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REVIEW

Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery

Stuart L. Schreiber

Modern drug discovery often involves screening small molecules for their ability to bind to a preselected protein target. Target-oriented syntheses of these small molecules, individually or as collections (focused libraries), can be planned effectively with retrosynthetic analysis. Drug discovery can also involve screening small molecules for their ability to modulate a biological pathway in cells or organisms, without regard for any particular protein target. This process is likely to benefit in the future from an evolving forward analysis of synthetic pathways, used in diversity-oriented synthesis, that leads to structurally complex and diverse small molecules. One goal of diversity-oriented syntheses is to synthesize efficiently a collection of small molecules capable of perturbing any disease-related biological pathway, leading eventually to the identification of therapeutic protein targets capable of being modulated by small molecules. Several synthetic planning principles for diversity-oriented synthesis and their role in the drug discovery process are presented in this review.

Modern methods for stereoselective organic synthesis have increased the efficiency with which small molecules can be prepared. These compounds include new drugs and drug candidates and reagents used to explore biological processes. However, it is a nearly four-decade-old method for purifying reaction products that is currently having the greatest impact on organic synthesis (*1*). Solid phase organic synthesis (*2–7*), adapted from the original solid phase peptide synthesis (*1*), promises to increase dramatically the diversity and number of small molecules available for medical and biological applications.

The evolution of stereoselective organic synthesis from the solution (*8*) to the solid (*2–7*, *9–11*) phase has created strategic challenges for organic chemists because it has provided the means to synthesize not only single target compounds or collections of related targets but also collections of structurally diverse compounds. Target-oriented syntheses are used in drug discovery efforts involving preselected protein targets, whereas diversity-oriented syntheses are used in efforts to identify simultaneously therapeutic protein targets and their small-molecule regulators. Target-oriented synthesis has benefited from a powerful planning algorithm named retrosynthetic analysis (*8*); a comparable algorithm for diversity-oriented synthesis is only now beginning to be developed. Planning diversity-oriented syntheses will become increasingly important for organic chemists as methods to screen large collections of small molecules become more effective and routine.

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Target-Oriented Synthesis and Retrosynthetic Analysis

Target-oriented synthesis has a long history in organic chemistry. In universities, the targets are often natural products, whereas in pharmaceutical companies, the targets are drugs or libraries of drug candidates. Beginning in the mid-1960s, a systematic method

to plan syntheses of target molecules, named retrosynthetic analysis, was devised (*8*). This problem-solving technique involves the recognition of key structural elements in reaction products, rather than reaction substrates, that code for synthetic transformations. Repetitive application of this process allows a synthetic chemist to start with a structurally complex target and find a structurally simple compound that can be used to start a synthesis. In the example given in Fig. 1A (*12*), the target is a cis-fused bicyclic ring containing olefin and ketone functionalities. Compounds having these functionalities separated by three sp^3-hybridized carbons, such as this target, can be synthesized with a version of the oxy-Cope rearrangement reaction. The oxy-Cope substrate that will provide the target, determined by considering the connectivity of atoms in the target and the mechanism of the oxy-Cope reaction, has an olefin-containing, bridged bicyclic ring with vinyl and hydroxyl groups attached to a ring carbon. Analysis of this target reveals that a logical precursor substrate is a bridged bicyclic ring containing a ketone functionality. Treating such a ketone with a nucleophilic vinyl group building block, such as a vinyl Grignard reagent, will produce the desired target compound. Continuing with this analysis, the bridged bicyclic ketone is seen to be the product of a Diels-Alder reaction of the simple starting materials, or building blocks, cyclohexadiene, and ketene. Although ketene itself will not undergo the desired Diels-Alder reaction, synthetic equivalents of it have been identified that undergo this reaction efficiently (*12*).

This example illustrates several key features of target-oriented syntheses. Reactions that join together two different building blocks, called fragment-coupling reactions, are of great importance. Reactions that generate structural complexity stereoselectively are also of considerable value. The oxy-Cope and Diels-Alder reactions are excellent examples and are used widely in target-oriented organic synthesis. Retrosynthetic analysis is the sine qua non of target-oriented synthesis and has been used in the synthetic planning of many target compounds of value in medicine and biology (see, for example, Fig. 1, B and C) (*13, 14*). It is also used in solid phase syntheses aimed at drug discovery, in particular in syntheses of "focused libraries," where collections of compounds with common structural features that facilitate binding to a preselected protein target are synthesized (*9–11*).

