Ladderanes: Uses and Synthesis

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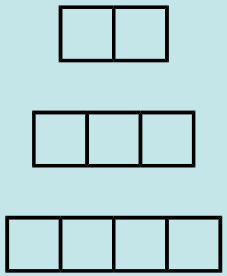
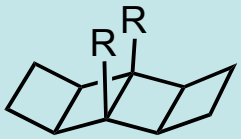
Denmark Group Meeting

October 28, 2008

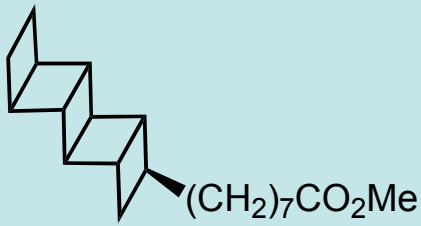
Outline



- Ladderane types and classifications
- Potential applications of ladderanes



- Synthesis of ladderanes
- Ladderane natural products



Types of Ladderanes - Linear

Length

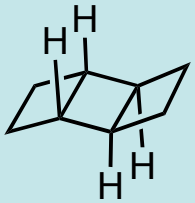
[2]-Ladderane

[3]-Ladderane

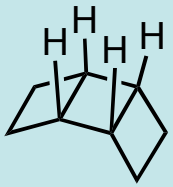
[4]-Ladderane

Increasing the number of fused cyclobutanes increases the heat of formation by ~20-23kcal/mol per ring

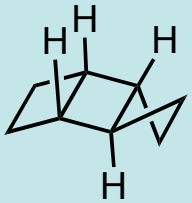
Stereochemistry



cis, anti, cis
Lowest energy



cis, syn, cis



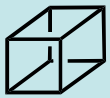
cis, trans
Highest energy

Nouri, D. H.; Tantillo, D. J. *Curr. Org. Chem.* **2006**, *10*, 2055-2074.

Types of Ladderanes - Cyclic

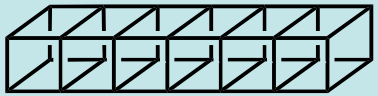
Named based on Size

[3]-Prismane

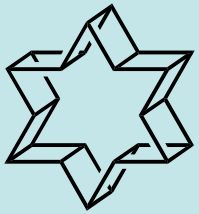


[4]-Prismane
(cubane)

[5]-Prismane



Hexa[4]prismane



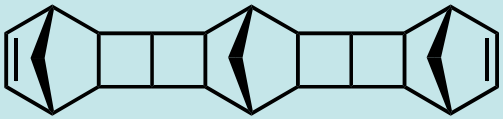
Israelane

Currently these structures are curiosities.

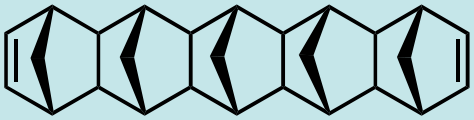
Nouri, D. H.; Tantillo, D. J. *Curr. Org. Chem.* **2006**, *10*, 2055-2074.

