



Understanding in synthetic chemistry: the case of periplanone B

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Abstract

Understanding natural phenomena is an important aim of science. Since the turn of the millennium the notion of scientific understanding has been a hot topic of debate in the philosophy of science. A bone of contention in this debate is the role of truth and representational accuracy in scientific understanding. So-called factivists and non-factivists disagree about the extent to which the theories and models that are used to achieve understanding must be (at least approximately) true or accurate. In this paper we address this issue by examining a case from the practice of synthetic chemistry. We investigate how understanding is obtained in this field by means of an in-depth analysis of the famous synthesis of periplanone B by W. Clark Still. It turns out that highly idealized models—that are representationally inaccurate and sometimes even inconsistent—and qualitative concepts are essential for understanding the synthetic pathway and accordingly for achieving the synthesis. We compare the results of our case study to various factivist and non-factivist accounts of how idealizations may contribute to scientific understanding and conclude that non-factivism offers a more plausible interpretation of the practice of synthetic chemistry. Moreover, our case study supports a central thesis of the non-factivist theory of scientific understanding developed by De Regt (Understanding scientific understanding. Oxford University Press, New York. <https://doi.org/10.1093/oso/9780190652913.001.0001>, 2017), namely that scientific understanding requires intelligibility rather than representational accuracy, and that idealization is one way to enhance intelligibility.

Keywords Scientific understanding · Factivity · Intelligibility · Synthetic chemistry · Philosophy of chemistry · Periplanone B

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1 Introduction

Nobody will deny that Kekulé's theory on the cyclic structure of benzene (1865) was a great advance in chemical understanding. But it is less straightforward to identify how precisely it enhanced chemists' understanding, and what the conditions for chemical understanding are. Of course, Kekulé's theory was based on empirical evidence and facilitated the synthesis of novel compounds and the discovery of new reactions (Berson, 2003, p. 63). But is there anything special about Kekulé's benzene ring that makes it an advance in chemical *understanding* rather than just an addition to the stock of chemical *knowledge*?

This is just one instance of a question that is hotly debated in contemporary epistemology and philosophy of science: Is (scientific) understanding just a species of knowledge, or is it of a fundamentally different nature? A bone of contention in this philosophical debate is the question of whether understanding is 'factive'. Knowledge is factive in the sense that one can only know p if p is true.¹ If understanding is simply a type of knowledge, as several philosophers have argued,² it must be factive as well. For example, Khalifa (2017, p. 11) defends the view that scientific understanding is nothing more than having "scientific knowledge of an explanation". If we adopt the view that understanding why p amounts to knowing the explanation of p , then the explanation of p must be true, or else one cannot know the explanation. Hence, on the understanding-as-knowledge view, understanding is factive.

While the factivist view of understanding may appear plausible at first sight, it turns out to be problematic when examined in more detail, at least in its naïve interpretation. The reason is that truth is a very strong condition. This becomes especially clear if we look at how understanding is achieved in scientific practice. Scientists often use representational devices (e.g. theories, models) that are far from true or accurate representations of the real world. In chemistry, for example, Kekulé's structure of benzene allowed chemists to gain insight into isomerism and the reactivity of a new class of compounds, despite the fictitious bond oscillation hypothesis that formed the basis of his theory (Berson, 2003, p. 58). Indeed, scientific models always involve idealizations, which by definition amount to a less accurate description of the object of understanding (the phenomenon that one wants to understand scientifically via the model). If such idealized models figure in scientific explanations, these explanations cannot be true, strictly speaking, and on the naïve factivist view they cannot contribute to understanding. Since it would be absurd to deny that much of modern chemistry (and science in general) provides understanding, this leads to a *reductio* of naïve factivism. Therefore, some philosophers have proposed a non-factivist conception of understanding—that severs the link between understanding and the truth of representational devices—while others have developed more sophisticated variants of

¹ Knowledge is factive on traditional philosophical accounts of it, such as the view of knowledge as justified true belief. There may of course be alternative accounts of knowledge that do not entail factivity. A discussion of these alternatives falls outside the scope of the present paper.

² Examples are Lipton (2004, p. 30), who writes: "Understanding is not some sort of super-knowledge, but simply more knowledge: knowledge of causes". Similarly, Mizrahi (2012, p. 240) suggests that "to understand why something is the case is to know what causes, processes, or laws brought it about". Other authors defending an understanding-as-knowledge view are Grimm (2006), Kvanvig (2009) and Kelp (2017).

factivism—that retain the link but allow for representational devices that can depart from the truth in specific ways.

In this paper, we address the central question in the debate about the factivity of understanding: Does scientific understanding require true theories and accurate representations or can it also be achieved by means of false theories or non-realistic, idealized models? We do so by presenting a detailed case study in a field that has as yet not received much attention in the philosophy of science literature: synthetic chemistry. The specific case concerns W. Clark Still's famous synthesis of periplanone B, in which there is a central role for highly idealized, representationally inaccurate models. Our case study supports a non-factivist view of understanding. In particular, it confirms a central thesis of the theory of scientific understanding developed by one of us (De Regt, 2017), namely that scientific understanding requires intelligibility rather than representational accuracy, and that idealizations are employed to enhance intelligibility.

The outline of the paper is as follows. Section 2 presents the case study of Clark Still's synthesis of periplanone B. To clarify our analysis, the representationally inaccurate models are highlighted in text boxes. Section 3 evaluates the case study in terms of the current philosophical debate on scientific understanding, especially in relation to the factivity issue (Sect. 3.1). In Sect. 3.2 we zoom in on two opposing analyses of how idealizations may contribute to scientific understanding (Khalifa vs. De Regt). Section 4 concludes.

2 Understanding in synthetic chemistry

2.1 Understanding through an inconsistent mix of qualitative concepts

Within chemistry there exists no doubt about the fact that the properties of molecules are fundamentally governed by quantum mechanics. The wave functions and energy levels of electrons and nuclei are found by solving the Schrödinger equation, and all chemical phenomena can be ultimately traced back to these solutions. Although the Schrödinger equation can be analytically solved only for very small molecules (i.e. the one-electron molecular ion H_2^+) due to the many-body problem, quantum-mechanical modelling methods exist which give increasingly accurate quantitative descriptions of molecular systems. However, while chemists firmly believe that quantum mechanics provides the true description of the nature of molecules, they often use simplified or non-realistic models and theories to understand the structure and reactivity of compounds at hand. A modern textbook on physical organic chemistry explains why:

With the advent of universally available, very powerful computers, why not just use quantum mechanics and computers to describe the bonding of any molecule of interest? In the early twenty-first century, it is true that any desktop computer can perform sophisticated calculations on molecules of interest to organic chemists. (...) However, for all their power, such calculations do not necessarily produce *insight* into the nature of molecules. A string of computer-generated numbers is just no substitute for a well-developed *feeling* for the nature of

bonding in organic molecules. Furthermore, in a typical working scenario at the bench or in a scientific discussion, we must be able to rapidly assess the probability of a reaction occurring without constantly referring to the results of a quantum-mechanical calculation. Moreover, practically speaking, we do not need high-level calculations and full molecular orbital theory to understand most common reactions, molecular conformations and structures, or kinetics and thermodynamics. (Anslyn & Dougherty, 2006, p. 3; original italics)

Arguing along similar lines, Hoffmann has noted that, despite their strong belief in realism, chemists use a “deeply inconsistent” mix of theories to generate piecemeal understanding (2007, p. 330). He adds that it is through this “partially irrational reasoning” that new compounds are synthesized and reactions discovered (*ibid.*, p. 334). This productivity is fueled by the use of chemical concepts: qualitative and somewhat vaguely defined models (especially when first introduced) which are often irreducible to physics. Examples of such concepts are aromaticity and functional groups (Hoffmann, 2007), oxidation states (Hoffmann, 1998), and hybridization (Shaik, 2007).

Whether or not such a concept is realistic and sufficiently well-defined does not determine the extent to which it drives scientific progress. In his book *Chemical Discovery and the Logicians’ Program*, Berson (2003) presents multiple historical cases of “false but nevertheless fruitful theories” (p. 133), including Woodward Fission and Kekulé’s theory of benzene. In the epilogue he concludes that “the experiences of science show that the quality of a theory as evaluated by logical standards is not a guarantor of the fruitfulness of the theory” (p. 180). Berson and Hoffmann explain the fruitfulness of such theories in similar ways. Berson states that flawed theories can “nevertheless organize a great body of empirical fact” (p. 174), while Hoffmann (2003, p. 11) notes that “they carry tremendous explanatory power (...) by classification, providing a framework (for the mind) for ordering an immense amount of observation.” To understand and manipulate an otherwise overly complicated object such as a molecule, these qualitative and idealized models are combined, each giving partial insight in its properties. When the chemist succeeds in making a molecule or finding a new reaction, it is irrelevant whether her understanding originated from such a self-contradicting mix of non-realistic theories. The result of a successful synthesis is the establishment of a way to make a molecule, and the utility of theories is validated by the success of the synthesis. The synthetic pathway remains understood through intelligible theories, while justification of the synthesis is found in the spectral data confirming the formation of the product.

