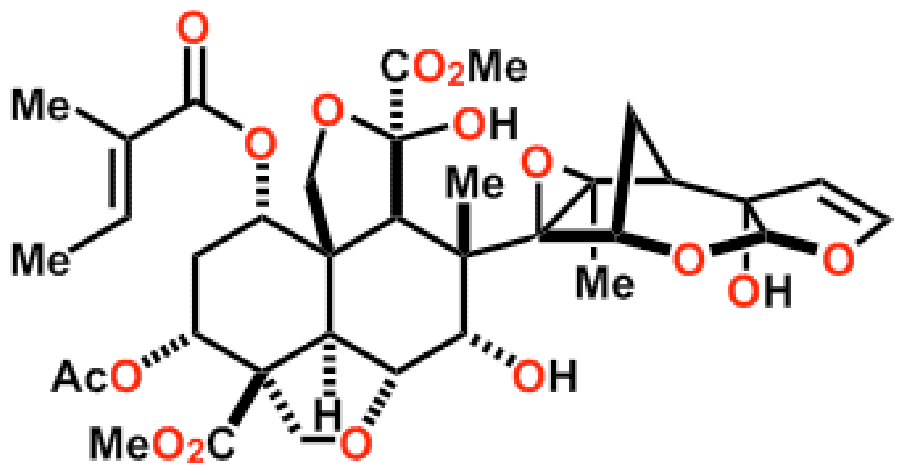
Total Synthesis of Azadirachtin: 22 Years to Harvest



Nathan Werner

Denmark Group Meeting

December 11th, 2007

Total Synthesis

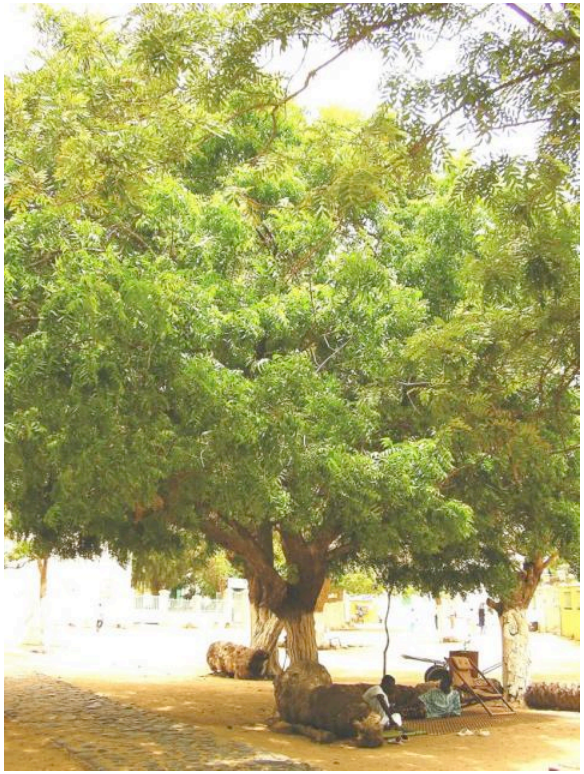
Natural-product synthesis:

- •originated in the 1820's when Friedrick Wöhler synthesized urea
- •has generated serendipitous discoveries such as the first synthetic dye, mauveine, by William Perkin in 1856 while attempting to synthesize quinine

Has modern natural-products synthesis outgrown it's usefulness?

Sanderson, K. *Nature* **2007**, 630-631.

Isolation of Azadirachtin



www.turfarm.com/Trees.aspx

goree.rice.edu/?q=taxonomy/term/7

- *Azadirachta indica* (Neem Tree) is native to tropical and subtropical areas of India
- First isolated from the ethanolic exctract of Neem seeds in 1968 by Morgan and coworkers

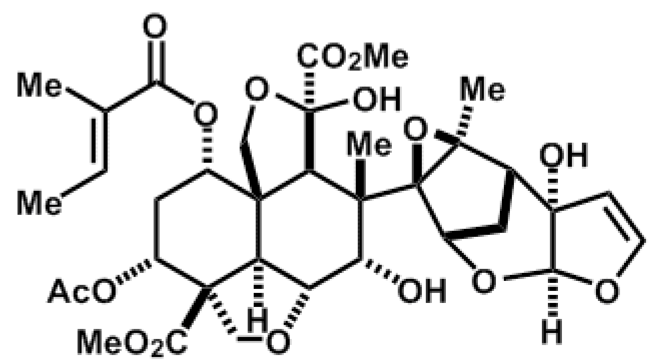
Morgan, E. D; et al. *Chem. Commun.* **1968**, 23-24.

Biological Activity

- Initial biological studies by Morgan and coworkers found Azadiractin to completely inhibit feeding by the desert locust *Schistocerca gregaria* at 1 ng / cm^2

- Further studies have revealed that azadirachtin exhibits potent anitfeedant and growth-disruptant properties against a broad spectrum of insects yet low mammalian toxicity (LD_{50}(rat) > 5 g / kg).

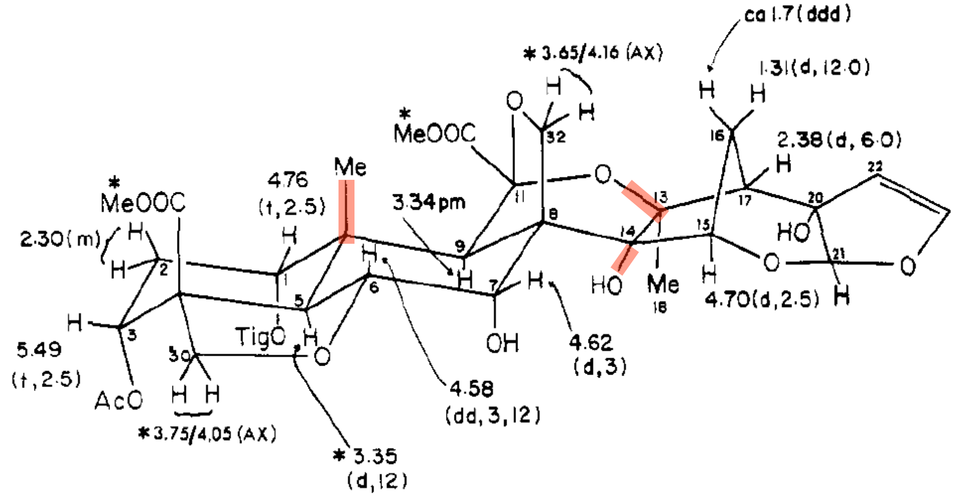
www.le.ac.uk/neurosciences/matheson.html



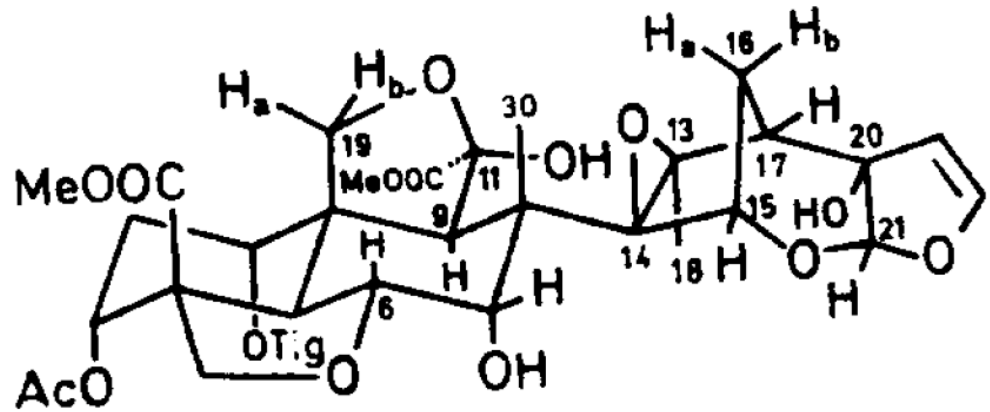
Morgan, E. D; et al. *Chem. Commun.* **1968**, 23-24.
Schmutterer, H. *The Neem Tree*, VCH, Weinheim, **1995**.

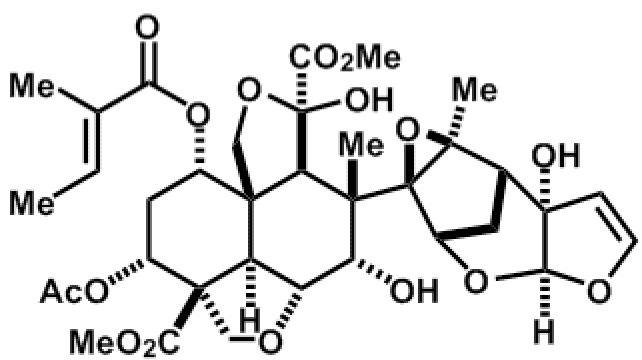
Structural Assignment

First complete structure of Azadirachtin by Nakanishi in 1975 using extensive NMR



Revised structure by Kraus in 1985 which proposed a C13-C14 epoxide



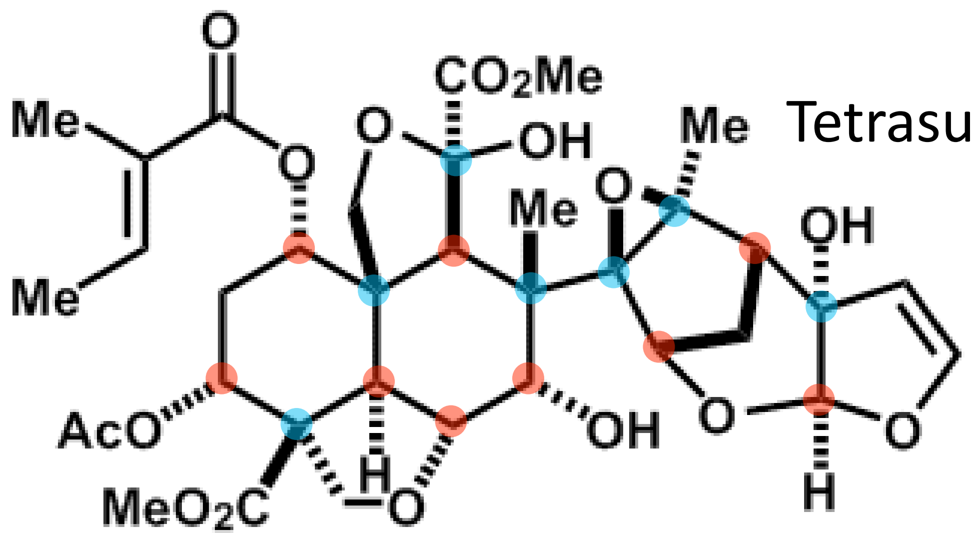


Nakanishi, K.; et al. *J. Am. Chem. Soc.* **1975**, 1975-1977.
Kraus, W. et al. *Tetrahedron Lett.* **1985**, 6435-6438.

