Enriching chemical space with diversity-oriented synthesis

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The search for new molecular entities in drug discovery and chemical genetic programs requires the screening of high-quality collections of structurally diverse small molecules. The design and synthesis of such collections remains a major challenge to synthetic chemists. Recent strategies and results are presented in the context of the chemical space being interrogated.

Keywords Chemical genetics, chemical genomics, combinatorial chemistry, DOS, molecular descriptors, structural diversity and complexity

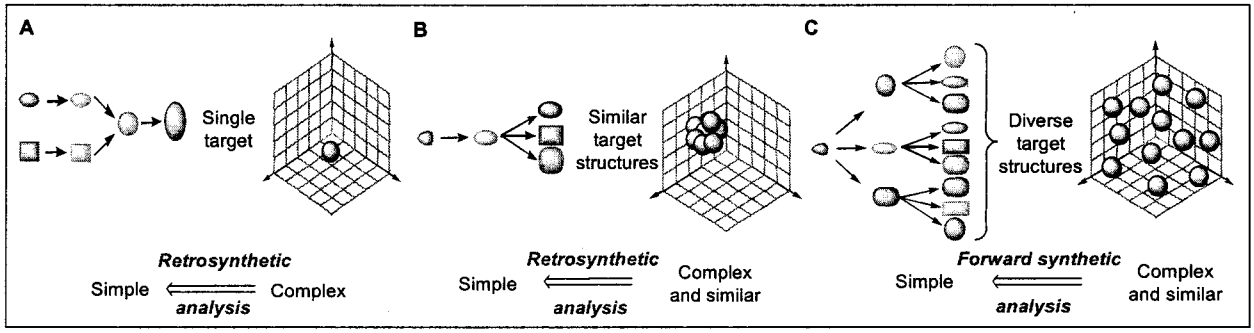
Abbreviations

3-D three dimensional, **ADME/Tox** absorption, distribution, metabolism, excretion and toxicity, **COX** cyclooxygenase, **DOS** diversity-oriented synthesis, **MOE** molecular operating environment, **MRSA** methicillin-resistant *Staphylococcus aureus*, **PCA** principle component analysis, **PMB** para-methoxybenzyl, $\mathbf{R_f}$ perfluoro alkyl, **^{t}Bu** *tert*-butyl, **Tf** triflate, **TFA** trifluoroacetic acid, **TIPS** triisopropylsilyl, **tr** trityl, **TsOH** toluenesulfonic acid

Introduction

The constant need to discover pharmaceutically active new molecular entities has led to the challenge of probing within chemical space. Historically, nature has provided many of these pharmaceutically active small molecules [1]. Unfortunately, there are disadvantages with screening natural product extracts; for example, the need for active component(s) identification, limited supply, and formidable analog synthesis. Another important aspect to screening natural products is that there is an assumption that the chemistry space encompassed by natural products is likely to be useful for discovering small molecules with biological properties of interest. This assumption is valid, but natural products do not occupy all regions of chemical space that are relevant to discovering bioactive compounds, as is demostrated by the fact that most drugs on the market did not originate from natural products. Therefore, a question posed is: are there more productive, uncharted areas of chemical space that should be investigated to discover new molecular entities? In the early 1990s chemists turned to combinatorial chemistry as a technique to efficiently synthesize large numbers of compounds by appending building blocks onto a core structure to find novel active compounds. Despite resulting in large numbers of compounds being synthesized, this methodology was not as successful as initially expected. The failure of the approach to discover a broad range of activities was due to the lack of structural diversity obtained. Any structural diversity of the products was only supplied by the building blocks and starting scaffold, while the resulting molecular framework was the same in every case. In order to achieve the highest levels of structural diversity the following factors must be varied: (i) the building blocks; (ii) the stereochemistry; (iii) the functional groups; and, most importantly, (iv) the molecular framework. Today chemists are investigating ways to synthesize libraries of compounds with a high degree of structural diversity. Efficiently enriching chemical space in this way has been termed diversity-oriented synthesis (DOS), which concentrates on the synthesis of structurally diverse (and complex) small molecules. The approach to DOS is in contrast to target-oriented synthesis, which aims to synthesize a single target, or traditional combinatorial chemistry, which generates structurally similar target structures [2,3]. Synthetic pathways in DOS are branched and divergent, and the planning strategy extends simple and similar compounds to more complex and diverse compounds. Retrosynthetic analysis traditionally focuses on the existence of a defined target structure. In DOS there is no single target structure and, therefore, retrosynthetic analysis cannot be used directly; instead a forward synthetic analysis algorithm is required (Figure 1).

Figure 1. A comparison of searching chemical space using different synthesis algorithms.



Target-oriented synthesis (**A**) versus traditional combinatorial chemistry (**B**) versus DOS (**C**). The 3-D grids of molecular descriptors illustrate the product(s) of the syntheses in chemical space.

Chemical space

The number of drug-like molecules possible in chemical space has been estimated to be 10^{62} [4]. By comparison, there are approximately 10^{51} atoms on earth. Therefore, it is impossible to synthesize every drug-like molecule and chemists must be selective. By representing these compounds as a series of chemical descriptors (molecular weight, lipophilicity, dipole moment, etc) it is possible to plot them in chemical space, or more correctly in chemical descriptor space [5].

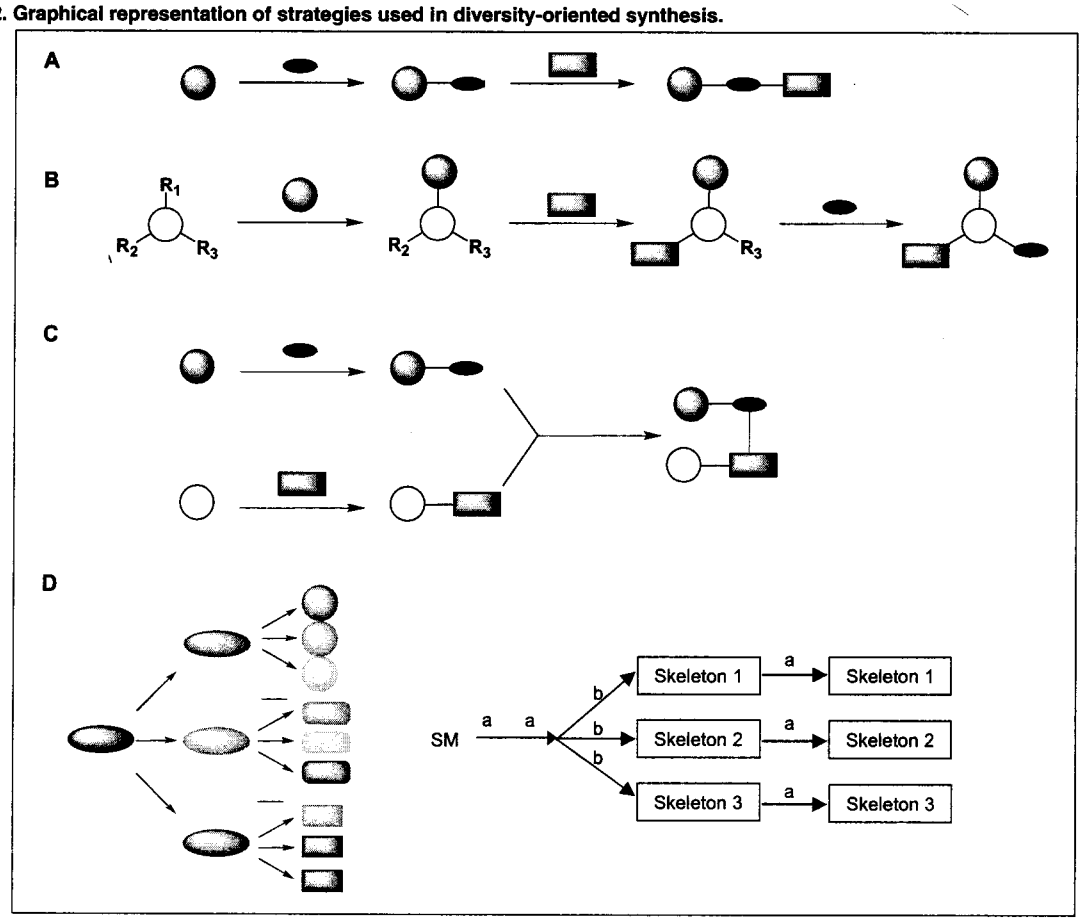
Not all drug-like compounds will fall into biologically relevant space [6,7], which is a small fraction of chemical space [8]. Nevertheless, small molecules are not just useful as drugs. They are essential in chemical genetics experiments to probe biological systems (usually by modulation of protein function). The chance of discovering a small molecule with desired properties for a chemical genetic experiment is very high relative to drug discovery [9,10]. Issues that affect the selection of small molecules for drug discovery such as pharmacokinetics and ADME/Tox are not considered for chemical genetics. The high rate of lead candidate attrition in drug discovery (98% drug discovery projects fail) is due to these extra issues which incorporate requirements for preclinical and clinical development.

