Pergamon

Bioorganic & Medicinal Chemistry 6 (1998) 1127–1152

BIOORGANIC & MEDICINAL CHEMISTRY

Chemical Genetics Resulting from a Passion for Synthetic Organic Chemistry

Stuart L. Schreiber

Department of Chemistry and Chemical Biology, Howard Hughes Medical Institute, and The Institute of Chemistry & Cell Biology, Harvard University, Cambridge, MA, 02138, USA

Seventeen years after completing my doctoral studies in synthetic organic chemistry at Harvard University with R. B. Woodward and Yoshi Kishi, I find myself back at Harvard, dreaming together with my students about a future where 'chemical genetics' provides seamless connections between chemistry, biology, and medicine. It is certainly not a world I envisioned in 1981. My love of synthesis has grown in unanticipated ways, and I never imagined that it would cause me to explore the functions of proteins in cells.

When I initiated my independent studies in May 1981 in the Department of Chemistry at Yale University, I knew nothing of biology, having never taken a course in modern biology. However, the aspects of organic chemistry that drew me to natural product synthesis, especially conformational analysis and reaction mechanism, together with explosive advances in neighboring disciplines, led naturally to the exploration of cellular processes. It also led to the tackling of these problems in a way that was unfamiliar to biologists. I am grateful to Sir Derek Barton for encouraging me to use this forum, the article that traditionally accompanies the Tetrahedron Prize for Creativity in Organic Chemistry, to review the events that led to what is referred to as chemical genetics, where natural products and natural product-like compounds are used to understand and control the cellular and physiological functions of proteins.

The first phase of my research, where stereoselective synthesis was used to prepare natural products. Planning my first Yale experiments while still a graduate student at Harvard, I studied the remarkable structure of periplanone-B, recently defined stereochemically through the collaborative efforts of Koji Nakanishi, Clark Still, and Jon Clardy.[1] Inspired by the rearrangement of vinyl allene oxides to cyclopentenones, I considered cascade rearrangement reactions that would energetically funnel downwards to the skeleton of periplanone-B. The plan for a periplanone-B total synthesis was eventually realized by my first graduate student, Conrad Santini, on Christmas eve of 1982 (Fig. 1).[2,3] It was the crude 'biological' assays with the synthetic pheromone that in the end would have its greatest impact on me. We searched successfully in the basement of the Chemistry building for females of *Periplaneta americana* (American cockroach), and then observed the remarkable influence of the pheromone on insect physiology. This experience reminded me of an earlier euphoric feeling, as an undergraduate at the University of Virginia, when I first became aware of molecules and chemical reactivity. Like envisioning a transition state in my mind's eye, I could imagine an intricate encounter of the pheromone with a (still) mysterious insect receptor, likely a protein. This idea was strengthened when Conrad and I witnessed an electrophysiological output on an oscilloscope following a puff of the synthetic pheromone onto a dissected cockroach antennae grasped with an alligator clip. Although our efforts (with Michael Lerner) to isolate the periplanone-B receptor proved unsuccessful, a seed had been planted.

My encounters with other natural products at Yale reinforced the research trail initiated by the periplanone-B project, as discussed below. While teaching a course in organic synthesis, a photocycloaddition reaction I had been discussing suddenly struck me as being related to the aldol reaction, which was attracting considerable interest in 1982. Immediately following the class, Amir Hoveyda, my second graduate student, and I brainstormed about the implications of the Paterno–Büchi reaction of furans and aldehydes to the aldol substructures contained within many natural products. Amir and Kunio Satake explored many facets of the 'photo-aldol' reaction,[4] eventually applying it to stereoselective syntheses of asteltoxin[5,6] and avenaciolide[3,7]

0968-0896/98/$—see front matter
PII: S0968-0896(98)00126-6

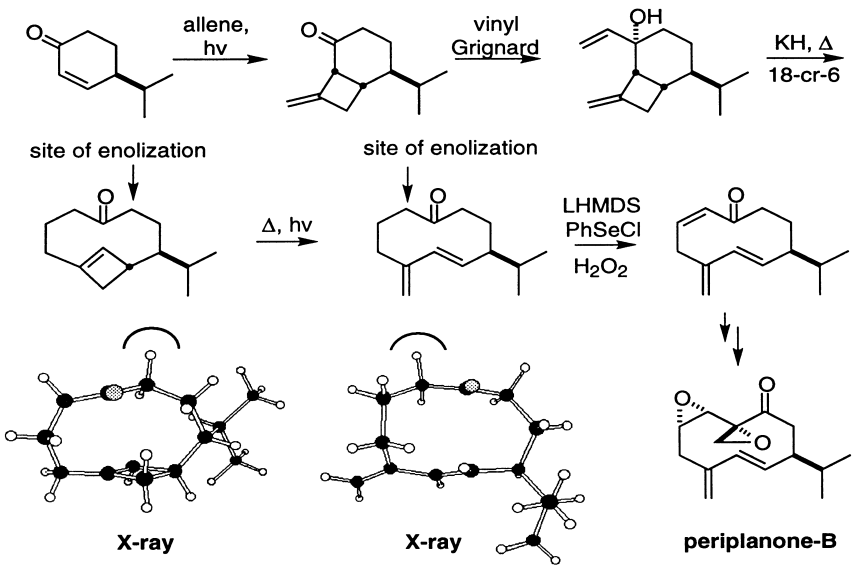

Figure 1. Cascade rearrangement reactions and conformational control of enolization in the course of a synthesis of periplanone-B. Semicircles indicate the preferred sites of enolization. These preferences can be rationalized by the conformations that the two ten-membered rings adopt in the solid state.[2,3]

(Fig. 2). Other natural product-based projects were initiated at this time. Considerations of medium and large ring conformations led Tarek Sammakia to develop stereoselective polyepoxidation reactions[8] (Fig. 3), Mike Klimas, Soroosh Shambayati, and Bill Crowe to develop stereoselective cyclooctanoid ring syntheses[9,10] (a process applied by Tim Jamison to the synthesis of the diterpene epoxydictymene[11] (Fig. 4)), and Jack Taunton, John Wood, and John Porco to synthesize methylated variants of dynemicin[12,13] (Fig. 5). Considerations of symmetry in natural product synthesis led Mark Goulet to determine the stereochemistry for the first time of members of the 'skipped polyol', polyene macrolide antibiotics, mycoticins A and B,[14,15] and Chris Poss and Scott Rychnovsky to develop a synthesis (+)-mycoticin A[16] (Fig. 6A and B). These synthetic studies illustrated the 'two-directional' chain synthesis strategy, where simultaneous double processing of chain termini and subsequent differentiation of the resulting homo-, enantio-, or diastereotopic groups at the chain termini are the defining features of the strategy.[17,18] The two-directional strategy has been used by a number of students and postdoctorals in studies resulting in syntheses of other natural products, including (+)-KDO,[19] (−)-hikizimycin[20,21] (Fig. 7) and (−)-FK506[22–24] (Fig. 8).

Each of the syntheses above had a similar, almost mystical effect on me personally. Like the original experience with periplanone-B, building these beautiful and complex natural objects from simple building blocks invariably led to a fascination with the cellular receptors to which they bind. I reasoned that these would often be proteins, themselves natural products. I began to puzzle over the conformational properties of proteins, especially the conformations of their sidechains that I envisioned wrapping around the 'small molecules' we had succeeded in synthesizing. This curiosity led me to a second phase of my synthetic chemistry research program. My move to Harvard in 1988 and my lab's research on FK506 catalyzed efforts in this area. The move forced me to think about the structure of the new labs I had been encouraged to design. Studying natural product interactions with proteins would surely require a lab equipped to handle proteins. Research on FK506 caused me to realize that an equally fascinating aspect of proteins concerns their functions inside of cells, and that natural products like FK506 (and now natural product-like compounds) could illuminate the mysteries of protein-mediated cellular processes in a powerful way.[25] So my new labs were designed to facilitate the synthesis of complex molecules, the analysis of protein–small molecule interactions, and the functions of proteins in cells.

The second phase of my research, where synthesis was used to respond to fascinating challenges posed by biology. Our efforts to apply the two-directional strategy to the synthesis of FK506 were initiated while we were synthesizing compounds designed to probe the interaction of another immunosuppressive natural product, cyclosporin, with its then recently discovered protein receptor,

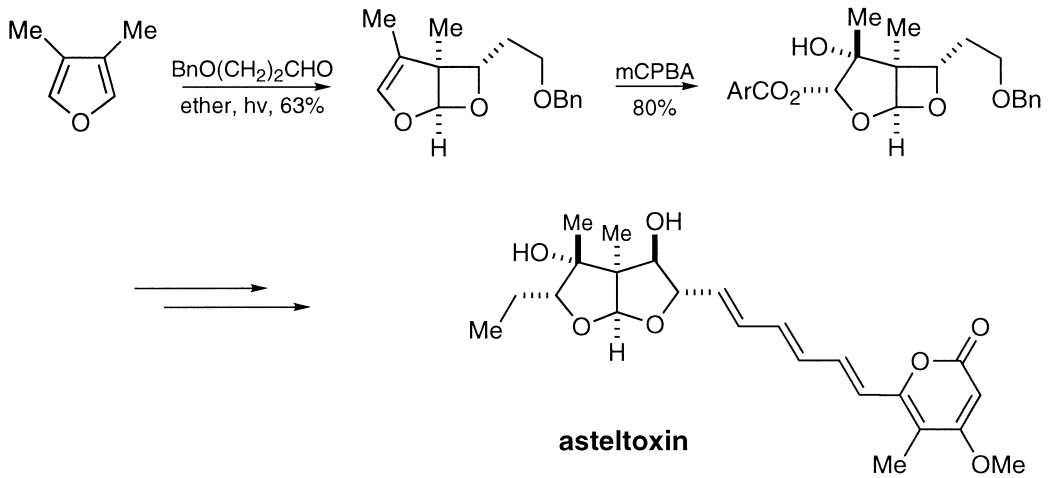

Figure 2. Application of the photo-aldol reaction to the synthesis of asteltoxin.[5,6]

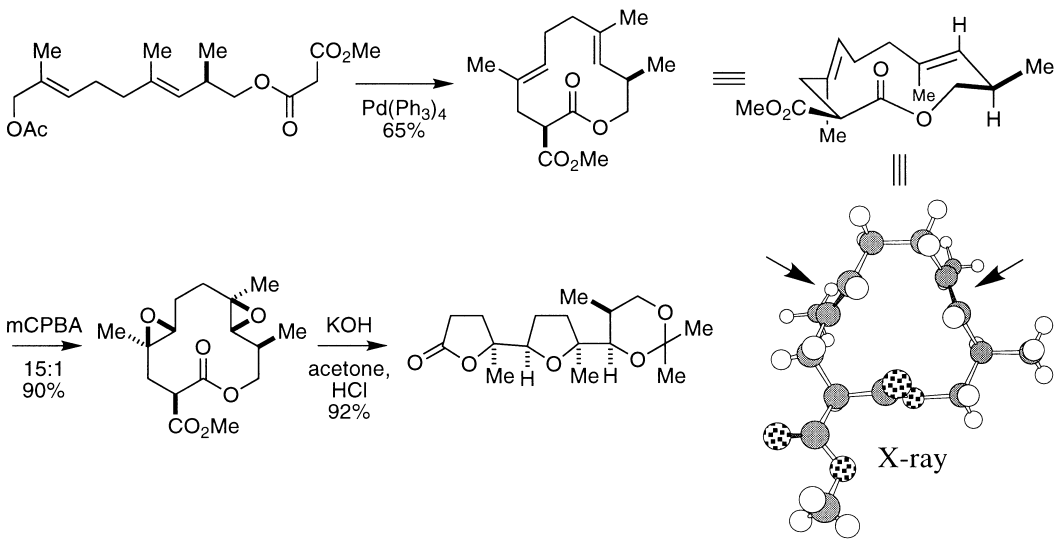

Figure 3. Conformational analysis leading to the design of a hexagonally shaped 12-membered ring. The epoxidation of the olefins proceeded as anticipated (see arrows), leading to a macrolide that was rearranged to a fragment found in the polyether antibiotic lonomycin.[8]

cyclophilin. The cyclosporin studies had sensitized us to the importance of understanding how FK506 exerted its actions on cells of the immune system. Our early plans to synthesize the FK506-related reagents that eventually led to the co-discovery (with scientists at Merck) of the FK506 and rapamycin receptor[26,27] (named FKBP12) and to the realization of a novel mechanism of cellular action (through our studies of the designed macrolide 506BD,[28,29] Fig. 9) were foolishly delayed by well over a year as I was caught up in a 'race' to synthesize the natural product. I learned from this mistake later when we were faced with the decision to either modify a protecting group strategy in order to finish a 'race' to synthesize natural dynemicin (rather than the methylated variants that Jack Taunton had just made), or to initiate new synthetic efforts to prepare trapoxin and trapoxin-related reagents. Trapoxin is a natural product that had been shown to alter the morphology of mammalian cells. Jack was unequivocal in his assessment of the relative merits of these two projects, and he immediately launched synthetic efforts aimed to illuminate trapoxin's mysterious actions on cells. His synthesis of the reagent we call 'K-trap'[30] (Fig. 10) proved to be the key advance that led to his discovery of the receptor for

