Polyprenylated Phloroglucinols

Shenvi Lab Group Meeting, September 12, 2011

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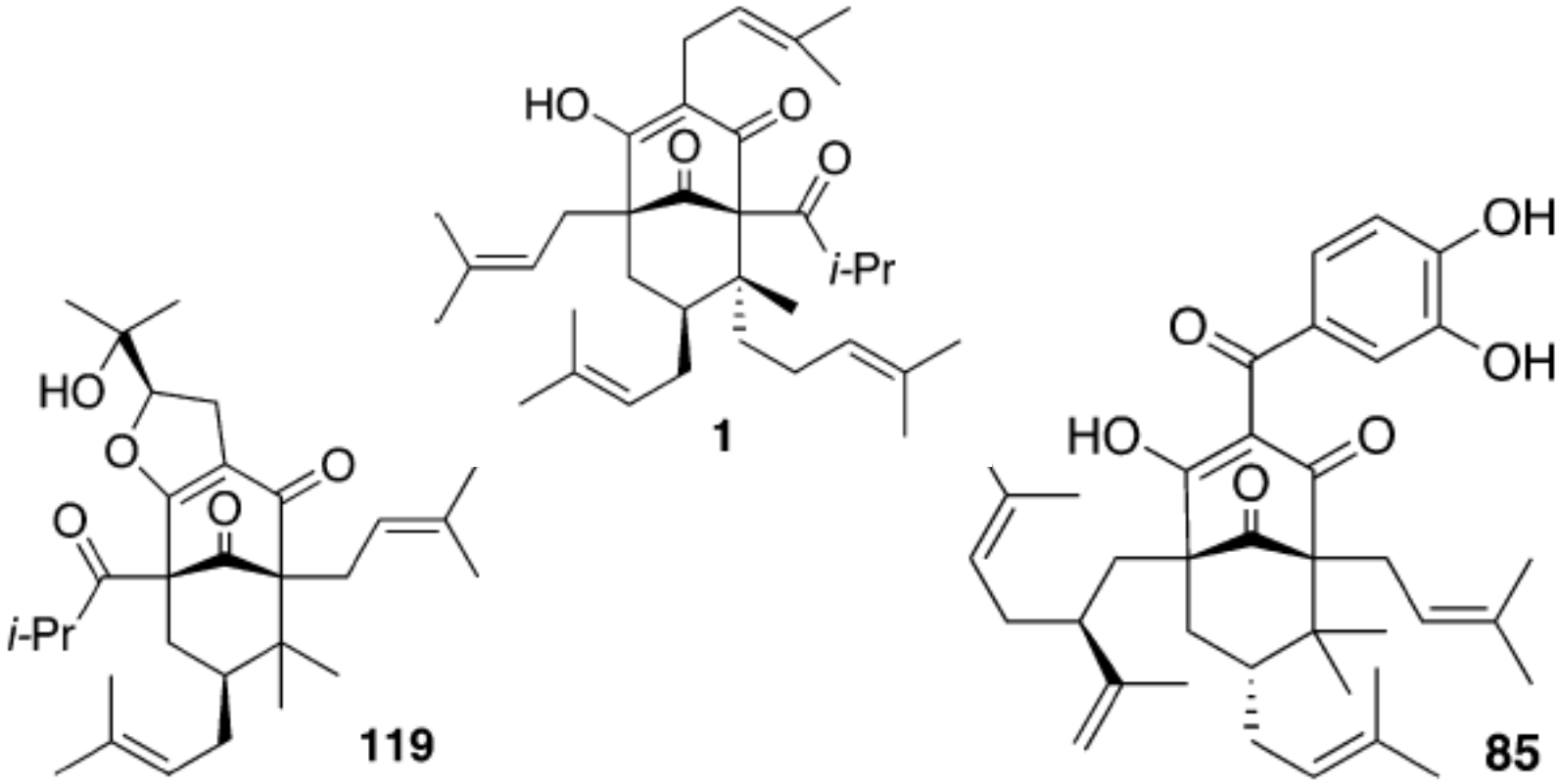
Main Structural Features

- Features a functionalized bicyclo[3.3.1]nonane-1,3,5-trione core
- Highly oxygenated and densely substituted decorated with prenyl/ geranyl side chains



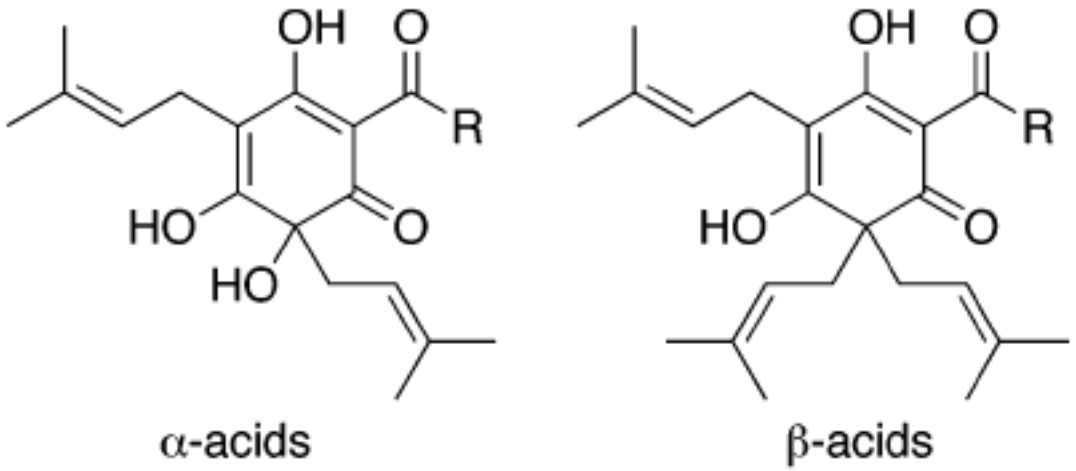
Synthetic Challenge

- Difficult to construct quaternary centers
- Extensive oxygen functionality

- Absolutely configuration of only 3 PPAP have been determined experimentally
  - Hyperforin, xanthochymol, isoxanthochymol
- Sensitive to light oxygen and heat
- Irreversible adsorption on chromatographic supports

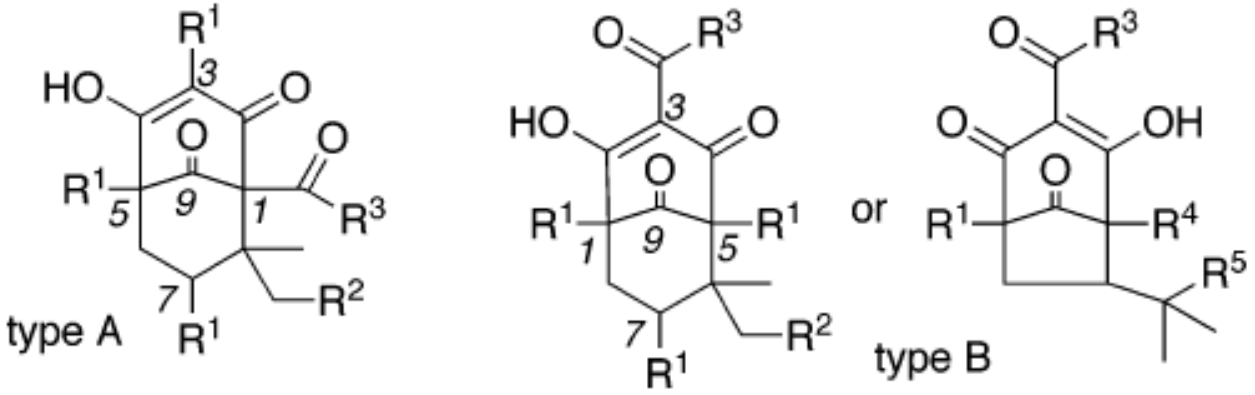
Monocyclic polyprenylated acylphloroglucinols (MPAPs)

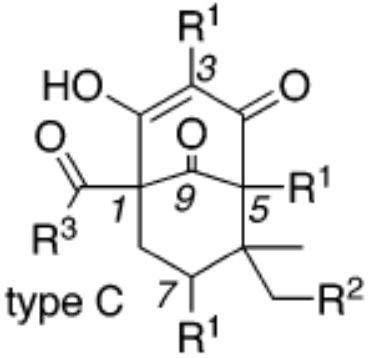
- Two classes
  - α-acids: diprenylated
    - Compounds responsible for flavor and bitter taste of beer
  - β-acids: triprenylated
    - Radical scavenging activity, lipid peroxidation, antimicrobial activity



Polycyclic polyprenylated acylphloroglucinols (PPAPs)

- Type A – acyl substituent at C1, adjacent to C8 quaternary center
- Type B (I/II) – acyl substituent at C3, adjacent to C8 quaternary center
- Type C – acyl substitent at C1, quaternary center at C6

