Advanced Organic Chemistry
Chemistry 242
Spring 2007

Instructor: Matthias Brewer 6-1042 Cook A335 Matthias.Brewer@uvm.edu
Lecture: 11:15am – 12:05pm MWF, Angell B203

Texts: Recommended textbook:

Advanced Organic Chemistry, Part B, 4th ed. F.A. Carey and R.J. Sundberg ISBN: 0-306-46245-1

Other books that will be useful:

Classics in Total Synthesis K.C. Nicolaou; E.J. Sorensen ISBN:3-527-29231-4
Classics in Total Synthesis II K.C. Nicolaou; S.A. Snyder ISBN: 3-527-30684-6
Protective Groups in Organic Synthesis T.W. Green; P.G.M. Wuts ISBN: 0-471-16019-9
The Logic of Chemical Synthesis Corey, E.J.; Cheng X.-M. ISBN: 0471-50979-5
Organic Synthesis The Disconnection Approach Warren, S. ISBN: 0-471-10161-3
The Art of Writing Reasonable Organic Reaction Mechanisms R.B. Grossman ISBN:0-387-95468-6 [in ref. section]
Writing Reaction Mechanisms in Organic Chemistry A. Miller ISBN: 0-12-496711-6
Advanced Organic Chemistry, J. March, 4th or 5th edition ISBN: 0-471-58589-0

Office Hours: By appointment or for quick questions just stop by. The easiest time to catch me is just after class.

Grading:

Two in-class quizzes	20% (Dates: Friday March 9th and Thursday May 10th [Dates are subject to change])
Proposed syntheses	70% (Dates: Described in detail below)
Presentation	10% (Date: TBA; Described in detail below)

Proposed Syntheses:

The purpose of this class is to enable you to devise reasonable synthetic routes to complex molecules, and a major portion of your grade will be based on your ability to do this. You will be assigned two natural products for which you must devise syntheses. **This is to be your own work.** There may be known syntheses of these molecules in the literature; **you may not base your synthesis on these previous examples.**

You will be required to submit three drafts of your work. The first draft should be a well defined retrosynthetic analysis that identifies the major challenges of the synthesis, and how you envision dealing with these challenges. I will look these over to make sure you are on the right track.

The second draft will be a complete forward synthetic route starting from commercially available starting materials. This draft should be written as a synthetic scheme and must include all steps and all specific reagents needed to complete the synthesis. I will again look these over and at this point will provide a more critical review of the work.

The final draft should be written as a synthetic proposal in which you describe your synthetic route with text and schemes. This should start with a discussion of the retrosynthesis that explains to the reader what the major challenges of the synthesis are and how you plan to deal with them. You will then go on to discuss the details of the synthesis and provide justification for all potential pitfalls and why you think they will be avoided. For example, if a reaction has the potential to produce a mixture of diastereomers you need to explain why the diastereomer that you desire will be the major product.

The final draft will be the only graded draft. However, the earlier drafts must be handed in on time (see dates below) or 10 points will be removed per day late.

Important Dates:

March 5th	First draft of Proposal 1 due
March 21st	Second draft of Proposal 1 due
April 2nd	Final draft of Proposal 1 due
April 16th	First draft of Proposal 2 due
April 30th	Second draft of Proposal 2 due
May 10th	Final draft of Proposal 2 due

Presentation:

Each student must dissect a published total synthesis of a natural product and present it to the class. The goal here is to highlight the key points of the total synthesis. You should aim to teach the audience, so plan to go in-depth about the import and interesting steps. The presentations should be 20 minutes in length. Know the mechanism of all important transformations and expect questions!

Course Outline (tentative):

Total synthesis background and principles
Oxidations/Reductions/Deoxygenations
Common alcohol manipulations
Copper catalyzed 1,4-addition reactions
Olefination reactions
Olefin manipulations
Organometallic reactions
Aldol chemistry and other carbonyl addition reactions
Selected total syntheses will be reviewed through out the course to highlight these methods

Academic Conduct: Cheating or plagiarism will be considered grounds for failing the course. Cases of cheating or plagiarism may lead to further disciplinary actions including dismissal from the University according to the rules set forth in The University of Vermont's *Code of Academic Integrity*.

If you do not have a copy of the Aldrich Catalogue (i.e. Aldrich Handbook) request one at: http://www.sigmaaldrich.com/Brands/Aldrich.html
This is a very valuable free resource and will be invaluable for this course.

Important Topics to review from Chemistry 241:

- Writing reasonable reaction mechanisms

- Conformational, Strain and Stereoelectronic Effects on Reactivity
  - Stereochemical control of reactivity via:
    - $A^{1,3}$ strain
    - Tortional strain
    - Steric interactions
    - Stereoelectronics
    - Cram's rule, Felkin model, Felkin-Anh model

- Pericyclic Reactions:
  - Cyclobutene / butadiene interconversion
    - Basis of stereospecificity
      - FMO explanation
      - Huckel / Mobius aromaticity
  - 3,3-Sigmatropic Rearrangements
    - Favored transition states and stereocontrol
  - Diels-Alder reaction
    - Stereospecificity
    - Substituent effects on rate
    - Regiocontrol based on substituents
      - FMO explanation of regiocontrol
    - Relative stereocontrol (endo selectivity)
    - Absolute stereocontrol
      - Chiral Lewis acids
      - MacMillan Organocatalysis

- Enolate Chemistry
  - Enolate Formation
    - Knowledge of pKa's
  - Enolate Alkylation
    - B-keto esters
      - Decarboxylation reactions
    - Ketone enolate alkylation issues
      - Steric effects
      - Internal proton return
      - Bulky electrophiles
      - C vs. O alkylation
      - Site of alkylation of conjugated enolates
    - Alkylation of imines and hydrazones
      - Imines derived from aldehydes
      - Chiral hydrazones
    - Enolate conjugate addition reactions
      - B-keto esters in 1,4-additions
      - Mukaiyama-Michael addition

        - Robinson annulation
        - D'Angelo's asymmetric 1,4-addition
- Acylation of Enolates
    - Claisen / Dieckmann condensation
    - Crossed Claisen
    - Mander's reagent
- Diastereoselective alkylations
    - Evans oxazolidinone
    - Meyers pseudoephedrin
    - Enders ramp/samp
- Aldol Condensation
    - Reversability
    - Relative stereocontrol
        - Syn/Anti
        - Zimmerman-Traxler T.S.
            - Enolate geometry
    - E vs. Z enolate formation
    - Achiral enolates + chiral aldehyde
        - Felkin-Ahn selectivity in T.S.
        - Cram chelate model