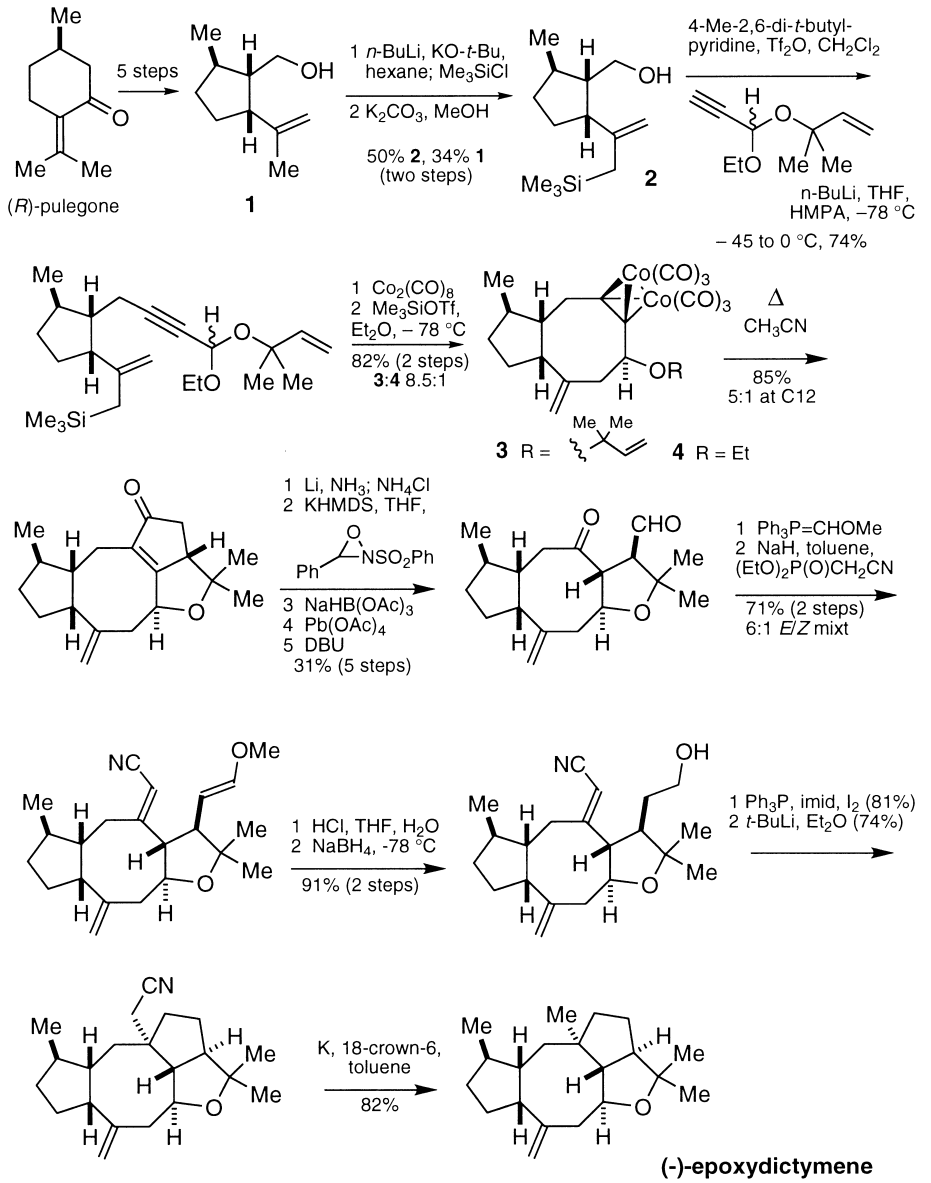

Figure 4. Organocobalt route to the synthesis of epoxydictymene.[11]

trapoxin, which we named histone deacetylase-1[31] (HDAC1), and then to an understanding of a novel mechanism for gene regulation involving this new family of HDAC proteins.[32–37]

These two studies illustrate some of our early efforts to explore cell biology using the principles of organic chemistry, with special reliance on organic synthesis.[25] It was an exciting period involving considerable change in the lab, and we were often faced with the need to learn new techniques, especially from molecular cell biology, in order to respond to research opportunities that our synthetic efforts had created. It was a period of time when we synthesized, among others, transmembrane ion channels having a gate that resulted from the rational incorporation of tartaric acid derivatives,[38–40] designed ligands to MHC[41,42] and immunophilin proteins (seco506[43] and tricycloCsA,[44] Fig. 11), and biopolymer-inspired oligomers of vinylogous amino acids (what Samuel Gellman refers to as 'foldamers').[45] But the most exciting moment came following a retrospective analysis of this research, when a general

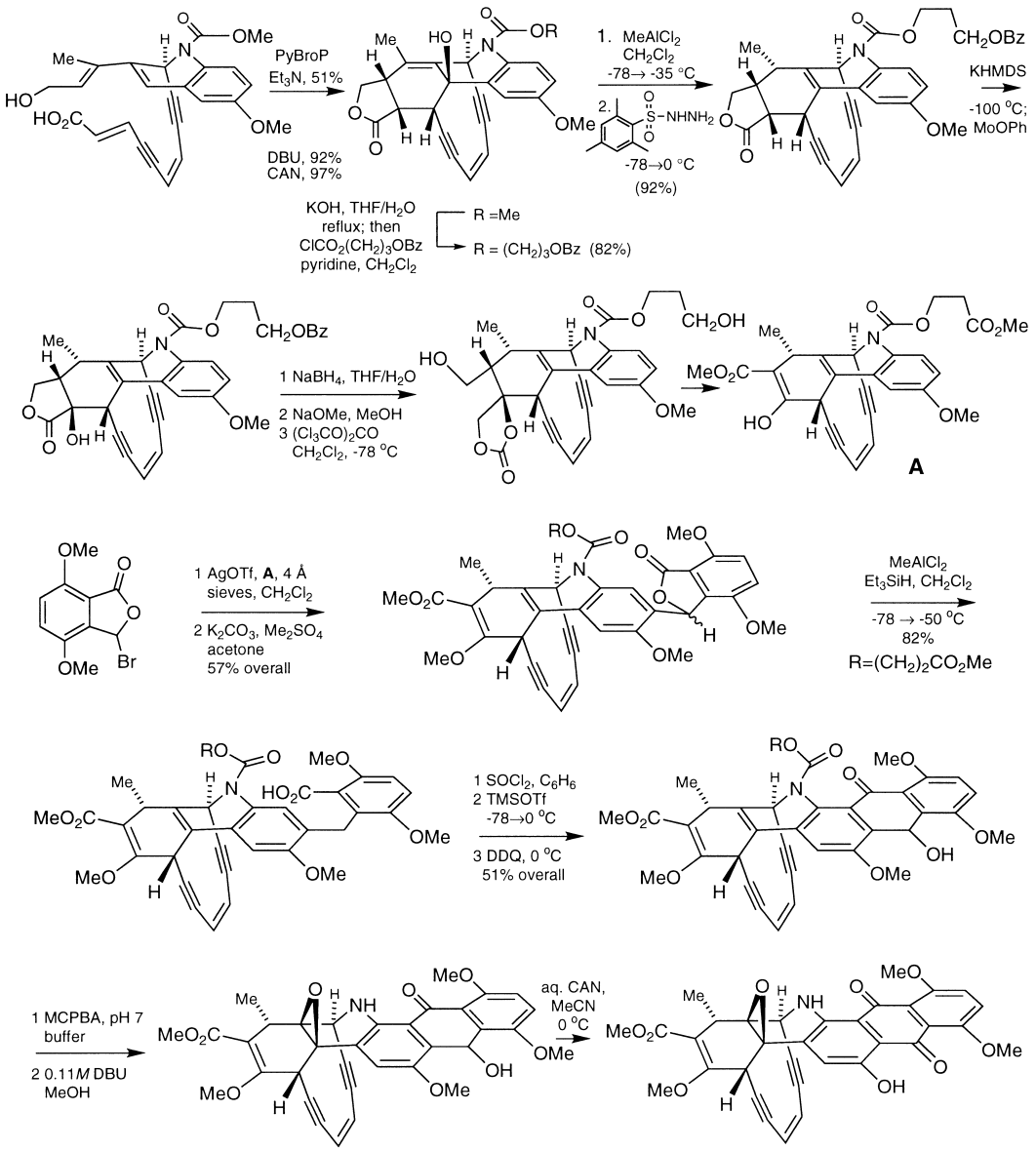

Figure 5. Transannular Diels–Alder route to methylated variants of dynemicin.[12,13]

approach to the study of protein function was recognized and eventually formalized. This approach forms the basis of all of our current research and will likely be the focus of research in my laboratory for many years to come.

Introduction to chemical genetics. Determining the cellular function of a protein generally requires a means to alter the function. The most common way of doing so is an indirect one involving the use of inactivating (e.g. deletion or 'knock-out') or activating (e.g. oncogenic) mutations in the genes encoding proteins of interest. This is the genetic approach, and it has been widely used in biology. A complementary and direct approach involves the use of small molecules that alter the function of proteins to which they bind (Fig. 12). Ligands exist that are capable of either inactivating (e.g. colchicine, which inactivates the function of tubulin) or activating (e.g. the steroid hormones, which activate the transcriptional properties of nuclear hormone receptors) protein function. This approach has been given a number of names, including the 'pharmacological approach'. So why do we give it a new name? I think the term chemical genetics is appropriate and important for

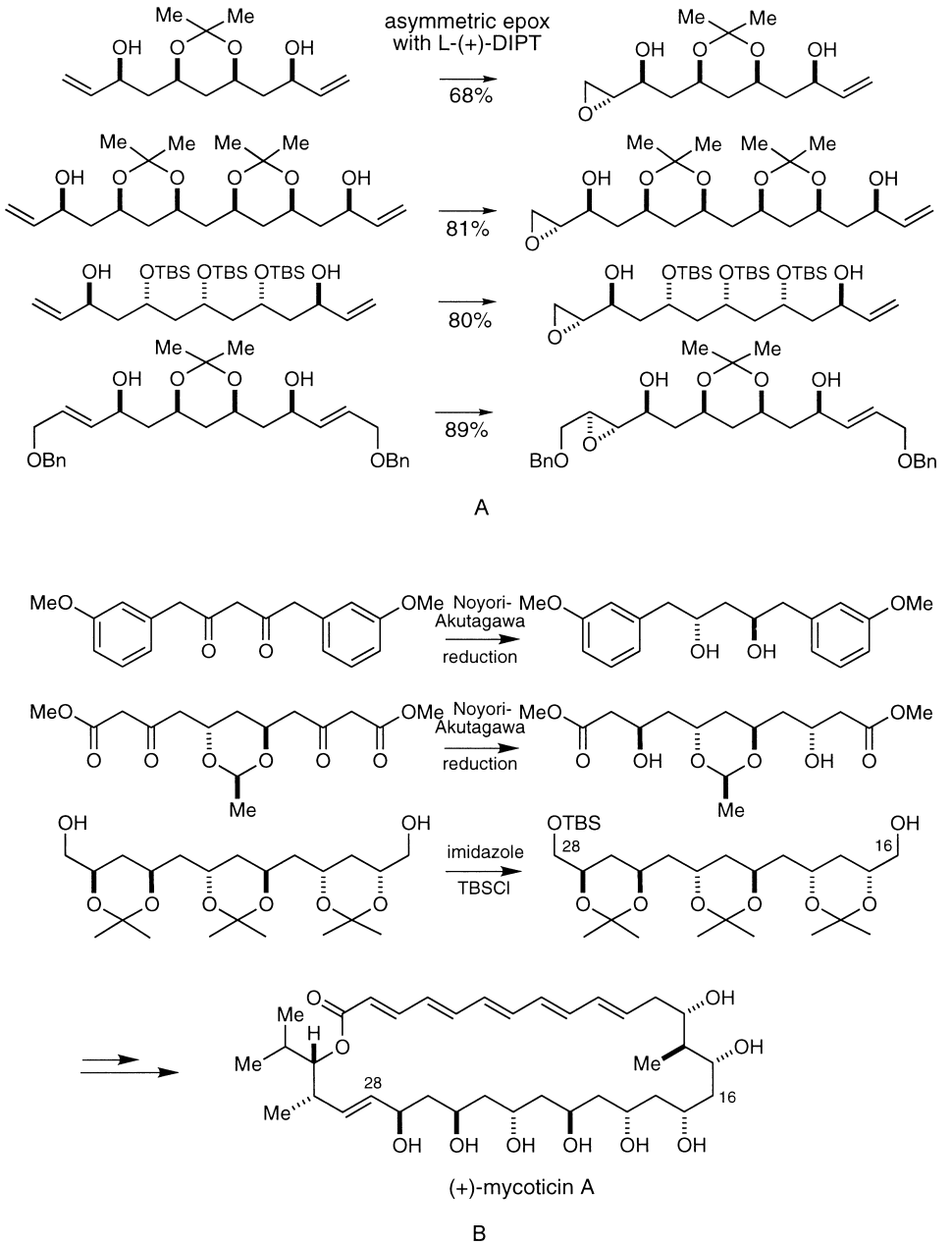

Figure 6. (A) Enantiotopic group selective reactions used in the two-directional chain synthesis strategy. Related reactions were applied to stereochemically defined syntheses of degradation fragments of (+)-mycoticin.[14,15] (B) Two-directional strategy applied to the total synthesis of (+)-mycoticin.[16]

three reasons. First, it 'raises the bar' in terms of specificity. Biologists often believe that organic compounds lack the specificity inherent in the deletion of a gene. They are correct in some instances, but not all. We have initiated some experiments using chip-based hybridization technology where the influence of small molecules and gene knock-outs can be compared directly (where the gene encodes the protein to which the small molecule binds). The preliminary results suggest that for some natural products, specificity can approach that of a gene knock-out. The second reason is that the name chemical genetics raises the bar in terms of generality. The genetic approach to understanding protein function can be time-consuming, but it is general. The chemical

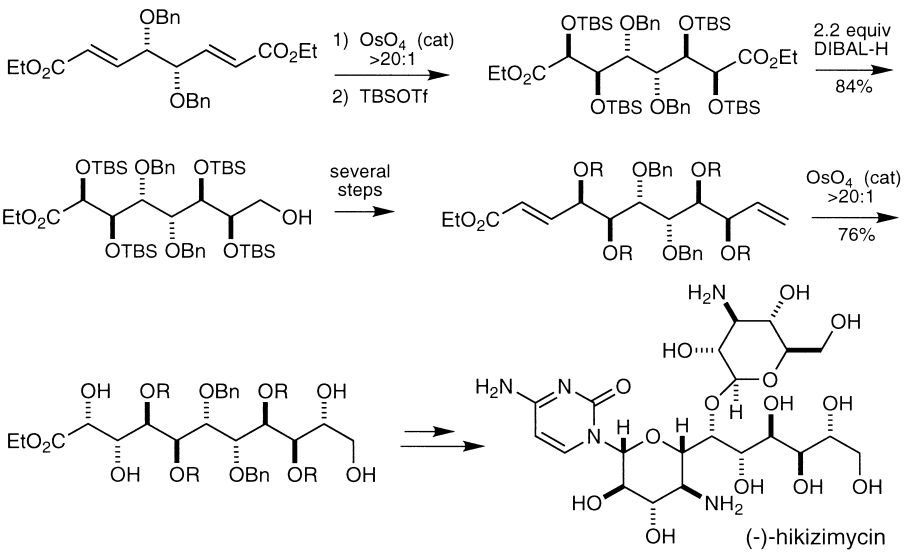

Figure 7. Two-directional strategy applied to the total synthesis of (−)-hikizimycin.[20,21]