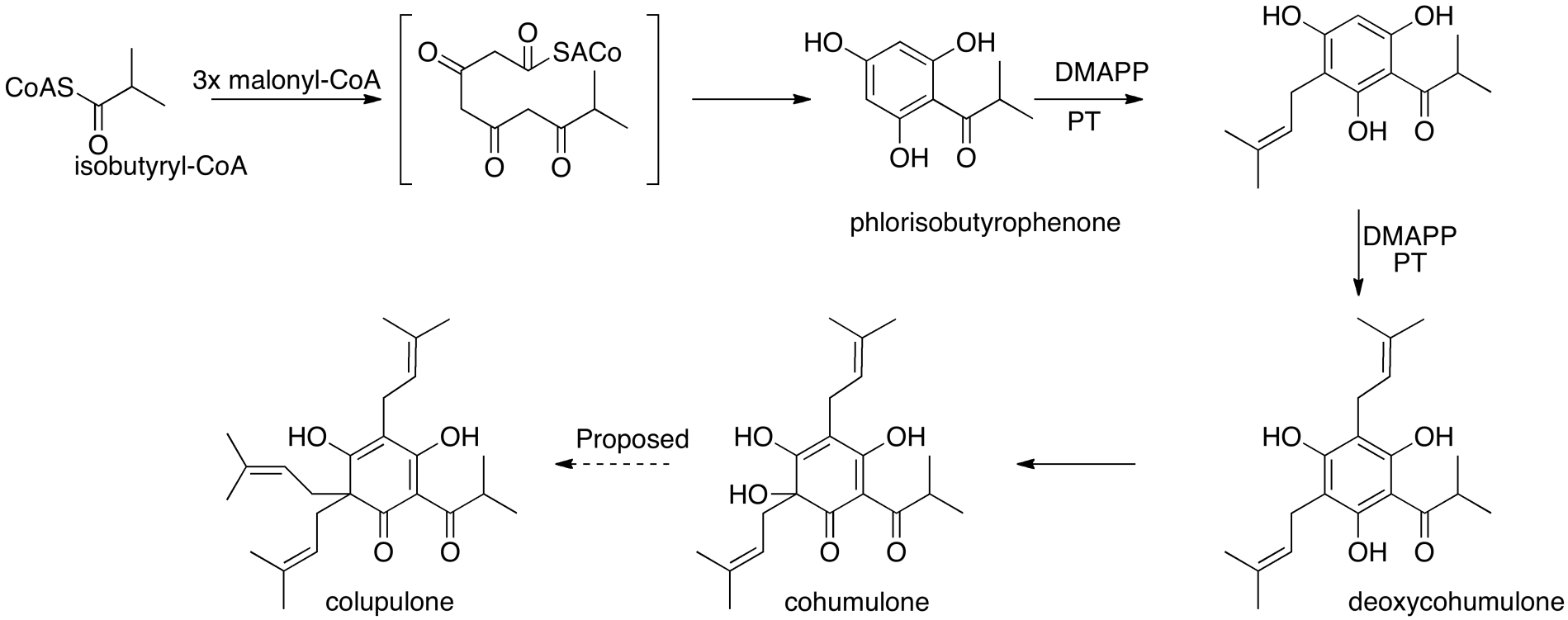




R^1 = Me, C_5H_9, or $C_{10}H_{17}$
R^2 = H or prenyl
R^3 = *i*-Pr, *i*-Bu, *s*-Bu, Ph,
3-$(HO)C_6H_4$, or 3,4-$(HO)_2C_6H_3$
R^4 = Me, R^5 = OH or R^4–R^5 = CH_2CHR^6
R^6 = H, $CMe{=}CH_2$, or CMe_2OH

Biosynthesis

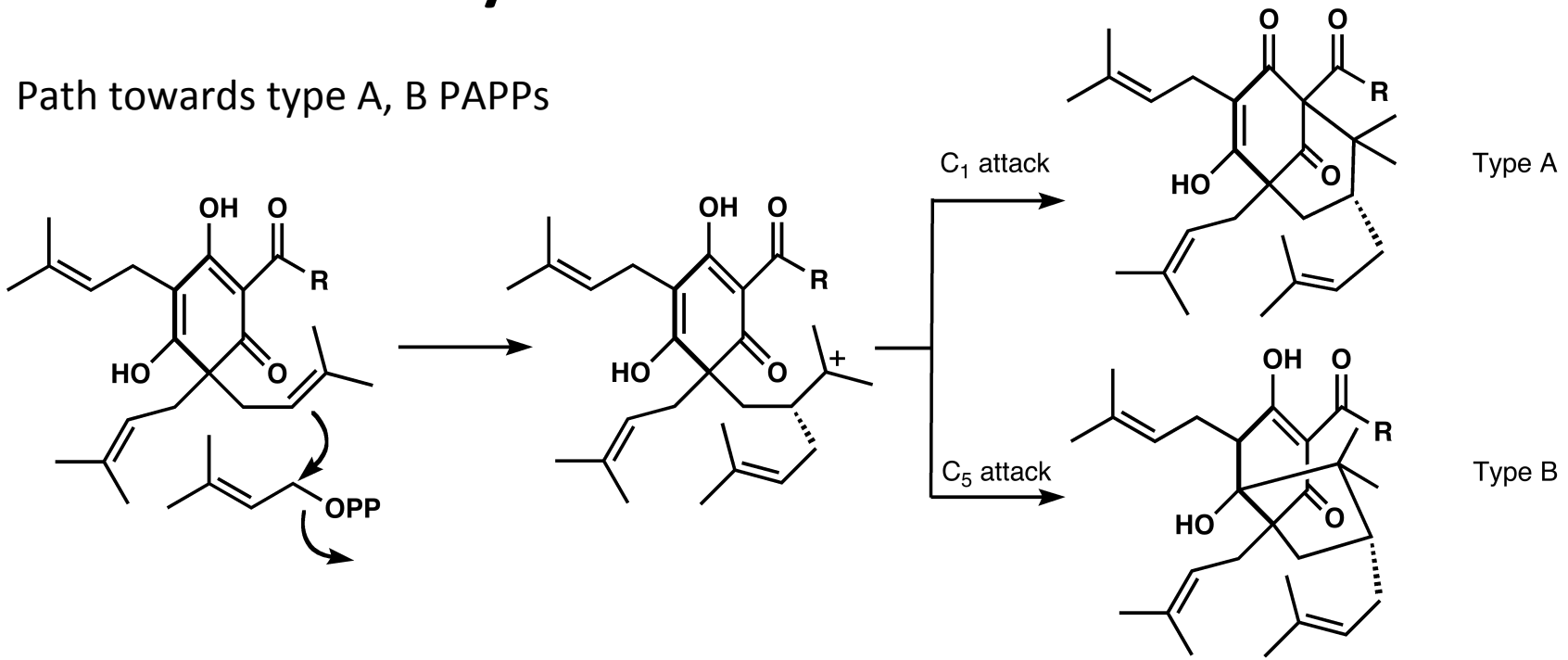
- PPAPs are derived from less complex MPAPs



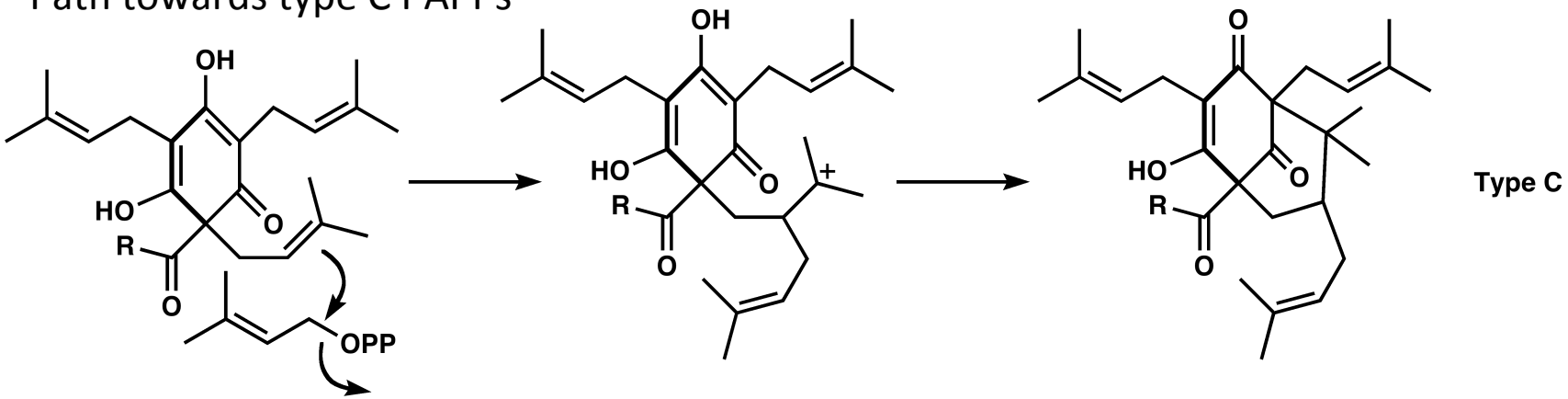
- Perhaps additional prenylation can form colupulone, a typical β-acid

