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Toward the library generation of natural product-like polycyclic derivatives by stereocontrolled diversity-oriented synthesis*

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Abstract: Due to the growing interest in small molecules that could help in understanding protein–protein interactions based on signal transduction, the demand for the generation of small-molecule libraries that are inspired by bioactive natural products has grown significantly. Many of these pathways are highly complex and present tremendous challenges with the use of classical tools. A rapid access to natural product-like small molecules having structural complexity and diversity is crucial for systematically dissecting the functions of complex protein networking and understanding cell signaling pathways. The complex nature, the three-dimensional architecture, and the number of protein binding functional groups presented in three-dimensional arrays are some of the attractive features to incorporate in small-molecule chemical probes to be used as modulators of protein function.

INTRODUCTION

The concept of *chemical genetics/genomics* has emerged recently in the chemical biology community in recognition of a renewed desire to generate small molecules and use these derivatives as chemical probes for understanding protein functions [1]. Parallel to genetic approaches, use of small molecules as highly specific modulators (i.e., inhibitors or activators) of protein functions is a powerful approach and is commonly applied for understanding dynamic processes that involve protein–protein interactions, protein networking, etc. [2]. In general, due to the irreversible effects caused by the genetic manipulations, these systems are difficult to study using traditional biological approaches [3]. An excellent viewpoint article from Strausberg and Schreiber [4] discusses the challenges that we face today in the postgenomic age, i.e., (i) what is the next step, (ii) how to move forward in developing better medicines, and (iii) how to benefit from knowing the gene(s)/gene products to modulating their functions.

For the success of the chemical genetics/genomics-based research programs, rapid access to diverse sets of small molecules is of prime importance because these derivatives pave the pathway for dissecting biological processes and are valuable tools as probes for understanding biological events [5]. Over the years, combinatorial chemistry has emerged as an important technology because it allows an

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efficient synthesis of many compounds in a parallel manner. In most cases, it has been successfully applied to the high-throughput synthesis of simple compounds (i.e., compounds with no stereogenic centers) [6]. With few exceptions, the development of combinatorial methods that allow the high-throughput synthesis of complex, highly functionalized, natural product-like polycyclic derivatives remains a daunting task [7]. The need for these efforts is increasing constantly due to (i) the rapid rise in new biological targets emerging from genomics and proteomics research, (ii) the growing interest in understanding protein–protein interactions in signal transduction, and (ii) the need for small molecules that can be used to search for highly specific modulators of protein functions.

Over the years, natural products have been widely utilized as small-molecule chemical probes in understanding biological pathways [8]. In several cases, it has been shown that compounds that exhibit specific cellular responses have complex, chiral, and highly functionalized structures. These properties are valuable in searching for a specific binding to protein targets or in differentiating related proteins. In recent years, several research groups have taken the challenge of developing stereoselective reaction-based methods on solid phase, and are utilizing them for the high-throughput syntheses of complex natural product-like derivatives. Some of the recent developments from our group and others are discussed in this article.

Due to the three-dimensional structural architectures, natural products have been a source of inspiration for developing efficient stereo- and enantioselective synthesis methods [9]. There are several examples (see Fig. 1 for a few bioactive complex natural products: Taxol, FK 506, Rapamycin, Vinblastine) in the literature where the complex architectures of natural products are the key to exhibiting highly specific cellular responses (i.e., highly specific modulators of protein functions). The unique shapes of natural products make them ideal as small-molecule candidates that could selectively bind to enzymes or proteins. Figure 2 highlights some of the combinatorial challenges that face us in the new age.

The term "diversity-oriented synthesis" (DOS) [10] was coined by Stuart Schreiber and is aimed at building natural product-like, complex architectures in a high-throughput manner. This was attributed to the growing need for having a rapid access to diverse natural product-like skeletons that could be further utilized in the library generation. Unlike traditional combinatorial approaches that were focused on the library generation of aromatic and heterocyclic products, building three-dimensional structural complexity by exploring stereo- and enantioselective reactions on solid phase is one of the thrust areas in

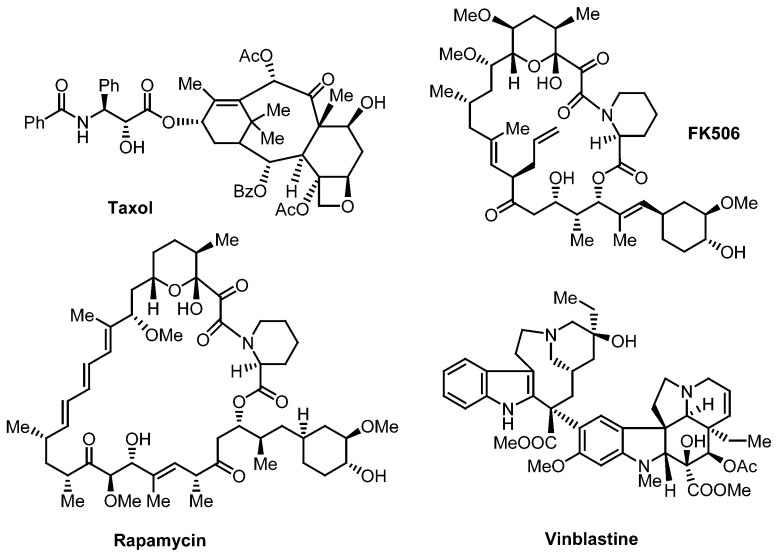


Fig. 1 A few examples of bioactive natural products.

Small Molecule Probes for Cell Biology-
The Emerging Combinatorial Challenges and Opportunities

- Natural Product-like Polycyclic Derivatives
- Highly Functionalized
- Rich in Stereogenic Functional Groups
- Polycyclics Having Medium Size to Macrocyclic Rings

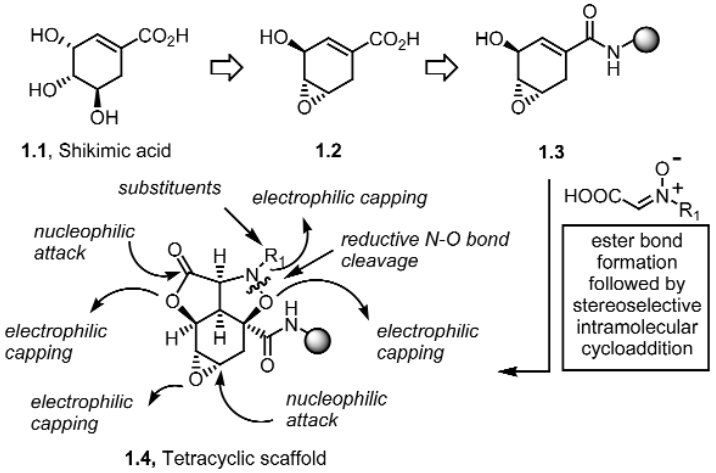
- Stereo- and Enantioselective Synthesis
- Populating the 3-Dimensional Space
- *Speed in Building Complexity and Diversity!*
- *Small Molecule Probes for Protein-Protein Interactions*

Fig. 2 The emerging combinatorial challenges.

