Chemistry & Biology, Vol. 9, 535–541, May, 2002, ©2002 Elsevier Science Ltd. All rights reserved. PII S1074-5521(02)00143-6

Teaching Target-Oriented and Diversity-Oriented Organic Synthesis at Harvard University

Crosstalk

Martin D. Burke[1] and Gojko Lalic
Department of Chemistry and Chemical Biology
Harvard University
12 Oxford Street
Cambridge, Massachusetts 02138

Diversity-oriented synthesis presents many formidable challenges to the practitioners of synthetic organic chemistry. Those challenges include the effective *teaching* of this new and evolving discipline to ensure that students are well positioned to begin exploring its full potential. Fortunately, the teaching of synthetic organic chemistry has a rich history in the context of target-oriented synthesis, and this precedent can serve as a strong foundation for meeting the challenges of teaching diversity-oriented synthesis.

Introduction

Since Wohler's pioneering synthesis of urea in 1828 [1], the field of organic chemistry known as "target-oriented synthesis" (TOS) has seen remarkable advancement, and it is now possible to synthesize very complex natural products with ever-increasing efficiency. Critical to this progression has always been the teaching of a new generation of chemists the collective wisdom of their predecessors to enable students to address hitherto unsolved problems and thus continue to advance the frontiers of the science of synthesis. The teaching of synthetic organic chemistry has a rich and evolving history, which has now come to include the challenge of teaching diversity-oriented synthesis (DOS). To meet this challenge, Harvard University offered a new synthesis course dedicated to the topic of DOS in the 2001 fall semester. This Crosstalk article aims to discuss the modern history and recent developments in the teaching of organic synthesis by using the experience at Harvard University as a model.

Target-Oriented Synthesis and Chem 115

Prior to 1960, Harvard had no course dedicated to the topic of organic synthesis; new synthetic transformations were taught in the context of other courses dedicated to topics such as physical chemistry or reaction mechanisms. As a new member of the Harvard faculty, Professor E.J. Corey recalls finding this situation unsatisfactory:

> "Through the 1950's and in most schools even into the 1970's synthesis was taught by the presentation of a series of illustrative (and generally unrelated) cases of actual syntheses. Chemists who learned synthesis by this "case" method approached each problem in an ad hoc way. The intuitive search for clues to the solution of the problem at hand was not guided by effective and consciously applied general problem-solving techniques." [2]

In an effort to change this, in 1957 Corey began to systematize the logic of chemical synthesis in the form of the retrosynthetic-analysis planning algorithm. Prior to this change, planning most syntheses involved selecting starting materials with structural resemblance to the target molecule and then working forward to seek suitable reactions that could convert this starting material into the desired target structure [3]. Conversely, in retrosynthetic analysis, the chemist starts by recognizing key structural elements in a complex target structure and then breaks it down into simpler structures by formally performing chemical reactions in the reverse direction (the reverse of a chemical reaction is called a transform). The iteration of this process can eventually bring the chemist back to simple commercially available or readily synthesized building blocks that can serve as effective starting materials for synthesis of the target molecule. For example, as shown in Figure 1, the natural product estrone (**1**) can be broken down into a simpler structure **2** by applying the *o*-quinonemethide-Diels-Alder transform. In turn, **2** can be rapidly simplified into readily synthesized building blocks **3**, **4**, and **5** by applying the sequence of alkylation and vinyl cuprate conjugate addition transforms. This series of reactions has been used in the forward direction in the laboratory by Kametani and coworkers to synthesize estrone and various unnatural derivatives [4].

Since its conception more than 40 years ago, retrosynthetic analysis has had a profound impact on the field of TOS and has revolutionized the way synthetic organic chemistry is taught. In the fall of 1960, Corey offered a new synthesis course, Chem 115, to graduate students at Harvard University with the goal "to teach the most important and useful synthetic chemistry and how to use it." Very early in the development of Chem 115, Corey began to incorporate the evolving planning algorithm of retrosynthetic analysis into his lectures, and he recalls receiving a very favorable response from his graduate students. Encouraged by this response and guided by continued input from students, Corey worked to fully integrate this planning algorithm into the course; he used it as a scaffold to teach an always-updated collection of the most powerful synthetic transformations and incorporated literature examples to reinforce these strategic concepts. William Roush, a student in Chem 115 in 1974 and now professor of organic chemistry at The University of Michigan, recalls,

