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The Building Block Approach to Unusual α-Amino Acid Derivatives and Peptides

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ABSTRACT
The building block approach was identified as a useful alternative to the commonly used Bücherer−Berg method for the preparation of cyclic unusual α-amino acid derivatives. The symmetrical building blocks were prepared by dialkylation of ethyl isocyanoacetate under solid−liquid phase transfer catalysis conditions while the unsymmetrical building blocks were prepared by a stepwise alkylation of the O'Donnell Schiff base. Metathesis reactions, Suzuki couplings, and cycloaddition reactions were utilized to assemble the building blocks.

Introduction

The demand for peptide-based drugs is likely to continue to increase in the future.[1] On several occasions unusual (unnatural or synthetic), α-amino acids (AAAs) have been used to modify the conformation and/or stability of a biologically active peptide.[2] The pharmacological properties of a peptide are a function of its conformation, which in-turn is dictated by the constituent AAAs. In this respect unusual AAAs are useful for carrying out more systematic studies (e.g., QSAR).[3] For example, incorporation of α-aminoisobutyric acid (Aib) into oligopeptides is known to rigidify the peptide backbone through the formation of β-turns or α-helices.[4] These well-defined structures are responsible for interesting biological properties.

Among the proteinogenic AAAs, phenylalanine (Phe) **1** is an important structural element present in several bioactive peptides. Representative examples of constrained Phe analogues (**2**−**6**) are shown in Figure 1. Replacement of Phe with constrained analogues is known to generate more effective therapeutics.[5] For example, when Phe **1** is replaced with constrained analogues such as 2-aminoindane-2-carboxylic acid **2** (Ind), the resulting peptides have shown enhanced pharmacological properties.[6] 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic) **3** is another Phe analogue where the dihedral angle is limited to a very small range because of its bicyclic nature. In connection with the design of topographically constrained peptides, Tic has been utilized in several instances for replacement of Phe or tyrosine (Tyr).[7]

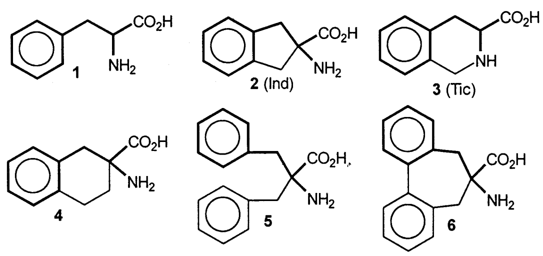

FIGURE 1. List of constrained Phe analogues (the thick line indicate Phe moiety).

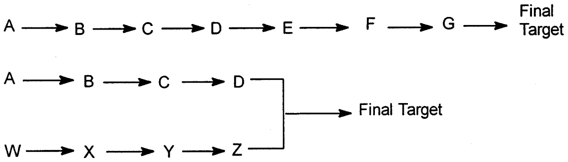

FIGURE 2. Linear and convergent synthetic approaches.

To overcome the problems associated with the commonly used Bücherer−Berg method for the synthesis of cyclic α,α-dialkylated amino acids (ααAAs),[8] we developed the building block approach for the synthesis of various constrained AAA derivatives. The motivation for these investigations is the expectation that new advances in the preparation of such building blocks might allow the synthesis of novel peptidomimetics and artificial proteins. Synthesis of unusual AAA also extends the availability of the synthons for the preparation of drugs and natural products.[9]

In this account our efforts to prepare various building blocks containing the AAA moiety and their subsequent utility in the synthesis of a series of unusual AAAs are summarized. More specifically, the synthesis of various constrained Phe analogues such as Ind **2**, Tic **3**, tetralin **4**, and dibenzylglycine **5** derived AAAs with varying electronic and topographical properties are described. Some of these building blocks were also incorporated into tri- and tetrapeptides, and the resulting peptides were modified by chemical processes.

To appreciate the importance of the building block approach, it is useful briefly to review the general synthetic strategies for the preparation of these types of compounds. While attempting the synthesis of complex targets two different strategies are usually employed.[10] These include linear and convergent synthetic approaches. In the linear synthetic strategy, the target molecule is assembled by a step-by-step process (Figure 2), while in the convergent synthesis, advanced intermediates are assembled from smaller fragments in separate sequences. At an appropriate stage these intermediates are then combined to assemble the final target (Figure 2).

Sambasivarao Kotha was born in Amarthalur, Guntur district, AP, India. He received his B.Sc. from Nagarjuna University in 1977 and M.Sc. from University of Hyderabad in 1979. In 1985, he obtained his Ph.D. under the supervision of Prof. G. Mehta at University of Hyderabad. Subsequently, he worked with Prof. R. J. Stoodley (1986−87) at UMIST, Manchester, U.K., and Prof. J. M. Cook (1987−89) at the University of Wisconsin, Milwaukee, as a research associate. He was a visiting scientist at Cornell University, where he worked in Prof. A. Kuki's group on AIB peptide synthesis. During 1992−93 he worked in Hoechst Celanese, TX, as a Research Chemist-II. In 1994 he joined IIT-Bombay as an Assistant Professor and was promoted to Professor in 2001. He was a recipient of the B. M Birla Prize in Chemical Sciences (1996) and the Professor N. S. Narasimhan Endowment Award (2000). His current research interests include methods in organic synthesis, unusual amino acids, peptide modifications, Suzuki coupling, metathesis, and theoretically interesting molecules.

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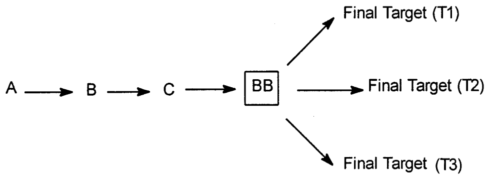


FIGURE 3. Synthetic strategy involving building block approach.

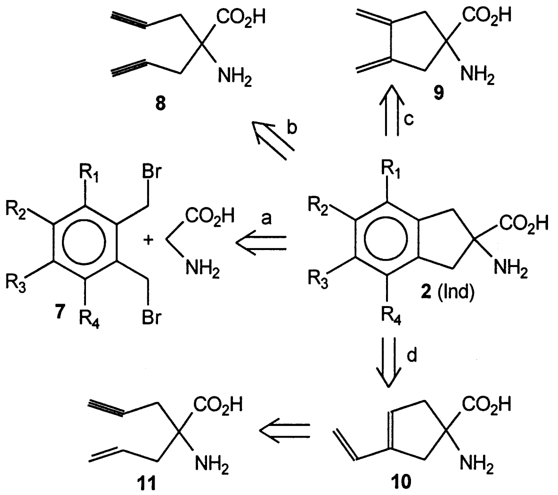


FIGURE 4. Retrosynthetic analysis of Ind.

