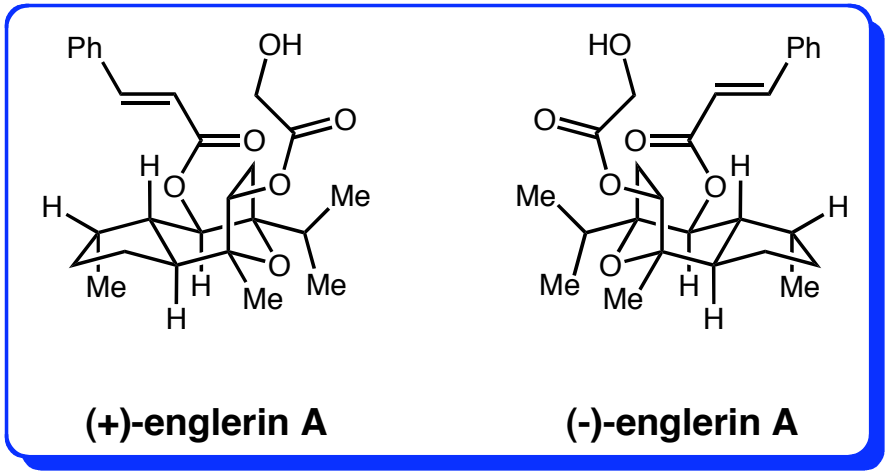
Total Synthesis of Englerin A

Willot, M.; Radtke, L.; Konning, D.; Frohlich, R.; Gessner, V.; Strohmann, C.; Christmann, M. *Angew, Chem, Int. Ed.* **2009**, *48*, 9105-9108

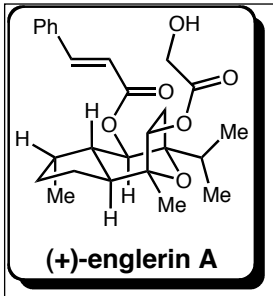
Zhou, Q.; Chen, X.; Ma, D. *Angew, Chem, Int. Ed.* **2010**, *early view*

Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew, Chem, Int. Ed.* **2010**, *early view*



(+)-englerin A **(-)-englerin A**

Antoinette Nibbs
Short Literature Presentation
18 May 2010



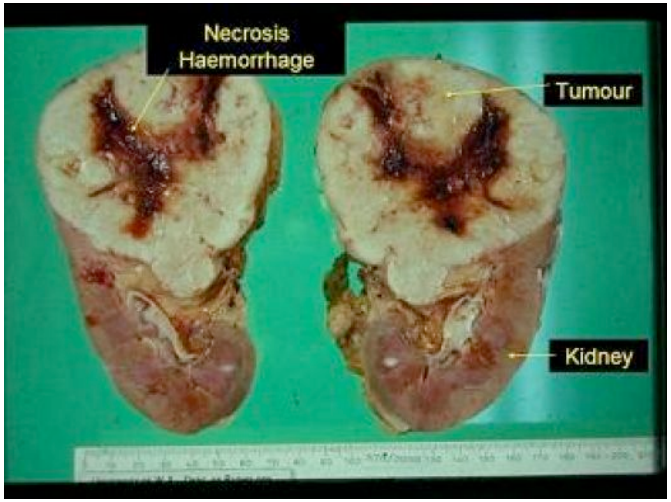
Renal Cell Carcinoma

•east African plant *Phyllanthus engleri*

•high selectivity and activity against renal cancer cells
GI_{50} values from 1-87nM

•when tested against other cancer cell lines, only moderate inhibition activity
GI_{50} 10-20 µM

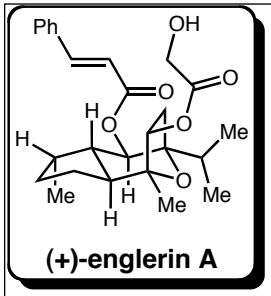
kidney cancer is a major cause of morbidity and mortality in adults



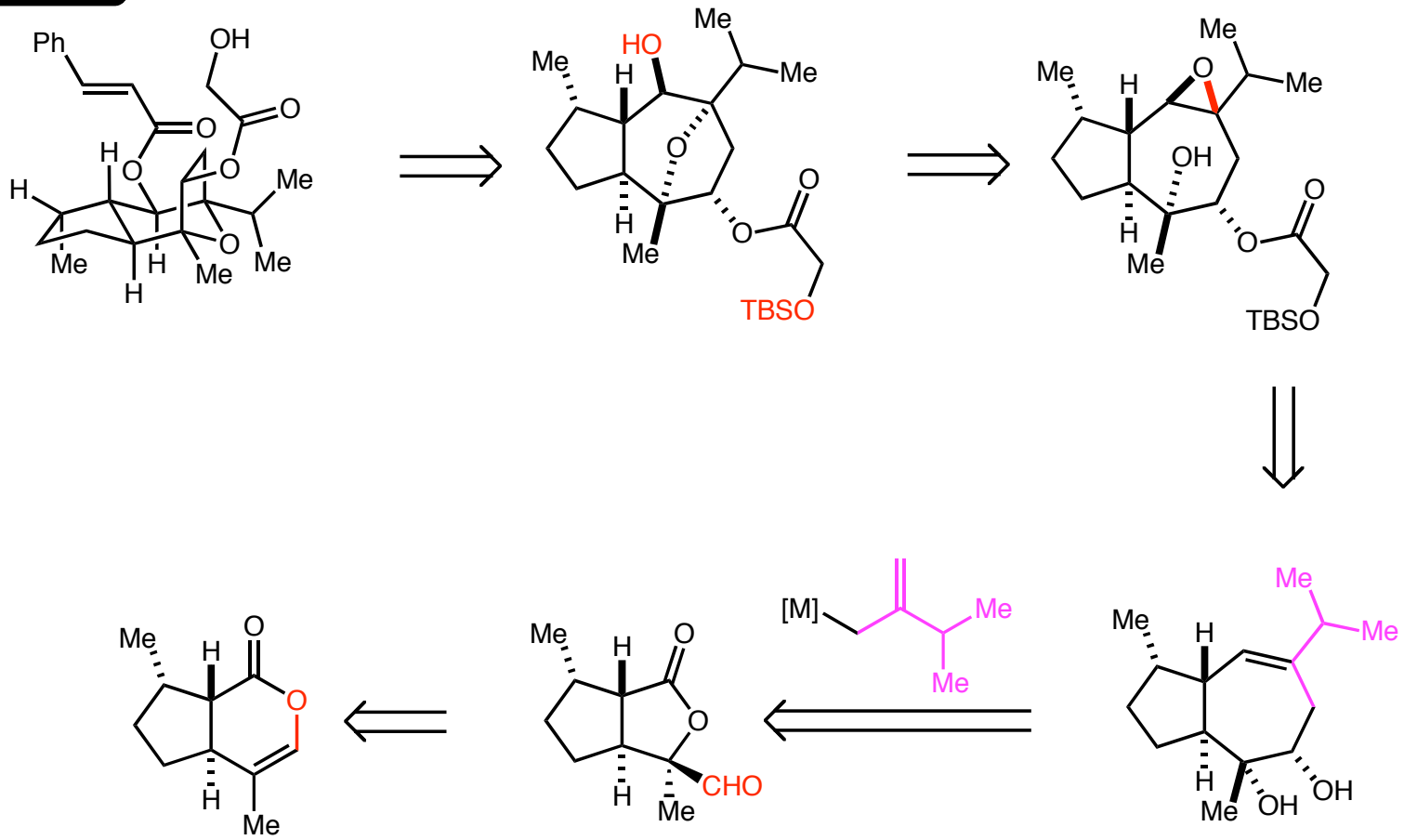
•active component isolated and structure elucidated except for absolute configuration (Beutler and coworkers, 2009)

Willot, M.; Radtke, L.; Konning, D.; Frohlich, R.; Gessner, V.; Strohmann, C.; Christmann, M.
Angew, Chem, Int. Ed. **2009**, *48*, 9105-9108

Retrosynthesis

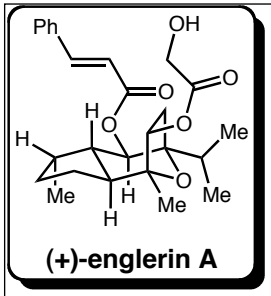


(+)-englerin A



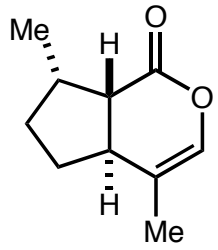
trans,cis-nepetalactone

Willot, M.; Radtke, L.; Konning, D.; Frohlich, R.; Gessner, V.; Strohmann, C.; Christmann, M.
Angew, Chem, Int. Ed. **2009**, *48*, 9105-9108

