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Function-Oriented Synthesis, Step Economy, and Drug Design

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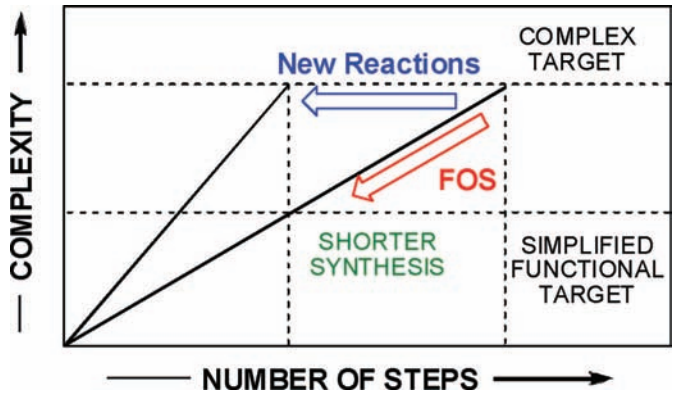
CONSPECTUS



This Account provides an overview and examples of function-oriented synthesis (FOS) and its increasingly important role in producing therapeutic leads that can be made in a step-economical fashion. Biologically active natural product leads often suffer from several deficiencies. Many are scarce or difficult to obtain from natural sources. Often, they are highly complex molecules and thus not amenable to a practical synthesis that would impact supply. Most are not optimally suitable for human therapeutic use. The central principle of FOS is that the function of a biologically active lead structure can be recapitulated, tuned, or greatly enhanced with simpler scaffolds designed for ease of synthesis and also synthetic innovation. This approach can provide practical access to new (designed) structures with novel activities while at the same time allowing for synthetic innovation by target design.

This FOS approach has been applied to a number of therapeutically important natural product leads. For example, bryostatin is a unique natural product anticancer lead that restores apoptosis in cancer cells, reverses multidrug resistance, and bolsters the immune system. Remarkably, it also improves cognition and memory in animals. We have designed and synthesized simplified analogs of bryostatin that can be made in a practical fashion (pilot scale) and are superior to bryostatin in numerous assays including growth inhibition in a variety of human cancer cell lines and in animal models. Laulimalide is another exciting anticancer lead that stabilizes microtubules, like paclitaxel, but unlike paclitaxel, it is effective against multidrug-resistant cell lines. Laulimalide suffers from availability and stability problems, issues that have been addressed using FOS through the design and synthesis of stable and efficacious laulimalide analogs. Another FOS program has been directed at the design and synthesis of drug delivery systems for enabling or enhancing the uptake of drugs or drug candidates into cells and tissue. We have generated improved transporters that can deliver agents in a superior fashion compared with naturally occurring cell-penetrating peptides and that can be synthesized in a practical and step-economical fashion.

The use of FOS has allowed for the translation of exciting, biologically active natural product leads into simplified analogs with superior function. This approach enables the development of synthetically innovative strategies while targeting therapeutically novel structures.

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Introduction

Synthetic chemistry has transformed our world, changing food, clothing, shelter, medicine, culture, and even art in fundamental but often not widely appreciated ways. Imagine art without the full complement of synthetic colors; imagine medicine without the drugs that synthesis has made possible. In this Account, we call attention to yet another area that is being transformed by synthesis, namely, drug discovery, and how a focus on biological function is increasingly being used to create novel leads that can be synthesized in a practical and step-economical fashion.[1]

Most current drug discovery strategies find precedent in Nature. All organisms screen their environment and select chemicals for synthesis, consumption, or use that provide evolutionary advantage. Bryozoa, for example, organisms of importance in this Account, are proposed to use a chemical produced by a symbiont to protect their progeny from predation.[2] Bacteria putatively employ chemicals to wage war against other bacteria for control of their ecological niche.[3] Ants and other organisms use chemicals for communication.[4] Emerging studies describe cases of animals using natural materials for self-medication.[5] As very recent players in this global chemical exchange, humans have also found products derived from a vast range of natural sources to be of great benefit. Daphnane extracts, for example, have been in continuously recorded therapeutic use for over 2000 years.[6] While less well documented, many other natural products have found similar use for centuries.

With rare exception, the molecules available for human use prior to the 19th century were principally those obtained from natural sources. Things changed dramatically with the advent of abiological synthesis and the ability to design and make new molecules. Organic synthesis enabled this dramatic chemical evolution, serving initially to supply scarce or inaccessible natural products, an activity still very much in demand today, and subsequently allowing for the conversion of natural, biologically active products into derivatives better suited for medicinal use. The evolution of β-lactam antibiotics from their initial natural structures to synthetically modified and therapeutically more effective derivatives is exemplary.[7] Mode of action studies greatly accelerated this evolution, providing an increasingly refined understanding of ligand–receptor interactions and allowing one not only to connect structure with biological function but, at a higher level of resolution, to connect subunits in a structure (pharmacophoric elements) with function. The design of small molecule opiod agonists and rapamycin analogs through the pharmacophoric analysis of endogenous endorphins and rapamycin protein complexes are illustrative.[8]

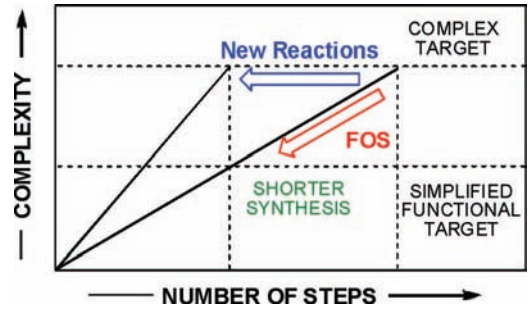


FIGURE 1. Improving step economy with FOS or new reactions.

