Recent Advances in the Solid-Phase Combinatorial Synthetic Strategies for the Benzodiazepine Based Privileged Structures

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Abstract: Benzodiazepine based heterocycles can be prepared efficiently on solid-support by employing different approaches. In this review, an effort has been made to highlight academic and industrial examples of combinatorial synthesis for this type of heterocycles published in the last decade. Therefore, it describes synthetic strategies for the generation of benzodiazepine privileged structures employing the corresponding resin-bound substrates. Further, the most relevant biological properties of these heterocycles have also been incorporated.

INTRODUCTION

The main aim in medicinal chemistry is to design and prepare a molecule that has potential for the clinical usage. Recently, the synthesis of combinatorial libraries [1, 2] has become a valuable tool for exploring new and novel lead structures. Development of solid-phase organic synthesis (SPOS) [3] is the main key for the success of combinatorial chemistry for drug discovery programs. SPOS provides an excellent opportunity for the preparation of molecules by employing new synthetic routes and enables the possibility for rapidly synthesizing drug-like molecules by avoiding tedious and time taking purification [4]. In the beginning, creation of libraries with molecular diversity for drug discovery process was mainly for the synthesis of peptide and nucleotide libraries. However, experience has shown that compounds with biological activity have been mostly derived from heterocyclic structures. Therefore, this structural class has received special attention in combinatorial synthesis and a number of methods have been developed for the preparation of heterocycles that have been transformed to solid-phase. Interestingly, small heterocycles that have been targeted has rigid and highly functionalized molecular scaffolds for biological activity. To fulfill this requirement, many useful chemical and biological methods have been developed for the generation of large combinatorial libraries for small organic compounds [5-9]. A number of factors may be considered in this class of library synthesis. In 1988, Evans and co-workers [10] introduced the concept of 'privileged structures', which was later updated by Patchett and co-workers [11]. A typical molecular framework that can provide ligands for a variety of receptors has been termed as a privileged structure. Benzodiazepine scaffold is one of the classical examples of privileged structures present in a number of pharmaceutically active compounds. Very often, these type of privileged structures have been employed as templates for carrying out the functional variation, which can be obtained at diverse positions through combinatorial approaches. The libraries prepared could then be utilized for different biological assays with a probability to discover a lead molecule for a specific disease condition. In this review, we highlight on methods for the synthesis of benzoannelated rings on solid-support as benzannelation [12] is considered as an efficient method for the diversification of heterocycles.

Presently, benzodiazepine ring consists of numerous type of substructures that comprise of 1,4-benzodiazepine-2-ones (**I**), 1,4-benzodiazepine-2,5-diones (**II**), 1,4-benzodiazepine-2,3-diones (**III**), 1,5-benzodiazepines (**IV**), 1,5-benzodiazepine-2-ones (**V**), 2,3-benzodiazepine-4-ones (**VI**), pyrrolo[2,1-*c*][1,4]benzodiazepine-5-ones (**VII**), pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones (**VIII**), 5,11-dihydro-benzo[*e*]pyrido[3,2-*b*][1,4]diazepine-6-ones (**IX**), triazadibenzoazulenone (**X**), triazolobenzodiazepines (**XI**) and circumdatins (**XII**), all of which have been synthesized on solid-support (Fig. (**1**)). Any modifications on these ring systems could produce new lead structures with better biological profile.

1,4-BENZODIAZEPINE-2-ONES

The biological activity of the 1,4-benzodiazepine-2-ones (**I**) is broad based, and the therapeutic application of benzodiazepines such as diazepam, triazolam, midazolam (Fig. (**2**)) are mainly related to the central nervous system including hypnosis, sedation, muscle relaxation, anxiolytic and anticonvulsant properties [13]. There are examples, which have shown other type of activities like antithrombotics and fibrinogen receptor antagonists [14, 15]. Interestingly, these were among the first class of small molecules synthesized on solid-support [16]. Following this, there have been several reports on the preparation of such skeletons involving 1,4-benzodiazepine-2-ones [16-27].

A large number of methods have been developed for the preparation of 1,4-benzodiazepine-2-ones on solid-support employing different type of approaches particularly, the cyclocondensation methods. The first report by Ellman and co-workers [16] on the solid-phase synthesis of 1,4-benzodiazepine-2-ones is based on the construction of this ring employing three components, i.e. 2-aminobenzo-phenones, amino acids and alkylating agents. The 2-aminobenzophenone derivatives (**4**) have been first attached to the polymer-support through either hydroxy or carboxylic functionality [28]. This resin-linked 2-aminobenzophenone (**5**) is coupled with Fmoc protected amino acid. Upon

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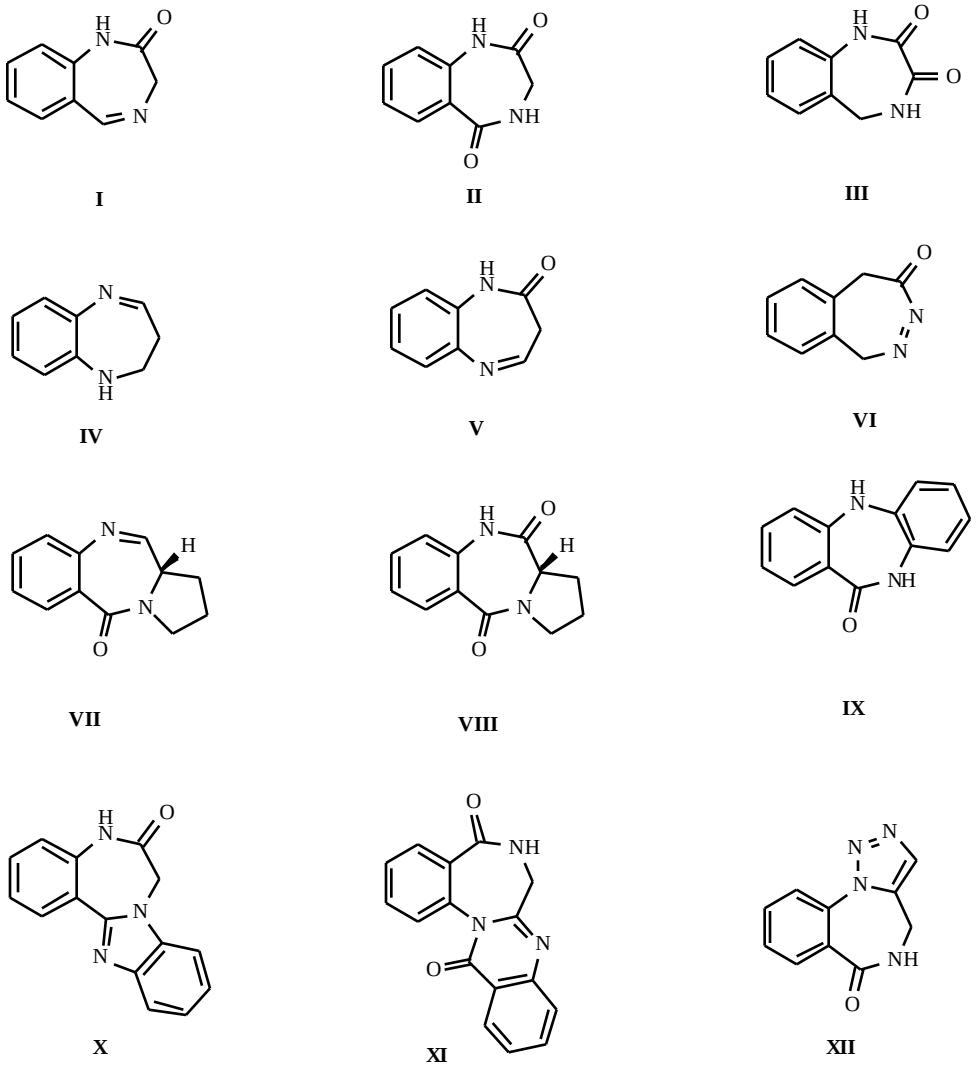


Fig. (1). Basic scaffolds of benzodiazepine based compounds.

removal of Fmoc group, the compound obtained is treated with acetic acid for the ring closure to afford benzodiazepine ring system (**7**). This upon treatment with lithiated 5-phenylmethyl-2-oxazolidinone followed by alkylation provides substitutions at N1. Finally, cleavage from the resin yields the benzodiazepine (**9**) with diversity at four places (Scheme **1**).

Based on this methodology a combinatorial library of 192 structurally diverse and specially separate 1,4-benzodiazepine derivatives have been prepared and evaluated for their biological activity [17]. DeWitt and co-workers [18] have designed an apparatus and method for the multiple, simultaneous synthesis of organic compounds and employed this method for benzodiazepines in which 40 discrete benzodiazepines have been synthesized.

Ellman and Plunkett [19] have also developed a rapid and efficient method for performing the Stille coupling reaction on a solid-support to prepare 2-aminoaryl ketone

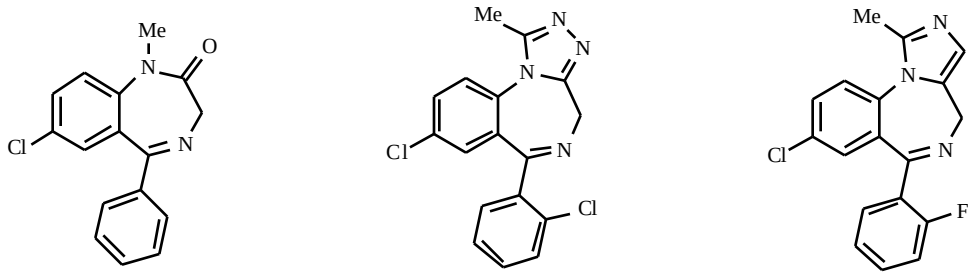
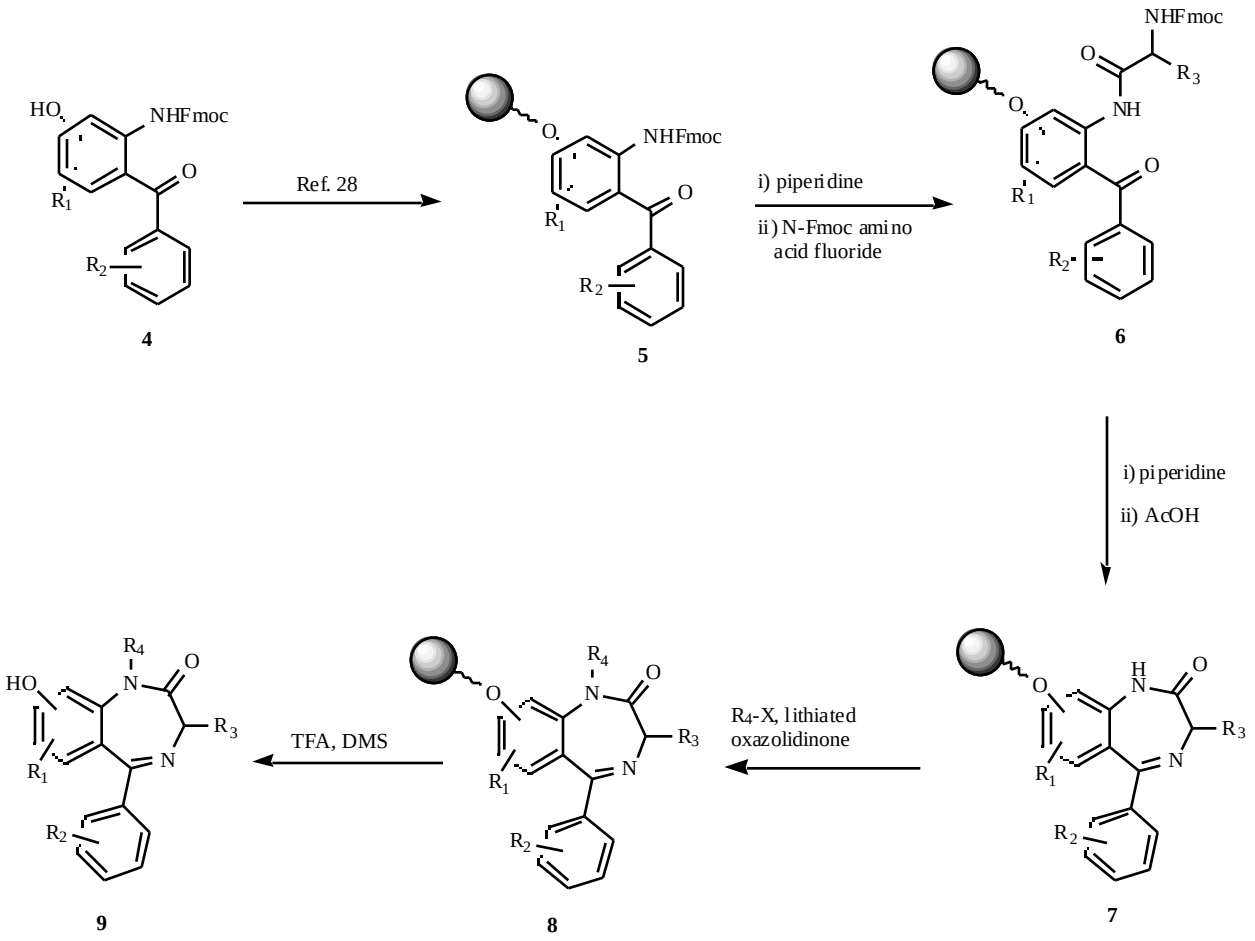


