Review

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Advances in Solution- and Solid-Phase Synthesis toward the Generation of Natural Product-like Libraries

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1. Introduction

There is a growing interest in the use of small molecules as chemical probes in parallel to classical genomic tools (gene expression, gene profiling, gene knockouts, and siRNA-based gene silencing, etc.) to understand biological functions.[1−8] Small molecule probes have the ability to modulate macromolecules such as proteins, DNA, RNA, or carbohydrates in a controlled and selective manner; furthermore, some of the unique advantages of small molecules over the classical biological tools include the ability of the probes to function in a nondestructive manner to induce subtle and generally reversible changes in macromolecule dynamics.[1,9,10] In addition to using them as chemical probes to understand biological function, these small molecules offer an excellent starting point in launching drug discovery programs and could further be developed as therapeutic candidates.

In the past few years, an interest in this area has sparked due to the growing desire to modulate (and dissect through perturbation) intracellular signaling pathways.[11] The era of postgenomic chemical biology (also known as the "chemical genomic age") is challenging the chemistry and biology community to develop programs in which small molecules could be extensively used to enhance our current understanding of intracellular signaling pathways.[8,12−22] These pathways are fundamental to cellular functions in both normal and deregulated cellular processes. Usually, these pathways involve multiple, highly complex, and dynamic protein−protein interactions that are challenging to understand due to limited technology and tools available for studying signaling pathways.[23−31] A lack of thorough understanding about their participation in various normal and deregulated processes combined with the formidable challenge to modulate protein−protein interactions in a controlled and in a reversible manner severely limits our ability to develop therapeutic

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Born in India, Jyoti Prokash Nandy completed his Ph.D. under the supervision of Prof. Javed Iqbal from the Indian Institute of Technology, Kanpur (IITK), in 2002 and joined Prof. Albert Eschenmoser's group as a postdoctoral fellow in the Scripps Research Institute, La Jolla, California. In 2004, he moved from Scripps and joined the National Research Council of Canada (NRC) as a postdoctoral fellow in Dr. Prabhat Arya's team. With his experience in the areas of peptidomimetics (IITK) and nucleoside-based chemistry (TSRI) from two previous laboratories, he is presently engaged in developing natural product-like molecular architectures with the vision of diversity oriented synthesis (DOS). His flavonoid-inspired library has been shared with several biomedical research groups in search of small molecule tools for modulating protein−protein interactions.

Michael Prakesch, born in Saverne, France (1974), graduated from the Ecole Nationale Supérieure de Chimie et de Physique de Bordeaux (ENSCPB) in 1997. He obtained his Ph.D. at the University of Rennes in 2002 under the supervision of Dr. René Grée in the area of enantioselective fluorination method development and their applications in total synthesis. After postdoctoral studies at the Institut de Recherche Clinique de Montréal under the direction of Dr. Yvan Guindon, he joined Dr. Prabhat Arya's team at the Steacie Institute for Molecular Sciences, National Research Council of Canada in Ottawa. At the NRC, he developed new methods leading to high-throughput generation of alkaloid natural product-inspired polycyclic derivatives and also worked on medicinal chemistry projects in the area of apoptosis and phosphatases. Recently, he joined the Ontario Institute for Cancer Research (OICR) in Toronto as the medicinal chemistry laboratory manager.

Shahriar Khadem was born in Iran. He received his B.Sc. in Pure Chemistry in 1990 and M.Sc. in Organic Chemistry from the Ferdowsi University, Mashhad, Iran, in 1996 under the supervision of Prof. Majid M. Heravi in heterocyclic synthesis. He has several years of experience in industry as a research chemist. He is currently a Ph.D. student at the University of Ottawa under the supervision of Dr. Prabhat Arya. His research is focused on developing solution- and solid-phase synthesis of tetrahydroquinoline-derived polycyclic derivatives to explore their function(s) as natural product-inspired bioactive chemical probes.

Thirupathi Reddy obtained his Ph.D. in the area of total synthesis of bioactive natural products under the supervision of Dr. J. S. Yadav, Director, Indian Institute of Chemical Technology (IICT), Council of Scientific and Industrial Research (CSIR), Hyderabad, India. Following this, he joined the research team of Dr. Prabhat Arya at the National Research Council of Canada in Ottawa and worked there for a two year period. In his postdoctoral tenure, he developed novel methods in solution and on a solid phase leading to high-throughput generation of indoline alkaloid-inspired compounds. He also gained experience in building these libraries on the solid phase using the IRORI 2D bar-coded technology. Small molecules being generated from his research were then shared with several biological groups interested in the discovery of chemical modulators of signaling pathways (e.g., FAK and Bcl-2 protein family). After completing his tenure at the NRC, he joined a pharmaceutical company (PainCeptor) in Ottawa working in the area of pain-related biological disorders and is utilizing his multistep solution- and solid-phase organic synthesis skills in the design of bioactive small molecules.

approaches that exploit these pathways for beneficial outcomes. It is anticipated that the successful development of small molecule modulators of protein−protein interactions will create excellent opportunities for biomedical researchers to develop novel therapeutic strategies that would no longer be constrained by the limited set of proteins with enzymatic activity that are encoded in the genome.[32−35]

In general, protein−protein interactions involve shallow surfaces and cover a relatively large surface area. While there are a few examples in the literature that support the use of "hot spots" in protein−protein interactions as small molecule targets, usually the lack of structural information about protein complexes and the overall dynamic nature of protein complexes inside the cellular environment have limited success using designed molecules.[36−39] Thus, rapid access to small molecules by high-throughput organic synthesis and screening (through dynamic assays) remains an attractive strategy for identifying small molecule modulators of protein−protein interactions. This leads to two important questions: (1) In the absence of any structural information, what types of small molecules are most likely to be successful for disrupting signaling pathways based on

Utpal Sharma was born in Sibsagar, India, in 1975. He received his M.Sc. degree from Gauhati University, India, in 1997. He obtained his Ph.D. degree from Dibrugarh University, India, in 2001 under the supervision of Dr. R. C. Boruah at the Regional Research Laboratory, Jorhat. His research focused on the synthesis of a new class of antitumor heterosteroid. In 2001, he joined Prof. Marcus A. Tius' group at the University of Hawai as a postdoctoral fellow, where he was involved in the synthesis of the hydroazulene section of guanacastepene A. In 2003, he joined Dr. Prabhat Arya's team at the Steacie Institute for Molecular Sciences, National Research Council of Canada in Ottawa. In his group, he developed solution- and solid-phase methods leading to the library generation of natural-product-like tetrahydroquinoline compounds to explore their biological properties. In 2005, he joined the medicinal chemistry group of Naeja Pharmaceuticals Inc., Edmonton, as a research scientist.

Prabhat Arya was born in Jammu, India (1958), and grew-up in the campus area of University of Delhi where he received his postsecondary education. Following a short stint in the laboratory of Professor Robert Corriu (Montpellier, France), he then worked as a postdoctoral fellow with Professors Ian Paterson, FRS (Cambridge University, UK), and Bill Chan (McGill University). He joined the NRC in 1989 and quickly rose through the ranks to become a Senior Research Officer (1999−2007). Currently, he is working with the Ontario Institute for Cancer Research (OICR). In addition to this, he holds several additional positions including Adjunct Professorships at Biochemistry, Microbiology and Immunology (BMI), University of Ottawa; Biochemistry, McGill University; and Chemistry, Queen's University, and Affiliate Investigator, Ottawa Health Research Institute (OHRI). The research in the Arya group is aimed at developing methods leading to high-throughput generation of natural product-inspired chemical probes with the objectives of hunting for functional small molecules, in particular, as modulators of protein−protein interaction-based signaling pathways. Chemical tools that are being developed in his laboratory are widely shared with several biomedical researchers interested in dissecting signaling pathways using small molecules.

dynamic protein−protein interactions? (2) Can these molecules serve as generalized scaffolds for the construction of libraries of compounds highly enriched in small molecules that are likely to disrupt protein−protein interactions?

2. Combinatorial Chemistry

To meet the growing challenges in search of functional small molecules, for more than two decades, the area of combinatorial chemistry is now very much engaged in the drug discovery arena.[22,40−57] While taking advantage of high-throughput access to DNAs/RNAs, peptides, and solid-phase synthesis tools, the next challenge was to bring this and other related technologies to the small molecule arena. During this time, several outstanding reviews, book chapters, and even books have been written on this topic. In general, as a community, we have been very successful in embracing this area of high-throughput organic synthesis in producing rather simple compounds that are rich in aromaticity and have high sp^2 content; moreover, these compounds often lack the features that are commonly found in bioactive natural products.

3. Natural Products as "Role Models" for Combinatorial Chemistry

Over the years, three-dimensional (3-D), architecturally complex natural products have been used as small-molecule probes for understanding protein function. The search for novel natural products with interesting biological properties is an ongoing exercise.[58−69] Imbedded in these natural products are a number of highly diverse, chiral functional groups, which are potential sites for protein binding. Although natural products from a variety of sources (plants, soil, sea, etc.) are very useful candidates for identifying lead compounds, the major limitation with natural products in most cases is their follow-up organic synthesis/medicinal chemistry efforts. In many cases, the availability of the natural product is not sufficient for the various desired biological assays, thereby limiting the exploration of their full potential. Developing similar relatively simple structural analogs to natural products with comparative biological responses often is a challenging and a highly time-consuming undertaking.

At this point, the development of natural product-inspired, high-throughput organic synthesis programs could be extremely useful. Several examples of generating natural product-like compound libraries that utilize the diversity-oriented synthesis (DOS) and the biology-oriented synthesis (BIOS) are discussed in this review. Both of these programs are aimed at populating the unexplored natural products-based chemical space that is currently unoccupied by conventional combinatorial chemistry.[1,70−83] The combinatorial chemistry program in DOS (and in BIOS) utilizes stereo- and enantioselective organic synthesis reactions and is designed to provide small molecules that are rich in (i) stereochemically defined polyfunctional groups and (ii) conformationally diverse, natural product-like skeletons. In contrast, with few exceptions, classical combinatorial chemistry efforts have led to simple compounds lacking three-dimensional architectures. These simple compounds may not be able to populate the chemical space that is occupied by bioactive natural products and may be less likely to be useful as modulators of protein−protein interactions and as chemical probes for dissecting dynamic signaling pathways. With DOS or BIOS, a synthetic platform is already established, resynthesis at any stage is achievable, and second generation compounds can be easily obtained.

Members of natural products including alkaloids,[84−91] flavonoids,[92,93] and several of their derivatives are known to

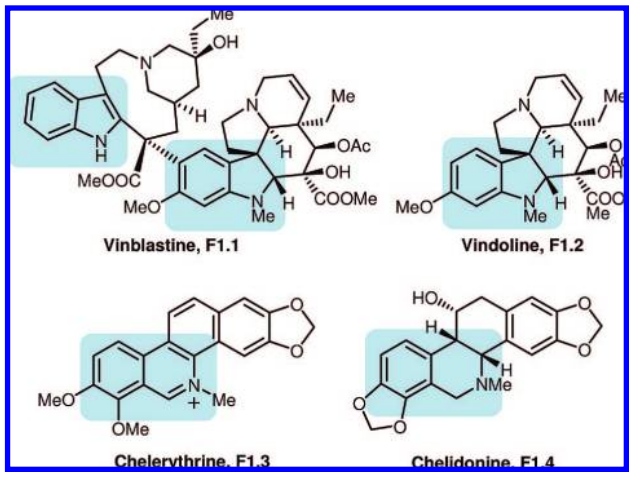


Figure 1. A few examples of bioactive alkaloid natural products.

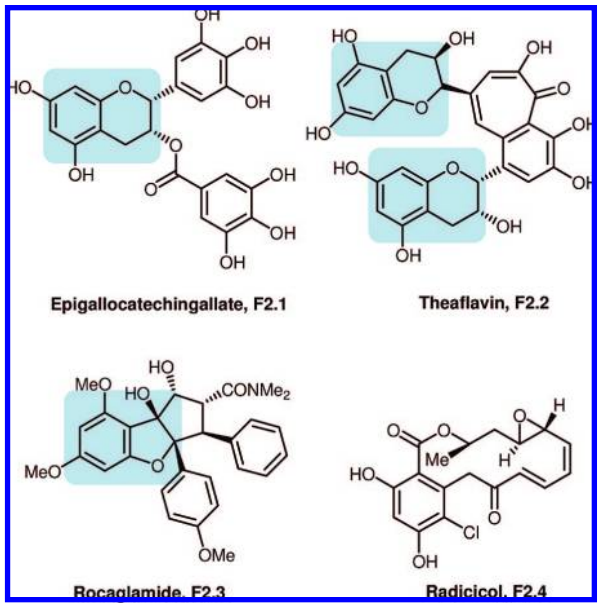


Figure 2. A few examples (**F2.1**−**F2.3**) of oxygen-enriched natural products (e.g., flavonoids and antibiotics). Epigallocatechingallate (**F2.1**) and theaflavin (**F2.2**) are known to function as modulators of protein−protein interactions. Radicicol (**F2.4**) is a phenolic-based macrolide antibiotic natural product.

possess a diverse range of biological properties. Commonly found in plants, most alkaloids and flavonoids are rich in nitrogen and oxygenated functional groups and contain "substructures" that are ideal for protein binding. Several alkaloid and flavonoid natural products are known to interfere with protein surfaces and exhibit a wide array of biological activities. Some of the bioactive alkaloids, polyphenolic natural products, and flavonoids are shown in Figures 1 and 2.

Belonging to the family of *Vinca* alkaloids, vinblastine (**F1.1**, Figure 1) and vindoline (**F1.2**) contain indole/indoline moieties and act as antimitotic agents because they inhibit microtubule formation.[94−96] Chelidonine (**F1.4**) is also an antimitotic alkaloid natural product and contains the tetrahydroisoquinoline moiety.[97] These three examples clearly demonstrate that a variety of alkaloid natural products and their synthetic analogs are known to interact with protein surfaces and exhibit specific bindings. This information offers a useful starting point for developing small-molecule chemical probes of biological pathways. These examples further validate the need for charting a chemical space that is currently occupied by bioactive alkaloid natural products.

Flavonoid natural products are commonly found in plants, and several of their derivatives have been shown to exhibit a diverse range of biological properties.[92,93,98−103] Most flavonoids are rich in oxygenated functional groups and contain polyphenolic moieties. These two features are ideal for protein binding, and several of these natural products are known to interfere with the protein surfaces and show a wide range of biological properties. The examples of bioactive polyphenolic natural products are shown in Figure 2. During a high-throughput *in silico* screening for small-molecule binders to the hydrophobic region of the Bcl-X_L protein, epigallocatechingallate (**F2.1**)[104] and theaflavin (**F2.2**)[92] were identified in order to develop compounds that could promote apoptosis. These two flavonoid natural products have been shown to interfere with the protein−protein interactions involving the Bcl-2 protein family and related proteins.[105,106] The ability to modulate these networks in a highly selective manner provides a means of obtaining a better understanding of these signaling pathways and their specific roles in apoptosis.[10,107−109] The rocaglamides (**F2.3**) are densely functare densionalized oxygen-enriched natural products and are shown to inhibit the NF-κB inhibitory activity at nanomolar concentrations in human T cells.[110,111] Several derivatives of this family are highly cytotoxic in human cancer cells with anticancer biological activities similar to that of Taxol.[112−114]

Radicicol (**F2.4**) is a phenolic-based macrolide antibiotic and is known to interact with heat shock protein 90 (Hsp90).[115−117] This protein is a molecular chaperone and plays an important role in stabilizing and correctly folding several oncogenic proteins. Finding inhibitors of this protein could be very useful for developing novel antitumor agents because Hsp90 inhibition could affect several deregulated signaling pathways.[118−121]

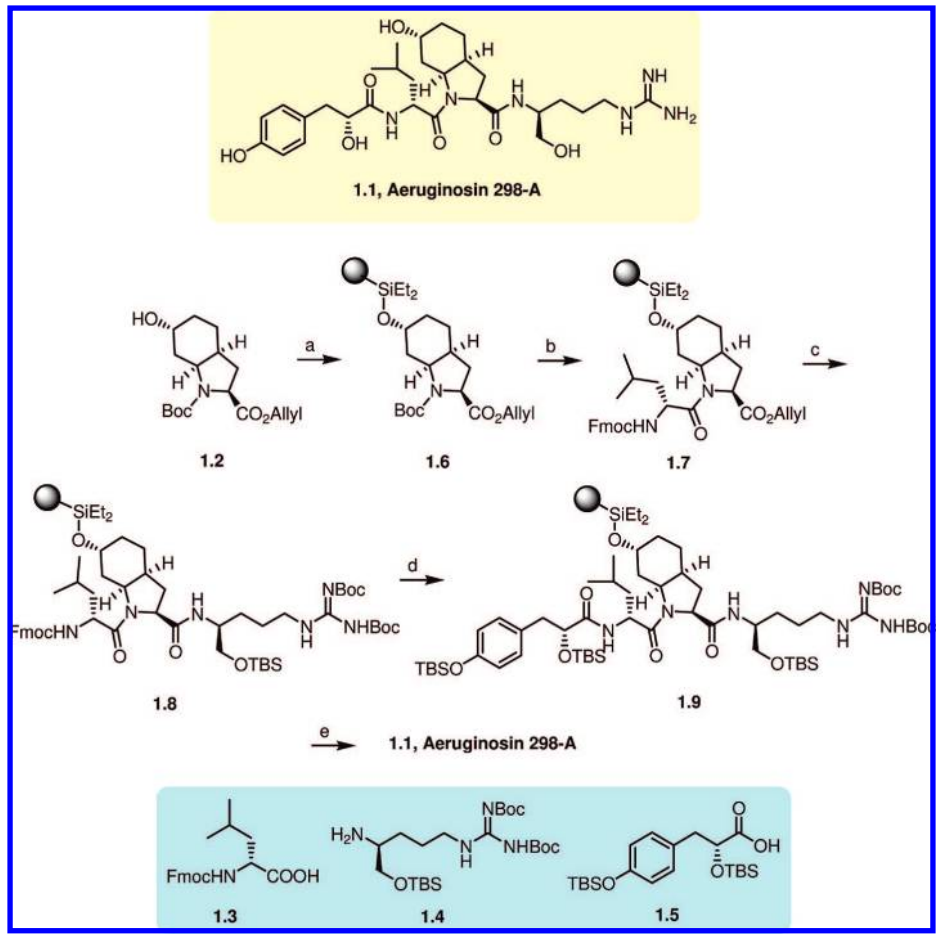
4. Solid-Phase Synthesis of Natural Products and Their Analogs

This section highlights the solid-phase synthesis of several bioactive natural products and their analogs. In particular, natural products that have not been covered in an earlier review[122] were selected for this section. Although attempts have been made to cover this activity mainly from years 2000 to 2006, we apologize to our readers for missing any major contributions to this area.

4.1. Aeruginosin 298-A

Aeruginosin 298-A (**1.1**, Scheme 1), a serine protease inhibitor containing an uncommon 2-carboxy-6-hydroxyoctahydroindole (L-Choi, **1.2**), a D-leucine (**1.3**), an L-argininol (Argol, **1.4**), and *p*-hydroxyphenyllactic acid (D-Hpla, **1.5**) moieties was isolated from *Microcystis aeruginosa* (NIES-298)[123,124] The combinatorial synthesis of aeruginosins and their analogs utilizing a silyl linker on a polymer support, and the biological evaluation were investigated by Takahashi and co-workers.[125] The units **1.2**, **1.4**, and **1.5** necessary for the construction of aeruginosin were separately synthesized. The attachment of **1.2** to PS-DESCl provided the polymer-supported **1.6**. Removal of the *N*-Boc group in **1.6**, followed by coupling with *N*-Fmoc-D-Leu-OH (**1.3**) using DIC-HOBt conditions, afforded the polymer-supported dipeptide **1.7**. Removal of the *O*-allyl ester in **1.7** and subsequent coupling

Scheme 1. Takahashi and Co-workers' Solid-Phase Synthesis of Aeruginosin Derivatives[a]



[a] Reagents and conditions: (a) PS-$SiEt_2Cl$, imidazole, CH_2Cl_2; (b) (i) TMSOTf, 2,6-lutidine, CH_2Cl_2; (ii) **1.4**, Fmoc-D-Leu-OH, DIC, HOBt, repeated twice; (c) (i) $Pd(PPh_3)$, dimedone, THF; (ii) **1.6**, DIC, HOBt; (d) (i) piperidine, DMF; (ii) **1.8**, DIC, HOBt; (e) (i) TFA, CH_2Cl_2, H_2O; (ii) PS-NMM, MeOH, CH_2Cl_2.

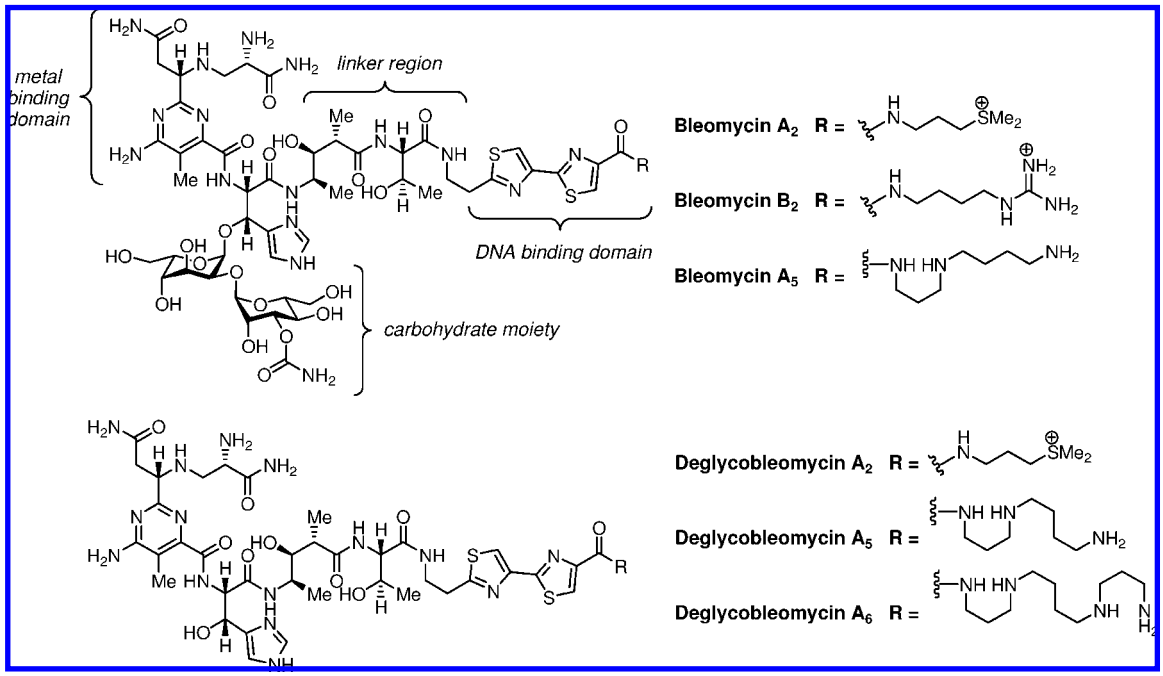
of the free acid with Argol (**1.4**) gave **1.8**. After *N*-Fmoc deprotection in **1.8**, the final fragment D-Hpla (**1.5**) was coupled using DIC-HOBt conditions giving the resin-bound aeruginosin 298-A derivative, **1.9**. Global deprotection of the *N*-Boc and *O*-TBS and simultaneous cleavage of the natural product (aeruginosin 298-A) from the resin were accomplished by TFA treatment, which afforded a mixture of the desired natural product and its trifluoroacetate salt. Treatment of this mixture with polymer-supported *N*-methyl morpholine (PS-NMM) in MeOH−CH_2Cl_2 finally removed the trifluoroacetate part, allowing access to 84% pure aeruginosin 298-A. On the basis of this solid-phase strategy, a 23-membered combinatorial library of aeruginosin derivatives was synthesized. One of the members (D-Hpla-D-Leu-L-Choi-Agma) exhibited strong inhibition against trypsin, 300 times more potent than the parent natural product aeruginosin.[125]

4.2. Bleomycin

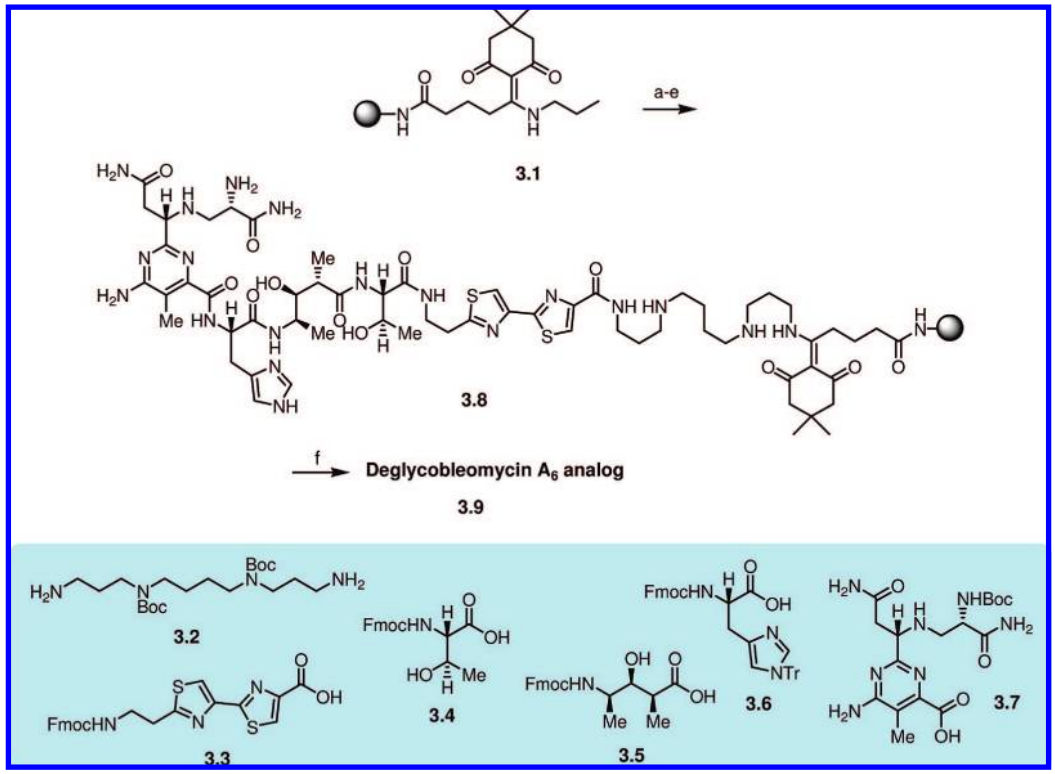
The bleomycins (Scheme 2) are known as antitumor antibiotics with glycopeptide skeleton, and they were first isolated as copper chelates from a culture broth of *Streptomyces verticillus*. Deglycobleomycin also shows similar properties as bleomycins and cleaves DNA in a sequence-selective manner. A Number of research groups have attempted the synthesis of deglycobleomycin, bleomycin, and their analogs over the past two decades to obtain a better understanding of its DNA degradation mechanism. An elegant solid-phase synthesis of deglycobleomycin A_5 was reported by Hecht and co-workers[126] that paved the way to access deglycobleomycins with varied C-termini[127] and the synthesis of bleomycin A_5 itself.[128] In a follow up study, Hecht and co-workers further reported the synthesis of conformationally constrained analogs of bleomycin A_5[129] and the solid-phase synthesis of a library of 108 unique deglycobleomycin analogs through a parallel synthesis approach.[130]

The library synthesis of deglycobleomycin A_6 analogs was carried out as shown in Scheme 3. The spermine-functionalized resin was obtained by treatment of *N*-di-Boc spermine **3.2** with the linker-bound resin **3.1** in the presence of DIPEA. In the following steps, the resin-bound material was sequentially attached to the bis-thiazole moiety of deglycobleomycin **3.3**, threonine moiety **3.4**, methylvalerate moiety **3.5** and histidine fragment **3.6** via standard peptide coupling conditions with usual unmasking of the N-protecting groups in between. Finally, the resin-bound pentapeptide resulting from the previous set of couplings was allowed to couple with *N*-Boc pyrimidoblamic acid **3.7** in the presence of BOP/DIPEA at 0 °C to afford fully protected deglycobleomycin A_6 analog in a near quantitative yield. Treatment of 90:5:5 TFA−Me_2S−triisopropylsilane allowed the global deprotection of the *N*-Boc functionalities to provide **3.8**, which was then exposed to a solution of 2% hydrazine in DMF to liberate the deglycobleomycin A_6 analog **3.9** from the resin.

Scheme 2. Bleomycins and Deglycobleomycins



Scheme 3. Hecht and Co-workers' Solid-Phase Sythesis of a 108-Membered Library of Deglycobleomycins[a]



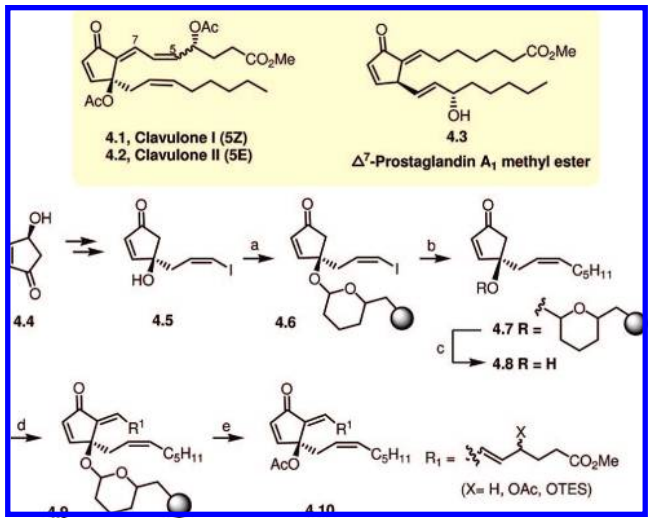
[a] Reagents and conditions: (a) (i) **3.2**, (^{i}Pr)$_2$NEt, DMF; (ii) **3.3**, HBTU, (^{i}Pr)$_2$NEt, DMF; (b) (i) 20% piperidine, DMF; (ii) **3.4**, HOBt, HBTU, (^{i}Pr)$_2$NEt, DMF; (c) (i) 20% piperidine, DMF; (ii) **3.5**, HOBt, HBTU, (^{i}Pr)$_2$NEt, DMF; (d) (i) 20% piperidine, DMF; (ii) **3.6**, HOAt, HATU, (^{i}Pr)$_2$NEt, DMF; (e) (i) 20% piperidine, DMF; (ii) **3.7**, BOP, (^{i}Pr)$_2$NEt, DMF; (iii) 90:5:5 TFA/^{i}Pr$_3$SiH/Me$_2$S; (f) 2% H_2NNH_2, DMF.

To synthesize a library of 108 analogs, Hecht and co-workers used three bithiazole, three threonine, three methylvalerate, and four β-hydroxyhistidine building blocks, which were either commercially available or readily synthesized using existing methods from the literature. The deglycobleomycin library was then subjected to supercoiled DNA plasmid relaxation assay to identify compounds that altered DNA cleavage activity. This study led to the discovery of two compounds (analogs of deglycobleomycin A_6) that are more active than deglycobleomycin A_6 itself.

4.3. Clavulones

The cross-conjugated dienone prostanoids like clavulone I and II or Δ^7-prostaglandin A_1 methyl ether (**4.1**, **4.2**, and **4.3**, respectively, Scheme 4) are important because of their

Scheme 4. Takahashi and Co-workers' Solid-Phase Synthesis of Clavulones[a]



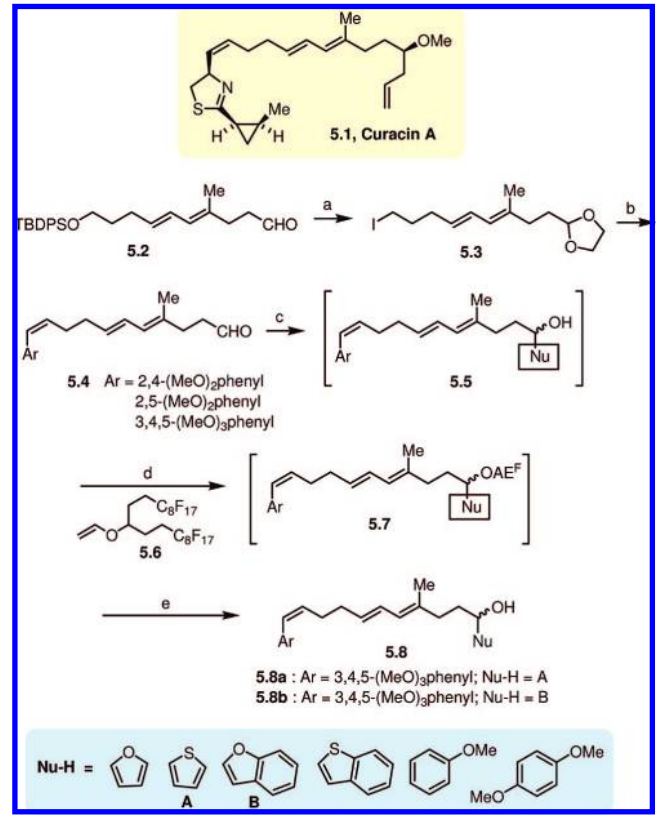
[a] Reagents and conditions: (a) 3,4-dihydro-2*H*-pyran-2-yl-methoxymethyl polystyrene, PPTS, CH_2Cl_2, 40 °C; (b) pentyl 9-BBN, $Pd(PPh_3)_4$, 2 M Na_2CO_3 (aq), THF, 45 °C; (c) TFA/CH_2Cl_2, RT; (d) KHMDS, THF, −78 °C, then R^1CHO, −78 °C; (e) (i) TFA/CH_2Cl_2, RT; (ii) Ac_2O, pyridine, DMAP, RT.

wide range of biological activities.[131,132] Takahashi and co-workers[133] reported an effective solid-phase synthesis of cross-conjugate prostanoids that is based upon incorporation of the α- and ω-chains via sequential carbon−carbon bond formation. The optically pure key cyclopentenone **4.5** bearing a *cis*-vinyl iodide side chain was prepared from cyclopentenone **4.4** in six steps and then immobilized onto the solid support using 3,4-dihydro-2*H*-pyran (DHP) polystyrene resin using its tertiary hydroxyl link to afford **4.6**. Treatment of pentyl 9-9-borabicyclo[3.3.1]nonane (9-BBN), obtained by *in situ* hydroboration of 1-pentene, with the solid-supported vinyl iodide **4.6** in presence of $Pd(PPh_3)_4$ and aqueous Na_2CO_3 completed modification of the ω-chain and afforded **4.7** in good yield. Aldol condensation of the ketone **4.7**, to install the α-chain, was successfully accomplished using six different aldehydes. The solid-supported ketone **4.7** was treated with potassium hexamethyldisilazane (KHMDS) at −78 °C and then subjected to the addition of different aldehydes to generate the solid-supported trienones, **4.9**. Cleavage from the resin under mild acidic conditions and subsequent acetylation provided the corresponding cross-conjugate dienones, the clavulones **4.10**, in moderate yields.

4.4. Curacin A

Lyngbya majuscula metabolite curacin A (**5.1**, Scheme 5) is an important marine natural product with significant antiproliferative activity.[134] The total synthesis of this thiazoline-based molecule was earlier published by several groups including an impressive report from Wipf and co-workers.[135] As a follow up attempt, Wipf and co-workers further reported the combinatorial synthesis of a six-compound mixture library using curacin A as the lead compound.[136] It was understood that the alkenyl thiazolidine moiety in curacin A might be responsible for the instability of the molecule *in vivo*. Thus, in an attempt to obtain further robust and possibly more potent analogs, the researchers decided to replace the thiazoline heterocyclic ring of curacin A with similar but different electron-rich aromatic rings or heterocycles. Again, the homoallylic methyl ether side was

Scheme 5. Wipf and Co-workers' Synthesis of a Library of Curacin A Analogs[a]

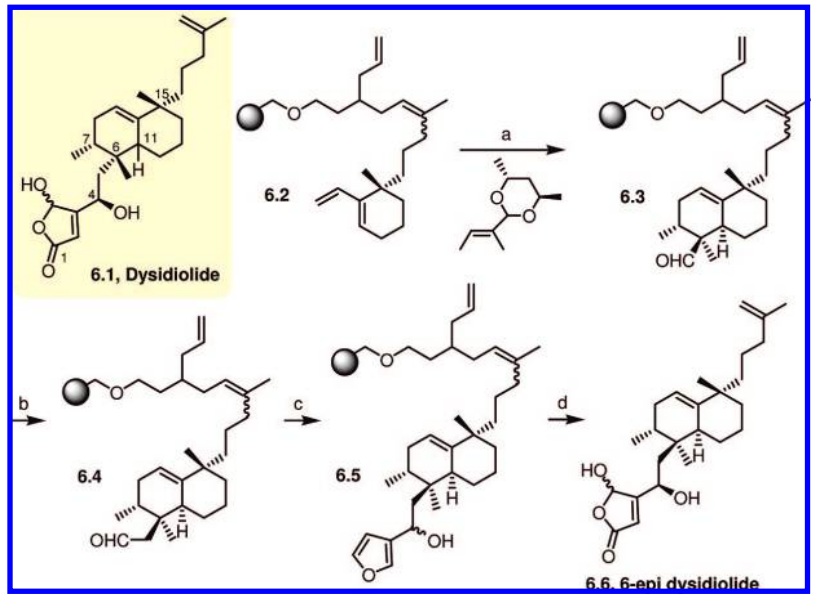


[a] Reagents and conditions: (a) (i) $(CH_2OH)_2$, *p*TsOH, PhH, reflux; (ii) TBAF, THF; (iii) MsCl, Et_3N, CH_2Cl_2; (iv) NaI, acetone, reflux; (b) (i) PPh_3, MeCN, reflux; (ii) NaHMDS, THF, −78 °C, ArCHO; (iii) TsOH, acetone/water; (c) Nu-H, *t*-BuLi, THF, −78 °C; (d) **5.6**, CSA, THF; (e) (i) FC-72/MeCN/H_2O; (ii) MeOH, Et_2O, CSA; (iii) FC-72/MeCN/H_2O.

modified by replacement with a broad range of more hydrophilic benzylic alcohols. Aldehyde **5.2**, a starting point of this synthetic plan, was obtained in solution phase by the steps mentioned in the previous report.[135] Three crucial building blocks, **5.4**, were prepared thereafter, again by classical solution synthesis from **5.2** via the dioxolane **5.3** using Finkelstein chemistry, followed by Wittig reactions as the key transformations (Scheme 5). To validate this approach, Wipf and co-workers synthesized seven mixtures of **5.5** by heteroatom-directed lithiation of **5.4** and other derivatives with a cocktail of three to six aryllithium reagents in excess. Due to the use of excess lithiation reagents, the resulting alcohols **5.5** were heavily contaminated with the organolithium material, which was eliminated by a three-phase liquid−liquid extraction process using perfluorinated solvent F-72 and MeCN−H_2O. The product mixture **5.5** was trapped with fluorous-tagged vinyl ether **5.6** prior to the extraction that allowed the resulting adduct **5.7** to slip into the F-72 layer leaving the organic and inorganic contaminants to remain in organic and aqueous environments, respectively. Methanol treatment of the F-72 layer liberated the organic material from the fluorous tag, and a second extraction with F-72/MeCN/H_2O finally brought the pure and structurally defined organic product mixture **5.8** into the organic layer.

Treatment of **5.4** with 2-lithiated furan, thiophene, benzofuran, benzothiophene, anisole, and 1,4-dimethoxybenzene afforded the most biologically active mixtures. One set of the mixture was found to be exceptionally active. Its individual components were synthesized in pure form and

Scheme 6. Waldmann and Co-workers Solid-Phase Synthesis of Dysidiolide-Derived Protein Phosphatase Inhibitors[a]



[a] Reagents and conditions: (a) (i) TMSOTf, CH_2Cl_2, −78 °C; (ii) *p*-toluenesulfonic acid, acetone, $ClCH_2CH_2Cl$, H_2O, heat; (b) (i) Ph_3PCH_2OMeCl, KO^{t}Bu, THF, RT; (ii) pyridinium-*p*-toluene sulfonate, THF, 1% H_2O, heat; (c) 3-bromofuran, *n*BuLi, THF, −78 °C; (d) (i) bengal rose, O_2, $(^iPr)_2N$ Et, *hν*, CH_2Cl_2, −78 °C, 5 h, then RT, 10 min; (ii) $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (2 × 10 mol %), CH_2Cl_2, RT.

then subjected to screening in living human carcinoma cells to check their potency in altering the cell cycle and the microtubule cytoskeleton. The most potent curacin A analogs identified by Wipf and co-workers in the present synthetic exercise were **5.8a** and **5.8b**, which inhibited tubulin polymerization with an IC_{50} of ∼1.0 μM. These analogs are really intriguing because despite being structurally simpler and chemically more robust than curacin A, they retain comparable biological activity to curacin A itself with higher water solubility.

4.5. Dysidiolide

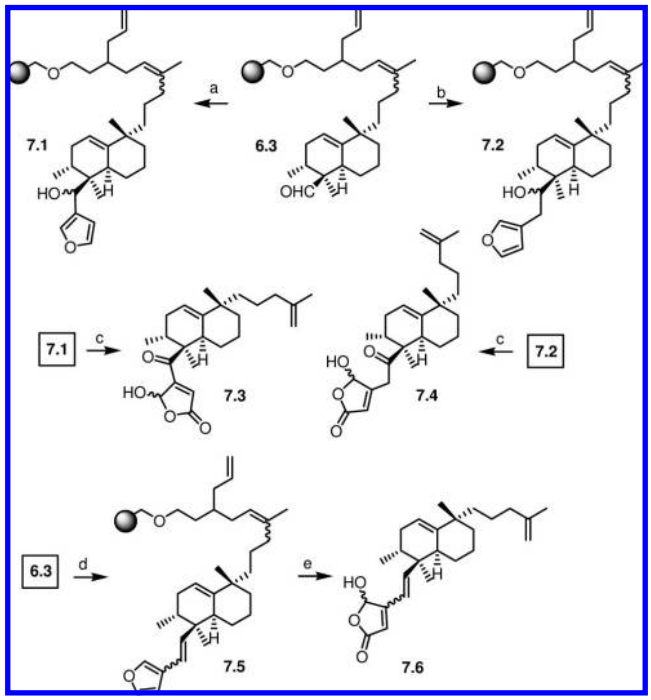
Dysidiolide (**6.1**, Scheme 6) is a sesquiterpene natural product that inhibits the dual specificity of the Cdc25 protein phosphatase family, which plays a crucial role in cell cycle regulation. It has a decalin-type architecture having a hydrophobic side chain with a terminal olefin moiety and a hydrophilic side chain with a secondary alcohol and γ-hydroxybutenolide unit. For the solid-phase synthesis of 6-epi-dysidiolide **6.6** reported by Waldmann and co-workers,[137] the polymer-bound compound **6.2** was subjected to Diels−Alder reaction with triglic aldehyde (converted into a quasi C_2-symmetric chiral acetal using (*R*,*R*)-2,4-pentanediol) to enhance the stereoselectivity. The resulting cycloadduct, upon removal of the chiral auxiliary, afforded the aldehyde **6.3** as a mixture of four isomers formed in the ratio endo/endo′/exo/exo′ 87:4:9:0.1. Homologation of the aldehyde by one carbon unit could then be achieved by a sequence of Wittig reaction followed by hydrolysis of the enol ether formed in that step. However, the reaction did not go to completion on the solid support. An alternative route employing the corresponding phosphonium chloride and KO-^{t}Bu as a base resulted in clean transformation. Further, hydrolysis of the enol ether was carried out with PPTS/THF/H_2O. Nucleophilic addition of furyllithium to resin-bound aldehyde **6.4** resulted in a 2:1 mixture of diastereomers **6.5**. Subsequently, furan **6.5** was oxidized with singlet oxygen in the presence of a mild base. Finally, release of the products **6.6** from the solid support was achieved in a traceless manner by performing an olefin metathesis using 20 mol % Grubbs' catalyst.

The next objective was to obtain the analogs of dysidiolide that differ from the natural product in chain length and in the substitution pattern. Dysidiolide analogs with a shortened carbon chain were obtained via the addition of 3-lithiofuran to aldehyde **6.3**, giving compound **7.1** (Scheme 7). This was then subjected to oxidation with Bengal rose and subsequent cleavage from the solid support by olefin metathesis. Further oxidation with IBX resulted in the corresponding ketone **7.3**. Similarly, compound **7.2** was obtained from **6.3** by a Grignard reaction with 3-bromomethylfuran and Mg in THF, which was then subjected to oxidation followed by cleavage from the solid support by olefin metathesis. Subsequent oxidation resulted in **7.4**. The same reaction sequence was also carried out on the homoaldehyde system. Finally, dysidiolide derivatives with a double bond between the anellated ring and the hydroxyl butenolide were also synthesized (see **7.5** and **7.6**). Treatment of **6.3** with the ylide, obtained from furylmethyltriphenylphosphonium bromide by reaction with KO^{t}Bu in THF at room temperature, resulted in **7.5**. The furan ring was oxidized with the singlet oxygen, and once again, the olefinic dysidiolide analog **7.6** was released by olefin metathesis. The dysidiolide analogs were then investigated as inhibitors of the protein phosphatase Cdc25c and in cellular cytotoxicity assays. Most of the analogs exhibited inhibition properties.

