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A strategy for the diversity-oriented synthesis of macrocyclic scaffolds using multidimensional coupling

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A prerequisite for successful screening campaigns in drug discovery or chemical genetics is the availability of structurally and thus functionally diverse compound libraries. Diversity-oriented synthesis (DOS) provides strategies for the generation of such libraries, of which the build/couple/pair (B/C/P) algorithm is the most frequently used. We have developed an advanced B/C/P strategy that incorporates multidimensional coupling. In this approach, structural diversity is not only defined by the nature of the building blocks employed, but also by the linking motif installed during the coupling reaction. We applied this step-efficient approach in a DOS of a library that consisted of 73 macrocyclic compounds based around 59 discrete scaffolds. The macrocycles prepared cover a broad range of different molecular shapes, as illustrated by principal moment-of-inertia analysis. This demonstrates the capability of the advanced B/C/P strategy using multidimensional coupling for the preparation of structurally diverse compound collections.

Diversity-oriented synthesis (DOS) represents an approach towards small-molecule library synthesis that seeks to incorporate a high degree of structural diversity in an efficient manner[1–3]. Structurally diverse compound libraries have proved to be valuable for drug discovery[4–6] and in chemical genetics[7]; indeed, numerous modulators of challenging biological targets have been identified from DOS-derived compound collections[8–12].

Biological macromolecules interact with the three-dimensional chemical information presented by potential modulators, and the functional diversity of a compound collection is linked directly to its structural diversity[13–15]. There are a number of ways to incorporate structural diversity into a compound collection, but variation of the molecular scaffold is widely thought the most important[16–18]. Moreover, the overall three-dimensional shape diversity of a library is primarily dependent on the diversity of the central scaffold[19].

The build/couple/pair (B/C/P) strategy[20] is one of the most commonly used approaches to create scaffold diversity. In the build phase, suitable building blocks are synthesized. These building blocks are then combined in the couple phase (Fig. 1a) using the same reaction to form linear precursors that are subsequently subjected to scaffold-defining reactions in the pair phase. We reasoned that the utilization of a set of diverse branching reactions in the couple phase starting from a pluripotent functional group (multidimensional coupling, Fig. 1b) rather than a sole coupling reaction would significantly increase the structural diversity of the linear precursors. This is because the structural diversity of the linear precursors would be defined not only by the nature of the building blocks employed, but also by the respective linking motif installed. Thus, multidimensional coupling would lead to a greater structural diversity of linear precursors, which in turn would lead to a significant increase in the structural diversity of the final compounds.

We were interested in applying this approach in the DOS of macrocycles. Macrocycles have played an important part in drug discovery based on natural products. Owing to their conformational preorganization, macrocycles can bind to extended protein surfaces without major entropic loss and show remarkable target affinity and selectivity[21]. However, the high complexity of macrocycles derived from natural products hampers their synthetic modification and pharmacokinetic optimization. Thus, synthetic macrocycles of medium complexity have moved into the focus of drug discovery in the past decade and many synthetic macrocyclic modulators with appropriate pharmacokinetic properties were identified for traditional as well as challenging new targets, such as protein–protein interactions[22,23]. Despite these encouraging examples, macrocycles are still underrepresented in pharmaceutical compound collections[24]. Although the construction of libraries of peptide and peptidomimetic macrocycles is well established[25,26], the efficient preparation of structurally diverse non-peptidic macrocycle collections remains a challenge[27].

Reported DOS approaches for the generation of diverse non-peptidic macrocycle collections include the use of ring expansion[28,29], fragment-based domain shuffling[30], two-directional synthesis[31] and, most frequently, the classical B/C/P strategy[32,33]. However, only a limited degree of scaffold diversity (approximately 20 distinct scaffolds) has been achieved using these approaches.

Here we report the application of the multidimensional B/C/P strategy to the DOS of a library of macrocycles with unprecedented scaffold diversity. This was achieved by exploiting the pluripotent reactivity of azide-derived aza-ylides. Starting from the common precursor **1** (Fig. 2), a series of diverse azido building blocks (such as **2** and **3**) was prepared in the build phase. In the multidimensional couple step, the attached azide group was transformed *in situ* into an aza-ylide, which was reacted with a set of diverse electrophiles in aza-Wittig reactions[34] that resulted in various structural motifs (for example, urea **4** and guanidine **5**). These aza-Wittig reactions proceeded with concomitant installation of either a new azide group (as in compound **4**) or a terminal alkene (as in compound **5**). Along with the initially attached terminal alkyne, these groups

