The Story of the Clavilactones

Total Synthesis of Clavilactones

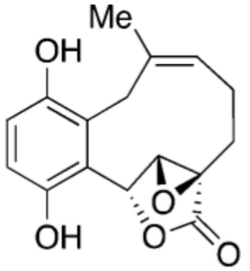
Takao *et al.* 2018

Overview

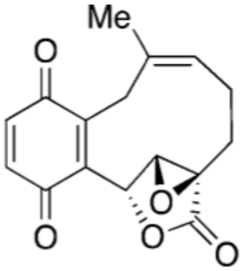
- Clavilactone Natural Products
- Previous Syntheses
  - Barrett (2006)
  - Leiyang (2014)
  - Suizu (2014)
- Their Original Synthesis (2013)
  - Total Synthesis of (+)-Clavilactone A and (-)-Clavilactone B by Ring-Opening/Ring-Closing Metathesis
  - An Impossible Epoxidation

Clavilactone Natural Products

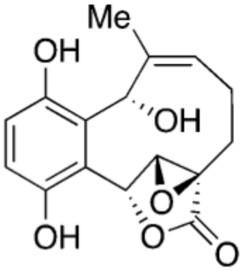
- The Incredible Edible *Clitocybe clavipes*
- Clavilactones



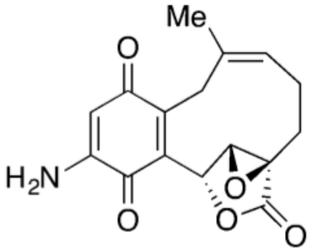
(+)-Clavilactone A (**1**)



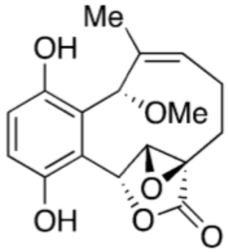
(–)-Clavilactone B (**2**)



(+)-Clavilactone C (**3**)



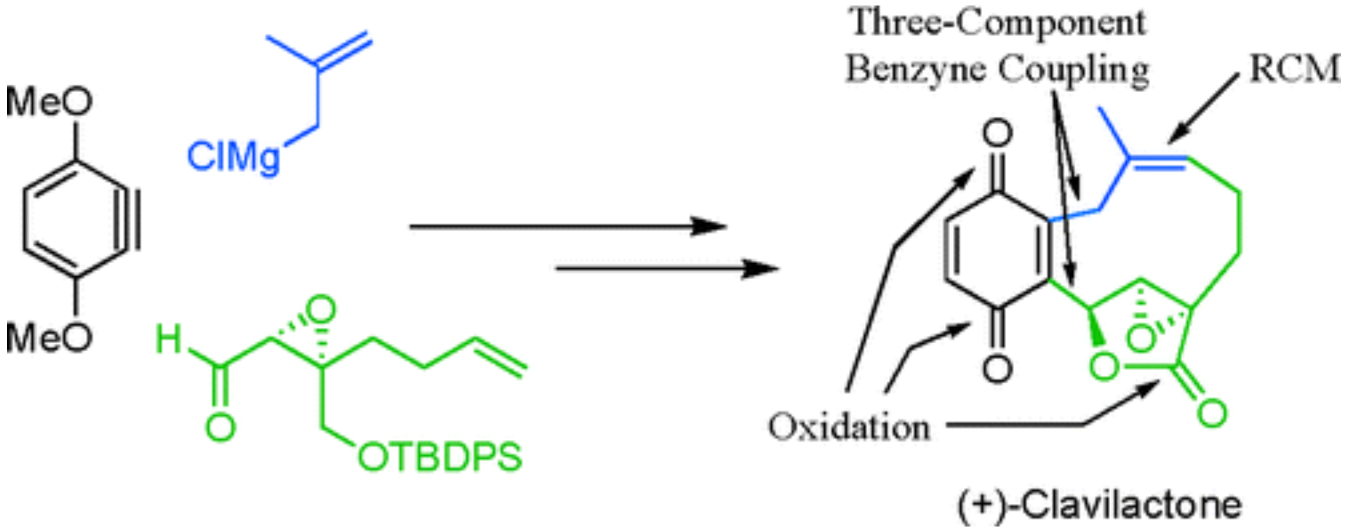
Revised structure of
(+)-Clavilactone D (**6**)



(+)-Clavilactone E (**5**)

- Tyrosine Kinase Inhibitors (EGFR and Ret/ptc 1)

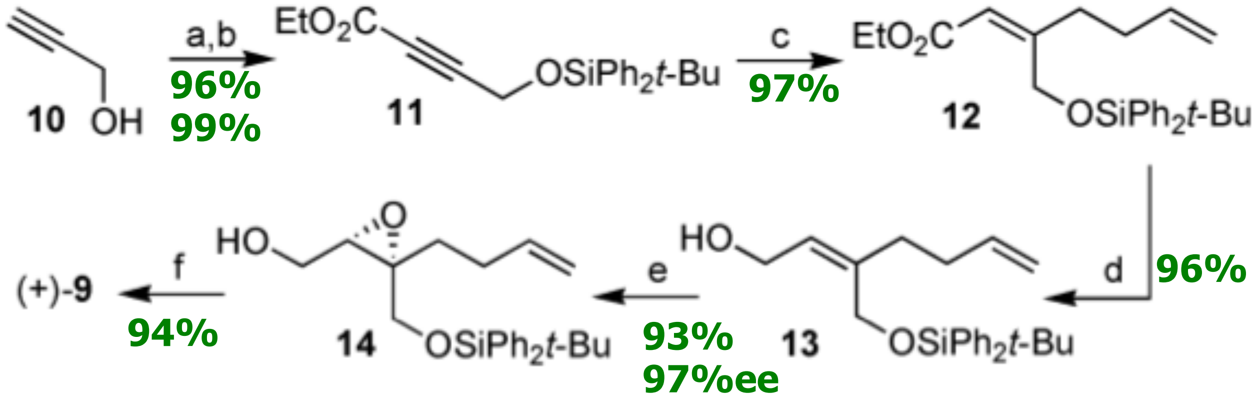
Barrett *et al*, 2006



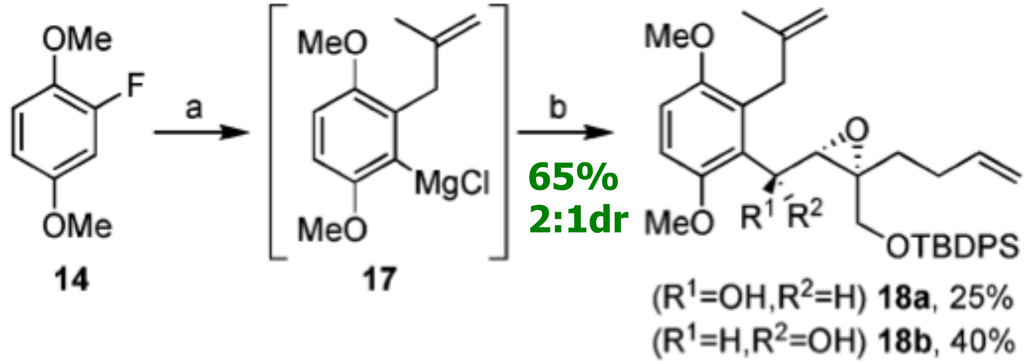
- First Asymmetric Synthesis of (+)-Clavilactone B
  - – Multicomponent Assembly
  - – Macrocyclization with Olefin Metathesis
  - – 11 Steps, 16.8% overall yield

