The Polymer-Supported and Combinatorial Synthesis of β-Lactam Compounds: An Update

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Abstract: Solid-phase organic synthesis (SPOS) has become an effective synthetic tool for the preparation of combinatorial libraries of non-oligomeric small molecules. Owing to their high efficacy and extremely safe toxicological profile, β-lactam antibiotics are the first choice for bacterial infectious diseases. Moreover, β-lactam compounds have also showed other biological activities that include inhibition of prostate specific antigen, thrombin, human cytomegalovirus protein, human leukocyte elastase and cholesterol absorption. Thus, the application of combinatorial and related methodologies to the chemistry of the β-lactam ring has been recognized as a very attractive challenge by different research groups around the world. This review covers the solid-phase and combinatorial chemistry related to mono-and multicyclic β-lactam compounds that has been reported in the literature from 1999 to 2004.

1. INTRODUCTION

Combinatorial chemistry and related parallel synthesis techniques have emerged as important tools for the discovery and development of new drugs, catalysts and materials [1]. In particular, solid-phase organic synthesis (SPOS) [2] has gained widespread acceptance in combinatorial chemistry related to drug discovery in order to accelerate lead generation and lead optimization. Building blocks and reagents can be added in excess in order to drive reactions to completion. Purification is facilitated by simple filtration, avoiding time-consuming separation techniques. Also, the "pseudo-dilution effect" [3], which is the result of using the polymeric solid support, makes intramolecular macrocyclizations a suitable process that could be carried out efficiently on solid-phase compared to solution phase where high dilution is generally required.

The β-lactam skeleton is the key structural element of the widely used penicillins, cephalosporins, thienamycins and other monocyclic β-lactam antibiotics [4] such as monobactams. The need for new antibiotics to overcome the rapid emergence of bacterial strains resistant associated to traditional antibiotics has maintained and even increased the interest in the chemistry of β-lactams [5]. Apart from their antibacterial properties, β-lactams also show biological activities that include inhibition of prostate specific antigen, thrombin, human cytomegalovirus protein, human leukocyte elastase, cholesterol absorption and cysteine protease [6]. Additional impetus has been provided by the introduction of the β-lactam synthon methodology [7], according to which enantiomerically pure β-lactams can be employed as useful intermediates for organic synthesis. The use of monocyclic β-lactams as a synthon for the synthesis of the side chain of taxol has solved a challenging problem in the synthesis of this compound from baccatin [8]. These compounds have also been regarded as peptidomimetics [9], which mimic certain aspects of proteins such as three-dimensional structure while conferring unique properties, such as enhanced stability to degradation or inhibition of normal peptide processing. Thus, new synthetic approaches of homochiral β-lactams could play a significant role in research efforts toward the enantioselective synthesis of β-lactams.

The application of combinatorial and related methodologies to the chemistry of the β-lactam ring is a very attractive challenge to modern medicinal chemistry, a fact that has been recognized by different research groups around the world.

This article updates our report [10] on solid phase and combinatorial synthesis of β-lactams.

2. MONOCYCLIC β-LACTAMS

2.1. Staudinger Reaction

Among the different strategies developed for the construction of the β-lactam ring, the Staudinger reaction [11] is the most frequently used and it is considered to be the most effective. The solid-phase version of the Staudinger reaction has been described for the preparation of polysubstituted β-lactams using different approaches [12]. Commercially available Fmoc-glycine tethered to Wang resin (**1**) was used as starting material (Scheme **1**) and then deprotected under standard conditions to obtain amine **2** that was condensed with an aldehyde (**3**) in 1% acetic acid in DMF according to the efficient methodology developed by Boyd [13] to give the imine **4**. The subsequent [2+2] cycloaddition with the ketene, obtained *in situ* from an acid chloride (**5**) in the presence of triethylamine. 10% Trifluoroacetic acid in dichloromethane demonstrated to be the most effective cleavage conditions: the β-lactam **7**, as its methyl ester, was obtained in good to very good yields for the five step synthetic sequence with exclusive formation of the *cis* isomer in all cases.

Asymmetric version using either chiral acid chlorides or chiral aldimines was also investigated. When using a ketene

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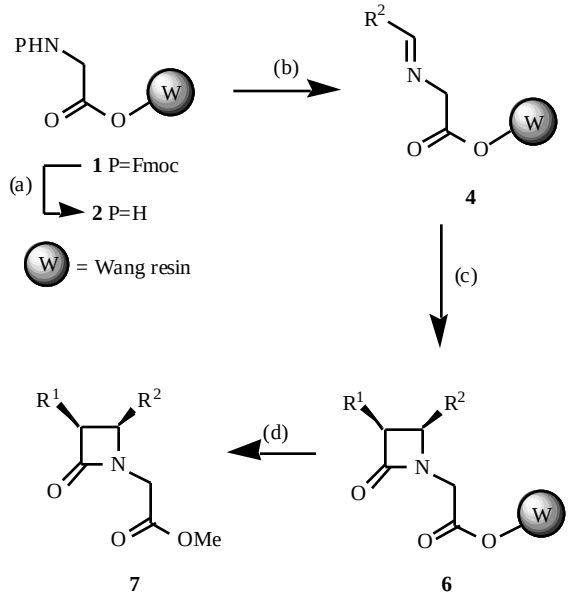
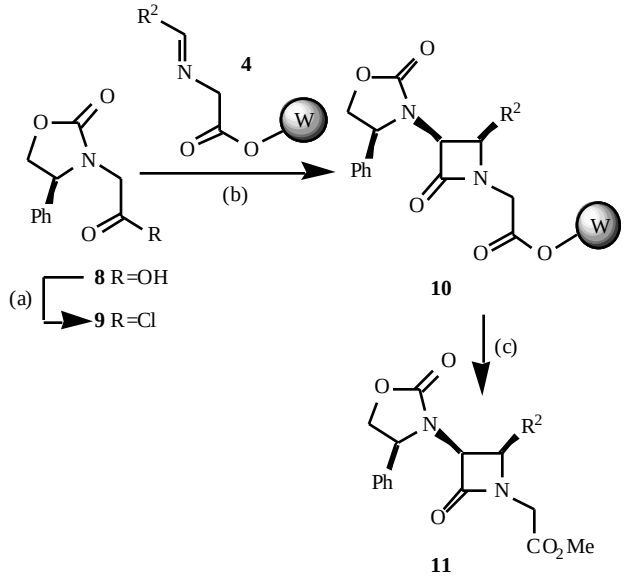
1389-5575/06 $50.00+.00

bearing a chiral oxazolidinone moiety, generated *in situ* from acid chloride **9**, good to very good overall yields of the β-lactam **11** were obtained, with diastereoselectivities ranging from 8:1 to greater than 25:1 (Scheme **2**) [12]. In the case of asymmetric induction from the imine component, different chiral aldehydes were condensed with resin-bound amines to give the corresponding chiral imines. The asymmetric Staudinger reaction of the resin-bound imines with achiral acid chlorides was accomplished with diastereoselectivities ranging from 2:1 to greater than 25:1.



Scheme 1. Reagents and conditions: (a) 30% piperidine in DMF. (b) R^2CHO (**3**) (5 equiv.), 1% v/v AcOH in DMF. (c) Et_3N (20 equiv.), R^1CH_2COCl (**5**) (15 equiv.), 0°C then r.t. overnight. (d) (i) 10% TFA in CH_2Cl_2. (ii) CH_2N_2.



Scheme 2. Reagents and conditions: (a) $(COCl)_2$, toluene, 3 h, 60°C. (b) CH_2Cl_2, Et_3N (20 equiv.), **9** (15 equiv.), 0°C then r.t. overnight. (c) (i) 10% TFA in CH_2Cl_2. (ii) CH_2N_2.

An interesting application of this methodology is the preparation of *trans* 3-alkyl β-lactams from nonactivated acid chlorides [14], these kinds of compounds are gaining interest as cholesterol absorption inhibitors (CAI). Nonactivated aliphatic acid chlorides, such as 5-phenylvaleroyl chloride (13), when used in excess, favor the formation of highly reactive acylketenes which react with the imine 12 to give the oxazinone 14 (Scheme **3**). Using a controlled excess of acid chloride this problem was avoided and the methodology was used for the rapid access to diverse *trans* 3-alkyl β-lactams (15) by solid-phase synthesis.

