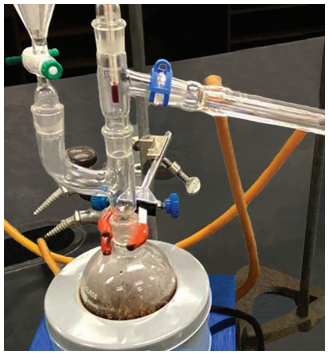
11.7 Natural Product Synthesis

"There is no denying (nor should there be any need to deny!) that the sheer sense of challenge posed by a complex molecular target serves to stimulate the creative impulses of the synthetic chemist." Samuel J. Danishefsky (Columbia University)



In a steam distillation, the essential oil of a plant is isolated as it co-distills with water.

Many significant synthetic achievements have been in the area of *natural product synthesis*. Compounds made by nature are often attractive targets for synthesis because they are likely to be biologically active. For thousands of years, humans have used herbal remedies to alleviate pain, treat wounds and cure various ailments. Therefore, it makes sense that we now explore plant materials in search of compounds that might have antibiotic properties or that can be used to fight cancer. *Natural product chemists* do exactly that—they gather samples of plants (leaves, roots, bark, seeds, etc.) and isolate the organic components that are present. The plant's essential oil, which contains volatile, fragrant components such as terpenes, might be isolated by steam distillation, and various extraction techniques can be used to isolate other compounds based on properties such as polarity or basicity. The search for interesting organic compounds is certainly not limited to plant materials; they can also be found in sea creatures and microorganisms and even snake venom! After the various organic compounds are isolated, their structures are determined by employing techniques we will learn about in Chapters 14 and 15: IR and NMR spectroscopy, in combination with mass spectrometry. In some cases, the three-dimensional structure of a crystal can be determined by observing how the crystal interacts with X-rays; this powerful technique is known as X-ray crystallography. Any novel compounds that are identified can then be screened for biological activity.

Recall from the WorldLink lesson on terpenes in Chapter 8 that plants produce organic compounds as a means for survival. Known as *secondary metabolites*, these compounds can help ward off predators, fight disease, or attract pollinators. Considering the abundance of interesting organic molecules that plants contain, it is certainly no accident that plants and plant products can have healing effects on humans! When a novel natural product is isolated and found to have biological activity, it is likely to catch the attention of the *synthetic chemist* who may adopt it as a new target molecule. Natural products often have complex structures with multiple chiral centers and functional groups, so they represent an intellectual challenge to the synthetic chemist. The presence of increasingly challenging structural features exposes weaknesses in existing methodology, calling on the investigator's creativity and ingenuity to fill those gaps. Indeed, it is usually in the pursuit of complex targets that new synthetic methods are developed—more selective reagents, better enantioselective techniques, novel methods for assembling various functional groups, and most importantly, new strategies to form carbon-carbon bonds. In addition to advancing the frontiers of science, research projects that are focused on organic synthesis train students and young scientists to be creative and resilient problem-solvers.

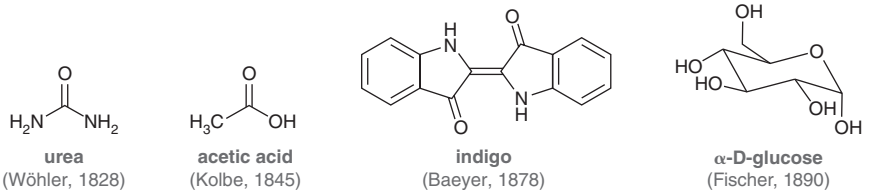
There are additional, practical reasons to pursue the synthesis of that which nature has already produced. As a new compound is gradually built up from a simpler, known compound, the details of the more complex structure are known with confidence. In some cases, the characterization of the synthetic compound (spectral data, specific rotation, physical properties, etc.) does not exactly match what was reported when the compound was first identified. As a result, corrections are made to the structure that was initially proposed, and a revised structure is presented in the literature. In addition to contributing to structural elucidation, a laboratory synthesis enables large-scale production for commercial purposes, or it can produce more of a scarce natural product so it can be studied further.

A flower produces a compound to attract pollinators, and then a chemist can modify the structure of the compound to fine-tune its biological activity.

Another advantage to being able to synthesize a natural product is the ability to modify its structure. Nature typically makes only a single enantiomer when producing a chiral compound, but the simplest laboratory synthesis is one that produces a racemic mixture. In many cases, the drug is marketed as the racemate, but separate testing of the unnatural enantiomer can only be achieved with a synthesized product. Once a synthetic method is developed, then analogs of the natural product can be synthesized and screened for activity. By modifying different parts of the structure and observing how the change affects the biological activity of the new compound, a *structure-activity relationship (SAR)* can be determined. Such a study might identify a derivative of the natural product that has more promising bioactivity—perhaps it lasts longer, has better chemical or physical properties, is less toxic, or has fewer side effects. In that way, we can improve upon what nature has to offer. As a result of the laboratory research efforts of natural product chemists, synthetic chemists, and biologists, roughly one-third of all drugs approved over the past 40 years are either natural products or compounds derived from natural product structures.

The field of natural product synthesis was born in 1828, when German chemist Friedrich Wöhler synthesized urea, a waste product of metabolism that is found in urine (Figure 11.1).