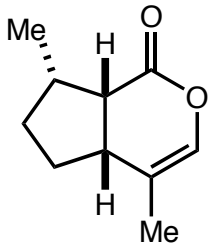


(+)-englerin A

Nepetalactones



trans-cis

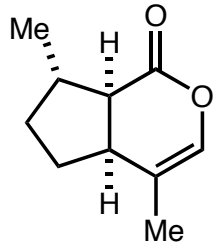


cis-cis

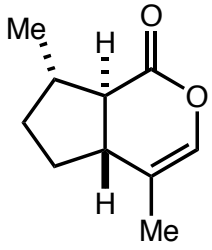
Nepeta cataria

+

=



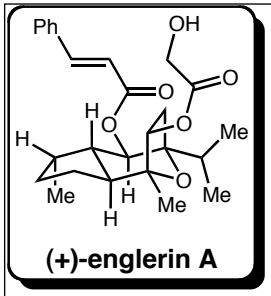
cis-trans



trans-trans

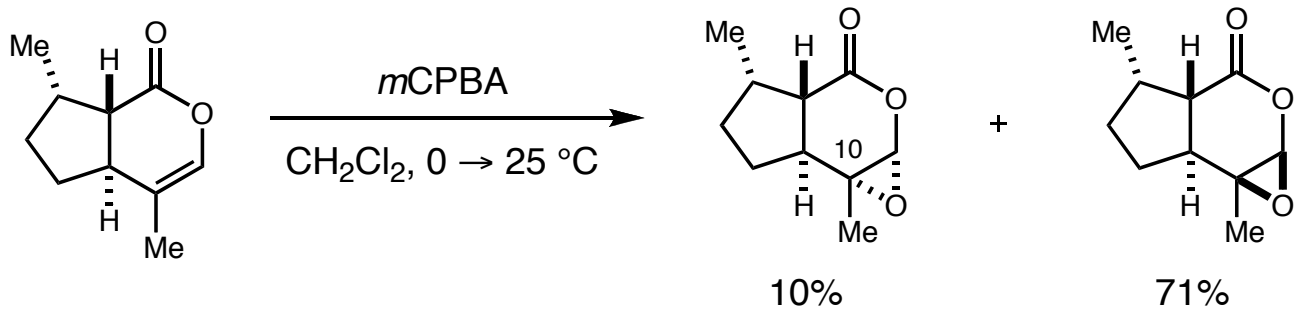
- can be obtained by distillation of commercially available catnip oil ($ 0.45 / g)
- insect repellent

Liblikas, I.; Santangelo E. M.; Sandell, J.; Baeckstrom, P.; Svensson, M.; Jacobsson, U.; Unelius, C. R.
J. Nat. Prod. **2005**, *68*, 886-890

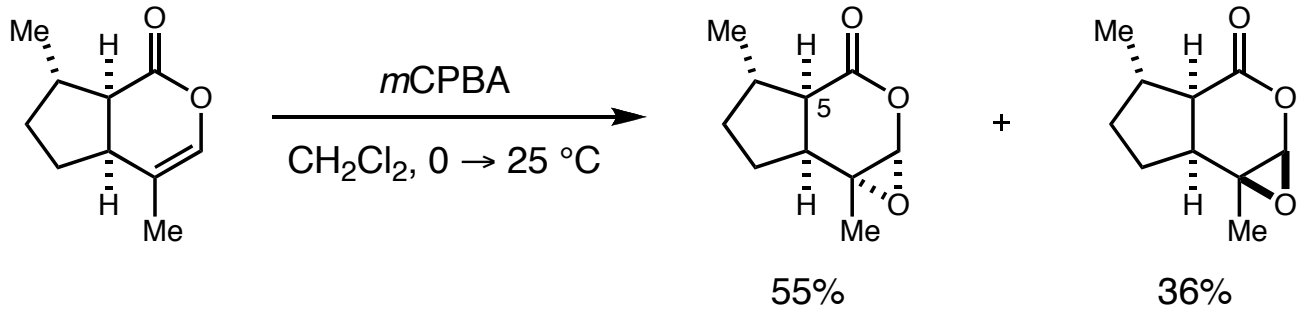


(+)-englerin A

Oxidation of Nepetalactones



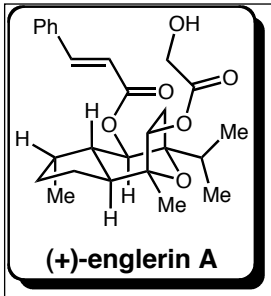
10% 71%



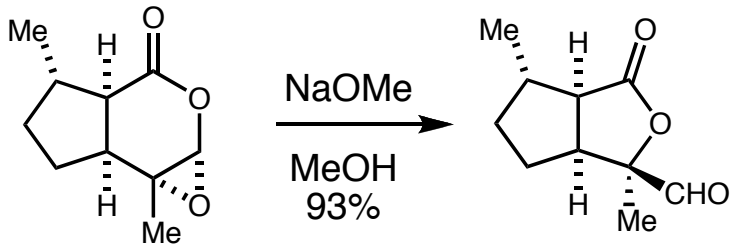
55% 36%

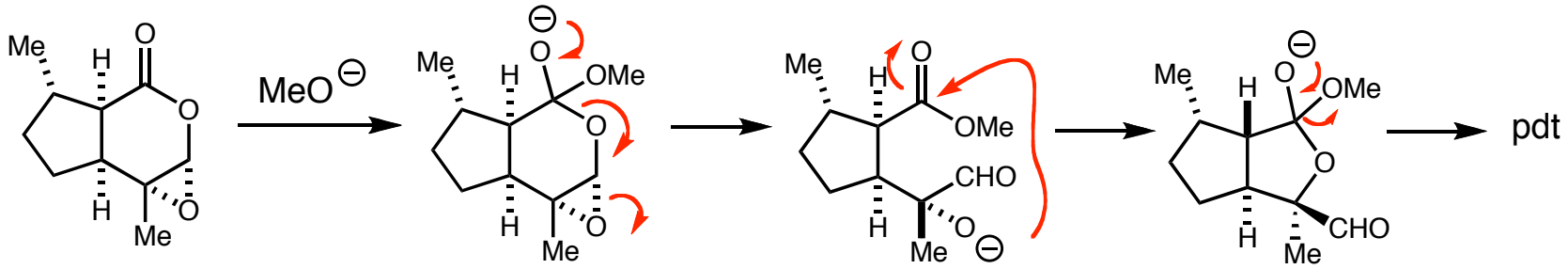
necessitated late-stage epimerization

Willot, M.; Radtke, L.; Konning, D.; Frohlich, R.; Gessner, V.; Strohmann, C.; Christmann, M.
Angew, Chem, Int. Ed. **2009**, *48*, 9105-9108

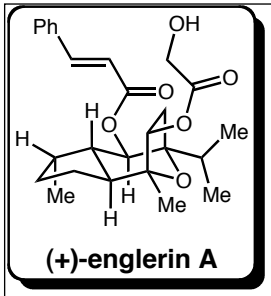


Oxidative Rearrangement

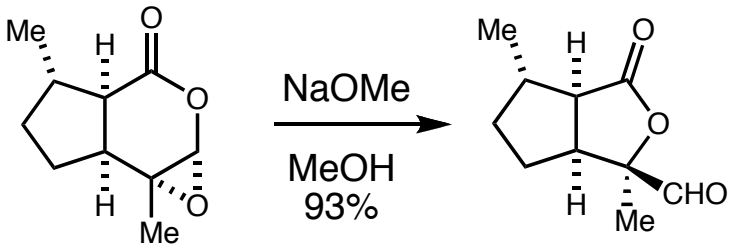


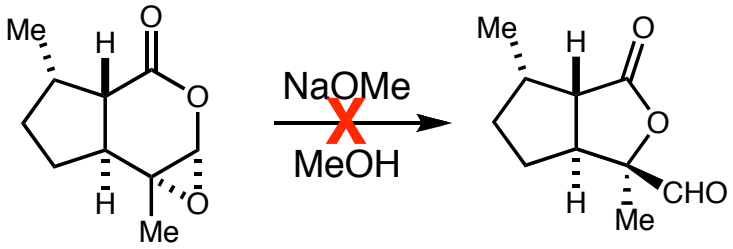


Willot, M.; Radtke, L.; Konning, D.; Frohlich, R.; Gessner, V.; Strohmann, C.; Christmann, M.
Angew, Chem, Int. Ed. **2009**, *48*, 9105-9108



