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# THE BASICS OF DIVERSITY-ORIENTED SYNTHESIS

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## 1.1 INTRODUCTION

In this chapter, the underlying ideas behind diversity-oriented synthesis are introduced. The relationship between diversity-oriented synthesis and combinatorial chemistry is discussed, and the rationale behind the use of diversity-oriented synthesis as a tool for the discovery of biologically active molecules is explained. Common synthetic strategies for the efficient generation of structurally diverse compound collections are then introduced. In the second part of the chapter we discuss recent examples of diversity-oriented syntheses, with examples taken from our own research and from the wider community. These examples seek to illustrate the imaginative ways in which the various synthetic strategies have been implemented and to represent the current state of the art in diversity-oriented synthesis.

## 1.2 WHAT IS DIVERSITY-ORIENTED SYNTHESIS?

The term *diversity-oriented synthesis* (DOS) first appeared in the chemical literature in the year 2000 in an article written by Stuart Schreiber [1]. In this article, which was written with a particular focus on drug discovery, the term was used to distinguish between compound libraries (or single compounds) synthesized with the intention of interacting with preselected protein targets [called *target-oriented synthesis* (TOS)] and those libraries used in "efforts to identify simultaneously therapeutic protein

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targets and their small molecule regulators" [1]. For TOS compounds, knowledge of the preselected targets can lead to some degree of rational design being implemented; however, according to Schreiber, the second class of library should benefit from high levels of structural diversity within the compound collection, so the deliberate synthesis of such libraries can be considered to be DOS. An alternative definition was offered later by our group, where it was suggested that "diversity-oriented synthesis involves the deliberate, simultaneous and efficient synthesis of more than one target compound in a diversity-driven approach to answer a complex problem" [2].

This statement leaves some room for interpretation; however, as the very nature of diversity, in a chemical sense, is to some degree subjective, it provides a useful general definition that can be applied across the majority of the examples of DOS that are published today. The "complex problem" mentioned in this definition usually refers to the discovery of novel biologically relevant compounds, and this is the context in which DOS is usually discussed. However, as mentioned, this does not have to be the case, as the DOS approach could potentially be applied to other problems, such as the discovery of a novel ligand or catalyst for a reaction [2].

## 1.3 SMALL MOLECULES AND BIOLOGY

The term *small molecules* has no strict definition; however, it usually refers to potentially orally bioavailable compounds that have a molecular weight of less than 1500 Da [3] and that are distinct from naturally occurring biological macromolecules: DNA, RNA, and proteins [4]. The label "small molecule" can therefore be applied across the vast majority of synthetic drugs and naturally occurring secondary metabolites.

The ability of small molecules to interact with biological macromolecules, in particular, proteins, and consequentially to exert specific effects, often in a selective and dose-dependent manner, has led to them being regarded as powerful tools for the study and manipulation of biological systems [5–7]. Indeed, the use of small molecules in this way, to modulate biological function deliberately and selectively, underpins the fields of medicinal chemistry (where molecules are used to treat disease states) and chemical genetics (where molecules are used as probes to study biological systems) [3,8,9].

The discovery of novel molecular entities or structural classes capable of these specific interactions represents a significant challenge. In cases where the biological target is well defined and understood, the rational design of ligands is sometimes possible, especially when the structure of a native ligand or its single protein target is known [6]. However, for other, less well understood disease states, or if a novel mode of binding or biological target is sought, this is not possible. In these cases high-throughput screening (HTS) of small-molecule libraries can provide an effective solution [10]. Clearly, the composition of these libraries, in terms of the chemical structures included within them, is an extremely important consideration [2]. As the biological activity of a given molecule is intrinsically related to its chemical structure, the greater the degree of structural variation between compounds within a library, the higher the likelihood of achieving broad-ranging and distinct biological activity across that library [11–13]. The presence of multiple structural classes within a

library being tested against a single target also increases the likelihood of discovering a molecule capable of binding to that target in a novel manner [14].

The molecules that comprise these libraries, or indeed any compound collection, may be obtained from either natural (natural products) or nonnatural (chemical synthesis) sources. Nature has produced huge numbers of biologically relevant secondary metabolites that have evolved to have specific and exquisite biological activity. These compounds have been used medicinally for millennia, still provide many lead compounds and drugs today [15,16], and almost certainly will continue to do so long into the future [17]. Also, there can be no argument that natural products do not represent a truly structurally diverse collection of compounds. Taking these factors into account, the screening of natural products for biological activity is clearly an extremely valuable thing to do. However, it is not realistic to suggest the production of large libraries based solely on natural products, due predominantly to difficulties in sourcing, isolating, and identifying the bioactive components, as well as in purifying and chemically modifying these often extremely complex structures [18]. Therefore, in terms of producing large numbers of compounds for screening, deliberate chemical synthesis is generally considered to be the most efficient approach [13,19].

With the advent of combinatorial chemistry in the 1990s, it became possible for chemists to produce very large numbers of compounds in an efficient manner. The use of split-and-pool techniques and advances in automation made it possible to synthesize literally millions of compounds in a short period of time [20]. These libraries were, however, generally made up of broadly similar structures, resulting in a fairly limited biological profile across the library. The molecules were usually synthesized by combining a number of building blocks in different ways using the same synthetic methods to generate distinct structures, so achieving a multiplicative increase in the final number of compounds synthesized with an additive increase in the number of building blocks used. This approach usually resulted in the variation of substituents (R-groups) around a common scaffold. Libraries of this sort have had limited success in the discovery of novel biologically active agents, a fact that is attributed primarily to the relative lack of structural diversity within the libraries [21]. It is therefore believed that the quality of the compounds that make up these screening collections, in terms of structural complexity and diversity, is as, if not more important than the total number of compounds present [2].

There are many commercially available or proprietary compound collections that can be seen to represent a source of small molecules without the need for de novo synthesis [12]. The compounds comprising these libraries are generally synthesized in a combinatorial fashion and so suffer from the limitations described above in terms of structural and hence functional diversity. These collections also suffer from limitations that can be attributed to the desire to produce very large numbers of compounds quickly: They are generally "flat" (based around aromatic core structuers containing few stereocentres), structurally simple, and similar [22].

There is also a belief that these compound collections are too heavily biased toward traits that are traditionally perceived to be desirable in drug-like molecules, such as the Lipinski rules for oral bioavailability [12,14,23]. These collections are therefore heavily weighted toward known bioactive chemical space (the region of chemical space spanned by known drug molecules and bioactive natural products). By

definition, the exploration of this region has been a fruitful endeavor for the discovery of biologically active and medicinally useful compounds; however, to restrict all screening campaigns to molecules with a relatively narrow range of properties risks the omission of many potentially biologically active molecules that reside in underrepresented and underexplored regions of chemical space [5]. Expanding the region of chemical space explored by screening collections may help to discover small-molecule modulators for classically undruggable targets and so serve to expand the "druggable" genome [24]: a key challenge in chemical biology [9]. In fact, a number of DOS campaigns have already discovered small molecules capable of modulating nontraditional drug targets such as protein–DNA interactions [25,26] and protein–protein interactions [27].

While both natural products and proprietary compound collections obviously have their place in the discovery of novel biologically active compounds, the deliberate synthesis of libraries of high-quality compounds (in terms of structural complexity and variety) represents a third, distinct option that can prove superior for some applications. This is where DOS comes in. As noted above, the term *diversity-oriented synthesis* did not appear in the literature until 2000 [1,28]; however, it is fair to say that many of the ideas behind DOS had existed for some time before then.

A review article from 1997 by Spaller et al. suggested that combinatorial libraries may be suggested to fall into two categories: *focused libraries*, where a number of closely related compounds based on a privileged structure are synthesized with a known target in mind, and *prospecting libraries*, where an entirely new lead compound is sought, so the objective is to screen a large number of structurally varied compounds in the hope of finding a lead with a novel mode of action [29]. The focused libraries can be considered to be the result of a "classical" combinatorial chemistry approach, and further reference made here to combinatorial chemistry refers to the synthesis of this type of library. On the other hand, it can be argued that the syntheses of these prospecting libraries could probably be considered to be early examples of diversity-oriented syntheses, as they were produced with aims similar to those of contemporary DOS libraries: to achieve high levels of structural variety and bioactive chemical space coverage. However, it was when the term *DOS* was coined in 2000 that the ideas and strategies underpinning modern diversity-driven synthesis began to become more formalized.

## 1.4 COMPARING DOS, TOS, AND COMBINATORIAL CHEMISTRY: FOCUSED LIBRARY SYNTHESIS

The aim of efficiently synthesizing large numbers of structurally diverse compounds capable of effectively interrogating useful areas of chemical space is not easy to realize, for a number of reasons. Principal among them is the fact that the synthetic challenge of producing a biologically relevant DOS library has to be approached from the direction opposite to that of more traditional chemical synthesis [1,2]. In both TOS (of natural and unnatural products) and focused library synthesis, a target structure (or structures) are in mind at the beginning of the synthetic campaign. These structures are then broken down rationally into simpler starting materials and building

blocks through the well-established and powerful process of retrosynthetic analysis. In complex molecule synthesis, retrosynthetic analysis breaks a molecule down into simple precursors or building blocks, which are then combined in a "convergent" fashion.

