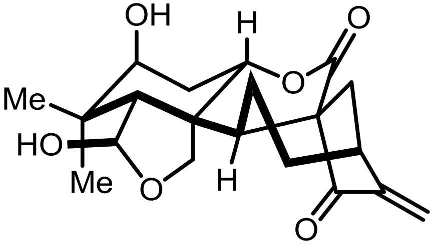
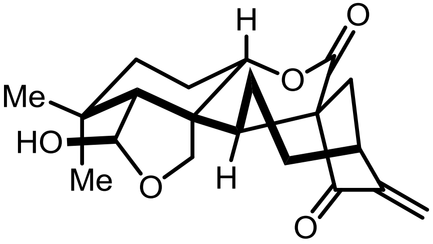
Divergent Total Syntheses of Enmein-Type Natural Products: (–)-Enmein, (–)-Isodocarpin, and (–)-Sculponin R

Saiyong Pan, Sicong Chen, and Guangbin Dong

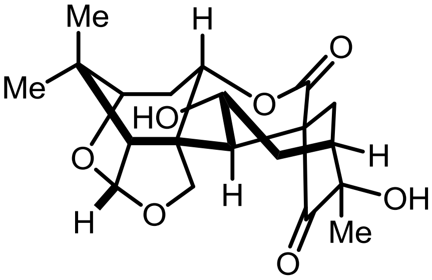
ChemRxiv. Preprint, 10.26434/chemrxiv.6081203.v1
Angew. Chem. Int. Ed. Accepted Article, 10.1002/anie.201803709



enmein



isodocarpin



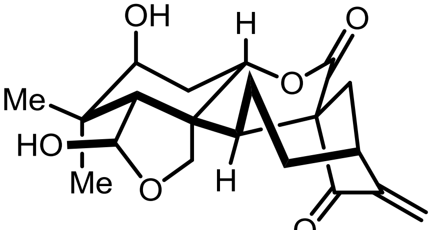
sculponin R

Ettore Rastelli
Wipf Group Current Lit
April 14, 2018

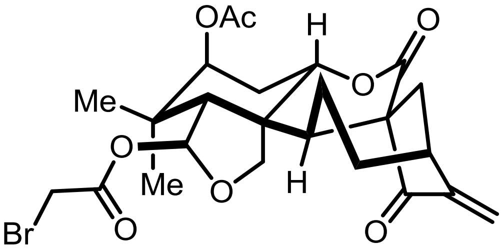
Diterpenoids from Isodon species

I. *japonicus*

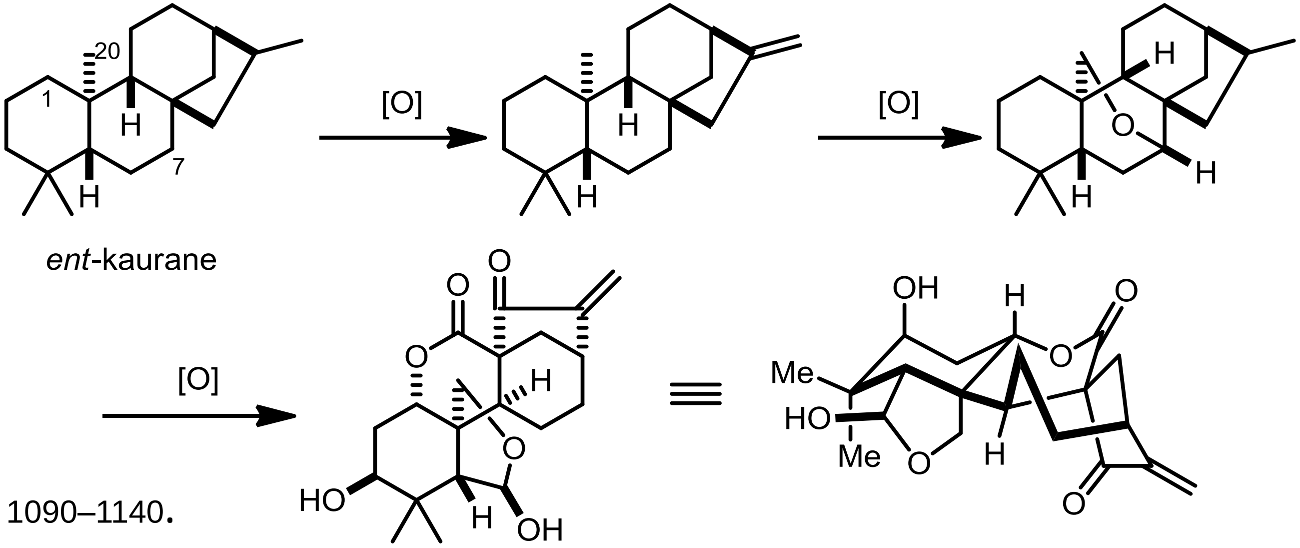
- Enmein isolated in Southeast Asia from I. *japonica* as the major bitter principle in 1958
- Named after e*nmei-so* “the grass effective for prolonging human life”
- Common Asian folk-medicine
- Classified as a seco-*ent*-kaurane (1,7-lactone) diterpenoid
- Structural features: 5 rings, δ-lactone, hemi-acetal, 8 stereogenic centers, 2 all-carbon quaternary centers
- Unambiguous structure determination X-Ray structure of an enmein derivative in 1966
- Proposed biosynthesis:



enmein



enmein derivative X-Ray



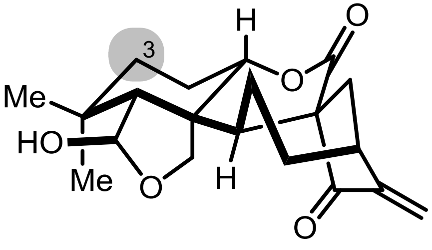
ent-kaurane

Pu, J.-X. *et al*. *Nat. Pro. Rep.* **2017**, *34*, 1090–1140.

