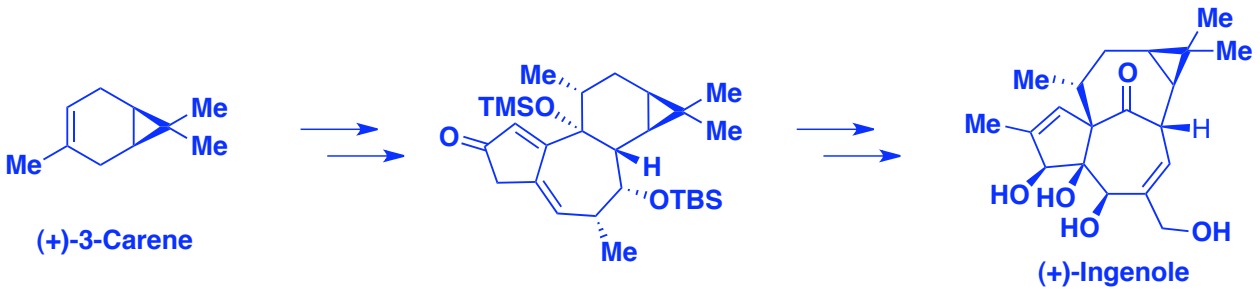
14-Step Synthesis of (+)-Ingenol from (+)-3-Carene

Lars Jørgensen, Steven J. McKerrall, Christian A. Kuttruff, Felix Ungeheuer, Jakob Felding, Phil S. Baran,
Science, Published online 1 August 2013, DOI: 10.1126/science.1241606

"…I think that most organic chemists had considered ingenol beyond the reach of scalable chemical synthesis…" P. S. Baran

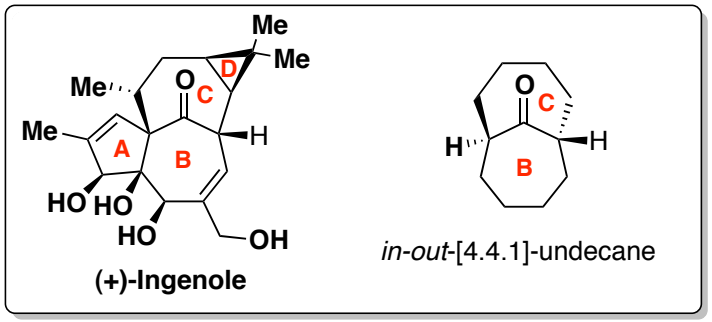


Raffaele Colombo – 8/24/2013

Ingenol

Ingenol is a diterpenoid first isolated by Hecker in **1968** from *Euphorbia ingens*

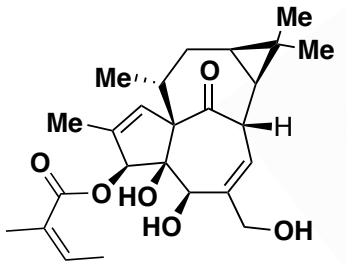
The structure was elucidated through X-ray crystallography by Hecker in **1970** and contains a unique bicyclo[4.4.1]undecan-11-one core (rings **BC**) whit a *in,out* intrabridgehead relationship



Ingenol esters showed:

- **anticancer activity *in vivo***
- **anti HIV activity *in vitro***

Ingenol mebutate (**Picato®, Leo Pharma**) is **FDA approved** (**2012**) for the treatment of actinic keratosi and has completed phase II clinical trials for the topical treatment of basal cell carcinomas



Picato®

Ingenol mebutate

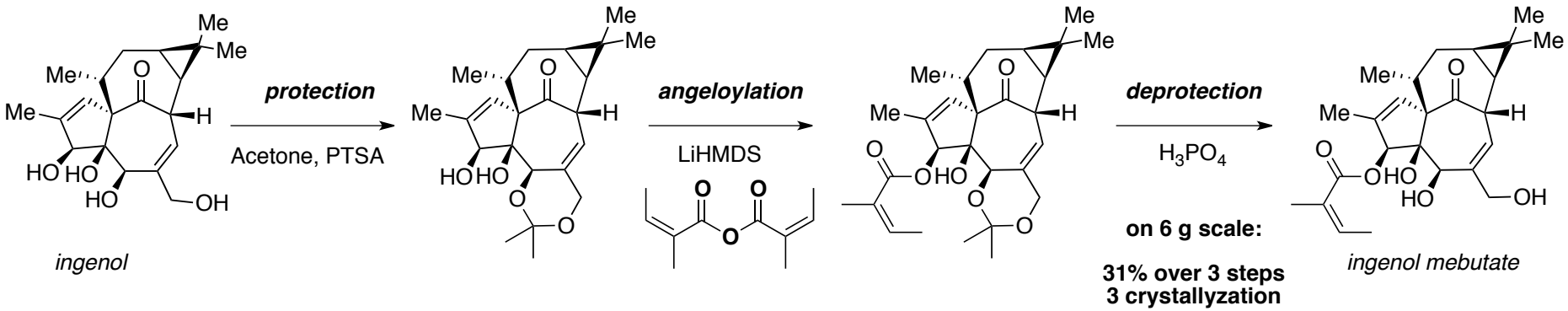
The current sources of ingenol mebutate are:

- direct isolation from *E. peplus* (commercial source)
- semisinthesis from ingenol

Isolation of ingenol mebutate and ingenol are:

1.1 mg of ingenol mebutate per Kg of *E. peplus*

275 mg of ingenol per Kg of *E. lathryis*



Synlett **2012**, *23*, 2647-2652 (Leo Pharma procedure)

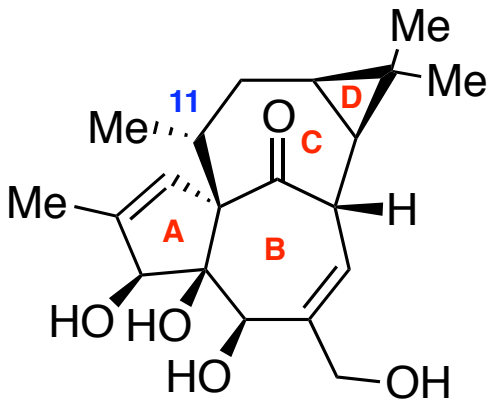
Ingenol - previous approaches

3 total synthesis:

- **Winkler** (***2002***): [2+2] photocycloaddition – 43 steps, 0.007% - racemic
- **Tanino/Kuwajima** (***2003***): pinacol rearrangement – 45 steps, 0.03% - racemic
- **Wood** (***2004***): ring close metathesis - 37 steps, 0.002% - asymmetric

1 formal synthesis:

- **Kigoshi** (***2004***): ring close metathesis – 36 steps, 0.01% based on Winkler's route, asymmetric

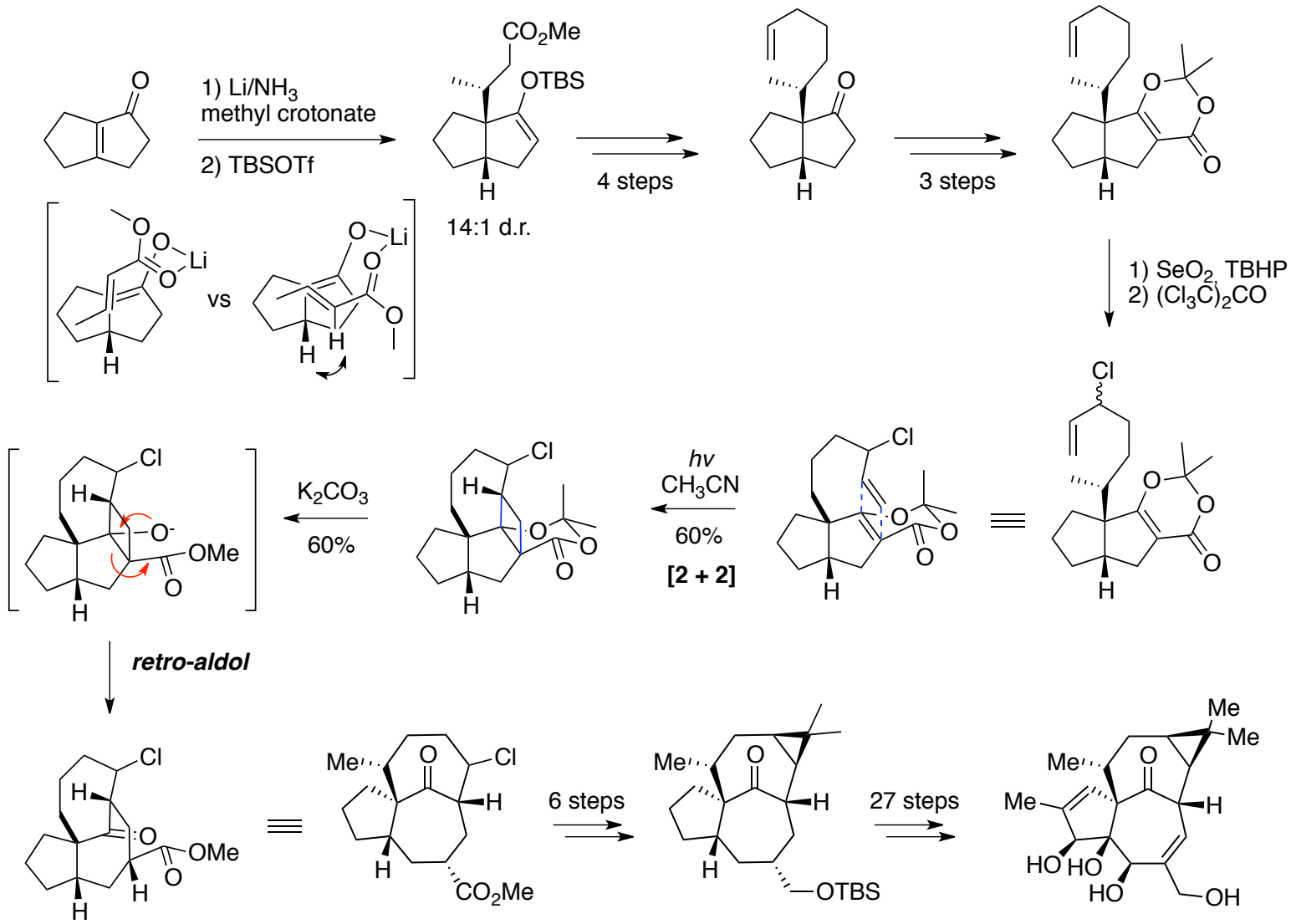


(+)-Ingenol

Synthethic challenges:

