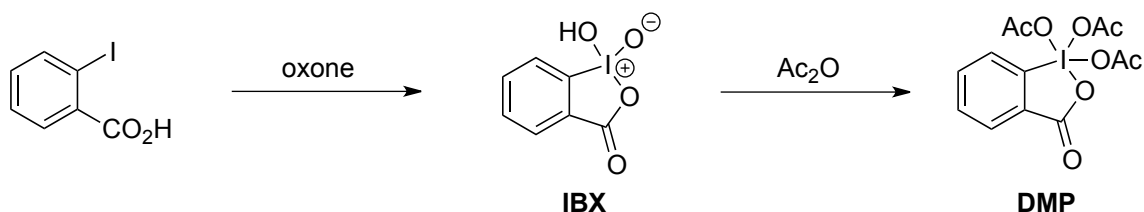


**CHEM 135: EXPERIMENTAL SYNTHETIC CHEMISTRY**  
**SPRING 2015**

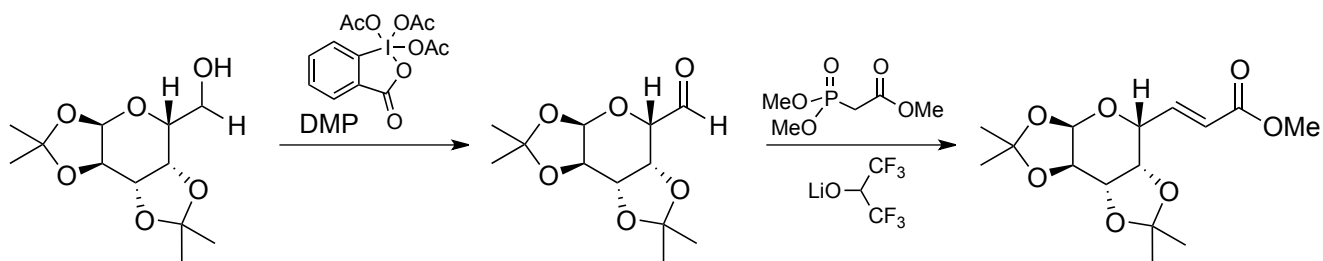
**EXPERIMENT 4:**  
**WEEKS 12 – 14**  
**(4/20/2014 – 5/2/2015)**

*(1) SYNTHESIS OF DESS-MARTIN-PERIODINANE*



*J. Org. Chem.*, **1999**, *64*, 4537–4538.

*(2) DESS-MARTIN OXIDATION; HORNER-WADSWORTH-EMMONS OLEFINATION.*



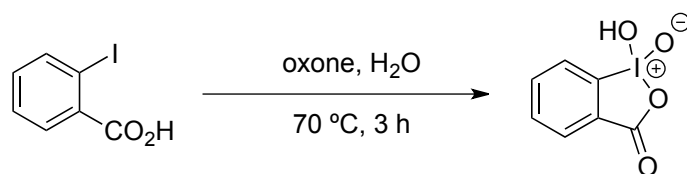
*Org. Lett.* **2005**, *7*, 4281-4283.

**NOTE:** While working in the lab you are required to wear lab coats and safety glasses at all times! Furthermore, you will have to complete a short online safety quiz before starting the experiment. The TF will evaluate your answers and based on your result you will either receive permission to start your experiment or you will have to go back and consult the instructions again.

*developed by Eugene E. Kwan and Andreas Roetheli*

## SYNTHESIS OF 2-iodoxybenzoic acid (IBX)

### Reaction Scheme



### Procedure

Reaction:  
ca. 4 h

*You should also take an NMR of the pure starting material.*

To a stirred suspension of oxone (90.98 g, 0.147 mol, 1.47 equiv.) in 325 mL water was added 2-iodobenzoic acid (25.05 g, 0.1000 mol, 1.000 equiv.) in one portion. The white suspension was warmed to 70 °C *and not higher*, and stirred at this temperature for three hours while carefully maintaining the internal temperature. At this point, <sup>1</sup>H NMR analysis of an aliquot in deuterated DMSO indicated complete consumption of the starting material.

Work-up:  
ca. 2 h

The mixture was allowed to cool to room temperature and then placed in an ice bath (0 °C) for 90 minutes. The white suspension was filtered through a large Büchner funnel to give a white, microcrystalline, granular powder, which was washed with cold water (6 × 75 mL) and then cold acetone (2 × 50 mL). The powder was then dried under high vacuum over night to afford the desired product as a white powder.

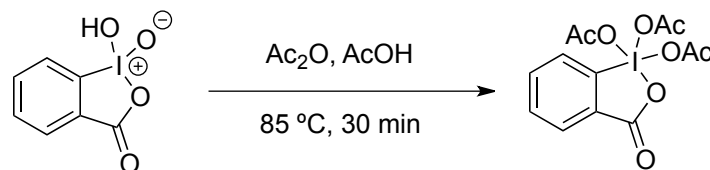
### Safety Remarks

#### & Tips

- IBX and the Dess-Martin reagent are impact-sensitive (i.e., potentially explosive).
- Oxone is a potent oxidizing agent.
- DMSO penetrates gloves easily, potentially carrying through toxic substances.