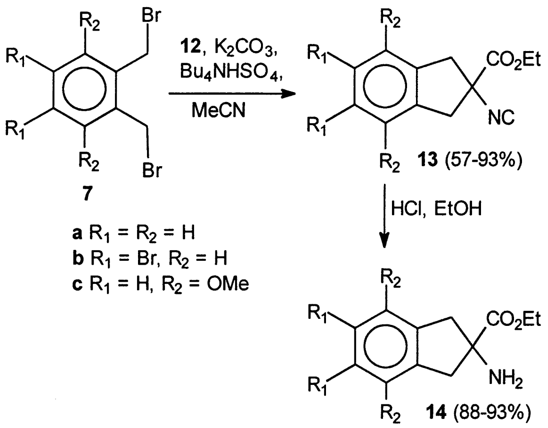
In our synthetic strategy, we have pursued the building block approach, which is different from the above approaches.[10] The building block approach (Figure 3) is a unified approach to prepare a large number of compounds starting from a common precursor (i.e., a building block, BB). The highlight of the building block approach is the potential to prepare libraries of compounds without repeating the whole synthetic sequence. This approach has found applications in combinatorial synthesis, where several targets have been prepared from a common building block by simply varying one of the reagents or components, which is not possible by a linear or a convergent approach.

New Strategies to Indane-Based AAA Derivatives

Four routes have been developed to prepare analogues of 2-aminoindane-2-carboxylic acid (Ind, **2**) (Figure 4). Path a involves dialkylation of glycine with α,α'-dibromo-*o*-xylenes (**7**). Path b relies on a [2+2+2] cycloaddition reaction as a key step, which requires preparation of a diyne building block **8**. The [4+2] cycloaddition strategy (paths c and d) use diene building blocks (**9** and **10**), which contain the AAA unit and a suitable dienophile. The symmetrical diene **9**, upon the Diels−Alder reaction with a suitable dienophile followed by dehydrogenation reaction, can lead to the linearly substituted Ind derivatives such as **2**.[11]

The inner−outer ring diene building block **10** is a useful precursor to generate angularly substituted (R_3=R_4=H) Ind derivatives (path d). These cycloaddition approaches[11] are strategically different from the known methods (e.g., path a) because they involve generation of the benzenoid system via a cycloaddition reaction, rather than manipulation of a preformed benzene derivative. Since the cycloaddition reaction can, by judicious selection of the reacting partners, create considerable functionality in the target molecule, these strategies (b, c, and d) have been used to generate several derivatives of Ind **2**.

Scheme 1



Synthesis of Indane-Based AAA Derivatives by the Phase-Transfer Catalysis Method

Initially, we explored path a (Figure 4) because several α,α'-dibromo-*o*-xylene derivatives can be readily prepared. Although a variety of glycine anion equivalents are available in the literature, ethyl isocyanoacetate (**12**) was found to be a suitable synthon for cyclic AAA derivatives preparation with various α,α'-dibromo-*o*-xylene derivatives under solid−liquid phase transfer catalysis (PTC) conditions.[12] Thus, the reaction of **7** with **12** using potassium carbonate as base in the presence of tetrabutylammonium hydrogensulfate (TBAHS) in refluxing acetonitrile gave the required coupling product **13** in good yield (Scheme 1).[13] In the absence of the phase transfer catalyst, the yield of the coupling product was low and also contaminated with several side products. By using chiral PTC catalyst, it may be possible to prepare optically pure AAA derivatives. Hydrolysis of the isonitrile derivative **13** gave the amino ester **14** in good yield. An additional advantage with the isonitrile functionality is that by varying the hydrolysis conditions different AAA derivatives can be obtained. For example, treatment of isocyanoester **13** with HCl in diethyl ether at −10 °C gives the N-formyl amino ester, whereas the N-formyl amino acid derivative is prepared by using KOH/EtOH/−10 °C.[14]

In general, the cyclization reaction is applicable to a wide range of substrates (Figure 5) containing electron-rich and electron-deficient functional groups. Cyclization was also effective for the formation of five-, six-, as well as seven-member ring compounds i.e., **14**, **15**, and **16**,[13c] respectively. It is interesting to note that the electron deficient AAA derivatives such as **17** or **18** were prepared in the literature by a lengthy route.[15] Using liquid−liquid PTC (10% aq NaOH/CH_2Cl_2) conditions with quinoxaline bromide **27**, the undesired product **29** was obtained,

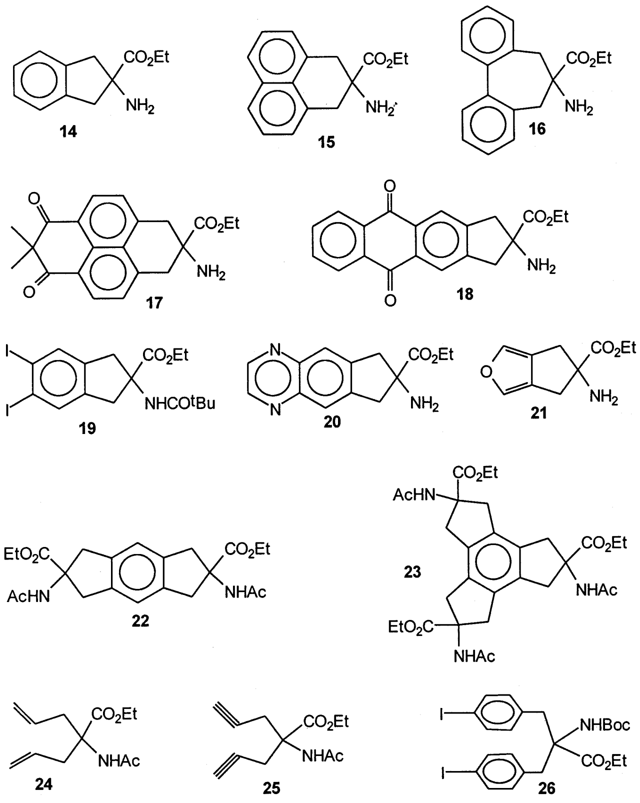
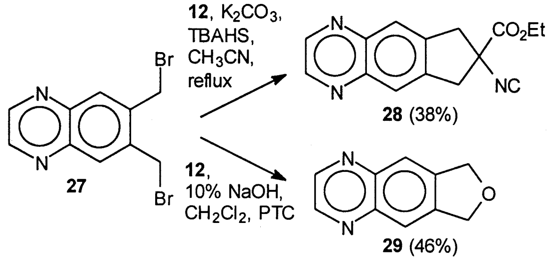


FIGURE 5. Amino acid derivatives prepared using PTC alkylation conditions.

