

Department of Chemistry: 305 CB, 335-1350

Instructor: Dr. Gregory K. Friestad

Office: E455 CB **Office hours:** Tues/Thurs 3:45-5:00, or by appointment

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Scheduled Lectures: Tuesday/Thursday, 2:30-3:45, C29 PC

Course Website: *icon.uiowa.edu*

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. Required Textbook: Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, VCH: New York, 1996.
3. Required Textbook: Lecture Notes, emphasizing current practices illustrated by examples from primary literature, distributed via the course website (*icon.uiowa.edu*)

Other Useful Reference Books:

- Warren, S. G. *Organic Synthesis, the Disconnection Approach*, New York : Wiley, 1982.
- 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*, 5th edition, Plenum: New York, 2007.
- Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed, Harper: New York, 1987.
- Mundy, B. P.; Eller, M. G. *Name Reactions and Reagents in Organic Synthesis*, Wiley: New York, 1988.

Copies of these books are available in the Chemistry collections in the Main 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 area in the Main 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)

Jan.	19	Course introduction; Stereochemistry: definitions, conventions, representations
	21	Conformation of acyclic systems: eclipsed, gauche, syn-pentane, and A-strain interactions
	26	Conformation of cyclic systems: 4, 5, 6, 7, and 8-membered rings; cyclohexenes
	28	Stereoelectronic effects: anomeric effect, Felkin-Anh, Baldwin's rules, Furst-Plattner rule
Feb.	2	Stereoelectronic effects: anomeric effect, Felkin-Anh, Baldwin's rules, Furst-Plattner rule
	4	Writing reaction mechanisms
	9	Retrosynthetic analysis: Strategic disconnections, polarity reversal (umpolung)
	11	Protecting group chemistry, orthogonality
	16	Preparative Methods: Aromatic substitutions, orthometalation
	18	Preparative Methods: Aromatic substitutions, orthometalation
	23	Preparative Methods: Interconversion of sp^3 C-X FG's
	25	Preparative Methods: Amines
Mar.	2	Preparative Methods: Amines
	4	Preparative Methods: Alcohols (a^1 : carbonyl reductions and additions)
	9	Preparative Methods: Alcohols (a^1 : C-O bond constructions)
	11	EXAM 1
	15-19	No class -- Spring Break
	23	Preparative Methods: Alcohols (d^1 and a^2 umpolung approaches)
	25	Preparative Methods: Carbonyl compounds (oxidations, interconversion of FG's)
	30	Preparative Methods: Carbonyl compounds (d^2 : enolate alkylation and acylation)
Apr.	1	Preparative Methods: Carbonyl compounds (d^2 : enolate alkylation and acylation)
	6	Preparative Methods: Carbonyl compounds (d^2 : aldol, Mannich, and related reactions)
	8	Preparative Methods: Carbonyl compounds (d^2 : aldol, Mannich, and related reactions)
	13	Preparative Methods: Carbonyl compounds (a^3 : Michael addition, Robinson annulation)
	15	Preparative Methods: Alkenes (pi-disconnection)
	20	EXAM 2
	22	Preparative Methods: Intro to Transition Metals in Organic Synthesis
	27	Preparative Methods: Alkenes (sigma-disconnection)
	29	Preparative Methods: Alkenes (metathesis) -- <i>Proposal First Draft Due (3 copies)</i>
May	4	Natural Product Synthesis: Selected Strategies
	6	Natural Product Synthesis: Selected Strategies -- <i>Proposal Critiques Due (3 copies)</i>
	14	FINAL EXAM (Fri 7:30 a.m.): Synthesis Presentations -- <i>Proposal Final Draft Due</i> <i>Note: A second alternative session of presentations will be arranged (time to be announced later).</i>

Graded Assignments: Due Dates

Problem Set 1. Conformation, Stereochemistry, Stereoelectronics	Due Feb. 9
Problem Set 2. Synthetic Planning, Aromatic Compounds	Due Feb. 25
Problem Set 3. Applications of Preparative Methods A	Due Apr. 13
Synthesis Proposal First Draft (three copies)	Due Apr. 29
Problem Set 4. Applications of Preparative Methods B	Due May 4
Synthesis Proposal Critique (three copies)	Due May 6
Synthesis Proposal Final Revised Draft	Due May 14
Synthesis Proposal Presentations (bring printout of slides)	May 14

Coursework Grading

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

Total	800 points
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Extra Credit Projects: One extra credit project 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.

Study Tip. For each semester hour credit, students should expect to spend two hours per week preparing for class sessions (i.e., six hours per week for this course). This counts *solid study time*, not the time you spend texting, chatting, surfing the internet, watching TV, etc., while the book sits in front of you! I recommend two hours at a time, three times per week. There will be some weeks which require more, and some less.

More About the Synthesis Proposal

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.

First Draft: 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 clearly 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 calendar day your first draft is overdue.*

Critique: You will each critically review another student's 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 calendar day your critique is overdue.*

Final Draft: The final draft will be a formal typewritten 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 must be used, and references in ACS style are required.

Presentation: You will present your synthetic route to the class using appropriate media (digital overhead camera or computer projection), being prepared to answer questions which may arise during your discussion. Presentations will be limited to 10–15 minutes (exact time to be announced later).

Statements of University and/or College Policy

Administrative Home. The College of Liberal Arts and Sciences is the administrative home of this course and governs matters such as the add/drop deadlines, the second-grade-only option, and other related issues. Different colleges may have different policies. Questions may be addressed to 120 Schaeffer Hall, or see the CLAS Student Academic Handbook.

Electronic Communication. University policy specifies that students are responsible for all official correspondences sent to their University of Iowa e-mail address (@uiowa.edu). Faculty and students should use this account for correspondences. (Operations Manual, III.15.2. Scroll down to k.11.)

Accommodations for Disabilities. A student seeking academic accommodations should first register with Student Disability Services and then meet privately with the course instructor to make particular arrangements. See www.uiowa.edu/~sds/ for more information.

Academic Fraud. Plagiarism and any other activities when students present work that is not their own are academic fraud. Academic fraud is a serious matter and is reported to the departmental DEO and to the Associate Dean for Undergraduate Programs and Curriculum. Instructors and DEOs decide on appropriate consequences at the departmental level while the Associate Dean enforces additional consequences at the collegiate level. See the CLAS Academic Fraud section of the Student Academic Handbook.

CLAS Final Examination Policies. Final exams may be offered only during finals week. No exams of any kind are allowed during the last week of classes. Students should not ask their instructor to reschedule a final exam since the College does not permit rescheduling of a final exam once the semester has begun. Questions should be addressed to the Associate Dean for Undergraduate Programs and Curriculum.

Making a Suggestion or a Complaint. Students with a suggestion or complaint should first visit the instructor, then the course supervisor, and then the departmental DEO. Complaints must be made within six months of the incident. See the CLAS Student Academic Handbook.

Understanding Sexual Harassment. Sexual harassment subverts the mission of the University and threatens the well-being of students, faculty, and staff. All members of the UI community have a responsibility to uphold this mission and to contribute to a safe environment that enhances learning. Incidents of sexual harassment should be reported immediately. See the UI Comprehensive Guide on Sexual Harassment for assistance, definitions, and the full University policy.

Reacting Safely to Severe Weather. In severe weather, class members should seek appropriate shelter immediately, leaving the classroom if necessary. The class will continue if possible when the event is over. For more information on Hawk Alert and the siren warning system, visit the Public Safety web site.

*These CLAS policy and procedural statements have been summarized from the web pages of the College of Liberal Arts and Sciences and The University of Iowa Operations Manual.