Experiments and Theory in the Preparative Sciences

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In this essay I consider, by way of the reflections of accomplished synthetic chemists, how the experimental work of the synthetic organic chemist supports the testing, refinement, and creation of theories of organic chemistry. The role of experiments in modern Baconian sciences like organic chemistry is contrasted with their role in fields of more traditional philosophical concern, such as experimental physics.

> Organic synthesis is healthy, its achievements measure for us the power and maturity of organic chemistry as a whole. (Woodward 1956, 158)

1. Toward a Philosophy of Experiment for Modern Baconian Sciences. Thomas Kuhn famously distinguished two traditions in the development of science. The classical, or mathematical, tradition had its origins in Greek science but persisted into the nineteenth century. This tradition required "little refined observation and even less experiment" (Kuhn 1977, 38) and, instead, attempted to develop mathematical theories of natural phenomena based largely on everyday observations. By contrast, the experimental, or Baconian, tradition "wished to see how nature would behave under previously unobserved, often previously non-existent, circumstances" (43). Scientists in this tradition downplayed the role of pure theory, scorned thought experiments, and instead aspired to "power over nature through manipulative and instrumental techniques" (59). Kuhn used his distinction both to pro-

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vide a bifurcated account of the scientific revolution and to identify the origin of modern physics in the gradual "lowering of the barriers, both conceptual and institutional" (62) between these traditions. While it might be correct to understand modern physics as a fusion of these two traditions, there are other modern sciences whose Baconian origins remain more prominent. Unfortunately, although these modern Baconian sciences constitute, by some estimates (Schummer 1997, 81–94), 90% of scientific activity, they have received little philosophical attention. This is particularly disturbing in the philosophy of experiment because, if Kuhn is right, the Baconian tradition is, historically, the ultimate source of the prominent place of experiment in contemporary science.

Modern philosophical work on scientific experimentation may be conceived of largely as the reawakening of philosophical interest in the Baconian origins of modern natural science. From this point of view, as Tiles (1993, 471) puts it, "the Baconian point is not that a properly conducted science studies only human products and human interventions, but that it must study a range of phenomena which include those products and interventions, if it is to achieve full understanding of purely natural objects and natural events."

Recognition of the essential role of human intervention in creating and understanding the phenomena of modern natural science has led to many of the characteristic concerns of the philosophy of experiment. The ubiquitous presence of scientific instruments is, for example, a concrete reminder of Bacon's lesson, while the vexed issue of the relationship between theory and experiment demonstrates the philosophical difficulties of its full assimilation. Though such philosophical work has made admirable efforts to understand scientists' need to "twist the lion's tail" in their investigations, there are other, living aspects of the Baconian tradition that have not been systematically explored. For example, Bacon did not just conceive of the manipulation and control of nature as a tool for generating theoretical understanding; rather, this manipulation and control were themselves the goal of scientific inquiry. He says, for example: "Now the true and the lawful goal of the sciences is none other than this: that human life be endowed with new discoveries and powers" (Bacon 1905, 280; quoted in Tiles 1993, 468). These discoveries and powers were, in turn, the appropriate measure of the epistemological standing of the theoretical products of science. "Practical results are," he claimed, "not only the means to improve well-being but the guarantee of truth" (Bacon 1964, 93; quoted in Tiles 1993, 468). These aspects of Baconianism live on in large swaths of the modern scientific landscape—sciences that in large measure create their own subject matters and evaluate their theoretical products in terms of the manipulative power and control that they provide over that subject matter. These modern Baconian sciences have rich experimental cultures, but this experimental work is not principally devoted to establishing the truth of abstract theory. Instead, both exper-

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imental work and the theories used to rationalize it are principally concerned to expand the range of the scientists' ability to manipulate and control their domain.

Central among, and perhaps representative of, these modern Baconian sciences is what Joachim Schummer has called "preparative chemistry" (1997, 81–94). Chemistry is the most active science (in terms of the number of papers produced per year), and—at least according to Schummer—most chemists are involved in the preparation of substances. The substances produced are for the most part new and do not exist in nature without human intervention. Those substances that do already exist are typically prepared, as in the total synthesis of a natural product, in novel ways. Although "before 1850, organic chemistry could boast of virtually no synthetic achievements" (Woodward 1956, 155), by May 2011 over 60 million chemical substances had been recorded in the Chemical Abstracts Service (CAS) database.[1] Over the course of the twentieth century, not only did the absolute number of synthetic products increase but so did the range. In fact, some chemists were willing to speculate that "there is practically no imaginable small molecule of reasonable stability that cannot be made by existing methods in sufficient quantity to examine its properties—given enough time, money and effort" (Cornforth 1993, 167–68). This enhanced manipulative ability and control over chemical reactions is the product of over a century of interaction between chemical theory and the laboratory work of organic chemists. In spite of the evident power of this interaction, very little philosophical attention has been paid to either the theoretical products of organic chemistry or how those products interact with the experimental work in the discipline. Perhaps because chemical theories do not assume the same mathematically intensive form as their counterparts in physics, fields like organic chemistry have been regarded instead, as some chemists have put it, as the "kingdom of crawling empiricism" (Smit, Bochkov, and Caple 1988, 455). Conceiving of organic chemistry, or other modern Baconian fields, in this way obscures the rich interactions between scientific theorizing, experimental work, and our capacity to manipulate and control the world. It is therefore, in my estimation, crucial for philosophers interested in scientific experimentation to acknowledge not only the Baconian currents in, say, modern physics but also the distinct experimental work in those sciences that have maintained the explicit Baconian focus on the manipulation and control of nature.

