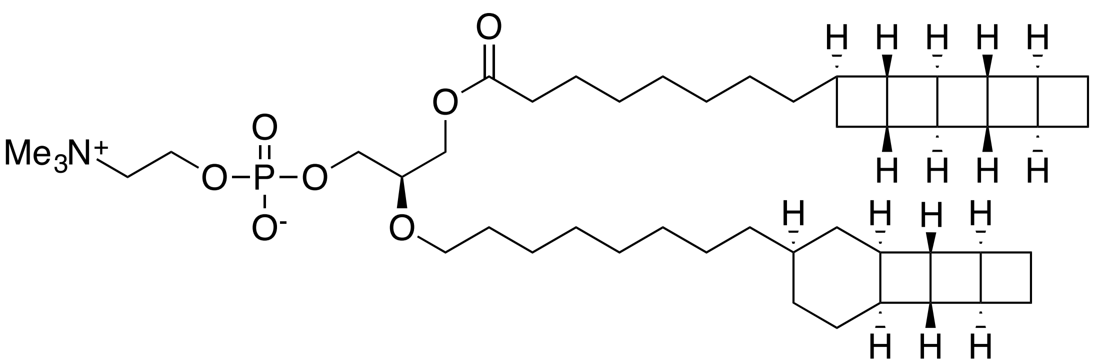
Chemical Synthesis and Self-Assembly of a Ladderane Phospholipid

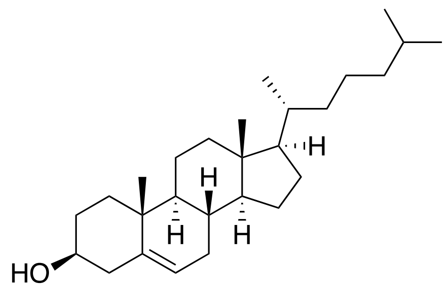
Mercer, J. A. M.; Cohen, C. M.; Shuken, S. R.; Wagner, A. M.; Smith, M. W.; Moss, F. R.; Smith, M.D.; Vahala, R.; Gonzalez-Martinez, A.; Boxer, S.G.; Burns, N. Z. *J. Am. Chem. Soc.* **2016**, *138*, 15854.



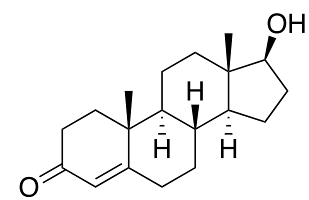
Michael Houghton
Wipf Group
12/24/16

General Uses and Types of Lipids

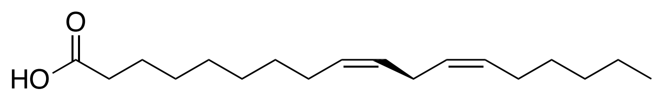
- Lipids are used to provide and store energy, absorb vitamins, cell membrane and general cell health, signaling, and numerous other biological activities.



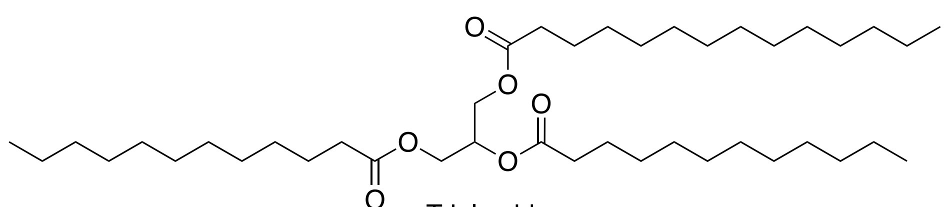
Cholesterol



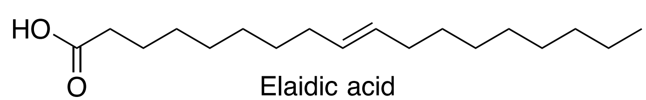
Testosterone



Linoleic acid



Triglceride
(coconut oil)