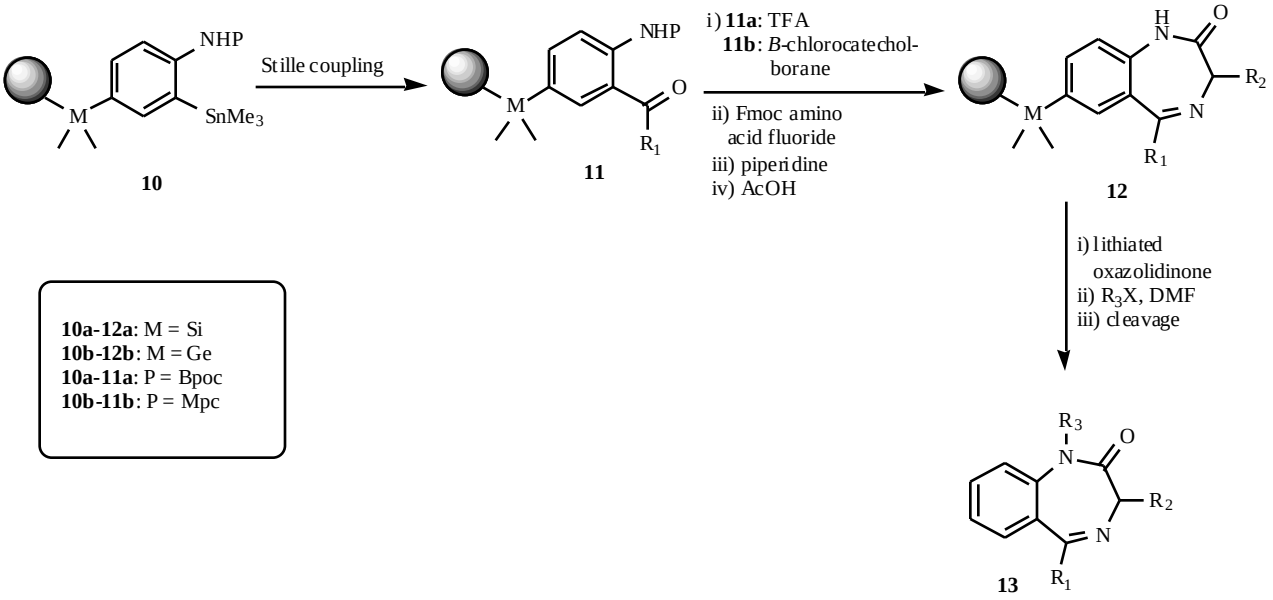
Fig. (2). Relevant molecules with benzodiazepine moiety.



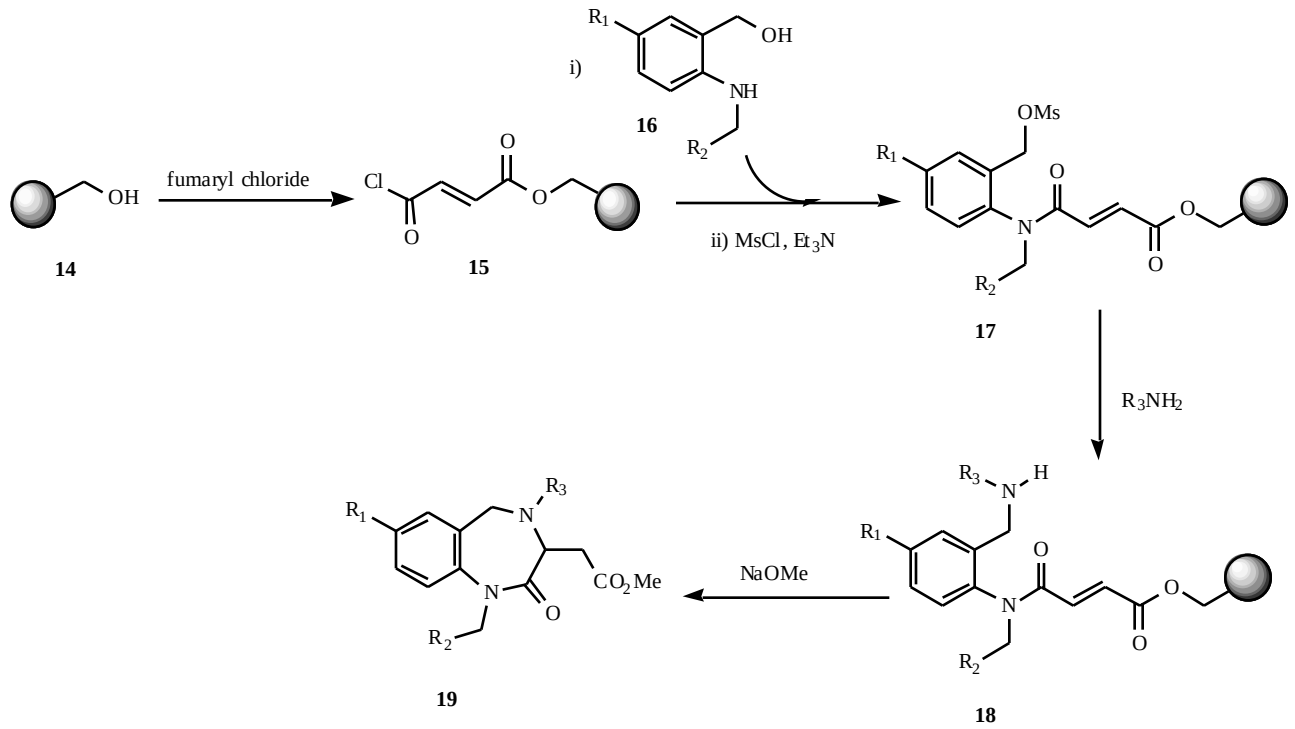
Scheme 1. Ellman's solid-phase synthesis of 1,4-benzodiazepine-2-ones [16-17].

derivatives that directs incorporation of these derivatives into 1,4-benzodiazepine with diverse chemical functionality in high yield. Later developments in the linkage strategies led to an alternate approach that leaves behind no trace or 'memory' of the solid-phase synthesis. This has been successfully demonstrated by employing silicon [20] and germanium [21] based linkers for the synthesis of 1,4-benzodiazepine-2-one derivatives (**13**) (Scheme **2**).

Bhalay and co-workers [22] successfully demonstrated the solid-phase synthesis oftetrahydro-1,4-benzodiazepine-2-



Scheme 2. Traceless solid-phase synthesis of 1,4-benzodiazepine-2-ones by Ellman and Plunkett [19-21].



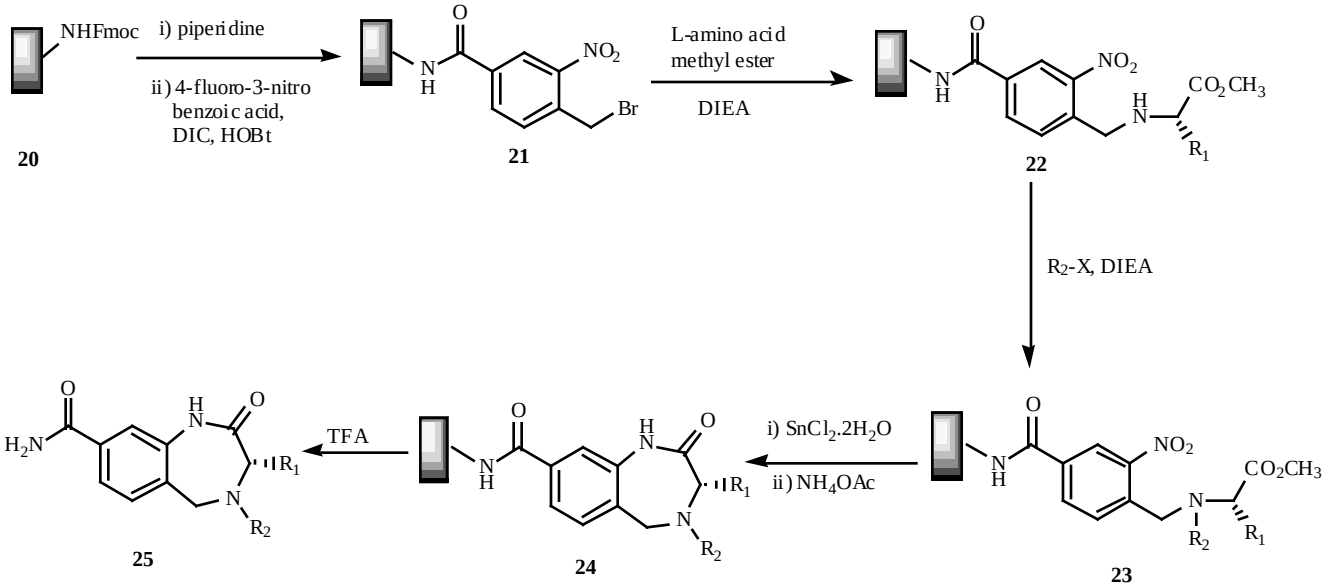
Scheme 3. Bhalay's solid-phase synthesis of a library of tetrahydro-1,4-benzodiazepine-2-ones [22].

ones, which allows the cyclization and cleavage of the resin in one step. Employing this protocol, about 120 compound library (**19**) with three points of diversity has been prepared (Scheme **3**). Alternatively, a novel resin has been developed by Lattmann and co-workers [23] and proved by synthesizing two 1,4-benzodiazepines as typical representatives.