The advancement and confluence of the disciplines of synthesis, mechanistic medicinal chemistry, and structural biology have more recently opened an even broader range of opportunities by allowing one to shift focus from the total structure of a biologically active natural product to the subset of its functionality that influences or determines its activity (function). This in turn has enabled a shift in many situations from structure- or target-oriented synthesis to function-oriented synthesis (FOS). The central principle of FOS is that the function of a biologically active lead structure can be emulated, tuned, or even improved by replacement with simpler scaffolds designed to incorporate the activity-determining structural features (or their equivalent) of the lead compound. This approach allows for the step-economical synthesis of novel structures with improved or new activities. FOS thus addresses a commonly encountered problem, namely, that many natural products are too complex to be prepared in a way that impacts supply. There are only two ways to resolve this problem: develop new reactions and synthetic strategies that allow for shorter routes to a target or, through FOS, design less complex targets with comparable or superior function that could be made in a practical and even synthetically novel manner (Figure 1). Both approaches rely on synthetic innovation and are driven by the importance of step economy, as it, in turn, determines most other factors that bear on practical supply including solvent and other waste streams (atom economy), separations, costs, time, environmental impact, and personnel requirements (unquestionably our most important "economy," human economy).

FOS addresses several concerns related to drug discovery. First natural products are not "designed" for human therapeutic use and as a consequence often have undesired side effects. By focusing on target-specific function, FOS can be used to minimize off-target activities and to enhance beneficial activities. Second, FOS can be used to optimize formulation, ADME, and pharmacokinetic performance, thereby

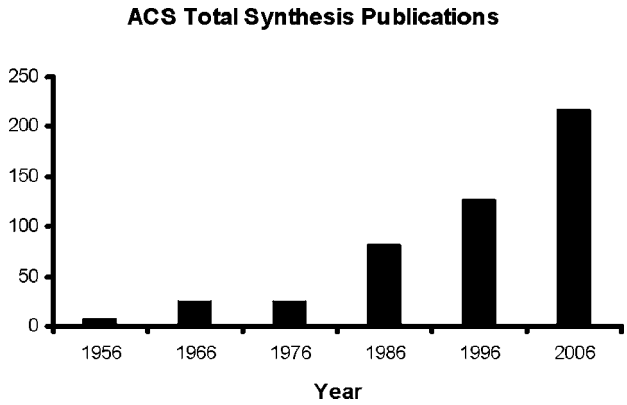


FIGURE 2. Number of total synthesis publications in ACS journals in the indicated year over the last five decades.[9]

avoiding problems exhibited by many natural products (e.g., the formulation of Taxol). Third, because the focus of FOS is function rather than structure, it can address the concern that some natural products are too complex to make in a practical fashion. As evident from a count of total syntheses in American Chemical Society journals over the last 50 years (Figure 2), our ability to make natural products has impressively improved with over 200 syntheses reported last year alone. Thus the concerns voiced about natural products being too complex are not whether they can be made but whether the synthesis can impact supply (i.e., whether it is practical), thereby enabling further research or use.

It is now evident that greatly simplified structures can mimic or exceed the function of those from which they are inspired and because of their simplified structure, be made in a practical, step-economical fashion (Figure 1, FOS). A recent review provides a measure of the increasing importance of FOS, indicating that from 1981 to June 2006, the majority (57%) of new chemical entities (NCEs) mimic natural products, were derived from natural products, or were designed based on a natural product pharmacophore.[10] Interestingly, only 5% of the 1184 NCEs introduced over this period were natural products themselves. Importantly, FOS is not restricted to complex bioactive natural product leads as a starting point as it is also an increasingly effective strategy for the advancement of simple, often modestly active, non-natural library "hits" to potent and effective clinical candidates. Finally, FOS can also drive design and synthetic innovation, as it requires the creative translation of a lead and often complex structure into a structure designed for superior performance and ease of synthesis. More generally, rather than relying on Nature to produce interesting targets, FOS allows the chemist, and especially those skilled in synthesis, to design targets with improved function and to do so in a way that allows for synthetic innovation.

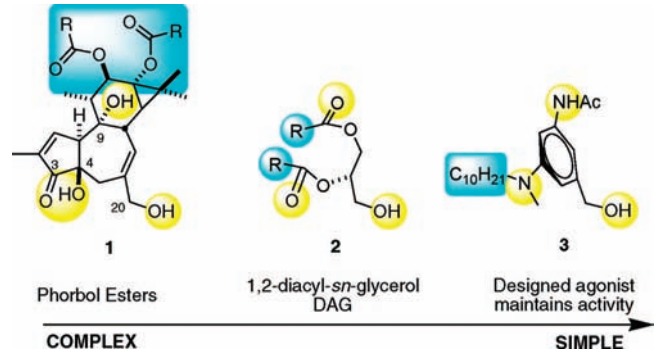


FIGURE 3. PKC modulators with key pharmacophoric atoms (yellow) and lipophilic regions (blue).

