JOC The Journal of Organic Chemistry

Perspective

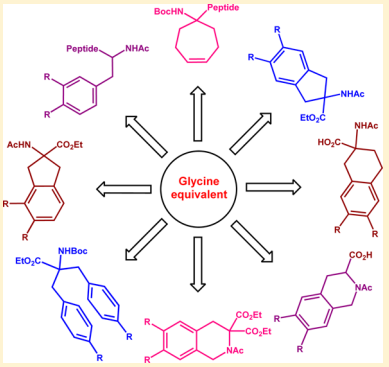
pubs.acs.org/joc

Diversity-Oriented Approaches to Unusual α-Amino Acids and Peptides: Step Economy, Atom Economy, Redox Economy, and Beyond

Sambasivarao Kotha,* Deepti Goyal, and Arjun S. Chavan

Department of Chemistry, Indian Institute of Technology Bombay Powai, Mumbai 400 076, India

ABSTRACT: Here we describe several useful strategies to a variety of unusual α-amino acid derivatives and peptides based on "building block" approach. These building blocks are suitable for modification at an amino acid as well as at a peptide level. Moreover, these methods have embedded several points for diversification and are capable of producing a library of modified amino acids and peptides. We have employed highly atom-economic processes such as the Diels–Alder reaction, [2 + 2 + 2] cycloaddition, Suzuki–Miyaura cross-coupling, and olefin metathesis as key steps to assemble various unnatural amino acid derivatives and peptides. In some instances, we have used rongalite to generate Diels–Alder precursors.



THE NEED TO DEVELOP NEW METHODS TO UNUSUAL AMINO ACIDS

Peptides and proteins play an important role in various biological processes. They are employed as natural messengers of living systems. Therefore, they can be useful as therapeutic agents with fewer side effects. However, their use is often hampered by biodegradation, nonselectivity, and high conformational flexibility.[1] Peptide-based drugs are commonly used for osteoporosis, diabetes, and hypertension, and the need for peptide-based drugs is likely to increase in the near future. To overcome the problems associated with the activity of peptide drugs, introduction of modified amino acids can be a useful alternative. On several occasions, unusual α-amino acids (AAAs) have been incorporated into peptides to modify the conformation and enhance the stability of the peptides. These modified peptides are found to be biologically more active than the natural analogues.[2] Motivated by such a need for postassembly peptide modification, there is an opportunity to design new strategies which are capable of modification at an amino acid as well as at the peptide level.

Here, we have compiled our efforts toward the synthesis of unnatural AAA derivatives. Some of them have been incorporated at the peptide level, and postassembly peptide modifications were performed by means of chemical methods.

CYCLIC AMINO ACID DERIVATIVES

Our initial approach to diverse AAA derivatives discussed here is based on the alkenylation of various glycine equivalents followed by ring-closing metathesis (RCM) sequence. We have used various ruthenium catalysts (Figure 1) to perform this metathesis protocol.

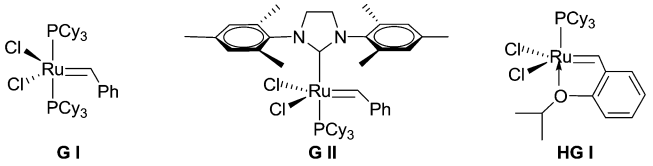


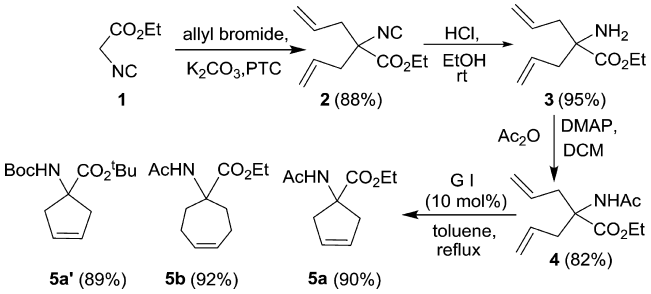
Figure 1. Catalysts used for metathesis.

To realize the diversity-oriented approach to unusual cyclic AAA derivatives, various methods were explored to achieve regioselective alkylation at the nitrogen, α-carbon, or oxygen atom of glycine. The alkylation protocol was further extended to design various unusual AAA derivatives based on 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic), and indane (Ind) ring systems. Initially, we identified RCM[3] as a key step to synthesize cyclic AAA derivatives. To this end, the required bis-alkylated derivative **2** was assembled from ethyl isocyanoacetate (**1**) using allyl bromide under phase-transfer catalysis (PTC) conditions. The unstable isonitrile **2** was converted to *N*-acetyl derivative **4** by acid hydrolysis in protic solvent followed by *N*-acetylation. The diallylated building block **4** was then subjected to RCM in the presence of Grubbs' first-generation catalyst to deliver the five-membered constrained AAA derivative **5a** (Scheme 1). By adopting the same methodology and varying the length of the electrophile during the alkylation sequence, we have synthesized the seven-membered cyclic AAA derivative **5b**.[4] The above strategy has been adopted by various other groups for the synthesis of unusual amino acid derivatives.[5] For example, the cyclic amino acid **5b** with Boc protection **5b′** has been used by Cativiela and

Received: September 18, 2013
Published: November 12, 2013

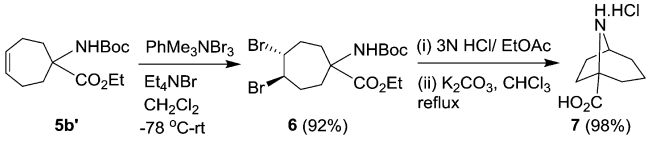
dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288–12313

Scheme 1



co-workers for the synthesis of azabicyclic derivative **7** (Scheme 2).[5a] In addition, similar types of cyclic AAA derivatives have

Scheme 2



been prepared by Plé and co-workers via a Claisen rearrangement–metathesis sequence.[6] Further, an AAA derivative of type **5a″** has been used for the preparation of bicyclic acidic amino acids **11** and **12**, which were later evaluated for anticonvulsant activity (Scheme 3).[7] Brunel reported the synthesis of another derivative of **5a** with different protecting groups (**5a′**) using the above strategy.[8] The synthesis of cyclic amino acid **17** was reported by other workers using different approaches involving alkylation followed by Curtius degradation (Scheme 4).[9]

Next, having developed an RCM approach to cyclic AAA derivatives; the logical extension seems to be the application of these methodologies to peptide modifications involving RCM as a key step.[10] In this regard, we have devised a new postassembly peptide modification strategy involving α, α'-cyclic peptides with restrained conformation by RCM. To this end, the dialkylated building blocks were incorporated in a peptide sequence. Thus, a suitable building block **19** was assembled from ethyl isocyanoacetate (**1**) in four steps, and it was incorporated in a peptide sequence with L-Phe methyl ester hydrochloride using a standard peptide coupling reagent such as DCC. The modified peptide **20** was then subjected to RCM to deliver the desired peptide **21a** (Scheme 5).[11] Various modified cyclic di- and tripeptides were assembled by this strategy. Variation in ring size has been accomplished by changing the length of alkenyl chain during the alkylation sequence. RCM strategy has been used by various other groups to assemble cyclic peptides.[12]

Later, our efforts were directed toward the synthesis of cyclic AAA derivatives where the nitrogen atom was situated as a part of cyclic system. In this regard, we have identified commercially available and inexpensive nucleophilic glycine equivalents such as diethyl acetamidomalonate (DEAM) **22** as a useful starting material. After a considerable amount of experimentation, it was found that regioselective *N*-alkenylation was feasible in the presence of potassium hydride as a base. Later, the *N*-alkenylated substrate **23a** was subjected to selective *C*-alkenylation using Cs_2CO_3. The dialkenylated substrate **24a** was then subjected to RCM under high dilution condition to deliver a six-membered nitrogen-containing aminomalonic acid derivative **25a** (Scheme 6). Eight- and nine-membered ring systems (**25b** and **25c**, respectively) were also realized by varying the length of the alkenyl chain attached to nitrogen.[13]

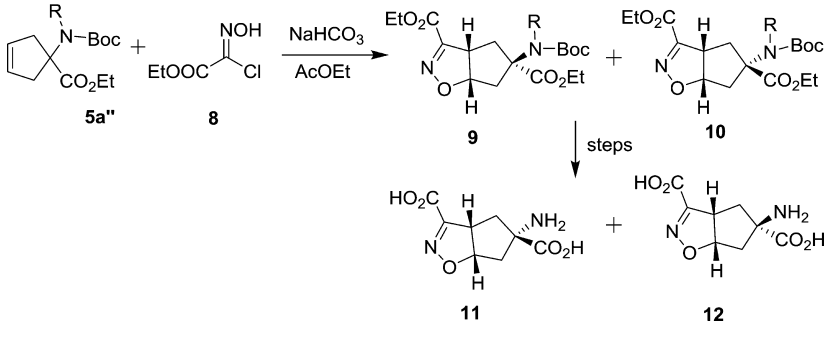
MACROCYCLIC AAA DERIVATIVES

Next, attention was directed to assemble a relatively unexplored and conformationally constrained amino acid derivative such as a seven- or eight-membered ring system. To this end, once again RCM was considered as a key reaction. Here, suitably protected allyl glycine was used as a key building block. The allyl glycine derivative **26** was treated with 4-bromo-1-butene to prepare *N*-alkenylated substrate **27a**. The RCM protocol of **27a** using G-II gave the seven-membered ring system **28a** (Scheme 7). Under similar reaction conditions, eight-membered ring system **28b** containing a constrained cyclic α-amino acid derivative has been prepared.