This amounts to a pragmatic approach, as has been pointed out by Weisberg (2008) in his discussion of the concept of the chemical bond. Different classical and quantum-mechanical concepts of the covalent bond are used, depending on their insightfulness in a certain context. Weisberg (2008, p. 933) notes that chemists, to his dissatisfaction as a philosopher, “simply demand that bonding theories be useful for making predictions and aiding in the synthesis of new molecules. The underlying ontological status of the bond holds little interest.” For the practical reason of generating understanding, localized representations of bonding are frequently used instead of their more realistic delocalized counterparts. Shaik (2007, p. 2016) explains that, even in the field of computational chemistry, “most chemists actually think with a localized representation,

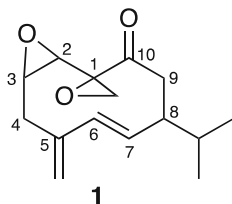


Fig. 1 Tentative structure of periplanone B

and at the same time they carry out computations with delocalized-dominated software packages, and many hold the belief that the delocalized description is the only correct representation of molecules, while the localized picture is somehow archaic and/or wrong.” While delocalized representations can be universally applied and are more consistent with quantum mechanics, the localized representations explain and help to intuitively predict the structure of a molecule (Hendry, 2008).³

2.2 Chemistry and chess: qualitative concepts to understand overwhelming complexity

To illustrate the role of these intelligible concepts in scientific practice, we will turn in the next section to an example from synthesis: the branch of chemistry concerned with the construction of molecules such as pharmaceuticals, dyes, or plastics. Before the introduction of powerful analytical techniques such as NMR spectroscopy, synthetic chemists often focused on making natural products to confirm their molecular structure. An example is the case we present in the next section: the synthesis of periplanone B by Clark Still (1979). Whether the goal is to confirm the structure of a natural product or to make a molecule of revolutionary architecture,⁴ the synthetic chemist needs to obtain the desired compound in the most efficient way and highest purity. In addition, a successful synthesis may reveal a path to a whole new class of molecules with a shared structural element. The knowledge gained during the synthesis of periplanone B, for example, could be used to make other molecules with ten-membered rings (Fig. 1).

A synthesis is developed from small, commercially available starting materials, which are transformed through a series of reactions to give the final product. The number of possible reaction paths is nearly infinite and the right pathway is not derivable through calculation. Instead, the chemist uses his piecewise understanding of chemical phenomena and a sense of intuition to select a few plausible routes to pursue and solve unexpected problems encountered during the process.

³ It has also been argued that the localized versus delocalized representation is an example of Bohr’s complementarity principle like the concept of wave-particle duality (Gu et al., 2017).

⁴ For instance, in drug development, a promising natural product may be found of which the pharmaceutical industry requests a synthesis in order to modify the molecule and increase its potency, decrease its toxicity, or facilitate its administration. In rare cases, such as the chemotherapy medication Paclitaxel or Taxol derived from the Pacific yew, the natural compound is extremely scarce, necessitating the development of a synthesis or semisynthesis.

The way an experienced chemist limits his choice from an inconceivable number of possibilities to a few synthetic routes may be compared to a game of chess. A chess player must know the rules to participate, but only becomes better by playing and learning to recognize patterns in the game. What marks the difference between a grandmaster and a beginner is not primarily the depth of their calculation, but their evaluation of chess positions. When a grandmaster encounters a certain position on the board, she is immediately able to exclude most options and consider just a handful of moves. When the grandmaster calculates a couple moves ahead, she again focuses on the few best moves in each possible position. In this way, she is able to calculate multiple moves deep as she narrows down the possible continuations by intuitively selecting the optimal variations. A beginner, on the other hand, is unable to narrow down his options and already gets overwhelmed in the starting position. Calculating ahead becomes impossible as the number of moves he needs to consider increases too quickly with the depth of his calculation.

In chess, the ability of identifying a few plausible moves stems from understanding or 'seeing' tactical and positional patterns, such as a double attack or fianchetto. While most chess computers evaluate positions 'realistically' by quantitatively assessing possible sequences,⁵ the grandmaster uses intuitive pattern recognition as a qualitative model to get insight in an otherwise overly complex system. As we demonstrate in the following section, in a similar vein chemists use chemical concepts to understand molecular structure and reactivity, to find a few persuasive synthetic pathways and think ahead to determine the suitable reaction order.⁶

2.3 A case study: the synthesis of periplanone B

In 1952 researchers discovered that female American cockroaches (*Periplaneta americana*) secrete an extremely potent sex pheromone (Roth & Willis, 1952). The male cockroaches turned out to be so excited by the compound (less than 10^{-12} g incites a response)⁷ that the tiniest impurity would ruin a bioassay. No matter how hard the researchers tried to separate and purify the fractions, the cockroaches would respond to every presented sample, preventing identification of the active component. Another complicating factor was the miniscule amount of pheromone (less than 10^{-6} g) stored by the female cockroaches. It took almost 25 years and an extraction program including 75,000 virgin female cockroach participants, before Persoons et al. (1976) finally solved the problem and isolated two active components: periplanone A and B. By characterization of its spectra, structure **1** was tentatively assigned to periplanone B

⁵ Although modern chess engines such as Stockfish use heuristics to limit the enormous tree of variations, they still evaluate millions of positions using previously assigned weights (e.g. for pieces or positional control). Recently, the neural network AlphaZero decisively defeated Stockfish after being trained solely by playing games against itself (Silver et al., 2018). The heuristics learned during its self-play session unfortunately remain unknown.

⁶ The reaction order is crucial because the reactant might not only modify the intermediate product at the desired place, but also affect other parts of the molecule. This makes it for example necessary to install the most vulnerable parts of the product in the final stages of the synthesis.

⁷ This amounts to almost 2.5 billion molecules, which is tiny compared to the 6×10^{23} H₂O molecules in just 18 mL of water.

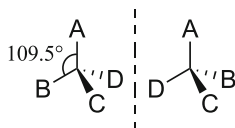


Fig. 2 Tetrahedral conformation of carbon atom

(Fig. 1), but the relative stereochemistry of the compound remained unknown.⁸ On his own, Still (1979) developed a highly elegant and flexible synthesis towards three stereoisomers of structure **1**, which is rather remarkable in a period characterized by extensive collaboration. One of these was identified to be periplanone B, since its spectral and biological data matched with those of the pheromone sample. Still's synthesis of periplanone B is noted for its flexibility, as his insight in the conformation of ten-membered rings allowed for selective preparation of multiple stereoisomers (Nicolaou & Sorensen, 1996, pp. 211–219).

The different stereoisomers of structure **1** arise from its asymmetry, or chirality as chemists say. When carbon atoms have four different substituents they are chiral, taking on an approximately tetrahedral geometry. This is represented in two-dimensional drawings with a bold line for the substituent in front of the plane and a dotted line for the one positioned behind the plane (see Fig. 2). The two stereoisomers of the molecule are mirror images of each other, which cannot be superposed (this can be confirmed by imagining to hold the molecule at substituent A and rotating it). In fact, all mirror images of asymmetric objects exhibit this property, for example left hands which cannot be superposed on right hands. Organisms use chiral molecules such as amino acids to build receptors, enzymes and other large biomolecules. The asymmetric building blocks lead to asymmetric receptors, and in the same way as only one of your hands will (properly) fit in a glove, two stereoisomers of a molecule will fit differently in the receptor. As a result, only one of all the possible stereoisomers of structure **1** will awaken the interest of the male cockroach, while the others will not fit in his receptor.

Structure **1** contains multiple chiral carbon atoms (i.e. C₁, C₂, C₃, and C₈) and hence many stereoisomers exist. Consequently, Still devised a flexible synthetic plan with key intermediate **2** (Fig. 3), which he could then convert to each of the possible stereoisomers until he found the one matching the spectral description. It is important to note here that EE is a so-called protective group, which prevents reactive parts of a molecule from reacting in unwanted ways and can be simply removed when the vulnerable parts need to be modified. Intermediate **2** contains a ten-membered ring and a pattern in its structure suggests a possible way of synthesizing it. The carbonyl (C=O) at C₁ and double bond between C₆ and C₇ of **2** remind the trained eye of an

⁸ For the reader who is unfamiliar with structural formulas, it is important to note that in drawings of molecules the carbon and hydrogen atoms are usually omitted for clarity. Looking at structure **1** in Fig. 1, every vertex between two lines (i.e. bonds) represents a C atom. For example looking at C₉, we can see that it is bonded to C₈ and C₁₀. C₉ is consequently a CH₂ group because carbon shares four bonds with neighboring atoms. The semiotics of chemistry visible here consists of idealized representations used for understanding and communication. Whether chemists use a structural formula or another type of model or symbol to signify a molecule to their readers, largely depends on the tradeoff between accuracy and intelligibility. For a detailed analysis on this and related topics, see (Hoffmann and Laszlo, 1991).

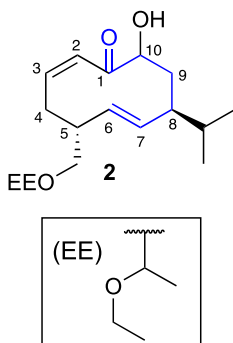


Fig. 3 Structure of the key intermediate in Still's synthesis

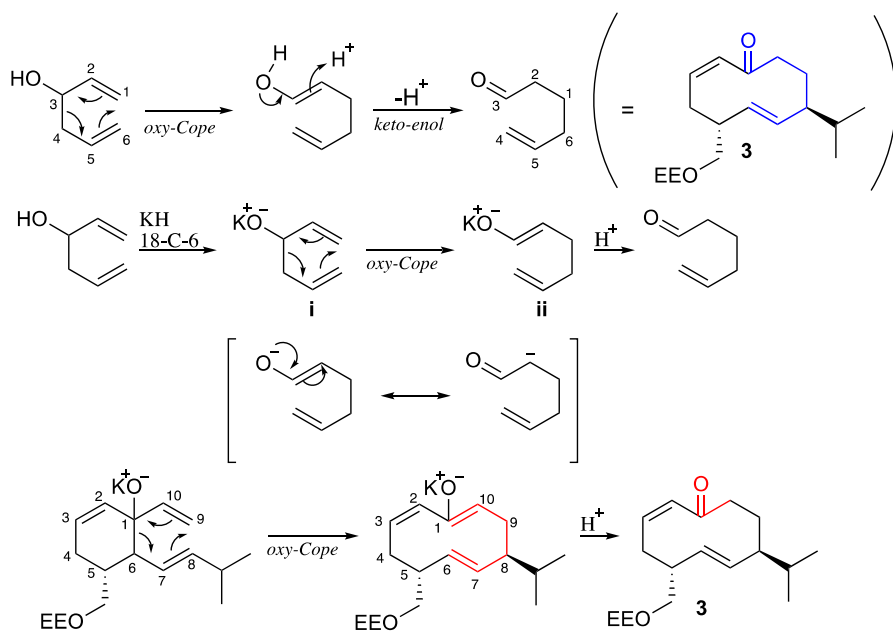


Fig. 4 Mechanism of the Oxy-Cope rearrangement used to form intermediate **3**

oxy-Cope rearrangement. The result of an 'oxy-Cope' is displayed in Fig. 4: the C₃–C₄ bond is broken and a C₁–C₆ bond formed, while the two double bonds shift position. Subsequently, a H atom switches position in a so-called *keto-enol* tautomerization to give the energetically favored carbonyl. Looking at the oxy-Cope rearrangement, we can see that if a six-membered ring is fused to C₃ and C₄, a ten-membered ring will form as in compound **3**.⁹

⁹ The reaction is stereocontrolled as product **3** contains one new chiral carbon atom (C₈), and one stereoisomer is selectively made with the isopropyl group in front of the plane (c.f. bold line). The stereocontrol originates from the ordered transition state of the reaction. For a detailed explanation see Paquette (1990).

