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Medicinal Chemistry

Synthesis of Natural Product Inspired Compound Collections

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Natural products, their derivatives, and their analogues are among the most important sources for new drug candidates and tools for chemical biology and medicinal chemistry research. Therefore, there is a need for the development of efficient synthesis methods which give access to natural product derived and inspired compound collections. To meet this challenge, the requirements of multistep stereoselective syntheses, and the logic and methodology of natural product total synthesis need to be translated and adapted to the methods and formats for the synthesis of compound collections. Recent developments in the synthesis of natural product inspired compound collections having carbocyclic and heterocyclic scaffolds highlight the fact that this goal can be successfully attained. The progress made has paved the way for the integration of natural product inspired compound collections into medicinal chemistry and chemical biology research.

1. Introduction

Bioactive secondary metabolites (natural products) isolated from all kingdoms of life have proven to be a rich source of disease modulating drugs throughout the history of medicinal chemistry and pharmaceutical drug development.[1] Additionally, they have served as efficient tools for the study of biological phenomena. For instance, the tubulin-affecting natural products colchicine and the vinca alkaloids have been used in the study of the cytoskeleton and its dynamics, as well as in the development of a new principle for the treatment of cancer, which gives rise to new drugs even today. This example demonstrates the mutual interplay between natural products and organic chemistry, biology, and medicinal chemistry. The pronounced biological activity of natural products has been rationalized by the fact that during biosynthesis, and while participating in their biological role, they interact with multiple proteins as substrates and targets.[2] Given that the number of structural motifs of proteins and natural products is limited (for a structural classification of natural products in a treelike arrangement [SCONP], see reference [2a]), the scaffolds characteristic of natural product classes can be regarded as "*privileged*", and the compound classes derived from or inspired by natural products classes can be regarded as *biologically relevant and prevalidated*.[3] This validation, together with properties such as structural complexity and drug likeness render these compound classes valuable, if not ideal, starting points for medicinal chemistry and chemical biology investigations. However, to satisfy the needs of the medium and high throughput approaches to meet the ever-increasing numbers and types of possible biological targets, such compounds must be accessible in the form of libraries of pure, individual, well-characterized molecules. Therefore, there is a great demand for the development of synthetic methodologies and sequences that combine the power of contemporary organic synthesis with the technology of combinatorial and parallel synthesis. This challenge raises the question as to whether the requirements of stereoselective multistep syntheses (typically >10 individual steps) yielding single stereoisomers can, in general, be met by using compound collection synthesis, and whether the solutions found in the syntheses of natural products can successfully be translated into the synthesis of natural product inspired compound collections.

In this short review we illustrate the state of the art in this field by highlighting selected examples from the recent

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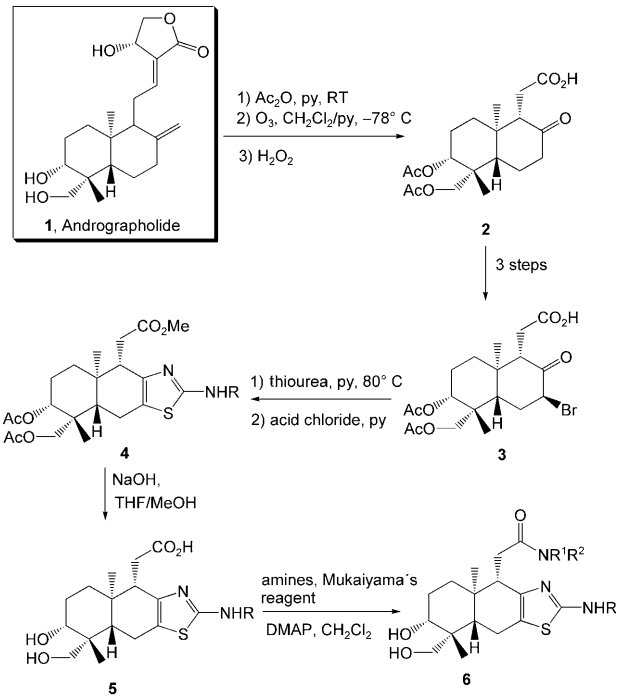
literature. For more comprehensive discussions[4] and early examples[5] the reader is referred elsewhere.

2. Natural Product Derived and Inspired Compound Collections

In the development of compound collections based on natural product structures, syntheses leading to natural products derived and inspired collections should be differentiated because they are characterized by fairly different synthetic requirements.[6] In natural product derived compound collections the library scaffold is identical to the scaffold of a leading natural product. The scaffold is typically obtained by chemical modification or degradation of the isolated natural product rather than by multistep synthesis. The substitution pattern is largely predetermined by the reactivity of the natural product and natural product scaffold structure, and variation of the stereochemistry is often not possible. The library members are usually synthesized in a step-by-step derivatization of the existing scaffold.

An illustrative example for the synthesis of a natural product derived collection is the andrographolide-derived library from Analyticon (Scheme 1).[7] Andrographolide is a diterpene lactone isolated from *Andrographis paniculata*, a plant used in traditional Chinese and Indian medicine. The synthesis of the library was initiated with the natural product itself. Andrographolide (**1**) was transformed into **2** in a three-step procedure involving acetylation, degradation through ozonolysis, and subsequent oxidative workup. The degradation product **2** was used as the starting point for the generation of several different libraries. For instance, to generate an andrographolide-based library having an embedded thiazole moiety, degradation product **2** was α brominated to give β-isomer **3**. The bromide was then subjected to thiazole formation using various thioureas. Subsequent acylation of the amino group using acid chlorides, then saponification of the methyl ester and the acetate groups using 5 N NaOH yielded diols **5** in good yield. The final step in the library synthesis consisted of the amidation of the free carboxylic acid with different primary and secondary amines to yield **6**.



Scheme 1. Synthesis of an andrographolide-derived library. py = pyridine, DMAP = 4-dimethylaminopyridine.

This parallel solution phase synthesis produced a 360-membered library. The selection of the synthesized compounds was based on a virtually generated library, and the assessment of its members with respect to physicochemical

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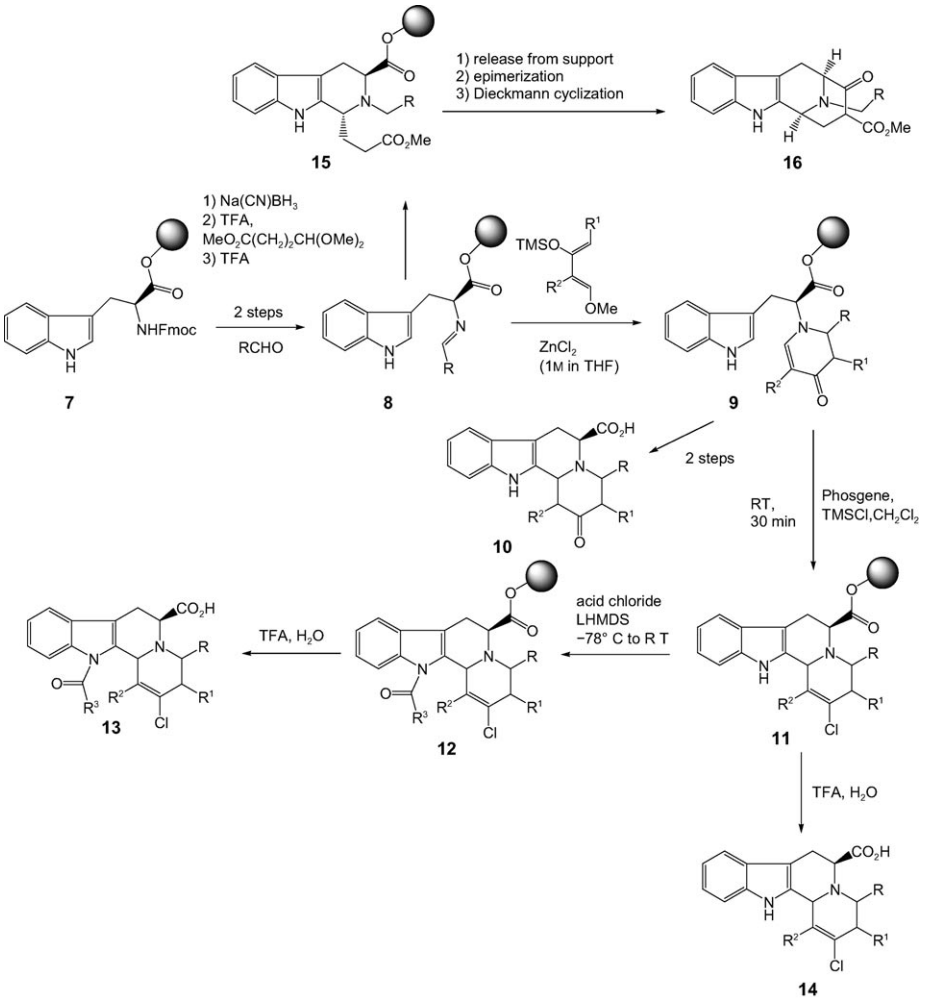
Kamal Kumar was born in Amritsar, in northwest India where he did his M.Sc in Pharma. Sciences at Guru Nanak Dev Univ. Amritsar and later completed his Ph.D. in 2000 under the supervision of Prof. M. P. S. Ishar at the same university. After research stays at Kyoto (Japan) with Prof. M. Node and at Rostock (Germany) with Prof. M. Beller, he moved to Dortmund in 2004 to join Prof. H. Waldmann in the Department of Chemical Biology at the Max Planck Institute of Molecular Physiology. Since May, 2006 he has been leading a group in the department of Chemical Biology at the same institute. His research interests include the development of new synthetic methodolgies for natural product based libraries, cascade reactions, organocatalyzed annulations, and probing biological functions using small molecules.

parameters such as oral bioavailability (e.g. Lipinski parameters[8] TPSA, and number of rotatable bonds[9]) and the absence of unwanted fragments, thus ensuring the pharmacological relevance of the compounds.

In natural product inspired compound collections the scaffold is typically closely related, but not identical, to scaffold of the guiding natural product. Individual library members are synthesized by multistep sequences during which the scaffold is built up from successively assembled building blocks, and the different substituents are introduced in the course of the synthesis rather than by subsequent derivatization of, for example, a particular functional group. The substitution pattern of the products may differ significantly from that of the guiding natural product, and importantly the stereochemistry may also be varied by synthesis (e.g. synthesis of enantiomers). Natural product inspired syntheses more closely resemble the logic and stringencies of natural product total synthesis endeavors. An illustrative example is the synthesis of a library having an indoloquinolizidine core structure (Scheme 2).[6]



Scheme 2. Synthesis of natural product inspired collections of indolo-quinolizidines and tetracyclic β-ketoester alkaloids. Fmoc = 9-fluorenylmethoxycarbonyl, TFA = trifluoroacetic acid, LHMDS = lithiumhexamethyldisilazide.