4.6. Epothilone

The epothilones (e.g., epothilone A, B and D, **8.1**, **8.2**, and **8.4**, Scheme 8) have attracted tremendous attention of the biomedical community, because these naturally occurring antitumor agents exhibit strong cytotoxicity toward a number of tumor cell lines including the ones that are resistant to Taxol (paclitaxel).[138−143] Coupled with their exotic molecular architecture and an exceptional potential as antitumor agents, the epothilones have remained a "hot" target for total synthesis during the past several years.[139,144−158] However,

Scheme 7. Dysidiolide Library (Continued)[a]



[a] Reagents and conditions: (a) 3-bromofuran, *n*BuLi, THF, −78 °C; (b) 3-bromomethylfuran, Mg, THF, RT to 50 °C; (c) (i) bengal rose, O_2, $(^iPr)_2NEt$, *hν*, CH_2Cl_2, −78 °C, 5 h, then RT, 10 min; (ii) $(PCy_3)_2Cl_2Ru{=}CHPh$ (2 × 10 mol %), CH_2Cl_2, RT; (iii) IBX, DMSO, RT; (d) 3-furylmethyltriphenylphosphonium bromide, KO^{t}Bu, THF, 60 °C; (e) (i) bengal rose, O_2, $Et(^iPr)_2N$, *hν*, CH_2Cl_2, −78 °C, 5 h, then RT, 10 min; (ii) $(PCy_3)_2Cl_2Ru{=}CHPh$ (2 × 10 mol %), CH_2Cl_2, RT.

there are only a few reports where the epothilone analogs were rationally designed and then synthesized to evaluate their biological potential. Nicolaou and co-workers were active in this area for several years. In one of the reports, the researchers described the rational design and synthesis of a number of epoxide and cyclopropane analogs of epothilone B and then screened them for the cytotoxicity against different human cancer cell lines.[141]

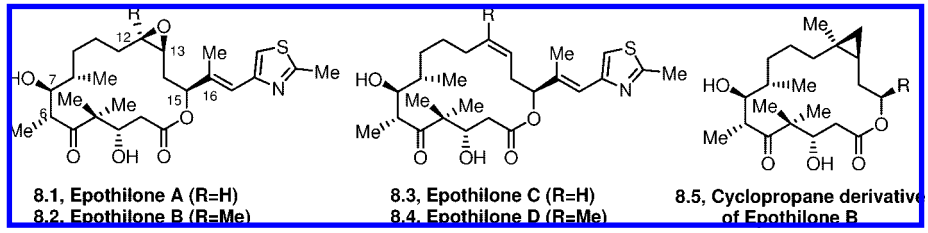
The solution-phase synthesis of epothilone B analogs with different thiazole and pyridine side chains was achieved via the key macrocyclic intermediate **9.1** (Scheme 9), which was coupled to different stannanes like **9.2** or **9.3** under Stille-type coupling conditions in the presence of $[PdCl_2(MeCN)_2]$, CuI, and $AsPh_3$ in DMF to provide **9.4** and **9.5**, respectively. Both of these analogs showed very impressive cytotoxicity. Interestingly, their previous structure−activity relationship (SAR) data revealed that the replacement of the epoxide ring in epothilone B with cyclopropyl does not change the biological activity. This prompted the Nicolaou group to explore the synthesis and biological properties of the cyclopropyl analogs as well. The synthesis of the cyclopropyl epothilones **9.9** was approached via the key aldehyde **9.6**, which was constructed from the natural monoterpene, nerol. Aldehyde **9.6** was allowed to react with vinyl iodides under Nozaki−Hiyama−Kishi coupling conditions. The resulting secondary alcohol (no significant diastereoselectivity) afforded **9.7** as a mixture of 1:1 epimers following the selective deprotection of the TMSE group at the carboxyl end of the molecule. Cyclization of these mixtures under Yamaguchi conditions allowed access to the desired 15*S* 16-membered lactones **9.8** (32−33% yield) together with their 15*R* epimer (separated by chromatography). Finally, removal of the TBS protecting groups gave the epothilone derivatives **9.9.** Depending on the iodide used in the Nozaki−Hiyama−Kishi coupling step, the side chain of the epothilones **9.9** was either a thiomethyl-substituted thiazole (**9.10A**) or a methyl-substituted pyridine ring (**9.10B**). The biological data revealed a cyclopropyl analog with the substituent **9.10A** as the most active molecule being six times more potent than the natural epothilone B itself.

An efficient solution-phase route to epothilone D analogs via a degradation approach was accomplished by Dong and co-workers.[159] Starting with epothilone D (**10.1**, Scheme 10) obtained by an enzymatic synthesis, Dong and co-workers first protected the molecule as the *O*-bis-TBS ether and then cleaved the macrocyclic ring across its olefinic bond by a sequence of OsO_4-mediated dihydroxylation followed by oxidative cleavage of the dihydroxy derivative with $Pb(OAc)_4$. The resulting keto aldehyde eliminated the hetereocyclic side chain on treatment with K_2CO_3 giving the corresponding acid, which was then protected as the methyl ester **10.2**. Treatment of dimethyltitanocene on **10.2** transformed its ketone end to a terminal olefin and the methyl ester was hydrolyzed to give the acid **10.3**. Coupling of **10.3** with different alcohols **10.4**, **10.5**, and **10.6** provided esters **10.7**, each with two appropriately spaced terminal olefinic bonds. Ring-closing metathesis of an ester **10.7** with Grubbs' second generation catalyst afforded a 1:1 mixture of *E*/*Z* isomers that gave the desired epothilone D analogs following *O*-TBS deprotection.

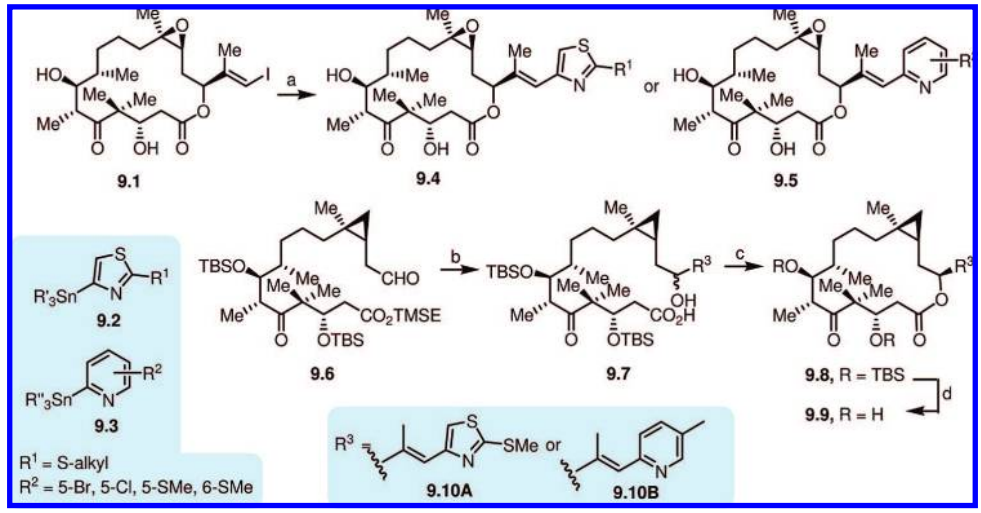
4.7. Erythromycin A

Macrolides are a class of antibiotic compounds that contain several sugars linked to a large 12−16-membered lactone (macro-olide) ring. For several decades, macrolides such as erythromycin A (Ery-A, **11.1**, Scheme 11) have been widely utilized for the treatment of bacterial respiratory tract infections.[160−162] Akritopoulou-Zanze and Sowin[163] developed an efficient solid-phase synthesis of a combinatorial library of macrolide derivatives that could be used for general biological or biochemical screening. Based on the previously reported procedures, the aldehyde **11.2** was synthesized from erythromycin A, **11.1**, in a few steps, and it was then used as a core structure to construct the library. For solid-phase synthesis, the aminomethylpolystyrene resin (with an extended modified Wang type linker) **11.3** was coupled to several *N*-Fmoc-protected amino acids **11.4** as the first diversity. The resulting resin **11.5**, after removal of the *N*-Fmoc protection, was coupled with the macrolide core **11.2** under reductive alkylation conditions to obtain the resin-bound macrolide **11.6**. The secondary amine formed in this step was further subjected to reductive alkylation conditions with several aliphatic aldehydes (in most cases, the aromatic aldehydes reacted very sluggishly or did not work at all, depending on the size of the secondary amine) to incorporate the second diversity. The third diversity was introduced to the resin **11.7** obtained in the previous step by a third round of reductive amination on the tethered primary amine (linked to the cyclic carbamate part of the macrolide) with a series of aromatic aldehydes. The products were then subsequently removed from the solid support by standard TFA treatment, to produce the desired library members **11.8**. This methodology allowed the researchers to construct a combinatorial library of nearly 70 000 derivatives of erythromycin A.

Scheme 8. Epothilone A, B, C and D and the Cyclopropane Derivative

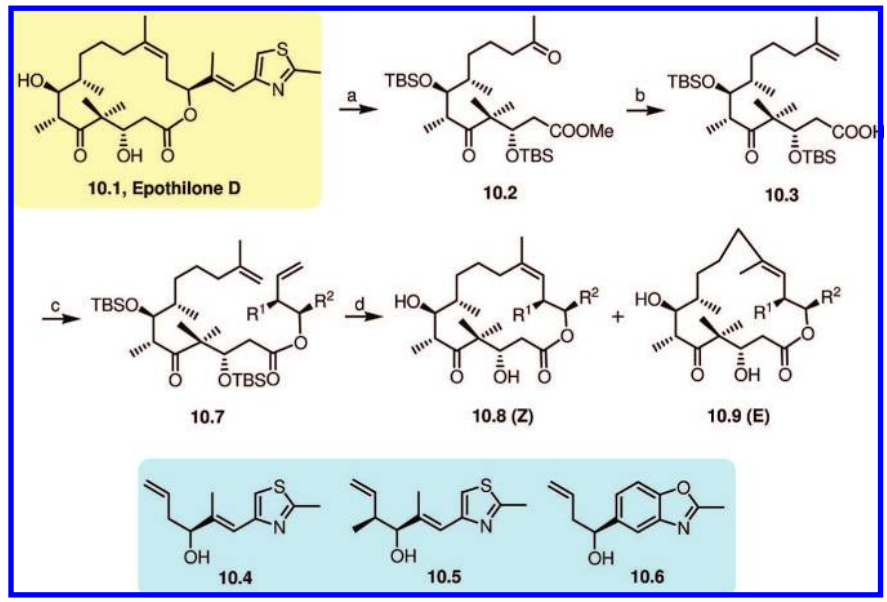


Scheme 9. Nicolaou and Co-workers' Synthesis of Epothilone Analogs[a]



[a] Reagents and conditions: (a) $[PdCl_2(MeCN)_2]$ (0.5 equiv), CuI (2.0 equiv), $AsPh_3$ (1.0 equiv), **9.2** or **9.3** (2.5 equiv), DMF, 25 °C; (b) (i) R^3I (3.0 equiv), $CrCl_2$ (10.0 equiv), $NiCl_2$ (0.2 equiv), 4-^{t}BuPy (30.0 equiv), DMSO, 25 °C; (ii) TBAF (2.0 equiv), THF, 25 °C; (c) 2,4,6-trichlorobenzoyl chloride (2.4 equiv), Et_3N (6.0 equiv), THF, 0 °C then DMAP (2.2 equiv), toluene, 75 °C; (d) TFA/CH_2Cl_2 (20% v/v), 25 °C.

Scheme 10. Dong and Co-workers' Synthesis of Epothilone Analogs[a]

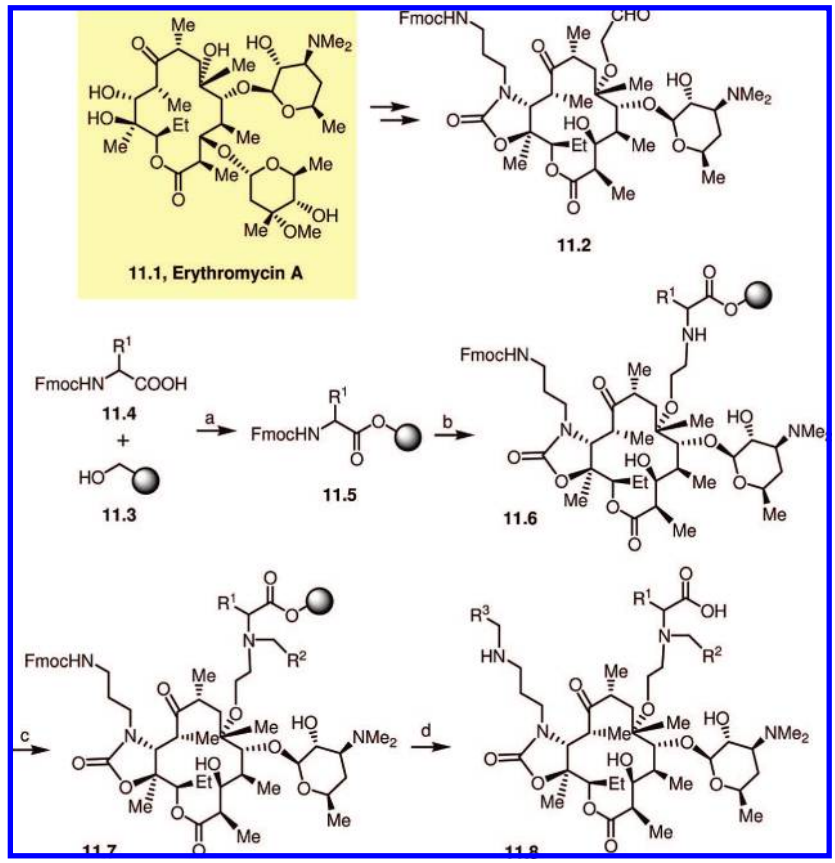


[a] Reagents and conditions: (a) (i) TBSOTf, $NHEt_2$, CH_2Cl_2, −78 °C; (ii) OsO_4, TMEDA, −78 °C then $NaHSO_3$; (iii) $Pb(OAc)_4$, PhH, then K_2CO_3, MeOH; (iv) $TMSCHN_2$, MeOH, PhMe; (b) (i) Cp_2TiMe_2, PhMe, 80 °C; (ii) LiOH, ^{i}PrOH, H_2O; (c) **10.4** or **10.5** or **10.6**, EDC, DMAP, CH_2Cl_2; (d) (i) Grubbs' 2nd generation catalyst (20 mol %), CH_2Cl_2, reflux; (ii) TFA, CH_2Cl_2, 0 °C to RT or HF−pyridine, THF, 0 °C to RT.

4.8. Estrone

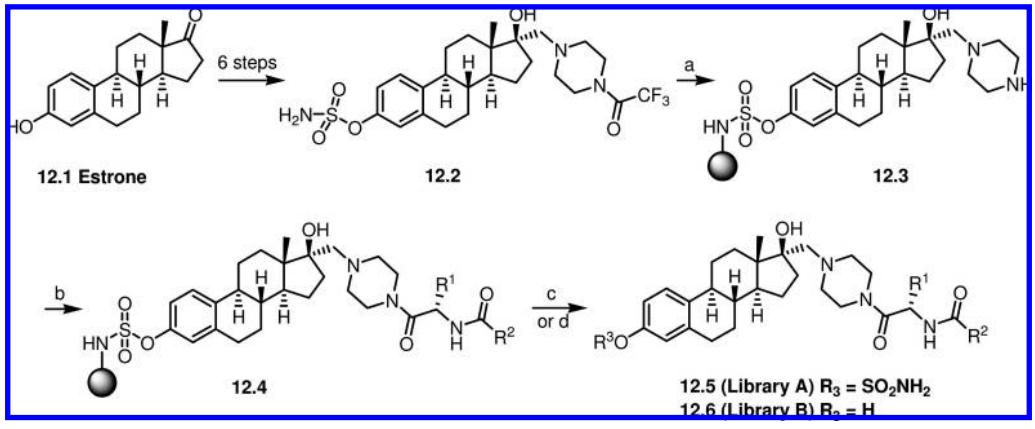
Poirier and co-workers reported earlier that the estrone derivatives with a C3 *O*-sulfamate group having a hydrophobic substituent at C17 can act as potent inhibitors of steroid sulfatase, a key enzyme active in estrogen-sensitive cancers.[164] In a following article, the same group[165] reported the construction of a large combinatorial library of such derivatives using the trityl chloride resin. The steroid **12.2** (Scheme 12), a key intermediate for the solid-phase synthesis, was first prepared in six steps from estrone **12.1** and then loaded onto the resin to give **12.3** following deprotection of the trifluoroacetyl group. Two model libraries of 25 phenols and 25 corresponding sulfamates were prepared by solid-phase parallel synthesis starting from **12.3**. First diversity

Scheme 11. Akritopoulou-Zanze and Co-workers' Solid-Phase Synthesis of Macrolide Analogs of Erythromycin A[a]



[a] Reagents and conditions: (a) (i) DIC, DMAP, CH_2Cl_2/THF; (ii) 20% piperidine/DMF; (b) **11.2**, 10% AcOH/DMF, wash, $NaCNBH_3$, 10% AcOH/DMF; (c) R^2CHO, 10% AcOH/DMF, $NaCNBH_3$; (d) (i) 20% piperidine/DMF; (ii) R^3CHO, 10% AcOH/DMF, wash, $NaCNBH_3$, 10% AcOH/DMF; (iii) 90% TFA/CH_2Cl_2.

Scheme 12. Poirier and Co-workers' Solid-Phase Parallel Synthesis of 17α-Substituted Estradiol Sulfamate and Phenol Libraries[a]



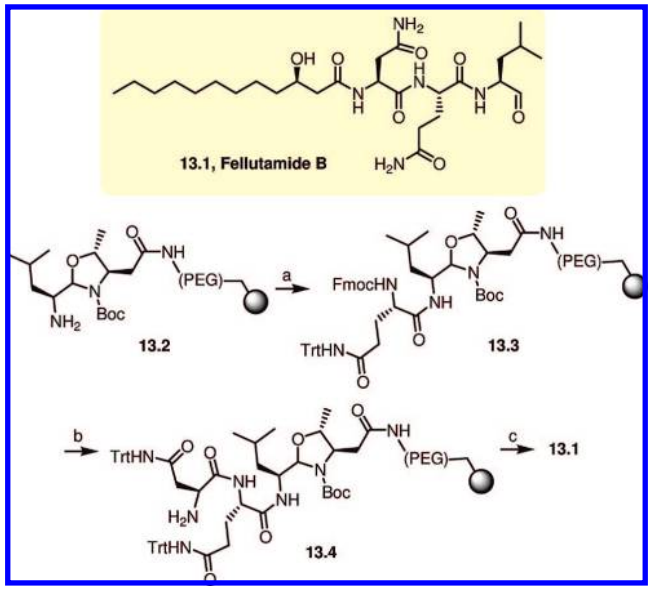
[a] Reagents and conditions: (a) (i) trityl chloride resin, $(^iPr)_2NEt$ (6 equiv), CH_2Cl_2, RT; (ii) NaOH (3 N), THF, RT; (b) (i) PyBrOP, HOBt, $R^1CH(NHFmoc)COOH$, $(^iPr)_2NEt$ (4 equiv), DMF, RT; (ii) 20% piperidine/CH_2Cl_2, RT; (iii) PyBOP, R^2COOH (3.0 equiv), $(^iPr)_2NEt$ (6.0 equiv), DMF, RT; (c) 5% TFA/CH_2Cl_2, RT (library A, sulfamates, 5 × 5 = 25 members); (d) piperazine (10 equiv), THF, 45−50 °C (library B, phenols, 5 × 5 = 25 members).

was introduced by coupling of five different *N*-Fmoc amino acid residues to the piperazine nitrogen of **12.3**. Deprotection of the *N*-Fmoc group and further coupling with five different acid residues gave the second diversity. At the end of the second amidation step, the resulting resin **12.4** was divided in two equal portions for the release of the phenolic steroids and sulfamates by two different methods of cleavage. The first portion of resins **12.4** was treated with a solution of 5% TFA in dichloromethane to obtain the sulfamate library A, **12.5**. The phenol library B **12.6** was obtained from the second portion of resins **12.4** by treatment with 10.0 equiv of piperadine in THF at 45 °C.

4.9. Fellutamide

The fellutamide class of natural products display potent activity in both the nerve growth factor (NGF) induction and cytotoxicity assays.[166] A combination of solid- and solution-

Scheme 13. Crews and Co-workers' Solid-Phase Synthesis of Fellutamide B[a]



[a] Reagents and conditions: (a) (i) Fmoc-Gln(Trt)-OH, HBTU, HOBt; (ii) 20% piperidine in DMF; (b) (i) Fmoc-Asn(Trt)-OH, HBTU, HOBt; (ii) 20% piperidine in DMF; (c) (i) (*R*)-(−)-3-hydroxydodecanoic acid, HBTU, HOBt; (ii) TFA; (iii) 0.1:40:60 TFA/MeCN/H_2O.

phase synthetic methods was utilized to accomplish the total synthesis of the neurotrophic lipopeptide aldehyde fellutamide B (**13.1**, Scheme 13) by Crews and co-workers.[167] The researchers utilized the commercially available leucinal-loaded beads **13.2** (H-Leu-methyloxazolidine NovaSyn TG resin) as a starting material in their synthesis. Coupling with the protected glutamine (*N*-Fmoc-Gln(Trt)-OH) yielded **13.3**, which after Fmoc removal was reacted with the protected asparagine (*N*-Fmoc-Asn(Trt)-OH) to afford **13.4**. Following the coupling with (*R*)-(−)-3-hydroxydodecanoic acid after the *N*-Fmoc removal, it was then subjected to global deprotection and cleavage of the peptide from the resin with 0.1% TFA in 2:3 MeCN/H_2O. Fellutamide B, **13.1**, was isolated after lyophilization from the resin cleavage solution. The *N*-octanoyl analog of fellutamide B was also synthesized using a similar strategy. Both of these compounds were tested on mouse fibroblast L-M cell lines and were found to be cytotoxic and also had the capacity to induce the NGF secretion.

4.10. Fumiquinazoline

Ganesan and co-workers described the adaptation of their four-step solution-phase total synthesis of the fumiquinazoline alkaloids[168] to solid-phase conditions.[169] The first goal in their study was to develop the solid-phase synthesis of (+)-glyantrypine, the simplest of these natural products. The solid-phase synthesis started with the coupling of anthranilic acid derivatives with the commercially available Wang resin loaded with *N*-Fmoc-L-Trp, **14.1**, following the *N*-Fmoc removal (Scheme 14). This was then subjected to aniline acylation using different *N*-Fmoc amino acid chlorides under two-phase Schotten−Baumann conditions. A key step in this approach was the dehydrative cyclization of the resulting linear tripeptide **14.2** to afford the oxazine **14.3**. Following the *N*-Fmoc removal under piperidine conditions, the amidine carboxamide **14.4** was obtained from the rearrangement of **14.3**. The cyclative cleavage from the resin yielded (+)-glyantrypine, **14.5**, or its derivatives in excellent yields after purification.

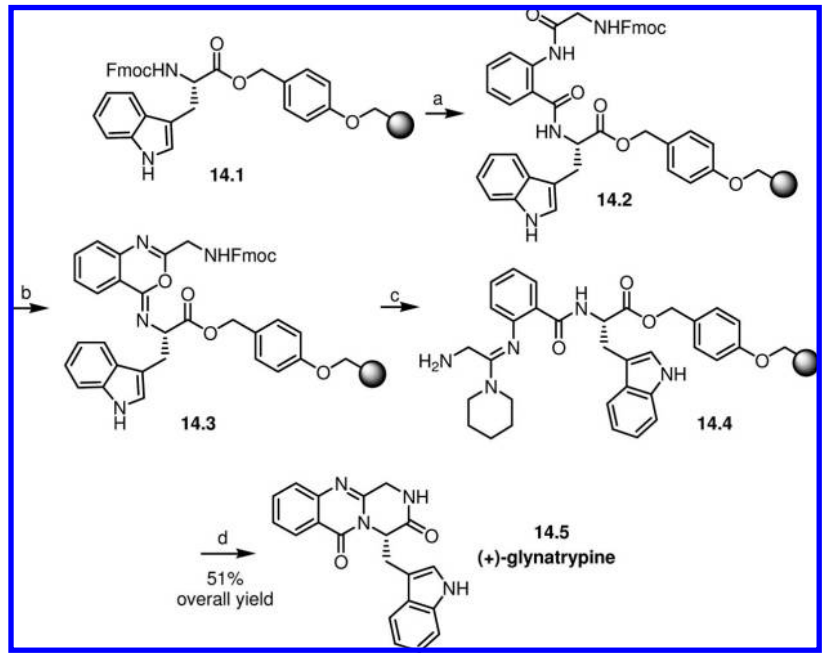
4.11. Gougerotin

Hexopyranosyl cytosines are a large class of RNA-binding natural products.[170−176] Members of this class are structurally related and contain a cytosine base attached to a pyran ring and often a modified peptidic moiety. The first solid-phase synthesis of the natural product gougerotin (**15.1**, Scheme 15) was accomplished by Migawa and co-workers.[177] The synthesis commenced by preparing the starting glycosyl donor **15.3** from commercially available galactoside **15.2**. Coupling of **15.3** with appropriate nucleobase afforded **15.4**, which was then subjected to deacetylation, followed by oxidation under TEMPO/bis(acetoxy)iodobenzene (BIAB) conditions to give the carboxylic acid **15.5**. Compound **15.6** as the *N*-Teoc dervative was then obtained via the protection of the *N*-4 exocyclic amino group. This was then coupled with ArgoGel Rink resin using HATU coupling to give the resin-bound material **15.7**. Under the tin(II) chloride reduction conditions, the azido group was reduced to obtain the corresponding amine. Subsequent HATU coupling with O′Bu-Fmoc-D-serine followed by *N*-Fmoc removal with 10% piperidine/DMF gave the amine **15.8**. Finally, the fully protected resin-bound gougerotin was obtained on further HATU-mediated coupling with *N*-Boc-sarcosine. This was then subjected to 0.4 M NaOH/MeOH (1:5) treatment for the hydrolysis of the carbamate protecting groups (i.e., benzoates and *N*-Teoc) and to TFA to obtain gougerotin, **15.1**, as the TFA salt. A small test library demonstrating this methodology was also prepared. One of the compounds showed an approximately 4-fold increase over the parent compound against pathogenic *Escherichia coli*.

4.12. Homocamptothecin

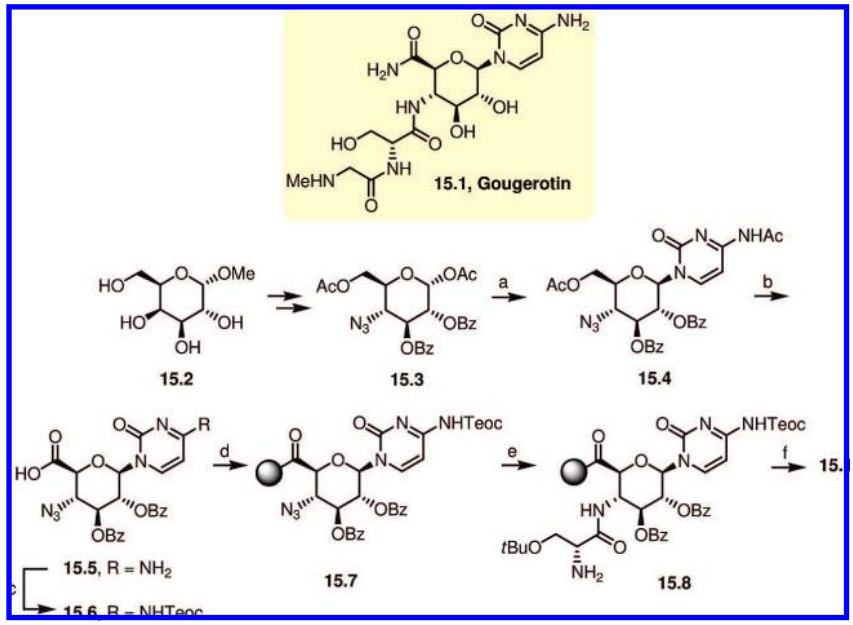
Homocamptothecin (hCPT, Scheme 16), synthesized by Lavergne and co-workers in 1997,[178] is a novel seven-membered E-ring homologue of an important anticancer agent camptothecin (CPT). It has been proposed that hCPT, which is emerging as a promising lead in drug design programs,[179] may not function in a similar manner to CPT for topoisomerase-induced DNA cleavage.[180] This observation sparked an interest in obtaining further analogs in the homocamptothecin series with the goal of developing antitumor agents. Curran and co-workers[181] developed a practical and efficient synthetic strategy for the homocamptothecin class of antitumor agents and accomplished the parallel synthesis of 115 analogs of homosilatecan, a close relative of homocamptothecin (hCPT). The synthetic pathway to homosilatecans is shown in Scheme 16. The synthesis of **16.5** (the key intermediate to hCPT and analogs) started with a known material, 3-formyl-4-iodo-2-methoxy-6-trimethylsilyl pyridine, **16.2**.[182] Treatment of iodoformyl pyridine **16.2** with $NaBH_4$ in EtOH at −40 °C afforded a hydroxymethyl pyridine intermediate, which was then protected with *O*-MOM. Treatment of this protected material with ^{i}PrMgCl at −40 °C, followed by the addition of CuCN/LiCl and quenching of the resulting cuprate reagent with propionyl chloride, provided the key ketone intermediate **16.3**. Methyl acetate was treated with LDA at −78 °C, and the resulting anion was exposed to **16.3**, promoting an aldol condensation to give a β-hydroxy ester. Treatment of that β-hydroxy ester

Scheme 14. Ganesan and Co-workers' Solid-Phase Synthesis of Fumiquinazoline Alkaloids (Glynatrypine)[a]



[a] Reagents and conditions: (a) (i) piperidine; (ii) anthranilic acid (10.0 equiv), EDC (12.0 equiv); (iii) Fmoc-Gly-Cl (7.0 equiv), pyridine (15.0 equiv); (b) $Ph_3P/I_2/(^iPr)_2NEt$ (11.0/11.0/22.0 equiv); (c) piperidine; (d) $MeCN/ClCH_2CH_2Cl$ (1:1), reflux.

Scheme 15. Migawa and Co-workers' Solid-Phase Synthesis of Gougerotin[a]



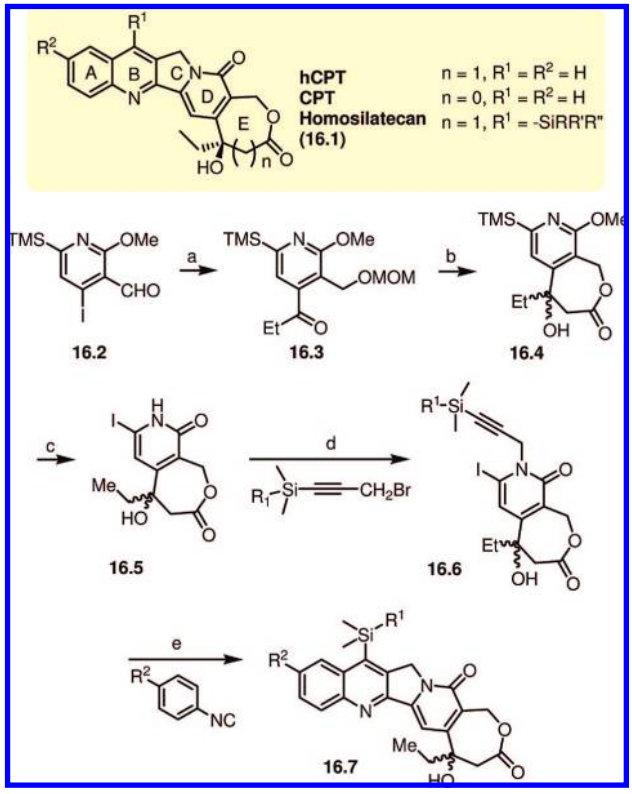
[a] Reagents and conditions: (a) *N*-acetylcytosine, $SnCl_4$, DCE, 80 °C; (b) (i) Et_3N, MeOH; (ii) TEMPO, BIAB, CH_3CN (aq); (c) Teoc-OSu, $(^iPr)_2NEt$, DMF; (d) resin-ArgoGEl-NH_2, HATU, $(^iPr)_2NEt$, DMF; (e) (i) $SnCl_2$, PhSH, Et_3N, CH_2Cl_2; (ii) ^{t}Bu-Fmoc-D-Serine, HATU, collidine, DMF; (iii) 10% piperidine/DMF; (f) (i) Boc-sarcosine, HATU, collidine; (ii) 0.4 M NaOH/MeOH (1:4); (iii) TFA.

with TFA at room temperature afforded the TMS-lactone **16.4**. Iodinative desilylation of **16.4** was achieved with ICl in CH_2Cl_2/CCl_4 to afford the corresponding iodolactone. Demethylation of the phenolic ether was accomplished by the addition of TMSCl to a mixture of the iodolactone and NaI in CH_3CN, providing iodopyridone **16.5**. The next step involved the parallel N-alkylation of **16.5** with several propargyl bromides to give **16.6** and parallel radical annulation of **16.6** with a collection of different isonitriles to generate homosilatecan analogs **16.7**. By this strategy, 115 new analogs were prepared, and the biological evaluations of these compounds were pursued.

4.13. Illudin

With an aim to develop modular methods that utilize C−C bond forming reactions to access natural products and complex natural product-like compounds, Pirrung and Liu[183] developed an approach to obtain illudin family based sesquiterpenes (Scheme 17). These compounds show a wide range of interesting biological activities in cancer that were initially discovered through the natural products illudin M and S from the Jack O'Lantern mushroom (*Omphalotus illudens*).[184−188] In the past, modular solution-phase synthetic methods to obtain several illudins were reported by Padwa

Scheme 16. Curran and Co-workers' Solution-Phase Parallel Synthesis of Homosilatecan Analogs[a]



[a] Reagents and conditions: (a) (i) $NaBH_4$; (ii) MOMCl, $(^iPr)_2NEt$; (iii) ^{i}PrMgCl, CuCN, LiCl; (iv) EtCOCl; (b) (i) LDA, $MeCO_2Me$; (ii) TFA, RT; (c) (i) ICl, CCl_4/CH_2Cl_2; (ii) TMSCl, NaI, MeCN; (d) NaH, LiBr; (e) $Me_3SnSnMe_3$, *hν*.

and Kinder.[189−191] Their approach involves the dipolar cycloaddition of a carbonyl ylide **17.3** (obtained from the carbene **17.4**) to an enone **17.5**. Following the same model, Pirrung and co-workers designed their solid-phase library using seven different diazocarbonyl, **17.6**, and seven different enone, **17.7**, building blocks. Cycloaddition reaction in the presence of rhodium octanoate as a catalyst in ether provided the cycloadduct **17.8** in good yield. To remove the polar By-products formed in this reaction along with the excess enone used to drive the reaction, a two-step high-throughput purification protocol was devised. The solid-phase extraction (SPE) with SiO_2/CH_2Cl_2 removed the polar materials, and the thiophenol scavenging resin removed the excess enone giving pure cycloadducts **17.8**. The exocyclic double bond was then introduced through a Wittig protocol, which was selective for the less hindered and more electrophilic carbonyl group. Compound **17.9** with the ether bridge was then subjected to KOH/MeOH treatment, which promoted elimination of the ether bridge and modified the side chains (bromides to methoxy and acetates to acids). The products were once again purified by SPE to provide **17.10** in good quantities. This method was utilized to obtain a library of 49 compounds, but it actually included 119 total compounds due to the stereoisomerism. Three of the library members showed complete inhibition of the growth of H460 cancer cells at 100 μM concentration.

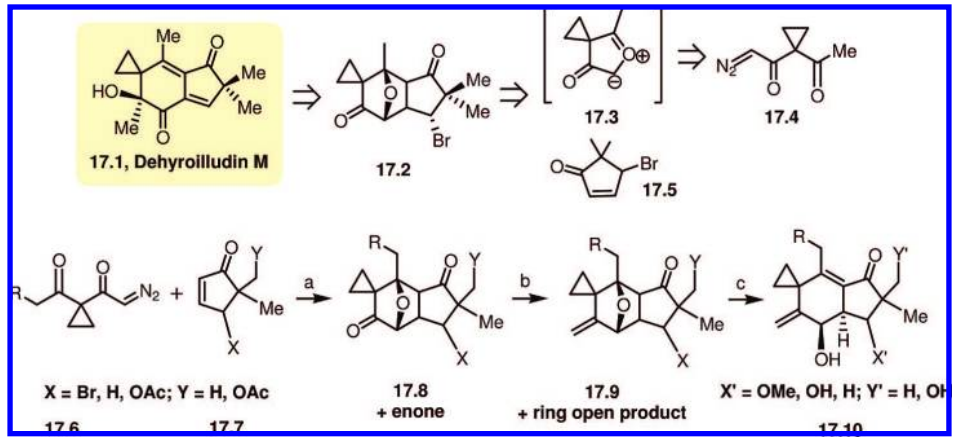
4.14. Macrosphelide

Isolated from the culture medium of *Macrospaeropsis* sp. FO-5050, macrosphelides A (**18.1**, Scheme 18) and B (**18.2**) strongly inhibit the adhesion of human leukemia HL-60 cells to human-umbilical-vein endothelial cells (HUVEC) in a dose-dependent fashion.[192−194] Takahashi and co-workers[195] reported the convergent solid-phase synthesis of a library of macrosphelide analogs that utilizes the palladium-catalyzed chemoselective carbonylation of vinyl halides. As shown in Scheme 18, three synthetic building blocks, **18.3**, **18.4**, and **18.5**, were utilized in developing the solid-phase synthesis program. This involved (i) the attachment of the secondary alcohol in block **18.3** to a polymer support, (ii) esterification with block **18.4**, (iii) chemoselective carbonylation of the vinyl iodide in unit **18.3** with alcohol **18.5** containing a vinyl bromide moiety, (iv) carbonylative macrolactonization of the polymer-supported **18.11**, and (v) cleavage from the polymer support. In the solid-phase synthesis, the block **18.3** was attached to a PS-DHP resin **18.6** using PPTS. The secondary hydroxyl group obtained after the *O*-TBS removal was subjected to esterification with acid **18.4** to obtain **18.9**. This was then followed by the palladium-catalyzed carbonylation of the vinyl iodide **18.9** with alcohol **18.5** at room temperature under 30 atm of carbon monoxide utilizing $PdCl_2(MeCN)_2$ as a catalyst to give **18.10**. The 4-methoxyphenylmethyl (MPM) group in **18.10** was then removed with DDQ to afford **18.11**, a polymer-supported starting material to explore the macrocyclic carbonylation. The palladium-catalyzed carbonylation of **18.11** was achieved at 80 °C utilizing $[Pd_2(dba)_3]$/dppf to provide macrolactone **18.12**. Finally, the desired macrosphelide **18.1** was obtained in 68% yield after the treatment of **18.12** with 4 N HCl. The successful manual solid-phase synthesis development then led to the generation of a macrosphelide combinatorial library with four variants of **18.3**, four variants of **18.4**, and eight variants of **18.5**, utilizing radiofrequency encoded combinatorial (REC) chemistry.[196] This split-and-pool method provided 122 macrosphelide analogs of **18.1** from 128 trials, isolated in good yields and purities.

4.15. Mappicine

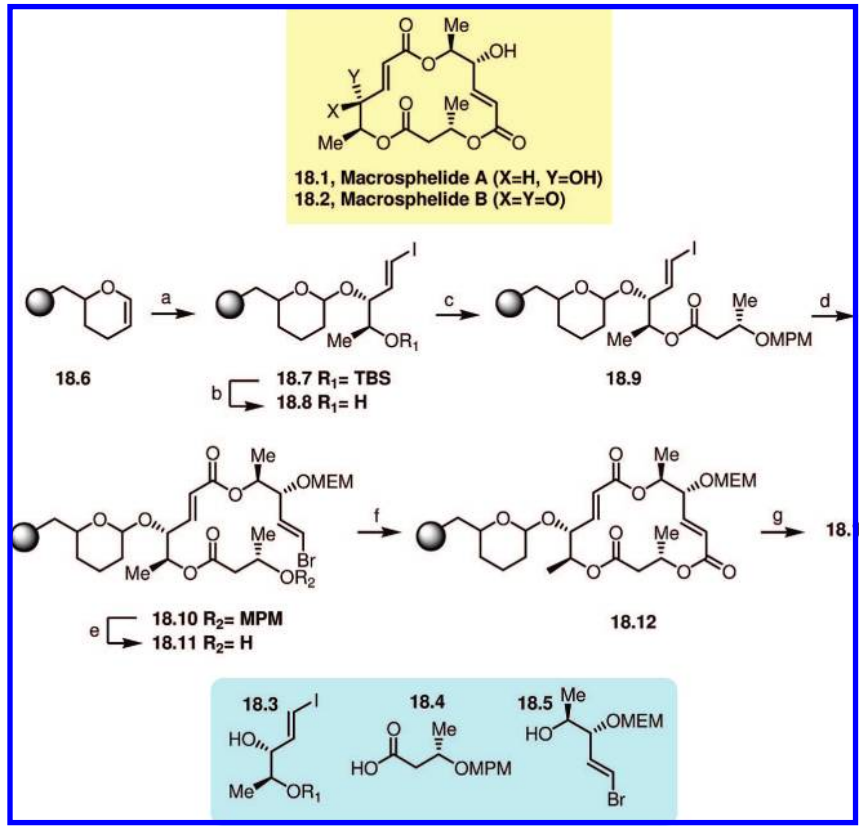
The metabolite (*S*)-mappicine (**19.2**, Scheme 19) was isolated from *Mappa foetida* in 1974. Mappicine ketone **19.1** is an oxidized derivative of mappicine and was isolated from *Nothapodytes foetida* in 1996. The keto derivative was found to be active against herpes viruses (HSV) and human cytomegalovirus (HCMV) in the low micromolar range (3−13 μM).[197,198] Curran and co-workers[199] reported an improved variant of their cascade radical annulation approach to the natural product mappicine. The goal of this study was to obtain new analogs of mappicine and mappicine ketone by utilizing the parallel synthesis techniques. In this approach, a pyridone D-ring **19.3** was subjected to alkylation with a suitable propargylating agent **19.4** bearing the B-ring substituent. This was then followed by a crucial cascade radical annulation with an isonitrile bearing the A-ring substituent **19.5** to obtain the mappicine analog. As a start, the formyl group in **19.6** was reduced to the methyl moiety, which then led to **19.7** following transmetalation and then the reaction with propionaldehyde; **19.8** was then obtained from **19.7** in a series of transformations that included (i) TMS−iodine exchange, (ii) demethylation, and (iii) N-propargylation, with an overall impressive yield. As shown in Scheme 19, this approach was also extended to obtain enantiomerically pure (*S*)-mappicine. This was achieved by an enantioselective reduction of the corresponding ketone with a chiral reducing

Scheme 17. Padwa and Kinder's Retrosynthesis Approach to Illudin and a Parallel Synthesis of Illudin Derivatives[a]



[a] Reagents and conditions: (a) $Rh_2(oct)_4$, ether; (b) (i) SPE; (ii) EtOH/(^{i}Pr)$_2$NEt, PS-thiophenol, RT; (iii) $Ph_3P{=}CH_2$ (excess); (iv) H_2O; (v) SPE; (c) (i) 30% KOH/MeOH; (ii) SPE.