Diterpenoids from Isodon species

I. *japonicus*

- Isodocarpin isolated in 1968 in Japan
- Structure solved by series of chemical transformations on enmein and eventually by X-ray structure
- Differs from enmein by deoxygenation at C3

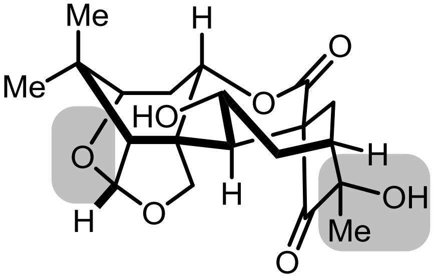


isodocarpin

Fujita, E. *et al*. *Chem and Pharm. Bull. (Japan)* **1968**, *16*, 1573–1575**.**

I. *Scuplponeatus*

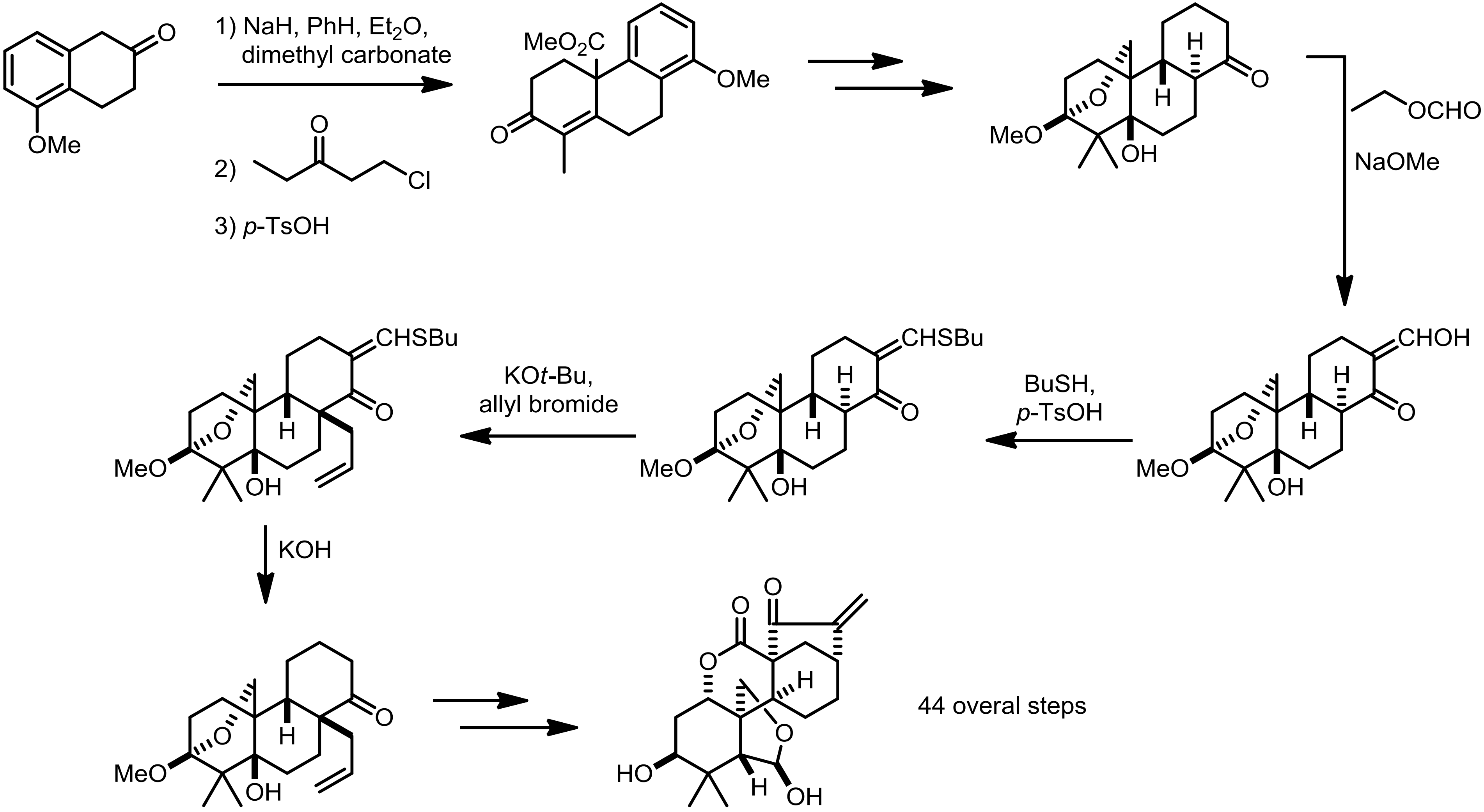
- Sculponin R isolated in 2013 in China
- Commonly used for the treatment of dysentery
- Structure unambiguously determined by X-ray
- Differs from enmein by inclusion of a caged acetal and oxidation of exocyclic olefin