Barrett *et al*, 2006

Scheme 2. Asymmetric Synthesis of Epoxy-Aldehyde **9**[a]



Scheme 3. Three-Component Benzyne Coupling[a]

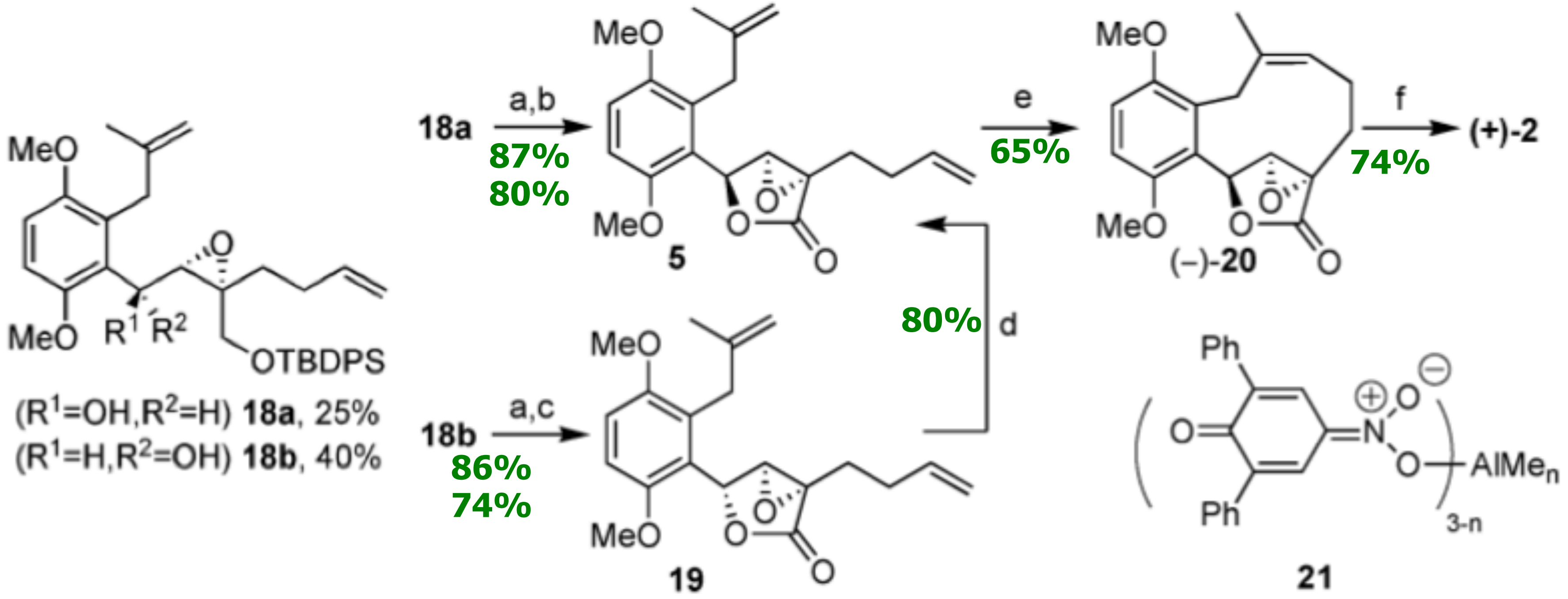


[a] Conditions: (a) *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, 96%; (b) *n*-BuLi; EtOCOCl, THF, −78 °C, 99%; (c) Mg, 4-bromo-1-butene, THF; CuBr·SMe_2, THF, −40 °C; **11**, THF, −78 °C, 97%; (d) DIBAl-H, PhMe, −78 °C, 96%; (e) $Ti(Oi\text{-}Pr)_4$, L-(+)-DET, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −20 °C, 93%, 97% ee; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 94%.

[a] Conditions: (a) *n*-BuLi, THF, −78 °C; $CH_2{=}C(Me)CH_2MgCl$ (**16**), −78 to 25 °C; (b) **9**, −78 to −35 °C, 65% (dr 2:1).

Barrett *et al*, 2006

Scheme 4. Synthesis of (+)-Clavilactone B (**2**)^a

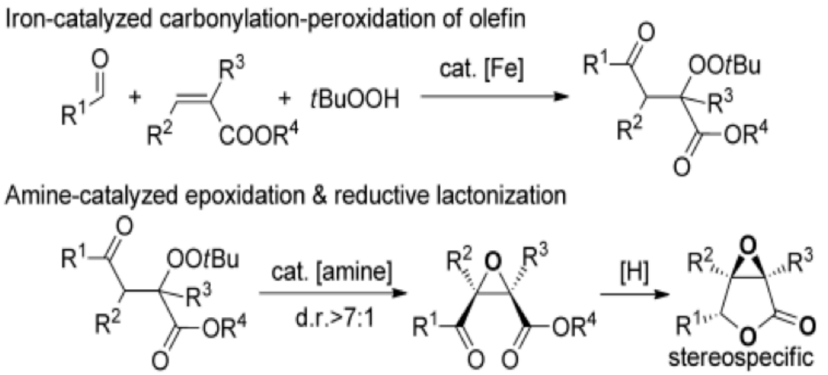


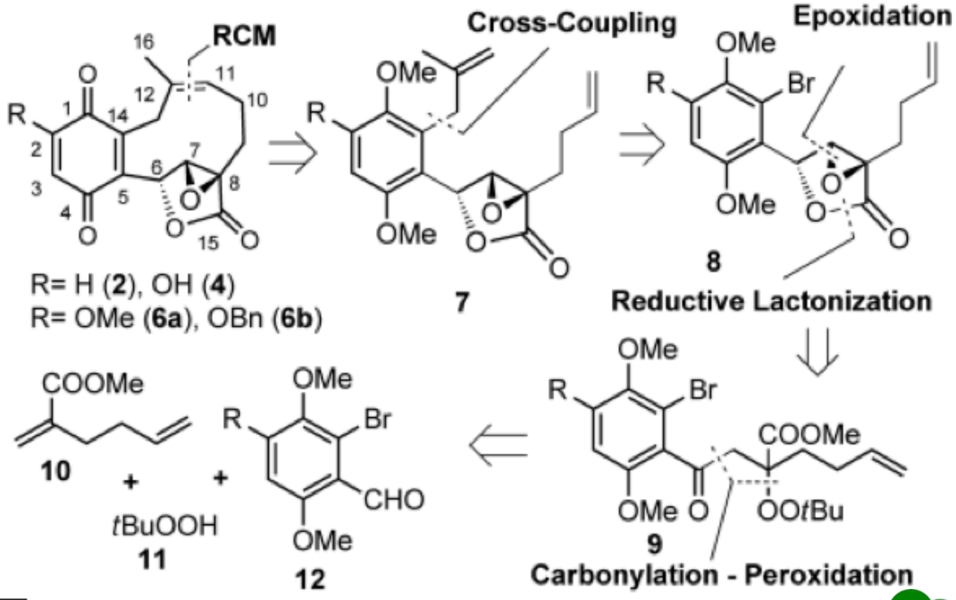
^{a} Conditions: (a) Bu_4NF (TBAF), THF, 87% (**6**), 86% (6-epi-**6**); (b) TEMPO (20 mol %), $PhI(OAc)_2$, CH_2Cl_2, 80%; (c) Pr_4NRuO_4 (TPAP) (15 mol %), NMO, 4 Å MS, MeCN, 74%; (d) **21** (60 mol %), CH_2Cl_2, 80%; (e) $Cl_2(Cy_3P)(sIMes)Ru{=}CHPh$ (40 mol %), tetrafluorobenzoquinone (80 mol %), PhMe, 80 °C, 65%; (f) CAN, MeCN, H_2O, 74%.