> "[Retrosynthetic analysis] was presented to us as a standard part of the course—it clearly was the way that Professor Corey thought about synthesis, and retrosynthetic design was the way he taught us to think about the subject. The project that I pursued as a graduate student in Woodward's group was conceived during Corey's Chem 115 class. EJ always concluded a lecture by assigning review articles or other key primary papers for us to read in preparation for his next class. One day somewhere near the middle of the course, Prof. Corey assigned Carlson's 1974 Ann. Rep. Med. Chem. review of the intramolecular Diels-Alder reaction (1974, 9, 270) [5]. At the beginning of the following lecture, EJ put the structure of dendrobine on the blackboard, and I immediately jotted the 'obvious' IMDA retrosynthetic analysis

[1]Correspondence: burke@slsiris.harvard.edu

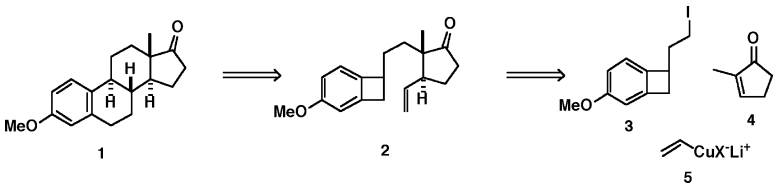


Figure 1. Retrosynthesis of the Natural Product Estrone

In retrosynthetic analysis the chemist starts with a complex target molecule and breaks it down into simpler building blocks by operationally performing chemical reactions in the reverse direction.

(see Figure 2) in my notebook, anticipating that this is what he would present to us in lecture. However, EJ instead described Kende's 1972 synthesis of the alkaloid which involved inter-, and not intra-, molecular Diels-Alder reactions. At the conclusion of the lecture I went to speak with Prof. Corey and asked him if anyone had made the molecule by an intramolecular Diels-Alder reaction. He said that no one had done so, but that someone should. ...Given EJ's supportive comments about the IMDA strategy for dendrobine, I decided that this would be my thesis research project with Prof. Woodward. This also marked the starting point of my fascination with the intramolecular Diels-Alder reaction."

Although the material in Chem 115 continues to evolve, the goals and general structure of the course have remained remarkably similar over the past 40 years. The course objectives, as stated in a recent course syllabus, are "to develop general problem solving skills for the design of synthetic routes to complex molecules; to provide an overview of important modern synthetic transformations" [6]. The biweekly lectures consist in general of three topics: general strategies for synthetic problem solving (retrosynthetic analysis), categorized chemical transformations (e.g., C-C bond-forming reactions, C=C bond forming reactions, transformations of C=C bonds, etc.), and literature examples of target-oriented syntheses that reinforce key concepts. As a result of this organization, students develop a *categorized, expandable toolbox of synthetic transformations* and general retrosynthetic strategies to effectively apply those tools to problems in target synthesis.

Great emphasis is placed throughout the course on the most important unsolved problems in TOS. When asked about his memories of his experience as a student in Chem 115 in 1965, Gary Posner, now professor of organic chemistry at Johns Hopkins University, recalls, "E.J. Corey challenged the students right from the first day ... to appreciate that, despite the vast amount of current knowledge and mechanistic understanding at any given time, the future will reveal at an incredibly fast pace significant new information and insights. Further, he insisted that we, the graduate students at that time, would be the future pioneers and discoverers of such new scientific advances." Andrew Myers, a student in Corey's course in 1981 and now professor of organic chemistry and instructor of Chem 115 at Harvard, echoes this same challenge to a new generation of synthetic chemists. Students are encouraged to continually strive for improvement of the field of TOS by regarding less successful syntheses as starting points for the pursuit of new methodology and seeking to develop more selective, efficient, functional-group-tolerant, and environmentally friendly reagents to effect known transformations.

