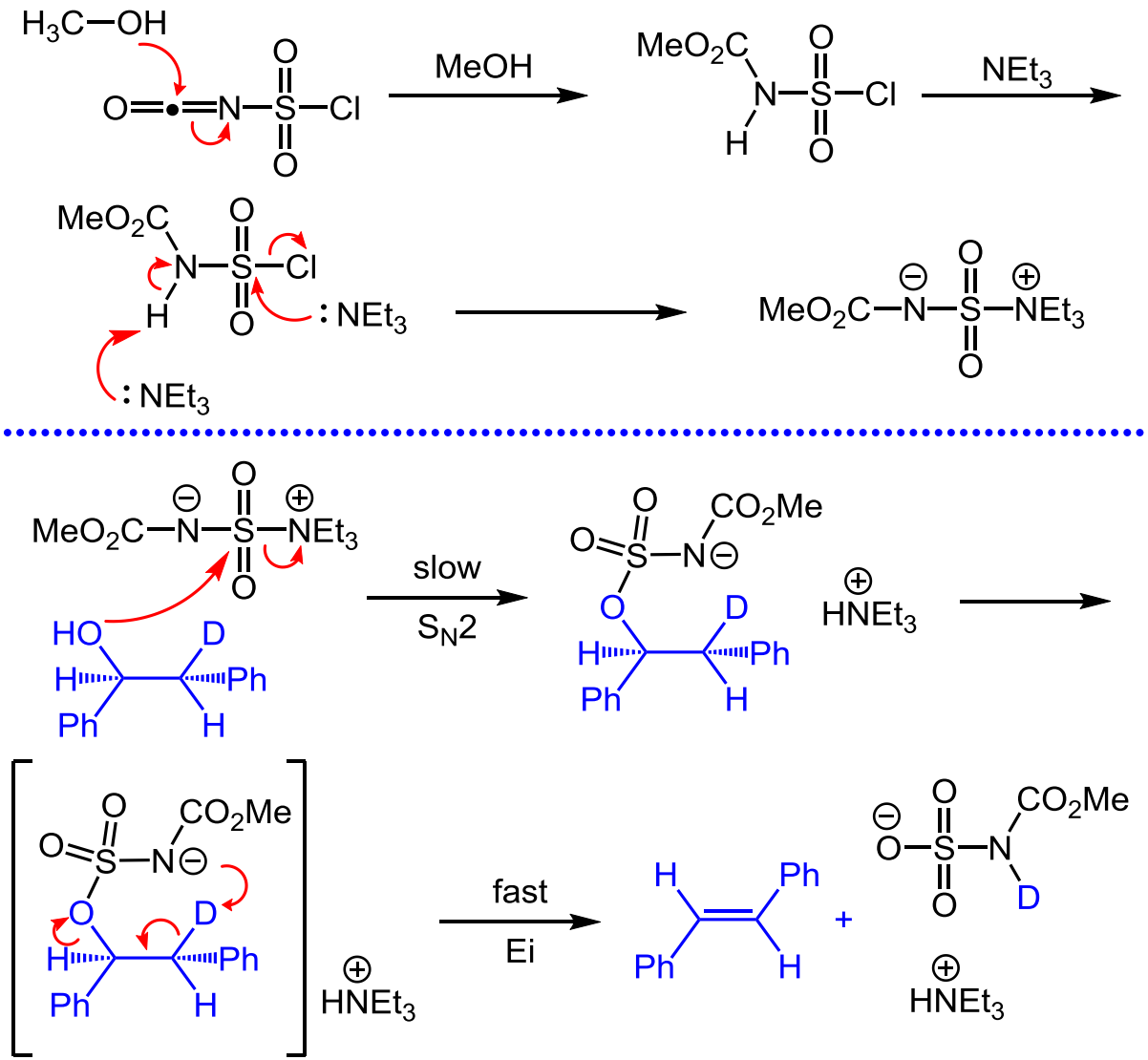




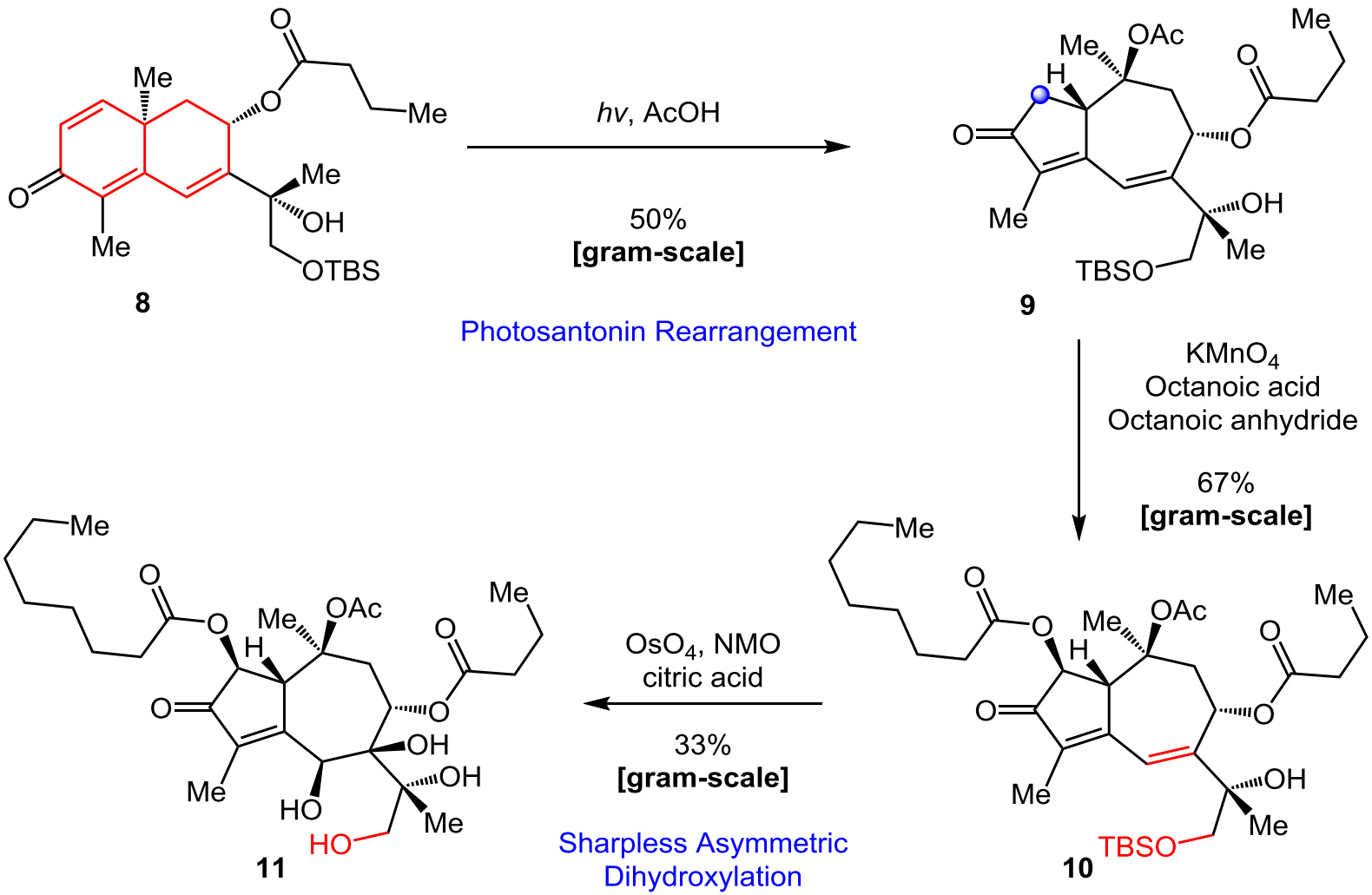




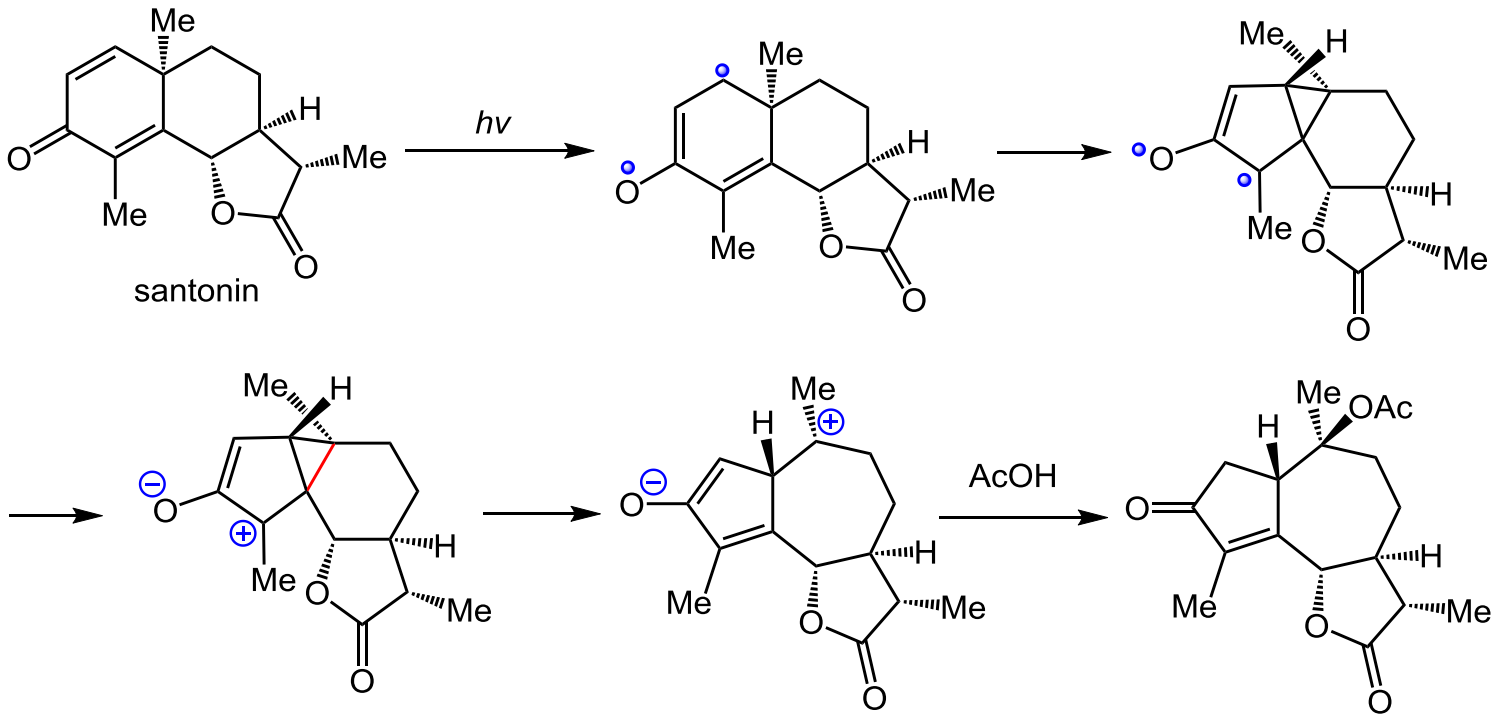
Burgess Reagent



