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Perspectives in total synthesis: a personal account

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Abstract—Endeavors in total synthesis provide unique opportunities to discover and invent new strategies and tools for constructing organic molecules and they shape the art, science, and technology of chemical synthesis. In this article, the author reflects back on his career highlighting a number of lucrative campaigns in this field and their impact on chemistry, biology and medicine.

1. Introduction

Born in the now occupied part of Cyprus, I was not exactly poised for an academic career in chemistry, certainly not one that would bring my pen to these pages. Rather, the privilege of writing this essay is due overwhelmingly to my good fortune of encountering so many resplendent people. These individuals opened paths and helped me travel a personal odyssey which led me westwards where I found a new home in California, not so different in landscape and beauty from the one I lost in Cyprus. It is, therefore, with great pleasure that I accepted the invitation from Professor Stephen Martin to write this essay in the tradition set by Sir Derek Barton. Through my words I would like to pay tribute both to my teachers, who kindled my interest in chemistry and shaped my philosophy, and to my students, who participated in the science that I am about to briefly describe. But, first, the beginning…

Growing up in the panoramic village of Karavas on the northern coast of Cyprus was an incredibly enriching experience, despite the absence of material goods other than those provided by nature. With the Mediterranean Sea defining the idyllic coast on one side, and the sharply ascending pine-covered mountains on the other, the village was buried in lemon groves, thereby earning its epithet as the 'Lemon Capital' of Cyprus, if not the whole of Europe. The cold spring waters gushing from the picturesque mountains ensured a year-round verdant canopy and an abundance of fruits and vegetables to accompany the fish and game which provided nourishment for the village inhabitants.

My father could only become a builder, having received schooling no further than the third grade, not an architect, a profession that he respected enormously—and one that he wanted me to enter. Yet, I must have found this idea too 'earthy', for I remember being much more interested in the ethereal and I was leaning towards the study of astronomy instead. While my father was concerned with my future, my mother was more interested in the immediate needs of the family, which included keeping me, my younger brother and four younger sisters fed, warm and well brought up. Being the eldest sibling, I had to contribute to the family's income and thus my first job begun in these early years; indeed, my opening assignment came at the age of seven and was to deliver milk to the wealthy locals on a secondhand bicycle my father had bought for me, and that made me the envy of my peers. Rising early, I collected the bottles filled with milk from our sole cow, another shrewd purchase of my father's, and set off precariously to undertake the task before the school-day commenced. Having spent my first 13 years in this humble environment beside the Mediterranean Sea attending primary school, farming in the fields and delivering goods, and playing in the most natural and placid surroundings, I was then sent to Nicosia, the capital of Cyprus, to attend the Pancyprian Gymnasium, a most prestigious and highly disciplined high school. My Uncle John provided me not only with a warm place to stay, but also with my first 'laboratory' where I could practice making cakes in his confectionary shop. There I quickly learned the art of making pastry, and I developed a love for it and a taste for the 'synthesized' products. In fact, I was flattered by several local professionals who thought that I was so creative at making pastries and birthday cakes that upon completion of high school I should stay in Cyprus

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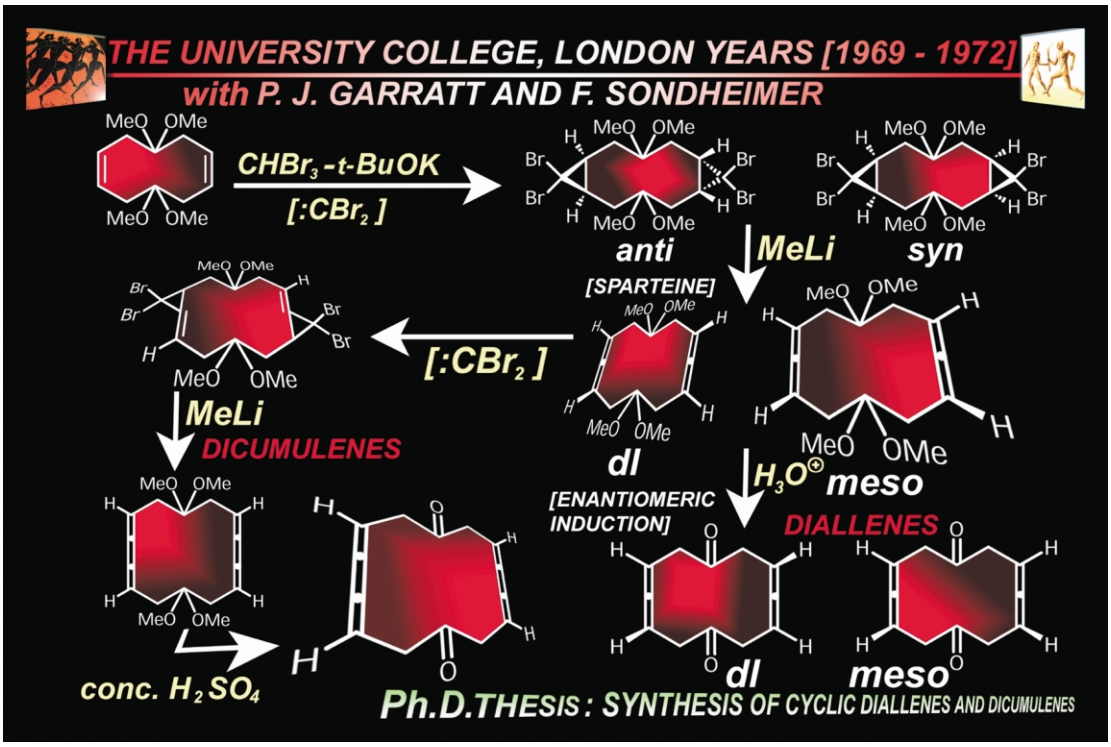

Figure 1. PhD studies at University College, London with Peter J. Garratt and Franz Sondheimer: cyclic allenes, cumulenes and an early asymmetric induction with sparteine.

where "I had a great future ahead of me practicing the art". Needless to say, I turned down the offer and traveled abroad to further my studies.

However, it was at that high school in Nicosia where I had the good fortune to encounter my first chemistry teacher, Dr Telemachos Charalambous, who immediately and decisively inspired me and instilled in me the passion for chemistry. For his guidance and enthusiasm and for showing me the way, I will be eternally grateful.

My journey west began upon graduation from the Pancyprian Gymnasium when, at the age of 18, I traveled to England where I intended to pursue studies in chemistry. Before entering University, however, I had to first learn English and then pass the required entrance examinations. I did both while undertaking a number of eclectic jobs, which included working in a rubber factory and a sausage establishment, but most frequently in 'fish and chip' shops. The latter endeavor once again brought me much 'fame' and my many admirers made me offers to go into partnerships with them for they saw 'a great future for me' in this sort of business as well. For a second time, I defied my aficionados and pushed forward with my original plan to study chemistry.

I entered Bedford College, London in 1966, where I studied chemistry under the watchful eyes of Drs Margaret Harris, Muriel Hall and Roger Bolton, among others, and by the summer of 1969 I had offers from both Sir Derek Barton and Franz Sondheimer to do my PhD under their tutelage. My intention was to visit their respective laboratories before making a final decision, yet I only partially executed this plan. My first visit was with Franz Sondheimer at University College, London (UCL), who introduced me to Peter Garratt, his protégé. I was so utterly mesmerized and fascinated by both men and their annulene and related chemistry that I accepted immediately, skipping the trip to Imperial College, London to meet Barton. I joined the Sondheimer–Garratt group in September of 1969 only to learn a month later that Derek Barton was the Nobel Prize winner in chemistry for that year. I could not help but wonder at the time whether I made a mistake in not choosing Barton over the UCL group; in retrospect, I think not. Indeed, that would have been a different pathway, whose richness I will never know. What I do know, however, is that the road I chose at that crucial fork led me towards an unimaginable adventure full of excitement and rewards, and I am grateful to both Peter and Franz for their caring mentorship.

My 3 years at University College were highly enjoyable and most fulfilling. In the group I met people like Andy B. Holmes, Brian Metcalf and K. C. P. Vollhardt, and worked on some captivating molecules of theoretical interest (see Fig. 1[†]),[1–6] apparently making enough of an impression on my mentors to be sent still further west, this time across the Atlantic to America where I would join the group of Thomas J. Katz at Columbia University. The sequence of events that led to my association with Tom Katz may also be of some anecdotal amusement. From London, I

[†] The figurines at the top left (foot race) and right (torch relay race) corners of each figure depict scenes from the Olympic Games in ancient Greece, symbolizing the competitive struggle of man to reach new heights and the passing of the torch of knowledge to the new generation.

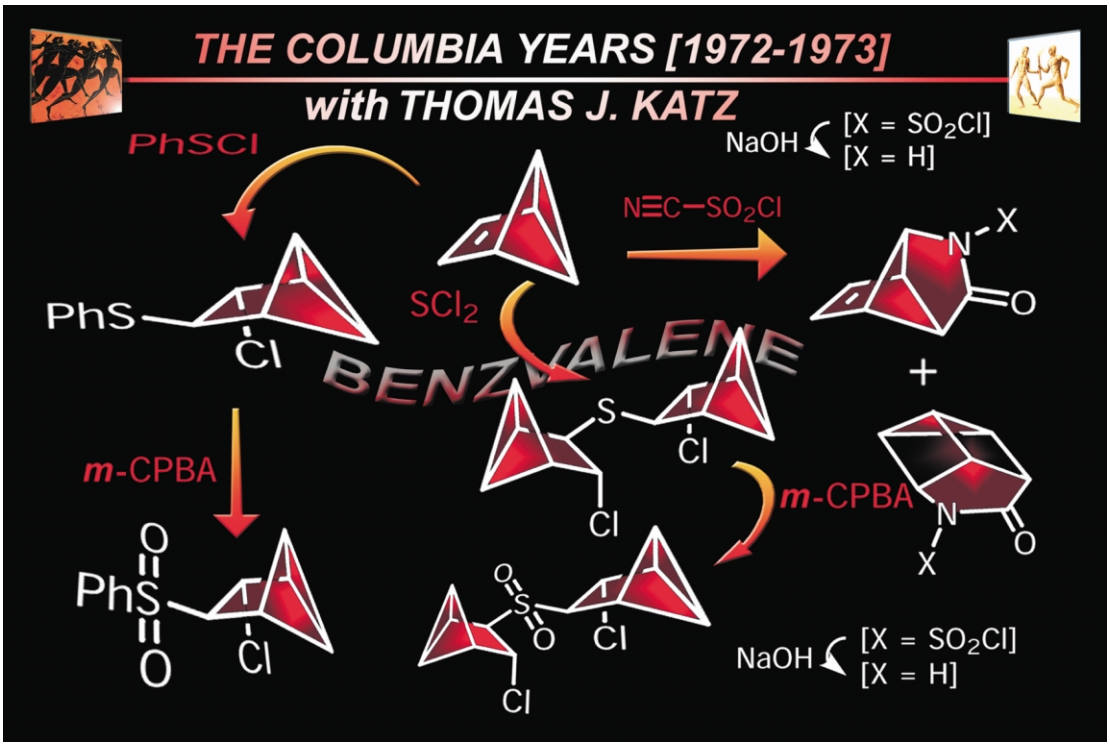

Figure 2. Postdoctoral studies at Columbia with Thomas J. Katz: experimenting with benzvalene after giving up attempts to synthesize tetrahedrane.

had written to E. J. Corey, Ronald Breslow and Tom Katz for a possible postdoctoral stint. E. J. was the first to reply with a succinct and polite no. Tom Katz, who happened to be Peter Garratt's PhD mentor, responded that he would love to have me, but unfortunately his NSF grant was in jeopardy, so he sent his regrets with apologies. That left Breslow, whom, in the meantime, I had the pleasure of meeting at University College where he had been invited to lecture. He was both charming and forthcoming with an offer which had settled the matter for me quite nicely until a few weeks before my departure for New York. Katz had dispatched a letter to us in London happily announcing that his grant had come through and that, if I was still interested, I could join his group. In an accompanying letter from Breslow, he explained that this would be okay with him and it was really up to me. I chose Katz in whose group I spent the first few months attempting, unsuccessfully I must admit, to synthesize tetrahedrane. But I did succeed in convincing Tom to let me move into another project involving the chemistry of benzvalene (see Fig. 2)[7] where I initially used some mercury compounds as reagents. That led, within days, to a euphoric excitement at Columbia where the Nakanishi group claimed to have isolated the 'first mercury-containing natural product'. Needless to say, however, this euphoria was soon dispelled and replaced by depression for them and total embarrassment for me, for it was my sample which had contaminated the mass spec, misleading the Nakanishi camp into their wishful thinking that they had landed a 'coup' in natural product chemistry. The success of my second project prompted a concerned inquiry from Tom as to what I wanted to do the following year, to which I replied: "Oh, maybe I will just go back to England for an industrial job somewhere". "Why?" he said; "don't you want to stay for another year?" "No", I replied, "Not unless I had the chance to work with somebody like Woodward or Corey". "Well", he said, "I know them both; do you want me to arrange a position with either of them?" "Maybe not…I am not sure. Really?" I said, "I will let you know tomorrow…" A strong force was pulling me back to England at the time so I had to deliberate, check, negotiate… The next morning as soon as Tom came in, I was in his office with a firm, "Yes!" Within a week I had two offers, one from Woodward and one from Corey… What to do was the next dilemma. Brief discussions with Katz, Breslow and Stork, among others, and my own gut feeling, led me to choose the younger man, of the two; so, a few months later, I arrived with my lovely newlywed bride, Georgette, at Harvard to work in E. J. Corey's laboratory—most likely it was unbeknown to him that I was the very same postdoctoral candidate whom he had turned down eighteen months earlier!

The Harvard years were delightful both scientifically and socially. Corey was a marvelous teacher–mentor and I learned from his incredible genius, methodical approach to science, and admirable discipline. And this is where I met people like Larry Blaszczak, Mark Bock, S. Chandrasekaran, Dale Boger, Robert H.-K. Chen, Rick Danheiser, Jean-Bernard Ducep, Dieter Enders, Harry Ensley, Camille Falk, Mike Fitzpatrick, Tapio Hase, Marty Haslanger, Paul Helquist, Peter Johnson, Sunggak Kim, Robert Lett, Yoshimasa Machida, Larry Melvin, Johhan Mulzer, Koichi Narasaka, Homer Pierce, Rama Rao, Peter Sheldrake, Masakatsu Shibasaki, Takeshi Toru, Eugene Trybulski, Skip Volante, and David Williams, among many other highly talented individuals, whose science has become legendary and continues to shape the world of chemical synthesis and medicinal chemistry to this day. My work in the Corey group took me from prostaglandins to macrolides (see Fig. 3). The 'Greek

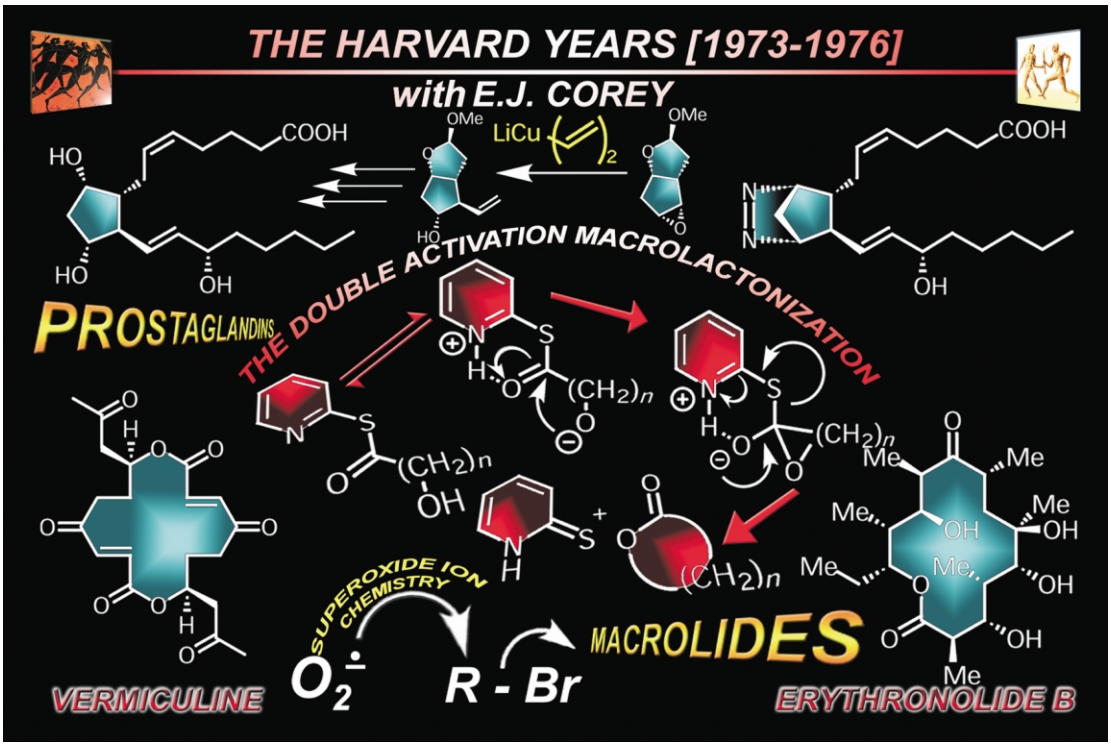

Figure 3. Postdoctoral studies at Harvard with E. J. Corey: targeting prostaglandins and macrolides and learning the art of major league synthesis.

Gods' and good luck must have been with me, for my efforts were met with considerable success in the form of 14 publications[8–21] which accumulated within a short period of time. But despite this impressive record and E. J.'s strong support, I was turned down for an academic position by several schools—both in Canada and the US. The University of Pennsylvania (Penn), however, came up trumps thanks to people like Mike Cava, Madeleine Joullié, Charles Price, Bryan Roberts, Amos Smith, and Ed Thornton, to all of whom I will be forever grateful for giving me a chance. I had arrived in Cambridge with one girl and I left with two: Colette, our daughter, was born on 17 June, 1976, at the Brigham and Women's Hospital. But, eventually, our family would be further blessed with three sons, Alexander, Christopher and P. J. Two months later we arrived in Philadelphia where I would begin my independent career at the University of Pennsylvania. It was Katz who initiated a crucial turning point in my career and Corey who launched me into it full throttle; to both I owe much…

My arrival at Penn in August 1976 was met most warmly by my organic chemistry colleagues in the department, but most notably by Madeleine M. Joullié. Indeed, it was with her generous and enthusiastic support that I began in earnest to set up a laboratory and to assemble a group of students to assist me as I embarked on my academic career as a teacher–scholar.

2. A total synthesis that went astray, new synthetic technologies, and chemical biology

One of the first projects initiated at Penn in 1976 was that which was directed towards the total synthesis of brefeldin A, a fungal metabolite with striking biological activity against the Golgi apparatus. The strategy went astray quickly, but a discovery was made along the way that would decisively shape things to come. Failing to cyclize a sensitive unsaturated carboxylic acid by the classical halolactonization reaction, we were lured by PhSeBr and related selenium reagents as potential initiators for ring closure such as the one we had failed to perform with bromine or iodine. It was thus that the phenylselenolactonization[22] and -etherification[23] reactions were developed. At precisely this time the structure of prostacyclin, the powerful vasodilator and antithrombotic agent, was disclosed by Sir John Vane, an event that would significantly influence our future research. Enticed by the remarkable biological activity of this arachidonic acid metabolite and in making the connection between its structure and the potential of our selenium-based synthetic technologies to construct analogs for biological studies we were afforded with a good reason to abandon the total synthesis of brefeldin A in favor of a program directed at the chemical synthesis and chemical biology explorations of the newly discovered prostacyclin and its related eicosanoid, thromboxane A_2, discovered earlier by Bengt Samuelsson. Thus was born the passion for defining research programs around biologically active natural products that would include, in addition to the main objective of total synthesis, the discovery and invention of new synthetic technologies and chemical biology studies. This early foray into such thematic endeavors led to the design and chemical synthesis of several novel prostacyclins and thromboxanes such as isoprostacyclins,[24,25] carboprostacyclin,[26] pinane thromboxanes A_2,[27] and carbocyclic thromboxane A_2,[28] compounds which greatly facilitated biological investigations in the eicosanoid field (see Fig. 4).[29] This investigative approach of weaving together total synthesis endeavors with the discovery and development of new synthetic methods

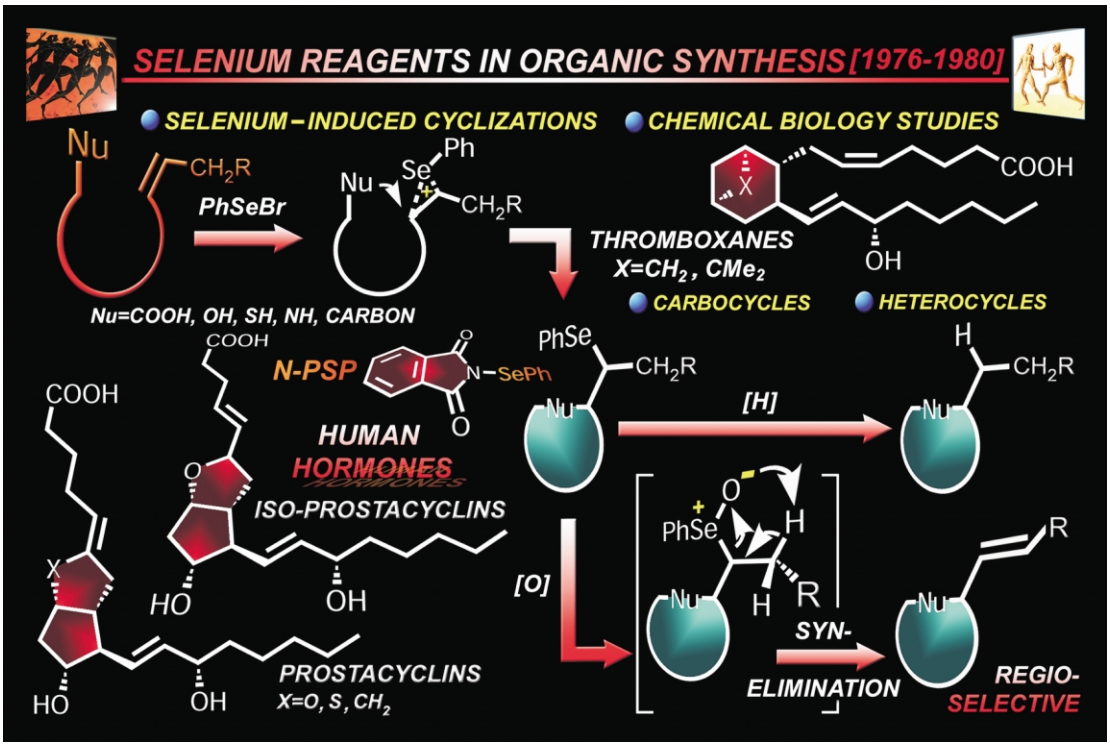

Figure 4. The first discoveries and inventions at Penn: plunging into the ocean of independent research with a total synthesis that never finished, but which led, nevertheless, to rewarding discoveries and inventions in new synthetic technologies, molecular design, and chemical biology studies.

and technologies, and with explorations in chemical biology served us well as it did the fields of chemistry, biology and medicine in the intervening 25 years. A glimpse at some exemplars at this stage may be instructive, serving to place in better perspective the highlights that will follow.