Scheme 18. Takahashi and Co-workers' Solid-Phase Synthesis of Macrosphelide A and Analogs[a]



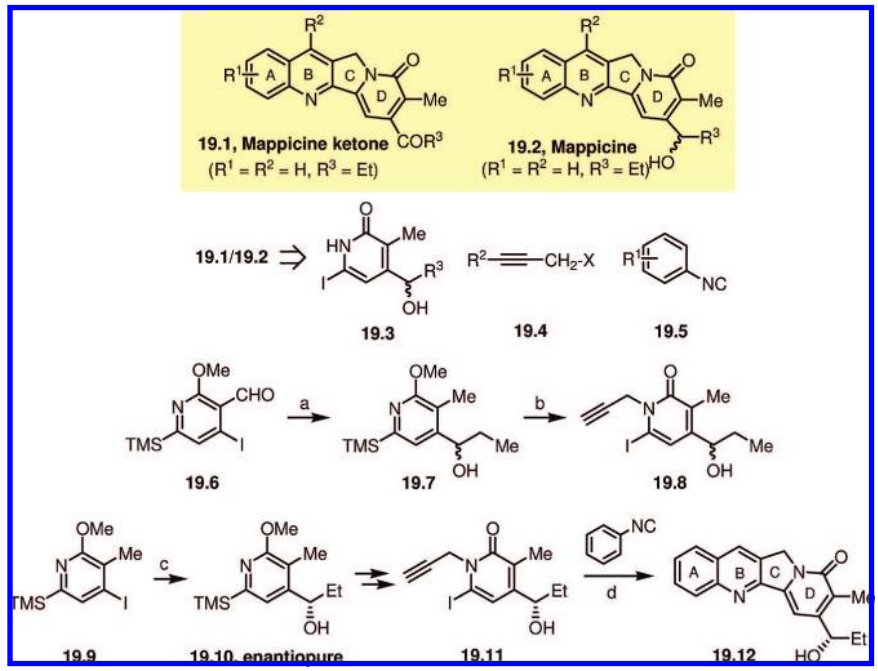
[a] Reagents and conditions: (a) **18.3**, PPTS (0.05 M), CH_2Cl_2, RT; (b) TBAF (0.3 M), THF, RT; (c) **18.4**, DIC (0.1 M), DMAP (0.001 M), CH_2Cl_2, RT; (d) **18.5**, [$PdCl_2(MeCN)_2$] (0.03 M), CO (30 atm), NEt_3 (0.2 M), DMAP (0.03 M), DMF, RT; (e) DDQ (0.3 M), aq $NaHCO_3$ (0.3 M), CH_2Cl_2/H_2O (1:1), RT; (f) [$Pd_2(dba)_3$]/dppf (0.03 M), CO (30 atm), NEt_3 (0.2 M), DMAP (0.03 M), DMF, 80 °C; (g) 4 N HCl in dioxane, RT.

agent to obtain **19.10**; **19.10** then led to **19.11** using the previously mentioned synthesis protocol. Finally, (−)-mappicine **19.12** was produced by the crucial radical cyclization between **19.11** and phenylisonitrile in the presence of hexamethylditin in benzene. The successful method development was further utilized in four separate parallel synthesis experiments in a 4 × 4 × 1 manner with four different isonitriles **19.5**, four different propargyl bromides **19.4**, and one iodopyridone **19.3** to generating a library of 64 mappicine analogs. By a similar approach, a 48-membered library of mappacin ketone analogs was also synthesized. Finally, the researchers also reported a library of 560 compounds as mappicine analogs by a fluorous mixture synthesis approach.[200]

4.16. Mniopetals and Marasmanes

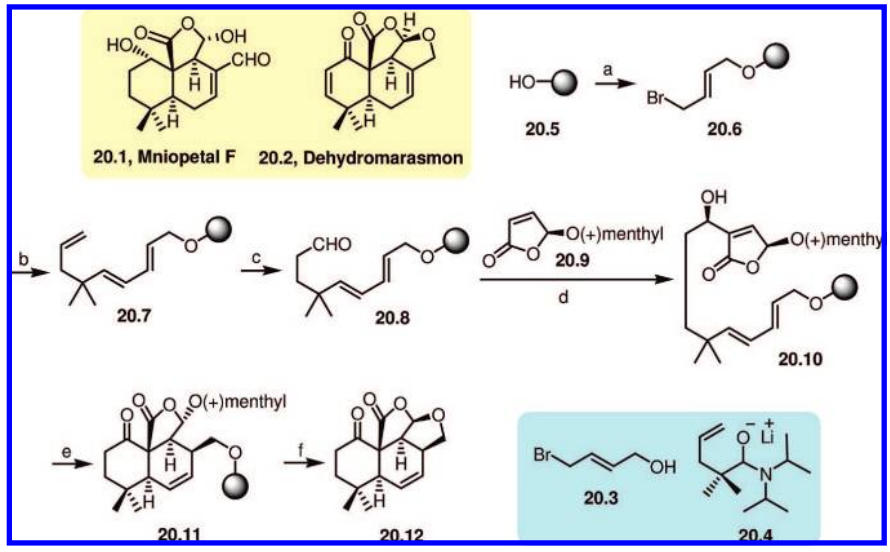
The solid-phase synthesis of an advanced building block for mniopetals and marasmanes and the libraries thereof was reported by Jauch and Reiser.[201] These natural products (**20.1** and **20.2**, Scheme 20) are inhibitors of HIV reverse transcriptase.[202,203] Based on the synthesis of an advanced intermediate in solution-phase chemistry by the same group,[204,205] the solid-phase approach was developed. Thus,

Scheme 19. Curran and Co-workers' Approach To Synthesize Mappicine Ketone Analogs[a]



[a] Reagents and conditions: (a) (i) Et_3SiH, $BF_3 \cdot OEt_2$, 60 °C; (ii) ^{i}PrMgCl, THF, −40 °C then EtCHO; (b) (i) ICl, CH_2Cl_2−CCl_4, 23 °C; (ii) TMSCl, NaI, MeCN, H_2O, 65 °C; (iii) NaH, LiBr, DME-DMF, 0 °C then propargyl bromide, 70 °C; (c) (i) ^{i}PrMgCl, CuCN, LiCl; (ii) EtCOCl, THF, −40 °C; (iii) (−)-DIP-chloride, THF, −25 °C; (d) $(Me_3Sn)_2$, *hν*, benzene.

Scheme 20. Jauch and Co-workers' Solid-Phase Synthesis Approach to Mniopetals[a]



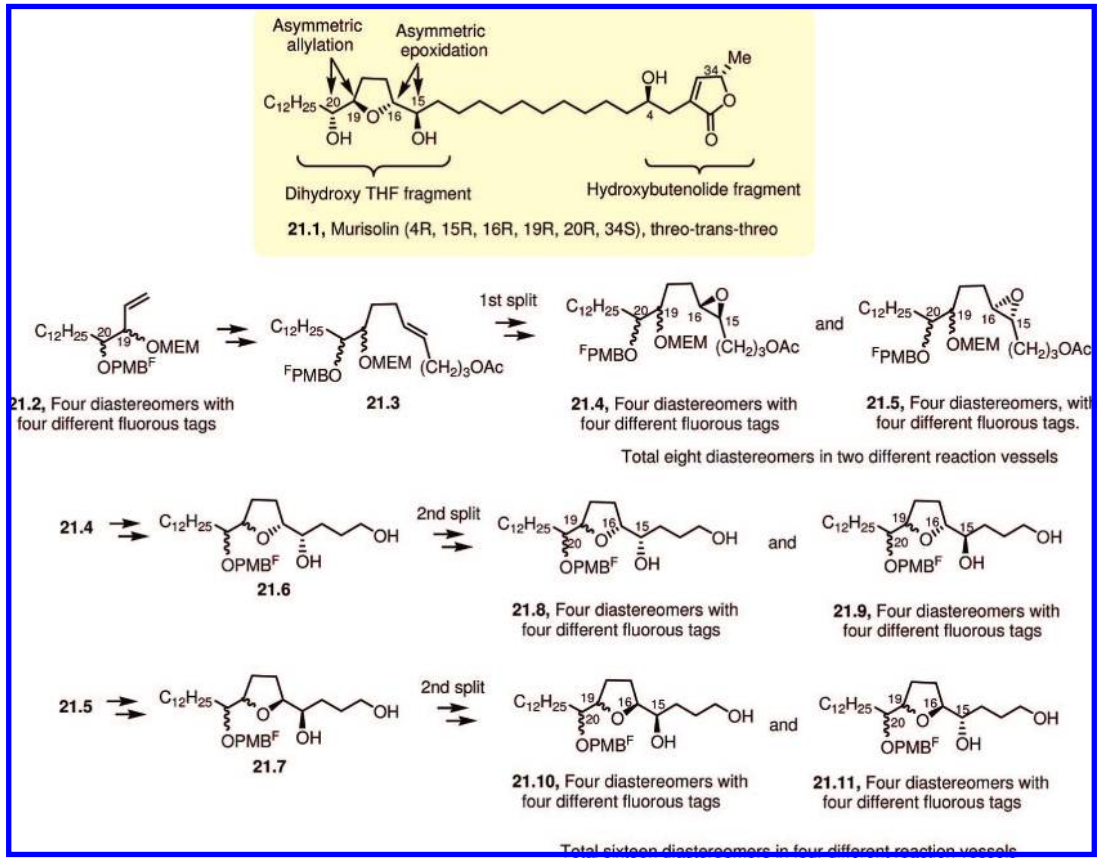
[a] Reagents and conditions: (a) (i) Cl_3CCN, DBU cat., RT; (ii) **20.3** (1.3 equiv), BF_3OEt_2 cat., 0 °C to RT; (b) (i) $P(OMe)_3$, 90 °C; (ii) **20.4** (3 equiv), −80 to −10 °C; (c) (i) 9-BBN (4 equiv), RT; (ii) H_2O_2/NaOH, RT; (iii) IBX (3−5.0 equiv), RT; (d) **20.9** (3.0 equiv), PhSeLi (5 equiv), −60 to −30 °C; (e) Dess−Martin periodinane (3.0 equiv), 2,6-lutidine (20.0 equiv), CH_2Cl_2, RT; (f) Me_2S, $MgBr_2.OEt_2$, RT.

(*E*)-4-bromo-2-butenol, **20.3**, was immobilized onto Wang resin, **20.5**, and converted to the phosphonate by standard methods. The phosphonate was then exposed to the lithium salt, **20.4**, at −80 to −10 °C to afford the triene **20.7**. The terminal olefinic moiety was manipulated to corresponding aldehyde, **20.8**, following regioselective hydroboration/alkaline hydrogen peroxide treatment and oxidation of the resulting primary alcohol by IBX. Exposure of **20.8** to chiral butenolide **20.9** and an excess of PhSeLi at −60 °C promoted a clean Balis−Hillman-type C−C bond forming transformation giving **20.10**. Tricyclic material **20.11** was then obtained from **20.10** by a domino sequence including activation of the chiral dienophile part by oxidation of the newly formed secondary alcohol and trapping of the dienophile by intramolecular 2 + 4 cycloaddition (IMDA). Cleavage of **20.11** with $Me_2S/MgBr_2 \cdot Et_2O$ finally afforded the tetracyclic derivative **20.12** with a marasmane-related core structure. Although no library was built, this report included the use of several key transformations, for example, Horner−Wordsworth−Emmons, Baylis−Hillman, and IMDA reactions on a solid support making this reaction path suitable for building solid-phase libraries.

4.17. Murisolin

Synthesis of small molecules as mixtures rather than as individual candidates in solution phase can bring efficiency

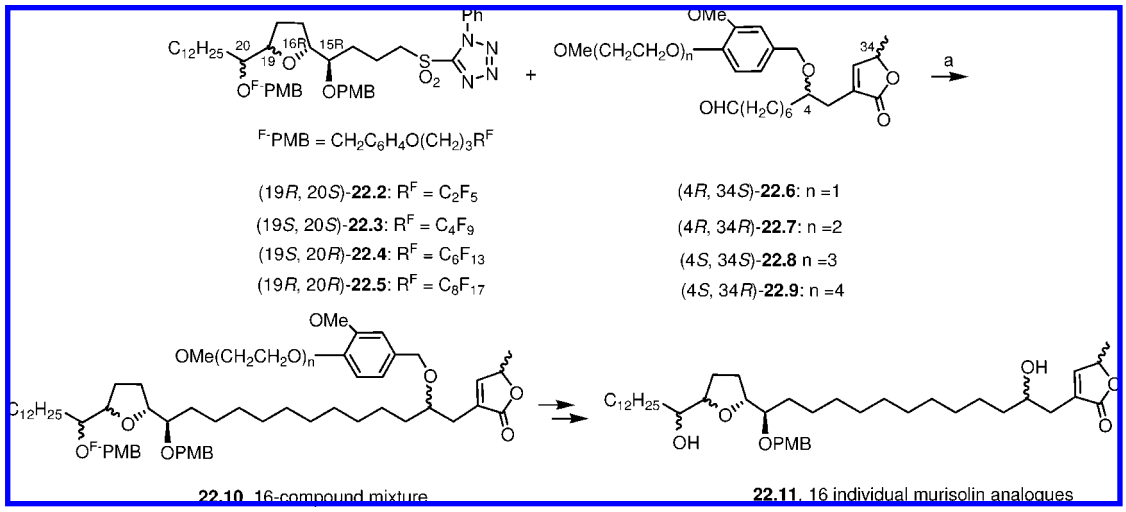
Scheme 21. Curran and Co-workers' Strategy for Synthesis of All Possible Diastereomers of the Dihydroxy-THF Fragment of Murisolin with an Aim To Isolate the Individual Diastereomer of Murisolin Based on the Fluorous Tags



and several unique advantages in developing the combinatorial approaches,[206] which often is offset by challenges in separation and characterization. A strategy for mixture synthesis that addresses these separation and identification problems was presented by Curran and co-workers.[207] In this technique, organic substrates were tagged with a series of fluorous tags of different fluorine content. The compounds were then mixed, and multistep reactions were conducted to make enantiomers or analogs of the natural product. The resulting tagged products were then demixed by fluorous chromatography (eluting in order of increasing fluorine content) to provide the individual pure components of the mixture, which were detagged to release the desired product. Scheme 21 shows this strategy applied to the synthesis and isolation of (+)-murisolin, **21.1**, a natural product belonging to the class of monotetrahydrofuran acetogenins, along with its 15 possible diastereomers due to asymmetry at C15, C16, C19, and C20.[208] The synthesis was initiated by assembling all four possible diastereomers of the diols **21.2** using an asymmetric Brown allylation followed by reversal of hydroxyl stereocenters for half-portion of the product. Individual diastereomers were then tagged with different fluorine-containing units (PMB^F) to form "quasi-diastereomers" (different fluorous tags had different formula weights; hence the diastereomers with different tags were not true isomers, although they will be referred as "diastereomers" in the rest of the present discussion) and mixed together to obtain a roughly equimolar mixture **21.2**. The protected diols with different chiralities at C19 and C20 were subjected to carbon homologation to obtain **21.3**, which was split into two vessels and subjected to a key Shi epoxidation using two opposite enantiomeric fructose-derived ketones to obtain optically pure protected epoxydiols **21.4** and **21.5** with opposite chiralities in two vessels. The protected epoxydiols were exposed to CSA, which readily unmasked the C19 alcohols, which in turn opened the epoxy rings intramolecularly to form the tetrahydrofuran rings with the desired asymmetric hydroxyl units at C15 in **21.6** and **21.7**. At this stage, the mixture of the four diastereomeric furans in each reaction vessel, **21.6** and **21.7**, was further split into two portions, and half of the epoxides coming from each set was subjected to Mitsunobu conditions to reverse the stereochemistry of the C15 alcohol. At the end of this exercise, Curran and co-workers obtained 16 (4 × 4) diastereomers due to asymmetry at C15, C16, C19, and C20 in four different vessels. Each vessel contained four products "marked" with different fluorous tags. These tetrahydrofuran units were then connected to an appropriate 4*R*,34*S*-hydroxyl butenolide fragment to complete the synthesis of the solution-phase library of (+)-murisolin and its 15 diastereomers (not shown in the scheme). The four individual isomers in each reaction vessel were isolated based on the difference in their fluorine content using fluorous chromatography to give 16 compounds in total. In this methodology, only 39 chemical transformations were required as compared with 156 steps that would have been required if the analogs were synthesized individually.

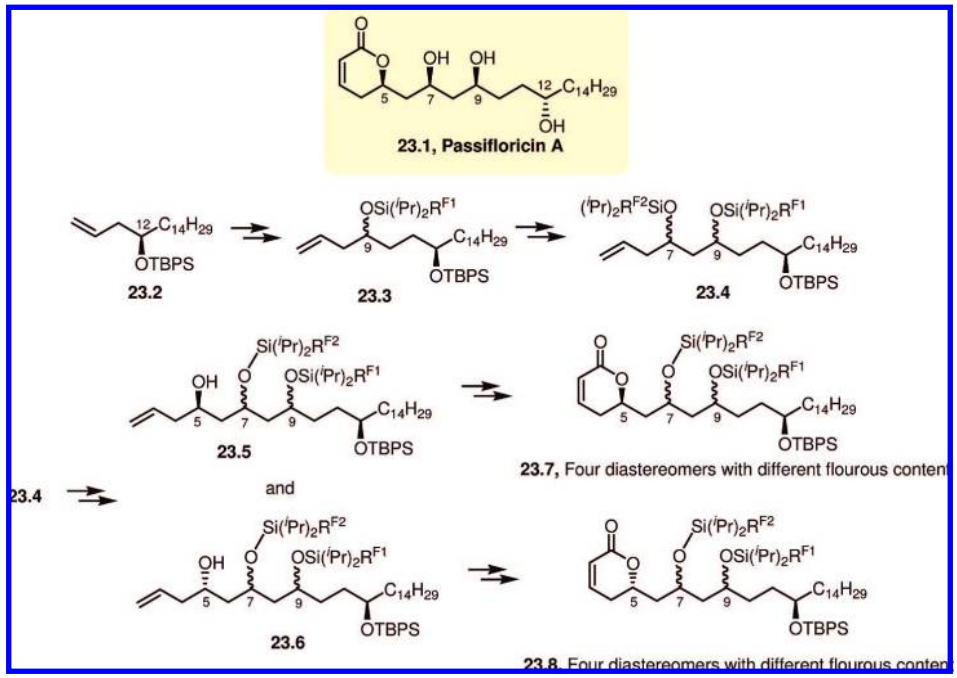
In a similar approach, Curran and co-workers once again reported the solution-phase library synthesis of another set of 16 diastereomers of (+)-murisolin by varying the stereocenters at C4, C19, C20, and C34.[209] In an excellent demonstration of an asymmetric synthesis echoed by the modern analytical technique, the researchers synthesized all these diastereomers in one vessel as a single mixture. Individual components were doubly tagged and subjected to a sequence of double demixing for isolation. The four possible diastereomers of the tetrahydrofuran subunit,

Scheme 22. Curran and Co-workers' Solution-Phase Library of 16 Murisolin Stereoisomers by Mixture Synthesis and Double Separation Tagging[a]



[a] Reagents and conditions: (a) (i) NaHMDS; (ii) H_2/[$RhCl(PPh_3)_3$].

Scheme 23. Curran and Co-workers' Strategy for the Synthesis of a Library of Eight Diastereomers of Passifloricin with an Aim To Isolate the Individual Diastereomers Based on Their Total Fluorous Content

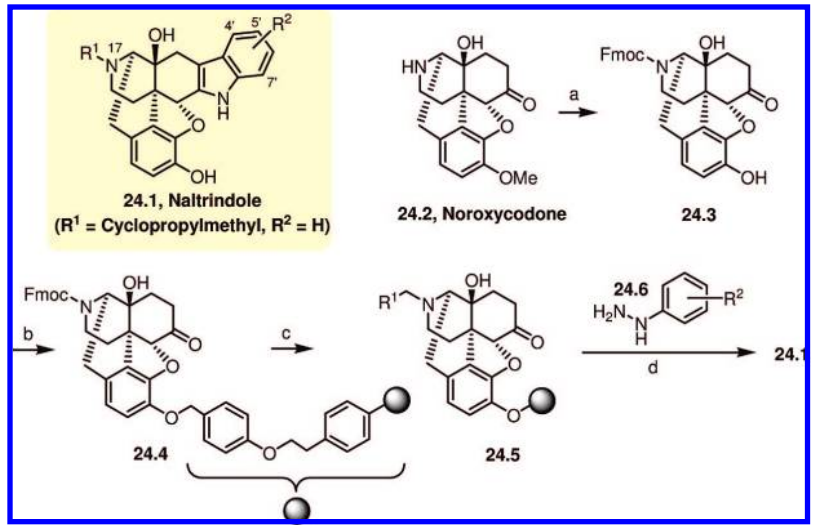


22.2−**22.5** (Scheme 22), with varying stereochemistry at C19 and C20, were synthesized by standard chemical transformations with C15 and C16 stereocenters fixed as *R* for both. These diastereomers (**22.2**−**22.5**) were tagged with different fluorous units. On the other hand, all four diastereomers of hydroxy butenolide fragment **22.6**−**22.9** with asymmetric carbon atoms at C4 and C34 positions were synthesized with orthoethylene glycol [OEG = $(OCH_2CH_2)_nOCH_3$] tags.[210] Kocienski−Julia coupling of these subunits **22.2**−**22.5** and **22.6**−**22.9** resulted in a 16-compound mixture, which was directly hydrogenated to saturate the newly formed alkene to give **22.10**. TLC analysis of this mixture on silica showed only four spots based on the OEG tags ($n = 1$, least polar, and $n = 4$, most polar), which were separated by usual flash chromatography on silica gel. All four components, separated by flash chromatography, contained four compounds each with different fluorous tags. These fractions were further subjected to demixing by fluorous chromatography to obtain all 16 individual diastereomers with protected hydroxyl groups. Finally, treatment with DDQ removed the PMB groups along with the fluorous and OEG tags to obtain 16 pure diastereomeric compounds **22.11**.

4.18. Passifloricin

Passifloricin A is a polyhydroxylated lactone isolated from *Passiflora foetida* and demonstrates antiparasitic activity against *Leishmania panamensis*.[211] Curran and co-workers used a fluorous mixture technique to synthesize a solution-phase library comprising the enantiomer of passifloricin A, **23.1** (Scheme 23), and its seven epimers at C5, C7, and C9.[212] Notably, unlike the previous example (**4.17**), the stereocenters were introduced and tagged en route during the synthesis. The synthesis commenced with the subjection of the enan-

Scheme 24. Takahashi and Co-workers' Solid-Phase Synthesis of Naltrindole Derivatives[a]



[a] Reagents and conditions: (a) (i) FmocCl, Na_2CO_3 aqueous THF, RT; (ii) BBr_3, CH_2Cl_2, 0 °C; (b) hydroxymethylphenoxyethyl polystyrene resin, DEAD, PPh_3, RT; (c) (i) 20% piperidine in CH_2Cl_2, RT; (ii) R^1CHO, $NaBH_3CN$, DMF-AcOH (100:1); (d) (i) **24.6**, 4 Å MS, AcOH-CH_2Cl_2 (1:1), RT; (ii) 10%TFA/CH_2Cl_2, RT.

tiopure silyl ether **23.2** to a sequence of hydroboration followed by Swern oxidation of the newly formed alcohol to aldehyde, and asymmetric allylation of the aldehyde in half-portions with both enantiomers of Duthaler−Hafner (DH) reagent.[213] This introduced the C9 hydroxy group in a facially selective manner, and the resulting two diastereomers (9*R*,12*R*; 9*S*,12*R*) were then tagged with two different fluorous units (R^{F1}). After the above sequence, the individual diastereomers were mixed together to obtain the mixture **23.3**, which was then subjected to oxidative cleavage of the allyl bond to generate the aldehyde followed by separation into half-portions and allylation of individual portions with two enantiomeric DH reagents to install the C7 OH asymmetrically resulting two pairs of two compound mixtures (one pair containing 7*S*,9*R*,12*R* and 7*S*,9*S*,12*R* and the other containing 7*R*,9*R*,12*R* and 7*R*,9*S*,12*R*). The pair of 7*R* and the pair of 7*S* isomers were tagged differently (R^{F2}). These four compounds were then mixed together to obtain **23.4** as a mixture of four diastereomers of the tagged diol having different chirality at C9 and C7 and each having different fluorine contents. Next, **23.4** was subjected to same set of transformations as on **23.3** but interrupted after asymmetric introduction of the C5 hydroxy group giving a set of four diastereomers (**23.5**) with 5*R* stereochemistry in one vessel and another set of four diastereomes (**23.6**) with 5*S* stereochemistry in the second vessel. Compounds **23.5** and **23.6** were separately acylated at C5 with cinnamoyl chloride and subjected to ring-closing metathesis conditions to obtain the two mixtures **23.7** and **23.8** containing four diastereomeric passifloricins each. Finally, the individual isomers were separated by fluorous chromatography based on the difference of their total fluorine content and detagged to obtain eight individual diastereomers. The researchers applied a similar methodology using fluorous tags in one of their earlier studies for the total synthesis of all 16 stereoisomers of the pine sawfly sex pheromone.[214]

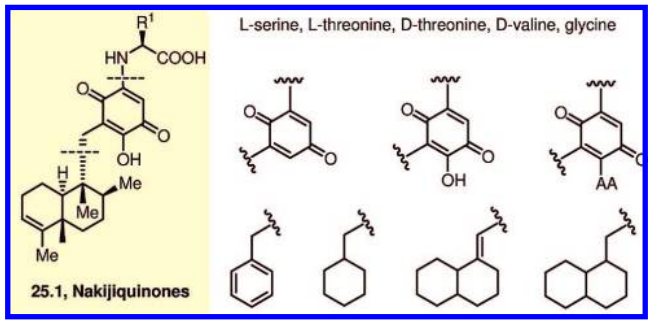
4.19. Naltrindole

Indoles constitute an important class of alkaloids, a well-known source for numerous biologically active compounds.[215−217] Despite a number of reports in the literature to develop new and effective synthesis of substituted indoles both in solution[218] and on a solid phase,[219−223] Fischer indole synthesis continues to be an effective and most commonly used method in this area. Typically, Fischer indole synthesis involves strong acid mediated cyclization of an intermediate aryl hydrazone that is formed by coupling of a ketone and the hydrazine. Takahashi and co-workers explored solid-phase synthesis to obtain the analogs of naltrindole (NTI, **24.1**, Scheme 24). An acid-labile Wang linker resin was used that released the product from the solid support simultaneously with the cyclization (formation of indole) at the final step.[224] Synthesis of a 30-membered library was initiated by *N*-17 protection of the naturally occurring opiate alkaloid noroxycodone, **24.2**, which was followed by unmasking of the phenolic group to obtain **24.3**. The subsequent loading of **24.3** using the phenolic oxygen onto the hydroxymethylphenoxyethyl resin under Mitsunobu conditions afforded **24.4**. As the first diversity step, *N*-17 protection was removed, and the resin-bound scaffold was subjected to reductive alkylation with six aldehydes under standard conditions. The resulting six tertiary amines **24.5**, which also carried a suitably placed ketone functionality were treated with five different substituted phenyl hydrazines **24.6** (ring substitution as the second diversity) under relatively mild acidic conditions (CH_2Cl_2/AcOH = 1:1) to form the intermediate hydrazones. Finally, exposure of the hydrazones to stronger acid (10% TFA/CH_2Cl_2) leads to one-pot cyclization and cleavage of the resulting indoles from the resin. The resin withstands mild acidic conditions necessary for the reductive alkylation or hydrazone formation but releases the products under stronger acid necessary for the cleavage.

4.20. Nakijiquinone

Based on the structure of nakijiquinones (**25.1**, Scheme 25), receptor tyrosine kinase inhibitors,[225,226] Waldmann and co-workers constructed a 74-membered solution-phase library and also screened the members for kinase inhibitors with highly similar ATP-binding domains.[227] The library was designed and built using standard transformations, based on the modular composition of nakijiquinones. These natural products have three main subunits: a core decalin (diterpene)

Scheme 25. Waldmann and Co-workers' Approach to Nakijiquinone Library



moiety, a *p*-quinone part, and an amino acid residue (typically glycine, valine, serine, and threonine). The researchers changed each subunit with the substituents as shown in Scheme 25 to explore the possibility of structural diversification. This library offered seven kinase inhibitors with high potency including four inhibitors of Tie-2, a kinase active in angiogenesis.

4.21. (+)-Plicamine

(+)-Plicamine (**26.1**, Scheme 26) is a naturally occurring alkaloid belonging to the amaryllidaceae subgroup, which is known for significant biological potency.[228−230] (+)-Plicamine and its enantiomer have an intriguing tetracyclic architecture with the 6,6-spirocyclic core with two skeletal nitrogens. Both of these isomers were synthesized using the solid-supported reagents and scavengers in multistep reaction sequences by Ley and co-workers.[231,232] For the synthesis of the (+)-enantiomer, a key fragment **26.3** was obtained from a 4-hydroxyphenylglycine-derived imine, **26.2**, by reduction with polymer-supported borohydride and subsequent protection of the resulting amine with trifluoroacetic anhydride in the presence of polymer-supported catalyst. Notably, **26.3** was synthesized starting from 4-hydroxyphenylglycine in six steps without any chromatographic purification in multigram scale with high overall yield (91%) and purity (>97%). The spirocyclic skeleton **26.4** was obtained from **26.3** as an exclusive product in a key intramolecular oxidative coupling in the presence of solid-supported hypervalent iodine reagent. The facial selective conjugate addition, controlled by the existing stereocenter was the next key transformation, which was accomplished in the presence of Nafion-H to afford **26.5**. The C4 carbonyl in **26.5** was stereoselectively reduced to alcohol **26.6** and then protected as the methyl ether **26.7**, mediated by the solid-supported borohydride and TMS-CHN_2 in the presence of sulfonic acid exchange resin, respectively. Treatment of **26.7** with an ion exchange hydroxide resin under microwave conditions then led to basic hydrolysis and thereby deprotection of the trifluoro acetate group to afford free amine **26.8**, which in turn was alkylated by 4-(2-bromoethyl)-phenol in the presence of a solid-supported carbonate, under microwave irradiation. Interestingly, excess bromide used in the alkylation step was scavenged by the aminothiol resin to afford **26.9** in excellent purity; **26.9** was oxidized to the corresponding amide using chromium trioxide and 3,5-dimethoxylpyrazole to obtain **26.1** in the pure form by scavenging the reaction mixture with Amberlyst 15 resin to remove the unreacted starting material and pyrazole. Finally, it was then passed through the Varian Chem Elut column to eliminate the chromium salts. The researchers also reported the synthesis of the (−)-enantiomer from the unnatural 4-hydroxyphenyl glycine following similar transformations. Although no library of analogs of (+)-plicamine was reported, this represents a unique and powerful example of multistep synthesis of a complex natural product avoiding conventional chromatographic purifications.

4.22. Saframycin

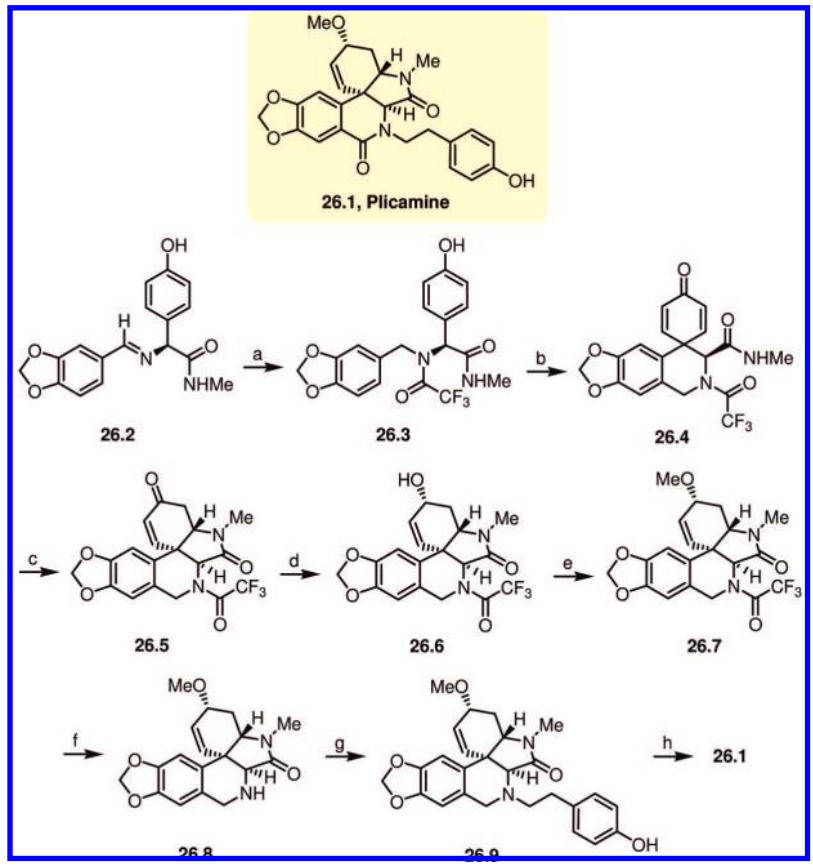
Saframycin A (**27.1**, Scheme 27) is a bis-quinone alkaloid with a bridged complex polycyclic framework with a characteristic cyanopiperazine core and is known to act as an antiproliferative agent.[233−238] Myers and co-workers[239] reported the successful adaptation of their earlier developed solution-phase synthesis of saframycin A[240] to a 10-step solid-phase protocol with the potential of building a large number of its analogs with structural modifications.

The synthesis was initiated with the quantitative loading of the *anti*-morpholino nitrile **28.1** (Scheme 28) onto the solid support as silyl ether **28.2**, which was connected to the resin via a morpholine-based "dual linker". Selective removal of the *O*-TBS protection and unmasking of the amino terminus afforded the phenolic amine intermediate, which was treated with excess *N*-protected α-amino aldehyde **28.3** to provide the corresponding resin-bound imine. This was then warmed in a saturated solution of anhydrous lithium bromide in 1,2-dimethoxyethane leading to a stereoselective Pictet−Spengler cyclization to furnish the *cis*-tetrahydroisoquinoline derivative **28.4** as the major isomer in an excellent overall yield. The ring nitrogen of the tetrahydroisoquinoline intermediate **28.4** was then methylated under a standard procedure followed by deprotection of the phenol and the secondary amine to afford **28.5**. Treatment of **28.5** with excess *N*-Fmoc-glycinal and warming the mixture at 40 °C induced a second Pictet−Spengler cyclization (following the formation of the imine) to generate the bis-tetrahydroisoquinoline derivative **28.6** in a quantitative yield with the desired *cis* stereochemistry. Finally, treatment of zinc chloride at 55 °C on **28.6** triggered the chain of transformations leading to the formation of saframycin analog **28.7** and an expulsion of the dual linker through a "cyclization−autorelease" process. A remarkable overall yield of 53% for the 10-step sequence from **28.1** was achieved in this synthesis pathway. This was then applied to generate a 16 (4 × 4)-membered library, diversifying from the intermediate **28.4** with four alkyl bromides for N-alkylation and from **28.5** with four aldehydes for the second Pictet−Spengler cyclization.

4.23. Stylostatin

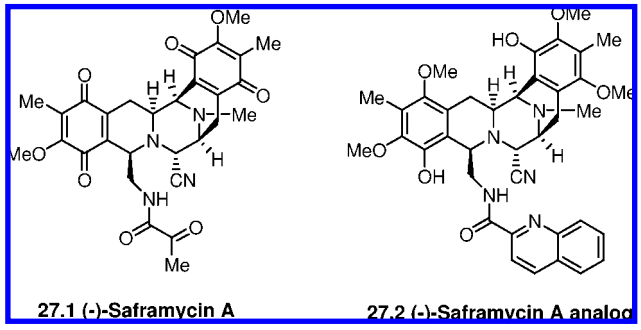
Waldmann and co-workers reported the successful application of a previously developed[241] oxidation-labile hydrazide linker for building cyclic peptides on a solid support and used this technique to synthesize naturally occurring cyclic heptapeptide, stylostatin 1 (**29.1**, Scheme 29).[242] The methodology relies on a resin with hydrazide "safety-catch" linker that is stable throughout the synthesis under acid/base conditions and is activated by oxidation to the corresponding acyl diazene at the end of building the peptide. Once the acyl diazene is formed, the free N-terminus of the peptide undergoes an intramolecular nucleophilic attack on the acyl carbon leading to cyclative cleavage of the peptide from the resin. The Waldmann group tested this strategy of "traceless synthesis" to synthesize the cyclic model peptide **29.5** using commercially available 2-*N*-Fmoc-hydrazinobenzoyl HM

Scheme 26. Ley and Co-workers' Solid-Phase Synthesis of Plicamine[a]



[a] Reagents and conditions: (a) (i) PS-borohydride, MeOH/CH_2Cl_2 (2:1); (ii) $(CF_3CO)_2O$, PVP (3.0 equiv), poly-DMAP (0.5 equiv), CH_2Cl_2, 0 °C; (b) PS-iodinium diacetate (1.5 equiv), 2,2,2-trifluoroethanol, −5 °C; (c) Nafion-H, 24 h; (d) PS-borohydride, MeOH/CH_2Cl_2 (1:1); (e) TMS-CHN_2, sulfonic acid resin, MeOH/CH_2Cl_2 (3:2); (f) Ambersep 900 (HO^-), MeOH, microwave, 100 °C; (g) (i) PS-carbonate (2.0 equiv), 4-(2-bromoethyl)-phenol (1.2 equiv), MeCN, microwave, 140 °C; (ii) PS-mercaptoaminomethyl resin; (h) (i) CrO_3 (2.5 equiv), 3,5-dimethylpyrazole (2.5 equiv), CH_2Cl_2, −45 °C; (ii) Amberlyst 15 (10.0 equiv); (iii) (1:1 w/w) montmorillonite K10/Varian Chem Elute CE1005 packing material.

Scheme 27. Saframycin A and Its Analog

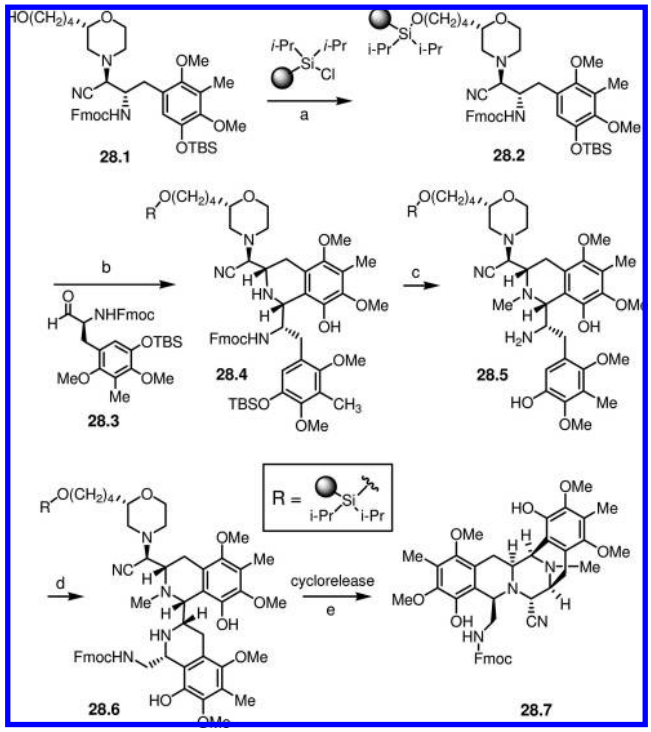


resin **29.2**. After removal of the *N*-Fmoc, the linear peptide **29.3** was synthesized under standard conditions and capped with bulky (in order to prevent acylation of the hydrazide nitrogens) pivalic acid anhydride. The N-terminus was then deprotected, and the resin was subjected to oxidation in the presence of NBS-pyridine, giving the acyldiazene **29.4**. Under basic conditions, the liberated N-terminus of **29.4** undergoes nucleophilic attack on the carbonyl of the acyl diazene resulting in the cyclative cleavage of the pentapeptide with an elimination of N_2. The researchers then extended this methodology to synthesize the natural product stylostatin 1, **29.1**, with two alternative cyclization sites; site I involving alanine and leucine afforded much superior overall yield compared with site II with sterically demanding proline and isoleucine moieties. This methodology was a significant addition to the strategies to achieve the traceless synthesis of cyclic peptides.

4.24. Ursolic Acid

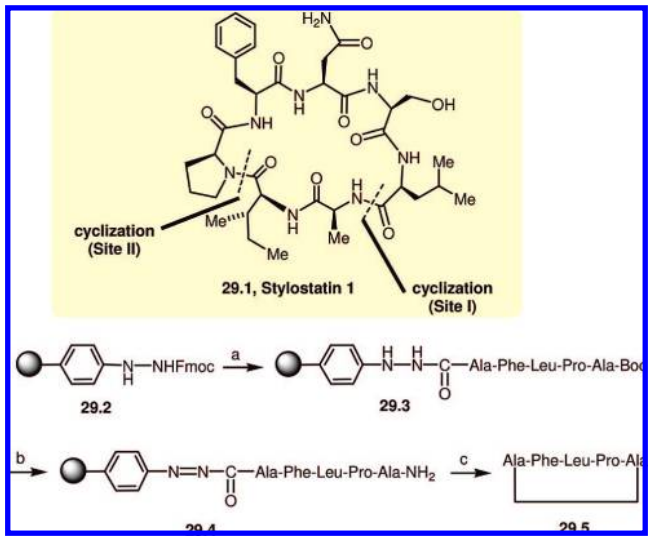
Lupane and ursane classes of terpenoids such as betulinic acid (**30.1**, Scheme 30) and ursolic acid (**30.2**) and their derivatives are studied in key therapeutic areas and provided several significantly active molecules.[243,244,246−249] Kundu and co-workers reported the solid-phase parallel synthesis of a series of their analogs using acid-labile Sieber amide resin **30.3**.[250] *N*-Fmoc-glycine and *N*-Fmoc-*β*-alanine were loaded on **30.3** as the first diversity, followed by coupling of the amino acid residues with terpenoid scaffolds **30.1** and **30.2** through the C28 carboxyl residue to generate the resin-bound materials **30.6** and **30.7**, respectively. The second level diversity was introduced at C3 by treatment of these immobilized terpenoids (see **30.6**) under two different approaches. In the first study, the hydroxyl group was esterified with a series of acids, for example, aliphatic, aromatic, and amino acids, followed by cleavage from the resin (TFA treatment) to afford **30.8**. In the second study, which was not taken to library generation, the C3 hydroxy was oxidized to ketone and subsequently coupled to hydroxyl amine to form an oxime. This afforded the hydroxyl group as the diversity site, which was then esterified with phenyl acetic acid to obtain **30.9**. A library of 18 derivatives of both natural products, **30.1** and **30.2**, was then synthesized using

Scheme 28. Myers and Co-workers' Stereoselective Solid-Phase Synthesis of Saframycin Analogs[a]



[a] Reagents and conditions: (a) imidazole, DMF, RT; CH_3OH, imidazole, RT; (b) (i) TBAF, AcOH, THF, RT; (ii) piperidine, DMF, RT; (iii) **28.3** (3.0 equiv), DMF, RT; (iv) LiBr, DME, 35 °C; (c) (i) CH_2O-H_2O, $NaBH(OAc)_3$, DMF, RT; (ii) TBAF, AcOH, THF, RT; (iii) piperidine, DMF, RT; (d) *N*-Fmoc glycinal, DCE, 40 °C; (e) $ZnCl_2$, 4 Å molecular sieves, THF, 55 °C.

Scheme 29. Waldmann and Co-workers' Solid-Phase Synthesis of Stylostatin 1[a]



[a] Reagents and conditions: (a) (i) 20% piperidine, RT; (ii) Boc-AA, DIC, HOBt (3.0 equiv), DMF, RT; (iii) 10% pivalic anhydride, pyridine, RT; (b) (i) 50% TFA, CH_2Cl_2; (ii) NBS, pyridine (2.0 equiv), CH_2Cl_2, RT; (c) Et_3N, CH_2Cl_2.

two diversity points of these scaffolds and then screened for biological activities.

4.25. Vitamin D_3

The biologically active metabolite of vitamin D_3, 1α,25-dihydroxyvitamin D_3 (**31.1**, Scheme 31), is a steroid hormone. This compound is known to exhibit several biological properties that range from the regulation of calcium and phosphorus metabolism[251−253] to cell differentiation and proliferation[254−256] and development of the immune system cells.[257−259] To obtain several analogs of this steroid hormone for providing a better understanding of its biological functions, Takahashi and co-workers[260,261] developed the solid-phase synthesis of the vitamin D_3 skeleton. A key strategy in their approach was to immobilize the CD ring system onto the solid support using a primary hydroxyl group (**31.2**). This scaffold was then coupled to the ring A moiety **31.3** under Horner−Wadsworth−Emmons conditions followed by side chain extension with the use of **31.4** in a Cu(I) Grignard reaction resulting in the desired target.

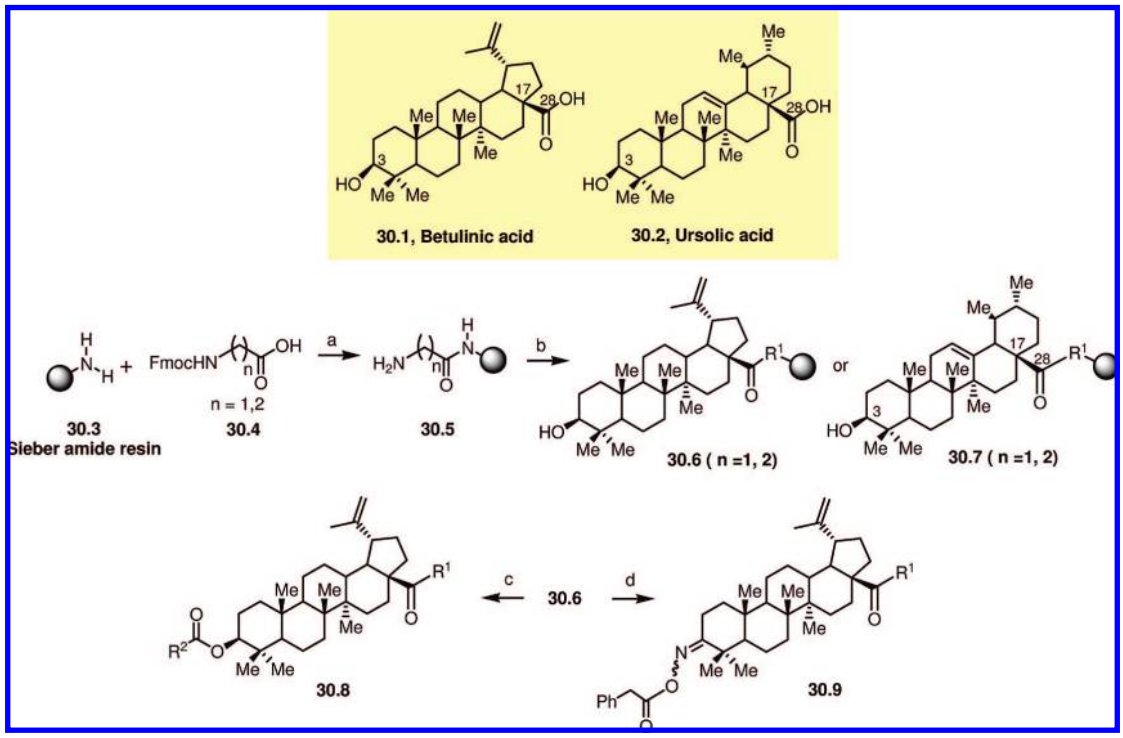
The primary hydroxyl group on the CD ring building block **32.1** (Scheme 32) prepared by solution synthesis was immobilized onto the solid support using a sulfonyl chloride linked to the polystyrene resin **32.2**. The resulting material, **32.3** was then subjected to Horner−Wadsworth−Emmons reaction with **32.4** to obtain the coupled product **32.5**. Finally, reaction with the Grignard reagent prepared from **32.6**, followed by deprotection under mild acidic conditions, afforded the desired material **32.7**. By variation of the CD ring scaffold (**33.1**−**33.3**, Scheme 33) and A-ring skeleton (**33.4**−**33.7**) and use of different side chains (**33.8**−**33.13**), a library of 72 compounds was obtained through the use of the radiofrequency encoded IRORI technology.