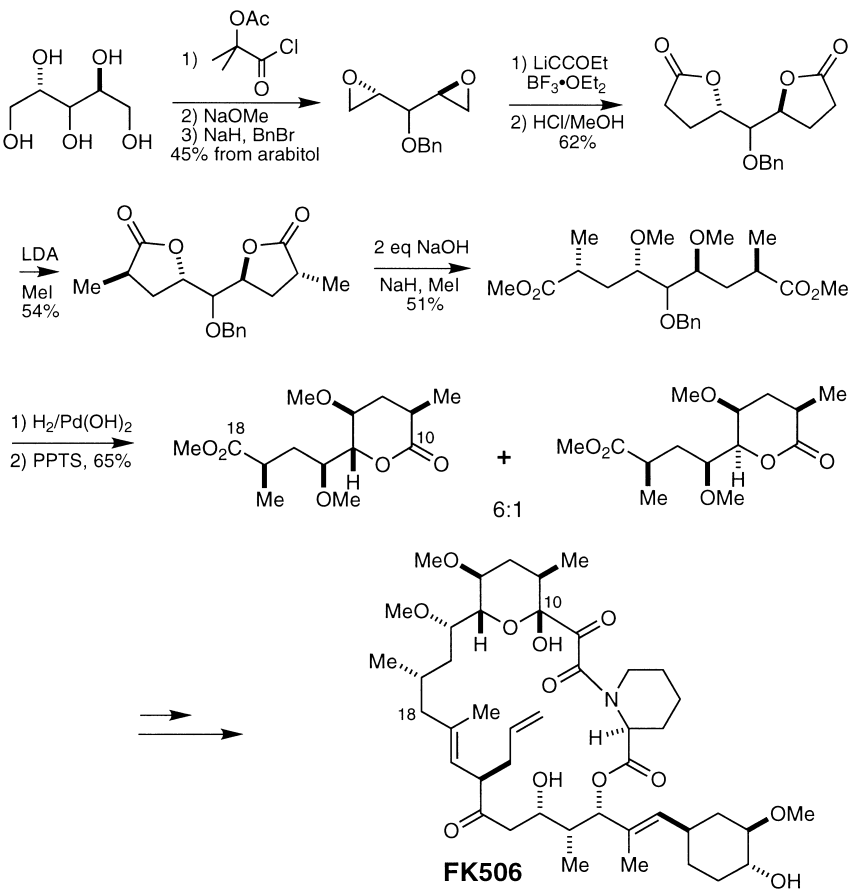

Figure 8. Two-directional strategy applied to the total synthesis of (−)-FK506.[22,23]

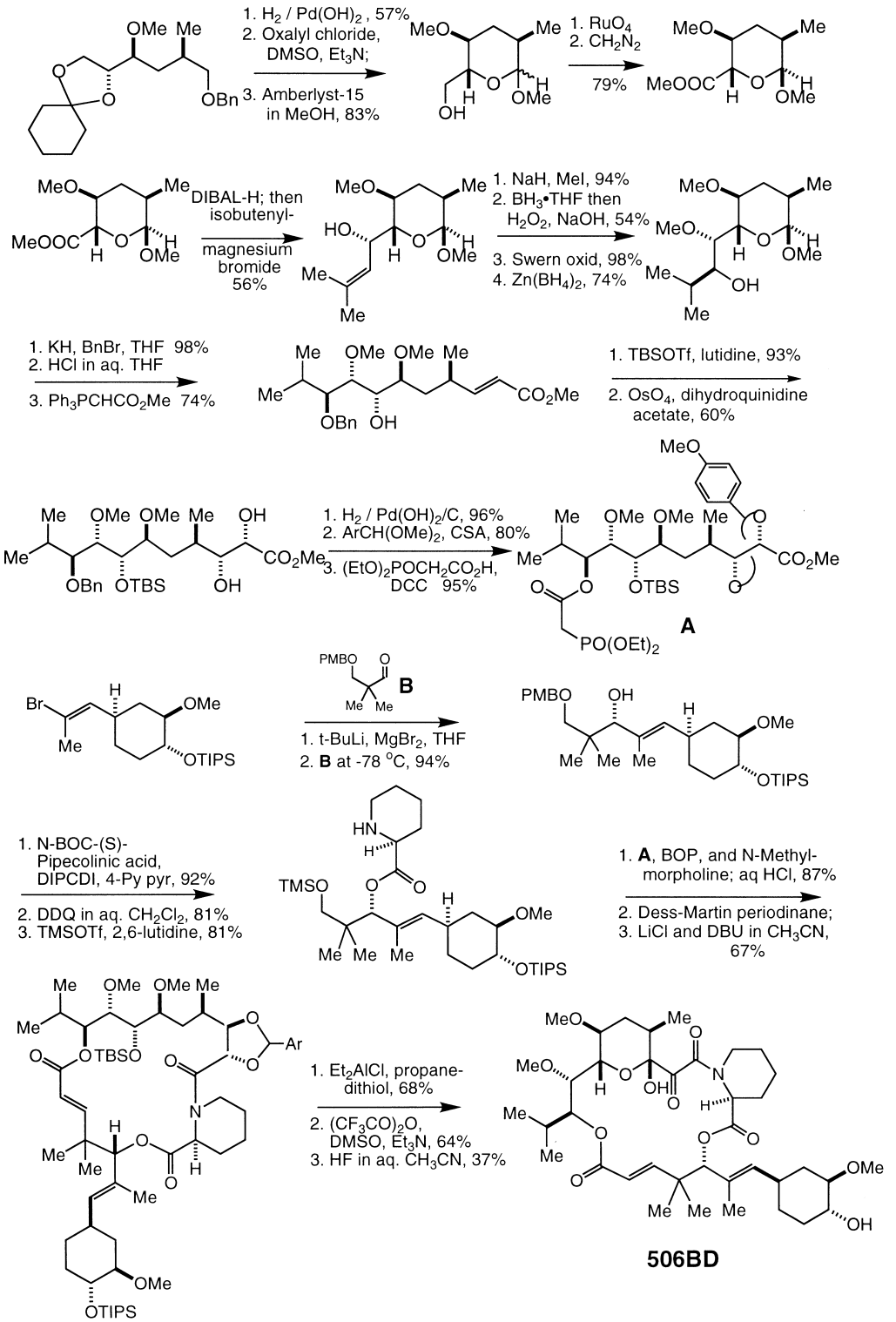

Figure 9. Synthesis of the immunophilin probe reagent 506BD. Cellular studies using 506BD led to the realization that the binding of FK506 and rapamycin to FKBP12 results in its gaining two new and distinct functions.[28,29] Later, we showed that the new functions are the ability to bind calcineurin and FRAP, respectively.[47]

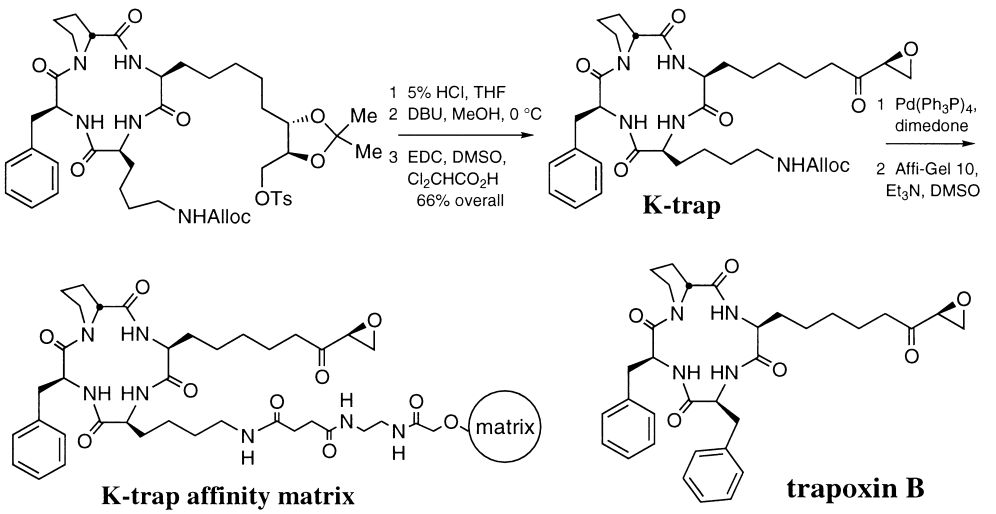

Figure 10. Total syntheses of trapoxin B and a trapoxin B-based affinity reagent named K-trap, which was used to discover the receptor for trapoxin, the nucleosome remodeling enzyme histone deacetylase-1 (HDAC1).[30,31]

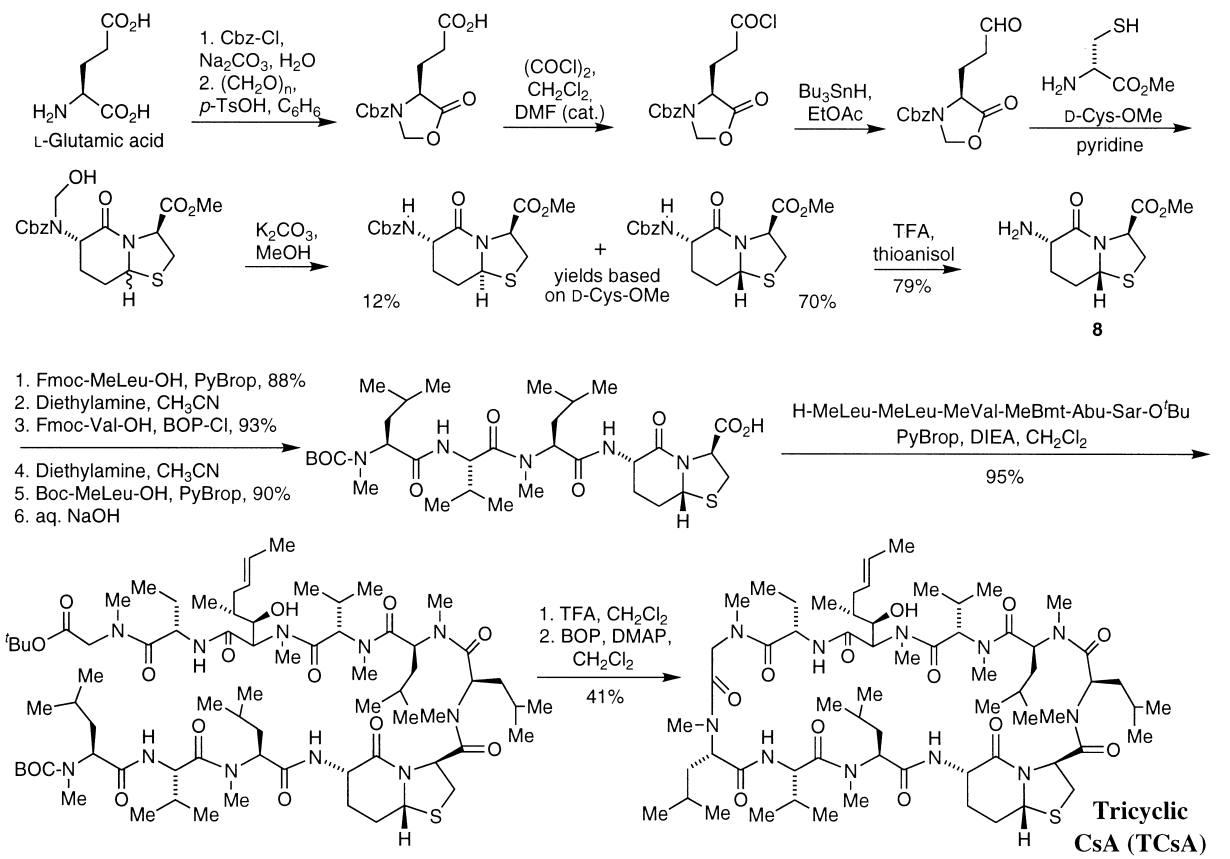

Figure 11. Synthesis of the immunophilin probe reagent tricyclosporin (TCsA).[44]

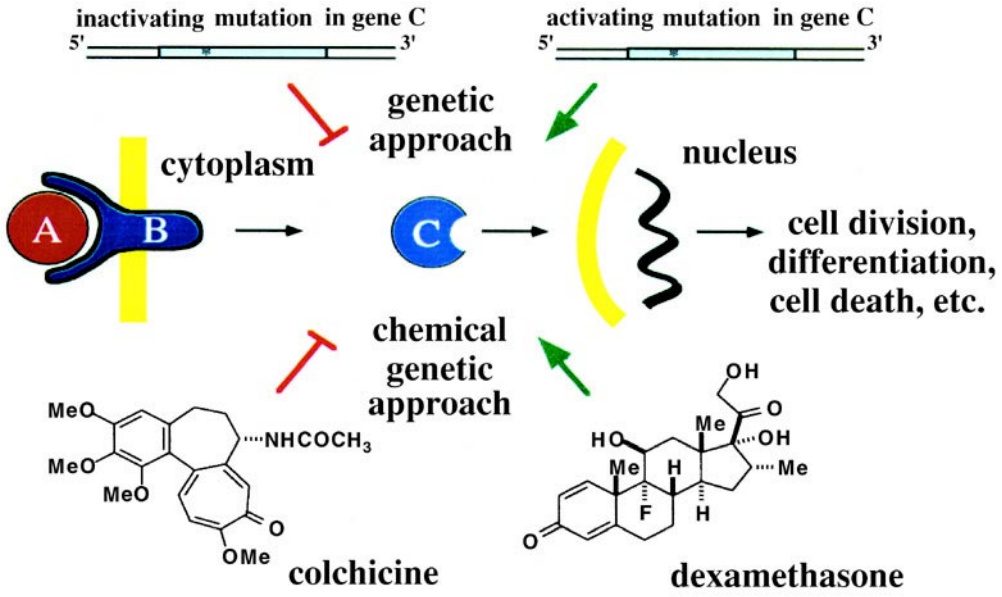

Figure 12. Both small molecules and mutations have been used to explore protein function. This figure emphasizes the relationship of genetics and chemical genetics (see: www-schreiber.chem.harvard.edu).

