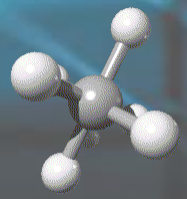
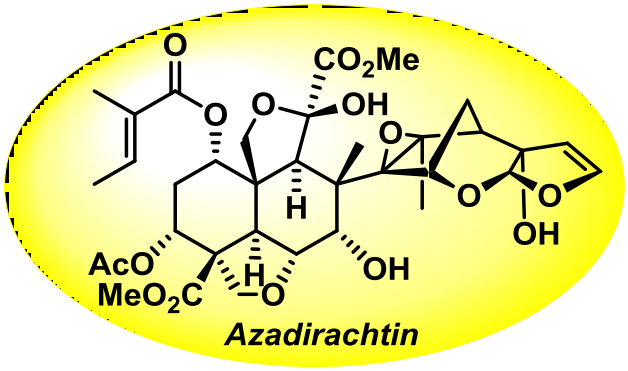
The Story of Azadirachtin



Weiwu Ren

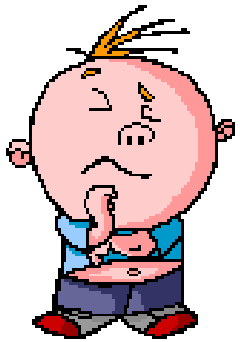
2015-12-17

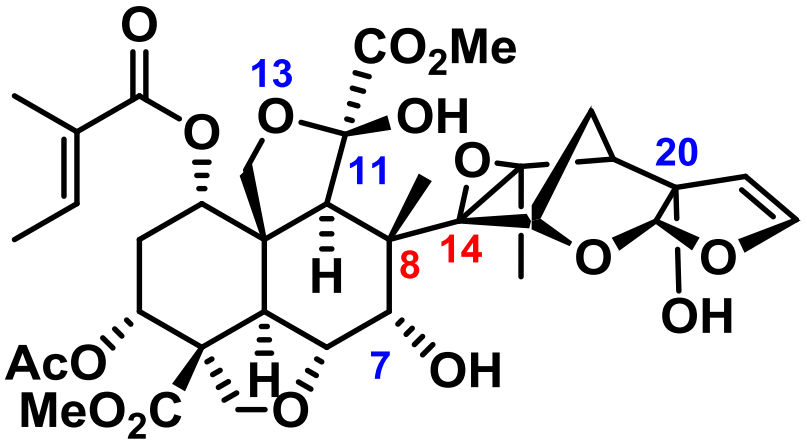
Content



Azadirachtin

Introduction





16 Contiguous stereogenic centers

7 Tetrasubstituted carbons

4 Different ester groups

2 Hydroxy groups

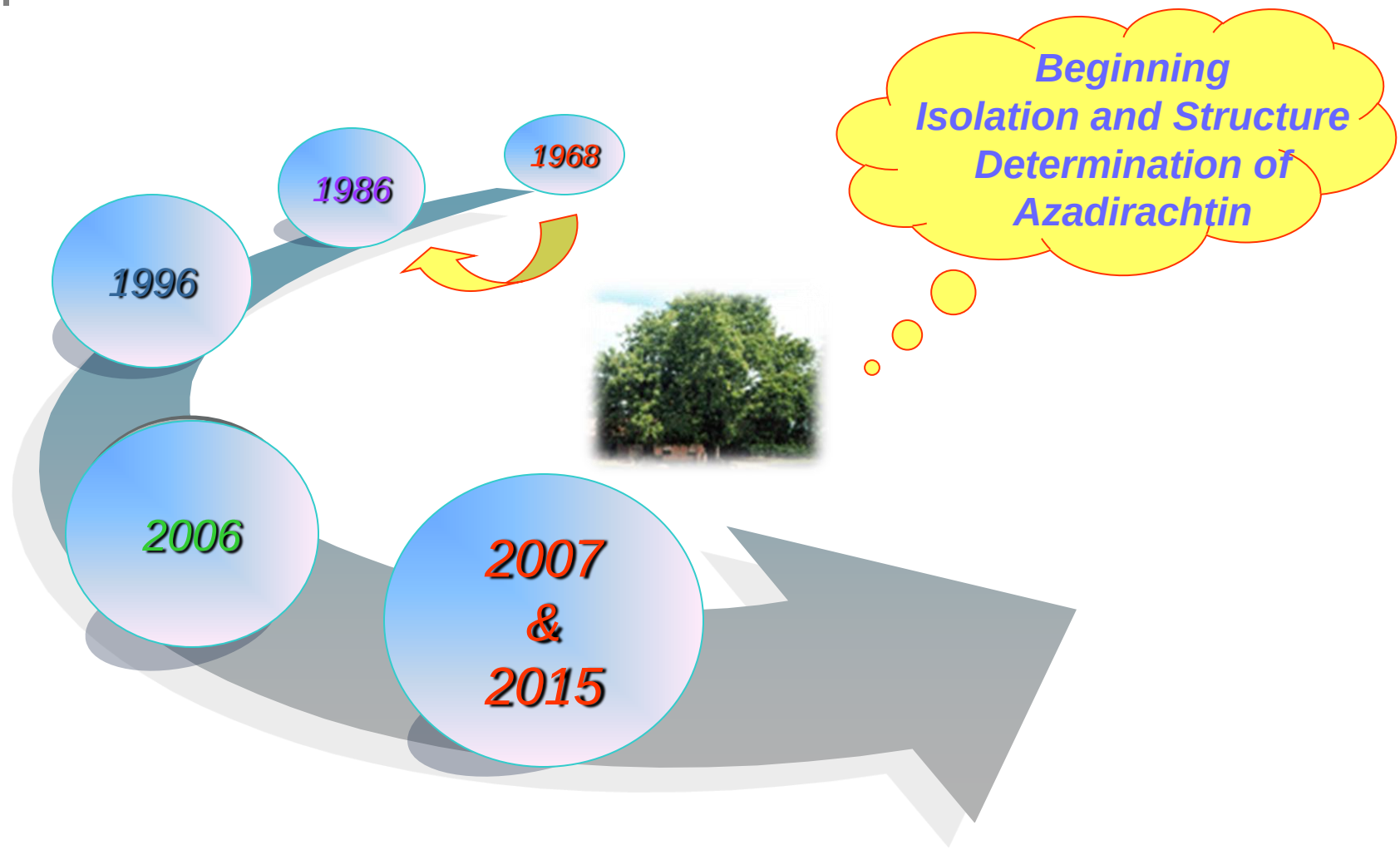
2 Intramolecular hydrogen bonds (strong: $C_{11}OH–O_{13}$ weak: $C_7OH–C_{20}OH$)

1 Acid and base-sensitive hemiacetal

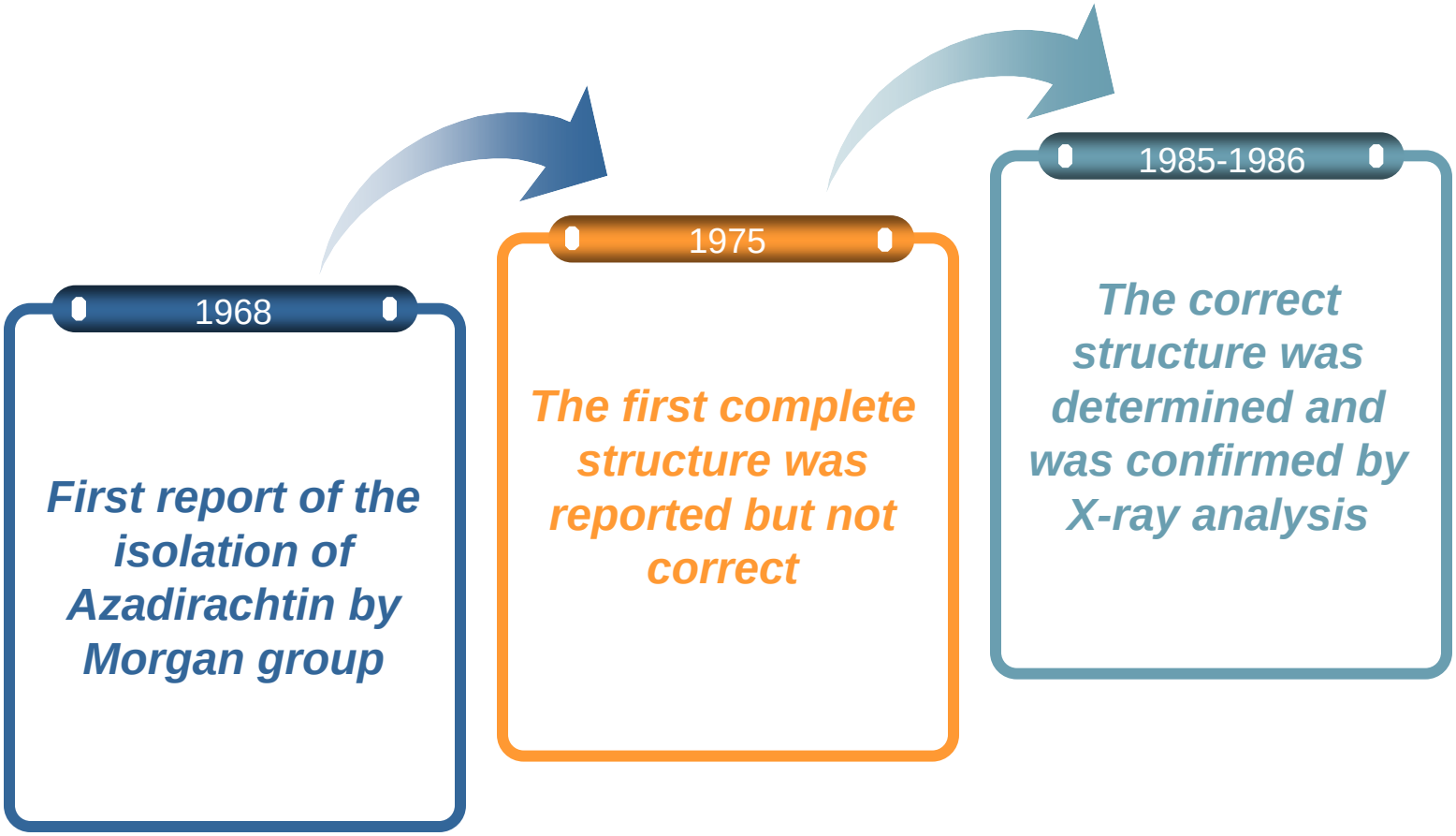
1 Strained and sterically-hindered epoxide

1 Highly congested C_8-C_{14} bond joining the decalin and hydroxyfuran acetal domains

Story Line


Beginning
Isolation and Structure
Determination of
Azadirachtin
1968
1986
1996
2006
2007
&
2015

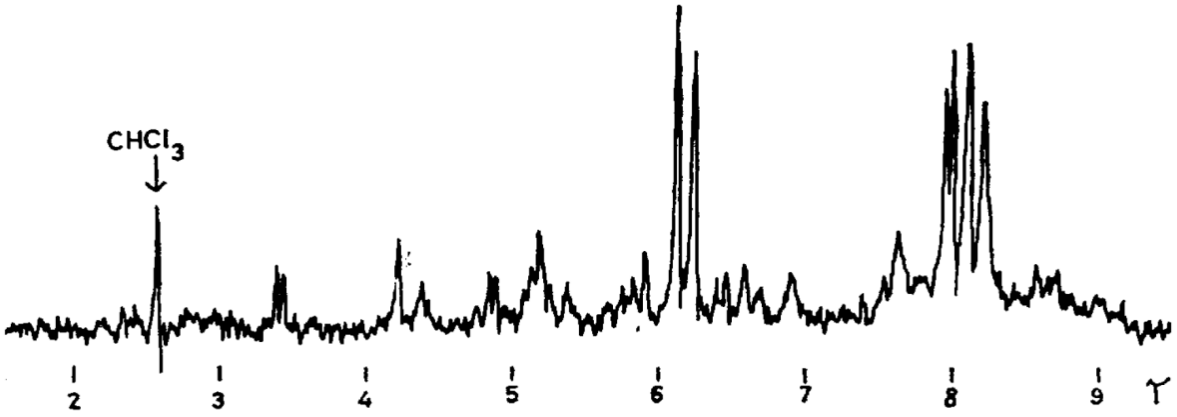
Hop Skip and Jump



First Isolation

Isolated from the seeds of Azadirachta indica (A. Juss) in India

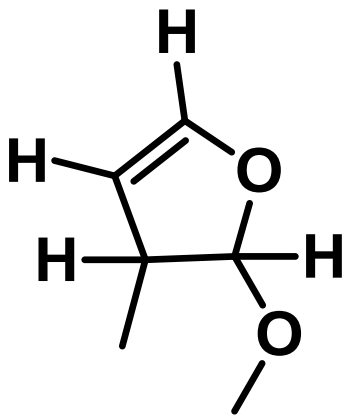
Named Azadirachtin (Azadirachta indica)

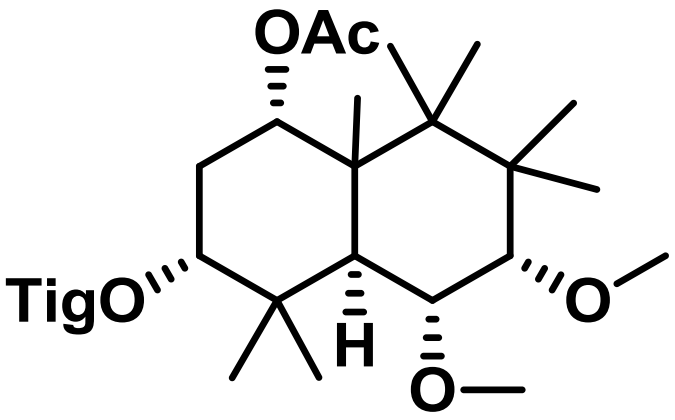


Butterworth, J. H.; Morgan, E. D. *J. Chem. Soc., Chem. Commun.* **1968**, 23.