In an attempt to prepare a nine-membered analogue, surprisingly, an isomeric mixture of 18-membered macrocyclic bis-α-amino acid derivatives **28c** and **28c′** was obtained as a major product along with a minor amount of compound **28b**. The formation of **28b** has been attributed to the isomerization of terminal alkene in substrate **27c** followed by RCM.[14]

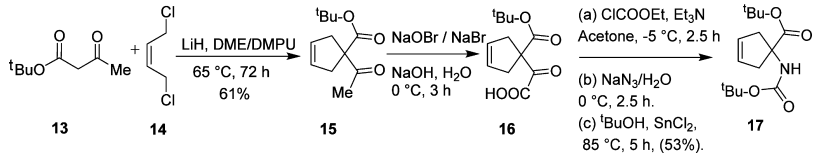
Recently, we have explored a tandem metathesis sequence to generate densely functionalized macroheterocycles with an amino acid scaffold. The required enyne building block **31** has been obtained from *N*-tosylglycine **29**. Thus, treatment of **29** with propargyl alcohol gave the propargylated ester **30**, which on treatment with the allyl bromide gave the enyne precursor **31**, which was then subjected to a tandem cross-enyne–ring-closing metathesis (CE-RCM) with 1,5-hexadiene as a coupling partner to deliver the 13-membered macrocyclic system **32a** and an open-chain product **33** (Scheme 8). Further, this strategy has been expanded to generate higher macrocyclic systems of ring sizes up to 14–16 members by varying the

Scheme 3

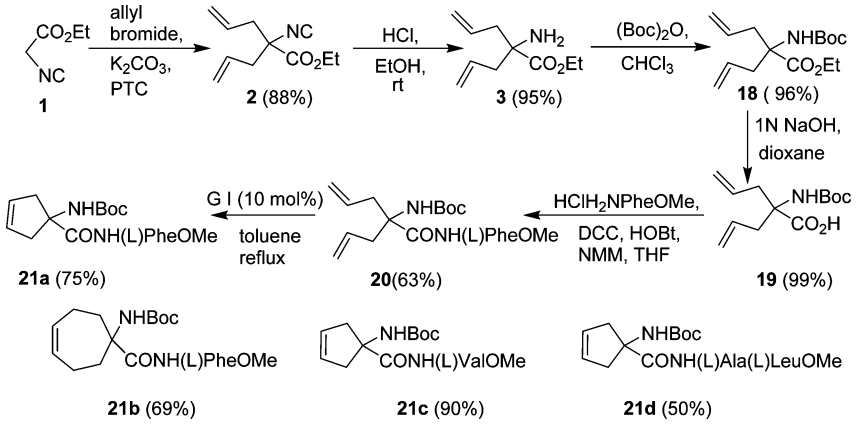


dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288–12313

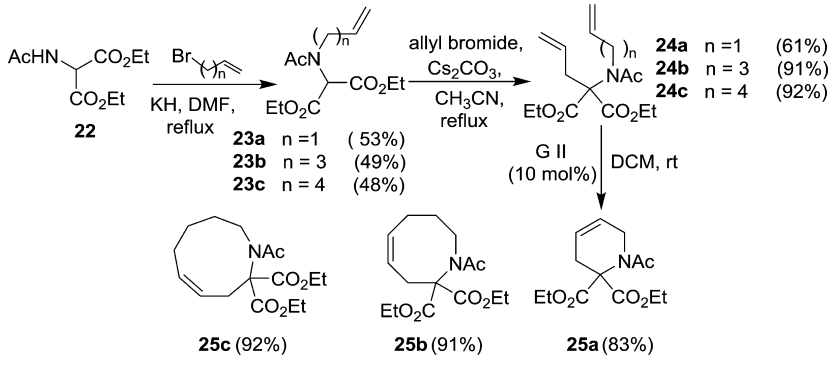
Scheme 4



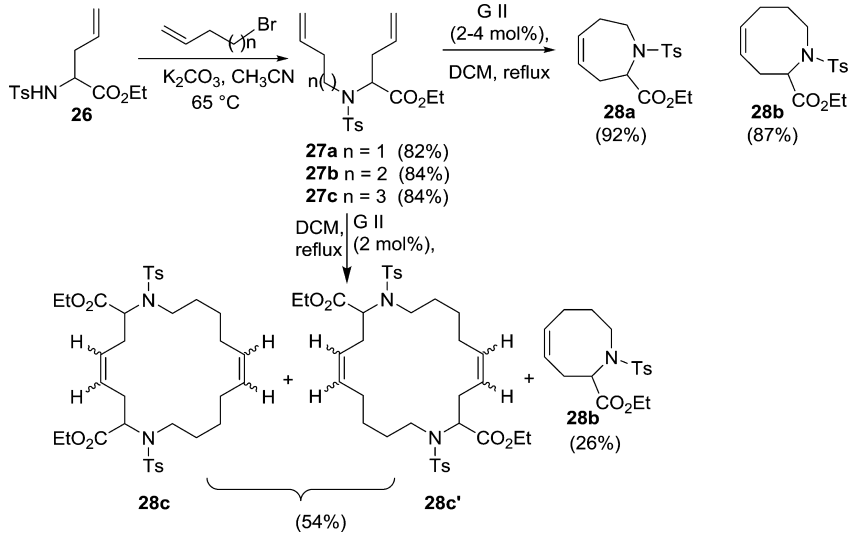
Scheme 5



Scheme 6

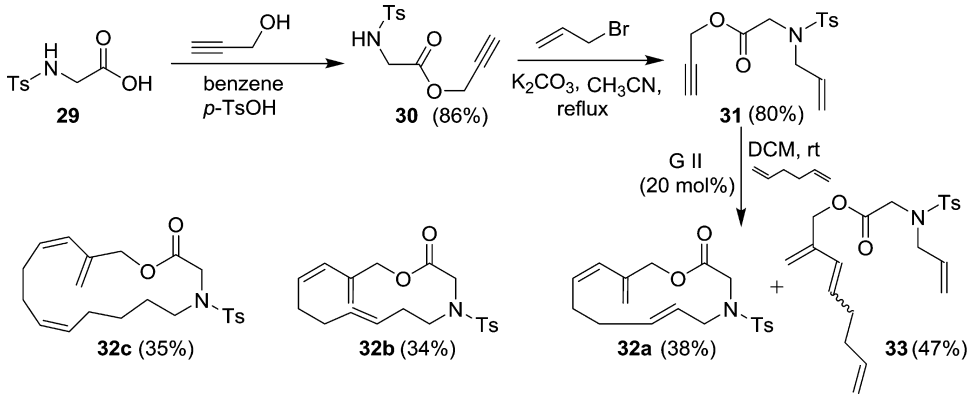


Scheme 7

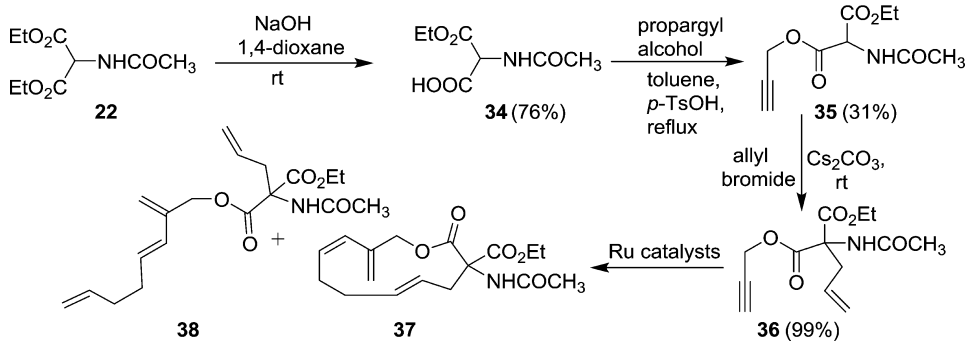


dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288−12313

Scheme 8



Scheme 9



length of alkenyl and alkynyl partners attached to the nitrogen and oxygen atoms.[15] This work has been highlighted in *Chemtracts—Org. Chem.* by Rolfe and Hanson.[16]

The above methodology was further extended to synthesize the C-α,α'-functionalized macrocyclic AAA derivative. Toward this goal, a suitable enyne precursor **36** was obtained from DEAM in three steps. Partial hydrolysis of DEAM followed by *O*-propargylation gave the diester **35**, which was then subjected to *C*-allylation to generate the required enyne building block **36**. Treatment of this enyne substrate **36** with 1,5-hexadiene in the presence of metathesis catalyst gave the desired 12-membered macrocyclic AAA derivative **37** in addition to open-chain AAA derivative **38** (Scheme 9). Systematic catalyst screening gave a selective formation of the desired macrocyclic AAA derivative **37**.[17] Surprisingly, these AAA derivatives **37** and **38** were found to give blue emission, which may open new application as chelators for metal ions and biosensors.