Scheme 2

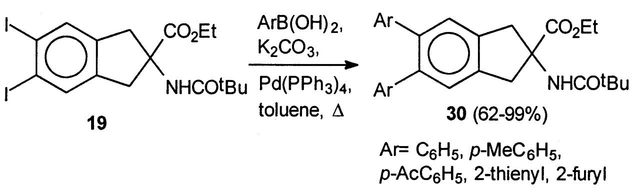


presumably by a nucleophilic substitution reaction (Scheme 2). Using solid−liquid PTC (K_2CO_3, TBAHS, CH_3CN) conditions, the desired product **28** was formed in 38% yield. Hydrolysis of the isonitrile derivative **28** gave the amino ester **20**.

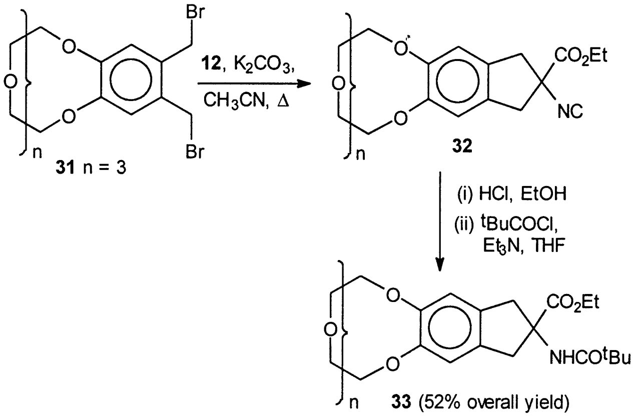
Since furan can undergo the [4+2] cycloaddition reaction with various dienophiles, the cyclic AAA derivative **21** may serve as a useful synthon for the synthesis of other unusual AAA derivatives. Halogen containing Ind derivatives, such as **19**, were not available by Schiff-base/*n*-BuLi conditions.[15] However, using PTC conditions these products were readily prepared. In addition, the halogen functionality present in **19** has been found to be useful for the introduction of various functional groups by the Suzuki−Miyaura (SM) cross-coupling reaction. In this regard, coupling of diiodo-derivative **19** with various arylboronic acids under Pd(0) catalyst conditions gave the required 5,6-disubstituted Ind derivatives **30** (Scheme 3).[16a]

Ethyl isocyanoacetate (**12**) was used to prepare indane-based AAAs containing a crown ether side-chain (e.g., **33**).

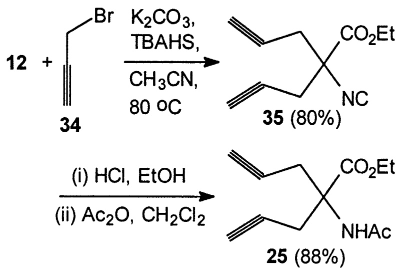
Scheme 3



Scheme 4



Scheme 5



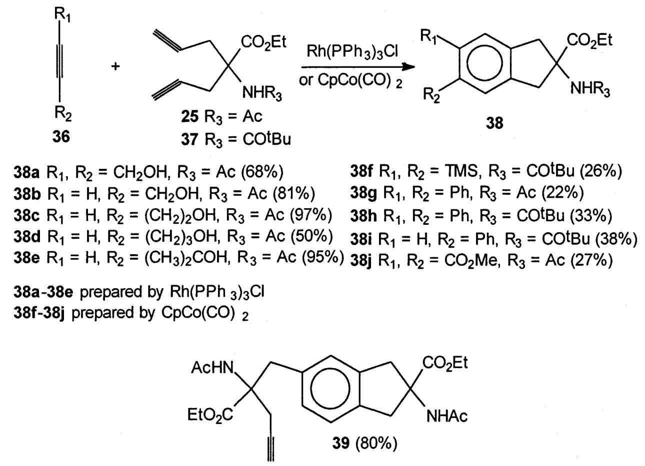
Reaction of the dibromo derivative **31** with **12** gave the desired product **32**, which was hydrolyzed to give the corresponding amino ester, and the protection of the amino group with trimethylacetyl chloride gave **33** (Scheme 4).[17]

Synthesis of Indane-Based AAA Derivatives and Modification of Peptides by a [2+2+2] Cycloaddition Strategy

Although the [2+2+2] cycloaddition is known in the literature, it had not been applied in a general way to AAA synthesis. The key dialkyne building block **25** containing the AAA moiety was readily assembled by dipropargylation of ethyl isocyanoacetate (**12**) with propargyl bromide (**34**) under solid−liquid PTC conditions. Since the isonitrile **35** was found to be unstable under the cycloaddition conditions, it was first hydrolyzed and protected as acetyl derivative **25** (Scheme 5).[18]

Wilkinson's catalyst[19] $Rh(PPh_3)_3Cl$ and the $CpCo(CO)_2$ catalyst[20] have been used in the co-trimerization reaction. Initially, the reaction of AAA derivative **25** with one equivalent of dimethyl acetylenedicarboxylate (DMAD) in the presence of 1 mol % of Wilkinson's catalyst in ethanol did not give the required product. When the reaction was carried out with 2-butyne-1,4-diol (**36**, R_1, R_2 = CH_2OH)