Structural Features

16 stereogenic centers

Hemi-acetal

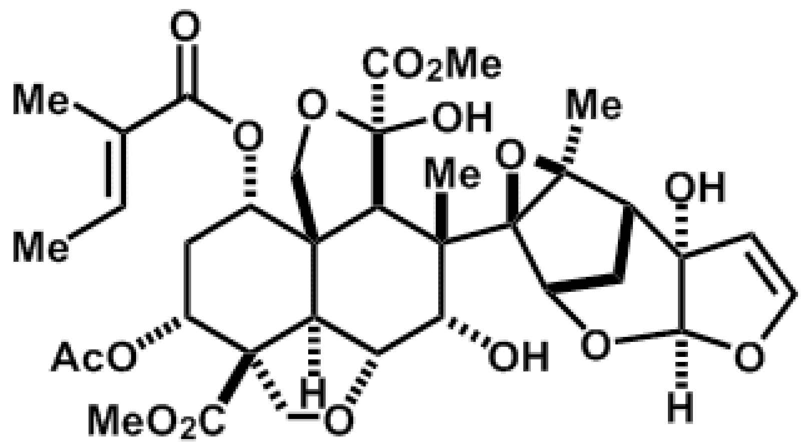


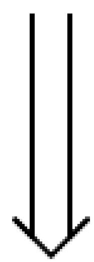
Tetrasubstituted epoxide

Enol ether

7 tetrasubstituted carbon atoms

Retrosynthetic Question

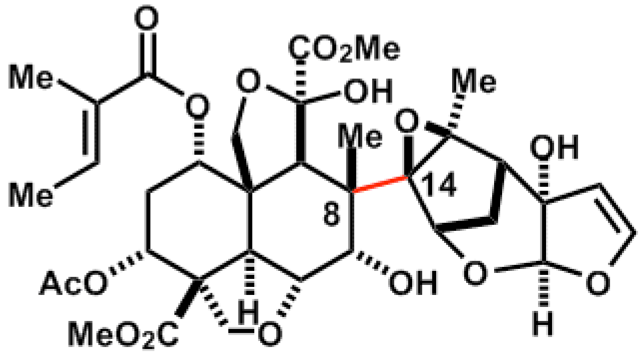




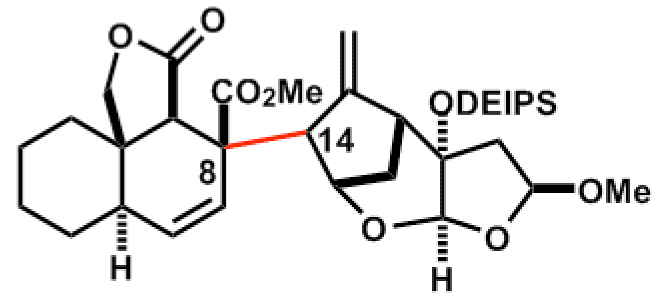
Please take a few minutes to come up with a general retrosynthetic analysis.

?

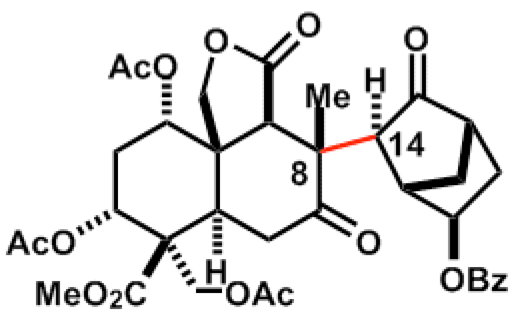
Synthetic Endeavors



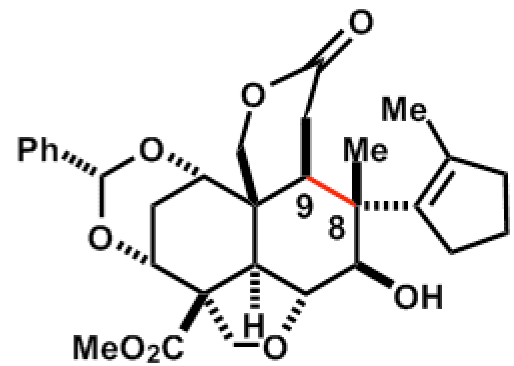
Ley 2007
C8-C14
Intramolecular Claisen



Murai 2002
C8-C14
Intramolecular Claisen



Nicolaou 2005
C8-C14
Radical Cyclization

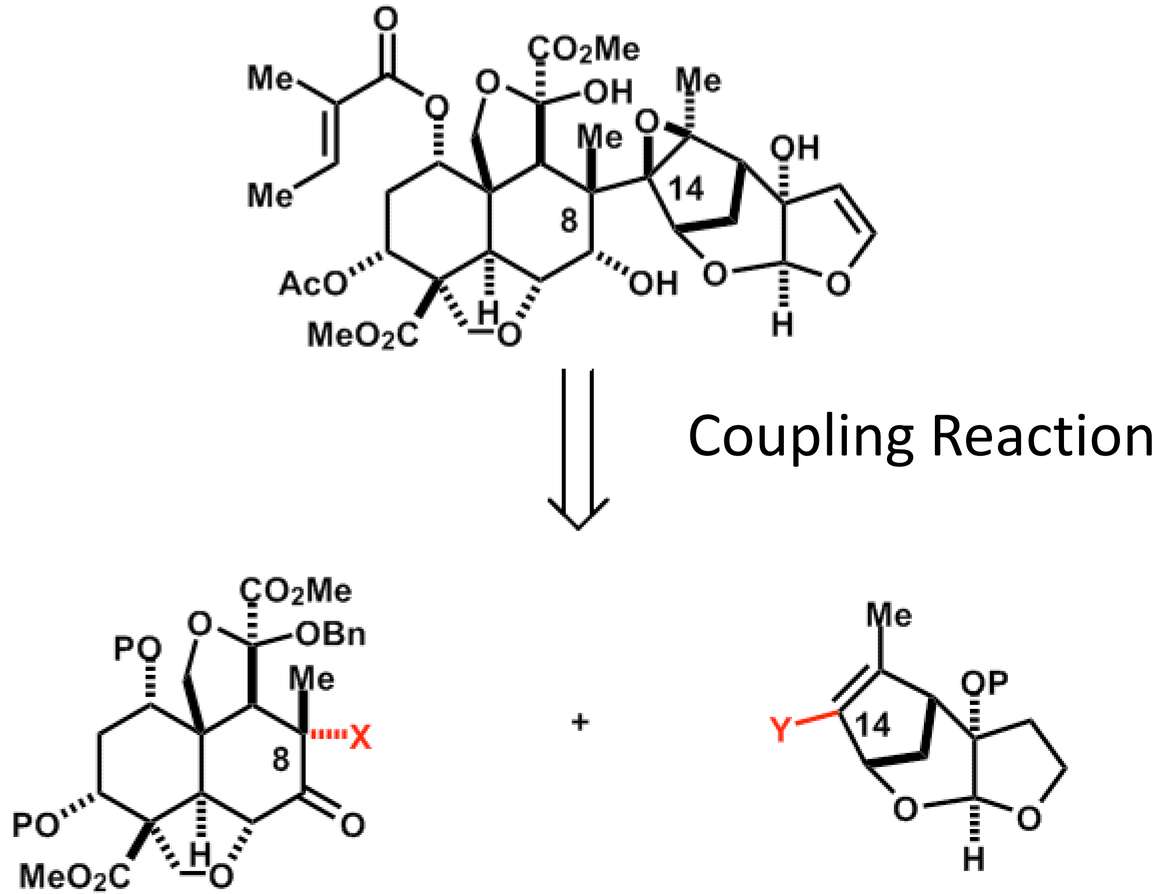


Watanabe 2007
C8-C9
Radical Cyclization

Ley, S. V.; et al. *Angew. Chem. Int. Ed.* **2007**, 7629-7632.
Nicolaou, K. C.; et al. *Angew. Chem. Int. Ed.* **2005**, 3443-3447.

Murai, A.; et al. *Org. Lett.* **2002**, 2877-2880.
Watanabe, H.; et al. *Angew. Chem. Int. Ed.* **2007**, 1512-1516.