In DOS an ideal stategy involves "divergent" synthesis, where a small number of compounds are transformed into many distinct structures. It is not possible then to apply retrosynthetic analysis directly to DOS pathways, so the synthetic analysis must be carried out in the forward direction [1,2]. This means that starting materials and intermediates must be chosen with a view to diverse reactivity at a later point in the synthetic sequence. Generally, DOS pathways make use of complexity-generating reactions to quickly build up molecular scaffolds and product–substrate relationships in which the product of one reaction is the substrate for the next. Figure 1.1 represents the synthetic strategies used in, and the chemical space coverage achieved by, TOS, focused library synthesis, and DOS.

## 1.5 MOLECULAR DIVERSITY

The absolute assessment of the degree of molecular diversity within a given set of compounds is not straightforward, although a number of possible methods do exist (see below). Any synthesis involving the production of more than one molecule, such as focused library synthesis, must contain some degree of diversity between the products, as the compounds produced are not identical, and therefore the term *DOS* can be used with some legitimacy to describe focused library synthesis. It has been emphasized, however, that this is not really in the "spirit" of DOS, where the aim should be to incorporate, as efficiently as possible, the maximum degree of structural diversity for a given synthetic sequence [19,30]. Ideally, this should involve incorporation of the four types of molecular diversity that are frequently identified in the literature [2,5,19,30,31]:

1. *Appendage or building block diversity*: variation resulting from the choice of starting materials or "building blocks" used, usually resulting in the variation of R-groups around a single scaffold. (This is the approach used most frequently, almost by definition, in combinatorial libraries.)
2. *Functional group diversity*: variation of the functional groups present in a molecule generally, and also at specific sites within the gross structure. This gives the potential for interactions with different polar, apolar, or charged groups present in biological macromolecules.
3. *Stereochemical diversity*: variation in the orientation of functional groups and potential macromolecule-interacting elements. This is clearly very important, as nature is a three-dimensional environment.
4. *Scaffold or skeletal diversity*: variation in the overall molecular framework, typically considered to be variation in ring structures and other rigidifying elements, resulting in molecules with distinct scaffolds and, consequently, distinct molecular shapes.

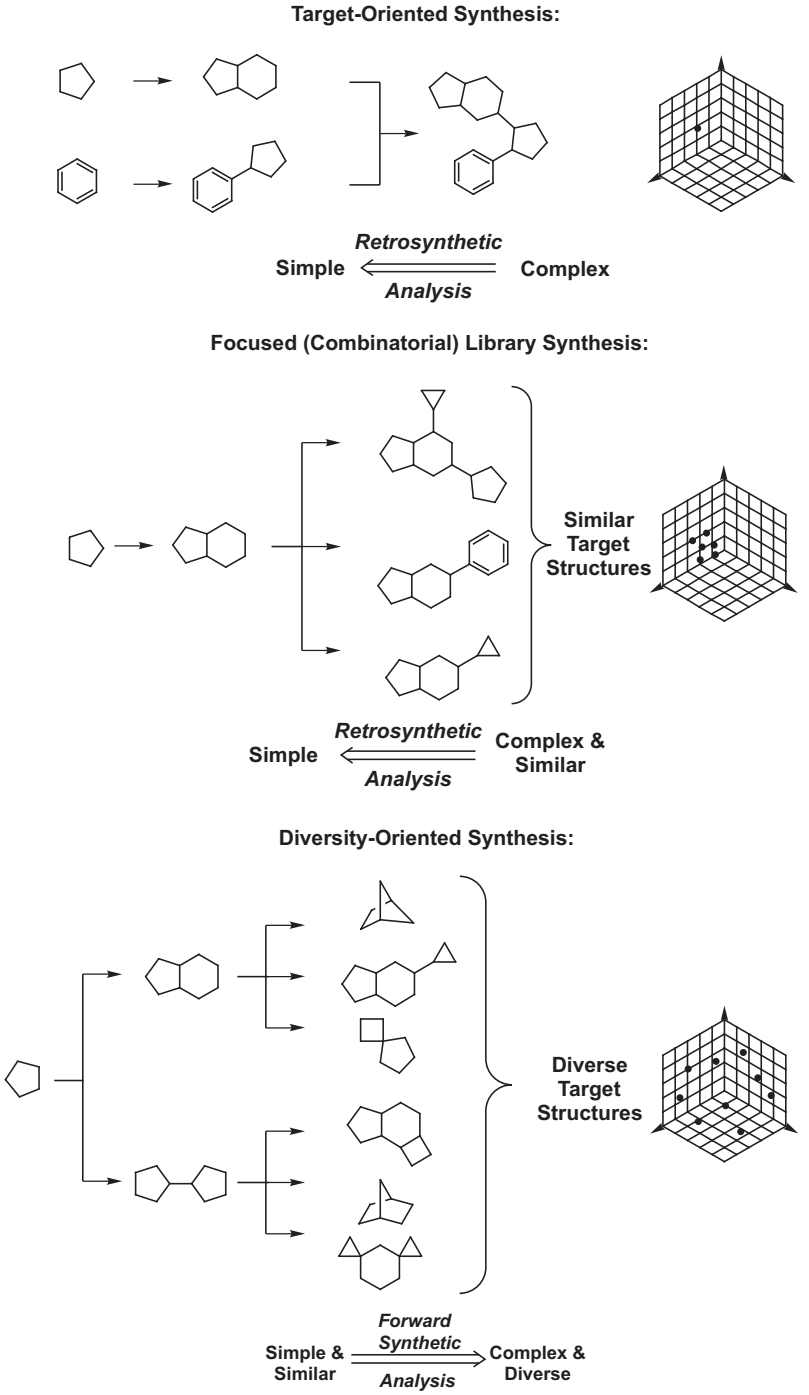



**FIGURE 1.1** Planning strategies and end goals involved in target-oriented synthesis, focused library synthesis (combinatorial synthesis), and diversity-oriented synthesis. The first two approaches use retrosynthetic analysis to design the synthesis of target compounds. DOS uses forward synthetic analysis to produce libraries that occupy diffuse regions of chemical space.

There also exists something of a hierarchy within these types of diversity that is based on both synthetic ease and the relative perceived value of each type. Appendage diversity is viewed as the easiest to achieve but is the least important when it comes to producing functionally (biologically) diverse compounds, and it is widely accepted that scaffold diversity is by far the most important and most difficult to achieve [2,32,33]. For this reason there are many published examples of DOS that focus almost entirely on producing diverse molecular skeletons [31,34].

Scaffold diversity is considered the most important diversity element because biomacromolecules are (on a molecular scale) large three-dimensional environments with more or less defined binding regions, pockets, and surfaces; as such, they will interact only with molecules that have complementary three-dimensional structure [13,35]. Therefore, it is the overall shape of a molecule that is the most important factor in terms of determining its biological effects, and this is linked intrinsically to the molecular scaffold or skeleton that the molecule possesses [36]. Libraries that contain large numbers of distinct molecular scaffolds should then cover the widest range of potential binding partners.

To provide a conceptually simple and easily interpretable comparison of the relative molecular diversity incorporated into different compound collections, Spandl et al. suggested the consideration of molecular diversity as a spectrum [19]. At one extreme of the spectrum is a single compound occupying a single point in chemical space, and at the fartherest extreme are all possible compounds giving the maximum chemical space coverage possible (Figure 1.2).

In this context, DOS aims to produce small-molecule libraries that occupy a position toward the right-hand side of the spectrum. This qualitative representation of molecular diversity on a sliding scale shows clearly the idea that DOS libraries should be considerably more diverse than their traditional combinatorial counterparts; however, it is not possible to use this spectrum to compare the relative diversity of compound collections in any meaningful way. More quantitative assessment of the relative diversity of compound collections can be achieved by looking at their comparative molecular descriptors and using them computationally to generate a visual representation of their positions in chemical space.

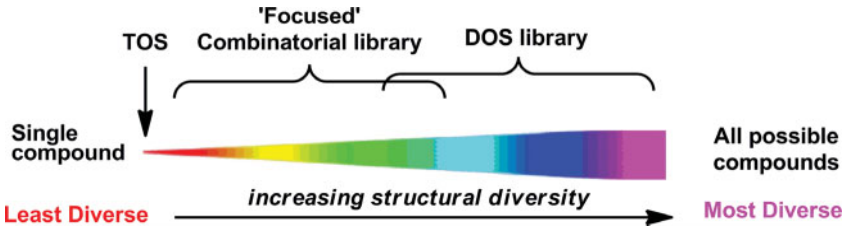



**FIGURE 1.2** Molecular diversity spectrum: a representation of the relative degrees of molecular diversity achieved using TOS, focused library synthesis, and DOS. (From [19], with permission of The Royal Society of Chemistry.) (*See insert for color representation of the figure.*)

## 1.6 MOLECULAR DIVERSITY AND CHEMICAL SPACE

Chemical space, or more properly, *multidimensional descriptor space*, encompasses all theoretically possible compounds and is therefore essentially infinite, limited only by the imagination of chemists and current synthetic methodologies [37,38]. Molecules occupy discrete points within chemical space with "similar" molecules grouped together and "dissimilar" molecules farther apart.† Molecules' positions in chemical space are determined by their comparable physical properties, such as molecular weight, log P, and polarizability as well as their topological features [37,39].