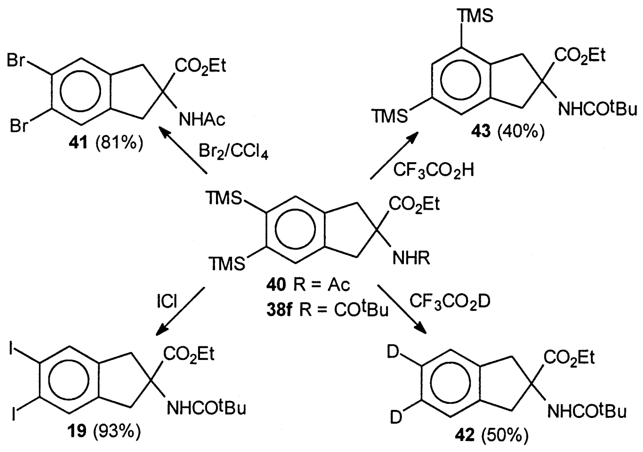
Scheme 6



$\mathbf{38a}$ R_1, R_2 = CH_2OH, R_3 = Ac (68%)
$\mathbf{38b}$ R_1 = H, R_2 = CH_2OH, R_3 = Ac (81%)
$\mathbf{38c}$ R_1 = H, R_2 = $(CH_2)_2OH$, R_3 = Ac (97%)
$\mathbf{38d}$ R_1 = H, R_2 = $(CH_2)_3OH$, R_3 = Ac (50%)
$\mathbf{38e}$ R_1 = H, R_2 = $(CH_3)_2COH$, R_3 = Ac (95%)
$\mathbf{38f}$ R_1, R_2 = TMS, R_3 = CO^tBu (26%)
$\mathbf{38g}$ R_1, R_2 = Ph, R_3 = Ac (22%)
$\mathbf{38h}$ R_1, R_2 = Ph, R_3 = CO^tBu (33%)
$\mathbf{38i}$ R_1 = H, R_2 = Ph, R_3 = CO^tBu (38%)
$\mathbf{38j}$ R_1, R_2 = CO_2Me, R_3 = Ac (27%)

38a-38e prepared by $Rh(PPh_3)_3Cl$
38f-38j prepared by $CpCo(CO)_2$

Scheme 7



(1 equiv), several products were observed. By using a 5−7-fold excess of the monoyne, the required co-trimerization product **38a** was obtained in 68% isolated yield (Scheme 6).[18]

It was found that monoalkynes containing hydroxy functional group were suitable substrates to undergo co-trimerization reaction with diyne **25** in the presence of Wilkinson's catalyst. Various other alkynols that underwent a [2+2+2] cycloaddition reaction with the diyne **25** to give Ind derivatives are shown in Scheme 6.[18] It is known that co-trimerization reactions catalyzed by Ni(0) are facilitated by hydroxy functionality in the monoyne due to the coordination of oxygen to the metal.[21] In connection with posttranslational peptide modifications via the building block approach, we have recently prepared several peptides by incorporating diyne **25** and have shown that Wilkinson's catalyst promotes the [2+2+2] cycloaddition reaction efficiently to yield modified peptides.[22,23]

Various other monoalkynes [e.g., bis(trimethylsilyl)-acetylene, BTMSA] failed to undergo the co-trimerization reaction with the diyne **25** under similar reaction conditions. In most cases self-trimerized product **39** was isolated in 50−80% yield.[24]

To expand the scope of the [2+2+2] cycloaddition strategy for the synthesis of unusual AAA derivatives, other catalyst conditions were explored. The $CpCo(CO)_2$ catalyst allows introduction of the trialkylsilyl group by a [2+2+2] cycloaddition reaction with BTMSA. Silyl substituents are known to be useful for electrophilic aromatic substitution reactions by *ipso* attack, and the trialkylsilyl group is known to impart nonpolar hydrophobic properties, which can be important for biological activity.[24]

Slow addition of the cobalt catalyst $CpCo(CO)_2$ in BTMSA by syringe pump to a refluxing solution of diyne **37** in BTMSA containing $CpCo(CO)_2$ under inert conditions gave the required 5,6-bis(trimethylsilyl) Indane derivative **38f**. Various other monoalkynes that underwent a [2+2+2] cycloaddition reaction with the diynes **25** and **37** in the presence of $CpCo(CO)_2$ to give Ind derivatives are included in Scheme 6.[25]

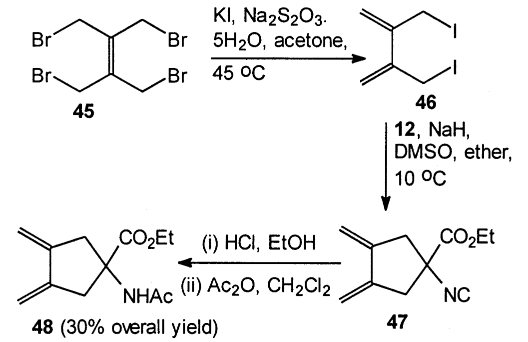
The trimethylacetyl derivative **37** was found to be much more soluble in BTMSA than other derivatives (e.g., acetyl or formyl derivatives), which resulted in an improved yield of the co-trimerized product. Electrophilic substitution reactions to generate various Ind derivatives were also explored. Thus, treatment of compound **40** with an excess of bromine in CCl_4 gave a clean bromodesilylation product resulting in the formation of 5,6-dibromoindane derivative **41** in 81% isolated yield (Scheme 7)**.** Similarly, reaction of the trimethylacetyl derivative **38f** with iodine monochloride gave the 5,6-diiodoindane derivative **19** in 93% isolated yield. Trifluoroacetic acid-*d* was reacted with compound **38f** to give the deuterated product **42**. However, reaction of trifluroacetic acid in CCl_4-MeOH (1:1) gave the rearranged product **43** (40%) (Scheme 7), as indicated by ^1H NMR spectral data.**[24]** With monoalkynes containing hydroxy functionality, we found that Wilkinson's catalyst is useful and proceeds with high yield, whereas alkynes containing TMS functionality cobalt catalyst is suitable, although the yields of the cobalt-catalyzed reactions are generally low.

Synthesis of Indane-Based AAA Derivatives by the Diels−Alder Approach[26]

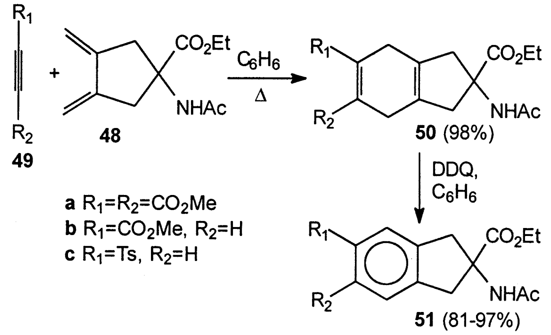
Until recently, only a few cyclic AAA derivatives have been prepared by the Diels−Alder methodology, which is due to a lack of general synthetic methods to deliver dienes or dienophiles containing the AAA moiety. In this regard, the synthesis of diene **48** involving 2,3-bis(halomethyl)-1,3-butadiene (e.g., **46**) as a key precursor was developed. The tetrabromide **45** was prepared from 2,3-dimethyl-1,3-butadiene (**44**) and was converted to the known diiodo compound **46** by reductive debromination. The reaction of ethyl isocyanoacetate (**12**) with **46** under mild reaction conditions (NaH/DMSO/diethyl ether) gave the coupling product **47**, which was converted to the corresponding acetyl derivative **48** as shown in Scheme 8.**[27]**