Representative Examples of FOS

A striking example of FOS is found in studies leading to the first designed protein kinase C (PKC) modulator.[11] PKC is an enzyme family critical to many cellular processes such as apoptosis, cell cycle regulation, gene expression, ion channel regulation, neuronal growth, and cellular differentiation.[12] Abnormal PKC signaling is implicated in several therapeutically important areas including cancer, cardiovascular disease, neuropathic pain, and cognitive function.[13] Agents that bind to the C1-regulatory domain of PKC and related C1-kinases can be used to selectively control kinase function, because only about 10% of the kinases in the human kinome contain a C1 domain.[14] Moreover, C1 ligands can activate or inhibit kinase activity, as opposed to ATP-binding site agents that only inhibit activity.[15]

One of the most important and widely studied C1 ligands is the potent tigliane phorbol (**1**, Figure 3), a complex target whose total synthesis requires 29 steps.[16] Interestingly, the endogenous activator of PKC, diacylglycerol (DAG, **2**), is a significantly simpler molecule that binds competitively to the same site as phorbol. Computer modeling suggests that these structurally distinct molecules achieve similar function (PKC binding) through a similar array of recognition elements corresponding to the C3/C4 carbonyl/hydroxyl, the C9 and C20 hydroxyl groups, and side chain lipids in phorbol (Figure 3). New PKC modulators could thus be designed by arraying a similar set of recognition elements on a structurally simplified scaffold. Based on this function-oriented design, the simplified arene **3**, incorporating the key recognition features of the leads, was synthesized (in only 7 steps vs 29 steps for lead **1**). It proved to be the first designed compound that bound to and activated PKC, mimicking a subset of the activities of phorbol.[11] Such designed mimics have been recognized for anticancer and immunomodulatory activity, and this approach has been extended successfully to the generation of preclinical candidates based on other leads such as bryostatin (vide

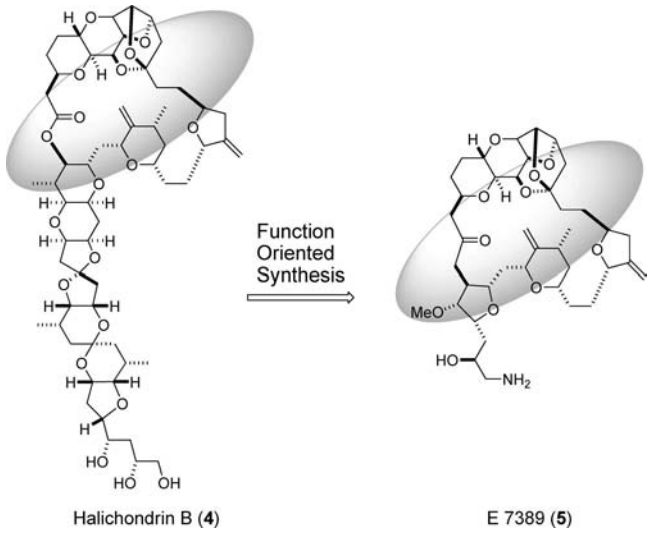


FIGURE 4. Halichondrin B and its simplified functional analog.

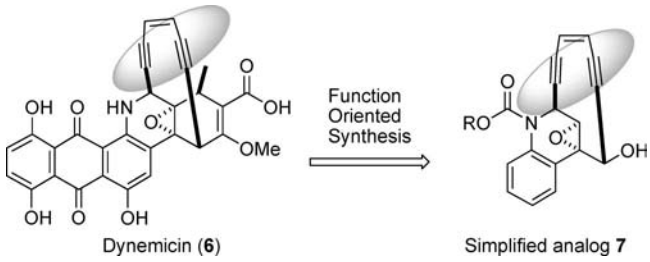


FIGURE 5. Dynemicin and a simplified functional analog.

infra) and to the design of other DAG analogs in our and other laboratories.[17]

Studies on halichondrin B (**4**, Figure 4), a potent marine natural product that displays antineoplastic activity based on its ability to destabilize microtubules, provide a more recent example of the enormous structural simplification and therefore enhanced step economy that can be achieved without sacrificing biological function. Halichondrin B cannot be supplied on scale from natural sources or synthesis due to its scarcity and complexity. However, studies have revealed that only the simplified analog **5**, currently in clinical trials, is needed for activity.[18]

Another exciting example in which a focus on function has enabled target simplication is found with "stapled peptides." These greatly simplified protein surrogates serve to mimic α-helices of proapoptotic proteins, are easier to make, and are efficacious in murine models of cancer.[19]

Studies in our laboratory on dynemicin (**6**, Figure 5), a complex enediyne antitumor agent, illustrate another use of FOS in which the sought-after "function," DNA cleavage, involves mimicking the generation of a reactive diradical species through a Bergman cyclization. The simplified analog **7** was designed to emulate this function. The racemic synthesis of dynemicin requires 33 steps,[20] while the synthesis of ana-

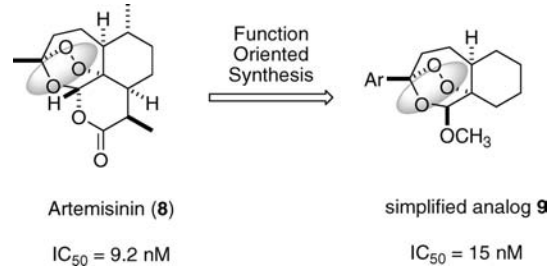


FIGURE 6. Artemisinin and its simplified functional analog.

