Literature Report 2

Stereocontrolled Synthesis of Kalihinol C

Reporter: Huanping Xie
Checker: Xiang Gao
Date: 2017-04-17

Reiher, C. A.; Shenvi, R. A. *J. Am. Chem. Soc*. **2017**, *139*, 3647−3650.

Contents

Biography

Ryan A. Shenvi
Associate Professor
in TSRI

Areas of interest:

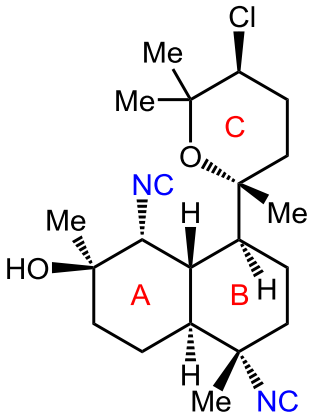
- Synthesis of natural products, or secondary meta-bolites, a vast molecular library for disease target identification, clinical study;
- The invention of new chemical methods to simplify complex molecule synthesis.

Research experience:

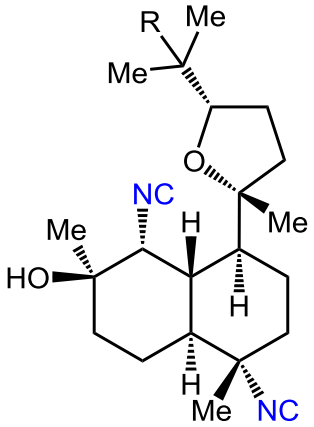
- 2008-2010 NIH Postdoctoral Fellow, Harvard University (E. J. Corey),
- 2003-2008 Ph.D., The Scripps Research Institute (P. S. Baran),
- 1999-2003 B.S., Pennsylvania State University (R. L. Funk).

Introduction

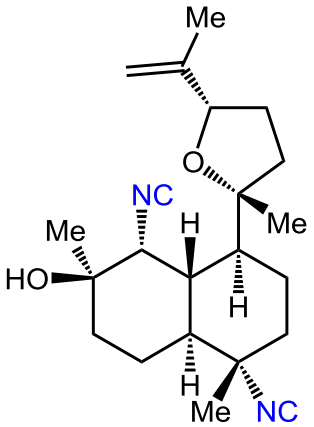
Examples of Kalihinols(卡利辛醇)



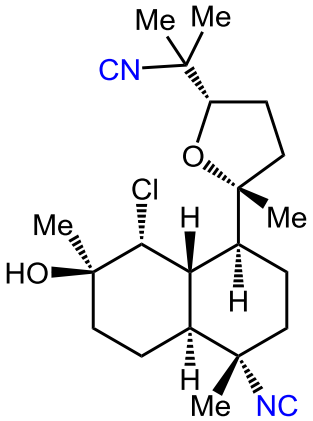
Kalihinol A



R = Cl **Kalihinol B**
R = NC **Kalihinol F**
R = SNC **Kalihinol G**



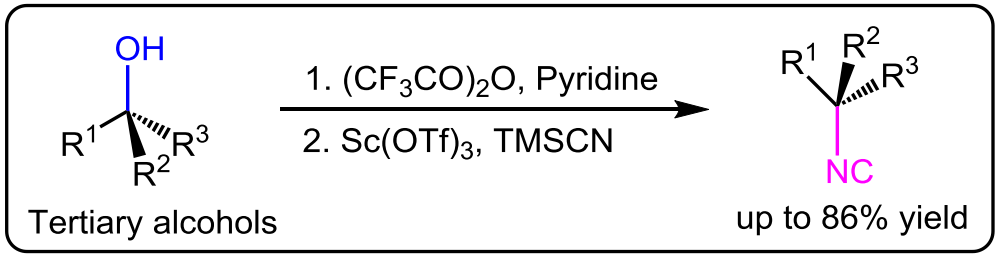
Kalihinol C



Kalihinol D

Reiher, C. A.; Shenvi, R. A. *J. Am. Chem. Soc*. **2017**, *139*, 3647.
Daub, M. E.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2015**, *137*, 4912.

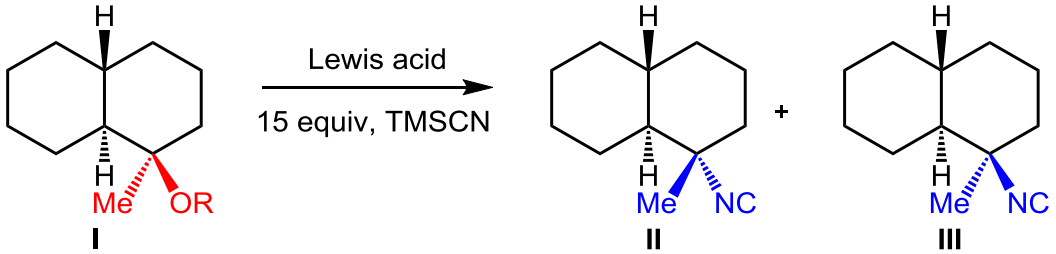
LA-catalyzed Isocyanation



- Stereoselective reaction with inversion of configuration;
- Works best on minimally branched linear tertiary alcohols and comformational inflexible alicyclic alcohols;
- Chemoselective for tertiary-trifluoroacetyl esters in preference to secondary or primary ones, stable in solvolysis conditions.

Pronin, S. V.; Reiher, C. A.; Shenvi, R. A. *Nature*, **2013**, *501*,195.