Given the less central roles of mathematized theories in fields such as organic chemistry, it evidently has been tempting to suppose that the experimental work of synthetic chemists has a "life of its own" in the sense that it swings largely independent of theory. And it is certainly true that serendipity,

1. See the CAS website at www.cas.org/newsevents/releases/60millionth052011.html.

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dumb luck, and 'chemical intuition' have played prominent roles in the histories of the preparative sciences; however, at least in synthetic organic chemistry, many of its most renowned practitioners are keen to emphasize the importance of interactions between "organic chemical theory" and the rapid expansion of our mastery of the world of organic molecules (Woodward 1956, 156). Most philosophical accounts of scientific experimentation and its interactions with theory were developed by reflecting on experimentation in physics. Experimentation in the synthetic laboratory is different in interesting ways from typical examples of experimentation in physics. It should not be too surprising, therefore, that the experimental work of the synthetic laboratory casts new light on philosophical issues surrounding scientific experimentation and its relation to theory. The bulk of this essay is devoted to exploring some of the distinctive features of the relationships between theory and experiment in this field. More specifically, not only does synthesis help to set the explanatory agenda of organic theory but it also allows for both theory testing and theory articulation. The way that synthesis experiments play these roles is, however, importantly different from more traditional conceptions of how experiments underwrite and expand the range of theory. Before considering such issues, though, I want to establish that it is appropriate to think of the laboratory efforts of the synthetic chemists as 'experiments' and then to highlight some of the distinctive features of this work.

2. Chemical Synthesis as Experiment. Current philosophical interest in the Baconian origins of modern science derives principally from Ian Hacking (by way of Thomas Kuhn), and so it seems appropriate to begin with his conception of scientific experimentation: "To experiment," Hacking claims, "is to create, produce, refine and stabilize phenomena" (1983, 230) where a "phenomenon is commonly an event or process of a certain type that occurs regularly under definite circumstances" (221). At least two aspects of this definition have been the source of recurring controversy. First is the thought that the phenomena encountered in an experiment are the creation, rather than the discovery, of the experimenter. Second is the lack of any explicit relationship to a background theory: according to Hacking, it is not essential to an experiment that it either presupposes a particular theory or addresses an explicit theoretical goal.[2] As a way of introducing the experimental work of synthetic organic chemists, I want to consider the extent to which it fits this definition and the senses in which it supports the controversial aspects of this definition.

A chemical synthesis is "the intentional construction of molecules by means of chemical reactions" (Cornforth 1993, 161). Much of the synthesis

2. Contrast this with someone like Parker (2009, 487), who claims "An *experiment* can be characterized as an investigative activity that involves intervening on a system in order to see how properties of interest of the system change, if at all, in light of that intervention."

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that goes on now takes place in industrial or commercial contexts where there are strong incentives to produce particular molecules under a variety of pragmatic constraints. Synthesizing compounds under these additional constraints no doubt requires "the solution of all sorts of complex instrumental, conceptual, and mathematical puzzles" (Kuhn 1996, 36) and so is a worthy context in which to study the process of normal science. I focus here, however, on synthesis in academic contexts where, as Kuhn might put it, the paradigm is articulated rather than applied. The classic academic form of the synthetic problem is to generate a total synthesis of a target compound. Target compounds are chosen for a variety of reasons, from the purely practical (penicillin) to the highly theoretical (prismane). When a chemist claims to have created a total synthesis, he or she is claiming that, "if . . . given adequate supplies of all the chemical elements composing [the] compound, [he or she] could make a specimen of the compound totally derived from the matter supplied" (Cornforth 1993, 158). Such a total synthesis typically consists of a laboratory-verified sequence of specific chemical reactions that begins with compounds that chemists already know how to synthesize and culminates with the target molecule (sometimes with a very small overall yield). This recipe is the ultimate product of what may well have been years of integrated theoretical and benchtop work. It is common to separate two components out of the process of creating a total synthesis: synthetic design and implementation. In practice, this separation is not clean, and there is feedback between attempts to come up with and attempts to implement a synthetic plan. Roughly speaking, though, the synthetic planning process is driven by organic theory, while the implementation phase involves educated groping for the particular conditions necessary to run the planned reactions.