Right Molecular Formula & Partial Structure

Molecular Formula : $C_{35}H_{44}O_{16}$ (Triterpenoid)

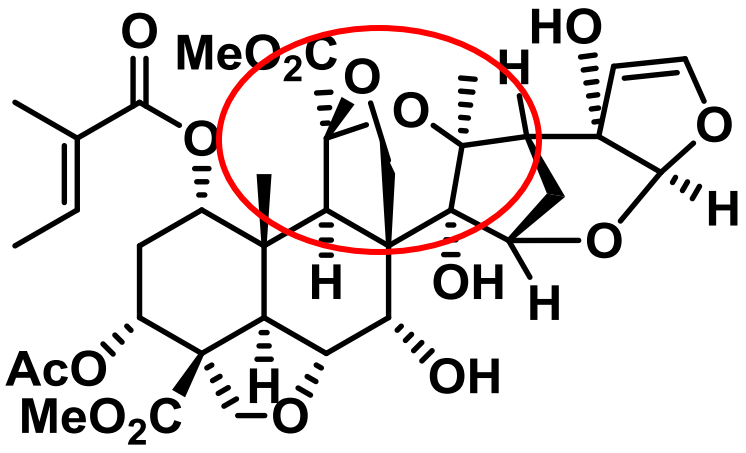


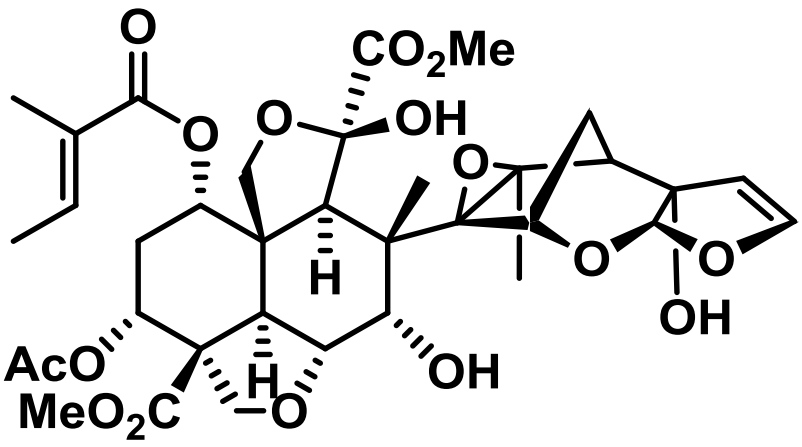


The presence of two acetate groups and the absence of either epoxide or hemiacetal functions?

Butterworth, J. H.; Morgan, E. D. *J. Chem.* Soc., *Perkin Trans. I.* **1972**, 2445.

The First Complete Structure



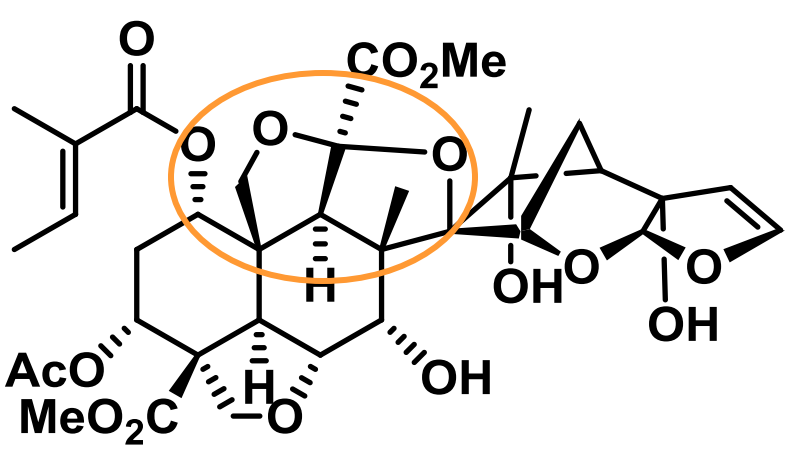


Nakanishi's Azadirachtin ***Correct Structure***

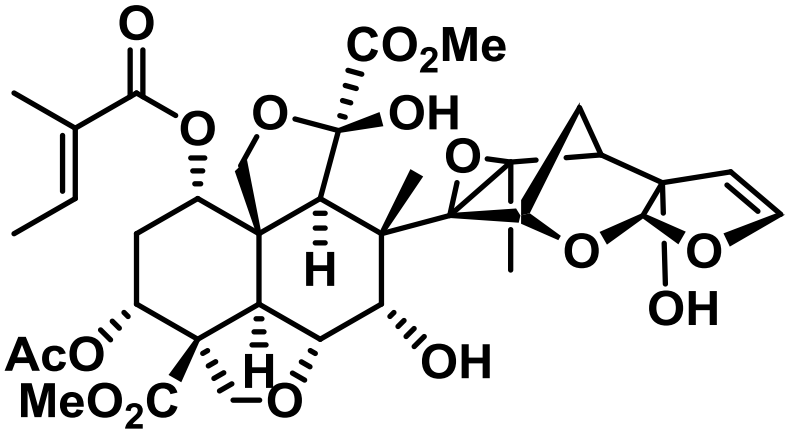
Based on: PRFT/CWD ^{13}C NMR
Hypothetical Relationship with Known Terpenoids

Zanno, P. R.; Muira, I.; Nakanishi, K. *J. Am. Chem. Soc.* **1975**, *97*, 1975.

Ley's Modification



Ley's Modification

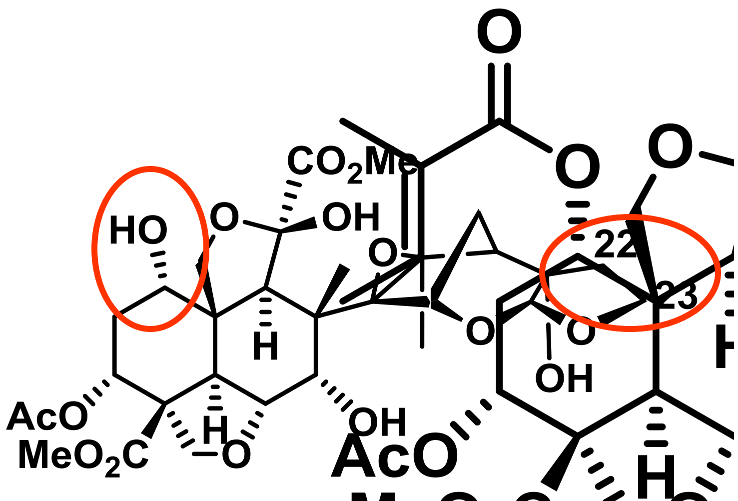


Correct Structure

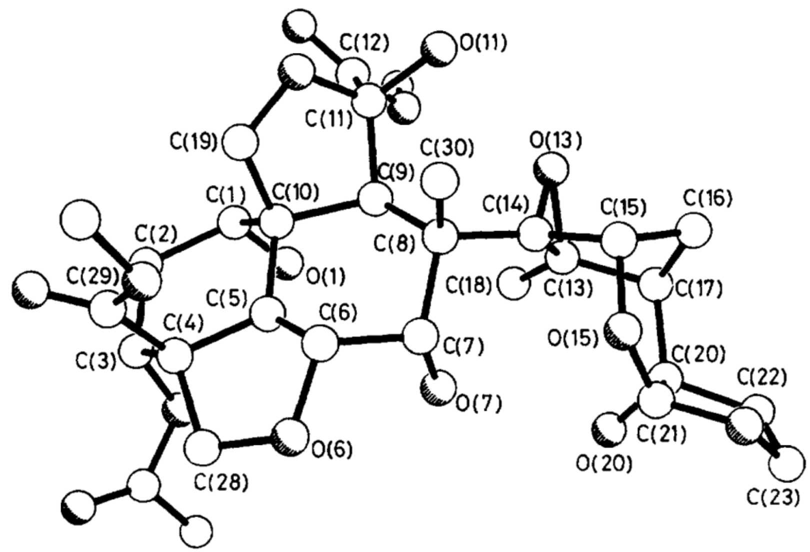
Based on: 1D NOE & 2D NOESY

Bilton, J. N.; Broughton, H. B.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1985**, 986.

Finally, the Correct Structure

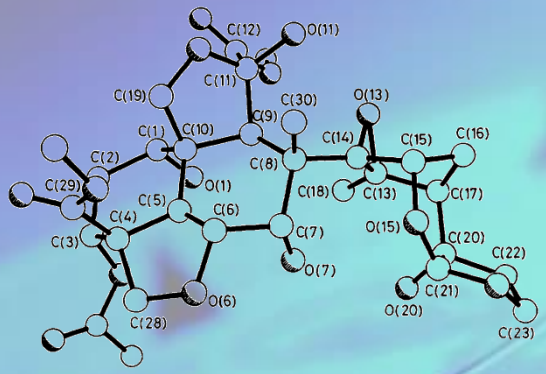


22,23-dihydrodetigloylazadirachtin



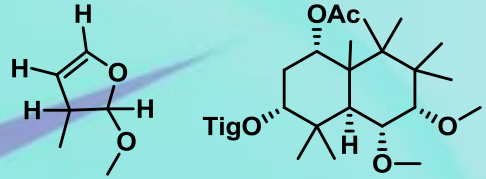
Azadirachtin

Kraus, W.; Bokel, M.; Klenk, A.; Pöhl, H. *Tetrahedron Lett.* **1985**, 26, 6435.
Broughton, H. B.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1986**, 46.

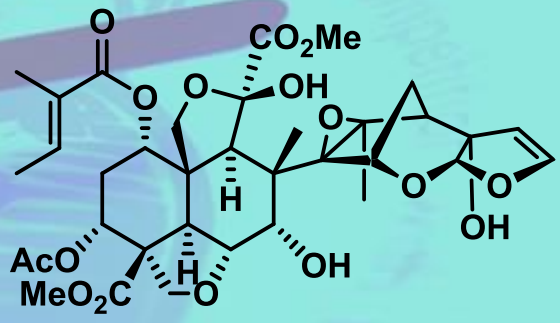


Confirmed by X-ray analysis(1986)

First isolated by Morgan(1968)

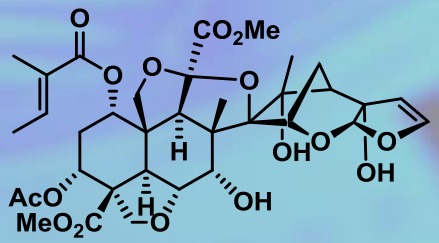


Partial Structure(1972)

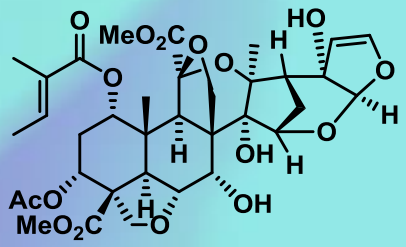


Azadirachtin

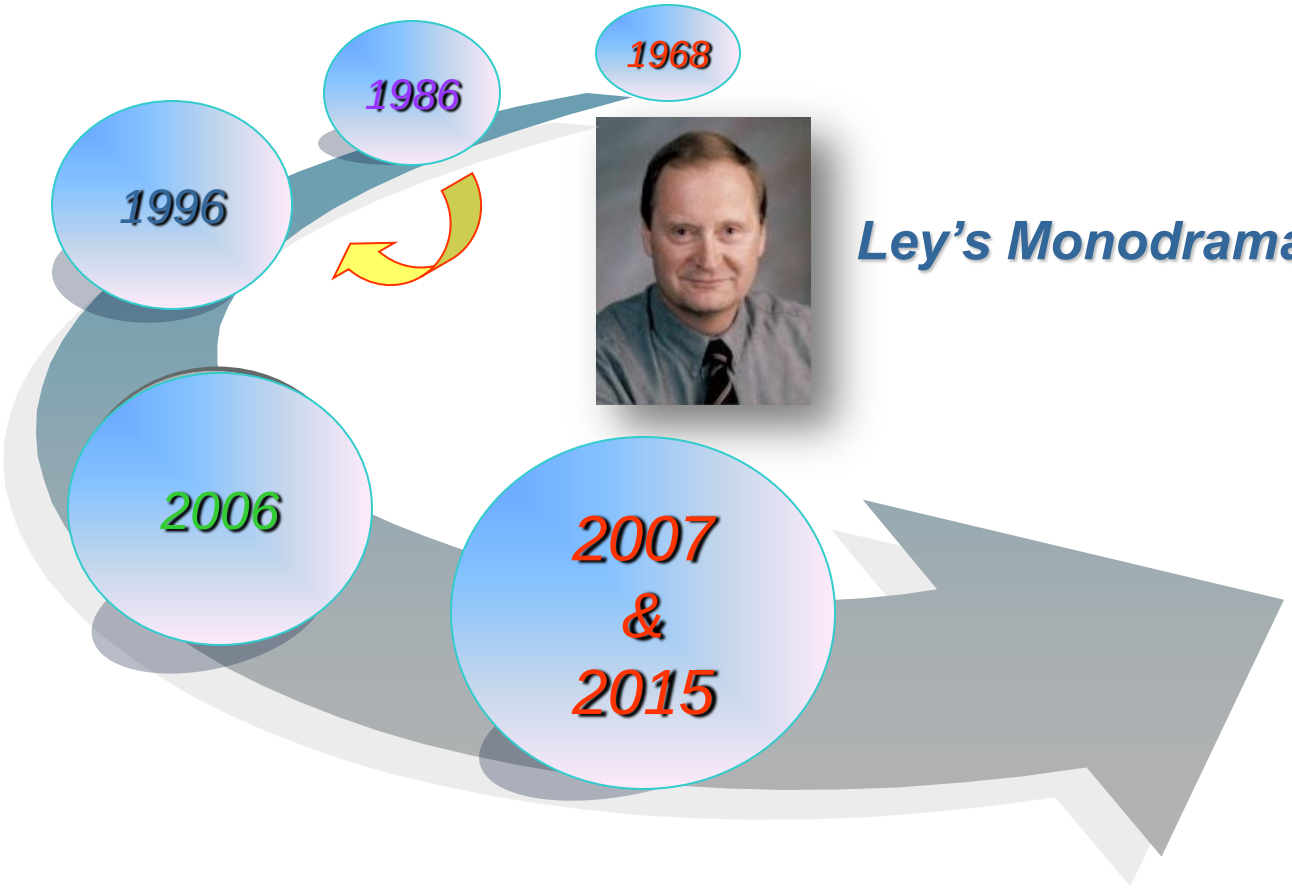
Ley's Modification (1985)