DOS. In general, the libraries generated by DOS are utilized as small-molecule chemical probes for understanding cellular processes and are not biased to a given biological target.

LIBRARY SYNTHESIS OF NATURAL PRODUCT-LIKE COMPOUNDS: A FEW EXAMPLES FROM THE LITERATURE

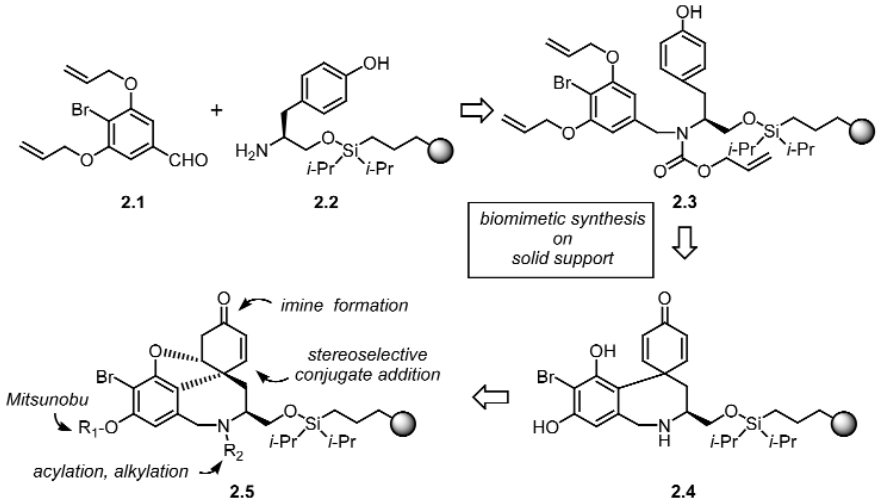
In 1998, Schreiber et al. developed a highly efficient, multistep synthesis to obtain an enantiomerically pure template **1.4** (Scheme 1) from shikimic acid, **1.1** [11]. Shikimic acid was first converted into both enantiomers of epoxycyclohexenol carboxylic acid derivative **1.2**, which was then coupled to a photocleavable linker immobilized onto Tentagel-S-NH_2 poly(ethyleneglycol)-polystyrene copolymer. Treatment of the resin-bound epoxycyclohexenol derivative, **1.3**, with various nitrone carboxylic acids under esterification conditions, followed by an intramolecular cycloaddition reaction yielded the tetracyclic scaffold **1.4** with complete regio- and stereoselectivity, via tandem acylation/stereoselective 1,3-dipolar cycloaddition reaction. The tetracyclic derivative **1.4** is rigid and densely functionalized, allowing it to undergo a variety of organic transformations without the use of protecting groups. On treatment with a variety of organic and organometallic reagents, this template can be utilized for obtaining highly functionalized bicyclic and tricyclic derivatives.



Scheme 1 Schreiber stereoselective diversity-oriented synthesis (DOS) to obtain natural product-like complex polycyclics.

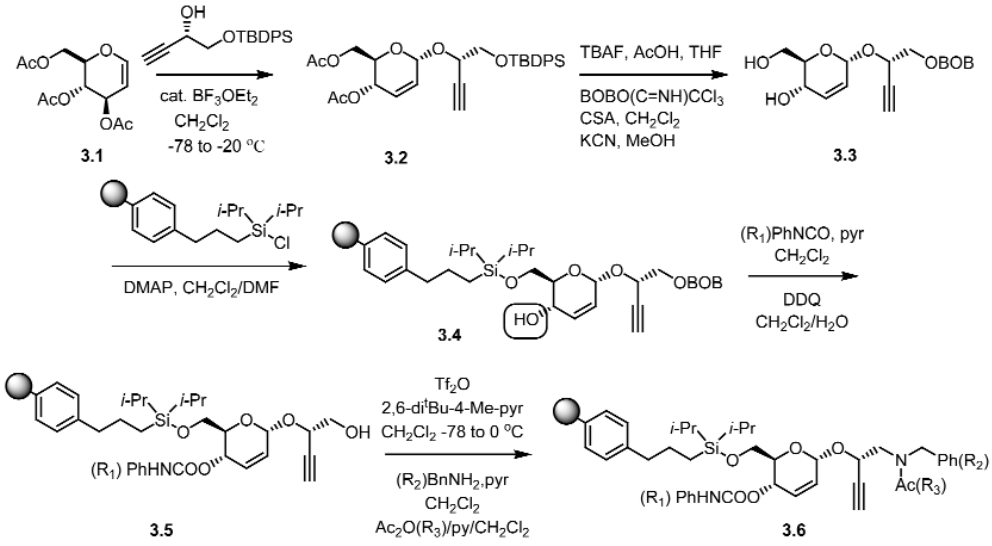
Shair et al. [12], demonstrated the use of a biomimetic-based DOS to discover galanthamine-like molecules (Scheme 2) with biological properties beyond those of the natural product, galanthamine. As first reported by Barton [13], a single precursor, norbelladine, was converted via specific oxidative phe-

nolic coupling pathways to an entire class of natural products, including the crimines, galanthamines, lycoranes, and pretazzetines. Each compound is structurally different and elicits a different biological response. Shair et al. utilized these characteristics in developing a biomimetic synthesis-based method on solid phase to obtain a chiral template for the diverse libraries of complex molecules. Scheme 2 outlined the amaryllidaceae alkaloid pathway by mimicking the oxidative phenolic coupling reaction with the hypervalent iodine reagent. By using a simple orthogonal protecting group strategy, a common dienone intermediate is then directed to cyclize on nitrogen to generate crimine- or galanthamine-type structures following selective liberation of the phenolic moiety. This was followed by split-and-mix-derived organic synthesis on two core systems to generate 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 [14] through the Si–O bond to generate derivative **2.5**. The reductive amination followed by protecting group adjustments yielded compound **2.3** anchored onto solid support, which on exposure to $PhI(OAc)_2$ afforded the oxidative derivative, **2.4**. The quinone derivative, **2.4**, was then converted to compound **2.5** via Pd-mediated deprotection and spontaneous intramolecular hetero-Michael-type reaction giving the cyclic derivative. The diversity steps were accomplished by (a) the phenolic hydroxyl group alkylation, (b) an intermolecular Michael-type reaction with thiols in the presence of *n*-BuLi, (c) an imine formation from the carbonyl group, and (d) the secondary amine alkylation or acylation. It is interesting to note that the intermolecular Michael-type reaction with various thiol-based nucleophiles is highly stereoselective on solid phase, giving a single diastereomer as the product. The product was finally cleaved from the solid support using HF-pyridine, and the library was then screened using a cell-based phenotypic assay. A new natural product-like derivative was identified as a potent inhibitor of a fluorescent fusion protein, VSVG-GFP movement from Golgi apparatus to the plasma membrane. Although as such, galanthamine has no observed effects on the secretory pathway.