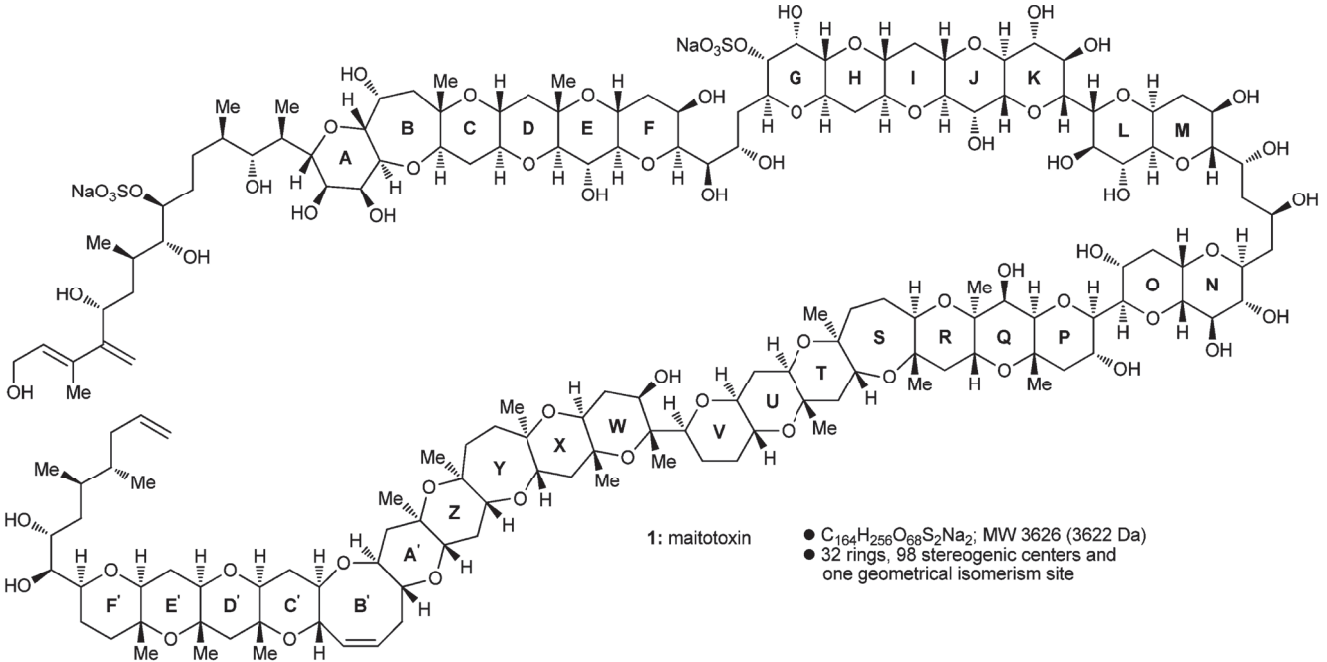
FIGURE 11.1
Several German chemists helped launch the field of natural product synthesis in the 19th century.



The synthesis of this simple, one-carbon molecule was a landmark achievement, because it proved that a human in a laboratory could create what was until that point exclusively a product of nature. Because Wöhler made urea from inorganic starting materials, the synthesis also revealed a flaw in the concept of *vitalism*. Vitalists believed that organic compounds could be produced only by living organisms which, unlike inanimate objects, contained "vital forces" (see Section 1.2). Vitalism theory suffered a more serious blow in 1845 when a German chemist who had studied under Wöhler, Hermann Kolbe, created the first carbon-carbon bond with his synthesis of acetic acid. Synthetic targets continued to become more complex, as demonstrated by the achievements of two more German chemists in the 19th century. In 1878, Adolf von Baeyer synthesized indigo, a plant extract with a blue color that is used as a dye for fabrics including denim. Baeyer was awarded the 1905 Nobel Prize in Chemistry, and because his mother was born Jewish, he is considered to be the first Jewish Nobel laureate. In 1890, Emil Fischer (of Fischer Projection fame) synthesized the sugar glucose. Fischer earned his PhD under Baeyer's supervision, yet Fischer was the first of the two scientists to earn a Nobel Prize in Chemistry, in 1902.

In 1905, as a result of his synthetic achievements (including the synthesis of indigo), German chemist Adolf von Baeyer became the first Jewish Nobel laureate.

Throughout the 20th century, the capabilities of natural product chemists to isolate and identify more complex structures grew steadily. This was great news for the synthetic chemists who were always in search of more challenging target molecules. Synthetic challenges include the overall size and stability of the molecule, the number and diversity of functional groups present, the number and types of rings in the structure, and the number of chiral centers present (with chiral quaternary carbon atoms being especially difficult to design). One of the most complex secondary metabolites identified at this time is maitotoxin (**1**), a potent toxin produced by the marine algae *G. toxicus*.



The image above is reproduced from a research article in the *Journal of the American Chemical Society* (JACS). The complexity of maitotoxin is mind-boggling, with 32 rings and 98 chiral centers! As of 2024, its total synthesis has not yet been achieved, but large portions of the molecule have been successfully built by several chemists including the research groups of K. C. Nicolau (The Scripps Research Institute and Rice University), Tadashi Nakata (Tokyo University of Science), and Tohru Oishi (Kyushu University, Japan).