In the 1980s, the group continued to make important contributions to the fields of total synthesis, new synthetic technologies, and chemical biology. Thus a series of total syntheses were accomplished, including those of the smooth muscle constricting substance zoapatanol, the first total synthesis to be accomplished in our laboratories, various leukotrienes, hydroxyarachidonic acids and lipoxins, carbomycin and leucomycin-related targets, antibiotic X14547A, forskolin, aurodox and efrotomycin, endiandric acids A–G, and amphotericin B (vide infra). It was also during the early 1980s that the group recognized the importance of carbohydrates in natural products chemistry and the synthetic deficiencies for their installation into complex molecular frameworks, and ventured into the carbohydrate field. Thus, as a part of the program directed towards the synthesis of *O*-mycinosyl tylonolide A_4, a new method for the attachment of the sugar to the aglycon was sought and found through the use of phenylthioglycosides as glycosyl donors under the activating influence of the electrophilic reagent *N*-bromosuccinimide (NBS). This discovery served as the cornerstone to the bridge between pre-existing knowledge on thioglycosides and one of today's most powerful glycosidation methods employing electrophilic reagents as activators. We were also able to elucidate the important connection between the stable thioglycosides and the highly reactive glycosyl fluorides by enlisting the action of the fluorinating agent DAST. Thus, the two-stage activation protocol for a reiterative glycosidation procedure for the synthesis of complex oligosaccharides was born. First applied in the total synthesis of efrotomycin (vide infra), this method found many subsequent applications. It was also during this period that our explorations in carbohydrate chemistry led to the discovery of the stereospecific and highly useful 1,2-phenylsulfenyl migrations within carbohydrate frameworks. Starting with 2-hydroxy phenylthioglycosides, these migrations allowed the development of efficient and stereocontrolled methods for the synthesis of α- and β-2-deoxyglycosides. In further forays, these reactions were extended to include migrations of methoxy, acetoxy and azido groups, with the latter opening an expedient entry into the important class of amino sugars. As a direct consequence of these breakthroughs in methodology, the total synthesis of a number of highly complex and biologically important oligosaccharides became possible. These included the biologically important rhynosporosides and globo- and lysoglobotriasylceramide (Gb_3, $LysGb_3$) (vide infra). Most significantly, the preconditions for new knowledge in chemistry and biology became a standard requirement for most of our future total synthesis projects.

The 1990s saw a notable surge in the research activities of the group in total synthesis, new synthetic technologies, and chemical biology, coinciding with our move to The Scripps Research Institute and the University of California, San Diego. During this 'Golden Age', these three lines of investigation were even more intimately and cohesively interwoven productively and in harmony within several projects, including those centered around the molecules of calicheamicin γ_1^I, rapamycin, Taxol™, zaragozic acid, balanol, brevetoxins A and B, epothilones, eleutherobins and sarcodictyins, vancomycin, the CP-molecules,

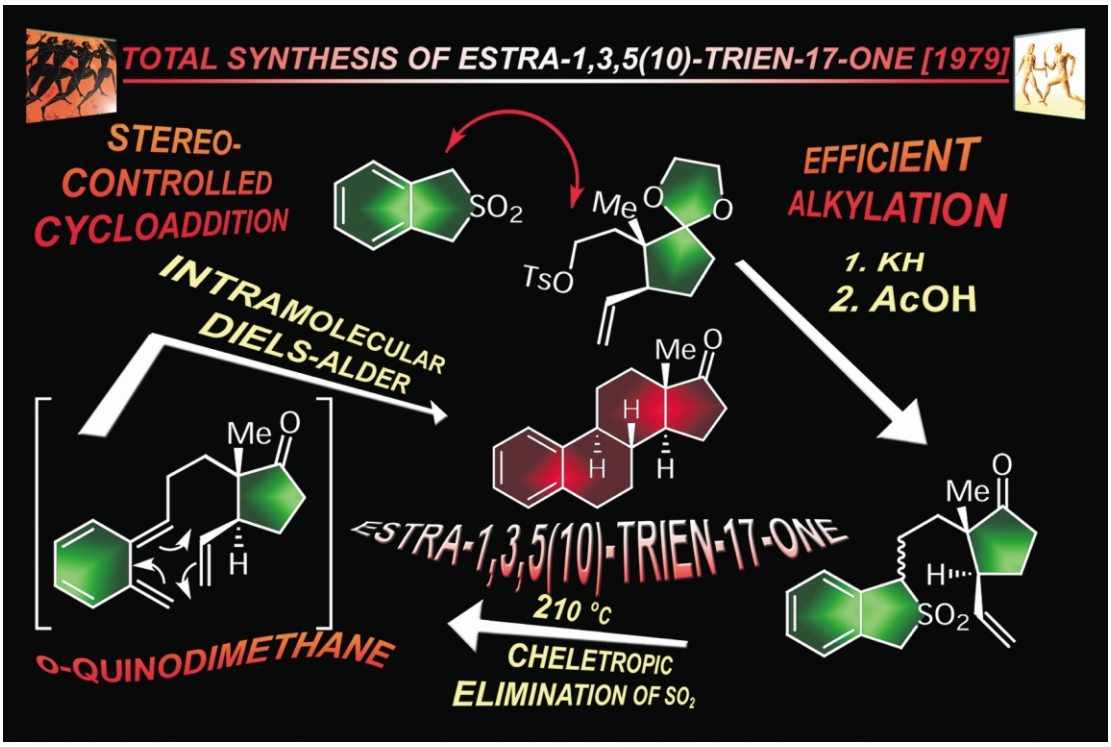

Figure 5. Expedient entry to the steroid nucleus via the intramolecular Diels–Alder reaction of an *o*-quinodimethane, generated by cheletropic elimination of SO_2.

everninomicin, the bisorbicillinoids, the benzopyran natural products, and psammaplin A, amongst others.

At the dawn of the 21st century, and with fidelity to the original theme of the art and science of total synthesis, the group continued in the pursuit of basic knowledge with new targets such as colombiasin A, hybocarpone, the hamigerans, apoptolidin, 1-*O*-methylforbesione, the coleophomones, and diazonamide A.

In order to appreciate the important developments in chemical synthesis and chemical biology derived from such total synthesis endeavors, a number of these projects are separately highlighted below.

3. Total syntheses

3.1. Estra-1,3,5(10)-trien-17-one

Despite the large body of synthetic work directed toward their structures, the steroid hormones have continued to serve as appealing targets to test the power of new synthetic strategies and technologies. In the late 1970s, we were intrigued by the possibility of producing such structures by the simple method of generating an *o*-quinodimethane through the cheletropic elimination of SO_2, and trapping it via an intramolecular Diels–Alder reaction. This proposition worked admirably well, requiring construction of two building blocks, coupling them to afford the precursor sulfone, and thermolysing the latter to give the targeted estra-1,3,5(10)-trien-17-one (see Fig. 5)[30] in an efficient and stereoselective manner.

3.2. Zoapatanol

Zoapatanol was the first natural product to succumb to total synthesis in our laboratories at Penn, and, as such, commands special status in our history. Isolated from the leaves of zaopatle (*Montanoa tomentosa*, a plant used by the Aztecs for centuries to induce both labor and abortion), this naturally occurring substance was constructed via a route that featured a chelation-controlled addition of a Grignard reagent to establish the tertiary center and a regioselective epoxide opening by an internal hydroxyl group to form the oxepane system of the target molecule in an efficient manner (see Fig. 6).[31] This initial accomplishment, modest as it was by today's standards, provided the group with the courage and confidence to undertake more daring projects with considerable success, as we shall see below.

3.3. Antibiotic X-14547A

The unusual structure and powerful biological activity of antibiotic X-14547A (later named indanamycin) provided enough enticement for the group to initiate a program directed toward its total synthesis. To be sure the challenging structure of this product raised the bar higher for us, testing our ability to tackle increasingly demanding levels of molecular complexity. An asymmetric installation of the first chiral center was followed by construction of a geometrically appropriate triene system and an intramolecular Diels–Alder reaction to furnish the indane segment of the target molecule, with its four chiral centers in their proper stereochemical arrangement. Coupling of this fragment with the tetrahydropyran segment through a Julia reaction and subsequent further elaboration allowed the

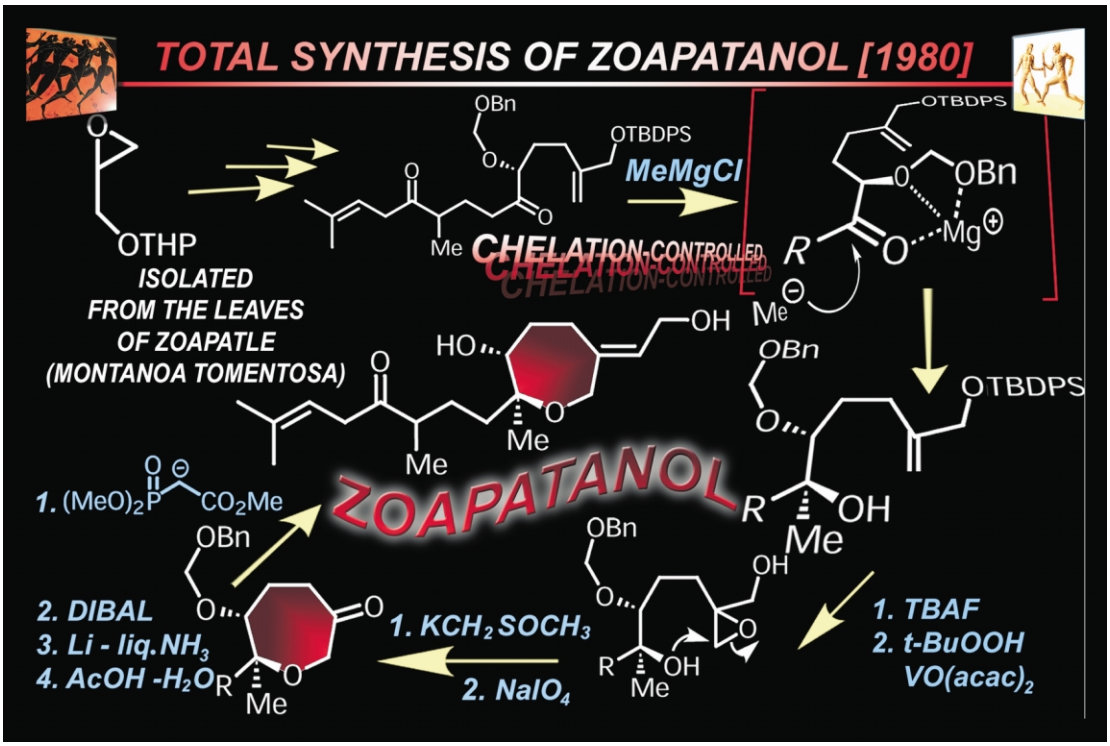

Figure 6. Zoapatanol: the first total synthesis of the group.

attachment of the ketopyrrole side-chain, a task facilitated by a new method specifically developed for this project (see Fig. 7).[32]

3.4. Mycinosyl tylonolide

The value of carbohydrates as building blocks for total synthesis did not escape our attention, as it did not a number of other practitioners of the art. Following the 'chiral pool' approach in the early 1980s, we initiated programs directed toward the 16-membered ring macrolide antibiotics, a subclass of the polyene macrolide antibiotics which had stood for a long time as bastions of resistance to total synthesis. The deadlock was overcome when our efforts

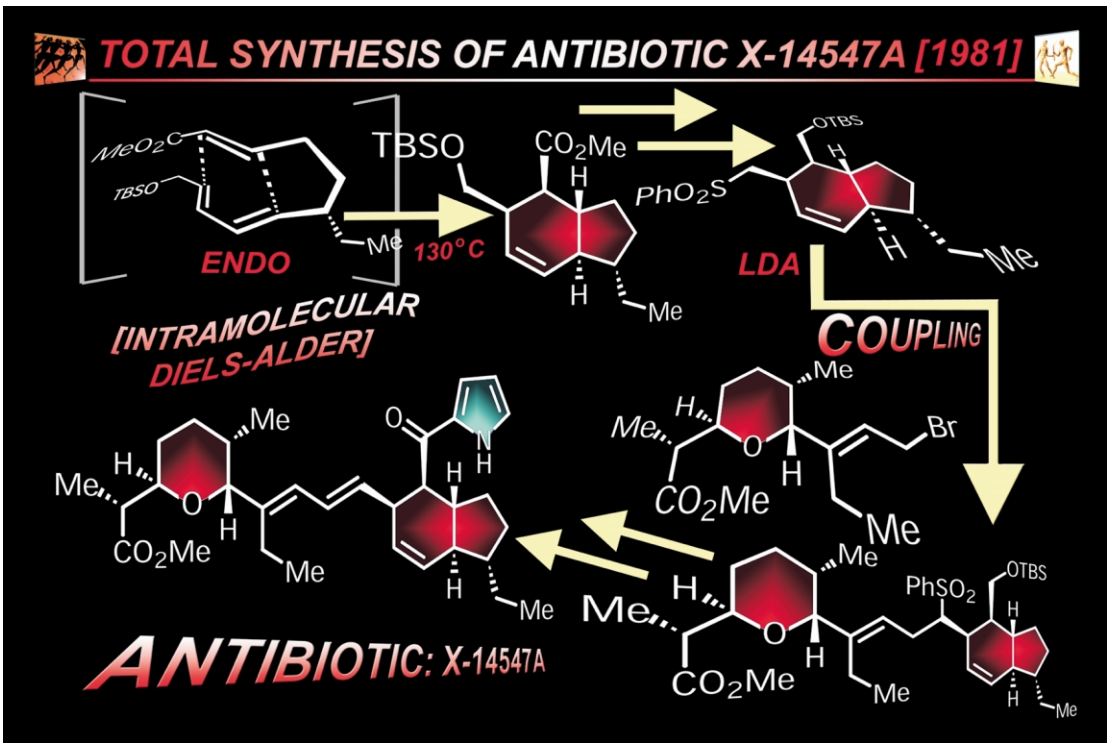

Figure 7. An intramolecular Diels–Alder reaction facilitates the stereocontrolled total synthesis of architecturally novel ionophone antibiotic X-14547A (Indanamycin).

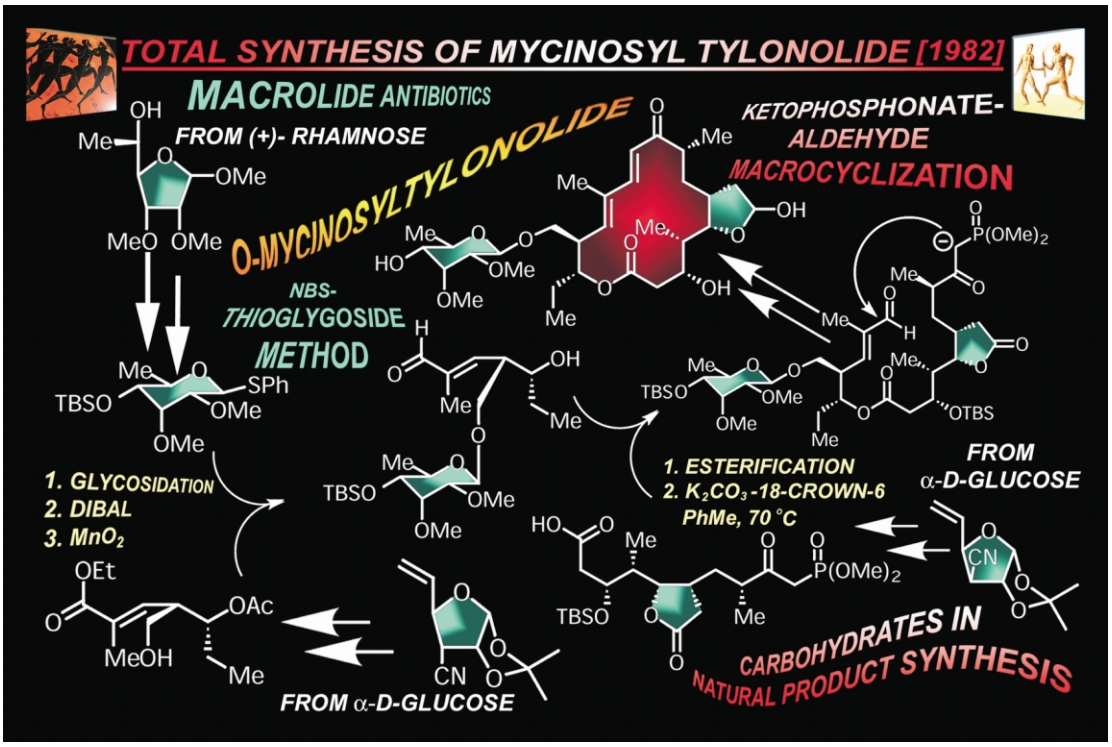

Figure 8. Carbohydrates in total synthesis: ketophosphonate-aldehyde condensations in the synthesis of polyene and related macrolide antibiotics, and thioglycosides as glycosyl donors are the signature new synthetic technologies developed in this early total synthesis endeavor by the group.

culminated, in 1982, in the total synthesis of mycinosyl tylonolide (see Fig. 8).[33] Among the groundbreaking discoveries and inventions made during this program were the demonstration of the use of carbohydrates as building blocks for the construction of complex natural products, the discovery of the NBS-thioglycoside glycosidation method[34] and the establishment of the intramolecular ketophosphonate–aldehyde coupling reaction as a powerful means to forge the macrocyclic rings of the polyene macrolides. These early technologies and successes enabled subsequent

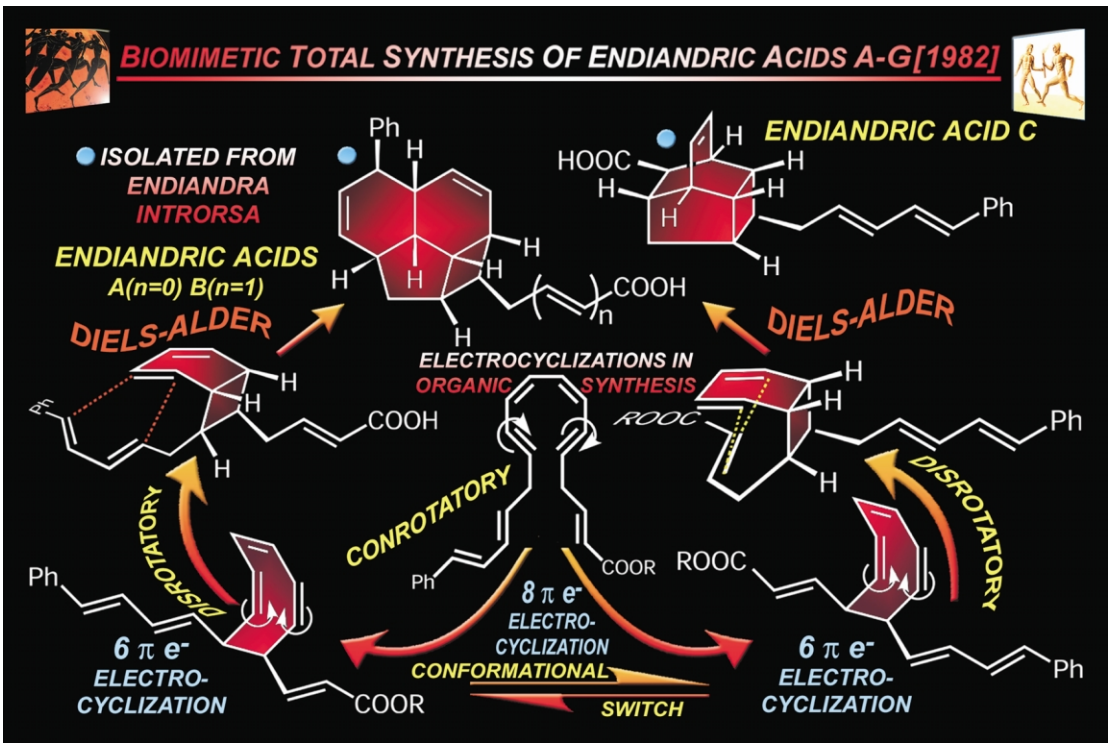

Figure 9. Involving a remarkable series of electrocyclization reactions, the 'biomimetic' total synthesis of endiandric acids furnished, simultaneously and in a stereospecific manner, two complex natural products, each containing four rings and eight stereogenic centers, from prochiral, polyunsaturated precursors.

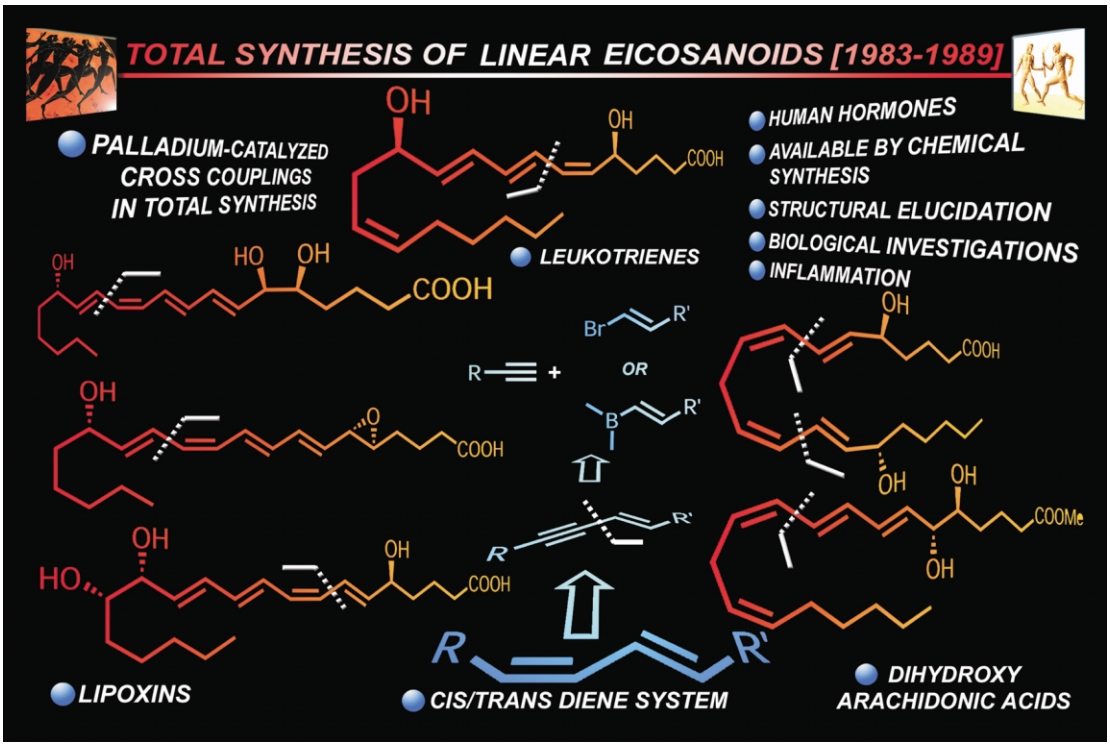

Figure 10. Representing some of the earliest applications of palladium-catalyzed coupling reactions in total synthesis, the chemical synthesis of leukotrienes, dihydroxy arachidonic acids and lipoxins facilitated chemical biology studies in the eicosanoid field.

developments in the field and pointed the way to further refinements leading to the current thioglycoside glycosidation methods.

3.5. Endiandric acids

Following the report of the isolation and possible biogenetic origins of the endiandric acids A, B and C, by St. Black et al. in 1980, we became fascinated by the possibility of producing these compounds in the laboratory by mimicking Nature's supposed route. Indeed, the group developed both stepwise and 'biomimetic' total syntheses to these and related compounds, some of which were later found to be naturally occurring as well (see Fig. 9).[35] Based on a splendid cascade of elecrocyclization reactions (a conrotatory 8π electrocyclization, a disrotatory 6π electrocyclization and an intamolecular [4+2] cycloaddition), the biomimetic strategy involved the construction of polyunsaturated, prochiral precursors containing at least seven sites of unsaturation, whose geometry was designed so as to allow the initiation of the sequence (*cis*, *cis* for the internal double bonds of the conjugated tetraene), and to ensure the stereospecific formation of all eight stereogenic centers present in each of the two types of natural products. This highly pleasing exploit stands as a classic example of biomimetic total synthesis and cascade reactions in organic synthesis alongside Sir Robert Robinson's tropinone synthesis and W. S. Johnson's cationic synthesis of steroids.

3.6. Linear eicosanoids: leukotrienes, dihydroxy arachidonic acids, and lipoxins

The discovery of several linear bioactive eicosanoids such as the leukotrienes, dihydroxy arachidonic acids, and lipoxins in the late 1970s and 1980s stimulated considerable interest in these human hormones. Chemical synthesis proved to be crucial to both their characterization and biological investigation.[36–38] In addition to aiding biological studies, our syntheses of these scarce, but valuable, substances exploited and decisively demonstrated the power of palladium-catalyzed coupling reactions in total synthesis (see Fig. 10);[39] much was to follow in this area of chemical synthesis. Thus, by verifying the applicability of palladium-catalyzed cross-coupling reactions in complex molecule construction and by enabling biological investigations, these early successes played a role in advancing the fields of both organic synthesis and chemical biology.

