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Distributed Drug Discovery: Advancing Chemical Education through Contextualized Combinatorial Solid-Phase Organic Laboratories

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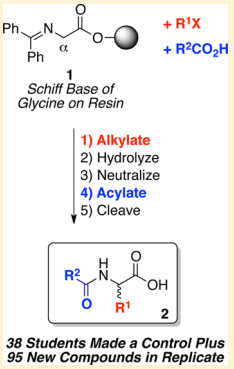
Supporting Information

ABSTRACT: The Distributed Drug Discovery (D3) program trains students in three drug discovery disciplines (synthesis, computational analysis, and biological screening) while addressing the important challenge of discovering drug leads for neglected diseases. This article focuses on implementation of the synthesis component in the second-semester undergraduate organic laboratory. The educational program was started at IUPUI in 2003 and has been carried out over 23 semesters with 65 lab sections by >1200 students. Since the chemistry component is most advanced, it serves as a model for the computational and biological modules in development. Synthetic procedures are based on well-documented, reproducible solid-phase combinatorial chemistry. They are carried out in a 2 × 3 combinatorial grid (Bill-Board) to create a control molecule and five new products (50 μmol scale, ∼10−20 mg product, typically high LC/MS purity). The first of these synthetic procedures (D3 Lab 1) utilizes a protected and activated derivative of glycine that is converted in a five-step synthetic sequence (alkylation, hydrolysis, neutralization, acylation, and cleavage from the resin) to N-acylated unnatural amino acids containing two variable diversity elements: a new α-side chain and an *N*-acyl group. Based on these combinatorial procedures, large virtual libraries/catalogs of student-accessible molecules can be created and computationally analyzed. Selected molecules are then synthesized and screened by D3 students. Active classroom learning experiences and recorded lectures or demonstrations are used to teach fundamental knowledge and skills in synthesis while enabling students to pursue, with no predetermined outcome, multidisciplinary, distributed, research-based experiments toward drug-lead discovery.



KEYWORDS: *Second-Year Undergraduate, Laboratory Instruction, Organic Chemistry, Hands-On Learning/Manipulatives, Problem-Solving/Decision Making, Synthesis, Amino Acids, Combinatorial Chemistry, Bioorganic Chemistry, Drugs/Pharmaceuticals*

INTRODUCTION

Students in the Distributed Drug Discovery (D3) program[1−12] are part of a globally "distributed" discovery project seeking potential drugs for neglected diseases.[13,14] At the same time, they are educated in synthesis, biology, and computational analysis. This article focuses on D3 laboratories in synthetic chemistry (started at IUPUI in 2003), the most highly developed of the components. It serves as a model for the teaching structure and specifications required of D3 lab modules. Complementary laboratories that address the biological (2012) and computational (2013) aspects of D3 are currently being developed.

D3 chemistry seeks to integrate research into the undergraduate lab curriculum. Seymour et al.[15] identified four methods to involve students in research. Of these, integrating research into laboratories early in the undergraduate science experience most closely reflects the guidelines suggested in the recent President's Council of Advisors on Science and Technology (PCAST) report, "Engage to Excel",[16] and by others.[17−19] The most common vehicles to accomplish this goal are problem-[20] or project-based laboratories.[21] While more resource-intense and possibly frustrating due to their open-ended nature,[20−22] it is widely held that these experiences also encourage higher-order cognitive skills,[23,24] ultimately preparing students for independent research.

A major obstacle in problem-based synthesis laboratories is that the published procedures used must first be adapted, typically by students, staff, or faculty. To enable problem solving with new molecules, D3 focuses instead on the application of proven processes. It provides faculty and students with preadapted, student-replicated procedures with combinatorial synthetic possibilities that allow students to select, synthesize, and test many new molecules to answer a given question or solve a particular problem. In this way, D3 chemistry laboratories can teach students, through a combinatorial approach and solid-phase organic synthesis methodology, basic synthetic transformations with an immediate application to problem solving. They learn the key research

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Table 1. Requirements of D3 Synthesis Labs