Diels−Alder reaction of the diene **48** with DMAD (**49a**) at ambient temperature gave the adduct **50a** in good yield, which on dehydrogenation in the presence of 2,3-

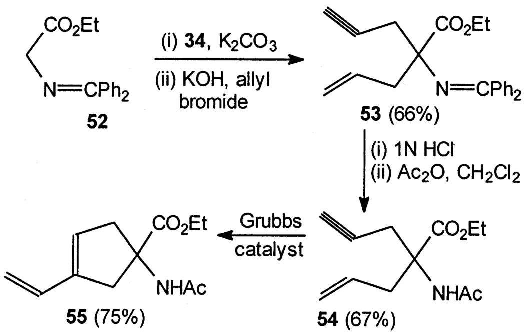
Scheme 8

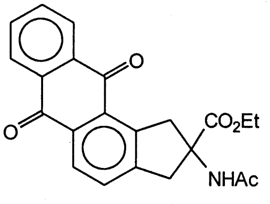


Scheme 9

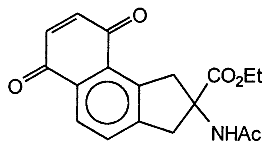


Scheme 10



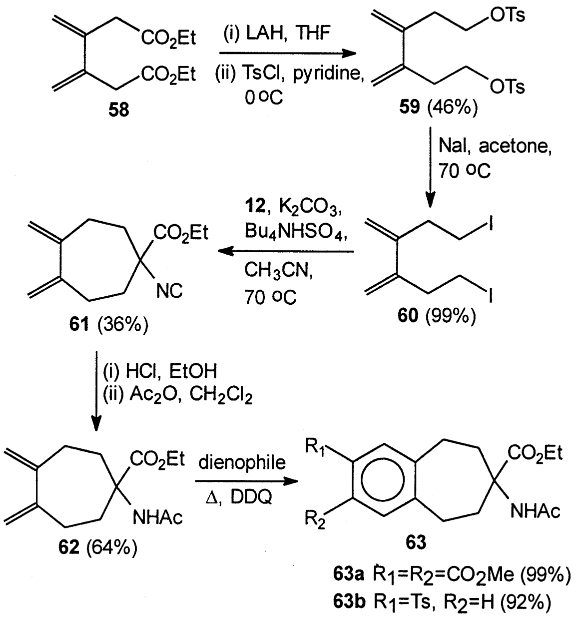


56 (87%)



57 (67%)

Scheme 11



dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) gave the 5,6-dicarbomethoxy Ind derivative **51a**. Other dienophiles such as methyl propiolate (**49b**) and ethynyl *p*-tolyl sulfone (**49c**) underwent the [4+2] cycloaddition reaction. Further oxidation of the Diels–Alder adducts **50b** and **50c** with DDQ gave the corresponding Ind derivatives **51b** and **51c** (Scheme 9).[26]

To prepare angularly substituted Ind derivatives via the Diels–Alder approach, the key inner–outer ring diene building block **10** was prepared from the acyclic enyne precursor **11** by an enyne-metathesis reaction (Figure 4).

Attempts to monoalkylate ethyl isocyanoacetate (**12**) with activated electrophiles gave dialkylated compound as the major product. Therefore, the required enyne building block **54** was synthesized by using O'Donnell Schiff-base **52** as a glycine anion equivalent.[28] Stepwise alkylation of **52** with propargyl bromide and subsequent allylation under solid–liquid PTC conditions gave the enyne derivative **53**. Hydrolysis of **53** followed by acetylation gave the enyne building block **54**, which was subjected to the catalytic metathesis reaction in the presence of the Grubbs catalyst [bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride] to give the inner-outer ring diene **55** in 75% isolated yield (Scheme 10). Initial attempts to resolve the enyne building block **54** by enzymatic methods were not successful.

Treatment of the diene **55** with various dienophiles in refluxing benzene or toluene gave the Diels–Alder adducts, which on dehydrogenation using DDQ gave the angularly substituted Ind derivatives (e.g., **56** and **57**).[29a]

To extend the above methodology for the synthesis of benzocycloheptene-based AAA derivatives (e.g., **63**), the key diene building block **58** was prepared by a double-orthoester Claisen rearrangement. Reduction, tosylation, and iodination of **58** gave the diiodo compound **60** through the formation of the compound **59.** Bis-alkylation of ethyl isocyanoacetate (**12**) with the diiodo compound **60** under PTC conditions gave the required coupling product **61**, which was immediately hydrolyzed to the corresponding amino ester, and then the amino ester was converted to the *N*-acetyl derivative **62** in 64% yield. Since the diene **62** was unstable, it was stored in the presence of a catalytic amount of hydroquinone at low temperature to avoid polymerization. Treatment of the diene **62** with various dienophiles in refluxing benzene gave the Diels–Alder adducts, which were subjected to the DDQ oxidation to give the benzocycloheptene-based AAA derivatives **63** in good yields (Scheme 11).[30]

Synthesis of 1,2,3,4-Tetrahydroisoquinoline-3-Carboxylic Acid (Tic) Derivatives by a [2+2+2] and a [4+2] Cycloaddition Strategy

Tic (**3**) is a Phe analogue in which the dihedral angle χ ($\chi^1 = N{-}C^\alpha{-}C^\beta{-}C^\gamma$, $\chi^2 = C^\alpha{-}C^\beta{-}C^\gamma{-}C^\delta$) is limited to a small range because of its bicyclic nature.[7c] In connection with the design of topographically constrained peptides, Tic has been utilized in several instances as a replacement of Phe or Tyr. For example, Tic has been used as a replacement of Phe in the design of δ-opioid peptide antagonists and these derivatives are found to have useful therapeutic applications.[31] Moreover, the tetrahydroisoquinoline unit is an important structural element in alkaloids and other medicinally important compounds. Tic derivatives prepared by this methodology may find useful application in meaningful QSAR studies.[31] Most of the known methods (e.g., Bischler–Napieralski reaction and Pictet–Spengler reaction) for Tic preparation start with the preformed benzene derivatives, and substrates with electron-withdrawing groups are not suitable starting materials for this purpose.[32] The proposed methodology involves generation of benzenoid ring system via the cycloaddition reaction, thus providing a unique opportunity to generate various inaccessible Tic derivatives by varying the dienophile.[33]

Various cycloaddition approaches to the Tic derivatives are shown in Figure 6. Path a involves a [2+2+2] cycloaddition strategy in which the linearly substituted Tic derivatives are the expected products. The other approaches are based on a [4+2] cycloaddition strategy wherein both the linearly and the angularly substituted racemic Tic derivatives can be generated by using structurally isomeric dienes (e.g., **65** and **68**). The inner–outer ring dienes can be assembled by a cycloisomerization reaction or via enyne-metathesis reaction of the appropriate enyne building blocks.