Ladderanes - Molecular Spacers

[10]-Ladderane



10σ binane

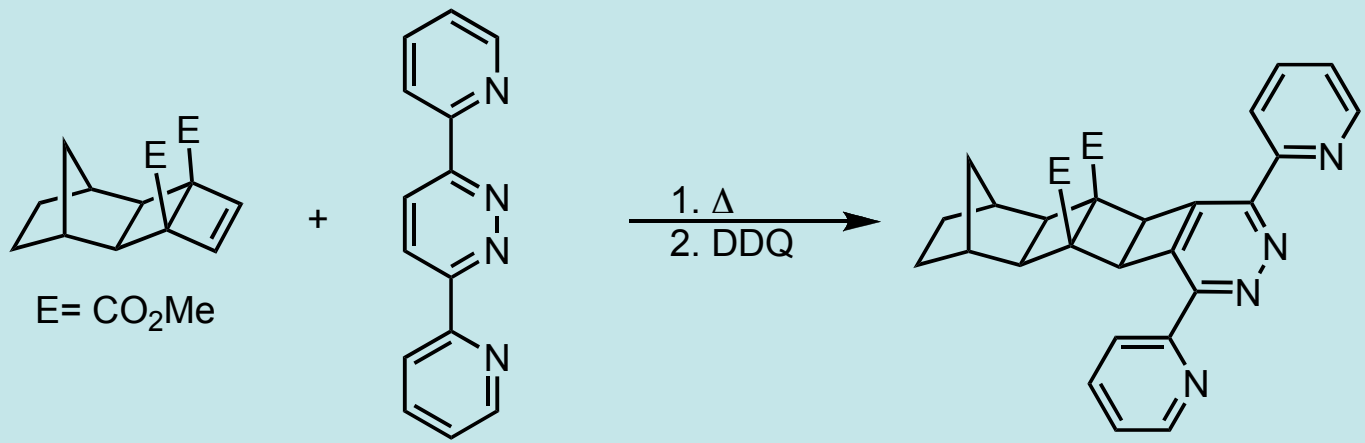


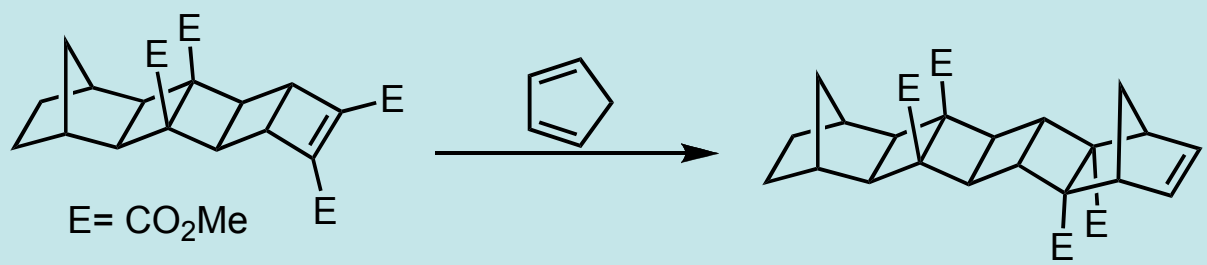
[5]polynorbornane

Warrener, R. N.; Abbenante, G. *J. Am. Chem. Soc.* **1994**, *116*, 3645-3646.

Ladderanes - Molecular Spacers

Examples of capping to yield end functionalized materials



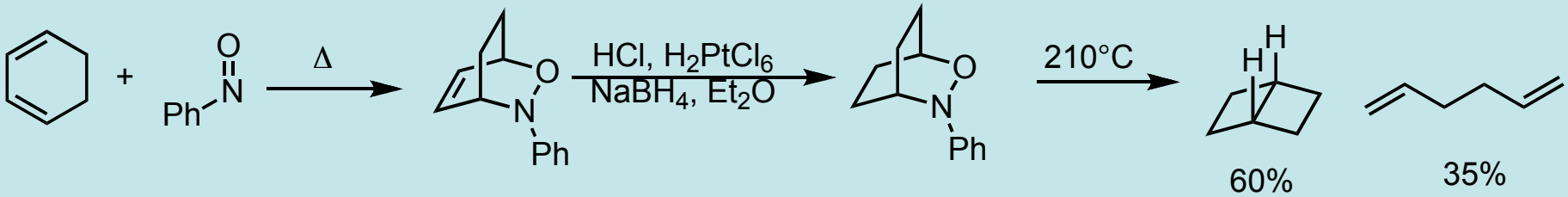


Possible applications to molecular electronics

Warrener, R. N.; Abbenante, G.; Kennard, C. H. L. *J. Am. Chem. Soc.* **1994**, *116*, 3645-3646.

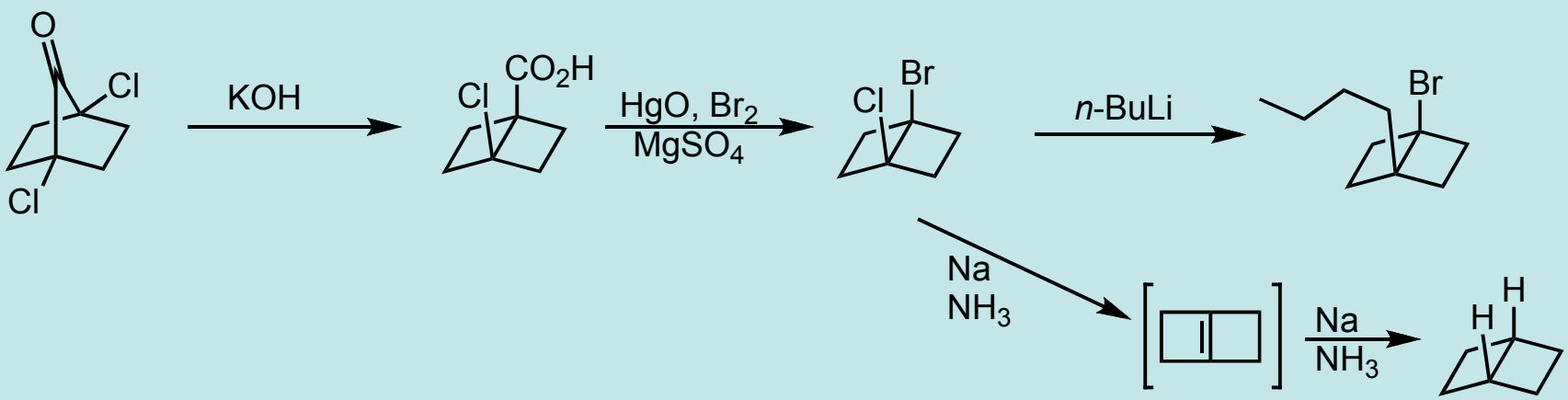
Synthesis of [2]-Ladderane

First optimized synthesis (1963):



