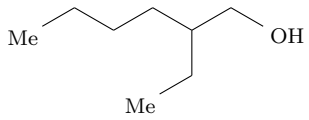
- We then form **cumene hydroperoxide**, an unstable intermediate, which rearranges and then fragments into the products.
- You would think that there is a simpler way to do this, but because it produces *two* value-added products at scale with cheap starting materials (benzene and propene are both products of petroleum cracking), it is more economical.

6.36 Review for Exam 4

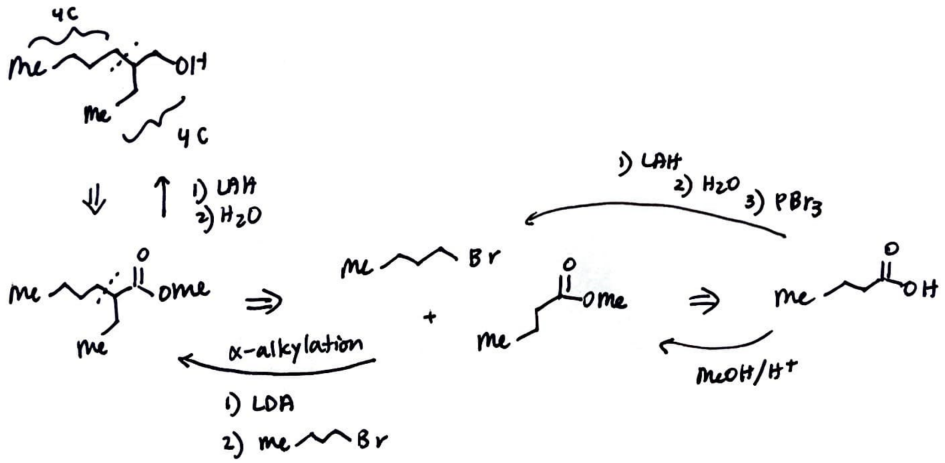
12/4:

- Lecture 35 recap.
  - Regioselectivity in the Beckmann rearrangement (Figure 6.27).
    - To clarify, the *anti* group is the group that lines up antiperiplanar with the N–O bond. Essentially, this is the C–R bond that is parallel in the same plane to the N–O bond.
    - Recall that stronger acids induce Baeyer-Villiger-type selectivity (e.g., dependent on "migratory aptitude").
  - Neighboring group participation (Figure 6.29).
    - Proceeds through an achiral intermediate.
    - Yields enantiomers.
- Announcements.
  - Prof. Buchwald will hold office hours today from 2:00-3:00 PM in his office (18-490).
  - Review sessions for Exam 4.
    - Tonight (W) from 7:00-9:00 PM in 1-190.
    - Tomorrow (R) from 7:00-9:00 PM in 1-190.
  - Course evaluations are live.
    - Constructive criticism is useful.
    - Taking potshots is less useful, but so be it if it makes you feel good.
  - On the exam, please use reactions learned in 5.12 or 5.13!!
    - "Do not use reactions from when you did research when you were 8 years old; we're all very impressed, but it makes grading your exam much harder and you definitely will not get bonus points."
  - The exam will look like the practice exams.
    - 1 mechanism question.
    - 2 synthesis questions.
    - Grading will be partially based on efficiency: If there's a compound you can make in 4 steps and you make it in 44 steps, you will lose a few points.
    - If you write more than one synthesis, cross out the one you don't want graded; otherwise, we will grade the first one we see.
- We'll now begin doing some review problems.

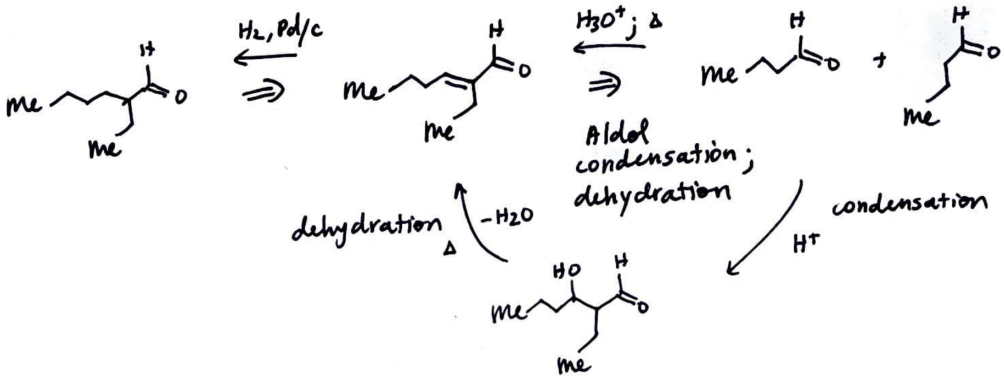
- TTQ: Synthesize the molecule in Figure 6.34a from a starting material of 4 carbons.



