

April 2002 CUME

Organic Chemistry

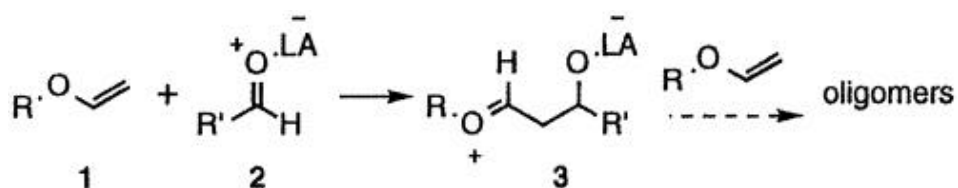
Department of Chemistry
University of Missouri—Columbia
Saturday, April 6th, 2002
Dr. Rainer Glaser

Announced Reading: "Prins Cyclization Reactions"

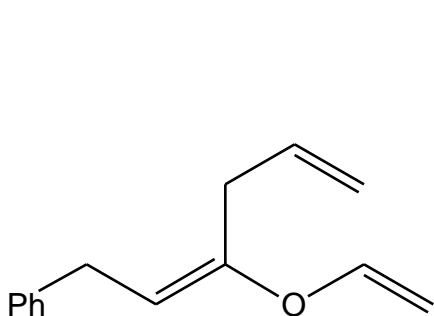
Question 1. Aldol-Prins Cyclization Reactions. (35 points)

Mukaiyama Aldol-Prins Cyclization Cascade Reaction: A Formal Total Synthesis of Leucascandrolide
A David J. Kopecky and Scott D. Rychnovsky *J. Am. Chem. Soc.* **2001**, *123*, 8420–8421.

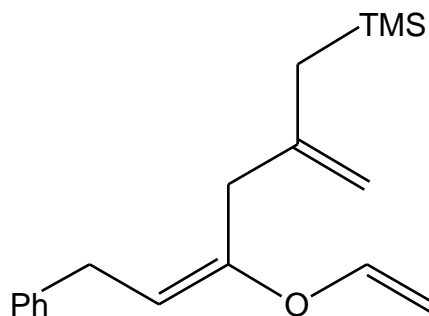
(a) In the introduction to this article, it is said that “electrophilic additions to alkyl enol ethers are often problematic because the intermediate oxocarbenium ion, for example, **3**, is a very reactive electrophile and can react with the starting enol ether to produce oligomers, Figure 1.” The relevant part of Figure 1 is reproduced. Show the steps of the oligomerization up to the formation of the oligomer incorporating three molecules of **1**. Use BF_3 as the Lewis acid in the oligomerization. (10 points)



(b) The key conceptual innovation in this paper concerns the intramolecular reaction of the intermediate oxocarbenium ion with a tethered nucleophile. It is found that substrates in which the nucleophile is an alkene “only partially suppress the competing oligomerization reactions.” On the other hand, allylsilanes were found to completely eliminate oligomerization. Explain this observation. Use a **proton** as the promotor for cyclization in your explanation. (10 points)

