Polymer-Supported Synthesis of Non-Oligomeric Natural Products**

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Introduction

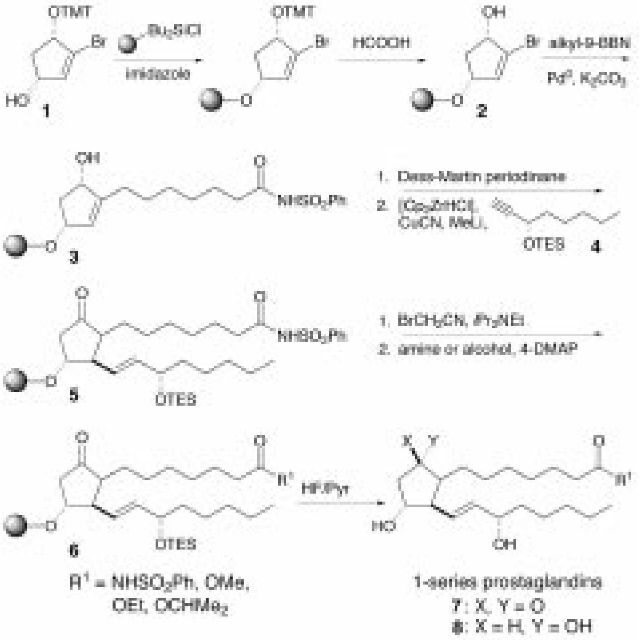
Combinatorial chemistry has become an important tool in the discovery of novel compounds for pharmaceutical research, materials science, molecular recognition, and asymmetric catalysis.[1] Solid-phase organic synthesis enables the most efficient preparation of libraries of compounds through the use of split-and-pool techniques and rapid, automated purification procedures. Since the pioneering work of Merrifield[2] in the 1960s, solid-phase synthesis of polypeptides[3] and oligonucleotides[4] has become routine, and more recently significant progress has been made in the synthesis of oligosaccharides[5] and small organic molecules.[6] However, further development in this area will require an increase in the scope of solid-phase chemistry and, in particular, the development of more sophisticated chemical transformations that operate reliably on the solid support.

Since the early days of organic chemistry, natural products have served as an inspiration for the development of new methodology and strategies in organic synthesis. Recently, a number of ground-breaking solid-phase syntheses of non-oligomeric natural products have been reported, which demonstrate the imagination and creativity required for success in this challenging field. This article will present an outline of the synthetic approaches as well as modifications employed to extend the chemistry to the generation of libraries.

Polymer-Supported Synthesis of Prostaglandins

Prostaglandins have inspired and challenged synthetic chemists for decades. Their complex structures, incorporating an array of sensitive functionalities, coupled with their potent biological activity have stimulated many total syntheses as well as the preparation of hundreds of analogues for pharmaceutical evaluation.[7] Even after so much research into the solution synthesis of these natural products, their preparation on a polymer support remains a significant challenge. Solid-phase reactions frequently require quite different conditions from those in solution, in part due to differences in steric hindrance and hydrophobicity within the resin matrix. For a successful solid-phase reaction to occur, a resin must be selected that swells well in the solvent of choice and is inert to the reaction conditions. The linker must also be stable throughout the synthesis, but ultimately must allow release of the natural product from the support. Moreover, since different resin-bound intermediates cannot be separated, it is crucial that reactions are driven to completion and side reactions are minimized to avoid formation of complex mixtures at the end of a multistep synthesis.

The approach to the synthesis of the 1-series prostaglandins adopted by Ellman et al. involved attachment of the cyclopentene core (**1**, Scheme 1) to a dibutylsilyl chloride substituted polystyrene resin.[8] Polystyrene swells well in many commonly used organic solvents, and it was envisioned that treatment with fluoride would result in release from the support along with removal of any silyl protecting groups. The nature of the silylalkyl groups had to be carefully optimized as



Scheme 1. Synthesis of the 1-series prostaglandins according to Ellman et al.[8] 9-BBN = 9-borabicyclo[3.3.1]nonane, 4-DMAP = 4-dimethylaminopyridine, Pyr = pyridine, TES = triethylsilyl, TMT = trimethoxytrityl.

