

Synthesis of Complex Natural Products as a Vehicle for Student-Centered, Problem-Based Learning

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Recent interest in problem-based group learning activities (1–3) as part of advanced undergraduate and graduate courses prompts us to report our course-management techniques for upper-level organic synthesis courses offered at Temple University. We have found that natural product syntheses are especially well suited to team-learning approaches and that there is no shortage of stimulating problems to serve as a basis for group work. Current issues of professional journals, such as *The Journal of Natural Products*, report myriad complex new organic structures accompanied by background on their biological properties. The analytical methods of organic synthesis, in which target molecules to be synthesized are broken down by repeated “disconnections” into smaller fragments and ultimately into possible starting materials, provide opportunities for both individual contributions and team work.

A typical outline of faculty and student responsibilities in a teacher-guided, student-directed, interdependent, small-group, problem-based synthesis course is shown in Table 1. At the outset students are apprised that the course goal is for them, as part of a team, to develop a proposal for the synthesis of a complex molecular structure by the end of the semester. Stu-

dent syntheses from previous years are circulated to motivate students and to dispel fears that fourteen weeks is too short a time to learn enough to be creative.

To start a peer-learning process, the students are asked to create provisional groups of four or five based upon class schedule compatibility, experience, perception of ability, and diversity factors. The class is now given a tour of the departmental library followed by a brief “find the reagents and synthetic procedures” group assignment that requires the use of varied library resources. Students next are asked to search appropriate journals in the library for potential target molecules for the synthesis project. The chosen targets are shown to the instructor for suitability. If the students and instructors can identify disconnections, stereochemical elements, and functional group complexity in target molecules that are reasonably suitable for a group project, then the molecules will be tentatively approved. Target molecules and group alliances on the term project may change until approval of disconnection schemes later in the course.

Control of major elements of the course now becomes the responsibility of the student groups. Once target molecules

Table 1. Outline of Faculty and Student Responsibilities

Week	Faculty Responsibilities	Student Responsibilities
1	Introduce the course. Present guidelines for the course goal: group efforts to propose rational syntheses of complex organic molecules. Show examples of prior student synthetic efforts. Give an entrance quiz and engage the class in discussion to gauge student preparedness for the course. Present guidelines for formation of student groups, discuss recommended textbooks, and introduce students to the use of the library.	Form representative groups, which meet student concerns. Work on a group library assignment. Begin to think about organic synthesis and engage in a literature search for target molecules suitable for a group synthetic effort.
2–3	Review and evaluate student synthetic targets. Interact with students in the development of a course syllabus. Create and assign problems based upon C–C disconnections learned in prior courses.	Continue the search for target molecules. Develop a working course syllabus, which uses instructor-recommended textbooks and other resources to supplement independent student learning. Work on group problem assignments.
4–9	Prepare and grade homework problem assignments. Prepare disconnection approach classroom exercises and give a midterm examination. Interact with the class in the discussion of progress on synthetic targets and give helpful hints.	Use the literature and textbooks outside of class to work teacher-designed problem sets related to retrosynthetic analysis and synthetic methods. Discuss the team progress on the disconnection of the synthetic targets; identify and address problems encountered with synthetic approaches to target molecules. Do assigned molecular disconnections and discuss homework problems in class. Develop a grading scheme for the course and decide what is suitable as a midterm examination.
9–12	Choose literature syntheses for class discussion that are relevant to the molecules chosen by the students. Keep the faculty–student dialog active about the synthesis projects so that intergroup and intragroup cooperation occurs.	Present a literature synthesis to the class as a group effort. Develop a grading scheme for your synthetic project, which allows other groups to evaluate your group effort and enables each group to evaluate the efforts of its members. Combine individual contributions to complete convergent syntheses of the target molecules.
12–14	Evaluate student synthetic efforts and give feedback on how and why those evaluations differ from students' evaluations. Negotiate with students to create a suitable final examination. Have students evaluate the course.	Present the completed group synthetic schemes to the class. Perform evaluations of peers both within and between groups. Discuss what constitutes an appropriate final examination. Perform a course evaluation.