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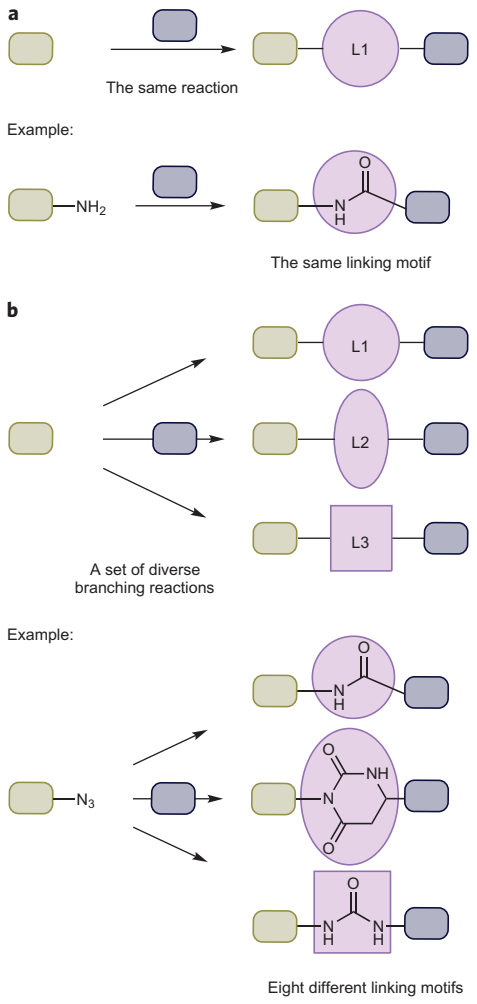

Figure 1 | Comparison of the couple phase in a classical B/C/P strategy with the multidimensional coupling phase introduced in our work. Building blocks (green and blue rectangles) are coupled via the formation of different linking motifs (L1–L3, purple). **a**, In the classical strategy, only one linking motif (for example, L1, amide functionality) is formed. **b**, In our approach, eight linking motifs (for example, L1–L3, amide, dihydrouracil and urea functionalities) can be generated starting from one common building block (green rectangle) using multidimensional coupling.

served as macrocyclization handles in the subsequent pair phase. Depending on the functionality installed in the couple phase, macrocyclizations were performed either by copper-catalysed[35,36] (for example, leading to **6**) and ruthenium-catalysed[37] azide–alkyne cycloadditions[38] (CuAAC and RuAAC) or by enyne metathesis[39] (for example, leading to **7**).

To take advantage of solution-phase combinatorial synthesis with the generic purification of product from reagents by fluorous solid-phase extraction[40,41], we installed a polyfluorocarbon tag on the common precursor **1**. In the final step of the synthesis, the fluorous tag could be cleaved divergently by transesterification, transamidation, ester hydrolysis and ester reduction (to provide compounds such as **8**–**12**) as a means of further diversification. In total, 73 macrocycles based on 59 distinct scaffolds were obtained in 4–5 steps from **1**.

Results

Build phase: preparation of azido building blocks. The starting unit **1** was prepared easily on a multigram scale in two steps from commercially available starting material (Supplementary Fig. S1). With this compound in hand, facile amide-bond formation via acyl chlorides was used to prepare efficiently seven azido building blocks (**2**, **3**, **13**–**17**) in the build phase (Fig. 3 and Supplementary Fig. S2). These building blocks differ not only chemically (aromatic versus benzylic and aliphatic azides), but also exhibit different rigid geometries. Thus, it was envisaged that they would induce distinct shapes in the final macrocyclic products.

Couple phase: multidimensional coupling using aza-Wittig reactions. In the multidimensional couple phase of the DOS, different aza-Wittig reactions were performed to convert the azido building blocks into various linear precursors for subsequent macrocyclizations. These reactions are discussed exemplarily for azido building block **3** (Fig. 3). The azide group was reacted initially with PPh_3 or $P(n\text{-}Bu)_3$ to form the corresponding aza-ylide **18**, which was not isolated but reacted directly with different electrophiles, such as carbon dioxide, isocyanates, acyl