Elaidic acid

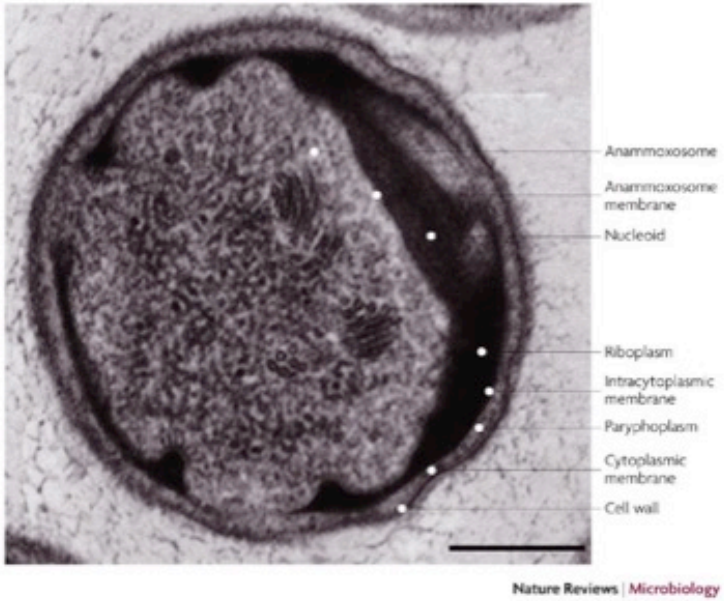
Ladderane Phospholipid is Found in Anammox Bacteria

- Anammox- Anaerobic Ammonium Oxidizing

- These bacteria convert ammonia and nitrite into dinitrogen and water

- This process takes place in a unique organelle, the anammoxosome, which is composed of ~ 90 % ladderane phospholipds.

- These densely packed phospholipds are believed to keep hydrazine and hydroxylamine waste products from damaging the rest of the cell.



- There are five types of known anammox bacteria: Brocadia, Keunenia, Anammoxoglobus, Jettenia and Scalindua.

- Anammox bacteria are used industrially to purify ammonia rich, contaminated water.

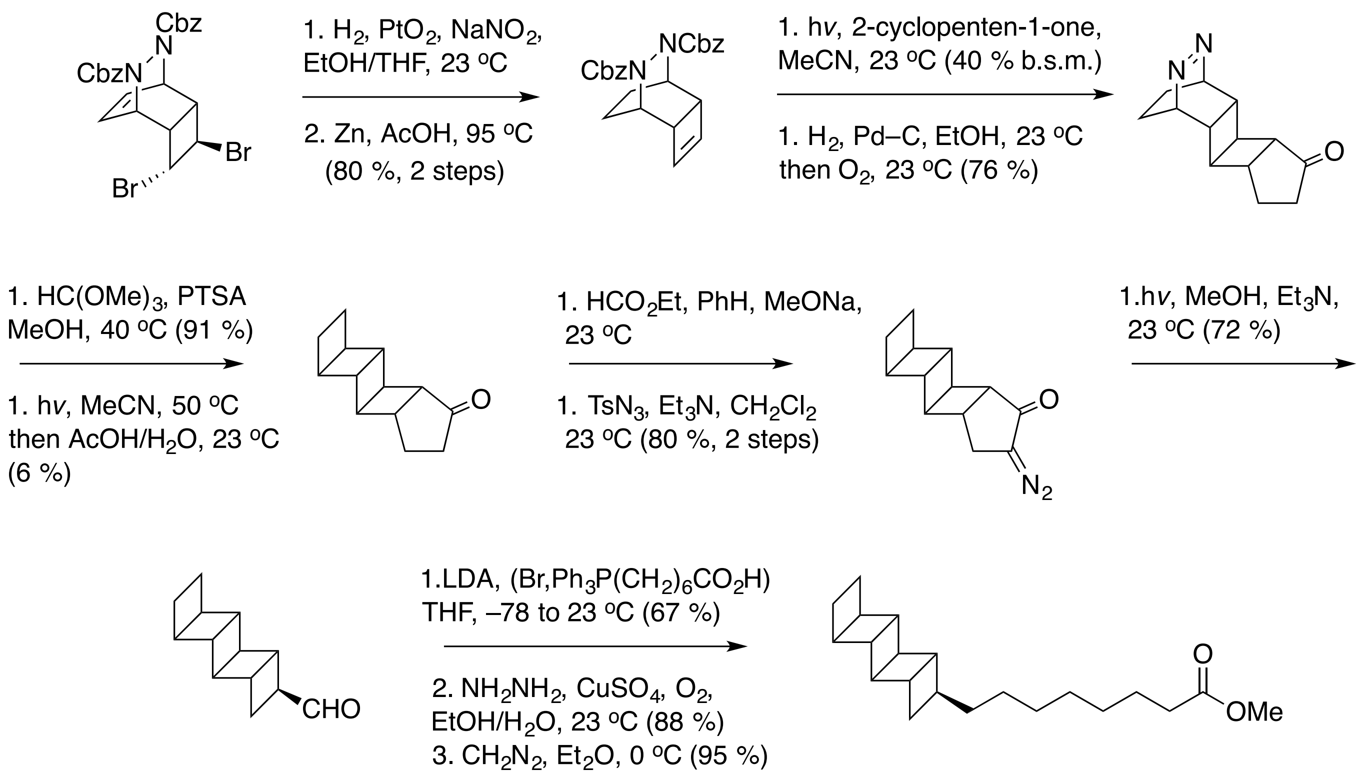
- Purification difficulties have prohibited the isolation of pure material and useful quantities of material.