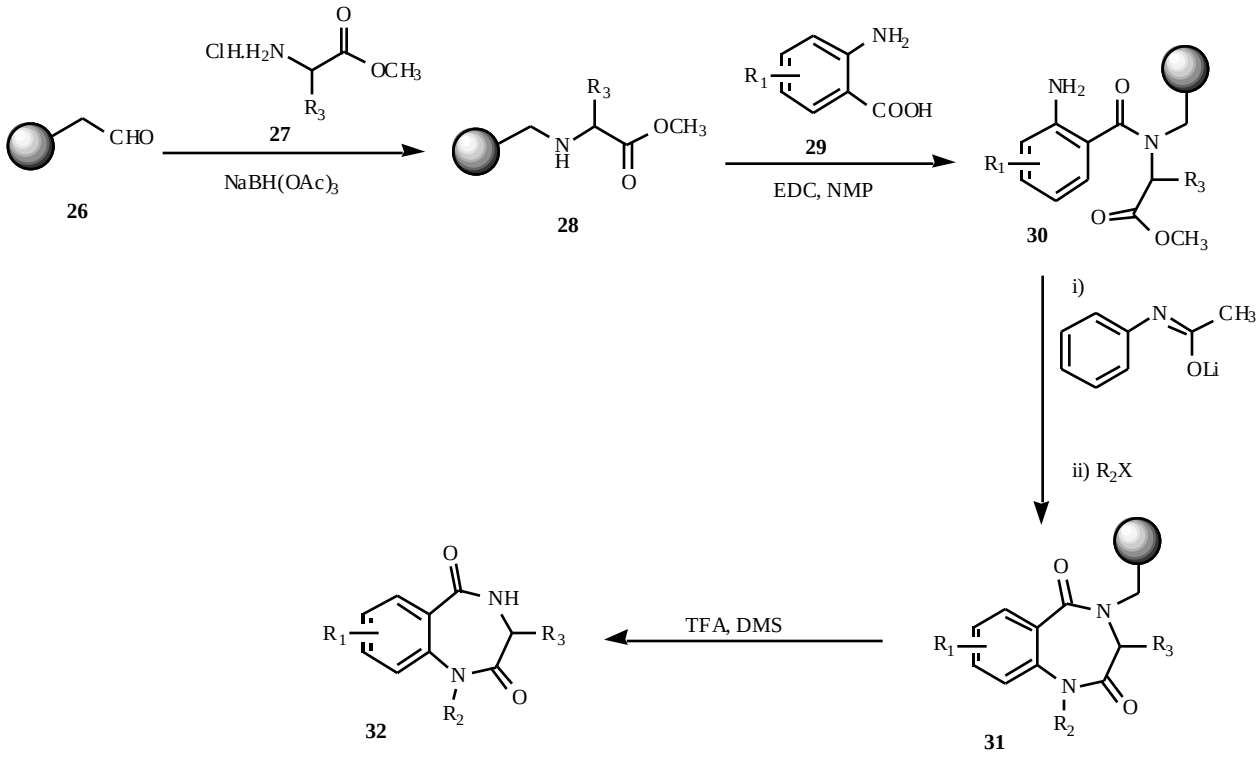
Evans and co-workers [24] described a differential release combinatorial chemical library of 1296 discrete 1,4-benzodiazepine-2-ones on 160 μM Tentagel beads. Several libraries of 1,4-benzodiazepine-2-ones have been synthesized by Wyatt and co-workers [25] through lead optimization.

Ede and co-workers [26] recently reported the use of a new hydrophilic grafted surface on SynPhase Lanterns in solid-phase organic chemistry and applied for the solid-phase preparation of 1,4-benzodiazepine-2-ones by employing these polyamide Lanterns. This approach involves a reductive cyclization of nitro methyl ester (**23**) with a mixture of $SnCl_2.2H_2O/NH_4OAc$ in water and ethanol at elevated temperature to provide the desired target 1,4-benzodiazepine-2-ones (**25**) (Scheme **4**).

Recently, a parallel solid-phase synthesis of a tetrahydrobenzo[*e*][1,4]diazepin-2-one library [27] has been described particularly, with three points of diversity that is



Scheme 4. Synthesis of tetrahydro-1,4-benzodiazepine-2-ones on hydrophilic poly amide SynPhase Lanterns [26].

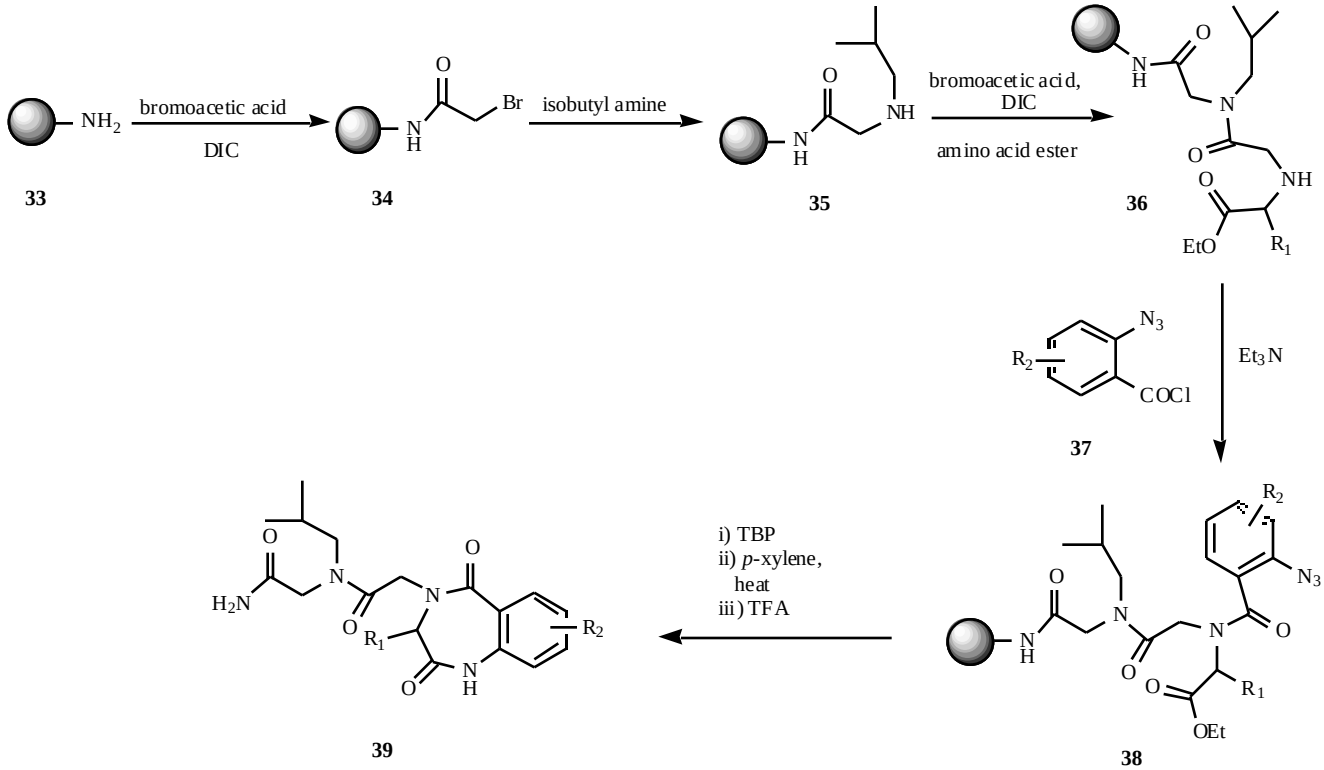


Scheme 5. Solid-phase synthesis of 1,4-benzodiazepine-2,5-dione library by Ellman and co-workers [29, 34].

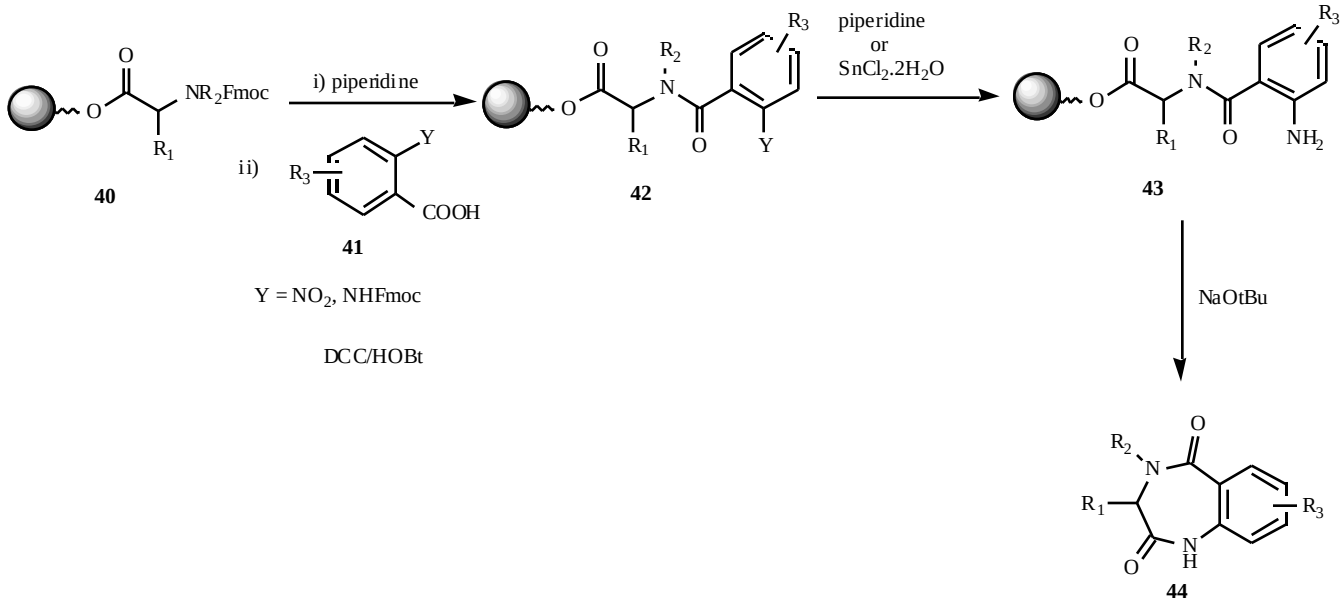
including C-7 position, with alkoxy derivatizations, as β-turn peptidomimetics. A library of 62 compounds has been generated using various building blocks by employing this synthetic strategy.

1,4-BENZODIAZEPINE-2,5-DIONES

1,4-Benzodiazepine-2,5-diones (**II**) are the second most studied benzodiazepine scaffold and are an important pharmacophore class. A large number of derivatives have



Scheme 6. Solid-phase synthetic pathway to 1,4-benzodiazepine-2,5-diones **39** using aza-Wittig reaction by Goff and Zuckermann [36].



Scheme 7. Solid-phase synthetic pathway to 1,4-benzodiazepine-2,5-dione (**44**) *via* cyclative cleavage by Mayer and co-workers [37].

been identified that posses selective activities against a wide range of biological targets including antibiotics, antithrombotics and antitumor activities [29]. These also function as opiate receptor antagonists, anticonvulsant agents, glycoprotein mimics and cholecystokinin receptor antagonists [30-33]. Therefore, this became a target for the development of several solid-phase synthetic strategies.

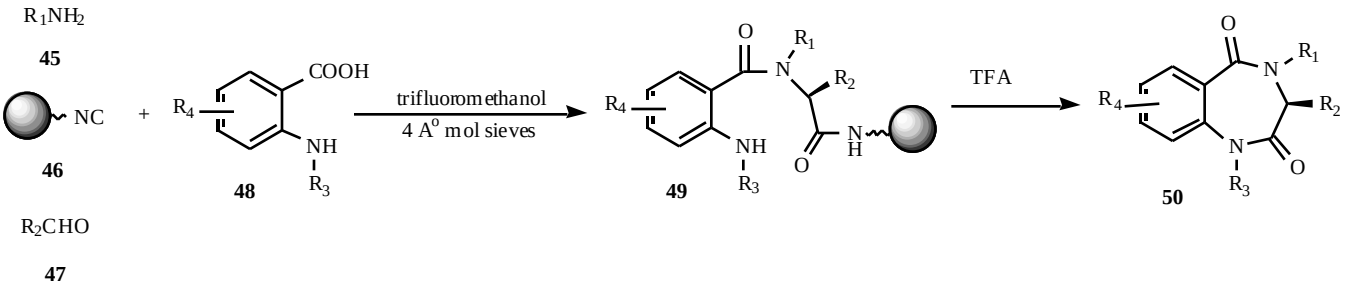
There are four combinatorial strategies for the synthesis of 1,4-benzodiazepine-2,5-diones. First described by Ellman and co-workers [34] utilizes three components namely anthranilic acids, α-amino esters, and alkylating agents for the construction of this library. Merrifield resin is derivatized by alkylation with the sodium salt of 4-hydroxy-2,6-dimethoxybenzaldehyde. The resin-bound aldehyde (**26**) is linked to α-amino ester *via* reductive amination. Amidation of these resin-bound amino esters (**28**) with corresponding anthranilic acids (**29**), followed by cyclization and alkylation gives the polymer-bound 1,4-benzodiazepine-2,5-dione derivatives (**31**). Finally, release of the solid-support provides 1,4-benzodiazepine-2,5-diones (**32**) without substitution at the N4-position (Scheme **5**). This protocol has been utilized to provide a library of about 2500 numbers [29].

