CHEM 424 - Organic Synthesis - Fall 2022

GENERAL INFORMATION

This course will develop the use of retrosynthetic analysis as a tool for designing practical multi-step syntheses of organic molecules. The concept of retrosynthesis has been used implicitly and explicitly in organic chemistry courses at the 300 level. In this course, you will learn a formal way of applying retrosynthetic analysis to the synthesis of complex target molecules, and you will receive opportunity to practice its use. The focus of CHEM 424 will be on synthesis design and on specific reactions used in executing a synthesis. All students should recognize that these two aspects of synthesis are not independent. Familiarity with basic organic transformations plus the ability to learn more advanced reactions will be essential, especially in preparing the final total synthesis proposal. The course is presented in a "reading" format supported by some lectures, discussions and presentations by students. Class discussions and lectures will not necessarily "cover" the textbook material. We will focus on key points, but also examine issues that arise from the material in the book and from recent literature. We will also discuss some important organic reactions that have changed how chemists approach synthesis design. In the event of extraordinary circumstances beyond the University's control, the content and/or evaluation scheme in this course is subject to change.

Instructor **Dr. Pat Forgione**
Office hours: By appointment, email me and please put "CHEM 424" in the subject.
Telephone: N/A
Email: pat.forgione@concordia.ca, please put "CHEM 424" in the subject line for ALL emails.

Course Format Lectures: 2.5 h / week, 26 sessions; Tu/Th 11:450-13, CC-305.

Required Materials Classics in Total Synthesis, Nicolau, Sorenson, Wiley-VCH, 1996, paperback ISBN 3-527-29284-5

Useful resources
1) Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry QD 262 C535 1991
2) Fieser and Fieser's reagents for organic synthesis, QD 262 F5.
3) Comprehensive organic functional group transformations, QD 262 C534 1995.
4) A very interesting read on the state of organic synthesis: K.C. Nicolaou: The Art and Science of Organic Synthesis at the Dawn of the Twenty-First Century - *Angew. Chem. Int. Ed.* **2000**, *39*, 44-122.
5) Interesting Read: Molecules that Changed the World, Nicolaou, K.C. Montagnon, T. Wiley-VCH, 2008 ISBN 978-3-527-30983-2

Molecular models: Using models helps considerably with many aspects of organic chemistry – many concepts require you to picture, rotate and draw 3D objects. Models **are** permitted in exams. You are strongly advised to buy a model kit.

Advice: The best way to do well in organic chemistry is to solve problems. The more you read and think about the different methods in which molecules can be constructed, the easier and more systematic synthesis will appear. While memorization of reactions may provide you with a larger synthetic 'tool-box', there is a certain degree of art in the design of total syntheses that can not be overlooked. Being able to use library resources effectively (searching journal articles, using Scifinder) is critical for success in this course. The chemistry librarian is available for trainings on these and other relevant resources, please schedule an appointment with her as soon as possible (ideally in small groups!): Krista Alexander <krista.alexander@concordia.ca>

GRADING SCHEME, DEADLINES & ABSENCES

To pass the course, you must earn ≥ 50% on the in-class tests and exam(s). The final grade will be weighted as follows:

Mid-Term Test:	15 %
Total Synthesis 1:	5 %
Total Synthesis 2:	10 %
Term Total Synthesis:	20 %
Total Synthesis Presentation:	15 %
Presentation Participation:	5 %
Final Exam:	30 % (*covers entire course content, scheduled by Exams Office*)

Total Synthesis Presentation: Each student will be required to present a portion of one of the chapters from the Nicolau/Sorenson text book. Each PowerPoint presentation should be about 10 -15 minutes long with a five-minute question period. Depending on how detailed each slide is, you should have between 10 – 13 slides max. Although this will be done

independently by each student, I will aid you in preparing the final presentation. In order for you to obtain feedback, you must send a preliminary copy to me 1 week before your presentation. This does not have to be a final version, but a rough draft to discuss what important aspects you should include, ensure you are not including too much material for a 10 minute presentation etc. ***Students who seek my help in advance have always been among the best presentations.*** However, if you come to me last-minute, I will not be able to do so, so please prepare accordingly! You must choose a portion of one of the following Chapters: 2, 3, 4, 6, 7, 8, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 22, 23, 27, 33, 37. **This must be done by September 27th and is on a first come, first served basis.** Please email me with the page numbers and schemes you would like to present, as some of the chapters may be giving to multiple students who will cover different portions of the synthesis. Each student must evaluate all the presentations they attend. An evaluation form will be provided before the presentations. The presentation evaluation will be weighted in the following way: 60% instructor and 40% classmates. If a student misses the day of their presentation, with a suitable note justifying the absence, they will be allowed to present in a subsequent class. If no note is provided within 1 week, the student will receive a grade of 0. In exceptional circumstances, if no class time is available for an in class presentation, the student will present directly to the instructor and the grade will be instructor only. To prepare chemical structures for the presentation, an excellent free tool is available here: https://chemaxon.com/products/marvin. Chemsketch is also a possibility: https://www.acdlabs.com/resources/free-chemistry-software-apps/chemsketch-freeware/