Students are evaluated on their performance in Chem 115 in two ways, a series of three exams and a final project. Both focus heavily on problem solving, rather than recitation of memorized lecture material, and require students to integrate synthetic problem-solving skills with a broad knowledge base of synthetic transformations. The structure of the exams has remained remarkably similar over the years, each consisting of a single page containing several target structures and instructions to provide detailed synthetic routes to a selected subset of these targets [7]. The independent final project challenges students to choose a target molecule from the literature, perform a retrosynthetic analysis, and present a detailed and referenced synthetic route. Grading for the final project places a heavy emphasis on problem selection as well as the demonstration of synthetic problem-solving skills and a mastery of the course material. Upon completing the course, students are well positioned to begin independently updating their own categorized, expandable toolbox of synthetic transformations and applying that set of tools toward new frontiers in TOS.

Diversity-Oriented Synthesis and Chem 117

In addition to the problems that remain in the context of TOS, the field of synthetic organic chemistry has begun to confront another set of challenges. The *targets* of TOS are most often natural products, molecules discovered by nature through many cycles of diversity generation and natural selection. There is rapidly growing enthusiasm in both academia and industry about the possibility of circumventing nature in this discovery process by generating large, diverse collections of synthetic molecules and using high-throughput screening (HTS) to discover solutions to otherwise intractably complex problems in chemistry, biology, and medicine. However, there is a key bottleneck in this screening-based discovery process—the chemists' inability to efficiently synthesize large collections of molecules with high levels of complexity and diversity. Meeting this formidable challenge is the goal of DOS.

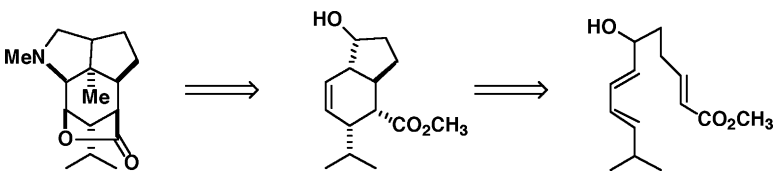


Figure 2. W.R. Roush's Retrosynthesis of (+)-Dendrobine

Roush conceived this retrosynthesis during a Chem 115 lecture in 1974. See text for details.

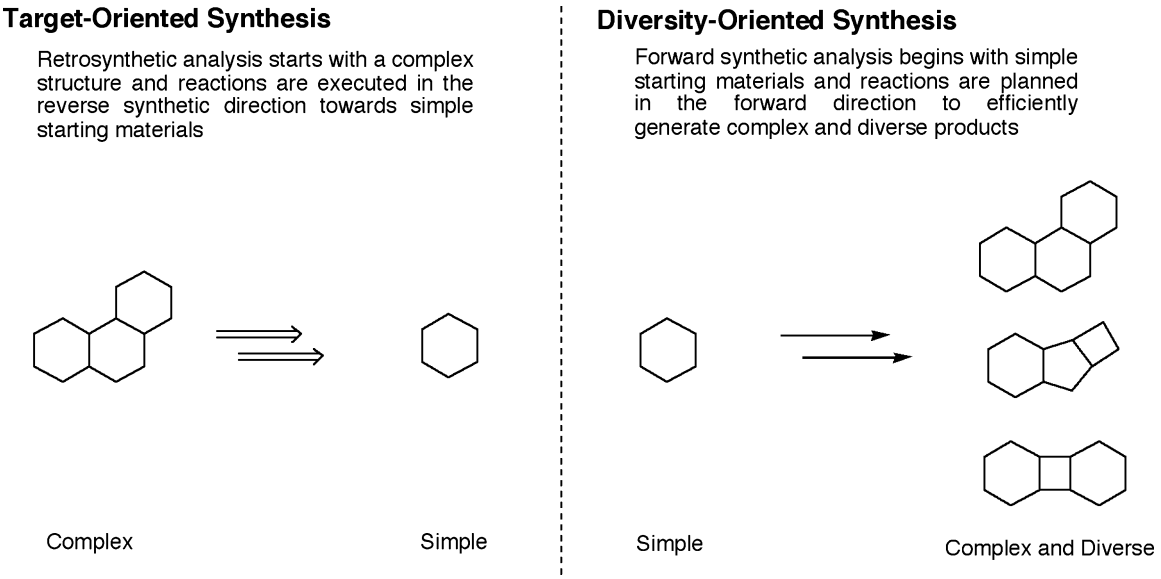


Figure 3. Planning Target-Oriented and Diversity-Oriented Syntheses

Target-oriented and diversity-oriented syntheses involve planning synthetic pathways in opposite directions.