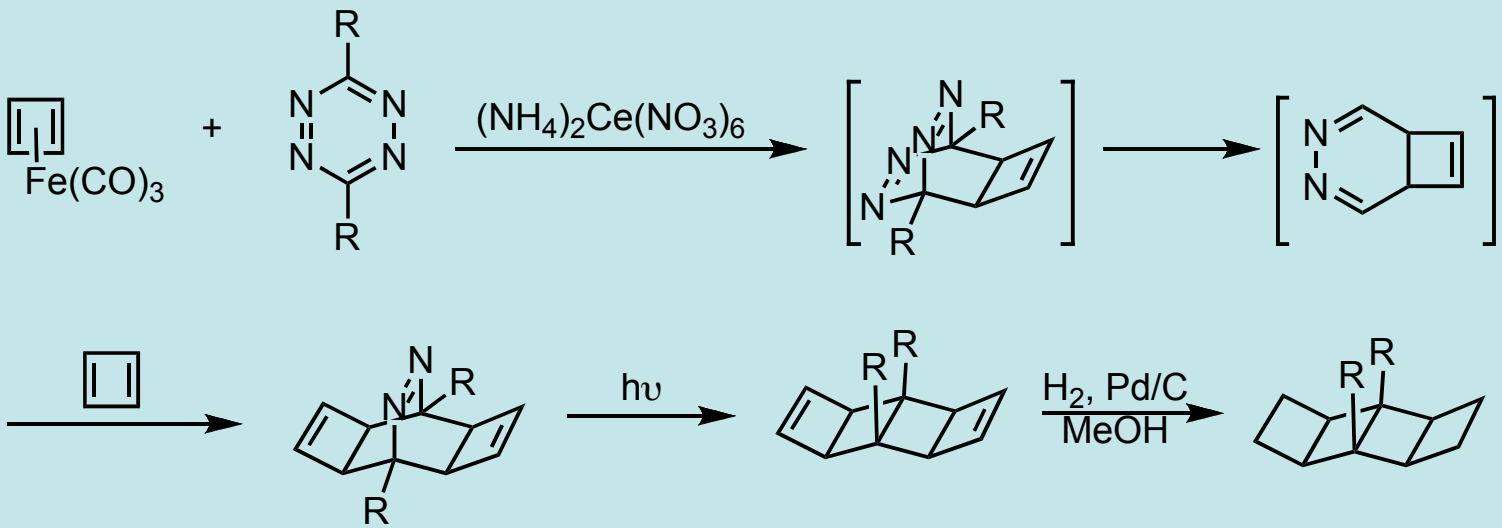
Thermally stable!

Alternative synthesis (1986):



Griffin, C. E.; Hepfinger, N. F.; Shapiro, B. L. *J. Am. Chem. Soc.* **1963**, *85*, 2683-2684.
Wiberg, K. B.; et al. *Tetrahedron*, **1986**, *42*, 1895-1902.

Synthesis of a [5]-Ladderane

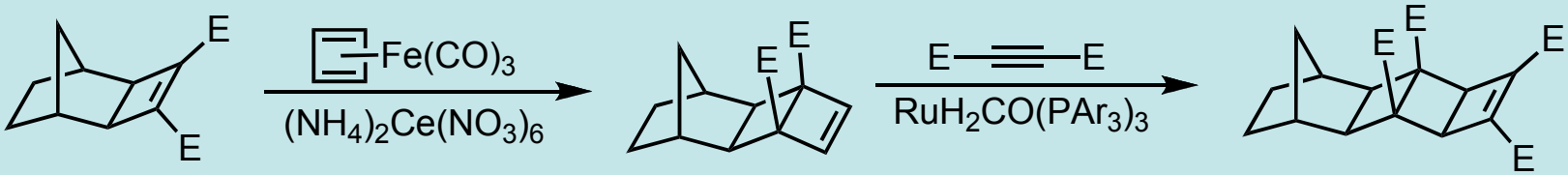


R= CO_2Me

- Synthesis of ladderanes has been accomplished
- Ladderanes are kinetically stable
- Cis-trans-cis isomers are typically obtained

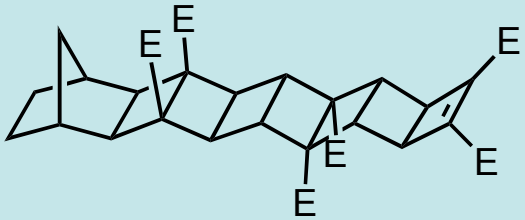
Martin, H.-D.; Hekman, M. *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 431-432.

Higher Order Ladderanes

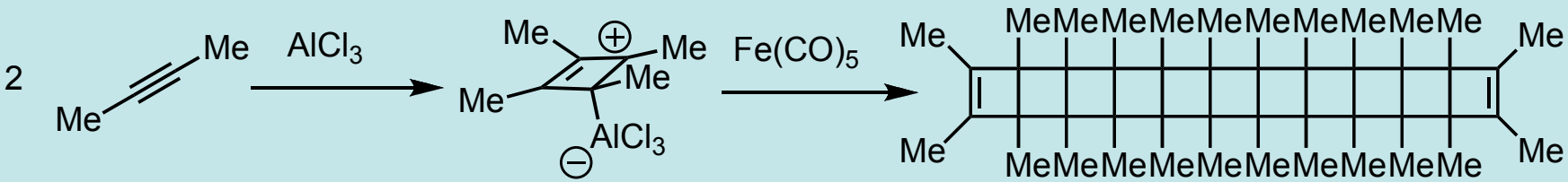


E= CO_2Me
Ar = *p*-FC_6H_4

ca. 60% (2 steps)



