The endeavor of total synthesis and its impact on chemistry, biology and medicine

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ABSTRACT

The synthesis of urea in 1828 set in motion the discipline of organic synthesis in general and of total synthesis in particular, the art and science of synthesizing natural products, the molecules of living nature. Early endeavors in total synthesis had as their main objective the proof of structure of the target molecule. Later on, the primary goal became the demonstration of the power of synthesis to construct complex molecules through appropriately devised strategies, making the endeavor an achievement whose value was measured by its elegance and efficiency. While these objectives continue to be important, contemporary endeavors in total synthesis are increasingly focused on practical aspects, including method development, efficiency, and biological and medical relevance. In this article, the emergence and evolution of total synthesis to its present state is traced, selected total syntheses from the author’s laboratories are highlighted, and projections for the future of the field are discussed.

Keywords: organic synthesis, natural products, chemistry, biology, medicine

INTRODUCTION

Considered by many as the central science, chemistry deals with the analysis, synthesis, and properties of matter. It emerged as a modern science in the 18th century, when new experimental methods allowed the isolation, characterization, and analysis of certain elements and naturally occurring substances. But it was only in the following century that chemistry experienced its most dramatic advances both in terms of theory and practice. Thus, the atomic theory was introduced at the dawn of the 19th century (John Dalton), and was followed first by the birth of organic synthesis (Friedrich Wöhler, Hermann Kolbe) and then by the understanding of the structure of the molecule (Kekulé and many others) [1]. The advent of organic synthesis and the molecular theory gave impetus and momentum to arguably the most creative and challenging branch of chemistry, that of replicating the molecules of living nature (secondary metabolites, commonly known as natural products) in the laboratory and the construction of all sorts of organic molecules (molecules whose primary element is carbon). The former is usually called total synthesis, the latter simply organic synthesis [2].

The crucial and fundamental role that natural products have played in human medicine for millennia is undeniable. It is far less known, however, that not only have humans been practicing self-medication employing natural products since ancient times, but also numerous other living creatures (including worms, birds and butterflies) have been engaged in self-medication activities in much the same way [3]. The practices to cure disease, therefore, seem to result from an innate survival instinct and constitute an evolutionary advantage of those species, a recognition that demonstrates the value of natural products as medicines and lead compounds for drug discovery and development. The ability of synthetic organic chemists to synthesize natural or designed molecules at will gave them the power to shape the landscape of molecular sciences and build myriad chemical entities from which some of our most precious medicines, but also materials and machines, have been developed and employed for the benefit of science and society [2].
Life on Earth employs and depends on certain chemical elements and their compounds, of which those composed primarily of carbon are the most complex and intriguing. Among them, nucleic acids, proteins, polysaccharides, and secondary metabolites constitute the core molecular systems in living creatures. The latter class of molecules, the natural products, are as diverse in structure as they are in function. Their isolation and structural elucidation has evolved to a highly sophisticated science, and continues to demystify nature at the molecular level. And yet the hundreds of thousands of natural products discovered thus far must represent only a fraction of nature’s vast library [4].

These intriguing, often biologically active, molecules inspire synthetic organic chemists to embark on their total synthesis. Their motivation for undertaking such total synthesis endeavors vary from confirming their structures to discovering new chemistry, from exploring their biological properties to the sheer challenge of the task, and from designing and synthesizing variations (analogues) of them to developing them or their analogues to drug candidates. To be sure, the glorious history of natural products chemistry—iso-lation/structural elucidation, total synthesis, biology, and medicine—boasts of contributions of enormous impact to society [5].

**HISTORICAL MILESTONES**

From the accidental synthesis of urea in 1828 by Wöhler [6], organic synthesis emerged and grew into one of the most influential disciplines of contemporary science. Occupying a central position within chemistry, this exact science can replicate the molecules of living nature in the laboratory. It can also be described as a fine art due to its creative nature in terms of strategy and ability to produce new chemical entities in the form of analogues of the target natural product, or other designed molecules. Such new molecules find applications in many scientific and technological endeavors as well as in our everyday lives. The engine that drives organic synthesis forward, the art of total synthesis, is also its flagship.