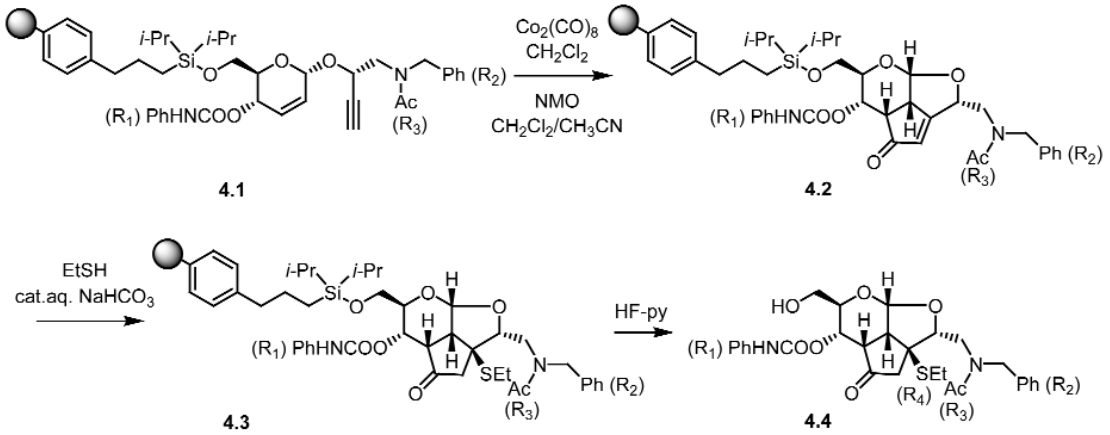
Scheme 2 Shair solid-phase synthesis of galanthamine-like compounds.

Schreiber et al. [15] developed an efficient, stereoselective synthesis of tricyclic compounds by exploring Ferrier and Pauson–Khand [16] reactions on a glycal template. This methodology was further utilized in developing a stereoselective synthesis of a library of 2500 compounds. Solid-phase synthesis was performed on 500–600 μm polystyrene alkylsilyl-derivatized macrobeads [14]. The initial loading element was synthesized according to the reaction shown in Scheme 3. Ferrier reaction of 3,4,6-tri-*O*-acetyl-glucal **3.1** with (*S*)-1-[(*tert*-butyldiphenylsilyl)oxy]-3-buytyn-2-ol gave the pseudo-



Scheme 3 Schreiber stereoselective DOS approach to glycals.

glucal as an α-anomer, whereas the Ferrier reaction with the (*R*)-isomer gave a mixture of both the α and β isomer in a ratio of 5:1 from which the α-anomer could be isolated by column chromatography. Deprotection of TBDMS protecting group followed by protection of the primary hydroxyl functionality as 4-butyloxybenzyl (BOB) ether, a compatible protecting group which could be easily deprotected by dichlorodicyano-p-benzoquinone (DDQ) without affecting the solid-phase silyl ether-based linking element resulted in **3.3**, which was then loaded onto 500–600 μm polystyrene alkylsilyl-derivatized macrobeads giving **3.4**. The first solid-phase diversity step (R_1) is the functionalization of the 4-hydroxy group of the pseudoglucal. Phenylisocyanate reacted quantitatively to afford the carbamate. Deprotection of the BOB group resulted in the alcohol **3.5**, which was the second diversity position after triflation followed by S_N2 reaction with primary amine. Reaction of the resulting secondary amine with different acylation agent resulted in the third diversity point, **3.6**. Pauson–Khand reaction on **4.1** (Scheme 4) resulted in tricyclic α,β-unsaturated ketone **4.2**, which was further subjected to a hetero-Michael reaction to result in the fourth diversity, yielding **4.3**. Finally, treatment of the macrobeads with HF-pyridine resulted in the tricyclic compound **4.4** with four diversity points. This methodology resulted in a library of 2500 compounds.



Scheme 4 Schreiber approach (cont'd.).

PRESENT WORK: TOWARD THE SOLID-PHASE SYNTHESIS/LIBRARY GENERATION OF NATURAL PRODUCT-LIKE POLYCYCLIC COMPOUNDS ON "PRIVILEGED SUBSTRUCTURES"

There are several natural products known in Nature that possess the indole and indoline scaffolds, and a number of these derivatives exhibit a wide range of biological activities [17]. Owing to the broad applications of indole- and indoline-based bioactive natural products, we initiated a program aimed at developing solid-phase synthesis leading to a variety of complex polycyclic derivatives. Figure 3 outlines our targets for developing a diversity-oriented, synthesis-based research program. The first milestone is to develop a practical synthesis of compound **F3.1** that could serve as the core scaffold for building a skeleton diversity leading to different scaffolds, such as compounds **F3.2**, **F3.3**, and **F3.4**. Aminoindoline derivative **F3.1** has several attractive features. It has four orthogonally protecting functional groups that could be utilized in building skeletally diverse complex polycyclic compounds. The phenolic hydroxyl group could then be utilized as an immobilization site in solid-phase synthesis. The ring-closing metathesis reaction is the key reaction to obtain aminoindoline-derived tricyclic derivatives **F3.2** and **F3.3**. Compound **F3.4** could be obtained from stereoselective hetero-Michael reaction, and this tricyclic derivative could also provide four diversity sites for the library generation. Our model studies with the simple indoline derivative are shown in Scheme 5. The synthesis of compound **5.1** was achieved in our group [18]. This derivative has three orthogonally protecting groups including a phenolic hydroxyl group that could further be utilized as an anchoring site. The primary hydroxyl group was then converted into an olefin, and following the *N*-alloc removal, the secondary amine was coupled with vinyl acetic acid. These transformations provided compound **5.2** in five steps from **5.1**. The ring-closing metathesis reaction went smoothly, giving the desired cyclic product, **5.3**, in 82 % yield. Further, the double bond was epoxidized with dioxirane and the epoxidation reaction was found to be highly stereoselective (only α-attack). The stereochemistry was assigned by NMR studies. Finally, the treatment with LDA provided the rearranged product in very high yield (95 %). To complete the model studies, the secondary hydroxyl group was acylated (potential first diversity site) and the enamide functional group was subjected to thiol addition. We were pleased to note that this reaction was very clean, giving only a single diastereomer (94 %, attack opposite to the acyl group!). The successful attempts with our model studies imply that this sequence could be nicely utilized toward the library generation by solid-phase synthesis. Our next model studies utilized a ring-closing metathesis (RCM) approach to the synthesis of tricyclic derivatives having an enamide group in a seven-membered ring and are shown in