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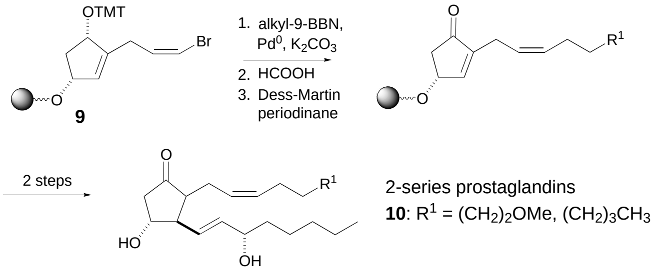
a result of the high sensitivity of the final prostaglandin structure: For example, release from a diisopropylsilyl linker required harsher conditions, which resulted in elimination of the β-hydroxy ketone functionality. The choice of alcohol protecting group was also crucial as deprotection of the more stable dimethoxytrityl group resulted in some cleavage from the resin.

The first side chain was incorporated by means of a Suzuki coupling on vinyl bromide **2**, under similar conditions to those reported by Johnson and Braun for the solution-phase reaction.[9] Oxidation of **3** to the corresponding enone was then achieved with Dess–Martin periodinane in refluxing THF. The efficiency of the synthesis might have been improved by incorporating the desired enone functionality at the start of the synthesis, as in the approach of Johnson and Braun; however, this resulted in some decomposition of the base-sensitive β-alkoxy group under the conditions of the Suzuki reaction. Subsequent addition of the cuprate derived from **4** gave ketone **5**, for which the stereochemistry of the α-chain was not reported. Elaboration of the sulfonamide was achieved by activation with bromoacetonitrile and then coupling to a series of nucleophiles to form acid derivatives **6**. Treatment with HF/pyridine resulted in the release of the prostaglandin E_1 analogues (**7**) from the resin in 49–58% yield (from **2**). Alternatively, ketone **5** could be reduced with L-selectride before further elaboration and cleavage, permitting access to prostaglandin $F_{1\alpha}$ derivatives **8**. In addition, simply using the chain-extended bromide **9** (Scheme 2) as the starting point for a similar synthetic sequence allowed ready access to the 2-series prostaglandins **10**. With modification of the separate components in the synthesis, Ellman et al. were able to prepare a number of analogous structures, thus forming a small library of prostaglandins.

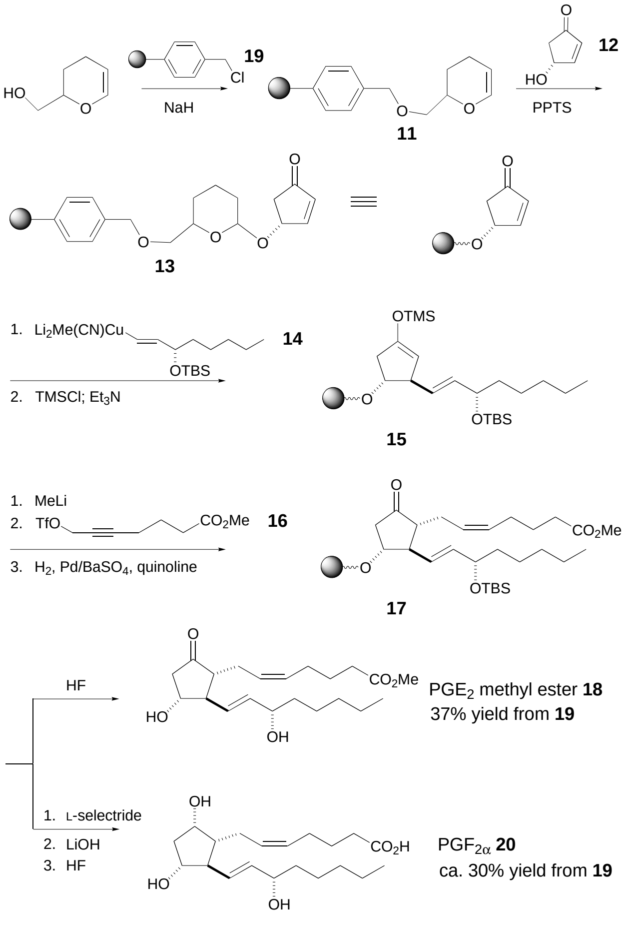


Scheme 2. Synthesis of the 2-series prostaglandins according to Ellman et al.[8]

This synthesis serves to illustrate some general features of solid-phase organic chemistry. It is obvious that optimized conditions for solution reactions cannot be applied directly to the solid phase, but must be reinvestigated on the resin-bound material. In addition, a large excess of reagents is often required to ensure complete conversion for solid-phase reactions. For example, five equivalents of the alkyl-9-BBN derivatives were employed in the above Suzuki coupling as compared to 1.5 equivalents of reagent in the corresponding solution transformation. Solid-phase reactions are also frequently carried out at higher temperatures and for longer times, as such reactions tend to be slower than their solution-phase counterparts.

