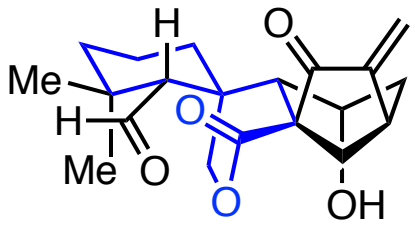
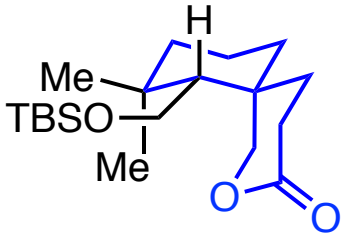
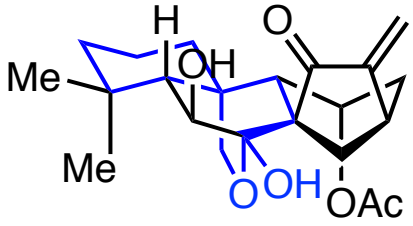
A Unified Strategy to *ent*-Kauranoid Natural Products: Total Syntheses of (–)-Trichorabdal A and (–)-Longikaurin E

John T. S. Yeoman, Victor W. Mak, and Sarah E. Reisman. *J. Am. Chem. Soc.* **2013**, *135*, 11764.



(–)-trichorabdal A

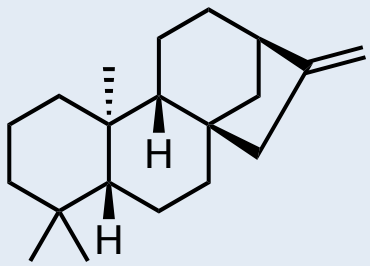




(–)-longikaurin E

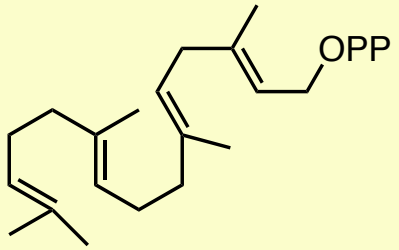
Kara George Rosenker
Wipf Group - Current Literature
24 August 2013

The *ent*-Kaurenes (Diterpenoids)



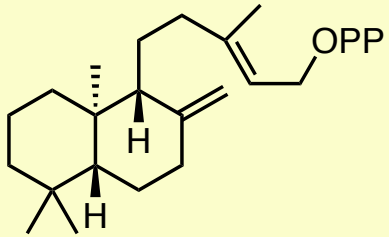
***ent*-kaurene**

- *Isodon* species have a long tradition in Chinese folk medicine for their curative properties
- Over 600 known *Isodon* diterpenoids (mainly *ent*-kaurenoids)
- Classified into 11 groups and 5 subgroups based on the different oxygenation and cleavage patterns
- Many of these compounds exhibit potent antibacterial, anti-inflammatory, and anticancer properties



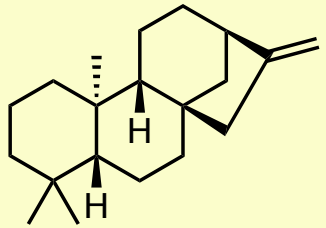
geranylgeranyl diphosphate (GGDP)

CPS



(–)-copalyl diphosphate

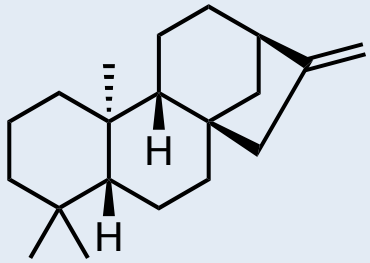
KS



***ent*-kaurene**

Sun, H.-D.; Huang, S.-X.; Han, Q.-B. *Nat. Prod. Rep.* **2006**, *23*, 673.
Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*. 3rd ed.; Wiley: Great Britain, 2008.

The *ent*-Kaurenes (Diterpenoids)



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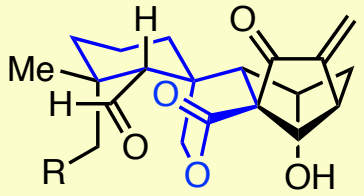
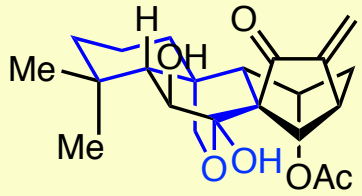
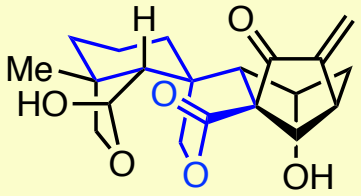


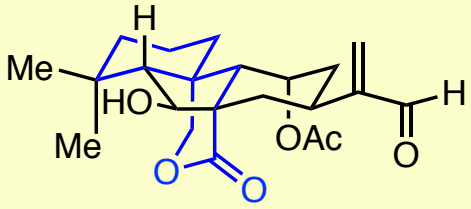
trichorabdal A (R = H)
trichorabdal B (R= OAc)