3.7. Efrotomycin

The complex structure of the antibiotic efrotomycin, containing an all-*cis* tetrasubstituted tetrahydrofuran moiety, three carbohydrate units and 28 sites of isomerism (21 stereocenters and 7 olefinic bonds), presented a formidable synthetic challenge in the early 1980s and certainly a higher level of complexity for the group. Several new and long-lasting synthetic technologies were developed during this project (see Fig. 11).[40] Thus, a solution for the construction of the unusually substituted tetrahydrofuran system was derived from an original study on intramolecular oligoepoxide openings, while the oligosaccharide segment of the molecule required the development of the two-stage activation procedure for oligosaccharide synthesis via phenylthioglycosides and glycosyl fluorides, eluded to above. It was rewarding to realize, in retrospect, that beyond the total synthesis of efrotomycin (and its naturally occurring sibling, aurodox), both these new synthetic techniques found extensive applications elsewhere

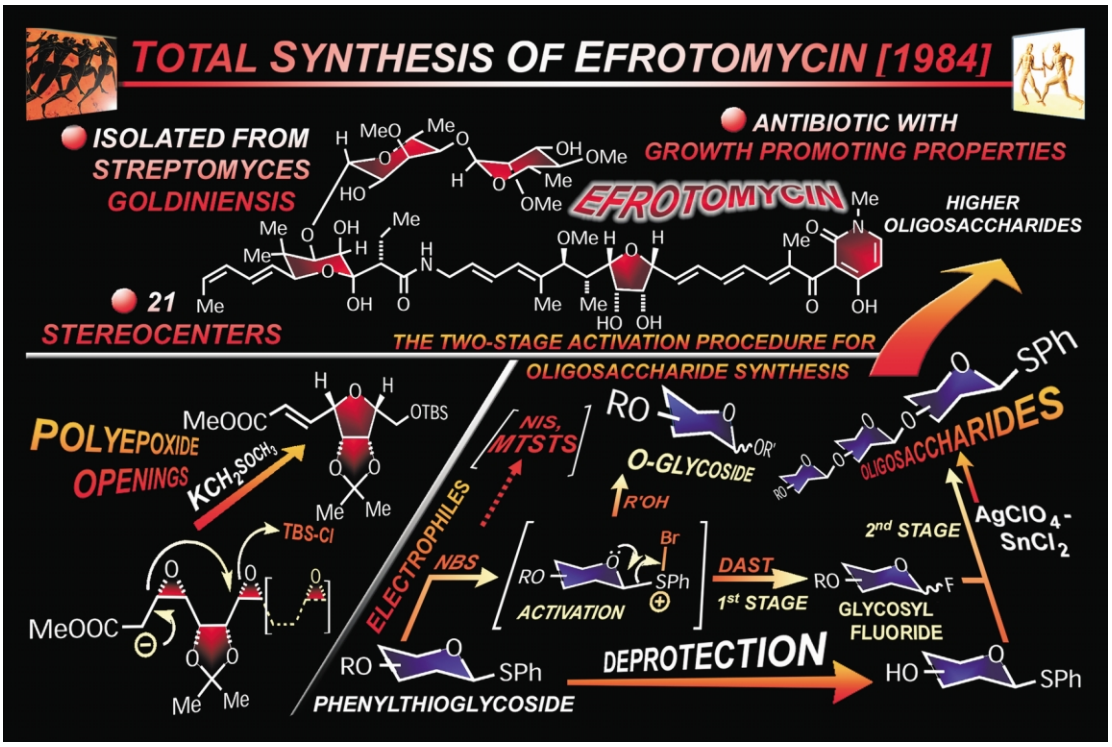

Figure 11. The total synthesis of efrotomycin introduced, for the first time, polyepoxide cyclization to form the all-*cis* tetrahydrofuran ring system of the target molecule, and the two-stage activation procedure for the construction of the oligosaccharide domain employing thioglycosides and glycosyl fluorides.

and led to several modifications in subsequent studies in many other laboratories.

3.8. Rhynchosporosides

As part of our vision for advancing carbohydrate chemistry, we considered the rhynchosporosides as important targets for chemical synthesis. Isolated from *rhynchosporium secalis*, these pentasaccharides were shown to cause scald disease in barley. Their structures provided a challenge to our thioglycoside-based two-stage activation procedure for oligosaccharide synthesis,[41] a task that was accomplished

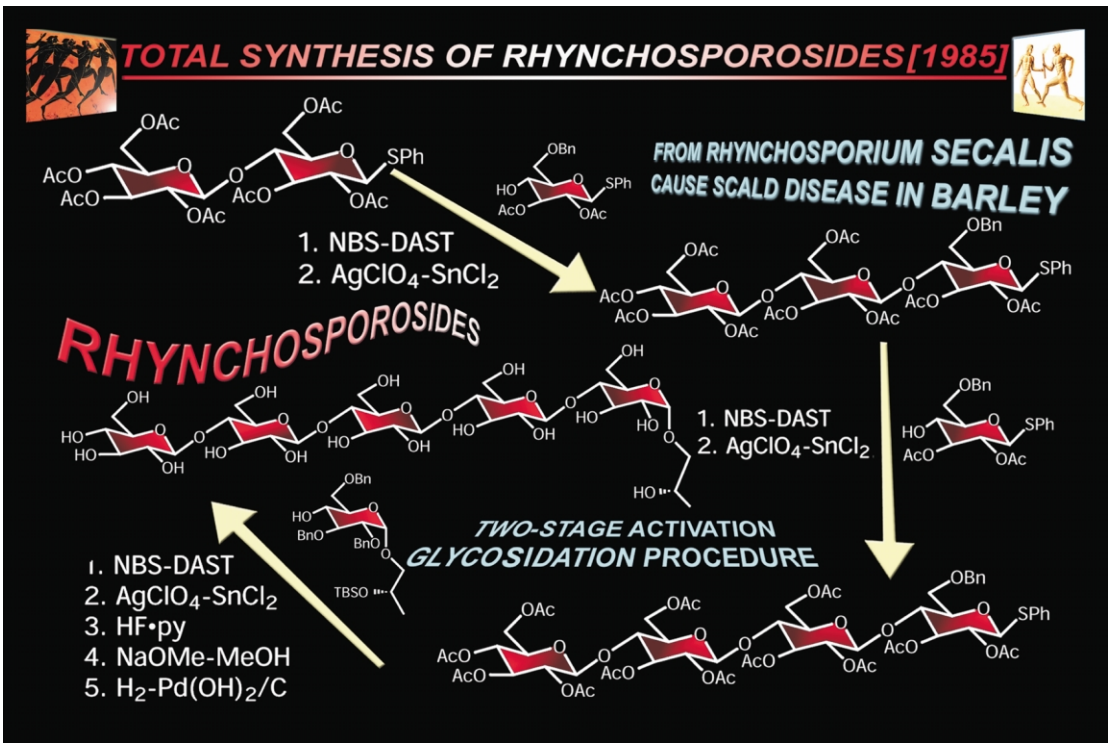

Figure 12. The total synthesis of the rhynchosporosides was a convincing demonstration of the power of the two-stage activation procedure in the synthesis of complex oligosaccharides.

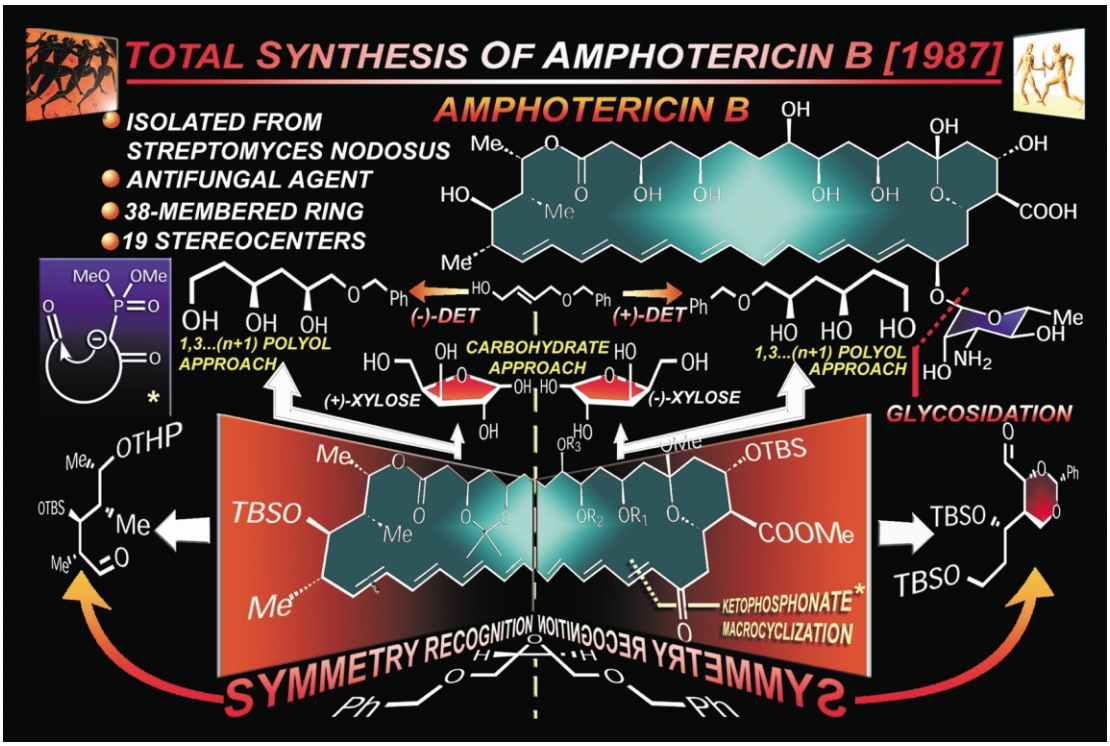

Figure 13. The total synthesis of amphotericin B featured both the chiral pool and asymmetric reactions to secure the molecule's multiple stereogenic centers. Characterized by a remarkable macrocyclization process involving a ketophosphonate-aldehyde condensation to form the 36-membered ring, this synthesis featured a number of novel synthetic maneuvers for the oxidative removal and stereocontrolled installation of the amino sugar moiety.

stereoselectively and efficiently in 1985 through application of the method (see Fig. 12).[42] This achievement would lay the foundation for our future successes in synthesizing oligosaccharides of higher complexity, as we shall discuss below.

3.9. Amphotericin B

In our quest to advance the field of total synthesis to new heights, the group searched for an even more complex target molecule to tackle. As a representative of the polyene class of macrolide antibiotics and a clinically used antifungal agent, amphotericin B represented an attractive, albeit highly complex, synthetic target in the 1980s. Besides providing a measure of the state of the art at the time, the total synthesis of this molecule,[43] accomplished by the group in 1987, had a number of impressive features associated with it (see Fig. 13). For example, it demonstrated the power of the intramolecular ketophosphonate–aldehyde condensation[44] in forming highly complex and sensitive macrocycles; in this instance, the record (for the time) 36-membered ring of the target molecule was attained. This mild and efficient method has since been called upon to solve numerous other challenging problems connected with macrocyclic ring construction. In addition, the designed strategy focused on a number of subtle symmetry elements in the structure of the target molecule, recognition of which allowed the utilization of a series of aesthetically pleasing maneuvers in the synthesis. Thus, the 'left' and the 'right' segments were both obtained from the same tartaric acid-derived epoxide, while the 'top' polyol system was constructed from either of the two enantiomeric xyloses, or the same allylic alcohol via asymmetric epoxidation employing the two enantiomers of diethyl tartrate to induce chirality transfer. The special strategies developed for the removal[45] and attachment of the target's rather unique amino sugar moiety are also worthy of note.

3.10. Tumor-associated Le^x glycosphingolipids

The Le^x family of tumor-associated glycosphingolipids includes several antigens of which trimeric Le^x is the most prominently complex. In an effort to demonstrate the power of our two-stage activation procedure[41] and in order to render these marker molecules available for chemical biology studies we initiated, in the 1980s, a program directed towards their chemical synthesis. These studies culminated in the construction of several members of the class as exemplified by the total synthesis of the undecasaccharide trimeric Le^x, which was accomplished in 1990 (see Fig. 14).[46] Special protecting groups and reaction conditions were employed in these syntheses; their reliance on the two-stage activation procedure was pivotal, leading to highly stereocontrolled and efficient chemical routes to these important glycoconjugates.

3.11. NodRm-IV factors

Isolated from *Rhizobium melitoti*, the NodRm-IV factors were found to affect organogenesis and root morphology of the grasses alfalfa and vetch. Their tetracyclic structures carrying an unsaturated chain, an amide bond and a sulfate group provided an interesting challenge to chemical synthesis. This demand was met in our laboratories in 1992 through the application of the glycosyl fluoride technology (see Fig. 15),[47] an achievement that

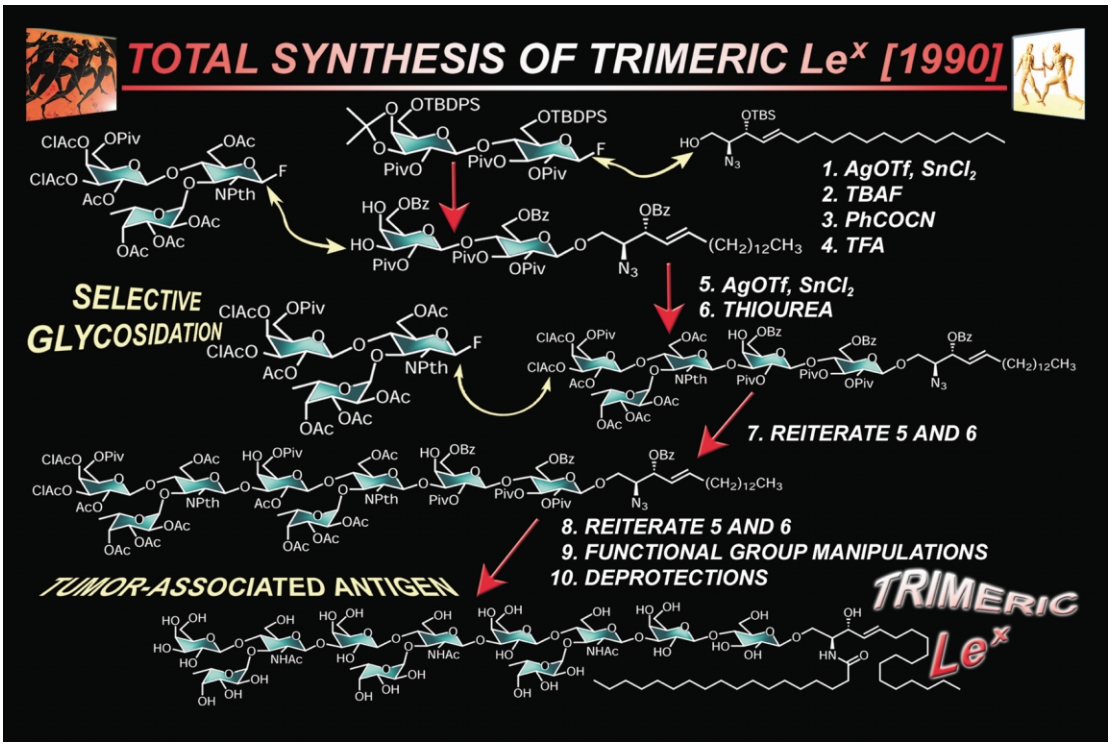

Figure 14. The total synthesis of complex tumor-associated antigens such as the trimeric Le^x, accomplished in 1990, demonstrated the power of chemical synthesis in rendering these naturally occurring, but scarce, substances readily available.

enabled their further biological investigation as nodulation signals.

3.12. Sialic Le^x and dimeric sialyl Le^x

The sialic Le^x ligand and related oligosaccharides moved to center stage in the early 1990s due to their binding affinities to ELAM-1 and other selectins implicated in inflammation processes. Their natural scarcity dictated the necessity for a chemical synthesis, a call that was answered by a number of groups, including ours.[48,49] The total synthesis[49] of dimeric sialyl Le^x, the most complex member of this family of

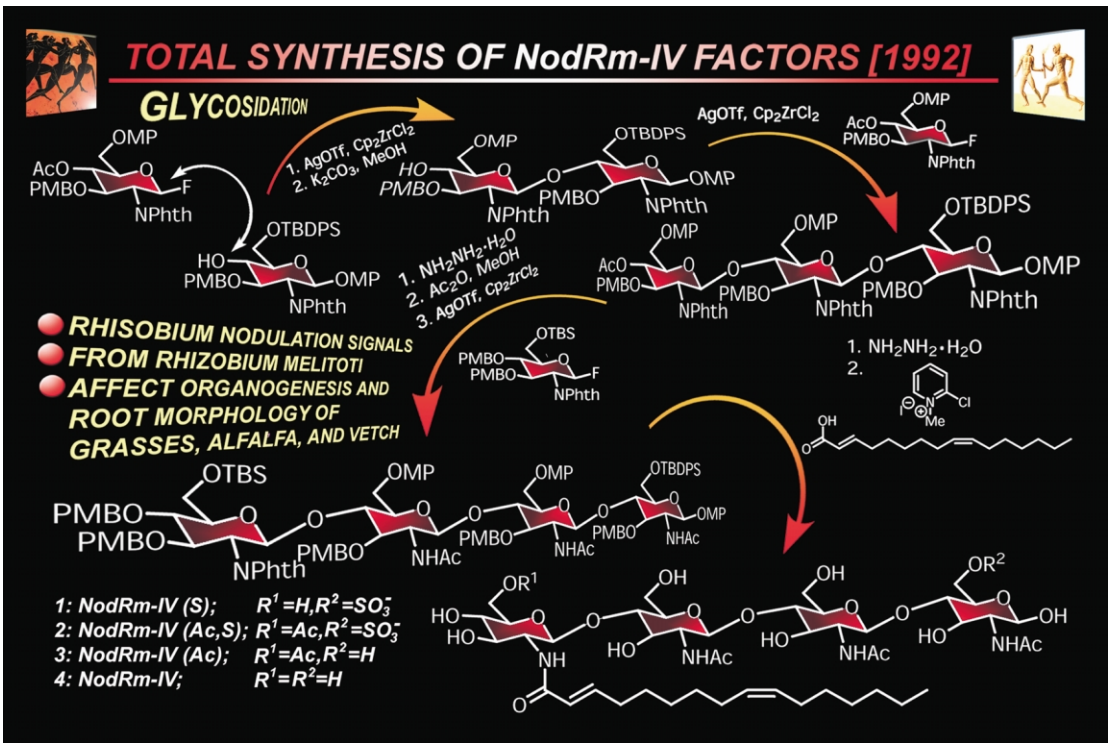

Figure 15. The total synthesis of the NodRm-IV factors demonstrated the power and enabling nature of chemical synthesis for chemical biology studies in plant morphology.

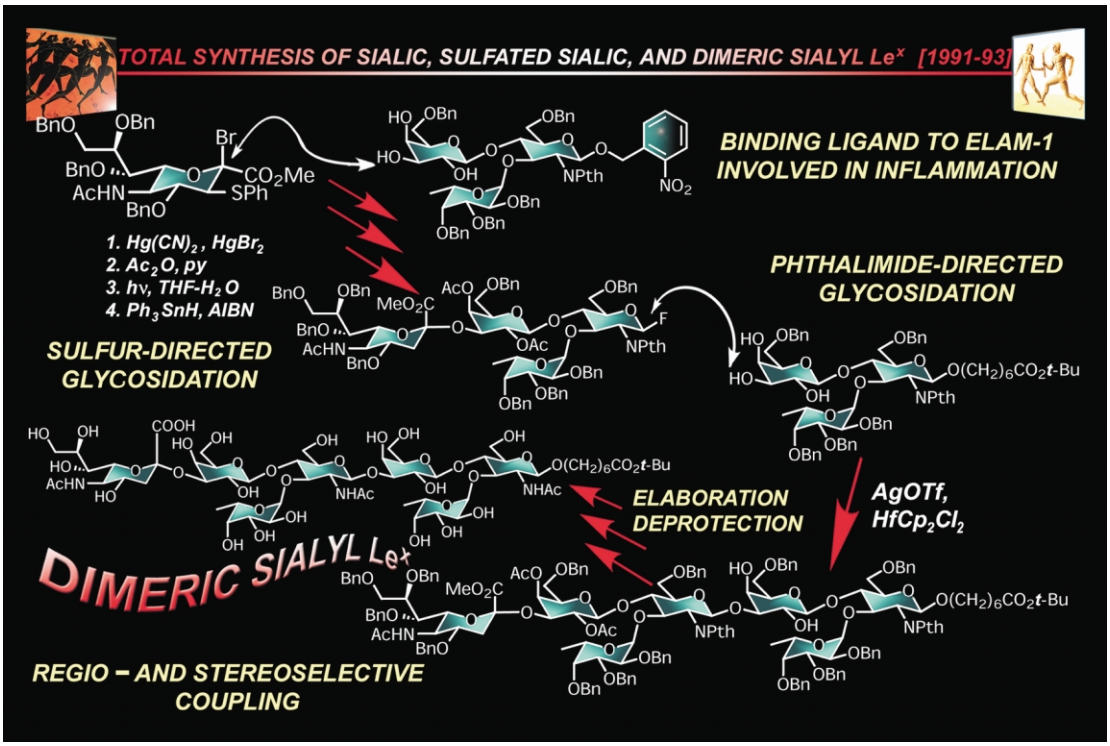

Figure 16. The total synthesis of sialic Le^x, sulfated sialic Le^x, dimeric sialyl Le^x, and related compounds enabled chemical biology studies in the area of inflammation.

oligosaccharides, accomplished in 1992, is exemplary of the group's work in this field (see Fig. 16). A site-selective, sulfur-directed glycosidation with a sialic acid derivative followed by a second regioselective coupling allowed incorporation of the seven carbohydrate units exhibited within this challenging structure. Once again, these syntheses enabled useful biological investigations and extended the reach of chemical synthesis into new realms of molecular complexity.

3.13. Calicheamicin and the enediynes

Rarely before had a project in total synthesis yielded as much information and knowledge in the fields of new synthetic technologies and strategies, physical organic chemistry, and chemical biology as the enediyne program did in our laboratories (see Fig. 17). Not only did the group carry out the first systematic study of the chemical properties of cyclic enediynes[50] and report the first synthetic enediyne to cleave DNA,[51] but also it was the first to achieve the total synthesis[52] of calicheamicin γ_1^I itself, the flagship of this fascinating family of antitumor antibiotics. Completed in 1992, the total synthesis of calicheamicin represented a new standard for us in terms of novelty and complexity of molecular architecture and importance of biological activity, and set an exciting pace for what was to follow in our laboratories for the rest of the decade.

The total synthesis itself constituted a rewarding combination of convergency and daring maneuvers to construct the enediyne core and the oligosaccharide domain of the structure. Notable features of this synthesis include an intramolecular [3+2] nitrile oxide cycloaddition, an intramolecular acetylide–aldehyde coupling reaction to form the 10-membered enediyne ring, a unique [3,3] sigmatropic rearrangement to construct the sulfur-containing sugar moiety, a stereoselective Mitsunobu-type reaction to install the unusual O–NH bond, and a key glycosidation procedure that forged the complete framework of the target molecule.

