Recent developments in combinatorial organic synthesis

A. Ganesan

The level of sophistication of combinatorial synthesis continues to increase at a heady pace. Fairly complex target molecules are now being assembled combinatorially using a broad palette of organic reactions both in solution- and solid-phase. This review highlights academic and industrial examples of combinatorial synthesis published within the last year. Recent advances in small-molecule synthesis are outlined, ranging from simple acyclic scaffolds to complex natural products.

A. Ganesan
Dept of Chemistry
University of Southampton
Southampton
UK SO17 1BJ
tel: +44 2380 593897
fax: +44 2380 596805
e-mail: ganesan@soton.ac.uk

The dawn of the 21st century heralds a new era in drug discovery. We now have access to the complete human genome sequence as well as the complete sequences of pathogenic organisms: information that will result in an avalanche of novel therapeutic targets. But will combinatorial chemistry be up to the challenge of translating this knowledge into medicinal agents? A decade ago, the answer would be equivocal at best. During the embryonic phase of combinatorial chemistry, much of the excitement came from the ability to build large collections of molecules. Often, the resulting libraries were poorly characterized and probably contained an incomplete representation of the potential members. A more serious problem was that only a few organic reactions were sufficiently robust for making such large libraries. Thus, the structures produced tended not to be drug-like, and were poor candidates for further progression to development.

Combinatorial chemistry strategies

Is combinatorial chemistry now in a position to deliver our future blockbuster drugs? Although nobody can answer this question with certainty, lessons from the past strongly suggest that drugs come in all shapes and sizes (Fig. 1). Consider the astonishingly simple calcium ion-channel antagonist nifedipine (Fig. 1, structure **1**), whose derivation by the Hantzsch dihydropyridine synthesis would be obvious to many undergraduates. One could argue that any scaffold resulting from a name reaction in heterocycle synthesis is a promising avenue for combinatorial chemistry. Ideally, it would be useful to build up sets of prospective libraries based on all such processes. Given the possible existence of future nifedipines, the potential benefit of such an exercise compensates for the modest effort needed to adapt a venerable name reaction for parallel array synthesis.

Although the phosphodiesterase inhibitor sildenafil (Fig. 1, structure **2**) or the HIV proteinase inhibitor indinavir (Fig. 1, structure **3**) are unlikely to fall directly out of a combinatorial library, the odds for the discovery of ancestral precursors are excellent. The origin of both drugs is based on sound mechanistic principles, featuring a substrate analogue of cyclic GMP in the case of sildenafil and a transition state analogue for peptide hydrolysis in the case of indinavir. This suggests a second powerful strategy for building combinatorial libraries by focussing on a family of related targets with similar substrate or cofactor requirements. In the purine nucleotide area, the best example to date is the exploration of numerous heterocyclic templates as ATP analogues for the inhibition of protein tyrosine kinases. Meanwhile, the modular nature of proteinase inhibitors, such as indinavir, lends itself particularly well to combinatorial chemistry. There is wide scope for variation in the building blocks as well as the tetrahedral transition state isostere, and indeed many such libraries have been reported for different classes of proteinases.

The last two examples exemplify the considerable proportion of our drugs that are derived from Nature: the supreme combinatorial chemist. Although the discovery of novel

1359-6446/02/$ – see front matter PII: S1359-6446(02)02087-6

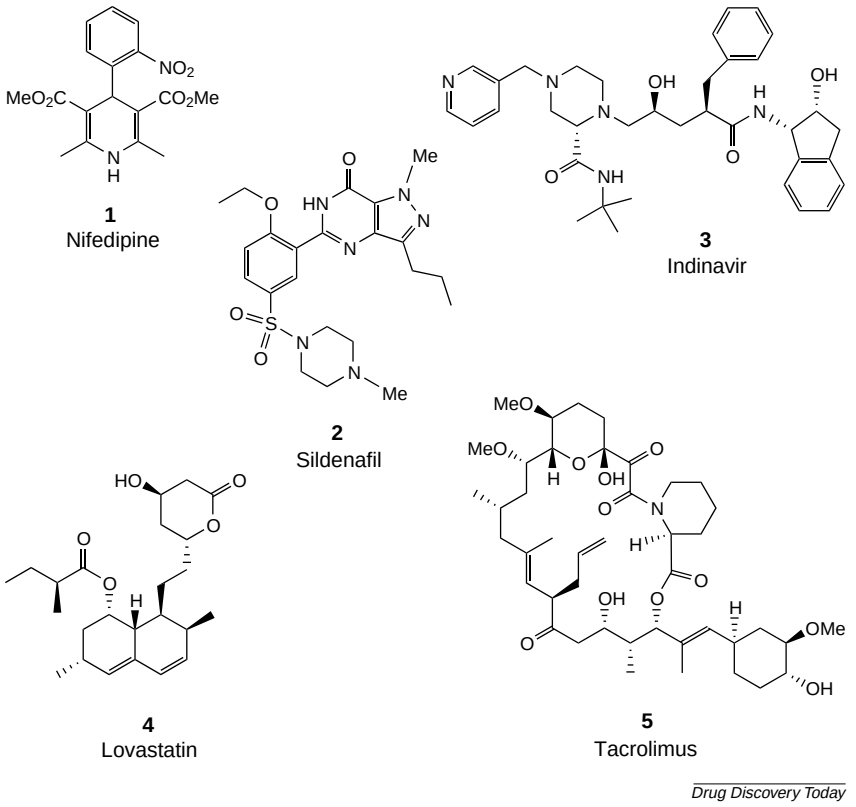

Figure 1. What will your next blockbuster look like?

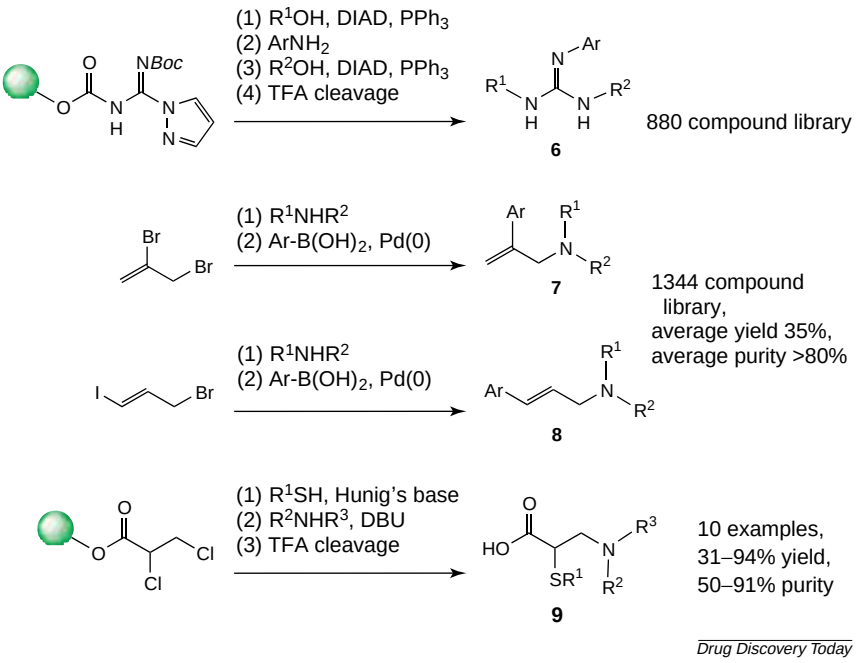

Figure 2. Examples of acyclic templates for combinatorial synthesis. Here and in later figures, the detailed structure of solid-phase resins and linkers is omitted. Abbreviations: DBU, 1,8-diazabicyclo[*5.4.0*]undec-7-ene; DIAD, diisopropyl azodicarboxylate; TFA, trifluoroacetic acid.