5. Solid-Phase Synthesis of Cyclic Peptides as Natural Products and Analogs

5.1. Beauveriolides

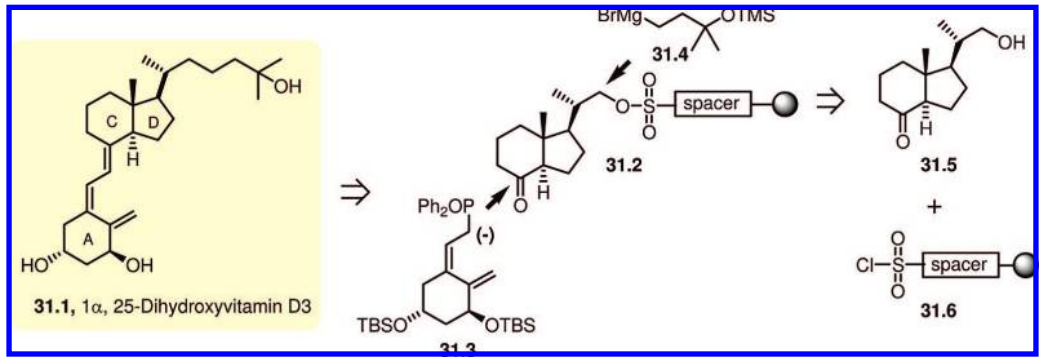
Beauveriolides are 13-membered ring depsipeptides available in nature and are promising lead compounds for the treatment of atherosclerosis.[262−264] Takahashi and co-workers generated an 81-membered library of beauveriolide III (**34.1**, Scheme 34) analogs in which all the coupling steps between the individual fragments were performed on a solid phase.[265] This was then followed by cyclization in solution under high dilution conditions. The library was initiated by an immobilization of *N*-Fmoc-L-alanine, **34.3**, onto 2-chlorotrityl resin, **34.2**, followed by the deprotection of the amino group and subsequent coupling to different *N*-Fmoc-L-phenylalanine derivatives, **34.4**, to obtain the resin-bound dipeptide **34.5**. This dipeptide **34.5** was coupled under PyBrop conditions to the key building block **34.6**, which was synthesized by a series of standard transformations in solution phase to obtain an acyclic derivative **34.7** bound to the resin. Under acidic conditions, **34.7** underwent two transformations, (i) *N*-Boc deprotection and (ii) cleavage from the acid-labile trityl resin, to afford **34.8** in solution with an excellent yield and high purity. During this study, Takahashi and co-workers observed that EDCI was the most effective reagent that suppressed the cyclic dimer formation and also promoted the desired cyclization of the depsipeptide **34.8** to **34.1** under high dilution conditions in solution phase. Using a parallel approach to solid-phase synthesis, they planned an 81-membered library with diversities at two locations with three different ester building blocks, **34.6**, and 27 different phenylalanine derivatives, **34.4**. In the end, 77 macrocycles were isolated after purification by reverse-phase HPLC and then subjected to biological studies to obtain the SAR data in a search of potential atherosclerotic agents.

Scheme 30. Kundu and Co-workers' Library of Betulinic and Ursolic Acid Derivatives[a]



[a] Reagents and conditions: (a) (i) HOBt, $(^{i}Pr)_2NEt$, TBTU, DMF; (ii) 20% piperidine, DMF; (b) **30.1** or **30.2**, HOBt, DIC, pyridine, DMF; (c) (i) R^2CO_2H, DMAP, DIC; (ii) 2% TFA, CH_2Cl_2; (d) (i) PDC/DMF; (ii) $NH_2OH \cdot HCl$/pyridine; (iii) $PhCH_2CO_2H$/DMAP/HOBt/DIC; (iv) 2% TFA, CH_2Cl_2.

Scheme 31. Takahashi and Co-workers' Solid-Phase Approach to Vitamin D_3



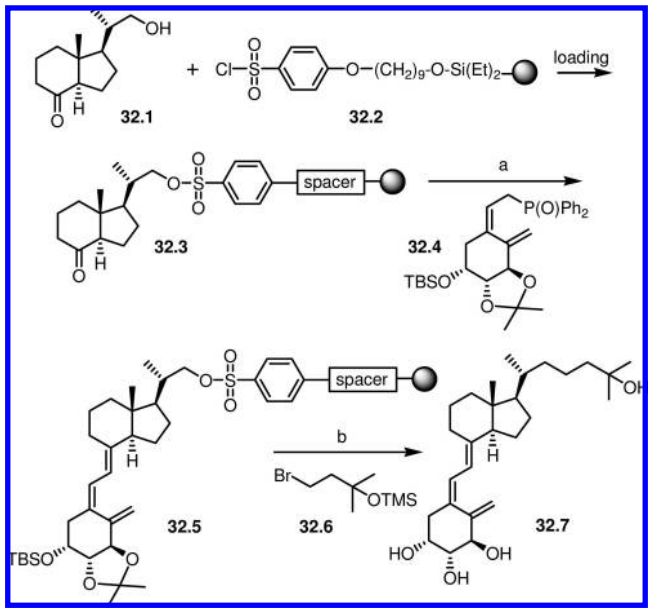
5.2. Chlorofusin

Chlorofusin is a naturally occurring macrocycle that is known to inhibit p53/mdm2 interaction and thus acts as a potent antitumor agent.[266,267] It has two main structural units: (a) densely functionalized nonpeptide chromophore and (b) a 27-membered ring cyclic peptide. The key features of this cyclic peptide include the presence of an L-ornithine side chain (which connects the nonpeptide chromophore to the peptide ring), a D-2-aminodecanoic acid moiety, two D-leucines, two L-threonines, and one L- and one D-asparagine residue. Searcey and co-workers successfully attempted the total synthesis of the chlorofusin cyclic peptide unit **35.1** (Scheme 35; a free amino group is incorporated on the ornithine side chain in place of the chromophore) involving all the coupling steps, including the final cyclization occurring on the solid support.[268] The synthesis was initiated with resin-bound asparagine **35.2** with its carboxyl end protected as the Dmab ester. The individual residues were then coupled to **35.2** in an appropriate sequence under standard peptide coupling conditions to construct the resin-bound acyclic peptide **35.5**. Interestingly, the researchers used racemic 2-aminodecanoic acid in order to synthesize the corresponding epimeric macrocycle also in the same pot. The Dmab protection was then removed from **35.5** by hydrazine treatment, and finally, head-to-tail cyclization of the resin-bound linear peptide was achieved under DIC/HOAt conditions (which was repeated under PyBOP/HOAt/DIPEA conditions to ensure the complete ring closure) to obtain **35.6**. Global deprotection of the side chains and simultaneous cleavage of the macropeptide was then achieved under standard acidic conditions to afford the target compound **35.1**, along with its epimer at the 2-aminodecanoic acid residue.

5.3. Cryptophycins

Cryptophycins are 16-membered ring cyclic depsipeptides belonging to the class of antimitotic agents that are active against several tumor cell lines in picomolar concentrations.[269−276] The low natural abundance of the cryptophycins coupled with their high clinical potential triggered considerable interest in the total synthesis of these depsipeptides and their analogs.[277−280] In a recent effort, Lautens and co-workers

Scheme 32. Vitamin D_3 by Solid-Phase Synthesis (Continued)[a]



[a] Reagents and conditions: (a) **32.4** (8.0 equiv), *n*-BuLi (7.5 equiv), THF, −40 to −10 °C; (b) (i) **32.6** (15.0 equiv), Mg (15.0 equiv), CuBr, Me_2S (1.0 equiv), THF, RT; (ii) CSA, MeOH, H_2O, 30 °C.

developed the solution-phase synthesis for a series of des-epoxy analogs of cryptophycin (**36.1**, Scheme 36) and also attempted to install the epoxy oxygen in a diastereoselective manner.[281] The strategy was to obtain three basic 16-membered ring des-epoxy scaffolds that were diastereomerically pure and could easily be manipulated to similar structures with different substitutions and, finally, bring the epoxy oxygen in a facial selective manner to complete the synthesis. The acyclic depsipeptide moiety **36.2** was prepared following standard transformations. The enantiomerically pure bishomoallylic alcohol building blocks **36.3** were obtained by rearrangement/allylation of 2-vinyloxiranes, followed by enzymatic resolutions, and were coupled to **36.2** under Yamaguchi conditions, following its deallylation in the same pot. The coupled products **36.4**−**36.6**, depending on the type and location of the halide substitutions (Br or I) and stereochemistry of the marked (*) carbon (Scheme 36), underwent ring-closing metathesis in the presence of Grubbs' first or second generation catalysts to afford three scaffolds, **36.7**−**36.9**. After constructing these scaffolds in gram quantities, Lautens and co-workers subjected them to C−C bond-forming cross-coupling protocols, for example, Sonogashira coupling or Suzuki−Miyaura reaction (utilizing the vinyl halide moieties) to introduce phenylacetylene or phenyl substitutions, respectively (R^3 = C≡CPh/Ph and R^4 = H or R^3 = H and R^4 = C≡CPh/Ph in **36.10**). Interestingly, these vinyl halides did not undergo the desired cross-coupling reaction when subjected to Stille coupling conditions or Suzuki−Miyaura conditions in the presence of strong base. After creating the des-epoxy analogs of cryptophycins, the researchers finally attempted a facial selective epoxidation, and the preliminary data reported in their article showed that Jacobsen's conditions[282] allowed them to achieve the epoxides **36.10** in moderate yields with good diastereoselectivity.

5.4. Kahalalide A

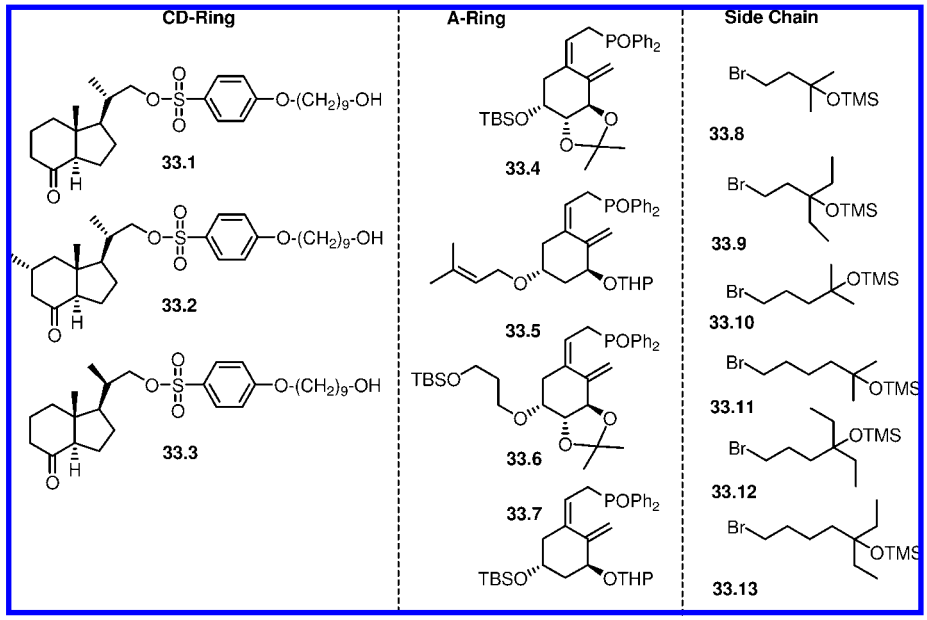
Total synthesis of kahalalide A (**37.1**, Scheme 37), a cyclic depsipeptide, on a solid phase was achieved by Ganesan and co-workers.[283] This natural product emerged as a promising lead that inhibits 83% of the growth of *Mycobacterium tuberculosis* at 12.5 μg/mL, and it does not exhibit cytotoxicity against various tumor cells.[284] With the target to obtain **37.1**, a 19-membered ring macrocycle in which the stereochemistry of one of the chiral centers (methylbutyrate side chain) was not established during the original isolation, the researchers attached *N*-Fmoc-D-Phe to the commercially available sulfonamide resin as the first step, giving **37.2**. This was then sequentially coupled with *N*-Fmoc-L-Thr(^{t}Bu)-OH and *N*-Fmoc-D-Phe-OH to afford the tetrapeptide **37.3**. At this point, the stage was set to bring the ambiguous methylbutyrate (MeBu) side chain. Because *R*-variety of 2-methylbutyric acid was not commercially available, the researchers separately coupled the *S*-enantiomer and the racemic version of 2-methylbutyric acid to the nitrogen end of the D-phenylalanine residue of **37.3** to obtain **37.4**. Deprotection of the threonine side chain in the presence of TFA/^{i}Pr_3SiH/H_2O followed by an ester bond formation with *N*-Fmoc-L-Ser(^{t}Bu)-OH and further chain extension with appropriate amino acid residues afforded the key linear heptapeptide **37.5**, which was ready for cyclization. Following a switch of *N*-Fmoc protection to a more compatible trityl group, the safety-catch linker[285] was activated by alkylation of sulfonamide with iodoacetonitrile. Trityl deprotection at this point set the amine free to undergo the cyclative cleavage from the resin to form the desired macrocyclic depsipeptide with ^{t}Bu capped threonine and serine side chains that were finally deprotected in the presence of TFA/^{i}Pr_3SiH/H_2O to afford **37.1** (and its MeBu diastereomer, in the case when (±)-2-methylbutyric acid was used in step b). Following the synthesis of the depsipeptide, Ganesan and co-workers confirmed the stereochemistry of the MeBu side chain by NMR studies. Their choice of *S*-methylbutyric acid in the synthesis because the other enantiomer was not commercially available turned out to be useful and provided the right diastereomer of the natural product, suggesting that the stereochemistry at the MeBu location of natural kahalalide A is *S*-configuration. Following this, six more analogs of kahalalide A (apart from the natural product with correct MeBu stereochemistry and the corresponding racemic version), each differing in the MeBu region, were then synthesized to study their antimicrobial activities.

5.5. Scytalidamide A

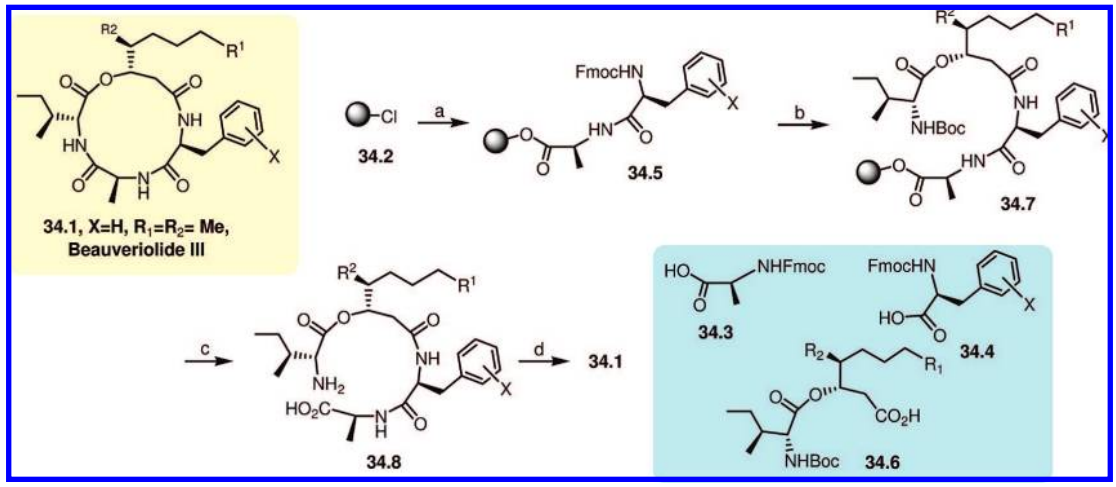
Scytalidamide A is a natural cyclic heptapeptide isolated from marine sources, and it has shown moderate but selective activity against colon cancer.[286] The first total synthesis of scytalidamide A (**38.1**, Scheme 38) was achieved on a solid phase by Gu and Silverman[287] using two different "traceless" linker resins: linker resin 1 (**38.3**), a phenylalanine silane resin, and linker resin 2 (**38.4**), a 4-methoxybenzaldehyde backbone resin. All the synthetic transformations including the final cyclization from the corresponding open chain heptamer **38.2** were performed on a solid support.

The synthesis using the phenylalanine silane linker resin **38.3** is illustrated in Scheme 39. The resin was prepared from butyldiethylsilane polystyrene **39.1** with *N*-Boc-4-iodophenylalanine methyl ester **39.2** using Pd(0) catalyst.[288] Deprotection of the amino group of **38.3** followed by coupling with

Scheme 33. Building Blocks Utilized in Library Generation of Vitamin D_3 Analogs by Parallel Synthesis



Scheme 34. Takahashi and Co-workers' Approach to the Synthesis of Beauveriolide III Analog Library[a]



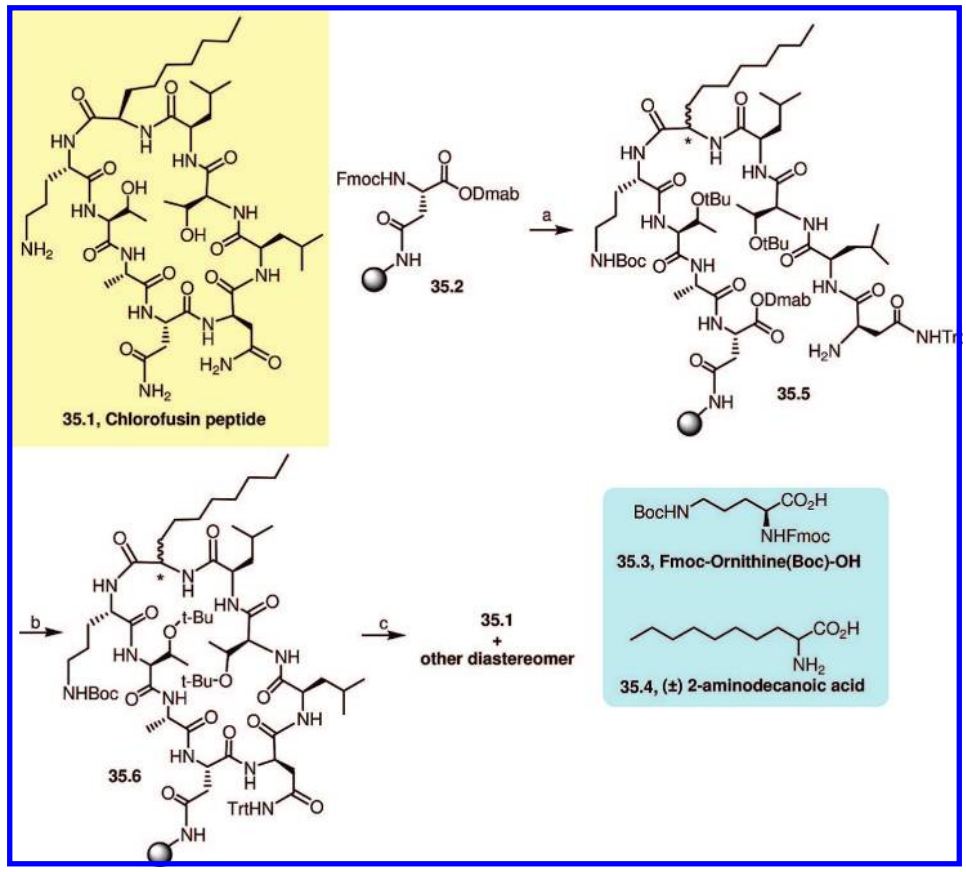
[a] Reagents and conditions: (a) (i) **34.3**, $(^i Pr)_2NEt$, CH_2Cl_2, RT; (ii) 20% piperidine/DMF; (iii) **34.4**, DIPCI, HOBt, CH_2Cl_2/DMF (4/1), RT; (b) (i) 20% piperidine/DMF; (ii) **34.6**, PyBrop, $(^i Pr)_2NEt$, CH_2Cl_2/DMF (4/1), RT; (c) 4 M HCl/1,4-dioxane, RT; (d) EDCI·HCl, $(^i Pr)_2NEt$, CH_2Cl_2, RT.

N-Boc-MePhe-OH (which normally does not undergo a facile amide bond formation) in the presence of DIPEA and HATU in NMP as the solvent afforded polymer-bound dipeptide **39.3**. Elongation of the peptide chain to obtain the linear peptide **38.2** was accomplished (via **39.4**) by stepwise coupling of the corresponding *N*-Boc-protected amino acids under the same conditions at each step. The key features of their synthesis were (i) the use of *N*-Boc protected amino acids in every step (compared to *N*-Fmoc protected residues) to reduce the possibility of diketopiperazine formation, (ii) the low loading level (0.09 mmol/g) in order to promote the intramolecular reaction in the crucial final step, and (iii) the switching to PyBOP from HATU as the coupling agent in the cyclization step to avoid guanidine formation at the free nitrogen end. Thus, **38.2** after ester hydrolysis and *N*-Boc deprotection underwent cyclization in presence of PyBOP and DIPEA in NMP to afford the resin-bound desired macrocycle, which was treated with neat TFA at room temperature for 24 h to release **38.1** with an overall yield of 20% for the 16-step solid-phase protocol. Application of the phenylalanine silane linker resin **38.3** is limited to the synthesis of peptides that have at least one phenylalanine residue. Silverman and co-workers demonstrated that the synthesis of scytalidamide A can also be achieved with a more versatile 4-methoxybenzaldehyde resin **38.4** following a similar set of transformations.

5.6. Tentoxin

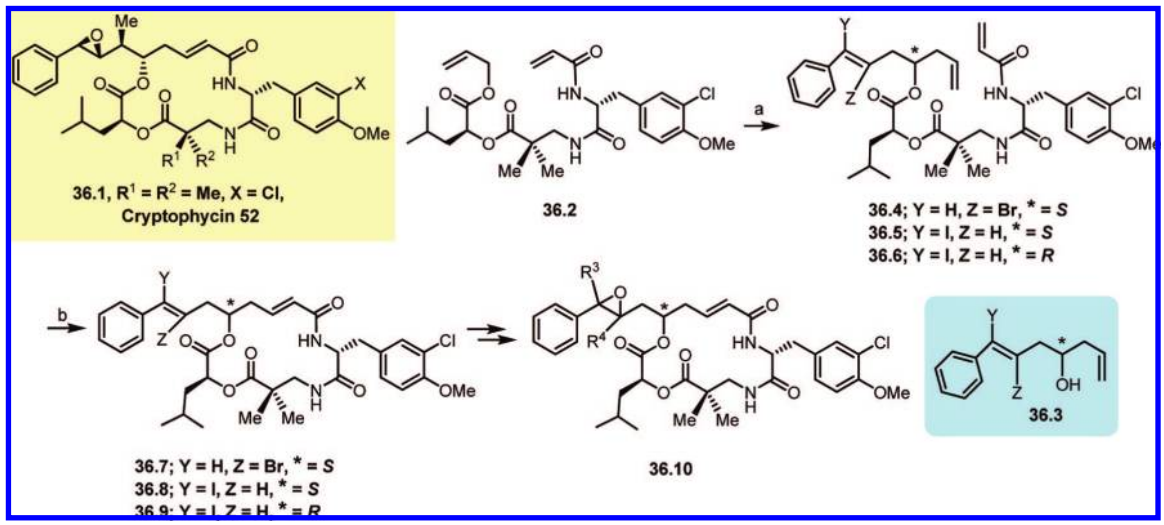
Albericio and co-workers[289] reported the total synthesis of the phytotoxic metabolite tentoxin (**40.1**, Scheme 40) on a solid phase and also generated a small library of its analogs. Tentoxin has several unique features: it is a cyclic tetrapeptide, that is, the smallest synthesizable cyclic peptide (apart from diketopiperazines), with a didehydroamino acid residue and *N*-methyl functionalities present in it. The synthesis was initiated with an immobilization of *N*-Fmoc-Gly-OH onto the hydroxyl linker resin **40.2**, which was then followed by coupling with appropriate amino acids to obtain the tetrapeptide **40.3**. The second residue from the carboxyl end in **40.3** was nonproteinogenic L/D-Phe(β-OH). The β-hydroxy group of the L/D-Phe residue in **40.3** was then activated with

Scheme 35. Searcey and Co-workers' Solid-Phase Synthesis of the Cyclic Peptide Part of Chlorofusin[a]



[a] Reagents and conditions: (a) (i) 20% v/v piperidine/DMF, RT; (ii) Fmoc-Ala-OH, HBTU, HOBt, (^{i}Pr)$_2$NEt, DMF, RT; (iii) repeat conditions i and ii for Fmoc-Thr(^{t}Bu)-OH, then **35.3**, then **35.4**, then Fmoc-D-Leu-OH, then Fmoc-Thr(^{t}Bu)-OH, then Fmoc-D-Leu-OH, and finally Fmoc-D-Asn(Trt)-OH; (iv) 20% v/v piperidine/DMF, RT; (b) (i) 2% v/v $N_2H_4 \cdot H_2O$/DMF, RT; (ii) DIC, HOAt, DMF, RT; (iii) PyBOP, (^{i}Pr)$_2$NEt, DMF, RT; (c) TFA/^{i}Pr$_3$SiH/H_2O (95: 2.5:2.5), RT.

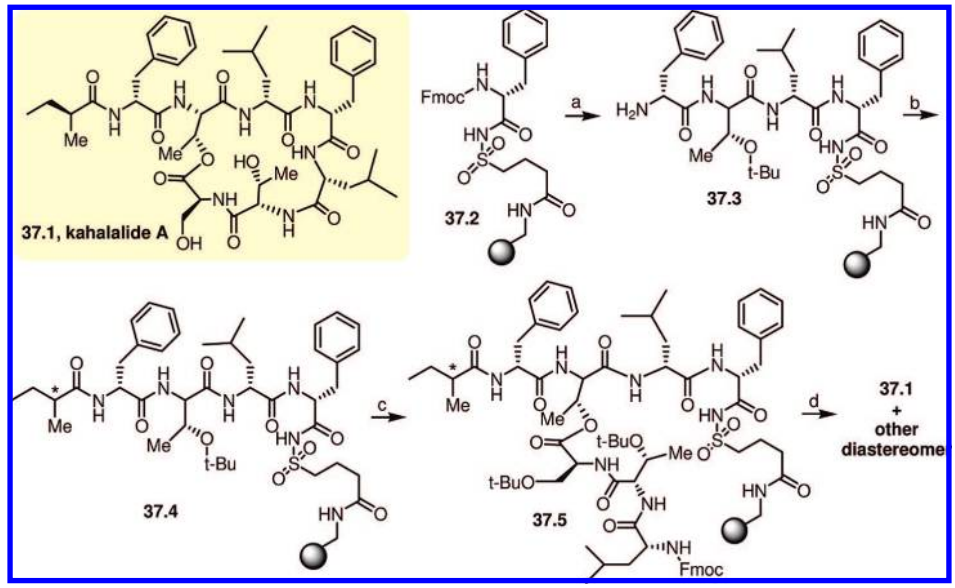
Scheme 36. Lautens and Co-workers' Approach to the Synthesis of Cryptophycin Analogs[a]



[a] Reagents and conditions: (a) (i) Pd(PPh$_3$)$_4$, THF, RT; (ii) **36.3**, 2,4,6-trichlorobenzoyl chloride, (^{i}Pr)$_2$NEt; (b) for **36.4**, Grubbs 2nd generation catalyst, CH_2Cl_2, RT; for **36.5** and **36.6**, Grubbs 1st generation catalyst, toluene, 80 °C.

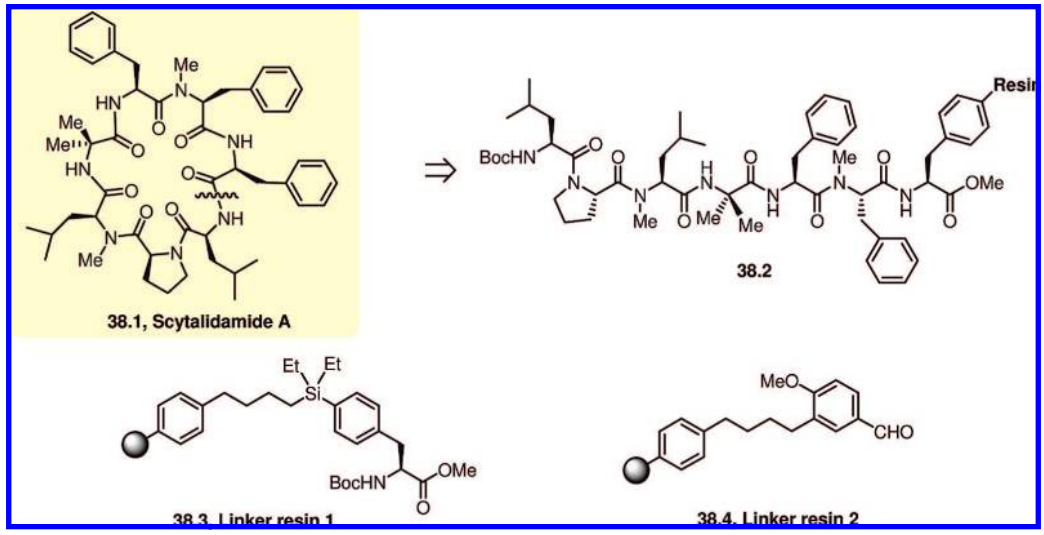
EDC·HCl the presence of CuCl to form the desired didehydrophenylalanine residue. The amide bond involving this dehydro amino acid residue, being more acidic, underwent a regioselective N-methylation in the presence of MeI/K_2CO_3 in the following step, which completed the synthesis of a linear version of the desired cyclic peptide. The linear tetrapeptide was then cleaved from the resin by TFA treatment to afford **40.4** in solution, which under DIC/HOBt conditions underwent cyclization to form the desired cyclic peptide, tentoxin **40.1**. After successfully achieving the total synthesis of tentoxin, the researchers synthesized eight analogs of tentoxin with diversities in the N-alkylating group of the dehydroamino acid residue (methyl, in case of tentoxin) and its N-terminal residue (leucine in case of

Scheme 37. Ganesan and Co-workers' Solid-Phase Total Synthesis of Kahalalide A and Analogs[a]



[a] Reagents and conditions: (a) (i) 20% piperidine/DMF; (ii) Fmoc-D-Leu-OH, DIC, HOBt, DMF; (iii) repeat conditions i and ii for Fmoc-Thr(^{t}Bu)-OH, then Fmoc-D-Phe-OH, then i; (b) (*S*)-2-methylbutyric acid or (±)-2-methylbutyric acid, DIC, HOBt; (c) (i) TFA/^{i}Pr$_3$SiH/H$_2$O (95:2.5:2.5); (ii) Fmoc-L-Ser(^{t}Bu)-OH, DIC, 0.4 equiv of DMAP, THF; (iii) 20% piperidine/DMF; (iv) Fmoc-L-Thr(^{t}Bu)-OH, DIC, HOBt; (v) 20% piperidine/DMF; (vi) Fmoc-D-Leu-OH, DIC, HOBt; (d) (i) 20% piperidine/DMF; (ii) 4 equiv of trityl-Cl, 8 equiv (^{i}Pr)$_2$NET, CH$_2$Cl$_2$; (iii) 10.0 equiv of ICH$_2$CN, 12.0 equiv of (^{i}Pr)$_2$NET, NMP; (iv) 5% TFA/CH$_2$Cl$_2$, then 3 equiv of (^{i}Pr)$_2$NET; (v) TFA/^{i}Pr$_3$SiH/H$_2$O.

Scheme 38. Silverman and Co-workers' Retrosynthetic Approach and the Linker Resins Used in the Total Synthesis of Scytalidamide A

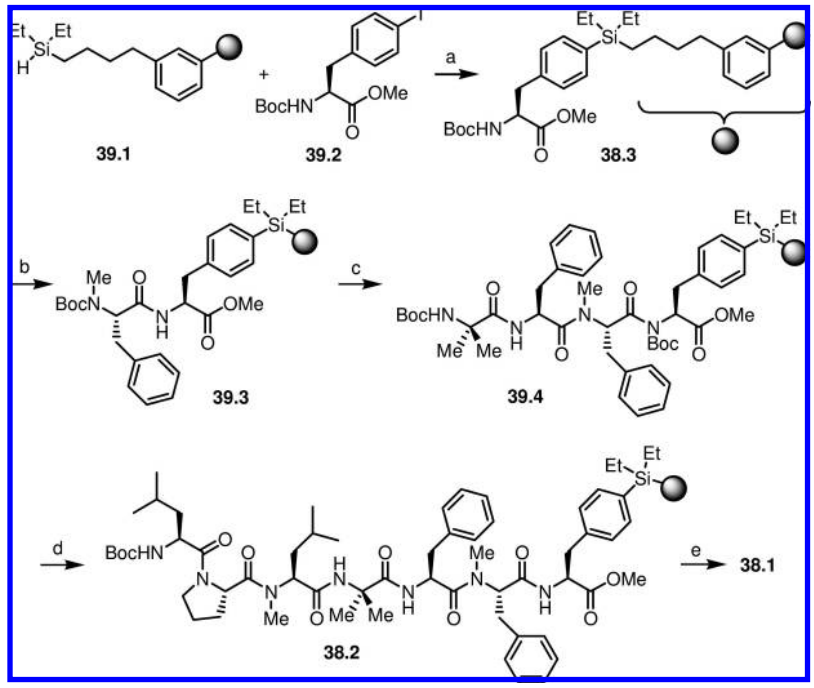


tentoxin). Interestingly, in all these cases, the final cyclization step was carried out in solution phase, although the rest of the steps were performed in the solid phase on the resin-bound substrates. The methods described in this report can be applicable to generate much larger combinatorial libraries based on tentoxin or other cyclic peptides with similar structural features.

5.7. Tenuecyclamides A−D

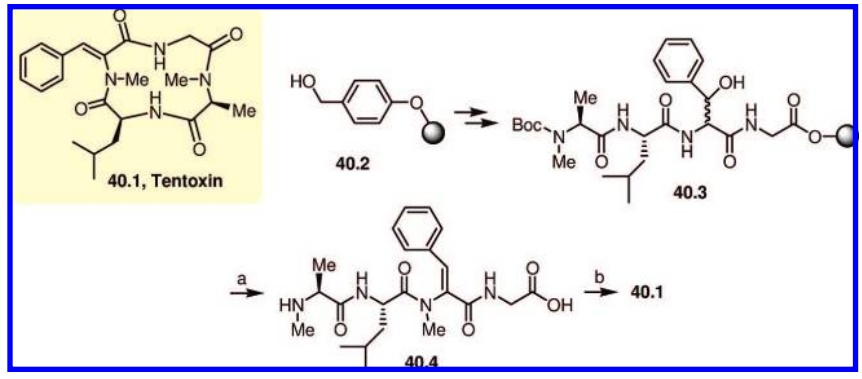
Many bioactive macrolactam natural products contain heterocyclic amino acids, consisting of thiazoles, oxazoles, thiazolines, and oxazolines.[290] Tenuecyclamides A−D (tenuecyclamide A, **41.1**, and tenuecyclamide C, **41.2**, are shown in Scheme 41) belong to the class of macrolactams in which the stereochemistry was not fully assigned after isolation from its natural source because of racemization at the chiral centers adjacent to thiazole rings during degradation. Tenuecyclamides A and B have two methyl side chains adjacent to two thiazole rings, whereas tenuecyclamides C and D have one methionine residue (sulfoxide, in case of tenuecyclamide D) adjacent to a thiazole ring. In all these compounds, the assignment of stereocenters was ambiguous. This warranted the total synthesis of all possible diastereomers of these macrolactams, varying those stereocenters for a complete and unambiguous assignment. Equipped with the methodologies to obtain thiazole or oxazole amino acids,[291,292] Kelly and co-workers[293] successfully undertook this objective and confirmed the absolute configuration of the stereocenters by synthesizing and comparing the NMR spectra to that of the material isolated from nature. The fragments of tenuecyclamide A, **41.1**, and tenuecyclamide C, **41.2**, shown in Scheme 41, were coupled using standard peptide coupling conditions

Scheme 39. Solid-Phase Synthesis of Scytalidamide A (Continued)[a]



[a] Reagents and conditions: (a) $Pd_2(dba)_3 \cdot CHCl_3$, KOAc, NMP, 110 °C; (b) (i) TFA/CH_2Cl_2 (1:1), RT; (ii) Boc-MePhe-OH, HATU, $(^iPr)_2NEt$, NMP, RT; (c) repeat conditions b(i) and b.ii with Boc-Phe-OH and then Boc-Aib-OH; (d) repeat conditions b(i) and b.ii with Boc-MeLeu-OH, then Boc-Pro-OH, HATU, and then Boc-Leu-OH; (e) (i) LiOH, H_2O/THF (1:7), RT; (ii) TFA/CH_2Cl_2 (1:1), RT; (iii) PyBOP, $(^iPr)_2NEt$, NMP, RT; (iv) neat TFA, RT.

Scheme 40. Albericio and Co-workers' Solid-Phase Total Synthesis of Tentoxin and Analogs[a]



[a] Reagents and conditions: (a) (i) EDC·HCl, CuCl, CH_2Cl_2/DMF (9:1); (ii) MeI, K_2CO_3, 18-crown-6, DMF; (iii) TFA/H_2O (19:1); (b) DIC/HOBt/$(^iPr)_2NEt$, CH_2Cl_2/DMF (99:1).

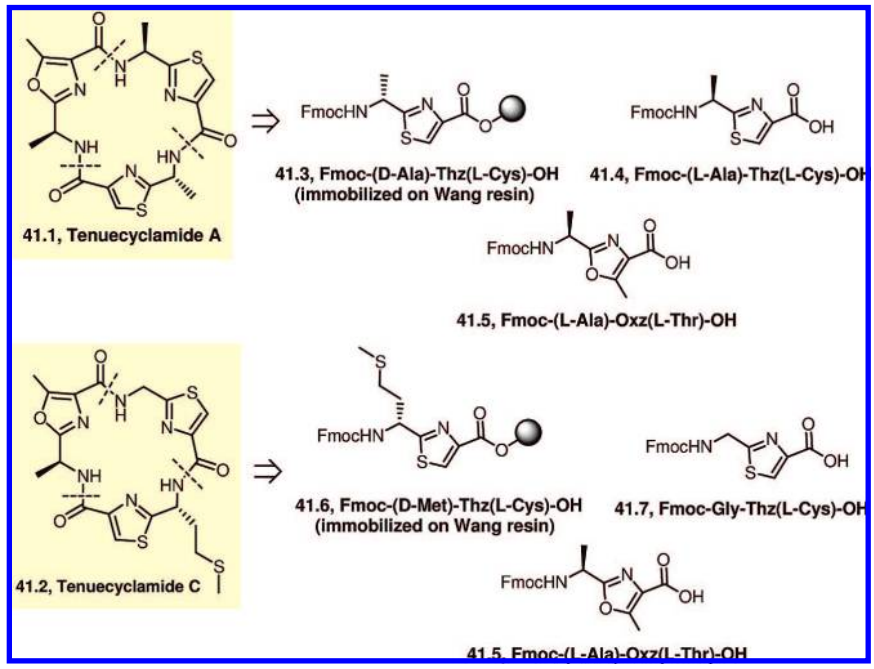
in an appropriate sequence on a solid phase. After the formation of the linear trimer, they were cleaved from the solid support, and then the final macrolactamization was performed in solution phase in each case. The nomenclature for the individual residues mentioned in Scheme 41 was proposed by the authors; the three letter code and configuration in the parentheses (next to "Oxz" or "Thz") represent the amino acid that were used to generate the heterocyclic amino acid, while Thz and Oxz indicating a thiazole and an oxazole heterocycle, respectively.

5.8. Peptoids

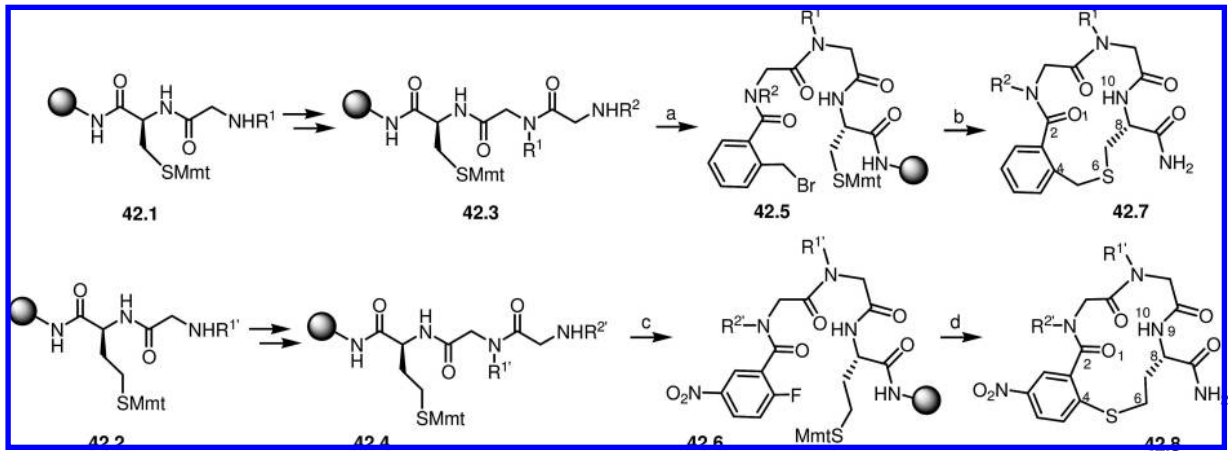
Peptoids, poly-N-alkylated glycine chains,[294−298] are an interesting class of compounds that can easily be constructed by solid-phase synthesis.[299] A wide number of amines can be used as starting material to build diverse structures in a short time frame, which makes it ideally suited for generating combinatorial libraries. However, when it comes to the application of the peptoids in the area of drug discovery, one major problem is their lack of rigidity. Thus, the next logical step in this research area is to have access to conformationally constrained peptoid analogs to lower the entropy loss on binding the target and to enhance the bioavailability. In one of the recent attempts toward this objective, the Burgess group, which has contributed considerably in the peptide-related literature,[300−305] described the solid-phase synthesis of what was termed "cyclic semipeptoids", that is, hybrid macrocycles consisting of a peptoid part and usual organic architecture, with the key cyclization step performed on a solid support under microwave irradiation.[306]

Synthesis of the semipeptoids (**42.7** and **42.8**, Scheme 42), each having two diversity sites (the peptoid nitrogens), was initiated with resin-bound cysteine **42.1** and homocysteine **42.2** coupled to N-substituted glycine. Both compounds **42.1** and **42.2** were subjected to a two-step sequence, (i) coupling with bromoacetyl chloride using the secondary nitrogen followed by (ii) nucleophilic displacement of the bromine atom with a primary amine to form **42.3** and **42.4**, respec-

Scheme 41. Kelly and Co-workers' Approach to the Solid-Phase Synthesis of Tenuecyclamide A and C



Scheme 42. Burgess and Co-workers' Synthesis of Cyclic Semipeptoids[a]



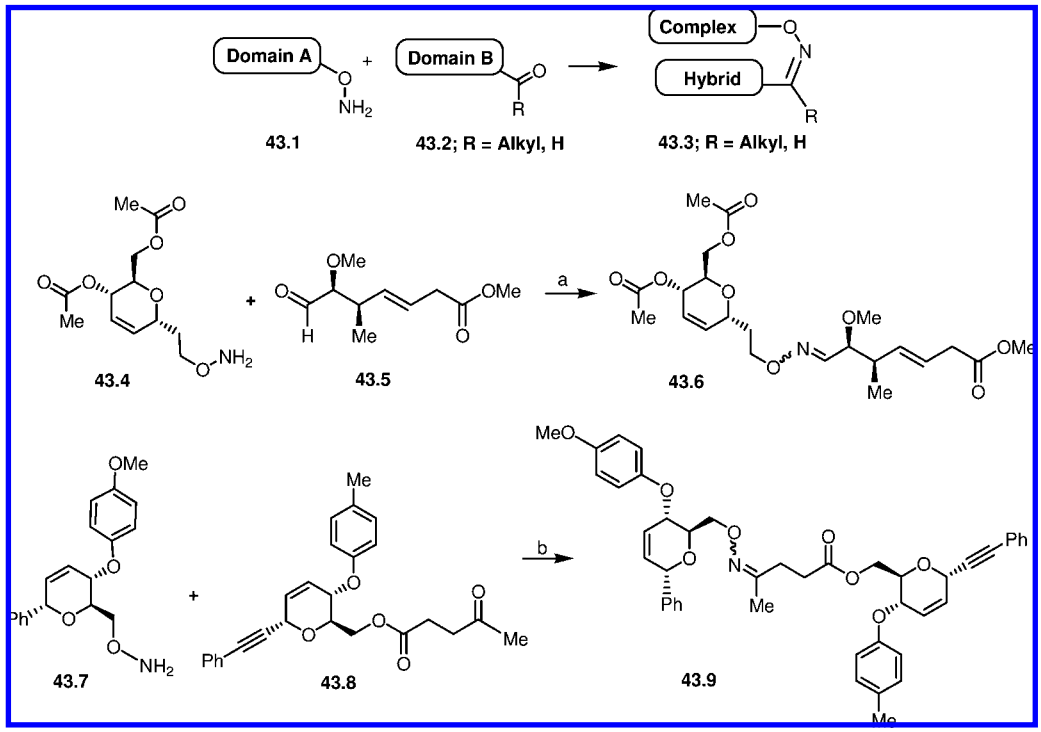
[a] Reagents and conditions: (a) 2-bromomethyl benzoyl chloride, $(^{i}Pr)_2NEt$, CH_2Cl_2; (b) (i) 3% TFA/$^{i}Pr_3SiH/CH_2Cl_2$; (ii) K_2CO_3, DMF, MW 50 °C, 10 min; (iii) 90% TFA/$^{i}Pr_3SiH$, H_2O; (c) 2-fluoro-5-nitro benzoyl chloride, $(^{i}Pr)_2NEt$, CH_2Cl_2; (d) (i) 3% TFA/$^{i}Pr_3SiH/CH_2Cl_2$; (ii) K_2CO_3, DMF, MW 50 °C, 15 min; (iii) 90% TFA/$^{i}Pr_3SiH$, H_2O.

tively (detail not shown in the scheme). The compounds **42.3** and **42.4** are essentially amino acid−peptoid hybrid molecules, each having one cysteine or homocysteine residue coupled to two N-protected glycine residues. At this stage, **42.3** was coupled to 2-bromomethyl benzoyl chloride under standard conditions to obtain the resin-bound acyclic compound **42.5**, which upon deprotection of the sulfur side chain underwent the crucial cyclization reaction via an intramolecular S_N2 attack of the sulfur atom on the bromomethyl group in the presence of a base under microwave irradiation.

