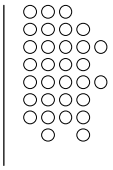
II. Special Topics

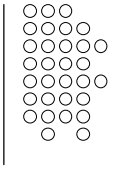
IIA. Enolate Chemistry & the Aldol Reaction



Boger Notes: p. 147 - 206 (Chapter VIII)
Carey/Sundberg: **B** p. 57-95 (Chapter **B** 2.1)

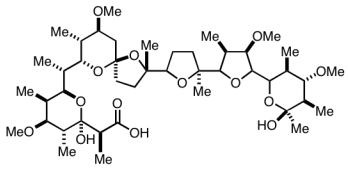
Problem of the Day: Wang, X.; Meng, Q.; Perl, N. R.; Xu, Y.; Leighton, J. L., "Tandem aldol-allylation and aldol-aldol reactions with ketone-derived enolsilanes: Highly diastereoselective single-step synthesis of complex tertiary carbinols." *J. Am. Chem. Soc.* **2005**, *127*, 12806-12807.

- Explain the stereoselectivity and the reaction mechanism

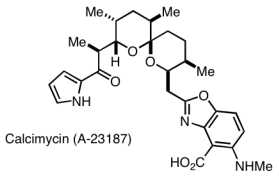


Cornforth: Nature is an organic chemist with a preference for the aldol reaction.

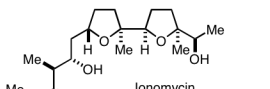
Many natural products contain polyhydroxylated carbon arrays, usually a mix of 1,2- and 1,3-diols; biosynthetically, these compounds are related and are commonly referred to as polyacetates/polypropionates.
Typical examples of polyether antibiotics isolated from *Streptomyces* are:



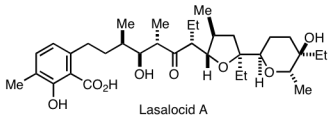
Lonomycin C



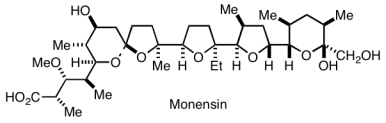
Calcimycin (A-23187)



Ionomycin



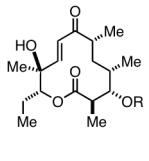
Lasalocid A



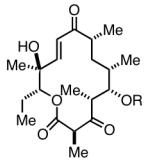
Monensin

Most of these compounds are metal chelators (ionophores). Monensin as a food additive kills bacteria in poultry by the transporting Na^+ outside the cell, thus increasing the intracellular osmotic pressure and causing the coccidia to explode.

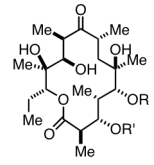
Macrolide antibiotics are characterized by the macrocyclic lactone moiety and can be grouped into: polyoxo, polyene, ionophore, and ansamycin macrolides.



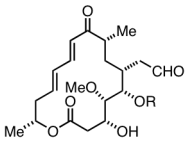
Methymycin
R = desoaminyl



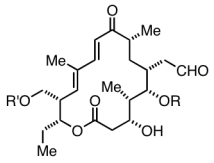
Pikromycin
R = desoaminyl



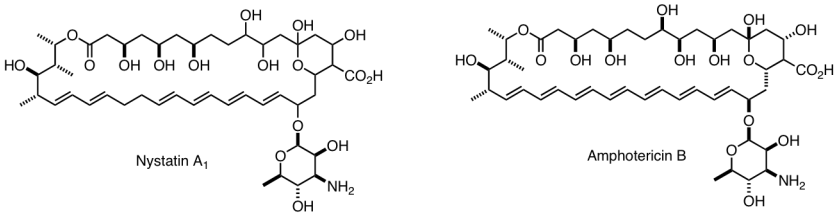
Erythromycin A
R = desoaminyl
R' = cladinosyl



Leucomycin A_1
R = mycarosyl-mycaminosyl

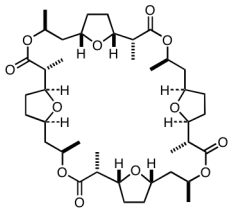


Tylosin
R = mycarosyl-mycaminosyl
R' = mycinosyl

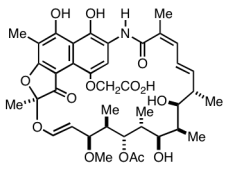


Nystatin A_1

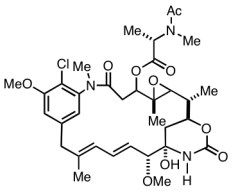
Amphotericin B



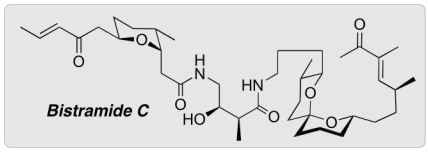
Nonactin

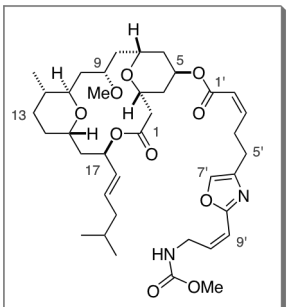


Rifamycin S

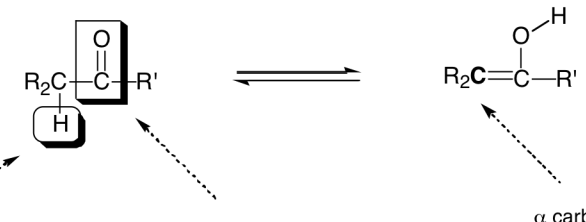


Maytansine





1. Introduction



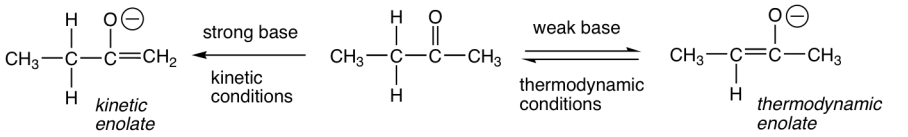
α proton is relatively acidic (pKa≈20); it can be removed by bases