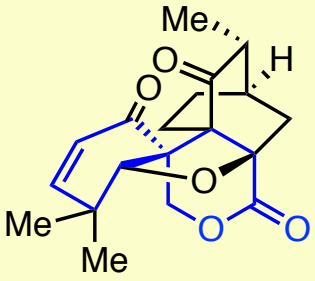
longikaurin E



shikodonin



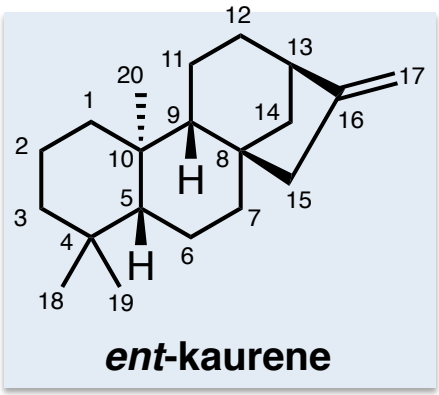
maoecrystal Z



maoecrystal V

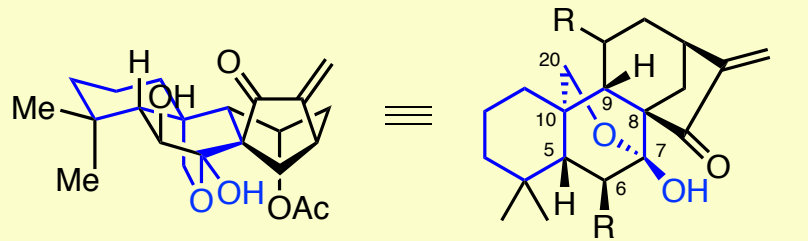
Sun, H.-D.; Huang, S.-X.; Han, Q.-B. *Nat. Prod. Rep.* **2006**, *23*, 673.

The *ent*-Kaurenoids: (–)-Trichorabdal A and (–)-Longikaurin E

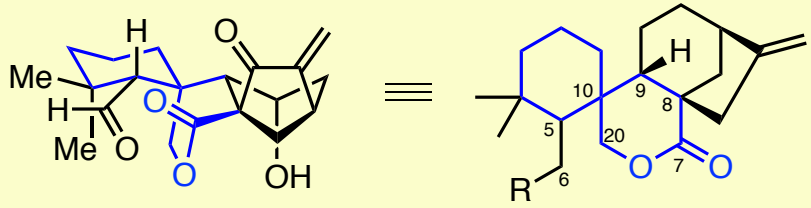


***ent*-kaurene**

- (–)-Longikaurin E was isolated in 1981 from *Rabdosia longituba*
  - *In vitro* growth inhibition against 5 human cancer cells lines (IC_{50}s < 10 μM; HL-60, SMMC-7721, A-549, MCF-7, SW-480)
- (–)-Trichorabdal A was isolated in 1981 from *Rabdosia trichocarpa*
  - Potent *in vivo* antitumor activity, IC_{50} = 548 nM (HeLa cells)
  - Modest antibacterial activity against *H. pylori*