Janda and co-workers adopted Noyori's convergent three-component strategy[10] for the synthesis of prostaglandin E_2 (PGE_2) methyl ester.[11] The synthesis was carried out in a liquid-phase rather than a solid-phase environment using noncross-linked chloromethylated polystyrene.[12] This support is soluble in most commonly employed organic solvents (CH_2Cl_2, $CHCl_3$, EtOAc, THF), so that reactions and product characterization can be carried out using standard solution techniques. As the polymer is insoluble in methanol and water, extraction of an organic reaction mixture with water removes inorganic contaminants, and then precipitation of the support with methanol separates the desired polymer-bound materials from unbound organic by-products. As in solid-phase synthesis, different polymer-bound components cannot be separated, and consequently many of the lessons learned using a liquid-phase support are applicable to solid-phase synthesis. Liquid-phase organic synthesis can also be applied to the construction of combinatorial libraries.

The soluble polystyrene resin was functionalized to the tetrahydropyran derivative **11** (Scheme 3), which was allowed to react with cyclopentene core **12** to generate the first support-bound intermediate (**13**). In a similar manner to the solution approach of Gooding,[13] the second component, the long-chain cuprate **14**, underwent a conjugate addition to the enone, and the resulting enolate was trapped with chlorotri-



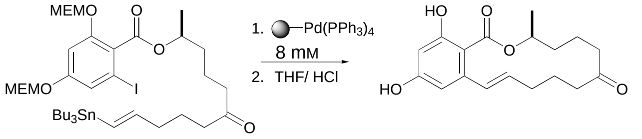
Scheme 3. Synthesis of prostaglandin E_2 methyl ester and prostaglandin $F_{2\alpha}$ according to Janda et al.[11] PPTS = pyridinium *p*-toluenesulfonate, TBS = *tert*-butyldimethylsilyl, TfO = trifluoromethanesulfonyl, TMS = trimethylsilyl.

methylsilane to give **15**. Generation of the more reactive lithium enolate followed by alkylation with triflate **16**, the third component, gave a complex alkyne which was reduced to form **17**. As in the solution synthesis, this combination of reactive enolate and reactive electrophile appeared to circumvent problems of enolate equilibration and β-elimination frequently observed in this system. Since the polymer support was soluble in the benzene/cyclohexane solvent mixture, the heterogeneous partial hydrogenation of the intermediate alkyne could be carried out under standard solution conditions and monitored by NMR analysis, minimizing over-reduction. Treatment with HF resulted in the release of **18**, the methyl ester of PGE_2, in 37% yield from **19**. As in the Ellman et al. synthesis, reduction of **17** with L-selectride before cleavage provided access to $PGF_{2\alpha}$ (**20**).

One of the advantages of the three-component strategy is the opportunity it provides for diversity. Thus the use of a range of functionalized cyclopentene cores, cuprates, and triflates could be envisioned to provide access to a library of prostaglandin analogues. Comparison of the liquid-phase and solution-phase approaches reveals that solution-phase reaction conditions could be applied with only minor modifications, as anticipated given the "solutionlike" environment of the soluble polystyrene resin.