carbonyl group is electrophilic; nucleophilic reagents add to carbonyl group

α carbon atom of enol is nucleophilic; it attacks electrophilic reagents

Carbonyl compounds exist in equilibrium with their tautomers, which are enols. They can express a variety of different kinds of chemical reactivity.

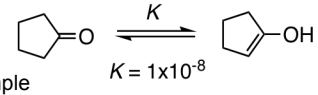
The enol tautomer is quite reactive toward electrophiles, and the above equilibrium rapidly regenerates new enols in the presence of acid or base catalysts. However, most reactions of electrophiles with carbonyl compounds take advantage of the higher nucleophilicity of the deprotonated enol, the enolate anion.



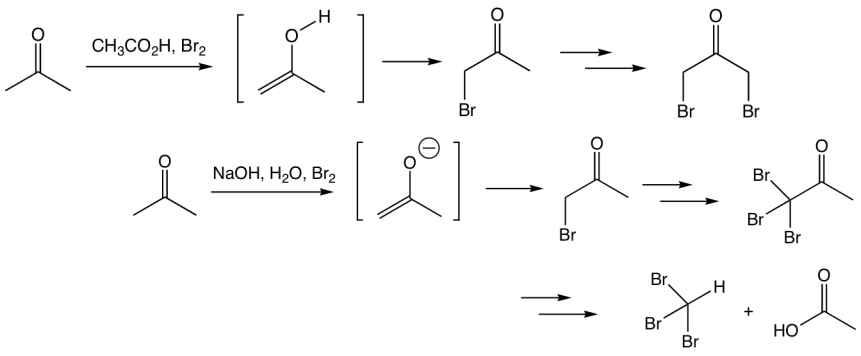
When unsymmetrical carbonyl compounds are converted to their enolates under conditions that allow equilibrium to be established (high temperatures and weak bases) the enolate anion with the more highly substituted double bond is formed. This ion is the more stable of the two possible enolates and is called the thermodynamic enolate. If the carbonyl compound is added to an excess of a strong base (usually LDA) at low temperatures, the least hindered hydrogen atom is removed. The ion with the less substituted double bond forms; it is the less stable of the two possible enolates but is the one that forms faster. For this reason, it is called the kinetic enolate.

Reactions of aldehydes and ketones that involve enol or enolate ion intermediates include:

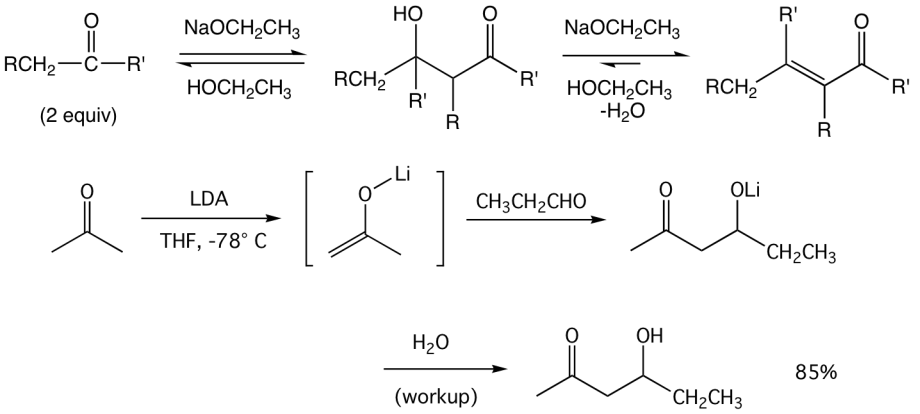
Enolization. Aldehydes and ketones exist in equilibrium with their enol forms. The rate at which equilibrium is achieved is increased by acidic or basic catalysts. The enol content of simple aldehydes and ketones is quite small; β-diketones, however, are extensively enolized.



α-Halogenation. Halogens react with aldehydes and ketones by substitution; An acid catalyst (or base) increases the rate of enolization (enolate formation), which is the rate-determining step. The reaction of a methyl ketone with a halogen in base is known as the haloform reaction. Once one of the α-H's is replaced by a halogen atom, the remaining H's are more acidic and are more easily substituted. C,C-bond cleavage is facilitated by the e-withdrawing effect of the halogens.

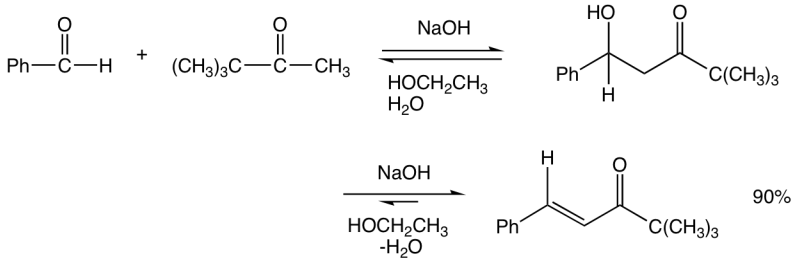


Aldol condensation. A reaction of great synthetic value for C,C-bond formation. Nucleophilic addition of an enolate ion (or an enol in the acid-catalyzed version of this process) to a carbonyl group leads to a β-hydroxy aldehyde or ketone (reversible!). Subsequent dehydration (acid- or base-catalyzed) yields an α,β-unsaturated carbonyl compound.

