Less Cookbook and More Research! Synthetic Efforts Toward JBIR-94 and JBIR-125: a Student-Designed Research Project in a Sophomore Organic Chemistry Lab

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Abstract

In light of the meaningful learning gains that can be obtained through a genuine research experience, chemistry educators have had a longstanding interest in making teaching labs less "cookbook-like" and more research-driven [1]. With this mindset, we recently restructured our two-semester sophomore organic chemistry lab course to include a synthesis project that was chosen, designed, and carried out by students. This led to progress toward the syntheses of JBIR-94 and JBIR-125, two antioxidative/anticancer natural products that have yet to be assembled through organic chemistry. The major drawback of our course redesign is that it requires close supervision by an instructor or TA experienced in synthetic chemistry and is limited to small class sizes. Its up-front cost is also prohibitive; however, this can be minimized by employing synthetic steps that involve reagents already available on-site. The advantage of this restructuring is encapsulated by highly-positive student feedback and enthusiasm, which led all participating students to continue working on the project after the semester had ended. Exam performance is

also discussed. For reference, complete and reproducible experimental details and full copies of student evaluation results are included as Supporting Materials.

Introduction

In light of the learning gains that can be obtained through a meaningful research experience [2-4], chemistry educators have long pondered the question of how to make teaching labs less "cookbook-like" and more research-centered [1]. This has led to various approaches, including problem-based [2b-c], guided inquiry [5], investigative learning strategies [6], and others [7]. In a seminal paper on the subject, Horowitz suggested that all such approaches "can be broadly categorized as discovery, inquiry, and project based" [8]. He further explained that although some educators may be "attracted to project-based experiments" [8], these are often limited by safety challenges, increased time investment by the instructor, and greater cost [8].

In contemplating the question of how to incorporate student-driven research into an undergraduate chemistry lab with non-chemistry-majors, our attention turned to a report by Gravert [9], in which an undergraduate organic chemistry lab course was restructured to allow students to choose any "reasonable" molecule they wished, design a synthesis of it, and then carry it out in the lab. Although Gravert reported that none of his students were able to finish their syntheses, disappointment was curbed by the advance warning that "actual research is much like this project: that is, 90% of attempted reactions may be unsuccessful" [9].

We recently strived to adapt and incorporate a related approach into our own two-semester organic lab course, carried out during Fall 2011 (Semester 1) and Spring 2012 (Semester 2). Our method differed slightly from Gravert's on two fronts. First, our students chose only two synthetic targets as a class, instead of individual students each selecting their own

molecules; and second, students worked on their syntheses in small groups, instead of doing it alone. Full experimental details of students' successful steps are included in our Supporting Materials.

Congruent with Horowitz's assessment, we found our new approach to require a much greater time investment from the instructor (which helped ensure proper safety), as well as an increased cost. Nevertheless, student feedback was highly positive, and all students involved later participated in the extracurricular lab research that the resulted from this work. Furthermore, students' year-end performance on a comprehensive, conceptual ACS exam was exemplary.

Results and Discussion

Our small, rural class consisted of five students (three male, two female, aged 20 to 24), who were all biology majors. The course regimen included one three-hour lab per week, spread over 15 weeks per semester, for two semesters. As Table 1 indicates, Semester 1 was delivered in an unaltered, "typical" format that encompassed 12 "cookbook" labs designed to expose students to fundamental techniques [10]. Semester 2, in contrast (Table 2), was altered to include a hybridized regimen of traditional "cookbook" experiments, done over nine weeks, with a class project that spanned six weeks. As Table 2 shows, two synthesis assignments were given during Weeks 1 and 5. For these assignments, students went through the process of selecting two molecules as a class and then designing a means of assembling them. Students then carried out their synthetic routes during Weeks 12-15. The results of this course redesign will now be addressed.

Table 1. Weekly Schedule for Semester 1.

Week	Technique/Topic Covered	Week	Technique/Topic Covered
1	Lab Safety	**9**	NMR spectroscopy
2	IR spectroscopy	**10**	Grignard addition
3	Distillation	**11**	Filtration/m.p. analysis
4	Extraction	**12**	Computational chemistry
5	Sublimation	**13**	Computational chemistry
6	Thin-layer chromatography	**14**	Makeup lab
7	Filtration	**15**	Lab cleanup/checkout
8	Running reactions at reflux		

Table 2. Weekly Schedule for Semester 2.

