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Joys of Molecules. 1. Campaigns in Total Synthesis†

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Our bodies are made of molecules, and it is from molecules that we derive our strength and joys. The joys of molecules manifest themselves in many ways. These include beautiful colors, exquisite aromas, distinct tastes, psychological ups and downs, and intellectual inspirations, among other forms of stimulation, material or spiritual. In this Perspective, written on the occasion of the 2005 American Chemical Society Arthur C. Cope Award address, I recount some of the joys I have experienced and shared with my students during campaigns to synthesize some of Nature's most intriguing and complex molecules.

Introduction

Ever since I remember, even as a small child, I was aware that molecules were all around me, just as they were obviously inside me, sustaining, inspiring, and pleasing me. Born and raised in the small town of Karavas, whose reputation for lemons transcended the island of Cyprus, my earliest encounters must have involved the molecules of limonene and citric acid, for lemons were my first fruit, both by abundance and necessity. I can now confirm that there are higher inspirations and joys to be derived from Nature's molecules than those I first experienced with "bitter lemons". Indeed, I have been extremely fortunate to have delved deeper into the world of molecules and to have had the privilege of working with so many talented individuals with whom I explored and shared the joys of these tiny but wondrous creations, full of beauty, character, and potential for biological action. The essence of total synthesis has been adequately articulated elsewhere[1] and for this reason will not be elaborated further at this time. My journey from the little lemon town in Cyprus via London, New York City, and Cambridge, to Philadelphia, where I settled into my first faculty appointment at the University of Pennsylvania (Penn) in 1976, has also been briefly reviewed[2] and will not be repeated here.

Returning to Nature for a moment, when we are attracted by the beautiful color of a flower in a field, it is a molecule that affords us the joy of its sight. When we approach this flower, it is again a molecule that conveys to us that exquisite joy of its aroma. Even more sensuous joys can be derived from that flower through the fruit it becomes, as a result of the actions of another molecule on our taste buds. If we get closer and investigate the flower, the fruit, or their parent plant for their constituents, we may find a molecule that could spread joys of happiness to us through its seemingly magical powers, such as those of relieving pain or curing disease. For us privileged scientists, there are joys of yet another kind that can be experienced from molecules, especially those designed and produced so elegantly by Nature. Inspirations, new knowledge, challenges, and conquests by synthesis are but some of these joys that we, in particular, as practitioners of the art of total synthesis, can enjoy from molecules. In this article I wish to share some of the joys I have experienced, with my students, in such encounters.

One of the first natural products we targeted at Penn, and the first to be synthesized in our laboratories, was zoapatanol[3] (this and the other naturally occurring molecules mentioned in this article are shown in Figures 1 and 2), a molecule remembered not so much for its sophistication but rather for what it meant for us. Although I had been involved in the total synthesis of a natural product earlier during my postdoctoral stint with Professor E. J. Corey at Harvard,[4] the zoapatanol accomplishment stands as a great moment for the group. Not only had we personally hammered yet another nail in the coffin of "vitalism", like so many before us since Frederich Wöhler in 1828 with his synthesis of urea,[5] but, most importantly, this success brought with it the psychological boost and confidence of the "first boot on the ground". Modest as it was in terms of its structure,

† Dedicated to Professor Albert Eschenmoser on the occasion of his 80th birthday.

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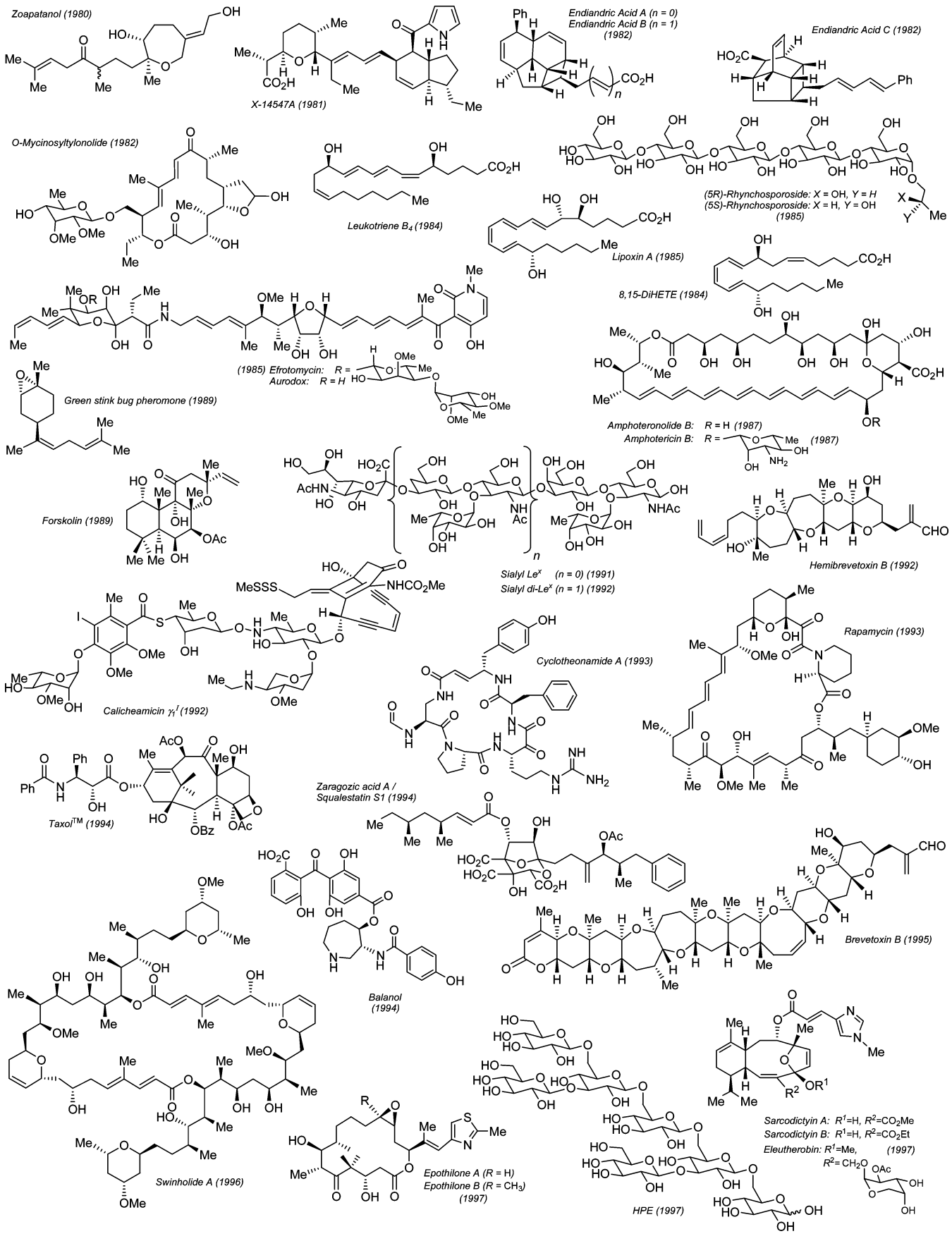

FIGURE 1. Selected natural products synthesized by the Nicolaou group (1980−1997).

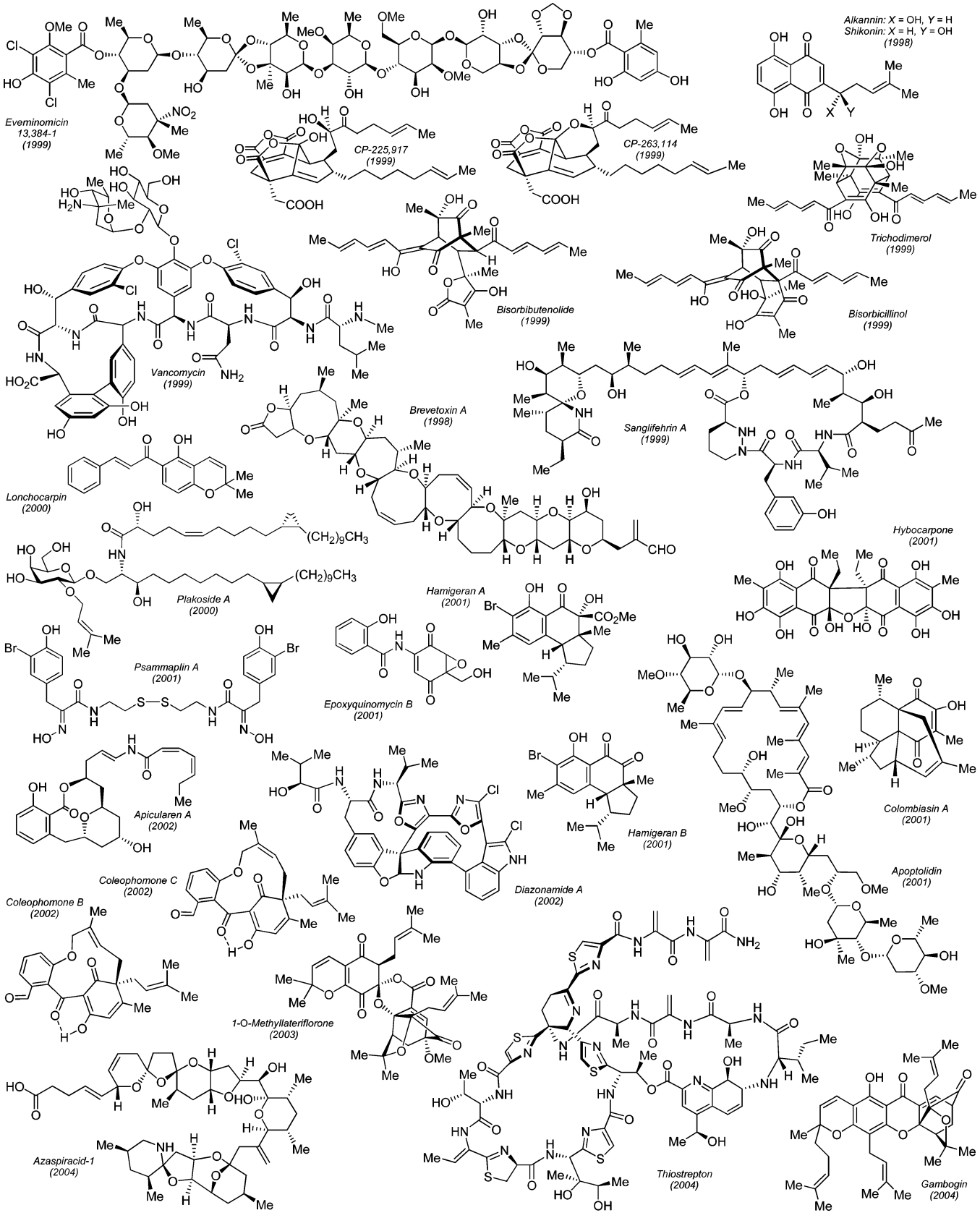

FIGURE 2. Selected natural products synthesized by the Nicolaou group (1998−2004).

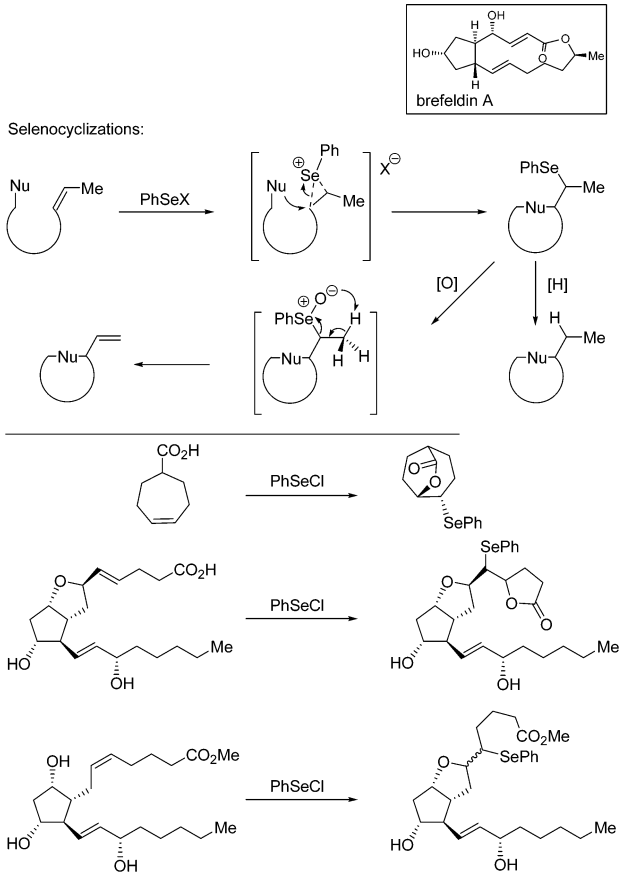

FIGURE 3. Brefeldin A and selenocyclization reactions (1976−77).

