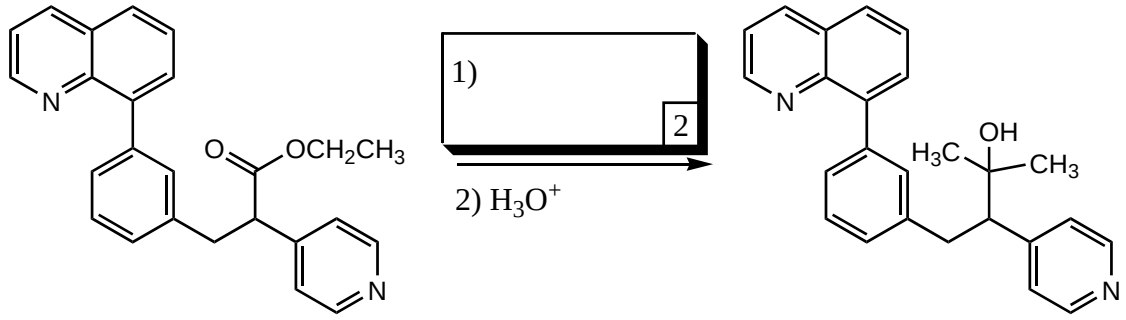
CEM 252
Summer 2006

Quiz 3 - 25 July 2006
20 points

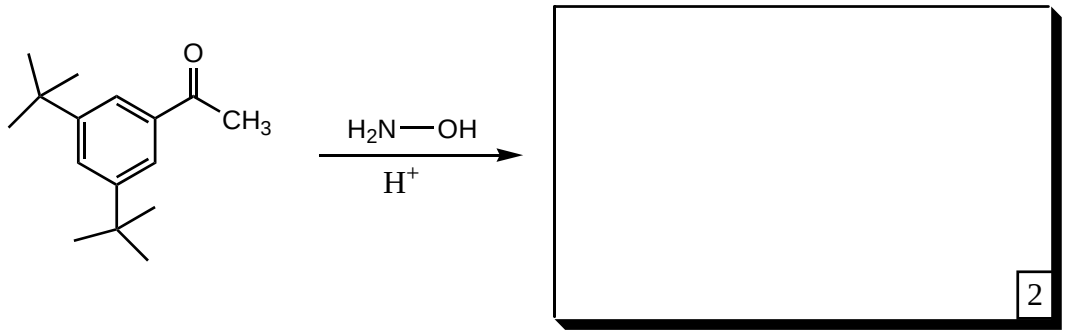
Name_____

1. Complete the following reactions:

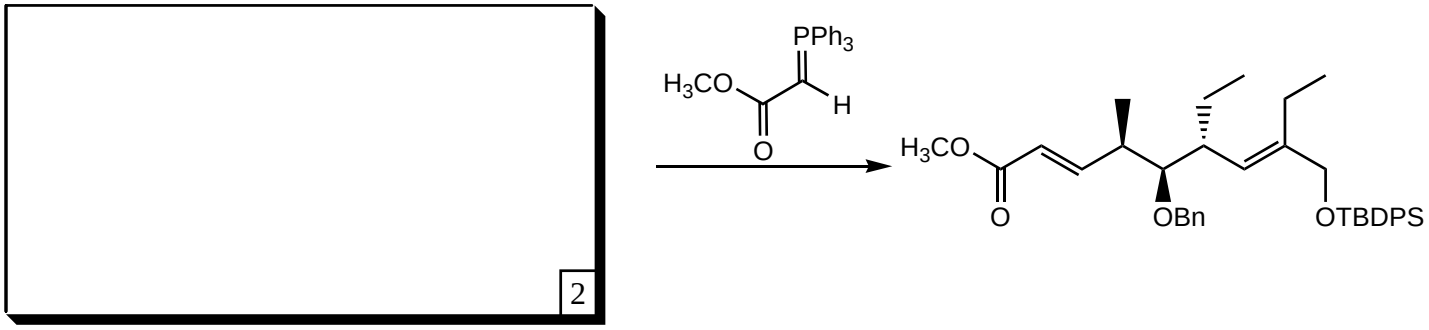
a) Synthesis of phosphodiesterase-4 inhibitors for asthma treatment (*Bioorg. Med. Chem. Lett.* **2005**, *15*, 5241-5246).



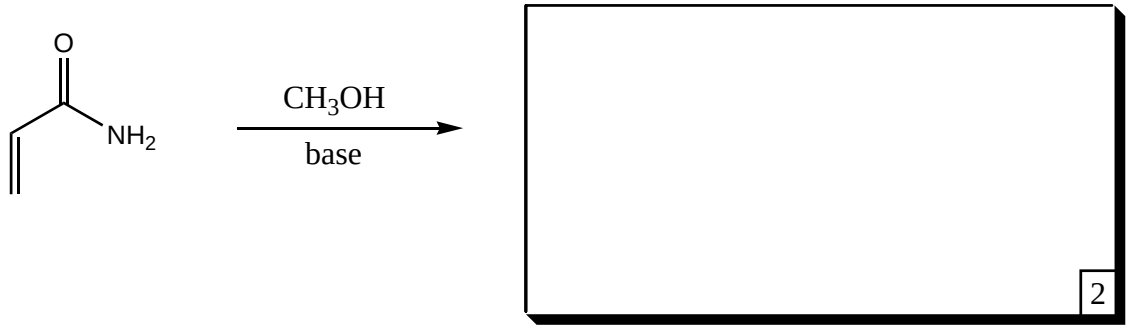
b) Development of retinoid X agonists for regulating gene expression (*Bioorg. Med. Chem. Lett.* **2006**, *16*, 2352-2356).



