# Organic Cumulative Exam

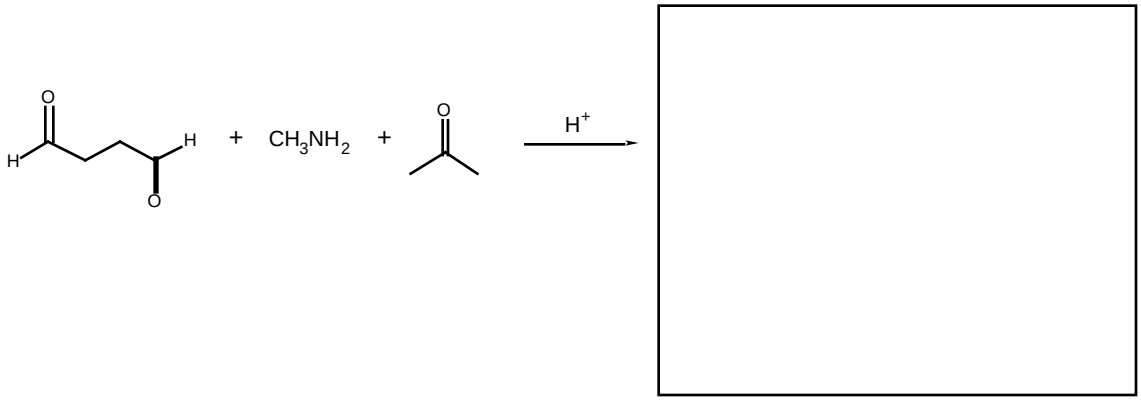
**December 1, 2001**

## The Chemistry of Professor Eric Sorenson
## (PLEASE WRITE ALL ANSWERS ON THE FRONT PAGE OF THE EXAM)

Professor Sorenson often derives ideas for his synthetic approaches by speculating on the reactions that are involved in the biosynthesis of the target molecule. That is, his synthetic approaches are "biomimetic". Sorenson also noted that this is *not* a new approach in organic synthesis. He cited Sir Robert Robinson's synthesis of tropinone. Long, long ago, Robinson took heed of the suggestion that enzymatic Mannich reactions might be involved in the biosynthesis of some alkaloids and used a Mannich reaction to prepare tropinone. (*J. Chem. Soc.* **1917**, 762)

**1.** Give the structure of tropinone and show a detailed mechanism for the reaction:

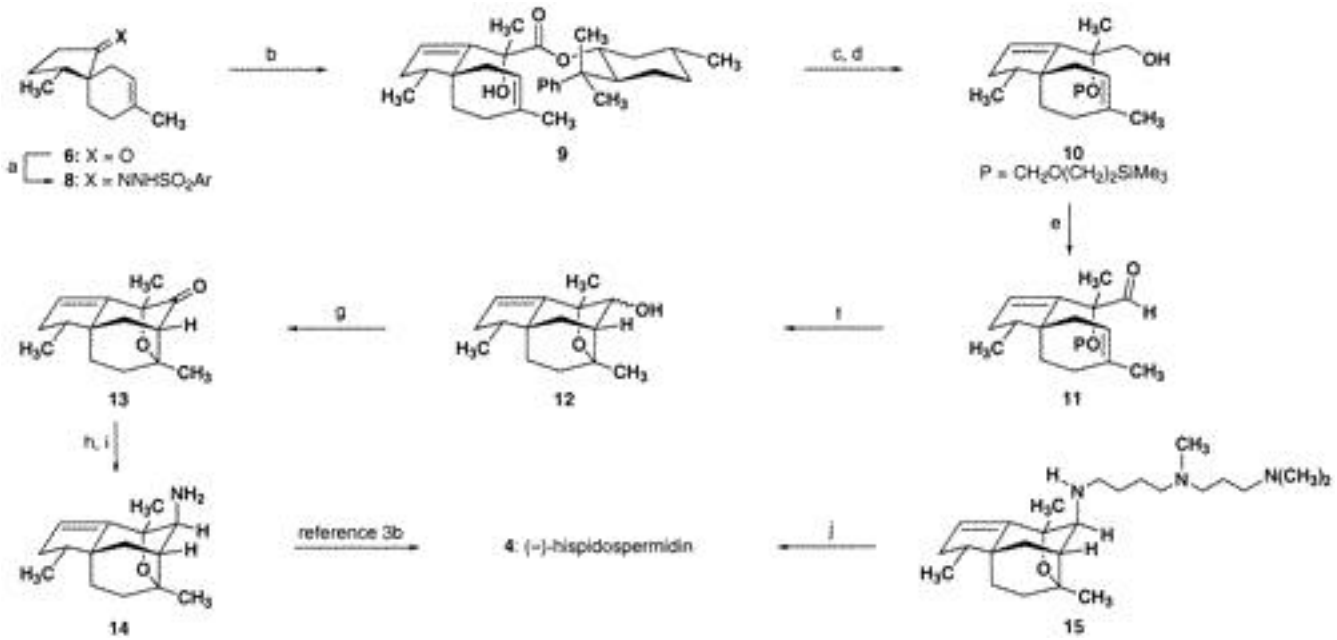
Hint: Remember that intramolecular reactions are faster than analogous intermolecular reactions.




