

Implementation and innovation in total synthesis

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Abstract This article investigates how understanding the theory of organic chemistry facilitates the total synthesis of organic compounds. After locating the philosophical significance of this question within the methodology or epistemology of applied science, I summarize the results of previous work on this issue—roughly that theoretical organic chemistry underwrites a sequence of heuristic policies that help to isolate plausible synthetic routes from the array of possibilities provided by structural or descriptive organic chemistry. While this prior account makes a solid start, it does not capture all of the ways that the theory of organic chemistry contributes to total synthesis. This article aspires to enrich this account by exploring some additional ways that theory contributes. More specifically, I investigate how understanding the theory of organic chemistry can facilitate both the development of novel synthetic reactions and the implementation of a synthetic plan. The role of theory in these aspects of total synthesis will be explored by considering a particular, novel synthesis of longifolene.

Keywords Organic chemistry · Total synthesis · Philosophy of applied science · Philosophy of technology

Introduction

Though there is substantial philosophical controversy over the extent to which the development of scientific knowledge is progressive or cumulative, there is little doubt that as science has evolved, it has increased our capacity to manipulate and control the world. Often, it is the successful application of science that are invoked in support of the claim that our scientific theories constitute an increasingly detailed and accurate representation of the world (see Pitt 1988 for attempts to cash out the “success” of science in terms of its technological applications). While it certainly seems plausible that the usefulness of a

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theory in developing applications speaks to its epistemic credentials, philosophers have not done much to explicate why this should be so. Furthermore, what little work philosophers have done to try to explain how a scientific theory facilitates application, and thus to provide a foundation for evaluating the inference from successful application to epistemic distinction, has been directed towards physics and/or engineering. This focus on mathematically oriented disciplines has led to some important insights, but it has also led to some distortions. Specifically, accounts of the applications of science have centered on the role of approximations and idealizations in the procrustean effort to find mathematical descriptions of (or laws governing) systems of practical interest (see Boon 2006 and Cartwright 1976 for examples). As a partial remedy for this, I have attempted to provide a general account of how the theory of organic chemistry underwrites the process of designing and implementing a synthetic plan. Though the theory of organic chemistry has become increasingly mathematically intensive, much significant synthetic work was—and continues to be—done without making use of the sort of quantitative laws characteristic of physics and engineering. As a result, the role of theory in the development of total syntheses looks significantly different from its role in facilitating the applications of engineering or physics.

Understanding in synthetic design

The design of a total synthesis requires coming up with a sequence of chemical reactions that will plausibly allow for the production of the compound of interest from compounds that are already available. Most, if not all, of the individual reactions that make up this sequence will be instances of reactions that have already been recognized to be synthetically useful. Synthetically useful organic reactions are typically characterized structurally; that is, these reactions are described in terms of certain recurring structural features that may be transformed by some particular reagents (in certain circumstances) into other recurring structural features. For example, the Diels–Alder reaction is a synthetically useful reaction that can be used to generate a cyclohexene structure from a diene and an alkene. Coming up with a plausible synthetic plan requires stringing together a sequence of such organic transformations such that, when this sequence is applied to accessible starting materials, it will likely result in a significant yield of the desired product. The generation of such a plan is an example of applied science because it makes use of our theories of organic reactions in order to solve a practical problem.

In order to bring out the role of the theory of organic chemistry in generating such plausible synthetic plans, it is useful to imagine one way that the problem could be systematically approached and then to consider where and how, in following that approach, one would have to invoke the theory of organic chemistry. This strategy, I hope, will reveal some of the central ways that theory impacts the design process even if, in actuality, there are a variety of different strategies that one might employ in arriving at a synthetic plan. The thought is that even if there is some flexibility in the overall approach taken to synthetic design, still the ways that theory facilitates design will be relatively constant. In line with this general strategy, I have in previous work (Goodwin [forthcoming](#)) used E. J. Corey's approach to synthetic design—known as retrosynthetic analysis—as my example of a systematic approach to synthetic design (Corey and Cheng 1989). Retrosynthetic analysis is especially useful for this purpose because Corey has characterized in some detail the steps and considerations that are part of his strategy; furthermore, he has explained how this process was used to come up with synthetic plans in specific cases.