Procedural and Educational Requirements	Practical Resource Requirements
• Simple procedures based on published work	• Modest expense
• Comprehensive reproducibility by undergraduates	• Low-tech equipment
• Educational value in skills and concepts learned	• Small-scale reactions (50 μmol); scale-up possible
• Enables virtual libraries of biomimetic molecules	• Minimal safety/environmental impact
• Active learning and prelab lecture curricula	• Sample storage protocols
• Report results in D3 online database	• D3 informatics and data management

role of multiple, reproducible experiments with both controls and variables. They are exposed to experimentation with no predetermined outcome and learn to distinguish between "failed" experiments and unexpected results that can lead to significant discoveries. In this way, they learn essential habits of research thought and practice applied to a critically important humanitarian challenge: finding drugs for neglected diseases.

Students use readily mastered, powerful synthetic procedures, equipment, and techniques to make individual members of large, virtual collections/libraries/catalogs (often >20,000)[2,3] of biomimetic molecules. Each molecule prepared can become a problem-solving probe testing predictions of structure-dependent molecule properties—from general physical characteristics to specific drug potential. The synthetic procedures are based on well-documented, reproducible solid-phase chemistry[25,26] carried out in a combinatorial fashion (50 μmol scale, typically 10−20 mg each, six simultaneous reactions) to allow each student or student team to synthesize a control and five new biomimetic molecules. Laboratories that target amino acid or peptide derivatives are particularly valuable in the undergraduate setting.[27−34] We describe our first D3 synthetic lab module (D3 Lab 1) and introduce other D3 laboratories that will be published in the future.

D3 CHEMISTRY LABORATORIES

Requirements

A major goal of D3 is to give undergraduate lab students at small or large institutions, with ample or limited resources, an authentic research process in which critical research habits of thought and practice can be developed. At the same time, the essential role of more traditional laboratories (providing students with opportunities to learn and master organic lab skills and synthetic transformations by successfully synthesizing a known compound) must be maintained. To accomplish these goals, requirements have been established for D3 synthetic laboratories (Table 1).

Meeting these requirements requires appropriate methodology, processes, and equipment. Combinatorial chemistry linked to solid-phase organic chemistry and simple equipment is key to D3's enablement. Informatics and data management provide the crucial links to other disciplinary modules.

Combinatorial Chemistry

Combinatorial chemistry is most powerfully exemplified in nature. All natural DNA sequences are constructed combinatorially from only four nucleotides. These sequences, in three nucleotide packets, then combinatorially encode the construction of all the amino acid sequences in peptides and proteins. Chemists now apply these combinatorial approaches in the laboratory.[1]

D3 synthesis laboratories utilize literature protocols preadapted by independent undergraduate researchers. These protocols support the synthesis of many compounds from variable inputs in a combinatorial process. These procedures facilitate a major goal of D3: enabling students to select and synthesize large numbers of new molecules to test their neglected-disease drug discovery hypotheses.

Solid-Phase Chemistry

The small-scale (10−100 μmol), multistep synthesis of polypeptides can be carried out on a solid support (polystyrene beads).[35] The success of this approach inspired chemists to adapt traditional organic chemistry to solid-phase and combinatorial methodologies. For D3, this is key to shifting the principle focus of organic laboratories from synthesizing one known molecule to allowing students to answer scientific questions by quickly, efficiently, and reproducibly synthesizing many molecular probes to test their research predictions.

A major advantage of solid-phase synthesis (SPS) over its solution-phase counterpart is that multiple synthetic steps (five steps in this lab) can be carried out by simply washing the resin-bound intermediate products with a series of solvents to remove excess reagents, soluble byproducts, and high-boiling solvents. In contrast, solution-phase synthesis typically involves an extractive workup at each step, often followed by purification of intermediate products.

Simple Equipment

To help students inexpensively and efficiently employ solid-phase combinatorial methodology, Bill-Board[1,2,36] equipment (Figure 1) was created (available through http://www.chemglass.com/pages/billboards.asp, accessed February 2015; Supporting Information, p SI-16). Six reactions can be conducted simultaneously in fritted glass reaction vessels. Bill-Board equipment keeps the solid-phase reactions organized in a grid (for potential combinatorial reaction sequences) and simplifies the essential steps of solid-phase synthesis: repeated cycles of reactions and washings followed by final cleavage, product collection, and solvent evaporation. On a typical 50 μmol scale, 50 mg of resin (loading of 1 mmol/g, ∼15 mg of resin-bound starting substrate) is used in each vessel. This leads to approximately 10−15 mg of each product (assuming product molecular weight = 300; yield >70%).

