

synthesis of libraries of compounds that are based on an isostere that mimics the tetrahedral intermediate for peptide hydrolysis as catalyzed by the therapeutically important aspartic-acid class of proteases.

For each library synthesis project the synthesis approach is designed to achieve three goals: 1) Several different building-block sets should be incorporated to provide rapid access to a large number of diverse compounds. 2) The chemistry should be compatible with the display of as much functionality as possible including reactive functionality that is commonly found in drugs such as alcohols, phenols, indoles, carboxylic acids, amides, nitriles, nitro groups, and halides. 3) The building blocks used in the synthesis of the library should be commercially available or at least readily accessible to facilitate rapid library synthesis. A considerable number of synthesis methods are explored in order

to achieve these goals. Two main areas of focus are C–C-bond forming processes and linkage strategies for attaching compounds to the solid support. Some of the solid-phase chemistry that is developed is based upon analogous chemistry in solution; however, much of chemistry that is developed does not have a current solution-phase counterpart.

According to the above strategies and goals we have generated libraries of thousands to tens of thousands of compounds. Library synthesis is performed in a microtiter plate format either using the *Chiron Mimotope* pin method initially developed by *Geysen* for peptide epitope mapping or by analogous bead-based approaches. Evaluation of these compound libraries has led to the identification of numerous ligands to different receptor targets to serve as tools to probe receptor function. Selected examples include the identification

of benzodiazepine-based inhibitors of pp60^{src} tyrosine kinase, which is implicated in cancer, in collaboration with *Victor Levine* at the *M.D. Anderson Cancer Institute*, benzodiazepine-based ligands to DNA-binding autoantibodies implicated in the autoimmune disease systemic *lupus erythematosus* which are currently being evaluated in mouse models of the disease in collaboration with *Gary Glick* at the University of Michigan, and hydroxyethylamine isostere-based nonpeptide inhibitors of cathepsin D with low nanomolar *Ki* values.

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The Solid-Phase Part of Supported Small-Molecule Synthesis

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Abstract. The synthesis of small molecules on solid phase must not only address the vagaries of C–C-bond formation and functional-group manipulation, but must also take into account solid-support issues such as ‘point of attachment’, ‘resin compatibility’, ‘reagent accessibility’, and ‘product liberation’. Hence, the resin plays a vital role in the solid-phase venture and the polymer advantages can be summarized as reactions can be driven to completion by addition of excess solution-phase reagents, reaction products are ‘isolated’ by filtration and washing, and multiple-step synthesis terminating with a ‘selective’ liberation step can deliver essentially pure product. These issues, as well as a number of strategies for the preparation and functionalization of resin supports, are discussed.

Introduction

Adapting solution-phase organic reactions to solid-phase techniques is one of the important challenges embraced by the burgeoning field of small-molecule combinatorial chemistry. In a solid-phase arena, strategic synthetic planning must not only address the vagaries of C–C-bond formation and functional-group manipulation, but must also take into account solid-support issues such as ‘point of attachment’, ‘resin compatibility’, ‘reagent accessibility’, and ‘product liberation’.

The Polymer Advantage

The pioneering small-molecule solid-phase work of *Leznoff* [1] and the more recent efforts of many academic and industrial chemists [2] have established three principal synthetic advantages of solid-phase techniques (*i.e.*, the *polymer advantage*): *i*) many solid-phase reactions can be driven to completion by addition of excess solution-phase reagents (removed by filtration and washing), *ii*) solid-phase reaction products are ‘isolated’ by filtration and washing, and *iii*) multiple-step

synthesis terminating with a ‘selective’ liberation step can deliver essentially pure product.

Collectively, these advantages suggest that the solid-support can play a much broader role in solid-phase chemistry than merely that of an inert matrix. When appropriately designed, its implications can be far reaching and can elevate solid-phase techniques to exceptional synthetic advantage. Consider the *sequent-auxiliary* concept [3] outlined in *Scheme 1* where a polymer-bound chiral auxiliary (AUX) is called upon to mediate a diastereoselective C α -alkylation reaction in *Step 1* and a diastereoselective iodolactonization reaction in *Step 2*. Thus, in addition to embracing the *polymer advantage*, there is significantly improved synthetic economy and atom efficiency in that the chiral auxiliary is called upon to mediate two diastereoselective transformations, and the chiral auxiliary can be recovered by simple filtration.

To effect this strategy, C₂-symmetric pyrrolidine-based auxiliary **1** was attached to *Merrifield* resin (® = polystyrene) and the remaining OH group blocked by benzylation to give the pseudo-C₂-symmetric auxiliary **2**. AUX-Mediated C α -alkylation (93.5:6.5 diastereoselectivity) followed by AUX-mediated iodolactonization (>99:1 diastereoselectivity) delivered targeted lactone **4** (R = CH₃) essentially

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pure in 87% ee and liberated the amine-functionalized resin for reuse (filtration). The recovered resin could be re-subjected to the N-acylation/ α -alkylation/iodolactonization sequence repeatedly with no loss in chemical yield or stereoselectivity. Furthermore, *polymer advantage (i)* was nicely illustrated by α -alkylation of $\text{AUX}-\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$ (excess LDA, excess MeI) followed by iodolactonization to give **5** ($\text{R} = -\text{H}_3$) with none of the unmethylated lactone ($\text{R} = \text{H}$) detected [4]!