Based on the same protocol Ettmayer and co-workers [35] have developed a solid-phase synthesis of 7-amino-1,4-benzodiazepine-2,5-diones and its acylation.

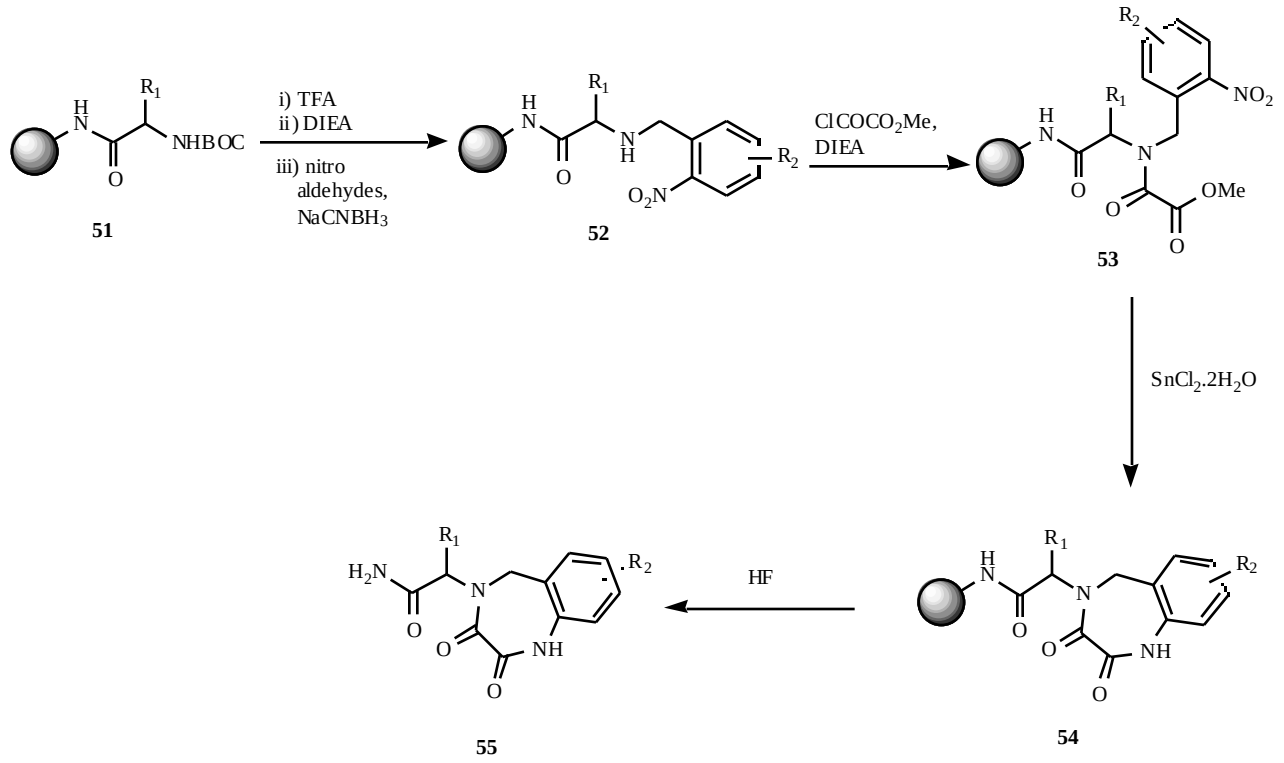
The second strategy reported by Goff and co-workers [36] employ α-amino esters to react with resin-bound bromoacetate (**34**) and then amidation is carried out with 2-azidobenzoylchloride (**37**). The azido group is reduced by tributylphosphine, i.e. Staudinger reaction and the intermediate is heated to 130 °C for this aza-Wittig reaction. The iminoether intermediate is hydrolyzed to the amide during acidolytic cleavage of the product from the Rink resin to afford the 1,4-benzodiazepine-2,5-diones (**39**) (Scheme **6**).

The third protocol devised by Mayer and co-workers [37] employs an α-amino ester on Wang resin and reacted with 2-nitrobenzoic acid or Fmoc protected anthranilic acid (**41**) to provide the corresponding amine. A number of cyclization conditions have been evaluated and optimal results have been obtained by heating the resin (**43**) in tetrahydrofuran with two equivalents of NaOtBu. This method has an advantage on the concurrent release of the resin-support during the cyclization step for the formation of 1,4-benzodiazepine-2,5-diones (**44**) (Scheme **7**). Alternatively, Moroder [38] proposed a procedure for resin-bound peptide precursors as an approach to library of 1,4-benzodiazepine-2,5-diones.

The fourth strategy introduced the universal Rink isonitrile resin (**46**) and its application in Ugi reactivity. The research groups of Hulme, Chen and Kennedy [39-42] have described this novel resin-bound universal isonitrile and



Scheme 8. 1,4-Benzodiazepine-2,5-dione combinatorial library synthesis *via* Ugi MCRs [39-42].



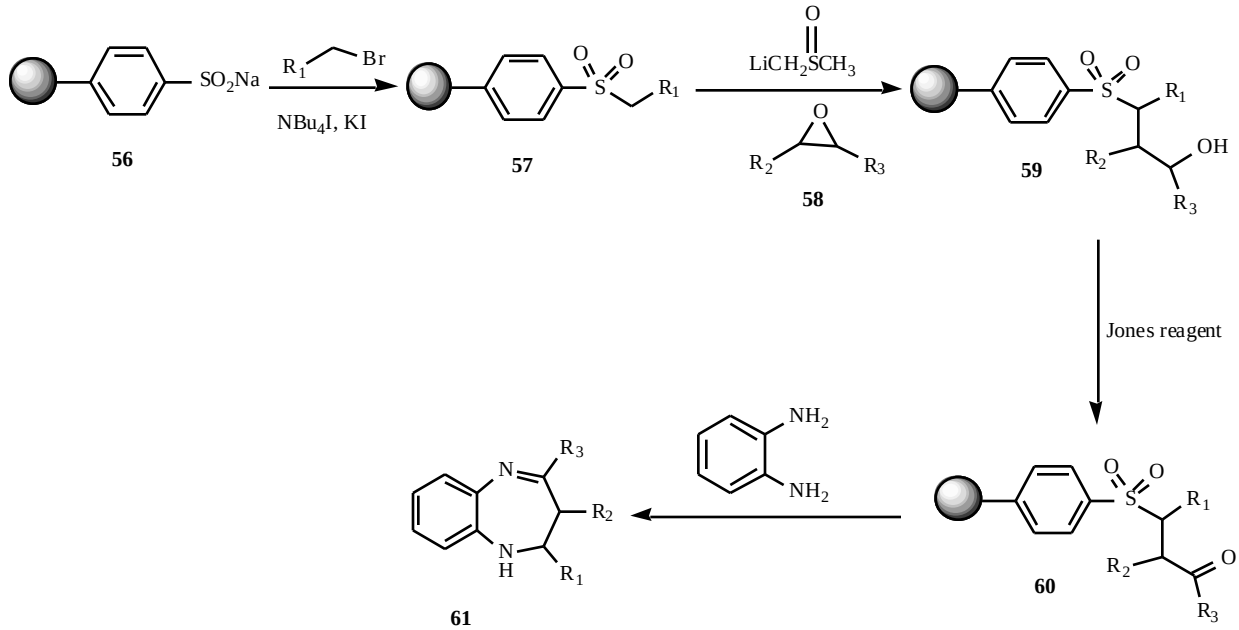
Scheme 9. Parallel solid-phase synthesis of 1,4-benzodiazepine-2,3-diones (**55**) [44].

utilized this in the Ugi multicomponent reactions (Ugi MCRs) as shown in Scheme **8**. This reaction provides an attractive method to assemble a broad range of molecular fragments into dipeptide moiety suitable for the cyclization of 1,4-benzodiazepine-2,5-dione targets (**50**).

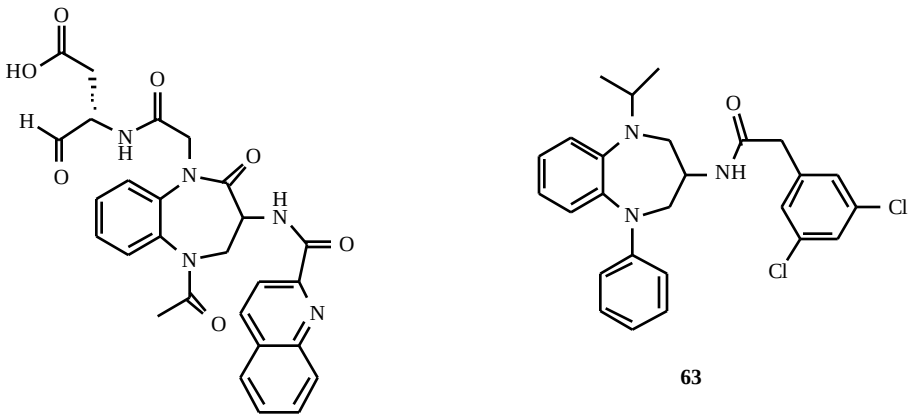
Recently, Fang and co-workers [43] have developed a liquid-phase synthesis for constructing a library of 1,4-benzodiazepine-2,5-diones as an alternative method to solid-phase by utilizing polyethylene glycol (PEG) bound benzaldehydes. Monitoring the progress of poly(ethylene glycol) (PEG)-bound liquid-phase reaction and analysis of the product mixture becomes feasible as the synthesis is conducted in homogeneous organic media. The synthetic pathway is almost similar to the strategy devised by Ellman and co-workers.

1,4-BENZODIAZEPINE-2,3-DIONES

The parallel synthesis of 4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-diones (**III**) has been reported by



Scheme 10. A traceless solid-phase synthesis of benzo[*b*][1,4]diazepine (**61**) by Lam and co-workers [46].



62 **63**

Fig. (3). Examples of biologically active 1,5-benzodiazepine-2-ones.

Houghten and co-workers [44] on the solid-phase employing the 'tea-bag' methodology [45]. By using this combinatorial approach, a library of 41 substituted 1,4-benzodiazepine-2,3-dione derivatives have been prepared. The reductive alkylation of resin-bound primary amine (**51**) with different substituted *o*-nitrobenzaldehydes generated a secondary amine (**52**), which was treated further with methyl chlorooxoacetate. The nitro group (**53**) was reduced with tin(II) chloride. During the overnight reduction, an in situ intramolecular cyclization occured (**54**), followed by HF cleavage to provide the 4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-dione (**55**) (Scheme **9**).

