Scaffold Synthesis

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Synthesis of Unprecedented Scaffold Diversity

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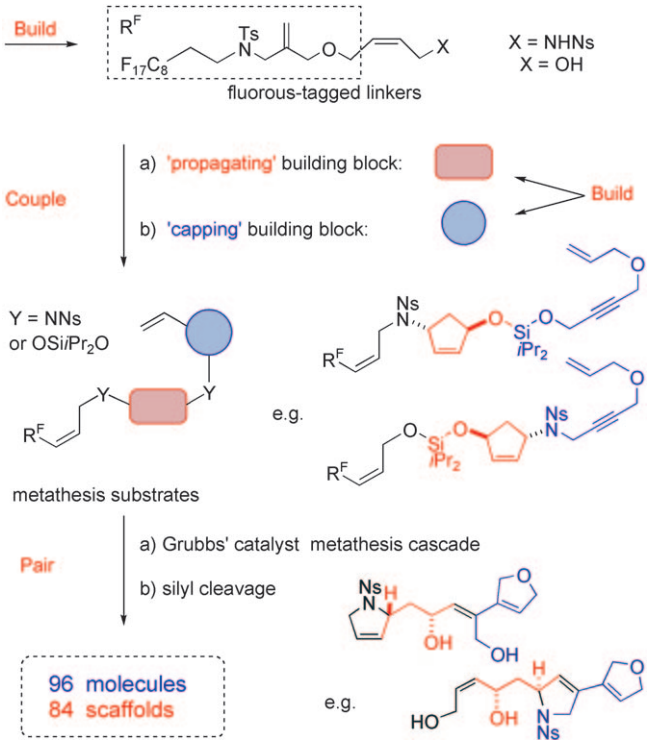
combinatorial chemistry · diversity-oriented synthesis · metathesis · molecular scaffolds · natural products

The screening of compound libraries to identify useful modulators of biological systems is a fundamental process in chemical biology studies. However, a crucial consideration is what compounds to use. When such processes are unbiased, for example in the case of a phenotypic screen where the biological target is unknown, libraries which contain compounds displaying a broad range of biological activities are particularly valuable.[1–3] As biological function is intrinsically dependent upon molecular structure, the design and synthesis of structurally diverse compound libraries has attracted considerable attention. In particular, variation in the molecular scaffolds present in the library (so-called scaffold diversity) is crucial, with small multiple-scaffold libraries generally regarded as superior to large single-scaffold libraries in terms of biorelevant diversity.[1,3,4] Consequently, recent years have witnessed considerable effort towards the development of methods to increase the scaffold diversity present in chemical libraries. The recent report by Nelson and co-workers[5] represents a significant breakthrough in this area. The authors describe an elegant method for the efficient generation of natural-product-like molecules with over eighty distinct scaffolds by using a diversity-oriented synthesis (DOS)[6] approach. A library with such a high degree of skeletal diversity should span a large region of total bioactive chemical space and consequently may prove valuable for the identification of biologically useful molecules.

Nature has traditionally served as a rich source of biologically active molecules which exhibit enormous structural diversity, including scaffold diversity.[6,7] Unfortunately, there are several problems associated with using natural products in screening experiments, including difficulties with purification, identification of the bioactive component, chemical modification, and analogue synthesis. These problems have spurred the development of several different synthetic approaches for the de novo creation of small-molecule collections. However, making molecules costs both time and money. Therefore the ideal synthesis of a structurally diverse small-molecule collection is one in which this diversity is achieved in the most efficient manner possible. Crucial to this goal is the efficient incorporation of scaffold diversity. DOS is an approach towards generating compound collections that aims to address this challenge.

The generation of skeletal diversity by a DOS approach has generally been achieved through the use of reagent-based branching reaction pathways[8] or by the use of substrate-based folding pathways,[9] which often utilize a build/couple/pair (B/C/P) strategy.[6d] The library synthesis of Nelson and co-workers[5] could be considered to fall within the remit of a B/C/P approach. Their method was based on the attachment of pairs of unsaturated functionalized building blocks (so-called "propagating" and "capping" groups synthesized in the "build" phase) to a fluorous-tagged linker (Scheme 1). This "couple" phase led to the formation of a wide variety of



Scheme 1. Outline of the synthetic route used in library synthesis.[5] Ns = nosylate, Ts = tosylate.

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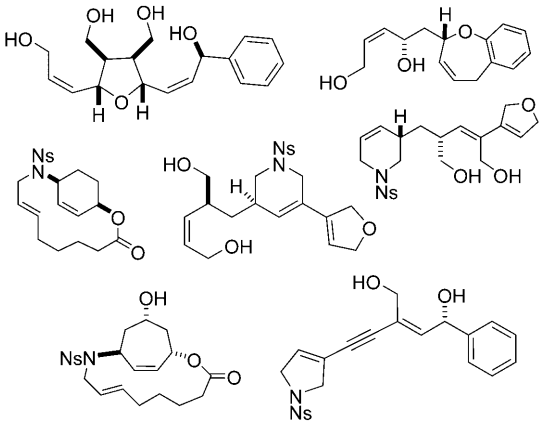
substrates, which contained a dense array of different structural features. Crucially each substrate was carefully designed such that a pair of terminal alkene groups (one from the linker, one from the "capping" building block) was present, together with additional unsaturated moieties. Treatment with a suitable metathesis catalyst led to intramolecular cyclization reactions that "paired" these unsaturated functional groups together, thus converting skeletally similar and simple substrates into a dense matrix of skeletally complex and diverse products (Scheme 2).