(a) The desired molecule.



(b) Retrosynthetic pathway 1.

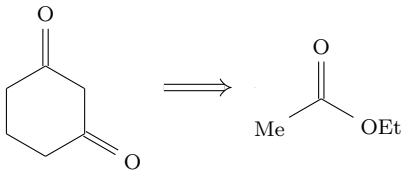


(c) Retrosynthetic pathway 2.

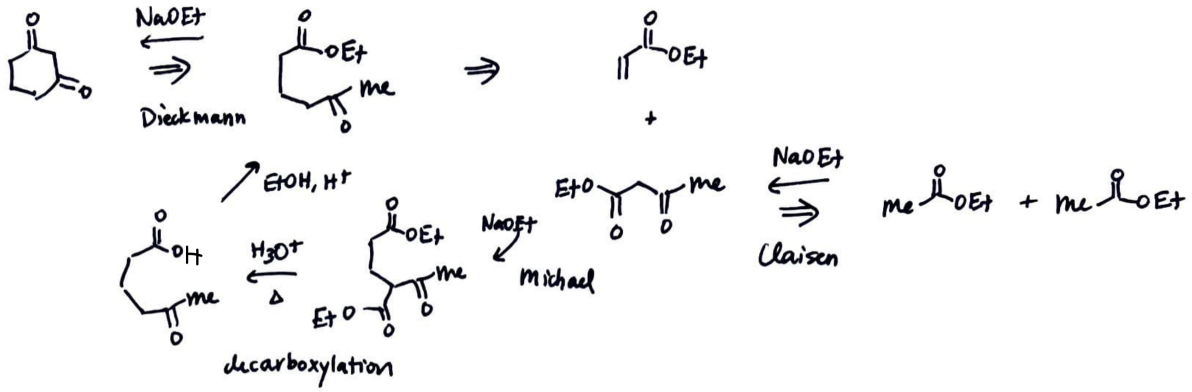
Figure 6.34: TTQ: Synthesis from a 4-carbon starting material.

  - The most straightforward answer cleaves the four carbons at left (Figure 6.34b).
  - Retrosynthetically, we can get back to butyric acid as our 4-carbon starting material.
    - In the forward direction, transform butyric acid into the ester via Fischer esterification.
    - We can also convert it into the bromide with reduction and alcohol bromination.
    - Then LDA-type alkylation chemistry would work, and reduction of the ester to the product.
  - Alternate pathway.
    - Transform the initial alcohol into an aldehyde.
    - Transform the aldehyde into an α,β-unsaturated aldehyde with H_2 / Pd/C.
    - Transform the α,β-unsaturated aldehyde into two equivalents of butyraldehyde via an aldol condensation.

- TTQ: Synthesize the molecule at left in Figure 6.35a from ethyl acetate and any compound with three or fewer carbons.



(a) The desired molecule and starting materials.

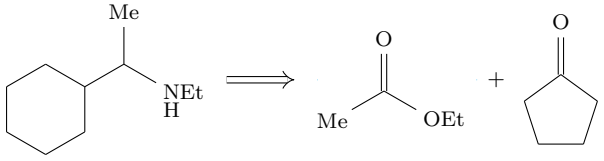


(b) Retrosynthetic pathway.