The isolation and structure elucidation of natural products, therefore, provided the reason for the development of the discipline of total synthesis and continues to challenge and drive it into new heights of efficiency and elegance. The impressive advances of the art and science of total synthesis were facilitated by a number of transformative discoveries and developments, including the atomic and molecular structural theory, the discovery of numerous practical synthetic methods, the introduction of powerful analytical methods for structure elucidation, the theory of retrosynthetic analysis, the emergence of modern catalytic reactions, and the device of powerful new synthetic strategies. A number of selected examples of total synthesis accomplishments since the preparation of urea are shown in Fig. 1.

**EXAMPLES OF ACCOMPLISHMENTS FROM THE AUTHOR’S LABORATORIES**

Comprehensive reviews describing our contributions to total synthesis have been published elsewhere [2]. As demonstrative examples, we include herein highlights of only a select number of these endeavors.

**Endiandric acids**

One of the most important aspects of total synthesis endeavors is the opportunity to discover and develop new synthetic strategies, methods, and technologies. Isolated and structurally elucidated in the early 1980s, the endiandric acids [91] offered a unique opportunity to test the applicability of electrocyclization reactions in total synthesis for the first time. Their generation in nature had been suggested [92] to rely on three thermally-allowed processes, namely an $8\pi$ electrocyclization, a $6\pi$ electrocyclization, and a $6\pi[4+2]$ cycloaddition (Diels–Alder reaction). We reasoned that, if successful, such a cascade sequence of reactions might provide confirmation of the biosynthetic hypothesis for these novel natural products, an environmentally friendly chemical process, and an aesthetically pleasing cascade-based strategy for complex molecule construction. The latter would be reminiscent of Robinson’s synthesis of tropinone (1917) [12] and Johnson’s synthesis of proges-terone (1968) [20], both of which involved cationic intermediates. Our strategy would demonstrate the use of concerted electrocyclizations and, perhaps, set in motion a new paradigm in organic synthesis with broad generality and scope. These expectations were realized as demonstrated in Fig. 2 [25] and by many other examples of such cascade strategies that followed. A number of these accomplishments have recently been reviewed [93] and, therefore, will not be dealt with further here. It suffices to say, however, that cascade reactions in natural products synthesis, catalysis, and organic synthesis in general have since become common, and provide significant advantages over stepwise strategies. They are much admired and sought after by practitioners of the art of
Figure 1. Selected historical milestones in total synthesis. A, Part I; B, Part II; C, Part III [6–90,100–105,109,130].
Figure 1. Continued
Figure 1. Continued
synthesis for their efficiency and elegance. The inspiration for their adoption or design often comes from proven or imagined biosynthetic hypotheses and deep mechanistic considerations. When the inspiration comes from the biosynthetic pathways, the term biomimetic total synthesis is used to describe the laboratory synthesis of the natural product. There is certain charm and aura of such biomimetic total syntheses, for they elicit feelings of satisfaction and admiration, not only for replicating nature but also for mimicking nature in the way it synthesizes its molecules. Many of nature’s biosynthetic pathways are based on cascade reactions—ionic, radical, or concerted—as in the endiandric acid case. All these types of cascade sequences have been developed by synthetic organic chemists as efficient laboratory processes, a fact that brings us closer to the dream of approaching nature in its elegance and efficiency.

