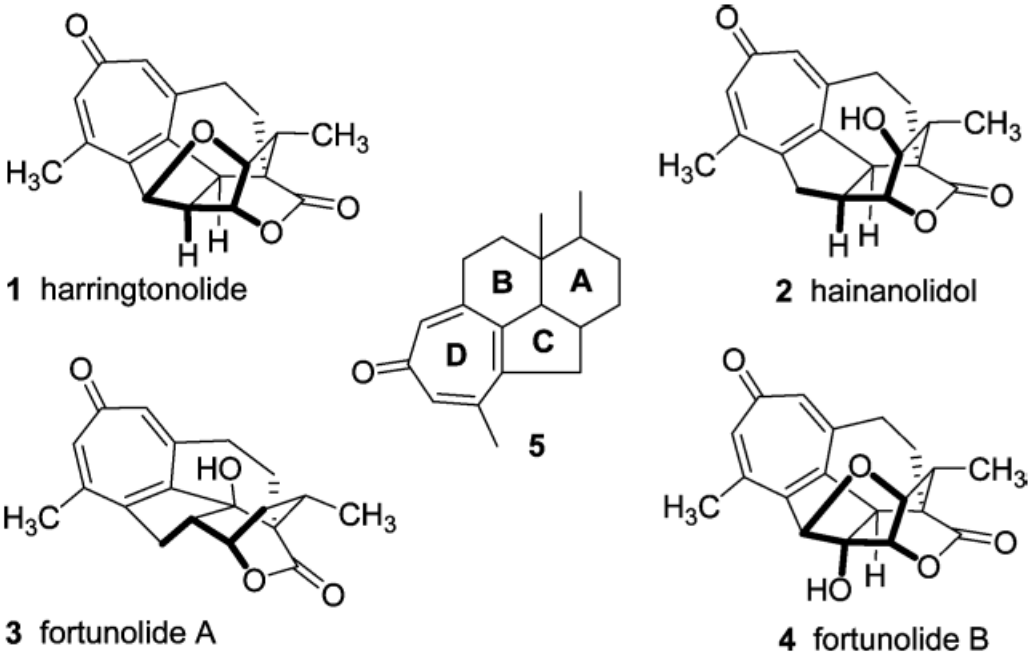
Stereoselective Total Synthesis of Hainanolidol and Harringtonolide via Oxidopyrylium-based (5+2) Cycloaddition

M. Zhang, N. Liu, W. Tang
University of Wisconsin

J. Am. Chem. Soc. **2013**, 135, 12434-12438

Introduction

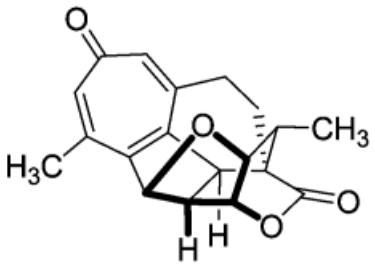


- *Cephalotaxus* norditerpenes (C19)
- Tetracyclic carbon framework
- Ring A: 5-6 contiguous stereogenic centers
- Tropone ring D
- **1** and **4** with additional THF ring

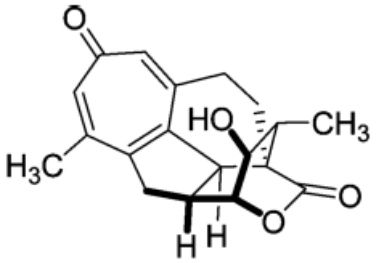
Introduction

- Harringtonolide first isolated in 1978
- from *C. harringtonia*
- Structure confirmed by X-ray.

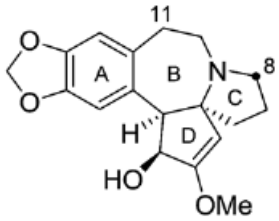
- In 1979, harringtonolide and hainanolidol isolated from *C. haiananensis*.



1 harringtonolide



2 hainanolidol



Antiviral activity
Antineoplasmic activity (nM range)

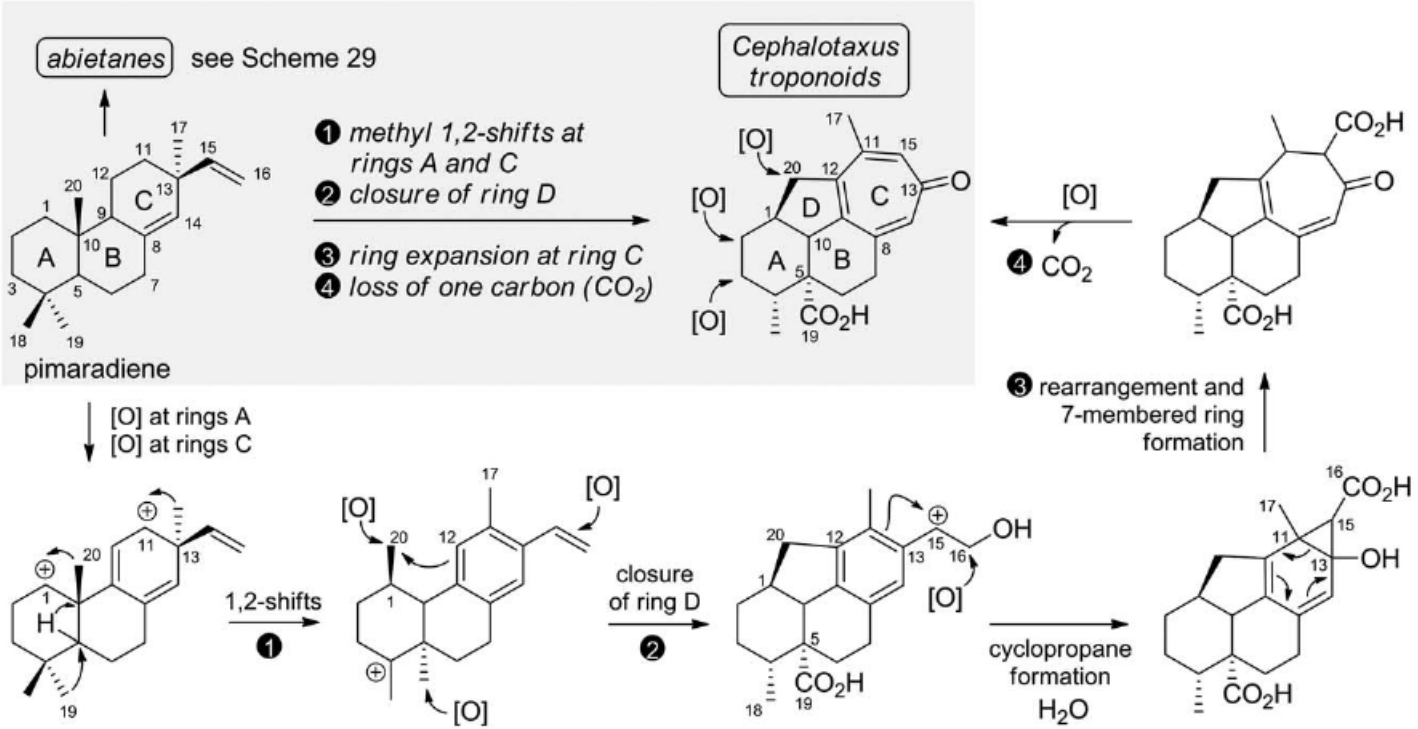
Inactive

Same plant
Different biosynthesis

THF ring seems to be important for activity: interest in determining mode of action!

Biosynthesis

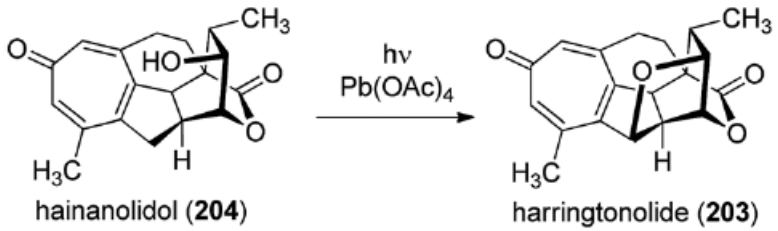
- No study has been conducted!
- Proposition



Scheme 30 Biosynthetic proposal for *Cephalotaxus* norditerpenes.

H. Abdelkafi and B. Nay, *Nat. Prod. Rep.* **2012**, 29, 845-869

First Semi-synthesis



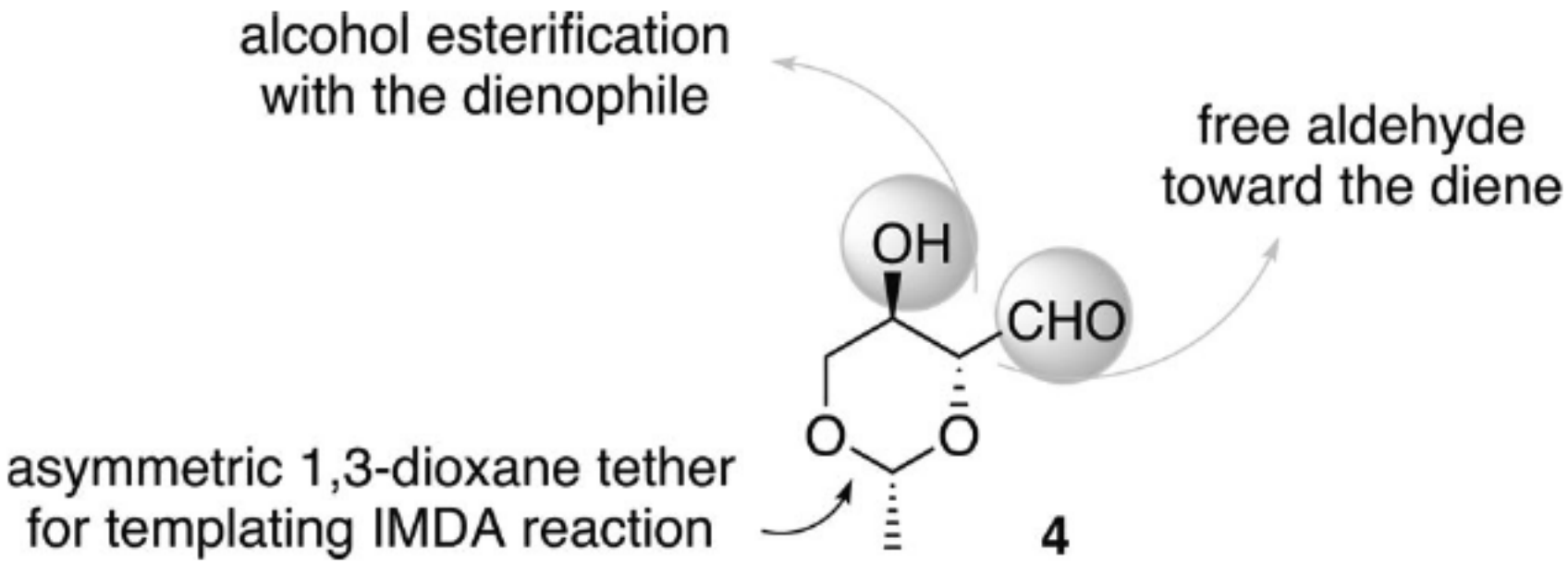
hainanolidol (**204**) harringtonolide (**203**)

hainanolidol is the biosynthetic precursor of *harringtonolide*

Z. Xue, N. J. Sun, and X. T. Liang, *Acta Pharm. Sinica*, 1982, 17, 236-237

Nay Strategy to the Asymmetric Harringtonolide Core

Strategy based on IMDA approach

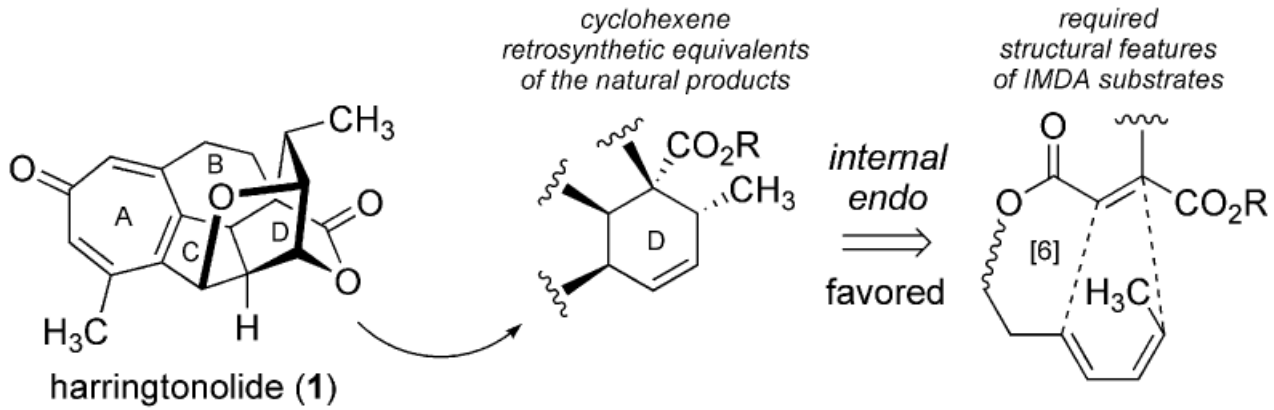


SM = glucose!