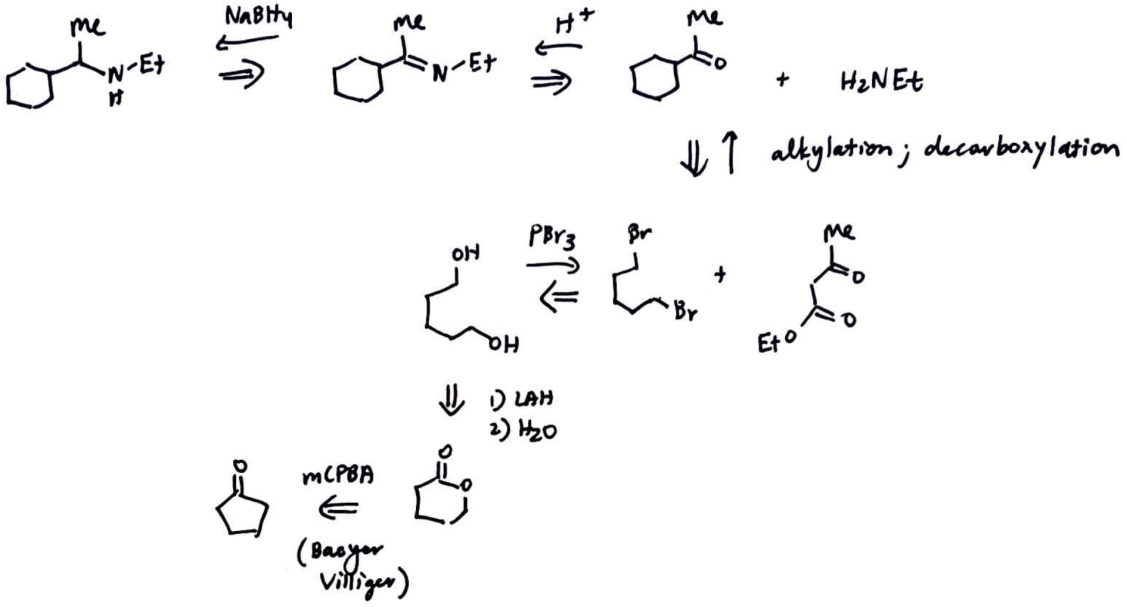
Figure 6.35: TTQ: Synthesis of a 1,3-dicarbonyl.

  - Transform the 1,3-dione into a ring-opened precursor via a Dieckmann condensation (an intramolecular Claisen; Prof. Buchwald will never test names).
    - The resultant 1,5-dicarbonyl should always have us thinking Michael.
    - Next step: Transform the precursor into a Michael donor and acceptor.
    - Next step: The Michael donor is ethyl acetoacetate, which can be prepared from 2 equivalents of the starting material via a Claisen condensation.
  - You *really, really, really* want to remember ethyl acetoacetate and dimethyl malonate!!
    - Remember their pK_a's, that their anions are stable, and that you can alkylate those anions!!
  - In the forward direction, we will need a hydrolysis-decarboylation following our acetoacetate synthesis.
    - This will also require that we subsequently restore the ester at top (because we have no way to selectively hydrolyze the ester we want to decarboxylate).

- TTQ: Synthesize the molecule at left in Figure 6.36a from ethyl acetate, cyclopentanone, and any compound with two or fewer carbons.



(a) The desired molecule and starting materials.

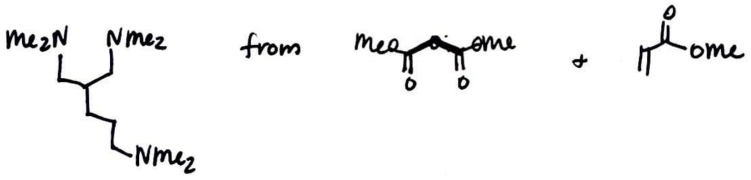


(b) Retrosynthetic pathway.

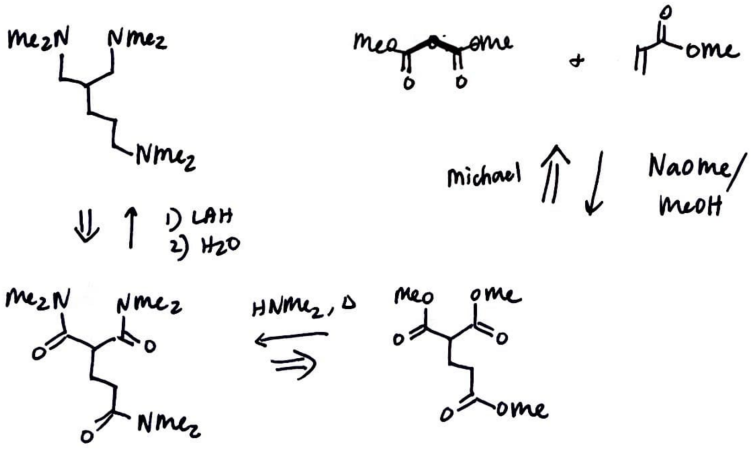
Figure 6.36: TTQ: Synthesis of an amine.