Diynes **69**, the starting materials for the synthesis of Tic derivatives (e.g., **71**), were synthesized starting from the benzophenone Schiff base ester by a four-step sequence.[33] Reaction of the diyne **69** with various monoalkynes **70** under Wilkinson's catalyst or $CpCo(CO)_2$ catalysis conditions gave various Tic derivatives in good to moderate yields (Scheme 12). Monoalkynes without hydroxy functionality gave poor yields under Wilkinson's catalyst conditions when compared with the cobalt catalysis conditions. In the case of BTMSA and DMAD, only the $CpCo(CO)_2$ catalyst was effective for the co-trimerization reaction.[33]

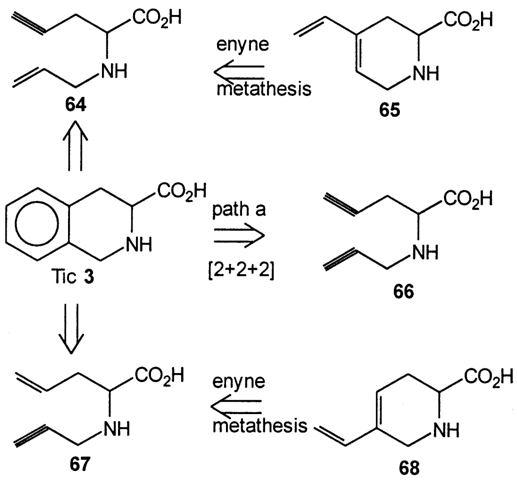
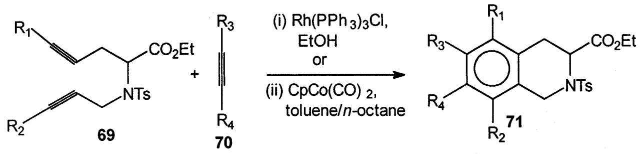


FIGURE 6. Retrosynthetic analysis for tic derivatives.

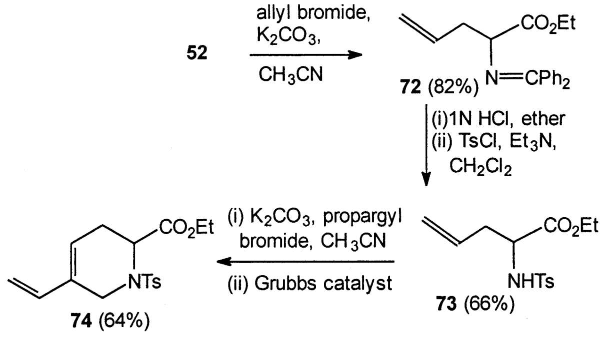
Scheme 12



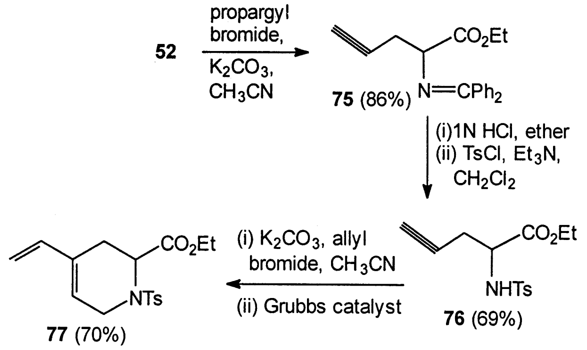
71a R_1, R_2= H R_3, R_4= CH_2OH (53%)
71b R_1, R_2= H R_3, R_4= TMS (20%)
71c R_1= H, R_2= TMS R_3, R_4= CO_2Me (45%)
71d R_1= H, R_2= TMS R_3, R_4= Ph (42%)

71a prepared by $Rh(PPh_3)_3Cl$
71b–71d prepared by $CpCo(CO)_2$

Scheme 13



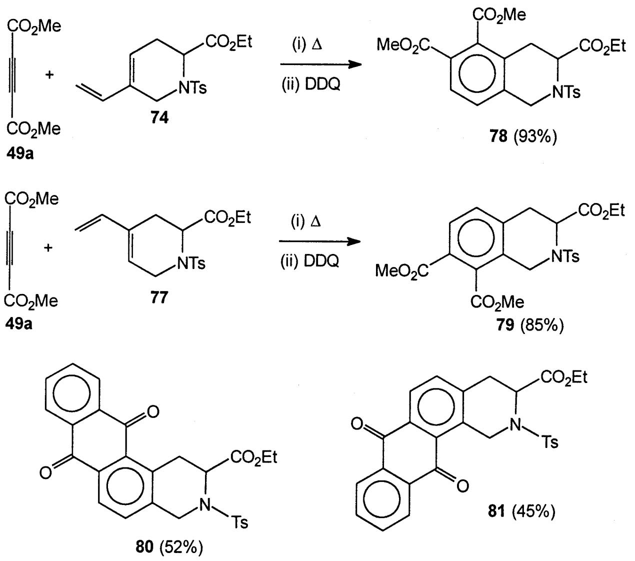
Scheme 14



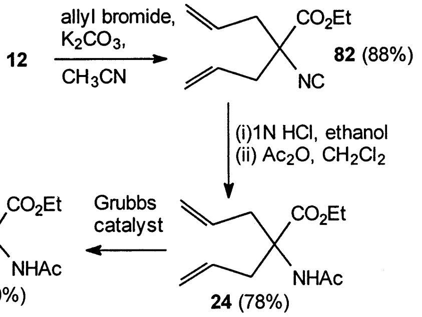
To realize the Diels–Alder approach for the synthesis of Tic derivatives, the diene building blocks **74** and **77** were synthesized using the enyne-metathesis reaction as a key step. The required starting materials for the enyne-metathesis reaction were prepared in excellent yield via a stepwise alkylation of the Schiff base ester followed by hydrolysis and N-protection. Treatment of enyne derivatives with the Grubbs catalyst in refluxing toluene gave the corresponding inner–outer ring diene building blocks **74** and **77** (Schemes 13 and 14).[34] The Diels–Alder reaction of the dienes **74** and **77** with DMAD and subsequent oxidation of the adducts generated the angularly substituted Tic derivatives (**78** and **79** respectively) in good yields (Scheme 15).[34]