**Calicheamicin γ₁**

In 1972, Robert G. Bergman reported his discovery of a novel cycloaromatization reaction that involved the thermal ring closure of open-chain conjugated enediyynes via benzenoid diradicals [94]. This fundamental discovery remained dormant for several years until nature showed us how to employ it to kill cancer cells through double strand DNA cuts, and with phenomenal potency. The first natural molecule to demonstrate this ability was calicheamicin γ₁, a marvelous molecular machine that includes in its structure a molecular warhead (a constrained but stable cyclic conjugated enediyne), a triggering device (a trisulfide unit) to activate the Bergman cycloaromatization that causes the DNA damage, and a docking system (an oligosaccharide moiety) that allows the lethal weapon to reach its target (the genetic material). The structure and mechanism of action of calicheamicin γ₁ was revealed in the late 1980s by scientists working at Lederle Laboratories (now Pfizer) and immediately captured the imagination of chemists and biologists alike around the world [95]. Indeed, rarely before had a molecule attracted so much admiration and attention, and it continues to do so today as scientists are attempting to employ it as a payload attached to targeting delivery systems (e.g. antibodies) through appropriate chemical linkers in order to devise highly selective anticancer drugs (e.g. antibody drug conjugates, adc’s). Our commitment to the total synthesis of calicheamicin γ₁ was immediate, for the opportunity to embark on an odyssey of discovery and invention was both obvious and irresistible. In 1992, the total synthesis of calicheamicin γ₁ was achieved in our laboratories (see Fig. 3), bringing with it a series of discoveries in synthetic strategies and technologies and new spinoff initiatives in molecular design, chemical synthesis, and chemical biology [37]. The field of enediyne antitumor antibiotics continues to be of great interest to academic groups and pharmaceutical and biotechnology companies as new members of the class are discovered from nature and new ideas emerge for their synthesis and use as
therapeutic agents for treating cancer and, potentially, other diseases [96]. One of the newest and most promising enediyne antibiotics is uncicalamycin, a marine natural product whose synthesis and full structural elucidation were recently completed in these laboratories [97,98].

**Taxol**

Taxol (paclitaxel), one of the top anticancer drugs of our time, has a fascinating history from its discovery in nature to its mechanism of action as a tubulin binding agent, and from its synthesis to its use in the clinic to treat cancer patients. Isolated in the 1960s from the Pacific Yew tree and structurally elucidated in the early 1970s, Taxol became a hotly pursued target for total synthesis in the 1980s and 1990s [99]. Its natural scarcity and high potential as an anticancer drug provided the impetus for the numerous campaigns to synthesize it in the laboratory. Initiated in the early 1990s, our total synthesis of Taxol was published in early 1994 [100]. A summary of this synthesis, in retrosynthetic format, is shown in Fig. 4. Its highlights include high convergency, stereoselectivity, and relative brevity. The significance of the Taxol synthetic endeavor lies in the discovery and development of new synthetic strategies and technologies, the design, synthesis and biological evaluation of numerous new Taxol analogues, and the symbolic demonstration of the power of chemical synthesis at the time. It should be mentioned that Taxol is manufactured today through a shorter and economically feasible process starting from an abundant naturally occurring precursor, 10-deacetyl baccatin III, which lacks the sidechain of the molecule.

The total synthesis of Taxol in our and other laboratories [101–106] was demonstrative of the power of organic synthesis as it stood in the 1990s and inspiring for its future development. Indeed, the era of the 1990s and 2000s emerged as a new golden era for total synthesis with numerous landmark achievements in the field, including those shown in Fig. 1 that were completed in that period and beyond.

**Brevetoxin B**

The ‘red tide’ phenomena have been a menace to the environment and society for millennia, and their harmful effects are increasing due to unwise human practices. The catastrophic poisoning of
marine creatures and humans consuming contaminated seafood stems from a number of neurotoxins, among which are the brevetoxins. The first brevetoxin to be discovered was brevetoxin B, whose isolation and structural elucidation were reported in 1981 [107]. Its ladder-like polyether molecular architecture stunned the world of chemistry due to its unprecedented structural motifs and potent neurotoxicity. Attracted by the challenge of its synthesis and the prospect of discovering new synthetic strategies and technologies, we embarked on its laboratory synthesis in the early 1980s. That synthetic campaign turned into an odyssey [108] of such discoveries and innovations, culminating in 1995 [42] with the completion of the total synthesis of brevetoxin B, which set the foundations for further developments to occur in the field. Figure 5 depicts the key elements of the developed synthesis highlighting its convergence and the reactions developed and deployed for this accomplishment. Marine neurotoxins continue to fascinate biologists and chemists alike for they provide biological tools for neurobiology and challenges for chemical synthesis [109]. Their mechanism of action involves binding to and modulating the function of ion channels resulting in rapid and damaging influx of metal ions such as sodium, potassium, and calcium. Studies in this area may elucidate neurobiological pathways and improve our understanding of how the brain works, leading to fundamental knowledge and drug discovery and development programs for the treatment of neurodegenerative diseases. From the chemistry point of view, the brevetoxin B synthetic campaign played a pivotal role in the discovery of new chemistry that allowed organic synthesis to reach new domains of molecular complexity and diversity, those of the ladder-like polyether marine neurotoxins, thereby rendering these scarce molecules available for biological investigations [110].