H. Abdelkafi et al., *Eur. J. Org. Chem.* **2011**, 2789-2800

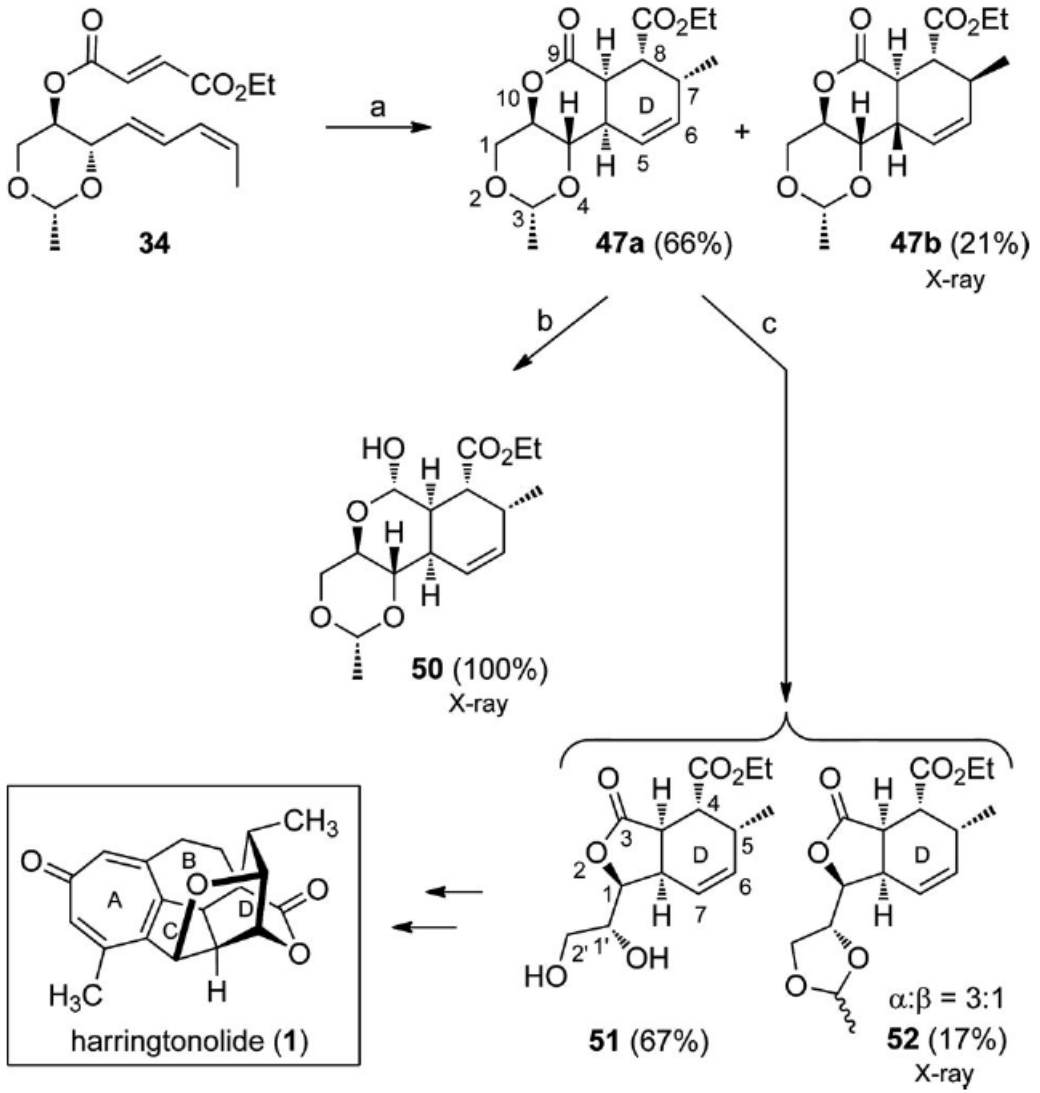
Nay Strategy to the Asymmetric Harringtonolide Core

Retrosynthesis of D-ring



H. Abdelkafi et al., *Eur. J. Org. Chem.* **2011**, 2789-2800

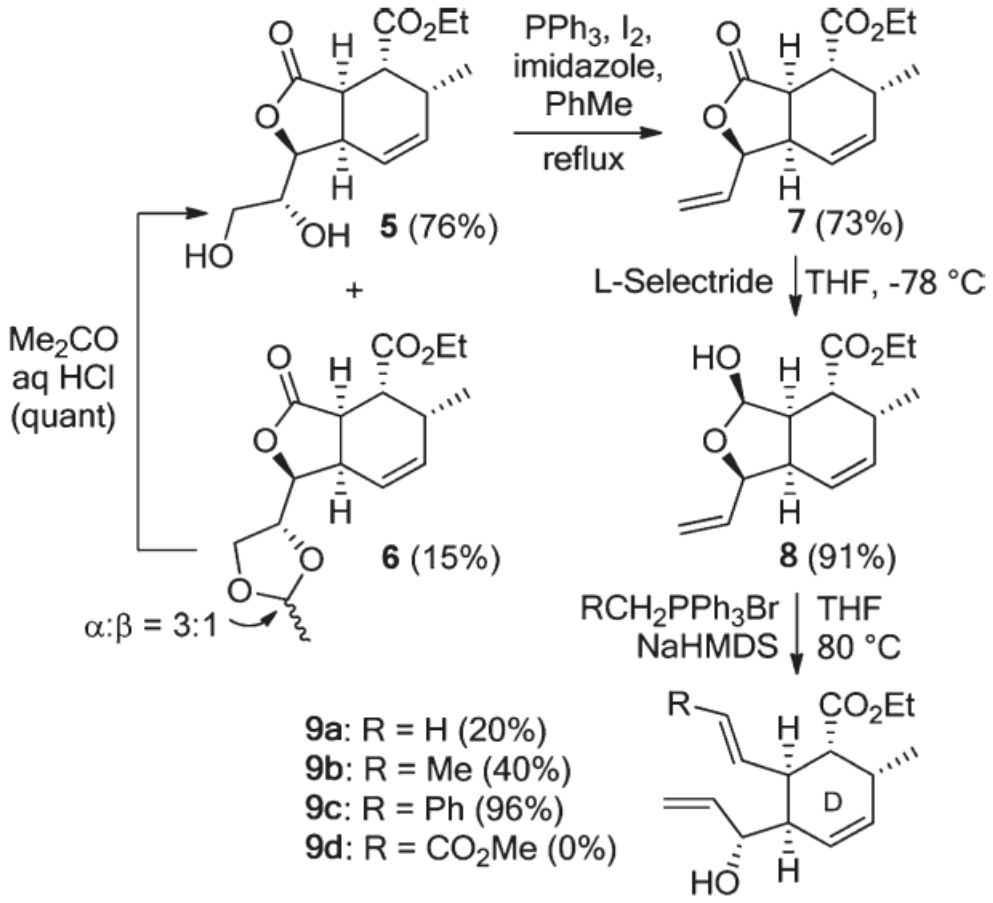
Nay Strategy to the Asymmetric Harringtonolide Core



Scheme 3. The 1,3-dioxane IMDA reaction applied to (*E*,*Z*)-dienyl fumarate **34**, as a key step in the synthesis of harringtonolide **1**. *Reagents and conditions:* (a) BHT (0.2 equiv.), toluene, 220 °C (sealed tube), 110 h; (b) L-Selectride, THF, –78 °C; (c) TFA/H_2O (1:1), 80 °C.

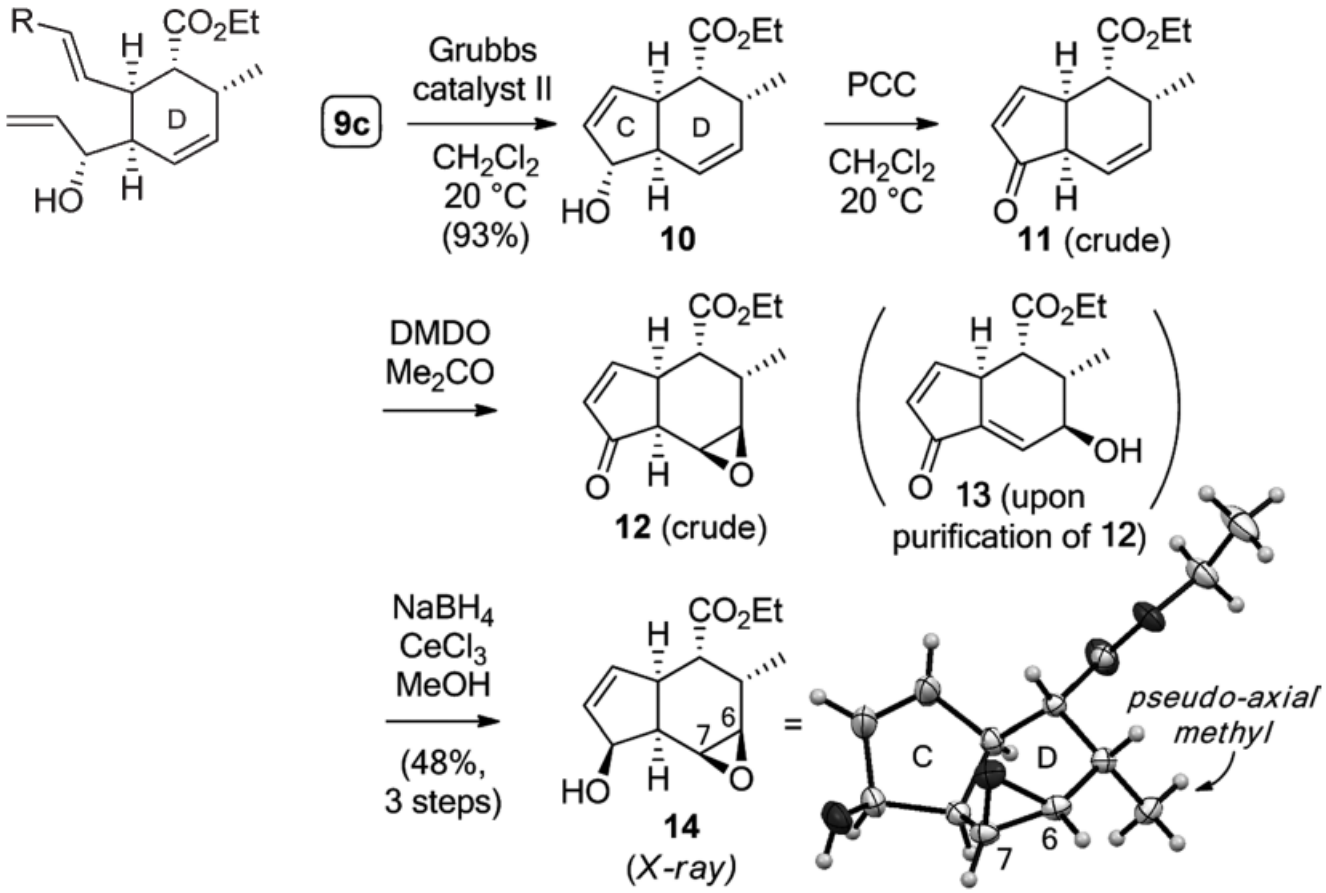
H. Abdelkafi et al., *Eur. J. Org. Chem.* **2011**, 2789-2800