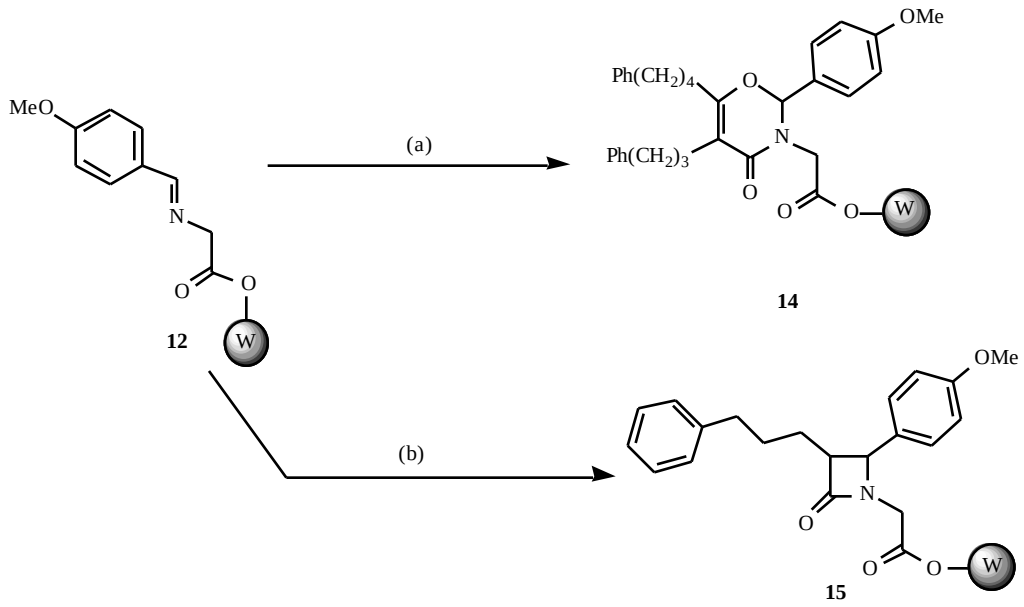
Also, the Staudinger cycloaddition using Mukaiyama's salt as dehydrating agent is a practical alternative to the use of acid chloride giving polisubstituted β-lactams in good to high yield and excellent diastereoselectivity when an oxazolidinone moiety is used as chiral auxiliary [15].

Solid-phase Staudinger reaction has been extended to the preparation of *N*-unsubstituted β-lactams. A new linker benzyloxyaniline has been developed to this end [16]. This is an acid stable linker that can be cleaved with Ceric Ammoniun Nitrate (CAN). TentaGel resin was selected as solid support for its better compatibility with the aqueous conditions required for CAN cleavage. Thus, *N*-unsubstituted β-lactams (**18**) were obtained in moderate to excellent yield (45-91%) (Scheme **4**). In a different approach, Banik *et al.* [17] have used Rink resin as support and the final detachment was achieved with 50% TFA in dichloromethane to give the *N*-unsubstituted β-lactams in good yield (61-68%).

Stella *et al.* have developed the solid-phase synthesis of a series of fluorine-containing-β-lactam compounds monitoring the whole process by ^{19}F NMR [18]. Interestingly, solid-phase synthesis of β-lactams was also amenable to scale-up. Raillard *et al.* [19] have prepared β-lactams using high-loading resin affording close to one gram of product per gram of resin. Higher reactant concentration can be employed, lowering the necessary stoichiometries without seriously compromising the final product yield and purity. According to the authors, high-loading Merrifield resins are attractive supports for developing fast scale-up on solid-phase: they offer a reduced resin costs and higher volume productivity (more product and less waste per gram of resin are produced), comparing with low-load resins.

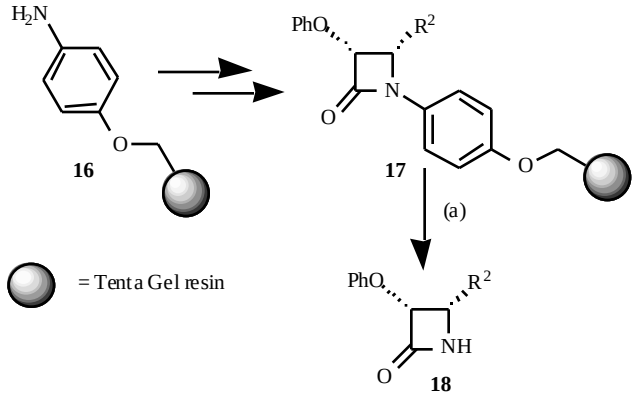
Despite of the dramatic growth of solid-phase organic synthesis in the last decade, research dealing with the development of new supports has been scare. One of the examples was the work by Janda devoted to the preparation of supports by parallel suspension polymerization [20]. Three polymerization variables were examined in this study: cross-linker structure, cross-link percent, and porogen. The porogen acts as an organic co-solvent and can affect the size of the micropores of the resulting resin. As much as 175 reactions were performed combinating seven cross-linkers, five cross-link percents, and five porogens. As result, cross-linker **21** showed good swelling properties (Scheme **5**). The resin **22**, derived from cross-linker **21** at 2 mol% with chlorobenzene as porogen, was prepared on a large scale and used for an explorative application to the synthesis of substituted β-lactams (**23**).

In recent years, soluble polymer methodology has emerged as an alternative route for library generation since it combines the positive aspects of both the traditional solution-phase synthesis and its solid-phase counterpart. However, the use of soluble supports has some drawbacks.



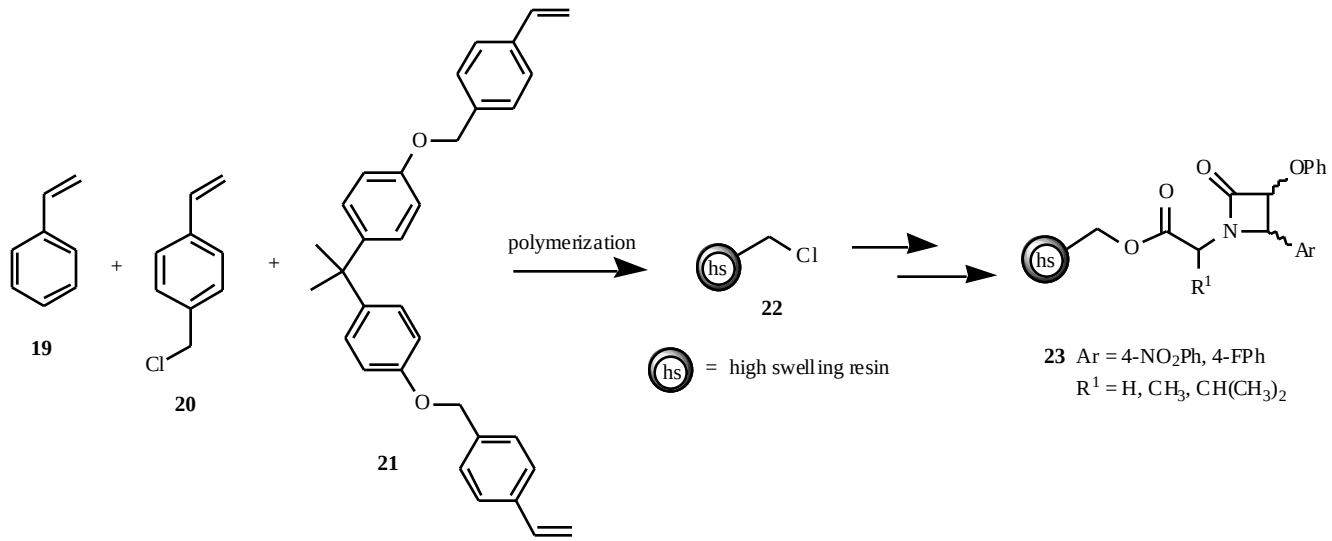
Scheme 3. Reagents and conditions: (a) $Ph(CH_2)_4COCl$ (**13**) (LARGE EXCESS), CH_2Cl_2, Et_3N. (b) $Ph(CH_2)_4COCl$ (**13**) (CONTROLLED EXCESS), CH_2Cl_2, Et_3N.

The major one is the low loading of the widely employed poly(ethylene glycol) monomethyl ether of MW 5000 (PEG_{5000}), typically 0.2 mmol/g. To overcome this problem, Cozzi *et al*. have developed a soluble PEG support of expanded functional group capacity by increasing the number of non-polymeric molecules that can be attached per PEG unit [21]. The synthetic sequence was initiated by loading dimethyl 5-hydroxyisophthalate (**25**) into a functionalized PEG_{4600} (**24**) to give the tetraester **26** (Scheme **6**). After a series of transformations, the tetraol **27** was obtained and further modified to the tetra-*N*-Boc glycinate **28**. The Boc protecting group was removed and the amine subsequently converted into the imine **29** by reaction with benzaldehyde. Classical Staudinger reaction using phenoxyacetyl chloride provided the tetra-β-lactam **30**, which was easily removed from the dendrimer-like soluble support by selective precipitation. Interestingly, tetraol **27** was recovered after cleavage and recycled.