Natural products containing the indolo[2,3-*a*]quinolizidine framework display a wide range of biological activities; for example, the antiplasmodial agent dihydrousambarensine,[10] the antiviral natural product hirsutine,[11] as well as the cytotoxic compound 10-hydroxyangustine.[12] A collection of 450 compounds containing this scaffold was synthesized on solid phase by means of a six to eight-step synthetic sequence employing the following key steps: 1) Lewis acid mediated Mannich/Michael reaction between immobilized D- or L-tryptophan imines **8** and electron-rich silyloxy dienes, 2) subsequent acid- or phosgene-mediated cyclization of enaminones **9** to tetracyclic ketones **10** and vinyl chlorides **11**, 3) derivatization, and 4) base- or acid-mediated release of indoloquinolizidines **11**, **13**, and **14** from the solid phase (Scheme 2). The target compounds were obtained in high overall yield, and the isomeric mixtures were separated by HPLC methods to give isomers in greater than 99% purity for subsequent screening.[6a,b]

Similarly, tryptophan imines **8** were employed to synthesize a collection of tetracyclic indole derivatives (**16**) reminiscent of macroline natural products, a family of more than 120 indole alkaloids having a common tetracyclic, cycloocta[*b*]indolo framework.[6c] The reductive amination of imines **8** and subsequent Pictet–Spengler reaction with methyl-4,4-dimethoxybutyrate resulted in the formation of 1,3-*trans*-β-carbolines **15**. However, a 1,3-*cis* arrangement of the pendant groups is required to access the tetracyclic framework. Therefore **15** was released from the solid support and then regioselectively epimerized under basic reaction conditions to yield the desired *cis* isomers, which were then subjected to Dieckmann cyclization to give the β-ketoesters **16**. On the basis of this sequence, a library of approximately 100 isomerically pure tetracyclic alkaloid analogues, having a purity of greater than 90%, was synthesized. From these natural product inspired compound collections (Scheme 2), two compounds having the scaffolds similar to **14** were found to inhibit the dual specificity phosphatase Cdc25A with a potency similar to that of the guiding natural products. Also, the natural product inspired collection yielded potent inhibitors of the tyrosine phosphatase MptpB.

Of course, the characterization of compound collections as natural product derived or natural product inspired may not have to be mutually exclusive and become a matter of semantics. It is easily conceivable that the synthesis of a

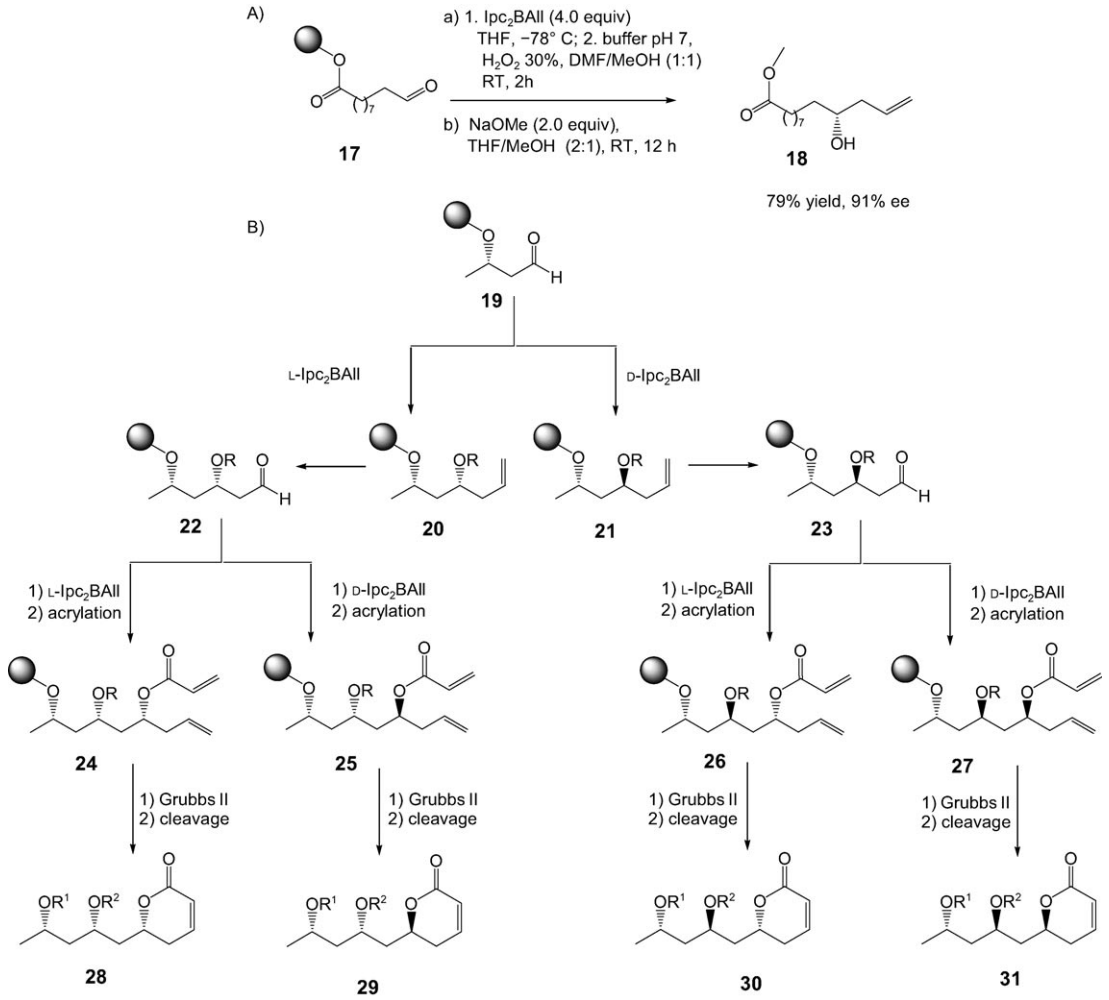
natural product inspired collection will lead to a scaffold identical to a natural product, and vice-versa, the synthesis of a natural product derived collection may include the variation of a stereocenter or substituent patterns. We employ these two terms primarily to differentiate between the basic synthetic approaches (derivatization versus assembly of the scaffold) and the associated differences in the synthetic strategies.

In light of the synthesis challenges described above, this review focuses on the synthesis of natural product inspired compound collections.

3. Synthesis Format: Solid Phase, Solution Phase, Tagging, and Cascade Reactions

For the synthesis of natural product based collections, different formats have been introduced. Very frequently the multistep synthetic sequences required for generating natural product inspired collections are executed on the solid phase.[13] This approach has the advantage that all intermediate reagents are readily removed at intermediary steps and the accumulation of reagents is avoided. However, it requires that the reaction conditions of the transformations established in solution be adapted to the requirements of the solid phase (e.g. solvent). One example is an enantioselective carbonyl allylation—one of the most important methods of organic synthesis—for the stereoselective solid phase synthesis of a collection of natural product inspired δ lactones (Scheme 3).[14] To identify the reaction conditions that would give rise to allylation products in high enantioselectivity and yield, the immobilized aldehyde **17**, a synthesized model compound on a polystyrene resin, was subjected to allylation with *B*-allyl(diisopinocamphenyl) borane (Ipc_2BAll) (Scheme 3) under different reaction conditions. After an oxidative workup, homoallyl alcohol **18** (Scheme 3 A) was released from the resin.

The high yields and enantiomeric excesses of the products from the solid-phase allylation of aldehydes, indicate the usefulness of this methodology in natural product based combinatorial synthesis. This methodology was eventually employed as the key reaction in the synthesis of all eight stereoisomers of the natural product cryptocarya diacetate, an α,β-unsaturated δ lactone isolated from *Cryptocarya latifolia*, which is representative of a large group of biologically active secondary metabolites. The synthesis design included multi-



Scheme 3. Enantioselective solid phase synthesis of a δ-lactone collection. Grubbs II = Grubbs catalyst, second generation, DMF = *N*,*N*-dimethylformamide.

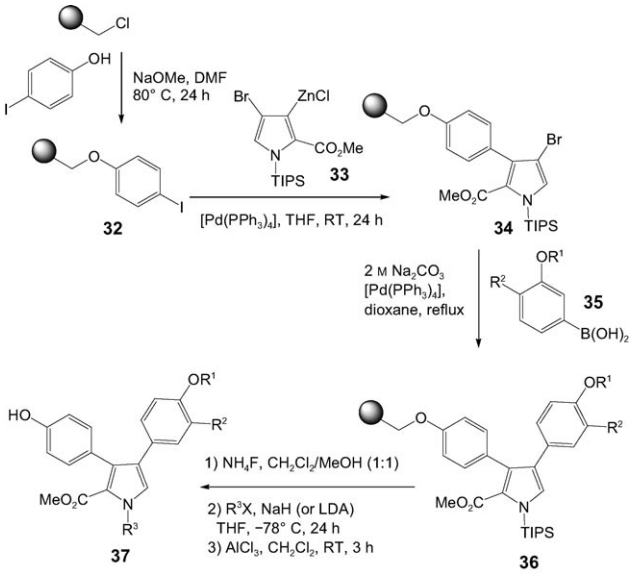
ple stereocomplementary allylation reactions on the solid phase and subsequent ring-closing metathesis to access the natural product analogues (Scheme 3 B). Initially, allylation of the polymer-bound aldehyde **19** using L-Ipc_2BAll yielded **20**, which was formed in a *syn*/*anti* ratio of 85:15. After careful ozonolysis of the double bond for six minutes, the resulting aldehyde was subjected to a second allylation using L-Ipc_2BAll, and the formed secondary alcohol was converted into acrylic acid ester **24**. A ring-closing metathesis reaction employing the Grubbs II catalyst led to formation of the α,β-unsaturated lactone **28**. The release of **28** from the solid support, consecutive cleavage of the silyl group by treatment with trifluoroacetic acid, and subsequent acetylation yielded a mixture of four stereoisomers, from which the all-*syn* isomer of cryptocarya diacetate was isolated (flash chromatography) in 11% overall yield after 11 steps. On the basis of this reaction sequence, the eight possible stereoisomeric configurations of the natural product scaffold were generated by employing the allylation reactions in a stereocomplementary fashion (Scheme 3).

This example highlights that long multistep synthetic sequences leading to natural product inspired collections of individual stereoisomers can be carried out successfully. Various established enantio- and diastereoselective organic synthesis methods, which define the state of the art in total synthesis, have successfully been adapted to the solid phase (see below and for a review see reference [15]).

The advances made in transition-metal-catalyzed coupling reactions and their successful implementation in solid phase synthesis has facilitated the synthesis of natural product based compound collections. For example, the lamellarins are an important group of marine natural compounds having a pyrrole ring as the core structure of their skeleton.[16] A modular approach to these natural products on solid phase, including assembly of the appropriate building blocks through palladium-catalyzed coupling reactions, was developed by Albericio and Álvarez (Scheme 4).[17]

Resin-bound iodophenol (**32**) was generated by displacing the Cl of the resin with a phenoxy anion. The palladium(0)-catalyzed Negishi cross-coupling reaction of the organometallic compound **33** with **32** yielded the bromopyrrole **34**. A Suzuki reaction served as the second palladium-catalyzed coupling reaction to facilitate an aryl–pyrrole bond formation. Boronic acids (**35**) and Pd catalysts were employed in refluxing dioxane to generate compounds **36**. Finally, removal of the TIPS group and N-alkylation of the pyrrole led to a lamellarine analogue collection (**37**). The synthesis provided an efficient solid-phase strategy for the preparation of the pyrrole-containing alkaloids, lamellarins Q and O.