Nay Strategy to the Asymmetric Harringtonolide Core



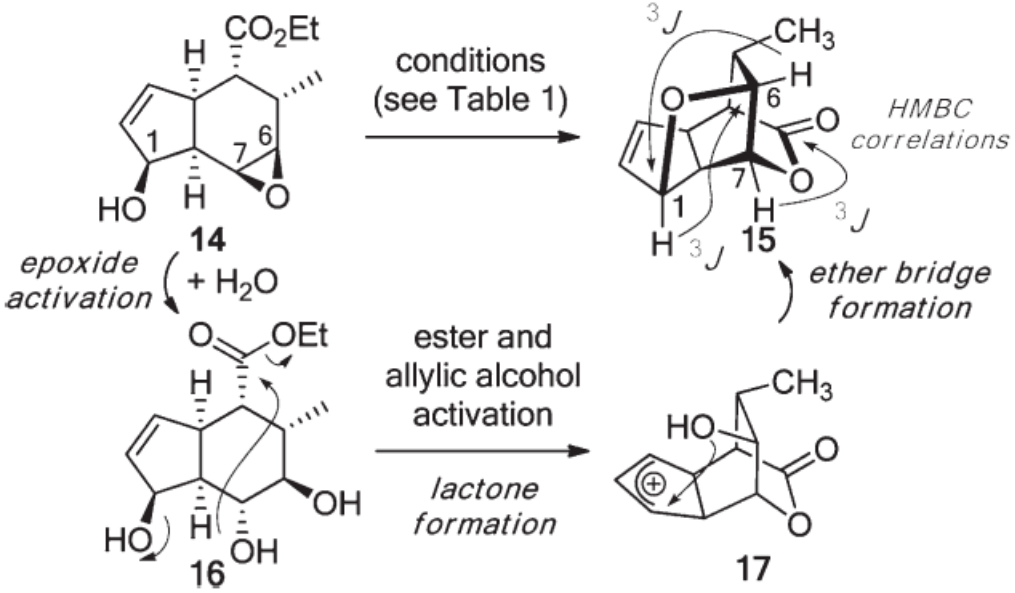
H. Abdelkafi, P. Herson, and B. Nay, *Org. Lett.* **2012**, 14, 1270-1273

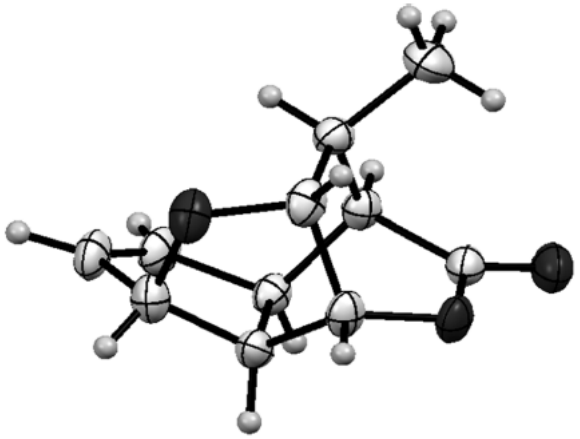
Nay Strategy to the Asymmetric Harringtonolide Core



H. Abdelkafi, P. Herson, and B. Nay, *Org. Lett.* **2012**, 14, 1270-1273

Nay Strategy to the Asymmetric Harringtonolide Core

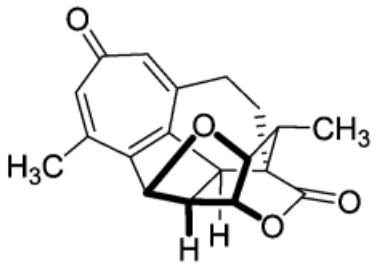




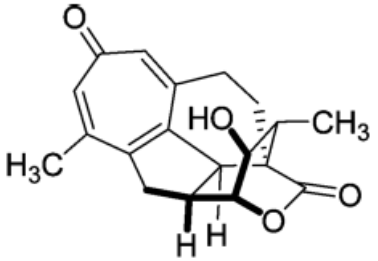
Conditions: $Yb(OTf)_3$ (1eq.), THF, 80 °C, yield: 57%