Scalable Synthesis of (−)-Thapsigargin by Baran



Photosantonin Rearrangement



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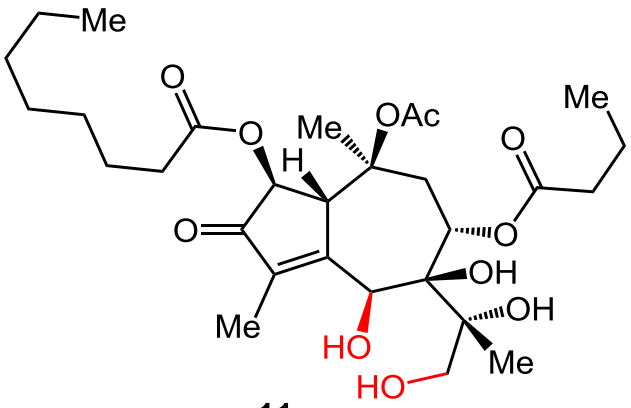
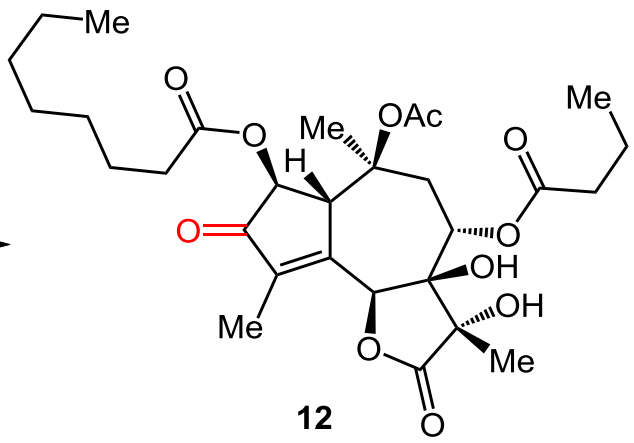


11

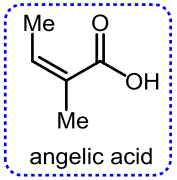
$Py•SO_3$, pyridine
DMSO, DIPEA

43%
[gram-scale]



12

[gram-scale endpoint]