Carrying out a total synthesis requires the use of an abundance of scientific theories. The role of mechanistic theories of organic chemistry is most obvious in synthetic design, where potential synthetic routes are explored and evaluated. There are, however, many additional roles for theory. For example, the structural theory, which describes chemical substances in terms of bonds between atoms and their three-dimensional arrangement in space, is required to even formulate the problem of total synthesis, since both the target molecule and the organic reactions that lead to it are characterized in structural terms. Theories of the instruments that allow for structure identification, such as nuclear magnetic resonance or infrared spectrometers, also play a crucial role in identifying the actual products of chemical reactions. So, in the sense that establishing a total synthesis requires the abundant use of theory, the experimental work of synthetic chemists is theory laden. However, it is less clear that the experiments of synthetic chemists must necessarily address some theoretical goal or question. In other words, it is not clear that the significance of syntheses is theory laden. The fact that a particular target molecule looks challenging and might be interesting enough to some-

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one that they will pay for the research often appears to be a sufficient reason to undertake a synthesis experiment.[3]

In one sense, of course, every successful synthesis does establish the truth of the theoretical claim that it is possible to construct the target compound from the elements. But this is a claim about what it is possible for humans to construct, not about the state of independent nature. In this, a total synthesis is like a Euclidean construction: it tells you something about what it is possible for human beings to do with a certain restricted set of tools (known chemical reactions as opposed to ruler and compass). In the case of chemical syntheses, those tools change over time as more reactions are added to the inventory of known chemical reactions. Indeed, one of the central purposes of the total synthesis of novel compounds is to seek out new chemical reactions that might add to that inventory. Because of this, total syntheses are not best thought of as tests of the truth or falsity of theoretical claims about independent phenomena, though sometimes their products are used for such purposes. Instead, these experiments are principally probes of the limits of chemists' powers of manipulation and control and vehicles for pushing that power into new areas.

As mentioned earlier, most of the current products of chemical synthesis are novel products. That is, the target molecule is, as far as anyone knows, an organic compound that did not exist prior to its construction by the chemist. Even when a total synthesis aims to produce a natural product, such as vitamin B_{12} or a cockroach pheromone, which is produced regularly and in abundant quantities in biological organisms, the process described by a chemist in a total synthesis is almost certainly a process that had never occurred before it was implemented in the chemist's lab. That is to say that even when the target of a total synthesis exists in independent nature, the phenomenon disclosed by the synthetic chemist does not. Synthetic chemists are often explicitly aware of and emphasize this aspect of their science. Berthelot is reported, in 1860, to have claimed, "Chemistry creates its own subject. This creative ability, similar to an art, is the main feature that distinguishes chemistry from the natural and humanitarian sciences" (quoted from Smit et al. 1998, 28). Similarly, Woodward (1956, 180) asserted that "organic chemistry has literally placed a new Nature beside the old." Not only does the organic chemist work largely in a world consisting of objects his or her own creation, but the principal goal of that work is to expand, understand, and control the

3. Cornforth (1993, 162) describes the attempts to synthesize a compound initially identified as a cockroach pheromone as follows: "There were then, as now, a considerable number of chemists looking hungrily for an excuse to synthesize something, and the effect of this structure was rather like that of a dead horse dropped into a lake of piranha fish." As it turns out, the compound was not a cockroach pheromone, and Cornforth reports a lady claiming "although this molecule wasn't very good at attracting male cockroaches, it certainly attracted a lot of organic chemists."

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chemical reactions that allow the chemist to manipulate and manage those objects.[4] In this sense, the phenomena created in organic experiments are doubly conditioned on human intervention. The phenomena produced in chemical syntheses are typically nonnaturally occurring, and the investigative agenda of the science is directed toward the manipulative powers of human beings.

It seems clear that establishing the total synthesis of a novel compound amounts to creating a process that will recur under definite circumstances. Indeed, what one does when publishing a total synthesis is to describe the recipe by which the process can be reproduced. A synthesis is then a phenomenon, according to Hacking, and its production by the chemist is an experiment. These experiments are strongly theory laden in the sense that it would not be possible to create such phenomena without the abundant use of a wide variety of scientific theories. Insofar as there is a theoretical goal for, or question to be addressed by, such experiments, however, this goal seems to be to probe and/or expand the range of organic molecules over which humans can claim mastery. And finally, there is a double sense in which the phenomena generated by the synthetic chemist bear the mark of their creators. Not only are the phenomena produced by the synthetic chemists artificial, in much the same way that an instrumentally realized phenomenon in physics is artificial, but the point of producing the phenomena is to establish something about human manipulative powers (to establish what it is possible for us to construct). It is this last feature that distinguishes what I have called the modern Baconian sciences from the more typical subjects of the contemporary philosophy of experiment. In the remainder of the essay I investigate, by way of the reflections of accomplished synthetic chemists, how that theoretical goal—the probing, expansion, and refinement of human manipulative abilities—colors the interactions between theory and experiment in organic synthesis. This investigation occurs along three axes. First, I consider how the 'explanatory agenda' of theoretical organic chemistry is shaped by the experimental goal of total synthesis. Second, I consider the sense in which a total synthesis experiment probes or tests the theory of organic chemistry. And finally, I consider how and in what circumstances total synthesis is used as a tool for further articulating the manipulative power and understanding of organic chemists. It is my hope that these considerations will provide a beginning from which more substantial philosophical work on the experimental and theoretical life of the modern Baconian sciences will develop.