Most significantly, the total synthesis of calicheamicin was accompanied by myriad new designs and discoveries in the fields of chemical synthesis and chemical biology. Thus, numerous enediynes were designed, and routes for their construction were developed. These designed enediynes ranged in molecular structure from very simple cyclic hydrocarbons to highly sophisticated systems equipped with triggering devices activated by light, pH changes, or other chemical means to induce Bergman cycloaromatization, leading to damaging benzenoid diradicals. The extensive chemical and biological studies of these synthetic enediynes defined parameters for the stability, activation and biological action of such systems, which set the stage for the evolution of the enediyne field, an area that continues to attract many investigators from chemistry, biology and medicine to this day. In addition to the enediynes, this project led to the discovery of the DNA-cleaving and cytotoxic properties of propargylic and allenic sulfones and to a new body of knowledge regarding DNA–oligosaccharide interactions. Indeed, it was the ability to synthesize several calicheamicin-type oligosaccharides—some with varied substituents on the aromatic ring (replacing iodide), and some tethered together as dimers and trimers—which allowed their interactions with duplex DNA to be studied by NMR spectroscopy as well as by DNA cleavage and electrophoresis techniques. Among the many impressive accomplishments of the group in this area, three stand out. The first is the construction of a head-to-tail calicheamicin

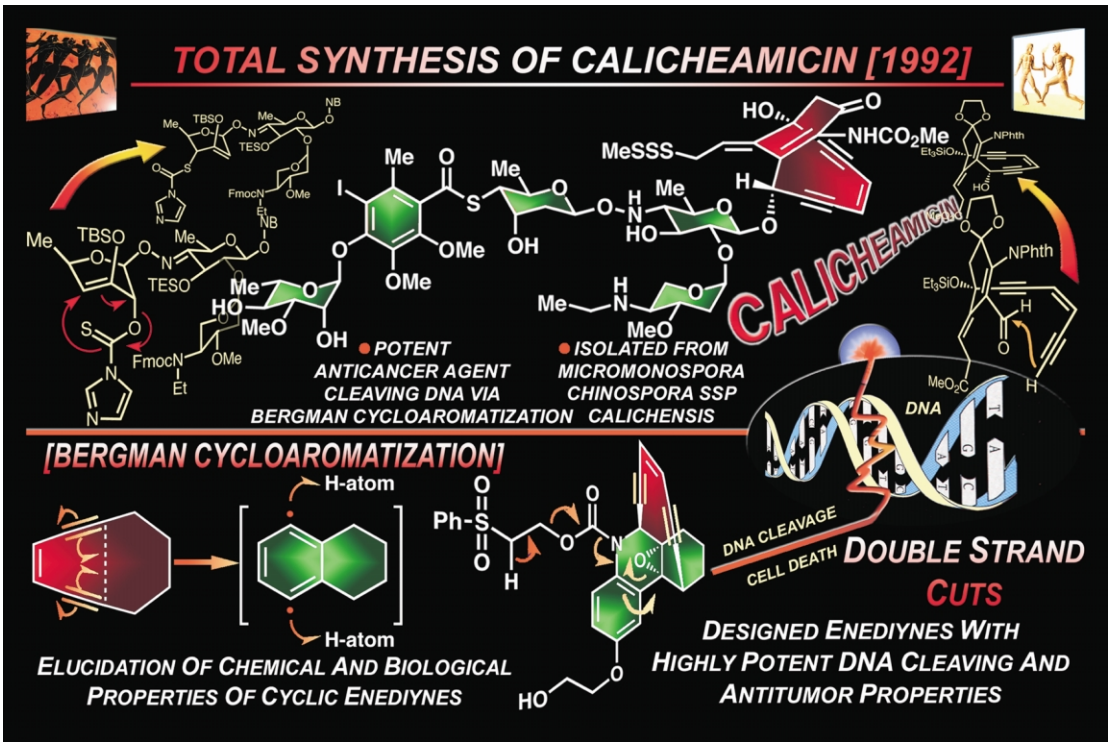

Figure 17. The enediyne program resulted in the first total synthesis of calicheamicin and the development of both new synthetic technologies and strategies for the construction of cyclic enediyne systems. The developed synthetic technology allowed the synthesis of designed enediynes with triggering devices and the elucidation of the physical, chemical and biological properties of these novel molecular entities. In addition to furnishing the first synthetic enediynes with DNA-cleaving properties, these studies also led to a number of extremely potent cytotoxic agents and shed considerable light on carbohydrate–DNA interactions.

oligosaccharide dimer that was found to exhibit subnanomolar affinity and high sequence specificity for certain duplex DNA strands,[53] and which also exhibited the ability to inhibit transcription factor binding to DNA. The second discovery came with the chemical synthesis of calicheamicin θ_1 (SAc instead of SSSMe) which proved to be more potent than the naturally occurring compound both in terms of cleaving DNA and killing tumor cells by initiating apoptosis.[54] The third notable development in the field was the design, synthesis and study of stable, but easily activated, enediynes[55] inspired by the structure of dynemicin, another naturally occurring enediyne antitumor antibiotic. Some of these in vivo activated compounds exhibited potencies against tumor cells at picomolar concentrations. Incidentally, calicheamicin γ_1^I conjugated to a recombinant human antibody has recently been approved by the FDA for the treatment of certain types of leukemia (Mylotarg™, American Home Products).[56]

3.14. Rapamycin

The field of immunosuppression and organ transplantation had taken a new life with the advent of cyclosporin, FK506 and rapamycin in the 1980s and 1990s. The latter compound, currently in clinical use (Rapamune™, American Home Products), became a 'hot' target for total synthesis in the early 1990s due to its recognized relationship to FK506, its fascinating mode of action involving binding to two proteins (FKBP-12 and FRAP), and because of its potential as an immunosuppressant and anticancer agent. The group was the first to accomplish the total synthesis of rapamycin in 1993 (see Fig. 18).[57] More importantly, this synthesis was accompanied by a number of interesting developments in the fields of synthetic technologies and chemical biology. Most remarkable, among the former was a rather spectacular and unprecedented maneuver involving a double Stille-stitching cyclization process to form the macrocycle of the molecule, a strategy that was subsequently followed by other investigators in their macrocycle-forming endeavors. Another important observation made during this project was the discovery that a designed rapamycin analog[58] possessing only the FKBP-12 binding domain of the molecule lacked biological activity despite its ability to bind to FKBP-12, a property that was in line with rapamycin's mechanism of action.

3.15. Taxol™

A daunting synthetic challenge of the 1980s and 1990s was that posed by the molecule of Taxol™. In 1994, the group was the first to report the total synthesis of Taxol™ in the journal Nature.[59] In this highly cited synthesis, the two flanking rings of the main framework of Taxol™, rings A and C, were constructed via Diels–Alder reactions, each of which is admirable for different reasons (see Fig. 19). Thus, while the first Diels–Alder reaction leading to ring A is remarkable in its exclusive regiochemistry despite the appearance of prohibiting steric congestion, the second cycloaddition leading to ring C is notable for the way it was coaxed to deliver the desired regiochemical result via boron tethering to appropriately orient the two reaction partners. Subsequent steps in this convergent synthesis included two important coupling processes, namely the rarely used in total synthesis Shapiro reaction, and the McMurry reaction

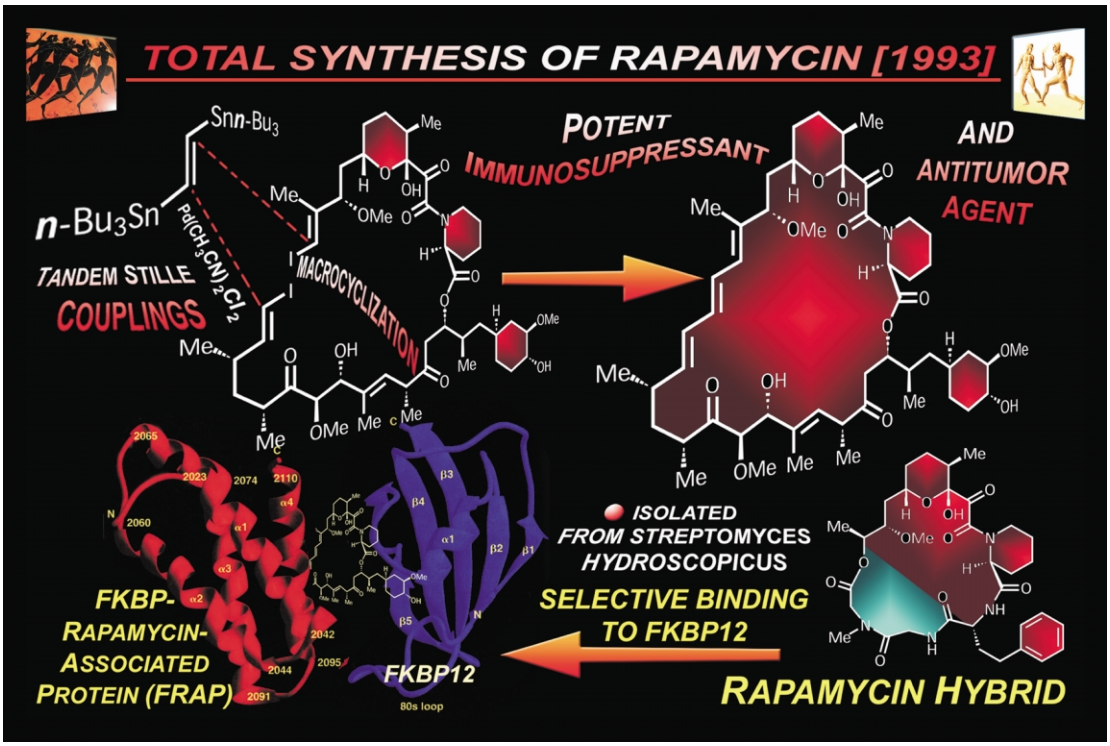

Figure 18. A most striking feature of the total synthesis of rapamycin was the palladium-catalyzed, double Stille 'stitching cyclization' procedure utilizing an acyclic divinyl iodide precursor and a *trans*-vinyldistannane to form the target molecule in a single step and without protecting groups. The developed technology enabled the construction of a designed rapamycin analog containing only the FKBP-12-binding domain which, despite its affinity for FKBP-12, exhibited no rapamycin-type biological activity since it lacked the ability to sequester FRAP.

which was employed as the key process to form Taxol™'s most challenging domain, ring B. Most significant were the chemical biology studies that accompanied this project. These included the design, synthesis and biological investigation of several water-soluble taxoids and prodrugs, a self-assembling Taxol™ derivative that formed helices in aqueous media,[60] and a number of fluorescent probes.[61] The availability of such molecules via chemical synthesis

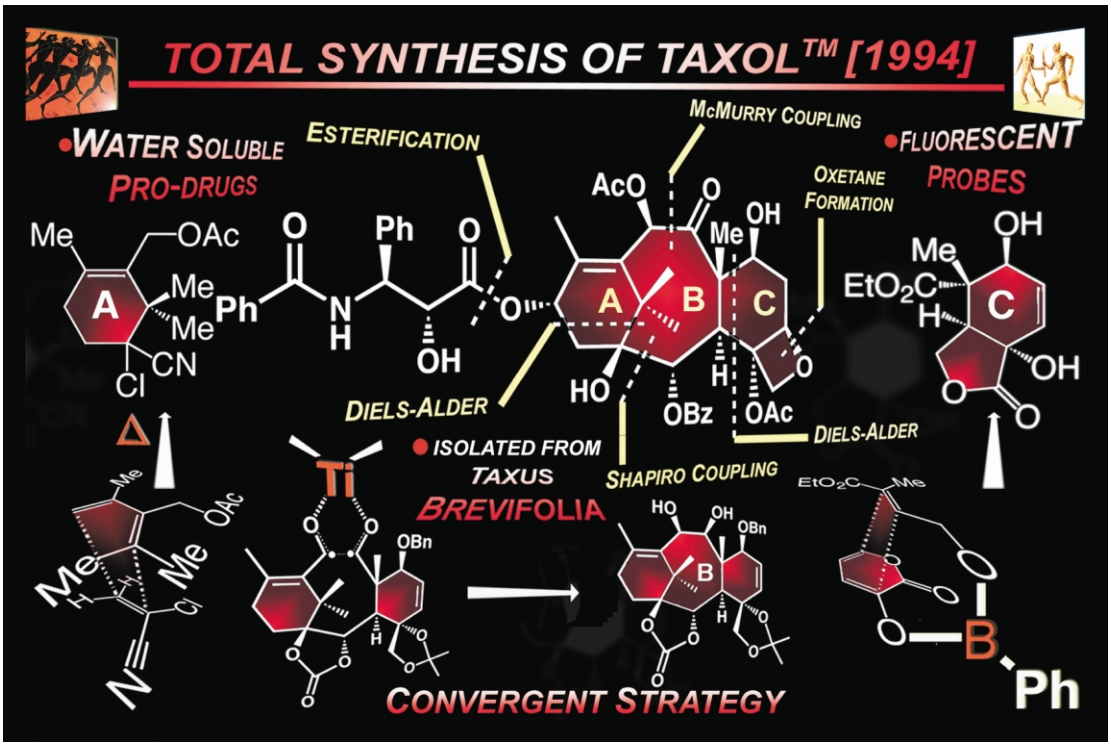

Figure 19. The highly convergent total synthesis of Taxol™ involved two remarkable and regio-controlled Diels–Alder reactions to construct rings A and C, a Shapiro coupling to join the two fragments, and an intramolecular McMurry-type reaction to form the strained, 8-membered ring of the molecule. Final elaboration included installation of the oxetane ring, attachment of the side-chain, and deprotection.

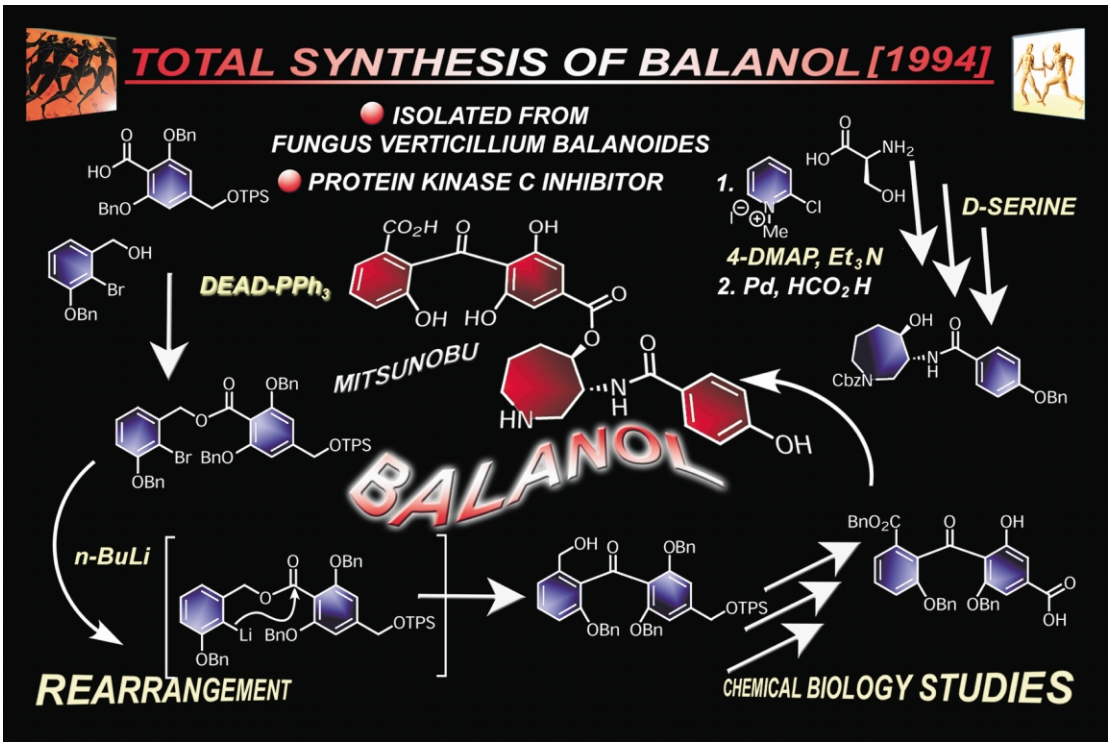

Figure 20. The total synthesis of balanol featured a convergent strategy and employed a facile rearrangement of an aryllithium ester to form the bis-aryl system of the molecule. Synthesized analogs facilitated studies in the protein kinase C and related fields.

facilitated conformational studies by NMR spectroscopy and tubulin binding investigations, and led to the identification of taxoid nanostructures with remarkable physical and biological properties. It is worth noting that Taxol™ has since become a best-selling anticancer agent used to treat cancer patients around the world. Taxotere™, a Taxol™ analog, is also in clinical use as an anticancer agent.[62]

3.16. Balanol

The enticement provided by balanol's novel molecular architecture was enhanced considerably by its high potency as an inhibitor of protein kinase C, a widely studied phosphorylation enzyme implicated in a variety of physiological states, including cardiovascular disorders and inflammation. The total synthesis of balanol was accomplished by a convergent strategy that involved construction and coupling of its two structural domains (see Fig. 20).[63] Most significantly, the developed synthetic technology was utilized to synthesize a series of designed balanol analogs that facilitated biological investigations within this family of enzymes.[64]

3.17. Zaragozic acid

The lure of the zaragozic acids, a class of substances isolated from extracts of certain fungal species, had its origins in both architectural and biological features. Amongst the members of this family of secondary metabolites, zaragozic acid A, due to its complexity and potent biological activity, commanded our primary attention. Its bicyclic ketal core was unprecedented while its inhibitory activity against squalene synthase was impressive as it led to dramatic cholesterol-lowering effects. Zaragozic acid A's unique structure was reached, in its enantiomerically pure form, by asymmetrically modifying a prochiral precursor to an advanced key intermediate which upon acid-induced rearrangement led, through a designed cascade sequence, to the molecule's highly oxygenated core (see Fig. 21).[65,66]

3.18. Brevetoxins A and B

The brevetoxin projects (A and B) began in the 1980s and were completed in the 1990s after long, but highly rewarding campaigns (see Fig. 22). The synthetic odyssey[67] directed towards the total synthesis of brevetoxin B is distinguished not only by the delivery of the most complex natural product targeted by the group, but also by its duration—12 years in all. Significantly, this project also distinguished itself as one of the most enriching in terms of new synthetic technologies and overall impact on the art and science of total synthesis. Thus, not only did the successful completion of the synthesis require redesigning the overall strategy several times, but also it necessitated the invention and development of numerous new synthetic methods for the construction of the cyclic ethers and carbon–carbon bonds associated with this structure. Among the most prominent of these methods are the following: (a) the regio- and stereocontrolled hydroxyepoxide openings for the synthesis of tetrahydropyrans effected by placing an olefinic moiety adjacent to the remote C–O bond of the epoxide group;[68] (b) the silver-promoted hydroxydithioketal cyclization for the construction of oxocene systems;[69] (c) the bridging of macrodithionolactones to form bicyclic systems induced by electron donating reagents such as sodium naphthalenide;[70] (d) the hydroxyketone cyclization induced by silicon reagents to form oxepane systems;[71] (e) the

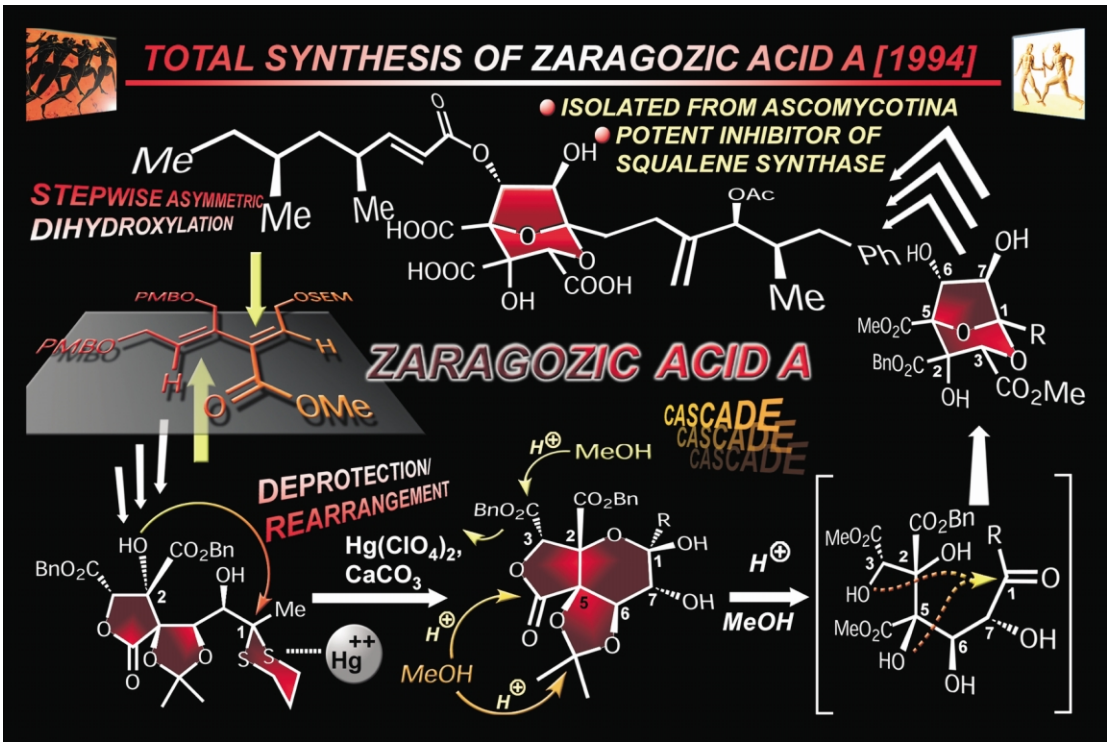

Figure 21. The total synthesis of zaragozic acid A served as a powerful demonstration of asymmetric synthesis techniques and featured a remarkable rearrangement brought about by an acid-induced cascade sequence.

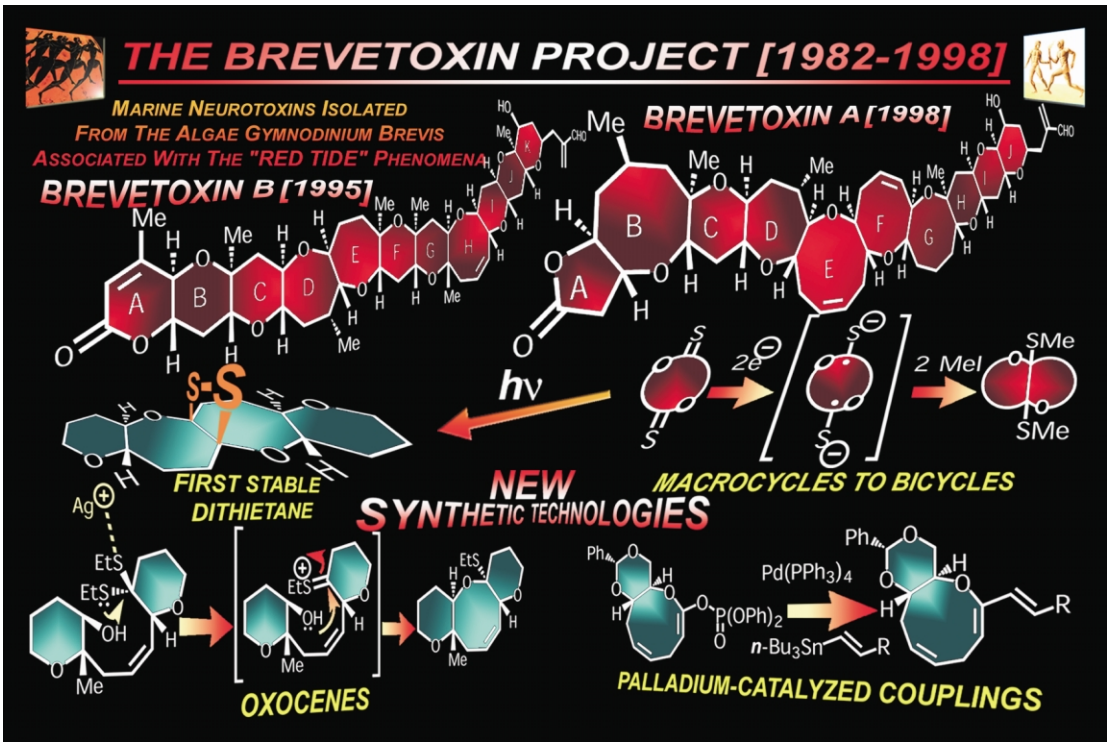

Figure 22. The total synthesis of brevetoxins A and B was a relentless campaign of discovery and invention of new synthetic technologies to solve the formidable challenges posed by the multiple rings contained within the structures of these target molecules. Among the most useful and intriguing methods for constructing medium-sized rings developed during this program were the hydroxydithioketal cyclization to form oxocenes, the palladium-catalyzed couplings of vinylketeneacetal phosphates with vinyl stannanes, and the bridging of macrodithionolactones to form bicycles of the type found in these polyether marine natural products. In addition to accomplishing the total syntheses of these highly complex and architecturally beautiful molecules and the plethora of new synthetic technologies arising during this synthetic odyssey, a number of theoretically interesting molecules, including a stable and crystalline 1,2-dithietane, were synthesized and studied for the first time.