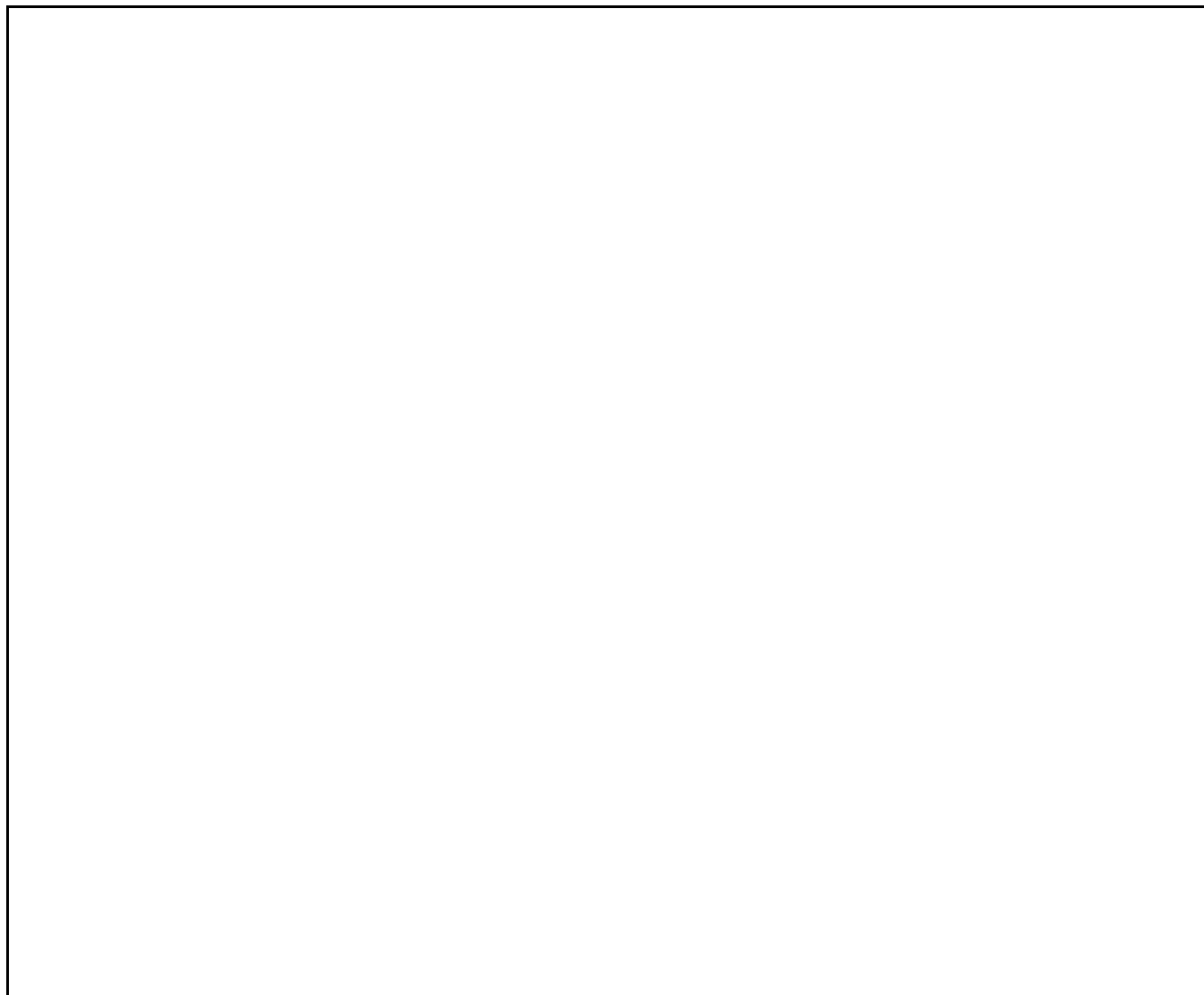
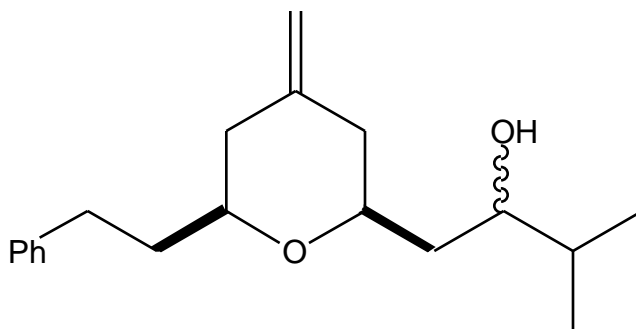