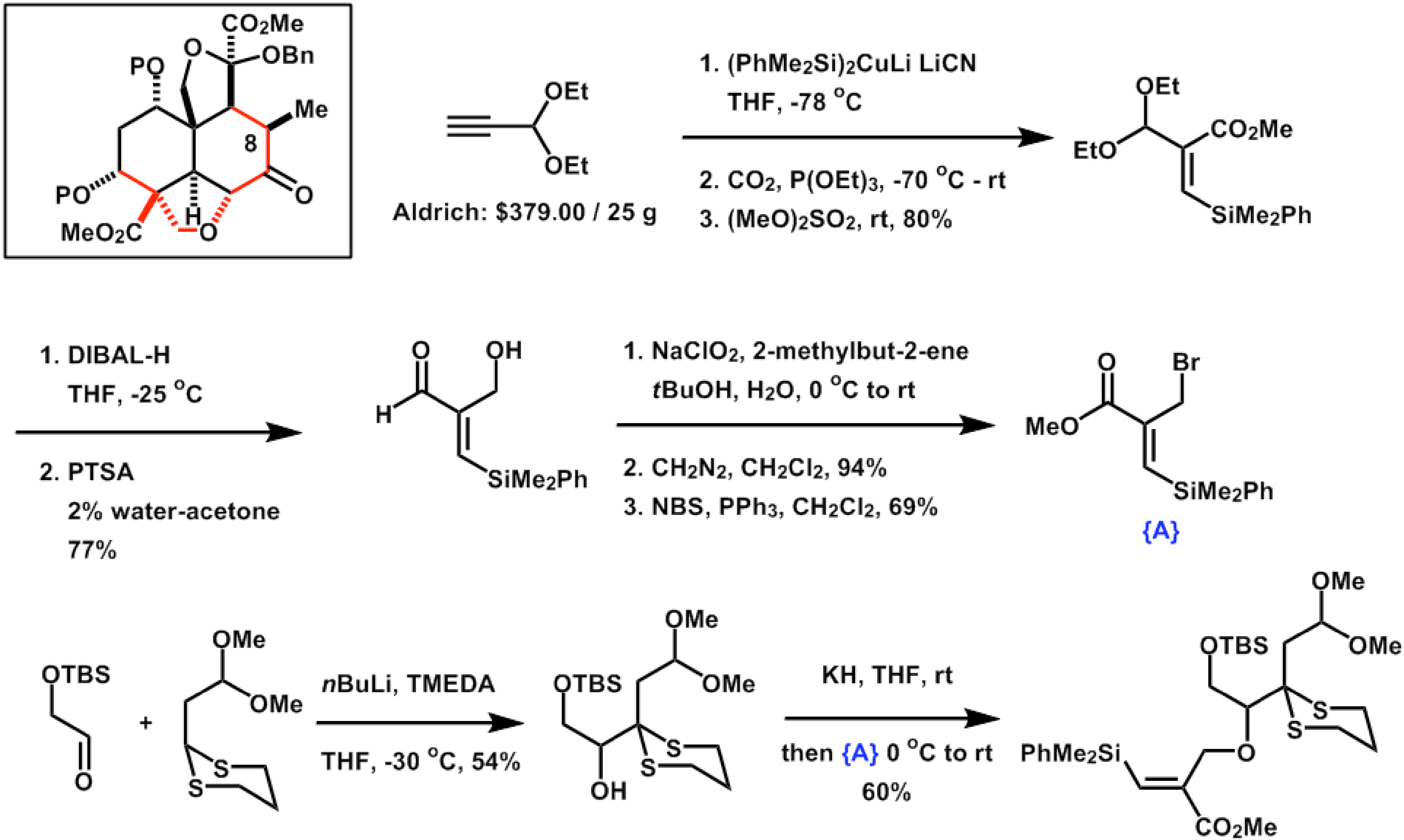
Ley's Original Retrosynthetic Analysis



Decalin Fragment

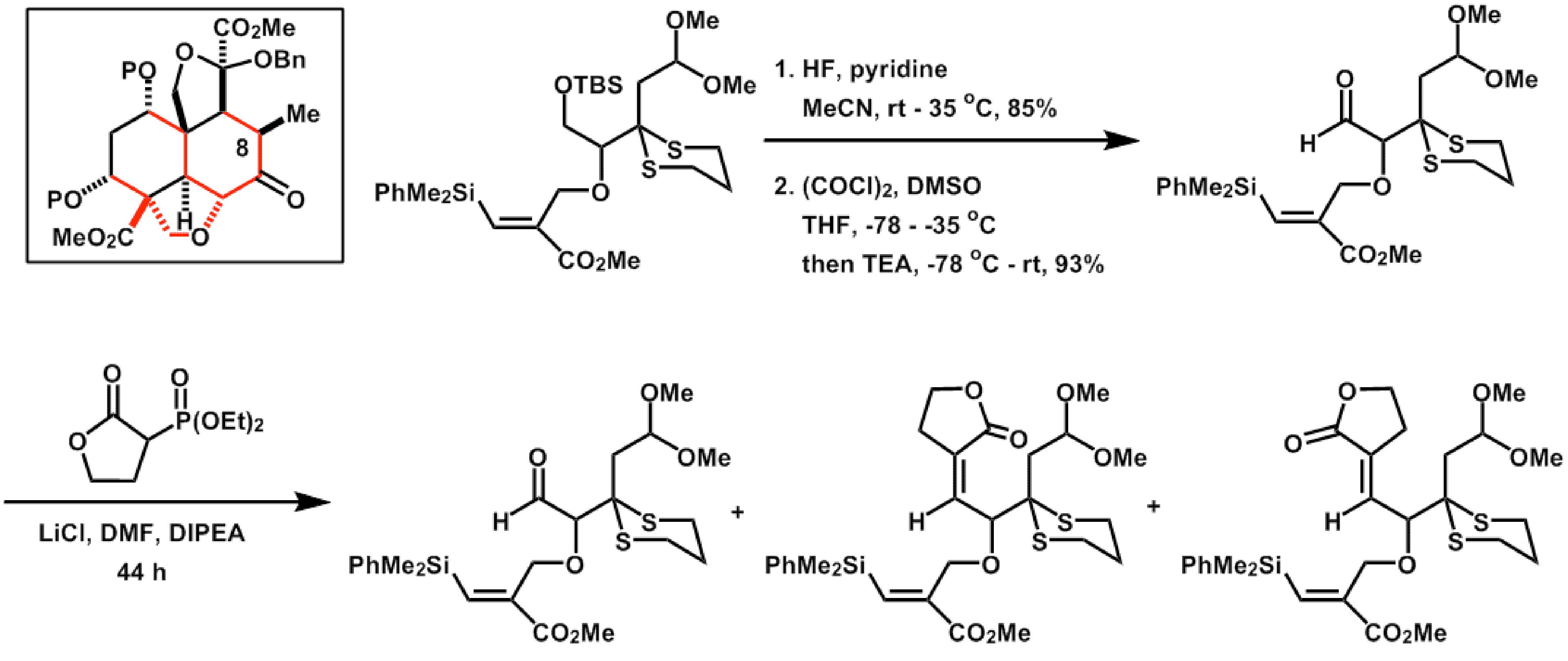
Pyran Fragment

Beginning – The Decalin Fragment



Ley, S. V.; et al. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2735-2762.

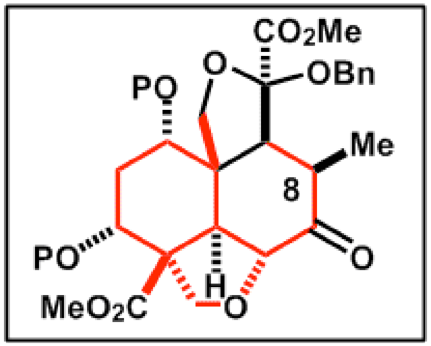
Synthesis of IMDA Precursor

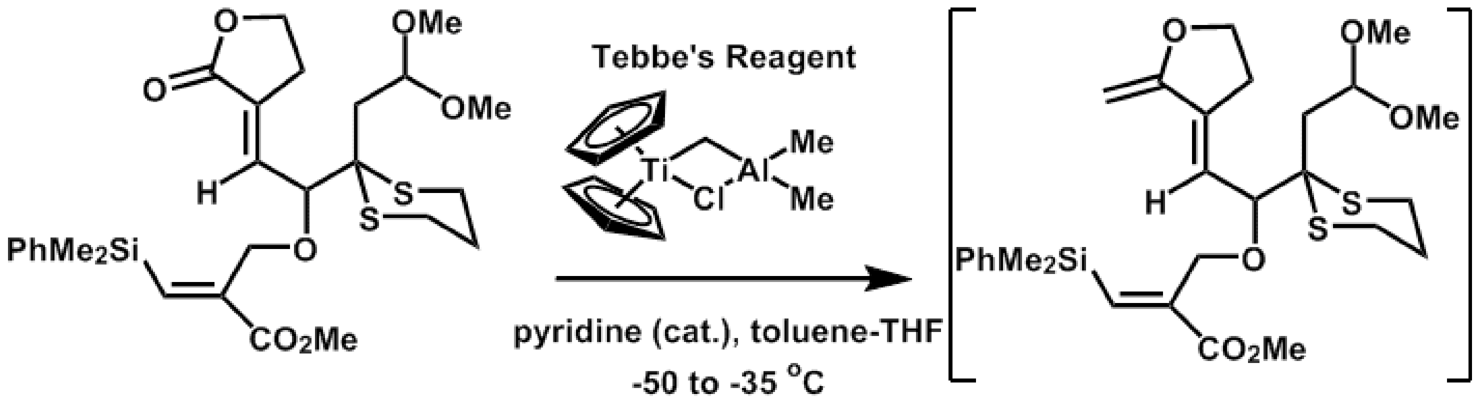


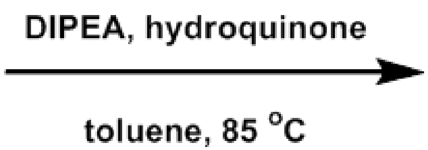
49% 13%-(*Z*) 34%-(*E*)

Ley, S. V.; et al. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2735-2762.

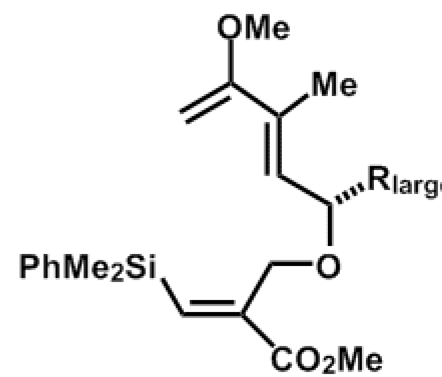
Intramolecular Diels-Alder Reaction





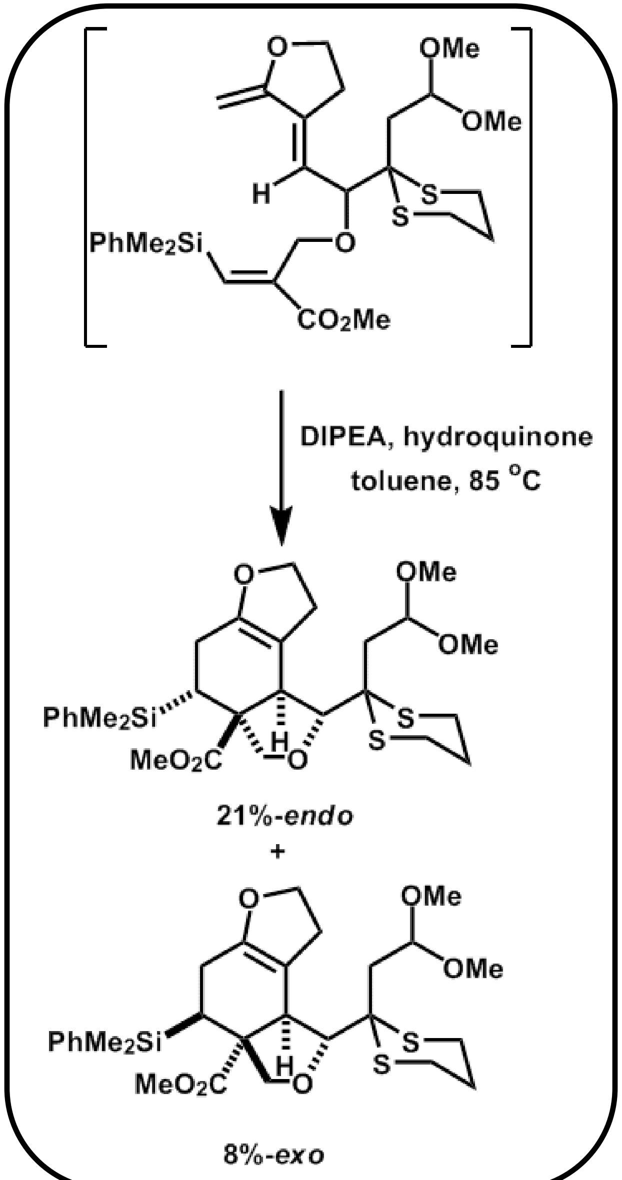


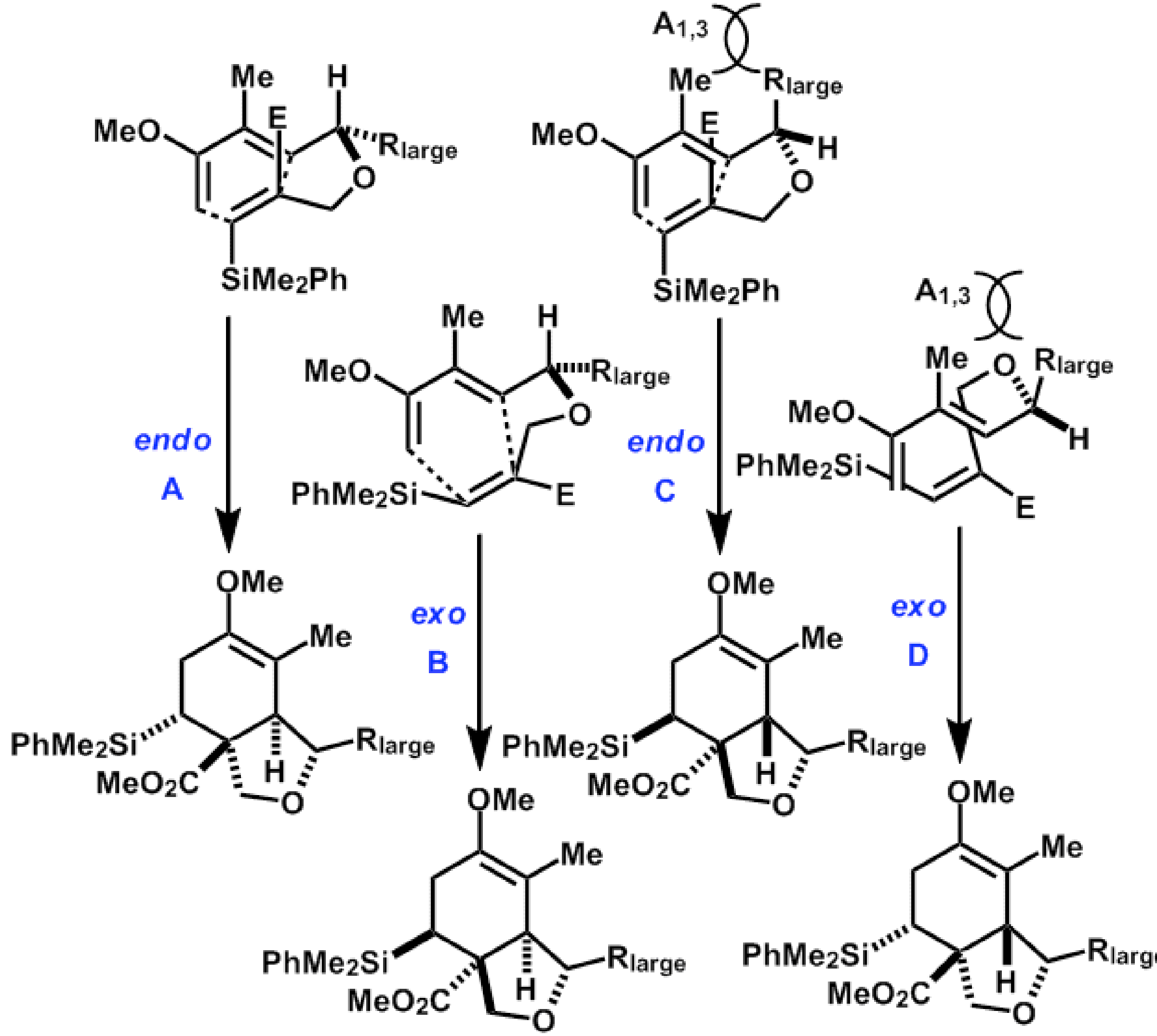
4 possible diastereomers; please make a general prediction of the product ratio by transition state structure analysis of this simplified model