**Vancomycin**

As its name implies, vancomycin is a molecule endowed with the ability to ‘vanquish’ bacteria, among them the lethal methicillin-resistant *Staphylococcus aureus* (MRSA). The structure of this naturally occurring antibiotic was determined in the 1950s during the ‘gold rush’ for such compounds from nature launched after the success of penicillin in the 1940s. Soon after its discovery [111] vancomycin became, and continues to be, one of our last lines of defense against bacteria even though vancomycin-resistant bacteria have emerged as formidable pathogens that cause untreatable and often lethal infections. The lure of vancomycin’s synthetically challenging molecular structure and the need for new antibiotics that may exhibit activity against drug resistant bacteria prompted the initiation of our program to synthesize it in the laboratory and develop methods for the construction of its analogues for biological investigations.

The first phase of our research was accompanied by the discovery and development of suitable synthetic strategies and technologies, a task that provided the foundation to achieve both the completion of the total synthesis of vancomycin [49] (see Fig. 6 for highlights shown in retrosynthetic format)
and the design, synthesis, and biological evaluation of a focused library of vancomycin analogues and derivatives. Significantly, a number of these compounds exhibited strong killing activities against vancomycin-resistant bacteria, rekindling hopes for further discoveries to occur that may place us ahead of these dangerous pathogens [112]. In terms of chemical discoveries, the vancomycin endeavor yielded a novel method for the synthesis of macrocyclic bisaryl ethers [113], a new selenium-based linker for solid-phase synthesis [114], and the so-called target-driven combinatorial synthesis of D-Ala-D-Ala binding vancomycin analogues [112]. Overall the vancomycin project proved highly rewarding, admirably combining discoveries and achievements in chemical synthesis and chemical biology.

**CP molecules**

Two of the most intriguing natural products to be isolated in the 1990s were the twins coined the CP molecules [115]. Beautifully arranged in space, their atoms are woven together in a demonic molecular architecture that puzzled and challenged synthetic organic chemists all over the world. The fascination with these molecules was also derived from their important biological properties, which included powerful cholesterol-lowering and cytotoxic activities.

Our motivation for undertaking the total synthesis adventure of the CP molecules was based on the uniqueness of their structures (and thus the challenge of their synthesis), their potent biological actions, and the opportunities they presented for discoveries in new synthetic methods and strategies. Our expectations were fulfilled beyond our wildest dreams [116], for not only were these molecules conquered by synthesis within a relatively short period of time through a relentless campaign [45], they also provided a rich harvest of synthetic reactions discovered [117] during the endeavor (for highlights see Fig. 7). Among the latter were new reactivity of hypervalent iodine reagents, cascade reactions for the construction of novel structural motifs,
and unique strategies and tactics for organic synthesis. These discoveries and inventions enriched the repertoire of synthetic methods and demonstrated the sharp state of the art at that time. These studies reiterated once again the richness of total synthesis campaigns for discovery and invention and demonstrated the power of the art of synthesis through which totally new types of molecular architectures could be reached through its prudent and appropriately designed applications.