Scheme 2. Representative examples of scaffolds generated.[5]

This work represents a significant landmark in the degree of skeletal diversity incorporated in a synthetically-derived small-molecule library. Through the use of only six basic reaction types (Mitsunobu reactions, silaketal formation, esterification, deacetylation, metathesis, and desilylation) 96 molecules based on a total of 84 distinct molecular skeletons were generated. Previous DOS approaches have yielded a maximum of 30 skeleton-types.[8a] Of central importance to the work of Nelson and co-workers was the remarkable synthetic utility of ring-closing metathesis. Although this is not the first time that this process has been applied in DOS context,[10] this work represents a significant advancement in scale and scope. The modular nature of the library synthesis enables a combinatorial variation of molecular scaffolds to be achieved. In addition, fluorous-phase separation methods were elegantly applied to expedite all stages of library synthesis. Of particular note was the inspired design of the fluorous-tagged linker, which ensured that only cyclized products were released from the fluorous-tag during the metathesis process; consequently fluorous solid-phase extraction provided a rapid and generic method for product isolation.

The molecular scaffolds formed can be considered to be "natural-product-like" in terms of the presence of structural features found in many natural products. Indeed, when the authors assessed the skeletal diversity of the library in terms of an hierarchical scheme,[11] the resultant scaffold tree was similar to that obtained upon analysis of natural products, with three classes of cyclic compounds being dominant[12] (azacycles, oxacycles, and carbacycles; Figure 1). Notably,

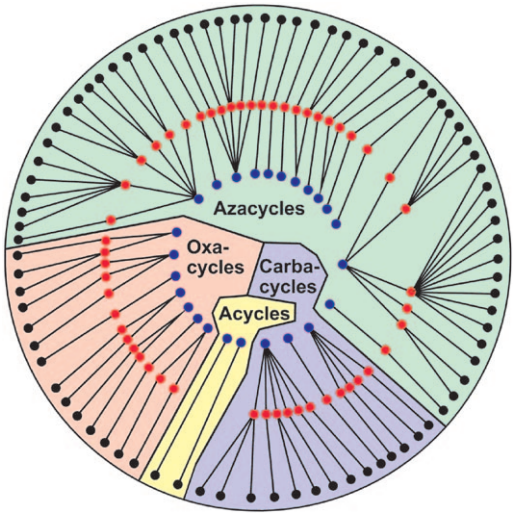


Figure 1. Hierarchical classification of the molecular scaffolds present in the small-molecule library[11] which illustrates the relationship between the 25 parent scaffolds (blue circle), 54 daughter scaffolds (red circle), and 84 molecular scaffolds (black circle). Nelson and co-workers state that at all levels of classification, the library has unprecedented scaffold diversity.[5]

the majority of the scaffolds in the library (ca. 65%) are novel. This outcome is important as the known universe of organic chemistry is generally dominated by a remarkably small number of molecular scaffolds; for example, in a recent study of known cyclic organic molecules, 0.25% of the molecular frameworks were found in 50% of the known compounds.[13] The high degree of skeletal diversity in the library should ensure that the compounds span a large region of chemical space, and the presence of scaffolds that are natural-product-like may bias this coverage towards biologically active regions. However, the fact that some of these scaffolds are not identical to those found in known natural products should enable the library to explore uncharted regions that may have been ignored by the process of natural evolution. Molecules from such areas should have exciting and unusual biological properties.

In addition to skeletal diversity, the library compounds also exhibit high levels of functional group and stereochemical diversity. Indeed, the compounds are remarkably natural-product-like in this sense, with a diverse range of different three-dimensional features and functionalization motifs present. Structural complexity is another characteristic that is important in small-molecule libraries. It has been argued that molecules that are structurally complex are more likely to interact with biological macromolecules in a selective and specific manner.[14]

Overall, the report by Nelson and co-workers represents an unprecedented advancement in the capability of synthetic chemists to rapidly generate structurally diverse and complex molecules based around natural-product-like scaffolds. However, there remain several areas where further exciting developments can be made in this field. Perhaps most crucial is the overall number of synthetic steps that are required to generate each unique scaffold. The skeletal diversity in this library comes from the reaction of the metathesis substrates.

These substrates need to be synthesized, which does detract in terms of the number of steps to the skeleton. Indeed, the modular nature of such substrate-based folding syntheses may be an inherent limitation in this context as numerous "propagating" and "capping" building-blocks need to be independently synthesized and combined, though this aspect unquestionably facilitates systematic modification of the resulting products. Perhaps the ultimate goal, in terms of efficient construction of skeletal diversity, would be a branching-type synthesis whereby every single reaction carried out on a simple starting material would result in a different molecular scaffold (e.g. 100 different scaffolds from 100 reactions?). A further area of consideration is: At what point during the library synthesis should structural complexity be generated? In the synthetic route of Nelson and co-workers most of the complexity and functionality of the final compounds is already present in the substrates used for the metathesis reactions. Is it possible to more effectively couple scaffold-diversity generation with the creation of molecular complexity, such that little of the functionality desired in the final compounds needs to be present in the starting substrates? This is a formidable challenge that can only be addressed by the development of radical new approaches towards the synthesis of small-molecule library. However, the rewards for this creativity, in terms of increased synthetic efficiency and expedient access to an extraordinary scope of new molecular structures, would certainly be worth the effort.

As a concluding thought, it is important to note that the ultimate success of any small-molecule library synthesis is determined by the biological relevance of the compounds it contains, rather than its overall structural diversity. Nelson and co-workers do not report any biological screening data for their library. However, the unprecedented level of scaffold diversity displayed by these compounds should allow access to large regions of biologically-relevant chemical space. Consequently, we are confident that there are numerous biologically useful molecules present in this collection, and we anticipate exciting future revelations regarding their identity and activity.

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