Electron pushing, as represented by the curved arrows in Fig. 4, is a formalism first introduced by Kermack and Robinson (1922) to denote the motion of pairs of electrons and illustrate reaction mechanisms. The curved arrows originate from a bond or an electron pair residing on an atom (e.g. the O-atom in the *keto-enol* step in Fig. 4) and point to the destination of the moving electrons. The electrons are shown in their new location after the straight 'reaction arrow' that indicates the progression from starting material to product. In reality, electrons do not migrate as orderly as the curved arrows indicate, but electron pushing is a helpful formalism to make reactions mechanisms more intelligible by signifying the role of each reactant and the order in which they participate. This is the first qualitative concept in chemistry that we mention and throughout the text we will highlight such auxiliary theoretical frameworks used for generating understanding.

The rate of the oxy-Cope rearrangement was improved by adding base, potassium hydride (KH, a very ionic reagent consisting of K^+ and H^-), which takes away the proton to form H_2 and puts K^+ in its place (Fig. 4). The reaction goes faster because the intermediate **ii** (an enolate) is stabilized relative to **i**, as can be seen from the resonance structures between squared brackets.

Resonance structures form an explanation of delocalization, introduced by Pauling (1931) to account for the special stability of molecules for which one can write two or more classical bonding patterns (i.e. Lewis structures). Resonance structures are non-realistic descriptions, as molecules do not actually alternate between these structures. The molecule rather exists as a single form which lies somewhere in between the extremes represented as resonance structures. The idea often marks stability, but just as often (e.g. in the case of an allyl anion) shows that one can write Lewis structures for a molecule in multiple ways and predict reactivity based on these.

Despite their inaccuracy, resonance structures provide insight in the nature of conjugated compounds (Berson, 2003, p. 65): in intermediate **ii** the negative charge partly resides on the oxygen and the carbon atom, while in compound **i** the oxygen atom has to carry the heavy load all by itself, which is thermodynamically unfavorable. The rate of the oxy-Cope rearrangement is thus enhanced by adding base (Nicolaou & Sorensen, 1996, p. 214), since the formation of intermediate **ii** becomes thermodynamically driven (a chemist's way of saying that a reaction amounts to a net release of free energy).

In addition to KH, crown ether 18-crown-6 (18-C-6) was used to further improve the reaction rate. This can be qualitatively understood in the following way: 18-C-6 has exactly the right dimensions to capture a K^+ ion (Fig. 5) and stabilize its positive charge through electron donation by the oxygen atoms in the ring. The K^+ ion will behave less

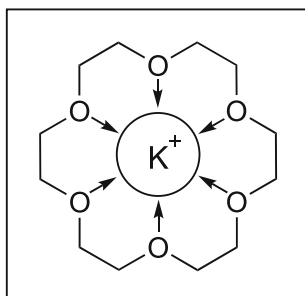


Fig. 5 Capturing of K^+ by 18-C-6

like a point charge once captured by 18-C-6, because the positive charge is smeared out over the crown ether ring. As a consequence, the negative charge on oxygen is less stabilized by the potassium counterion, and the formation of **ii** becomes even further thermodynamically driven. In addition, the crown ether and its captive form a complex much larger than the free K^+ ion, which cannot get as close to the negatively charged oxygen atom. If the K^+ counterion is less effective in alleviating the negative charge and a ‘naked anion’ is created, then the relative thermodynamic advantage of **ii** over **i** increases because its surplus electron density is stabilized through resonance (Fig. 4).

A key concept is **electronegativity**, which is instrumental to understanding nucleophilic attacks and other reactions, for instance in acid–base chemistry. Electronegativity is defined as the ability of an atom to attract a pair of electrons. Although electronegativity had been studied since the time of Avogadro (Jensen, 1996), it was Pauling who developed the first scale (1932). There are different methods of assigning electronegativity values to atoms, which are all based on empirical data such as bond-dissociation energy. Electronegativities are not observables, but a relative scale providing qualitative understanding. Electronegative elements such as fluorine and oxygen attract electrons more strongly than the less electronegative carbon and hydrogen.

Elaborating on every reaction step towards key intermediate **2** would require too detailed explanations. Instead, we will go into the main rationale and include some of the highlights of the journey. The synthetic route towards **2** starts from cyclohexenone derivative **4**, whose hydroxyl group (C–OH) is protected with an ethoxyethyl ether (EE, c.f. structure in Fig. 3). Compound **4** is converted to its enolate **5** using the strong base LDA (Fig.

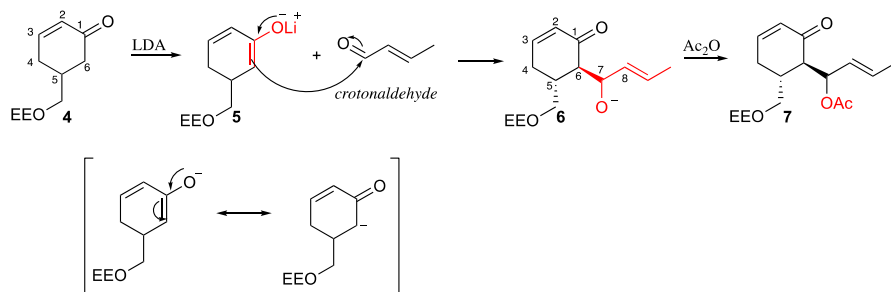


Fig. 6 Aldol reaction and acylation leading to compound **7**

6). Again, the resonance structures between square brackets show that the negative charge is partitioned between the oxygen and carbon atom. Because both atoms consequently have extra electron density, they can act as nucleophiles. A large share of chemical reactions occurs between electron-rich molecules called nucleophiles and electron-deficient compounds or electrophiles.

Hence, when oxygen and carbon share a bond, the oxygen atom becomes electron-rich and the carbon atom electron-deficient, resulting in a C–O bond which is stronger than C–C or O–O bonds.¹⁰ This also holds for the carbonyl in crotonaldehyde (Fig. 6), making this carbon atom electron-deficient, electrophilic and hence susceptible to nucleophilic attack by the electron-rich enolate. After this aldol reaction, product **6** is reacted with acetic anhydride (Ac_2O) to give **7**.

The newly installed –OAc of **7** is a leaving group, a very useful concept defined as a part of a molecule which can be removed as a formal anion, eventually to be replaced by some other desired piece. Before the leaving group can be kicked off, compound **7** first needs to be further protected, because its enone group is susceptible to attack and needs to be preserved (Fig. 7). As can be seen in the example given of butenone and butene, an enone will react with a nucleophile, while an alkene will not because the negative charge ends up on carbon rather than oxygen. Because carbon is less electronegative than oxygen and hence less able to stabilize the negative charge, the product is in this case energetically unfavored compared to the butene starting material. Compound **7** is first protected with LiSnMe_3 as Me_3Sn^- attacks the enone moiety (in the same way as a hypothetical nucleophile reacts with butenone in the example above) to give enolate **8**, which is then protected with trimethylsilyl chloride (TMSCl) resulting in **9** (Fig. 7).

Now all vulnerable parts are tucked in, compound **9** is subjected to so-called $\text{S}_{\text{N}}2'$ displacement with lithium dimethylcuprate to install a second methyl group,¹¹ after which acetate departs as the leaving group (Fig. 8). The protective groups on product **10** are then removed through oxidation with *m*-chloroperbenzoic acid (*m*CPBA) to

¹⁰ One way to think about the resulting bond is that in addition to the sharing of electrons between atoms, there is an additional component that is electrostatic as opposite charges attract each other.

¹¹ The $\text{S}_{\text{N}}2'$ reaction is an important class of reaction mechanisms, involving substitution in nucleophilic fashion and 2 molecules. The apostrophe in $\text{S}_{\text{N}}2'$ denotes that the nucleophilic attack is happening at an atom different from where the leaving group is removed (see Figs. 8, 9, 10).