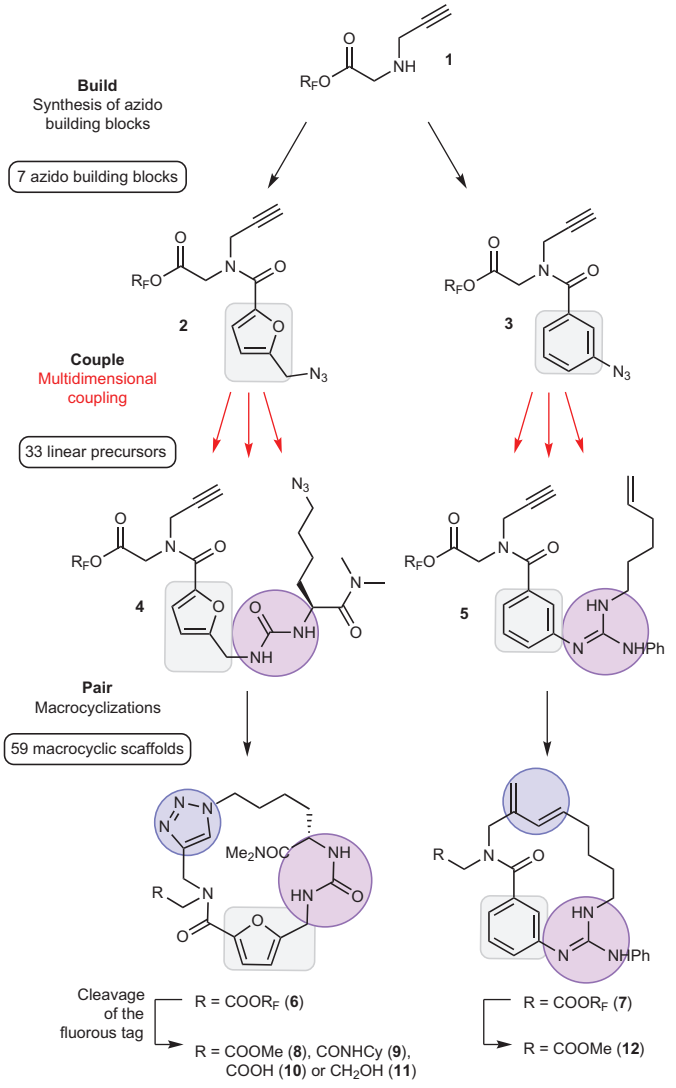

Figure 2 | Outline of the synthetic strategy used for the construction of the macrocyclic DOS library. Azido building blocks (for example, **2** and **3**) were synthesized from one common fluorous-tagged precursor **1**. Multidimensional coupling (represented by multiple arrows; only one reaction product is shown) led to the formation of linear precursors (such as **4** and **5**), which were subsequently macrocyclized using AAC (leading to **6**) or enyne metathesis (leading to **7**). Divergent cleavage of the fluorous tag delivered the final macrocycle library members (for example, **8**–**12**). R_F, $(CH_2)_2C_8F_{17}$.