Armed with the experience of designing various macrocyclic AAA derivatives, next our efforts were directed to alkylate the nitrogen, oxygen, and carbon atoms of glycine equivalents to assemble other unusual AAA derivatives such as Tic, 2-aminotetralin-2-carboxylic acid (Atc) and indane-based amino acid derivatives (Figure 2).

These unusual AAAs are considered as constrained analogues of phenylalanine (Phe)[18] and constitute an important structural core of many biologically active compounds (Figure 3).[19] If one can generate a simple and general method to these unusual amino acids then they can be incorporated into biologically active peptides and generate diverse analogues for structure—activity or conformational activity relationship studies.

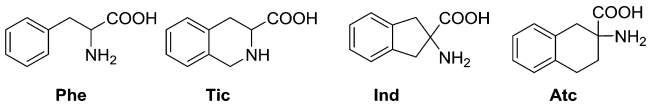


Figure 2. Constrained analogues of Phe.

1,2,3,4-TETRAHYDROISOQUINOLINE-3-CARBOXYLIC ACID (TIC)

Tic is a constrained analogue of Phe where the dihedral angle is limited to a small range (χ = +60°, −60°).[20] Thus, Tic is used to impart conformational constraint in the peptide backbone, which is useful in modulating the pharmacological properties of a given peptide. Introduction of Tic in δ-opioid receptors was found to enhance their selectivity and binding affinity.[21] Thus, there is a need to design a simple and general synthetic strategy to generate diverse Tic derivatives starting from easily accessible materials. We have used diverse synthetic strategies such as [2 + 2 + 2] cyclotrimerization,[22] enyne metathesis, and base-induced alkylation to assemble Tic derivatives. In the [2 + 2 + 2] cycloaddition strategy, linearly substituted Tic derivatives are the expected products, whereas by the [4 + 2] cycloaddition route both linearly as well as angularly substituted Tic derivatives can be assembled (Figure 4).

[4 + 2] cycloaddition and [2 + 2 + 2] cycloaddition are somewhat complementary in the sense that in the [4 + 2] cycloaddition strategy the dienophile component contains an electron-withdrawing group(s) (e.g., dimethyl acetylenedicarboxylate (DMAD)), whereas the [2 + 2 + 2] cycloaddition strategy utilizes but-2-yne-1,4-diol **43** as a co-trimerization partner. Utilization of but-2-yne-1,4-diol **43** is useful for further expansion of these substrates to design sultine intermediates suitable for DA chemistry. The later synthetic strategy ensures redox economy because the diol **43** is the reduced form of

dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288−12313

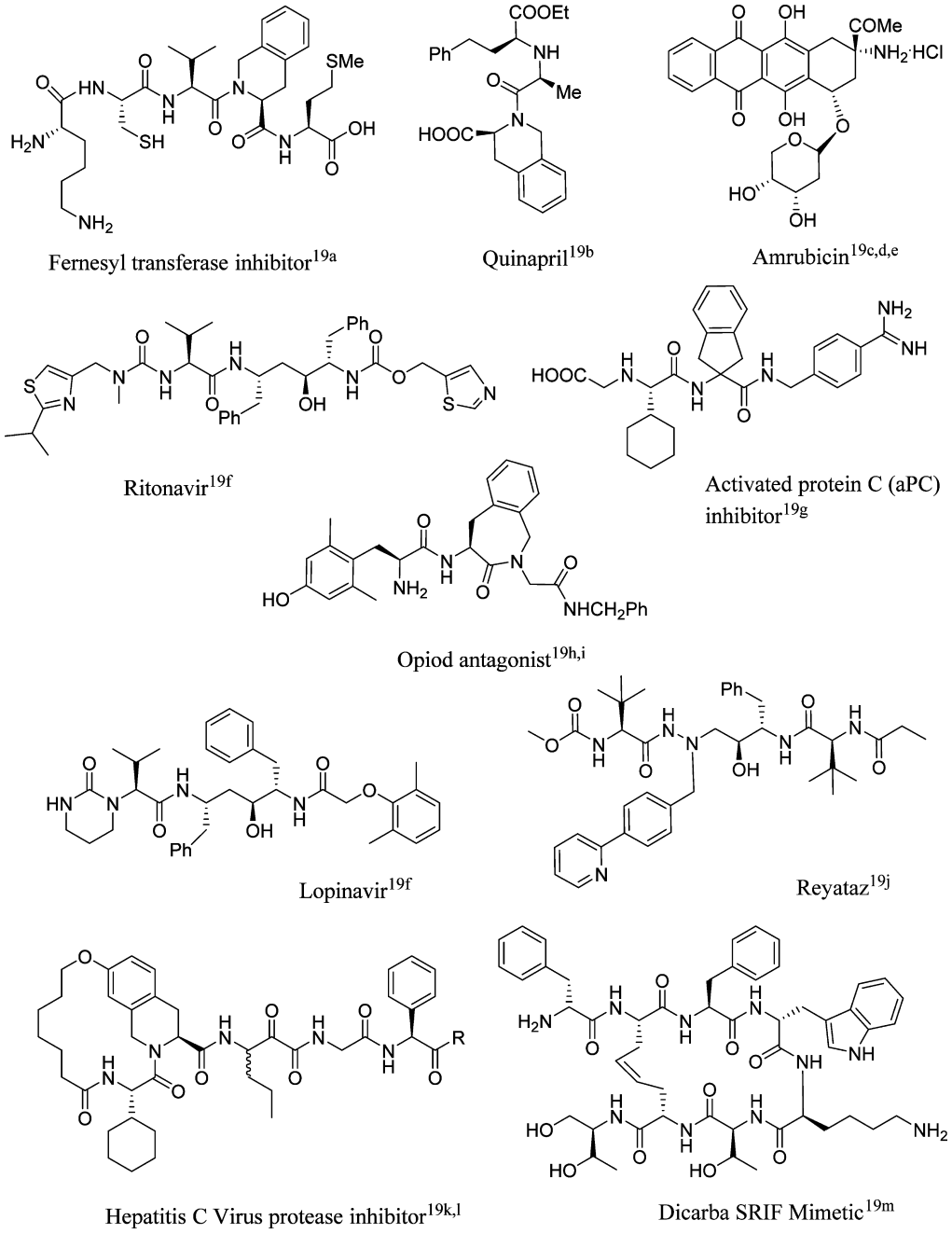


Figure 3. Biologically active compounds containing sterically constrained Phe analogues.

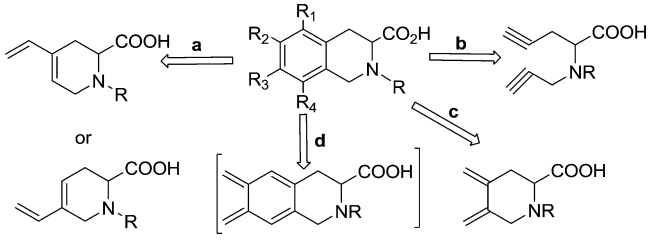


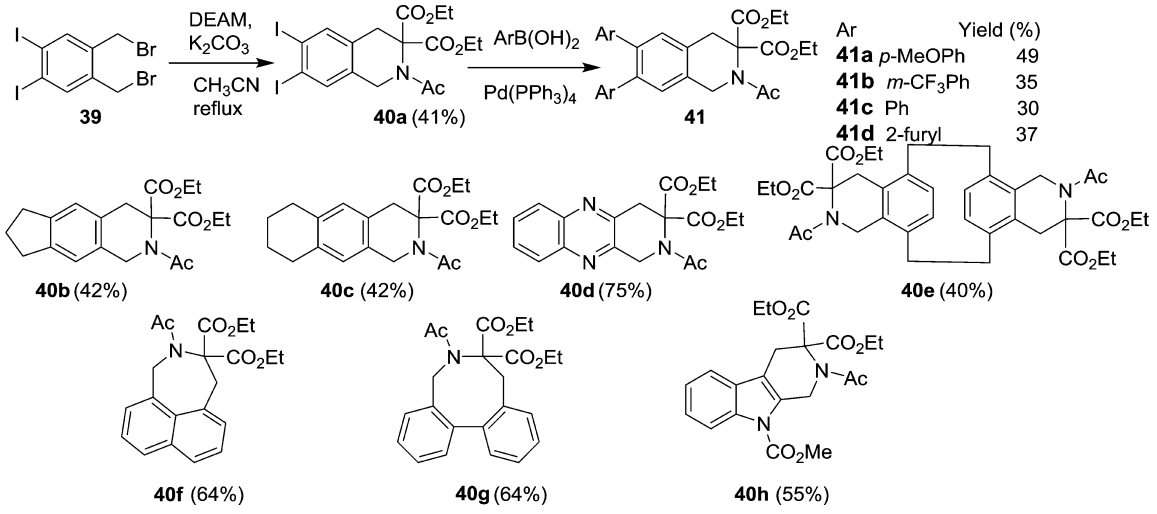
Figure 4. Retrosynthetic approaches to Tic derivatives.

DMAD, and its incorporation in Tic derivative allows the further utility of the end products in assembling various inaccessible AAA derivatives by DA strategy.

