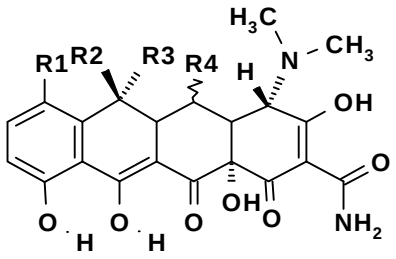
# TOTAL SYNTHESIS OF A TETRACYCLINE

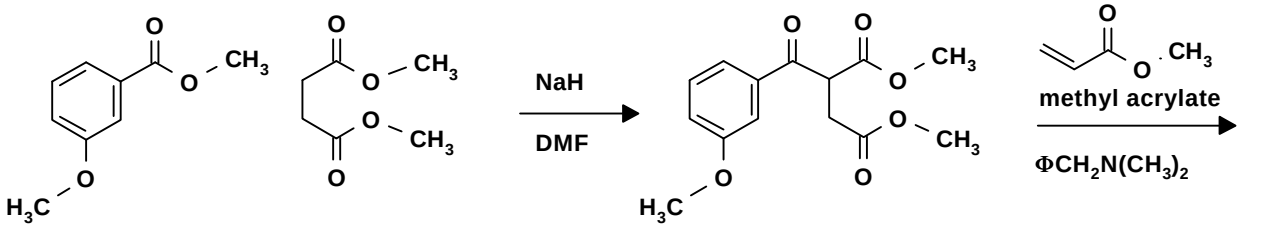
The first synthesis of the tetracycline skeleton by the legendary Robert B. Woodward and a group at Pfizer, was published in *J. Am. Chem. Soc.* **1962**, *84*, 3222 - 4. This compound, now called sancycline, is active as an antibiotic but not used as often as terramycin. Other members of the family with $R_2$ or $R_4$ = OH are much more difficult to synthesize because they are very sensitive to acid and base. This synthesis is linear, i.e. each step follows the previous one; the authors did not report their percent yield, but if each of the 18 steps had produced an 80% yield, the overall yield would have been only 1.8%, $(.8)^{18}$. Later syntheses were more efficient, in that substantial parts of the molecule were synthesized separately and then assembled; this convergent synthesis improves the overall yield to $(.8)^n$, where n is the number of *consecutive* steps.

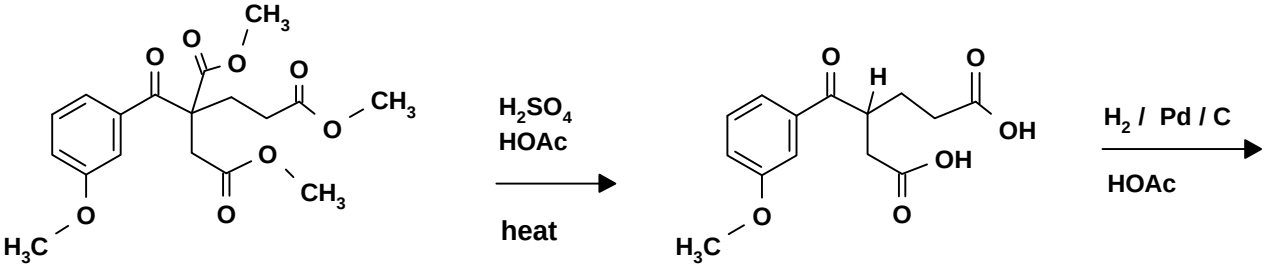
Most of the reactions used are seen in a two-semester organic chemistry course; however, most have non-standard catalysts, chosen for their ability to provide the best yield of product for that particular substrate, usually after many trial runs with other catalysts. This synthesis provides a dramatic illustration of the importance and creativity of organic chemistry. I suggest that you try to identify the reactions as a review; there are only a couple that will not be familiar. Note also that tetracycline has a large number of carbonyl groups, many of which are β to each other and thus exist primarily with one of the two in the enol form, so be aware that a ketone may be hidden as an enol. I have put them in the form that the authors reported (usually enol) but have not shown the hydrogen bonds (you can add them).