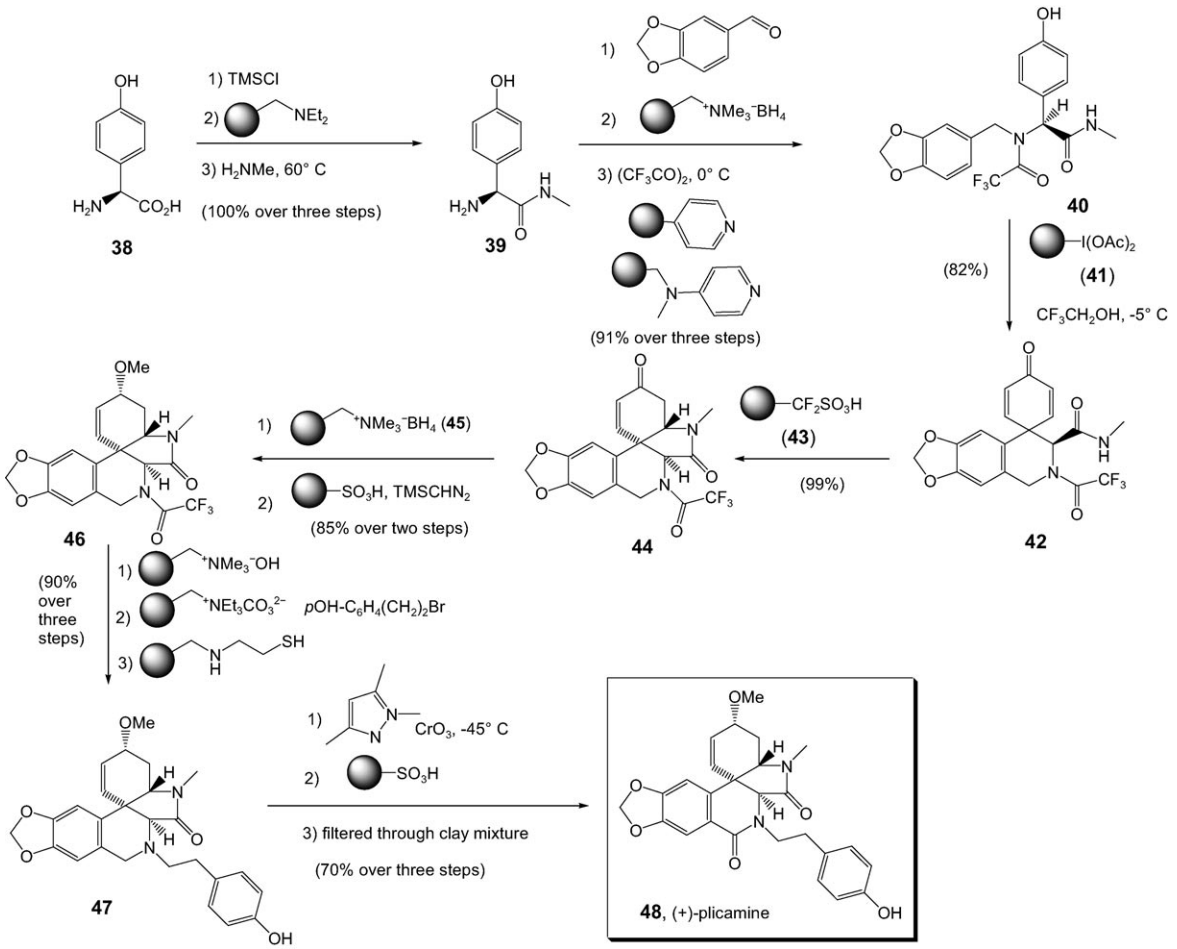
A viable alternative to solid phase synthesis of natural products inspired collections is a multistep solution phase synthesis that proceeds without isolation of the intermediates. Surprisingly, in many cases successive multistep sequences can be carried out in one pot, leading to product mixtures which then need to be separated. Such approaches often involve the development of domino and multicomponent reactions, however, they have not been employed often for the synthesis of natural product inspired compound collections.[18]



Scheme 4. Solid phase synthesis of a lamellarin-based collection. TIPS = triisopropylsilyl, LDA = lithium diisopropylamide.

A powerful technology is the use of polymer-immobilized scavenger reagents for trapping excess reagents after intermediate steps, thereby avoiding interference of the reagents with subsequent reaction steps, and rendering the final reaction mixture amenable to product separation.[19] An illustrative example comes from the structure of (+)-plicamine, a member of the *Amaryllidaceae* alkaloids. Ley and co-workers reported the first total synthesis of this alkaloid and its enantiomer, which included a combination of supported reagents and scavengers to effect the synthetic steps.[20] The polymer supported hypervalent iodine reagent **41** (Scheme 5) was used to convert **40** into spirodienone **42**, which was then converted into **44** by a Nafion-H (fluorosulfonic acid resin, **43**) catalyst to quantitatively form the pentacyclic core (**44**) of the natural product. After stereo- and regioselective reduction of **44** using resin-bound borohydride, the sterically hindered intermediate alcohol was then methylated by treatment with trimethylsilyl diazomethane and sulfonic acid resin to give **46**. Compound **46** was then transformed into **47** in three steps. The final oxidation of amine **47** to (+)-plicamine (**48**) was rather tricky, and was achieved using CrO_3 and 3,5-dimethylpyrazole, and then Amberlyst 15 resin as a scavenger. The chromium salts were efficiently removed by filtration through a mixture of Varian Chem Elut CE 1005 and Montomorillonite k10 clay to yield (+)-plicamine (**48**, Scheme 5).

An elegant alternative to this strategy is fluorous synthesis which employs "tagging" of the building blocks during library synthesis by using fluorinated hydrocarbons to encode structure and facilitate product isolation.[21] Fluorous synthesis successfully integrates solution-phase reaction conditions with phase-tag separation in "beadless" high-speed synthetic technology. Fluorous molecules contain a perfluorinated domain for fluorous separation, which can be achieved by fluorous silica gel-based solid-phase extraction or HPLC methods, without necessitating the use of fluorous solvents.[22]

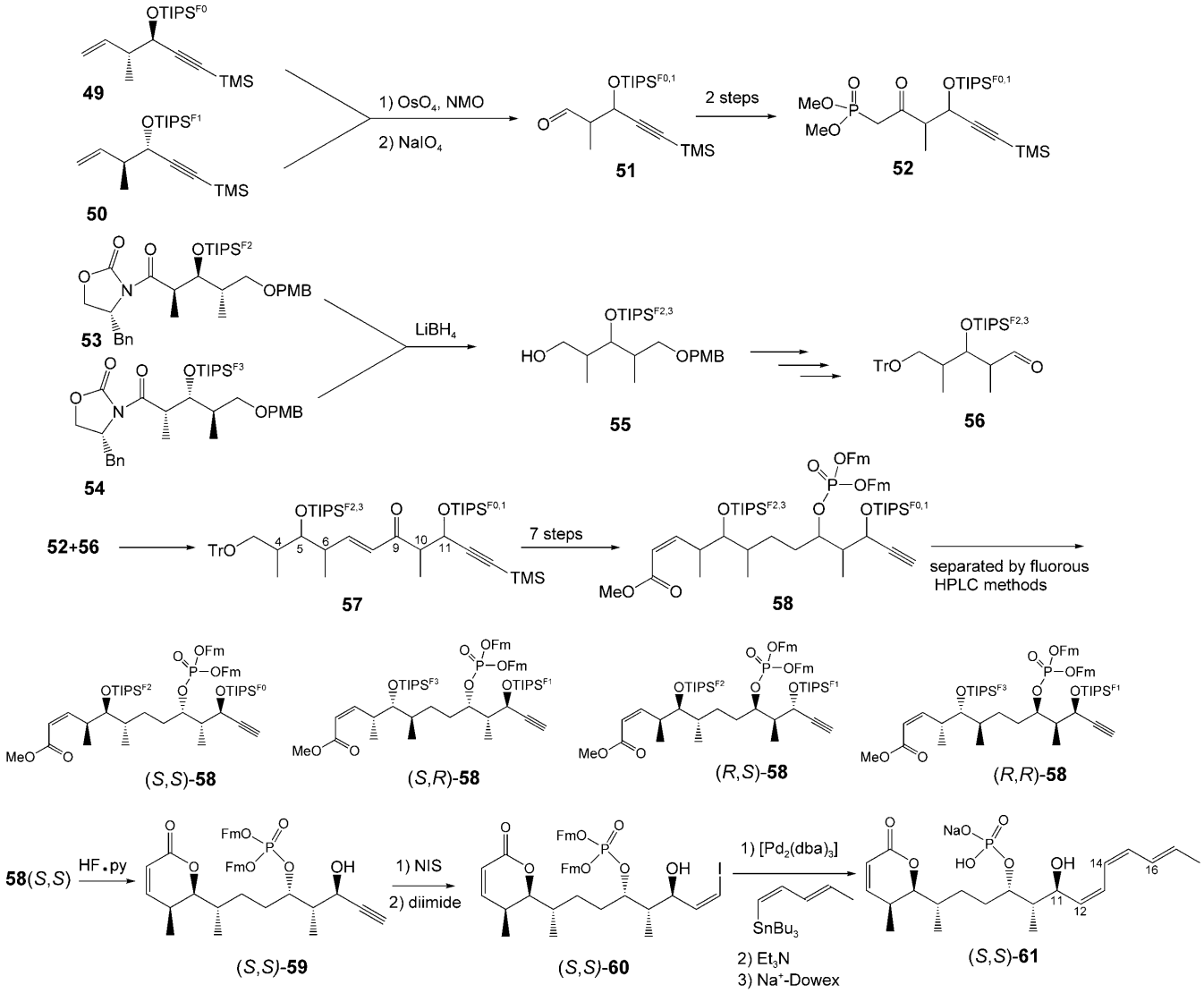


Scheme 5. Total synthesis of (+)-plicamine using supported reagents.

Curran and co-workers used the fluorous synthesis technique to synthesize the four isomers of cytostatin,[23] an anticancer natural product which was isolated from the culture broth of *Streptomyces sp.* (Scheme 6). The four isomers were obtained in several steps from a single four-compound mixture of fluorous-tagged quasiisomers **57** ("quasi" because the compounds have different fluorous tags and are not true isomers). Quasiisomers **57** were obtained from the coupling between fluorous-tagged quasiracemic aldehydes **56** and quasiracemic ketophosphonates **52** by a Horner–Wadsworth–Emmons (HWE) reaction. The configurations of the stereocenters at C4–C6 (*SSS* or *RRR*) and C9–C11 (*SSS* or *RRR*) were encoded using differing silyl groups. Since each quasiisomer has a different number of fluorine atoms, the separation[22a] of a late stage mixture by fluorous HPLC methods can be used to provide its individual components. The fluorine atoms are distributed over two silyl groups, so their approximate additivity upon HPLC separation is important. The syntheses of quasiracemates **56** and **52** are summarized in Scheme 6. To access the quasiracemate **56**, a readily available Evans aldol adduct and its enantiomer were tagged with different fluorous silyl groups to encode the configurations, and then the tagged products **53** and **54** were combined. Reductive removal of the Evans auxiliary using $LiBH_4$ afforded the primary alcohol **55** in 77% yield, which was then protected with a trityl group. Selective removal of the *para*-methoxybenzyl (PMB) group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and subsequent oxidation using Dess–Martin periodinane (DMP) gave the fluorous quasiracemic mixture of aldehydes **56** in 84% yield.