Many research groups have calculated where currently available drugs are located in chemical space and it has been noted that they cluster together [11•]. There are two schools of thought on how to use this information. One approach is to look for new molecular entities based on 'privileged' core structures, which are known to be commonly bioactive [12]. Another approach is to look for new molecular entities in uncharted regions of chemical space, by synthesizing new core structures. Both approaches use DOS.

Diversity-oriented synthesis

DOS has recently emerged as a new methodology to synthesize diverse libraries of natural product or drug-like molecules for use in biological screens, which aid both biological and medicinal discoveries [13,14]. There are several methodologies used to introduce high levels of structural diversity into the libraries: linear divergent synthesis (reagent-based differentiation or substrate base folding [15,16]); convergent synthesis [17]; branching pathways [18]; and creating libraries from other libraries [19] (Figure 2).

Figure 2. Graphical representation of strategies used in diversity-oriented synthesis.



(**A**) Linear divergent oligomer synthesis; (**B**) linear divergent scaffold modification synthesis; (**C**) convergent synthesis; and branching pathways or libraries from other libraries (**D**). **a** Building block propagation, **b** multiple functional group manipulation, **SM** starting material.

The computational assessments of the levels of diversity obtained through library synthesis are readily available [9]. However, the degree of diversity obtained within individual libraries is subjective: some libraries are reliant on a large number of appendages while others focus on synthesizing different core (skeletal) structures. Recent studies have shown a varied approach to DOS. This review covers the research carried out in the following three areas during the last two years: reaction methodology for DOS, natural products and privileged structures libraries, and synthetic libraries of unnatural products.

Reaction methodology for DOS

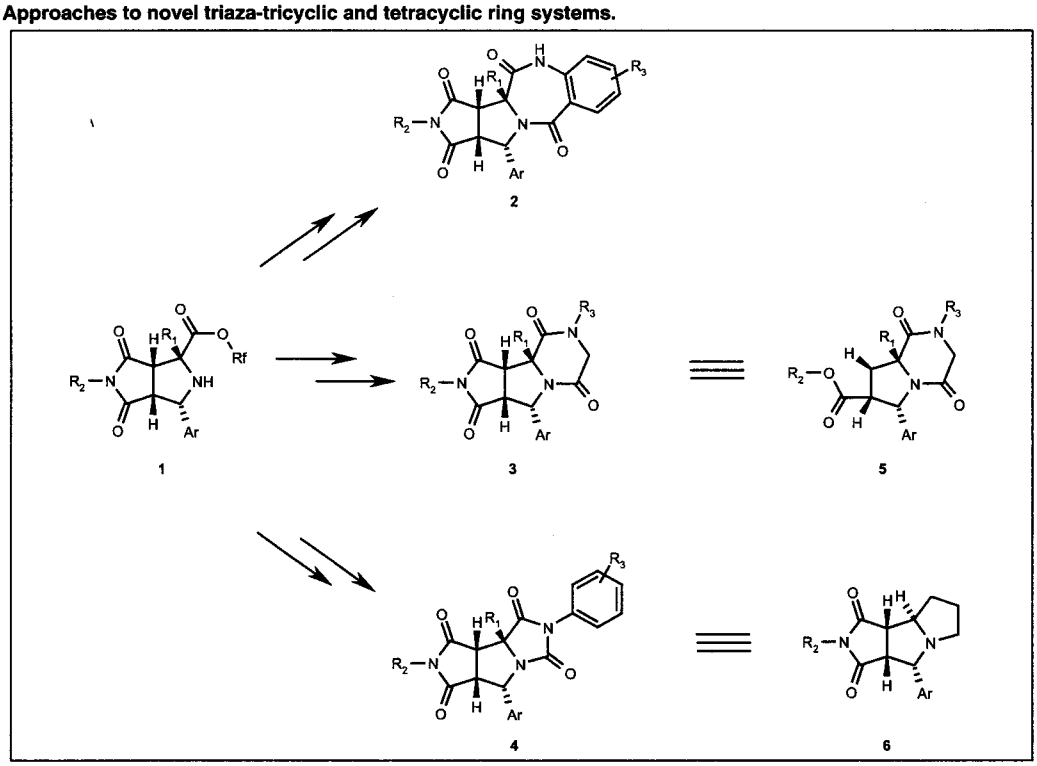
Zhang *et al* used fluorous technology to develop three branching reactions from a single bicyclic starting material **1** (Scheme 1). The reactions were conducted as a one-pot, three component [3+2] cycloaddition of azomethine ylides, generating three core structures based on benzodiazepinedione- (**2**), piperazinedione- (**3**) and hydantoin-fused (**4**) compounds (Scheme 1).

Each of these core structures is comparable to naturally occurring products. The hydantoin-fused compounds **4** are similar to tricyclic thrombin inhibitors **6**, piperazinedione-fused compound **3** represents diketopiperazine-based inhibitors of human hormone-sensitive lipases **5** and benzodiazepinedione-fused compounds **2** contain the privileged benzodiazepine motif [20].

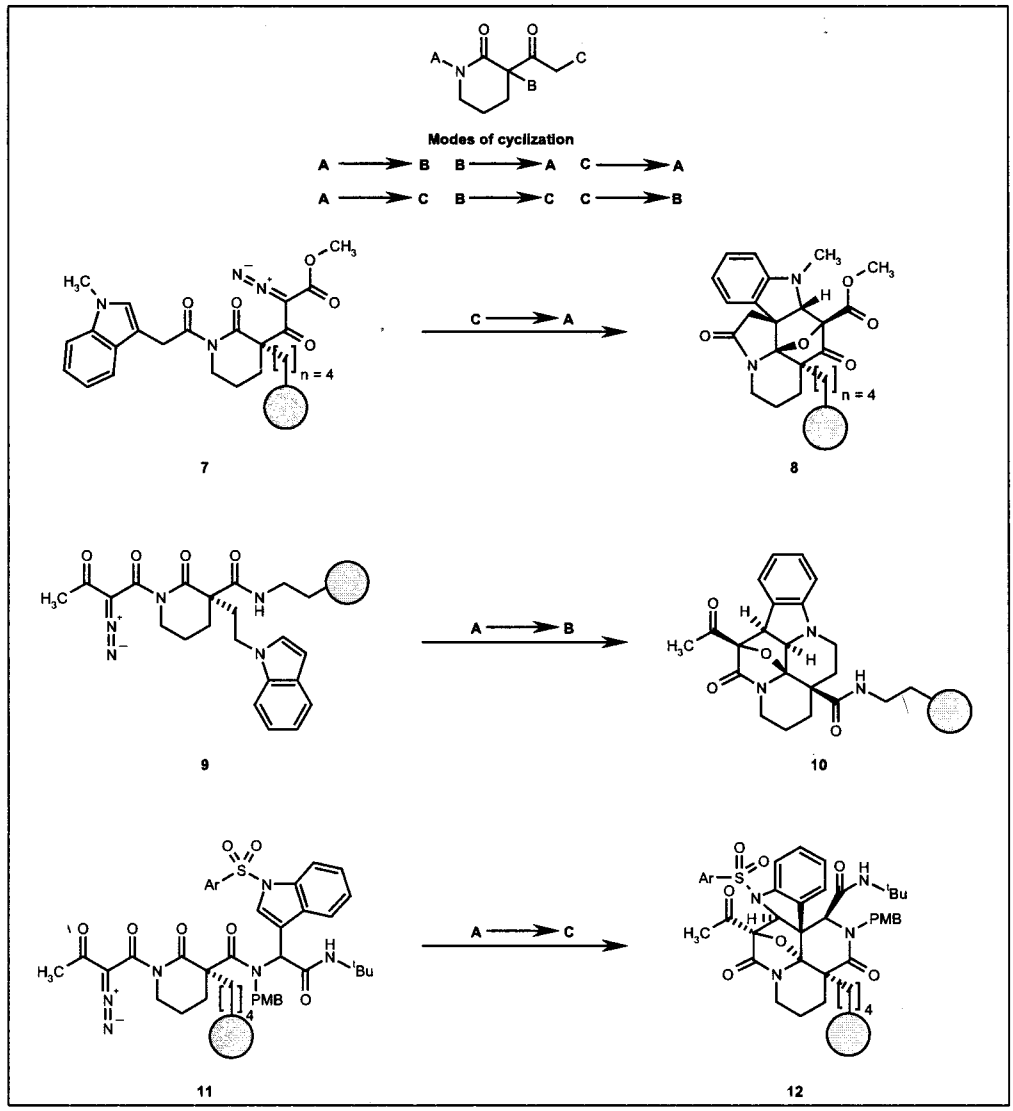
Oguri *et al* used the approach of substrate-based folding to develop pathways with potential application in a DOS library. Six structurally different products (compounds **7** to **12**; Scheme 2) are prepared in a single step from a collection of starting materials. The starting materials contain the same functional groups, but in different positions (positions A, B and C; Scheme 2), enabling them to undergo the same reaction to form a variety of skeletons. Basing the chemistry on the structures of the naturally occurring and biologically active indole alkaloids, Oguri *et al* used a rhodium (II)-catalyzed consecutive cyclization-cycloaddition to introduce structural diversity. The position of the carbonyl ylide and the dipolarophile (either one at position A, B or C) dictates how the starting material folds to create structurally diverse products. The aim of this research is to use the library of compounds prepared using this methodology as probes for chemical genetic studies [16].