- 13 Steps, 10.94% Overall Yield

Leiyang *et al,* 2014

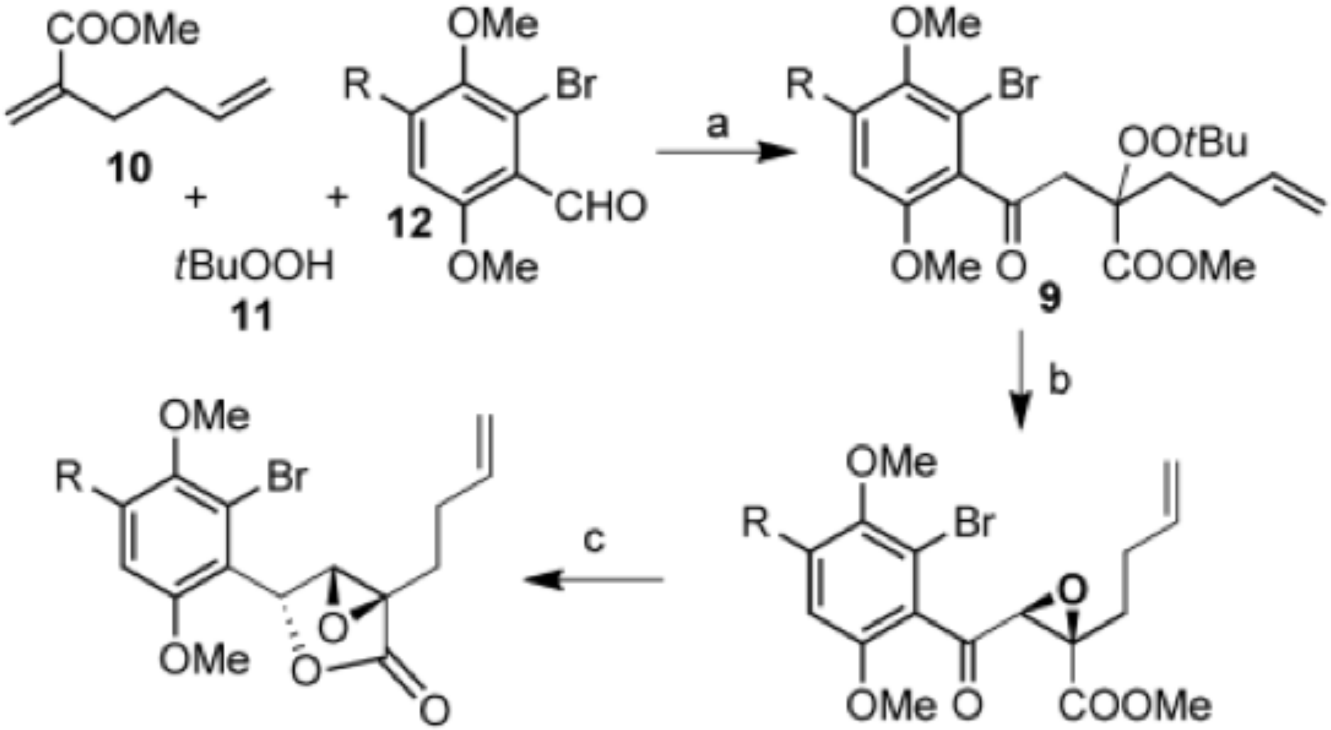
- First Asymmetric Synthesis of (+)-Clavilactone B
  - – Iron-Catalyzed Carbonylation–Peroxidation of Olefin
  - – Stereoselective Reductive Lactonization
  - – Goal of Expanding to Clavilactones C, D





Leiyang *et al,* 2014

R = H
= OCH_3
= OBn

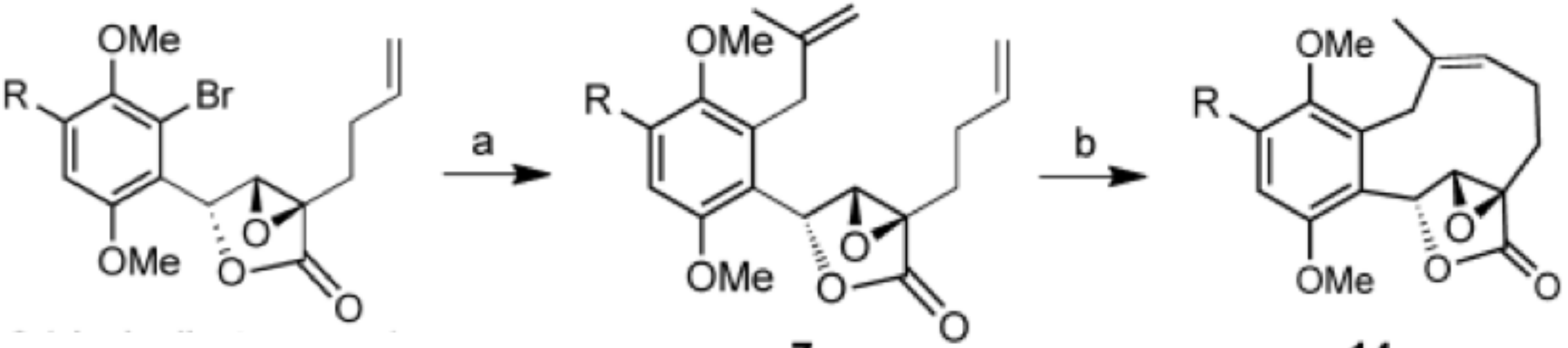


8 (single diastereomer)

13 (d.r.>4:1)