Combinatorial approaches, whether split-mix or array, uniquely require the assistance of *polymer advantage (ii)*.

Small-molecule combinatorial chemistry combines the potentially limitless diversity of synthetic organic reactions *and* the potentially limitless diversity of organic reagents in the search for targeted activity. However, discovery potential would be severely limited if a combinatorial approach remained saddled with the normal work-up and isolation techniques of solution-phase chemistry. Consider even our small demonstration library of 27 compounds prepared in a search for water-soluble antioxidants (*Scheme 2*) [5].

In this project, Merrifield resin ($\text{R} = \text{CH}_2\text{C}_6\text{H}_4$) was used to *O*-alkylate three different carboxylate salts giving resin **6**.

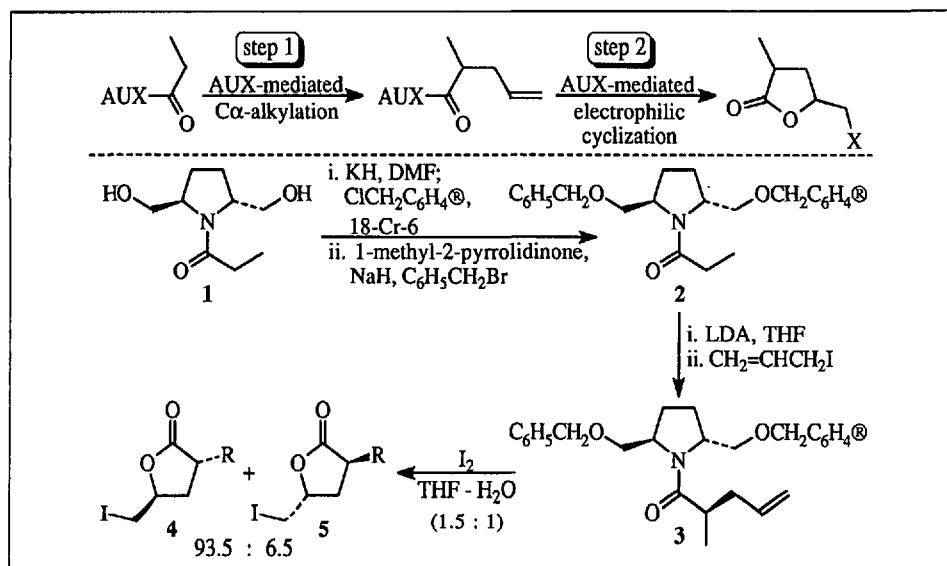
These three esters were mixed and the resulting resin divided into nine separate flask. Zinc-enolate formation followed by aldol condensation produced 27 aldol products of general structure **7**. The targeted 1,3-diols **8** were liberated from the polystyrene resin by ester reduction (diisobutylaluminum hydride (Dibal-M) proved to be superior to lithium aluminum hydride as the latter was plagued by significant retroaldolization) and a 96-well format colorimetric ferric thiocyanate assay was used in a deconvolutive assay of this antioxidant analogue library (27 component mixture) and sublibraries (three-component mixtures). This procedure identified **8*** as a novel water-soluble antioxidant.

Clearly, the scope of this antioxidant project with its preparation and evaluation of only 27 candidates could have been accomplished by normal solution-phase serial synthesis and single-compound assay. However, normal solution-phase serial synthesis would have required the isolation and purification of 30 synthetic intermediates plus the 27 final products; clearly a daunting task, especially if each of the 27 compounds required chromatographic purification. In contrast, this split-mix solid-phase synthetic approach required only resin filtration and washing to obtain the 30 intermediates and filtration/solvent evaporation to obtain the 27 products.