4. Schummer (1997, 85), based on a study of the aims of chemical research, claims "nearly half of preparative chemistry can be considered as producing new substances in order to improve abilities to produce more new substances. That is, producing new substances is actually an end in itself here."

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3. Synthesis and the Explanatory Agenda of Organic Theory. When reflecting on the history of their discipline, synthetic chemists frequently comment on the essential role of "organic chemical theory" in facilitating the development of synthetic chemistry. R. B. Woodward (1965 Nobel Prize in Chemistry), perhaps the past century's most illustrious synthetic organic chemist, claimed that there had been two great revolutions in organic chemical theory, each accompanied by a corresponding dramatic expansion in synthetic power. The first revolution was the development of structure theory in the nineteenth century. This revolution was not only the necessary precondition for a rational approach to synthesis but it also allowed for the identification of functional groups and the use of structural analogies in crafting syntheses. Only with the second revolution, however, did synthetic chemists develop the potential for realistic synthetic planning. This planning depended on the fact that organic theory had reached the point where "the outcome of very few organic reactions is unexpected, and fewer inexplicable" (Woodward 1956, 156). According to E. J. Corey (1990 Nobel Prize in Chemistry), because of the elucidation of reaction mechanisms and the analysis of the structural factors influencing reactivity, "It was easier to think about and evaluate each step in a projected synthesis. . . . It was simpler to ascertain the cause of difficulty in a failed experiment and to implement corrections. It was easier to find appropriate selective reagents or reaction conditions" (Corey and Cheng 1989, 4). When coupled with important technological developments, these theoretical innovations led, by the end of the twentieth century, to increasing confidence that "no stable [organic compound] was beyond the possibility of synthesis in the not too distant future" (4). Evidently, synthetic organic chemists are quite confident in their capacity to experimentally create specific phenomena, and that confidence rests, in large part, on the power of their theoretical tools.

If these chemists are right, theory does play a crucial role in (at least some of) the modern Baconian sciences. These are not fields explored by 'random groping' and characterized by simple descriptive generalizations. Rather, they are theory-driven sciences that can craft at will (at least in some cases) arbitrary phenomena in the domain that they have constructed for themselves. This raises the philosophical question of how the theoretical tools of synthetic chemists are able to convey such manipulative and creative power. This question is made all the more interesting because of the many significant ways that the theories of organic chemists differ from those in domains that have traditionally received the most philosophical attention. For example, the theory of organic chemistry is not, for the most part, formulated mathematically. There are few, if any, generalizations that might appropriately be called Laws of Nature that play a prominent role. Instead, there are mechanisms and accounts of how specific structural differences affect the reactive behavior of model reactions. Still, using this theory, synthetic chem-

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ists are able to craft elaborate synthesis of novel complex molecules. In the remainder of this section, I argue that the character of theoretical organic chemistry—in particular, its explanatory agenda—is shaped by the goal of facilitating synthetic design. If this is right, it will show that the particular sorts of experiments pursued in preparative chemistry are at least partially responsible for its distinctive theoretical approach. Rather than being reasons to dismiss synthetic organic chemistry as immature or merely descriptive, the distinctive features of 'organic chemical theory' instead reflect its modern Baconian goals.

According to Woodward (2003, 191), explaining phenomena involves situating them within "systematic patterns of counterfactual dependence." We explain why something happened by bringing out the ways that the world might have been changed so that the outcome would have been different in some specific sense. To do this, scientists must invoke generalizations about the possible ways that the world might be. Such generalizations may be limited in scope, but so long as they imply that if certain changes were made, the world would have been different in certain specific ways, this is enough to support scientific explanations. Explanations are useful, from this point of view, because to explain a phenomenon one must be able to identify interventions that would, at least in principle, change the phenomenon some specific way. That is, one could predict how things would turn out differently if one were able to alter the conditions by such an intervention. The changes in circumstances that are particularly important to a scientific discipline, according to Woodward, "help to set the explanatory agenda" (262) for that field. This means that scientists concerned with changes of a particular sort seek modally robust generalizations that hold up across those changes; these are the generalizations that allow them to infer what would happen if such changes were to occur.

The explanations of organic chemists are, according to Goodwin (2003), largely directed toward providing structural accounts of product distributions, relative rates, and some other related features of organic reactions (such as mechanistic pathways). Most of these explanations are contrastive, in that they take place against a backdrop of alternatives (the contrast class). For example, they might attempt to explain why a reaction is stereospecific rather than leading to a mix of stereoisomers, or why the dominant product is X rather than Y or Z, or why one reactant reacts so much more quickly than another. Certain kinds of differences between the alternatives in the contrast class are particularly salient for organic chemists, namely, structural differences. So a satisfying explanation must identify which structural features of the molecules being considered are responsible for the contrastive fact being explained. In Woodward's terms, the space of alternatives into which particular phenomena are situated in this approach is a *space of alternative structures*. Explaining why some contrastive fact is true about a particular mole-