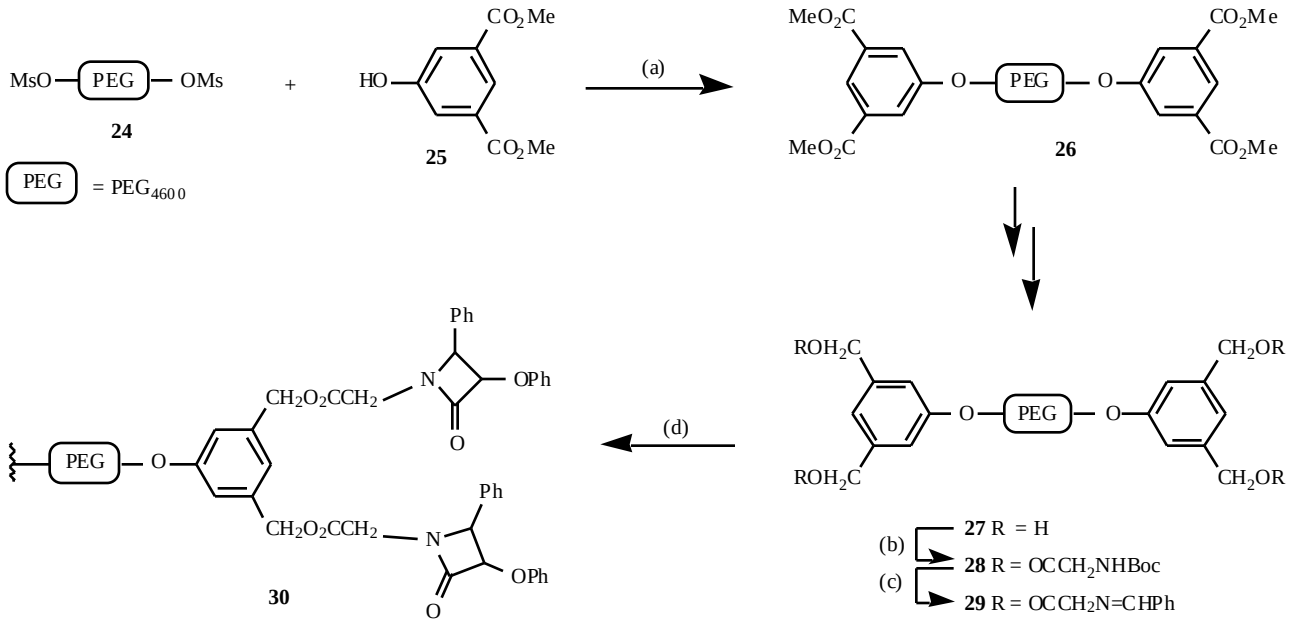


Scheme 4. Reagents and conditions: (a) CAN, $MeCN/H_2O$ (2:1).

In all of the previous examples, the imine was generated from a polymer-bound amine, but it may also be generated from polymer-bound aldehydes. This approach was explored



Scheme 5.



Scheme 6. Reagents and conditions: (a) Cs_2CO_3 in DMF, 50°C, 15h. (b) *N*-Boc glycine, DCC, DMAP (cat.), CH_2Cl_2, 40°, 5h. (c) (i) 2:1 TFA:CH_2Cl_2, r.t., 2h, then $NaHCO_3$. (ii) benzaldehyde (neat), 80°, 2h. (d) phenoxyacetyl chloride, Et_3N in CH_2N_2, r.t., 18h.

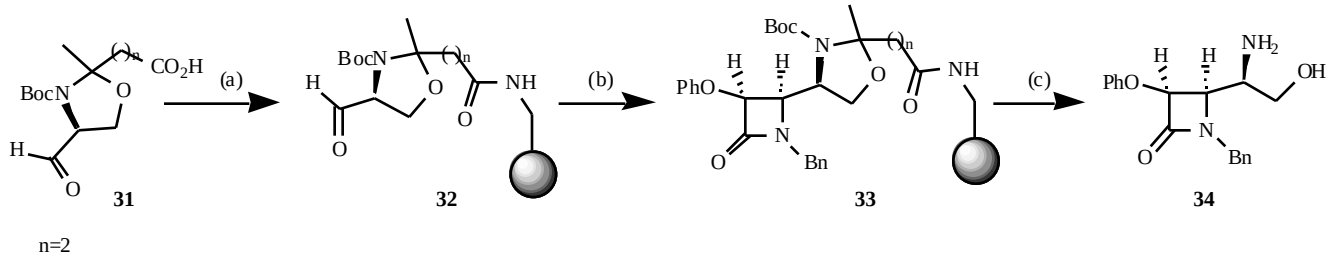
to achieve the synthesis of enantiomerically enriched β-lactams starting from a polymer-bound version of Garner's aldehyde [22] (Scheme **7**). Aldehyde linker **31** was made in solution and loaded onto an aminomethylated Merrifield resin to give the polymer-supported Garner's aldehyde **32** which was, in turn, transformed into the β-lactam **33**. Final cleavage of **33** with 10% TFA in DCM gave the chiral β-lactam **34** in high yield (75%) and optical rotation comparable with the literature value.

2.2. Enolate-Imine Condensation

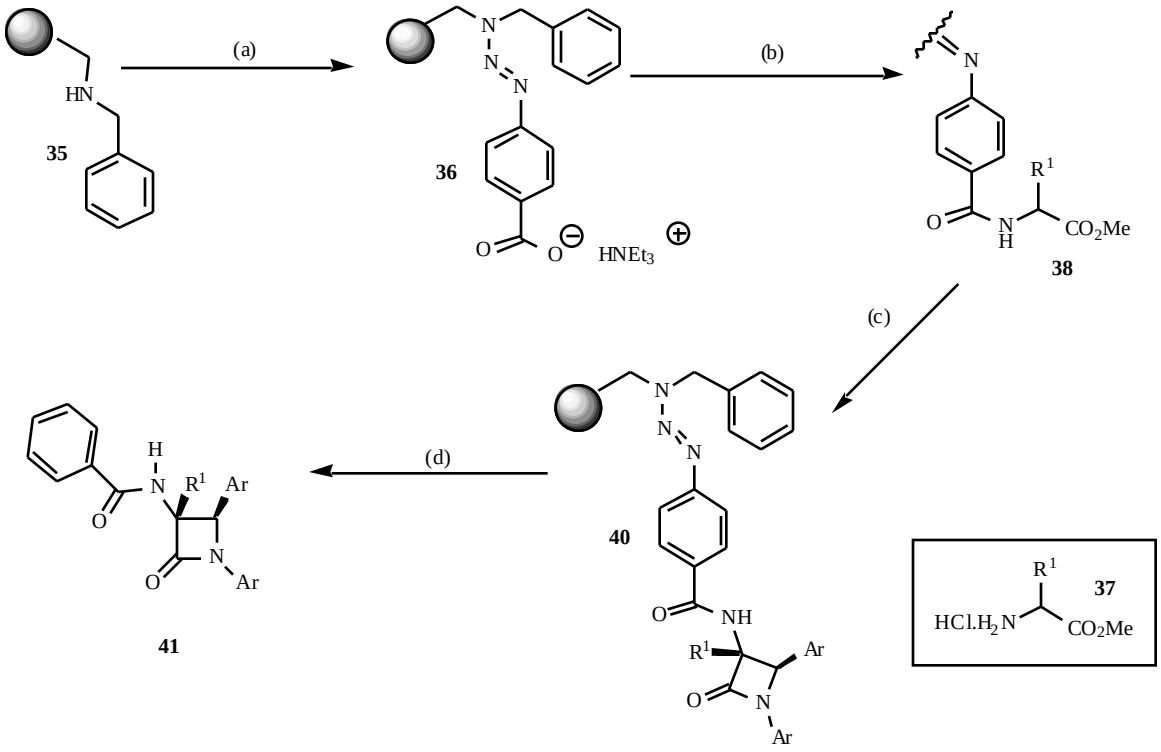
The enolate-imine condensation approach has been also used for the preparation of β-lactams on solid-phase. Enders *et al*. [23] have developed a methodology where the ester enolate immobilization was achieved *via* a triazene linker (Scheme **8**). Benzylamine resin **35** was treated with the respective diazonium salt to give the resin bound triazene **36**. Coupling the amino acid **37** by Mukaiyama's procedure led to the ester **38** which, in turn, gave the polymer-bound β-lactams **40** after treatment with base and the arylimine **39**. Traceless cleavage was accomplished by 5% trifluoroacetic acid followed by decomposition of the diazonium salt with THF/DMF at 60°C, to give the 1,4-bisaryl-β-lactams (**41**) in moderate to high yields (26-71%).