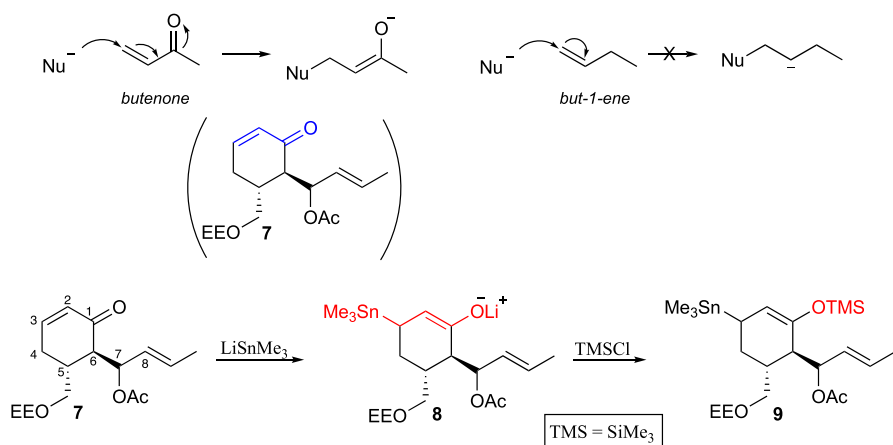


Fig. 7 Reactivity of the enone group necessitates its protection in compound **7**

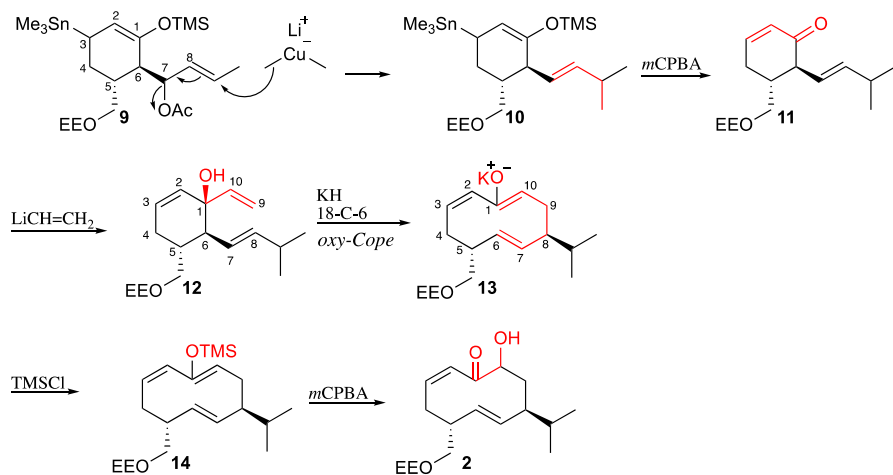


Fig. 8 Synthesis of key intermediate **2** through an S_N2' reaction, oxy-Cope rearrangement, and oxidation

give enone **11**. Construction continues on **11** as the recovered carbonyl is reacted with vinyl lithium to give **12**. The final carbon arm is now in place for the oxy-Cope rearrangement and formation of the ten-membered ring compound **13**. To turn **13** into key intermediate **2**, the enolate is first reacted with trimethylsilyl chloride and then converted to **2** through Rubottom oxidation with *m*CPBA, of which the details are of no concern here.

In the previous reaction schemes, the attentive reader might have spotted results which seem inconsistent at first glance. Comparing the reactions of compounds **7** and **11** in Figs. 7 and 8, we see that two enone groups react in different ways as nucleophiles add either to the C–C double bond (in the case of **8**) or carbonyl group

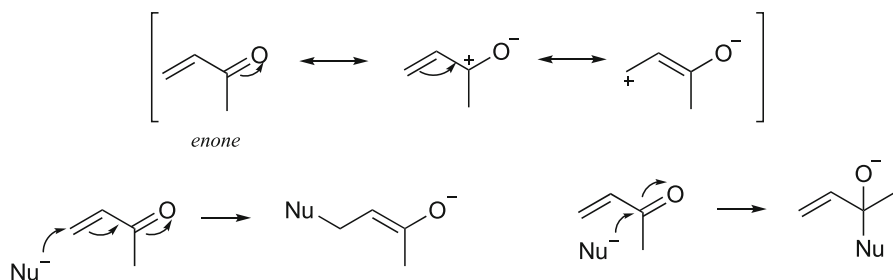


Fig. 9 Resonance structures of an enone used to understand its reactivity

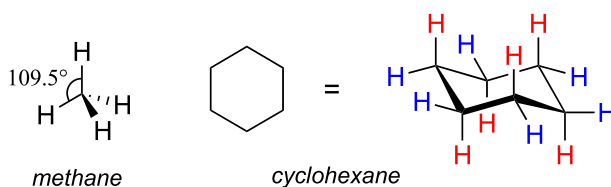


Fig. 10 Conformations of methane and cyclohexane

(in **12**). To understand how to modify such compounds in the desired way, chemists use a combination of explanations. Looking at the resonance structures of the enone in Fig. 9, it becomes clear that it contains two electrophilic sites, both of which could be attacked by a nucleophile. The carbon of the carbonyl group is more electron-deficient because it is closer to the electronegative and hence electron-withdrawing oxygen atom. The electrostatic interaction between the more electron-deficient carbon and the nucleophile is stronger, increasing the rate of the reaction. Addition to the C–C double bond gives an enolate product (and ketone after protonation), which is thermodynamically more favorable than the product of the other reaction. The slow addition to the C–C bond gives the product with the lowest energy, but addition to the carbonyl proceeds quicker. By choosing the right reaction conditions, one of the two additions can be promoted. At low temperatures and short reaction times, the reaction occurs under ‘kinetic control’ and the fast addition to the carbonyl becomes predominant. If the reaction is performed at high temperatures and allowed to proceed for a longer time, an equilibrium is established which strongly favors the formation of the thermodynamic product. So, under ‘thermodynamic control’, addition to the C–C double bond is the main reaction.

A second way of understanding the reactivity of enones is by looking at the nature of the nucleophile and electrophile, which can be classified using the HSAB concept (hard and soft acids and bases).¹²

¹² HSAB describes the behavior of Lewis acids and bases.

The **HSAB concept** was developed by Pearson (1963) and states that ‘hard’ species preferably form bonds with other hard species, and ‘soft’ molecules also preferably bind to other soft molecules. Hard compounds are small, charged species like H^+ and CH_3O^- which have strong electrostatic interactions, while soft compounds such as I^- and CH_3S^- are large, have a low charge density and their interactions are covalent in character. Hard–hard interactions are driven by attracting partial charges, while soft–soft interactions originate from orbital overlap of the base (filled orbital) and acid (empty orbital). The concept is especially useful in inorganic chemistry to match metals with suitable ligands.

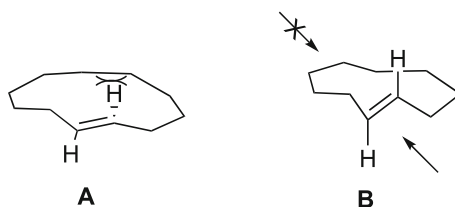
The addition reactions to the enone groups of **7** and **11** were performed with the large, soft Me_3Sn^- nucleophile and the small, hard $\text{H}_2\text{C}=\text{CH}^-$ nucleophile. The hard $\text{H}_2\text{C}=\text{CH}^-$ species indeed added to the carbonyl carbon of **11**, the most electron-deficient, charged and hardest site, while the soft Me_3Sn^- nucleophile bonded to the less charged and softer C–C double bond. Hence, the seemingly inconsistent results are in fact controlled outcomes achieved by setting the right reaction conditions and choosing the suitable type of nucleophile.

For the remaining task of synthesizing the possible stereoisomers of **1** from intermediate **2**, two epoxides (an oxygen bonded to two carbon atoms) must be introduced at C_2 and C_1 (Fig. 1). By installing a fourth substituent on C_1 and C_2 these carbon atoms become chiral, so reactions need to be found which produce one stereoisomer selectively. The reactivity of **2** depends on the shape of the ten-membered ring.

The shape of a molecule, called the conformation, is to a large extent explained by steric effects, which arise from the size or bulkiness of a molecule. If atoms within a molecule are positioned close to each other, the result is repulsion. Ultimately, it is the negative charged electrons of one atom which repel on the other atom if they come too close. In the same way, the concept of **steric hindrance** is used to understand how the size or bulkiness of a molecule can slow down or prevent a reaction from happening: if a reactive center of a molecule is surrounded by bulky groups, it cannot form a bond with other molecules due to the repulsion exhibited by the large substituents. An analogy would be a dog wearing an Elizabethan collar after surgery. The dog’s head (the nucleophile) wants to reach the itchy stitches (the electrophile), but the steric hindrance of the collar prevents him from doing so.

The optimal conformation of a molecule is a compromise between favorable electronic interactions and minimized steric repulsion between its constituent atoms. A carbon atom with four substituents, for example methane (CH_4), preferably adopts a tetrahedral conformation with bond angles of 109.5° to place the substituents as far apart as possible to minimize steric repulsion (Fig. 10). Unlike methane, most carbon

Fig. 11 Two possible conformations of a ten-membered cyclic alkene



atoms do not have four identical substituents and hence will deviate slightly from the 109.5° angle.¹³ Although the exact bond angles within a specific molecule can be approximated with computational methods, the qualitative concept of steric effects is needed to provide understanding of the structure of whole classes of compounds and to intuitively make inferences about their reactivity.

The conformation of cyclic molecules is especially complicated because concepts such as ring strain come into play. To start with a molecule free from ring strain, cyclohexane is displayed in Fig. 10. Although it is usually represented as a flat hexagon in structural formulas, the molecule actually adopts a ‘chair’ conformation which allows the structure to have approximately the ideal tetrahedral geometry angles of 109.5° (Fig. 10). Another important property of cyclohexane is that not all positions on the ring are the same, while in methane all hydrogens are identical. From studies of more and less bulky substituents the conclusion was drawn that axial substituents (in red) experience more mutual steric repulsion than the equatorial substituents (in blue): if cyclohexane carries one bulky substituent, it will preferentially adopt a conformation with the largest group in equatorial position. Cyclic molecules with rings smaller and larger than cyclohexane do experience ring strain. The three carbons of cyclopropane form an equilateral triangle with bond angles of 60° (a large difference indeed from the ideal 109.5°), leading to steric repulsion between the carbon atoms and a tendency to undergo ring-opening reactions to relieve this strain. Rings larger than cyclohexane, such as the ten-membered ring in compound **2**, do not have the problem of angle strain like cyclopropane. They do, however, experience transannular strain, which is the steric repulsion between substituents on other positions on the ring.

