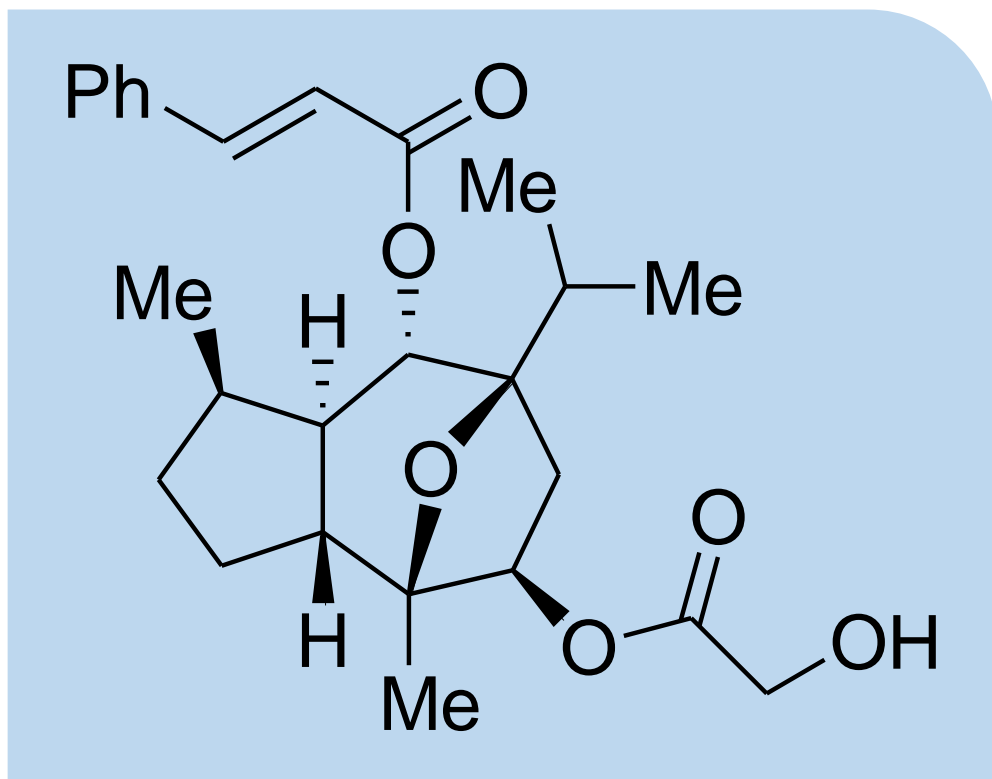


Synthesis of (-)-Englerin A, a potent anti-renal cancer agent



Dong Group Literature Talk
Hee Nam Lim
April, 9, 2014

Isolation



From *Phyllanthus engleri*



Tanzania



Zimbabwe

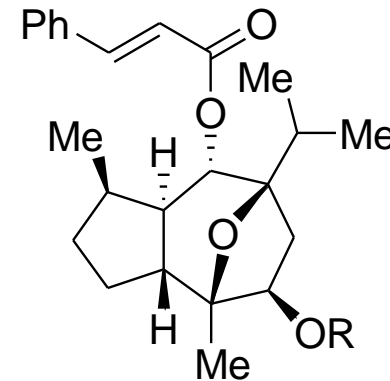
Bioassay-guided identification

Beutler et al in NCI

Bioassay-guided fractionation of the stem bark extract



Chromatography and HPLC-C18



englerin A: R = COCH₂OH

englerin B: R = H

englerin B acetate: R = Ac

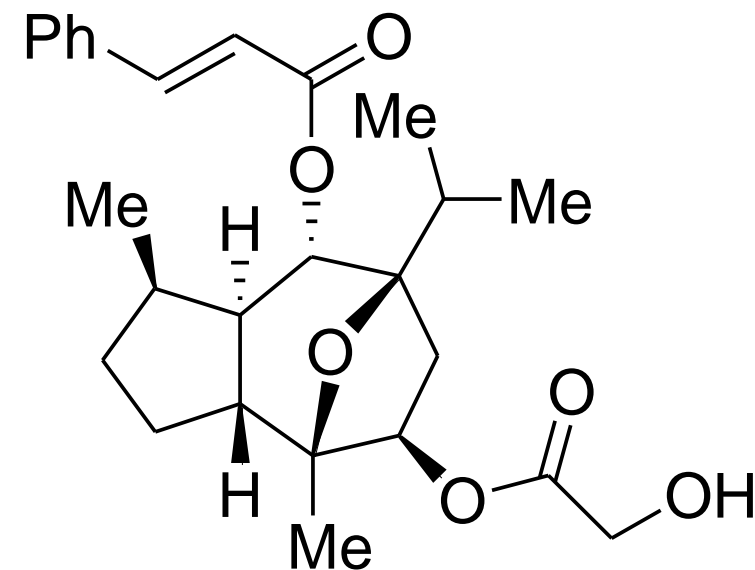
Why people pay attention to this molecule?

Highly selective and low nanomolar activity to renal cancer cell lines.

Table 2. Renal Cancer Cell Growth Inhibition Data (Mean GI₅₀ in μ M) for Englerin A (**1**), Compared to Average Values for Taxol

renal cell line	1	Taxol
786-0	<0.01	0.034
A498	<0.01	0.10
ACHN	<0.01	0.65
CAKI-1	15.5	0.35
RXF-393	0.011	0.041
SN12C	0.087	0.018
TK-10	15.5	0.11
UO-31	<0.01	0.45

2 or 3 folds more potent than current medicines



7-contiguous stereocenters

5-6-5 oxabridged tricycle

Stereochemistry of the ring junction is not obtained by thermodynamic controlled reaction.

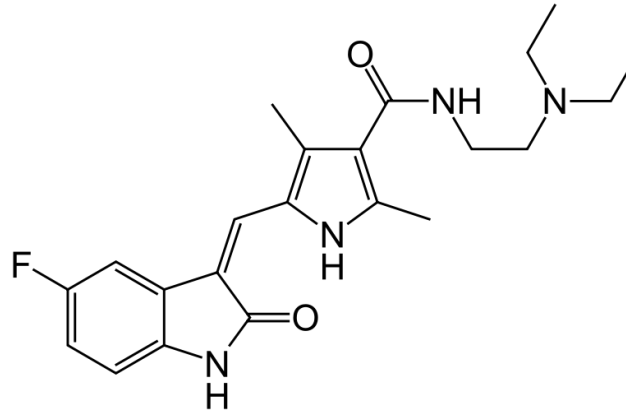
Glycolate is critical

Current Drugs for renal cancer

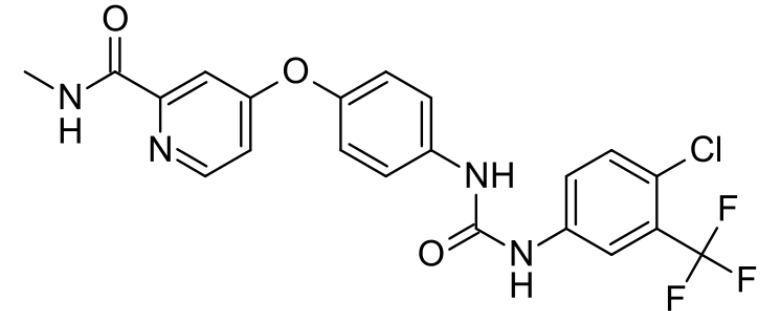
Bevacizumab (Avastin, Genetec, 2004)



Sunitinib (Sutent, Pfizer, 2006)



Sorafenib (Nexavar, Bayer and Onyx Pharmaceuticals, 2005)



- 1) Gastrointestinal (GI) perforation. A hole that develops in your stomach or intestine
- 2) Wounds that don't heal.
- 3) Serious bleeding
- 4) Birth defects or death of an unborn baby
- 5) High blood pressure

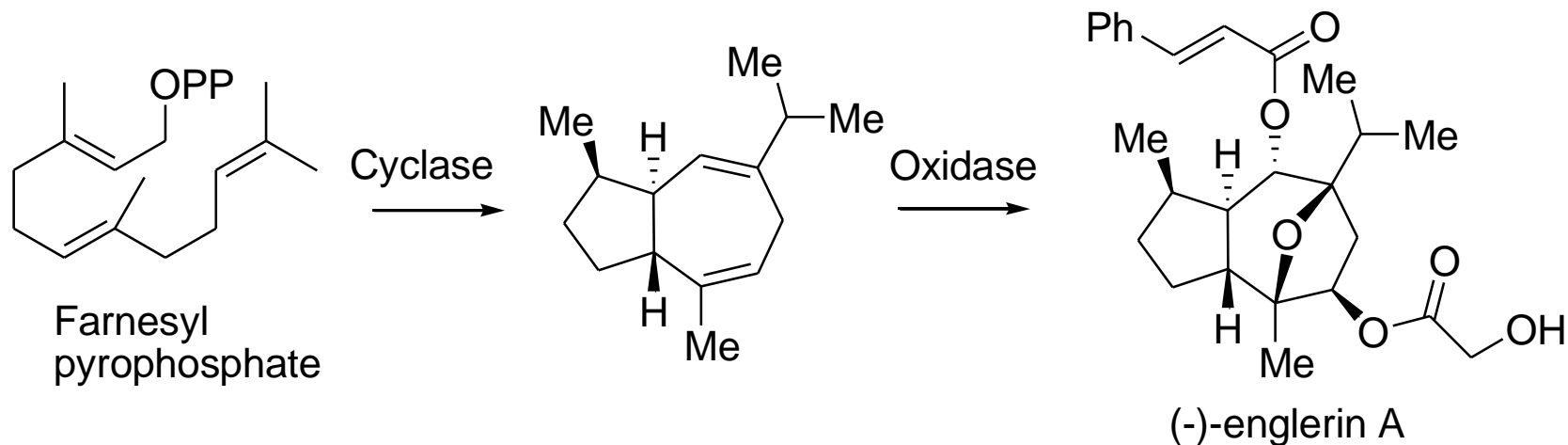
<http://www.nexavar-us.com/scripts/pages/en/patient/about-nexavar/possible-side-effects/>

<http://www.sutent.com/possible-side-effects.aspx>

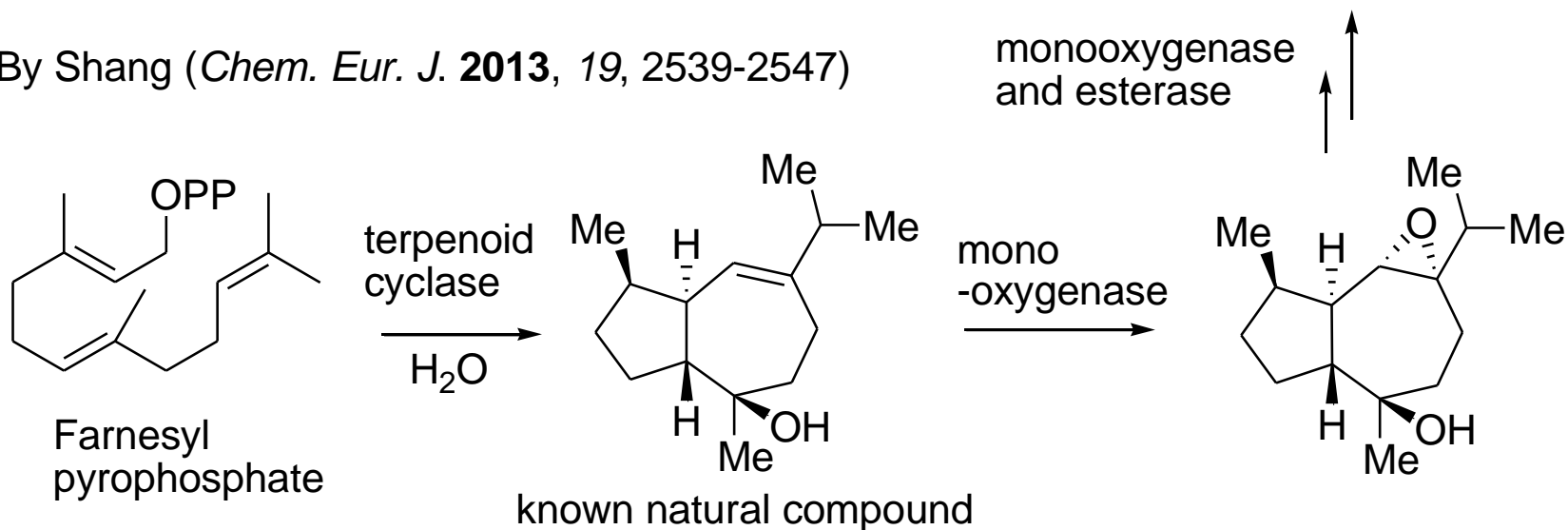
<http://www.avastin.com/patient/overview/side-effects>

Proposed Biosynthesis

By Christmann (*Nature Chem*, **2010**, 2, 519-920)



By Shang (*Chem. Eur. J.* **2013**, 19, 2539-2547)



Synthesis of (-)-englerin A (about 4.5 years since isolation)

Total Synthesis – 9 papers

[Christmann](#) – *Angew. Chem. Int. Ed.* **2009**, 48, 9105-9108.

[Nicolaou and Chen](#) – *J. Am Chem. Soc.* **2010**, 132, 8219-8222.

[Ma](#) – *Angew. Chem. Int. Ed.* **2010**, 49, 3513-3516.

[Echavarren](#) – *Angew. Chem. Int. Ed.* **2010**, 49, 3517-3519.

[Christmann](#) – *Angew. Chem. Int. Ed.* **2011**, 50, 3998-4002.

[Chain](#) – *J. Am. Chem. Soc.* **2011**, 133, 6553-6556.

[Hatakeyama](#) – *J. Org. Chem.* **2012**, 77, 7365-7370.

[Metz](#) - *Angew. Chem. Int. Ed.* **2013**, 52, 5390-5392.

[Shen](#) – *Tetrahedron Lett.* **2014**, 55, 1339-1341.

Formal Synthesis

[Theodorakis](#) – *Org. Lett.* **2010**, 12, 3708-3711.

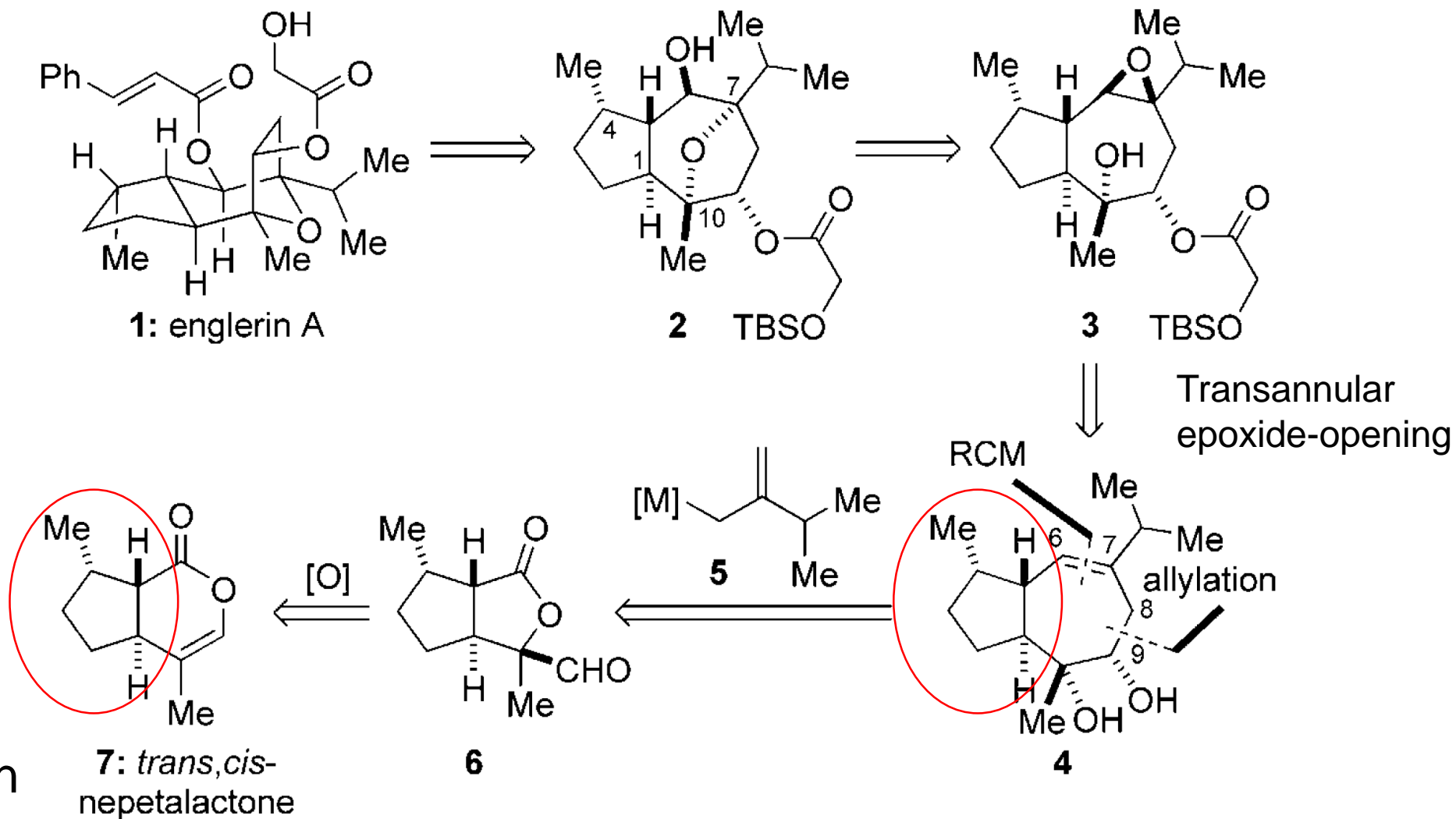
[Maier](#) – *Org. Lett.* **2011**, 13, 2090-2093.

[Parker](#) – *Org. Lett.* **2012**, 14, 2682-2685.

[Cook](#) – *Org. Lett.* **2012**, 14, 3340-3343.

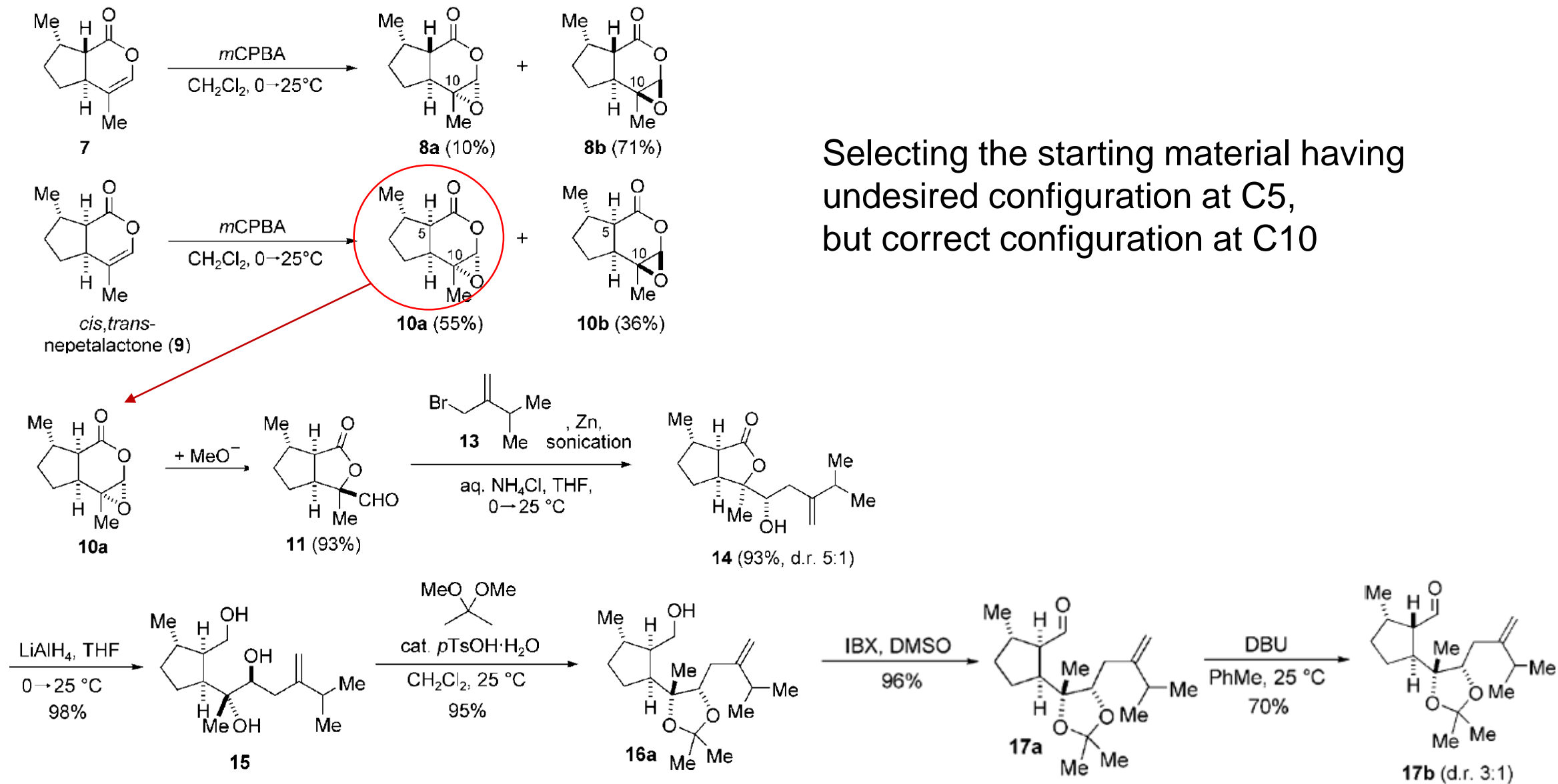
[Lin and Shang](#) –
Tetrahedron Lett. **2011**, 52, 2155-2158.
Synlett. **2012**, 23, 263-266.,
Chem. Eur. J. **2013**, 19, 2539-2547.