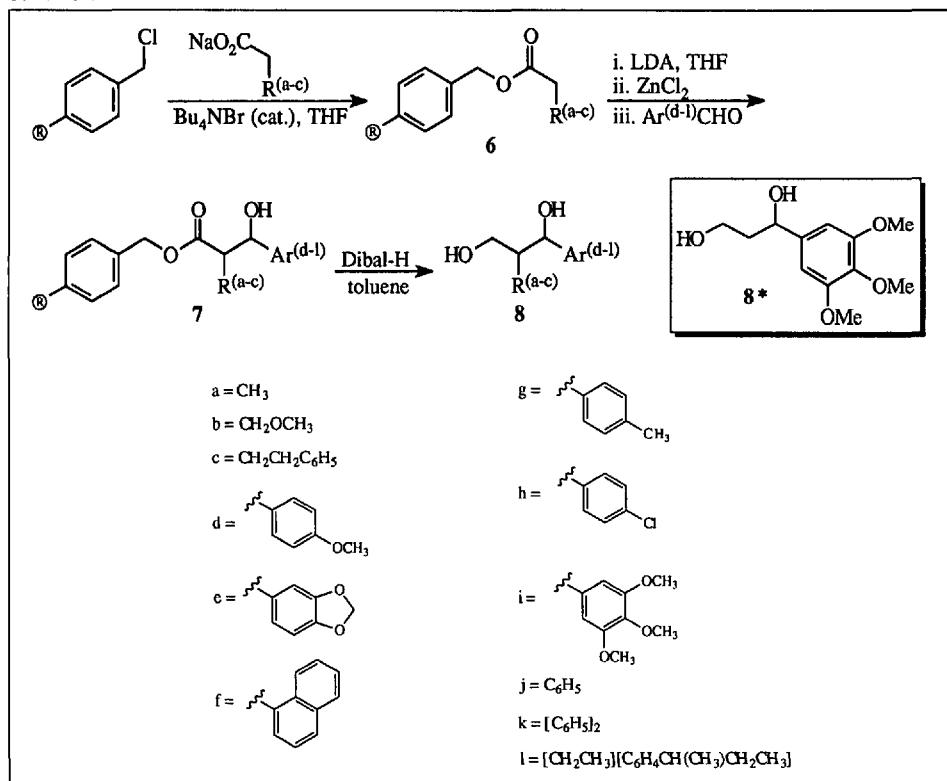
Polymer advantage (iii) can be of particular importance in planning a multiple-step solid-phase synthetic sequence. The three-step solution-phase route ($\text{R} = \text{CH}_3$) outlined in *Scheme 3* delivers cyclic ethers **12** and **13** in 43% overall yield as a 4:1 mixture of diastereoisomers, respectively [6]. Interestingly, the other product obtained in the reaction of heterocycle **11** with iodine monochloride is *p*-anisaldehyde. Several observations came from these solution-phase studies. First, we noted that the allylic stereogenic center is completely dominant (vis-a-vis the stereogenic center $C\beta$ to the nitro group) in directing the face selectivity of the 1,3-dipolar cycloaddition step. Second, we noted that electrophilic cyclization step **11** \rightarrow **12** + **13** is only moderately stereoselective under a wide variety conditions (**12**/**13** \leq 4:1). Third, we noted that the electrophilic cyclization step requires that the aryl group at $C\beta$ to the nitro group be electron-rich; when an unsubstituted phenyl ring was employed, no cyclization was observed. Finally, we noted that effective solution-phase conversion of **9** to **12**/**13** required isolation and chromatographic purification of intermediates **10** and **11**.

Scheme 4 outlines the preparation of

Scheme 1



Scheme 2



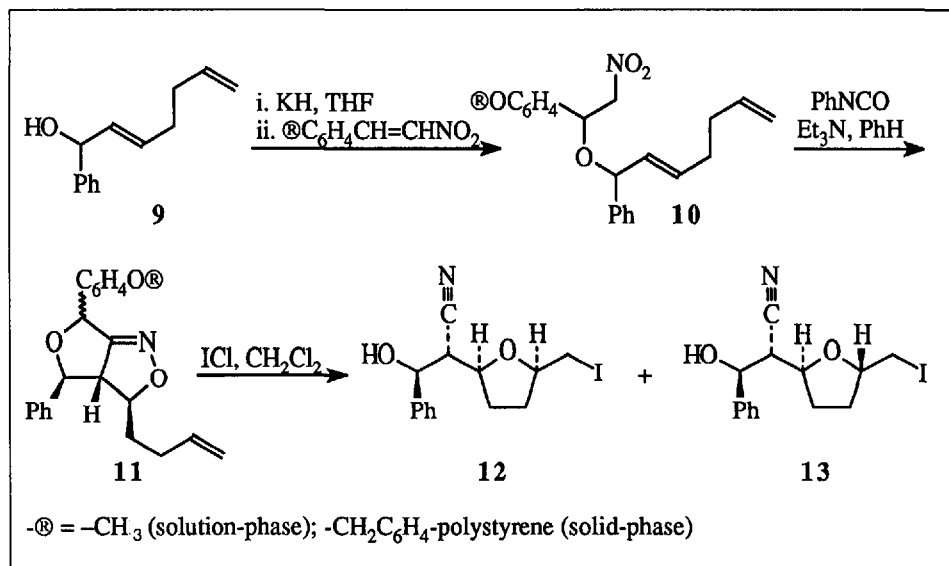
the resin required for the solid-phase version of this chemistry [7] and it is noteworthy that this approach allowed us to incorporate the requisite *p*-alkoxy group [8][9]. The solid-phase version of the chemistry in *Scheme 3* afforded two important advantages. First, the four solid-phase steps leading from **14** to **12/13** proceed in higher overall yield than the corresponding solution-phase steps (43% vs. 49%) and reaction manipulations are greatly simplified (filtration/washing vs. standard aq. work-up/chromatography). Second, the solid-phase electrophilic cyclization reaction liberates essentially pure product even after five linear steps with no purification! Why? Only substrates successfully undergoing this final transformation can be released into solution. Any unwanted side products remain resin-bound. For example, we often see small amounts of iodine-monochloride addition products as contaminants in the solution-phase electrophilic cyclization reaction. *Polymer advantage (iii)* circumvents these contaminants by 'selective' liberation of only product.

