Natural Product Synthesis

Angewandte International Edition Chemie

International Edition: DOI: 10.1002/anie.201902043
German Edition: DOI: 10.1002/ange.201902043

Total Synthesis of (−)-Indoxamycin A

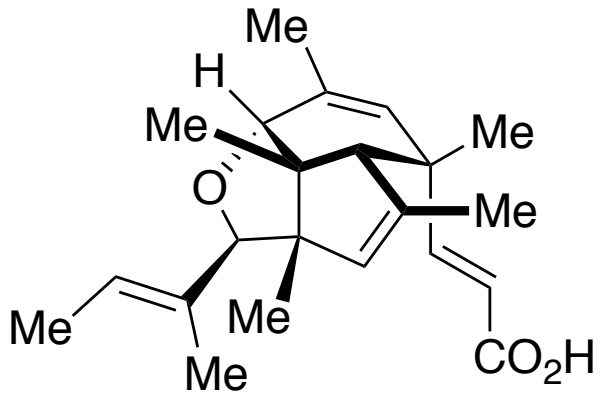
*Naifeng Hu, Changming Dong, Cuifang Zhang, and Guangxin Liang**

[*] N. Hu, C. Dong, C. Zhang, Prof. G. Liang
State Key Laboratory of Elemento-organic Chemistry,
College of Chemistry, Nankai University, Tianjin 300071 (China)
E-mail: lianggx@nankai.edu.cn

Angew. Chem. Int. Ed. **2019**, *58*, 6659–6662

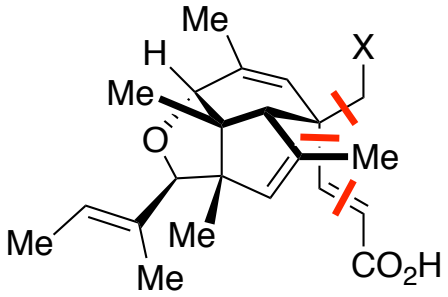
Kevin Byrne
Liu Research Group
September 12th, 2019

- Isolated by Sato (2009) from a marine-derived *actinomyces* culture.
- Novel class of polyketides that display anti-tumor properties.
- Highly-congested [5.5.6] tricyclic skeleton with six contiguous stereocenters.
  - Two vicinal, all-carbon quaternary centers.
- First total synthesis of indoxamycin B reported by Carreira (2012).
  - Asymmetric total syntheses of indoxamycins A-F reported by Ding (2014).
- This work: concise asymmetric total synthesis of indoxamycins A and B from inexpensive *R*-carvone.
  - Substrate-controlled: potential to synthesize enantiomers from *S*-carvone.



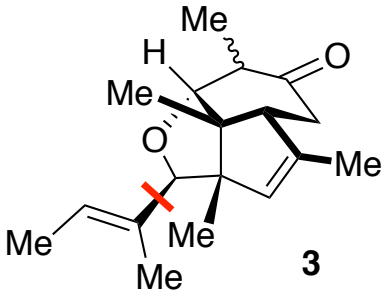
Indoxamycin A

Retrosynthetic Analysis:



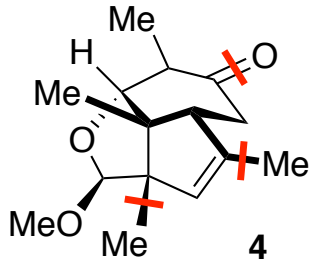
indoxamycin A (**1**): X = H
indoxamycin B (**2**): X = OH

