Synthesis of Alkenes, Control of Stereochemistry

1. A word about the control of stereochemistry of disubstituted alkenes

1.1. Two choices cis or trans

1.2. Trans is easier to get.

1.2.1. Trans is most stable by approx. 2 kcal/mol.

1.2.2. This translates to usable ratios of

1.2.3. \( \Delta G = -RT \ln K_{eq} \)

1.2.4. \(-2 \text{ kcal/mol} = -2 \times 10^{-3} \text{kcal/(moleK)(298 K)} \ln K_{eq} \)

1.2.5. 28.6/1 or ~97 % trans

2. Alkenes from Alkynes

2.1. Lindlar catalyst-from alkene gives the cis alkene.

2.2. Dissolving metal (Na, Li) and alkyne gives the trans alkene.

3. From ketones and aldehydes

3.1. Non-stabilized Wittig generated with Li+ counter ions give trans disubstituted olefins.

3.2. Horner-Emmons reagents give trans olefin.


5. Cis selective non-stabilized Wittig olefination.

5.1.1. These reactions have early transition states

5.1.2. Salt free conditions

5.1.2.1. Those below and

5.1.2.2. KHMDS/ 10%HMPA/ THF
6. Stabilized ylides tend to be *trans* selective
   
   **6.1.1.** This reflects the stability of the *trans*-oxaphosphatane
   
   **6.1.2.** *trans*-oxaphosphatane is more stable than cis
   
   **6.1.3.** Both reactions are under kinetic control
   
7. **(KINETIC versus THERMODYANMIC CONTROL)**
   
   **7.1.** non-equilibrium conditions opens the way to possible kinetic control.
   
   Thermodynamic control of product distribution is always reflective of the relative free-energies of the products.

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8. Stabilized ylides possess \( \equiv \text{CO}_2\text{R} \) or \( \equiv \text{--CO}_2\text{R} \) or \( \equiv \text{CN} \) groups adjacent to the anion center.
   
   **8.1.** or any other group that stabilizes negative charge
   
   **8.2.** Stabilized ylides \( \rightarrow \) trans alkenes
8.3. Unstabilized ylides in the absence of oxophilic cations (Mg and Li) -> cis alkenes

8.4. There are exceptions to the above

9. THE NEXT SECTION OF THIS LECTURE IS DESIGNED TO CONVICE YOU THAT TRISUBSTITUTED ALKENES ARE CHALLENGING TO SYNTHESIZE.

9.1. A good question at this point might be: why should they be synthetically complex?

9.2. When there are two equivalent substituents on the same side of the alkene, cuprate mediated non-polar additions to alkynes is a general solution.


10. 1970's Normant developed the stereospecific addition of organocopper reagents to alkynes.

10.1. The above protocol looks good in theory

10.2. In practice

10.3. Problems

10.3.1. In general the regiochemistry gets worse if the alkyne is di-substituted.

10.3.2. There are a few cases in which groups on the alkyne effectively direct the regiochemistry of the addition. For these see the citation above.
Synthesis of Cecropia-C18 Juvenile Hormone

Molecular structure of Cecropia-C18 Juvenile || Cecropia Moth, the silk moths (Hyalophora cecropia).

In the next three syntheses of the Cecropia-C18 Juvenile Hormone think about general principles and specific reactions. Do not conceptualize the following information in terms of your instructor wanting you to memorize or even study three synthetic approaches to the Cecropia-C18 Juvenile Hormone.

10.4. That the synthesis appears to be convergent is the first thing you should notice. The solution to the molecular complexity in the form of trisubstituted alkenes is the second thing you notice in the synthesis below.
10.5. The retro-ene reaction runs with the double bond in an S-cis relationship to the cyclopropane ring. The pericyclic transition state is tight, C—H—C proximity at near bond distance needs to be attained. This favors the developing cis-double bond in the 6 electron transition state. You can convince yourself with a model.


11. The end game of cecropia synthesis

11.1. Yield for the removal of the THP group was not reported. I suspect it was low due to non-orthogonality issues with trisubstituted alkenes. These are acid sensitive and you need acid to remove the THP group.

11.2. The rest of the synthesis was accomplished by Corey-Ganem oxidation to the carboethoxy functionality.
12. The following approach to Cecropia C18 Juvenile hormone is instructive and provides a more general solution to stereocontrol in trisubstituted olefins than the synthesis above.

12.1. General is good!


13. This synthesis of juvenile hormone centers around the stereoselective reduction of alkynes by LAH with the hydroxide as the directing group.

13.1. The rest of the synthesis was designed around this idea.

13.1.1. The intermediates have C-M functionality (carbon/metal bonds), this means it should be able to construct C-X (oxidation) or C-C bonds (substitution) with electrophiles.

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \text{Al} \\
\text{CH}_2\text{OH} & \quad \text{CO}_2\text{Me} \\
\text{OMe} & \quad \text{CH}_2\text{OH} \\
\text{CH}_2\text{OH} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

14. The triple bonds were operated on stereospecifically make double bonds.

14.1. Stereocontrol from lineland to flatland.

14.1.1. Alkene to alkyne is usually less complex.

14.1.2. The retrosynthesis simplifies the target (from the standpoint of molecular complexity) by the following criteria
14.1.2.1. The triple bond has no stereochemical complications

14.1.2.2. $sp$ C-H bond is easily deprotonated for anionic disconnections

14.2. The enol ether reacts instead of the other double bond during ozonolysis in the second step.

14.2.1. Why?

14.3. Reduction the aldehyde in the presence of the ester is usually a simple matter.

14.3.1. Why?

14.4. Birch reduction:

14.4.1. Is tough to predict the products. Normally a mixture of products results.

14.4.2. Regioselective protonation of the birch intermediate.

14.4.3. Birch reduction preserves the conjugated double bond.

14.4.4. LOOK UP the Birch Reduction. Get comfortable with the mechanism and the kind of molecules you can make with this procedure. Realize that Birch reduction and the dissolving metal reduction of alkynes are related.