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cule or reaction involves identifying what structural feature might be changed so that that contrastive fact would no longer hold true. For example, if one explains that a particular reaction proceeds quickly, relative to some standard, because of neighboring-group effects, then this is to say that if the substrate were changed into a different structure that no longer had this neighboring group, it would no longer proceed as quickly relative to that standard. Supporting such a claim requires appealing to generalizations that hold up across some range of changes in structure. In this example, one might appeal to a claim such as "electron-releasing neighboring groups stabilize carbocations." This is a generalization that is fairly robust across changes in both the structure of the neighboring group and the structure of the cation. It allows one to conclude that the reaction would probably not proceed as quickly if the neighboring group were replaced by a nonelectron-releasing substituent. In virtue of knowing this, the organic chemist can make a range of specific predictions about how an entire class of alternative substrates (all those that have different neighboring groups but are otherwise similar) would behave. This predictive ability, in turn, supports the chemist's ability to manipulate and control organic reactions. To wit, it underwrites a maxim of the following form: if you want to speed up (slow down) a reaction that proceeds through a carbocation intermediate, then consider manipulating the substrate by adding (removing) an electron-releasing neighboring group.

I hope to have made it plausible that many of the explanations and predictions of organic chemists depend on generalizations about what structural features might be swapped out of an organic molecule in order to change its behavior in specific ways. I now want to show that these are just the right sort of changes or alternatives for organic chemists to keep track of given that their goal is to come up with syntheses of novel compounds. Designing the synthesis of a novel compound can be thought of as the process of progressively pruning the 'retrosynthetic tree' of the target molecule.[5] The retrosynthetic tree of a compound is a branching collection of potential synthetic pathways that is determined by the known synthetic transformations available to the designer. One can imagine generating such a tree by working backward from the target molecule in stages. In the first stage, one considers all the ways that one might generate the target molecule as the product of a known reaction and writes down the structures all of the reactants that would be needed to run these reactions. These structures are the nodes of the first stage. In subsequent stages, one considers all the ways that one might generate the nodes of the previous stage and writes down a new array of nodes

5. This way of talking is derived from the work of E. J. Corey (see Corey and Cheng 1989), but I do not mean to suggest that it is original to him or that his is the only, or best, way to think about synthetic design.

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corresponding to the reactants for these reactions. The process continues until potential pathways end by generating nodes that one already knows how to synthesize.

As indicated by Woodward and Corey above, the power of the theory of organic chemistry comes from its usefulness in making intelligent decisions about which of the routes in the synthetic tree are worth pursuing. The selective exploration and evaluation of the retrosynthetic tree can be thought of, again following Corey and Cheng (1989), as occurring in three stages: strategic pruning, plausibility assessment, and optimization (for details, see Goodwin 2009a). Each of these stages involves making assessments of what would happen should a previously known synthetic reaction be applied to a novel molecule. In order to do this, organic chemists need to know something about how that synthetic reaction occurs (its mechanism) and something about how the particular environment of the novel molecule will influence or modify the mechanism and/or reaction. Synthetic reactions are typically discovered, and their mechanisms investigated, in chemical structures substantially different from the novel molecules for which synthetic chemists must make these assessments. As a result, these chemists are required to evaluate how the characteristics of the known reaction would change should the structure of the substrate be modified in particular ways. In other words, they must evaluate the effects of swapping out parts of the standard structure (the structure on which the synthetic reaction was initially investigated) for the structural features relevant to the novel molecule that they are investigating. Doing this, in turn, requires appealing to generalizations that are robust across changes in structure, claims that span exactly the same space of possibilities as those employed in the explanations and predictions described in previous paragraphs. This is why the mastery of the theory of organic chemistry demonstrated in the explanations described earlier is useful in synthetic design and therefore why the explanatory agenda of theoretical organic chemistry is the space of alternative structures.

The application of these generalizations in making assessments of the reactive possibilities of novel molecules is, however, often more complicated than it is in standard cases of explanation or prediction. Complex novel molecules often differ from the compounds in standard reactions in multiple overlapping, and possibly conflicting, ways (they might have some features that promote a reaction and some that inhibit it). This typically puts them outside, in previously unanticipated ways, the empirically investigated scope of the generalizations that are being used in these assessments. The result is that these assessments rely on heuristics and make predictions that are often only contrastive (this will work better than that), qualitative (this is not likely to be stereospecific), or disjunctive (this is the range of possible results). Still, given the evident success of synthetic organic chemistry, these theoretically grounded heuristics are an extremely effective tool for synthetic design.

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The experiments of synthetic chemists depend on theoretical organic chemistry for the plausibility assessments that are crucial to synthetic design. These assessments require appeal to generalizations that span a range of ways that organic structures might be modified, and this is at least part of the reason that the explanatory agenda of organic chemistry is focused on the space of alternative structures. Since their goal is to be able to synthesize novel molecules, preparative chemists must find ways to use facts about the behavior of relatively simple molecules in standard conditions to craft a plausible sequence of reactions through uncharted territory. 'Organic chemical theory' is responsive to these needs, but, perhaps as a result, it lacks some of those characteristics that have come to define, at least in philosophical circles, mature physical theories (e.g., quantitative laws that support nondisjunctive, numerical predictions). Thinking of mature scientific theories in this way masks important differences between the sciences. For a modern Baconian science like synthetic organic chemistry, it seems more appropriate to gauge its maturity by the level of mastery that it provides over its domain. By this criterion, it is hard to imagine a theory that is more mature than organic chemistry, in spite of the distinctive features of its theoretical tools.

