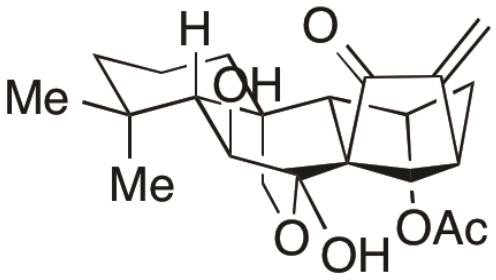
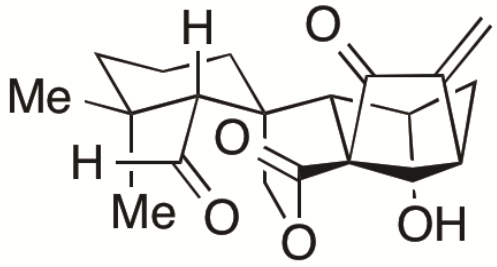
Sarah E Reisman

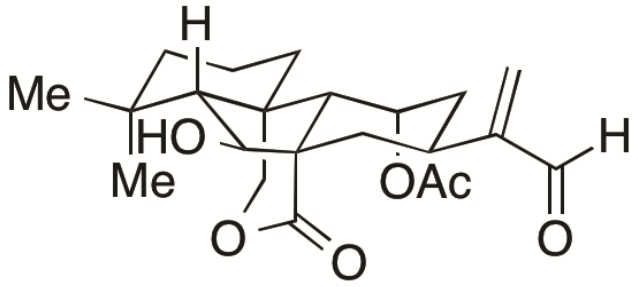
A Unified Strategy to ent-Kauranoid Natural Products



(–)-longikaurin E



(–)-trichorabdal A



(–)-Maoecrystal Z

2014/1/11

M1 Takahiro Shrai

Index

Sarah E Reisman

Curriculum vitae

2008

Assistant professor.

California Institute of Technology, Pasadena, CA

2006-2008

NIH Postdoctoral Fellow. with Professor Eric N. Jacobsen

Harvard University, Cambridge, MA

2002-2006

Ph.D. with Professor John L. Wood

Yale University, New Haven, CT

1999-2001

B.A. with Professor Timo V. Ovaska

Connecticut College, New London, CT

Award

Tetrahedron Young Investigator Awards 2014

Reisman's Group Home Page
http://reismangroup.caltech.edu/aboutSarah.html

Her Strategy

Her directions are to

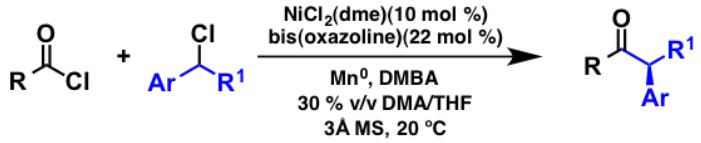
discover, develop, and study new chemical reactions within the context of natural product total synthesis.

Her ultimately hope is to

expand upon the general principles of reactivity through mechanistic studies in order to develop widely applicable chemistry

Her Project

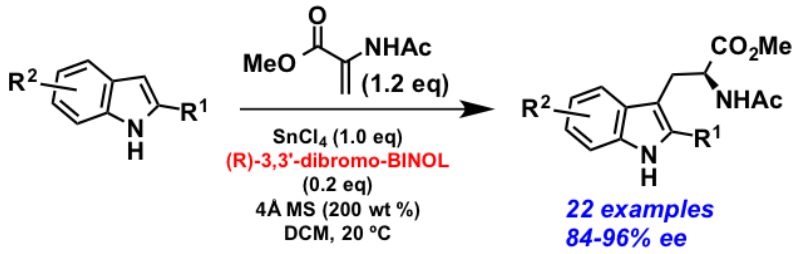
Synthesis of Enantioriched acylic α,α-disubstituted ketones



direct ketone formation
no preparation of organometalic reagents
no stoichiometric chiral auxiliaries
no epimerization of tertiary center

J. Am. Chem. Soc. **2013**, *135*, 7442.

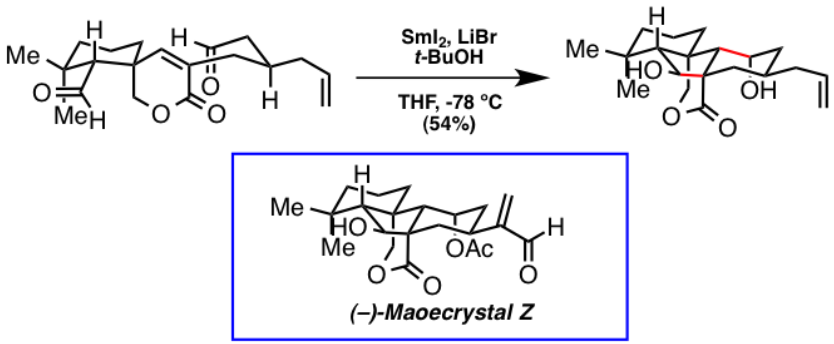
Enantioselective Synthesis of Tryptophan Derivatives



22 examples
84-96% ee

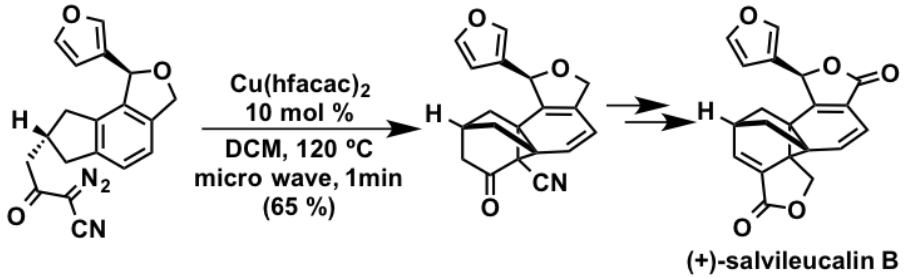
J. Am. Chem. Soc. **2012**,*134*, 5131.

A Concise Total Synthesis of (–)-Maoecrystal Z



J. Am. Chem. Soc. **2011,** *133*, 14965.

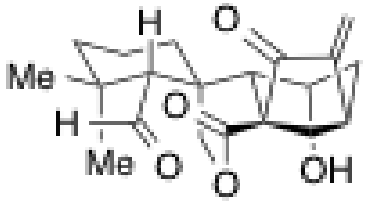
Enantioselective Total Synthesis of (+)-Salvileucalin B.



J. Am. Chem. Soc. **2011**, *133*, 774.

Bioactivity

These *ent*-kauranoids demonstrate potent antibacterial, anti-inflammatory, and anti-cancer properties.

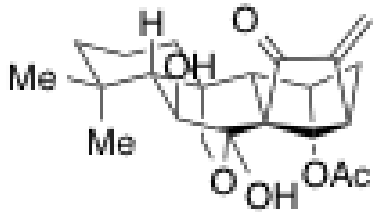


(–)-trichorabdal A

Rabdosia trichocarpa

A very strong in vitro antibacterial activity against Helicobacter pylori.

*Zentralblatt für Bakteriologie.*1997.63.

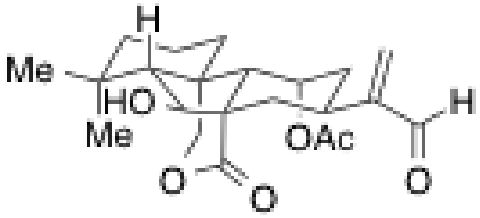


(–)-longikaurin E

Rabdosia Zongituba

Exhibit in vitro cytotoxicity against several human cell lines.

J. Nat. Prod. **2011**, 74, 1213–1220.



(–)-Maoecrystal Z

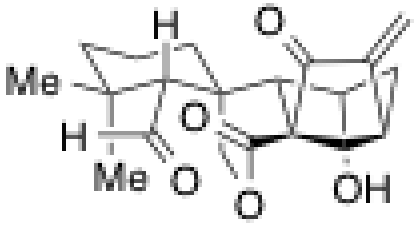
Isodon eriocalyx

exhibited comparable inhibitory effect against several human tumor cells.

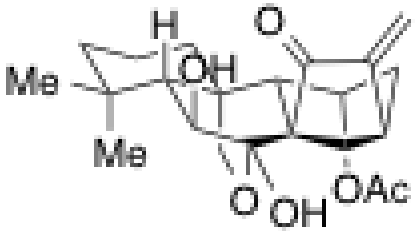
Org. Lett. **2006**, 8, 4727.

Synthetic Features

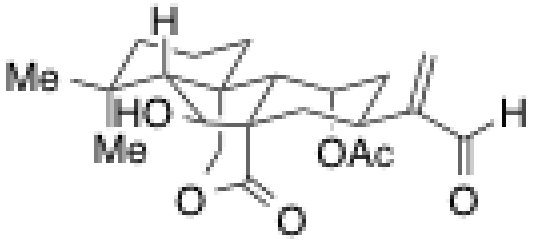
Spirolacton core *ent*-kauranoids



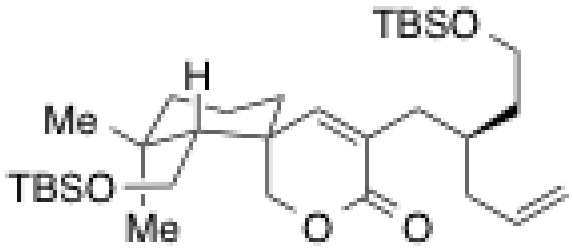
(–)-trichorabdal A (1)
15 steps



(–)-longikaurin E (2)
17 steps



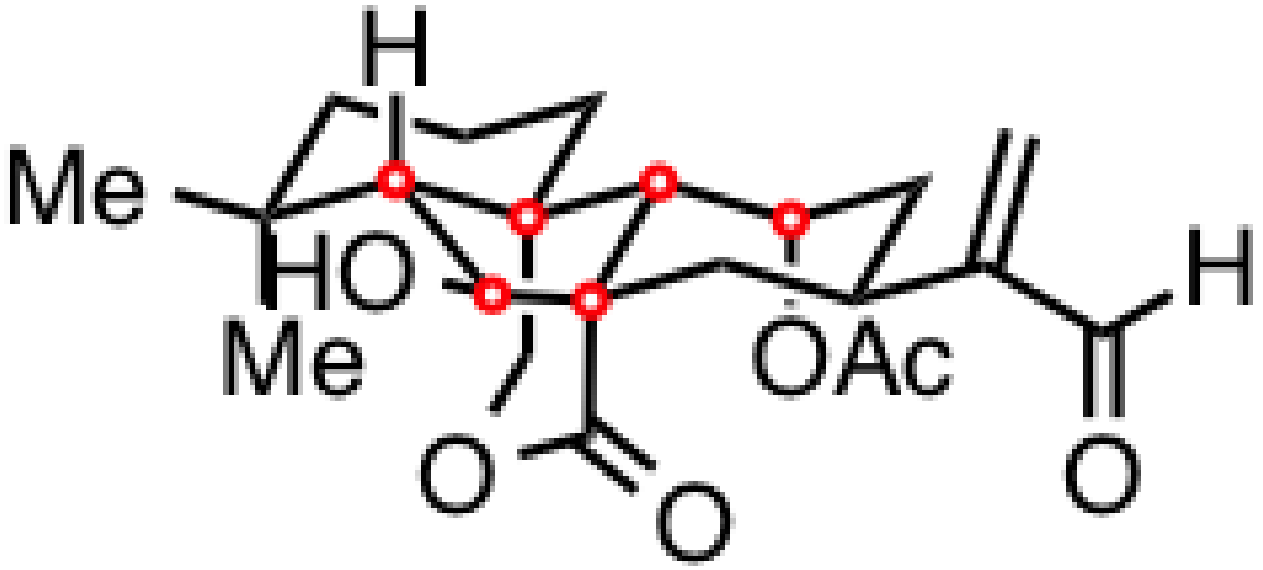
(–)-Maoecrystal Z (3)
12 steps



Common intermediate (4)