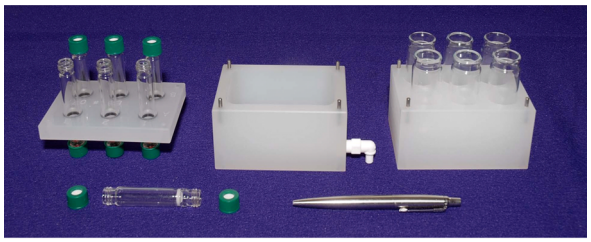

Figure 1. Bill-Board equipment for solid-phase synthesis.

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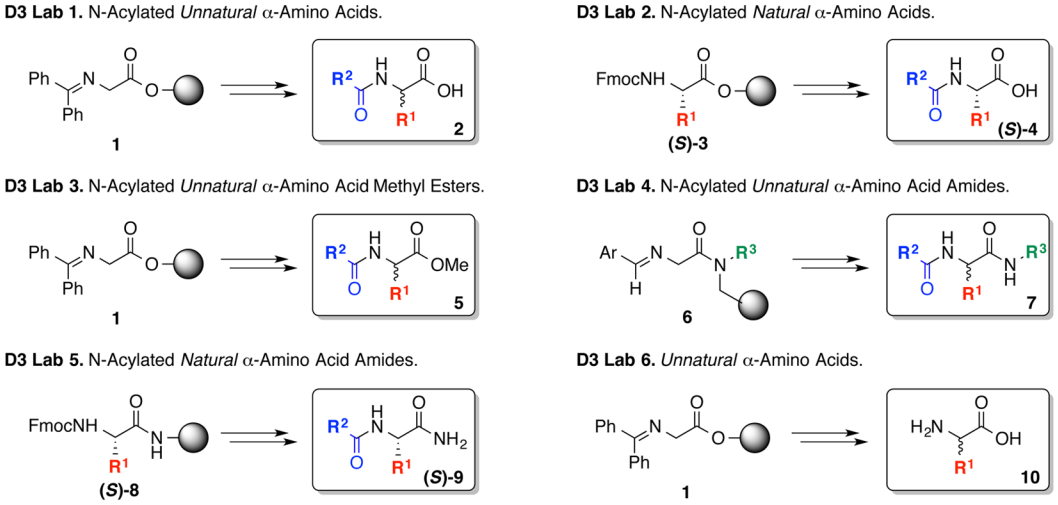
Scheme 1. Operational Distributed Drug Discovery (D3) Laboratories[a]



[a]Separate instances of R^1 and R^2 represent different groups. The numbers relate to different sites of diversity: R^1 = α-carbon substituent; R^2 = acyl group substituent.

Implementing the Synthetic Component

The D3 synthetic component consists of four- to five-period undergraduate organic lab sequences (Scheme 1). It utilizes the basic framework of α-amino acids, the building blocks of life, as combinatorial biomimetic scaffolds on which "sites of diversity" or new groups are added (e.g., new α-side chains, new N-terminal substituents, and/or various carboxylic acid derivatives: $-CO_2H$, $-CO_2Me$, $-CONH_2$, $-CONHR$).

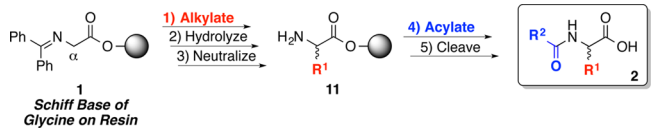
The α-amino acid framework, nitrogen to α-carbon to carbonyl, is ubiquitous in nature and present in many therapeutic agents. A recent *Technology Report* published in this journal[37] presented an online poster of the top 200 pharmaceuticals by number of U.S. prescriptions in 2011. Ten percent (11/116 unique compounds) contain the basic α-amino acid framework, and five of these 11 are D3-like N-acylated α-amino acids, demonstrating the importance of this class of molecules in drug discovery.