Using retrosynthetic analysis as a representative approach to synthetic design is therefore a useful way of bringing out how understanding the theory of chemical reactions helps in arriving at a plausible synthetic sequence; however, nothing about this use of retrosynthetic analysis depends upon, or endorses, claims that it is a uniquely successful or original approach to synthetic design.

From the perspective of retrosynthetic analysis, the problem of synthetic design can be conceived of as the process of selecting one path from a complicated, branching tree of alternatives. This tree is generated by beginning with the synthetic target structure (the compound that one is trying to synthesize) and working backward sequentially. In the first step of this process, one works through the complete catalog of synthetically useful organic transformations identifying which of these transformations would, for some reactant structure or structures, generate the synthetic target. All of the reactant structures that could, by some such transformation, result in the target constitute the first stage in the tree. To each of these initial reactant structures, the same search for possible antecedent structures can be run, resulting in another stage of the tree. This process is then repeated for each possible intermediate structure until one arrives at a compound that is already available, terminating the branch. In principle, someone who had a complete catalog (up to some particular point in history) of synthetically useful reactions and available starting materials could—as long as they knew how to manipulate structural formulas appropriately—generate the retrosynthetic tree for a given synthetic target. However, because there are so many structurally characterized synthetically useful organic reactions and because it may require the application of many reactions to reach an available starting material, the complete retrosynthetic tree for a given target compound can be exceptionally complex. As a result, synthetic chemists do not typically generate complete retrosynthetic trees for their synthetic targets. Instead, the job of the synthetic chemist in the process of synthetic design is to somehow selectively explore the retrosynthetic tree for the target compound and identify one particular path that, after optimization, can then be taken into the lab for attempted implementation. It is in the process of selectively exploring the retrosynthetic tree that the theory of organic chemistry contributes to the process of synthetic design. In previous work (Goodwin [forthcoming](#)) I have—drawing on Corey's analysis—characterized three different stages in the synthetic design process (strategic pruning, plausibility assessment, and optimization) and described how the theory of organic chemistry contributes to each of them. Before going on to summarize those results, however, I briefly want to describe what understanding the theory of organic chemistry (as I am using that locution in this article) consists in.

By the theory of organic chemistry I mean those concepts and devices, along with the norms governing their application, that are used to explain many of the observable characteristics of organic transformations. For example, one might appeal to a mechanism (a theoretical device) along with the steric hindrance (a theoretical concept) obvious in a transition state (another theoretical concept) in order to explain why a particular reaction proceeds much slower than a related standard reaction. An understanding of the theory of organic chemistry manifests itself in the capacity to employ these devices and concepts to explain and sometimes predict the chemically interesting characteristics of organic transformations. As I have detailed in earlier work (Goodwin 2003, 2007, 2008), understanding the theory of organic chemistry requires being able to use a relatively small number of robustly applicable structural concepts (along with relevant mechanisms) to account for the energetic differences that are responsible for, according to the standard formal models of chemical transformations, most of the interesting properties of these organic reactions. While it is sometimes possible to make numerical predictions of relative

rates or the position of an equilibrium in organic chemistry, this is not an essential component of explanation and prediction in the discipline. In many cases, particularly the sort of novel cases that are relevant to synthetic design, organic chemists can provide at best qualitative predictions of, say, which of a set of possible products will be preferred or which of a collections of reactions is likely to have a faster rate. Furthermore, in cases where there are multiple structural features that have opposing influences on the energy of some relevant structure, it may not even be possible (in any practical sense) to predict which “effect” will win out, and thus what the observable outcome (e.g., will the reaction proceed to significant extent, or will side reactions dominate) will be. Nonetheless, it may still be possible to explain after the fact why such a reaction turned out in the way that it did. Given the typically contrastive, and frequently qualitative predictions and explanations supported by the theory of organic chemistry, it can begin to look puzzling how such a theory can facilitate the development of applications at all—particularly when standard philosophical accounts of applications focus on the ways that predictive, quantitative laws are fitted so that they apply to the concrete situations relevant to the application. As I will describe in the following paragraphs, however, it is perfectly possible to understand how the theory of organic chemistry—contrastive and qualitative though its predictions and explanations may be—guides and grounds the synthetic design process.