In TOS the goal is to synthesize a particular target molecule; retrosynthetic planning starts with a complex target structure, and reactions are executed in the reverse-synthetic direction toward simple starting materials. In DOS the chemist instead aims to synthesize efficiently pure compounds that collectively comprise a "library" with maximal structural complexity and diversity. Therefore, because there is no particular target structure in DOS, the planning algorithm of retrosynthetic analysis is ineffective in this context. As a result, problems in DOS have thus far been approached in a rather ad hoc way. Recognizing that designing diversity-oriented syntheses requires synthetic planning in the *forward* direction, Stuart Schreiber, professor of organic chemistry at Harvard, has proposed and begun to develop a *forward synthetic analysis*, which aims to assist in the design of synthetic pathways that maximize *complexity, diversity, and efficiency* (see Figure 3) [8].

In the evolving algorithm of forward synthetic analysis, complexity is generated via tandem complexity-generating reactions and conformational analysis, and the problem of diversity is subdivided into three key elements: building blocks, stereochemistry, and molecular skeleton (See Figure 4). Demonstrating the efficient generation of building-block diversity, Matthew Shair, professor of organic chemistry at Harvard University, recently reported the synthesis of a library of ~3000 unique small molecules in which a core skeleton resembling the structure of the natural product galanthamine was orthogonally functionalized with four diverse sets of building blocks [9]. These building blocks included primary alcohols, thiols, aldehydes, acid chlorides, isocyanates, hydrazines, and hydroxylamines (see Figure 4A).

Generating high levels of stereochemical and skeletal diversity is especially challenging. Shair emphasizes that "in order to achieve stereochemical diversity, reagent-based stereocontrol is crucial. For instance, if you wanted to construct a collection of polyketide-like molecules where every possible stereoisomer was represented in the library, you could not rely on substrate-based control since each substrate might react with a different diastereoselectivity to an achiral reagent. Therefore, you would need very powerful reagents that could override the inherent biases of the substrate to deliver a single diastereomeric product." In an early example demonstrating the power of reagent-based stereocontrol to achieve stereochemical diversity, Sharpless and Masamune used the Sharpless asymmetric epoxidation to override substrate bias and achieve the synthesis of all eight naturally occurring hexoses (see Figure 4B; [10]).

Schreiber has proposed one strategy for achieving skeletal diversity in the form of *branching reaction pathways*, in which a single molecular skeleton is exposed to different reaction conditions to effect unique rearrangements into alternative skeletons [11]. For example, as shown in Figure 4C, exposure of a functionalized 12-membered ring skeleton to either the epoxidizing reagent dimethyl dioxirane or the sequence of alkylation, epoxidation, and base-mediated rearrangement produces alternative molecular skeletons.

Realizing the full potential of DOS will require chemists to meet many formidable scientific as well as educational challenges. To address the latter, Shair taught a new synthesis course, Chem 117 [12], in the 2001 fall semester at Harvard University. This new course aims to complement Chem 115 and teach the fundamentals of organic synthesis in the context of DOS and forward synthetic analysis.

Shair says his goals for Chem 117 are to teach students the important chemistry and planning strategies that they can use to independently design efficient syntheses that maximize complexity and diversity. The topics of the biweekly lectures include the evolving algorithm of forward synthetic analysis, complexity-generating re-