An algorithm based on a large number of these descriptors can be used to create a representation of chemical space based on the descriptors used and the limits placed on them. A molecule's position within this particular multidimensional descriptor space can then be calculated. To give a visually accessible representation of multidimensional descriptor space, it is necessary to use principal components analysis (PCA) [40] to condense the information into two- or three-dimensional scatter plots. These plots then provide a means to easily compare the relative coverage of multidimensional descriptor space achieved by compound collections. It is, however, worth mentioning that these plots are not absolute assessments of diversity or chemical space coverage, as there is the potential for a molecule's relative and absolute position to move depending on the molecular descriptors chosen and any weighting scheme applied to the analysis [41]. Because of this potential, scatter plots are often produced with two or more compound collections superimposed on each other so that their relative diversity can be compared. Figure 1.3 shows an example of chemical space analysis produced using chemical descriptors and PCA.

## 1.7 SYNTHETIC STRATEGIES FOR CREATING MOLECULAR DIVERSITY

As noted earlier, the challenge of creating molecular diversity efficiently is a considerable one, requiring strategies that differ from the majority of traditional chemical syntheses. Since the beginnings of DOS in the early 2000s, two distinct strategies for the generation of molecular diversity (in particular, skeletal diversity) have been identified in the literature [5]. They are: (1) a *reagent-based approach*, where subjecting a given molecule to a range of reaction conditions allows the synthesis of a number of distinct compounds; and (2) a *substrate-based approach*, where a number of starting materials containing preencoded skeletal information are transformed under the same conditions into a range of molecular structures (Figure 1.4). These

†The words *similar* and *dissimilar* are used with caution, as these terms require a point of reference against which to compare. As such, the same set of molecules could be considered similar or dissimilar, depending on how they are compared (the descriptors used). However, within a given analysis more "similar" molecules should group closer together than those with traits that are more different.

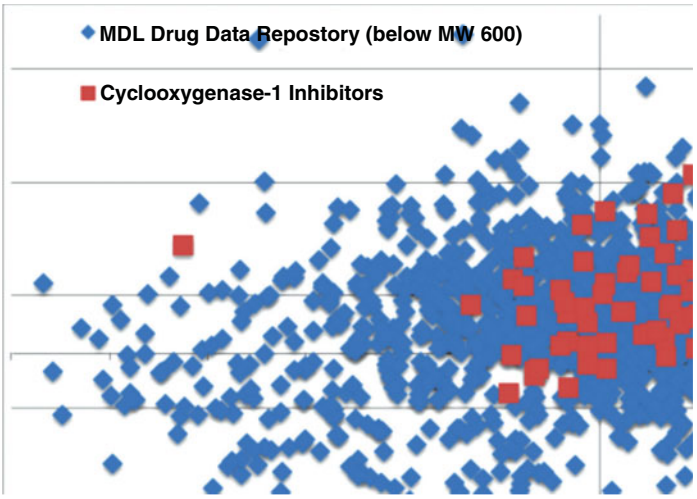



**FIGURE 1.3** Chemical space analysis plot of cyclooxygenase-1 (COX-1) inhibitors (red squares) and MDDR compounds (blue diamonds), created using chemical descriptors and principal components analysis. The plot shows that COX-1 inhibitors occupy a wide range of chemical space. (*See insert for color representation of the figure*.)

strategies are not orthogonal to each other, and many DOS campaigns will contain aspects of both. Reagent-based diversification (also known as a *branching reaction pathway*) can be used at any stage of a DOS; it can be used in the early stages to create diverse functionality or in later stages to transform prefunctionalized molecules into distinct molecular scaffolds. Generally, there are considered to be two approaches to reagent-based diversification: the use of "pluripotent" functionality, where a single functional group can be transformed under a range of reaction conditions to give distinct functionality or molecular scaffolds; and the use of densely functionalized molecules, where different functional groups can be transformed orthogonally. The latter approach is generally used to pair functional groups and so create diverse molecular skeletons [19,30]. Substrate-based diversification is generally used in the later stages of a DOS to react strategically placed functional groups intramolecularly and so *fold* compounds into distinct molecular structures. For this reason, it is often referred to as a *folding reaction pathway*.

Some of these ideas were further refined by Schreiber when he identified the use of a *build/couple/pair strategy* as a common feature in the production of small-molecule collections for biological screening [42]. In the *build* stage, the required, ideally chiral starting materials are synthesized or obtained from the chiral pool. These starting materials are then *coupled* together to produce densely functionalized molecules; multicomponent reactions are often used at this stage to couple three or more building blocks together. The *pair* stage then involves intramolecular reactions of the attached functional groups to generate distinct molecular

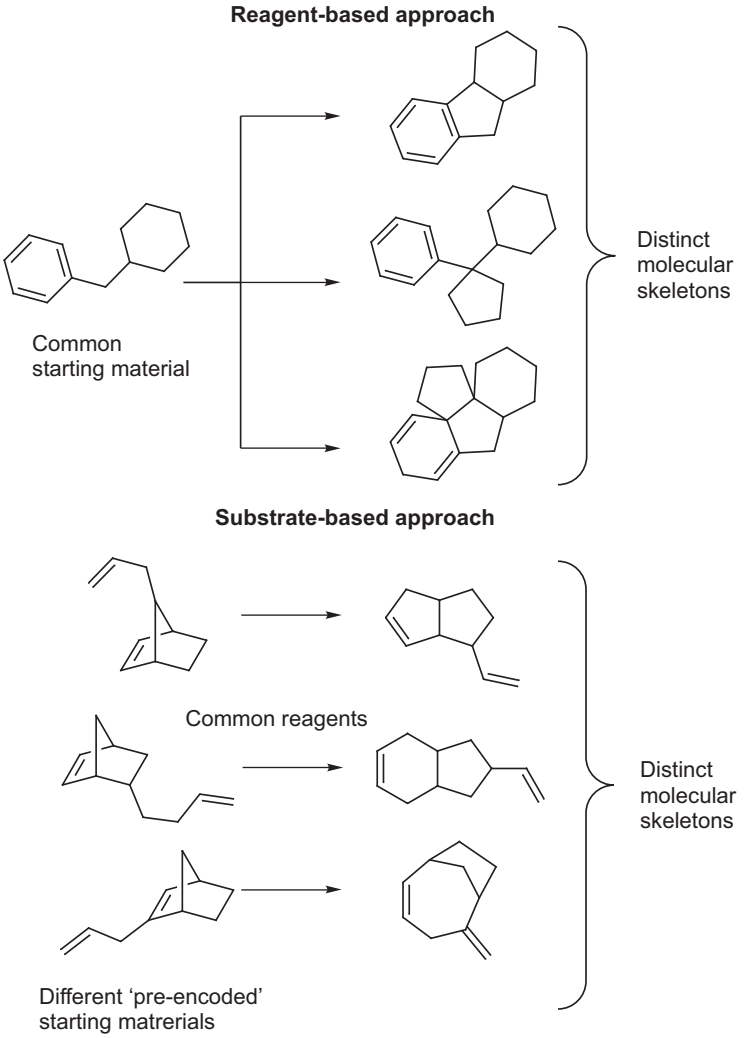



**FIGURE 1.4** Representation of the two general strategies for the creation of chemically and skeletally diverse molecules.

scaffolds. The pair stage can generate diversity either by reagent-based pathways, where different functional groups can be paired under orthogonal reaction conditions, or by substrate-based pathways, where the same functional groups are paired under common reaction conditions (Figure 1.5). In the latter case, the diversity generated in the pair stage is due to the relative positions of the functional groups that are paired together. The build/couple/pair approach has subsequently been widely adopted in the literature [43–45].

Important examples of DOS using these various strategies are discussed next.