biologically active natural products is a time consuming and expensive exercise, it can have substantial payoffs as many of these drugs have no synthetic competitors. Thus, Nature's evolutional optimization of the scaffold represents a third and attractive starting point for libraries. This approach is gaining in favour among both academic groups engaged in traditional natural product synthesis and combinatorial chemists. Even complex structures like the HMG CoA reductase inhibitor lovastatin (Fig. 1, structure **4**) are now realistic targets for combinatorial synthesis. The immunosuppressive agent tacrolimus (Fig. 1, structure **5**) represents a further substantial increase in structural complexity, although a library of tacrolimus analogues has yet to be reported in the literature. However, the bottleneck in such a project is not the actual combinatorial aspect, but the resource allocation needed to assemble a set of building blocks from scratch. Tacrolimus is also a flagrant violator of our general idea of what constitutes drug-like material, and begs the question of whether too much adherence to such considerations when designing libraries will miss similar important exceptions. For a subset of therapeutic targets, there will be no leads that faithfully follow Lipinski's 'rule of five'.

In the following sections, I will highlight some examples of synthetic and natural-product scaffolds published within the past year. Hopefully, this will provide a convincing arguement that state-of-the-art combinatorial organic chemistry is sufficiently mature and sophisticated to discover meaningful new leads that will culminate into next-generation therapeutics.

Acyclic scaffolds

As the majority of drugs are heterocycles, it is not surprising that they are the most popular choice for combinatorial scaffolds. Nevertheless, many

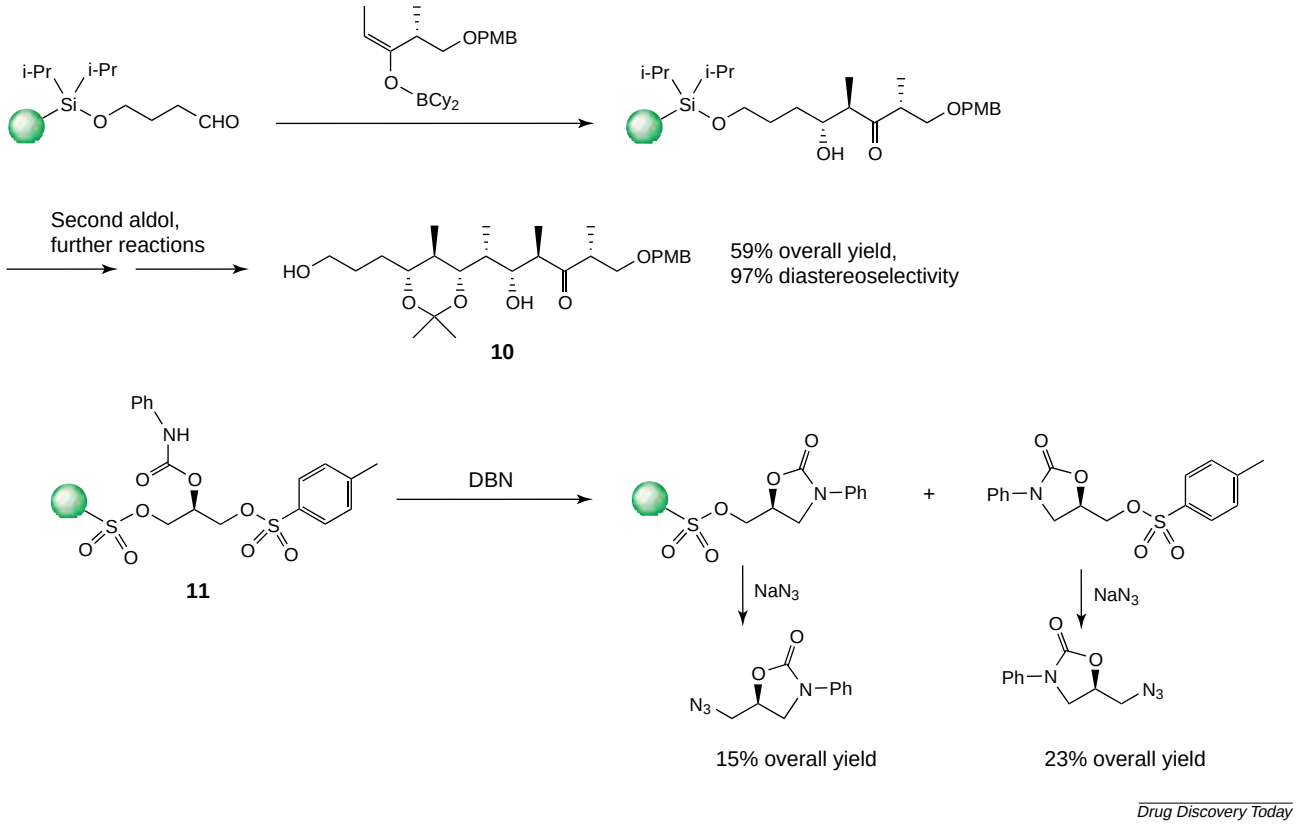

Figure 3. Examples of stereoselective solid-phase synthesis. Abbreviations: Cy, cyclohexyl; DBN, 1,5-diazabicyclo[*4.3.0*]non-5-ene; PMB, *p*-methoxybenzyl.

acyclic pharmacophores are also important in drug discovery, such as the guanidine functional group, which is present in numerous biologically active molecules. Most combinatorial routes to guanidines do not provide diverse substitution patterns at the position of all three nitrogens. A recent exception is the Mitsunobu alkylation of a resin-bound *bis*-carbamoyl pyrazole followed by displacement of the pyrazole by anilines, and a second Mitsunobu alkylation to yield the trisubstituted guanidine (Fig. 2, structure **6**) after cleavage [1]. The Suzuki cross-coupling of boronic acids with vinyl bromides featured in a solution-phase library synthesis of *cis* and *trans* allylic amines [2] is shown in structures **7** and **8** (Fig. 2). This route involves two sequential nucleophilic substitutions, a strategy also demonstrated on solid-phase with 2,3-dichloropropionic acid to give α-substituted β-amino acids [3] (Fig. 2, structure **9**).