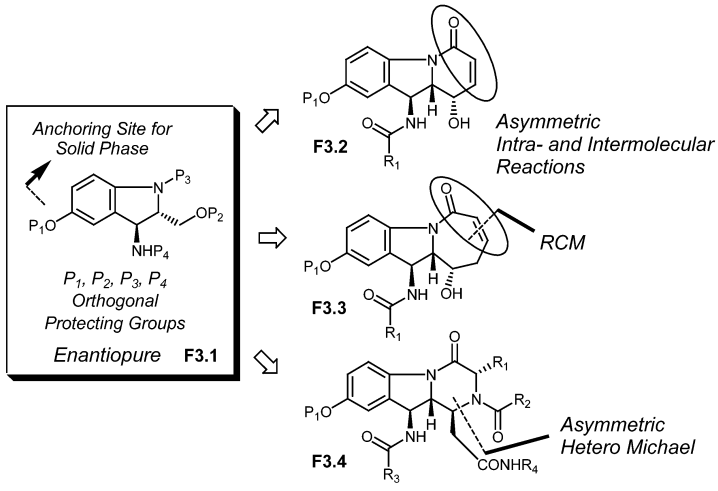
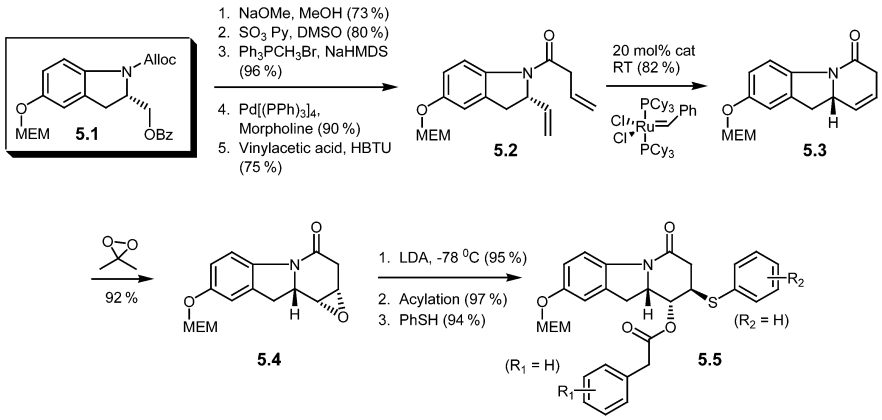
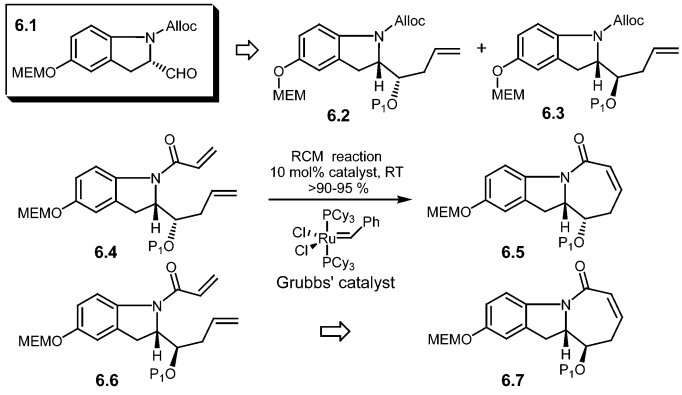


Fig. 3 Plans for the library generation of functionalized indoline-derived, natural product-like polycyclic compounds.

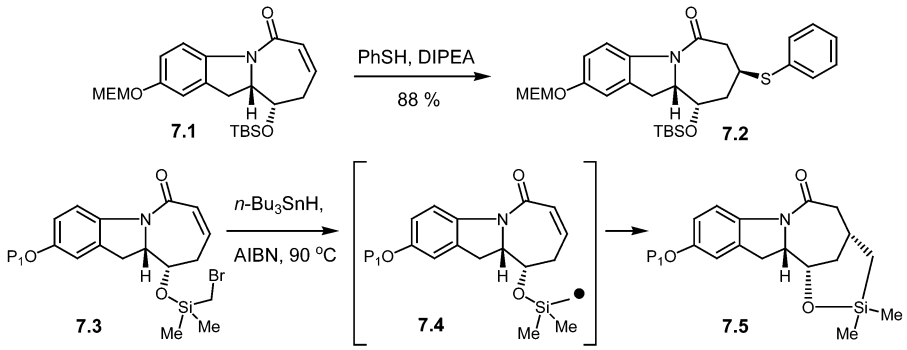


Scheme 5 Toward the first-generation library design: tricyclic derivatives by RCM.

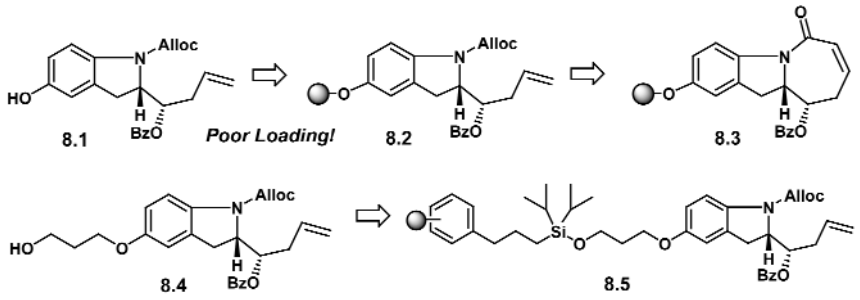


Scheme 6 Tricyclic derivatives with a seven-membered ring by RCM.

