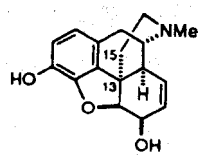
ORGANIC CUMULATIVE EXAM
August 30, 1997

I. Even though they may not be in our specific field, synthesis papers provide a useful format for us to test our current knowledge of transformations and their mechanisms. The paper by James D. White, Peter Hrnciar, and Frank Stappenbeck (JOC **1997** ***62*** 5250-5251) describes a recent synthesis of the enantiomer of the potent alkaloid analgesic, (-)-morphine.



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1. Numerous syntheses of (±) morphine have appeared. The first synthesis of (-) morphine, without resolution, was presented by the Overman group in 1993.

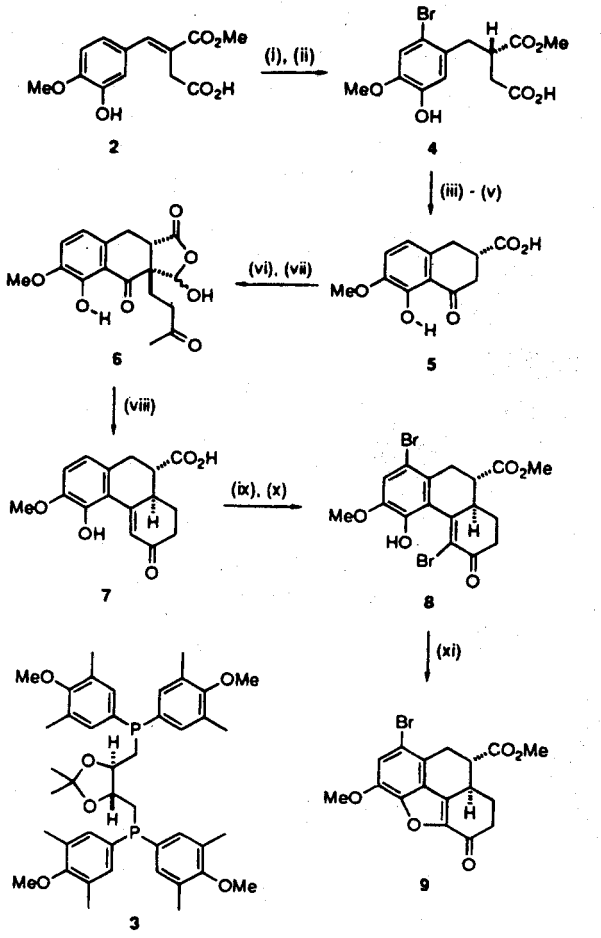
a) (5) Why should there be interest in a synthesis of a chiral substance which does not involve resolution?

b) (3) Why would anyone want to synthesize the unnatural (+) enantiomer of morphine?

c) (5) Could an asymmetric synthesis of (+) morphine be applied to (-) morphine? Discuss.

The first steps in the White's synthesis of morphine are depicted in Scheme 1.

Scheme 1[a]



[a] (i) H_2, $[Rh(COD)Cl]_2$, (4*R*,5*R*)-(−)-MOD-DIOP, 100%, (94% ee); (ii) Br_2, HOAc, 93%; (iii) MsOH, P_2O_5, 75%; (iv) H_2, Pd/C, $NaHCO_3$, 100%; (v) LiOH, THF−H_2O, 100%; (vi) KH, HCO_2Me, DME, 0 °C, 85%; (vii) MVK, Et_3N, CH_2Cl_2, 95%; (viii) NaOH, H_2O, THF, 95%; (ix) CH_2N_2, Et_2O−CH_2Cl_2, 99%; (x) Br_2, $NaHCO_3$, CH_2Cl_2, 80%; (xi) DBU, C_6H_6, 50 °C, 90%.

2. a) (7) The starting compound **2** can be made from the Stobbe condensation of a common diester. (Note that you do not have to know what the Stobbe condensation is to answer this question correctly. Just think of what kind of diester is required.) Give the reaction for the preparation of **2**.

b) (5) An intermediate is formed in the condensation which leads to the half-acid ester **2**. Give the structure of that intermediate (Hint: If you. Write the mechanism it should become apparent what is going on.)

3. (10) Note that a Br is introduced to make 4 but then the Br is removed in one of the steps leading from 4 to 5. By means of structures and words show why the Br was introduced.

4. (20) Give mechanisms for the two steps involved in the conversion of 5 to 6 (vi and vii).

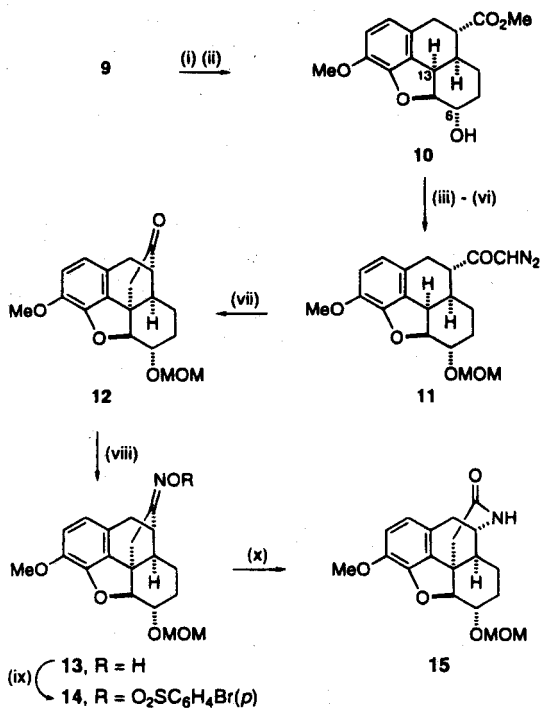
Step vi

Step vii

5. (10) Give a mechanism for the conversion of 8 to 9.

The morphine skeleton was completed as shown in Scheme 2. The oxime **13** could not be converted to the desired lactam through the Beckmann rearrangement without forming the brosylate **14**.

Scheme 2[a]



[a] (i) $NaBH_4$, *i*-PrOH–CH_2Cl_2, 99%; (ii) H_2, Pd/C, MeOH, 78%; (iii) $CH_2(OMe)_2$, P_2O_5, $CHCl_3$ 80%; (iv) LiOH, THF–H_2O, 99%; (v) $(COCl)_2$, C_6H_6; (vi) CH_2N_2, 63%; (vii) $Rh_2(OAc)_4$, CH_2Cl_2, 50%; (viii) $H_2NOH{\cdot}HCl$, NaOAc, MeOH, 90%; (ix) *p*-$BrC_6H_4SO_2Cl$, Et_3N; (x) AcOH, rt, 62% from **13**.

6. a) (5) How does brosylate facilitate the Beckmann rearrangement? Think about the mechanism,

b) (5) Two regioisomeric lactams could have been formed, but the one shown was produced in 11:1 ratio. What determines the regiochemistry of Beckmann rearrangements?