In Fig. 11, two conformations of a ten-membered ring with a double bond are shown schematically, resembling the shape of compound **2**. Compound **2** will not adopt conformation **A** (or omelet if you like), because one of the hydrogens of the double bond will collide with atoms at the opposite side of the ring, resulting in unfavorable ‘transannular interactions’. Conformation **B** is therefore adopted, in which the plane of the double bond is perpendicular to the plane of the ring. Still was well aware of this tendency and realized what the consequences for the reactivity of compound **2** could be. In conformation **B**, an incoming reactant can only approach the double bond from the outside of the ring (i.e. peripheral attack) and not the inside, because it would be too sterically hindered on its way. As a result, only one stereoisomer will be formed in such a reaction. If the molecule adopts conformation **A**, by contrast, a reactant could approach from either above or below the omelet, resulting in the formation of

¹³ For instance, because two of the four substituents are larger and therefore positioned further apart from each other to minimize repulsion.

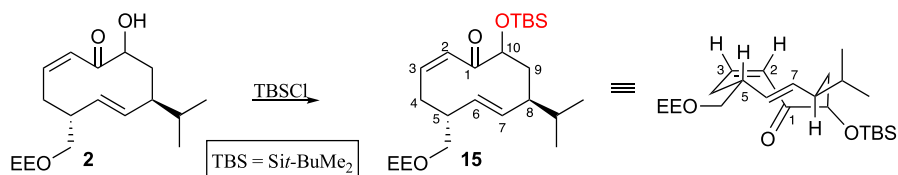


Fig. 12 Protection leading to compound **15**, of which the conformation is determined by the OEE group in equatorial position

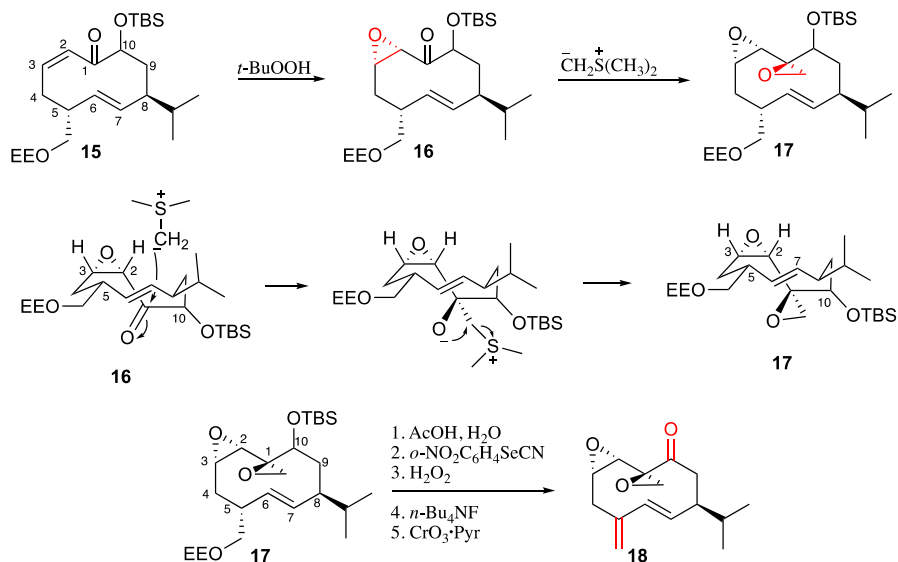


Fig. 13 Synthesis of **18**, which turned out to be different from periplanone B

two stereoisomers. Still noted that this theory is by no means infallible and added that “this approach to stereochemical control in medium-ring systems must be used with caution”. Nevertheless, this method gave the desired result. Before the C₂–C₃ double bond could be epoxidized,¹⁴ the reactive hydroxyl group was first protected to give **15** (Fig. 12). From the expected conformation of **15** it can be deduced that the incoming oxygen atom can only approach the C₂–C₃ double bond from below: the large OEE group must be in equatorial position to minimize steric repulsion, locking the hydrogen atoms at C₂ and C₃ above the ring, while the interior of the ring shields off the other side. Epoxidation indeed went as expected resulting in the formation of a single stereoisomer **16** (Fig. 13). The second epoxide of **17** was introduced by attack of the carbonyl group of **16** by dimethylsulfonium methylide. Again, the stereocontrol derives from peripheral attack as the nucleophile can only approach from behind the ring and force the oxygen atom to the front. Through a series of reactions of which

¹⁴ The C₆–C₇ double bond is present in the final structure **1** of periplanone B and must remain intact. Fortunately, the C₂–C₃ double bond is more reactive because it is part of an enone (see Fig. 7).

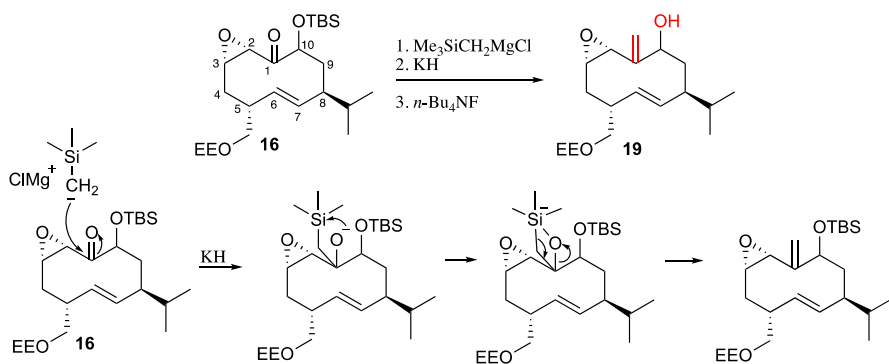


Fig. 14 Removal of the carbonyl group in compound **16** and deprotection of the alcohol to access stereoisomers with an opposite configuration at C₁

the details are not of concern here, the protective groups of **17** were removed to form the carbonyl and C₅ double bond in structure **18**.¹⁵ All structural elements were now in place (c.f. structure **1**) and the spectral data of **18** were compared to a periplanone B sample from the cockroach. Unfortunately, the spectra did not match and a second stereoisomer had to be tried instead.

Before we continue with Still's synthesis, let us take stock of the qualitative concepts he uses and expects his readers to understand. Some of the concepts we have seen are resonance structures; chirality; isomerism; steric effects; leaving groups; electrostatics; electronegativity; protecting groups; substituent effects; and the general idea of activation energy, leading to kinetic and thermodynamic control of reactions. The conclusions drawn from these concepts could also have originated from more realistic quantum-mechanical calculations, reaction by reaction. These conclusions would be generated in a bare and quantitative form, however, and would not provide the understanding required for thinking of new synthetic pathways towards the target molecule, let alone towards other compounds.¹⁶

Starting from compound **16**, Still's next goal was to synthesize a stereoisomer with opposite configuration at C₁ with the oxygen atom of the epoxide sticking to the back of the molecule (the coat-hanger is turned around). In the synthesis of the first stereoisomer **18**, the epoxidation was performed on the carbonyl group. This strategy inevitably leads to the wrong configuration, because incoming nucleophiles can only approach from the back through a peripheral attack, pushing the oxygen atom to the front. Therefore, the carbonyl needed to be removed and Still converted it into a double bond through Peterson–Chan olefination, giving **19** after removal of the TBS protective group (Fig. 14). During the olefination, the carbonyl is first attacked by the silyl carbanion, after which potassium hydride is added to displace the magnesium cation and increase the electron density on the negatively charged

¹⁵ The consecutive reactions were performed: acid hydrolysis of the EE protective group, selenylation, selenoxide elimination to form the C₅ double bond, desilylation to remove the TBS protective group, and finally Collins oxidation to convert the hydroxyl to the ketone.

¹⁶ For an interesting and extensive discussion on the relation between quantitative assessment in the form of simulation and understanding, see the tripartite essay by Hoffmann and Malrieu (2019).

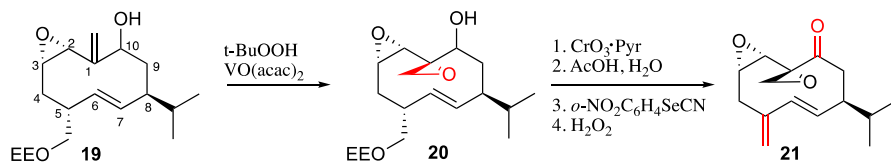
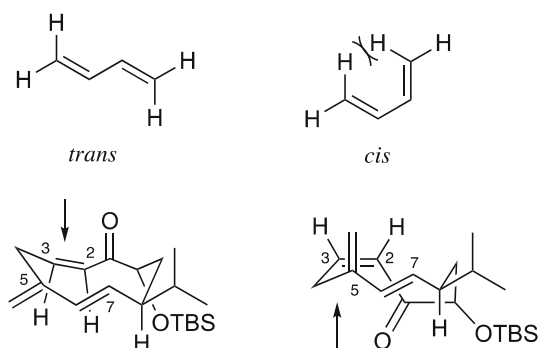


Fig. 15 Selective epoxidation at C₁ to form stereoisomer **21** with an opposite configuration at C₁

Fig. 16 Favorability of the *trans* conformation enabling selective epoxidation from above



oxygen. This makes the oxygen atom more reactive and drives the elimination of trimethylsilylanolate, generating the double bond.

In contrast to the epoxidation of compound **15** (Fig. 13), which only targeted the more reactive double bond of the enone, selective epoxidation of **19** looks difficult because the double bonds at C₁ and C₆ are quite similar. Fortunately, there is one element of **19** differentiating the two double bonds, which Still used to his advantage. The hydroxyl group at C₁₀ can lure certain reagents to the back side and this hydroxyl-directed epoxidation gave the desired stereoisomer **20** (Fig. 15). The vanadium species is the catalyst here, which coordinates to both the hydroxyl group and *t*-BuOOH, arranging their marriage. Because this time the oxygen approaches and again a peripheral attack must occur, the configuration of the resulting epoxide is reversed. The same reactions towards the final structure were repeated producing stereoisomer **21**,¹⁷ which turned out to be different from periplanone B.