Ley, S. V.; et al. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2735-2762.

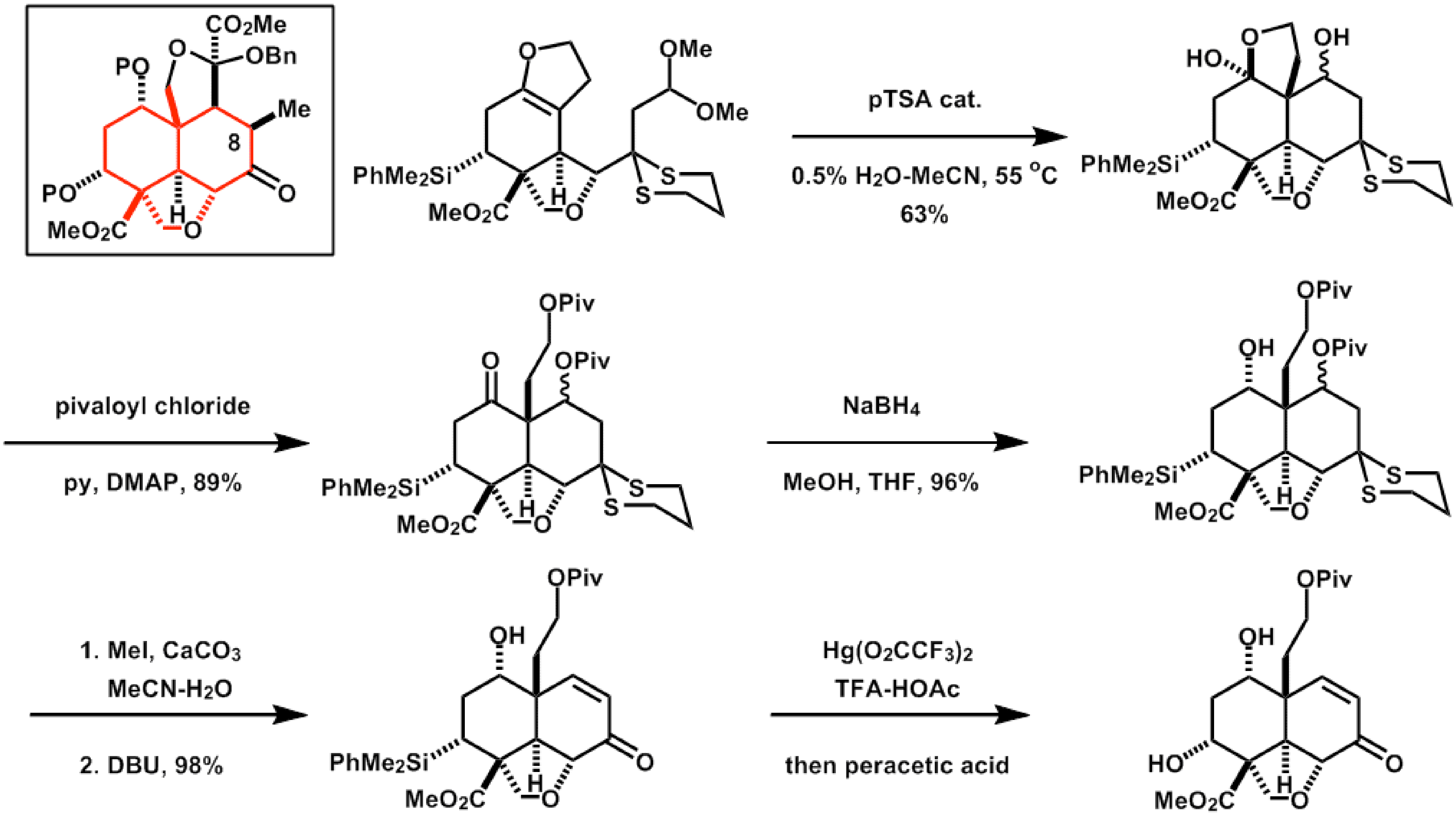
IMDA Answer





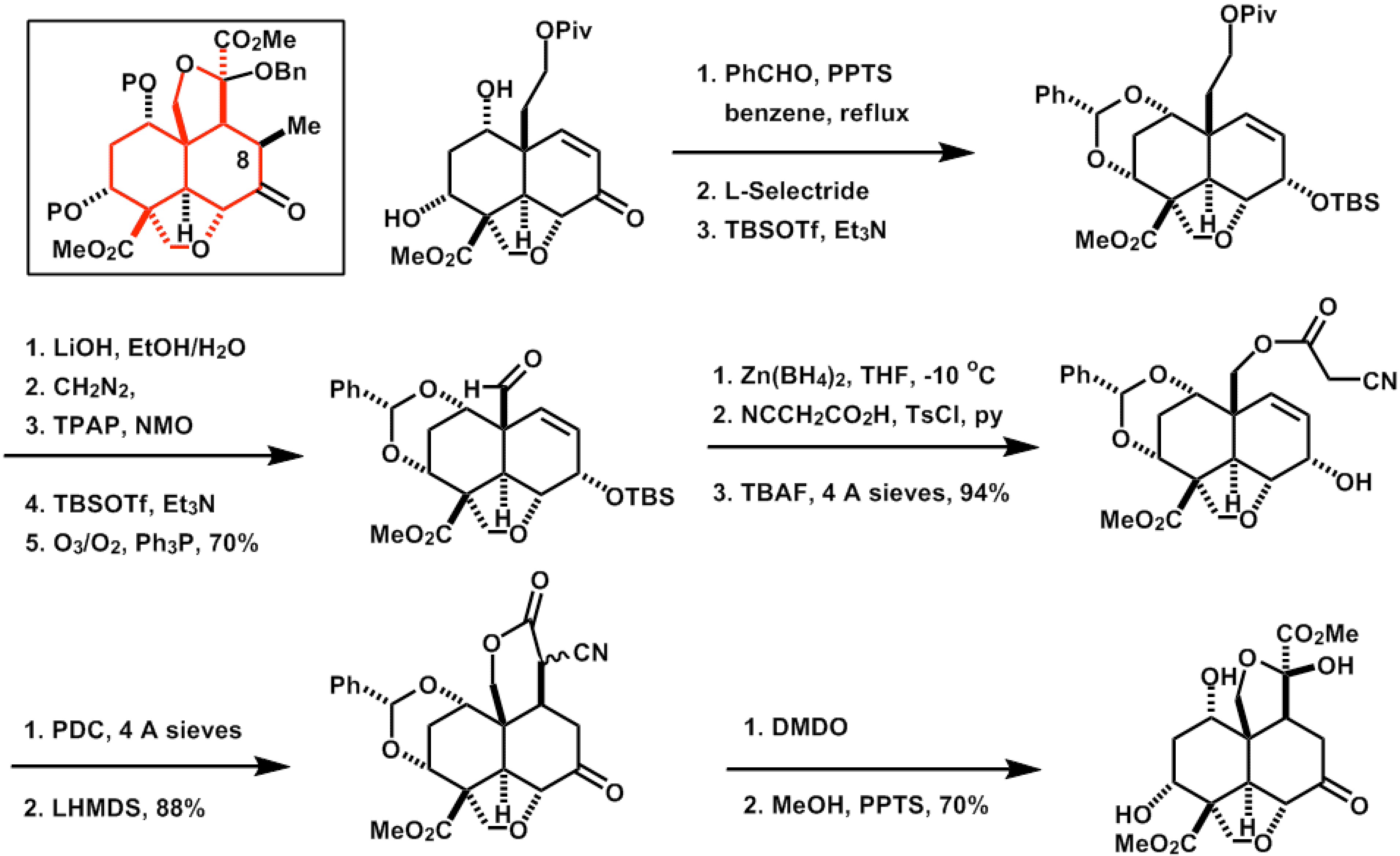
Ley, S. V.; et al. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2763-2777.