## SYNTHESIS OF DESS-MARTIN-PERIODINANE

### Reaction Scheme



### Procedure

Reaction:  
ca. 1 h

*Ensure that the reaction is complete by aliquot NMR.*

A 500 mL three-neck round bottom flask was charged with IBX (*all of your IBX*, 1.0 equiv.) and a stir bar, and the flask was purged and back-filled with nitrogen three times. To the solid IBX was added acetic acid (13.0 equiv.) and acetic anhydride (9.1 equiv.) sequentially by syringe. The flask was heated to  $85\text{ }^\circ\text{C}$  (internal temperature monitored by thermocouple) and stirred vigorously at this temperature for another 30 minutes. At this point, the white suspension became a yellow solution.

Isolation:  
ca. 4 h

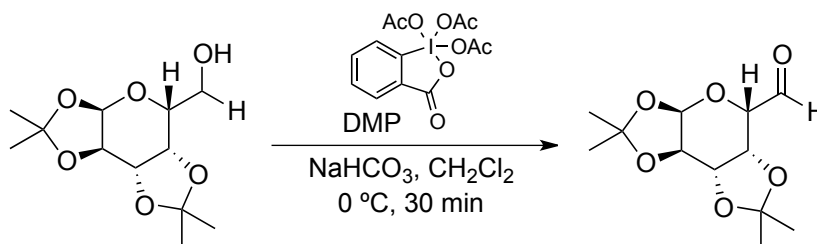
The heating block was turned off, the reaction flask was wrapped in aluminum foil and allowed to cool slowly to room temperature under inert atmosphere. The solution was chilled to  $-30\text{ }^\circ\text{C}$  for two hours and the granular white precipitate collected by vacuum filtration in a Büchner funnel under a flow of nitrogen. The solid was washed three times with 25 mL portions of chilled diethyl ether. The product was dried under high vacuum for 24 hours to afford the desired DMP as a white solid.

### Safety Remarks

- Acetic acid and acetic anhydride are corrosive. They should only be handled with gloves inside a fume hood.
- Calculate the required amount of acetic acid and acetic anhydride based on your IBX yield obtained from the previous reaction.
- DMP is very moisture sensitive. Exposure of the reagent to too much moisture is the primary cause of failure for this experiment.
- Store the reagent in a tightly sealed container under a blanket of nitrogen in the freezer.

## OXIDATION OF A 1° ALCOHOL USING DESS-MARTIN-PERIODINANE

### Reaction Scheme



### Procedure

Reaction:  
ca. 2 h

*Dispense the alcohol by gently heating it with a heat gun, then pour it into your flask.*

Work-up:  
ca. 3 h

*Slow addition of the aqueous solution is important;  $\text{CO}_2$  is evolved.*

Sodium bicarbonate (3.87 g, 46.1 mmol, 4.00 equiv.) and the Dess–Martin periodinane (9.78 g, 23.05 mmol, 2.00 equiv.) were added in sequence to a solution of 1,2:3,4-di-O-isopropylidene- $\alpha$ -D-galactopyranose (3.00 g, 11.5 mmol, 1.00 equiv.) in dichloromethane (50 mL) at room temperature. Monitor the reaction by TLC (dichloromethane/ethyl acetate 9:1, stain with CAM), and when TLC indicates complete conversion, verify this by  $^1\text{H}$  NMR in  $\text{CDCl}_3$  of an aliquot.

The reaction mixture was diluted with 50 mL of diethyl ether, followed by slow addition of a 1:1:1 mixture of saturated aqueous sodium thiosulfate solution (35 mL), saturated aqueous sodium bicarbonate (35 mL), and water (35 mL, total volume 105 mL). The resulting biphasic mixture was stirred vigorously for 1 h resulting in two clear layers. The layers were separated and the aqueous layer was extracted three times with diethyl ether. The ethereal solution was then washed three times with water and once with brine; the combined organic layers were dried over magnesium sulfate. The solids were removed by filtration, and the filtrate was concentrated *in vacuo*. The crude aldehyde was obtained as a yellowish oil. The purity of the aldehyde was ascertained by  $^1\text{H}$  NMR; your TF will help you decide if the material is pure enough to carry forward. If it is not, repeat the aqueous workup.