To synthesize the quasiracemate **52** (Scheme 6), the isomerically pure and tagged enantiomers (*R*,*R*)-**49** and (*S*,*S*)-**50** (prepared by the Brown–Ramachandran allylboration and then protection using a tagged silyl group) were combined and then treated with OsO_4 and *N*-methylmorpholine-*N*-oxide (NMO) in *t*BuOH/H_2O (1:1) to provide a mixture of diols, which was then treated with $NaIO_4$ to afford **51** in 90% yield over two steps. Treatment of aldehyde **51** with the lithium salt of $(MeO)_2P(O)CH_3$, and subsequent oxidation using DMP, afforded the fluorous quasiracemic mixture of keto phosphonate **52** in 82% yield over two steps.

The coupling of the fragments and the subsequent seven-step synthesis were carried out using the mixture of the four quasiisomers. A HWE reaction between **52** and **56** provided the enone **57** in 80% yield. A seven-step procedure involving selective enone and ketone reductions, oxidation of an alcohol to an aldehyde, and Still–Gennari olefination gave α,β-unsaturated esters **58** in good overall yield. Prior to removal of the fluorous tags, the mixture was separated into



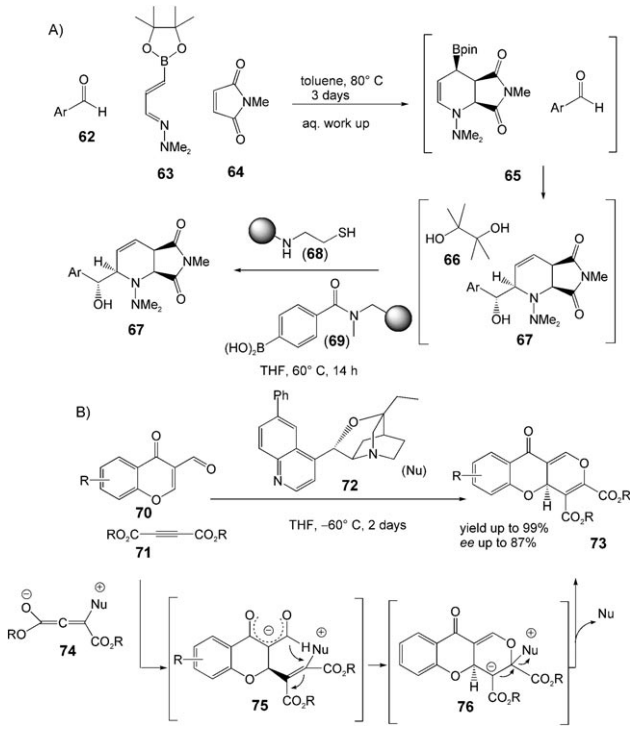
Scheme 6. Synthesis of cytostatin analogues employing a fluorous tagging strategy. Bn = benzyl, Fm = 9-fluorenylmethyl, TIPSF = triisopropylfluorosilyl, dba = dibenzylideneacetone.

the four individual quasiisomers [(*S*,*S*)-**58**, (*S*,*R*)-**58**, (*R*,*S*)-**58**, (*R*,*R*)-**58**] by preparative fluorous HPLC methods.

The remaining steps were carried out on each isomer individually (Scheme 6). The two silyl groups in (*S*,*S*)-**58** were removed using HF/pyridine to provide lactone (*S*,*S*)-**59** in 59% yield. Iodination of the triple bond with *N*-iodosuccinimide (NIS) in the presence of a catalytic amount of $AgNO_3$ afforded an iodoalkyne, which was then reduced to the *Z*-iodoalkene (*S*,*S*)-**60** having a diimide. A Stille coupling was performed using a stannane and $[Pd_2(dba)_3]$ to provide the (12*Z*,14*Z*,16*E*)-triene, which was carefully purified by preparative HPLC methods. The cleavage of the fluorenylmethyl group under basic reaction conditions and subsequent ion-exchange using Dowex provided the cytostatin stereoisomer (*S*,*S*)-**61**. Similarly, the other three isomers [(*R*,*S*)-**61**, (*S*,*R*)-**61**, and (*R*,*R*)-**61**] were synthesized by the same sequence of reactions starting from the appropriate isomer of **58**.

Among the different synthesis formats discussed above, the stepwise solution- and solid-phase syntheses have been investigated most intensively. Domino and cascade reactions have not been developed to a comparable extent for the synthesis of natural product inspired compound collections, despite the early proof-of-principle reported by Tietze et. al.[18d] in which compound classes having natural product scaffolds, or scaffolds closely approximating them, could be accessed efficiently by this approach. The design of such domino sequences leading to natural product inspired compound collections certainly is far from trivial, and possibly of limited generality. However, they offer the potential to access complex molecular scaffolds and libraries derived from an efficient one-pot synthesis. They therefore deserve additional development, and two recent examples supporting this need are highlighted in Scheme 7.

Hall and co-workers developed a one-pot three-component reaction wherein the 1-aza-4-boronbutadiene **63** first undergoes a [4+2] cycloaddition with N-substituted maleimide **64** to afford the bicyclic allylic boronate intermediate **65** (Scheme 7 A).[24] The intermediate **65** then reacts with an aryl



Scheme 7. A cascade/domino approach to library synthesis: A) tandem one-pot synthesis of polysubstituted piperidines; B) organocatalyzed synthesis of natural product inspired tricyclic benzopyrones. pin = pinacol.

aldehyde in a stereocontrolled fashion to give the final polysubstituted piperidine **67**. The efficiency of this tandem synthesis was additionally improved by employing scavenger resins like **68** to remove the excess aldehyde and maleimide, and supported boronic acid **69** to remove the pinacol by-product (**66**). By using a diversitry of hydrazines, maleimides, and aldehydes, a library of 944 polysubstituted piperdines was synthesized.

Inspired by natural products having a tricyclic benzopyrone core and displaying antibacterial activity, a novel [4+2] annulation strategy was developed recently to generate a compound collection of tricyclicbenzopyrones **73** (Scheme 7 B).[25] Two electron-deficient systems, oxadiene **70** and acetylenecarboxylates **71**, were successfully annulated by using nucleophilic catalysis. The zwitterion **74**, generated by treatment of alkynes **71** with organocatalyst **72**, underwent a Michael addition/Michael addition/elimination cascade to generate the desired target structure. By emplyoing a cinchona derived β-isocupreidine, a stereoselective route to (*S*)-**73** was developed.

4. Natural Product Inspired Compound Collections

4.1. Compound Collections Having Carbocyclic Core Structures

Although natural products very often embody oxa- and aza-heterocycles, purely carbocyclic compounds occur frequently in nature. Their structures and biological activities have inspired various compound collection syntheses.

4.1.1. Illudin-Inspired Compound Collection

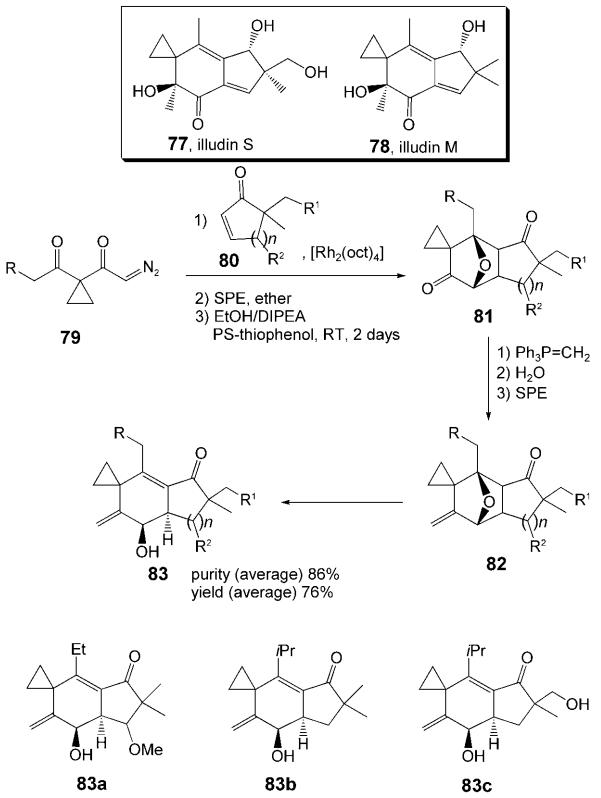
The illudins are sesquiterpenes that were initially discovered as the natural products illudin M and S from the Jack O'Lantern mushroom (*Omphalotus illudens*).[26] They possess an interesting carbocyclic scaffold having a fused cyclohexenone/cyclopentenol ring, and they show a broad range of interesting anticancer activities. To gain additional insight into their biological activities, a 49 member collection of molecules having the illudin core structure was prepared by Pirrung and Liu by using a parallel solution phase approach involving resins for scavenging.[27] The design for the library synthesis was inspired by the work of Padwa et. al and Kinder and Bair,[28] in which the rhodium-catalyzed dipolar cycloaddition of carbonyl ylides and enones was reported. As such, different diazocarbonyl compounds **79** and enones **80** were employed, and in some instances the more accessible enones were used in excess. Polar byproducts were removed by solid-phase extraction (SPE) using SiO_2/CH_2Cl_2, and after solvent exchange the excess enone was removed by means of a thiophenol scavenging resin[29] to give **81** in approximately 70% yield. Subsequent modifications involved selective olefination of a carbonyl group and elimination of the ether bridge to generate **83**. The use of a parallel synthesizer and solid-phase extraction as a purification method facilitated the reaction sequence (Scheme 8).

The library was evaluated for growth inhibition of MCF7 breast cancer cells, H460 non-small lung cancer cell, and SF-268 CNS cells. Three products (**83a–c**) showed complete inhibition of the growth of H460 cells at a 100 μM concentration.

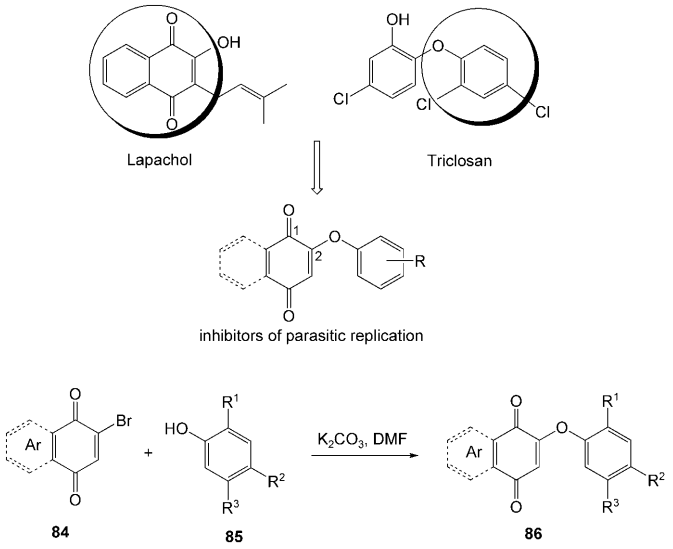
4.1.2. Lapochol-Inspired Naphthoquinone Collection

The design and synthesis of natural product structure-based compound collections are particularly attractive if a link already exists between a given compound class and the desired biological activity.[30] Such a connection was exploited by Cavalli and co-workers in the design of a library endowed with anti-trypanosomal and anti-lesihmanial activity.[31] For the library design, the quinone unit of naturally occurring naphthoquinones was selected as the core structure to which various groups could be introduced.