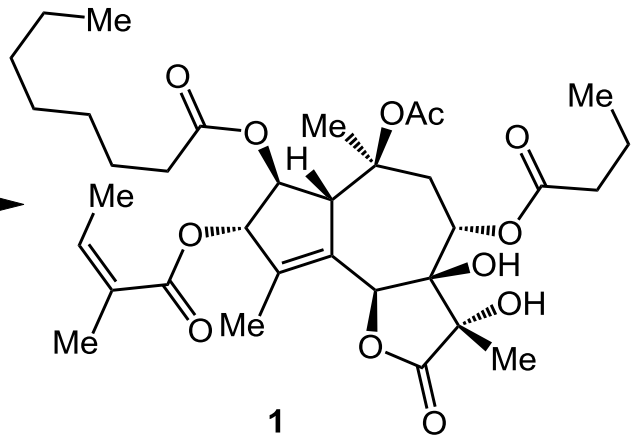


angelic acid

1. $Zn(BH_4)_2$
2. $PhCOCl$, Et_3N, angelic acid

52%

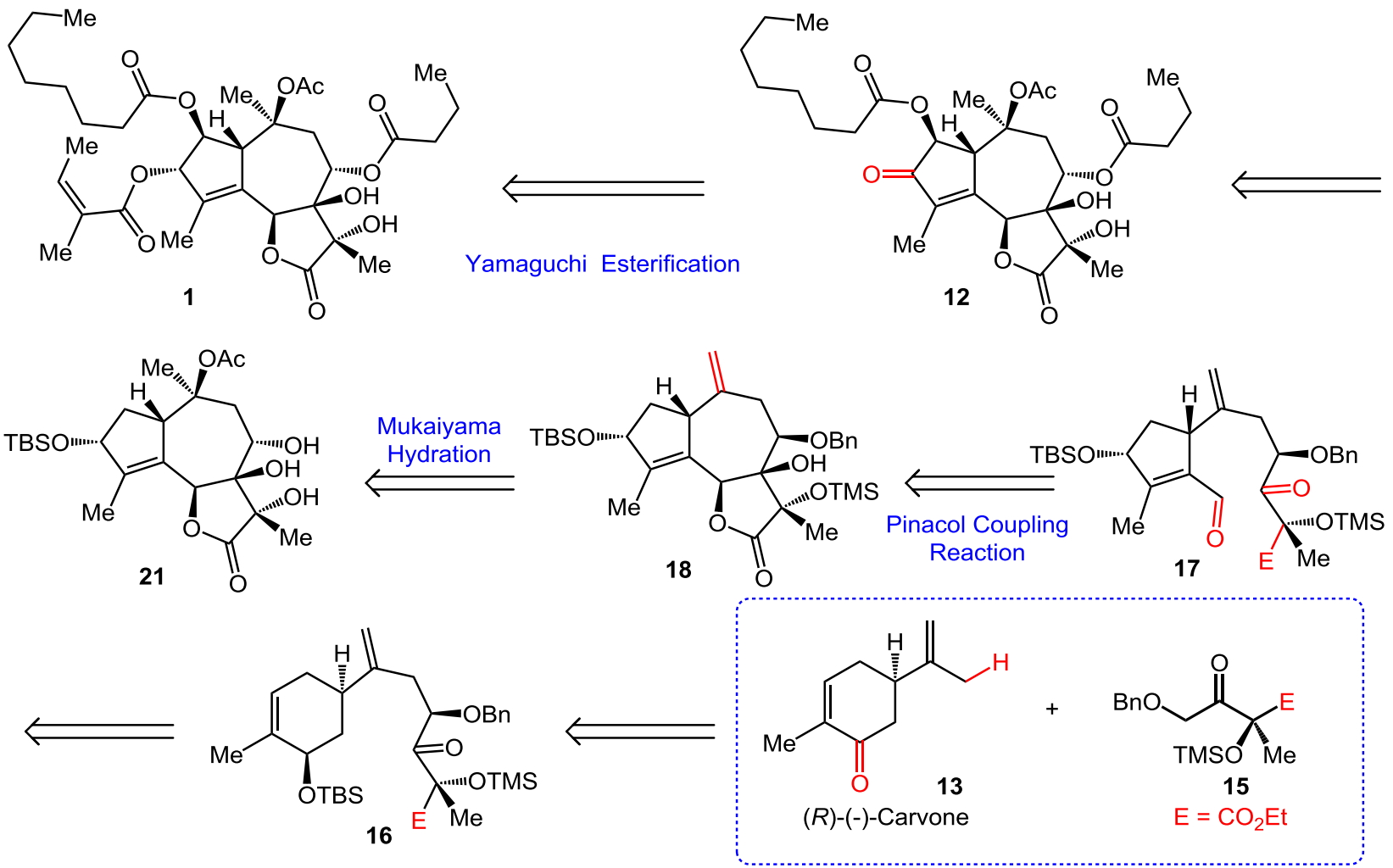
Yamaguchi Esterification



1

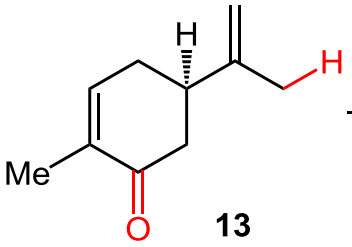
(-)-Thapsigargin

Retrosynthetic Analysis of (-)-Thapsigargin



Evans, P. A.; Chen, D. *J. Am. Chem. Soc.* **2017**, *139*, 6046

Scalable Synthesis of (−)-Thapsigargin by Evans



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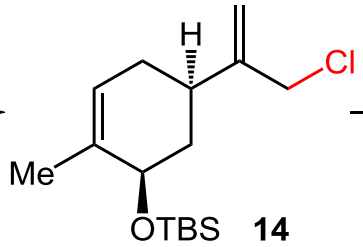
(*R*)-(-)-Carvone