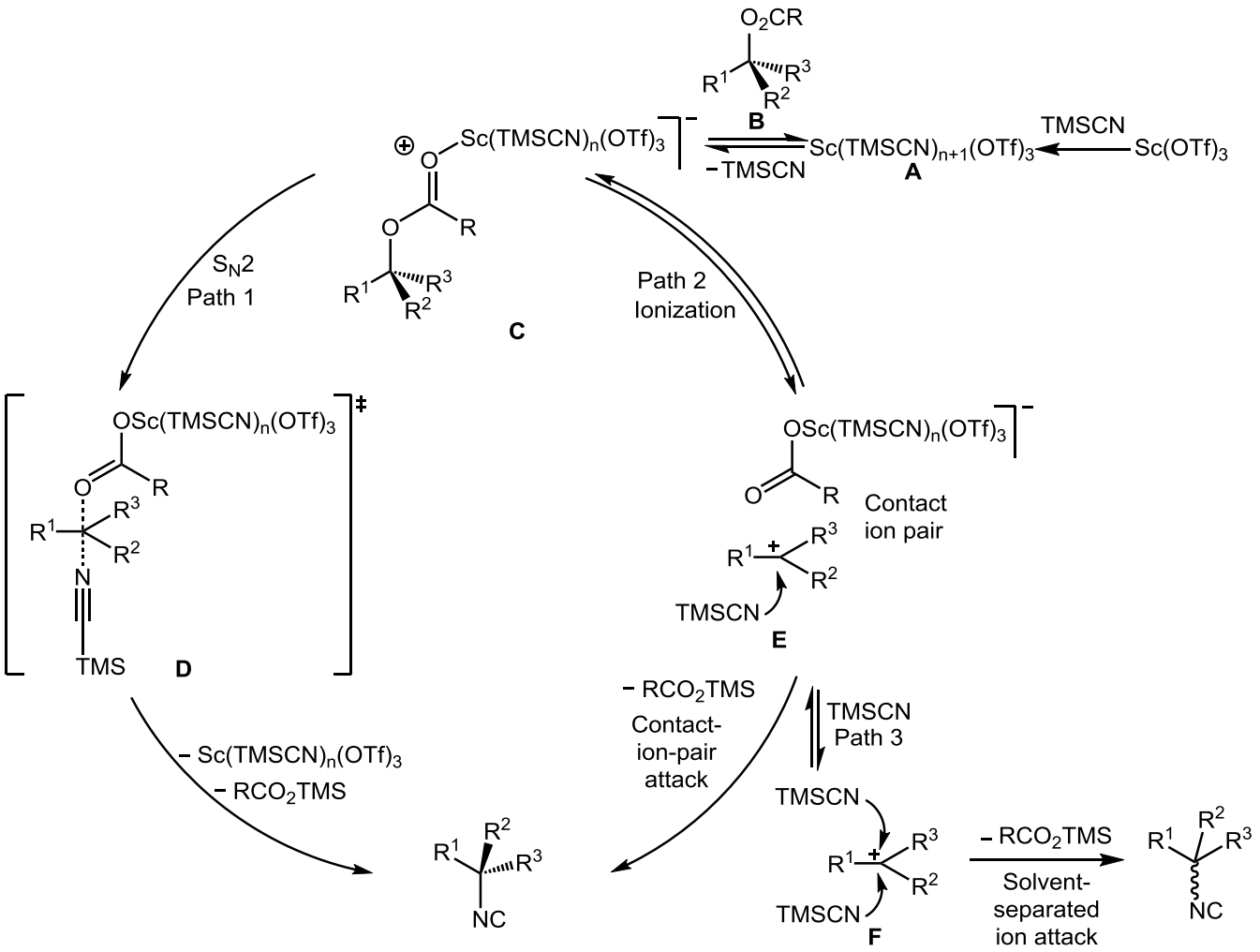
Optimization for Isocyanation



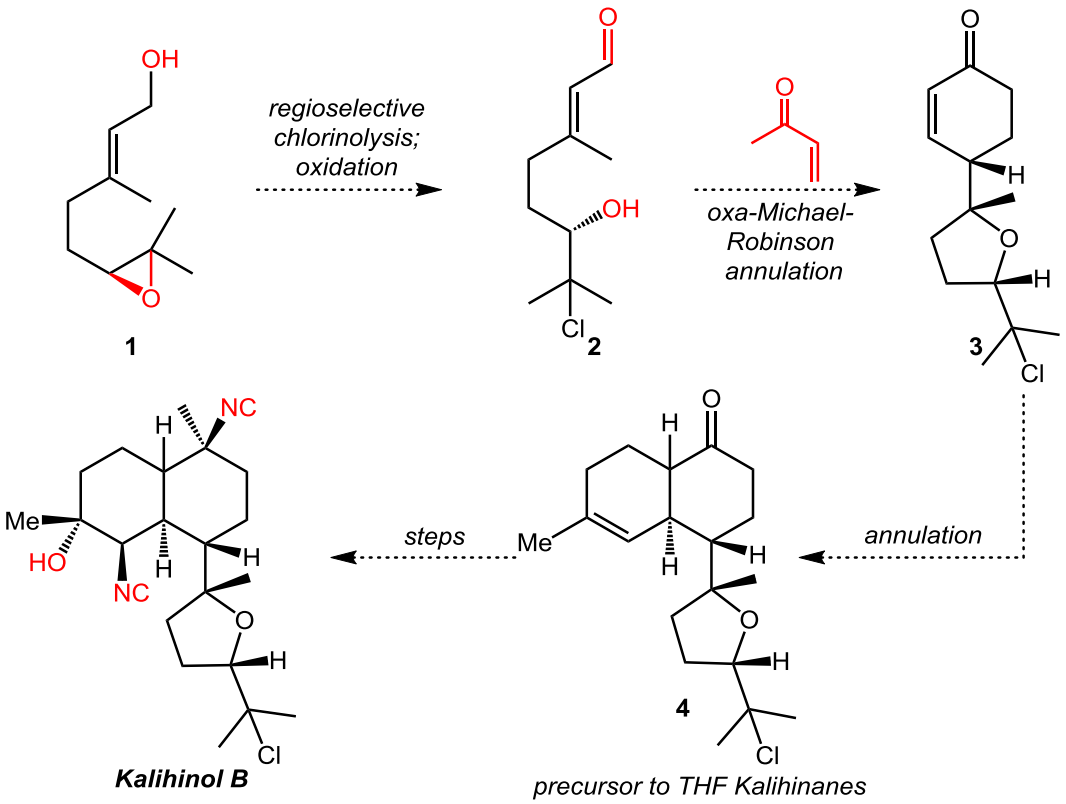
Entry	mol%	Lewis acid	R	Yield (%)	d.r.
1	10	$ZnBr_2$	TFA	0	n/a
2	5	$Mg(OTf)_2$	TFA	0	n/a
3	5	$Bi(OTf)_3$	TFA	14	49:51
4	5	$Y(OTf)_3$	TFA	70	84:16
5	3	$Sc(OTf)_3$	TFA	86	88:12
6	3	$Sc(OTf)_3$	H	0	n/a
7	3	$Sc(OTf)_3$	Ac	75	76:24
8	3	$Sc(OTf)_3$	CHO	61	66:34
9	3	$Sc(OTf)_3$	$C(O)C_2F_5$	69	85:15
10	3	$Sc(OTf)_3$	$C(O)C_3F_7$	79	87:13

Pronin, S. V.; Reiher, C. A.; Shenvi, R. A. *Nature*, **2013**, *501*,195.