Before discussing various cycloaddition approaches to Tic-based AAA derivatives, a simple methodology to Tic derivatives by alkylation sequence is discussed. In this regard, alkylation of DEAM with a suitable 1,2-bis(bromomethyl)-4,5-diiodobenzene or 4,5-diiodo-α,α'-dibromo-*o*-xylene (**39**) has been used to generate various Tic derivatives. For example, compound **39** was reacted with DEAM in the presence of K_2CO_3 under PTC conditions to generate Tic derivative **40a**, which undergoes a Suzuki−Miyaura (SM) cross-coupling reaction with various boronic acids to deliver different Tic derivatives **41a−d** (Scheme 10).[23] This methodology was also extended to synthesize carbocyclic ring fused Tic (**40b,c**), heterocyclic Tic derivative (**40d**), cyclophane-based Tic derivative (**40e**), and higher analogues of Tic (Sic and Hic, **40f,g**) by reacting the corresponding dibromo compound with DEAM. Furthermore, this methodology was used to obtain the indole-based Tic **40h** (tetrahydro-β-carboline) derivative. The structure of the AAA

dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288−12313

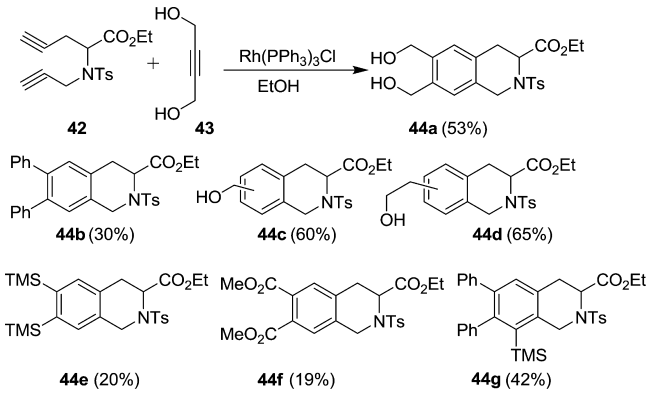
Scheme 10



derivative **40h** has been unambiguously established on the basis of single-crystal X-ray diffraction studies.[24]

Our next strategy to assemble Tic derivatives involved a building block approach based on the [2 + 2 + 2] cycloaddition reaction as a key step. The [2 + 2 + 2] cyclotrimerization approach to benzoannulated products is an atom-economical process. Here, one can use a redox-economy precursor such as but-2-yne-1,4-diol **43** as a co-trimerization partner. Diyne building block **42** was reacted with monoalkyne **43** in the presence of Wilkinson's catalyst to give the desired Tic derivative **44a** (Scheme 11).[25] Cobalt catalysis seems to be

Scheme 11



better than Wilkinson's catalyst with monoalkynes devoid of hydroxyl functionality. For example, the trimerized product was obtained in the presence of cobalt catalyst with bis(trimethylsilyl)acetylene (BTMSA) and dimethyl acetylenedicarboxylate (DMAD). Thus, a library of multifunctional Tic derivatives (**44a**−**g**) were synthesized using transition-metal-catalyzed [2 + 2 + 2] cycloaddition reaction as a key step. Recently, Dixneuf and co-workers have used this strategy for assembling fluorinated Tic derivatives.[26] Further, the [2 + 2 + 2] strategy described above (Scheme 11) has been synergistically combined with the Diels−Alder (DA) chemistry involving sultine derivative **46** as a precursor to *o*-xylylene intermediate **46a** to assemble highly functionalized Tic-quinone hybrids (Scheme 12). By utilizing but-2-yne-1,4-diol **43**, one can generate sultine derivatives (e.g., **46**) easily without involvement of the protecting groups. The required diol precursor **44a** was obtained from dialkyne building block **42** involving a [2 + 2 + 2] cycloaddition sequence.[25]

Subsequent heating of the sultine **46** at 85−90 °C gave the transient *o*-xylylene intermediate **46a**. Trapping the transient diene **46a** with various dienophiles in a DA fashion gave the cycloadducts, which on aromatization with activated MnO_2 gave densely functionalized Tic derivatives (**48a**−**e**) (Scheme 12) in an efficient and atom-economic manner.[27,28]

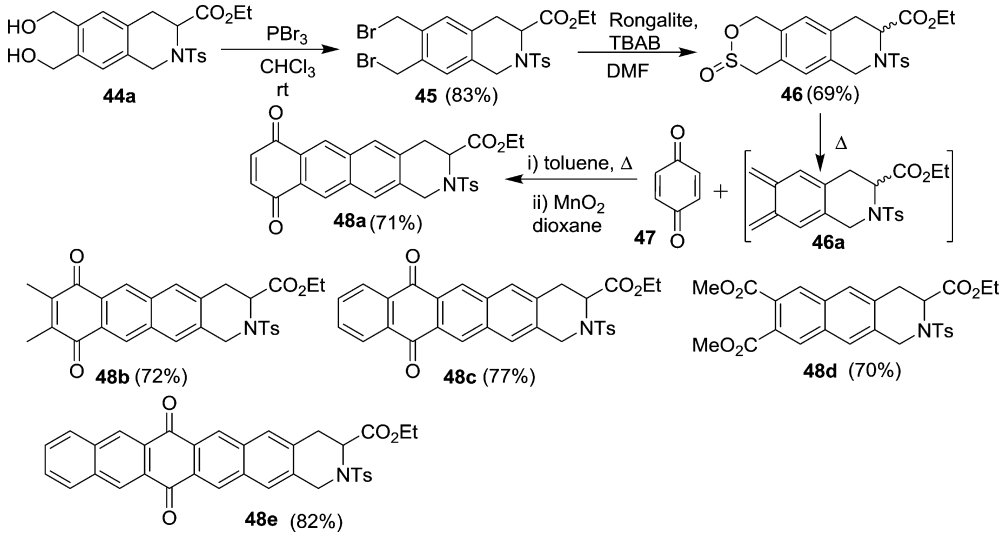
Later efforts were directed to combine enyne metathesis (EM) and the DA reaction[29] to synthesize angularly substituted Tic derivatives. The cycloaddition approach to Tic derivatives is better than the traditional methods such as the Pictet−Spengler or the Bischler−Napieralski reaction.[30] These classical methods generally do not accommodate densely functionalized benzene derivatives as starting materials. In our approach, various inner−outer diene building blocks (e.g., **52** and **54**) were assembled to prepare Tic derivatives.[31] In this regard, the pioneering efforts of Stork[32] and O'Donnell[33] dealing with alkylation of Schiff's base **49** are useful to prepare allylated synthon, and some of these methodologies have been used to prepare indane-based amino acid derivatives.[34] These diene building blocks were further elaborated to functionalized Tic derivatives via the DA approach (Scheme 13). Using this strategy, various topographically constrained Tic derivatives (**53a**−**d**), were synthesized that are inaccessible by other known methods. This strategy involves atom-economic reactions such as enyne metathesis and DA reaction which is also employed by other groups.[35] During these studies, we have isolated a minor product **55**, and it is derived via a Pauson−Khand reaction. It is a useful precursor to the tecomanine-type of alkaloid.[31b] This observation seems to be the basis of the two subsequent reports by Schore[36] and Gais.[37] Later, the same strategy was used to assemble a higher analogue of Tic **53e** by increasing the chain length of the alkenyl component.[38] The enyne substrate **51** with different protecting groups has been explored for the synthesis of polycyclic pyrrole-2-carboxylates by Yamamoto's group via a domino coupling relay approach.[39]

2-AMINOTETRALIN-2-CARBOXYLIC ACID (ATC) DERIVATIVES

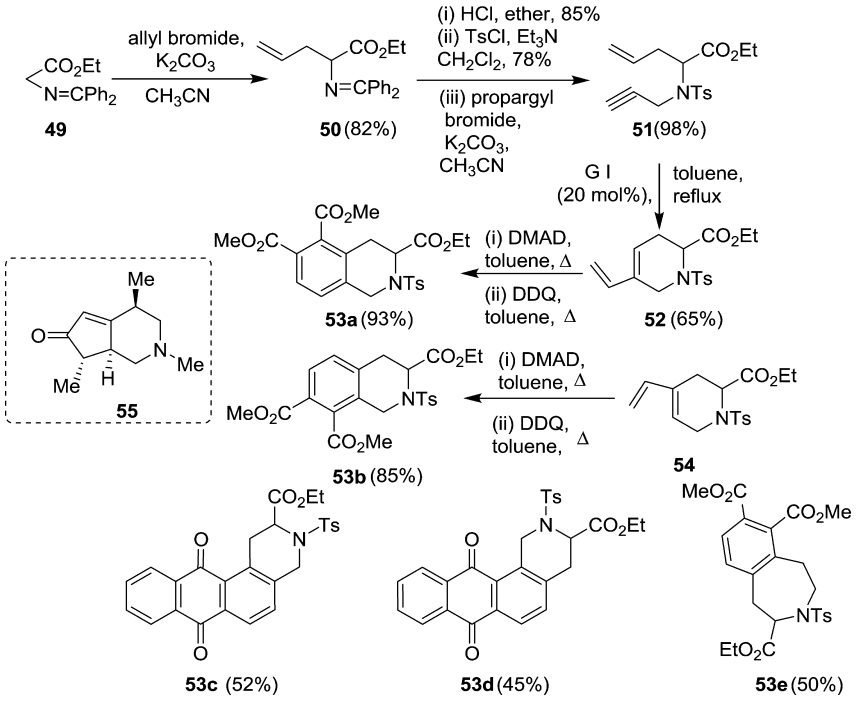
Tetralin-based AAA derivative is a constrained analogue of Phe, which has been extensively used to design bioactive peptides.

dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288−12313

Scheme 12



Scheme 13



Modified analogues of dynorphin-containing Atc has been synthesized as a potential analgesic, neuroprotective, and anticonvulsant agent by Aldrich and co-workers.[40a] Researchers at the NIH have designed the synthesis of arylphosphonate **58l** based on Atc in connection with cellular signal transduction process.[40b]

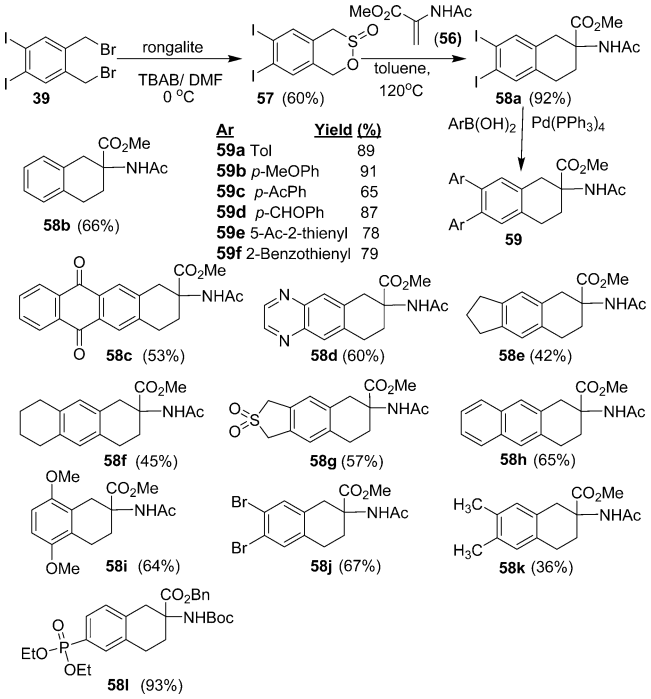
Classical methods such as the Bucherer–Bergs (BB) reaction are generally used to synthesize Atc derivatives and require drastic conditions for the hydrolysis of an intermediate spirohydantoin. Therefore, several sensitive substrates are not accessible by such a traditional method.[41] Thus, we conceived a new and general strategy to highly functionalized Atc derivatives by trapping transient *o*-xylylene intermediate[42,43] with 2-acetamidoacrylate **56**. To create a library of AAA derivatives, the dibromo compound **39** was treated with sodium hydroxymethanesulfinate (rongalite)[43] to generate the sultine derivative **57**. It was then treated with 2-acetamidoacrylate **56** to deliver the tetralin-based AAA derivative **58a** (Scheme 14).[44,45] Further, AAA derivative **58a** was functionalized via an SM coupling sequence.[44a] It is worth mentioning that a synthetic method (e.g., BB or Strecker method) to compound **58c** require several steps involving use of protecting groups due to the presence of keto functionality. Moreover, the preparation of the starting keto precursor required (i.e., 2-tetralone)[46] is not a trivial exercise. AAA derivative **58i** is a useful precursor to amrubicin (Figure 3). In this regard, Ishizumi and co-workers prepared this intermediate by the BB method.[47]

■ INDANE-BASED α-AMINO ACID DERIVATIVES

The indane ring system is a core structural unit present in several biologically important products.[18i,j] Modified AAAs containing an indane ring find useful applications in

dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288–12313

Scheme 14



peptidomimetics. Replacement of Phe with 2-indanylglycine in peptide modification results in enhanced desirable properties.[48]

We have designed various strategies to indane derivatives using diverse routes such as [2 + 2 + 2] cycloaddition, [4 + 2] cycloaddition, and EM as key steps. Enyne metathesis gives angularly annulated indane derivatives; whereas [2 + 2 + 2] cycloaddition and [4 + 2] cycloaddition approaches deliver linearly annulated indane derivatives (Figure 5). Cross-coupling

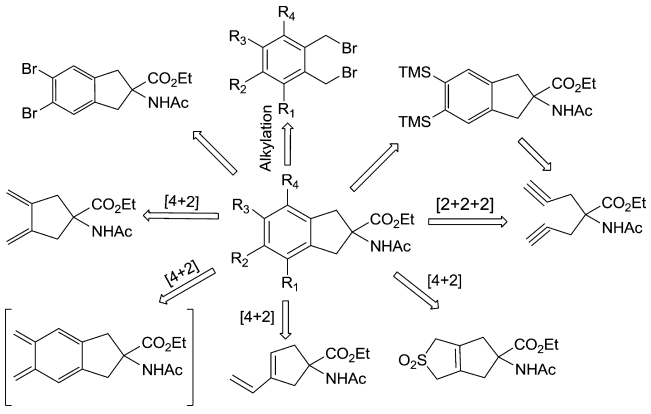


Figure 5. Diversity-oriented approaches to indane-based AAA derivatives.

strategy provides aromatic functionalized indane derivatives. Initially, we chose a simple strategy to prepare indane-based AAA derivatives. This approach involved coupling of various α,α'-dibromo-*o*-xylene derivatives with ethyl isocyanoacetate **1**[49,50] and was applicable to most of the substrates containing either electron-rich or electron-deficient moieties. A simple example of this strategy is demonstrated in Scheme 15.[51] The dibromide **60** was reacted with ethyl isocyanoacetate (EICA) **1** under solid−liquid PTC (Bu_4NHSO_4, K_2CO_3, MeCN reflux) conditions to generate the coupling product **61a** in 93% yield. In the absence of PTC conditions, a complex mixture of products was obtained. A library of functionalized indane-based AAA derivatives was assembled by this strategy.

This strategy is useful in assembling five-, six-, as well as seven-membered ring compounds via **61a−e**, **61f**, and **61g**[51,52] and also suitable for heteroaromatic systems such as furan. Since furan can undergo DA reaction, the cyclic AAA derivative **61e** may serve as a useful synthon for the synthesis of highly functionalized AAAs. Later, this methodology was extended to assemble not only linear but also angular indane-based AAA derivatives, i.e., **61h−i** by choosing an appropriate dibromo precursor.[53] This strategy was also used to synthesize diindane-based AAA precursor **61j**.[51,54] A sulfone-containing indane-based AAA **61k** was also assembled by this methodology.[55] It is worth mentioning that the sulfone moiety is a useful handle for further synthetic exploration.[56] This methodology was further used to synthesize anthracene-based indane systems **61l−m**.[57] Various halogenated indane-based AAA derivatives **61o−q** were also assembled. The halogen atom present in these AAA derivatives can serve as a handle for further synthetic manipulation.[58]

In an another report, Ni(II) complex serves as a nucleophilic glycine equivalent to generate indane-based amino acid **63** and its derivatives.[59] EICA has been used by Tanaka and co-workers[60] to synthesize the unusual amino acid derivative **63** which was later incorporated into peptide (Scheme 16).[61]

Recently, Mash and co-workers reported the synthesis of tyrosine analogues of enantiomerically pure (*R*)- and (*S*)-5-hydroxy-2-aminoindan-2-carboxylic acid by using EICA as a glycine equivalent and our alkylation method to synthesize intermediate precursor **65** (Scheme 17).[62] Our phase-transfer conditions were used by Mazaleyrat and co-workers for the synthesis of short peptides containing an ant Aib (2-amino-2,3-dihydro-1*H*-cyclopenta[*b*]anthracene-2-carboxylic acid) unit and to study their photophysical properties (Scheme 18).[63] In 1970, the Lewis group[64] reported the synthesis of indane-based AAA **76** by a multistep process (Scheme 19), whereas adoption of our alkylation strategy can yield the same AAA derivative in a single step.