Biosynthesis of PPAPs

- Path towards type A, B PAPPs

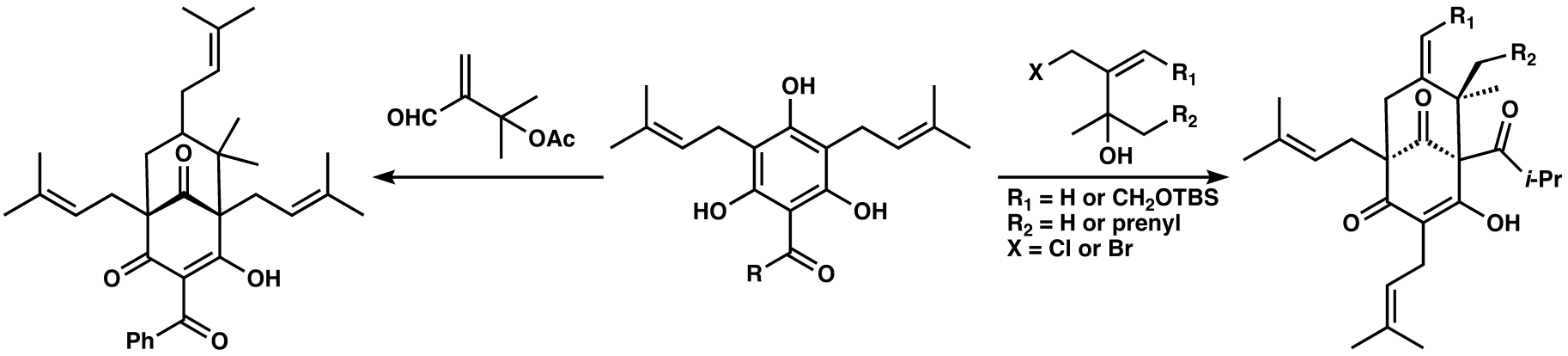


- Path towards type C PAPPs



Biomimetic Strategies

- From all literature reports of syntheses of PAPPs, two biomimetic strategies exist:
  - Based on a double alkylation on a functionalized B ring
  - Construction of the A ring via cation-based alkylative dearmatization



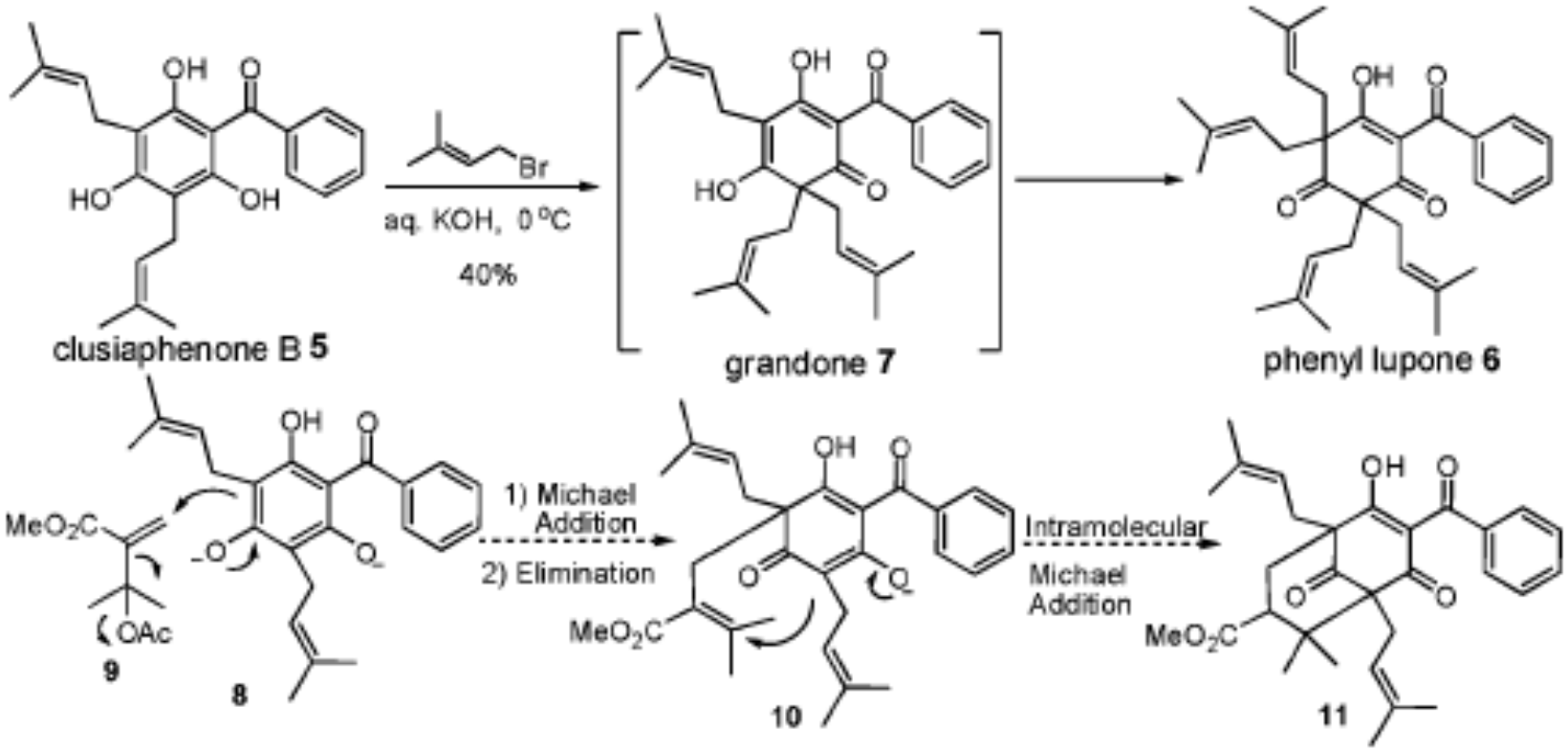
- Able to construct fully functionlized core of type A and type B PAPPs

Notable Syntheses

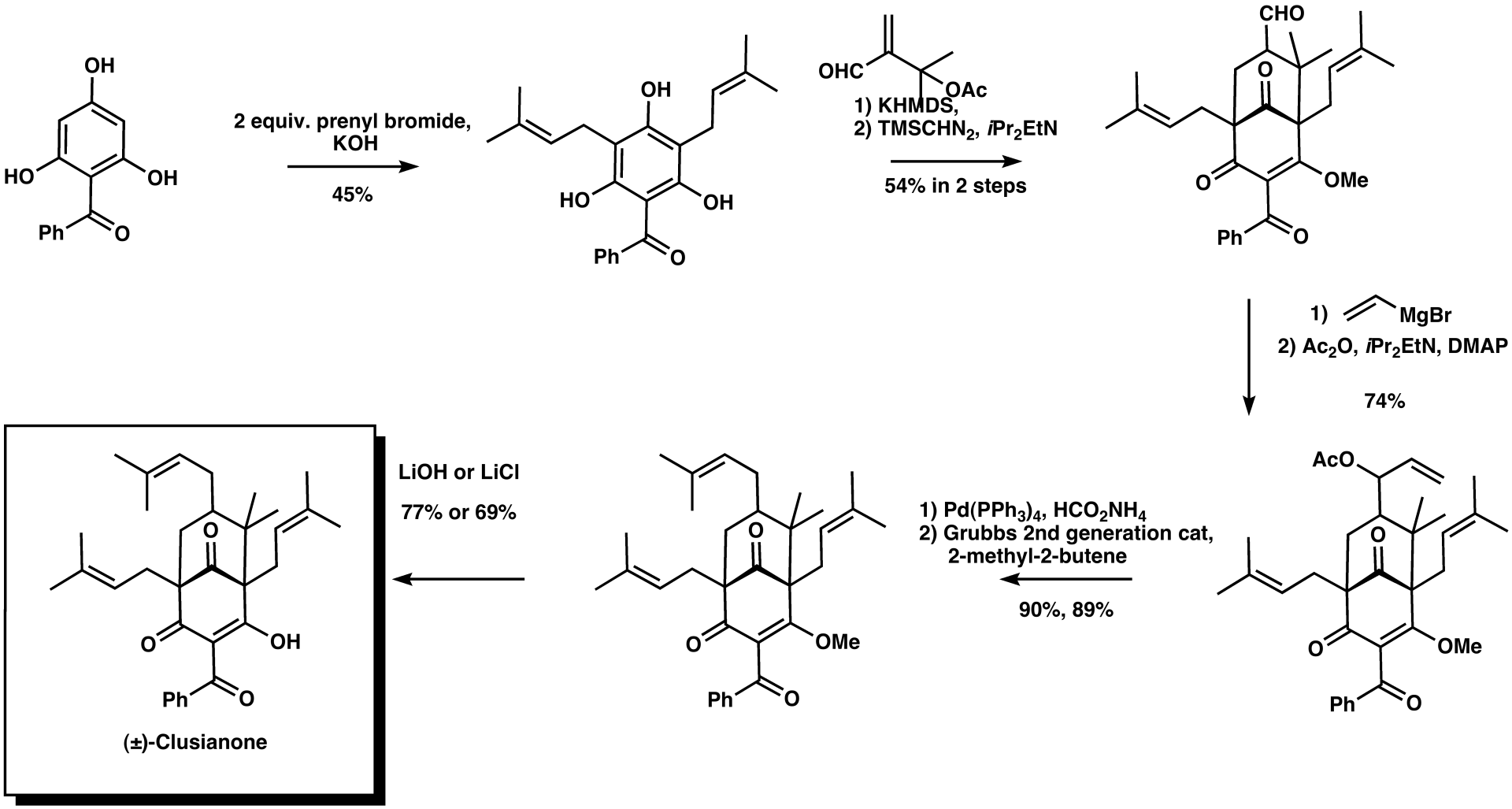
- (±)-Clusianone (Porco, 2007/Danishefsky, 2007)
  - Qi, J.; Porco, J. A. *J. Am. Chem. Soc.,* **2007** *129* (42), 12682-12683
- Nemorosone (Danishefsky, 2007)
  - Tsukano, C., Siegel, D., Danishefsky, S. *Angew. Chem. Int. Ed.* **2007 (**46), 8840-8844
- (±)-Garsubellin A (Shibasaki, 2005)
  - Kuramochi, A.; Usuda, H.; Yamatsugu, K., Kanai, M., Shibasaki, M. *J. Am. Chem. Soc.,* **2005** *127* (41), 14200-14201
- *ent*-Hyperforin (Shibasaki, 2010)
  - Shimizu, Y., Shi, S.-L., Usuda, H., Kanai, M. and Shibasaki, M. *Angew. Chem. Int. Ed.* **2010 (**49), 1103-1106