Further examples of reaction pathways with the potential to be used in DOS libraries include the research of Fayol *et al* who developed a novel three-component synthesis of a epoxy-tetrahydronaphthyridine **16** (Scheme 3). On treatment with TFA or TsOH, the tetrahydronaphthyridine breaks down to form differently substituted 5,6,7,8-tetrahydro-1,7-naphthyridines **17** and **18**, respectively. This methodology is of potential interest as a simple route to structurally rigid equivalents of 2-(3-pyridyl)ethylamine (**19**), which binds to dopaminergic and cholinergic receptors [21].

Scheme 1. Approaches to novel triaza-tricyclic and tetracyclic ring systems.



Scheme 2. Folding strategy for the synthesis of indole alkaloid-like skeletons.



These reactions demonstrate how research groups are beginning to develop diversity-minded reactions that generate more than one core structure from a single starting material. All these reactions could be used to synthesize a library of compounds that can be screened to find leads exhibiting biological activity.

Libraries based on natural products and privileged structures

Synthesized libraries can be weighted toward finding biologically active molecules within a known area of chemical space by introducing further structural diversity to natural product templates. Compounds in libraries that are based on core structures known to exhibit biological activity will have a higher intrinsic ability to bind to targets than those compounds in a library not based on natural products. Goess *et al* have developed a solid-supported divergent split-pool synthesis of a library utilizing carpanone **20** as the core structure (Figure 3) [22].

Multicomponent reactions were employed to diversify from the enone functionality with a variety of amines and hydroxylamines (branching point 1; Figure 3). Primary amines, thiols and azides were exploited in a conjugate addition reaction, either in the presence of the hydroxylamine or in a stepwise fashion. The use of thiols and azides provided handles within the library for further diversification. At branching point 2 the core structure was further diversified by altering the substituents on the phenyl ring through Mitsunobu copper-catalyzed biaryl coupling, and carbamate formation reactions. Employing this methodology enabled a library of 10,102 members to be synthesized in high purity. These compounds were screened in a phenotypic assay and several were found to perturb the

Scheme 3. Structural diversification from epoxy-tetrahydronaphthyridine to generate structurally constrained 2-(3-pyridyl)ethylamine equivalents.

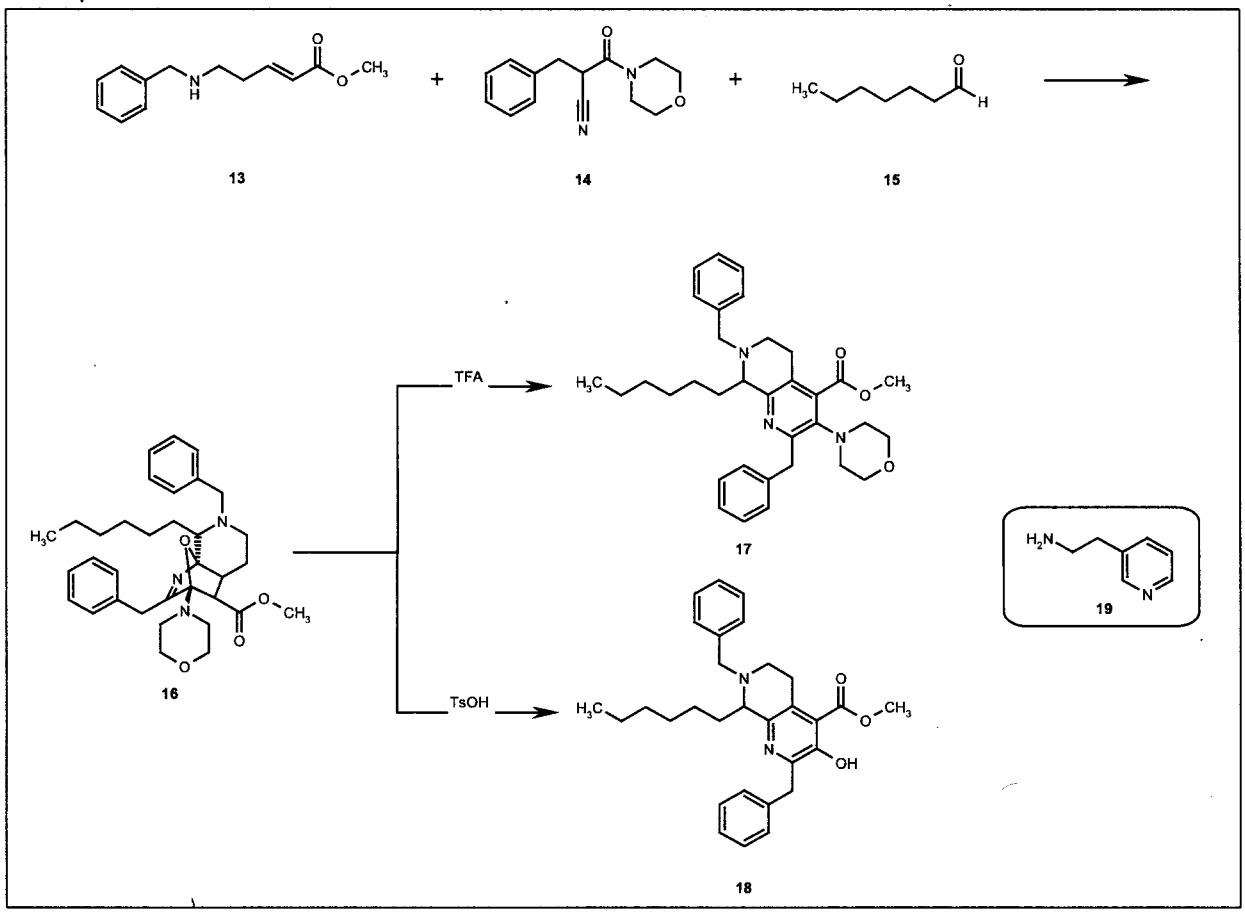
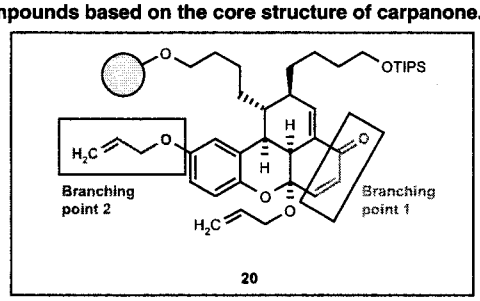


Figure 3. Branching points to introduce diversity into a library of compounds based on the core structure of carpanone.