sculponin R

Sun, H.-D. *et al*. *J. Nat. Prod.* **2013**, *76*, 2113–2119**.**

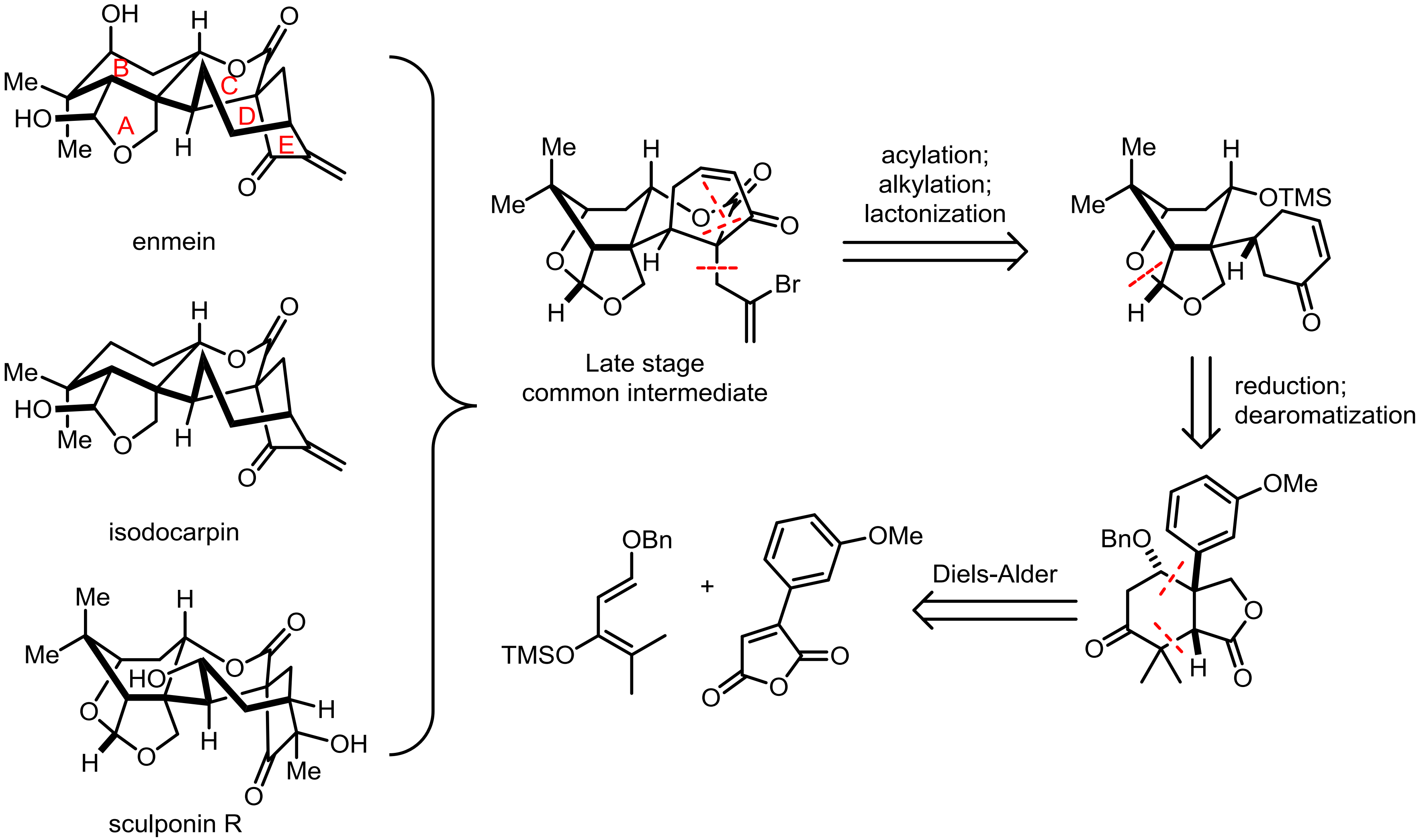
Original synthesis of enmein



44 overal steps

Fujita, E. *J. Chem. Soc., Chem. Commun.* **1972**, 1107.
Ireland, R. E. *J. Org. Chem.* **1962**, *27*, 1615–1619.