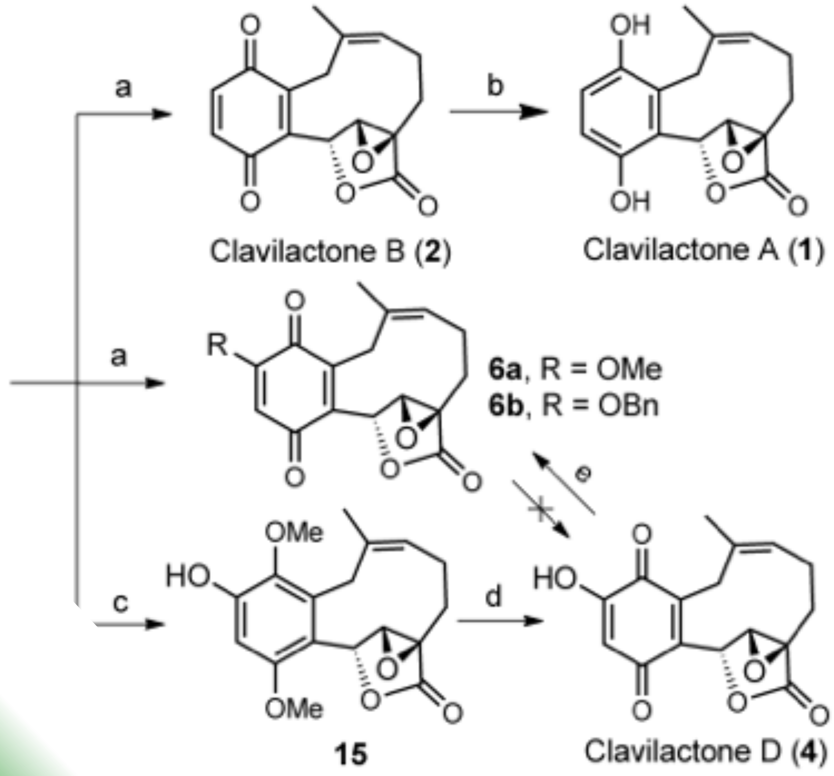
Reagents and conditions: a) $FeCl_2$, MeCN, 85 °C, 3 h, R=H (**9 a**, 60 %), OMe (**9 b**, 74 %), OBn (**9 c**, 70 %); b) pyrrolidine, MeCN, 0 °C, 3 h, R=H (**13 a**, 87 %, d.r. 5:1), OMe (**13 b**, 90 %, d.r. 4:1), OBn (**13 c**, 91 %, d.r. 4:1); c) $NaBH_4$, EtOH, 0 °C, 3 h, R=H (**8 a**, 73 %), OMe (**8 b**, 71 %), OBn (**8 c**, 78 %).

Leiyang *et al*, 2014



7

14

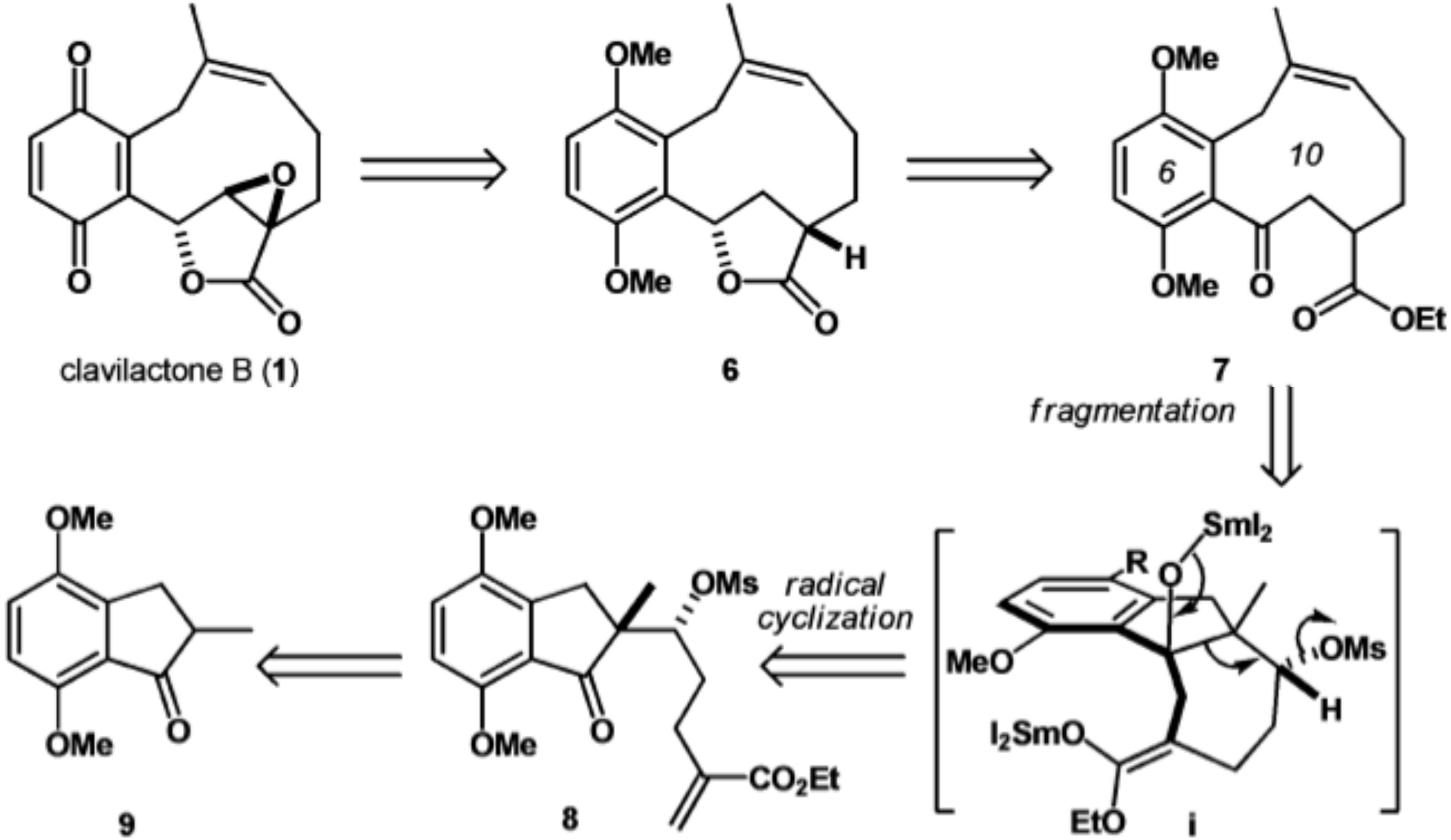


a) tributyl(2-methyl-allyl)stannane, [Pd(PPh3)4], CsF, MeCN, 100 °C, 12 h, R=H (**7 a**, 87 %), OMe (**7 b**, 82 %), OBn (**7 c**, 88 %); b) [Cl2(Cy3P)(sIMes)RuCHPh], tetrafluoro-benzoquinone, toluene, 80 °C, 18 h, R=H (**14 a**, 65 %), OMe (**14 b**, 43 %), OBn (**14 c**, 42 %).

a) CAN, MeCN/H2O (2:1), 0 °C, R=H (**2**, 70 %), OMe (**6 a**, 65 %), (**6 b**, 60 %); b) NaBH4, EtOH, 0 °C, 5 min, (**1**, 99 %); c) 10 wt % Pd/C, 1,4-cyclohexadiene, EtOH, 25 °C, 1 h, (**15**, 99 %); d) CAN, MeCN/H2O (2/1), 0 °C, 10 min (**4**, 85 %); e) K2CO3, Me2SO4, 25 °C,3 h, (**6 a**, 70 %). CAN=ceric ammonium nitrate.

