Natural-product-like chiral derivatives by solid-phase synthesis

Prabhat Arya* and Myung-Gi Baek

In this genomics and proteomics age, highly functionalized natural products or natural-product-like compounds are likely to play important roles in understanding the functions of emerging biological targets because they serve as small-molecule chemical probes in modulating a target's specific actions (i.e. activation or deactivation). Development of stereoselective reaction-derived methods on solid phase provides a means of obtaining functionalized chiral core structures that may be used for high-throughout syntheses.

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Abbreviations

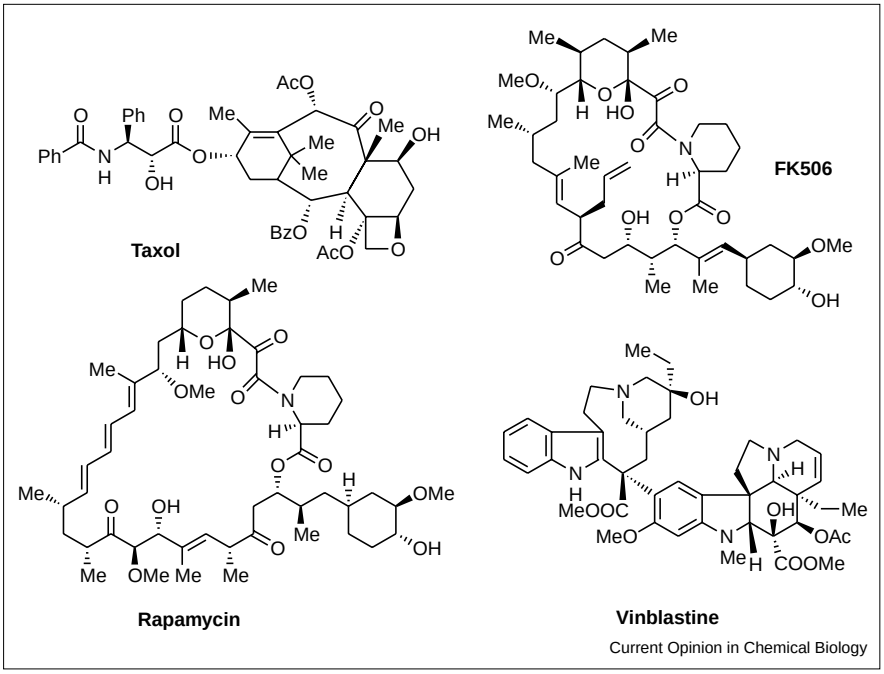
Cbz	benzyloxycarbonyl
DMP	Dess–Martin periodinane
HF	hydrofluoric acid
IBX	*o*-iodoxybenzoic acid
IEDDA	inverse electron demand Diels–Alder

Introduction

Use of cedar leaf extracts for the treatment of skin-related diseases goes back centuries in Canada. This, along with many other historical examples, helped establish strong interests in medicinally relevant plants. Isolation of bioactive natural products and development of modern organic synthesis for obtaining these compounds, as well as their analogs, is a true paradigm of classical medicinal chemistry.

For several decades, challenges in the syntheses of complex natural products have been a driving force in developing stereoselective and enantioselective organic reactions [1•]. Use of chiral reagents and chiral catalysts for development of enantioselective reactions has been a landmark in the synthesis of natural products and their derivatives. One issue has clearly emerged over the years: total synthesis takes a long time in this arena. This leads to a slow process for identification of drug-like candidates. Solid-phase synthesis, combinatorial synthesis (e.g. mix and split) and automation for high-throughput synthesis are emerging tools commonly utilized to address the time factor [2–4]. This is an active area of research, in which the community involved is constantly rising to the challenges of synthesizing complex derivatives on solid phase that could be subjected to automation for high-throughput syntheses. So far, success has been achieved in developing solid-phase, high-throughput synthesis of rather simple compounds having no multiple stereocenters. Highly functionalized chiral derivatives, such as taxol, FK506, rapamycin and vinblastine for example (Figure 1), have proven to be effective as highly potent, bioactive, clinically

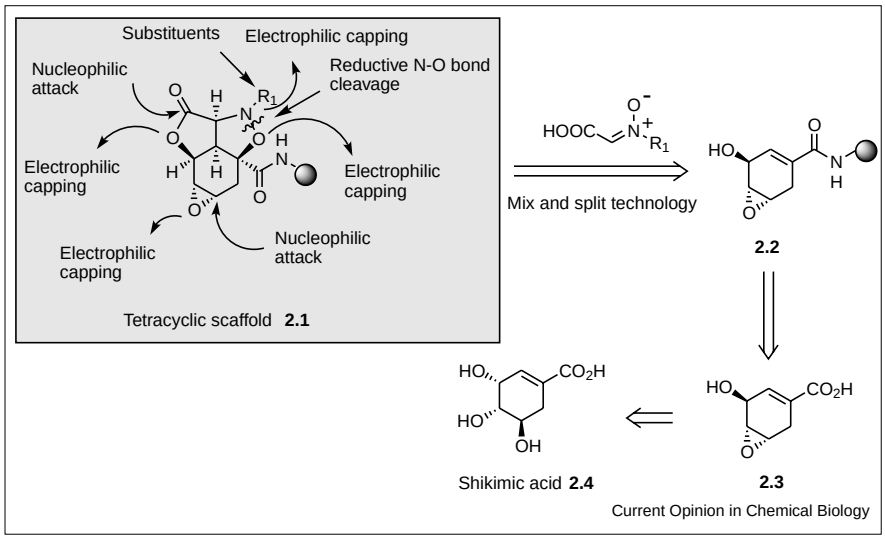
Figure 1



Highly functionalized biologically active natural products such as taxol, FK506, rapamycin and vinblastine have been challenging targets for total synthesis.