In the early days of combinatorial chemistry, less attention was paid to stereochemical homogeneity, and diastereomeric mixtures of compounds were often produced. In the future, a greater reliance on methods of asymmetric synthesis to furnish enantiopure compounds is probable. The potential to build synthetic macrolides, for example, is illustrated by solid-phase iterative asymmetric aldol methodology combined with stereoselective reduction to prepare [4] chiral polyols such as structure **10** (Fig. 3) with seven stereocentres. Interestingly, the solid-phase synthesis of structure **10** had a higher overall yield than the same sequence in solution-phase, with the added advantage of not having to purify intermediates. The desymmetrization of *meso* compounds is another popular route to chiral compounds that is starting to be used in combinatorial chemistry. A solid-phase example [5] features a quasi-*meso* *bis*-sulfonate (Fig. 3, structure **11**), which partitions into a pair of quasi-enantiomeric sulfonates, one resin-bound and the other cleaved, depending on the direction of intramolecular cyclization. Subsequently, nucleophilic displacement affords two enantiomeric products that are building blocks for the oxazolidinone class of antibacterials.

Heterocyclic scaffolds

The cyclization of enamine intermediates to dihydropyridones has been independently reported by two groups [6,7]. These complementary approaches provide compounds such as **12** and **13** (Fig. 4) with differing substitution patterns. In a separate report, synthesis of a library of substituted indoles began with the acylation of eight substituted

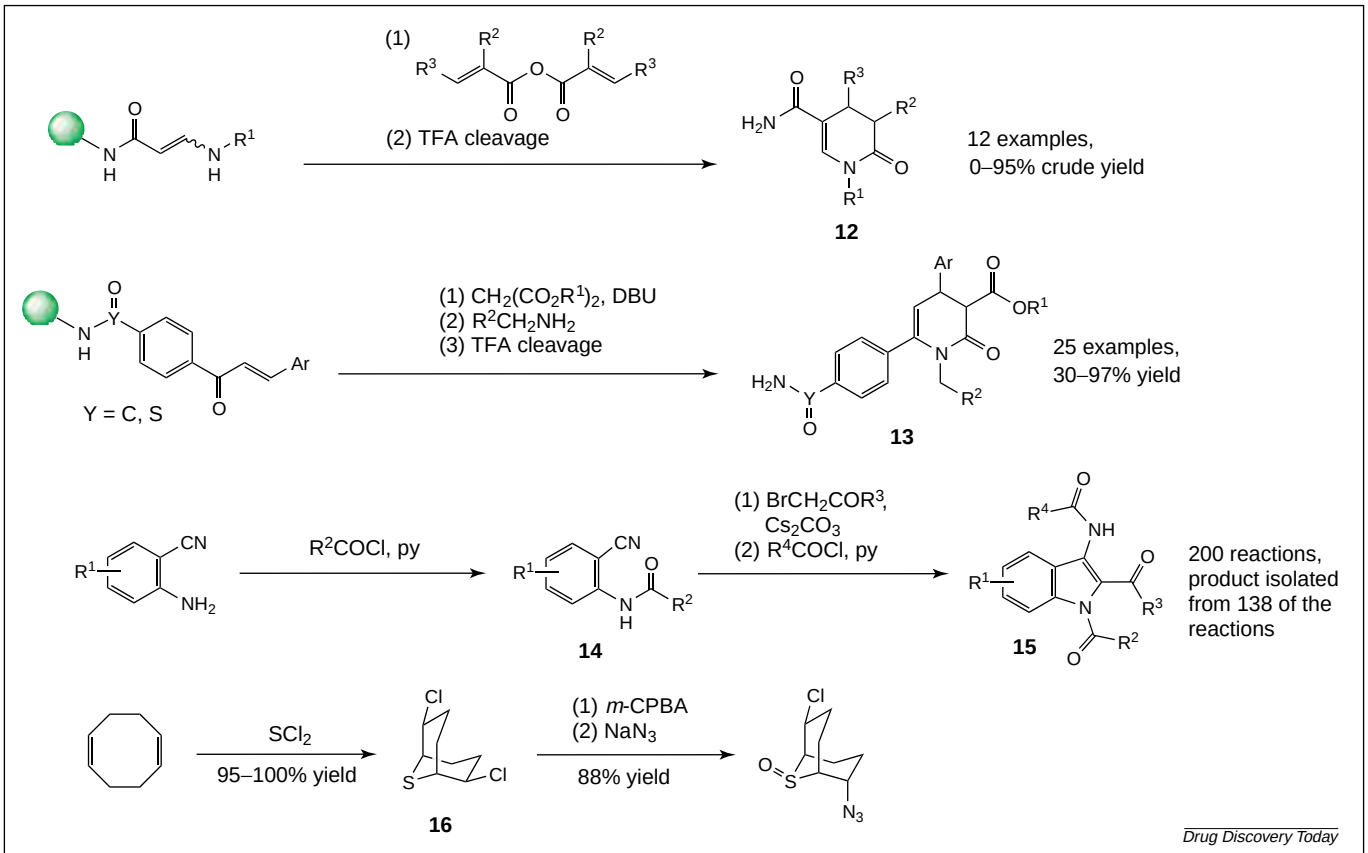

Figure 4. Examples of combinatorial heterocycle synthesis.

