1-23-19

Syllabus
CEM 852
Spring 2019

Comprehensive Tactical Methods in Organic Synthesis

General Information

General Goal: To provide an introduction to tactical methods in organic synthesis organized by functional groups. Focus will be on the use of these reactions in designing synthesis of organic molecules.

Instructor: William D. Wulff
Office 530
Phone: 353-0503
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Class Time: M, W, F 9:10-10:00 AM, room 127
Saturday, 10:00 AM to ~12:00 to 1:00 PM, room 581 W

Required Text: *None*.

Recommended Text: "Strategic Applications of Named Reactions in Organic Synthesis", Kurti and Czako, 2005.

Recommended Reading:

1) "Organic Synthesis: Strategy and Control", Wyatt and Warren, 2007.
2) "Modern Methods or Organic Synthesis, Carruthers and Coldham, 4th Ed., 2004
3) " Organic Synthesis", Michael Smith, Third Edition, 2010.
4) "The Way of Synthesis", Hudlicky and Reed, 2007.
5) "Organic Chemistry, the Name Game", Nickon and Silversmith, 1987.
6) "Classics in Total Synthesis III", Nicolaou and Chen, 2011

Recommended Reference:

1) "Comprehensive Organic Transformations", By Richard Larock, second edition, 1999.
2) "Protecting Groups in Organic Synthesis", Wuts and Greene. Fourth edition, 2007.
3) March's Advanced Organic Chemistry, Smith and March, sixth edition, 2007.
4) Essential Reagents for Organic Synthesis, by Fuchs, Charette, Rovis and Bode, 2016, Wiley

Exams

There will be three exams that will be held on the following dates:

1. Friday, February 22, 2019
2. Friday, March 29, 2019
3. Friday, April 26, 2019

Location:	Room 136
Start Time:	7:00 PM
Finish Time:	When you give up.

Grading System

The following is the tabulation of the point system to be used in calculating the final grade:

1)	Exams	300 points
2)	Database Contribution	50 points
3)	Total Synthesis Presentations	50 points
4)	Research Proposal	100 points

THERE ARE FIVE COMPONENTS TO THE COURSE

A. Lectures

I. Organization of the Lectures

The foundation for all synthetic planning is one's knowledge of organic reactions. Thus the focus of the lectures in this course will be learning new organic reactions. The lectures will consist of the presentation of various reactions that are of synthetic value. The organization of these reactions will be by the functional group that is produced in the reaction. The order in which these functional groups will be covered is indicated below with the order of functional group priority. This type of organization is not common among advanced textbooks in organic synthesis, but is the organization found in *Comprehensive Organic Transformations* by Richard Larock.

Functional Group Priority:

1. Alkanes
2. Alkenes, Allenes and Arenes
3. Alkynes
4. Halides
5. Ethers
6. Epoxides
7. Alcohols and Phenols
8. Sulfur and Selenium Compounds
9. Amines (including nitro compounds)
10. Carbonyl compounds
11. Nitriles

The organization of the material to be presented for the formation of each functional group (Functional Group of Destination, FGD) will be further organized by the functional groups from which they are prepared (Functional Group of Origin, FGO). The Rules for determining FGD and FGO are given below.

Rules for Determining the Functional Group of Origin (FGO) and the Functional Group of Destination (FGD):

1) Functional group must directly participate in the reaction.
2) Functional group must be unique to the transformation
3) Protected forms of functional groups are not considered as a different functional group.
4) If the functional group is not common, the functional group of origin must be sought over 2 steps.
5) If more than one functional group meets the above criteria, then the highest priority functional group will take precedent.
6) The FGO should not contain or be the source of the FGD (except in isomerization reactions).
7) If the FGO and FGD are both contained in the same starting material, the functional group with the highest priority becomes the FGO.

II. Selection of a Synthetic Method for Any Given Transformation

Priority will be given to the presentation of those methods of proven synthetic value as revealed by the frequency in which they appear in the database of all of the total syntheses of natural products published in 2011 (1652 natural products). Additional considerations will be given to those methods that allow for transformations that are not available by other methods.

