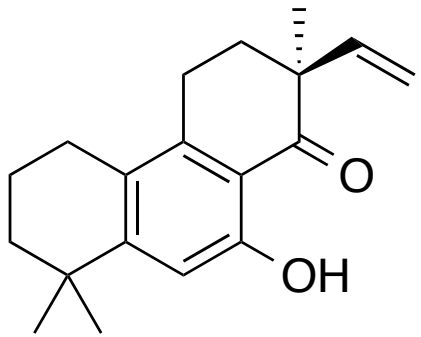
Palladium-Catalyzed Decarbonylative Dehydration for the Synthesis of α-Vinyl Carbonyl Compounds and Total Synthesis of (–)-Aspewentins A, B, and C

Yiyang Liu, Dr. Scott C. Virgil, Prof. Robert H. Grubbs and Prof. Brian M. Stoltz

Angew. Chem. Int. Ed. **2015**, 54, 1 – 5



(-)-Aspewentin **B**

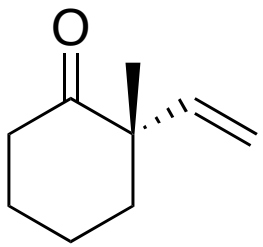
Ruiting Liu

Wipf Group Current Literature

08/07/2015

1

(*S*)-2-methyl-2-vinylcyclohexan-1-one

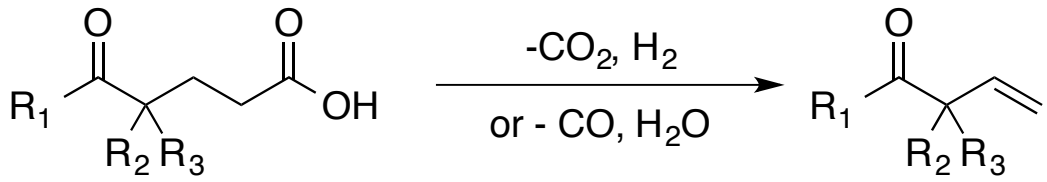


- A common structural motif in many natural products
- Not known as a single enantiomer in the literature
- Synthesis - vinylation of carbonyl compounds

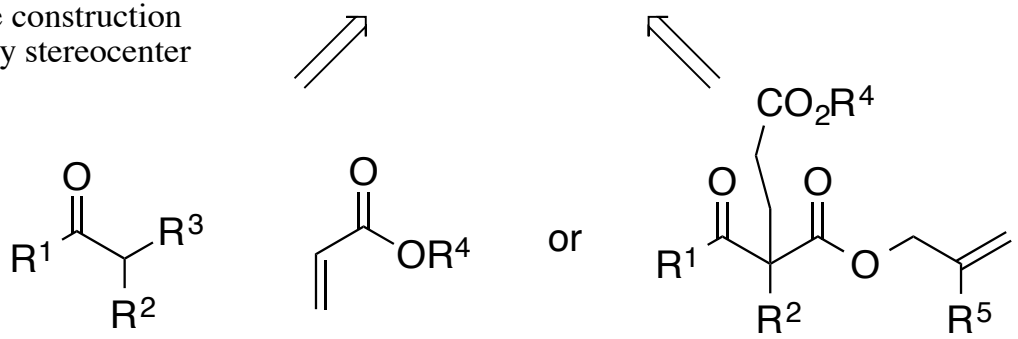
- direct coupling of an enolate nucleophile with a vinyl electrophile, limited to 1,3-dicarbonyl compounds or those with only one enolizable position

- addition of the enolate nucleophile to a vinyl surrogate followed by elimination. No catalytic or enantioselective result so far