On the other hand, **42.4** was separately coupled with 2-fluoro-5-nitro benzoyl chloride under similar conditions to afford resin-bound **42.6**. Deprotection of the homocysteine side chain in **42.6** triggered a similar cyclization reaction under similar conditions, this time via intramolecular S_NAr displacement of the fluoride by the sulfur atom. The cleavage of the macrocycles from the resin finally afforded the desired macrocycles **42.7** (starting from **42.5**) and **42.8** (starting from **42.6**). Burgess and co-workers synthesized 13 different semipeptoids **42.7** with substitutions (R^1 and R^2) and seven different semipeptoids **42.8** with substitutions ($R^{1'}$ and $R^{2'}$) in good yields and purities. Interestingly, some of their semipeptoids had substitutions with free amino/hydroxyl/guanine/carboxyl residues, which could potentially be used to introduce further diversities in the macrocycles to generate a much larger combinatorial library. The preliminary conformational studies on selected examples from each set of the macrocycles suggested that these molecules could be designed to mimic β-turns.

In section 5, we discussed the solution- and solid-phase methods applied to several macrocylic bioactive natural products. Macrolide architectures that are inspired by bioactive natural products belong to an attractive class of compounds and are shown to interact with a wide variety of protein targets.[307−312] Due to the presence of the restricted conformation(s), a major advantage with this class of compounds is their ability to interact with the large binding surface of protein targets. Often, macrolides with more than 10 atoms in the ring show multiple low-energy conformations. Variations in the position, stereochemistry, and nature

Scheme 43. Porco and Co-workers' 168-Membered Solution-Phase Library Synthesis of Hybrid Molecules[a]



[a] Reagents and conditions: (a) (i) AcOH, EtOAc, RT; (ii) PL-MIA resin; (b) (i) AcOH, THF, microwave radiation (150 W), 100 °C, 20 min; (ii) PL-MIA resin.

of the substituents can alter the energetics of a ring conformation.[313]

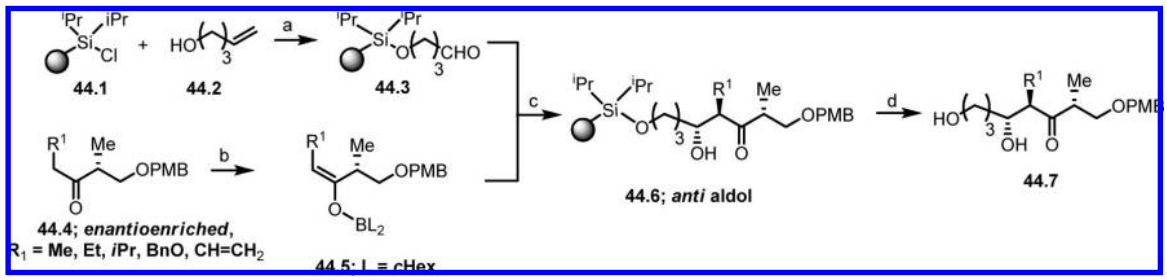
6. Solid-Phase Synthesis of Oxygen-Enriched Natural Product-Inspired Compounds

The combinatorial chemistry examples discussed in the previous section allow access to small-molecule analogs of a given bioactive natural product, which tends to populate the chemical space currently occupied by the existing natural products. Parallel to this approach, the goal of DOS is to populate the unexplored chemical space by developing methods that allow rapid access to natural product-like compounds having three-dimensionally complex architectures.[1,70−83] In addition to generating the libraries of natural product derivatives, interest is also growing in developing methods for obtaining bioactive natural product-inspired scaffolds. These scaffolds could then be utilized in the library generation protocols. It is anticipated that the small molecules being generated from this program are likely to exhibit interesting biological responses because they would aim to reach the chemical space currently being occupied by bioactive natural products. Another major advantage with this approach is that following the identification of bioactive leads, these compounds could easily be subjected to classical medicinal chemistry approaches for further refining their biological activities and the pharmacological properties. Thus, identification of biologically active chemical probes offers an excellent starting point in quickly reaching drug candidates. Highlighted in this section is the work from several laboratories in developing methods leading to the library generation of oxygen-enriched and flavonoid-inspired compounds.

Bioactive hybrid molecules make an interesting class of compounds that often exhibit enhanced activity compared with the parent fragments in the case of both naturally occurring ones[314] and the synthetically derived ones. Inspired by this observation, Porco and co-workers developed a solution-phase library of 168 hybrid oximes by a convergent approach involving a concept that was termed "chemical domain shuffling".[315] In their approach, domain A alkoxyamines, **43.1** (Scheme 43), were coupled with domain B carbonyls, **43.2**, to generate the hybrid oximes **43.3**. The library was constructed with 12 structurally complex and optically pure alkoxyamine monomers including β-hydroxy alkoxyamines, pyran, carbohydrate, and other heterocycle-derived alkoxyamines and 14 complex carbonyl derivatives. The carbonyl monomers were also complex and optically pure including napthahydrins, pyridoazepines, pyrans, polyketide-like fragments, angular scaffolds, and pipecolate ester. As shown in Scheme 43, pyran-containing alkoxyamine **43.4** reacted under acid-catalyzed conditions with polyketide-like carbonyl **43.5** to give the hybrid oxime **43.6** as a mixture of geometrical isomers. Similarly, another pyran-derived alkoxyamine **43.7** was coupled with complex pyran carbonyl **43.8** to afford **43.9** under microwave-assisted acid-catalyzed conditions. Thus, a combination of 26 (14×12) monomers provided a solution-phase collection of 168 complex hybrid structures as a mixture of geometrical isomers. In all the cases, the reactions were scavenged by PL-MIA resin. This library showed anticipated results in preliminary screening as one of the library members was identified as a significantly active human small cell lung carcinoma inhibitor with its monomers (e.g., alkoxyamine and carbonyl fragments) being completely inactive.

The polyketides represent an elegant class of structurally complex, often biologically active natural products having potentially diverse therapeutic importance as antibiotics, anticancer agents, antifungals, antiparasitics, immunosuppressants, and cardiovascular agents.[69,316−319] In one of the early examples of sophisticated asymmetric synthesis of

Scheme 44. Paterson and Co-workers' Solid-Phase Synthesis of a Library of β-Hydroxy Ketones[a]



[a] Reagents and conditions: (a) (i) (^{i}Pr)$_2$NEt, DMAP, CH_2Cl_2, RT; (ii) O_3, CH_2Cl_2, −78 °C; then Ph_3P, RT, sonication; (b) (*c*Hex)$_2$BCl, Et_3N, Et_2O, −78 to 0 °C; (c) (i) Et_2O, −78 °C to RT (two cycles); (ii) H_2O_2 (30% aq), MeOH, DMF, pH 7 buffer, 0 °C; (d) HF·pyridine, pyridine, MeCN, RT.

small molecules on solid support, Paterson and co-workers[320] achieved the synthesis of diverse polyketide-type architectures with multiple stereocenters using iterative aldol chemistry on readily accessible chiral building blocks. Notably, the researchers demonstrated that the solid-phase yields for multistep reaction sequences were markedly better than the solution-phase equivalents and the high degree of diastereoselectivity was maintained in the solid phase as well. The diversity of unnatural polyketides was achieved elegantly through variation in the building blocks different chain extensions, stereochemistry, oxidation state, and introduction of the acetonide rings in the solid phase.

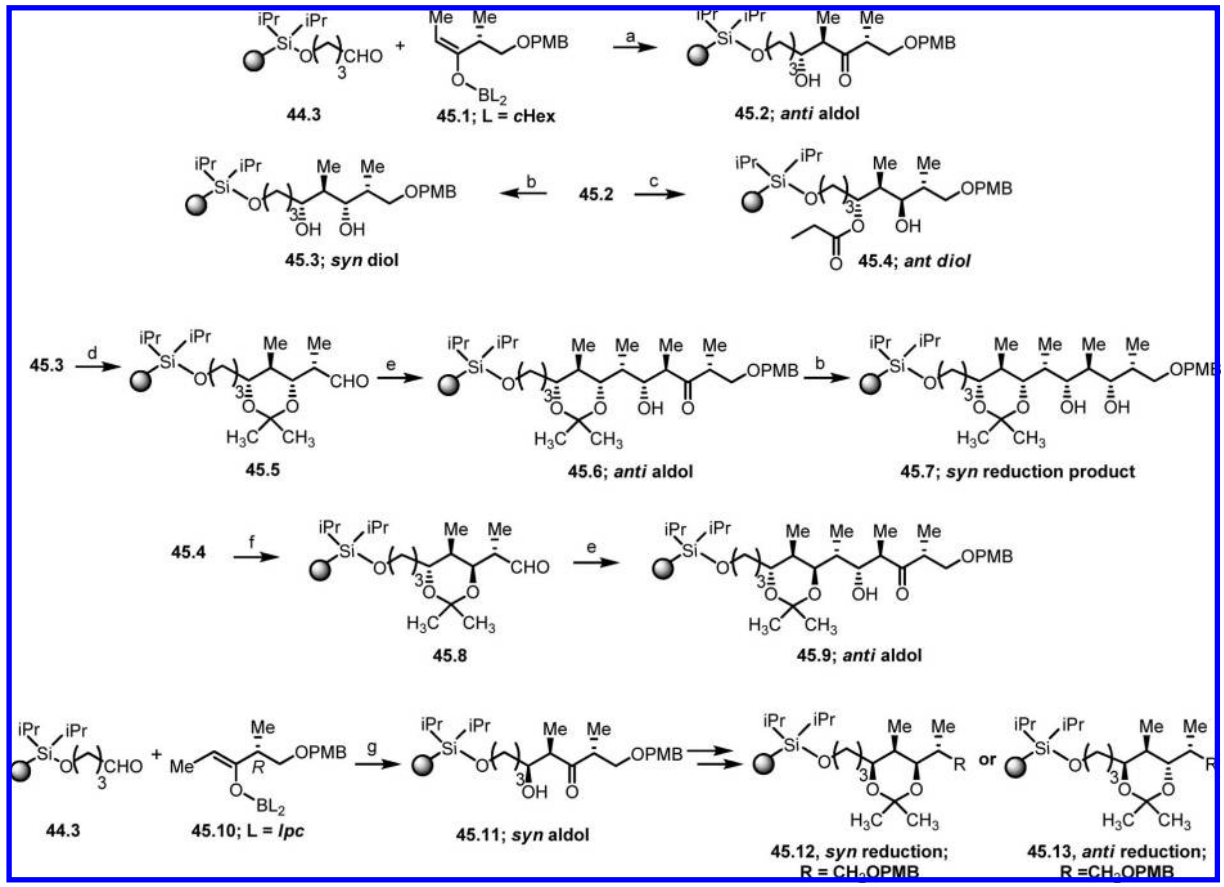
The solid-phase synthesis of a small library of β-hydroxy ketones **44.7** (Scheme 44) was performed using five different chiral ketones **44.4** (R_1 = Me, Et, ^{i}Pr, BnO, CH=CH_2) and resin-bound aldehyde **44.3** via a stereocontrolled aldol reaction. 4-Penten-1-ol, **44.2**, was loaded onto chlorodiisopropylsilyl polystyrene, **44.1**, to deliver the resin-bound aldehyde **44.3**, following ozonolysis with a reductive workup.[321] On the other hand, five different chiral (*R*)-ketones, **44.4**, were treated with (*c*Hex)$_2$BCl/Et_3N in Et_2O at −78 °C to generate different (*E*)-boron enolates,[322−324] **44.5**. The aldehyde **44.3** was then split into five vessels and allowed to react with five different boron enolates **44.5** in Et_2O at low temperature to form the desired *anti*-aldols. Oxidative workup of these aldol adducts using H_2O_2 in buffered conditions, followed by cleavage from resin with HF−pyridine, resulted in the library of *anti*-configured β-hydroxy ketones **44.6** in good to excellent yields with a high level of diastereoselectivity.

Apart from the development of a small library of hydroxyketones on a solid phase, Paterson and co-workers reported the synthesis of polyketides having longer sequence and increasing structural complexity (e.g., precursor of the erythromycin) and stereochemical diversity (Scheme 45).[320] The aldehyde **44.3** was subjected to asymmetric aldol reaction with the (*E*)-enol dicyclohexylborinate **45.1** to yield the *anti*−*anti* isomer of the hydroxy ketone **45.2** with high diastereoselectivity (≥97%). To introduce stereochemical diversity, the β-hydroxy ketone was reduced by using two different reduction protocols. First, *syn*-selective reduction on the solid phase was performed with modified Narasaka[325] reduction conditions using (*c*Hex)$_2$BCl and Et_3N to regenerate the dicyclohexylboron aldolate, followed by reduction with $LiBH_4$ affording the 1,3-*syn*-diol **45.3** in excellent yield and diastereoselectivity. On the other hand, an Evans−Tishchenkoreduction protocol[326] using a stoichiometric amount of SmI_2 was successfully employed for *anti*-selective reduction of **45.2** to the 1,3-*anti*-diol ester **45.4** with at least 97% diastereoselection. After the successful installation of four stereocenters on the growing chain anchored to the resin, the secondary hydroxy groups of the diols **45.3** and the one derived from **45.4** by reduction of the ester linkage were protected as *syn*- and *anti*-acetonides and then converted to **45.5** and **45.8**, respectively, by unmasking the primary hydroxy and subsequent oxidation.[327] On a second cycle of *anti*-aldol addition with (*E*)-enolate **45.1**, the aldehydes **45.5** and **45.8** generated the ketones **45.6** and **45.9**, respectively, with impressive yield and high diastereoselectivity. In fact, **45.9** was obtained in an average yield of 94% for eight steps in the solid phase. When subjected to s*yn*-reduction protocol, **45.6** afforded the resin-bound 1,3-diol **45.7** with remarkable eight contiguous stereocenters. Cleavage of all the products from the solid support was performed under standard HF−pyridine conditions.

With a smart twist to this protocol, Paterson and co-workers synthesized the *syn* aldol **45.11** by treatment of the resin-bound aldehyde **44.3** with (*Z*)-boron enolate **45.10**. The enolate **45.10** was obtained by treatment of (+)Ipc_2BOTf/DIPEA on the ketone **44.4** (R_1 = Me) in CH_2Cl_2 at −78 °C. *Syn* and *anti* reductions of **45.11** and subsequent acetonide formations afforded another set of structurally and stereochemically distinct molecules **45.12** and **45.13**, respectively, in high diastereomeric purity and excellent yield. This report has efficiently demonstrated the preparation of structurally complex and diverse polyketide-type molecules in a multistep stereoselective synthesis on a solid support with high efficiency and accuracy.

Exploiting the solid-phase methodology as described in Schemes 44 and 45, Paterson and co-workers[328] attempted the generation of another library of polyketides (for other approaches to solid-phase polyketide synthesis)[329−331] with increasing stereochemical complexity from simpler aldehydes. Accordingly, the resin-bound aldehyde **46.3** (Scheme 46), attached through a secondary alcohol moiety to a polystyrene support via a silyl linker, was subjected to aldol chain extension with chiral ketone modules, such as (*R*)-**46.5** and (*S*)-**46.6**, leading to the expedient construction of defined sequences of stereocenters. Diverse polyketide-type libraries of tetrapropionates **46.9** and **46.12** that resembled configurationally the segments of the *seco*-acid of 6-deoxyerythronolide B and discodermolide[332−335] were generated using this concept. The resin-bound aldehyde **46.4** was prepared from chiral α-hydroxy ketone **46.1** in few standard steps including loading over hydroxymethyl Merrifield resin to afford **46.3**. Deprotection of the PMB ether and subsequent Dess−Martin oxidation provided the key aldehyde **46.4**. The researchers adopted two different aldol reaction protocols to achieve different stereochemical sequences, thereby expanding the polyketide diversity. Under the *anti*-aldol reaction conditions, the aldehyde **46.4** was coupled with (*E*)-

Scheme 45. Paterson and Co-workers' Solid-Phase Synthesis of Long-Chain Polyketide Sequences[a]

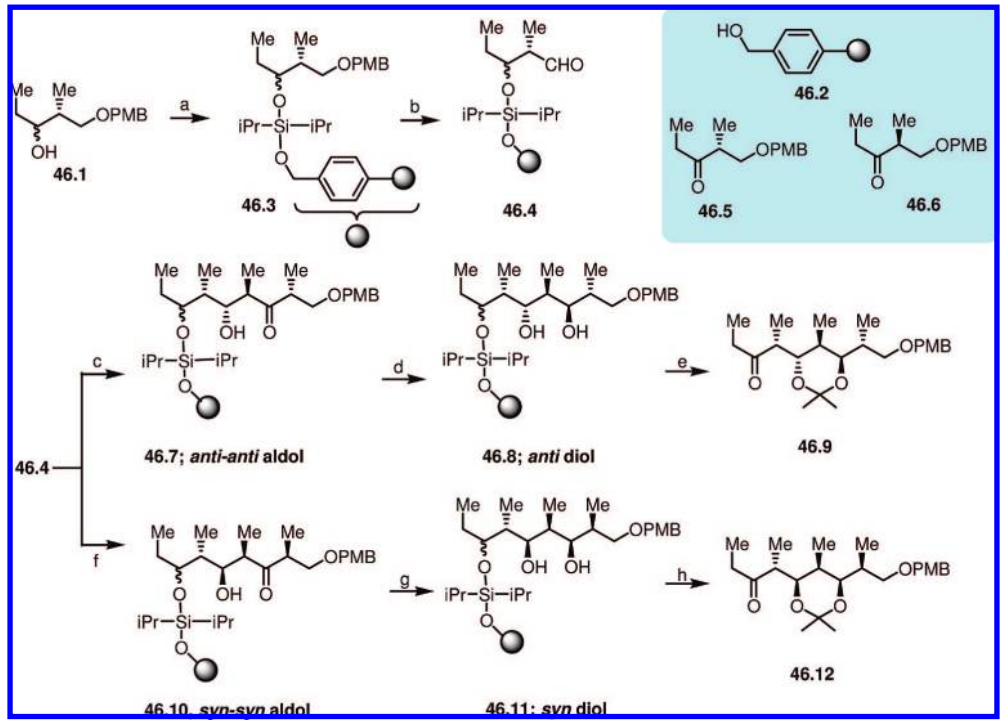


[a] Reagents and conditions: (a) (i) Et_2O, −78 to 0 °C; (ii) H_2O_2 (30% aq), MeOH, DMF, pH 7 buffer, 0 °C; (b) (i) $(cHex)_2BCl$, Et_3N, Et_2O, 0 °C; (ii) $LiBH_4$, Et_3N, −78 °C; (iii) H_2O_2 (30% aq), MeOH, NaOH (10% aq), CH_2Cl_2, RT; (c) EtCHO, SmI_2, THF, −10 to 0 °C; (d) (i) $(MeO)_2CMe_2$ or $MeOC(Me)=CH_2$, CSA, CH_2Cl_2, RT; (ii) DDQ, pH 7 buffer/CH_2Cl_2 (20/1), RT; (iii) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, 0 °C; (e) (i) **45.1**, Et_2O, −78 to 26 °C; (ii) H_2O_2 (30% aq), MeOH, DMF, pH 7 buffer, 0 °C; (f) (i) $LiBH_4$, THF, −78 to RT; (ii) repeat steps d; (g) CH_2Cl_2, −78 to −26 °C.

enol dicyclohexylborinate of (*R*)-**46.5** in Et_2O followed by standard oxidative workup to generate *anti*−*anti* adduct **46.7** with a high level of diastereoselectivity. Similarly, under the *syn*-aldol addition reaction conditions, the aldehyde **46.4** reacted with the (*Z*)-enolate of (*S*)-**46.6** ($Ti(O^iPr)_2Cl_2$-mediated enolization)[336,337] in CH_2Cl_2 (−78 °C, 5 h) to afford the *syn*−*syn* adduct **46.10** in excellent yield and diastereoselectivity (90%, 95:5). The *anti*−*anti* adduct **46.7** was then subjected to the Evans−Tishchenko reduction protocol for *anti*-selective reduction, followed by reduction of the resulting ester group to afford the resin-bound *anti*-diol **46.8**. Protection of **46.8** as an *anti*-acetonide, followed by release from the silyl linker and finally oxidation of the resulting secondary alcohol, allowed access to the ketone **46.9** as the end product. In a similar protocol, the *syn*−*syn* aldol **46.10** was subjected to stereocontrolled *syn*-selective reduction using $Zn(BH_4)_2$ in CH_2Cl_2 to afford the 1,3-*syn*-diol **46.11**. Protection of **46.11** as *syn*-acetonide followed by a similar sequence of cleavage of the product from resin and oxidation of the alcohol afforded the second target **46.12** in excellent overall yield and diastereoselectivity. In summary, Paterson and co-workers reported a highly stereocontrolled solid-phase synthesis of tetraketides related to sizable fragments of 6-deoxyerythronolide B and discodermolide. This study demonstrated the efficiency of this methodology in solid-phase polyketide synthesis, along with the general suitability of the silyl linker for the attachment of hindered secondary alcohols to the resin.

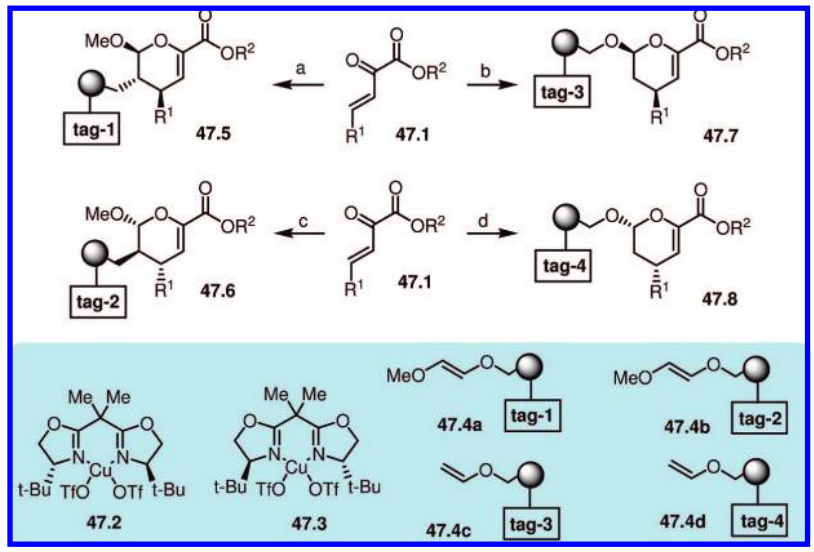
The asymmetric hetero-Diels−Alder reaction of α,β-unsaturated carbonyls with electron-rich alkenes catalyzed by C_2-symmetric bis(oxazoline) Cu(II) complexes (Lewis acid catalysts) provides an expedient entry into enantioenriched dihydropyrans.[338] A number of α,β-unsaturated acyl phosphonates and β,γ-unsaturated α-keto esters and amides have been successfully employed as heterodienes, while enol ethers and sulfides and certain ketone silyl enol ethers have functioned well as dienophiles in solution phase.[339,340] Although commonly utilized in classical target-oriented synthesis projects, the use of enanantioselective catalysis in natural product-inspired library generation has not been explored extensively. To achieve this goal, Stavenger and Schreiber[341] reported the enantioselective synthesis of 2*H*-pyran derivatives on a solid phase that utilized C_2-symmetric chiral bis(oxazoline)-derived Lewis acid catalysts (**47.2** and **47.3**, Scheme 47). In their approach, the vinyl ethers anchored onto encoded alkylsilyl macrobeads (**47.4a**, **47.4b**, **47.4c**, and **47.4d**) were allowed to react with the ketoester **47.1**, giving structurally different 2*H*-pyrans (**47.5**, **47.6**, **47.7**, and **47.8**) through a stereoselective 4 + 2 cycloaddition reaction. The use of encoded split-and-mix technology on macrobeads allowed the researchers to obtain a library of 4320 compounds.[342] The enantioselective cycloaddition reaction worked well on a solid phase, and the products were obtained in good yields and with moderate enantioselectivity. Along with other compounds, this library was arrayed and tested for small-molecule binders that modulate the tran-

Scheme 46. Paterson and Co-workers' Solid-Phase Synthesis of Library of Polyketides That Are Structurally Analogous to Fragments of Discodermolide and *seco*-Acid of 6-Deoxyerythronolide B



Reagents and conditions: (a) (i) $^{i}Pr_2SiCl_2$, DMF, imidazole, **46.2**; (b) (i) DDQ, CH_2Cl_2; (ii) DMP, pyridine, CH_2Cl_2; (c) **46.5**, (cHex)$_2$BCl, Et_3N, Et_2O; (d) (i) MeCHO, SmI_2, THF; (ii) $LiBH_4$, THF; (e) (i) $(MeO)_2CMe_2$, CSA, CH_2Cl_2; (ii) HF−pyridine, pyridine, CH_3CN; (iii) DMP, pyridine, CH_2Cl_2; (f) **46.6**, $Ti(O^{i}Pr)_2Cl_2$, $(^{i}Pr)_2NEt$, CH_2Cl_2, −78 °C; (g) $Zn(BH_4)_2$, CH_2Cl_2; (h) (i) MeOC(Me)=CH_2, CSA, DMF; (ii) TBAF; (iii) DMP, pyridine, CH_2Cl_2.

Scheme 47. Schreiber and Co-workers' Asymmetric Heterocycloaddition, Split-Pool Synthesis of Dihydropyronocarboxylates[a]

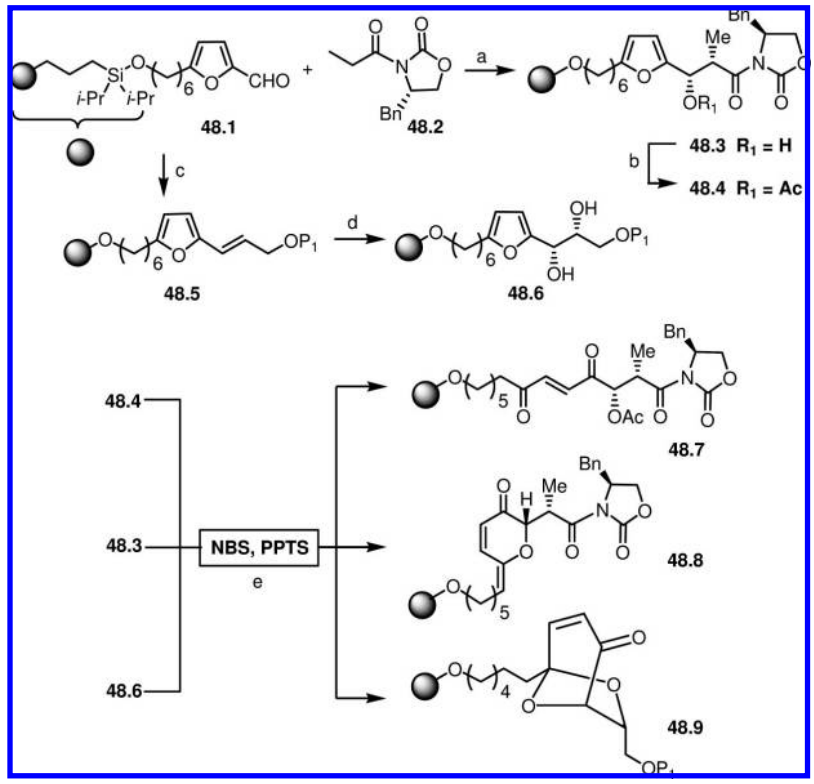


[a] Reagents and conditions: (a) **47.4a**, **47.2** (20 mol %), THF, molecular sieves; (b) **47.4c**, **47.2** (20 mol %), THF, molecular sieves; (c) **47.4b**, **47.3** (20 mol %), THF, molecular sieves; (d) **47.4d**, **47.3** (20 mol %), THF, molecular sieves.

scriptional activity of the protein Hap3p,[343] and an active dihydropyran ligand was identified from this library.

Another elegant example of method development on a solid phase that has been used to obtain several natural product-inspired small molecules having stereochemically defined chiral functional groups and conformationally diverse structures was reported by Schreiber and co-workers.[344] After successful results in solution phase to create novel, distinct, and diverse complex skeletons from a furan-based scaffold, the researchers aimed at library generation using this method. The library generation on a solid phase was successfully accomplished by using alkylsilyl macrobeads (500−560 μm). Furaldehyde was immobilized onto the macrobead-based solid support to obtain **48.1** (Scheme 48), which was subjected to Evans asymmetric aldol reaction[345] with (*S*)-(+)-4-benzyl-3-propionyl-2-oxazolidinone, **48.2**, in the presence of n-Bu_2BOTf and Et_3N in CH_2Cl_2, followed by oxidative work up giving the *syn* aldol α-hydroxy furan product **48.3** in 90% purity with 20:1 diastereoselectivity. Subsequently, acylation of aldol adduct **48.2** afforded the α-acetoxyalkyl furan **48.4** (90% purity) with no nucleophilic hydroxyl groups. In a different experiment, resin-

Scheme 48. Schreiber and Co-workers' Approach to Generating Skeletal Diversity through a Combinatorial Method[a]

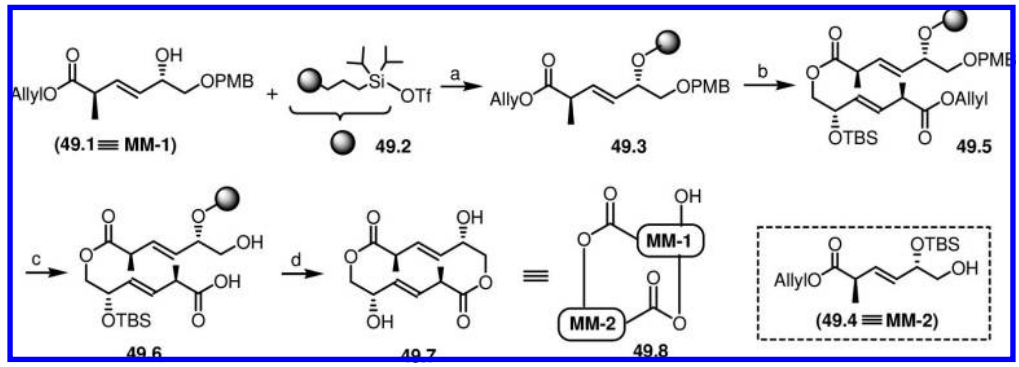


[a] Reagents and conditions: (a) (i) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to 0 °C; (ii) 30% aqueous H_2O_2, pH 7 buffer, MeOH, 4 °C; (b) Ac_2O, $(^iPr)_2NEt$, DMAP, CH_2Cl_2, RT; (c) (i) allyldiethylphosphonoacetate, LiOH, THF, RT; (ii) $Pd(PPh_3)_4$, thiosalicylic acid, THF, RT; (iii) isobutylchloroformate, 4-methylmorpholine, $(^iPr)_2NEt$, THF, 0 °C; $LiBH_4$, $(^iPr)_2NEt$, THF, 4 °C; (iv) phenyl isocyanate, pyridine, CH_2Cl_2, RT; (d) OsO_4, $(DHQD)_2PHAL$, 4-methylmorpholine *N*-oxide, TEAAT, acetone/H_2O (10:1), 4 °C; (e) (i) NBS, $NaHCO_3$, NaOAc, THF/H_2O (4:1), RT; (ii) PPTS, CH_2Cl_2, 40−45 °C.

bound furaldehyde **48.1** was subjected to a sequence of transformations: Horner−Wadsworth−Emmons olefination with allyldiethylphosphonoacetate (chain extension), followed by deallylation, reduction, and carbamate formation that led to the protected allylic alcohol derivative, **48.5**. Subjection of **48.5** to Sharpless asymmetric dihydroxylation reaction[346] using OsO_4, $(DHQD)_2PHAL$, and 4-methylmorpholine *N*-oxide gave **48.6** with 90% purity and good enantiomeric excess. Compounds **48.3**, **48.4**, and **48.6** are useful intermediates for obtaining skeletally diverse derivatives. Accordingly, these three scaffolds were exposed to the same optimized set of "folding conditions" (NBS, $NaHCO_3$, and NaOAc in THF/H_2O (4:1) at room temperature for 1 h followed by PPTS in CH_2Cl_2 at 40 °C for 20 h) to obtain the products having three different skeletons. Compound **48.4** with the masked hydroxyl group gave a linear skeleton having a *trans*-olefin moiety **48.7**. In contrast, the remaining two compounds **48.3** and **48.6** having free nucleophilic hydroxyl groups underwent an initial oxidative ring expansion to cyclic hemiketals followed by an acid-mediated (PPTS-catalyzed) dehydration reaction to provide the stereochemically defined alkylidene-pyran-3-one derivatives **48.8** and **48.9**, respectively. Notably, under these oxidative ring expansion conditions, the diol **48.6** was converted into the bicyclic derivative **48.9**. Thus, starting from a common starting material (furaldehyde), several skeletally diverse compounds could be obtained that utilized the substituted furan moiety as a source for creating the diversity. After these reactions were developed on a solid phase, they were then utilized in generating a library by split-and-mix synthesis technology. An extension to this approach was further tried with bromo- and aryl-substituted furaldehydes. The incorporation of the bromo or aryl functional group on the furan moiety provided an additional site that could be further subjected to structural diversification. Thus, the Evans' aldol derivatives (with resulting secondary hydroxy-protected and unprotected) of the substituted furfurals were subjected together to similar conditions as mentioned in the previous case to provide four structurally unique molecules in good yields. Overall, this is an excellent example of stereocontrolled DOS that requires the use of different building blocks and a methodology that results in small-molecule libraries having stereochemically and skeletally diverse natural product-like architectures.

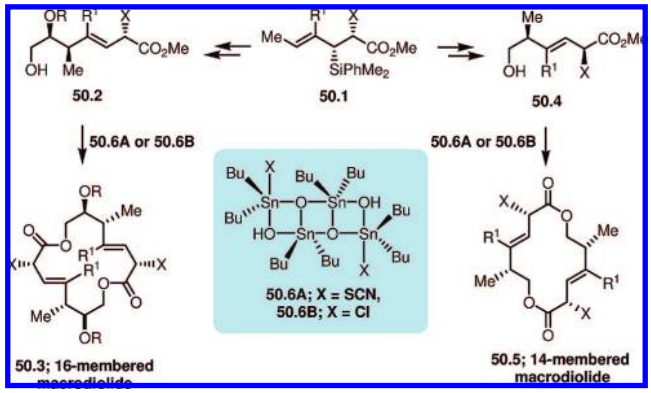
To obtain functionalized natural product-like macrocyclic compounds, Schreiber and co-workers[347] reported the sequential addition of monomers (used for cyclization) to obtain macrolactones. For the model study on solid phase synthesis of 14-membered macrolides **49.8**, Scheme 49 (elaborated with the example of **49.7**, one of the library members), the PMB-protected hydroxyester monomer (MM-1) **49.1** was anchored onto the resin **49.2** to give **49.3**. Deprotection of the allyl ester on **49.3** under standard conditions afforded the free carboxylic acid, which was then reacted with the second monomer (MM-2) **49.4** under standard ester coupling conditions to obtain **49.5**. Subsequent unmasking of the carboxyl and the primary hydroxyl groups afforded compound **49.6**. Finally, the crucial macrocyclization was achieved by employing the Yamaguchi protocol followed by simultaneous *O*-TBS deprotection and cleavage of the product from the resin using HF−pyridine. Use of different monomers (MM-1 and MM-2) allowed the researchers to obtain a series of 14-membered macrolides (for example, **49.7**) in overall good yields.

Scheme 49. Schreiber and Co-workers' Solid-Phase Approach for a Pilot Library with Exploration of the Controlling Factors for Macrocyclization[a]



[a] Reagents and conditions: (a) 2,6-lutidine, CH_2Cl_2; (b) (i) $Pd(PPh_3)_4$, thiosalicylic acid, THF; (ii) **49.4**, EDCI, DMAP, CH_2Cl_2; (c) (i) $Pd(PPh_3)_4$, thiosalicylic acid, THF; (ii) DDQ, H_2O/CH_2Cl_2; (d) (i) 2,4,6-trichlorobenzoyl chloride, $(^iPr)_2NEt$, THF, DMAP; (ii) HF−pyridine, THF.

Scheme 50. Porco, Jr., and Co-workers' Stereochemical Diversity through Cyclodimerization for the Synthesis of Polyketide-like Macrodiolides



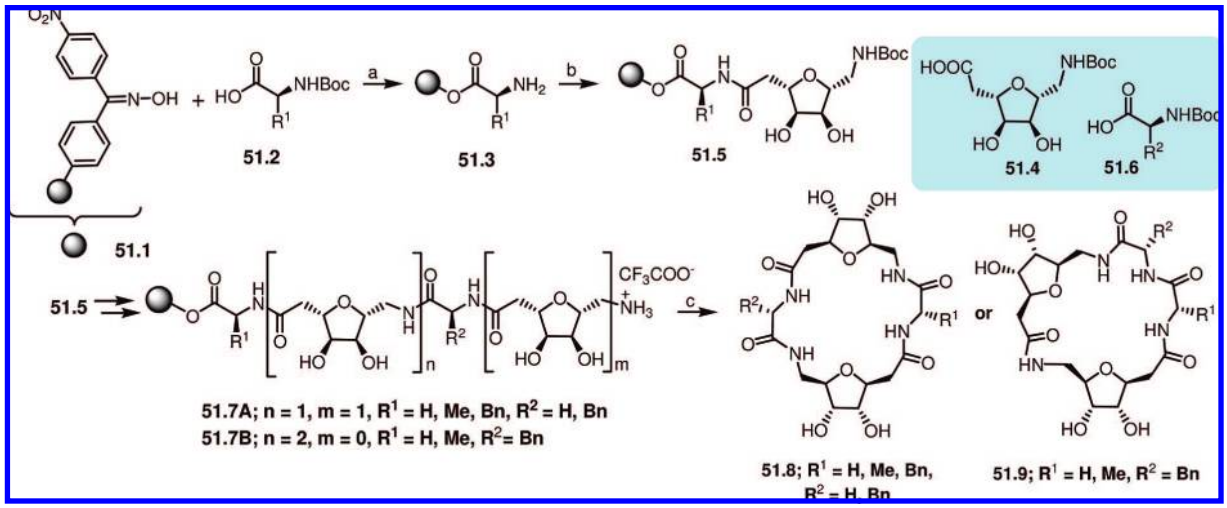
Macrocyclic dilactones (macrodiolides) are well represented in nature as both homo- and heterodimers and offer a wide variety of skeletons, ring sizes, and functional groups. Natural products with macrodiolide frameworks are also known to exhibit a wide range of biological properties including antibiotic, antifungal, and antileukemic activities. Macrocyclic frameworks present an ideal environment for library generation and for the exploration of skeletal and stereochemical diversity.[14,341,348,349] Based on studies previously reported by Seebach and co-workers,[350] Porco and co-workers[351] employed allylic silane intermediates **50.1** bearing C-centered chirality in a transesterification sequence to produce stereochemically diverse macrodiolides having good structural resemblance to polyketide-derived natural macrodilactones.[352] Scheme 50 summarizes Porco and co-workers' approach to synthesize the 14- and 16-membered macrodiolides **50.3** and **50.5**, which involved cyclodimerization of hydroxyl esters **50.2** and **50.4**, respectively, in the presence of distannoxane *trans*-esterification catalyst **50.6A** or **50.6B**. The first transesterification of the hydroxyl ester provided an acyclic dimer intermediate, which lead to the formation of macrodiolide product following an intramolecular transesterification. The feasibility of cyclodimerization was studied using different solvents and concentrations known to work in distannoxane-mediated transesterification. Reactions were sensitive to solvent choices; however, high dilutions reduced the amount of oligomers formed. Apart from 14- and 16-membered polyketide-like macrocycles, this methodology was further used for the synthesis of a 22-membered macrodiolide with both polyketide and peptide features, and heterodimeric macrodiolides were also formed using two different monomeric units. The Porco and Panek groups created further diversities on these macrodiolides by peripheral epoxidation of the olefinic bonds followed by base-catalyzed opening of the epoxides.

Cyclodextrins are artificial receptors that can accommodate different types of guest molecules inside their cavities; hence, these compounds are the subject of extensive study in present day biomedical research.[353] Inclusion of structural features of cyclophanes in cyclodextrins produces hybrid molecules that have been reported to have enhanced ability to act as selective receptors.[354] Following the same concept, Van Boom and co-workers[355] attempted the solid-phase synthesis of two types of tetrameric cyclic sugar amino acid (SAA)/amino acid (AA) hybrids, **51.8** and **51.9** (Scheme 51), consisting of hydrophobic AAs and a randomly chosen D-allo-furanoid SAA.[356,357] In **51.8**, two SAAs are separated by one AA residue (i.e., glycine, alanine, or phenylalanine), where a dimeric SAA unit is connected to a dipeptide in **51.9**.

After obtaining the SAA monomers in conventional solution chemistry, the first step of an automated parallel solid-phase synthesis involved the coupling of oxime resin **51.1** with *N*-Boc-protected amino acid **51.2** under DIC/HOBt conditions (two cycles), followed by removal of the *N*-Boc group with TFA (25% in DCM) to afford resin-bound monomer **51.3**. SAA **51.4**, synthesized from 2,3-*O*-isopropylidene-D-ribose was allowed to couple with immobilized AA **51.3** in the presence of BOP and DIPEA to give a dimer **51.5**. The stepwise extension of **51.5** with AA **51.6** and SAA building block **51.4**, and then a final *N*-Boc-deprotection afforded the immobilized tetramer **51.7A**. In a similar manner, the immobilized linear precursor **51.7B** was obtained by the sequential elongation of **51.5** with the appropriate AAs and SAA **51.4.** Finally, cyclization of the linear peptides and concomitant release of the target molecules **51.8** (starting from **51.7A**) and **51.9** (starting from **51.7B**) from the solid support was achieved in the presence of 1:1 mixture of DIPEA and acetic acid.

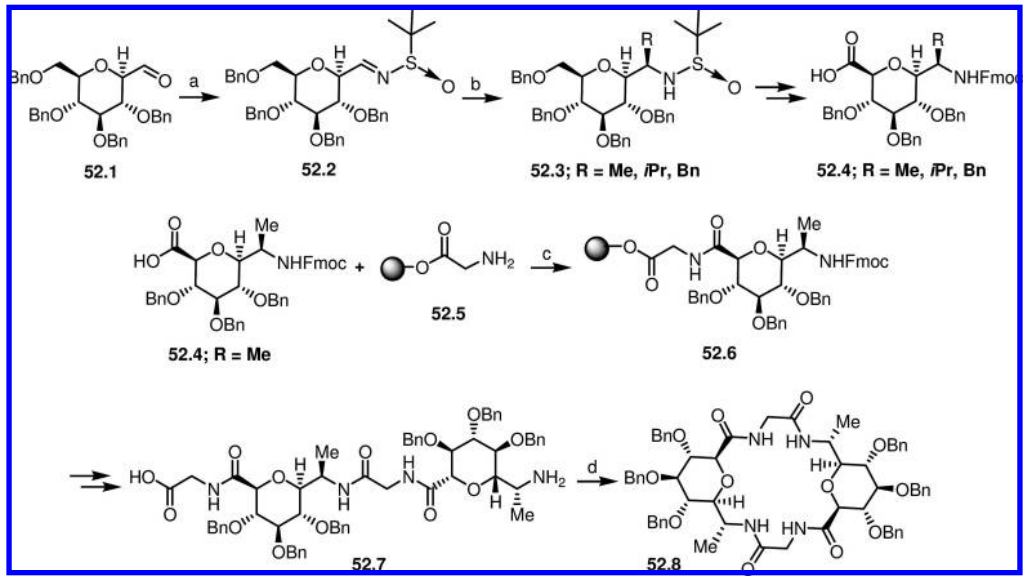
Sugar amino acids (SAAs) having an amine and a carboxylate attached to a furan or pyran core are highly versatile scaffolds for the construction of conformationally locked dipeptide isosteres, which are highly useful in the preparation of a broad range of carbohydrate-based peptidomimetics.[358,359] Overhand and co-workers[355,360] reported an interesting solid-phase synthesis of a highly functionalized D-Ala-Ser/Thr mimic to obtain a cyclic tetramer **52.8**

Scheme 51. Van Boom and Co-workers' Parallel Solid-Phase Synthesis of Cyclic Sugar Amino Acid/Amino Acid Hybrid Molecules 51.8 and 51.9[a]



[a] Reagents and conditions: (a) (i) DIC, HOBt, NMP/CH_2Cl_2; (ii) 25% TFA, 1% TIPS, CH_2Cl_2; (b) **51.4,** BOP, HOBt, $(^iPr)_2NEt$, NMP; (c) $(^iPr)_2NEt$, AcOH, DMF.