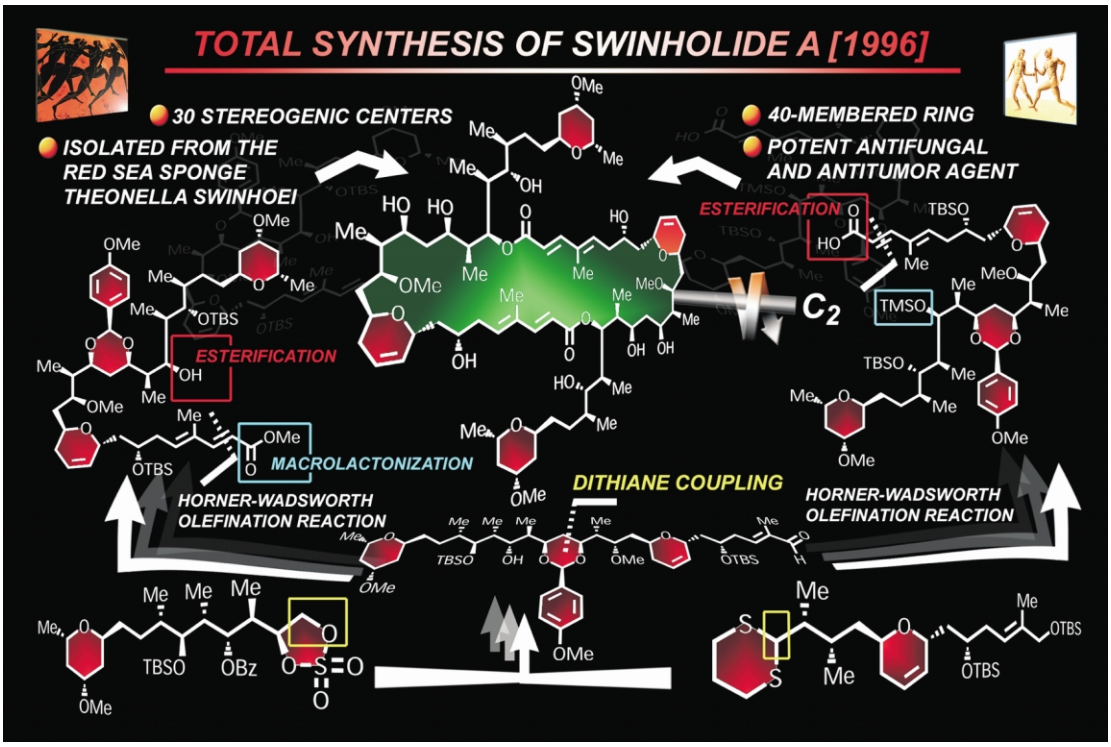

Figure 23. The stereocontrolled total synthesis of swinholide A utilized a number of novel synthetic reactions for carbon–carbon and carbon–oxygen bond formation, including a Yamaguchi-type macrocyclization.

photolytic bridging of dithionoesters to form oxepanes upon extrusion of sulfur;[72] (f) the addition of nucleophiles to thionolactones as a means to convert lactones to cyclic ethers;[73] and (g) the deoxygenation method for converting lactones to cyclic ethers involving radical-based reduction of the corresponding thionolactones.[74]

These methods were supplemented with several other synthetic technologies emerging from the brevetoxin A project[75] (Fig. 22) and work related to other complex polyether natural products. Thus, a powerful method was developed for functionalizing lactones[76] and lactams[77] to various intermediates by palladium-catalyzed carbon–carbon bond formation between the corresponding ketene-acetal phosphates and a number of organometallic reagents such as vinylstannanes and zinc reagents. As such, a variety of strained, medium-sized cyclic ethers, including the 9-membered ring of brevetoxin A, were synthesized and an asymmetric synthesis of cyclic amino acids was developed. In addition to this methodology, a number of olefin metathesis-based technologies were designed specifically for the construction of cyclic polyether systems directly from olefinic esters, and were successfully applied to the construction of several of maitotoxin's (a highly complex relative of the brevetoxins) structural domains.[78]

Further benefits from the brevetoxin projects included the synthesis of the first stable 1,2-dithietane ring system[79] (see Fig. 22), whose X-ray crystallographic analysis revealed its theoretically interesting structural parameters. Finally, a truncated brevetoxin B, containing only seven of the natural product's rings, was constructed for chemical biology studies shedding light on the mechanism of action of this neurotoxin.[80]

It is pleasing to note that the chemistry of marine polyether-based neurotoxins and related bioactive compounds continues to this day to be vigorous and vibrant, especially from the synthetic point of view.

3.19. Swinholide A

Isolated from the sponge *Theonella swinhoei*, this marine natural product was traced to symbiotic heterotrophic unicellular bacteria. Swinholide A possesses potent antifungal and antitumor activities and its challenging structure is characterized by C_2 symmetry, a 40-membered macrolide ring, two conjugated diene systems, two trisubstituted pyran systems, two disubstituted dihydropyran rings, and 30 stereogenic centers. The scarcity and important biological properties of this molecule prompted us to embark on its total synthesis, a task that was accomplished in our laboratories in 1996 (Fig. 23).[81] The synthesis featured a number of new synthetic reactions, including a novel cyclization to form the dihydropyran systems and a coupling reaction based on a nucleophilic opening of a cyclic sulfate as well as a Yamaguchi macrolactonization to forge the molecule's large ring. Extensions of the developed technology included construction of swinholide A's relatives, preswinholide A and its methyl ester, and hemiswinholide A.

3.20. Epothilones and radiofrequency encoded combinatorial chemistry

Hailed to be superior to Taxol™ as potential anticancer agents because of their ability to kill taxol-resistant tumor cells, the epothilones rose to high priority status as synthetic targets in the mid 1990s. The attraction was not only due to

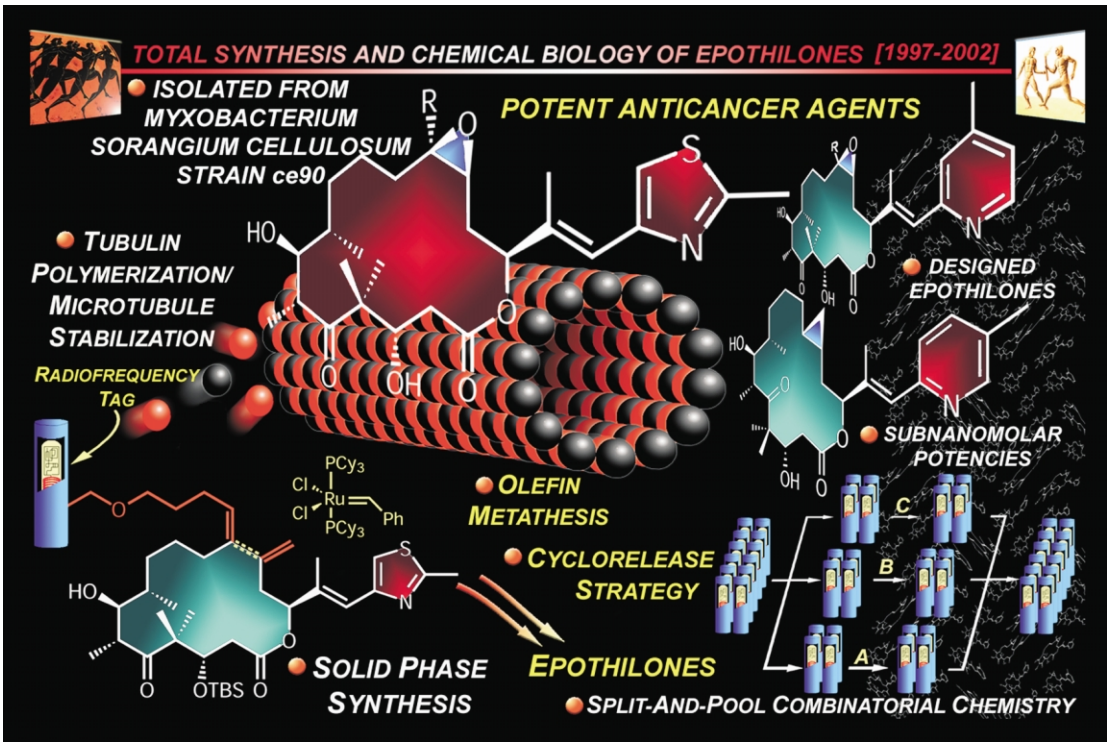

Figure 24. In addition to the total syntheses of several naturally occurring epothilones, the epothilone project resulted in a multitude of new and enabling synthetic technologies and chemical biology discoveries. Among them are the solid phase cyclorelease-based strategy for combinatorial synthesis involving olefin metathesis and using IRORI Microkans™, as well as the design, synthesis and biological investigation of highly active antitumor agents such as a series of cyclopropane and pyridine analogs.

their novel molecular architecture, but also because of the opportunity they presented for the development of new and enabling synthetic technologies for chemical biology studies and their promise as novel chemotherapeutic agents. The group's endeavors in this area contributed significantly to both the fields of total synthesis and chemical biology (see Fig. 24).[82] Importantly, the group also exploited the opportunity to demonstrate, for the first time, the power of solid phase chemistry and radiofrequency encoded combinatorial synthesis[83] in complex molecule construction. Thus, having accomplished the total synthesis of epothilones A and B in solution by two distinctly different strategies using either olefin metathesis[84] or macrolactonization[85] as key ring-forming reactions, the group moved to design and execute a solid phase total synthesis of epothilone A by an olefin metathesis-based strategy involving a cyclorelease step.[86] The developed synthetic technology was then applied in conjunction with the previously developed IRORI technology to the combinatorial synthesis of compound libraries for biological screening.[87] The latter included tubulin polymerization and in vitro cytotoxicity assays and, in certain cases, in vivo studies. The combinatorial chemistry developed in this project represents the first example where analog libraries of complex natural products were synthesized by solid phase total synthesis and a classic example of the use of the IRORI radiofrequency-based technology. The combined solution and solid phase synthetic studies, together with the indispensable biological investigations, led to the discovery of a number of highly potent epothilones, including a series of pyridine-, cyclopropyl- and thiomethyl-containing analogs.[88] Most significantly, these studies led to a comprehensive structure–activity relationship picture in the epothilone field and set the stage for follow-up studies in academic and industrial laboratories. A number of epothilones including one from this group, are currently in clinical trials as anticancer agents.

3.21. Eleutherobins and sarcodictyins

Related to Taxol™ and epothilones A and B by a common mechanism of action, the eleutherobins and sarcodictyins are potent antitumor agents exerting their cytotoxicity via tubulin polymerization and microtubule stabilization. Their scarce natural abundance as marine natural products elicited the group's interest in their total synthesis, a task that was accomplished in 1997[89] (see Fig. 25). Starting with the abundantly available (+)-carvone, these targets were synthesized by a route which involved an intramolecular acetylide–aldehyde coupling reaction to form the molecule's 10-membered ring. This was followed by further elaboration, a second ring closure of the tertiary alcohol, appropriately positioned by the adjacent *cis* double bond, onto a carbonyl group to secure the 5-membered ring system, and final manipulation of the side-chains and protecting groups. A solid phase synthesis of these molecules was also developed and applied to the construction of combinatorial analog libraries for biological investigations.[90] In addition to allowing assignment of the absolute stereochemistry and providing the naturally occurring substances in quantity for in vivo studies, the endeavor resulted in new synthetic technologies, both for solution and solid phase chemistry, and in the discovery of a number of potent cytotoxic agents, some more active than the natural products.

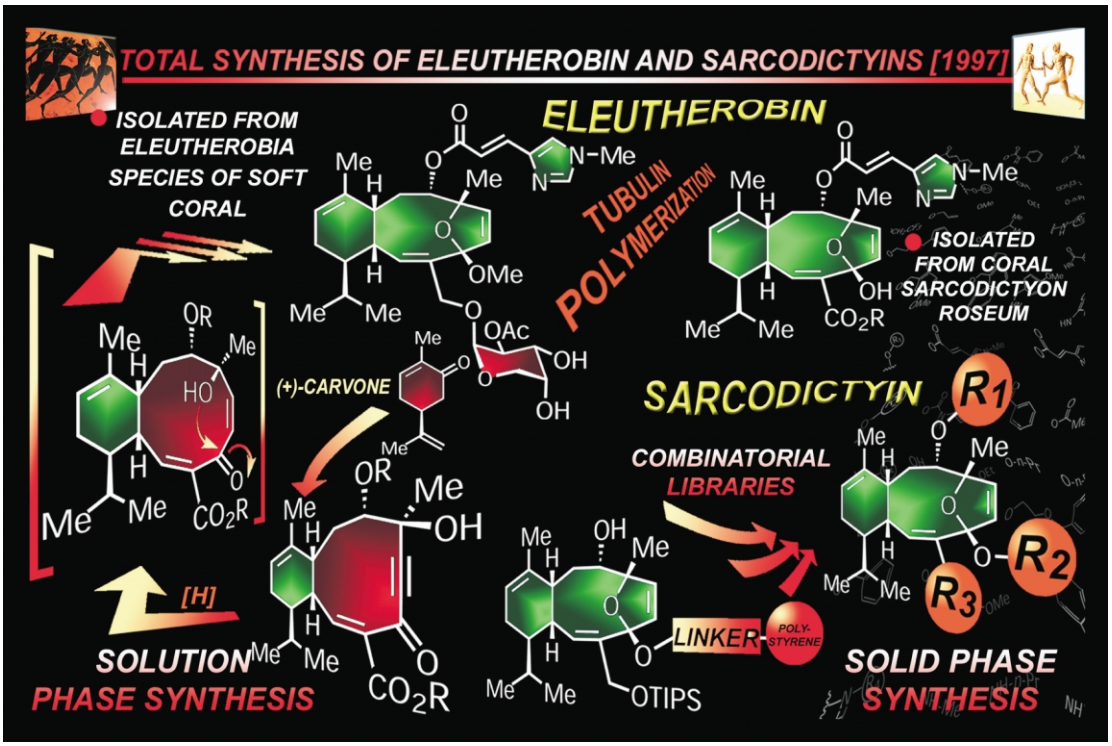

Figure 25. Starting with (+)-carvone, the eleutherobin and sarcodictyin total syntheses involved two novel ring closures and aspects of solid phase chemistry, thereby enabling the assignment of absolute stereochemistry and the construction of analog libraries. Chemical biology studies facilitated by these chemical syntheses allowed extensive investigations of these scarce natural products and identification of a number of potent tubulin binding analogs with promising antitumor properties.

3.22. Solution and solid phase synthesis of complex oligosaccharides

The field of solid phase oligosaccharide synthesis is currently assuming center stage due to the potential importance of these molecules in glycobiology and medicine. The group has made a number of early and influential contributions to this field. These investigations

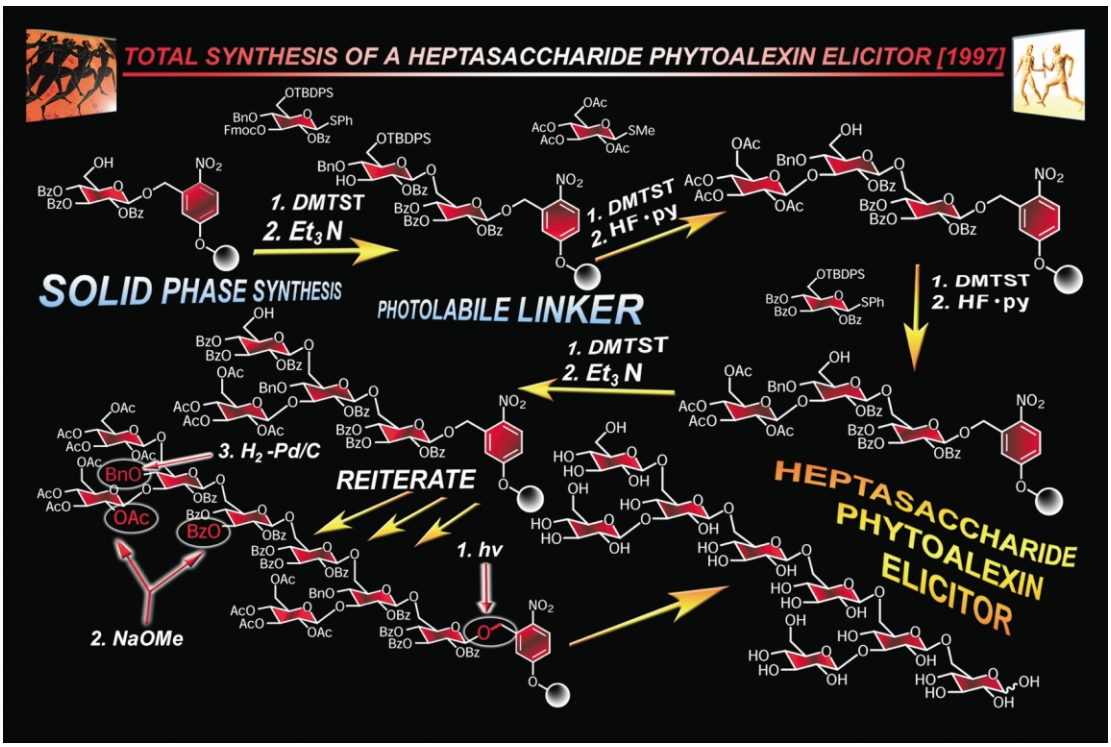

Figure 26. The development of a photolabile linker for solid phase chemistry allowed the rapid construction of a heptasaccharide phytoalexin elicitor, demonstrating the power of thioglycoside activation in complex oligosaccharide synthesis.

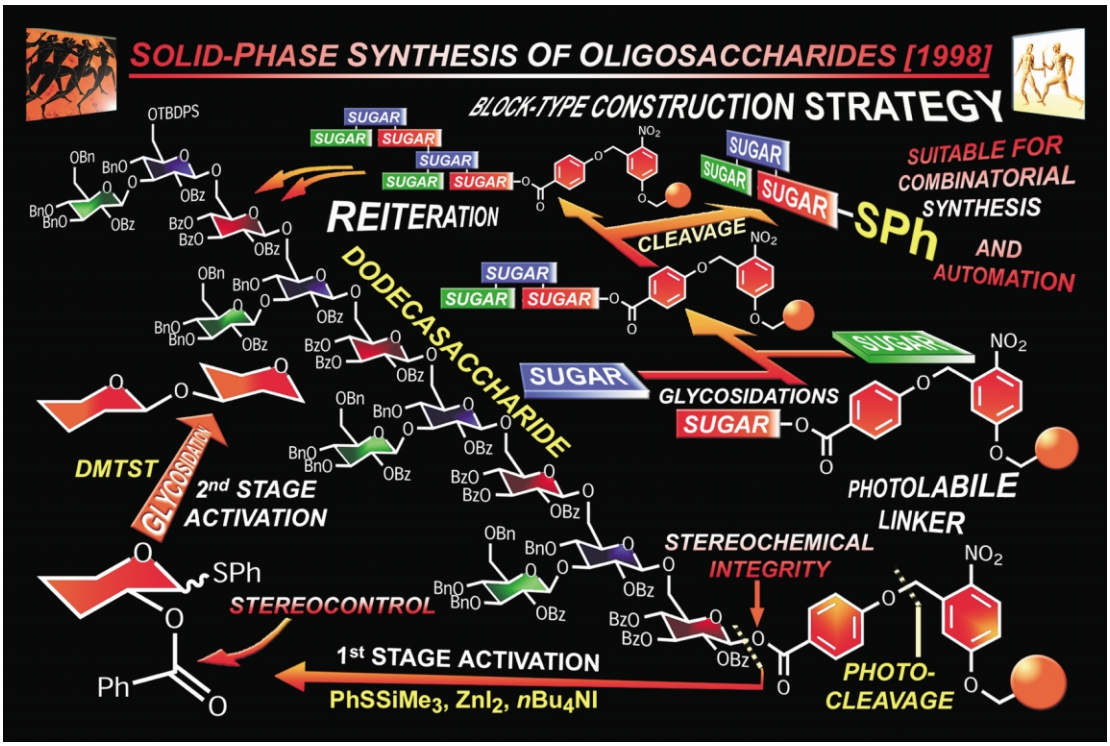

Figure 27. The solid phase synthesis of complex oligosaccharides involving a doubly cleavable linker proceeded through a block-type, reiterative strategy which capitalized on the ease with which thioglycosides can be prepared and their ability to serve as glycosyl donors upon electrophilic activation. Amenable to automation, this highly efficient strategy has been employed to synthesize an array of complex oligosaccharides, including a naturally occurring heptasaccharide and a designed dodecasaccharide.

began with the discovery that electrophilic reagents such as NBS could be used to activate the stable and readily available thioglycosides for glycosidation reactions with stoichiometric amounts of glycosyl acceptors[34] as already mentioned above. Reported in 1982, this development was the basis for the two-stage activation glycosidation procedure[41] involving thioglycosides and glycosyl fluorides, and served as a precursor to several other newer technologies employing related electrophilic reagents such as DMTST and NIS. In a climactic campaign to synthesize complex oligosaccharides with important biological activities, the group applied such technologies to the construction of the tumor-associated Le^x-type antigens (1990, see Fig. 14),[46] the binding ligands to ELAM-1, sialyl Le^x and dimeric sialyl Le^x (1992, see Fig. 16),[48,49] the Rhizobium nodulation signals NodRm-IV factors (1992, see Fig. 15) and the sulfated E-selectin ligands Le^x and Le^a (1993).[91] In 1997 and 1998, the group utilized similar thioglycoside-based chemistry in combination with a block-type strategy to develop a practical solid phase synthesis of several additional complex oligosaccharides. Thus, a naturally occurring heptasaccharide (HPE) (1997, see Fig. 26)[92] and a designed dodecasaccharide (1998, see Fig. 27)[93] were constructed on polystyrene-derived resins. Highlights of the latter technology included the design and incorporation of a photo-labile linker, which was also susceptible to cleavage by base or sulfur-nucleophiles, leading to various anomeric derivatives. Of particular interest in this approach are the so derived thioglycosides, which are ready for incorporation into the growing oligosaccharide chain, allowing for an iterative and convergent strategy for solid phase chemistry amenable to combinatorial synthesis and automation (see Fig. 27). We were pleased to see how these original contributions have subsequently impacted favorably the oligosaccharide field.

3.23. Alkannin and shikonin

The enantiomerically related natural products alkannin and shikonin isolated from European and Oriental plants, respectively, were intriguing to us not only due to their fascinating structures, but also because of their unique biological activities.[94] Their total synthesis[95] featured a divergent approach leading, from a common prochiral precursor, to the two required enantiomeric alcohols via asymmetric reductions and a final anodic oxidation-deprotection protocol which delivered each natural product selectively and efficiently through an electronically-driven tautomerization event (see Fig. 28).