Synthesis of Decalin Fragment



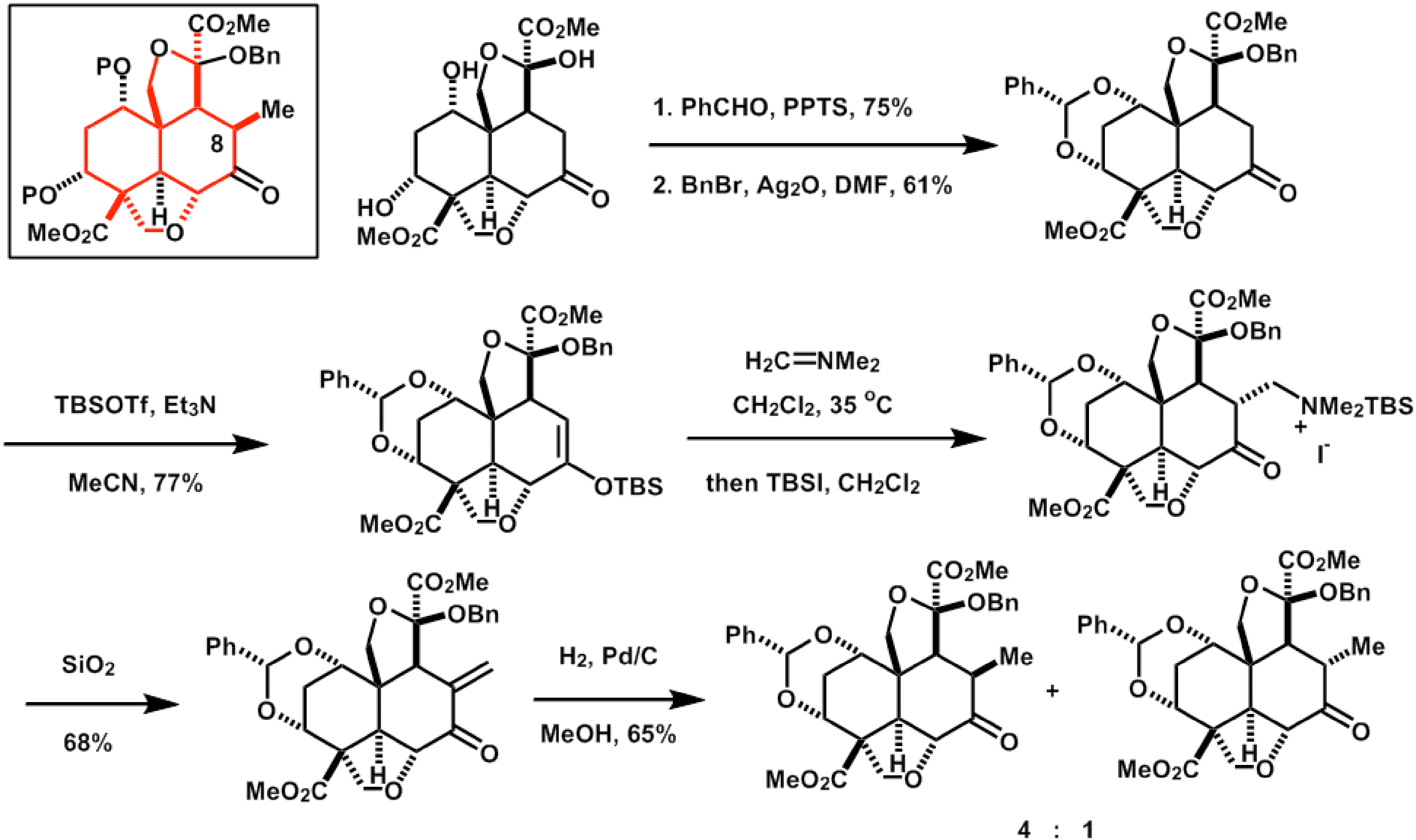
Ley, S. V.; et al. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2735-2762.

Formation of the Hemi-Acetal



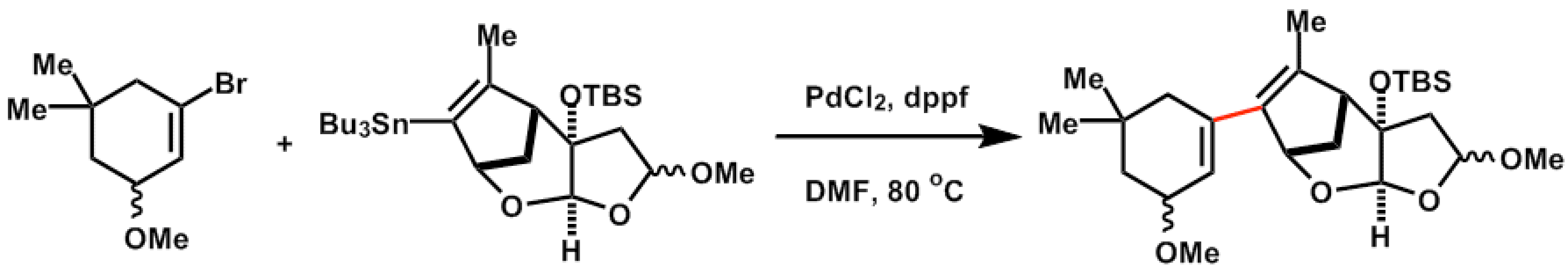
Ley, S. V.; et al. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2735-2762.

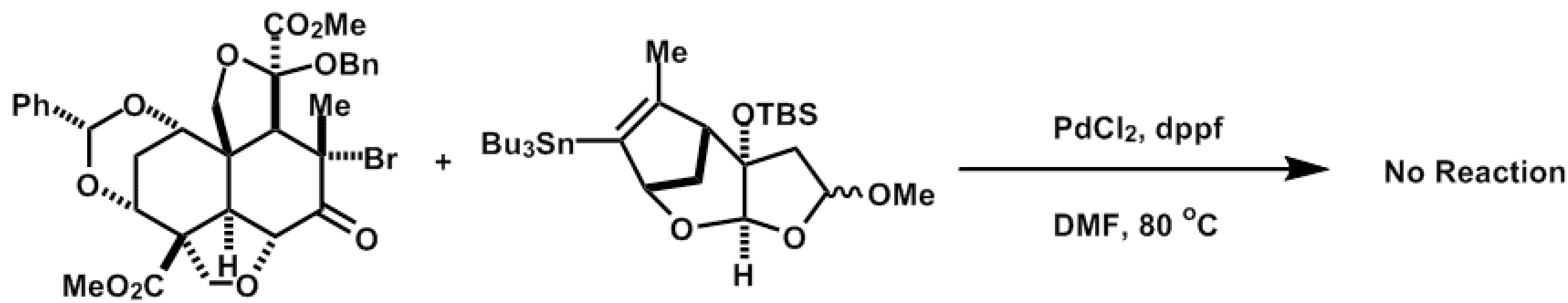
Synthesis of Decalin Fragment

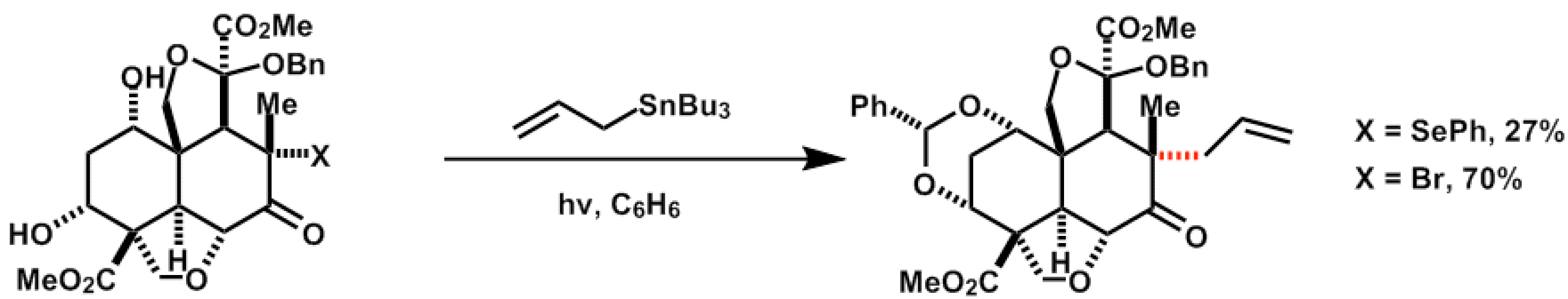


Ley, S. V.; et al. *Pure Appl. Chem.* **2005**, 1115-1130.