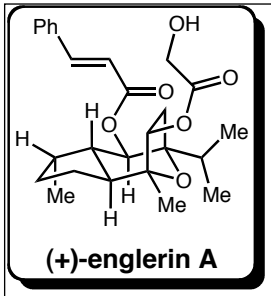
Oxidative Rearrangement





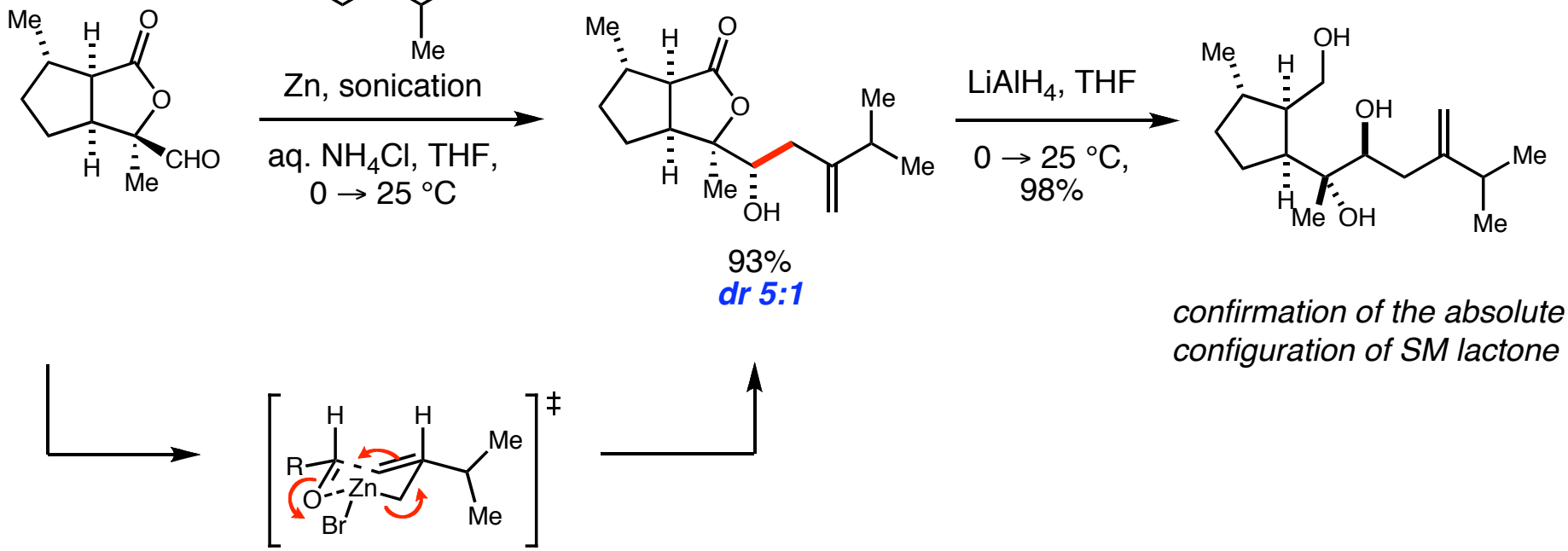
strain from trans-bicyclo-[3.3.0]octane scaffold

Gordon, H. L.; Freeman, S.; Hudlicky, T. *Synlett* **2005**, 2911-2914



(+)-englerin A

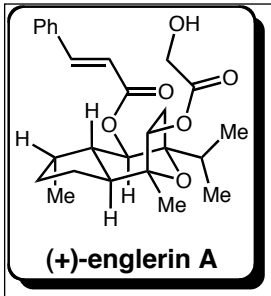
Installation of the Remaining Carbon Framework



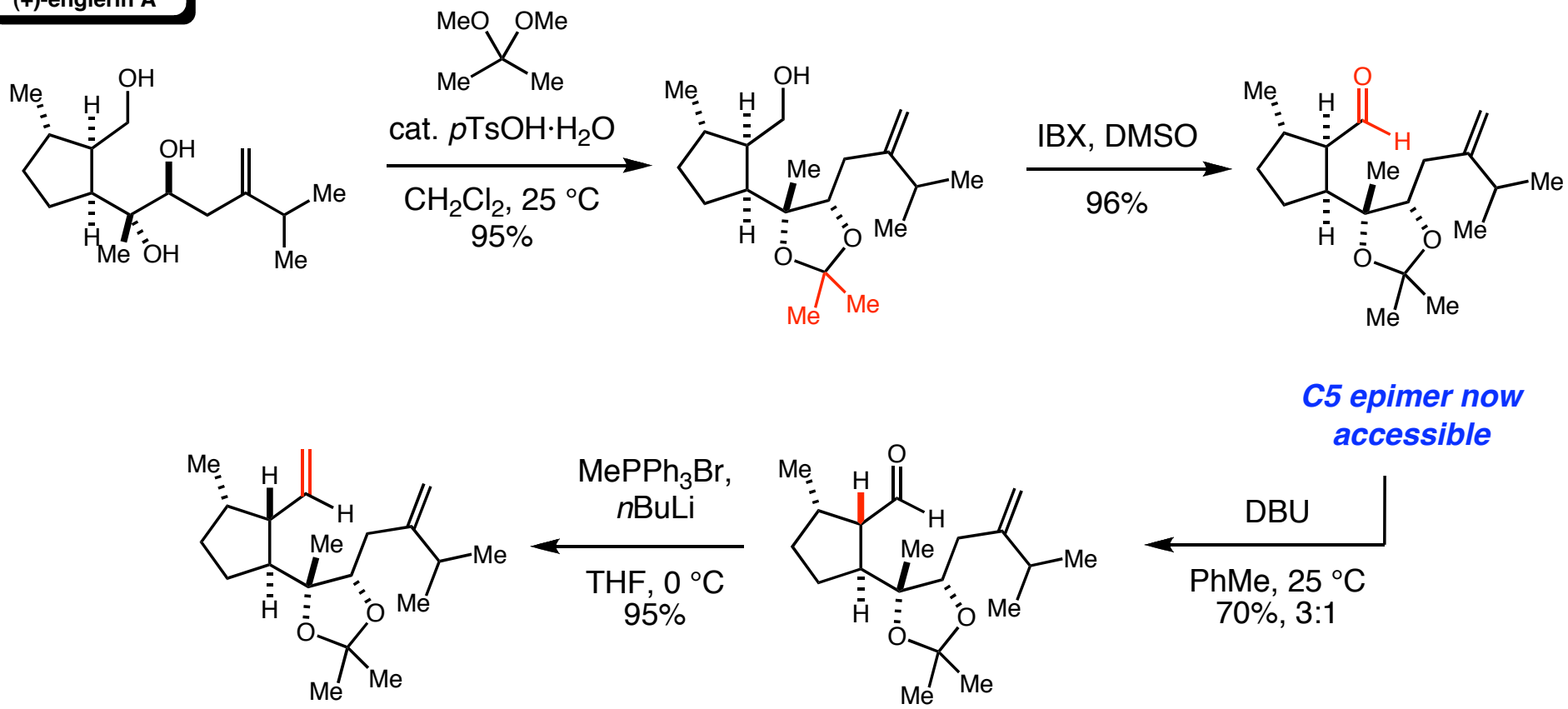
confirmation of the absolute configuration of SM lactone

Willot, M.; Radtke, L.; Konning, D.; Frohlich, R.; Gessner, V.; Strohmann, C.; Christmann, M.
Angew, Chem, Int. Ed. **2009**, *48*, 9105-9108