Retrosynthesis of Enmein-type natural products



enmein

isodocarpin

sculponin R

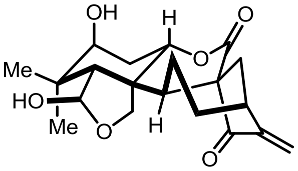
Late stage
common intermediate

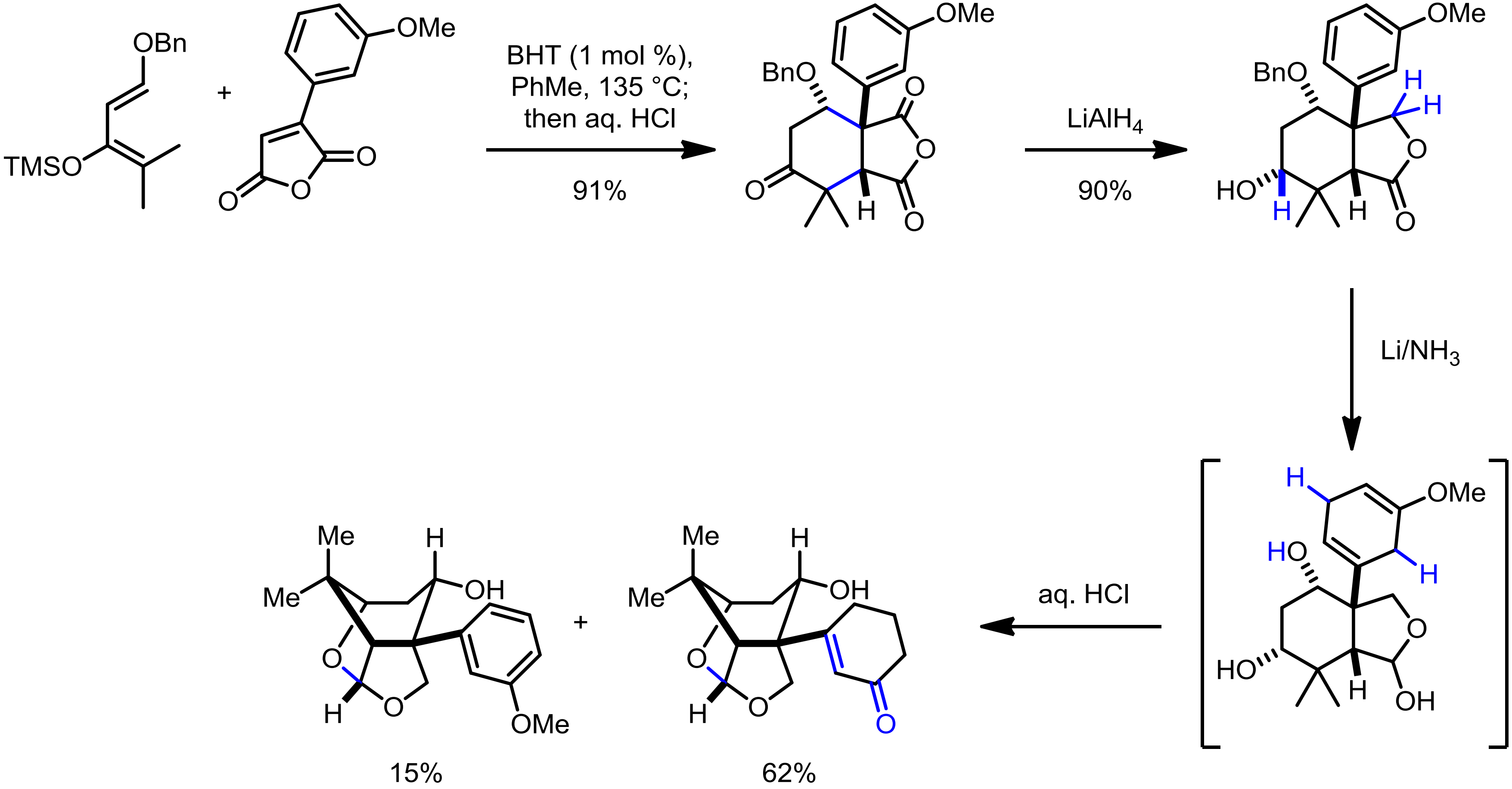
acylation;
alkylation;
lactonization

reduction;
dearomatization

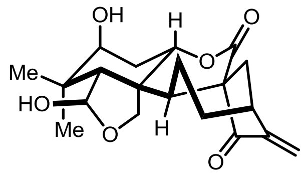
Diels-Alder