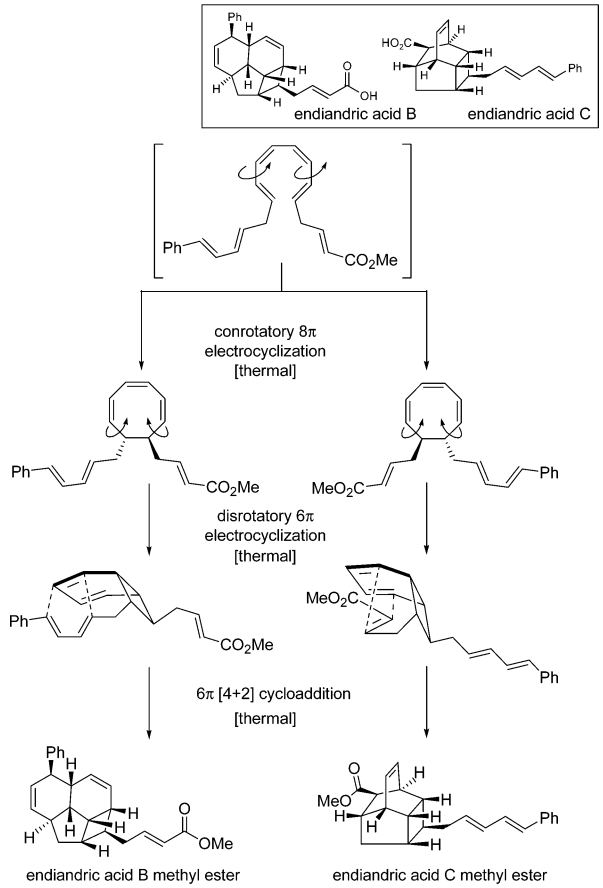

FIGURE 4. Endiandric acids and 8π-/6π-electrocyclization reactions in total synthesis (1982).

the molecule of zoapatanol constitutes the beginning of what became a private collection of molecules whose joys can only be fully appreciated by those who shared them with me at the time. Incidentally, zoapatanol was not the first natural product to be targeted by us at Penn, as that distinction must go to brefeldin A,[6] the synthesis of which was never taken to completion because we became too busy plundering the gold mine we discovered on the way to it. This treasure took the form of new selenium-based synthetic technologies for the formation of cyclic systems (Figure 3).[7,8] There was another naturally occurring substance, prostacyclin, which we targeted before zoapatanol, but synthesized only by a partial synthesis. Although this project yielded its own golden nuggets through biological studies,[9] it does not count as much as the zoapatanol accomplishment in terms of the theme of total synthesis. However, in the prostacyclin work one can find amalgamated the philosophy of our research programs over the last 29 years. That philosophy is the blending of natural product synthesis with the discovery of new synthetic technologies and chemical biology investigations. While, in this perspective, I restrict myself to those aspects of our research programs relating to total synthesis and new synthetic technologies, our chemical biology endeavors will be described in a separate article.[10]

Having established ourselves on the scene of natural product synthesis with zoapatanol, the Penn group moved on to more complex and sensitive structures. A number of molecules were targeted, and those which fell included antibiotic X-14547A in 1981,[11] endiandric acids A−F and *O*-mycinosyltylonolide in 1982,[12,13] several eicosanoids such as di-HETEs,[14] leukotrienes,[15] and lipoxins[16] in 1984/1985, aurodox and efrotomycin in 1984,[17] 5-(*R*)- and 5-(*S*)-rhynchosporosides in 1985,[18] and the clinically important antifungal agent amphotericin B in 1987.[19]

Particularly satisfying from these early endeavors were those directed toward the endiandric acids, aurodox and efrotomycin, the linear eicosanoids and amphotericin B. It was during the endiandric acid campaign that we demonstrated, for the first time, the power of 8π-/6π-electrocyclization cascade reactions in total synthesis (Figure 4), a theme that appears not to have been missed by Nature, the master synthetic artisan who used such methods before us, nor by subsequent workers who employed them after us. It is especially rewarding to see the current renaissance of this type of electrocyclization cascade in total synthesis.[20] With regard to efrotomycin, its joys came in the form of the discovery of novel cascade epoxide openings (Figure 5a), which later became a popular choice for ring construction, and new synthetic strategies and technologies for oligosaccharide synthesis based on thioglycosides and glycosyl fluorides (Figure 5b).

I have often been asked why the story of efrotomycin was published only in the form of full papers, since after all it was a thrilling saga, and one worthy of publication as an urgent communication in a top scientific journal. You may be interested to know that two such communications were submitted, accepted, and in press in

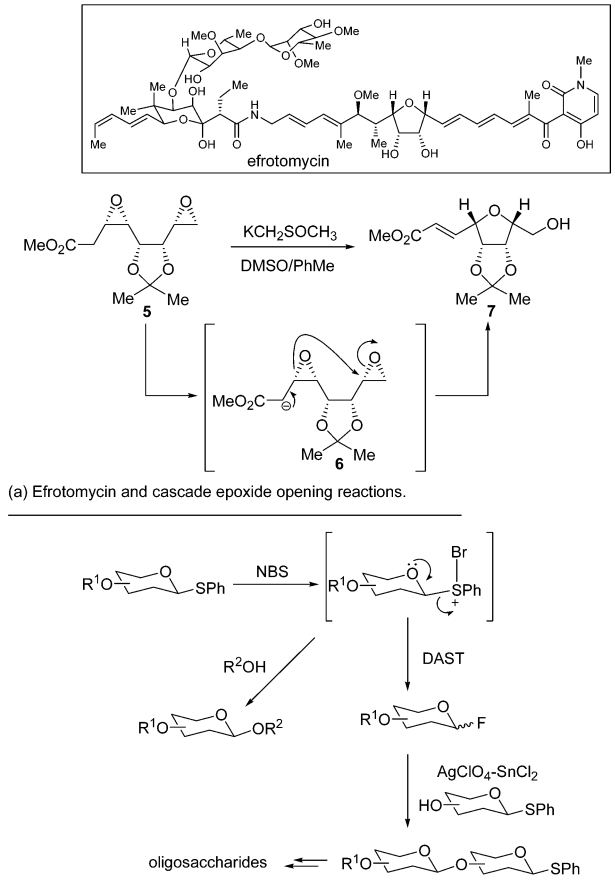

FIGURE 5. Aurodox and efrotomycin campaign (1984).

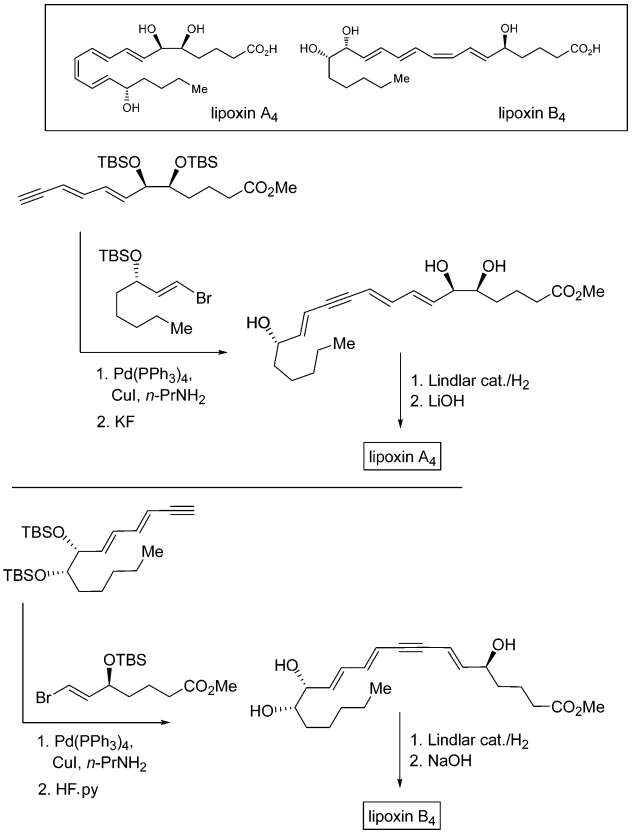

FIGURE 6. Pd-catalyzed synthesis of the lipoxins (1985).

the *Journal of the American Chemical Society* (*JACS*) but were stopped in their tracks on the basis of the so-called "embargo rule". This is a rule followed by most scientific journals, including *JACS*, whereby a magazine cannot publish a story on an article scheduled to appear in another journal prior to the publication date of said article. It so happened that *Chemical and Engineering News* (*C&E News*), the popular magazine of the ACS, did break the embargo, an act that prompted the stop-the-press action on the communications which were, kindly, accepted as full papers after appropriate modification. You may be amused to know that it was the same ACS journals that broke their own and same "embargo rule" 10 years later. To be specific, a story on two communications on the total synthesis of Taxol was published in *C&E News* before the papers had appeared in *JACS*.[21] This exception to the rule was justified on the basis of another paper that was about to appear a week before said communications in *Nature* on the total synthesis of Taxol,[22] ours, and that was about to make the news!

The stereoselective palladium-catalyzed total syntheses of lipoxin A_4 and lipoxin B_4 (Figure 6) is illustrative of our strategy toward the linear eicosanoids,[23−25] molecules that became important in the 1970s and 1980s. These syntheses represent some of the earliest applications of palladium-catalyzed cross-coupling reactions in complex molecule construction, a trend that was to become one of today's most influential themes in total synthesis.[26]

During the amphotericin B project, we were gifted with a golden opportunity to display the virtues of the intramolecular ketophosphonate−aldehyde condensation reaction in forming macrocycles, a reaction that we, among others, had previously developed. In this instance, the red-orange 38-membered ring bound for amphotericin B was formed from its yellow-colored precursor upon exposure to mild basic conditions (Figure 7).

Among the other joys of the Penn years were the seeds we put in the ground for the synthesis of several naturally occurring molecules as diverse as certain complex oligosaccharides, the beautiful brevetoxins and the stunning enediynes, and the inspirations we derived from them. Although these projects had already begun to bear fruit in the 1980s, the main harvest was not to come in this, our first and most beloved home institution. Winds westward would bring us to our new homes at The Scripps Research Institute and the University of California, San Diego. It was here that the rest of the molecules shown in Figures 1 and 2 would be tamed and conquered, some in battles that became legendary not only because of their fierceness, but also for their successes.

Among the first to fall in the "campaigns of the West" were the inflammation-relevant molecules of sialyl Le^x and sialyl dimeric Le^x (1991−92),[27] hemibrevetoxin B (1992),[28] and calicheamicin γ_1^I (1992).[29] Especially sweet was the conquest of calicheamicin γ_1^I, which was accompanied by the joy of confirming its initially unbelievable and stunningly beautiful structure, while gifting us a new-found confidence from setting a new record of synthetic complexity for the group. We all have moments

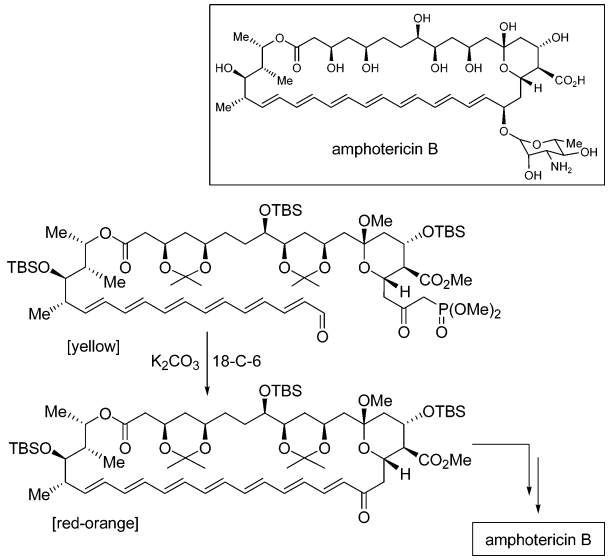

FIGURE 7. Amphotericin B and ketophosphonate−aldehyde condensations in macrocycle formation (1987).

in our lives that we cannot forget; one of mine was the first time I laid eyes on calicheamicin's proposed structure at Lederle Laboratories one day in 1987. On the invitation of Robert Babine, I drove up to New York from Pennsylvania, parked my car, and entered the building where I was to meet Bob at Lederle Laboratories (today, American Home Products). He walked me to a small conference room, stopping on the way for me to sign the obligatory confidentiality agreement, which I did with my pen pressing on the paper against the wall. Upon arrival to the room, I was met by a few additional researchers who immediately and proudly presented me a page with the structure of their newly discovered, and phenomenally active, molecule. The silence that followed was long, its longevity prolonged by me, overwhelmed, stunned and mesmerized. I wanted to jump up and down with joy, but I restrained myself, not quite knowing how to react in a more rational way. I finally began by expressing mixed feelings of awe, excitement, and doubt. Overriding these was, however, a serene sense of pleasure as I anticipated the discoveries to come from tackling this magnificent example of molecular engineering by Nature. I immediately congratulated calicheamicin's discoverers for their achievement and promised them that I would work hard on its total synthesis.