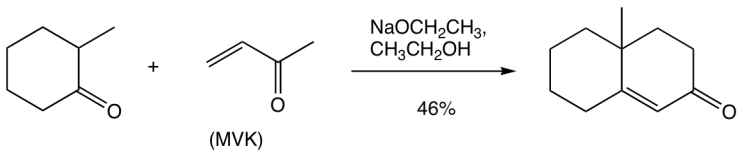


The irreversible, rapid enolization of carbonyl compounds with very strong base (LDA), followed by addition of aldehydes or ketones, allows the direct formation of a single aldol product in **crossed aldol** condensations.

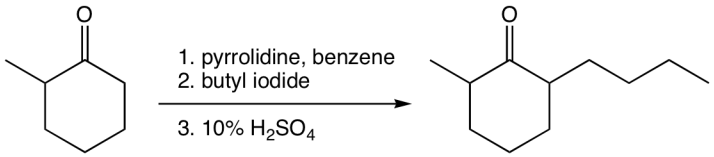
Claisen-Schmidt reaction. A crossed aldol condensation in which a non-enolizable aldehyde reacts with an enolizable aldehyde or ketone.



Robinson annulation. A combination of conjugate addition of an enolate anion to an α,β-unsaturated ketone (**Michael addition**) with subsequent intramolecular aldol condensation. Michael additions are typical for soft nucleophiles, including enols, cyanides, cuprates and thiol(ate)s. In contrast, hard nucleophiles (hydrides, Grignard and lithium reagents) prefer 1,2-addition.

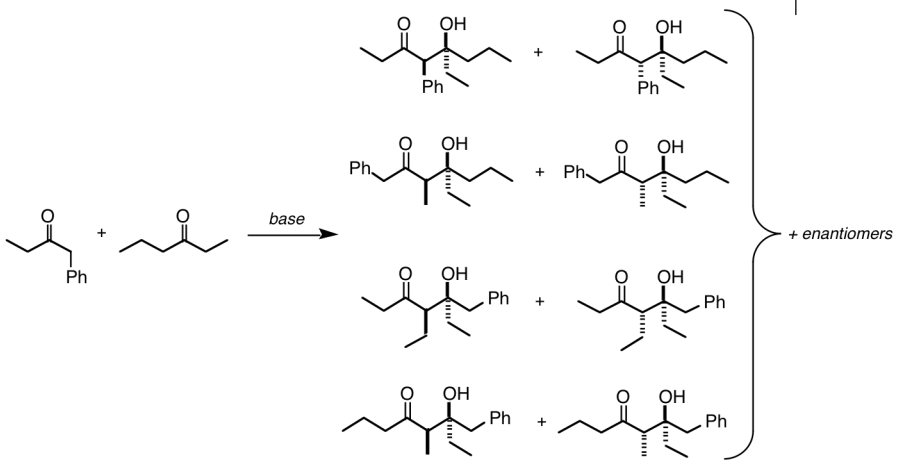


Alkylation reactions. Treatment of enolates with halides provides a means for carbon chain extensions at the α-position. However, polyalkylation can be a problem, and the use of a strong, nucleophilic base or the enamine is recommended.