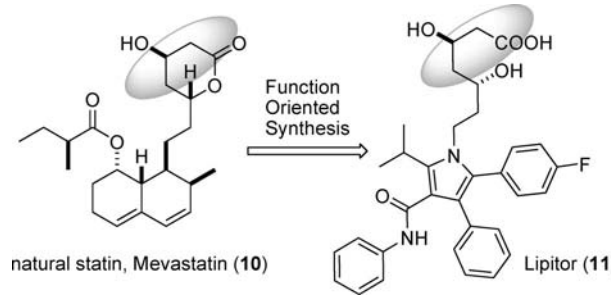


FIGURE 7. Design of Lipitor from the naturally occurring compound.

logs such as **7** requires only 7–8 steps.[21] Significantly, **7** serves as an effective functional mimic of **6**, exhibiting the ability to efficiently cleave DNA upon irradiation or pH change.

A related example in which "function" is associated with emulating chemical change is found in simplified analogs of the antimalarial artemisinin. The simplified but functional analogs show in vitro antimalarial activities comparable to that of the natural product and are also effective in rodent models (Figure 6).[22]

The development of the synthetic statin, atorvastatin (Lipitor, **11**, Figure 7) from naturally occurring statin **10** is another example of function being retained on a more synthetically accessible scaffold. The mevalonolactone pharmacophore of the natural complex statins is retained in **11** in the form of a dihydroxy acid. The attached hydrophobic ring structure serves to enhance binding.[23]

While FOS often takes advantage of natural product leads, the concept can also be applied to non-natural systems and non-natural functions. Examples include work by Chang on designed boronate probes for real-time cellular monitoring of H_2O_2.[24] Indeed, the whole field of real-time imaging is driven by the desire to produce functional molecules with the ability to report change in complex living systems. Using metals as function modulators, Meggers has shown that organometal complexes can be used to achieve active analogs of the natural product staurosporine, an ATP binding site inhibitor.[25] These examples represent ways in which the intersection of synthesis and design have generated novel non-natural molecules with novel biological function.

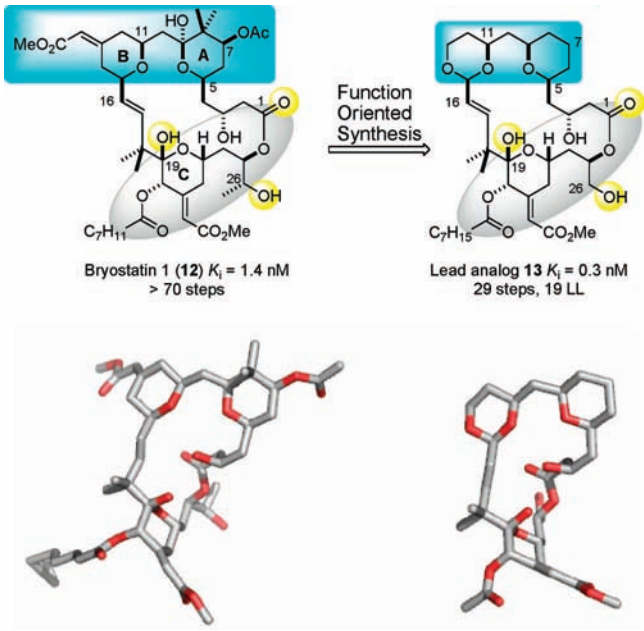


FIGURE 8. Bryostatin 1 (**12**) and lead analog **13** with pharmacophoric atoms (yellow) and the lipophilic region (blue). Modeling comparisons between bryostatin and **13** indicate close similarity in the spatial array of pharmacophoric atoms (rmsd = 0.22 Å).

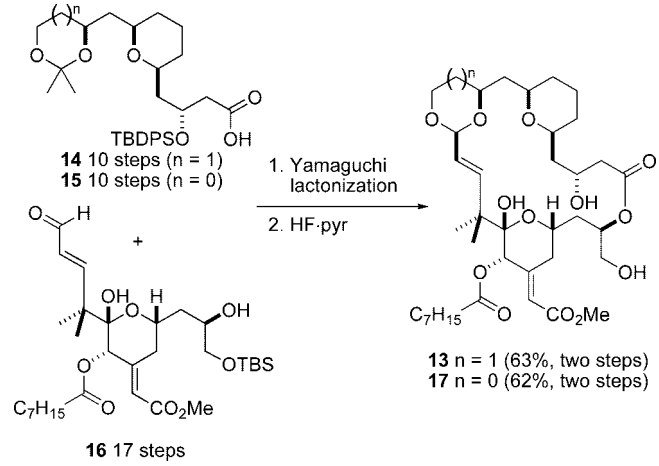
FOS and the Design of Bryostatin Analogs

