

The Synthesis of Cubane

I am showing you this synthesis because it is elegant and exemplifies many different concepts. We can use it to talk *in context* about the philosophical aspects of synthesis that we have discussed thus far.

Some questions and answers that we will get out of this example synthesis:

Q: What is the first retrosynthetic step when presented with an unfunctionalized molecule?

A: Functionalize!

Q: What is most complex about the structure of cubane? What elements in the structure make cubane most difficult to synthesize?

A1: Strain!

For more on ring strain see: Wiberg, K. B. (1986). "The Concept of Strain in Organic Chemistry." *Angew. Chem., Int. Ed. Engl.* **25**: 312. This paper is very well written. A must read for all card-carrying organic chemists.

A2: compact polycycle

Q: How was the issue of strain solved in this synthesis of cubane?

A1: Diels-Alder reaction: a natural driving force trading π -bonds for σ -bonds.

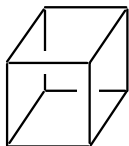
A2: The ΔpK_a that accompanies the Favorskii rearrangement.

A3: Photochemical cyclization $E = h\nu$

The Cubane System: Cole, T.W.; Eaton, P.E. *J. Am. Chem. Soc.* **1964**, *86*, 962-964.

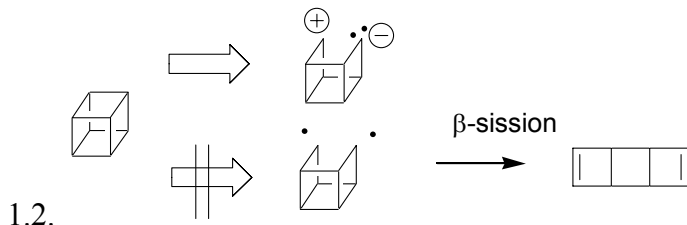
1. Retrosyntheses.

1.1. CUBANE



1.1.1. How do I make the C-C connections (disconnections, thinking retrosynthetically); there is no functionality.

1.1.2. The key is to functionalize the molecule in a first retrosynthetic step.



2. Broadly, there are at least two ways bonds form.

2.1. Nucleophilic substitution.

2.1.1. retroarrow 1 (synthons)

2.1.2. What might drive the ring contraction above?

2.1.2.1. Loss of small molecule $-T\Delta S$

2.1.3. ΔpK_a is proportional to $\Delta\Delta G$

2.2. Radical coupling.

2.2.1. retroarrow 2

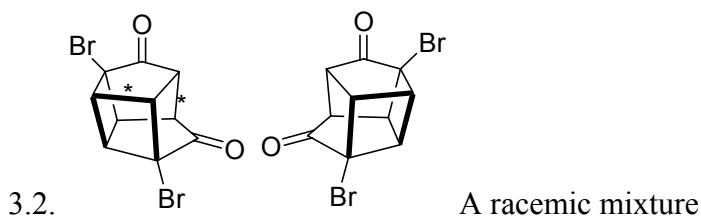
2.2.2. With the radical coupling you are more at the mercy of the strain energy.

2.2.3. Under these conditions strained rings tend to break open via β -scission.

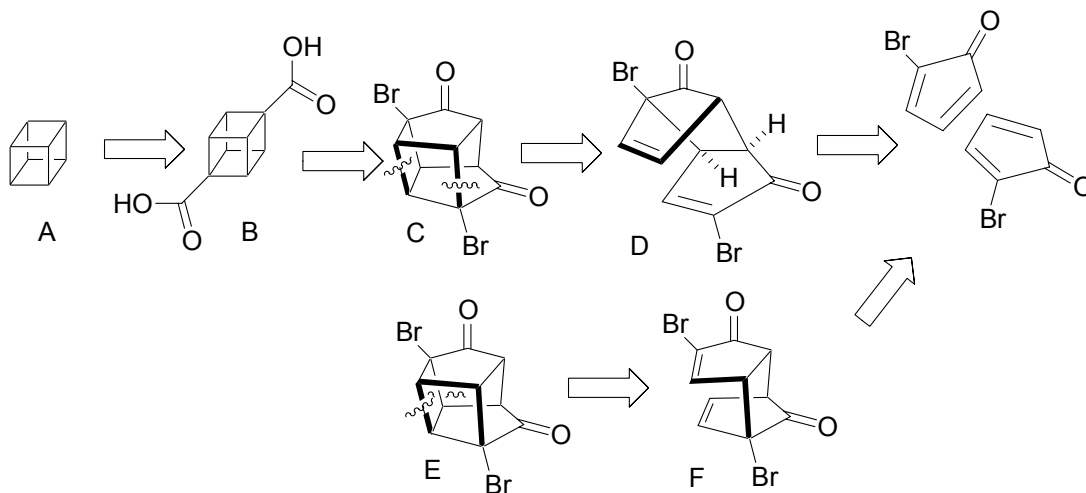
2.2.4. Due to ring strain and the possibility of beta scission retroarrow 2 is probably not the road to travel.

