1

Diversity-Oriented Syntheses of Natural Products and Natural Product-Like Compounds

Ling-Min Xu, Yu-Fan Liang, Qin-Da Ye, and Zhen Yang

1.1

Introduction

Natural products have proven to be valuable sources for the identification of new drug candidates, and also as tools for chemical biology and medicinal chemistry research [1]. In fact, if we trace back human history, many natural products have also long been used to treat various human disorders and distinguished by their drug-like properties [2]. To date, tens of thousands of bioactive compounds have been isolated from plants, microbes, marine invertebrates, and other sources [3]. Consequently, these chemical structures have been employed by chemists as references to scan the diversity space for drug discovery efforts [4]. It is estimated that 50–70% of launched drugs in the marketplace are either natural products themselves or natural product-derived molecules [5].

So, what features of natural products make them effective drug candidates? Natural products play important roles in biomedical research and drug discovery largely attributable to their structural complexity and diversity, which Nature has engineered to facilitate optimal functions of living systems. Structural complexity and diversity enable natural products to modulate biological targets of human diseases. The drug-likeness of natural products often possesses common factors including molecular complexity, ability to bind to proteins, structural rigidity, and three-dimensionality [6]. Compared with synthetic molecules, the chemical structures of natural products are more constrained, which allows the accumulation of reliable structure–activity relationship (SAR) data for studying protein target–chemical ligand interactions [7]. Recently, much attention has been devoted to the natural products which are an obvious violation of ‘‘Rule-of-Five’’ [8], but still possess reasonable biopharmaceutical and pharmacokinetic properties, for example, ciclosporin A. Thus, exploitation of such types of natural products could not only significantly broaden the chemical space beyond the ‘‘Rule-of-Five’’ domain for the purpose of drug discovery, but also give us the opportunity to appreciate and investigate how Nature selects and optimizes natural products which are able to bind to and disrupt the function of biological targets through evolution.

We should also recognize that natural products were optimized in living systems presumably not for the same purpose as is desired to serve in a biomedical research

Organic Chemistry – Breakthroughs and Perspectives, First Edition. Edited by Kuiling Ding and Li-Xin Dai.

setting. Their residence in host systems determines that natural products can be optimized to the largest extent that a balance remains within the host systems, and that feasible biosynthetic pathways are in existence. These constraints might in theory explain why many natural products exhibit intolerable toxicity and certain other pharmacokinetics which are undesirable for human therapeutic use. In addition to the above deficiencies, many natural products are scarce or difficult to obtain from natural sources. Also, many possess highly complex structures and can hardly be synthesized in a practical fashion to impact supply.

For those in the chemistry field who are enthusiastic toward natural products, the complexity and diversity of natural products should mean opportunities in the search for new strategies and methodologies to sharpen insights into natural products and also to advance synthetic innovation.

Historically, natural product synthesis has been a very challenging area due to the structural complexity inherent in these molecules. Although synthetic chemists have long been fascinated by natural products, for the most part they have focused on developing the chemistry in order to make precise replicates of the compounds purified from natural sources. Recently, synthetic targets concerning natural products have not been limited to precise replication of the naturally occurring compounds. The accumulation of insights and learning in total synthesis over the last few decades should enable organic chemists to ‘‘aim higher,’’ to integrate natural products more closely with advances in biomedical research. Today, chemists can develop synthetic strategies to make both natural products and natural product-like compounds that are comparable to true natural products in size and complexity. The ability to synthesize *in vitro* complex natural products, combined with the strategy of diversity-oriented synthesis (DOS) of natural product-like molecules, which allows very large numbers of natural product-based compound libraries to be made quickly, has made it possible for chemists to accelerate evolution *in vitro* in this process.

For this chapter, we selected several typical examples, such as DOS, diverted total synthesis (DTS), and function-oriented synthesis (FOS), to illustrate the impact of these synthetic strategies on the efficient synthesis of natural product-like compounds.

1.2
Diversity-Oriented Synthesis (DOS)

DOS is aimed at the efficient synthesis of a collection of structurally complex and diverse small molecules, which are screened for their ability to modulate a biological pathway in cells or organisms, without regard to any particular protein target. In other words, DOS is a means to identify simultaneously therapeutic protein targets and small molecules that can modulate the functions of these therapeutic targets.

As a strategy, DOS is based on forward-synthetic analysis [9] to guide its library synthesis. DOS allows many structurally complex and diverse compounds to be prepared efficiently in a flexible and modular way for biological assays. Because compounds generated from DOS by altering stereochemistry and skeletal arrays would display diverse chemical information in three-dimensional space, screening of such compounds would likely generate more hits poised for optimization. Screening of these would generate more hits [10].

It should be noted that DOS as a synthetic strategy was not originated specifically for natural product synthesis. Yet it goes without saying that the DOS approach can be used to generate analogs of natural products and thus enrich life science discovery. Therefore, DOS can obviously maximize the value of natural products in biomedical research by addressing unfavorable features of natural products. For instance, natural products tend to modulate biological targets that have general functions, but do not seem to modulate more specialized targets and processes. This challenge can perhaps be tackled by means of DOS.

DOS is an important synthetic strategy in the light of advances in genomics studies which have identified many biological pathways and processes as ideal points for therapeutic intervention. Today, chemical biology still requires thousands of compounds to be available for screening in biological assays, and DOS shows tremendous promise in this respect.

1.2.1

Diversity-Oriented Synthesis of Skeletally and Stereochemically Diverse Small Molecules [10a]

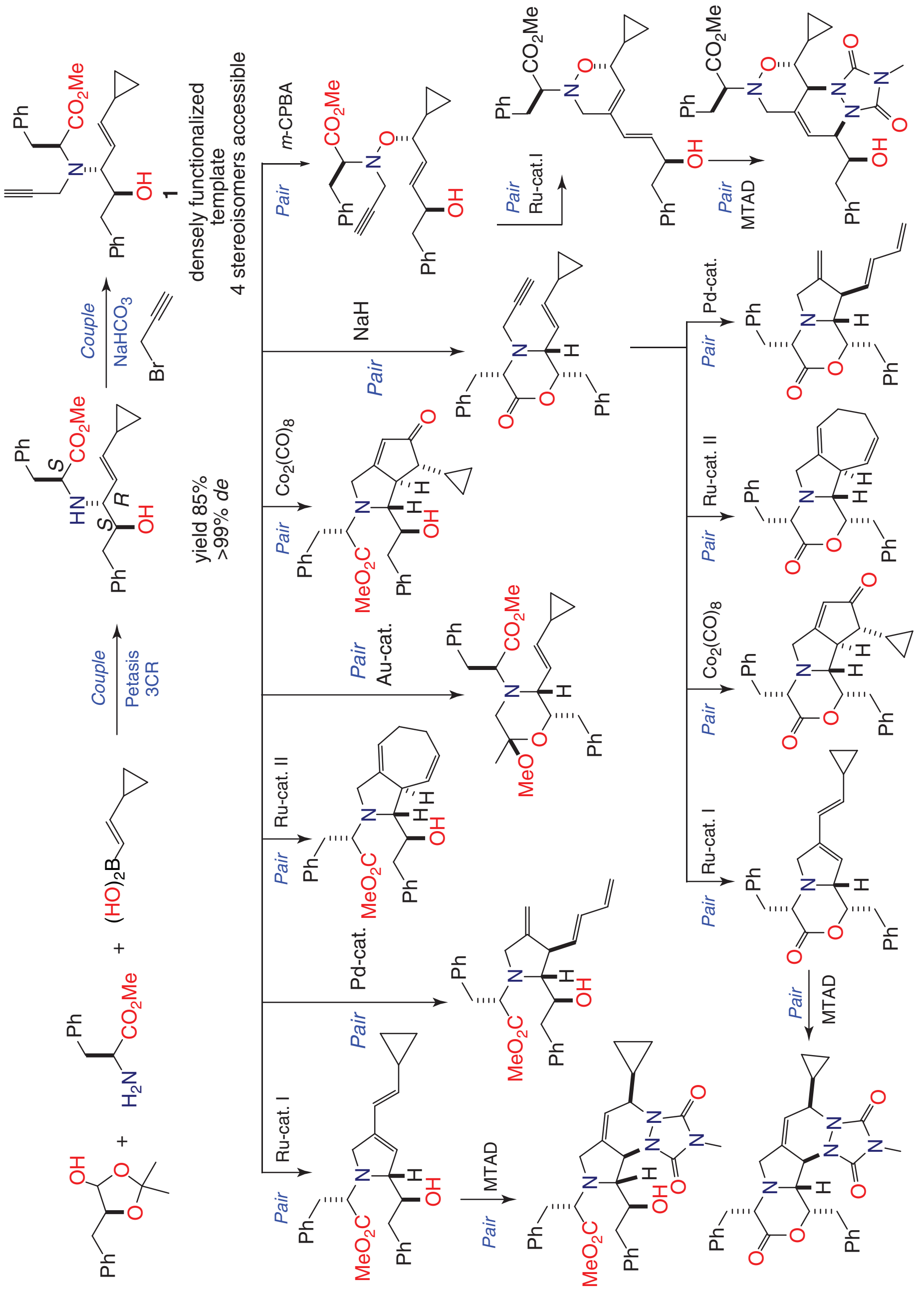
A typical example in the build–couple–pair strategy [9c] developed by Schreiber and co-workers is illustrated in Scheme 1.1. In the build phase, both *R* and *S* stereoisomers of building blocks are readily available. The couple phase employs the diastereoselective Petasis three-component reaction followed by propargylation to yield densely functionalized template **1**. This enables four stereoisomers to be synthesized and is regarded as stereochemical diversification. In the pair phase from **1**, a series of reagent-controlled reactions which selectively pair the nonpolar or the polar functional groups allow skeletal diversification to be achieved and afford 15 structurally complex and diverse small molecules as shown in Scheme 1.1. Appendage diversification may also be achieved by variation of the lactol and amine building blocks.

1.2.2

Biomimetic Diversity-Oriented Synthesis of Galanthamine-Like Molecules

By application of the strategy of biomimetic solid-phase synthesis, Shair and co-workers developed a DOS of galanthamine-like molecules inspired by biosynthesis of galanthamine (Figure 1.1) [10]. The chemistry developed allowed four diversity-generating reactions to be performed.

The general transformations are shown in Figure 1.1. Accordingly, Mitsunobu reaction was employed to introduce R^1 diversity. Conjugated addition of thiols was utilized for diversification of R^2. The last two diversity steps involved acylation/alkylation of the amine and imine formation. Finally, the compounds were detached from the solid support by desilylation. Figure 1.2 shows the building blocks used in the library synthesis of galanthamine-based molecules, which reached a total of 2527.



Scheme 1.1 Build–couple–pair strategy to access skeletally and stereochemically diverse small molecules.

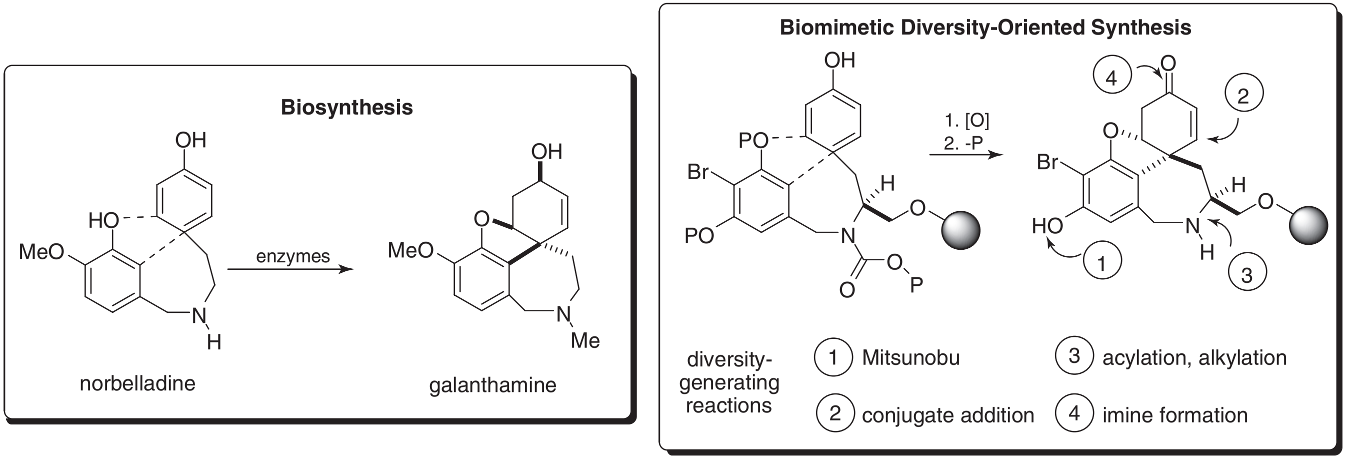


Figure 1.1 Biomimetic diversity-oriented synthesis parallels the biosynthesis of galanthamine.