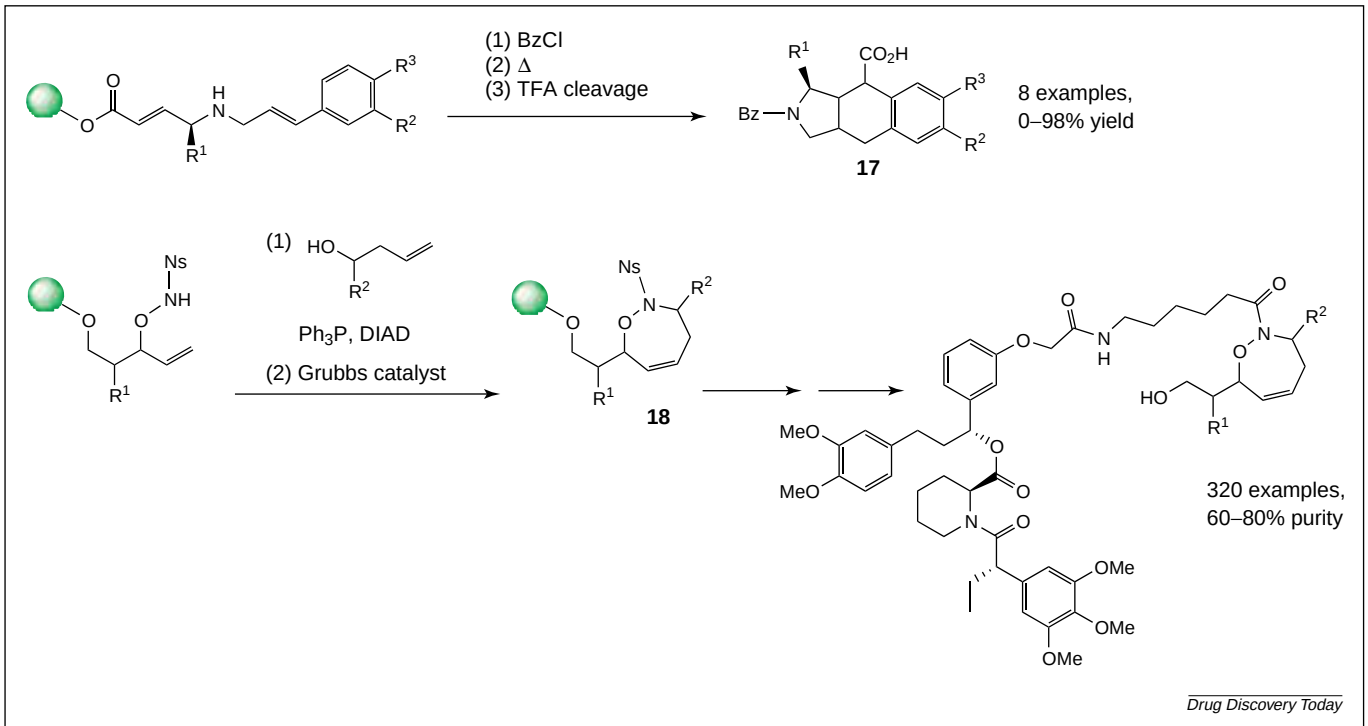

Figure 5. Recent examples of intramolecular cyclizations leading to heterocycles. Abbreviations, *m*-CPBA, *meta*-chloroperbenzoic acid. Ns, 4-nitrobenzenesulfonyl.

α-aminobenzonitriles with a set of acid chlorides [8]. Out of the resulting amides (Fig. 4, structure **14**), the 48 of highest purity were selected for condensation with α-bromoketones in 280 discrete reactions, and the product further acylated to provide indole (Fig. 4, structure **15**) in acceptable yields. Among some of the recent novel scaffolds, the bicyclic heterocycle (Fig. 4, structure **16**) reported by Sharpless [9] stands out for the simplicity of its preparation from inexpensive cyclooctadiene. Nucleophilic displacement of both or one of the two halides was then possible.

Among ring forming reactions, the Diels–Alder cycloaddition in its various guises continues to attract attention, and an intramolecular example by Murray [10] uses vinyl benzenes as the 4π component to give substituted isoindoles (Fig. 5, structure **17**). Another increasingly common cyclization process is ring-closing metathesis, as used in the synthesis of tetrahydrooxazepines [11] (Fig. 5, structure **18**). A library of 320 compounds linked to a synthetic ligand for FK506-binding protein was screened for novel protein–protein heterodimerizers.

Macroheterocycles are of interest for their unusual conformational constraints, and ring closure by carbon–carbon bond formation on solid-phase was the key step in two recent cases. Deslongchamps reported the intramolecular alklyation of a set of allylic chlorides by various malonate esters to give compounds such as structure **19** [12] (Fig. 6). In a library of 96 compounds, 15 out of 24 macrocyclizations were successful. An example from Schreiber involves lithium–halogen exchange and transmetallation, followed by oxidative coupling to produce the kinetically favoured biaryl atropisomer [13] (Fig. 6, structure **20**). The biaryl could also be isomerized to predominantly the thermodynamic atropisomer by heating before resin cleavage.

The ability to transform a common synthetic intermediate into different heterocyclic libraries is an efficient combinatorial strategy. For example, the solid-phase Zincke reaction resulted in pyridinium compounds (Fig. 7, structure **21**), which could also be reduced to tetrahydropyridines (Fig. 7, structure **22**) and piperidines [14] (Fig. 7, structure **23**). A small library of 18 members was prepared as acyclic analogues of vesamicol, an inhibitor of the vesicular acetylcholine transporter. Another example of this strategy featured 1,2-diaza-1,3-butadienes, which were precursors to thiazolinones (Fig. 7, structure **24**) and