The first stage of the synthetic design process is strategic pruning. The chemist must analyze the structure of the target molecule and identify the sources of synthetic complexity within it. With these sources of complexity in mind, the design process focuses on identifying branches in the retrosynthetic tree that are progressively decreasing in complexity. Such branches correspond to synthetic routes that generate the complex structural features of the target molecule out of structurally simpler components. The less complex a branch gets, the more likely it is to eventually terminate in a compound that is already available, and so to result in a plausible synthetic route. The business of assessing synthetic complexity, and the appropriate policies for dealing with various sorts of complexity, depend upon both the collective experience of synthetic chemists and their understanding of the theory of organic chemistry. For instance, in assessing the stereochemical complexity of a target molecule, Corey focuses on identifying the number of “clearable” stereocenters—symmetric carbons that can be retrosynthetically removed in a relatively straightforward way—in the molecule. Whether or not, a particular asymmetric carbon in the target molecule is “clearable” or not depends upon the prospects for a stereoselective synthesis of it. These prospects, in turn, depend not only upon the arsenal of stereoselective synthetic reactions available, but also on the detailed structural environment of the asymmetric carbon. It is in evaluating the prospects for a selective synthesis of a particular asymmetric carbon within the detailed structural environment of the target molecule that the chemist must rely upon his understanding of the theory of organic reactions. In many cases, none of the reactions being considered will have ever been attempted on these particular substrates before. To assess their plausibility the chemist must instead rely upon an understanding of both the mechanisms of the possible reactions and the implications of the relevant features of the structural environment on these reactions. Once the stereochemical complexity of a molecule has been assessed, then (if this is the dominant form of synthetic complexity in the molecule) the retrosynthetic tree can be pruned, limiting the potential routes that need to be investigated to those that lead to a progressive reduction in stereochemical complexity.

After the large-scale strategic pruning of the retrosynthetic tree, the next step in synthetic design can be thought of as a series of relative plausibility assessments. Generally, there will be a wide variety of particular approaches that are compatible with the overall

strategic plan of a synthesis. In order to sort through these approaches and settle upon one (or perhaps a few) that can be further tuned in the last stage of synthetic design, most of these particular approaches must be eliminated. These eliminations occur by way of theoretically grounded assessments of synthetic plausibility. These relative assessments can occur at both the level of individual synthetic steps, as well as at the level of sequences of such steps. For instance, if it has been decided that it is strategic to consider synthetic pathways that form one particular bond in the target molecule, the different synthetic reactions capable of forming such a bond need to be evaluated for their relative plausibility. In some cases, it may be possible to conclude, on the basis of the structural environment of the target molecule, that only one such synthetic reaction is likely to be synthetically successful. In other cases, it may be necessary to consider the sorts of functional group adjustments that are necessary for each of several potential synthetic reactions. These sequences of reactions can also be compared, either in terms of the plausibility of their individual steps, or in the overall number of complications that would be involved in each sequence. At the basis of these plausibility comparisons is the chemist's understanding of both the mechanisms of the proposed reactions and the structural features that influence the effectiveness of a proposed reaction. Those reactions or sequences of reactions that propose to employ a reaction in the presence of either significant inhibiting structural features or features that would lead to a proliferation of products can be eliminated. Even when it is not possible to predict the precise products or rates of individual reactions—as will often be the case when considering complex structural environments—it is still possible to assess the likely sources of complications in performing a particular synthetic reaction. By comparing the number and severity of these potential complications, theoretically well-motivated choices between potential synthetic routes can be made, even without being able to predict the outcomes of individual reactions.