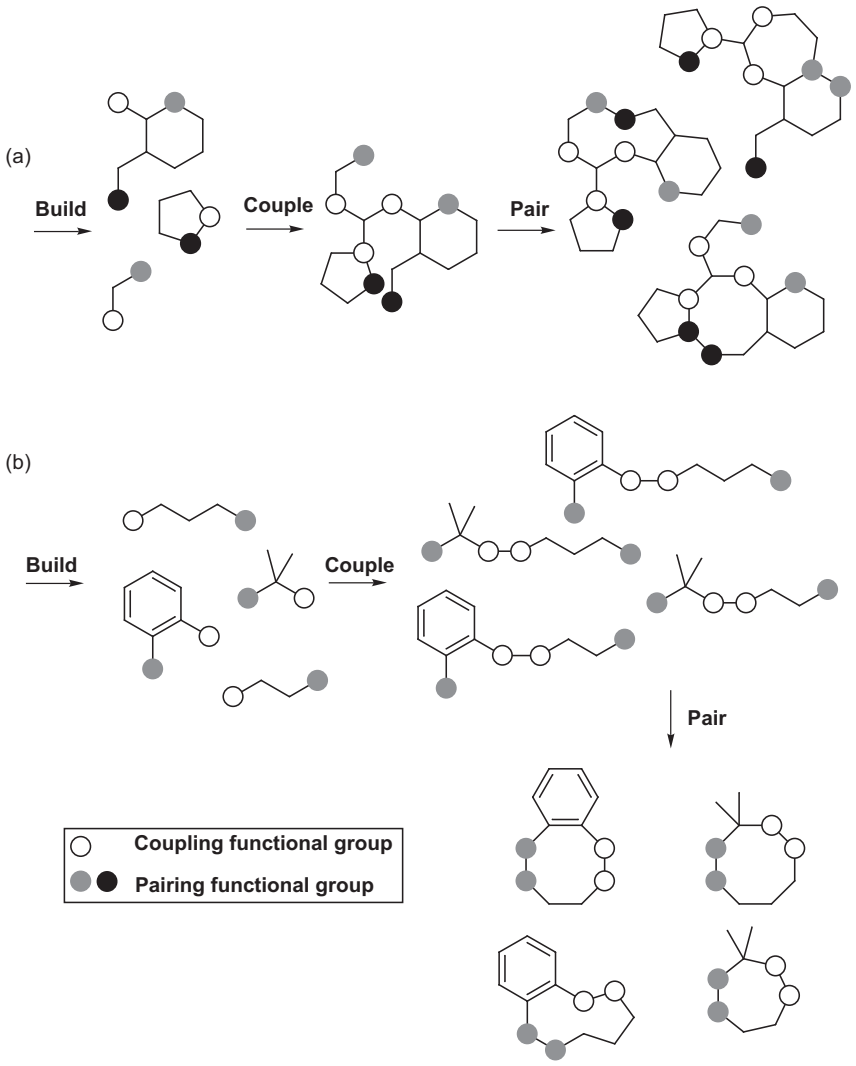
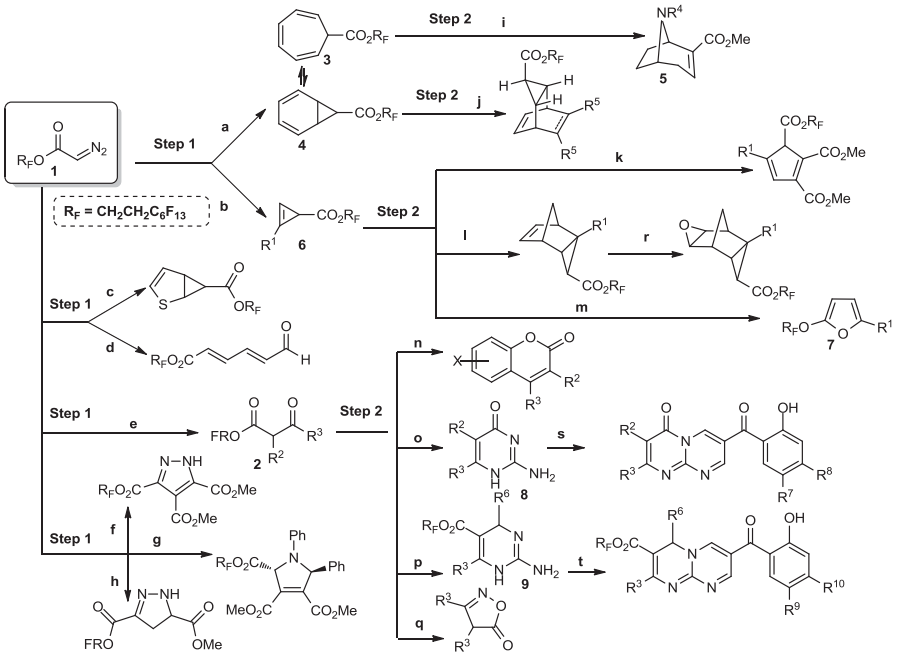



**FIGURE 1.5** Build/couple/pair strategy utilizing (a) reagent-based diversification and (b) substrate-based diversification.

## 1.8 REAGENT-BASED APPROACHES TO DIVERSITY GENERATION

### 1.8.1 Use of Pluripotent Functional Groups

The use of pluripotent functionality in DOS can be neatly illustrated by two libraries. These libraries were produced from small simple starting materials, which were then subjected to a number of complexity-generating reactions to give a range of diverse and structurally complex compounds in a small number of synthetic steps.



**SCHEME 1.1** DOS of a library of small molecules from a simple diazoacetate starting material **1**. Step 1 refers to the first step of the DOS, Step 2 refers to the second step of the DOS. Reagents and conditions: (a) $C_6H_6$, $Rh_2(OCOCF_3)_4$; (b) $R^1CCH$, $Rh_2(OAc)_4$, $CH_2Cl_2$; (c) thiophene, $Rh_2(OAc)_4$; (d) furan, $Rh_2(OAc)_4$ then $I_2$; (e) LDA $-78^\circ$C then $R^2COR^3$, THF then $Rh_2(OAc)_4$, $CH_2Cl_2$; (f) DMAD; (g) PhCHO, $PhNH_2$ then DMAD, $Rh_2(OAc)_4$ or PhMe $[Cu(OTf)]_2$, $CH_2Cl_2$; (h) methyl acrylate; (i) $R^4NH_2$, NaOH, $H_2O$, 180°C then MeOH, $H_2SO_4$, 60°C; (j) dienophile, toluene, reflux; (k) DMAD, toluene, 100°C; (l) cyclopentadiene, $CH_2Cl_2$, 0°C to rt; (m) Grubbs's second-generation catalyst, toluene, ethylene, reflux; (n) phenol derivative, conc. $H_2SO_4$; (o) guanidine, EtOH, reflux; (p) guanidine, $R^6CHO$, DMF, 75°C; (q) $NH_2OH$, THF, reflux; (r) *m*CPBA, $CH_2Cl_2$, rt; (s) substituted 3-formyl chromone, EtOH, reflux; (t) substituted 3-formyl chromone, EtOH, reflux.

The first library, synthesized in 2006 by Wyatt et al., used a fluorous-tagged diazoacetate species (**1**) as a two-carbon starting unit (Scheme 1.1) [46]. This compound can be considered to be pluripotent, as under a range of conditions it is able to act as both a nucleophilic and an electrophilic species. In total, a library of 223 small molecules was synthesized, based around 30 distinct molecular skeletons. This synthesis was achieved in two to four synthetic steps from the diazoacetate species, clearly exemplifying the powerful nature of this type of approach to molecular diversity generation.

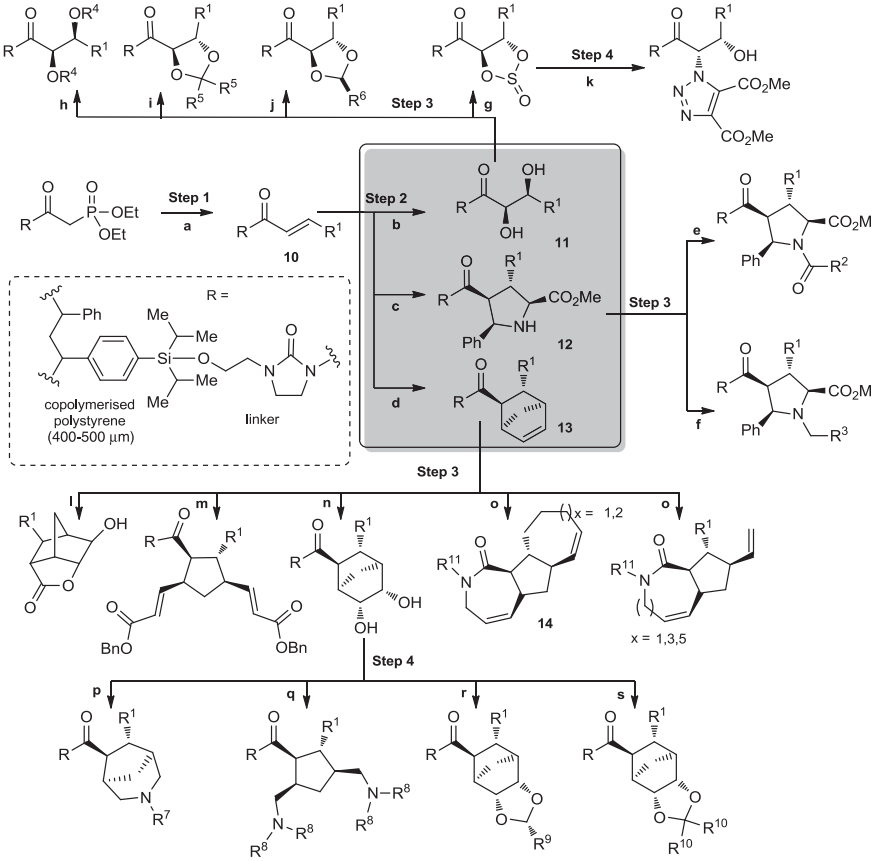
An initial three-way branching strategy was employed, involving three-membered ring formation by addition of rhodium carbenoids to alkene species; α-deprotonation

and subsequent quenching with nucleophiles, followed by carbene formation and extrusion of nitrogen to give compounds with general structure **2**; and 1,3-dipolar cycloaddition with a range of dipolarophiles. The products of these reactions were then subjected to further complexity-generating reactions to complete the library synthesis. These further transformations included the trapping of cyclohexatriene **3** (generated by electrocyclic ring opening of fused cyclopropane **4**) with primary amines to give ecgonine-type scaffolds **5**; an unusual Grubbs II–mediated rearrangement of cyclopropene **6** to give furan **7**; and Biginelli-type three-component reactions to give dihydropyrimidines **8** and **9**.