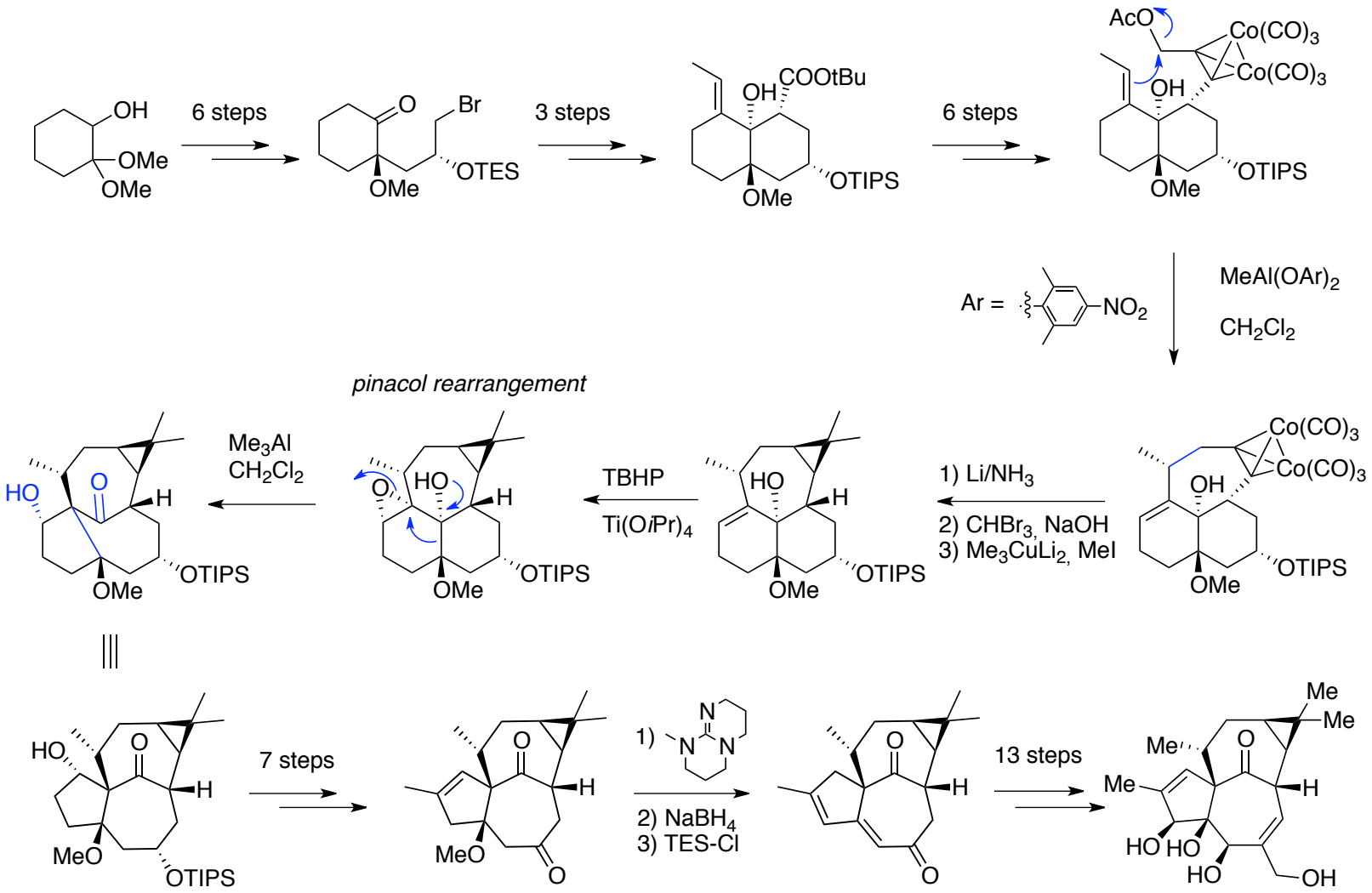
- *in-out* intrabridgehead stereochemistry
- 4 hydroxyl groups int the south part
- Sterochemistry at C-11

Winkler's strategy



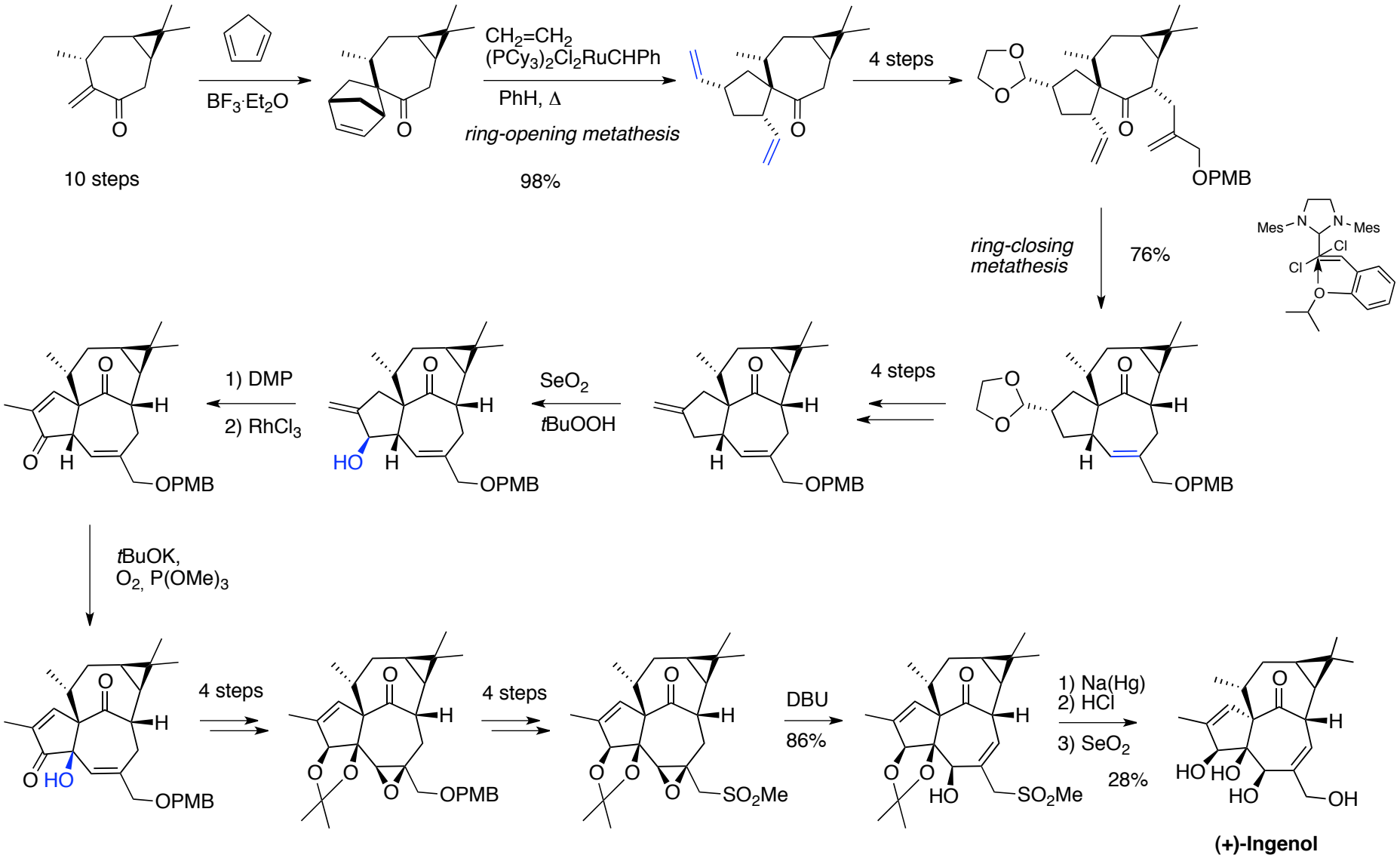
Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.*. **2002**, *124*, 9726-9728.

