

**Cumulative Exam**  
**Organic Chemistry**

*December 5, 2019*

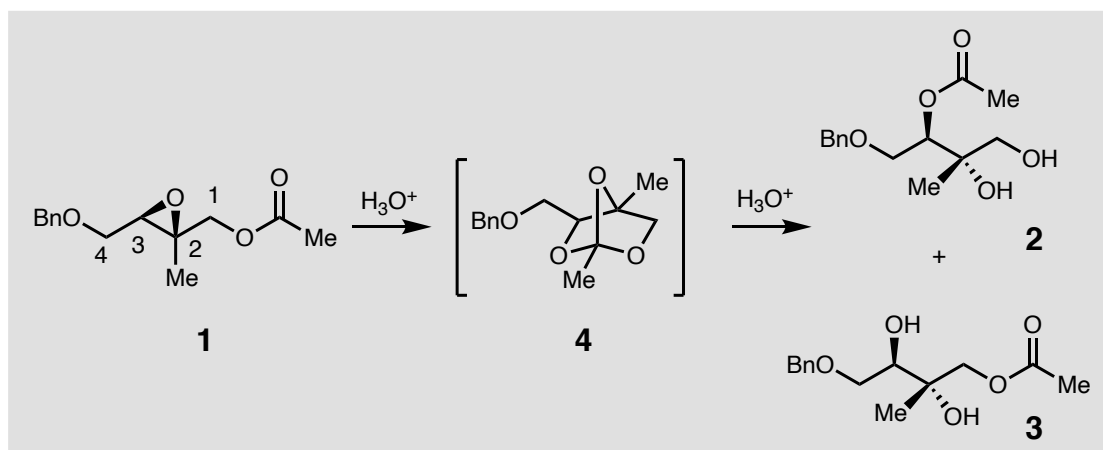
NAME \_\_\_\_\_

Page	Grade	Points
2	_____	35
3	_____	65
Total		100

## Question 1

*NGP, Hydrolysis of Acetals, Baldwin Rules*

Epoxy ester **1** effectively rearranges to a 1:1 mixture of acetate esters **2** and **3** under acidic conditions (0.5 M H<sub>2</sub>SO<sub>4</sub> in THF/H<sub>2</sub>O 9/1). It is believed that the reaction occurs through the formation of an orthoester intermediate **4** that is subsequently hydrolyzed in the acidic medium. This route provides a convenient method for the synthesis of polyhydroxylated compounds with control of stereochemistry during the ring-opening step.



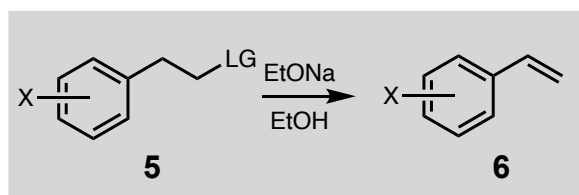
Orthoester **4** has been characterized by NMR upon treatment of **1** with 0.5% trifluoroacetic acid (TFA)/CDCl<sub>3</sub> for 1 h. The study of the reaction mechanism was carried out in TFA/CDCl<sub>3</sub> starting from **1** labelled with <sup>18</sup>O in the carbonyl oxygen. The location of the label in the orthoester intermediate was determined by <sup>13</sup>C-NMR spectroscopy, through the characterization of upfield shifts (in parts per billion, ppb) of the carbon signals when bonded to the heavy isotope. The <sup>13</sup>C-NMR spectrum of labeled **4** showed upfield shifts of the signals corresponding to the orthoester carbon (120.5 ppm,  $\Delta\delta = 25$  ppb) and C-2 position (85.5 ppm,  $\Delta\delta = 35$  ppb).

- Considering the ability of the acetoxy substituent as a neighboring group, draw an arrow-pushing mechanism for the formation of orthoester **4** which accounts for the observed labelling pattern. (20 pts)
- Why do orthoesters hydrolyze so easily in acidic aqueous media? (5 pts)
- Draw an arrow-pushing mechanism for the hydrolysis of **4** to form both **2** and **3**. (10 pts)

## Question 2

### Linear Free Energy Relationships

The rates of E2  $\beta$ -eliminations of a series of *m*- and *p*-substituted (R) 2-phenylethyl derivatives **5** correlated with rho ( $\rho$ ) values for different leaving groups (LG) are given in the table below.



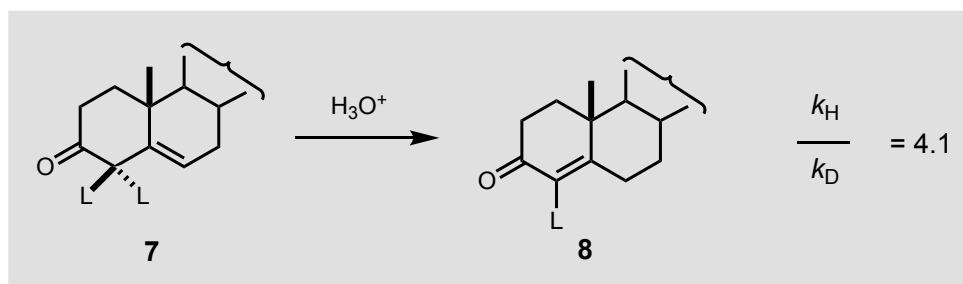
<b>X</b>	I	Br	OTs	Cl	<sup>+</sup> SMe <sub>2</sub>	F	<sup>+</sup> NMe <sub>3</sub>
<b><math>\rho</math></b>	2.07	2.14	2.27	2.61	2.75	3.12	3.77

- a. Given the sign of the  $\rho$  values given above, is this elimination process accelerated or retarded by electron-withdrawing substituents? (10 pts)
- b. Comment on the relationship between  $\rho$  and the identity of the leaving group (LG). Make sure that you note the degree of charge development in the transition state of this reaction. (15 pts)

## Question 3

### Isotope Effects

- a. Draw a reasonable arrow-pushing mechanism for the acid-catalyzed conversion of  $\beta,\gamma$ -unsaturated ketone **7** to form  $\alpha,\beta$ -unsaturated ketone **8**. L = H or D. (20 pts)



- b. Explain why  $\Delta G^\circ$  is negative for this reaction. (10 pts)
- c. Given the magnitude of the observed kinetic isotope effect, indicate which step in your proposed mechanism is rate determining. (10 pts)