The first complete structure (1975)

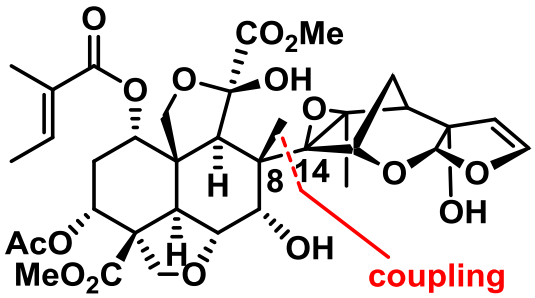


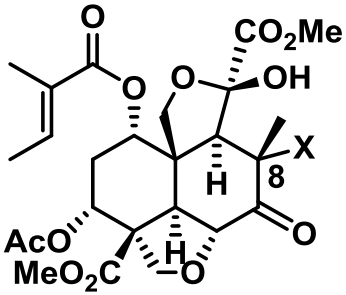
Story Line



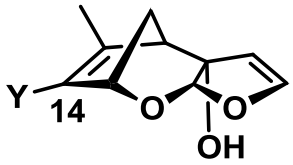
Ley's Monodrama

Ley's Idea





Left half: Decalin



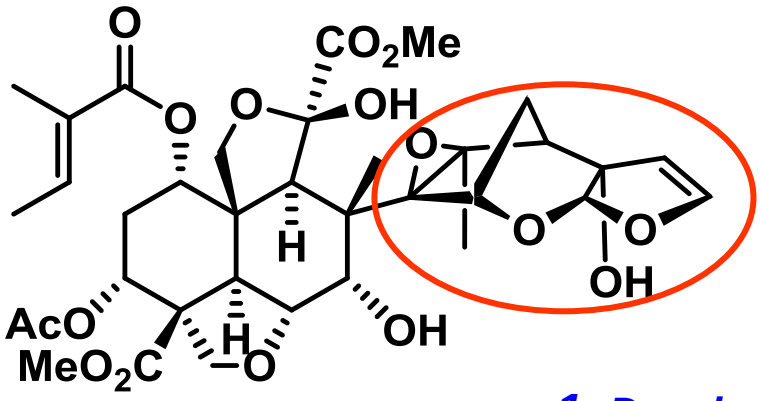
Right half: Hydroxyfuran acetal

We recoganize this coupling involves the formation of a difficult bond, but therein lies the challenge.

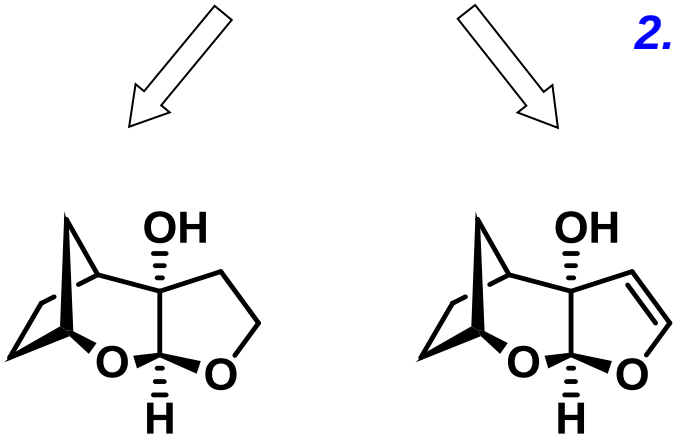
---- S. V. Ley

Ley, S. V. *Pure Appl. Chem.* **1994**, *66*, 2099.

First Report on the Synthesis of Azadirachtin

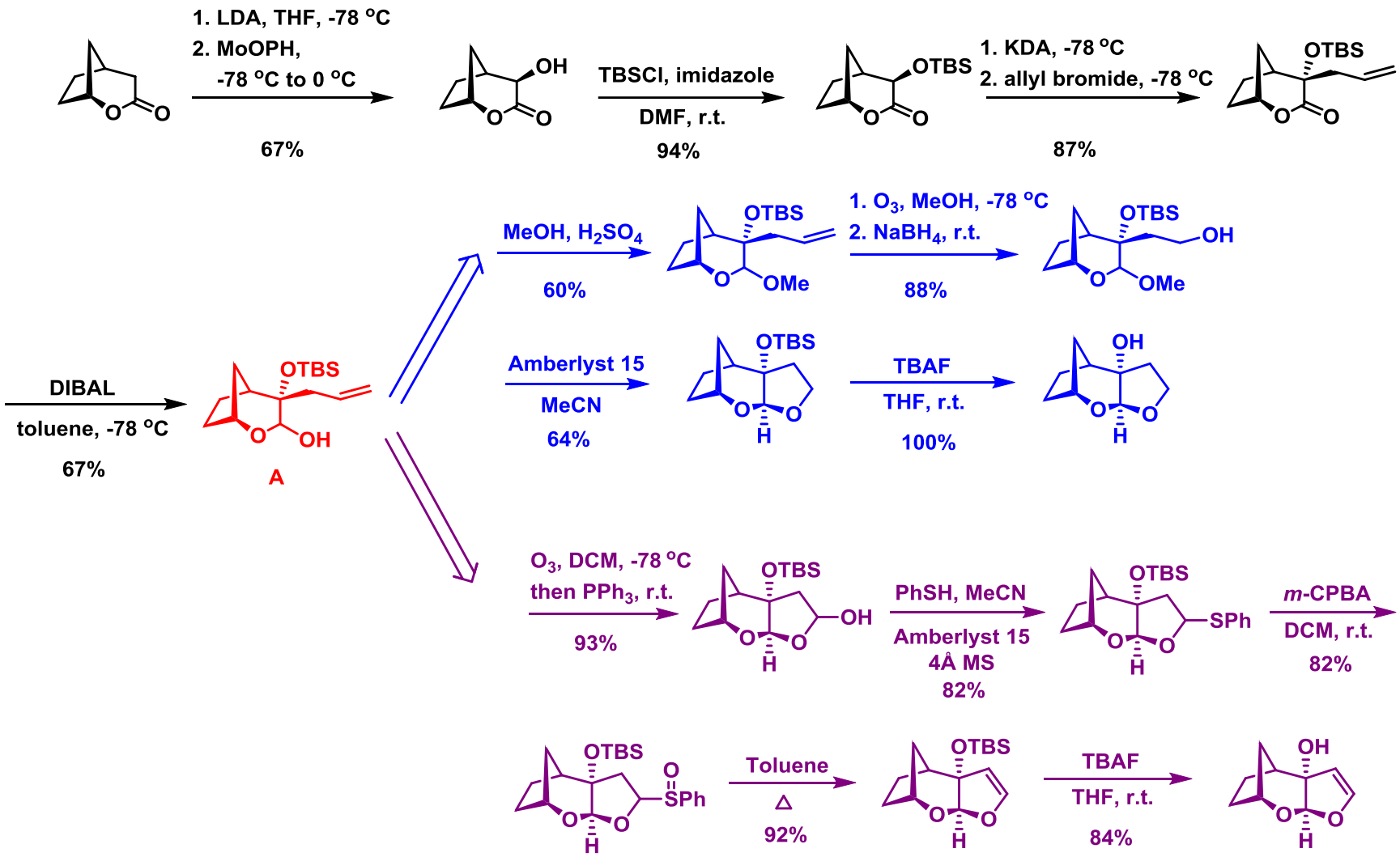


1. *Develop a flexible approach for the total synthesis*
2. *Study the functional groups responsible for bioactivity (potential active center)*



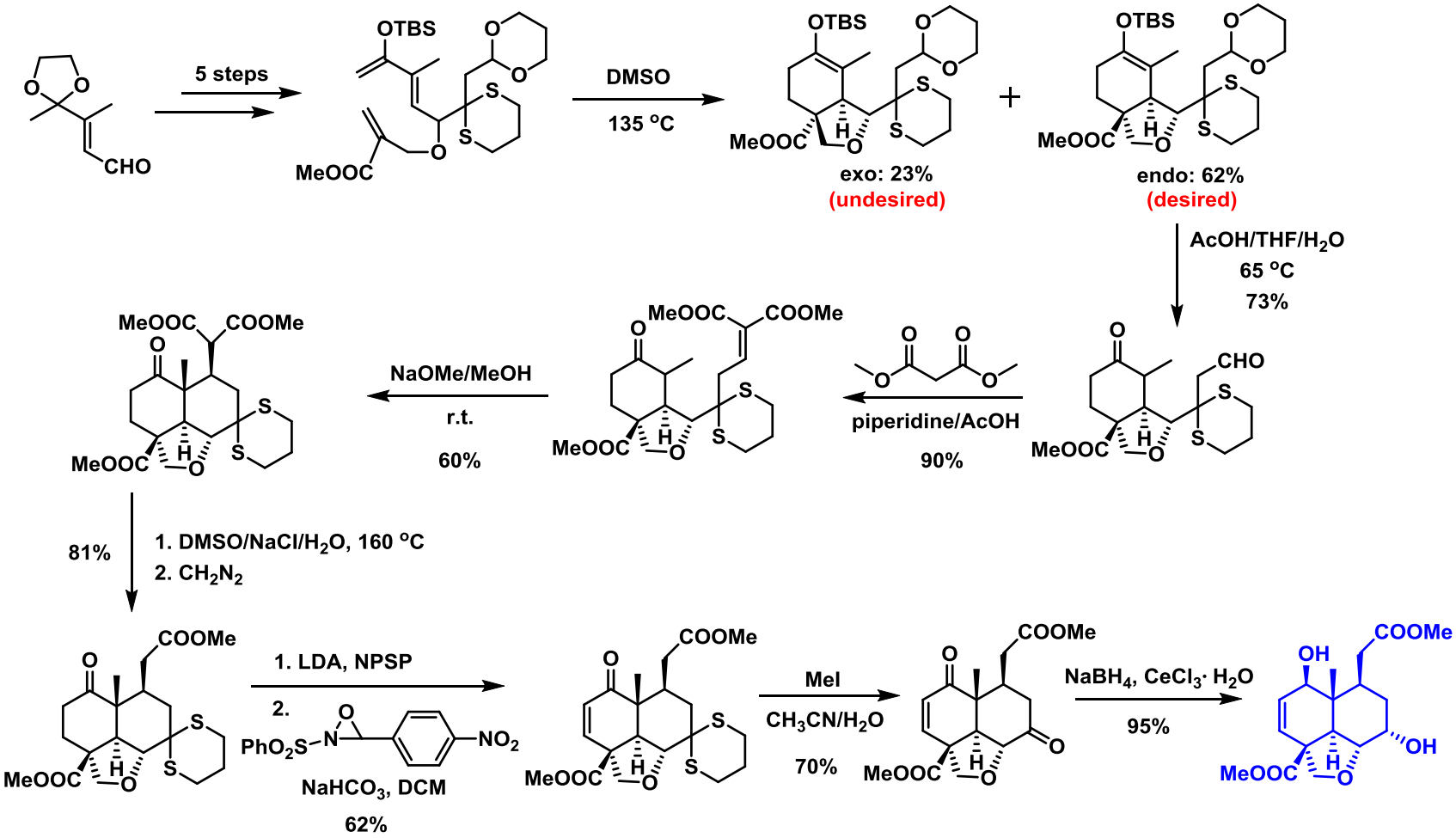
Ley, S. V.; Santafianosa, D. *Tetrahedron Lett*. **1987**, *28,* 221.

Simple but Important



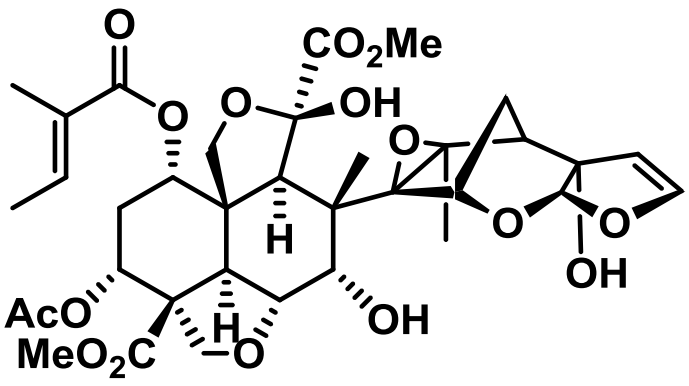
Ley, S. V.; Santafianosa, D.*Tetrahedron Lett*. **1987**, *28,* 221.

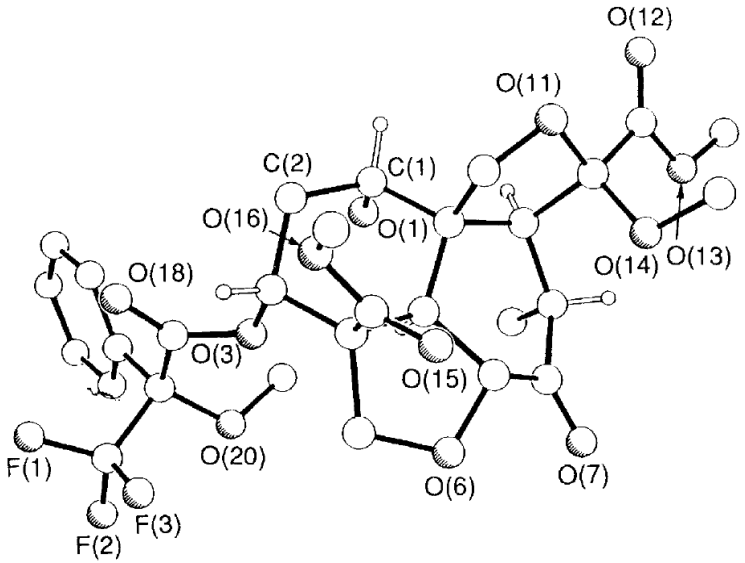
The Left Part



Ley, S. V.; Somovilla, A. A. *Tetrahedron Lett*. **1988**, *29,* 1853.