Figure 2

From a shikimic acid derivative anchored onto solid support, Schreiber and co-workers [17,18•] synthesized a chiral polycyclic template by a tandem acylation, 1,3-dipolar cycloaddition reaction. The template has several active functional groups (lactone, epoxide etc.), which were utilized for introducing diversity in synthesis.



useful natural products. With few exceptions, however, the degree of complexity that can be achieved by stereoselective solution-phase organic synthesis is still beyond the limits of solid phase for developing high-throughput synthesis [5,6•,7–10].

Research in genomics, proteomics and microarray technologies is expected to provide massive quantities of data concerning novel genes and proteins. The challenge in the post-genomics and proteomics era is to understand their functions in a timely manner and to benefit from the acquired information for development of highly selective, improved drug-like candidates. Organic synthesis is expected to continue playing an important role in the development of novel methods, preferably on solid phase. This will involve accessing small-molecules as chemical probes for understanding the biological functions of novel genes and proteins emerging from genomics and proteomics research. In contrast to labor-intensive mutation-derived research efforts, small-molecules could directly be used for modulating protein functions, a process commonly known as chemical genetics [11]. Success of the chemical genetics approach largely depends upon the availability of functionalized, chiral, natural-product-like compounds in a high-throughput manner, followed by the

Figure 3

Stereoselective, solid-phase synthesis of a chiral template by tandem acylation, 1,3-dipolar cycloaddition reaction. This is then subjected to palladium-mediated iodoaryl coupling with several alkynes, opening of the lactone moiety with several amines, followed by the acylation of the hydroxyl group generated from the opening of the lactone moiety. DIPC, diisopropyl carbodiimide; DIPEA, diisopropylethyl amine; DMAP, dimethylaminopyridine; HATU, (*O*-7-azabenzotriazo-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; PyBrop, bromo-tris-pyrolidino-phosphorium hexaflurophosphate.

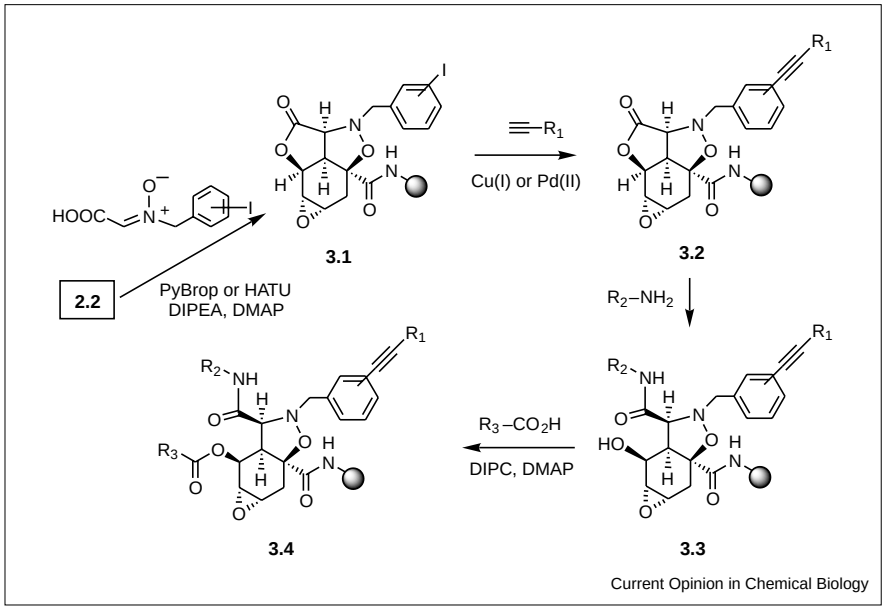
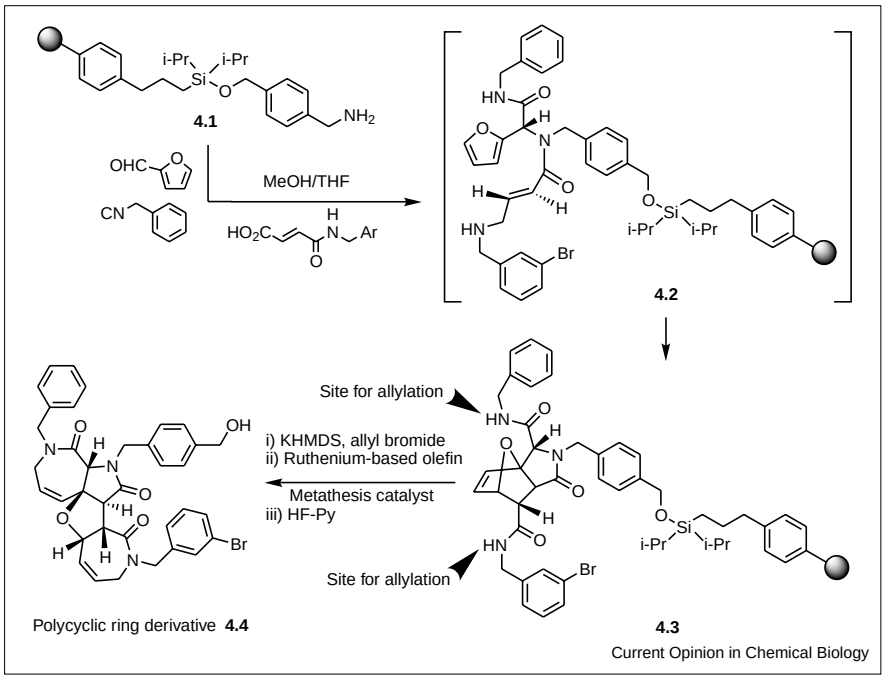