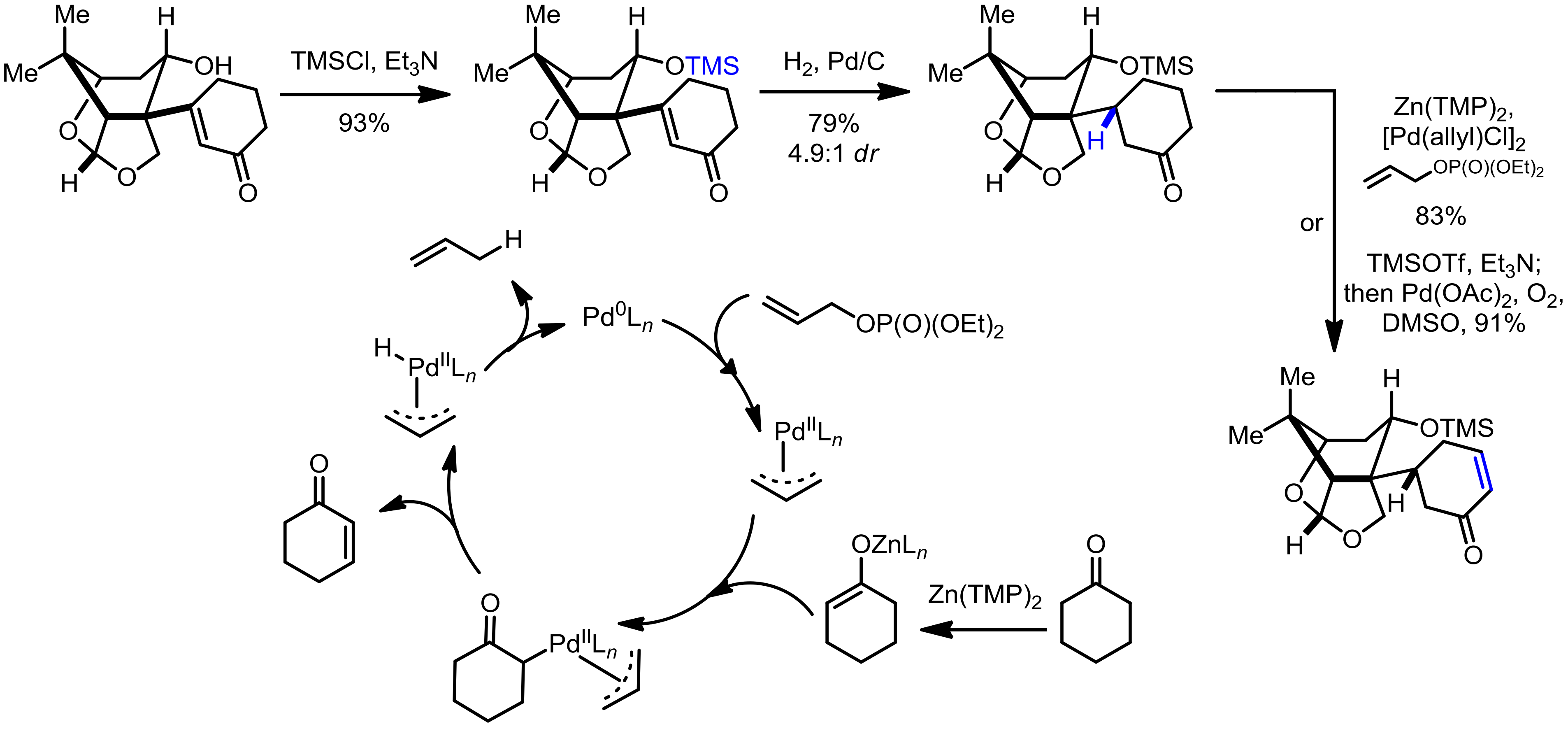
Formation of caged acetal





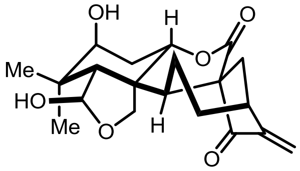
Formation of common intermediate

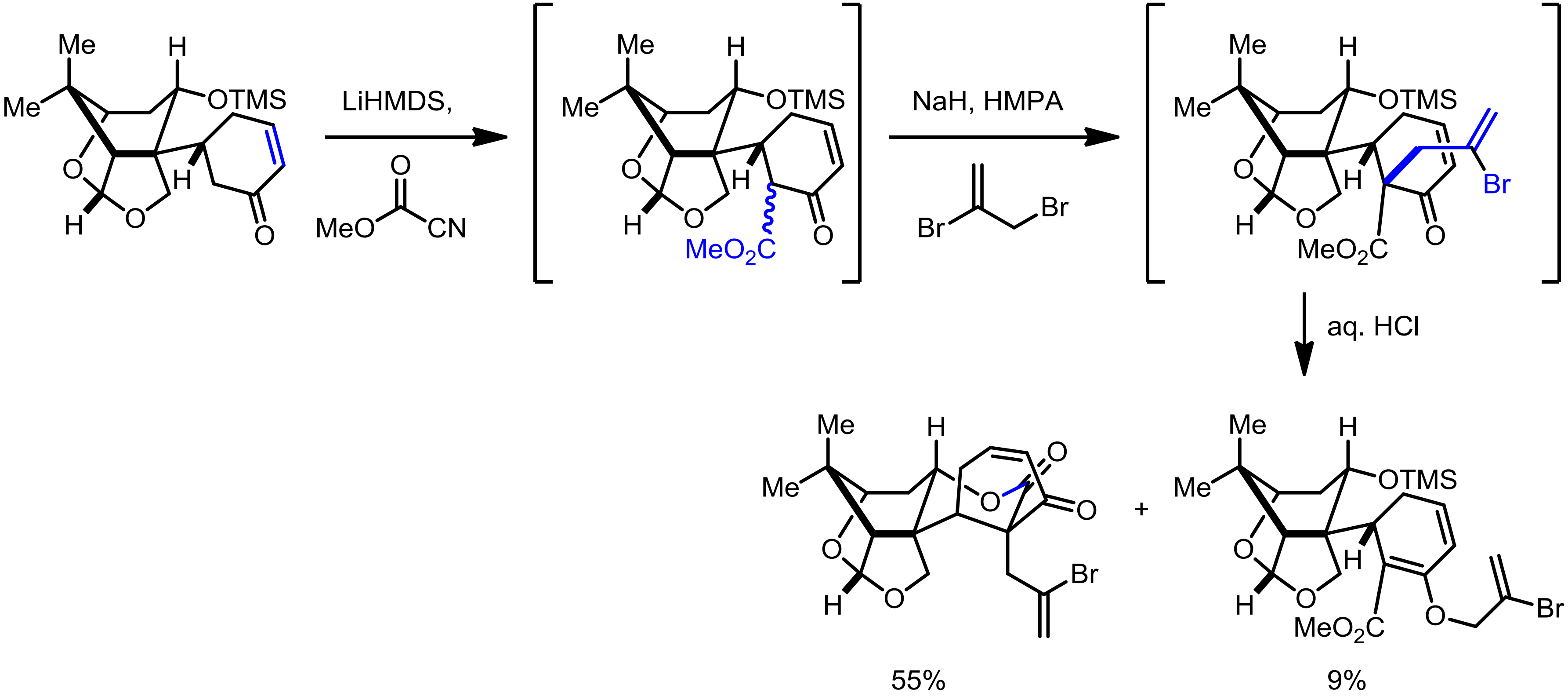




Newhouse, T. R. *Org. Lett.* **2018**, *20*, 684–687.

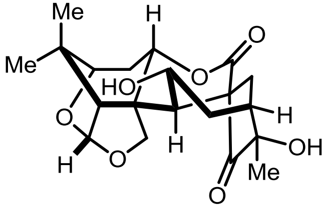
One-pot acylation/alkylation/ lactonization protocol