(–)-longikaurin E ≡ **7,20-epoxy-*ent*-kaurane**

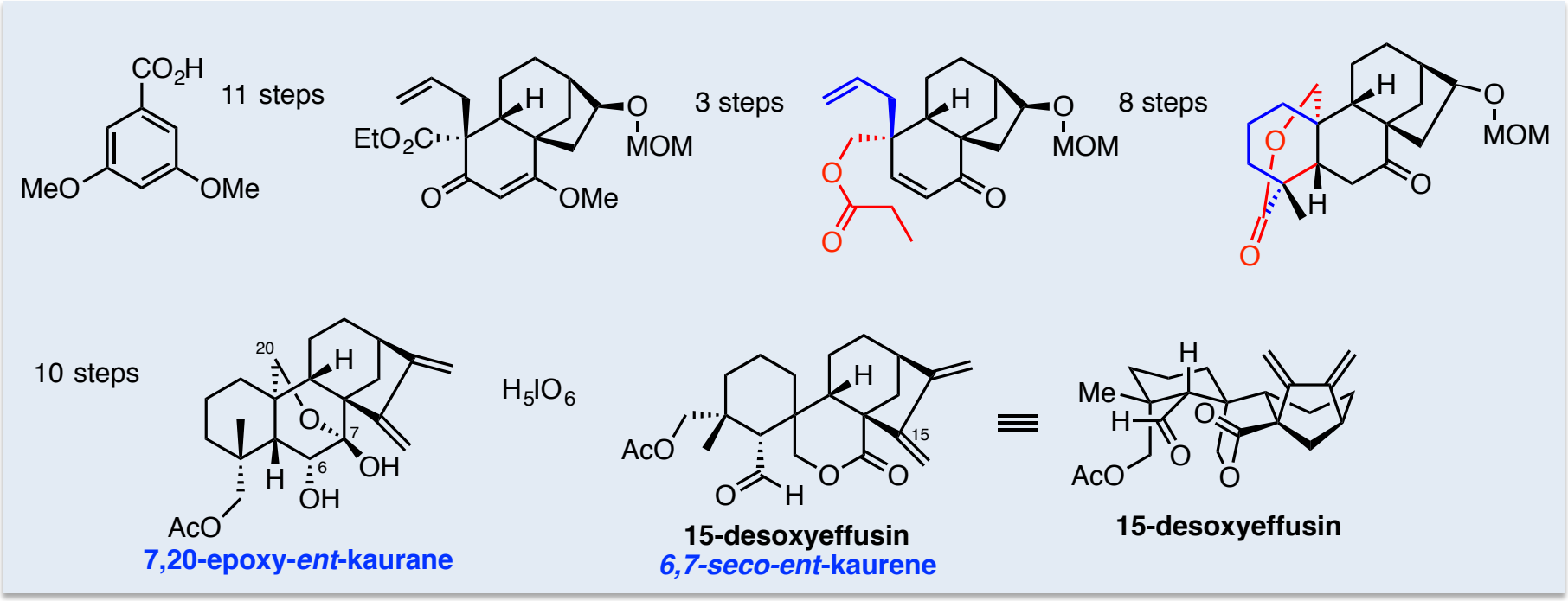


(–)-trichorabdal A ≡ ***6,7-seco-ent*-kaurene**

Fujita, E.; Fuji, K.; Sai, M.; Node, M.; Watson, W. H.; Zabel, V. *J. Chem. Soc. Chem. Commun.* **1981**, 899.; Fuji, K.; Node, M.; Sai, M.; Fujita, Takeda, S.; Unemi, N. *Chem. Pharm. Bull.* **1989**, *37*, 1472.; Kadota, S.; Basnet, P.; Ishii, E.; Tamura, T.; Namba, T. *Zbl. Bakt.* **1997**, *286*, 63. Fujita, T.; Takeda, Y.; Shingu, T. *Heterocycles* **1981**, *16*, 227. Zhao, W.; Pu, J.-X.; Du, X.; Su, J.; Li, X.-N.; Yang, J.-H.; Xue, Y.-B.; Li, Y.; Xiao, W.-L.; Sun, H.-D. *J. Nat. Prod.* **2011**, *74*, 1213.