1. ^{t}BuOCl
2. DIBAL-H
then TBSCl
88%
[gram-scale]

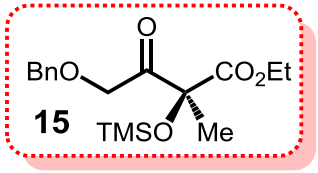


14

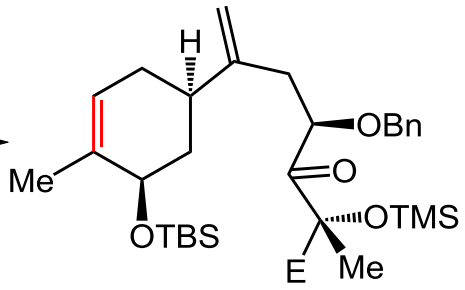
dr > 19:1

$Pd_2(dba)_3$
(*S*)-BINAP, LiCl
then **15**, LiHMDS

93%
[gram-scale]

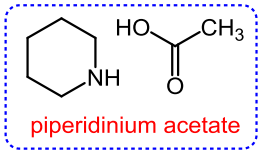


15

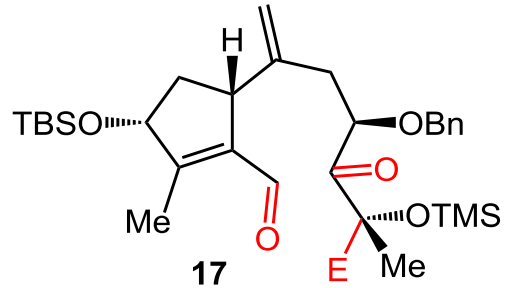


E = CO_2Et **16**
dr = 8:1

O_3, Ph_3P
then
piperidinium
acetate



piperidinium acetate

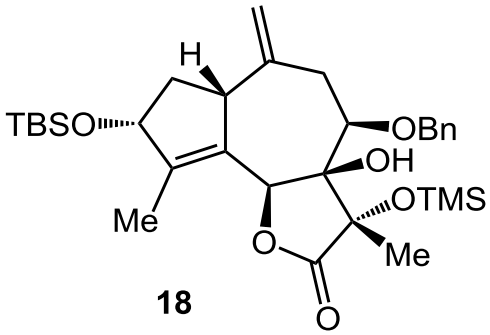


17

55%
[gram-scale]
dr > 19:1

$VCl_3(THF)_3$, Zn, HMPA

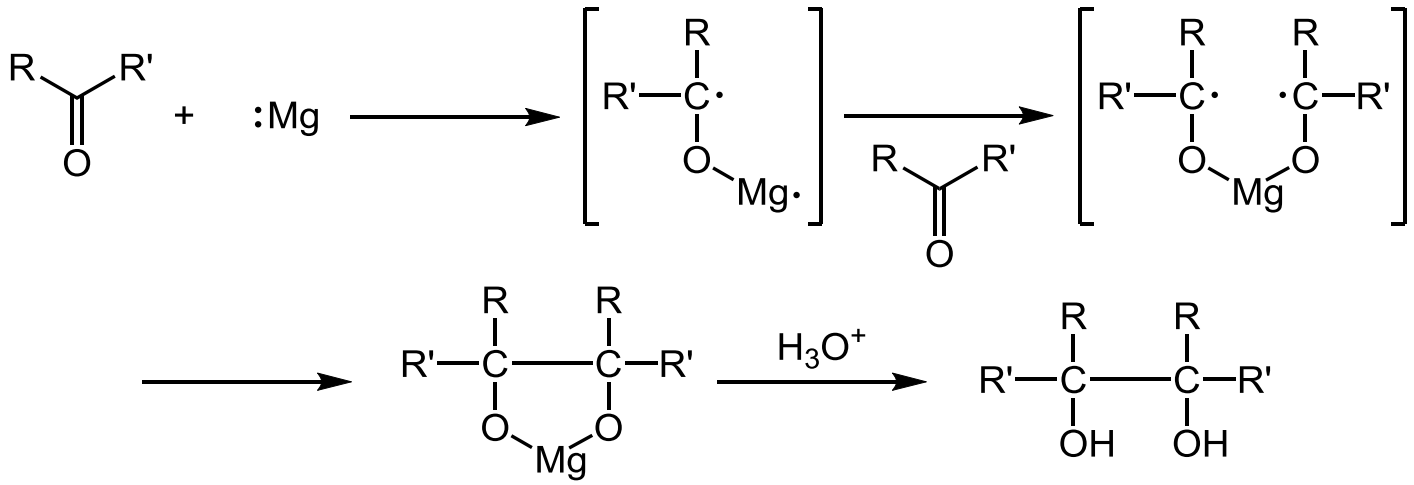
Pinacol Coupling Reaction



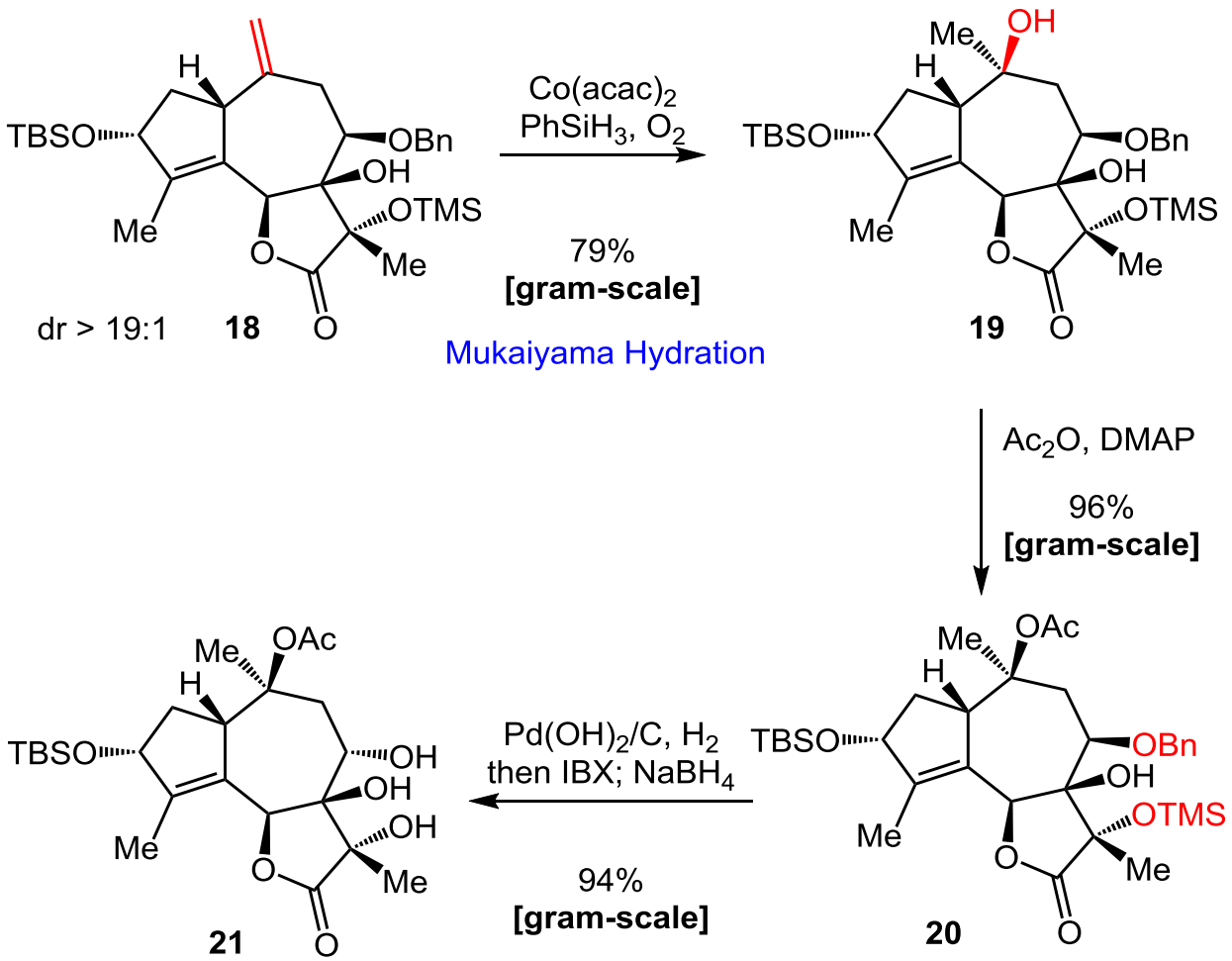
18

60%
[gram-scale]
dr > 19:1

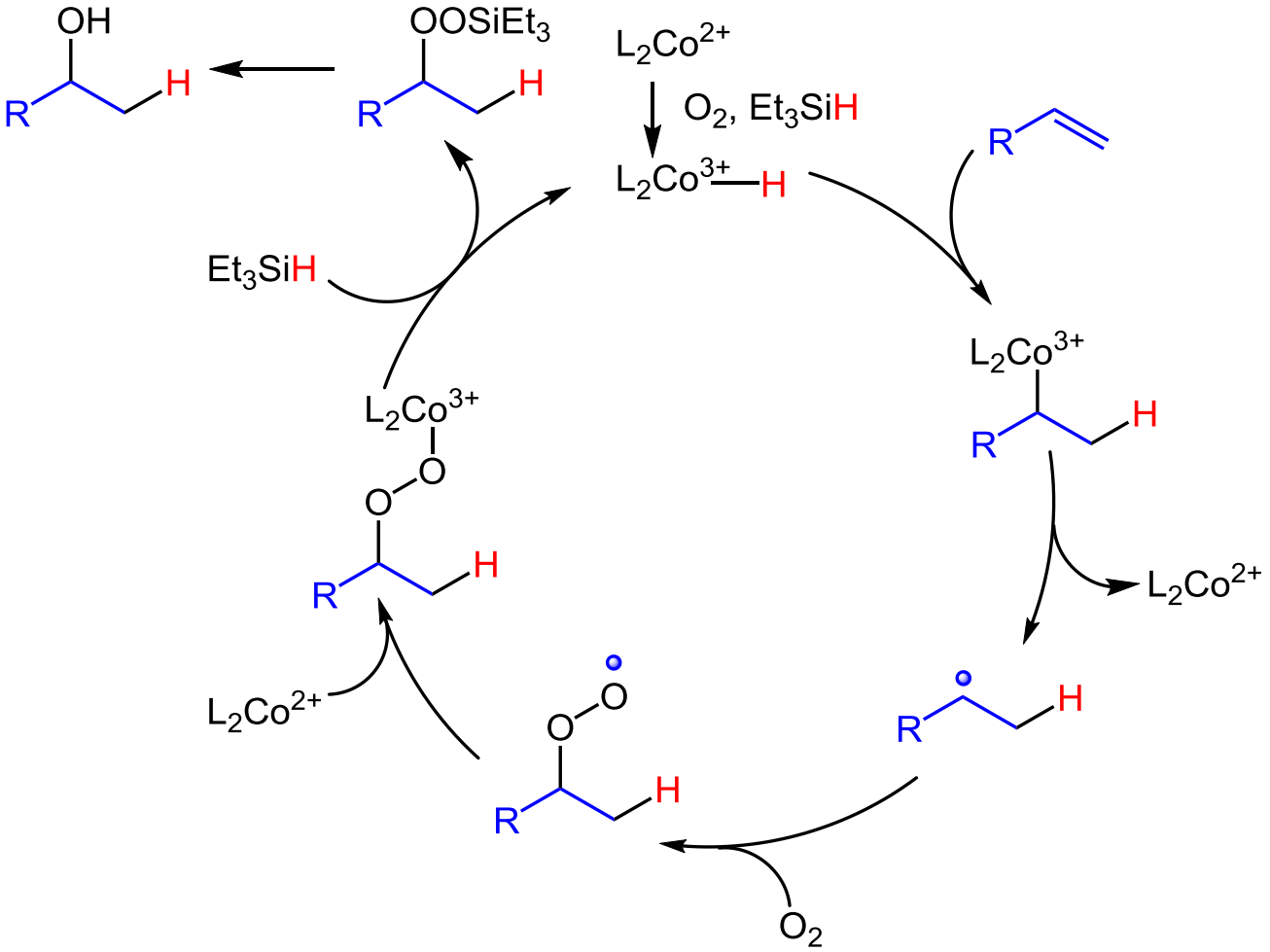
Pinacol Coupling Reaction