Features
***Spiro-fused cyclic ring system**
***Many vicinal stereocenters**

Total Synthesis of (−)-Maoecrystal Z



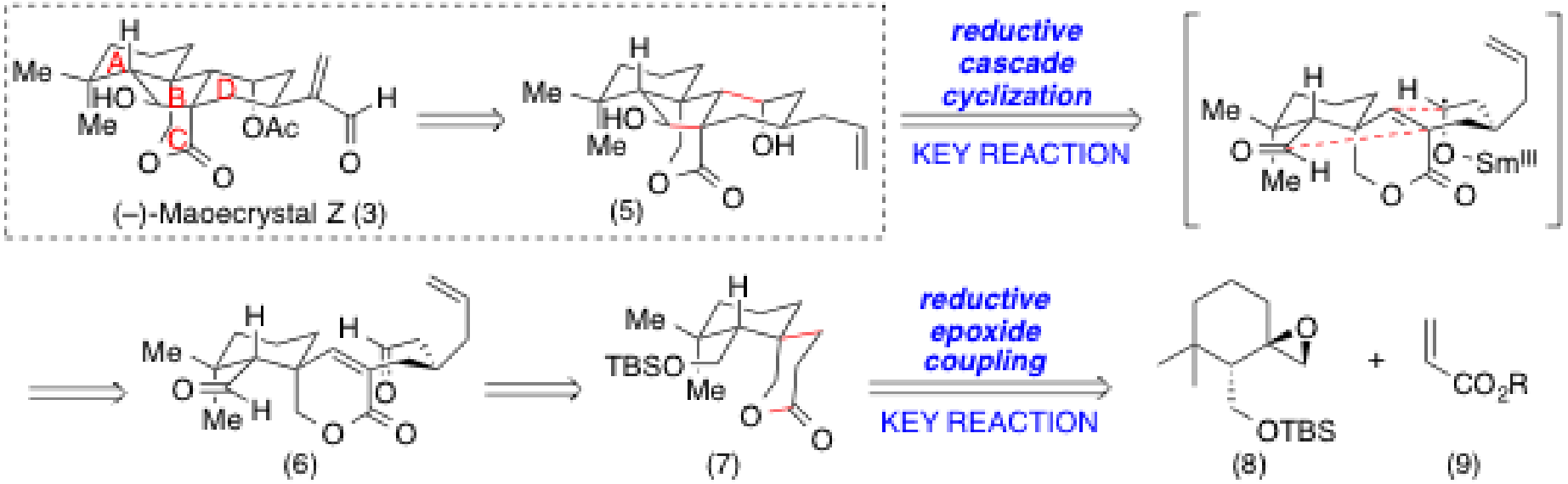
***(−)-Maoecrystal Z* (3)**

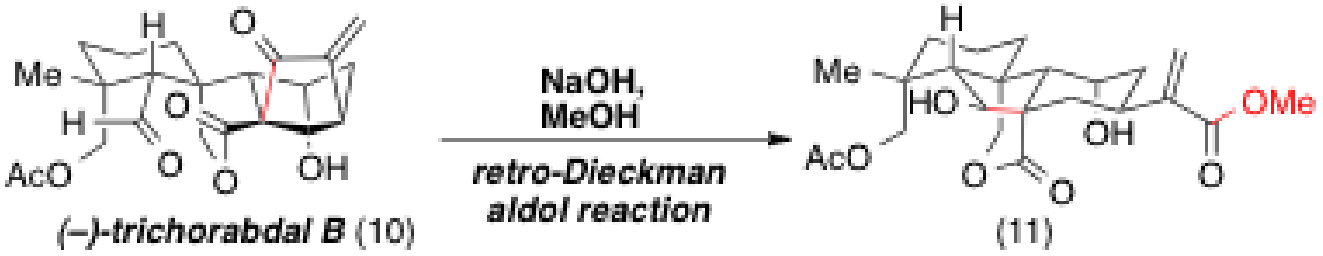
Key reaction

1.Sm(II)-mediated cascade cyclization

2.Ti(III)-mediated reductive coupling

Retro Synthesis of (−)-Maoecrystal Z

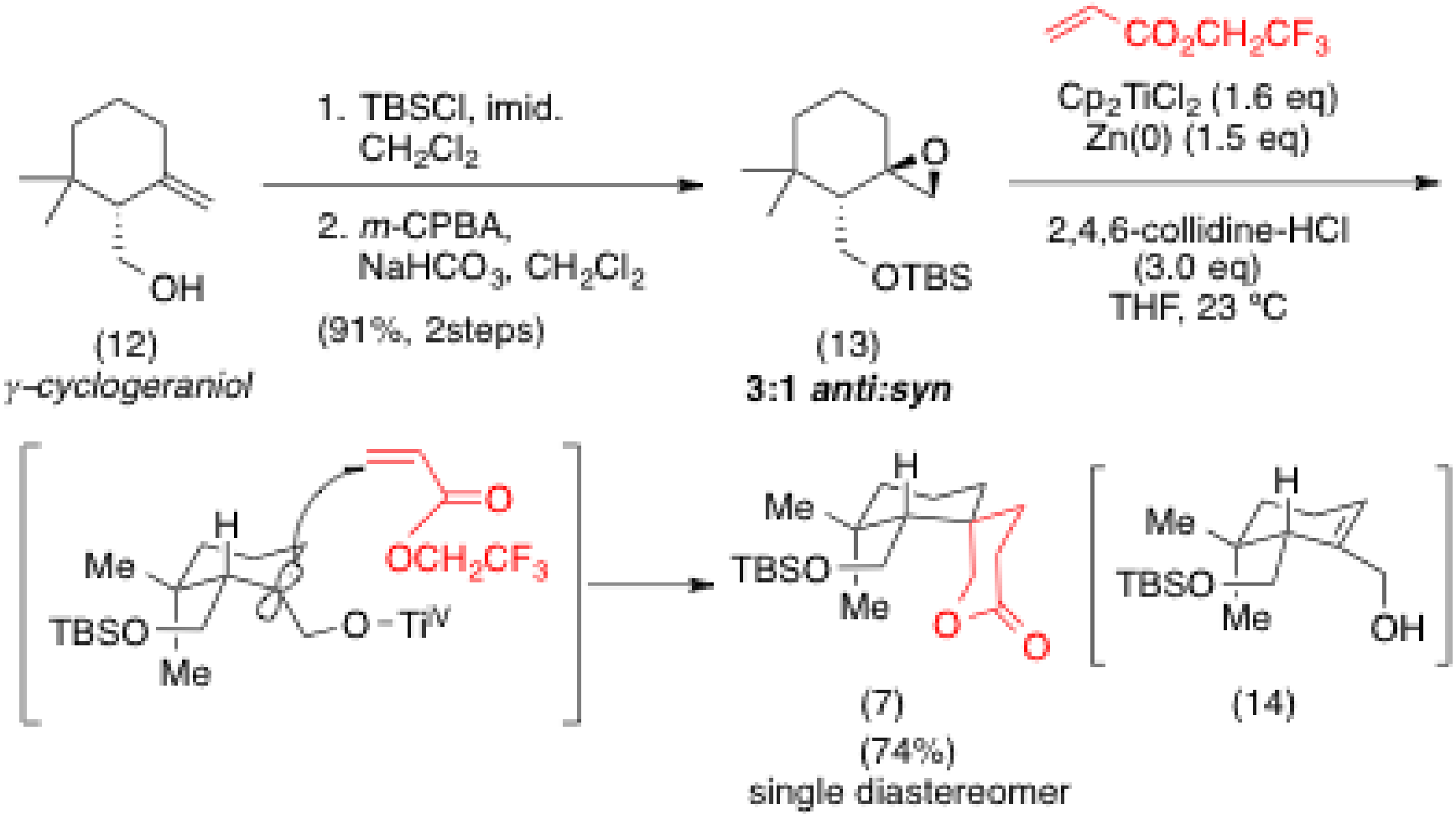




Fujita, E. *et al. J. Chem. Soc., Chem. Commun.* **1981**, 899.