Scheme 52. Overhand and Co-workers' Solid-Phase Synthesis of Cyclic Oligomers of Sugar Amino Acids and Natural Amino Acids[a]



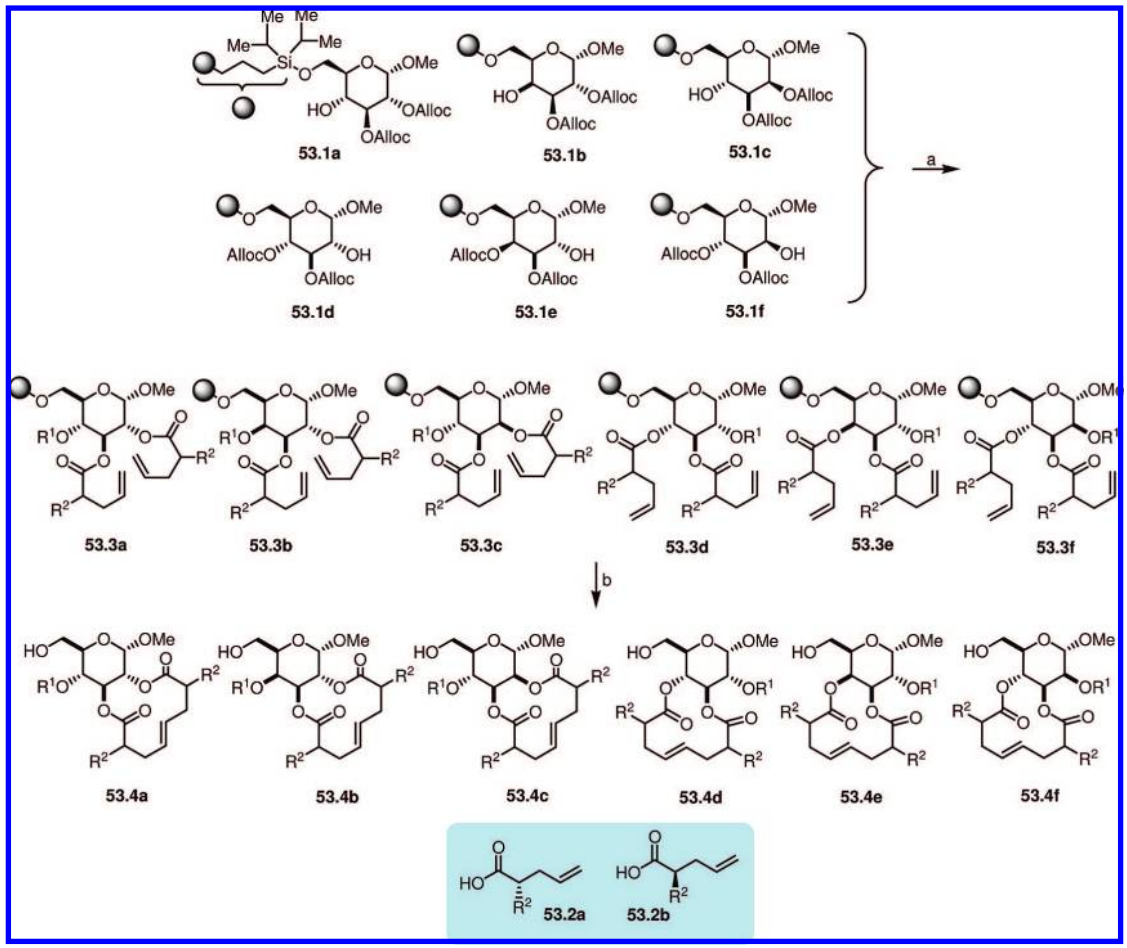
[a] Reagents and conditions: (a) (*R*)-*tert*-butylsulfinamide, $CuSO_4$ (anh), CH_2Cl_2, RT; (b) RMgBr, $PhCH_3/CH_2Cl_2$, −78 °C; (c) HATU, HOAt, 2,4,6-collidine, DMF, CH_2Cl_2, RT; (d) HATU, HOAt, 2,4,6-collidine, DMF, 4 °C.

(Scheme 52). The key transformation in the synthesis involved the diastereoselective introduction of an alkyl/aryl group onto the carbohydrate-derived sulfinimine. The SAA generated in this manner was subjected to simple peptide coupling sequences to obtain the desired cyclic tetramer.

Thus, a known material, formyl tetra-*O*-benzyl-β-D-*C*-glucopyranoside, **52.1**, was subjected to Cu(II)-mediated condensation with commercially available (*R*)-*t*-butylsulfinamide to afford **52.2**, which was treated with appropriate Grignard reagents at low temperature (−78 °C) to afford the facial selective alkyl/aryl adducts **52.3** with excellent diastereomeric excess (>95%). Following standard transformations, **52.3** was converted to the suitably protected SAA **52.4** that was used in the solid-phase protocol. The glycine-functionalized Wang resin **52.5** was coupled with **52.4** under standard amide coupling conditions to give **52.6**, which was then readily transformed to the desired linear tetramer following *N*-Fmoc removal and sequential coupling with an appropriate AA or the SAA residue **52.4**. After final deprotection of *N*-Fmoc, TFA-mediated cleavage from the solid support afforded the resin-free linear tetramer **52.7**. HATU/HOAt-mediated cyclization of **52.7** under high dilution conditions (c = 0.001 M) resulted in the formation of benzylated cyclic tetramer **52.8** in excellent overall yield. This methodology can be potentially useful for the synthesis of large hybrid type peptide/peptidomimetic combinatorial libraries.

With the goal of exploring the relationship between stereochemistry and skeletal diversity of small molecules in biological assays, Schreiber and co-workers[361] developed an approach for the synthesis of a carbohydrate-based library for multidimensional screening (Scheme 53).[362] Six differentially bis-protected, carbohydrate-derived diol scaffolds were anchored onto the 500−560 μm polystyrene alkylsilyl-

Scheme 53. Schreiber and Co-workers' Synthesis of Test Library of Monocyclic and Bicyclic Compounds[a]

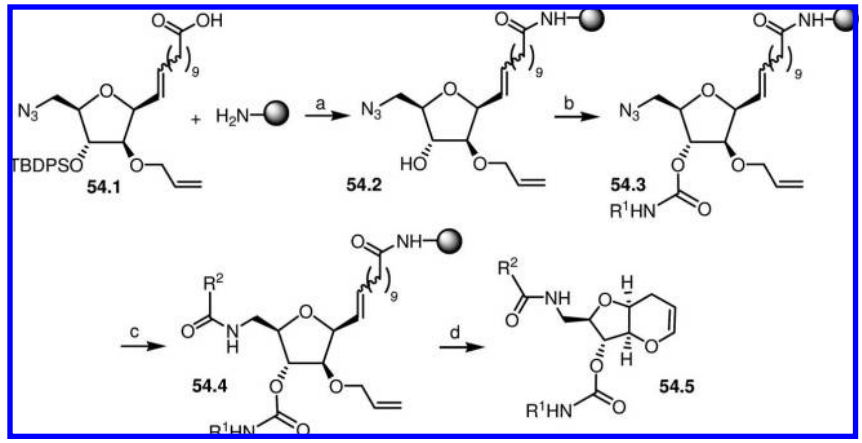


[a] Reagents and conditions: (a) (i) ArNCO or BzCl, DMAP, 20% pyridine/CH_2Cl_2 (v/v), RT; (ii) 2-thiosalicylic acid, $Pd(PPh_3)_4$, THF, RT; (iii) **53.2a** or **53.2b**, DIC, DMAP, CH_2Cl_2, RT; (b) (i) Grubb's catalyst-II, CH_2Cl_2, 40 °C; (ii) HF·pyridine, THF, RT, TMSOMe, RT.

derivatized macrobeads using a standard loading procedure to obtain **53.1a**−**53.1f**. To introduce the first diversity (R^1), each set of macrobead-bound substrates was split into four parts and treated with benzoyl chloride or three different isocyanates to form carbamates or benzoates. *N*-Alloc removal, followed by coupling with two sets of differentially substituted ω-pentenoic acids, **53.2a** and **53.2b**, to the resulting diols under standard conditions (second diversity, R^2) afforded the monocyclic bis-pentenoates **53.3a**−**53.3f** with two terminal olefinic arms (Scheme 53) in high purity and yield. A portion of each of these diesters was subjected to HF·pyridine cleavage to obtain a set of 122 monocyclic molecules with 12 distinct stereochemical patterns arising from a combination of three carbohydrate templates, two (3,4- and 4,5-protected) substitution patterns, and two absolute configurations of the second diversity, R^2 (**53.2a** or **53.2b**). The remaining portion of bis-pentenoate monocycles **53.3a**−**53.3f** was subjected to ring-closing metathesis with second-generation Grubbs' catalyst,[363] followed by resin cleavage, resulting in a set of 122 corresponding bicyclic derivatives **53.4a**−**53.4f** in high yield. This 244 (2 × 122)-membered DOS library with an equal number of mono- and bicyclic candidates was utilized to study the relationship between cellular measurement space and stereochemical and skeletal diversity of small molecules.

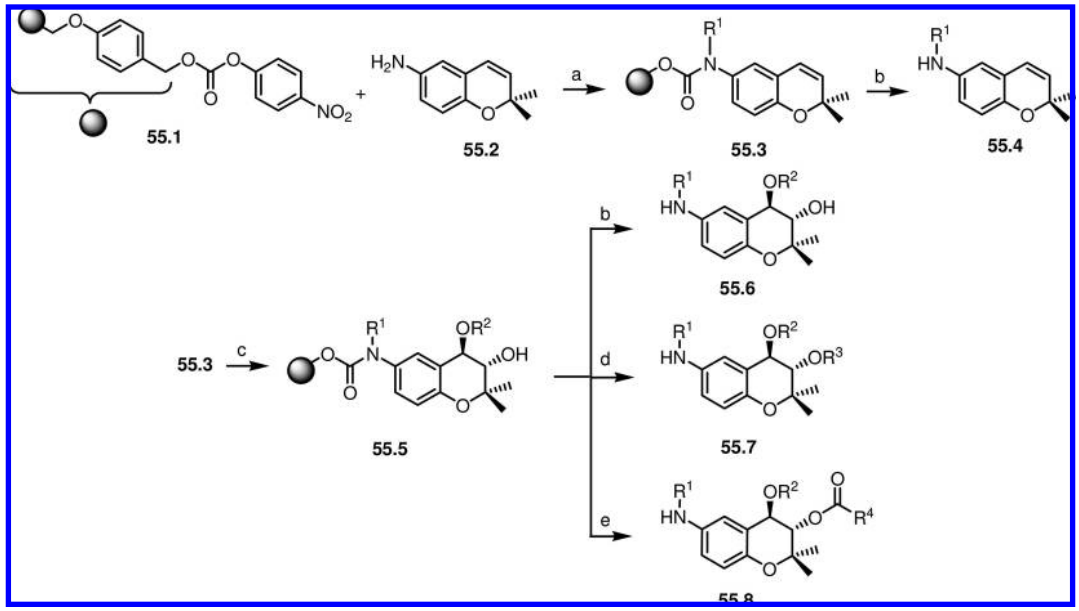
Transformation of glycosides to orthogonally protected building blocks for constructing combinatorial libraries is a popular technique that has been used by many groups since the middle of the past decade.[364−370] However, when it comes to the synthesis of pharmaceutically relevant candidates, conformational flexibility of the molecules obtained by this approach, especially from monosaccharide sugars, can be a potential disadvantage. In an interesting study, the Van Boom and Overkleeft group[371] demonstrated a practical and efficient protocol for the solid-phase synthesis of conformationally locked *cis*-fused pyranofurans by using a highly functionalized sugar template, which was synthesized from the monosachharide D-(+)-mannitol in a few steps (Scheme 54). Loading of the scaffold onto the solid support via an olefinic linker and subsequent introduction of pharmacophoric diversities around the scaffold was followed by a ring-closing metathesis cyclization/cleavage to afford a series of functionalized and conformationally constrained fused oxacycles. The sugar diene **54.1** was immobilized onto the Rink-amide resin in the presence of BOP and DIPEA to give **54.2**. The first diversity was introduced in the following step using the free secondary hydroxyl group (obtained by TBDPS deprotection). Reaction of alcohol **54.2** with benzyl, methoxyphenyl, or phenyl isocyanate under the standard coupling conditions afforded carbamates **54.3**. Staudinger reduction of the individual azides **54.3**, followed by coupling of free amines with three acid chlorides, diphenylcarbamoyl, benzyloxycarbonyl, or benzoyl chloride, allowed incorporation of the second diversity. The resulting resin-bound molecules **54.4** were finally treated with 5 mol % Grubbs' catalyst II in refluxing dichloromethane to trigger cyclative cleavage,

Scheme 54. Overkleeft and Co-workers' Solid-Phase Synthesis of a *cis*-Fused Pyranofuran Library[a]



[a] Reagents and conditions: (a) (i) TBAF, THF; (ii) BOP, $(^{i}Pr)_2NEt$; (b) $R^1-N=C=O$, Et_3N; (c) (i) Me_3P, THF, then H_2O/dioxane; (ii) R^2COCl, $(^{i}Pr)_2NEt$; (d) Grubbs' catalyst-II, CH_2Cl_2, reflux.

Scheme 55. Gong and Co-workers' Solid-Phase Library of 2000 Analogs of Substituted Benzopyran Derivatives[a]

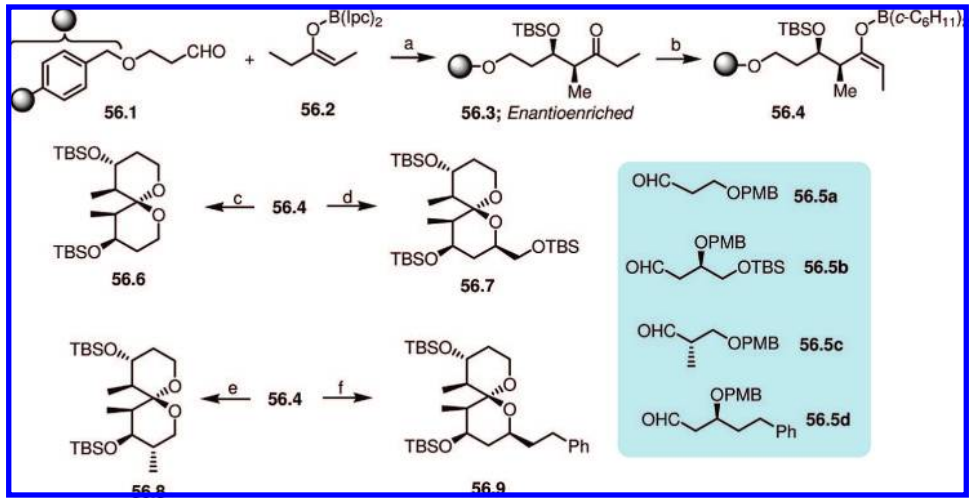


[a] Reagents and conditions: (a) (i) $(^{i}Pr)_2NEt$, DMA; (ii) R^1Cl, $^{t}BuOLi$, DMSO; (b) TFA/CH_2Cl_2 (1:3); (c) *m*-CPBA, R^2OH, CH_2Cl_2, then step b; (d) (i) R^3Cl, $^{t}BuOLi$, DMF; (ii) TFA/CH_2Cl_2 (1:3); (e) (i) R^4COCl, pyridine, DMAP, CH_2Cl_2; (ii) TFA/CH_2Cl_2 (1:3).

affording the desired *cis*-fused pyranofurans **54.5** in good to excellent yields. Thus, exploration of two diversity points in a nine-membered (3 × 3) library of conformationally rigid sugar derivatives was efficiently achieved through a solid-phase approach.

The development of methods for obtaining natural product-inspired libraries having the benzopyran scaffold has been an active area of research in the past.[372−378] Among several heterocyclic small molecules, the benzopyrans have attracted significant attention in medicinal chemistry because of their remarkable range of biological activity as antioxidants, diabetes treatments, cardiovascular agents, multidrug resistance therapies, anti-HIV agents, ischemia treatments, etc.[379−381] Therefore, the solid-phase synthesis of benzopyran-containing natural and unnatural products has become an active area in current biomedical research.[374,375] Gong and co-workers[382] reported solid-phase library synthesis of 2000 analogs of 6-amino-2,2-dimethyl-3,4,6-trisubstituted-2*H*-1-benzopyran using a 6-amino-2,2-dimethylchromene scaffold and the Wang resin as a solid support (Scheme 55). *p*-Nitrophenyl carbonate resin **55.1** obtained by coupling of *p*-nitrophenyl chloroformate with Wang resin in CH_2Cl_2 was exposed to 6-amino-2,2-dimethylchromene **55.2** under basic conditions in *N*,*N*-dimethylacetamide (DMA) for loading. The resulting resin-bound material was alkylated at the carbamate nitrogen with different alkyl or benzyl halides (R^1Cl) under strong basic conditions giving **55.3**. A portion of resin **55.3** was subjected to TFA cleavage to give a series of N-alkylated 6-amino-2,2-dimethylchromene compounds **55.4** in high yield and purity. The remaining carbamate resin **55.3** was subjected to a modified epoxidation protocol with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of different alkyl or benzyl alcohols (R^2OH) so that the alcohols could open the resulting racemic epoxides *in situ* to provide resin-bound hydroxyalkoxy intermediates **55.5**. Different combinations of R^1 and R^2 allowed them to synthesize 26 distinct racemic hydroxyalkoxy benzopyran intermediates **55.5**, a portion of which on deprotection under TFA conditions offered a series of resin-free derivatives **55.6** with two diversities in good yields. Rest of the racemic material **55.5**

Scheme 56. Waldmann and Co-workers' Asymmetric Solid-Phase Synthesis of 6,6-Spiroketals[a]



[a] Reagents and conditions: (a) (i) 3-pentanone, $(^{i}Pr)_2NEt$, CH_2Cl_2, −78 to 0 °C; (ii) 30% aqueous H_2O_2/MeOH/DMF/buffer (pH 7) (1.5:4:4:1), 0 °C; (iii) TBSCl, DMAP, imidazole, DMF/CH_2Cl_2 (1:1), RT; (b) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, 0 °C; (c) (i) **56.5a**, Et_2O, −78 to 20 °C; (ii) 30% aqueous H_2O_2/MeOH/DMF/buffer (pH 7) (1.5:4:4:1), 0 °C; (iii) TBSCl, DMAP, imidazole, DMF/CH_2Cl_2 (1:1), RT; (iv) DDQ, CH_2Cl_2/buffer (pH 7) (20:1), 0 °C to RT. (d, e, f) Similar conditions as step c with aldehydes **56.5b**, **56.5c**, and **56.5d**, respectively.

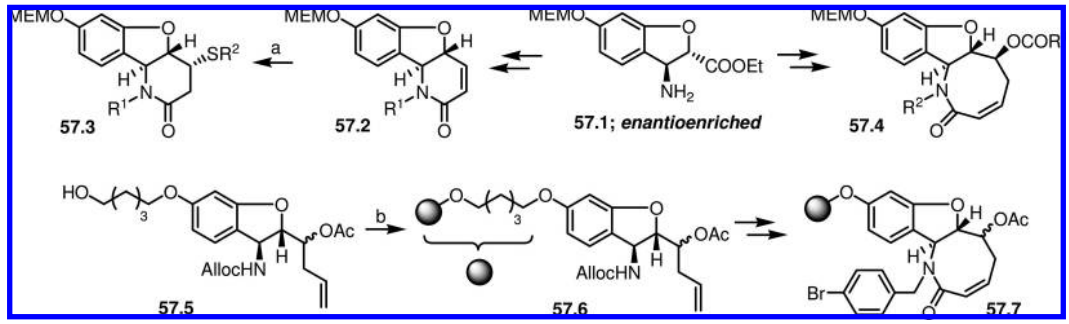
was split into two parts and subjected to the protection of the hydroxyl group under standard conditions either with different alkyl/benzyl halides (R^3Cl) for one part or different acid chlorides (R^4COCl) for the other part. These steps were followed by cleavage of the resulting compounds from the resin to afford the third and the fourth series of the chromene derivatives **55.7** and **55.8**, respectively, as racemic mixtures. With different combinations of R^1, R^2, R^3, and R^4, the Gong group synthesized 2000 different 6-amino-2,2-dimethyl-3,4,6-trisubstituted 2*H*-1-benzopyran derivatives using no more than three transformations on the solid phase and subsequent cleavage from the resin.

6,6-Spiroketals are present in many important natural products with differing biological activity, such as the spongistatins and okadaic acid.[383,384] Structurally simplified spiroketals derived from natural products significantly retain the biological activities of the corresponding natural products. Thus, the 6,6-spiroketal structures are considered as one of the privileged scaffolds for the development of combinatorial libraries of natural product derived compounds.[385,386] In an interesting study to obtain different spiroketals, Waldmann and co-workers[387] explored an asymmetric aldol reaction-mediated solid-phase synthesis of this scaffold and generated a small library of spiroketal derivatives (Scheme 56). The resin-bound aldehyde **56.1** was subjected to asymmetric aldol reaction using chiral boron *Z*-enol ether **56.2**, followed by oxidative workup and protection of the secondary hydroxyl group to provide the TBS-protected *syn*-aldol **56.3**. In the following step, the *E*-enolate **56.4** was generated from **56.3** using a standard protocol from the aldol literature. At this stage, the *E*-enolate **56.4** was split into four parts and allowed to react with different chiral aldehydes **56.5a**, **56.5b**, **56.5c**, and **56.5d**, leading to the formation of the corresponding *anti*-aldols as the exclusive products (not shown in the scheme). Oxidative workup of these aldols and protection of the incipient hydroxyl group with TBS made the resulting ketones ready for the cyclative cleavage. Similar to the observations in solution-phase studies, treatment with DDQ in a mixture of dichloromethane under aqueous buffer conditions afforded simultaneous cleavage of resin (analogous to removal of PMB protection in solution phase) followed by spirocyclization to afford the target spiroketals **56.6** to **56.9** as exclusive stereoisomers. As observed, **56.6** was obtained in this 12-step solid-phase sequence with an overall yield of 16%, which corresponds to a remarkable average of 86% per step. Importantly, this spiroketal obtained from the solid-phase synthesis had the same stereoselection as that obtained from the solution-phase synthesis emphasizing the correlation between solution- and solid-phase protocols for asymmetric transformations.

As discussed earlier in the Introduction section (see rocaglamide, **F2.3**, Figure 2), there are several examples of bioactive natural products known to have the "benzofuran substructure" in their architectures displaying a wide range of biological properties.[111,113,388−391] With the goal of exploring the chemical space around the benzofuran scaffold, Arya and co-workers[392] developed a practical, enantiocontrolled synthesis of benzofuran scaffold **57.1** containing β-amino functionality[393] (Scheme 57). This highly versatile scaffold can be obtained quickly in gram quantities, and it could lead to several structurally different architectures, both in solution and on solid-phase. These tricyclic derivatives, **57.2** and **57.4**, with two potential diversification sites were obtained in solution phase from compound **57.1** (Scheme 57). The unsaturation in the six-membered lactam ring in **57.2** was further exploited to generate additional diversity with 1,4 addition of different thiols to obtain **57.3** in a diastereoselective manner. Following the successful solution method development, compound **57.5** was utilized as the starting material to embark on the solid-phase synthesis program. With polystyrene macrobeads having an alkylsilyl-linker and a standard solid-phase loading protocol, **57.5** was loaded onto the resin to obtain **57.6**. Similar to the solution-phase synthesis, the tricyclic lactam **57.7** was obtained in the solid phase with excellent yield and purity. A library generation is ongoing using this methodology. Meanwhile, one of the compounds obtained from the solution-phase protocol has been found to act as a cell motility inhibitor.

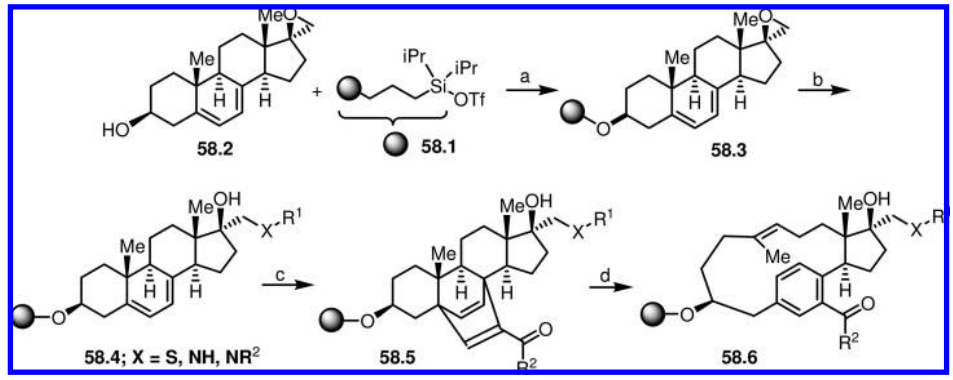
With the target of generating skeletal diversity using steroidal frameworks, Schreiber and co-workers[394] explored a short synthetic pathway leading to small molecules having three distinct skeletal architectures along with other unique structural features. In this protocol, a diene was first manipulated to a bridged polycyclic system and then to a

Scheme 57. Arya and Co-workers' Solution- and Solid-Phase Modular Approach To Obtain Benzofuran-Based Different Tricyclic Architectures with Unsaturated Lactam Rings[a]



[a] Reagents and conditions: (a) R^2SH, *n*BuLi, THF, −78 °C; (b) silicon-derived macrobeads, TfOH, 2,6-lutidine, CH_2Cl_2.

Scheme 58. Schreiber and Co-workers' Solid-Phase Synthesis of Complex Polycyclic Systems[a]

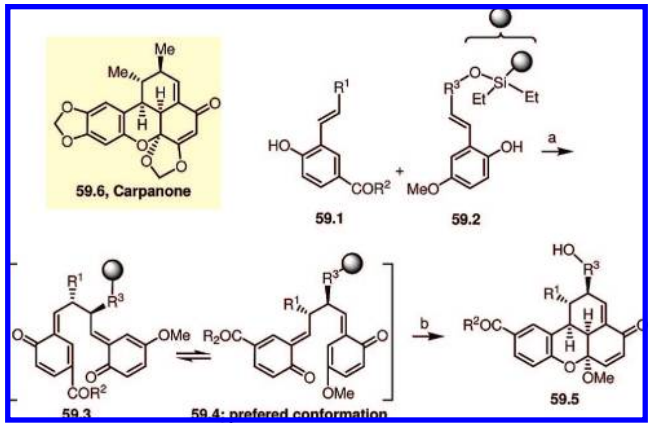


[a] Reagents and conditions: (a) TfOH, 2,6-lutidine, CH_2Cl_2; (b) (i) R^1R^2NH or R^1NH_2 or R^1SH, $LiClO_4$, THF; (ii) alkylation, acylation, or oxazolidine formation when primary amine is used in step i; (c) ynones, Et_2AlCl, CH_2Cl_2, RT; (d) heating of the "dry" beads at 110 °C.

fused bicycle with the larger ring containing a paracyclophane. Sequential Diels−Alder and retro-Diels−Alder reactions reported earlier by Winterfeldt and co-workers[395,396] were used as the key transformations. The steroidal diene epoxide **58.2** (Scheme 58), synthesized from a commercially available steroid derivative, was immobilized on the silyl macrobeads **58.1** under a standard protocol to give **58.3**. Lewis acid catalyzed opening of the epoxy ring with different thiols and primary or secondary amines introduced the first diversity, which was further diversified (in the case of primary amines) by N-alkylation, N-acylation, or spirocyclic oxazolidine formation to afford **58.4**. The dienes **58.4** were then subjected to the crucial Diels−Alder 2 + 4 cycloaddition with different ynones in the presence of a Lewis acid catalyst to afford the cycloadducts **58.5** as the exclusive products. Interestingly, these 2 + 4 cycloadducts were not isolable when the reactions were carried out without a catalyst; the researchers always ended up with the paracyclophanes **58.6**, which were the end products of a domino Diels−Alder/retro-Diels−Alder reaction sequence. A series of Lewis acid catalysts were then tried to find a suitable candidate that would preferentially accelerate the cycloaddition over the retro-Diels−Alder and allow the intermediate cycloadduct to be isolated. Et_2AlCl stood out as the only catalyst effective in both solution- and solid-phase conditions. Thus, the resin-bound cycloadducts **58.5** were isolated in Et_2AlCl-catalyzed transformation and then heated at 110 °C in the absence of any solvent to induce the retro-Diels−Alder reaction affording the corresponding paracyclophanes **58.6** in a "punctuated" manner. Over 4000 unique and complex natural product-like small molecules were generated in this short reaction sequence, with effective use of intermolecular and intramolecular transformations, both altering the carbon skeletons.

The experience gained from Nature's biosynthesis of a vast variety of complex natural products has prompted the synthetic community to look for efficient pathways to create diverse, novel, complex biologically relevant molecules using simple starting materials and a minimal number of steps. Based on the reactions reported in Nature's biosynthesis of carpanone,[397,398] Shair and co-workers developed the methodology aiming to generate a combinatorial library of carpanone-like molecules using split and pool synthesis.[399] The key steps of their synthetic strategy relied on oxidative diastereoselective heterocoupling of two different *o*-hydroxystyrenes followed by an intramolecular inverse electron demand Diels−Alder reaction. This methodology was used for the first reported biomimetic synthesis of carpanone via Pd-mediated homocoupling followed by an intramolecular Diels−Alder reaction a few decades ago.[400] In the present approach, the Shair group immobilized oxidatively more reactive (electron-rich) phenol onto silicon-linked resin to obtain **59.2** (Scheme 59) and that was then exposed to electron-deficient phenol **59.1** under $PhI(OAc)_2$-mediated conditions to give the heterocoupled product **59.3**. Under thermal conditions, **59.3** via its more electronically matched conformer **59.4** underwent a rapid *endo*-selective inverse electron demand Diels−Alder cycloaddition to form the tetracycle **59.5** with five new stereocenters and four diversity points. Several conditions were screened to increase the ratio of the desired heterocoupled product **59.3** and the undesired homocoupled product (not shown in the scheme) in the

Scheme 59. Shair and Co-workers' Solid-Phase Biomimetic Synthesis of Carpanone-like Molecules[a]



[a] Reagents and conditions: (a) $PhI(OAc)_2$, CH_2Cl_2/THF, RT; (b) HF·pyridine, RT, TMSOMe.

coupling step, and some interesting observations were made. For instance, $PhI(OAc)_2$ was the only catalyst (among the ones screened) that preferentially promoted the heterocoupling over homocoupling, and the presence of an amide-based spacer (R^3) between the functional part of the molecule and the resin with a silyl attachment to the resin in **59.2** led to the best hetero/homo ratio. Six cases of biomimetic solid-phase synthesis of carpanone-like molecules were reported that were compatible with a range of functionality, making the process suitable for the construction of DOS libraries.

As a follow up of the previous work, Shair and co-workers later reported an elegant DOS library of 10 000 compounds starting from the carpanone-like core structure **60.1**, derived by $PhI(OAc)_2$-mediated dimerization and subsequent intramolecular cycloaddition reactions (Scheme 60).[401] Their initial attempt at generating more diversified skeletons did not work on the solid phase; therefore, the group focused on manipulating the enone moiety and the phenolic hydroxyl group to generate a large number of compounds.

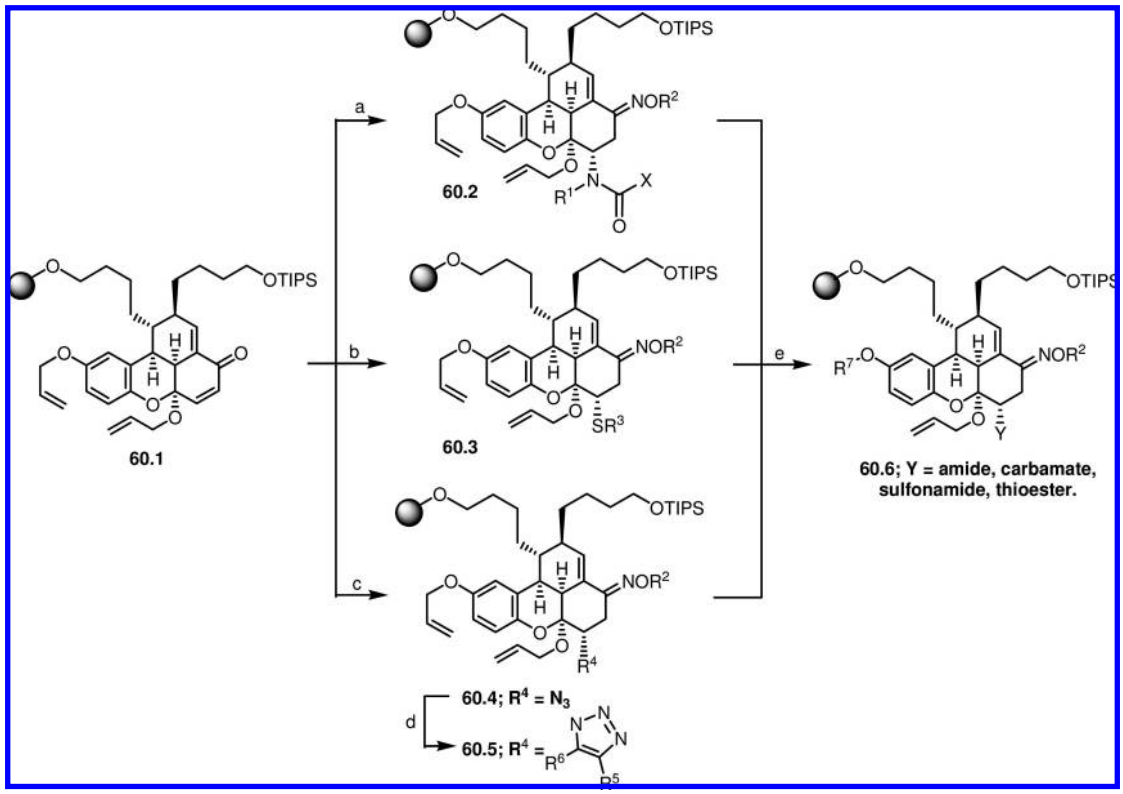
Multicomponent reactions (MCR) involving a primary amine (R^1NH_2) and a substituted hydroxylamine (R^2ONH_2) undergoing 1,4 conjugate addition and an oxime formation at the carbonyl carbon, respectively, were successful on the core structure, **60.1**, and afforded a series of aza-Michael adducts. The newly formed secondary amines were further derivatized to obtain different amides, sulfonamides, carbamates, and ureas (**60.2**). The second protocol involved conjugate addition of different thiols (R_4SH) and oxime formations with substituted hydroxyl amines (R^2ONH_2) giving **60.3** in good yields and purity. In the third case, another MCR with $TMSN_3$ and hydroxylamines (R^2ONH_2) on **60.1** furnished the adducts **60.4**. In this case, the azide functionality was converted to triazole substructures to obtain **60.5** with further diversity. At this stage, all the molecules obtained by three MCR process (except the molecules with triazole subunit **60.5** and urea subunits, that is, some members of the collection **60.2**) were finally subjected to selective (allyl-) deprotection at the phenolic oxygen followed by coupling with different alcohols, isocyanates, and boronic acids to afford a large library of 8670 compounds.

One of the objectives of high-throughput organic synthesis is to obtain small molecules that are inspired by natural products but have biological properties beyond those found in naturally occurring molecules. Working with this goal, galanthamine, **61.1**, a benzofuran-based natural product, decorated with multiple functional groups in a rigid framework was chosen by Shair and co-workers in another example[402,403] of biomimetic synthetic strategy applied for library generation on solid support (Scheme 61). The galanthamine framework **61.3** was obtained from the advanced solid-supported intermediate **61.2** in a crucial hypervalent iodine-mediated intramolecular oxidative coupling followed by Pd-catalyzed allyl deprotection and spontaneous facially selective cyclization. Four diversity points in **61.3** were then exploited to build a library of 2500 unique galanthamine-like small molecules using the split−pool technique. The phenolic hydroxy in **61.3** was treated with several alcohols under Mitsunobu conditions to obtain phenolic ethers, **61.4**, as the first diversity, which was followed by diastereoselective 1,4 addition of thiols to give the adducts **61.5** with two diversities. The third and fourth diversities were introduced by manipulation of the ring nitrogen in **61.5** by reductive alkylation or acylation, followed by imine formation on the carbonyl group to obtain the resin-bound final derivatives **61.6**. The collection of 2500 molecules was cleaved from the silicon-based macrobeads by HF-Py treatment and subjected to phenotypic screening to identify a useful small molecule probe for understanding the mechanism of protein trafficking in secretory pathways.[403]

Schreiber and co-workers[404] explored the use of a triene in cycloaddition reactions for the generation of structurally diverse complex natural product-like small molecules (Scheme 62). Synthesis of the triene was accomplished by a method previously reported by Fallis and co-workers[405] in which indium-mediated alkylation was the key step. The substituted hydroxyl group could undergo elimination, leading to the desired triene. As exemplified with 4-hydroxy-3-methoxybenzaldehyde, **62.2**, different aldehydes were immobilized on alkylsilyl macrobeads, **62.1**, and subsequently subjected to indium-mediated alkylation followed by hydroxyl elimination, giving the triene **62.3**. This triene was then subjected to two different cycloaddition conditions. In one case, it was treated with different tri- or tetra-substituted dienophiles, which led to a single stereoselective Diels−Alder reaction affording only the bicyclic product **62.5** (explained with trisubstituted dienophile **62.4**). However, when **62.5** was subjected to another round of cycloaddition with different dienophiles, it afforded the tetracyclic product **62.6** in a stepwise manner. In the second case, an interesting observation was made; the reaction of the triene **62.3** with a disubstituted dienophile (e.g., **62.7**) underwent two consecutive cycloaddition reactions resulting in the formation of biscycloadduct **62.8** with complete stereocontrol. This method is highly practical, and by the split-and-mix synthesis protocol, an encoded library of 29 400 compounds was obtained from 40 different aldehydes and a series of di-, tri-, and tetra-substituted dienophiles.

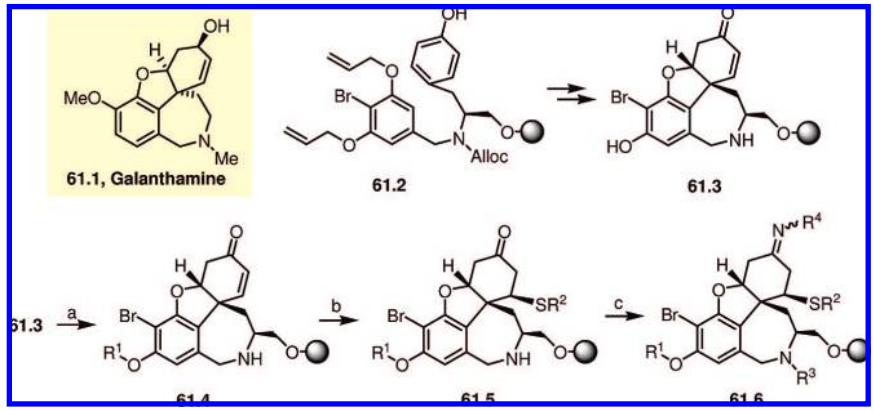
Schreiber and co-workers[406] reported an effective short method for the solid-phase library generation of complex polycycles involving the Ugi four-component coupling, intramolecular Diels−Alder,[407] and ring-opening−closing olefin metathesis reactions as the key steps[408−410] on alkylsilyl macrobeads (500−600 μm) (Scheme 63). The sequence commenced with an immobilization of the amine component **63.2** of the Ugi reaction via its free hydroxyl end onto the silicon-based macrobeads **63.1** and subsequent removal of the *N*-Fmoc protection under standard conditions giving **63.3**. The immobilized amine **63.3** was then treated with excess furfural **63.4**, benzyl isocyanide **63.5**, and fumaric acid (3-

Scheme 60. Shair and Co-workers' 10 000-Membered Library of Carpanone-like Molecules[a]



[a] Reagents and conditions: (a) (i) R^1NH_2, *o*-R^2ONH_2·HCl, Et_3N, *p*-TsOH, MeOH, CH_2Cl_2; (ii) XCOCl, 2,6-lutidine, THF; (b) (i) R^3SH, Et_3N, THF; (ii) *o*-R^2ONH_2·HCl, Et_3N, *p*-TsOH, MeOH, CH_2Cl_2; (c) (i) $TMSN_3$, *o*-R^2ONH_2·HCl, Et_3N, AcOH, MeOH, CH_2Cl_2; (d) symmetrically or unsymmetrically substituted acetylenes, heating or Cu(I)-mediated coupling, depending on substitutions; (e) (i) $Pd(PPh_3)$, $PhSiH_3$, CH_2Cl_2; (ii) isocyanates, alcohols, or aryl boronic acids were used as R^7 substituents to generate carbamates, ethers, and biaryls, respectively, under standard conditions.

Scheme 61. Shair and Co-workers' Solid-Phase Biomimetic Synthesis of Galanthamine-like Molecules[a]



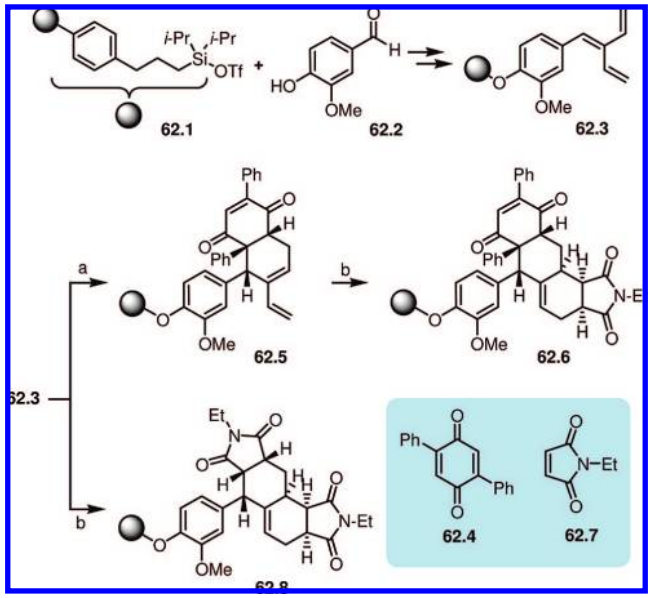
[a] Reagents and conditions: (a) R^1OH, PPh_3, DIAD, THF, 0 °C; (b) R^2SH, 2,6-lutidine, *n*BuLi, THF, 0 to 40 °C; (c) (i) R^3CHO, AcOH, MeOH−THF, then $NaCNBH_3$ in MeOH, or R^3COCl, 2,6-lutidine, CH_2Cl_2, RT, or R^3NCO, CH_2Cl_2, RT; (ii) R^4NH_2, AcOH, MeOH−CH_2Cl_2, RT.

bromobenzyl) monocarboxamide **63.6** to undergo a tandem Ugi four-component coupling (to the intermediate **63.7**), followed by a tandem intramolecular Diels−Alder reaction resulting in a highly functionalized and complex tricyclic system **63.8** with two suitably placed amide groups. Next, the macrobeads were treated with an excess amount of KHMDS and allyl bromide in THF giving bis-allylated material, which was then subjected to Grubbs' second generation catalyst to trigger a ring-opening−closing olefin metathesis. This leads to a highly complex 7−5−5−7-membered fused tetracyclic derivative on the solid support. Finally, treatment of the resin-bound tetracycle with HF−pyridine in CH_2Cl_2 for 2 h resulted in the release of the desired material **63.9** from the macrobeads. A notable feature of this report is the use of two pairs of tandem transformations as the complexity generation steps in a short sequence creating a remarkably complex small molecule.

7. Solid-Phase Synthesis of Alkaloid Natural Product-Inspired Compounds

As mentioned earlier, due to often unforeseen interactions between small molecules and their target proteins, the challenges in the high-throughput organic synthesis programs are to obtain natural product-inspired molecules with maximum skeletal, stereochemical, conformational, and functional group diversities in order to maximize the possibility of finding a "hit" that can modulate the activity of a single

Scheme 62. Schreiber and Co-workers' Synthesis of Complex Polycyclic Systems[a]



[a] Reagents and conditions: (a) **62.4**, toluene, RT; (b) **62.7**, toluene, RT.

protein or a network of proteins involved in physiological processes. With the objective of obtaining rapid access to tetrahydroisoquinoline alkaloid natural product-like compounds, Schreiber and co-workers[411] reported a three-step synthetic strategy to obtain a series of complex alkaloid-like molecules. As discussed in the Introduction section, tetrahydoquinoline and tetrahydroisoquinolines belong to an important family of bioactive alkaloid natural products that display a wide range of biological properties.[84,85,412−415] Immobilization of 7-hydroxyisoquinoline **64.2** (Scheme 64) and 3-(4-pyridyl)propan-1-ol **64.5** onto silylalkyl macrobeads **64.1** using a standard procedure afforded the resin-bound materials, which were subjected to alkylation using 2-bromobenzyl bromide to give the corresponding iminium salts **64.3** and **64.6**, respectively. Vinylation of **64.3** and **64.6** afforded the desired intermediates dihydroisoquinoline **64.4** and dihydropyridine **64.7**, respectively, in quantitative yield. These materials, otherwise unstable in solution (even when kept in frozen benzene), can be preserved on a solid support at room temperature for one month without degradation. With the intermediates **64.3** and **64.6**, the Schreiber group carried out a series of diversity-generating one-step transformations, for example, 2+2 cycloaddition, 3 + 2 cycloaddition, reduction, Diels−Alder reactions, or simple alkylations, to obtain 12 distinct natural product-like skeletons, all of them containing a hydroxyl group, useful for printing the molecules on a small molecule microarray.

Convergent biosynthesis of natural product hybrids is common in nature. In an attempt to answer whether non-natural hybrid small molecules[416,47] with natural product-like fragments would show special protein binding/modulating properties, Schreiber and co-workers[417] synthesized libraries of hybrid synthetic molecules. In their approach, the researchers utilized bridged piperidines, fused pyrrolidines, and spirocyclic oxindoles as sub-stuctures in building two different hybrid libraries. The fused pyrrolidine sublibrary **65.1** (Scheme 65) immobilized on the macrobead solid support was coupled with the bridged piperidine sublibrary **65.2** (prepared in solution) to obtain the bridged piperidine/fused pyrrolidine hybrid library **65.3**.