Scalable Synthesis of (−)-Thapsigargin by Evans



Mukaiyama Hydration



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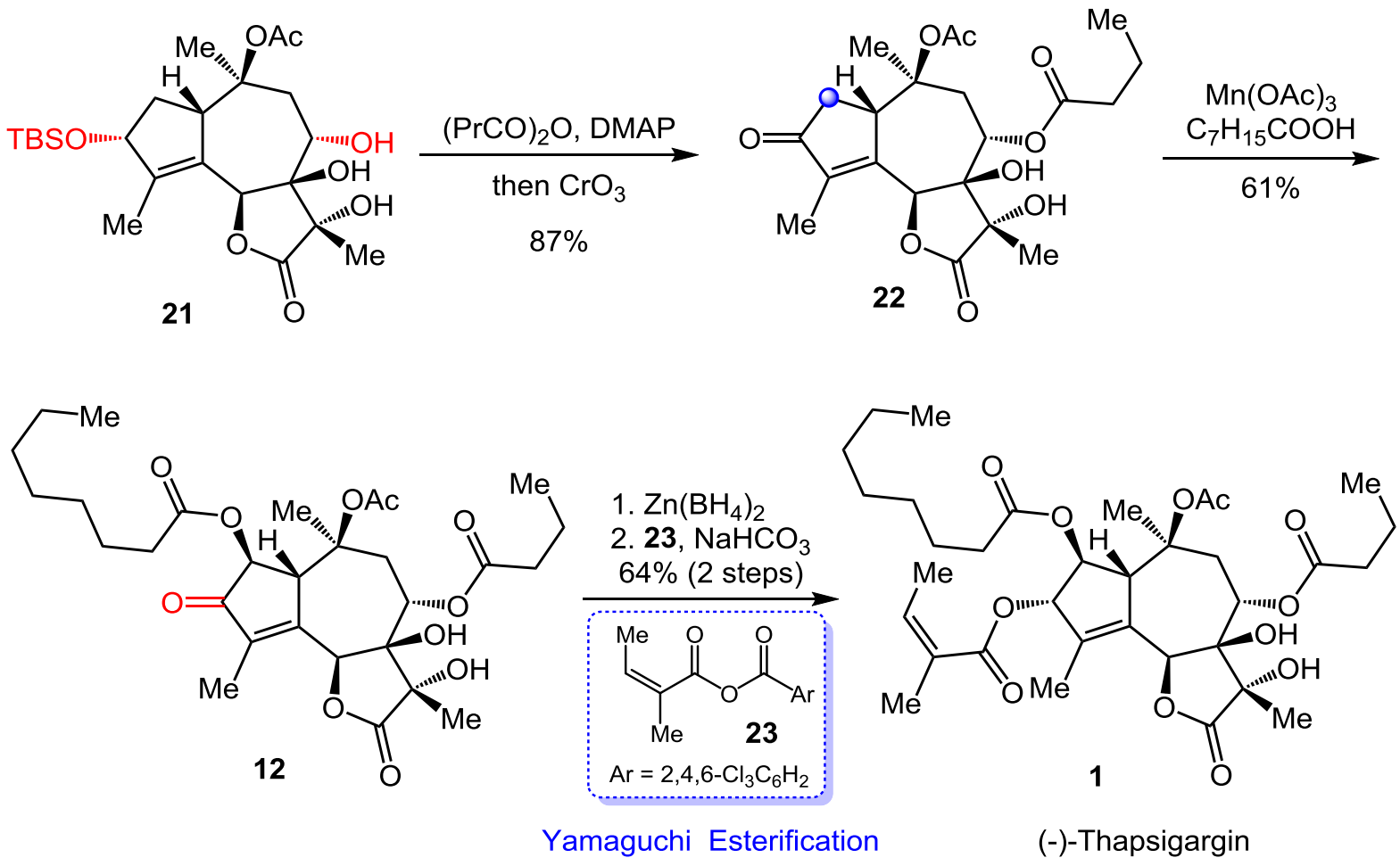
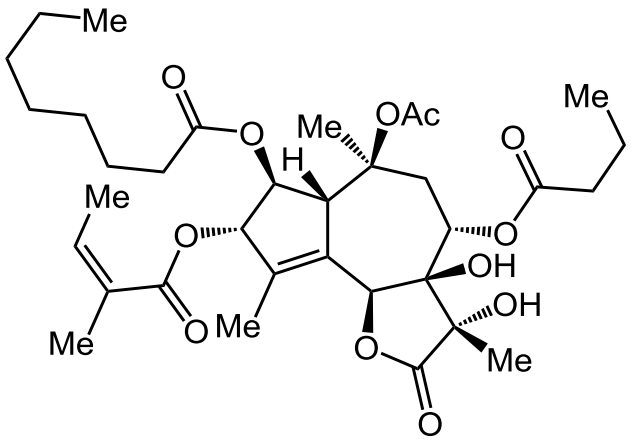


Summary



(-)-Thapsigargin

Baran' work	◆ 11 steps and 0.14% overall yield; ◆ photosantonin rearrangement; ◆ precisely choreographed installation of the multiple oxygenations.
Evans' work	◆ 12 steps and 5.80% overall yield; ◆ pinacol coupling reaction; ◆ Mukaiyama hydration.

The First Paragraph

The structure of thapsigargin was elucidated in 1978, but its use can be anecdotally traced back to ancient times as a popular folk medicine. As one of the most highly oxidized members of the venerable guaianolide sesquiterpene family, represents a classic target for total synthesis. One measure of the difficulty in approaching a total synthesis of this natural product is the percentage of skeletal carbon atoms that bear an oxygen atom (53%). For reference, notoriously difficult targets such as ingenol, phorbol and Taxol, range from 25 to 42%.

The First Paragraph

For this reason, the sole successful effort to reach thapsigargin required 42 steps, respectively. Thapsigargin is a potent inhibitor of the SERCA-pump protein, with potential for applications in a variety of medicinal areas. In this article, the execution of a concise, scalable, two-phase total synthesis of thapsigargin is presented featuring a single-step construction of the carbon framework followed by precisely choreographed oxygenation events.

The Last Paragraph

The route described here benefits from an effective strategy rather than a recent methodological advance, with Sharpless AD being the newest method employed. Rather, it was the twophase approach that enabled scalable access to these highly oxygenated and complex natural products. Indeed, a 2015 review on these terpenes stated: “Approaches utilizing semisynthesis or total synthesis are currently far from being economically feasible.” Total synthesis is now a potentially viable option for the scalable procurement of thapsigargin with deep-seated modifications.

Acknowledgement

Thanks

for your attention