(±)-Clusianone (Porco, 2007)

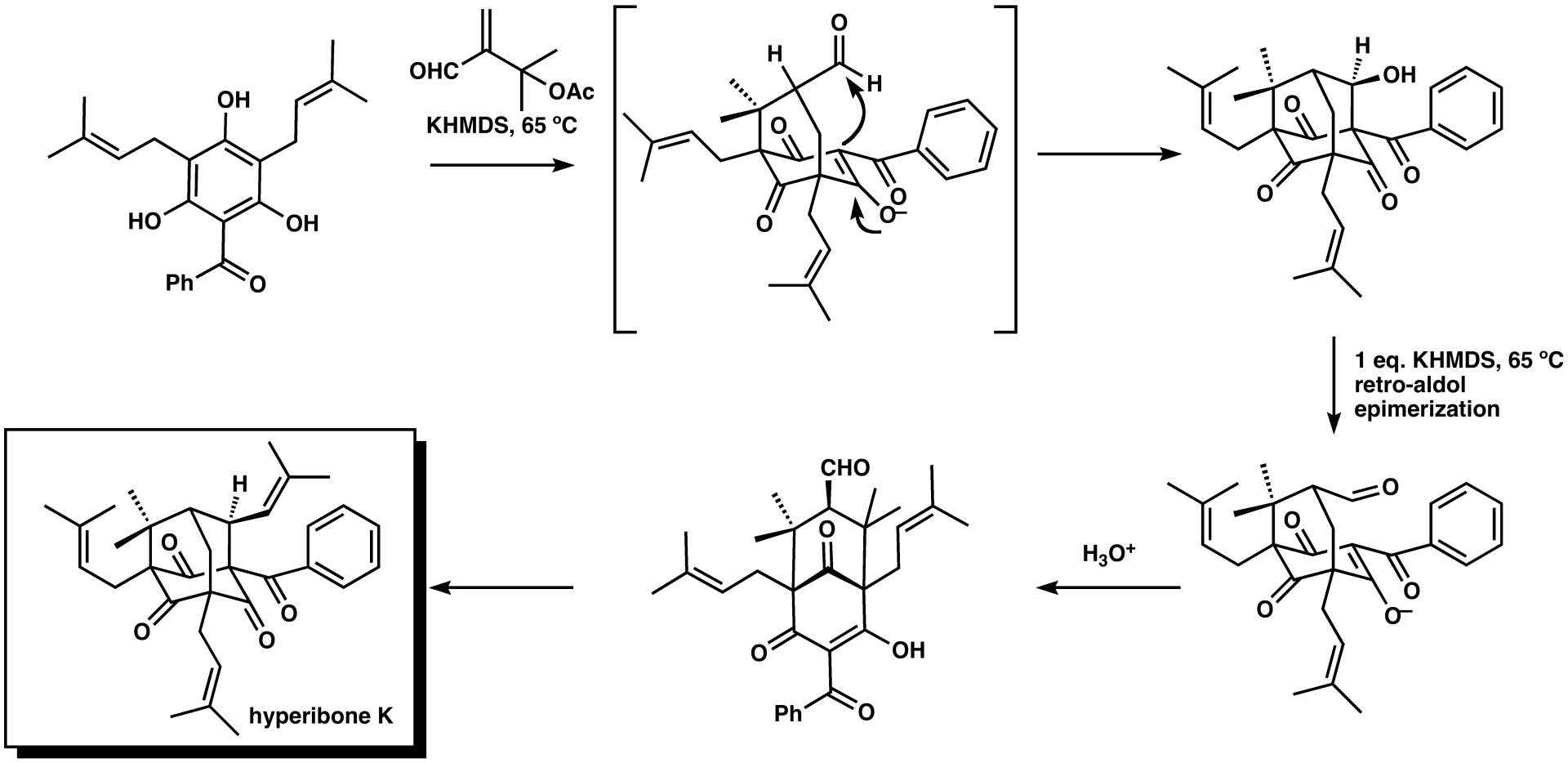
Synthetic Plan



(±)-Clusianone (Porco, 2007)



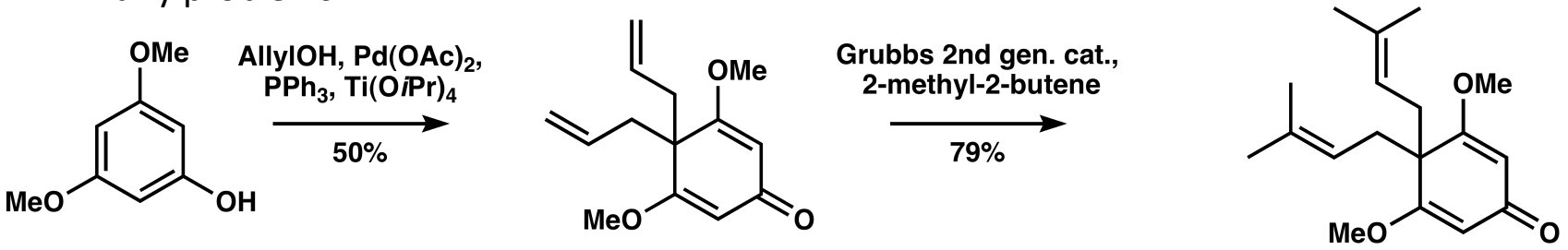
Double Michael reaction



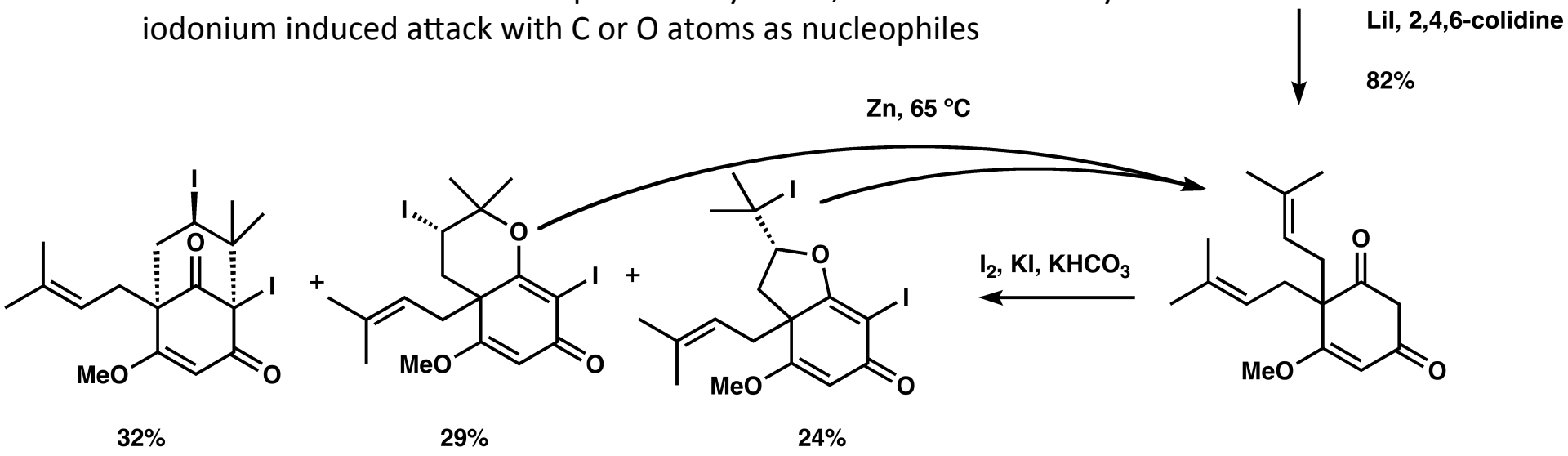
4 quaternary carbon centers formed in 1 step

(±)-Clusianone (Danishefsky, 2007)