14.5. ozone-

14.5.1. Made by striking an arch across an atmosphere of O₂.

14.5.2. Electrophilic 1,3-dipolar cycloaddition.

14.5.3. Mechanism on next page.

14.5.4. Slow addition allows for kinetically differentiate between the two double bonds in the birch reduced product.

14.6. Borohydride reduction

14.6.1. Usually done in methanol or ethanol

14.6.2. Takes place from the more reactive boroester at about pH = 10 or so

14.6.2.1. Careful, pH refers strictly to aqueous solution. To facilitate discussion, this rule is broken all the time.

14.6.3. Very mild reducing agent, by moderating temperature you can selective reduce aldehydes and ketones in the presence of esters and enones.
14.7. Reductive defunctionalization.

14.7.1. Tosylation is sophomore org chem. It is a method by which alcohols are activated toward substitution. If necessary, look it up.

14.8. THP protection of -OH functionality.

14.8.1. THP ethers are stable in the presence of base and almost any reducing agent. Do you know why?

14.8.2. In the presence of acid and excess alcohol THP ethers are deprotected.

14.8.3. The authors took a beating on the yield here (30%) what else can happen to the substrate in the presence of H+ and MeOH

14.9. At this point the material is >1:1000 isomerically pure cis!

14.10. LAH reduction of propargyl alcohols

14.10.1. Results in the formation of an alkenylaluminum species.

14.10.2. At this point that this alkenylaluminum is quenched with iodide, the stereochemistry of alkene is set.

14.10.2.1. Remember, In general, don't try to control stereochemistry at anions.

14.10.2.2. Neither sp² nor sp³ anions are good at trapping electrophiles stereospecifically.

14.10.2.3. These reactions are not stereoselective

14.10.3. The cuprate is known to conserve the stereochemistry of addition to akenylhalides
14.10.3.1. Cuprate reagent reacts with alkenyliodides because it can offer the alkenyl iodide a d orbital-based mechanism.

\[
\begin{align*}
\text{Et-Cu} & \text{Et} \\
\text{Li} & \text{R} \\
\rightarrow &
\end{align*}
\]

\[
\begin{align*}
\text{Oxidative Addition} \\
\pi\text{-complex}
\end{align*}
\]

Copper III

14.10.3.2. In the oxidative addition step the copper has gone from oxidation I to oxidation state II

14.11. 3-lithio-1-trimethylsilylpropyne

14.11.1. TMS as a surrogate proton

14.12. Silver + desilylation

14.13. Homologation with formaldehyde


\[
\begin{align*}
\text{Mn} & \quad \text{O} \\
\text{O} & \\
\rightarrow &
\end{align*}
\]

Mn 4+

\[
\begin{align*}
\text{Mn} & \quad \text{O} \\
\rightarrow & \\
\text{Mn} & \quad \text{O} \\
\text{NaCN} & \\
\rightarrow &
\end{align*}
\]

NaCN
15. Final oxidation of the last alkene
   15.1. N-bromosuccinamide/dimethoxyethane water mixture
     15.1.1. Intermediate bromohydrin
     15.1.2. Isopropoxide in isopropyl alcohol
     15.1.3. Epoxide final product

16. Testing final product: 0.05 µg of the product injected in 50 µg of chemically pure olive oil blocked silk worm maturation.

17. The Take Home Lesson and how to study this material
   17.1. You need to determine the points in the synthesis of the natural product that gave rise to stereoselective olefin synthesis and why.
   17.2. You need to remember how the carbon-carbon bonds were formed and be able to apply the method to general problems you will get throughout the semester.

18. Another synthetic approach to the Cecropia Juvenile hormone:
   18.2. The main focus is the control of the stereochemistry of the trisubstituted alkene.
   18.3. Retrosynthetic analysis:
18.3.1. In this retrosynthetic analysis the molecule is simplified from two trisubstituted alkenes to two methylene substructures. The stereochemistry of the allylic alcohols at the carbinol carbons does not matter. These are marked with * in structure 4.

18.3.2. The material at this point is a mixture of diastereomers.

18.3.3. Look at 8 and 9.

18.3.3.1. Do you know why the enolate preferentially substitutes the Br on the sp$^3$ carbon atom instead of the sp$^2$ carbon atom?

18.3.3.2. Do you know why 5 had to be protected at the alcohol oxidation state with a ketal?

18.3.3.3. Do you know why dianion 6 preferentially reacted with aldehyde 5 at the carbanion instead of the alkoxide?

18.3.3.4. You should know what is driving the reaction from 12 to 3 forward.

18.3.3.5. You should know how to get from 3 to 1 from our previous discussions.
18.4. The basis of the stereoselectivity of the 2,3-sigmatropic rearrangement.

18.4.1. This type of interaction is called 1,2-allylic strain.

18.4.2. The production of the E-alkene is more facile than the production of the Z-alkene.

18.4.3. In the transition state above R and the Me group are on opposite sides of the bond. They are anti. This anti relationship leads to a *trans* relationship between these two groups.

18.4.4. The transition state below is inhibited by interaction between the R and the Me groups. If this transition occurred preferentially then the syn Me and the R groups would be *cis* to one another in the product.
18.4.5. The diagram above outlines another way to look at the transition that determines the stereochemistry in Still’s 2,3-sigmatropic shift. Could you see this better if you made a model?

18.4.6. **Read the following review on the 2,3-sigmatropic rearrangement and its utility as a synthetic tool.**