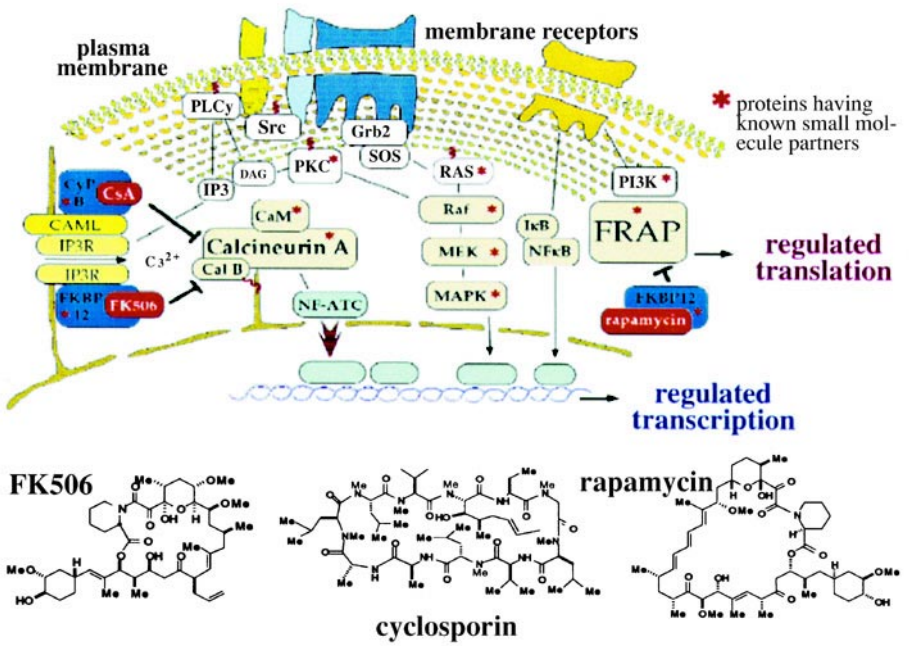

Figure 13. Small molecule-based studies of signal transduction and the chemical structures of three natural products that have been used to gain new insights into calcineurin and FRAP-dependent signaling.[47]

genetic approach relies upon the existence of highly specific ligands, which at this point come primarily from Nature and exist for only a limited set of proteins. The third reason for using the name chemical genetics is that it points to a means to achieve specificity and generality, by emulating the principles of genetics with chemistry. These three points are elaborated further.

Chemical genetic research. During the past 10 years, we synthesized numerous natural products and their variants

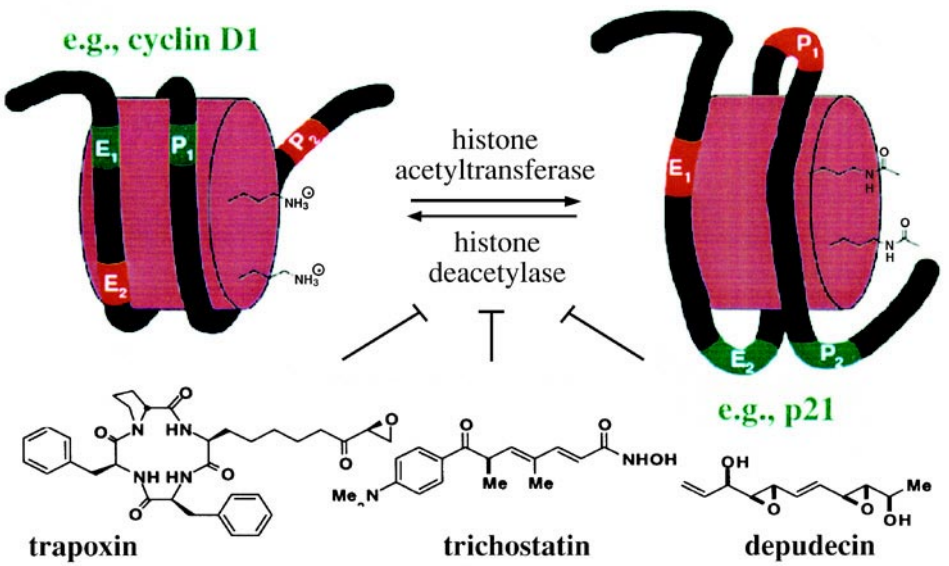

Figure 14. Small molecule-based studies of gene regulation and the chemical structures of three natural products that have been used to gain new insights into histone deacetylase-dependent nucleosome structure and function.[30–37]

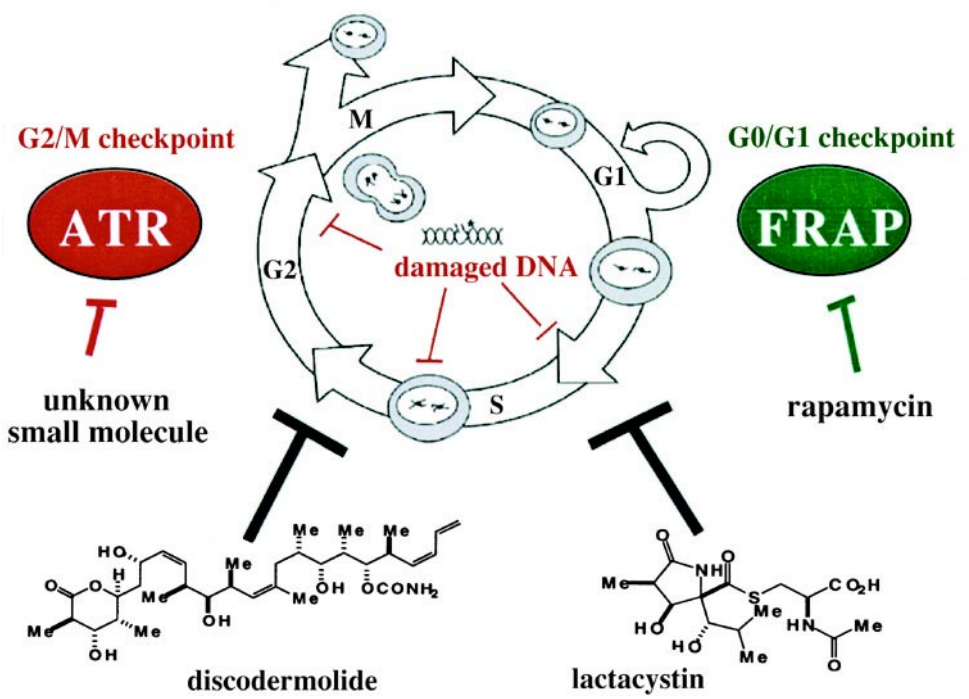

Figure 15. Small molecule-based studies of the cell cycle and cell cycle checkpoints and the chemical structures of two natural products (discodermolide and lactacystin) that have been used to gain new insights into mitotic spindle and proteasome-dependent cell cycle progression.[50–55]

in order to provide the means to explore the function of cellular proteins. FK506, cyclosporin, and rapamycin are used to study signal transduction[26,46–48] (Fig. 13). Trapoxin,[32,33] trichostatin,[33] and depudecin[37,49] are used to study gene regulation by HDAC-mediated chromatin remodeling[34–37] (Fig. 14). Discodermolide[50–53]

and lactacystin[54,55] are used to study the cell cycle and cell-cycle checkpoints (Fig. 15). However, these studies also illustrate the greater generality of genetics when compared to chemical genetics. Rapamycin was used to discover the protein FRAP, which mediates a cell cycle checkpoint.[48] While searching for homologs of FRAP, Karlene Cimprich, Tae Bum Shin, and Curtis Keith discovered the protein ATR,[56,57] which mediates a DNA damage checkpoint.[58] Since a small molecule ligand to ATR is not known, in contrast to the situation with its family member FRAP, the approach we have used to explore ATR function thus far has relied on the use of mutant forms of ATR, produced by making mutations in the DNA encoding ATR.[58]

The first illustration of a more general role for chemical genetics came from our studies of small molecule 'dimerizers' (sometimes referred to as chemical inducers of dimerization, CIDs). During the past five years my lab has participated in an exciting and fruitful collaboration with Gerald Crabtree and his co-workers at Stanford to prepare small molecule dimerizers that activate the function of numerous proteins that regulate many important cellular processes.[59] As I will discuss below, dimerizers allow the functions of proteins to be explored even when small molecule ligands are unknown. A limited number of such reagents have been synthesized that control the function of a much larger number of proteins (expressed as fusions of proteins of interest linked to a small molecule-responsive dimerization domain), and the list of proteins will undoubtedly grow without the need to make more dimerizers. These are unique features of the system our two labs has developed, and it is these features that provide the means to apply chemical genetics in situations where small molecules that bind to a protein of interest have not yet been identified.

At the outset of our studies, several experiments were beginning to suggest an important role for proximity and orientation effects in mediating information transfer in biology, in direct analogy to the role of these effects in determining the rates of reactions in organic chemistry[60,61] (Fig. 16). In fact, the biological outcomes are due to an increased rate of chemical reactions between biological molecules, often an enzyme and its substrate. For example, a protein growth factor such as PDGF can transmit a signal across the cell membrane by causing the intracellular tail of its receptor to phosphorylate itself. This occurs because the tail has protein kinase activity, its substrate is another molecule of itself, and the growth factor dimerizes its receptor (Fig. 16). The growth factor has rendered the phosphorylation reaction essentially intramolecular by inducing a proximal relationship between the enzyme and its substrate. Like the indicated transesterification, the growth factor (or bicyclic ring system) has increased the effective molarity of the reactants. In both cases, the result is an increase in the rate of the associated reaction. However, proximity alone does not ensure a high effective molarity and large reaction rate. This point is made by a famous reaction conceived and studied by Albert Eschenmoser,[62] where an improper orientation of reactants results in a slow rate of intramolecular reaction (Fig. 16). This is reminiscent of the

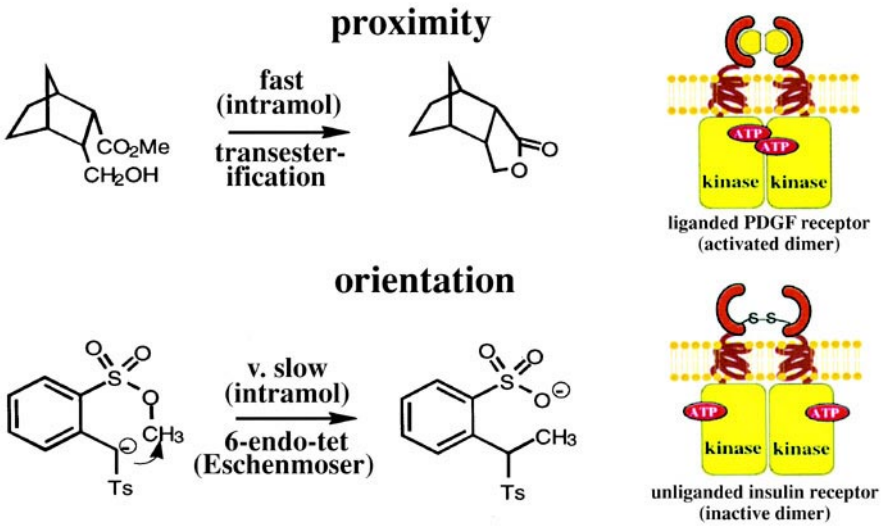

Figure 16. Effective molarity in chemistry and biology. Both proximity and orientation play a role in chemical and biological processes facilitated by achieving a high effective molarity.[59,60]

insulin receptor, which is a disulfide-bonded dimer in the absence of its activating ligand, insulin. Despite this enforced proximity, the receptor does not transphosphorylate itself in the absence of insulin. Presumably the kinase active sites are improperly oriented in the unliganded dimer, and insulin induces a reorientation that facilitates transphosphorylation. Effective molarity is controlled by proximity and orientation effects, and these are relevant to both chemistry and biology.

Our small molecule dimerizers have proved to be powerful reagents for controlling the cellular and physiological functions of proteins (usually by activation) and have illuminated the fundamental roles of proximity and orientation effects in biology in a variety of contexts.[59–61]

Signal transduction pathways have been activated and genes have been regulated in cells and transgenic animals by a variety of semisynthetic compounds. For example, our two labs have developed several methods to activate the Fas receptor-mediated signaling pathway that cells use to kill themselves (Fig. 17).[63–65] The dimerizer procedure involves expressing in cells or transgenic mice target proteins fused to a second protein that serves as a small molecule-dependent dimerization site (e.g. Fig. 18). We have synthesized both dumbbell-shaped (as in Figs 18–21)[63,65–68] and rapamycin-shaped (as in Figs 22–24) dimerizers,[69] and these molecules have been used to activate signaling pathways by either dimerizing receptors at the cell surface (e.g. the insulin,[70] erythropoietin,[71] PDGF,[70]

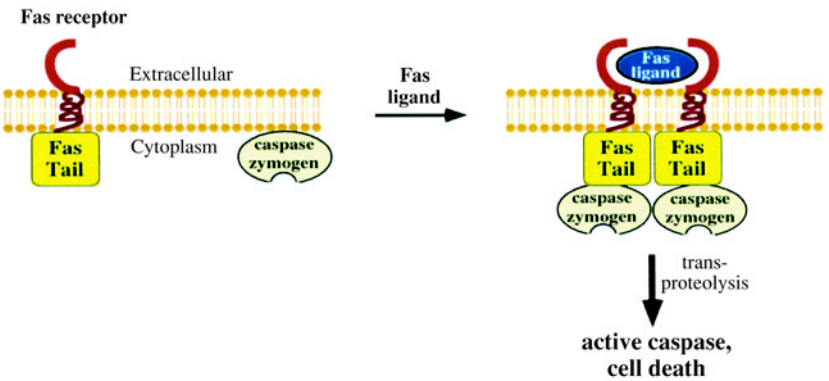

Figure 17. Many membrane receptors, including the Fas receptor, are activated by an extracellular protein ligand that dimerizes or oligomerizes the receptor, causing the intracellular tails to have a proximal relationship. As these tails, and sometimes tail-associated proteins, often have an enzyme–substrate relationship, ligand-induced dimerization achieves a high effective molarity of the enzyme and substrate and thus a large reaction rate.[61]