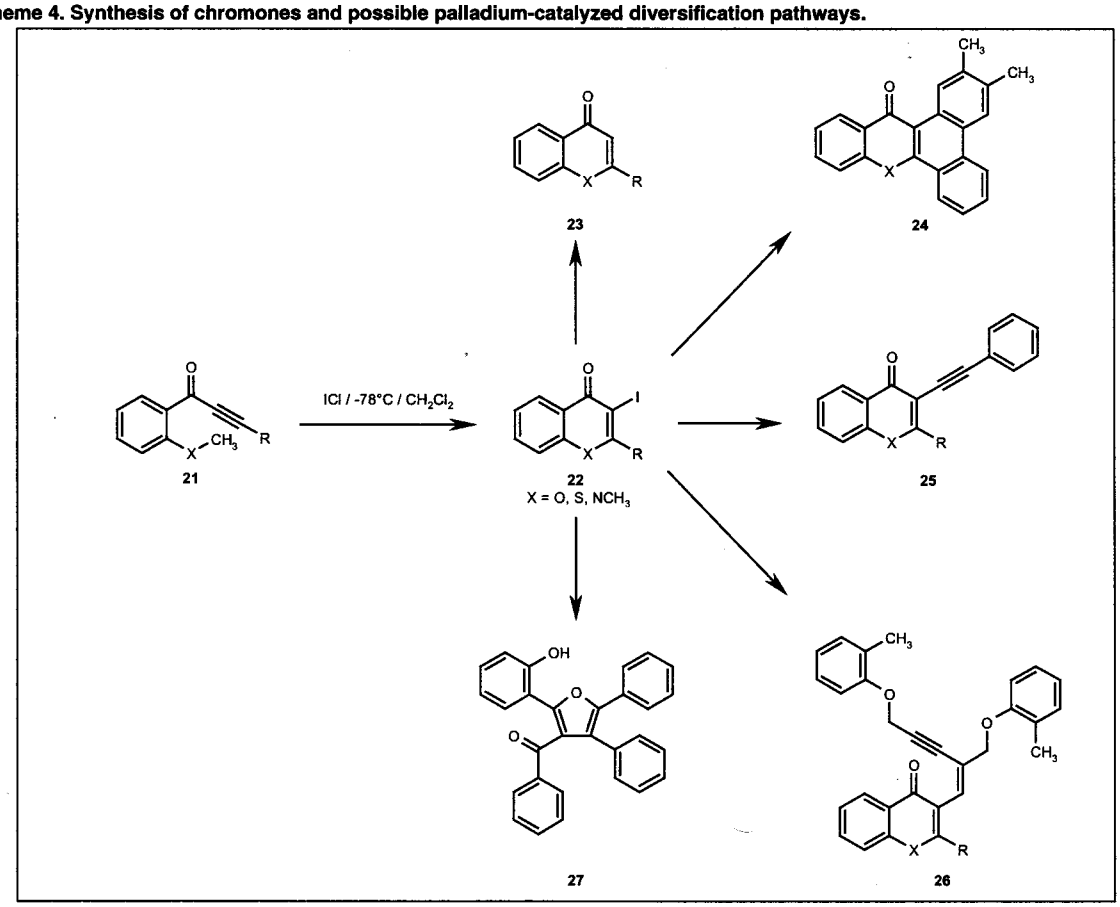


secretory pathway by inhibiting the exit of proteins from the Golgi apparatus [22]. This study demonstrates that synthesizing a library of compounds around a known core structure is a useful method for identifying biologically active compounds with new functions.

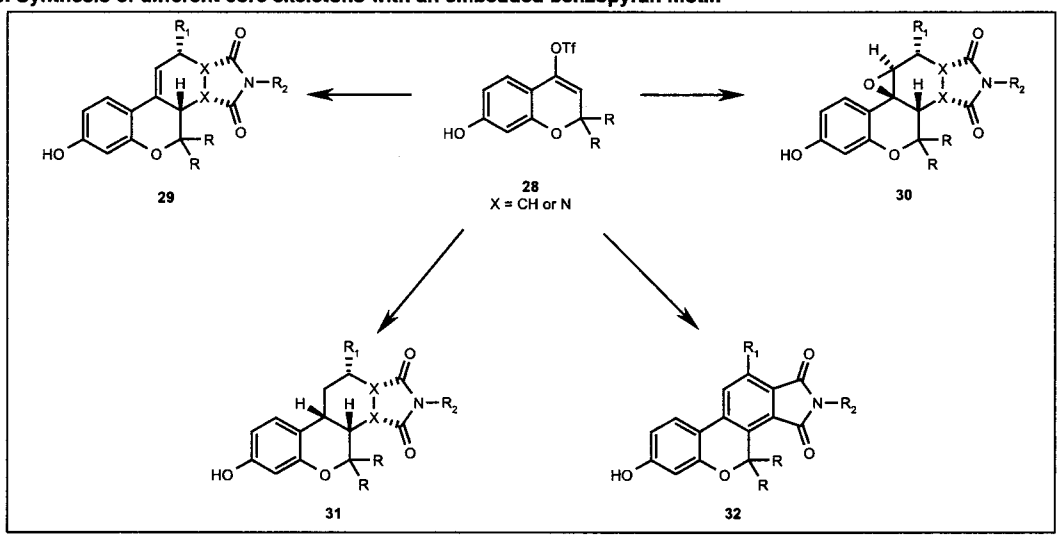
Chromones are naturally occurring, pharmacologically attractive molecules which display a wide range of biological activity, for example, as anticancer agents and antiviral drugs. Therefore, chromones or 'privileged' structures make attractive targets for discovery chemists. Zhou *et al* have developed a mild and efficient approach to various 3-iodochromones **22** using an iodine chloride-induced cyclization, and suggested five potential palladium-catalyzed branching reactions which would result in more highly substituted chromones (compounds **23** to **27**; Scheme 4) [23]. The research team went on to demonstrate that this methodology could be used to prepare 2,3-diarylchromones, which are known to be COX-2 modulatorary, antihypertensive and anti-inflammatory agents [23].

Park and co-workers have also taken advantage of the privileged chromone substructure, building a natural product-like library with an embedded benzopyran motif **28** (Scheme 5) [24]. A branching DOS strategy was exploited to maximize skeletal diversity. In particular a Diels-Alder reaction and subsequent transformations were exploited to give four distinct core skeletons (compounds **29** to **32**) using a library from library approach (Scheme 5).

Scheme 4. Synthesis of chromones and possible palladium-catalyzed diversification pathways.



Scheme 5. Synthesis of different core skeletons with an embedded benzopyran motif.



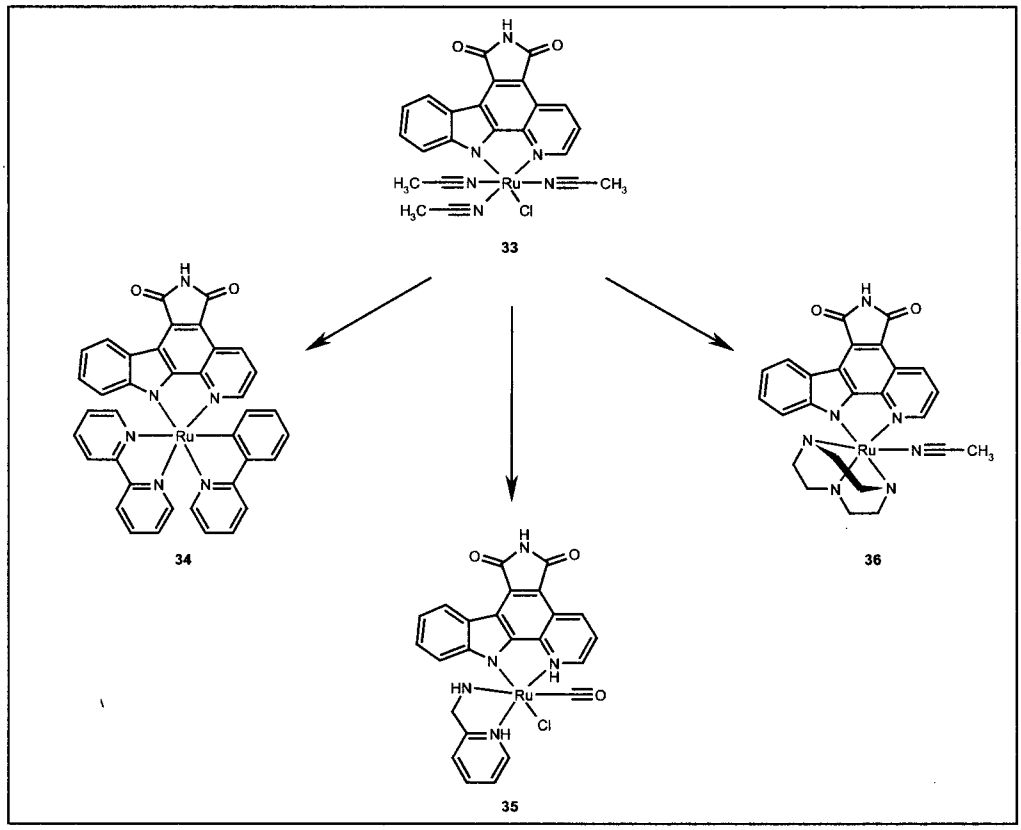
A total of 22 unique core skeletons were generated and these were tested *in vitro* in a cytotoxicity assay against human cancer cell lines. The compounds exhibited a wide range of IC_{50} values, demonstrating the importance of the link between core skeletons, and not appendices, and their biological activities [24].