Presentation Participation: Each student is required to ask (at least) 2 questions over the entire presentation periods. Questions will be evaluated on quality and questions that engage the class in learning. You may not obtain more points by asking more than two questions, but you are certainly welcome to ask more. Each student must also evaluate all the presentations and assign a grade, if this is not done by 1 week after the final presentation is completed, the student will receive a grade of "0" for the presentation portion of the course. If a student misses more than 25% of the presentations without a suitable note provided within 1 week of the missed class(es), they will obtain a score of 0 for the participation grade.

Term Total Synthesis: Each student is required to provide a total synthesis of a molecule that has not been previously synthesized. The best way to find such a molecule is to search the *Journal of Natural Products, Natural Product Reports or Natural Product Updates* for recently isolated compounds. The instructor must approve the molecule that is chosen by **September 27th**. The final approved structure should be sent to me by email (subject CHEM 424 Total Synthesis) that includes the chemical structure drawing, chemical formula, chemical name (if applicable) and references by the above date. Although highly unlikely, if two students choose the same molecule, this will be assigned on a first come, first served basis. ***As we all have access to search engines, simply replicating a published synthesis is unacceptable and will be graded with a zero!*** Three examples of what is expected can be found in the textbook by Michael Smith, *Organic Synthesis*, Chapter 14. The level of molecular complexity in the targets will be similar to that of the first example (the *isocedrene ester*) shown in Smith (on page 1493 in the first edition and page 1237 in the second edition). Smith provides a *poor* proposal, followed by two reasonable ones. Look at both the poor example and the good proposals before deciding how to approach your own proposal. Another good example can be found here: http://pubs.acs.org/doi/pdf/10.1021/ja9024403. The final report should contain the summarized retrosynthesis, the ***full*** forward synthesis, multiple possibilities for transformations that you anticipate may be problematic and must include the copies of the journal articles you used as precedence for your key transformations. The starting materials that incorporate carbon atoms into your molecule you use for the synthesis should cost $10/g or less for from either of these two companies: https://www.sigmaaldrich.com/canada-english.html or https://aksci.com. Catalysts are exempt from this price consideration. This should not be a huge document, but it should be 10-15 double spaced pages including schemes in addition to any photocopied reference articles. Grading will be based on the originality of the proposal (10%), the legibility and quality of the writing/chemical structures (20%), proper referencing (ACS style) and formatting (20%) and feasibility of the proposal (50%). Please see me if you need additional information for the expectations. Each step in your proposal should have a "predicted" yield that estimates how successful you feel each transformation will be. **Due date TBA, but usually the second last class of the term (late submissions – 10% / day!)**.

Total Synthesis 1 and 2: Two small molecule total syntheses will be due throughout the term. These will be assigned by the instructor and be a way to practice total synthesis problem solving as you build towards your final molecule. Some of the syntheses provided by students will be discussed in class to provide guidance to everyone on what and what not to do in future assignments (specific student names will not be revealed).

Mid-Term Test: The mid-term will be held on October 13th and cover all material up to and including the October 7th lecture (but not the October 11th lecture.

Final Exam: The final exam is comprehensive and covers all the material covered throughout the entire course. It will be given out after the final course lecture (due date/time TBD).

If absent from a test and/or an examination, you must produce a written excuse on letterhead paper, appropriately signed (*e.g.,*

by doctor or employer), **no later than one week** after the exam. The Department determines the validity of the absence and necessary arrangements will be made. If **no valid excuse** is produced, the student will receive a **zero** grade for the missed test.