Solid Phase Synthesis

The synthesis of polypeptides requires little strategic planning because these compounds comprise repeating amino acid building blocks linked by the readily synthesized amide bond. Solid phase peptide synthesis was first introduced to overcome the technical challenge of performing many such couplings to yield long chains. The nascent polypeptide chain is immobilized in this method, most commonly to spherical polystyrene beads, allowing coupling reagents to be added in high molar excess and by-products (including the unused reagents) to be removed simply by washing the insoluble beads. Although it did not require much time for solid phase peptide synthesis to be adapted to nonpeptidic small molecules (*2–7*), solid phase organic synthesis has become widely used only in recent years (*9–11, 15–17*).

Simplification of the purification of synthetic intermediates in organic synthesis through the solid phase method led to an increase in synthetic productivity. Again taking a lead from solid phase peptide (and oligonucleotide) synthesis (*18–20*), solid phase syntheses have been performed in parallel (*15–17*); that is, similar reactions are performed, but the structures of the building blocks in key fragment-coupling steps are varied. Solid phase, parallel synthesis is an example of what is commonly referred to as combinatorial synthesis and is most commonly used by medicinal chemists in pharmaceutical companies and universities to synthesize a focused library of related compounds sharing structural features necessary for binding to a preselected protein target, allowing the general principles of retrosynthetic analysis to be applied readily.

Current methods for parallel synthesis provide a modest increase in synthetic throughput, but a second variation of solid phase synthesis, one that extends it beyond a mere purification technique, can provide a staggering increase in the ability of organic synthesis to produce collections of small molecules. This potential was realized originally in peptide synthesis with the invention of the split-and-pool (split-pool) strategy of synthesis (*21–25*). The strategy has more recently also been used in organic synthesis, resulting in structurally complex and diverse libraries of synthetic small molecules (*9–11, 26*). In this method, a collection of beads is split into reaction vessels that subsequently each receive a unique set of reagents, for example, one of a collection of building blocks. Cycles of pooling, resplitting, and further chemistry then result in large collections of compounds that are spatially segregated on unique beads. Split-pool synthesis is referred to as the "one bead–one compound" approach, and it is analogous to genetic recombination. Encoding methods, which are analogous to the genetic code, have been developed that record the chemical history of the synthetic compounds, allowing the structures of compounds selected in screens to be inferred (*27–29*).

Diversity-Oriented Synthesis in Biology and Medicine

Access to structurally complex and diverse small molecules through synthesis is driving recent efforts to dissect biological pathways in ways analogous to those used in genetics, where random mutations are first generated and then screened in search of a specific cellular or organismic phenotype. Finding small molecules or mutations that affect a specific pathway and identifying the cellular target of the small molecule or the molecular sequence of the mutant gene can shed light on the pathway. From the perspective of drug discovery, the small-molecule approach offers the means for the simultaneous identification of proteins that can serve as targets for therapeutic intervention ("therapeutic target validation") and small molecules that can modulate the functions of these therapeutic targets ("chemical target validation") (*30*,