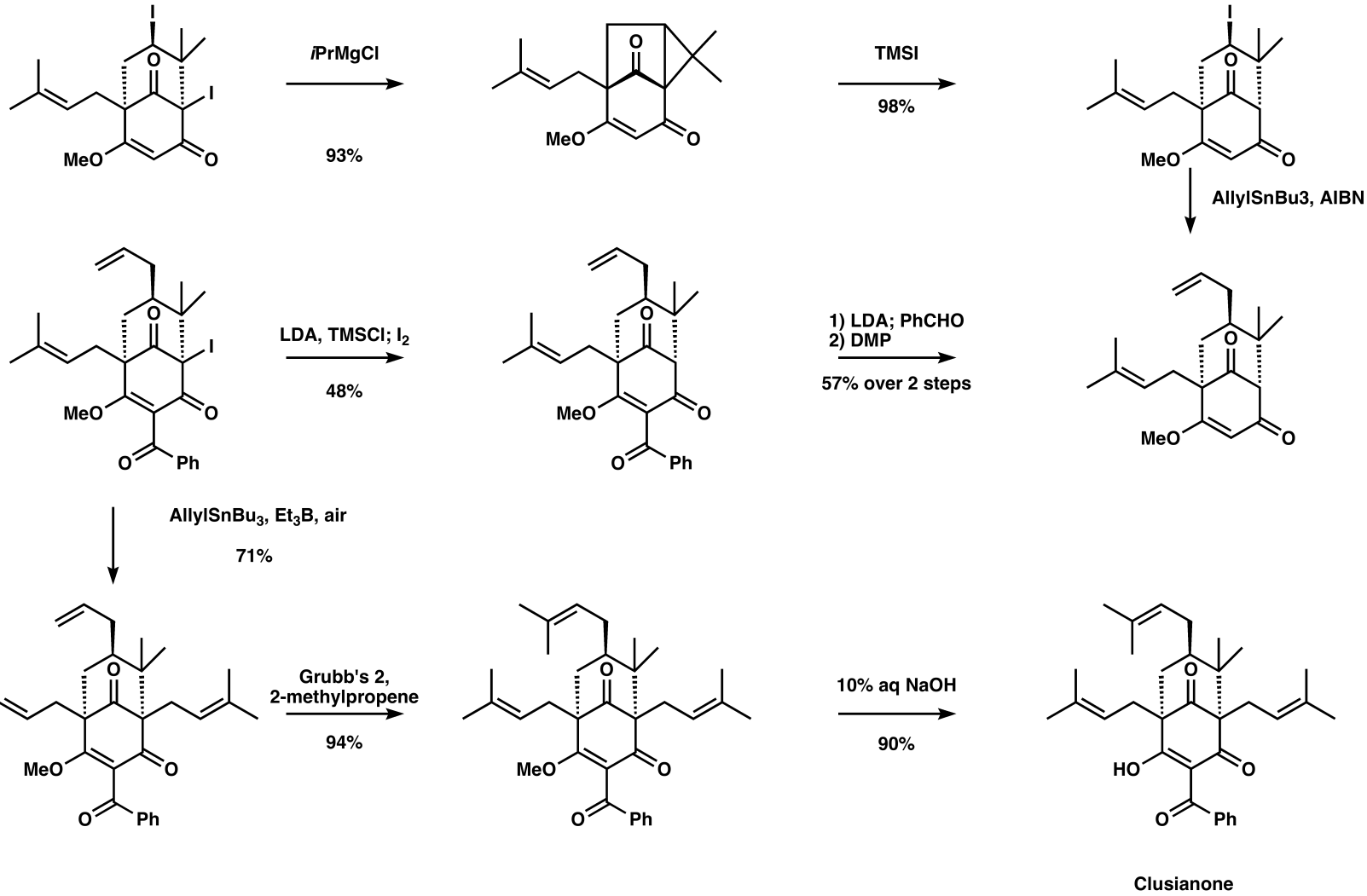
- Early problems



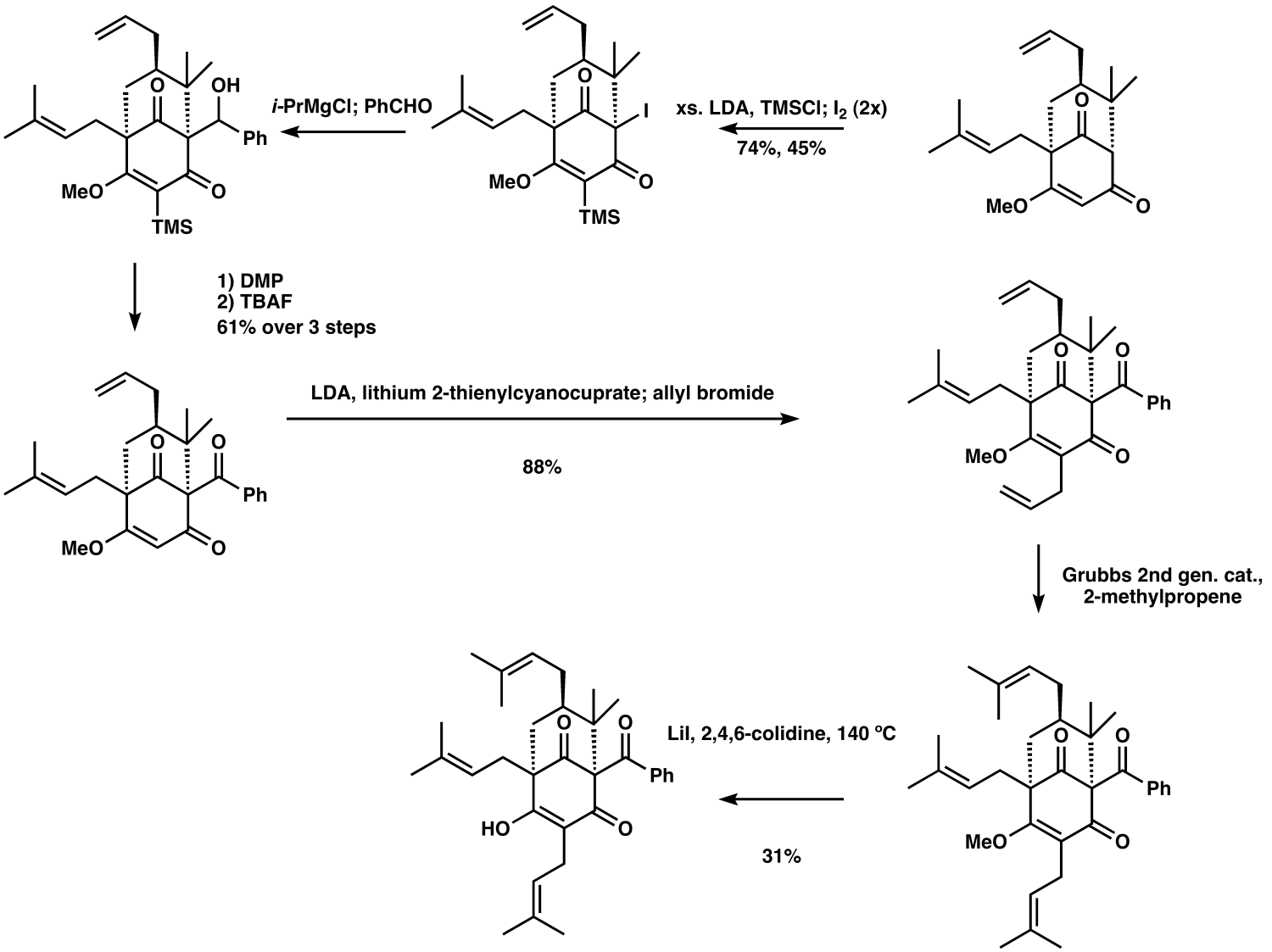
- Initial iodination occurs at the β-dicarbonyl locus, in turn followed by iodonium induced attack with C or O atoms as nucleophiles



(±)-Clusianone (Danishefsky, 2007)

