Total Syntheses of Highly Oxidized *ent*-Kaurenoids Pharicin A, Pharicinin B, 7-O-Acetylpseurata C, and Pseurata C: A [5+2] Cascade Approach

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J. Am. Chem. Soc., **DOI:** 10.1021/jacs.7b02746

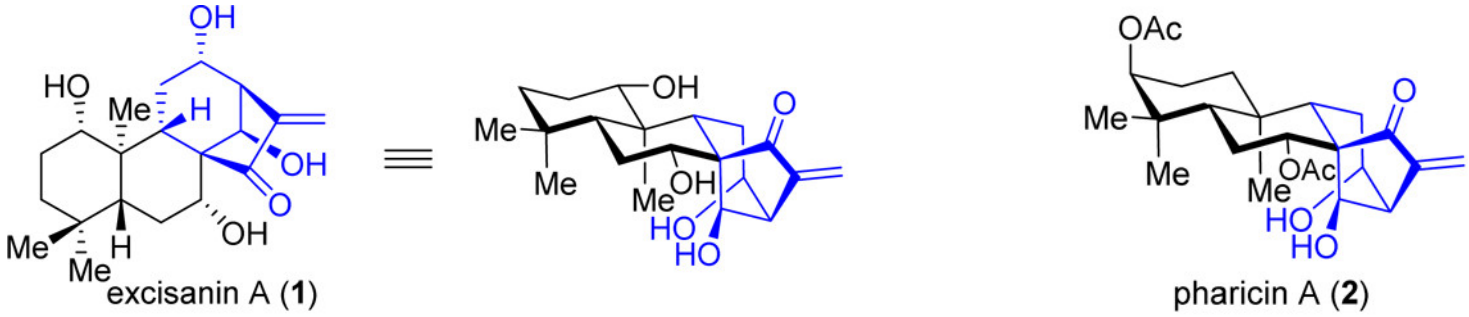
Liming Cao
Wipf Group Current Literature
5/6/2017

Ent-Kaurene Diterpenoids

- Ent-kaurene diterpenoids are majority of the isodon diterpenoids isolated to date.

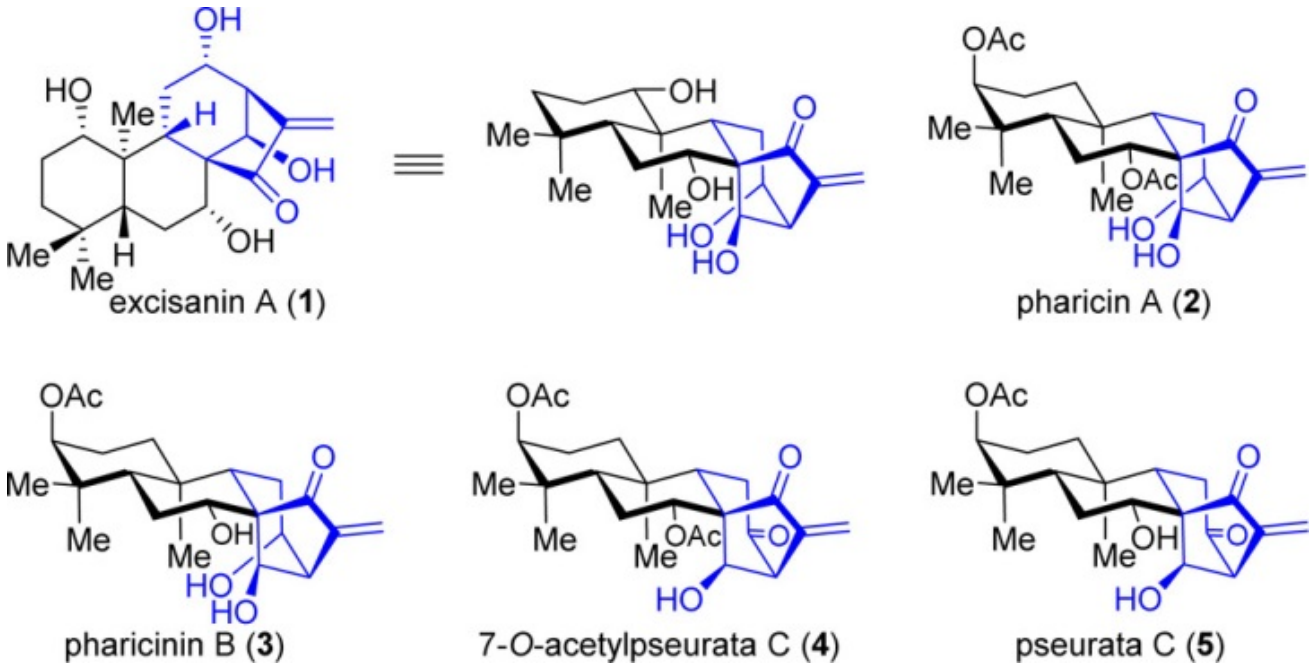
- They as potential medicinal leads resulted in the discovery of several promising congeners embedded with a highly oxygenated bicyclo[3.2.1] octane ring system.