The first implementation of D3 (D3 Lab 1, Scheme 1) was conducted in 2003 as part of a second-year undergraduate organic lab course (C344). Since then, it and other modules have been utilized over 23 semesters with 65 lab sections by >1200 students. At IUPUI, independent D3 research has been carried out by 24 undergraduates from IUPUI and elsewhere (Howard University, Morehouse College, Northwestern University, Palacky University Czech Republic). Five additional amino-acid-based D3 chemistry laboratories (Scheme 1) have been developed and implemented. These laboratories are rooted in basic synthetic research[1−4,25,26] adapted by our undergraduate researchers for ready incorporation into existing organic teaching laboratories.

D3 Lab 1

D3-1 will be used to illustrate the process and power of the approach (Scheme 2). It exemplifies how laboratories can be used to educate students in organic synthesis while simultaneously allowing them to participate in scientific research. The first step, alkylation, introduces an unnatural α-side chain (R^1 in red) onto the basic α-amino acid structure. The second diversity element is introduced in the fourth step, an N-acylation (R^2CO in blue). Multiple variations in these two diversity elements are possible, enabling the synthesis of large numbers of biomimetic molecules **2**, as is typical in a combinatorial chemistry protocol.

Scheme 2. D3 Lab 1: Synthesis of N-Acylated *Unnatural* α-Amino Acids



In D3-1, each student or student group prepares a control (A1) plus five new compounds. The five synthetic reactions are accomplished in the reaction vessels of the 2 × 3 Bill-Board grid (Figure 2). The combinatorial aspect of these syntheses,

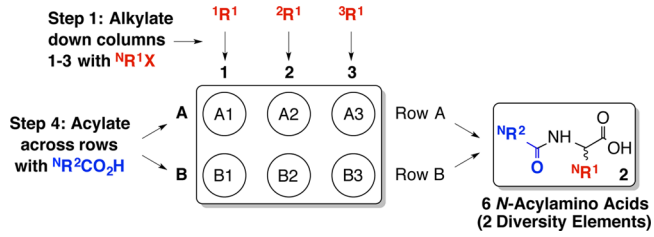


Figure 2. D3 Lab 1: 2 × 3 Bill-Board depicting diversity steps in the synthesis of **2**.

whereby many compounds are generated from a few reagents, is highlighted in red and blue colors (Figure 2, products **2**). Three different alkyl halides are added down columns 1−3 to attach the red α-alkyl groups to the glycine scaffold via alkylation. Then, in the N-acylation reaction, two different carboxylic acids are added across rows A and B to introduce the *N*-acyl groups in blue.

A representative D3-1 synthesis completed by undergraduate C344 students in spring 2009 is shown in detail (Scheme 3). The starting material **1** is the Schiff base of the natural amino acid glycine attached by an ester linkage to the solid-phase Wang resin. The S_N2 alkylation (step 1) is used to attach an α-side chain (red R^1 from **12**) to the α-carbon of glycine (which does not itself possess a side chain). This synthesis results in a

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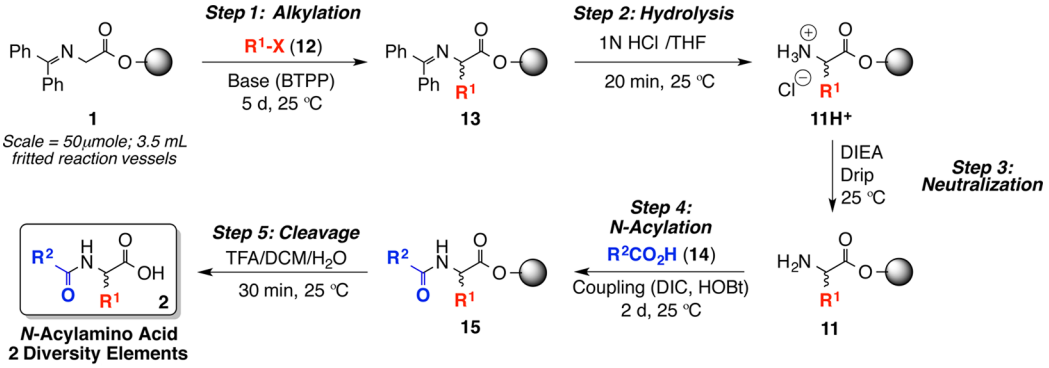
Scheme 3. D3 Lab 1: Synthetic Details To Prepare N-Acylated *Unnatural* α-Amino Acids[a]



