

Department of Chemistry: 305 CB, 335-1350

Instructor: Dr. Gregory K. Friestad

Office: 415 CB **Office hours:** Monday 10:20-12:20, or by appointment

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Scheduled Lectures: Monday, Wednesday, Friday; 9:30–10:20

Location: C31 PC (Pomerantz Center)

Course Goals

- Build a solid knowledge base of current methods and applications in organic synthesis
- Develop literature research skills and critical thinking by application of course content to practical problem solving (written and oral presentation of an original synthesis proposal)

Textbooks and Course Materials

1. Required Textbook: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part B: Reactions and Synthesis*, 5th edition, Plenum Press: New York, 2007.
2. Handouts distributed in class

Other Useful Reference Books:

- Warren, S. G. *Organic Synthesis, the Disconnection Approach*, New York : Wiley, 1982.
- Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, VCH: New York, 1996.
- Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*, VCH: New York, 2003.
- March, J. *Advanced Organic Chemistry*, 4th edition, Wiley: New York, 1992.
- Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, USB: Mill Valley CA, 1994.
- Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*, Wiley: New York, 1994.
- Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd edition, 1987.
- Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A*, 4th edition, Plenum: New York, 2001.
- Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed, Harper: New York, 1987.
- Mundy, B. P.; Ellerd, M. G. *Name Reactions and Reagents in Organic Synthesis*, Wiley: New York, 1988.

Copies of these reference books are available in the Chemistry library, and also may be checked out from the instructor for 1-hour periods.

The references listed below are found in the reference section of the Chemistry Library.

- *Comprehensive Organic Functional Group Transformations*, 1995, volumes 1-7.
 - *Comprehensive Organic Transformations*, Larock, R. C., VCH: New York, N.Y., 1989.
 - *Encyclopedia of Reagents for Organic Synthesis*, Paquette, Ed.; Wiley: New York, 1995.
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Course Outline

- A. Stereochemistry, Conformation, Stereoelectronic Effects
- B. Some Foundations for Thinking About Organic Synthesis: Writing Mechanisms; Retrosynthetic Analysis, Polarity Reversal (Umpolung); Protecting Groups
- C. Preparative Methods in Organic Chemistry: A Retrosynthetic Perspective
- D. Natural Product Synthesis: Strategies and Tactics

Calendar of Lecture Topics (tentative, subject to occasional schedule changes)

- Aug. 27 Course introduction; Stereochemistry: definitions, conventions, representations
29 Conformation of acyclic systems: eclipsed, gauche, syn-pentane, and A-strain interactions
31 Conformation of cyclic systems: 4, 5, 6, 7, and 8-membered rings; cyclohexenes
- Sept. 3 (*Labor Day — no class*)
5 Stereoelectronic effects: anomeric effect, Felkin-Anh, Baldwin's rules, Furst-Plattner rule
7 Stereoelectronic effects: anomeric effect, Felkin-Anh, Baldwin's rules, Furst-Plattner rule
10 Writing reaction mechanisms
12 Retrosynthetic analysis: Strategic disconnections
14 Retrosynthetic analysis: Disconnections with polarity reversal (umpolung)
17 Protecting group chemistry, orthogonality
19 Preparative Methods: Aromatic substitutions, orthometalation
21 Preparative Methods: Aromatic substitutions, orthometalation
24 Preparative Methods: Interconversion of sp^3 C-X FG's
26 Preparative Methods: Amines
28 Preparative Methods: Alcohols (a^1 : carbonyl reductions and additions)
- Oct. 1 Preparative Methods: Alcohols (a^1 : C-O bond constructions)
3 Preparative Methods: Alcohols (d^1 and a^2 umpolung approaches)
5 Preparative Methods: Carbonyl compounds (oxidative methods)
8 Preparative Methods: Carbonyl compounds (a^1 : interconversion of carbonyl FG's)
10 Preparative Methods: Carbonyl compounds (d^2 : enolate alkylation and acylation)
12 **EXAM 1**
15 Preparative Methods: Carbonyl compounds (d^2 : enolate alkylation and acylation)
17 Preparative Methods: Carbonyl compounds (d^2 : enolate alkylation and acylation)
19 Preparative Methods: Carbonyl compounds (d^2 : aldol, Mannich, and related reactions)
22 Preparative Methods: Carbonyl compounds (d^2 : aldol, Mannich, and related reactions)
24 Preparative Methods: Carbonyl compounds (d^2 : aldol, Mannich, and related reactions)
26 Preparative Methods: Carbonyl compounds (a^3 : Michael addition, Robinson annulation)
29 Preparative Methods: Alkenes (π -disconnection)
31 Preparative Methods: Alkenes (π -disconnection)
- Nov. 2 Preparative Methods: Intro to Transition Metals in Organic Synthesis
5 Preparative Methods: Alkenes (σ -disconnection)
7 Preparative Methods: Alkenes (σ -disconnection)
9 Preparative Methods: Pericyclic reactions: orbital symmetry considerations
12 **EXAM 2**
14 Preparative Methods: Sigmatropic rearrangements
16 Preparative Methods: Sigmatropic rearrangements
19-23 (*Thanksgiving Recess — no class*)
26 Preparative Methods: Cycloadditions
28 Preparative Methods: Cycloadditions
30 Preparative Methods: Cycloadditions
- Dec. 3 Natural Product Synthesis: Strategies and Tactics -- *Proposal First Draft Due*
5 Natural Product Synthesis: Strategies and Tactics
7 Natural Product Synthesis: Strategies and Tactics
10 Natural Product Synthesis: Strategies and Tactics -- *Proposal Critiques Due*
12 Natural Product Synthesis: Strategies and Tactics
14 Natural Product Synthesis: Strategies and Tactics
21 **FINAL EXAM (7:30 a.m.):** Synthesis Presentations -- *Proposal Final Draft Due*