3. The authors realized that cubane has a high degree of symmetry, O_h .

3.1. They realized that they could work on at least two bonds in the cubane structure at one time due to the symmetry of the molecule



- 3.2.1. The asterisks in the figure above indicate the C_2 axis of symmetry in the synthetic intermediate.
- 3.3. Symmetry can make molecules simple (easier to synthesize)
- 3.3.1. Asymmetry contributes to molecular complexity.
- 3.4. The key intermediate (above left or **C** below) represents a relatively small change in the cubane skeleton and is a chiral molecule.
- 3.5. The C_2 axis is its only symmetry element.
- 3.6. The authors successfully applied nucleophilic general retrosynthetic analysis 1 above to the synthesis of cubane.
- 3.6.1. Their precedent for attempting this route was the known method of ring contraction called Favorskii Rearrangement.
- 3.6.2. This protocol can be used to make four and three membered rings



- 3.7.
- 3.8. From A to B with addition of the carboxy substituent we have gone up in molecular complexity on a few fronts. Let's identify them.
- 3.8.1. elemental content
- 3.8.2. functionality
- 3.8.3. symmetry (less symmetrical; cubane contains many symmetry operations;

3.8.4. Compound B only has the C_2 axes and a few mirror planes).

3.8.4.1. Point group D_{2d} or D_{3d} depending if you average tautomers and rotamers.

3.8.5. Reactivity

3.9. When you are looking at a synthesis problem involving a defunctionalized structure you have to be creative.

3.9.1. Do something retrosynthetically even though it's wrong.

3.10. Structure C, retro2 opens/closes the ring

3.11. Favorskii rearrangement

3.11.1. <http://www.organic-chemistry.org/frames.htm?http://www.organic-chemistry.org/namedreactions/>

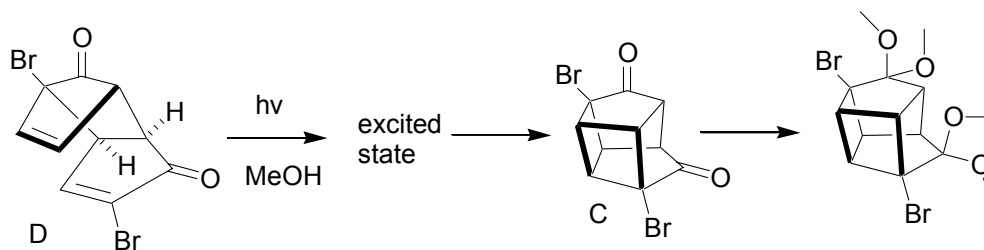
3.11.2. <http://orgchem.chem.uconn.edu/namereact/favorskii.html>

3.11.3. precedent: the formation of highly strained four and three membered rings

3.11.4. semibenzylic mechanism

3.11.5. C can be converted to A by refluxing w/ 50% KOH in minutes followed by recrystallization in 30% yield

3.12. If these conditions are carried on for several hours then cubane is obtained



3.13. **RETRO arrow 3:** 2+2 photochemical cyclization

3.13.1. MeOH, HCl, $h\nu$

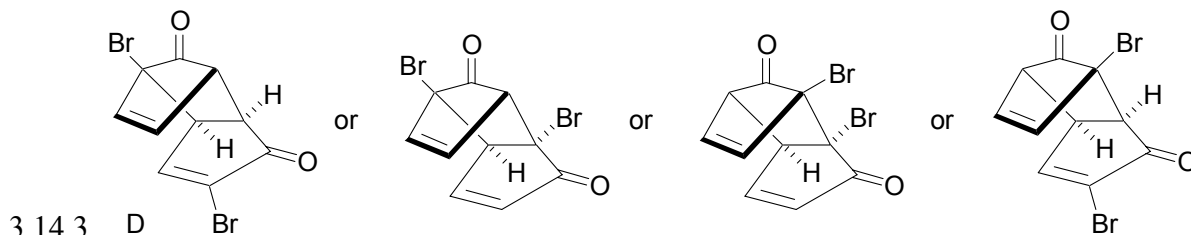
3.13.2. this protocol makes the methylhemiacetal