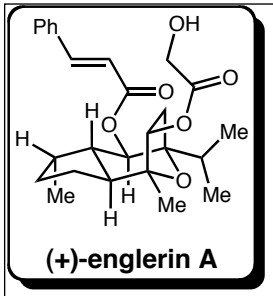
Functional Group Manipulations



(+)-englerin A

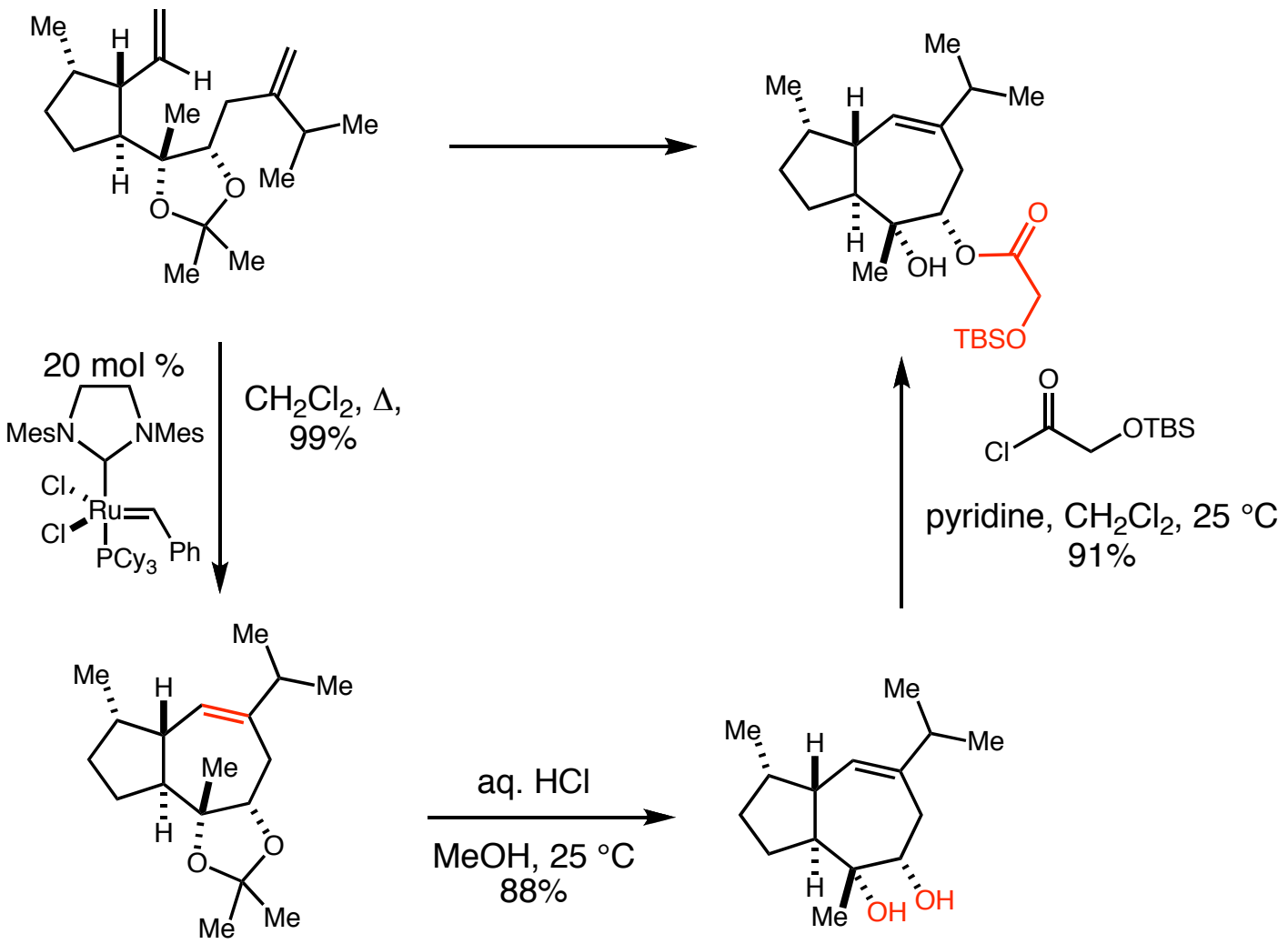


Willot, M.; Radtke, L.; Konning, D.; Frohlich, R.; Gessner, V.; Strohmann, C.; Christmann, M.
Angew, Chem, Int. Ed. **2009**, *48*, 9105-9108



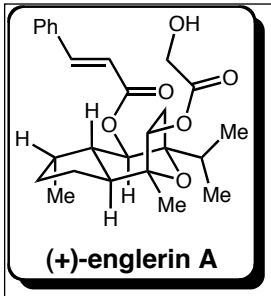
(+)-englerin A

RCM RCM RCM

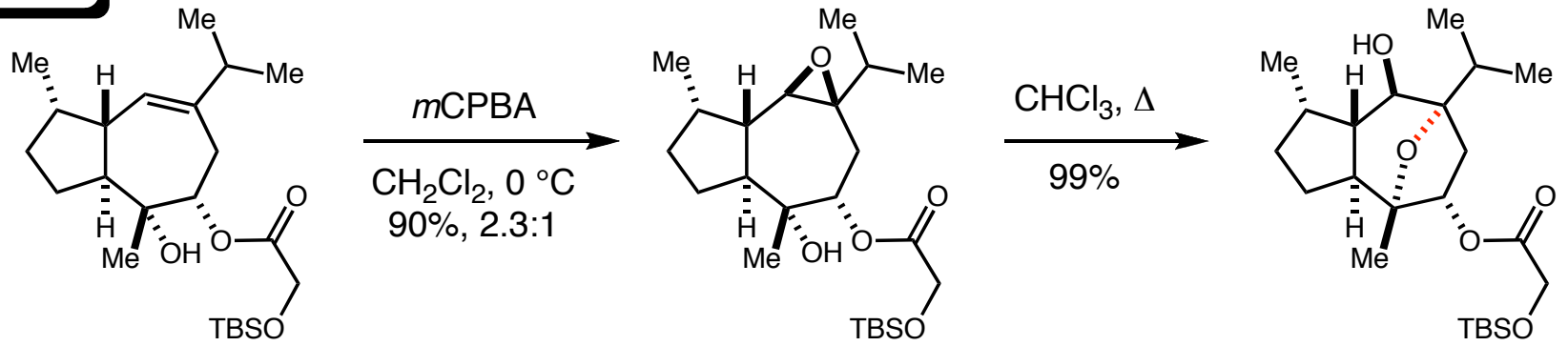


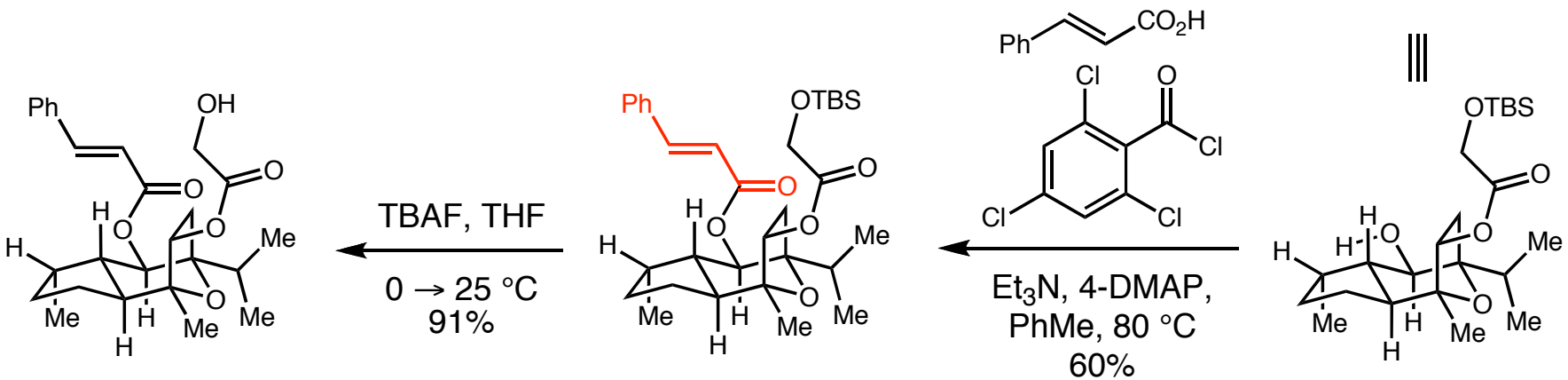
Gradillas, A.; Perez-Castells, J.; *Angew. Chem. Int. Ed.* **2006**, *45*, 6086-6101;
Hamel, C.; Prusov, E. V.; Gertsch, J.' Schweizer, W. B.; Altmann, K. H. *Angew. Chem. Int. Ed.* **2008**, *120*, 10081-10085

Home Stretch



(+)-englerin A





^{1}H NMR, ^{13}C NMR, UV matched
natural **(–)-englerin A**: optical rotation $[a]_D$ = –63 (*c*= 0.13, MeOH)
synthethic: optical rotation $[a]_D$ = +51 (*c*= 0.58, MeOH)