alkene



allylsilane

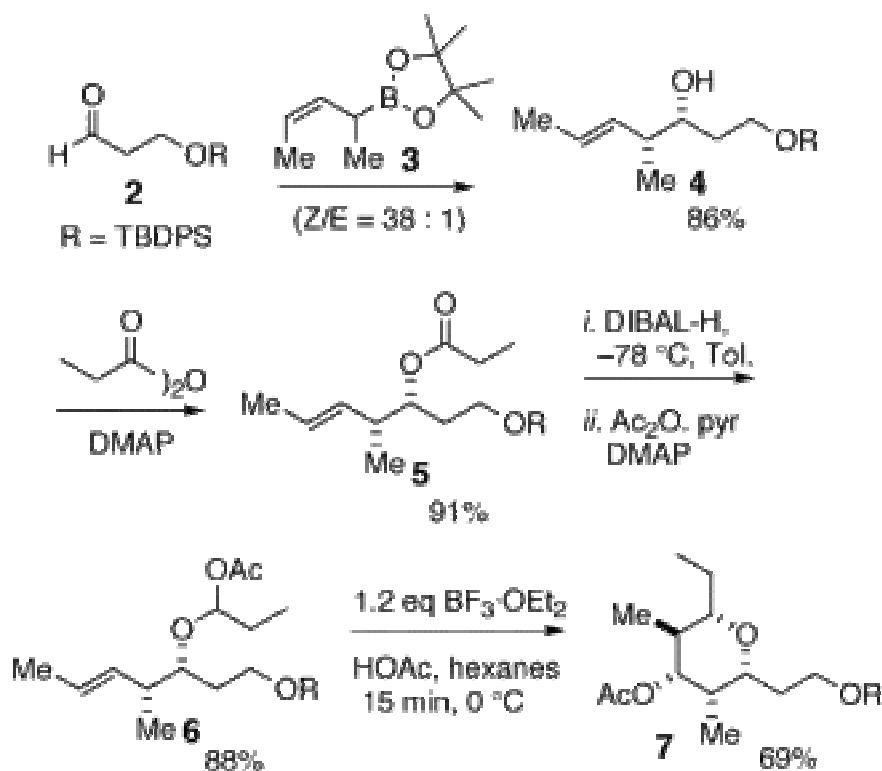
(c) The product shown is formed with 98% yield and an epimer ratio of 1:1 by way of an aldol-Prins cyclization reaction. Show the structures of the substrate enol and of the substrate carbonyl compounds. Provide a mechanism for product formation (do not worry about stereochemistry). Use **trifluoroborane** as the promotor for cyclization in your explanation. (15 points)