Acylation
Alkylation
HWE Olefination



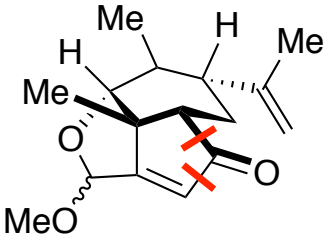
3

retro-oxa-Michael addition/
oxa-Michael addition



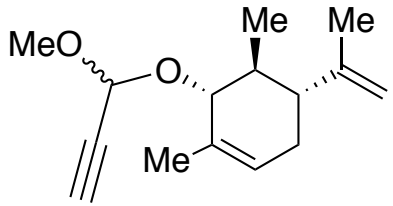
4

Conjugate Addition
Ozonolysis
Negishi Cross-Coupling

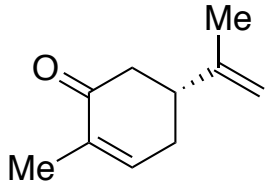


5

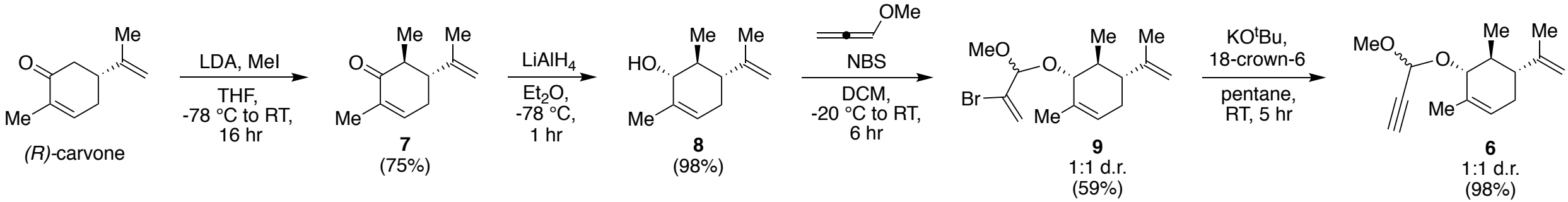
Paulson-Khand
Cyclization



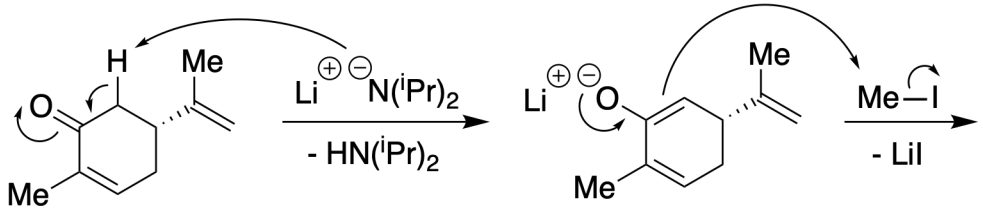
6



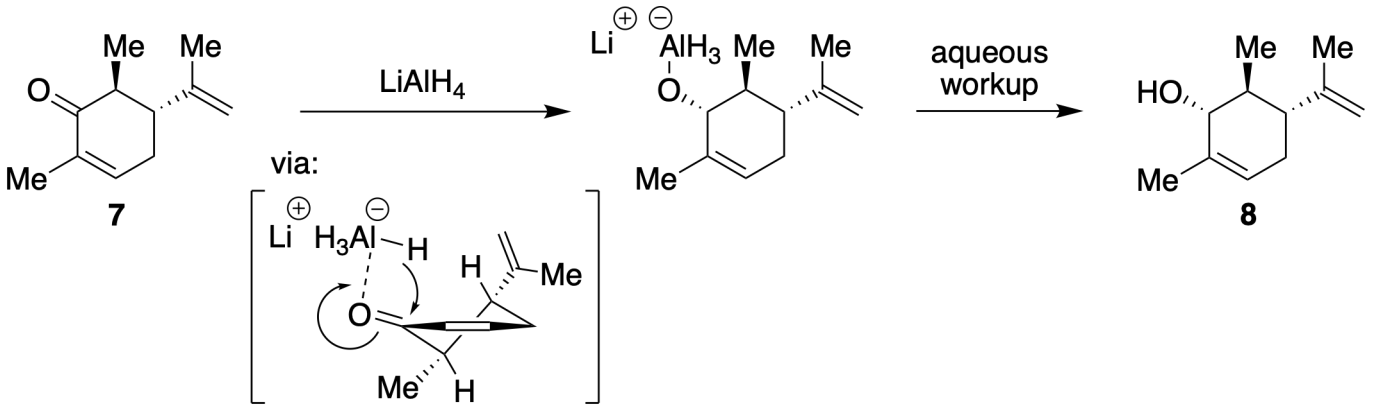
***(R)*-carvone**
$0.53/g



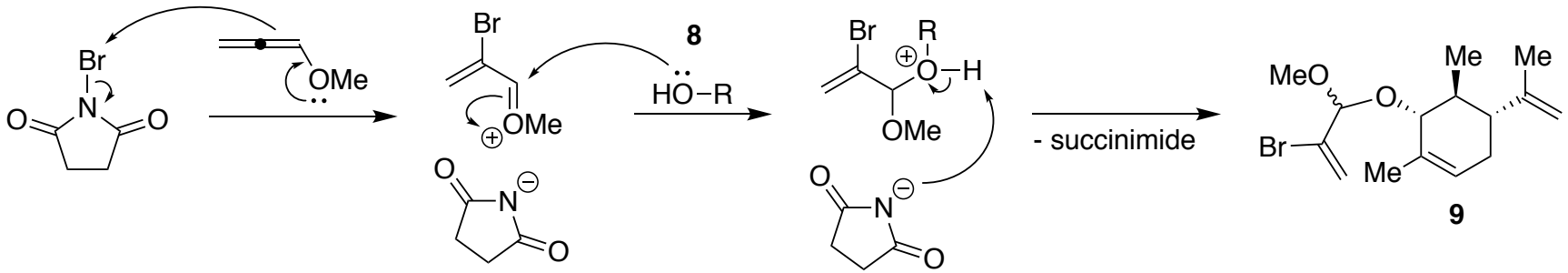
Methylation:

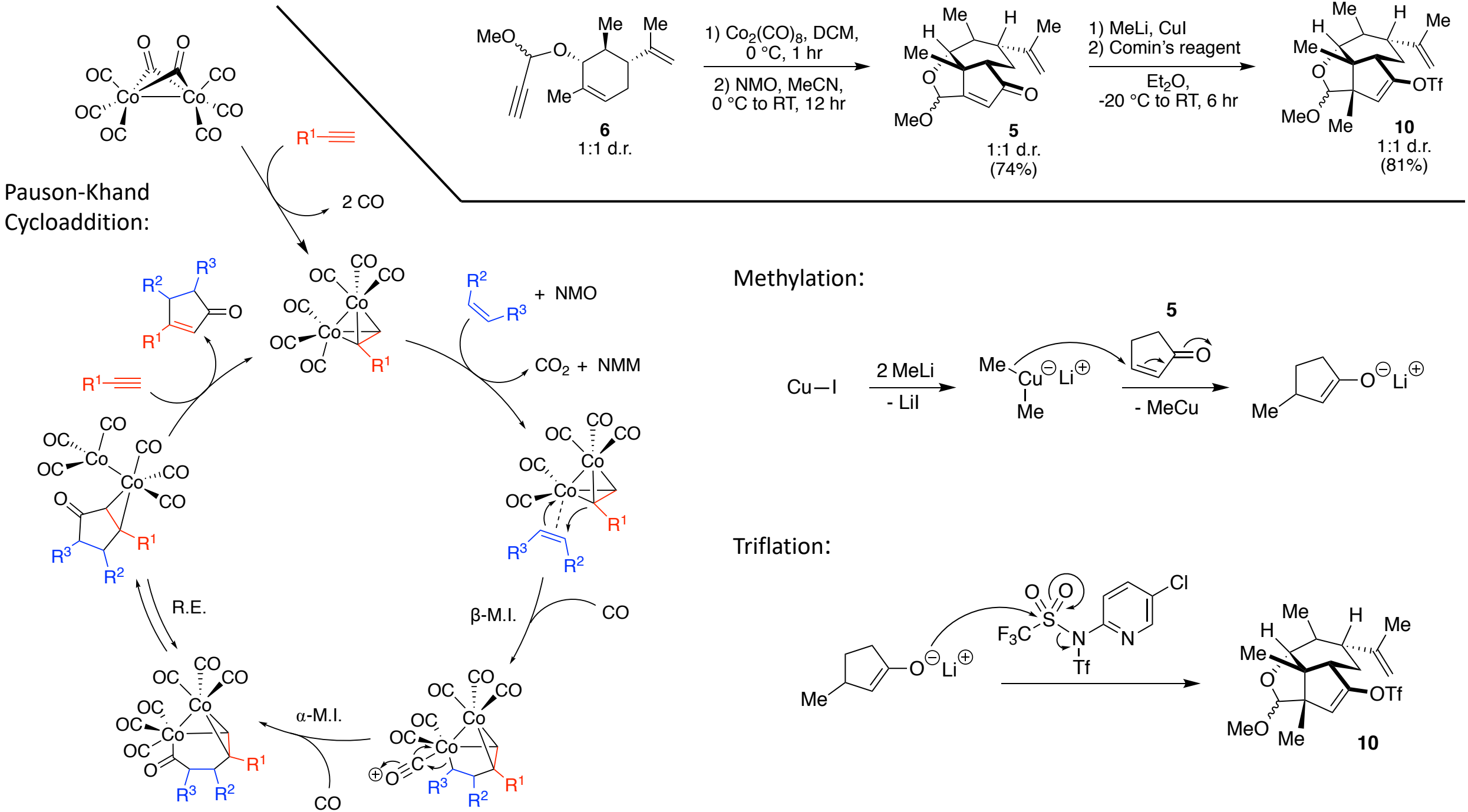


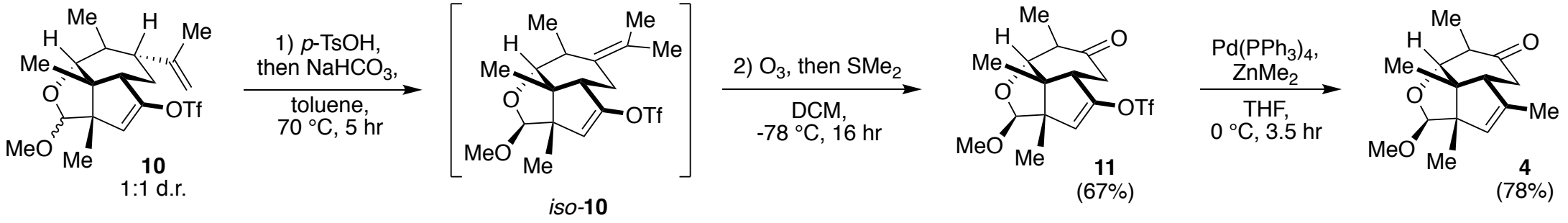
$LiAlH_4$ Reduction:



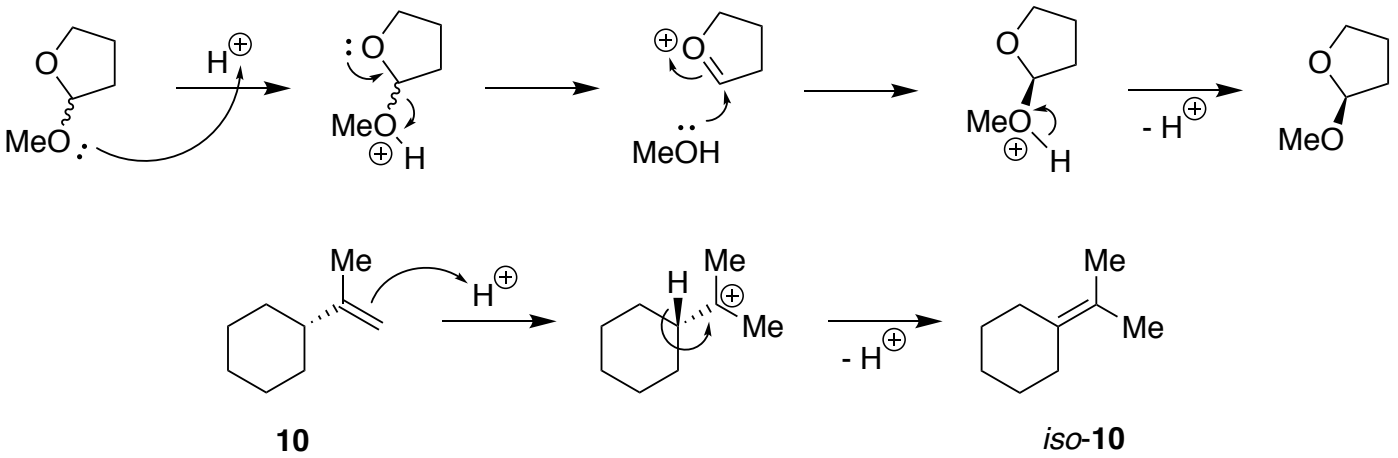
Acetalization:



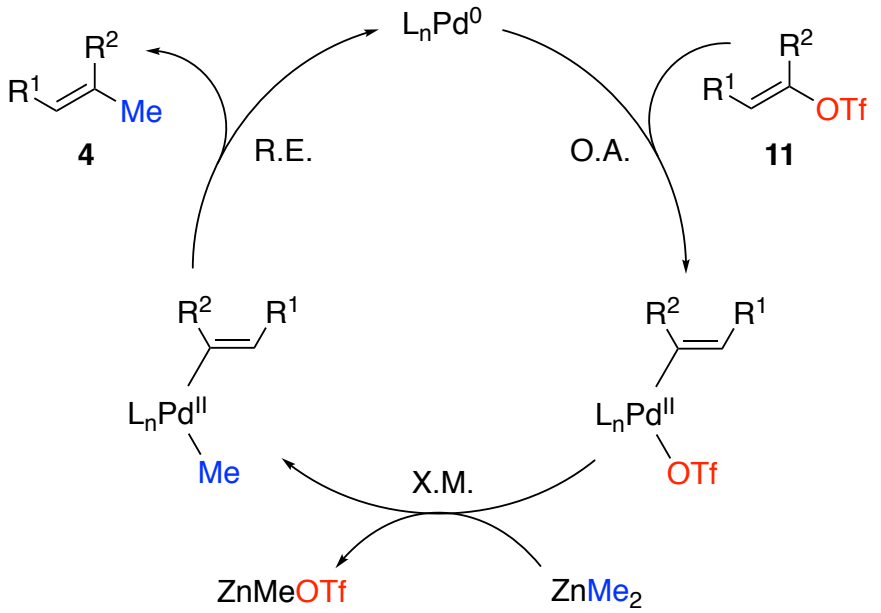

Pauson-Khand Cycloaddition:
2 CO
+ NMO
CO2 + NMM
R.E.
β-M.I.
CO
α-M.I.
CO
6
1:1 d.r.
1) Co2(CO)8, DCM, 0 °C, 1 hr
2) NMO, MeCN, 0 °C to RT, 12 hr
5
1:1 d.r.
(74%)
1) MeLi, CuI
2) Comin's reagent
Et2O, -20 °C to RT, 6 hr
10
1:1 d.r.
(81%)
Methylation:
Cu—I
2 MeLi
- LiI
- MeCu
Triflation:
Tf
10