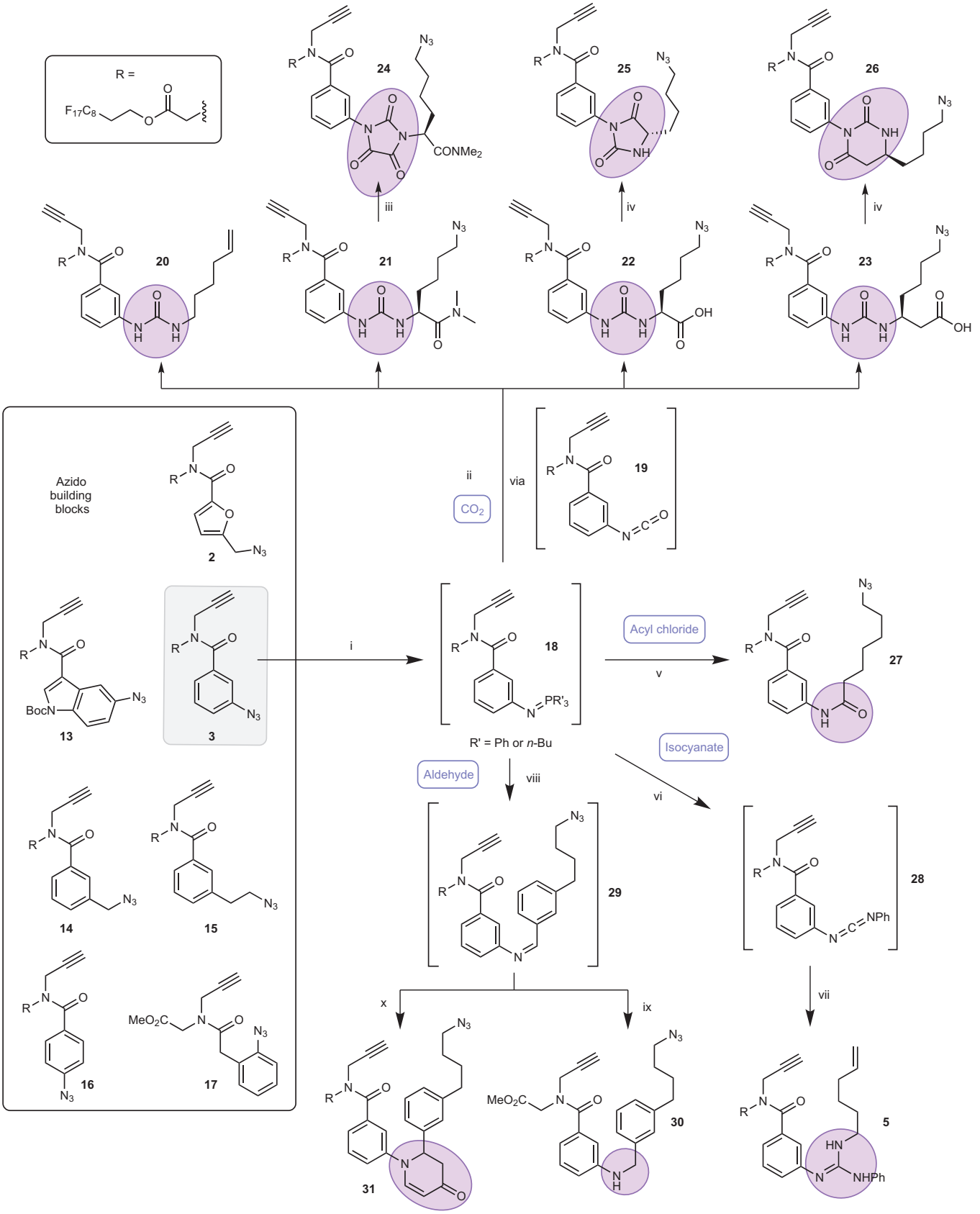

Figure 3 | Multidimensional coupling exemplified for azido building block 3. The intermediate aza-ylide **18** was reacted with various electrophiles, including CO_2, acyl chlorides, isocyanates and aldehydes. Reagents and conditions: (i) PPh_3 or $P(n\text{-}Bu)_3$, THF; (ii) hex-5-en-1-amine hydrochloride or a derivative of an amino acid hydrochloride, CO_2, DIPEA; (iii) $(COCl)_2$, pyridine, CH_2Cl_2; (iv) *N,N′*-diisopropylcarbodiimide, *N*-hydroxysuccinimide, 4-(dimethylamino)pyridine, THF; (v) 7-azidoheptanoyl chloride; (vi) PhNCO; (vii) hex-5-en-1-amine hydrochloride, DIPEA; (viii) 3-(4-azidobutyl)benzaldehyde; (ix) $NaBH_4$, MeOH; (x) Danishefsky's diene, $AgOSO_2CF_3$.