The final stage of synthetic design is optimization, where the precise sequence of synthetic steps is worked through and control steps are added. The purpose of the control steps is to eliminate the complicating factors identified by carefully working through the proposed synthetic route. These control steps work by adding chemical groups to the synthetic intermediate that either eliminate the influence of complicating structural factors (called protecting groups) or promote the formations of particular products or intermediates during the course of subsequent reactions (called activating groups). After these control groups have done their job, they are removed at a later stage of the synthesis. The final ordering of the reactions in a synthesis depends upon what control steps are added during the course of optimization, and which control steps are necessary, or viable, can depend on the proposed ordering of a sequence of reactions. As a result, both aspects of the optimization of a synthetic plan must be worked out together. The entire process of optimizing a synthetic plan depends on an understanding of theoretical organic chemistry. First, the identification of where and when control groups are needed depends upon understanding how the structural environment influences a proposed reaction. Second, the selection of appropriate control groups depends on evaluating the plausibility of the synthetic reactions needed to add and remove the control group in the context of the relevant synthetic intermediate. And last, assessments of the optimal ordering of a sequence of synthetic reactions depends on comparing potential complications, and the need for control groups, among the various options. Considering, then, the important role of understanding both the mechanisms and structural factors affecting the progress of organic transformations in all three stages of synthetic design, I hope to have established that, and to a certain extent how, an understanding of theoretical organic chemistry facilitates the synthetic

design aspect of total synthesis problems (a concrete example of synthetic design is presented in Goodwin [forthcoming](#)).

Beyond synthetic design: a novel synthesis of longifolene

Though a theoretically well-motivated synthetic plan can aid tremendously in the process of developing a total synthesis, the “time, effort, and expense required to reduce a synthetic plan to practice are generally greater than are needed for the conception of the plan” (Corey and Cheng 1989, p. 2). Furthermore, it is often the case that an interesting new total synthesis makes use of novel synthetically useful organic transformations. The above account of synthetic design made no attempt to assess or characterize the role of the theory of organic chemistry in either of these important aspects of the practice of synthetic chemists. Synthetic design, as I portrayed it above, stops at the laboratory door and retrosynthetic analysis takes place against a fixed background of synthetically useful organic reactions. Obviously, then, any complete assessment of how understanding the theory of organic chemistry facilitates total synthesis must consider the role of theory in both the implementation of synthetic plans and the development of novel organic transformations. In the remainder of this article, I will attempt to fill out my account of the role of theory in total synthesis by considering both of these aspects. Before going on to do this, however, I want to explain why I think there will be less to be said, generally, about the role of theory in these areas. First, the implementation of a synthetic plan requires a lot of hard work and a lot of trial and error. Though theory is often useful in diagnosing errors, suggesting solutions, and constraining the range of things that need to be tried out, it is hard to say much in general about how this works. The role of theory in directing implementation is highly situation dependent and hasn’t been codified in a set of heuristic policies (like the steps in retrosynthetic analysis) that I exploited in the case of synthetic design. Similarly, the discovery of novel synthetic reactions is likely to be highly idiosyncratic. Many philosophers have remarked on the difficulties involved in describing what happens within the: “context of discovery”. The source of these difficulties seems to be that plausible accounts of how particular people come up with particular new ideas often seem to rely upon details of personal history and psychology. Though it is probably true, as Louis Pasteur said, that “chance favors the prepared mind”, and so that the more one understands the more likely one is to recognize and exploit opportunities for innovation, it seems unrealistic to expect much from a broadly applicable account of how this takes place.