Tanino/Kuwajima's strategy



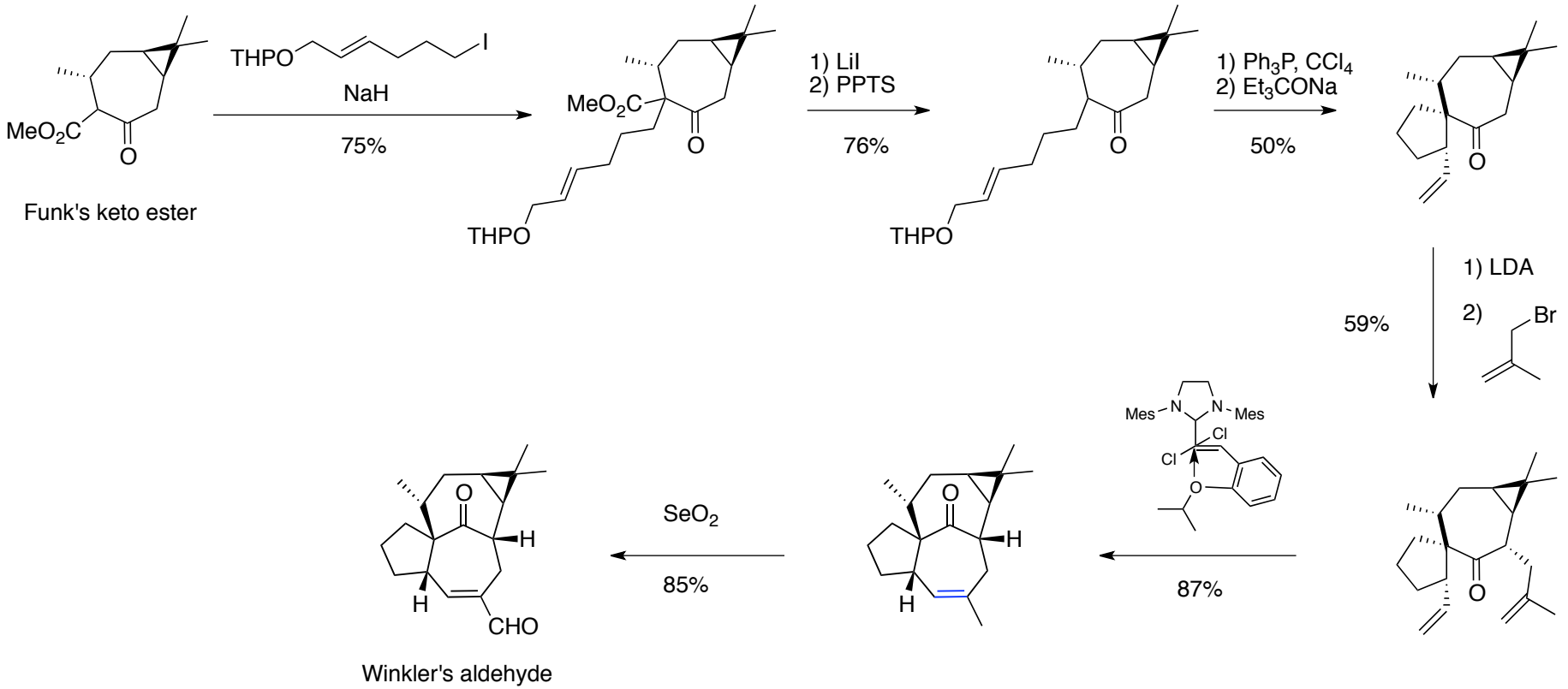
Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.*. **2003**, *125*, 1498-1500.

Wood's strategy



Total Synthesis of Ingenol. Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.;. Greene, B.; Yusuff, N.; Wood, J. L.. *J. Am. Chem. Soc*. **2004**, *126*, 16300-16301

Kigoshi's strategy (formal synthesis)



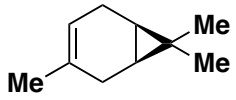
Watanabe K, Suzuki Y, Aoki K, Sakakura A, Suenaga K, Kigoshi H. *J. Org. Chem.* **2004**, 69, 7802-7808

This work

Highly stereocontrolled synthesis of (+)-ingenole starting from (+)-carene ($10.2/mol)

14 steps 1.2% overall yield

2 phases strategies: cyclase and oxidase

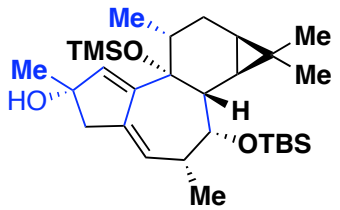


(+)-3-Carene

7 C-C bonds
5 stereocenters

cyclase phase

7 steps

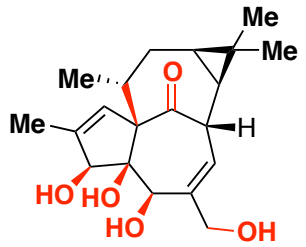


(1.08 g)

4 C-O bonds
4 stereocenters

rearrangement/ oxydase phase

7 steps



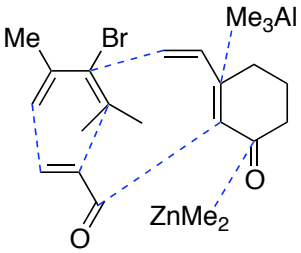
(+)-Ingenole

This work

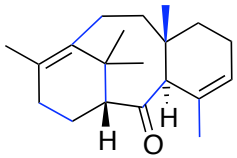
Highly stereocontrolled synthesis of (+)-ingenole starting from (+)-carene ($10.2/mol)

14 steps - 1.2% overall yield

2 phase strategy: cyclase and oxidase



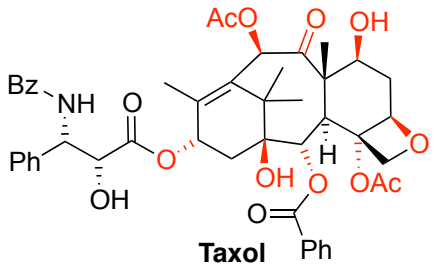
cyclase phase



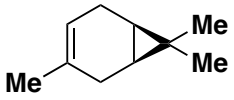
(+)-"taxadienone"

8 steps, 18-20% overall yield

oxidase phase



Taxol

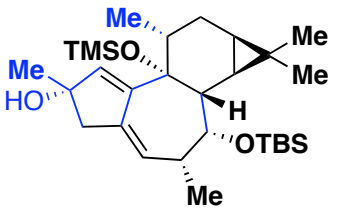


(+)-3-Carene

7 C-C bonds
5 stereocenters

cyclase phase

7 steps

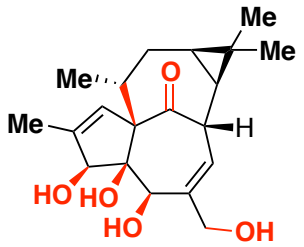


(1.08 g)

4 C-O bonds
4 stereocenters

rearrangement/ oxydase phase

7 steps

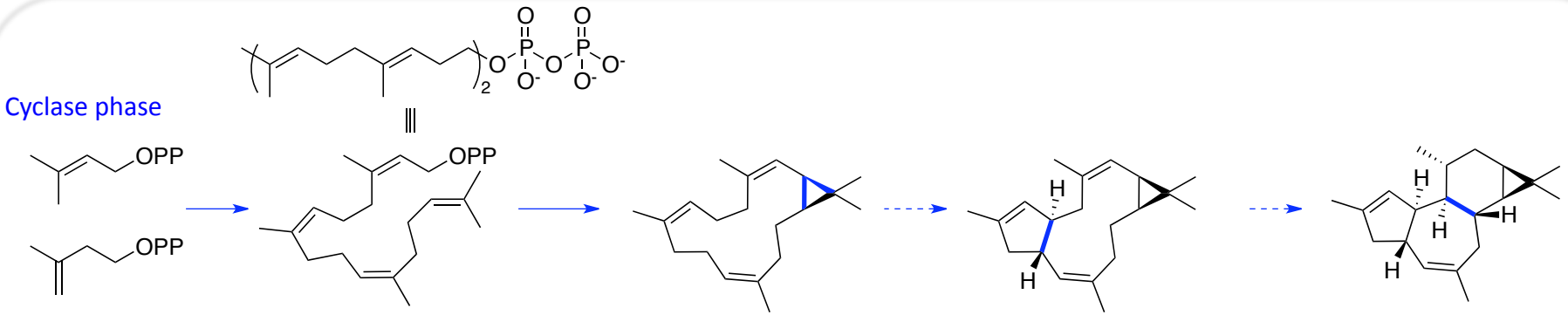


(+)-Ingenole

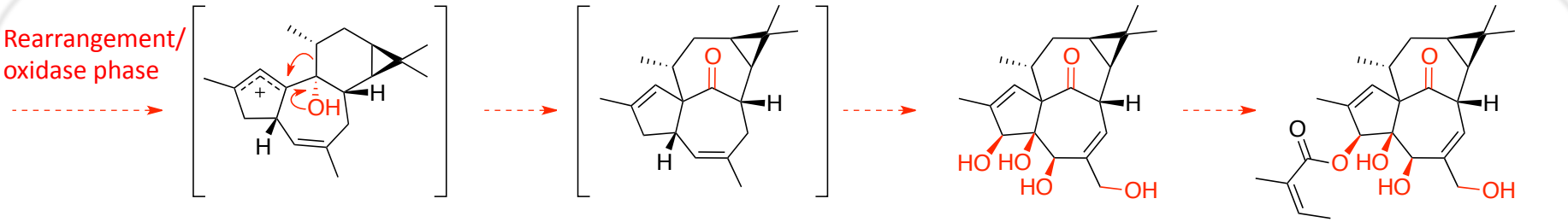
A. Mendoza, Y. Ishihara, P. S. Baran. *Nature Chemistry* **2012,** *4*, 21–25