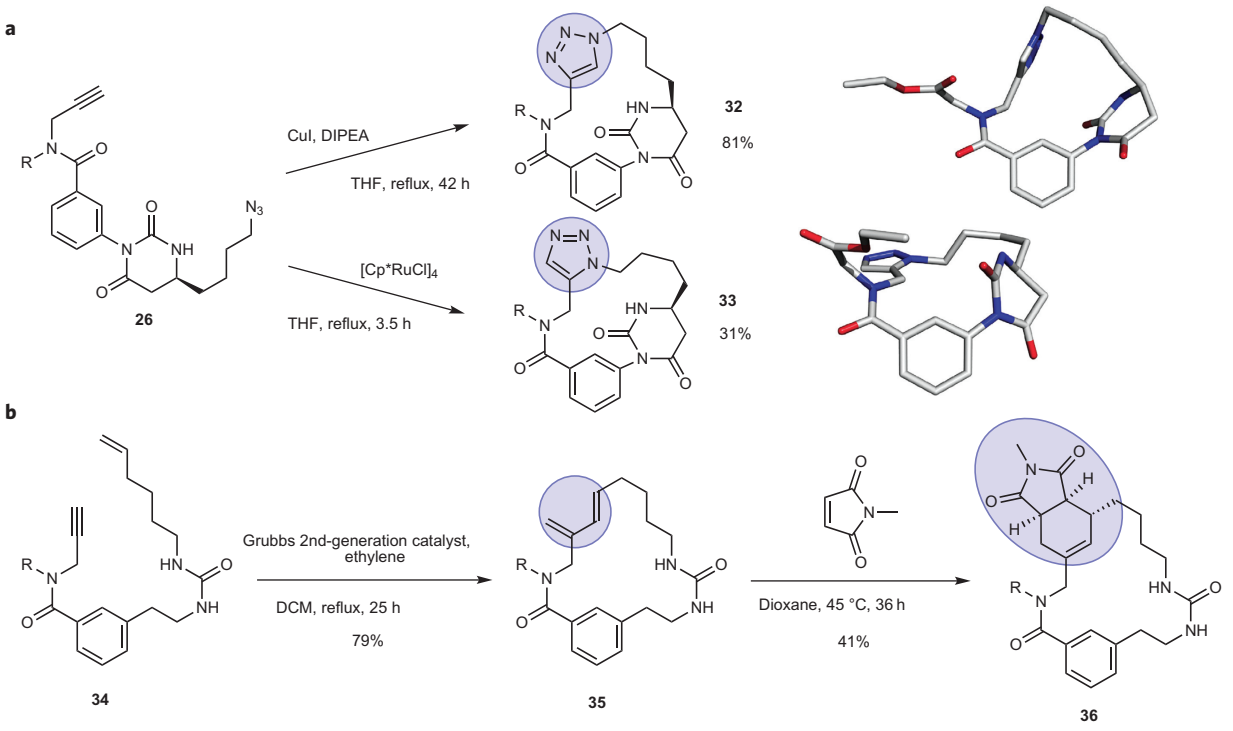

Figure 4 | Illustrative macrocyclizations of the pair phase. a, CuAAC (leading to **32**) and RuAAC (leading to **33**) macrocyclizations afford distinctive molecular shapes, as illustrated by the lowest-energy conformation of the corresponding polyfluorocarbon-tag cleaved final products (for further details, see Supplementary Information p. S115). **b**, Macrocyclization by enyne metathesis results in dienes (such as **35**) that can be further diversified using Diels–Alder reactions (leading to **36**). R, $CH_2COO(CH_2)_2C_8F_{17}$.

chlorides and aldehydes, to form the corresponding aza-Wittig products.

The reaction of the aza-ylide with carbon dioxide led to the formation of the corresponding isocyanate **19**, which was instantly trapped by different amines in a one-pot procedure[42–45] to afford ureas **20**–**23**. The ureas were used directly as linear precursors in macrocyclizations (for example, **20** and **21**) and/or were further diversified in a second reaction. For instance, urea **21** was converted easily into the corresponding oxalylurea **24** by reaction with oxalyl chloride in the presence of pyridine. Ureas **22** and **23** were cyclized via mild activation of the acid functionality using *N,N′*-diisopropylcarbodiimide in the presence of *N*-hydroxysuccinimide to afford hydantoin **25** and dihydrouracil **26**, respectively. Using an acyl chloride as an electrophile in the aza-Wittig reaction of **18** led to the smooth formation of amide **27**. The reaction of the aza-ylide **18** with an isocyanate afforded the corresponding unsymmetric carbodiimide **28**, which was converted directly into guanidine **5** by addition of an amine in a one-pot procedure. Finally, aza-ylide **18** was reacted with an aldehyde to obtain the resulting imine **29** as an intermediate. Without isolation, imine **29** was either reduced with $NaBH_4$ to give amine **30** or used as a dienophile in an aza-Diels–Alder reaction with Danishefsky's diene under Lewis-acid activation[46] to obtain dihydropyridinone **31**.

Pair phase: macrocyclizations. In the pair phase of our strategy the linear precursors were macrocyclized divergently. Depending on whether an azide or a terminal alkene had been attached in the couple phase, CuAAC and RuAAC or enyne metathesis were carried out (Fig. 4). In general, the macrocyclization methods used in this study (CuAAC, RuAAC, enyne metathesis) proved to be very robust and delivered the desired macrocyclic products in moderate-to-good yields (see Supplementary Information p. S12 for some limitations).