Figure 4



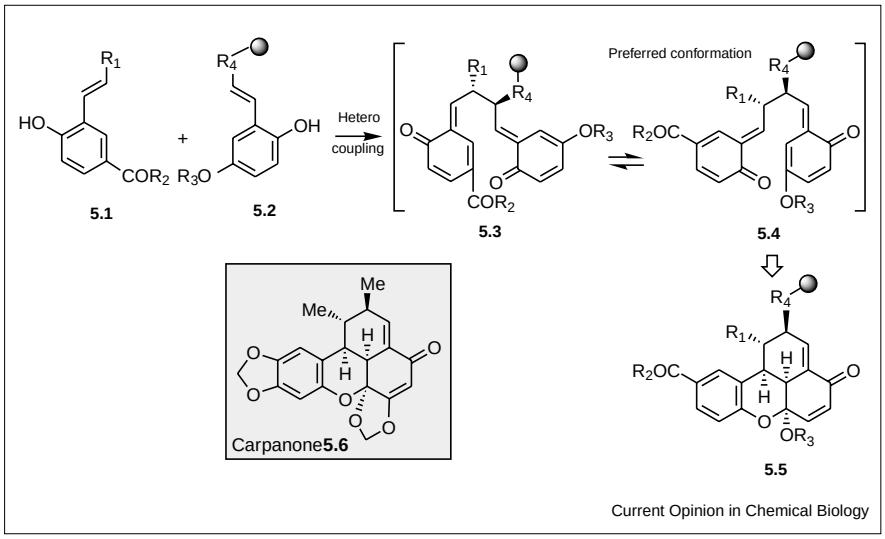
An example of a stereoselective Ugi four-component reaction on solid phase. A bis-allyl derivative of the Ugi product is then subjected to ring-closing olefin metathesis reaction giving a chiral polycyclic derivative with a high degree of stereocontrol. KHMDS, potassium hexamethyldisilazane; THF, tetrahydrofuran.

identification of key compounds responsible for specific activities (i.e. activation or inactivation) [12,13,14•,15•,16]. This approach is highly practical, free from the undesired side effects that one may encounter during mutational experiments and allows synthetic chemists to play important roles in the genomics and proteomics fields.

Highly functionalized polycyclic derivatives

Access to natural products is one approach that may be taken to search for specific compounds involved in modulating biological targets (i.e. precisely controlled specific cellular processes). To gain significant progress by applying chemical genetics, it is imperative that several methodologies leading to natural-product-like compounds by high-throughput process become available. With this in mind, Schreiber and co-workers [17,18•] developed a novel method to obtain the enantiomerically pure template **2.1** (Figure 2) from shikimic acid (**2.4**) on solid phase. Using a mix-and-split approach combined with encoding technology and a tetracyclic template immobilized onto TentaGel-S NH_2 poly(ethyleneglycol)-polystyrene copolymer, several reactions were tested for the library synthesis. The template

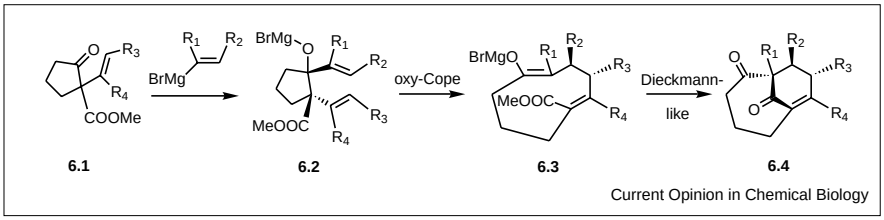
Figure 5



A biomimetic cycloaddition reaction strategy that involves electron-rich and electron-deficient phenolic derivatives. This approach has proven to be highly efficient in obtaining carpanone-like natural products on solid phase.

Figure 6

An example of stereoselective solution-phase synthesis of a polycyclic ring derivative from a simple starting material by tandem alkylation, anion-accelerated oxy-Cope reaction, followed by transannular Dieckmann-type cyclization.



2.1 meets the criteria of rigidity and is highly functionalized (i.e. isooxazoline, lactone and epoxide on the template). On treatment with a variety of organic and organometallic reagents, this template could be utilized for obtaining highly functionalized bicyclic and tricyclic derivatives. An important factor in the plan was the limited use of protecting groups, a challenging task when it comes to the synthesis of complex molecules.

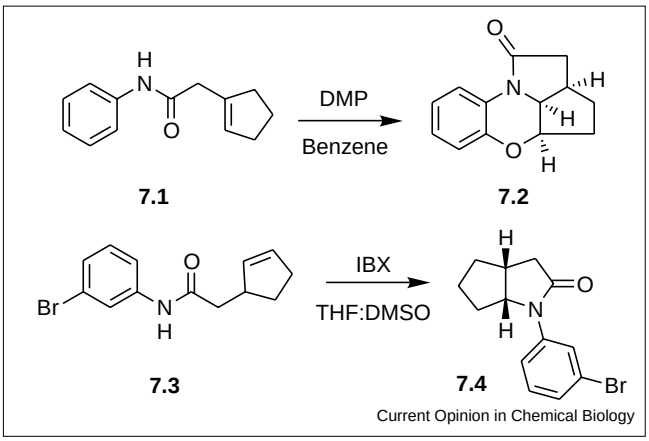
Several key steps were thoroughly tested and optimized before the library synthesis was undertaken using mix-and-split technology. It was shown that the lactone and the epoxide moiety in template **2.1** readily reacted with nucleophiles (e.g. $BuNH_2$, PhNCO, Et_2NH, and PhCN) in the synthesis of hydroxyl derivatives. Subsequently, the generated alcohols were shown to couple with carboxylic acids or acid halides to obtain ester derivatives. Anchored onto beads, the iodoaryl tetracyclic template **3.1** (Figure 3) was synthesized from the epoxide **2.2**. The palladium-catalyzed cross-coupling reaction with the iodo derivative gave the corresponding alkyne derivative **3.2** in high yield. This was then subjected to lactone aminolysis (to give **3.3**) followed by esterification of the hydroxyl group (to give **3.4**) yielding a library of approximately 2.18 million enantiomerically pure compounds. The library was analyzed to identify compounds with activity in rapamycin-based growth inhibition in *Saccharomyces cerevisiae*, in *Xenopus lavis* oocyte extract assay and in mink lung cell proliferation [18•].