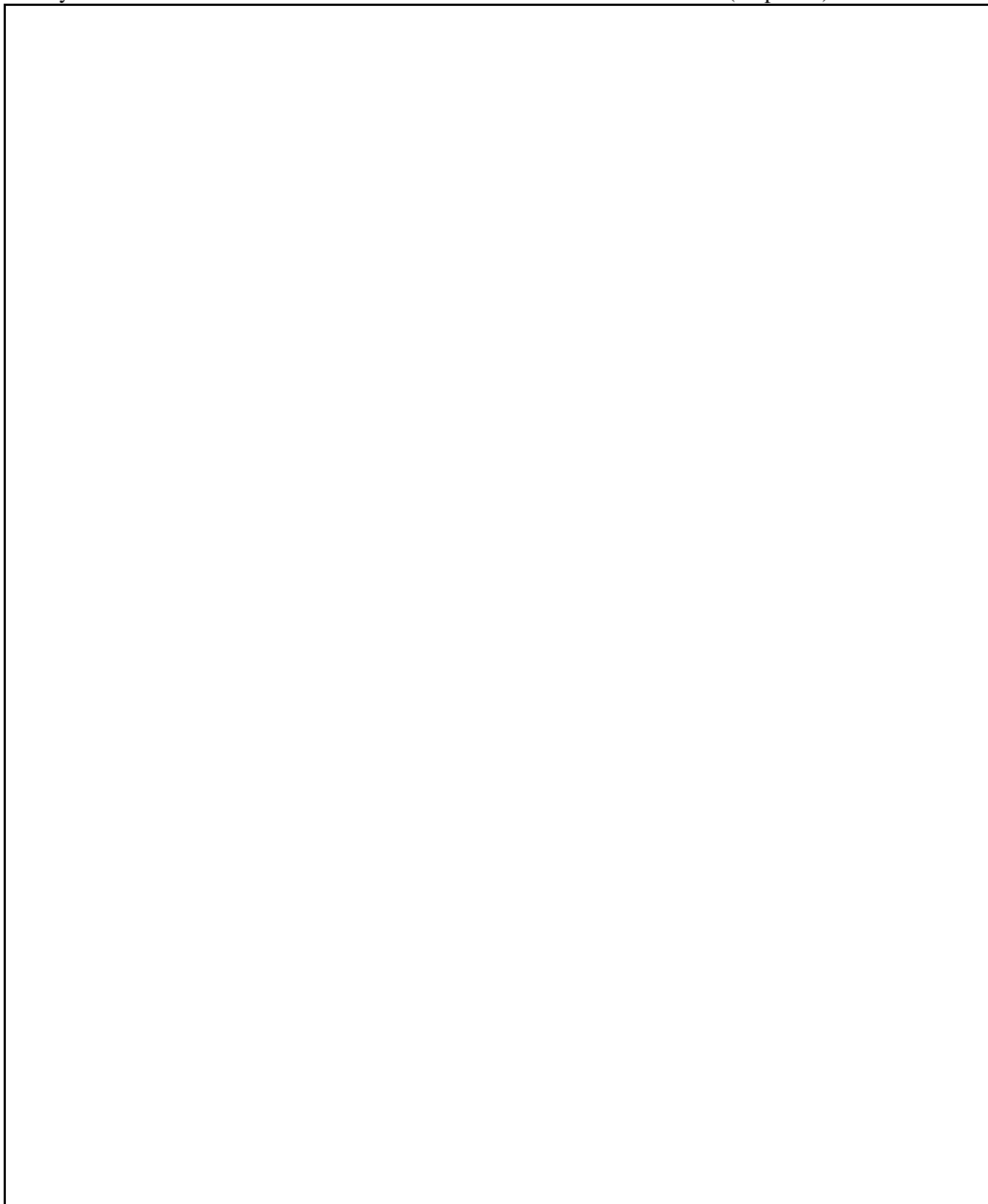
Question 2. Phorborazole by Stereoselective Prins Cyclization. (15 points)

Synthesis of the C22-C26 Tetrahydropyran Segment of Phorboxazole by a Stereoselective Prins Cyclization Scott D. Rychnovsky and Christian R. Thomas *Org. Lett.* **2000**, *2*, 1217-1219.

From the paper (slightly adapted): ... Segment 1 of phorboxazoles **1** includes the C20-C26 tetrahydropyran. There are a number of possible Prins cyclization precursors for **1**, but none of them are ideal for our strategy because they either involve (a) reductive acetylation of an α,β -unsaturated ester or (b) Prins cyclization of an allylic alcohol that might be expected to fragment. To avoid these potential problems, we settled on a strategy in which the trisubstituted alkene would be incorporated after the Prins cyclization. The key elements of this approach were explored in the model study shown in Scheme 1. Aldehyde **2** was coupled with Hoffmann's (*Z*)-pentenyl boronate **3** to produce homoallylic alcohol **4**. Alcohol **4** incorporates the requisite *syn* stereochemistry and the (*E*)-alkene geometry that should lead to the correct configuration in the tetrahydropyran. Esterification and reductive acetylation proceeded uneventfully to give α -acetoxy ether **6** in 80% overall yield from alcohol **4**. Activation with $\text{BF}_3 \cdot \text{OEt}_2$ and acetic acid in hexanes at 0 °C gave tetrahydropyran **7** as a single isomer in 69% yield. The configuration of **7** was confirmed by NOE measurements and coupling constant analysis.