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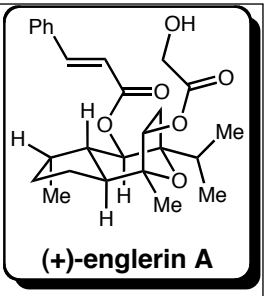
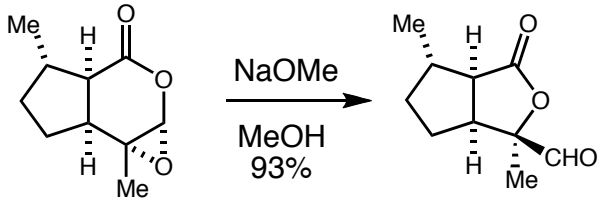
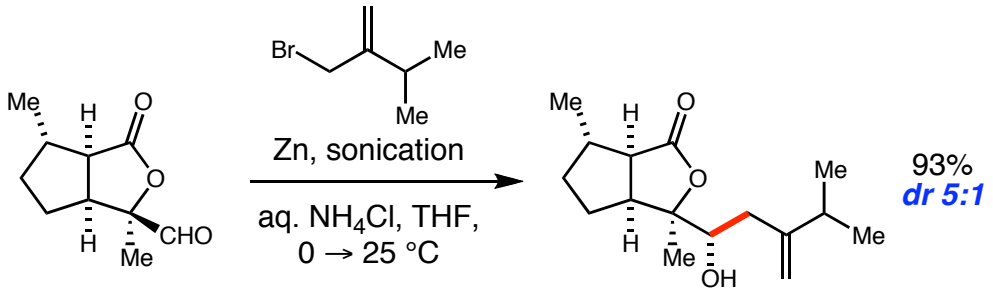
First Total Synthesis of (+)-Englerin A



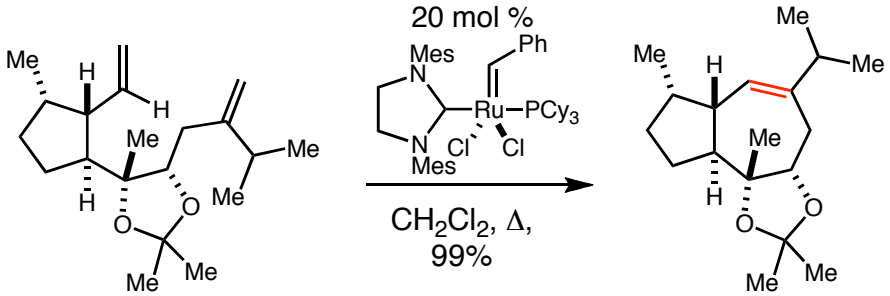
epoxylactone rearrangement



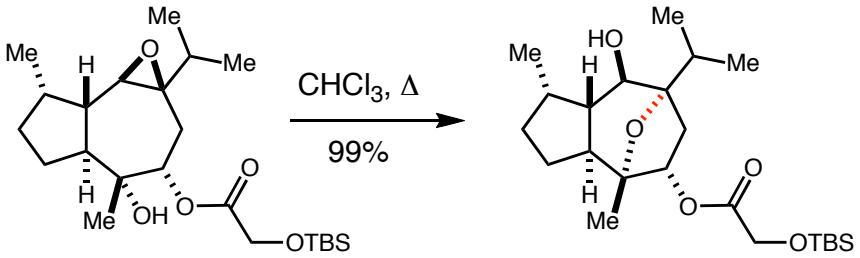
diastereoselective Barbier reaction



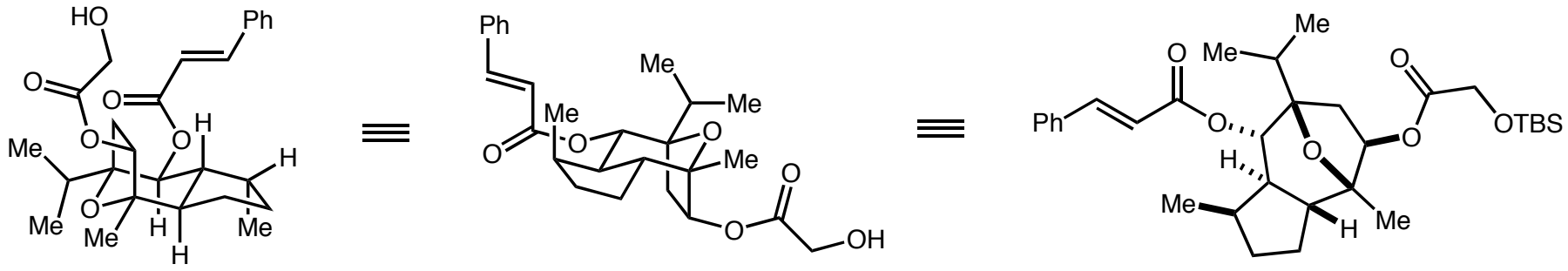
ring-closing metathesis



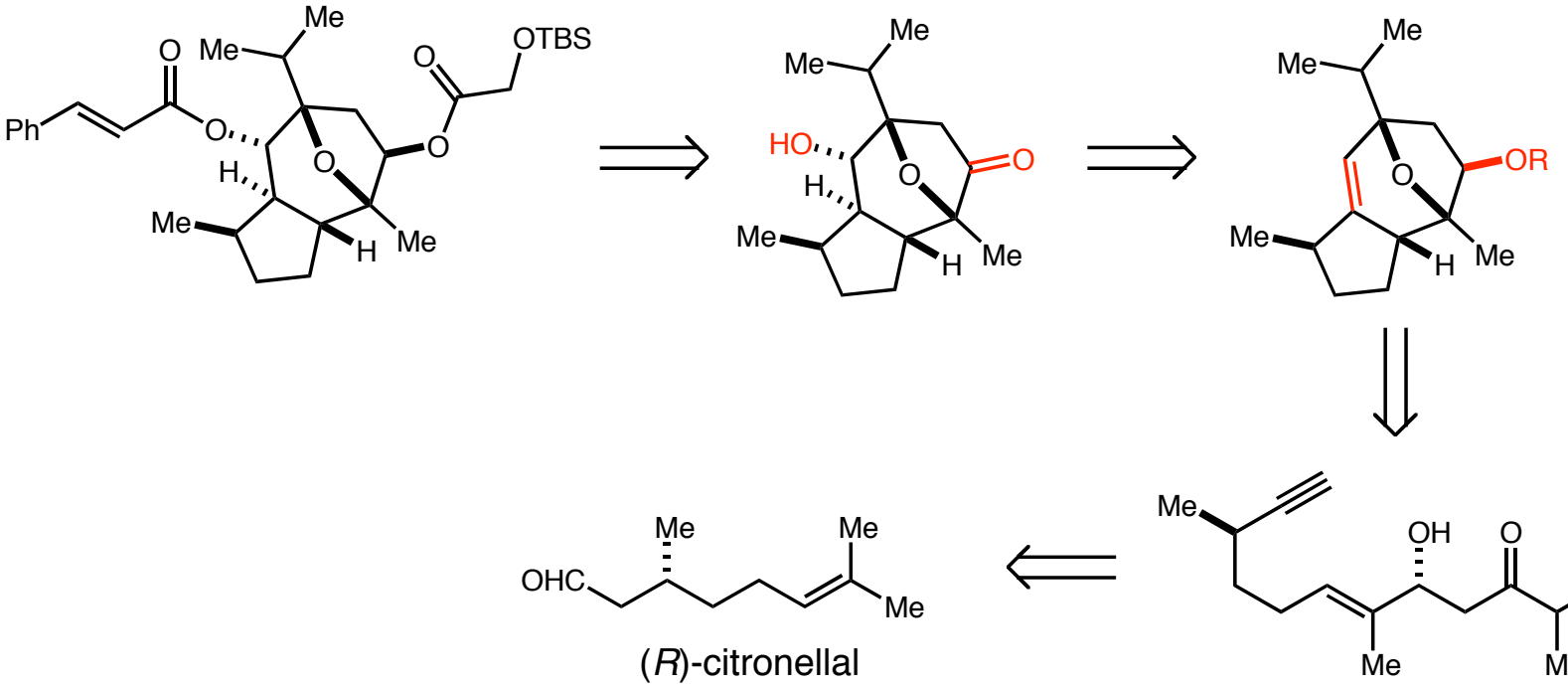
transannular epoxide opening



First Total Synthesis of (–)-Englerin A

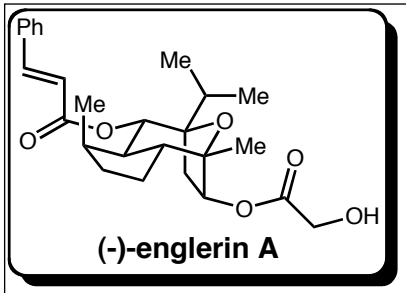


(-)-englerin A



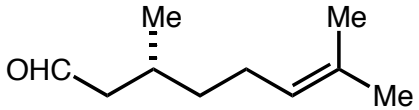
(*R*)-citronellal

Zhou, Q.; Chen, X.; Ma, D. *Angew, Chem, Int. Ed.* **2010**, *early view*



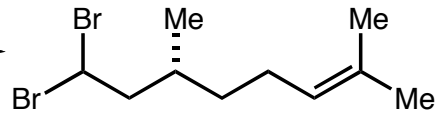
(-)-englerin A

Generation of Cyclization Precursor

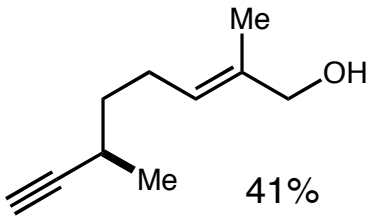


$P(OPh)_3$, Br_2, Et_3N
−78 °C → 23 ° C

quantitative

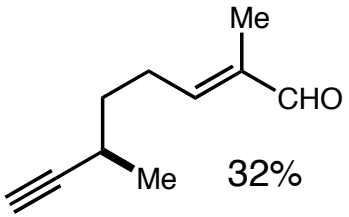


1. *t*-BuOK, 18-cr-6, pet. ether, Δ, 12 h, 41 %
2. SeO_2, TBHP, salicylic acid, CH_2Cl_2, 23 °C, 32%