Having briefly reviewed the *polymer advantage* of solid-phase synthesis with examples from my laboratory (*Schemes 1–3*), one final point is noteworthy. Namely, product purity from solid-phase synthesis often seems to exceed that which would be anticipated based solely on overall product yield. For example, we undertook the chemistry outlined in *Scheme 5* to evaluate the applicability of multiple-step solid-phase synthesis to library preparation with a particular eye towards assessing the product purity of **19** (library of nine with R = CH₃, C(CH₃)₄, or C₆H₅ and Ar = C₆H₅, *p*-ClC₆H₄, or *p*-CH₃C₆H₄) [10]. While the overall yield of each compound was only 20–25% from the starting polymeric trityl chloride (five steps; *ca.* 75% yield per step), each crude sublibrary of three compounds – *i.e.*, the crude mixture obtained by formic-acid solvolysis of the trityl ether – gave a very clean capillary GC trace. In our experience, these results with *Wittig*- and *Michael*-based chemistry are not unique. We have come to conclude that overall chemical yield does not adequately reflect the product purity in these multiple-step solid-phase reaction sequences.

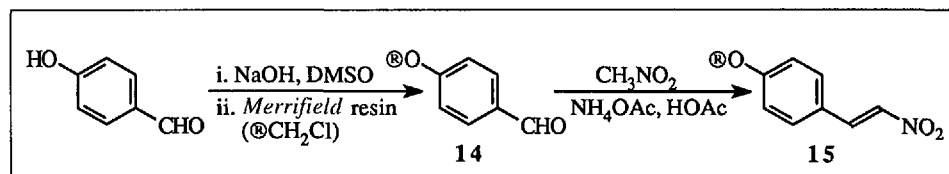
Functionalized Polymers

The synthetic routes outlined above were accomplished using a polystyrene/2% divinyl-benzene copolymer (see **20** in *Scheme 6*; ® = styrene monomer/© = di-

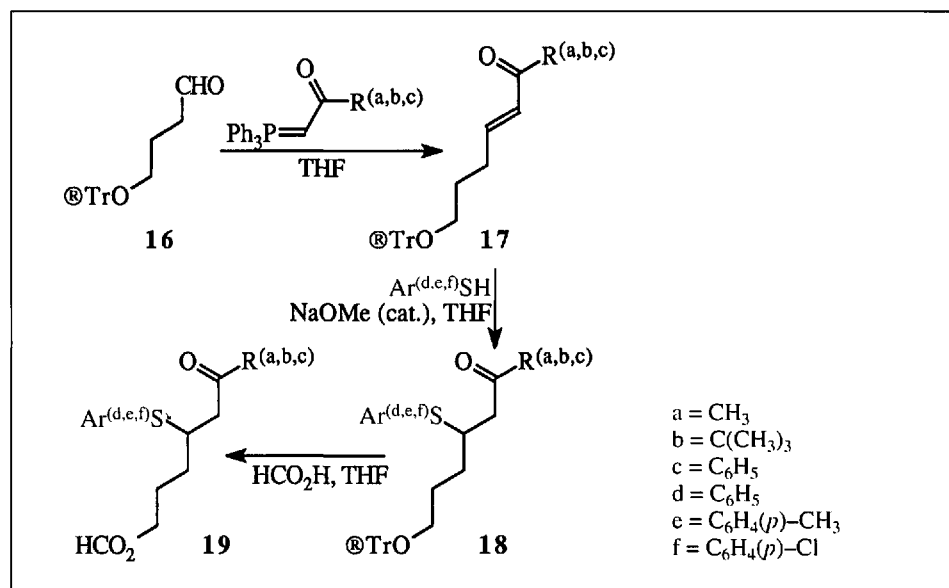
Scheme 3



Scheme 4



Scheme 5

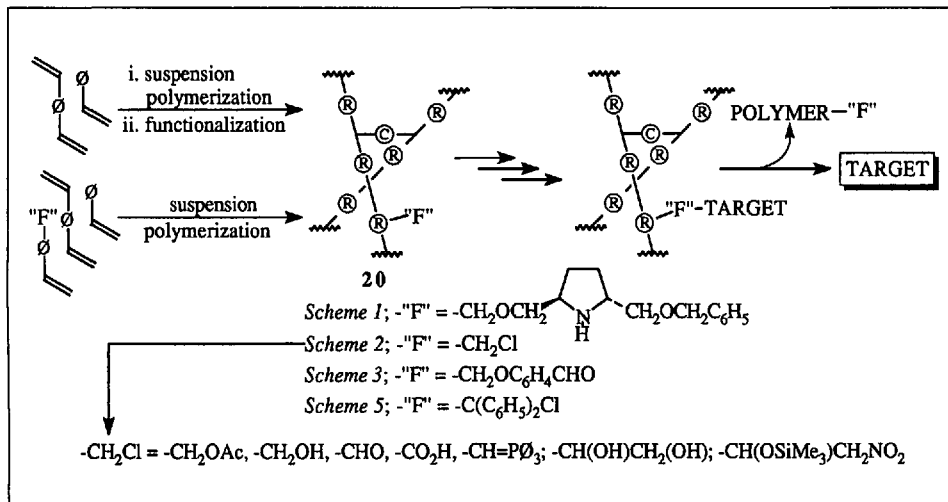


vinylbenzene monomer) as the solid-phase matrix. The cross-link density in these resins was 2% (*i.e.*, w/w ratio of ® to © being 98:2) and the functional-group loading (*i.e.*, F in **20**) varied from *ca.* 0.6 to 1.5 meq/g of resin. *Merrifield* resin (chloromethylated polystyrene/divinylbenzene copolymer; **20** where F = CH₂Cl) is a versatile starting point for a number of solid-phase reaction sequences and is prepared by one of two methods: *i*) suspension polymerization of styrene/divinylbenzene followed by chloromethylation