1. Reimann, J.; Jetten, M. S.; Keltjens, Jan T. Metal Ions in Life Sciences. **15**. Springer. 257-313. 2. Strous, M. *et al*. *Nature*. **1999**, *400*, 446-449. 3. Kartal, B.; Keunen, J. G.; Van Loosdrecht, M. C. *Science*. **2010**, *328*, 702-703.

Previous Synthetic Efforts – Racemic

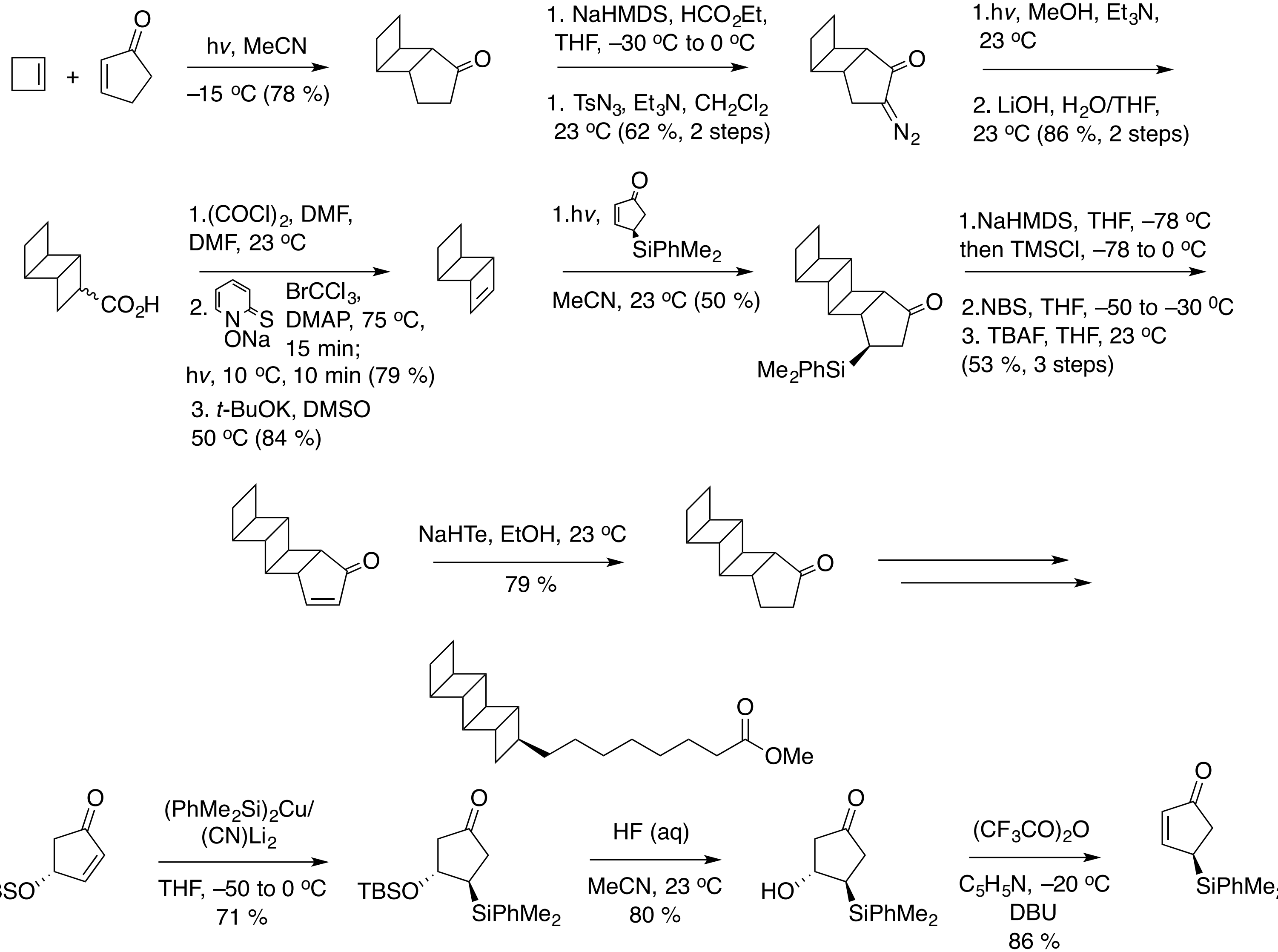
"The recent report of the remarkable pentacyclic C_{20}-fatty acid methyl ester from the anammoxic microbe *Candidatus Brocadia anammoxidans* opens a fascinating new chaper in the field of natural products."