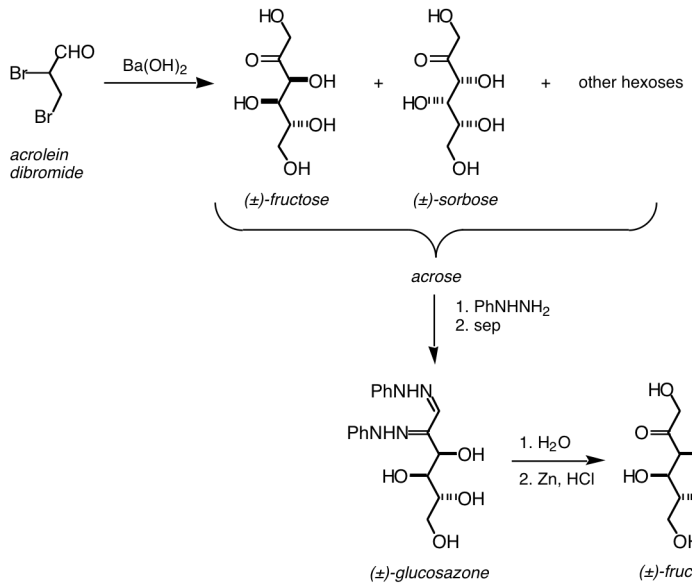


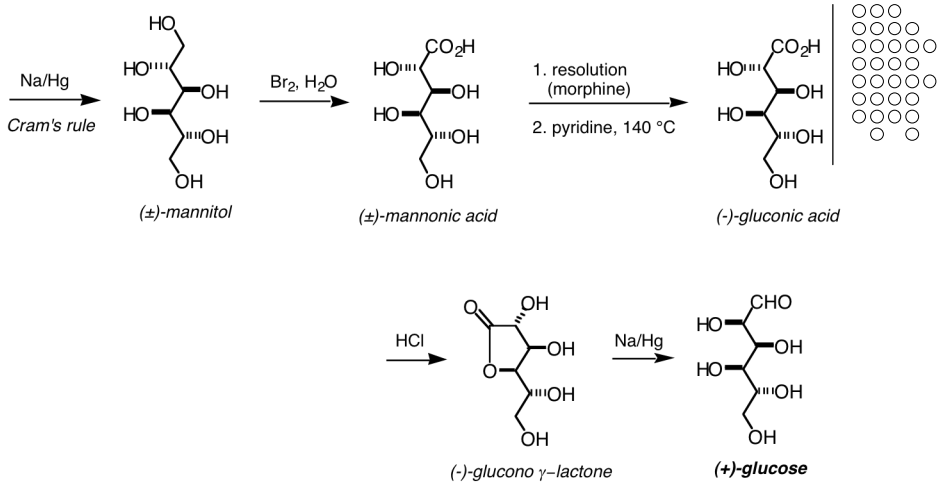
2. Aldol Methodology

Synthetic problem: control of aldol regio- and stereoselectivity.



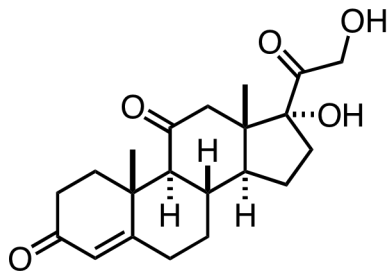
i.e. Fischer's glucose synthesis (Fischer, E. *Ber.* **1890**, *23*, 799).





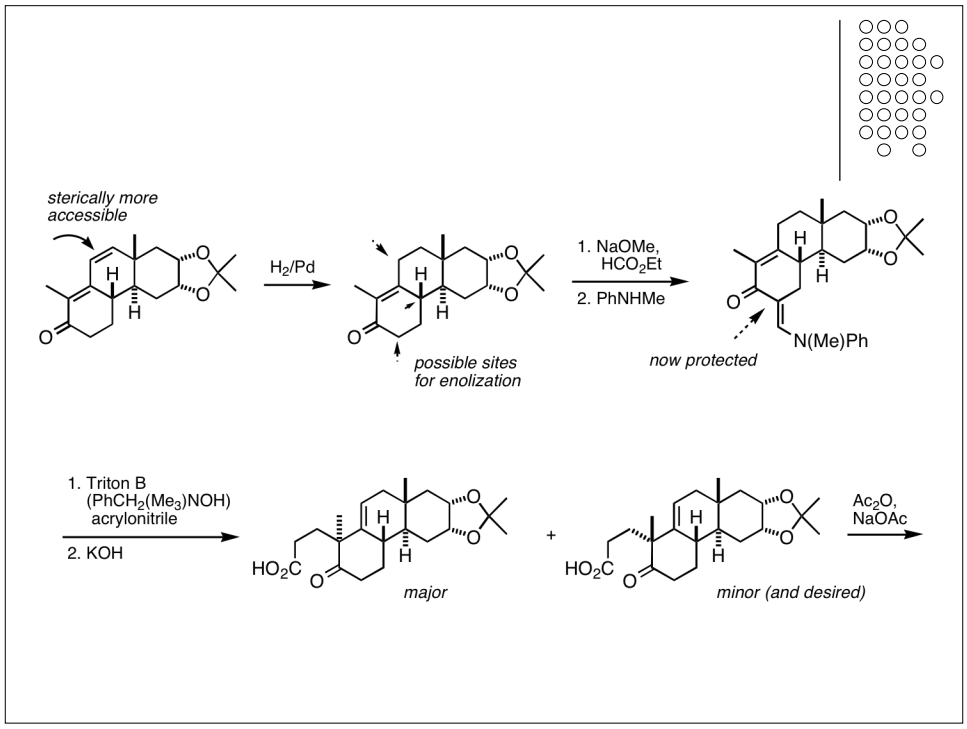
limitations:
- only few reactions are available
- no protective groups
- difficulty of stereochemical control (separations necessary)

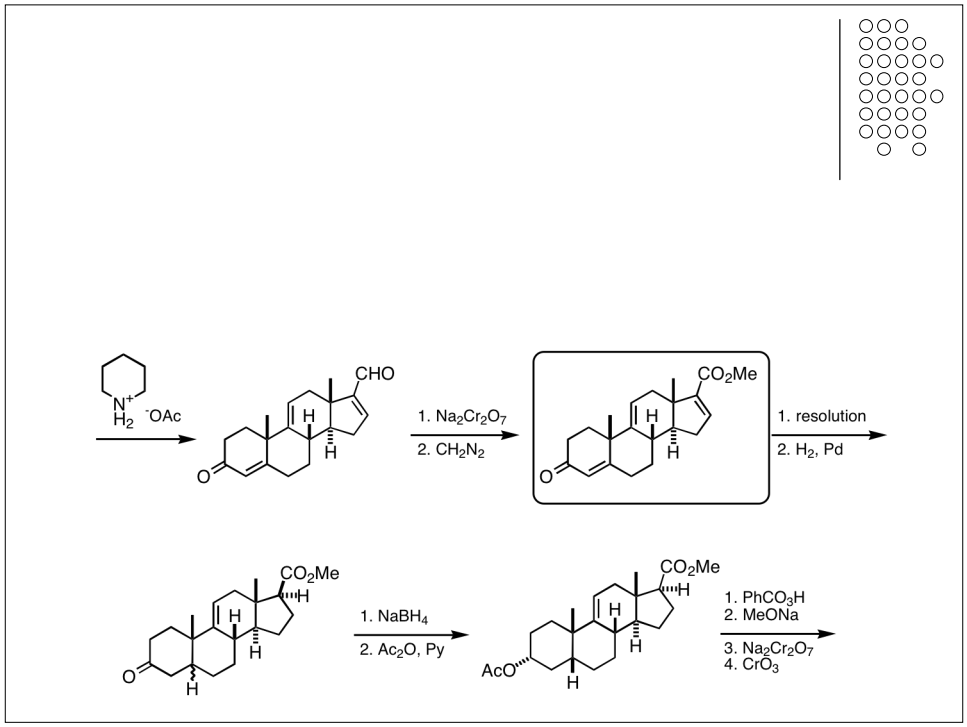
Woodward's synthesis of cortisone (Woodward, R. B. et al. *J. Am. Chem. Soc.* **1952**, *74*, 4223):