Naphthoquinones and related quinones constitute one of the major natural product classes having significant activity against leishmania and trypanosoma.[32] Lapachol (Scheme 9) exhibits marked anti-trypanosomal and anti-leishmanicidal activities, without having serious toxic effects in humans.[33] Therefore, based on the 1,4-naphthoquinone and 1,4-anthraquinone natural scaffolds, a small focused collection of 16 compounds was synthesized; a selection of aromatic groups that would mimic a structural element of triclosan were incorporated at position two. Triclosan is a general biocide which was recently demonstrated to kill both procyclic forms and bloodstream forms of *Trypanosoma brucei*.[34] From this small compound collection, several



Scheme 8. Synthesis of an illudin-inspired compound collection. oct = octadiene, DIPEA = *N*,*N*-diisopropylethylamine.

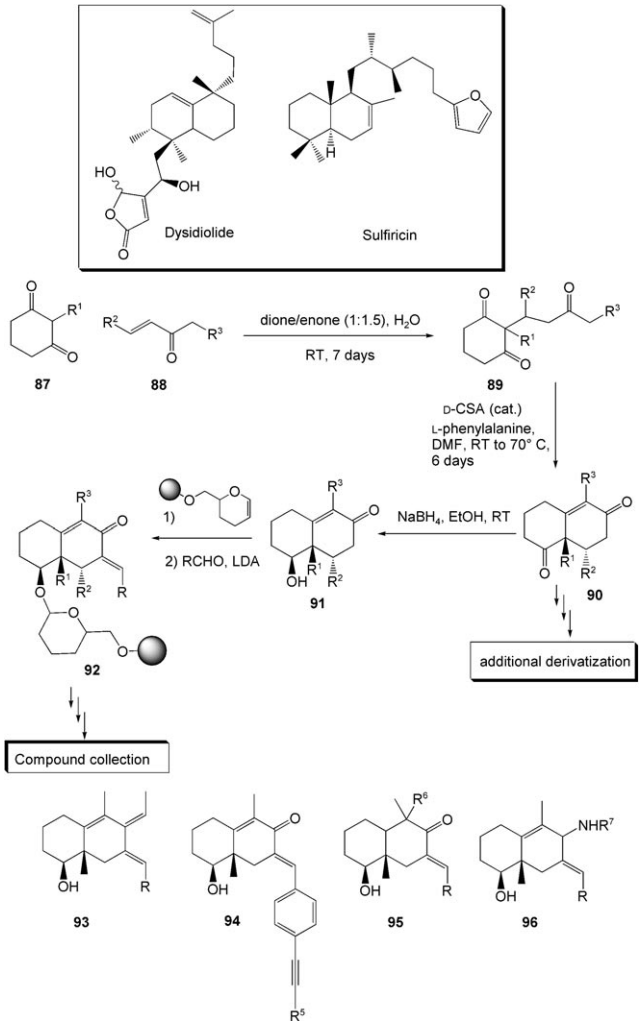


Scheme 9. Synthesis of a naphthoquinone collection inspired by lapochol.

molecules were active against trypanosomes at low concentration, and **86a** (Ar = Ph, $R^1 = R^2 = R^3 = H$) showed an IC_{50} value of 80 nM against the cells of subspecies *T. b. rhodesiense* and a selectivity index (SI) of 74, which is very close to the specifications required by the WHO/TDR for **86a** to be considered an anti-trypanosomatid hit.

4.1.3. A Compound Collection Having a Decalin Core Structure

The decalin core occurs with high frequency in natural products for instance, dysidiolide and sulfiricin (Scheme 10) are natural product inhibitors of the Cdc25A protein phosphatase which is a target in anticancer drug development.[35,36]

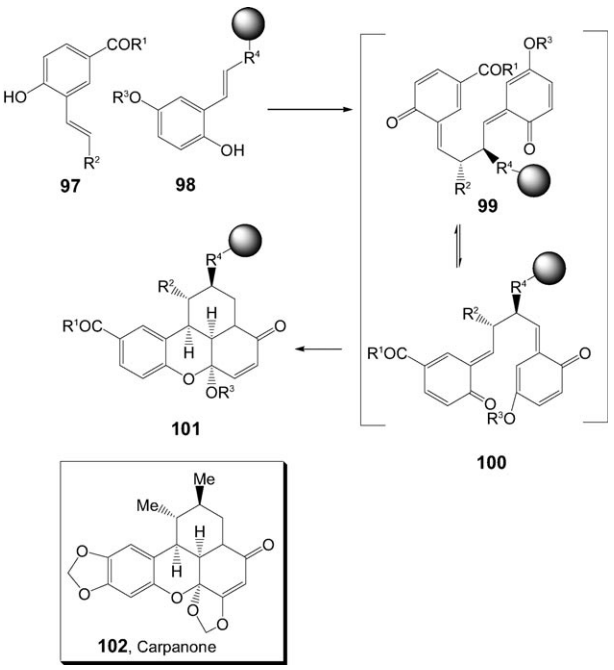


Scheme 10. Solid phase synthesis of a compound collection having a decalin core structure. CSA = camphorsulfonic acid.

Interestingly, a systematic study using sulfiricin revealed that replacing the decalin scaffold of the compound with analogues bearing benzimidazole, benzothiazole, or naphthalene resulted in the loss of the phosphatase-inhibiting activity. Therefore, the decalin moiety can be considered a "privileged" core structure,[37] inspiring the solid phase synthesis of a library having decalin as a core structure. This example of a *biology oriented synthesis* (BIOS)[6,38] demonstrated that natural product inspired compound collections can provide hits not only for a single protein, but also for a group of proteins clustered according to structural similarity in their ligand-sensing cores (*Protein Structure Similarity Clustering*, PSSC).[39]

Differently functionalized decalin derivatives were synthesized in solution and used as building blocks for additional derivatization on the solid support (Scheme 10). Unsaturated decalinols **91** were synthesized by employing the enantioselective Robinson annulation as the key C–C bond-forming step. In addition, intermediate **90** was further derivatized for extension of the compound collection. The decalin-derived alcohols were immobilized on Merrifield resin equipped with a dihydropyranyl linker, and the immobilized aldol condensation products **92** were then subjected to a variety of different transformations to increase the diversity of the library. These reactions included Sonogashira, Suzuki, and Heck reactions, copper-catalyzed conjugate additions, Grignard reactions, alkylation reactions at the α position to a ketone, Wittig reactions, and reductive aminations to yield compound classes **93**–**96** (Scheme 10).

After release from the solid support by treatment with trifluoroacetic acid, the desired compounds were obtained in purities of 23–98 % and then additionally purified by means of preparative HPLC methods. In total, 483 compounds were obtained in multimilligram amounts. Typical overall yields were 40–60 % after the three- to five-step reaction sequences on the polymeric resin using the tea bag method[, 85] in combination with radio frequency encoding to increase the efficiency of the synthesis and to guarantee practicality.



Scheme 11. Solid phase synthesis of a carpanone-inspired compound collection.

4.2. Compound Collections Having oxa-Heterocyclic Scaffolds

Statistically natural products are richer in oxygen atoms than in nitrogen atoms. Yet the presence of oxa-heterocycles is a key determinant of their biological activity. This insight and the structural complexity of oxa-heterocyclic natural products inspired various syntheses of natural product based compound collections.

4.2.1. Carpanone-Inspired Compound Collection

Solid-phase reactions that can increase molecular complexity while simultaneously accessing diverse structures open up new opportunities for the discovery of molecules with novel biological properties. In this sense Shair and coworkers used biomimetic solid-phase reactions which resulted in the one-step construction of tetracyclic molecules **101** (Scheme 11) from readily accessible starting materials.[40]

The key step in this strategy was the intermolecular oxidative heterodimerization of *o*-hydroxystyrenes on solid phase. The resin-bound electron-rich phenols **98** were coupled with the electron-deficient phenols **97** in a heterocyclization in the presence of $PhI(OAc)_2$. A subsequent inverse electron-demand Diels–Alder (IEDDA) cycloaddition gave the desired carpanone-like compounds **101** via the intermediate **100**. Electronic control during the IEDDA led to exclusive formation of a single isomer of **101**.

This synthetic sequence provides an elegant example of a stereoselective solid-phase synthesis of a complex molecular architecture bearing five stereogenic centers. In the six experiments reported, the biomimetic solid-phase reaction tolerated a range of functionality, making it amenable to diversity-oriented synthesis (DOS)[41] and the construction of libraries of carpanone-like molecules.

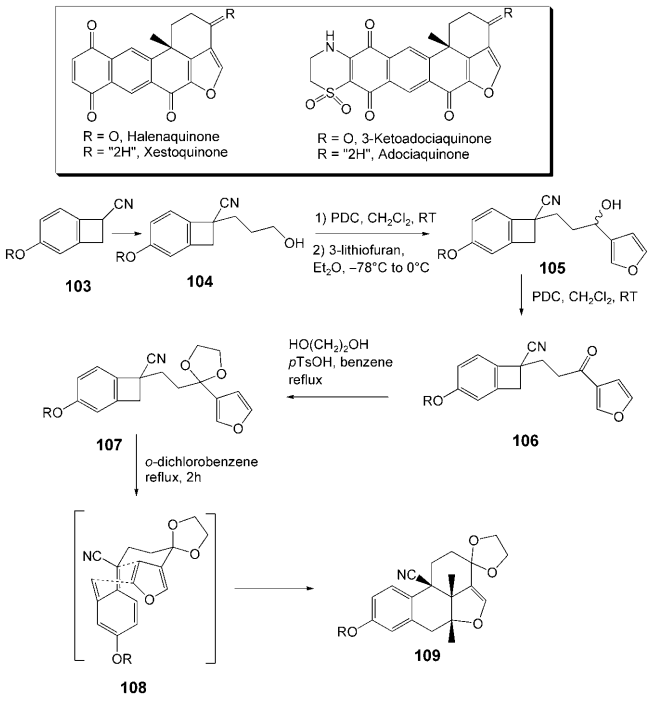
4.2.2. Furan-Fused Tetracyclic Compound Collection

Naturally occurring furan-fused polycyclic compounds exhibit significant biological activities,[42] which include antibiotic, cardiotonic, protein tyrosine kinase inhibitory, and antiviral activity as displayed by halenaquinone and related natural compounds.[43] A lead structure having a furan-fused tetracylic structure[44] inspired Nemoto and co-workers to synthesize a library of furan-fused molecules with natural product type architecture.[45] The core structure associated with such natural products was synthesized by using an intramolecular [4+2] cycloaddition of *o*-quinodimethanes, which were generated by thermal ring-opening of benzocyclobutane derivatives as the key step (Scheme 12).[46] Highly stereoselective syntheses were successfully achieved using furan-containing benzocyclobutene derivatives as substrates.

The various derivatives synthesized were examined for their inhibitory activity on virus growth by using a hemagglutinin method. Promising new candidates as antiviral drugs having a high activity and good therapeutic index were discovered. Halenaquinone and related natural products are known for their protein kinase inhibitory activities,[42, 43, 47] and some of them also inhibit Cdc25B phosphatase.[48] Therefore these scaffolds could be interesting starting points for developing novel libraries to discover novel drug candidates.