4. Total Synthesis as Theory Probe. In a famous piece reflecting on the status of his science, R. B. Woodward characterized the achievements of organic synthesis as a measure of "the power and maturity of organic chemistry as a whole" (1956, 158). The experiments conducted by synthetic chemists were understood, in other words, to underwrite normative judgments about the condition of their science. In this sense, at least from Woodward's point of view, these syntheses play a role analogous to theory testing in more traditional experimental contexts. The differences between organic syntheses and more traditional experiments, which reflect the modern Baconian character of organic chemistry, affect how these experiments bear upon the theories that support them. In what follows, I explore some of these differences and their impacts upon experimental theory appraisal.

As befits its modern Baconian character, the theoretical products of organic chemistry are used, particularly in a synthetic context, as tools to support the manipulation and control of organic molecules. Consequently, there is not generally a particular theoretical claim (or competing set of claims) at stake in a synthesis experiment. Instead, the success or failure of a total synthesis supports evaluations of the overall manipulative powers of organic chemists. Whereas experiments are normally thought of as deciding the truth or falsity of particular theoretical assertions, in the synthetic case, experiments probe the limits of what it is possible for chemists to construct. These limits do reflect, however, the theoretical tools at the synthetic chemist's command. As Woodward puts it, "Synthesis must always be carried out by plan, and the synthetic frontier can be defined only in terms of the degree to

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which realistic planning is possible, utilizing all of the intellectual and physical tools available. It can scarcely be gainsaid that the successful outcome of a synthesis of more than thirty stages provides a test of unparalleled rigor of the predictive capacity of the science, and of the degree of its understanding of its portion of the environment" (1956, 155).

By underwriting synthetic design and planning, the theory of organic chemistry facilitates complex multistep synthesis that would not otherwise be possible. Using theoretically grounded heuristic principles (see Goodwin 2009a), the synthetic chemist can often make reasonable predictions about which branches of the retrosynthetic tree constitute plausible syntheses.[6] If all goes well, a synthetic plan based on one of those branches may be implemented, most likely in a modified form, in the laboratory. A successful experiment of this sort certainly demonstrates understanding, at least in the sense that the chemist can characterize a rationally motivated and laboratory-verified process for constructing the target molecule from its elements. Furthermore, it shows that the theory's predictions, as used in synthetic planning, are reliable enough to make the target molecule. What such an experiment does not do, however, is attempt to isolate and bear upon the truth or falsity of a particular theoretical claim. Indeed, the prominent role of natural product syntheses, where chemists attempt to create in a laboratory setting target molecules that have been isolated from nature, would make little sense if the point of a synthesis experiment were to establish the stability or existence of a particular organic structure. It is already known that a natural product is stable and can be synthesized (by natural means); what is not known is whether it is possible for chemists to synthesize the compound given current tools—this is what is revealed by the synthesis experiment. Consequently, synthesis experiments allow normative assessment of the theoretical tools of organic chemists by way of the manipulative powers and control that they underwrite, not principally by acting as evidence for their truth or falsity.

A related difference between synthesis and more traditional experiments concerns how the phenomenon produced in the experiment relates to the set of clear consequences of the theory being evaluated by the experiment. In a traditional experiment designed to test a theory, the goal is to craft a situation in which the consequences of the theory, or theories, being tested are clear. So, for instance, a well-designed crucial experiment deciding between T1 and T2 would attempt to create a phenomenon about which both T1 and

6. I take it that these are the sorts of predictions that Woodward has in mind in this quote. He is careful to point out, later in the article, that organic theory often only indicates that "several outcomes are possible" (1956, 156) and does not necessarily indicate which one will obtain. This is the sort of disjunctive prediction that frequently plays a role in synthetic design.

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T2 make unambiguous and distinguishable predictions. By observing the phenomena and deciding which (if any) of those predictions come out true, one would hopefully be able to decide between the theories. The difficulty of experimental design, in these traditional situations, comes in finding places where the theories speak clearly. This aspect of traditional experiments reflects their role in assessing the truth or falsity of the theories they are used to evaluate. Synthesis experiments are different; the phenomena that they hope to create are meant to push beyond the clear range of application of the theories that they test. This reflects the fact that such experiments are not meant to test the truth or falsity of those theories but, rather, to test the boundaries of the manipulative power that they supply. The predictions supplied by organic theory in the synthetic design of complex, novel molecules are typically contrastive, qualitative, and/or disjunctive; that is, they often do not speak clearly and definitively about what to expect in the situation considered. That would be bad if one were using those predictions principally to test the truth of the theory because it would be hard to evaluate the extent to which the predictions were born out or shown to be incorrect. It is neither unexpected nor a barrier, however, to pushing that theory into situations never previously encountered and deciding whether it results in effective guidance.