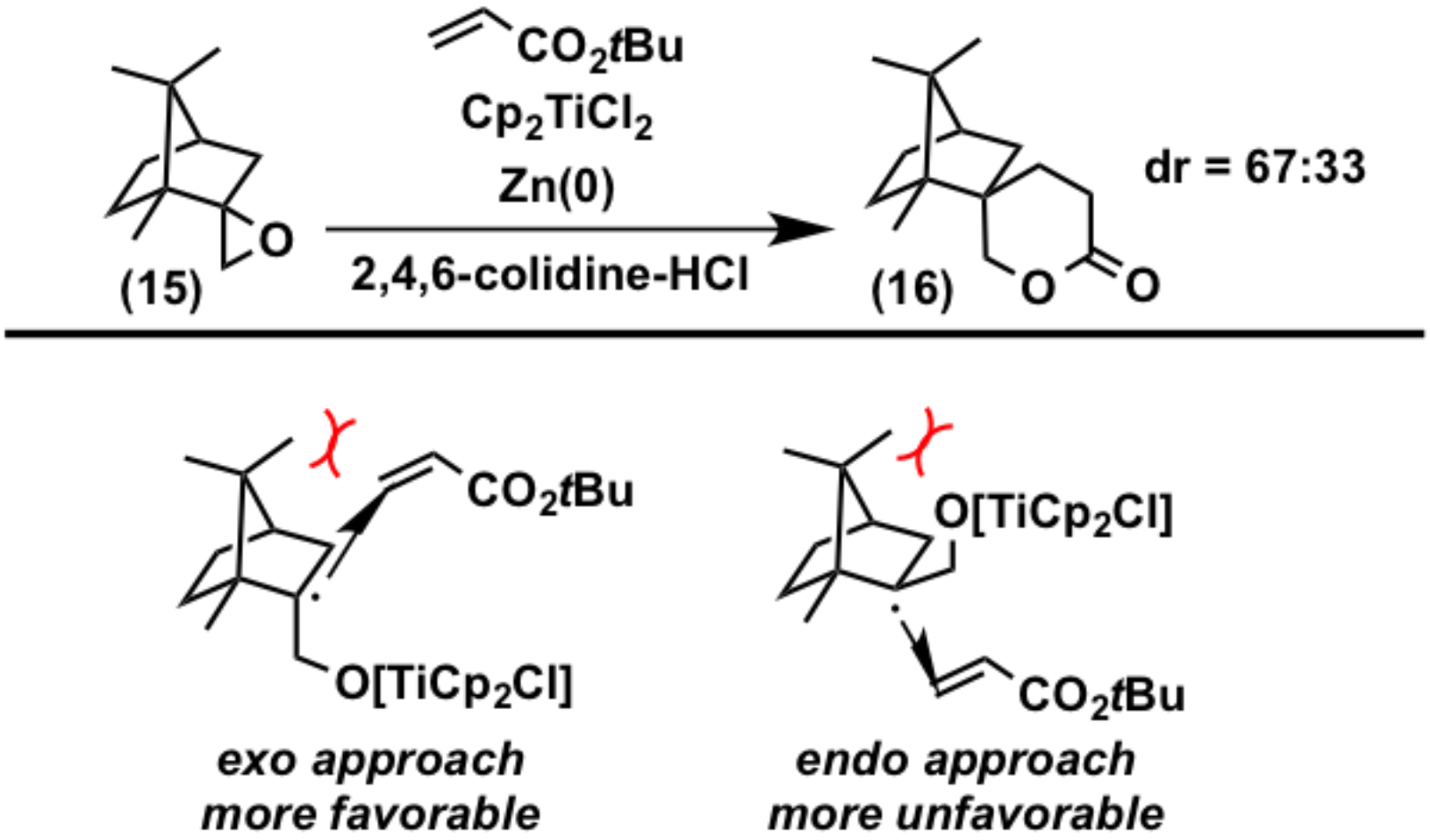
Sarah E. Reisman, *et al. J. Am. Chem. Soc*. **2011, *133,* 14965.**

Preparation of Spirolactone
Ti(III)-mediated Reductive Coupling



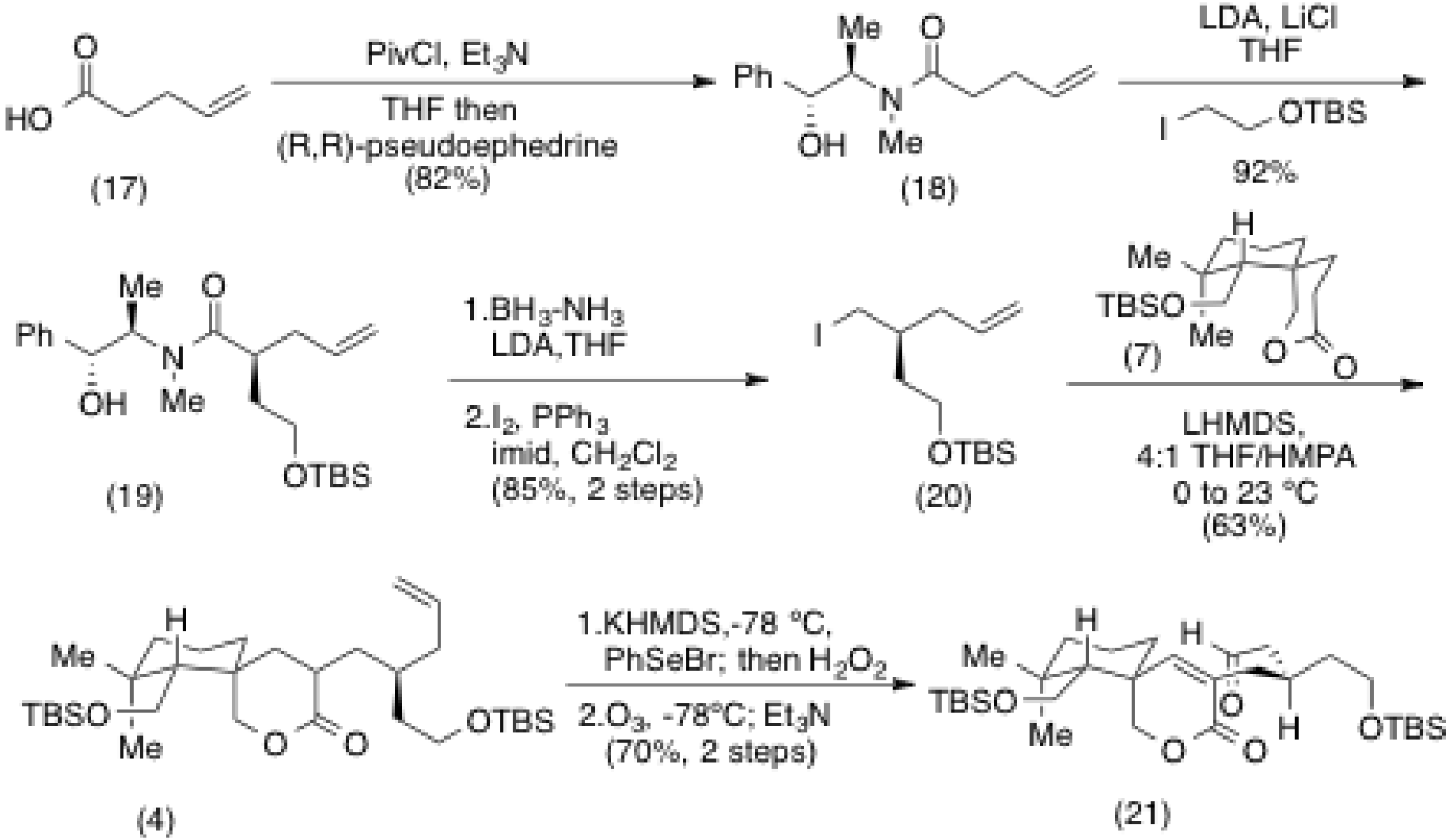
$$2Cp_2TiCl_2 + Zn(0) \longrightarrow 2Cp_2TiCl + ZnCl_2$$

Diastreoselectivity in Addition

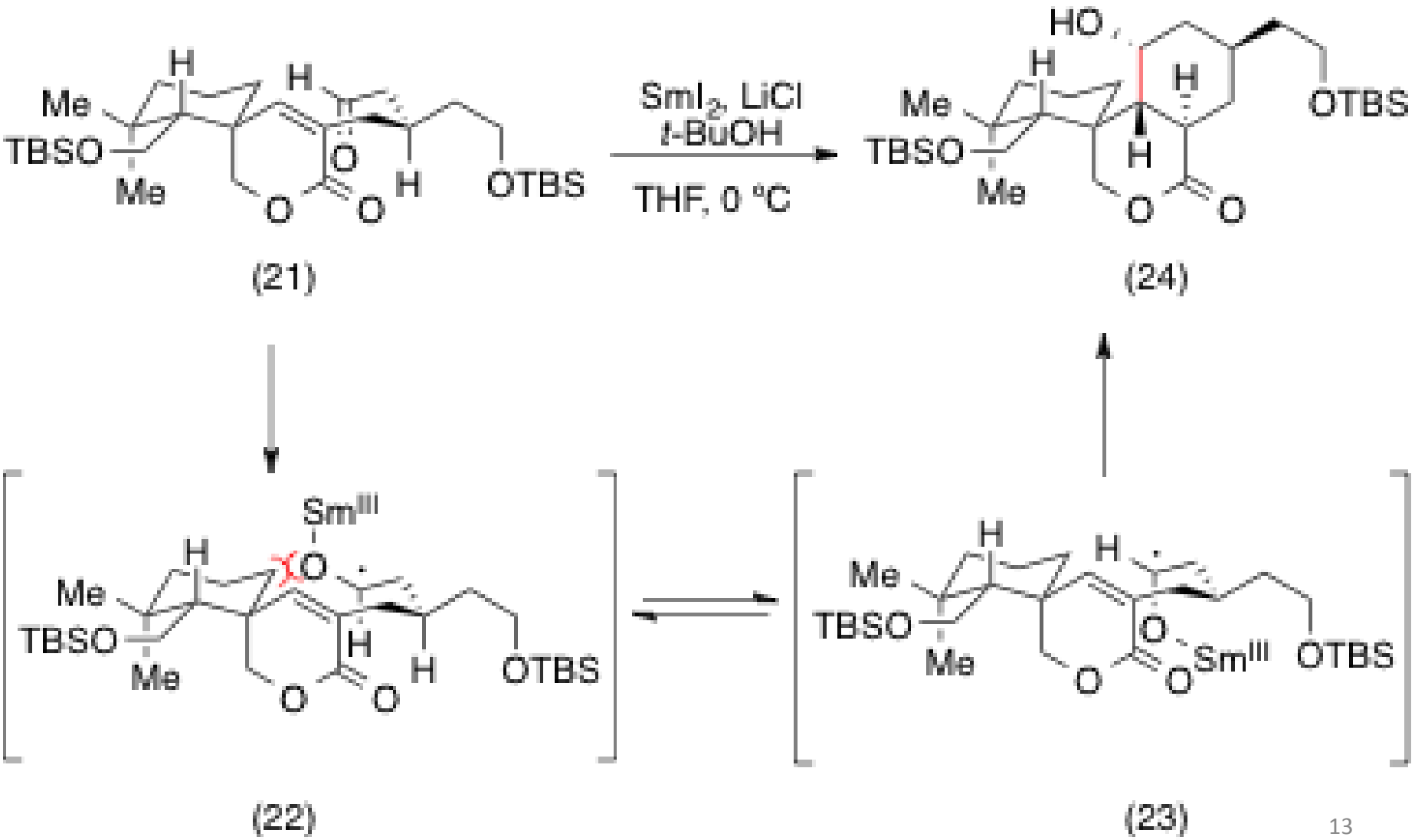


Chem.–Eur. J. **2003**, 9, 531.