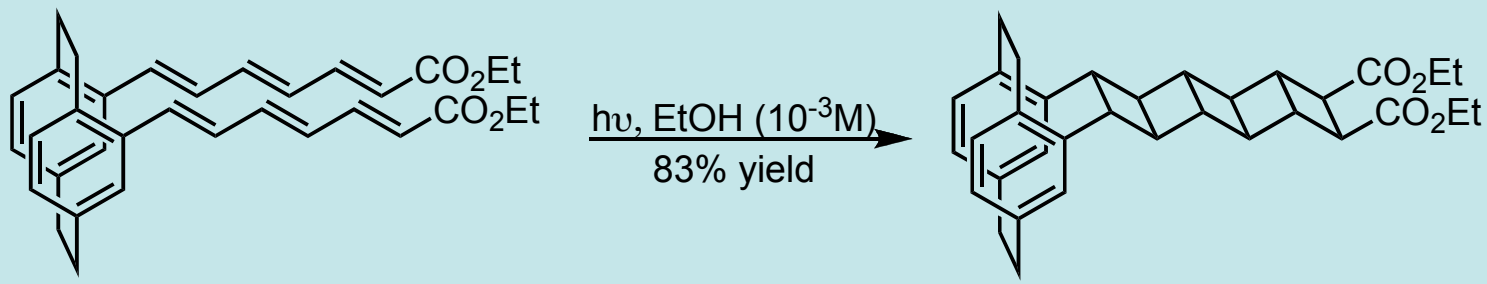
[7]-Ladderane

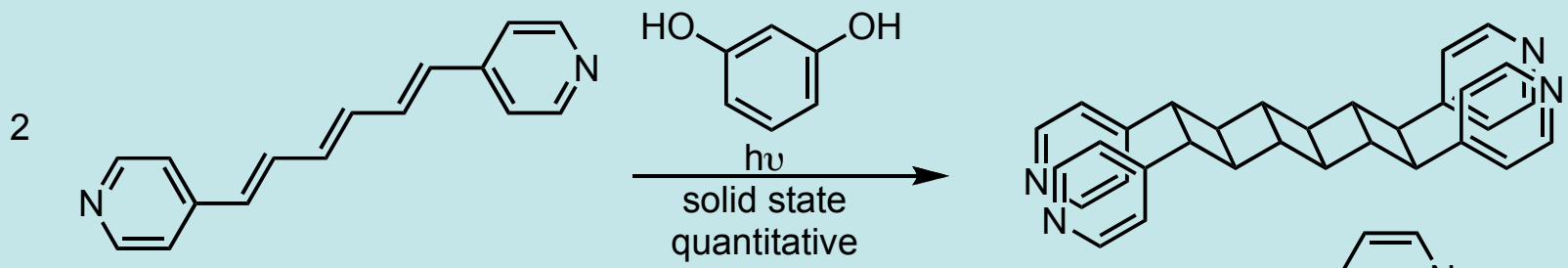


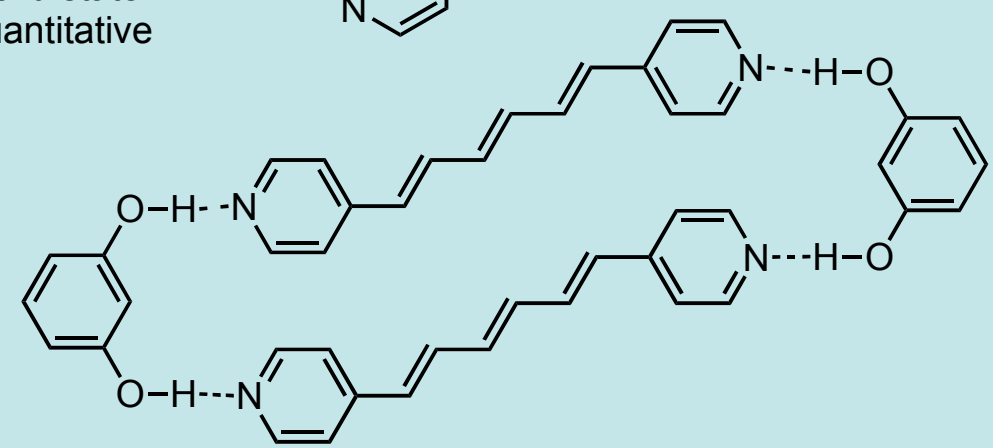
Formed a statistical mixture of up to [11]-Ladderane

Warrener, R. N.; Abbenante, G. *J. Am. Chem. Soc.* **1994**, *116*, 3645-3646.
Marsella, M. J.; et al. *Synlett* **2004**, 192-194.

One Step Synthesis







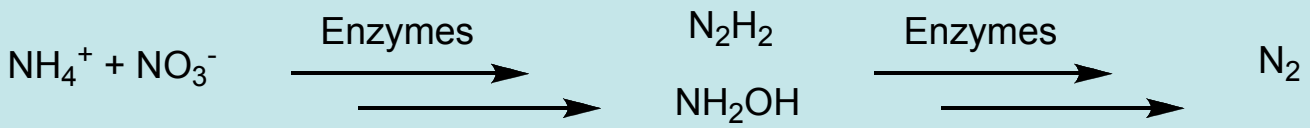
Isolated polyolefins have not yet been shown to form ladderanes

Hopf, H.; et al. *Eur. J. Org. Chem.* **2005**, 567-581.
Friscic, T.; MacGillivray, L. R. *Supramol. Chem*. **2005**, *17*, 47-51.