Treatment of the dienes **74** and **77** with 1,4-naphthoquinone in refluxing toluene gave the Diels–Alder adducts, which on dehydrogenation using DDQ gave the

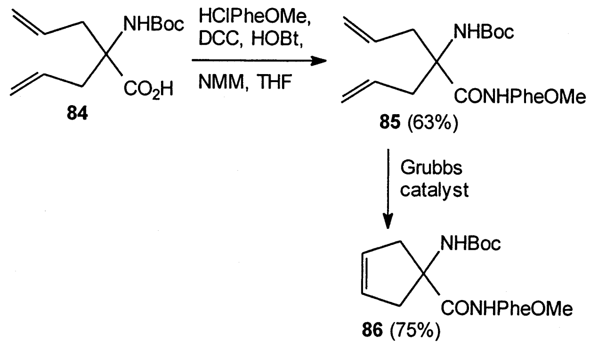
Scheme 15



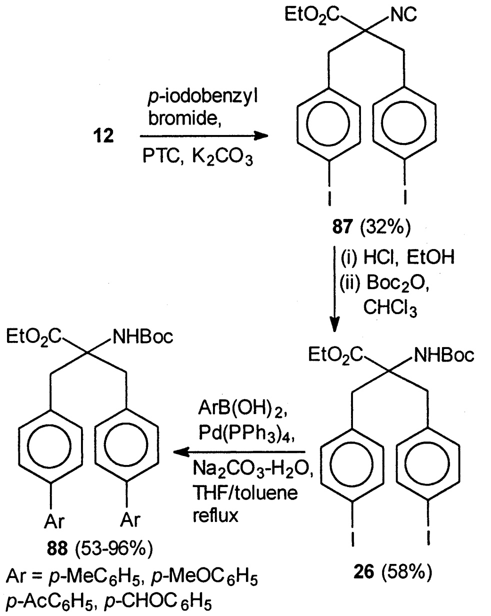
Scheme 16



Scheme 17



Scheme 18



angularly substituted Tic derivatives (e.g., **80** and **81** respectively).

Synthesis of Cyclic AAA Derivatives and Modification of Peptides by the Ring-Closing Metathesis (RCM) Reaction[35]

Cyclic AAAs with additional functional groups can be useful for further synthetic transformations. In this regard, the RCM reaction provides an additional double bond in the cyclic system. To prepare cyclic AAA derivatives such as **83** by the RCM reaction, the required diolefin derivatives were synthesized by dialkylation of ethyl isocyanoacetate (**12**) using appropriate electrophiles under solid–liquid PTC conditions. The unstable isonitrile derivative **82** was converted to the *N*-acetyl derivative **24** by hydrolysis followed by N-protection. The diene building blocks were then subjected to RCM reaction using the Grubbs ruthenium catalyst to yield five-membered cyclic α,α-AA derivative (Scheme 16).[35a]

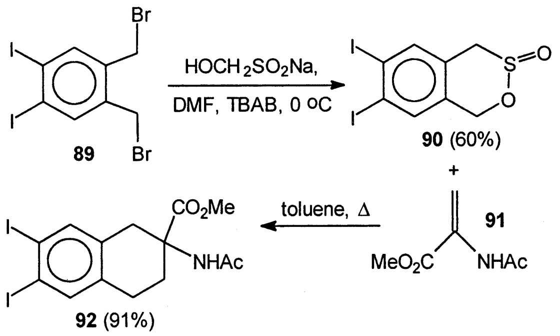
This strategy was extended to a seven-membered AAA derivative. To apply the RCM methodology for peptide modification, several peptides were synthesized by incorporating *tert*-butyloxycarbonyl (Boc) derivatives of the diene building block **84** into short peptides. The RCM reaction of various peptide derivatives (e.g., **85**) gave the desired RCM products (e.g., **86**) in good yields (Scheme 17).[35b]

Synthesis of Dibenzylglycine Derivatives

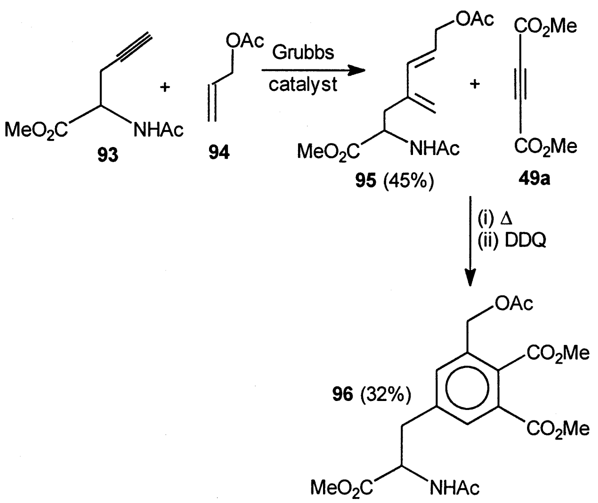
Preparation of dibenzylglycine (Dbzg) derivatives via the Bücherer–Berg method is not a trivial exercise because the starting carbonyl compounds are not readily available and, moreover, the hydrolysis of the intermediate hydantoins is difficult to achieve. In this regard, ethyl isocyanoacetate (**12**) was alkylated with *p*-iodobenzyl bromide under solid–liquid PTC conditions [TBAHS, K_2CO_3, CH_3CN, reflux], and the unstable isonitrile derivative **87** was converted to the corresponding N-Boc derivative **26** as shown in Scheme 18**.** Various other benzyl bromide derivatives also underwent dialkylation under these conditions.[36]

The SM cross-coupling reaction of the diiodo compound **26** with various arylboronic acids gave the products **88** in good yields. These may not be accessible by direct alkylation of ethyl isocyanoacetate (**12**), as the highly functionalized benzyl bromides are difficult to prepare and dialkylation of glycine derivatives with sterically hindered benzyl bromides can be difficult, as indicated by recent reports.[37] In addition, preparation of the building block