- Excisanin A (**1**) has been found to induce tumor cell apoptosis and suppress tumor growth.
- Pharicin A (**2**) represents a novel class of small molecule compounds capable of perturbing mitotic progression and initiating mitotic catastrophe.



Molecules **2007**, *12*, 455
Mol. Cancer Ther. **2009**, *8*, 873
Cell Cycle **2010**, *9*, 2969

Ent-Kaurene Diterpenoids



- Congeners embedded with a highly oxygenated bicyclo[3.2.1]octane ring system.

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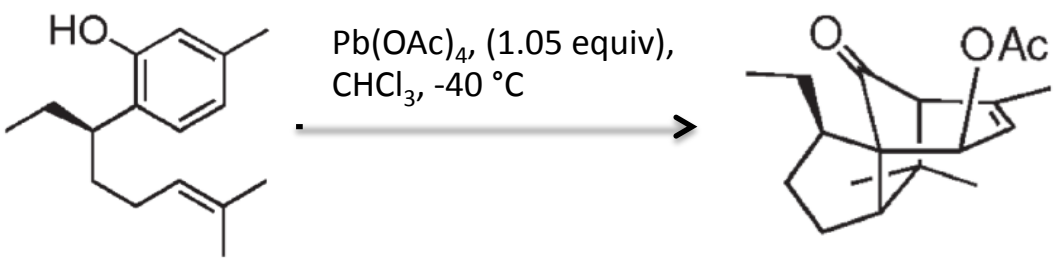
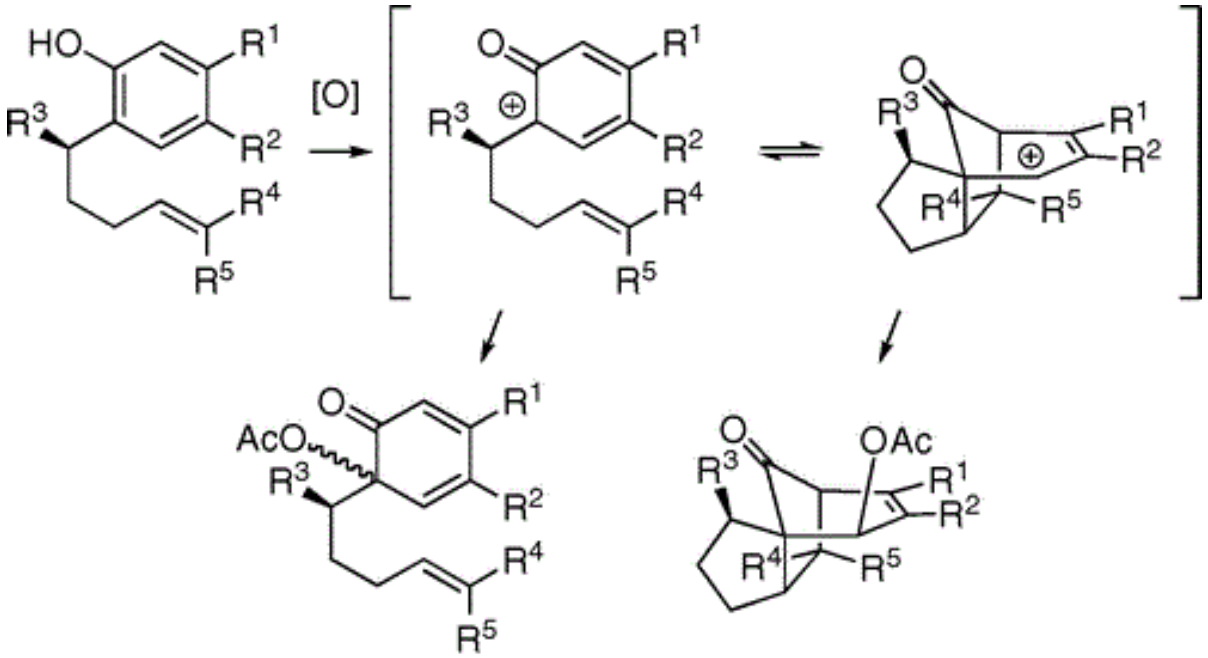
Dearomatization of *ortho*-(Pent-4-enyl)-phenols

Pettus:

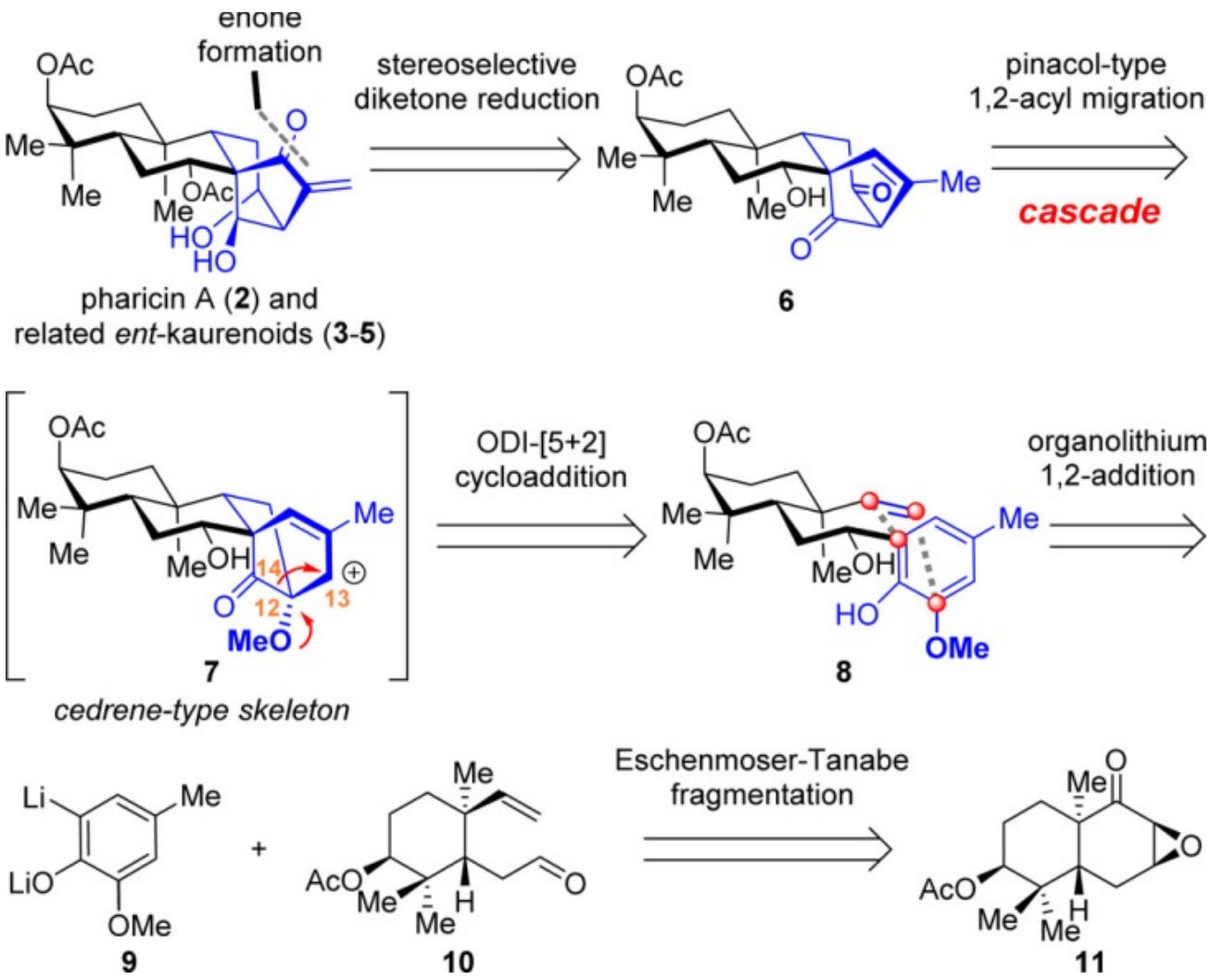


52% (2.2:1 byproduct)



J. Am. Chem. Soc. **2011**, *133*, 1603

Retrosynthetic Analysis



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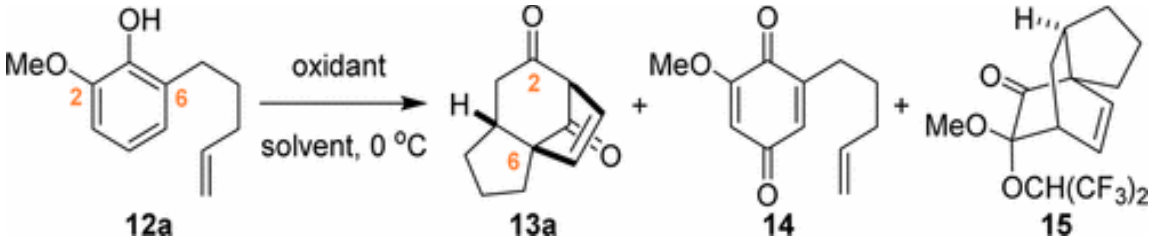
Optimization of the ODI-[5+2] Cycloaddition/Pinacol-Type 1,2-Acyl Migration Cascade