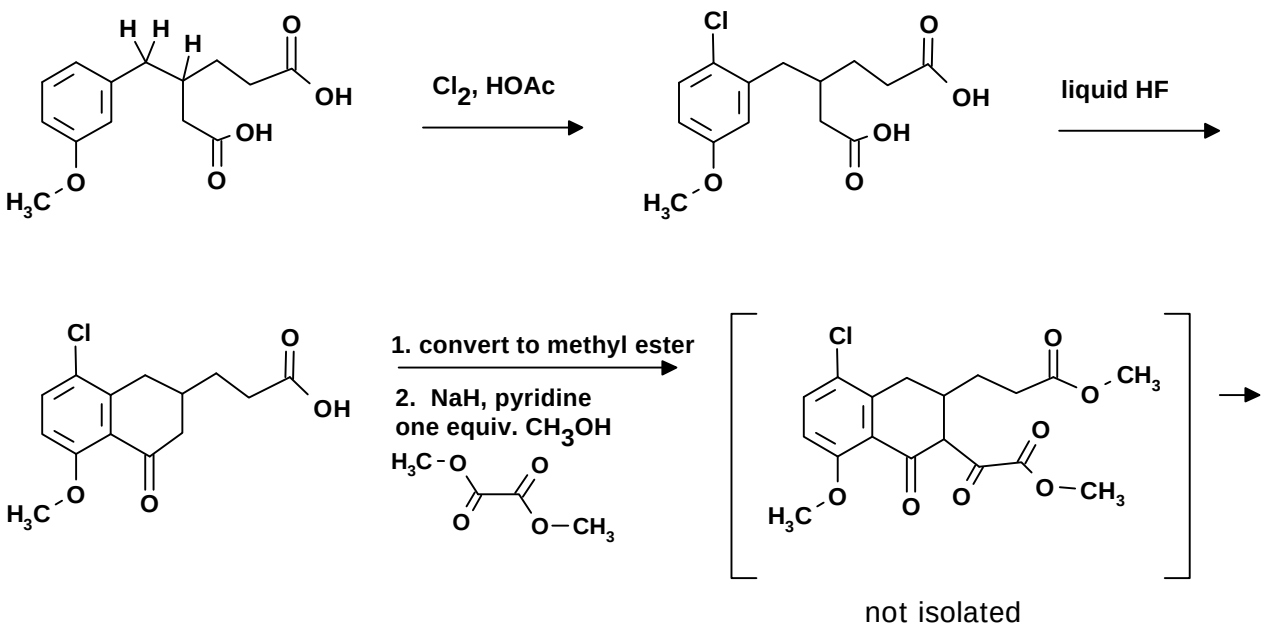


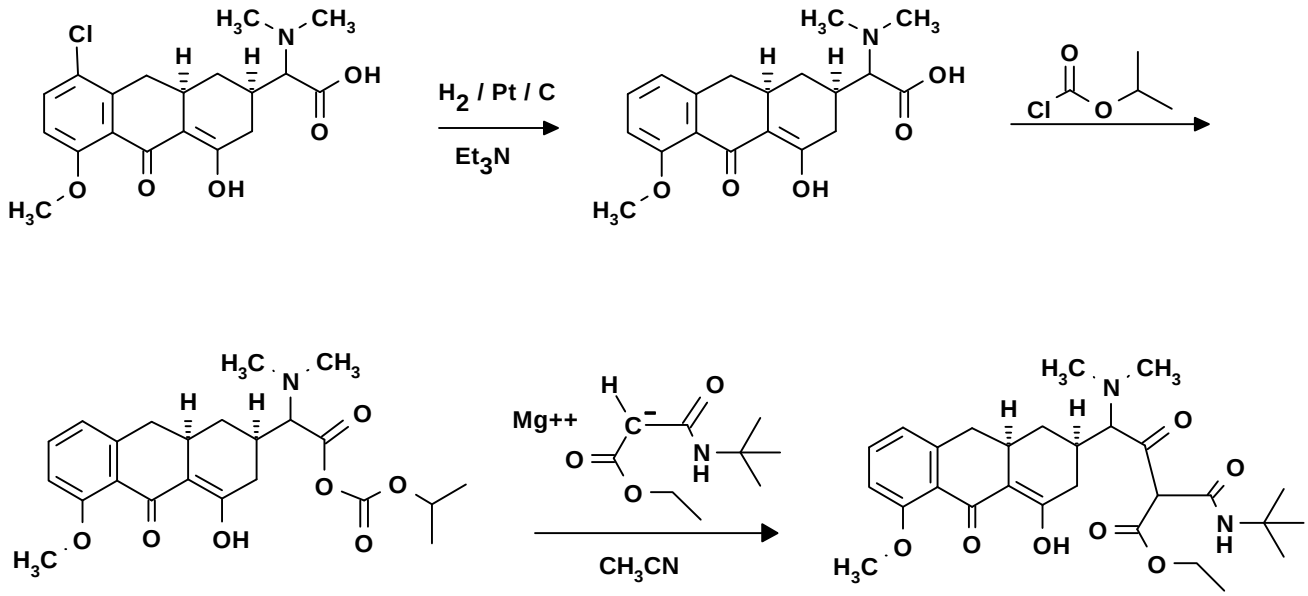

The tetracycline family has a variety of different R's in the positions indicated:

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| Tetracycline | H | OH | Me | H |
| Terramycin | H | OH | Me | OH |
| Chlortetracycline | Cl | OH | Me | H |
| Sancycline | H | H | H | H |




Cl2, HOAc
liquid HF
1. convert to methyl ester
2. NaH, pyridine
one equiv. CH3OH
not isolated
HCl, HOAc
Mg(OCH3)2
toluene, heat
NH(CH3)2
observed
stereochem
NaBH4
DME
H+
Zn
HCO2H


H2 / Pt / C
Et3N
Mg++
CH3CN
NaH
DMF
48% HBr
O2, DMF, CH3OH
pH 5
Not a reaction like any you have seen

LMS 73, 97