Synthesis of 6,7-*seco*-*ent*-Karanoids

- In 1986 Mander and co-workers reported a 33-step synthesis of 15-desoxyeffusin

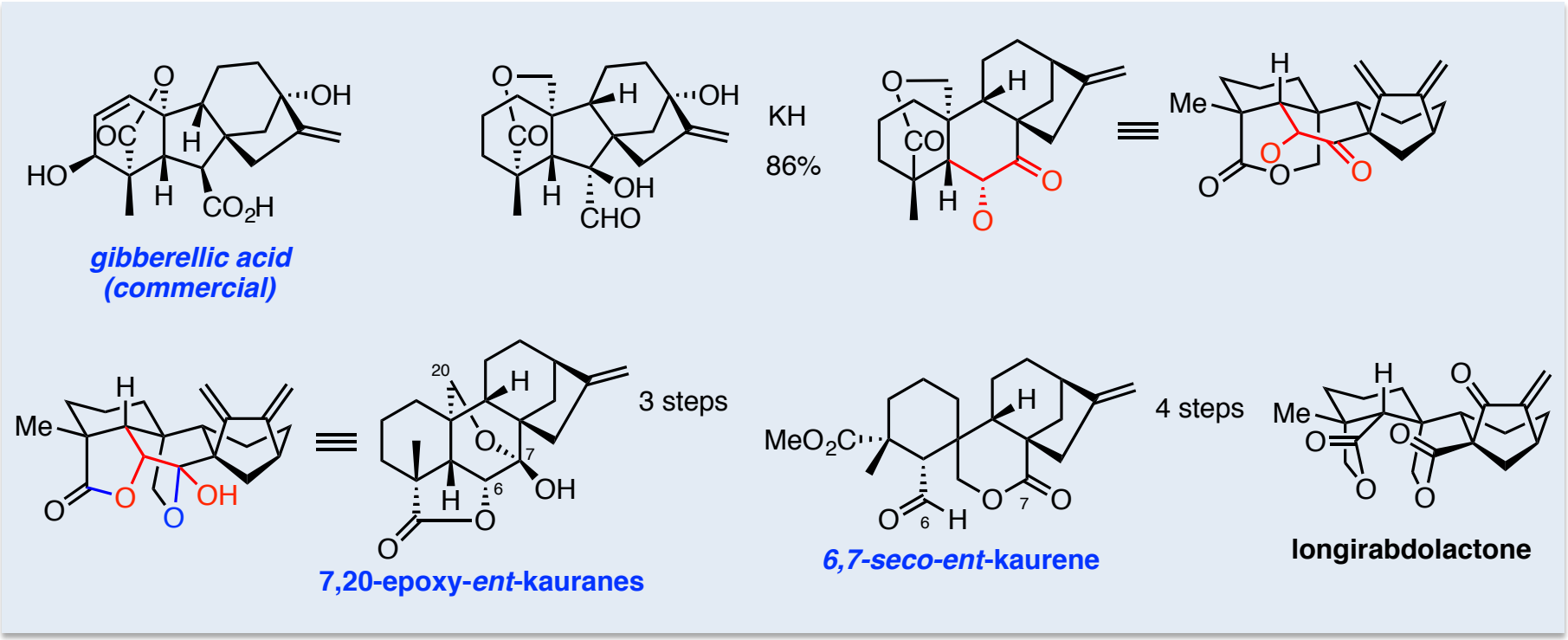


7,20-epoxy-*ent*-kaurane

Kenny, M. J.; Mander, L. N.; Sethi, S. P. *Tetrahedron Letters* **1986**, 27, 3923.
Kenny, M. J.; Mander, L. N.; Sethi, S. P. *Tetrahedron Letters* **1986**, 27, 3927.

Synthesis of 6,7-*seco*-*ent*-Karanoids

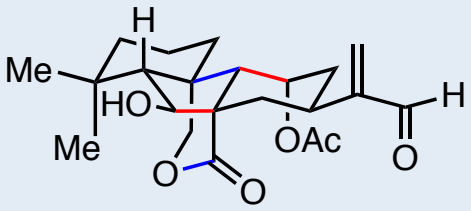
- 12 years later this group completed a 29-step semisynthesis of longirabdolactone



Adamson, G.; Mander, L. N. *Aust. J. Chem.* **2003**, *56*, 805.

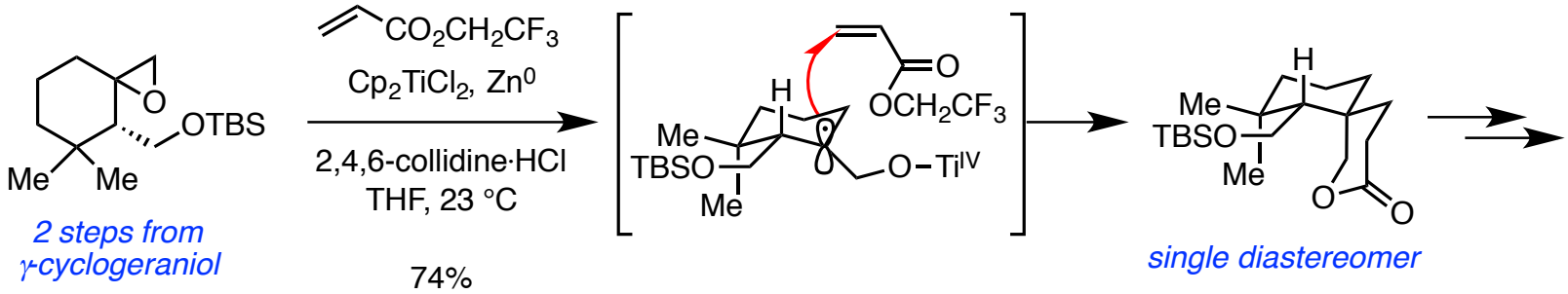
Total Synthesis of (–)-Maoecrystal Z

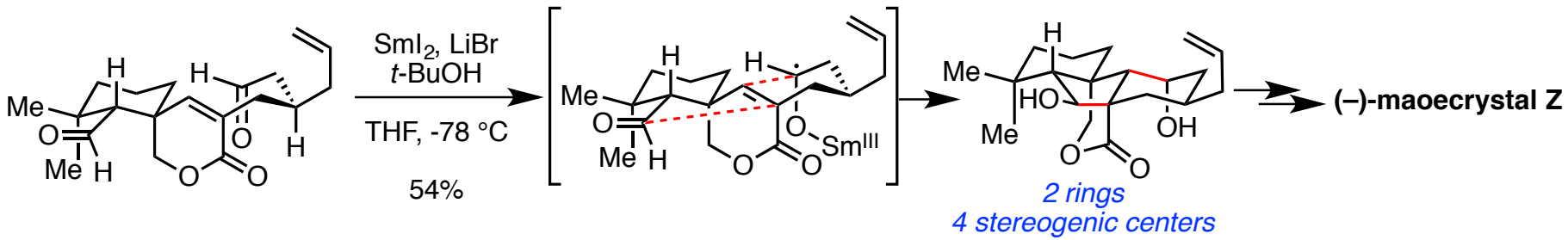
- First total synthesis of maoecrystal Z was reported in 2011 by Reisman and co-workers – 12 steps from (–)-γ-cyclogeraniol



(–)-maoecrystal Z

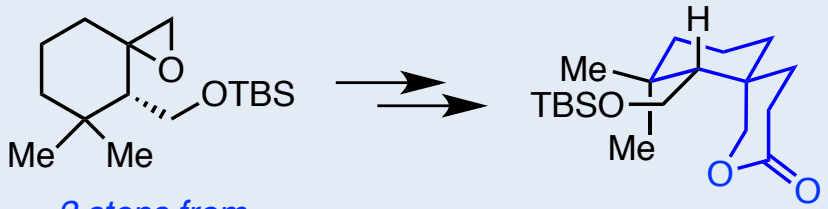
– Ti^{III}-mediated reductive epoxide coupling
– Sm^{II}-mediated reductive cascade cyclization