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entry	oxidant	solvent	yield (%)[b] 13a	14	15
1	$Pb(OAc)_4$[c]	$CHCl_3$	7	15	
2	$PhI(OAc)_2$	$CHCl_3$	16	30	
3	$PhI(OAc)_2$	TFE	42	23	
4	$PhI(OAc)_2$	HFIP	63	<5	18
5	$PhI(CF_3CO_2)_2$	HFIP	78	<5	<5

a Unless stated otherwise, the reactions were performed with **12a** (0.2 mmol) and oxidant (1.1 equiv) in solvent (4 mL) at 0 °C for 20 min.

b Isolated yields.

c Run at −40 °C for 10 min. TFE = 2,2,2-trifluoroethanol, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

Three rings and three stereogenic centers including one quaternary were created in a single operation by this cascade cyclization.

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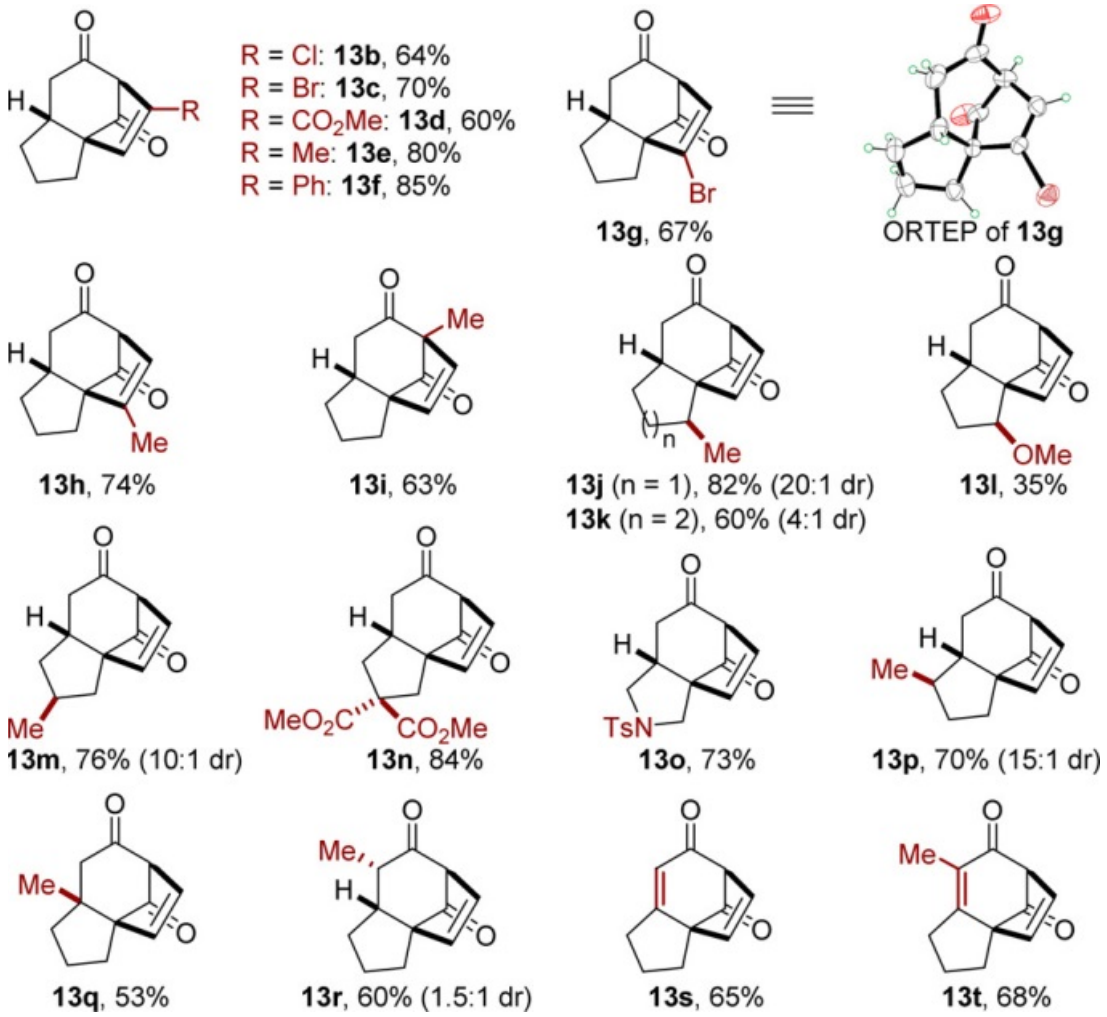
Scope of the Cascade Cyclization