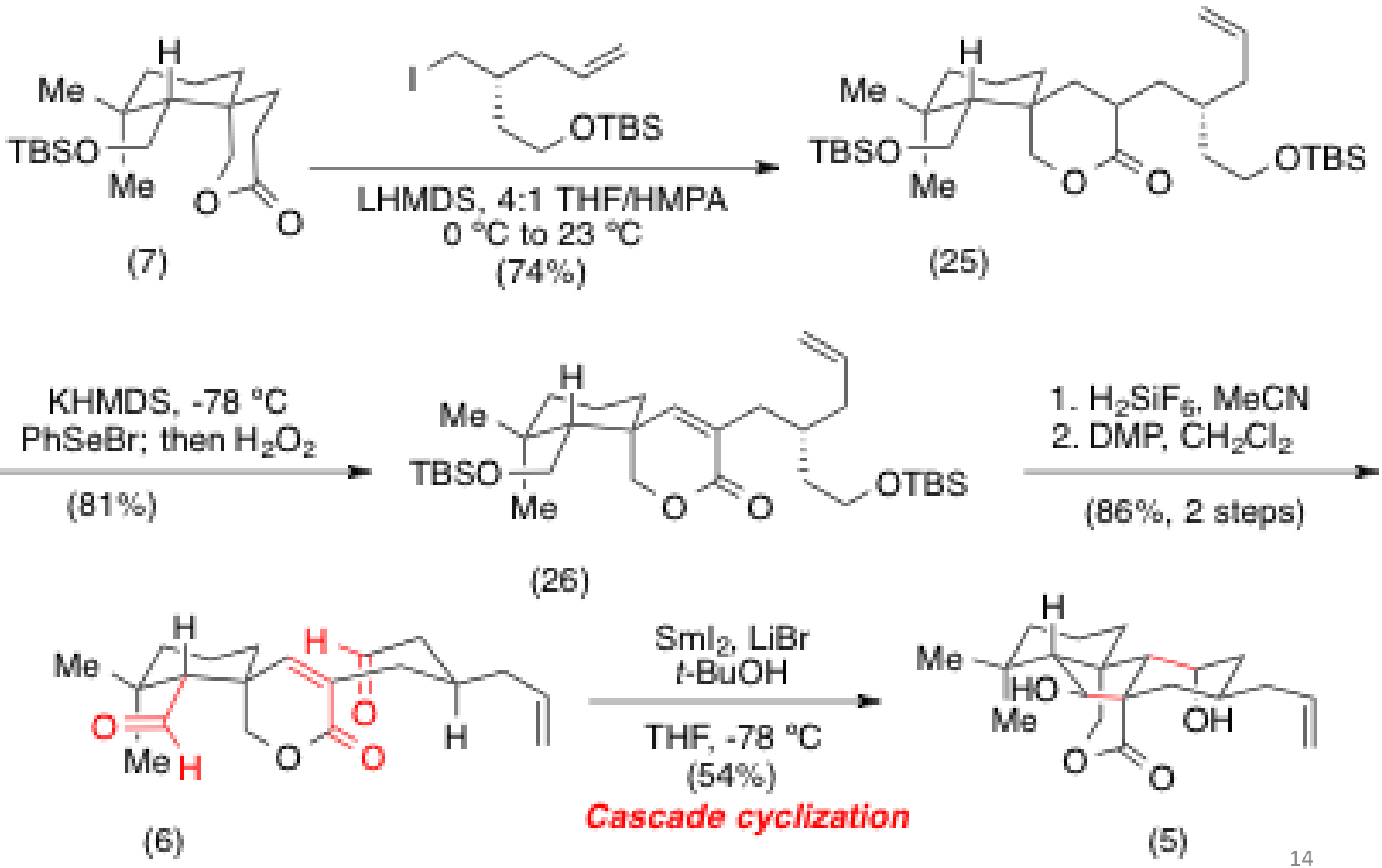
Preparation of Reductive Cyclization



Sm(II)-Mediated Reductive Cyclyzation



Reductive Cascade Cyclization



Sm Cascade Cyclization

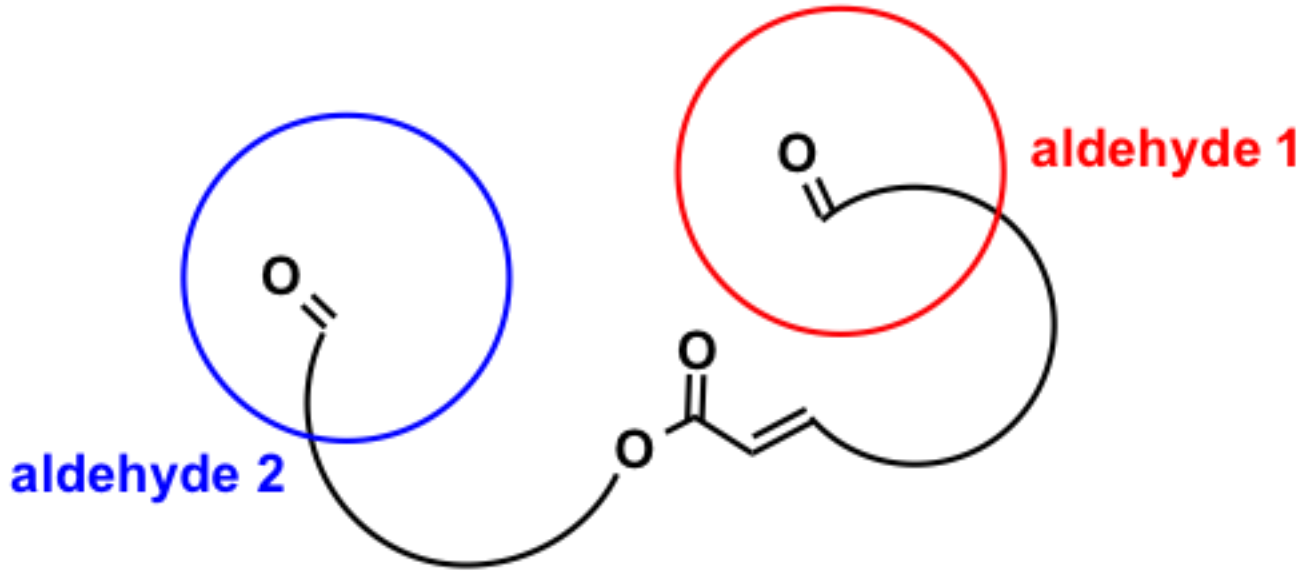
- Precedent

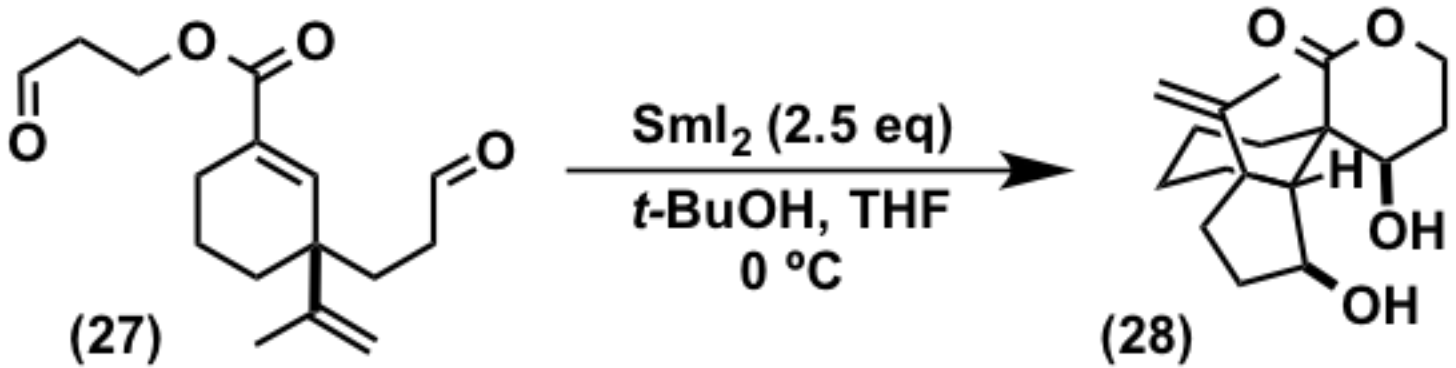
  Dialdehyde Cascade cyclization
- Protonation solvent

  Difference of alcohol solvent
- Additive’s role

  LiCl or LiBr

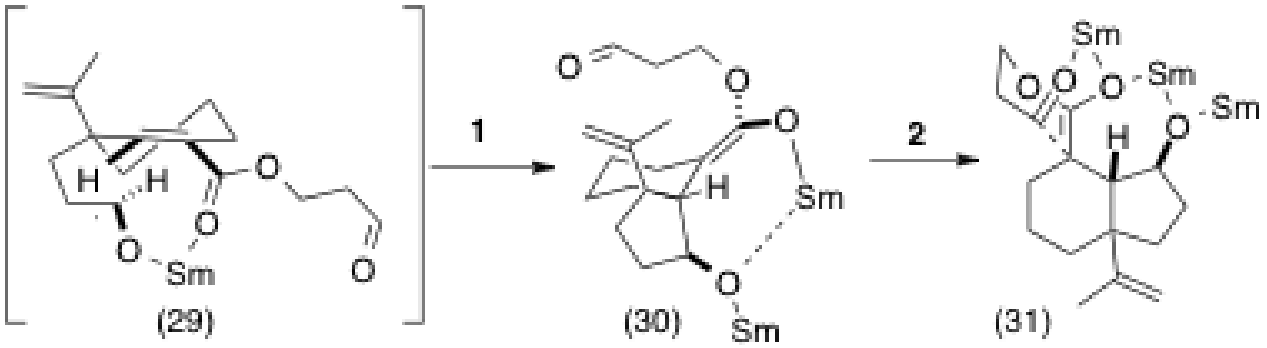
Dialdehyde Cascade Cyclization



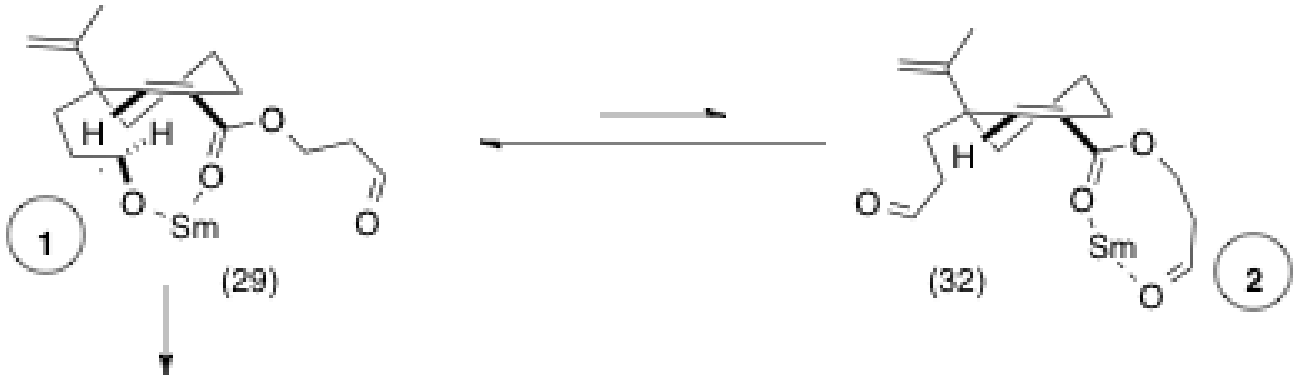


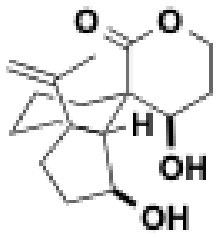
David J. Procter. *et al.* ***Tetrahedron.*** **2009*. 65.* 10816**