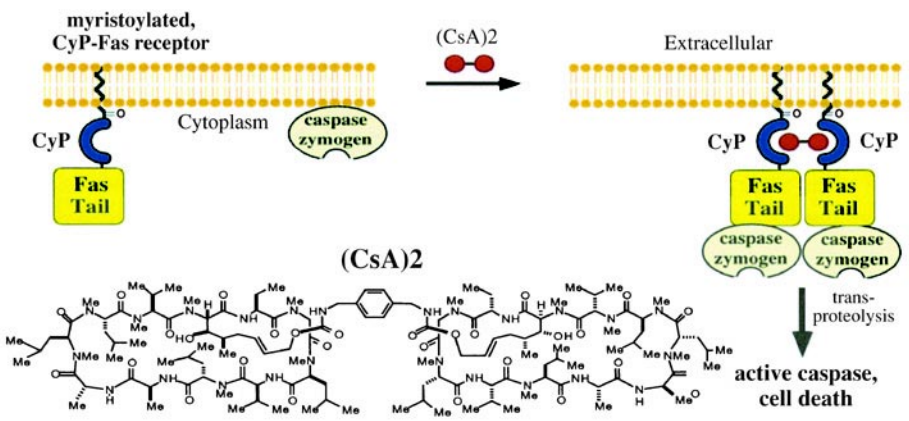

Figure 18. Controlling Fas signaling with the small molecule dimerizer (CsA)2 and a rationally designed fusion protein encoded by an expression vector.[65]

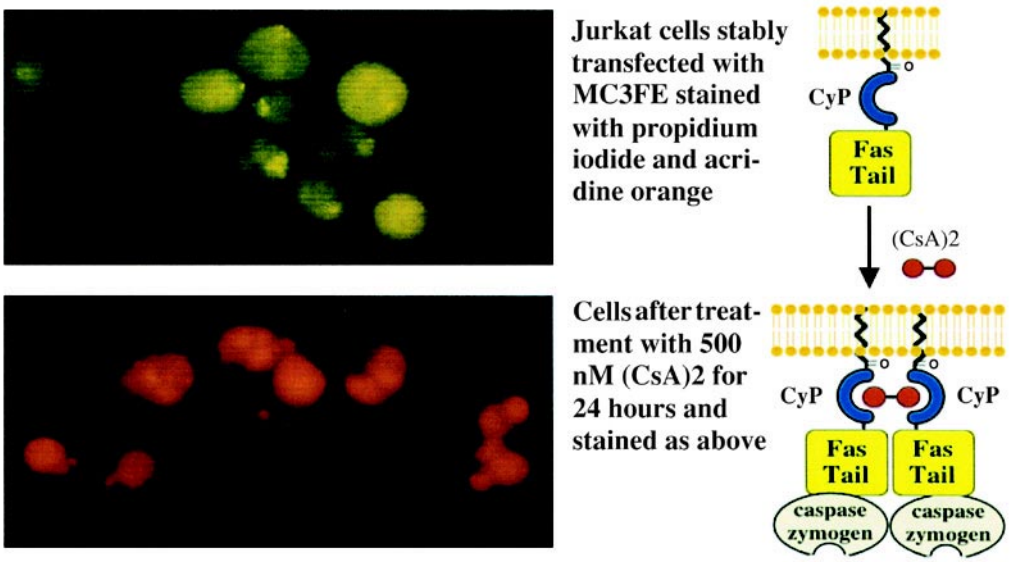

Figure 19. Small molecule activation of the Fas signaling pathway leading to apoptotic cell death of human T cells expressing the designed receptor and treated with the otherwise non-toxic dimerizer (CsA)2.[65]

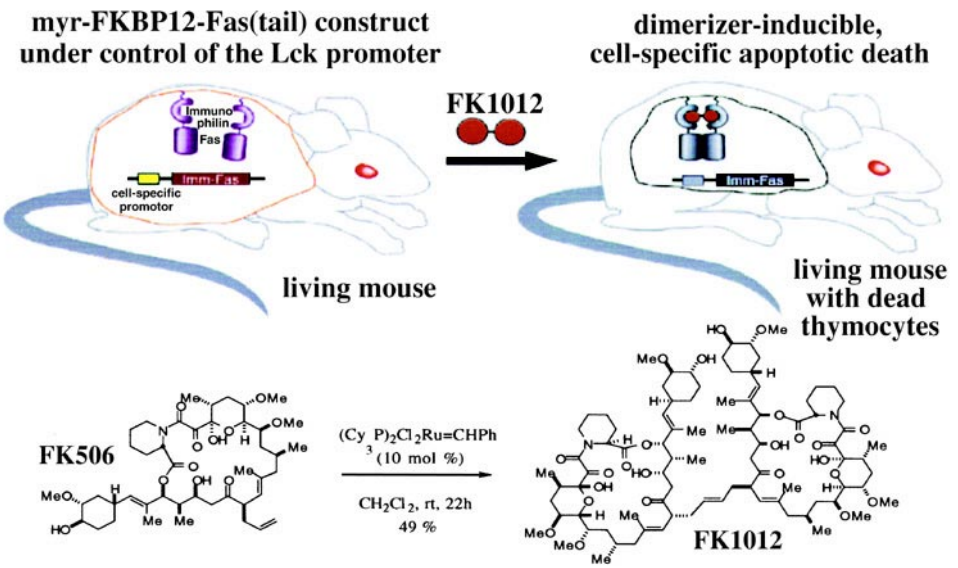

Figure 20. Controlling Fas signaling spatially and temporally in transgenic mice with a new and readily synthesized FK1012.[64,68]

TGFβ,[72,73] Fas,[63–65] and T cell receptors[66,67]), to recruit intracellular signaling proteins to the plasma membrane, allowing them to signal (ZAP,[74] Raf,[75,76] Sos,[77] Src,[78] Lck,[78] Fas[63]), to regulate gene transcription by recruiting activation domains to target genes,[63,79] and to import[63] and export[80] target proteins to and from the nucleus. A partial listing of processes controlled by small molecule dimerizers is provided in Fig. 25.[59]

Originally to improve the specificity of our dimerizers, we developed a strategy for creating new protein–small molecule combinations from pre-existing ones, referred to as the 'bump-hole' strategy.[81] This has proved to be an especially useful technique not only for preparing non-toxic dimerizers[69] (Fig. 22), but also, as Peter Belshaw showed, for preparing highly specific inhibitors of phosphatases, even ones that target phosphatases in a cell-specific way[82] (Figs 26 and 27). Placing a 'bump' alone on

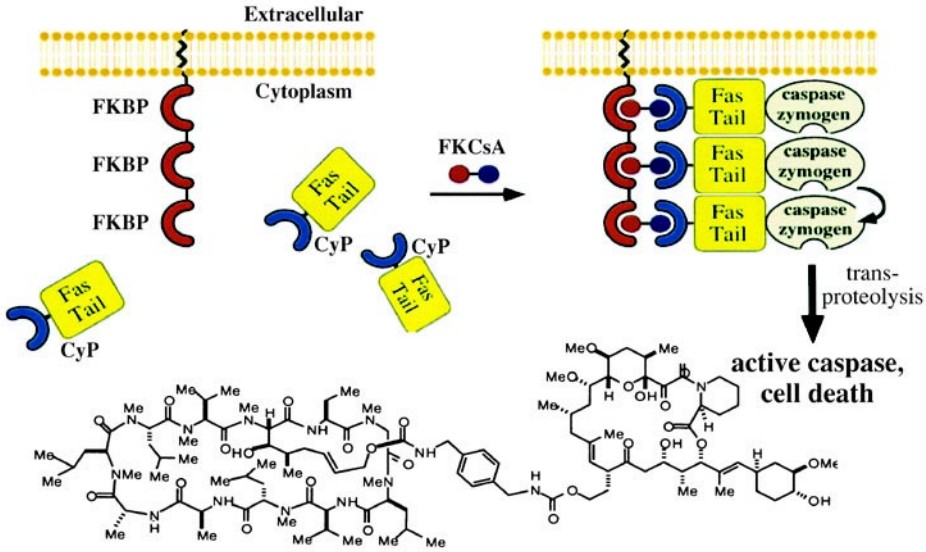

Figure 21. Controlling Fas signaling with the heterodimerizer FK-CsA. The heterodimerizer in this particular capacity is conceptually related to the phorbol esters in that it binds to a cytoplasmic signaling protein and recruits it to the site of the cell where it becomes active, the inner leaflet of the plasma membrane. The difference is that FK-CsA can be used to recruit virtually any signaling protein of interest, and it does so with nearly complete specificity.[63]

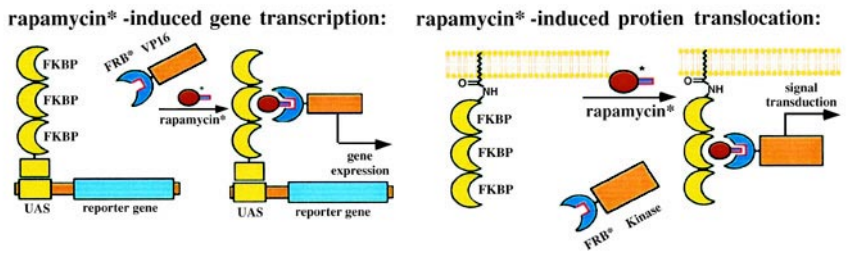

Figure 22. Displacement of the C16-methoxy substituent with a variety of larger substituents ('bumps') and selection of FRB mutants having compensitory 'holes' results in non-toxic rapamycins* that function as heterodimerizers.[69]

a protein target allows its small molecule ligand to inactivate the function of the unmodified, wild-type form and the bumped, recombinant form to complement the lost activity. In the first example, the 'bump' was a methyl group added to serine 2035 of the FRAP protein (by site-directed mutagenesis) and this rapamycin-resistant mutant of FRAP was used to explore the precise function of cells whose endogenous FRAP had been inactivated by treatment with rapamycin.[83] More recently, the bump-hole strategy was extended in Kevan Shokat's laboratory to the synthesis of specific inhibitors of kinases.[84]

The third and current phase of my research, where stereoselective synthesis of natural product-like compounds is the engine that drives biological research. The preceding examples provide illustrations of the equivalency of ligands and mutations in the study of cellular protein function. Thus far, with only few exceptions, the ligands have been either natural products or their synthetic variants (e.g. synthetic dimers of natural products). To extend the ligand-based approach, powerful methods of ligand discovery are required. The principles defined by geneticists to identify mutations that illuminate protein function are likely to be of value in the search for new ligands with similar properties. The geneticist generates large numbers of mutations, chooses from the myriad of methods to prepare the library of mutations, and selects the desired mutations through the use of an effective screen. Likewise, the chemical geneticist is now able to synthesize

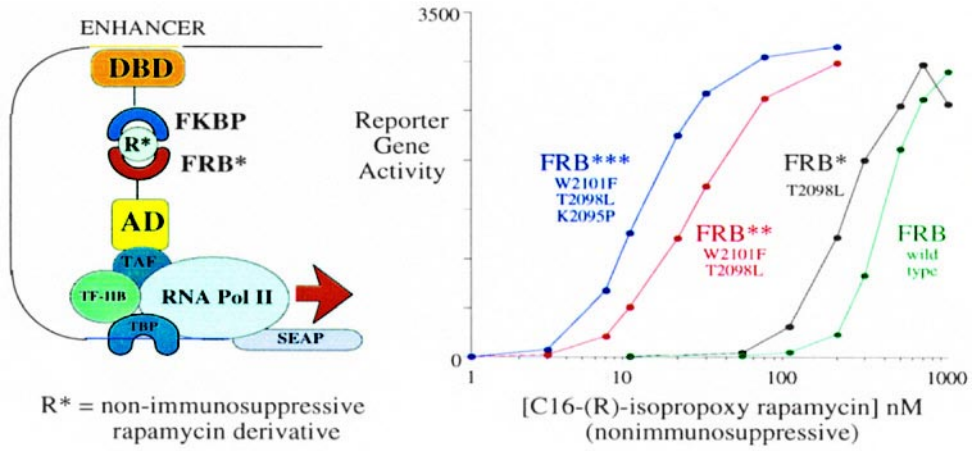

Figure 23. Inducible transcription with a non-toxic rapamycin*. By testing the ability of rapamycins* to recruit a transcription activation domain to the vicinity of a reporter gene, a triple mutant FRB* domain was selected from a library of structure-based mutants that has a compensatory hole accomodating the bump on rapamycin.[69]

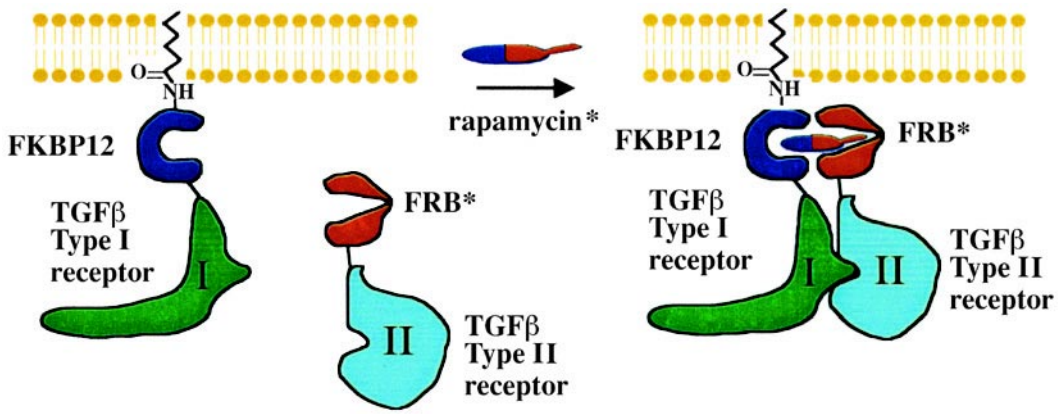

Figure 24. Controlling TGFβ signaling with a small molecule, non-toxic heterodimerizer, rapamycin*. Signaling occurs when the type II receptor is recruited to the membrane-anchored Type I receptor. By increasing effective molarity of this enzyme-substrate pair, the rate of phosphorylation of the Type I receptor by the Type II receptor is dramatically increased. Signal transduction continues when the now activated Type I receptor phosphorylates Smad proteins, causing them to translocate into the nucleus and upregulate TGFβ-responsive genes.[72,73]

vast numbers of small molecules (using 'split-and-pool' synthesis or, theoretically, massively parallel synthesis), choose from the myriad of methods to synthesize complex, natural product-like molecules, and select the desired ligands through the use of screens compatible with the split-and-pool method of small molecule generation (Fig. 28). This personal view of chemical genetics is admittedly biased toward proteins, since they have been the object of my affection during the past 15 years. Research in the area of small molecule recognition of nucleic acids could easily add another dimension to the field, a sentiment supported by the recent and remarkable progress made in this area, primarily in the laboratory of Peter Dervan.[85]