[a]Reaction times shown are influenced by laboratory scheduling.

racemic (50:50) mixture of the *R*- and *S*-enantiomeric products **13**, providing easy access to both enantiomers of the target and many amino acid side chains R^1 beyond those present in human proteins. The alkylation is followed by hydrolysis (step 2) to remove the benzophenone Schiff base-protecting and -activating group needed in the first step. Neutralization of the amine salt **11H**$^+$ (step 3) gives **11**, an unnatural amino acid on resin. N-Acylation with carboxylic acid **14** (step 4) condenses the second diversity element, the acyl group (blue R^2CO), to the nitrogen of **11**, thereby forming **15**, the final product on the resin. Cleavage of ester **15** from the resin (step 5) gives the final product **2**, now in solution (see Supporting Information for full details).

Solid-phase synthesis using simple equipment offers a number of advantages over solution-phase chemistry. The ability to carry out, in each of six separate reaction vessels, a five-step synthesis starting with 50 μmols of **1** (12.5 mg of resin-bound $Ph_2C{=}NCH_2CO$) is certainly noteworthy as is the economy of price and safety of microscale chemistry in terms of reactants, reagents, and solvents. Since the four intermediate products are all resin-bound, it is not necessary to workup each reaction in the conventional sense if the chemistry is robust; the resin is simply rinsed after each step with a series of solvents. All of these steps, which include carbon−carbon (step 1) and carbon−nitrogen (step 4) bond constructions, two functional group interconversions (steps 2 and 5), and a neutralization (step 3), are conveniently carried out on solid phase. They represent a wide variety of fundamental chemical transformations (Schemes 2 and 3) that are typically discussed in the organic lecture course but now can be performed in a real lab setting.

HAZARDS

All reagents and solvents should be handled in a well-ventilated hood while wearing the proper personal protective equipment, including safety goggles, gloves, and appropriate shoes and clothing. Research-based laboratories are especially susceptible to safety hazards[22] as more freedom is given to students. Constant oversight is needed in the planning and execution of these laboratories. Key concerns include (1) flammability and toxicity of solvents, (2) toxicity of alkyl halides, (3) care needed in capping/uncapping/transfer processes, (4) use of trifluoroacetic acid, a hazardous, volatile, and lipophilic acid, and (5) neurotoxicity of *n*-hexane[38] (see Supporting Information, p SI-14). The Globally Harmonized System of Classification and Labeling of Chemicals (GHS) is tabulated for this laboratory in the Supporting Information.[39]

RESULTS

The spring 2009 introductory organic D3 Lab 1 demonstrates the power of D3 combinatorial synthesis. Thirty-eight students had access to 39 alkylating agents and 20 acylating agents. In principle, they could have made 780 (39 × 20) different racemic products, though not all combinatorial possibilities were explored in the actual lab. Across two laboratory sections (38 students total), each of 19 students carried out a different combinatorial synthesis to make six unique products—one control and five new compounds (Figure 2). In this fashion, 19 Bill-Boards created 96 unique products (i.e., the control in A1, replicated 19 times, plus 95 new compounds, 5 × 19, in the other five positions). Each of the 19 unique Bill-Boards was replicated by one of the remaining students. This gave a total of 38 samples of replicated A1 (the control) and duplicate samples of all 95 new compounds.

The success of these reactions was measured using a number of analytical techniques: weight of crude product, TLC, LC/MS, and ^{1}H NMR spectroscopy. The crude controls in A1 were purified by very efficient short-column chromatography: purification of 10−15 mg of crude product **2** required only a small amount of eluent (~20 mL *total* hexane[38]/acetone, 500 mg of cyano-silica gel cartridge). The structure of A1 was then confirmed by ^{1}H NMR spectroscopy. Detailed synthetic procedures for D3-1 are provided in the Supporting Information, along with complete lists of the 39 alkyl halides and 20 carboxylic acids used, the 96 replicated product structures synthesized, and the crude yield and purity for each. Overall synthetic results are summarized in Figure 3.