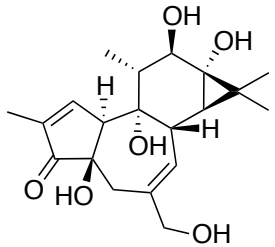
Biosynthetic inspiration

Cyclase phase



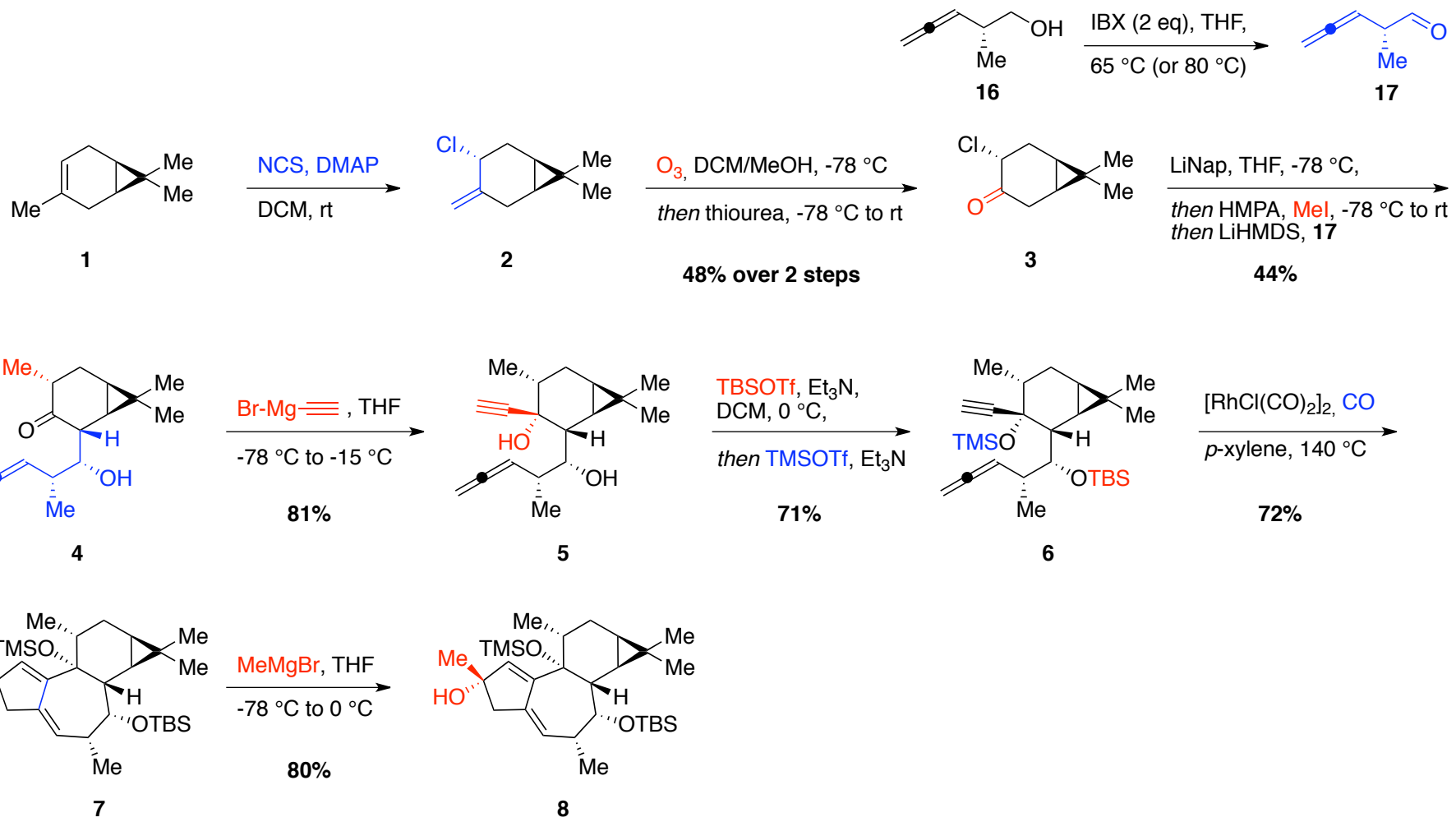
Rearrangement/ oxidase phase



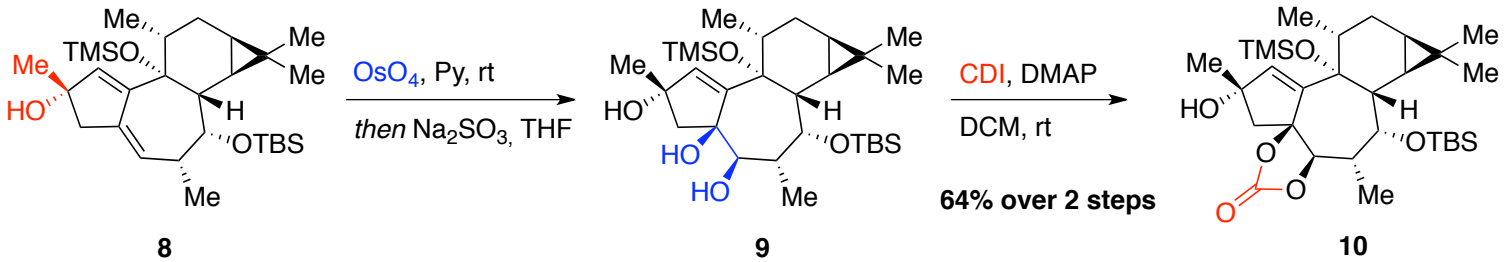


1 total synthesis (36 steps)

Cyclase phase

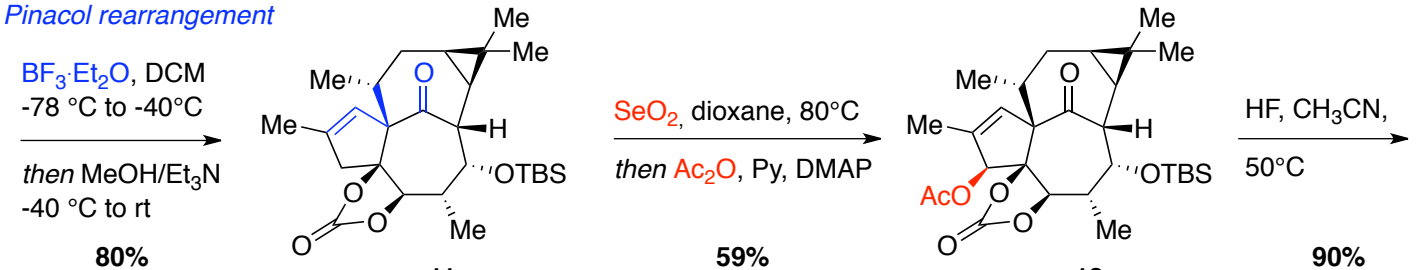


Rearrangement/oxidase phase

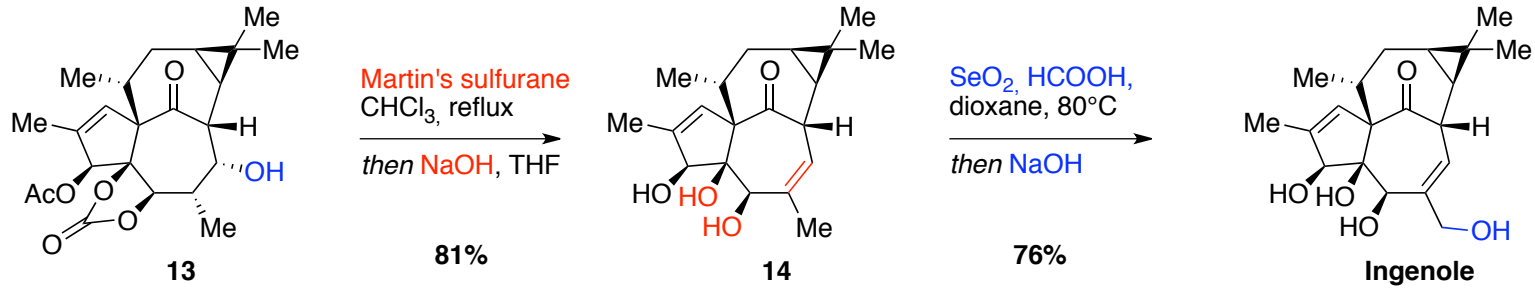


8 **9** **10**

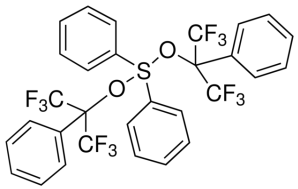
Pinacol rearrangement



11 **12**



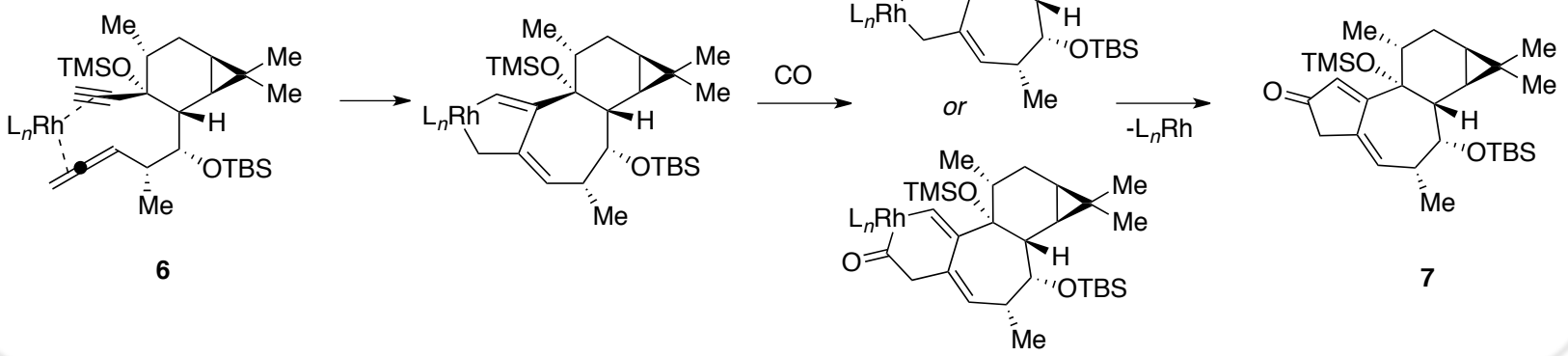
13 **14**

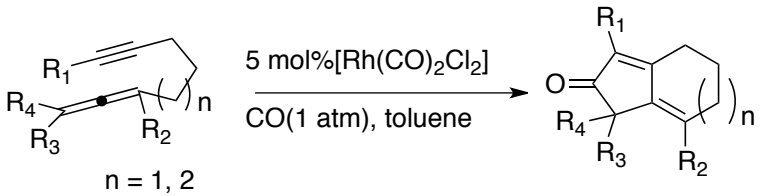


Martin's sulfurane

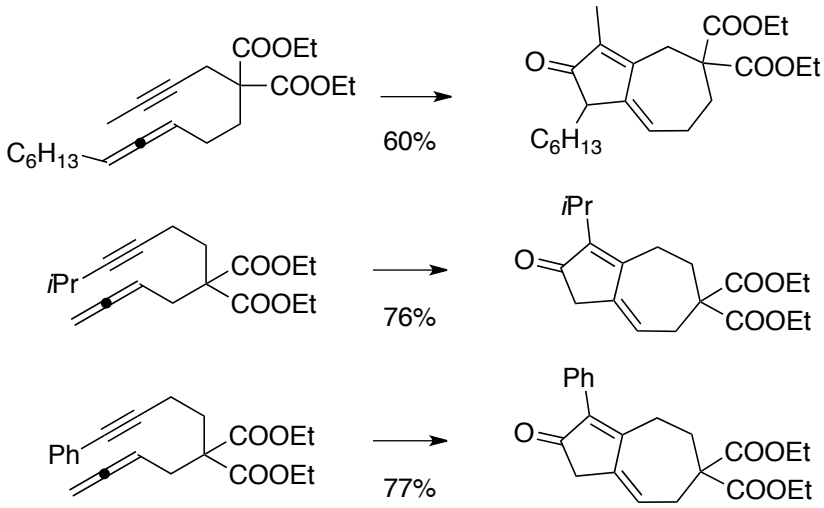
Key step 1

Pauson - Khand [2 + 2 + 1]