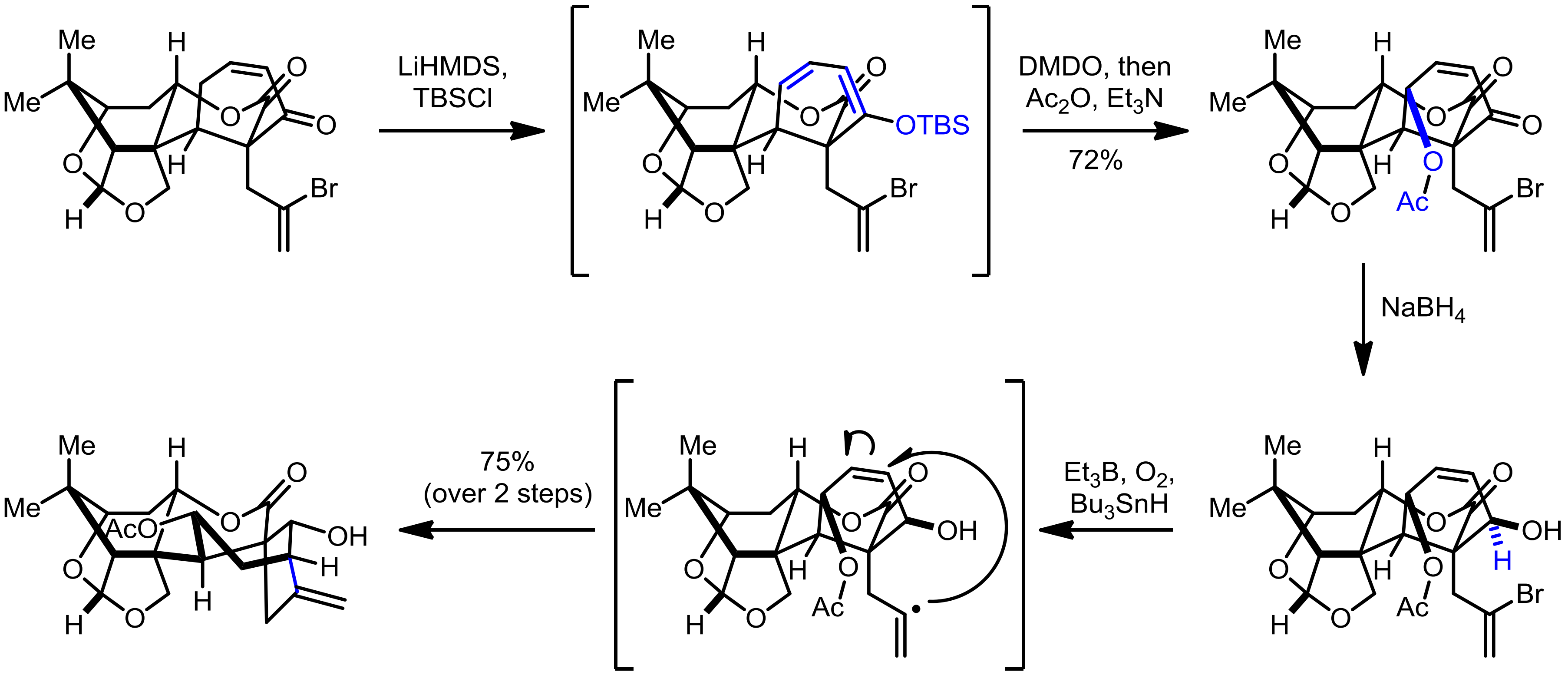




Late stage
common intermediate

Radical cyclization





LiHMDS, TBSCl

DMDO, then Ac_2O, Et_3N

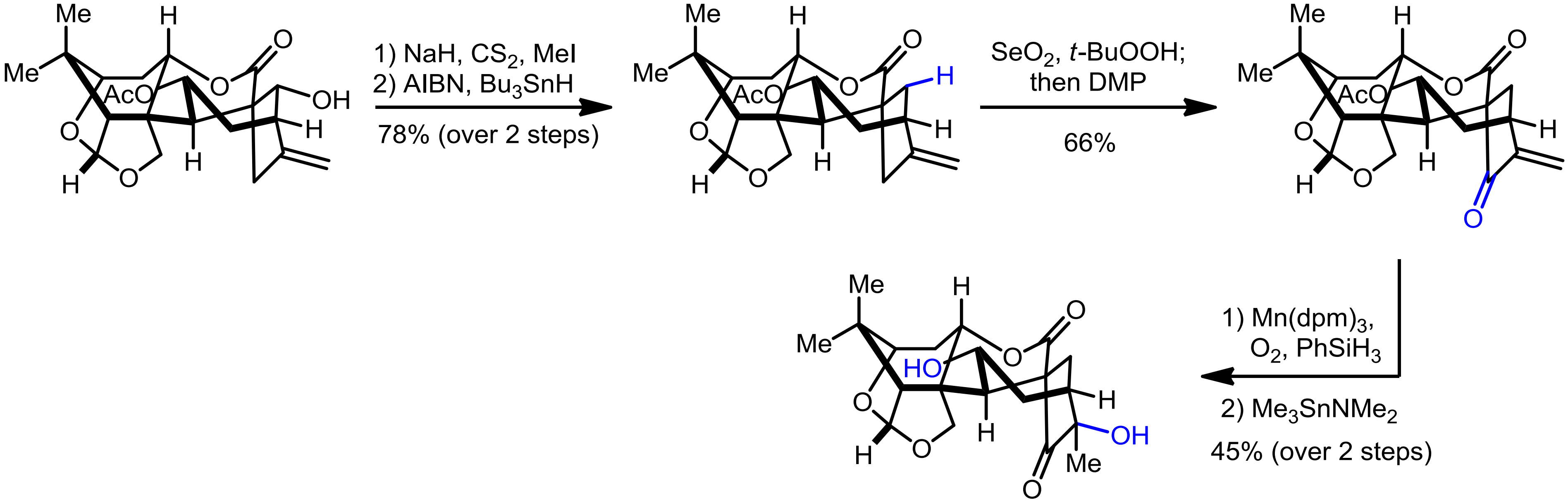
72%

$NaBH_4$

Et_3B, O_2, Bu_3SnH

75% (over 2 steps)