III. Selection of References for a Given Synthetic Method:

In preparing each lecture, the selection process for choosing references gives preference to those articles that include the original report of the reaction or method and those references that further define the scope of the reaction or method. Technical advances such as polymer supported or combinatorial processes or microwave or ultrasound mediation will not be covered unless substantial changes to the scope or efficiency is noted. Specific applications not of general interest will not be covered. Applications to synthesis of complex natural or unnatural products will be presented in some instances to highlight the reaction of interest. These will not be chosen by any rigorous selection process but rather by my particular interests or by examples that I happen to be aware of. Methods for the synthesis of aromatic heterocycles will generally be avoided unless the reaction or method has been widely used or will serve to illustrate the broader scope of the utility of the reaction or method. Reactions that involve functional group protection/deprotection will not be covered and the student is directed to the excellent book by Wutts and Greene.

IV. Schedule of Topics for Spring 2019.

The reactions for the formation of all functional groups will be covered over three semesters in the years 2018 – 2020. In the Spring of 2019 the functional groups alkynes, halides, ethers and epoxides will be covered. There are of course other important reactions involving other functional groups classes that those in the class of 2019 need to know and these will be worked in to the examples used to illustrate the synthesis of alkynes, halides, ethers and epoxides. The Saturday meetings will also expose members of the class to synthetically important reactions.

January 7		Alkynes
January 9		
January 11		
January 14		
January 16		
January 18		
January 21	Martin Luther King Day	
January 23		
January 25		
January 28		
January 30		
February 1		
February 4		
February 8		Halides
February 11		
February 13		
February 15		
February 18		
February 20		
February 22		Exam I
February 25		Ethers
February 27		
March 1		
March 4		
March 6		
March 8		
March 11		
March 13		Epoxides
March 15		
March 18		
March 20		
March 22		
March 25		
March 27		
March 29		Exam II
April 1		
April 3		
April 5		
April 8		
April 10		
April 12		
April 15		Alcohols
April 17		
April 19		
April 20		Proposal Presentations
April 22		
April 24		
April 26		Exam III

B. Exams

I. General Comments on Exams

There will be three exams during the semester given on the dates and times indicated above. The exams consist of a series of molecules for which one is to provide a proposed synthesis starting from a compound that is available form Aldrich Chemical Company. The use of cell phones and other internet devices is not permitted during the exam and for that reason each student will be provided with a copy of the Aldrich catalog. The problems will be designed such that at least one of the reactions covered in the lectures can be employed in a possible synthesis for each molecule. However, all syntheses will be acceptable whether or not they employ any of the reactions presented in class. The only requirement is that each reaction would work as proposed with the indicated reagents. It is certainly anticipated that success in devising syntheses to these problems will require a not only a knowledge or the reactions presented in the lectures, but also a working knowledge of all of the basic organic reactions typically covered in a sophomore organic course.

II. Exam Tips

A collection of common errors that have been made in answers to proposed syntheses by students over the years has been assembled and is posted on the CEM 852 website. Nonetheless, even armed with this list of tips, it is amazing that a large number of these same mistakes have been made by past students on their exams.

III. Synthesis Problem Bank.

All of the 692 problems from exams given over the last 38 years have been collected and sorted by the functional group of destination (the functional group that is created in the reaction). These will be posted by functional group on the CEM 852 website as they are covered in lectures. The answer keys to these problems will be posted separately.

C. Database

I. Creation of a Database of Reactions from all of the Total Syntheses published in 2011.

A database is being compiled in Filemaker Pro of all of the 1652 natural products for which total syntheses were published in the year 2011. These syntheses were collected from 64 different journals that publish total syntheses of natural products. This was initiated in 2012 and at the present time ~1,250 molecules have been entered. Each step is entered as a separate record with each record containing 30 information fields. Presently, 23,301 individual chemical steps have been entered.

The members of the class will be paired into teams that will be responsible for entering additional molecules into the database. Each team will meet with the instructor for one hour a week to enter new molecules and they should bring a copy of the paper for the particular molecule with them to the meeting. The time that it will take to enter each molecule will of course vary depending on the size of the molecule. Thus some teams will finish their assigned molecules indicated below before the end of the semester, and in that case, additional assignments will be made. Speed of entry is not an issue and emphasis should be given to accuracy.

In preparation for each team meeting, each team needs to identify the starting material. This in turn, of course, requires the identification of the longest linear sequence. The longest linear sequence will be entered first followed by the entry of each branch in the synthesis in the order in which they occur. Identifying the starting material is often the most difficult part of the process because authors are not

particularly respectful of this issue (it makes a synthesis look longer). Typically the author will reference the preparation of a simple starting material to a previous publication that has described its preparation and, if this is the case, copies of these publications should be brought to the meeting. In some cases no reference is given for the preparation of the starting material at all. If it is not available from Aldrich, you should search the compound on SciFinder to find a published procedure for its preparation. If the compound is available from either Aldrich or other commercial suppliers but should cost less that $100 per gram. No self-respecting (or fiscally observant) synthetic chemist would pay $500 per gram for a starting material in a 30 step synthesis.