In a unique approach, Bregman *et al* explored a new area of chemical space using compounds containing metals [25•]. They planned to use the metal as a hypervalent carbon equivalent by utilizing coordinative bonds that are kinetically inert and thus stable in biological environments. Using an indole[2,3-*a*]carbazole moiety

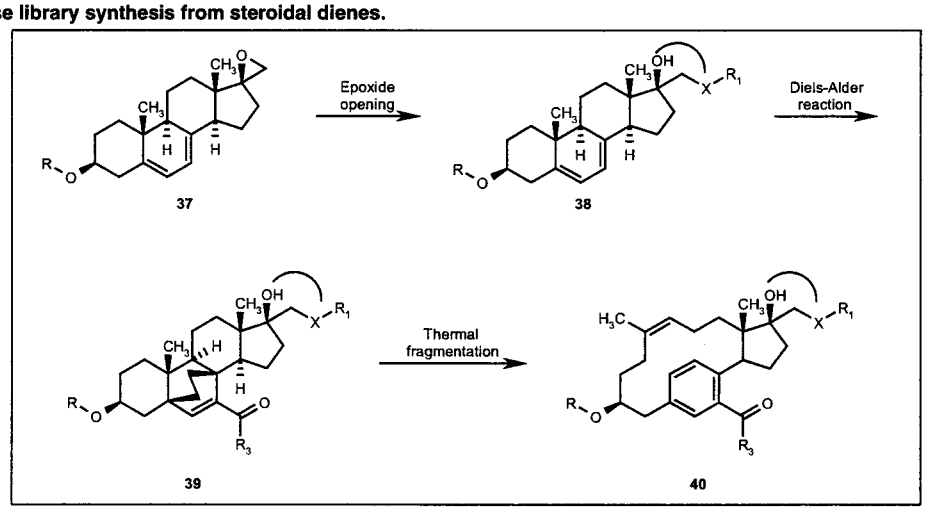
attached to ruthenium (**33**; Scheme 6), Bregman *et al* prepared and screened a range of ligands (eg, compounds **34** to **36**), resulting in the discovery of a novel octahedral ruthenium complex that acts as a potent protein kinase inhibitor [25•]. By accessing a previously uncharted area of chemical space, Bregman *et al* have identified a new class of active compounds.

Kumar *et al* have prepared a library of diverse compounds, using a divergent pathway, containing three distinct core structures. Utilizing the benefits of solid-supported synthesis, a library of over 4000 compounds was prepared by converting steroidal dienes (**37**) to bridged polycycles **39** (Scheme 7), then to a fused bicycle containing 5- and 14-membered rings (compounds **40**) [26].

Scheme 6. Examples of ligands screened in the search for a selective protein kinase inhibitor.



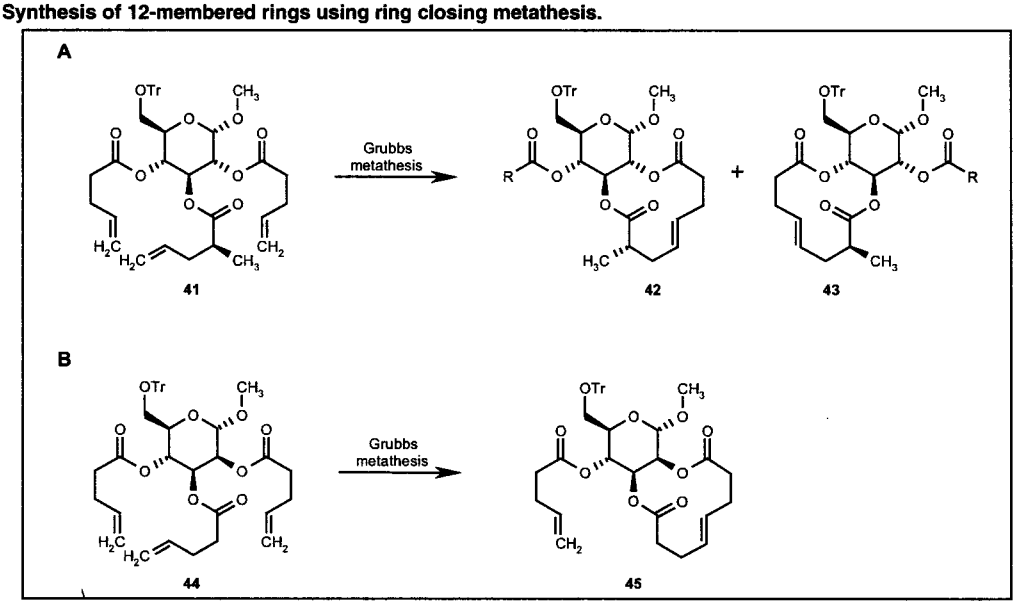
Scheme 7. Diverse library synthesis from steroidal dienes.



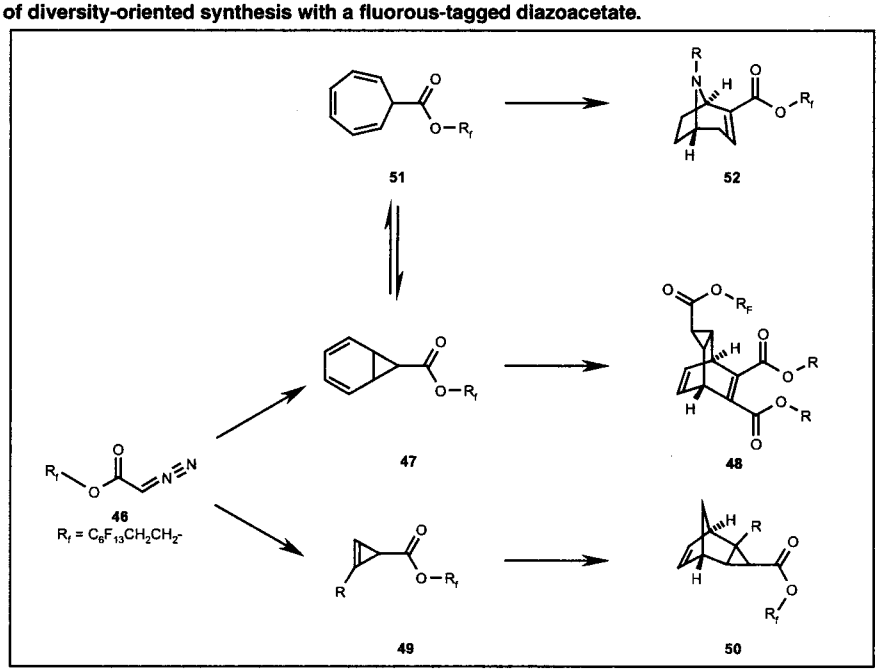
Schreiber and co-workers have also used a branching pathway methodology to prepare a library of compounds that have undergone multidimensional screening and statistical and clustering analysis [27••]. This approach allows an investigation into the roles of stereochemistry and skeleton-based conformation on the biological activity of small molecules. The research team built a library of carbohydrate-derived small molecules differing in stereochemistry and containing appendage diversity, which could be joined to form a 12-membered ring (eg, compounds **42**, **43** and **45**, Scheme 8A and 8B). The library generated contained 244 compounds, with 122 comprising two acyclic, unsaturated ester appendages and 122 containing 12-membered rings formed by ring closing metathesis. The compounds were screened using assays that reported on a wide range of biological processes. The conformationally restricted compounds (those containing 12-membered rings) displayed higher levels of biological activity [27••].

The branching pathway methodology was also utilized by Wyatt *et al* who exploited the fluorous-tagged diazoacetate **46** (Scheme 9) as a powerful starting unit in the generation of a uniquely diverse library (eg, compounds **48**, **50** and **52**) [18].