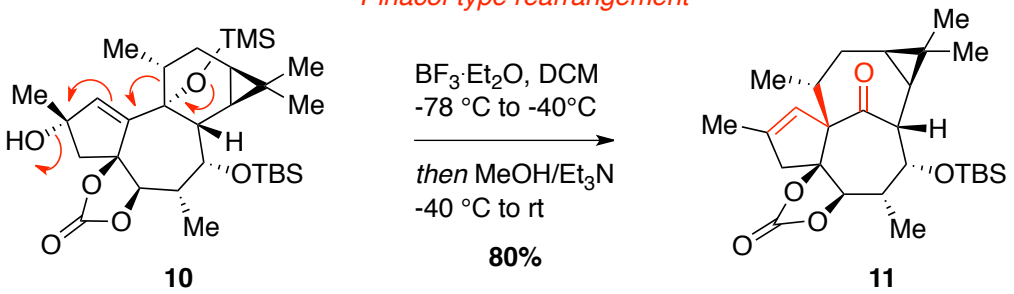


K. M. Brummond, H. Chen, K. D. Fisher, A. D. Kerekes, B. Rickards, P. C. Sill, S. J. Geib. *Organic Letters*, **2002**, *4*, 1931-1934



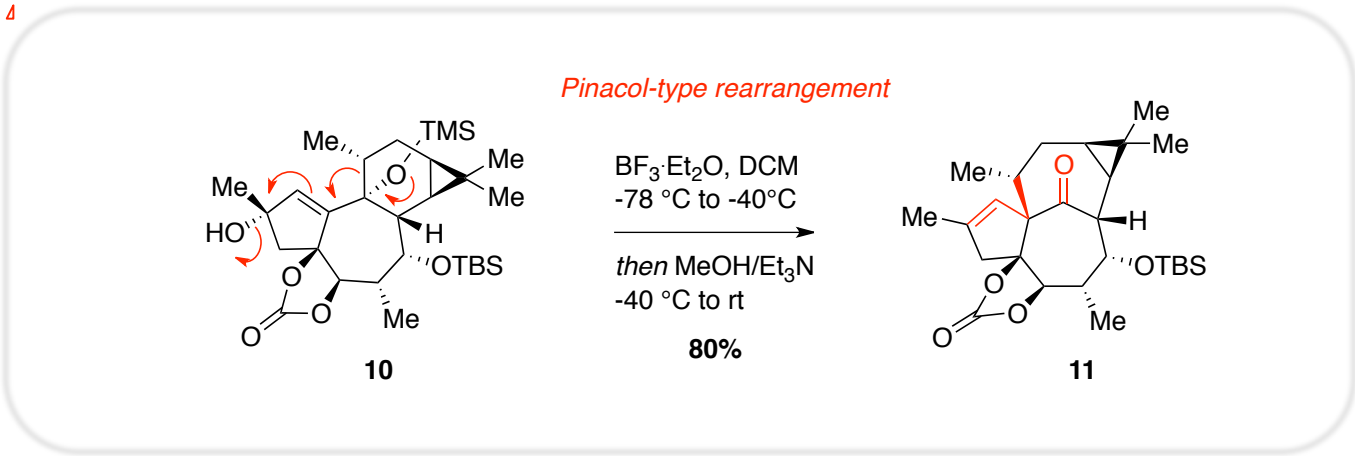
Key step 2

Pinacol-type rearrangement

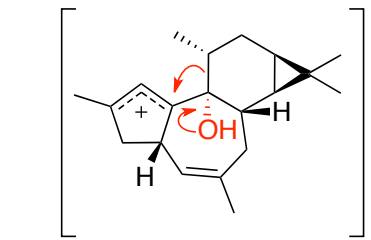


10 **11**

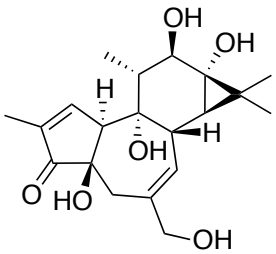
Key step 2



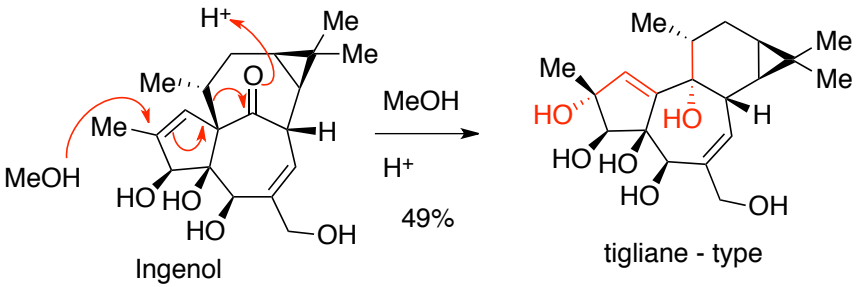
"Bio" vs "chem" inspiration



[putative biosinthetyc intermedie]



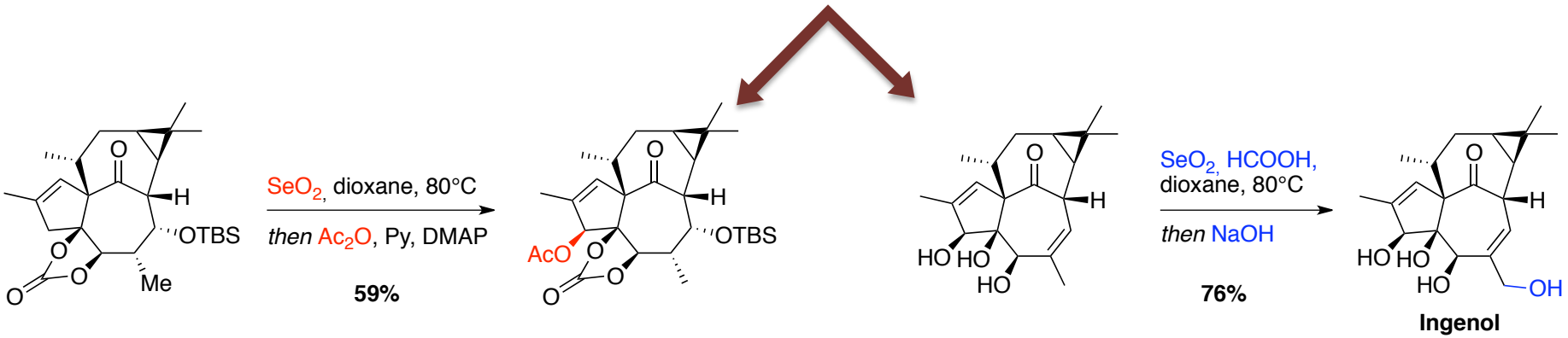
phorbol



G. Appendino, G. C. Tron, G. Cravotto, G. Palmisano, R. Annunziata, G. Baj, N. Surico, *European Journal of Organic Chemistry*, **1999**, *12*, 3413–3420

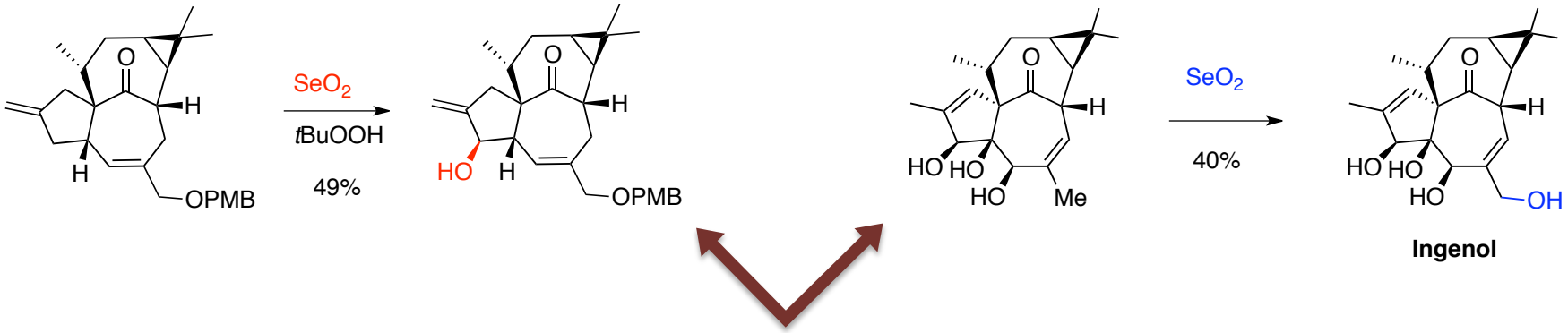
SeO_2 oxidations

Baran



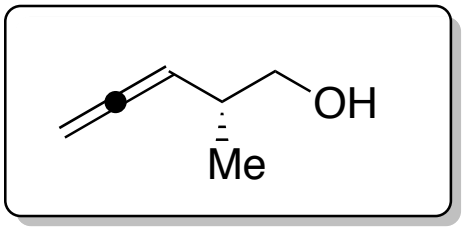
(Shibuya's condition)