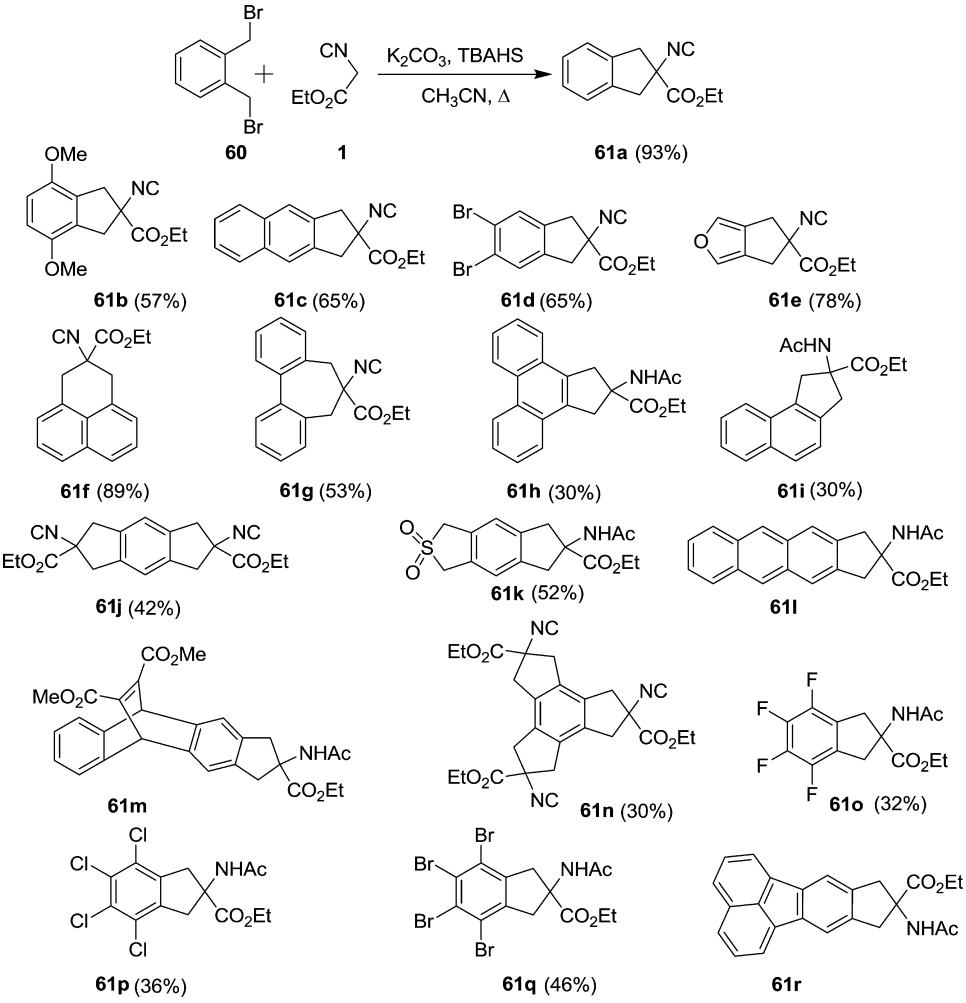
Mazaleyrat and co-workers have recently used EICA (**1**) under PTC conditions for the synthesis of anthracene-based constrained AAA derivatives.[63] The EICA strategy was also used as a key step for the synthesis of compound **77** (Figure 6), which is useful for crystal engineering studies.[65,66] Mash and co-workers have used AAA **61j** for the synthesis of conformationally constrained diaminodicarboxylic acid derivatives.[67] Further, EICA (**1**) was used as a intermediate to prepare organic crystalline material such as 1,4-piperazine-2,5-diones[68] and also for the synthesis of cyclobutane analogues of Phe.[69]

Halogen-containing Ind derivatives such as **78a** and **78b** were not accessible by Schiff-base/*n*-BuLi conditions.[34] However, PTC conditions allows such substrate preparation with ease, starting with the appropriate dihalo derivatives. Moreover, the iodo functionality present in **79** has been found to be useful for the introduction of various aromatic moieties by the application of SM cross-coupling reaction as a key step. Thus, coupling of the iodo-derivative **79** with various arylboronic acids under Pd(0) catalyst conditions gave the required 5,6-disubstituted Ind derivatives **80a−f** in good yields (Scheme 20).[70]

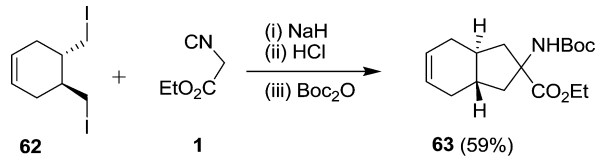
It is interesting to note that electron-deficient AAA derivatives such as **83** and **86** are easily assembled under PTC conditions.[51] These AAA derivatives were prepared

dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288−12313

Scheme 15



Scheme 16

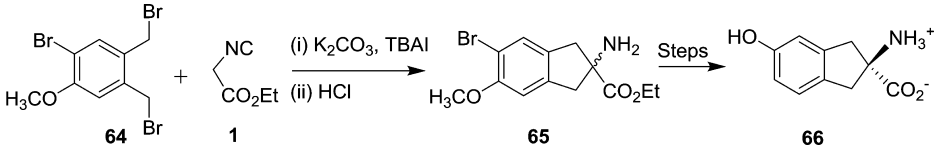


previously by a lengthy route involving protecting group strategy.[34] The electron-deficient molecules participate in an undesired single-electron-transfer process and deliver dimerization products during the base-catalyzed alkylation procedure. Therefore, it was necessary to use protective group strategies for assembling such types of AAA derivatives. The route involving EICA (**1**) allows utilization of highly electron-withdrawing substrates (e.g., **81** and **84**)[49,50] without involvement of protective groups and therefore shorten the synthetic sequence (Scheme 21) and achieve step economy.

Similarly, electronically active substrates such as quinoxalin dibromide **87** gave either undesired cyclic ether **88** during alkylation with EICA (**1**) under conventional reaction conditions (e.g., KO^{t}Bu, 40% aqueous NaOH, LDA, NaHMDS, KHMDS) or the coupling product **89** in low yield. To circumvent this problem, solid−liquid PTC conditions have been employed and under these conditions the required product **90** has been obtained in a moderate yield (Scheme 22).[71] At another junction, Stefanowicz and co-workers describe the solid-phase synthesis of quinoxaline-containing peptides, as these molecules show interesting pharmacological properties.[72]

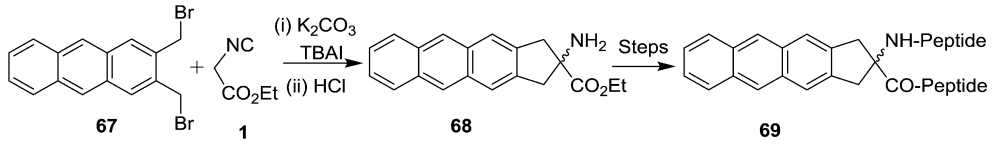
Various carbocyclic ring fused indane-based AAA derivatives such as **92a−d** were prepared under PTC conditions. The corresponding dibromide **91** was reacted with EICA (**1**) under PTC conditions, and subsequent hydrolysis followed by acetyl protection delivered the product **92a**.[53] Later, this strategy was

Scheme 17

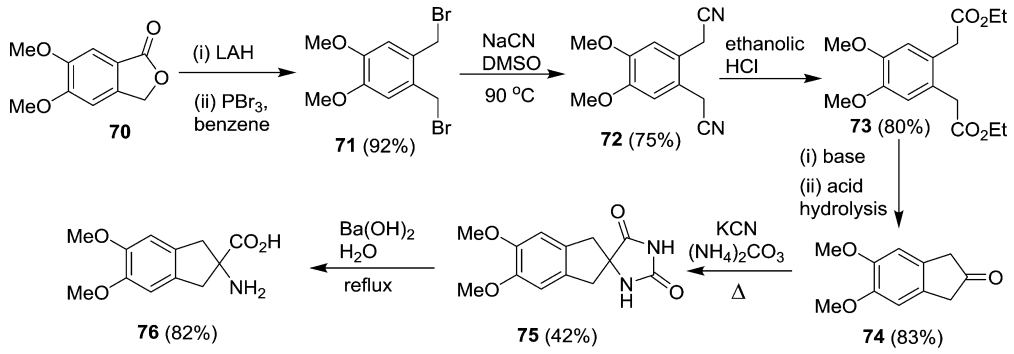


dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288−12313

Scheme 18



Scheme 19



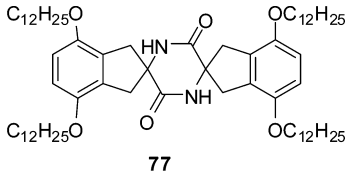


Figure 6. 1,4-Piperazine-2,5-dione derivative.

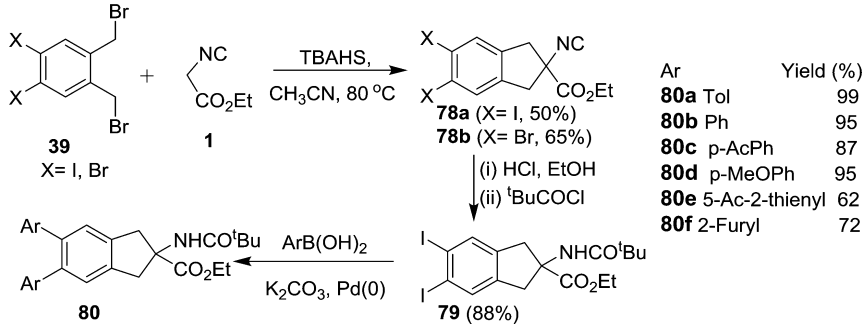
used to synthesize five-, six-, as well as seven-membered ring compounds (Scheme 23).

Further, indane-based AAAs derivatives containing crown ether side chain **95a,b** were also synthesized using the above methodology (Scheme 24).[73] This was the first reported synthesis of crown-based AAA derivatives **95a,b**. In another report, AAA derivatives containing crown based peptides were assembled and studied for metal ion complexation.[74] Based on the above examples, it is clear that this strategy can deliver a series of indane-based AAA derivatives with varying shape, size, and redox properties within a very short period of time starting with a readily accessible precursors.