Possible Reaction Pathways

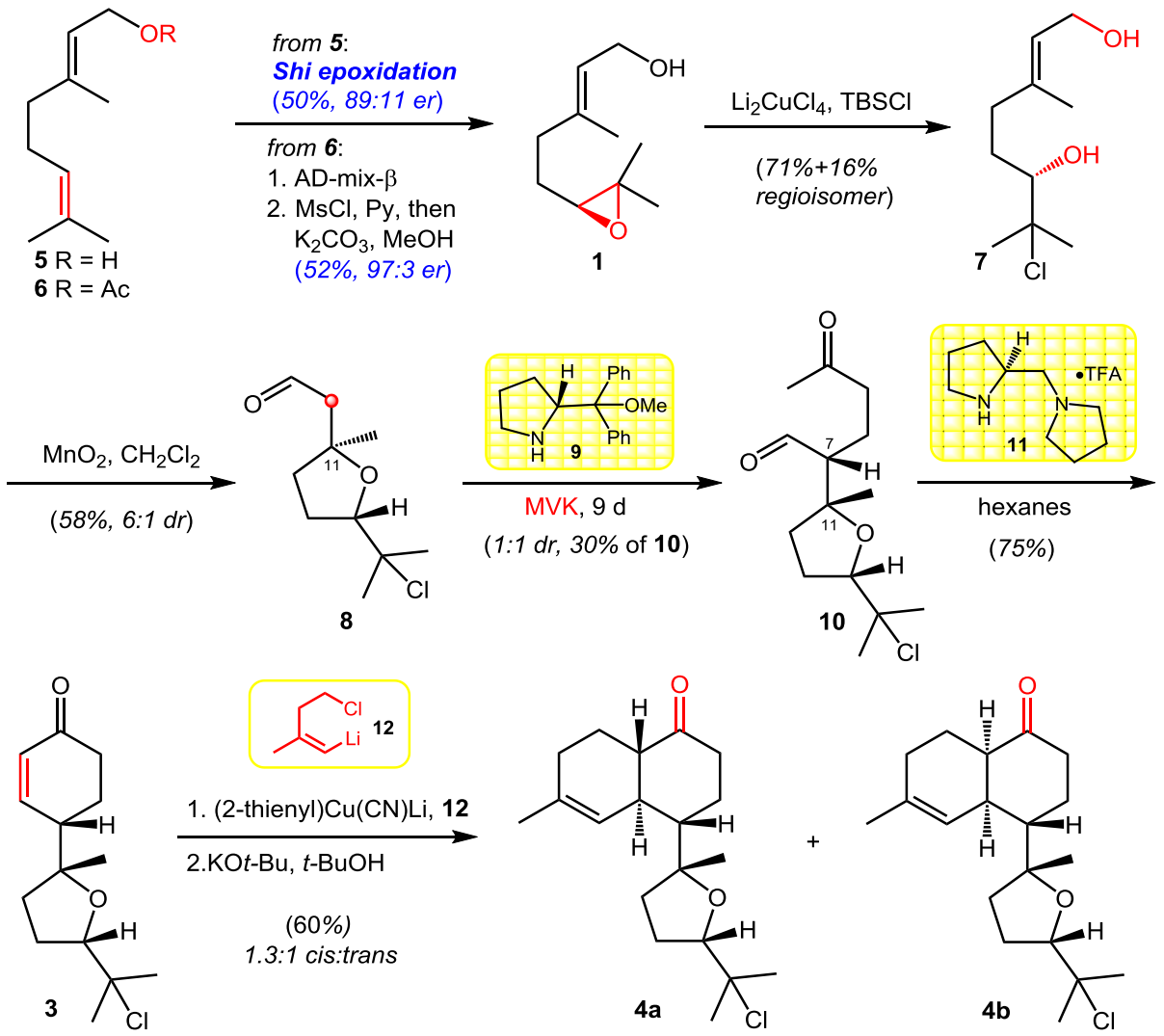


Strategy To Acess the THF Kalihinanes

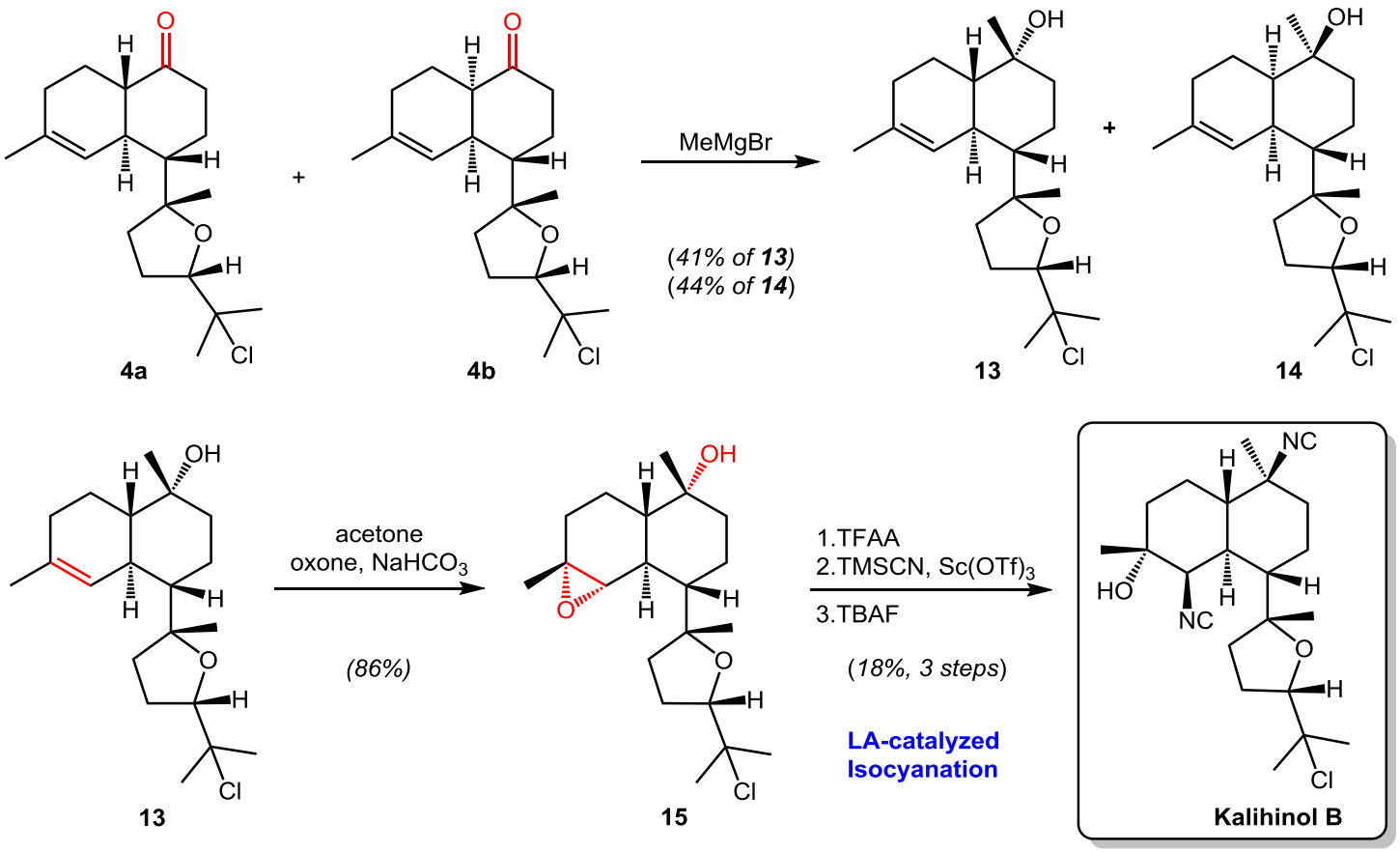


Daub, M. E.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2015**, *137*, 4912.