The second library to use pluripotent functionality was published in 2008 by Thomas et al. This library used an *E*-selective Horner–Wadsworth–Emmons reaction to generate the solid-supported enone substrate (**10**) that they used as the pluripotent functional group in their initial branching pathway [47]. This group was then transformed using three catalytic enantioselective processes: a Sharpless asymmetric dihydroxylation to give **11**, a [3 + 2] cycloaddition with an imino ester to give substituted pyrrolidine **12**, and a [4 + 2] cycloaddition with cyclopentadiene to give bridged bicycle **13** (Scheme 1.2). These initial compounds (and variations of them) were eventually transformed into a library of 242 compounds based on 18 distinct molecular skeletons, including a novel *cis-trans*-fused 7-5-7 tricycle (**14**) generated by ring opening–ring closing metathesis of a decorated norbornene.

The compounds produced in these libraries were screened for their effects against three strains of UK epidemic *Staphylococcus aureus*: methicillin-susceptible *S. aureus* (MSSA), and two strains of methicillin-resistant *S. aureus* (EMRSA-15 and EMRSA-16). Of the 223 compounds screened from the library of Wyatt et al., 64 were found to modulate the growth of EMRSA-15 and EMRSA-16 at concentrations between 10 and 100 μM [48]. Of these active species, the vast majority were based around four nitrogen heterocycle frameworks. Inspection of these compounds led to the identification of a number of structural features generally associated with higher levels of antibacterial activity, so an additional focused library of 35 compounds was synthesized. The screening of these compounds against the same strains of bacteria led to the discovery of a number of more potent compounds, the most potent of which was named *emmacin* [48]. Mode-of-action studies suggested that emmacin acts as a prokaryote-selective dihydrofolate reductase (DHFR) inhibitor. The nitrogen heterocycle core of emmacin is reminiscent of that of other reported DHFR inhibitors [49,50]; however, the exact heterocycle, a dihydropyrimidine, is believed to represent a new structural subclass.

The library of Thomas et al. produced a lower hit rate; however, three compounds that reproducibly inhibited the growth of the strains were discovered. The most active compound, *gemmacin*, showed comparable activity against both strains of MRSA to the widely used antibiotics erythromycin and oxacillin. In the original DOS, gemmacin was made racemically, but the enantiomerically pure compounds were subsequently synthesized and showed comparable activity, with (–)-gemmacin being slightly more potent. Structure–activity relationship (SAR) studies were then carried out on gemmacin, resulting in the discovery of the analog gemmacin B, which




**SCHEME 1.2** Diversity-oriented synthesis of 242 compounds based around 18 discrete molecular frameworks by Thomas et al. Conditions: (a) LiBr, 1,8-diazabicyclo[5.4.0]undec-7-ene, $R^1CHO$, MeCN; (b); AD-mix, (DHQD)PHAL, THF/$H_2O$ (1:1); c) (*R*)-QUINAP, AgOAc, *i*-$Pr_2NEt$, THF, $-78^\circ C \rightarrow 25^\circ C$; (d) chiral bis(oxazoline), $Cu(OTf)_2$, 3 Å MS, $CH_2Cl_2$, $C_5H_6$; (e) $R^2COCl$, DMAP, pyridine, $CH_2Cl_2$; (f) $R^3CHO$, $BH_3$·pyridine, MeOH; (g) $SOCl_2$, pyridine, $CH_2Cl_2$, 40°C; (h) $R^4Br$, $Ag_2O$, $CH_2Cl_2$, 40°C; (i) $R^5C(O)R^5$, TsOH, DMF, 65°C; (j) $R^6CHO$, TsOH, DMF, 65°C; (k) $NaN_3$, DMF, 100°C then DMAD, PhMe, 65°C; (l) *m*CPBA, $CH_2Cl_2$ then MeOH, 65°C; (m) $CH_2{=}CHCO_2Bn$, PhMe, 120°C, Grubbs II, $CH_2{=}CH_2$; (n) $OsO_4$, NMO, $CH_3C(O)CH_3/H_2O$ (10 : 1); (o) $RNH_2$, $Me_2AlCl$, PhMe, 120°C, then NaH, $R^{11}X$, DMF, THF then PhMe, 120°C, Grubbs II, $CH_2{=}CH_2$; (p) $NaIO_4$, THF/$H_2O$ (1 : 1) then $R^7NH_2$, $NaBH(OAc)_3$, $CH_2Cl_2$; (q) $NaIO_4$, THF/$H_2O$ (1:1) then $R^8NHR^8$, $NaBH(OAc)_3$, $CH_2Cl_2$; (r) $R^9CHO$, DMF, TsOH, 60°C; (s) $R^{10}C(O)R^{10}$, DMF, TsOH, 60°C. (From [47], with permission of John Wiley & Sons; copyright (© 2008 John Wiley & Sons.)

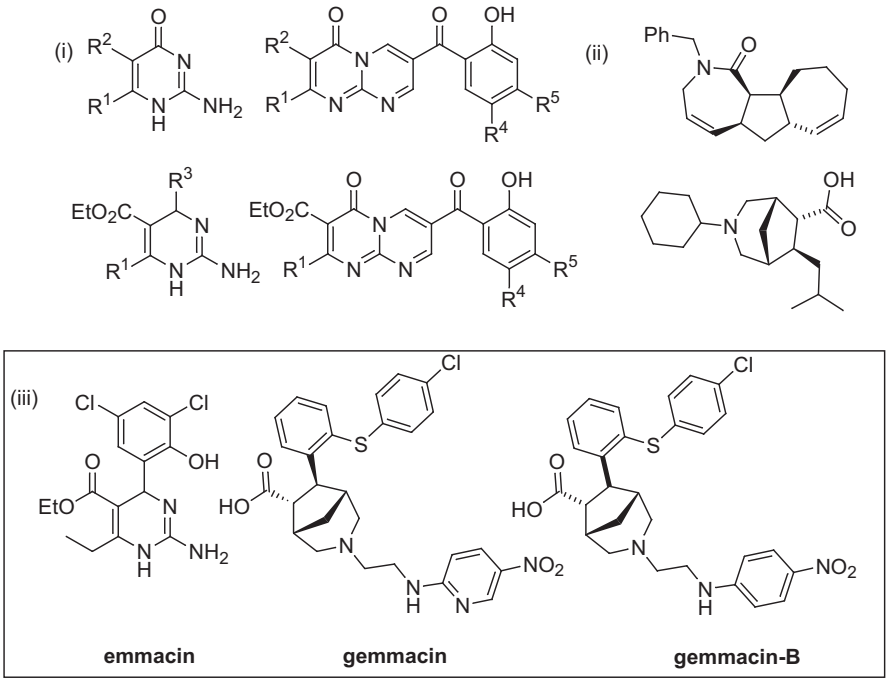



**FIGURE 1.6** Examples of compounds and scaffolds that exhibited anti-MRSA activity, including (i) the four nitrogen heterocycle scaffolds from the library of Wyatt et al. [46]; (ii) active compounds from the library of Thomas et al. [47]; (iii) emmacin, (−)-gemmacin, and (±)-gemmacin B.

showed increased efficacy in restricting bacterial growth [51]. Assays for common antibacterial modes of action were performed (such as DHFR reductase inhibition, protein synthesis, and ATP synthesis decoupling), but gemmacin proved inactive in all of these assays. However, gemmacin did show activity in an assay to test for the generation of reactive oxygen species, which suggests that gemmacin (and gemmacin B) may act as bacterial cell-membrane disruptors [51]. The discovery of these two antibacterial compounds, both of which represent a novel structural class (or subclass), illustrates the power of the DOS approach for the discovery of novel bioactive species. Figure 1.6 shows an overview of the structures of the antibacterial compounds produced by the two DOS libraries, and the $MIC_{50}$ values of the most active compounds against MSSA and two strains of MRSA are reported in Table 1.1.

### 1.8.2 Use of Densely Functionalized Molecules

A recent example of the use of a reagent-based pathway to generate diversity from densely functionalized molecules can be found in the work of Schreiber's

**TABLE 1.1 The Comparable Effects of Emmacin, the Enantiomers of Gemmacin, Gemmacin B, Erythromycin, and Oxacillin on Three Strains of *Staphylococcus aureus***