Five years later, it was all over, having proven to be one of the most exciting total synthesis campaigns ever in my group.[30] In terms of aesthetically pleasing transformations, this campaign was exceptionally bountiful. These rewards included a stereospecific 3,3-sigmatropic rearrangement employed to install the sulfur atom on one of the molecule's carbohydrate units (Figure 8a), the stereoselective construction of the novel NH−O glycoside bond (Figure 8b), the use of the Ramberg−Bäcklund reaction for the preparation of enediynes (Figure 8c) and the casting of calicheamicin's signature structural motif, its enediyne system, followed by a neighboring group-assisted inversion of stereochemistry through a novel lactonization (Figure 8d). Additionally, the spontaneous conglomerate resolution of calicheamicin's fully substituted aromatic moiety in two enantiomeric forms (Figure

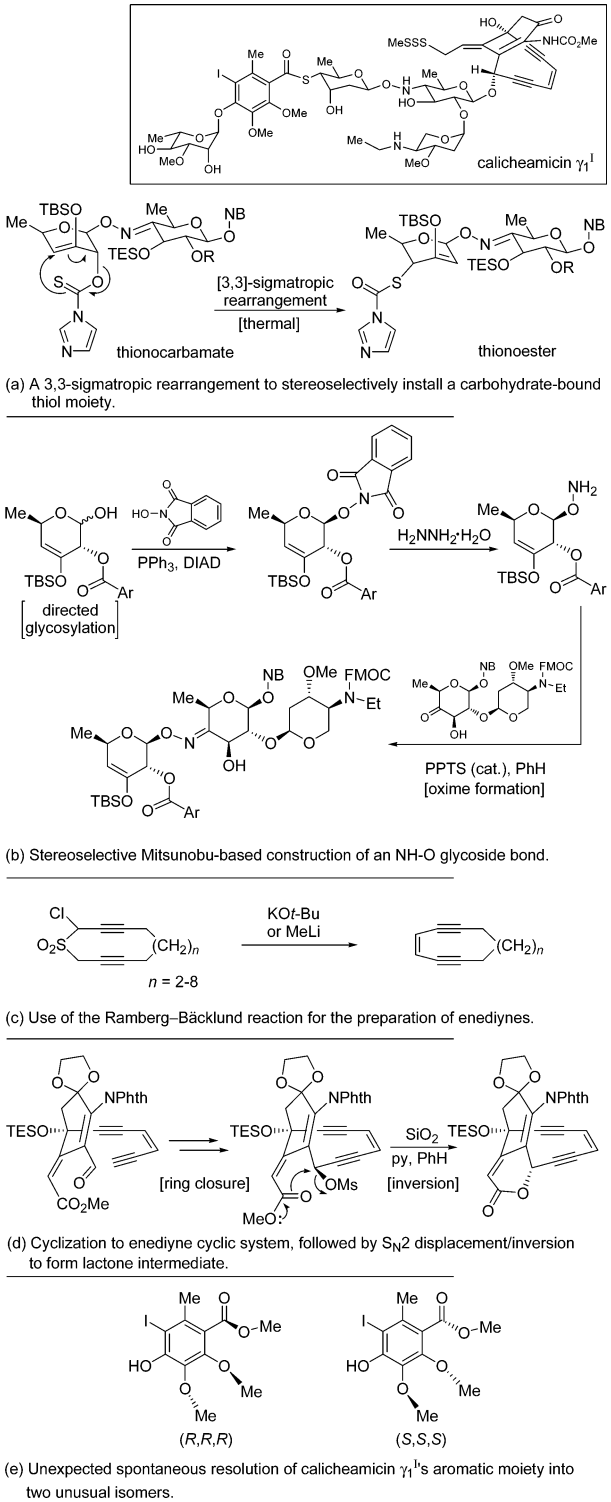

FIGURE 8. Calicheamicin γ_1^I campaign (1988−1992).

8e),[31] structurally determined by X-ray crystallographic techniques, was both surprising and reminiscent of Pasteur's resolution of tartaric acid. Other important spin-offs from this project included the synthesis and study of designed enediynes and oligosaccharides, whose chemical and biological properties were extremely revealing.[32]

The accomplishment of the total synthesis of calicheamicin γ_1^I in 1992 heralded a golden age for the group.

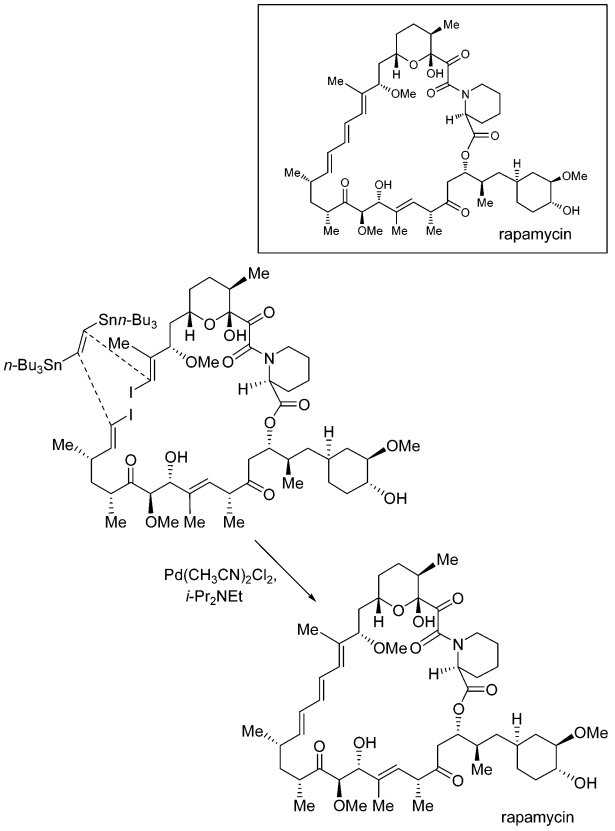

FIGURE 9. Rapamycin and distannane−diiodide stitching cyclizations in total synthesis (1993).

Cyclotheonamide, a molecule brought to our attention by Bruce Maryanoff, yielded to our collective efforts in 1993,[33] the same year that also saw rapamycin fall.[34] The latter molecule, in particular, standing as the newest immunosuppressant agent on the scene at the time (and the most complex of them all), presented a formidable, and hence inviting, challenge to us. This was met by a successful strategy that brought many joys, including one derived from its challenging macrocyclization. This final step involved the daring stunt of a "double stitching" cyclization brought about by a double Stille coupling reaction, performed between an open-chain divinyl diiodide precursor and a *trans*-ethylene distannane (Figure 9). It was with much pleasure that we observed the subsequent proliferation of this concept into other applications in total synthesis.[35]

The year 1994 was to bring unprecedented joys to us, for it was the time of balanol,[36] zaragozic acid A,[37] and Taxol.[22,38] While it was highly pleasing to see the total syntheses of balanol and zaragozic acid come to a successful conclusion (see Figures 10 and 11 for some of the synthetic maneuvers that led to these successes), it was Taxol that brought the most drama and excitement in that year.

We became interested in Taxol not only because of its highly complex structure but also because of its celebrity status as the "holy grail" of synthesis in the 1980s and 1990s. A "race" had been established for its total synthesis with several groups claiming the lead at different times. Being one of the last groups to join this race, we did not count on being first to finish, nor did it seem to

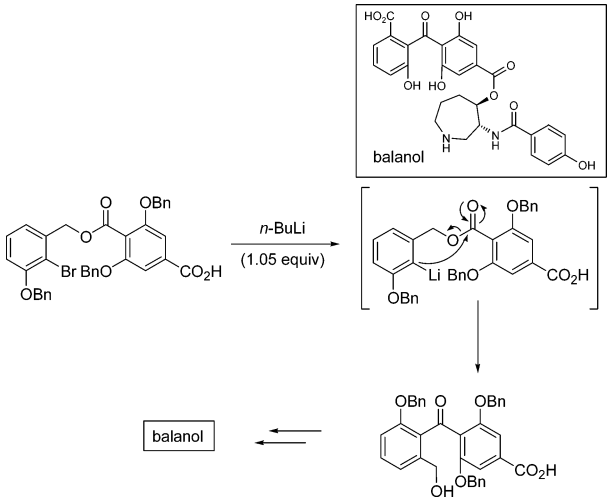

FIGURE 10. Balanol and carbon−oxygen to carbon−carbon bond switching (1994).

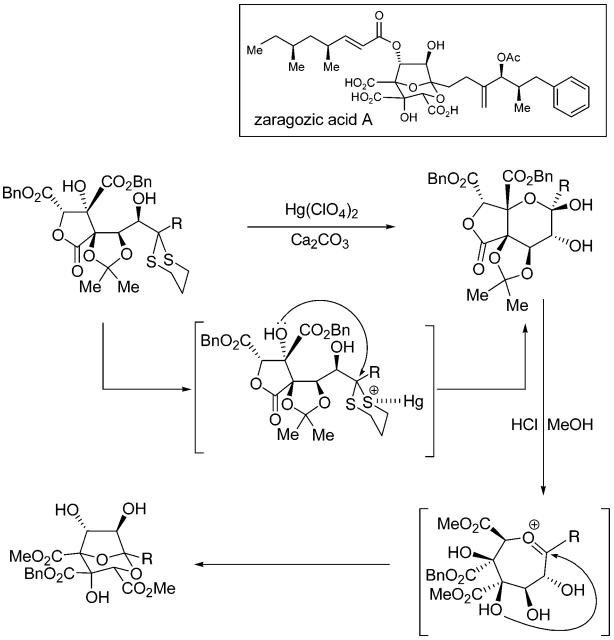

FIGURE 11. Zaragozic acid A and cascade reactions in total synthesis (1994).

matter to us too much. We did, however, expect new science to emerge from the endeavor, since our planned approach was different to those of the others involved. It was extremely satisfying to experience the wealth of discoveries and inventions as they were occurring during the period of 1992−94. That we were also the first to publish the total synthesis of Taxol is a credit to those students and postdoctoral fellows that fought so bravely and intelligently in my group, and, perhaps, a result of intervention by serendipity, as the adventures of the *Three Princes of Serendip* often have the last word in total synthesis. Among the many moments of excitement, one stands out. It was, I remember, around eleven o'clock at night sometime in January 1994. My wife gently woke me up to tell me that there was someone on the telephone with a foreign accent that wanted to talk to me. Tired as I was from an intense day in the lab, I sent her away to

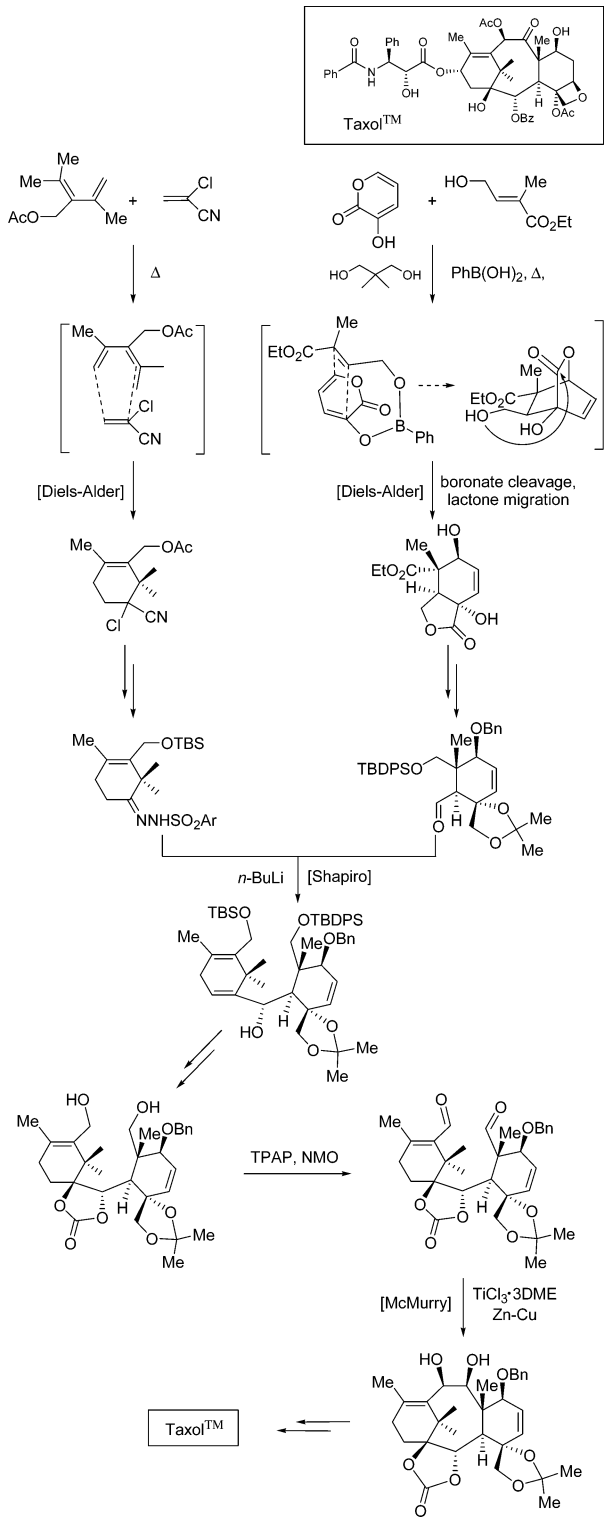

FIGURE 12. Conquest of Taxol (1994).

tell him, whoever he was, that I was asleep. She came back a few moments later to reawaken me, announcing this time that the person insisted and would not go away until he spoke to me, so I reluctantly took the call. "We made Taxol" someone said on the other end of the line. Within minutes, I was in my car driving to the lab in my jogging suit, running color-blinded through all traffic lights and overwhelmed with anticipation and joy for what I was about to see: the two identical ^{1}H NMR spectra of the synthetic and naturally derived materials. Indeed it was true, Taxol had been made and now it was time to polish the work and publish it. The equally dramatic events between this moment and the time of publication of the total synthesis of Taxol will, perhaps, be told another time.... Be that as it may, this experience underscores the unpredictable aspects of total synthesis. You can plan in the most detailed way, and you should, but you cannot predict with absolute certainty the outcome, nor its timing. In the case of Taxol, both the outcome and the timing of the endeavor[39] proved exquisite and were highly joyous and celebratory (Figure 12).