Enantioselective Synthesis of Kalihinol B

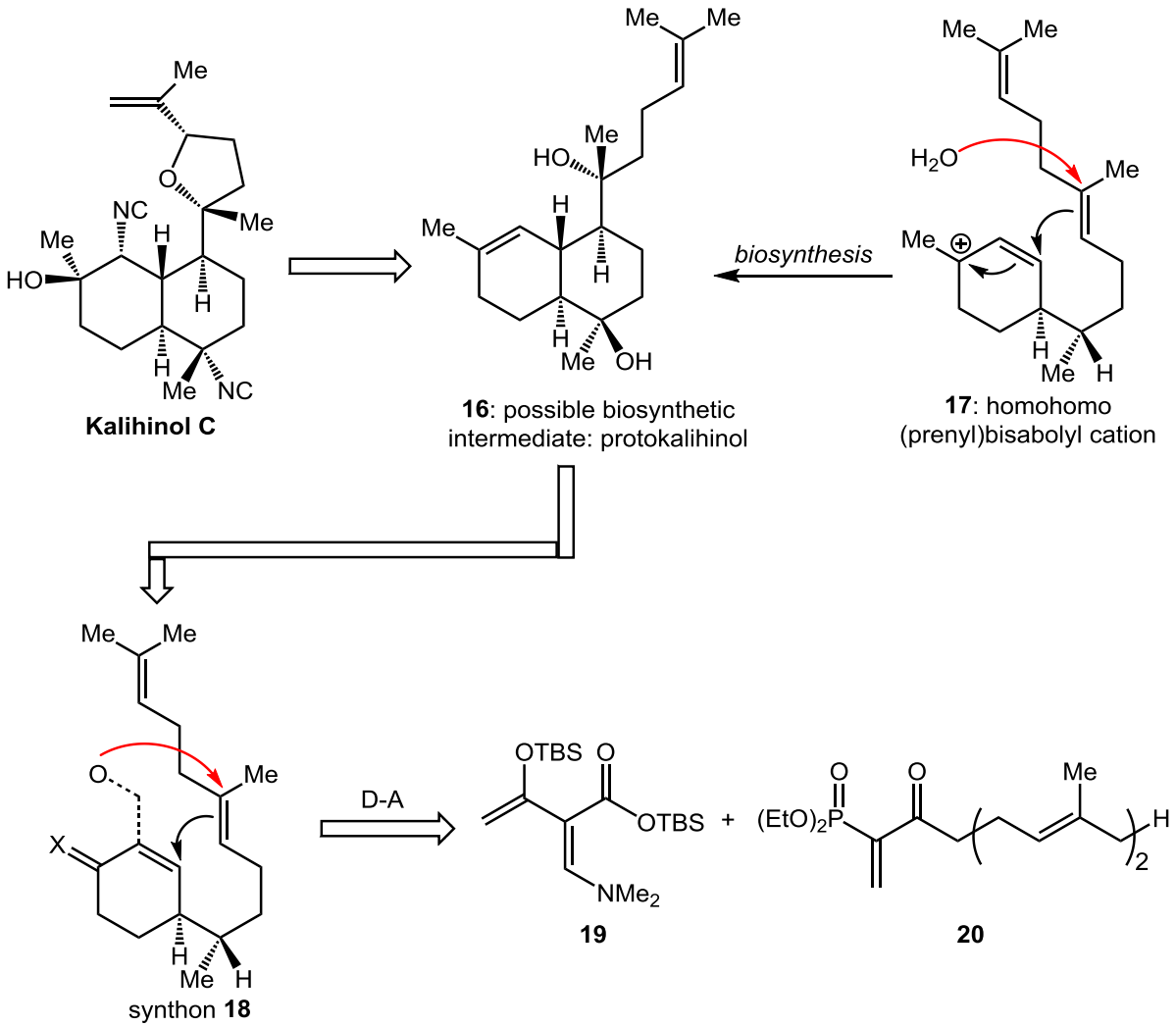


Enantioselective Synthesis of Kalihinol B



12 steps, 0.13% overall yield, poor stereocontrol

Retrosynthetic Convergence