H. Abdelkafi, P. Herson, and B. Nay, *Org. Lett.* **2012**, 14, 1270-1273

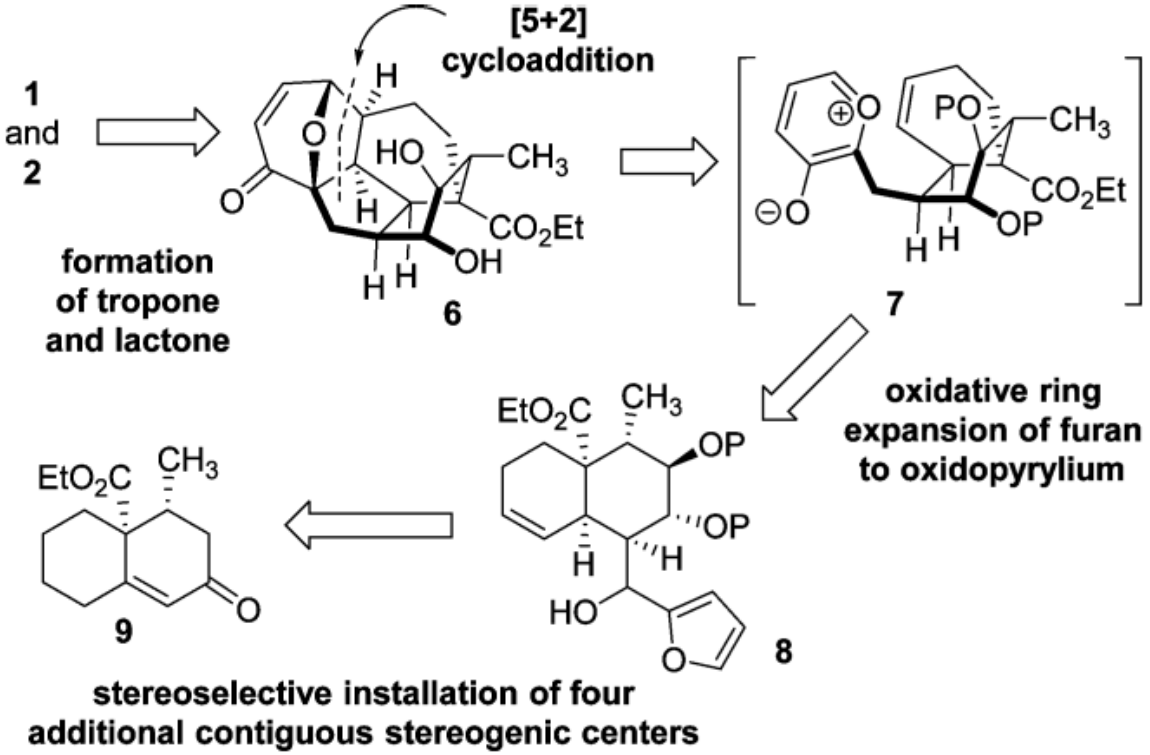
Zhang Retrosynthesis



1 harringtonolide



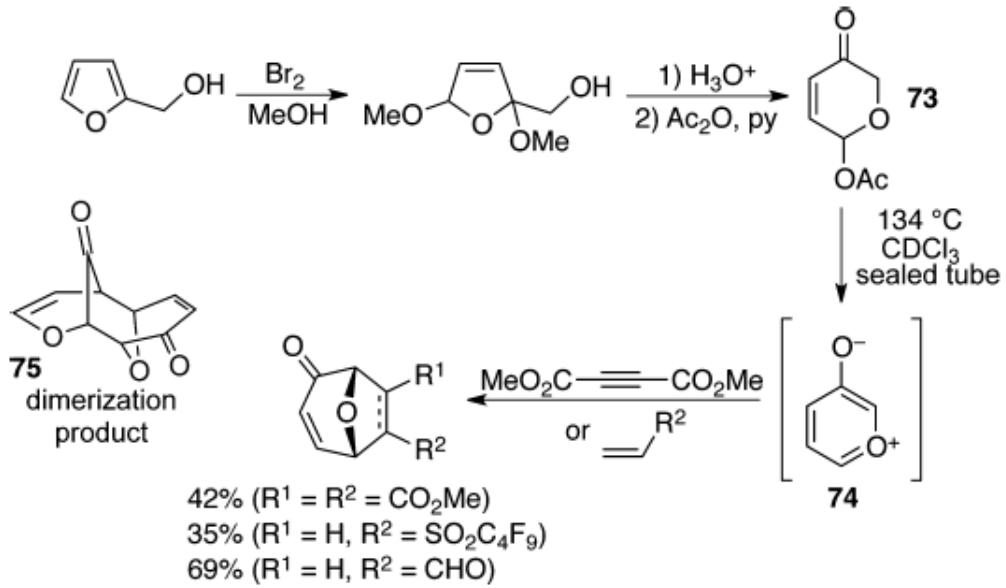
2 hainanolidol



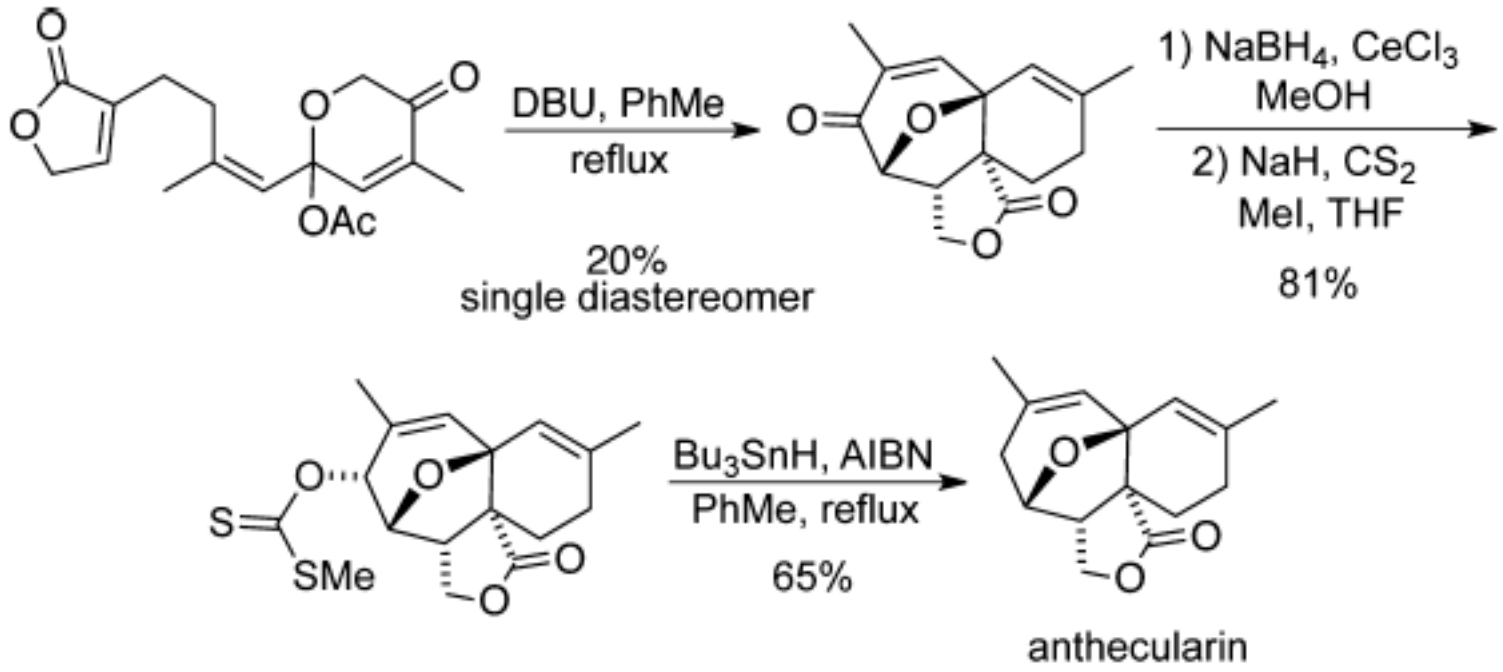
5+2 cycloaddition

5+2 addition via group elimination

Oxidation of furan: Achmatowicz reaction



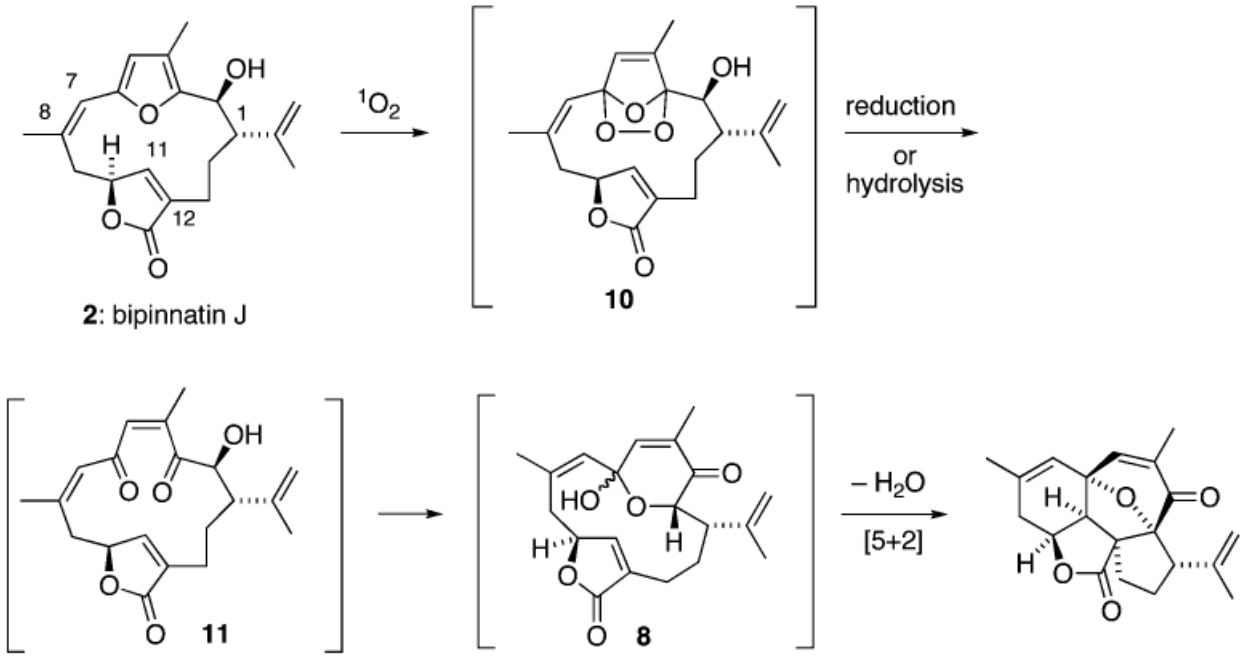
5+2 cycloaddition



G. Pattenden et al., *Org. biomol. Chem.,* **2009**, 7, 639

5+2 cycloaddition

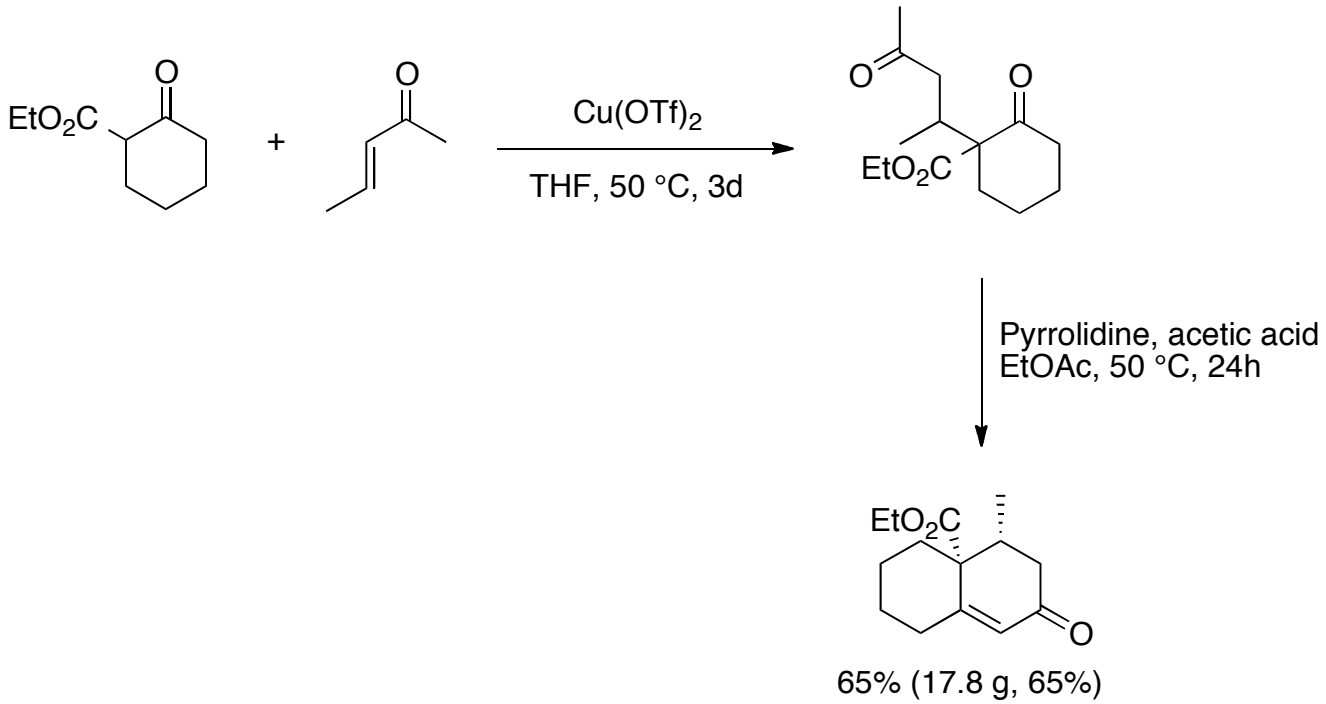
Biosynthetically inspired total synthesis of intricarene for bipinnatin J



P. A. Roethle, P. T. Hernandez, D. Trauner, *J. Org. Chem.*, **2006**, 8, 5901-5904

Synthesis

Preparation of starting material

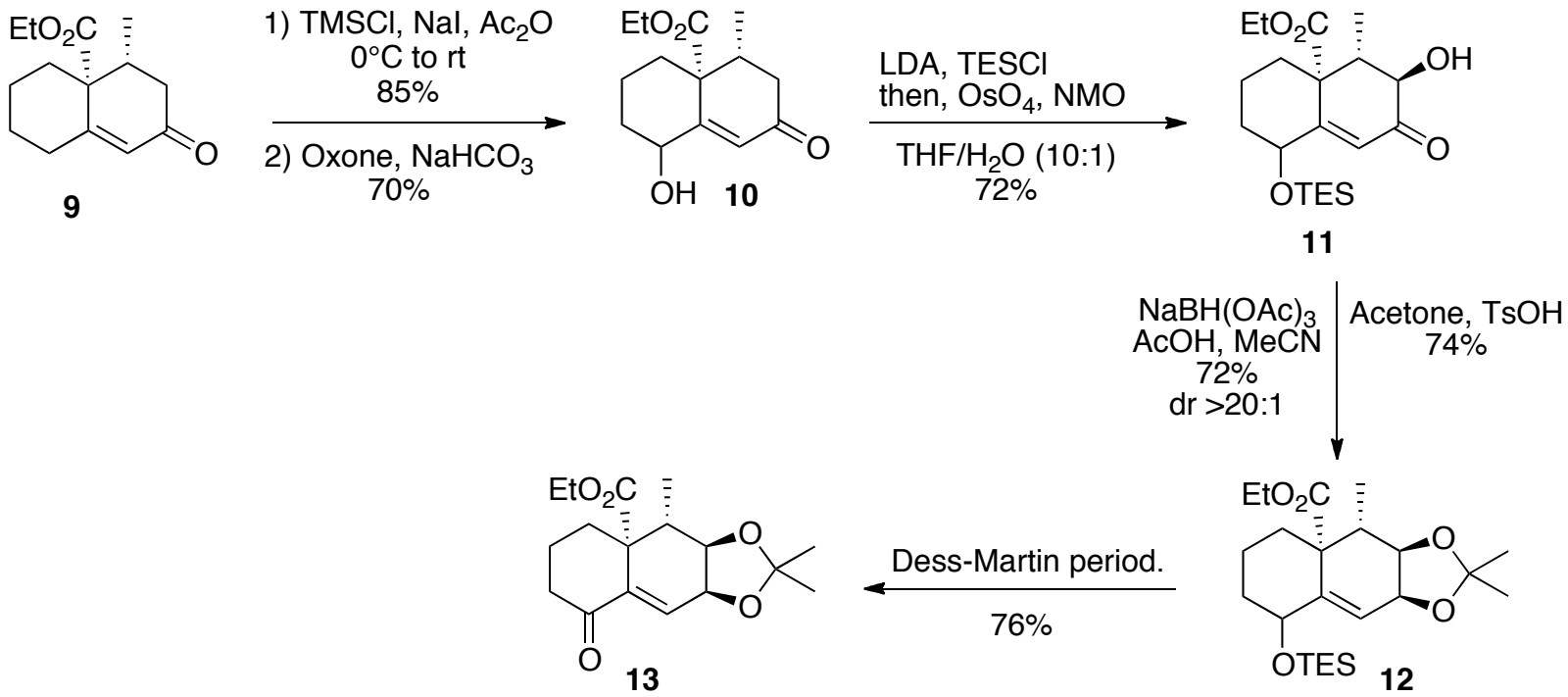


65% (17.8 g, 65%)

Addition of different chiral ligand failed to give good yield and ee!