4.2.3. Calanolide-Inspired Compound Collection

(+)-Calanolide A (Scheme 13 A) is the first natural product identified as being active against HIV-1 and has recently

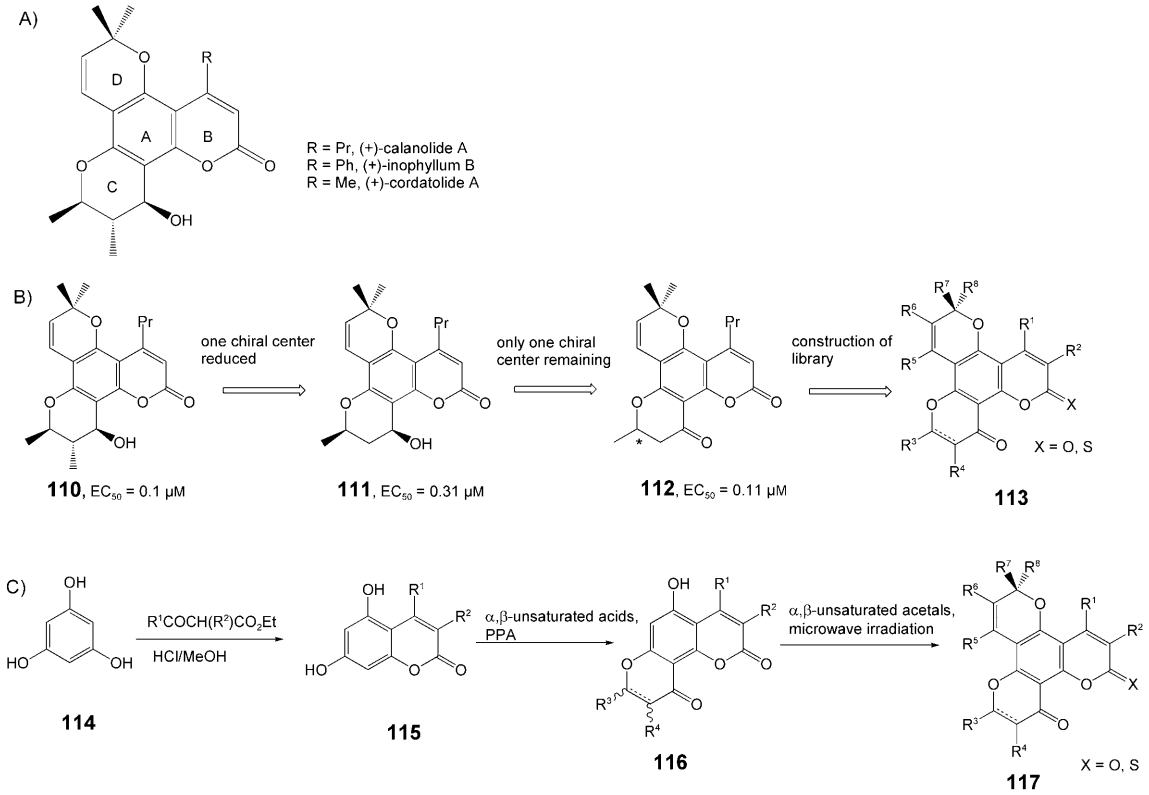


Scheme 12. Solution phase synthesis of a collection of furan-fused tetracyclic compounds. PDC = pyridinium dichlorodichromate.

been investigated in phase II/III clinical trials.[49] Other coumarin analogues, such as (+)-inophyllum B[50] and (+)-cordatolide A[51] have been isolated from plants of the genus *Calophyllum* and identified as specific HIV-1 reverse transcriptase inhibitors. They have the tetracyclic dipyranocoumarin as a common scaffold, but different substituents at the C4-position.

Liu and co-workers demonstrated that (±)-11-demethyl calanolide A (**111**) also has inhibitory activity against HIV-1 and exerted synergistic effects in combination with indinavir, AZT, and T-20.[52] Whereas this compound was toxic, the 11-demethyl-12-oxo calanolide A (**112**) displayed inhibitory activity against HIV-1 with a better therapeutic index. This finding encouraged Liu and co-workeres to design a library based on the tetracyclic dipyranocoumarin scaffold to pursue additional structure-activity realationship studies.[53] Within the library, nine diversity points were introduced by structural modifications of the core tetracyclic scaffold (**113**, Scheme 13 B).

By using phloroglucinol (**114**) as the starting material, racemic calanolide A was obtained through consecutive construction of the three skeletal rings, that is coumarin (rings A and B, **115**), 2,3-dimethylchromanone (ring C, **101**), and 2,2-dimethylchromene (ring D, **117**). The acylation of 5,7-dihydroxy-4-propyl-2*H*-chromen-2-one (**115**) and ring closure were achieved simultaneously through a Friedel–Crafts reaction using tigloyl chloride in polyphosphoric acid (PPA), which served as both the catalyst and solvent to give **116**. Compounds **117** were obtained by condensation of **116** with 1,1-diethoxy-3-methyl-2-butene under microwave irradiation using pyridine as the catalyst. The 10,11-*trans* and 10,11-*cis* isomers were separated from the mixture by silica gel column chromatography. A total of 85 compounds were synthesized in parallel.

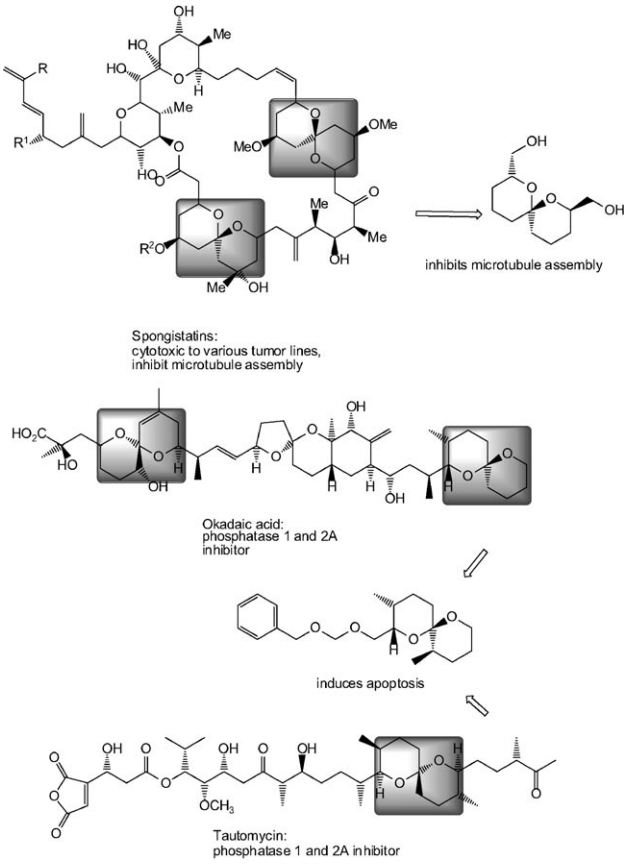


Scheme 13. Solution phase synthesis of a calanolide-inspired compound collection.

Biological evaluation revealed that the novel compound 10-bromomethyl-11-demethyl-12-oxo calanolide A (**117**, $R^3 = Br$)had a much higher inhibitory potency and therapeutic index ($EC_{50} = 2.85$ nM, TI > 10526) than calnolide A. This finding indicates that modifications of the C ring at the C10 position may be instrumental to obtaining drug candidates having better activity against HIV-1.

4.2.4. Compound Collection Having a Spiroacetal Core Structure

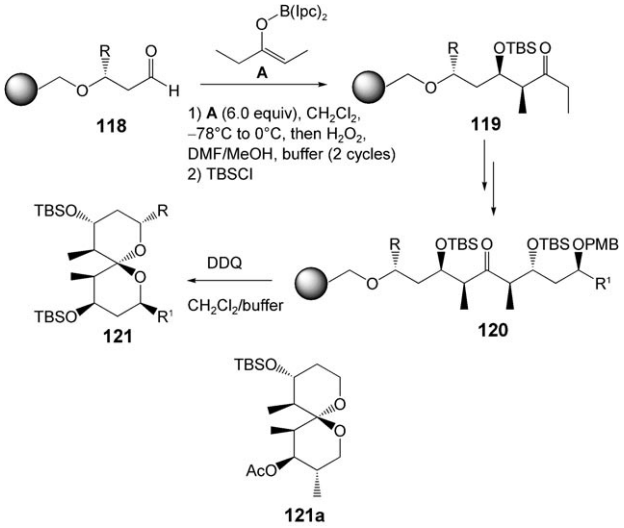
Natural products having spiroacetal structures occur across the insect kingdom, and are known for their pheromonal activities.[54] The spiro[5.5]ketal is a rigid molecular framework and occurs as a fragment in various complex natural products displaying a wide range of biological activities (Scheme 14). For example, the extraordinarily



Scheme 14. Structures of natural products with spiroacetal structures and simplified analogues displaying biological activity.

potent tubulin polymerization-inhibiting spongistatins,[55] the protein phosphatase inhibitor okadaic acid,[56] tautomycin,[57] and the HIV-1 protease inhibitor integramycin[58] display spiroacetals. Interestingly, structurally simplified but characteristic spiroketals derived from the parent natural products frequently retain biological activity similar to the parent natural product,[59] therefore inspiring the synthesis of natural product collections having spiroacetal core structures.

In the development of an asymmetric solid-phase synthesis of spiro[5.5]ketals[60] (Scheme 15), an aldol reaction of the resin-bound aldehyde **118** with the preformed *Z*-boron enolate **A** gave the enantioenriched aldol adduct **119**. In

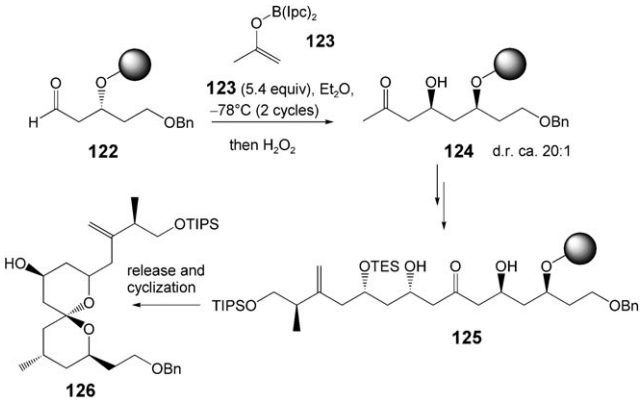


Scheme 15. Solid phase asymmetric synthesis of a spiroacetal collection. TBS = *tert*-butyldimethylsilyl.

contrast to the reaction conditions in solution, two cycles using six equivalents of the chiral reagent **A** were necessary to achieve complete conversion of the aldehyde. The stereocontrolled formation of an *E*-boron enolate on the solid phase was a prerequisite to controlling the course of a second, *anti*-selective aldol reaction with a set of aldehydes to generate the protected bis(β-hydroxyketone)s **120**, which were advanced precursors of the final spiroacetals **121**. Simultaneous removal of the PMB group and acetalization was performed by oxidative cleavage using DDQ, thereby releasing the spiroketals from the resin. Analysis of the diastereomeric ratios showed that a matched case in the second aldol reaction led to exclusive formation of one isomer, whereas mismatched cases proceeded with lower stereoselectivity.

Compound **121a** (Scheme 15) which was obtained from this collection, was found to be an inhibitor of the phosphatases VHR and PTP1b with IC_{50} values of 6 and 39 μM respectively. In addition, compound **121a** distorted the correct organization of the microtubuli network in a human carcinoma cell line.