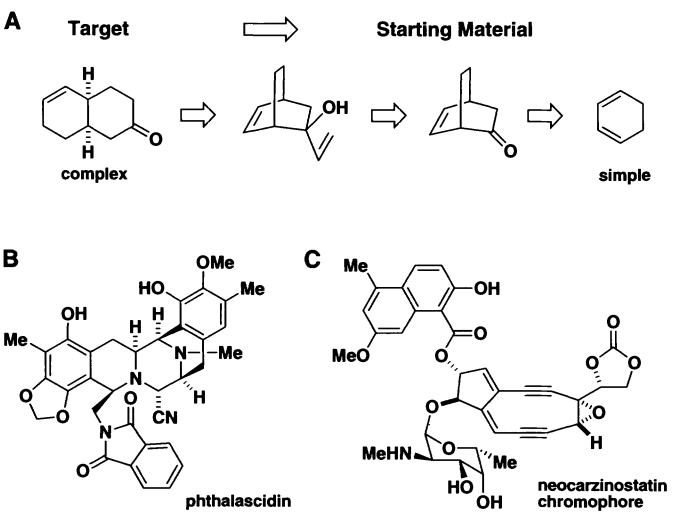

Fig. 1. Target-oriented organic synthesis and retrosynthetic analysis. (**A**) An example of retrosynthetic analysis used to plan a target-oriented synthesis (*12*). Beginning with a complex target (illustrated) or a collection of targets ("focused libraries"; not illustrated), the analysis leads to the identification of simple starting materials (also referred to as "building blocks"). (**B** and **C**) Small molecules synthesized with retrosynthetic analysis: (B) phthalascidin, a nonnatural synthetic compound with promise as an anticancer agent (*13*), and (C) neocarzinostatin chromophore, a natural product that has potent antiproliferative actions on cells in culture (*14*). Me, methyl.

31). The structures of the small-molecule modulators provide leads for the drug discovery process, where, for example, pharmacokinetic and pharmacodynamic properties can be optimized. The overall process differs from the current primary means of drug discovery, where biological methods are first used to select proteins targets for therapeutic intervention, followed by chemical efforts to determine whether the protein target can be modulated by small molecules. The latter process involves screening small molecules for their ability to bind the preselected protein target.

Diversity-Oriented Synthesis and an Evolving Synthetic Analysis

Whether it is possible to dissect biological pathways and validate (therapeutically and chemically) targets effectively with pathway-based screening depends on the nature of the syntheses that yield the small-molecule modulators. In contrast to target-oriented syntheses, diversity-oriented syntheses are not aimed at one particular target, and retrosynthetic analysis can therefore not be applied directly. They are instead aimed at a collection of many compounds having structural complexity and diversity (Fig. 2). Complexity is important because many biological processes are critically dependent on protein-protein interactions, and many of the small molecules known to disrupt these interactions are structurally complex natural products. Increasing the size and number of rigidifying and protein-binding elements in small molecules is generally viewed as essential in order for these compounds to bind tightly to sites of protein-protein interactions, which tend to be relatively flat in comparison with the concave topography characteristic of enzyme active sites.

Achieving structural diversity is equally important as structural complexity. A collection of diverse compounds is more likely to be successful in genetic-like, phenotypic screens involving cells or organisms than a collection of related compounds. The latter, resulting from target-oriented synthesis aimed at focused libraries, is frequently used in screens involving a preselected target protein for which the structure of a small-molecule substrate or inhibitor is known. A collection of diverse compounds is essential in phenotypic screens because there is no one particular target in cell-based or organism-based screens and any one of the cell's or organism's entire collection of macromolecules could be an eventual target (*30, 31*).

Diversity-oriented syntheses are analyzed in the direction of the chemical reactions, that is, from reactants to products (Fig. 2A) (*32*). They are beginning to yield many new compounds (see, for example, Fig. 2, B and C) (*33, 34*). This direction of analysis is analogous to target-oriented synthesis before the development of retrosynthetic analysis. Planning such syntheses in a way that provides large collections of spatially segregated small molecules requires only that building blocks be incorporated with split-pool synthesis, preferably with encoded split-pool synthesis so that compounds scored as positives in screens can be readily characterized structurally. Planning in a way that achieves structural complexity and diversity requires considerably more thought. Nevertheless, guiding principles have emerged that provide a means to plan such syntheses systematically (Figs. 3 and 4), in analogy to retrosynthetic analysis in target-oriented synthesis.

Planning Syntheses of Structurally Complex Small Molecules

Complexity and diversity can be analyzed separately, although in designing an actual synthetic pathway, the ideas concerning each of them should be integrated as a final step in the analysis. Certain reactions in organic synthesis are noteworthy for the resulting complexity they generate in their products. Attempts have even been made to quantitate this complexity-generating property (*35*). In diversity-oriented synthesis, pairs of such reactions, in which the product of the first is a substrate for the second, are especially useful (*34, 36–38*). These complexity-generating reaction pairs represent a subset of what are generally referred to as tandem reactions.