Scheme 19



Scheme 20



26 provides for the synthesis of highly substituted Dbzg derivatives.[36]

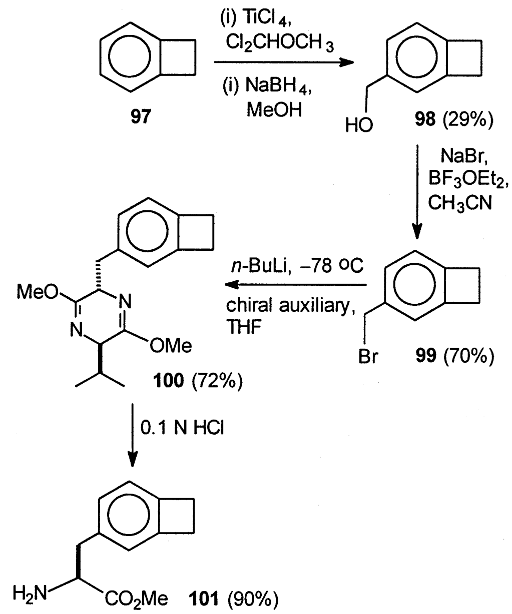
Synthesis of Tetralin-Based Constrained AAA Derivatives by the Diels-Alder Strategy

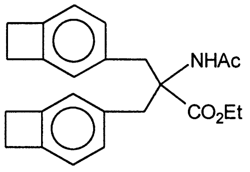
Tetralin-based constrained AAA derivatives such as **92** have been prepared by *o*-xylylene intermediate by extrusion of sulfur dioxide from the sultine derivative **90**, which was prepared from 4,5-diiodo-*o*-xylene dibromide **89**. The Diels–Alder reaction of **90** with 2-acetamidoacrylate (**91**) gave the tetralin-based AAA derivative **92** (Scheme 19).[38]

Synthesis of Miscellaneous AAA Derivatives

To expand the building block approach for various unusual AAA derivatives, we have developed a useful methodology to highly functionalized Phe derivatives, benzocyclobutene (BCB) and cyclophane based unusual AAA derivatives (e.g., **96**, **101** and **105**). Synthesis of the Phe derivative **96** was accomplished by the cross-enyne metathesis followed by a Diels–Alder reaction as shown in Scheme 20.[39] BCB-based AAA derivative **101** was prepared by alkylation of the Schöllkopf chiral auxiliary with suitably substituted BCB derivative as shown in Scheme 21.[40] BCB derivatives are thought to be useful because of their ability to undergo the Diels–Alder reaction via *o*-xylylene intermediates.[41] We also found that ethyl isocyanoacetate (**12**) is useful to prepare dibenzocyclobutenylglycine derivative **102**.[42]

Scheme 21

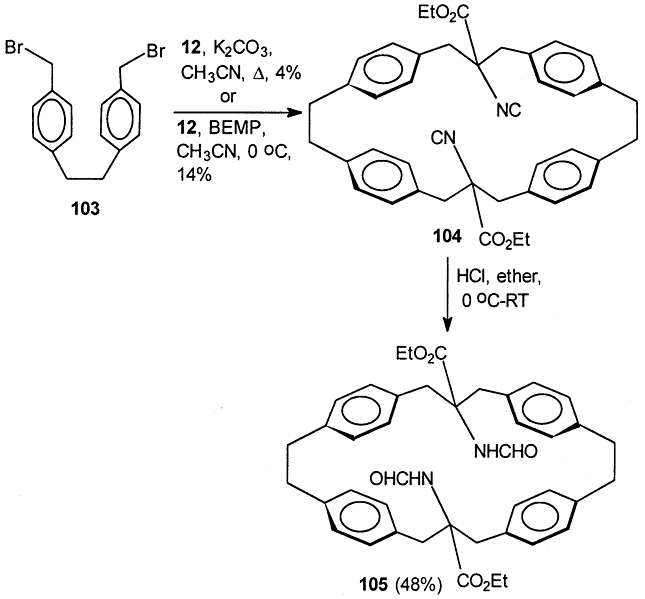




102 (44% overall yield from **12**)

Cyclophane-based unusual AAA derivative **105** has been prepared as shown in Scheme 22.[43]

Scheme 22



Conclusions

We have demonstrated that the building block approach is useful to prepare highly constrained cyclic AAA derivatives. Metathesis reactions (e.g., ring-closing metathesis, enyne metathesis, cross-enyne metathesis), the Diels–Alder reaction, the [2+2+2] cycloaddition reaction, and the Suzuki coupling reaction have been used to prepare various unusual AAA derivatives. Also, it has been shown that posttranslational peptide modifications are feasible by using RCM,[35b] [2+2+2] cycloaddition,[22] and Suzuki coupling reactions.[2b] In view of the expanding market for peptide drugs, these results will be of interest to bioorganic and medicinal chemists. Since a number of building blocks have been prepared, these methodologies should find useful applications in solid-phase synthesis and combinatorial chemistry. With the available techniques in molecular biology,[44] it may be possible to incorporate these unusual AAA derivatives into proteins and thus providing a useful tool for protein engineering.

I would like to thank my former and present group members, whose names appear in the reference section, for their valuable contributions. Financial support from the DST is gratefully acknowledged. I thank RSIC-Mumbai for providing the spectral data. I would also like to thank Professors G. Mehta and A. Srikrishna for helpful discussions.

Abbreviations

Glossary

AAA	α-amino acid
ααAA	α,α-dialkylated α-amino acid
Aib	α-aminoisobutyric acid
BB	building block
BCB	benzocyclobutene
Boc	*tert*-butyloxycarbonyl
BTMSA	bis(trimethylsilyl)acetylene
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DMF	N, N-dimethylformamide
DMSO	dimethyl sulfoxide
DMAD	dimethylacetylenedicarboxylate
Dbzg	dibenzylglycine
HOBt	1-hydroxybenzotriazole
Ind	2-aminoindane-2-carboxylic acid or 2-indanylglycine
LAH	lithium aluminum hydride
NMM	*N*-methylmorpholine *N*-oxide or 4-methylmorpholine-*N*-oxide
Phe	phenylalanine
PTC	phase-transfer catalyst
QSAR	quantitative structure activity relationship
RCM	ring-closing metathesis
SM	Suzuki–Miyaura
TBAHS	tetrabutylammonium hydrogen sulfate
TBAB	tetrabutylammonium bromide
Tic	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
Ts	*p*-toluenesulfonyl
Tyr	tyrosine

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