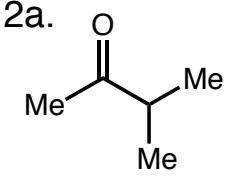
41%

+



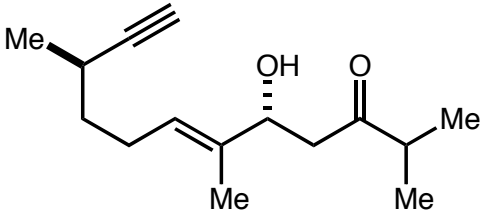
32%

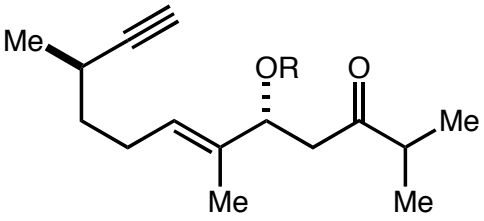
1. IBX, EtOAc, Δ, 95%

2a. 

, (−)-Ipc_2BCl, Et_3N, 0 °C

b. CHO, −78 °C
c. MeOH, pH 7 buffer, H_2O_2
95%, 4:1 dr

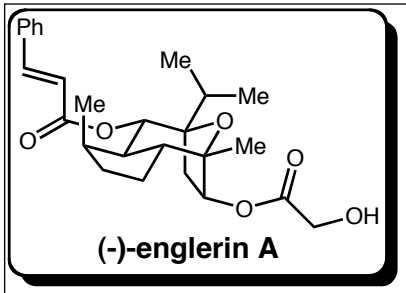




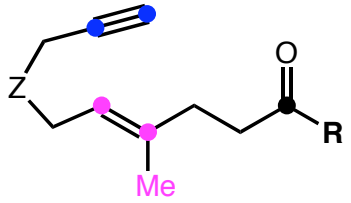
R = TBS, TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 90%
R = TES, TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 63%
R = Me, $TMSCHN_2$, HBF_4, CH_2Cl_2, 0 °C, 50%

Zhou, Q.; Chen, X.; Ma, D. *Angew, Chem, Int. Ed.* **2010**, *early view*

Gold-Catalyzed Cyclization

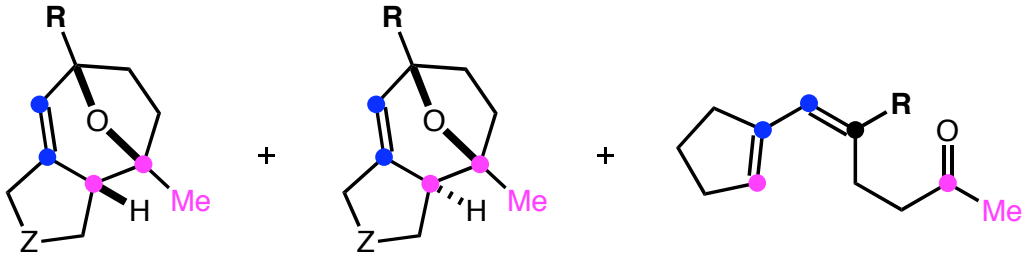


(-)-englerin A



[Au]

CH_2Cl_2, 23 °C
5-30 min



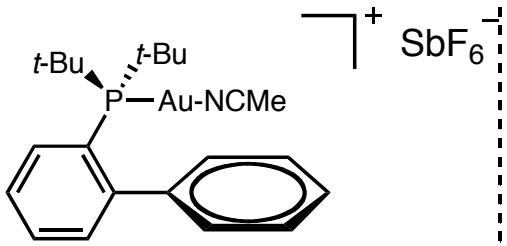
Z = $C(CO_2Me)_2$, NTs
R = H, Me, *i*-Pr

up to 84% yield

catalysts

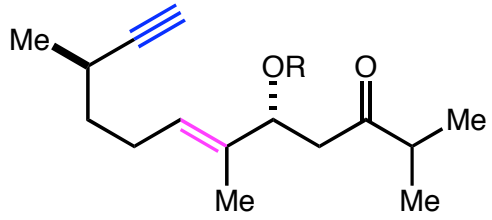
AuCl

$Au(PPh_3)Cl/AgSbF_6$

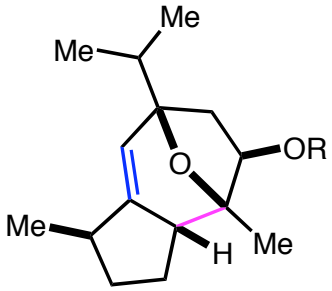


Jimenez-Nunez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45, 5452*

Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2009**, *45,* 7327

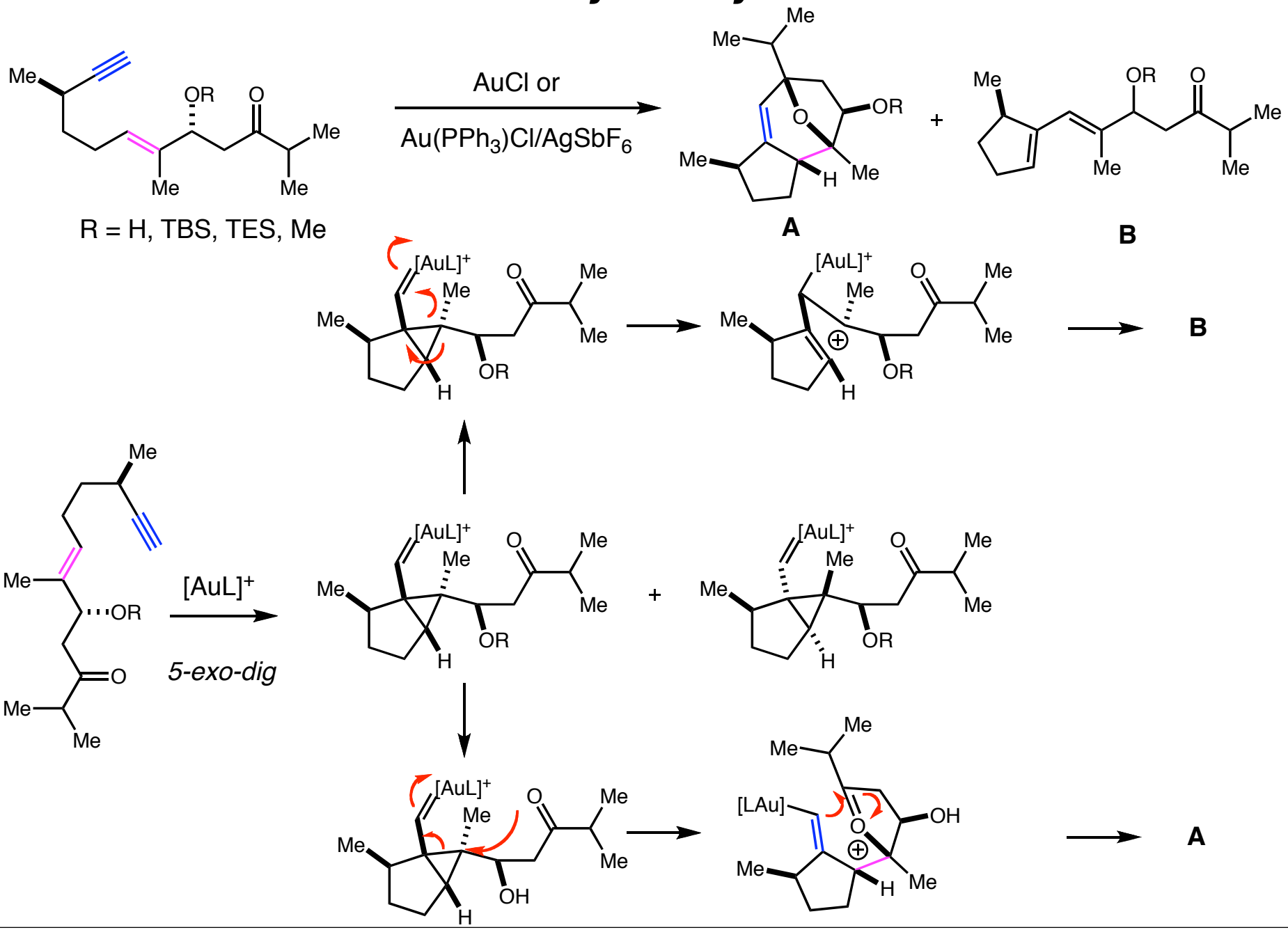


[Au]