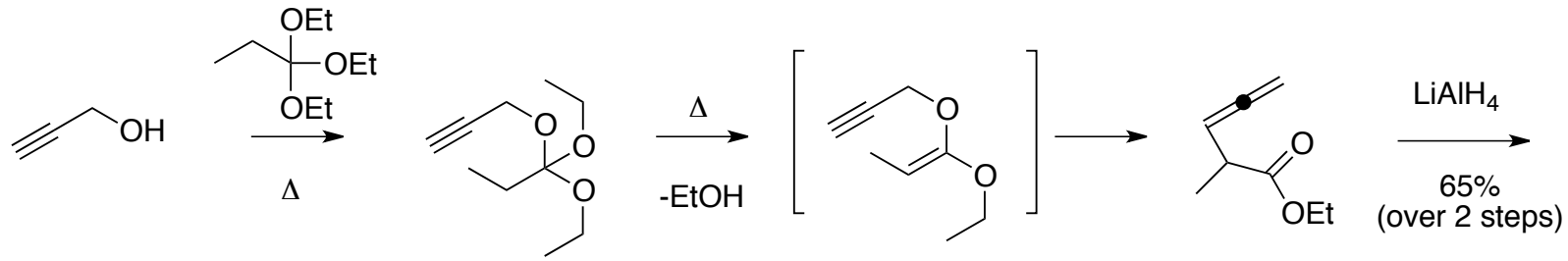
Shibuya, K., *Synth. Commun.*, **1994**, *24*, 2923-2941

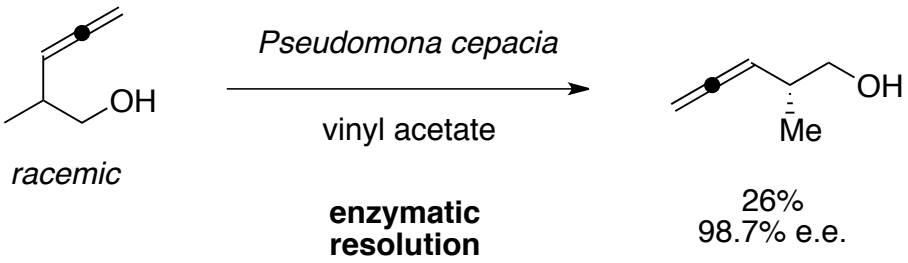


Wood

“Hidden” steps







3 more steps, 17% overall yield


Here We Go
Steelers
Here We Go
Wipf Group

Key step procedures

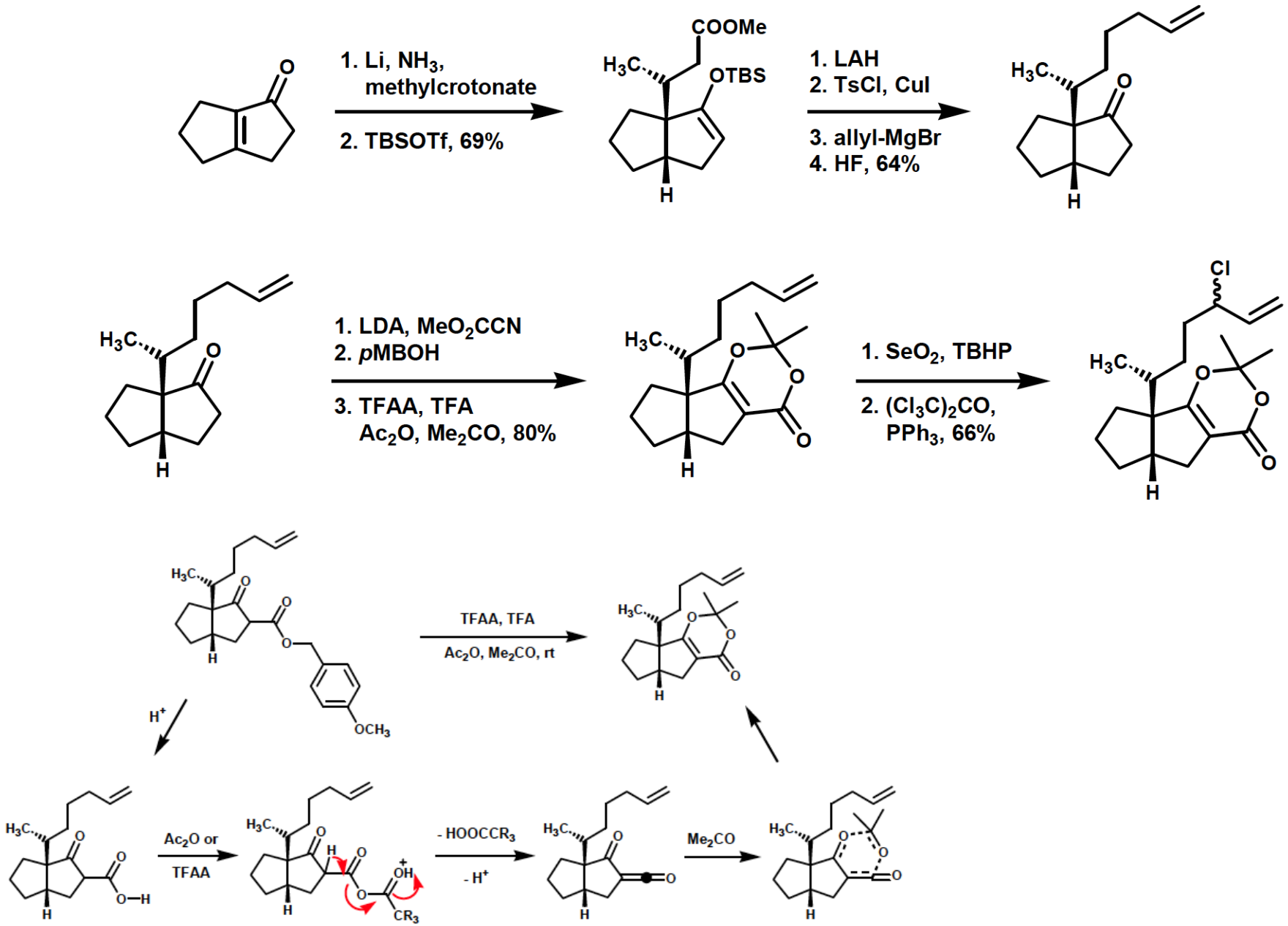
Pauson Khand

*A 1L three-neck flask was charged with a solution of **6** (1.5 g, 3.25 mmol, 1.0 equiv) in anhydrous p-xylene (650 mL) and the solution was degassed using carbon monoxide under sonication. [RhCl(CO)2]2 (126.3 mg, 0.325 mmol, 0.1 equiv) was added and the reaction mixture was transferred into a preheated oil bath and stirred at 140 °C under 1 atm of CO for 12 h.*

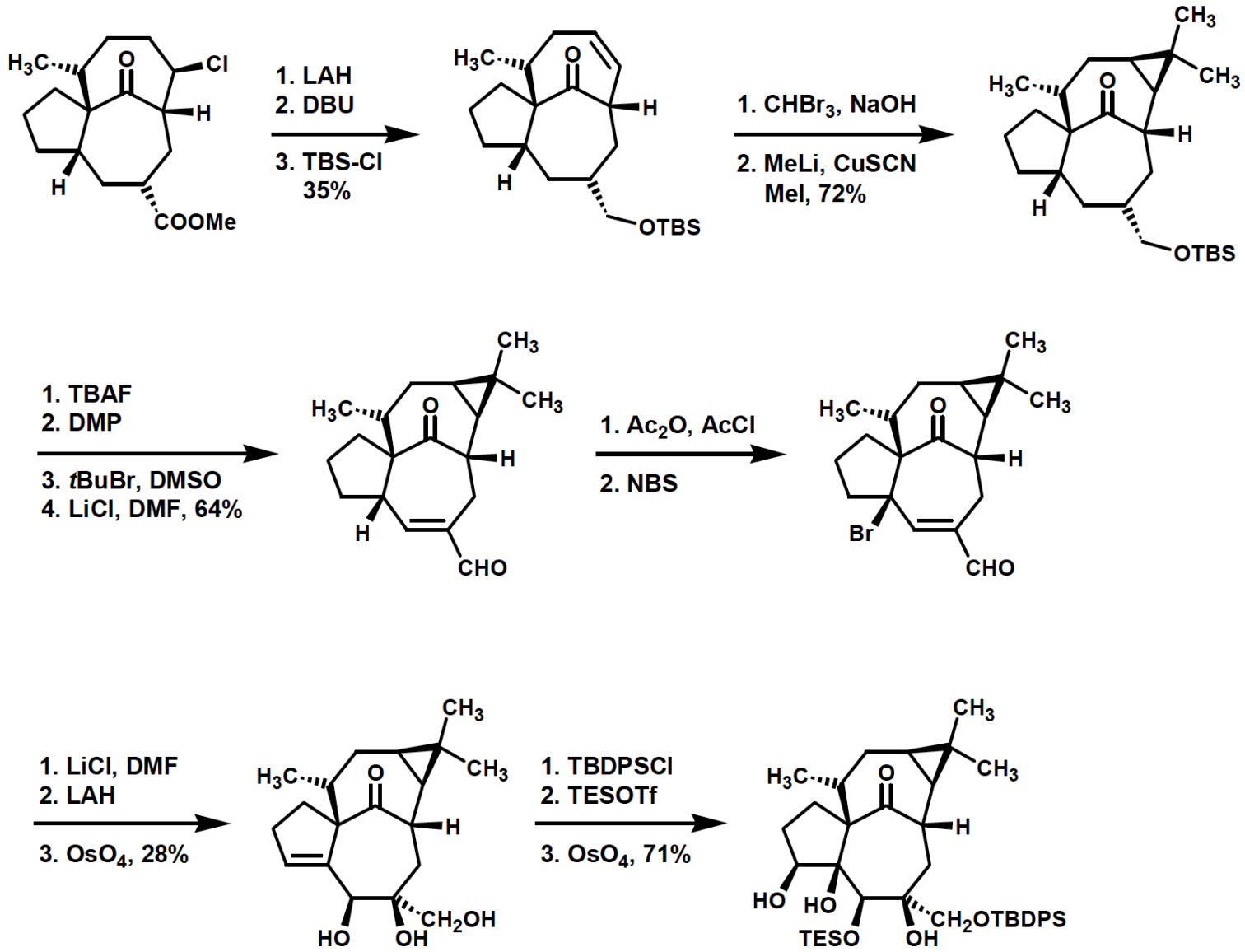
Pinacol rearrangement

*To a solution of **10** (191 mg, 0.338 mmol, 1.0 equiv) in DCM (7 mL) was added BF3.Et2O (420 **µ**L, 3.38 mmol, 10 equiv) dropwise at -78 °C. The reaction mixture was stirred at this temperature for 2 min before being warmed to -50 °C. After 30 min, a 1:1 mixture of Et3N/MeOH (3 mL) was added at -40 °C, the solution was stirred for 2 min and saturated aqueous NaHCO3 (5 mL) was added…*