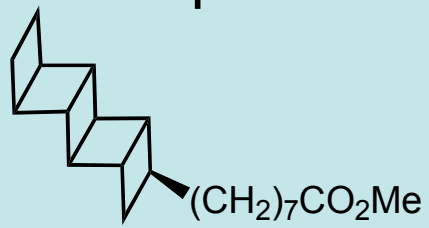
Ladderanes in Natural Products

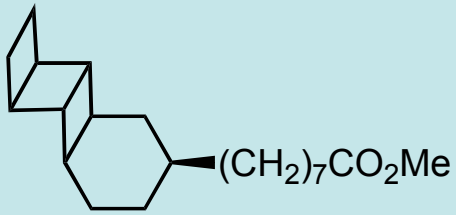
Anammox bacteria

- Deep sea bacteria
- Capable of ammonia oxidation



- Produce N_2H_2 and NH_2OH
  - Highly toxic intermediates
  - Membrane permeable
- Ladderane lipids isolated from the bacteria

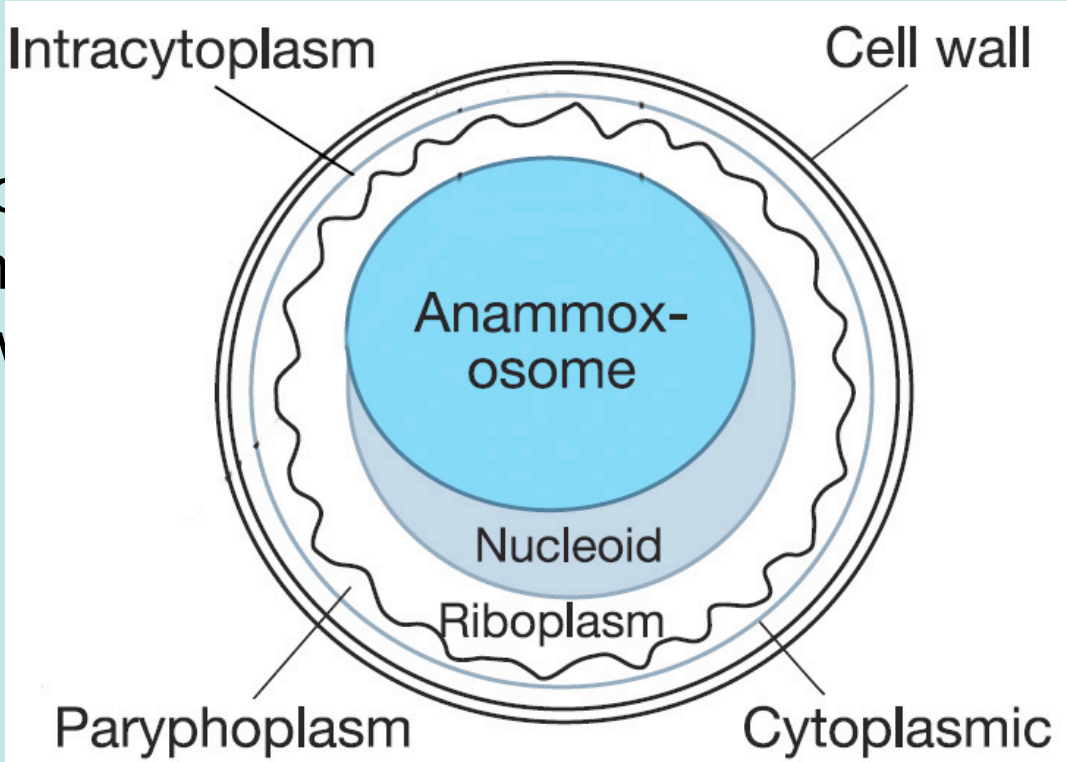




Damsté, J. S. S.; et al. *Nature*, **2002**, 419, 708-712.

Ladderanes in Natural Products

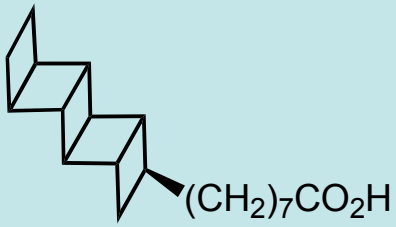
- Ladderane lipids form dense lipid bilayers
  - Ladderane lipid bilayers: 1.5 kg/dm^3
  - Normal lipid bilayers: 1.2 kg/dm^3
- Denser bilayers prevent diffusion of N_2H_2 and NH_2OH



- Study o availability
  - ~3n ox bacteria
  - Slov
    -

Damsté, J. S. S.; et al. *Nature*, **2002**, 419, 708-712.
Damsté, J. S. S.; et al. *FEBS Journal*, **2005**, 4270-4283.