- E. J. Corey



Mascitti, V.; E. J. Corey, *JACS* **2004**, *126*, 15664-15665.

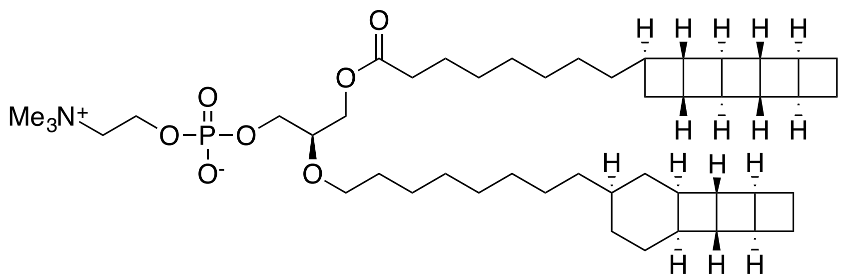
Previous Synthetic Efforts – Enantioselective



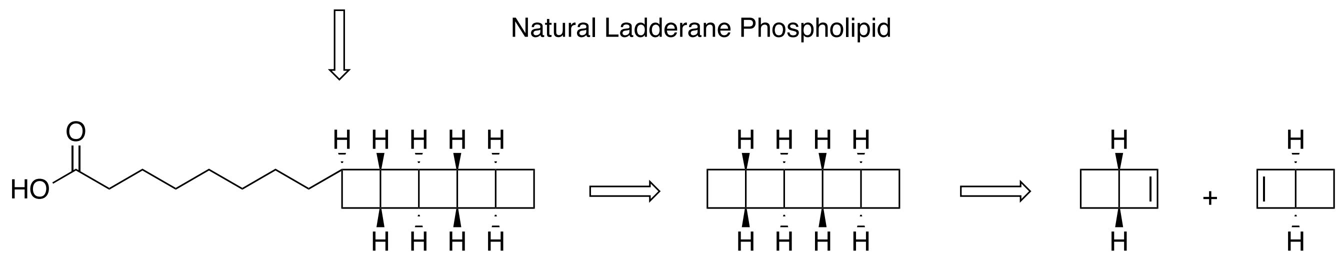
5

Mascitti V.; E. J. Corey, *JACS* **2006**, *128*, 3118-3119.