3.24. Vancomycin

Due to its highly complex molecular architecture, vancomycin, the antibiotic of last resort, resisted total synthesis until the late 1990s.[96] The group was among the first to report the total synthesis of the aglycon portion of vancomycin in 1998,[97] and the first to accomplish the total synthesis of the entire structure (1999, see Fig. 29).[98] Most importantly, the accomplished synthesis was accompanied by the development of new synthetic technologies such as the method utilized to construct the two macrocyclic bis-arylethers of the target natural product.[99] The developed triazene-driven, arylether-forming reaction has been proven to be highly general and is applicable to both cyclic and acyclic systems as well as extendable to the formation of thioethers. Another notable development in

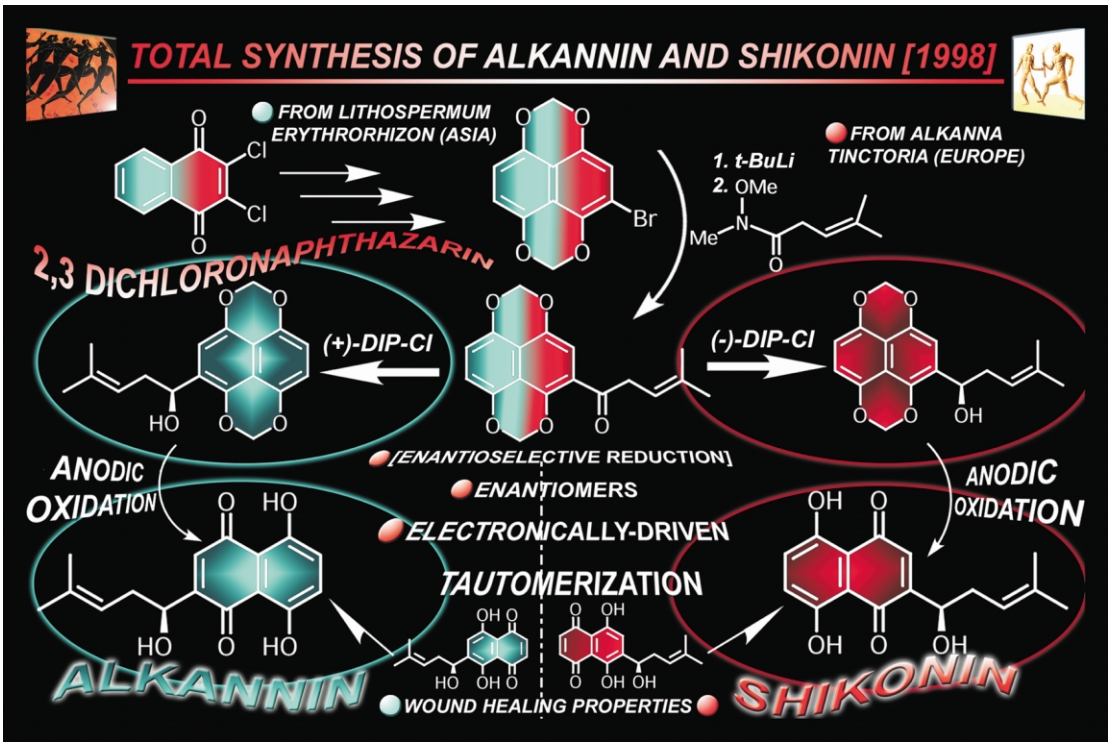

Figure 28. The expedient total syntheses of the enantiomeric wound-healing natural products alkannin and shikonin relied on a subtle, electronically driven tautomerization of the quinone–dihydroquinone system.

this program was the asymmetric synthesis of enantiomerically enriched atropisomers of biphenyl-type molecules.[98] The vancomycin project also led to new enabling technologies for solid phase synthesis and combinatorial chemistry. Thus, a new selenium-based linker was developed through which carboxylic acids, amines and alcohols could be attached to a solid support for elaboration and final cleavage, leading to easily removable Alloc-protected

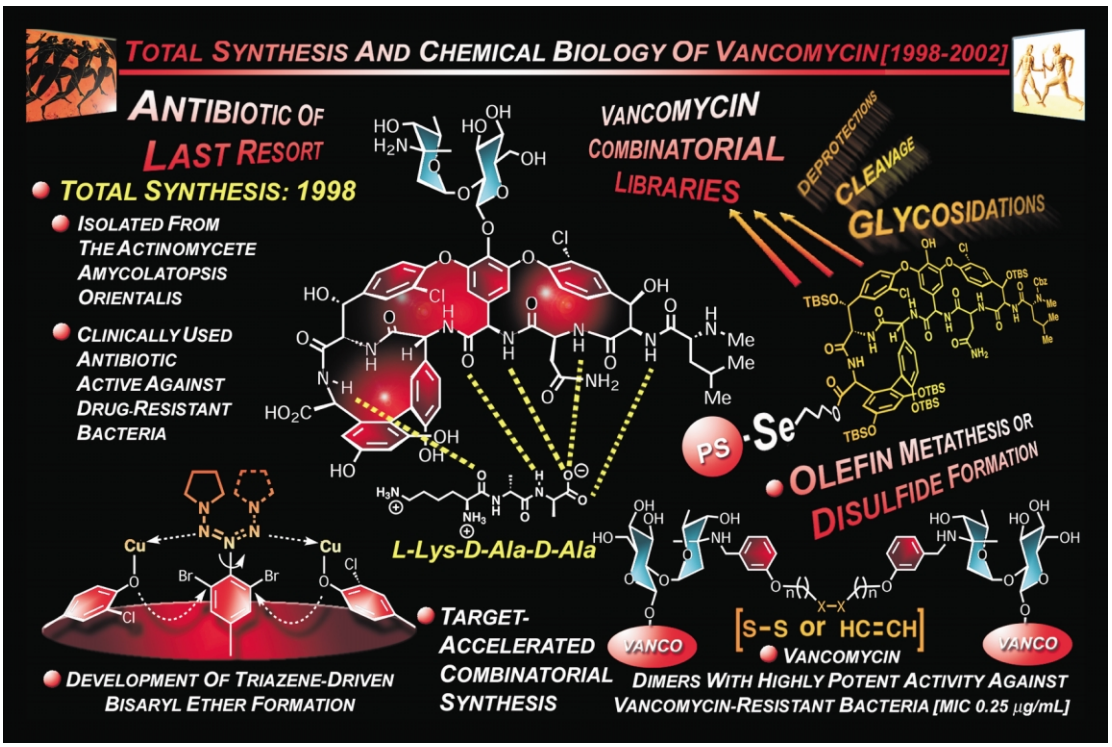

Figure 29. In addition to culminating in the first total synthesis of the natural product, the vancomycin program included aspects of new synthetic technologies such as the triazene-driven cyclization to form macrocyclic bis-aryl ethers, solid phase and combinatorial chemistry such as the design of novel linkers and the target-accelerated combinatorial synthesis strategy that facilitated the discovery of a series of highly potent antibacterial agents active against vancomycin-resistant bacteria.

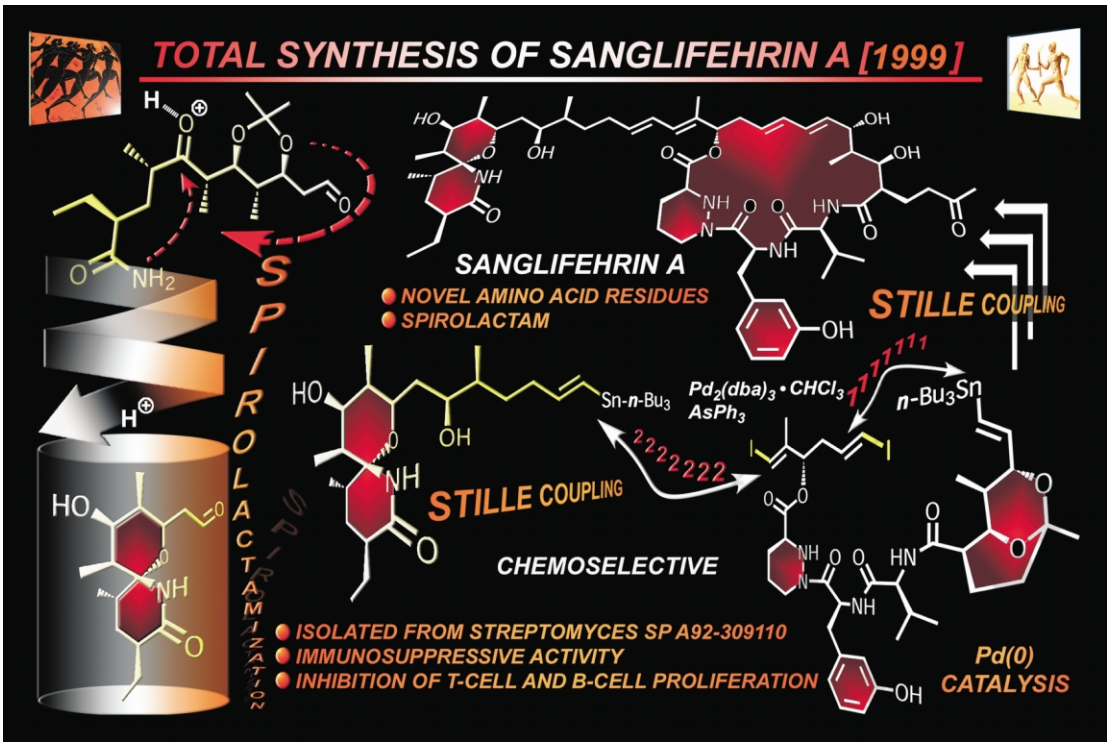

Figure 30. The total synthesis of sanglifehrin featured a novel spirolactamization reaction and a double Stille coupling reaction to assemble the macrocycle and the diene moiety bridging the two domains of the molecule.

systems. This technology was instrumental in loading vancomycin onto a polystyrene-type resin and degrading it to its aglycon for re-construction and generation of analogs to produce combinatorial libraries for biological screening.[100] A second combinatorial strategy was developed for the synthesis of vancomycin dimers. Termed target-accelerated combinatorial synthesis because it was carried out in the presence of vancomycin's biological target, L-Lys-D-Ala-D-Ala, this strategy was rationally designed[101] using previously delineated dynamic library construction principles and the knowledge that vancomycin dimers were known to exhibit higher affinities for the antibiotic's biological target. By utilizing either olefin metathesis or disulfide bond formation, this combinatorial approach enabled the rapid identification of a number of extremely potent antibiotics effective against methicillin- and vancomycin-resistant bacteria (most potent compounds reported to date, MIC~0.25 μg/mL).[102] Overall, this highly rewarding program in total synthesis led to contributions in several areas, including methodology, solid phase synthesis, combinatorial chemistry, and chemical biology. In light of the fact that the last line of defense provided by vancomycin has recently been broken by some vancomycin-resistant bacteria, the discovery of new vancomycin-based antibiotics active against these strains is highly significant.[103]

3.25. Sanglifehrin

Sanglifehrin, a compound isolated from *Streptomyces* sp. A92-309110 by Novartis scientists, provided a particularly appealing synthetic target due to its unusual structure and potent immunosuppressive properties. A research program in our group culminated, in 1999, in the first total synthesis of this novel naturally occurring substance (see Fig. 30).[104] The cornerstone reaction of the developed stereocontrolled strategy was the palladium-catalyzed Stille coupling which was utilized twice and in a chemoselective manner in this synthesis, first to construct the macrocycle and second to effect the union of the two major domains of the molecule. Other highlights in this endeavor included the use of the Paterson aldol protocol to construct the spirolactam fragment and carbodiimide-based methodology to assemble the rather unusual peptide backbone.

3.26. Bisorbicillinoids

The bisorbicillinoids are a fascinating group of naturally occurring substances, most of which are related by isomerism, though not necessarily by molecular architecture (see Fig. 31). Most prominent among them are trichodimerol, bisorbibutenolide, and bisorbicillinol. These substances are characterized by novel and seemingly unrelated molecular structures and possess biological activities ranging from inhibition of tumor necrosis factor α (TNF-α) production to antioxidant properties. A close inspection of the structures of these molecules led to a hypothesis for their biosynthesis pointing to sorbicillin, a natural product itself, as a possible biogenetic precursor. Thus, initial enzymatic oxidation of sorbicillin at a specific site was envisioned to trigger two distinctly different cascade sequences leading to the bisorbicillinoids. The group was the first to propose a plausible biosynthetic pathway for the generation of trichodimerol[105] and among the first to execute,[106] in the laboratory, biomimetic total syntheses of all three natural products mentioned above. The biomimetic total synthesis of trichodimerol (also reported by E. J. Corey)[107] commenced from sorbicillin by lead tetraacetate oxidation followed by an admirable

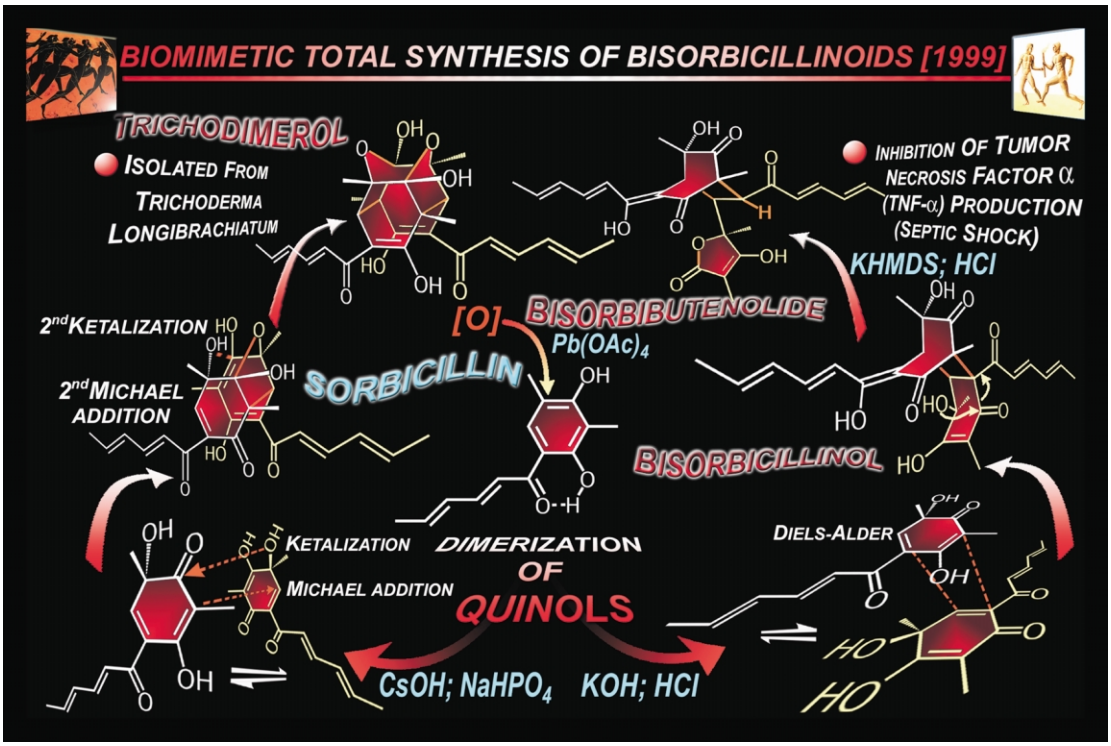

Figure 31. The biomimetic total syntheses of the bisorbicillinoids trichodimerol, bisorbibutenolide and bisorbicillinol involved two distinctly different cascades, one proceeding through two Michael reactions and two ketalizations, and the other through a Diels–Alder reaction, both initiated by dimerization of an oxidized form of sorbicillin.

double Michael reaction/ketalization sequence between an equilibrated mixture of two quinols which proceeded under certain, carefully controlled conditions. Equally impressive was the coaxing of this quinol mixture towards the bisorbicillinol structure under a different set of conditions. Subsequent base-induced rearrangement of bisorbicillinol led directly to bisorbutenolide. These investigations provided a highly pleasing set of biomimetic strategies toward natural products and, together with the endiandric acid cascades discussed above, stand as signature contributions in biomimetic total synthesis, a theme which has constantly been a part of the group's endeavors.

3.27. Everninomicin

As one of the most promising antibiotics, everninomicin 13,384-1 presented an attractive synthetic target in the mid-1990s. The synthetic appeal of this molecule was enhanced by its novel and challenging molecular architecture that included no less than 13 rings and 35 stereocenters. Particularly challenging within everninomicin's structure were the two orthoester linkages, not only because of their lability, but also due to their stereochemical arrangement (see Fig. 32). In addition, the molecule boasted several other synthetically challenging features, including multiple 2-deoxy glycoside bonds and the 1,1′-disaccharide bridges linking rings F and G, and their corresponding stereochemical requirements. In 1999, the group reported the total synthesis of everninomicin,[108] representing, perhaps, the most complex oligosaccharide-based molecule to be synthesized in the laboratory to date. Most significantly, this accomplishment was marked with numerous new synthetic technologies, among which the most prominent being the selenium-based stereoselective method for the construction of orthoester moieties and 2-deoxy glycoside bonds.[109] Involving a 1,2-phenylseleno-migration, this sequence proceeds in a highly efficient and stereocontrolled manner both in solution and on solid phase, and complements the group's previously developed phenylsulfeno-migrations which have found several applications in carbohydrate chemistry.[110] Other synthetic technologies developed during the everninomicin program included a stereoselective tin acetal-based method[109,111] for the synthesis of 1,1′-disaccharides and 1′,1′,1″-trisaccharides and various new approaches to carbohydrate-based molecular diversity.[109]

3.28. CP-molecules

The unprecedented structures of the CP-molecules, reported in the mid-1990s, and the formidable challenge they posed to synthetic chemistry elicited considerable research activities directed towards their total synthesis around the world. In addition, due to their inhibitory activities against squalene synthase (lowering cholesterol levels) and farnesyl transferase (pointing to potential leads to cancer chemotherapy), these molecules offered opportunities for biological explorations and potential medical applications. In 1999, the group accomplished the first total synthesis[112] of the CP-molecules and shortly thereafter determined their hitherto unknown absolute stereochemistry[113] (see Fig. 33). The aesthetic appeal of the delicately crafted strategy for the total synthesis of these molecules was only surpassed by the bounty of new synthetic technologies garnered during this campaign.[114] Thus, a series of cascade sequences and a number of new reactions were discovered or invented.

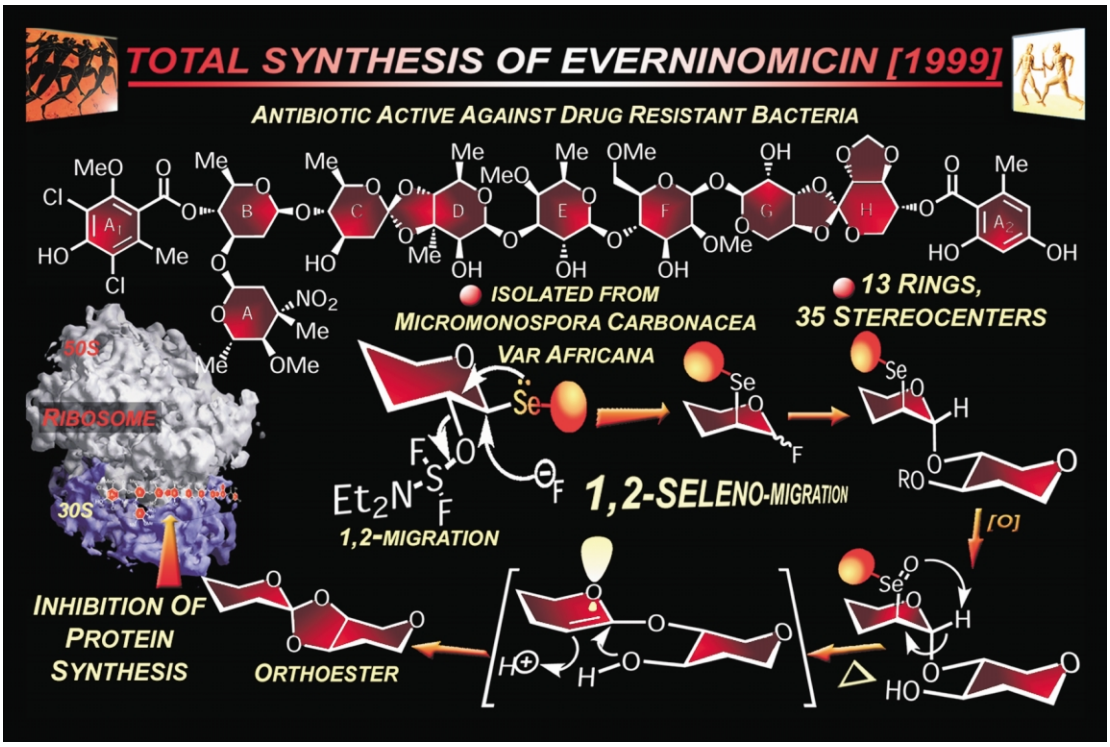

Figure 32. The total synthesis of everninomicin followed a delicate and convergent strategy and required the development of several new synthetic technologies and strategies. Among them are the tin acetal-based method for the stereoselective construction of 1,1′-disaccharide linkages and the 1,2-phenylseleno-migration reaction which allowed the stereocontrolled synthesis of the highly sensitive orthoesters.

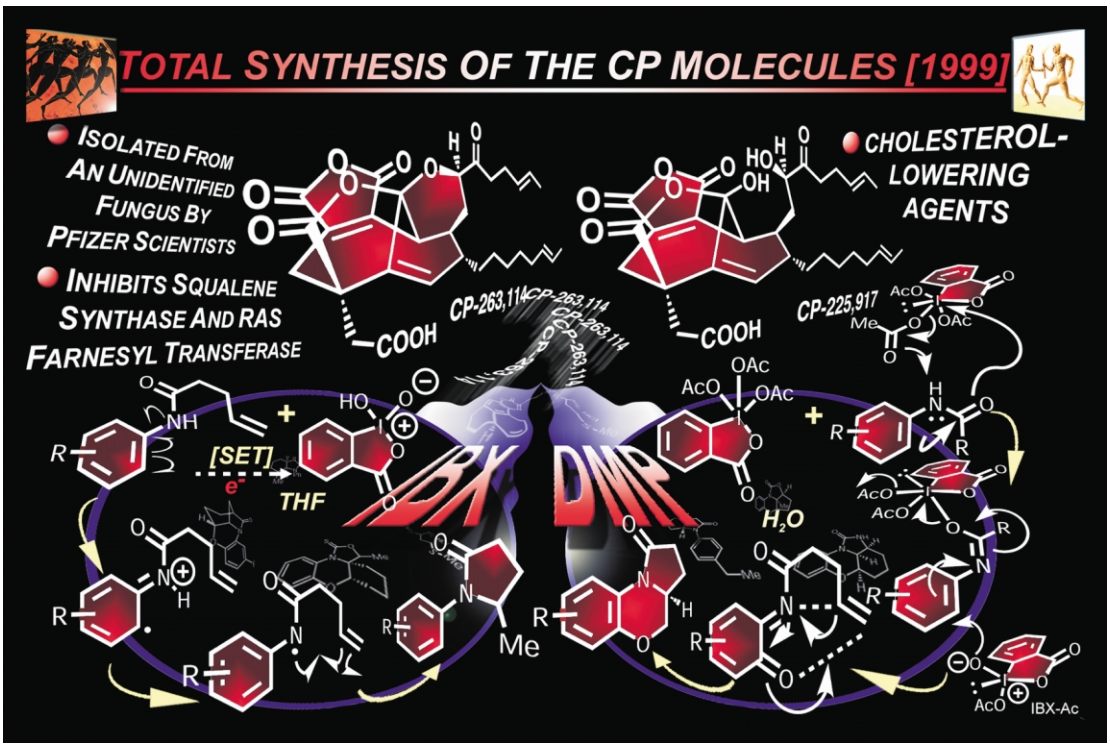

Figure 33. With their novel molecular architectures and challenging structural features, the CP-molecules offered a unique opportunity for total synthesis and the discovery of new synthetic technologies. Among the most mechanistically intriguing and synthetically useful reactions discovered during this program were those facilitated by DMP and IBX. The numerous cascade reactions discovered and developed during this campaign added significantly to the overall contributions of the project.