Recently, Wang *et al*. have described a protocol for the synthesis of *trans*-β-lactams using of poly(ethylene glycol) monomethyl ether (MPEGOH) as the soluble polymer support (Scheme **9**) [24]. The key step in this work was a Reformatsky-type reaction between imines **42** and carboxamide **43** where the generation of the *trans*-β-lactams (**44**) could be explained by the chair-like transition state (**45**) that involves the corresponding (Z)-enolate.

Dendritic polymers are a novel class of macromolecules characterized by a densely branched backbone and large number of reactive groups. They are currently receiving a great deal of attention as soluble supports. Using this methodology, a small library of β-lactams was prepared from a properly functionalized carbosilane dendrimer (Scheme **10**) [25]. A Me_2SiCl terminated carbosilane dendritic molecules, such as $Si[CH_2CH_2CH_2SiMe_2Cl]_4$ (**46**), was utilized as starting material and converted to the ester functionalized dendrimer (**47**) after several synthetic transformations. Deprotonation of **47** with LDA in THF in the presence of $ZnCl_2$ afforded the corresponding zinc-enolate (**48**) as the precursor for the enolate-imine condensation. Then, zinc-enolate functionalized dendrimer (**48**) reacted with the *N*-(trimethylsilyl)phenylimine to give the β-lactam **50**, with the simultaneous releasing from the carbosilane support (**49**). After hydrolysis and separation from the support by



Scheme 7. Reagents and conditions: (a) aminomethylated polystyrene resin, DIC, HOBt, CH_2Cl_2/DMF, r.t., 24h. (b) (i) $BnNH_2$, 4Å MS, CH_2Cl_2, r.t., 1 h. (ii) Et_3N, $PhOCH_2COCl$, 0°C to r.t. (c) 10% TFA/CH_2Cl_2, r.t., 1h.



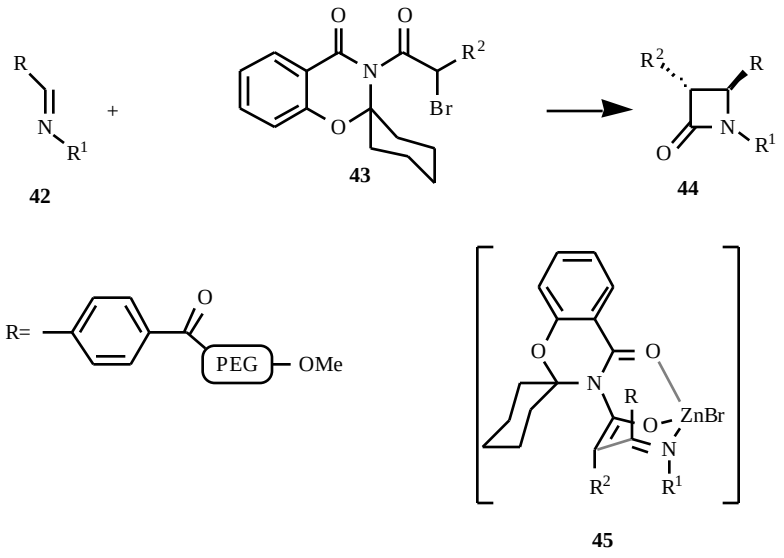
Scheme 8. Reagents and conditions: (a) (i) *p*-aminobenzoic acid, $BF_3.Et_2O$, *t*-BuONO. (ii) **35**, pyridine/DMF, Et_3N (b) **37**, Mukaiyama reagent, Et_3N. (c) (i) LiHMDS. (ii) ArCH=NAr (**39**). (d) (i) 5% TFA. (ii) THF/DMF 60°C.

preparative Gel Permeation Chromatography (GPC) techniques, β-lactam **51** was obtained with high *trans* selectivity (>95%) and yield (85%). In order to show the potential of this new methodology, a prototype, small (four-membered) combinatorial library of β-lactams was also prepared by combination of a dendrimer functionalized with two different esters, and two different imines.

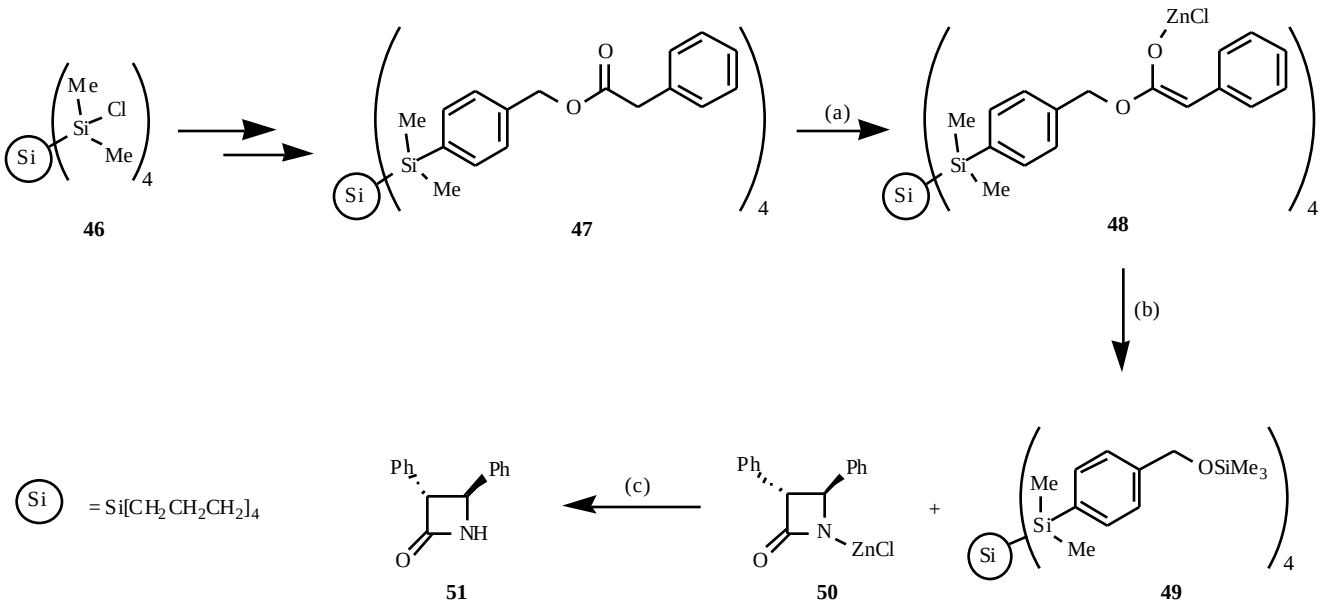
2.3. Cyclization Methods

Another approach that has been applied to the solid-phase synthesis of monocyclic β-lactams was the C_4-N_1 bond formation *via* the Miller hydroxamate. This strategy was used by Taddei *et al*. for the preparation of a series of *N*-unsubstituted-β-lactams [26] (Scheme **11**).

A polystyrene resin carrying a *O*-trityl-hydroxylamine linker (**52**) was coupled with L-Cbz-serine using (4,6-dimethoxy-[1,3,5]-triazin-2-yl)-4-methyl-morpholinium chloride (DMTMM) [27] as coupling agent. The hydroxamate **53** was then cyclized under Mitsunobu conditions to give the resin bound β-lactam **54**. The resin was treated with 5% TFA in CH_2Cl_2 for 3 h followed by quenching with triethylamine and aqueous work-up gave *N*-

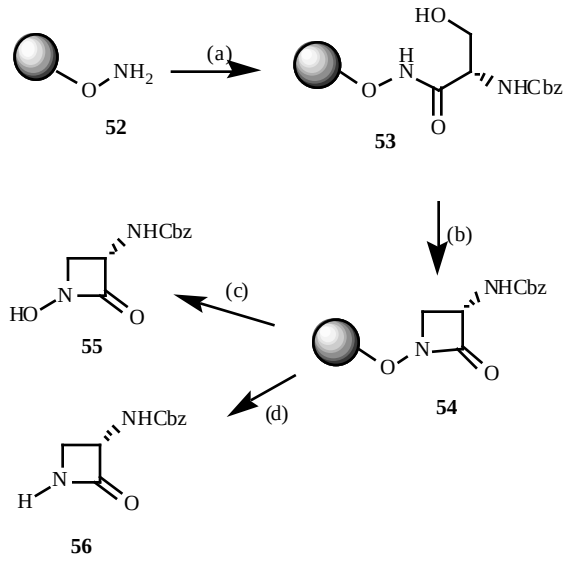


Scheme 9. Reagents and conditions: (a) Zinc powder, THF, reflux, 3h.