Because of the anticipated difficulties in providing a general account of how theory contributes to these neglected aspects of total synthesis, I am going to approach this question by considering a particular total synthesis. This synthesis involves a novel synthetically useful transformation and it encountered some typical implementation difficulties in the laboratory. By articulating how theory helped in the development of this novel transformation and in avoiding the difficulties encountered during implementation, I hope to convey some sense of how theory contributes to the development of total syntheses, above and beyond its more obvious role in synthetic design. The synthesis that I am going to consider is, like the examples I used in earlier work (Goodwin [forthcoming](#)), a synthesis of longifolene (Volkman et al. 1975); however, it was developed over a decade after Corey’s original synthesis (Corey et al. 1964). This synthesis was interesting to synthetic chemists, in spite of the fact that a way of making longifolene was already known, because it made use of a new technique for the formation of bridged tri-cyclic structures; furthermore, it dramatically increased the overall yield of longifolene from

starting materials (from less than 8% to 21%). Whereas in Corey's original synthesis the rings in longifolene were fused together in a sequence of distinct synthetic steps, Volkmann's synthesis creates the tri-cyclic structure of longifolene in one step. Since each step in a synthesis diminishes the overall yield, it is generally advantageous to design syntheses using a few steps as possible. By characterizing and demonstrating the synthetic utility of a new technique for bridged ring formation, Volkmann's work provides synthetic chemists with a valuable new tool. This tool can subsequently take its place in the array of synthetically useful transformations considered during retrosynthetic analysis.

Volkmann and his collaborators apparently stumbled upon the possibility of a novel synthesis of longifolene while working on a completely different synthetic problem. They were experimenting with ways to make two-ring hydroazulene systems using acid catalyzed cyclizations in anhydrous conditions (a sample hydroazulene structure can be found in Fig. 1, where it is identified as an undesirable side product). In the course of their experiments, they got a side product with spectral properties that indicated that it was a tricyclic alcohol with the same basic carbon skeleton as longifolene. By making some subtle adjustments in their starting materials, it looked like it might be possible to generate a structure closely related to longifolene by running a reaction analogous to the one that had led to their accidental discovery. To work out whether this analogous reaction was plausible and, if so, how to run it so that it would favor the production of the longifolene analog rather than the hydroazulene structure, they considered the likely mechanism of the transformation.

Using their understanding of acid catalyzed cyclization reactions and the factors that contribute to the stability of carbocation intermediates, Volkmann and co-workers were able to make some plausible guesses about how and why the tricyclic longifolene analog would be produced during the course of reactions of the sort they had initially run. By considering the carbocation intermediate that would be generated while proceeding through the mechanism of the initial cyclization reaction, they discovered that there was potential for this intermediate to undergo an additional internal cyclization rather than reacting with an external nucleophile to form the hydroazulene (as had been originally intended). If the intermediate underwent this additional internal cyclization, then a tricyclic carbocation would be formed. Upon reaction with water, this carbocation would give a tricyclic alcohol analogous to longifolene (see Fig. 1 where the proposed mechanism is indicated in brackets). The problem with this proposed mechanism is that the tricyclic carbocation intermediate appears to violate (a natural extrapolation of) a rule of thumb, called Bredt's rule, which may be used to assess the stability of the proposed carbocation intermediate. Bredt's rule says that in small rings, carbons that are part of more than one ring (called bridgehead carbons) are not generally double bonded to any neighboring carbons because of the angle strain involved (Lowry and Richardson 1987, p. 8). In other words, Bredt's rule indicates that structural arrangements with a double-bonded carbon at a bridgehead tend to be energetically unstable, and the intermediate proposed by Volkmann and co-workers involves just such a structure (and so is likely to have significant angle strain). In the particular case of the proposed tricyclic carbocation, however, the angle strain indicated by Bredt's rule is counteracted by stabilization due to "homoallylic participation". Stabilization of this sort occurs when a double bond in an appropriate orientation contributes some of its electron density to the carbocation, thereby delocalizing the positive charge (Lowry and Richardson 1987, pp. 449–454). As a result, even though their proposed carbocation intermediate had some structural features that indicated that it would not be stable, the mechanism was still plausible because of compensating stability due to a different structural feature.