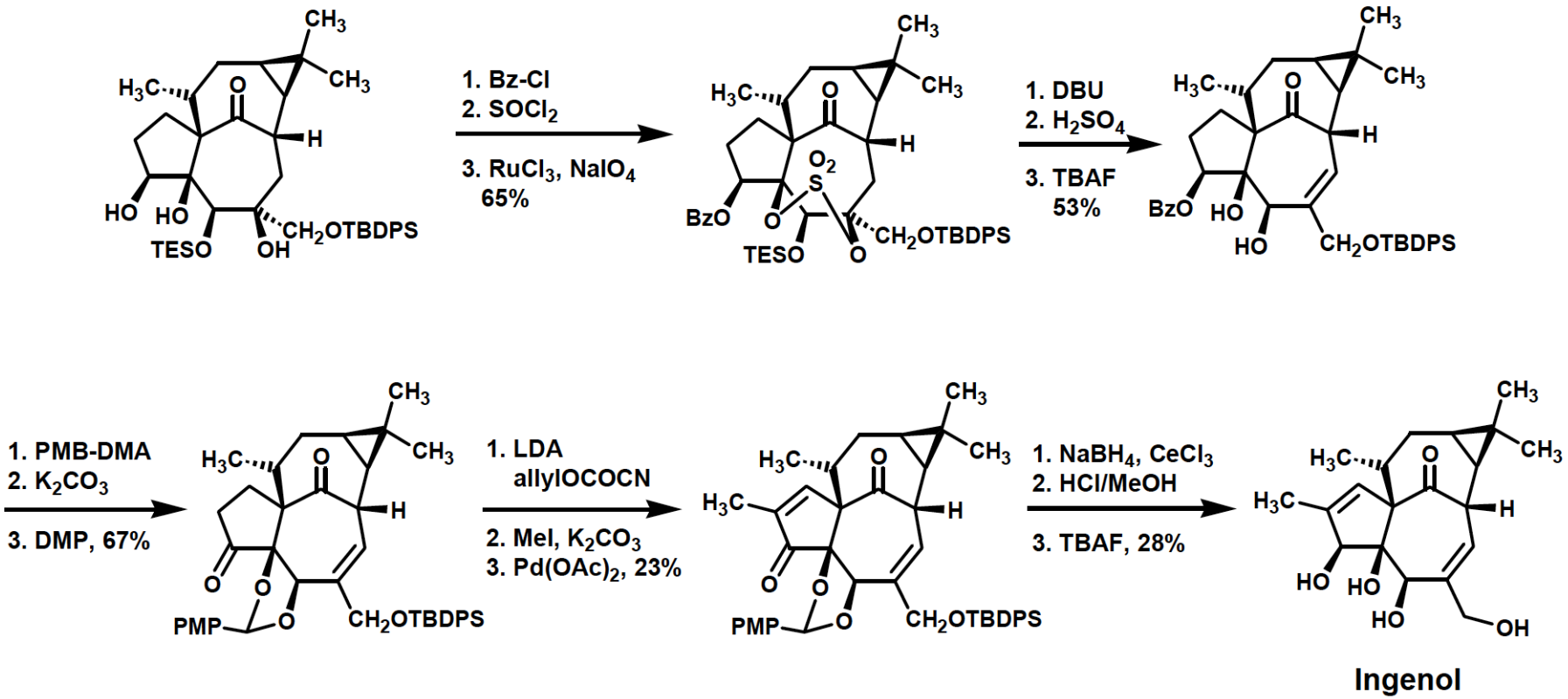
Winkler: first steps



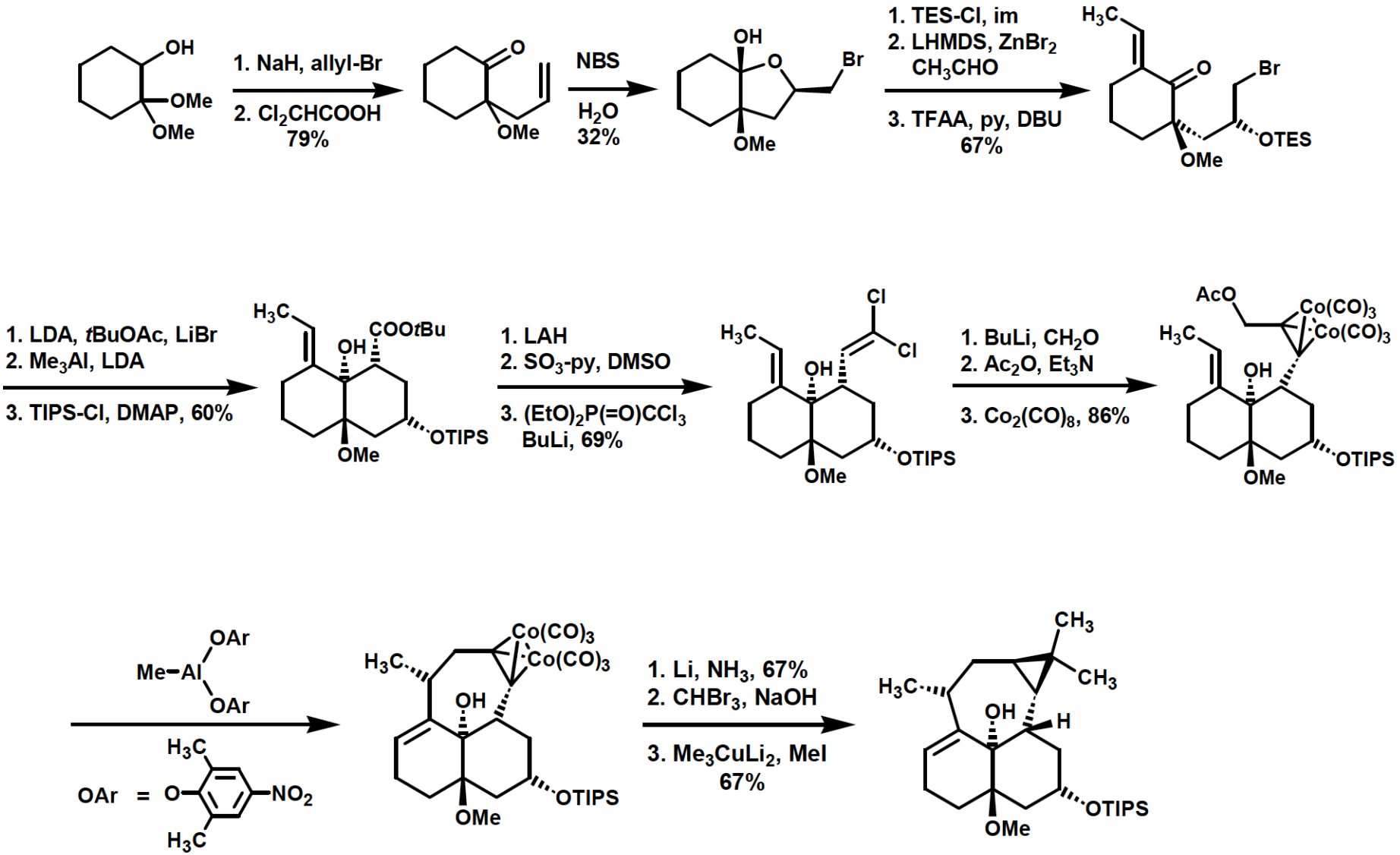
Winkler: last steps



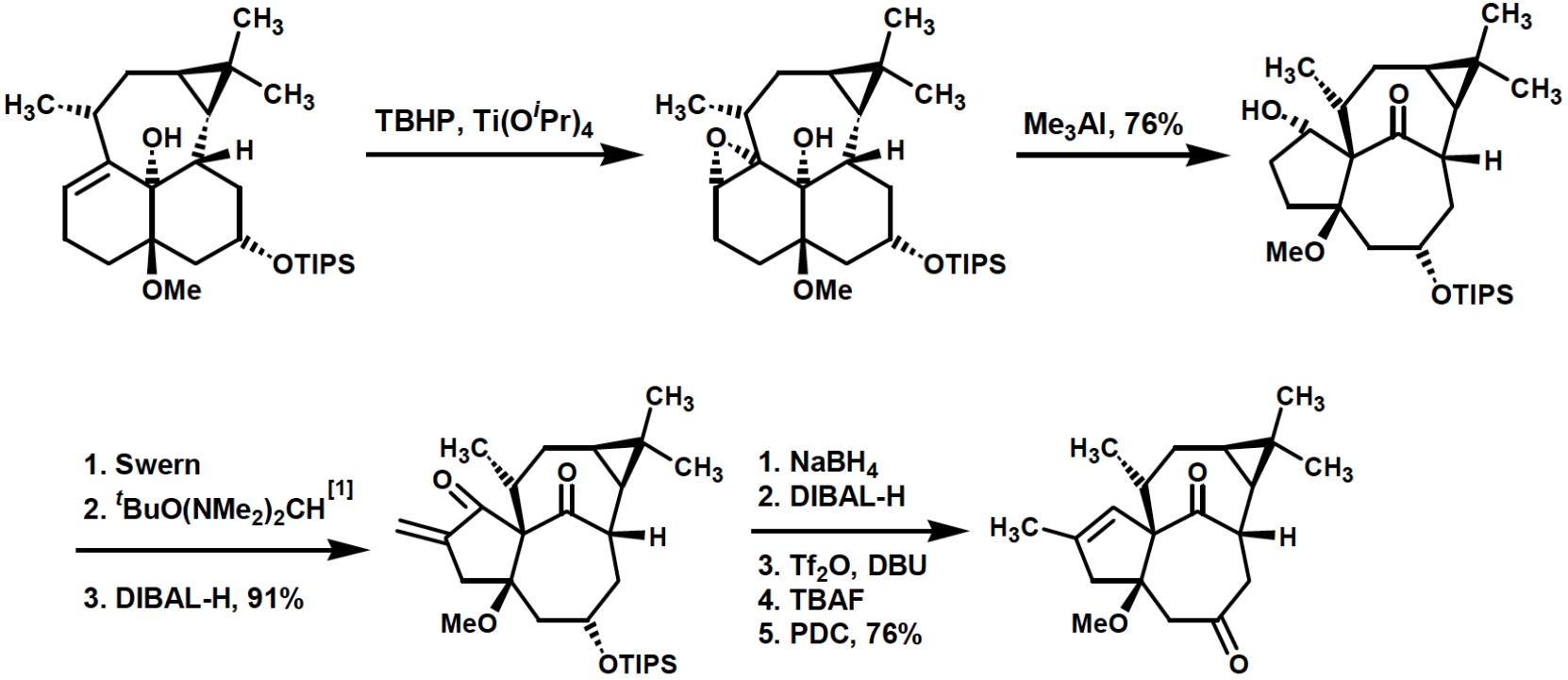
Winkler: final steps



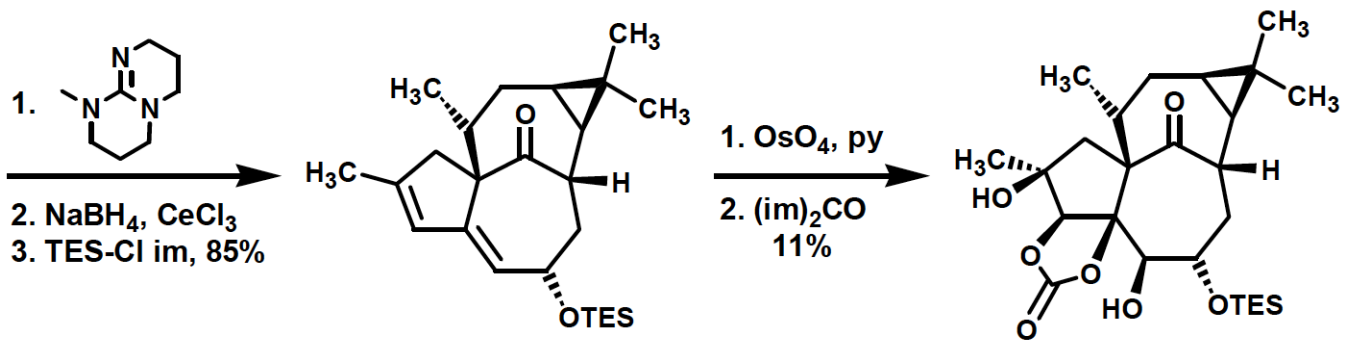
Tanino: first steps