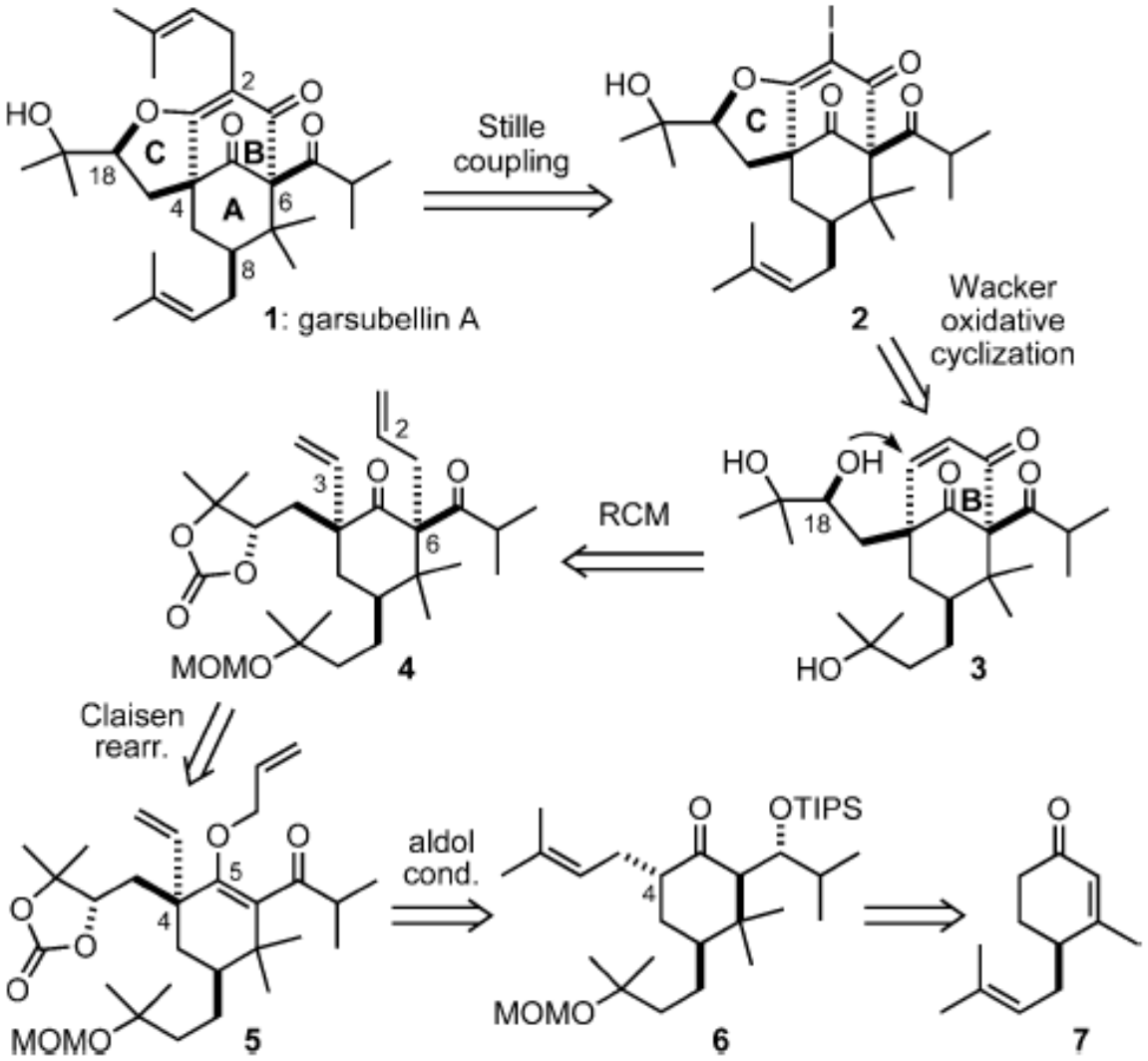


Nemorosone (Danishefsky, 2007)

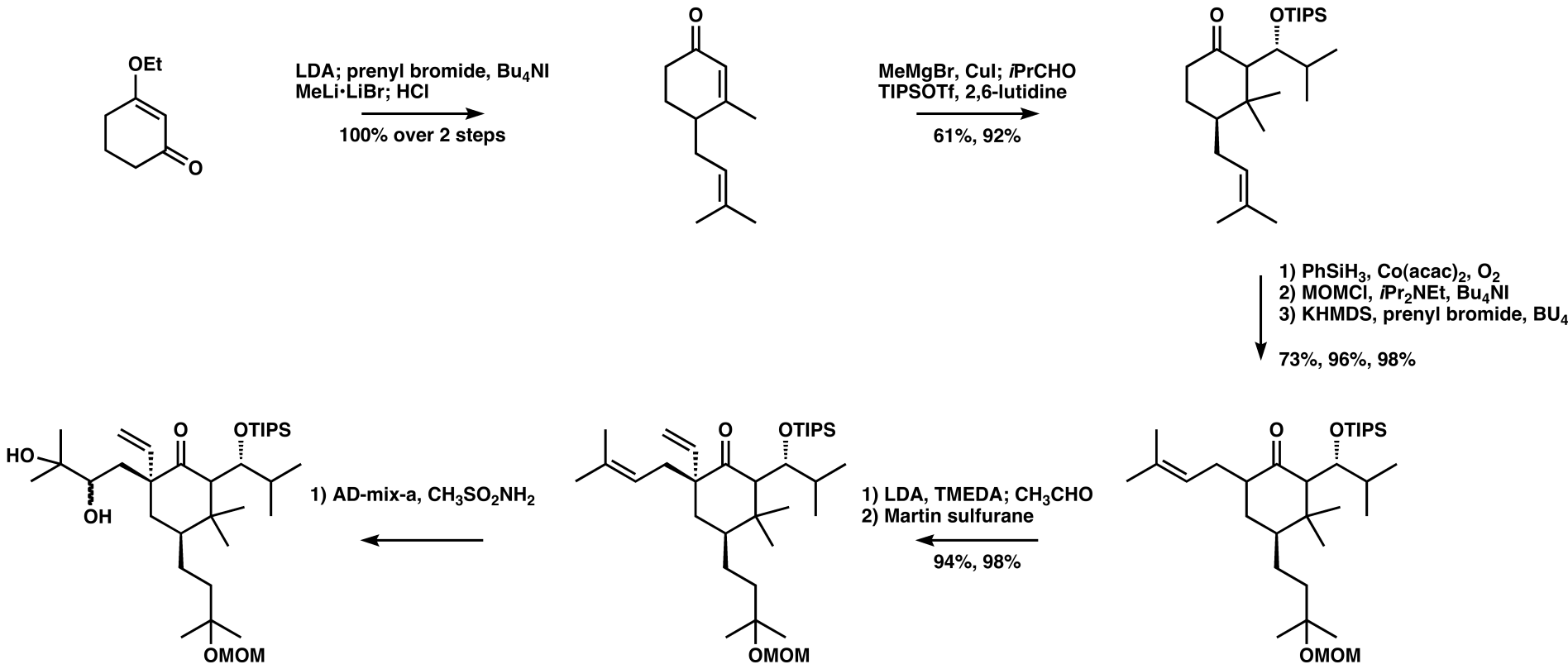


(±)-Garsubellin A (Shibasaki, 2005)

- Might have potential for the treatment of Alzheimer's disease
- Potent neurotrophic activity by inducing choline acetyltransferase ChAT
- Inhibits the release of α-glucuronidase and histamine (IC50 = 15.6 μM)



(±)-Garsubellin A (Shibasaki, 2005)



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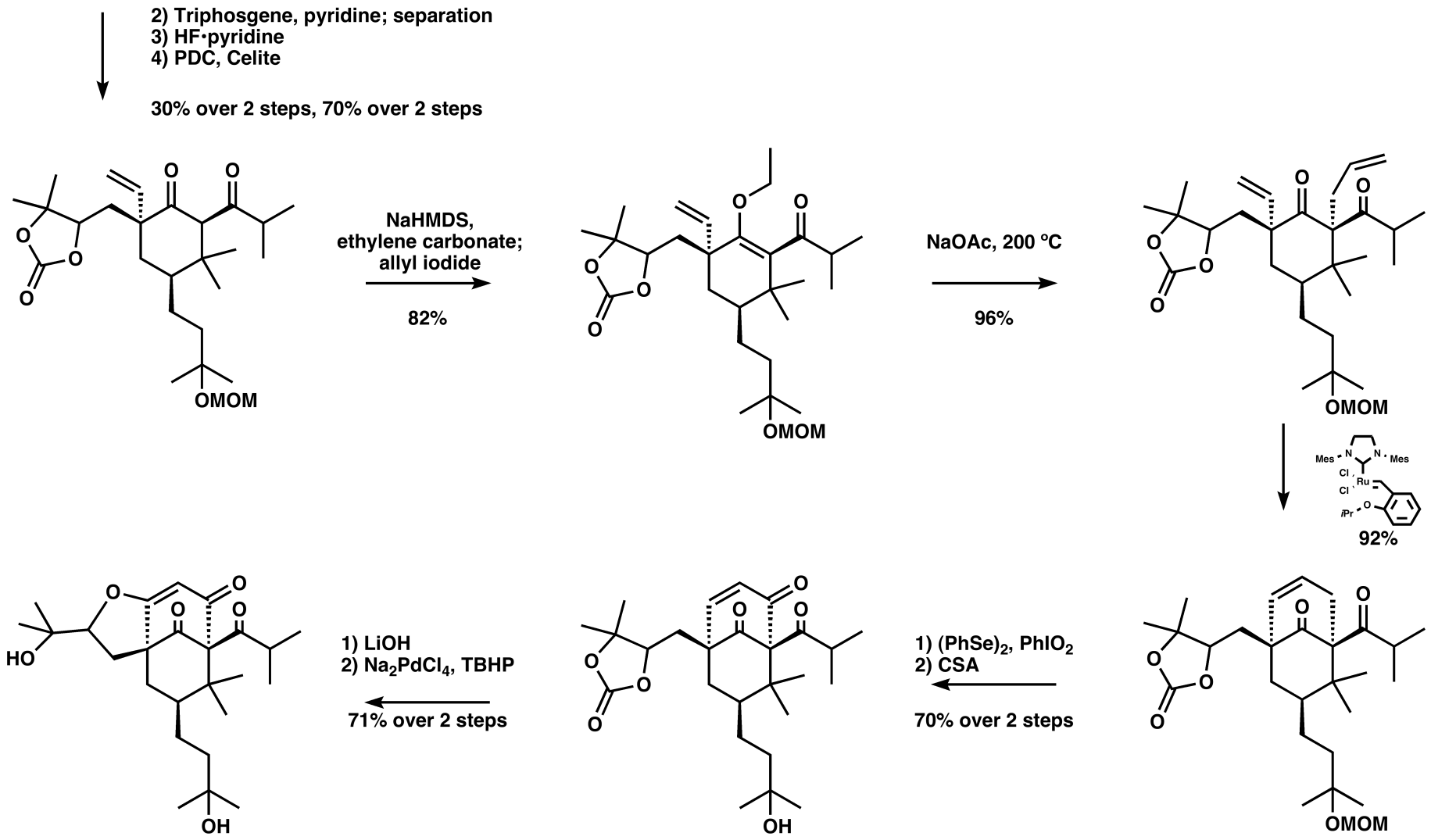