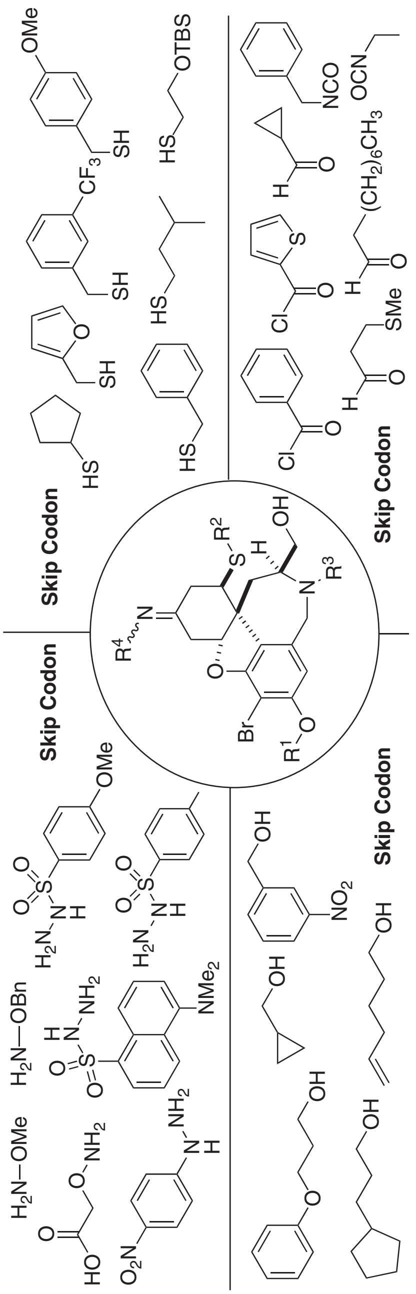


Figure 1.2 Building blocks used in the library synthesis.

1.3
Diverted Total Synthesis (DTS)

Natural products, although highly valuable, are not optimized in a pharmaceutical sense. First, natural products are resident in host systems, therefore they presumably can only be optimized to the extent that a balance can still be maintained within the host systems; second, optimization within host systems requires the existence of feasible biosynthetic pathways. Thus, the strategy of DTS is aimed at tackling these constraints existing in the biosynthetic setting by way of chemical synthetic methods. Relying on the ‘‘advanced intermediate’’ yielded in classic total synthesis, DTS may be employed to reach chemical space having higher or lower complexity than that of the natural product itself. In other words, the employment of the DTS method can achieve ‘‘molecular editing’’ of unnecessary or even undesirable structural features, the kind of optimization which cannot be achieved biosynthetically. On the other hand, these diverted structures often cannot be arrived at from the natural product, owing to chemical limitations. Hence DTS could be used to permit the development of natural product-like biological probes and pharmaceutical agents without recourse to the natural product itself [11].

1.3.1
Diverted Total Synthesis of the Migrastatins

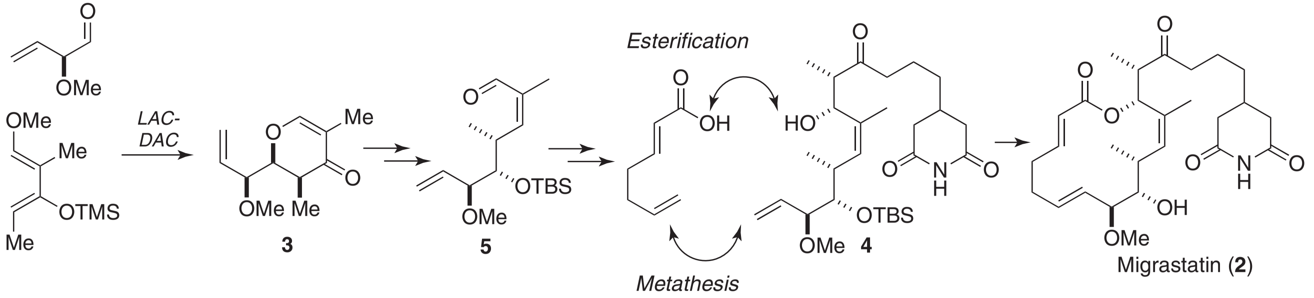
Migrastatin (**2**), isolated from a cultured broth of *Streptomyces*, is a 14-membered macrolactone that reportedly inhibits tumor cell migration [11a,b]. The first asymmetric total synthesis of (+)-migrastatin was accomplished by Danishefsky and co-workers.

As shown in Scheme 1.2, the key step for the synthesis of intermediate **3** is a Lewis acid-catalyzed diene aldehyde condensation (LAC–DAC) with the formation of three contiguous stereocenters. The construction of a glutarimide-containing side chain in intermediate **4** was achieved by an *anti*-selective aldol addition of Evans propionyloxazolidinone to aldehyde **5**, and a Horner–Wadsworth–Emmons (HWE) reaction as the key steps. Finally, Yamaguchi esterification followed by a highly *E*-selective ring-closing metathesis led to macrocyclization and afforded migrastatin (**2**) after desilylation.

Despite migrastatin’s rather modest inhibitory activity, Danishefsky and co-workers attempted to apply as a lead compound to yield more potent analogs. The total synthesis of migrastatin, which was developed efficiently in a convergent way, allows variations of different regions of migrastatin. These variable regions are highlighted in different colors in Figure 1.3.

The C2–C3 double bond is a potential site for deactivation by 1,4-addition of nucleophiles. The lactone functionality renders the molecule susceptible to hydrolysis and thus diminishes its stability. Furthermore, the highly functionalized C6–C12 portion of migrastatin is regarded as biologically relevant, and the glutarimide moiety might be indispensable for activity.

With these considerations in mind, a set of structurally simplified analogs were designed and synthesized with variations at these regions. Such a DTS strategy takes advantage of the advanced key intermediates **4** and **5**, utilizing them as branching points to yield a diverse set of analogs which could not easily be accessed from the natural



Scheme 1.2 Key steps in the total synthesis of migrastatin (**2**).

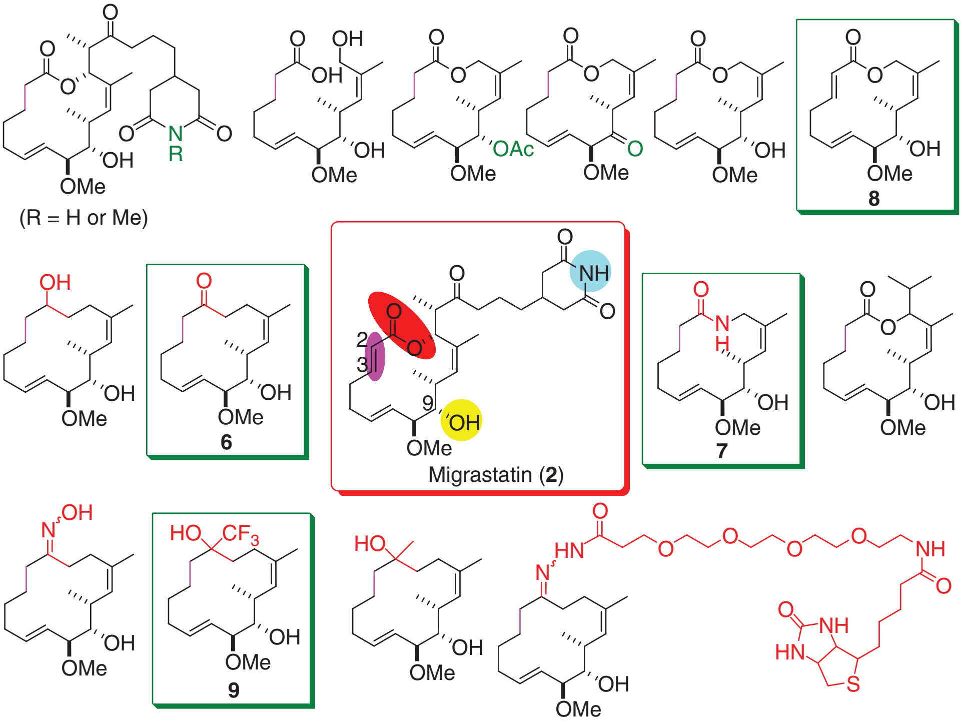


Figure 1.3 Syntheses of migrastatin analogs through diverted total synthesis.

product itself. In total 15 analogs have reportedly been generated, among which **6**–**9** are the most promising candidates which have demonstrated increased activities compared with the natural product, but without the appending glutarimide moiety.

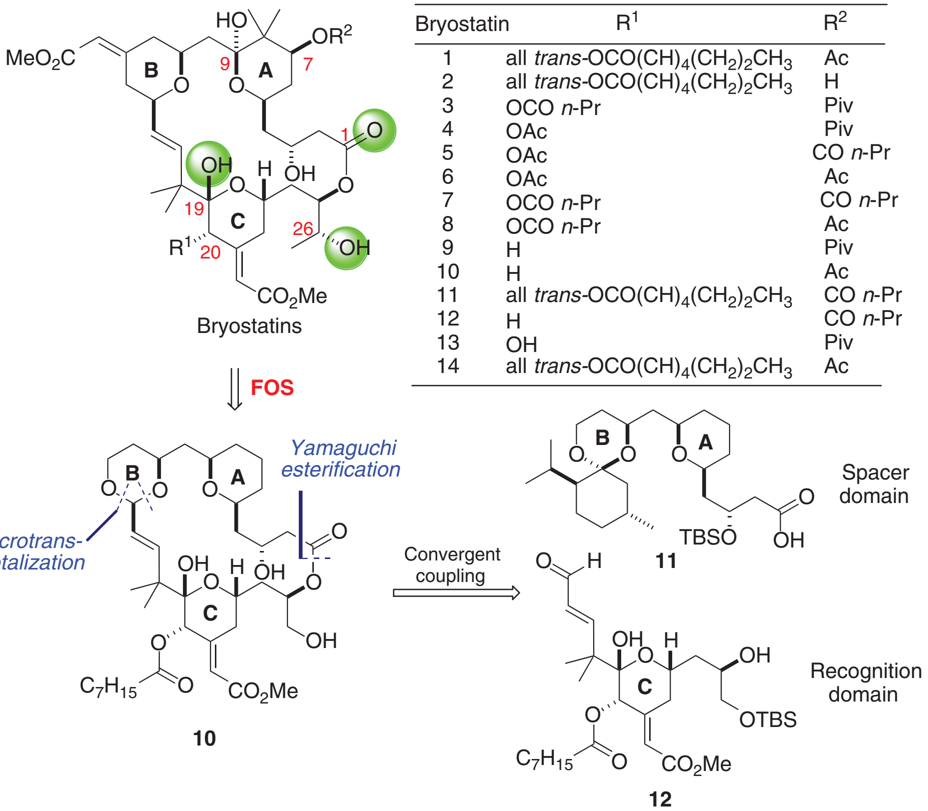
1.4
Function-Oriented Synthesis (FOS)

The aim of FOS is to address several common problems associated with natural product leads: natural products are often too complex to be made in a practical fashion, and many carry undesired side effects given they are not "designed" for human therapeutic use. Use of the FOS strategy focuses on the function of a natural product, rather than its total structure, to design structurally simplified analogs by incorporating the activity-determining structural features (or their equivalent) of the natural product. Employment of FOS yields natural product analogs with comparable or superior function that could be prepared in a step-economic (i.e., cost-effective) manner. Also, by focusing on a specific function, the FOS can be used to enhance beneficial activities and also to minimize off-target activities better suited for biomedical research or medicinal use [12–14].

1.4.1
Syntheses of Novel and Highly Potent Analogs of Bryostatin

Bryostatins 1–14 are marine-sourced natural products that it is hoped to guide the discovery of medicines to cure cancer and Alzheimer's disease [12]. Unfortunately, their availability from marine sources is extremely limited. Before Wender applied FOS to the synthesis of bryostatin analogs, total syntheses of bryostatins had required more than 70 steps. Recently, Trost's group completed a similar synthesis in 39 steps.

Wender and co-workers believed bryostatins to be ideally suited for FOS considering that its therapeutic activity was connected to only a subset of its structure, and that a pharmacophore could be designed into a simplified target more readily accessed through synthesis. It was inferred from their previous study that the C1 carbonyl, C19 and C26 alcohols, and a corresponding lipophilic region of the bryostatin were likely to be key binding elements. Analog **10** was thus designed with simplified A- and B-rings and an intact C-ring (Figure 1.4). Moreover, the C26 methyl group was deleted to emulate other C1 binders and allow for closer association in the receptor binding pocket.