We also found that the [2 + 2 + 2] cycloaddition reaction is useful for the synthesis of indane-based AAA derivatives (Scheme 25). In this regard, the key dialkyne building block **96** has been assembled by dipropargylation of EICA (**1**) under solid−liquid PTC conditions.[75,76] The isonitrile derivative **96** was then converted to *N*-acetyl derivative **98a** involving a hydrolysis and *N*-acetylation sequence. Co-trimerization of **98** was then performed under Wilkinson's catalyst $Rh(PPh_3)_3Cl$ or cobalt catalyst $CpCo(CO)_2$ conditions . The dialkyne building block **98a** was reacted with 2-butyne-1,4-diol **43** to deliver the indane-based AAA derivative **99a** (Scheme 25).[77] The cyclotrimerization is compatible with Boc- and CO^tBu-protected dialkyne building blocks. Various monoalkynes undergo trimerization reaction to generate a library of indane-based AAAs derivatives (**99a−i**). Our ability to incorporate various protecting groups at nitrogen atom of amino acid functionality enhances the diversity of this methodology. Roglans and co-workers used same strategy for the synthesis of nonproteinogenic AAA **102** derivatives (Scheme 26).[78] In 2007, Dieters and co-workers found that the [2 + 2 + 2] strategy was useful for the synthesis of various natural and unnatural indanone derivatives.[79] Yamamoto's group has used the [2 + 2 + 2] strategy for assembling sugar amino acids.[80]

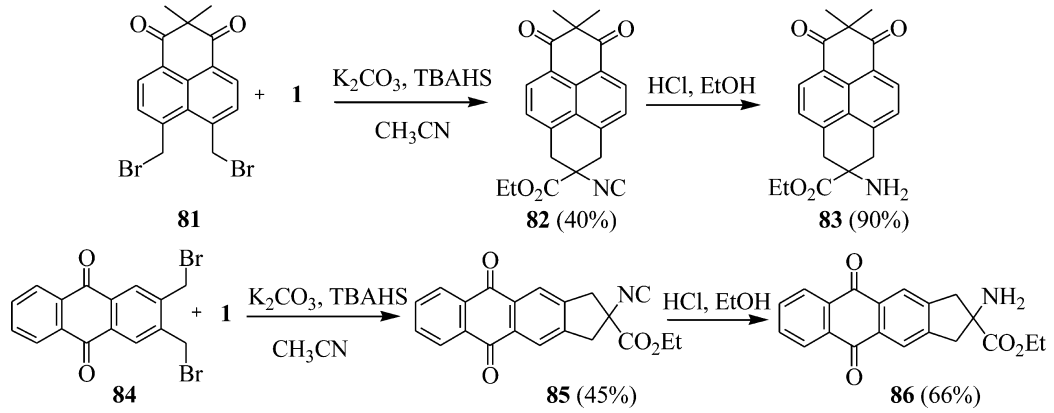
The Ind derivative **99a** has been used to generate the *o*-xylylene intermediate **105** via the sultine derivative **104**, prepared from dibromo compound **103** using rongalite as a source of sulfoxylate dianion. The sultine building block **104** was then reacted with various dienophiles (e.g., DMAD) at toluene reflux temperature (120 °C) to generate the corresponding DA adducts. Subsequent oxidation of DA adduct **106** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone

Scheme 20

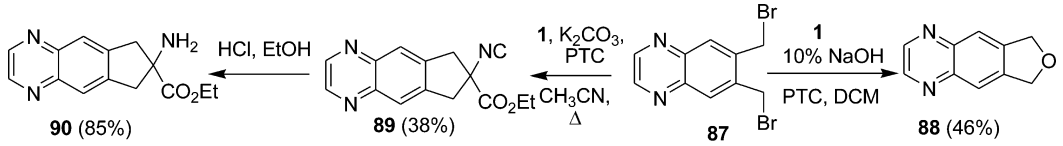


dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288−12313

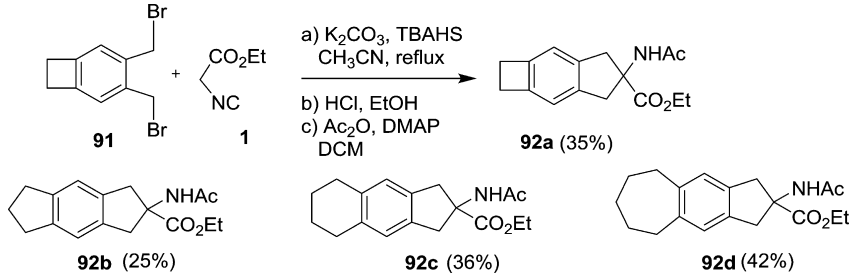
Scheme 21



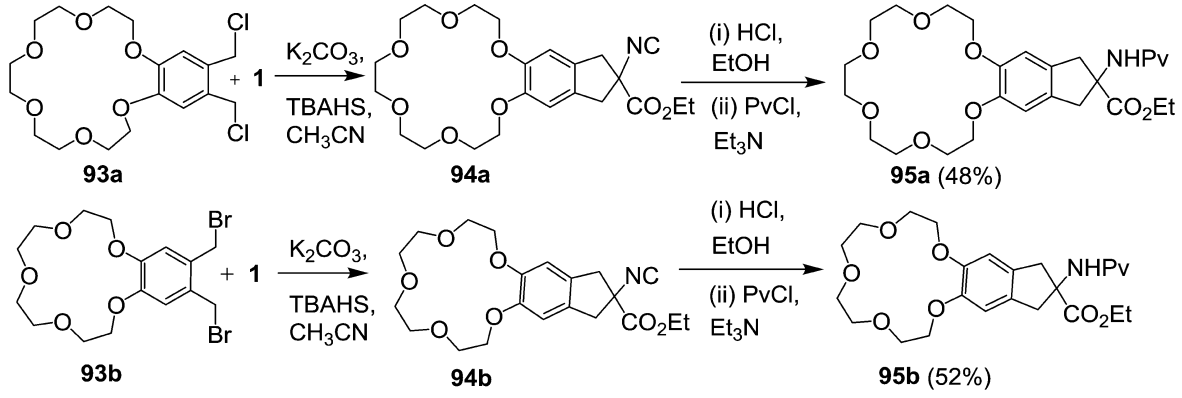
Scheme 22



Scheme 23



Scheme 24



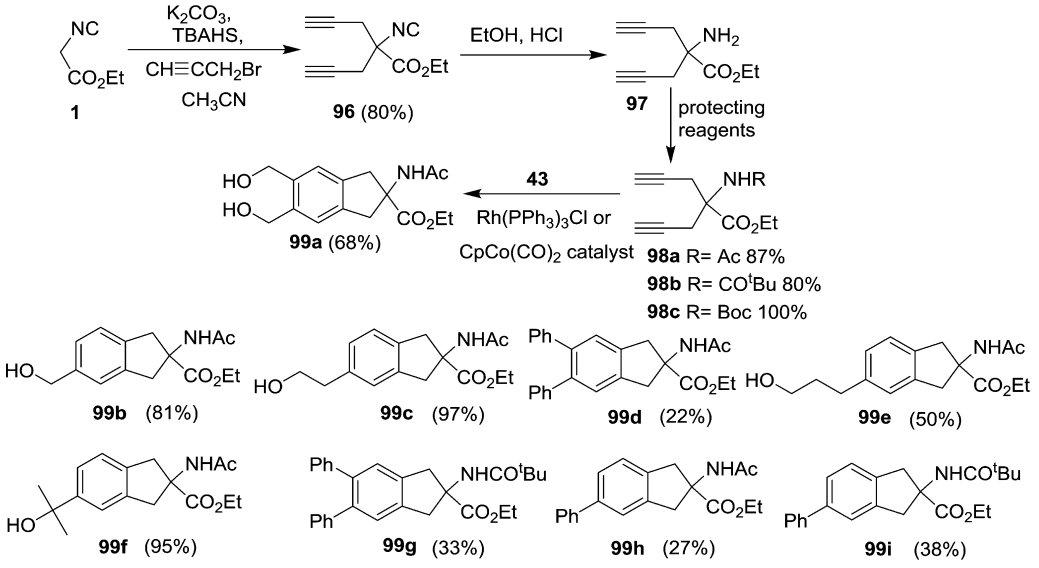
(DDQ) gave benzo-annulated indane-based AAA derivative **107** in good yield (Scheme 27).[81] This methodology provides an easy access to highly functionalized Ind AAA derivatives. For example, some of the AAA derivatives synthesized here contain a keto functionality and are not easily accessible by conventional methods such as Bucherer−Bergs method.