Scheme 6. For test studies, compounds **6.2** and **6.3** were obtained by allylation of indoline aldehyde **6.1**. To our pleasant surprise, the RCM reaction with compounds **6.4** and **6.6** was very fast and the final products could be obtained in yields greater than 90 %. When subjected to RCM reaction, both diastereomers (**6.4** and **6.6**) were found to be very reactive and gave the cyclic products. Our attempts to explore the asymmetric diversity-oriented reactions on one diastereomer **7.1** are shown in Scheme 7. In one case, the thiol reaction was found to be highly stereoselective (with α-attack only). We also successfully demonstrated that it is possible to carry out an asymmetric free radical-based C–C bond forming reaction giving a product **7.5** from **7.3**. Both these reactions may be very useful in library generation. We then selected compound **8.1** (Scheme 8) to anchor onto the solid support for solid-phase synthesis leading to the library generation. The plan is to first build the tricyclic scaffold on solid phase, and then explore this scaffold in diversity-oriented reactions. To date, all the attempts to load this compound onto a solid support using BromoWang resin or the silyl linker-based macrobeads [14] gave us a poor loading. Further work is in progress to improve the loading by using compound **8.4**, in which a spacer has been introduced between the aromatic moiety and the hydroxyl group. The loading experiments with this compound are in progress and will be reported as appropriate.

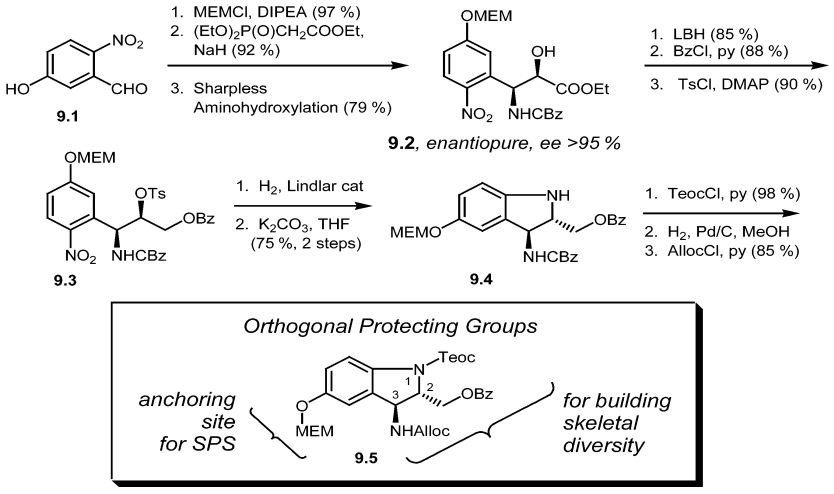


Scheme 7 Exploration of diversity-oriented reactions (test studies).

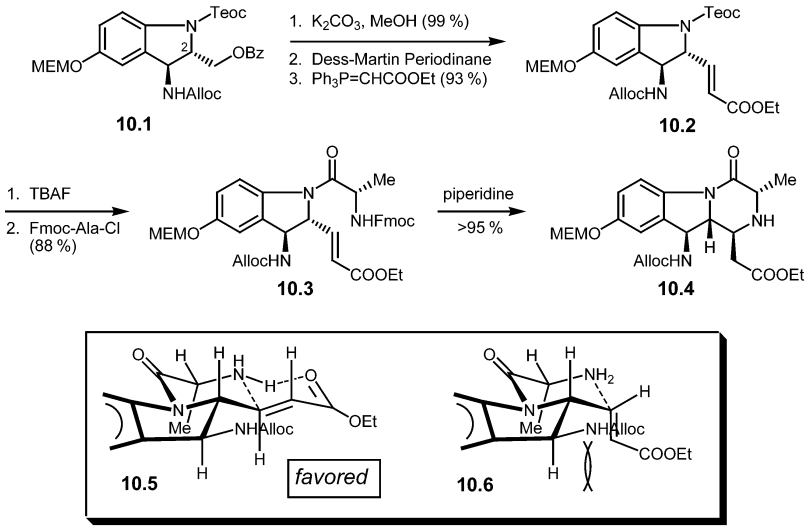


Scheme 8 Loading attempts for solid-phase synthesis.

Scheme 9 shows our solution-phase synthetic approach to obtain aminoindoline-based bicyclic derivative **9.5** in a number of steps from **9.1**. The method reported in this scheme is highly practical and allows us to obtain this compound in large quantities. Further, this derivative has several attractive features, i.e., four orthogonally protected functional groups that could further be modified in building complex molecular architectures. As in earlier examples, the phenolic hydroxyl group could be utilized as an anchoring site in solid-phase synthesis. To begin with, the hydroxynitrobenzaldehyde (**9.1**) was converted into compound **9.2** by asymmetric Sharpless aminohydroxylation as the key step. The expected product has a high, >95 % ee (determined by chiral HPLC). This was then converted into the corresponding α-*O*-tosyl derivative **9.3** in three steps. Finally, the aminoindoline product **9.4** was obtained after reductive cyclization. The synthesis of compound **9.5** was achieved in three steps from **9.4** that involve (i) *N*-teoc protection of the dihydroaminoindoline nitrogen, (ii) the *N*-Cbz removal of the benzylic amine, and, finally, (iii) the *N*-alloc protection. Our model studies to demonstrate the feasibility of asymmetric hetero-Michael reaction are shown in Scheme 10. As test studies, the primary hydroxyl group of the dihydroaminoindoline moiety at C-2 was converted into conjugated unsaturated carboxyl ester **10.2** that require the hydroxyl deprotection, oxidation, and the Wittig reaction. The dihydroaminoindoline secondary amine was deprotected, and then coupled with *N*-Fmoc protected alanine chloride (88 % yield). We were pleased to note that the Michael reaction proceeded under the *N*-Fmoc deprotection conditions (piperidine). These reaction conditions are extremely mild, and the final product **10.4** was obtained as the major isomer in which the vicinal protons have a *trans* relationship. The stereochemistry was assigned by NMR studies. We propose a chair-like transition state (see **10.5** in

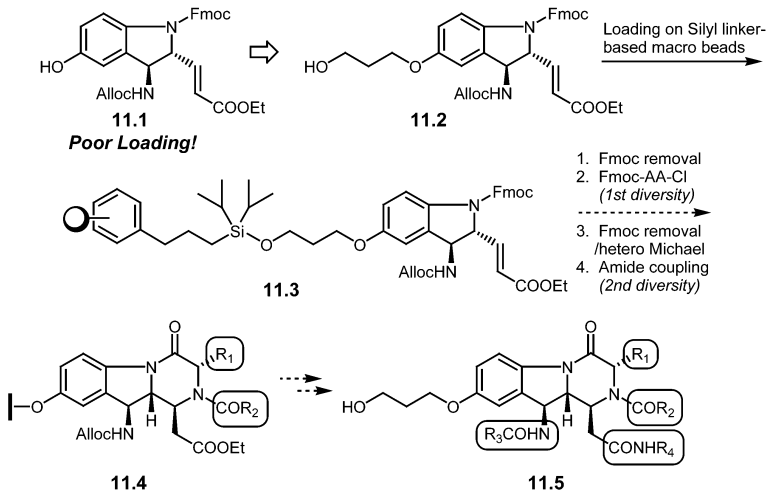


Scheme 9 Second-generation design: enantiopure aminoindolines for DOS.