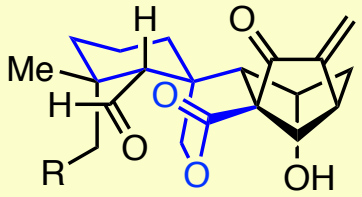




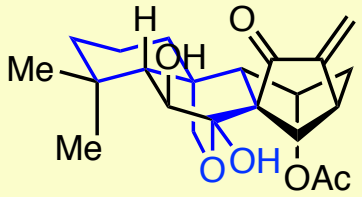
Cha, J.Y.; Yeoman, J. R. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964.
Szostak, M.; Procter, D. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 9238.

A Unified Strategy to *ent*-Kauranoid Natural Products

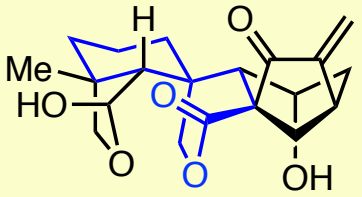




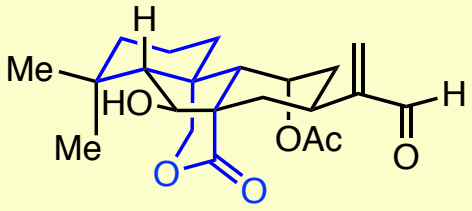
trichorabdal A (R = H)
trichorabdal B (R= OAc)



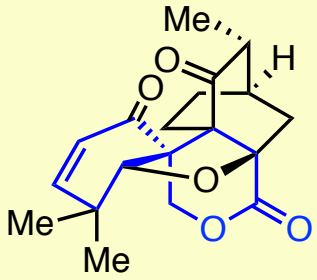
longikaurin E



shikodonin



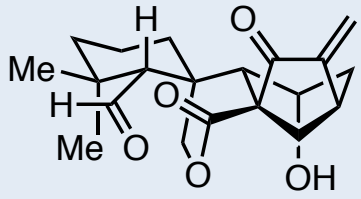
maoecrystal Z



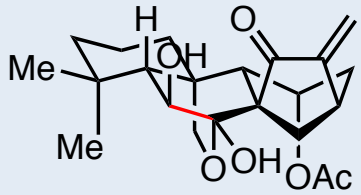
maoecrystal V

Cha, J.Y.; Yeoman, J. R. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964.
Yeoman, J.T. S.; Mak, V.W.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 11764.