Azaspiracids

The investigations leading to the discovery of azaspiracid-1 began in the 1990s when an unusual occurrence of diarrhetic shellfish poisoning in the Netherlands prompted Yasumoto, Satake and colleagues to search for its causative agent. In 1998, they reported the isolation of this novel marine neurotoxin from the mussel species Mytilus edulis and proposed two possible structures for it based on NMR spectroscopic analysis [118]. In the absence of an X-ray crystallographic analysis, and in order to elucidate fully the structure of azaspiracid-1 and deliver material for biological studies, a total synthesis campaign toward this intriguing but scarce molecule was highly justified. The fascinating structural proposal featured a bis-oxaspiroketal region, 20 stereogenic centers, and an azaspiroketal, all embedded within a complex carbon backbone. In 2003, our group succeeded in synthesizing both of the proposed structures of azaspiracid-1, only to find that their spectroscopic data did not match those of the authentic material [119]! Instead of abandoning our efforts at this stage, we entered into a collaboration with the Satake group, who had in their possession the few remaining micrograms of azaspiracid-1, determined to uncover the true structure of our target molecule. After an additional thrilling year, in 2004 we successfully synthesized azaspiracid-1 (see highlights in Fig. 8) [63]. Our strategy relied on the construction and union of three key building blocks: the ABCD
Figure 7. Highlights of the total synthesis of the CP molecules.

Thiostrepton

Thiostrepton is an impressive naturally occurring antibiotic whose use, surprisingly, is limited thus far to the treatment of pets and other animals. It belongs to the class of thiopeptide antibiotics of which it is the flagship member by virtue of its magnificently complex molecular structure and important use as an anti-infective agent. Despite its discovery several decades ago [123], the total synthesis of this important molecule had to wait until early in the 21st century, no doubt partly due to its complexity. Inspired by this molecular complexity and uniqueness as compared to previously synthesized molecular architectures, we embarked on the total synthesis of thiostrepton expecting challenges and setbacks that would inevitably drive us into discoveries in synthetic strategy design and new applications of modern synthetic methods and techniques [124].

The total synthesis of thiostrepton was accomplished in our laboratories in 2004 through a strategy that featured prominently a novel Diels—Alder/dimerization reaction of a complex azadiene system [65]. This remarkable process forged thiostrepton’s unusual tetrahydropyridine structural motif with its three thiazole substituents onto which the rest of the molecule was carefully crafted in a convergent and stereoselective fashion (see highlights in Fig. 9). The thiostrepton success set the foundation for further developments in the
Figure 8. Highlights of the total synthesis of azaspiracid-1.

Figure 9. Highlights of the total synthesis of thiostrepton.

field [125], including the total synthesis of other members of the thiopeptide class of antibiotics such as GE2270A, GE2270T, and GE2270C1 [126], as well as amythiamycins A, B, and C [127].

Sporolide B

Sporolide B was isolated [128] from a marine source and recognized as a metabolite of presporolide, a ‘phantom’ molecule of the enediyne type that
was postulated as its labile precursor [129]. Because of the striking molecular architecture of these molecules and the potential importance of pre-sporolide as a lead compound for novel anticancer drug discovery, we initiated a research program directed at the development of a total synthesis of sporolide B.

The molecular structure of sporolide B is unprecedented in natural products chemistry and highly complex. The most stunning structural feature of sporolide B is the dioxane moiety that forms a double bridge within its macrocyclic motif. Its construction posed a formidable puzzle to synthetic chemistry with no reliable clues as to its solution. A potential, but highly risky approach to this domain of the molecule was that involving an unprecedented intramolecular [4+2] cycloaddition reaction of an ortho-quinone with the indene olefinic bond of a suitable precursor. This daring hypothesis provided additional impetus for undertaking the synthesis of this molecule, for if its implementation was successful, the accomplishment would be admirable and significant and constitute an elegant solution to a difficult problem, thereby breaking new ground in the art of total synthesis.