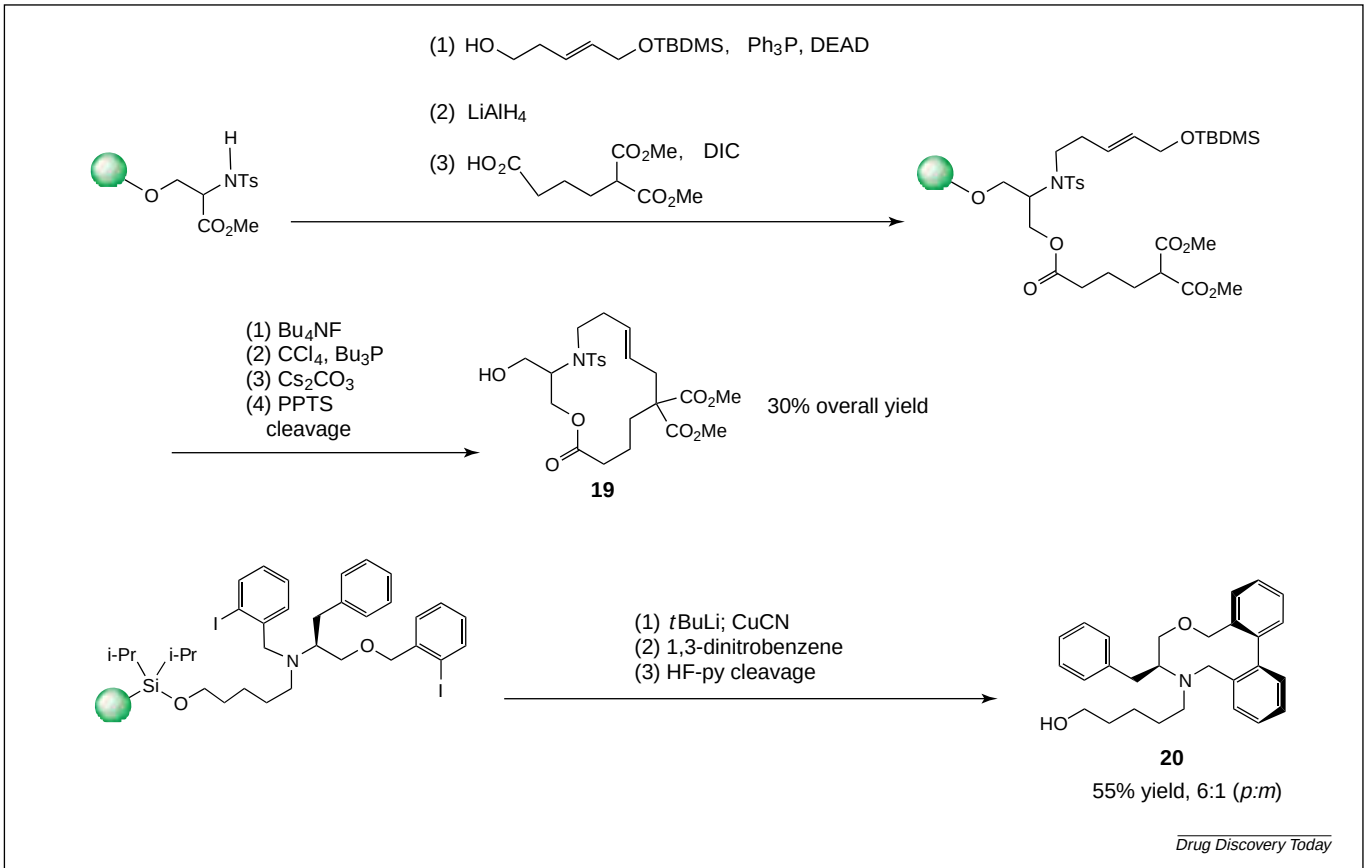

Figure 6. Carbon–carbon bond-forming macrocyclizations on solid-phase. Abbreviations: DEAD, diethyl azodicarboxylate; DIC, diisopropyl carbodiimide; PPTS, pyridinium *para*-toluenesulfonate; TBDMS, *tert*-butyldimethylsilyl; Ts, *para*-toluene sulphonyl.

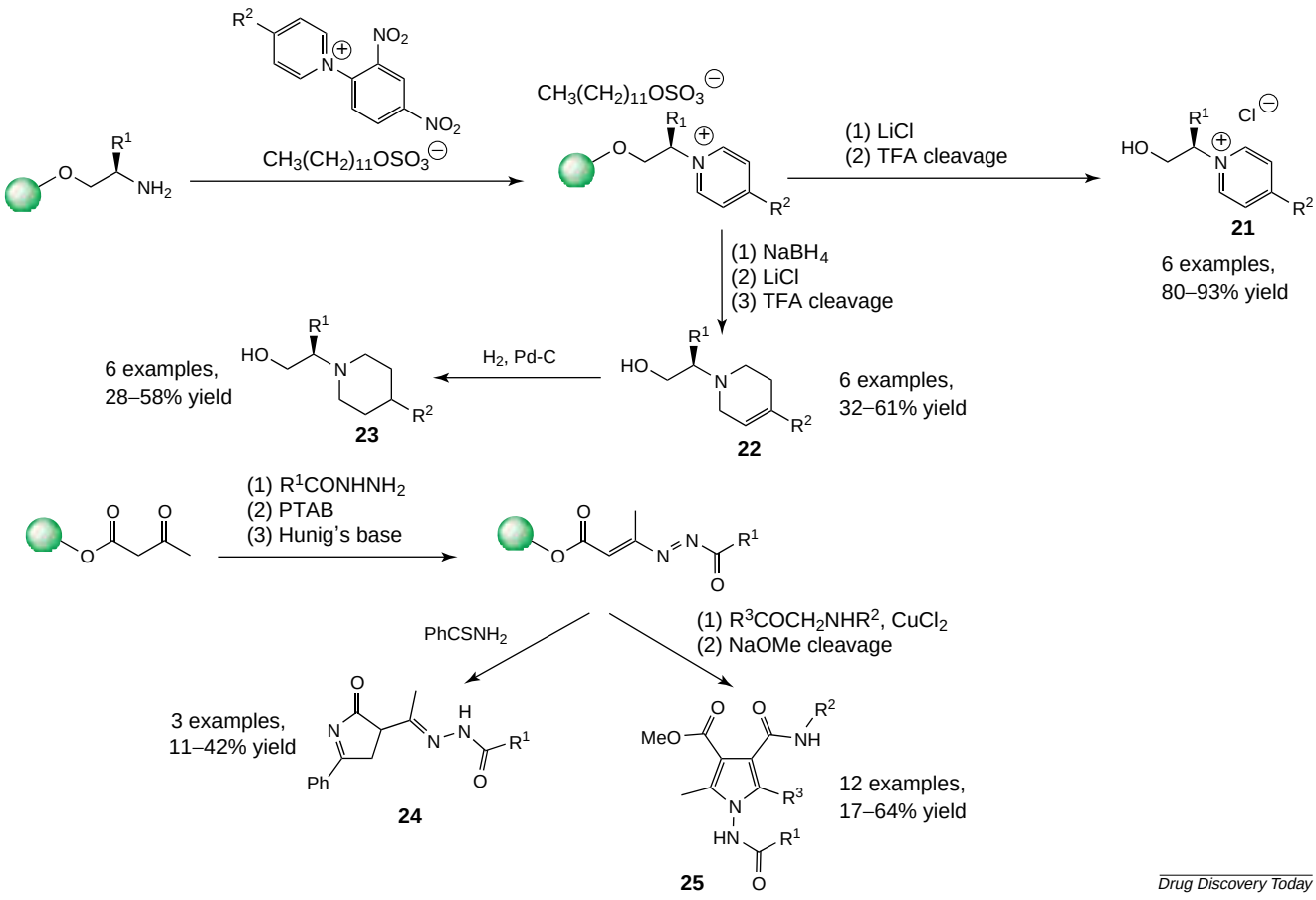

Figure 7. Diverse heterocycles from a common intermediate. Abbreviation: PTAB, phenyltrimethylammonoium bromide.

fully substituted pyrroles [15] (Fig. 7, structure **25**).

Natural product scaffolds

One approach to complex scaffolds is the derivatization of existing natural products. A recent example starts with the cheap alkaloid scopolamine, which was deoxygenated and converted to carbamates [16] (Fig. 8, structure **26**). Mitsunobu inversion of the alcohol to benzoate (Fig. 8, structure **27**) provides an entry to the diastereomeric series, while reductive amination of tropinone followed by isocyanate addition gave ureas (Fig. 8, structure **28**).