Completion of sculponin R



1) NaH, CS_2, MeI
2) AIBN, Bu_3SnH
78% (over 2 steps)

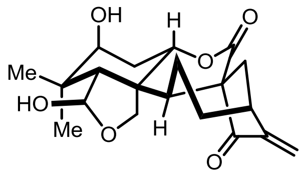
SeO_2, *t*-BuOOH;
then DMP
66%

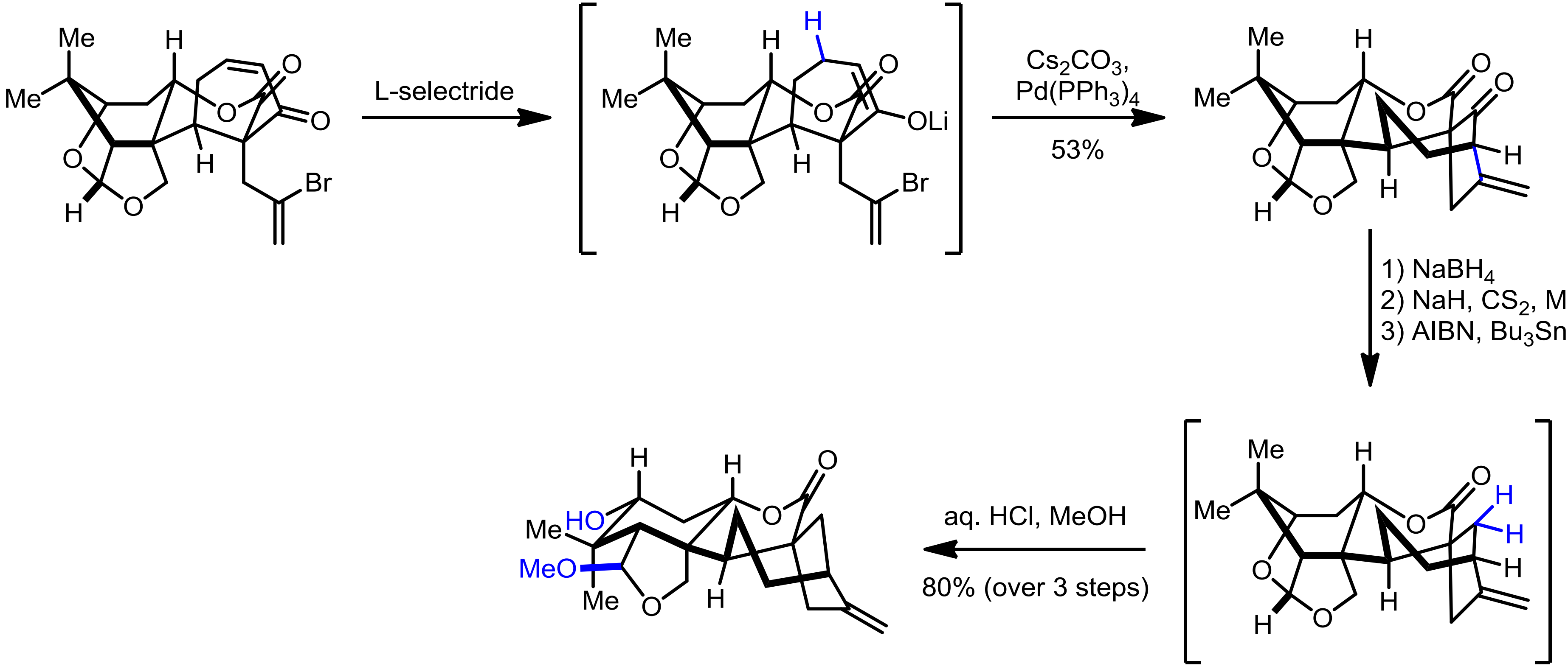
1) $Mn(dpm)_3$, O_2, $PhSiH_3$
2) Me_3SnNMe_2
45% (over 2 steps)

sculponin R

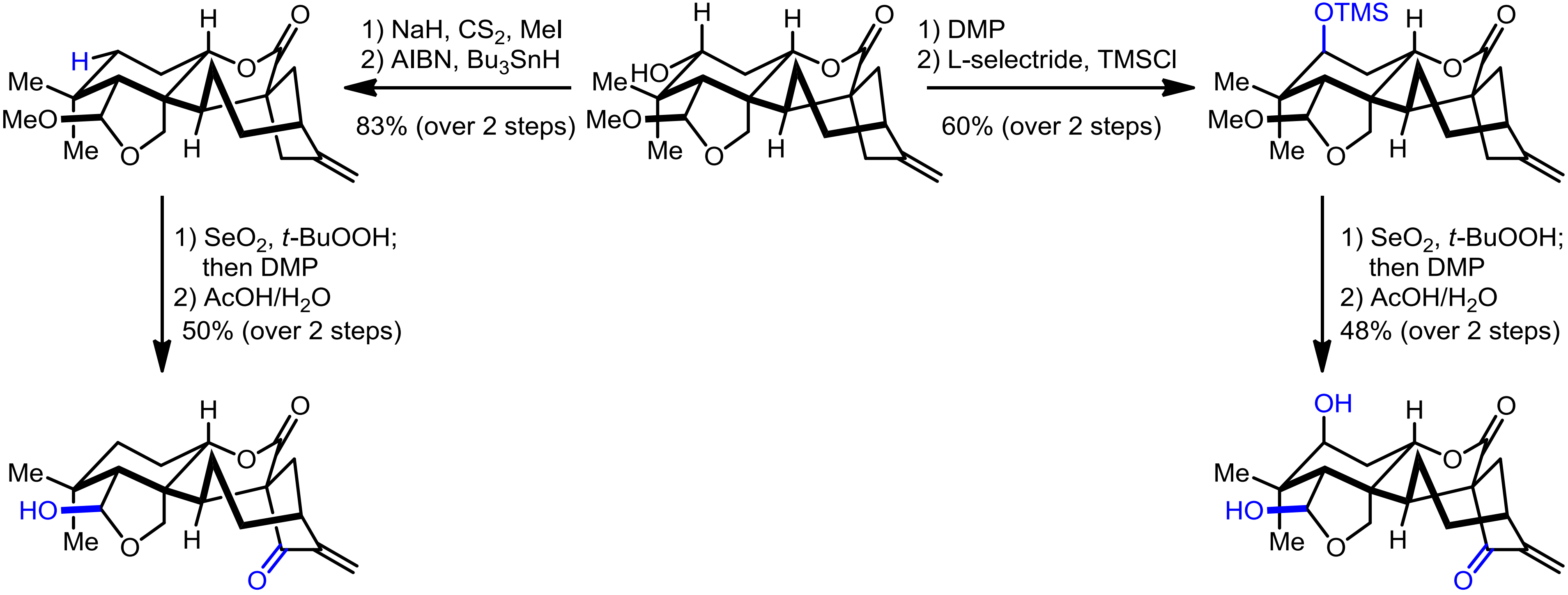
Lappert, M. F. *J. Chem. Soc. C.* **1969**, 2265–2568.