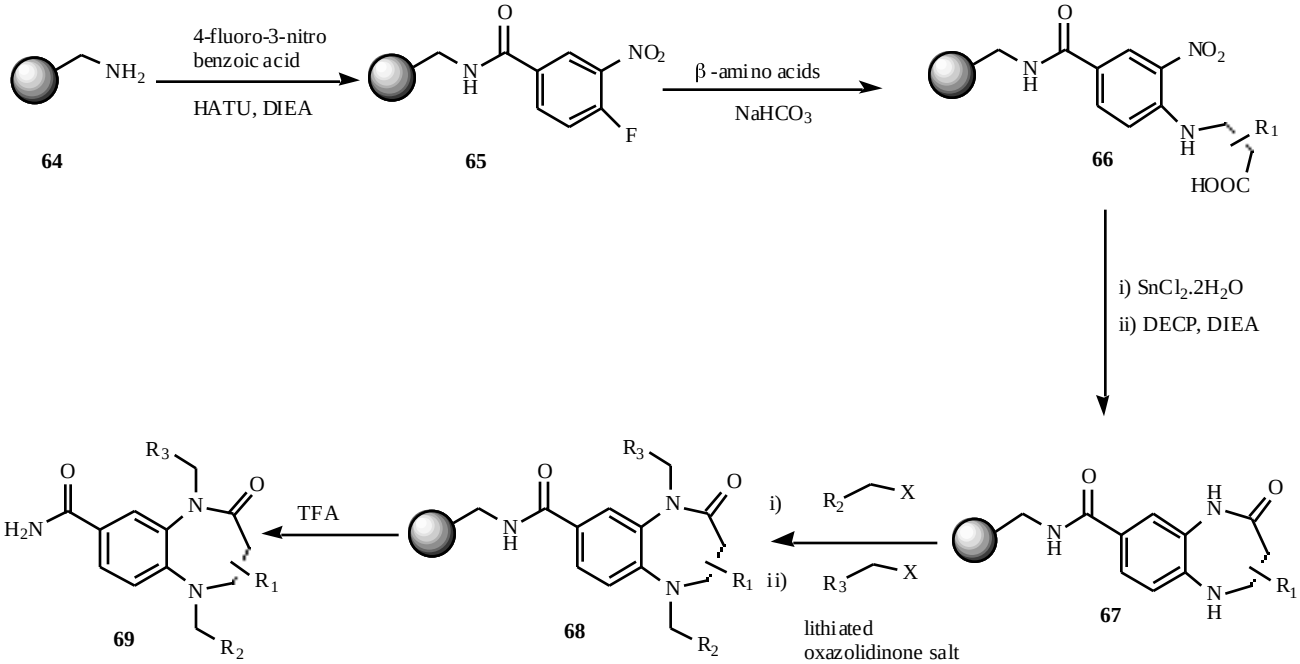
1,5-BENZODIAZEPINES

Recently, fused benzo[*b*][1,4]diazepine (**IV**) [46] derivatives have been synthesized using traceless solid-phase sulfone linker strategy. The key steps of this pathway involve: (i) sulfinate S-alkylation (**57**), (ii) sulfone anion alkylation with an epoxide (**59**), (iii) γ-hydroxyl sulfone→ γ-ketosulfone oxidation (**60**), and (iv) traceless product release by a one-pot elimination-cyclization process (**61**) (Scheme **10**). BTX radio ligand assay has been used to assess the compounds binding affinities to neuronal sodium channels. Some of the compounds have been found to be neuronal sodium channels blocker.

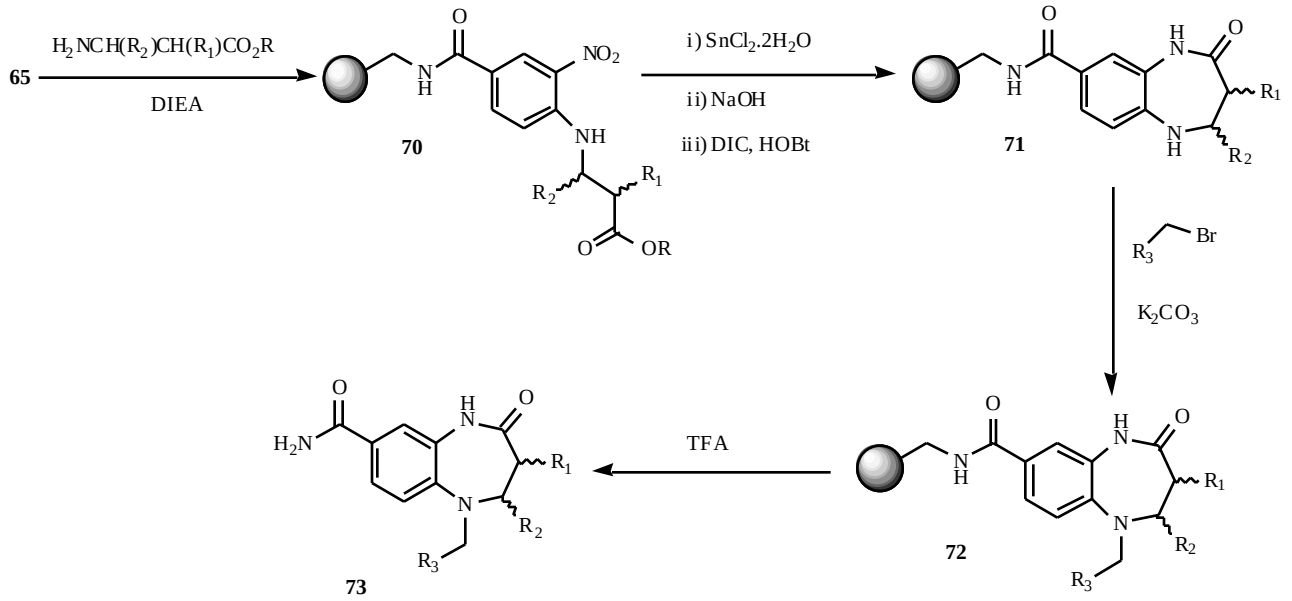
1,5-BENZODIAZEPINE-2-ONE

In comparison to 1,4-benzodiazepine-2-one not much attention has been given to 1,5-benzodiazepine-2-ones (**V**). This scaffold also exhibits biological activity ranging from interleukin-1β-converting enzyme (ICE) inhibitors to delayed rectifier potassium current blockers (I_K) (Fig. (**3**)) [47].

The reports describing the solid-phase synthesis of compounds with this ring system has been prepared either



Scheme 11. Solid-phase synthesis of 1,5-benzodiazepine-2-ones by Schwarz and co-workers [48].



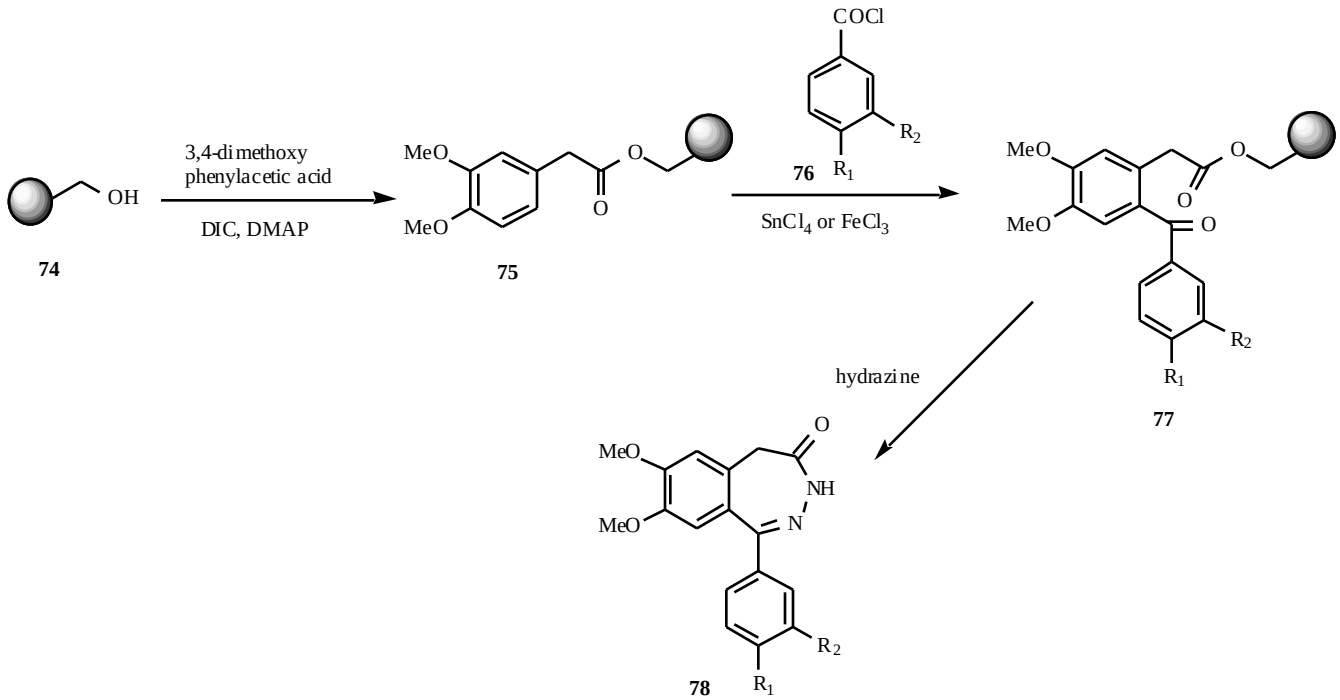
Scheme 12. Synthesis of trisubstituted 1,5-benzodiazepine-2-ones (**73**) on solid-support [50].

by using N1/C2 ring closure or by a pre-assembled ring system scaffold [47]. Schwarz and co-workers [48] have prepared a library of 1,5-benzodiazepine-2-ones by employing the ring closure strategy. Resin-bound 4-fluoro-3-nitrobenzoic acid (**65**) is reacted with different β-amino acids, followed by nitro group reduction and formation of the seven-membered ring (**67**). Subsequent alkylations at N5 and N1 afforded the 1,5-benzodiazepine-2-ones (**69**) in high yields (Scheme **11**).

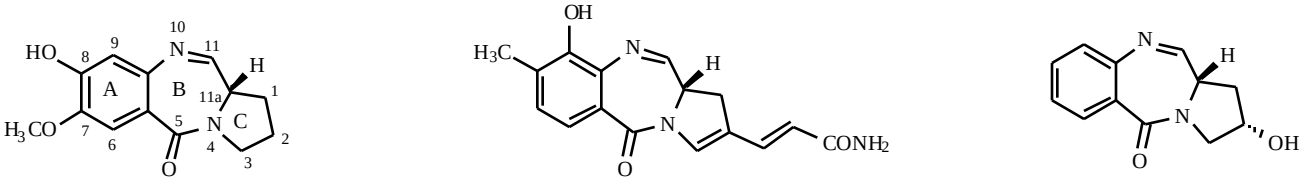
In a similar synthetic pathway about 35 compounds of 1,5-benzodiazepine-2-ones with variation of three point of diversity elements have been synthesized by Lee and co-workers [49] (Scheme **12**). A pre-assembled 1,5-benzodiazepine-2-ones have been utilized by Herpin and co-workers [47] to prepare a 10,000-membered library of 1,5-benzodiazepine-2-ones. A similar strategy has also been employed by Sun and co-workers [50] to prepare a library of N-substituted benzodiazepines by the use of polyethylene glycol mono-methyl ether (MeO-PEG-OH), a polymer carrier that is soluble in many organic solvents and could be selectively precipitated out in various solvents.

2,3-BENZODIAZEPINE-4-ONES

Solid-phase synthesis of 1-aryl-3,5-dihydro-4*H*-2,3-benzodiazepine-4-one (**VI**) [51] has been described. This



Scheme 13. Synthesis of 2,3-benzodiazepines (**78**) on the solid-support using Friedel-Crafts acylation [51].



DC-81 (**79**) Anthramycin methyl ether (**80**) Abbeymycin (**81**)

Fig. (4). Naturally occuring pyrrolo[2,1-*c*][1,4]benzodiazepines.

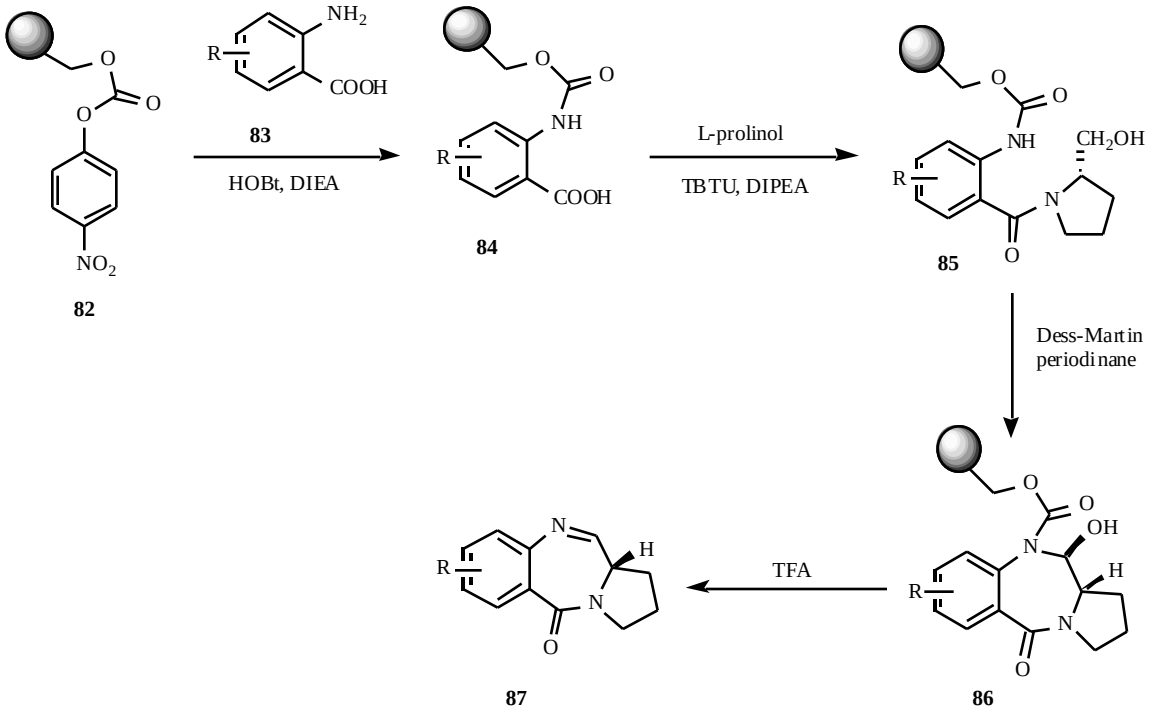
methodology involves Friedel-Crafts acylation with various acyl chlorides (**76**) of resin-bound 3,4-dimethoxyphenyl acetate (**75**) to give resin-bound ketones (**77**). These upon treatment with hydrazine provided the corresponding 2,3-benzodiazepine-4-ones (**78**) (Scheme **13**). The cleavage-cyclization in one-step using substituted hydrazine strategy could generate diversity as their N-substituted benzodiazepine-4-ones. The molecules on this ring system are potentially useful for the treatment of epilepsy [52].