Scheme 8. Synthesis of 12-membered rings using ring closing metathesis.



Scheme 9. Example of diversity-oriented synthesis with a fluorous-tagged diazoacetate.

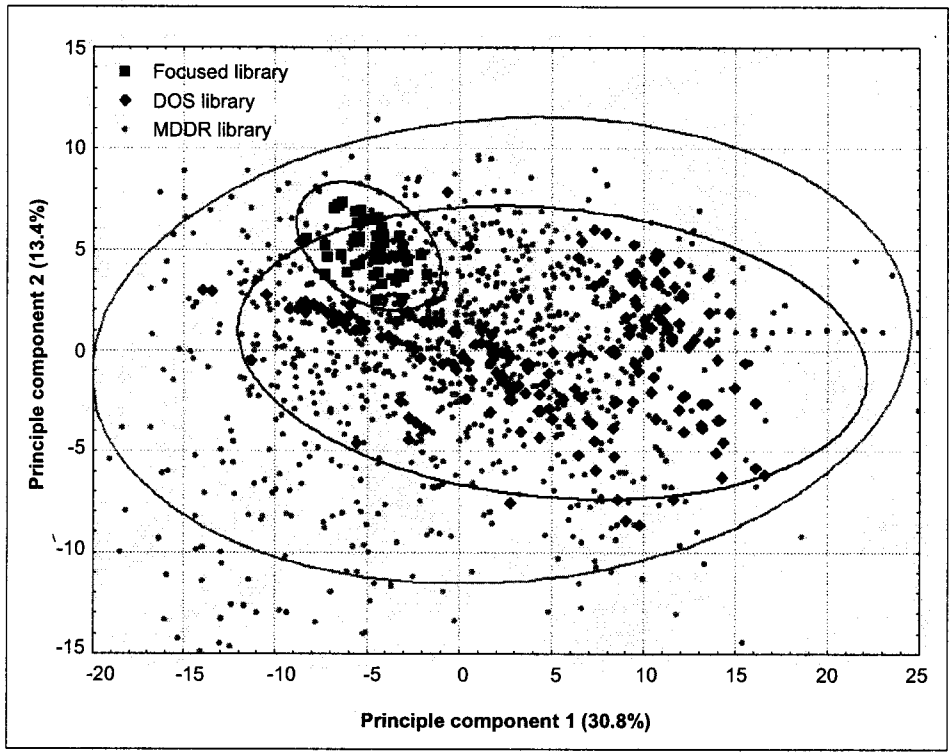


A total of 223 molecules based around 30 discrete molecular frameworks were synthesized, incorporating elevated levels of skeletal diversity and complexity in order to explore biologically relevant regions of chemical space. Phenotypic screening experiments showed that a high proportion of the compounds modulated the growth of pathogenic strains of MRSA. Significantly, a visual representation of the collection in chemical space shows that the library compares favorably with databases containing pharmacologically active compounds and natural products (Figure 4) [18]. The DOS library spans a large part of chemical space, illustrating the value of DOS to deliver diverse products.

Synthetic libraries of unnatural products

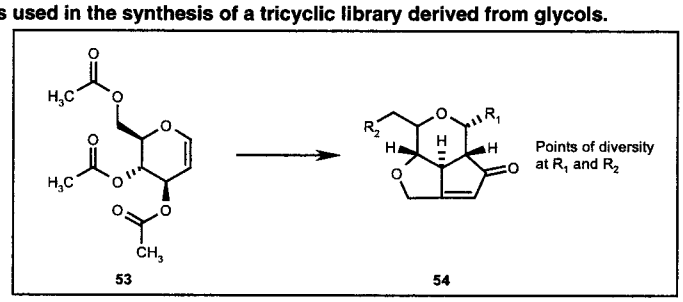
Generating libraries around new or underexploited templates with the aim of generating structurally, skeletally and functionally diverse compounds has been more common in recent years. Hotha *et al* have synthesized a 25-membered pilot library around the tricyclic core structure **54**, prepared using a Ferrier reaction followed by a Pauson-Khand reaction with glycal **53** as the starting material (Scheme 10). The researchers were able to introduce functional group diversity into their library by exploiting a linear divergent pathway and a range of diverse starting materials [28].

Figure 4. Visual representation of the diversity of different chemical collections in physicochemical and topological space using MOE descriptors followed by PCA.

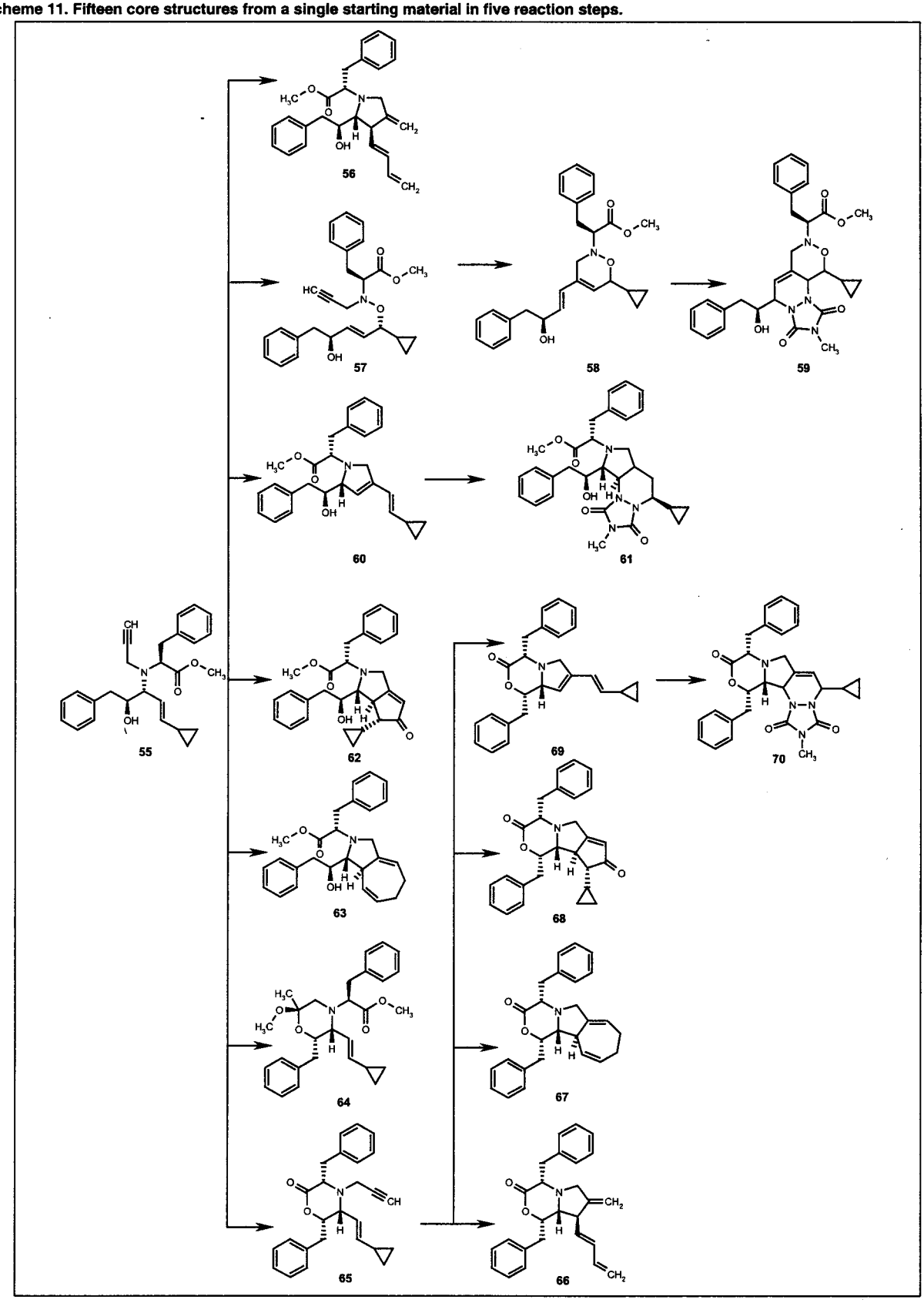


The DOS library is depicted as small diamonds. For comparison, a focused library (dark squares) and the MDL Drug Data Repository (gray dots) are also depicted.
(Reproduced with permission of The Royal Society of Chemistry and Wyatt EE, Fergus S, Galloway WRJD, Bender A, Fox DJ, Plowright AT, Jessiman AS, Welch M, Spring DR: ***Skeletal diversity construction via a branching synthetic strategy.*** *Chem Commun (2006) (31):3296-3298. © 2006 The Royal Society of Chemistry.)*

Scheme 10. Branching points used in the synthesis of a tricyclic library derived from glycols.