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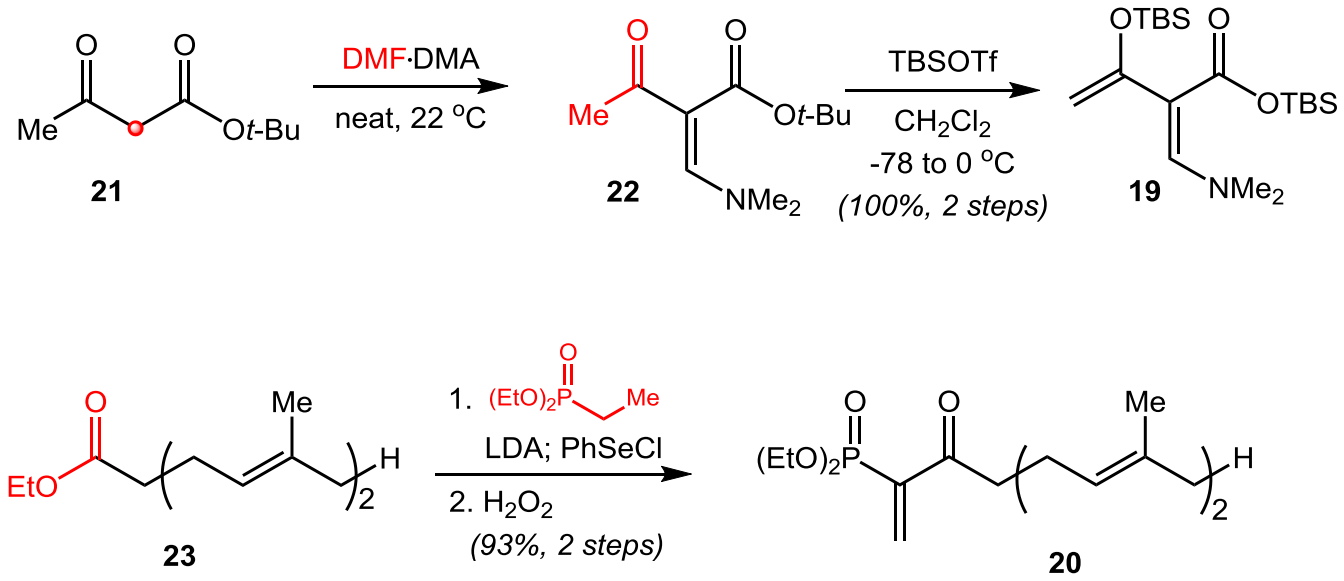
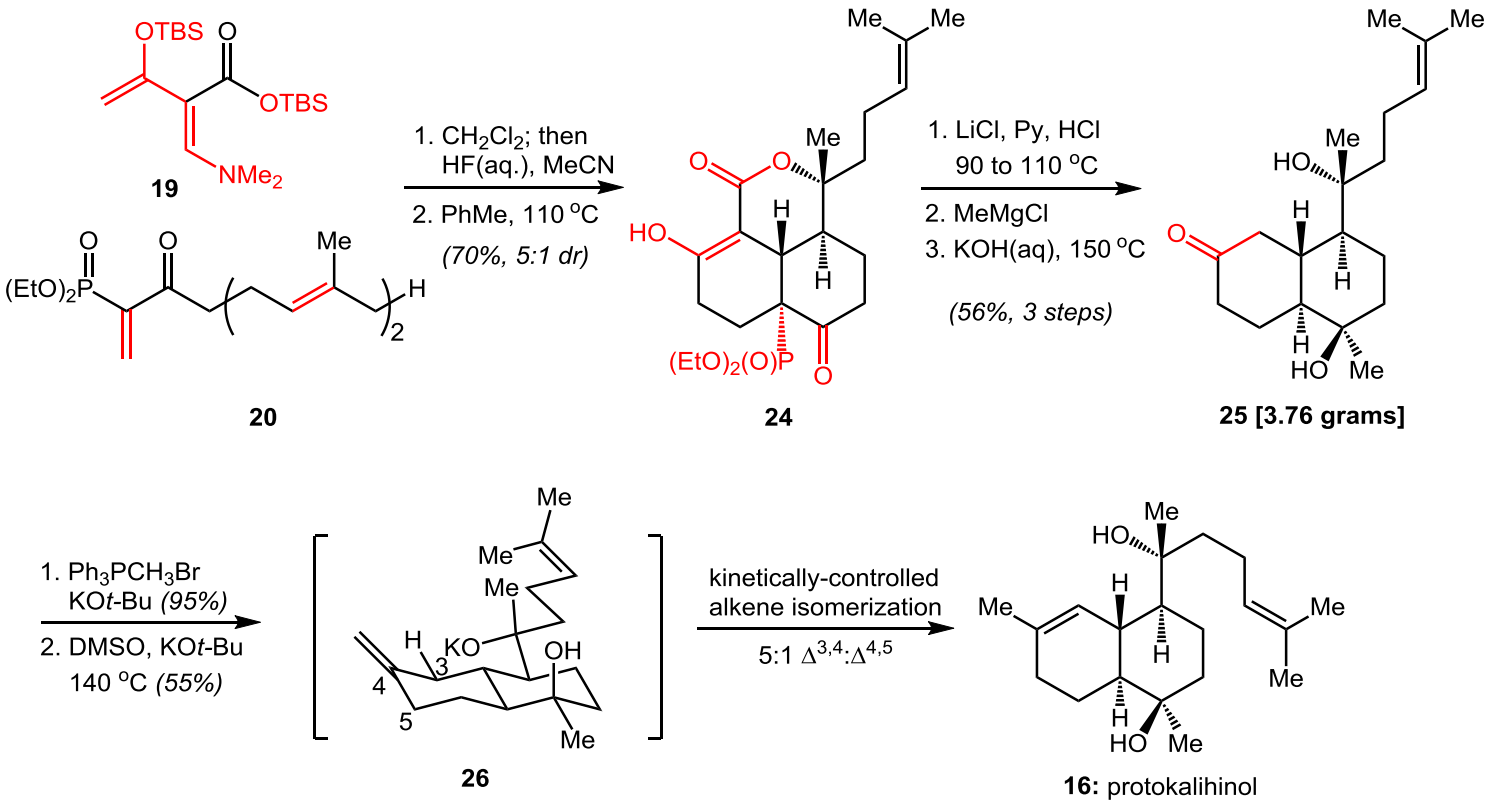
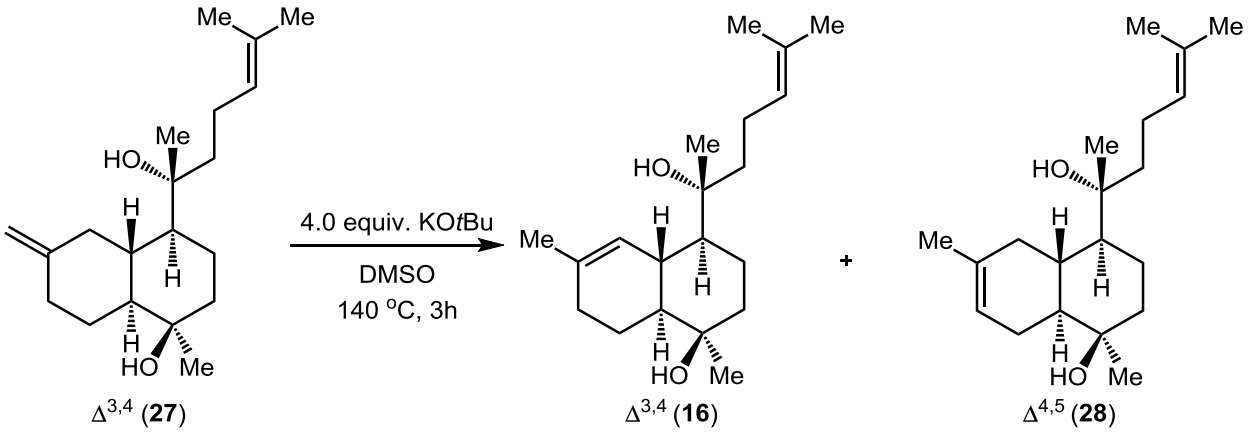
Routes to Building Blocks 19 and 20