In a recent report [19••], Schreiber presented an excellent overview concerning the role of diversity-oriented and target-oriented synthesis in medicinal chemistry research for discovery of drug-like candidates. Although target-oriented synthesis has dominated in the past, the era of genomics and proteomics is expected to drive the need for developing processes that lead to complex natural-product-like compounds in a high-throughput manner. To keep up with the pace of the discovery of novel genes and proteins, combinatorial synthesis is expected to play an important role in understanding their biological functions by providing chemical probes that could rival the available natural products.

The Ugi four-component reaction [20] leading to complex natural-product-like compounds was utilized by Schreiber and co-workers [21], the goal being the development of diversity-oriented synthesis. The stereoselective synthesis of highly complex compounds by Ugi followed by intramolecular Diels–Alder reaction and ring opening-closing olefin metathesis is an attractive strategy, which leads to the 7-5-5-7-membered fused, tetracyclic derivative **4.4** (Figure 4) on solid phase.

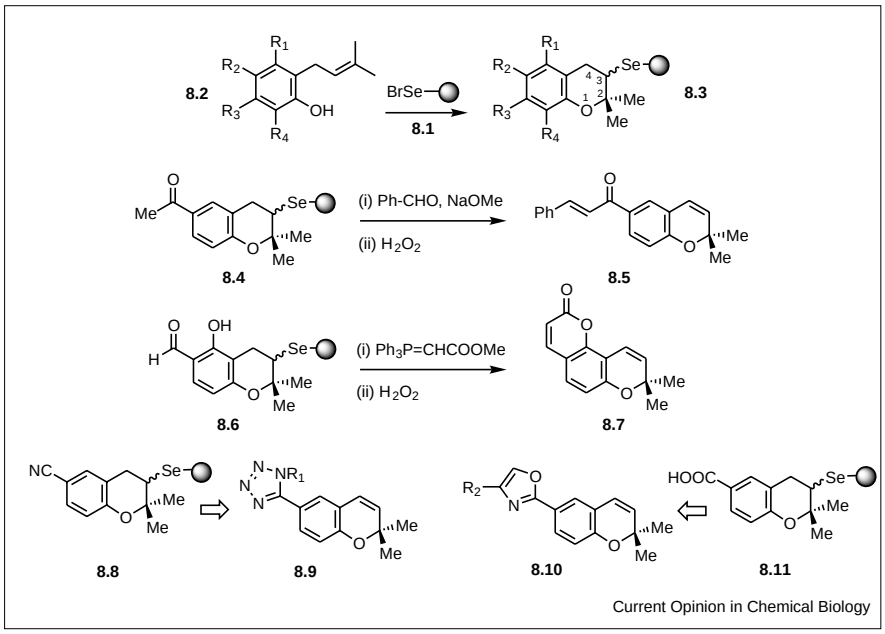
Briefly, the free hydroxyl group of an Fmoc-protected amine derivative was immobilized onto polystyrene beads that contained a carbon–silicon linker. The release of the product from the resin was achieved by the standard cleavage of the silicon–oxygen bond using hydrofluoric acid (HF) in pyridine. The resin-bound amine **4.1** was treated with excess furfural, benzyl isocyanide, and fumaric acid (3-bromobenzyl) monocarboxamide to give the complex product **4.3** via intermediate **4.2**. Bis-allylation of secondary amides was achieved by reaction with allyl bromide and potassium hexamethyldisilazane. This was then subjected to olefin ring opening-closing metathesis in the presence of ruthenium catalyst. The resin was treated subsequently with HF-pyridine to give the desired polycyclic compound **4.4** in high yield. The stereoselective Ugi reaction, combined with intramolecular Diels–Alder reaction and olefin ring opening-closing metathesis, has proven to be a highly efficient strategy for one-pot preparation of highly functionalized, natural-product-like compounds.

Figure 7



An unexpected observation in the synthesis of CP molecules led to the discovery of new reactions giving novel heterocyclic compounds from simple precursors (i.e. anilides, carbamates, thiocarbamates, urea etc.), upon treatment with DMP or IBX (reactions in the figure are shown with anilides only) .