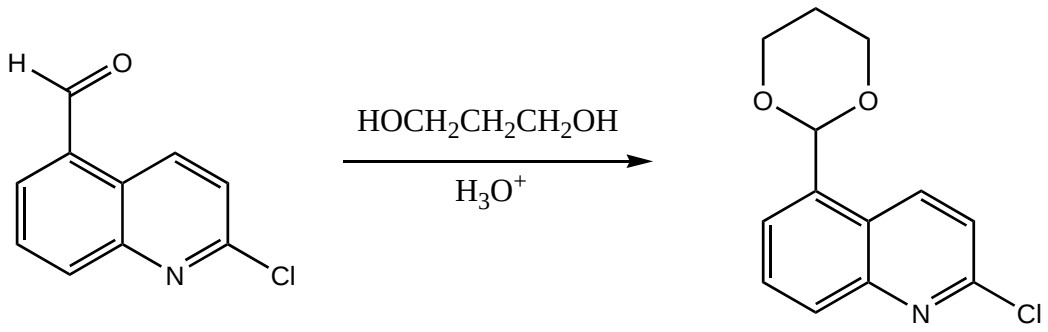
c) Synthesis of spiculoic acid, a potential anti-breast cancer drug (*Org. Lett.* **2005**, *7*(25), 5569-5572).



d) from *J. Org. Chem.* **2004**, *69*, 6496-6499.



2. Draw the complete, step-wise, curved-arrow mechanism for the following reaction, reported recently as a step in the synthesis of molecules to control protein-protein interactions related to gene expression and cell proliferation (*Org. Biomol. Chem.* **2005,** *3*, 2543-2557). You may use "R" as an abbreviation in your mechanism for any unaffected portion of the molecule.



3. On the back of this quiz is a page from an article in the latest *Journal of Organic Chemistry*, "Total Synthesis of Valilactone." This compound is known to block the absorption of fat by inhibiting an enzyme in the pancreas. It was originally found in a bacterium and this article presents its first synthesis. Look through the structures on the page and give an example of each of the following compounds:

a cyclic ester (lactone) 2

a thioacetal 2

a carboxylic acid 1

an amide 2

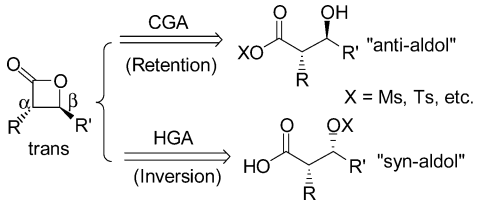


FIGURE 2. Retrosynthetic analyses of formation of the β-lactone ring, which may be constructed from either the "anti aldols" through carboxylic group activation (CGA) or the "syn aldols" through hydroxyl group activation (HGA).

hydroxyl group activation (HGA[7]) with readily accessible enantiopure syn aldol as the precursor.

Results and Discussion

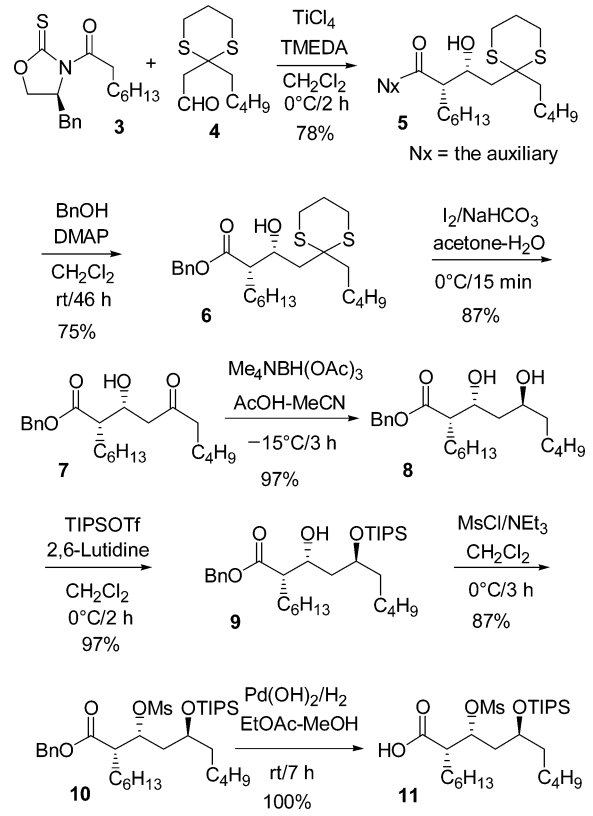
Essentially all the bio-active β-lactones so far known are α,β-disubstitued, with the two substituents on the 2-oxetanone ring trans to each other. The bioactivity of these compounds is dependent critically not only on the presence of an intact β-lactone ring but also on the absolute configurations of the stereogenic centers on the lactone ring. Therefore, construction of the trans disubstitued β-lactone moiety is one of the key issues in the synthesis of these compounds.