It was with considerable trepidation that we embarked on this project, a journey that soon led to the realization of the joyful ortho-quinone intramolecular trapping with the indene double bond within the appropriate substrate (see highlights in Fig. 10) [130]. This achievement set the beachhead from which the remaining structural motifs were pursued and cast into the structure of the final product, sporolide B. This success confirmed our o-quinone intramolecular [4+2] cycloaddition hypothesis and pointed to a potential pathway for the synthesis of the enediyne pre-sporolide and stable versions of it. It also demonstrated the power of ruthenium-catalyzed [2+2+2] cycloaddition reactions for the construction of highly complex indene derivatives, for it was precisely this process that was employed to synthesize the substrate of our ortho-quinone/olefin intramolecular reaction. Overall, this endeavor enriched and advanced the art of organic synthesis in general, and total synthesis in particular.

Epidithio- and bis(methylthio)diketopiperazines

The dithiodiketopiperazine natural products and related polythioderivatives are a growing family of naturally occurring substances possessing an impressive array of molecular structures and biological properties, including antiviral, antibacterial, antifungal, and cytotoxic activities [131]. However, and despite their potential importance to biology and medicine, they remain scarce, underexplored, and difficult to synthesize.

It was with the intention of rendering them readily available for biological investigations that we

Figure 10. Highlights of the total synthesis of sporolide B.
decided to embark on a research program directed toward the discovery and development of improved strategies and methods for their synthesis, and biological investigation. This three-pronged pursuit of total synthesis of bioactive natural products represents a paradigm shift in total synthesis endeavors and is ideal for optimum discovery, invention and transformative benefits to chemistry, biology, and medicine.

The dithiodiketopiperazine project in our group was initially directed toward the total synthesis of the bis-methylthiodiketopiperazine epicoccin G and related compounds (e.g. 8,8′-epi-ent-rostratin B, emethallicin E, and haematocin) whose structures are characterized by C2-symmetry [132]. This project exemplifies how total synthesis endeavors serve as a driving force for reaction development, as evidenced by the discovery of improved methods for the sulfenylation of diketopiperazine scaffolds to afford the required bis-sulfenylated structural motifs [133]. The two methods that emerged from this phase of the program were then applied to synthesize the target molecules through an aesthetically pleasing two-directional strategy (see highlights in Fig. 11) and to construct a small library of designed molecules patterned after their structures. Finally, a select number of the synthesized compounds were subjected to biological testing for activity against Plasmodium falciparum (the causative agent of malaria) and the Polio virus. These investigations revealed low micromolar potencies against the former species and low nanomolar potencies against the latter, demonstrating the value of total synthesis campaigns in biomedical research [132]. Overall, this example set a new standard for total synthesis by exemplifying the benefits of blending together multifaceted research pursuits under the umbrella of a carefully conceived and executed research program in total synthesis.

**Viridicatumtoxin B**

Viridicatumtoxin B is a member of a family of fungal-derived hybrid terpenoid-polyketide tetracycline-like natural products. Originally isolated in 2008...
[134] from a *Penicillium* strain, viridicatumtoxin B was found to display potent antibacterial activity against a variety of Gram-positive bacterial strains, including the highly dangerous MRSA. Despite its exciting biological activity, its structural assignment remained incomplete at the time of its isolation and until our total synthesis. In order to clarify the structure of viridicatumtoxin B, and with the intent of ultimately providing analogues of the natural product for antibacterial and anticancer testing, we decided to embark on its total synthesis. Our convergent approach, reported in 2013 [90], relied on the construction and union of four building blocks through the carefully orchestrated forging of six carbon-carbon bonds (see Fig. 12). The completion of the synthesis was facilitated by the strategic recognition of unique and often frustrating reactivity patterns within the complex polycyclic structure of the growing molecule. As a result of this total synthesis endeavor, we were able to assign the configurations of all three unassigned stereogenic centers within the molecular structure and revise the originally proposed epoxy-hemiacetal structural motif to the more reasonable hydroxy ketone structure shown in Fig. 12.