of the resulting resin or *ii*) suspension polymerization of styrene/divinylbenzene/(chloromethyl)styrene. The resins used in *Schemes 1–3* were prepared from *Merrifield* resin by nucleophilic displacement of chloride. In addition, we have prepared numerous other resins starting from *Merrifield* resin (see *Scheme 6* for a partial list).

The trityl resin used in *Scheme 5* has been prepared by two routes: *i*) random metalating the polystyrene/divinylbenzene copolymer with butyllithium followed by

Scheme 6



Scheme 7

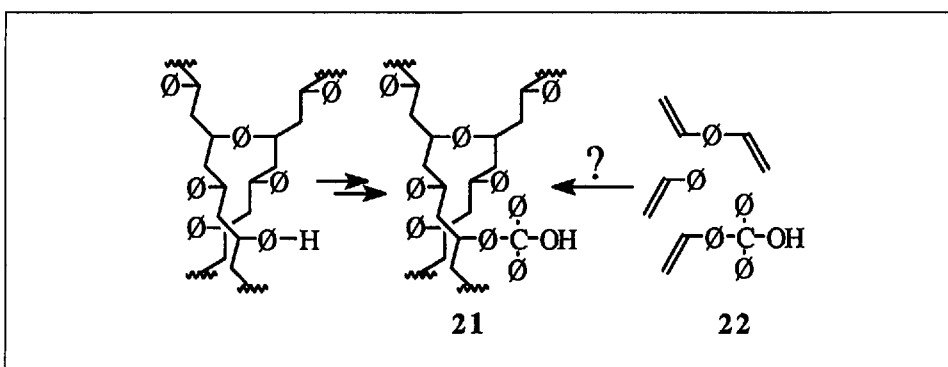
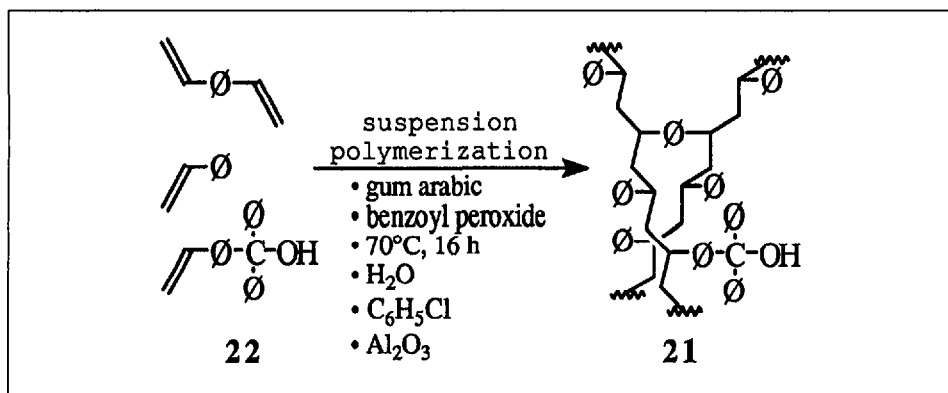


Fig. 1

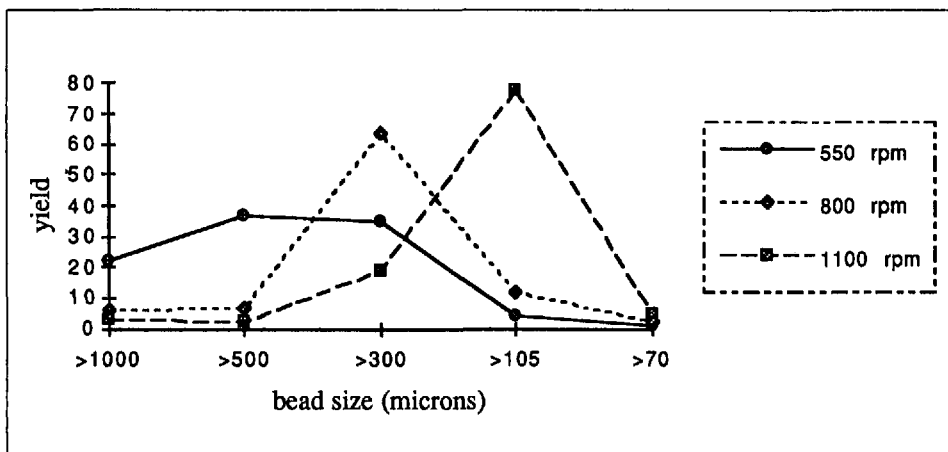


Fig. 2

quenching the resulting polymeric phenyllithium with benzophenone [11] and ii) *Friedel-Crafts* acylation of polystyrene/divinylbenzene copolymer with benzoyl chloride followed by addition of phenyllithium [12]. Subsequent trityl alcohol \rightarrow trityl chloride conversion was accomplished by treatment with refluxing acetyl chloride in benzene. In our hands, the former is the more reliable of the two methods.

