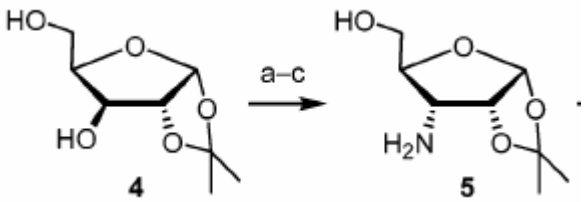
ORGANIC CHEMISTRY – QUALIFYING EXAM **01/21/2008**

The questions are based on the following article:

Shie *et al.*, **Synthesis of Tamiflu and its Phosphonate Congeners Possessing Potent Anti-Influenza Activity**

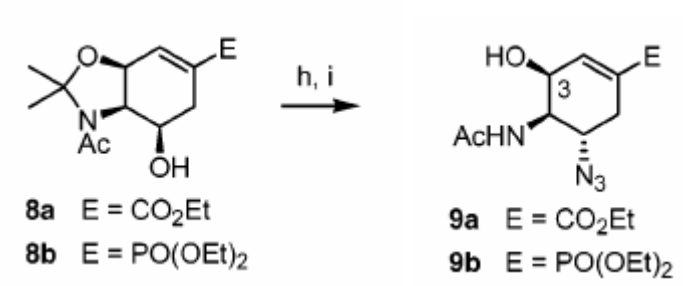
J. Am. Chem. Soc. **2007**, *129*, 11892.

(1) Propose a *reasonable* pathway (intermediate products) and classify the individual reactions (e.g. oxidation, reduction, A_E, S_N, Ar_{SE}, A_N etc.) for the following reaction sequence. Explain the major reason for the change in stereochemistry. **(5 points)**



The reaction conditions can be found in Scheme 1 below.

(2) Classify (and name) the reaction that is carried our under conditions (h), determine the absolute configuration of each stereocenter (in both **8** and **9**), and explain the stereochemistry change in the **9a/b**. Describe briefly why (i) was carried out after and not before (h). **(5 points)**