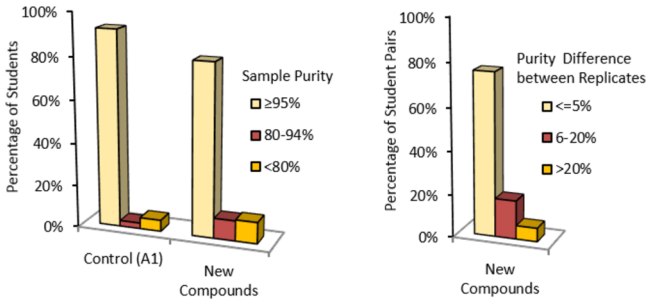


Figure 3. Purity of control (A1) and new compounds (left) and purity difference between student pair replicates of new compounds (right).

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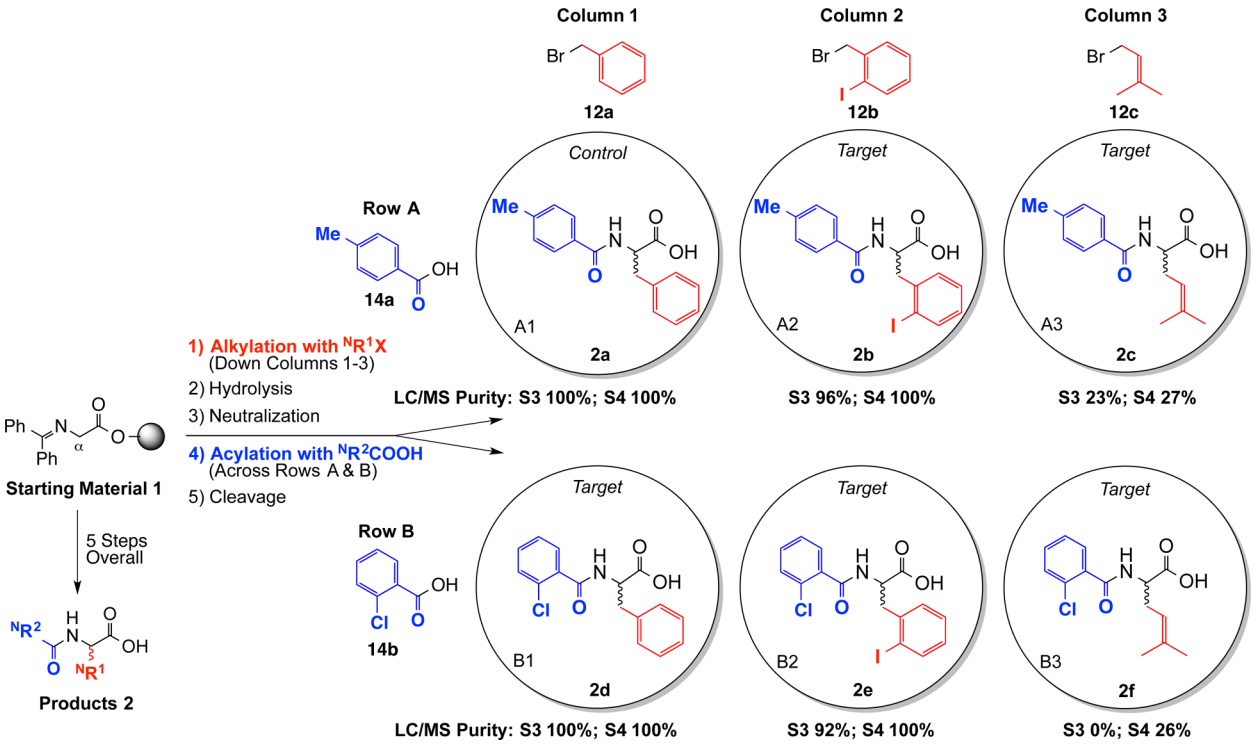
Table 2. D3 Lab 1: Laboratory Skills Gained