Title Paper: Retrosynthetic Design for Trichorabdal A and Longikaurin E

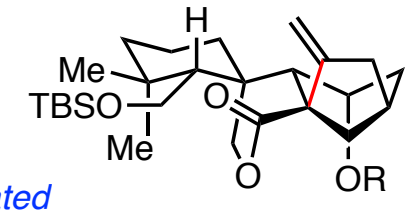


(–)-trichorabdal A

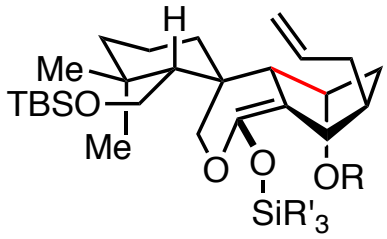


(–)-longikaurin E

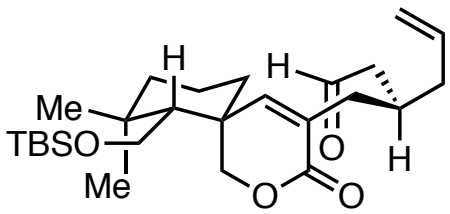
Sm-mediated reductive cyclization

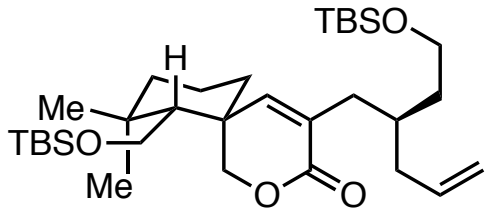


Pd-mediated oxidative cyclization

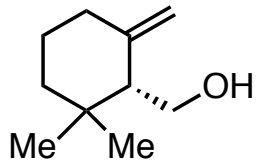


Sm-mediated reductive cyclization





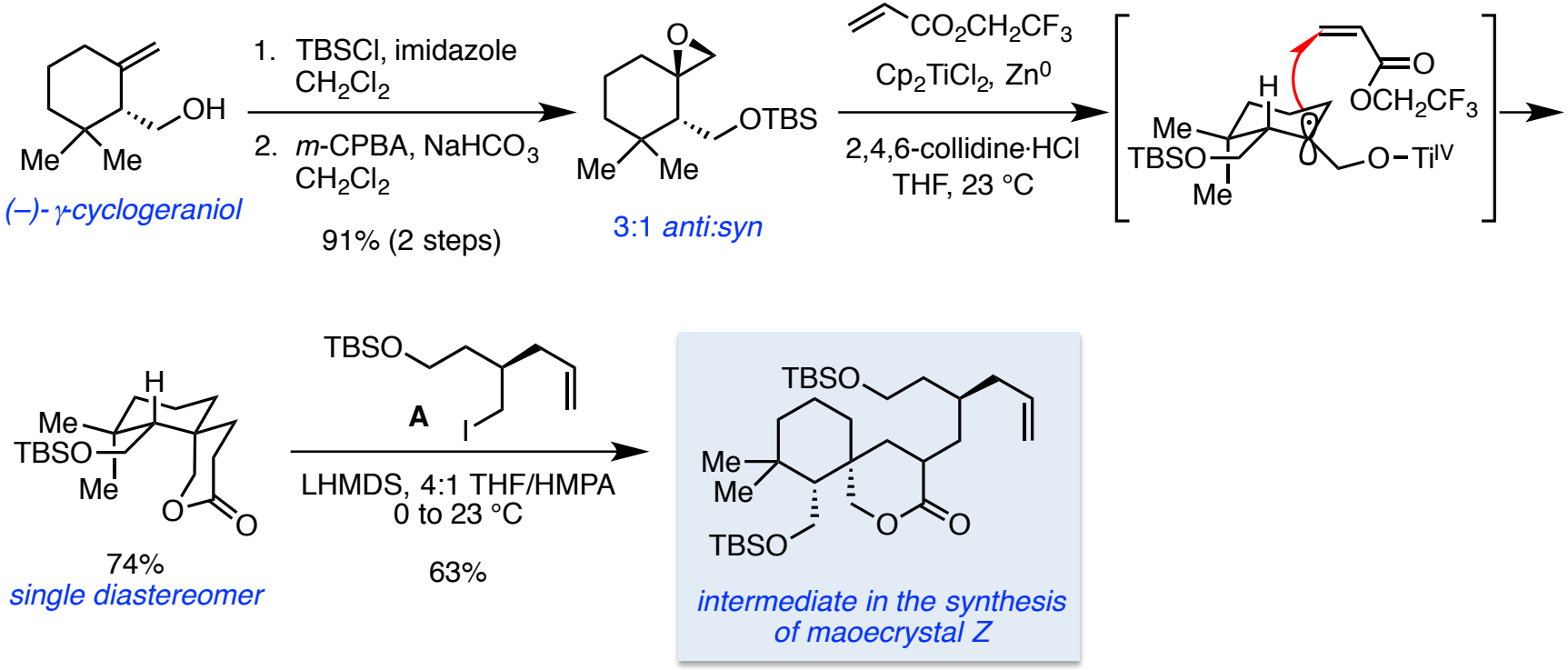
intermediate in the synthesis of maoecrystal Z

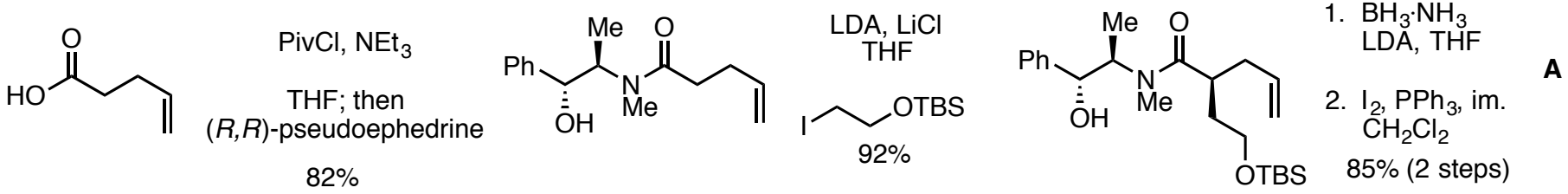


(–)-γ-cyclogeraniol

Yeoman, J. T. S.; Mak, V. W.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 11764.