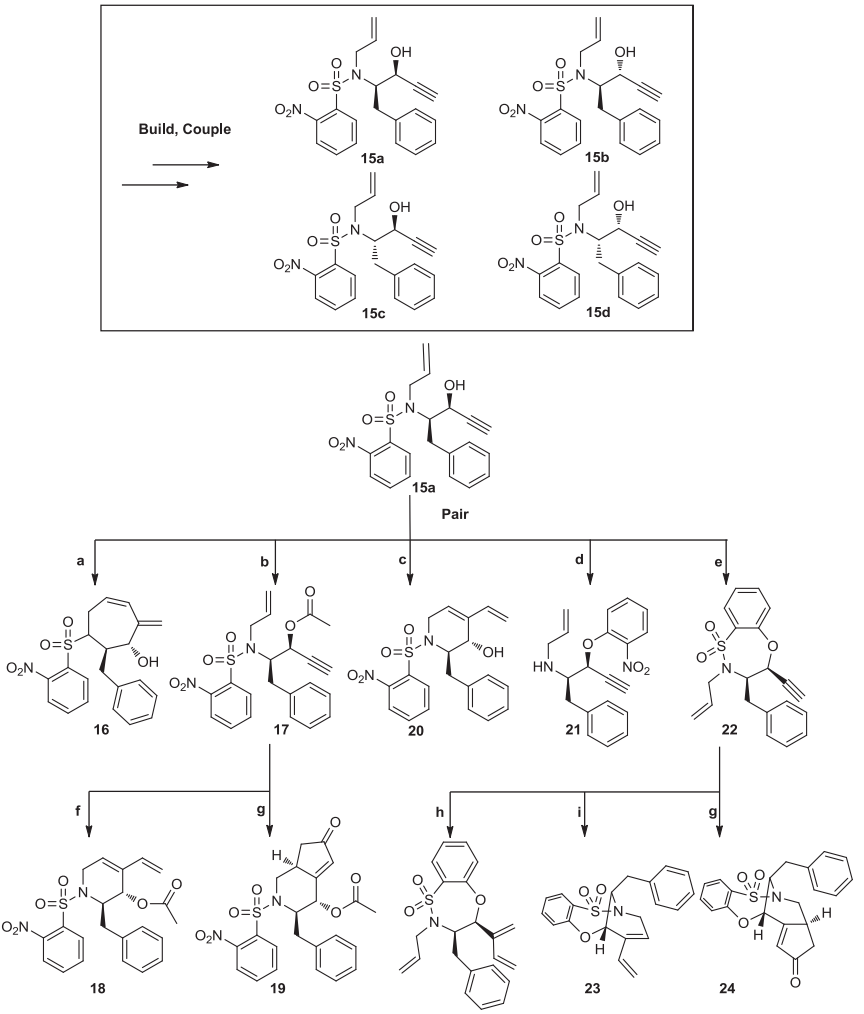
| | $MIC_{50}$ (μg/mL) | | |
|---|---|---|---|
| | MSSA | EMRSA-15 | EMRSA-16 |
| Emmacin | 2 | 9 | 9 |
| (±)-Gemmacin B | Not determined | 8 | 8 |
| (±)-Gemmacin | 2 | 16 | 32 |
| Erythromycin | 0.5 | >64 | >64 |
| Oxacillin | 0.5 | >32 | >32 |

group [52]. Their synthesis could also be considered to be an example of the build/couple/pair approach. In what could be identified as the build and couple stages, they synthesized the four possible diastereomers of *N*-allylpropargylic amino alcohol **15a–d** in six steps from (*R*)- and (*S*)-phenylalanine using standard methods [53]. They were then able to transform these compounds into a range of interesting scaffolds, by pairing functional groups using transition metal–catalyzed enyne cyclizations. When **15a** was used, they saw unusual endoselectivity in an enyne metathesis cyclization to give seven-membered ring product **16**. Then, protecting the free hydroxyl group in **15a** as the corresponding acetate **17** gave complete selectivity for the more usual six-membered exoproduct **18**, and also allowed bicyclic cyclopentenone **19** to be synthesized via a cobalt-catalyzed Pauson–Khand reaction. Treating **15a** with $InCl_3$ under microwave conditions gave **20**, and treatment with TBAF resulted in a Smiles rearrangement to give **21**. Interesting bridged bi- and tricyclic structures **23** and **24** were synthesized by initial $S_NAr$ cyclization to give **22**, followed by subsequent enyne metathesis and Pauson–Khand cyclizations (Scheme 1.3).

Similar cyclizations were carried out on other isomers of **6** to give a small library of structurally complex single stereoisomer small molecules. This DOS pathway provides a useful illustration of the versatility of enyne functionality; this versatility makes the use of enyne functionality very popular in DOS campaigns [54,55].

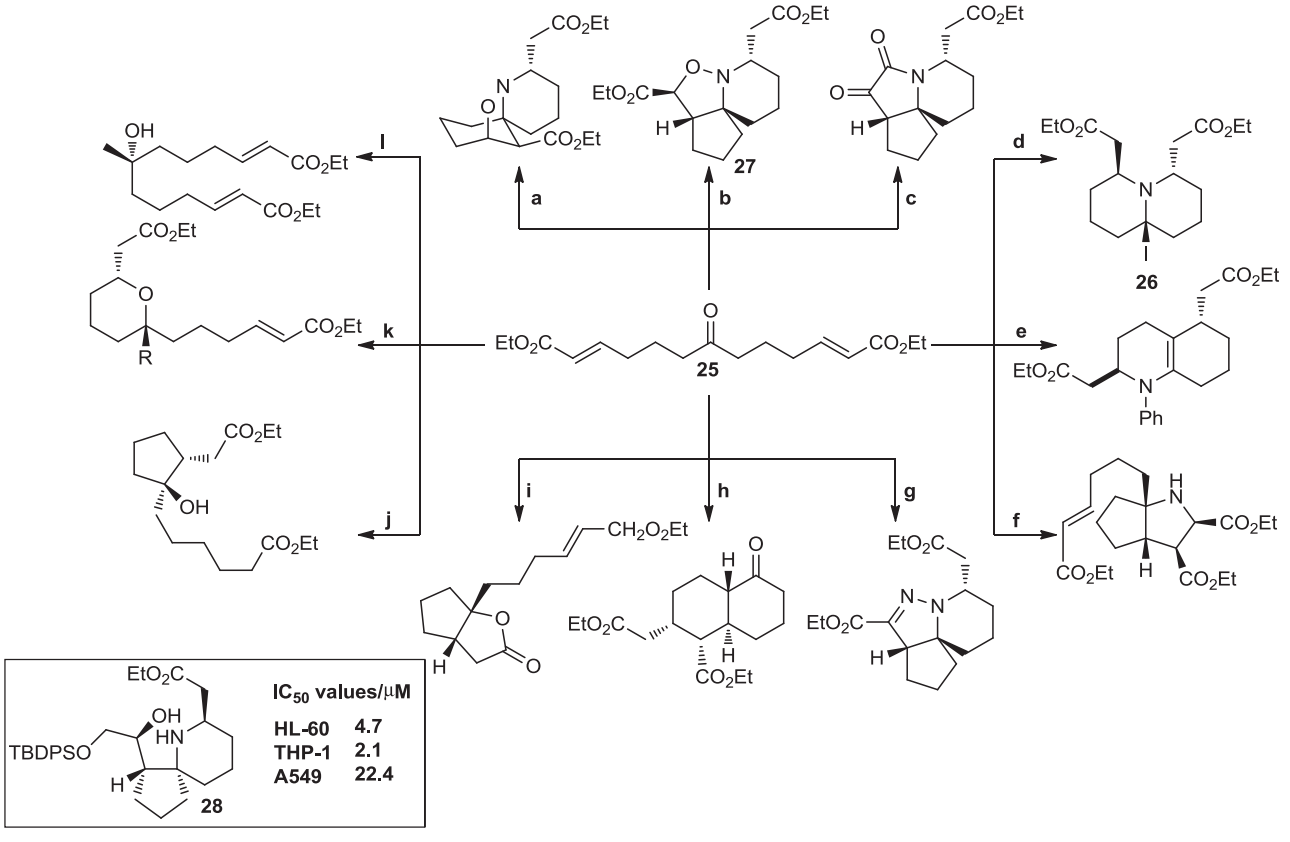
### 1.8.3 Twelve-fold Branching Strategy

The strategies described above are intended to highlight the general themes of pluripotent reactivity and dense functionality commonly utilized in DOS. However, these concepts are not exhaustive, and there are many examples of DOS campaigns that resist such generalization, as they do not fall neatly within either category. One such example is the 12-fold branching strategy reported in 2011 by Robbins et al. (Scheme 1.4) [56]. In this work, the authors combined two-directional synthesis and tandem reactions to transform a symmetrical linear ketone **25** into 12 distinct scaffolds. Their strategy involved the initial transformation of the central ketone group




**SCHEME 1.3** Reagent-based diversification using a densely functionalized molecule. (a) Hoveyda–Grubbs II, ethylene, toluene, rt; (b) $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$ 0°C; (c) $InCl_3$, 1,2-DCE, 90°C μw; (d) TBAF, THF, 0°C; (e) NaH, THF, −10°C; (f) Hoveyda–Grubbs II, ethylene, $CH_2Cl_2$, 45°C; (g) $Co_2(CO)_8$, NMO, THF, rt; (h) Hoveyda–Grubbs II, ethylene, benzene, rt; (i) Grubbs I, $CH_2Cl_2$, rt, then $Pb(OAc)_4$. (Adapted from [52], with permission; )

into various nucleophilic functionalities able to react with the α,β-unsaturated esters at the chain termini. In some cases this led to essentially symmetrical products such as **26** being produced, and in other cases, such as the oxime formation followed by tandem aza-Michael reaction and [3 + 2] cycloaddition to give tricycle **27**, desymmetrization was achieved efficiently.