Absolute Configuration



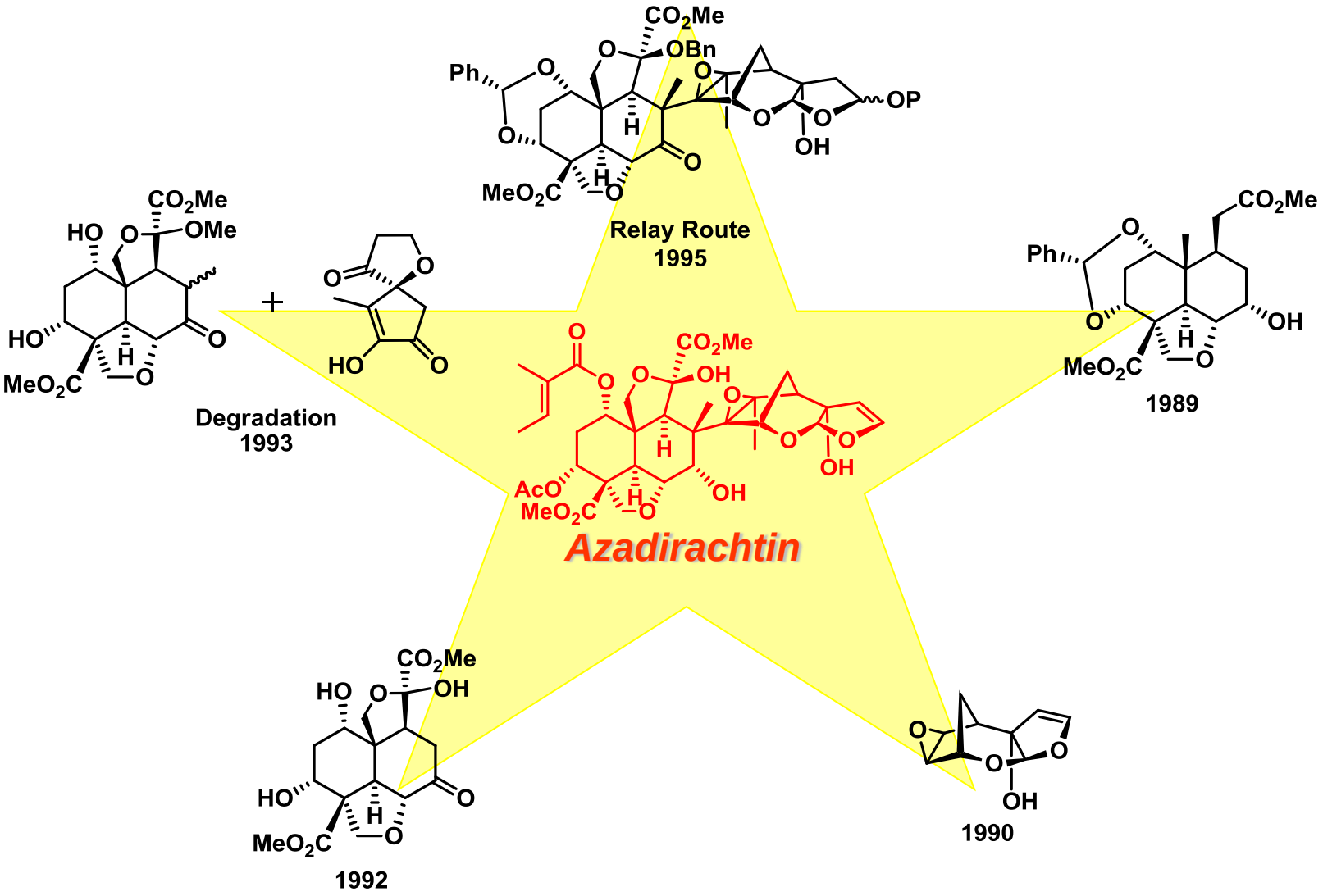


Method:

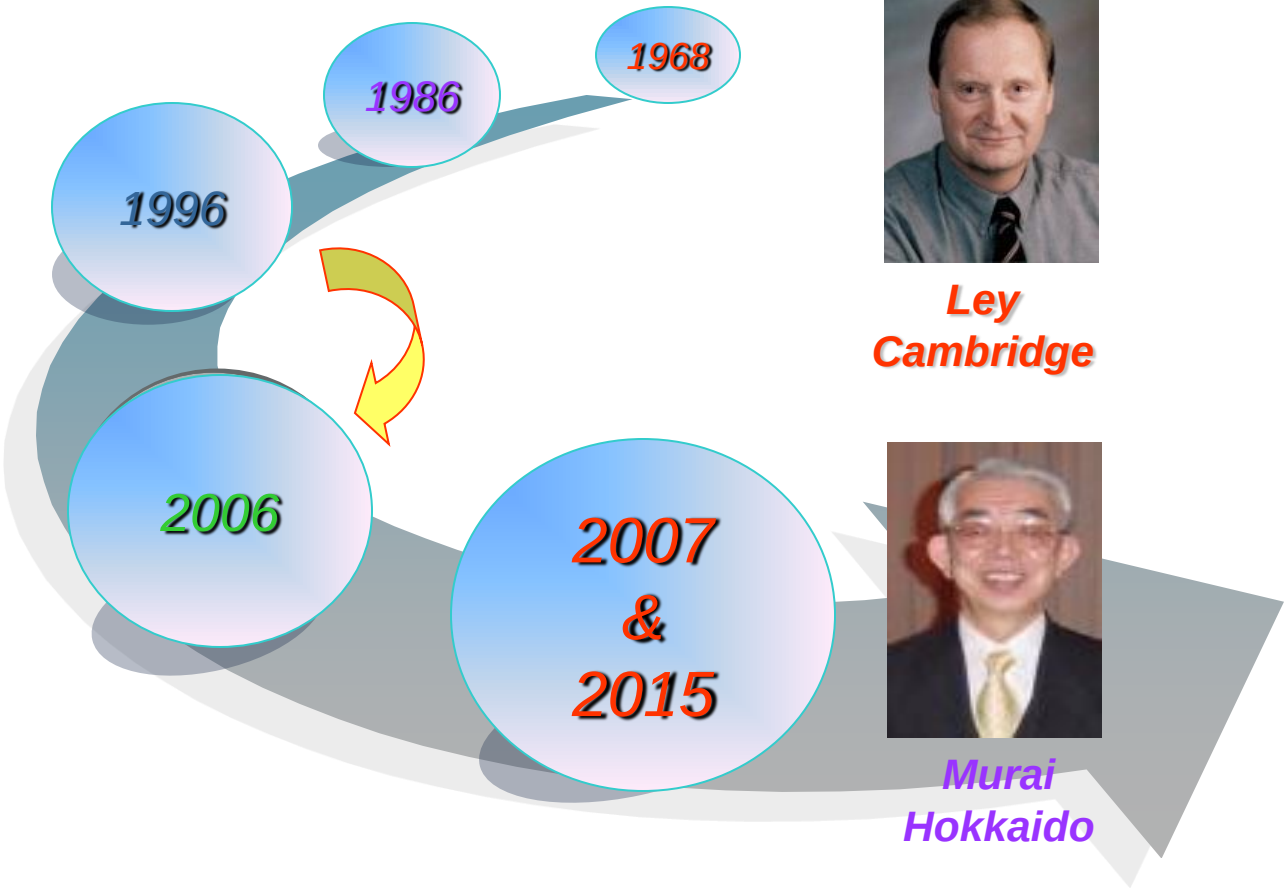
Modified Mosher methodology using high field FT NMR techniques

Ley, S. V.; Lovell, H. *J. Chem. Soc., Chem. Commun.* **1992**, 1304.

Ley's Other Work



Story Line



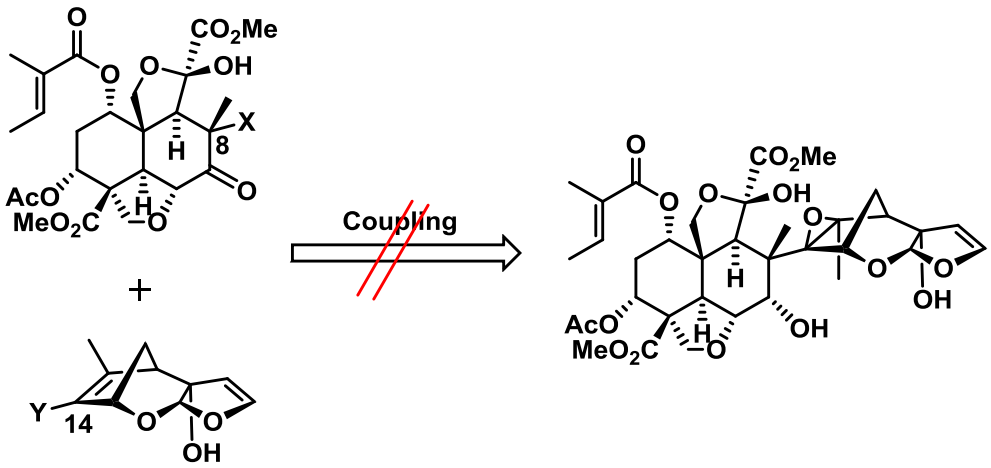
Ley
Cambridge

Nicolaou
Scripps

Murai
Hokkaido

Watanabe
Tokyo

Ways to Go



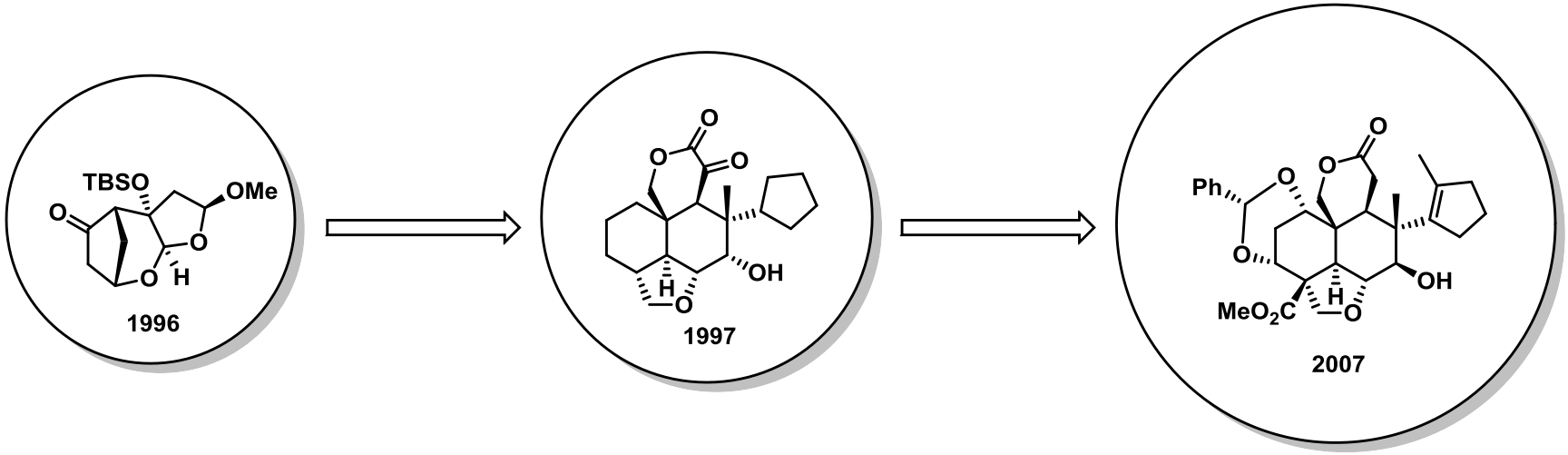
introduce this bond in an earlier step of the synthesis!

Prof. Watanabe

connect the two parts through other functional groups and then close the desired bond intramolecularly!