Week	Technique/Topic Covered	Week	Technique/Topic Covered
1	Choosing Synthetic Targets **(Synthesis Assignment 1)**	**9**	Green chemistry
2	Radical chemistry	**10**	Diels-Alder chemistry
3	GC analysis/kinetics	**11**	Column chromatography
4	Meet to discuss and vote on Assignment 1	**12**	**Total Synthesis: Step 1** (Group 1: hydrogenation Group 2: cleaving a methyl ether)
5	Using SciFinder to design a synthesis **(Synthesis Assignment 2)**	**13**	**Total Synthesis: Step 2** (Group 1: protecting an alcohol I Group 2: chromatographic purification)
6	Gas chromatography	**14**	**Total Synthesis: Step 3** (Group 1: DCC-amidation I Group 2: protecting an alcohol II)
7	Qualitative analysis	**15**	**Total Synthesis: Step 4** (Group 1: DCC-amidation II Group 2: hydroboration/oxidation)
8	Boiling point determination		

Semester 2, Assignment 1 (Week 1): Choosing Synthetic Targets

During Week 1 of Semester 2 (Table 2, entry 1), students were taught how to properly search current literature, with the accompanying lecture being video-recorded and posted online after class for reference [11a]. Each student was then assigned to find and choose at least two molecules that might serve as potential synthesis candidates. Students were encouraged to avoid overly complex molecules and to focus on simple, bioactive natural products that had never been assembled by total synthesis before. After three weeks, class members reconvened with the instructor to share their findings (Table 2, entry 4) and written reports, which had to include the following for full credit: (1) the structures and reported biological properties of the molecules they chose; (2) the literature source(s) in which they were found; and (3) why they were selected.

On the day these reports were due, we held a round-table student/teacher discussion to share our findings (see Table 2, entry 4), and the ensuing dialogue proved to be very positive and enthusiastic. One pre-dental student, for example, chose four molecules applicable to oral health [12], and one pre-med student with a military background chose spider silk for its potential to replace Kevlar [13]. Other students submitted molecules that included daphnetoxin [14], xanthohumol [15], berkazaphilone B [16], olympicin A [17], tauromantellic acid [18], adenosines A_1 and A_{2A} [19], and amyrisin C [20]. Following this discussion, an anonymous online vote was taken to compile each student's top two nominees. The winning contenders from this vote, shown in Figure 1, were JBIR-94 (**1**) and JBIR-125 (**2**), two recently-discovered natural products [21] that possess antioxidative/anticancer properties comparable to α-tocopherol, the active constituent of Vitamin E [22].

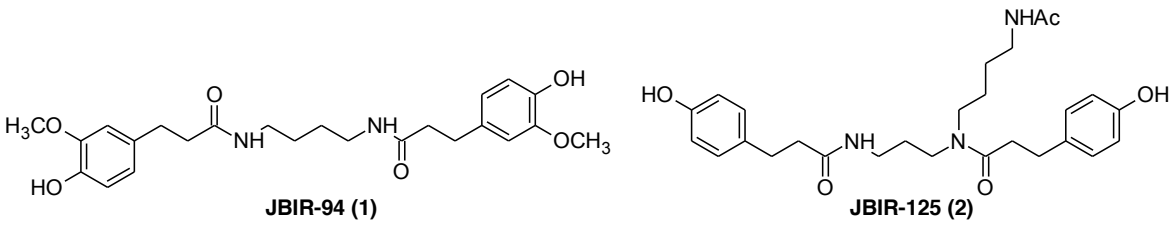


Figure 1. JBIR-94 (**1**) and JBIR-125 (**2**).