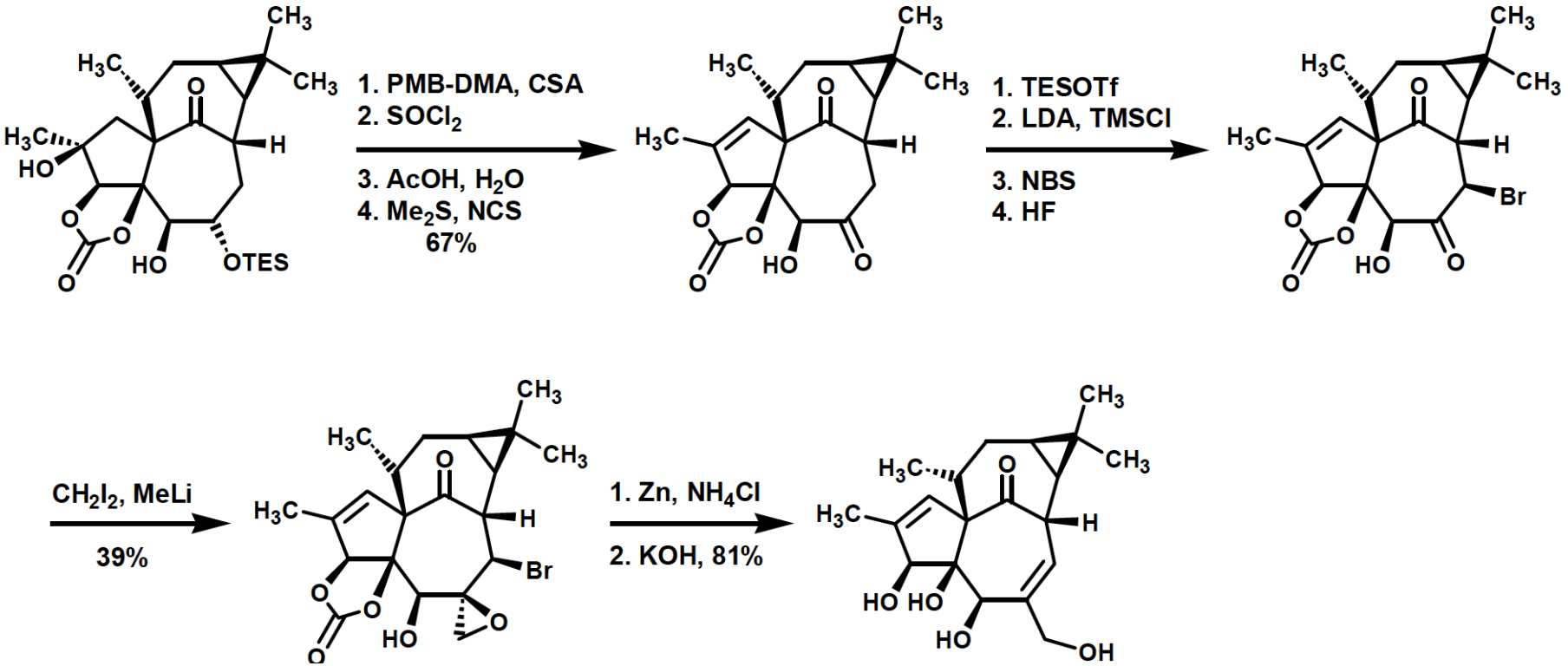
Tanino: final steps



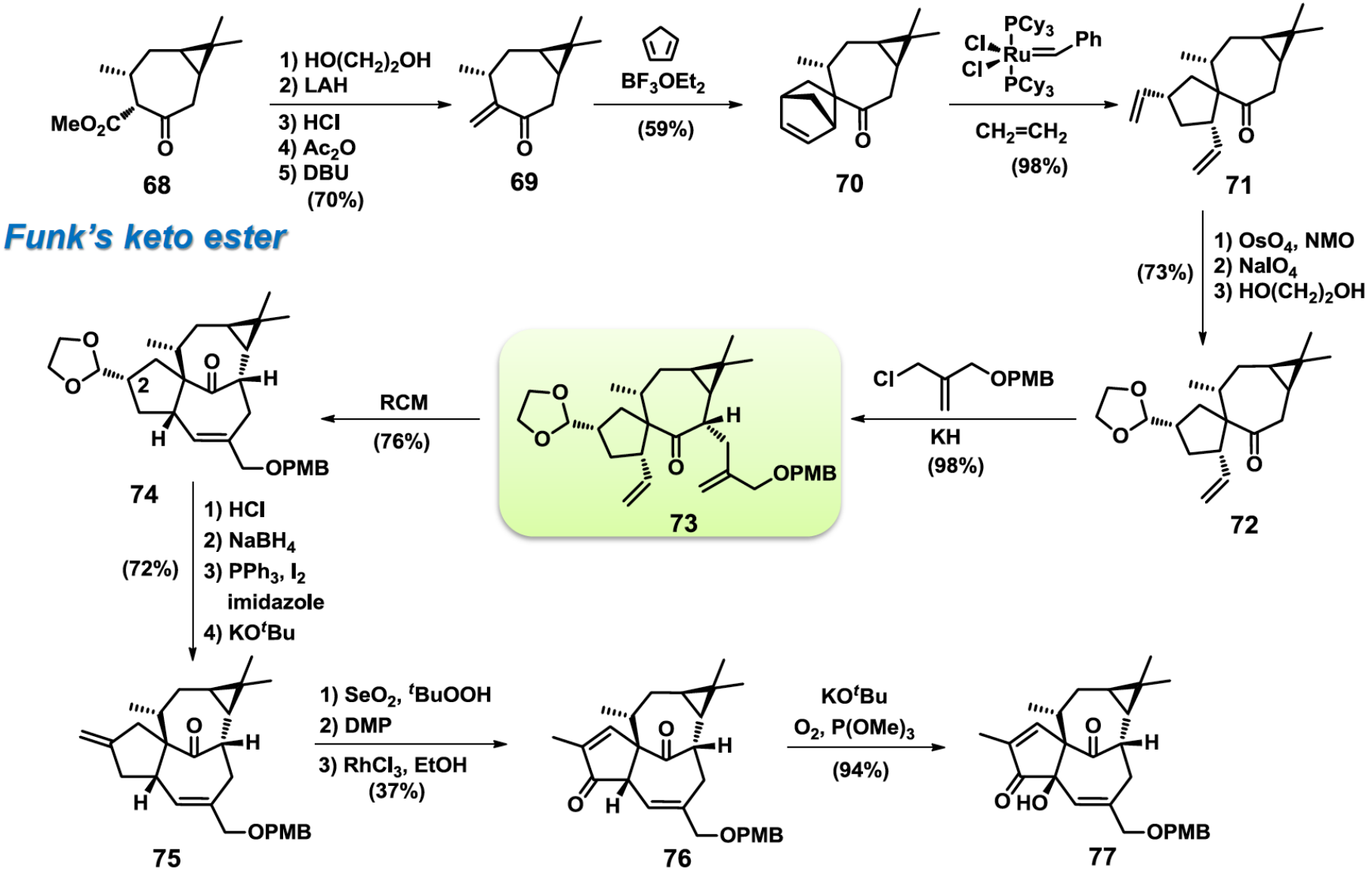
[1] Trost, B. M.; Preckel, M. *J. Am. Chem. Soc.* ***1973,*** *95*, 7862-7864



Tanino: final steps



Wood: first steps



Wood: final steps