First Total Synthesis- Christmann; Retrosynthesis



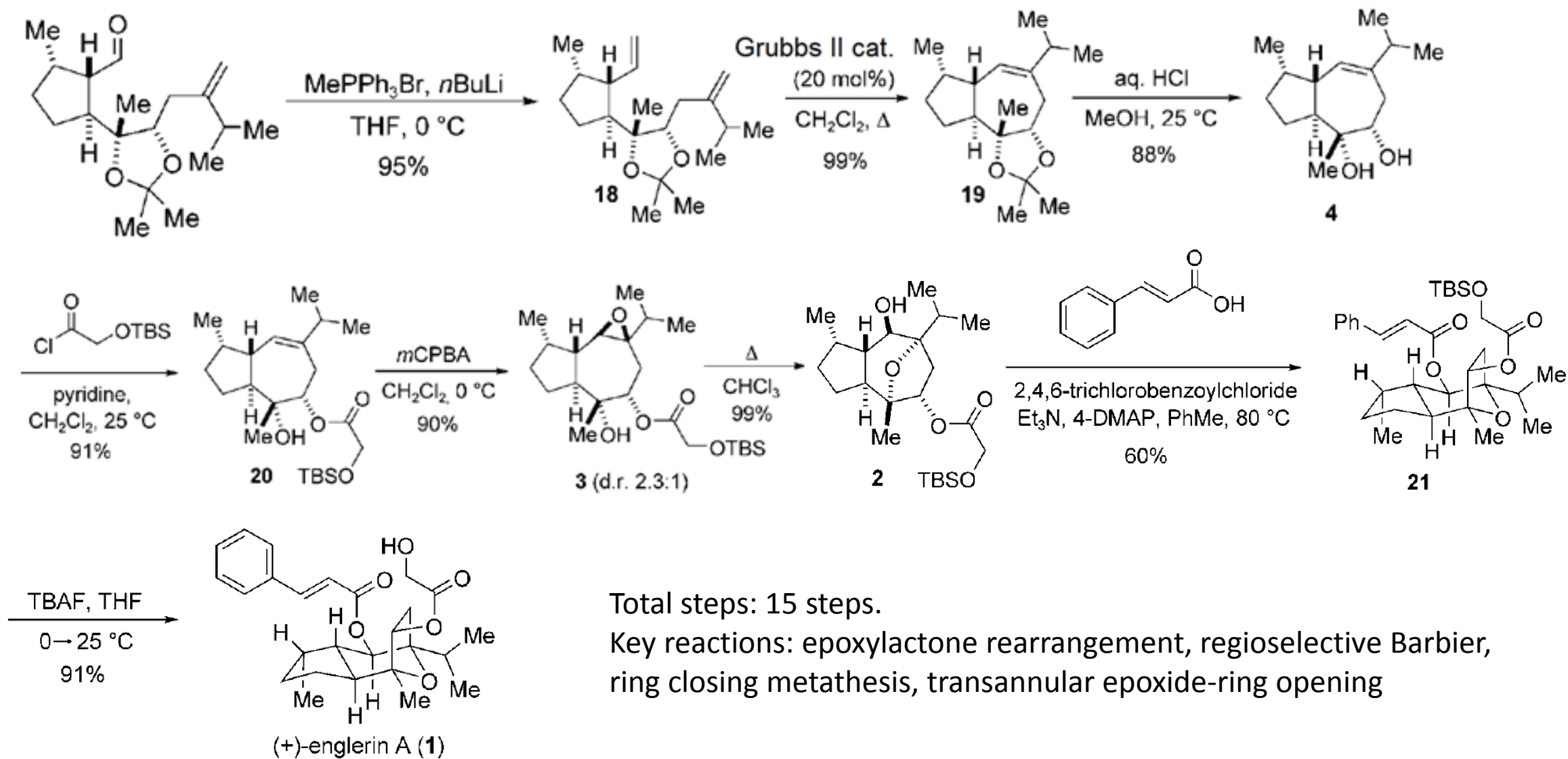
computer-based
search of the carbon
-framework

First Total Synthesis- Christmann; cont'd

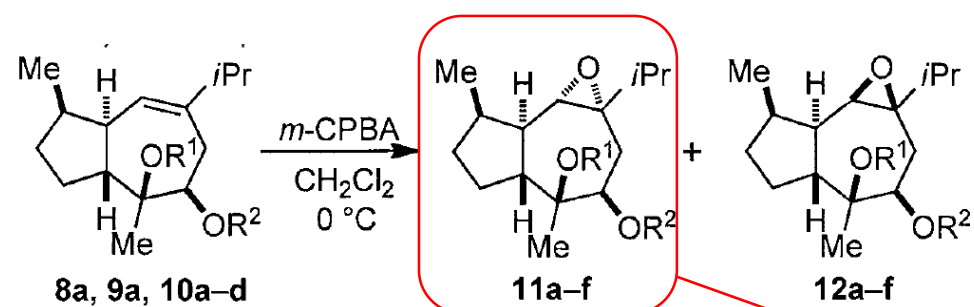
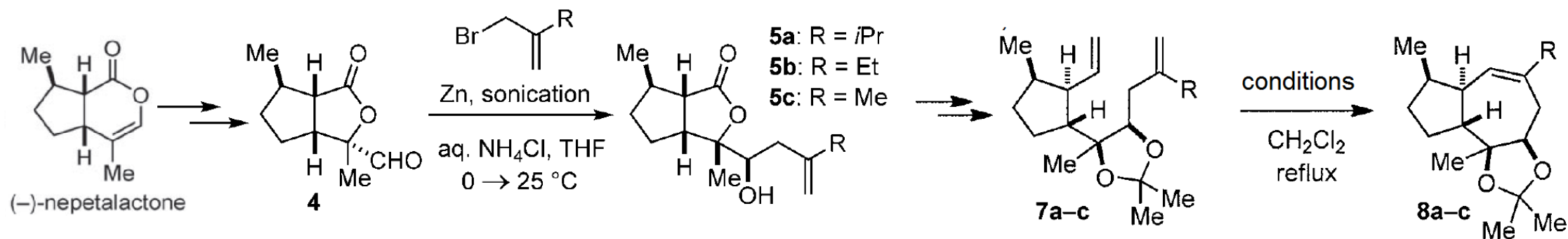


Selecting the starting material having undesired configuration at C5, but correct configuration at C10

First Total Synthesis- Christmann; cont'd 2

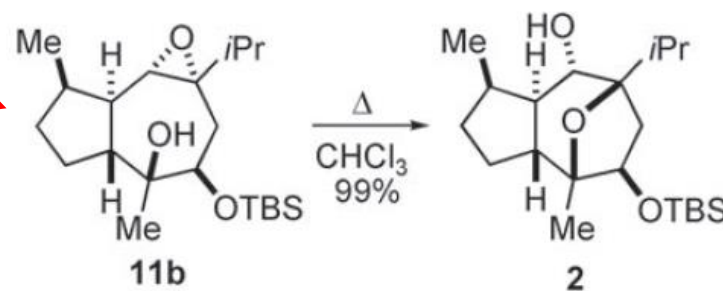


Multigram synthesis- Christmann's second paper



			time	yield
7a:	<i>i</i> Pr	Grubbs II (15)	60	99
7b:	Et	Grubbs II (15)	60	88
7c:	Me	Grubbs II (5)	23	99

Entry	Alkene	R ¹	R ²	Epoxide	11/12	Yield [%] ^[a]
1	10a	H		11a,12a	2.3:1	90
2	10b	H	TBS	11b,12b	5.4:1	91
3	10c	TBS	TBS	11c,12c	9:1	99
4	10d	H	Troc	11d,12d	1:20	73
5	8a	1,2-acetonide		11e,12e	11:1	78
6	9a	H	H	11f,12f	1:3	99

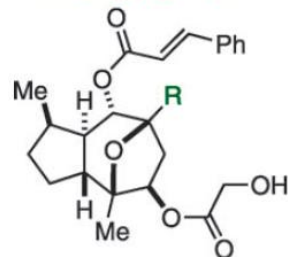


- point of diversion
- highly crystalline
- 7.8 g prepared

[a] Yield of isolated product. Troc = trichloroethoxycarbonyl.

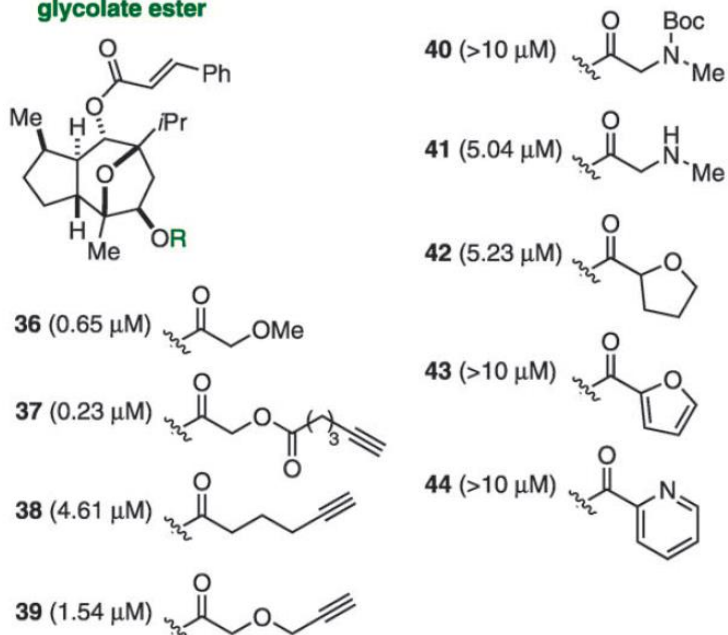
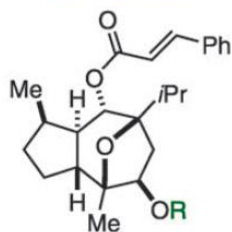
SAR study- Christmann's second paper

Variation of the isopropyl group

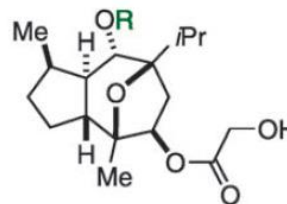


- (-)-1: R = *i*Pr (45 nM)
 (+)-1: R = *i*Pr (> 1 μM)
 13: R = Et (0.95 μM)
 14: R = Me (4.64 μM)

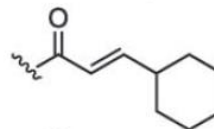
Variation of the glycolate ester



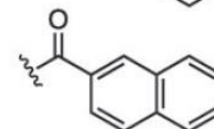
Variation of the cinnamoyl ester



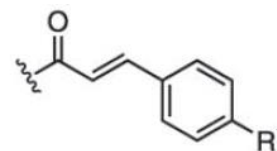
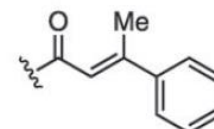
15 (25 nM)



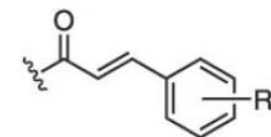
16 (24 nM)



17 (26 nM)

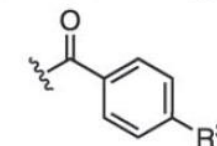
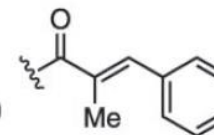


- 18: R¹ = F (0.72 μM)
 19: R¹ = Cl (4.59 μM)
 20: R¹ = Br (>10 μM)
 21: R¹ = NO₂ (>10 μM)
 22: R¹ = *i*Pr (>10 μM)

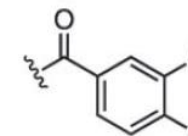


- 23: R² = 3,4-OCH₂O (4.88 μM)
 24: R² = 2-Cl,6-F (92 nM)
 25: R² = 3,4,5-OMe (>10 μM)

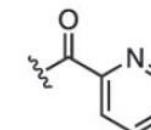
26 (>10 μM)



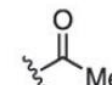
- 27: R³ = H (>10 μM)
 28: R³ = F (>10 μM)
 29: R³ = Cl (1.48 μM)
 30: R³ = NO₂ (1.84 μM)



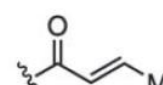
31 (0.28 μM)



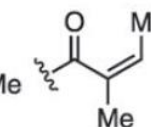
32 (>10 μM)



33 (>10 μM)



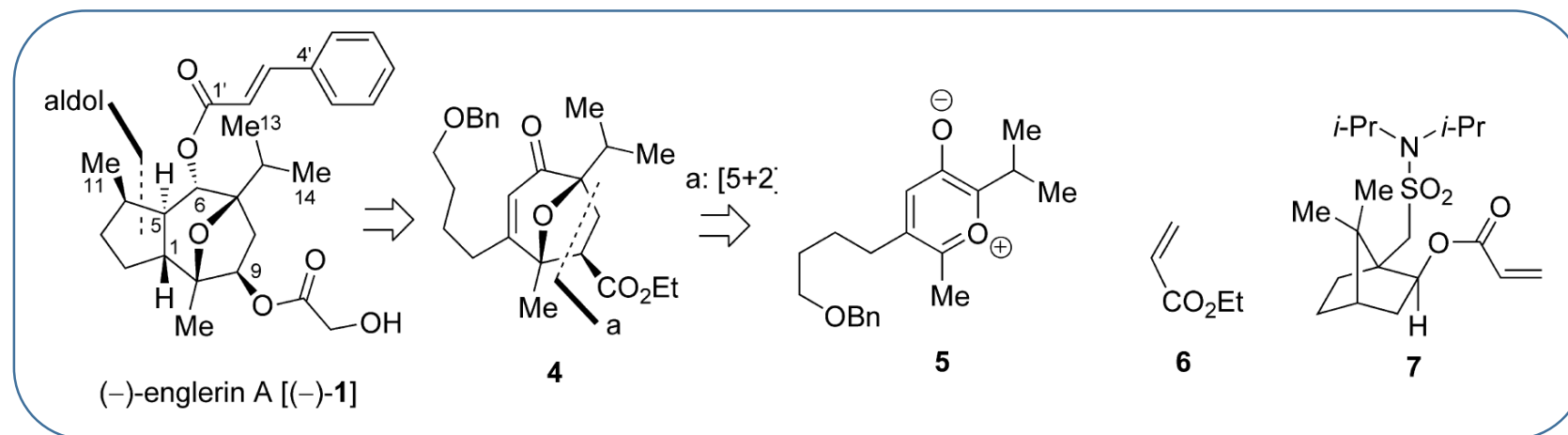
34 (>10 μM)



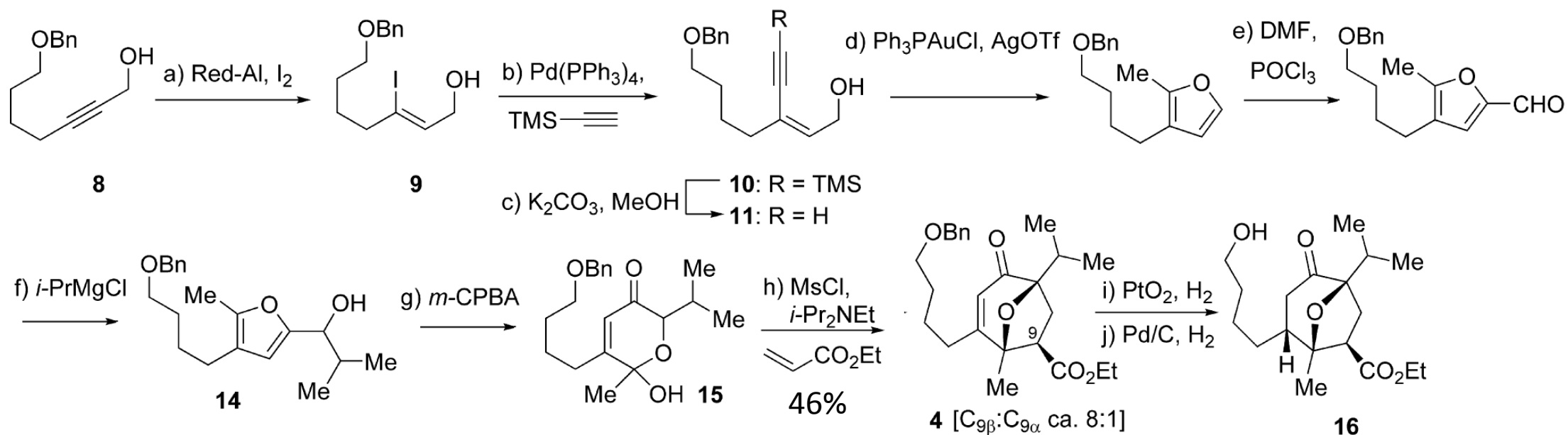
35 (>10 μM)

Nicolaou and Chen's synthesis

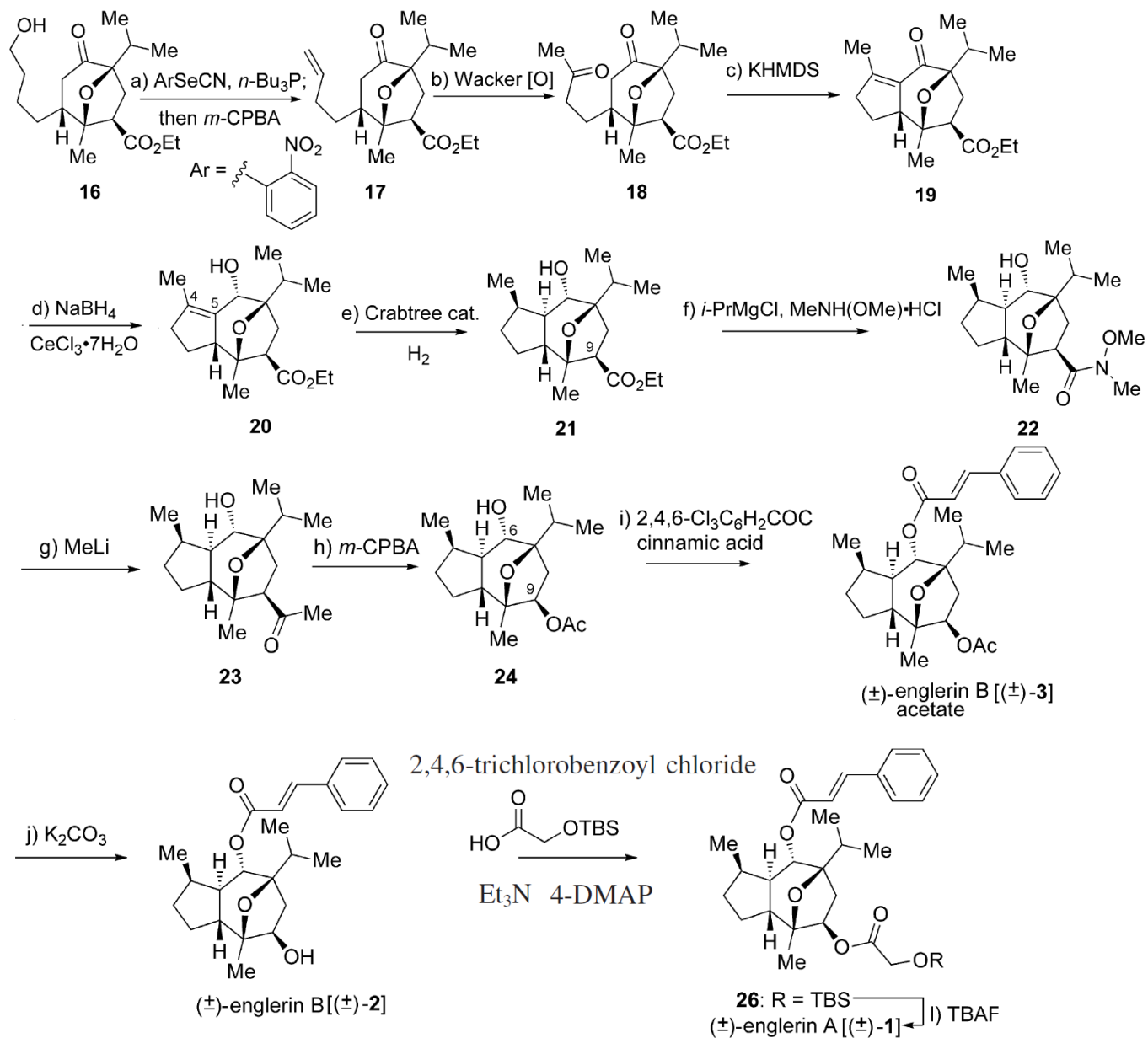
Retrosynthesis



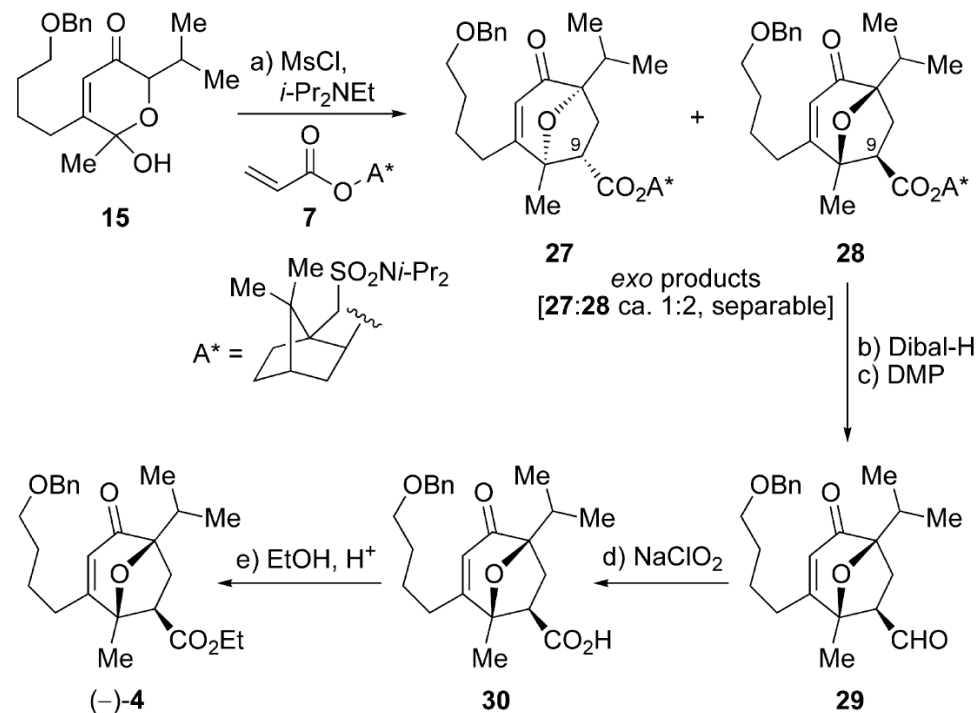
(+/-)-englerin A



Nicolaou and Chen's synthesis; cont'd



Asymmetric Synthesis



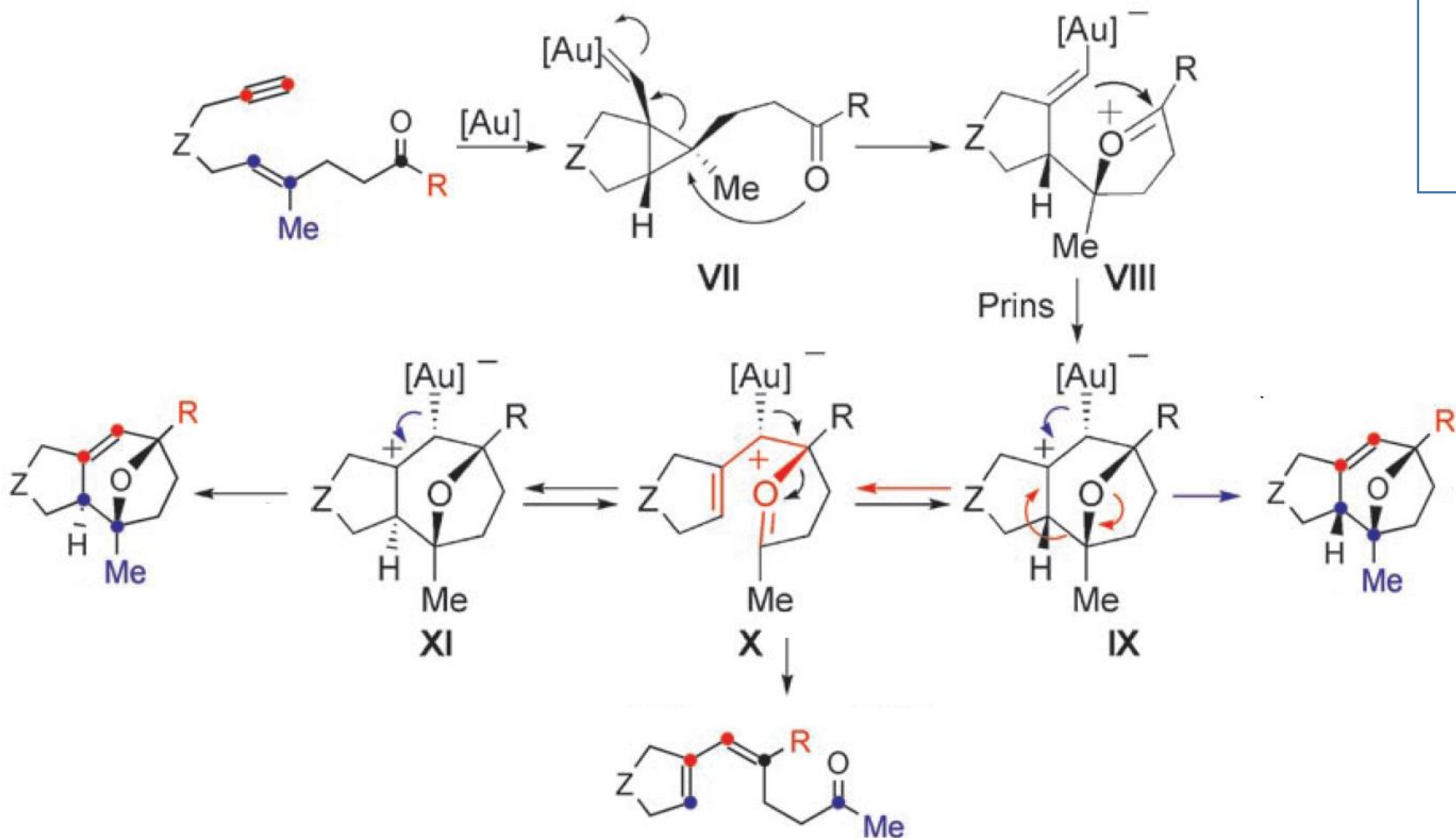
Cytotoxicity of synthetic racemic engerin A still showed high potency and selectivity toward renal cancer cell lines.