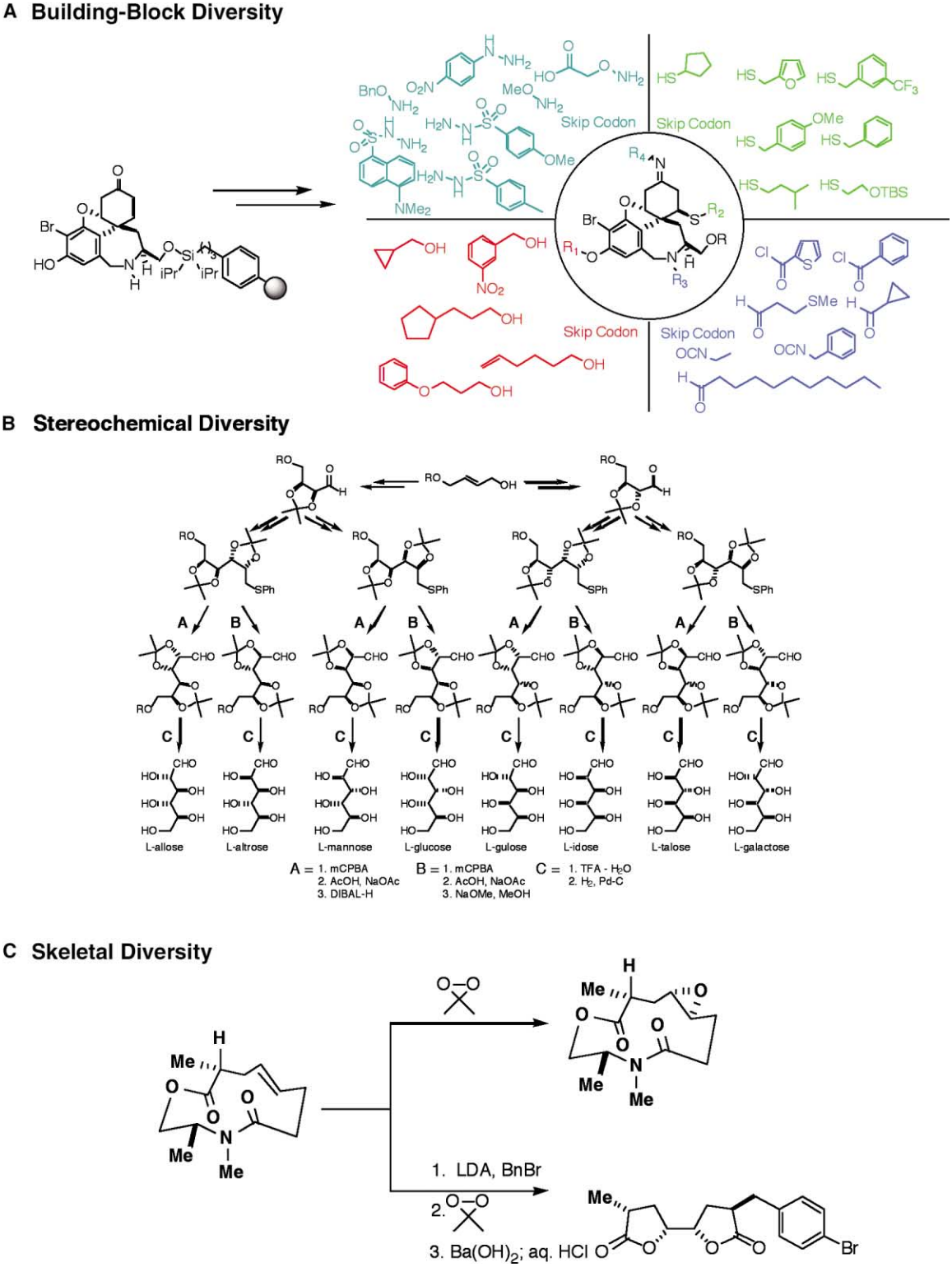


Figure 4. Three Elements of Molecular Diversity: Building Blocks, Stereochemistry, and Molecular Skeleton

In Forward Synthetic Analysis, the Problem of Diversity Is Subdivided into Three Key Elements: Building Blocks, Stereochemistry, and Molecular Skeleton

(A) Shair's diversity-oriented synthesis of ~3000 unique small molecules in which a core skeleton resembling the structure of the natural product galanthamine was orthogonally functionalized with four sets of building blocks.

(B) In an early example of achieving stereochemical diversity, Sharpless and Masamune used the Sharpless asymmetric epoxidation to override substrate bias and achieve the synthesis of all eight naturally occurring hexoses.