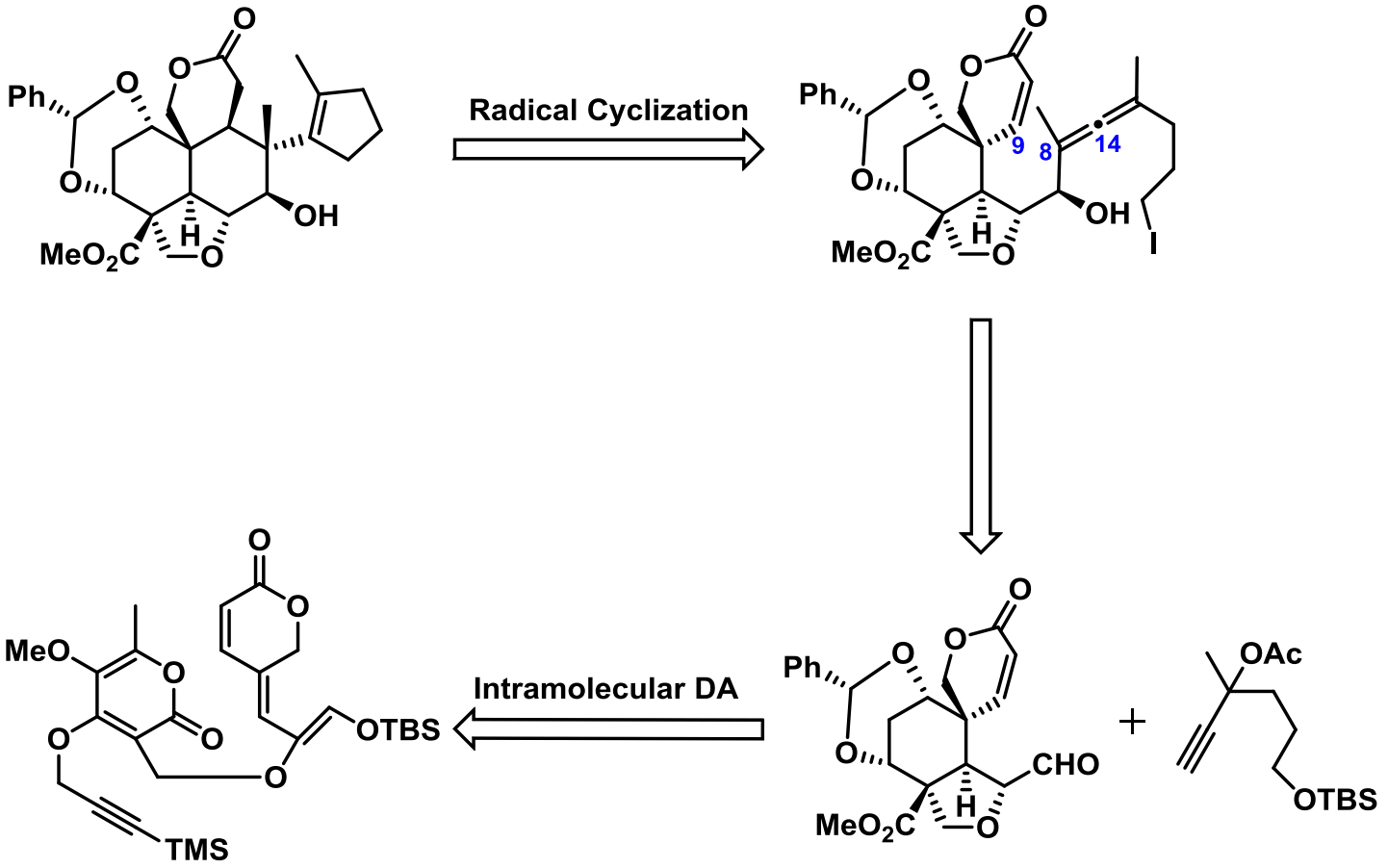
Prof. Ley & Prof. Nicolaou & Prof. Murai

First Participant — Watanabe



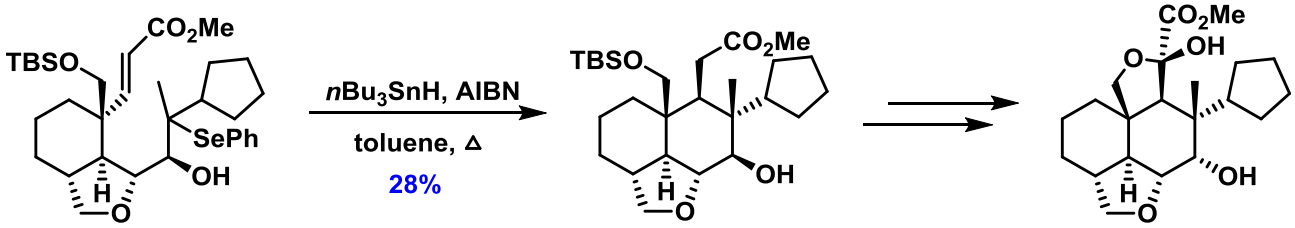
1) Watanabe, H.; Watanabe, T.; Mori, K.*Tetrahedron* **1996**, *52*, 13939;
2) Watanabe, H.; Watanabe, T.; Mori, K.; Kitahara, T. *Tetrahedron Lett*. **1997**, *38*, 4429;
3) Watanabe, H.; Mori, N.; Itoh, D.; Kitahara, T.; Mori, K. *Angew. Chem., Int. Ed*. **2007**, *46*, 1512.

Watanabe's Model

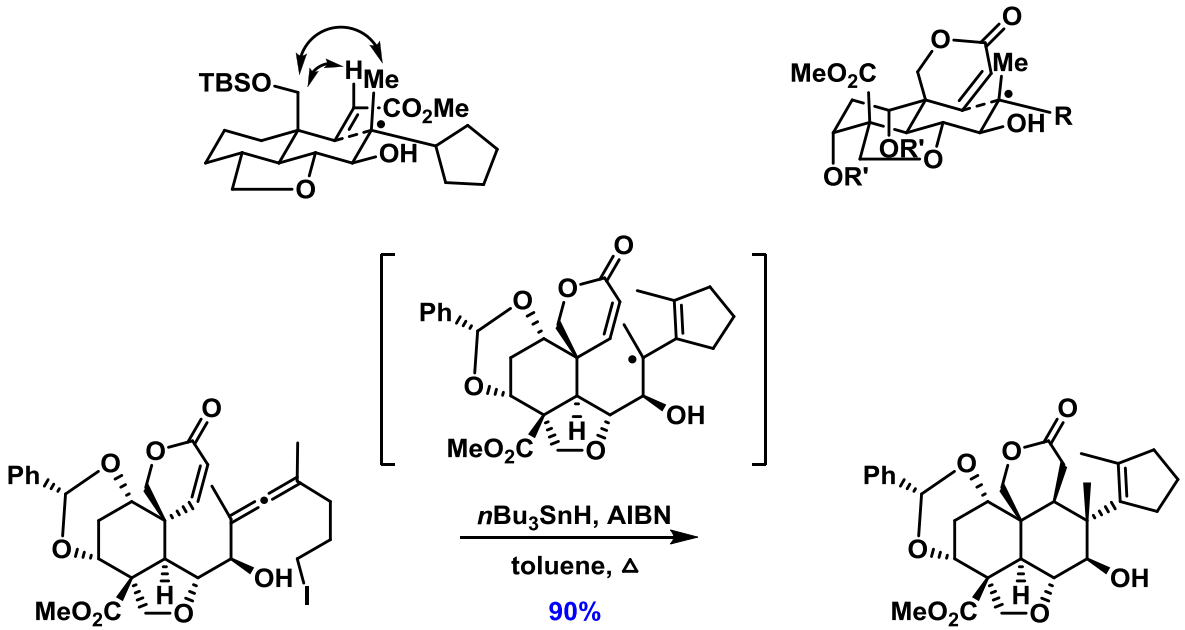


Watanabe, H.; Mori, N.; Itoh, D.; Kitahara, T.; Mori, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1512.

Tandem Radical Cyclization

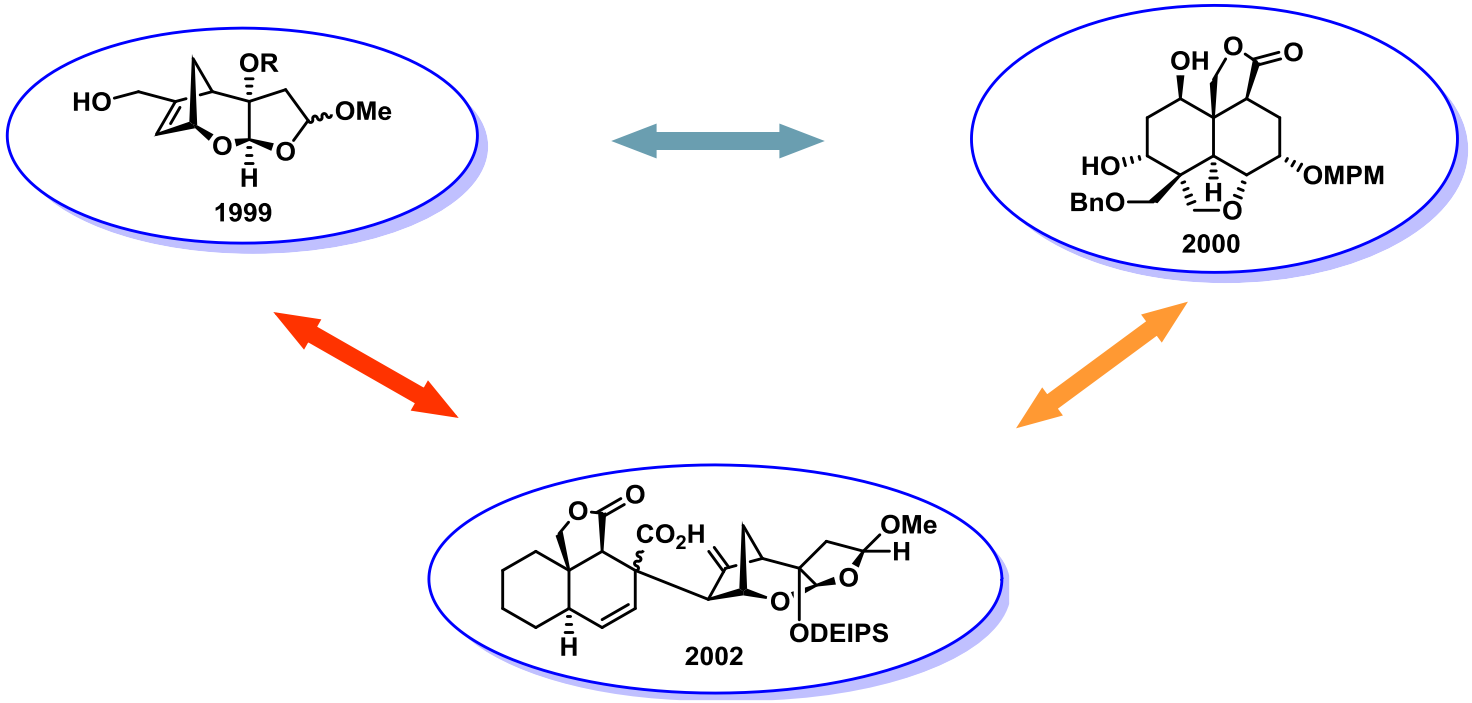


Watanabe, H.; Watanabe, T.; Mori, K.; Kitahara, T. *Tetrahedron Lett.* **1997**, *38*, 4429.



Watanabe, H.; Mori, N.; Itoh, D.; Kitahara, T.; Mori, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1512.

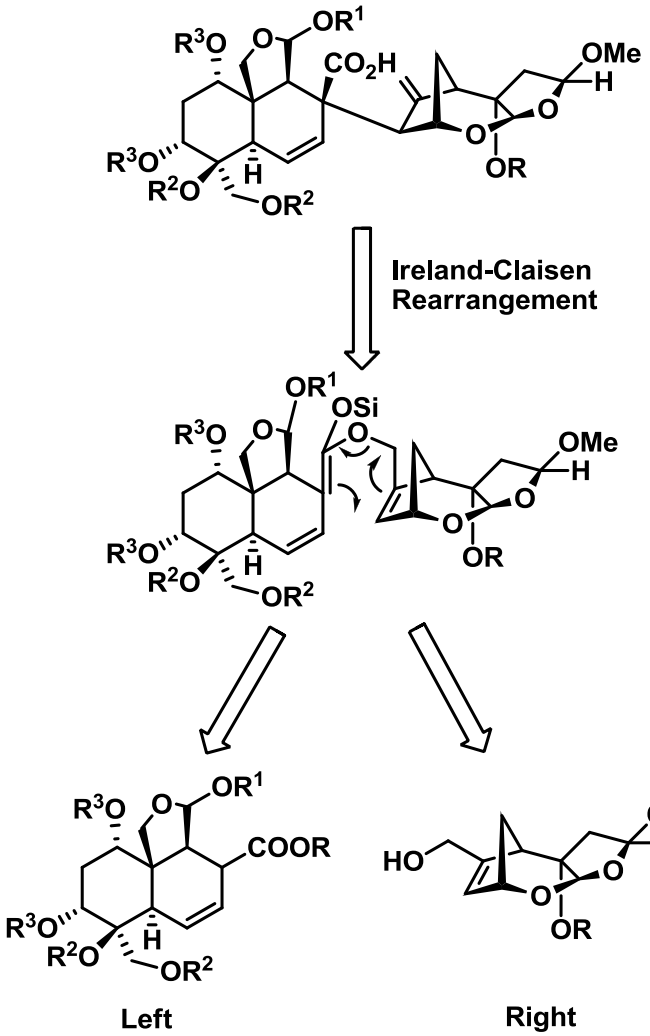
Murai's Strategy

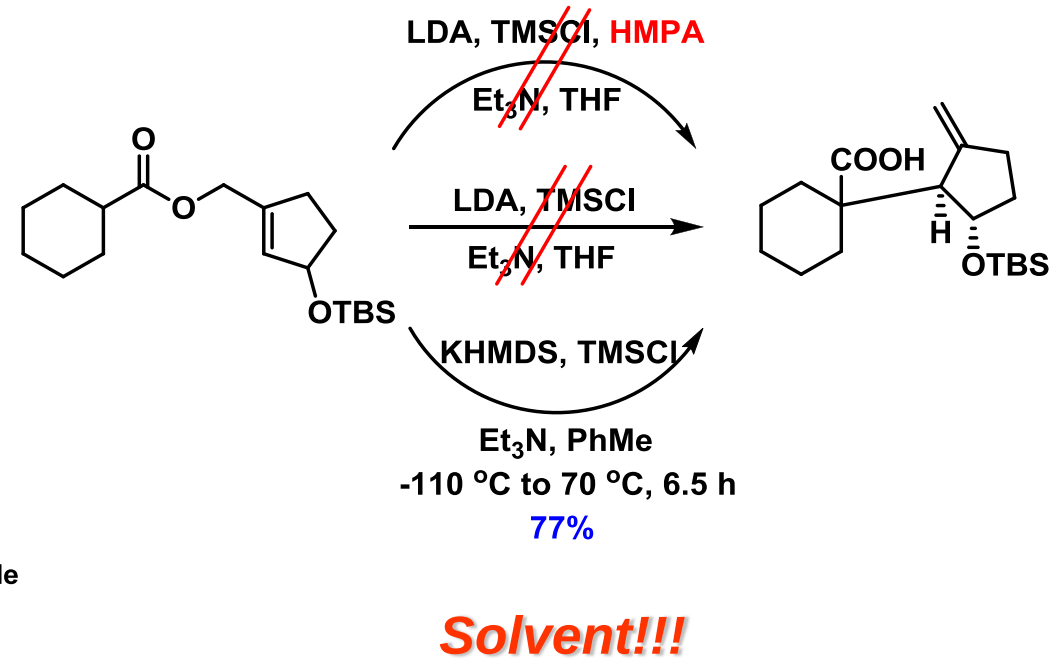


Ireland–Claisen Rearrangement

1) Ishihara, J.; Fukuzaki, T.; Murai, A. *Tetrahedron Lett*. **1999**, *40*, 1907;
2) Yamamoto, Y.; Ishihara, J.; Kanoh, N.; Murai, A. *Synthesis* **2000**, 1894;
3) Fukuzaki, T.; Kobayashi, S.; Ishihara, J.; Kanoh, N.; Murai, A. *Org. Lett*. **2002**, *4*, 2877.