This concept is especially powerful when it is used in an iterative manner (Fig. 3A). The first reaction illustrated, named the Ugi four-component reaction, is noteworthy for its ability to generate complex structures from simple building blocks. By judicious selection of diene- and dienophile-containing building blocks among the four components, the product of this reaction is a substrate for the intramolecular Diels-Alder reaction, another complexity-generating reaction (*39, 40*). The pair of reactions can therefore proceed in a single operation, and thus four simple components are converted into a complex tricyclic ring structure in a single operation. The product of this tandem reaction contains a cis-alkene within a strained five-membered ring. This functionality is a substrate for another complexity-generating reaction, the ring-opening, ring-closing olefin metathesis reaction (*41*). Although the additional functional groups required for such a reaction (two allyl groups) were added in a separate transformation, the metathesis reaction provides a product containing two seven-membered and two five-membered rings, and it again illustrates the unique product-substrate relation described above (*40*). Through the consecutive use of tandem complexity-generating reactions, four simple components are converted efficiently into a complex polycyclic ring skeleton.

Planning Syntheses of Structurally Complex Small Molecules Having Large Rings

The above example illustrates syntheses of compounds containing five-, six-, and seven-membered rings. Larger "macrocyclic" rings can provide an even more effective means to display a stereochemically complex array of substituents in a defined manner for potential interactions with biological macromolecules. However, their synthesis en masse by the split-pool strategy presents a special challenge, because the longer chains of their acyclic precursors can usually achieve many conformations not suited for ring closure. In one strategy for overcoming this limitation, acyclic precursors to larger rings are designed that have conformational features well suited for ring closure. In the example given in Fig. 3B, the features of short chains that ensure efficient closure to six-membered rings were preserved in precursors to 12-membered rings by rationally inserting three unsaturated and isostructural units—an ester, an amide, and an olefin—into a conceptual (six-membered ring) progenitor (*42*). In general, synthesizing structurally complex

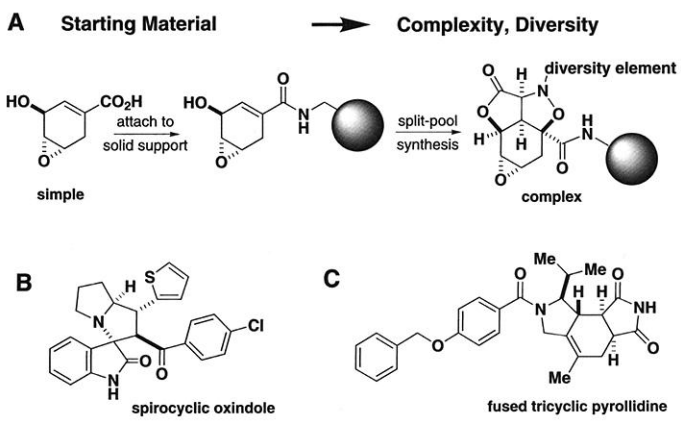

Fig. 2. Diversity-oriented organic synthesis and forward synthetic analysis. (**A**) An example of a forward analysis used to plan a diversity-oriented synthesis (*26*). Beginning with a simple building block, the analysis provides a synthetic pathway leading to a large collection of structurally complex and diverse compounds. (**B** and **C**) Small molecules synthesized with forward synthetic analysis: (B) a spirocyclic oxindole (*33*) and (C) a fused tricyclic pyrollidine (*34*) are representative structures of small molecules that can be used to modulate disease-related biological pathways.

compounds en masse will require careful consideration of conformational principles to ensure successful outcomes.

Planning Syntheses of Structurally Diverse Small Molecules

Structural diversity in split-pool syntheses can be achieved by at least three different methods. A simple one involves the use of different building blocks at steps involving the splitting of a synthetic intermediate into separate reaction vessels (*43*). For example, the building blocks shown in Fig. 4A were used, together with other building blocks, in a reaction pathway that produced over 2 million distinct and spatially segregated small molecules (*26*). A second, related method uses stereochemistry to generate diversity (Fig. 4B) (*42*). Stereoisomeric products increase the diversity of the final collection even though stereoisomeric compounds are constitutionally identical. Their topographical differences cause them to interact with chiral macromolecules in distinct ways.