PLAGIARISM AND OTHER FORMS OF ACADEMIC DISHONESTY – Highly Encouraged QUIZ AND SEMINAR

As part of this course, you are ***encouraged*** to (i) attend a Chemistry and Biochemistry Departmental Seminar on the academic conduct code and the appropriate use of information sources and (ii) pass the online quiz associated with this seminar (note: passing grade for the quiz is 100%). The aim of this seminar is to clarify the academic conduct code in terms of what practices will be considered unacceptable with regards to work submitted for grading in Chemistry and Biochemistry courses. Should you have already attended these sessions you are not required to repeat them this semester. This short seminar (1 hour) will be held at the times as posted outside the main Chemistry and Biochemistry office (SP-201.01). The academic code of conduct can be found in section 16.3.14 of the academic calendar in either printed or the online (http://registrar.concordia.ca/calendar/pdf/sec16.pdf) versions. Any form of cheating, copying or plagiarism found in this course will be reported and the appropriate sanctions applied. The mandatory seminar is a clear and fair opportunity to learn what our faculty regards as academic misconduct. Failure to take part in this learning opportunity and thus ignorance of these regulations is no excuse and will not result in a reduced sanction in any case where academic misconduct is observed.

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Class notes will be posted on the course moodle site throughout the term.

How to search the organic synthesis literature:

1. Useful reference texts that relate closely to the content of this course
"The Logic of Chemical Synthesis." Corey and Chang, Wiley, 1989.

2. Encyclopedias and Reference Books:
• **Strategic Applications of Named Reactions in Organic Synthesis**
Laszlo Kurti and Barbara Czako (Elsevier Academic Press)
• **Reagents for Organic Synthesis** (Fieser and Fieser, Vol 1-16)
(provides references and summaries of reagents used in organic synthesis)
• **Encyclopedia of Reagents for Organic Synthesis** (Paquette)
(a more modern treatment of the subject than Fieser and Fieser)
• **Organic Synthesis**
(a multi-volume series as well as collective volumes that survey useful / common organic syntheses)
• **Compendium of Organic Synthetic Methods**
(a multi-volume series that illustrates synthetic methods in reaction schemes, arranged by functional group)
• **Comprehensive Organic Synthesis** (Trost and Flemming, Pergamon Press, 1991) (a comprehensive review of modern synthetic chemistry arranged by reaction type)
• **Comprehensive Heterocyclic Chemistry** (Katritzky and Rees, Pergamon Press, 1984)
(a comprehensive review of modern heterocyclic chemistry)
• **Comprehensive Functional Group Transformations** (Larock, VCH, 1989) (Review of functional group interconversions arranged by functional group types with citations to primary literature)
• **Protective Groups in Organic Synthesis, 3rd Ed.** (Greene, Wuts, John Wiley and Sons, 1999)
(a survey of protecting groups used in organic synthesis)
• **Catalogues of chemical suppliers:** (e.g. Aldrich, Lancaster, VWR, Fluka, BDH and Acros)
(these catalogues often cite useful lead references along with their reagents)

3. Journals
• Journal of the American Chemical Society
• Angewandte Chemie, International Edition, English
• Journal of Organic Chemistry
• Organic Letters
• Chemical Communications
(These journals often have excellent examples of total synthesis and new methods useful for total synthesis)

4. Journals (Reviews)
• Chemical Reviews
• Accounts of Chemical Research
(These journals provide detailed review articles relating to various topics in organic synthesis)

5. How to search the chemical literature:

SciFinder Scholar and Beilstein: The library has access to SciFinder Scholar but Beilstein is another very useful

search engine. In both cases, structures or partial structures are drawn and the search engine provides references relating the synthesis or use of the drawn compound. Danielle Dennie is willing to provide training on the use of refresher course on the use of SciFinder Scholar, please see me if you are interested.

PARTIAL LIST OF CONCORDIA UNIVERSITY SERVICES…take advantage, they are there for your benefit!

1. Concordia Counselling and Development offers career services, psychological services, student learning services, etc. **http://cdev.concordia.ca/**
2. The Concordia Library Citation and Style Guides: **http://library.concordia.ca/help/howto/citations.html**
3. Advocacy and Support Services: **http://supportservices.concordia.ca/**
4. Student Transition Centre: **http://stc.concordia.ca/**
5. New Student Program: **http://newstudent.concordia.ca/**
6. Access Centre for Students with Disabilities: **http://supportservices.concordia.ca/disabilities/**
7. Student Success Centre: **http://studentsuccess.concordia.ca/**
8. The Academic Integrity Website: **http://provost.concordia.ca/academicintegrity/**
9. Financial Aid & Awards: **http://web2.concordia.ca/financialaid/**
10. Health Services: **http://www-health.concordia.ca/**
11. among others