Good tests of the manipulative power conveyed by a theory require pushing beyond the boundaries of known behavior. Perhaps for this reason, desirable target molecules are often imported from other fields, as in natural products synthesis. This ensures that the structures being pursued are not chosen to make it easy on the synthetic chemist and that they are stable enough to be produced (any failure is a failure of the chemist, not a testimony to the instability of the molecule). Whatever the structural complexities of newly encountered natural products, they are not likely to fit comfortably within the bounds of previously explored chemistry. This is what makes them good tests of the current state of the theory, including the range of known synthetic reactions. If the procrustean effort to find a synthetic path using known reactions does not pay off, this is not likely to be considered a black mark on the track record of organic theory. Instead, it would be evidence that further articulation of that theory was required in the vicinity of the recalcitrant target molecule. In this sense, probing organic theory by attempting novel total synthesis fits cleanly into Kuhn's model of "normal science." The truth or falsity of the theory is not really at stake; instead, challenging puzzles are sought that, when they are amenable to solution given the tools on hand, provide evidence for the current power of the theory and, when they are not so amenable, identify opportunities for further theory articulation.

5. Using Synthesis to Articulate Organic Theory. As indicated above, organic synthesis experiments are not merely tests of the current state of

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organic theory but also probes that create opportunities for refining knowledge of particular areas, for expanding the range of synthetic reactions, and for developing new theoretical concepts or devices. As the tools (chemical, theoretical, and physical) available to organic chemists continue to develop, more and more target molecules become accessible to known methods. Consequently, the value of a straightforward 'confirmation' of the current theory is diluted, and more emphasis is placed on the articulating role of these experiments. To articulate organic chemistry, a synthesis must push into regions where the theory is vague or where it breaks down. Sometimes target molecules do this all by themselves, but, increasingly, constraints over and above novelty and complexity are imposed upon total syntheses in order to ensure that the phenomena produced by synthetic chemists result in significant articulations (such as the quest for 'elegant', or short, syntheses). In other words, the articulating role of synthesis experiments requires that chemists flirt with failure. In this sense, theory articulation in the context of a Baconian science like synthetic organic chemistry is importantly different from theory articulation as Kuhn originally conceived it. Kuhn emphasized that in the process of trying to fit the world into the conceptual boxes supplied by his or her paradigm, normal scientists "concentrate on problems that only their own lack of ingenuity should keep them from solving" (1996, 37). While it is probably true that synthetic chemists largely work on problems that they believe to be solvable, at the same time their interest in expanding the range and power of their synthetic tools encourages them to work under self-imposed constraints that push them beyond the current toolbox supplied by organic chemistry.

One straightforward way to ensure the value of a synthesis is to target molecules that are significant for some extrinsic reason, such as their value to investigations in biology. Such targets, even if they can be synthesized using standard methods, force the chemist to "delve into the chemistry of the target compounds" (Smit et al. 1998, 25). This delving need not involve major theoretical innovations, or even the elucidation of novel classes of synthetic transformation, in order to be useful and important going forward. As mentioned earlier, the synthetic planning supported by organic theory for novel compounds is in the form of general heuristics, which are often qualitative or disjunctive. The resulting synthetic plans can be rough and typically require refinement and modification throughout the process of trying to implement them. The benchtop work of implementing such a plan forces the chemist to concretely explore among the theoretically live options. Inevitably, many of these live options fail, but hopefully some of them succeed. By navigating such failures, the synthetic chemist develops a working sense of which theoretical options can be practically implemented in the chemical environment of the particular target molecule. In other words, chemists gain experience with particular sorts of structures by synthesizing them. This experience can

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pay off in terms of an enhanced ability to manipulate and control molecules in the same general structural neighborhood. For example, though the total synthesis of penicillin did not turn out to be commercially viable, it did reveal a lot about the chemistry of penicillins, which are synthetic modifications of the original penicillin structure, many of which have turned out to be useful antibiotics. Similarly, once chemists have figured out how to synthesize a particular natural product, they are often able to modify that synthesis in specific ways that allow them to "put loaded questions to a living organism" (Cornforth 1993, 164) by supplying isotopically labeled versions of those products or their precursors. So one way that organic chemistry is articulated by synthesis experiments is by learning, in much more detail than is supplied by the general theory, how particular classes of structure behave. Even when such knowledge is completely compatible with the general theory, it often constitutes a substantial and useful refinement of it, which translates into more precise and predictable syntheses of related targets in the future.