Efforts are underway in many drug discovery groups to analyze the diversity of small molecules computationally (*44*). Typically, such studies aim to identify an optimal collection of building blocks to be appended onto a common skeletal array of connected atoms, termed a scaffold. A sophisticated analysis might also take into account the effective use of stereochemical considerations, as described above. Although these approaches may prove to be of value to synthetic chemists in the future, my personal belief is that strategic considerations in synthesis, such as the one described below, will prove to be of greater value. Such considerations can result in synthetic pathways that lead to compounds having many building blocks appended to many different scaffolds.

An ambitious goal of diversity-oriented synthesis is to design a synthetic pathway leading to a collection of compounds with a large number of different scaffolds, in the limit where each compound has a unique scaffold. This type of diversity requires the development of synthetic pathways having branch points, where a splitting step is followed by the addition of reagents to different reaction vessels that cause the common substrate to be transformed into products having different atomic skeletons (Fig. 4C) (*42*). In the pathway illustrated in Fig. 4C, one 12-membered ring scaffold is converted into three different scaffolds, including one containing two linked five-membered rings. These products can be pooled and split and the resulting collection of differing scaffolds subjected to a new set of reagents. If their different scaffolds render such a process problematic, one may avoid the pooling step and continue with additional splitting steps using reaction vessels having single scaffolds.

Although it might be easiest initially to analyze planning elements relevant to complexity and diversity separately, a final optimized synthetic pathway must integrate each of these considerations. For example, synthetic pathways could be devised that use pairs of complexity-generating reactions (Fig. 3A) and that have branch points that use new scaffold-generating reactions (Fig. 4C). If encoding methods are used, the synthetic pathways must be compatible with the chemistry associated with the encoding process. To take full advantage of the one bead–one compound nature of split-pool synthesis, solid supports should be used that have the capacity to produce quantities of compounds adequate for a large number of assays.

Conclusions

Organic synthesis, especially diversity-oriented synthesis, will likely play a vital role in drug discovery in the future. Retrosynthetic analysis can be used to plan target-oriented syntheses effectively, but we have, at this stage, an incomplete set of guiding principles for planning diversity-oriented syntheses. In this review, I have outlined a few concepts for planning syn-