**Tropinone**

Hint: formula $C_8H_{13}NO$

2. Some questions regarding Professor Sorenson's synthesis of (-)-hispidospermidin (shown below): *J. Am. Chem. Soc.* **2000**, *122*, 9556.

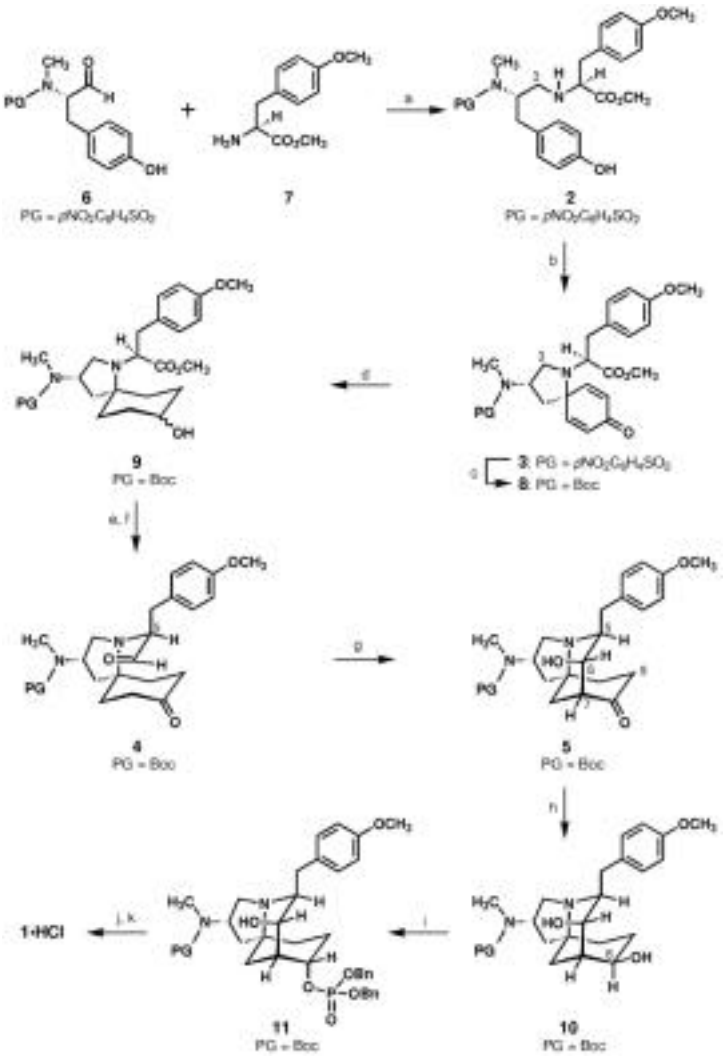



Reagents and conditions: (a) 2,4,6-triisopropylbenzenesulfonyl hydrazide, HCl (1.2 equiv), CH3CN, room temperature, 75%. (b) n-BuLi (2.05 equiv), Et2O/THF, -78 to -20 C; then MgBr2·OEt2, -78 C; then 7, -78 C to room temperature, 55% from 8. (c) SEMCl, n-Bu4NI, i-Pr2NEt, CH2Cl2, 50 C, ca. 100%. (d) Dibal-H, toluene, -78 C, 93%. (e) (COCl)2, DMSO, CH2Cl2, -78 C; then i-Pr2NEt, -78 C to room temperature, ca. 100%. (f) AcOH, room temperature, 2 d, 83% or AcOH, 80 C, 3 h, 87%. (g) (COCl)2, DMSO, CH2Cl2, -78 C; then i-Pr2NEt, -78 C to room temperature, ca. 100%. (h) HONH2·HCl, NaOAc·3H2O, EtOH, room temperature, ca. 100%. (i) LiAlH4, NiCl2, Et2O, room temperature, 97%. (j) Rh/C (2 equiv), EtOAc, H2, 1100 psi, (70% yield of a 3:1 mixture of epimers favoring 4). Ar = 2,4,6-triisopropylbenzene.