Author's approach-decarboxylative elimination of d-oxocarboxylic acids

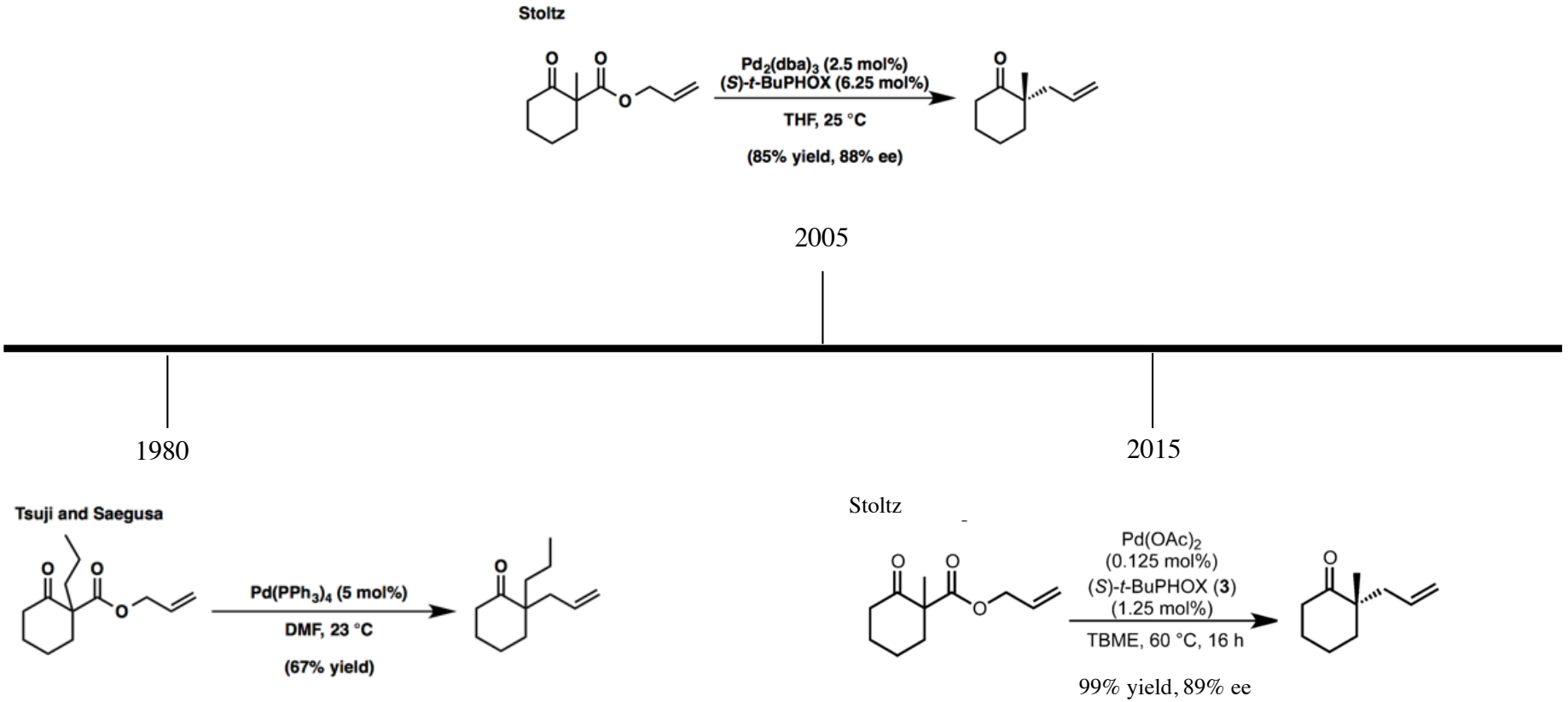


enantioselective construction
of the quaternary stereocenter



J. Am. Chem. Soc. 1985, 107, 273 – 274.
Angew. Chem. Int. Ed. 2005, 44, 6924 – 6927

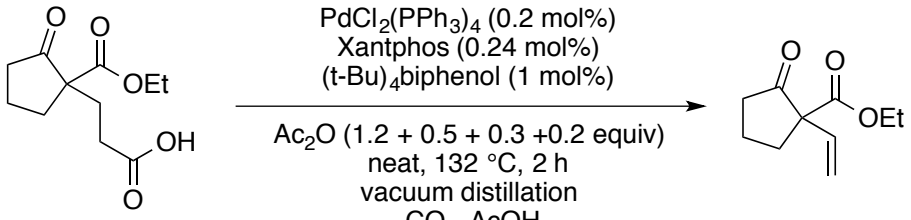
Decarboxylative Allylic Alkylation

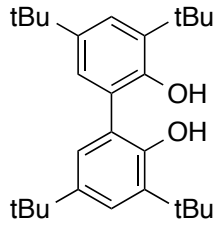


J. Am. Chem. Soc. 1980, 102, 6381–6384.
Tetrahedron Lett. 1980, 21, 3199–3202.
Angew. Chem., Int. Ed. 2005, 44, 6924–6927.
Adv. Synth. Catal. 2015, 357, 2238 – 2245

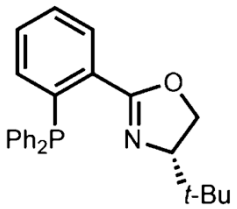
Optimized reaction conditions and results

For large scales:

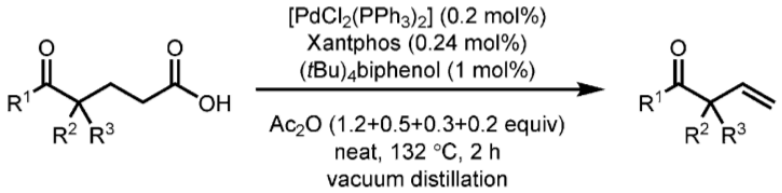