Synthesis	Analysis
• Six simultaneous five-step syntheses	• LC/MS analysis (M + H^+, % purity by UV)
• Microscale synthesis (~50 μmol, <20 mg)	• Small column purification (<20 mL solvent)
• Solid-phase synthesis	• Thin-layer chromatography
• Combi-chem synthesis (2 points of diversity)	• ^{1}H NMR analysis of control

Table 3. D3 Labs: Research Habits of Thought and Practice

Habits of Thought	Habits of Practice
• Scientific subjectivity vs objectivity	• Research cycle: observation, hypothesis, prediction, experimentation, and data analysis
• Openness to the unexpected	• Well-documented procedures
• Balancing theory and experimentation	• Experimental design: variables and controls
• Self-corrective scientific mechanism	• Reproducibility and significance
• Ethics in science	

Scheme 4. D3 Lab 1: Replicated Bill-Board Results for Students S3 and S4



DISCUSSION

Control A1 syntheses were almost universally successful, with crude purities routinely reported as 100%. It is unlikely that these samples were 100% pure, as minor LC peaks (<5%) were not included in the integration. Nevertheless, LC traces were remarkably free of other UV-active components. Most of the 95 new compounds were successfully synthesized, with over 90% of the samples showing a peak in the MS consistent with product and UV purity >90%. Crude yields for both control A1 and new compounds were variable, with many over 100% due to two factors: the difficulty of accurately weighing samples in the 15 mg range and the variable presence of residual unevaporated solvent. In current laboratories, a more thorough evaporation is done before weighing. Thus, D3 successfully trained students in numerous lab skills (Table 2).

Research Habits of Thought and Practice

D3 allows students to use these skills quickly and effectively in a way that furthers the development of research habits of thought and practice (Table 3) with potential application to drug discovery. Learning in organic laboratories now becomes a means to an end rather than an end in itself, thus providing opportunities for a more authentic research experience.

One of the 19 Bill-Board sets, produced by students S3 and S4, illustrates how D3 laboratories can uniquely teach students important aspects of the research process (Table 3). In a replicated fashion, these two students used the same alkyl halide (benzyl bromide) and carboxylic acid (4-methylbenzoic acid) in column 1 and row A, respectively, two new alkyl halides (2-iodobenzyl bromide and 2,2-dimethylallyl bromide) in columns 2 and 3, and a new carboxylic acid (2-chlorobenzoic acid) in row B. Compounds made with purities for each crude product are shown in Scheme 4. (Detailed results for S3 and S4, with reproduced LC/MS data for each of the six replicated syntheses and the ^{1}H NMR spectra of their purified A1 controls, are highlighted on pp SI-48−SI-56 of the Supporting Information.)

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The multiple results of students S3 and S4 illustrate several key points:

(1) Students can synthesize the A1 control (**2a**) in good purity, with no other identifiable peaks in the LC/MS trace. They are very reproducible control reactions, demonstrating that students S3 and S4 mastered the experimental protocol. These students also successfully chromatographed A1 and obtained good ^{1}H NMR spectra, consistent with product. These are attributes of a typical, sound undergraduate organic laboratory.

(2) Three out of five of their new compounds (**2b**, **2d**, and **2e**) were synthesized in duplicated good "crude" purity (95 ± 5%), demonstrating that students can readily make new compounds that are pure enough to serve as useful research probes. Clearly, many compounds from the D3 virtual catalogs are amenable to student synthesis. This independent replication of new synthesis results exposes students to a key aspect of sound research practice not traditionally encountered in an undergraduate lab.

(3) The other two compounds, **2c** and **2f** (A3 and B3, respectively), gave poor crude purities (23% for S3-A3, 27% for duplicate S4-A3; 0% for S3−B3, 26% for duplicate S4−B3). These low purities, replicated by two different students with demonstrated competence synthesizing controls and other new compounds, are therefore not "failures" but rather challenges for data interpretation and further student research.

Students are shown that (2) and (3), with the presence of controls and replicated unexpected observations, can lead to authentic research and fundamental discoveries. For example, a replicated "unexpected" observation in one of the D3 laboratories led to publication on the structure-dependent hydrolytic instability of amide bonds in simple N-acylated amino acid amides.[12] New molecules that undergraduate students synthesize in the D3-1 chemistry lab provide problem-solving probes that can be used to further the discovery of drug leads effective against neglected diseases, thus giving context to the students' scientific learning. Subsets of student molecules from the D3-1 lab have been submitted to the NIH for biological screening. Computational and biological screening modules are being developed to complement the synthesis component of D3 and expose students to all aspects of early stage drug discovery: prediction, synthesis, testing, analysis of results, and refinement of predictions.