**SCHEME 1.4** Twelve-fold branching strategy employed by Robbins et al. (a) $NH_2OH\cdots HCl$, NaOAc, MeCN then toluene 140°C, μw; (b) $NH_2OH\cdots HCl$, NaOAc, MeCN, 60°C; (c) $NH_2OH\cdots HCl$, NaOEt, EtOH; (d) $NaBH_4$, $NH_3$, EtOH, $Ti(OEt)_4$ then AcOH; (e) $PhNH_2$, $TiCl_4$, $CH_2Cl_2$, rt; (f) DIPEA, $H_2NCH_2CO_2Et$; (g) $NH_2NHTs$, toluene, reflux; (h) NaH, THF; (i) $SmI_2$ (2 equiv), THF, MeOH, −78°C; (j) $SmI_2$ (5 equiv), THF, MeOH, −78°C; (k) superhydride, THF; (l) MeMgBr, THF. (From [56], with permission of The Royal Society of Chemistry.)

The authors suggest the concept of considering the linear ketone as a "molecular rope" which they were then able to "tie into knots" using tandem reactions, and so produce a range of three-dimensional scaffolds. In some ways this approach could be considered to be a combination of the use of pluripotent functionality (provided by the ketone and α,β-unsaturated ester groups) and densely functionalized molecules (generated in situ), followed by tandem pairing reactions. However, such a classification is largely irrelevant, and regardless of nomenclature, this 12-fold pathway represents an ingenious use of reagent-based diversification. Overall the work generated a range of mono-, bi-, and tricyclic scaffolds possessing fused bridged and cyclic architecture from a single linear substrate. They then synthesized a set of analogs of compound **27** for testing against three cancer cell lines (HL-60, THP-1, A549), which resulted in the discovery of a number of compounds showing low micromolar activity against all three cell lines, including their best compound **28**, which showed sub-10-μM activity against two of the cell lines.

## 1.9 SUBSTRATE-BASED APPROACH TO SKELETAL DIVERSITY GENERATION

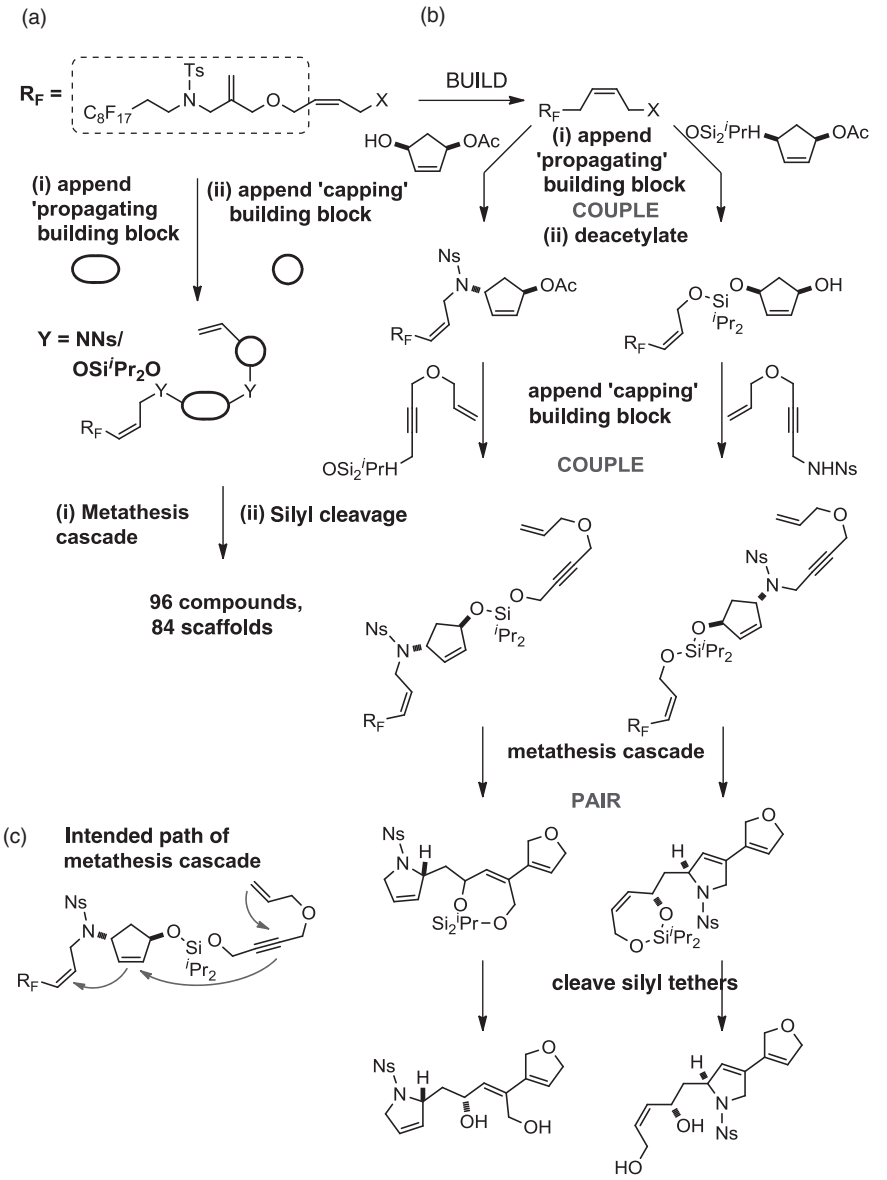
An impressive example of a folding pathway in the generation of skeletal diversity was devised by Morton et al., who used metathesis cascade processes to produce a library consisting of over 80 distinct scaffolds [57]. This was achieved by attaching two of a number of building blocks ("called a propagating" building block in the center of the molecule and a "capping" building block on the end) to a fluorous tagged linker to give densely functionalized linear intermediates containing several unsaturated groups able to take part in the metathesis cascade (Scheme 1.5). The fluorous tagged linker group was also designed to take part in the metathesis cascade, with the final cyclization intended to cleave the linker and allow easy generic purification of the desired products from uncyclized material.

In total, 86 linear substrates were prepared, and from these 96 final products were obtained, based around 84 molecular scaffolds. The molecules also contain a high degree of stereochemical diversity and structural complexity and as such can be considered to be "natural product–like." This work represents the largest number of scaffolds present to date in a deliberately synthesized DOS library.

As for the work of Schreiber's group, this DOS library could be considered to follow the build/couple/pair synthetic plan. First, the fluorous tag and the propagating and capping building blocks are built, they are then coupled together to give the linear precursors, and finally, the unsaturated groups are paired in the metathesis cascade.

## 1.10 OTHER BUILD/COUPLE/PAIR EXAMPLES

As indicated by some of the examples discussed above, the build/couple/pair paradigm has become very widespread in DOS. Two additional examples published in 2011 will now be discussed; these are intended to illustrate the range of structural



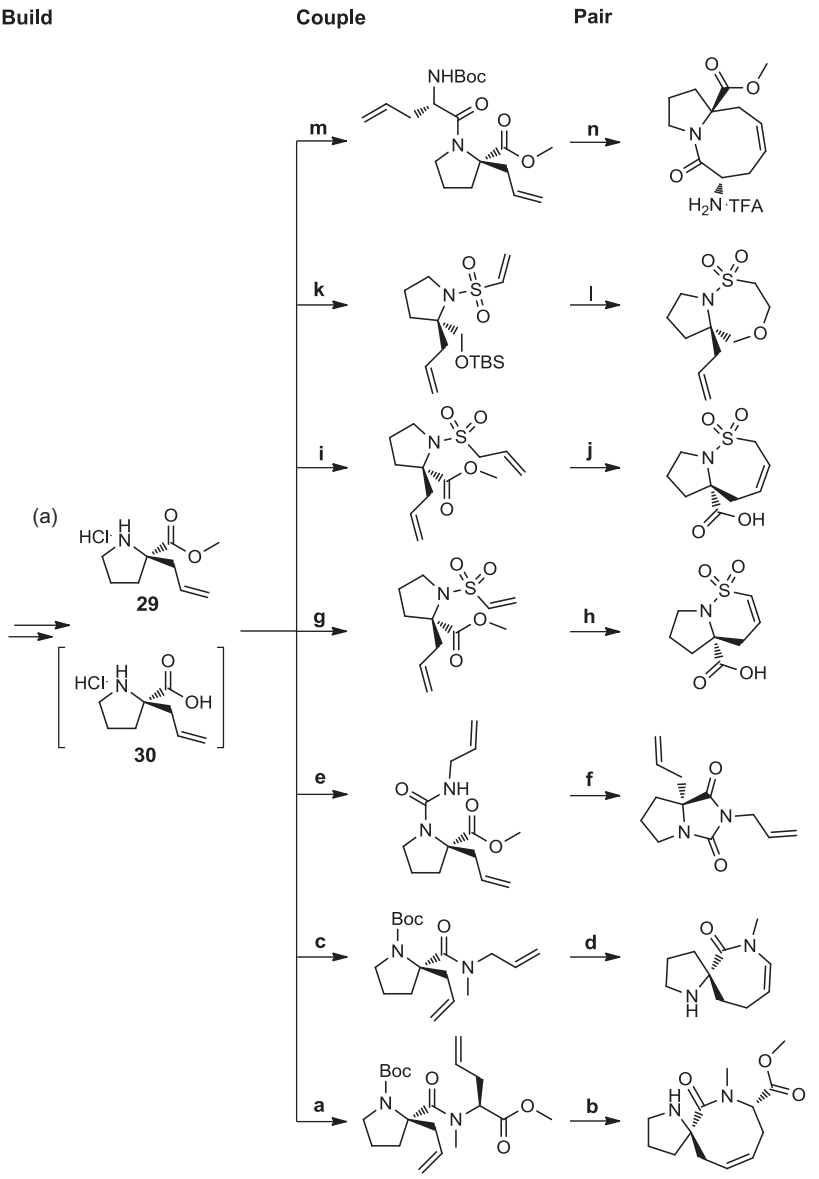

**SCHEME 1.5** Folding pathway for skeletal diversity generation employed by Morton et al. [57]: (a) general scheme for the synthesis; (b) synthesis of 2 out of 96 library members with the build/couple/pair stages highlighted; (c) the intended path for the metathesis cascade, culminating in cleavage of the fluorous tag.

classes to which the build/couple/pair approach can be applied. The first example is focused toward the synthesis of three-dimensional fragments for potential use in fragment-based drug discovery. The work highlighted was carried out by Hung et al. and is part of a larger synthetic effort aimed at producing a range of chiral bicyclic corestructures that could be used to enrich existing fragment collections that are generally biased toward "flat"$sp^2$-rich compounds [58]. The authors employed the build/couple/pair approach to efficiently provide a number of fused bicyclic and spirocyclic compounds that were compliant with the fragment rule of 3, the number of physicochemical parameters that can be applied to fragment-based drug discovery (Scheme 1.6) [59].