Synthesis of 16



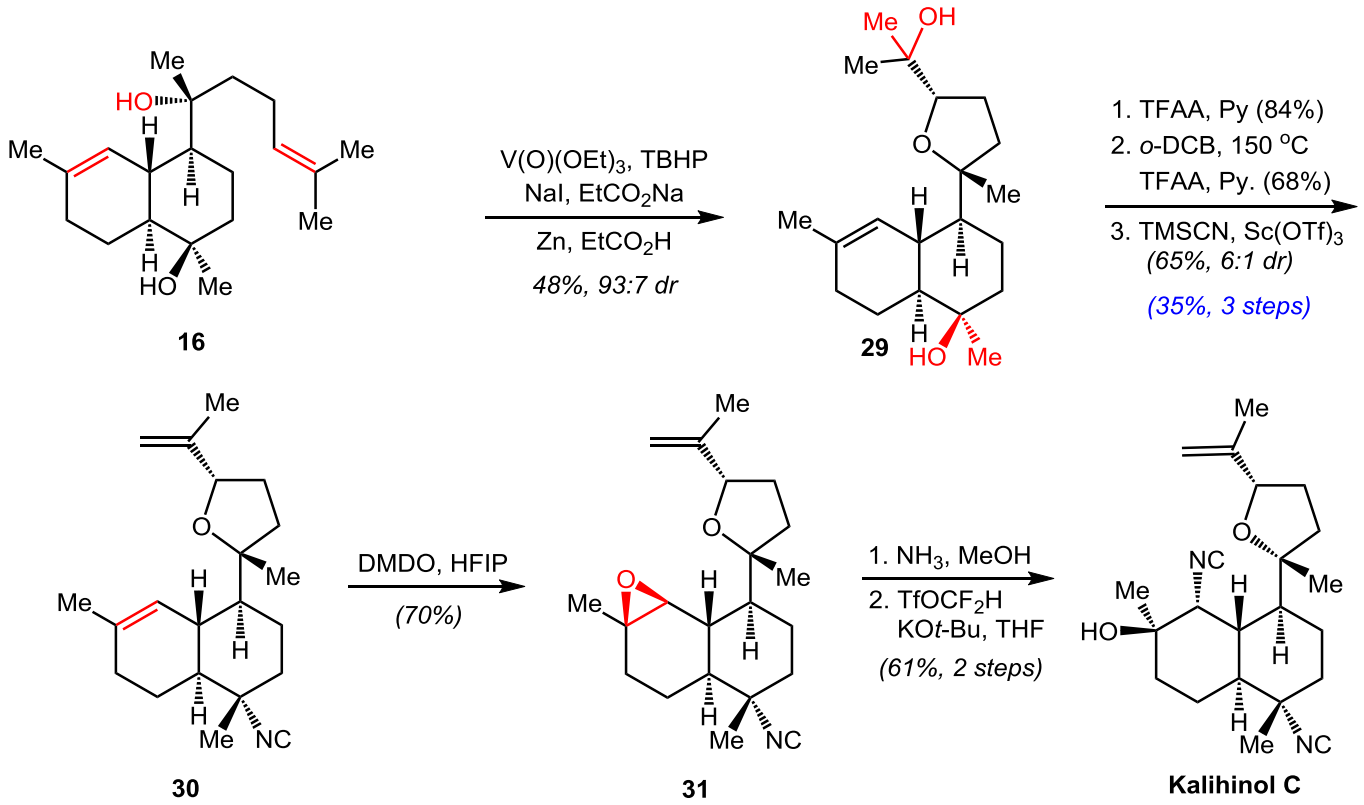
Alkoxide-Directed Alkene Isomerization



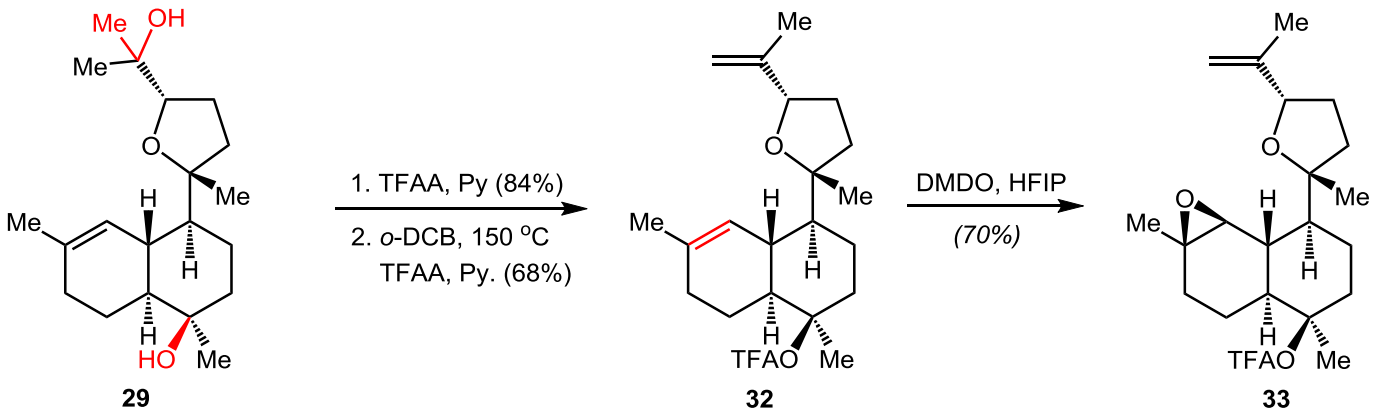
$\Delta^{3,4}$ (**27**) $\Delta^{3,4}$ (**16**) $\Delta^{4,5}$ (**28**)

