The questions are based on the following article:

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


(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)*

![Reaction Scheme 1](image)

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)*

![Reaction Scheme 2](image)

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.

Reagents and reaction conditions: (a) MesCCOCl, pyridine, 0 °C, 8 h, 99%. (b) DCC, 3,5-dinitrobenzoic acid, 3 h, 68%. (c) LiAlH₄, THF, 0 °C, then reflux 1 h. (d) Ac₂O, pyridine, 25 °C, 3 h, 98%. (e) Bu₄NOBF₄, toluene, 0–25 °C, 24 h, 85%. (f) 2,2'-dimethoxypropane, toluene, catalyst P-Tol, 80 °C, 4 h, 90%. (g) Et₂O, pyridine, CH₂Cl₂, −15 °C, 2 h, EtOCCCH₃PO(EO)₂ or H₂C(PO)(EO)₂, NaH, catalyse 15-crown-5, DMF, 25 °C, 24 h, 80% for 2a and 73% for 2b. (h) H₂, Pd/C, EtOH, 25 °C, 24 h, NaOH, THF, 25 °C, 1 h, 83% for 3a, or NaOEt, EtOH, 25 °C, 3 h, 80% for 3b. (i) (PhO)₂FON⁺, 2,2',6,2'-terpyridine, PP₃NCl, THF, 25 °C, 48 h. (j) HCl, EtOH, reflux, 1 h, 83% for 9a and 74% for 9b. (k) T₃O, pyridine, CH₂Cl₂, −15 to −10 °C, 2 h, KNO₂, 18-crown-6, DMF, 40 °C, 24 h, 76% for 10a and 71% for 10b. (l) H₂, Lindlar catalyst, EtOH, 25 °C, 48 h, 85% for 3b. (m) H₃PO₄, EtOH, 40 °C, 1 h, 91% for 11a. (n) KOH, THF/H₂O, 0–25 °C, 1 h, 88% for 2 and 81% for 14a. (o) TMSBr, CHCl₃, 25 °C, 24 h, 85% for 3 (as the ammonium salt), 72% for 13b and 75% for 14b. (p) N,N'-bis(tert-butylocarbonyl)thiourea, HgCl₂, Et₃N, DMF, 0–25 °C, 10–15 h, 78% for 12a and 58% for 12b. (q) TFA, CH₂Cl₂, 0 °C, 1 h, 85% for 13a.