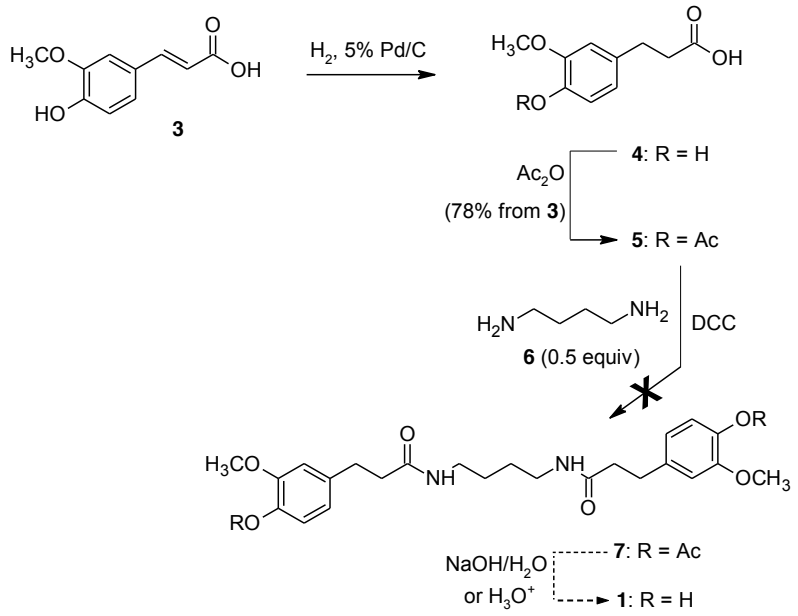
Semester 2, Assignment 2 (Week 5): Designing Total Syntheses

During Week 5 of Semester 2 (Table 2, entry 5), students were taught how to use SciFinder Scholar to design a total synthesis. The accompanying lecture was video-recorded and posted online for reference [11b-c]. Students were then asked to use SciFinder to devise their own synthetic routes to JBIR-94 (**1**) and JBIR-125 (**2**) using any conditions they found in the literature. After three weeks, students turned in their reports, which for full credit had to include their proposed synthetic routes to **1** and **2** and every literature reference employed. Once student designs were submitted, the instructor combined their most pragmatic elements to construct the routes shown in Schemes 1 and 2. Though not required for the assignment, every reaction condition used in these pathways was one that students had learned in the separate lecture course taken concurrently with the lab.

The execution of these reactions was intentionally postponed until Weeks 12-15 (Table 2, entries 12-15) to allow sufficient time for ordering and receiving all the needed reagents. Students conducted more traditional experiments in the interim, as seen in entries 6-11 of Table 2.

Semester 2, Assignment 2 (Weeks 12-15): Carrying out the Syntheses

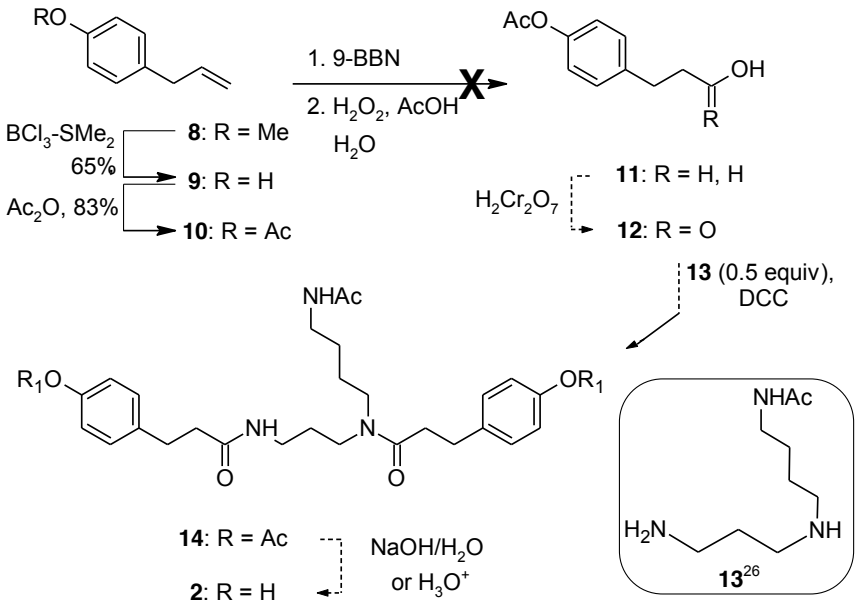
During Weeks 12-15 of Semester 2, students separated into two groups, one focusing on compound **1** and the other on compound **2**. Each reaction undertaken followed exact or related literature procedures [23-25], which have been reworded and fully-illustrated in a more student-friendly and thorough manner in our Supporting Materials. Thus, using conditions that students found themselves during their literature search [23], Group 1 successfully reduced *trans*-ferulic acid **3** to intermediate **4** using H_2 gas and 5% Pd/C (Scheme 1). Subsequent treatment with acetic anhydride during Week 13 achieved conversion of compound **4** to intermediate **5** in 78% yield over two steps from **3** [24]. Over Weeks 14-15, various attempts to form diamine-linked intermediate **7** led to only complex mixtures of unidentifiable byproducts.