CuI and *N,N*-diisopropylethylamine (DIPEA) in refluxing THF proved to be reliable conditions for the CuAAC macrocyclizations that led to 1,4-triazole structures (for example, **32**, Fig. 4a). $[Cp^*RuCl]_4$ (Cp^* = pentamethylcyclopentadienyl) in refluxing THF was used to promote the RuAAC to obtain 1,5-triazole-containing macrocycles (such as **33**, Fig. 4a). In both cases the reactions were performed at high dilution (1 mM) to prevent dimerization. The AAC macrocyclizations gave highly selective access to the desired regioisomer, and only one linear precursor delivered a mixture of two regioisomers on RuAAC (precursor **25**, see Supplementary Information, p. S66). The CuAAC macrocyclization products were isolated in an average yield of 61% and the RuAAC macrocyclization products were obtained in an average yield of 42%.

For linear precursors that contained a terminal alkene (such as linear precursors **5** and **20** in Fig. 3), enyne metathesis was used to construct macrocyclic architectures in the pair phase (Fig. 4b). Grubbs second-generation catalyst was used under an initial atmosphere of ethylene. After the alkyne had converted into the corresponding intermediate linear diene, the ethylene atmosphere was replaced by argon to force the subsequent ring-closing metathesis to completion. In total, seven macrocyclic dienes (for example, **35**, Fig. 4b) were obtained in an average yield of 43%. The diene motif present in these products provides a synthetic handle for further diversification using Diels–Alder reactions. As an example, diene **35** reacted with *N*-methylmaleimide to provide the macrocyclic Diels–Alder product **36** (Fig. 4b).

Cleavage of the fluorous tag. Cleavage of the polyfluorocarbon tag was used to diversify the library further (Fig. 2 and Supplementary Fig. S3). The ester functionality that linked the fluorous tag to the macrocycle was converted into various esters (for example, **8**) or amides (such as **9**). Furthermore, it was hydrolysed to the corresponding acid (for example, **10**) or reduced to the corresponding alcohol (such as **11**).