3.13.3. hemiacetal comes apart with facile hydrolysis

3.14. Diels-Alder cycloaddition

3.14.1. Regiochemistry of the dimerization is not something I would have predicted a priori (before hand)

3.14.2. Two products could have been obtained see below.



3.14.4. Endo Stereochemistry

3.14.5. Know what it is. Know why! Look it up.

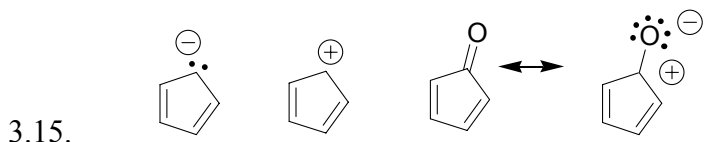
3.14.6. more on the Diels-Alder later

3.14.7. For now refresh your memory by looking in an organic chemistry text, sophomore level!

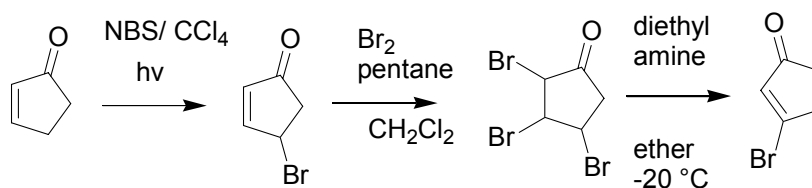
3.14.8. Why is the dimerization facile?

3.14.8.1. Aromaticity (antiaromaticity) issue

3.14.8.2. Cyclopentadienone fulvenone has antiaromatic character.



3.15.1. The fulvenone has an antiaromatic component in the five membered ring.

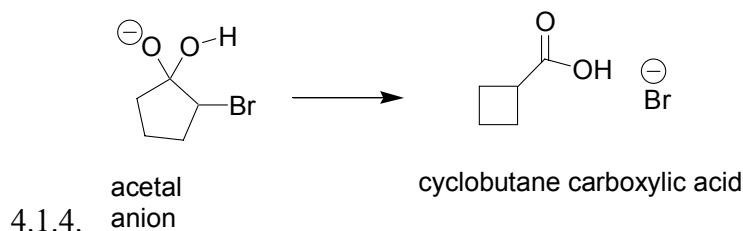


4. Buried in the cubane synthesis is a ΔpK_a argument. Why should the Favorskii

4.1.1. Rearrangement be able to assemble the cubane skeleton because cubane is so strained

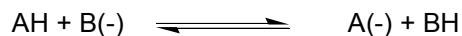
4.1.2. 154.6 kcal/mol is a big number as far as the thermodynamics of organic compounds is concerned.

4.1.3. The answer lies in the fact that the material changes ΔpK_a on the fly.
 ΔpK_a is the driving force in the reaction.



5. The pKa of the acetal is approximately 16.5 and that of HBr is -9.

5.1. This change drives the reaction.



the half reaction in water



has an equilibrium constant associated with it

$$K_{eq} = \frac{[A][H_3O]}{[AH][H_2O]}$$

The terms in this equation are concentration. The molarity of water, $[H_2O]$ is 55 M: 55 moles/Liter

The acidity constant is

$$K_a = \frac{[A][H_3O]}{[AH]}$$

Thus,

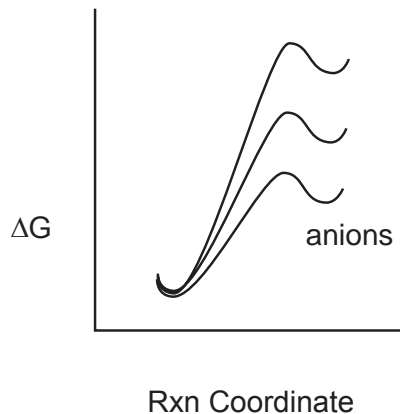
$$K_a = K_{eq}[H_2O]$$

Taking the negative log of both sides and multiplying by RT gives:

$$-RT \log K_a = -RT \log (K_{eq}[H_2O]) = -RT \log K_{eq} - RT \log [H_2O]$$

$$-2.30RT \log K_a = -RT \ln K_{eq} - RT \ln [H_2O]$$

but $-\log K_a = pK_a$



and $-RT\ln K_{eq} = \Delta G$

$2.30RTpK_a + RT\ln[H_2O] = \Delta G$

- The last equation above says that there is a linear relationship between the stability of the anions in the deprotonation reaction and the pKa of the conjugated carbon acid.