Dialdehyde Selectivity



1.Chelation to Sm(III) leads to selective enolate formation
2.Diastreoselectivity aldol cyclization

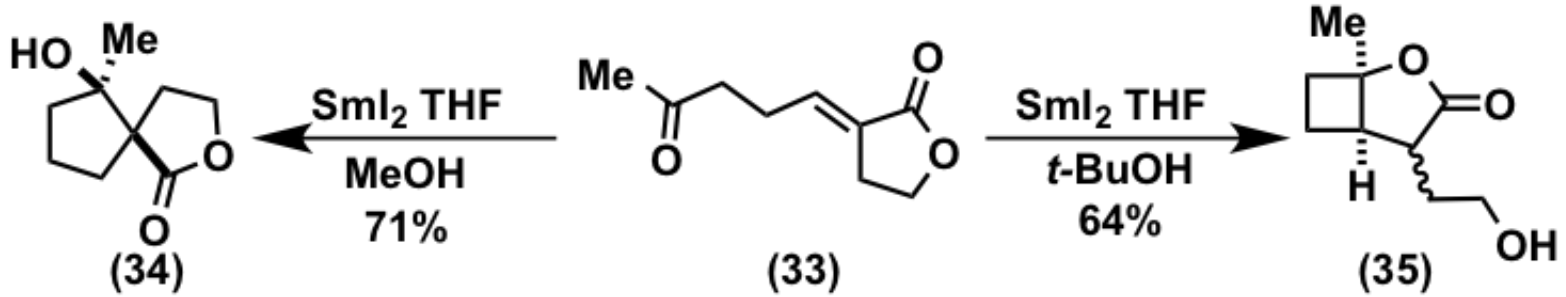


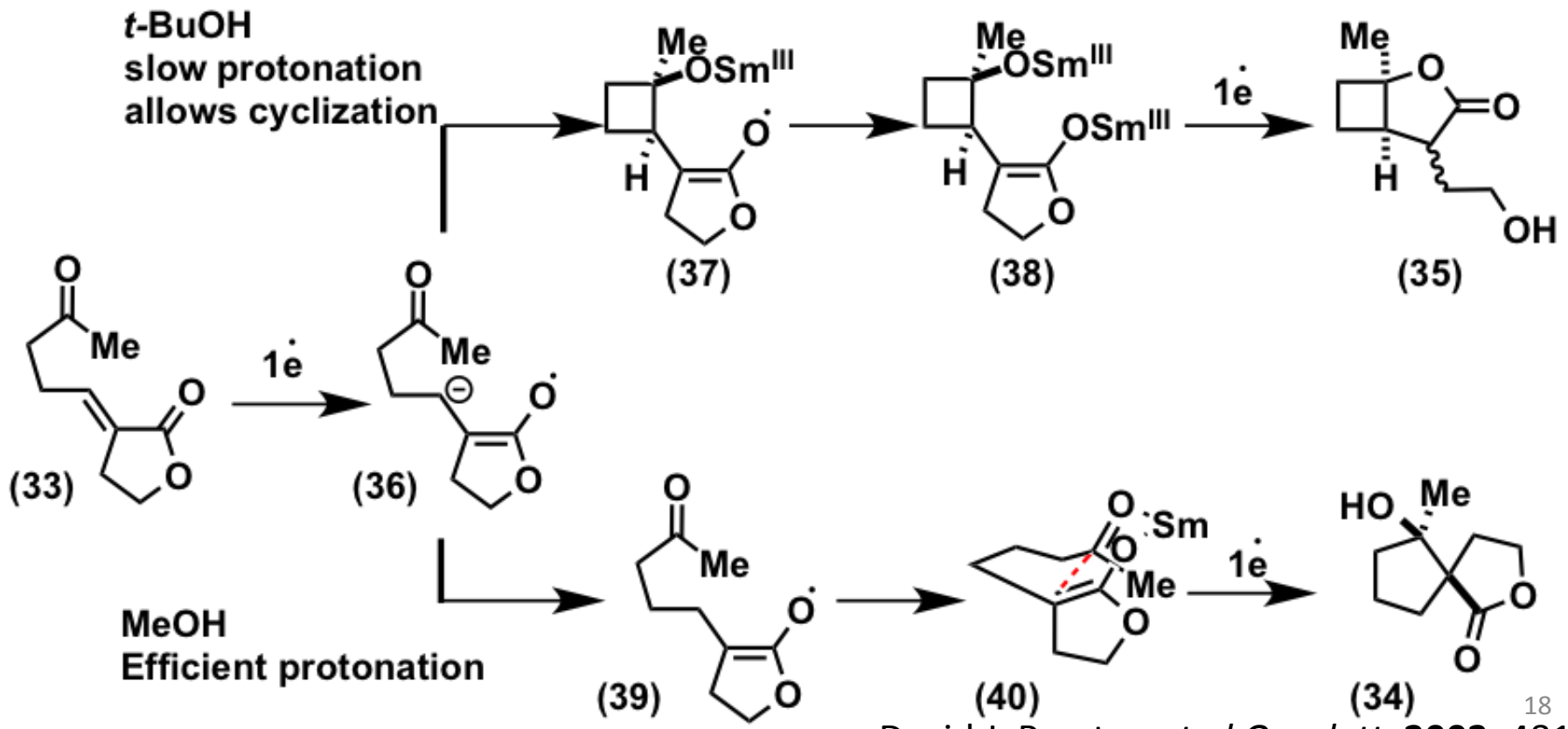


1:The reduction of carbonyl groups with SmI_2 is reversible,with the ketyl radical anion being drained from the equilibrium by cyclization.
As only aldehyde group1 is able to undergo facile cyclization, that aldehyde is seen to react in the presecence of the other.

2:Pre-coordination of Lewis acidic samarium to the carbonyl and unsaturated ester components in ketyl-olefin cyclization is important for promoting reaction and controlling the diaselectivity.

Protonation Solvent Effect





David J. Procter. *et al.Org. lett*. **2003**, 4811.

LiCl and LiBr Play an Important Role

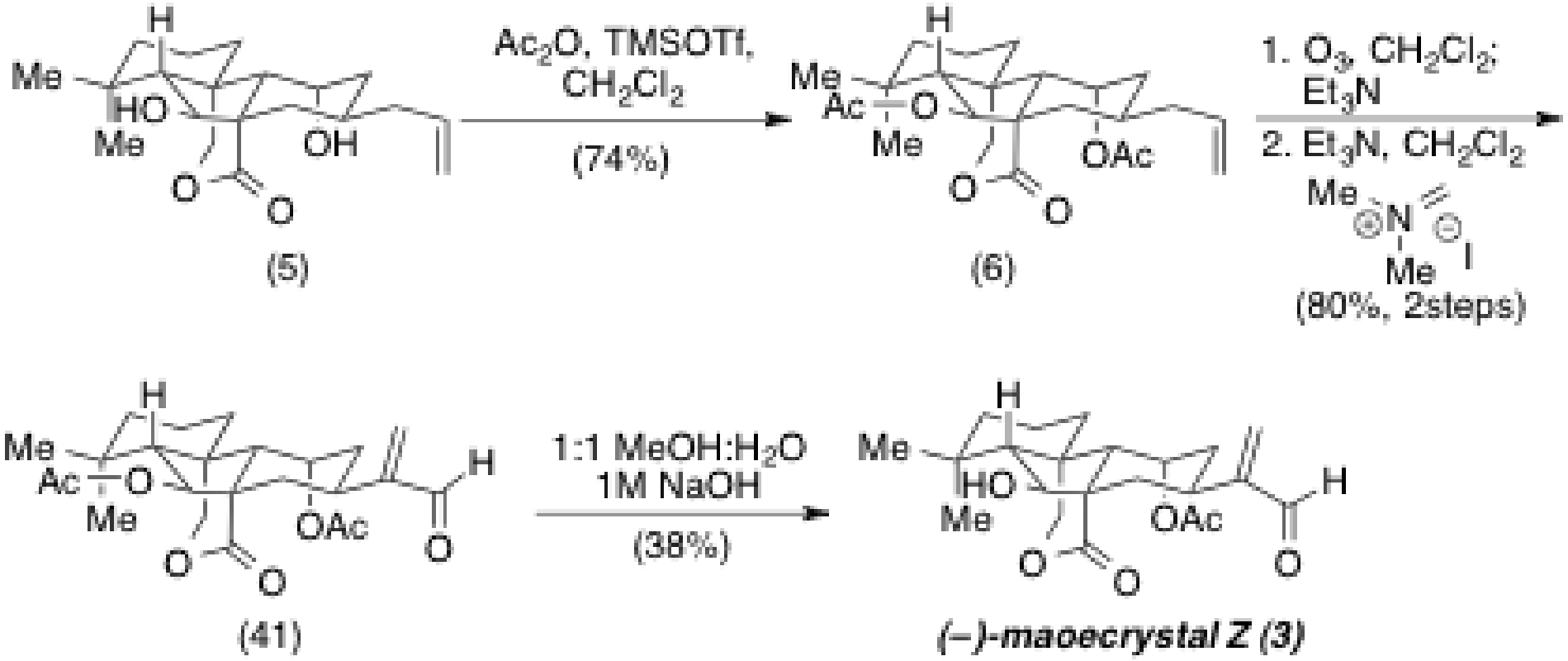
SmI_2-additives	$E_{1/2}$ (V) - oxidation potential
SmI_2	–0.98±0.04
SmI_2-LiBr	–1.55±0.07
SmI_2-LiCl	–1.78±0.10

SmI_2–LiBr and –LiCl combinations are more powerful reductants than SmI_2

*Measured by cyclic voltammetry

Robert A. Flowers. *et al*, *J. Am. Chem. Soc.* ***2000, 122, 7718.***

Completion of The Synthesis of (–)-Maeocrystal Z



Summary (1)