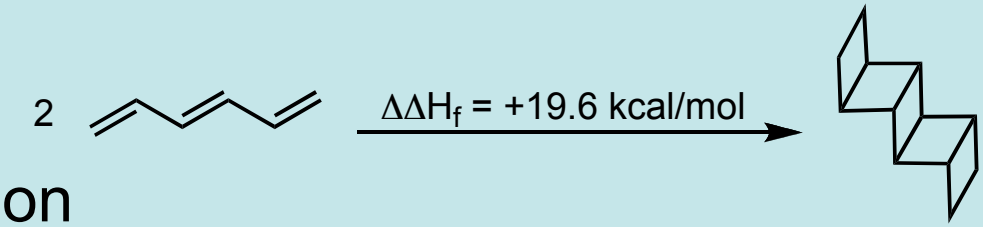
Pentacycloanammoxic Acid Synthesis



Pentacycloanammoxic Acid

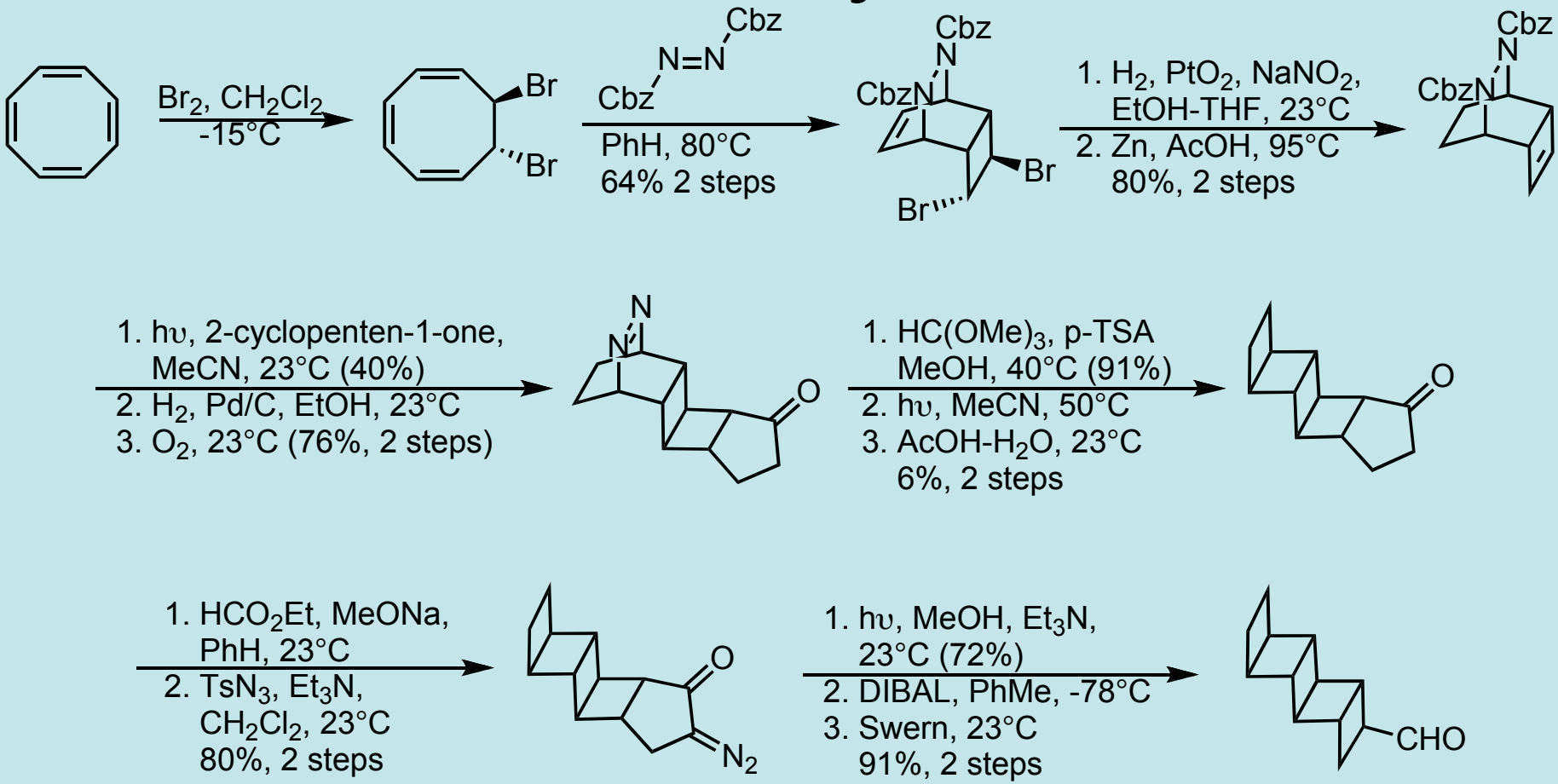
Goals of Total Synthesis:
- Verify structure
- Determine absolute stereochemistry
- Provide a larger amount of material

Potential Problems:
- Highly strained core
- Very little functionalization
- 9 Contiguous stereocenters



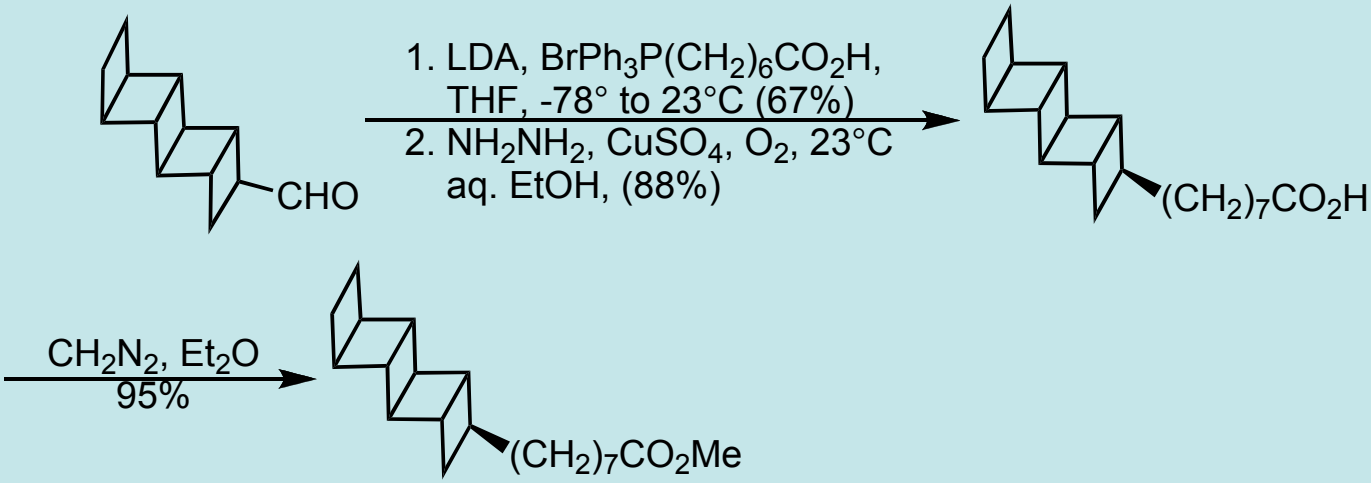
Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2004**. *126*, 15664-15665.