A more common strategy, particularly in academia, involves the *de novo* construction of a natural product scaffold. Alcohols (Fig. 9, structure **29**)

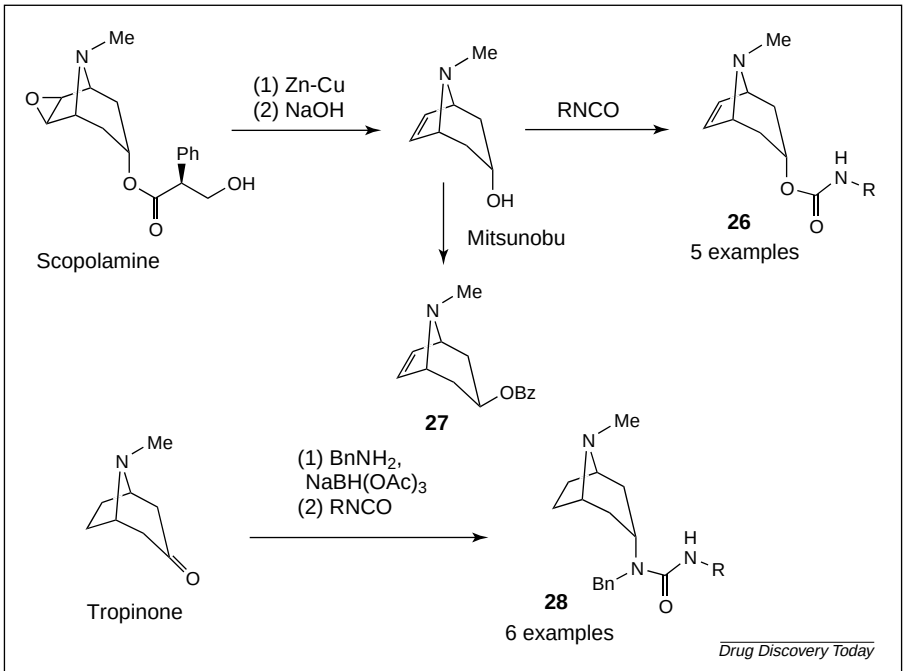

Figure 8. Derivatization of inexpensive natural products.

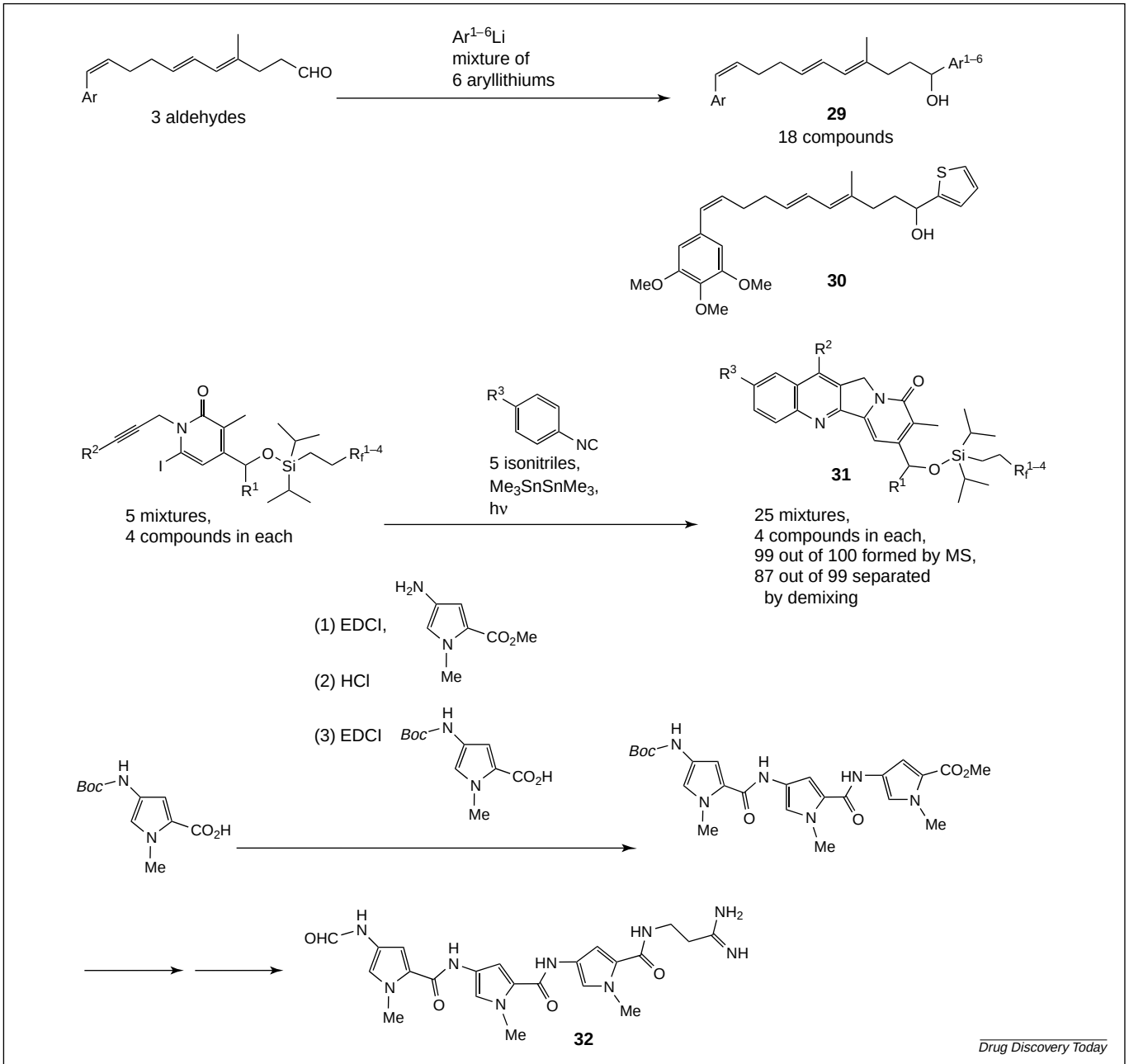

Figure 9. Solution-phase combinatorial synthesis of natural product scaffolds. Abbreviation: EDCI, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

were prepared [17] as pools of six compounds as analogues of the natural product curacin, a tubulin polymerization inhibitor. From the resulting library of 18 compounds, the micromolar lead structure **30** (Fig. 9) was identified. A library of mappicine analogues (Fig. 9, structure **31**) was prepared as mixtures in sets of four, with individual components containing fluorous tags of varying chain length [18]. De-mixing by fluorous chromatography was used later to separate the mixtures back into discrete compounds. Solution-phase synthesis with acid-base workup was used in the total synthesis of distamycin A [19] (Fig. 9, structure **32)**, and the method was then adapted to the preparation of 2640 analogues, which led to the identification of a number of novel DNA-binding polyamides. These novel approaches provide an alternative to the derivatization of existing natural products.