- Transform the product into the imine via sodium borohydride.
  - Next step: Transform the imine into the ketone and ethylamine via acid-catalyzed imine formation.
  - Next step: Transform the ketone into a synthetic equivalent of an acetone anion (which is ethyl acetoacetate), and a synthetic equivalent of a 1,5-dication (which is 1,5-dibromopentane).
    - In the forward direction, a hydrolysis-decarboxylation can give us the ketone following an acetoacetate synthesis.
  - Next step: Transform 1,5-dibromopentane into pentane-1,5-diol.
    - In the forward direction, pentane-1,5-diol can be prepared from cyclopentanone via a Baeyer-Villiger oxidation followed by reduction of the lactone (a fancy term for a cyclic ester) using LAH and a water workup.
- Note the mixed use of content from Units 3-6!! Questions like this are fair game for the exam.

- TTQ: Synthesize the molecule at left in Figure 6.37a from dimethyl malonate and methyl acrylate.



(a) The desired molecule and starting materials.

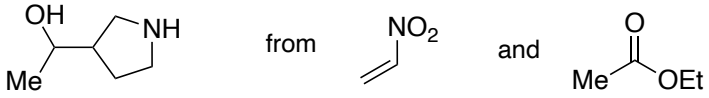


(b) Retrosynthetic pathway.

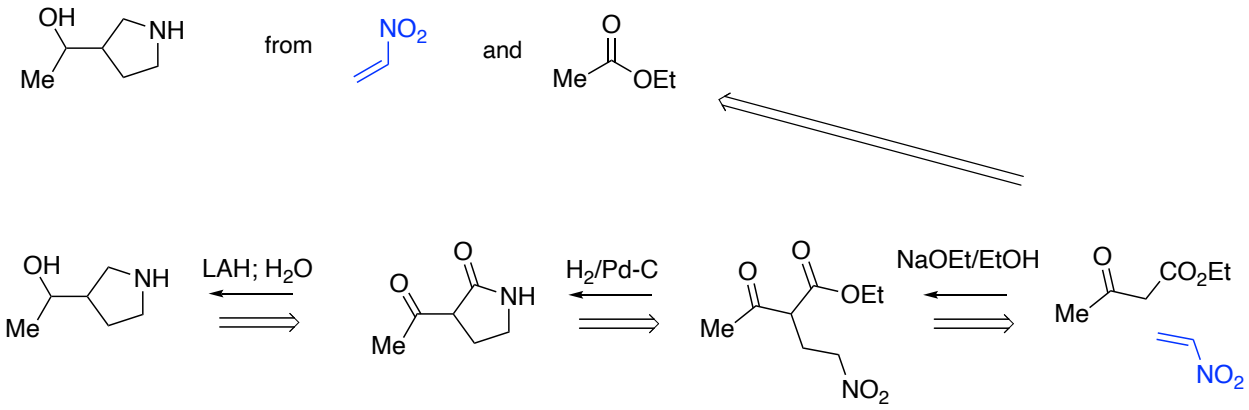
Figure 6.37: TTQ: Synthesis of a triamine.

- Break the tertiary center into a symmetric chunk and an asymmetric bottom tail.
  - The symmetric chunk will come from dimethyl malonate.
  - The bottom tail will come from Michael addition to methyl acrylate.
- Retrosynthetically, all of the amines could come from amides via a triple LAH reduction.
  - Next step: Transform the amides into esters via $HNMe_2$ and heat.
  - Next step: Then this triester can be prepared from straight Michael addition of the starting materials.

Design an efficient synthesis of the compound shown below using the provided starting material.



Solution



- Nitroethylene looks a bit like methyl acrylate.
  - Indeed, nitro groups are even stronger EWGs than esters, so nitroethylene is a *super* good Michael acceptor.
- Retrosynthetically, the nitrogen in the pyrrolidine could come from the nitrogen in the nitroethylene.
  - Also, the pyrrolidine could come from the lactam (cyclic amide).
  - This could then come from the neighboring amide and ester, which could be assembled via Michael addition.
- The amine-ester molecule will spontaneously close because it's an intramolecular reaction to produce a more stable amide.