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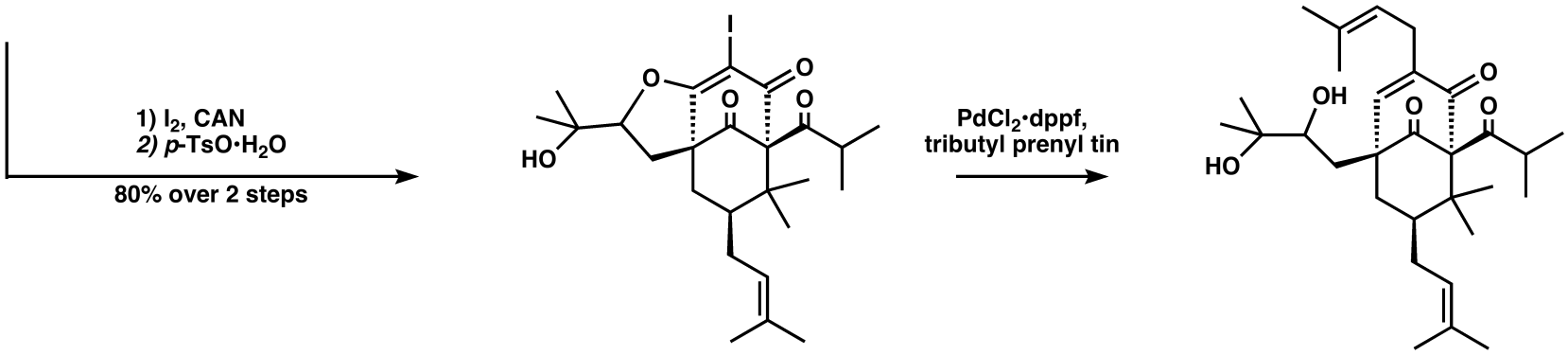
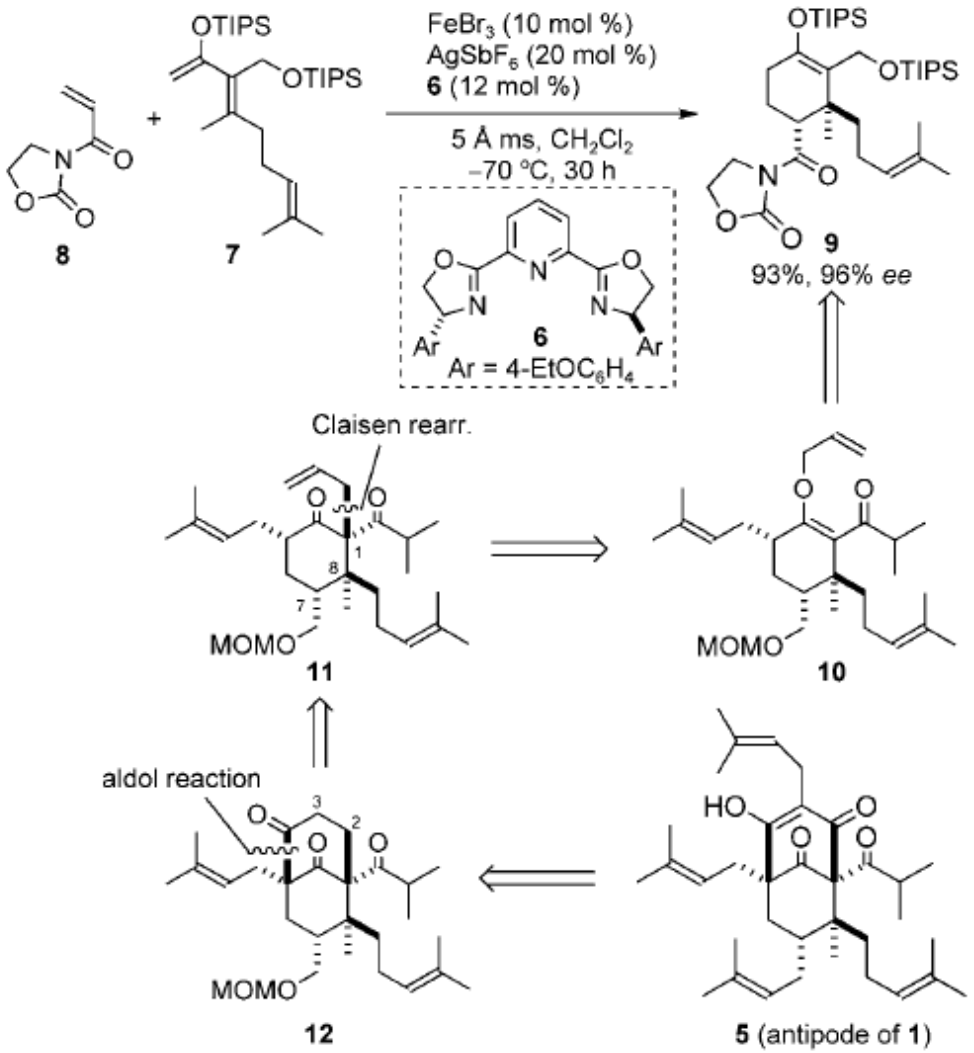


ent-Hyperforin (Shibasaki, 2010)

- Hyperforin exhibits various biological activities, including:
  - mild antidepressant activity
  - antimalarial activity
  - human histone deacetylase inhibitoryactivity
  - CYP3A4 induction activity
- Contains additional chiral quaternary center compared to garsubellin A, nemorosone, and clusianone



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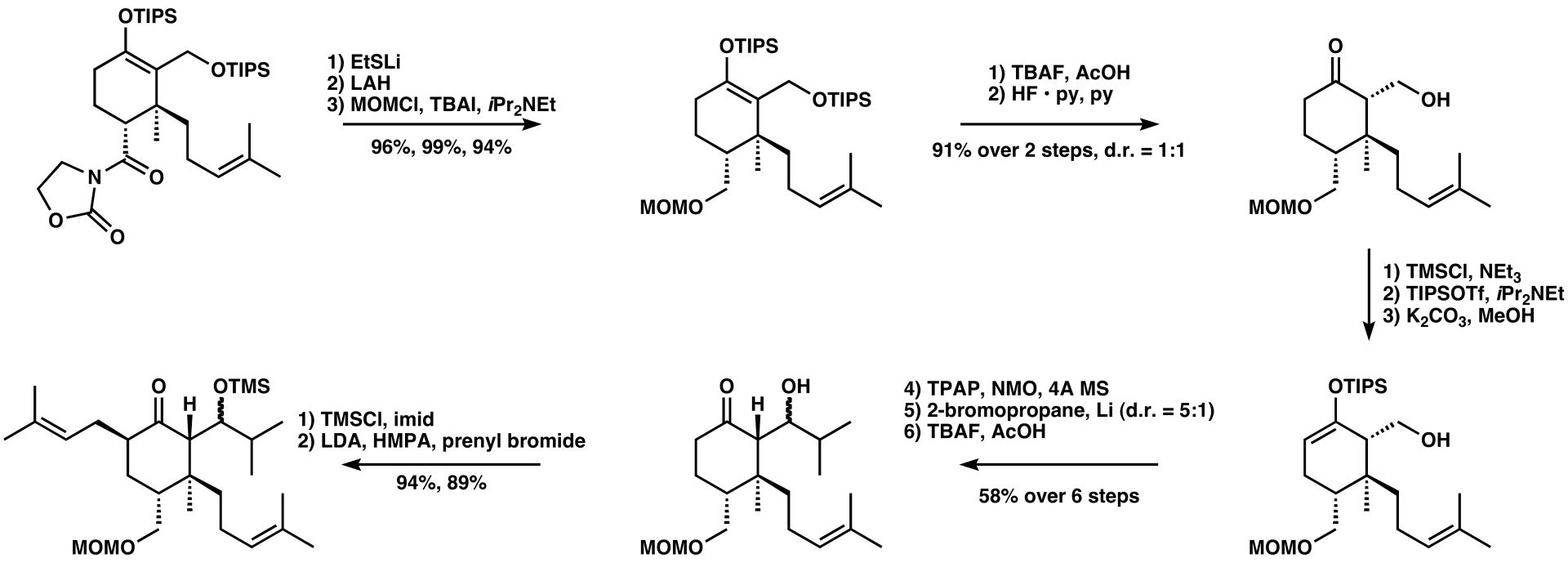