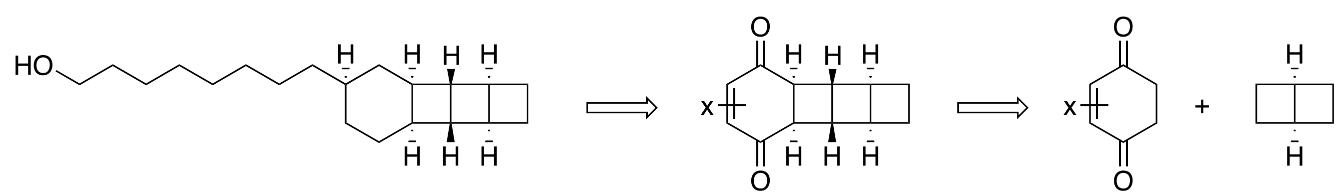
Retrosynthetic Analysis



Natural Ladderane Phospholipid



[5]-ladderanoic acid



[3]-ladderanol

Route to [5]-Ladderanoic Acid

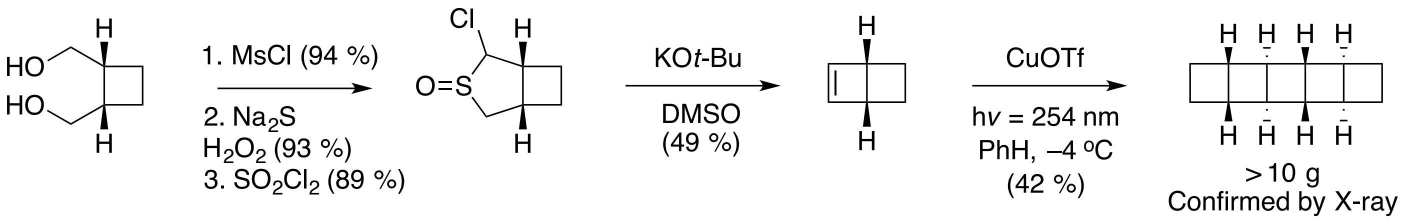
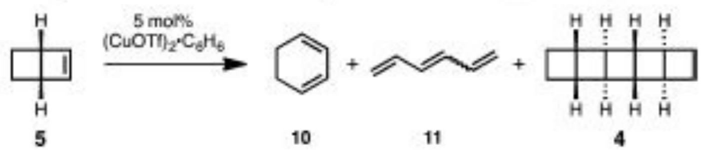


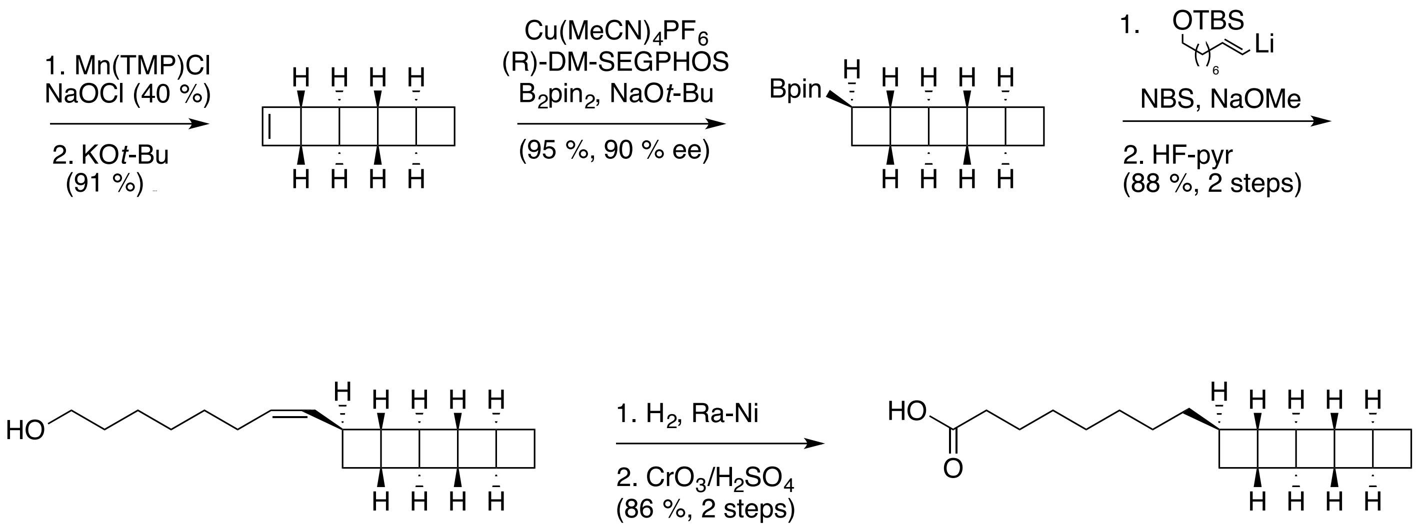
Table 1. Optimization of Bicyclohexene [2 + 2][a]