Pentacycloanammoxic Acid Racemic Synthesis



Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2004**. *126*, 15664-15665.

Pentacycloanammoxic Acid Racemic Synthesis

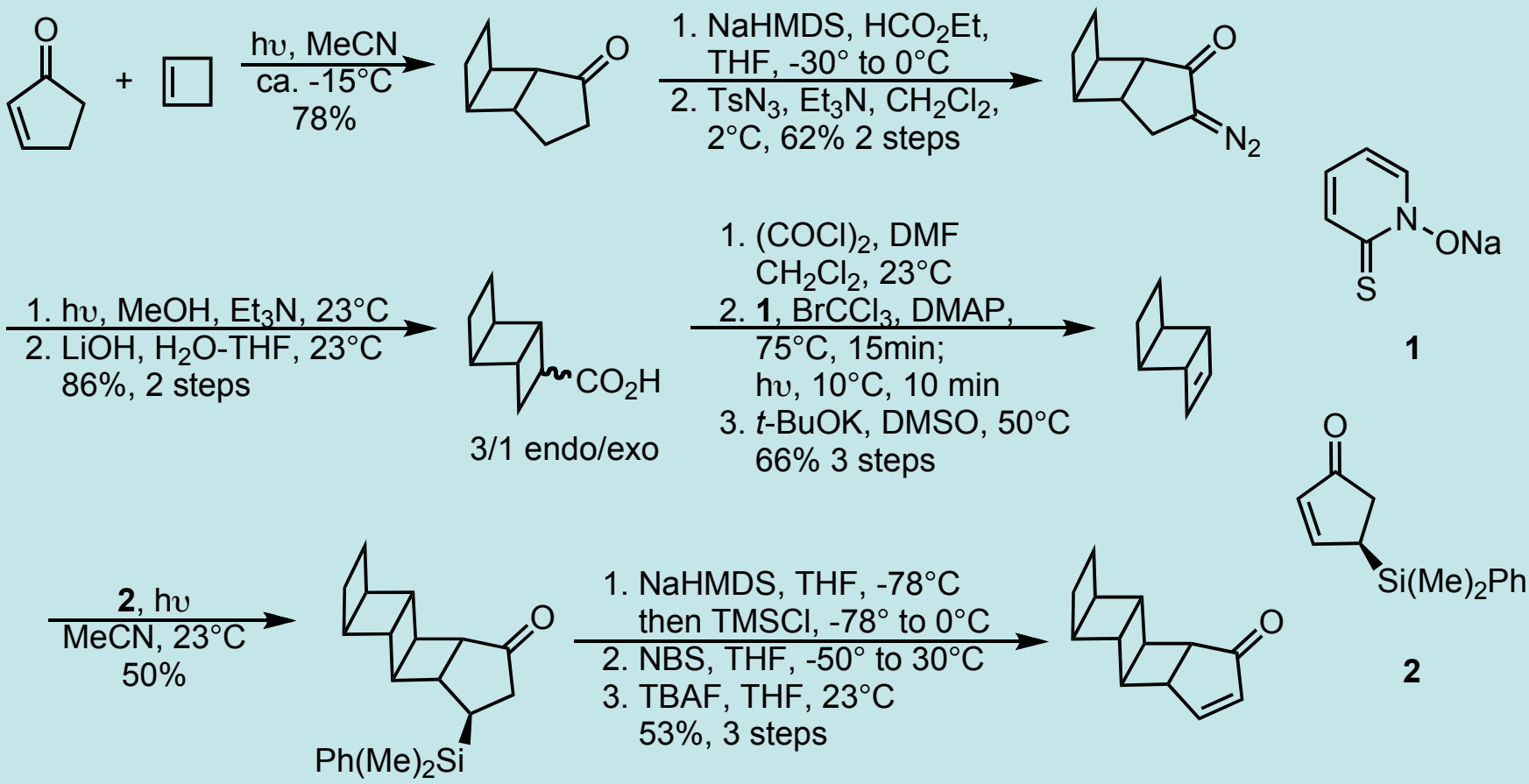


Overall yield: 0.25%

- Successful structure confirmation
- Did not establish the absolute configuration
- Did not provide a convenient route to large quantities of material