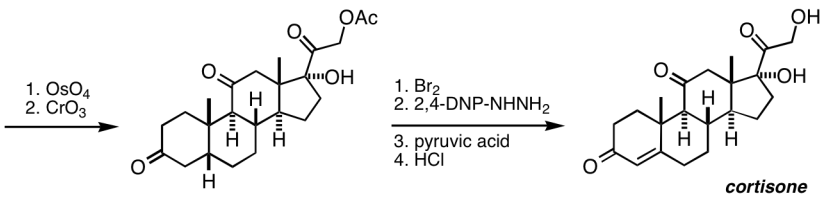


cortisone

Target molecule: 6 chiral centers, 64 possible stereoisomers.
This synthesis illustrates, rather ingeniously, the selective manipulation of functionalities on six-membered rings, and a vastly increased synthetic arsenal.

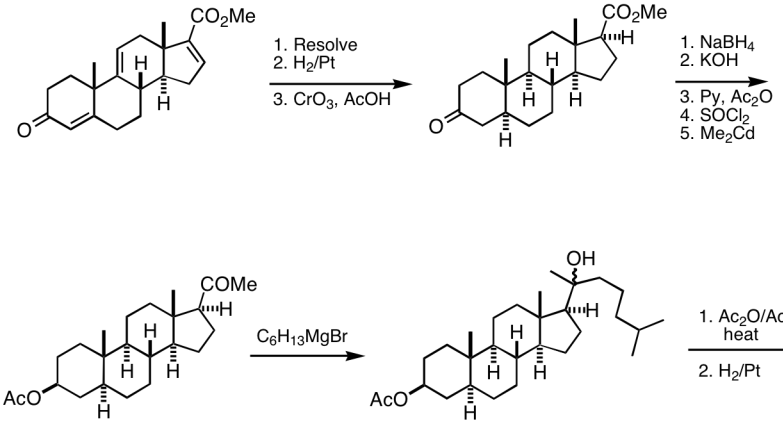

sterically more accessible
H2/Pd
possible sites for enolization
1. NaOMe, HCO2Et
2. PhNHMe
now protected
N(Me)Ph
1. Triton B (PhCH2(Me3)NOH) acrylonitrile
2. KOH
major
minor (and desired)
Ac2O, NaOAc

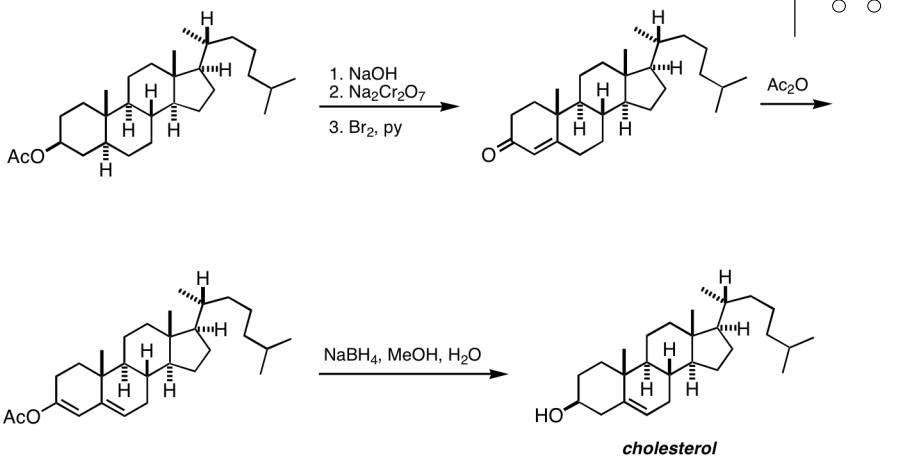

OAc
CHO
1. Na2Cr2O7
2. CH2N2
CO2Me
1. resolution
2. H2, Pd
1. NaBH4
2. Ac2O, Py
1. PhCO3H
2. MeONa
3. Na2Cr2O7
4. CrO3
AcO



cortisone

Extension of strategy to cholesterol synthesis:

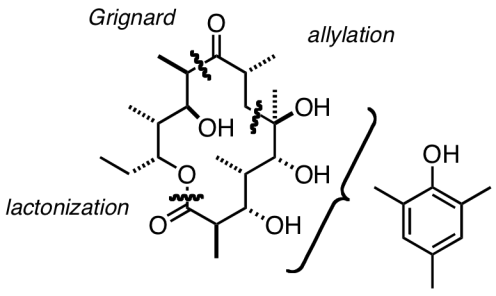


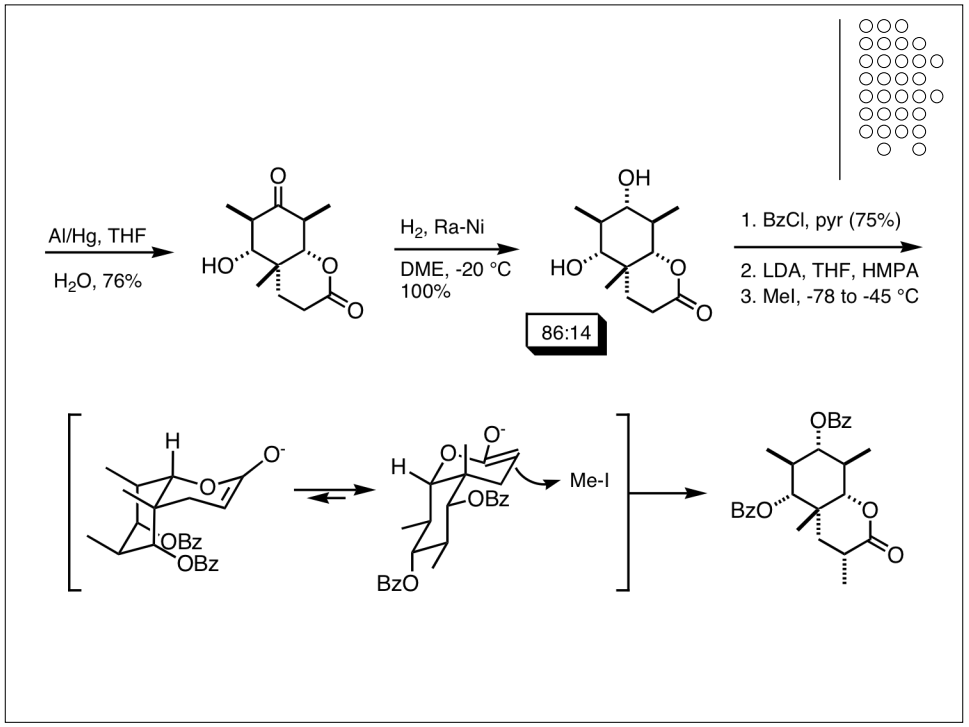


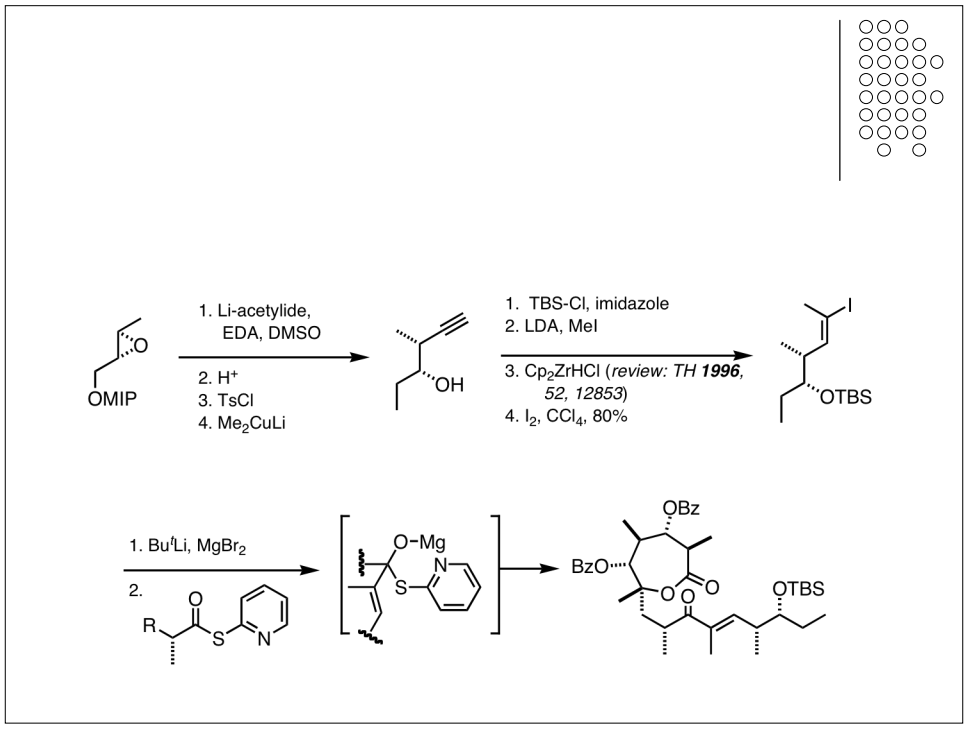
cholesterol

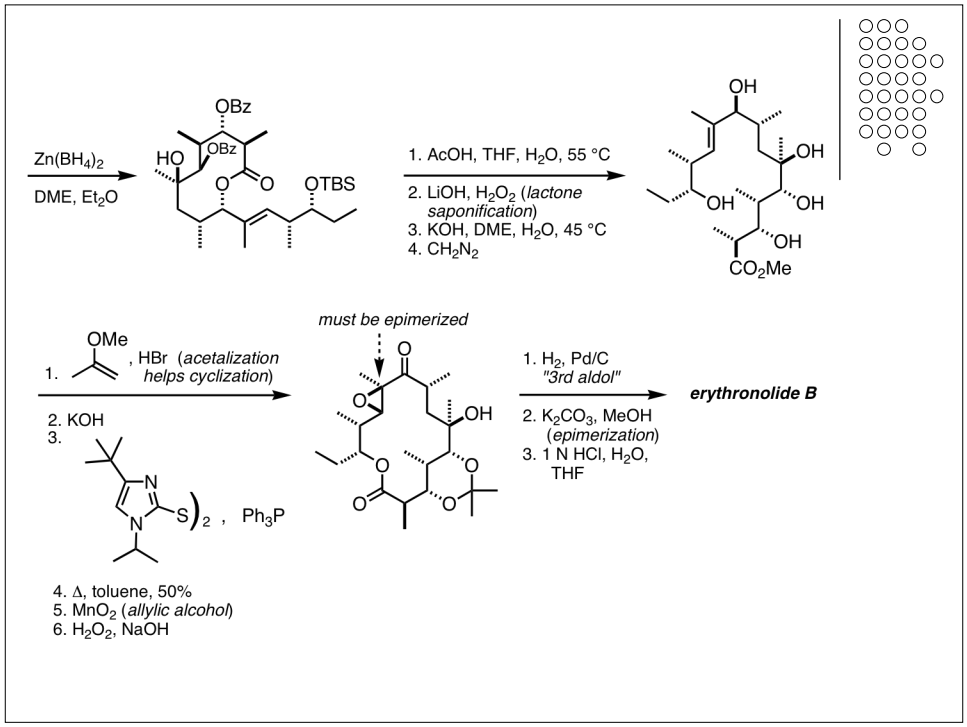
Corey's synthesis of erythronolide B (*J. Am. Chem. Soc.* **1978**, *100*, 4618, 4620). Use of a ring scaffold to set relative stereochemistry in a large size ring system.

Use of ***retrosynthetic analysis***:

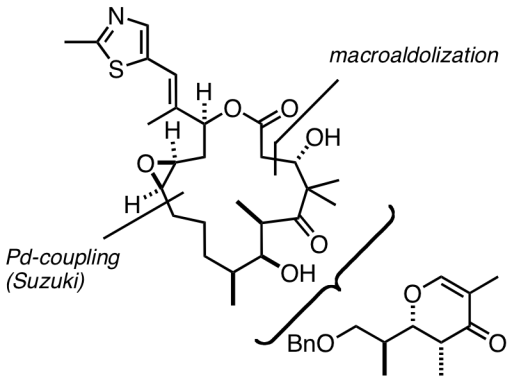