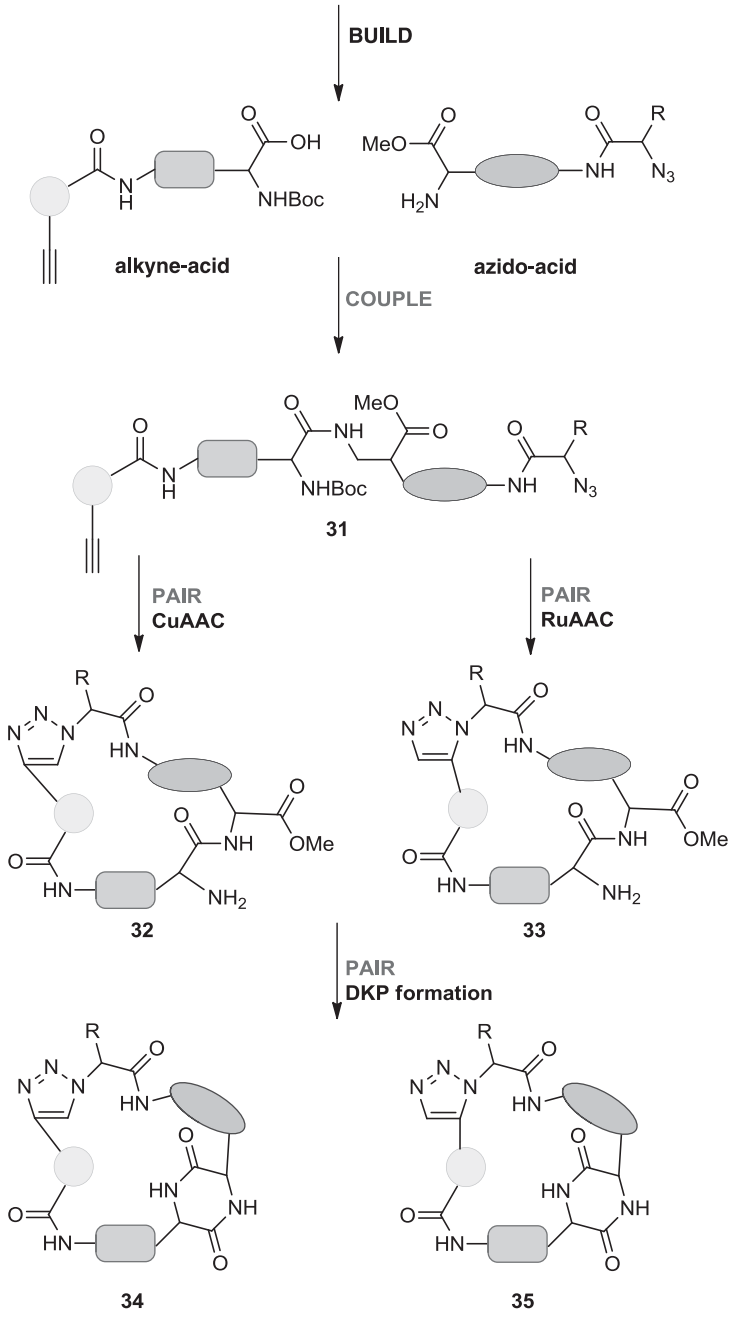
The build stage of the synthesis involved the synthesis of **29** from proline employing Seebach et al.'s concept of self-reproduction of chirality [60] or the purchase of the commercially available derivative **30**. The couple stage then involved the addition of other latently reactive appendages, by either functionalization of the proline nitrogen or by peptide coupling of amine groups to the free carboxylic acid of **30**. These groups were then paired to generate the bicyclic architectures desired. In the majority of cases, this was achieved by the ring-closing metathesis of alkene groups but two other approaches: hydantoin formation and oxy-Michael addition to a vinyl sulfone. In a slight addition to the standard build/couple/pair protocol, the authors suggested a post-pairing stage, where the functional group diversity of the compound collection is increased. Two post-pairing modifications—methyl ester hydrolysis and reduction of the alkene groups to give the saturated species—were implemented, which altered the electronic and conformational properties of the fragments but did not significantly change the molecular weight. Then the authors used computational methods to compare their compounds to an existing fragment collection and found that although, as expected, the shapes of the compounds in the various collections were mutually exclusive, their physical properties remained comparable and thus within the desired range for fragments [58].

The second example was targeted toward the synthesis of a small library of macrocyclic compounds. In this work, Isidro-Llobet et al. produced a small library of macrocyclic peptidomimetics in an efficient manner employing the build/couple/pair approach (Scheme 1.7) [61]. In the build stage they produced a number of alkyne-acid and azido-amine building blocks using standard methods. These building blocks were then coupled to give the required linear azido-alkyne precursor (**31**), and macrocyclization was achieved by the pairing of these functional groups in two variations of the azide-alkyne cycloaddition reaction to produce a triazole. The copper-catalyzed azide-alkyne cycloaddition (CuAAC) provided the 1,4-isomer of the triazole (**32**), and the ruthenium-catalyzed variant (RuAAC) gave the 1,5-isomer (**33**). This use of different catalysts for essentially the same process to produce molecular diversity has been dubbed "catalyst control" [62].

Further diversity was then introduced into their compound set when the attached ester and and amine functionalities were paired to give diketopiperazine (DKP) moieties (**34** and **35**). In total, they were able to produce a small proof-of-concept library of 14 macrocyclic compounds.




**SCHEME 1.6** Synthesis of structurally diverse bicyclic "fragments" by Hung et al. [58] using the build/couple/pair approach. (a) (*S*)-Allylglycine methyl ester, 1-ethyl-3-(3-dimethylaminopropane), ethyl(hydroxyimino)cyanoacetate, $Et_3N$, $CH_2Cl_2$; NaH, MeI, DMF; (b) Grubbs II, $CH_2Cl_2$ reflux; TFA; (c) allylamine, 1-ethyl-3-(3-dimethylaminopropane), ethyl(hydroxyimino)cyanoacetate $Et_3N$, $CH_2Cl_2$; NaH, MeI, DMF; (d) Grubbs II, toluene, TFA; (e) allyl isocyanate, $CH_2Cl_2$; (f) NaH, DMF; (g) 2-chlorosulfonyl chloride, $Et_3N$, $CH_2Cl_2$; (h) Grubbs II, $CH_2Cl_2$, reflux; (i) prop-2-ene-1-sulfonyl chloride, $Et_3N$, $CH_2Cl_2$; (j) Grubbs II, $CH_2Cl_2$, reflux; (k) $LiAlH_4$, THF, *t*-butyldimethylsilylchloride, $Et_3N$, $CH_2Cl_2$; 2-chlorosulfonyl chloride, $Et_3N$, $CH_2Cl_2$; (l) tetrabutylammonium fluoride, THF; (m) (*S*)-*N*-Boc-allylglycine, 1-ethyl-3-(3-dimethylaminopropane), ethyl(hydroxyimino)cyanoacetate $Et_3N$, $CH_2Cl_2$; (n) Grubbs II, $CH_2Cl_2$, TFA.




**SCHEME 1.7** Overview of Isidro-Llobet et al.'s synthesis of a library of macrocyclic peptidomimetic compounds. (From [61]; copyright © 2011 National Academy of Sciences, U.S.A.)

## 1.11 CONCLUDING REMARKS

In the decade since the DOS concept was introduced, the field has matured considerably, with numerous sophisticated approaches to the generation of molecular diversity being developed. Emphasis on the generation of scaffold diversity has become integral to the field, as there is an overriding, and justified, opinion that the incorporation of this type of diversity into a compound collection is most important in terms of producing a functionally (biologically) diverse library. As such, many modern examples focus on the production of compound collections containing a high degree of three-dimensional scaffold and shape diversity. As the examples highlighted in this chapter show, the DOS approach has been applied toward the synthesis of a range of compound collections with varying molecular parameters. In the majority of cases, the libraries produced are intended to span known drug-like chemical space; however, as the later examples in this chapter show, the ideas can also be applied effectively to the synthesis of other structural classes, such as low-molecular-weight fragments or larger macrocyclic compounds.

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