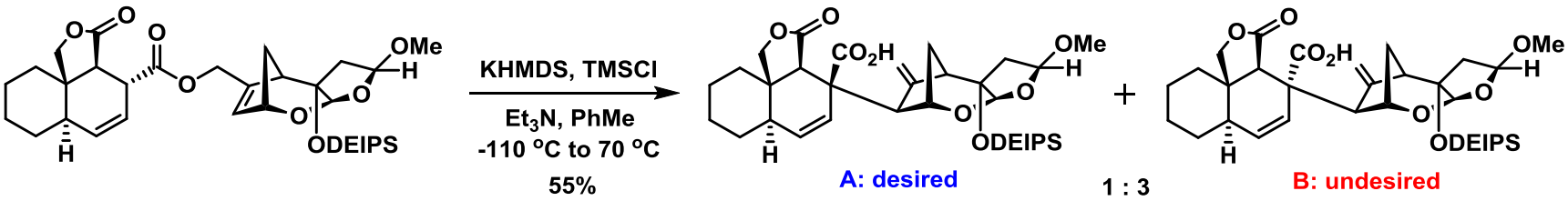
Ireland-Claisen Rearrangement



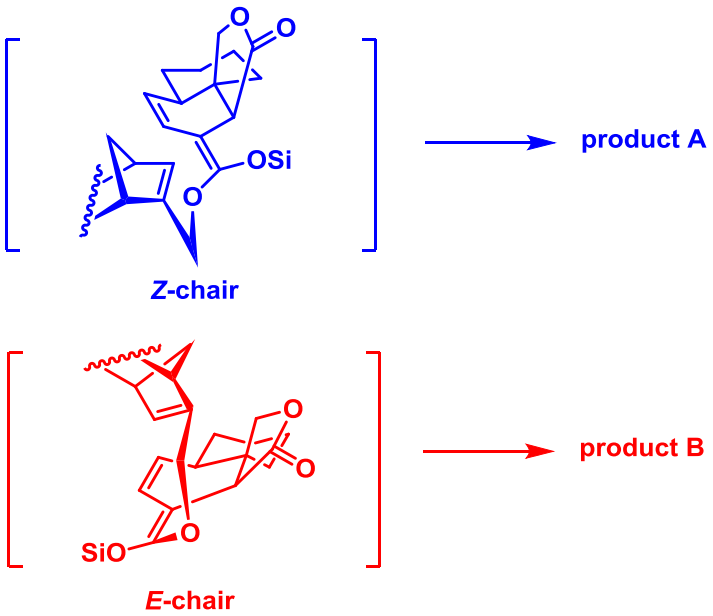


Solvent!!!

Diastereoselectivity

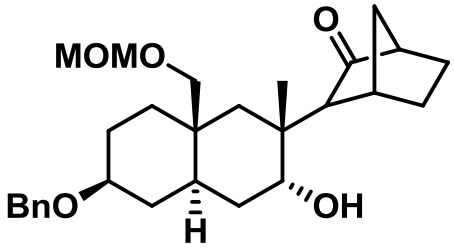


entry	reagent	base	solvent	A:B	yield (%)
1	Me_3SiCl	KHMDS	PhMe	1:3.0	55
2	Me_3SiCl	KHMDS	THF	1:1.6	61
3	Me_3SiCl	KHMDS	THF−HMPA	1:1.4	56
4	Me_2SiCl_2	KHMDS	PhMe	1:1.6	41
5	Me_2SiCl_2	LHMDS	THF	1.7:1	81
6[a]	Me_2SiCl_2	LHMDS	THF	1.6:1	68
7	Me_2SiCl_2	LHMDS	PhMe	4.0:1	87
8	$MeSiCl_3$	LHMDS	PhMe	2.1:1	94
9	Me_3SiOTf	KHMDS	THF	dec	
10	$Me_2Si(OMe)_2$	KHMDS	THF	N.R.	

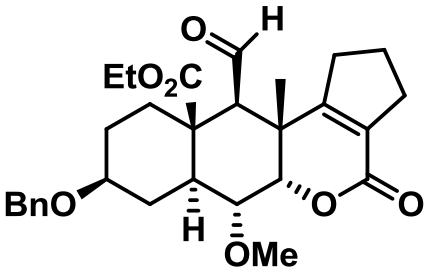


Fukuzaki, T.; Kobayashi, S.; Ishihara, J.; Kanoh, N.; Murai, A. *Org. Lett*. **2002**, *4*, 2877.

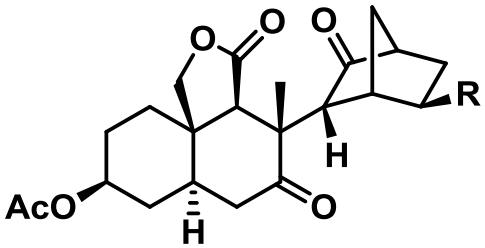
Nicolaou's Model Study



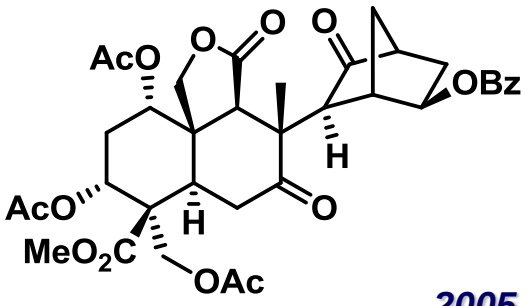
2002
Radical



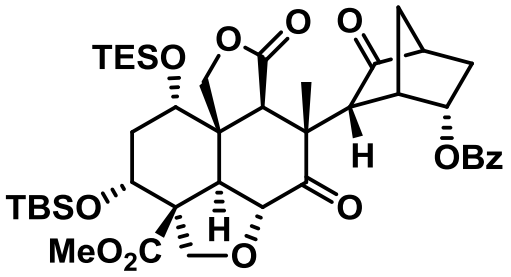
2002
Organometallic



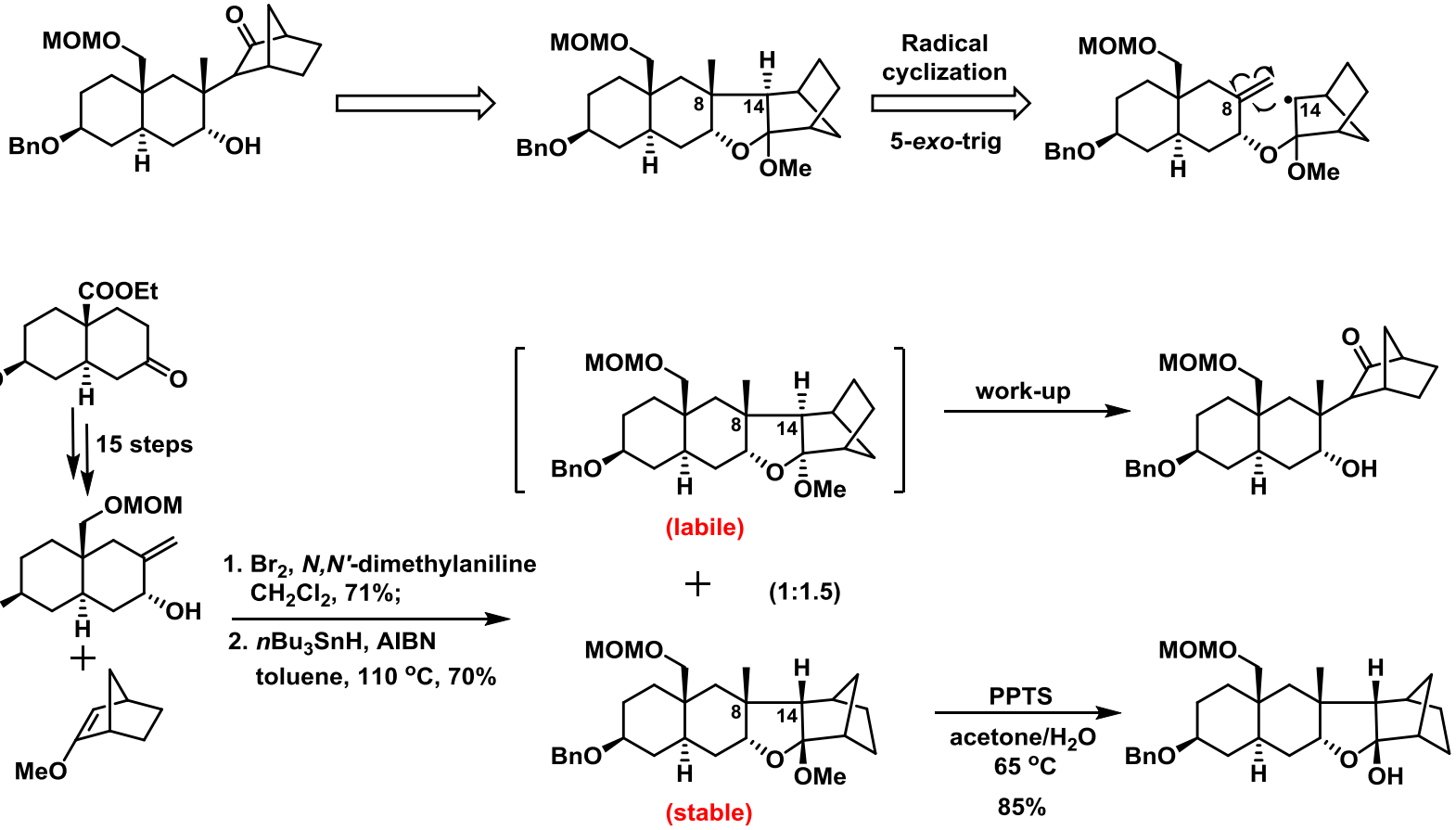
2003



2005

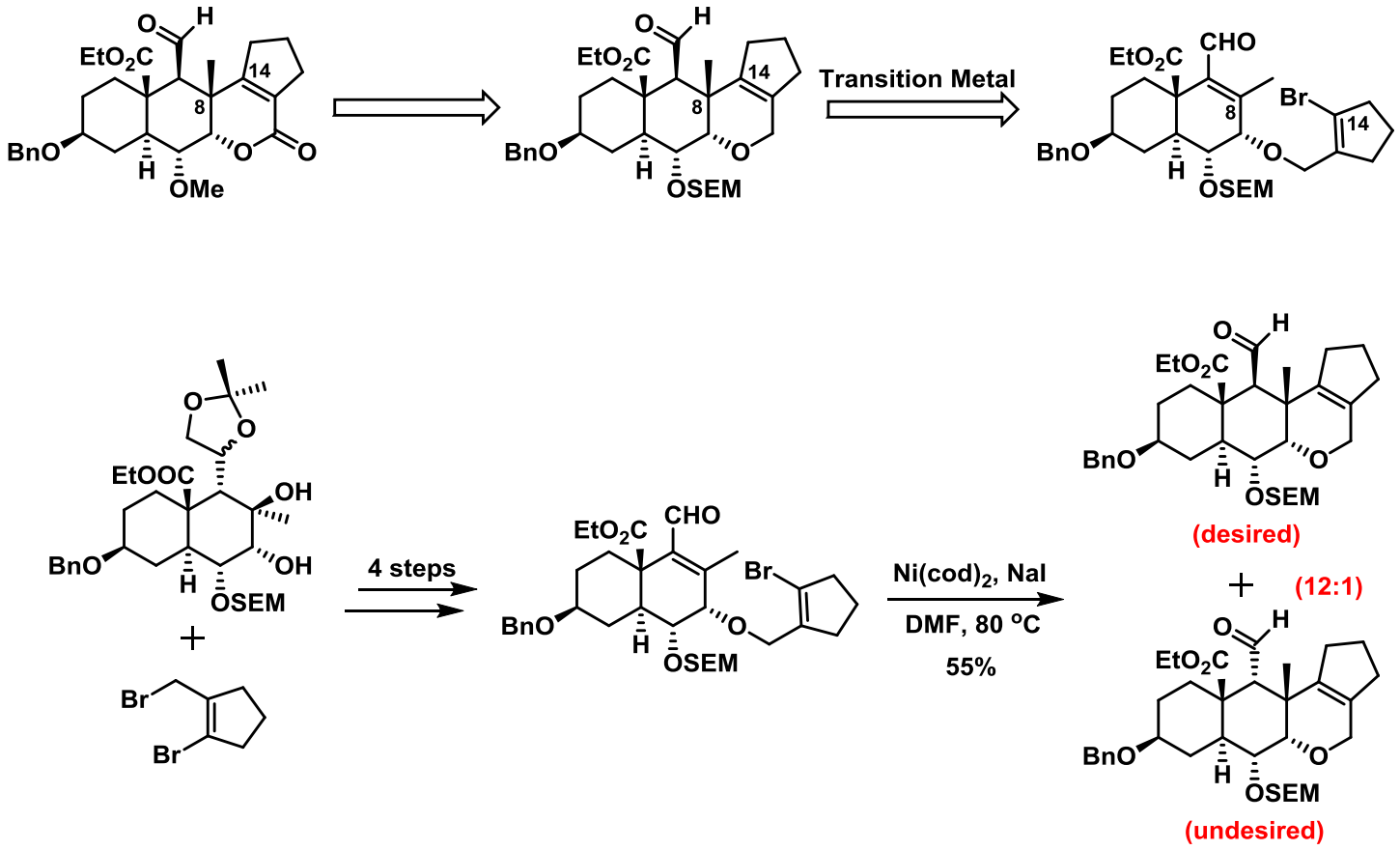


From Radical Chemistry



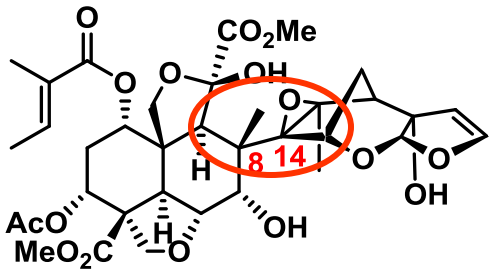
Nicolaou, K. C.; Follmann, M.; Roecker, A. J. *Angew. Chem., Int. Ed*. **2002**, *41*, 2103.