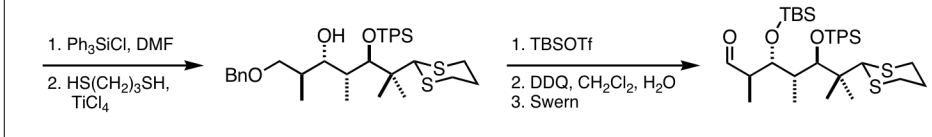

Al/Hg, THF
H2O, 76%
H2, Ra-Ni
DME, -20 °C
100%
86:14
1. BzCl, pyr (75%)
2. LDA, THF, HMPA
3. MeI, -78 to -45 °C
Me-I
OBz
BzO

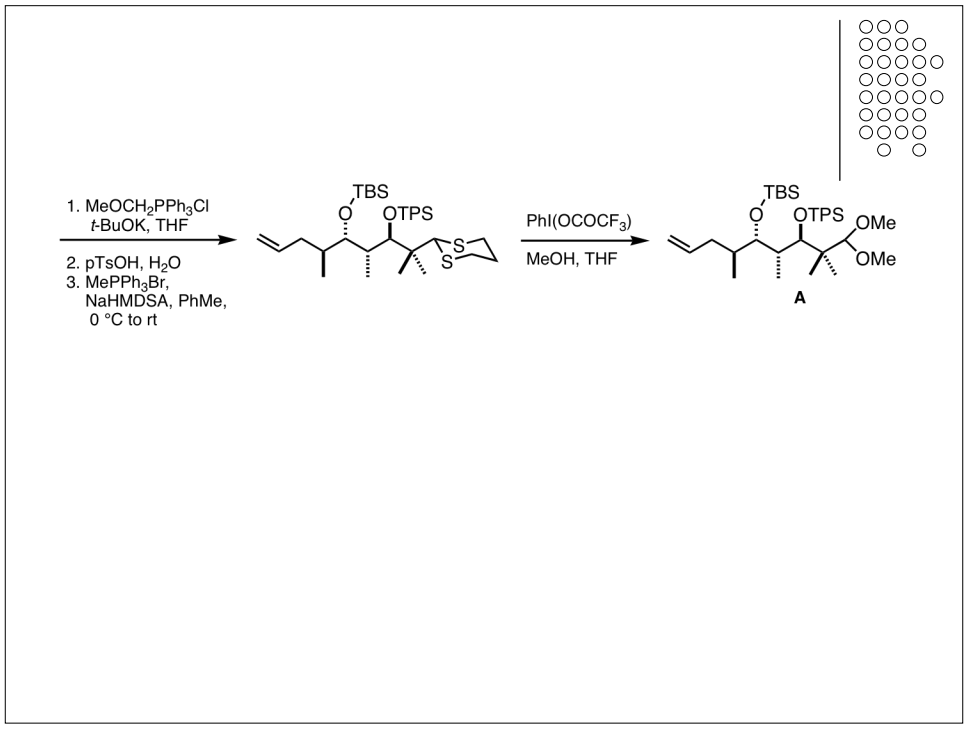

1. Li-acetylide, EDA, DMSO
2. H+
3. TsCl
4. Me2CuLi
OMIP
OH
1. TBS-Cl, imidazole
2. LDA, MeI
3. Cp2ZrHCl (review: TH 1996, 52, 12853)
4. I2, CCl4, 80%
I
OTBS
1. BuLi, MgBr2
2.
O-Mg
N
S
R
O
S
N
OBz
BzO
O
O
O
OTBS