II. Considerations for Data Gathering:

1. The longest linear sequence is presented which begins with a compound that is commercially available from Sigma-Aldrich (or an alternative supplier). If it is stated by the author that the starting material used is commercially available then this will be identified as the starting material even if the author does not specify the supplier. It of course can't be determined if the author actually used the commercial material and thus the author's word is assumed to be good. The same would be true for the starting materials of any of the branches of the synthesis. If the preparation or reference to a non-commercial starting material is not given, then a search for its synthesis on Sci-Finder is used to find a published preparation. The choice of preparation among multiple hits is made on the basis of which gives full experimental details.

2. The synthesis of chiral auxiliaries are included as steps in the synthesis but not the synthesis of catalysts or ligands for the catalysts.

3. If there is a discrepancy between the data from the text and the experimental (yields, reagents, etc.), the data in the experimental is used.

4. A transformation is counted as two steps if there is a workup. A transformation is counted as two steps if the transformation produces an intermediate organic compound that can't go on to the product unless new reagents are added. Example: aldol condensation. If the elimination does not occur under the conditions for the aldol step, then this is considered two steps: aldol plus eliminaton. This will be two steps even if a workup is not employed or the intermediate is not isolated. The in-situ generation of a reagent (Grignard, ylide, lithium enolate, organoborane or organozinc, etc.) is not considered as a separate step unless it is specifically indicated that the reagent is isolated or purified. The generation of an intermediary organic compound is considered a chemical step. For example, acid to acyl azide, acyl azide to isocyanate and isocyanate to carbamate would be three steps even if there is no workup or isolation. The in-situ formation of an enolate is not considered a separate step. The generation of an acid halide or an acid anhydride is considered a separate step.

5. The yields are based on the limiting reagent. If recovered starting material is recycled in a second reaction and the yield (and conditions) for the second cycle is given, then the yield is indicated as the combined yield for the two (or more) cycles.

6. If the yield for a given step is different than that from the literature, the yield from the literature is used unless an experimental procedure is given.

7. If at all possible, compounds will be named according to the system used by Aldrich.

8. A Total Synthesis Worksheet is posted on the CEM 852 website. It is not necessary for each team to fill out this form, but some people like to use it.

III. *List of database teams:*

Team 1:	Smith, Brendyn and Bedford, Sophie	Thursday, 1:00 to 2:00 PM
Team 2:	Peruzzi, C. and Yadav, A.	Monday, 3:00 to 4:00 PM
Team 3:	Chen, C.-P. and Chhabra, A.	Monday 2:00 to 3:00 PM
Team 4:	Olesky, T. and Vanecek, A.	Friday 2:00 to 3:00 PM
Team 5:	Staerz, S. and Lin, P.-H.	Friday 1:00 to 2:00 PM
Team 6:	Vahdani, A. and Mansour, P.	Friday 12:00 to 1:00 PM

IV. *List of database team assignments for Spring 2019.*

6	cusparine galipinine	molecule # 1026 molecule # 1027	*J. Org. Chem.* **2011,** *76,* 8891.
5	deactoxy-12-epi-scalarafuranacetate	molecule # 1028	*J. Org. Chem.* **2011,** *76,* 7216.
4	lennoxamine	molecule # 1029	*J. Org. Chem.* **2011,** *76,* 9856.
3	merrekentrone C	molecule # 1031	*Org. Biomol. Chem.* **2011,** *9,* 5655.
2	nuevamine	molecule # 1032	*Org. Biomol. Chem.* **2011,** *9,* 7643.
1	schulzeine B	molecule # 1057	*Tetrahedron* **2011**, *67,* 6281.
6	guineensine	molecule # 1064	*J. Asian Nat. Prod. Res.* **2011**, *13,* 128.
5	bilobol adipost	molecule # 1065 molecule # 1066	*J. Asian Nat. Prod. Res.* **2011**, *13,* 290.
4	balsamiferoe cedrelopsin	molecule # 1067 molecule # 1068	*Arkivoc* **2011**, *(ix),* 68.
3	arylomycin B-C16	molecule # 1069	*J. Nat. Prod.* **2011**, *74,* 956.
2	avenolide	molecule # 1070	*J. Antibiot.* **2011**, *74,* 956.
1	conhydrine balanol	molecule # 1071 molecule # 1072	*Adv. Synth. Catal.* **2011**, *353,* 2137.
6	botryolide E	molecule # 1073	*Bioorg. Med. Chem. Lett.* **2011**, *21,* 997.
5	dimethyldodecanal	molecule # 1074	*Nat. Prod. Res.* **2011**, *25,* 560.
4	dioncoquinone B	molecule # 1075	*Eur. J. Med. Chem..* **2011**, *46,* 5778.
3	pentosidine	molecule # 1076	*J. Heterocyclic Chem..* **2011**, *48,* 426.
2	schulzeine B schulzeine C	molecule # 1058 molecule # 1059	*Tetrahedron* **2011**, *67,* 8034.
1	pyripyropene A	molecule # 1077	*Tetrahedron.* **2011**, *67,* 8195.