Although a genetic-like approach to ligand discovery has only recently been tested in the laboratory, it has been used widely in nature to produce the natural product ligands described above. For example, bacterial geneticists have uncovered the global outline of polyketide synthesis, leading to polyketide natural products such as rapamycin and FK506 (Fig. 29).[86] These molecules are synthesized by an iterative sequence involving a Claisen condensation, ketone reduction, dehydration, and enone reduction. The polyketide synthases containing the enzyme modules that perform these functions are encoded within single bacterial operons. These modules appear to have been shuffled throughout evolution by genetic recombination, which

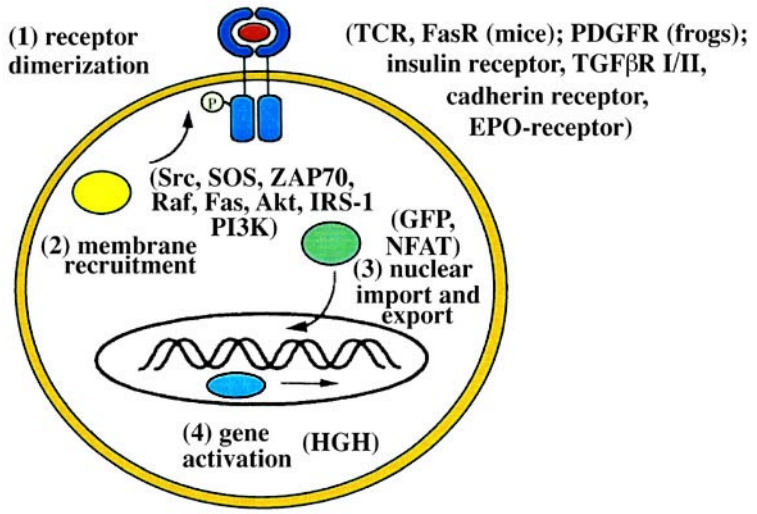

Figure 25. Activating cellular pathways with small molecule dimerizers: Controlling effective molarity in biology. A partial listing of receptors and signaling proteins that have been activated with synthetic dimerizers.[59] Dimerizer reagents have been distributed to over 125 laboratories, and can be accessed by academicians at no cost through the World Wide Web at www.ariad.com

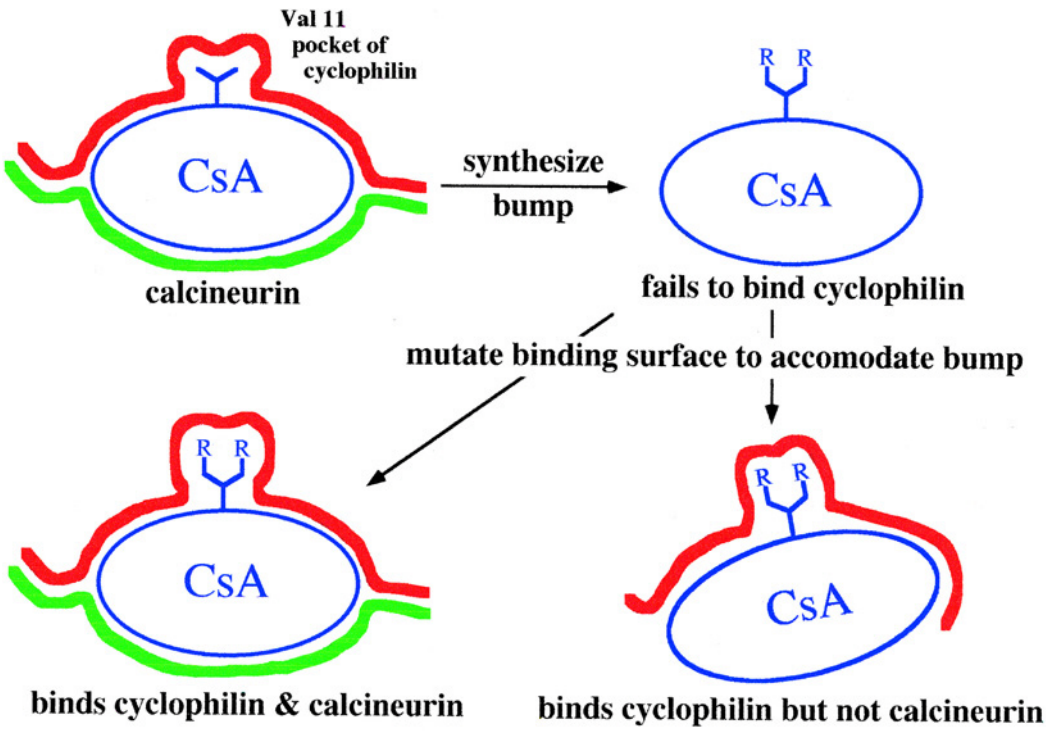

Figure 26. Bump-hole strategy for preparing novel receptor–ligand complexes: Creating inhibitors of calcineurin that inhibit the enzyme only in targeted cells or tissues.[81,82]

split-and-pool synthesis emulates. Other types of gene modifications, such as mutations in the ketoreductase modules, further enhance the structural complexity of the natural polyketide library. Finally, the process of natural selection leads to the existing members of this family of polyketide ligands. Their frequent use in present day cell biological studies stems from their selection, over a billion years, as protein ligands.

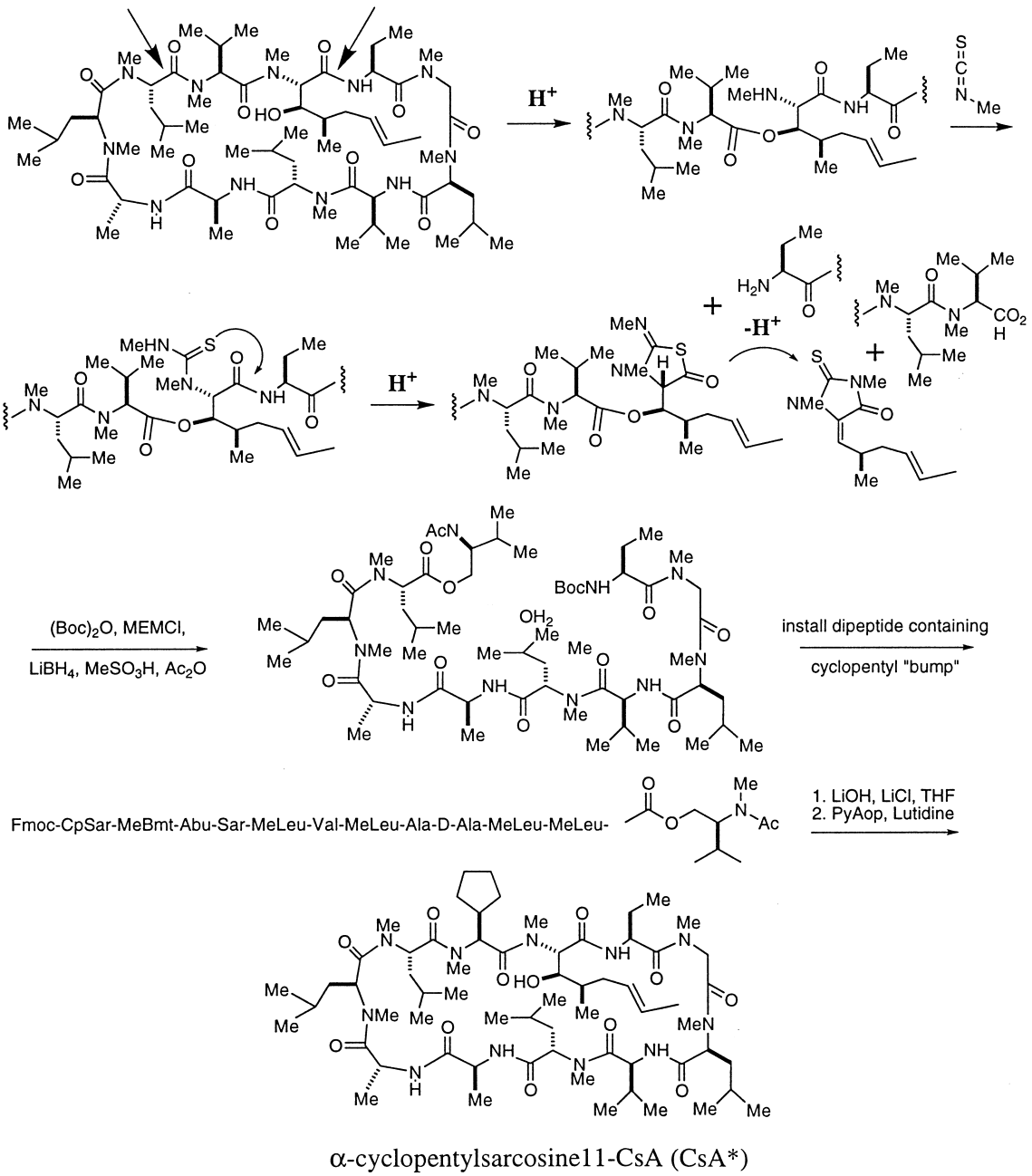

Figure 27. Synthesis of a 'bumped' cyclosporin that binds to a mutant cyclophilin with extremely high affinity and specificity, yet does not bind natural cyclophilin. The arrows indicate the sites at which a dipeptide was excised from the CsA starting material. Two acyl rearrangement reactions were used to excise the dipeptide fragment by two different means, as indicated.[81,82]

My lab has been developing a genetics-inspired research plan to synthesize natural product-like compounds and to assess their actions on a wide range of cellular processes during the past four years. Two years ago, it became evident that the plan was sound, yet it was depending more than ever on advances from several neighboring disciplines.[87–90] These included disciplines not routinely encountered in a chemistry department. With the blessing of the President of Harvard University and the Deans of the Faculty of Arts and Sciences and the Medical School, my colleagues, Tim Mitchison, Marc Kirschner, Eric Jacobsen, Greg Verdine, Matthew

Shair, Rebecca Ward, and I created the Harvard Institute of Chemistry and Cell Biology (ICCB).[91] The ICCB is devoted to advancing the field of chemical genetics by creating a multidisciplinary environment involving synthetic organic chemistry, molecular cell biology, miniaturization and imaging sciences, and engineering. It offers a new training environment for students, postdoctorals, visiting scientists, and faculty interesting in developing chemical genetics and using it to explore protein function.

I believe that our major challenge will be to synthesize complex, natural product-like compounds, the types of compounds that Nature may have sampled but not selected on the billion year path that led to FK506. These would be polyketide-related compounds, but chemical synthesis does not limit us to the acetate, propionate, and butyrate building blocks used in Nature. It also does not limit us to polyketide-like natural products, and we in fact have projects aimed at making compounds related in structure to members of natural alkaloid and terpene families. I am excited by the group of bright and fearless synthetic chemists that have joined me in my efforts to undertake these challenges. We are gaining momentum, which I hope will be evident from the reports now being prepared for publication. For example, Derek Tan, Michael Foley and Matthew Shair have synthesized over two million compounds having structural features both reminiscent of natural products and compatible with miniaturized cell-based assays.[92]

Harvard Institute of Chemistry & Cell Biology

genetics → mutations	chemical genetics → ligands
• large number of mutations	• large number of ligands: **split-pool synthesis**
• "quality" of mutations	• "quality" of ligands: **modern asymmetric synthesis**
• effective screen	• effective screen: **nanodroplets, transcript arrays**

Figure 28. Genetic principles and ligand discovery: Expanding the universe of natural product-like compounds by pushing the limits of synthetic chemistry.

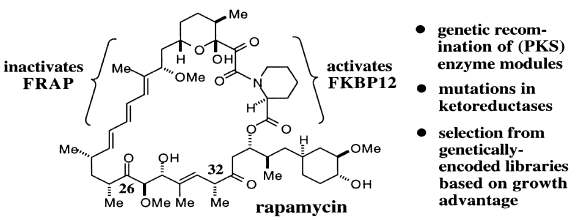

Figure 29. Natural origins of encoded combinatorial synthesis.

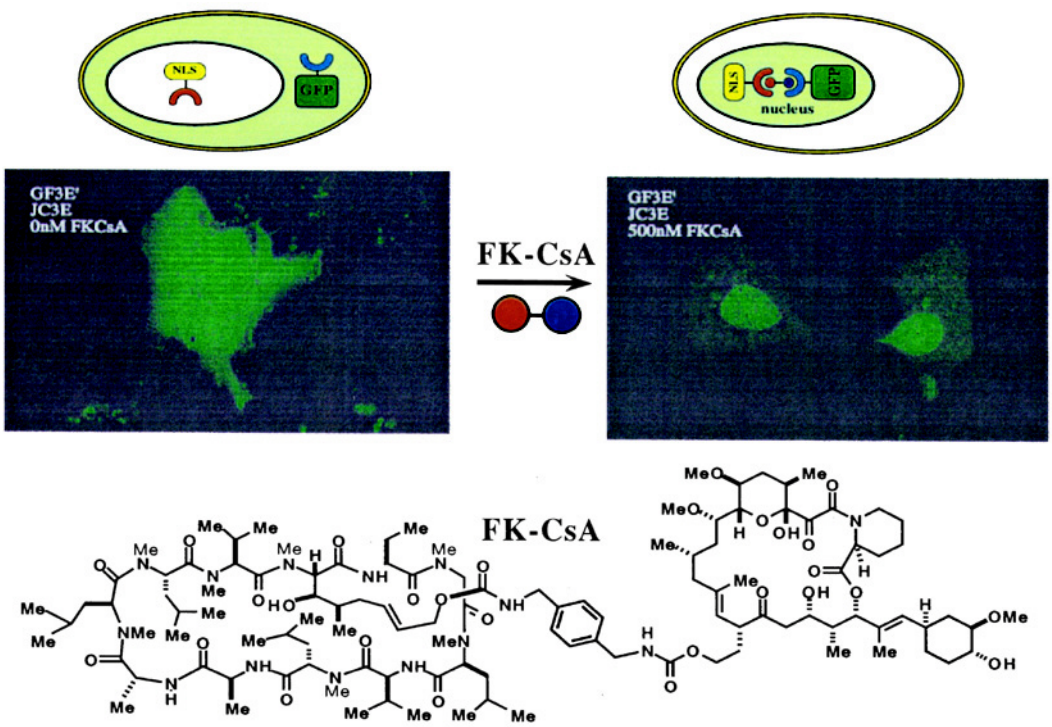

Figure 30. FKCsA-induced nuclear translocation: Optical detection of the binding of a small molecule to a protein in living mammalian cells.[63]

We also have the power to alter stereochemistry in a logical way. But the application of stereoselective methods to this new area of synthesis will demand careful planning, including a kind of planning not to my knowledge encountered in classical natural products synthesis. I will offer one example. We have recently initiated an effort to synthesize tens of millions of methymycin-related compounds. The natural product contains a 12-membered macrolide. In designing a synthesis of the natural product, consideration might be given to a 12-membered ring-closing step. Experience tells us that the efficiency of the ring closure will be dependent on the substitution pattern of the acyclic precursor, including the identity of protecting groups, and to the reaction conditions. Ad hoc solutions to the ring closure step, however, are not acceptable when the synthesis of tens of millions of methymycinoids is undertaken. However, a subset of these compounds can be designed that have as a common feature conformational preferences that ensure facile twelve-membered ring closure, as in the case of the designed 12-membered macrolide shown in Figure 3.[8] These compounds can be viewed as expanded six-membered rings, where a two atom unsaturated linkage has been inserted into every other ring C–C bond.