Problem solving with D3 molecules is not limited to neglected disease drug discovery. Individual educators and students can creatively use D3 laboratories to synthesize molecules to test other student hypotheses as well. For example, students could pursue projects that focus on predicting molecular properties (e.g., R_f on TLC, solubility) or mechanistic questions (reactivity in alkylation or acylation reactions). Other students might choose to improve existing D3 laboratories or even to develop new ones. Some D3 projects involve optimizing a procedure from a safety or ecological perspective.

Students are challenged to employ, discuss, and debate research habits that are rarely addressed in regular laboratories. D3 laboratories facilitate this process by providing students with extensive quality data sets to analyze and the opportunity to test their own hypotheses through subsequent cycles of synthesis and testing. Examples of topics for discussion include:

(1) How can data be manipulated? How might selecting a particular wavelength to determine compound purity by LC/MS increase the apparent purity of the desired compound?
(2) Why are controls and independent replication important?
(3) Do more experiments, with multiple variations, increase the probability of "unexpected" observations?
(4) What is the danger of "selection of the fittest" data in scientific research?

IMPACTS OF D3 ON STUDENT DEVELOPMENT

The evaluation study of the Distributed Drug Discovery (D3) program was conducted by the Center for Urban and Multicultural Education (CUME) at IUPUI. Students in both the experimental D3 laboratories and the control laboratories (synthesis of DEET, *N*,*N*-diethyl-3-methylbenzamide) reported that participation in the laboratories was a positive experience that helped them to learn the intended content. However, survey analysis showed a number of statistically significant gains for D3 participants relative to students in control laboratories. D3 students found the experience to be more relevant to solving real world problems using authentic methods and found the D3 experience to be more engaging than other undergraduate lab experiences. Focus groups with participants indicated that the program strengthened student motivation, provided opportunities for students to think critically and to transfer basic research to applied knowledge, and delivered knowledge regarding procedures of drug development. When interviewed with the question, "*What have you learned that you didn't know before?*", D3 participants were able to articulate many insightful gains. Students indicated that they (1) obtained better understandings of various areas of knowledge in chemistry, seeing how projects are integrated and inter-related; (2) obtained hands-on research experiences, learning to deal with the unknown and with increasing tolerance of dealing with uncertainty; and (3) learned to think autonomously, learning to be more patient, more precise, and more accurate, thus providing a bigger picture for them to see their positions in relation to the larger world.

In summary, D3 promoted positive impacts on student attitudes in science education through promoting student self-growth and motivating student learning by its humanitarian values with practical connections to the real world. Additional details and outcomes are provided in the Supporting Information. In keeping with the PCAST recommendations,[16] the D3 project allows faculty to design educational programs in which critical research habits of thought and practice can be developed with a focus on better preparing their graduates to work in today's world, with an interdisciplinary emphasis on real life problems and solutions.

FINAL NOTE

Our long-term experience with these laboratories allows us to manage the complexity associated with multiple reagents and reactions. Students can still learn most of the concepts and skills when the number of new compounds synthesized is reduced. They can be teamed up in groups of two per Bill-Board, for example, and can be instructed to perform 3- or 4-fold replicated syntheses. When implementing a D3 lab, we recommend starting small, first by testing the lab with one or two independent undergraduates and then expanding as confidence builds. We find it beneficial, both educationally

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and practically, to enlist experienced D3 students as assistants in the expanded laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Detailed D3 Lab 1 procedure; chemical hazards; tables of alkylating and acylating agents, as well as student assignments; LC/MS results for each of the 38 Bill-Boards; LC/MS printouts and sample interpretations for a replicated pair of Bill-Boards with ^{1}H NMR spectra of controls; instructor summary including tasks and timelines as well as a sample spreadsheet of calculations; information about reagents, solvents, alkylating/acylating agents, and miscellaneous procedures. This material is available via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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