Scheme 1. Student-designed route to JBIR-94 (**1**).

Given its greater structural complexity, students' proposed route to JBIR-125 (**2**) was predictably longer (Scheme 2). Thus, during Week 12, Group 2 treated 4-allylanisole **8** with BCl_3•SMe_2 [25]

to unveil free phenolic intermediate **9** in 65% yield. This was then acylated during Week 13 to give **10** in 83% yield, as indicated. At this stage (Weeks 14-15), two attempts were made to convert **10** to **11** through hydroboration/oxidations conditions [24]. Disappointingly, both failed, precluding access to **11**, en route to **12**, **14**, and ultimately **2**. Modified routes to **1** and **2** are currently underway and will be disclosed once the synthesis is completed.



Scheme 2. Student-designed route to JBIR-125 (**2**).

For every week of the semester, including Weeks 12-15, students were required to hand in a journal-style, typed lab report for full credit. For experiments that did not succeed (Weeks 14-15), students had to include, in their "Results/Discussion" sections, possible explanations for reaction failures and proposals for future alternative conditions.

Safety and Time Investment

A major challenge we face in organic chemistry teaching labs is the difficulty of converting real-world synthetic procedures into an undergraduate-appropriate format. For instance, many reactions take too long or involve too many safety concerns for a typical lab course. In the case of our project specifically, two of our reactions (**1 → 2** in Scheme 1 and **8 → 9** in Scheme 2) required overnight stirring, which obviously could not be done start-to-finish in a three-hour timeframe.

This problem was circumvented by running these reactions in duplicate, so students could experience both the setup and the quench portions of each procedure without having to wait through the hours of reaction time in-between. Thus, for these two steps (**1 → 2** and **8 → 9**), the instructor set up each reaction the night before. The next day, students were tasked with both quenching the previous night's reaction *and* setting up that reaction again (to be quenched by the instructor the following day). Students could thereby experience both halves of the procedure (setup and quench) and then perform purifications and analyses on the resulting products, all within a three-hour timeframe. This obviously required a greater time investment from the instructor. Furthermore, specific safety concerns, such as the flammability of Pd/C and the corrosivity of BCl_3•SMe_2, were addressed by close and judicious instructor supervision. Specific procedural and safety details are found in the Supporting Materials.

Cost Breakdown and Extracurricular Student Participation

Congruent with Horowitz's assertions [8], the up-front costs, summarized in Table 3, remain a prohibitive factor for this type of course restructuring. These were minimized, however, by the fact that many of the general reagents needed were already available on-site in the instructor's

adjacent research lab. As Table 3 illustrates, the cost-per-experiment was highest during Week 12, where gram-scale amounts of the initial starting materials were required. These costs decreased over the ensuing weeks because previously-synthesized intermediates were taken on in smaller amounts during successive steps. (A more in-depth cost analysis is given in the Supporting Materials.)

Table 3. Cost breakdown summary.

	Group 1 (3 students)			**Group 2 (2 students)**			
Week	**Up-Front Cost**	**Cost Per Experiment**	**Total Cost Per Student**	**Week**	**Up-Front Cost**	**Cost Per Experiment**	**Total Cost Per Student**
12	$180.11	$17.36	$5.79	**12**	$470.17	$25.62	$12.81
13	$208.07	$1.65	$0.56	**13**	$715.00	$0.27	$0.14
14	$26.30	$0.30	$0.10	**14**	$0.00*	$1.07	$0.54
15	$0.00*	$0.30	$0.11	**15**	$215.56	$1.95	$0.97
Total	**$414.48**	**$19.61**	**$6.54**	**Total**	**$1400.73**	**$28.91**	**$14.47**

*The up-front costs for these steps were counted as $0.00 because all needed reagents were purchased in earlier experiments.

Despite the up-front cost being considerable ($414.48 for Group 1 and $1400.73 for Group 2), the cost-per-experiment and cost-per-student were fairly reasonable for the two groups ($19.61 and $28.91, respectively), as Table 3 indicates. Thus, costs can be minimized if the synthetic steps chosen involve common reagents that are already available on-site. In a more honest sense, however, the *true* cost-per-experiment and per-student can only be minimized if the purchased supplies are reused with subsequent students, which we did not do. Consequently, our reagents and supplies had to be paid for by subsidizing the cost using the instructor's startup research funds.