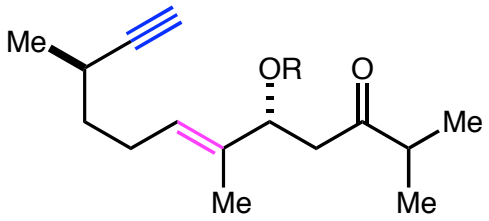


R = H, TBS, TES, Me

Gold-Catalyzed Cyclization



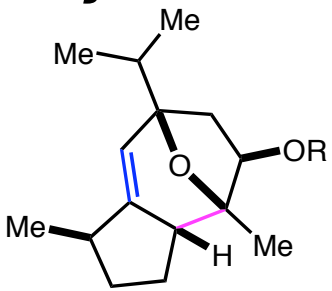
Gold-Catalyzed Cyclization



R = H, TBS, TES, Me

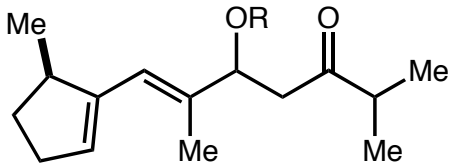
AuCl or

$Au(PPh_3)Cl/AgSbF_6$

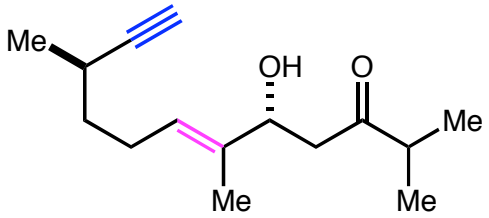


A

+

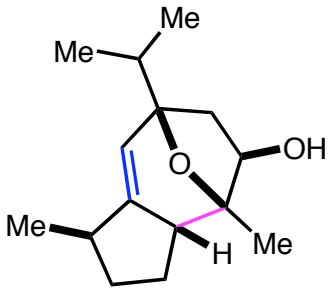


B



AuCl (10 mol %)

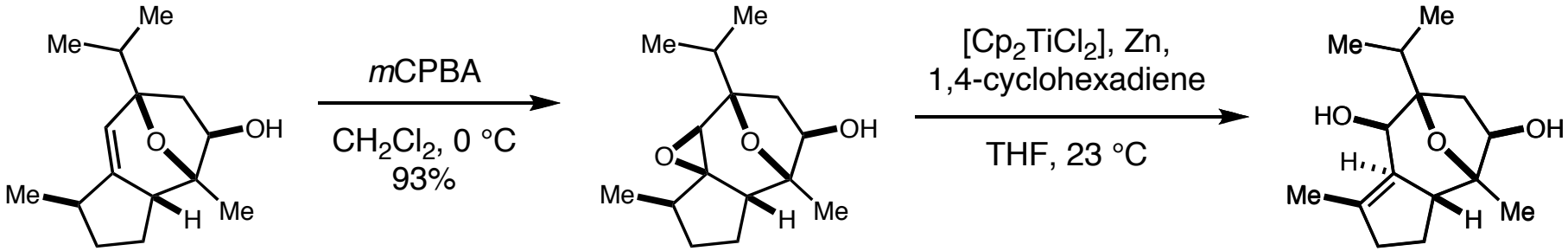
CH_2Cl_2, 23 °C,
20 min, 48%

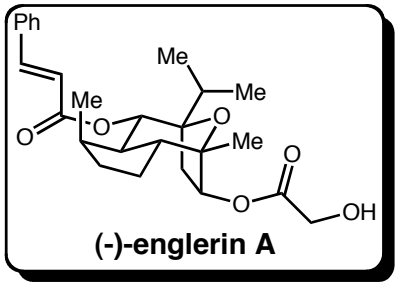


+

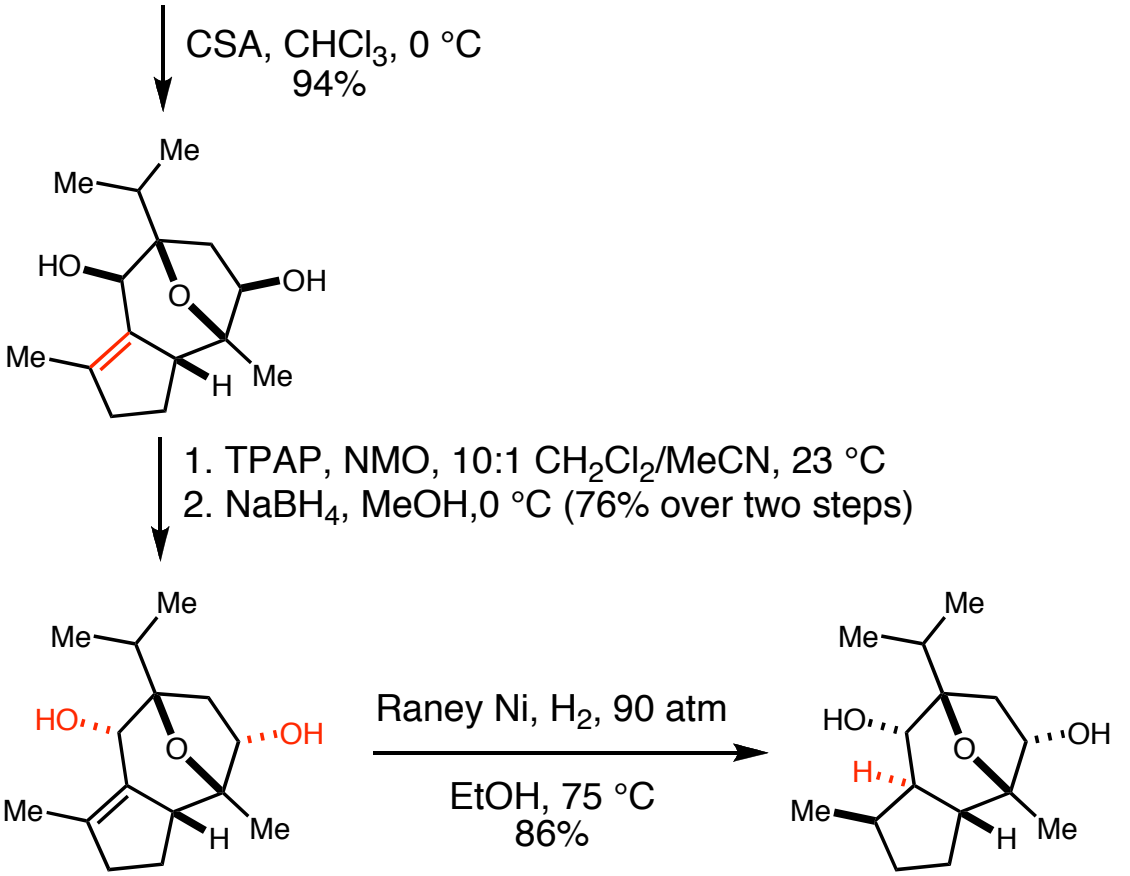
"some unidentified side products"

Gold-Catalyzed Cyclization





(-)-englerin A



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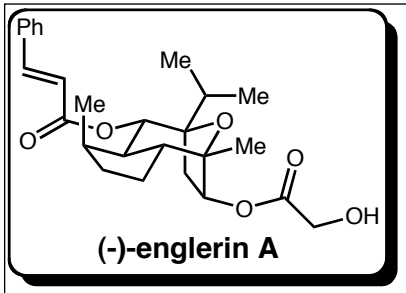
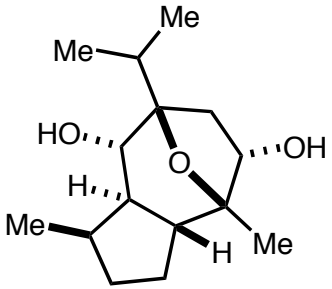
Home Stretch