Bryostatin	R^1	R^2
1	all *trans*-OCO(CH)$_4$(CH$_2$)$_2$CH$_3$	Ac
2	all *trans*-OCO(CH)$_4$(CH$_2$)$_2$CH$_3$	H
3	OCO *n*-Pr	Piv
4	OAc	Piv
5	OAc	CO *n*-Pr
6	OAc	Ac
7	OCO *n*-Pr	CO *n*-Pr
8	OCO *n*-Pr	Ac
9	H	Piv
10	H	Ac
11	all *trans*-OCO(CH)$_4$(CH$_2$)$_2$CH$_3$	CO *n*-Pr
12	H	CO *n*-Pr
13	OH	Piv
14	all *trans*-OCO(CH)$_4$(CH$_2$)$_2$CH$_3$	Ac

Figure 1.4 Bryostatins and their more active analog **10** derived from FOS.

These have met the requirements for the development of a convergent synthesis. Retrosynthetic analysis of **10** led to the C1–C13 spacer domain **11** and C15–C26 recognition domain **12**, which featured Yamaguchi esterification and macrotransacetalization. The FOS approach led to the realization of bryostatin analogs that bind to protein kinase C (PKC) with affinities comparable, and in some cases superior, to bryostatins (K_i value of 0.3 versus 1.4 nM). Moreover, these analogs can be made in 29 steps, significantly shorter than the previous pathway for the total synthesis of bryostatins.

Further modification of bryostatins on the fragments of the A-, B-, and C-rings led to the efficient synthesis of a library of 31 analogs. Importantly, the analogs show greater potency than bryostatin when tested for growth inhibitory activity against the US National Cancer Institute panel of human cancer cell lines.

In summary, FOS 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 effective methods for convergent macrolide formation. An advantage of FOS was demonstrated in this study, namely that superior function can be achieved in fewer steps with simplified structures while enabling synthetic innovation.

1.4.2
Discovery of Potent and Practical Antiangiogenic Agents Inspired by Cortistatin A

Among 10 related natural products of the cortistatin family, cortistatin A (**13**) and cortistatin J (**14**) show the most promising antiangiogenic activity [14]. Rather than embarking on the total synthesis of these natural products, Corey's group started the journey by designing analogs with less complexity for access while still possessing equal or even enhanced biological activity.

After analyzing the structures of **13** and **14**, they drew the conclusion that the dimethylamino group at the C3 position and the isoquinoline appendage at C17 were required for biological activity, whereas the hydroxyl groups at C1 and C2 were not essential. The above information led to the design of analog **15** possessing a steroidal core and a double bond at C16–C17 (Figure 1.5).

By varying the C17 appendage and C3 amino group, a series of analogs were synthesized, as shown in Figure 1.5. The antiangiogenic activity of these analogs was evaluated *in vitro*, based on which the data indicate that the most active compounds are those underlined.

1.5
Target-Oriented Synthesis (TOS)

Target-oriented synthesis (TOS) is an effective synthetic strategy to generate natural products and natural product-like molecules in a concise, convergent, and systematic manner. One major deficit in natural product-based research is the inaccessibility of identified natural products, because they exist in only trace amounts in Nature, which prevents biological evaluation of natural products in a systematic manner. Therefore, accessing by way of chemical synthesis these valuable gifts of Nature derived from

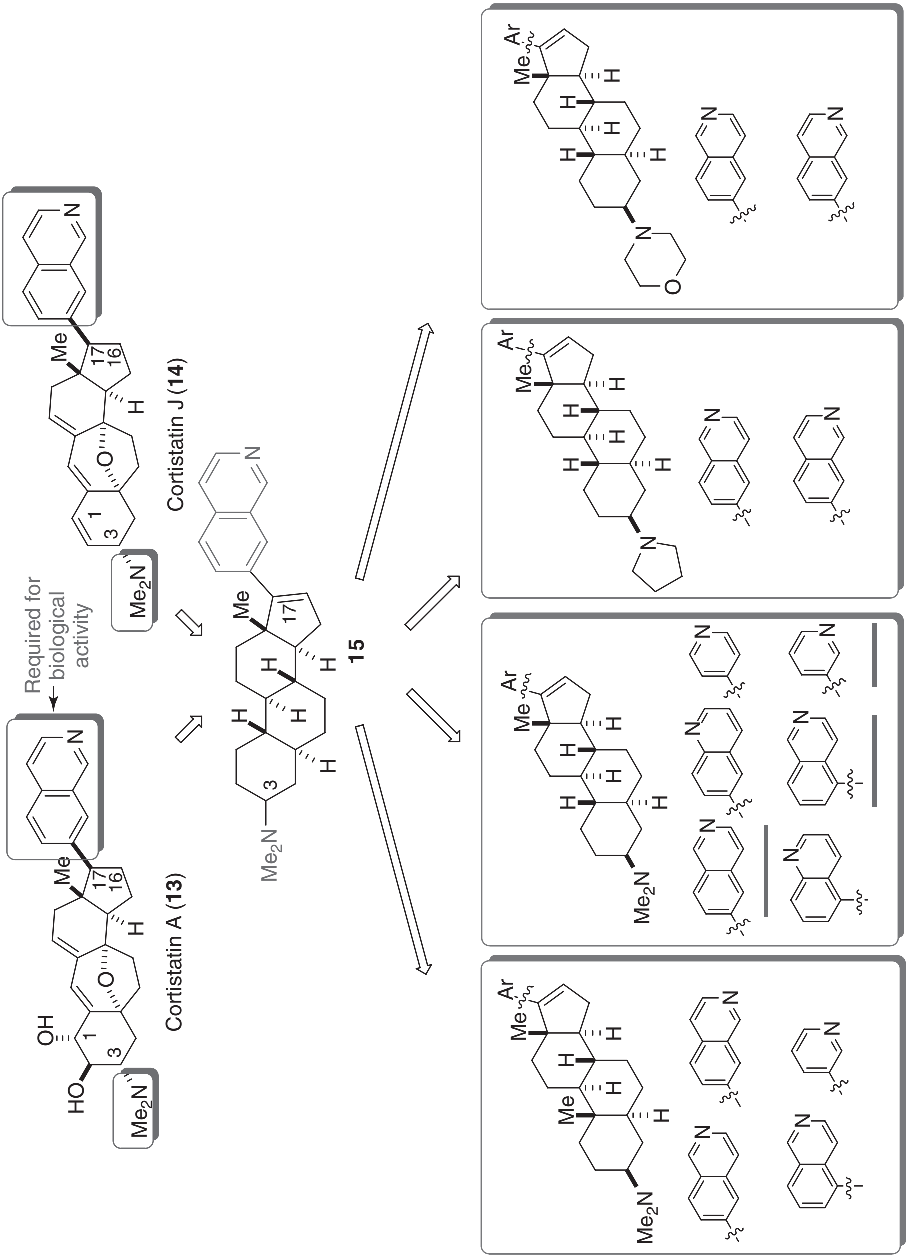


Figure 1.5 Design and syntheses of structurally simple analogs of cortastatin A.

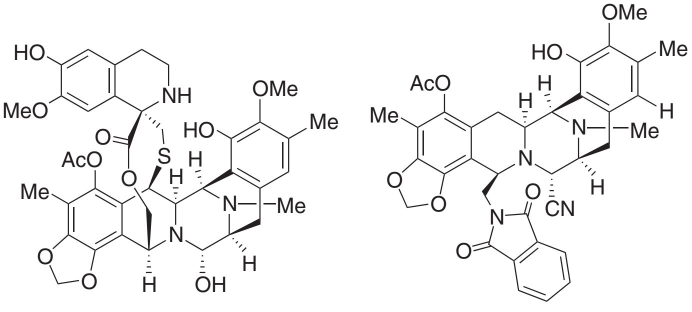
millions of years of evolution represents a sizable challenge to organic chemistry, yet equally holds tremendous promise in biomedical research and drug discovery. TOS of natural products, which has been fueled by the methodology of retrosynthetic analysis since the mid-1960s, is an effective strategy to produce scarce and inaccessible natural products in laboratories. Today, many organic chemists are passionate about the total synthesis of newly discovered natural products and optimizing known synthetic steps. These synthetic missions continuously generate new experimental and intellectual challenges to organic chemists. As natural products are often biologically relevant, a principle of biomimetic synthesis is usually applied for guidance, which allows access to natural products with high efficiency.

1.5.1
Synthetic Studies and Biological Evaluation of Ecteinascidin 743

Ecteinascidin 743 (**16**) is an exceedingly potent and rare marine-derived antitumor agent that acts by inducing DNA–protein cross-linking [15b], and is now in advanced clinical trials (Figure 1.6) [15].

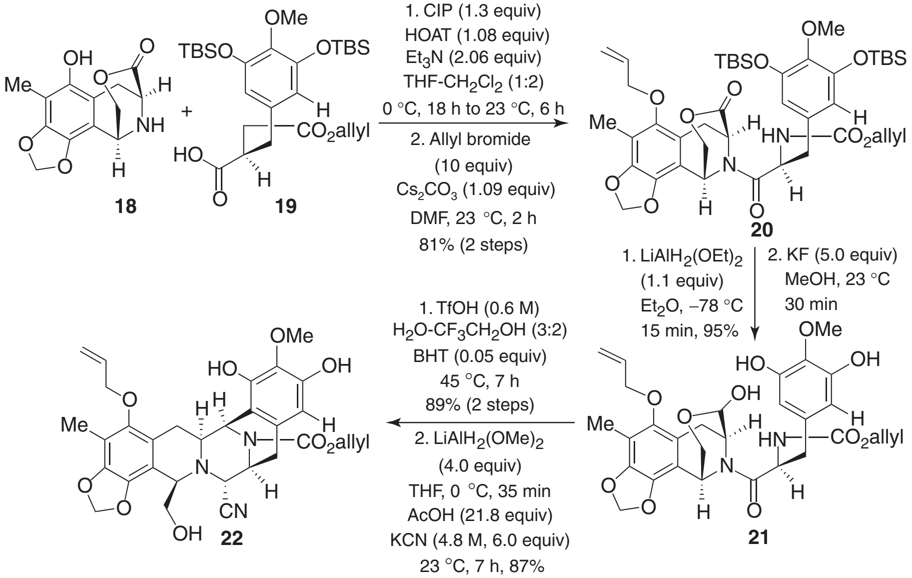
In the past 20 years, Corey's group has made tremendous efforts to optimize the synthetic route to ecteinascidin 743 (**16**). The concise and convergent route for the construction of its core structure was eventually developed successfully and is summarized in Scheme 1.3.

Key steps in this synthesis involve the following: (i) amide bond formation between **18** and **19**, followed by allylation to give **20**; (ii) selective reduction of lactone to its lactal was achieved by the reduction with $LiAlH_2(OMe)_2$, and **21** was obtained after desilylation with KF–MeOH; and (iii) the pentacyclic core was formed by treatment of **21** with TfOH in H_2O–CF_3CH_2OH mixed solvents in the presence of butylated hydroxytoluene (BHT), and the formed pentacyclic lactam was first reduced with $LiAlH_2(OMe)_2$ to afford the corresponding cyclic aminal, which upon exposure to HCN provided pentacyclic aminonitrile **22** in high yield. The significance of this synthesis is its overall high yield (57% in six steps) and its reliability in a large-scale synthesis. A critical element to the



Ecteinascidin 743 **(16)**　　Phthalascidin **(17)**

Figure 1.6 Ecteinascidin 743 (**16**) and phthalascidin (**17**).



Scheme 1.3 The concise and convergent route to the core structure (**22**) for ecteinascidin 743 (**16**).

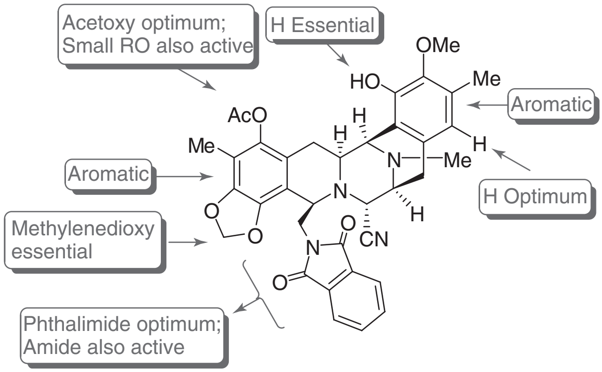


Figure 1.7 SAR of phthalascidin (**17**).

success of this synthesis was the utilization of $LiAlH_2(OMe)_2$ as an efficient reducing agent, which had not been used frequently previously.

From the common intermediate **22**, a series of totally synthetic molecules that are structurally related to phthalascidin (**17**) were prepared and evaluated as antitumor agents [15b] (Figure 1.7).