25 steps in lls

Ma and Echavarren's synthesis

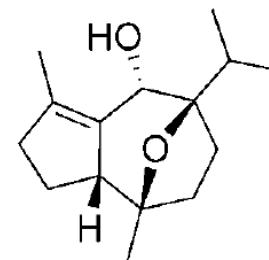
Echavarren's gold catalysis

[2+2+2]-cycloaddition (alkyne/alkene/carbonyl)

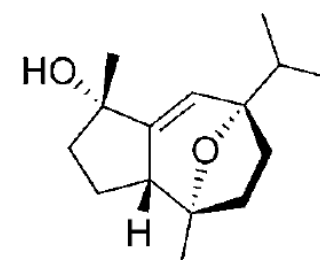


Synthesized natural products

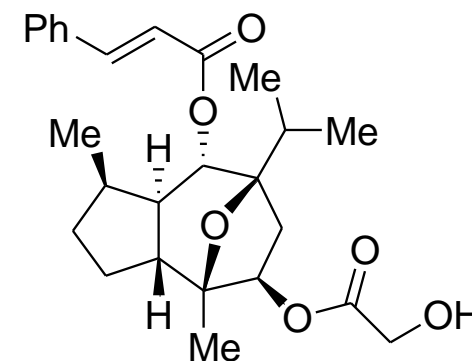
Chem. Commun., 2009, 7327–7329



(+)-orientalol F

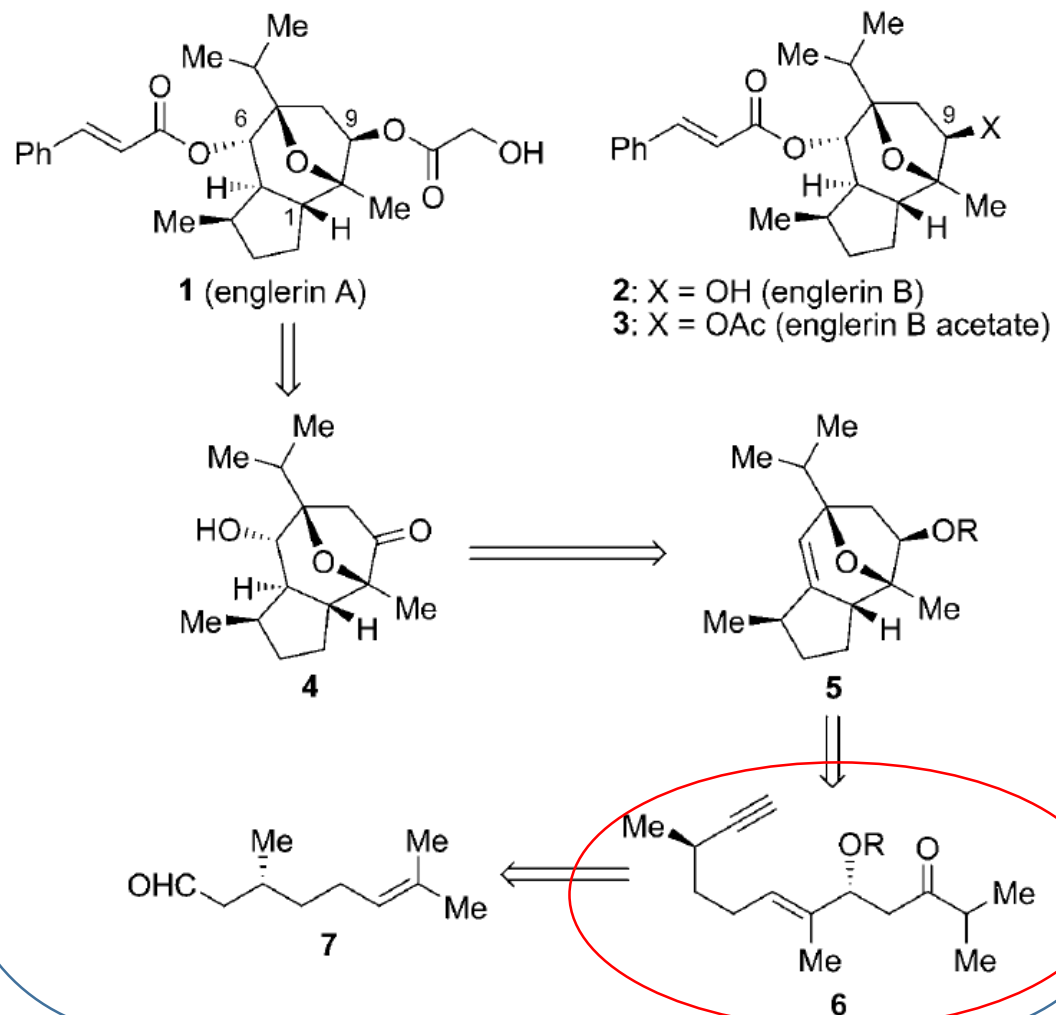


(+/-)-pubinernoid

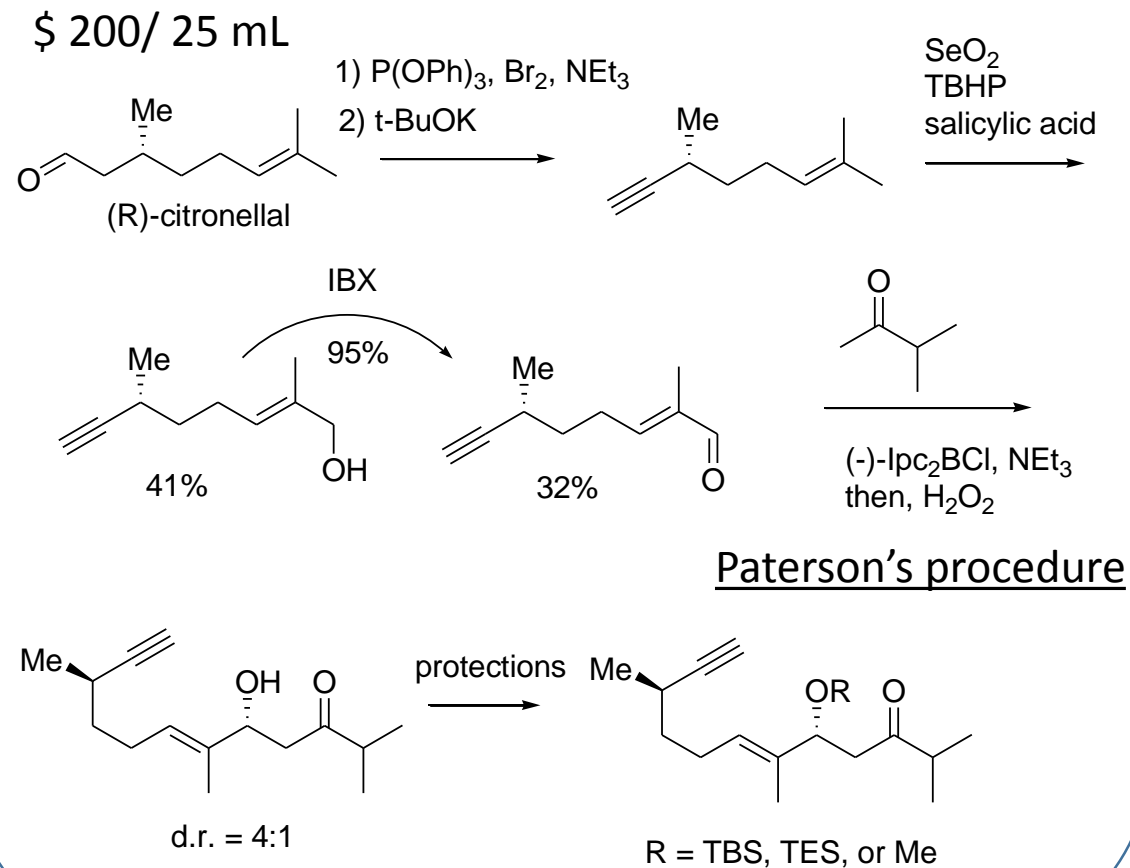


Ma's synthesis

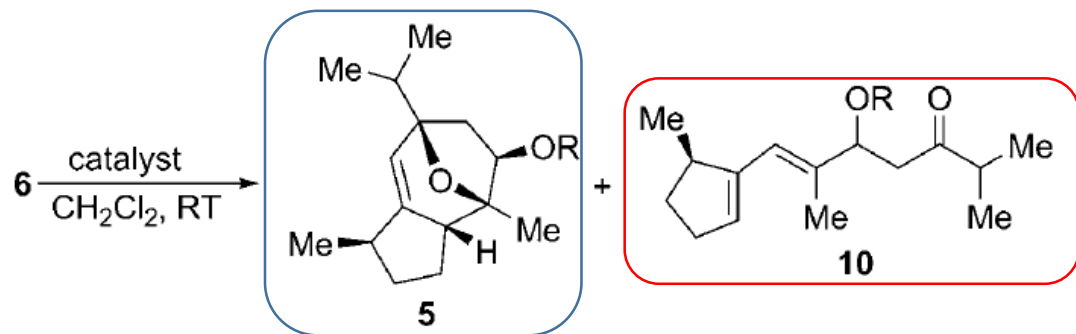
Retrosynthesis



Synthesis of the precursor for Au-catalysis

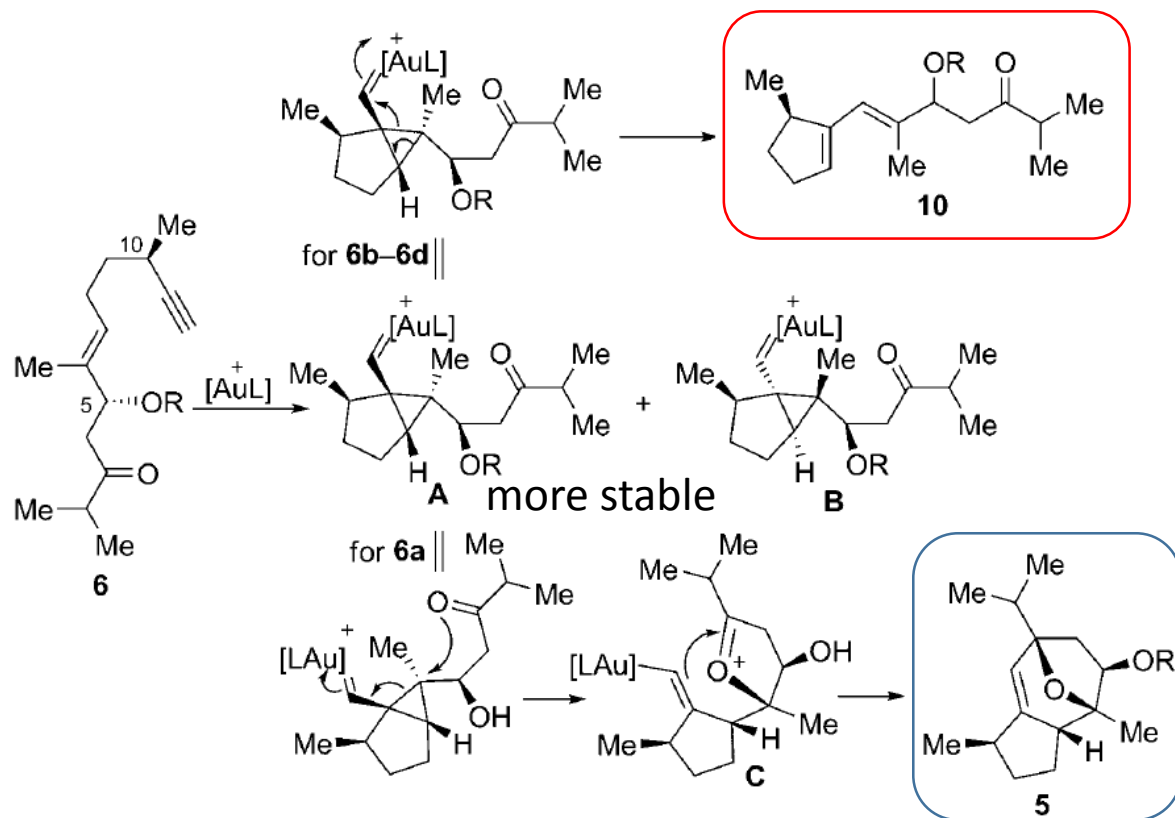


Ma's synthesis



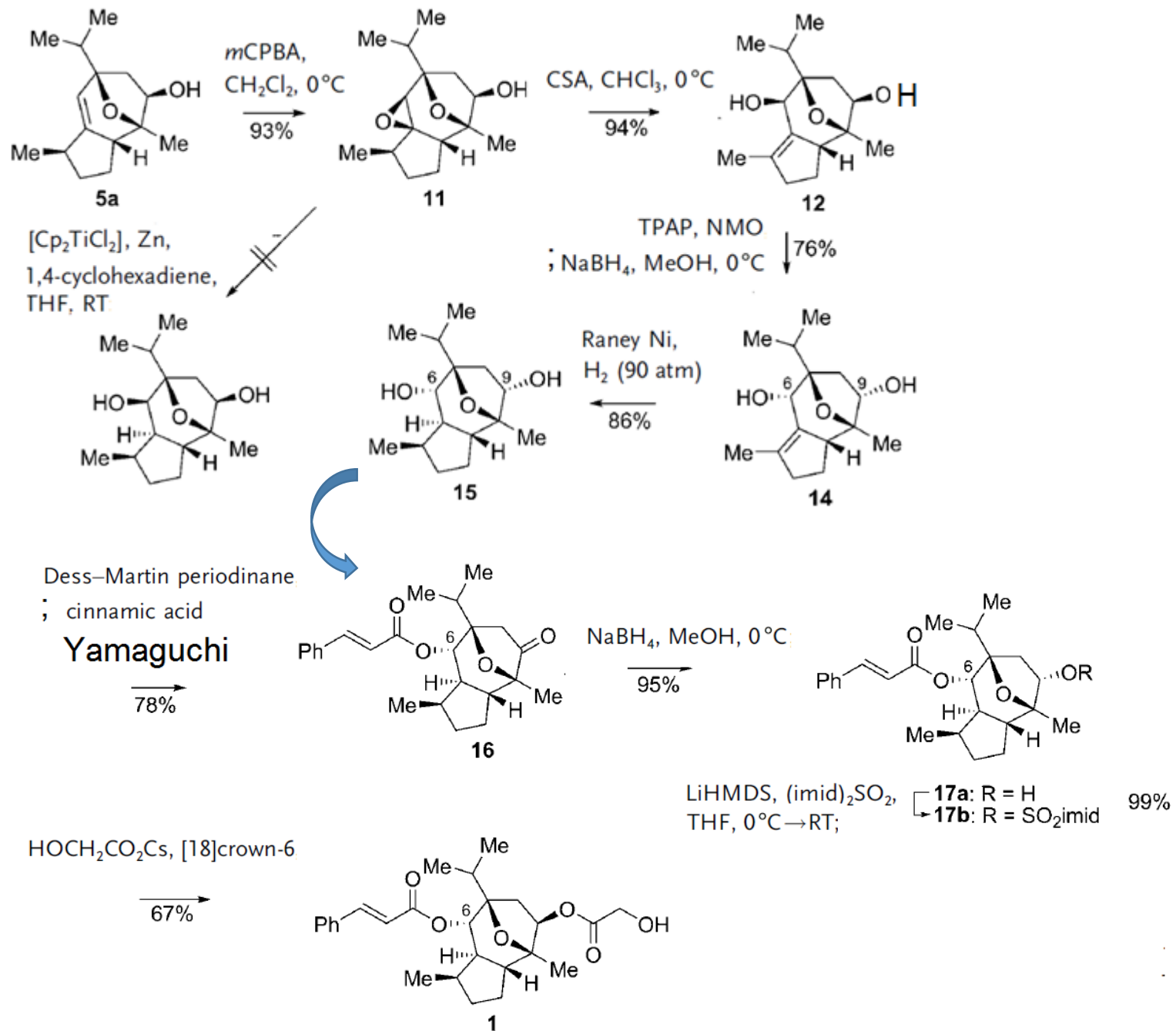
Entry	R	Catalyst	t [min]	Product (yield [%]) ^[b]
1	TBS	A	30	10b (80)
2	TBS	B	30 ^[c]	10b (40)
3	TES	A	20	10c (90)
4	Me	A	30	— ^[d]
5	Me	B	30 ^[e]	10d (10)
6	H	A	20	5a (48)
7	H	B	20 ^[c]	5a (20)

[a] Reaction conditions: enyne (0.1–0.5 mmol), catalyst (10 mol%), CH_2Cl_2 , RT; **catalyst A: AuCl**, **B: [Au(PPh₃)Cl]/AgSbF₆**, [b] Yield of isolated product, [c] 50% conversion was observed. [d] a complex mixture was obtained. [e] 20% conversion was observed.