(C) Schreiber has demonstrated the potential of "branching pathways" to generate skeletal diversity; exposure of a functionalized 12-membered ring skeleton to either the epoxidizing reagent dimethyl dioxirane or the sequence of alkylation, epoxidation, and base-mediated rearrangement produces alternative core skeletons.

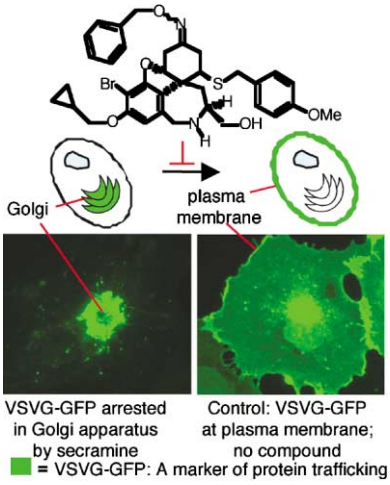
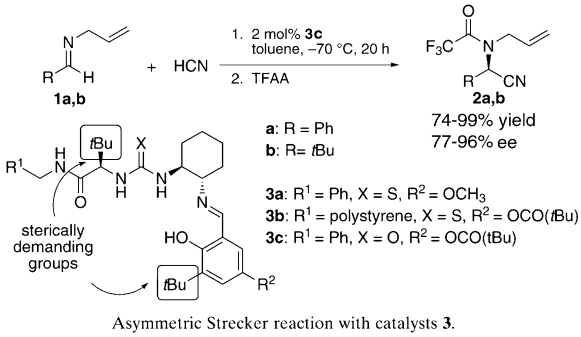


Figure 5. DOS and HTS Used to Discover a Modulator of a Biological Pathway

The products of the DOS presented in Figure 4A were used in a cell-based phenotypic screen to discover the molecule "secramine" that blocks protein trafficking from the Golgi apparatus to the plasma membrane.



Asymmetric Strecker reaction with catalysts **3**.

Figure 6. DOS and HTS Used to Discover an Asymmetric Catalyst

Jacobsen and coworkers used DOS/HTS to discover an unprecedented metal-free Schiff base catalyst that effects the highly asymmetric Strecker reaction on a broad range of substrates in high yield.

actions, diversification strategies, and HTS strategies. Recognizing Nature as the master of DOS, the course concludes with a series of lectures on the diversity-generating pathways found in biological systems. Following the model of Chem 115, Chem 117 highlights literature examples that reinforce various key concepts and demonstrate some early successes in the application of DOS/HTS to discover molecules with new and useful properties. For example, Yan Feng and Tomas Kirchhausen at the Harvard Institute for Chemistry and Cell Biology developed a cell-based phenotypic assay designed to identify molecules that perturb protein trafficking through the secretory pathway. In theory, such a small molecule could serve as a valuable tool for dissecting this important piece of cellular physiology. In collaboration with the Shair lab, Feng and Kirchhausen screened the library of galanthamine-like small molecules (see Figure 4A) in this assay and identified a library member, now called "secramine," with the ability to block protein trafficking from the Golgi apparatus to the plasma membrane (see Figure 5) [9].

The use of DOS/HTS has also been successful in the context of catalyst discovery. Jacobsen et al. used DOS to construct a library of Schiff base-metal complexes and then screened the library for asymmetric catalysis of the Strecker reaction [13]. The non-metal-ligated Schiff bases were also included in the catalyst screen and were surprisingly discovered to effect the highest degree of asymmetric induction. Subsequent optimization led to a metal-free Schiff base catalyst that effects the highly asymmetric Strecker reaction on a broad range of substrates in high yield (see Figure 6).