The bryostatins (**12**, Figure 8) are significantly complex molecules that have attracted attention as anticancer agents due to a unique range of activities, including their ability to induce apoptosis,[26] reverse multidrug resistance,[27] and modulate the immune system.[28] Bryostatin also synergizes with other antineoplastic agents and is currently in clinical trials for the treatment of cancer.[29] Exciting recent work has also shown that bryostatin can enhance memory and learning in animals, with potential implications for the treatment of Alzheimer's disease.[30]

Unfortunately, access to bryostatin is extremely limited, as it is obtained in a low yield of only 0.00014% from marine bryozoa.[31] In addition to seasonal variations in the amount of bryostatins, large scale harvesting from a marine source would create problems in the delicate marine ecosystem. Genetic engineering offers another source, but this is limited to those structures that arise through biosynthesis and thus not necessarily structures optimized for therapeutic use. Total synthesis offers greater flexibility, but current syntheses require >70 steps and thus at present do not impact supply.[32]

The problems and opportunities presented by bryostatin are ideally suited for FOS because its therapeutic activity is connected to only a subset of its structure and that pharmacophore could be designed into a simplified target more readily accessed through synthesis. Bryostatin potently binds

SCHEME 1. Two-Step Convergent Route to Analogs, Coupling Spacer (**14** or **15**) and Recognition (**16**) Domains



to the C1 domain of PKC (K_i = 1.4 nM). Based on our previous pharmacophoric analysis (Figure 3), the C1 carbonyl and C19 and C26 alcohols as well as a corresponding lipophilic region of bryostatin were hypothesized as key binding elements (Figure 8).[33] An analog was thus designed with simplified A- and B-rings and an intact C-ring, putatively required for enzyme recognition. One of the attractive and innovative aspects of designing one's own target is that one can select not only for function but also for ease of synthesis and for the development of new methodology. Toward these ends, the C26 methyl group was deleted at the design stage to emulate other C1 binders and allow for closer association in the receptor binding pocket.[34] Further, the hydropyranyl B-ring of bryostatin was replaced with a 1,3-dioxane, allowing both for its introduction using a novel macrotransacetalization that would set the C15 stereocenter under thermodynamic control and for optimal convergency in target assembly. Importantly, this design simplified the original synthetic problem, enabling a highly convergent synthesis in which an AB-ring system is coupled to a C-ring fragment in the final two steps of the synthesis. This late stage convergency allows facile access to many analogs of the AB-rings or C-rings without executing both arms of the entire synthesis.

Representative of how this plan played out, spacer domain **14** and recognition domain **16** were coupled in two steps to produce analog **13** (Scheme 1, $n = 1$).[35] The remarkable macrotransacetalization proceeds with global deprotection and thermodynamically controlled B-ring closure correctly setting C15. This method is general, being used in the synthesis of >40 bryostatin analogs including those with five-membered B-rings (**17**, Scheme 1, $n = 0$).[36] More recently this design and synthesis concept has proven successful in Smith's work leading to a highly potent phorboxazole analog.[37]

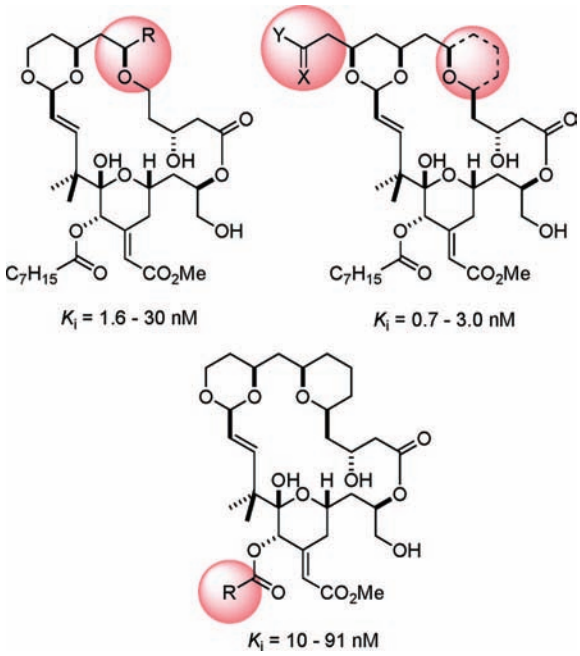


FIGURE 9. Representative bryostatin analogs and their binding affinities.

Significantly, this FOS approach led to the realization of analogs that bind to PKC with affinities comparable, and in some cases, superior to bryostatin (K_i = 0.3 nM vs 1.4 nM). These analogs can be made in 29 steps, a savings of >40 steps over the shortest synthesis of bryostatin.[38] This study demonstrates a central advantage of FOS, namely that superior function can be achieved in fewer steps with simplified structures while enabling synthetic innovation. Given the potency of bryostatin (<1.2 mg is needed cumulatively for an 8−12 week dosing regimen in humans), this synthesis can supply sufficient quantities for clinical studies. This route has been scaled to produce multigram quantities of advanced intermediates. Moreover, because the supply of bryostatin has been limited, this work also opens the door for much needed fundamental mode of action research and the possible uses of these bryologs for indications other than cancer.