Figure 8

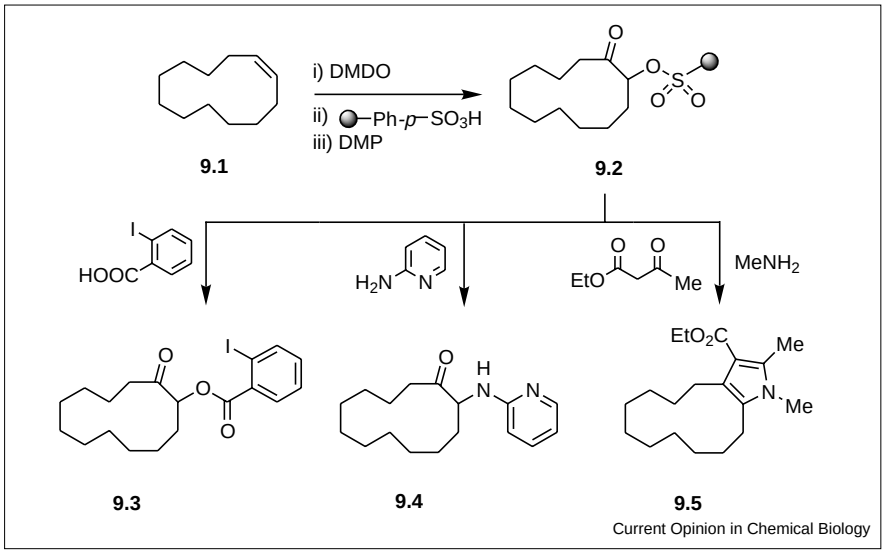


ortho-Prenylated phenols on reaction with selenuim-functionalized resin gave the 2,2-dimethylbenzopyran scaffold anchored onto support. The benzopyran derivative can further undergo several transformations on solid phase. Cleavage from the support by oxidative conditions resulted in a variety of natural-product-like compounds.

Using a biomimetic approach, the total synthesis of carpanone (**5.6**, Figure 5) was accomplished by Chapman *et al.* [22]. The synthetic pathway involved diastereoselective oxidative homocoupling of the electron-rich *o*-hydroxystyrene by endoselective inverse electron demand Diels–Alder (IEDDA) cycloaddition reaction. Shair and co-workers [23•] utilized this idea in developing a solid-phase biomimetic synthesis of carpanone-like compounds. The key step in this strategy was to explore the intermolecular oxidative heterodimerization of dissimilar *o*-hydroxystyrenes on solid phase. The resin-bound electron-rich phenol **5.2** was coupled with the electron-deficient phenol **5.1** in a heterocyclization in the presence of $PhI(OAc)_2$. A following IEDDA cycloaddition gave the desired, carpanone-like compound **5.5** via the intermediate. In this study, the heterocoupled adduct was exclusively isolated indicating complete electronic control during the IEDDA cyclization. This methodology is a nice illustration of a stereoselective synthesis of a complex molecular architecture bearing five stereogenic centers on solid phase.

A convergent synthesis of bridgehead enone-containing polycyclic ring derivatives has been reported by Shair and co-workers [24]. A highly stereoselective tandem reaction that utilized alkylation (to give **6.2**, Figure 6), anion-accelerated oxy-Cope rearrangement (to give **6.3**) and

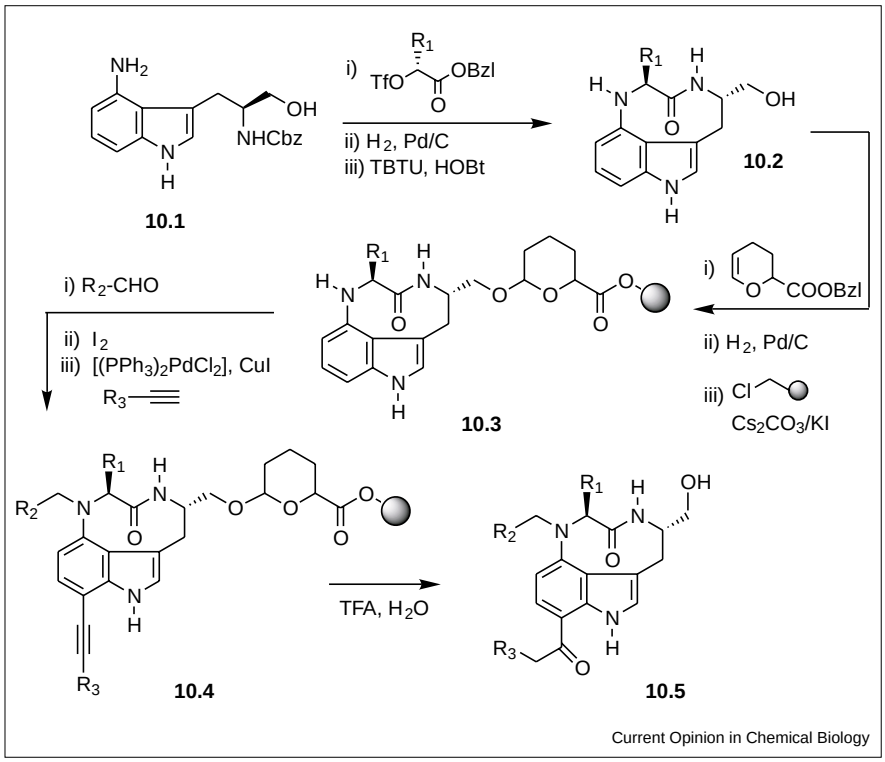
Figure 9



An α-sulfonated ketone derivative was anchored onto a support via reaction of the epoxide with the sulfonic acid immobilized onto resin. This was then cleaved from the support under several reaction conditions (only three examples are shown in the figure) giving novel molecular structures. DMDO, dimethyldioxirane.

Figure 10

The amino alcohol **10.1** was utilized as a template for library synthesis of indolactam-type compounds. The cyclic derivative **10.2** was synthesized from compound **10.1** on reaction with the α-hydroxyl carboxyl ester, and immobilized onto solid support using a tetrahydropyran derivative as a linker. Key steps in the library synthesis were the reductive amination and coupling of the iodoaryl moiety with several alkynes. HOBt, *N*-hydroxybenzotriazole; TBTU, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate.