Interestingly, another way to ensure the importance of a synthesis experiment is by failing to solve the problem using known methods. Failure, according to many eminent synthetic chemists, is what forces both innovation in the array of available synthetic reactions and novelty in organic theory. Smit and colleagues (1998, 26) claim, for example, that "the origin of many outstanding discoveries in organic chemistry can be traced to the initial failures of synthetic plans, to those 'misfires' that prompted chemists to revise their current views." As an example, they describe the development of conformational analysis, which is the study of the energetics of rotations around single bonds (or, roughly, the detailed three-dimensional arrangement of organic compounds). Conformational analysis is central to contemporary organic theory, but it arose only in the 1950s in an attempt to understand unexpected problems that arose in the synthesis of steroid hormones and their derivatives (see Goodwin 2009b). Similarly, Cornforth reports that the "triggering event for Woodward's generalizations on orbital symmetry was a reaction in the B12 synthesis that did not go as expected" (1993, 160). Orbital symmetry rules predict the stereochemistry of certain cyclic reactions and have also become important tools in contemporary organic theory. Both of these important theoretical tools emerged out of the failures that result when confronting and attempting to control the previously unexplored chemical environments that arise during synthetic experiments.

It is not just theoretical innovations that emerge from failure but also additions to the array of synthetically useful reactions. New reactions are demanded when the current choices do not offer any appealing alternatives. Increasingly, synthetic chemists have sought to make their experiments significant by contributing such new reactions, even when they might not be strictly necessary. Though "synthesis of a complex molecule is still consid-

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ered per se to be an outstanding achievement," Smit and colleagues (1998, 453) report that "greater applause" is accorded to those syntheses that require "the elaboration of novel methodology for carrying out a previously unknown conversion at a key step of the strategic plan." Such results not only confirm the manipulative power of organic chemistry but also enrich "greatly the entire arsenal of synthetic methods" (453). In an era of cheap confirmation, one way to increase the value of synthesis is to raise the bar for 'success' by insisting on more elegant, novel, or illuminating synthetic routes. With additional constraints on what constitutes a successful outcome, it once again becomes possible for synthesis experiments to fail. Chemists are prompted to take shortcuts and avoid the meandering but sure paths provided by known chemistry. In these shortcuts lie new synthetically useful reactions and new theories designed to rationalize them.[7] Whereas complex natural products once provided ample supplies of failure, contemporary synthetic chemists must work to provide this important commodity. In order to articulate their theory and to expand their arsenal, they must seek out and create opportunities for their tools to fail.

In some senses, then, synthetic organic chemistry progresses in a way more reminiscent of Popper's method of conjectures and refutations than Kuhn's paradigm articulation. Chemists seek out synthetic targets that provide challenging tests of their current manipulative powers. When they are able to provide total syntheses of those targets using their current tools, this reinforces their confidence in those tools and adds to the details, and usefulness, of their theory. Real progress occurs, however, when the current tools fail, because this forces the synthetic chemist to try to understand what went wrong and then, perhaps, to design new synthetically useful reactions that allow for the completion of the experiment. In a Baconian context like synthetic chemistry, however, it is not refutations of the current theory that are pursued in experimental work. For the most part, the truth or falsity of the theory is not at stake. The failure of a synthetic experiment instead reflects on the range of current tools. Tools can be perfectly good within their domain and worthless outside of it. Synthesis experiments help to map out the space of organic molecules within which chemists can be confident about their abilities and prompt the expansion of that space when particular chemical environments are found to lie outside of it.

6. Conclusion. The point of a modern Baconian science like preparative chemistry is to assess and expand the human capacity to manipulate and con-

7. Cornforth (1993, 169–70) advocates a research program where organic chemists seek to emulate enzymes by designing catalysts specific to particular reactions. Rather than using the effective but elaborate and unwieldy array of protecting groups, he aspires to much shorter and more selective syntheses, on the natural model.

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trol a particular domain. In the case of organic chemistry, that domain is "the material basis for the functioning of all known forms of life on our planet" (Smit et al. 1998, 454) as well as the foundation for large swaths of modern technological culture. Not only are many organic materials useful for technological purposes but the power to manipulate and control these molecules allows for the sophisticated interventions necessary to study biological systems. It is obvious, then, why humans seek the capacities developed by organic chemists. What is perhaps not so obvious is that understanding and controlling the organic molecules that occur in natural systems (e.g., vitamin B_{12}) and in technological applications (such as dyes of various sorts) has required embedding those molecules within a much more expansive domain largely of our own creation. Major theoretical achievements such as the structural theory and modern mechanistic organic chemistry have allowed for the systematic organization and rationalization of large parts of this domain. With these theories (as well as additional technological achievements) in hand, synthetic organic chemists are now quite confident in their abilities to manipulate and control organic molecules, both natural and artificial. Not only must scientists create phenomena in order to investigate nature, sometimes they must craft whole new departments of reality in order to situate natural objects within a theory-governed system; such has been the case with organic chemistry.

The interrelations between theory and experiment in synthetic organic chemistry have been a recurring source of interest to its most accomplished practitioners. Perhaps because their science is significantly different from standard models of "good" or "mature" sciences, these practitioners have made repeated efforts to explain both why their experimental work is important and how it depends upon and supports theory. Indeed, throughout this essay I have used these reflections to help bring out some of those significant differences. I hope to have made it obvious that while the differences are real and interesting, they do not license any negative evaluations of the status of organic chemistry as a science. Instead, if they reflect anything, it is the philosophical neglect of a large, important, and interesting facet of our scientific efforts not only to understand but also to create and manipulate our world.

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