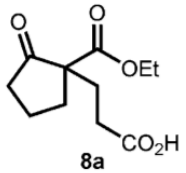
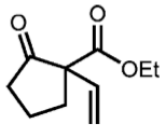
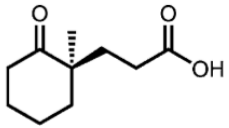
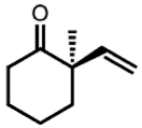
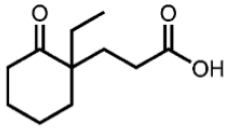
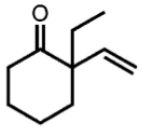
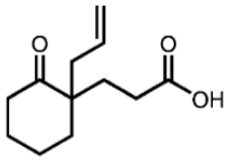
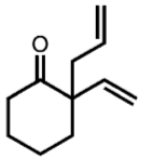
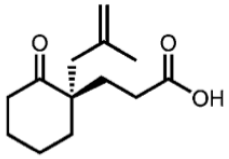
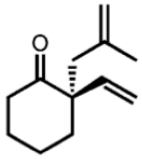
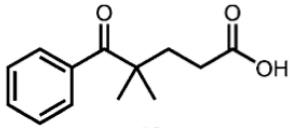
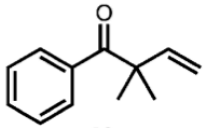


- Acetic anhydride converts the stearic acid into stearic anhydride, which then undergoes oxidative addition by Pd(0)
- Buildup of acid in the reaction mixture was responsible for olefin isomerization and erosion of alpha selectivity.