The following year, 1995, was just as exciting as the year before, for it was the time brevetoxin B came home, or more accurately, we arrived at brevetoxin B, our "Ithaca". The preceding twelve years were spent wandering around, not only battling the Cyclops and facing the Sirens, but collecting treasures and wisdom of untold worth, experiences that we would never have encountered had we not embarked on that daring odyssey. While this journey and its joys have been described adequately before,[40] I feel compelled to mention here two moments that stand out: the first time I laid my eyes on the beautiful structure of brevetoxin B (Philadelphia, 1981), and the moment I looked at the ^{1}H NMR spectrum of synthetic brevetoxin B (Athens, Greece, 1995). These were moments of joy with different feelings, but both to be cherished and remembered forever. Only the connoisseurs of organic synthesis will ever know what I mean, and they alone will understand how I long for more moments such as those. Figure 13 should serve as a reminder of some other exciting times of joy during the brevetoxin B campaign and their lasting impact on the art and science of chemical synthesis.[41]

Not to be forgotten, the year 1996 was marked with the conquest of swinholide A, a molecule whose giant macromolecular structure contributed decisively to its selection as a target for total synthesis a few years earlier.[42] The total synthesis of this symmetrical target was achieved through a convergent route employing sequential esterification and macrolactonization to give the 44-membered macrolide (Figure 14).

The same year also ushered in the epothilone era, for the first member of this family of anticancer agents, epothilone A, was synthesized in our group in 1996 (although these novel natural products are officially categorized as a 1997 accomplishment due to the date of publication).[43] Several other epothilones, some natural, some designed, were also synthesized in that same year.[44] The year 1997 was also to witness the total synthesis of the marine-derived sarcodictyins A and B[45] and their more complex sibling eleutherobin,[46] as well as the heptasaccharide phytoalexin elicitor (HPE).[47] All these projects brought us wonderful gifts in the form of new synthetic technologies and strategies, some of which are reflected in Figures 15 and 16.

The epothilones, in particular, shaped a wonderful chapter in our book of endeavors, for they provided unique opportunities for adventure and discovery. In addition to the accomplishment of the total synthesis of several members of the class, the epothilones gifted us with a most stringent test for the solid-phase synthesis

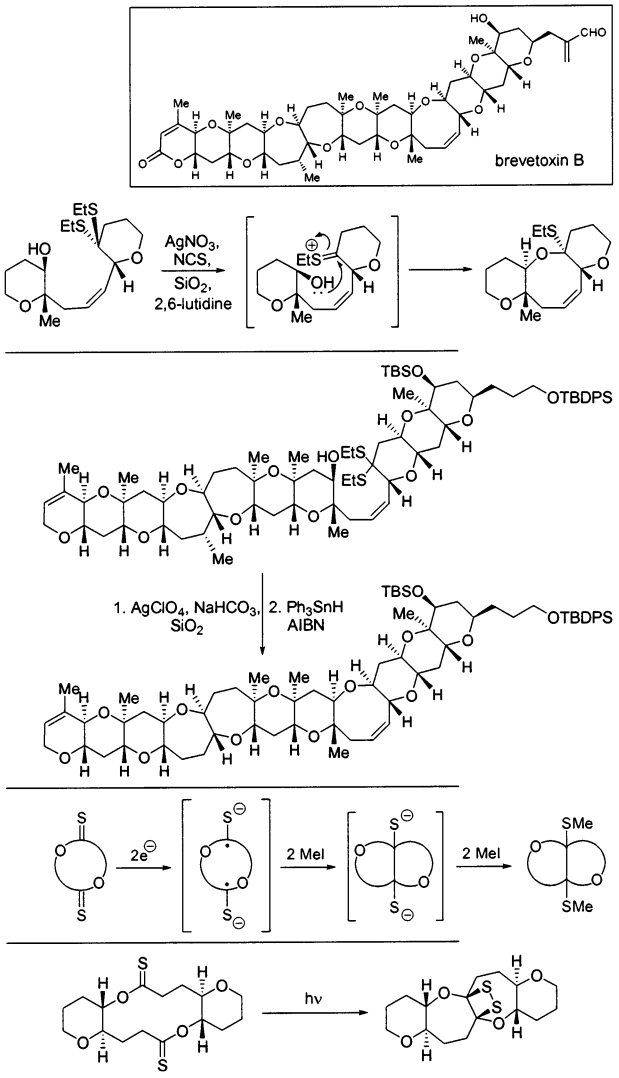

FIGURE 13. Brevetoxin B and cyclic ether formations (1995).

of natural products in general and for the olefin metathesis reaction in particular, two new and fashionable trends at the time (Figure 17).[48] Both approaches performed admirably and significantly enabled the third important development within the epothilones project, that of the combinatorial synthesis of designed analogues by the radio frequency encoded split-and-pool strategy.[44d] In synergy, these developments led to the emergence of a series of highly active designed epothilones, including a drug candidate currently in clinical trials as an anticancer agent.[49]

As the battle for brevetoxin B was raging in the late 1980s, its beautiful sister, brevetoxin A, emerged from the waves of the Atlantic Ocean in the "red tides" that were punishing the east coast of North and Central America.[50] Its aesthetic appeal as an architectural gem, displaying all ring sizes from 5- to 9-membered within its structure, was simply too challenging to ignore, and so we placed it on our marauder's map. In 1998, this conquest would come to an end with joys that included not only the total synthesis of brevetoxin A[51] but also a series of powerful synthetic methods and strategies (Figure 18).

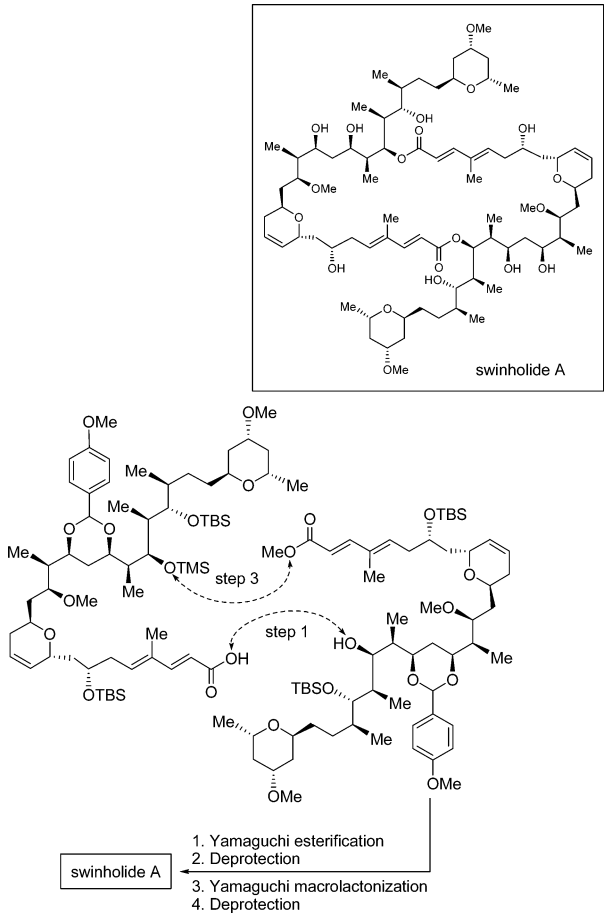

FIGURE 14. Highly convergent synthesis of swinholide A (1996).

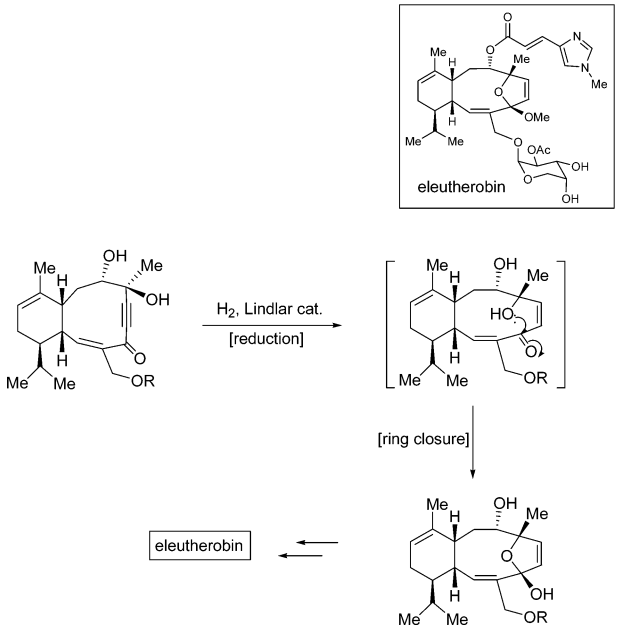

FIGURE 15. Eleutherobin and cascade reactions in total synthesis (1997).

The year 1998 was also the time of alkannin and shikonin, the two enantiomeric natural products found, intriguingly, in the northern and southern hemispheres

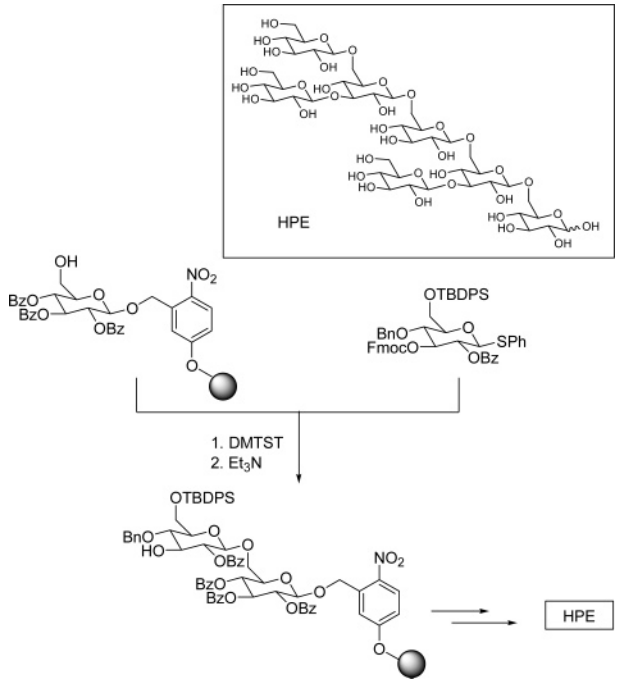

FIGURE 16. Heptasaccharide phytoalexin elicitor (HPE) and solid-phase oligosaccharide synthesis (1997). DMTST = dimethylthiomethylsulfonium triflate.

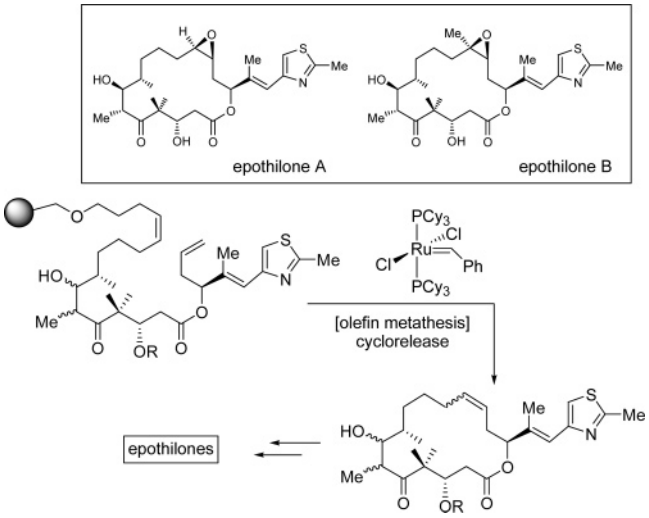

FIGURE 17. Epothilones A and B, solid-phase synthesis and combinatorial chemistry (1996−97).

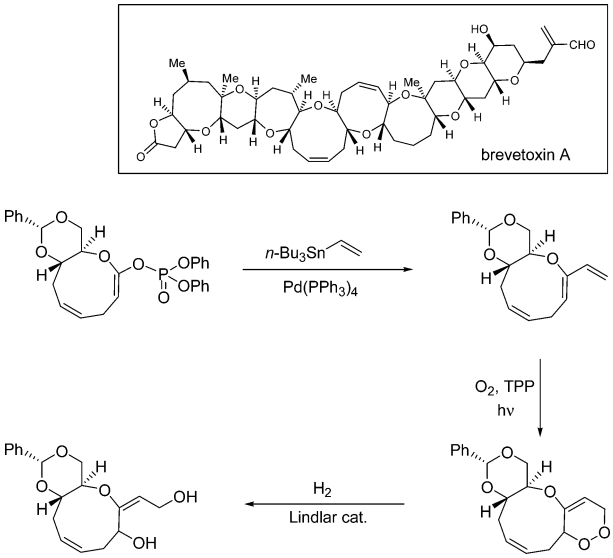

FIGURE 18. Brevetoxin A and ketene acetal phosphonates in cyclic ether formation. TPP = tetraphenylporphine.