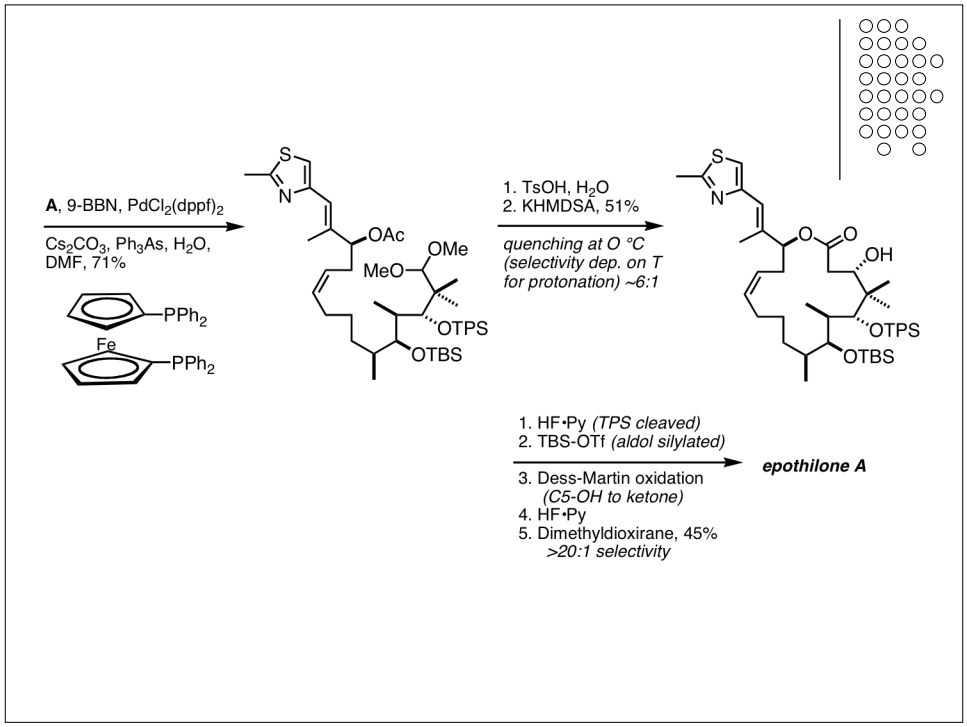

Zn(BH4)2
DME, Et2O
OBz
HO
OBz
O
O
OTBS
1. AcOH, THF, H2O, 55 °C
2. LiOH, H2O2 (lactone saponification)
3. KOH, DME, H2O, 45 °C
4. CH2N2
OH
OH
OH
OH
CO2Me
must be epimerized
1.
OMe
, HBr (acetalization helps cyclization)
2. KOH
3.
N
S
2
,
Ph3P
4. Δ, toluene, 50%
5. MnO2 (allylic alcohol)
6. H2O2, NaOH
O
O
OH
O
O
O
O
1. H2, Pd/C
"3rd aldol"
2. K2CO3, MeOH
(epimerization)
3. 1 N HCl, H2O,
THF
erythronolide B

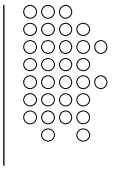
Danishefsky's synthesis of epothilone A (*Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801). Illustrates the renaissance of cycloaddition chemistry and the power of transition metal catalyzed cross-coupling.






1. MeOCH2PPh3Cl
t-BuOK, THF
2. pTsOH, H2O
3. MePPh3Br,
NaHMDSA, PhMe,
0 °C to rt
TBS
O
OTPS
S
S
PhI(OCOCF3)
MeOH, THF
TBS
O
OTPS
OMe
OMe
A


A, 9-BBN, PdCl2(dppf)2
Cs2CO3, Ph3As, H2O,
DMF, 71%
PPh2
Fe
PPh2
S
N
OAc
OMe
MeO
OTPS
OTBS
1. TsOH, H2O
2. KHMDSA, 51%
quenching at O °C
(selectivity dep. on T
for protonation) ~6:1
S
N
O
O
OH
OTPS
OTBS
1. HF•Py (TPS cleaved)
2. TBS-OTf (aldol silylated)
3. Dess-Martin oxidation
(C5-OH to ketone)
4. HF•Py
5. Dimethyldioxirane, 45%
>20:1 selectivity
epothilone A

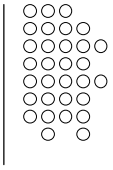


Summary:

masked aldol synthesis:
- Robinson annulation
- halolactonization of enones (erythronolide)
- α-deoxigenation of α,β-epoxy ketones (erythronolide)
- hetero-Diels-Alder synthesis of pyranones (epothilone)

1,2-diol synthesis:
- diazoketone hydrolysis (cortisone)
- dihydroxylation of acrylonitrile (cortisone)
- Baeyer-Villiger of aldol (erythronolide)
- glycidol opening (epothilone)

Question: What other alternatives to the aldol reaction do you know?



Maruoka, K.; Sato, J.; Yamamoto, H., "Practical asymmetric synthesis of both erythro and threo aldols: Unusual effect of silyl groups." *J. Am. Chem. Soc.* **1991**, *113*, 5449-5450.