FUSED BENZODIAZEPINE SYSTEMS

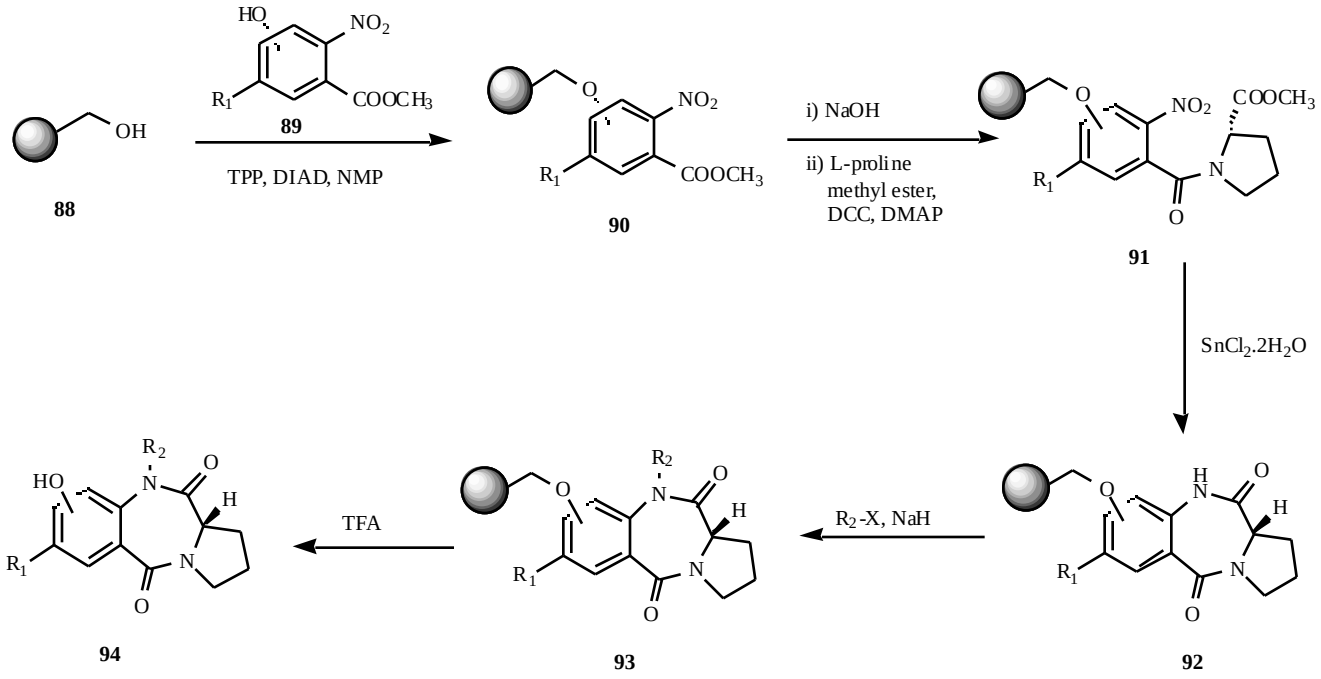
PYRROLO[2,1-*c*][1,4]BENZODIAZEPINE-5-ONES AND 5,11-DIONES

Pyrrolo[2,1-*c*][1,4]benzodiazepine-5-ones (PBDs) (**VII**) are a group of potent, naturally occurring antitumour antibiotics produced by various *Streptomyces* species [53]. A variety of A-ring substitution patterns exist, with simple examples containing unsubstituted C-rings, e.g. DC-81 (**79**), and more complex ones with substituents at C2, e.g. anthramycin (**80**) and abbeymycin (**81**) (Fig. (**4**)). These compounds bind selectively in the minor groove *via* a covalent aminal bond between the electrophilic C11-position of the PBD and nucleophilic C2 amino group of a guanine base [54], resulting in the biological activity. The *S*-configuration at the chiral C11a-position provides the PBD structure with the necessary right-handed twist to fit snugly within the minor groove of DNA, spanning three base-pairs with a preference for 5'-PuGPu sequences. Recently, these compounds have been employed in the development of gene-targeting agents with the potential to down-regulate genes of therapeutic interest [55]. The pyrrolo[2,1-*c*][1,4]benzo-diazepine-5,11-diones (**VIII**) have been used for a number of biological applications, including as a template for the design and assembly of peptidomimetic agents, as anxiolytic drugs, anticonvulsants, antiphage activity, analgesic antagonist and anti-inflammatory activity, psychomotor depressant activity, sedative activity and herbicidal properties [56, 57]. This tricyclic ring system has also been employed as an intermediate for the imine-containing pyrrolobenzodiazepine-5-ones [58-61]. Further, these diones are also known as non-covalent ligands for the DNA minor groove [62].

The first solid-phase synthesis of DNA interactive PBDs has been reported by Thurston's group [63] employing *p*-nitrophenyl carbonate Wang resin (**82**) involving a variety of oxidation and cyclization procedures. In the first step anthranilic acids (**83**) are coupled with *p*-nitrophenyl



Scheme 14. Solid-phase synthesis of pyrrolobenzodiazepines (**87**) using a cyclocondensation by Thurston and co-workers [63].

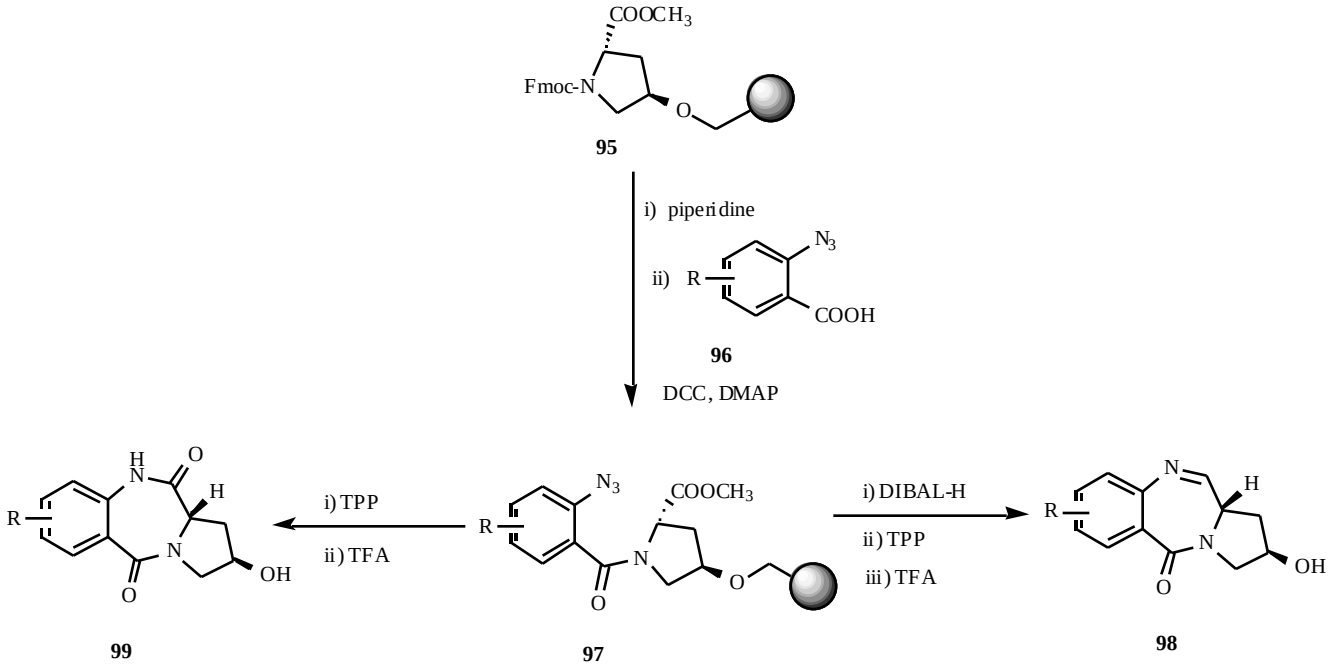


Scheme 15. Solid-phase synthesis of pyrrolobenzodiazepine-5,11-diones *via* reductive cyclization approach [57].

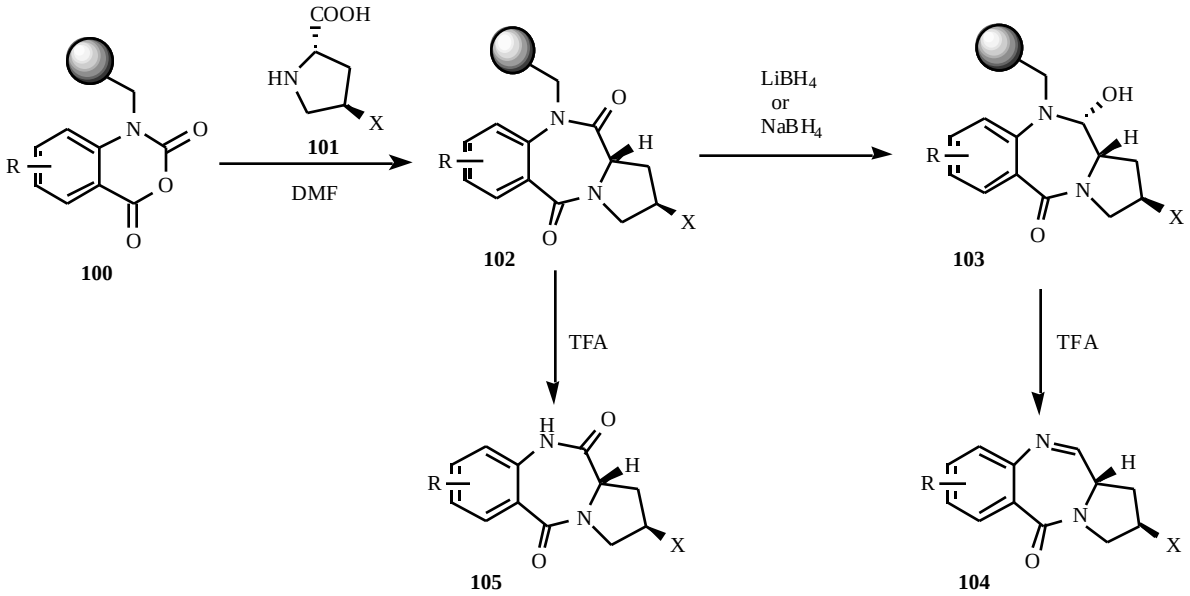
carbonate Wang resin (**82**). To the immobilized A-ring, is added L-prolinol and the ring closure takes place by an oxidative process (Dess-Martin periodinane) to give the pyrrolobenzodiazepine tricyclic ring system (**86**). Finally, cleavage of the solid-support provides the imine containing PBDs (**87**) (Scheme **14**).