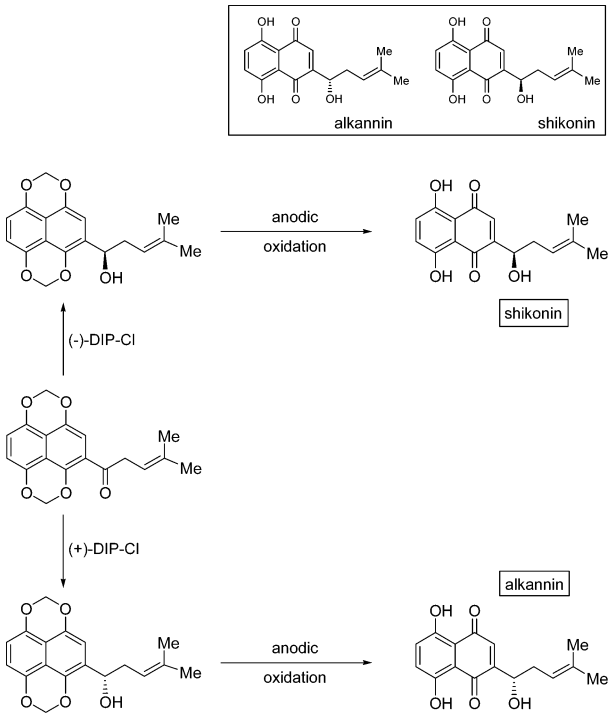

FIGURE 19. Alkannin, shikonin, and anodic oxidations in organic synthesis (1998).

and which were used independently as medical extracts by the Western and Oriental civilizations, respectively, for centuries prior to their structural elucidation. In our hands, these molecules proved inspirational and joyful in that they presented us with the opportunity to invent a rather simple but pleasing route for their stereo- and regioselective total synthesis via anodic oxidation (Figure 19).[52]

1999 was a particularly productive year. Vancomycin,[53] the CP molecules,[54] sanglifehrin,[55] everninomicin 13,384-1,[56] and the bisorbicillinoids[57] all yielded to the relentless efforts of the respective teams working so methodically and skillfully to synthesize them. Each project brought volumes of new synthetic technologies and novel strategies accompanied by the sought-after personal satisfaction and joy of success.

Lured by the highly unusual molecular architecture of vancomycin and its stubbornness to surrender to the heroic efforts of those who dared before us to contemplate its total synthesis, we set out on a journey into the unknown with only a dim light and a blurred road map, but with a sharp focus on the molecule. Full of adventure and excitement, the road to vancomycin brought us untold challenges and joys.[58] One after the other we encountered the intricacies of its unique structural motifs and invented solutions to address their special demands.

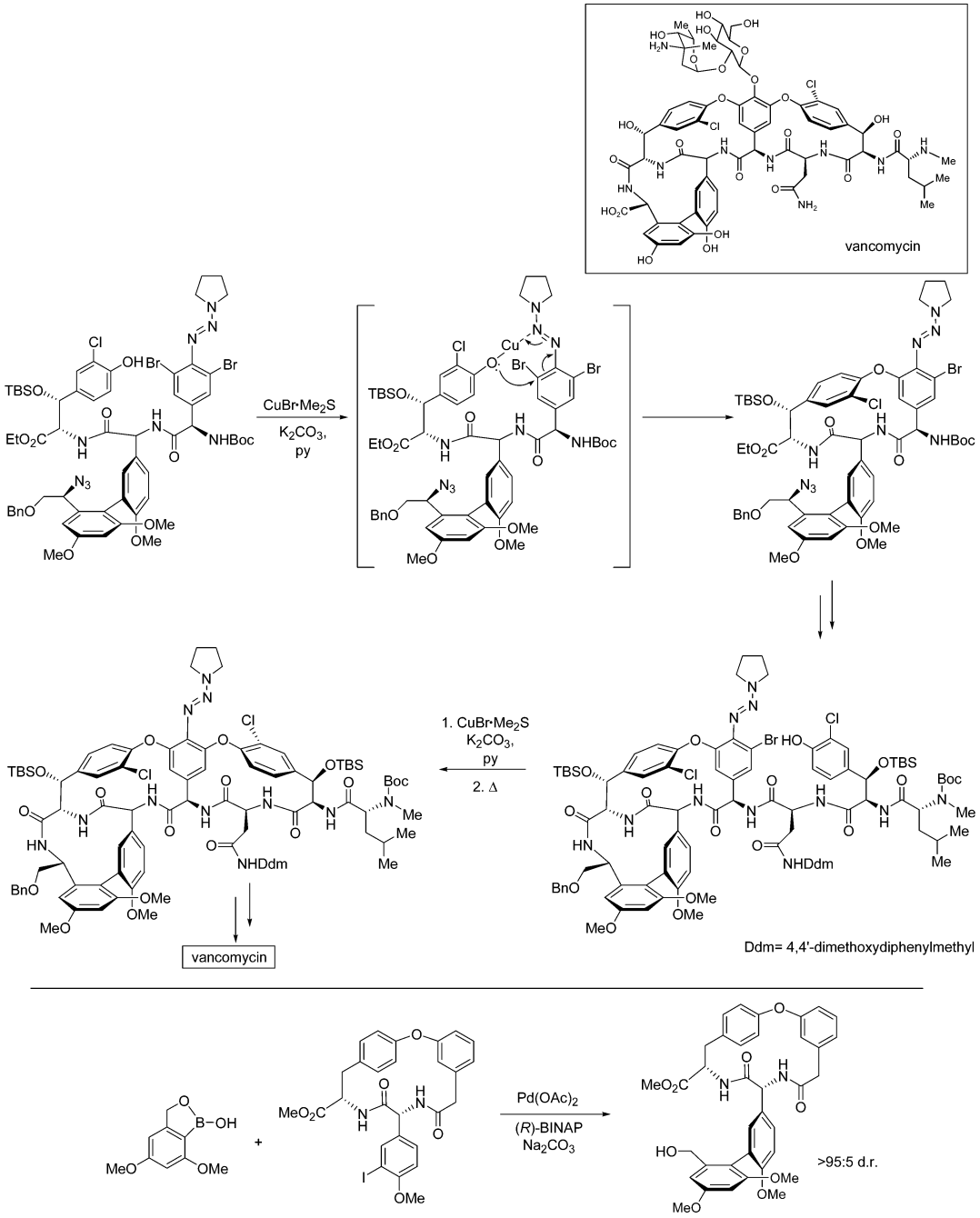

FIGURE 20. Vancomycin, bis-aryl ether, and asymmetric bis-aryl formations (1998−99).

Figure 20 displays some of these synthetic technologies and strategies, including a new method for bis-aryl ether formation and an asymmetric synthesis of bis-aryl frameworks.[59]

The CP molecules were a very special adversary, for their dazzling molecular architectures were so demonic in their complex bond connectivity and functionality that, in many chemists' minds, their structures could just as well have been wrong. This alone constituted a provocation to chemical synthesis, for there was no X-ray crystallographic analysis to back up their daringly proposed structural assignment. This weakness was compounded by the fact that the world had first seen them in the popular press and not in a peer-reviewed journal, something that would only come later. Irrespective of these issues, we fell in love with these magnificent structures and decided to begin work toward their total synthesis. In the end, their diabolical structures were not only defeated, but equalled, and perhaps outdone, by the wonderful synthetic cascades and powerful synthetic technologies that emerged during the campaign to synthesize them. Additionally, their total synthesis proved their structures to be correct and went further to establish their absolute stereochemistry.[60] The collection of transformations shown in Figure 21 is only a sample, but it serves to convey the sense of discovery and invention that accompanied this project and the joys shared by each of us intimately involved in it.[61]

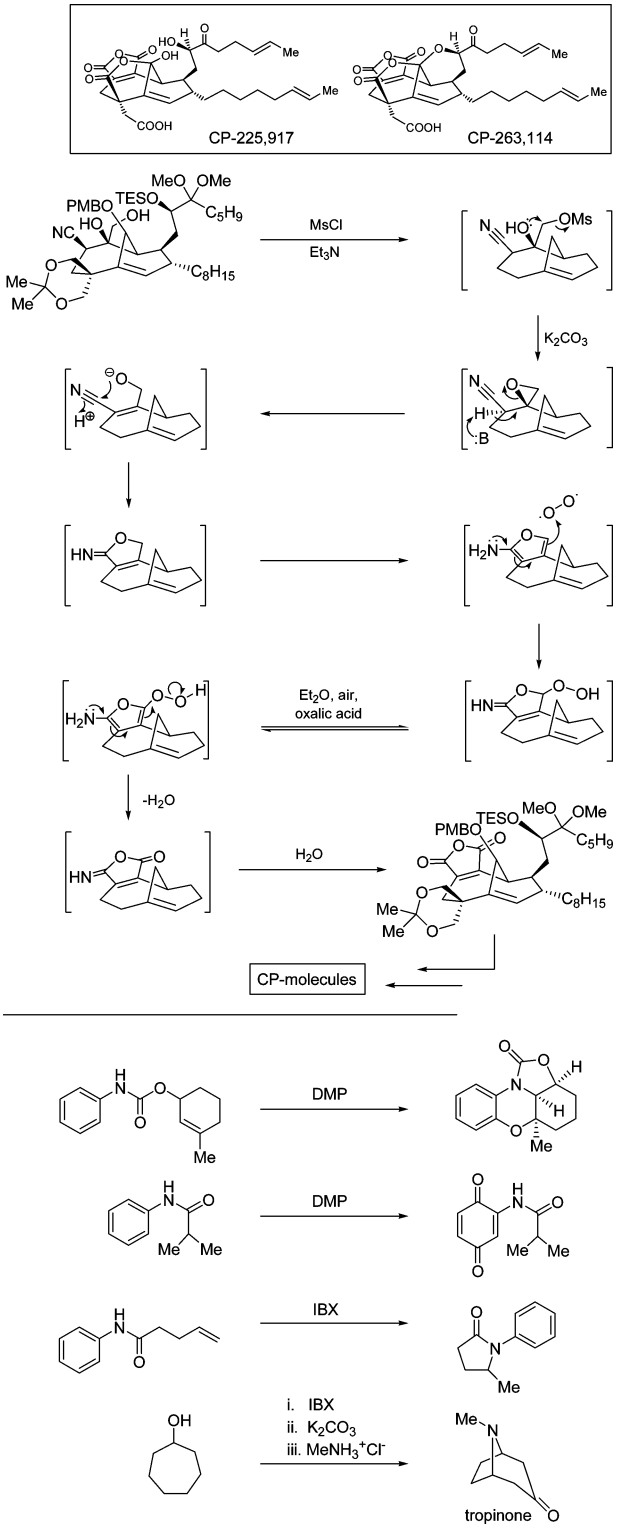

FIGURE 21. CP molecules, cascade reactions, and hypervalent iodine reagents in chemical synthesis (1999).

Sanglifehrin, with its unique spiroaminal and macrocycle, bearing two conjugated diene systems and several other novel structural motifs, established itself as a new structural type in the 1990s and, therefore, a worthy target for our attention. Soon it would prove its worthiness as a "foe" by forcing us to be inventive and by providing us with the opportunity to demonstrate new

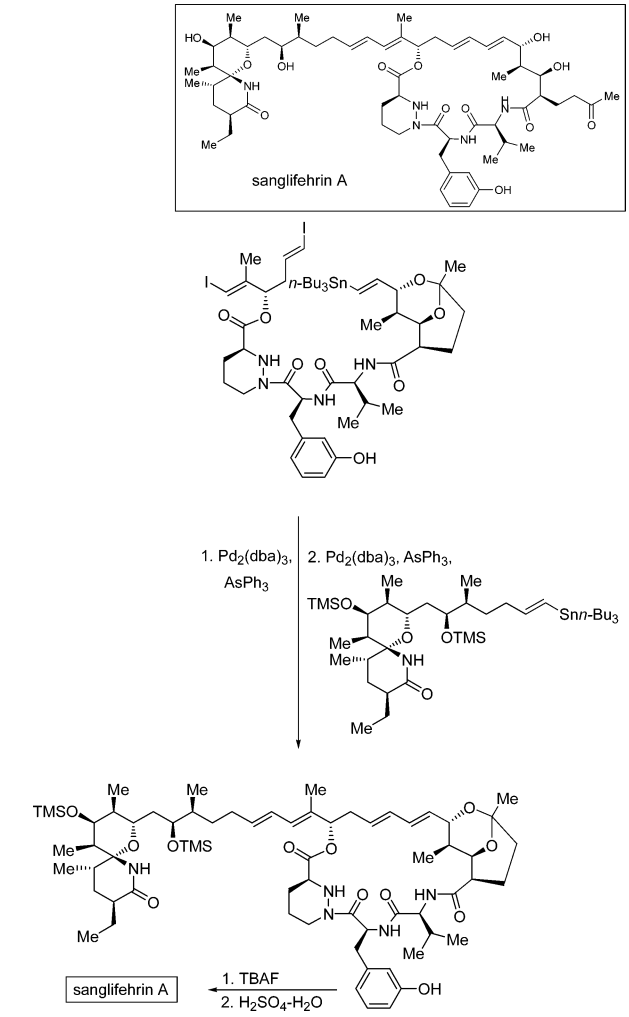

FIGURE 22. Sanglifehrin A and the Stille coupling reaction in total synthesis (1999).

aspects of the Stille coupling reaction in natural products synthesis as highlighted in Figure 22.[62]