In a similar approach, Paterson et. al. synthesized a fragment of the natural product spongistatin, which contained the core spiroketal structure **126** (Scheme 16), on the solid phase.[61] The immobilized β-hydroxy aldehyde was subjected to stereoselective aldol reactions.[62] The chiral boron/enolate **123** reacted with the solid phase-bound aldehyde **122** (immobilized by a silyl linker) to yield **124** with a diastereomeric ratio of greater than 20:1. Also, a second aldol reaction was performed after the enolate formation. The protected polyol **125** was converted into the final compound **126** upon cleavage from the resin and in situ cyclization.



Scheme 16. Solid phase synthesis of a spongistatin fragment on solid support. TES = triethylsilyl.

These examples demonstrate that the high stereoselectivity obtained in solution reactions can also be achieved for immobilized substrates. However, as a limitation to these syntheses, complete conversion in the aldol steps required two reaction cycles and an excess of chiral reagents.

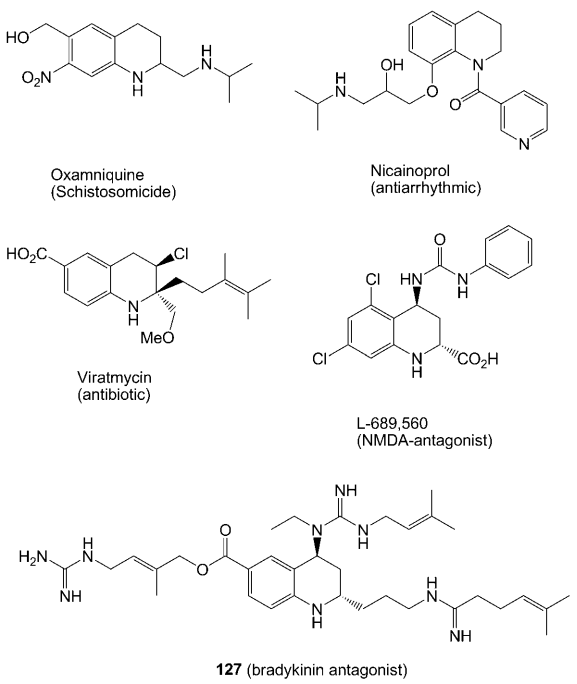
4.3. Compound Collections Having aza-Heterocyclic Scaffolds

Heterocycles are widely distributed in nature and in contrast to oxa-heterocycles, they occur in high frequency within drug candidates.[63] It is therefore not surprising that numerous natural and synthetic N-heterocyclic compounds have found applications as pharmaceutical and agricultural chemicals.[64] In recent years, a steep increase in the number of polymer-supported syntheses, which provide a variety of N-heterocyclic compounds and are also amenable to combinatorial synthesis, has emerged (for reviews see reference [65]). In the following sections, some of the libraries that are based on the aza-ring systems present in natural products are discussed.

4.3.1. Compound Collection Having a Tetrahydroquinoline Core Structure

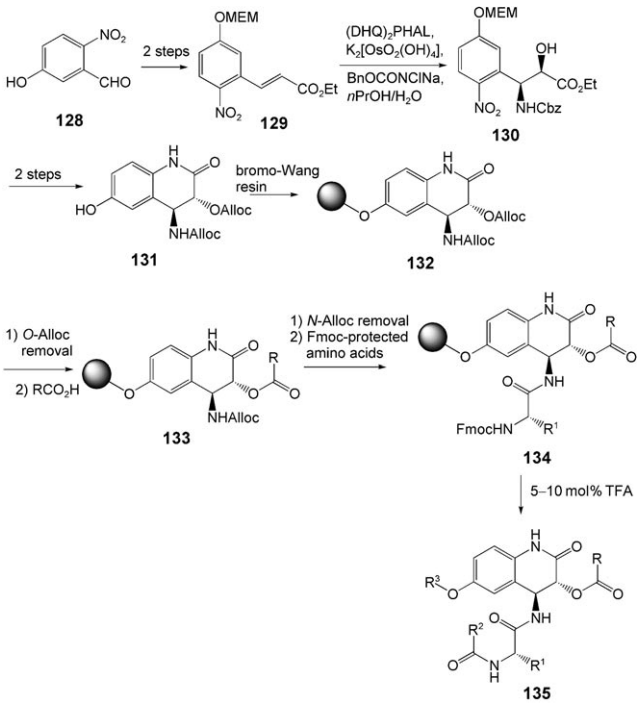
1,2,3,4-Tetrahydroquinolines, several of which occur in nature, are of interest to medicinal chemistry because of their biological activities. 2-Methyl- 1,2,3,4-tetrahydroquinoline is present in the human brain[66] and discorhabdin C is a marine alkaloid.[67] Dynemycin, a natural antitumor antibiotic, has a complex structure built on the tetrahydroquinoline system.[68] The 2,4,6-trisubstituted tetrahydroquinoline **127** (Scheme 17), which is isolated from *Martinella iquitosensis*, exhibits activity as a bradykinin antagonist and interacts with α-adrenergic, histaminergic, and muscarinic receptors.[69] Many relatively simple synthetic 1,2,3,4-tetrahydroquinolines are already being used or have been tested as potential drugs. Among them are oxamniquine (a schistosomicide),[70] nicainoprol (an antiarrhytmic drug),[71] virantmycin (a novel antibiotic), [72] and L-689,560 (Scheme 17).

Given this potential for bioactivity, the core-structure of tetrahydroquinoline was targeted by Arya and co-workers in



Scheme 17. Biologically active molecules with tetrahydroquinoline structure.

developing medium-sized libraries.[73] A practical synthesis of the enantiomerically pure tetrahydroquinoline scaffold was developed by using the asymmetric aminohydroxylation reaction as the key step in this strategy (Scheme 18).[74] The



Scheme 18. Combined solution and solid phase synthesis of a tetrahydroquinoline collection. MEM = methoxyethoxymethyl, $(DHQ)_2PHAL$ = hydroquinine-1,4-phthalazinediyldiether, Cbz = carbobenzyloxy, Alloc = allyloxycarbonyl.

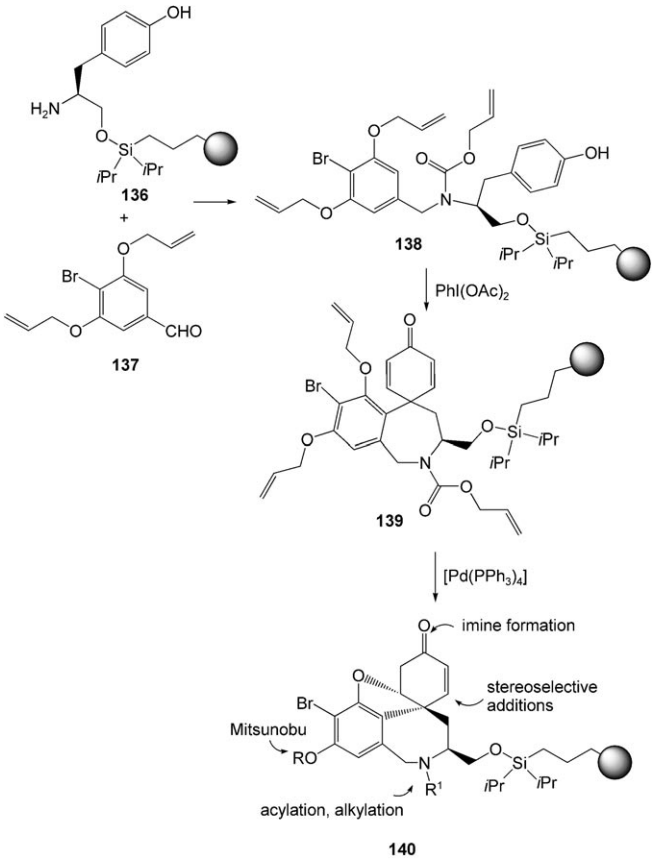
tetrahydroquinoline scaffold **131** was anchored to the solid support using a bromo-Wang resin (**132**), and then subjected to *O*-Alloc removal by treatment with NaOMe in methanol. Structural diversity was generated at the free alcohol by coupling it with various carboxylic acids to give **133**. The *N*-Alloc group was removed by palladium catalysis and the free amine generated therein was subsequently coupled with Fmoc-protected amino acids leading to **134**. Diversity was additionally increased by using an amidation reaction between the free amino group generated after Fmoc removal and different carboxylic acids, thereby yielding **135**.

The same research group developed several efficient solid- and solution-phase syntheses having the tetrahydroquinoline as a part of several diverse polycyclic scaffolds[73b–f] and macrocyclic rings.[73g]

4.3.2. Galanthamine-Inspired Compound Collection

Inspired by the idea developed earlier by Barton and coworkers[75] to convert the single precursor norbelladine into an entire class of natural products (including the crimines, galanthamines, lycoranes, and pretazzetines), Shair and coworkers developed a biomimetic synthesis of galanthamine-like molecules (Scheme 19) which have biological properties beyond those of the natural product galanthamine.[76] A chiral template was synthesized on solid phase for the respective libraries of complex molecules (Scheme 19). The *Amaryllidaceae* alkaloid biosynthesis pathway was represented by mimicking the oxidative phenolic coupling reaction with a hypervalent iodine reagent. By using an orthogonal protecting group strategy, a common dienone intermediate (**139**, Scheme 19) was cyclized to generate either crimine- or galanthamine-type structures, which were then subjected to selective liberation of the phenolic moiety. Split-and-mix synthesis[86] based on the two core systems generated a structurally rich *Amaryllidaceae* alkaloid-based library. The library synthesis commenced with the attachment of tyrosine derivatives to 500–600 μm high-capacity polystyrene beads through a Si–O bond to generate derivative **136** (Scheme 19). Reductive amination and subsequent protecting group adjustments yielded compound **138**, which upon exposure to $PhI(OAc)_2$ afforded the oxidized derivative **139**. This intermediate was then converted into compound **140** by palladium-mediated deprotection and a spontaneous intramolecular hetero-Michael-type reaction giving the cyclic derivative.

This template was used for additional diversity generating steps which were accomplished by: 1) alkylation of the phenolic hydroxy group, 2) intermolecular Michael-type reaction with thiols, 3) imine formation at the carbonyl group, and 4) alkylation or acylation of the secondary amine. The products were finally cleaved from the solid support using HF/pyridine, and the library was then screened by using a cell-based phenotypic assay. A new natural product-like derivative was identified as a potent inhibitor of the transport of the fluorescent VSVG-GFP protein conjugate from the Golgi apparatus to the plasma membrane. Galanthamine itself had no effect on the secretory pathway.

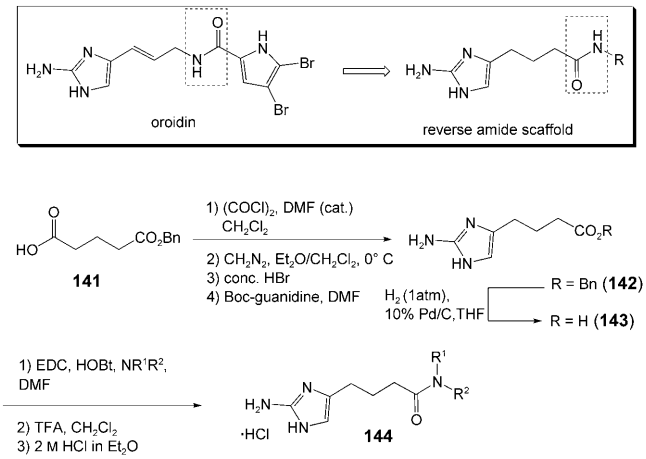


Scheme 19. Solid phase synthesis of a galanthamine-based library.