This was not a purely altruistic move, as twenty of the 25 reagents/supplies used in this project are extremely common to synthetic work and would eventually be used in the instructor's research anyway. The cost of the "truly unique supplies" (those that were specific to this project) came to $240.24 for the entire class, or 13.23% of the total up-front expense of $1,815.21. This work proved to be additionally beneficial, as it eventually evolved into a research project for the instructor's group. This occurred at the semester's end, when all participating students were invited (if they chose) to continue working on the syntheses of **1** and **2**. All five students eventually did. One of them even wrote two institutional grant proposals to help fund the continued research, and two helped coauthor this paper. With an upcoming synthetic publication on the horizon, this project has proved to be mutually beneficial for both students and the instructor.

Student Feedback and ACS Exam Performance

Our success in meeting our original objective –to create a new course structure to provide a student-driven research project—was gauged through anonymous end-of-year student evaluations. This was done using the Diagnostic Form Report from the IDEA Center Student Ratings system [27], for which full results are included in the Supporting Materials section. The number of student comments was somewhat limited, given the small class sizes at our rural campus, but responses to the student-driven research project were highly positive. Following are some of the representative student comments:

> Best class ever! I love that [the professor] involved us in a total synthesis during the last four weeks of class. I am so excited to go to each lab class. I feel like I

> have learned so much more doing work for the synthesis project than any of the other "cookbook" labs that we have done.
>
> I think that the best part of this course was that we were able to design a synthesis and produce a compound of our choosing and make it in the lab. I liked that we didn't follow the book the whole time and were able to see what it is like to be in a real lab designing a synthesis. It was an awesome experience and made the class that much more amazing. Also the labs went with the material being taught in the Organic Chemistry lecture. I loved this because I would learn about it in class and then experience what I learned in the lab.
>
> I think it would be really fun and educational to do more of the syntheses than the "cookbook" labs.

In typical fashion for this lab, our five enrolled students also took a separate organic chemistry lecture course during the same semester. The final for the lecture course was a normalized, comprehensive ACS exam [28], on which these five students' scores averaged in the 87th national percentile [29]. This exam was not a lab-specific one, but mostly conceptual in nature. However, our redesigned lab structure cannot be ruled out as a contributing factor in students' exemplary comprehension of organic chemistry. Future findings in this area will be shared in a later disclosure.

Conclusions

To create a new course structure that would provide a positive, student-driven research experience, we recently followed the example of Gravert [9] by redesigning our two-semester sophomore organic lab course to include a synthesis project that was chosen, designed, and carried out by students. This resulted in progress toward the total syntheses of JBIR-94 (**1**) and JBIR-125 (**2**) [21], two antioxidative/anticancer compounds with properties comparable to those of α-tocopherol, the active constituent of Vitamin E [22]. Our course redesign has the significant drawback of requiring close supervision by an instructor or TA with experience in synthetic chemistry, narrowing its applicability to smaller class sizes. Its up-front cost is also prohibitive, but can be minimized by employing synthetic steps that involve reagents already available on-site and extending the findings into an accompanying research setting. Despite these shortcomings, the highly positive student feedback, exemplary student performance on an ACS normalized exam [28], and continued research participation by all registered students after the class had ended, are indicative of the beneficial nature of this type of classroom approach.

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Description of Supporting Materials

The Supporting Materials include full experimental details (including spectroscopic data, full-color photographs, and illustrations), written with sufficient clarity to be employable in synthetic lab courses, for the following transformations: **3 → 4** and **4 → 5** from Scheme 1, and **8 → 9** and **9 → 10** from Scheme 2. It also includes full copies of student evaluations, which were administered using the IDEA Center Student Ratings system [27], course syllabi, and a detailed cost breakdown.

References

1. For examples, see: (a) Holt, C. E.; Abramoff, P.; Wilcox, L. V.; Abell, D. L. Investigative Laboratory Programs in Biology: A Position Paper of the Commission on Undergraduate Education in the Biological Sciences. *BioScience*. **1969**, *19*, 1104-1107. (b) Venkatachelam, C.; Rudolph, R. W. Cookbook versus creative chemistry: A new approach to research-oriented general chemistry laboratory. *J*. *Chem*. *Educ*. **1974**, *51*, 479-482. (c) Wade, Jr. L. G. Chemistry without a cookbook: An effective alternative. *J*. *Chem*. *Educ*. **1979**, *56*, 825-826. (d) Pickering, M. A physical chemist looks at organic chemistry lab. *J*. *Chem*. *Educ*. **1988**, *65*, 143-144. (e) Potter, N. H.; McGrath, T. F. Getting away from the cookbook in the organic laboratory. *J*. *Chem*. *Ed*. **1989**, *66*, 666-667. (f) Ruttledge, T. R. Organic Chemistry Lab as a Research Experience. *J*. *Chem*. *Educ*. **1998**, *75*, 1575-1577. (g) Domin, D. S. A