The oligosaccharide class of antibiotics, just like the polyene macrolide antibiotics before them, boasted not only a growing number of defiant members, but also seemingly intransigent structural motifs. To cast the myths of impossibility aside, as in the case of amphotericin B a decade earlier, we chose the flagship of the group, everninomicin 13,384-1, as the target for total synthesis. This idea is not so different from that of targeting the king of an army faced in battle! And what a "king" everninomicin 13,384-1 turned out to be, this ever so adversarial molecule. Magnificent in its entire structure and armed with two sensitive but stereochemically sharp *ortho* esters, a 1,1′-disaccharide bridge, as well as several other glycoside bonds including 2-deoxy linkages with special stereochemical features, everninomicin 13,384-1 required new innovations in strategy and methodology for its construction. Sure enough, these new discoveries and inventions came by 1999, ensuring the final conquest of everninomicin through a path full of twists and turns, in addition to many joys. Among them, the 1,2-phenylseleno migration and the stereoselective *ortho* ester formation stand out as being particularly pleasing (Figure 23).[63]

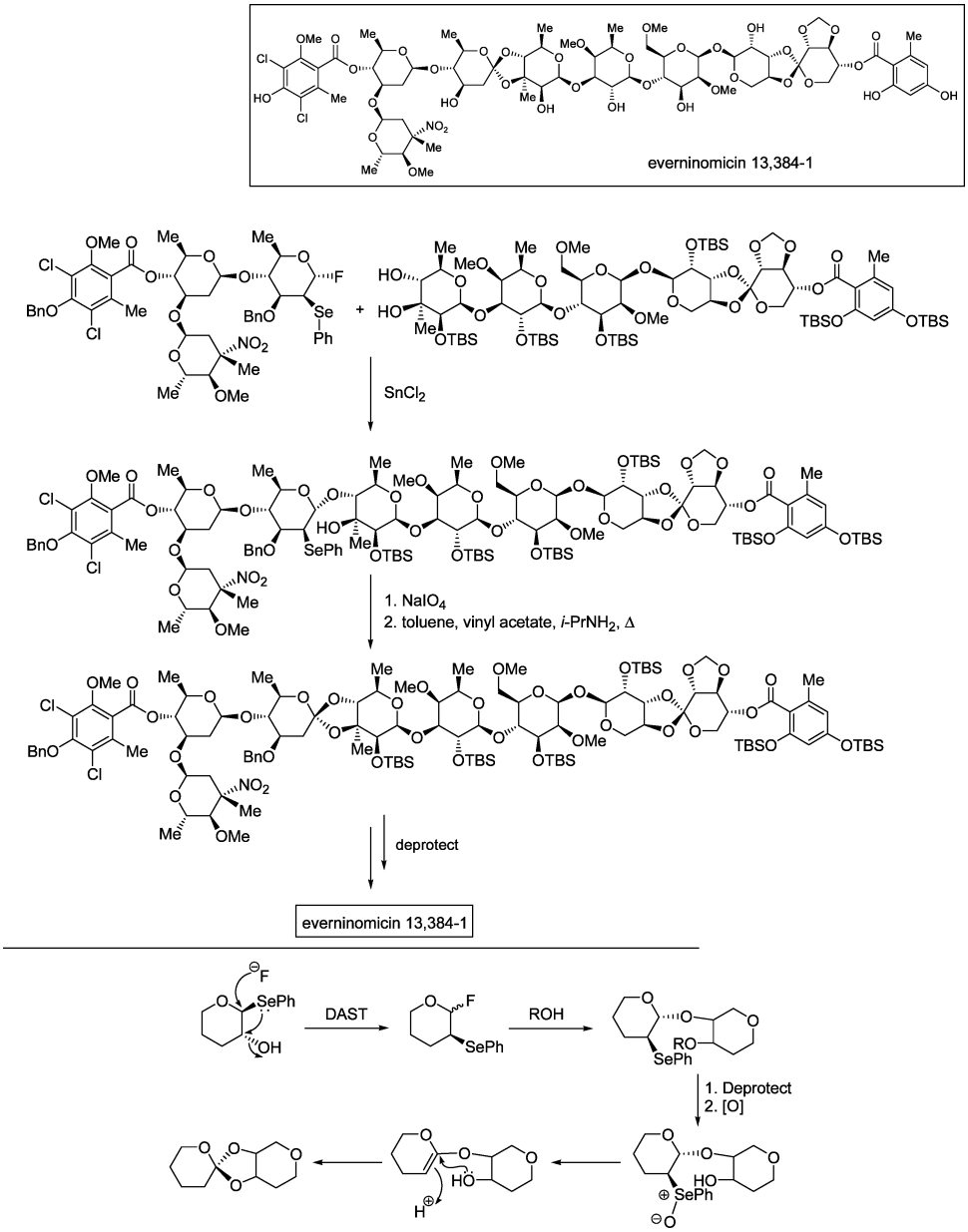

FIGURE 23. Everninomicin 13,384-1 and stereoselective *ortho* ester formation (1999).

We then came to bisorbicillinol, bisorbibutenolide, and trichodimerol, three beautiful molecules with intriguing and, therefore, inviting architectures. Collected together under the name of bisorbicillinoids, these natural products were also speculated to be connected in biosynthetic terms, heightening their appeal as synthetic targets. The appeal of their structures was surpassed only by the beautiful cascade-type reactions employed for their total synthesis, accomplished in 1999 (see Figure 24).[64] Indeed, on the basis of biosynthetic considerations, these cascade reactions were, in their nature, pleasingly reminiscent of the endiandric acid cascades that we experienced several years earlier at Penn.

A lean year as it was—for this happens in total synthesis as well!—2000 was not without its excitements, for this was the year of the benzopyrans,[65] the plakosides,[66] and epoxyquinomycin B.[67] But if this was a low year as measured by the number and complexity of targets synthesized, it was certainly not so in terms of enabling technological advances. Figure 25 summarizes some of the inventions of the year as they were applied to benzopyran-type libraries and which exemplify the contributions of the group to the solid-phase synthesis and combinational chemistry fields.

The year 2001 saw more impressive cascade-type, and biomimetically inspired, strategies reported as the group successfully completed the total syntheses of hybocarpone,[68] hamigerans A and B,[69] and colombiasin A.[70] Figure 26 depicts some of these novel strategies and tactics as they were applied to the total synthesis of the hamigerans.[71] Of particular joy was the ballet-like sequence to hybocarpone that began with a single electron transfer-based dimerization of a monomeric benzoquinone unit and ended with a spontaneous hydration of a fleeting hexacarbonyl intermediate (Figure 27).[72] While the colombiasin A total synthesis had its own moments

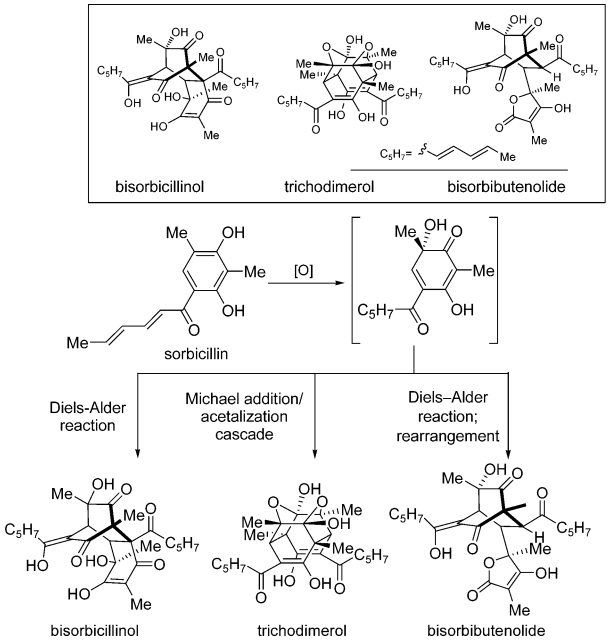

FIGURE 24. Bisorbicillinoids and biomimetic cascade reactions (1999).

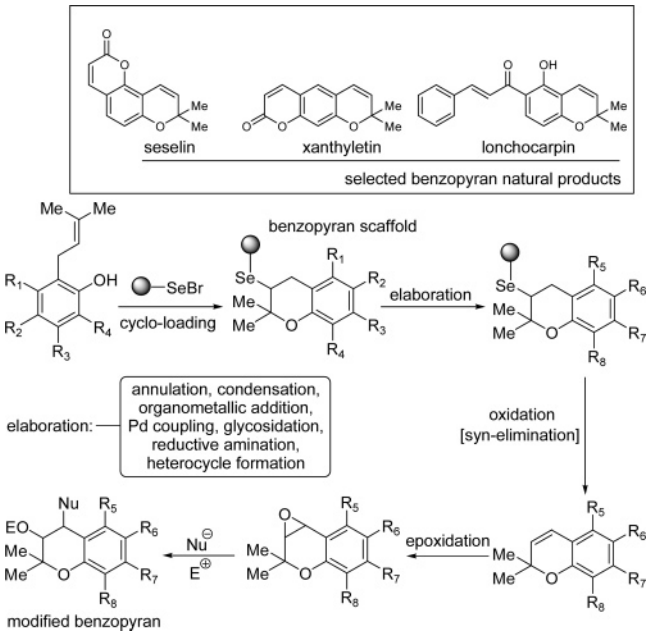

FIGURE 25. Benzopyran natural products and compound libraries thereof (2000).

of joy in terms of synthetic fireworks (see Figure 28), it also led to the assignment of the absolute stereochemistry of the natural product.[73]

Apoptolidin, a highly complex macrolide structure that had attracted our attention a few years earlier, was one of the other conquests of the group in 2001.[74] Full of adventure and frustrating ups and downs, this synthesis (Figure 29) will be remembered for the fierce resistance put up by the molecule in the final stages of the battle, as our struggle to rescue it from its protecting groups conflicted with its sensitive, often self-destructive, nature. Some attributed one of my rare visits to the hospital, for

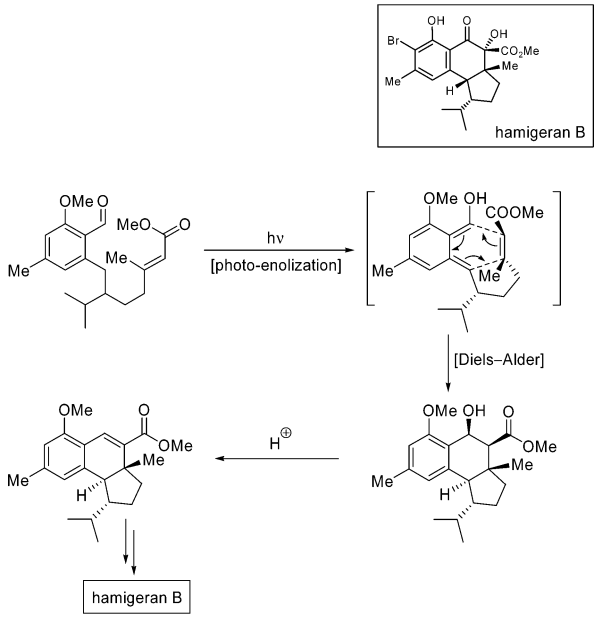

FIGURE 26. Photoenolization/Diels−Alder cascade sequences and total synthesis of hamigerans (2001).

a thyroid checkup, to the agony caused by this defiance! That we succeeded in capturing it intact is a credit to the heroic efforts of the team and their exquisite experimental skills.

Coleophomones B−D were all synthesized in 2002.[75] Particularly pleasing was the route to coleophomones B and C in which a common intermediate was diverted into two macrocyclization precursors, each of which served admirably and stereospecifically as the progenitor to a single geometrical isomer of the macrocycle from which the individual coleophomones B and C emerged. Representing the impressively growing body of metathesis applications in total synthesis,[76] this pleasant olefin metathesis-based flow of ring closures is summarized in Figure 30.