- Substituents compatible
- Minimization of steric interactions

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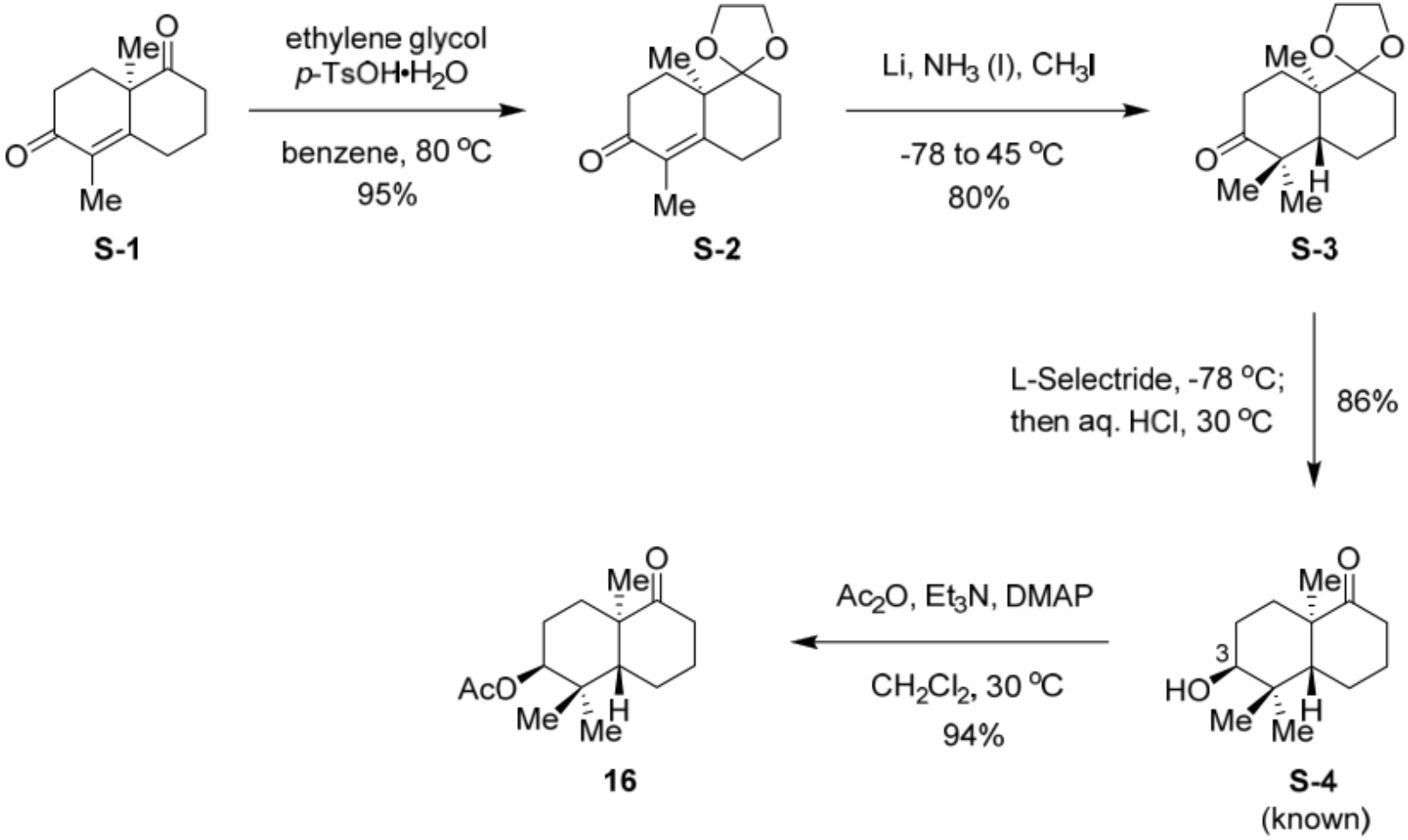
Synthesis of Starting Material



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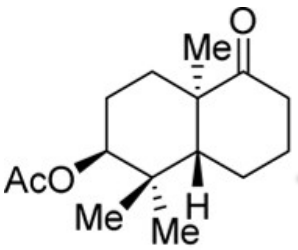
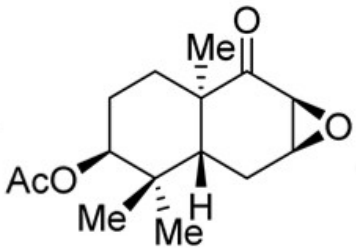
Construction of Tetracyclic Diketone C7-*epi*-**6**



16, 95% ee

1. IBX, DMSO/toluene, 85 °C, 24 h;
2. H_2O_2, NaOH, MeOH/H_2O, 0 °C, 30 min; 85%, (2 steps)



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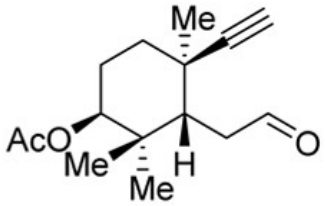
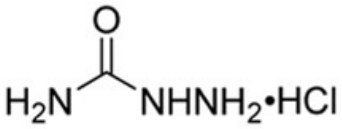
1. NaOAc, EtOH/H_2O; **17**, 30 °C, 1 h;
2. Pb(OAc)4, DCM, 0 °C, 1 h; 65% (2 steps)