Third time's a charm? Still now aimed for the stereoisomer with a reversed configuration of the epoxide at C₂. As the conformation in Fig. 12 showed, epoxidation of **15** at C₂ will inevitably occur from below because it is the less sterically hindered site, making this compound unsuited for the task. Still realized that *first* installing the double bond at C₅, could force the ten-membered ring into a conformation wherein the top of the double bond would be exposed. This insight was derived from the preference of 1,3-dienes, such as butadiene in Fig. 16, for adopting the *trans* conformation over a *cis* conformation, in which the hydrogens collide leading to steric repulsion. Still noted that this preference “might be enough to drive the medium ring into a new conformation”, which proved to be a valuable insight.

¹⁷ Except the deprotection reaction, which had already been performed (the third reaction in Fig. 14).

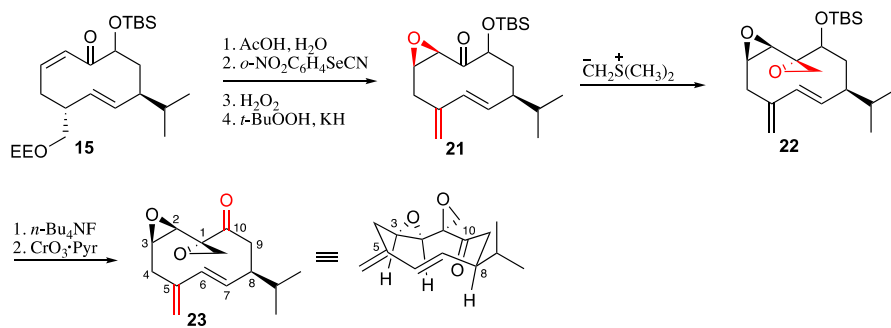


Fig. 17 Final steps in the synthesis of periplanone B

The double bond at C₅ was installed through the same three reaction steps as before (Fig. 17), after which epoxidation indeed generally proceeded from above,¹⁸ producing a mixture of stereoisomers predominantly consisting of **21**. Still noted that his “expectations appear to have been largely realized for” and continued after purification by adding dimethylsulfonium methylide. In the same way as the epoxidation of **16** (Fig. 14), the carbonyl is subjected to a peripheral attack, resulting in compound **22**, after which the familiar deprotection and oxidation steps give the third stereoisomer **23** (Fig. 17). The spectra of **23** were identical to those of the isolated compound, and male cockroaches also took a liking to the substance (even in amounts as tiny as 10⁻⁷ μg), confirming periplanone-B to be compound **23**.

3 Scientific understanding, truth, and representational accuracy

3.1 Clark Still's synthesis and the nature of scientific understanding

The case study in the previous section shows that the understanding that led Clark Still to the discovery of a new synthetic pathway towards periplanone B is a cognitive achievement in its own right, rather than just another piece of scientific knowledge. This contradicts views that understanding is simply a form of knowledge, as defended for example by Lipton (2004), Mizrahi (2012), and Khalifa (2017). As we have seen in Sect. 1, the identification of understanding with (a specific type of) knowledge implies that understanding—like any type of knowledge—must be *factive*, which suggests that understanding can only be achieved with theories that are true and models that accurately represent reality. Applied to Clark Still's understanding, however, naïve factivism turns out to be problematic, and this case is certainly not exceptional: many scientific theories and models that are used in scientific practice are strictly speaking false. Science abounds with idealized models, which are inaccurate representations of their target systems in reality. A classic example is the ideal gas model, which pictures a gas as a collection of randomly moving point particles without any intermolecular

¹⁸ The C₂ double bond is again more reactive than the C₆ and C₇ double bonds because it is part of the enone functional group.

forces, behaving according to the ideal gas law $PV = nRT$. The assumption that there are no intermolecular forces is an idealization: in real gases such forces are always present. So, can we invoke the ideal gas model to understand the fact that in many circumstances the behavior of real gases conforms (approximately) to the ideal gas law? A naïve factivist should answer this question in the negative: ideal gases are fictions that cannot be used to explain and understand how real gases behave.

However, philosophers with factivist intuitions have responded to this challenge by developing more sophisticated versions of their position. A first attempt was made by Kvanvig (2009, p. 341), who introduced *quasi-factivism*, which asserts that not all of the elements of a theory or model have to correspond to reality: understanding of (a part of) reality “is related, presumably, to various pieces of information, and on the quasi-factive view, the pieces of information that are central to the understanding must be true.”¹⁹ In a similar vein, quasi-factivist Mizrahi (2012, p. 239) argues that as long as the ‘central’ elements are true, the ‘peripheral’ elements may be false. A quasi-factivist approach to scientific understanding implies that the idealizing assumptions in a model are relatively unimportant (‘peripheral’), and not essential for understanding. This in turn suggests that de-idealization always leads to an increase of understanding, as is indeed argued by Mizrahi (2012, p. 244) with reference to the example of the van der Waals state equation. We submit, however, that this is generally not the case: the usual situation is that idealizations are not peripheral but essential to the enhancement of scientific understanding, because they enhance intelligibility.²⁰

Our case study clearly demonstrates the value of idealizations: the non-realistic models and qualitative concepts that Clark Still used to arrive at the synthesis of periplanone B were crucial to his success. Indeed, a de-idealized approach (using quantum-mechanical calculations) would not have revealed the desired synthetic pathways. For example, electronegativity and steric hindrance (explained in the respective text boxes in Sect. 2.3) are qualitative concepts that are used to predict the reactivity of molecules but do not have a counterpart in reality. There is no way in which these two concepts could be de-idealized such that understanding would be increased. On the contrary, such de-idealization—if possible at all—would decrease their applicability and restrict their use to assignment of a numerical value to isolated cases. The merit of these concepts is their ability to reveal patterns of reactivity and make whole classes of compounds intelligible, which is precisely what is needed for the design of a novel synthetic route. Another example showing that quasi-factivism is at odds with the way in which idealized models are used in chemistry is the use of localized representations of chemical bonding, discussed above in Sect. 2.1. Although delocalized representations are more realistic (and consistent with quantum mechanics) the more intuitive localized representation remains essential for understanding molecular structure.

Some philosophers in the factivist camp have acknowledged that idealizations are conducive to achieving scientific understanding and have proposed alternative accounts of how understanding can be gained from idealized models and inaccurate representations. Thus, Rice argues that “a highly idealized model can produce

¹⁹ Kvanvig focuses on objectual understanding, which differs from propositional understanding. For our purposes, this distinction is not essential.

²⁰ Cf. Lawler (2021, p. 6867) for a different argument against the peripheral nature of idealizations.

scientific understanding of a phenomenon even if it is an inaccurate representation of most (or perhaps even all) of the features of real-world systems” (Rice, 2021, pp. 199–200) According to Rice, “scientific understanding is factive because in order to genuinely understand a natural phenomenon *most* of what one believes about that phenomenon—especially about certain contextually salient propositions—must be true” (2021, p. 205, original italics). He adds that there are no universal criteria for determining exactly how much must be true; this can be decided only on a case-by-case basis. But what if the idealized model is completely non-realistic? According to Rice (2021, p. 207), it can still produce factive understanding of a phenomenon “if it enables an agent or a community to grasp some true information about the phenomenon and the agent or community grasps how that information can be systematically incorporated into a larger body of information in which most of their contextually salient beliefs about the phenomenon are true”. These true beliefs may concern modal information about the behavior of the target system. Even when the model inaccurately represents the target system, this can be the case, for example if model and target system are in the same universality class.

Rice’s factivism is considerably weaker than both naïve factivism and Kvanvig’s and Mizrahi’s quasi-factivism. In fact, it rather looks like a variety of non-factivism: Rice defines factivism in such a way that the truth requirement needs not apply at all to the representational devices (models, theories) but may concern beliefs about the target phenomenon only, for instance modal claims about its behavior. So, on this conception of factive understanding, also wildly inaccurate models like Ptolemy’s geocentric model, and false theories like phlogiston theory, can in principle provide understanding of the phenomena. And the same holds for the non-realistic models that, as we have seen in Sect. 2.3, are used by chemists to understand and devise the synthetic pathway towards target molecules such as periplanone B. In sum, Rice’s account accommodates the contribution of idealizations to scientific understanding, but its appeal to the truth is diluted so strongly that it boils down to non-factivism. (Obviously, also non-factivists hold that truth plays *some* role in understanding, for example in getting the empirical facts right; see below.)

A stronger kind of factivism appears to be defended by Strevens (2017, p. 40), who states that “[u]nderstanding why is a matter of grasping facts about the world out there – it is a matter of grasping, roughly, the causes of the phenomenon to be explained, and the facts in virtue of which they are causes”. Given this conception of understanding, Strevens asks how it can be that explanations often feature idealizations, which are patent falsehoods, in order to enhance understanding (p. 37). His answer employs a difference-making account of explanation: since explanations highlight causal difference-makers, idealizations serve to eliminate non-difference-makers. For example, the ideal gas model tells you that certain properties of real gases, such as molecular size and intermolecular attraction, do not make a difference to the phenomena to be explained (e.g. macroscopic gas laws).²¹ Strevens (2017, pp. 44–46) compares what he calls a ‘canonical explanatory model’, which “carefully circumscribes all non-difference-makers by painstaking specifications of exactly what does make a difference”, with an idealized model, in which the non-difference-makers are

²¹ A similar analysis is given by Khalifa (2017, p. 174); see Sect. 3.2.

simply removed. Both kinds of models can contribute to explanatory understanding, as defined by Strevens: they may help us (1) to grasp the difference-makers—and thereby the non-difference-makers—for the phenomenon, and (2) to grasp why they make—or do not make—a difference. Strevens argues that canonical models are more effective in achieving (2). So why do scientists use idealized models? The reasons to prefer those are, in Strevens view, pragmatic: with idealized models prospective understanders are less likely to make mistakes in achieving (1), and the derivations of the phenomena-to-be-explained are simpler and more tractable.