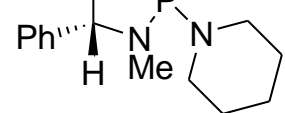
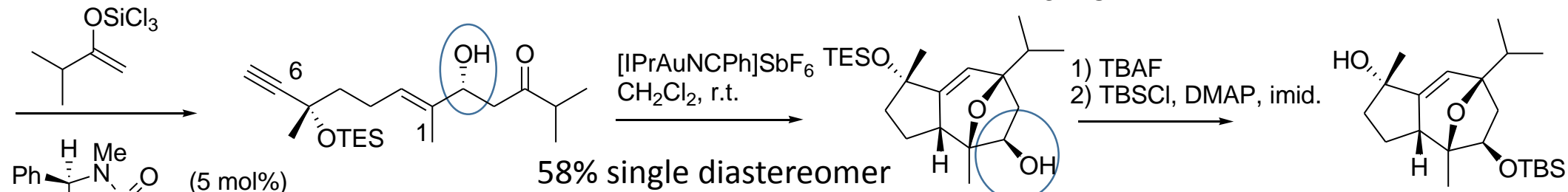
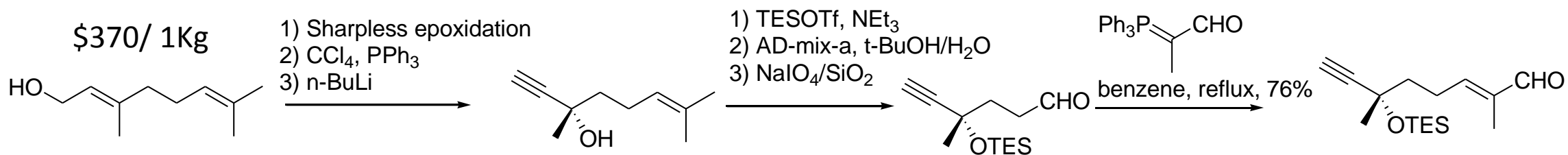


Ma's synthesis

15 steps!
8.1% overall

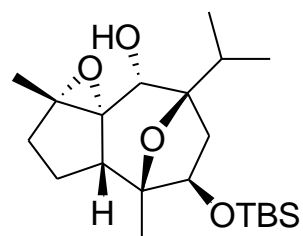


Echavarren's synthesis

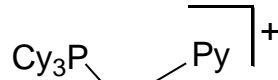
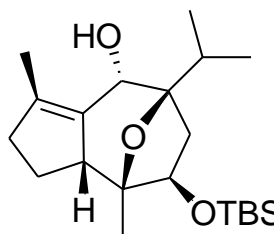


Denmark's procedure

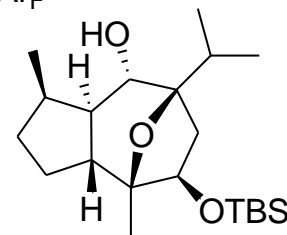
CrO₃(3,5-dimethyl
pyrazole)



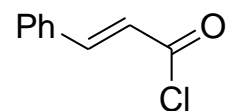
WCl₅, n-BuLi



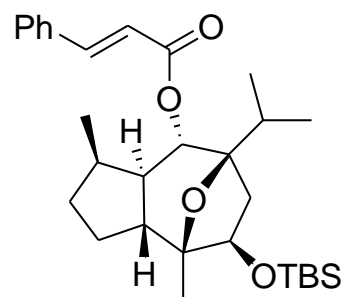
BHAr_F⁻



+ isomer (1:1)



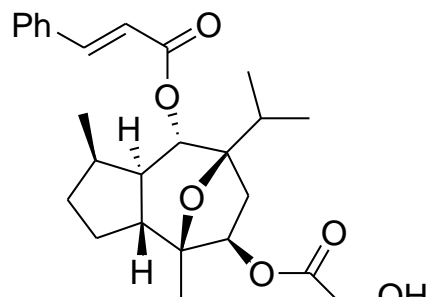
DMAP



TBAF

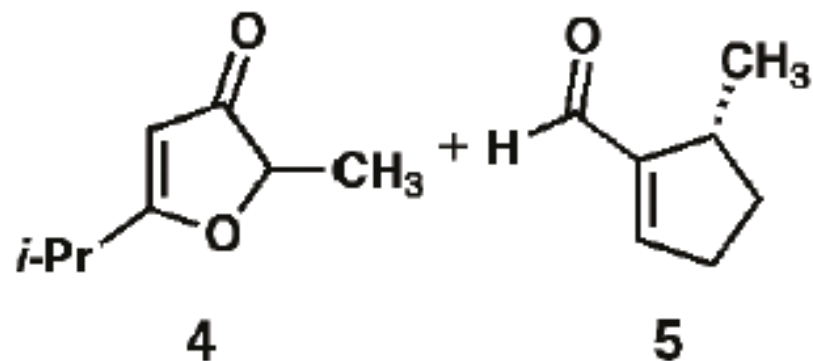
TBDPSO-CH₂-CO₂H
Yamaguchi protocol

then TBAF

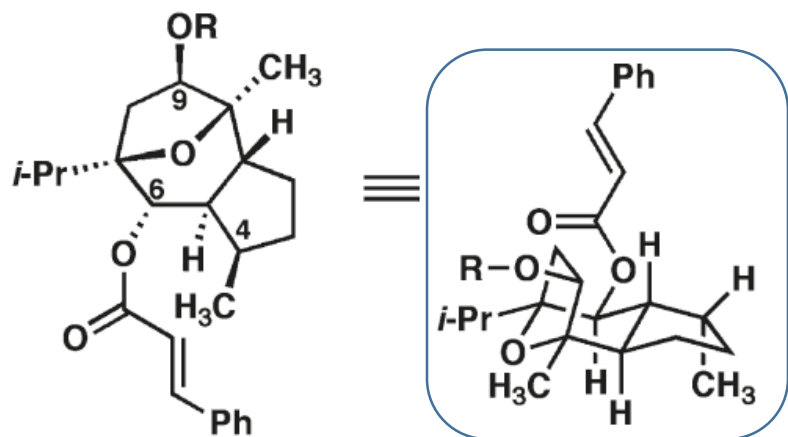


18 steps, 7% overall yield

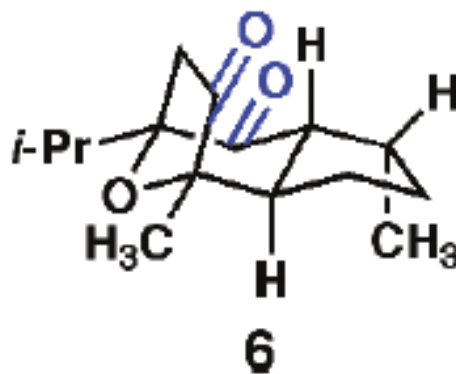
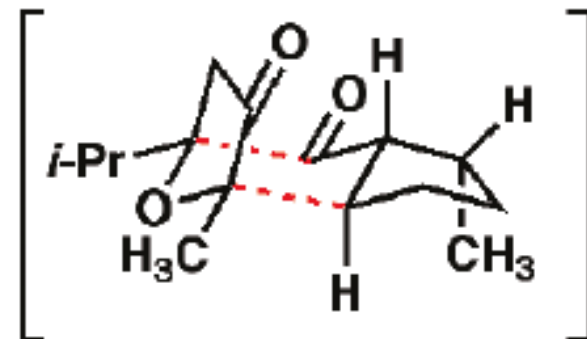
Chain's shortest synthesis



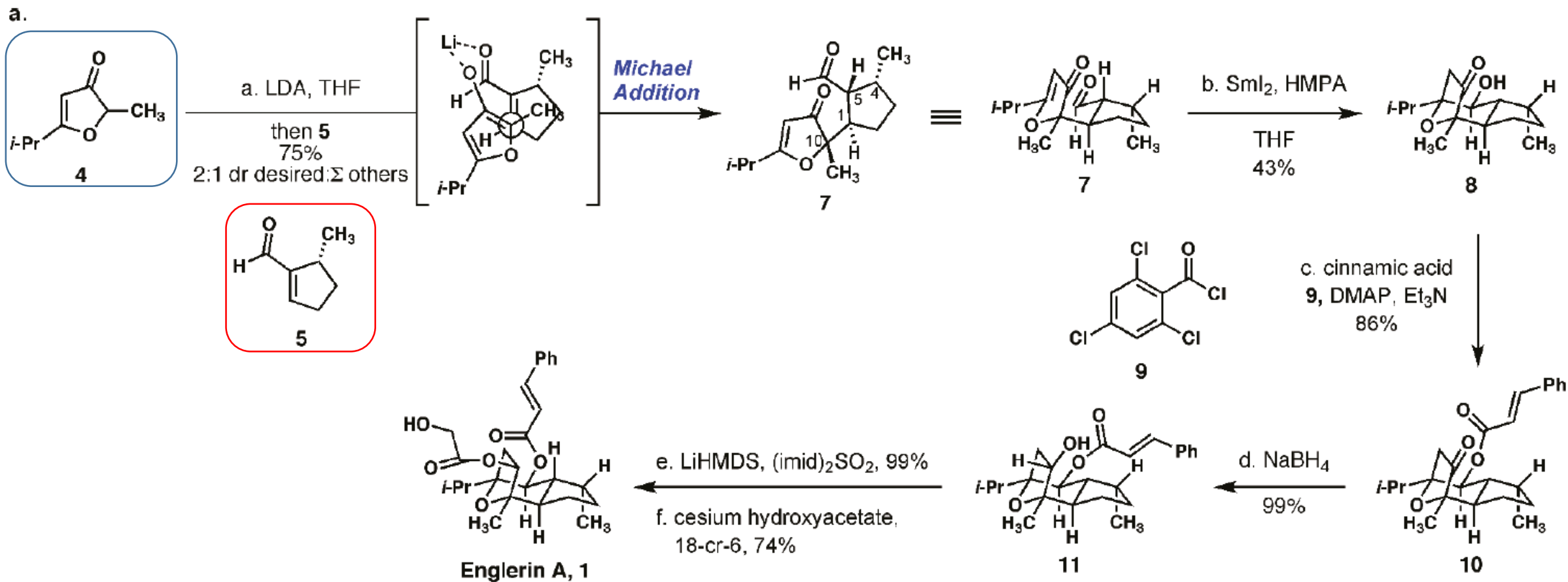
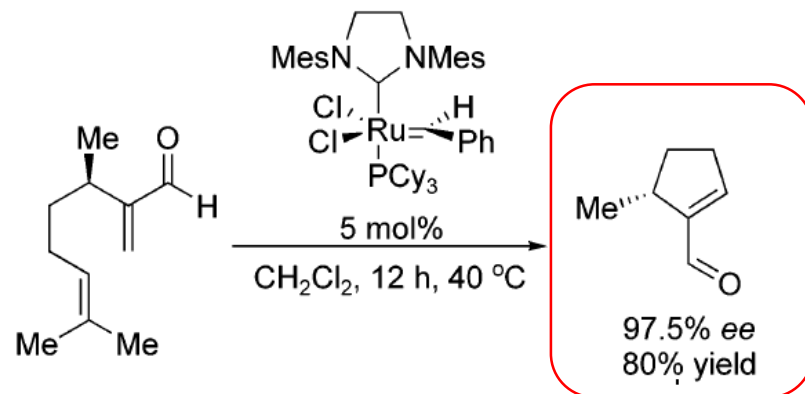
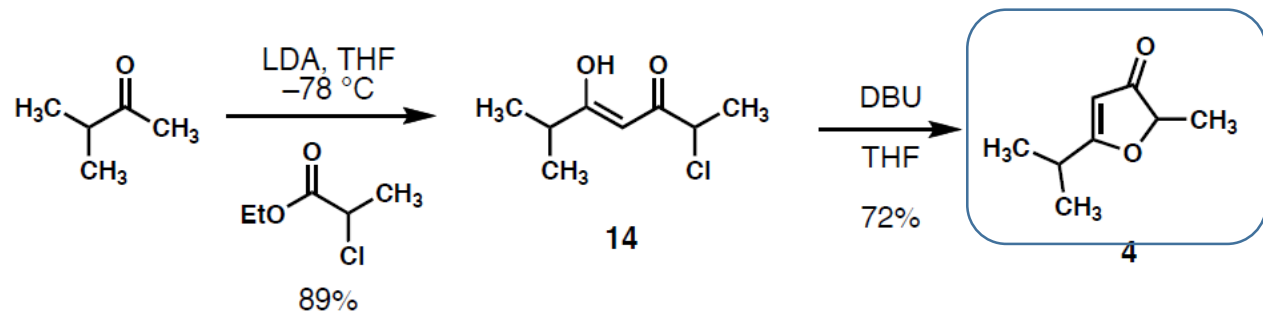
new aspect to see the molecule



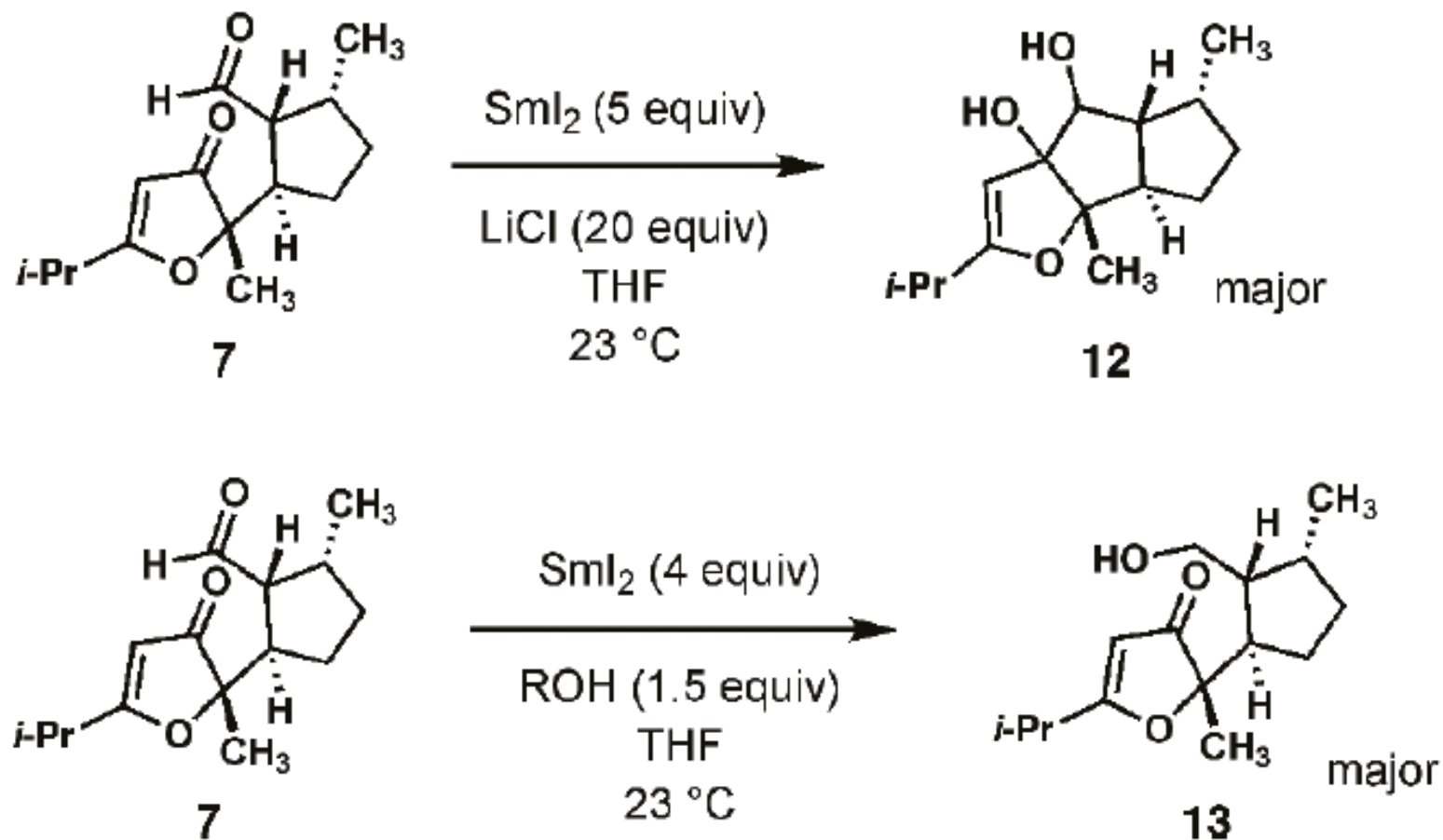
**Carbonyl-Enabled
Cyclization Sequence**



Chain's shortest synthesis



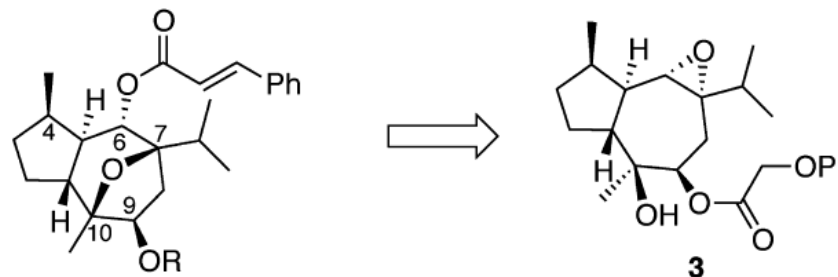
Chain's key SmI₂-mediated reaction; undesired products in different conditions



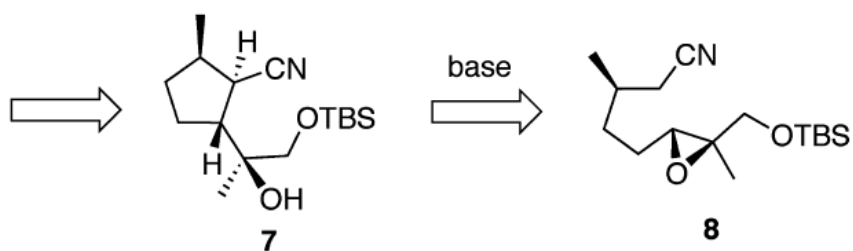
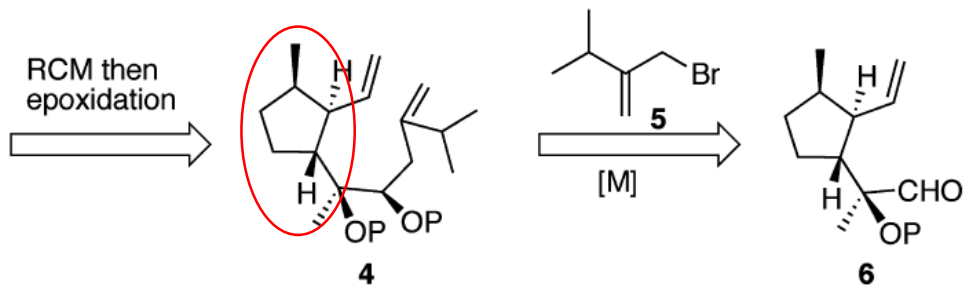
Also, intramolecular Stetter reaction did not give any product...

Hatakeyama's synthesis

Scheme 1. Retrosynthetic Analysis of Englerin A

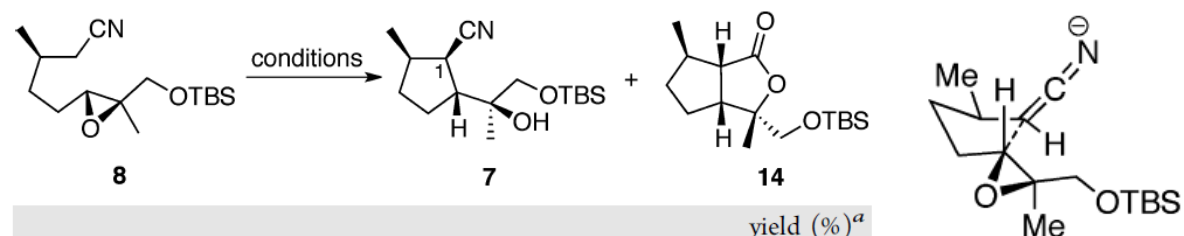
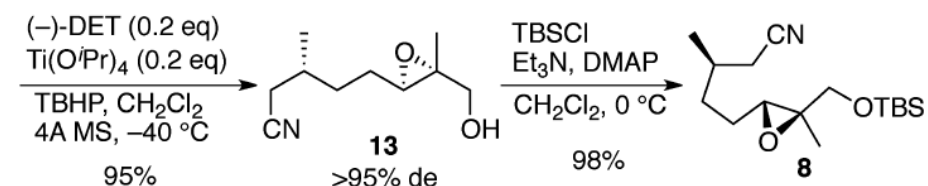
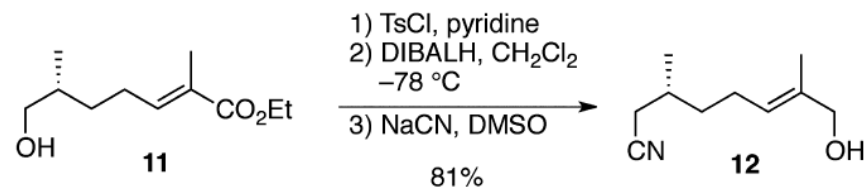
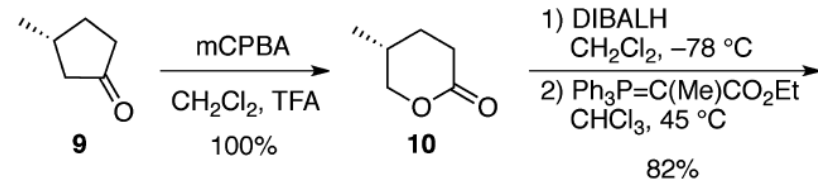


englerin A (1): R = C(=O)CH₂OH
englerin B (2): R = H



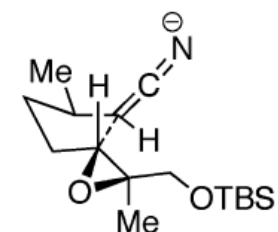
Similar work to Christmann's approach

\$85/ 1G
sigma

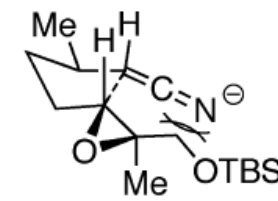


entry	conditions	yield (%) ^a	
		7	14
1	NHMDS (1.5 equiv), toluene, 0 °C, 6 h	46	0
2	NHMDS (3.0 equiv), toluene, rt, 6 h	46	4
3	KHMDS (1.5 equiv), toluene, 0 °C, 6 h	62	0
4	KHMDS (3.0 equiv), toluene, rt, 1 h	53	3
5	LHMDS (1.2 equiv), THF, 0 °C, 2 h	84 ^b	0
6	LHMDS (2.0 equiv), THF, 0 °C, 2 h	76 ^b	0
7	LHMDS (2.0 equiv), toluene-THF (2:1), 0 °C, 3 h	87	0

^aIsolated yield. ^bObtained as a 1:1 mixture of 7 and its C1-epimer.