- 6-7 Steps, 14.9-15.1%

Suizu *et al,* 2014


clavilactone B (**1**)

6

7

i

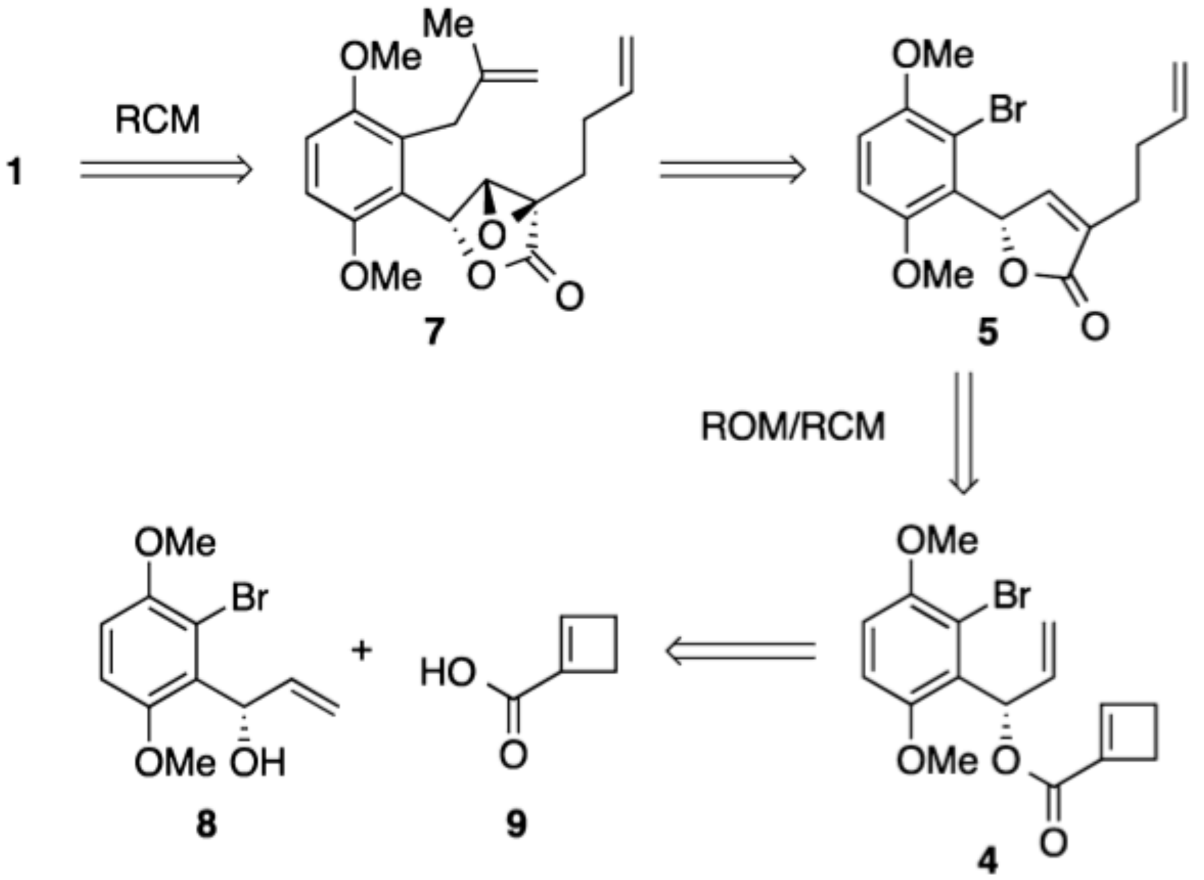
8

9

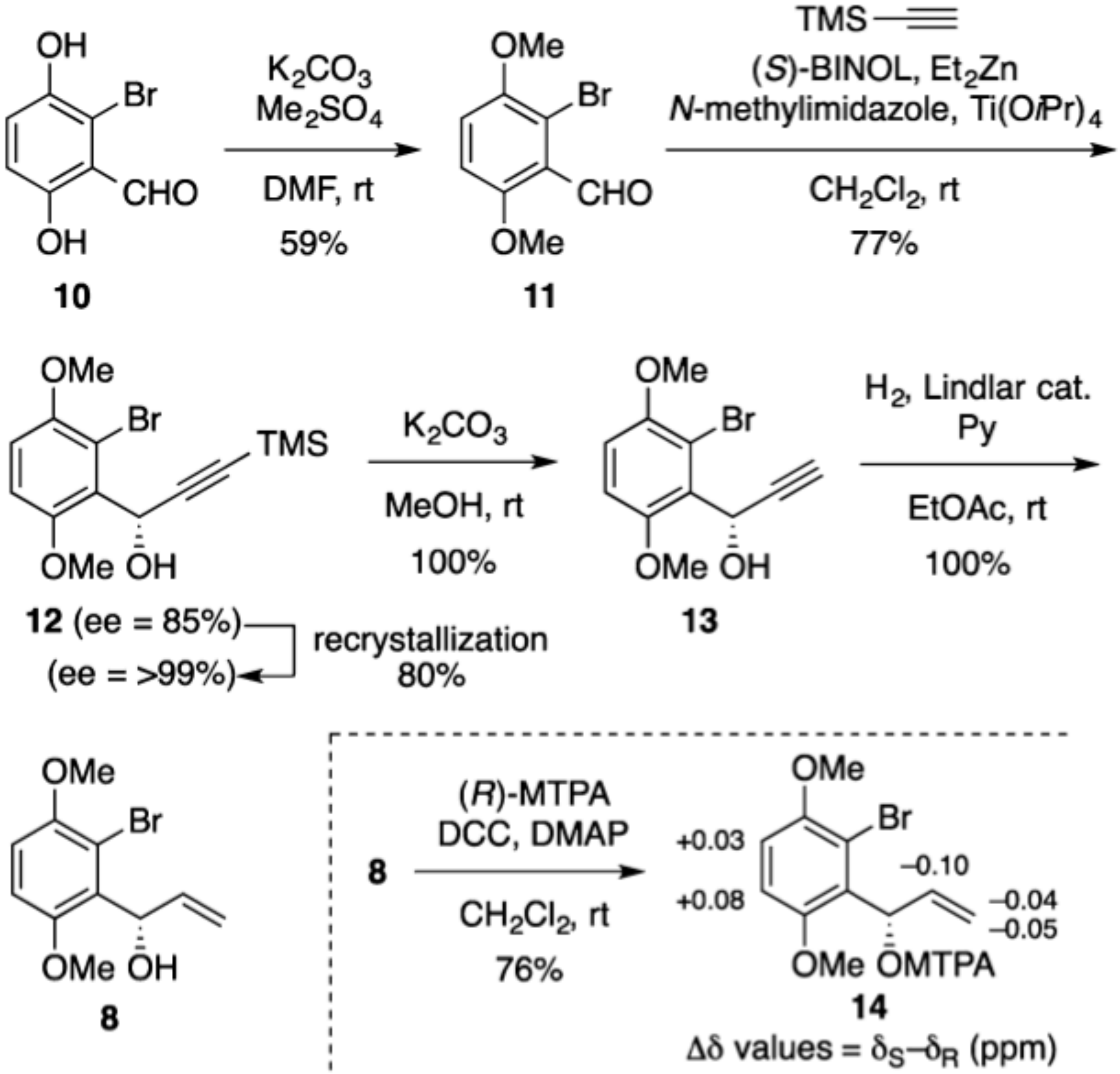
- 8 Steps, 8.59% Overall Yield

Takao *et al,* 2013 (Original Work)