Cyclorelease Strategies in Solid-Phase Synthesis

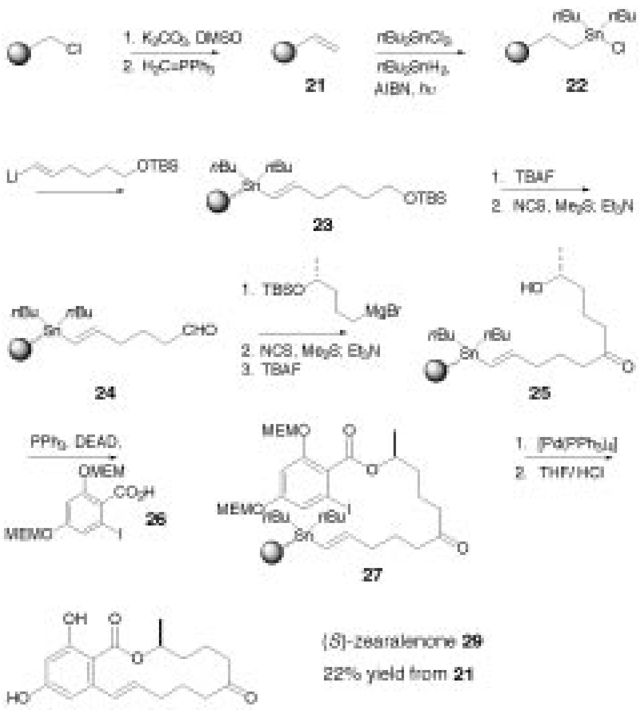
While the structure of the prostaglandins includes a convenient handle for attachment to the solid support, the synthesis of natural products lacking such functionality demands a different strategy. Nicolaou and co-workers have employed a series of cyclorelease approaches to the synthesis of the natural products zearalenone, muscone, and epothilone A, where cleavage from the resin results in concomitant ring formation. The solid-phase synthesis of zearalenone[14] closely followed a solution approach by Hegedus et al. (Scheme 4) in which an intramolecular Stille reaction on **28** under high dilution conditions generated the 14-membered macrocyclic ring of the natural product (**29**).[15] Nicolaou et al. aimed to employ the same disconnection; however, the macrocyclization precursor would be coupled to a solid support through the tin moiety.



28 (*S*)-zearalenone **29**

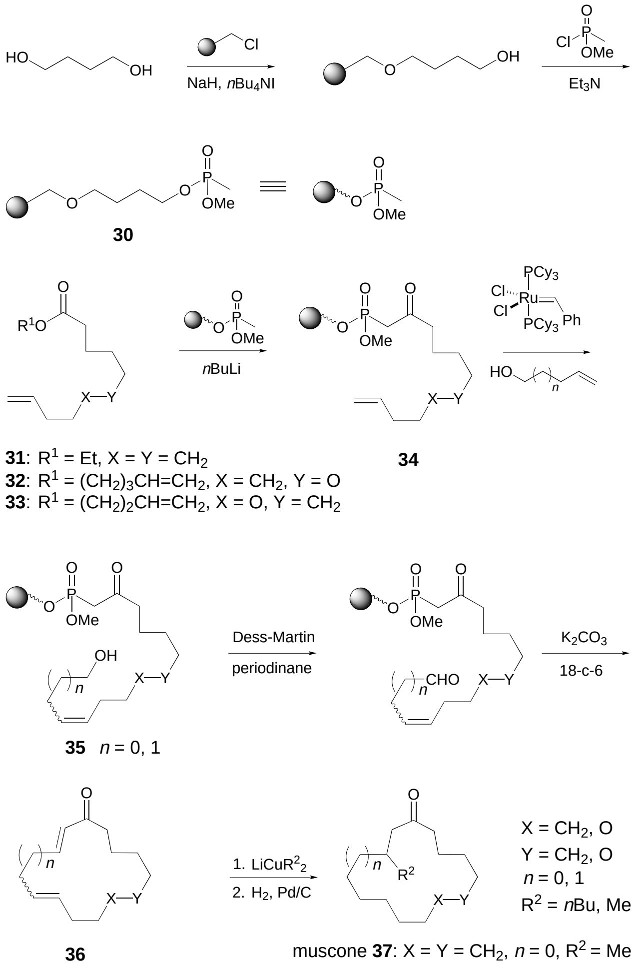
Scheme 4. Solution-phase approach to the synthesis of (*S*)-zearalenone according to Hegedus et al.[15] MEM = 2-methoxyethoxymethyl.

The starting point was the preparation of a polymer-supported tin reagent (Scheme 5). Elaboration of Merrifield resin (cross-linked polystyrene) to form alkene **21** was followed by the addition of nBu_2SnHCl in the presence of AIBN. Reaction of the resulting functionalized resin (**22**) with a vinyllithium reagent gave vinyltin intermediate **23**. The chain was further elaborated through Grignard addition to aldehyde **24** followed by a series of functional group interconversions to form **25**. Esterification with **26** under Mitsunobu conditions resulted in the formation of the final resin-bound intermediate **27**, analogous to the solution-phase cyclization precursor (**28**, Scheme 4). The crucial intramolecular Stille coupling proceeded smoothly in the presence of a Pd^0 catalyst, releasing the protected natural product into solution. Acid-mediated removal of the MEM groups resulted in the isolation of zearalenone (**29**) in approximately 22% overall yield (from **21**). Once the optimal link to the resin support had been established (through **23**), the solid-phase reactions were carried out under very similar conditions to those in solution, although a greater reagent excess was generally employed.