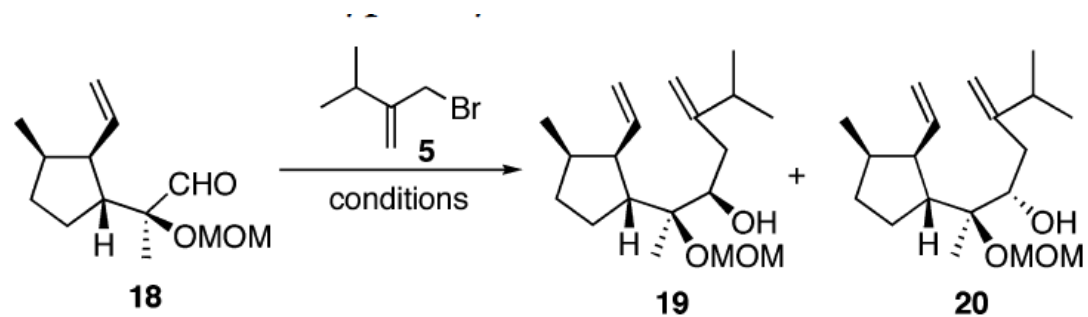
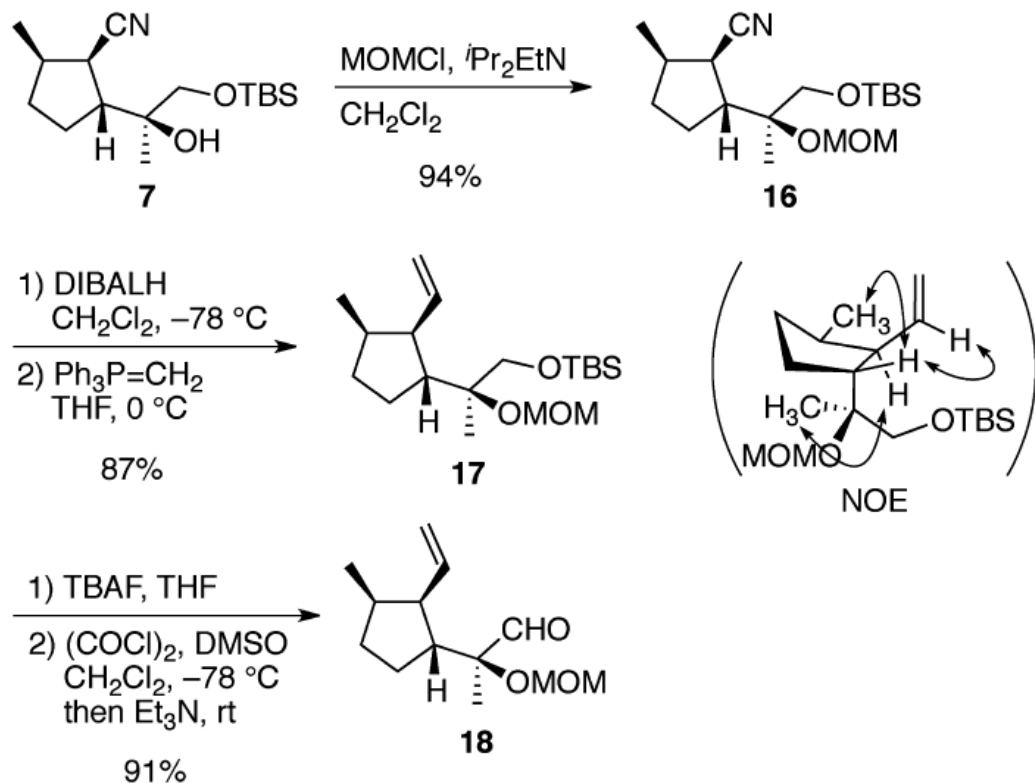


15a



15b

Hatakeyama's synthesis

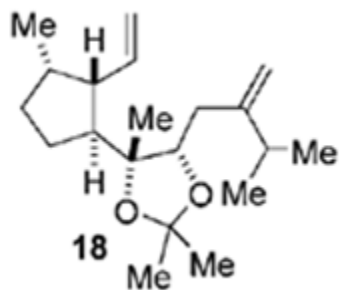
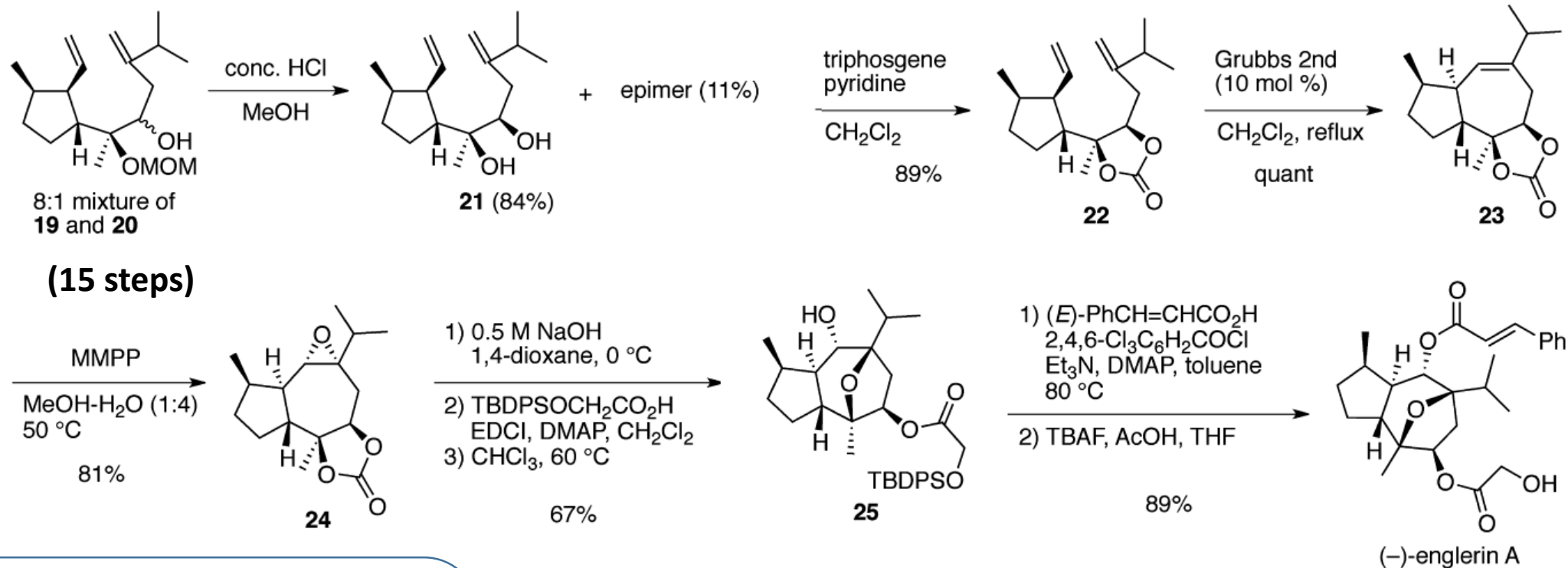


entry	conditions	yield (%) ^a 19 + 20	ratio 19:20 ^b
1	5 (2 equiv), Zn (3 equiv), aq NH ₄ Cl/THF, rt, 2 h; then sonication, rt, 1 h	47 (87)	1.5:1
2	5 (4 equiv), Zn (6 equiv), aq NH ₄ Cl/THF, rt, 2 h; then sonication, rt, 1 h	62 (97)	1.7:1
3	5 (4 equiv), Zn–Cu (6 equiv), aq NH ₄ Cl/THF, sonication, rt, 3 h	22 (44)	1:1
4	5 (4 equiv), CrCl ₂ (6 equiv), THF, rt, 3 h	82	1:1
5	5 (6 equiv), In (4 equiv), THF, 0 °C, 4 h	95	8:1
6	5 (4 equiv), In (4 equiv), InBr ₃ (4 equiv), THF, 0 °C, 12 h	30	8:1

^aThe yields in parentheses are based on the recovered aldehyde 18.

^bDetermined by ¹H NMR analysis.

Hatakeyama's synthesis

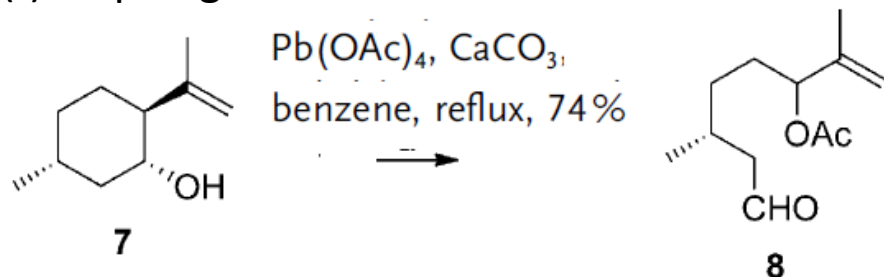


Christmann's intermediate (7 steps)

24 steps, 14% overall

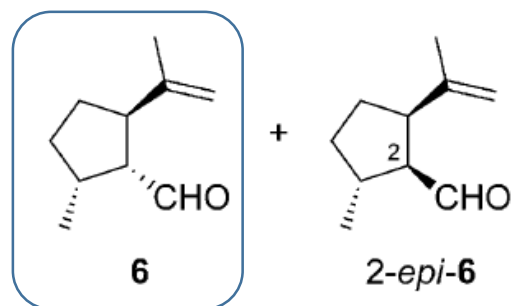
Metz's synthesis

(-)-isopulegol



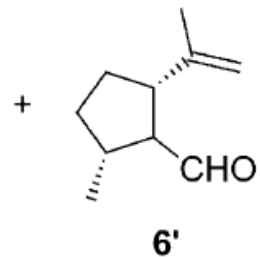
\$ 128/ 1Kg

5 mol% $[\text{Pd}(\text{PPh}_3)_4]$,
40 mol% pyrrolidine,
 Et_3N , THF, -10°C , 89%

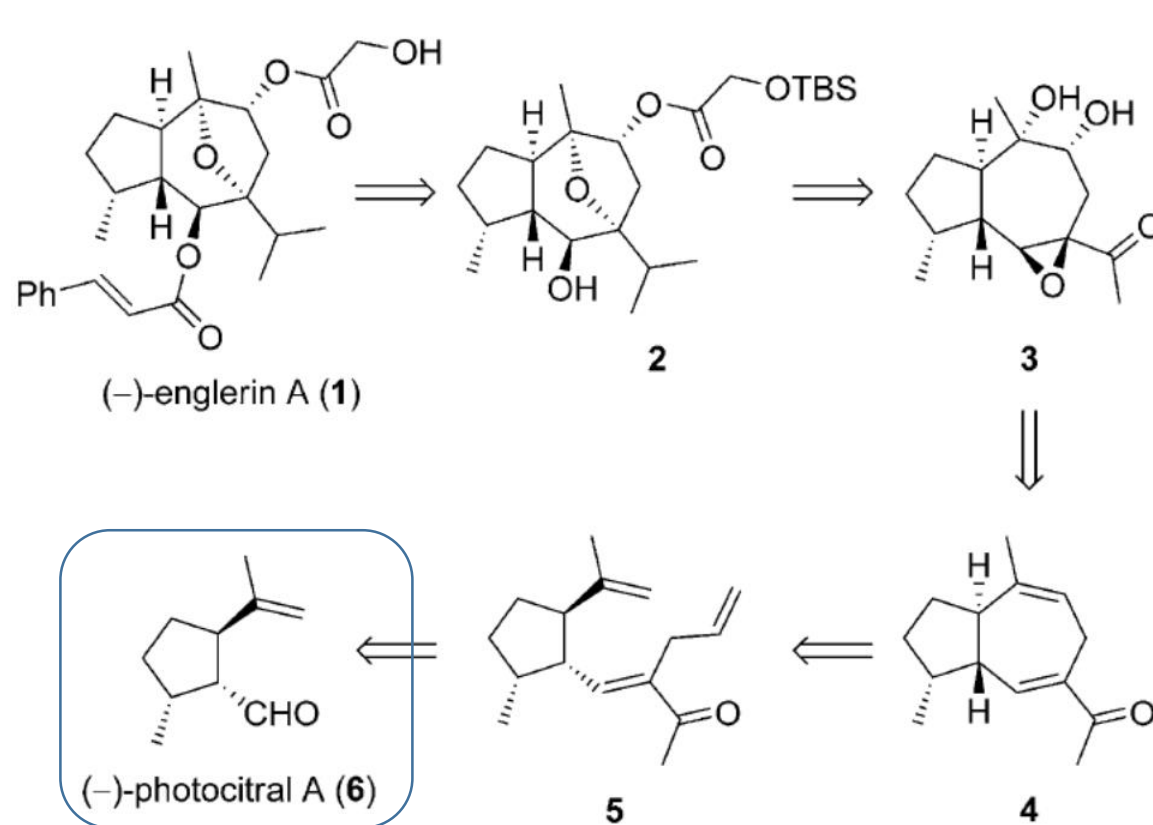


(-)-photocitral A

$6/2\text{-epi-6}/6' = 47:43:10$



Retrosynthesis

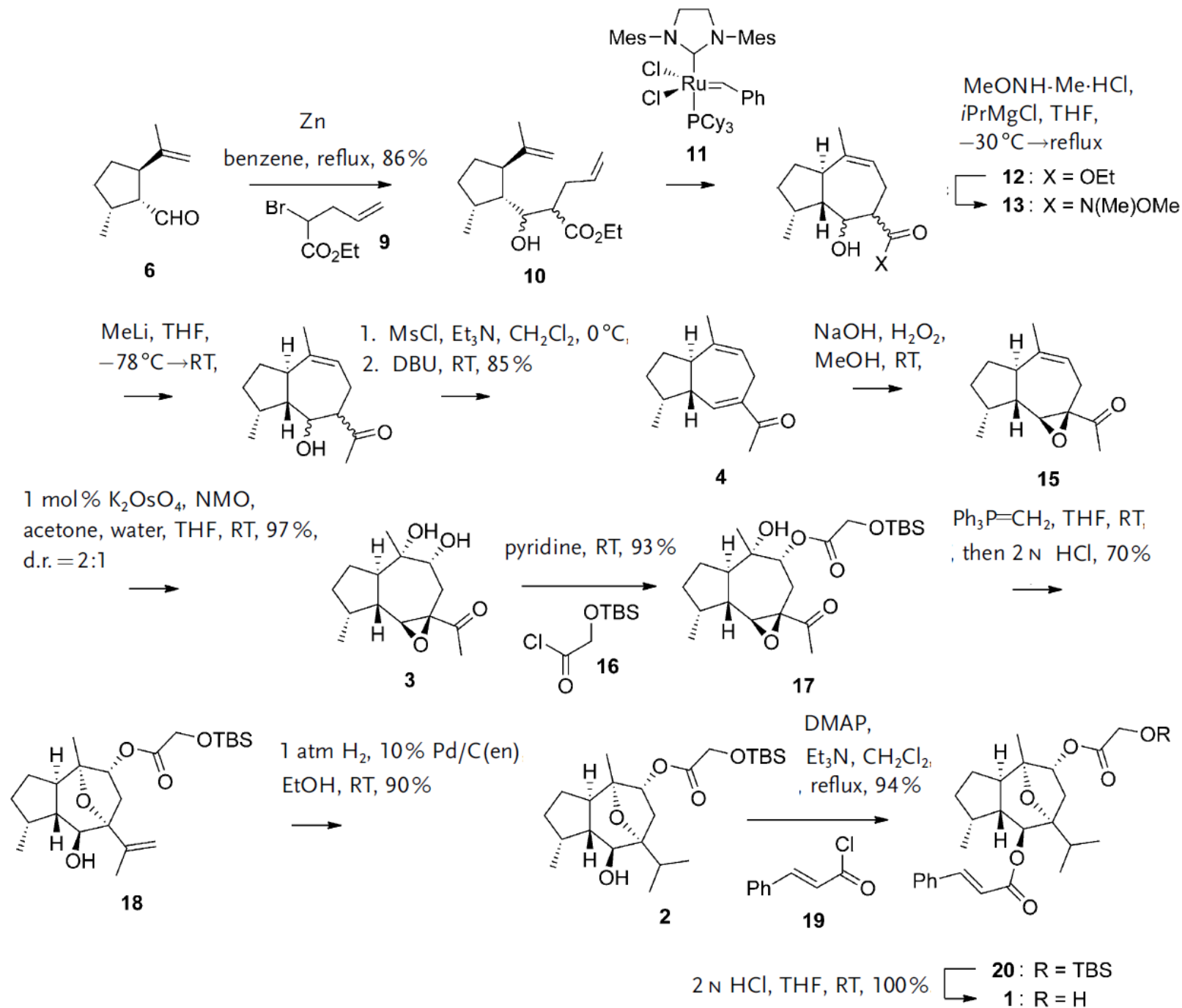


RCM + Chiral pool

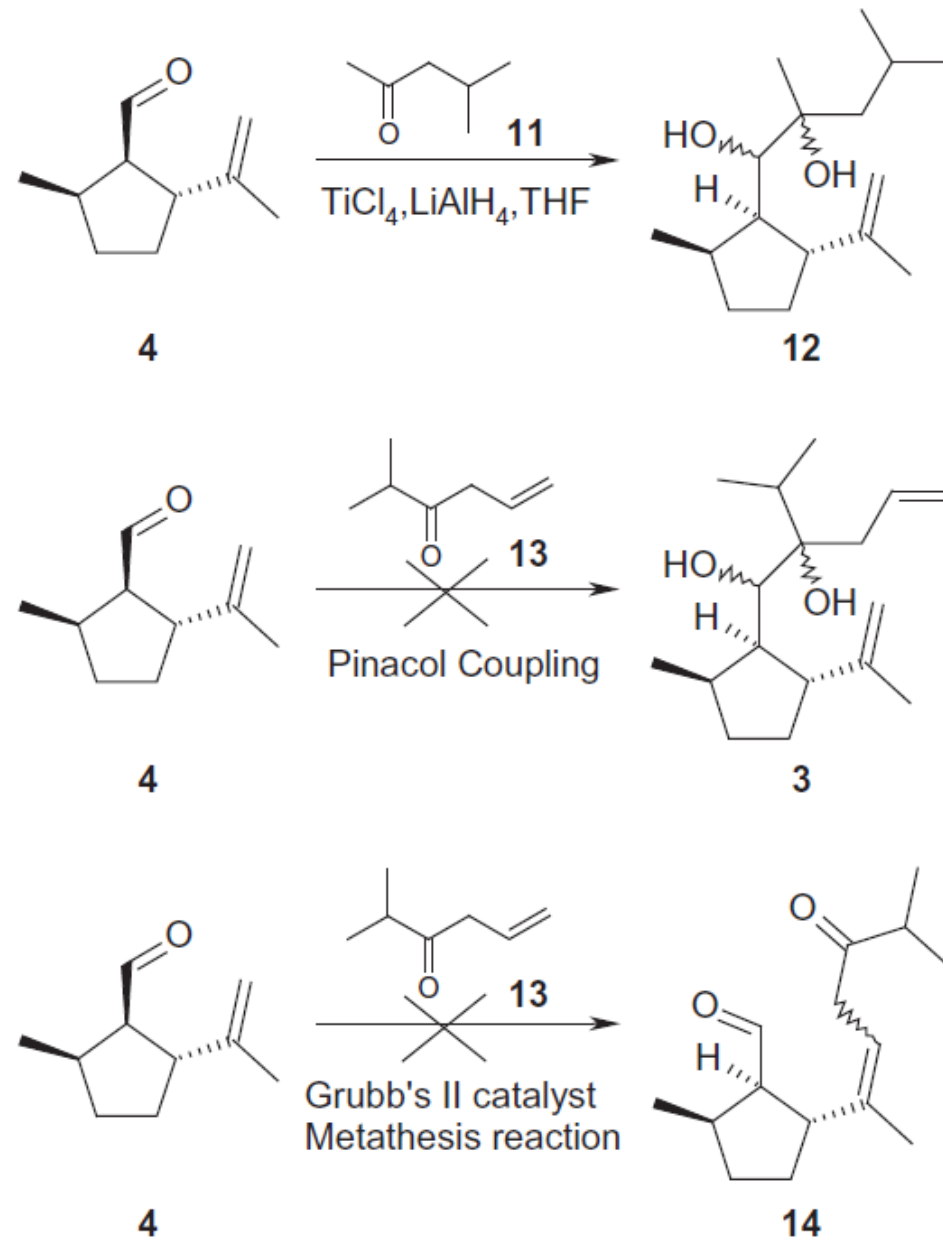
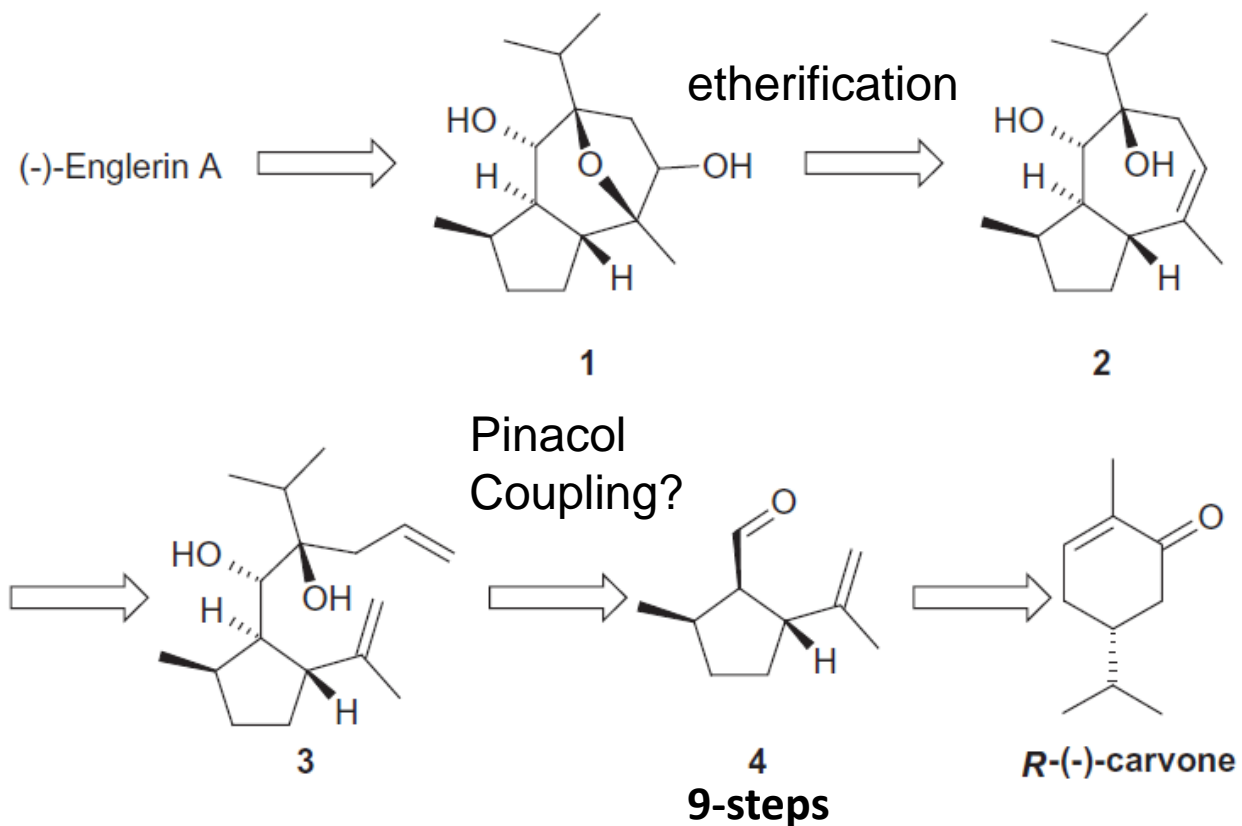
Metz's synthesis