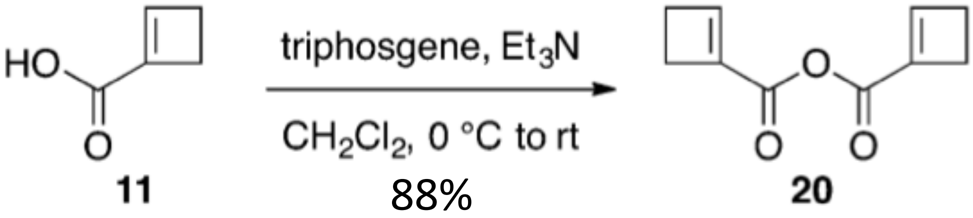
- Features strain-driven butenolide synthesis via olefin metathesis

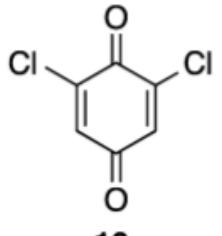


Takao *et al,* 2013

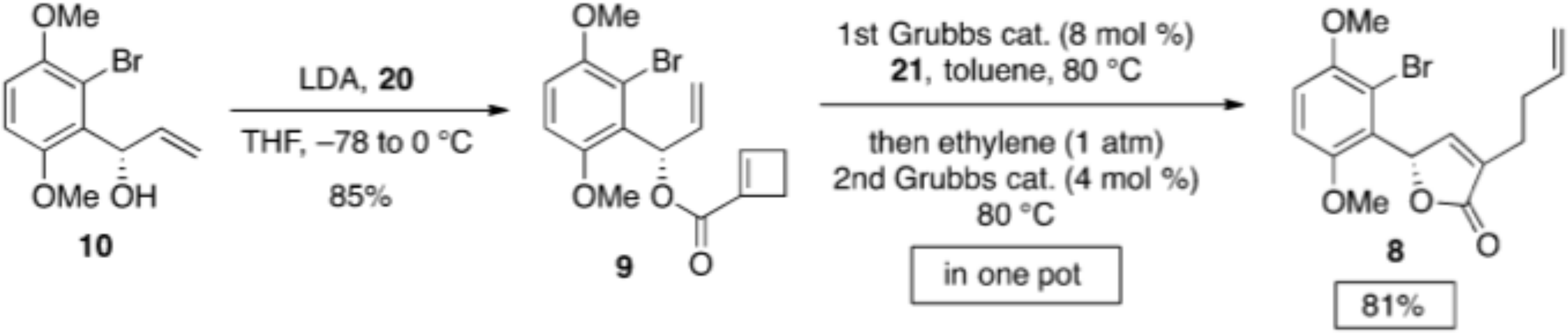


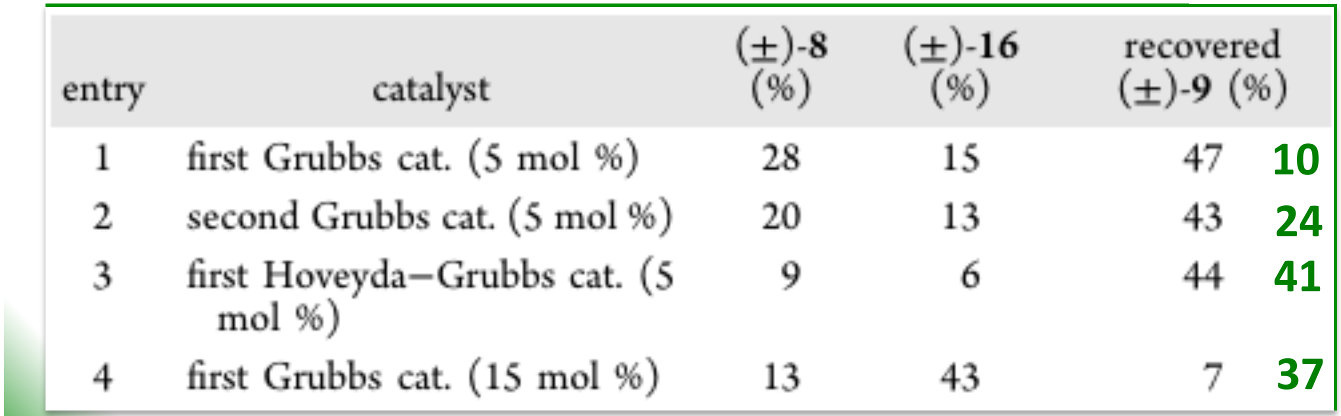
Takao *et al*, 2013



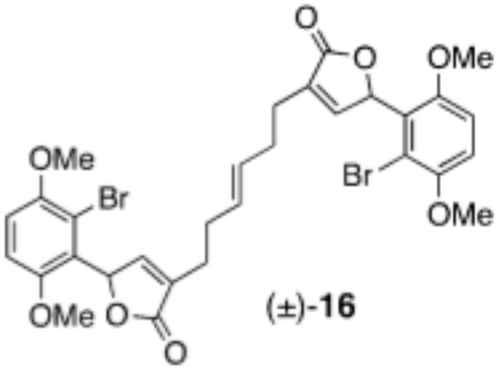


16



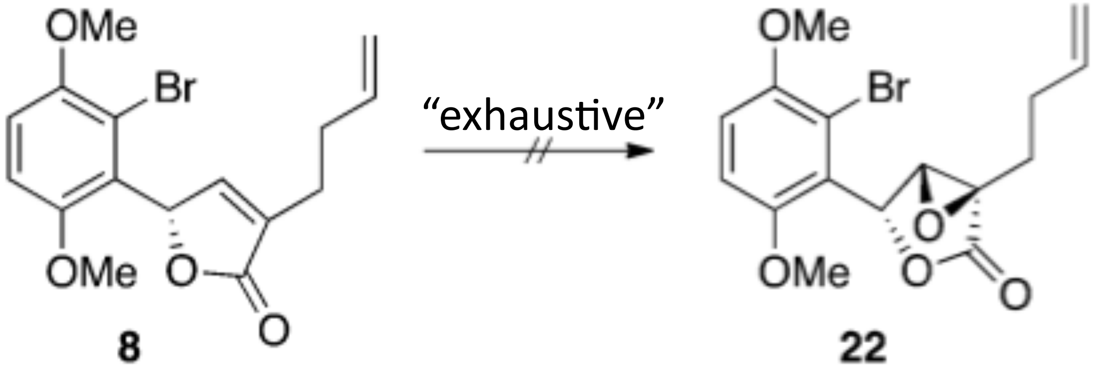


entry	catalyst	(±)-**8** (%)	(±)-**16** (%)	recovered (±)-**9** (%)	
1	first Grubbs cat. (5 mol %)	28	15	47	**10**
2	second Grubbs cat. (5 mol %)	20	13	43	**24**
3	first Hoveyda–Grubbs cat. (5 mol %)	9	6	44	**41**
4	first Grubbs cat. (15 mol %)	13	43	7	**37**