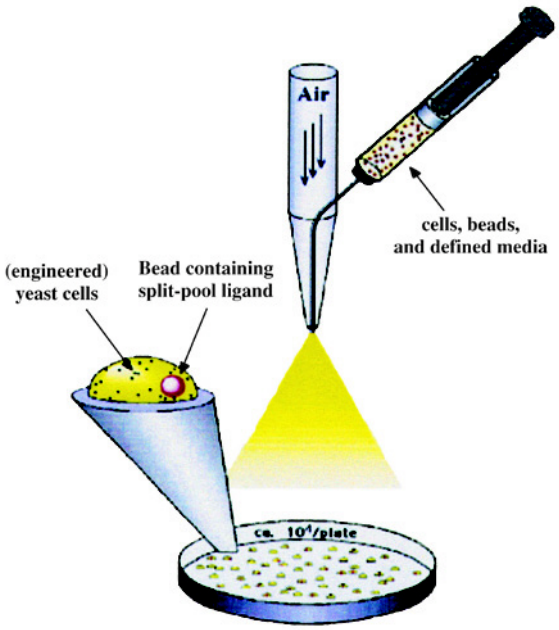

Figure 31. Ligand-containing beads and cells in spatially-separated nanodroplets.[93]

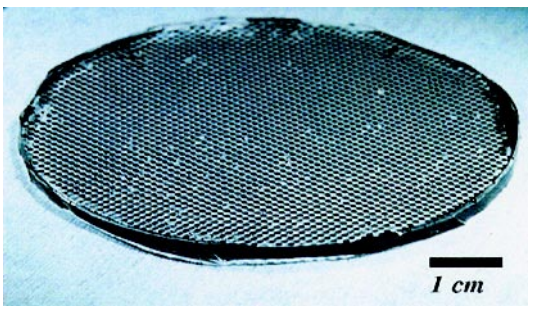

Figure 32. Arrayed nanodroplets on plastic (PDMS) molds prepared using photolithography.[94]

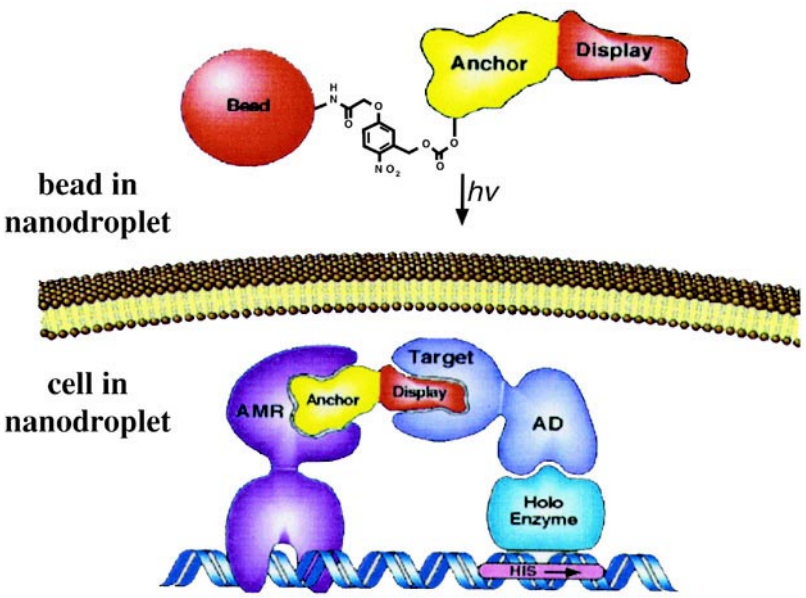

Figure 33. Using an anchor ligand to display small molecules in living cells: small molecule-binding leads to the rescue of cell growth.[93]

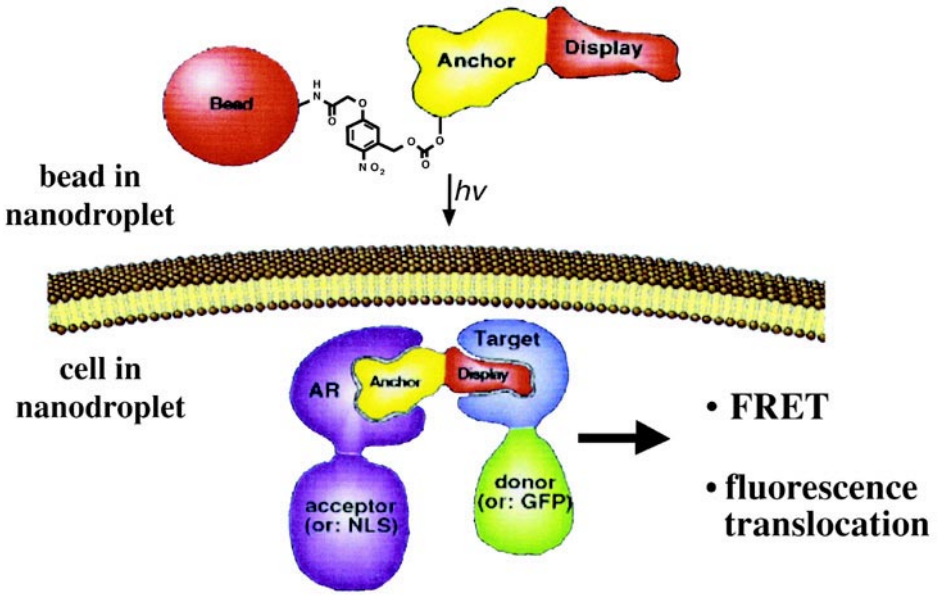

Figure 34. Using an anchor ligand to display small molecules in living cells: small molecule-binding leads to fluorescence translocation (see also Fig. 30).[63,93]

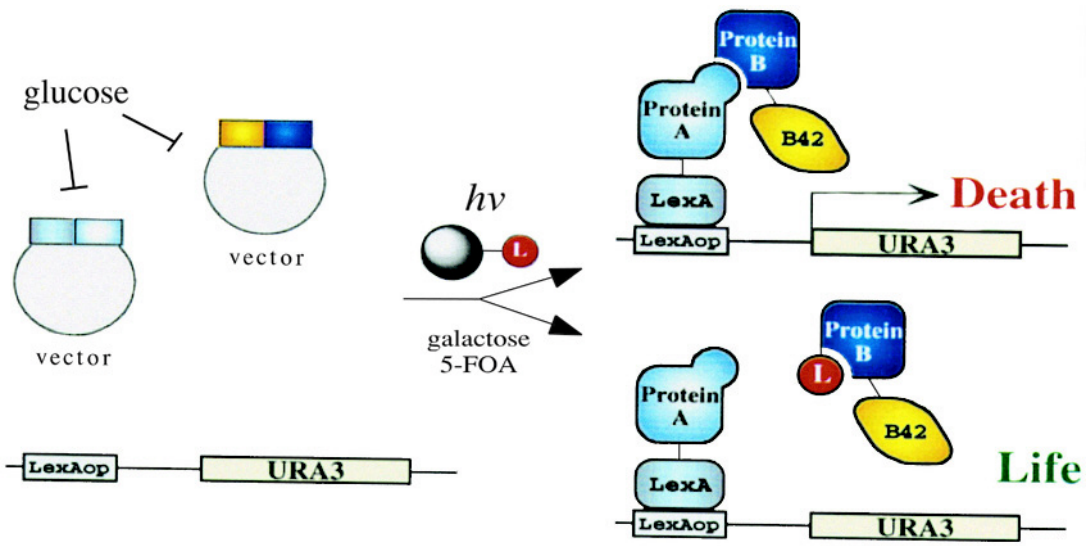

Figure 35. Genetic selection of small molecule inhibitors of protein–protein interactions: general scheme.[95]

It was the intellectual challenge of retrosynthetic analysis that first attracted me to the field of natural products synthesis. I am finding the field of natural product-like synthesis to be rich with these same challenges, and even new ones like that described above. Earlier, I stated that the major challenge in efforts to generalize chemical genetics will be in synthesis, but it is by no means the only one. Molecular cell biology will be needed to engineer cells to serve as reporters of many types of cellular processes, preferably by emitting light when a small molecule has inactivated or activated the function of its target protein[63] (Fig. 30). Making many millions of compounds requires that chemists be able to run millions of experiments that assess the actions of their synthetic compounds on cells. Miniaturization is key to the success of this aspect of the research. An example is seen in the two techniques we have developed for creating tiny 50–200 nanoliter droplets of cell culture on a vast scale[93,94] (Figs 31 and 32). These nanodroplets can be used to detect small molecules that bind proteins

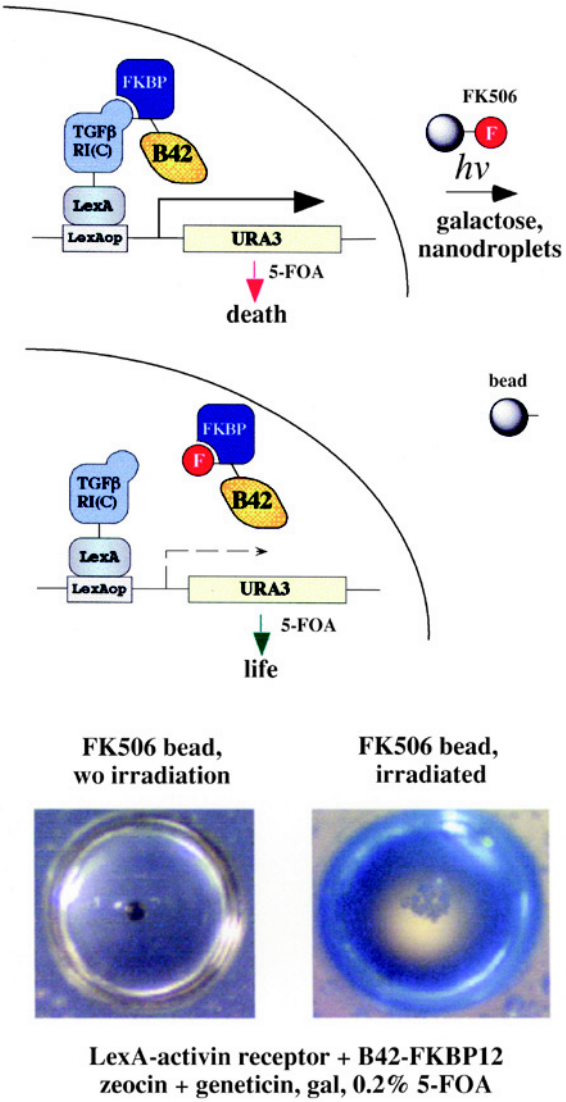

Figure 36. Small molecule inhibition of the activin receptor–FKBP12 complex detected in a nanodroplet.[95]

and that disrupt protein–protein interactions when generated with suitably engineered cells[95] (Figs 33–36).

Conclusions

I would like to conclude this essay with a view to the future of this third phase of research. There are many unanswered questions. Foremost in my mind is the question of whether we as synthetic chemists will ever be able to create in the laboratory compounds with the extraordinary specificity of natural products. Although I do not know the answer, I am optimistic for a variety of reasons. The DNA chip/hybridization array technology provides us with at least one method for determining the specificity of a synthetic compound when incubated with a living cell, with its enormous collection of proteins, and others are bound to emerge. This technique has shown that a natural product can have the absolute specificity previously only associated with a gene deletion mutation, so it proves the principle of small molecule specificity. New technology from a variety of disciplines has allowed every individual step of a classical genetic screen to be emulated with chemistry. Not one of the steps has yet been optimized, but there appears to be no theoretical impediments, no insurmountable activation barriers associated with any individual step. Will the full power of stereoselective methods in synthesis be brought to bare in split-pool or massively parallel syntheses of millions or billions of natural product-like compounds? Even more ambitiously, will we be able to recapture the many millions of presumed 'transient' natural products that were evolutionarily de-selected along the paths that eventually led to the natural products synthesized on Earth today? It is true that even the first goal has not yet been demonstrated, but I cannot imagine that in a young synthetic chemist's lifetime, it will not be accomplished. And if it is realized, and effective means for assessing the properties of these compounds are perfected, the impact on the life sciences would be significant. Chemical genetics, like genetics, can be used to understand protein function. Although it is important to use small molecules that alter function with the specificity of a gene knock-out, the discovery of such molecules will allow the instantaneous alteration of function, not possible in classical genetics, even in cells and animals not readily amenable to genetic analysis. Instantaneous alteration of function allows the kinetic time course of events to be determined, which can shed a bright light on complex cellular processes. Perhaps most importantly, in chemical genetics the tools that are used to alter function, small molecules, can be used to control the function of proteins. This promises to build more direct connections between biology and medicine, ones made possible by the awesome power of synthetic chemistry.