Review of Laboratory Instruction Styles. *J*. *Chem*. *Ed*. **1999**, *76*, 543-547. (h) Mohrig, J. R. The Problem with Organic Chemistry Labs. *J*. *Chem*. *Educ*. **2004**, *81*, 1083-1085. (i) Monteyne, K.; Cracolice, M. S. What's Wrong with Cookbooks? A Reply to Ault. *J*. *Chem*. *Educ*. **2004**, *81*, 1559-1560. (j) Bruck, L. B., Bretz, S. L. & Towns, M. H. Cosmochemistry: Introduction. *J*. *Chem*. *Ed*. **2008**, *38*, 52–58. (k) Brownell, S. E.; Kloser, M. J.; Fukami, T.; Shavelson, R. Engaging Undergraduates Through Interdisciplinary Research in Nanotechnology. *J*. *College Science Teaching*. **2012**, *41*, 36-45. (l) Un-cooking the Lab: A Guide to Constructing Inquiry-based Labs in Biology. The Wisconsin Program for Scientific Teaching. University of Wisconsin-Madison. http://scientificteaching.wisc.edu/documents/Uncook_handout.pdf (accessed Aug 20, 2013).

2. (a) Newton, T. A.; Tracy, H. J.; Prudenté, C. A Research-Based Laboratory Course in Organic Chemistry. *J*. *Chem*. *Educ*. **2006**, *83*, 1844-1849. (b) Browne, L. M. Teaching Introductory Organic Chemistry: A Problem-Solving and Collaborative-Learning Approach. *J*. *Chem*. *Educ*. **1999**, *76*, 1104-1107. (c) Gallet, C. Problem-Solving Teaching in the Chemistry Laboratory: Leaving the Cooks... *J*. *Chem*. *Educ*. **1998**, *75*, 72-77. (d) Kroll, L. Teaching the research process via organic chemistry lab projects. *J*. *Chem*. *Ed*. **1985**, *62*, 516-518.
3. Lazarowitz, R.; Tamir, P. In *Handbook of Research on the Science of Teaching and Learning*; Gable, D.; Ed.; MacMillan: New York, 1994; pp. 94–121.
4. (a) Lopatto, D. Undergraduate Research Experiences Support Science Career Decisions and Active Learning. *CBE – Life Sciences Education*. **2007**, *6*, 297-306. (b) Seymour, E.; Hunter, A.-B.; Laursen, S. L.; Deantoni, T. Establishing the benefits of research experiences for

undergraduates in the sciences: First findings from a three-year study. *Sci*. *Educ*. **2004**, *88*, 493-534.

5. (a) Weaver, G. C.; Russell, C. B.; Wink, D. J. Inquiry-based and research-based laboratory pedagogies in undergraduate science. *Nature Chemical Biology*. **2008**, *4*, 577-580. (b) Cummins, R. H. "Prompted" Inquiry-Based Learning in the Introductory Chemistry Laboratory. *J*. *Chem*. *Educ*. **2004**, *81*, 239-241. (c) Wood, W. B. Inquiry-Based Undergraduate Teaching in the Life Sciences at Large Research Universities: A Perspective on the Boyer Commission Report. *CBE Life Sciences Education*. **2003**, *2*, 112-116. (d) Grant, A.; Latimer, D. Bromination and Debromination of Cholesterol: An Inquiry-Based Lab Involving Structure Elucidation, Reaction Mechanism, and 1H NMR. *J*. *Chem*. *Educ*. **2003**, *80*, 670-671.
6. (a) Herman, C. Inserting an Investigative Dimension into Introductory Laboratory Courses. *J*. *Chem*. *Educ*. **1998**, *75*, 70-72. (b) Kharas, G. B. A New Investigative Sophomore Organic Laboratory Involving Individual Research Projects. *J*. *Chem*. *Educ*. **1997**, *74*, 829-831. (c) Kharas, G. B. A New Investigative Laboratory for Introductory Organic Chemistry Involving Polymer Synthesis and Characterization. *J*. *Chem*. *Educ*. **1995**, *72*, 534-535.
7. (a) Livengood, K.; Lewallen, D. W.; Leatherman, J.; Maxwell, J. L. The Use and Evaluation of Scaffolding, Student Centered-Learning, Behaviorism, and Constructivism To Teach Nuclear Magnetic Resonance and IR Spectroscopy in a Two-Semester Organic Chemistry Course. *J*. *Chem*. *Educ*. **2012**, *89*, 1001-1006. (b) Draper, A. J. Integrating Project-Based Service-Learning into an Advanced Environmental Chemistry Course. *J*. *Chem*. *Educ*. **2004**, *81*, 221-224. (b) Kandel, M. Personalized Lab Experiences through Cooperative Projects. *J*.