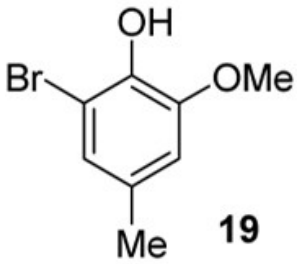
18

1. Lindlar Cat., H_2, SiO_2, hexane, 30 °C, 30 min;
2. **19**, *n*BuLI, THF, -78 °C, 10 min; THF, -78 °C, 1 h

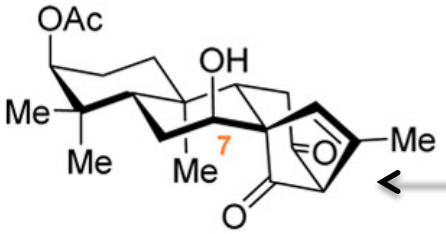
80% (2 steps)
8a/**8b** = 2:1



17



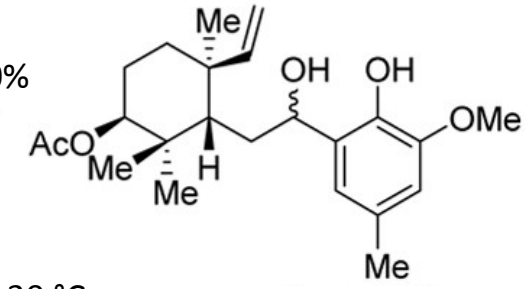
19



C7-*epi*-**6**

$PhI(CF_3CO_2)_2$, K_2CO_3, HFIP, 0 °C, 20 min, 70%

[gram scale]



1. SiO_2, PDC, DCM, 30 °C, 30 min;
2. $NaBH_4$, EtOH, 0°C, 30 min; 84% (2 steps)

8a/**8b** = 3:1

8a (α-OH)
8b (β-OH)

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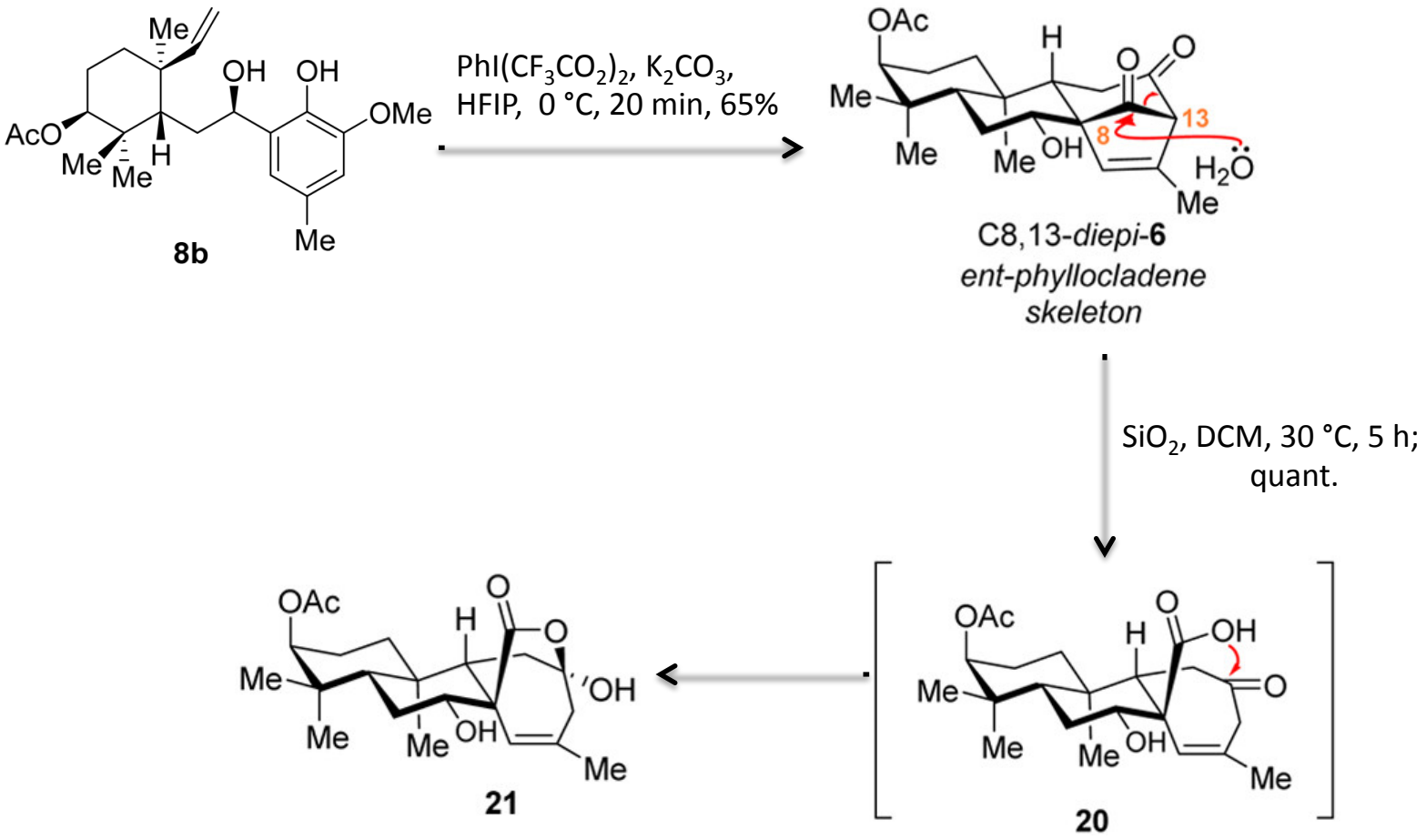
Construction of Tetracyclic Diketone C7-*epi*-**6**