Mirroring Chem 115, Chem 117 places great emphasis on the many unsolved problems in DOS. For example, Shair challenges the students to think about proposing a synthetic plan that would yield a spatially arrayed collection of pure and unique compounds that have the complexity of, for example, palytoxin and that represent a complete set of all possible stereoisomers, without the benefit of purification of the various synthetic intermediates. Additionally, students are challenged to design a synthetic pathway that would yield a large, spatially arrayed collection of complex molecules, each of which has a unique molecular skeleton. When one contemplates these questions, it is immediately clear that

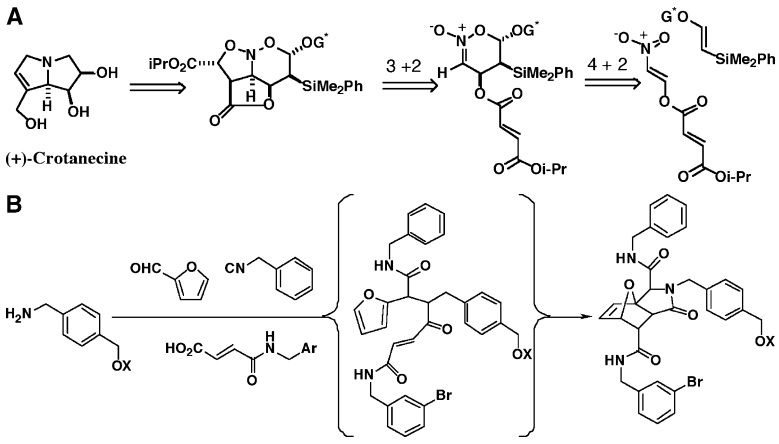


Figure 7. Complexity-Generating Reactions Are Highly Valuable in Both TOS and DOS

(A) Denmark's retrosynthetic analysis of (+)-crotanecine involving tandem application of transforms corresponding to complexity-generating reactions

(B) Schreiber's forward synthetic analysis involving recognition of a pairwise relationship. The product of one *complexity-generating reaction* is the substrate for another.

the challenges are daunting, maybe even beyond reach with current state-of-the-art synthetic methods.

Shair argues, "Practicing DOS on a high level, meaning incorporating concepts of stereochemical diversity and [skeletal] diversity, would require the development of reagents that do not exist today … DOS also requires reagents with selectivity beyond stereochemical selectivity. If one is performing split-pool synthesis, there may be thousands of compounds in the reaction vessel at one time. Each of these compounds must react with the reagent with selectivity for a specific site on the molecule and not react with other sites." It is therefore anticipated that pursuing the goals of DOS will promote the discovery of new reactivity and the improvement of known reactions to give nearly quantitative yields, with very high chemo-, regio-, and stereoselectivity. Additionally, achieving these goals will require not only an enhanced ability to assemble complex molecular skeletons rapidly with tandem complexity-generating reactions but also innovative planning strategies for incorporating these reactions into synthetic pathways that maximize complexity, diversity, and efficiency.

Like students in Chem 115, those in Chem 117 are evaluated with three exams and a final project. For the latter, students are asked to choose a challenging problem in chemistry or biology and to propose a DOS and HTS that together have potential to discover molecules that address the chosen problem. In the evaluation of these final projects, a great deal of emphasis is placed on problem selection. In addition, proposals are evaluated on the potential of the proposed synthetic pathway to generate complexity and diversity and the potential for discovery via the proposed screen.

Despite the different problems addressed in TOS and DOS, many synthetic transformations have and will find great utility in both disciplines. For example, in both TOS and DOS, reactions that markedly increase molecular complexity, so-called *complexity-generating reactions,* can be particularly valuable. In TOS, application of the transform corresponding to a complexity-generating reaction allows a complex target structure to be greatly simplified, and tandem application of such transforms can lead to a plan for a remarkably efficient synthesis. For example, in Denmark's retrosynthetic analysis of (+)-crotanecine (Figure 7A), a tandem intramolecular 3 + 2 cycloaddition transform followed by an intermolecular 4 + 2 cycloaddition transform readily converts a crotanecine precursor into simple, readily synthesized building blocks [14]. Likewise, in DOS, for which rapid generation of molecular complexity is a high priority, complexity-generating reactions are critical. Moreover, forward recognition of pairwise relationships in which the product of one complexity-generating reaction is the substrate for another are particularly valuable. For example, as shown in Figure 7B, Schreiber and coworkers have demonstrated that by coupling in the forward direction the complexity-generating Ugi 4-component coupling reaction and a spontaneous intramolecular furan Diels-Alder reaction, one can achieve a high degree of overall structural complexity in a single step [15].