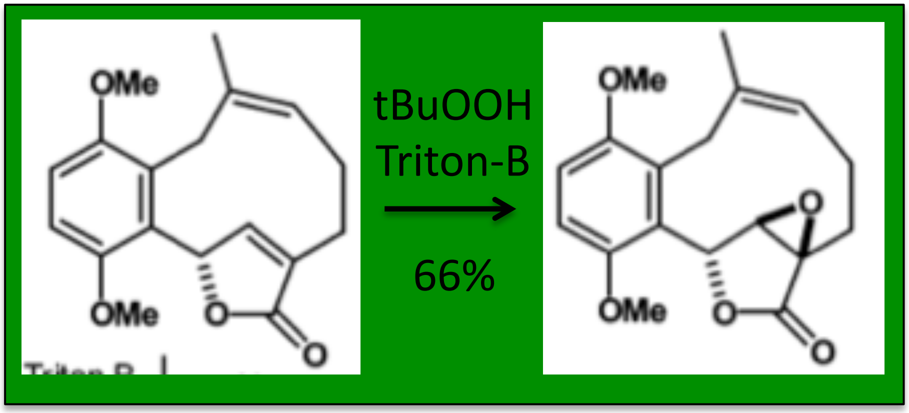


(±)-**16**

Takao *et al,* 2013 : Epoxidation



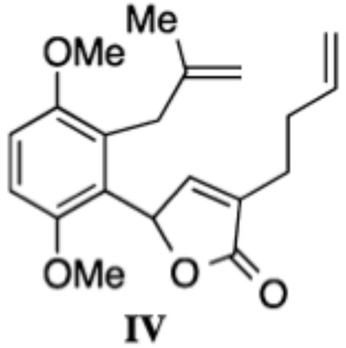
“There have been few successful examples of epoxidation of γ-aryl-γ-butenolides”



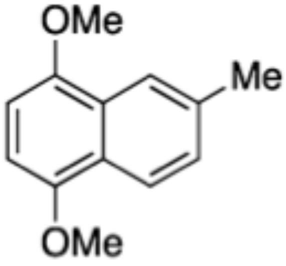
tBuOOH
Triton-B

66%

Suizu *et al,* 2014

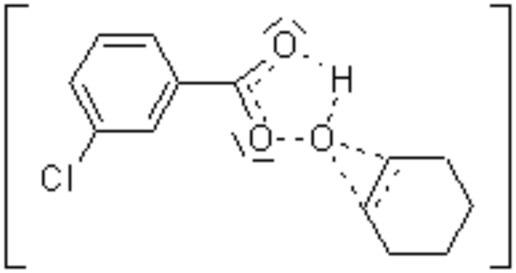


IV



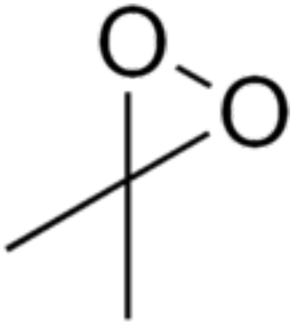
V

Selective Epoxidation

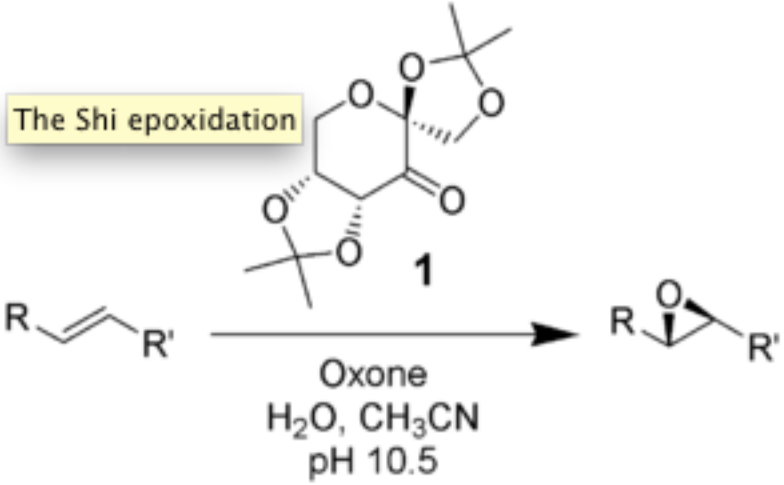


- Prilezhaev Epoxidation
  - Peracids such as MCPBA
  - e^--rich alkenes (electrophilic)
- Juliá–Colonna Epoxidation
  - H_2O_2, NaOH
  - e^--poor alkenes (α,β-unsaturated carbonyls, nucleophilic)
- Sharpless Asymmetric Epoxidation of Allylic -OH
  - (+ or -) diethyl tartrate and $Ti(OiPr)_4$
  - tBuOOH oxidizing agent

More Epoxidation



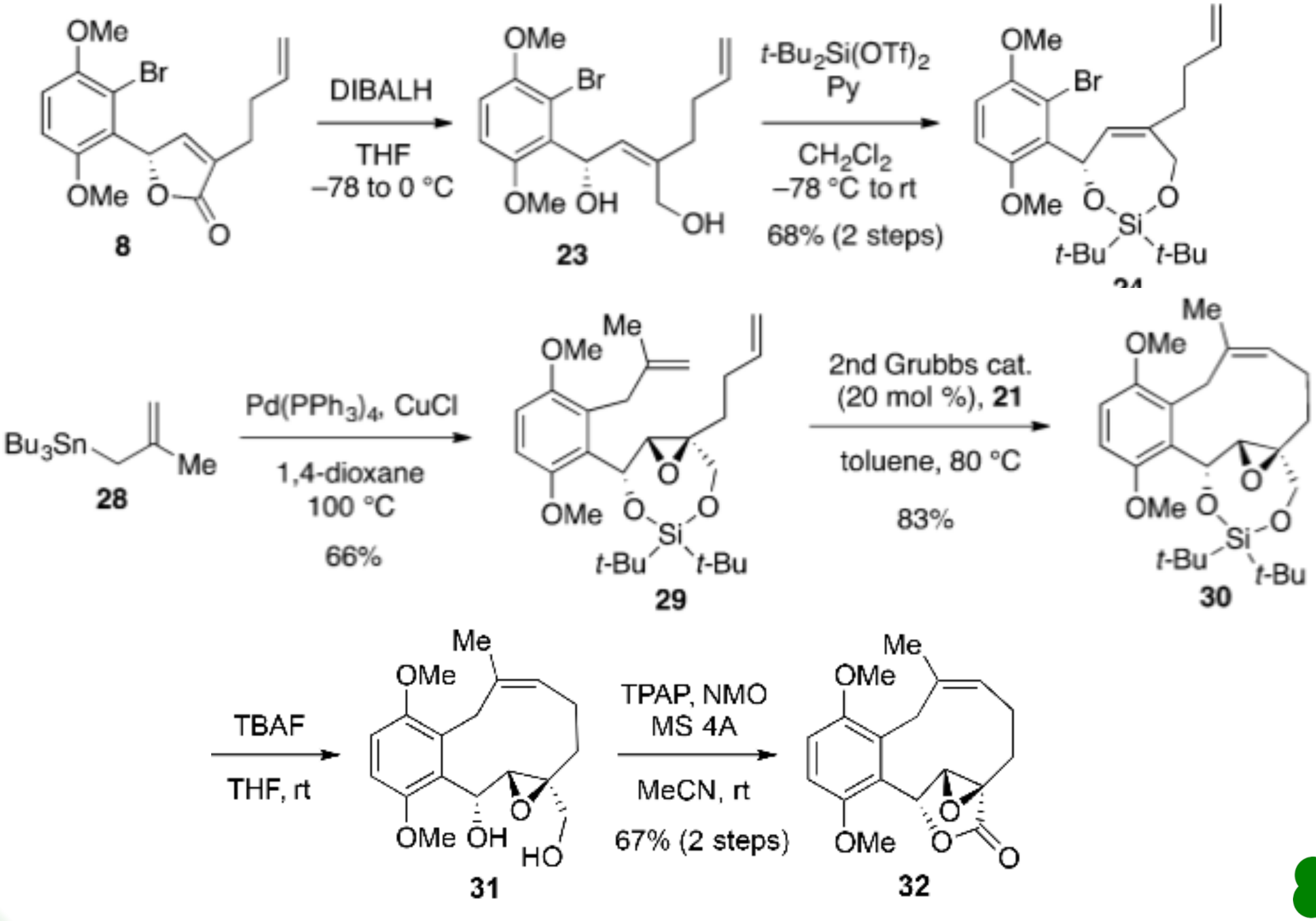
- Murray Reagent (DMDO)
  - Oxidation of –NH_2, -SH, alkenes
  - Nef Reaction: -NO_2 to ketone
  - e$^-$-poor alkenes oxidized more quickly
- Shi Epoxidation
  - Oxone and Organic Catalyst