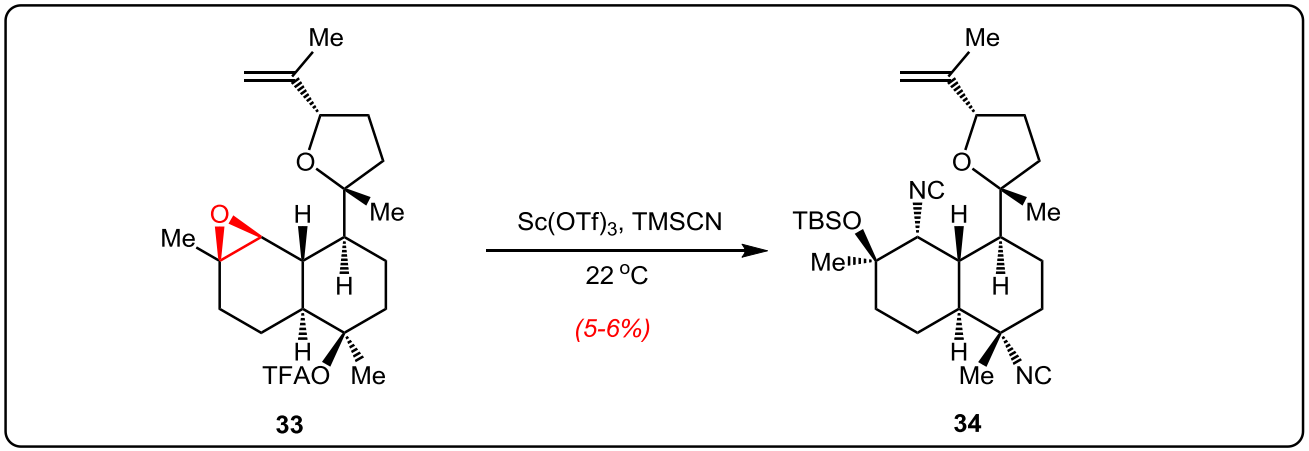
Entry	Conditions	Conversion (%)	**16**:**28**	%**16**
1	1.2 equiv. KH, DMSO	78	7:1	54
2	**4.0 equiv. KO*t*-Bu, DMSO**	**82**	**5:1**	**55**
3	16.0 equiv. KO*t*-Bu, DMSO	86	1:1	28
4	1.2 equiv. *n*-BuLi, DMSO	0		0
5	1.2 equiv. KH, DMPU	0		0

Synthesis of Kalihinol C

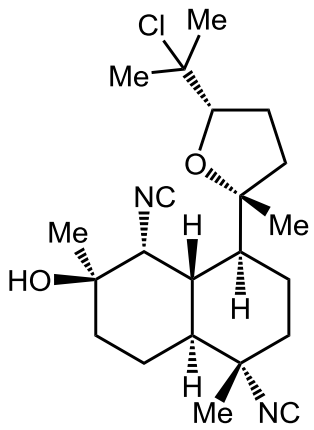


Tandem Isonitrile Formation





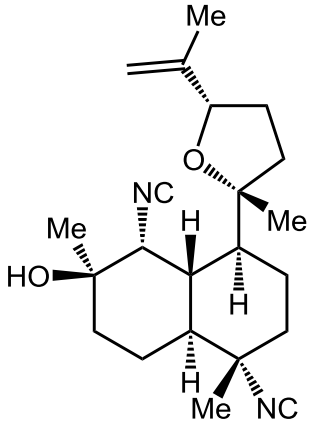
Summary



Kalihinol B

- 12 Steps,0.13% overall yield
- LA-catalyzed isocyanation
- Oxa-Michael−Robinson annulation

Daub, M. E.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2015**, *137*, 4912.



Kalihinol C

- 17 Steps,1.3% overall yield
- Directed alkene isomerization
- New strategy for isocyanation

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The first paragraph

The kalihinols possess the highest skeletal and functional group complexity of the biologically enigmatic isocyanoterpene (ICT) class. As part of a program to investigate the biological activity of ICTs, we have begun to develop effective chemical syntheses and associated methods to produce and modify three main structural classes: amphilectenes, adocianes, and kalihinols. Prior syntheses of the kalihinol class have fought to control stereochemistry in the functionally dense scaffolds, and each contains at least one uncontrolled (ca. 1:1 d.r.) stereogenic step. Here we report a short and fully stereocontrolled synthesis of kalihinol C enabled by a new heterodendralene building block, a directed alkene isomerization, and a new method for isonitrile synthesis.

The last paragraph

In summary, we have demonstrated a concise route to access the kalihinol ICTs via a putative biosynthetic intermediate, protokalihinol, that we anticipate can be divergently advanced to the natural series of metabolites. The synthesis compares favorably to the current best approach to the kalihinols by Vanderwal: it is longer in total step count (17 vs 12), but higher in yield by one order of magnitude (1.3% vs 0.13%). The higher efficiency derives from solutions to stereochemical and chemoselectivity problems raised by prior work, but left unsolved. Some of these solutions include (1) a method to synthesize the kalihinol stereotetrad using an iterative cycloaddition of the new building block, “heterodendralene”;

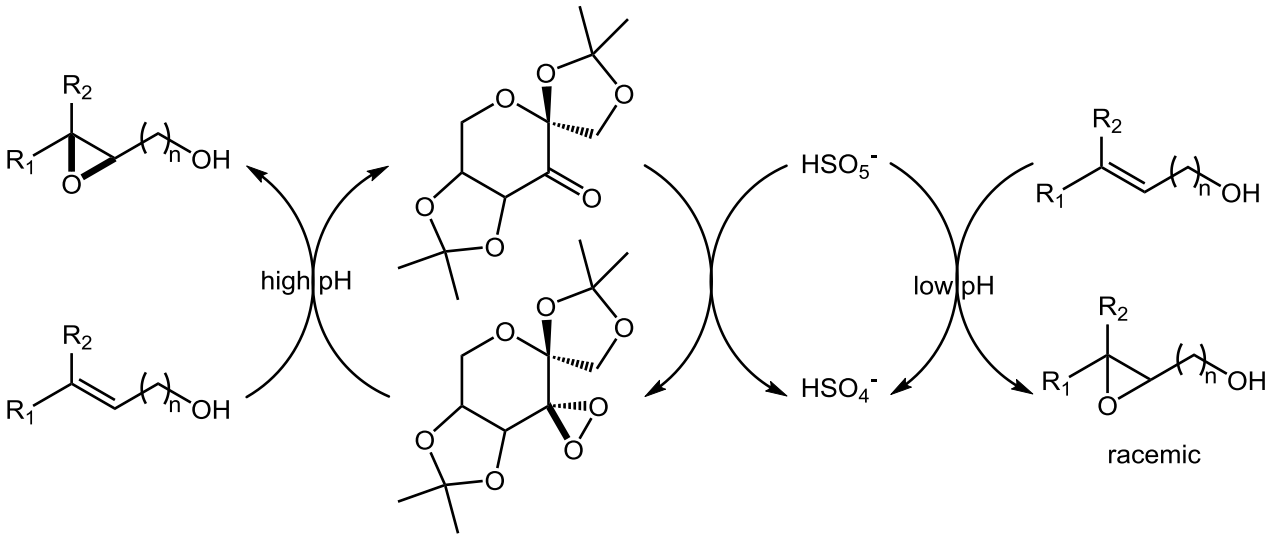
The last paragraph

(2) an alkoxide-directed isomerization method to access the thermodynamically disfavored $\Delta^{3,4}$ unsaturated trans-bifloran skeleton found throughout the diterpene class, and (3) a short, high-yielding, regio- and stereoselective strategy for installing the A-ring isocyanohydrin motif, including difluorocarbene-mediated isonitrile synthesis. This short and divergent route from protokalihinol allowed us to generate several analogs related to the metabolite series. We are currently using these compounds to interrogate the antiplasmodial activity and mechanism(s) of the kalihinol class.