Reductive alkenylation





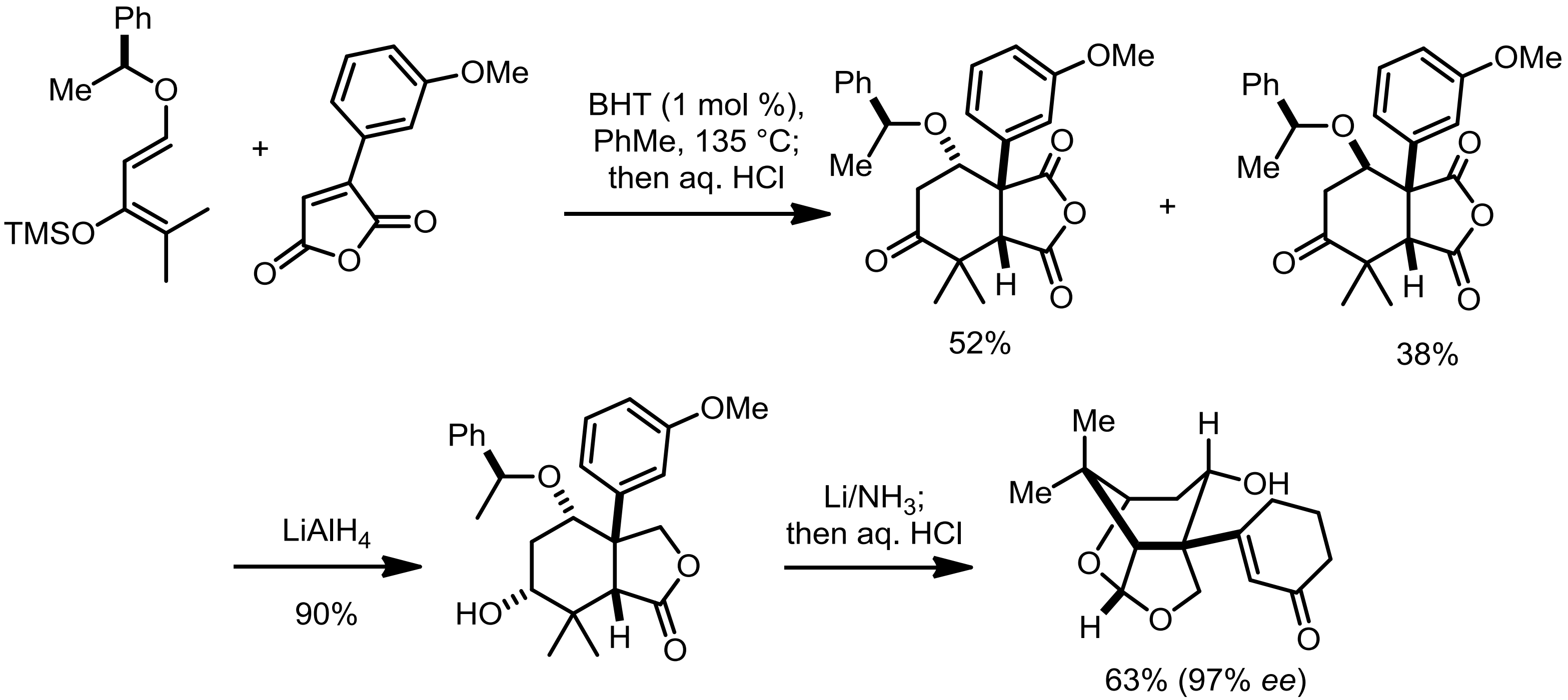
Completion of isodocarpin and enmein



isodocarpin

enmein

Asymmetric Diels-Alder



Conclusion

- Total synthesis of 3 enmein-type natural products
    - sculponin R - 15 steps, 2.5 % overall yield
    - isodocarpin – 15 steps, 3.5 % overall yield
    - enmein – 16 steps, 2.4 % overall yield

- Synthesis rendered asymmetric via Diels-Alder cycloaddition with a chiral auxililary

- Synthesis is modular by the use of a late-stage common intermediate