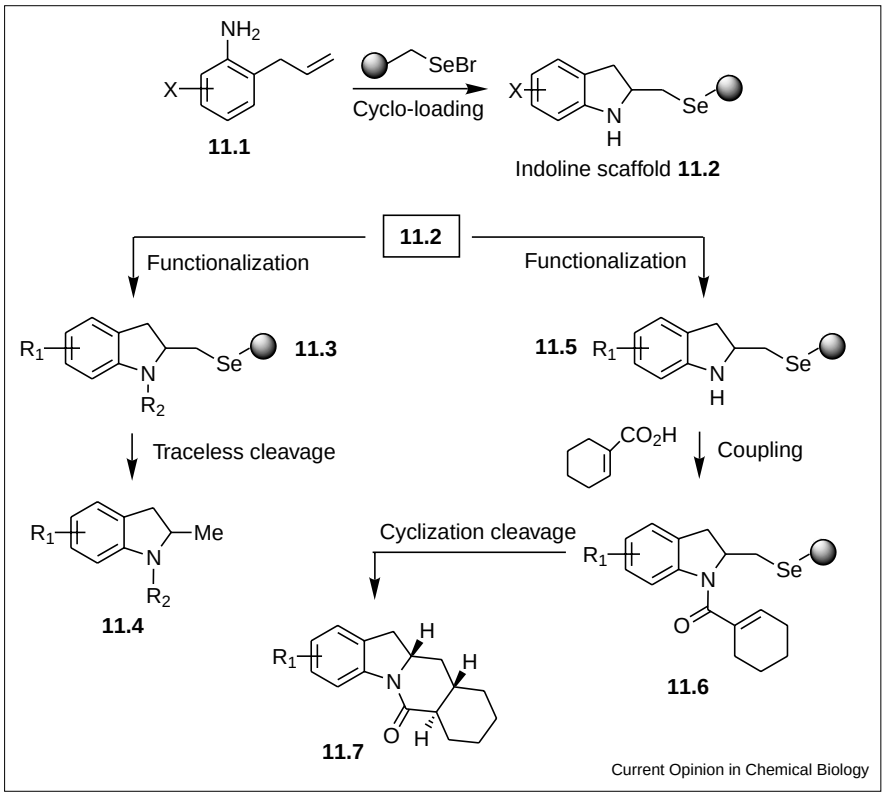


transannular Dieckmann-like cyclization (to give **6.4**), was the key feature of this plan. Interestingly, the series of domino reactions yielded complex tricyclic derivatives with remarkable stereoselectivities. Although the studies were performed in solution phase, the approach developed by Shair and co-workers is highly practical for the stereoselective synthesis of complex polycyclic derivatives and has the potential to be successful on solid phase.

During the course of a total synthesis of CP molecules [25,26], an unexpected cyclization mediated under oxidative conditions, was observed by Nicolaou and co-workers [27,28]. Discovery of this reaction led to development of new chemical processes for obtaining molecular diversity. Thus, novel natural-product-like heterocyclic derivatives were prepared in high yields, either by Dess–Martin periodinane (DMP) [27] or IBX (*o*-iodoxybenzoic acid; 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide) conditions [28]. For example, anilide **7.1** (Figure 7) led to stereoselective synthesis of a polycyclic derivative **7.2** on exposure to DMP in benzene. In another example, the bromoanilide **7.3** was treated with IBX to yield the bicyclic lactam derivative **7.4** with high stereoselectivity. The IBX reaction conditions were found to tolerate the presence of air and water. The methods reported here utilized solution-phase reactions but appear to be very promising for exploration on solid phase for developing high-throughput synthesis.

Use of selenium-functionalized resins for synthesis of natural-product-like compounds has been reported by Nicolaou *et al.* [29•]. In a typical example, the polystyrene resin gave the methyl selenium derivative on reaction with dimethyl diselenide which, after treatment with bromine, resulted in the generation of the selenenyl bromide resin **8.1** (Figure 8). This resin not only functions as a linker in facilitating loading of the scaffold, but also acts as a robust tether through the sequence of operations for further functionalization until it is cleaved under oxidative conditions. This core was selected for the study because of the abundance of the 2,2-dimethylbenzopyran moiety in several natural products (e.g. flavonoids, coumarins and stilbenoids). The selenenyl bromide resin was prepared and subsequently reacted with *o*-prenyl phenol derivative **8.2** to give the resin-bound benzopyran **8.3**. In cases where the aromatic ring contains an acetyl group (e.g. **8.4**), it was shown to react with the benzaldehyde in the presence of NaOMe, giving the chalcone framework **8.5** by a condensation and *in situ* elimination reaction. Similarly, the resin-bound derivative **8.6**, having an aldehyde group on the aromatic ring, afforded the tricyclic compound **8.7** by Wittig olefination followed by lactone formation. In addition, functionalized benzopyrans **8.9** and **8.11** were obtained from the corresponding precursors **8.8** and **8.10**, respectively [30,31]. The method developed by Nicolaou *et al.* is an efficient approach for the synthesis of highly functionalized phenolic-derived natural-product-like compounds.

Figure 11



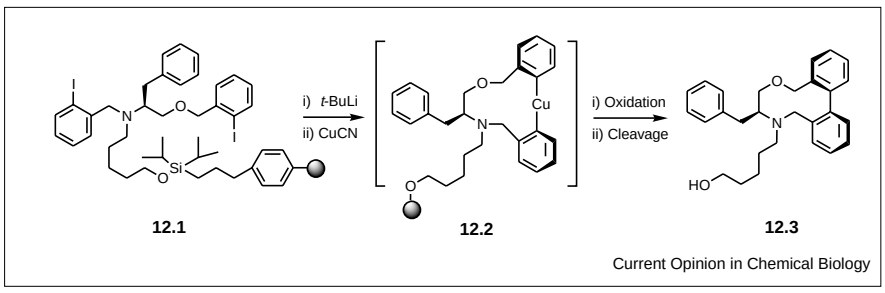
Under Lewis acid conditions, *o*-allylaniline was reacted with selenenyl bromide resin yielding the indoline scaffold anchored onto solid support. After functionalization (i.e. secondary amine to amide), the cleavage was accomplished under free radical reaction conditions (n-Bu_3SnH, AIBN). In a separate experiment it was also shown that the carbon-centered free radical, generated under the reaction conditions, could undergo Michael-type reaction giving the tetracyclic product in high yields.