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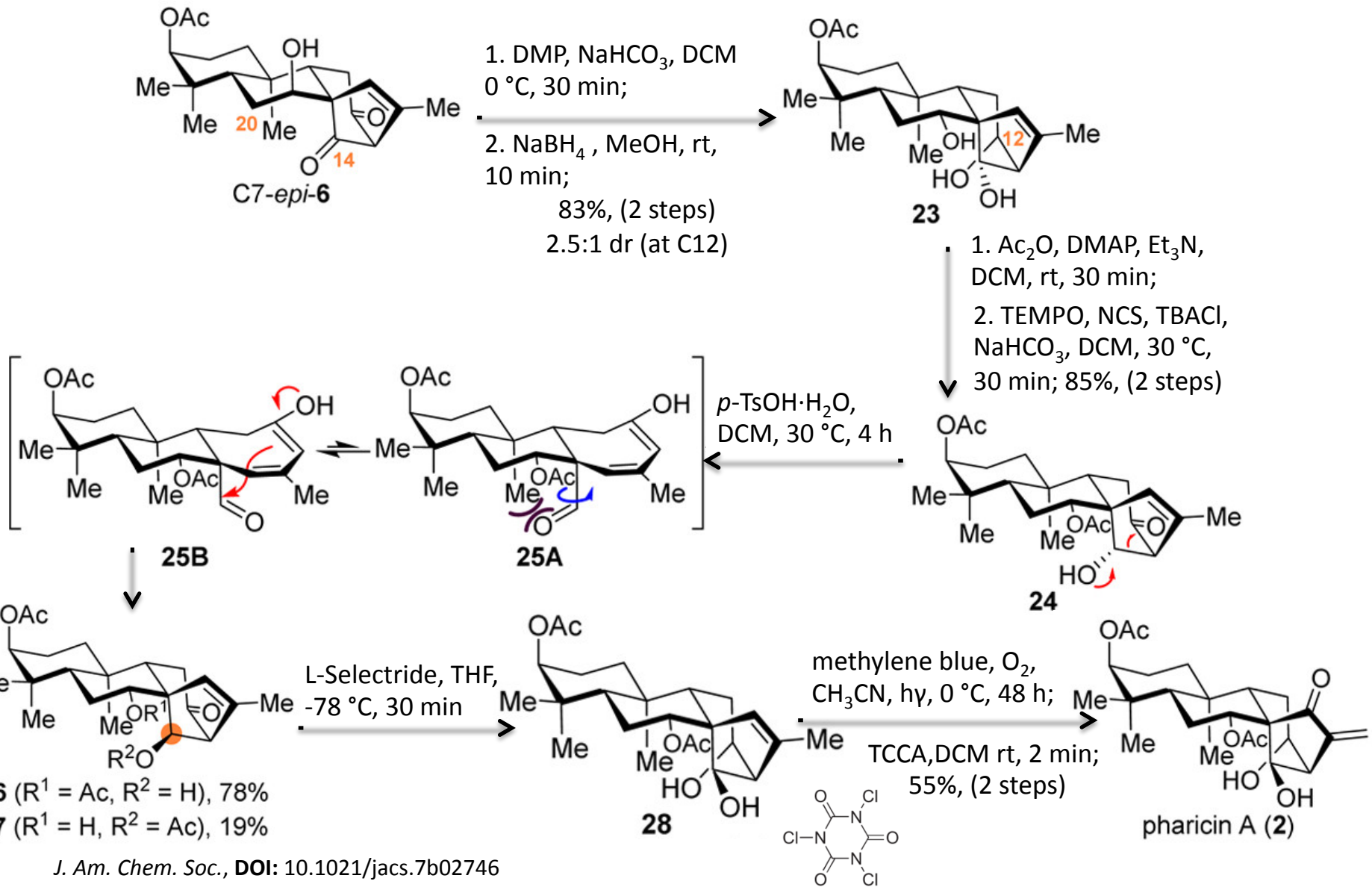
Total Syntheses of *ent*-Kaurenoids **2–5**