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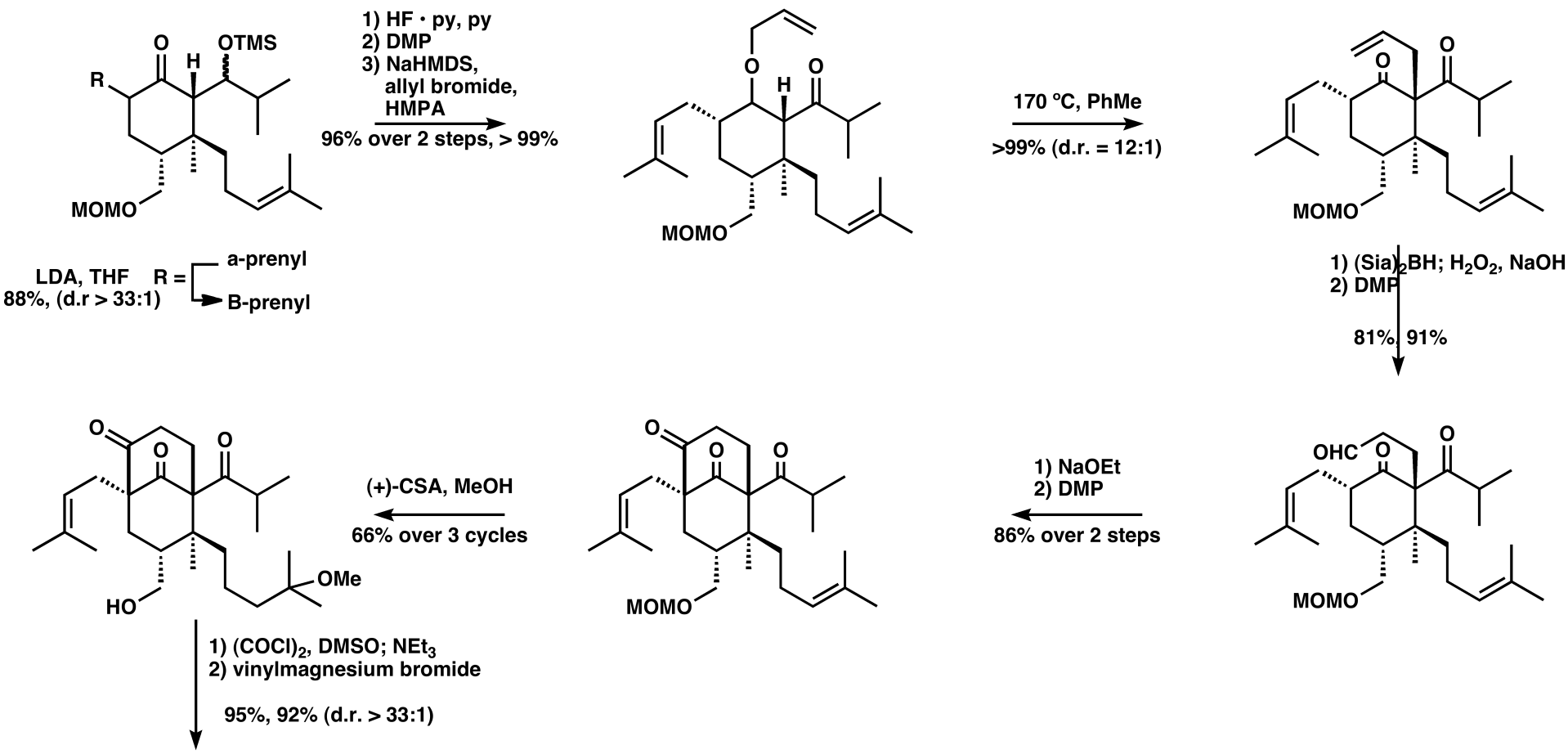

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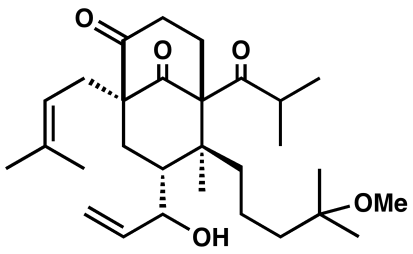
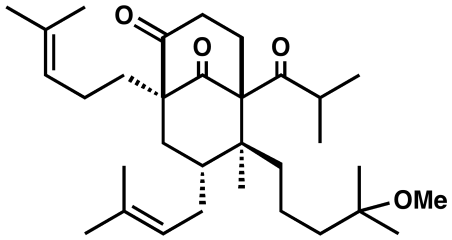
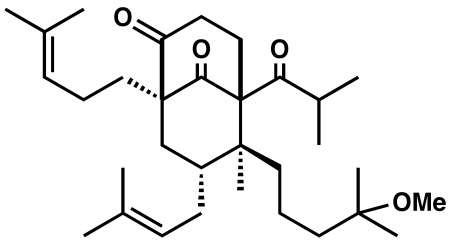


1)Ac_2O, DMAP, iPr_2EtN
2) $[Pd(PPh_3)_4]$ (20 mol %), HCO_2NH_4
3) Hoveyda-Grubbs 2nd generation cat. (15 mol %), 2-methyl-2-butene

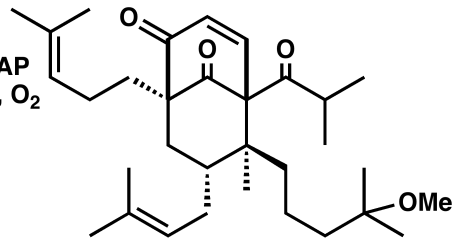
98%, 95%, >99%





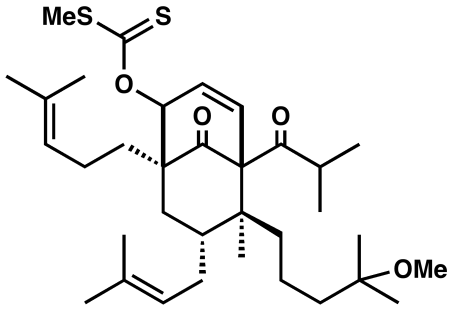
1) TMSCl, NEt_3, DMAP
2) $Pd(OAc)_2$, DMSO, O_2

84%, >99%



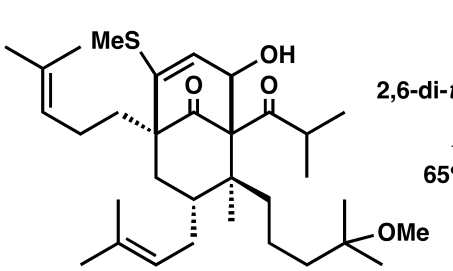
1) $NaBH_4$, MeOH
2) CS_2, NaH; MeI

95% (d.r. = >33:1, >99%



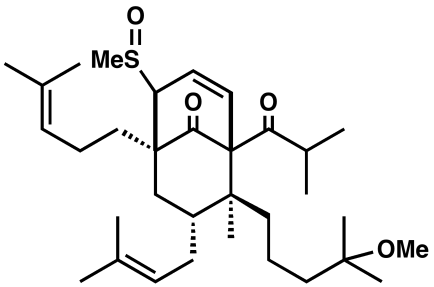
150 °C, PhMe

ent-Hyperforin (Shibasaki, 2010)



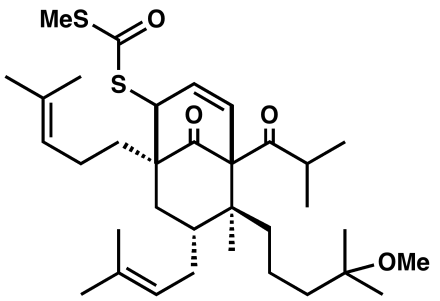
TFAA,
2,6-di-*tert*-butylpyridine;
H_2O

65% (d.r. > 33:1)



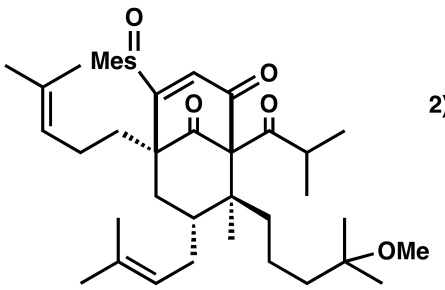
1) EtSLi; MeI, NEt_3
2) $NaBO_3 \cdot 4\ H_2O$, AcOH

98% over 2 steps,
95% (d.r. = 1.3:1)



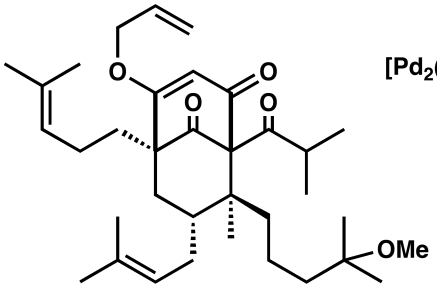
1) H_2O_2, HFIP
2) DMP

87% (d.r. = 9:1), 86%



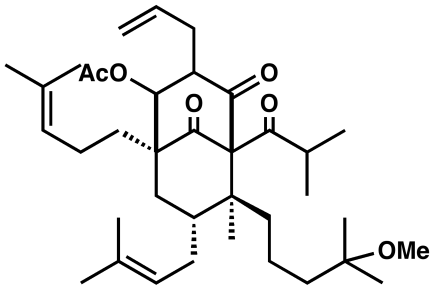
1) Amberlyst 15
2) LiH, allyl alcohol

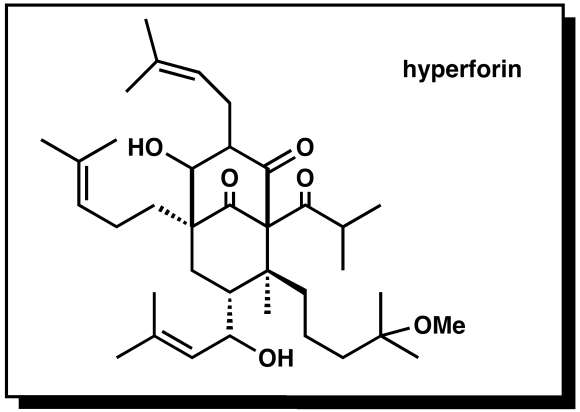
67%



$[Pd_2(dba)_3]$, (S)-tol-binap; Ac_2O, py

50%





1) Hoveyda-Grubbs 2nd generation cat.,
2-methyl-2-butene
2) K_2CO_3, MeOH

34%, 94%