Scheme 10. Reagents and conditions: (a) LDA, THF, -70°C, $ZnCl_2$. (b) $PhCH=NSiMe_3$. -78°C, 1h, then r.t., 17h . (c) aqueous hydrolysis.

hydroxy-β-lactam (**55**) in modest yield (~35%). Alternatively, a reductive cleavage of **54** with a solution of SmI_2 in THF followed by hydrolytic work-up, gave *N*-unsubstituted-β-lactam (**56**) in acceptable overall yield (45 %).



Scheme 11. Reagents and conditions: (a) Cbz-Ser-OH, DMTMM. (b) DEAD, PPh_3. c) 5% TFA, then aqueous work-up. d) SmI_2 0.1 M in THF, then hydrolytic work-up.

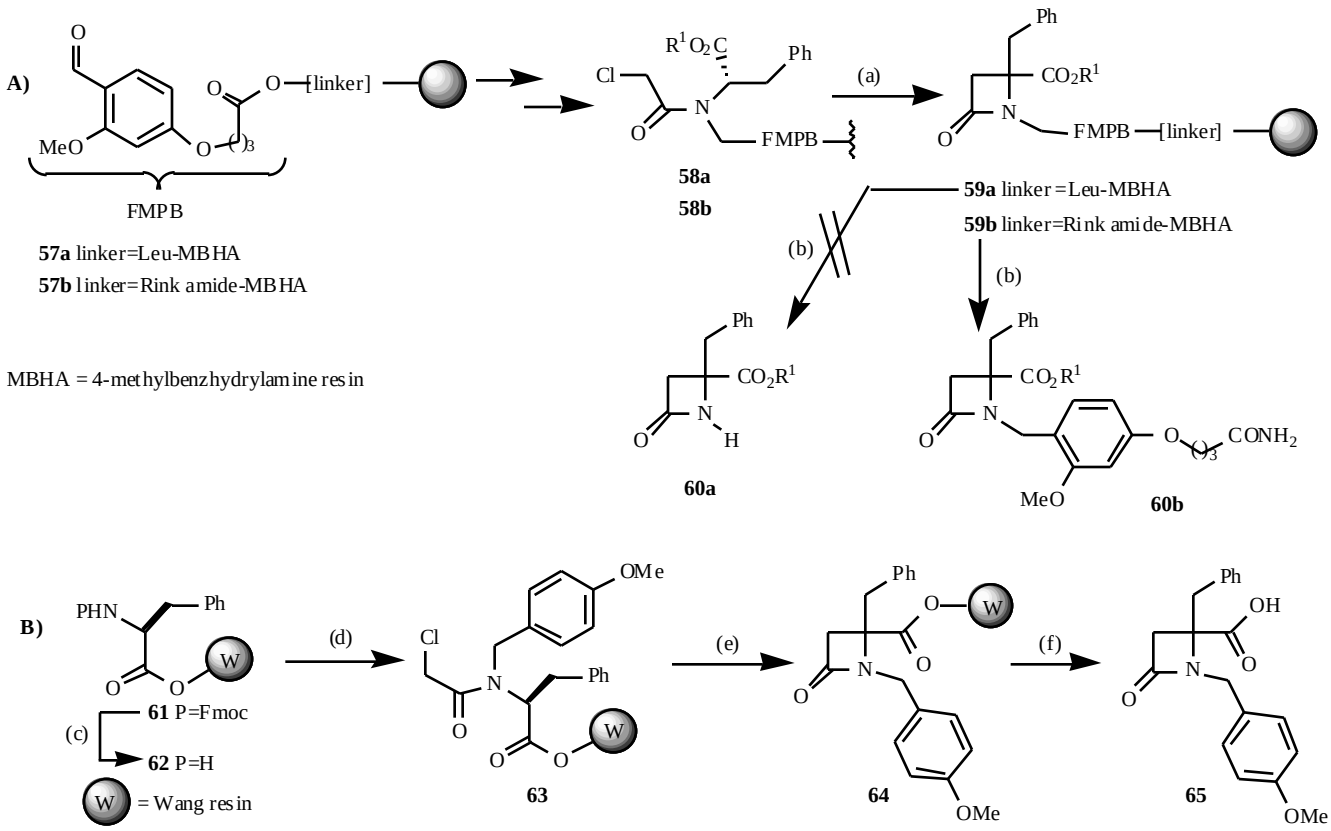
A novel solid-phase approach for the construction of the β-lactam ring has been recently developed by González-Muñiz *et al.* [28]. Two strategies involving a base-assisted intramolecular alkylation of *N*-chloroacetyl amino acid derivatives were described. The first strategy was designed for the synthesis of *N*-unsubstituted-β-lactams starting from a resin with a FMPB linker (**57a**) (Scheme **12A**). However, although cyclization with base BTPP [*tert*-butylimino-tri(pyrrolidino)phosphorane] gave the desired β-lactam **59a**, according to the MAS ^1H NMR, final cleavage to give *N*-unsubstituted-β-lactam (**60a**) was unsuccessful even in neat TFA. Only when the dual linker **57b**, a combination of Rink amide and the FMPB, was used the 1-substituted β-lactam **60b** was obtained as major product.

A second strategy, attaching the solid support through position 4 of the β-lactam ring, was achieved in a more efficient manner starting from Fmoc-Phe-Wang resin (**61**) (Scheme **12B**) [28]. After deprotection, condensation with anisaldehyde, reductive amination and acylation with chloroacetyl chloride, the polymer-supported precursor **63** was obtained. Cyclization was more efficient using BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,2,3-diazaphosphorine) as base and cleavage with TFA-H_2O (19:1) gave the 4,4-disubstituted-β-lactam **65** in good yield (60%) and purity (86 % by HPLC).

Multicomponent reactions (MCRs) are organic reactions in which three or more compounds react in a "single-pot" mode to give a durable scaffold structure with diverse substitution patterns. These features make MCRs particularly attractive for parallel combinatorial synthesis because large arrays of compounds can be prepared in one step, starting from readily available builing blocks [29]. Recently, Fülöp *et al*. have applied a variation of the Ugi four component reaction (U-4CR) to the solid-phase synthesis of bicyclic *cis*-azetidinones [30]. The Ugi reaction was carried out using resin-bound aldehydes such as **66**, isocyanides (**68**), and cyclic β-amino acids (**67**), that provide the carboxylic acid and amine functional groups (Scheme **13**). Acidic conditions necessary to remove Wang resin linker led to azetidinone ring hydrolysis (path a). Bicyclic β-lactams (**71**) were obtained using milder acidic conditions when Sasrin linker was used as support (path b).

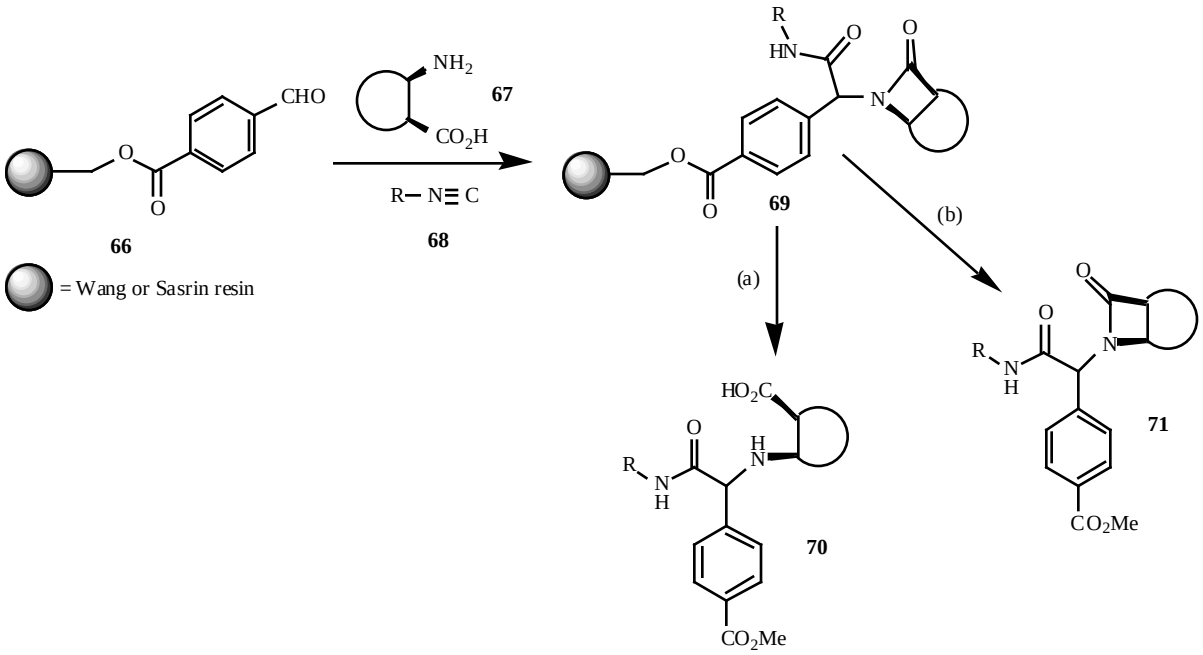
2.4. Polymer Supported Chemical Transformations on a Preformed Azetidinone Ring