Additional analogs involving A-ring,[39] B-ring,[40] and C20 ester variations (Figure 9) have been generated based on modeling studies using a crystal structure of a PKC C1 domain. In total, 31 analogs of bryostatin have been efficiently synthesized that retain single-digit nanomolar affinity to PKC (K_i < 10 nM).[41] Importantly, when tested for growth inhibitory activity against the NCI panel of human cancer cell lines, the analogs evaluated thus far generally show greater potency than bryostatin. For some cell lines, the potencies of the analogs exceed that of bryostatin by 2−3 orders of magnitude. In this application, FOS has led to more potent analogs that can be supplied in quantity and tuned for performance and at the same time allowed for the development of a simple, effective method for convergent macrolide formation.

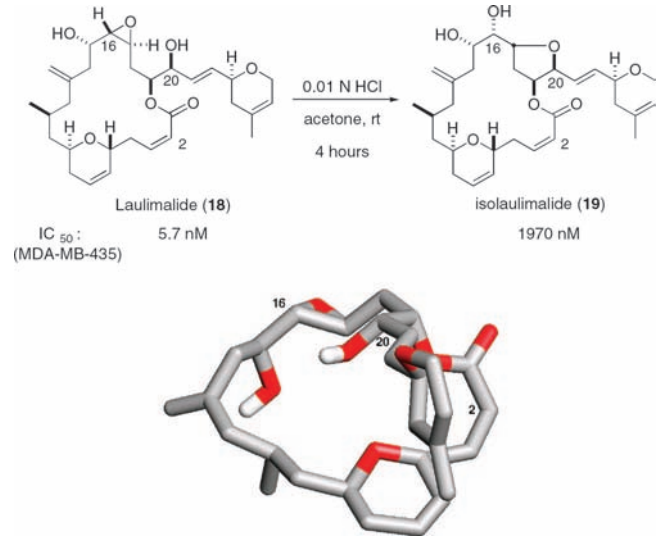


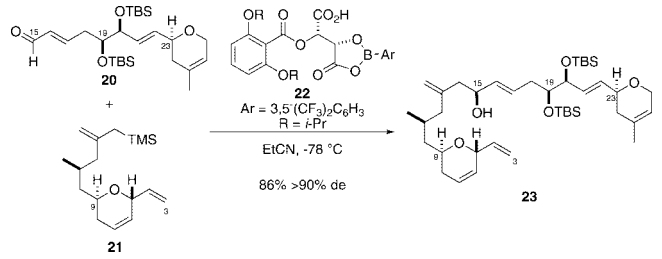
FIGURE 10. Laulimalide (**18**) converts to isolaulimalide (**19**) in mildly acidic media. Molecular modeling indicates that the C20 hydroxyl is well-positioned for epoxide opening.

FOS and the Design of Laulimalide Analogs

Laulimalide (**18**, Figure 10) is a potent, microtubule-stabilizing, anticancer lead.[42] Like Taxol, laulimalide disrupts microtubule dynamics, leading to apoptosis.[43] However, laulimalide and Taxol have different binding sites on tubulin.[44] As a result, laulimalide is unaffected by mutations in the taxane binding site, retaining efficacy against Taxol-resistant cancers. Laulimalide is also a poor substrate for the drug efflux P-glycoprotein and therefore retains antiproliferative activity against drug-resistant cell lines.

Like bryostatin, the yield of laulimalide from its marine source is extremely low (~0.00016%). In addition, laulimalide is isolated along with an isomer, isolaulimalide (**19**, Figure 10). It was shown that laulimalide quickly converts to isolaulimalide in mildly acidic media by attack of the C20 alcohol on the proximal epoxide.[42] Molecular modeling indicates that the C20 hydroxyl group is poised for backside attack on the C17 C−O bond of the epoxide in a low-energy conformation (Figure 10). Importantly, the IC_{50} values of **18** and **19** in MDA-MB-435 drug sensitive cell lines are 5.7 and 1970 nM, respectively, indicating that isolaulimalide is significantly less efficacious. This 3 orders of magnitude drop in potency of **19**, coupled with the fact that stable and superior analogs of **18** could be more readily accessed and entered into preclinical studies, prompted our group to develop a total synthesis[45] that in turn was used to access novel analogs.[46]

SCHEME 2. A Uniquely Complex Example of an Asymmetric Sakurai Reaction



In this case, FOS was used to design and synthesize simplified analogs that would retain the antiproliferative activity of laulimalide but exhibit enhanced stability. The latter was achieved by elimination of the path of decomposition, an internal S_N2-like reaction, through removal of the electrophilic epoxide (**24**, Figure 11), reduction of the nucleophilicity of the C20 hydroxyl group (**25**), and conformational modification of the macrocyclic core (**26**).[47] Our approach was based on a uniquely concise plan incorporating several synthetic features including a highly complex example of an asymmetric Sakurai reaction (Scheme 2).[45]

Analogs **24**, **25**, and **26** were tested in MDA-MB-435 cells, providing IC_{50} values of 120, 240, and 2500 nM, respectively. While less potent than laulimalide, analogs **24** and **25** do not suffer from the instability problems found with laulimalide. These analogs also retain a mechanism of action similar to that of laulimalide and are effective against multidrug-resistant cell lines.[48] Analogs **24** and **25** were also shown to synergize with Taxol and 2-methoxyestradiol more effectively than laulimalide.[49] While the step savings at this point is modest, the ability to access stable analogs eliminates a problem associated with the natural product and allows for an investigation of the features of laulimalide that control its activity.