Scheme 10 Asymmetric hetero-Michael model studies.

Scheme 10) to explain the stereochemical outcome of this reaction. Our solid-phase synthesis related work in this project is shown in Scheme 11. As observed earlier, compound **11.1** was found to have a poor loading onto the solid support, and this led us to synthesize compound **11.2** in which a spacer has been introduced between the aromatic group and the hydroxyl functionality. Herein, we are exploring the use of silyl-based macrobeads [14] in our solid-phase synthesis. Further, work is in progress to test the loading of compound **11.2** onto the solid support and to complete the sequence including asymmetric hetero-Michael reaction leading to utilization of potential four diversity sites.



Scheme 11 Toward the library generation by using silyl linker-based macrobeads.

In another approach, we describe a solution- and solid-phase synthesis of three polycyclic derivatives, **F4.2**, **F4.3**, and **F4.4** (Fig. 4), from enantiopure tetrahydroquinoline-based β-amino acid **F4.1** [19]. The extensive usefulness of quinoline and tetrahydroquinoline-based natural products prompted us to develop a DOS strategy of natural product-like polycyclic derivatives having this privileged structure. Central to this idea is the development of an efficient solution method to obtain enantiopure tetrahydroquinoline-based β-amino acid **F4.1**. This derivative is a versatile building block. For model studies, the synthesis of enantiopure tetrahydroquinoline β-amino acid **12.5** (Scheme 12) was carried out as follows. 2-Nitropiperonal was converted to unsaturated carboxyl ester by Wittig reaction (95 %), and then subjected to Sharpless dihydroxylation reaction giving enantiopure dihydroxyl derivative, **12.2** (88 %, >90 % ee, determined by chiral HPLC). Following the acetonide protection, the carboxyl ester was then reduced by lithium borohydride, **12.3**. Further, compound **12.4** was then obtained from **12.3** in few transformations. This was then subjected to nitro group reduction and then treatment with LDA or NaH to obtain the hetero-Michael product, **12.5**, as a single diastereomer. The stereochemistry of the new stereogenic center was assigned by nOe (H-2 and H-4). The reaction seems to be independent of

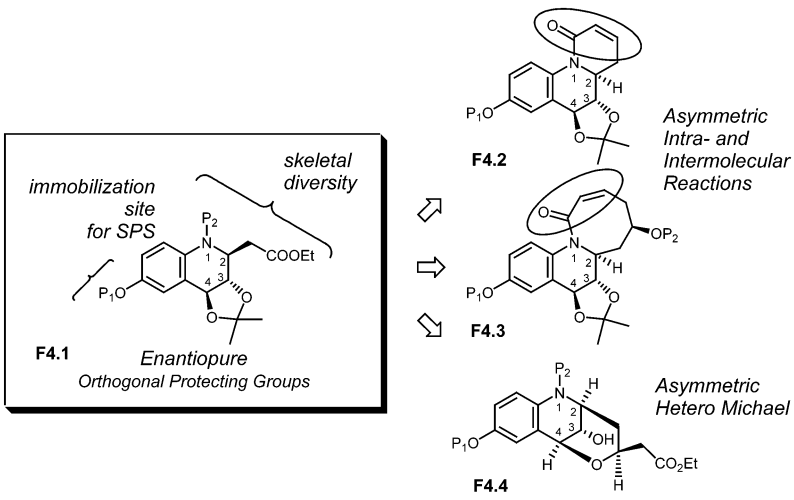
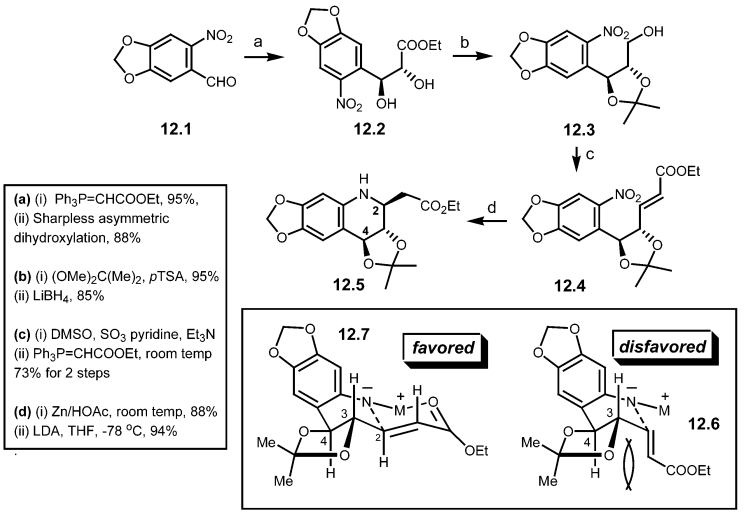
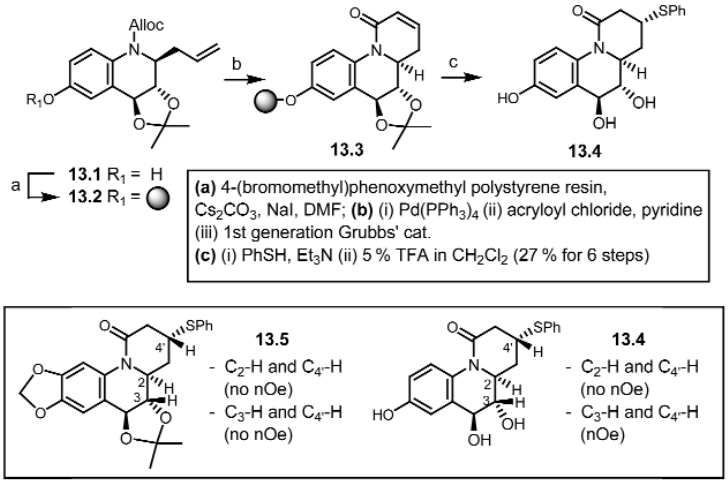


Fig. 4 DOS plans to obtain tetrahydroquinoline-based natural product-like polycyclic compounds.