Scheme 5. Synthesis of (*S*)-zearalenone according to Nicolaou et al.[14] AIBN = 2,2′-azobisisobutyronitrile, DEAD = diethyl azodicarboxylate, NCS = *N*-chlorosuccinimide, TBAF = tetra-*n*-butylammonium fluoride.

A Horner–Wadsworth–Emmons/cyclorelease strategy was employed by Nicolaou et al. in the synthesis of a racemic muscone library.[16] A novel phosphonate-functionalized resin (**30**, Scheme 6) was prepared by coupling $CH_3PO(OMe)Cl$ to Merrifield resin through a C_4 linker. The library of muscone analogues was generated very efficiently using standard combinatorial split-and-pool techniques where individual compounds were identified by radiofrequency tagging.[17] Thus groups of functionalized resin beads were enclosed in individual SMART microreactors (SMART = single or multiple addressable radiofrequency tag) which contained a semiconductor unit capable of storing radiofrequency information. Each microreactor was subjected to a unique series of reagents, and the synthetic history was recorded in the radiofrequency code. The first combinatorial step involved the treatment of methylphosphonate **30** with $nBuLi$ and a series of esters (**31**–**33**) to give β-oxophosphonates **34**. Another opportunity for diversity came in the olefin meta-



Scheme 6. Synthesis of muscone and a library of muscone analogues according to Nicolaou et al.[16] 18-c-6 = [18]crown-6.

thesis reaction with different alkenes to give alcohols **35**, where the olefin geometry was not controlled. Oxidation was followed by cyclization and release through an intramolecular Horner–Wadsworth–Emmons reaction, resulting in enones **36** in 35–65%. The synthesis was completed in solution by addition of cuprate and then hydrogenation to yield a series of saturated macrocycles including muscone itself (**37**). At any stage in the solid-phase synthesis, the progress of the reactions could be monitored by reaction of the intermediate phosphonate with benzaldehyde and potassium carbonate. This resulted in release of the intermediate from the polymer support, allowing full compound characterization.

The authors highlight the excellent purity obtained after cyclorelease. This is partly due to the fact that incomplete conversion and side reactions result in resin-bound compounds which are not capable of undergoing the cyclization/cleavage reaction. In addition, the environment of the polymer support has been reported to provide pseudo high dilution conditions in some cases, which may limit the formation of dimers and higher order macrocycles.[18]

The epothilones, a group of highly cytotoxic natural products, have stimulated intense interest in the synthetic community, resulting in total syntheses by Danishefsky, Nicolaou, Schinzer, Mulzer, and their co-workers.[19] The array of stereocenters, double bonds, and the macrocyclic ring makes the epothilones a demanding group of synthetic targets, even with the huge repertoire of reactions available to chemists today. To be able to synthesize such compounds on a resin support would represent a major achievement and would be a significant advance towards handling complex structures and carrying out sophisticated reactions in the solid phase.