FOS and the Design of Molecular Transporters

"Molecular transporter" is a term that we introduced to collectively describe a growing number of agents which, when covalently linked to or complexed with a cargo, enable or enhance its entry into cells or tissue. Such agents have enormous potential in fundamental as well as applied research. For example, most drugs that enter cells by passive diffusion are generally designed to conform to a certain log *P* range because they must be soluble in both the extracellular milieu (polar) and the plasma membrane (nonpolar). Highly polar (e.g., siRNA) and highly nonpolar drugs (e.g., Taxol) or probes are problematic, but even for those in the preferred log *P* range, enhanced uptake is often desirable. Our FOS studies in

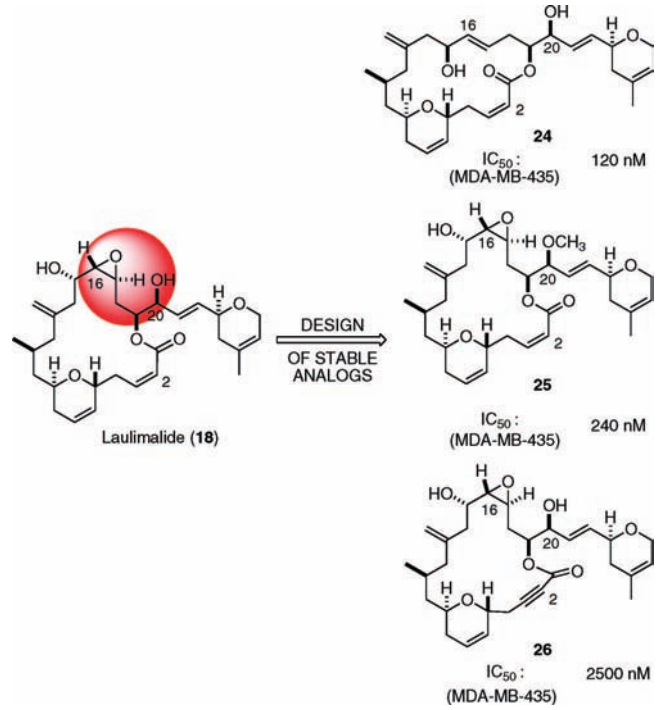


FIGURE 11. Laulimalide and its designed stable analogs.

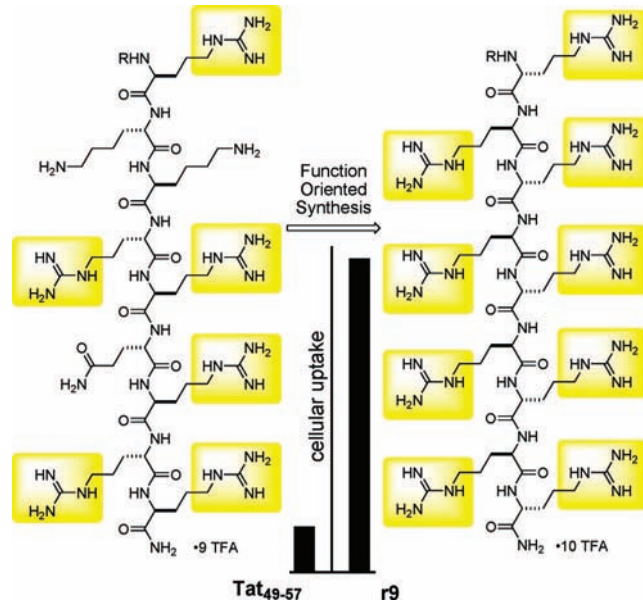
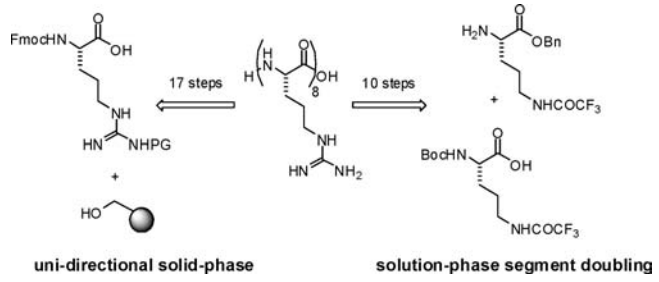


FIGURE 12. Polyarginine transporters derived from Tat and their cellular uptake.

this area started in 1996 prompted by the observation that the nuclear transcription activator protein (Tat) crosses the plasma membrane of cells[50] and that this ability is proposed to be associated with the highly basic sequence of amino acid residues 49−57 (Tat_{49-57}, Figure 12).[51] Significantly, Tat_{49-57} is a highly water-soluble polycation yet exhibits the ability to cross the nonpolar membrane of cells.