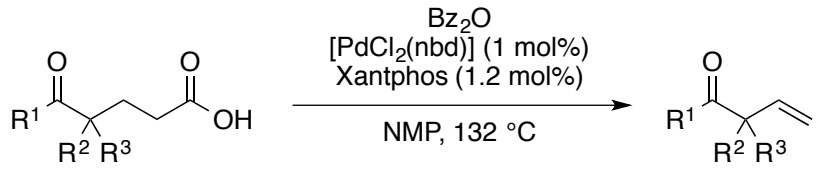


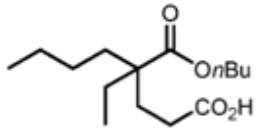
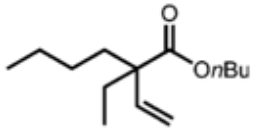
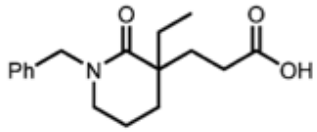
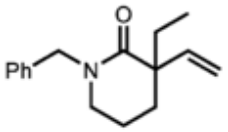
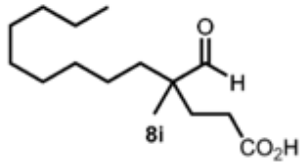
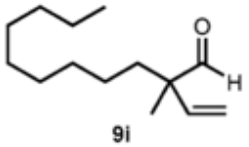
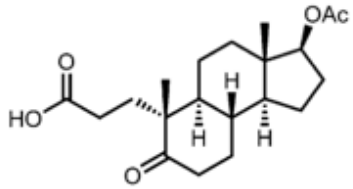
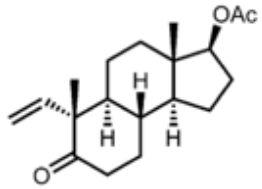
3
(*S*)-*t*-Bu-PHOX



Entry[a]	δ-Oxocarboxylic acid	Product	Yield and *ee*
1	 **8a**	 **9a**	67%
2	 **8b**	 *ent*-**7**	60% 92% *ee*
3	 **8c**	 **9c**	66%
4	 **8d**	 **9d**	54%[b]
5	 **8e**	 **9e**	69% 92% *ee*
6	 **8f**	 **9f**	75%

For small scales:



7	 8g	 9g	50%
8[c]			51%
9[c]	 8h	 9h	57%
10[c]	 8i	 9i	77%
11[c]			41%

nbd = 2,5- norbornadiene

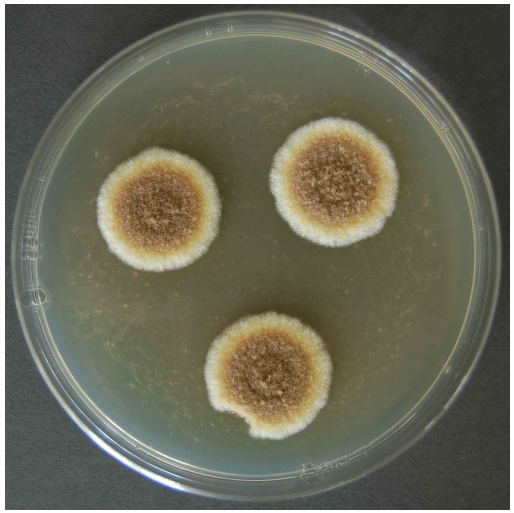
(+)-Aspewentins A, B, and C

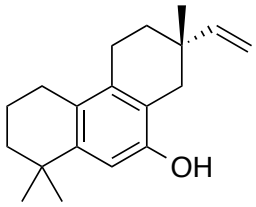
- Norditerpene natural product isolated from Aspergillus wentii
- Growth inhibition –

B: toxic to marine zooplankton (Artemia salina) , LC50 is 6.36 µM

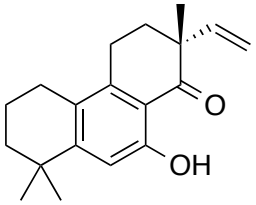
A: toxic to marine phytoplankton species (Chattonella marina, Heterosigma akashiwo), LC50 values is 0.81 and 2.88 µM

C: toxic to Alexandrium sp., with an LC50 of 8.73 µM.