Recently, a group from Bristol-Myers Squibb has developed SAR studies of azetidinones as tryptase inhibitors

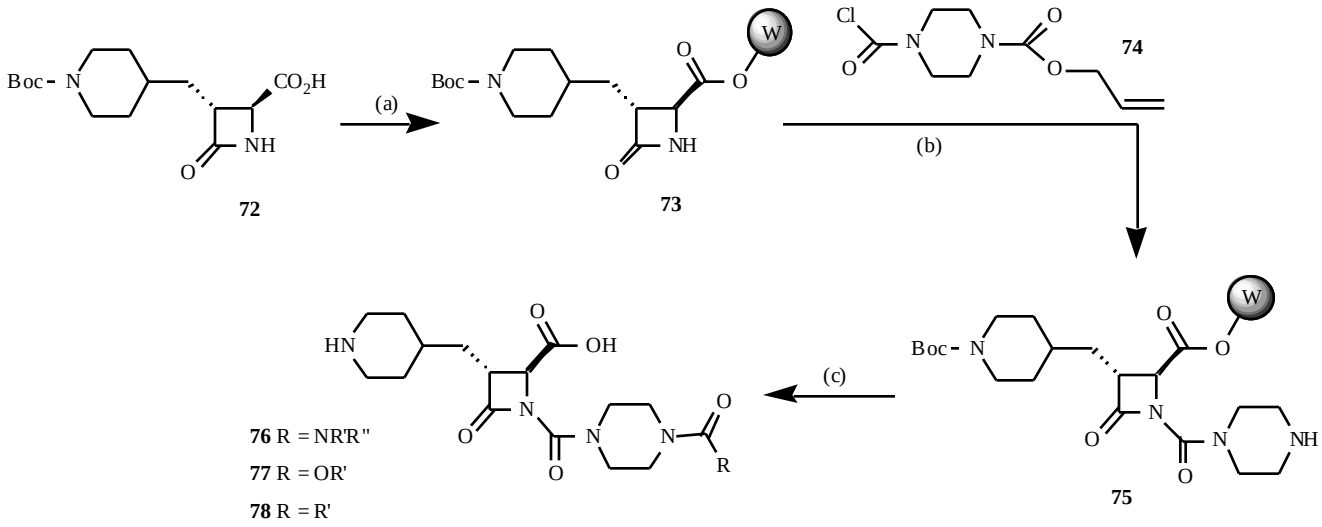


Scheme 12. Reagents and conditions: (a) BTPP,NMP, r.t., 15h. (b) TFA. (c) piperidine in DMF. (d) (i) $MeOC_6H_4CHO$, $(MeO)_3CH$, r.t., 6h. (ii) $NaBH_3CN$, $(MeO)_3CH$, AcOH (1%), r.t., 16h. (iii) $ClCH_2COCl$ in DMF, r.t., 4h. (e) BEMP, CH_2Cl_2, r.t., 15h. (f) TFA:H_2O (19:1), 4h.

[31]. In this approach, optically active (3*R*,4*S*)-4-carboxy-2-azetidinone **72** was immobilized to Wang resin to provide **73**, which was, in turn, *N*-acylated with the carbamoyl chloride of Alloc-piperazine (**74**), to give the activated resin-bound azetidinone **75** (Scheme **14**). After removal of Alloc protecting group, treatment of the amine with isocyanates, chloroformates and carboxylic acids gave the library of ureas **76**, carbamates **77** and amides **78**, that were used for SAR studies.



Scheme 13. Reagents and conditions: (a) For Wang resin: 10% TFA/CH_2Cl_2. (b) For Sasrin resin: 1% TFA/CH_2Cl_2, then CH_2N_2.

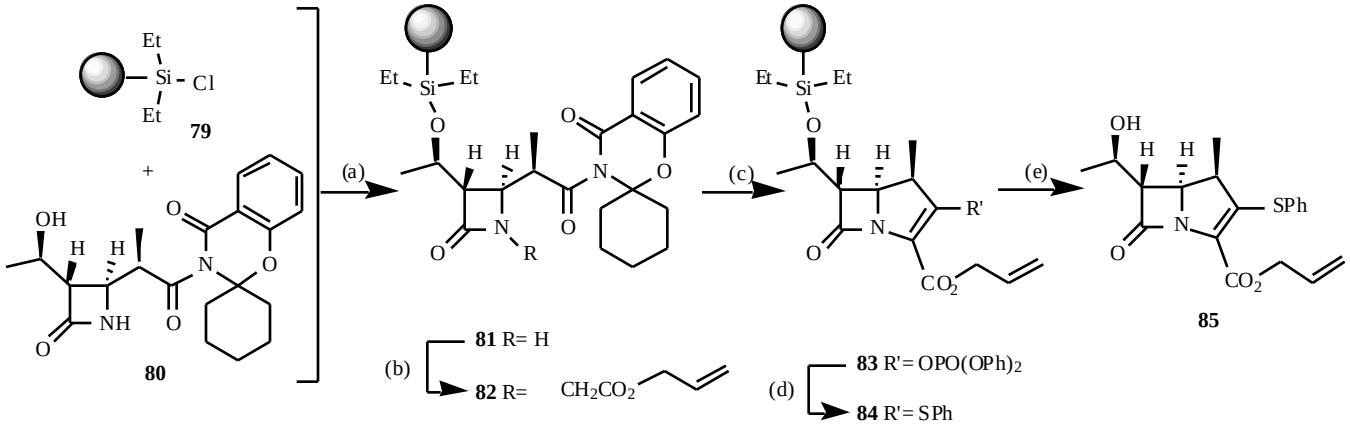


Scheme 14. Reagents and conditions: (a) Wang resin, MSNT (1-mesitylene-2-sulfonyl)-3-nitro-1*H*-1,2,4-triazole), *N*-methyl-imidazole. (b) (i) **74**, Et_3N, DMAP. (ii) $Pd(Ph_3P)_4$, $PhSiH_3$. (c) (i) isocyanate or chloroformate, Et_3N, DMAP or carboxylic acid, DIC, HOAt. (ii) 20% TFA.