12 steps from the known **6**

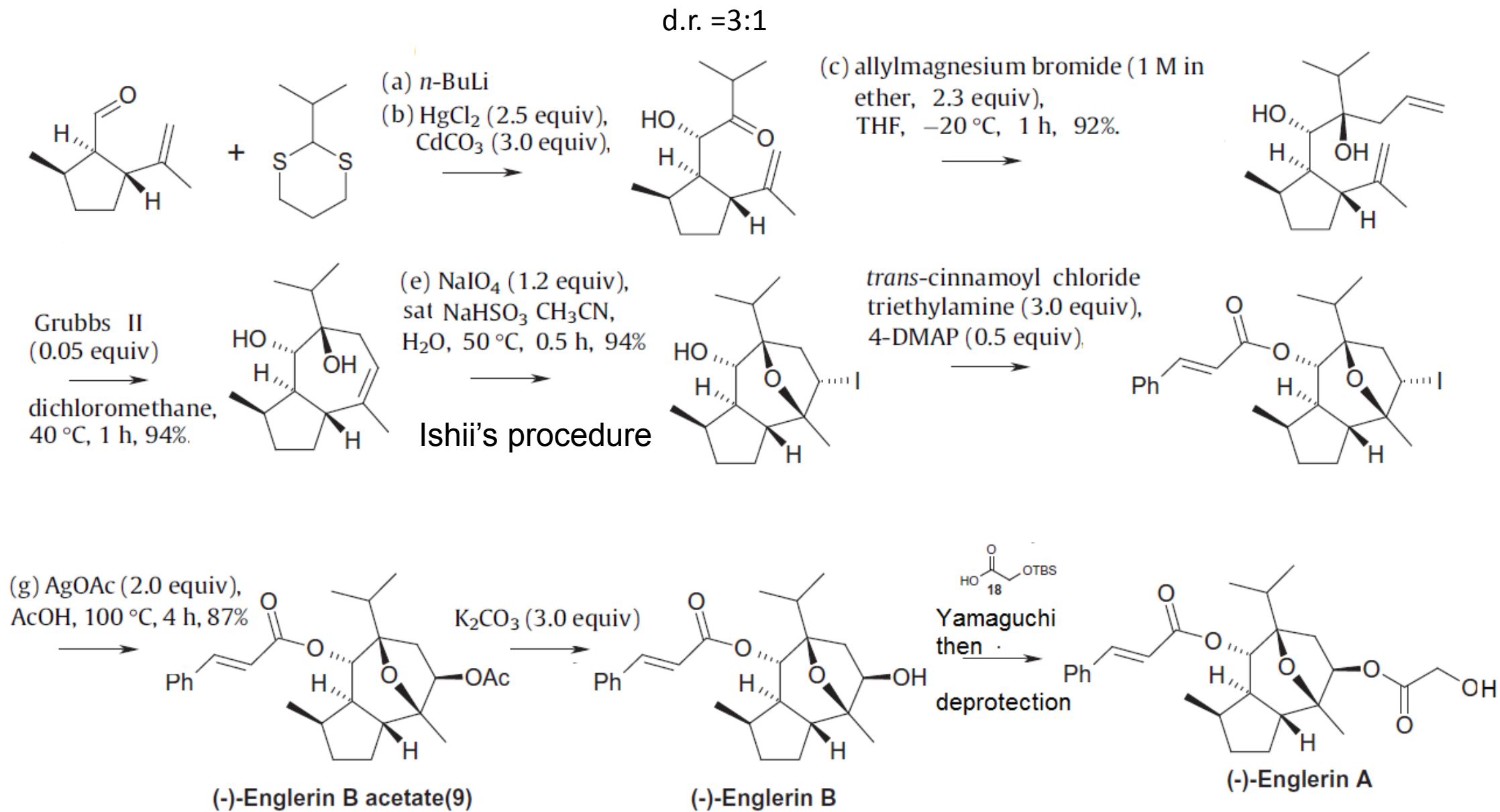
16% overall



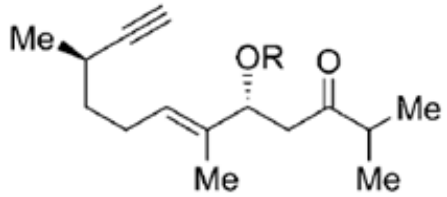
Shen's synthesis



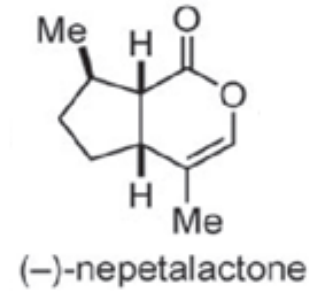
Shen's synthesis



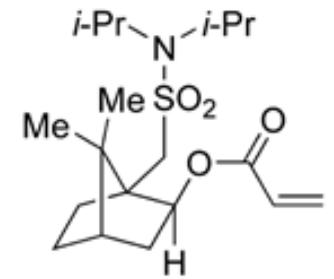
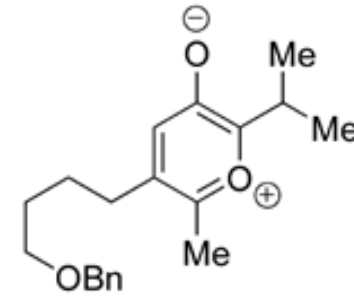
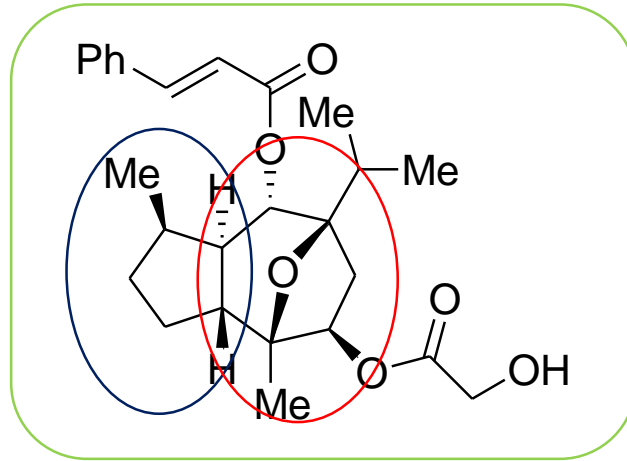
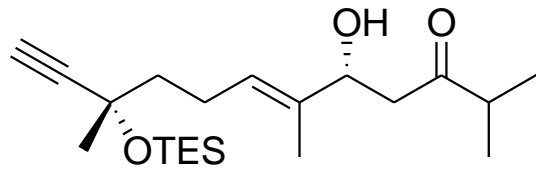
Summary of Total Synthesis



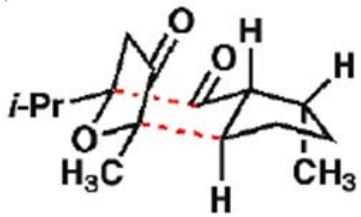
Ma and Echavarren
Gold-catalyzed cycloisomerization



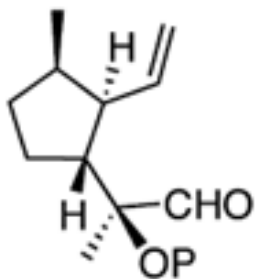
Christmann; **chiral pool**
RCM/Transannular
ring opening of epoxide



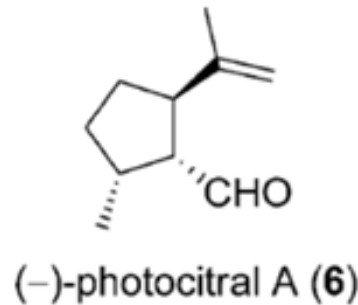
Nicolaou and Chen – [5+2] to give **oxabicycle**



Chain
Michael addition
reductive coupling



Hatakeyama
; **chiral pool**
RCM

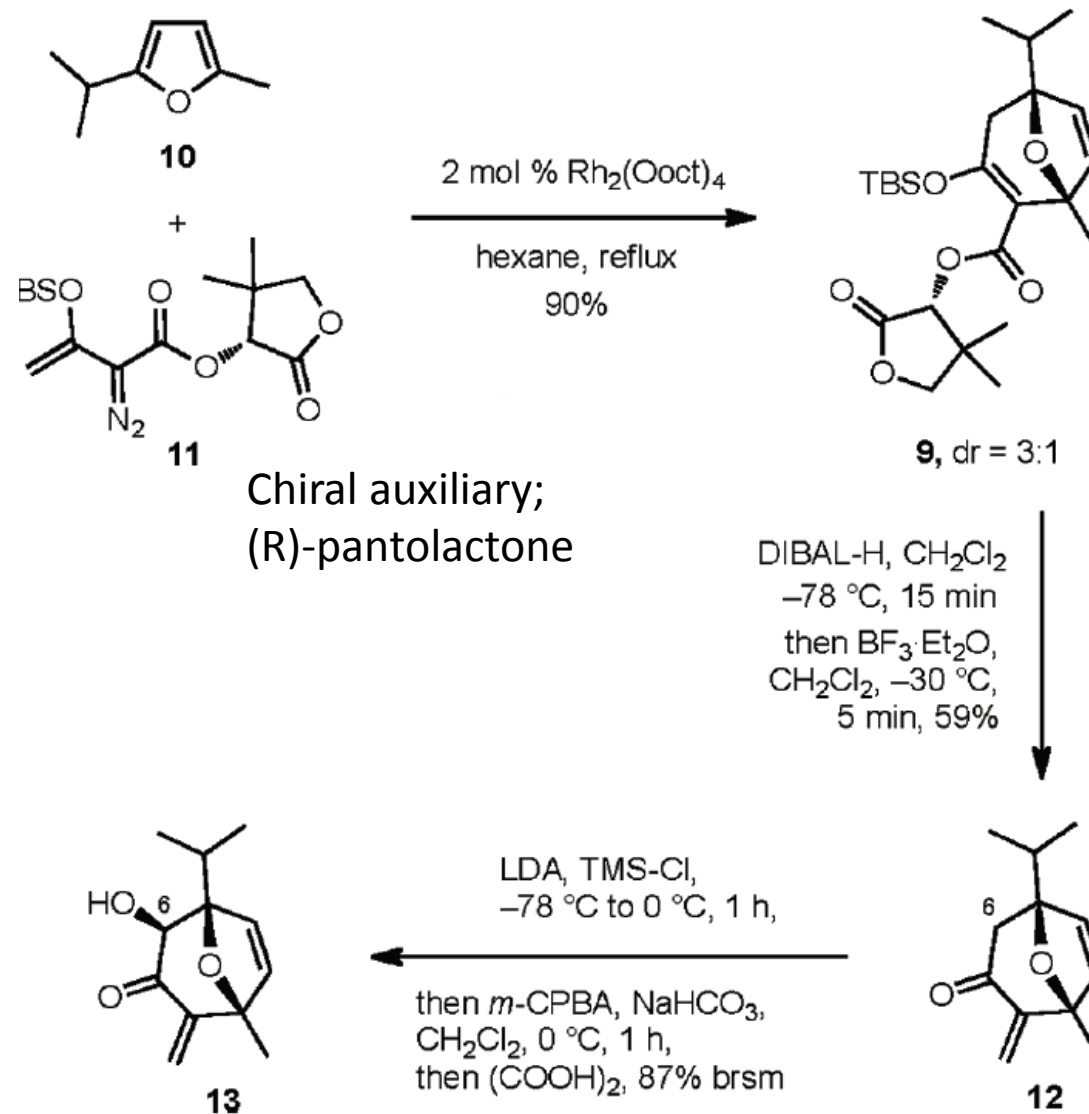
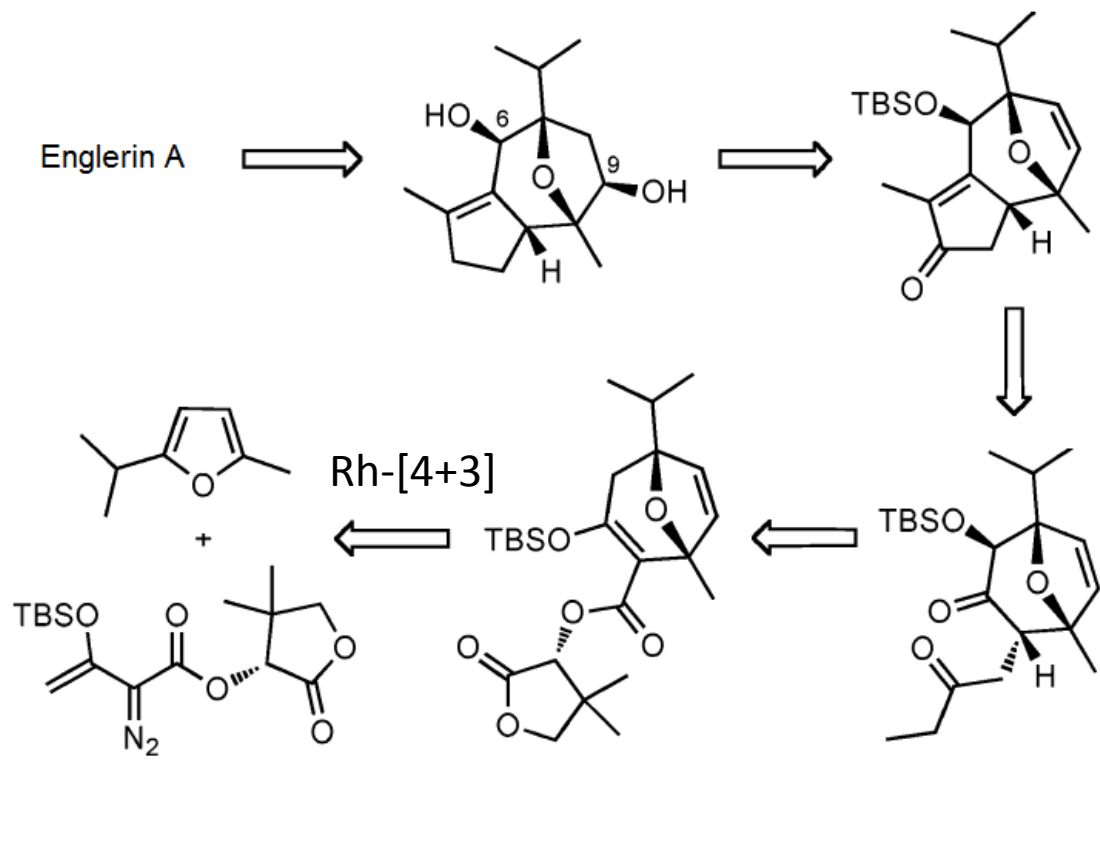


Metz;
chiral pool
RCM

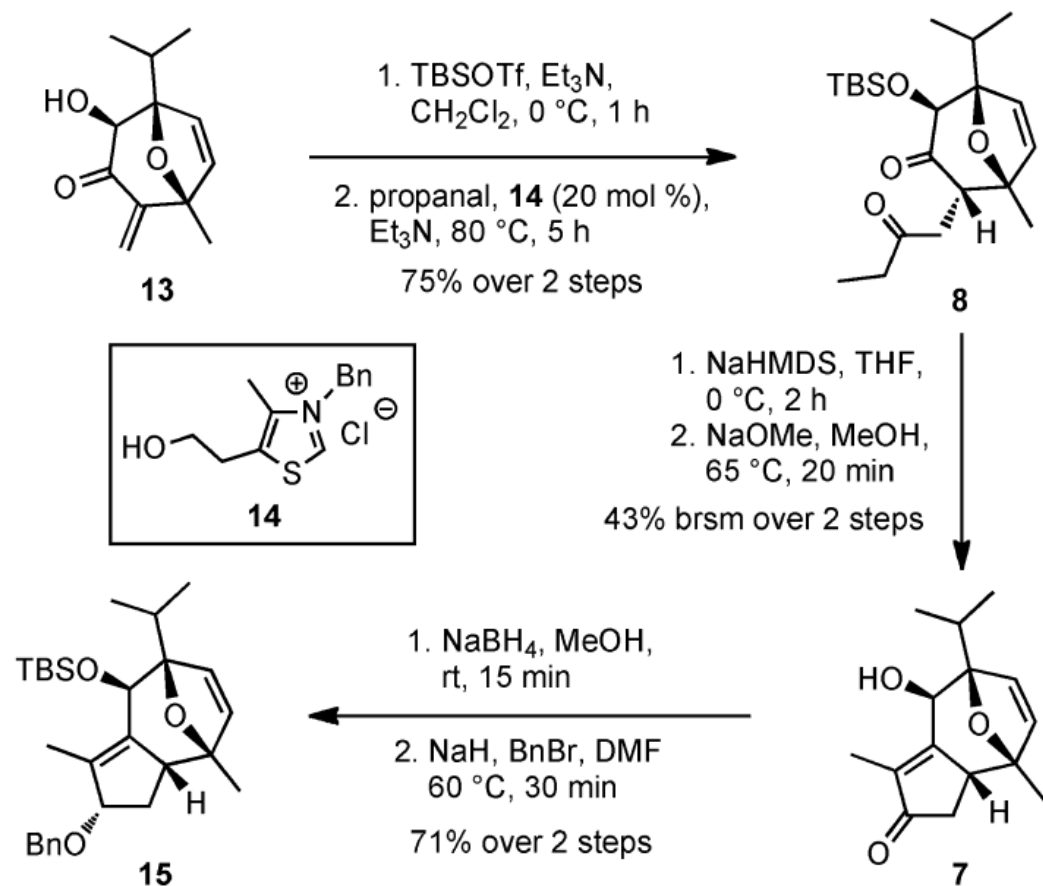
Shen;
Chiral pool from R(-)-Carvone
RCM; iodoetherification

Theodorakis' approach

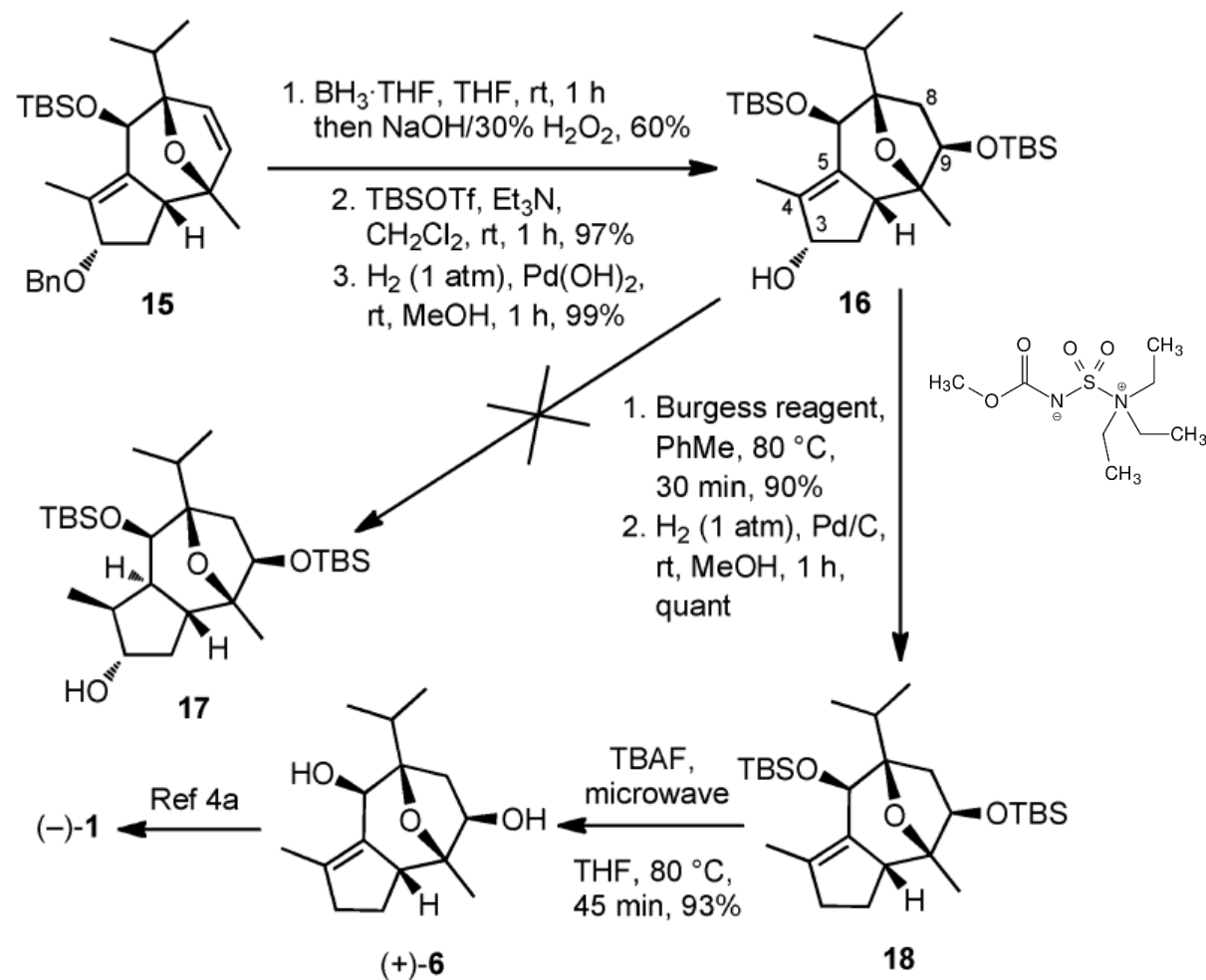
Rh-Catalyzed [4+3] cycloaddition



Theodorakis' approach

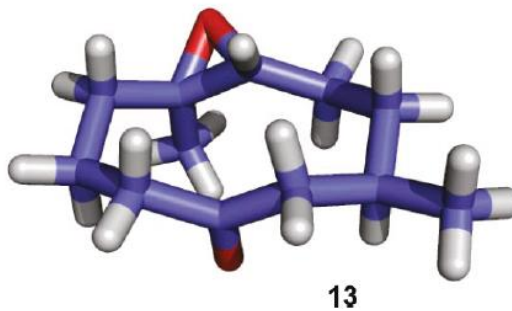
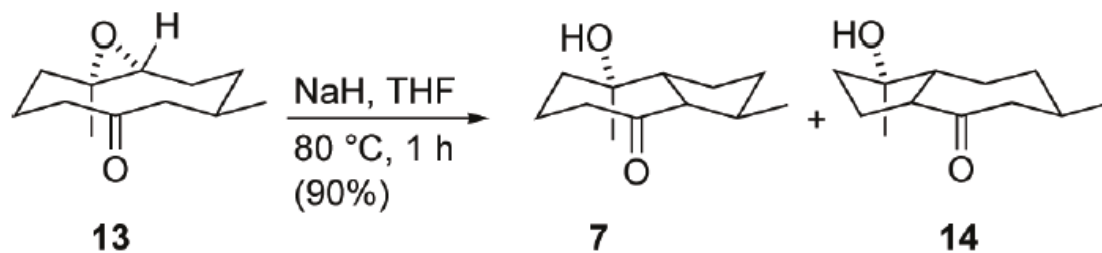
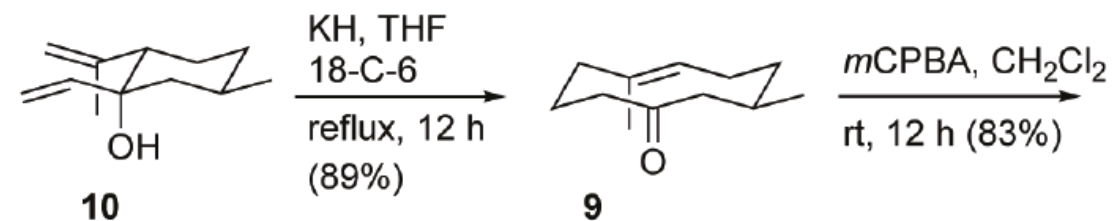
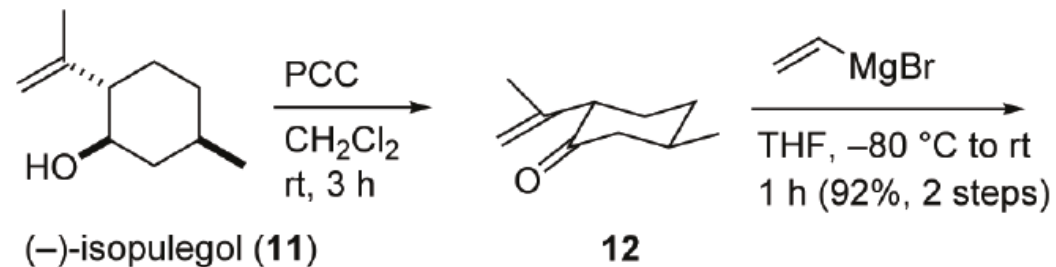
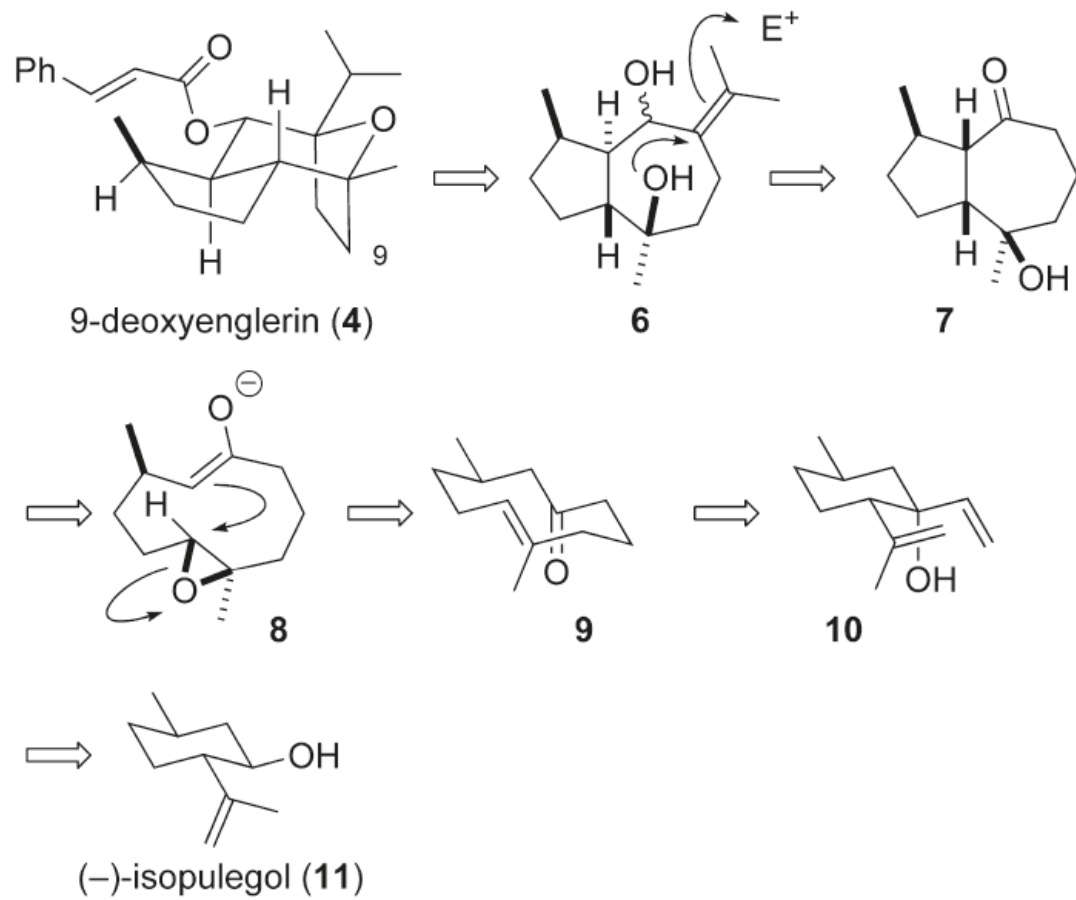