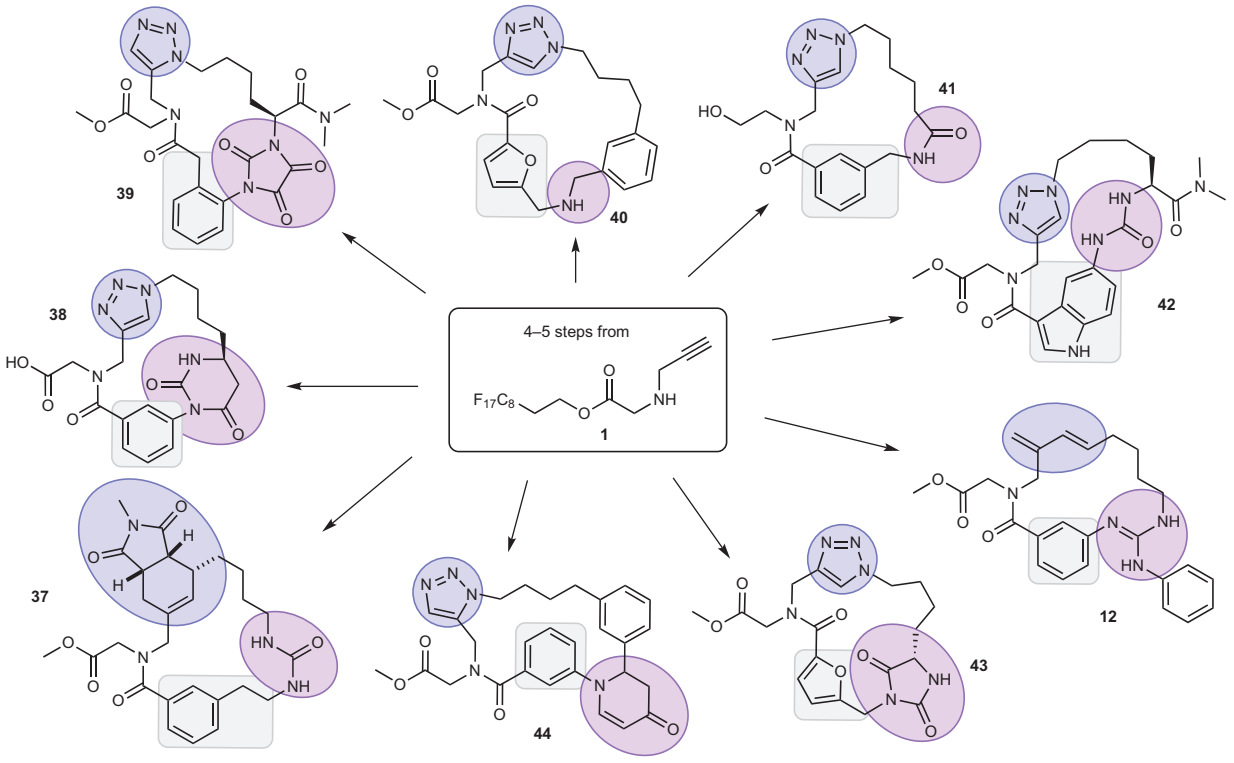

Figure 5 | Illustrative members of the DOS library. In total, 73 macrocycles based on 59 distinct scaffolds were generated. Major scaffold-defining parameters are the variation of the building block (highlighted in grey), the formation of different linking motifs using multidimensional coupling (highlighted in purple) and divergent macrocyclization (highlighted in blue).

The library. Using the strategy outlined above, a DOS of 73 macrocyclic compounds was achieved, which contains 59 distinct macrocyclic scaffolds among other unique structural features (Fig. 5 and Supplementary Fig. S4). Apart from the diversity introduced by using different building blocks, multidimensional coupling led to a large variety of linking structural motifs (highlighted in purple). Each compound was prepared from the common starting unit **1** in not more than five steps. The library was made using parallel synthetic techniques that led to 1–48 mg of each final product (molecular mass range 357–558, mean value 444). All library members were assessed for their identity and quality (high-resolution mass spectroscopy, HPLC), and purified, if necessary, by flash chromatography or preparative HPLC to ensure a high purity (mean value 98% according to HPLC) of final products. Full characterization was undertaken for the compounds derived from building blocks **2**, **3**, **13**, **14** and **16** (68% of final products). All NMR spectra needed to be recorded at elevated temperatures because of slowly interconverting conformers at room temperature.

Diversity assessment. To assess the degree of overall shape diversity obtained in this macrocyclic DOS library, we compared our set of macrocycles with three reference collections[29,47]: (1) a set of 40 top-selling brand-name drugs, (2) a set of 60 diverse natural products and (3) a set of 24 macrocyclic natural products. Based on the lowest-energy conformations of all depicted molecules, normalized ratios of principal moment-of-inertia (PMI) descriptors were calculated and plotted on a triangular graph, as previously reported[19]. The resulting PMI plot (Fig. 6) visualizes intuitively the shape diversity of each of the four collections in 'molecular shape space' spanned by the three basic shape types, 'rod-like', 'disc-like' and 'spherical'.

Although the drug reference set predominantly exhibits rod-like shapes with a varying proportion of disc-like features, the non-macrocyclic and macrocyclic sets of natural products possess significantly higher shape diversity with much more pronounced spherical characteristics. We were pleased to find that our macrocyclic library covers a molecular shape space comparatively as broad as that of the selected natural products and thus displays very high molecular shape diversity.

Discussion

Variation of the basic molecular scaffold is thought to be the most important feature to enhance structural and thus functional diversity of a compound collection. The advanced DOS strategy reported herein addresses the need for such scaffold-diverse libraries. The multidimensional coupling within the B/C/P algorithm employs a pluripotent functional group to assemble the building blocks using various reactions, rather than only a sole coupling reaction. Thus our strategy enables the generation of a much higher degree of structural diversity that is not only defined by the nature of the building blocks used, but also by the type of linking motif installed.

We applied this strategy to the preparation of a macrocycle library, as macrocycles are an underrepresented structural class in screening collections. Azide-derived aza-ylides were identified as a fruitful multidimensional coupling handle. A structurally diverse collection of different azido building blocks was prepared efficiently during the build phase. Using aza-Wittig reactions and a few subsequent transformations, eight different linking motifs were generated by multidimensional coupling. Divergent macrocyclization in the pair phase led to a large number of distinct macrocyclic scaffolds. In total, 73 compounds based on 59 discrete scaffolds were prepared efficiently in not more than five steps from a common precursor. Polyfluorocarbon-tag technology was used to facilitate purification. The synthetic route is highly modular, which allows for the facile synthesis of analogues of the first-generation library members. Both different building blocks and different linking motifs contribute simultaneously to the structural diversity, which results in a