The Shi epoxidation

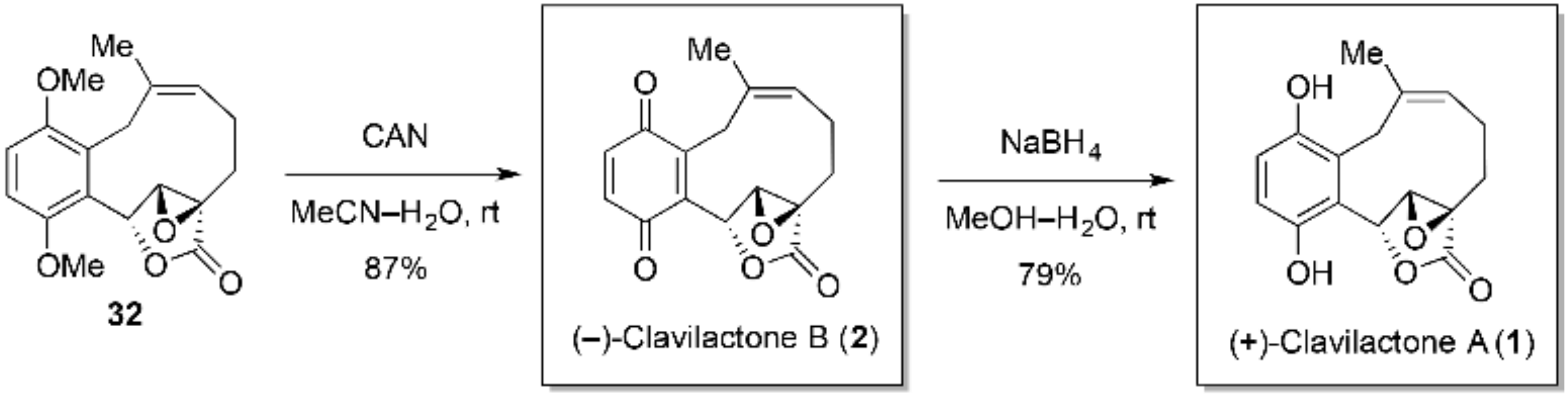
1

Oxone
H_2O, CH_3CN
pH 10.5

Takao *et al,* 2013: Workaround



Takao *et al,* 2013: Finishing A and B

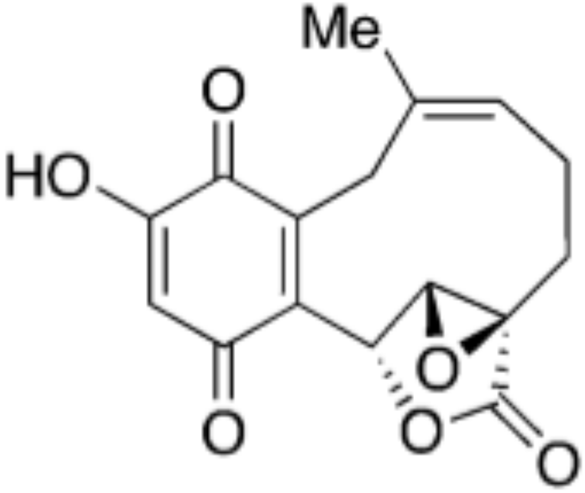


- (B) 6.79% over 13 steps
- (A) 5.37% over 14 steps

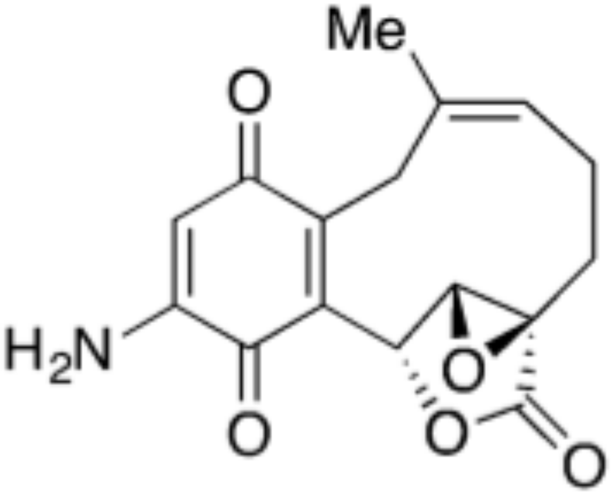
Comparison of Total Syntheses

- Barrett (2006) - 13 Steps, 10.94% (A)
- Leiyang (2014) –
  - (B) 6 Steps, 15.1%
  - (A) 7 Steps, 14.9%
- Suizu (2014) - 8 Steps, 8.59% Overall Yield (A)
- Takao (2013)
  - (B) 13 Steps, 6.79%
  - (A) 14 Steps, 5.37%

Revision of Clavilactone-D



Originally proposed structure of (+)-Clavilactone D (**4**)



Revised structure of (+)-Clavilactone D (**6**)

- Aniline peak at 6.59 ppm had been disregarded
- Misinterpretation of couplings led to incorrect substitution pattern

Conclusion

- Achieved total synthesis of Clavilactones A and B in 13-14 steps and ~6% overall yield
- Most steps and lowest yield of all other syntheses
- Revised Structure of Clavilactone D

Questions?

Access to Further Reading / References

- Article: https://pubs.acs.org/doi/pdf/10.1021/acs.joc.7b03268
- Previous Syntheses
  - Barrett: https://pubs.acs.org/doi/pdf/10.1021/ja0662671
  - Leiyang: http://onlinelibrary.wiley.com/doi/10.1002/anie.201400326/full
  - Suizu: https://pubs.acs.org/doi/abs/10.1021/ol503356m
  - Original Synth: https://pubs.acs.org/doi/abs/10.1021/ol4027842

Other works from Takao