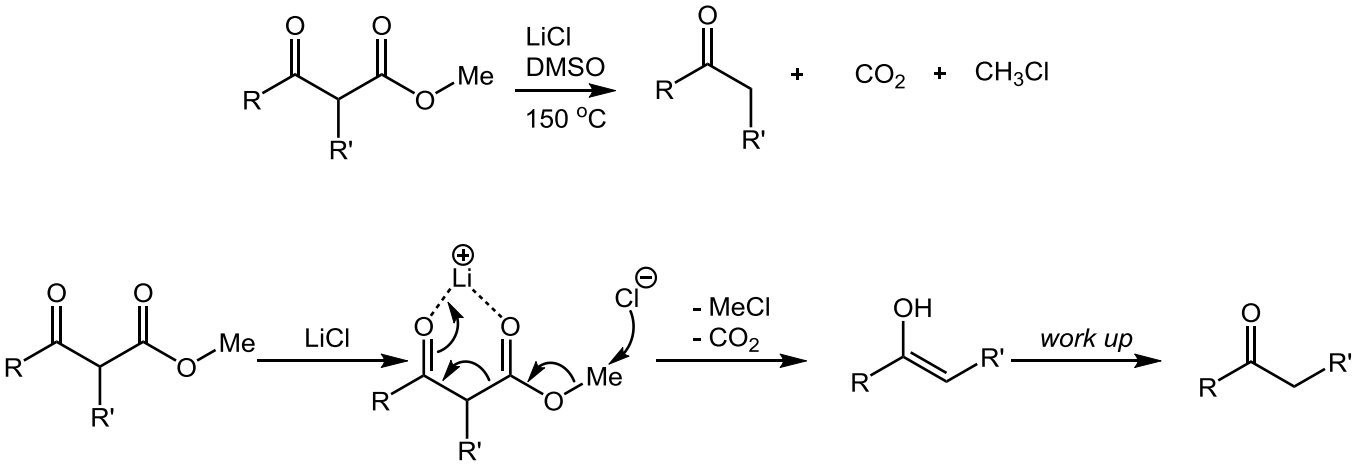
Acknowledgement

Thanks for your kind attention!

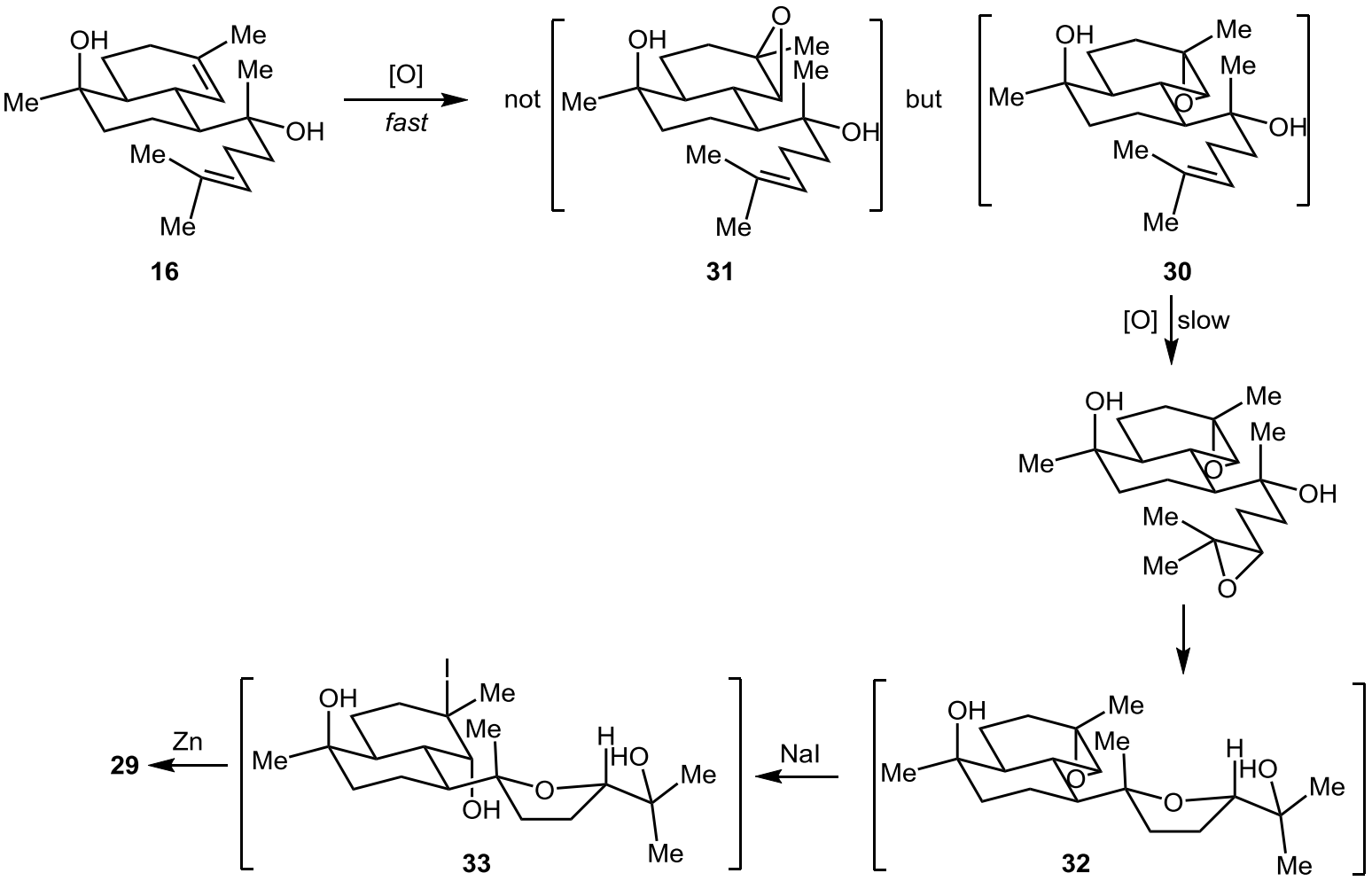
Shi Epoxidation



Krapcho Decarboxylation



Synthesis of kalihinol C



Synthesis of 24