A novel one-pot synthesis of α-sulfonated ketones has been achieved via olefins by Nicolaou *et al.* [32], both in solution and on solid phase with the concurrent formation of various heterocyclic molecular frameworks. The ease of reaction of α-sulfonated ketones anchored onto polystyrene resin with several nucleophiles, provides a fast entry for obtaining a variety of molecular structures in high yields. In a typical example, cyclododecene **9.1** (Figure 9) was transformed to the corresponding epoxide by dimethyldioxirane-mediated epoxidation. In the same flask, the resin-bound sulfonic acid derivative was added, forming an α-hydroxytosyl derivative, followed by the DMP oxidation to give an α-tosyloxy ketone, **9.2**. Because of stabilization and activation effects of the sulfonate moiety, the scaffold was readily exposed to various reagents (i.e. *o*-iodobenzoic acid, ethylacetoacetate and *o*-aminopyridine) leading to highly functionalized compounds (**9.3**, **9.4** and **9.5**) in good yields.

N-Containing heterocyclic ring derivatives

Protein kinase C plays an important role in signal transduction pathways and is involved in the regulation of various cellular responses such as gene expression, apoptosis and tumor development [33,34]. This kinase is known to be controlled by a natural product, indolactam V. Waldmann and co-workers [35–37] reported their solid-phase efforts to prepare a diversity-enriched framework leading to an indolactam library. The core scaffold of the indolactam tricyclic structure appears to be important for control of protein kinase C. Briefly, selectively *N*-protected amino alcohol derivative **10.1** (Figure 10), prepared from *N*-tri-isopropylsilyl-protected

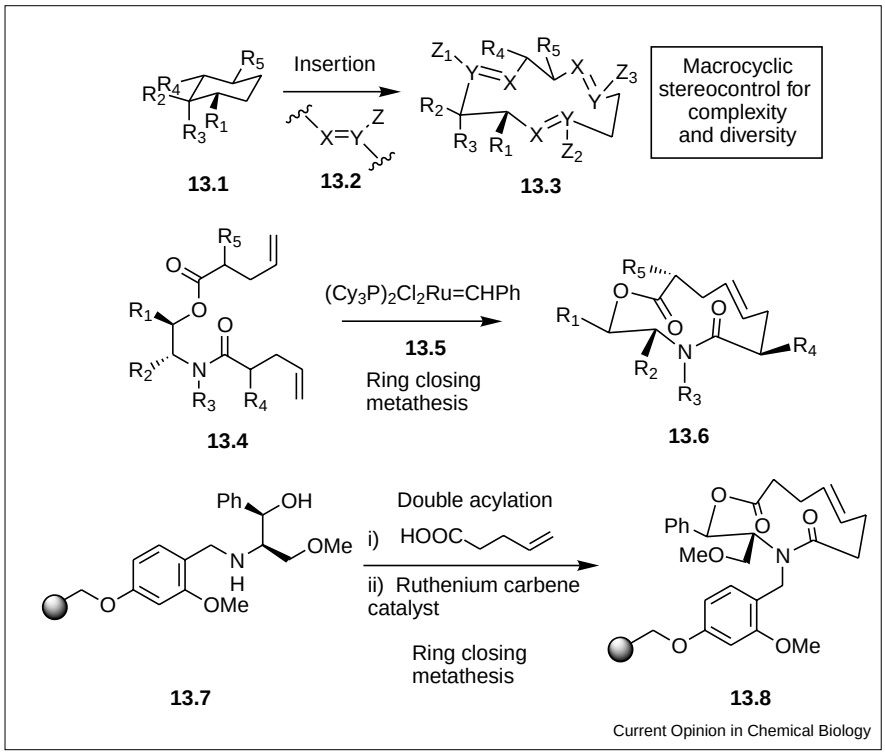
Figure 12



Chiral diiodo aryl derivative 12.1 was subjected to lithiation and then reacted with copper cyanide giving an asymmetric cyclic cuperate on solid phase. The cuperate derivative 12.2, upon treatment with the oxidant, resulted in a stereoselective synthesis of medium ring compound having an asymmetric biaryl moiety.

Figure 13

Ring closing metathesis reaction on chiral amino alcohol **13.4** gave a stereoselective synthesis of the macrocycle **13.6**. This was also successfully applied on solid phase. The concept was derived from the fact that it is possible to obtain a 12-membered ring macrocycle by inserting sp^2 hybridized *trans*-olefins at alternate positions of a fully saturated six-membered ring, **13.1**. Schreiber and co-workers [40••] utilized the acyclic precursor having structural elements that would favor the conformation to allow the macrocyclic ring closure.



gramine, was employed as a template. Alkylation of the aromatic amine with α-hydroxy acid ester triflate introduced the additional stereocenter in the core structure. Subsequent removal of the benzyloxycarbonyl and the benzyl protecting groups followed by the amide bond formation yielded nine-membered ring derivative **10.2**. Acetal formation with the prelinker, hydrogenolysis of the benzyl functional group followed by coupling with the chloromethylated polystyrene resin, yielded indole derivative **10.3** in high yields. This resin-bound indole was subjected to consecutive three-step reactions for introduction of diversity elements R_2 (by reductive amination) and R_3 (by iodoaryl coupling with acetylenes) in **10.4**, then released from the resin to give the corresponding indolactams **10.5**.