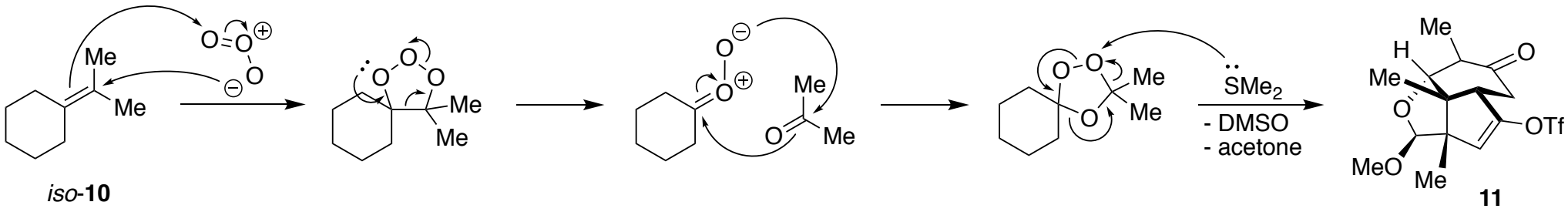
Isomerizations (acid-catalyzed):

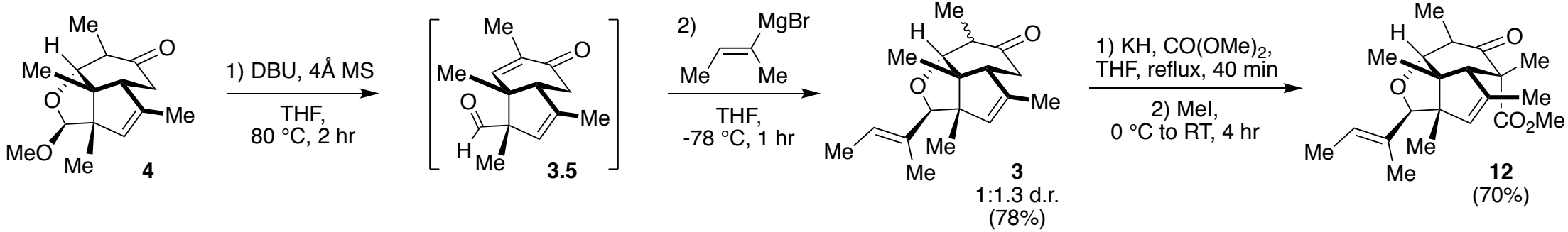


Negishi Cross-Coupling:

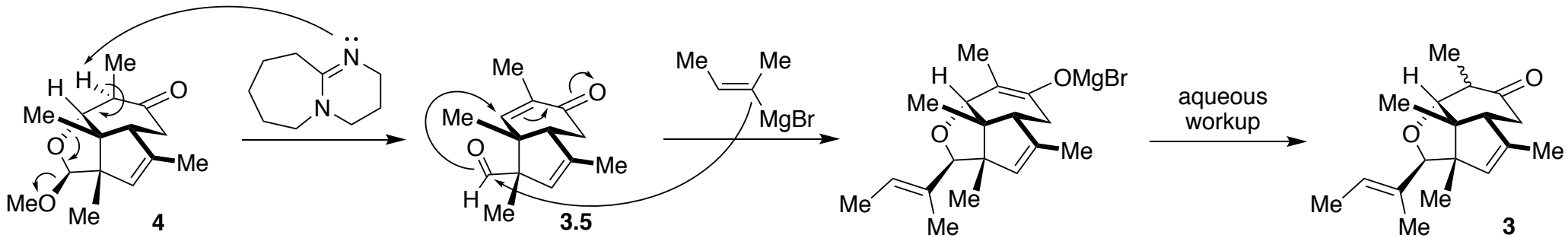


Ozonolysis:

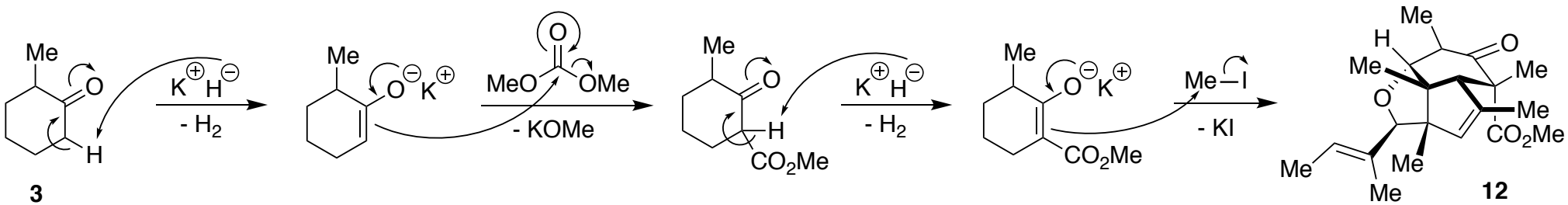


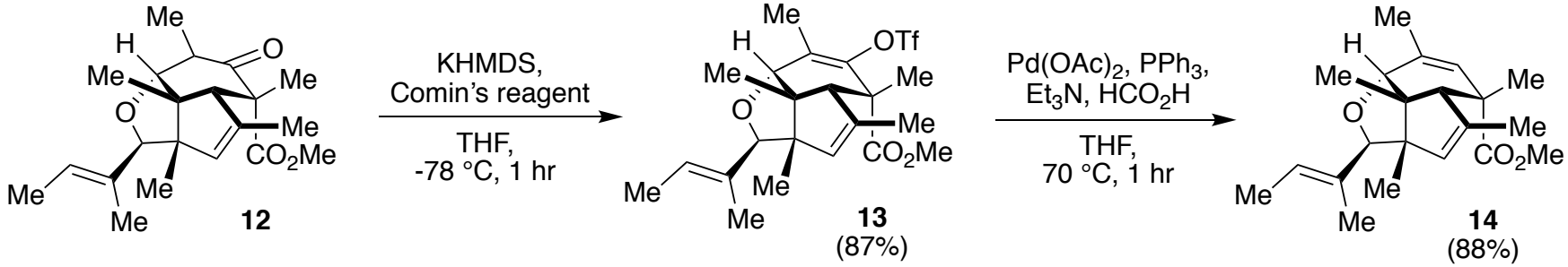


retro-oxa-Michael Addition/
oxa-Michael Addition:

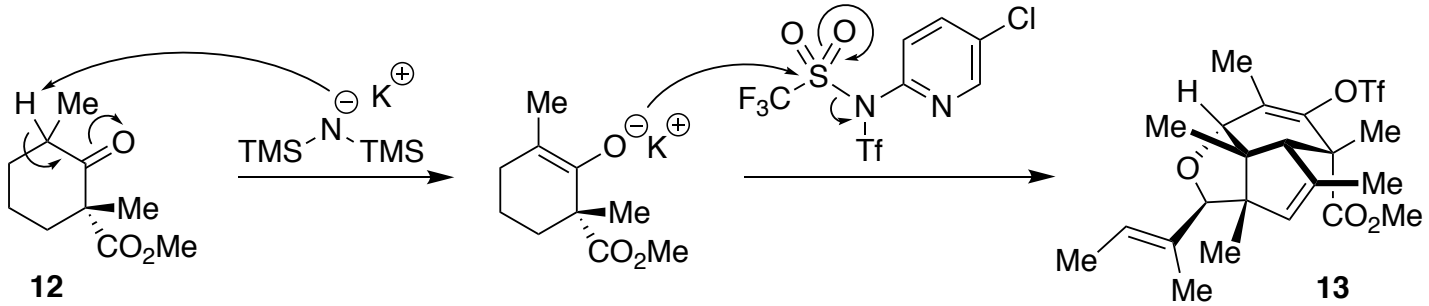


Acylation/Methylation:

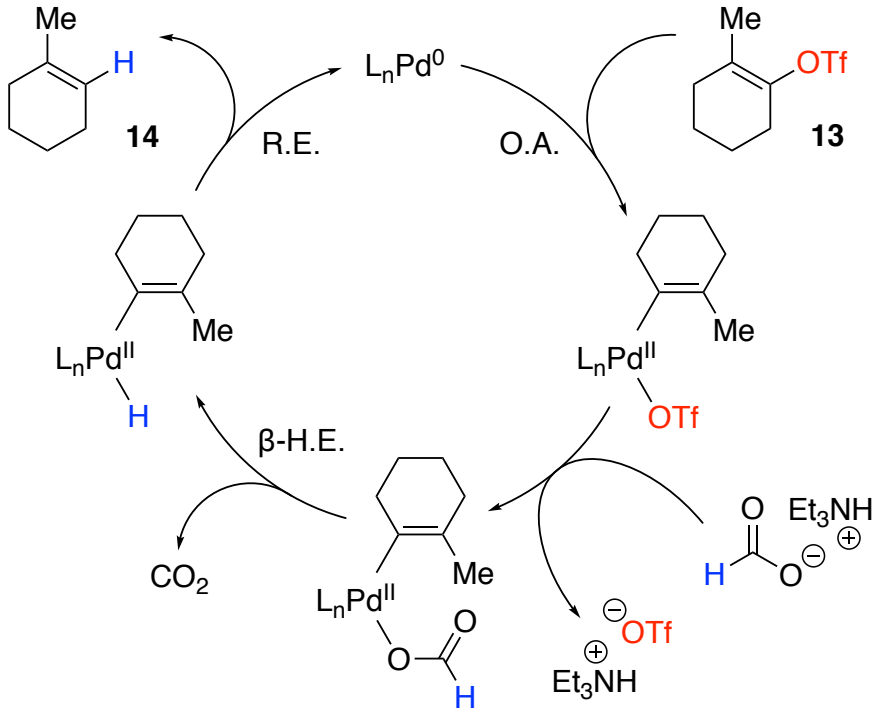


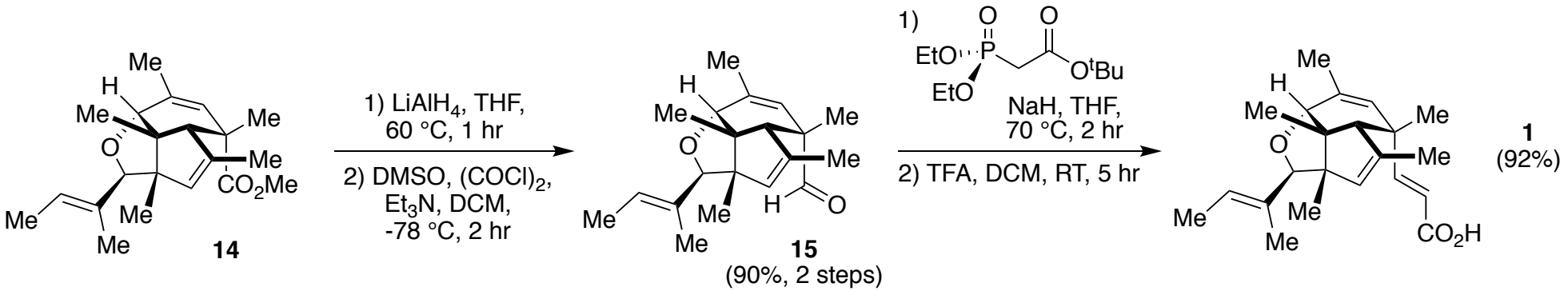


Triflation:

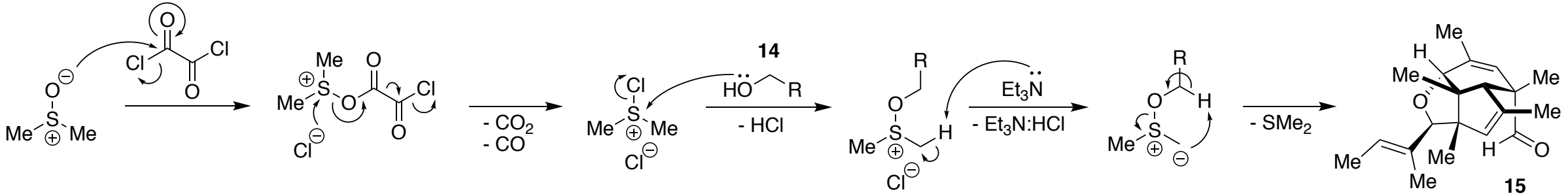


Reductive Detriflation:

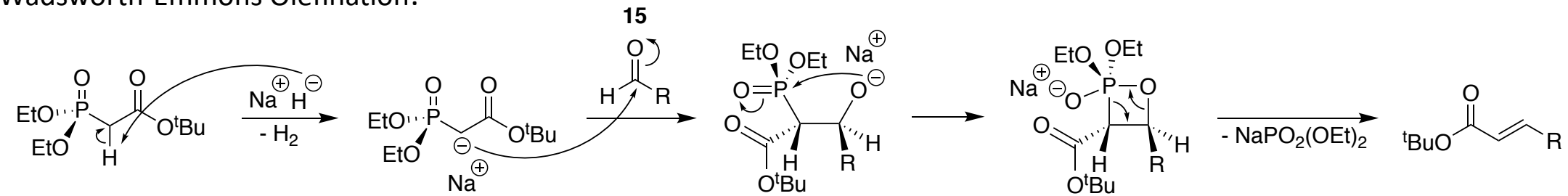




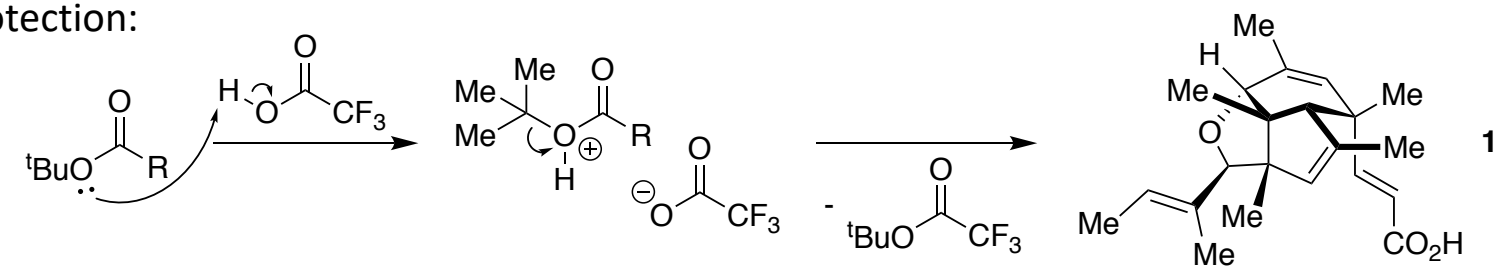
Swern Oxidation:



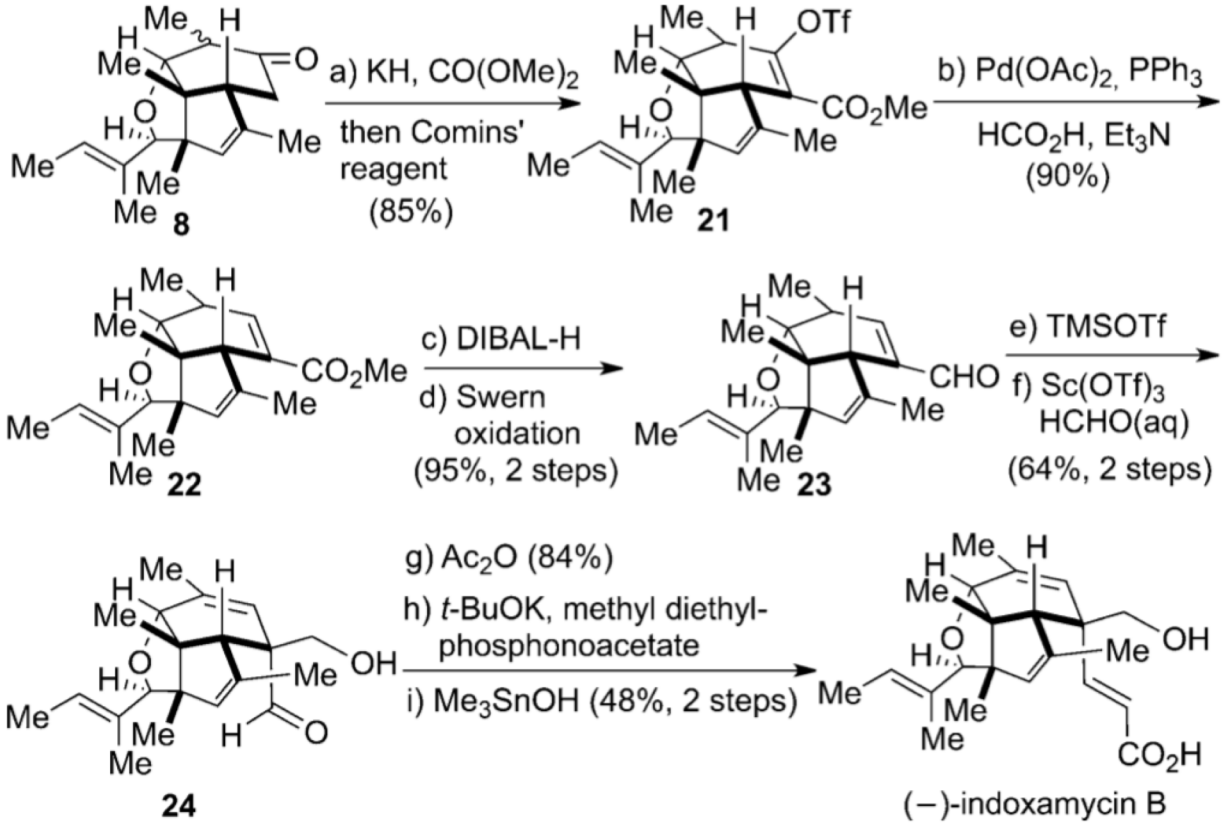
Horner-Wadsworth-Emmons Olefination:



tert-Butyl Deprotection:



Bonus: Indoxamycin B



Scheme 4. Total synthesis of (−)-indoxamycin B. Reagents and conditions: a) KH (3.0 equiv), $CO(OMe)_2$ (5.0 equiv), THF, reflux, then Comins' reagent, 0 °C, 1.5 h, 85%; b) $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.4 equiv), HCO_2H (10 equiv), Et_3N (12 equiv), THF, 70 °C, 1 h, 90%; c) DIBAL-H (2.5 equiv), CH_2Cl_2, −78 °C, 0.5 h; d) oxalyl chloride (1.5 equiv), DMSO (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, −78 °C, 1 h, 95% for two steps; e) TMSOTf (2.5 equiv), Et_3N (4.0 equiv), CH_2Cl_2, 0 °C, 0.5 h; f) $Sc(OTf)_3$ (0.1 equiv), HCHO (37% wt%, 10 equiv), THF, RT, 0.6 h, 64% for two steps; g) Ac_2O (2.0 equiv), pyridine (3.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, RT, 0.5 h, 84%; (h) *t*-BuOK (2.0 equiv), **24** (3.0 equiv), THF, RT, 48 h, 59% (88% brsm); i) Me_3SnOH (2.0 equiv), 1,2-dichloroethane, 90 °C, 20 h, 80%. DIBAL-H = diisobutylaluminium hydride, TMSOTf = trimethylsilyl trifluoromethanesulfonate, DMAP = 4-dimethylaminopyridine.