From this study, phthalascidin (**17**) was identified as the most active antitumor agent, and is now in advanced clinical trials. Its antiproliferative activity ($IC_{50} = 0.1-1$ nM) is greater than that of the agents of paclitaxel (Taxol), camptothecin, adriamycin, mitomycin C, cisplatin, bleomycin, and etoposide by 1–3 orders of magnitude. Because phthalascidin

(**17**) is more stable than ecteinascidin 743 (**16**) and considerably easier to make, it could potentially be a more practical therapeutic agent.

1.5.2
Total Synthesis and Biological Evaluation of Biyouyanagin A and Analogs

Biyouyanagin A was isolated from the *Hypericum* species *H. chinese* L. var. *salicifolium* and was originally assigned as structure **24a** based on NMR spectroscopic analysis (Figure 1.8) [16].

As ambiguity about the stereocenters at C24 and around the cyclobutane ring exists, retrosynthetic analysis featuring a photoinduced [2 + 2]-cycloaddition (a potential

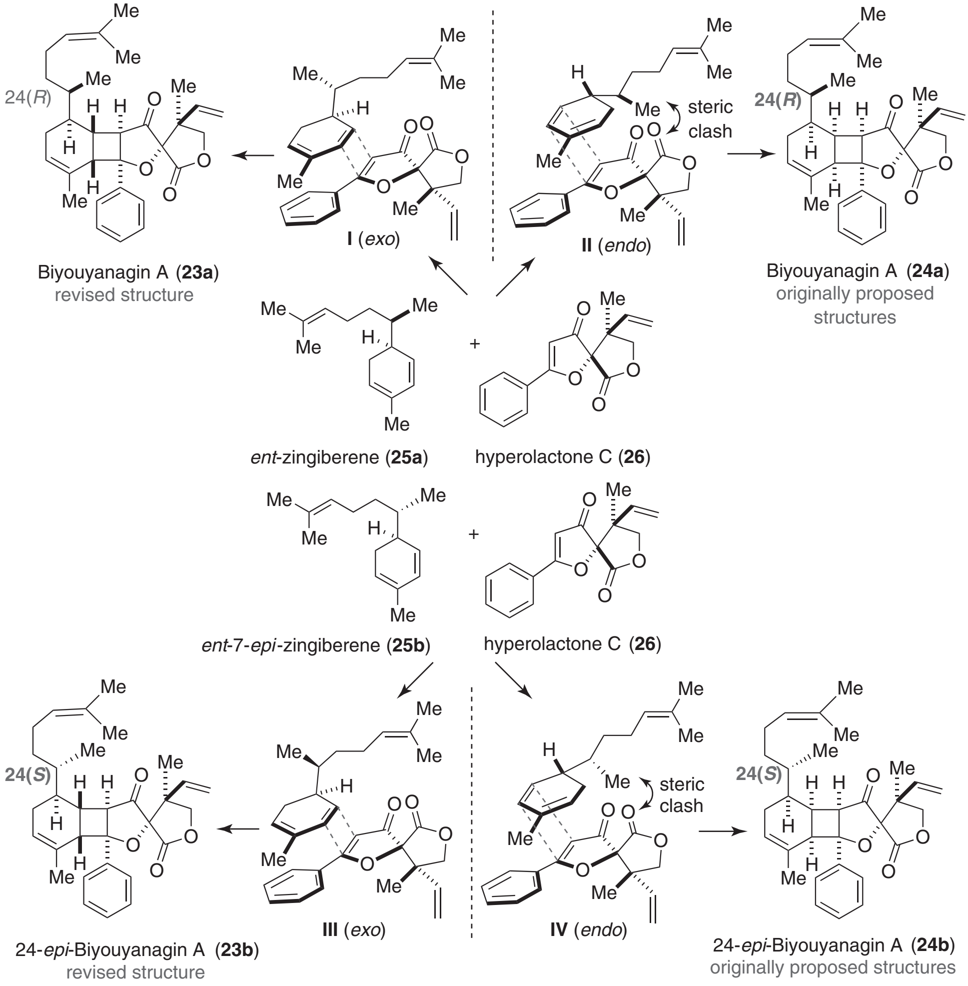
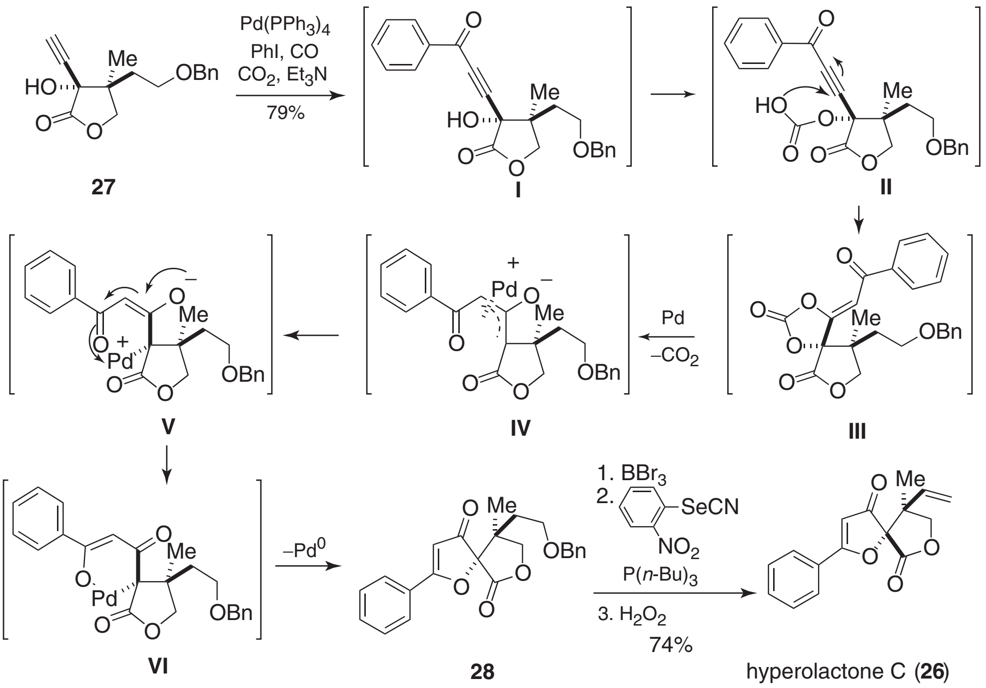


Figure 1.8 Biyouyanagins and their potential biosynthetic pathway.



Scheme 1.4 Synthesis of hyperolactone C (**26**) through Pd-catalyzed reactions.

biosynthetic pathway) constitutes a perfect solution to this problem. Two transition states could be envisioned in this key reaction, with the more favorable *exo* transition state **I**, leading to **23a** as the natural product.

The journey began with the construction of *ent*-zingiberene (**25a**) and hyperolactone C (**26**), considering they are naturally occurring substances. Scheme 1.4 shows the details of the synthesis of hyperolactone C (**26**), which could be derived from **27** through palladium-catalyzed cascade sequences to deliver **28**, the stereochemistry of which was confirmed by X-ray crystallographic analysis (Scheme 1.4). The completion of the synthesis of hyperolactone C (**26**) required debenzylation (BBr_3), selenenylation, and oxidation/*syn*-elimination.

The key photoinduced [2 + 2]-cycloaddition of **26** with **25a** proceeded with the desired regio- and diastereoselectivity, leading to **23a** (Figure 1.8). NMR spectroscopic data for **23a** were consistent with those reported for the natural product biyouyanagin A, the structure of which was further verified by X-ray crystallographic analysis.

Having established [2 + 2]-cycloaddition as an efficient and concise way to build up the scaffold of biyouyanagin A, a further nine biyouyanagin A analogs (Figure 1.9) were synthesized via the same synthetic strategy as illustrated in Figure 1.8, and their biological activities were profiled.

Accordingly, all the newly synthesized compounds **23b** (Figure 1.8) and analogs in Figure 1.9 displayed similar activities against HIV-1 replication and cytotoxicities against

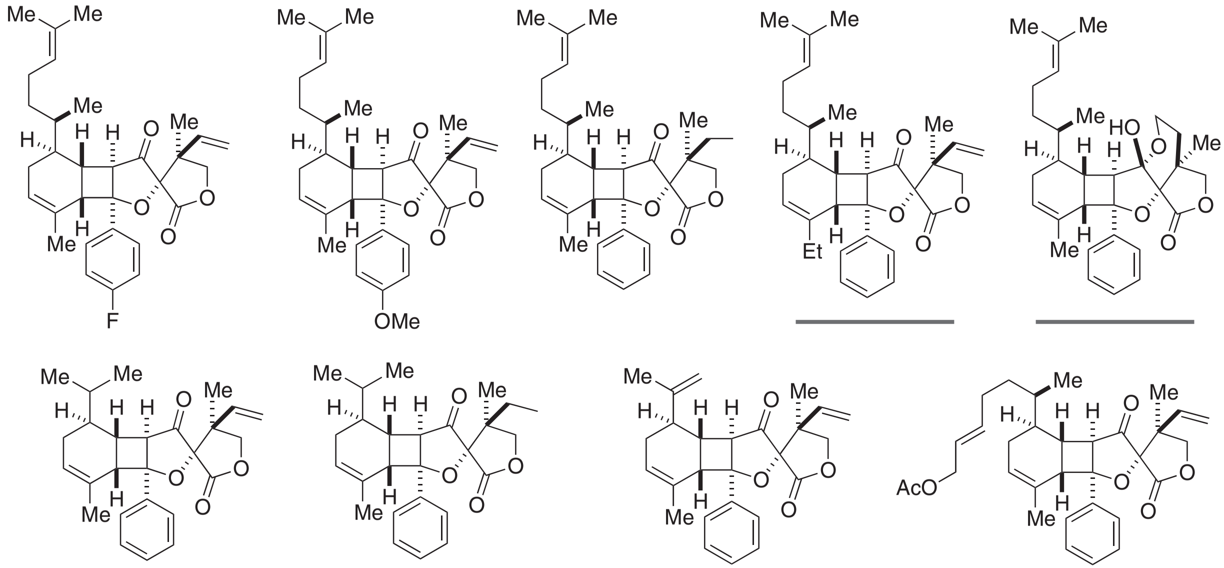


Figure 1.9 Synthesis of additional analogs of biyouyanagin A.

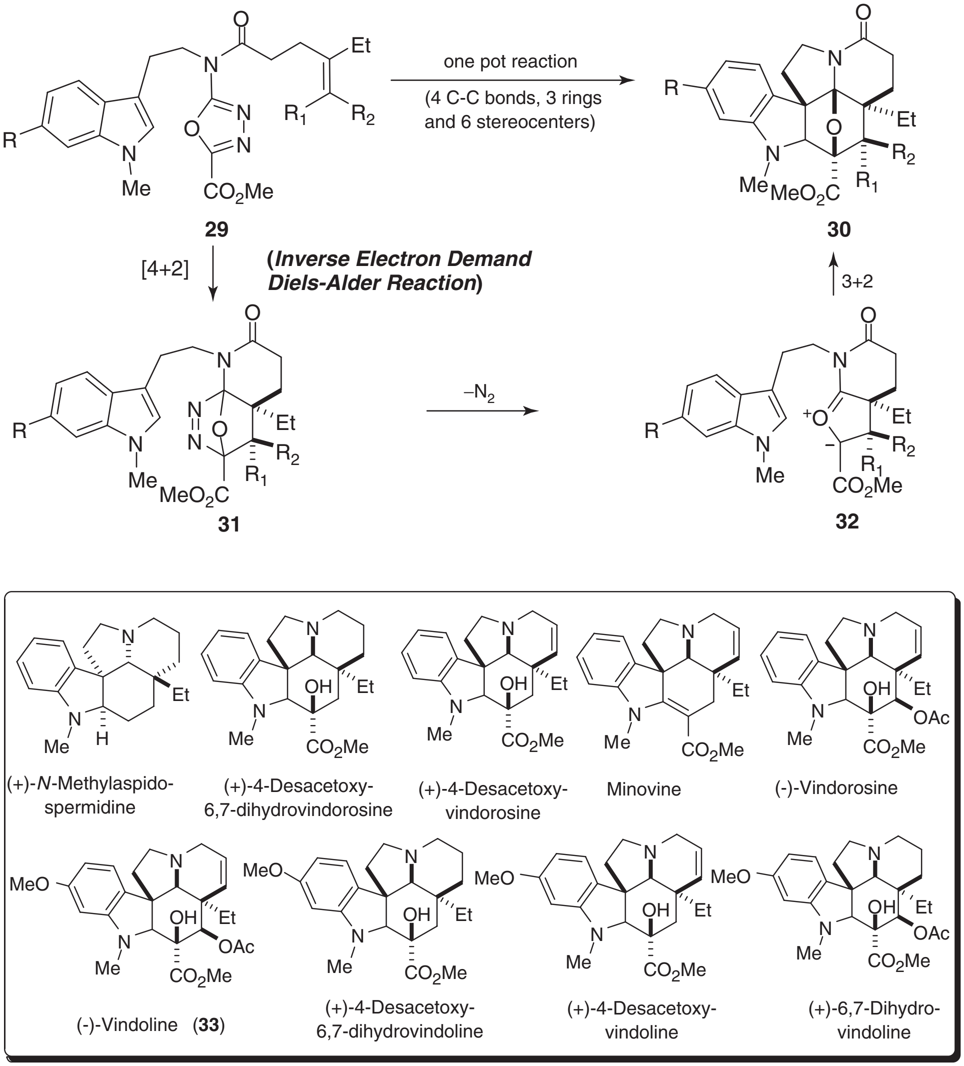
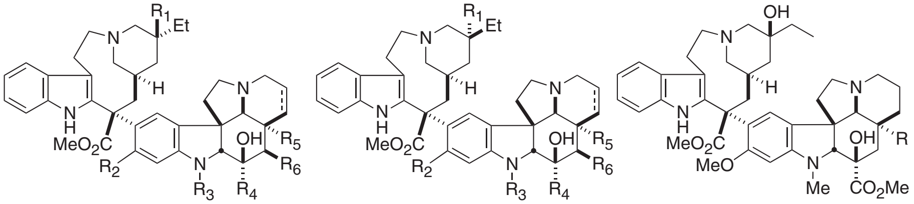


Figure 1.10 Synthesis of vindoline-related natural products via a [4 + 2]/[3 + 2]-cycloaddition cascade.

the MT-2 lymphocytes, with the two underlined analogs being the most potent against HIV-1.