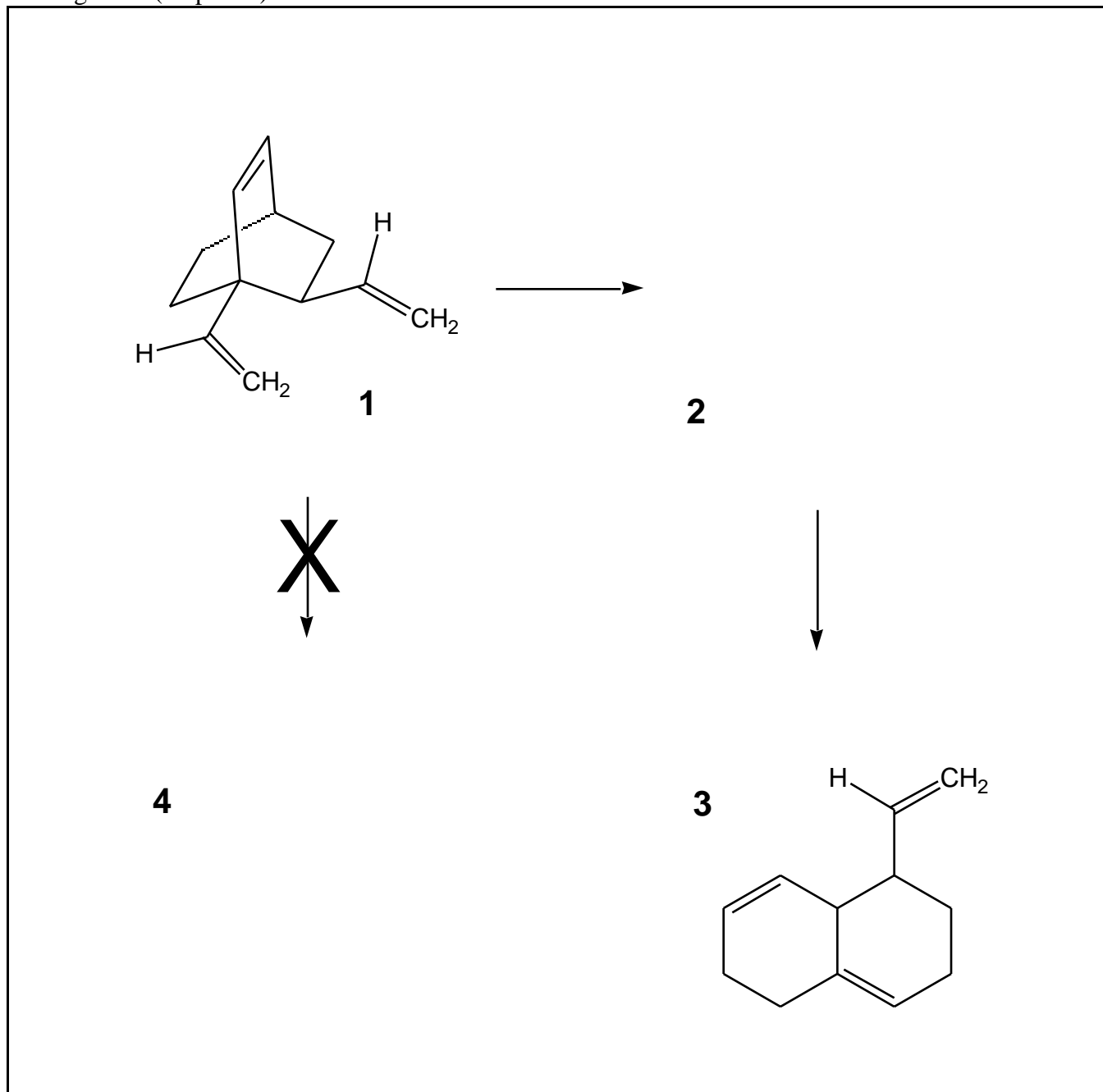
Explain the origin of the stereochemistry of **7**. Draw the transition state structure as best as you can and clearly show all substituents. Indicate the direction of attack of the acetate. (15 points)