high pressure with various catalysts – not working

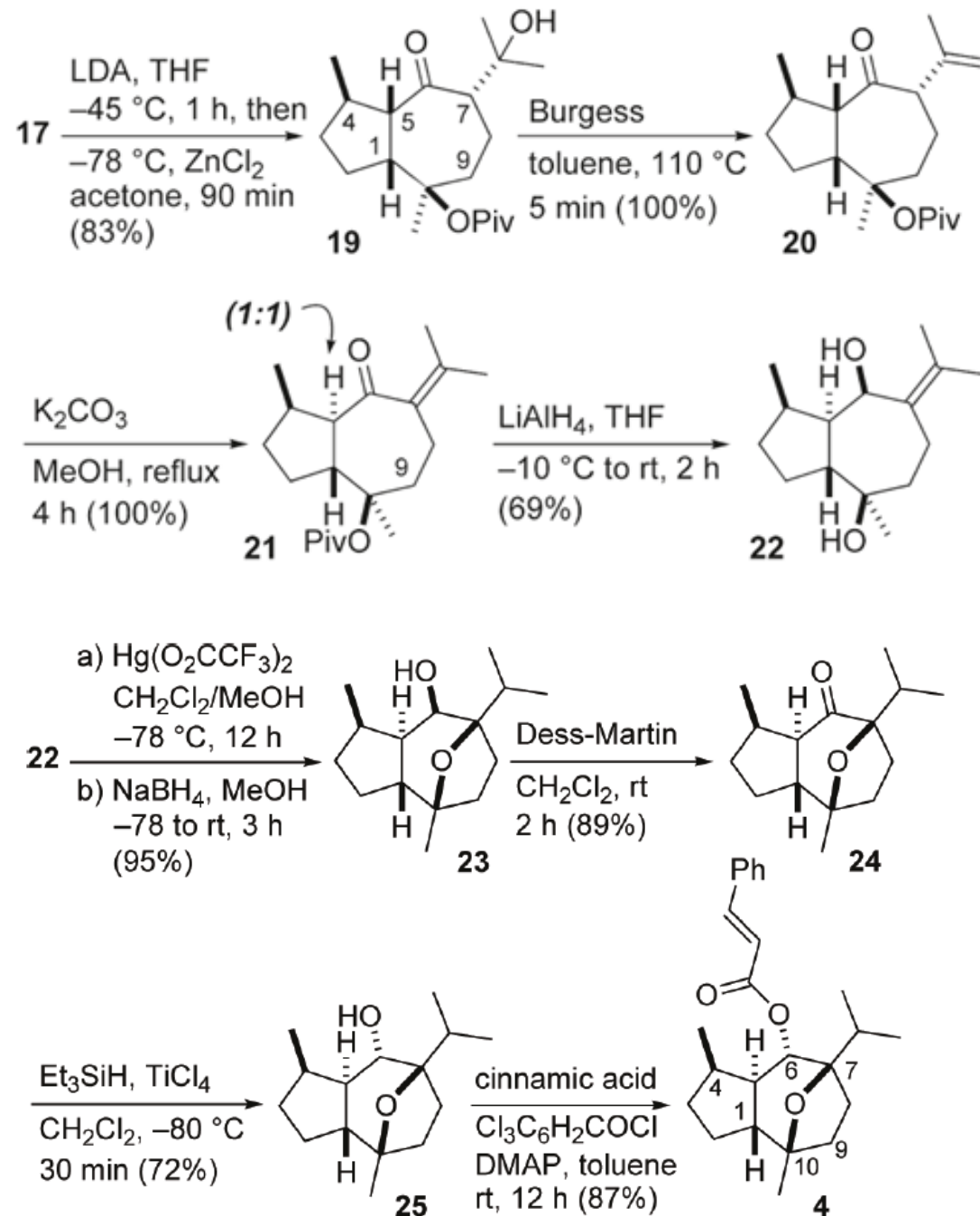
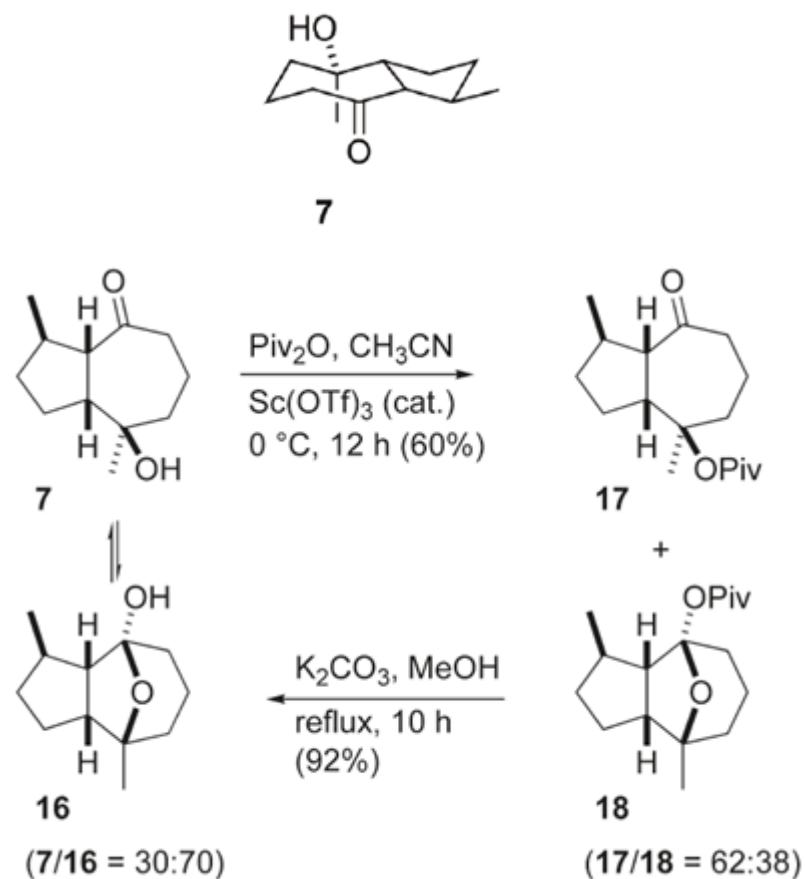


Ma's intermediate

Maier's approach

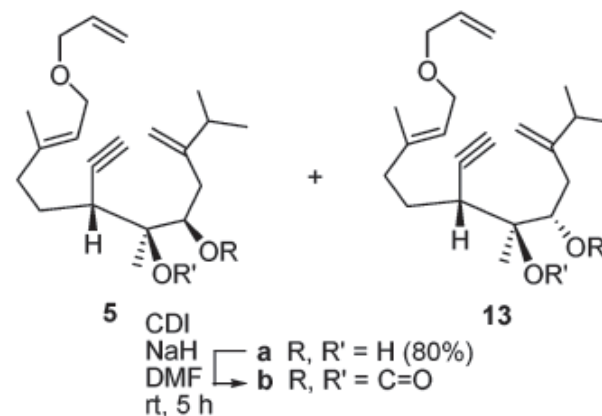
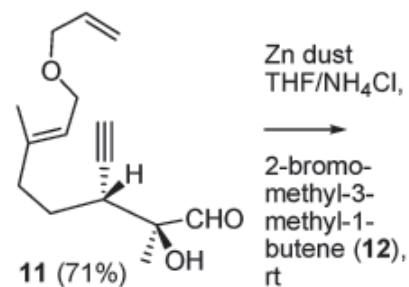
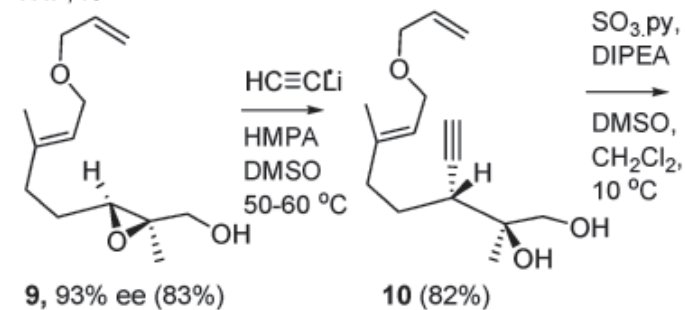
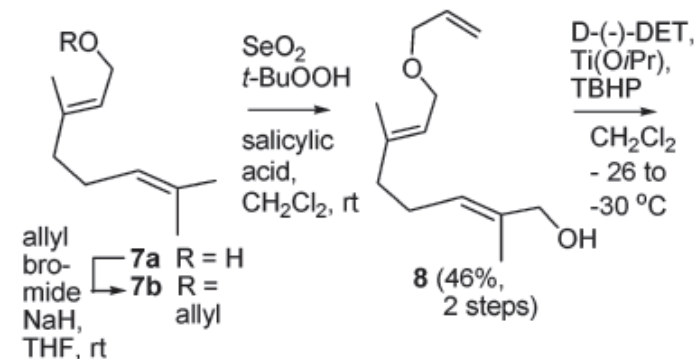
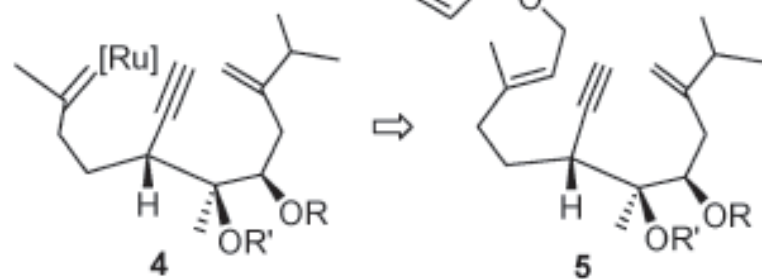
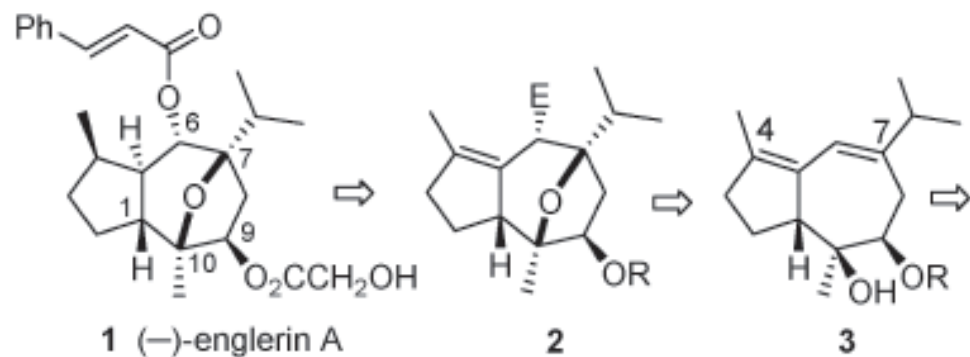


Maier's approach

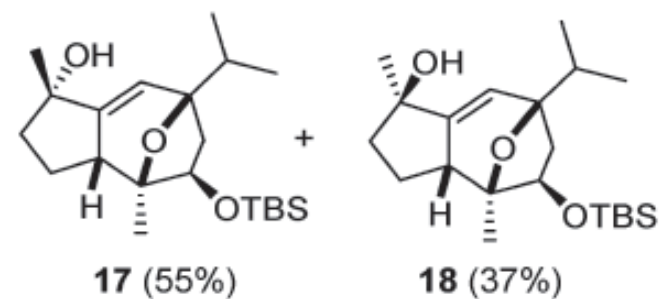
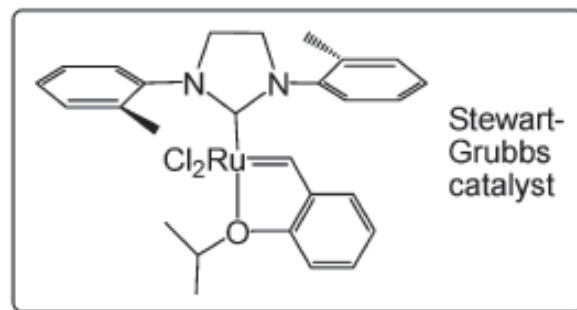
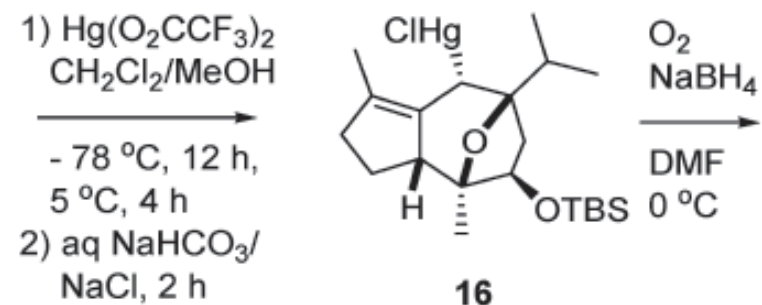
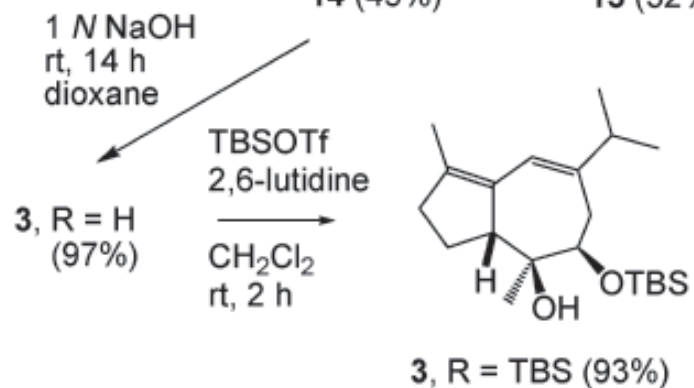
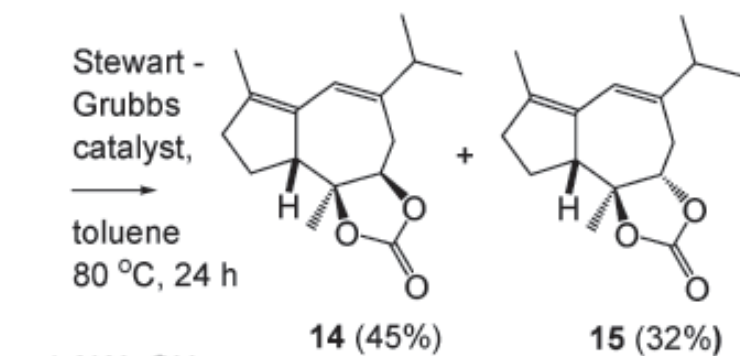
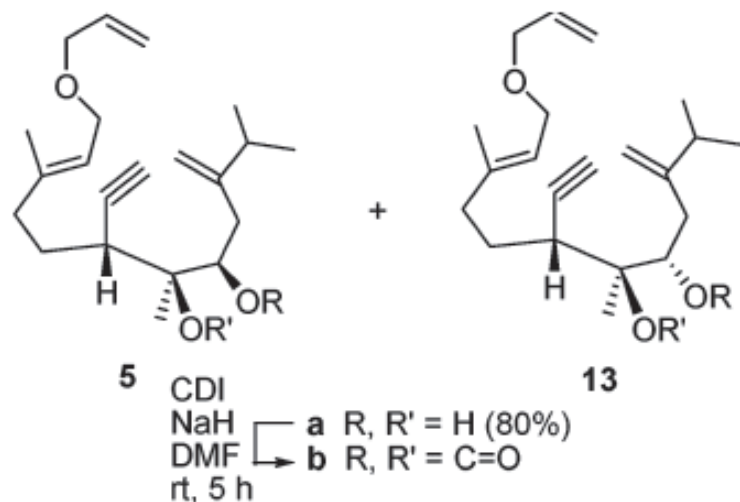


Parker's approach

Retrosynthesis



Parker's approach

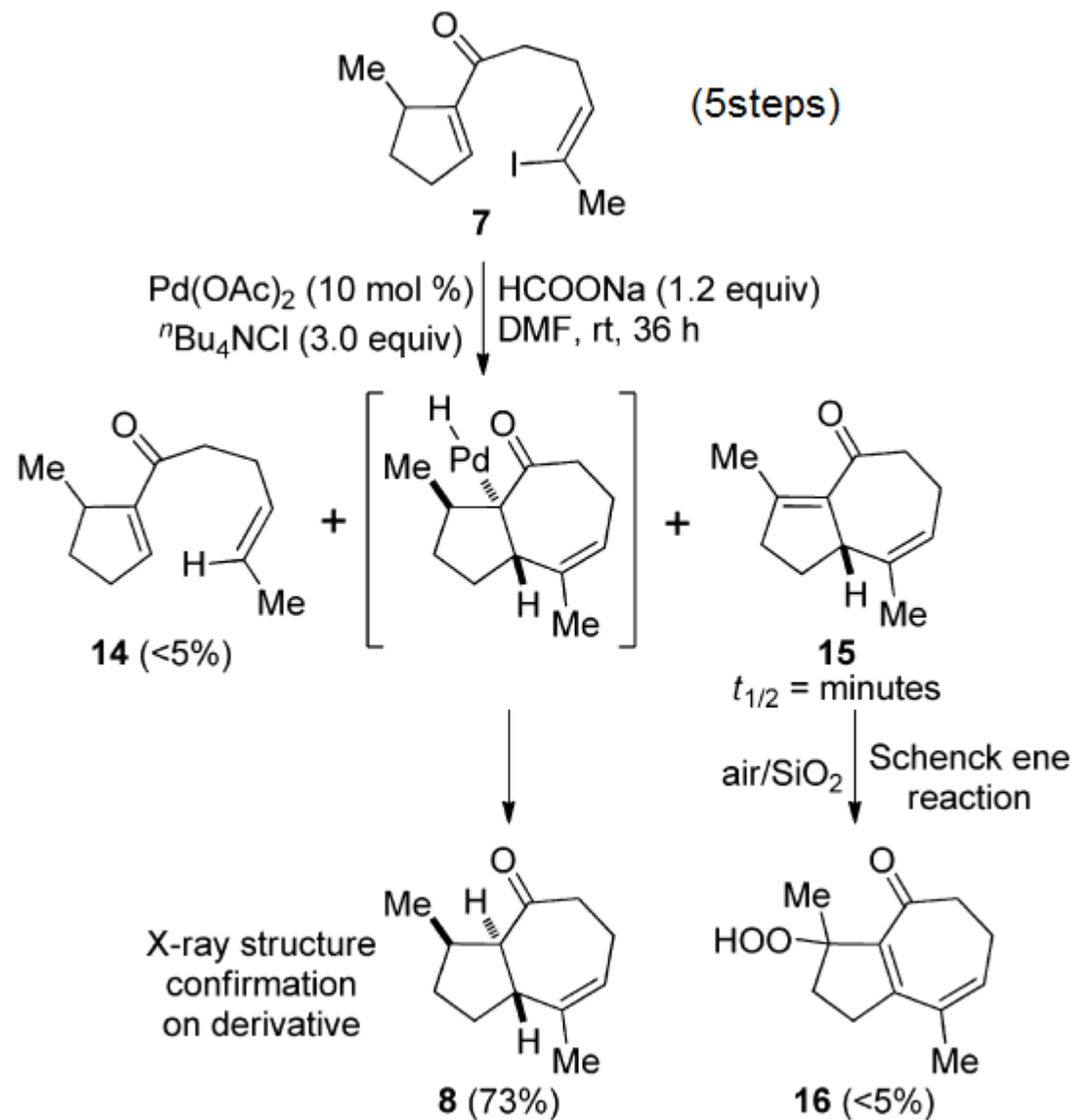
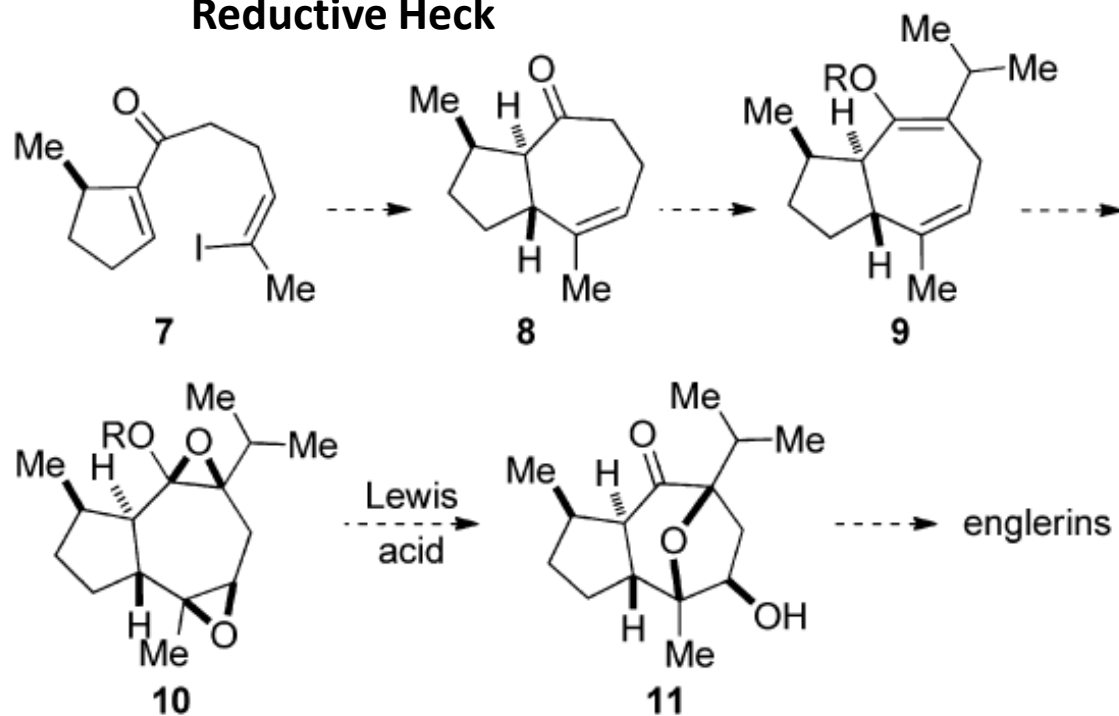