have been chosen, the class creates a course syllabus to organize the resources needed to learn the skills and information required to devise complex syntheses. Inevitably, the class recognizes there is a general need to know more about the disconnection approach, the scope, mechanisms, and stereochemical aspects of general types of carbon-carbon bond-forming reactions, and methods for effecting various types of functional group transformations. Typically the class chooses to have the first half of the semester dedicated to a discussion of problems in relevant chapters in retrosynthesis (4) and synthesis (5) textbooks. Answers to these instructor-assigned problems are handed in for group grades. The major purpose of these exercises is to stimulate peer learning and to have students develop methods for distribution of labor and assuring individual responsibility to the group. Students typically choose to have these group problem assignments count as 20–30% of the course grade. The balance of our evaluation of students is from scores on individual exams (40–60%) and the group projects (20–30%). The students have input into both the form and appropriate content of the exams and are asked to suggest appropriate questions.

During the early learning stages when we are encouraging group cooperation, we often use nonevaluative "team competitions" as part of the class format (6). Student groups (companies) are assigned a list of 10–20 target compounds typical of material to be studied and variable in difficulty according to class experience. During the class competitions, companies choose by lottery which target molecule syntheses they will present in class to the customer (the instructor), who also acts as a facilitator for this exercise. Each member of the group makes a presentation of a separate molecule and then fields questions and comments from the class and instructor. A successful presentation earns a company "account" a point. A challenge by another company with a superior method based upon efficiency, yield, hazards, etc. can wrest the point from the account (and also earn a point). The most successful company earns the most points. Tangible rewards in this competition are not necessary. Self-satisfaction and peer recognition are sufficient to fuel productive group competition, facilitate peer learning (1), and generate classroom enthusiasm.

After groups of 3–6 students have coalesced around target molecules, class time is provided for groups to present disconnection approaches for their structures and to receive peer feedback at all stages of the creative process. By the midterm, students will have identified major components of their synthetic plans and groups will have assigned responsibility for synthesis of defined parts (synthons) to specific individuals. The synthons then will be combined in convergent steps to generate the target molecules.

In the latter part of the term, there are student-led discussions of primary literature syntheses (7), chosen for their relevance to the student projects. As in a research proposal (8), the creation of each student's molecular fragment will be accompanied by a discussion of stereochemical control elements, introduction and removal of protecting groups,

possible competing processes and by-products, expected yields, and appropriate references to the literature. It is the task of the group as a whole to see that they have chosen suitable protecting groups for each contributed part and that connection of synthons is made in a timely fashion so that incompatible functional groups are not present (9).

Students develop a grading rubric for their projects only after each group has become intimately familiar with the effort put into its own project. Grading schemes take into account the need for alternatives to risky steps, the importance of references, and the requirements of regioselectivity, stereoselectivity, and functional group selectivity (chemoselectivity). Using the developed rubrics, class periods are then devoted to intergroup peer grading of the projects for input to the instructor, who retains final grade authority. A percentage of the project grade is reserved for intragroup peer grading. Typically, as voted by the class, each student receives 90% of the points awarded to a project. The remaining points are divided among the members of the group for distribution to the group peers. The peer evaluation points and a rationale for each award are given directly to the instructor. Nearly invariably, students reward both effort *and* creativity by their peers.

Students leave our synthesis courses able to use texts and library resources and with a knowledge of the methods and tools of organic synthesis. They also learn how cooperation makes it possible to perform tasks that otherwise would be overwhelming. As instructors we have noted that the synthesis projects give students self-confidence, pride, and an appreciation of the abilities of their classmates. Students have praised our synthesis courses, which bring together concepts learned in other classes and apply them to real-world problems, as the highlight of their educational careers. We ourselves leave our courses intellectually stimulated and ever amazed at the creativity of our students, once they are given the guidance and opportunity.

Literature Cited

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