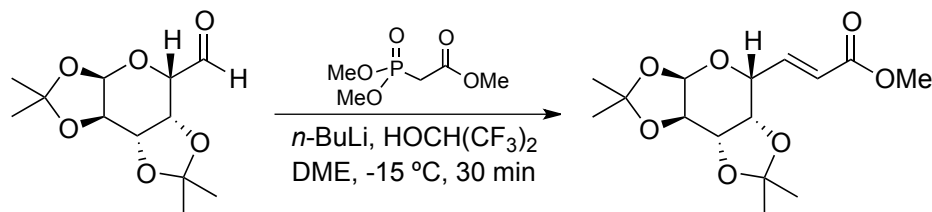
### Safety Remarks

#### & Tips

- It is not necessary to flame dry the reaction flask or be particularly careful about excluding moisture from the reaction. In fact, there is a beneficial effect of small amounts of water on the rate of the reaction. For additional information consult *J. Org. Chem.* **1994**, *59*, 7549.
- Follow the reaction carefully by TLC. If incomplete conversion is observed, add more DMP.

## HORNER-WADSWORTH-EMMONS OLEFINATION OF AN EPIMERIZABLE ALDEHYDE

### Reaction Scheme



### Procedure

Reaction:  
ca. 2 h

*As always  
when working  
with  
organolithium  
reagents,  
flame-dry your  
glassware.*

A solution of freshly titrated *n*-butyllithium in hexanes (ca. 2.5 M, 1.18 equiv.) and trimethyl phosphonoacetate (1.5 mL, 9.3 mmol, 1.2 equiv) were added *in sequence* to a solution of 1,1,1,3,3,3-hexafluoroisopropanol (1.0 mL, 9.6 mmol, 1.24 equiv) in 1,2-dimethoxyethane (16 mL) at -15 °C under nitrogen. A solution of 1,2:3,4-di-*O*-isopropylidene-*D*-galactohexodialdo-1,5-pyranose (2.00 g, 7.74 mmol, 1.00 equiv.) in 1,2-dimethoxyethane (10 mL, followed by one 6-mL rinse) was added via syringe, causing a white precipitate to form. The reaction suspension was stirred for 30 min at -15 °C and the conversion checked by TLC (hexanes/ethyl acetate 4:1).

Work-up:  
ca. 1 h

The mixture was diluted with water (2 mL) and the solvents were removed *in vacuo*.

Purification:  
ca. 2 h

*This may be a  
challenging  
separation; make  
sure your column  
is relatively long.*

The product was purified by flash-column chromatography (SiO<sub>2</sub>, hexanes/ethyl acetate 8:1, then 5:1) to afford methyl (*E*)-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-*α*-*D*-galacto-oct-5-enopyranuronate as a white solid.

### Safety Remarks

- *n*-Butyllithium is pyrophoric. HFIP is toxic.
- In order to get a -15 °C cooling bath you will have to add ice and NaCl in a ratio of about 3:1 to a water bath and then mix it. Alternatively you can try to keep an acetone/dry-ice bath at -15 °C by allowing most of the dry ice to sublime and adding it in small portions (a thermocouple is very useful for this method).

### What to Hand In

Please hand in a typed report to your TF that contains:

- (1) A copy of all lab notebook entries relevant to this experiment, including drawings of TLC plates and calculated  $R_f$  values.
- (2) Experimental procedure for the synthesis of IBX in *JOC* format.
- (3) For IBX: a  $^1\text{H}$  NMR spectrum and data in ACS format, including peak assignments.
- (4) Experimental procedure for the synthesis of DMP in *JOC* format.
- (5) For DMP: a  $^1\text{H}$  NMR spectrum and data in ACS format, including peak assignments.
- (6) Experimental procedure for the oxidation of the sugar in *JOC* format.
- (7) For the aldehyde: a (crude)  $^1\text{H}$  NMR spectrum and data in ACS format, including peak assignments.
- (8) Experimental procedure for the Horner-Wadsworth-Emmons olefination reaction in *JOC* format.
- (9) For the olefin:  $^1\text{H}$ ,  $^{13}\text{C}$ , IR, and ESI mass spectra and data in ACS format, including peak assignments and all assignable *J*-values.
- (10) Answers to the following questions:
  - a. The sugar you employed in the DMP oxidation reaction exists in a single chair conformation. Draw that conformation; why is the other chair inaccessible?
  - b. Two other methods for the mild oxidation of primary alcohols to aldehydes are commonly employed: oxidation with pyridinium chlorochromate (PCC) and the Swern oxidation, which employs oxalyl chloride and DMSO. Why is the DMP oxidation we have employed in this experiment preferable in this case?
  - c. What is the role of hexafluoroisopropanol (HFIP) in the Horner-Wadsworth-Emmons reaction you performed?

### Grading Scheme

total: 19% of course grade

#### Laboratory component

- complete first attempt (+2)
- complete second attempt (+2)
- obtain >20 g of pure DMP (+2)
- successfully used own DMP for oxidation (+2)
- obtain >1 g of pure olefin (+2)
- obtain >2 g of pure olefin (+1)

#### Written component

- lab notebook entries (+1)
- experimental procedures (+2)
- characterization data (+2)
- lab questions (+1)
- lab stewardship (+2)