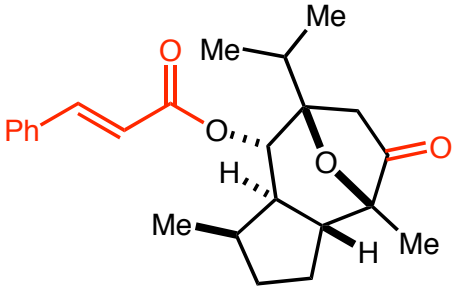


(-)-englerin A

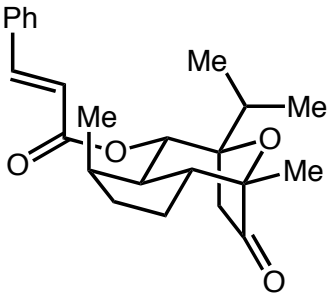


1. DMP, $NaHCO_3$, CH_2Cl_2, 0 °C → 23 °C

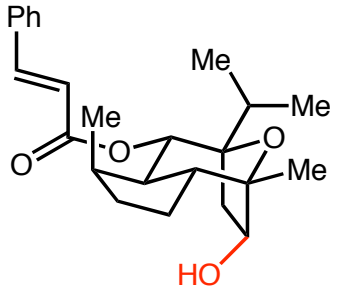
2. cinnamic acid, 2,4,6-TCBC, 4-DMAP, Et_3N, 78% over two steps



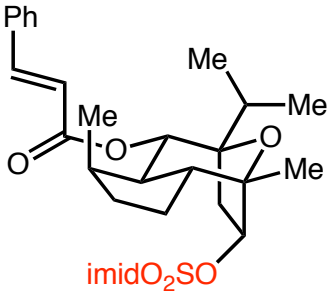
≡



$NaBH_4$, MeOH, 0 °C, 95%

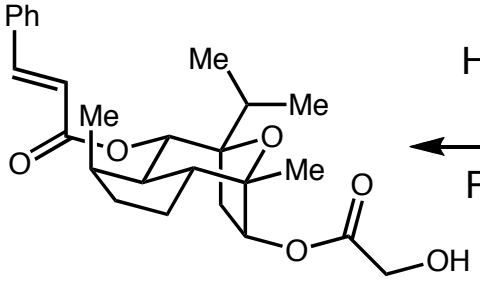


LiHMDS, $(imid)_2SO_2$, THF, 0 °C → 23 °C, 99%



$HOCH_2CO_2Cs$, 18-cr-6

PhMe, Δ, 48 h, 67%



synthetic np: [a]D = –47 (*c*=0.55, MeOH)
reported: [a]d = –63 (*c*=0.13, MeOH)
(*R*)-citronellal from TCI: 77% ee

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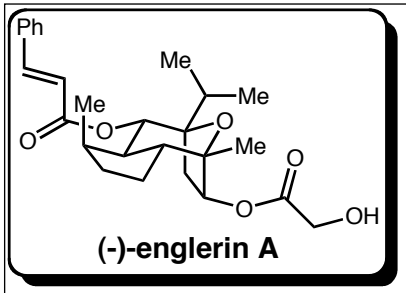
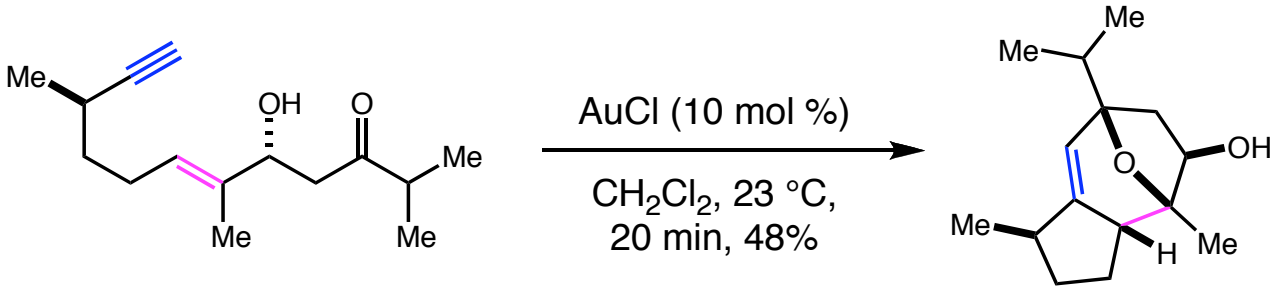


(-)-englerin A

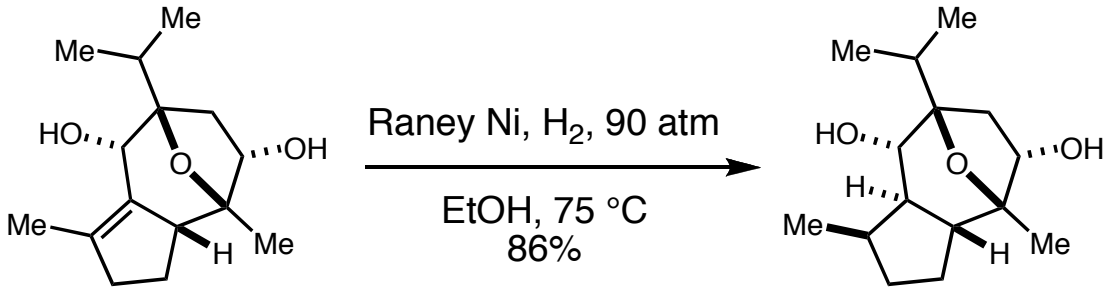
Total Synthesis of (–)-Englerin A

15 steps, 8.1% overall yield starting from (*R*)-citronellal

gold-catalyzed enyne cyclization



hydroxy-directed hydrogenation of an olefin



in the final route, no protecting groups need

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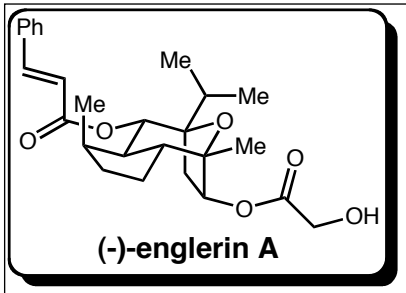
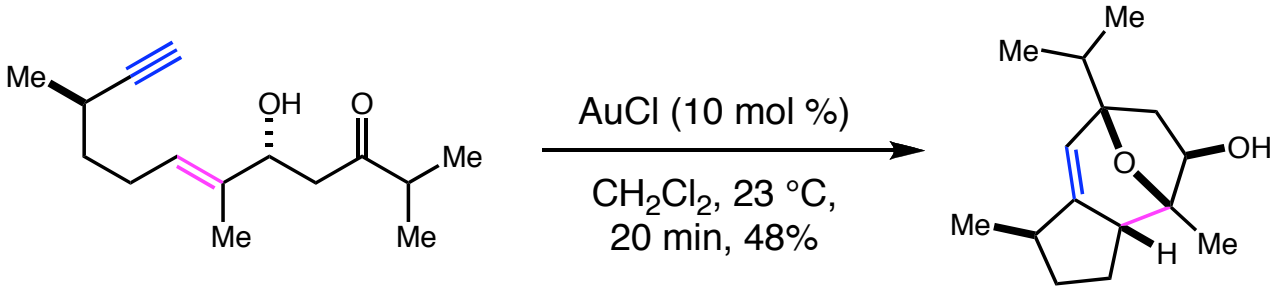


(-)-englerin A

Total Synthesis of (–)-Englerin A

gold-catalyzed enyne cyclization



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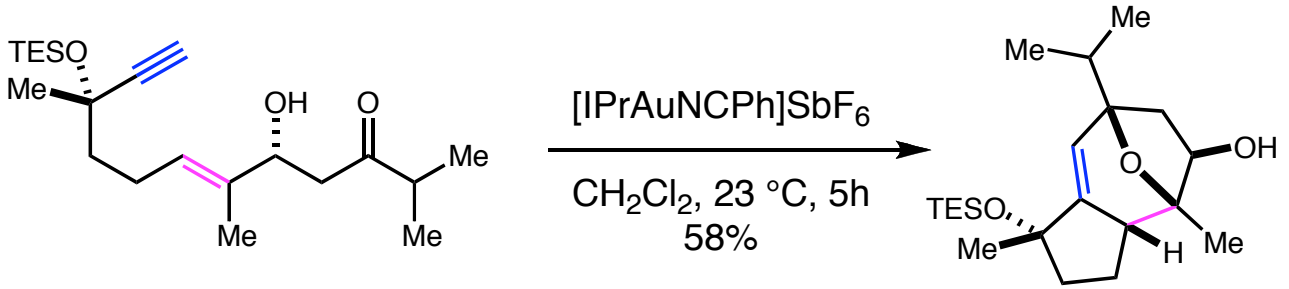
hydroxy-directed hydrogenation of an olefin



18 steps, 7% overall yield starting from geraniol

Molawi, K.; Delpont, N.; **Echawarren**, A. M. *Angew, Chem, Int. Ed.* **2010**, *early view*