A solid-phase synthesis of PBD-5,11-diones has been developed by our research group [57] using Wang resin through amide formation and reductive cyclization process with the diversity at N10-position, which has been achieved before the final cleavage of the solid-support (Scheme **15**). Earlier in the solid-phase synthesis of 1,4-benzodiazepine-2,5-diones, discussed the PBD-5,11-diones as an example. However, there is no evidence on the library generation of such compounds [37].

A solid-phase synthetic methodology for imine-containing PBDs and 5,11-diones has also been reported by our research group [64] employing a similar reductive cyclization approach, with a difference of having resin in the C-ring instead of A-ring. However, Hanessian protocol [53] has been employed in this methodology by having the resin in the C-ring where as earlier report includes the Mitsunobu



Scheme 16. Solid-phase synthesis of pyrrolobenzodiazepines *via* aza-Wittig cyclization protocol [64].



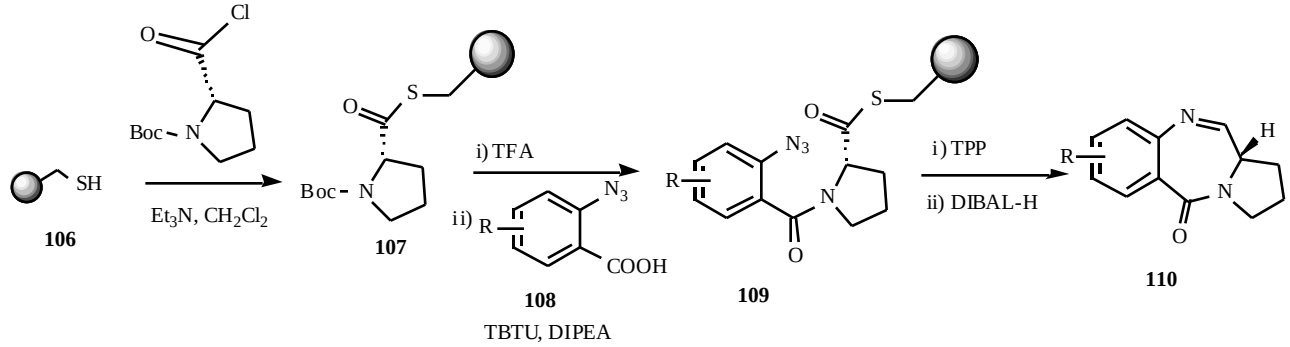
Scheme 17. Solid-phase synthesis of DNA-interactive pyrrolobenzodiazepines [68].

protocol having resin in the A-ring. The Fmoc deprotected resin containing proline methyl ester is then coupled with the corresponding 2-azido benzoic acids (**96**) using DCC and DMAP. The reduction of polymer-bound azido benzoyl proline methyl ester (**97**) with DIBAL-H followed by reductive cyclization (aza-Wittig) and cleavage employing TPP and TFA affords the imine compounds (**98**). Further, the cleaved dilactam (**99**) has been obtained by the reductive cyclization (aza-Wittig) of the polymer-bound compound (**97**) employing TPP and TFA (Scheme **16**). Interestingly, after the cleavage of the resin 2-hydroxy substituted PBDs are obtained. The presence of a hydroxy group at the C2 position has been considered to play an important role in non-covalent interaction of the DNA and the generation of such compounds is of great value for understanding the biological implications. Similarly, solid-phase synthesis of PBD-5-ones and 5,11-diones have been carried with the nitro/azido reductive cyclization protocols employing indium metal [66] and Al-$NiCl_2.6H_2O$ or Al/NH_4Cl [67]. Most of these reducing reagents like tin(II) chloride or indium metal can provide the pyrrolobenzodiazepine ring system by reductive cyclization. However, these reagents will only reduce the azido or nitro functionality for 1,4-benzodiazepine-2-one ring system substrates, which require a further step of cyclization [26, 27].

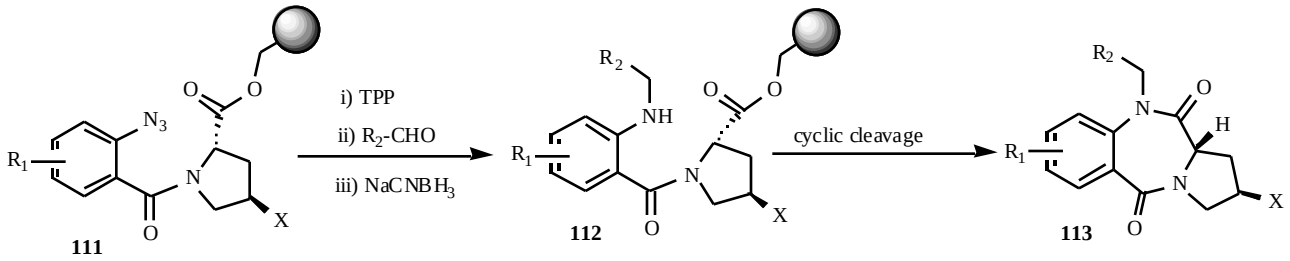
Another interesting solid-phase synthetic strategy for PBD-5-ones and 5,11-diones developed [68] utilizes Wang resin linked isatoic anhydrides (**100**). The use of ultrasound in the cycloaddition of polymer-bound isatoic anhydrides (**100**) with the corresponding proline (**101**) in DMF reduces the reaction time as well as reaction takes place around 50 ^oC instead of >100 ^oC. These polymer-bound tricyclic compounds (**102**) are reduced using very mild conditions, and successively cleaved from the resin to afford the desired imine-containing PBDs (**104**) (Scheme **17**). This short protocol generates a combinatorial library of PBD-5-one (**104**) and 5,11-diones (**105**) with diversity in both the A and C-rings.

Recently synthesis of PBD-5-ones on solid-support has been reported, based on reductive cleavage followed by intramolecular aza-Wittig cyclization employing DIBAL-H [69] (Scheme **18**).

Based on a similar protocol, a versatile combinatorial approach has been developed by our research group [70] and is utilized for the rapid synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (**113**) library comprising of more than 200 compounds with varied substitutions in A, B and C-rings. The key aspect of this approach is based on aza-Wittig mediated annulation strategy. The synthetic design



Scheme 18. Solid-phase synthesis of pyrrolobenzodiazepines involving reductive cleavage strategy [69].



Scheme 19. Solid-phase synthesis of a library of pyrrolobenzodiazepine-5,11-diones [70].

includes generation of iminophosphoranes from the resin-bound 2-azidobenzoyl proline acids (**111**), and the solid-phase aza-Wittig reaction of the iminophosphorane intermediates to imino derivatives followed by their reduction to the corresponding amino compounds (**112**) and the resin cleavage occurs through intramolecular cyclization (Scheme **19**). Most of the compounds from the generated library showed interesting *in vitro* activity against *Mycobacterium tuberculosis* at 50 μg/mL concentration.[a]

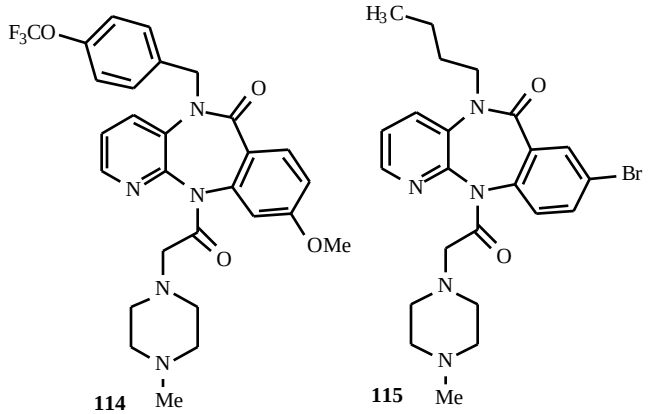


Fig. (5). Biologically active pirenzipines.

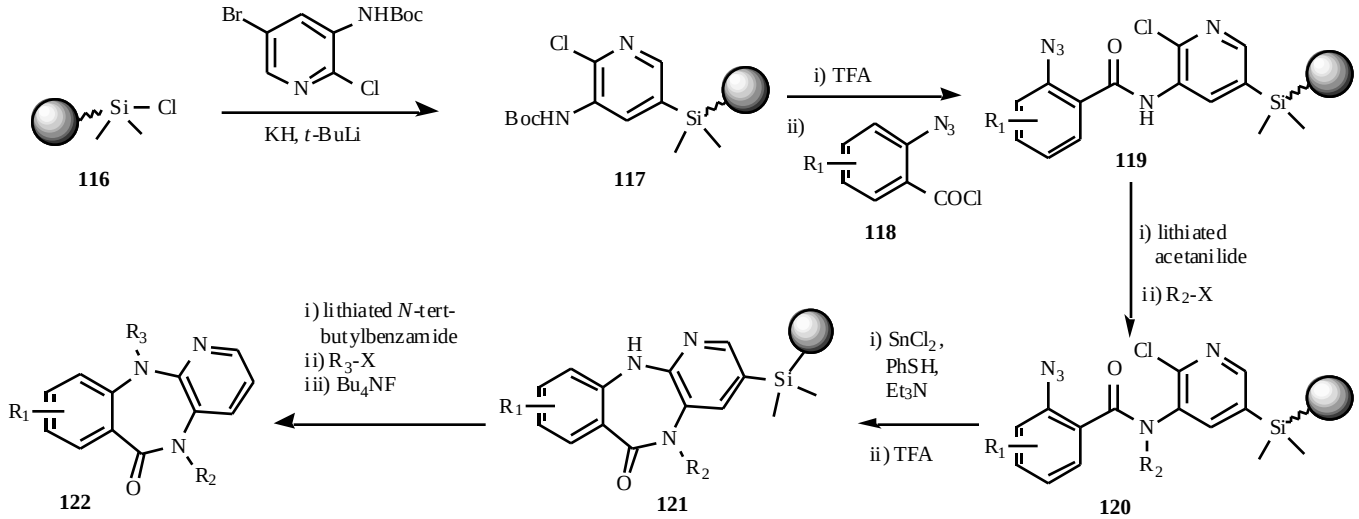
5,11-DIHYDRO-BENZO[*e*]PYRIDO[3,2-*b*][1,4]DIAZE-PINE-6-ONES

5,11-Dihydro-benzo[*e*]pyrido[3,2-*b*][1,4]diazepine-6-ones (**IX**) exhibits a wide range of biological activities and closely related structurally to most of the compounds discussed earlier in this section. Basically, this class of compounds have 1,4-benzodiazepine-5-one skeleton which is fused to a pyrimidine ring. Such fused benzodiazepines posses a variety of therapeutic activities like HIV-1 reverse transcriptase and muscarinic receptor inhibition [71] and some of the compounds have been used for different disease conditions like ulcer treatment [72-75] (Fig. (**5**)).

The solid-phase synthesis for these compounds has been carried out by employing a ring closure through amide bond formation between N4 and C5, which has been generally adapted employing the strategy of 1,4-benzodiazepines. Ellman and co-workers [76] have reported the synthesis of fused 1,4-benzodiazepines by the utilization of a silicon linker. In this traceless synthesis of pyridine-based tricycles, the designed silicon linker (**116**) is attached to the resin, N-Boc 3-amino-5-bromo-2-chloro pyridine is added to the linker upon treatment with potassium hydride followed by halogen metal exchange and addition to silyl resin (**117**) (Scheme **20**).