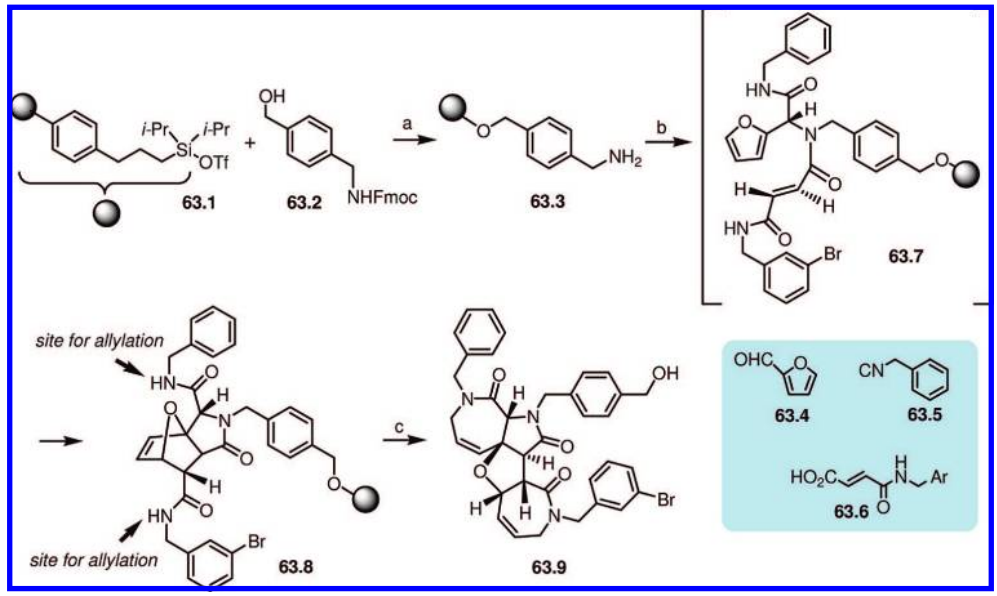
In another example, the spirocyclic oxindole sublibrary **65.4** after cleavage from the solid support was then coupled with fused pyrrolidine sublibrary **65.1**, which led to the generation of the second hybrid library **65.5**. Using the tools of asymmetric synthesis, the researchers had obtained both enantiomeric forms of **65.1**, **65.2** and **65.4** sublibraries, which were further utilized in coupling reactions. This convergent approach led to a 480-membered bridged piperidine/fused pyrrolidine hybrid library, **65.3**, and a 384-membered spirocyclic oxindole/fused pyrrolidine hybrid library **65.5**.

With the goal of generating libraries of natural product-like compounds having the features of indole alkaloids, Schreiber and co-workers[418] reported the generation of a 3520 compound library employing a stereoselective Williams' three-component reaction to synthesize the spirocyclic oxyindole−pyrrolidine core (Scheme 66). In a process catalyzed by a Lewis acid, the four solid-supported aldehydes were then reacted with two morpholinones and two dipolarophiles to obtain a library of spirooxyindole derivatives, **66.4**. These compounds were further diversified using the Sonogashira coupling, an amidation of the carboxyl moiety following the deprotection (i.e., alloc removal) and the N-acylation, thus generating a 416-membered library.

Another approach to generate a small-molecule library of nine-membered, biaryl-containing rings by Schreiber and co-workers[419] involved a regio- and stereoselective cyclization/double cyclization. Vancomycin[420−422] and pterocaryanin C[423] are two bioactive natural products that contain an asymmetric biaryl moiety having 10- and 12-membered rings. The polymer-supported aldehyde **67.1** (Scheme 67) was subjected to stepwise reductive amination to obtain amino alcohol **67.3** via **67.2**. This then led to the cyclization precursor **67.4** via a Mitsunobu reaction. Interestingly, the stereochemistry was retained in the Mitsunobu product, **67.4**. This was then followed by magnesium-bromide exchange ($^{i}PrBu_2MgLi$), transmetalation (magnesium to copper), and further oxidation of the C−C bond giving a nine-membered ring derivative, **67.5**, after the cleavage from support. This solid-phase methodology was then successfully applied to generate a library of 202 discrete compounds.

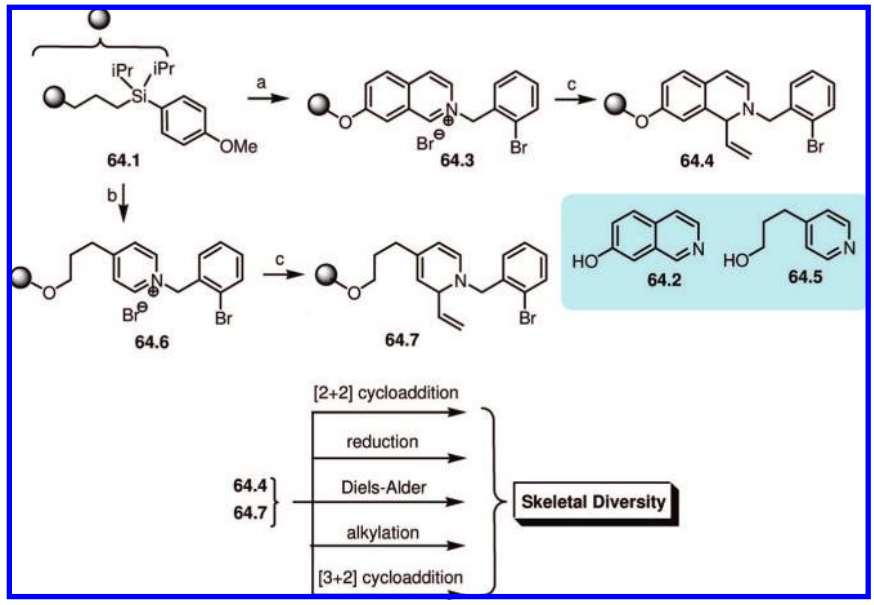
Schreiber and co-workers[424] reported the use of rhodium(II)-catalyzed consecutive cyclization−cycloaddition methodology, earlier developed by Padwa and co-workers,[425] for the synthesis of skeletally diverse compounds that are inspired by naturally occurring and biologically active indole alkaloids. In this approach, they used scaffold **68.1** (Scheme 68), which has three potential sites for anchoring either α-diazoketocarbonyl or indole groups through the use of lactam, ester, or β-ketocarbonyl functionalities. The addition of these groups could further lead to six distinct modes of rhodium-catalyzed intramolecular cycloadditions. In the first example, C-alkylation of **68.1** at low temperatures installed the indolyl group at site B. The ester group was then converted to an amide bearing a linker and the terminal silyl-ether, and treatment with 2,2,6-trimethyl-[1,3]-dioxin-4-one, followed by MsN_3, led to the formation of an α-diazoimide **68.5**. This was then refluxed with a catalytic amount of the rhodium(II) octanoate dimer in benzene to obtain hexacyclic **68.6** with complete diastereoselectivity. Similarly, in the second example, introduction of the alkyl linker at site B followed by the conversion of an ester to β-keto ester and further addition of the respective indole functionality at site A led to the formation of **68.8**, which was then cyclized using the Rh(II) catalyst to obtain **68.9** as a single isomer. In the

Scheme 63. Schreiber and Co-workers' Solid-Phase Synthesis of Complex Polycyclic Systems[a]



[a] Reagents and conditions: (a) (i) lutidine; (ii) piperidine; (b) **63.4**, **63.5**, **63.6**, MeOH/THF (2:1); (c) (i) KHMDS, allyl bromide, THF; (ii) Grubbs' catalyst-II, CH_2Cl_2, 40 °C; (iii) HF·pyridine, CH_2Cl_2.

Scheme 64. Schreiber and Co-workers' Synthesis of Skeletally Diverse Alkaloid-like Compounds Using DOS Strategy[a]

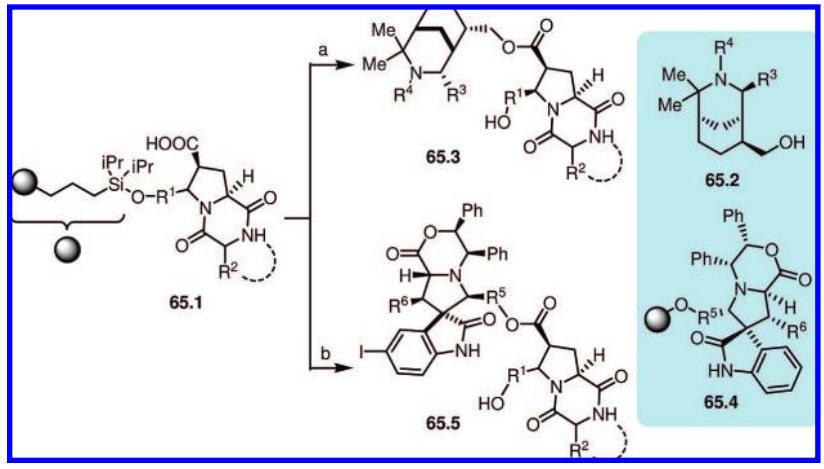


[a] Reagents and conditions: (a) (i) TfOH; (ii) 2,6-lutidine, **64.2**; (iii) 2-bromobenzyl bromide; (b) (i) TfOH; (ii) 2,6-lutidine, **64.5**; (iii) 2-bromobenzyl bromide; (c) vinylmagnesium bromide, −78 to 0 °C.

final example, compound **68.11** was obtained using the Ugi-4CC conditions, which on exposure to the Rh(II) catalyst provided **68.12**.

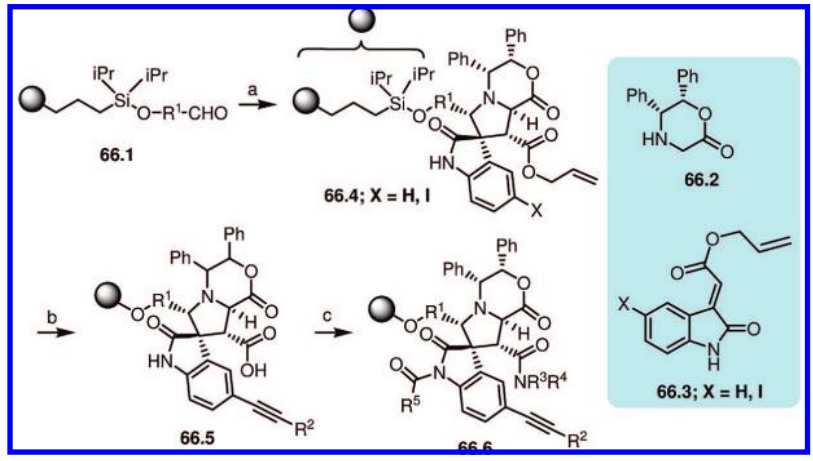
Nucleosides are associated with a wide array of therapeutically important targets in biological systems. Among them, carbocyclic nucleosides have sparked considerable interest because they have been identified as antiviral as well as antitumor agents. For example, carbovir, **69.1**, and abacavir, **69.2**,[426,427] (Scheme 69) have both displayed significant inhibitory activity toward HIV. Crimmins and co-workers[428] reported an efficient solid-phase synthesis of a small library of carbocyclic nucleosides analogs to these bioactive molecules. The chiral allylic benzoate template **69.3** was loaded onto the *p*-nitrophenyl Wang carbonate resin[429] **69.4** under basic conditions to afford the resin-bound template **69.5**, which served as the pseudosugar portion of the carbocyclic nucleoside. Subsequently, **69.5** was allowed to react with 2,6-dichloropurine and 2-amino-6-chloropurine under different palladium-catalyzed coupling conditions (and finally optimized to one condition shown in Scheme 69) to form the purine-derived carbocyclic nucleosides **69.6** as the exclusive product. No isomer with N7 purine linkage was detected, which is significant in solution-phase synthesis. Presumably, the solid support provides the additional hindrance to the already hindered trajectory of the nucleophile for N7 product and eliminates it completely. At this point, a diverse range of nitrogen nucleophiles including primary and secondary amines, anilines, hydrazides, and alkoxyamines were brought in to the purine ring system by S_NAr substitution of the Cl-atom at the 6-position to form **69.7**. Finally,

Scheme 65. Schreiber and Co-workers' Convergent Solid-Phase Synthesis of Small-Molecule Hybrids[a]



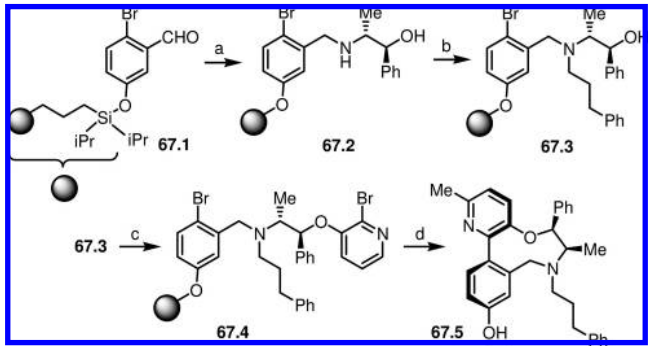
[a] Reagents and conditions: (a) (i) **65.2**, PyBOP, DMAP, CH_2Cl_2, RT; (ii) HF−pyridine, THF, RT, then TMSOEt; (b) (i) **65.4**, HF−pyridine, THF, RT, then TMSOEt; (ii) repeat step a.

Scheme 66. Schreiber and Co-workers' Three-Component Coupling Strategy on Solid Phase To Obtain Spirooxindoles[a]



[a] Reagents and conditions: (a) **66.2**, **66.3**, $Mg(ClO_4)_2$, pyridine, $HC(OMe)_3$, toluene, RT; (b) alkyne, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N/DMF, RT; (c) (i) amine, PyBOP, $(^iPr)_2NEt$, CH_2Cl_2/DMF, RT; (ii) N-acylation conditions.

Scheme 67. Schreiber and Co-workers' Synthesis of Nine-Membered Biaryl Rings on a Solid Phase[a]



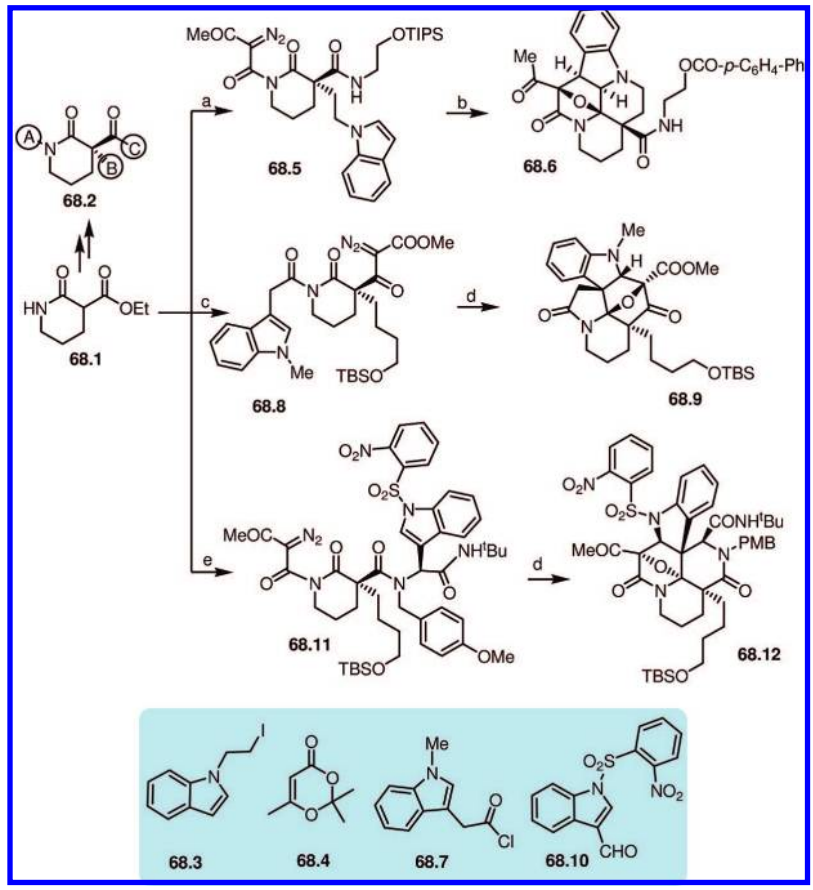
[a] Reagents and conditions: (a) (i) (1*S*,2*R*)-ephedrine, $(MeO)_3CH$, RT; (ii) $NaBH_3CN$, THF/MeOH/AcOH (10:10:1), RT; (b) (i) hydrocinnamaldehyde, $(MeO)_3CH$, RT; (ii) $NaBH_3CN$, THF/MeOH/AcOH (10:10:1), RT; (c) 2-bromo-3-pyridinol, nBu_3P, TMAD, THF, −78 °C to RT; (d) (i) $^iPr(nBu)_2MgLi$, 2-MeTHF, 0 °C; (ii) CuCN·2LiBr, 0 °C; (iii) m-$C_6H_4(NO_2)_2$, 0 °C; (iv) HF−pyridine, then TMSOMe.

the nucleosides were cleaved from the resin by exposure to TFA and subjected to chromatographic purification to afford the products **69.8** in good to excellent yields, including the potent anti-HIV molecule abacavir, **69.2**. Thus, an efficient solid-phase methodology for the generation of potentially a larger combinatorial library of carbocyclic nucleosides with diversities in sugar or nucleobase and substitutions in the base was demonstrated in this report.

The solid-supported aza [4 + 2]/allylboration MCR was carried out by Hall and co-workers,[430,431] using SASRIN-*p*-MBA resin **70.1** (Scheme 70), diene **70.2**, and benzaldehyde **70.3**. The cleavage of different solid-supported materials **70.4** gave the corresponding compounds **70.5**, **70.6**, or **70.7** and unreacted dienophile **70.8**.

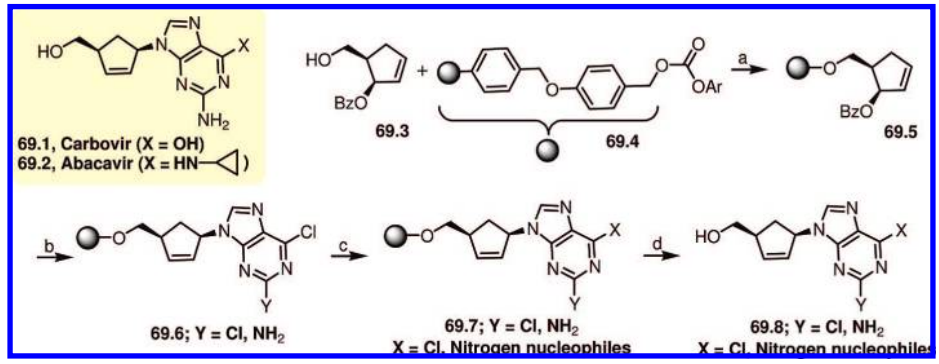
A broad variety of biologically active natural and synthetic compounds contain the hydantoin and tetrahydro-β-carboline scaffolds. This ring skeleton could be constructed by the classical hydantoin synthesis where a urea intermediate, usually obtained by coupling of an appropriate amine and an isocyanate, undergoes an intramolecular cyclization. Ganesan and co-workers[432] were interested in developing a different method to obtain scaffolds **71.5** and **71.6** that avoids the use of isocyanates and is adaptable to parallel solid-phase synthesis. In a model study, activated carbamates **71.3** and **71.4** (Scheme 71) were successfully obtained from an individual treatment of *cis* and *trans* isomers of the known material tetrahydro-β-carboline (**71.1** and **71.2**). These two products upon heating with a primary amine in the presence

Scheme 68. Schreiber and Co-workers' Solution-Phase Approach To Generate Indole Alkaloid-like Compounds[a]



[a] Reagents and conditions: (a) (i) **68.3**, *n*BuLi, THF, −78 to 60 °C; (ii) LiOH, ^{i}PrOH/H_2O; (iii) ethanolamine, EDC, HOBt; (iv) TIPSCl, imidazole; (v) **68.4**, toluene, reflux; (vi) MsN_3, Et_3N, CH_3CN; (b) (i) $Rh_2(O_2CC_7H_{15})_4$, benzene, 50 °C; (ii) TBAF; (iii) 4 Å MS, Et_3N, 4-biphenylcarbonyl chloride; (c) (i) $I(CH_2)_4OTBS$, *n*BuLi, THF, −78 to 60 °C; (ii) LiOH, ^{i}PrOH/H_2O; (iii) CDI, CH_2Cl_2, RT; (iv) hydrogen methyl malonate, ^{i}PrMgBr; (v) **68.7**, 4 Å MS, CH_2Cl_2; (vi) MsN_3, Et_3N, CH_3CN; (d) $Rh_2(O_2CC_7H_{15})_4$, benzene, 50 °C; (e) (i) $I(CH_2)_4OTBS$, *n*BuLi, THF, −78 to 60 °C; (ii) LiOH, ^{i}PrOH/H_2O; (iii) 4-methoxy-benzylamine, 2-isocyano-2-methyl-propane, **68.10**, MeOH, reflux; (iv) **68.4**, toluene, reflux; (v) MsN_3, Et_3N, CH_3CN.

Scheme 69. Crimmins and Co-workers' Solid-Phase Synthesis of Carbocyclic Nucleosides[a]

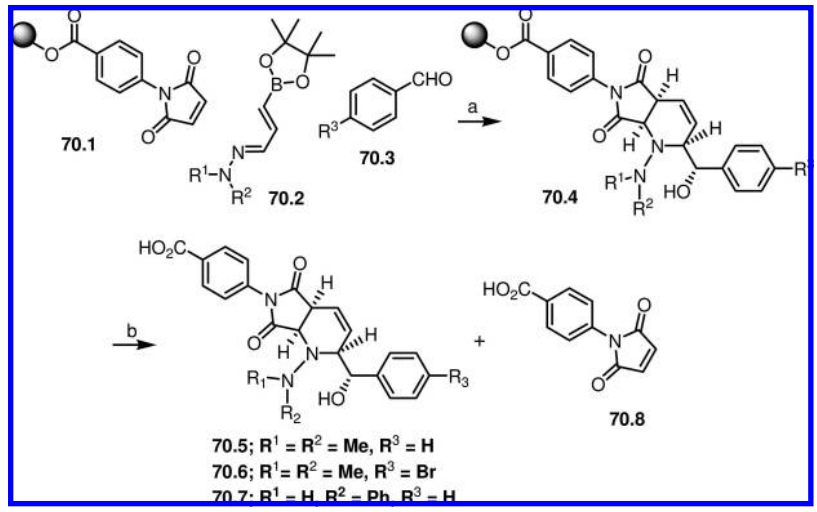


[a] Reagents and conditions: (a) (^{i}Pr)$_2$NEt, DMAP in CH_2Cl_2, 40 °C; (b) $Pd_2(dba)_3$, PPh_3, pempidine, 2,6-dichloropurine/2-amino-6-chloropurine, THF/DMSO (1:1), 45 °C; (c) nitrogen nucleophile (5.0 equiv), (^{i}Pr)$_2$NEt, BuOH, 80 °C; (d) 5% TFA in CH_2Cl_2.

of base afforded the hydantoins **71.5** and **71.6**. Interesting to note was the observation that both *cis*-**71.3** and *trans*-**71.4** produced only the *trans*-hydantoins. An epimerization of the *cis* compound adjacent to the carbonyl center to the thermodynamically more stable *trans*-tetrahydro-*β*-carboline was believed to be the reason. Following the successful method development in solution, this approach was then tried on the solid-phase using L-tryptophan immobilized on the polystyrene-Wang resin **71.7**. The use of protic Pictet−Spengler reaction on **71.7** in the presence of different aldehydes, followed by acylation with *p*-nitrophenyl chloroformate or a direct *N*-acyliminium version of the reaction provided the expected intermediates **71.8**, which on heating with different primary amines under basic conditions afforded the hydantoins following a cyclative cleavage (shown with benzaldehyde and benzyl amine in the scheme).

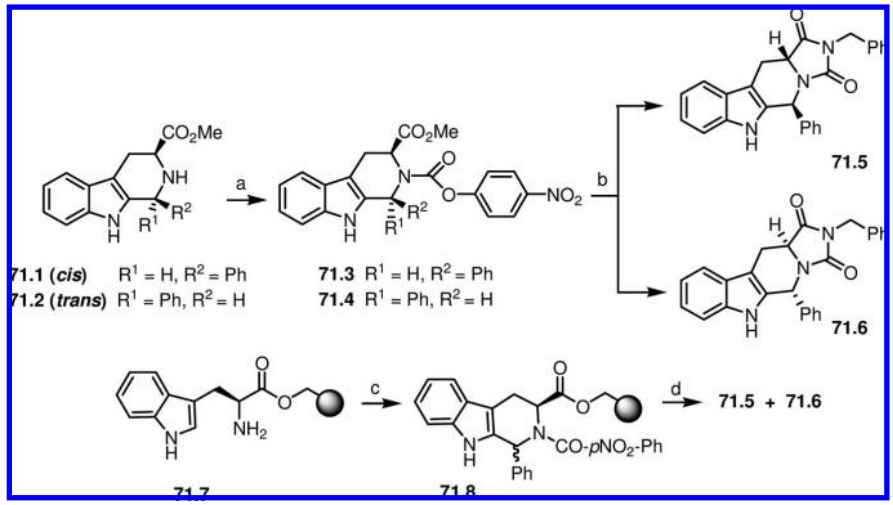
With the goal of obtaining angular epoxyquinol scaffolds, which are commonly found in a wide variety of bioactive natural products, Porco and co-workers[433] synthesized a complex chemical library of 244 derivatives. In their approach, the stereoselective reduction of the epoxyketone **72.1** (Scheme 72) followed by the *O*-TBS protection and

Scheme 70. Hall and Co-workers' DOS Approach for Synthesis of Polysubstituted Piperidines Using Tandem Aza [4 + 2]/Allylboration[a]



[a] Reagents and conditions: (a) toluene, 80 °C; (b) 0.5% TFA/CH_2Cl_2, RT.

Scheme 71. Ganesan and Co-workers' Solution- and Solid-Phase Synthesis of Tetrahydro-β-carbolinehydantoins[a]

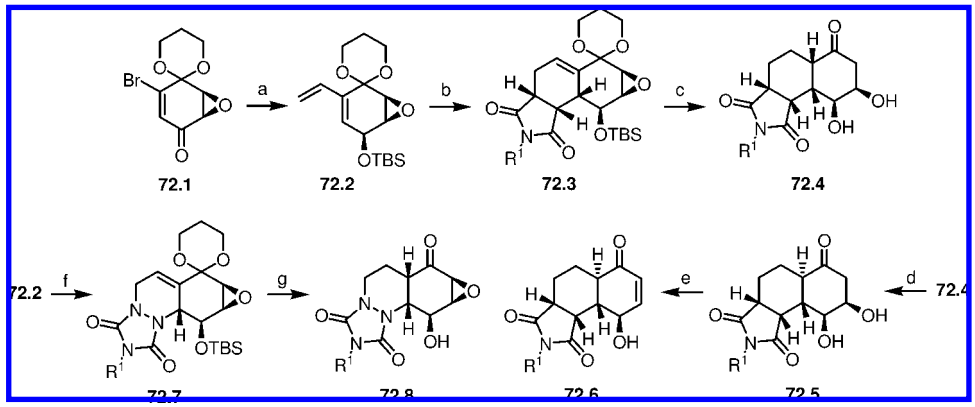


[a] Reagents and conditions: (a) *p*-NO_2−C_6H_4−OCOCl, Et_3N, CH_2Cl_2/THF (1:1), RT; (b) $PhCH_2NH_2$, Et_3N, DMF, 90 °C; (c) acid-catalyzed Pictet−Spengler (i) PhCHO, 1% TFA, CH_2Cl_2, RT; (ii) *p*-NO_2−C_6H_4−OCOCl, Et_3N, CH_2Cl_2/THF (1:1), RT; or (c) *N*-acyliminium Pictet−Spengler (i) PhCHO, CH_2Cl_2/$CH(OMe)_3$ (1:1), RT; (ii) *p*-NO_2−C_6H_4−OCOCl, pyridine, DMAP, CH_2Cl_2, RT; (d) $PhCH_2NH_2$, Et_3N, DMF, 90 °C.

the Stille cross-coupling reaction, yielded a chiral diene, **72.2**, in good yields. The *endo*-selective [4 + 2] Diels−Alder cycloaddition of **72.2** with either the N-substituted maleimide or N-substituted triazolinedione gave **72.3** or **72.7** exclusively. Following this, the scaffold diversification was performed using the hydrogenation and epimerization reaction conditions. The deprotection of the cyclic ketal and *O*-TBS ether in **72.3** followed by the hydrogenation using 5 wt % Adams' catalyst led to the *cis* diol **72.4** as the major product. An acidic epimerization of **72.4** gave **72.5**, which on a serendipitous dehydration gave **72.6**. The hydrogenation of **72.7** using 15 wt % Adams' catalyst further generated **72.8** as a single isomer of *cis*-decalin derivative, which could not be epimerized as in the case of **72.4**. Finally, compounds **72.4**, **72.5**, and **72.8** were further diversified using different alkoxyamines and carbamates.

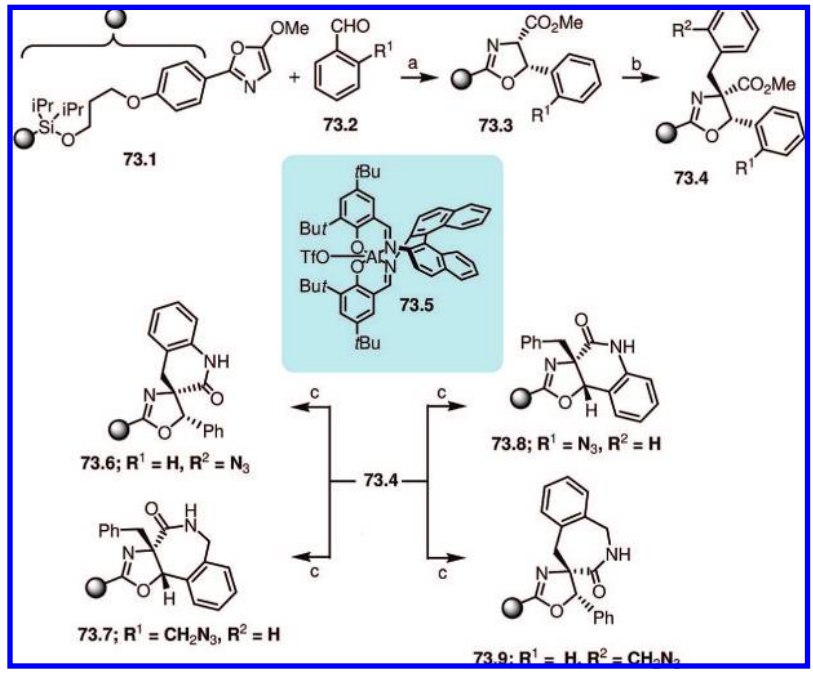
Shaw and co-workers[434] demonstrated that a linear synthetic sequence, differing only by the incorporation of a single functional group, could produce different core 3D architectures. The solid-phase variant of an enantioselective Suga−Ibata reaction[435] was adopted to synthesize **73.3** (Scheme 73) in high yields and with complete diastereoselectivity. This was achieved by the reaction of the methoxy-substituted oxazole derivative loaded onto the alkylsilyl-linker polystyrene macrobeads, **73.1**, with the aromatic aldehyde **73.2**. The alkylation of oxazoline **73.3** at the α-position to the carbonyl group using strong neutral phosphazene bases successfully led to **73.4** in high yields and >94% diastereoselectivity. The aromatic aldehydes **73.2** could have either the azido or the azidomethyl substituent at an *ortho*-position (R^1), which served as the manipulative component. A similar circumstance applies for the ortho substitution in the electrophile used in the alkylation step (R^2). The reduction/cyclization sequence between the strategically placed azide groups and the ester functionalities in **73.4** using Staudinger-type conditions generated four different types of lactam cores in >95% conversion. The mix and split alkylation of the respective amide −NH functionality induced the formation of spirocyclic (**73.6** and **73.9**) and fused lactams (**73.7** and **73.8**). This sequence was applied by the researchers to synthesize a library of 529 complex natural product-like compounds.

Scheme 72. Porco, Jr., and Co-workers' Generation of a Complex Library of Compounds via Elaboration of Angular Epoxyquinol Scaffolds[a]



[a] Reagents and conditions: (a) (i) super-hydride, THF, −78 °C; (ii) TBSCl, imidazole, DMF, RT; (iii) $Pd_2(dba)_3$, $AsPh_3$, tributyl(vinyl)stannane, toluene, 90 °C; (b) (i) maleimide derivative, toluene, 80 °C; (ii) polymer-supported anthracene dienophile scavenger resin; (c) (i) 5% HF, CH_3CN, TMSOMe; (ii) Adams' cat. 5 wt %, H_2, EtOAc, RT; (d) anhydrous HCl, CH_2Cl_2, RT; (e) MP-TsOH, CH_2Cl_2, RT; (f) (i) triazolinedione derivative, toluene, 60 °C; (ii) polymer-supported anthracene dienophile scavenger resin; (g) (i) Adams' cat. 15 wt %, H_2, EtOAc, RT; (ii) 20% HF, CH_3CN, RT, TMSOMe.

Scheme 73. Shaw and Co-workers' Library Generation of Complex, Natural Product-like Products from Oxazole 73.1[a]

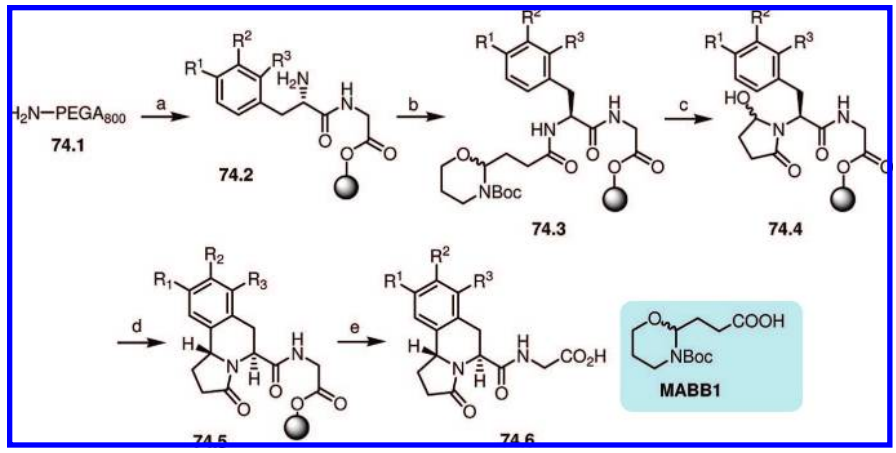


[a] Reagents and conditions: (a) (*R*)-**73.5**, $LiClO_4$, 3 Å MS, CH_2Cl_2, RT; (b) BTPP or BEMP, $BrCH_2$-*o*-C_6H_4-R^2, Bu_4NI, NMP, RT; (c) Me_3P/DBU, dioxane/H_2O, RT.

A solid-phase synthesis of pyrroloisoquinolines via the intramolecular *N*-acyliminium Pictet−Spengler reaction was reported by Meldal and co-workers.[436] The base-labile hydroxymethylbenzoic acid (HMBA) linker was attached to the amino-functionalized PEGA resin **74.1** (Scheme 74), and the hydroxyl group of the linker was esterified by treatment with MSNT-activated Fmoc-Gly-OH. After incorporation of the first amino acid fragment, *N*-Fmoc was removed, and then the unprotected product was coupled to substituted *N*-Fmoc-protected phenylalanine under TBTU coupling conditions to afford **74.2** following the *N*-Fmoc removal. The free amine was coupled with racemic masked aldehyde building block MABB1 to obtain **74.3**. Further treatment with 10% TFA in CH_2Cl_2 afforded **74.4** as a mixture of 1:1 diastereomers; **74.4** was then subjected to Pictet−Spengler cyclization under 50% TFA in CH_2Cl_2, yielding tricyclic compound **74.5**, which was finally cleaved from the resin using 0.1 M NaOH (aq) to obtain **74.6**.

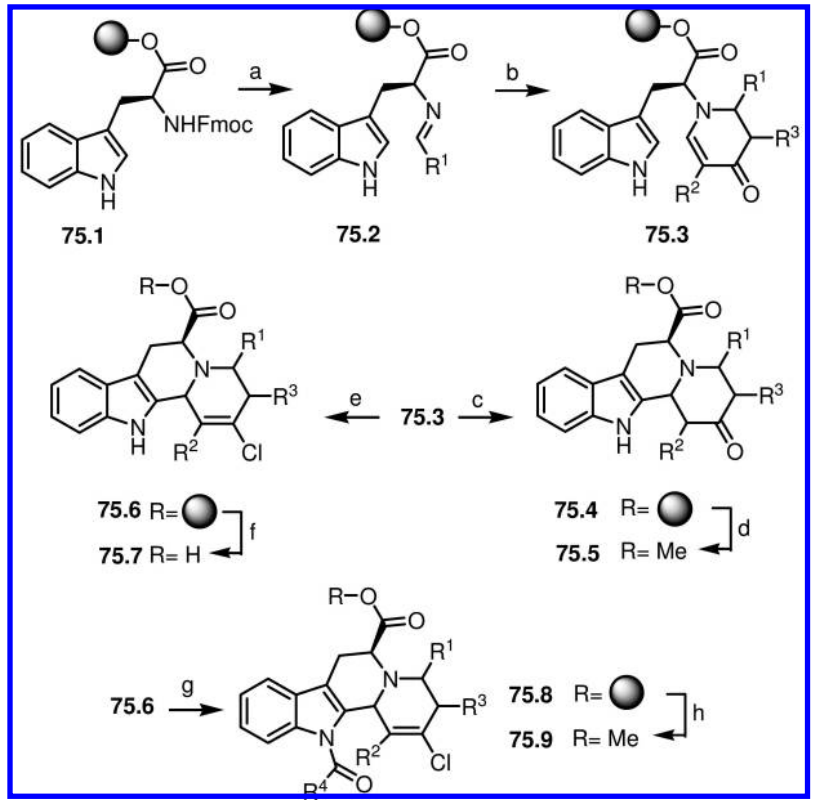
Waldmann and co-workers[437] reported a synthetic approach to making yohimbine indole alkaloid natural products, using a Mannich−Michael process on a solid phase. This strategy led to the synthesis of appropriately functionalized polycyclic indoloquinolizidines, which form the core of various yohimbine and reserpine indole alkaloid-like derivatives. *N*-Fmoc-tryptophan **75.1** (Scheme 75) was loaded onto Wang or 4-(hydroxymethyl) benzoic acid amide (HMBA) resin and, following *N*-Fmoc removal, was reacted with several aldehydes to form imines **75.2**. These imines were then subjected to Lewis-acid mediated, tandem Mannich−Michael reaction conditions with the electron-rich Danishefsky's dienes. The reaction yielded immobilized enaminones **75.3** with variable diastereomeric ratios (i.e., 65:35 to 90:10). The variation in

Scheme 74. Meldal and Co-workers' Solid-Phase Synthesis of Pyrroloisoquinolines via Intramolecular *N*-Acyliminium Pictet−Spengler Reaction[a]



[a] Reagents and conditions: (a) (i) HMBA, TBTU, NEM, DMF; (ii) Fmoc-Gly-OH, MSNT, MeIm, CH_2Cl_2; (iii) 20% piperidine in DMF; (iv) Fmoc-Phe-OH, TBTU, NEM, DMF; (v) 20% piperidine in DMF; (b) MABB1, TBTU, NEM, DMF; (c) 10% TFA (aq), RT; (d) Brønsted acid (50% TFA in CH_2Cl_2 or 10% H_2SO_4 in AcOH), RT; (e) 0.1 M NaOH (aq).

Scheme 75. Waldmann and Co-workers' Solid-Phase Synthesis of Indole Alkaloid-like Tetracyclic Compounds[a]

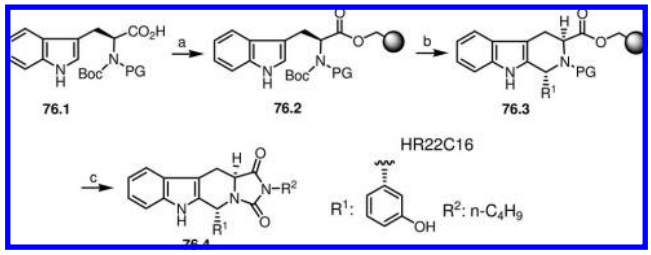


[a] Reagents and conditions: (a) (i) piperidine, DMF, RT; (ii) R^1CHO, trimethylorthoformate/CH_2Cl_2, RT; (b) $R^3CH{=}C(OTMS)C(R^2){=}COMe$, $ZnCl_2$, propionitrile, 0 °C to RT; (c) TFA, TMSCl, CH_2Cl_2, RT; (d) NaOMe, MeOH/1,4-dioxane, 50 °C; (e) phosgene, TMSCl, CH_2Cl_2, RT; (f) TFA, H_2O, RT; (g) R^4X, LiHMDS, HMPA, −78 °C to RT; (h) (i) TFA, H_2O, RT; (ii) EDC·HCl, pyridine/MeOH/CH_2Cl_2, RT.

Danishefsky's diene structures was helpful in generating diversity in the newly formed heterocyclic ring skeleton (i.e., diversity at R^2 and R^3) in **75.3**. When exposed to TFA in the presence of TMSCl, **75.3** led to the formation of tetracyclic ketones **75.4** as single diastereomers, which were cleaved from the resin and obtained as methyl esters **75.5** upon treatment with NaOMe. Divergently, the treatment of **75.3** with phosgene and TMSCl induced the formation of the solid-supported vinyl chlorides **75.6** with a 2:1 diastereoselectivity for the newly generated chiral center. Release of **75.6** from the solid support afforded **75.7** upon exposure to aqueous TFA. The N-acylation on **75.6** provided further derivatization giving **75.8**, which was cleaved from the solid support and finally esterified to yield **75.9**.

Inspired by indole alkaloids, a 50 member library of HR22C16 analogs was achieved by Kapoor and co-workers (Scheme 76).[438] HR22C16 is a cell-division inhibitor discovered from a forward-chemical-genetic screen.[439] The resin-bound amino acid **76.2**, which was obtained from the coupling of N_b-Boc-N_b-allyl-L-tryptophan **76.1** with hydroxy-TentaGel resin, was subjected to Pictet−Spengler cyclization using a variety of aldehydes. Following this, the protected

Scheme 76. Kapoor and Co-workers' Diastereoselective Synthesis of HR22C16 Analogs[a]



[a] Reagents and conditions: (a) NovaSyn TG-S-OH, 1,1′-carbonyldiimidazole, CH_2Cl_2, RT; (b) R^1CHO, trifluoroacetic acid (5% in CH_2Cl_2), 50 °C; (c) (i) deprotection of the ring nitrogen; in the case of allylic protecting groups, $Pd(PPh_3)_4$, *N*,*N*′-dimethylbarbituric acid, CH_2Cl_2, 50 °C; (ii) R^2NCO (10 equiv), THF, 55 °C.

cyclic amine was deprotected, derivatized on reaction with different isocynates, **76.3**, and then subjected to hydantoin-forming cleavage from the resin giving **76.4** as analogues to HR22C16. The overall yield of HR22C16 analogues was 46%, and the products were obtained in >90% purity as determined by HPLC analysis. These compounds were tested using *in vitro* assays with recombinant Eg5, and the testing identified a lead compound (R^1 = *m*-phenol and R^2 = $(CH_2)_5NH_2$) with an IC_{50} value of 90 ± 40 nM, thus making it the most potent inhibitor currently available for this key cell-division protein.

The indole/indoline substructure is considered a privileged scaffold and is found in a wide variety of common alkaloid natural products.[87,215−217,440,441] Arya and co-workers [442−444] launched a synthesis program that was aimed at designing functionalized indoline derivatives that could further be used for building different, natural product-inspired polycyclic architectures. The first and second generation synthetic targets, **F3.1** (racemic) and **F3.2** (enantioenriched), are shown in Figure 3. The indoline scaffold **F3.1** contains an amino alcohol functionality that could be further utilized in the design and synthesis of tricyclic structures. Through functioning as an anchoring site, the presence of the phenolic hydroxyl group allows development of solid-phase synthetic methodologies. The second generation indoline scaffold, **F3.2**, is densely functionalized and can be easily obtained in an enantioenriched manner. In addition to having the functional groups that were present in the first generation design, **F3.2** also contains an amino group that is orthogonally protected from the indoline secondary amine. The presence of multiple functional groups on this scaffold make it highly attractive for developing modular approaches for obtaining three-dimensionally different tricyclic architectures.

Arya and co-workers[445] described a solution- and solid-phase library synthesis of hydroxyindoline-derived tricyclic compounds using Mitsunobu reaction as a key reaction. The first generation of indoline scaffold, **77.1** (Scheme 77), was used in a solution-phase sequence involving (i) alloc removal with Pd(0), (ii) *N*-Fmoc-protected phenylalanine coupling under DIC, HOBt conditions, (iii) *N*-Fmoc removal with piperidine, (iv) protection of the free amine as an *o*-nosyl derivative, and (v) benzoyl removal to generate the compound **77.2** with a free hydroxyl group. This compound was cyclized under Mitsunobu conditions with an excellent yield (92%). Then the secondary amine was coupled with *p*-tolyl acetic acid under DIC, HOBt conditions, and the last step of THP removal in PTSA gave the final indoline-derived tricyclic compound **77.3**. The solid-phase sequence was then performed using the same sequence of reactions, and a 100-membered library was obtained by an IRORI[196] split-and-mix-type approach using the two acid couplings as diversity sites (10 × 10). The solid-supported indoline **77.5** (overall 65% yield in six steps after cleavage from the support) was then subjected to intramolecular Mitsunobu reaction conditions, which went smoothly on the solid phase as observed earlier in solution-phase synthesis. To complete the synthesis, the *o*-nosyl group was removed, and the free amine was then coupled to introduce the second diversity using different acids under DIC and HOBt conditions. Cleavage from the support on treatment with 10% TFA in CH_2Cl_2 provided the desired indoline-derived tricyclic derivative **77.6**.

Arya and co-workers[442] used the first generation of indoline scaffold **78.1** (Scheme 78) to generate skeletally diverse tricyclic architectures using the ring-closing metathesis (RCM) strategy. From the starting compound **78.1**, several steps of modification on both nitrogen and hydroxyl group of the indoline scaffold by introducing different groups bearing a terminal alkene gave derivatives **78.2**−**78.6**. These compounds were used in RCM reactions using Grubbs' catalyst to generate the corresponding tricyclic compounds. On the first three tricyclic derivatives, the α,β-unsaturated ketone was used successfully in a subsequent addition reaction introducing stereoselectively the thiophenol group giving compounds **78.7**−**78.9**. All ring sizes from five to eight members of the fused cycle bearing the indoline scaffold could be achieved using that strategy.