1.5.3
Total Synthesis of Vindoline, Related Natural Products, and Structural Analogs

Boger's group developed a tandem intramolecular [4 + 2]/[3 + 2]-cycloaddition cascade of a 1,3,4-oxadiazole (**29**) to construct the vindoline skeleton (**30**), in which three



Type A, 19 compounds
R_1 = H, OH, TEMPO
R_2 = H, OMe
R_3 = H, Me, CHO
R_4 = CO_2Me, $CONH_2$, $CONHNH_2$
R_5 = H, Et
R_6 = H, OH, OAc
C6-C7 : C=C, C-C

Type B, 17 compounds
R_1 = H, OH, TEMPO, NO, NH_2, N_3
R_2 = H, OMe
R_3 = H, Me
R_4 = CO_2Me
R_5 = H, Et
R_6 = H, OH, OAc
C6-C7 : C=C, C-C

Type C
R = H, Me, Pr, CCH, CHO, CH_2OH, $CH(OH)CH_2OH$

Figure 1.11 Design of structural analogs.

rings, four C–C bonds, and six stereocenters are formed in a single step (Figure 1.10) [17].

The success of this cascade was based on the precise design of reacting partners, in which the electron-rich enol ether is matched with the electron-deficient oxadiazole in the inverse electron demand Diels-Alder reaction. Loss of N_2 in intermediate **31** provides the 1,3-dipole product **32**, which is stabilized by the electron-deficient substituent. A diastereoselective *endo* [3 + 2]-cycloaddition then takes place at the less hindered face to deliver **30**.

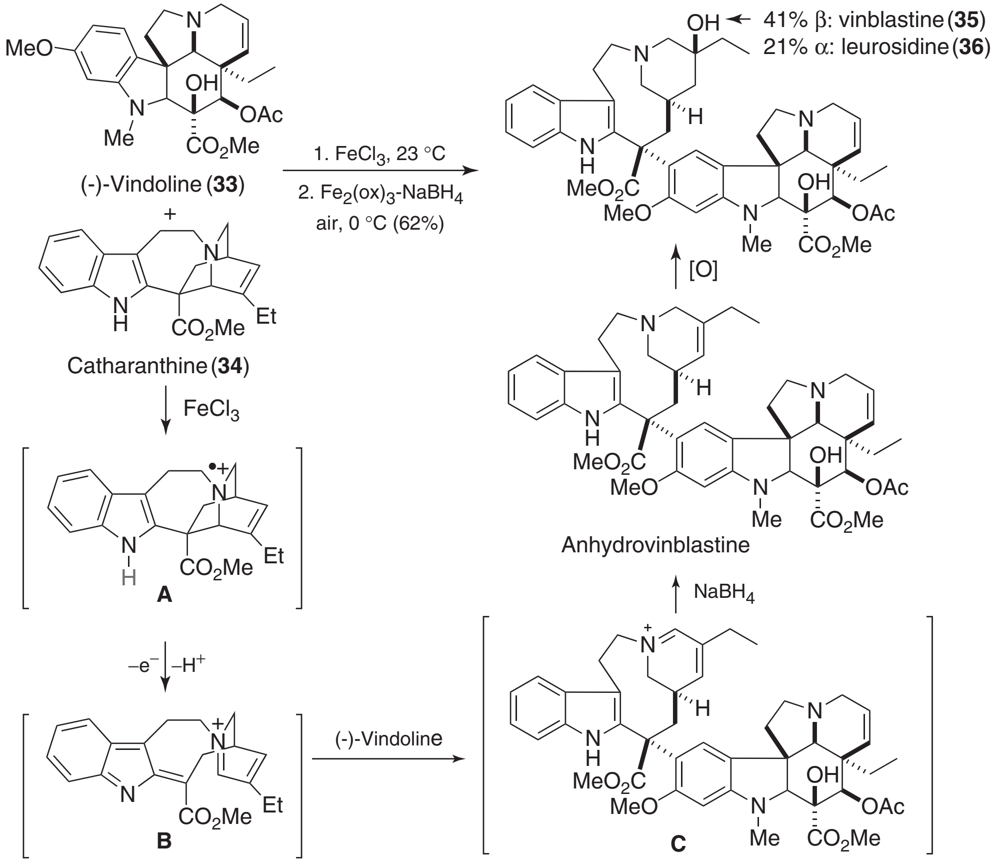
[4 + 2]- and [3 + 2]-cycloadditions belong to the type of pericylic reactions, which usually proceed selectively. As a result, the asymmetric syntheses of nine naturally occurring products were achieved as a single isomer, which allowed their stereochemistry to be established (Figure 1.10).

The chemistry developed eventually led to the synthesis of a compound library of more than 40 members based on the scaffolds of vinblastine and leurosidine (Figure 1.11).

Vinblastine (**35**) and leurosidine (**36**) are bisindole alkaloids, and are believed to be made through direct coupling of catharanthine (**34**) with vindoline (**33**) under oxy-reduction conditions (Scheme 1.5). In this event, when catharanthine amine was oxidatively treated with $FeCl_3$, radical cation **A** could be generated, which then underwent further oxidation, followed by biomimetic coupling with vindoline (**33**) to give intermediate **C**, a single diastereoisomer. Intermediate **C** was subjected to reduction with $NaBH_4$ to give anhydrovinblastine, which was then oxidatively converted to vinblastine (**35**) and leurosidine (**36**) in 12 steps.

1.5.4
Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations

The total synthesis of eudesmane terpenes by Baran's group was inspired by the biosynthesis of terpenes, which often comprise a "two-phase" process (cyclase phase and oxidase phase) [18]. Among the eudesmane family, dihydrojuenol (**37**) constitutes one of the lowest oxidized members.



Scheme 1.5 Biomimetic synthesis of vinblastine (**35**) and leurosidine (**36**).

Starting from **37**, terpenes possessing different levels of oxidation state can be accessed by sequential, site-selective C–H oxidations (Figure 1.12). A simple and superior route to **37** (corresponding to the cyclase phase) has been developed which involves a nine-step sequence and allows enantioselective and gram-scale preparation.

To plan a biomimetic synthesis, the trifluoroethyl carbamate directing group was introduced to deliver **43**. Its electron-withdrawing property renders H1 and H5 most prone to be oxidized. Thus, site-specific oxidation and halogenation were realized to afford intermediates **43** and **44**, respectively, which finally gave 4-epiajanol (**38**) and dihydroxyeudesmane (**39**), the structures of which were verified by X-ray crystallography.

To access the higher oxidized targets in the retrosynthesis pyramid diagram, **43** was converted into bromide **46** via the similar site-specific halogenation (Figure 1.13). Subsequent silver-assisted cyclization to carbonate **48** and hydrolysis afforded pygmol (**40**). Alternatively, **46** was subjected to basic elimination conditions to deliver the

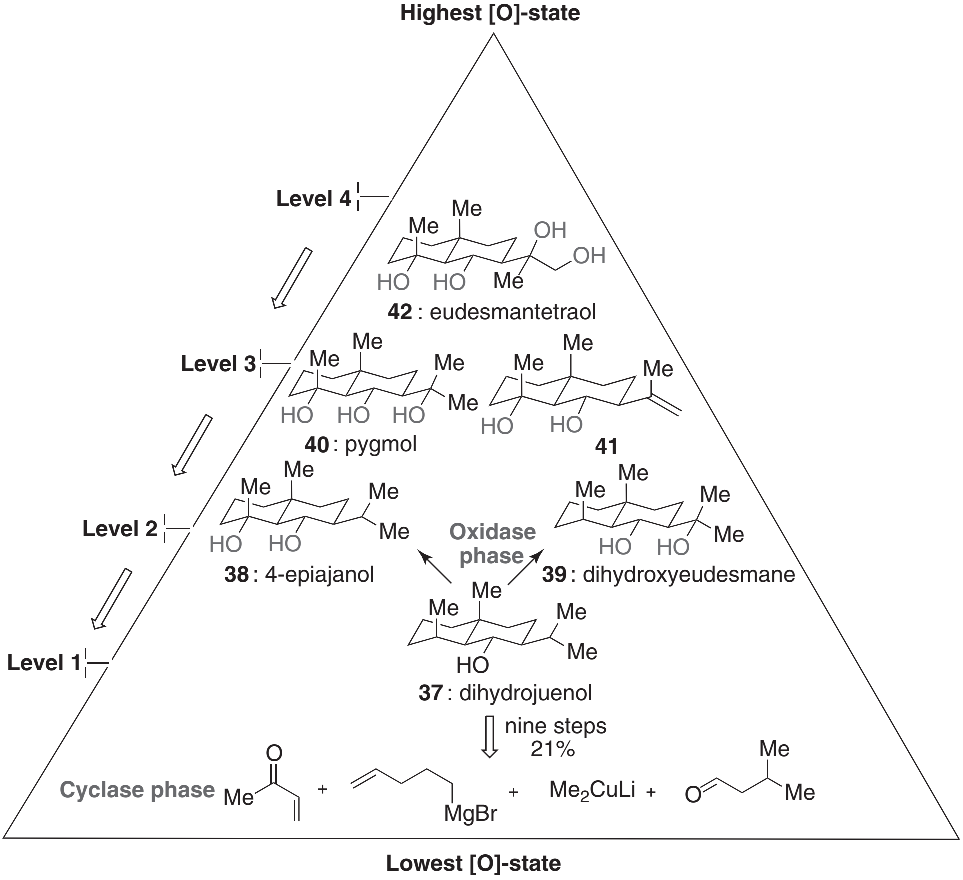


Figure 1.12 Pyramid diagram for the retrosynthetic planning of terpene synthesis using a "two-phase" approach.

alkene **47**. As the direct dihydroxylation of **47** proved ineffective, the neighboring group participate oxybromination followed by hydrolysis generated **48**, which was exposed to dilute acid to afford eudesmantetraol (**42**) by net inversion.

1.5.5
Total Synthesis of Bipinnatin J, Rubifolide, and Coralloidolides A, B, C, and E

The furanocembranoids are a family of diterpenoid natural products with a diverse level of oxidation states [19]. As bipinnatin J (**49**) was identified as a key precursor in the biomimetic synthesis, its first total synthesis was targeted as shown in Scheme 1.6. It features a ruthenium-catalyzed Alder–ene reaction, a Stille cross-coupling, and an intramolecular Nozaki–Hiyama–Kishi allylation as key steps.