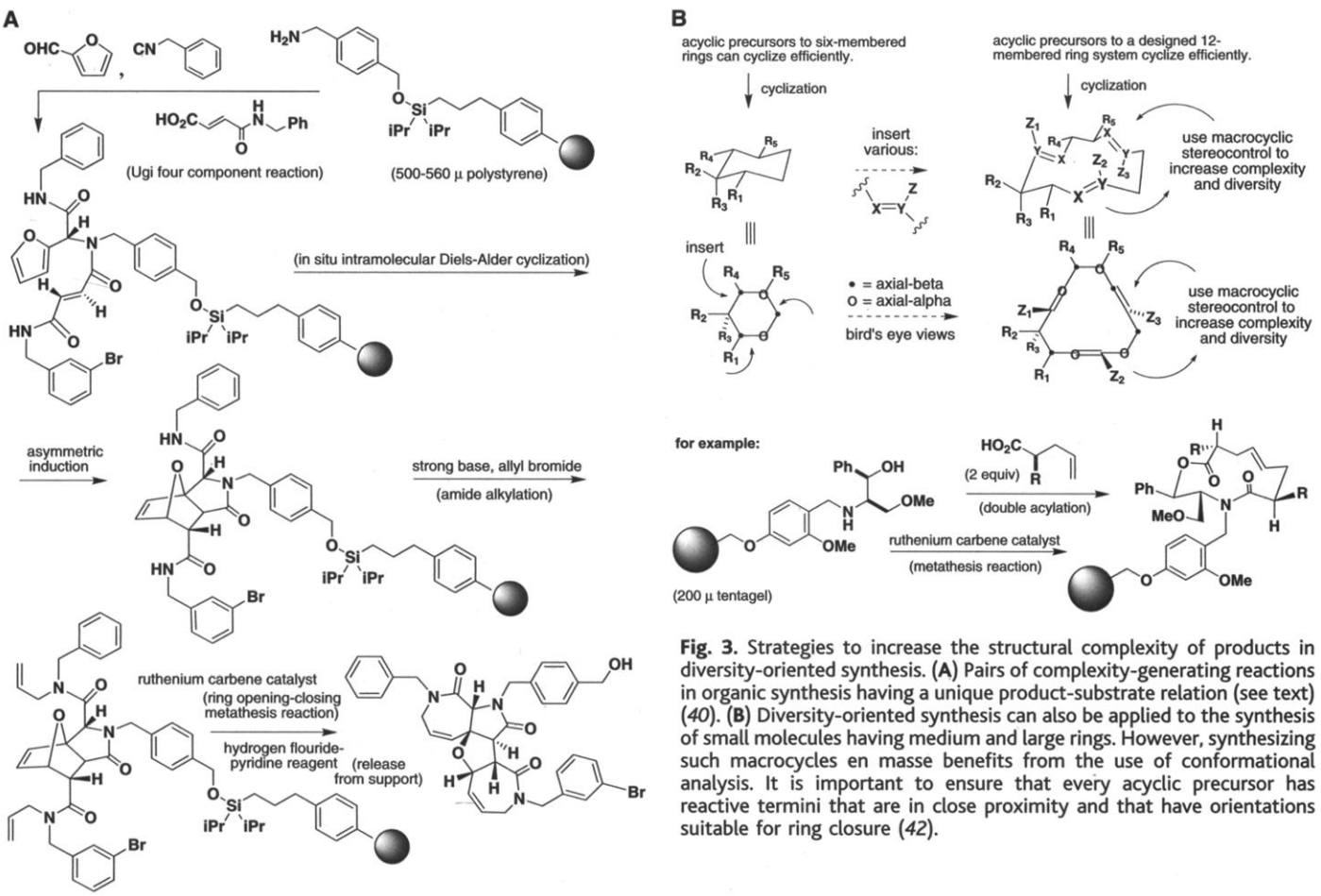

Fig. 3. Strategies to increase the structural complexity of products in diversity-oriented synthesis. (**A**) Pairs of complexity-generating reactions in organic synthesis having a unique product-substrate relation (see text) (*40*). (**B**) Diversity-oriented synthesis can also be applied to the synthesis of small molecules having medium and large rings. However, synthesizing such macrocycles en masse benefits from the use of conformational analysis. It is important to ensure that every acyclic precursor has reactive termini that are in close proximity and that have orientations suitable for ring closure (*42*).