8a E = CO_2Et

8b E = $PO(OEt)_2$

9a E = CO_2Et

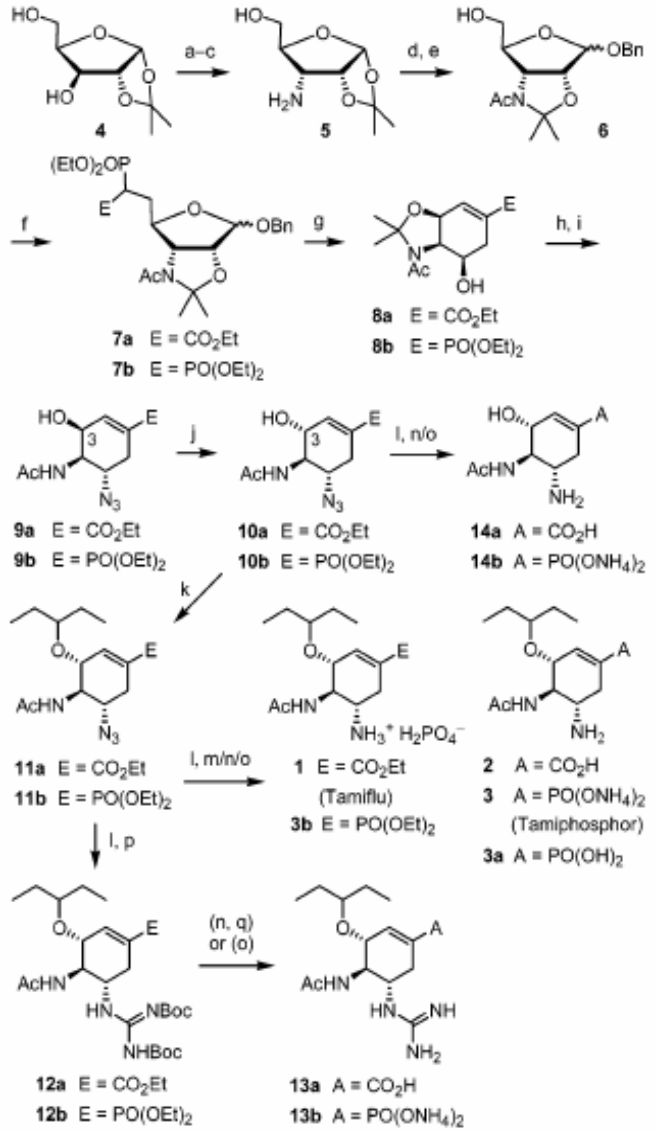
9b E = $PO(OEt)_2$

The reaction conditions can be found in Scheme 1 below.

Green Chemistry: **(2 points)**

Analyze the reaction steps (f), (g) and (j) from Scheme 1. Compare the 3 reactions (a Table like format is recommended) in all possible points of green chemistry. Based on your analysis name the reaction (from these three) that is the most benign for the environment.

Scheme 1. Synthesis of Tamiflu **1**, Oseltamivir **2**, the Guanidine Analogue **13a**, and the Phosphonate Congeners **3**, **3b**, and **13b**[a]



[a] Reagents and reaction conditions: (a) Me_3CCOCl, pyridine, 0 °C, 8 h; 89%. (b) PDC, Ac_2O, reflux, 1.5 h; $HONH_2$−HCl, pyridine, 60 °C, 24 h; 82%. (c) $LiAlH_4$, THF, 0 °C, then reflux 1.5 h; 88%. (d) Ac_2O, pyridine, 25 °C, 3 h; HCl/1,4-dioxane (4 M), BnOH, toluene, 0−25 °C, 24 h; 85%. (e) 2,2′-dimethoxypropane, toluene, catalyst *p*-TsOH, 80 °C, 4 h; 90%. (f) Tf_2O, pyridine, CH_2Cl_2, −15 °C, 2 h; $EtO_2CCH_2PO(OEt)_2$ or $H_2C[PO(OEt)_2]_2$, NaH, catalyst 15-crown-5, DMF, 25 °C, 24 h; 80% for **7a** and 73% for **7b**. (g) H_2, Pd/C, EtOH, 25 °C, 24 h; NaH, THF, 25 °C, 1 h, 83% for **8a**; or NaOEt, EtOH, 25 °C, 5 h, 80% for **8b**. (h) $(PhO)_2PON_3$, (*i*-Pr)N=C=N(*i*-Pr), PPh_3, THF, 25 °C, 48 h. (i) HCl, EtOH, reflux, 1 h; 83% for **9a** and 74% for **9b**. (j) Tf_2O, pyridine, CH_2Cl_2, −15 to −10 °C, 2 h; KNO_2, 18-crown-6, DMF, 40 °C, 24 h; 70% for **10a** and 71% for **10b**. (k) $Cl_3CC(=NH)OCHEt_2$, CF_3SO_3H, CH_2Cl_2, 25 °C, 24 h; 78% for **11a** and 82% for **11b**. (l) H_2, Lindlar catalyst, EtOH, 25 °C, 16 h; 85% for **3b**. (m) H_3PO_4, EtOH, 40 °C, 1 h; 91% for **1**. (n) KOH, THF/H_2O, 0−25 °C, 1 h; 88% for **2** and 81% for **14a**. (o) TMSBr, $CHCl_3$, 25 °C, 24 h; aqueous NH_4HCO_3, lyophilization; 85% for **3** (as the ammonium salt), 72% for **13b** and 75% for **14b**. (p) *N*,*N*′-bis(*tert*-butoxycarbonyl)thiourea, $HgCl_2$, Et_3N, DMF, 0−25 °C, 10−16 h; 78% for **12a** and 58% for **12b**. (q) TFA, CH_2Cl_2, 0 °C, 1 h; 88% for **13a**.