From Organometallic Chemistry



Nicolaou, K. C.; Roecker, A. J.; Follmann, M. *Angew. Chem., Int. Ed*. **2002**, *41*, 2107.

Challenge



Greatest Challenge: C_8-C_{14} Bond

Azadirachtin

Ley

Watanabe

Murai

Nicolaou

Story Line

1968

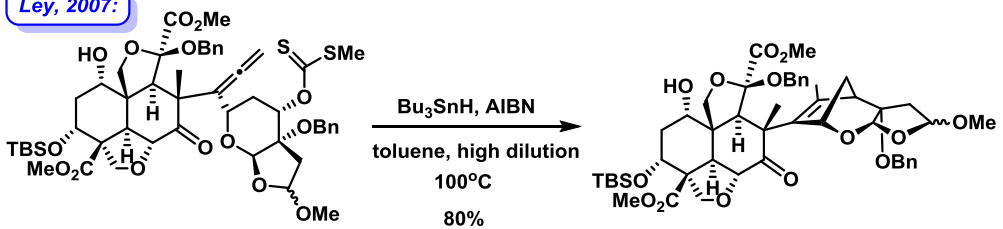
1986

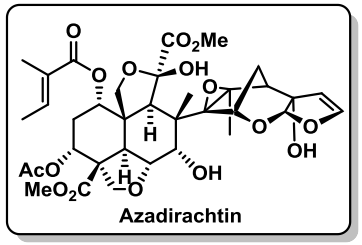
1996

2006

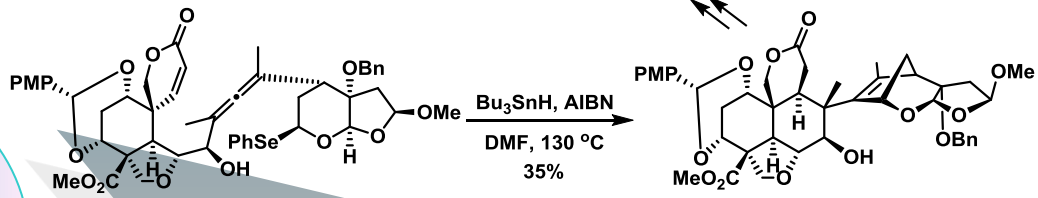
2007 & 2015

Ley, 2007:

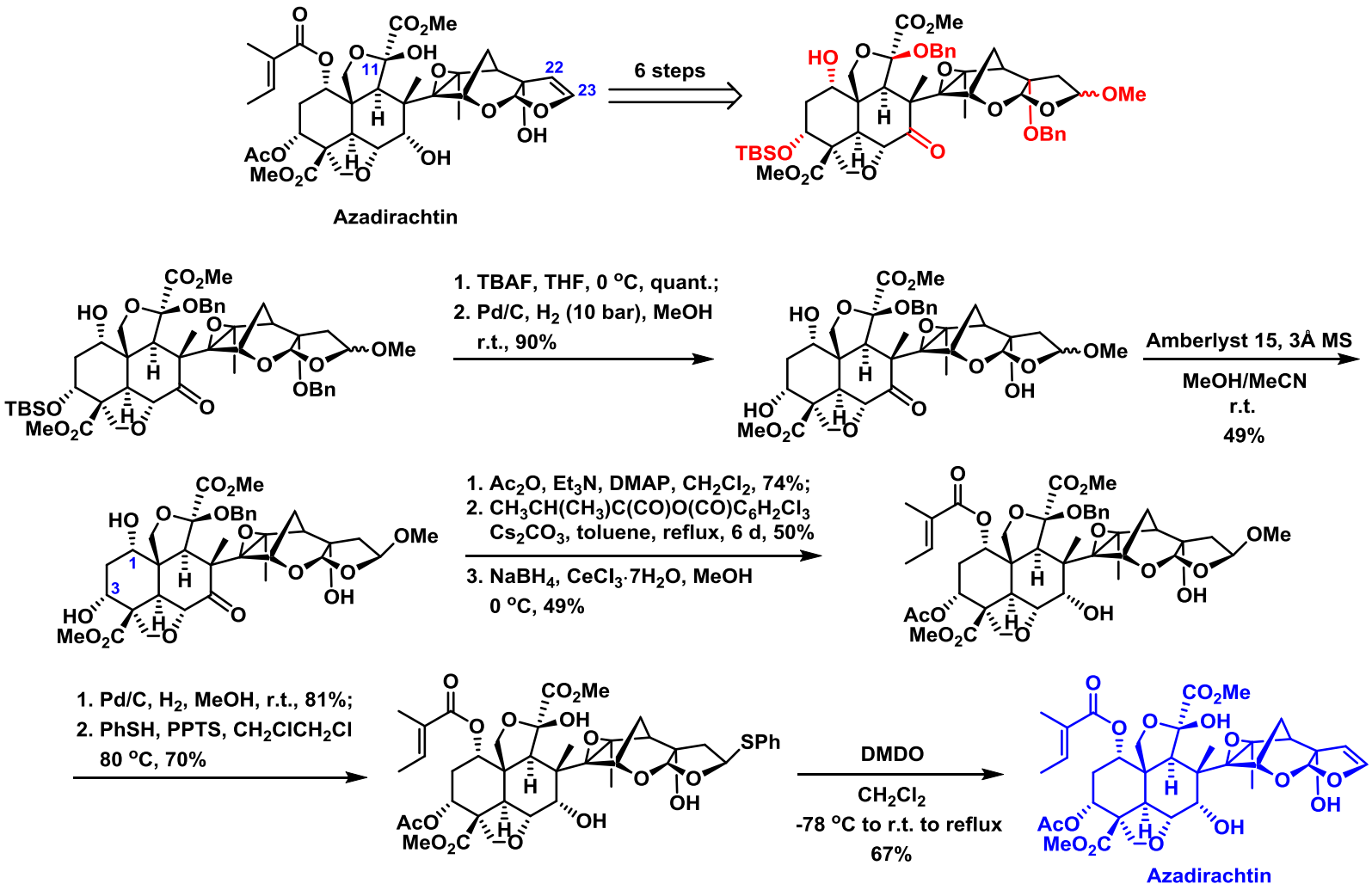




Watanabe, 2015:

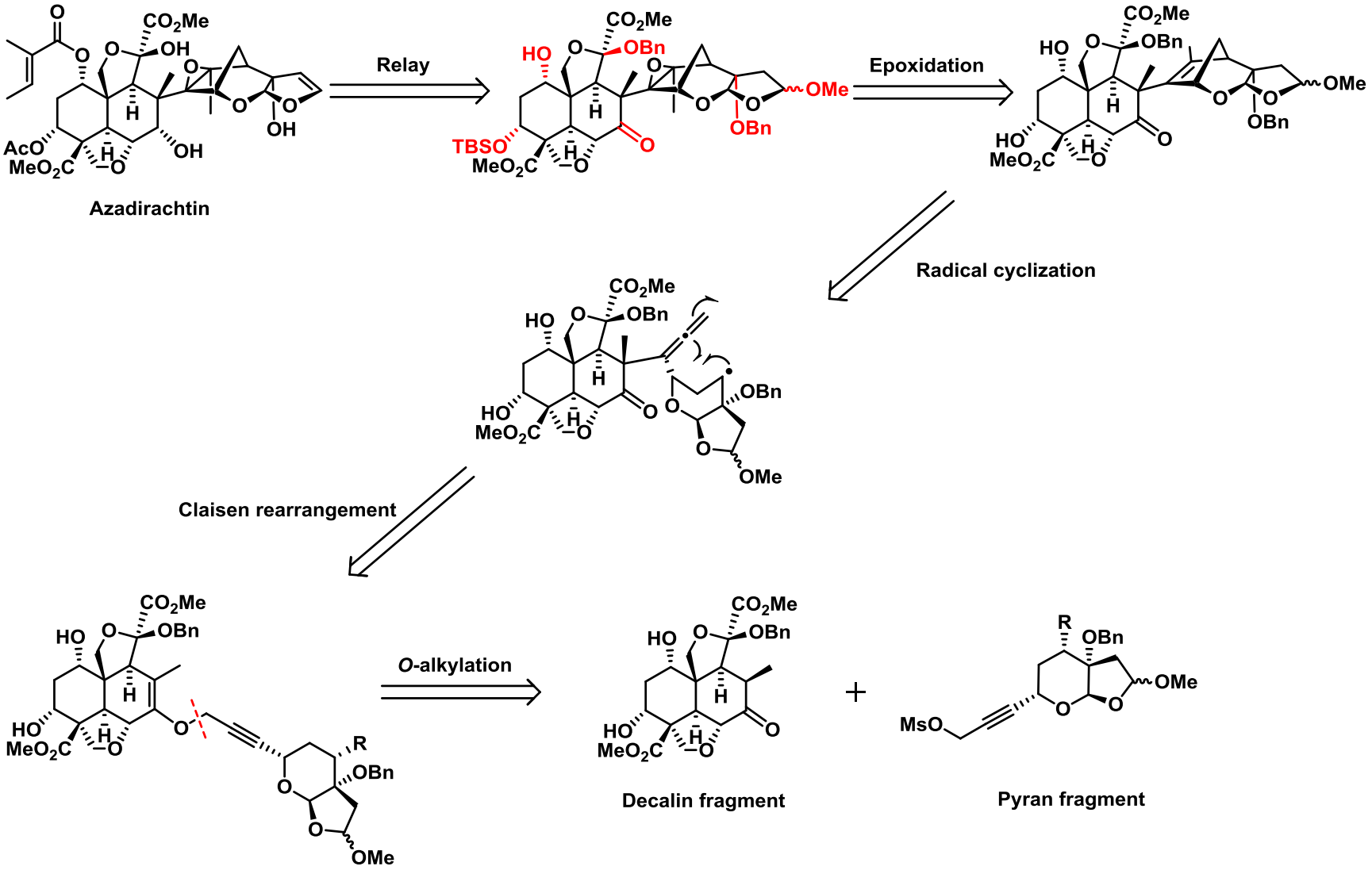


Relay Study

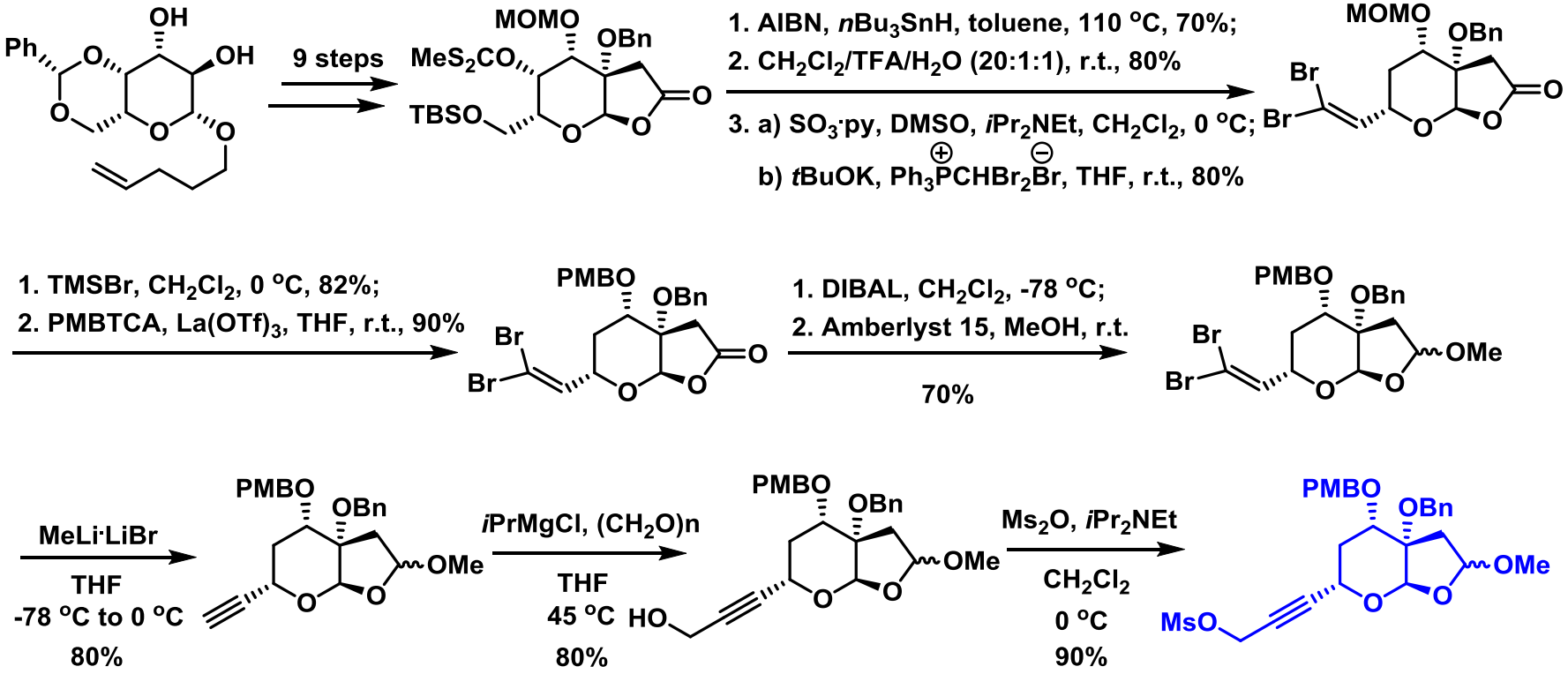


Veitch, G. E.; Beckmann, E.; Burke, B. J.; Ley, S. V. *Angew. Chem., Int. Ed*. **2007**, *46*, 7633.