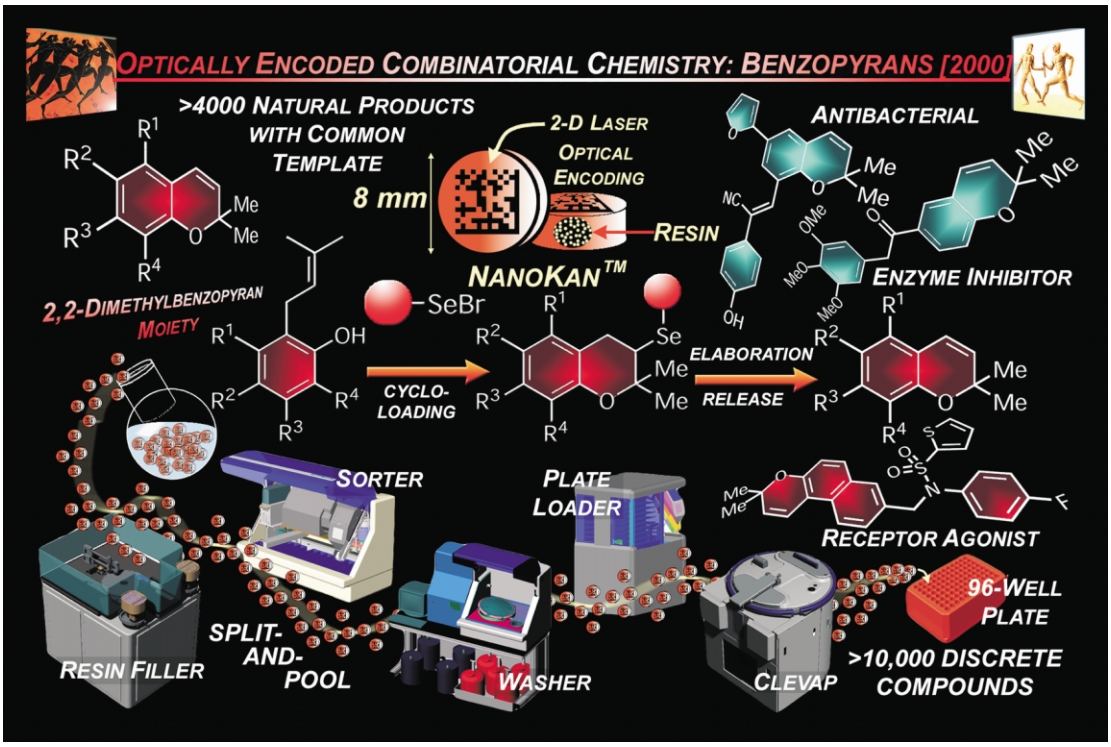

Figure 34. The abundance of benzopyran-type natural products and their wide-ranging biological activities prompted a combinatorial approach toward their total synthesis and analog libraries thereof. Among the new synthetic technologies developed in this program were a number of selenium-based resins which facilitated cyclo-loading of certain substrates and provided a robust linker for further elaboration, with final cleavage under mild conditions producing discrete compounds of high purity. Libraries of over 10000 compounds were synthesized expeditiously using the split-and-pool strategy, facilitated by optically encoded IRORI NanoKans™ and robotic systems. Subsequent biological screening of these libraries led to the discovery of several important lead compounds and potential drug candidates.

Among the most impressive cascade sequences are those leading to the maleic anhydride moiety of these molecules, the one-pot DMP-induced conversion of 1,4-diol systems to the lactonol ring, and the several DMP-initiated processes opening entries into a wide range of molecular diversity from aryl amides. A separate, but equally useful, set of reactions based on the special reactivity of IBX were discovered and developed during this program. These reactions included radical-based ring closures to form novel heterocycles, the introduction of unsaturation adjacent to carbonyl functions, benzylic oxidations, and a number of mild deprotection procedures. In addition to these methods, the CP project led to the development of a mild and effective procedure for the generation of sterically hindered diazoketones based on the chemistry of acyl mesylates, a new protocol for the one-carbon homologation of aldehydes, and several DMP-based technologies for the synthesis and exploitation of reactive species such as *p*-quinones and *o*-azaquinones. In parallel, solution and solid phase methods for the utilization of α-sulfonated ketones to construct arrays of heterocyclic systems and other synthetic building blocks were developed.[115] Although the initial discovery of the DMP-induced cascade leading to polycyclic systems was serendipitous—underscoring this mode of discovery during total synthesis endeavors—it was clearly the mechanistic investigations and insights that led to the rational design and invention of the majority of these new chemical processes. Overall, the CP program was proven to be one of the most fertile in terms of generating new synthetic strategies and enabling technologies serving, in that respect, as a paradigm of how endeavors in total synthesis should be carried out these days.[116]

3.29. Benzopyran natural products and libraries thereof and optically encoded combinatorial chemistry

With over 4000 naturally occurring benzopyran-type substances possessing a diverse range of biological activities, a large benzopyran compound library containing not only such natural products, but also other biologically and medicinally relevant compounds appeared attractive (see Fig. 34). In order to prepare such libraries expeditiously and in sufficient quantities for multiple biological assays, suitable synthetic methodology and automation was needed. While the automation issue had already been solved with the IRORI technology utilizing optical encoding operating in conjunction with a sophisticated robotic system, the problem of the required chemistry was addressed by way of developing a new resin and a robust, yet synthetically fertile, linker. Specifically, the group synthesized, starting with polystyrene, an arylselenenyl bromide resin which rapidly absorbs suitably substituted *ortho*-prenyl phenols forming benzopyran scaffolds via a cyclo-loading process.[117,118] A highly branching scheme was then implemented to elaborate these scaffolds into a variety of products which were oxidatively released by simple exposure to hydrogen peroxide, furnishing the desired benzopyran compounds with concomitant introduction of a double bond in the pyran ring. The latter functionality was then utilized to expand the library via epoxidation, followed by nucleophilic lysis leading to a second generation library

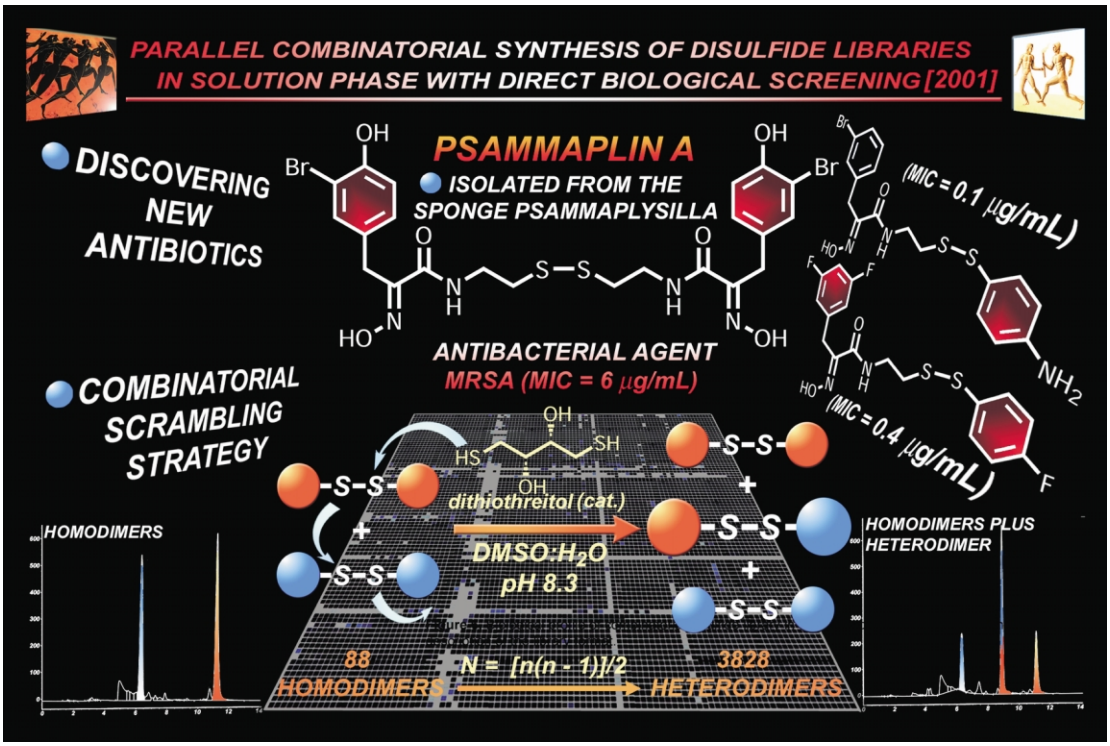

Figure 35. Psammaplin A, a marine natural product with antibacterial properties and a symmetrically arranged disulfide structure provided the opportunity for the development of a rapid combinatorial strategy to synthesize heterodimeric disulfide-type compounds. Termed 'combinatorial scrambling,' this strategy allowed the construction of thousands of compounds, screening of which led to the discovery of a number of highly potent antibacterial agents.

enjoying a wide range of diversity. The elegant split-and-pool strategy for combinatorial synthesis was employed in conjunction with IRORI's optically encoded[119] NanoKans™ and a multi-station robotic system, allowing completion of the library in short order. Biological screening of this library of over 10000 compounds is still ongoing in various laboratories, but investigations[120] so far have already revealed a number of leads and optimized compounds with antibacterial, antitumor, and antiviral properties as well as enzyme inhibitors and receptor agonists and antagonists. Inspired by natural product chemistry, and being the first application of optically encoded combinatorial synthesis of drug-like small organic molecules, this new technology for combinatorial chemistry may well represent the state of the art in the field at the dawn of the 21st century.

3.30. Psammaplin and combinatorial scrambling strategy for discovering new antibiotics

Inspired by the structure of the marine natural product psammaplin A, the group developed a general combinatorial strategy for the generation of disulfide heterodimers (see Fig. 35).[121] A symmetrically arranged disulfide (homodimer), psammaplin A is an antibiotic effective against methicillin-resistant bacteria with MIC value of 6 μg/mL. The developed method for combinatorial synthesis of heterodimer libraries, termed combinatorial scrambling strategy, involves initial parallel synthesis of a number of homodimeric disulfides which are then combined, two at a time, in wells in DMSO–H_2O pH 8.3 buffer solutions. Each combination is then treated with catalytic amounts of dithiothreitol, leading rapidly and cleanly to an equilibrium mixture of the two original homodimers plus the corresponding heterodimer. The total number of heterodimers (N) is given by the formula $N=[n(n-1)]/2$ where n=number of homodimers employed. Thus, from 88 homodimers, a library of 3828 heterodimeric disulfides was generated and tested, resulting in the discovery of a number of lead compounds which were rapidly optimized, furnishing new antibacterial agents with activities down to 0.1 μg/mL, which rival vancomycin at least in vitro.

This combinatorial scrambling technology can be generalized, in principle, to include all kinds of building blocks and an array of biological assays. Furthermore, once a lead compound is found, the disulfide linkage may be replaced (to improve metabolic stability if necessary) by a more robust functionality. The concept, which may also be extended to other equilibrating processes such as the olefin metathesis reaction, is expected to facilitate chemical genomics studies and drug discovery efforts.

3.31. Colombiasin A

Isolated and characterized on the basis of potential biological activity against the H37Rv strain of tuberculosis bacteria, the diterpene colombiasin A offers a unique and challenging molecular architecture for the synthetic chemist (see Fig. 36). Key structural elements of this tetracyclic natural product include six stereogenic carbons, two of which are adjacent quaternary centers, as well as a periphery decorated with four methyl groups, two carbonyl functions, two olefins, and one hydroxyl group. Additionally, despite elegant spectroscopic studies which led to the full elucidation of the colombiane skeleton, the absolute

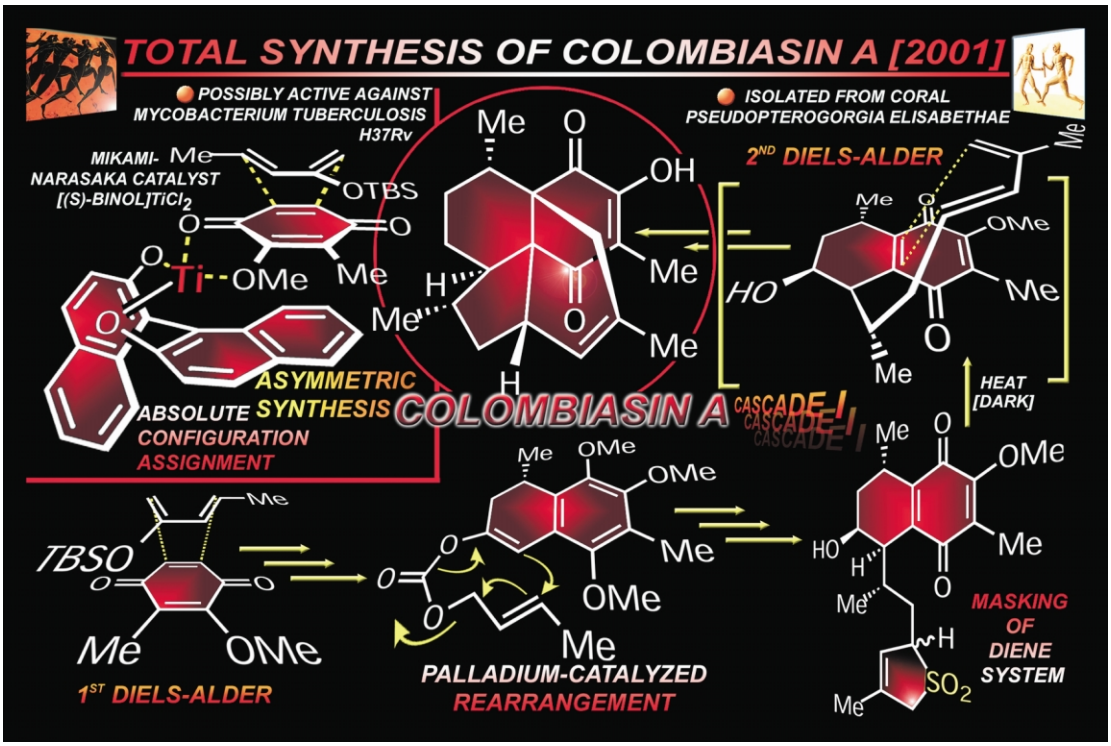

Figure 36. The marine terpenoid colombiasin A was synthesized based on a putative biosynthetic pathway, employing an iterative Diels–Alder strategy to append three rings onto a quinone core. Thus, the complete tetracyclic framework of the target molecule, including its two adjacent and seemingly formidable quaternary centers, was efficiently constructed. An asymmetric version of the total synthesis led to the assignment of the absolute configuration of the natural product.

stereochemistry of the natural product was unknown. In 2001, the group was the first to achieve a total synthesis of this challenging natural product.[122] The biosynthetically-inspired synthesis included an iterative set of Diels–Alder reactions to append the three rings onto the central quinone core of the molecule, and served to assign its absolute configuration.[123] Starting from an initial asymmetric Diels–Alder reaction induced by the Mikami–Narasaka catalyst, a subsequent novel palladium-catalyzed allylation involving highly substituted olefins set the stage for the second intramolecular Diels–Alder cycloaddition. In this instance, cheletropic elimination of SO_2 from a masked diene system completed the colombiasin framework as a single *endo* adduct. Although this approach is certainly impressive based on the efficient construction of the complete tetracyclic skeleton of the molecule, including the two adjacent quaternary carbons, perhaps even more striking is the stereochemical control achieved throughout the synthesis based on the installation of a lone chiral center during the initial asymmetric Diels–Alder reaction. As such, these investigations enabled a full structural assignment of colombiasin A, as well as produced numerous analogs of the natural product which may facilitate future chemical biology studies with this new class of compounds.

3.32. Hybocarpone and the hamigerans

The unique and cytotoxic natural product, hybocarpone, was isolated from mycobiant cultures derived from the lichen *Lecanora hybocarpa* (see Fig. 37). Possessing an aesthetically pleasing C_2-symmetric structure, this naturally occurring substance appears to render itself to a biosynthetic hypothesis whereby a precursor naphthazarin moiety dimerizes to afford a polycarbonyl system whose hydration leads to the final structure. This hypothesis was confirmed by the group in 2001 with an expedient total synthesis of hybocarpone[124] which utilized this analysis. After an exhaustive search of suitable single electron transfer (SET) reagents, it was discovered which use of cerium ammonium nitrate (CAN), followed by a basic work-up, led to the desired parent structure in protected form that was readily converted to the natural product upon treatment with BBr_3. This SET-initiated dimerization cascade sequence is particularly remarkable, as it enabled concomitant formation of a highly hindered carbon–carbon bond and selective installation of four stereogenic centers.

Among the steps employed to prepare the dimerization precursor, one crucial transformation of note was the generation of an intermediate hydroxy-*o*-quinodimethane from an aromatic aldehyde using ultraviolent irradiation, which successfully engaged methyl-2-ethylacrylate in a Diels–Alder cycloaddition to form the requisite bicyclic system. Although scant reports of this process with simple precursors had been reported in the chemical literature, the process was virtually unexplored in total synthesis endeavors. As such, this particular example in the context of hybocarpone represents one of the most complex achieved to date. Based on the numerous benzannulated natural products which potentially could be accessed by this type of reaction, the group pursued and achieved the optimization of this technology for both intra- and intermolecular cycloadditions using numerous and chemically diverse aryl aldehydes and dienes.

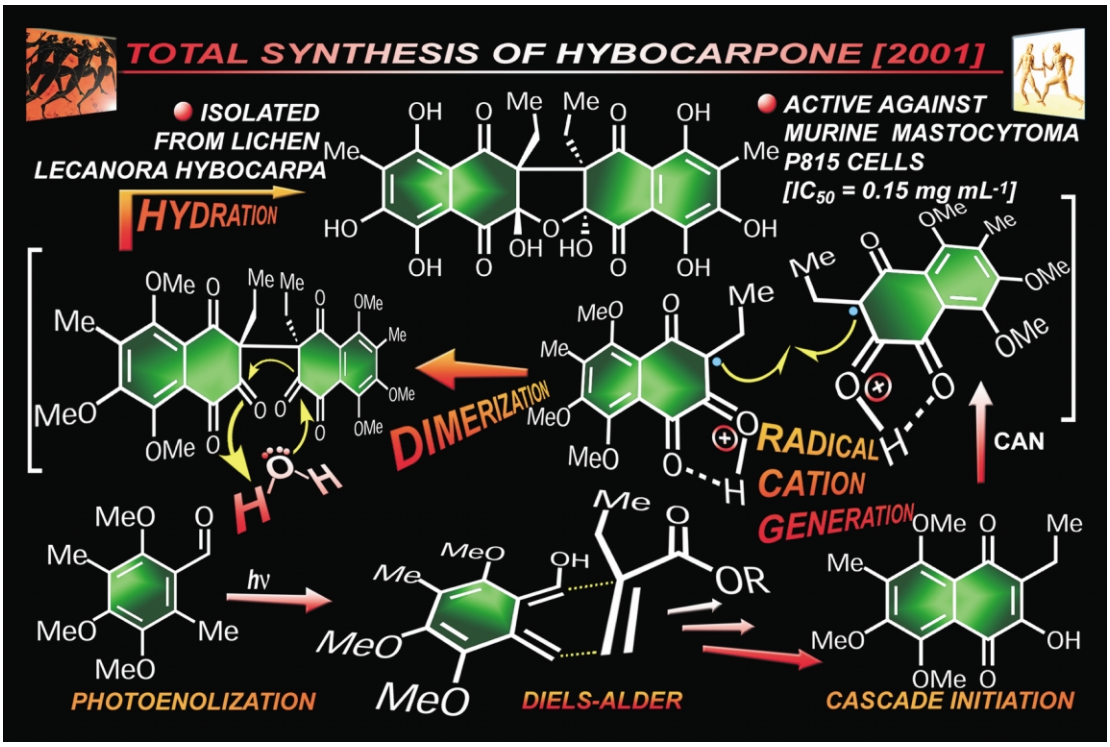

Figure 37. The total synthesis of hybocarpone featured the photo-induced generation and trapping of an hydroxy-*o*-quinodimethane in a Diels–Alder reaction and a radical-initiated cascade dimerization–hydration reaction.

Having clearly defined the methodological parameters necessary for successful reaction,[125] this transformation was then swiftly applied in the total syntheses of several members of the hamigeran class of marine natural products,[126] where hydroxy-*o*-quinodimethane generation followed by an intramolecular Diels–Alder reaction with an appropriately functionalized tethered diene smoothly resulted in the formation of the requisite [4.3.0] carbocyclic system of the target molecules (see Fig. 38). A series of well designed steps, including further cascade reactions, allowed the group to reach the hamigerans and a number of their analogs in an expeditious way.

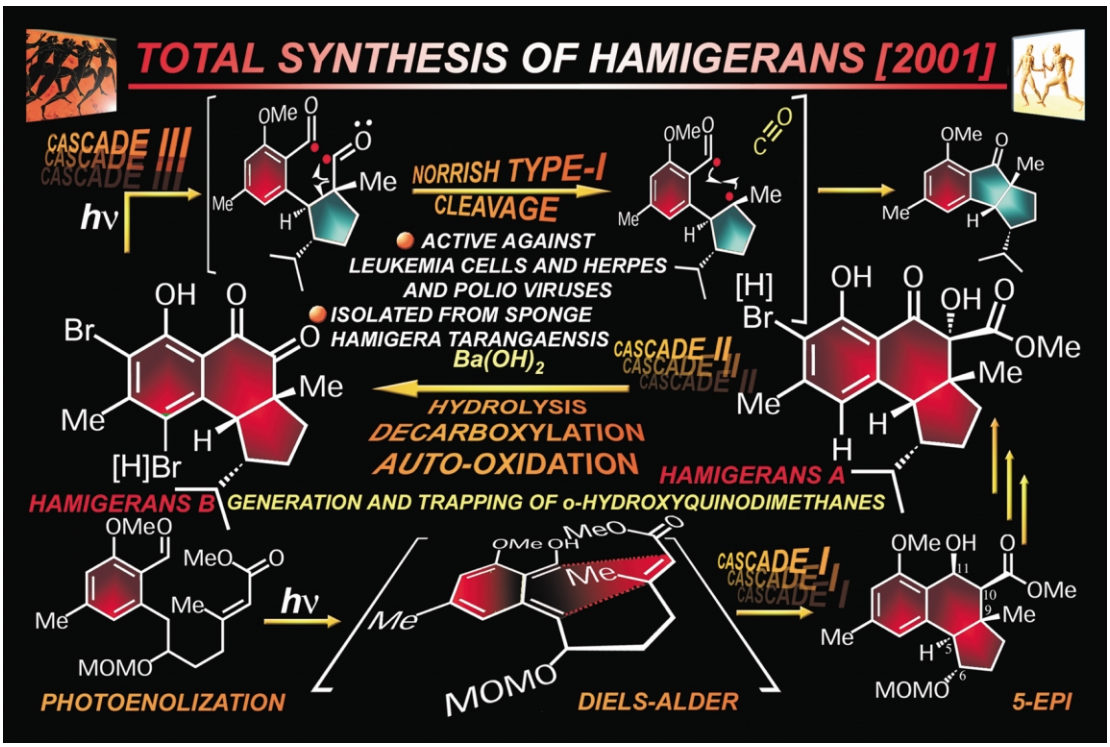

Figure 38. Intramolecular capture of photo-generated hydroxy-*o*-quinodimethanes allowed entry into tricyclic skeletons that served as precursors to the hamigeran family of natural products. The strategy towards these molecules also featured a number of other unique cascade reactions.