Solid-phase routes to natural product and natural-product-like scaffolds are increasingly common. The intramolecular cyclization of linear tripeptides followed by a

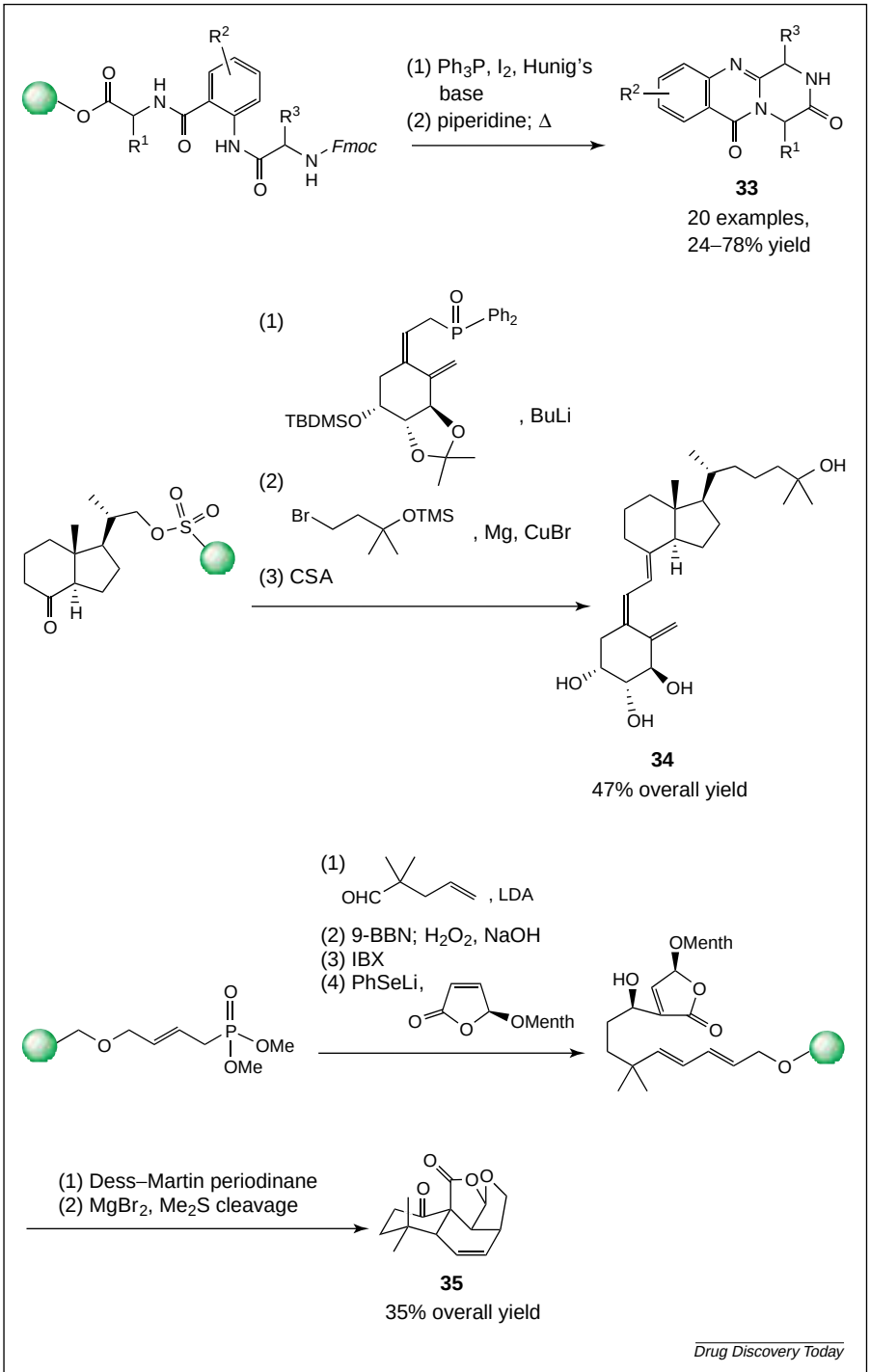

Figure 10. Solid-phase routes to natural product scaffolds. Abbreviations: 9-BBN, 9-borabicyclo[*3.3.1*]nonane; CSA, camphorsulfonic; IBX, *ortho*-iodoxybenzoic acid; LDA, lithium diisopropylamide; Menth, menthyl; TMS, trimethylsilyl.

heterocyclic rearrangement was used in a concise synthesis of fumiquinazoline alkaloids [20] (Fig. 10, structure **33**). The classical vitamin D synthesis by addition of A-ring phosphine oxides to CD-ring synthons was adapted to solid-phase array synthesis to give analogues such as structure **34** [21] (Fig. 10). A recent approach [22] to the framework of marasmane sesquiterpenes features three separate carbon–carbon bond-forming reactions on solid-phase: Horner–Wadsworth–Emmons condensation; a phenylselenide Baylis–Hillman equivalent; and an intramolecular Diels–Alder cycloaddition,to give a tetracycle (Fig. 10, structure **35**).

Solid-phase synthesis is generally preferable to solution-phase synthesis for the preparation of large libraries, as illustrated by two recent examples of natural-product-like scaffolds. The Nicolaou group has disclosed a number of transformations involving selenide resins. For example, a set of *ortho*-prenyl phenols was cyclized to give nine intermediate benzopyran scaffolds [23] (Fig. 11, structure **36**). Depending on the other functionality, these could be further elaborated by various reactions before resin cleavage, and a 10,000-member library was prepared with Irori (San Diego, CA, USA) radio frequency (RF) encoding technology . Phenol oxidative coupling is an important biosynthetic reaction, and it formed the basis for a solid-phase library synthesis of galanthamine analogues [24] (Fig. 11, structure **37**).

Concluding remarks

In a certain sense, it is difficult to decipher the contribution of combinatorial chemistry to the development of therapeutics in the third millennium. The underlying principles and techniques are now so well entrenched within the pharmaceutical industry that it is hard to imagine lead discovery or optimization without a combinatorial component. What is indisputable is that high-throughput synthesis offers unique opportunities to accelerate the preparation of novel compounds. Gratifyingly, we are no longer constrained in the types of structures or organic reactions amenable to parallel synthesis and further advances can be absolutely guaranteed.