Coupling of Fragments

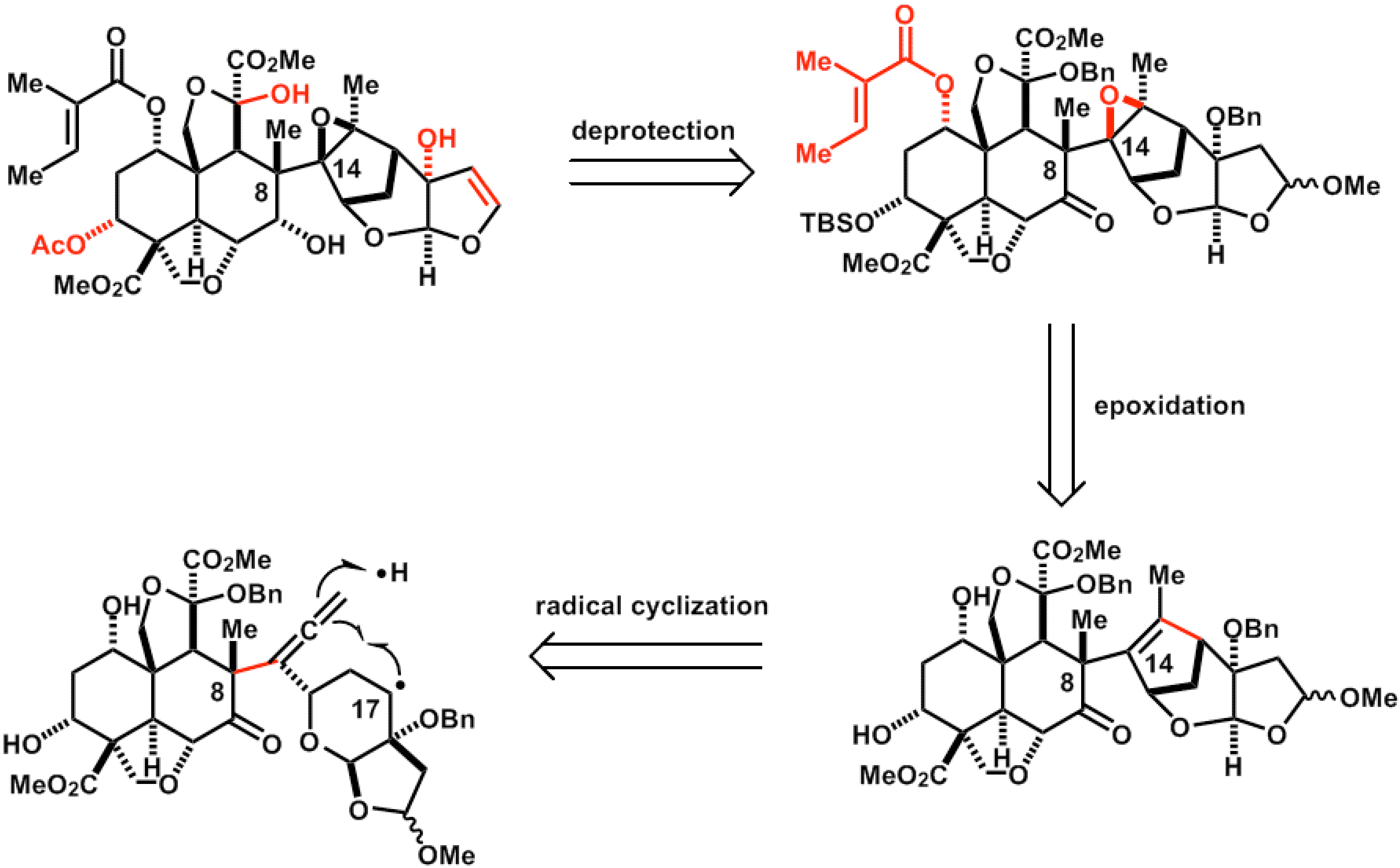






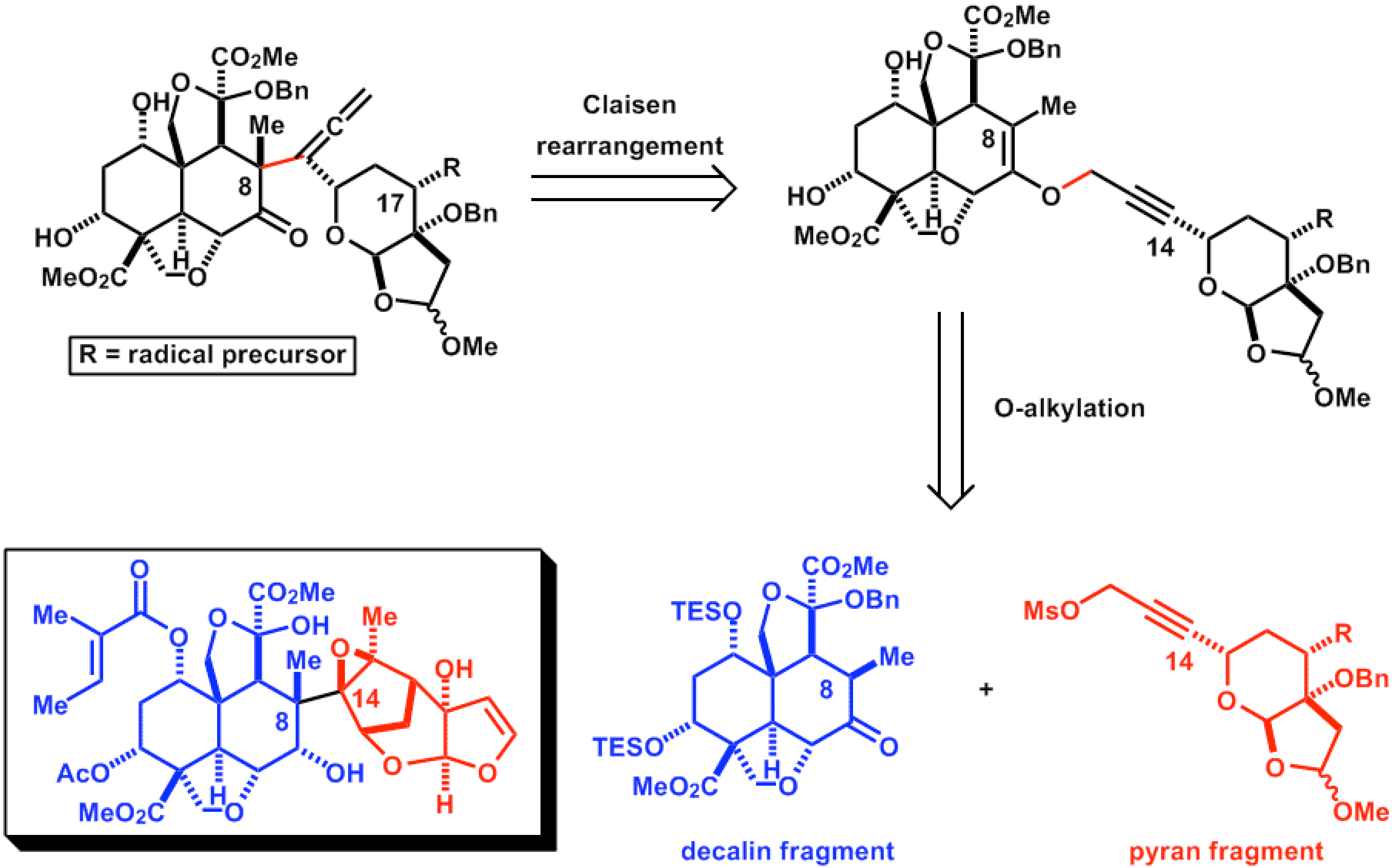
Ley, S. V.; et al. *Pure Appl. Chem.* **2005**, 1115-1130.

Ley's Revised Retrosynthetic Analysis



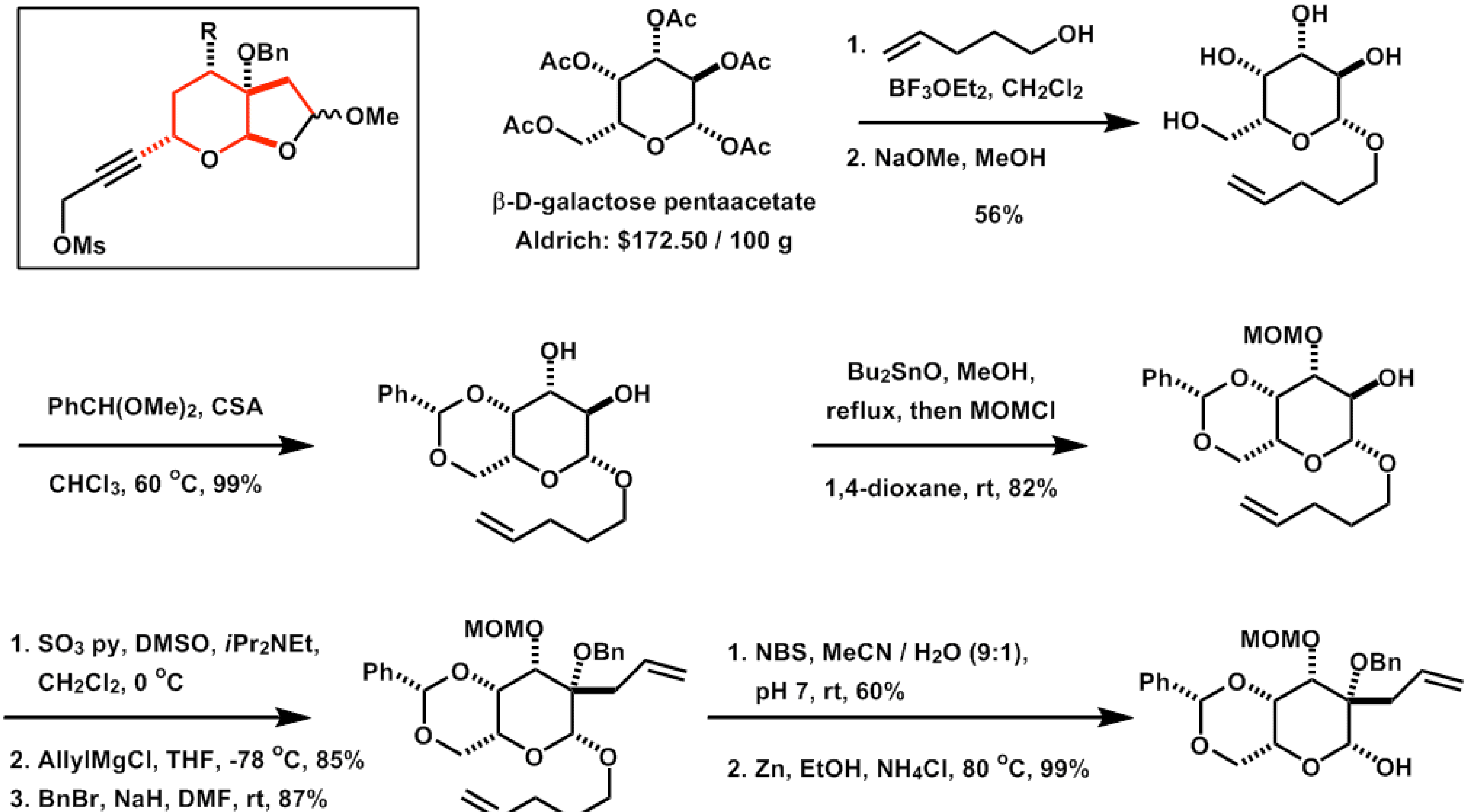
Ley, S. V.; et al. *Angew. Chem. Int. Ed.* **2007**, 7629-7632.

Ley's Revised Retrosynthetic Analysis



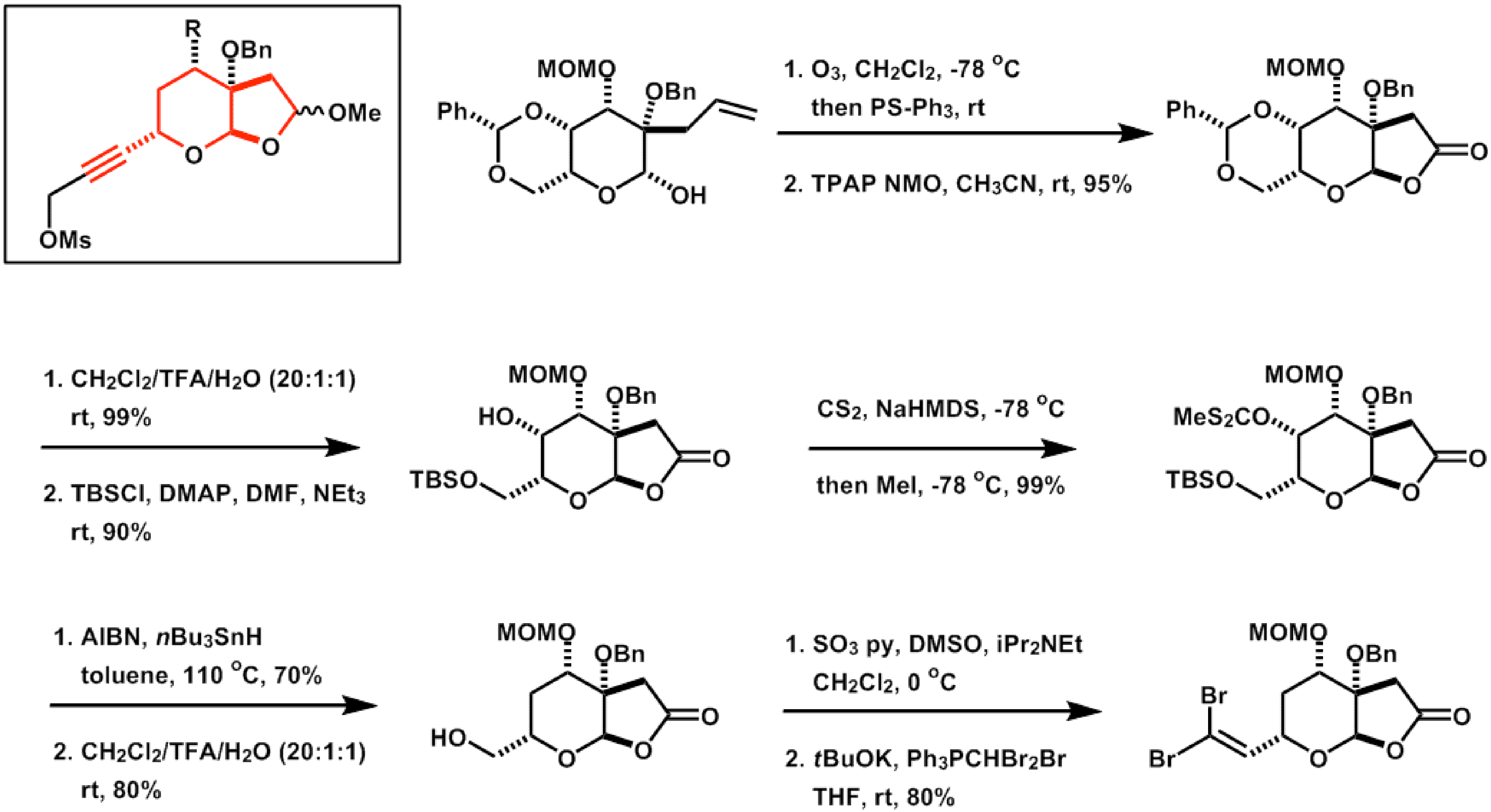
Ley, S. V.; et al. *Angew. Chem. Int. Ed.* **2007**, 7629-7632.