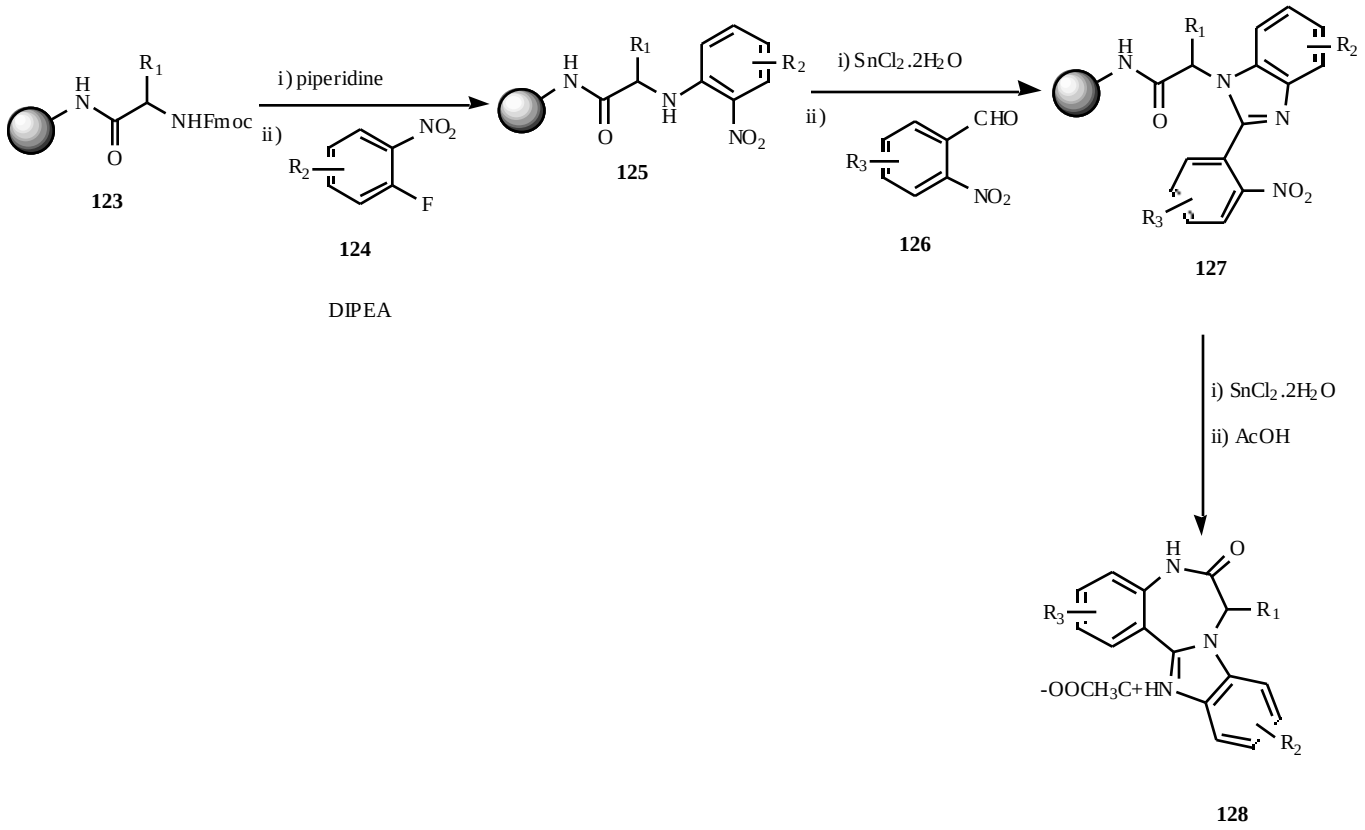
TRIAZADIBENZOAZULENONE

A solid-phase synthetic strategy for the preparation of triazadibenzoazulenone (**X**) has been recently reported by Kundu and co-workers [77]. This method involves incorporation of at least three compounds that can be independently and readily varied for introducing diversity (Scheme **21**). Using this synthetic strategy 48 compound



Scheme 20. Traceless synthesis of pyridine-based tricycles on solid-support by Ellman and co-workers [76].

[a]Kamal, A.; Reddy, K.L.; Devaiah, V.; Shankaraiah, N.; Reddy, G.S.K.; Raghavan, S. (unpublished results).



Scheme 21. Solid-phase synthesis of triazabenzoazulenone by Kundu and co-workers [77].

library has been prepared employing eight amino acids, three 1-fluoro-2-nitrobenzenes and two *o*-nitrobenzaldehydes. The structural diversity of the monomers had no effect on the yield and purity of the products.

SYNTHESIS OF PYRROLOBENZODIAZEPINES, TRIAZOLOBENZODIAZEPINES AND CIRCUMDATINS BY EMPLOYING POLYMER-SUPPORTED REAGENTS

Solid-phase as well as solution-phase synthesis has been used extensively for the production of chemical libraries. Considerable attention has also been given for the parallel synthesis of low molecular weight compound libraries by employing a number of solution-phase methods. The use of solid-phase reagents in the solution-phase library generation is emerging as a leading strategy that is not only advantageous for the isolation and purification of the product but also provides the traditional benefits of solution-phase reactions [78-82].

Recently, the synthesis of DNA interactive pyrrolo[2,1-*c*][1,4]benzodiazepines and their 5,11-diones has been reported by our research group [83] employing polymer-supported reagents. The synthetic protocol consists of the coupling of L-prolinol with 2-azido benzoic acid (**129**) by using polymer-supported cyclohexylcarbodiimide to give azido alcohol (**130**). This upon oxidation by modified Swern procedure using polymer-supported sulfoxide affords the azido aldehyde (**131**). The intramolecular reductive cyclization with polymer-supported phosphine, affords the desired imine-containing the pyrrolobenzodiazepine ring system (**132**). Polymer-supported reagents employing L-proline methyl ester instead of L-prolinol afforded the PBD dilactams (**134**) (Scheme **22**).

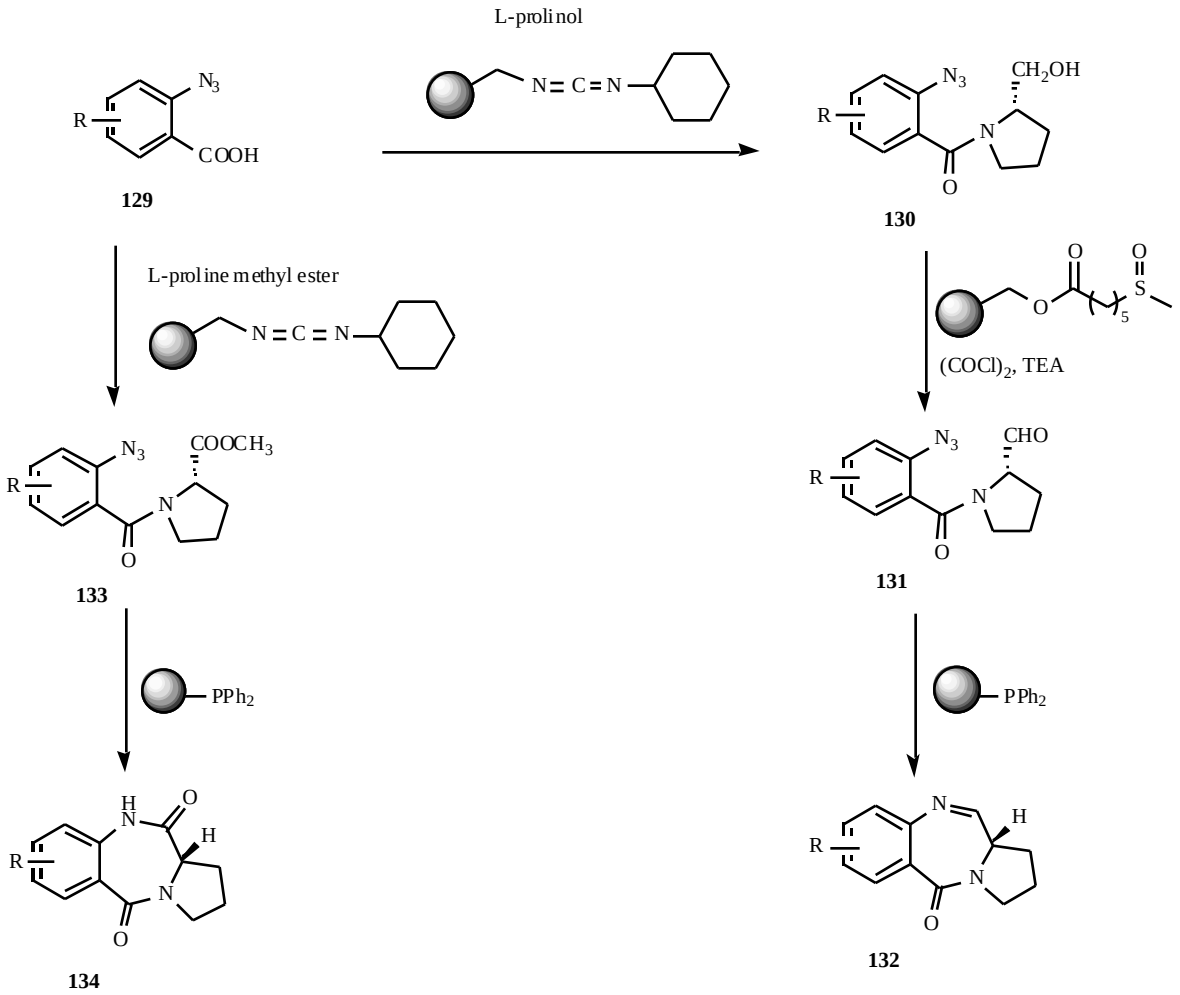
This protocol is of great significance from the 'green' chemistry point of view as these reagents could be recovered and reused.

One pot synthesis of [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepine-6(4*H*)-ones (**XI**) has been reported [84] starting from anthranilic acid by a four step sequence involving diazotization, azide addition followed by amide bond formation, more importantly employing polymer-supported carbodiimide and finally 1,3-dipolar cycloaddition reaction.

Recently, employing a polymer-supported phosphine-mediated intramolecular aza-Wittig reaction step a diverse library of benzodiazepine-quinazolinone alkaloids (circumdatins) (**XII**) has been reported [85]. The simplest member Sclerotigenin of the benzodiazepine-quinazolinone family has been prepared employing this type of strategy and the construction of multi-arrayed library to produce four sub-libraries of natural products. This synthetic sequence is short, relies on a modified Eguchi protocol employing polymer-supported phosphine and accessible to benzodiazepine dione derivatives.

CONCLUSION

The solid-phase synthesis of benzodiazepine based heterocycles described in the literature have employed a variety of approaches that could handle the preparation of libraries of biologically potential molecules giving rise to



Scheme 22. Synthesis of pyrrolobenzodiazepines employing polymer-supported reagents [83].

the development of novel structures. Parallel synthesis has become one of the key aspects for the enhancement of productivity in the area of medicinal chemistry. Recently, the application of solid-support reagents has provided a variety of transformations and eventually became highly popular.

ACKNOWLEDGMENT

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ABBREVIATIONS

AcOH = Acetic acid

AcCl = Acetyl chloride

Ac_2O = Acetic anhydride

BOP = Benzotriazole-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate

Bpoc = 1-Methyl-1-(4-biphenyl)ethoxy carbonyl

DCC = *N*, *N*'-Dicyclohexylcarbodiimide

DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DEAD = Diethylazodicarboxylate

DECP = Diethyl cyanophosphonate

DIAD = Diisopropyl azodicarboxylate

DIBAL-H = Diisobutylaluminium hydride

DIC = *N*, *N*'-Diisopropylcarbodiimide

DIEA = *N*, *N*'-Diisopropylethylamine

DIPA = Diisopropylamine

DIPEA = *N*, *N*'-Diisopropylethylamine

DMA = Dimethylacetamide

DMAP = *N*, *N*'-Dimethylaminopyridine

DMF = *N*, *N*'-Dimethylformamide

DMS = Dimethyl sulfide

EDCI = 1-[3-(Dimethylamino)propyl]-3-ethylcarobodiimide hydrochloride

Fmoc = 9-Fluorenylmethoxy carbonyl

HATU = 2-(7-Aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

HBTU = *O*-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluoroborate

HOBt = 1-Hydroxybenzotriazole

LHMDS = Lithium hexamethyldisilazide

Mpc = 4-(Methyl thio)phenoxy carbonyl

MsCl = Methanesulfonyl chloride

NaOtBu = Sodium *tert*-butoxide

NaOMe = Sodium methoxide

NMP = *N*-Methylpyrrolidinone

TBP = Tributylphosphine

TBTU = *O*-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate

TFA = Trifluoroacetic acid

THF = Tetrahydrofuran

TPP = Triphenylphosphine

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