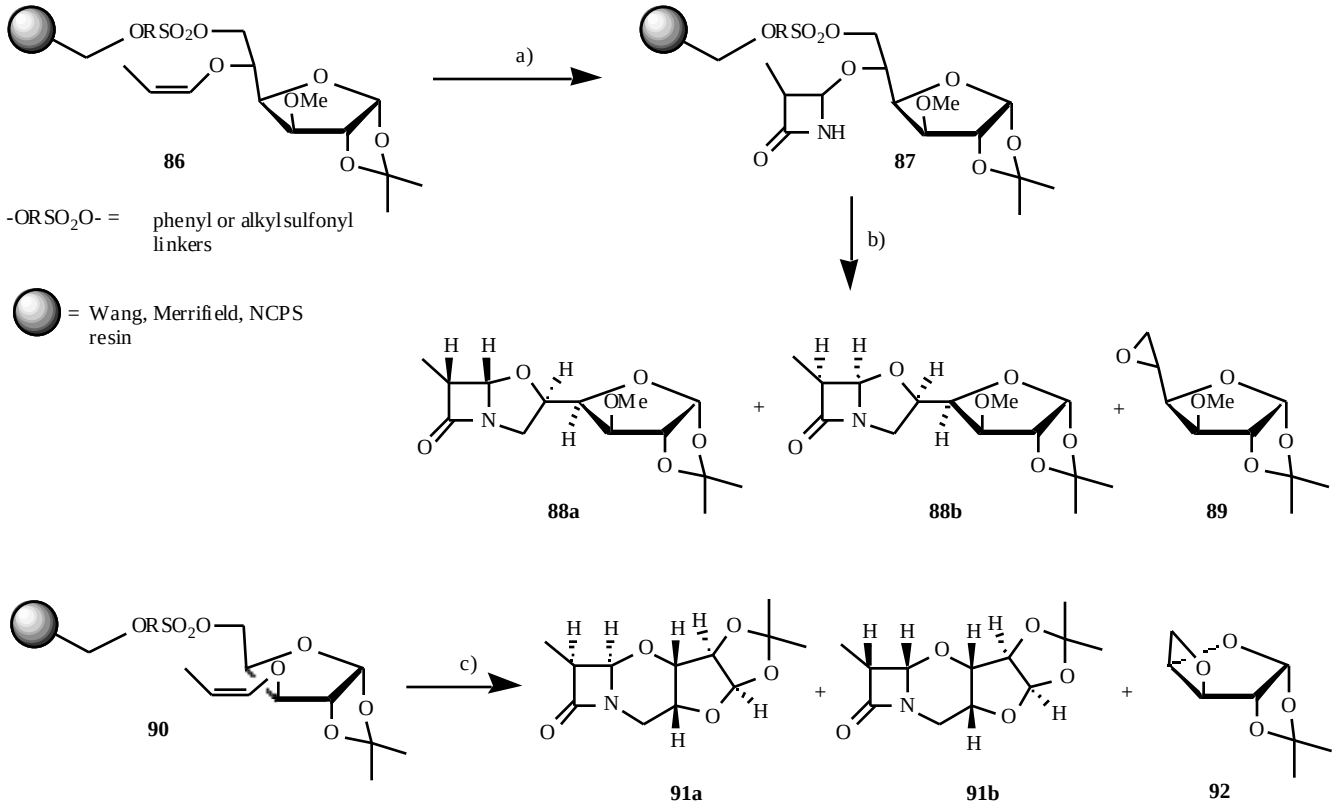
3. BICYCLIC β-LACTAMS

Bicyclic β-lactams include penicillins, cefalosporins, penems, carbapenems, carbacefems, oxacefems, clavams and other biologically interesting structures [4]. In a recent work, Wang *et al.* have described the synthesis of 1-β-methylcarbapenems involving the cyclization of the second ring on solid-phase but starting from a solution-phase preformed azetidinone [32]. In this approach the polystyrene-diethylsilane chloride resin (PS-DES) (**79**) was used for the immobilization of the starting chiral azetidinone **80** (Scheme **15**). After appropriate functionalization at N-1, the resin-bound azetidinone **82** underwent a Dieckmann-type cyclization to give the carbapenem **83**. Treatment with thiophenol gave the resin **84** and final cleavage was accomplished with TBAF-AcOH-THF to afford, after column chromatography, the 1-β-methylcarbapenem **85** in 32% overall yield.

Chmielewski *et. al.* have carried out a comprehensive study on the tandem [2+2] cycloaddition between chlorosulfonyl isocyanate (CSI) and polymer-supported vinyl ethers followed by a cyclization/cleavage to yield partially functionalized oxacephans and clavams [33]. Sulfonyl linkers were used to immobilize propenyl ethers of protected α-D-glucofuranose (**86**) (Scheme **16**). The addition of CSI to **86** provided, after removal of the chlorosulfonyl substituent, the expected *trans*-3,4-disubstituted azetidinone (**87**) as a mixture of diastereoisomers [34]. The cyclization/cleavage step was accomplished in the presence of strong organic bases, such as BEMP or DBU providing the clavams **88a,b** with low selectivity, and the oxirane **89**. A similar strategy using resin-bound propenyl ethers of α-D-xylofuranose (**90**) lead to oxacephams **91a,b** accompanied by the oxetane **92**. Different sulfonyl linkers and supports were used to immobilize propenyl ethers in order to improve selectivity and yield, although they were mostly unsuccessful. However, when the second generation soluble polymer noncrosslinked chloromethylated polystyrene (NCPS) [35] was used, the sequence proceeds similarly to that carried out in solution [36].



Scheme 15. Reagents and conditions: (a) imidazole, CH_2Cl_2, r.t. (b) allyl bromoacetate, NaHMDS, THF, -50°C then r.t. (c) (i) NaHMDS, THF, -20°C. (ii) TMSCl, -20°C. (iii) diphenyl phosphorochloridate (DPPC), -20°C then r.t. (d) PhSH, THF-MeCN, r.t. (e) TBAF-AcOH-THF, r.t.



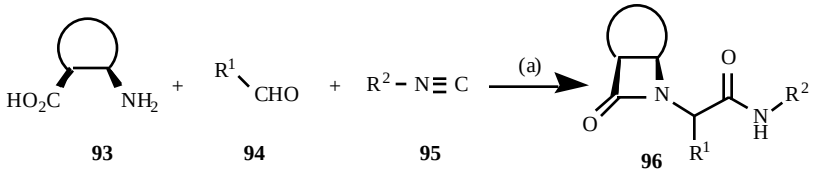
Scheme 16. Reagents and conditions: (a) (i). CSI, Na_2CO_3, CH_2Cl_2/toluene, -78 to -30°C, 2 h. (ii). Red-Al. (b) BEMP or DBU, CH_3CN, 1.5 h. (c) (i) CSI, Na_2CO_3. (ii). Red-Al. (iii) BEMP or DBU.

4. LIQUID-PHASE COMBINATORIAL SYNTHESIS

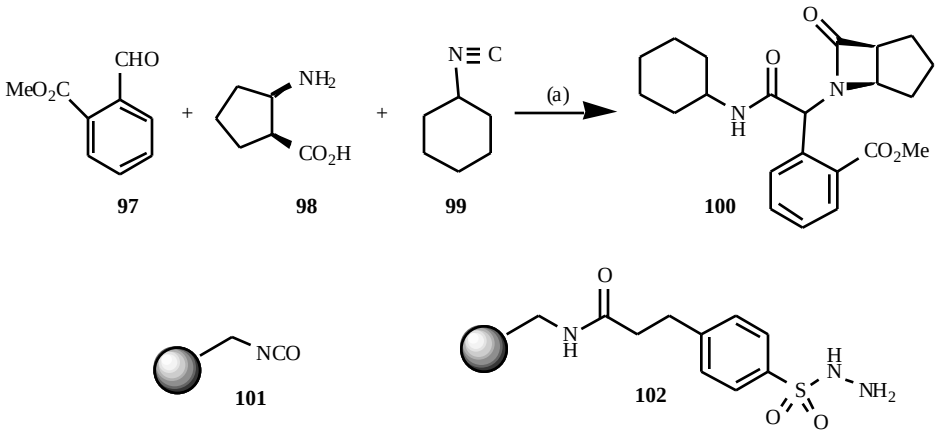
In recent years, a series of solution-phase combinatorial approaches have become of interest as an alternative drug discovery avenue for the generation of chemical libraries [37]. In this sense, the Ugi four-center three-component reaction was used for a parallel liquid-phase synthesis of bicyclic β-lactams [38]. The reaction was performed by using cyclic β-amino acids (**93**), aldehydes (**94**) and isocyanides (**95**) (Scheme **17**). As expected, *trans* β-amino acids failed to give the corresponding *trans* β-lactams because of the ring strain. Nine different bicyclic *cis* β-lactams (**96**) were obtained in moderate to good yields by stirring the mixture in methanol at room temperature for 24 h. Using this approach, a small (six-membered) mixture-based combinatorial library was also generated. Two cyclic β-amino acids, three aldehydes and one isocyanide were combined to give a library where all of the six products were present in the mixture.

The use of polymer-supported reagents and scavengers provides an attractive and practical method for the development of solution-phase parallel synthesis [39]. Polymer-supported scavengers are reactive species linked to a support material that quench or sequester by-products of the reaction or remove excess starting materials and may be removed by filtration. Bicyclic β-lactam **100** was synthetized by solution-phase chemistry using resin scavengers [30]. 2-Aminocyclopentanecarboxylic acid (**98**) and cyclohexyl isocyanide (**99**) were added to methyl 2-formylbenzoate (**97**) in MeOH and stirred for 24 h (Scheme **18**). Unreacted excess of amine **98** was removed by addition of polymer-bound isocyanate (**101**), followed by removal of the excess of aldehyde **97** by adding the polymer-bound *p*-toluenesulfonyl hydrazide (**102**). β-Lactam **100** was then obtained in 66% yield and 94% purity by HLPC.