An alternative route (see Fig. 1) to postfunctionalization of a preformed resin is copolymerization with a functionalized monomer. Two benefits of this approach are 1) it can afford more homogeneous functional group distribution (a consequence of comparable polymerization rates between the component monomers) and 2) predictable functional-group loading (a consequence of molar ratios of the component monomers). Postfunctionalization by direct metalation, on the other hand, is believed to result in more clustered functionality and affords less predictable loading. With this backdrop, our initial foray in the copolymerization arena targeted trityl-functionalized resin **21** from the monomers divinylbenzene, styrene, and trityl monomer **22** which was readily prepared by reductive metalation of 4-bromostyrene (*tert*-butyllithium, Et₂O) and quenching with benzophenone [13].

Suspension copolymerization was achieved through the dispersion of water-insoluble monomers in an aq. phase (typically there is little or no mass transfer between the aq./organic phases). Benzoyl peroxide, the radical initiator used in the preparation of **21**, was solubilized in the organic phase and promotes polymerization by thermally induced homolytic cleavage to yield radicals. Initiation, propagation, and termination steps proceed in each individual organic droplet. The aq. phase was charged with a stabilizer (a water-soluble polymer such as methyl cellulose, poly(vinyl alcohol), salts of poly(methacrylic acid), gum arabic; here gum arabic was used) which adsorbs on the surface of monomer droplets and suppresses droplet coalescence. Organic droplets were formed with agitation of the biphasic solution by rapid stirring (mechanical stirrer) during polymerization. While many factors influence suspension copolymerization, the geometry and shape of the polymerization flask and impeller have a pronounced effect on the quality and size distribution of the final resinous bead.

Suspension polymerization of **22** plus styrene cross-linked with 2% divinyl benzene was achieved by dissolving stabilizer in warm water in a three-necked *Morton*

flask; indentations force the suspended mixture in towards the rotating stir blade, thus ensuring a more homogeneous shearing environment for monomer droplets which results in more uniform droplet sizes. After the solution was deoxygenated with bubbling N_2 gas, the organic monomers were added and the impeller was lowered into the biphasic solution which was stirred at a constant rate. Next, the radical initiator was added and the flask was sealed with a condenser on one side neck and a rubber septum on the other. The polymerization flask was lowered into a 90° preheated oil bath and the system kept under a continuous flow of nitrogen for the duration of the polymerization. When polymerization was complete, the beads were collected and sized with *Teflon* screens.

We found, it was possible to target a specific range of bead sizes and tailor the polymerization process to obtain a preponderance of a particular bead size (see Fig. 2). We found that bead yield was ca. 90% for impeller speeds of 600–1000 rpm, but bead yield dropped at higher speeds due to shearing.

To synthesize 0.5 mmol/g trityl-functionalized resin, a 12.3:60.8:2.7 mass ratio of **22**/styrene/divinylbenzene was used. Polymerization at 700 rpm gave a bead yield of 79% and incorporation of monomer **22** was demonstrated by the presence of an OH absorption in the IR spectrum (KBr; 3463 cm^{-1}).

Bead swelling in organic solvents is important for efficient chemistry to occur on microporous solid supports as swelling allows for effective diffusion of solution-phase reagents to polymer-bound functionalities. Swelling data for resin **21**, relative to unfunctionalized polystyrene/divinylbenzene copolymer, is depicted in Fig. 3.

The resin prepared by suspension polymerization (**21**; Scheme 7) was employed in the serial synthesis of **26** as outlined in Scheme 8. Trityl-chloride resin **23** was prepared by refluxing **21** with acetyl chloride in benzene and the chloride content determined by titration (0.52 mmol/g). Butane-1,4-diol was attached to give **24** (IR: 3459 cm^{-1}) and excess diol was rigorously removed by *Soxhlet* extraction (24 h). Oxidation of the alcohol with the sulfur trioxide-pyridine reagent gave resin **25** (IR: 1724 cm^{-1}) which upon treatment with phenylmagnesium bromide and hydrolysis gave diol **26** in 32% overall yield from **21**. We were pleased to find that the resin recovered in **25** \rightarrow **26** could be reconverted to trityl-chloride resin **23** with a chloride content of 0.51 mmol/g.