With bipinnatin J (**49**) in hand, biomimetic transformations of it into other natural products were examined (Scheme 1.7). Luckily, reductive deoxygenation of the hydroxyl

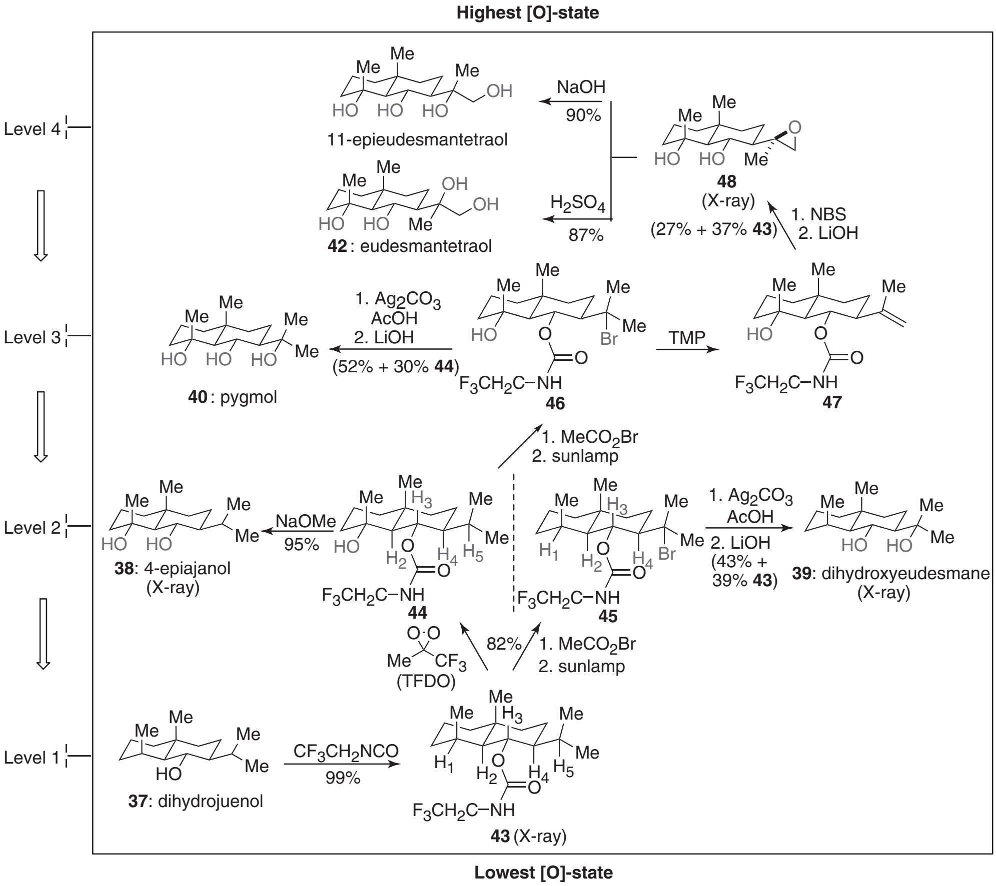
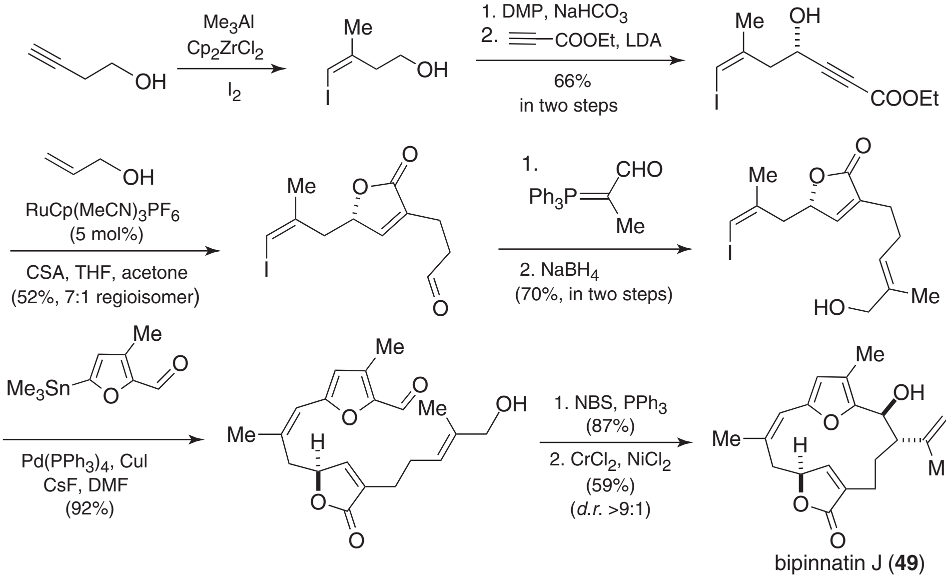


Figure 1.13 Biomimetic synthesis of eudesmantetraol.

group in bipinnatin J (**49**) delivered rubifolide (**50**), which was subjected to *m*-CPBA oxidative cleavage of the furan ring to yield isoepilophodione B (**51**) smoothly. Alternatively, Achmatowicz oxidation of bipinnatin J (**49**) proceeded cleanly to afford the sensitive hydroxypyranone **56** as a single stereoisomer which was then protected as its acetate followed by elimination of acetic acid to undergo 1,3-dipolar cycloaddition to afford intricarene (**57**). Rubifolide (**50**) could also be selectively epoxidized to afford coralloidolide A (**52**). Subsequent oxidative cleavage of the furan ring generated coralloidolide E (**53**) with dienedione functionality. Upon treatment with scandium triflate hydrate, it was ultimately converted into coralloidolide B (**54**). A transannular aldol reaction employing *N*,*N*′-dibutylurea (DBU) as the base generated coralloidolide C (**55**) in modest yield. Hence the total syntheses of natural products of furanocembranoids were realized in no more than 13 steps through this biomimetic synthesis without protecting groups.



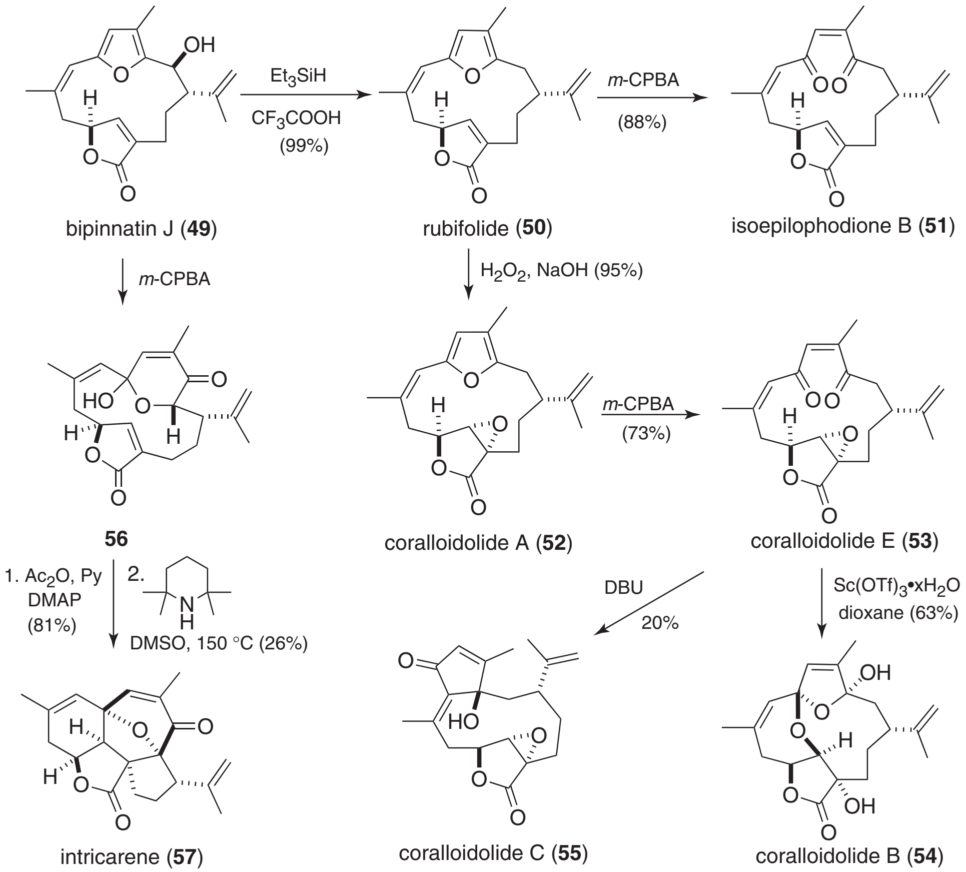
Scheme 1.6 Total synthesis of (±)-bipinnatin J (**49**).

1.5.6
Total Synthesis of Diverse Carbogenic Complexity Within the Resveratrol Class from a Common Building Block

The resveratrol family represents an important group of natural products with potential clinical applications [20]. However, owing to the structural complexity and liability, most members of the family could not be accessed in large quantities, either through synthesis or from natural resources.

To probe a biosynthetic pathway, Snyder's group identified a common building block, **58**, distinct from Nature's monomers. With alteration of the substituents in the aromatic rings, and careful control of the reaction conditions, cascade sequences initiated by relatively simple reagents could deliver one of the natural products selectively, as delineated in Scheme 1.8.

Exposure of **58** to acid initiated a proton-induced cyclization followed by capture with a thiol nucleophile to give intermediate **59**, which could be converted smoothly to **60**. Utilizing the skeleton of **60** as a branching point, a halogen electrophile-based cascade involving bromination and Friedel–Crafts alkylation delivered two new types of skeletons after dehalogenation [including natural products ampelopsin F (**61**) and pallidol (**62**)]. If **58** is first oxidized to ketone before cyclization, subsequent Friedel–Crafts alkylation induced by bromonium or dioxirane would lead to the seven-membered ring as represented by **63**–**65**. Alternatively, treatment with acid triggered a Friedel–Crafts/retro Friedel–Crafts sequence to deliver **66**. Subsequent

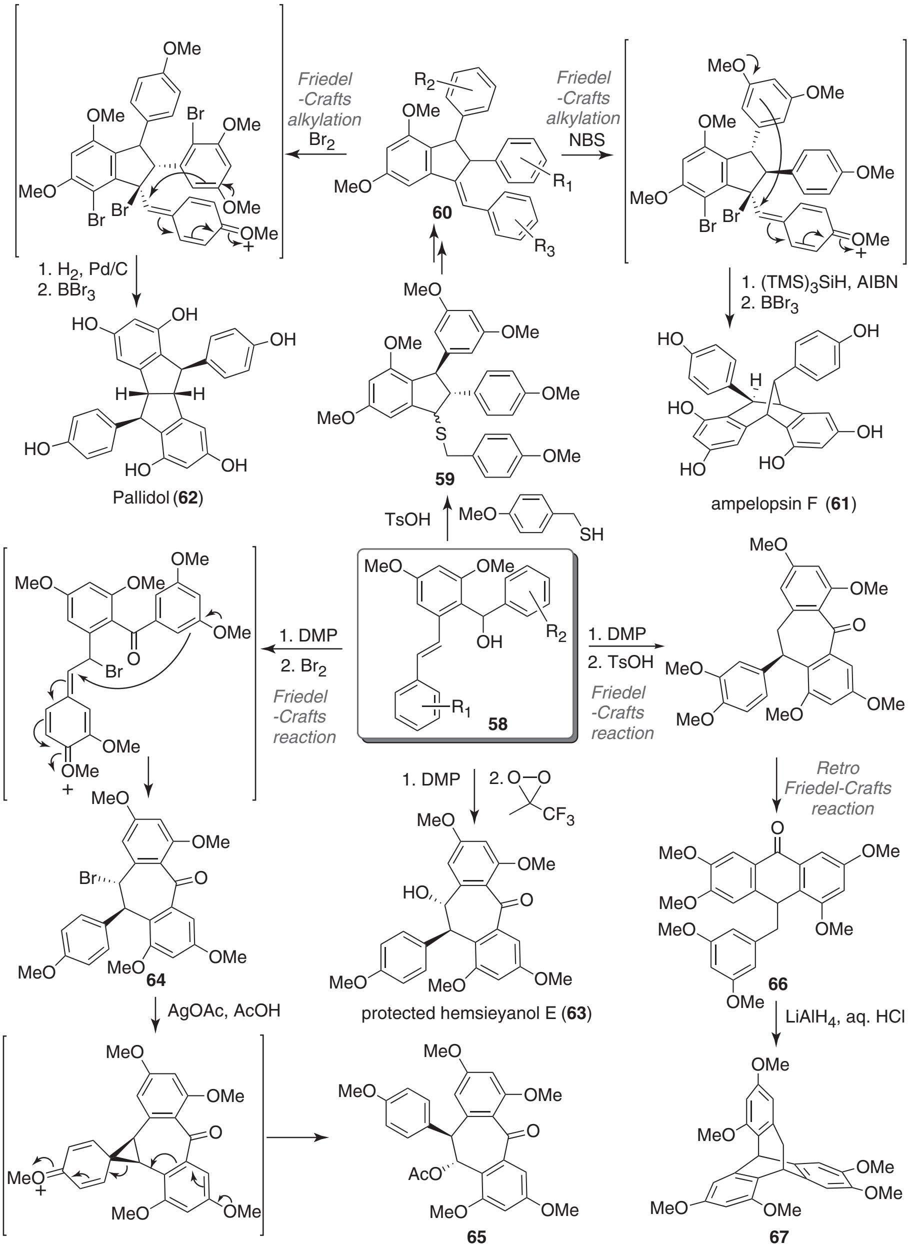


Scheme 1.7 Biomimetic synthesis of furanocembranoids.

reduction followed by acidic quenching allows a second Friedel–Crafts reaction to provide the [3.2.2]-bicycle (**67**). Overall, a series of natural products and analogs have been synthesized on a relatively large scale and in fewer than 10 steps, including 11 natural products (nine of which were synthesized for the first time) and 14 natural product-like analogs.