J. A. Marshall, H. Faubl, T. M. Warne, *Chem. Commun.* **1967**, 753

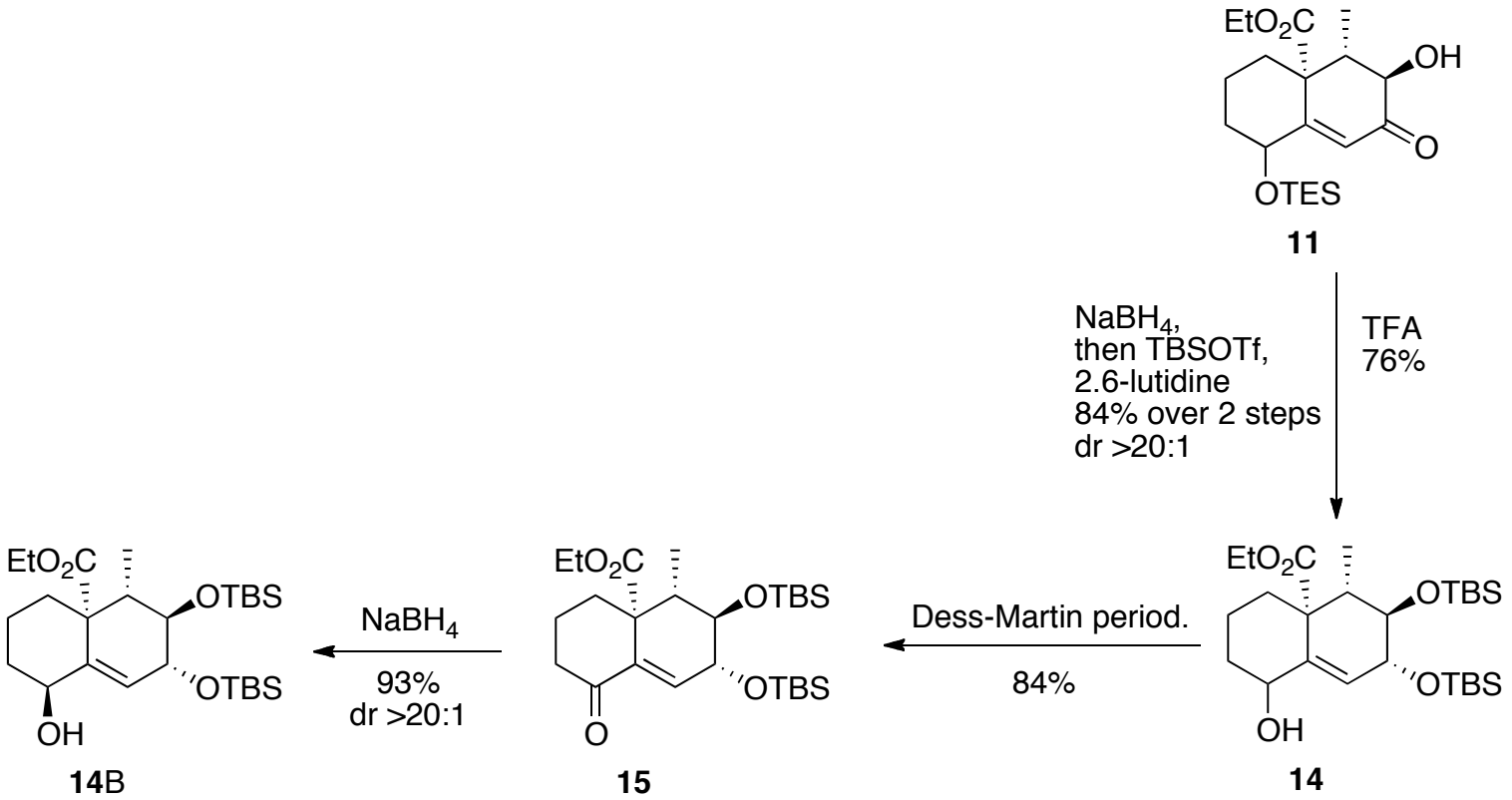
Synthesis



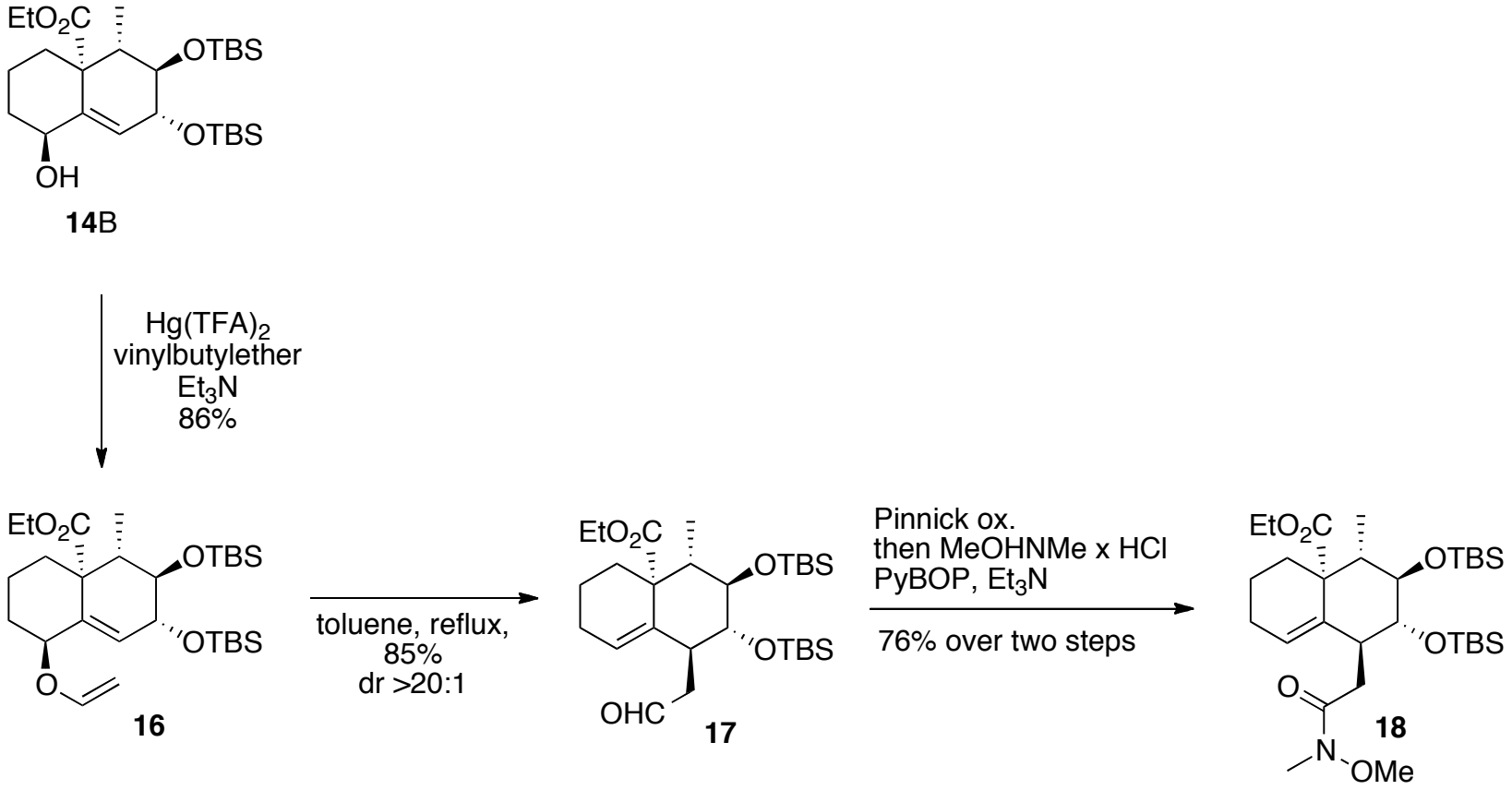
Cis-diol obtained because protection as acetonide possible

Need the *trans*-diol!

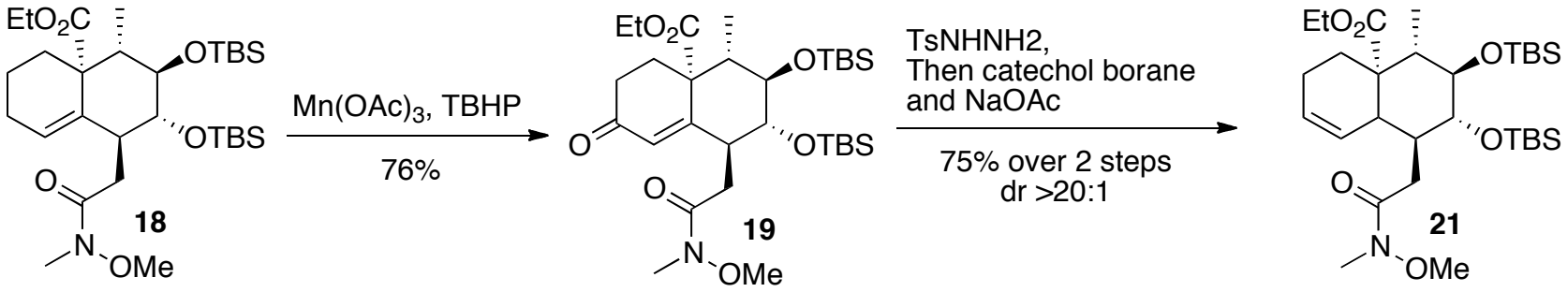
Synthesis: *trans*-diol

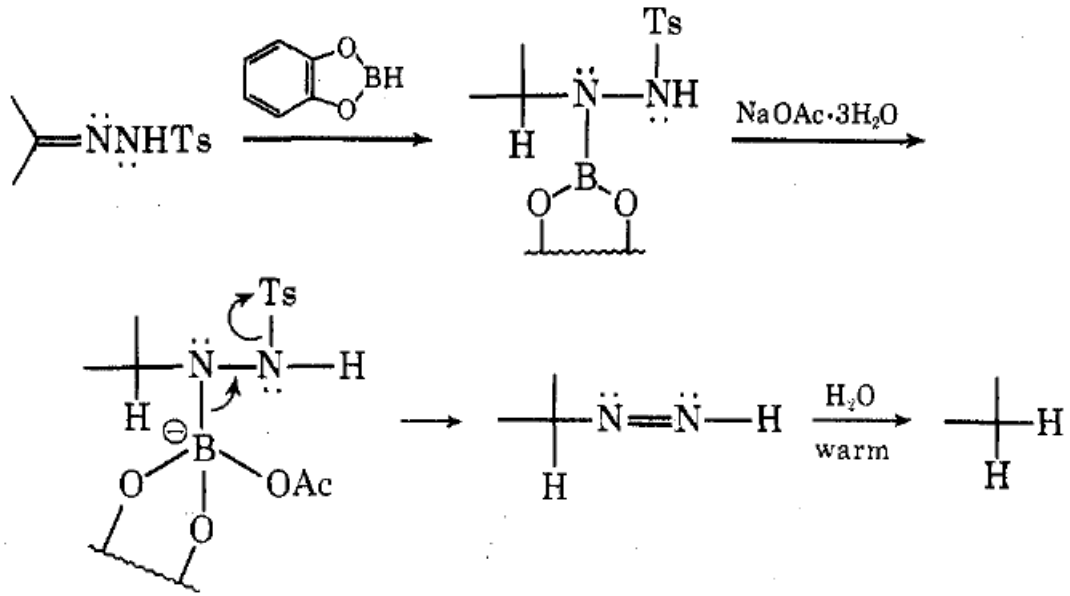


Synthesis: Weinreb amide **18**

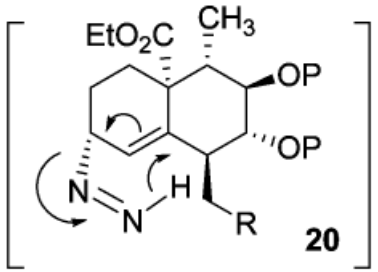


Synthesis



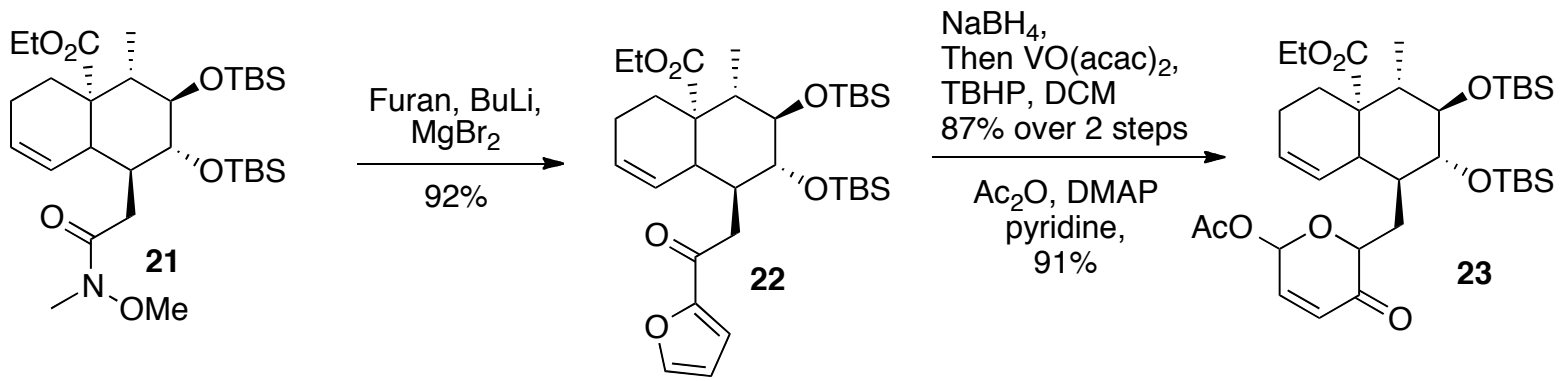


Via:

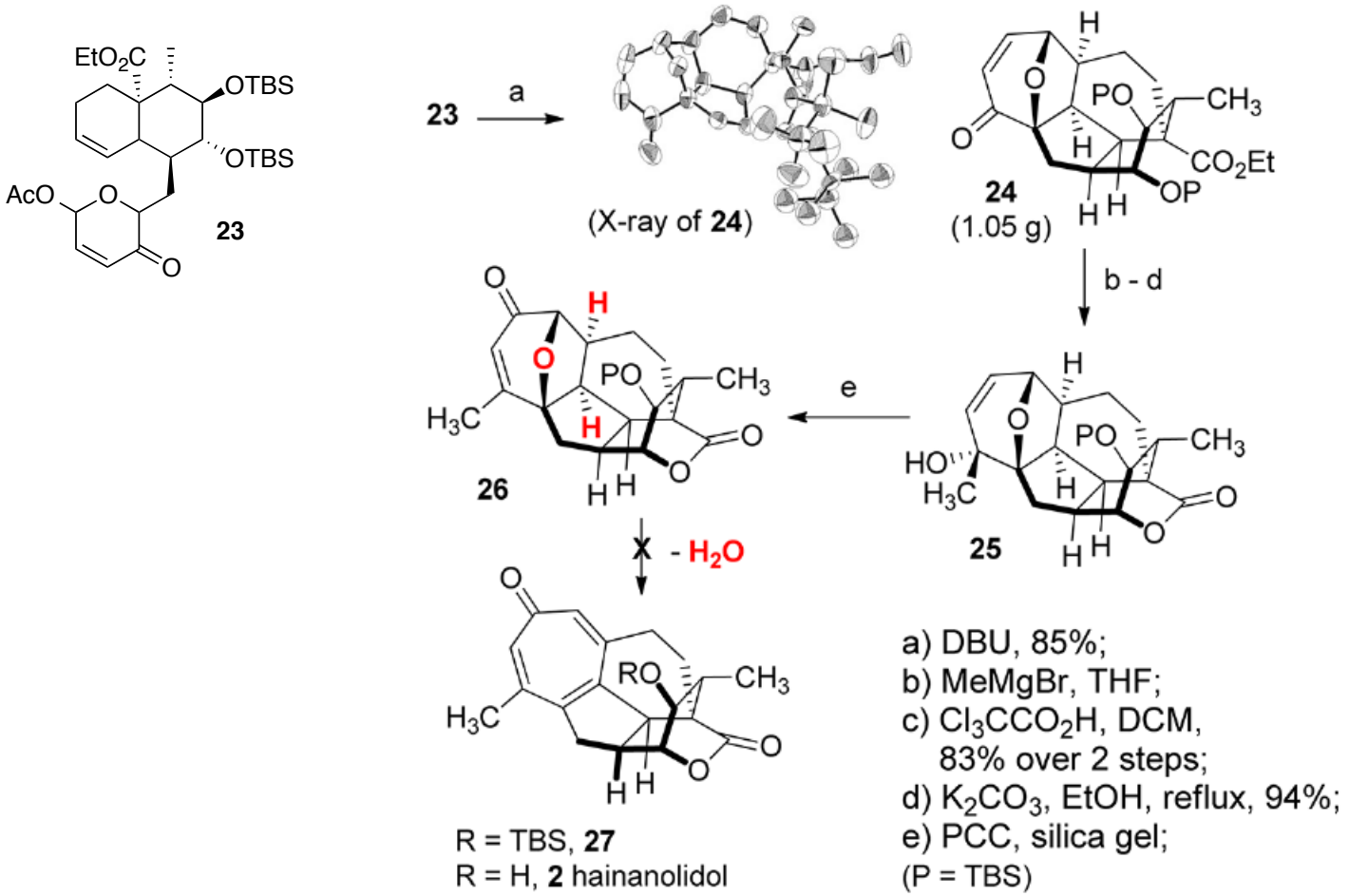


G. V. Kabalka, D. T. C. Yang and J. D. Baker, *J. Org. Chem.* **1976**, 41, 574-576

Synthesis


EtO2C
OTBS
OTBS
O
N
OMe
21
Furan, BuLi,
MgBr2
92%
EtO2C
OTBS
OTBS
O
O
22
NaBH4,
Then VO(acac)2,
TBHP, DCM
87% over 2 steps
Ac2O, DMAP
pyridine,
91%
EtO2C
OTBS
OTBS
AcO
O
O
23

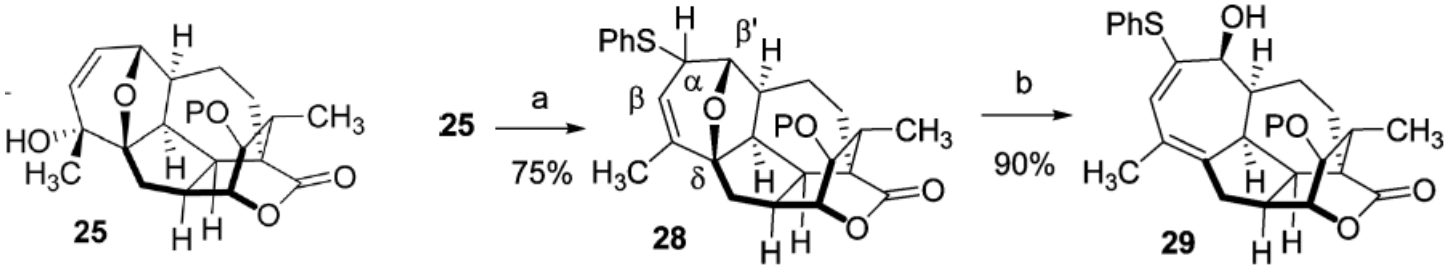
Completion of the synthesis



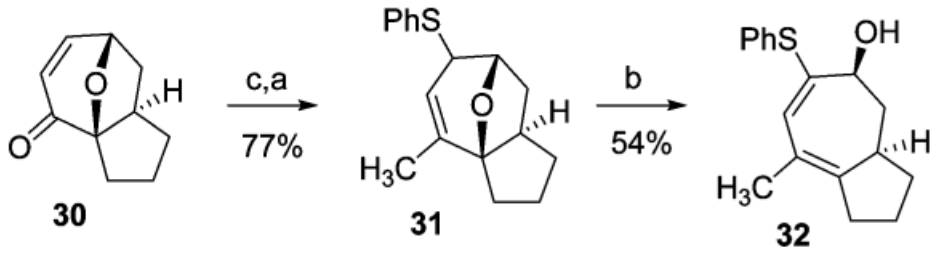
Opening of the ether bridge proved impossible!

Alternative strategy

2 Step sequence: S_N1' Substitution with thiophenol and deprotonation



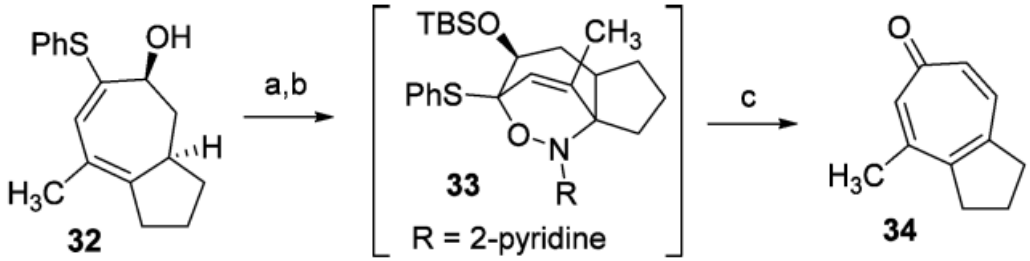
Model:
(tropone installation)



[a](a) PhSH, $BF_3 \cdot OEt_2$; (b) LDA, HMPA, THF; (c) MeMgBr; (P = TBS).

Model: Tropone formation

Hetero Diels-Alder reaction with nitrosoarene

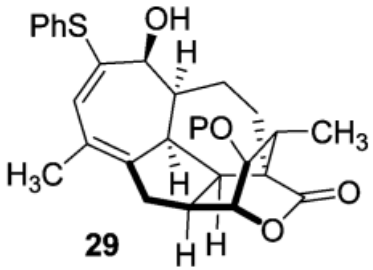


[a](a) TBSOTf, 2,6-lutidine, DCM; (b) 2-nitrosopyridine, DCM, 90% over two steps; (c) $SnCl_2$, EtOAc, 50%.

This strategy proved not successful on the elaborated intermediate!

Hydrolysis of thio ether not possible as well!

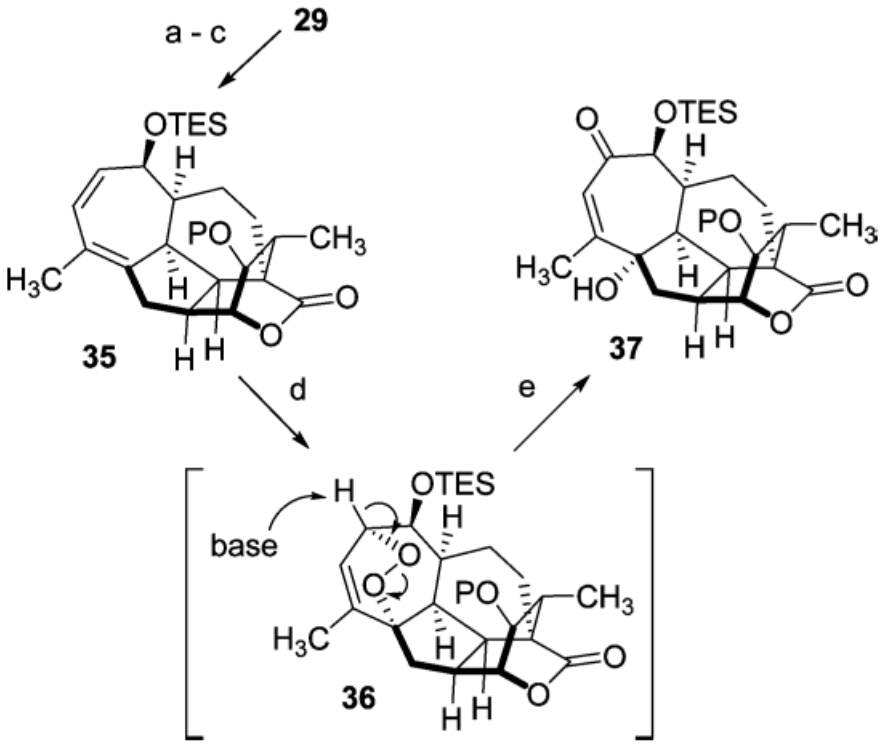
Removal of thio ether



29

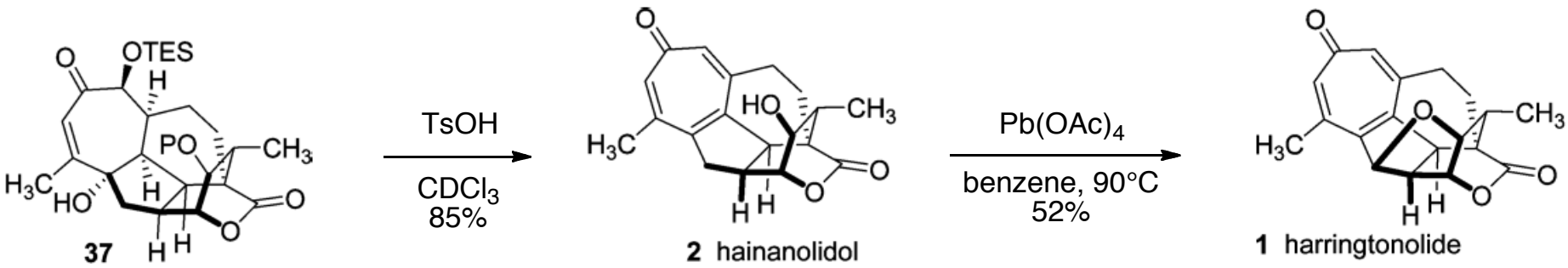
1) Protection of alcohol
2) Oxidation of thiol to sulfoxide
3) Reduction using SmI_2

Reduction with SmI_2 known for sulfone!



[a](a) TESCl, DMAP, TEA, DCM; (b) MMPP on silica gel, DCM; (c) SmI_2, DMPU, MeOH, THF, 70% over three steps; (d) O_2, TPP, light, CH_3CN, 40%; (e) DBU, DCM; (f) TsOH, $CDCl_3$, 85% over two steps; (g) $Pb(OAc)_4$, benzene, 90 °C, 52%. (P = TBS).