4.3.3. Oroidin-Inspired Aminoimimidazole Collection

Microbial infections are often mediated by surface associated microcolonies of bacteria or biofilms.[77] Bacteria that reside within the biofilm state display different phenotypes than their planktonic brethren and become more resistant to many antibiotics and biocides.[78] Melander and co-workers exploited the oroidin class of marine alkaloids for the development of anti-biofilm compounds.[79] The activity of oroidin has been documented in studies on bacterial attachment and colonization.[80] In the design of the library the amide bond, which connects the bromopyrrole tail of oroidin to the 2-aminoimidazole head, was reversed (Scheme 20).

The synthesis of the scaffold began with conversion of the monobenzylester **141** into the corresponding benzyl protected α-bromoketone. The cyclization of this intermediate yielded Boc-protected-2-aminoimidazole **142**, which upon deprotection underwent EDC/HOBt couplings to generate alkyl chain analogues. The final step required removal of the Boc group with TFA/CH_2Cl_2 (1:1). The analogues **144** were assayed for the prevention of biofilm production from PAO1 and PA14, two strains of the medicinally relevant c-proteobacterium *Pseudomonas aeruginosa.* Analogues that contained a long, linear alkyl chain were more potent inhibitors, than the natural product, at preventing the formation of PAO1 and PA14 biofilms. The most active compound in the series could disperse PAO1 and PA14 biofilms at low micromolar concentrations.



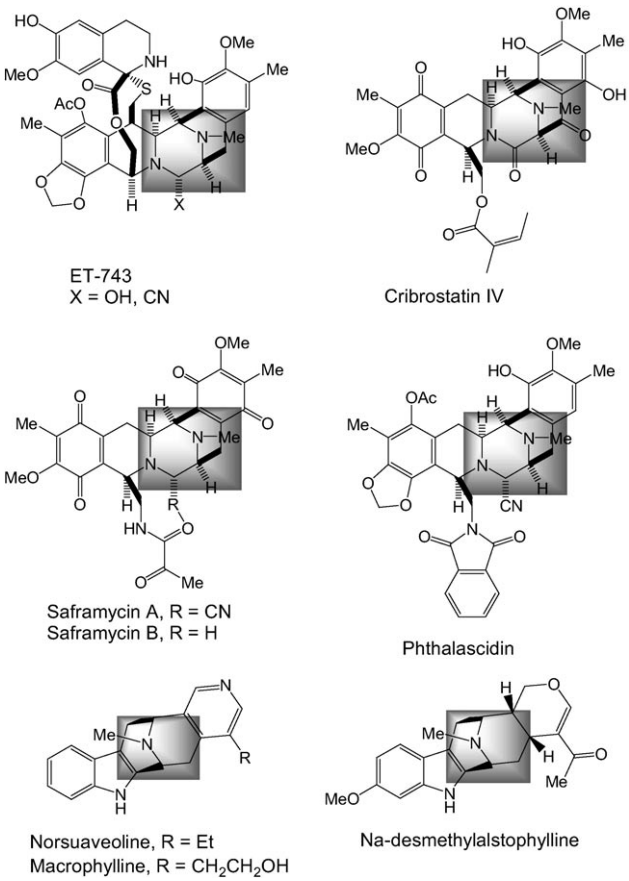
Scheme 20. Synthesis of a compound collection based on the structure of oroidin. Boc = *tert*-butoxycarbonyl, EDC = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide.

4.3.4. Natural Product Inspired Compound Collections Having Diazabridged Core Structures

The ecteinascidins are a family of marine-derived tetrahydroisoquinoline alkaloids having potent antitumor activity.[81] One such marine alkaloid, Yondelis (ET-743, Scheme 21), was adopted in 2005 in the U.S. by the FDA for the treatment of ovarian cancer. Myers and Lanman[82] reported a related solid-phase synthesis of a small series of analogues of (−)-Saframycin A. In addition, several indole alkaloids[83] were identified as having similar cyclic ring system. However, their natural scarcity and the complexity of the above mentioned synthetic methods have limited their development as antitumor drugs. Therefore, Lee and Park developed a synthesis of a natural product-like small molecule library which included a common diaza-bridged cyclic structural motif, which may display various biological activities (Scheme 22).[84] One of the essential requirements for parallel solid-phase combinatorial syntheses is that the procedures should be simplified and optimized to produce high yields of diastereomerically enriched small molecules.

To fulfill this requirement, the amination of bromoacetal resin **145** in DMSO was performed to yield **146**. The resin-bound secondary amine **146** was coupled separately with Fmoc-protected tryptophan and Fmoc-protected (*O*-DiTBS)-DOPA (DOPA = 3,4-dihydroxyanaline) to generating **147** and **148**, respectively (Scheme 22). Diversity in the core structure was established by amide and urea bond formation after removal of the Fmoc group from **147** and **148**, thus generating **149** and **150** as tryptophan derivatives and **151** and **152** as DOPA derivatives. The final step was performed in neat formic acid to synchronize the compound release from the solid support and the Pictet–Spengler-type cyclization via in situ generated cyclic iminium ions. The cyclization step was regioselective and diastereoselective, giving the final products as single diastereomers in high yields and purities (determined by NMR and LC/MS analysis).

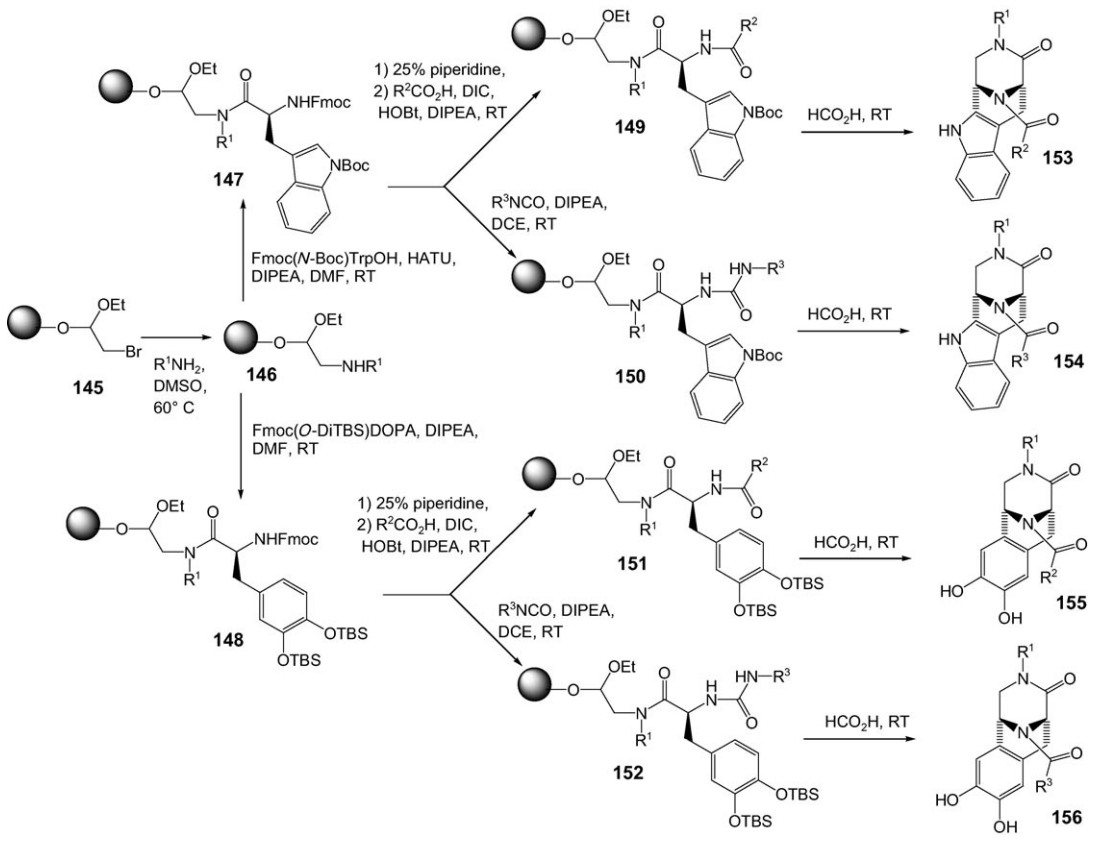
A 384 member library of 3,9-diazabicyclo- [3.3.1]non-6-en-2-one skeletons, fused with indole and dihydroxybenzene, and diversified at two bridging nitrogen atoms was prepared using the solid-phase parallel synthesis without additional purification.



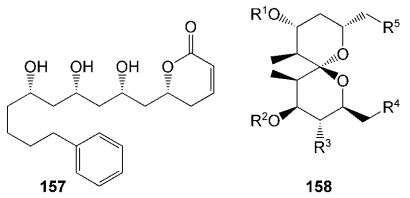
Scheme 21. Structures of naturally occurring compounds having bridged aza-heterocycles

5. Conclusions and Outlook

The examples discussed above convincingly demonstrate that the synthesis of compound collections inspired by the structures of biologically active complex natural products in different synthesis formats is feasible today. In several cases, long multistep sequences in solution and on the solid phase have been successfully implemented, and several of the most important and powerful methods of organic synthesis and NP total synthesis have successfully been adapted to the requirements of solid phase synthesis. Among other examples, the combinatorial variation of all possible isomers of a natural product cryptocaya diacetae (Scheme 3, **28**–**31**) as well as the 14-step stereoselective synthesis of the natural product analogue **157**[14a] and the synthesis of natural product inspired spiroacetal collections (**158**)[60,61] employing iterative enantioselective carbonyl allylation and aldol reactions, respectively, as key transformations provide compelling examples that both characteristics of complex natural product total synthesis can successfully be implemented in the formats of compound collection synthesis. The reported examples for syntheses of



Scheme 22. Synthesis of a compound collection with diaza bridged core structure. DIC = diisopropylcarbodiimide, DCE = 1,2-dichloroethane, HATU = 2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, DMSO = dimethylsulfoxide.



157 158

natural product inspired compound collections span the range of carbocycles, oxa- and aza-heterocycles, and prove that the resulting libraries yield compounds that are active in biochemical and biological assays with high frequency at small library size.

Given the proven feasibility of the approach and the undisputed and continuing success of natural products, derivatives thereof, and natural product analogues in the development of drugs, it seems the synthesis and evaluation of naturap product derived and inspired compound collections should be integrated into the standard procedures of chemical biology and medicinal chemistry research. The efforts required for the synthesis of such compound collections, although proven, may initially be higher than for the synthesis of non-natural product based and often achiral compound collections. However, because of the proven biological relevance and pre-validation of natural product scaffold structures, it is to be expected that collections delineated therefrom will also be enriched in biologically relevant compounds. Therefore, the greater effort may turn out to be particularly rewarding.

Our research efforts in the synthesis of natural product inspired compound collections were supported by the Deutsche Forschungsgeschaft, the Max Planck Society, the Humboldt-Stiftung, the Europäischer Fonds für Regionale Entwicklung (Zentrum für Angewandte Chemische Genomik "ZACG"), and the Volkswagen Foundation. The synthesis of natural product inspired compound collections emanating from our laboratories was developed by a group of motivated and enthusiastic Ph.D. students and Postdoctoral Fellows. Their names are given in the respective publications.

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