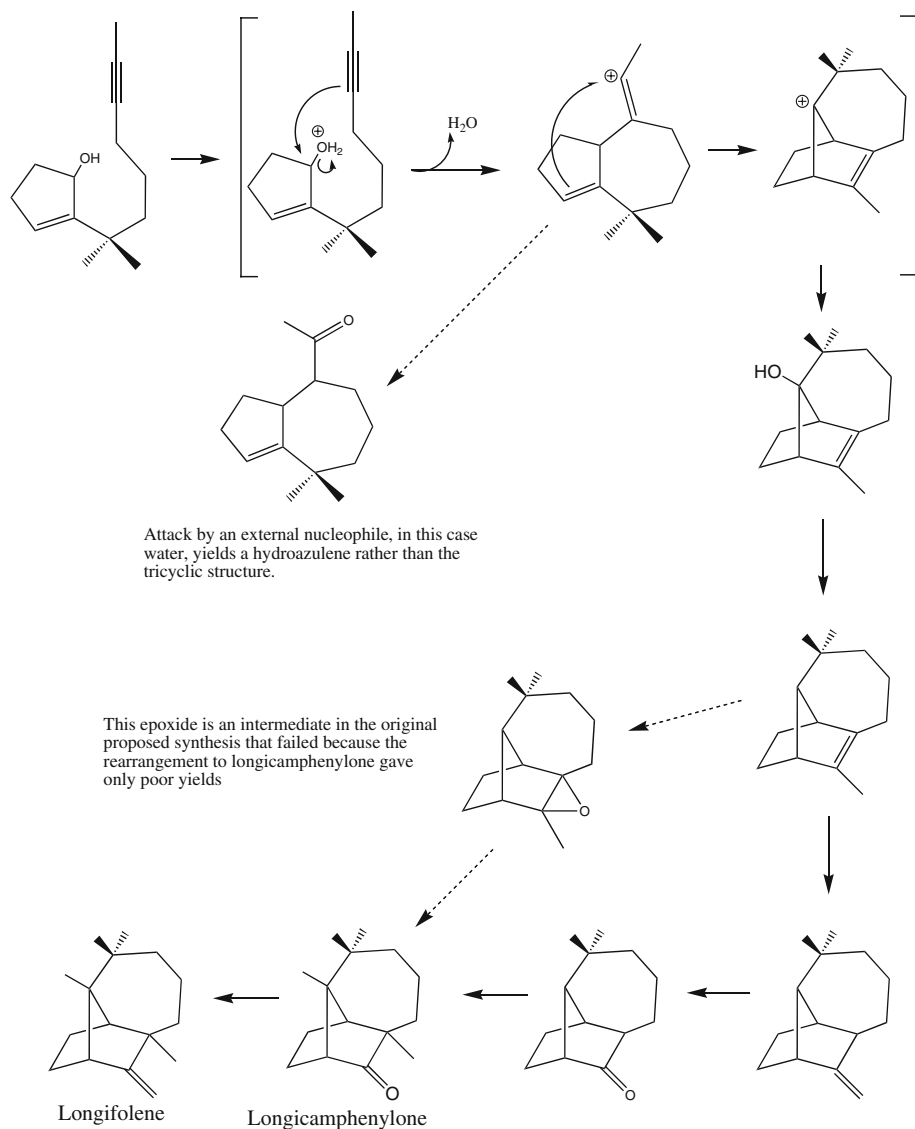


Fig. 1 Sketch of a novel synthesis of longifolene. A possible mechanism for the crucial step, with important side product indicated by the dashed line, is in brackets. An alternative, shorter route that failed in the lab is also indicated with dashed lines