D. Total Synthesis Presentations:

I. Tactics vs. Strategy in Organic Synthesis.

One's internal database of organic reactions (i.e., your brain) serves as the origin of the tactical design that is needed for the planning of a total synthesis. Thus, an increase in proficiency in this regard requires learning new organic reactions. On the other hand, increased proficiency in strategic design is not so easy to come by. Here, the emphasis is on the right combination of and right order of incorporation of the various organic reactions. Here there is much more room for creativity and as R. B. Woodward once said in 1956, "there can be great art in organic synthesis." One of the best ways to gain an appreciation for the importance of and the workings of strategy in total synthesis is to witness the outcome resulting from various strategies found in the total synthesis of experienced practitioners of the art. It is with this in mind that an analysis of 28 total syntheses from the year 2017 will be presented by all of the members of the class. Each Saturday three members of the class will present a total synthesis and this will continue each week of the semester. The analysis will consist of a step by step break-down of the total synthesis of each molecule and, where needed, a description of the reactions involved. The Schedule for these presentations is given below and will occur on Saturdays mornings at 10:00 AM in room 581W.

II. Guide For the Preparation of a Presentation for a Total Synthesis.

1. Each step should be presented individually, i.e, one arrow per reaction. Many papers will have multiple reactions per arrow but this is to save space. In addition, it is often not clear whether one or two steps is indicated and you can tell this from the experimental procedure. The **complete** structure of the starting material(s) and product(s) should be presented. A compound should never be represented by just a number. Substituents should never be indicated as R. The stoichiometry of each reaction should be given with the number of equivalents of each reagent, the solvent, the reaction temperature and the reaction time should be given for each individual reaction. This information in most cases will be found in the Supporting Information.
2. The synthesis should be presented back to a compound that is commercially available and this should be done for the longest linear sequence as well as for any branches in the synthesis. In most papers this is often not done. Typically the author will reference the preparation of a simple starting material to a previous publication that has described its preparation. In some cases no reference is given for the preparation of the starting material at all. If it is not available from Aldrich, you should search the compound on SciFinder to find a published procedure for its preparation.
3. Acronyms should not be used except for the most common of chemical entities such as THF and DMF. Others such as LDA and DIBAL should be indicated by chemical formulas. The identity of all reagents and catalysts should be indicated by chemical structures or in the case of simple molecules such as dimethyl sulfoxide by a chemical formula; Me_2SO.
4. If the synthesis is a formal synthesis tying into an advanced intermediate previously prepared by another group, the final steps to the target from the previous work should be included in the presentation.
5. Some papers are a combination of methodology and total synthesis. The methodology should not be included in the presentation except for those reactions necessary to the synthesis.
6. Actual yields should be given, not brsm (based on recovered starting material).
7. Some papers present a combination of synthesis and biological testing. For the purposes of this class, the details of the biological testing should not be presented.

8. Many full papers will include approaches that do not work. If they don't know why then you need not present them. However, if they understand why then you may present failed approaches.

9. If a paper includes the synthesis of several molecules, you need present only the molecule that is indicated since they are often related and have the same steps. However, if the syntheses are sufficiently different, you certainly may include other molecules as well.

10. Some papers will present computational studies to support various approaches. These need not be presented. The focus in this class will be learning new reaction and how to use them.

11. You should understand the mechanism of each reaction that is used. If you think a certain mechanism is one that the class may not know, you should present a possible mechanism for this reaction from the literature.

12. If a reaction involves a name reaction you should be prepared to give a synopsis of the reaction if asked.

13. The molecules should be in the same orientation from step to step.

14. In addition to yields, include the %ee, the dr or the E/Z ratio if appropriate.

III. Schedule for Total Synthesis Presentations (Saturday, 10:00 AM, room 581W).

Your presentation should be sent to the instructor as a Power-Point file shortly after your presentation was made and any corrections have been made. These will be posted on the CEM 852 website.