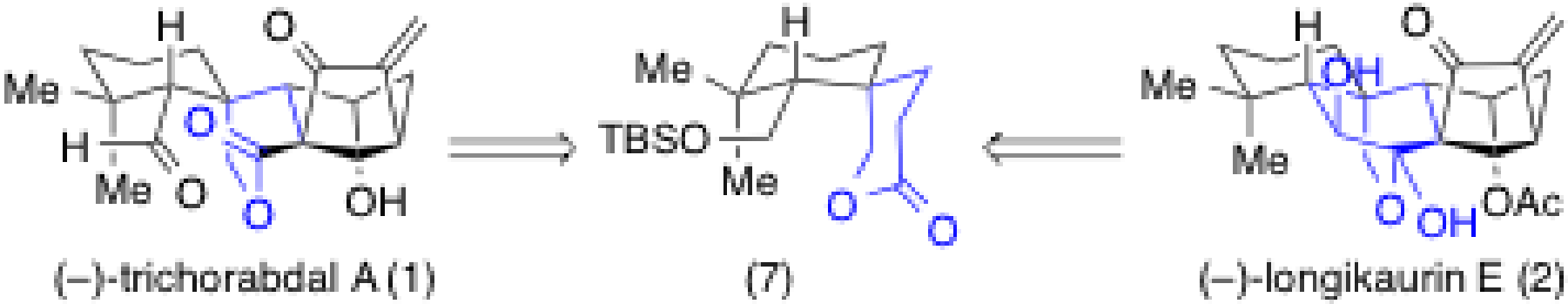
The first total synthesis of (–)-maoecrystal Z had accomplished in 12 steps from (–)-γ-cyclogeraniol.

The key steps include a high diaselective

- ***Ti^{III}-mediated reductive epoxide coupling**
- ***Sm^{II}-mediated reductive cascade cyclization**

The utility of single electron chemistry for the preparation of congested polycyclic systems bearing vicinal stereogenic centers

Total Synthesis
(–)-Trichorabdal A, (–)-longikaurin E

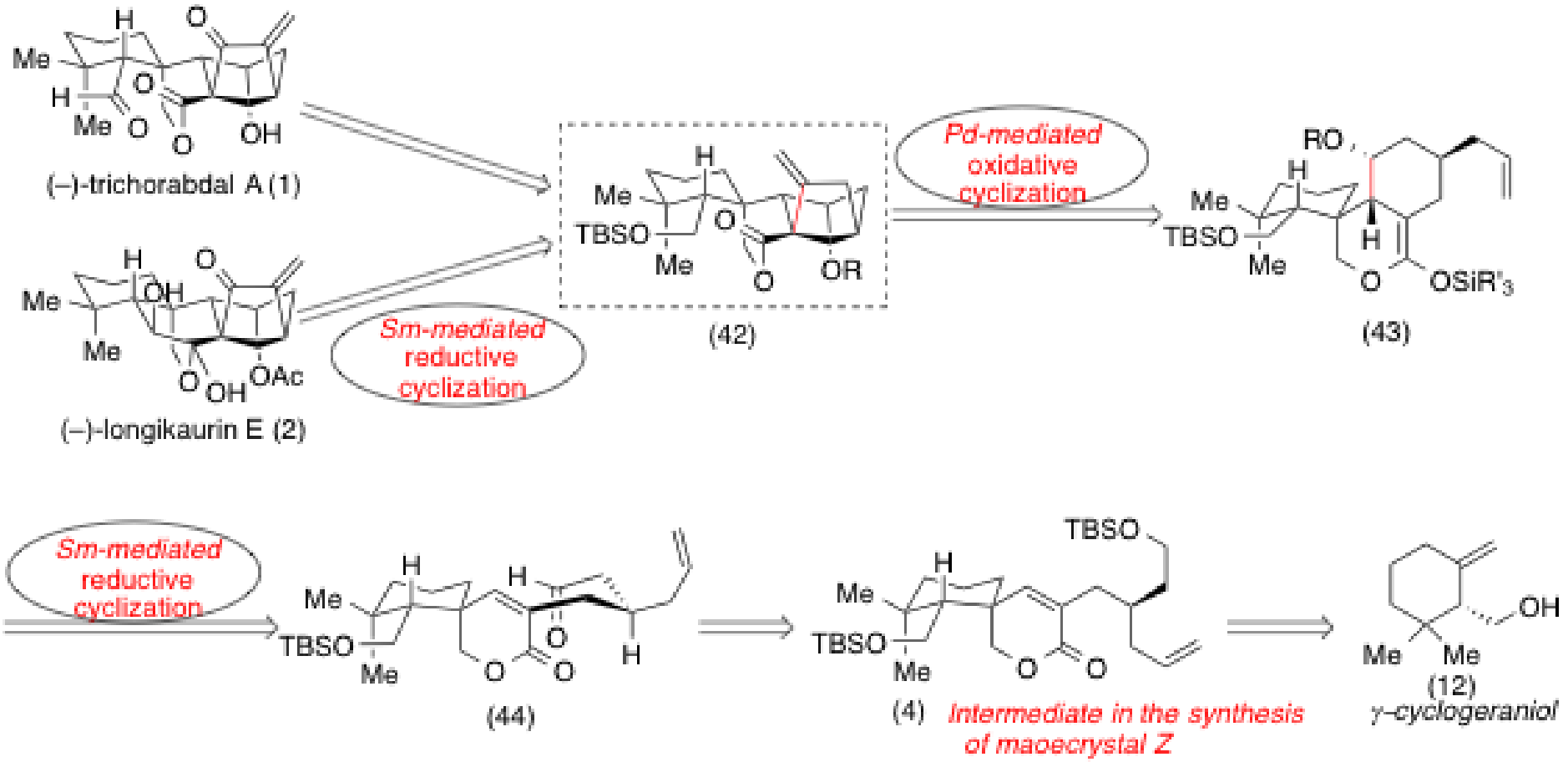


Key reaction

Sm(II)-mediated cascade cyclization

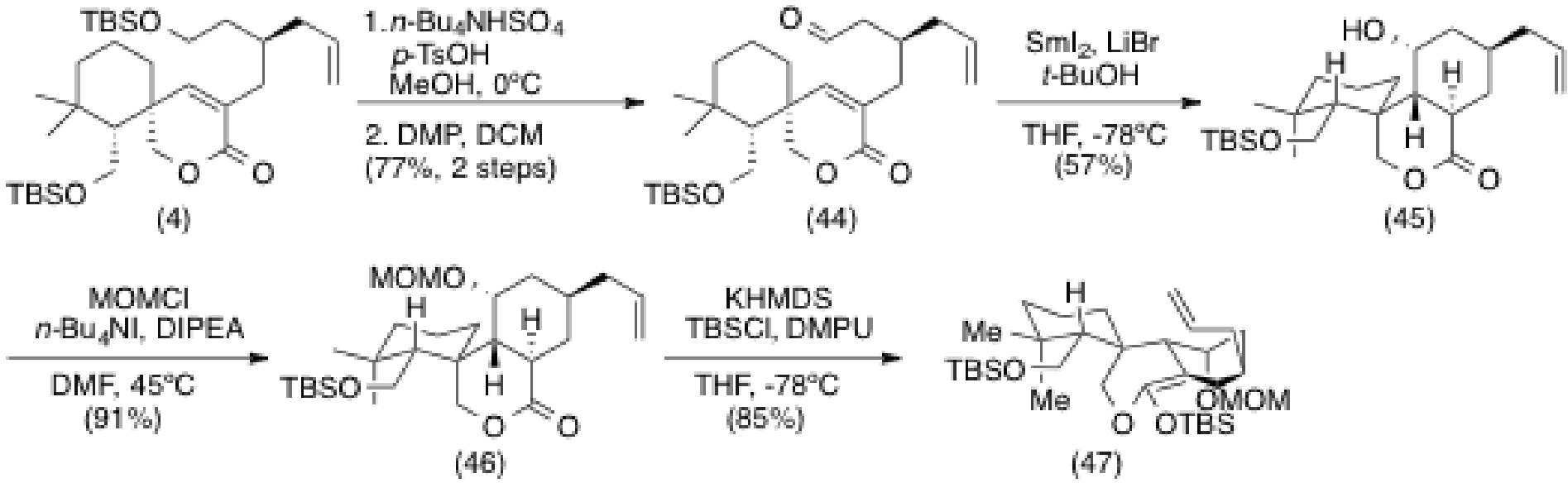
Pd(II)-mediated oxidative cyclization

Retro Synthesis of (−)-Trichorabdal and Longikaurin E

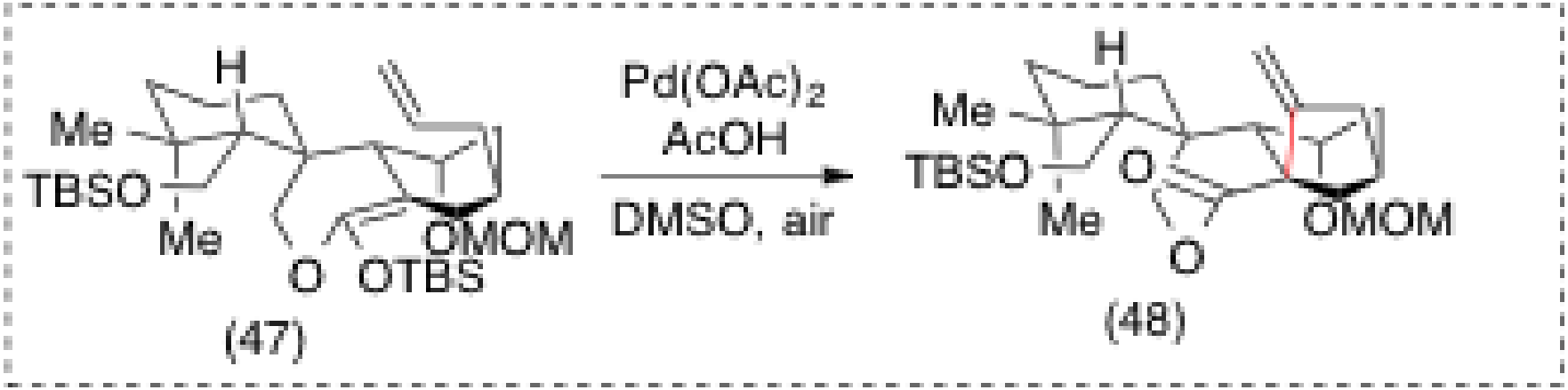


Sarah E. Reisman, *et al. J. Am. Chem. Soc*. **2013, *135*, 11764.**

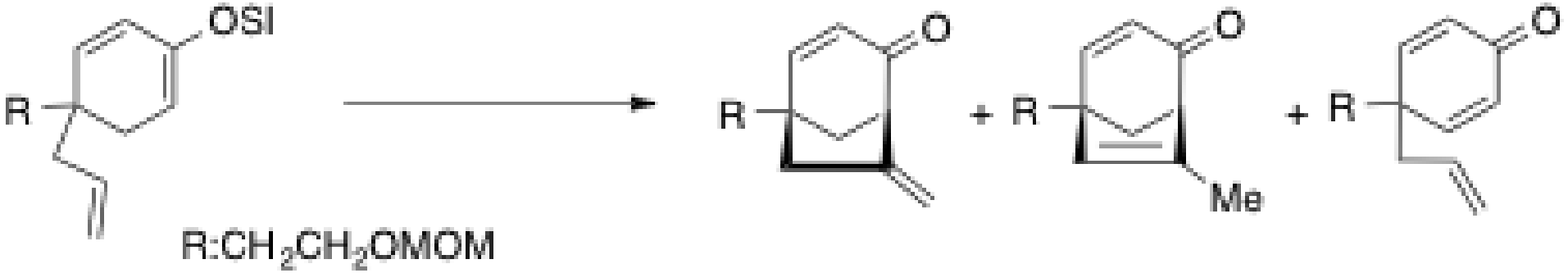
Synthesis of an Oxidative Cyclization Substrate