Beginning - Pyran Fragment



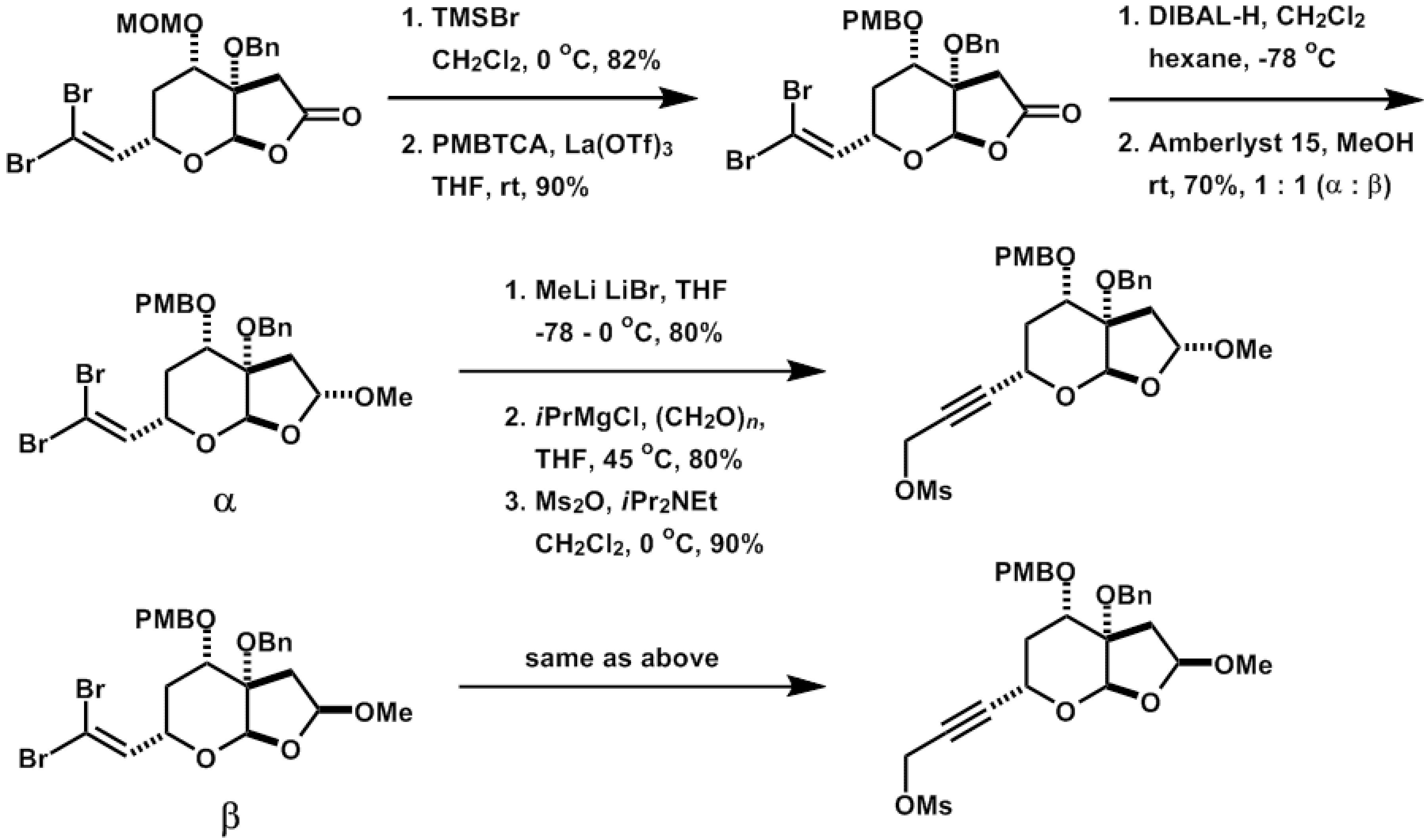
Madsen, R.; et al. *J. Chem. Soc. Perkin Trans. 1* **2001**, 543-551.
Ley, S. V.; et al. *Angew. Chem. Int. Ed.* **2007**, 7629-7632.

Formation of the Furan Ring



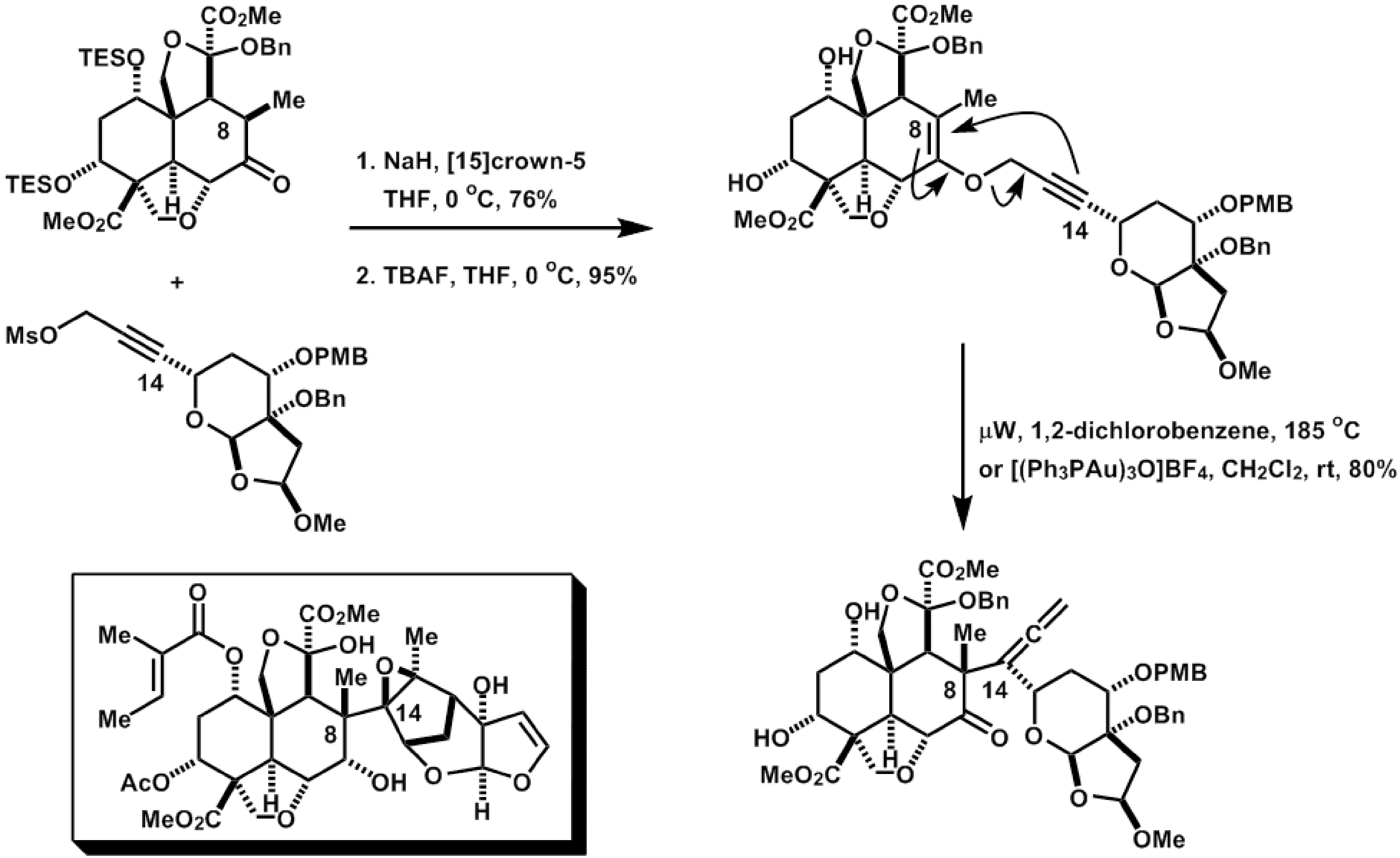
Ley, S. V.; et al. *Angew. Chem. Int. Ed.* **2007**, 7629-7632.

Synthesis of Pyran Fragment



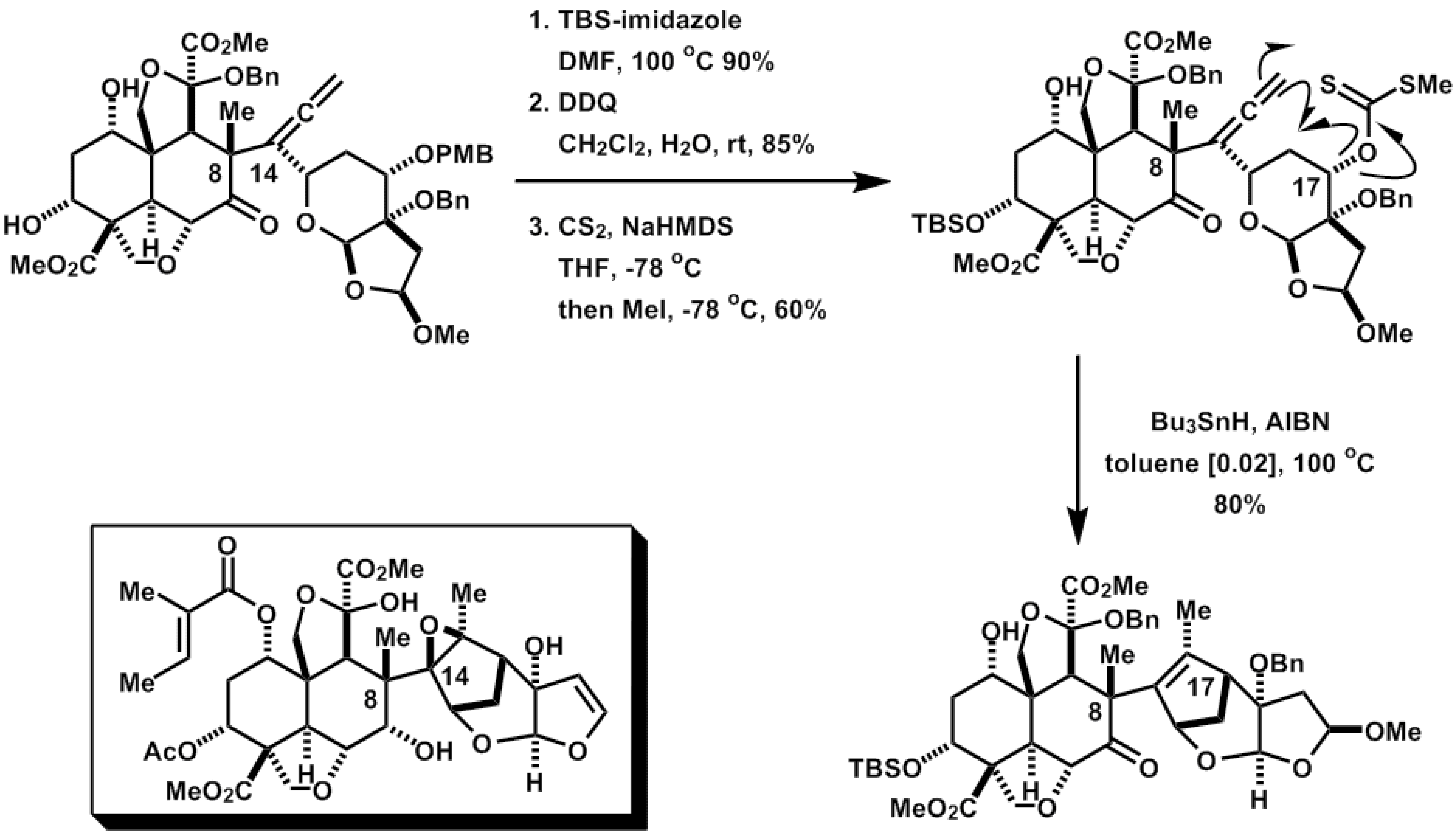
Ley, S. V.; et al. *Angew. Chem. Int. Ed.* **2007**, 7629-7632.