Strevens does not explicitly discuss factivism, but on his view (explanatory) understanding appears factive by definition: it is “a matter of grasping facts about the world out there”, where the facts are “the causes of the phenomenon to be explained, and the facts in virtue of which they are causes”. If one accepts this definition of understanding and identifies ‘grasping’ with ‘knowing’, then understanding is factive and idealizations have merely pragmatic value. But oftentimes scientific practice belies this definition. In our case study, for example, chemists acquire understanding of the molecular structure and reactivity of periplanone B and of the reaction pathways that constitute its synthesis. These phenomena are understood via non-realistic models and concepts, such as resonance structures, HSAB and steric hindrance, which are treated as causes in the language of chemists but aren’t causal *facts* in Strevens’ sense. Electronegativity values of elements and functional groups, for example, have no direct counterpart in reality and are measured on a relative scale. Yet they are ascribed a causal role in most types of reactions, because relative differences in electronegativity values explain the affinity between electronegative and electropositive groups and atoms. Such understanding is *sui generis*, rather than a pragmatic road to some more accurate understanding given by a ‘canonical model’.

The idea that idealizations are merely a ‘ladder’ to achieve understanding, to be thrown away as soon as the understanding is obtained, is also defended by Lawler (2021). On her account, which she terms the ‘extraction view’, “falsehoods can play an epistemic *enabling role* in the process of obtaining understanding but are not elements of the explanations or analyses that constitute the content of understanding” (Lawler, 2021, p. 6860). Thus, Lawler distinguishes between understanding as a *product* (that has ‘content’, namely a systematic account of the phenomenon, typically an explanation) and the *process* by which such understanding is acquired (ibid., p. 6875). She endorses a factive view of understanding, because “its content can only contain true propositions (or at least approximations to the truth)” (ibid., p. 6860). Idealizations and other “felicitous legitimate falsehoods [...] function as tools that help us to build systematic accounts of the phenomena of interest; they help us to extract relevant information” (ibid., p. 6875). But they are not part of the content of understanding, which is defined as “true information” about the phenomenon (ibid., p. 6884). Thus, Lawler’s account acknowledges that understanding can be obtained by means of inaccurate or non-realistic representations but identifies the understanding itself as (factive) true knowledge about the phenomenon. Indeed, she writes: “The extraction view decouples representation and understanding” (ibid., p. 6877). Note, however, that this is how we have characterized non-factivism in Sect. 1. So there may be consensus after all.

Comparing the various positions in the debate about scientific understanding, it appears that disagreements about whether understanding is factive are rooted in different views of how both understanding and factivism should be defined. If one defines understanding as knowledge of an explanation, understanding is factive and non-factive representations can be a means to achieve such knowledge but cannot be part of it. If, by contrast, understanding is defined as the activity of scientists ('grasping') to produce knowledge and explanations, non-factive representations can be ineliminable parts of understanding. We submit that the latter conception of understanding is more in line with how scientists themselves think about understanding, as shown in the case study presented in Sect. 2.3. Non-factive representations and concepts figure in the process of understanding, as acknowledged by Khalifa, Strevens, Rice and Lawler. But our case study illustrated that process and product are complementary components of the understanding: in the synthesis of a novel substance the understanding revolves around the establishment of the route and procedures leading towards the desired molecule. The product, which is in this case the detailed procedure to synthesize one particular molecule, is only one part of the obtained understanding. The ability to contrive a successful pathway, which depends on the strategy and explanations used to gain the necessary insights, could be seen as the process and is in many ways more valuable. Understanding of the process enables establishment of future syntheses and hence reaches further than a single target molecule, such as periplanone B. Synthetic chemists would agree that their science is concerned with the development of new methodologies to allow for more efficient production of increasingly complicated molecules. Grasping and formulating new synthetic pathways is hence the core of this discipline, which as we have shown does not exclusively depend on true information and makes frequent use of non-realistic concepts and models to obtain understanding.

While one may see it as merely a semantic issue, we submit that a non-factivist conception of scientific understanding is more in line with scientific practice.²² Such non-factivism regarding understanding is defended by, for example, Catherine Elgin and Angela Potochnik.²³ In her book, Potochnik (2017) offers a detailed investigation of the role of idealizations in achieving the aims of science. One of her conclusions is summarized by the title of the fourth chapter of her book: "Science isn't after the truth". Rather, science's epistemic aim is understanding, and "contributors to understanding, including idealizations, must be epistemically accepted [...] but they need not be believed" (Potochnik, 2017, p. 97). According to Potochnik (2017, p. 95), "idealizations contribute to generating understanding by revealing causal patterns and thereby enabling insights about these patterns that would otherwise be inaccessible to us". An idealized model can achieve this while deviating strongly from the target phenomenon, and thus "an idealization can be radically untrue but nonetheless facilitate understanding" (ibid., p. 101). In chemistry, notable examples of such idealizations are resonance structures and the electron-pushing arrows as explained in the text boxes of Sect. 2.3. With respect to the question of whether understanding is factive, Potochnik's

²² Alternatively, it may be argued that the factivism/non-factivism opposition is unfruitful and should be abandoned altogether.

²³ Non-factivism is also defended in De Regt (2015), De Regt and Gijsbers (2017), Bangu (2017), and Doyle et al. (2019). De Regt's views will be discussed below.

answer is an unambiguous ‘no’: “less truth can, in the proper circumstances, lead to greater understanding than would more truth” (ibid., p. 103).

A similar view is adopted by Elgin (2017), who focuses on objectual understanding, emphasizing that it involves more than just knowledge. Understanding is “a success term for having a suitable grasp of or take on a topic”, and “a nonfactive explication of ‘understanding’ yields a concept that better suits epistemology’s purposes than a factive one” (Elgin, 2017, p. 38). Elgin argues that understanding “involves an adeptness in using the information one has, not merely an appreciation that things are so” (ibid., p. 46). This is confirmed by our case study in synthetic chemistry: while computer-based calculations can yield accurate quantum-mechanical descriptions of molecular structure, such information does not suffice for creating and manipulating (and hence, understanding) chemical substances like periplanone B. As Anslyn and Dougherty (2006, p. 3) write: “such calculations do not necessarily produce *insight* into the nature of molecules. A string of computer-generated numbers is just no substitute for a well-developed *feeling* for the nature of bonding in organic molecules.” A feeling for stability derived from qualitative concepts such as electronegativity, resonance structures, and steric effects gives the chemist a sense of intuition to understand and predict the reactivity of the substances at hand. Such an intuitive feeling requires intelligible concepts and models, such as those employed by Clark Still in his synthesis of periplanone B.²⁴

3.2 Non-factive understanding: a philosophical discussion

We have argued that chemists rely on intuitive feeling and intelligible concepts, but what exactly does this involve? What are the requirements and conditions for intelligibility? When is a concept or model intelligible for chemists, so that they can use it intuitively to enhance their understanding? These questions are answered in the contextual theory of scientific understanding developed by one of us.²⁵ This theory is based on the idea that understanding crucially involves skills. It states that scientists achieve understanding of empirical phenomena if they succeed in constructing empirically adequate explanations of those phenomena on the basis of an intelligible theory, where intelligibility is defined as “the value that scientists attribute to the cluster of qualities of a theory (in one or more of its representations) that facilitate the use of the theory” (De Regt, 2017, p. 40). Intelligibility is essential for achieving understanding because the construction of models and explanations requires skills, and these have to be geared toward the qualities of the theory. Since intelligibility is a contextual value, judgments of whether a theory is intelligible may change with the historical, social or disciplinary context. This in turn implies that in one context theory T_1 may

²⁴ It should be emphasized that non-factivists do not claim that facts and truth are irrelevant to scientific understanding. Surely, in order to provide understanding a theory or model should at least get the relevant empirical facts right, although the degree to which it does so may vary with the context. In this sense “understanding somehow answers to facts”, as Elgin (2007, p. 37) observes. But she continues: “The question is how it does so”, and her answer is that it doesn’t require true theories or representationally accurate models.

²⁵ See De Regt (2015), De Regt (2017, esp. pp. 129–137), and De Regt and Gijsbers (2017) for a defense of a non-factive view of scientific understanding.

be the most intelligible one, while in another context theory T_2 is more intelligible. However, while intelligibility is contextual, it is not a purely subjective notion: there are objective ways to test whether a theory is intelligible to scientists in a particular context. De Regt (2017, p. 102) presents a criterion that functions as such a test: “CIT₁: A scientific theory T (in one or more of its representations) is intelligible for scientists (in context C) if they can recognize qualitatively characteristic consequences of T without performing exact calculations.”

De Regt suggests that it is the intelligibility rather than the truth of the theory that determines its success in providing explanatory understanding. A theory that is true but unintelligible cannot be used to construct satisfactory explanations, while a theory that is false but intelligible can in the right circumstances be useful for constructing explanations.²⁶ De Regt’s emphasis on the importance of intelligibility (rather than truth) reflects the idea that understanding is a skill (rather than a type of knowledge), and thereby leads to a non-factive conception of understanding. His account accommodates the ubiquitous use of idealizations in scientific practice. Applied to our case study, it explains why qualitative concepts and non-realistic models are preferred over exact quantum-mechanical calculations in the search for synthetic pathways.

De Regt’s non-factivist position has recently been challenged by Khalifa (2017), who endorses the thesis that understanding is a species of knowledge and hence holds that scientific understanding is factive.²⁷ On Khalifa’s ‘Explanation-Knowledge-Science’ (EKS) model of explanatory understanding, scientific understanding is nothing more than having “scientific knowledge of an explanation” (Khalifa, 2017, p. 11). The EKS-model is a comparative account of understanding, stating conditions for when “ S_1 understands why p better than S_2 ” (2017, p. 14). Thus, there are degrees of understanding, and Khalifa suggests that these range from minimal understanding, via everyday understanding and typical scientist’s understanding, to ideal understanding. Minimal understanding of why p is achieved when “ S believes that q explains why p , and q explains why p is approximately true” (ibid., p. 14). Since even minimal understanding requires approximate truth, understanding is factive, according to Khalifa.