Because of this overlap of utility for synthetic transformations in TOS and DOS, there is great potential for coordinating the structure and content of two courses such as Chem 115 and Chem 117 to allow both expansion and appropriate reinforcement of the chemistry to which students are exposed. Such coordination would allow students taking both courses to acquire a single, consistently categorized, and readily expandable toolbox of synthetic transformations. In addition, students would acquire two different planning algorithms that would assist them in assembling those transformation into efficient synthetic pathways that yield either complex target structures with known or predicted properties or complex and diverse collections of molecules suitable for use with HTS to discover unprecedented molecules with desired properties.

Summary

In addition to the numerous problems that remain unsolved in TOS, synthetic chemists face another set of challenges in the context of DOS. This includes the formidable challenge of teaching this new and evolving discipline. Fortunately, a highly effective teaching model exists for TOS in the form of Chem 115. It is the goal of Chem 117 to draw on the strengths of this model to meet the educational challenges of DOS, and thus empower a new generation of organic chemists to begin exploring its full potential.

***Chemistry & Biology* invites your comments on this topic. Please write to the editors at chembiol@cell.com.**

Acknowledgments

We would like to thank Professors E.J. Corey, Matthew Shair, William R. Roush, Gary H. Posner, Andrew G. Myers, and Stuart L. Schreiber for sharing their memories and insights. We would also like to thank M.-Christina White, Matthew Kanan, Glenn C. Micalizio, Eric Berger, Young-Kwon Kim, Stephen Haggarty, and Henry Pelish for their thoughtful review of this manuscript. The Howard Hughes Medical Institute is gratefully acknowledged for a predoctoral fellowship to M.D.B.

References

1. Solomons, T.W.G. (1992). Organic Chemistry, Fifth Edition. (New York: John Wiley and Sons), pp. 2–3.
2. Corey, E.J., and Cheng, X.-M. (1995). The Logic of Chemical Synthesis. (New York: John Wiley and Sons).
3. Corey, E.J. (1991). The logic of chemical synthesis: multistep synthesis of complex carbogenic molecules (Nobel lecture). Angew. Chem. Int. Ed. Engl., 445–465.
4. Kametani, T., and Nemoto, H., (1981). Recent advances in the total synthesis of steroids via intramolecular cycloaddition reactions. Tetrahedron *37*, 3–16.
5. Carlson. (1974). The intramolecular Diels-Alder reaction in organic synthesis. Ann. Rep. Med. Chem. *9*, 270.
6. Myers, A.G. (1999) Chem 115 Course Handout #1.
7. Exam Archives, Department of Chemistry Library. Harvard University
8. Schreiber, S.L. (2000). Target-oriented and diversity-oriented organic synthesis in drug discovery. Science *287*, 1964–1969.
9. Pelish, H.E., Westwood, N.J., Feng, Y., Kirchhausen, T., and Shair, M.D. (2001). Use of biomimetic diversity-oriented synthesis to discover galanthamine-like molecules with biological properties beyond those of the natural product. J. Am. Chem. Soc. *123*, 6740–6741.
10. Masamune, S., and Sharpless, K.B. (1983). Total synthesis of the L-hexoses. Science *220*, 949–951.
11. Lee, D., Sello, J.K., and Schreiber, S.L. (1999). A strategy for macrocyclic ring closure and functionalization aimed toward split-pool synthesis. J. Am. Chem. Soc. *121*, 10648–10649.

12. Harvard University. Chem 117. http://www.courses.fas.harvard.edu/~chem117.
13. Sigman, M.S., and Jacobsen, E.N. (1998).) Schiff base catalysts for the asymmetric strecker reaction identified and optimized from parallel synthetic libraries. J. Am. Chem. Soc. *120*, 4901–4902.
14. Denmark, S.E., and Thorarensen, A. (1997). Tandem [4+2]/[3+2] cycloadditions of nitroalkanes. 11. The synthesis of (+)-crotanecine. J. Am. Chem. Soc. *119*, 125–137.
15. Lee, D., Sello, J.K., and Schreiber, S.L. (2000). Pairwise use of complexity-generating reactions in diversity-oriented organic synthesis. Org. Lett. *2*, 709–712.