Another joyful event in the group in 2002 was the first total synthesis of diazonamide A,[77] a mysteriously connected marine-derived molecule whose originally assigned structure had been revised a year earlier following a synthesis of the nominal diazonamide A.[78] Besides confirming the newly proposed structure, the diazonamide campaign yielded a bounty of pleasing new synthetic technologies and strategies (Figure 31). Indeed, together with a second total synthesis of diazonamide A that would be completed in the following year (2003), these discoveries gifted us with joys that far outweighed the many disappointments and frustrations we encountered along the way.[79,80]

The structure of 1-*O*-methyllateriflorone represents the flagship of a rather large class of plant-derived natural products with unusual molecular architectures and diverse biological activities. The novelty of the structure lies not only in its cagelike [7.4.1.0.^{2,7}0^{2,11}]tetradecane system but also in its hemiquinone spiroacetal δ-lactone moiety whose seemingly fragile nature and stereochemical disposition is enough to scare away most synthetic chemists. A few, however, dared, including some from my own group, who were rewarded with the joy of forging together this molecule in 2003 in a most delightful way,

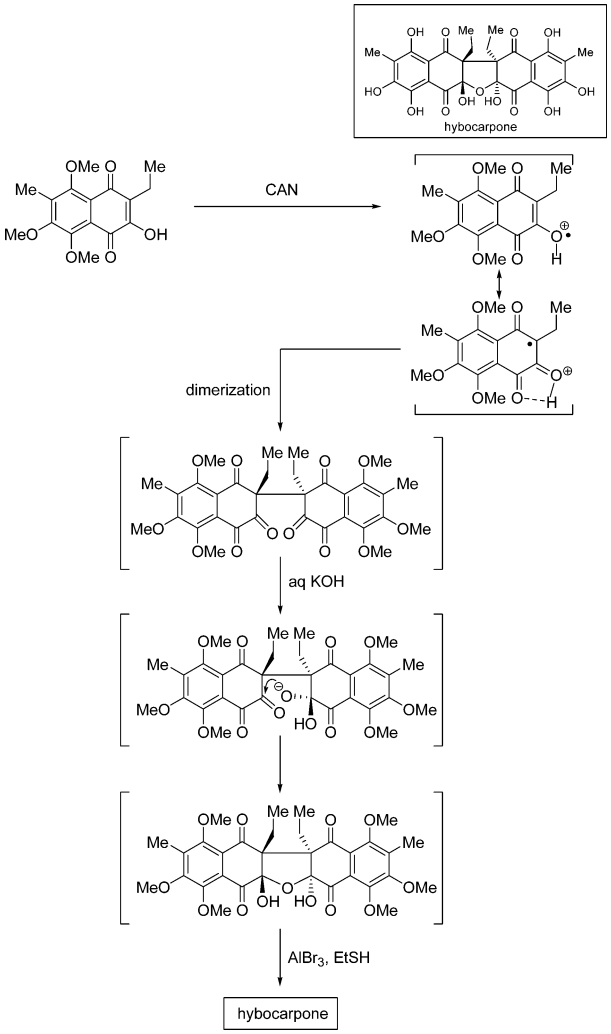

FIGURE 27. Hybocarpone and biomimetic cascade reactions in total synthesis (2001).

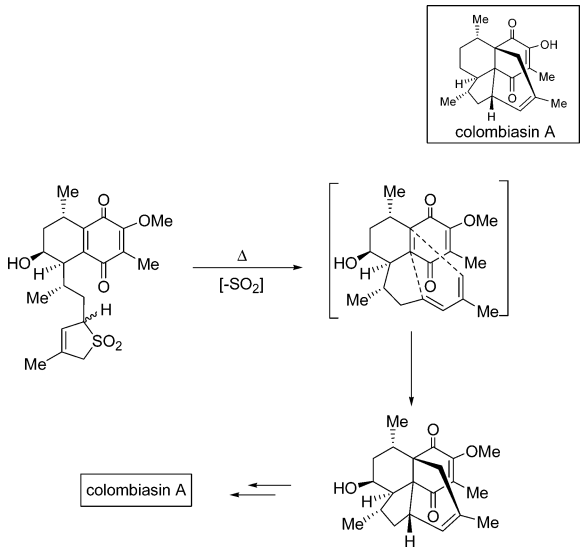

FIGURE 28. Colombiasin A and cascade reactions in total synthesis (2001).

whereby all its structural motifs and stereocenters found themselves in their right place (Figure 32).[81] I must admit that the stereochemical outcome in the last step of this

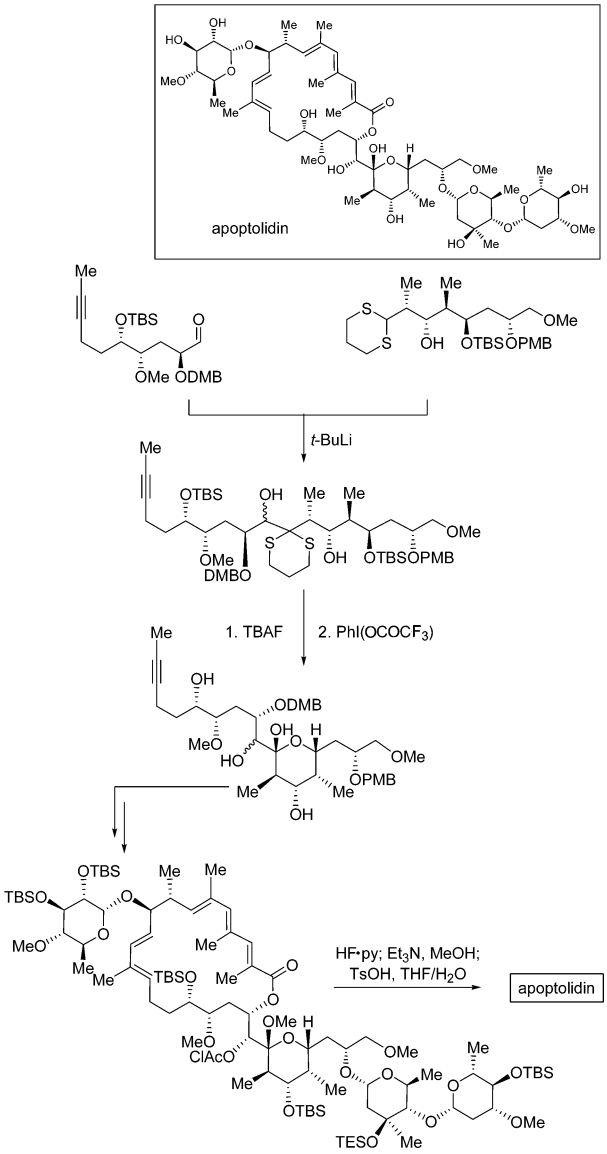

FIGURE 29. Apoptolidin and the careful final global deprotection steps (2001).

construction, uncertain as it was, proved once again that Mother Nature is not always cruel to synthetic chemists. Indeed, sometimes she responds positively to the faith we place in her to drive things in the right direction.

The year 2004 began with gambogin,[82] a relative of 1-*O*-methyllateriflorone and of 1-*O*-forbesienone that had previously (2001) been synthesized in our group.[81,83] Despite this achievement, undoubtedly the big trophies of the year were azaspiracid-1 and thiostrepton. A notorious marine neurotoxin, azaspiracid-1 poisons mussels whose consumption by humans causes serious health hazards, particularly in Europe. Its isolation in miniscule amounts allowed a structural elucidation that was published in 1998[84] and which stimulated much activity directed toward the total synthesis of this complex molecule. The race to construct azaspiracid-1 in the laboratory reached a milestone in 2003 when we synthesized the published structure.[85] This moment of joy was, however, fleeting as we realized that its assigned structure was wrong! Faced with the grim recognition of the

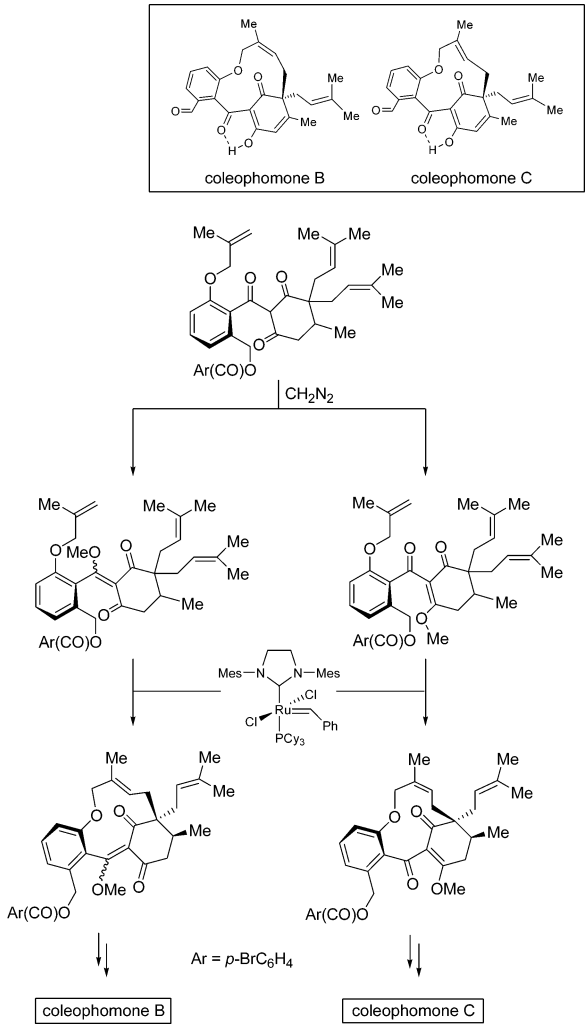

FIGURE 30. Coleophomones B and C and olefin metathesis in total synthesis (2002).

fact that we had been chasing the wrong molecule, we doubled our efforts to unravel the mystery of its true structure by chemical synthesis. The final joy came a year later in 2004 when, after a campaign that will read not unlike a detective story worthy of Sherlock Holmes, we finally arrived again at our "Ithaca" (see Figure 33 for some pieces of the azaspiracid-1 puzzle). With seven incorrect stereocenters and a double bond shifted out of position, the initially proposed structure misled and teased us for a while and held us at bay. This stretched our imagination and resolve, but in the end the struggle was worthwhile. Not only did we rejoice for the conquest that demystified the riddle of its molecular structure, including its absolute stereochemistry, but we could also share our joy of success with those biologists who were desperate for a sample of azaspiracid-1 in order to investigate its activity.[86]

Incidentally, this campaign, and that driven by diazonamide A mentioned above, prompted us to write their sagas within a review article entitled "Chasing Molecules That Were Never There: Misassigned Natural Products and the Role of Chemical Synthesis in Modern Structure Elucidation", in which we pointed out the frequent mistakes made in assigning structures to natural products.[87] However, we ourselves committed an ironic mistake in structural assignment, for in attempting

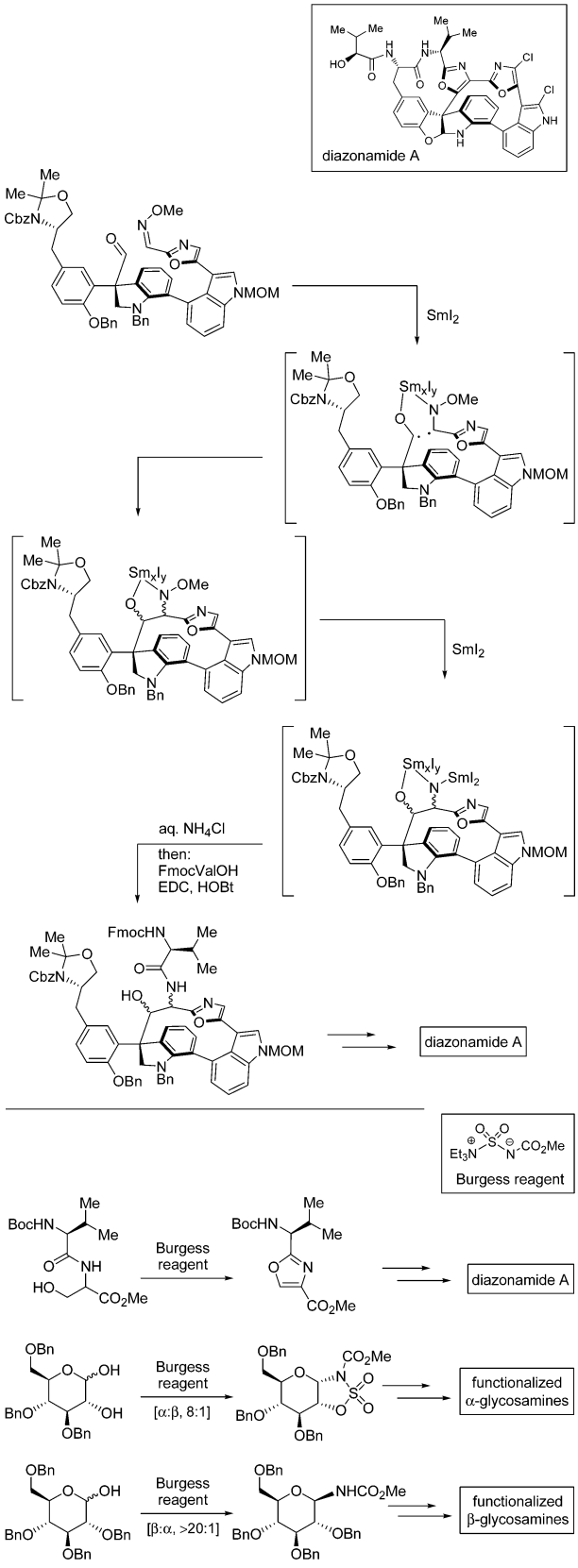

FIGURE 31. Diazonamide A and new applications of Burgess-type reagents in chemical synthesis (2002–03).