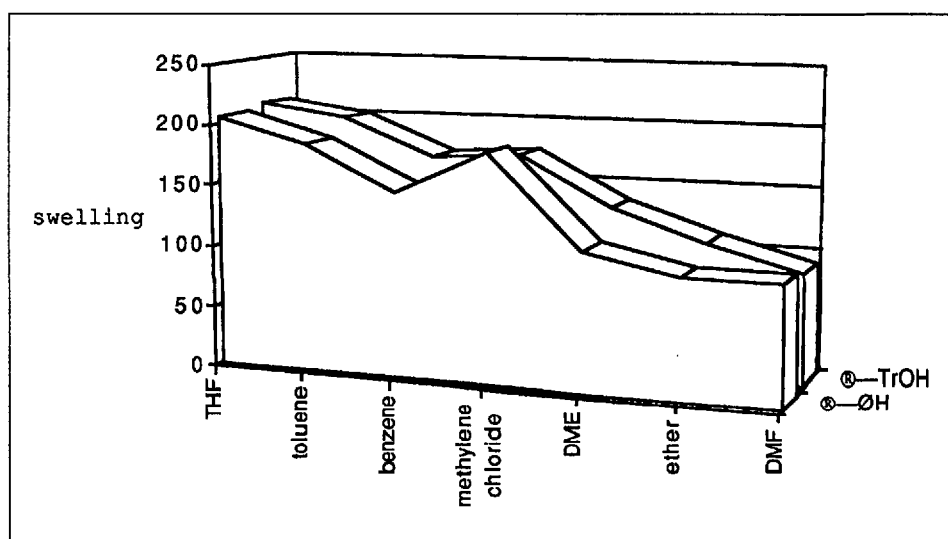
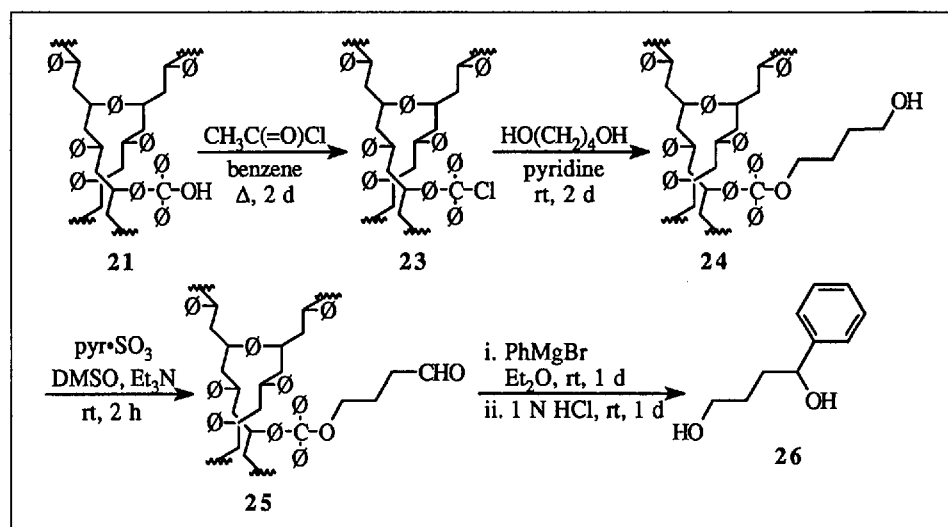
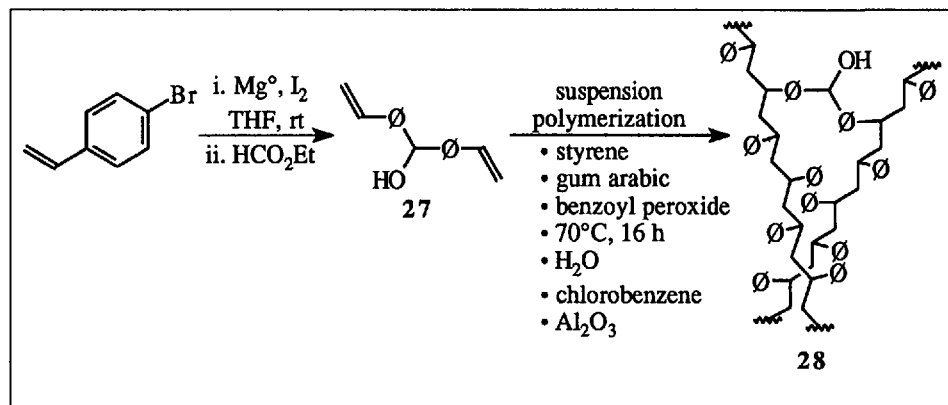


Fig. 3

Scheme 8



Scheme 9



It is clear from inspection of generalized resin **20** that the bulk monomer ($CH_2=CH_2$), the functionalized monomer ($CH_2=CH$ -F), and the cross-linking monomer ($CH_2=CH$ -CH=CH $_2$) are all subject to manipulation in a given suspension polymerization reaction. Thus, one of our objectives is to systematically

vary these components to probe the consequences in subsequent solid-phase synthetic applications. Monomer **27** (Scheme 9), a promising functionalized cross-linker, is easily prepared from the Grignard reactant of 4-bromostyrene and ethyl formate. Subsequent suspension copolymerization with styrene delivers resin **28**. The

synthetic potential of this type of resin is currently under investigation.

Conclusion

The potential of solid-phase organic chemistry is impressive and intriguing possibilities are rapidly unfolding in the development of combinatorial techniques, in the creation of synthetic sequences and reaction types, and in the discovery of novel resins and linkers. It is a privilege to participate in this unfolding.