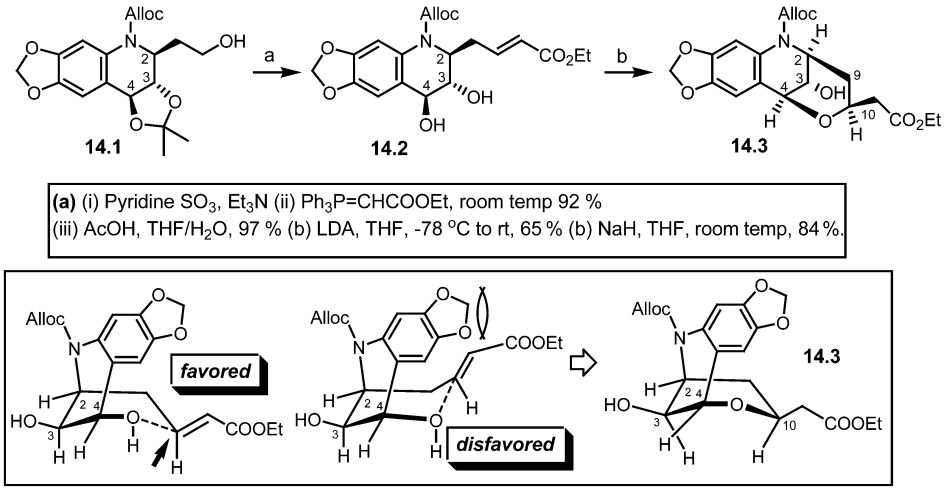
Scheme 12 Tetrahydroquinoline-based β-amino acids by asymmetric hetero-Michael approach.

the choice of the base and provides an easy access to enantiopure β-amino acid on a large scale. It appears that acetonide protection of vicinal hydroxyls at C_3 and C_4 is an important factor (see **12.6** and **12.7**) in asymmetric hetero-Michael reaction. Tetrahydroquinoline α-amino acid contains several important features, (i) vicinal hydroxyls at C_3, C_4 and (ii) a phenolic moiety that could be further utilized as an anchor site in solid-phase synthesis. The solid-phase synthesis of tetrahydroquinoline-based tricyclic derivative **13.3** having an enamide functional group is shown in Scheme 13. Compound **13.1** was obtained from hydroxy-nitrobenzaldehyde and then anchored onto solid support using 4-(bromomethyl)phenoxymethyl polystyrene resin (loading 93 %). Following *N*-alloc removal and acryloylation, the RCM reaction gave the cyclic enamide product **13.3**. As observed in solution studies, compound **13.4** was obtained as a single diastereomer (attack from the α-face) on reaction with PhSH after cleavage from the solid support (27 % overall yield for 6 steps). The facial selective approach of the thiol in solid phase was found to be similar to the addition of the thiol in solution synthesis (see compound 15.5). The NMR studies with compound **13.4** showed nOe between C_3–H and $C_{4'}$–H.

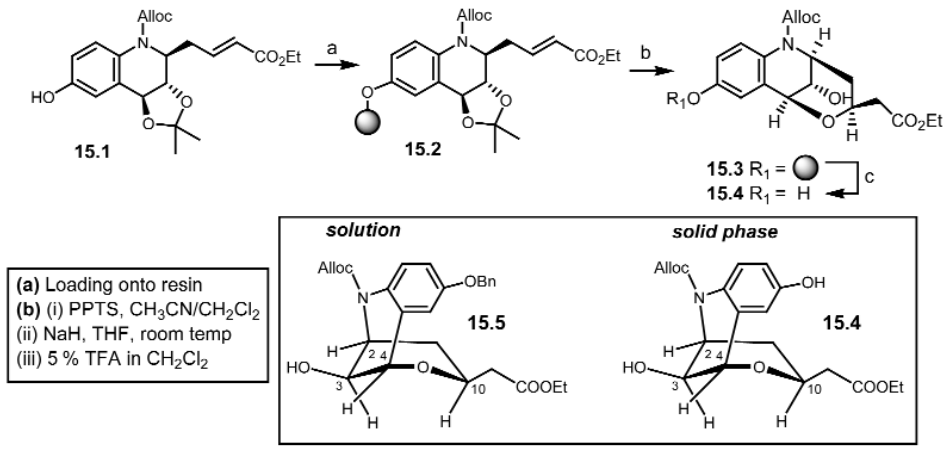


Scheme 13 RCM-based stereocontrolled DOS.

In a model study for the regio- and stereoselective hetero-Michael approach shown in Scheme 14, an enantiopure tetrahydroquinoline β-amino acid **14.1** was converted into free dihydroxyl derivative **14.2**. With compound **14.2** as the starting material, the stage was now set to explore the asymmetric hetero-Michael reaction. We were pleased to note that this reaction proceeded very smoothly and gave a single diastereomer in high yield (84 %)! The tetrahydroquinoline-based tricyclic derivative **14.3** was well characterized by MS and NMR. As observed earlier, this reaction seems to be independent of the choice of the base and is an excellent example of a highly regio- and stereoselective (reaction with benzylic –OH at C_4 only!) hetero-Michael reaction. Based upon extensive NMR studies that showed no nOe between C_2–H and C_4–H (note: compound **14.2** showed nOe between C_2–H and C_4–H), we proposed a boat-like structure for the newly formed pyran ring via a boat-like transition state. The regio- and stereoselective outcome could be envisioned by a pseudo-axial occupation of functional groups at C-2, C-3, and C-4, allowing facial selective attack of the oxygen nucleophile onto the Michael site. For the solid-phase synthesis of **15.4** (Scheme 15), compound **15.1** was immobilized onto the resin (**15.2**) as with the previous example (loading 86 %). The free hydroxyl derivative obtained after the acetonide



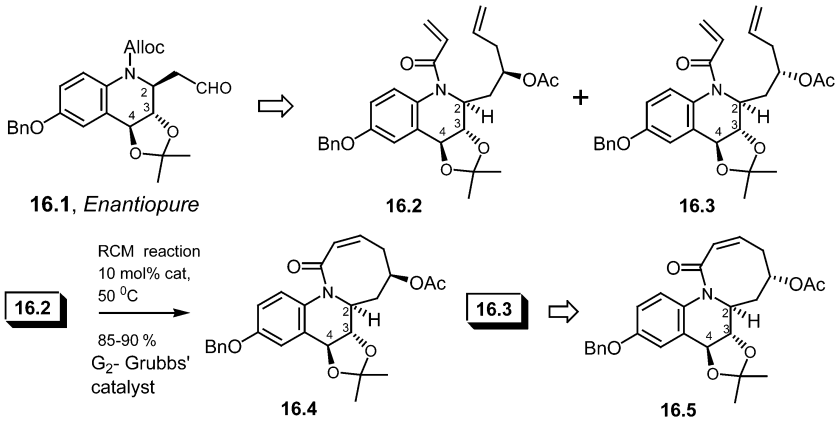
Scheme 14 Model studies: regio- and stereoselective hetero-Michael approach to obtain tetrahydroquinoline-based polycyclic compounds.