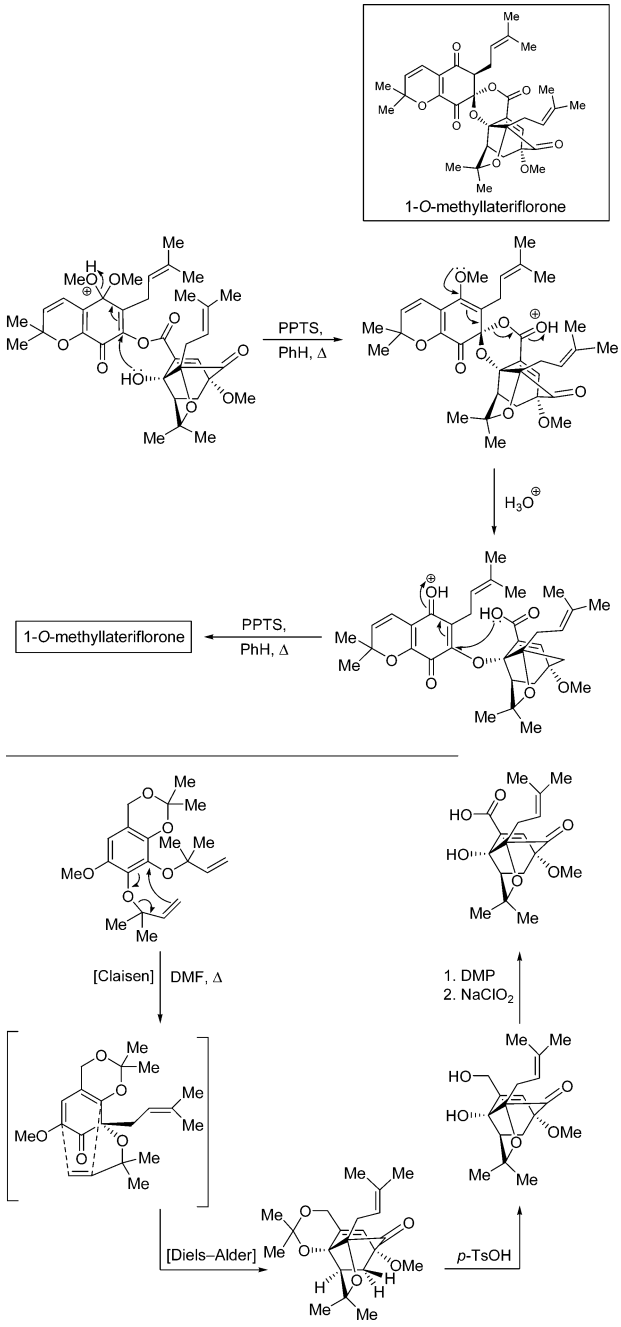

FIGURE 32. 1-*O*-Methyllateriflorone and cascade reactions in total synthesis (2003).

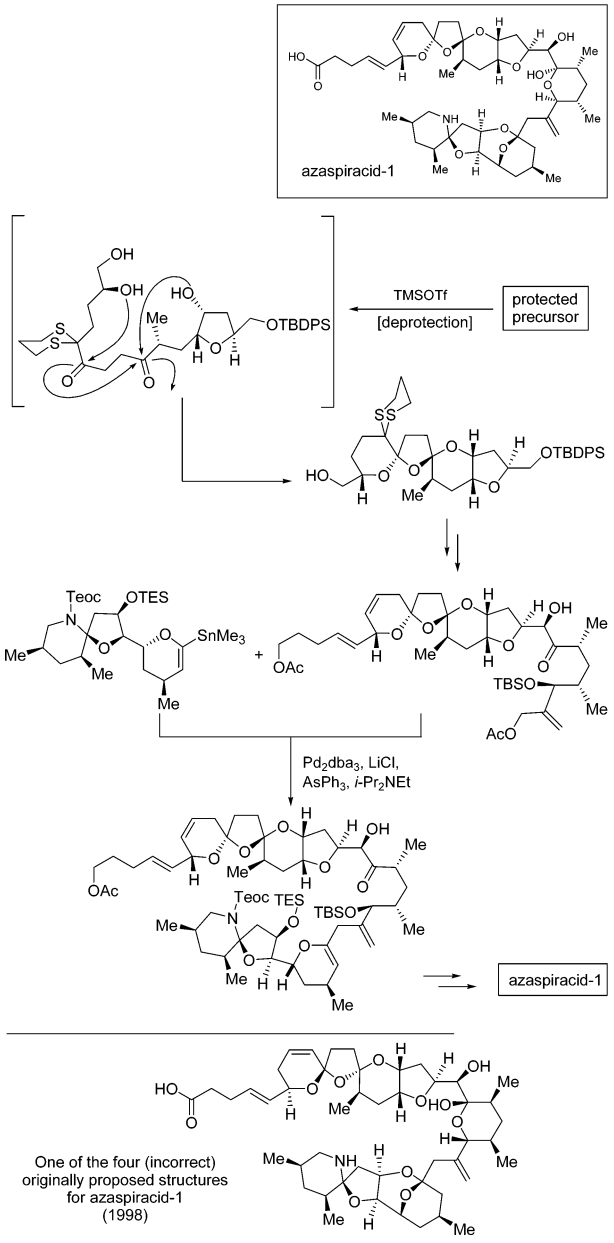

FIGURE 33. Azaspiracid-1 puzzle—finding and assembling the pieces of Nature's jigsaw (2004).

to show the historically important misassignment of the structure of cholesterol by Wieland and Windaus, we showed, on the first page, the wrong misassigned structure and, as if that was not enough, our structure included a pentavalent carbon! Needless to say, we were embarrassed, but thankful to the gentleman from Europe who politely pointed this out to us.

As alluded to above, azaspiracid-1 was not alone in surrendering its mystique in 2004. Not to be outdone, thiostrepton, a magnificent molecule endowed with impressive biological activities and reigning over the thiopeptide class of antibiotics, made its joyful debut on the scene of our conquests before the end of the year.[88] Possessing a striking molecular architecture, thiostrepton was enticing to us not only because of its highly complex and sensitive functionality but also due to our desire to pay another visit to the land of heterocyclic chemistry. This allowed us to take on yet another arrogantly standing molecular devil, the likes of which had never been seen before. Particularly provocative were its novel thiazoline- and quinaldic acid-containing macrocyclic rings, its dehydropiperidine core whose substituents included three thiazole rings and a primary amine residue, and its dehydroalanine tail. Indeed, it was there, within these particular structural motifs, that we encountered the most resistance as we approached this target molecule. But the joys of accomplishment kept coming, as one by one these challenges were met by intelligent design and redesign and skillful experimenting and re-experimenting. Of special intrigue was the taming of the dehydropiperidine core, whose Gordian

knot-like connectivity kept showing its mischievous character until it was finally capped safely in place by a peptide bond.

Another highly useful and pleasurable discovery of this project was the emergence of one of the mildest of methods for hydrolyzing a methyl ester group to the corresponding carboxylic acid. Indeed, this Me_3SnOH-based technology, developed as part of this campaign, saved the day for us time and time again, and in places where many other reagents failed to spare the molecule from destruction.[89] Figure 34 presents selected highlights of this memorable campaign, including the Diels–Alder dimerization of an aza-diene system to give the dehydropiperidine moiety, a process that must share the title of the most valuable reaction of the synthesis with the Me_3SnOH ester hydrolysis method. The latter must, however, concede to the former the crown for "the most beautiful reaction of the endeavor", for the hetero-Diels–Alder reaction was by far the most pleasing and joyful of them all!

I am often asked how we choose target molecules for total synthesis. This is not so different from asking an individual how he or she chose their partner, for often it is love at first sight that initiates the first move. Upon closer inspection and more intimate appreciation of the intricacies and inner character of the molecule, one can make a judgment as to its potential for discovery and invention (and for art!). While there is no formula to use, a number of criteria must be taken into consideration. The molecular architecture is paramount, for it is here that lies the problem of total synthesis itself. Is the structure new? And, if yes, is it challenging, or can it be made by well-established chemistry? Clearly, the more novel and challenging the structure, the more appealing it is because it is more likely to provide an opportunity to invent and discover new chemistry. We then look at the biological activity of the molecule, for here may lie an additional opportunity to contribute to biology and medicine. This is often possible through the design and synthesis of fine-tuned and novel variants of the natural product possessing improved biological and pharmacological properties. There are also other issues to be considered. Is the molecule associated with a special mechanism of action—known or speculative? Such characteristics may enrich the program considerably in terms of both inspirations and accomplishments. Additionally, one may ask, is the molecule associated with a novel biosynthetic hypothesis, proven or postulated, or can you conceive of a biosynthetic scheme? Here again may lie some unique opportunities to demonstrate some interesting cascade sequences or special reactions and to provide support for such biosynthetic conjectures. Another issue is, of course, that of supply, for the chemical synthesis of a scarce but biologically important substance may impact so heavily on biology and medicine as to override all other considerations. As we have seen above, total synthesis provides the final proof of the structure of a natural product, for even today, with all the technology we have at hand, structural misassignments are not uncommon. Last but not least, occasionally the structure is so beautiful that the connoisseur synthetic chemist does not need any further incentives to initiate the chase. An ideal synthetic target is one which fulfills all of the above criteria.

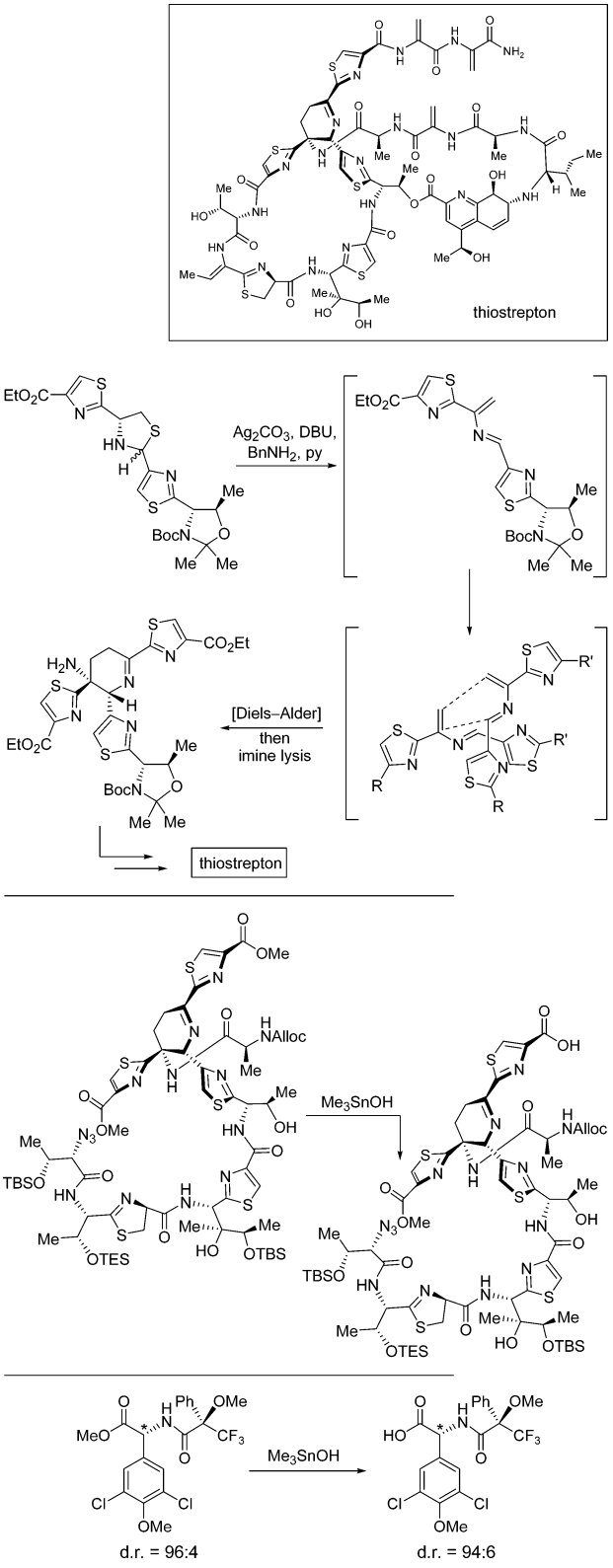

FIGURE 34. Thiostrepton campaign (2004).

Targeting natural products is also a matter of personal preference and choice. I believe that choices of molecules for synthesis reflect, among other things, the personality

of the practitioner, and as such they should be respected for what they are. For us, it is the structural novelty, artistic beauty, and biological activity that count the most, followed closely by the medical significance and mode of action of the molecule. As seen in this article, we have also chosen to target, in addition to complexity, molecular diversity as revealed by Nature. It is, thus, not an accident that you have seen in this Perspective representative molecules from classes as diverse as eicosanoids, macrolides, carbohydrates, glycolipids, polyethers, terpenoids, cyclopeptides, enediynes, thiopeptide antibiotics, alkaloids, and heterocyclic natural products of various types. We like to think that no molecule, no matter its structural type, is out of the reach of chemical synthesis. The real question, however, is how elegantly and efficiently can we synthesize such complex molecules, and it is here that the synthetic chemists have to concentrate their efforts the most. Chemical synthesis is an exceedingly exciting, challenging, and fulfilling discipline, one that will always appeal to those talented youngsters who are destined to shape it further and ensure the continuation of its proud tradition as they strive to equal or even surpass Nature at her own game.

Acknowledgment. In acknowledging the brilliant contributions of my many co-workers whose names appear on the cited papers, I wish to express one more joy, the pleasure of having been able to share with them all the joys described in this article. I also wish to express my humble thanks and appreciation to my wife, Georgette, and to my children, Colette, Alexander, Christopher, and P. J., for their understanding and unconditional love, without which my life would not have been so enjoyable and rewarding. My deep gratitude and appreciation are also extended to my long-serving staff members Vicky Nielsen Armstrong and Janise Petrey for their crucial contributions over the years and to Dr. James Crawford for his help with this manuscript. I gratefully acknowledge the National Institutes of Health, The Skaggs Institute for Chemical Biology, and my many friends from the pharmaceutical and biotechnology industries for their financial support over the years.

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