entry	solvent	temperature	*hv*	5[b]	10 + 11[b]	4[b]
1	THF	27 °C	254 nm		60%	
2	Et_2O	27 °C	254 nm		86%	
3	heptane	27 °C	254 nm		51%	7%
4	heptane	23 °C	dark	24%	46%[c]	
5	heptane	−4 °C	dark	70%	2%[c]	
6	heptane	−4 °C	254 nm	43%	39%	18%
7	toluene	−4 °C	254 nm	24%	46%	28%
8	benzene	−4 °C	254 nm	21%	37%	42%

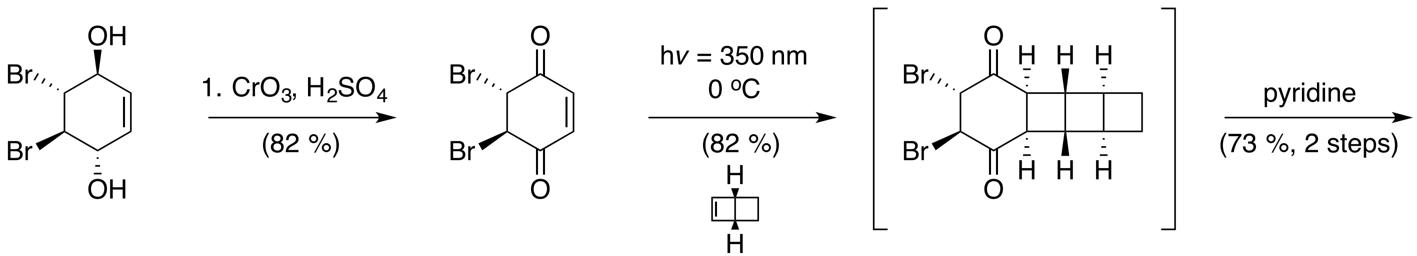
[a]Reactions were conducted on 1 mmol scale in 1 mL indicated solvent. [b]Yields calculated by comparison to ^1H NMR internal standard. [c]Only **10**.

Route to [5]-Ladderanoic Acid



> 600 mg synthesized

Route to [3]-Ladderanol



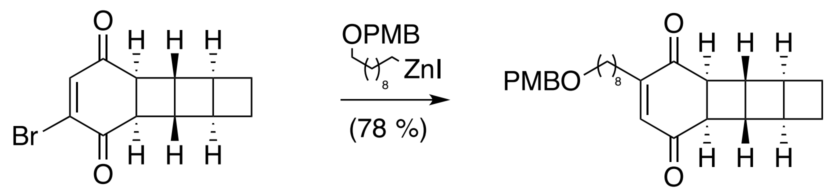
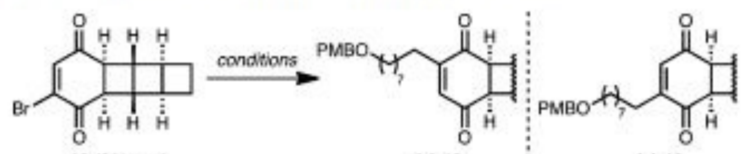