Completion of the synthesis



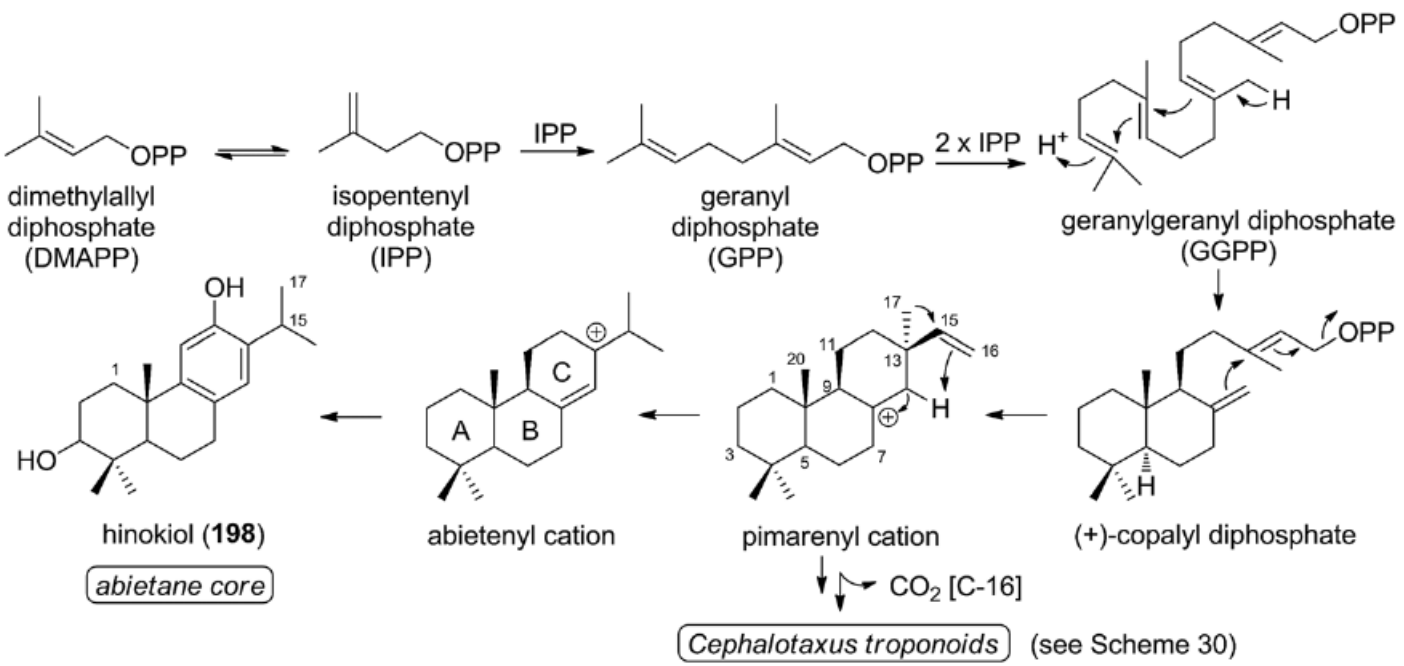
Conclusion

Synthesis of *haianolidol* featuring:

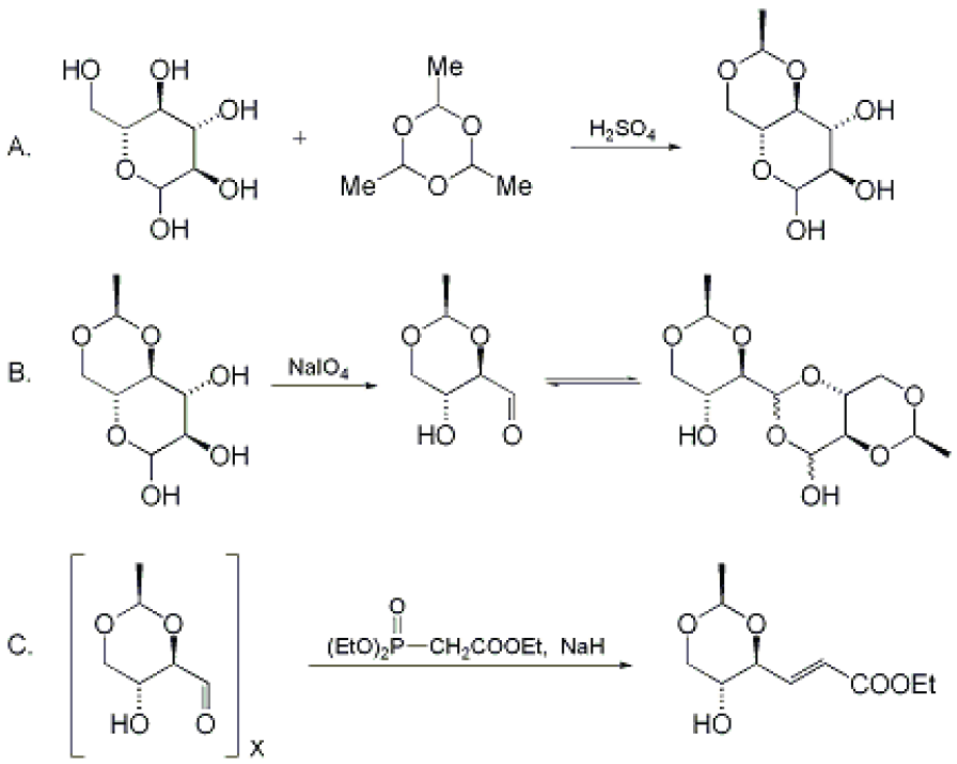
1) 2 stereoselective 3+3 sigmatropic rearrangement
2) Oxydopyrylium-based 5+2 cycloaddition
3) Formation of tropone

This synthesis will allow preparation of derivatives and investigation of the mode of action.

Biosynthesis

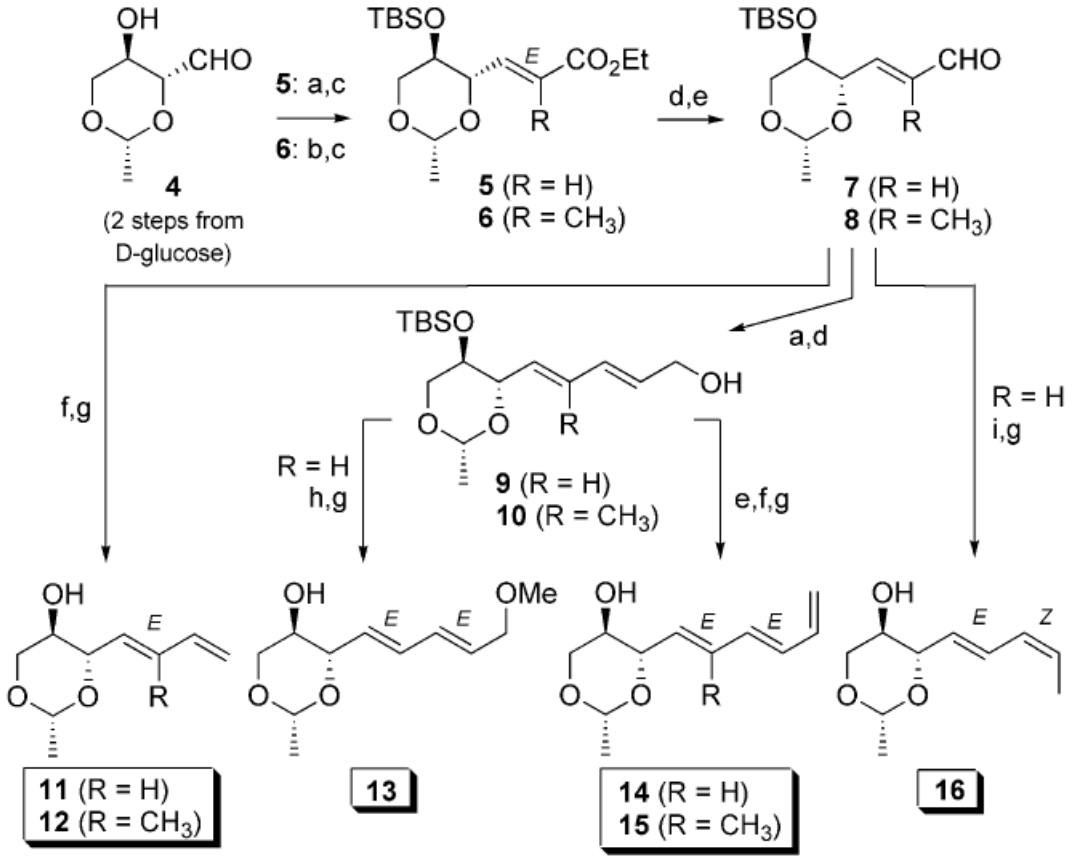


Synthesis of chiral template



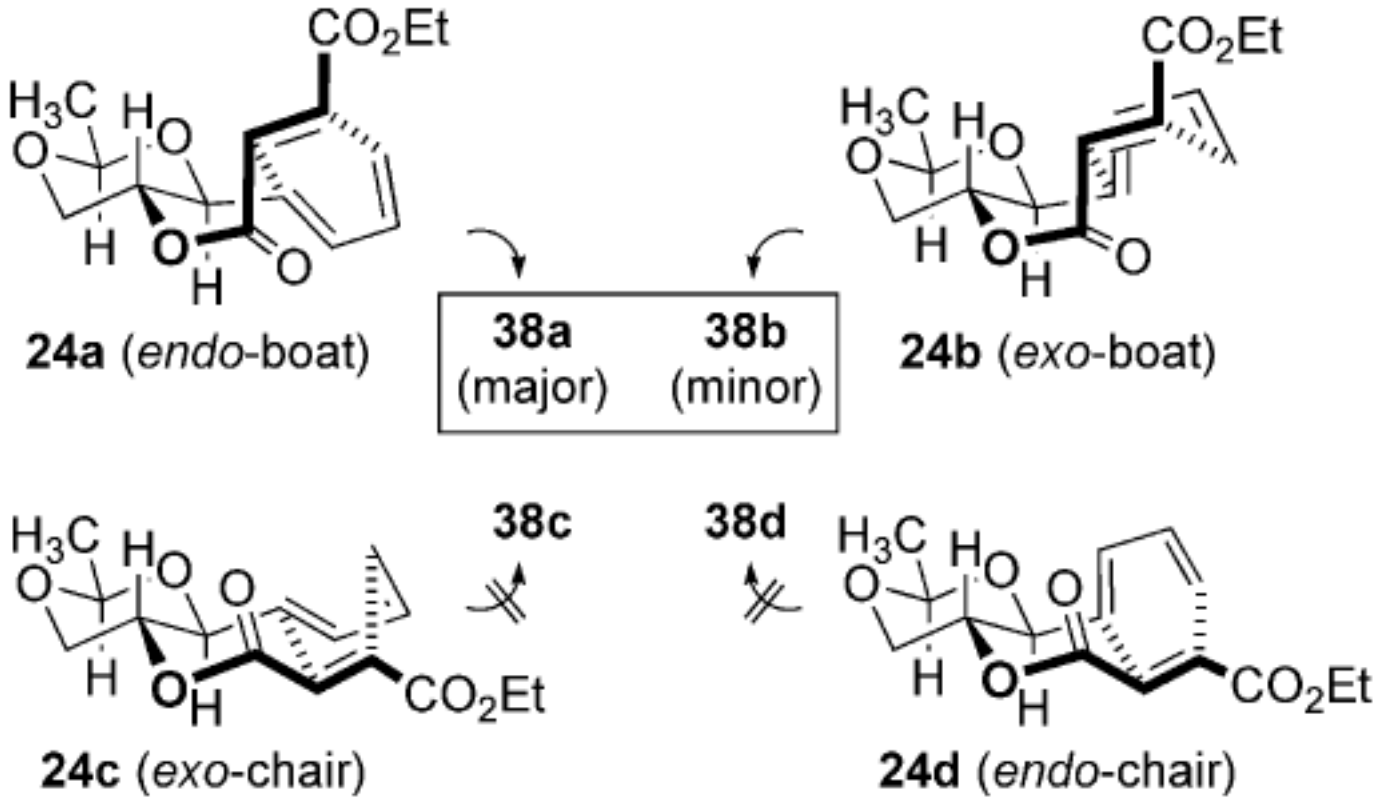
M. Fengler-Veith, O. Schwardt, U. Kaut, B. Krämer, and V. Jäger, Org. Synth., **2004**, *78*, 123

Synthesis of chiral template

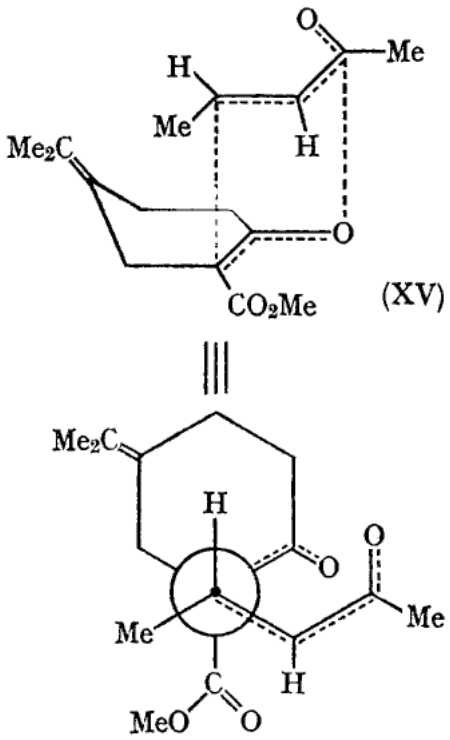


Scheme 1. Divergent synthesis of the diene substrates. *Reagents and conditions:* (a) triethylphosphonoacetate, NaH, THF, 0 °C (74%); (b) triethylphosphonopropionate, BuLi, LiBr, MeCN, 0 °C (48%); (c) TBSCl, imidazole, DMAP, CH_2Cl_2, reflux (**5**: 86%; **6**: 90%); (d) DIBAL-H, CH_2Cl_2, –78 °C (**9**: 89%; **10**: 70%, two steps); (e) MnO_2, CH_2Cl_2, reflux (**7**: 92%; **8**: 78%, two steps); (f) $MePPh_3PBr$, NaHMDS, THF, –78 °C; (g) TBAF, THF, 0 °C (**11**: 70%; **12**: 67%; **13**: 85%; **16**: 84%, two steps; **14**: 90%; **15**: 58%, three steps); (h) NaH, THF, then MeI, 0 °C; (i) $EtPPh_3PBr$, NaHMDS, THF, –78 °C.