12 steps yields from **3**, R = TBS.
Echavarren intermediate

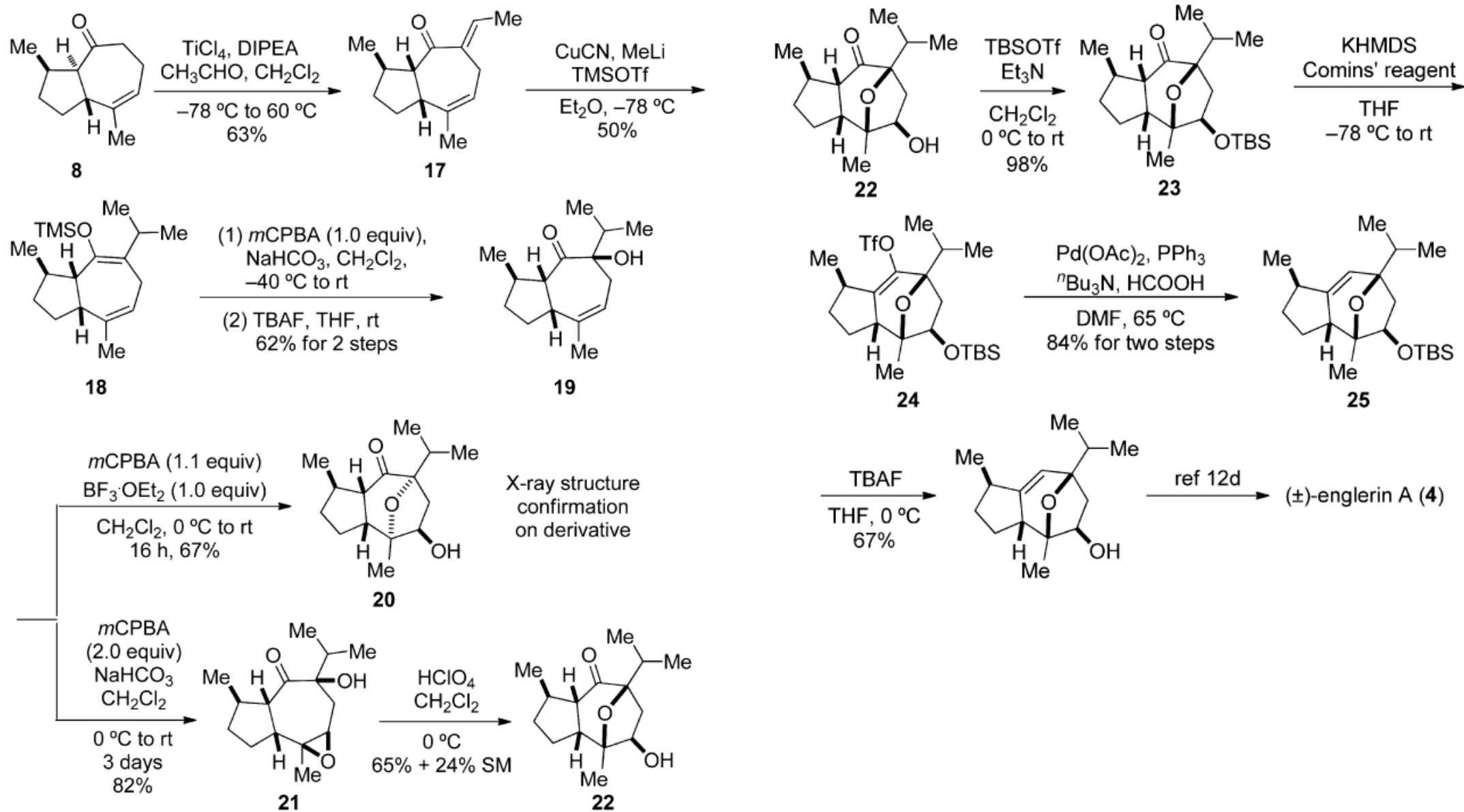
Cook's approach

Plan

Reductive Heck

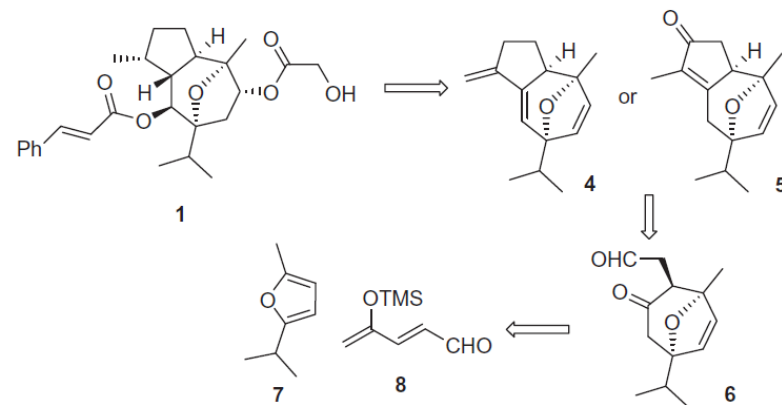
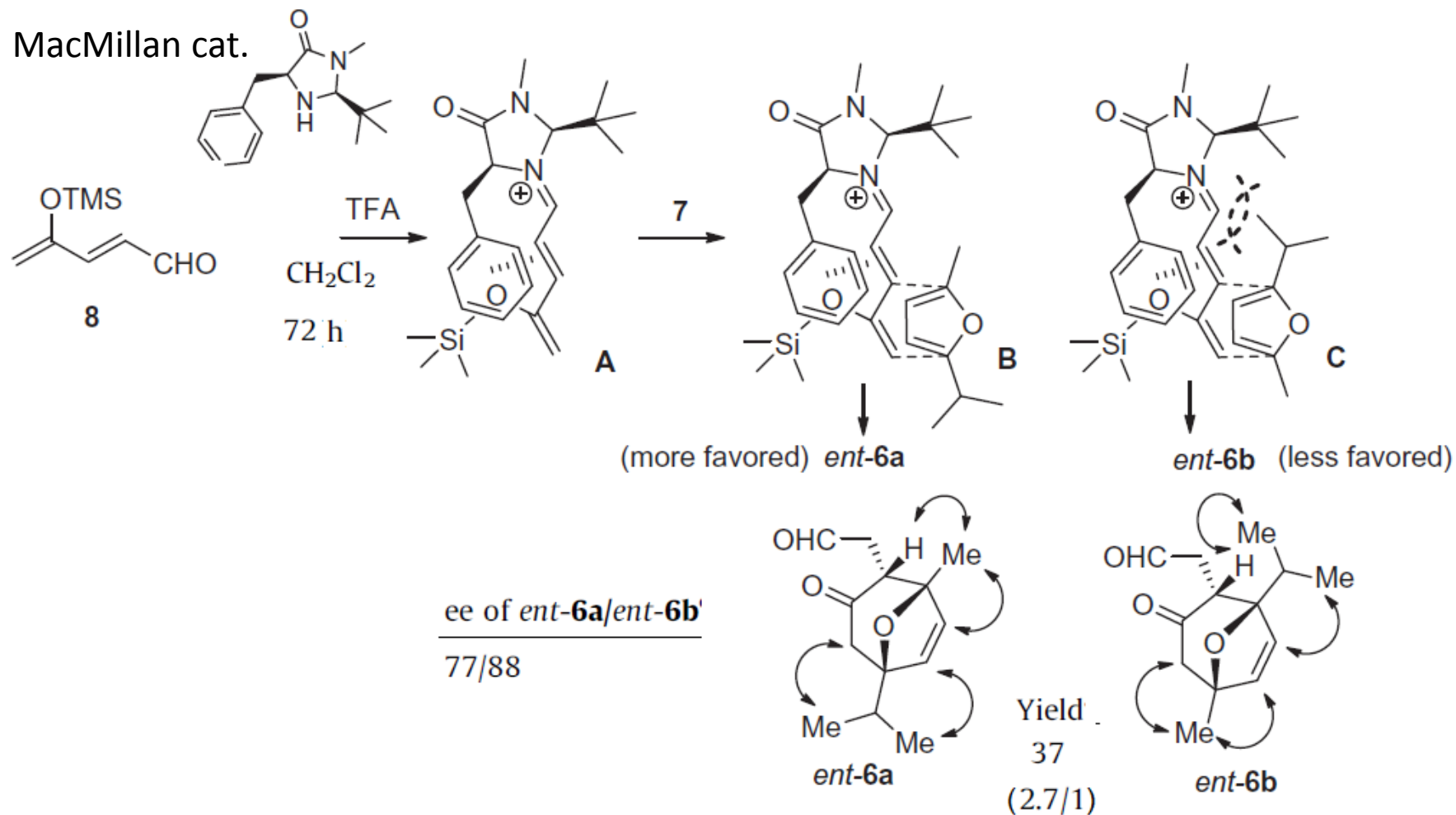


Cook's approach



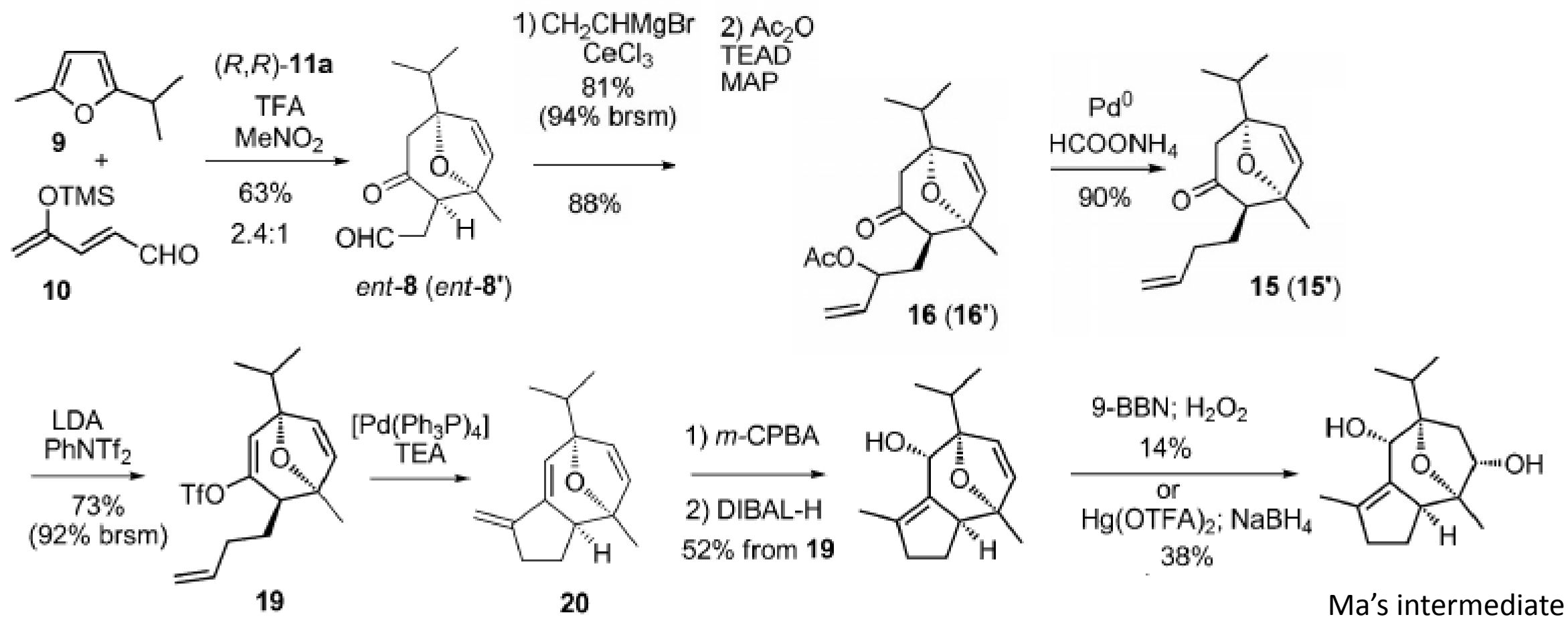
Lin's approach to (+)-englerin A

Organocatalytic [4+3]



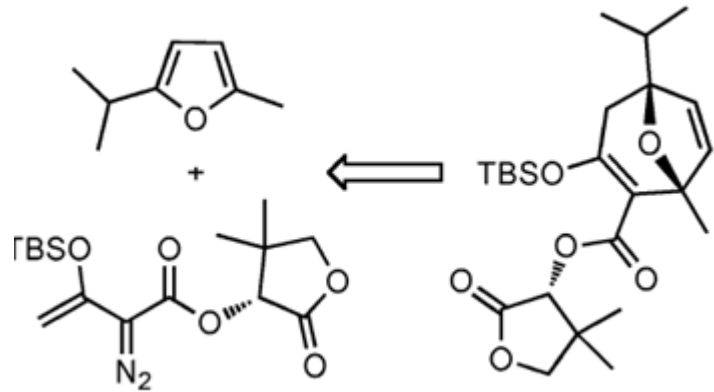
Harmata's procedure
JACS, 2003, 125, 2058-2059.

Lin and Shang's approach

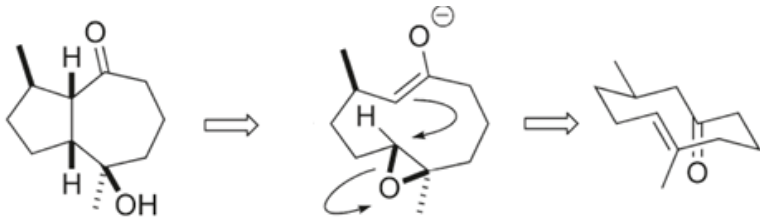


Summary of Formal Total Synthesis

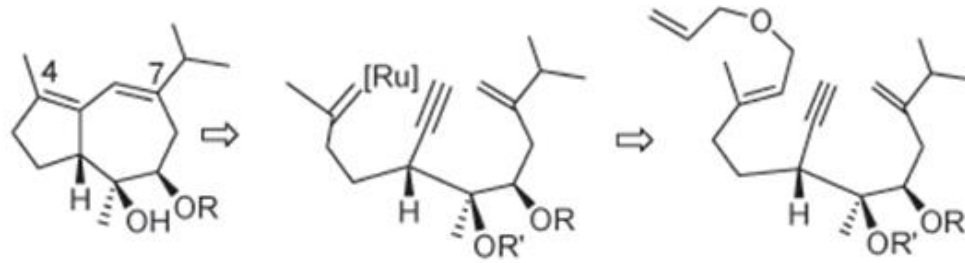
Theodorakis: **Rh-catalyzed [4+3]**



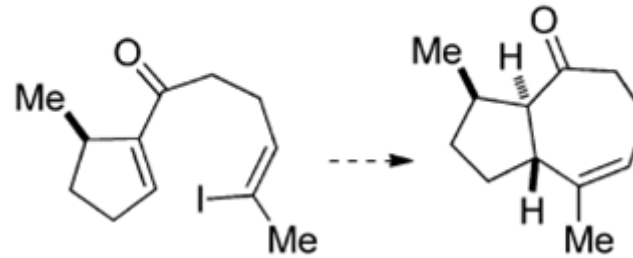
Maier: **epoxide ring opening**



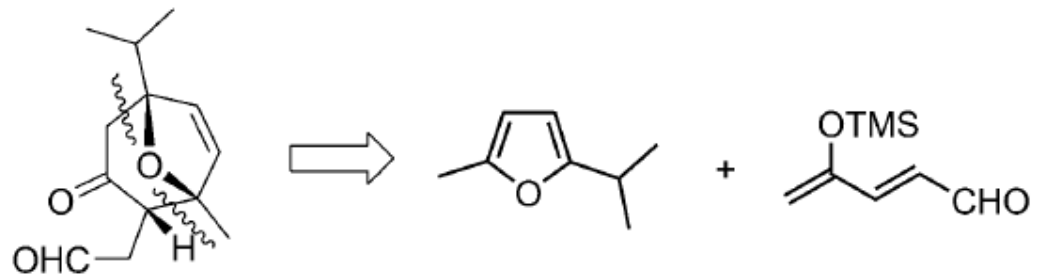
Parker: **relay RCM**



Cook: **reductive Heck reaction**

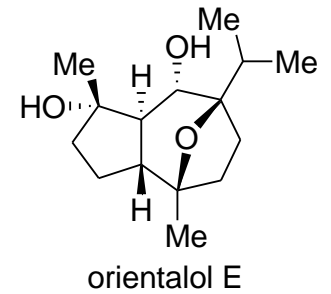
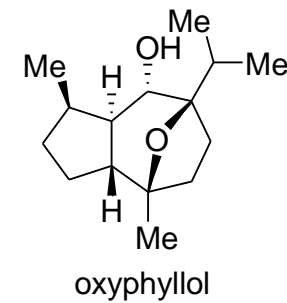
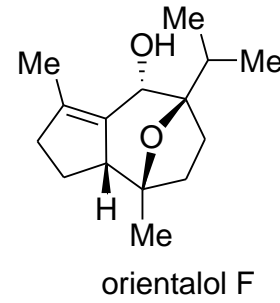
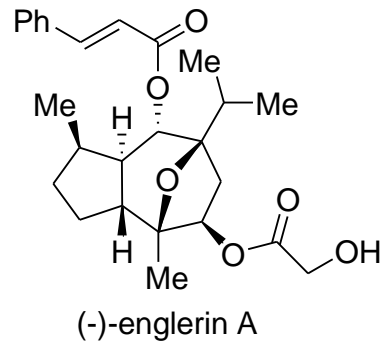


Lin and Shang: **organocatalytic [4+3]**

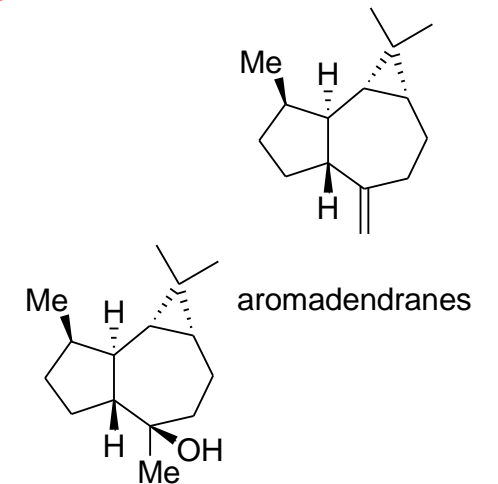
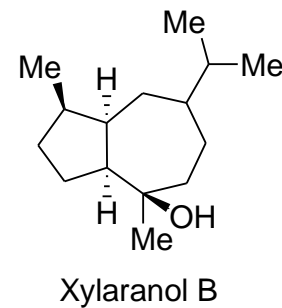
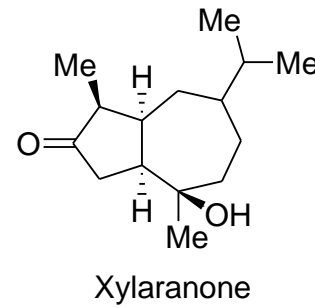
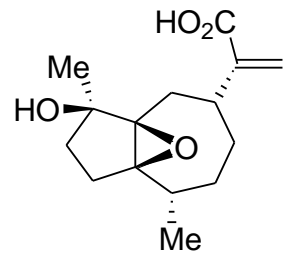
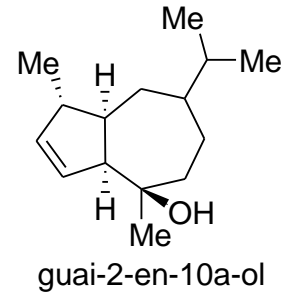
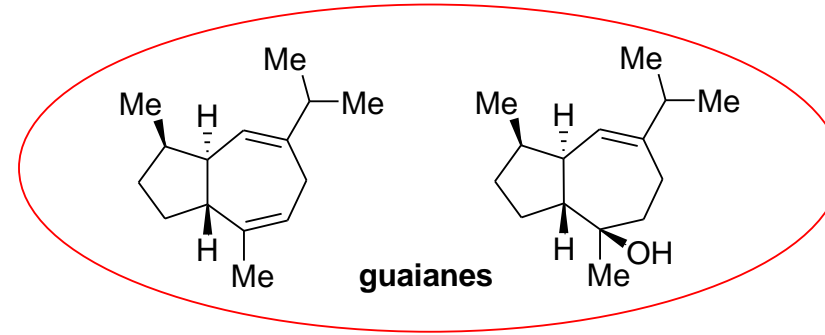
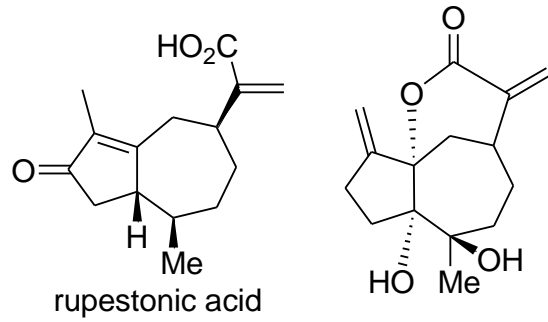


Direct C-H Oxidation?

Yes, we can find an opportunity for site-selective and stereoselective biomimetic procedure.



[5,3,0]bicyclic structure



Q&A
You have
Questions
We have
Answers

Thank You!