Arya and co-workers[442] again used the RCM strategy to obtain the first generation indoline scaffold bearing six- and seven-membered fused rings, **79.4** and **79.7** (Scheme 79). Compound **79.4** was achieved from the successful loading of compound **79.1** onto alkylsilyl macrobeads to give compound **79.2**. After two more steps involving (i) *N*-alloc removal and (ii) acid chloride coupling with but-3-enoyl chloride, compound **79.3** was cyclized in RCM reaction with Grubbs' catalyst to give compound **79.4**. After the loading of the compound **79.5**, the loaded resin **79.6** was cyclized in a RCM reaction, and final addition of a thiophenol derivative gave the compound **79.7** where the last Michael addition was performed with a complete stereocontrol generating only one isomer.

A library of 90 members of indoline-alkaloid-like polycyclic compounds was achieved by Arya and co-workers.[443] Amino alcohol **80.2** (Scheme 80) was prepared from commercially available 5-hydroxy-2-nitro-benzaldehyde (**80.1**) by the protection of phenolic alcohol by MEM group followed by treatment with Horner−Wittig reagent and Sharpless amino hydroxylation reaction with (>92% ee). The aminoindoline **80.3**, which was obtained from **80.2** in several steps, was treated with PTSA to deprotect the MEM group selectively. The three carbon spacer was introduced using Cs_2CO_3 and THP-protected tosylated diol. The material that could be loaded to a solid support was obtained after the *O*-Bz removal, oxidation of the hydroxyl to an aldehyde, Wittig reaction to introduce the electron-deficient olefin, and replacement of the *N*-Teoc group by the *N*-Fmoc group to promote compatibility for the solid phase using silylalkyl macrobeads (loaded compound, **80.4**). The next series of steps were then attempted on the solid support. The indoline amine was first deprotected of its *N*-Fmoc group and then coupled with the *N*-Fmoc-protected amino acid chloride (first diversity) to give the amino acid coupled product, **80.5**. Several attempts were then made to optimize the conditions

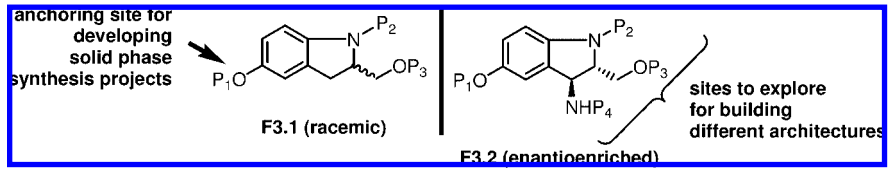
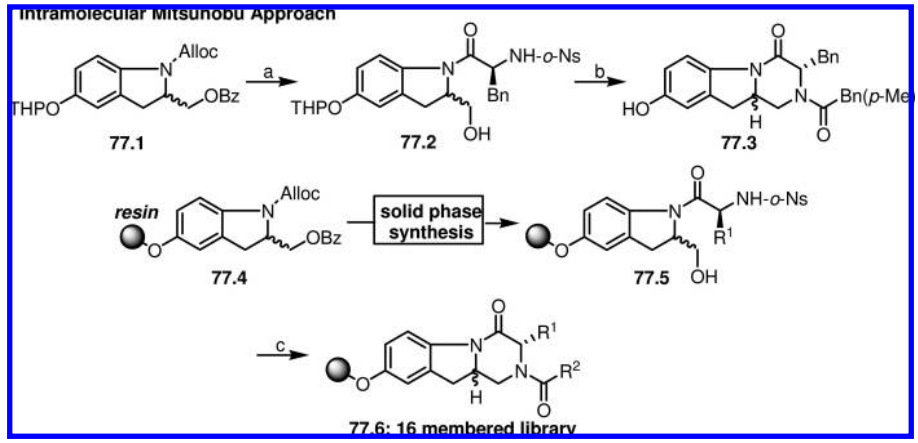


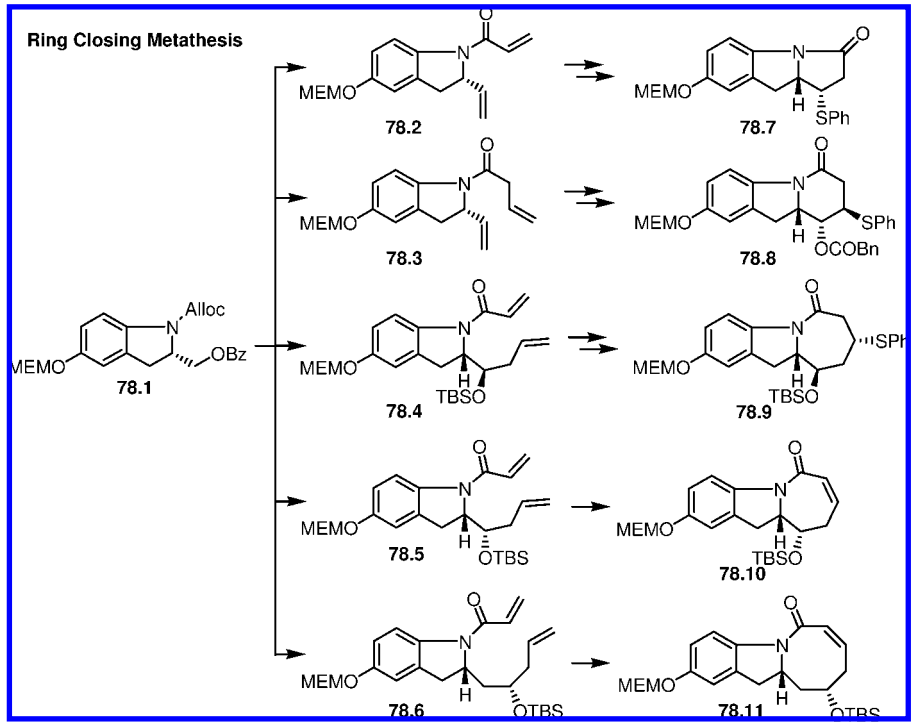
Figure 3. First and second generation functionalized indoline scaffolds from Arya and co-workers.

Scheme 77. Arya and Co-workers' Solution- and Solid-Phase Synthesis from the Racemic, First Generation Indoline Scaffold To Obtain a 16-Membered Library by an Intramolecular Mitsunobu Approach[a]



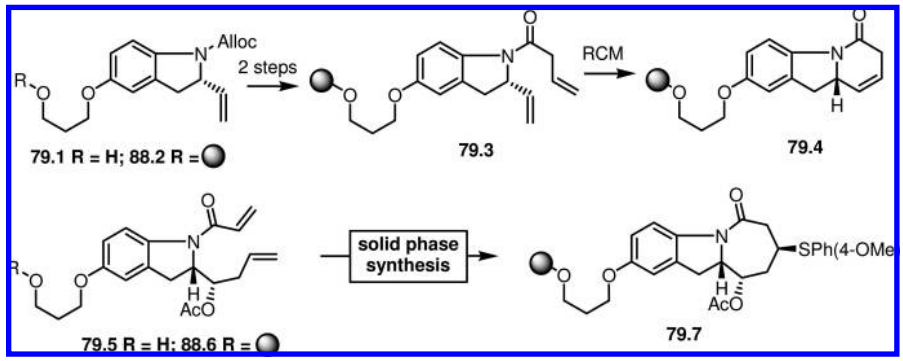
[a] Reagents and conditions: (a) (i) $Pd(PPh_3)_4$, *N*-methyl morpholine, CH_2Cl_2; (ii) Fmoc-Phe-OH, HOBt, DIC, DMF; (iii) 20% piperidine, CH_2Cl_2; (iv) 2-nitrobenzensulfonyl chloride, $(^iPr)_2NEt$, CH_2Cl_2; (v) NaOMe, MeOH; (b) (i) EtOOC−N═N−COOEt, Ph_3P, THF; (ii) K_2CO_3, PhSH; (iii) *p*-tolyl acetic acid, HOBt, DIC, DMF; (iv) PPTS, EtOH, 50 °C; (c) from **86.4** (i) $Pd(PPh_3)_4$, *N*-methyl morpholine, CH_2Cl_2; (ii) Fmoc-AA(R^1)-OH, HOBt, DIC, $(^iPr)_2NEt$, DMF; (iii) 20% piperidine, DMF; (iv) 2-nitrobenzensulfonyl chloride, CH_2Cl_2; (v) NaOMe, MeOH/THF; (vi) EtOOC−N═N−COOEt, Ph_3P, THF; (vii) PhSH, DBU, DMF; (viii) HOBt, DIC, R^2CO_2H, DMF; (ix) 10% TFA, CH_2Cl_2.

Scheme 78. Arya and Co-workers' Solution Synthesis from the First Generation Indoline Scaffold to Obtain Diverse Indoline-Alkaloid-Inspired Polycyclic Architectures

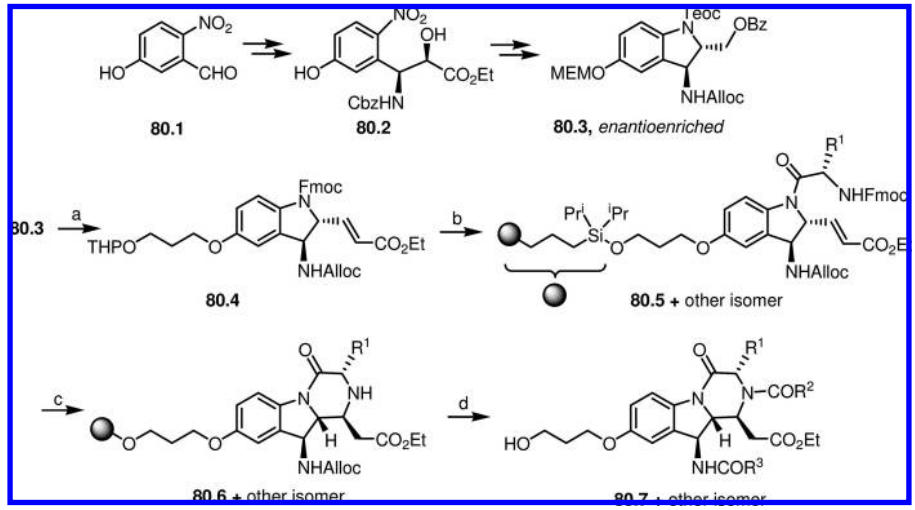


for the solid-phase coupling reaction, and the use of collidine as a base gave the best results. The coupled product, **80.5**, was then treated with piperidine, and as observed in the synthesis carried out in solution, the authors were pleased that the primary amine was trapped with the conjugated carboxyl ester to give the tricyclic derivative during the removal of the *N*-Fmoc group. Once again, as with the solution-state synthesis, the *in situ* conjugate hetero-Michael reaction was highly reproducible in the solid phase. The mild conditions for this cyclization reaction are highly appealing and attractive to explore its potential in the generation of a modular library. The stereochemical outcome of this reaction was found to be dependent upon the choice of the amino acid, and the ratio of the two diastereomers, **80.6** and the

Scheme 79. Arya and Co-workers' Manual Solid-Phase Synthesis from the First Generation Indoline Scaffold To Obtain Two Tricyclic Architectures



Scheme 80. Arya and Co-workers' Solid-Phase Synthesis To Obtain Aminoindoline Alkaloid-like Tricyclic Compounds by in Situ, Aza-Michael Approach[a]



[a] Reagents and conditions: (a) (i) *p*-TSA, EtOH, 50 °C; (ii) 3-(tetrahydro-2*H*-pyran-2-yloxy) propyl 4-methylbenzenesulfonate, Cs_2CO_3, DMF; (iii) K_2CO_3, MeOH; (iv) Dess−Martin periodinane; (v) Ph_3P=CHCOOEt; (vi) TBAF, THF; (vii) Fmoc-Cl, aq $NaHCO_3$, EtOAc; (viii) PPTS, EtOH, 55 °C; (b) (i) (4-methoxyphenyl) diisopropylsilyl- propyl polystyrene macrobeads (500−560 μm, loading 1.29mmol/g), TFA, 2,6-lutidine; (ii) 20% piperidine, DMF; (iii) Fmoc amino acid chloride, collidine; (c) (i) 20% piperidine, DMF; (ii) R^2COCl, pyridine, CH_2Cl_2; (iii) $Pd(PPh_3)_4$ PPh_3, *N*-methyl morpholine, AcOH, CH_2Cl_2; (iv) R_3COCl, pyridine, DMF; (d) pyridine−HF.

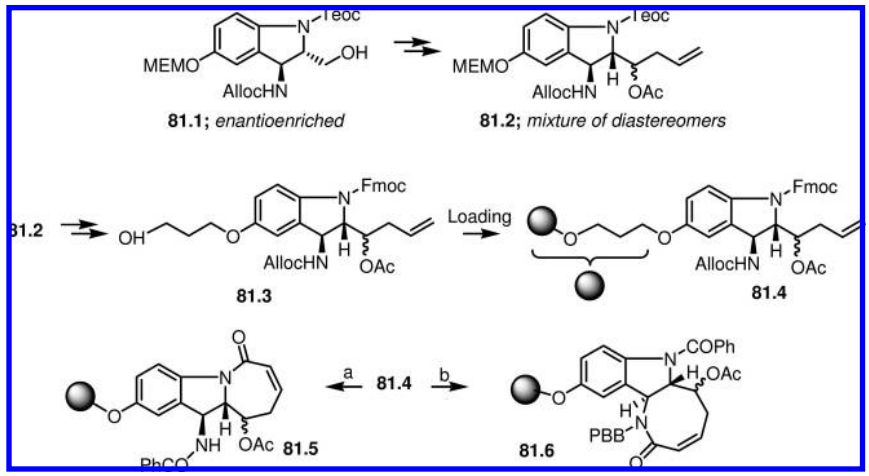
other isomer, varied from 5:1 to 1:1. To complete the test sequence in the solid phase, **80.6** was then subjected to (i) an amide coupling reaction to introduce the second diversity, (ii) removal of the protecting group to give the free amine, and (iii) reaction with carboxylic acid chloride to introduce the third diversity to give **80.7** and the other isomer. Finally, compounds **80.7** and the other isomer were obtained upon cleavage of the substrates from the support under desilylation conditions. Interestingly, compounds **80.7** and the other isomer were obtained from the loaded resin in seven steps with 80−85% overall yield.

With the goal of obtaining two different tricyclic derivatives having an indoline substructure, compound **81.2** (Scheme 81) was obtained from **81.1** by Arya and co-workers[444] who utilized the orthogonally protected amines (i.e., *N*-Teoc and *N*H-Alloc) and developed a modular ring-closing metathesis. Two different unsaturated lactams with seven- (**81.5**) and eight-membered rings (**81.6**) were obtained. An attractive feature of this approach is that by a simple choice of either of the amine moieties, it was possible to obtain two different functionalized indoline-based tricyclic architectures. Following the successful method developed in solution, this synthesis was effectively undertaken on a solid phase where compound **81.3**, obtained from **81.2**, was anchored onto the alkylsilyl-linker-based polystyrene macrobeads, giving product **81.4**. As observed in solution synthesis, this strategy produced two different indoline-based natural product-like tricyclic architectures, **81.5** and **81.6**.

Tetrahydroquinoline and tetrahydroisoquinoline are other highly privileged substructures that are commonly found in a wide variety of alkaloid natural products. With the objective of exploring the chemical space around the tetrahydroquinoline substructure, Arya and co-workers developed a highly practical, enantioselective synthesis of several tetrahydroquinoline scaffolds, **F4.1**, **F4.3**, and **F4.4**, with an increase of complexity and the enantioselective synthesis of hydroquinoline-2-one scaffold **F4.2** (Figure 4). Several features of the most complex **F4.4** scaffold make it versatile and amenable to the production of a wide variety of different polycyclic architectures. The key features include the presence of (i) the β-amino acid moiety, (ii) the δ-amino acid moiety, (iii) the γ-hydroxy carboxyl ester functionality, and (iv) the phenolic hydroxyl group that could be used as an anchoring site during solid-phase synthesis.

A novel solution- and solid-phase methodology to construct a tetrahydroquinoline-based polycyclic scaffold with a 10-membered ring was developed by Arya and co-workers.[446] The enantiopure tetrahydroquinoline scaffold **82.2** (Scheme 82) was obtained in several steps from compound **82.1**. Further functional group manipulations were performed

Scheme 81. Arya and Co-workers' Solid-Phase Approach To Obtain Two Different Types of Aminoindoline-Based Tricyclic Compounds Having Medium-Sized Unsaturated Lactams[a]



[a] Reagents and conditions: (a) (i) $Pd(PPh_3)_4$, PPh_3, *N*-methyl morpholine, AcOH, CH_2Cl_2; (ii) benzoyl chloride, 2,6-collidine, CH_2Cl_2; (iii) 20% piperidine, DMF; (iv) acryloyl chloride, 2,6-collidine, CH_2Cl_2; (v) Grubbs' catalyst-II (40−50 mol%), CH_2Cl_2, 40 °C; (b) (i) 20% piperidine, DMF; (ii) benzoyl chloride, 2,6-collidine, CH_2Cl_2; (iii) $Pd(PPh_3)_4$, PPh_3, *N*-methyl morpholine, AcOH; (iv) 4-bromobenzaldehyde, $NaCNBH_4$, MeOH, AcOH, TMOF; (v) acryloyl chloride, 2,6-collidine; (vi) Grubbs' catalyst-II (40−50 mol%), CH_2Cl_2, 40 °C.

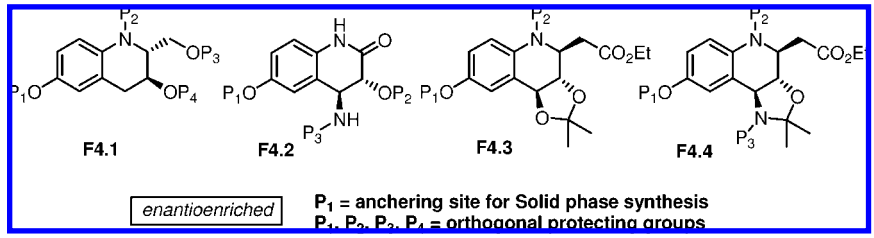


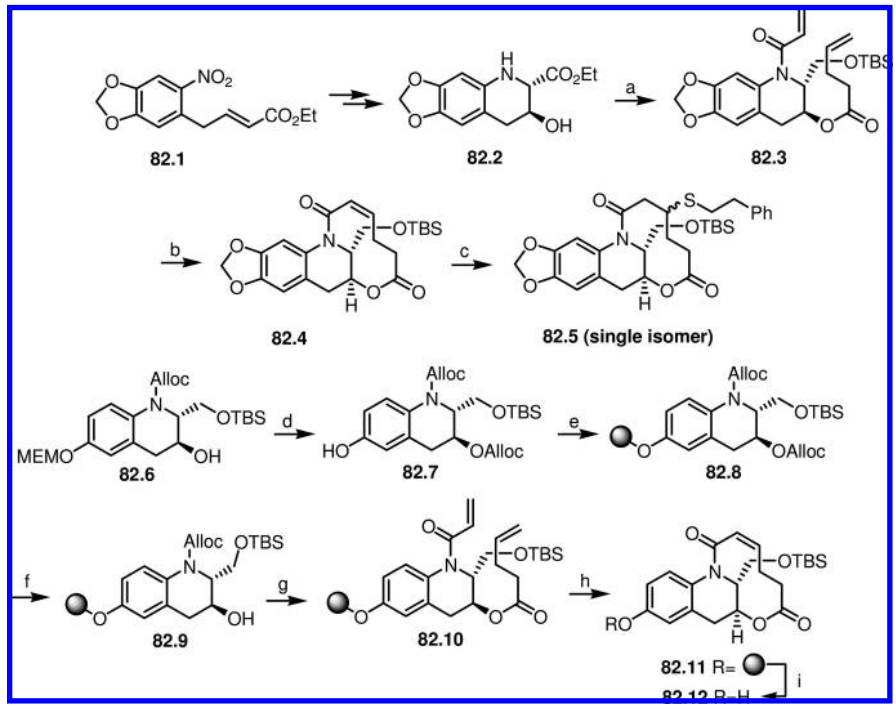
Figure 4. Tetrahydroquinoline scaffolds designed by Arya and co-workers.

on **82.2** that included the reduction of the carboxyl ester with lithium borohydride, a selective *N*-alloc protection, O-silylation of the primary hydroxyl, the protection of the secondary hydroxyl group, the removal of the *O*-Alloc group using mild base, acylation with pentenoic acid, *N*-Alloc removal, and N-acylation using acryloyl chloride, giving compound **82.3**. Ring-closing metathesis went readily, giving only the *cis* olefin-based 10-membered ring **82.4** in high yields, having an enamide functional group. An X-ray structure of the compound **82.4** could be obtained. It appears that the 10-membered ring is projected out of the tetrahydroquinoline plane and that the double bond is not aligned with the amide functional group. To explore the scope of a macrocyclic ring-conformation-controlled reaction, compound **82.4** was then subjected to thioaddition reaction to obtain **82.5** as single isomer. As expected, the approach of the thiol nucleophile occurred only from one side, giving the hetero-Michael product as a single isomer.

For developing a solid-phase synthesis, compound **82.7**, in which the phenolic hydroxyl moiety could be utilized as an anchoring site for the solid phase, was required. Thus, an enantioselective synthesis of compound **82.6** was developed that utilized an approach similar to that discussed earlier. Subjecting the compound to secondary hydroxyl protection with the alloc group, followed by the *O*-MEM removal from the phenolic hydroxyl moiety, provided the required the starting material **82.7**. This compound was then immobilized onto the solid support. The solid-phase synthesis was carried out on the bromo-Wang resin (1.70 mmol/g), and the loading of the phenolic derivative was accomplished nicely (85% loading after cleavage of the product from the solid support). Following the immobilization, compound **82.8** was subjected to *O*-Alloc removal under basic conditions (NaOMe) to give **82.9**. This derivative was treated with pentenoic acid under DIC/DMAP coupling conditions to remove the alloc protecting group, and the acryloyl moiety was coupled to give RCM precursor **82.10**, which was subjected to RCM reaction using Grubbs' (II) catalyst to give the 10-membered ring **82.11** on the solid phase and derivative **82.12** after cleavage from the solid support.

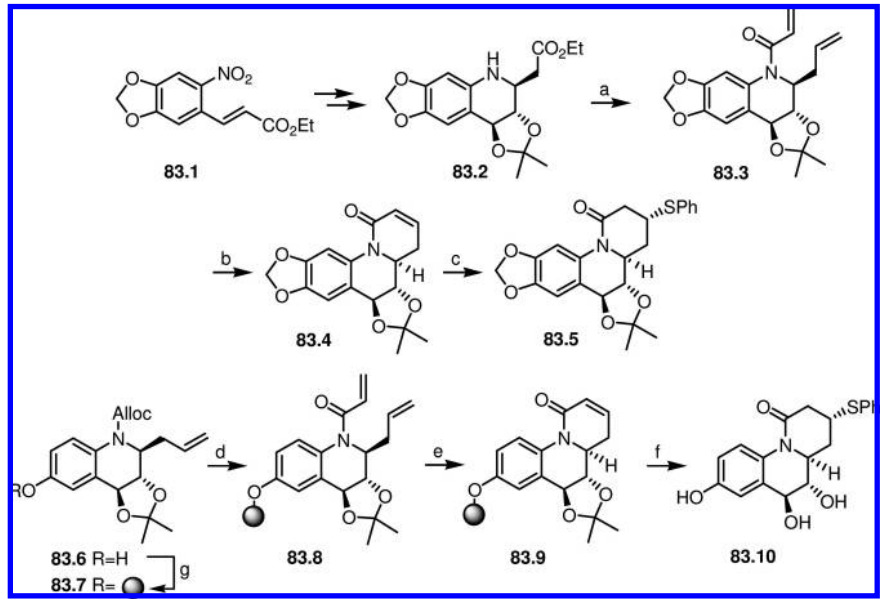
The solid-phase synthesis of tetrahydroquinoline-based polycyclic derivatives using an alternative hetero-Michael strategy was demonstrated by Arya and co-workers.[447] In several steps, compound **83.2** (Scheme 83) was obtained from **83.1** by a series of reactions. The carboxyl ester of compound **83.2** was then reduced to an alcohol and subjected to an amino group protection (*N*-alloc). The oxidation followed by a Wittig reaction, *N*-alloc removal, and finally N-acryloylation with acryloyl chloride gave the compound **83.3**. The ring-closing metathesis using first generation Grubbs' catalyst gave the enamide **83.4** (65%). Further reaction with thiophenol produced compound **83.5** (78%) as a single diastereomer, in which the nucleophile approached the Michael acceptor site from the *Re* face (no NOE between C2−H and C4′−H). The same sequence was applied on the solid support. The compound **83.6** was prepared from 2-nitro-5-hydroxy benzaldehyde using protection of phenol with a Bn group, and a similar reaction sequence was used in solution-phase conditions; **83.6** was loaded onto 4-(bromomethyl) phenoxymethyl polystyrene resin (loading 93%) giving **83.7**. After *N*-alloc removal and acryloylation, the ring-closing metathesis reaction on **83.8** gave the cyclic enamide product **83.9**. As observed in solution, compound **83.10** was

Scheme 82. Solution- and Solid-Phase Synthesis of Tetrahydroquinoline-Alkaloid-like Polycycles[a]



[a] Reagents and conditions: (a) (i) $LiBH_4$; (ii) allylchloroformate, pyridine; (iii) TBDMSCl, imidazole; (iv) allylchloroformate, pyridine; (v) NaOMe, MeOH; (vi) 4-pentenoic acid, DIC, DMAP; (vii) $Pd(PPh_3)_4$, morpholine, CH_2Cl_2, 0 °C; (viii) acryloyl chloride, pyridine, 0 °C; (b) 20 mol % Grubbs' catalyst (II), CH_2Cl_2, reflux, 1 h; (c) $PhCH_2CH_2SH$, BuLi; (d) (i) allylchloroformate, pyridine; (ii) $ZnBr_2$; (e) bromo-Wang resin, NaI, Cs_2CO_3; (f) NaOMe, MeOH; (g) (i) 4-pentenoic acid, DIC, DMAP; (ii) $Pd(PPh_3)_4$, *N*-methylmorpholine, Ac_2O; (iii) acryloyl chloride, pyridine; (h) Grubbs' catalyst (II), dicholoromethane, reflux; (i) 5% TFA.

Scheme 83. The Solution- and Solid-Phase Synthesis of Tetrahydroquinoline-Based Polyclic Compounds[a]

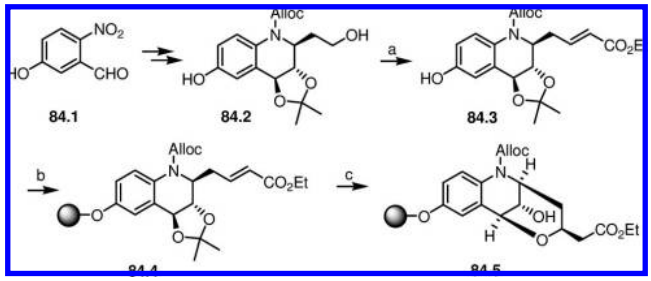


[a] Reagents and conditions: (a) (i) $LiBH_4$; (ii) AllocCl, pyridine, 0 °C to RT; (iii) SO_3 pyridine, Et_3N; (iv) Ph_3P, CH_3Br, NaHMDS, 0 °C; (v) $Pd(PPh_3)_4$; (vi) acryloyl chloride, pyridine; (b) 20 mol % Grubbs' catalyst (I), CH_2Cl_2, reflux; (c) PhSH, Et_3N; (d) 4-(bromomethyl) phenoxymethyl polystyrene resin, Cs_2CO_3, NaI, DMF; (e) (i) $Pd(PPh_3)_4$; (ii) acryloyl chloride, pyridine; (f) Grubbs' catalyst (I), CH_2Cl_2, reflux; (g) (i) PhSH, Et_3N; (ii) 5% TFA in CH_2Cl_2.

obtained as a single diastereomer by reaction with PhSH after cleavage from the solid support (27% overall yield for six steps).

In an another approach, solution- and solid-phase synthesis of tetrahydroquinoline-like complex polycyclic compounds using stereoselective hetero-Michael reaction was demonstrated by the same group.[447] Alcohol **84.2** (Scheme 84) was prepared from nitro derivative **84.1** by a series of reactions. Oxidation of the alcohol by SO_3·Py followed by Wittig reaction with $(Ph)_3P{=}CHCOOEt$ yielded **84.3**. In solution phase, the phenolic group of compound **84.3** was protected with a benzyl group (not shown in Scheme 84) and, after the acetonide removal and treatment with NaH, gave the hetero-Michael adduct. The same sequence was repeated on a solid support after loading of compound **84.3** onto 4-(bromomethyl) phenoxymethyl polystyrene resin (loading

Scheme 84. Arya and Co-workers' Approach To Obtain Tetrahydroquinoline-Based Polycyclic Compounds Using Hetero-Michael Reaction[a]



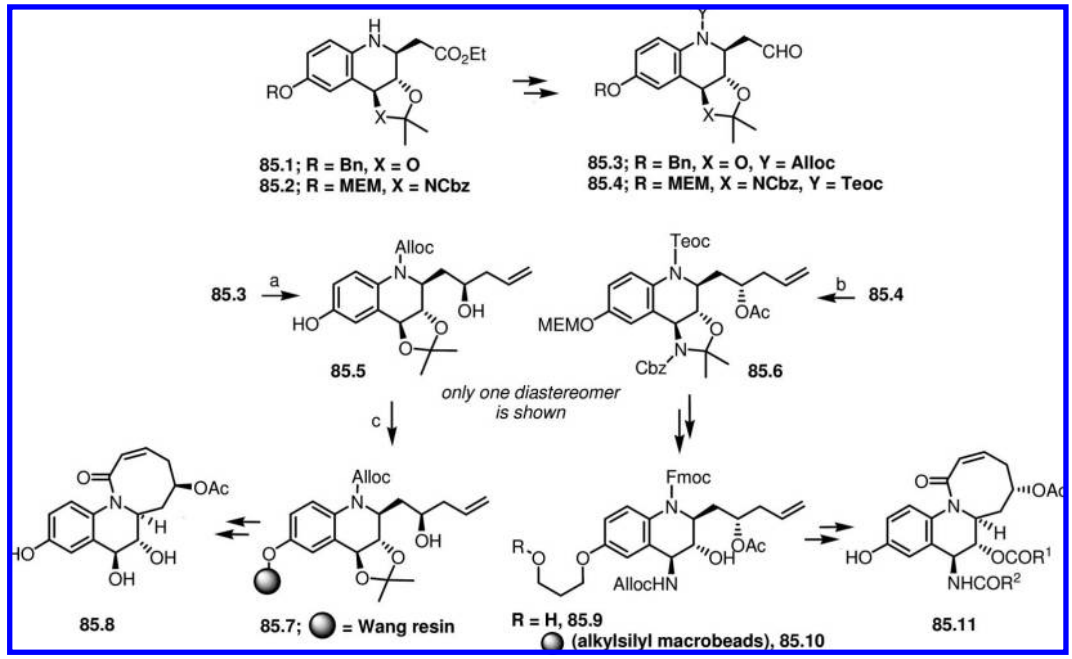
[a] Reagents and conditions: (a) (i) DMSO, SO_3 pyridine, Et_3N; (ii) $Ph_3P{=}CHCO_2Et$; (b) 4-(bromomethyl) phenoxymethyl polystyrene resin, Cs_2CO_3, NaI, DMF; (c) (i) PPTS, CH_3CN/CH_2Cl_2; (ii) NaH, THF.

84%) giving the loaded resin **84.4**. Removal of acetonide by treatment with PPTS and further treatment with NaH gave **84.5**. The hetero-Michael product was cleaved from the resin by treatment with 5% TFA in CH_2Cl_2.

The solid-phase synthesis of natural product-like tetrahydroquinoline-based polycyclic architectures having a medium size ring was achieved by Arya and co-workers.[448] In this approach, the key aldehydes, **85.3** and **85.4** (Scheme 85), obtained from **85.1** and **85.2**, respectively, were then subjected to allylation reaction to yield the corresponding alcohols (**85.5** and **85.6**, only one diastereomer is shown in both cases). In one study, **85.5** was loaded onto bromo-Wang resin (loading 91%, determined after cleavage from the support with 5% TFA). The loaded alcohol, **85.7**, was acetylated by treatment with Ac_2O and DMAP and after was subjected to *N*-alloc removal and coupling with acryloyl chloride. This was then subjected to RCM using Grubbs' (II) catalyst to give the eight-membered ring (**85.8**) after cleavage (5% TFA) from the solid support. With the goal of charting the chemical space around the tetrahydroquinoline scaffold by introducing an eight-membered-ring unsaturated lactam, compound **85.11** (Scheme 85) was obtained from **85.4**. In a similar manner, compound **85.9**, obtained from **85.6** in a series of steps, was loaded onto the alkylsilyl-based macrobeads. The loaded compound **85.10** then successively gave the tricyclic product **85.11** after the cleavage from the beads, in which the ring-closing metathesis was the key step. This methodology developed on a solid phase opens an attractive opportunity for producing a library of tetrahydroquinoline-based tricyclic architectures with eight-membered unsaturated lactam rings.

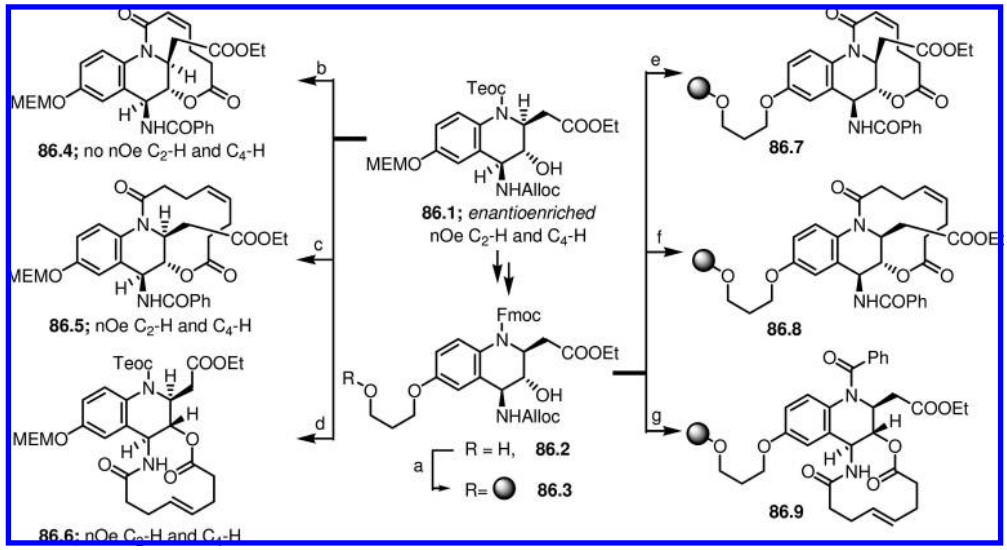
Arya and co-workers[449] reported a modular approach to obtain complex polycyclic alkaloid-like derivatives. By a ring-closing metathesis strategy, three different tricyclic structures were obtained in solution phase (**86.4**, **86.5**, and **86.6**, Scheme 86). Compound **86.4** is unique because it contains a bridged 10-membered ring with an unsaturated lactam moiety. The structure of the lactam was determined by NMR experiments. The second compound, **86.5**, has a bridged 12-membered ring with the *cis*-olefin that was obtained by the ring-closing metathesis. Finally, compound **86.6** was obtained with *trans*-fused ring skeletons. The development of the solid-phase synthesis of these compounds involved generating compound **86.2** in a number of steps from **86.1**. This was then successfully loaded onto the alkylsilyl-linker-based polystyrene macrobeads with full regiocontrol, giving **86.3**. The solution-phase ring-closing methodologies were then applied on the solid phase, and three products, **86.7**, **86.8**, and **86.9**, were successfully obtained in a modular manner. This approach for obtaining different macrocyclic ring-based functionalized architectures is highly attractive because it allows the production of libraries on three different polycyclic structures. Work toward this objective is progressing and the applications of these libraries will be reported as they become available.

Scheme 85. Arya and Co-workers' Solid-Phase Synthesis of Natural Product-like Tetrahydroquinoline-Based Polycyclic Architecture Having a Medium Size Ring[a]



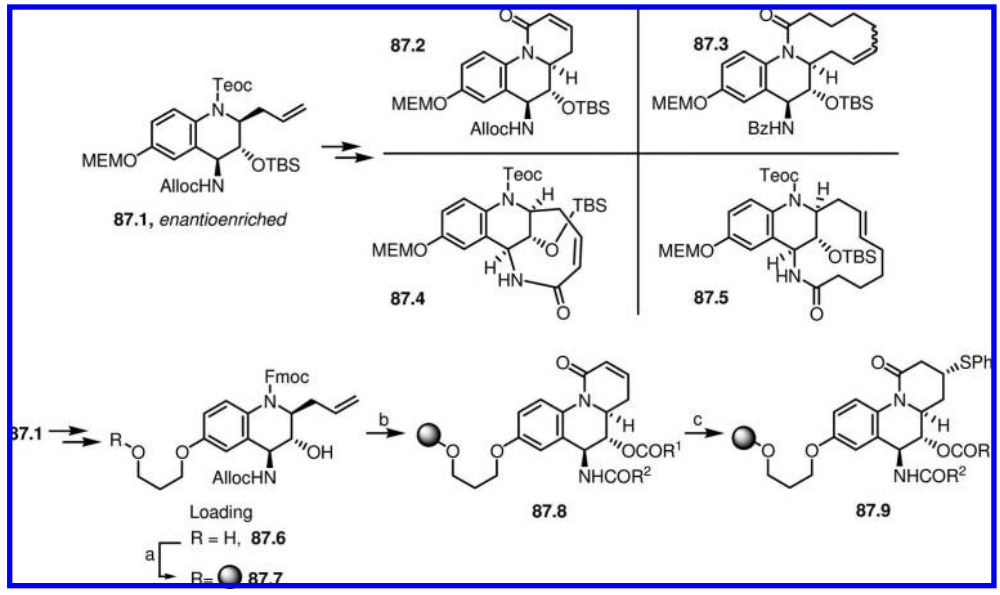
[a] Reagents and conditions: (a) $ZnCl_2$, allylMgBr; (b) (i) $ZnCl_2$, AllylMgBr, −78 °C; (ii) Ac_2O, DMAP, CH_2Cl_2, 0 °C to RT; (c) bromo-Wang resin, NaI, Cs_2CO_3.

Scheme 86. Arya and Co-workers' Modular Solid-Phase Approach To Obtain Different Tetrahydroquinoline-Based Tricyclic Compounds Containing Macrocyclic Rings[a]



[a] Reagents and conditions: (a) alkylsilyl linker-based polystyrene macrobeads (1.0 equiv), TfOH (6.0 equiv), 2,6-lutidine (10.0 equiv), **86.2** (0.5 equiv); (b) (i) 4-pentenoic acid, DMAP, DIC; (ii) TBAF; (iii) acryloyl chloride, NEt_3; (iv) $Pd(PPh_3)_4$, morpholine; (v) PhCOCl, NEt_3; (vi) Grubbs' catalyst-II; (c) (i) 4-pentenoic acid, DMAP, DIC; (ii) TBAF; (iii) 4-pentenoyl chloride, NEt_3; (iv) $Pd(PPh_3)_4$, morpholine; (v) PhCOCl, NEt_3; (vi) Grubbs' catalyst-II; (d) (i) 4-pentenoic acid, DMAP, DIC; (ii) $Pd(PPh_3)_4$, morpholine; (iii) 4-pentenoyl chloride, NEt_3; (iv) Grubbs' catalyst-II; (e) (i) 4-pentenoic acid, DMAP, DIC; (ii) 20% piperidine; (iii) *trans*-crotonoyl chloride, 2,4,6-collidine; (iv) $Pd(PPh_3)_4$, PPh_3, 4-methyl morpholine, CH_3CO_2H; (v) PhCOCl, 2,4,6-collidine; (vi) Grubbs' catalyst-II; (f) (i) 4-pentenoic acid, DMAP, DIC; (ii) 20% piperidine; (iii) 4-pentenoyl chloride, 2,4,6-collidine; (iv) $Pd(PPh_3)_4$, PPh_3, 4-methyl morpholine, CH_3CO_2H; (v) PhCOCl, 2,4,6-collidine; (vi) Grubbs' catalyst-II; (g) (i) 4-pentenoic acid, DMAP, DIC; (ii) 20% piperidine; (iii) PhCOCl, 2,4,6-collidine; (iv) $Pd(PPh_3)_4$, PPh_3, 4-methyl morpholine, CH_3CO_2H; (v) 4-pentenoyl chloride, 2,4,6-collidine; (vi) Grubbs' catalyst-II.

Scheme 87. Arya and Co-workers' Modular Solution- and Solid-Phase Approach To Obtain Tetrahydroquinoline-Based Tricyclic Compounds Containing Different Unsaturated Lactam Rings and Macrocyclic Rings[a]

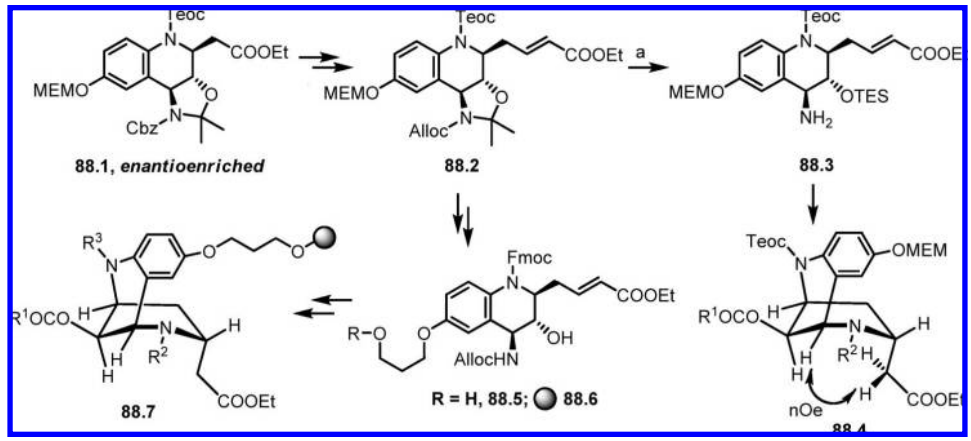


[a] Reagents and conditions: (a) alkylsilyl-linker-based polystyrene macrobeads (1.0 equiv), TfOH (6.0 equiv), 2,6-lutidine (10.0 equiv), **87.6** (0.5 equiv); (b) (i) 20% piperidine, CH_2Cl_2; (ii) Et_3N, acryloyl chloride, −10 °C, CH_2Cl_2; (iii) Grubbs' catalyst-II (30 mol %), CH_2Cl_2; (iv) NaHMDS, acyl chloride, THF; (v) piperidine, $Pd(PPh_3)_4$ (10 mol %), CH_2Cl_2 (vi) Et_3N, acyl chloride, CH_2Cl_2; (c) Et_3N, benzenethiol, CH_2Cl_2.

Using compound **87.1** (Scheme 87) having an allylic group at the C2 as the starting material, Arya and co-workers[450] reported the synthesis of four different tricyclic architectures (**87.2**, **87.3**, **87.4**, and **87.5**) that were obtained using ring-closing metathesis strategy. For the solid-phase synthesis, compound **87.6** was obtained from **87.1** and was successfully loaded onto the alkylsilyl-linker-based polystyrene macrobeads, providing **87.7**. In one study, compound **87.7** was successfully transformed using ring-closing metathesis on the solid phase into the six-membered-ring unsaturated lactam **87.8**. This compound was used in a subsequent Michael reaction using thiophenol and gave the adduct **87.9** with complete stereocontrol.

Finally, an unprecedented *in situ* aza-Michael approach developed by Arya and co-workers[451] allowed the production of tetrahydroquinoline-based bridged tricyclic architectures under very mild reaction conditions. In a typical example, enantioenriched compound **88.1** (Scheme 88) was converted to **88.2** in a series of steps. Surprisingly, following the acetonide and *N*-alloc removal, there was no sign of the free

Scheme 88. Arya and Co-workers' in Situ, Bridged Aza-Michael Approach in Solution and on a Solid Phase To Obtain Tetrahydroquinoline-Based Tricyclic Compounds[a]



[a] Reagents and conditions: (a) (i) acetic acid/THF/H_2O, RT; (ii) TESOTf, pyridine, CH_2Cl_2, −40 °C; (iii) $Pd(PPh_3)_4$, morpholine, CH_2Cl_2, RT; (iv) Et_3N, benzoyl chloride or cinnamoyl chloride, CH_2Cl_2, 0 °C to RT.

amine derivative **88.3**, but instead, compound **88.4** was obtained as single diastereomer. Under these mild reaction conditions, the in situ aza-Michael cyclization producing the bridged architectures is novel and highly attractive for developing this methodology on a solid phase. Indeed, this reaction was found to work equally well in solution- and on a solid-phase. Compound **88.5** was therefore loaded onto the alkylsilyl-linker-based polystyrene macrobeads and produced the expected bridged tricyclic product **88.7** with a complete diastereocontrol.

8. Summary and Outlook

There is a growing interest in the biomedical research community to obtain natural product-derived and natural product-inspired small molecules to understand biological processes. In particular, the interest is growing to access small molecules as chemical modulators and dissectors of signaling pathways. The chemical probes that fulfill these criteria are not easy to find and are in great demand. In addition to using these chemical probes for better understanding of normal and disease-related biological processes, these chemical entities could also provide useful starting points in probe discovery research. Inspired by bioactive natural products that have shown a proven track record in this arena, the need to access natural product analogs and natural product-like compounds with the goals of charting the natural product chemical territory has also grown. The examples covered in this review clearly demonstrate the growing research community that is committed to the young field of "exploring the natural product chemical territory". In many cases, the high-throughput synthesis methods have been successful in generating complex natural product-like architectures, and in a few cases, their applications are emerging in probe discovery research. Although the examples covered are taken from the recent literature (2000−2006) and, in many cases, the biological evaluation of these chemical probes is not fully realized yet, this is an area that will be given careful watch in the coming years; developing newer methods with the potential of generating natural product-inspired compounds in a high-throughput manner is the first major step toward reaching this dream—small molecule modulators (and dissectors) for all the signaling networks!

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