Scheme 11. Fifteen core structures from a single starting material in five reaction steps.



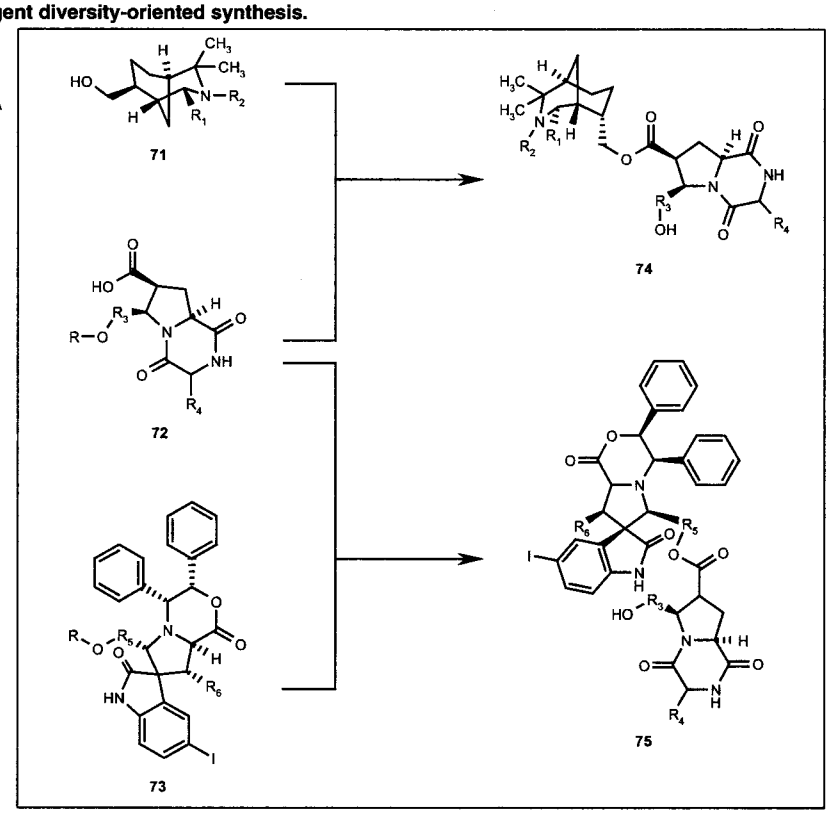
Kumagai *et al* have published the synthesis of a library containing 15 different types of skeleton as an example of a divergent pathway approach to DOS [29••]. The synthesis requires three to five steps, starting from an amino alcohol **55** (Scheme 11). The research team employed a Petasis three-component, boronic acid Mannich reaction followed by an amine propargylation to yield the β-amino alcohols (**56** to **70**; Scheme 11). The functional groups within these molecules act as handles allowing further skeletal diversity to be introduced. For example, a range of cycloisomerization, Pauson-Khand, and enyne metathesis reactions may be performed. Such reactions lead to compounds that are suitable for, among others, intra- and intermolecular Diels-Alder reactions. Using the products from these initial reactions, Kumagai *et al* were able to carry out further branching reactions, thus incorporating significantly more skeletal diversity than would be possible in a single branching pathway. The highly diverse, rigid and complex small molecules prepared using this methodology were screened in cell-based assays, enabling the identification of clusters of compounds exhibiting important properties [29••]. The biological properties of these compounds had not been disclosed at the time of writing this review.

In a second example, Chen *et al* prepared a library of small molecules using a convergent DOS pathway, incorporating natural product fragments [30•]. Two distinct libraries were prepared, a solution-phase bridged-piperidine library **71**, and an immobilized fused-pyrrolidine library **72** (Scheme 12). Compounds in these two libraries were then coupled together to form a bridged-piperidine/fused-pyrrolidine hybrid library (compounds **74**). A spirocyclic-oxindole library **73** was also coupled to the immobilized fused-pyrrolidine library **72** to form a spirocyclic-oxindole/fused-pyrrolidine library **75** (Scheme 12). A total of 864 compounds were prepared using this methodology and are to be screened for biological activity [30•].

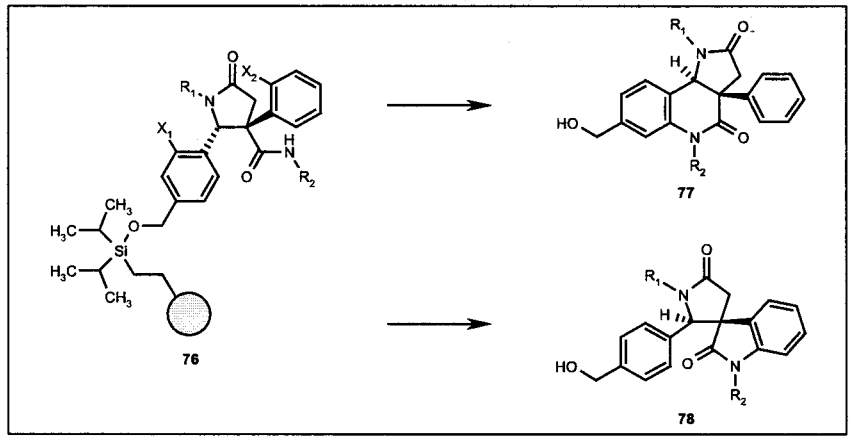
Shaw *et al* have published two examples of using a linear DOS pathway that relied on the manipulation of a single functional group to generate different core structures [15]. They prepared a library of polycyclic lactams **77** and fused and spirobicyclic γ-lactams **78** using this strategy (Scheme 13). For the synthesis of fused and spirobicyclic γ-lactams, the structural complexity results from the strategic placement of key functional groups. In these lactam examples it is the position of an iodine atom that defines the 3-D structure of the products [15].

In the second example Mitchell and Shaw prepared a series of oxazoline products with various azido substituents (compounds **80** to **84**; Scheme 14), which undergo a Staudinger-type reduction. This reaction results in spontaneous cyclization to form either spirocyclic or fused lactams, which were further elaborated by N-alkylation reactions. The research team produced five core structures overall and found several compounds comprising these core which promote the growth of yeast, while others were cytotoxic to HeLa cells in a dose-dependant manner [19].

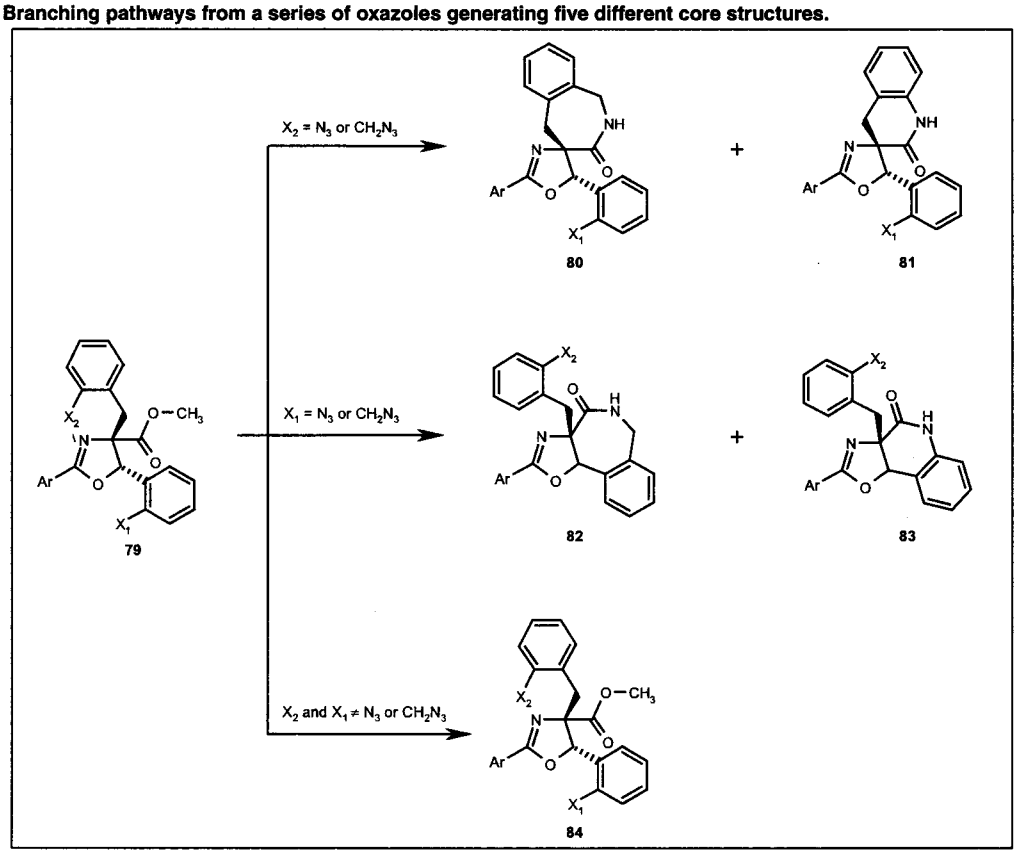
Scheme 12. Convergent diversity-oriented synthesis.