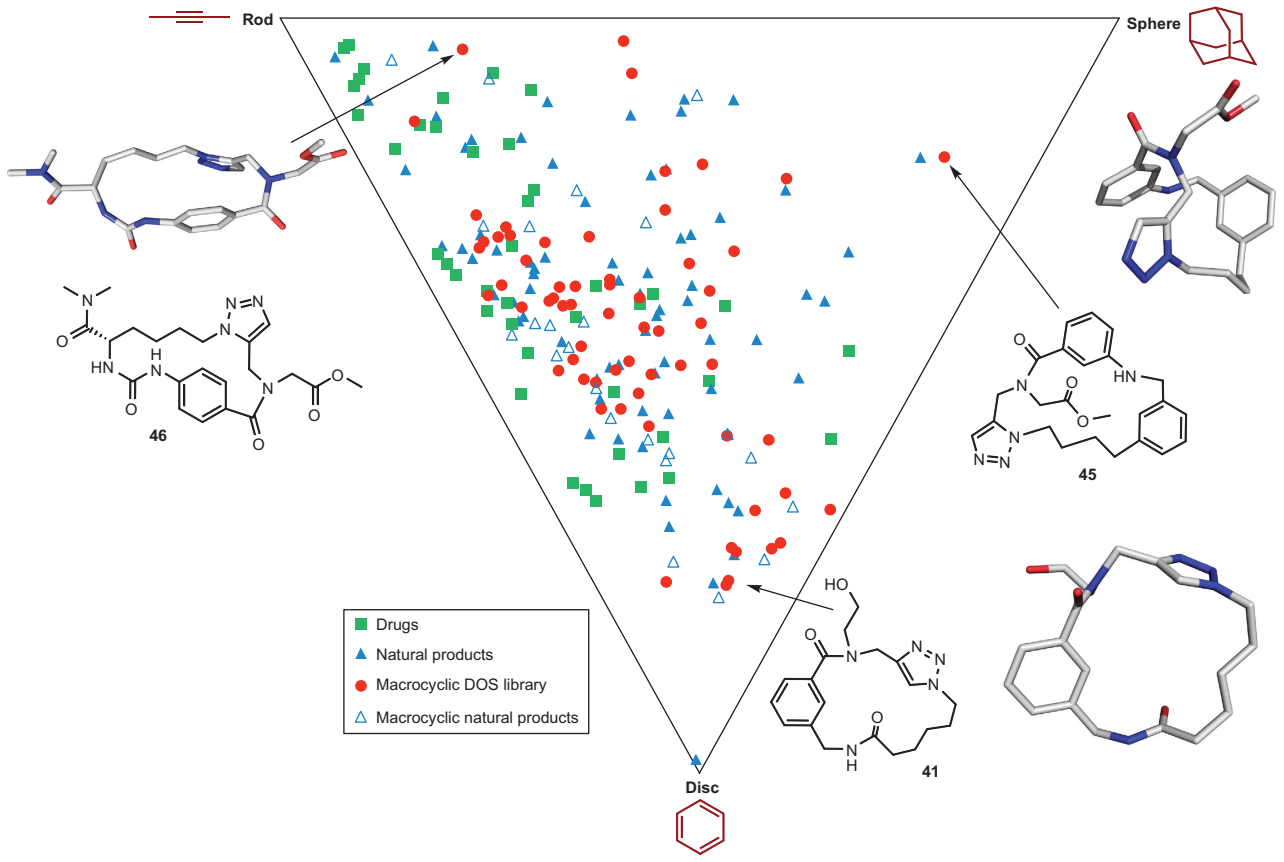

Figure 6 | Principle moment of inertia plot. The molecular shape diversity of the DOS library (red dots) and comparison with reference sets of 40 top-selling brand-name drugs (green squares), 60 diverse natural products (filled blue triangles) and 24 macrocyclic natural products (open blue triangles). For further details, see Supplementary Information p. S115.

broad coverage of molecular shapes by the macrocycles prepared, as demonstrated by the PMI plot. The synthesized macrocycle library exhibits molecular shape diversity comparable to that of natural products. This demonstrates the capability of the advanced B/C/P strategy using multidimensional coupling for the preparation of shape-diverse scaffolds. Currently, the first-generation library members are being screened in phenotypic assays for antibacterial activity against different multidrug-resistant bacterial strains, as well as for antiproliferative activity and their ability to disrupt selected protein–protein interactions.

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Author contributions

H.S.G.B., D.W. and D.R.S. conceived and supervised the project. H.S.G.B., F.N., C.E.H., H.J. and D.W. planned, performed and evaluated the experiments. Y.S.T. performed the molecular informatics studies. H.S.G.B., F.N., D.W. and D.R.S. wrote the paper. All authors discussed the results and commented on the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to D.R.S.

Competing financial interests

The authors declare no competing financial interests.