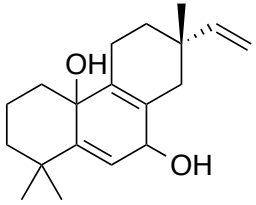




(+)-Aspewentin A



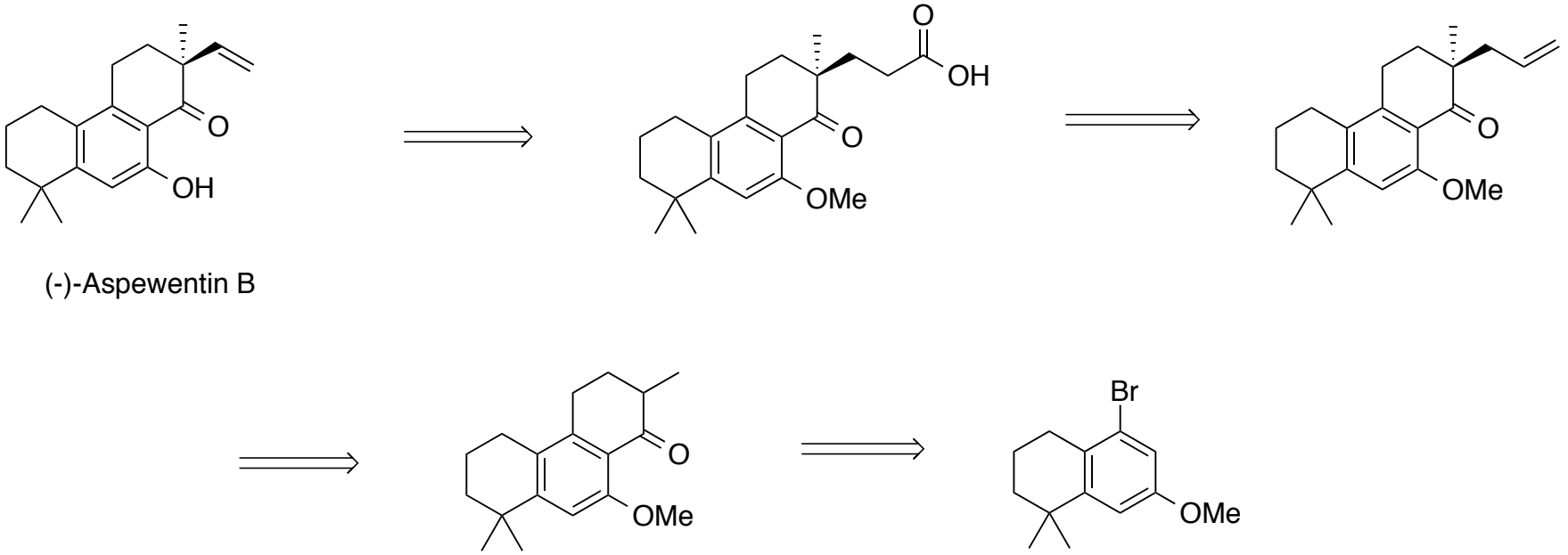
(+)-Aspewentin B



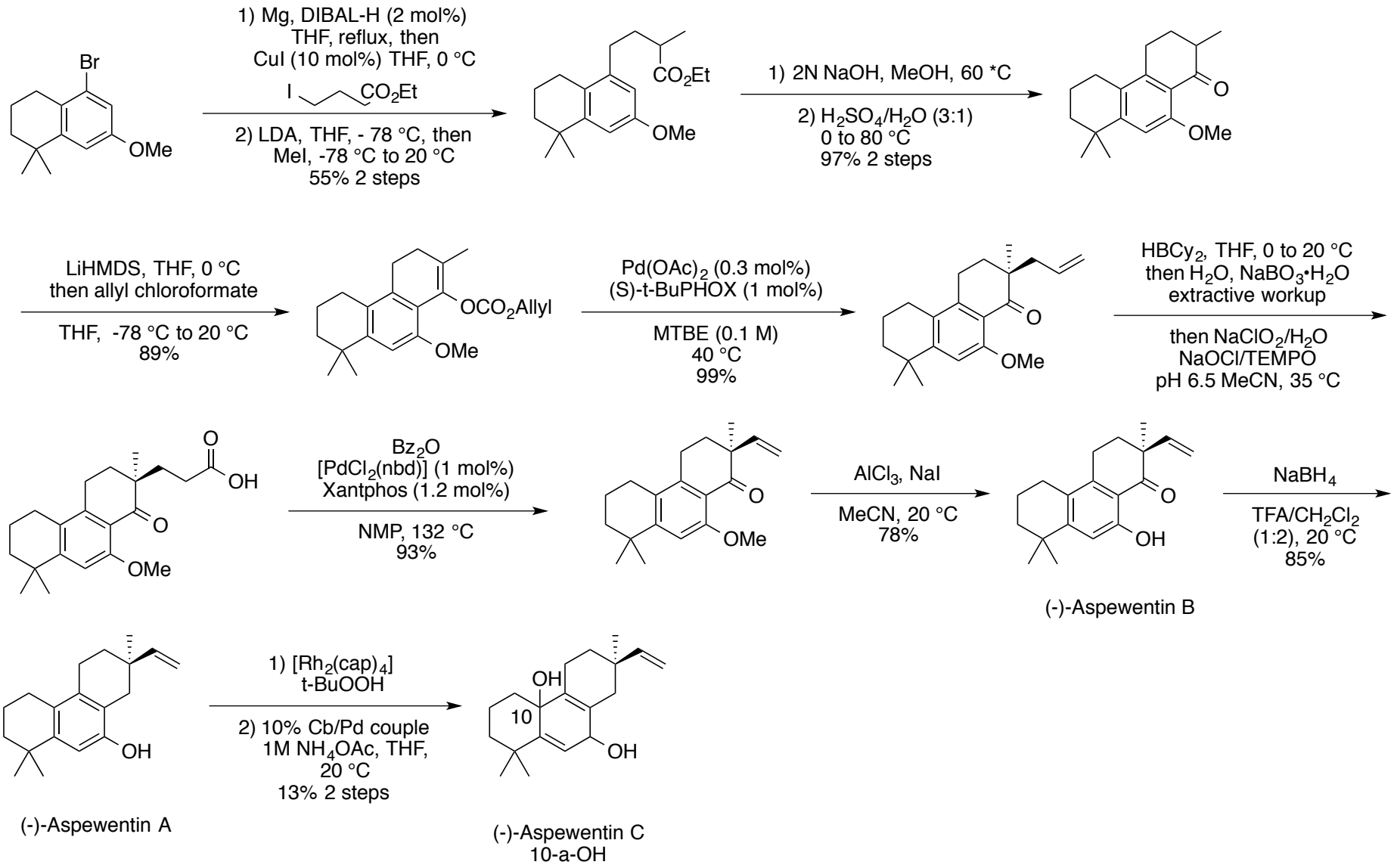
(+)-Aspewentin C

J.Nat.Prod. 2014,77, 429 – 432.

Retrosynthesis



(-)-Aspewentin B


1) Mg, DIBAL-H (2 mol%)
THF, reflux, then
CuI (10 mol%) THF, 0 °C
I CO2Et
2) LDA, THF, - 78 °C, then
MeI, -78 °C to 20 °C
55% 2 steps
1) 2N NaOH, MeOH, 60 *C
2) H2SO4/H2O (3:1)
0 to 80 °C
97% 2 steps
LiHMDS, THF, 0 °C
then allyl chloroformate
THF, -78 °C to 20 °C
89%
Pd(OAc)2 (0.3 mol%)
(S)-t-BuPHOX (1 mol%)
MTBE (0.1 M)
40 °C
99%
HBCy2, THF, 0 to 20 °C
then H2O, NaBO3•H2O
extractive workup
then NaClO2/H2O
NaOCl/TEMPO
pH 6.5 MeCN, 35 °C
Bz2O
[PdCl2(nbd)] (1 mol%)
Xantphos (1.2 mol%)
NMP, 132 °C
93%
AlCl3, NaI
MeCN, 20 °C
78%
NaBH4
TFA/CH2Cl2
(1:2), 20 °C
85%
(-)-Aspewentin B
1) [Rh2(cap)4]
t-BuOOH
2) 10% Cb/Pd couple
1M NH4OAc, THF,
20 °C
13% 2 steps
(-)-Aspewentin A
(-)-Aspewentin C
10-a-OH

Conclusion

- New approach to access a-vinyl quaternary carbonyl compounds by palladium-catalyzed decarbonylative dehydration of d-oxocarboxylic acids
- First enantioselective total synthesis of (-)-Aspewentins A, B, and C