In Chapter 6 of his *Understanding, Explanation, and Scientific Knowledge* (2017), Khalifa attempts to counter two arguments for non-factivism: the historical argument and the argument from idealizations. In the present paper we will focus on the latter argument: scientists’ use of idealized models in generating understanding.²⁸ Khalifa (2017, pp. 166–181) presents an extensive discussion of this argument, which he summarizes as follows (ibid., p. 167):

- I1. Some scientists accept idealized explanations of a phenomenon.
- I2. All idealized explanations are false.

²⁶ Of course, not any intelligible theory will be useful for this purpose. Astrology, for example, will probably not do in any context (see De Regt 2017, p. 93).

²⁷ To be sure, Khalifa (2017, pp. 154–156) describes himself as a quasi-factivist, where “quasi-factivism is simply a denial of non-factivism” and non-factivism is defined as: “Understanding why p does not require belief in any approximately true explanations of p .”

²⁸ See De Regt (2023) for a discussion of the historical argument and Khalifa’s response.

I3. These scientists nevertheless have some understanding of why that phenomenon has certain properties.

→ NF (Non-Factivism): Understanding why p does not require belief in any approximately true explanations of p .

Khalifa suggests that this argument can be rendered harmless via two different strategies. The first he calls the “Splitting Strategy”, because it splits idealized explanations into idealizations and explanations, where the former are merely *accepted* while the latter are *believed*. This strategy may work in cases where the idealizations consist in disregarding or removing factors that are explanatorily irrelevant to the phenomenon-to-be-explained. In our case study, for instance, the concept of resonance structures involves the migration of double bonds, which would count as an idealization that is accepted but not believed. Khalifa (2017, p. 174) puts this in a slogan: “explanations cite difference-makers, idealizations flag difference-fakers”. However, this strategy assumes that the idealizations are not essential to the explanation. We submit, by contrast, that idealizations often do play an essential role in attaining explanatory understanding: they allow for the application of an intelligible theory to the model system. In our case study, resonance structures were used to determine the stability of compounds and locate potential reaction sites, for example regarding the enones in Fig. 9. Resonance structures could be applied to any enone or even any compound containing alternating bonds, while a quantum-mechanical calculation would give an assessment of just a single molecule.

At this point Khalifa will reply by invoking his alternative “Swelling Strategy”, which broadens the concept of knowledge such that it does not require belief but also allows for mere acceptance as a condition for knowledge. Applied to his EKS-model of explanatory understanding, this strategy expands the definition of minimal understanding as follows (2017, p. 176; boldface in original):

(EKS₂*) S has minimal understanding of why p if and only if, for some q ,

- (A) S believes that q explains why p , and q explains why p is approximately true;
or
 (B) S **accepts** that q explains why p , and q explains why p is **effective**.

Khalifa (ibid.) adds that “[i]n this way, the notion of minimal understanding ‘swells up’ to include an acceptance clause that can even host the idealized explanations that take the longest holidays from the truth”. That may indeed be the case, but it seems to us that with this move Khalifa leaves the factivist camp, contrary to his intentions. To see this, first note that he has *en passant* introduced the notion of effectiveness in the definition of understanding: explanations that are merely accepted but not believed, have to be effective rather than true. Remarkably, Khalifa does not explain why accepted explanations need to be effective, nor does he explicate the term. But we can infer from his use of the term (e.g. on pp. 178–179) that an effective claim is one that reliably advances one’s particular (scientific) goals, which can apparently vary with the context (and do not have to include truth). The thesis that acceptance of a claim that q explains why p is sufficient for understanding why p , as long as that claim is effective for achieving certain (context-dependent) scientific goals, is in line with a non-factivist approach to understanding. In particular, it agrees with De Regt’s

contextual account, which is based on the idea that scientific understanding requires intelligibility (rather than truth) of a theory, where intelligibility is associated with the qualities of a theory that facilitate its use. That Khalifa's modified account resembles De Regt's becomes even more apparent when we compare it to the presentation of the latter in De Regt and Gijsbers (2017), who argue for replacing the "veridicality condition" with an "effectiveness condition on understanding", where effectiveness is defined as "intelligibility + reliable success" (De Regt & Gijsbers, 2017, p. 55). They add that "scientific effectiveness is the tendency to produce useful scientific outcomes of certain kinds", which "include correct predictions, successful practical applications and fruitful ideas for further research" (ibid., pp. 51, 72). De Regt and Gijsbers (2017, pp. 61–66) illustrate their point with an analysis of phlogiston theory, arguing that it was an effective theory with which eighteenth-century scientists understood many chemical phenomena. Similarly, on Khalifa's revised EKS-model (EKS₂^{*}) phlogiston theory should qualify as providing scientific understanding, because it was accepted by many eighteenth-century chemists and effective (since it allowed them to describe and predict various aspects of combustion and other chemical phenomena).

Moreover, Khalifa (2017, p. 179) states that "sometimes acceptance will eclipse belief when certain tradeoffs arise", for example when a less accurate explanation is preferred because it is more effective to achieve certain goals. Such preference for acceptance over belief can indeed be witnessed in many of the examples that we discussed in Sect. 2 and is in line with a non-factivist conception of scientific understanding. Thus, by admitting that acceptance rather than belief, and effectiveness rather than truth, is sufficient for scientific understanding, Khalifa has de facto become a non-factivist.²⁹ What is more, since effectiveness can be analyzed in terms of intelligibility plus reliable success, it turns out that there is a crucial role for skills (an explanation accepted by *S* can only be effective if *S* has the skills to effectively use it to achieve her goals; see De Regt & Gijsbers, 2017, p. 59). We conclude that the Swelling Strategy stretches the concept of knowledge in such a way that it becomes indeed conceivable that it covers understanding as well. While we sympathize with this approach, we consider it to be a surrender to a (non-factivist) skill-based conception of understanding rather than a successful rescue attempt of the understanding-as-knowledge view.

4 Conclusion

Although we have only skimmed over the surface of synthetic chemistry and could not include important explanations such as qualitative molecular orbital theory, we have highlighted some elements of the "deeply inconsistent" mix of theories that enables the piecemeal understanding of structure and reactivity (Hoffmann, 2007). It is exactly this non-realistic and "partially irrational reasoning", based on qualitative concepts like steric hindrance, electronegativity, HSAB, and resonance structures, that makes the nature of compounds intelligible. Using quantum-mechanical modelling methods to generate a realistic and quantitative assessment of a compound does not produce

²⁹ Note that Khalifa's Swelling Strategy also aligns with Potochnik's (2017, p. 97) non-factivist statement, cited above in Sect. 2.1, that "contributors to understanding, including idealizations, must be epistemically accepted [...] but they need not be believed".

insight in how a molecule can be successfully modified, let alone how a complete synthetic plan towards a final product may be designed. Calculating the ground state energy of structure **23** will not help chemists to find a way of making it, but inferences from electron-pushing arrows and steric repulsion do. In sum, understanding in synthetic chemistry is obtained via idealized, non-realistic models and qualitative concepts rather than through exact, quantitative calculation.

It might be objected that synthetic chemistry is not concerned with producing scientific understanding, but rather with scientifically producing new substances. In Khalifa's terminology, one might invoke the Wrong Benefit Objection: synthetic chemists are concerned with "procedural or practical understanding-*how* [rather than] explanatory understanding-*why*" (Khalifa, 2017, p. 165). However, this would be an underestimation of the achievements of synthetic chemistry. Synthesizing a molecule does not merely involve understanding *how* to make it but also understanding *why* it has a particular reactivity and other relevant properties. The insights gained during the synthesis of, for example, periplanone B can hence be used in future syntheses, thus progressing the field as a whole. This is full-blooded explanatory understanding generated by idealized, non-realistic models and qualitative concepts.

Moreover, the synthesis is understood through these non-realistic models not only during discovery, but also after its completion. Realistically justifying the understanding of the synthesis would be to state that a sequence of reactions with negative free energy was derived from an inconceivable number of possibilities. This is equivalent to saying that a grandmaster understood and won her game of chess because she accurately assessed the 10^{120} possible positions and found a winning line (Shannon, 1950). Perhaps a chess computer 'understands' the game by analyzing a fraction of those possibilities, but it would be nonsensical to ascribe this mode of understanding to human players. In the same way, a chemist does not find and understand the synthetic path towards periplanone B by numerically solving the Schrödinger equation. Through intelligible but strictly speaking false theories, a highly complex situation is understood, in the discovery and justification of both winning moves and successful syntheses.

We conclude that synthetic chemistry supplies ample evidence for a non-factivist conception of scientific understanding. Idealized models play a crucial role in realizing and understanding a chemical synthesis, and the idealizing assumptions are essential to the understanding. By sacrificing representational accuracy of theories and models, intelligibility is enhanced, which allows skilled scientists to use them effectively. As Potochnik (2017, p. 95) argues, "idealizations contribute to generating understanding by revealing causal patterns and thereby enabling insights about these patterns that would otherwise be inaccessible to us". It is this function of idealizations that lies at the basis of successful synthetic chemistry. The way in which understanding is generated in synthetic chemistry is also in line with De Regt's contextual theory of scientific understanding, in which the notion of intelligibility plays a central role and qualitative reasoning is an indicator of intelligibility (criterion CIT₁). Potochnik's and De Regt's analyses entail a non-factivist conception of understanding, and our case study of understanding in synthetic chemistry provides additional evidence for non-factivism regarding scientific understanding. In synthetic chemistry intelligibility

outplays representational accuracy. Intelligibility is crucial for scientific understanding, and—at least in synthetic chemistry—an increase in intelligibility typically goes hand in hand with a loss of representational accuracy.

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