Recently, the use of a polymer-supported Mukaiyama reagent has been described for the preparation of β-lactams in solution [40]. The β-lactams **106** were obtained by generating the ketene from a carboxylic acid **104** with the modified Mukaiyama reagent **103** followed by reaction with the imine **105** (Scheme **19**). To achieve acceptable yields, the reaction had to be performed under sonication with excess of the imine (2 equivalents). At the end of the reaction, the excess of the imine was removed by reduction with sodium borohydride followed by acid scavenging; the

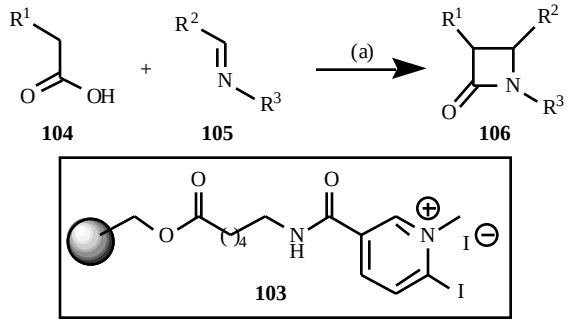


Scheme 17. Reagents and conditions: (a) MeOH, r.t., 24 h.



Scheme 18. Reagents and conditions: (a) MeOH, r.t., 24 h, then scavengers **101** and **102** were added for purification of crude mixture.

resulted crude product was then purified by crystallization or short column chromatography. Using this protocol, different 1,3,4-trisubstituted β-lactams (**106**) were obtained in yields ranged from 62 to 88%.



Scheme 19. Reagents and conditions: (a) **103**, Et_3N, CH_2Cl_2, sonication.

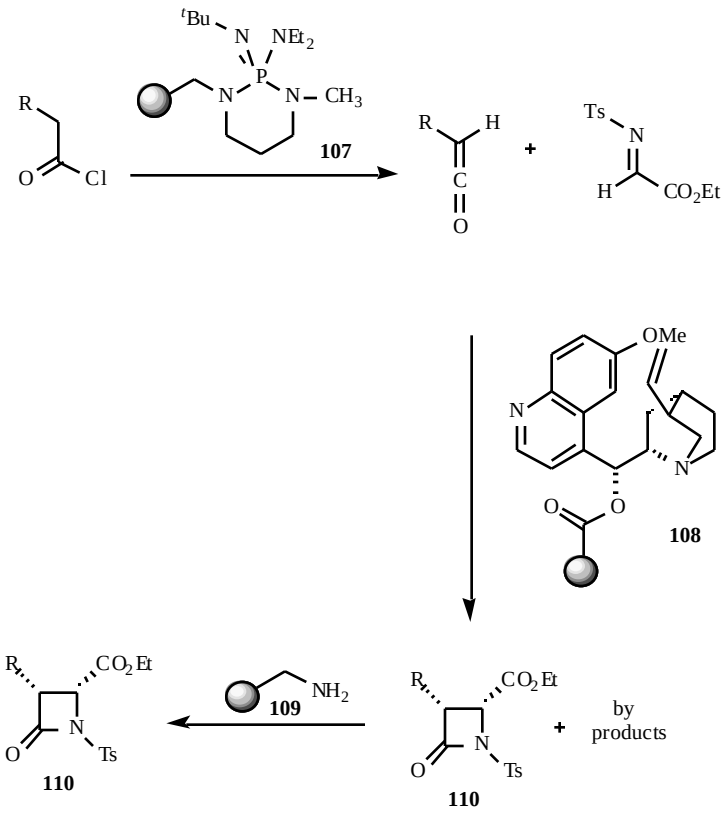
5. SEQUENTIAL COLUMN ASYMMETRIC CATALYSIS OF β-LACTAMS

One of the most interesting technological advances in synthetic chemistry is the sequential column asymmetric catalysis technique (CAC). In this strategy, developed by Lectka *et al*. [41], reagents and catalysts are attached to a solid-phase support and loaded onto sequentially-linked columns (see Scheme **20**). The substrates are present in the liquid phase that flows through the column. As a substrate encounters each successive column, it grows in complexity. Consequently, one can imagine a number of flow systems that consist of columns attached in series and/or in parallel that synthesize a fairly complex molecule. In addition, to be attractive to industry the process should avoid the use of column chromatography, and additional reagents and solvents must be reusable whenever possible. CAC procedure has been applied to the catalytic, asymmetric synthesis of β-lactams [42]. The chemical steps in this synthesis includes: ketene generation step (upper column), catalytic step (middle column), and a purification step (lower column) (Scheme **20**). Resin-bound dehydrohalogenation reagents are used to produce contaminant-free ketene solutions under inert atmosphere at reduced temperature. The extremely basic resin BEMP (**107**), containing a triaminophosphoramide imine bound to a polymeric support [43], produces ketenes rapidly and in high yield. The middle column is packed with a polymer-supported quinine derivative **108**, that acts as nucleophile-based solid-phase asymmetric catalyst [44]. Interestingly, the length of the linker between cinchona alkaloid derivative and the support was crucial to the success of the reaction since short linkers gave poor results, probably due to the steric hindrance of the polymeric support. Between the two columns, the imine is added to the system. An additional column is packed with a scavenger resin (**109**) to remove any unreacted ketene or imine from the eluent. The eluted reaction mixture was concentrated to afford sequential column asymmetric catalysis β-lactams **110** in good yields, good to excellent diastereoselectivity and enantioselectivity.

In a different column assembly, Leckta reported the used of the polymer-supported amine catalyst (**108**) together with fine-mesh powdered potassium carbonate as the stoichiometric base [45]. In this concept, only two columns were used with a mixture of catalyst-loaded beads **108** and powdered carbonate in the upper column and the scavenger resin **109** in the lower one. Resin **108** effects dehydrohalogenation and presumably transfers their protons to the neighboring solid carbonate. After passing through the scavenger resin **109**, the eluted reaction mixture was concentrated to give the β-lactam in 91% ee. The special appeal of this reaction is that it can be scaled-up easily. For example, one gram of the pure β-lactam **110** could be obtained simply by increasing the amount of carbonate proportionally while employing the same loading of catalyst beads (10/1 ratio of carbonate catalyst).

6. CONCLUDING REMARKS

In summary, this review shows that a great deal of work has been done during the last few years on the application of solid-phase and combinatorial methodologies to the chemistry of the β-lactam ring. Robust methodologies have been achieved in the solid-phase construction of the β-lactam ring by either the Staudinger reaction or the enolate-imine condensation. Other cyclization methods have also been developed. However, the more complex solid-phase synthesis of byciclic β-lactams have been only scarcely explored, and the total solid-phase synthesis of biologically interesting byciclic β-lactams still remains to be reported. In



Scheme 20.

any case, it is clear that combinatorial technologies are being investigated and will continue to be key tools for drug discovery in the area of β-lactam systems.

ACKNOWLEDGEMENT

Financial support from Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina; Agencia Nacional de Promoción Científica y Tecnológica (Argentina); Fundación Antorchas (Argentina), Universidad Nacional de Rosario (Argentina) and Royal Society of Chemistry (U.K.) is gratefully acknowledged.

ABBREVIATIONS

Alloc = Allyloxycarbonyl

BEMP = 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,2,3-diazaphosphorine

Boc = *t*-butyloxycarbonyl

BTPP = *tert*-butyliminotri(pyrrolidino)phosphorane

Cbz = Benzyloxycarbonyl

DEAD = Diethylazodicarboxylate

DBU = 1,8-diazobicyclo[5,4,0]undec-7-ene

DCC = Dicyclohexylcarbodiimide

DIC = Diisopropylcarbodiimide

DMAP = 4-dimethylaminopyridine

DMF = Dimethylformamide

Fmoc = 9-fluorenylmethoxycarbonyl

HOAt = 7-aza-1-hydroxybenzotriazole

HOBt = *N*-hydroxybenzotriazole

LDA = Lithium diisopropylamide

LiHMDS = Lithium hexamethyldisilazide

MAS 1H NMR = 1H magic angle spinning-nuclear magnetic resonance

NaHMDS = Sodium hexamethyldisilazide

NMP = *N*-methyl-pyrrolidinone

TBAF = Tetrabutylammonium fluoride

TFA = Trifluoroacetic acid

THF = Tetrahydrofuran

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Received: March 21, 2005 **Revised: April 20, 2005** **Accepted: June 05, 2005**