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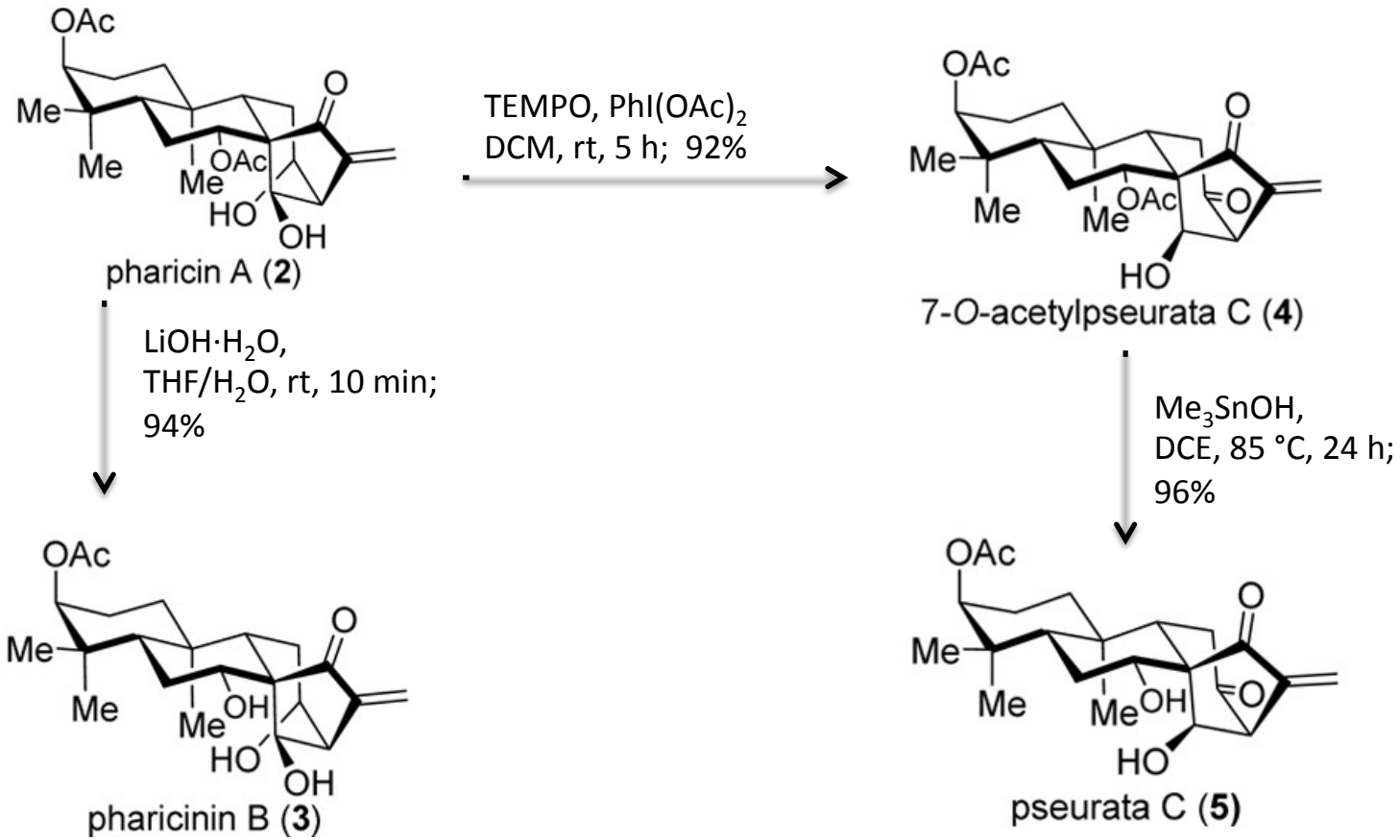

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Conclusion

- A new and efficient ODI-[5+2] cycloaddition/pinacol-type 1,2-acyl migration cascade for directly constructing the highly oxygenated bicyclo [3.2.1]octane core structure of *ent*-kaurene diterpenoids;
- A retro-aldol/aldol process and a singlet oxygen ene reaction;
- First asymmetric total syntheses of pharicin A, pharicinin B, 7-*O*-acetylpseurata C, and pseurata C;