January 26	Smith, B.	Resiniferatoxin A *J. Am. Chem. Soc.* **2017**, *139*, 16420.
	Bedford, S.	Virosaine A *Angew. Chem. Int. Ed.* **2017**, 56, 10830.
February 2	Peruzzo. C.	Lungshengenin D *J. Am. Chem. Soc.* **2017**, *139*, 2932.
	Yadav, A.	Hydroxykempenone *Angew. Chem. Int. Ed.* **2017**, 56, 15861.
February 9	Chen, C.-P.	Palhinines A and D *J. Am. Chem. Soc.* **2017**, *139*, 4282.
	Chhabra, A.	Communesin F *Angew. Chem. Int. Ed.* **2017**, 56, 14237.
February 16	Olesky, T.	Lancifodilactone G Acetate *J. Am. Chem. Soc.* **2017**, *139*, 5732.
	Vanecek, A.	Corymine *Angew. Chem. Int. Ed.* **2017**, 56, 7484.
	Staerz, S.	Cheloviolenes A and B *J. Am. Chem. Soc.* **2017**, *139*, 7192.
March 2	Lin, P.-H.	Sarcandrolide J, Shizukaol D *Angew. Chem. Int. Ed.* **2017**, 56, 637.
	Vahdani, A.	Wortmannin *J. Am. Chem. Soc.* **2017**, *139*, 6815.
	Mansour, P.	Chivosazole F *Angew. Chem. Int. Ed.* **2017**, 56, 645.
March 9	Olesky, T.	Caribenol A *J. Am. Chem. Soc.* **2017**, *139*, 4117.
	Bedford, S.	Tetracenomycins C and X *Angew. Chem. Int. Ed.* **2017**, 56, 12608.
	Peruzzo, C.	Nahuoic Acid C1 *J. Am. Chem. Soc.* **2017**, *139*, 13668.
March 16	Yadav, A.	Albocycline *Angew. Chem. Int. Ed.* **2017**, 56, 5909.
	Chen, C.-P.	Himalensine A *J. Am. Chem. Soc.* **2017**, *139*, 17755.
	Chhabra, A.	Aplydactone *Angew. Chem. Int. Ed.* **2017**, 56, 8187.
March 23	Preliminary Presentation of Proposal from All Members of the Class.	
April 6	Staerz, S.	Andirolide N *J. Am. Chem. Soc.* **2017**, *139*, 631..
	Vanecek, A.	Waihoensene *Angew. Chem. Int. Ed.* **2017**, 56, 8254.
	Smith, B.	periconianone A *J. Am. Chem. Soc.* **2017**, *139*, 16096.
April 13	Lin, P.-H.	Pepluanol A *Angew. Chem. Int. Ed.* **2017**, 56, 8898.
	Vahdani, A.	Thansigargin *J. Am. Chem. Soc.* **2017**, *139*, 6046.
	Mansour, P.	Compounds **1** and **2** *Angew. Chem. Int. Ed.* **2017**, 56, 15049.

E. Proposals

Part of the grade for the course will derived from an independent research proposal for the synthesis of a natural product that you will create and present to the class at the end of the semester on Saturday, April 20, 2019. The natural product that will be assigned to you will be a recently isolated natural product from the year 2018 and thus there will be no prior published syntheses.

The proposal will be presented to the class on Saturday, April, 20 2019 in room 581 beginning at 9:00 AM and should be no more than 30 minutes. You will be required to present to me an electronic copy of your proposal (powerpoint would be fine) by noon on Friday, April 19. It should include the retrosynthetic analysis and detailed proposed synthesis as well as the background to the molecule, literature background to support the key steps, alternatives to key steps that are considered risky, and arguments to support the outcome of the key steps (stereochemistry, etc.). There will be a preliminary presentation of each proposal on March 23. These should consist of a brief outline (10 minutes) of your proposed synthesis covering only key transformations but not the details. In the final presentation on April 20, you should bring with you hardcopies of the presentation to be distributed to the entire class during the presentation. The presentation of your proposal should be made with Powerpoint or Keynote. The proposals will be graded by a vote from each member of the class using the NIH scoring system (the presenter will be dismissed from the room during the vote). I withhold the right to override the grade determined by the class if I feel an injustice has been done (this has only happened once in 39 years).