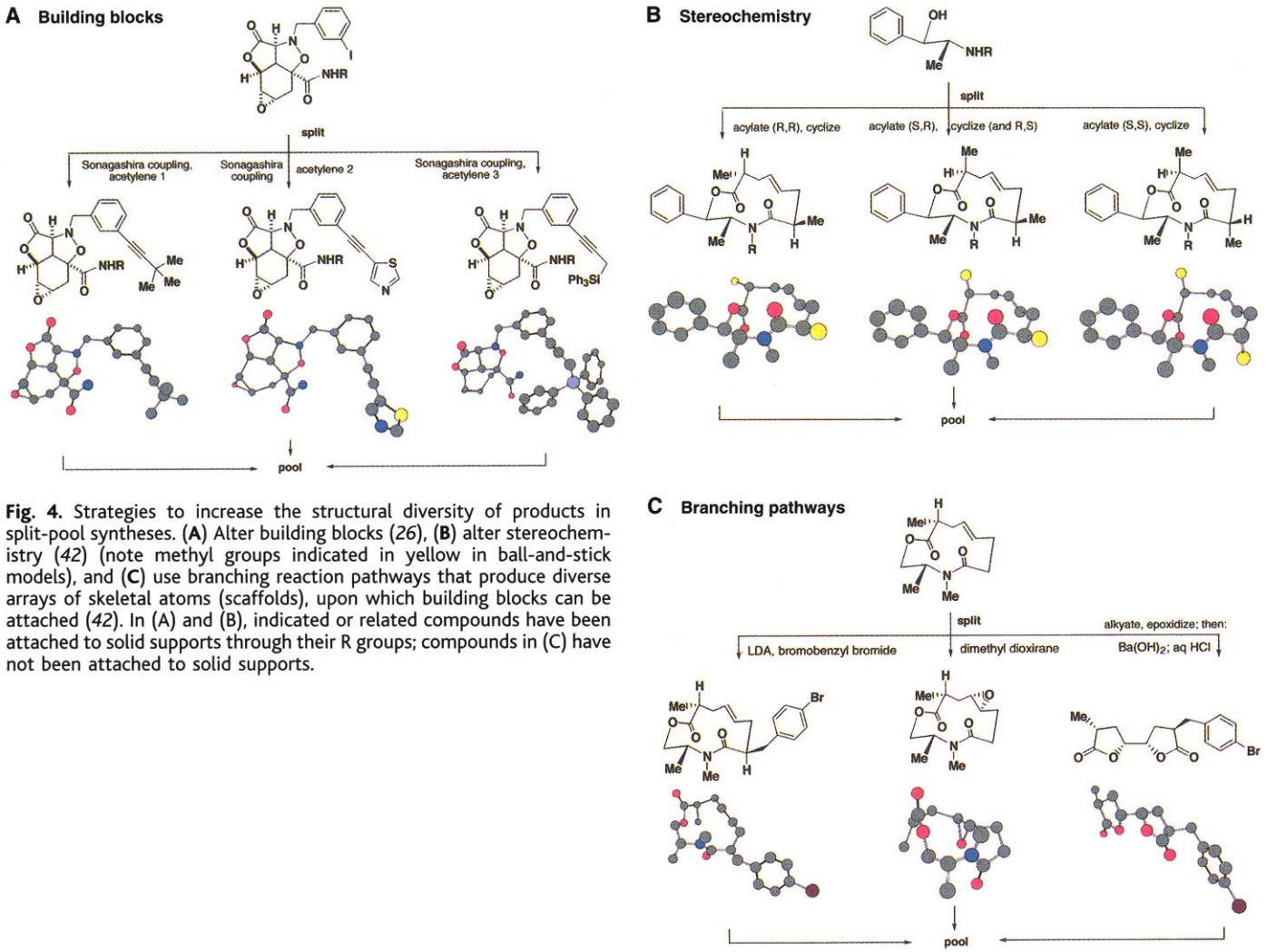

Fig. 4. Strategies to increase the structural diversity of products in split-pool syntheses. (**A**) Alter building blocks (*26*), (**B**) alter stereochemistry (*42*) (note methyl groups indicated in yellow in ball-and-stick models), and (**C**) use branching reaction pathways that produce diverse arrays of skeletal atoms (scaffolds), upon which building blocks can be attached (*42*). In (A) and (B), indicated or related compounds have been attached to solid supports through their R groups; compounds in (C) have not been attached to solid supports.

thetic pathways that yield structurally complex and diverse small molecules. The identification of pairs of complexity-generating reactions that have a unique product-substrate relation, the use of conformational analysis, and the use of branching reaction pathways that allow many different building blocks to be appended to many different skeletal arrays of atoms are likely to be useful planning elements. However, our ability to plan currently lacks guidance from our growing knowledge of small molecule–binding sites on biological macromolecules. This knowledge could in principle be used to constrain the structures of synthetic compounds to those optimally fitted for binding. Input from structural, biophysical, and theoretical studies may therefore provide additional guiding principles. An understanding of the evolutionary principles underlying the selection of biosynthetic pathways and their small-molecule products may also be helpful. For example, both structural and evolutionary considerations could facilitate the effective use of moderately reactive elements, such as electrophilic epoxides and Michael acceptors commonly found in natural products, in diversity-oriented syntheses.

There are many new challenges, both intellectual and technical, for synthetic organic chemists engaged in diversity-oriented synthesis. It is a fertile ground for chemists, one that is beginning to facilitate the discovery of new drugs today and that promises to make many new connections to biology and medicine in the future.