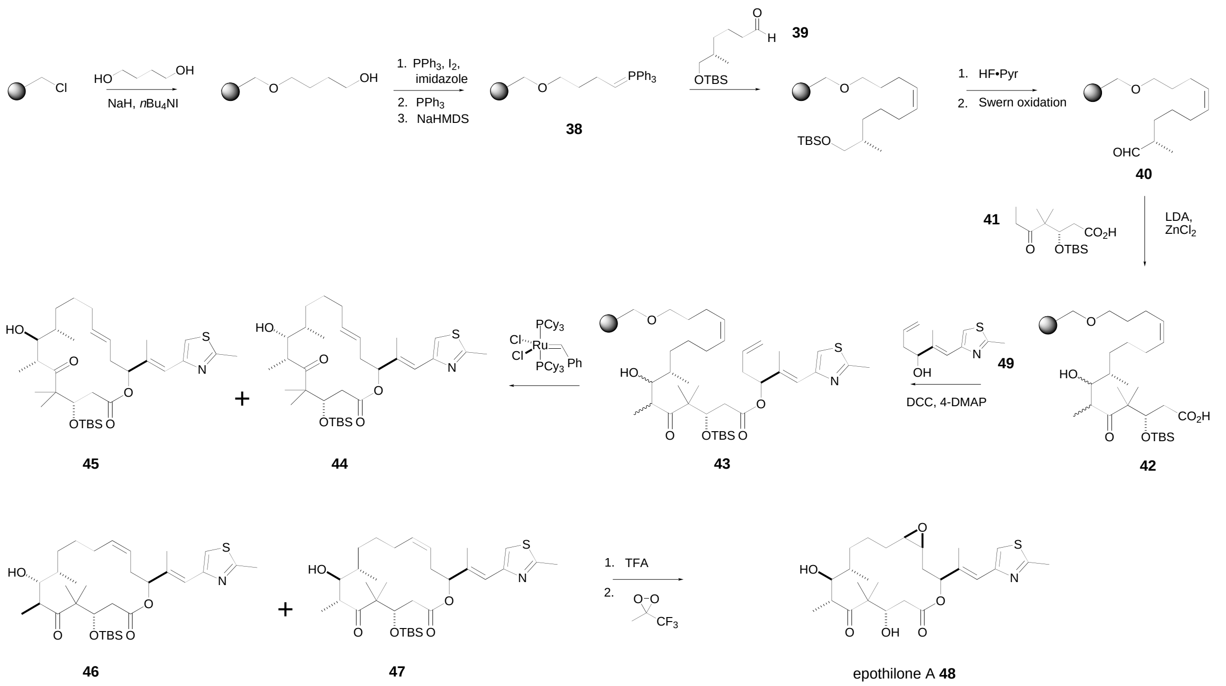
After completion of the solution synthesis of epothilone A,[19c] Nicolaou et al. aimed to simplify the generation of analogues for biological screening by means of a solid-phase approach through related synthetic intermediates.[20] The key step was the alkene metathesis/cyclorelease which would result in macrocyclic ring formation and cleavage from the solid support. The first olefin was incorporated through a Wittig reaction. Thus Merrifield resin with a C_4 linker was elaborated to phosphorane **38** by deprotonation of the corresponding phosphonium salt (Scheme 7). Reaction with aldehyde **39** yielded the desired olefin, one component of the metathesis reaction. Early introduction of this double bond aided monitoring of the solid-phase reactions, as treatment of the resin-bound intermediates with ozone resulted in release from the support, allowing standard solution analysis. The next stereocenter was incorporated by reaction of aldehyde **40** with the enolate derived from ketone **41**. The reaction was not stereoselective, and a mixture of compounds was formed (**42**). Acylation of this acid gave the complex intermediate **43**, the macrocyclization precursor. The metathesis reaction proceeded smoothly to release four compounds into solution (**44**–**47**) resulting from the unselective aldol reaction as well as a mixture of *cis* and *trans* olefins formed in the cyclization reaction. Compound **47** incorporated the correct stereochemistry and double bond geometry for epothilone A, and a two-step elaboration in solution resulted in isolation of the natural product (**48**).

Overall, the solution chemistry could readily be applied to the solid phase with few modifications; for example, the solid-phase acylation employed five equivalents of alcohol **49** versus two equivalents in the solution-phase reaction. Since excess reagents can simply be washed away after a polymer-supported reaction, this does not complicate purification; however, use of such a large excess of a complex intermediate becomes expensive in terms of both time and resources.

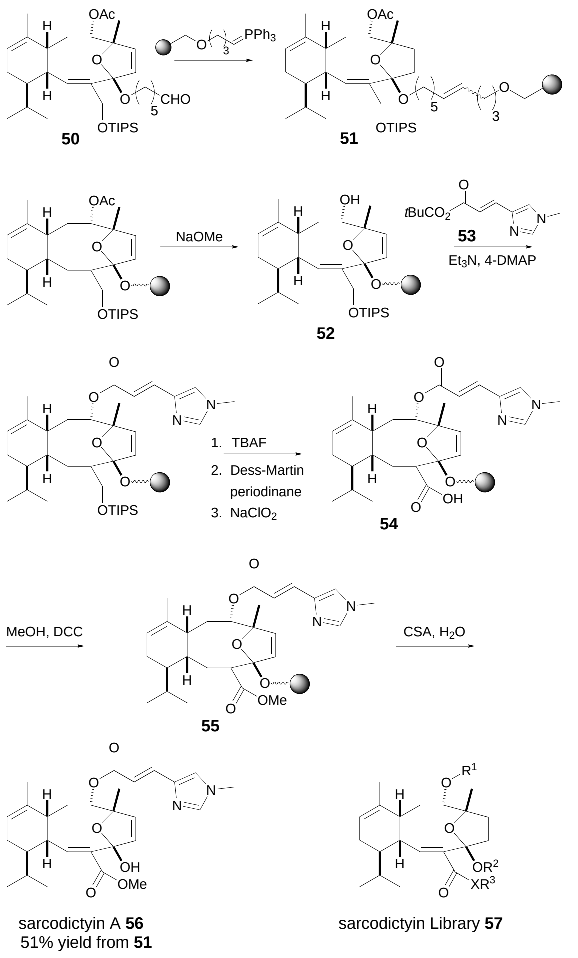
The convergent nature of this synthesis made it very amenable to the preparation of a library of epothilone analogues.[21] Thus simply varying the three key components (**39**, **41**, and **49**) would generate a large number of structures. Using split-and-pool methodology with the radiofrequency tagging system described previously, a 47-membered library was prepared through the reaction of a range of aldehydes, ethyl ketones, and heterocyclic alcohols.