Problem Sets

Problem Set 1. Conformation, Stereochemistry, Stereoelectronics	Due Sept. 12
Problem Set 2. Mechanisms, Retrosynthesis, Protecting Groups	Due Sept. 26
Problem Set 3. Applications of Preparative Methods A	Due Oct. 29
Problem Set 4. Applications of Preparative Methods B	Due Nov. 28

Synthesis Proposal and Presentation

First Draft (three copies)	Due Dec. 3
Proposal Critique (two copies)	Due Dec. 10
Presentation	Dec. 21 (Final Exam)
Final Revised Draft	Due Dec. 21

A standard benchmark for the competence of a synthetic organic chemist is the ability to propose a reasonable multistep synthesis of a complex molecular target. In this course, you will develop and apply your organic synthesis skills by writing a proposed synthetic route to a recently discovered natural product. Selected targets will be assigned to you by random drawing early in the semester.

You will each critically review another students' first draft (randomly assigned) and *provide constructive suggestions*. Your grade for this critique will be assigned based on your ability to (a) identify any problems with the feasibility of the proposed synthesis and (b) suggest appropriate corrections. If your critique is submitted late, your colleague will have less time to make any corrections. You will lose 10 points for each day your critique is overdue.

The first draft will consist of two parts: (a) a detailed retrosynthetic analysis, which will identify and highlight the major problems to be addressed in the synthesis, (b) a complete synthetic route, showing all steps (with literature precedents for your solutions to the highlighted major problems) required to prepare the target from commercially available materials. The first draft may be hand-written, but will be rejected if the structures or writing are not legible. If your first draft is rejected and/or submitted late, your colleague will have less time to complete the critique. You will lose 10 points for each day your first draft is overdue.

The final draft will be a formal written proposal, which should be presented with clear, concise text. You should explain the importance of the target, the key synthetic challenges posed by its structure, and any special explanations of how specific unusual reactions should work. Electronic structure drawing programs must be used, and references in ACS Style are required.

You will present your final synthetic route to the class using overhead transparencies, being prepared to answer questions which may arise during your discussion.

Coursework Grading

Problem Sets: 4 x 50 pts	200 points
Synthesis Proposal	200 points
Critique: 50 points	
Oral Presentation: 50 points	
Final Draft : 100 points	
Exam 1	200 points
Exam 2	200 points

Total	800 points
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Extra Credit Projects: One extra credit project (TBA) may be substituted for a Problem Set grade.

Class attendance and participation will not be graded in this class. However, the instructor reserves the right to use these factors for determination of grades in borderline cases. It is to your advantage that these factors appear in the most positive light.

Statements of University and/or College Policy

For each semester hour credit in the course, students should expect to spend two hours per week preparing for class sessions (e.g., six hours per week for this course).

I would like to hear from anyone who has a disability which may require seating modifications or testing accommodations or accommodations of other class requirements, so that appropriate arrangements may be made. Please contact me during my office hours.

This course is given by the College of Liberal Arts and Sciences (CLAS), and class policies regarding requirements, grading, and sanctions for academic dishonesty are governed by CLAS. Students wishing to add or drop this course after the official deadline must receive the approval of the Dean of the CLAS. Details of the University policy of cross enrollments may be found at:

<http://www.uiowa.edu/~provost/deos/crossenroll.doc>

All students in the College have specific rights and responsibilities. You have the right to adjudication of any complaints you have about classroom activities or instructor actions. Information is available in the College's Student Academic Handbook (*http://www.clas.uiowa.edu/students/academic_handbook/*). You also have the right to expect a classroom environment that enables you to learn, including modifications if you have a disability.

Your responsibilities to this class — and to your education as a whole — include attendance and participation. You are also expected to be honest and honorable in your fulfillment of assignments and in test-taking situations (the College's policy on plagiarism and cheating is on-line in the College's Student Academic Handbook). You have a responsibility to the rest of the class — and to the instructor — to help create a classroom environment where all may learn. At the most basic level, this means that you will respect the other members of the class and the instructor, and treat them with the courtesy you hope to receive in turn.

If a complaint about the class is not resolved by discussing it with the instructor, the student should discuss the matter further with the departmental executive officer. If the matter remains unresolved, the student may submit a written complaint to the Associate Dean for Academic Programs, 120 Schaeffer Hall (335-2633). (Graduate students should be directed to the offices of the Graduate College, 205 Gilmore Hall, 335-2137.)