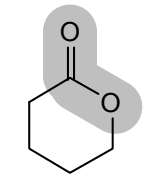
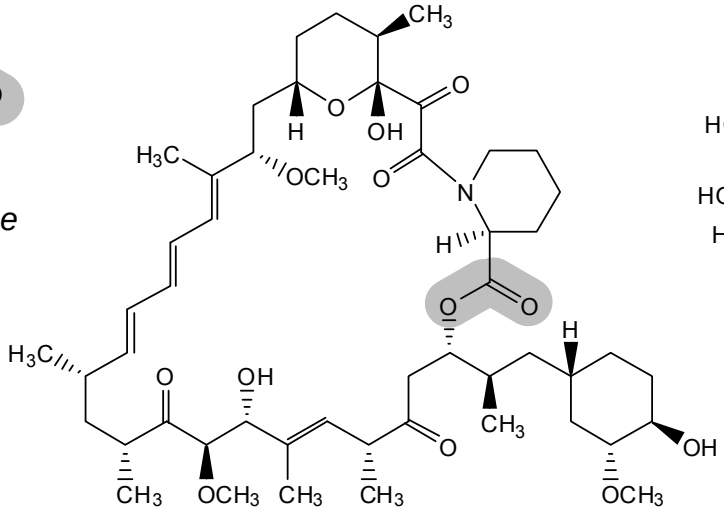
Chemistry 2302

Workshop 13
Mechanisms of Macrolactonization

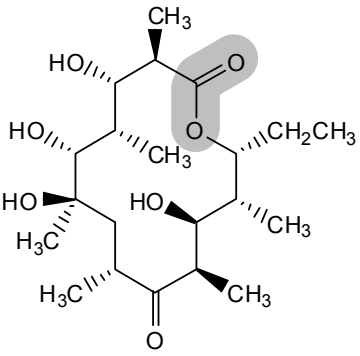
Many important pharmaceuticals are *macrolactones*—cyclic esters containing more than eight atoms in the ring.



a lactone



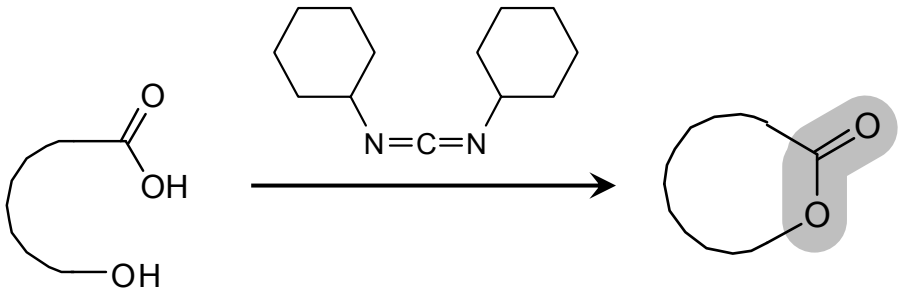
rapamycin
(a macrolactone;
immunosuppressant, anti-rejection drug
for transplant recipients)



erythronolide B
(a macrolactone;
core structure of many
antibiotics)

Often, the last step in the synthesis of these molecules is macrolactonization, formation of the cyclic ester from a precursor with a carboxylic acid and an alcohol.

1. One way this has been accomplished is to use DCC to couple the acid and alcohol in situ, as shown in the cartoon representation below. On the next page, show the mechanism for this reaction.



2. In order to improve macrolactone yields, chemists have investigated alternatives to carbodiimides for activating carboxylic acids. One alternative is Mukaiyama's salt, which also converts the carboxylic acid into a more reactive, intermediate acid derivative in the presence of a base like triethylamine (NEt_3). Draw a mechanism for this process. (*Hint:* Mukaiyama's salt reacts via addition to the C=N bond.)