Pd(II)-Mediated Cascade Cyclization



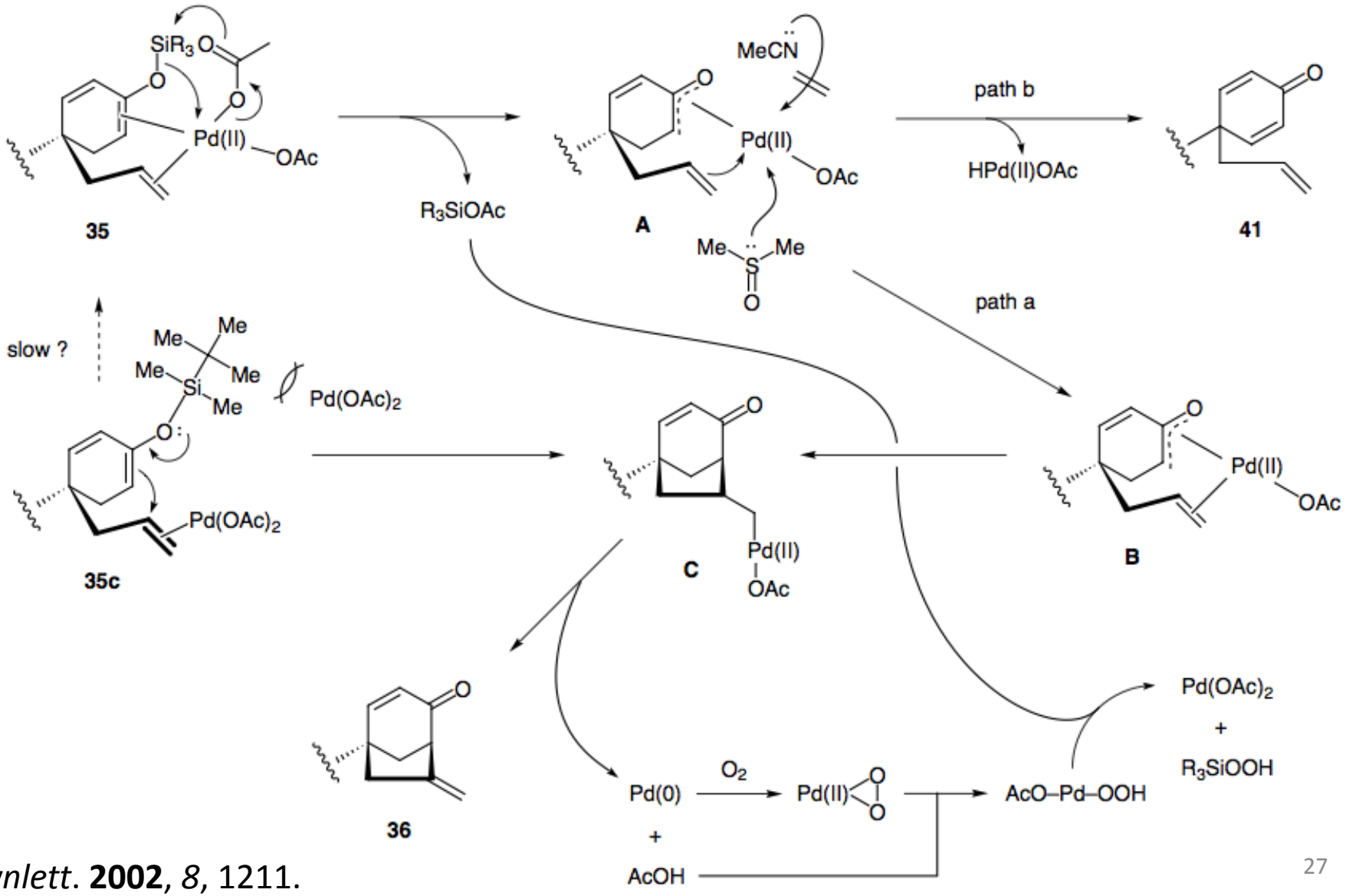
Pd(II)-Mediated Cascade Cyclization
Silyl Enol Ether and Solvent Effect



Run	Si	$Pd(OAc)_2$	Solvent (0.05M)	50	51	52	49
1	TMS	10 mol %	DMSO	62	trace	21	–
2	TES	10 mol %	DMSO	76	trace	14	–
3	TBS	10 mol %	DMSO	81	4	5	–
4	TBS	10 mol %	MeCN	37	trace	trace	trace

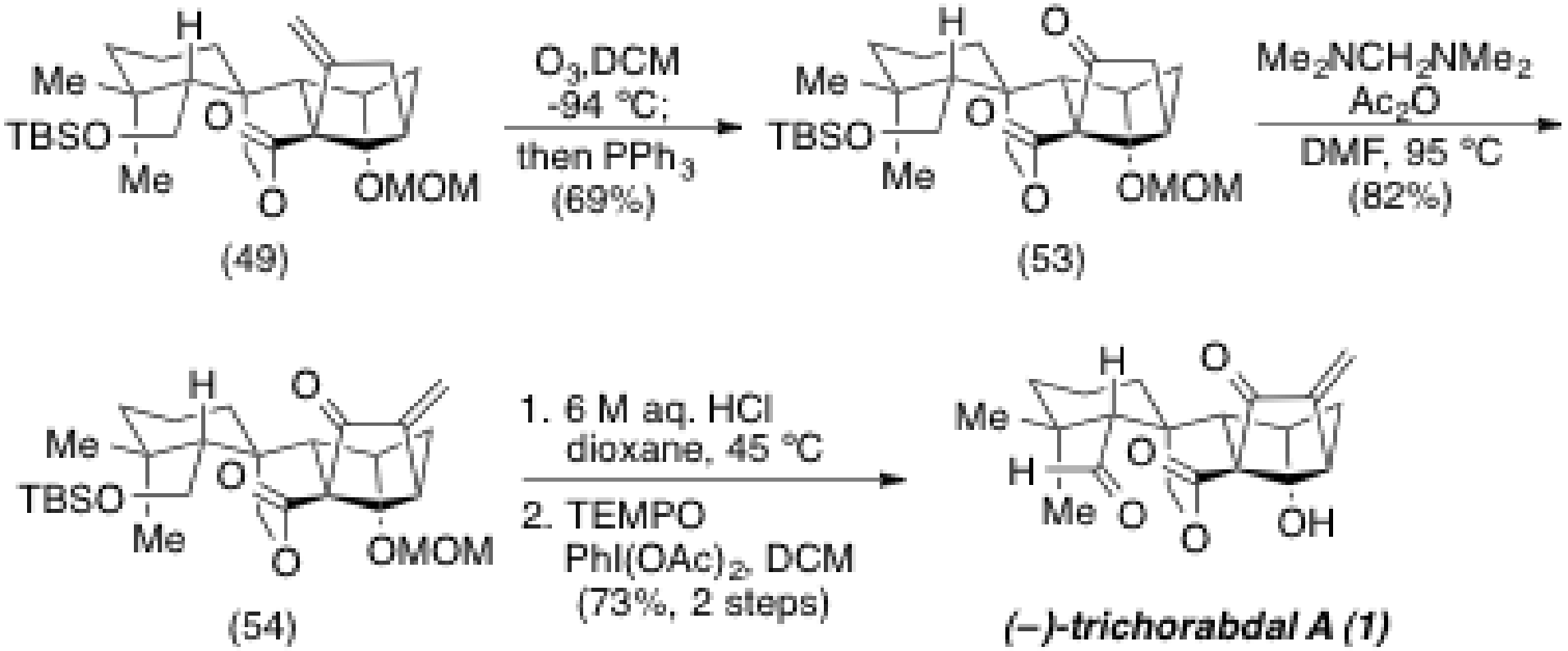
Synlett. **2002**, *8*, 1211.

Mechanism of Pd(II) cascade cyclization

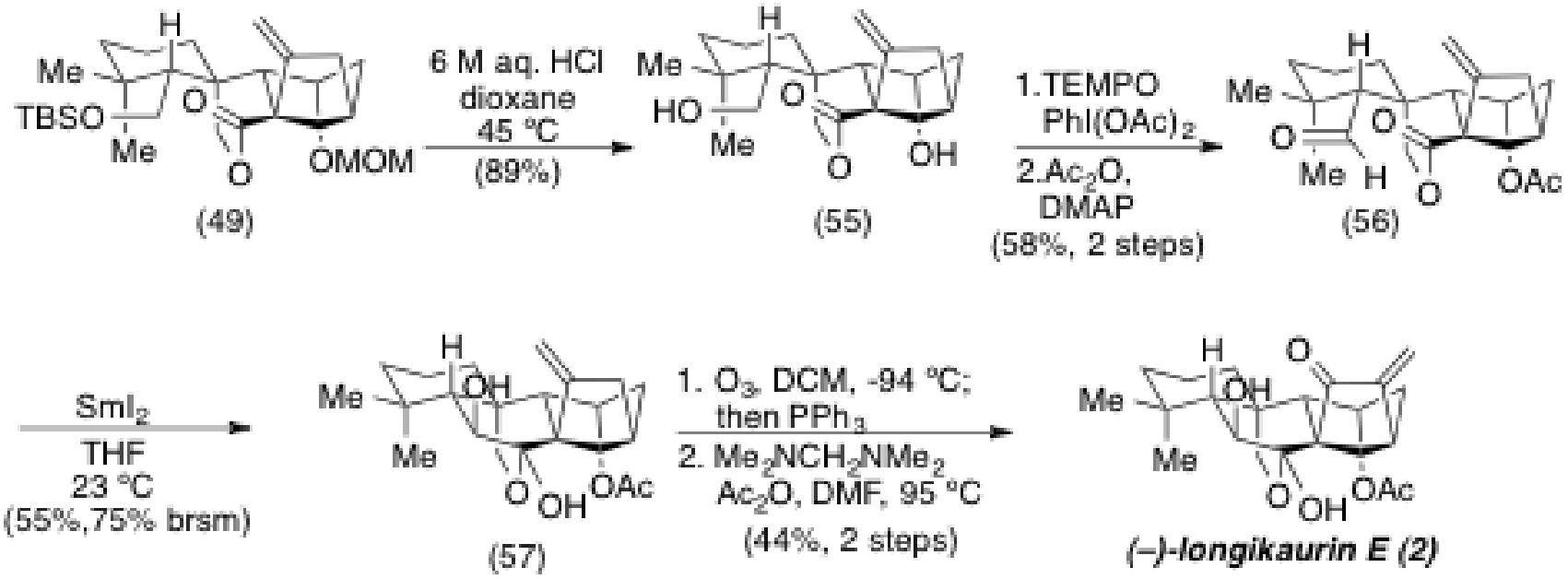


Synlett. **2002**, *8*, 1211.