Question 3. Cope Rearrangements. (25 points)

(a) Provide an example for a Cope rearrangement. Classify the reaction type (e.g. cycloaddition, ...). Indicate how many electrons are involved in the reaction. Draw the transition state structures as best as you can, clearly indicating where the electrons are. (10 points)

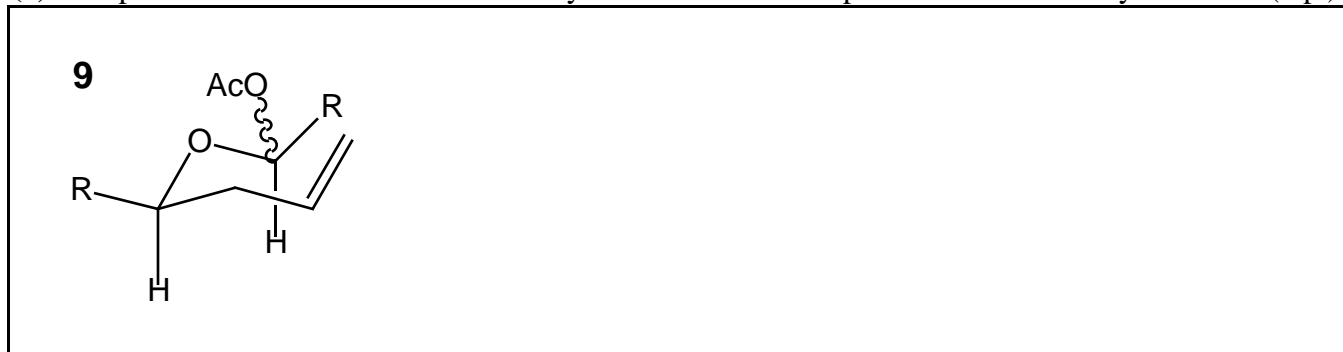
(b) Source: <http://chemistry.gsu.edu/glactone/modeling/Magid/cope/cope.html> and based on an article by Guevel, R.; Paquette, L. A. *J. Am. Chem. Soc.* **1994**, *116*, 1776. The triene **1** is, in principle, capable of undergoing two different Cope rearrangements. Only the rearrangement involving bonding of C1 to C6 is observed – the exclusive product is **3** which, presumably, arises by a second Cope rearrangement on undetectable intermediate **2** (not shown). It's interesting that **1** does not give the alternative Cope rearrangement (bonding of C1 to C6') leading to **4**. Draw the structures of **2** and **4**. Explain how **3** is formed from **2**. Try to formulate an explanation for the observed exclusivity of the Cope reaction leading to **2**. (15 points)