Scheme 13. Skeletal diversity introduced into a library of fused and spirobicyclic γ-lactams.



Scheme 14. Branching pathways from a series of oxazoles generating five different core structures.



Conclusion

A large amount of research has been carried out in the field of DOS over recent years. Of particular interest is the development of reactions that generate a number of new core structures and the synthesis of libraries that use known biologically active compounds as templates. The real challenge for the future lies in the ability to synthesize libraries containing a high degree of structural diversity. This would enable the exploration of the biological activity of previously uncharted regions of chemical space. The ability to rapidly access these novel compounds may have huge advantages in the drug discovery industry where new molecular entities are constantly being sought.

References

•• of outstanding interest
• of special interest

1. Clardy J, Walsh C: **Lessons from natural molecules.** *Nature* (2004) **432**(7019):829-837.

2. Messer R, Fuhrer CA, Häner R: **Natural product-like libraries based on non-aromatic, polycyclic motifs.** *Curr Opin Chem Biol* (2005) **9**(3):259-265.

3. Seitz M, Reiser O: **Synthetic approaches towards structurally diverse γ-butyrolactone natural-product-like compounds.** *Curr Opin Chem Biol* (2005) **9**(3):285-292.

4. Bohacek RS, McMartin C, Guida WC: **The art and practice of structure-based drug design: A molecular modeling perspective.** *Med Res Rev* (1996) **16**(1):3-50.

5. Lipinski C, Hopkins A: **Navigating chemical space for biology and medicine.** *Nature* (2004) **432**(7019):855-861.

6. Koch MA, Schuffenhauer A, Scheck M, Wetzel S, Casaulta M, Odermatt A, Ertl P, Waldmann H: **Charting biologically relevant chemical space: A structural classification of natural products (SCONP).** *Proc Natl Acad Sci* (2005) **102**(48):17272-17277.

7. Haggarty SJ: **The principle of complementarity: Chemical versus biological space.** *Curr Opin Chem Biol* (2005) **9**(3):296-303.

8. Dobson CM: **Chemical space and biology.** *Nature* (2004) **432**(7019):824-828.

9. Fergus S, Bender A, Spring DR: **Assessment of structural diversity in combinatorial synthesis.** *Curr Opin Chem Biol* (2005) **9**(3):304-309.

10. Spring DR: **Chemical genetics to chemical genomics: Small molecules offer big insights.** *Chem Soc Rev* (2005) **34**(6):472-482.

11. Lloyd DG, Golfis G, Knox AJ, Fayne D, Meegan MJ, Oprea TI: **Oncology exploration: Charting cancer medicinal chemistry space.** *Drug Disc Today* (2006) **11**(3-4):149-159.
• *Studies the charting of areas of chemical space and offers an idea of where to search for new anticancer agents.*

12. Reayi A, Arya P: **Natural product-like chemical space: Search for chemical dissectors of macromolecular interactions.** *Curr Opin Chem Biol* (2005) **9**(3):240-247.

13. Tan DS: **Diversity-oriented synthesis: Exploring the intersections between chemistry and biology.** *Nat Chem Rev* (2005) **1**(2):74-84.

14. Arya P, Joseph R, Gan Z, Rakic B: **Exploring new chemical space by stereocontrolled diversity-oriented synthesis.** *Chem Biol* (2005) **12**(2):163-180.

15. Massee CE, Ng PY, Fukase Y, Sánchez-Roselló M, Shaw JT: **Divergent structural complexity from a linear reaction sequence: Synthesis of fused and spirobicyclic γ-lactams from common synthetic precursors.** *J Comb Chem* (2006) **8**(3):293-296.

16. Oguri H, Schreiber SL: **Skeletal diversity via a folding pathway: Synthesis of indole alkaloid-like skeletons.** *Org Lett* (2005) **7**(1): 47-50.

17. Beeler AB, Schaus SE, Porco JA Jr: **Chemical library synthesis using convergent approaches.** *Curr Opin Chem Biol* (2005) **9**(3):277-284.

18. Wyatt EE, Fergus S, Galloway WRJD, Bender A, Fox DJ, Plowright AT, Jessiman AS, Welch M, Spring DR: **Skeletal diversity construction via a branching synthetic strategy.** *Chem Commun* (2006) (31):3296-3298.

19. Mitchell JM, Shaw JT: **A structurally diverse library of polycyclic lactams resulting from systematic placement of proximal functional groups.** *Angew Chem-Int Ed* (2006) **45**(11):1722-1726.

20. Zhang W, Lu Y, Chen CHT, Curran DP, Geib S: **Fluorous synthesis of hydantoin-, piperazinedione-, and benzodiazepinedione-fused tricyclic and tetracyclic ring systems.** *Eur J Org Chem* (2006) **26**(9):2055-2059.

21. Fayol A, Zhu J: **Multicomponent synthesis of epoxy-tetrahydronaphthyridine and structural diversification by subsequent fragmentation.** *Tetrahedron* (2005) **61**(48):11511-11519.

22. Goess BC, Hannoush RN, Chan LK, Kirchhausen T, Shair MD: **Synthesis of a 10,000-membered library of molecules resembling carpanone and discovery of vesicular traffic inhibitors.** *J Am Chem Soc* (2006) **128**(16):5391-5403.

23. Zhou C, Dubrovsky AV, Larock RC: **Diversity-oriented synthesis of 3-iodochromones and heteroatom analogues via ICl-induced cyclization.** *J Org Chem* (2006) **71**(4):1626-1632.

24. Ko SK, Jang HJ, Kim E, Park SB: **Concise and diversity-oriented synthesis of novel scaffolds embedded with privileged benzopyran motif.** *Chem Commun* (2006) (28):2962-2964.

25. Bregman H, Carroll PJ, Meggers E: **Rapid access to unexplored chemical space by ligand scanning around a ruthenium center: Discovery of potent and selective protein kinase inhibitors.** *J Am Chem Soc* (2006) **128**(3):877-884.
• *A library of compounds is prepared which contains a metal core, enabling access of a new area of chemical space.*

26. Kumar N, Kiuchi M, Tallarico JA, Schreiber SL: **Small-molecule diversity using a skeletal transformation strategy.** *Org Lett* (2005) **7**(13):2535-2538.

27. Kim YK, Arai MA, Arai T, Lamenzo JO, Dean EF 3rd, Patterson N, Clemons PA, Schreiber SL: **Relationship of stereochemical and skeletal diversity of small molecules to cellular measurement space.** *J Am Chem Soc* (2004) **126**(45):14740-14745.
•• *The total sequence of a library synthesis and subsequent screening is described.*

28. Hotha S, Tripathi A: **Diversity-oriented synthesis of tricyclic compounds from glycals using the Ferrier and Pauson-Khand reactions.** *J Comb Chem* (2005) **7**(6):968-979.

29. Kumagai N, Muncipinto G, Schreiber SL: **Short synthesis of skeletally and stereochemically diverse small molecules by coupling petasis condensation reactions to cyclization reactions.** *Angew Chem-Int Ed* (2006) **45**(22):3635-3638.
•• *An example of a large number of different skeletons formed from a single starting material during a short divergent DOS pathway.*

30. Chen C, Li X, Neumann CS, Lo MM, Schreiber SL: **Convergent diversity-oriented synthesis of small-molecule hybrids.** *Angew Chem-Int Ed* (2005) **44**(15):2249-2252.
• *A convergent DOS library is prepared using both solution- and-solid-phase methodologies.*