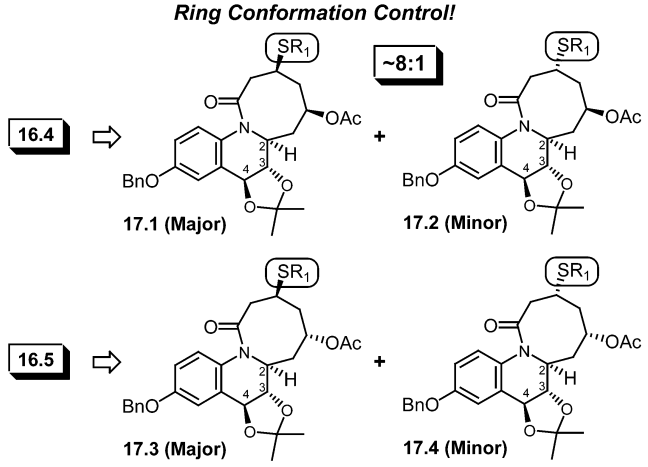
Scheme 15 Stereocontrolled solid-phase synthesis of tetrahydroquinoline-based, natural product-like, polycyclic compounds.

removal in compound **15.2** was subjected to crucial hetero-Michael reaction. The use of NaH as a base at room temperature provided the expected product **15.3**. After cleavage from the support, the crude sample was purified giving product **15.4** (25 % overall yield for 4 steps) that was further assigned by NMR. As observed in solution synthesis, it was interesting to note this unusual regio- and stereoselective hetero-Michael reaction worked on solid phase in a similar manner. For comparison purposes, compound **15.5** was also synthesized by solution synthesis.

Our solution synthesis to obtain tetrahydroquinoline-based tricyclic derivatives having an eight-membered ring is shown in Scheme 16. For this study, compound **16.1** was synthesized and then this derivative was subjected to Lewis acid-mediated Grignard reaction. Both isomers **16.2** and **16.3** were obtained in near equal yields and then utilized further to explore the scope of ring-closing metathesis reaction. For example, compound **16.2** was subjected to *N*-alloc removal and acryloylation, and it was then subjected to RCM reaction. This reaction was found to be very fast, giving the desired cyclic enamide derivative **16.4** in >85 % yield. The product was well characterized by 2D-NMR studies. Upon similar conditions, the other allylic alcohol derivative **16.3** gave the expected cyclic enamide product in very high yield. In both cases, the stereochemistry of the –OAc group in eight-membered ring was assigned by nOe studies. Further, model studies with hetero-Michael reaction on the enamide functional group in the eight-membered rings are shown in Scheme 17. Compounds **16.4** and **16.5** were inde-

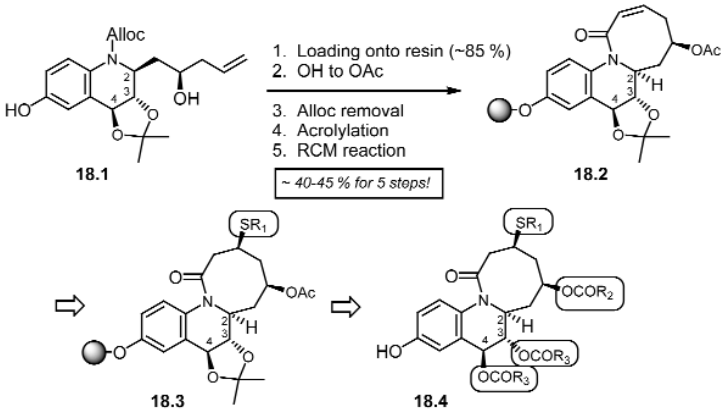


Scheme 16 Polycyclics having a medium-size ring by RCM.



Scheme 17 Ring conformation control: asymmetric hetero-Michael as a diversity-oriented reaction.

pendently subjected to the thiol addition. To our surprise, in both cases, the major product was influenced by the ring conformation and it was independent from the stereochemistry of the –OAc group in the eight-membered ring. In both cases, the two isomers were found to be in ratio ~1:6–1.8. One could explain this reaction as the ring conformation control and it has a very little influence from the chiral group present on the mid-size ring system. This conformational control asymmetric hetero-Michael reaction opens an attractive approach to introducing asymmetric diversity in solid-phase synthesis. Our progress to date in solid-phase synthesis leading to the library generation is shown in Scheme 18. Compound **18.1** was immobilized onto the solid support using a bromoWang resin (loading ~85 %, determined after cleavage from the support). To continue further, this compound was subjected to *N*-alloc removal followed by acryloylation. Following this, it was then subjected to ring-closing metathesis that successfully gave the cyclic product. Thus, compound **18.2** was obtained from **18.1** in overall 40–45 % yield for 5 steps. Further, work is in progress to complete the remaining steps on solid phase and to obtain a mid-size library by IRORI split-and-mix-type technology. It would be interesting to examine the stereochemical outcome of the thio reaction on solid phase and to compare these results with the solution synthesis.



Scheme 18 Manual solid-phase synthesis and toward the library generation.

Finally, Fig. 5 shows our next-generation plans toward the tetrahydroaminoquinoline-based, artificial amino acid, **F5.1**, and utilization of this highly versatile building block in obtaining skeletally diverse complex polycyclic compounds. Our preliminary studies toward these goals resulted in a practical, enantioselective synthesis of compound **F5.2**. Having a successful method in hand for obtaining compound **F5.2**, work is now ongoing toward the solution synthesis of complex polycyclic derivatives. Following the successful completion of solution-phase synthesis work, the solid-phase synthesis project will then be undertaken.

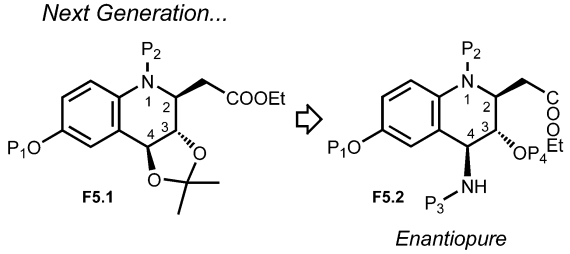


Fig. 5 Next-generation design: aminoquinoline-derived artificial amino acid.

CONCLUSION

The early days of combinatorial chemistry efforts in which simple heterocyclic compound-based library generation was the main thrust are now challenged with the growing need for developing efficient high-throughput synthesis methods leading to natural product-like complex polycyclic compounds. An evolving area of stereo- and enantioselective DOS, and the development of novel methods leading to the three-dimensional skeletally diverse polycyclic derivatives is likely to play an important role in terms of populating the required chemical space for providing a rapid access to natural product-like compounds. An efficient mapping of the desired chemical space and its appropriate function in developing highly effective therapeutics will be a topic of discussion for the years to come. Whatever the outcome of this exercise, the synthetic community is well positioned to undertake some of these challenges.

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