Synthesis of Common Intermediate





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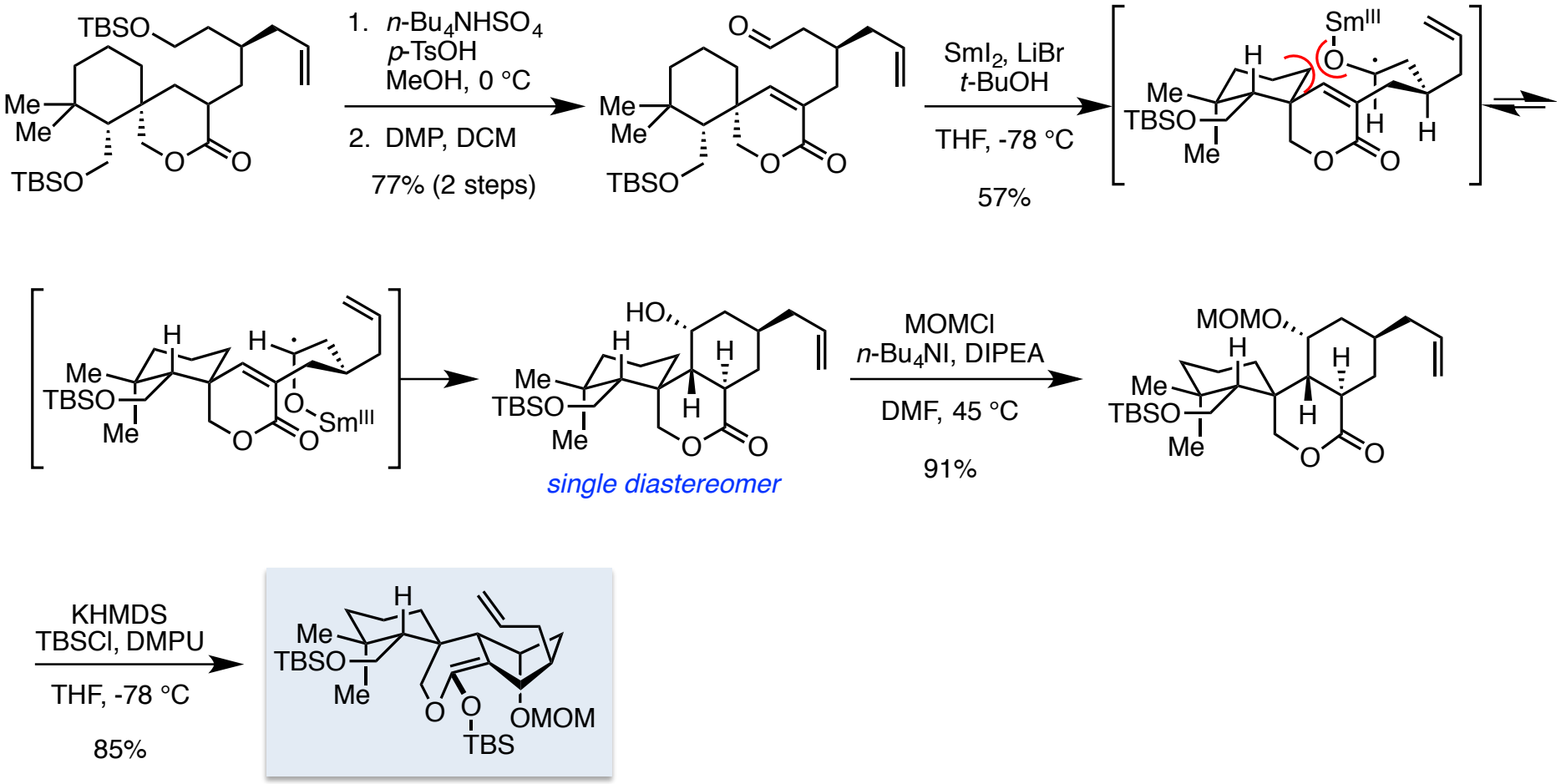
Yeoman, J.T. S.; Mak, V.W.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 11764.

Synthesis of Oxidative Cyclization Substrate



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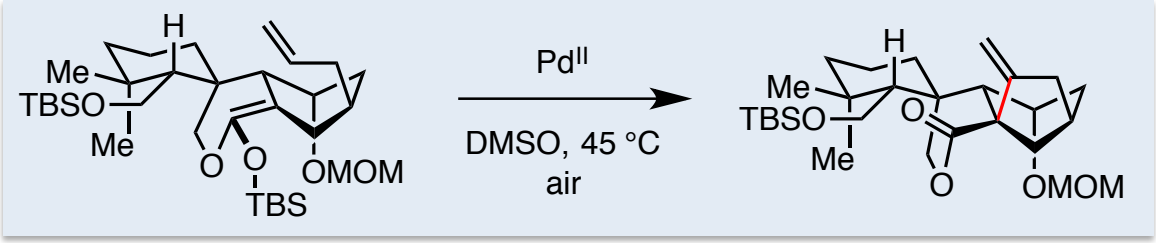
Reaction Optimization: Pd-Mediated Oxidative Cyclization



entry	Pd source	additive	yield (%)
1	$Pd(OAc)_2$ (0.1)	–	7
2	$Pd(OAc)_2$ (1.0)	–	35
3	$Pd(OAc)_2$ (1.0)	–	28*
4	$Pd(TFA)_2$ (1.0)	–	19
5	$PdCl_2$ (1.0)	$AgBF_4$ (2.0)	5
6	$PdCl_2$ (1.0)	–	0
7	$Pd(OAc)_2$ (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

- Little difference observed when the reaction was conducted under an air or oxygen atmosphere
- Entry 3 conducted in MeCN gives lower yield and increased side product formation
- All other solvents tested gave only trace quantities of product (toluene, glyme, dioxane, *t*-BuOH, DMF)

First example of a Pd-mediated oxidative cyclization of a silyl ketene acetal to generate an all-carbon quaternary center