2(a). The Swern oxidation was used two times in this synthesis (steps e and g); thus, is crucial to the success of this route. What is the mechanism of the Swern reaction?

2(b) When conducting organic reactions it is crucial to anticipate the ways in which your reaction might *fail*. Such anticipation may allow you to choose optimal reaction conditions or design alternate routes. The key step in Sorenson's hispidospermidin synthesis is the cyclization reaction "f". In the optimized reaction that they report the yields are good (~85%), but they are not quantitative. We can be certain that Sorenson's student anticipated all possible side reactions in this step. Use your knowledge of the Prins Reaction to retrace her footsteps and propose two reasonable side products that might be formed in this reaction and, thus, might account for the "missing" mass balance. Of course, please show the mechanisms by which your proposed products form.

3. Some questions regarding the synthesis of FR901483 (*Angew. Chem. Int. Ed.* **2000**, *39*, 4593).



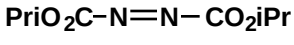
Scheme 2. Synthesis of FR901483 (1)HCl: a) 6 (1.0 equiv), 7 (1.5 equiv), NaBH(OAc)3 (1.5 equiv), 4 Å MS, 0 ∞C, 1 h, then RT, 24 h, 80 %; b) PhI(OAc)2, (1.1 equiv), (CF3)2CHOH, RT, 10 min, 51 % (based on 70 % consumed 2); c) NaSPh (1.5 equiv), DMSO, RT, 3 h; then (Boc)2O (2 equiv), pyr (2 equiv), RT, 12 h, 71 % from 3; d) H2, Raney Ni, EtOAc/EtOH (2:1), RT, 15 h, 93 %; e) LiAlH4 (3 equiv), THF, -78 ∞C, 1 h then 0 ∞C, 2 h, 90 %; f) (COCl)2 (8 equiv), DMSO (16 equiv), CH2Cl2, -78 ∞C, 30 min; then iPr2Net (20 equiv), -78 ∞C, 30 min; then 0 ∞C, 1 h, 100 %; g) NaOMe (1.1 equiv), MeOH, 0 ∞C, 2 h, 34 % of 5 (74 % total yield of aldol adducts); h) H2, Raney Ni, EtOAc/EtOH (1:10), RT, 4 h, 92 %; i) dibenzyl hydrogen phosphate (6 equiv), tris(4-chlorophenyl)phosphine (3 equiv), DIAD (3 equiv), Et3N (10 equiv), toluene, RT, 26 h, 37 % of 11+17 % of alkene; j) H2, Pd/C, MeOH, RT, 5 h, 95 %; k) 4 n HCl, dioxane, 0 ∞C, 30 min; then RT, 2 h, 84 % of 1HCl (precipitated from MeOH with Et2O). MS=molecular sieves, RT=room temperature, Boc=tert-butoxycarbonyl, pyr=pyridine, DIAD=diisopropyl azodicarboxylate, Bn=benzyl.

3(a) Show a complete mechanism for the first step (a) in the synthesis. What is this reaction called?

3(b) The first critical step in this synthesis is the so-called "azaspirocyclization". The group was concerned about one potential unwanted side reaction in this step. It turned out that the desired "spiro" reaction occurred and the side product did *not* predominate… nonetheless, show the feared side product and give a detailed mechanism for its formation (including the $PhI(OAc)_2$ oxidation).

3(c) The second key step in this synthesis involves an aldol condensation. Here the yield of the desired product (**5**) is not so good, but the researchers know why. The reason for the low yield of **5** is that two (expected) side products are also formed in significant yield. What are the side products? Show the mechanism for the formation of each under the NaOMe/MeOH reaction conditions shown.

3(d) The final step involves conversion of an alcohol to a phosphate with inversion of configuration. This was performed via a Mitsunobu reaction. Please show the mechanism for this reaction.




(DIAD)

3(d) Why is it possible to selectively modify only one of the free hydroxyl groups in **10**?