Chem. *Educ*. **1994**, *71*, 513. (c) Research Experiences to Enhance Learning (REEL). http://www.ohio-reel.osu.edu/evaluation.php (accessed Aug 20, 2013).

8. Horowitz, G. The State of Organic Teaching Laboratories. *J*. *Chem*. *Educ*. **2007**, *84*, 346-353.
9. Gravert, D. J. Two-Cycle Organic Chemistry and the Student-Designed Research Lab. *J*. *Chem*. *Educ*. **2006**, *83*, 898-901.
10. This course used the following text: Mohrig, J. R.; Hammond, C. N.; Schatz, P. F.; Morrill, T. C. *Modern Projects and Experiments in Organic Chemistry: Miniscale and Standard Taper Microscale;* W. H. Freeman and Co.: New York, 2003; Vol. 2.
11. See (a) How to Choose a Synthesis Target and Search Current Literature. http://www.youtube.com/watch?v=Cv86ZNKnnOU&list=PLBwHfJmqJz5i86aUIHzY6q4kURaGNdokv&index=3 (accessed Jun 10, 2013). (b) How to Use SciFinder Scholar. http://www.youtube.com/watch?v=1B9v34LgAzM&list=PLBwHfJmqJz5i86aUIHzY6q4kURaGNdokv&index=2 (accessed Jun 10, 2013). (c) How to Design a Total Synthesis. http://www.youtube.com/watch?v=9jRfAJJO7mM&list=PLBwHfJmqJz5i86aUIHzY6q4kURaGNdokv&index=4 (accessed Jun 10, 2013).
12. The molecules chosen by this student were oleanolic acid, myricetin, kaempferol, and kaempferol-7-methyl ether.
13. (a) Barrie, A. Body Armor Made from Spider Silk. *Discovery News* [Online] Jan 15, 2012. http://news.discovery.com/tech/body-armor-spider-silk-121015.html (accessed Aug 20, 2013). (b) Gosline, J. M.; DeMont, M. E.; Denny, M. W. The structure and properties of spider silk. *Endeavour*. **1986**, *10*, 37-43. (c) Vollrath, F.; Knight, D. P. Liquid crystalline spinning of spider silk. *Nature* **2001**, *410*, 541-548.

14. Vidal, V.; Potterat, Ol; Louvel, S.; Hamy, F.; Mojarrab, M.; Sanglier, J.-J.; Klimkai, T.; Hamburger, M. Library-Based Discovery and Characterization of Daphnane Diterpenes as Potent and Selective HIV Inhibitors in Daphne gnidium. *J*. *Nat*. *Prod*. **2012**, *75*, 414-419.
15. Festa, M.; Capasso, A.; D'Acunto, C. W.; Masullo, M.; rossi, A. G.; Pizza, C.; Piacente, S. Xanthohumol Induces Apoptosis in Human Malignant Glioblastoma Cells by Increasing Reactive Oxygen Species and Activating MAPK Pathways. *J*. *Nat*. *Prod*. **2011**, *74*, 2505-2513.
16. Stierle, A. A.; Stierle, D. B.; Girtsman, T. Caspase-1 Inhibitors from an Extremophilic Fungus That Target Specific Leukemia Cell Lines. *J*. *Nat*. *Prod*. **2012**, *75*, 344-350.
17. Shiu, W. K. P.; Rahman, M. M.; Curry, J.; Stapleton, P.; Zloh, M.; Malkinson, J. P.; Gibbons, S. Antibacterial Acylphloroglucinols from Hypericum olympicum. *J*. *Nat*. *Prod*. **2012**, *75*, 336-343.
18. Clark, V. C.; Harinantenaina, L.; Zeller, M.; Ronto, W.; Rocca, J.; Dossey, A. T.; Rakotondravony, D.; Kingston, D. G. I.; Shaw, C. An Endogenous Bile Acid and Dietary Sucrose from Skin Secretions of Alkaloid-Sequestering Poison Frogs. *J*. *Nat*. *Prod*. **2012**, *75*, 473-478.
19. Shook, B. C.; Rassnick, S.; Wallace, N.; Crooke, J.; Ault, M.; Chakravarty, D.; Barbay, J. K.; Wang, A.; Powell, M. T.; Leonard, K.; Alford, V.; Scannevin, R. H.; Carroll, K.; Lampron, L.; Westover, L.; Lim, H.-K.; Russell, R.; Branum, S.; Wells, K. M.; Damon, S.; Youells, S.; Li, X.; Beauchamp, D. A.; Rhodes, K.; Jackson, P. F. Design and Characterization of Optimized Adenosine A2A/A1 Receptor Antagonists for the Treatment of Parkinson's Disease. *J*. *Med*. *Chem*. **2012**, *55*, 1402-1417.