Coupling of Fragments and Key Intramolecular Claisen



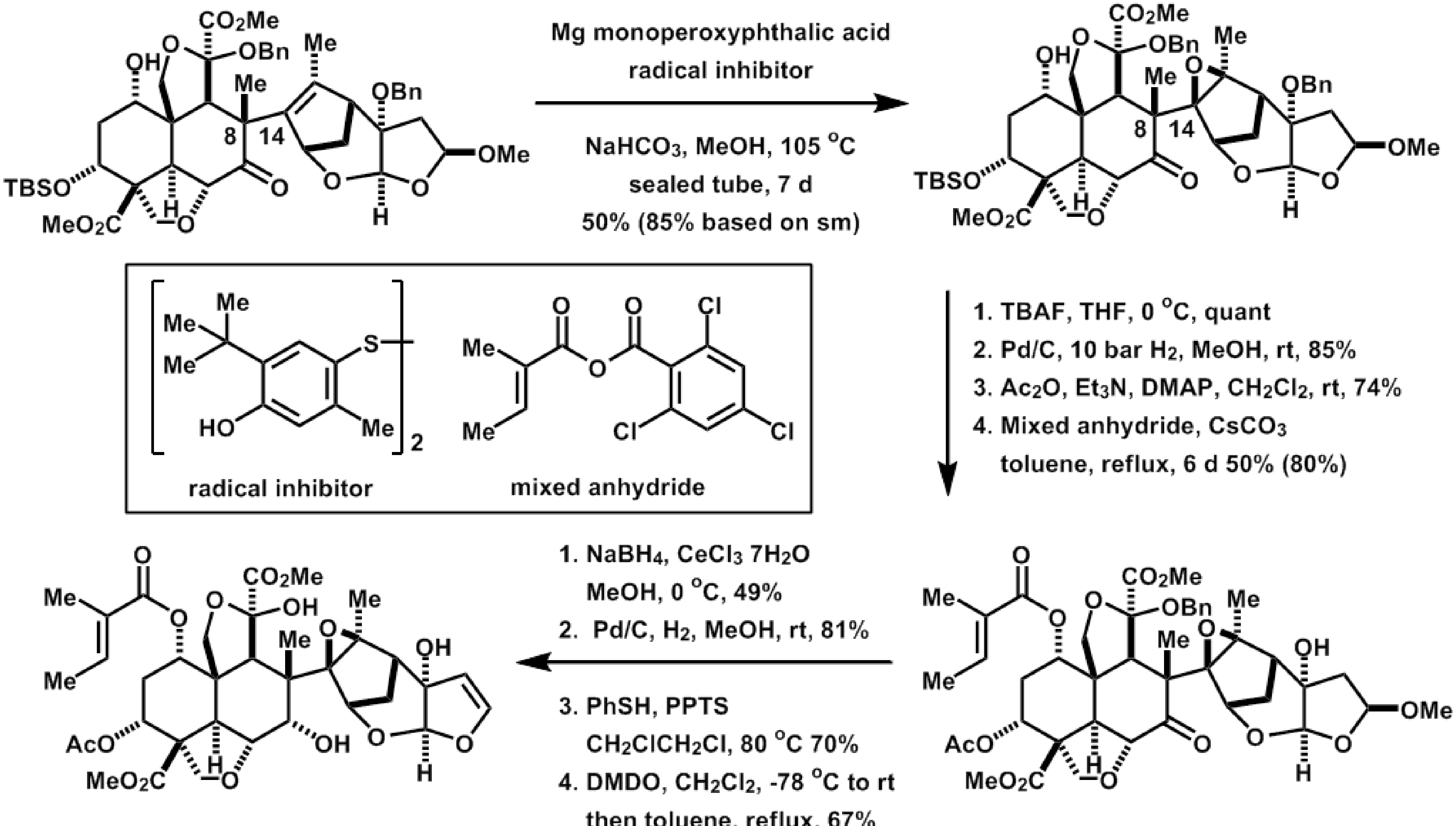
Ley, S. V.; et al. *Angew. Chem. Int. Ed.* **2007**, 7629-7632.

Radical Cyclization



Ley, S. V.; et al. *Angew. Chem. Int. Ed.* **2007**, 7629-7632.

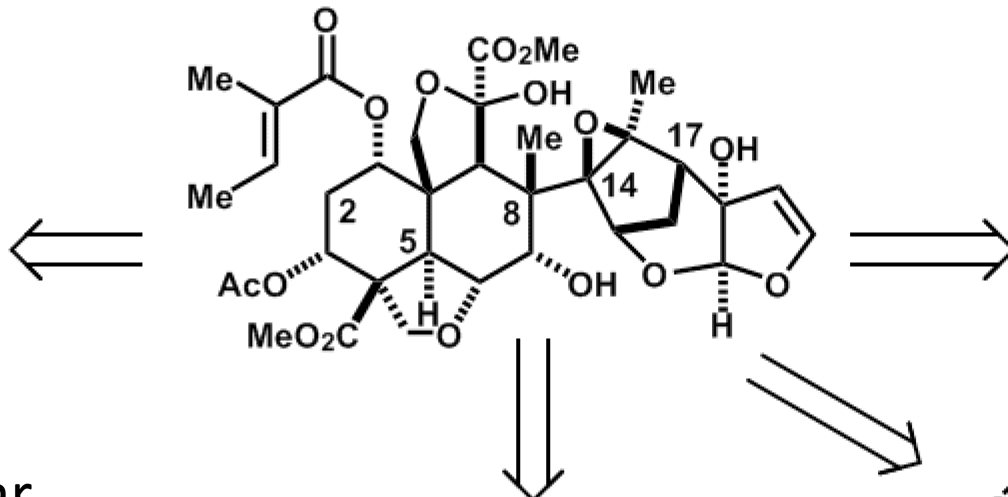
Epoxidation / End-Game

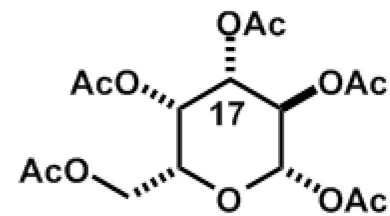


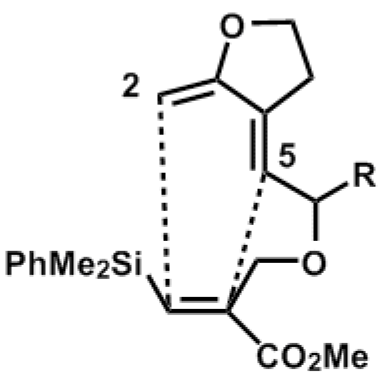
Azadirachtin

Ley, S. V.; et al. *Angew. Chem. Int. Ed.* **2007**, 7629-7632.
Ley, S. V.; et al. *Angew. Chem. Int. Ed.* **2007**, 7633-7635.

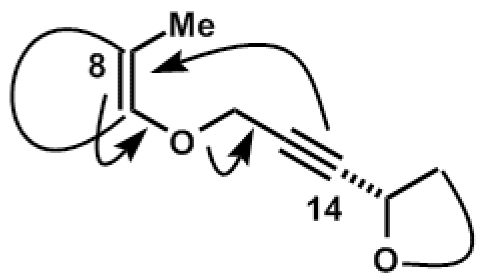
Summary of Synthesis



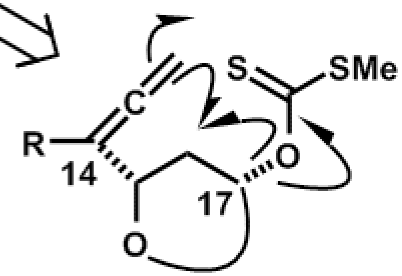




Intramolecular
Diels-Alder reaction



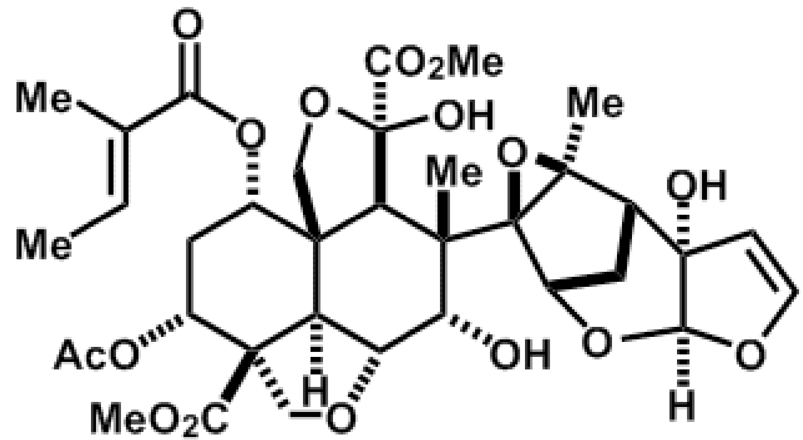
Intramolecular
Claisen rearrangement

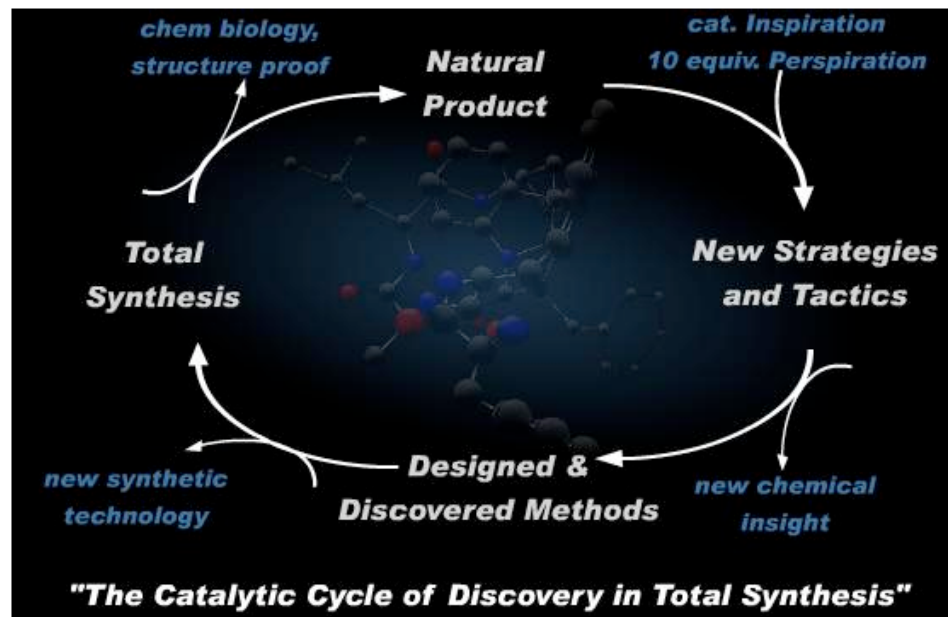


Intramolecular
radical cyclization

Summary and Comments

- 0.00015% Overall Yield
- 71 Synthetic Steps
- 48 Step longest linear sequence
- More than 35 co-workers
- Interesting Chemical Reactions:
    - Intramolecular (IM) Diels-Alder reaction
    - IM Claisen rearrangement
    - IM radical cyclization





www.scripps.edu/chem/baran/html/home.html

Was new synthetic technology reaped over the course of the 22 year synthesis?

Do elegant syntheses have aesthetic and monetary value?

Jauch, J.; et al. *Angew. Chem. Int. Ed.* **2007**, ASAP.