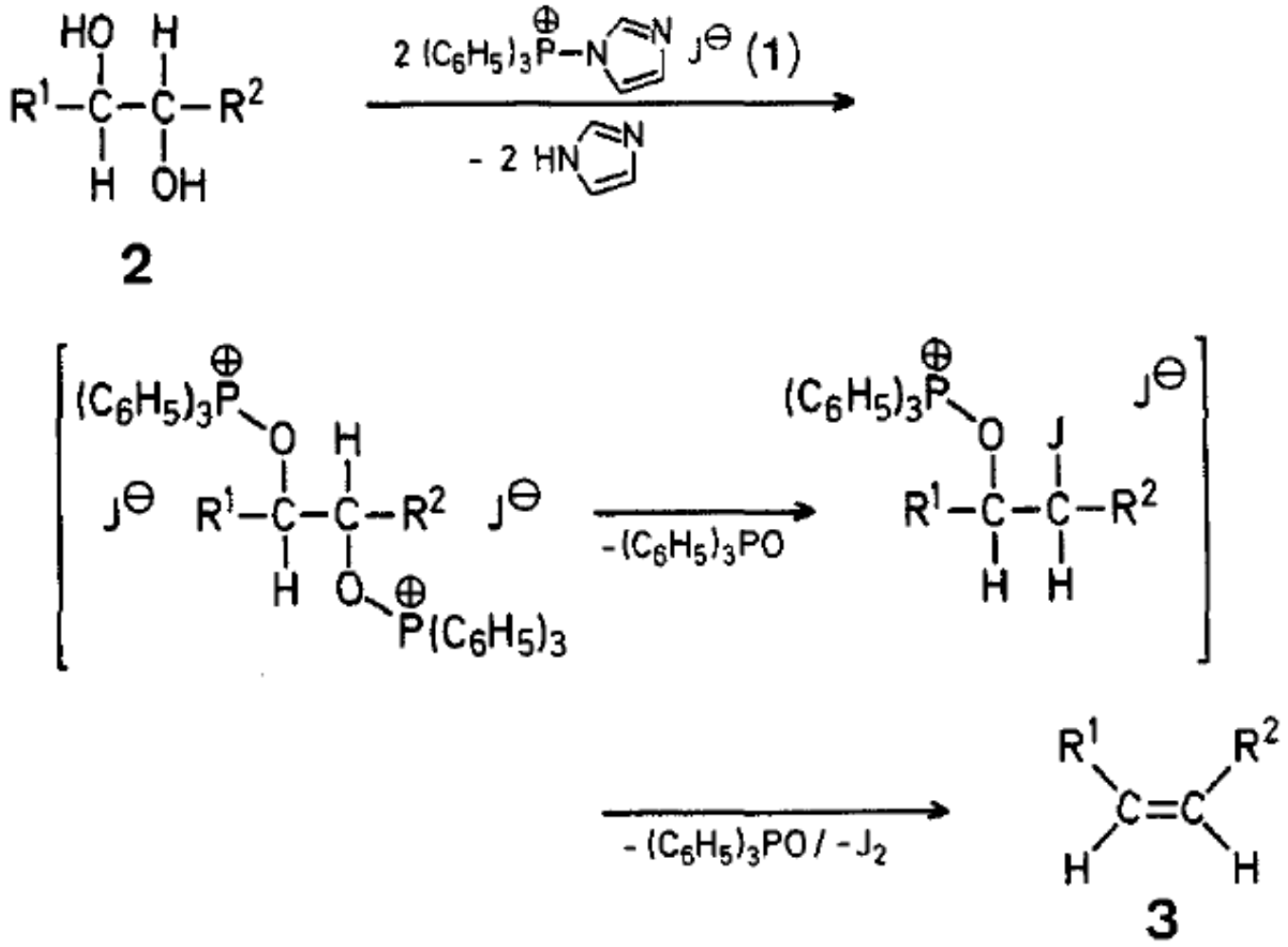
IMDA Selectivity



Diastereoselectivity

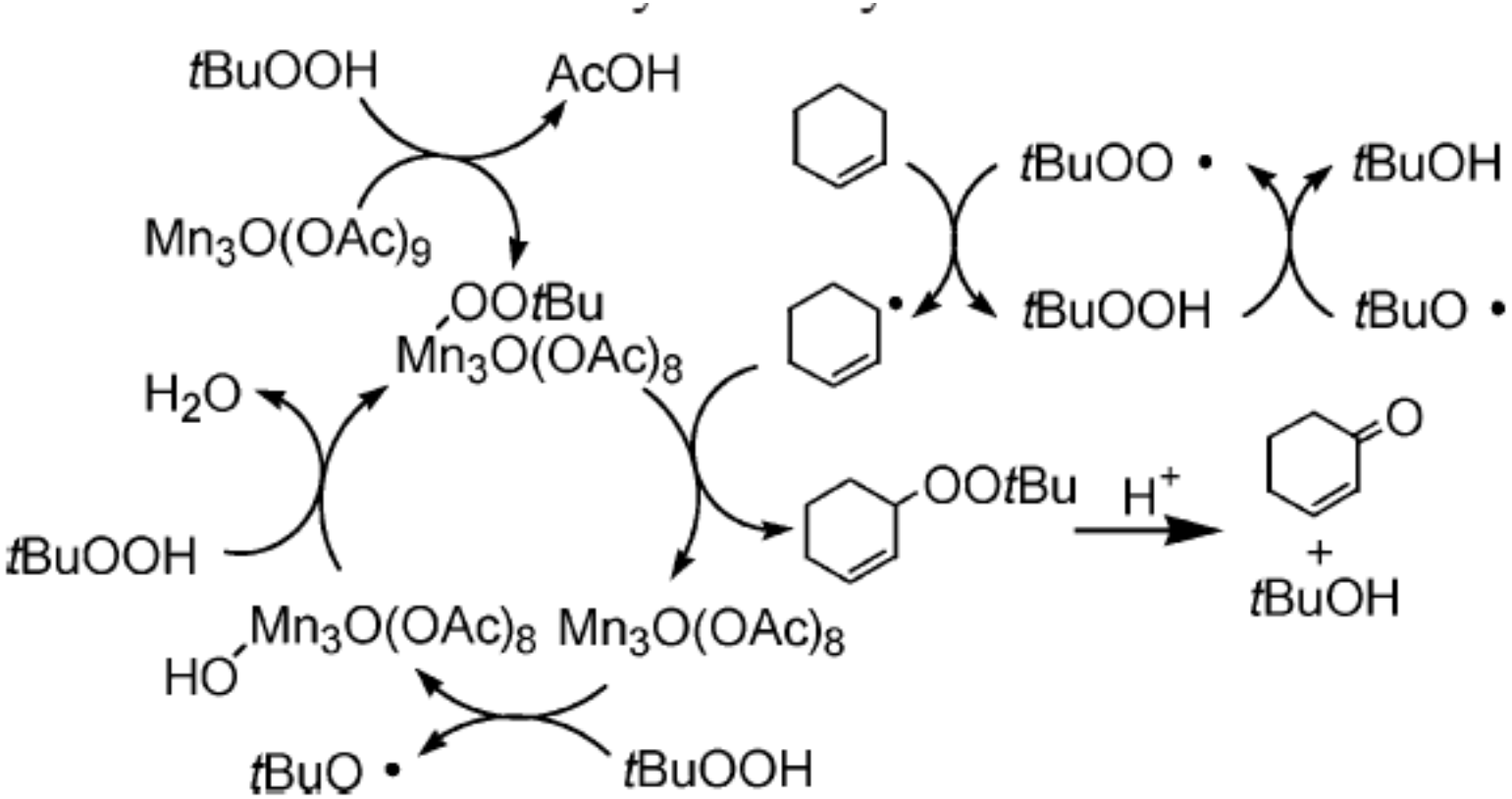


Diol into double bond

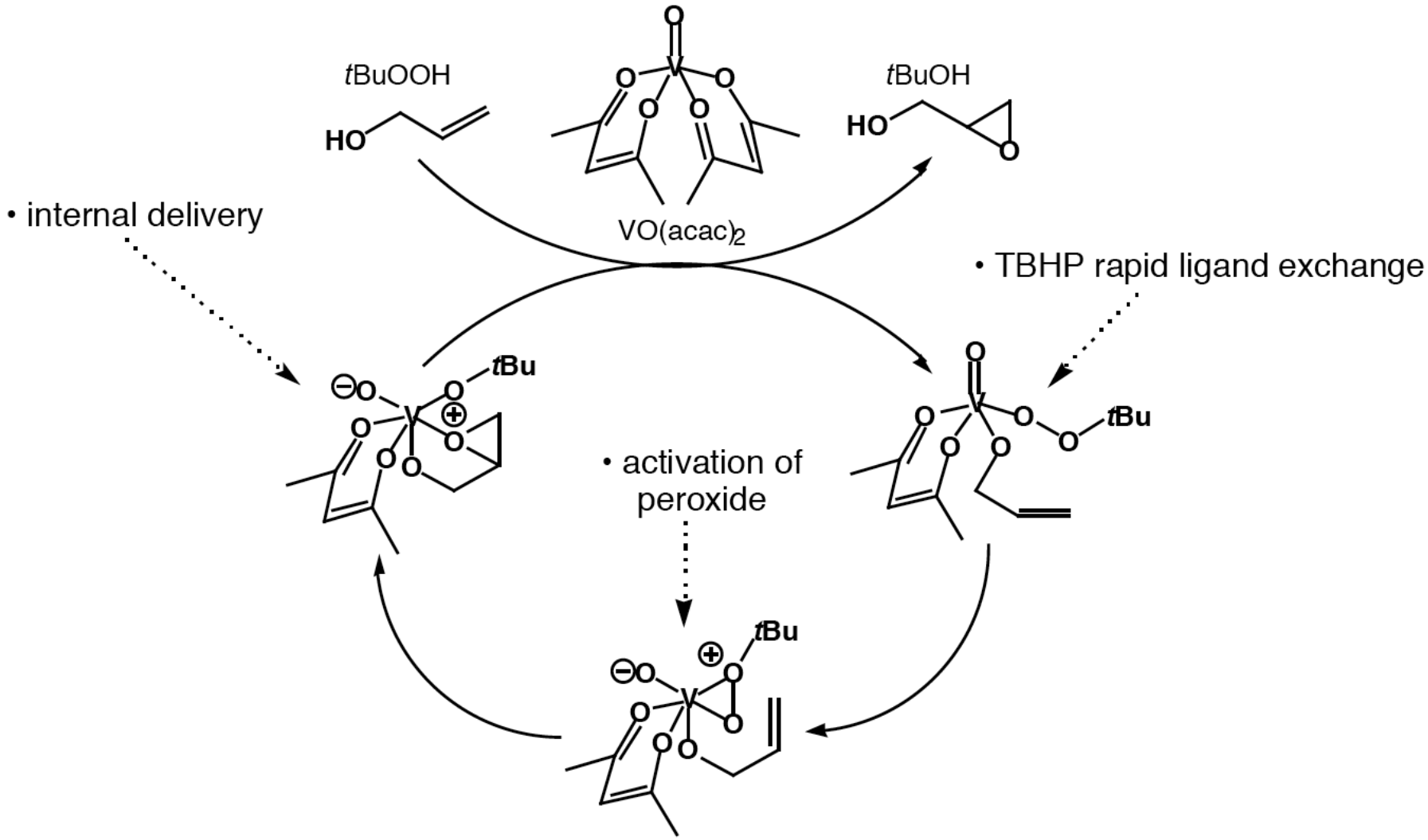


P. J. Garegg, B. Samuelsson, *Synthesis*, **1979**, 469

Oxidation Mn (III)



Oxidation $VO(acac)_2$



Mercury salt assisted vinylation