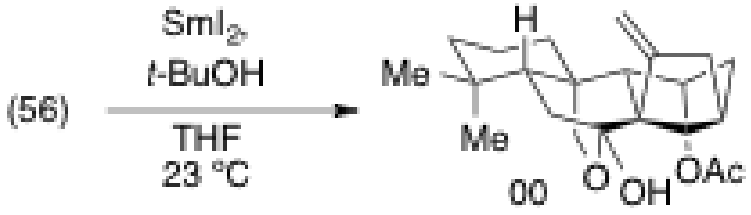
Total Synthesis of (–)-Trichorabdal A



Total Synthesis of (–)-longikaurin E



Sm^{II}-mediated pinacol type coupling - additives such like LiCl, LiBr, or *t*-BuOH.



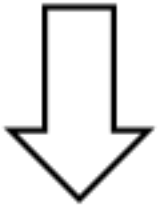
Over-reduction of the product

Direct reduction of the aldehyde to the primary alcohol

Summary(2)

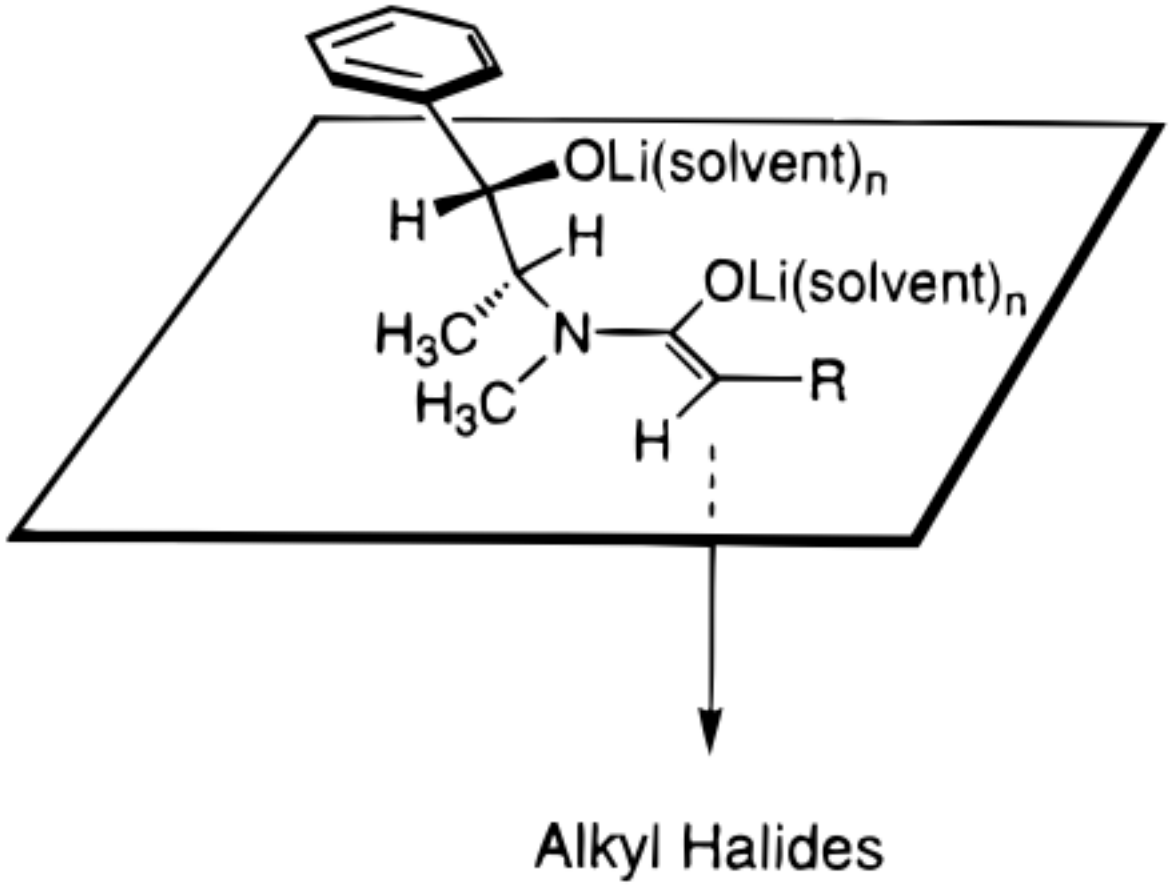
A unified synthetic stratedy has enabled the fisrt total synthesis of (–)-trichorabdal A and (–)-longikaurin E in 15 and 17 steps, respectively, from (–)-γ-cyclogeraniol.

A unfied synthetic strategy is employed that
relies on a Pd-mediated oxidative cyclization to
***generate all-carbon quaternary center**
***builds the bicyclo[3.2.1]octane frame work.**



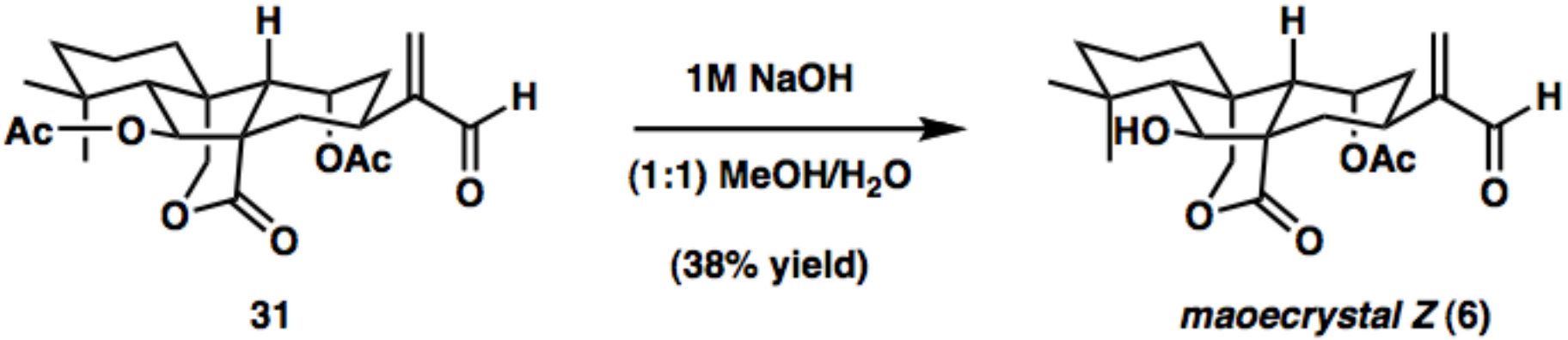
These studies have identified a clear, non-biomimetic, synthetic relationship several structually distinct *ent*-lauranoid diterpenoids.

Proposed Reactive Conformation



Bryant H. *Yang, et al ,J. Am. Chem. Soc*. **1997**, 119, 6496.

Mono Deacetylation

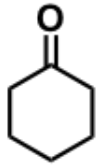
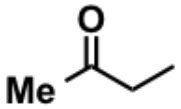
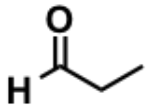
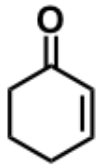
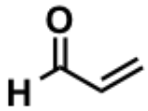
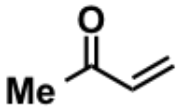


31

maoecrystal Z (6)

Conditions for selective hydrolysis:	6	diol	C6-monoacetate
1M NaOH, EtOH	1	4	0
1M NaOH, THF	0	100	0
1M NaOH, 1:1 MeOH/H_2O	1.6	1	1
1M NaOH, 1:4 MeOH/H_2O	1	4	0.1

Reduction Potential

compound		$E_{1/2}$ (V) - reduction potential
cyclohexane		-2.45
methyl ethyl ketone		-2.25
propionaldehyde		-1.8
cyclohex-2-en-1-on		-1.55
acrolein		-1.50
methyl vinyl ketone		-1.42

*Measured by cyclic voltammetry

Optimization of Oxidative Cyclization

Table 1. Reaction Optimization for the Formation of 20

entry	Pd source (equiv)	additive (equiv)	yield **20** (%)[a]
1	$Pd(OAc)_2$ (0.1)	–	7
2	$Pd(OAc)_2$ (1.0)	–	35
3[b]	$Pd(OAc)_2$ (1.0)	–	28[c]
4	$Pd(TFA)_2$ (1.0)	–	19
5	$PdCl_2$ (1.0)	–	0
6	$PdCl_2$ (1.0)	$AgBF_4$ (2.0)	5[d]
7[e]	$Pd(OAc)_2$ (1.0)	H_2O (5.0)	38
8	$Pd(OAc)_2$ (1.0)	K_2CO_3 (5.0)	0
9	$Pd(OAc)_2$ (1.0)	AcOH (0.5)	56
10	$Pd(OAc)_2$ (0.1)	AcOH (0.5)	7
11	$Pd(OAc)_2$ (1.0)	AcOH (1.0)	31
12	$Pd(OAc)_2$ (1.0)	*p*-TsOH (0.5)	46
13	$Pd(OAc)_2$ (1.0)	BzOH (0.5)	32
14	$Pd(OAc)_2$ (1.0)	PivOH (0.5)	40

[a]Isolated yield. [b]Reaction conducted in MeCN at 23 °C. [c]Product isolated as an inseparable 4.3:1 mixture with an olefin isomerization side product. [d]13% yield of a Wacker oxidation product was also isolated. See Supporting Information. [e]Run under a N_2 atmosphere.