20. Peng, J.; Hartley, R. M.; Fest, G. A.; Mooberry, S. L. Amyrisins A–C, O-Prenylated Flavonoids from Amyris madrensis. *J*. *Nat*. *Prod*. **2012**, *75*, 494-496.

21. Kawahara, T.; Izumikawa, M.; Otoguro, M.; Yamamura, H.; Hayakawa, M.; Takagi, M.; Shin-ya, K. JBIR-94 and JBIR-125, Antioxidative Phenolic Compounds from Streptomyces sp. R56-07. *J*. *Nat*. *Prod*. **2012**, *75*, 107-110.

22. (a) Poiroux-Gonord, F.; Bidel, L. P. R.; Fanciullino, A.-L.; Gautier, H.; Lauri-Lopez, F.; Urban, L. Health Benefits of Vitamins and Secondary Metabolites of Fruits and Vegetables and Prospects To Increase Their Concentrations by Agronomic Approaches. *J*. *Agric*. *Food Chem*. **2010**, *58*, 12065-12082. (b) Hyatt, J. A.; Kottas, G. S.; Effler, J. Development of Synthetic Routes to d,l-α-Tocopherol (Vitamin E) from Biologically Produced Geranylgeraniol. *Org*. *Process Res*. *Dev*. **2002**, *6*, 782-787. (c) Kamil, A.; Chen, C.-Y. O. Health Benefits of Almonds beyond Cholesterol Reduction. *J*. *Agric*. *Food Chem*. **2012**, *60*, 6694-6702 (d) Pietta, P.-G. Flavonoids as Antioxidants. *J*. *Nat*. *Prod*. **2000**, *63*, 1035-1042.

23. Arterburn, J. B.; Pannala, M.; Gonzalez, A. M.; Chamberlin, R. M. Palladium-catalyzed transfer hydrogenation in alkaline aqueous medium. *Tetrahedron Lett*. **2000**, *41*, 7847-7849.

24. Boschi, D.; Tron, G. C.; Lazzarato, L.; Chegaev, K.; Cena, C.; Di Stilo, A.; Giorgis, M.; Bertinaria, M.; Fruttero, R.; Gasco, A. NO-Donor Phenols: A New Class of Products Endowed with Antioxidant and Vasodilator Properties. *J*. *Med*. *Chem*. **2006**, *49*, 2886-2897.

25. Denton, R. M.; Scragg, J. T.; Saska, J. A concise synthesis of 4′-O-methyl honokiol. *Tetrahedron Lett*. **2011**, *52*, 2554-2556.

26. *N*-[4-[(3-aminopropyl)amino]butyl]-acetamide, CAS #13431-24-8.

27. The IDEA Center Home Page. http://www.theideacenter.org/ (accessed Aug 20, 2013).

28. ACS Division of Chemical Education Examination: Organic Chemistry, Stock Code OR08.

29. Christiansen, M. A. “Reflections on Flip-Teaching in Undergraduate Organic Chemistry.” 6th Annual Provost’s Series on Instructional Excellence at Utah State University, Logan, UT, United States, February 26, **2013**. https://www.youtube.com/watch?v=LHpnM17l-Xk (accessed Aug 20, 2013).