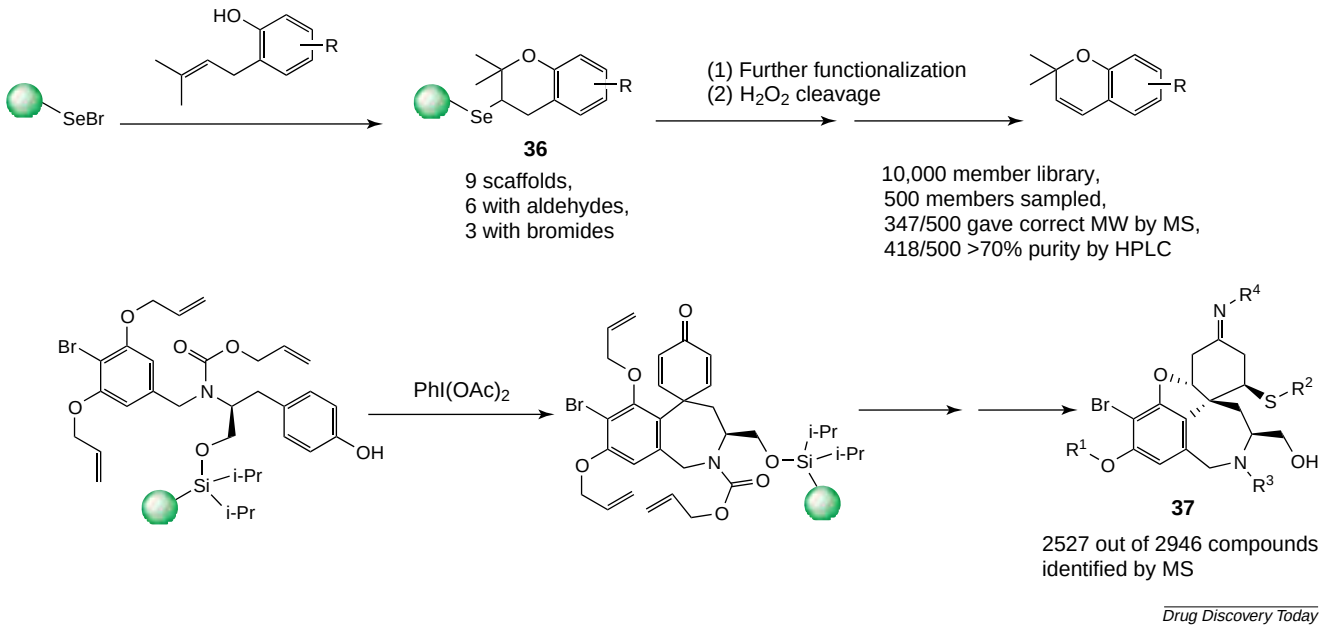

Figure 11. Examples of large natural product-like libraries.

References

1 Pátek, M. *et al.* (2000) Solid-phase synthesis of substituted guanidines using a novel acid labile linker. *J. Comb. Chem.* 2, 370–377

2 Organ, M.G. *et al.* (2001) Solution phase synthesis of libraries of variably substituted olefin scaffolds: a library of allylic amines. *J. Comb. Chem.* 3, 64–67

3 Zaragoza, F. and Stephensen, H. (2000) Sequential nucleophilic substitution: a powerful strategy for the solid-phase production of diverse compound libraries. *Angew. Chem. Int. Ed.* 39, 554–556

4 Paterson, I. *et al.* (2000) A combinatorial approach to polyketide-type libraries by iterative asymmetric aldol reactions performed on solid support. *Angew. Chem. Int. Ed.* 39, 3315–3319

5 ten Holte, P. *et al.* (2001) Polymer-aided stereodivergent synthesis (PASS): a new concept for the discrete preparation of optical antipodes. *Org. Lett.* 3, 1093–1095

6 Paulvannan, K. and Chen, T. (2000) Solid-phase synthesis of 1,2,3,4-tetrahydro-2-pyridones via aza-annulation of enamines. *J. Org. Chem.* 65, 6160–6166

7 Wagman, A.S. *et al.* (2000) Simple and efficient synthesis of 3,4-dihydro-2-pyridones via novel solid-supported aza-annulation. *J. Org. Chem.* 65, 9103–9113

8 Nettekoven, M. (2001) Combinatorial synthesis of libraries of indole derivatives. *Bioorg. Med. Chem. Lett.* 11, 2169–2171

9 Converso, A. *et al.* (2001) 2,6-Dichloro-9-thiabicyclo[*3.3.1*]nonane: a privileged, bivalent scaffold for the display of nucleophilic components. *J. Org. Chem.* 66, 4386–4392

10 Sun, S. *et al.* (2000) Vinyl benzenes as dienes in mild solid-phase Diels–Alder reactions. *J. Org. Chem.* 65, 2555–2559

11 Koide, K. *et al.* (2001) A synthetic library of cell-permeable molecules. *J. Am. Chem. Soc.* 123, 398–408

12 Ramaseshan, M. *et al.* (2000) Solid phase combinatorial synthesis of a library of macro-heterocycles and related acyclic compounds. *J. Comb. Chem.* 2, 615–623

13 Spring, D.R. *et al.* (2000) Towards diversity-oriented, stereoselective syntheses of biaryl- or bis(aryl)metal-containing medium rings. *J. Am. Chem. Soc.* 122, 5656–5657

14 Eda, M. and Kurth, M.J. (2001) Solid-phase Zincke route to pyridinium, tetrahydropyridine, and piperidine derivatives: vesamicol analogs. *Tetrahedron Lett.* 42, 2063–2068

15 Attanasi, O.A. *et al.* (2001) Solid-phase synthesis of 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones, 4-aminocarbonylpyrroles, 4-methoxy-1*H*-pyrazol-5(2*H*)-ones and 2-thiazolin-4-ones from polymer-bound 1,2-diaza-1,3-butadienes. *Tetrahedron* 57, 5855–5863

16 Aberle, N.S. *et al.* (2001) Parallel modification of tropane alkaloids. *Tetrahedron Lett.* 42, 1975–1977

17 Wipf, P. *et al.* (2000) Synthesis and biological evaluation of a focused mixture library of analogues of the antimitotic marine natural product curacin A. *J. Am. Chem. Soc.* 122, 9391–9395

18 Luo, Z.Y. *et al.* (2001) Fluorous mixture synthesis: a fluorous-tagging strategy for the synthesis and separation of mixtures of organic compounds. *Science* 291, 1766–1769

19 Boger, D.L. *et al.* (2000) Total synthesis of distamycin A and 2640 analogues: a solution-phase combinatorial approach to the discovery of new, bioactive DNA binding agents and development of a rapid, high-throughput screen for determining relative DNA binding affinity or DNA binding sequence selectivity. *J. Am. Chem. Soc.* 122, 6382–6394

20 Wang, H. and Ganesan, A. (2000) Total synthesis of the fumiquinazoline alkaloids: Solid-phase studies. *J. Comb. Chem.* 2, 186–194

21 Hijikuro, I. *et al.* (2001) Parallel synthesis of a vitamin D-3 library in the solid-phase. *J. Am. Chem. Soc.* 123, 3716–3722

22 Reiser, U. and Jauch, J. (2001) Synthetic studies towards mniopetals (III). Solid phase organic synthesis of a key intermediate for combinatorial synthesis of mniopetals, kuehneromycins and marasmanes. *Synlett* 90–92

23 Nicolaou, K.C. *et al.* (2000) Natural product-like combinatorial libraries based on privileged structures. 2. Construction of a 10,000-membered benzopyran library by directed split-and-pool chemistry using NanoKans and optical encoding. *J. Am. Chem. Soc.* 122, 9954–9967

24 Pelish, H.E. *et al.* (2001) Use of biomimetic diversity-oriented synthesis to discover galanthamine-like molecules with biological properties beyond those of the natural product. *J. Am. Chem. Soc.* 123, 6740–6741