Solid-Phase Synthesis of the Sarcodictyins

More recently, Nicolaou and co-workers were able to demonstrate the solid-phase synthesis of sarcodictyin A along with a library of analogues (Scheme 8).[22] Like the epothilones, this family of natural products has been the focus of substantial synthetic effort due to their potent cytotoxic



Scheme 7. Synthesis of epothilone A according to Nicolaou et al.[19c] DCC = 1,3-dicyclohexylcarbodiimide, LDA = lithium diisopropylamide, NaHMDS = sodium bis(trimethylsilyl)amide, TFA = trifluoroacetic acid.



Scheme 8. Synthesis of sarcodictyin A and a library of sarcodictyin analogues according to Nicolaou et al.[22] CSA = 10-camphorsulfonic acid, TIPS = triisopropylsilyl.

activity and the difficulty associated with isolating significant quantities from natural sources.[23] The approach to the solid-phase synthesis of sarcodictyin A started with attachment of advanced intermediate **50**, representing the core of the natural product, to a polystyrene support. After formation of **51** by a Wittig reaction, the acetate group was removed and the free alcohol (**52**) was acylated with mixed anhydride **53**. This would be the first opportunity for diversity in a sarcodictyin library. Conversion of the TIPS-protected primary alcohol into an acid led to the formation of **54**, which was esterified with methanol to form **55**. Again, the use of a range of nucleophiles at this stage would increase the number of possible library members. Finally, the natural product was released from the resin under acid conditions to give **56** in 51 % yield (from **51**). Further diversity could be generated in this final step by transketalization with different alcohols. This route was employed to prepare a 66-membered library of sarcodictyin analogues (**57**). It should be noted that in some cases low yields were observed for the acylation reaction used to incorporate the heterocyclic side chain, and these compounds had to be prepared in solution.

It is evident from this synthesis that there are still major limitations on the utility of solid-phase chemistry. Construction of the core of the sarcodictyins was arguably the most challenging and stimulating aspect of the reported solution syntheses. Solid-phase chemistry could only be used at a late stage, after the assembly of the core had been accomplished in solution.

Conclusions

Solid-phase chemistry has progressed significantly since the days of Merrifield and peptide synthesis, such that the synthesis of complex organic molecules on polymer supports is now a realistic goal. Of course enormous challenges still remain. The choice of resin and linker is crucial to the success of the synthesis, and new functionalized polymer supports would be a welcome addition to the solid-phase arsenal. One of the advantages of the liquid-phase approach reported by Janda is the ability to monitor reactions directly by NMR spectroscopy. The other syntheses required cleavage of intermediates before characterization, which takes considerable time and results in loss of material. Recent applications of magic angle spinning NMR spectroscopy and single-bead IR spectroscopy and mass spectrometry should simplify the characterization of resin-bound intermediates and accelerate the optimization of solid-phase reactions.[24]

The extension of solid-phase natural product synthesis to the generation of libraries of complex organic molecules is even more demanding. It seems unlikely at this stage that the high yields and reliability seen in peptide couplings could be achieved for the range of reactions required in non-oligomeric natural product synthesis, making the preparation of large libraries extremely difficult. However the work presented here demonstrates that small libraries can be prepared efficiently on the solid phase, even in the case of very complex structures, allowing the discovery of novel compounds with interesting and varying activity.

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