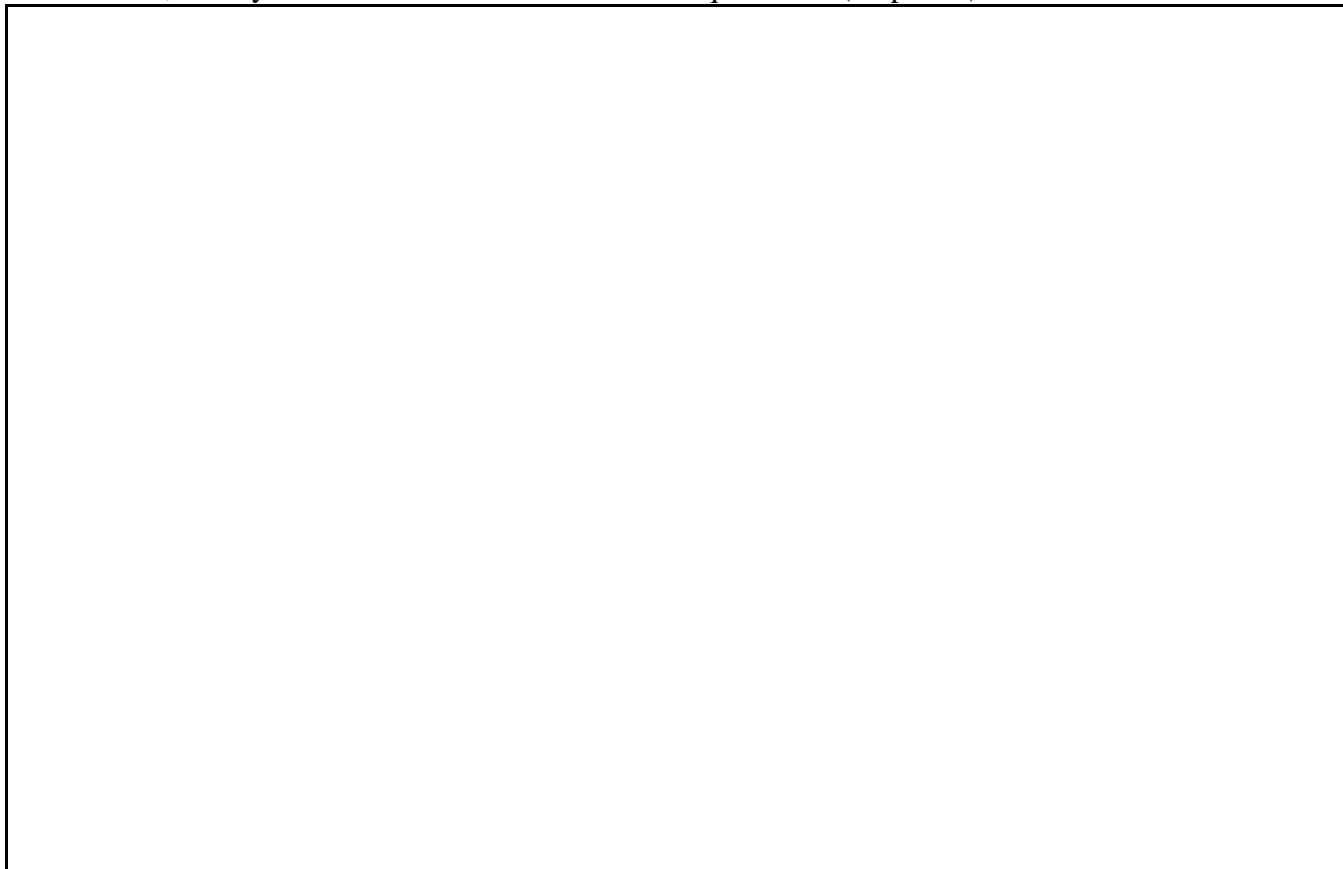
Question 4. 2-Oxonia Cope Rearrangements. (25 points)

Role of 2-Oxonia Cope Rearrangements in Prins Cyclization Reactions Scott D. Rychnovsky,* Shinji Marumoto, and James J. Jaber *Org. Lett.* **2001**, 3, 3815 -3818.

(a) Compound **9** is a substrate for a Prins Cyclization. Draw the product of the Prins cyclization. (5 p.)



(b) Draw the oxocarbenium ion derived directly from **9**. Using curved arrows, show how this oxocarbenium can undergo an oxonia-Cope rearrangement and draw the product of this rearrangement. Draw chairs, clearly indicate whether “R” is axial or equatorial. (10 points)



(c) Compound **16** was subjected to Prins cyclization conditions (BF_3 , CH_2Cl_2) in the presence of triethylsilane (5-fold excess). Draw the structures of the two products of reduction as best as you can. The acyclic reduction product is racemic. Explain why this product is racemic and what this stereochemical outcome says about the oxonia-Cope rearrangement. (10 points)