Success with the selenium-based polystyrene resin for obtaining benzopyran-derived natural-product-like compounds led to further development of another novel cyclo-loading strategy, for the synthesis of new types of heterocyclic indoline derivatives [38•]. The substituted *o*-allylaniline **11.1** (Figure 11) was reacted with the selenenyl-bromide-derived polystyrene resin. The reaction proceeded via 5-*exo*-trigcyclization to give the resin-bound indoline scaffold **11.2**. Functionalization of the substituents at the aromatic moiety and of the secondary amino group of the indoline derivative **11.2** was performed by addition of phosgene followed by reaction with various amines to obtain **11.3**. This was then cleaved in a traceless manner (i.e. free-radical-mediated cleavage) yielding 1-methylindolines **11.4**. In another approach, the carbon-centered radical, generated upon cleavage of the selenium resin, was reacted in a Michael-type reaction to enhance the complexity within the target compound. The feasibility of this idea was tested on the indoline derivative **11.6** that was obtained from compound **11.5** by coupling with the 1-cyclopentene-1-carboxylic acid. The free-radical-mediated (*n*-Bu_3SnH and catalytic azoisobutyronitrile) carbon–selenium cleavage generated the carbon-centered radical that reacted in an expected Michael-type reaction giving the tetracyclic-derived indoline derivative **11.7**.

Medium- and large-ring-based natural-product-like derivatives

Schreiber and co-workers [39•] reported their efforts in a recent publication, with the goal being development of diversity-oriented synthesis for provision of chiral medium ring compounds. Their plan was to incorporate a chiral biaryl group, in addition to having medium-sized rings, within a given derivative. Natural products such as vancomycin, a highly potent antibiotic, possess an asymmetric biaryl moiety implanted in the macrocyclic ring system. The key reaction forming a medium-sized ring, mediated by copper, led to synthesis of asymmetric biaryl-derived natural-product-like compounds on solid phase. The asymmetric biaryl coupling was achieved from the corresponding chiral diiodo derivative **12.1** (Figure 12) anchored onto solid support. The driving force for the asymmetric aryl–aryl bond formation was the presence of a chiral group in compound **12.1**. It was treated with *t*-BuLi followed by CuCN-mediated coupling to give the cyclic

compound **12.2**, which afforded the asymmetric biaryl derivative **12.3** in good yields with a high degree of stereocontrol upon exposure to 1,3-dinitrobenzene, the oxidant. The reaction conditions utilized by Schreiber and co-workers [39•] could also be applied to several electron-rich and electron-poor aromatic rings (i.e. thiophenes, pyridines etc.). The method developed by Schreiber and co-workers is an attractive approach for obtaining asymmetric medium-sized ring derivatives on solid phase.

Another interesting example of development of an efficient synthesis of macrocyclic compounds on solid phase was published by Schreiber and co-workers [40••]. A key step in their strategy involved application of a well-known ring-closing metathesis reaction [41] for developing asymmetric macrocyclic ring derivatives. The intent was to explore several reactions on the macrocycle that could be performed stereoselectively because of the asymmetric nature of the macrocycle (i.e. commonly known as macrocyclic-based stereocontrol reactions). Several biologically active natural products and a number of antibiotics (e.g. erythromycin) belong to the category of macrocyclic-based highly functionalized bioactive compounds.

In general, cyclization reactions leading to six-membered ring derivatives are efficient and high yielding. As described by Schreiber and co-workers [40••], a similar response could be seen during macrocyclic ring closure with examples having structural and functional elements that would favor ring cyclization. By inserting the *trans*-olefinic moieties **13.2** (Figure 13) into alternate bonds of a six-membered ring, **13.1** would release the *trans*-annular effects and the torsional strains, favoring the macrocycle ring closure to give **13.3**. It is important that the reactive termini in both acyclic precursors are oriented in close proximity to foster the ring-closing metathesis reaction. After the synthesis of asymmetric macrocyclic compounds, functional groups such as olefins and carbonyl groups present in the macrocycle could then undergo various macrocyclic-based stereocontrolled reactions (i.e. epoxidation, enol ether reactions etc.). Macrocyclic ring closures catalyzed by a ruthenium complex successfully afforded the corresponding macrocycles **13.6** and **13.8** both in solution and on solid phase.

Conclusions and future perspectives

The era of genomics and proteomics drug discovery has challenged the chemical and biological community to develop a molecular-level understanding of complex cellular biological pathways. In the world of chemical biology, one such approach is to develop biologically relevant small molecules as molecular probes for understanding complex intracellular processes and pathways (i.e. small molecules that modulate intracellular events in a highly organized manner). Several biologically active natural products that exhibit such effects are known in the literature and are commonly utilized as lead compounds for developing drug-like candidates. To benefit from the technical advances made in genomics and proteomics research, it is imperative that these efforts are combined with the development of biologically relevant natural products and natural-product-like compounds in a high-throughput manner. The combinatorial community has been very successful in developing high-throughput syntheses of rather simple compounds. Natural products similar to taxol, rapamycin, FK506 and vinblastine, to name a few, are still beyond the capacity of solid-phase synthesis leading to high-throughput development. Optimization of several stereoselective organic reactions on solid phase is a prime requirement, and novel methodologies leading to complex structures from simple starting materials are likely to play important roles.

To summarize, with growing demand for obtaining complex chiral natural-product-like compounds in a high-throughput manner, the game has only just begun! Once again, the synthetic community has been challenged to exhibit the power of synthesis in the arena of genomics and proteomics research, which goes beyond natural products.

Acknowledgements

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- • of special interest
- •• of outstanding interest

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