SCHEME 3. Step Count Advantage of Segment Doubling



With Tat_{49-57} as a lead, it was envisioned that simpler and more effective transporters could be made using FOS principles. A systematic approach was employed to elucidate the structural requirements for cellular translocation. A series of Tat_{49-57} analogs were synthesized, attached to fluorescent probes, and analyzed for cellular uptake in Jurkat cells by FACS analysis and confocal microscopy. Truncations of either the amine or the carboxyl terminus as well as substitutions of individual amino acids with alanine all gave analogs with diminished cellular uptake.[52] Moreover, charge alone was not sufficient for uptake, because oligomers of lysine (K9), histidine (H9), and ornithine (Orn9) all showed less uptake than Tat_{49-57}.[56] However, a homo-oligomer of arginine (R9) provided a significant increase in uptake compared with Tat_{49-57}. Additionally, the oligomer of unnatural arginine (r9) resulted in even greater uptake, most likely due to decreased proteolysis (Figure 12).[52] Eventually, it was shown that the guanidinium group was key to both the water solubility and the mechanism of uptake. Incorporation of this group into peptoids, peptides, spaced peptides, oligocarbamates, and dendrimers enables their use as molecular transporters. Studies from other groups have greatly extended this list.

Throughout the early stages of this project, the interplay of design (directed at better function) and synthesis (directed at step economy) was critical. The selection of homo-oligomers and then an 8-mer was not arbitrary but dictated by uptake performance and the potential for step economy in synthesis. With respect to the latter, solid-phase synthesis of a mixed oligomer such as Tat_{49-57} requires two operations per unit attached. A hetero-8-mer would thus require 17 synthetic steps including resin cleavage. In contrast, FOS guided selection of a homo-oligomer of eight units because it was expected to have activity comparable to the hetero-8-mer and because of its symmetry, it was expected to be accessible through a novel nine-step segment doubling strategy. Representative of this approach, an arginine precursor is N- and C-protected, and the resultant products are coupled to produce a dimer. The dimer is split, one half is then C-activated

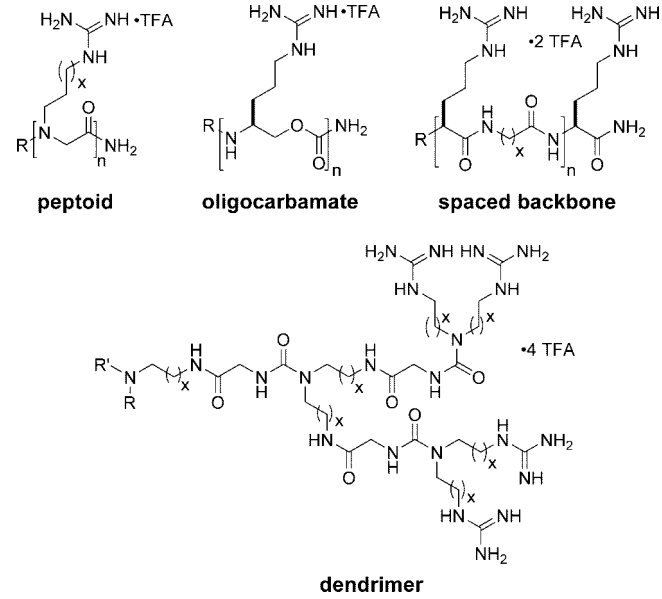


FIGURE 13. Varying scaffolds for polyguanidine transporters.

and the other N-activated, and the resultant products are coupled to produce a tetramer. A third cycle of three steps produces the 8-mer, which on global deprotection and guanidinylation produces the transporter in 10 steps overall (Scheme 3). The step economy associated with this process significantly reduces the cost of synthesis, and importantly, because the use of resins is avoided, the synthesis can be easily scaled in solution phase.[53]

Further studies showed that the transport function of arginine oligomers can be surpassed by peptoids (Figure 13).[52] In addition, replacement of the amide backbone with a carbamate and an increase in the spacing of the guanidinium-containing sidechains (1,4 → 1,6) also produced highly efficient transporters. Furthermore, a library of spaced oligomers containing seven arginines interdigitated with non-α-amino acids also exhibited increased cellular uptake, with a maximal level seen for the maximally spaced system. Finally, branched transporters, such as dendrimers, show in some cases superior uptake relative to oligoarginine.[54]

Through FOS, transporters superior to those found in Nature have been developed. These transporters can be synthesized in a step-economical fashion, a key to their use in fundamental and clinical studies. It is noteworthy that the arginine transporters have been advanced to phase II clinical trials and have more recently been used to develop novel assays for the real-time quantification of uptake and release of transporter probe conjugates in transfected cells and transgenic animals.[55]

Conclusions and Future Prospects

Nature has produced a diverse array of natural products with an exceptional range of activities. Organic synthesis can often compete with Nature in supplying these molecules. However, as the complexity of the natural products increases, the length of syntheses also increases, often leading to a decreased impact on supply. There are principally two ways to address this supply/performance problem: expand the lexicon of new reactions and thus the strategies that would enable more step-economical syntheses or design new but simplified molecules that would be superior in function to the natural product lead and synthesized in a practical fashion. While natural product synthesis continues to be of great value, designing new molecules with superior function has enormous potential at both fundamental and applied levels. Importantly, FOS offers access to novel structures not found in Nature and it encourages advances in the science of synthesis. Indeed, it provides an exciting opportunity for innovation because designed targets can inspire synthetic innovation as much as those produced by Nature. It is clear that targeting natural products will continue to have value for advancing synthesis as well as biology and medicine. It is also clear that function-oriented design and synthesis offers an increasingly powerful and efficacious way of achieving similar if not superior results.

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