**CONCLUSION AND FUTURE PERSPECTIVES**

The art and science of total synthesis has a long and glorious history [5]. Its emergence and evolution is almost synonymous with the more general and broader discipline of organic synthesis, of which it is a branch, from which it benefits and to which it decisively contributes [1, 2]. Each is driven by the other, and synergistically they constitute the foundation on which all material sciences and technologies dealing with organic compounds are based. The enabling power of organic synthesis stems from the creative nature and unique capability of manipulating matter at the molecular level, replicating the molecules of nature in the laboratory, and delivering new chemical entities for all kinds of applications. Such applications include healthcare items in the form of vitamins, diagnostics and medicines, high tech machines and devices such as computers, cars, spaceships, and medical devices, and cosmetics such as perfumes, dyes and clothing, as well as numerous reagents and probes for biomedical research. Synthesis also contributes to agriculture through pesticides and other molecules that improve food production, as well as...
to energy and the environment in a variety of direct and indirect ways.

The advancement of organic synthesis is, therefore, of paramount importance to science and society. Endeavors in total synthesis serve to enrich and advance the mother field of organic synthesis, thereby serving as the locomotive that drives it forward and stands as the barometer and symbol of its power at any given time. As demonstrated above, total synthesis endeavors provide opportunities to test the applicability and scope of newly developed methods, to discover and develop new synthetic reactions, and to render natural and designed molecules readily available for biological investigations. It also serves to test proposed biosynthetic hypotheses and to design and execute biomimetic synthetic strategies in the laboratory. Besides the obvious benefits of these endeavors, the practice of total synthesis provides unique opportunities for education and training of young students in science. It does so by requiring and demanding the best in human nature, including creativity and imagination, strong experimental skills, resourcefulness, discipline and persistence, and the ability to emerge from the abyss of failure with renewed strength, new ideas, and determination to succeed. Education and training under such conditions are, therefore, ideal for selecting and working on important problems, acquiring problem solving skills to provide solutions, and making discoveries and inventions.

Like other areas of research, total synthesis is constantly moving into new domains and evolving into new paradigms. Indeed, from its original aims in the 19th century to confirm the structures of natural products, synthesis moved in the latter part of the last century to include method development and to embrace biology and medicine through interdisciplinary collaborations. It is currently moving even closer to biology and medicine through research programs of transdisciplinary nature in which scientists from various disciplines in academia and industry fuse their knowledge and expertise toward mission oriented research. Such activities are of great importance in accelerating inventions and applications, resulting in new products and economic growth. But they should be carefully crafted so as to allow transfusion of methods and their applications to the benefit of the overall goal of the mission, often defined as a grand challenge. Indeed, humanity faces many such challenges, including food production, healthcare, energy, climate change and environmental protection. Central to the field of total synthesis is transdisciplinary research directed toward drug discovery and development. Indeed, empowered by the advances in the art of synthesis, synthetic organic chemists are poised to enter into such collaborations with biologists, clinicians, bioinformaticians, and logicians in order to improve the drug discovery and development process and apply it to deliver better and broader medications, which includes unmet needs, orphan diseases, and personalized medicine.

In concluding this article, we wish to underscore the importance of fundamental research as the mother of all truly innovative inventions and technological advancements. In the case of total synthesis, fundamental research includes the discoveries of new chemical reactivity and function as well as their assimilation in new synthetic and biomedical strategies. The creativity of the modern practitioner of total synthesis may manifest itself in more than one way and it includes molecular design, reaction discovery and development, and synthetic strategy design. It should be stressed that the essence of the latter endeavor encompasses the assimilation of both the new and the old reactions.

ACKNOWLEDGEMENTS

We would like to acknowledge the magnificent contributions of our co-workers, whose names are found in the papers cited, to the work described in this article. The highlighted research was supported by grants from the National Institutes of Health (USA), the National Science Foundation, The Skaggs Institute for Chemical Biology, and A*STAR Singapore. Nicolaou is grateful to Rice University and Cancer Prevention Research Institute of Texas for financial support and Hale acknowledges the NSF for Graduate Research Fellowship. We would also like to thank our supporters and friends from the pharmaceutical industry for their generous financial support over the years.

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