Table 2. Enantiodivergent Coupling Strategies[a]

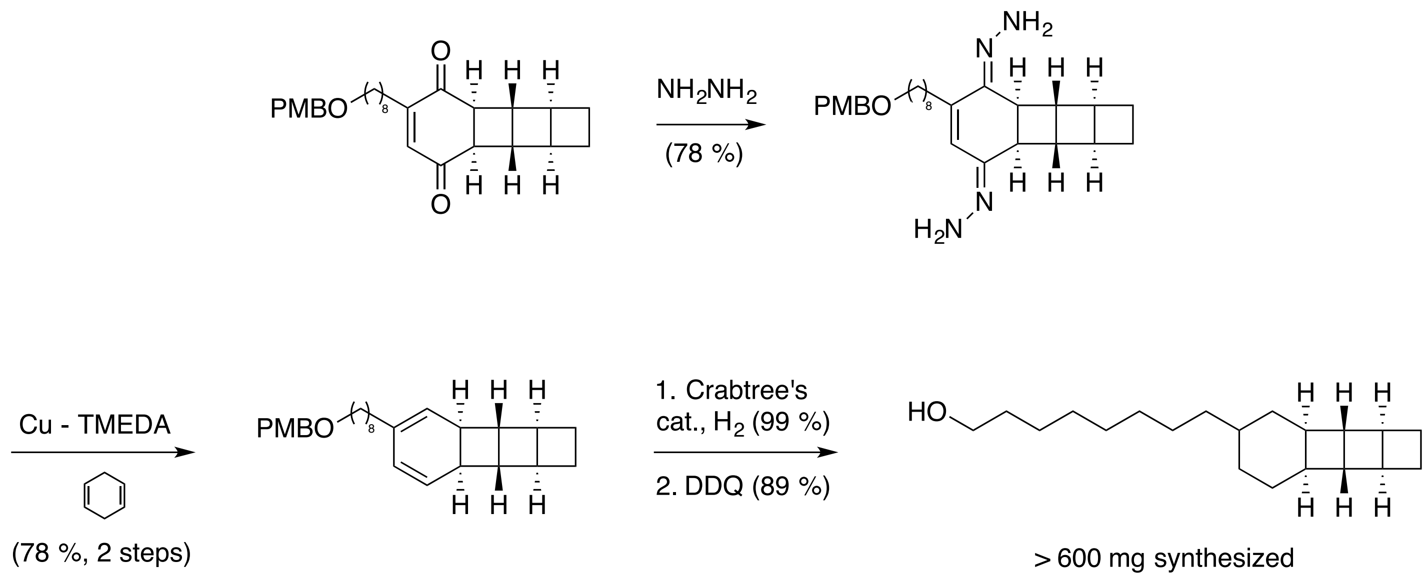


18 (80% ee) (−)-19 (+)-19

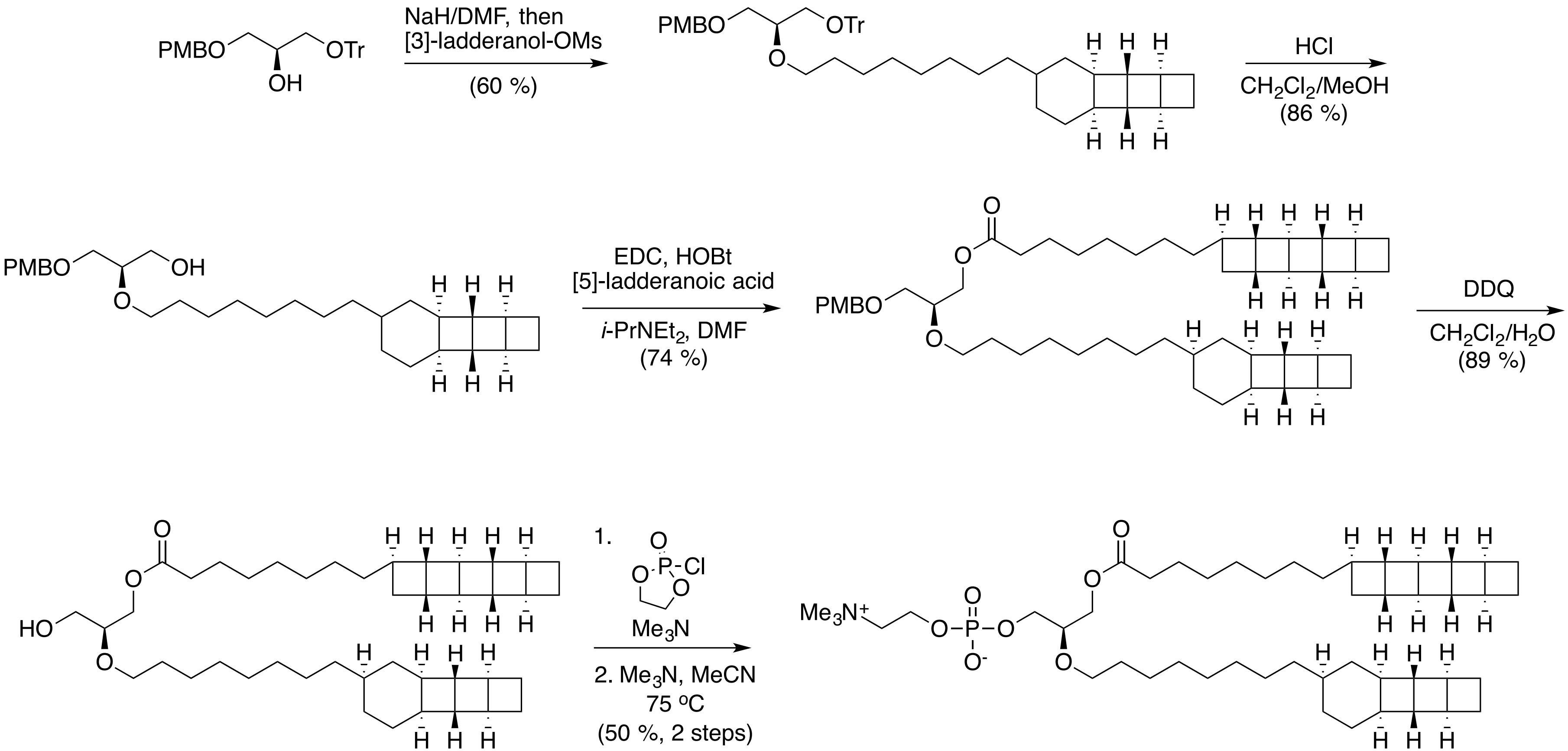
entry	nucleophile	catalyst	yield[b]	ee[c]
1	PMBO–(CH2)6–ZnI	$Pd(OAc)_2$ + XPhos	88%	+30%
2	PMBO–(CH2)6–ZnI	none	64%	−80%
3	PMBO–(CH2)6–BF_3K	$PdCl_2(dppf)\cdot CH_2Cl_2$	68%	+80%

[a]Reactions conducted with 80% ee **18**. [b]Yields reflect isolated yields after silica chromatography. [c]Enantiomeric excess determined by chiral HPLC.

Route to [3]-Ladderanol



Final Route to Ladderane Phosopholipid



Conclusions

- Successfully completed first enantioselective selective synthesis of a complete ladderane phospholipid

- Provided first proof of absolute configuration of natural ladderane.

- Developed novel dimerization of bicyclohex[2.2.0]ene to form the fused pentacyclobutane core.

- Confirmed Wipf *et al* computations on sign of *Trans*-(*R*)-ladderane

Zuber, G.; M.-R.; Beratan, D. N.; Wipf, P. *Chirality* **2005**, *17*, 507-510.