Retrosynthetic Analysis

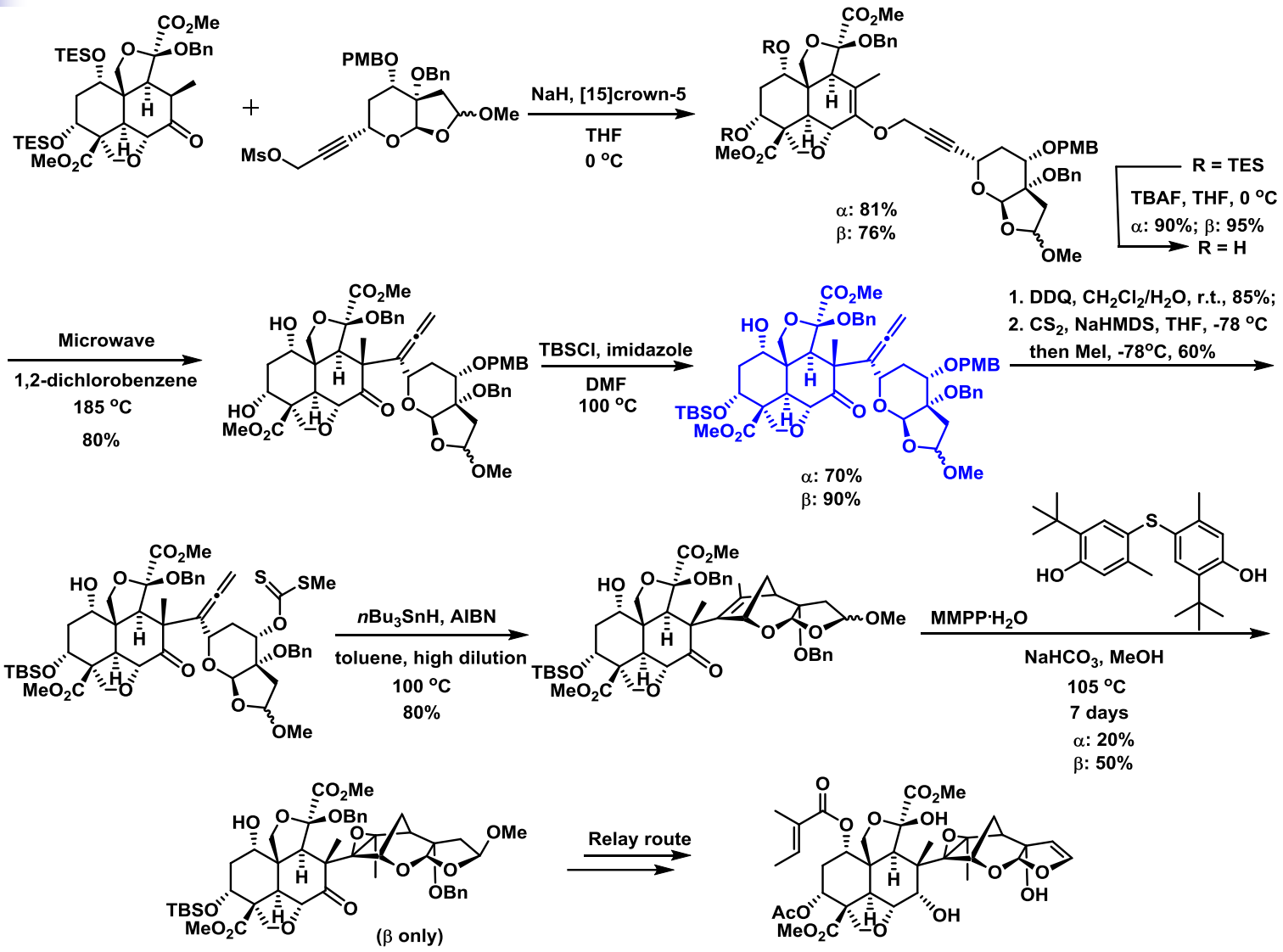


Right 'Arm'



Veitch, G. E.; Beckmann, E.; Burke, B. J.; Ley, S. V. *Angew. Chem., Int. Ed*. **2007**, *46*, 7633.

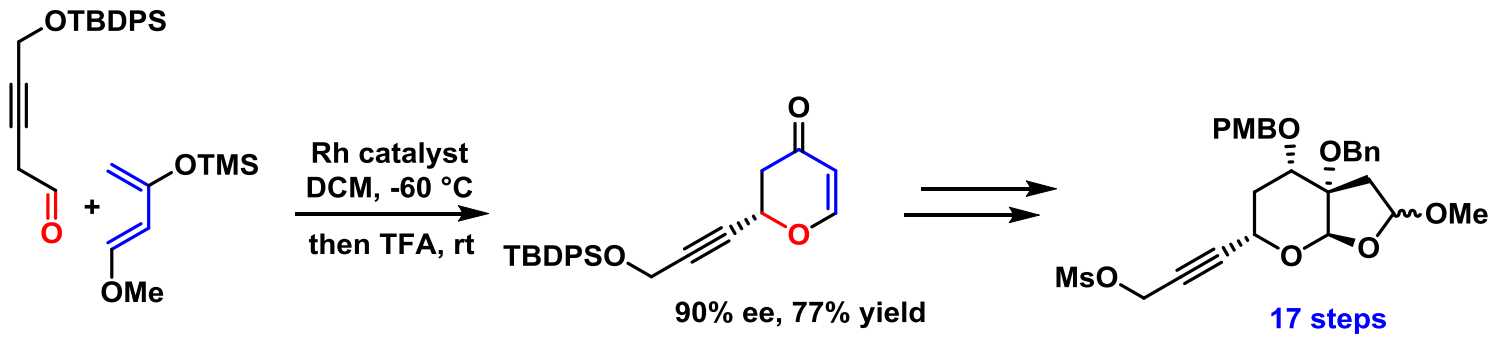
Total Synthesis



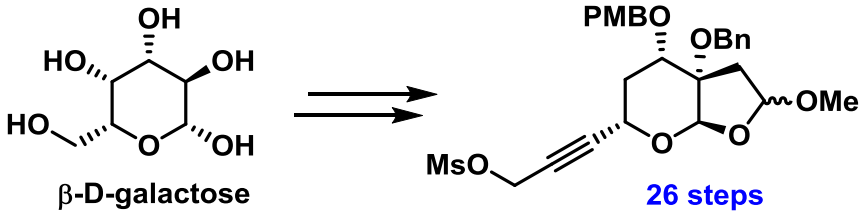
Veitch, G. E.; Beckmann, E.; Burke, B. J.; Ley, S. V. *Angew. Chem., Int. Ed*. **2007**, *46*, 7633.

2nd-Generation Synthesis

2nd-Generation Synthesis:

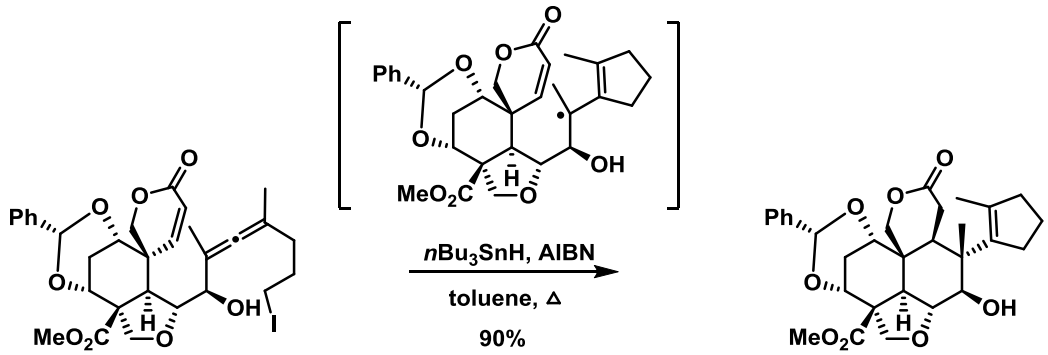


1st-Generation Synthesis:

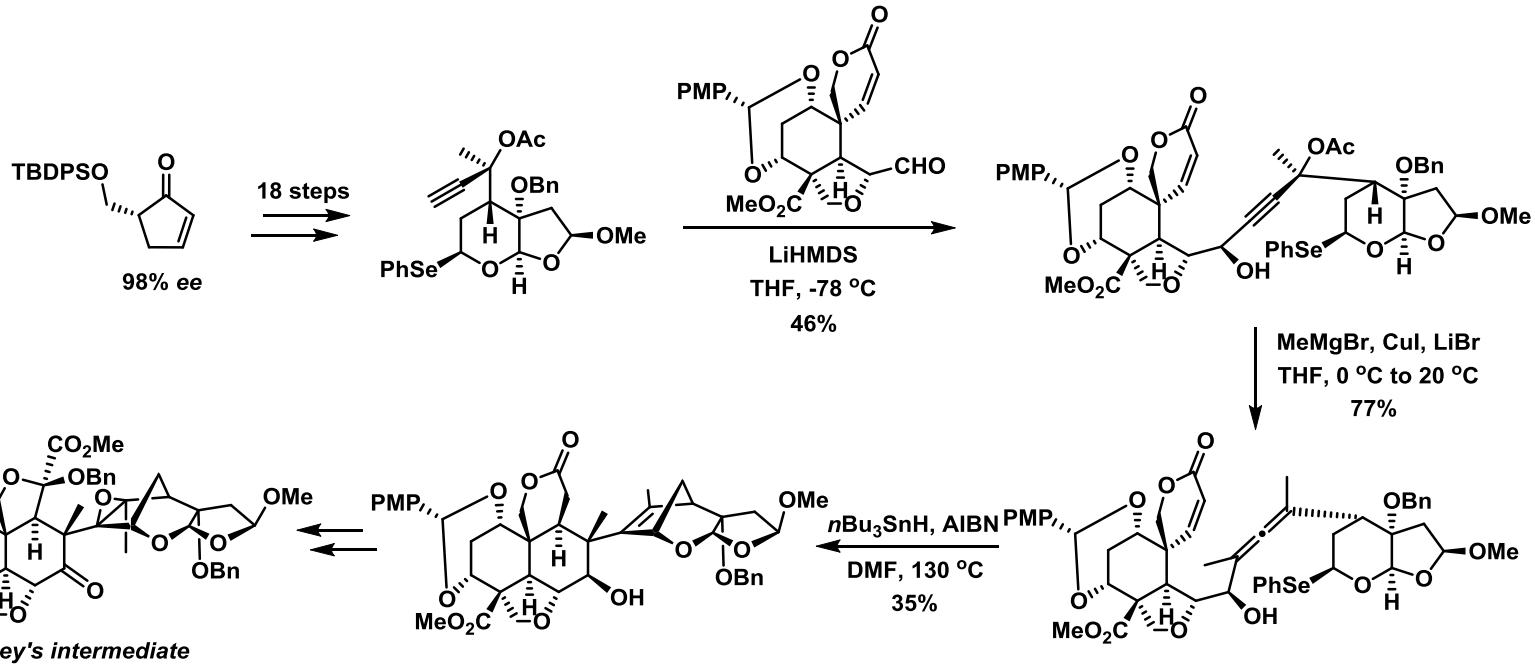


Boyer, A.; Veitch, G. E.; Beckmann, E.; Ley, S. V. *Angew. Chem., Int. Ed*. **2008**, *48*, 1317.

Watanabe's Formal Synthesis



Watanabe, H.; Mori, N.; Itoh, D.; Kitahara, T.; Mori, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1512.

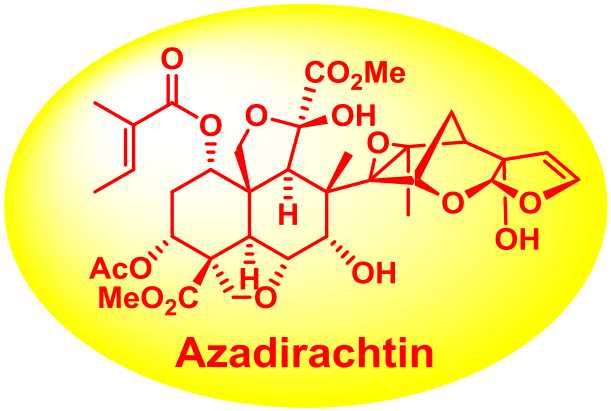


Mori, N.; Kitahara, T.; Mori, K.; Watanabe, H. *Angew. Chem., Int. Ed*. **2015**, *54*, 14920.

Summary

Isolation and Structure Determination (18 years)

Total Synthesis:
Prof. Ley: 22 years
Prof. Watanabe: 26 years



Azadirachtin

Total Steps:
Prof. Ley: 71 Steps (longest linear sequence 48 steps)
Prof. Watanabe: 63 Steps (longest linear sequence 39 steps)

Total Yield:
Prof. Ley: 0.00015%
Prof. Watanabe: 0.00078%

Thank you!