1.6
Conclusion and Perspectives

The need to identify fast and efficient synthetic methodologies and strategies for the generation of both natural products and natural product-like compounds has revolutionized the state-of-the-art of synthetic chemistry, demonstrating organic chemists' tireless



Scheme 1.8 Syntheses of the resveratrol family from a common building block.

efforts to design and synthesize compound collections more efficiently, practically, and with a greater chance of further optimization at a later research stage, compared with previous approaches. Among those efforts, the synthesis of natural products remains of great value in providing teaching and inspiration traceable to their biological activities, structural complexity and diversity for organic chemists to advance synthetic strategies and methodologies.

Synthetic targets concerning natural products are not limited to the precise replication of the naturally occurring compounds. The accumulation of insights and learning in total synthesis over the last few decades should enable organic chemists to ''aim higher,'' to integrate natural products more closely with advances in life science discovery. During that process, synthetic chemists will aim to find a new paradise to refine continuously the beauty of synthetic art.

Acknowledgments

We thank for the Professor Ye-Feng Tang for his helpful comments. Financial support was provided by the National Science Foundation of China.

References

1. (a) Clardy, J. and Walsh, C. (2004) *Nature*, **432**, 829–837; (b) Nicolaou, K.C. and Montagnon, T. (2008) *Molecules that Changed the World*, Wiley-VCH Verlag GmbH, Weinheim.
2. (a) Breinbauer, R., Vetter, I.R., and Waldmann, H. (2002) *Angew. Chem. Int. Ed.*, **41**, 2878–2890; (b) Kumar, K. and Waldmann, H. (2009) *Angew. Chem. Int. Ed.*, **48**, 3224–3242.
3. Weber, L. (2002) *Drug Discov. Today*, **7**, 143.
4. Koch, M.A., Schuffenhauer, A., Scheck, M., Wetzel, S., Casaulta, M., Odermatt, A., Ertl, P., and Waldmann, H. (2005) *Proc. Natl. Acad. Sci. U. S. A.*, **102**, 17272–17277.
5. (a) Grifo, F., Newman, D., Fairfield, A.S., Bhattacharya, B., and Grupenhoff, J.T. (1997) in *The Origins of Prescription Drugs* (eds. F. Grifo and J. Rosenthal), Island Press, Washington, DC, p. 131; (b) Arvigo, R. and Balick, M. (1993) *Rainforest Remedies*, Lotus Press, Twin Lakes, WI.
6. Arya, P., Joseph, R., and Chou, D.T.H. (2002) *Chem. Biol.*, **9**, 145.
7. (a) Langer, T. and Hoffman, R.D. (2001) *Curr. Pharm. Des.*, **7**, 509; (b) Woolfrey, J.R. and Weston, G.S. (2002) *Curr. Pharm. Res.*, **8**, 1527; (c) Klavunde, T. and Hessler, G. (2002) *ChemBioChem*, **3**, 928.
8. Lipinski, C. and Hopkins, A. (2004) *Nature*, **432**, 855–861.
9. (a) Schreiber, S.L. (2000) *Science*, **287**, 1964–1969; (b) Burke, M.D. and Schreiber, S.L. (2004) *Angew. Chem. Int. Ed.*, **43**, 46–58; (c) Nielsen, T.E. and Schreiber, S.L. (2008) *Angew. Chem. Int. Ed.*, **47**, 48–56.
10. (a) Kumagai, N., Muncipinto, G., and Schreiber, S.L. (2006) *Angew. Chem. Int. Ed.*, **45**, 3635–3638; (b) Goess, B.C., Hannoush, R.N., Chan, L.K., Kirchhausen, T., and Shair, M.D. (2006) *J. Am. Chem. Soc.*, **128**, 5391–5403; (c) Pelish, H.E., Westwood, N.J., Feng, Y., Kirchhausen, T., and Shair, M.D. (2001) *J. Am. Chem. Soc.*, **123**, 6740–6741; (d) Lindsley, C.W., Chan, L.K., Goess, B.C., Joseph, R., and Shair, M.D. (2000) *J. Am. Chem. Soc.*, **122**, 422–423.
11. (a) Wilson, R.M. and Danishefsky, S.J. (2006) *J. Org. Chem.*, **71**, 8329–8351;

(b) Gaul, C., Njardarson, J.T., Shan, D., Dorn, D.C., Wu, K.D., Tong, W.P., Huang, X.Y., Moore, M.A.S., and Danishefsky, S.J. (2004) *J. Am. Chem. Soc.*, **126**, 11326–11337; (c) Paterson, I., Gardner, N.M., Poullennec, K.G., and Wright, A.E. (2008) *J. Nat. Prod.*, **71**, 364–369; (d) Fürstner, A., Kirk, D., Fenster, M.D.B., Aïssa, C., Souza, D.D., Nevado, C., Tuttle, T., Thiel, W., and Müller, O. (2007) *Chem. Eur. J.*, **13**, 135–149.

12. (a) Wender, P., Verma, V.A., Paxton, T.J., and Pillow, T.H. (2008) *Acc. Chem. Res.*, **41**, 40–49; (b) Wender, P.A. and Hinkle, K.W. (2000) *Tetrahedron Lett.*, **41**, 6725–6729; (c) Wender, P.A., Baryza, J.L., Bennett, C.E., Bi, F.C., Brenner, S.E., Clarke, M.O., Horan, J.C., Kan, C., Lacôte, E., Lippa, B., Nell, P.G., and Turner, T.M. (2002) *J. Am. Chem. Soc.*, **124**, 13648–13649; (d) Wender, P.A., Hilinski, M.K., and Mayweg, A.V.W. (2005) *Org. Lett.*, **7**, 79–82; (e) Wender, P.A., Clarke, M.O., and Horan, J.C. (2005) *Org. Lett.*, **7**, 1995–1998; (f) Wender, P.A. and Horan, J.C. (2006) *Org. Lett.*, **8**, 4581–4584; (g) Wender, P.A. and Verma, V.A. (2008) *Org. Lett.*, **10**, 3331–3334; (h) Wender, P.A., Horan, J.C., and Verma, V.A. (2006) *Org. Lett.*, **8**, 5299–5302; (i) Wender, P.A., DeChristopher, B.A., and Schrier, A.J. (2008) *J. Am. Chem. Soc.*, **130**, 6658–6659; (j) Wender, P.A. and Baryza, J.L. (2005) *Org. Lett.*, **7**, 1177–1180; (k) Wender, P.A., Hegde, S.G., Hubbard, R.D., and Zhang, L. (2002) *J. Am. Chem. Soc.*, **124**, 4956–4957; (l) Wender, P.A., Hilinski, M.K., Skaanderup, P.R., Soldermann, N.G., and Mooberry, S.L. (2006) *Org. Lett.*, **8**, 4105–4108; (m) Wender, P.A., Hegde, S.G., Hubbard, R.D., Zhang, L., and Mooberry, S.L. (2003) *Org. Lett.*, **5**, 3507–3509.

13. (a) Smith, A.B. III, Razler, T.M., Meis, R.M., and Pettit, G.R. (2008) *J. Org. Chem.*, **73**, 1201–1208; (b) Smith, A.B. III, Razler, T.M., Meis, R.M., and Pettit, G.R. (2006) *Org. Lett.*, **8**, 797–799.

14. Czakó, B., Krti, L., Mammoto, A., Ingber, D.E., and Corey, E.J. (2009) *J. Am. Chem. Soc.*, **131**, 9014–9019.

15. (a) Corey, E.J., Gin, D.Y., and Kania, R.S. (1996) *J. Am. Chem. Soc.*, **118**, 9202–9203; (b) Martinez, E.J., Owa, T., Schreiber, S.L., and Corey, E.J. (1999) *Proc. Natl. Acad. Sci. U. S. A.*, **96**, 3496–3501; (c) Martinez, E.J. and Corey, E.J. (2000) *Org. Lett.*, **2**, 993.

16. (a) Nicolaou, K.C., Wu, T.R., Sarlah, D., Shaw, D.M., Rowcliffe, E., and Burton, D.R. (2008) *J. Am. Chem. Soc.*, **130**, 11114–11121; (b) Nicolaou, K.C., Lister, T., Denton, R.M., and Gelin, C.F. (2007) *Angew. Chem. Int. Ed.*, **46**, 7501–7505; (c) Nicolaou, K.C., Li, A., Edmonds, D.J., Tria, G.S., and Ellery, S.P. (2009) *J. Am. Chem. Soc.*, **131**, 16905–16918.

17. (a) Ishikawa, H., Elliott, G.I., Velcicky, J., Choi, Y., and Boger, D.L. (2006) *J. Am. Chem. Soc.*, **128**, 10596–10612; (b) Ishikawa, H., Colby, D.A., Seto, S., Va, P., Tam, A., Kakei, H., Rayl, T.J., Hwang, I., and Boger, D.L. (2009) *J. Am. Chem. Soc.*, **131**, 4904–4916; (c) Va, P., Campbell, E.L., Robertson, W.M., and Boger, D.L. (2010) *J. Am. Chem. Soc.*, **132**, 8489–8495; (d) Sasaki, Y., Kato, D., and Boger, D.L. (2010) *J. Am. Chem. Soc.*, **132**, 13533.

18. (a) Chen, K. and Baran, P.S. (2009) *Nature*, **459**, 824–828; (b) Richter, J.M., Ishihara, Y., Masuda, T., Whitefield, B.W., Llamas, T., Pohjakallio, A., and Baran, P.S. (2008) *J. Am. Chem. Soc.*, **130**, 17938–17954; (c) Su, S., Seiple, I.B., Young, I.S., and Baran, P.S. (2008) *J. Am. Chem. Soc.*, **130**, 16490–16491; (d) O'Malley, D.P., Yamaguchi, J., Young, I.S., Seiple, I.B., and Baran, P.S. (2008) *Angew. Chem. Int. Ed.*, **47**, 3581–3583; (e) Seiple, I.B., Su, S., Young, I.S., Lewis, C.A., Yamaguchi, J., and Baran, P.S. (2010) *Angew. Chem. Int. Ed.*, **49**, 1095–1098.

19. (a) Kimbrough, T.J., Roethle, P.A., Mayer, P., and Trauner, D. (2010) *Angew. Chem. Int. Ed.*, **49**, 2619–2621; (b) Roethle, P.A. and Trauner, D. (2006) *Org. Lett.*, **8**, 345–347; (c) Roethle, P.A., Hernandez, P.T., and Trauner, D. (2006) *Org. Lett.*, **8**, 5901–5904; (d) Malerich, J.P., Maimone, T.J., Elliott, G.I., and Trauner, D. (2005) *J. Am. Chem. Soc.*, **127**, 6276–6283; (e) Miller, A.K. and Trauner, D. (2005) *Angew. Chem. Int. Ed.*, **44**, 4602–4606; (f) Sofiyev, V., Navarro, G., and Trauner, D. (2008) *Org. Lett.*, **10**, 149–152.

20. Snyder, S.A., Breazzano, S.P., Ross, A.G., Lin, Y.Q., and Zografos, A.L. (2009) *J. Am. Chem. Soc.*, **131**, 1753–1765.

Commentary Part

Comment 1

Michael Foley

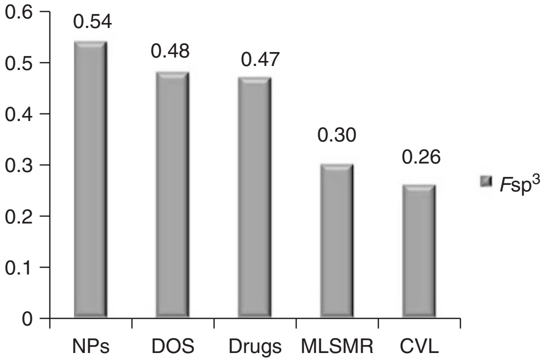
Ling-min Xu, Yu-Fan Liang, Qin-da Ye, and Zhen Yang present an excellent overview of strategies developed by modern synthetic organic chemists to create natural products and collections of compounds that are natural product-like. The strategies include DOS, DTS, FOS, and TOS. Natural products have been an important source of new drugs and continue to be an inspiration to chemists charged with creating collections of compounds that will be used for drug discovery. Despite their proven value in drug discovery, large collections of discrete purified natural products are not widely available for high-throughput screening (HTS) because the structural complexity of natural products makes it very difficult to replicate their structure precisely on a scale that is useful for drug discovery even for a single compound, much less for thousands of compounds. However, as the authors point out, it is structural complexity that makes natural products so useful in drug discovery. Until recently, it has been difficult to describe structural complexity in a straightforward way that can be coupled to the strategies described in this review. There is a great need for new chemical matter to modulate the function of the new biological targets emerging from modern biology and perhaps structural complexity is the key to success.