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Consideration of Solid-Phase Synthesis with Reference to Quinolone Antibiotics

Alasdair A. MacDonald^{a)}*, Sheila H. DeWitt^{b)}, and Robert Ramage^{a)}

Abstract. The general utility of solid-phase synthesis for creating libraries of compounds will be discussed with particular reference paid to the development of a solid-phase organic synthetic route to quinolones. Using the DIVERSOMER[®] technology a library of quinolones have been prepared, purified and analyzed. Additionally, the issue of resin impurities and by-products will be discussed.

1. Introduction

1.1. Development of Solid-Phase Synthesis

The concept of solid-phase synthesis (SPS) was introduced by R.B. Merrifield in 1963 with the synthesis of a tetrapeptide [1]. Since then, solid-phase peptide syn-

thesis (SPPS) has rapidly progressed allowing for the automated synthesis of biologically active peptides of over a hundred amino acids. Oligonucleotide [2] and oligosaccharide [3] chemistry have similarly adopted solid-phase approaches. More recently, the synthesis of combinatorial compound libraries has utilized the methodology for solid-phase organic synthesis (SPOS) of small molecules [4]. Consistent with this trend, most of the top selling drugs on the market today are low-molecular weight (< 700 g/mol), heterocyclic based compounds [5].

1.2. Advantages of Solid-Phase Synthesis

The advantages of SPS over traditional solution-based methods are clearly evident. Most notably, excess reagents are readily tolerated by the solid support, which

typically increases reaction kinetics, and drives reactions to completion. No purification of reaction intermediates is required, with product isolation improved by washing away excess reagents from the solid support. In many cases resin-bound intermediates are generally more stable and easier to handle than the corresponding solution-phase analogues. Additionally, site isolation allows for selective attachment of a bifunctional compound to a solid support leaving the second active site free for further activation and derivatization. Finally, as successfully demonstrated by peptide and oligonucleotide chemistry, SPS is amenable to automation.

1.3. Solid Supports

A variety of polymers have been described for SPS, yet the literature related to polymeric supports is dominated by functionalized cross-linked polystyrene-divinylbenzene [6]. SPPS has largely used polystyrene-based solid supports for the synthesis of peptides and proteins. However, cross-linked polystyrene is highly hydrophobic and good resin swelling is only obtained in non-polar, aprotic solvents such as dichloromethane (DCM) and *N,N*-dimethylformamide (DMF), as demonstrated by Merrifield resin 1 (*Fig. 1*).

Polystyrene-poly(ethylene glycol) (PS-PEG[™]) graft copolymers have also been used in SPS [7]. More commonly referred to as Tentagel[®] 2 (*Fig. 1*) this polystyrene-based resin has a PEG spacer between the dense polystyrene network and the linker [8]. This creates a more hydrophilic solid support that provides an environment that more closely resembles solution-phase chemistries. Subsequently, Tentagel[®] resins are easily solvated in both polar and

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1.1. Development of Solid-Phase Synthesis

The concept of solid-phase synthesis (SPS) was introduced by R.B. Merrifield in 1963 with the synthesis of a tetrapeptide [1]. Since then, solid-phase peptide syn-

thesis (SPPS) has rapidly progressed allowing for the automated synthesis of biologically active peptides of over a hundred amino acids. Oligonucleotide [2] and oligosaccharide [3] chemistry have similarly adopted solid-phase approaches. More recently, the synthesis of combinatorial compound libraries has utilized the methodology for solid-phase organic synthesis (SPOS) of small molecules [4]. Consistent with this trend, most of the top selling drugs on the market today are low-molecular weight (< 700 g/mol), heterocyclic based compounds [5].

1.2. Advantages of Solid-Phase Synthesis

The advantages of SPS over traditional solution-based methods are clearly evident. Most notably, excess reagents are readily tolerated by the solid support, which

typically increases reaction kinetics, and drives reactions to completion. No purification of reaction intermediates is required, with product isolation improved by washing away excess reagents from the solid support. In many cases resin-bound intermediates are generally more stable and easier to handle than the corresponding solution-phase analogues. Additionally, site isolation allows for selective attachment of a bifunctional compound to a solid support leaving the second active site free for further activation and derivatization. Finally, as successfully demonstrated by peptide and oligonucleotide chemistry, SPS is amenable to automation.

1.3. Solid Supports

A variety of polymers have been described for SPS, yet the literature related to polymeric supports is dominated by functionalized cross-linked polystyrene-divinylbenzene [6]. SPPS has largely used polystyrene-based solid supports for the synthesis of peptides and proteins. However, cross-linked polystyrene is highly hydrophobic and good resin swelling is only obtained in non-polar, aprotic solvents such as dichloromethane (DCM) and *N,N*-dimethylformamide (DMF), as demonstrated by Merrifield resin 1 (Fig. 1).

Polystyrene-poly(ethylene glycol) (PS-PEG[™]) graft copolymers have also been used in SPS [7]. More commonly referred to as Tentagel[®] 2 (Fig. 1) this polystyrene-based resin has a PEG spacer between the dense polystyrene network and the linker [8]. This creates a more hydrophilic solid support that provides an environment that more closely resembles solution-phase chemistries. Subsequently, Tentagel[®] resins are easily solvated in both polar and

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