According to Volkmann, these theoretical reflections on the mechanism of the proposed new synthetic transformation had the effect of “increasing our optimism about the success of the envisaged synthetic scheme” and of suggesting that “the formation of [the tricyclic alcohol] might be favored over the bicyclic product by minimizing the availability of nucleophiles in the cyclization medium” (Volkmann et al. 1975, p. 4777). In other words, he figured out, using his understanding of the mechanism, how the cyclization reaction could be run under conditions that would favor the production of the tricyclic product. So, their understanding of theoretical organic chemistry allowed them to understand how they

might have gotten a side product analogous to longifolene in their work with hydroazulenes. Furthermore, it enabled them to exploit this understanding by making theoretically informed decisions about the sort of reaction conditions that would make the reaction useful for the synthesis of tricyclic alcohols instead. While it may have been mere “chance” that Volkmann produced an analog of longifolene as a side product in a hydroazulene synthesis, the development of a novel, synthetically useful transformation required more than luck. Not only did Volkmann have to be prepared to recognize the potential importance of his side product, but also—as we have seen—he used his understanding of both the mechanisms of cyclization reactions and the structural features influencing the stability of carbocations to craft a synthetically useful transformation from his understanding of how the side product had been generated.

After Volkmann and co-workers had worked out the precise reaction conditions that optimized the production of the tricyclic alcohol in the novel step of their synthesis of longifolene, they still had to implement the remainder of their synthetic plan. As is common, if not typical, in synthesis, they found that they were unable to implement their original plan because it included a synthetic step that gave only very poor yields in the lab. In response to this setback, they devised an alternative, but less direct, synthetic route that avoided this difficult synthetic step. The original plan (see Fig. 1 and follow the dashed arrows from the alkene) had been to convert the tricyclic alcohol generated in their novel step into an alkene (by replacing the hydroxide group with a hydrogen) and then to epoxidate the alkene. It was hoped that the resulting epoxide would rearrange into longicamphenylone, which is one straightforward synthetic step from longifolene. It proved impossible to get the epoxide to rearrange into longicamphenylone in synthetically acceptable quantities, and so they began investigating alternative pathways from the tricyclic alcohol to longicamphenylone. Eventually, they worked out a less direct way to produce longicamphenylone (see Fig. 1 and follow the solid arrows from the alkene). The new strategy depended upon relieving the angle strain evident in the alkene (due to its violation of Bredt’s rule) generated by the first step in their original plan. In acid conditions, this alkene isomerized into an alkene with its double bond outside the ring (which is no longer in violation of Bredt’s rule), which could then be oxidized and methylated to form longicamphenylone. So when it proved impossible to implement their original plan, Volkmann and co-workers analyzed the structure of the intermediate where they had gotten stuck and found that it had a structural feature (the angle strain), the relief of which might be exploited as driving force behind an alternative synthetic route. Thus it was, at least in part, their understanding of the structural features influencing the stability of the relevant intermediate that helped Volkmann and co-workers to devise a way around the obstacles that emerged when attempting to implement their original synthetic plan.

We have seen, then, several additional ways that understanding the theory of organic chemistry aids in the solution of total synthesis problems. Theory can help the synthetic chemist explain what happened when a synthetic step does not perform as anticipated. This understanding can, in the implementation phase, be used to make theoretically grounded adjustments to the reaction conditions in the hope of getting the reaction to perform as desired. Furthermore, as in the Volkmann case, understanding how a side product may have arisen can suggest the possibility of a new synthetic tool. The subsequent refinement of such a suggestive possibility into a synthetically useful reaction also depends upon the chemist’s understanding of theory. In the Volkmann case, the probable mechanism of the proposed new reaction was examined to figure out ways to favor the desired product. Similarly, an analysis of energetically relevant structural features was used to both assess the plausibility of the proposed novel reaction and to design a viable alternative route when

the original synthetic plan proved difficult to implement. In spite of the fact the theory of organic chemistry often provides only contrastive, qualitative explanations (or predictions), it still manages to provide a foundation for not only the complex heuristics of synthetic design, but also for the implementation and innovation which are essential parts of the business of total synthesis.

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