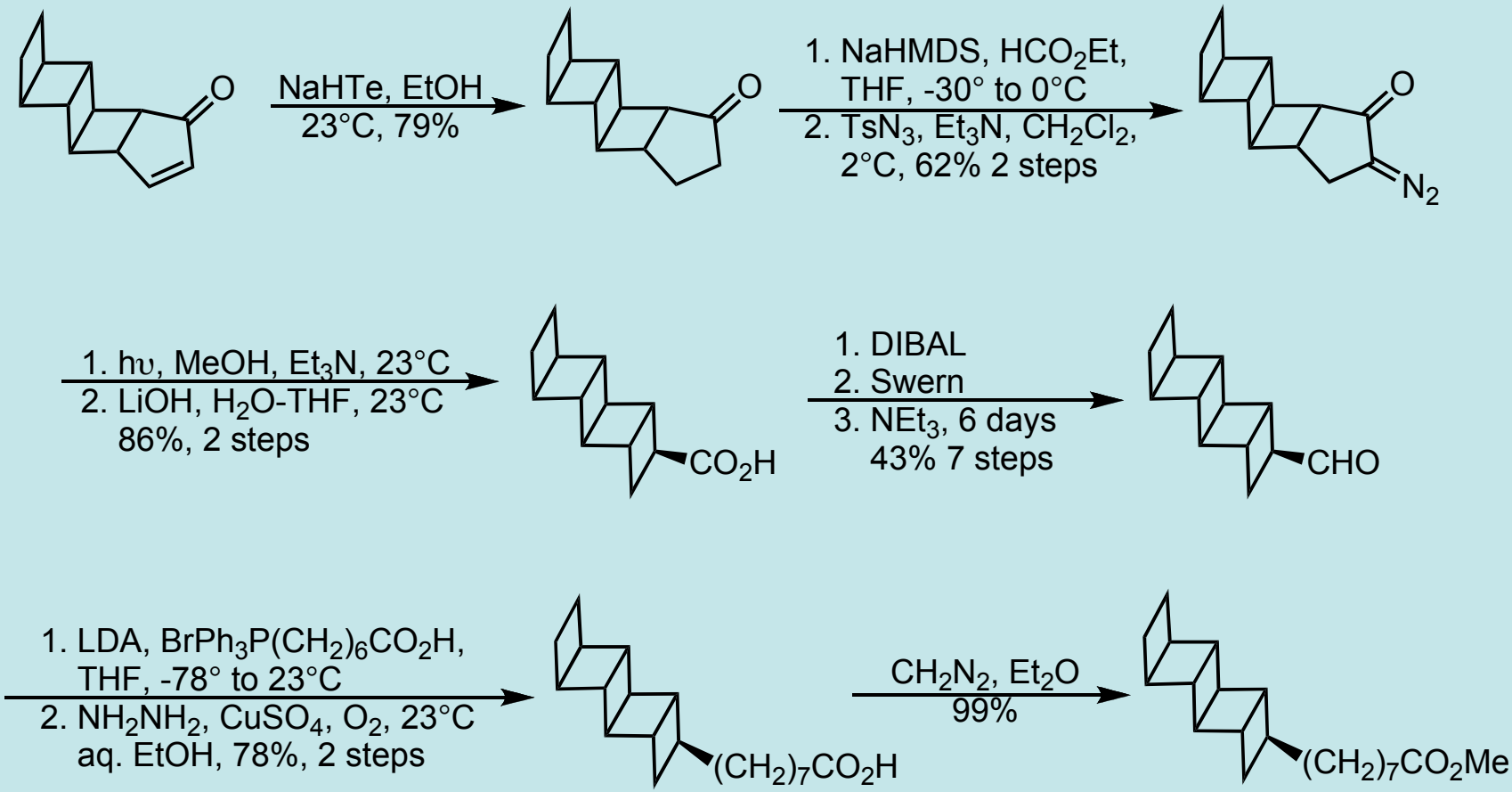
Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2004**. *126*, 15664-15665.

Pentacycloanammoxic Acid Enantioenriched Synthesis



Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2006**. *128*, 3118-3119.

Pentacycloanammoxic Acid Enantioenriched Synthesis

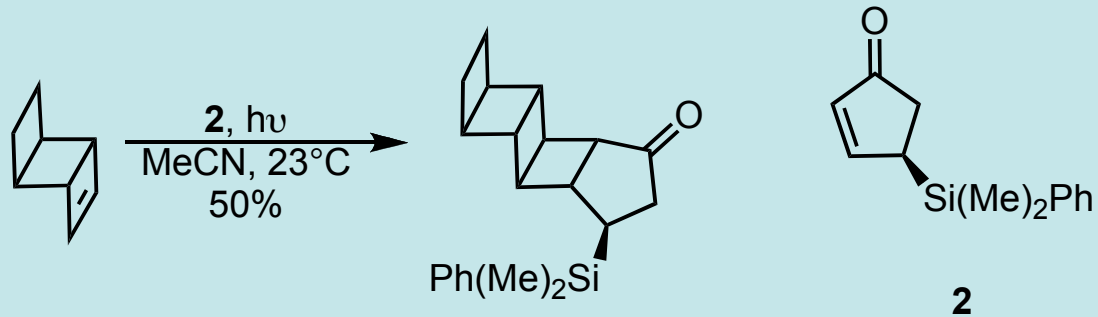


Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2006**. *128*, 3118-3119.

Pentacycloanammoxic Acid Enantioenriched Synthesis

Overall yield: 1.9%, 17 steps

- Reconfirms the molecular structure
- Enantiopure product will allow determination of absolute stereochemistry of natural product



- Provides only a slightly more convenient route to the natural product

- Development of an asymmetric [2+2] cycloaddition

Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2006**. *128*, 3118-3119.

Conclusions

- Synthesis of small ladderanes is well developed
- Synthesis of larger ladderanes and prismanes is less well developed
- While ladderanes have a number of potential uses, they need to be further investigated
- The appearance of ladderane natural products is exciting and the recent development of a reasonable synthesis of the natural product should allow their continued investigation