New insights into how genomic changes contribute to disease have rapidly expanded the list of important targets and pathways that are relevant to drug discovery. Although the strength of the evidence is increasing that transcription factors, regulatory RNAs, protein–protein, and protein–DNA interactions are involved in disease processes, such targets are often described as "undruggable" because when they are screened against current HTS compound collections few, if any, hits are found. These new targets represent a great opportunity for the treatment of disease, but can the chemistry community provide high-quality hits, leads, and drugs against them to improve treatment outcomes for patients in the future?

Unfortunately, the initial results do not look very promising. A particularly striking example of the failure of a screening collection to provide high-quality hits in genomics-derived, target-based, HTS was published by researchers at GSK in 2007 [C1]. GSK screened its entire compound collection in an effort to find hits against 70 separate antibacterial targets derived from their genomic information. Disappointingly, this effort delivered few leads and, remarkably, most screens failed to produce any hits at all. The authors cited the need for new chemical matter and new approaches to attack undruggable targets in order to overcome these lackluster results.

In order to modulate the function of new biological targets with small molecules, HTS compound collections must be updated regularly with new chemical matter. Screening compounds can come from a variety of sources, including medicinal chemistry programs, commercial vendor libraries commercial vendor library (CVLs) and natural products. Although most synthetic compounds created for use in HTS obey Lipinski's "Rule-of-Five" [C2], many of the most important natural product drugs do not obey this rule [C3]. Since the "Rule-of-Five" was published, medicinal chemists have looked for correlations between the physical properties of their compounds and success in transitioning through the various steps of the drug discovery process. In parallel with the development of the "Rule-of-Five," new technologies that allowed the creation of large collections of compounds for HTS emerged. These technologies, coupled with a strict focus on the "Rule-of-Five," produced achiral aromatic compounds that were high in sp^2-hybridized carbon content and lacked the complexity of natural products. The majority of compounds used in HTS are purchased from CVLs, and produced with the new technologies and with strict adherence to the "Rule-of-Five," so it should not be surprising that they have failed to deliver high-quality hits against the important targets and pathways illuminated by modern biology because they are so dissimilar to natural products in terms of their complexity.

Complexity can be quantified by the fraction of sp^3-hybridized carbons (Fsp^3), where Fsp^3 = number of sp^3-hybridized carbons/total carbon count. Interestingly, compounds with a greater sp^3 carbon content have higher success rates in progressing from screening to drug approval [C4]. We applied this measure of complexity to five different compound collections used in HTS and compared the average Fsp^3 for the AnalytiCon Discovery Natural Product collection, Broad



NPs = Natural products from AnalytiCon Discovery
DOS = DOS compounds in Broad collection
Drugs = Drugs from Drug Banks
MLSMR = NIH Molecular Libraries Small-Molecule Repository
CVL = Commercial Ven dor Libary compounds in Broad collection

Figure C1 Complexity analysis of different compound collections as measured by $F\text{sp}^3$, where $F\text{sp}^3$ = number of sp^3-hybridized carbons/total carbon count.

Institute DOS collection, Approved Drug collection from Drug Bank, NIH Molecular Libraries Small Molecule Repository (MLSMR) collection, and the Broad Institute CVL collection (Figure C1). The results revealed that natural products, DOS compounds, and drugs share a similar degree of complexity, with natural products being the most complex. The MLSMR collection and the CVL, which are most similar to typical HTS collections used in pharmaceutical companies and major academic screening centers, were significantly less complex and predicted by this analysis to be less likely to succeed in drug discovery. We speculate that if a similar analysis were performed on compounds emerging from the DTS, FOS, and TOS strategies described in this review, those compounds would look more like natural products, drugs, and DOS compounds in their $F\text{sp}^3$.

The clear correlation between complexity and success in the drug discovery process demands that modern synthetic chemists strive to increase the efficiency with which they can prepare both natural products and natural product-like compounds. The strategies described in this review provide tools for chemists to begin to create collections of compounds with both the complexity and desirable physicochemical properties not only to modulate the function of the new targets emerging from modern biology but also to become drugs.

Comment 2

Scott A. Snyder

If organic chemists are to play a role in addressing the largest biomedical challenges facing society, our ability both to identify and to create functional small molecules rapidly with unique properties must improve dramatically. The question, of course, is how best to achieve this lofty objective, a problem with which the field has been grappling for many years, particularly over the course of the past two decades as new and more ominous health threats such as drug-resistant strains of bacteria and HIV have been identified. One avenue that has attracted much attention is the structural modification of natural products. Given that the architectures of these materials have been honed over millennia to achieve specific biochemical activity, they afford highly attractive starting points for investigations to improve upon their potency, selectivity, and pharmacology within humans.

The problem is the overall time and effort required for these investigations to reach fruition. Although simple adjustment of the natural product itself through derivatization of outlying functional handles sometimes succeeds, such as was the case for the creation of aspirin from salicylic acid in 1897 [C5], recent clinical leads by altering the side-chain of Taxol [C6], and converting an epoxide linkage within the epothilones to an aziridine [C7], these outcomes are unfortunately all too rare. Instead, fully fledged medicinal chemistry efforts involving the synthesis of hundreds, if not thousands, of analogs with major structural modifications over the course of many years are typically needed to identify suitable properties. Medicines such as Lipitor (atorvastatin) is a recent example of highly successful programs along these lines [C8], one that has saved thousands of lives. The goal for the future, however, has to be far more of these success stories achieved in a much shorter period of time.

This chapter by Zhen Yang and co-workers explores efforts to achieve that goal through alternate paradigms for natural product structure alteration. Through seven examples encompassing concepts from DOS, DTS, and FOS, and efforts to divert or co-opt biogenetic pathways to achieve much structural diversity from a single starting material, the authors provide a compelling array of potential approaches that could convert natural products more quickly into clinical agents. Rather than offer any recap of the stories they provide, in which I am honored to have some of my group's work included, I just wish to note a couple other examples along these lines that have proven inspirational to me in my thinking on natural product synthesis within a drug discovery paradigm. The first is the Corey group's identification of phthalascidin [C9], a derivative of the large and highly complex natural product ecteinascidin 743 [C10], which is now in advanced clinical trials. The second is the recent rapid assembly of vinblastine and related molecules by Boger's group through a cascade of pericyclic reaction processes [C11], efforts which not only afford an expedient synthesis of the drug itself, but also provide a number of analogs that may well lead to unique activity and new thoughts on the biogenesis of this important material. In my opinion, the main message of these, and also all the endeavors mentioned in this chapter, is that the process of identifying clinical agents can likely be accelerated, given that each of these programs was achieved in a relatively short period of time by only a few researchers. It is hoped that the fruits of these, and other, approaches will be harvested in the near future. I am, however, left with some questions for the future, and I will close my commentary with these queries:

1) Despite the promise shown for these approaches, they are all dependent at the most basic level on the existence of a unique natural product architecture to serve as a forum for exploration. Given the reluctance of major pharmaceutical companies to continue investment in natural product isolation efforts, together with a decrease in the ease of federal funding for such programs and the increasing challenge of structural elucidation for materials of increasing complexity found in ever more minute scales, how can the future of natural products in the drug discovery process be secured?
2) To what extent can China potentially lead in this endeavor, not only because of enhanced governmental and private sector funding, but also because of the rich history of traditional medicines which are only now beginning to be thoroughly explored?
3) How should synthetic chemists, natural product isolation scientists, and those at the frontiers of biosynthetic engineering best work together to achieve shared goals in identifying clinical candidates?

Comment 3

Da-Wei Ma

For a long time, synthetic chemists in academia have focused their attention on how to construct the complex structures of natural products and how to complete the total synthesis of these molecules. The achievements within this challenging area during the last century have been astonishing. These efforts are well recognized as the driving force for organic chemistry development because during the total synthesis numerous new synthetic reactions and methods have been discovered. However, in addition to its inherent beauty, total synthesis also opens the gates widely to a better understanding of biological processes and the development of pharmaceutically interesting substances. Indeed, natural products have been proven to be a rich source for the development of therapeutic agents and pharmaceutical tools, as is evident from the fact that over 50% of clinically used drugs came from natural products themselves, natural product derivatives, and natural product mimics. In recent years, more and more synthetic chemists have realized that they could combine their synthetic efforts with biological studies to make total synthesis more valuable.

This trend has stimulated the birth of concepts such as diversity-oriented organic synthesis, DTS, FOS, and, TOS, although the differences between some of them are not very obvious.

In this chapter, Zhen Yang and co-workers give a comprehensive summary of recent achievements in this emerging field. Through these results one can find three remarkable characters. The first is that via synthetic efforts, accessible derivatives can be used to modify the biological activity of the natural products and to shed light on their role in biological systems, as exampled by Danishefsky's DTS of the tumor cell migration inhibitor migrastatin that delivered several migrastatin mimics with increased activities, and Wender's FOS of the PKC activator bryostatin that provided potent analogs with simplified structures. The second is that cycloaddition methods are powerful tools for quickly generating natural product mimics, as indicated by Nicolaou's TOS of the HIV-1 replication inhibitor biyouyanagin A via $[4+2]$- and $[2+2]$ cycloadditions, and Boger's total synthesis of the antitumor agent vindoline and its analogs via a $[4+2]/[3+2]$-cycloaddition cascade. The third is that biomimetic transformations are frequently considered in the DOS of natural products, as demonstrated by Shair's synthesis of galanthamine-like molecules, Baran's total synthesis of eudesmane terpenes by site-selective C-H oxidation, Trauner's biomimetic syntheses of furanocembranoids from the natural product bipinnatin J, and Snyder's syntheses of the resveratrol family from a common building block.

Authors' Response to the Commentaries

We greatly appreciate the reviewers' comments and are very encouraged by their support of the work presented. We have revised the text based on the reviewers' comments. Following Prof. Snyder's comments, we have added Corey's group's identification of phthalascidin in the text. Since the synthesis of vinblastine by Boger was already included, we have provided additional references recommended by Prof. Snyder. We believe that these revisions, as suggested by the reviewers, improve the quality of our chapter and thanks are due for their efforts.

References

C1. Payne, D.J., Gwynn, M.N., Holmes, D.J., and Pomplano, D.L. (2007) *Nat. Rev. Drug Discov.*, **6**, 29–40.

C2. Lipinski, C.A., Lombardo, F., Dominy, B.W., and Feeney, P. (1997) *J. Adv. Drug Deliv. Rev.*, **23**, 3–25.

C3. Lipinski, A.H. (2004) *Nature*, **432**, 855–861.

C4. Lovering, F., Bikker, J., and Humblet, C. (2009) *J. Med. Chem.*, **52**, 6752–6756.

C5. For a review on this molecule, see: Nicolaou, K.C. and Montagnon, T. (2008) *Molecules that Changed the World*, Wiley-VCH Verlag GmbH, Weinheim, pp. 21–28.

C6. For a recent review on approaches to the taxanes, see: Ishihara, Y. and Baran, P.S. (2010) *Synlett*, 1733.

C7. Regueiro-Ren, A., Borzilleri, R.M., Zheng, X., Kim, S.H., Johnson, J.A., Fairchild, C.R., Lee, F.Y.F., Long, B.H., and Vite, G.D. (2001) *Org. Lett.*, **3**, 2693.

C8. Roth, B.D. (2002) *Prog. Med. Chem.*, **40**, 1.

C9. Martinez, E.J., Owa, T., Schreiber, S.L., and Corey, E.J. (1999) *Proc. Natl. Acad. Sci. U. S. A.*, **96**, 3496.

C10. (a) Corey, E.J., Gin, D.Y., and Kania, R.S. (1996) *J. Am. Chem. Soc.*, **118**, 9202; (b) Martinez, E.J. and Corey, E.J. (2000) *Org. Lett.*, **2**, 993.

C11. (a) Sasaki, Y., Kato, D., and Boger, D.L. (2010) *J. Am. Chem. Soc.*, **132**, 13533; (b) Va, P., Campbell, E.L., Robinson, W.M., and Boger, D.L. (2010) *J. Am. Chem. Soc.*, **132**, 8489; (c) Ishikawa, H., Colby, D.A., Seto, S., Va, P., Tam, A., Kakei, H., Rayl, T.J., Hwang, I., and Boger, D.L. (2009) *J. Am. Chem. Soc.*, **131**, 4904.