In principle, trans β-lactones can be derived from either anti aldols through carboxylic group activation[7] (CGA) or from syn aldols through HGA (cf. Figure 2). In practice, however, HGA is much less common than CGA, although syn aldols are readily attainable in enantiopure forms via, for instance, Evans[8] or Crimmins[9] aldolization.

From the outset of this work we planned to make use of enantiopure syn aldols as the chirality source of the stereogenic centers of the β-lactone moiety. As shown in Scheme 1, the synthesis started with a $TiCl_4$-mediated asymmetric aldol condensation[9] between **3** and **4**,[10] which afforded the syn aldol **5** as the only detectable product in 78% yield (along with 16% of recovered starting **3**). The chiral auxiliary[11a] in **5** was then nondestructively removed[11b−c] with concurrent protection of the carboxylic group as a benzyl ester. The resulting **6** was treated with I_2 in the presence[12] of $NaHCO_3$ to give ketone **7** in 87% yield.

Generation of the 1,3-anti diol motif and the subsequent selective protection of the remote hydroxyl group were done in a manner similar to that in Ghosh's[5b] synthesis of **1**. The substrate chirality induced asymmetric reduction with $Me_4NBH(OAc)_3$[13] was performed at −15 °C, which was more convenient

SCHEME 1



than −40 °C, but the diasteoemeric selectivity (22:1) was the same as that obtained at −40 °C in Ghosh's[5b] synthesis of **1**.

The diastereomers were separated on silica gel, and the remote hydroxyl group (δ to the carbonyl group) in **8** was then selectively protected[5b] with TIPSOTf ($(i\text{-Pr})_3SiOSO_2CF_3$) at 0 °C, leaving the β OH as the only open site for further transformation.

The key β-lactone functionality was constructed through a three step sequence, which was first introduced by Lenz[14a] in the synthesis of 4-methyl-oxetan-2-one (a much less hindered β-lactone with no substituent on the α-carbon and only one small methyl group on the β-carbon): (1) converting the hydroxyl group into a good leaving group by treatment with $MsCl/NEt_3$, (2) cleaving the benzyl group by hydrogenolysis under neutral conditions to release a free carboxylic group without affecting the liable β-OMs functionality, and (3) treating the newly generated carboxylic acid with a base to initiate an intramolecular S_N2 reaction, yielding a β-lactone ring with concurrent configuration inversion at the β carbon. It should be noted that in sharp contrast to the facile conversions observed in the successful literature cases,[14,15] the ring-closure of the α,β-dialkyl substituted substrates was often very tricky when the substituents

(7) Mulzer, J.; Bruntrup, G.; Chucholowski, A., *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 622−623.

(8) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1990**, *113*, 1047−1049.

(9) (a) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883−7884. (b) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775−777. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894−902.

(10) Woessner, W. D.; Ellison, R. A. *Tetrahedron Lett.* **1972**, 3735−3738.

(11) (a) For a very convenient procedure for synthesizing such auxiliaries, see Wu, Y.-K.; Yang, Y.-Q.; Hu, Q. *J. Org. Chem.* **2004**, *69*, 3990−3992. (b) Wu, Y.-K.; Sun, Y.-P.; Yang, Y.-Q.; Hu, Q.; Zhang, Q. *J. Org. Chem.* **2004**, *69*, 6141−6144. (c) Su, D.-W.; Wang, Y.-C.; Yan, T.-H. *Tetrahedron Lett.* **1999**, *40*, 4197−4198.

(12) Nicolaou, K. C.; Bunnage, M. E.; McGarry, D. G.; Shi, S.; Somers, P. K.; Wallace, P. A.; Chu, X.-J.; Agrios, K. A.; Gunzner, J. L.; Yang, Z. *Chem.—Eur. J.* **1999**, *5*, 599−617.

(13) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

(14) (a) Zhang, Y.; Gross, R. A.; Lenz, R. W. *Macromolecules* **1990**, *23*, 3206−3212. (b) De Angilis, F.; De Fusco, E.; Desiderio, P.; Giannessi, F.; Pibrizio, F.; Tinti, M. O. *Eur. J. Org. Chem.* **1999**, 2705−2707. (c) Bernabei, I.; Castagnani, R.; De Angelis, F.; De Fusco, E.; Giannessi, F.; Misiti, D.; Muck, S.; Scafetta, N.; Tinti, M. O. *Chem.—Eur. J.* **1996**, *2*, 826−831. (d) Sato, T.; Kawara, T.; Nishizawa, A.; Fujisawa, T. *Tetrahedron Lett.* **1980**, *21*, 3377−3380. See also another related case with inversion at the β position: (e) Griesbeck, A.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1320−1325.

(15) Wu, Y.-K.; Sun, Y.-P. *Chem. Commun.* **2005**, 1906−1908.