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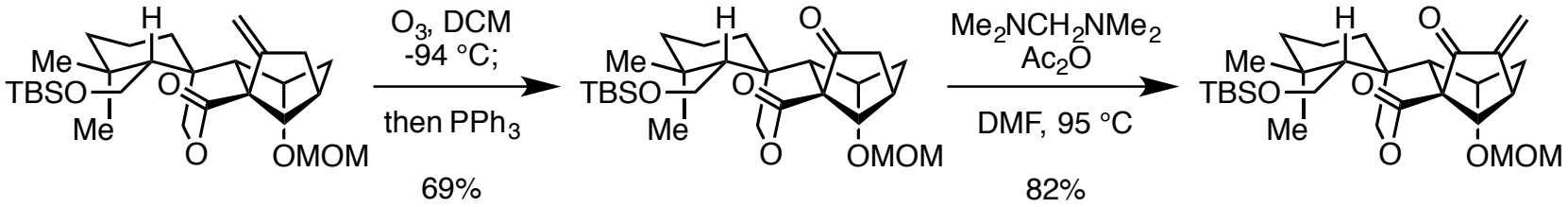
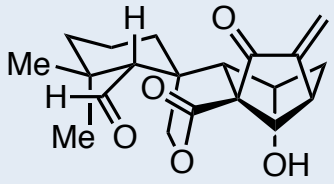
Total Synthesis of (–)-Trichorabdal A



1. 6 M aq. HCl
   dioxane, 45 °C
2. TEMPO, $PhI(OAc)_2$
   DCM

   73% (2 steps)

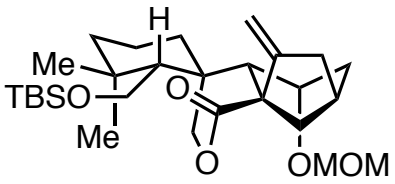


(–)-trichorabdal A

15 steps from (–)- γ -cyclogeraniol

Yeoman, J. T. S.; Mak, V. W.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 11764.

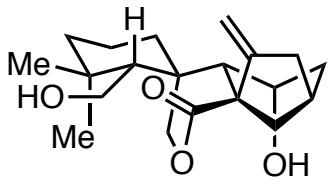
Total Synthesis of (–)-Longikaurin E



6 M aq. HCl

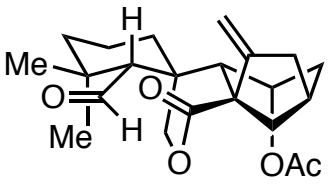
dioxane, 45 °C

89%



1. TEMPO
   $PhI(OAc)_2$
2. Ac_2O
   DMAP

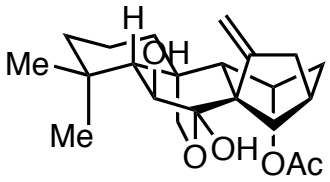
58% (2 steps)



SmI_2

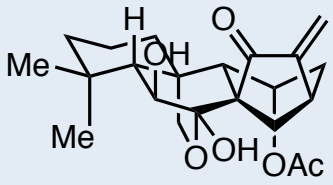
THF, 23 °C

55%
(75% BRSM)



1. O_3, DCM, -94 °C;
   then PPh_3
2. $Me_2NCH_2NMe_2$
   Ac_2O, DMF, 95 °C

44% (2 steps)



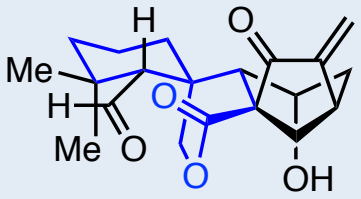
(–)-longikaurin E

17 steps from (–)- γ -cyclogeraniol

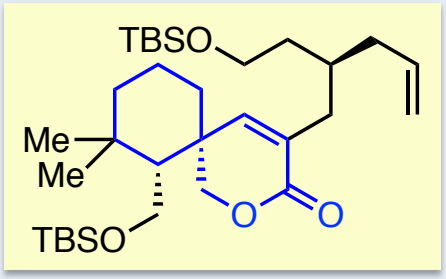
Yeoman, J. T. S.; Mak, V. W.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 11764.

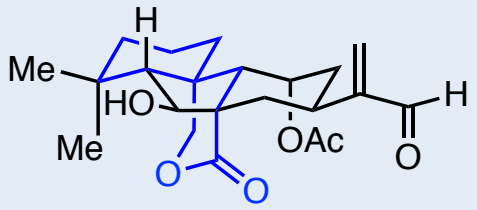
Conclusions and Outlook

- A unified synthetic strategy has been applied to the first total syntheses of (–)-trichorabdal A and (–)-lonikaurin E
  - 15 and 17 steps, respectively from (–)- γ -cyclogeraniol
- Pd^{II}-mediated oxidative cyclization reaction was employed to generate the an all-carbon quaternary center and build the bicyclo[3.2.1]octane core
- Three architecturally distinct *ent*-kauranoids were prepared from a common spirolactone intermediate

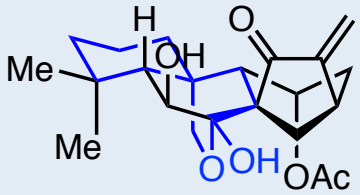


(–)-trichorabdal A





(–)-maoecrystal Z



(–)-longikaurin E