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REVIEW

Mechanism-Based Target Identification and Drug Discovery in Cancer Research

Jackson B. Gibbs

Cancer as a disease in the human population is becoming a larger health problem, and the medicines used as treatments have clear limitations. In the past 20 years, there has been a tremendous increase in our knowledge of the molecular mechanisms and pathophysiology of human cancer. Many of these mechanisms have been exploited as new targets for drug development in the hope that they will have greater antitumor activity with less toxicity to the patient than is seen with currently used medicines. The fruition of these efforts in the clinic is just now being realized with a few encouraging results.

In some areas of the world, cancer has become or shortly will become the leading disease-related cause of death of the human population. For example, in the United States, cancer is the second leading cause of death behind cardiovascular disease, and it is projected that cancer will become the leading cause of death within a few years. There are two main reasons for this change. First, cancer is a disease of multiple accumulating mutations that are becoming manifest in human populations, which have enjoyed an increasingly prolonged life-span (*1*). Second, cardiovascular-related deaths are decreasing as a result of an increased understanding of the mechanisms underlying the disease, the identification of risk factors, which indicate life-style changes that can reduce the onset of disease, and the development of targeted molecular therapies. In contrast, the medical treatment of cancer still has many unmet needs. The main curative therapies for cancer—surgery and radiation—are generally only successful if the cancer is found at an early localized stage. Once the disease has progressed to locally advanced cancer or metastatic cancer, these therapies are less successful. Existing chemotherapeutic treatments are largely palliative in these advanced tumors, particularly in the case of the common epithelial tumors such as lung, colorectal, breast, prostate, and pancreatic cancers (*2*). Sometimes, sound mechanistically based chemotherapies are effective but only for a defined period of time. For example, antihormonal treatments of prostate cancer can initially shrink tumors but eventually fail when the residual tumor cells become hormone-independent. Although a few chemotherapeutic regimens have yielded lasting remissions or cures (for example, in testicular cancer and childhood leukemias), it is clear that new therapeutic options are necessary.

In the development of new chemotherapeutic agents, several issues need to be addressed, including improved and durable antitumor efficacy, reduction of toxicities, which can prevent effective dosing of potentially efficacious drugs, and prevention of drug resistance caused by the inherent genomic instability of tumors. Upon the discovery some 20 years ago of the first oncogene defects in cancer (*3*), it was envisioned that the genetic information could be translated into therapeutics that could selectively ablate tumors without the systemic side effects often associated with cancer drugs. The translation of that scientific information into potential new medicines is now starting to emerge. In looking ahead at new targets and new approaches to cancer drug discovery, it can be useful to look at which pharmacological treatments have worked in other diseases, such as cardiovascular disease, and over which time frame these developments occurred.

Medicines to treat hypertension evolved over a 40-year period (*4*). In the 1950s and 1960s, the drugs of choice included reserpine and methyldopa, both of which act in the central nervous system. An understanding of receptor pharmacology led to development of peripherally acting adrenergic receptor antagonists in the 1970s, and this evolved in the 1980s and 1990s to peripherally acting non-adrenergic agents, such as inhibitors of angiotensin-converting enzyme and angiotensin-receptor antagonists, which have far fewer side effects than the early centrally acting agents. The lessons to be learned here are that basic research discoveries on the fundamental mechanisms responsible for a disease state often lead to the most direct pharmaceutical approaches to manage the disease. However, successful treatments emerge from an iterative process that depends not only on the scientific learning curve but also on feedback from clinical trials where we learn whether our mechanistic ideas are having a therapeutic benefit and what the drawbacks are in terms of side effects. The development of initial drugs and subsequent pharmacological improvements also benefits from knowledge of the specific molecular target of the drug, such as a receptor or enzyme. It takes decades to learn what approaches can initially provide some benefit for a disease and to then progress to a point where the disease is effectively managed with medicines essentially devoid of side effects.

Where Are We in Cancer?

Cancer chemotherapy emerged in the 1940s from toxicological studies of nitrogen mustard–based war gas (*2*). The anticancer activity of nitrogen mustard is due to DNA alkylation, and many other cancer drugs were developed on the basis of this general concept (modification of DNA, which impairs accurate replication) and then optimized on the basis of cytotoxicity in growth proliferation models. Mechanism-based approaches have also been explored for several decades. Antimetabolite drugs (for example, methotrexate and mercaptopurine) were developed on

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