The original goal of the human genome project was 'to sequence every gene'. With that goal within sight, I suggest we consider a new goal for this project, one that can only be realized through the creative use of chemistry, 'to identify a small molecule partner for every gene product'.

Acknowledgements

The research described in this article was performed by a remarkable group of co-workers, to whom I am indebted. Their dedication, creativity, and spirit have enriched my life in immeasurable ways. I hope their individual accomplishments will 'come to life' for the

readers by searching through a website prepared in part for this purpose: www-schreiber.chem.harvard.edu. I am also grateful to the National Institute of General Medical Sciences, which, since 1981, has served as a primary source of funding for the research described in this paper, and to the Howard Hughes Medical Institute, which has played a vital role in the growth of chemical genetics during the past four years.

References and Notes

1. Adams, M. A.; Nakanishi, K.; Still, W. C.; Arnold, E. V.; Clardy, J.; Persoons, C. J. *J. Am. Chem. Soc.* **1979**, *101*, 2495.

2. Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038.

3. Schreiber, S. L. *Science* **1985**, *227*, 857.

4. Schreiber, S. L.; Hoveyda, A. H.; Wu, H.-J. *J. Am. Chem. Soc.* **1983**, *105*, 660.

5. Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1983**, *105*, 6723.

6. Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1984**, *106*, 4186.

7. Schreiber, S. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1984**, *106*, 7200.

8. Schreiber, S. L.; Sammakia, T.; Hulin, B. *J. Am. Chem. Soc.* **1986**, *108*, 2106.

9. Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128.

10. Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749.

11. Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353.

12. Wood, J. L.; Porco, Jr., J. A.; Taunton, J. W.; Lee, A. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5900.

13. Taunton, J.; Wood, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10378.

14. Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718.

15. Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120.

16. Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360.

17. Schreiber, S. L. *Chemica Scripta*, **1987**, *27*, 563.

18. Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9.

19. Smith, D. B.; Wang, Z.; Schreiber, S. L. *Tetrahedron*, **1990**, *46*, 4793.

20. Ikemoto, N., Schreiber, S. L., *J. Am. Chem. Soc.* **1990**, *112*, 9657.

21. Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 2524.

22. Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583.

23. Schreiber, S. L.; Ragan, J. A.; Standaert, R. F. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic: San Diego, 1991; Vol. 3, pp 417–461.

24. Schreiber, S. L. *Science* **1991**, *251*, 283.

25. Schreiber S. L. *C. & E. News* **1992** (October 26), 22–32.

26. Harding, M. W.; Galat, A.; Uehling, D. E.; Schreiber, S. L. *Nature* **1989**, *341*, 758.

27. Standaert, R. F.; Galat, A.; Verdine, G. L.; Schreiber, S. L. *Nature* **1990**, *346*, 671.

28. Bierer, B. E.; Somers, P. K.; Wandless, T. J.; Burakoff, S. J.; Schreiber, S. L. *Science* **1990**, *250*, 556.

29. Somers, P. K.; Wandless, T. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 8045.

30. Taunton, J.; Collins, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10412.

31. Taunton, J.; Hassig, C. A.; Schreiber, S. L. *Science* **1996**, *272*, 408.

32. Hassig, C. A.; Fleischer, T. C.; Billin, A. N.; Schreiber, S. L.; Ayer, D. E. *Cell* **1997**, *89*, 341.

33. Nagy, L.; Kao, H.-Y.; Chakravarti, D.; Lin, R.; Hassig, C. A.; Ayer, D. E.; Schreiber, S. L.; Evans, R. M. *Cell* **1997**, *89*, 373.

34. Hassig, C. A.; Schreiber, S. L. *Curr. Opin. Chem. Biol.* **1997**, *1*, 300.

35. Hassig, C. A.; Tong, J. K.; Schreiber, S. L. *Chem. Biol.* **1997**, *4*, 783.

36. Hassig, C. A.; Tong, J. K.; Fleischer, T. C.; Owa, T.; Grable, P.; Ayer, D. E.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3519.

37. Kwon, H. J.; Owa, T.; Hassig, C. A.; Shimada, J.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3356.

38. Heinemann, S. H.; Sigworth, F. J.; Stankovic, C. J.; Delfino, J. M.; Schreiber, S. L. *Science* **1989**, *244*, *813*.

39. Stankovic, C. J.; Heinemann, S. H.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 3702.

40. Stankovic, C. J.; Schreiber, S. L. *Chem. Tracts, Org. Chem.*, **1991**, *4*, 1.

41. Weiss, G. A.; Collins, E. J.; Garboczi, D. N.; Wiley, D. C.; Schreiber, S. L. *Chem. Biol.* **1995**, *2*, 401.

42. Weiss, G. A.; Valentekovich, R. J.; Collins, E. J.; Garboczi, D. N.; Lane, W. S.; Schreiber, S. L.; Wiley, D. C. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 10945.

43. Andrus, M. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10420.

44. Alberg, D. G.; Schreiber, S. L. *Science* **1993**, *262*, 248.

45. Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568.

46. Schreiber, S. L.; Crabtree, G. R. *Immunol. Today* **1992**, *13*, 136.

47. Schreiber, S. L. *Cell* **1992**, *70*, 365.

48. Brown, E. J.; Schreiber, S. L. *Cell* **1996**, *86*, 517.

49. Shimada, J.; Kwon, H. J.; Sawamura, M.; Schreiber, S. L. *Chem. Biol.* **1995**, *2*, 517.

50. Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621.

51. Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *Chem. Biol.* **1994**, *1*, 67.

52. Hung, D. T.; Chen, J.; Schreiber, S. L. *Chem. Biol.* **1996**, *3*, 287.

53. Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054.

54. Fenteany, G.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. *Science* **1995**, *268*, 726.

55. Fenteany, G.; Schreiber, S. L. *J. Biol. Chem.* **1998**, 273, *8545*.

56. Cimprich, K. A.; Shin, T. B.; Keith, C. T.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 2850.

57. Keith, C. T.; Schreiber, S. L. *Science* **1995**, *270*, 50.

58. Cliby, W. A.; Roberts, C. J.; Cimprich, K. A.; Stringer, C. M.; Lamb, J. R.; Schreiber, S. L.; Friend, S. H. *EMBO J* **1998**, *17*, 159.

59. Crabtree, G. R.; Schreiber, S. L. *TIBS* **1996**, *21*, 418.

60. Austin, D. J.; Crabtree, G. R.; Schreiber, S. L. *Chem. Biol.* **1994**, *1*, 131.

61. Klemm, J. D.; Schreiber, S. L.; Crabtree, G. R. *Ann. Rev. Immunol.* **1998**, *16*, 569.

62. Tenud, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *Helvetica. Chim. Acta* **1970**, *53*, 2059.

63. Belshaw, P. J.; Ho, S.; Crabtree, G. R.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 4604.

64. Spencer, D.; Belshaw, P.; Chen, L.; Ho, S.; Randazzo, F.; Crabtree, G. R.; Schreiber, S. L. *Curr. Biol.* **1996**, *6*, 839.

65. Belshaw, P. J.; Crabtree, G. R.; Schreiber, S. L. *Chem. Biol.* **1996**, *3*, 731.

66. Spencer, D.; Wandless, T. J.; Schreiber, S. L.; Crabtree, G. R. *Science* **1993**, *262*, 1019.

67. Pruschy, M. N.; Spencer, D. M.; Kapoor, T. M.; Miyake, H.; Crabtree, G. R.; Schreiber, S. L. *Chem. Biol.* **1994**, *1*, 163.

68. Diver, S. T.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 5106.

69. Liberles, S. D.; Diver, S. T.; Austin, D. J.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 7825.

70. Yang, J.; Symes, K.; Mercola, M.; Schreiber, S. L. *Curr. Biol.* **1997**, *8*, 11.

71. Blau, C. A.; Peterson, K. R.; Drachman, J. G.; Spencer, D. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 3076.

72. Stockwell, B. R.; Schreiber, S. L. *Curr. Biol.* **1998**, *8*, 761.

73. Stockwell, B. R.; Schreiber, S. L. *Chem. Biol.* **1998**, *5*, 385.

74. Graef, I. A.; Holsinger, L. J.; Diver, S.; Schreiber, S. L.; Crabtree, G. R. *EMBO J.* **1997**, *16*, 5618.

75. Farrar, M. A.; Alberola-lla, J.; Permutter, R. M. *Nature* **1996**, *383*, 178.

76. Luo, Z.; Tzivion, G.; Belshaw, P. J.; Vavvas, D.; Marshall, M.; Avruch, J. *Nature* **1996**, *383*, 181.

77. Holsinger, L. J.; Spencer, D. M.; Austin, D. J.; Schreiber, S. L.; Crabtree, G. R. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 9810.

78. Spencer, D. M.; Graef, I.; Austin, D. J.; Schreiber, S. L.; Crabtree, G. R. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 9805.

79. Ho, S. N.; Biggar, S. R.; Spencer, D. M.; Schreiber, S. L.; Crabtree, G. R. *Nature* **1996**, *382*, 822.

80. Klemm, J. D.; Beals, C. R.; Crabtree, G. R. *Curr. Biol.* **1997**, *7*, 638.

81. Belshaw, P. J.; Schoepfer, J.; Liu, K.; Morrison, K.; Schreiber, S. L. *Angew. Chem., Int. Ed. Eng.* **1995**, *34*, 2129.

82. Belshaw, P. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 1805.

83. Brown, E. J.; Beal, P.; Keith, C. T.; Chen, J.; Shin, T. B.; Schreiber, S. L. *Nature* **1995**, *377*, 441.

84. Bishop, A. C.; Shah, K.; Liu, Y.; Witucki, L.; Kung, C.-Y.; Shokat K. M. *Curr. Biol.* **1998**, *8*, 257.

85. Gottesfeld, J. M.; Neely, L.; Trauger, J. W.; Baird, E. E.; Dervan, P. B. *Nature* **1997** *387*, 202.

86. Hopwood, D. A. *Chem. Rev.* **1997** *7*, 2465.

87. Chen, J. K.; Schreiber, S. L. *Angew. Chem., Int. Ed. Eng.* **1995**, *34*, 953.

88. Combs, A. P.; Kapoor, T. M.; Feng, S.; Chen, J. K.; Daude-Snow, L. F.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 287.

89. Kapoor, T. M.; Andreotti, A. H.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 23.

90. Morken, J. P.; Kapoor, T. M.; Feng, S.; Shirai, F.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 30.

91. http://www. hms. harvard. edu/iccb

92. Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* in press.

93. Borchardt, A.; Liberles, S. D.; Biggar, S. R.; Crabtree, G. R.; Schreiber, S. L. *Chem. Biol.* **1997**, *4*, 961.

94. You, A.; Jackman, R. J.; Whitesides, G. M.; Schreiber S. L. *Chem. Biol.* **1997**, *4*, 969.

95. Huang, J.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 13396.

Bibliography

Stuart L. Schreiber, Ph.D., is the Loeb Professor of Chemistry and Chemical Biology at Harvard University, Investigator at the Howard Hughes Medical Institute, and Founder and Co-Director of the Harvard Institute of Chemistry and Cell Biology.

Dr. Schreiber was born February 6, 1956 and raised in the countryside of Virginia by his parents Colonel Thomas and Mary Geraldine (Gerrie) Schreiber. He married Mimi Packman on August 9, 1981. After receiving a B.A. degree at the University of Virginia in June of 1977, he carried out graduate studies at Harvard University under the supervision of R. B. Woodward and Y. Kishi. Following completion of his doctoral studies, he joined the faculty at Yale University in May of 1981. He was promoted to Associate Professor with tenure in 1984 and to Full Professor in 1986. In the Fall of 1988, he returned to Cambridge. He is now an Investigator at the Howard Hughes Medical Institute and the Loeb Professor at Harvard University where he is a Member of the Department of Chemistry and Chemical Biology, an Associate Member of the Department of Molecular and Cellular Biology, and Founder and Co-Director of the Harvard Institute of Chemistry and Cell Biology. He is also an Affiliate of the Department of Cell Biology at the Harvard Medical School and a Member of the Graduate Programs in Biophysics at Harvard University and in Immunology at the Harvard Medical School.

Dr. Schreiber's research results from the melding of synthetic organic chemistry with cell biology. In these studies, cell permeable molecules have been synthesized and used to understand and control the cellular function of proteins, in analogy to the use of mutations in classical genetics. These organic ligands are used to either conditionally inactivate or activate protein targets. A loss of function results from synthetic ligands that bind specifically to the encoded protein, whereas a gain of function results from the use of synthetic 'dimerizers' that bring two proteins or two halves of a protein together. Using split-pool synthesis of natural product-like compounds, molecular and cellular biology, and miniaturization science, he has also provided illustrations of how 'chemical genetics' can be generalized and extended.

Dr. Schreiber has received a number of honors and awards, which include: Dreyfus Grant for Newly Appointed Faculty, 1981; Searle Scholar Award, 1982; Camille and Henry Dreyfus Teacher–Scholar Award, 1985; Alfred P. Sloan Foundation Fellow, 1985; NSF Presidential Young Investigator, 1985; ICI Pharmaceuticals Award for Excellence in Chemistry, 1986; Arthur C. Cope Scholar Award, American Chemical Society 1986; Award in Pure Chemistry, American Chemical Society, 1989; the Arun Guthikonda Memorial Award 1990, the Ciba–Geigy Drew Award for Biomedical Research, 1992, the Thieme–IUPAC Award in Synthetic Chemistry, 1992, an NIH Merit Award, 1992, the Eli Lilly Award in Biological Chemistry, American Chemical Society, 1993, the Rhone-Poulenc Silver Medal, Royal Society of Chemistry, 1992, the Leo Hendrik Baekeland Award, 1993, the Award for Creative Work in Synthetic Chemistry, American Chemical Society,

1994, the Paul Karrer Gold Medal, University of Zurich, 1994; Warren Triennial Prize (co-recipient with Leland Hartwell), Massachusetts General Hospital, 1995; Ledlie Biennial Prize, Harvard University, 1995; DuPont Merck Young Investigator Award of the Protein Society, 1995, Harrison Howe Award, Rochester Section of ACS, 1995, Elected to the National Academy of Sciences and the American Academy of Arts & Sciences, 1995; Harvey Society Lecture, 1996; Tetrahedron Prize for Creativity in Organic Chemistry, 1997. Dr. Schreiber is a Founder and Co-Editor (with Dr. K. C. Nicolaou) of the journal *Chemistry & Biology*.