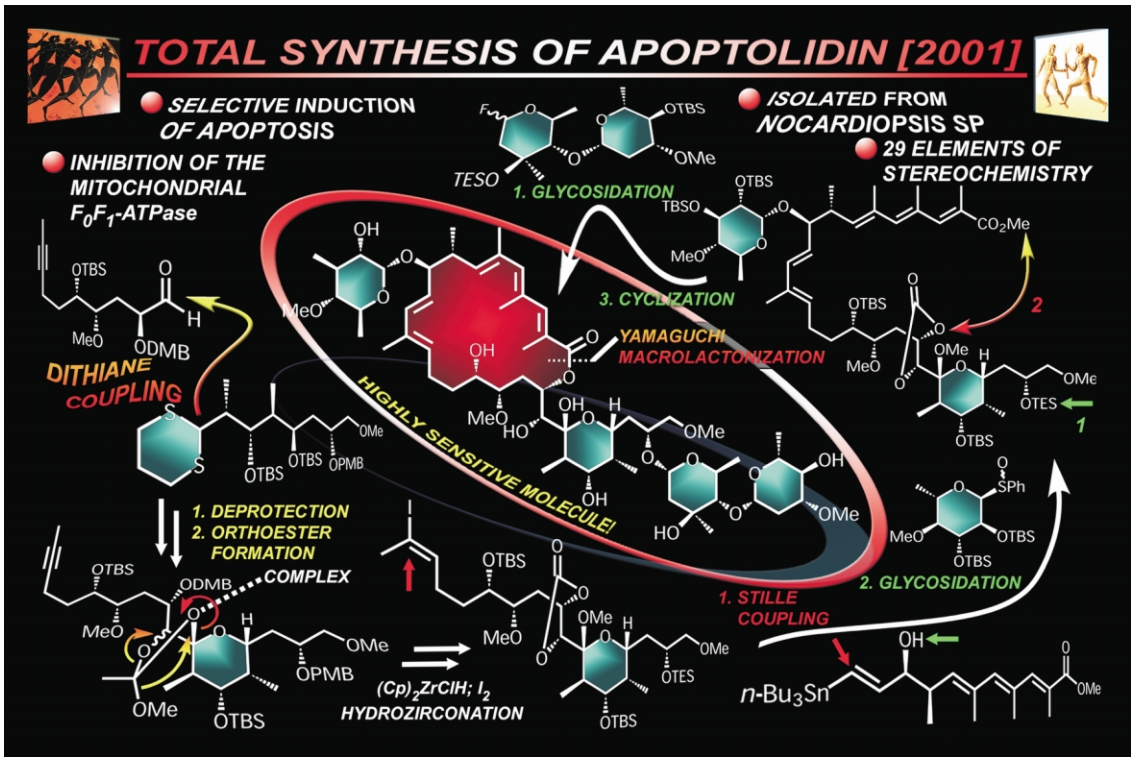

Figure 39. The total synthesis of apoptolidin involved a highly convergent strategy and featured a number of modern coupling reactions and unexpected observations. The synthetic technology developed was applied to the construction of designed analogs, biological evaluation of which shed light on structure activity relationships within the apoptolidin class.

3.33. Apoptolidin

Although numerous methods have been developed over the past several years to efficiently and stereoselectively synthesize members of the macrolide class of natural products, one recent isolate from *Nocardiopsis* sp., apoptolidin, stood out as a target which certainly challenged and potentially defied existing synthetic methodology. Named for its unique biological activity, the selective induction of apoptosis in oncogenic rat glia cells in the presence of normal cells, apoptolidin has a daunting molecular framework which includes no less than 30 stereogenic elements (25 stereocenters and 5 geometrical sites), a highly unsaturated 20-membered macrocyclic system, and four carbohydrate units (see Fig. 39). To heighten the challenge, apoptolidin also possesses unique chemical sensitivity as prolonged dissolution at ambient temperature, chromatographic manipulation, or exposure to either acid or base leads to numerous conjugates and by-products of the natural product. Although this knowledge has implications for the final steps of any total synthesis endeavor, the perceived lability of apoptolidin's conjugated systems, glycoside bonds, lactol moiety, and macrocyclic ring could likely lead to unforeseen as well as undesired events during all stages of the synthetic journey. In 2001, these issues were successfully addressed by the group with the first total synthesis of this natural product[127] via a strategy which featured a Stille coupling reaction and a Yamaguchi macrolactonization to prepare the molecule's macrocyclic core, as well as a dithiane-based addition to append a fragment suitable for elaboration to the final C-ring glysocide. Of particular importance in this synthesis are the subtle modifications of reaction protocols to overcome the noted idiosyncrasies of the target molecule toward numerous reagents and conditions, the specific protecting group ensembles which were carefully orchestrated for selective deprotection at key junctures, and the collapse of the anomeric orthoester to the corresponding methyl glycoside during a critical hydrozirconation step. Additionally, the highly convergent nature of the synthesis, using five key building blocks of roughly equal stereochemical complexity, should provide considerable flexibility for the construction of simpler analogs to explore more fully the chemical and biological profile of this important substance.

3.34. 1-*O*-Methylforbesione

In a novel demonstration of the power of tandem biomimetic schemes for the rapid construction of complex molecular architectures, the group achieved the first total synthesis of 1-*O*-methylforbesione in 2001 (Fig. 40).[128] The synthetic challenge of the unusual 4-oxatricyclo [4.3.1.0] decan-2-one system characterizing an expanding class of natural products was met by a biomimetic cascade strategy in which a Claisen rearrangement was followed by an intramolecular Diels–Alder reaction and a second Claisen rearrangement to complete the targeted framework. Application of this synthetic technology toward the construction of other members of this class, some of which possess cytotoxic properties, and to combinatorial compound libraries may be anticipated.

3.35. Coleophomones B and C

Coleophomones B and C were discovered in certain species

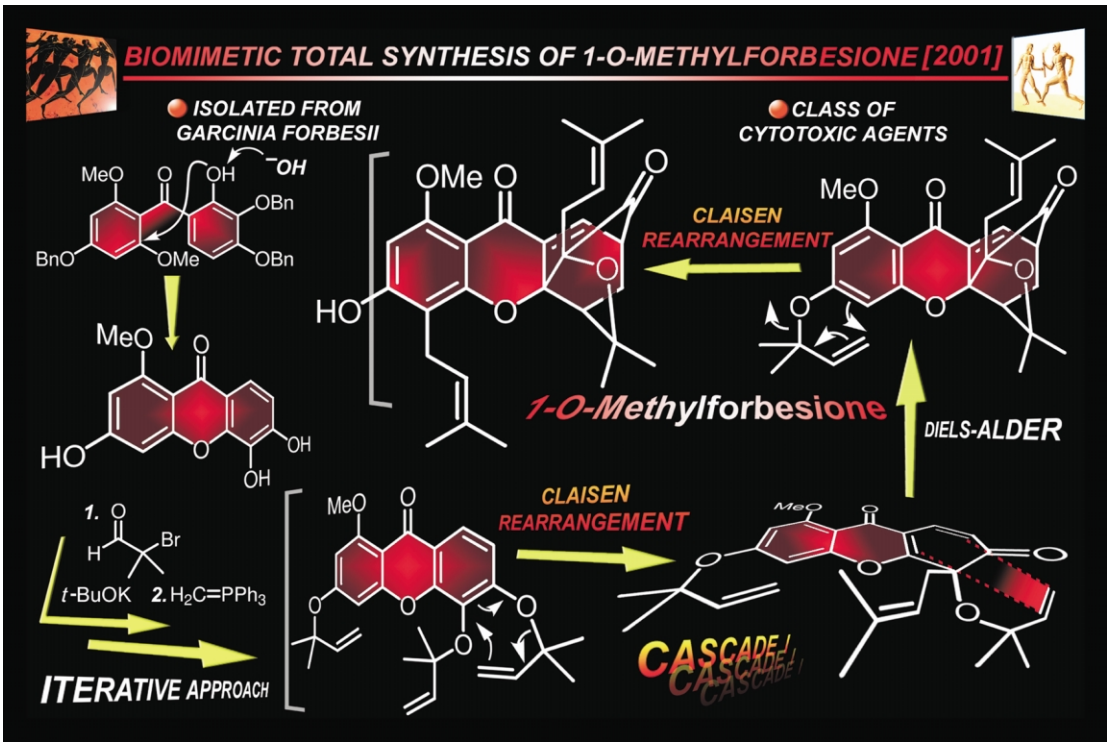

Figure 40. The total synthesis of 1-*O*-methyiforbesione involved a cascade sequence featuring two Claisen rearrangements and an intramolecular Diels–Alder reaction to convert a 'flat' precursor to the desired cage-like framework of the target molecule.

of fungi and shown to possess impressive biological properties including inhibition of chymase, antifungal and antibacterial activities. Their highly strained and rigid molecular structures characterized by an 11-membered ring carrying either a *Z*- or an *E*-double bond, respectively, and a labile polycarbonyl system presented a taxing synthetic challenge that was successfully addressed by an olefin metathesis-based strategy. The total synthesis[129] developed involved an initially convergent route to obtain an advanced intermediate, followed by divergence to allow stereospecific access to both coleophomones C (*Z*-isomer) and B (*E*-isomer) (see Fig. 41). Requiring the use of the

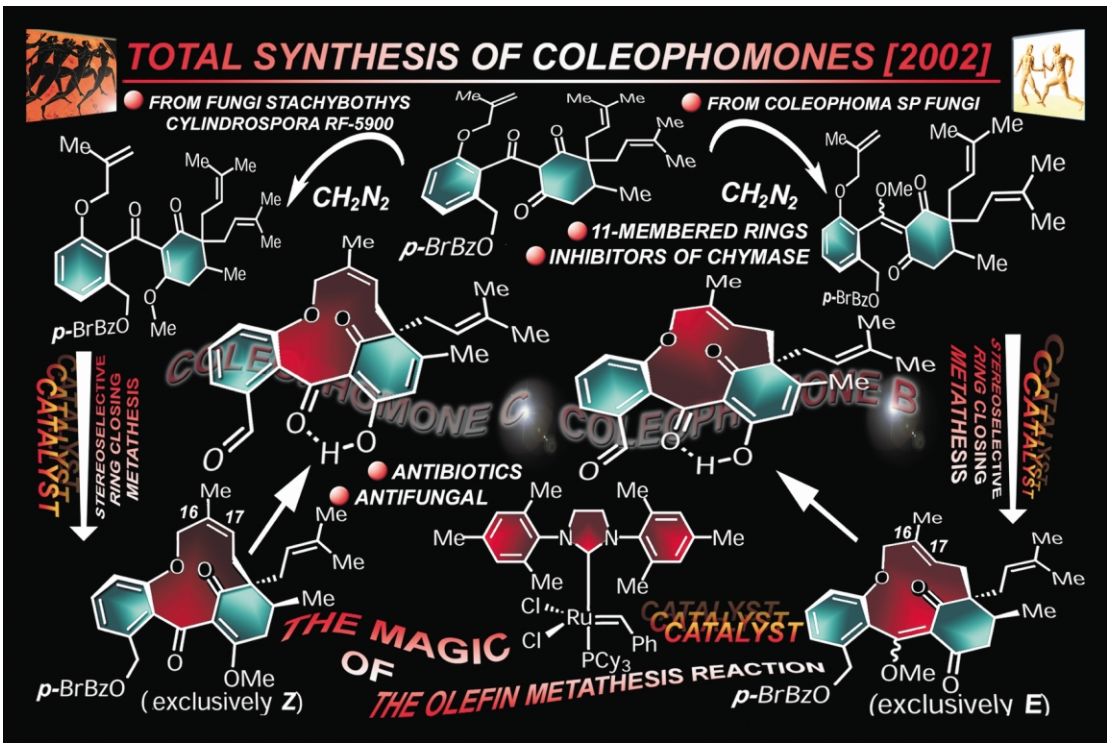

Figure 41. Coleophomones B and C provided a most stringent test for the olefin metathesis reaction, a challenge that was admirably met through a unique strategy that delivered both natural products in a stereoselective manner.

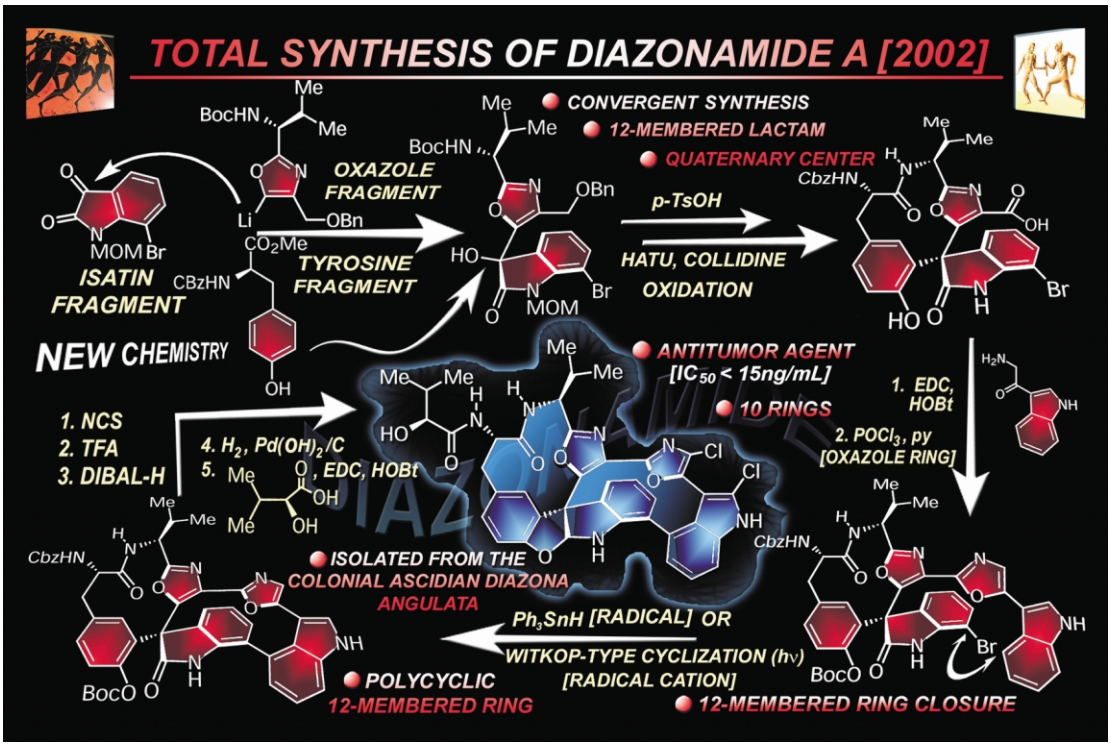

Figure 42. The diazonamide A adventure resulted in several new synthetic technologies and strategies, and enabled chemical biology studies by rendering both the natural product and certain designed analogs available for investigation.

second generation Grubb's catalyst, this total synthesis extended the reach of this process in terms of the complex and challenging molecular diversity that could be accessed by the olefin metathesis reaction and opened the way to analog construction for biological investigations within the coleophomone class.

3.36. Diazonamide A

The marine natural product diazonamide A, isolated from the colonial ascidian *diazona angulata* and possessing impressive antitumor activity captured our interest not only due to its biological activity and natural scarcity, but also because of its highly unusual molecular architecture. To make the project more tantalizing, the structure of this challenging natural product was proven to be wrongly assigned,[130] an error that came to light[131] in the midst of our campaign to synthesize it, dictating an obligatory change of synthetic plan.

Even more complex than the originally proposed structure, the revised diazonamide A structure demanded a unique strategy for the construction of its crowded quaternary center and extremely strained polycyclic framework which was comprised of no less than ten rings (see Fig. 42). In addition to finally settling this structural puzzle, this first total synthesis[132] of diazonamide A resulted in the development of several new synthetic technologies and rendered this valuable naturally occurring substance available for biological investigations, thereby facilitating extensive chemical biology studies through analog construction.

4. Summary and future perspectives

With only one carbon atom, urea's molecule seemed like an appropriate start for the first synthetic organic chemist. That the total synthesis of this naturally occurring substance took only one step simplifies the exercise even more. However, this seemingly trivial step towards a small molecule, performed by accident by Wöhler in 1828, turned out to be a giant step for science. To be sure, Wöhler's discovery marked the beginning of both organic chemistry and natural products total synthesis, two interwoven disciplines whose advancement and applications have contributed enormously to mankind. Wöhler's landmark synthesis of urea was followed by H. Kolbe's synthesis of acetic acid (1845), E. Fischer's total synthesis of glucose (1890), R. Robinson's synthesis of tropinone (1917), and H. Fischer's total synthesis of haemin (1929), among a few other landmark accomplishments. These advancements in total synthesis were followed by unprecedented new strides after World War II as led by practitioners such as R. B. Woodward and E. J. Corey.[133]

As the 20th century was coming to an end, a new avalanche of natural products with amazing structures and biological activities were discovered from plants, microorganisms and marine creatures. These stunningly diverse, challenging, and unprecedented molecular architectures with enticing and potentially useful biological profiles greatly invigorated the field of total synthesis[134] by providing unique opportunities for discovery and invention. Particularly attractive to us were the endeavors of total synthesis directed towards a selected group of these molecules. We saw within their

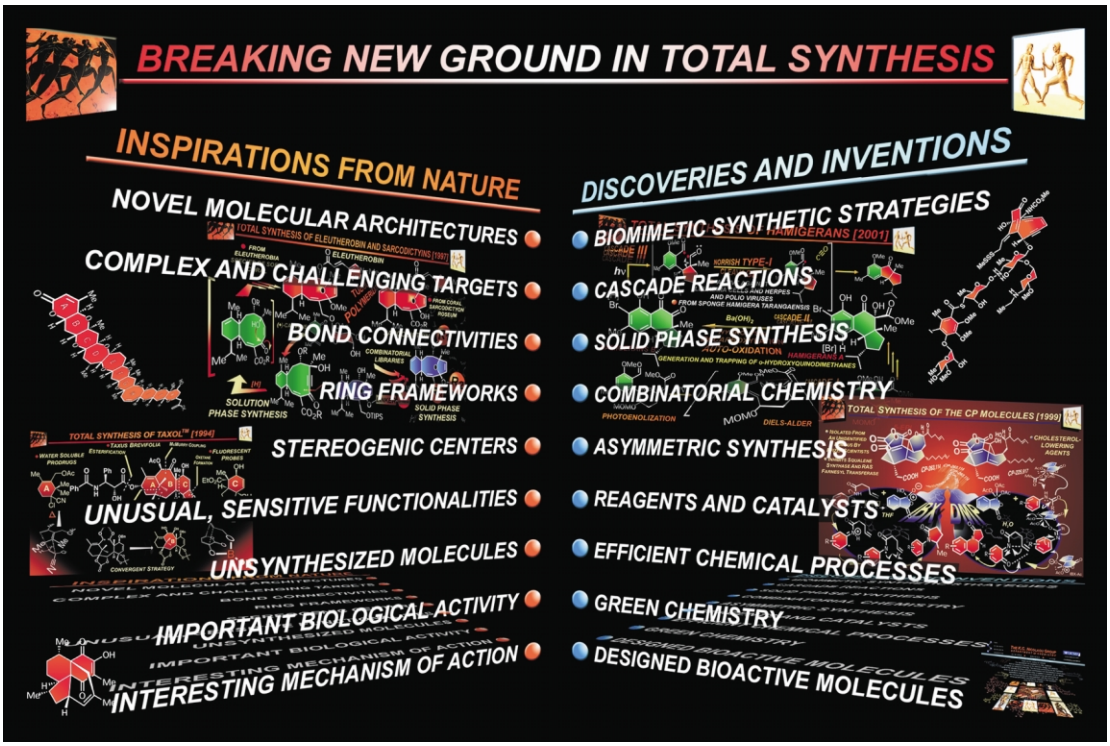

Figure 43. Breaking new ground in total synthesis often requires the selection of targets which combine novel molecular architectures, important biological activities and interesting mechanisms of action. Discoveries and inventions made along the contours of such endeavors sharpen the tools of chemical synthesis and advance the drug discovery and development process.

structures the opportunity to design and discover new chemistry and the inspiration to synthesize structural analogs of them endowed with powerful properties that could be tamed to probe biology and serve medicine. In selecting our targets for total synthesis, we applied several criteria, primary amongst which were the novelty of molecular architecture, the importance of biological activity posed by the target, and the fascination of its mechanism of action. Thus, the inspirational value of Nature's most complex and intriguing molecules was found not necessarily in their size, but rather in their bond connectivities, ring frameworks and sensitive functionalities from which their properties emerge. Attempting the total synthesis of a new structural type where unprecedented structural features would require new synthetic strategies and methods was more important than synthesizing yet another member of the same class. We considered that in judging the harvest of a total synthesis we would have to evaluate the discoveries and inventions that accompanied the endeavor, in addition to its aesthetic appeal. Such developments included biomimetic strategies, cascade reactions, solid phase synthesis, combinatorial chemistry and myriad of designed biologically active molecules (see Fig. 43). It would be enormously pleasing if this philosophy of research (Fig. 44), which has been embraced by many other laboratories around the world, has pushed the state of the art of total synthesis forward and expanded considerably its scope.[135] Nowadays the bar sits very high for endeavors in total synthesis, for the expectations include both beauty as well as discoveries and inventions in chemistry, biology and medicine. To be sure this trend will continue, for it will be further fueled by Nature's as yet unrevealed secrets and humanity's needs and demands.

What does the future hold for this field? After all, some will say, the power of chemical synthesis is so awesome that one can synthesize any molecule no matter what its size or complexity, given enough manpower and money. And therefore, they conclude, the end of the field is here! But how can we be so arrogant about our newly acquired ability to synthesize in front of Nature's truly magical power to construct molecular complexity? While the statement above may be true, the question is not whether we can make a complex molecule, but how and with what didactic remunerations and advances for chemistry. If we judge the state of our science by these strict criteria and compare its present power with that of Nature, then we will understand that, despite its glorious past and proud lineage, the art and science of chemical synthesis is still in its youth and in need of much improvement and advancement for its own sake.

In concluding this essay, I hope that the case has been convincingly made that with their complexity and diversity, Nature's most intriguing molecules are indispensable sources of light, guiding science into new realms of knowledge with enormous dividends to mankind.[136,137] The challenge they provide for total synthesis often forces the practitioner to create and invent new science in chemistry and biology, which is often translated into far-reaching applications in medicine. While one should refrain from making predictions, I dare say that the field will continue to blossom as we strive to mimic Nature in her exquisite elegance and efficiency in constructing her molecules. Progress will be measured not only by higher efficiencies and fewer numbers of steps but also in terms of environmentally clean chemistry and overall cost. Biomimetic and

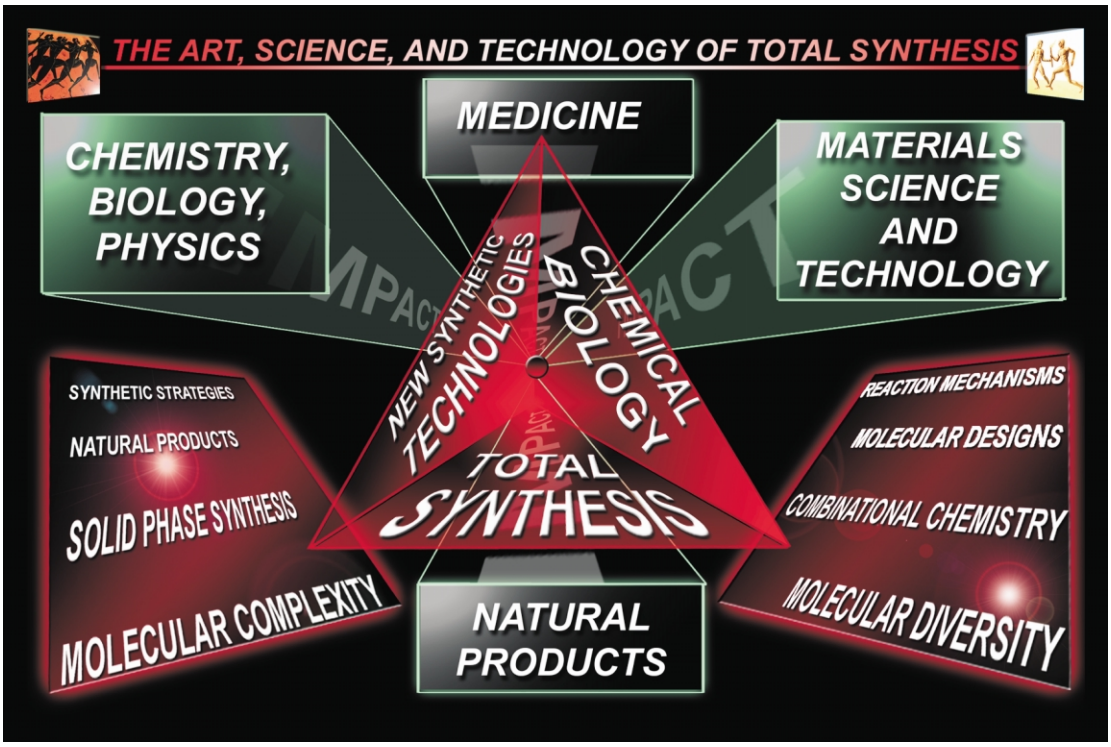

Figure 44. Merging endeavors in total synthesis with new synthetic technologies and chemical biology studies provides opportunities for advancing the field of organic synthesis, whose impact on science, technology and medicine is broadly and deeply felt.

cascade synthetic strategies[138,139] are sure to play a major role in the future, just as new reactions, reagents and catalysts will, as we move into new vistas of molecular complexity and diversity whose constitutions are still held secret by their living hosts.

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