This methodology has also been extended for the synthesis of fullerene-based AAA derivative **108** which may be a useful substrate for biological applications (Scheme 28).[81] Further, the C_{70} fused indane system was also assembled by application of this methodology. These AAA derivatives are potential candidates for biological applications due to the hydrophobic nature of fullerene moiety and moreover the fullerenes can act as an electron sink.[82]

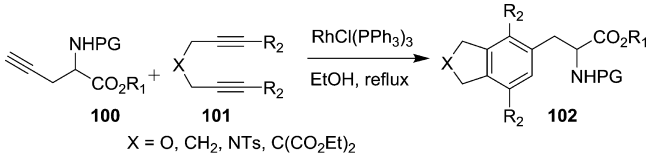
The cyclotrimerization reaction was further extended to synthesize indane-based AAA derivatives such as **110a−b** containing trialkyl silyl group (Scheme 29).[83] The silylated amino acid derivative **110a** is a useful precursor for electrophilic aromatic substitution reaction to deliver various functionalized AAA derivatives such as **79** and **111−113**. Also trimethylsilane (TMS) containing AAA derivative when incorporated in the peptide chain can enhance the hydrophobic nature of the

dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288−12313

Scheme 25



Scheme 26



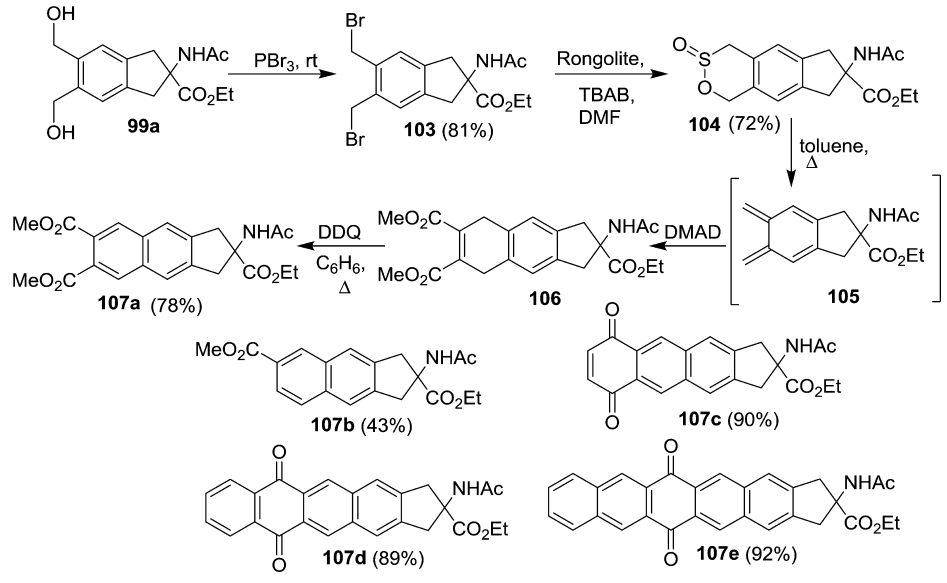
resulting peptide, which is a desirable property to enhance the biological activity.[84] The formation of compound **112** during the acid-catalyzed rearrangement is facilitated due to relief of steric interaction of the TMS group.[85]

Indane-based AAA derivative **79** reacts with trimethylsilylacetylene **114** in the presence of $Pd(PPh_3)_4$ catalyst and CuI to generate the Sonogashira coupling product **115** in good yield. Compound **115** undergoes desilylation in the presence of potassium carbonate in methanol to give dialkyne building block **116**, which may be a useful precursor for the synthesis of biphenylene-based AAA derivatives via a [2 + 2 + 2] cycloaddition reaction as a key step (Scheme 30).[86]

Additionally, the diyne building block **98** has been incorporated in a peptide chain, and later the peptide backbone was modified by a [2 + 2 + 2] cycloaddition reaction in the presence of Wilkinson's catalyst leading to a conformationally constrained Phe peptide **118a** (Scheme 31). Various modified peptides **118b–e** were assembled by this strategy. This methodology may find various applications in the synthesis of peptidomimetics and also in combinatorial chemistry.[75,87] It may be relevant to mention that dipropargyl substituted glycine derivatives have been used as a critical building blocks for the preparation of fulleropyrrolidine by Pauson–Khand reaction.[88]

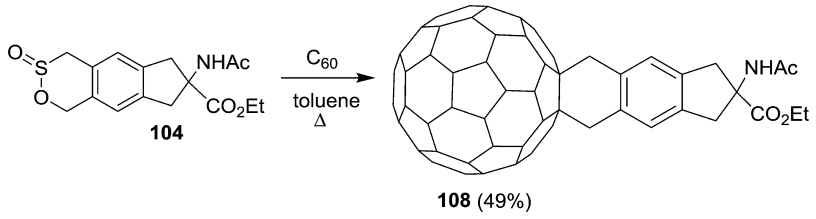
The diversity-oriented approach to indane-based AAA derivative has been enriched by realizing several conceptually different strategies. For example, the DA approach involving the five-membered outer diene had generated linearly annulated and highly functionalized indane-based AAA derivatives,

Scheme 27

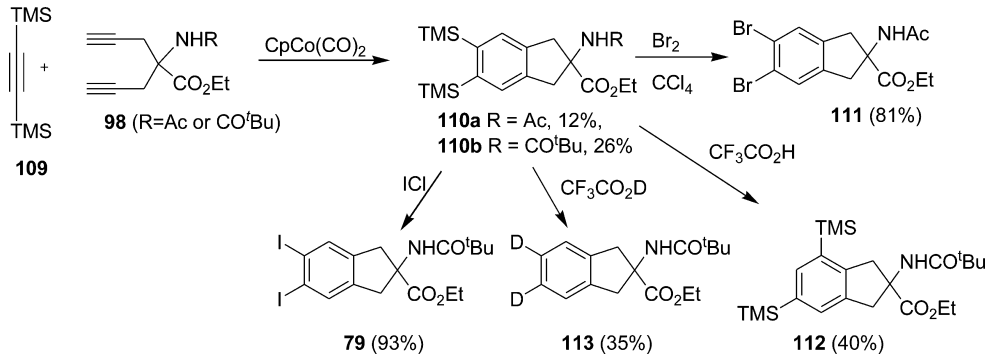


dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288–12313

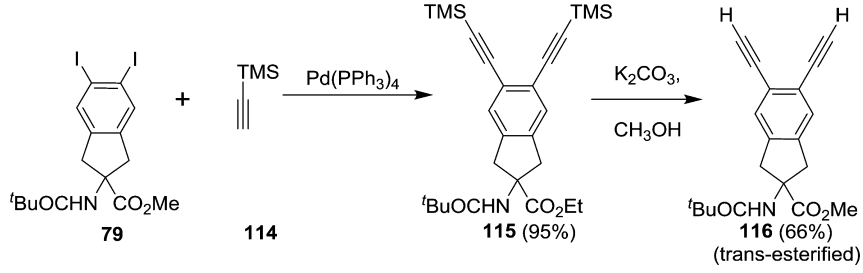
Scheme 28



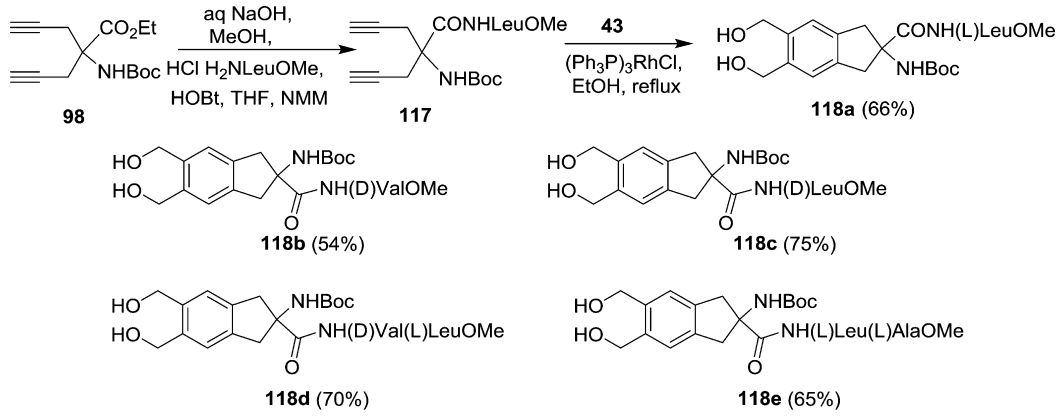
Scheme 29



Scheme 30



Scheme 31



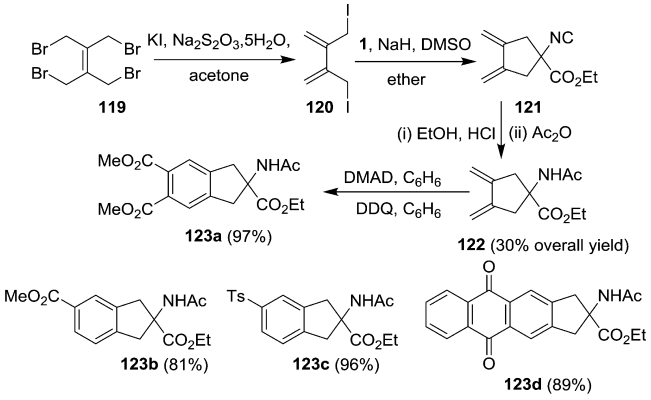
whereas a [2 + 2 + 2] cycloaddition approach generated linearly annulated indane derivatives containing a different kind of functional group in the aromatic ring. In case of the DA approach, generally one needs to use a dienophile-containing electron-withdrawing group(s). In the case of a [2 + 2 + 2] cycloaddition approach, one will be in a position to use but-2-yne-1,4-diol **43** such as a cotrimerization partner. Use of 1,4-diol derivative provides product where the reduced form of DMAD has been incorporated in the final target. Alternatively, in the DA strategy, where DMAD is used as a dienophile partner, a complementary functional group is introduced in the product. Overall, the [2 + 2 + 2] strategy incorporates the redox-economy in the final target.

In another event, 5-membered ring containing diene amino acid building block **122** was synthesized starting from tetrabromide **119**, which in turn was prepared from 2,3-dimethyl-1,3-butadiene and then converted to the known di-iodo compound **120** by reductive debromination. Coupling of EICA **1** with **120** under NaH/DMSO/diethyl ether conditions delivered the coupling product **121**, which was hydrolyzed and

dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288−12313

protected as acetyl derivative **122** (Scheme 32).[89] The diene was then reacted with various dienophiles to deliver the

Scheme 32



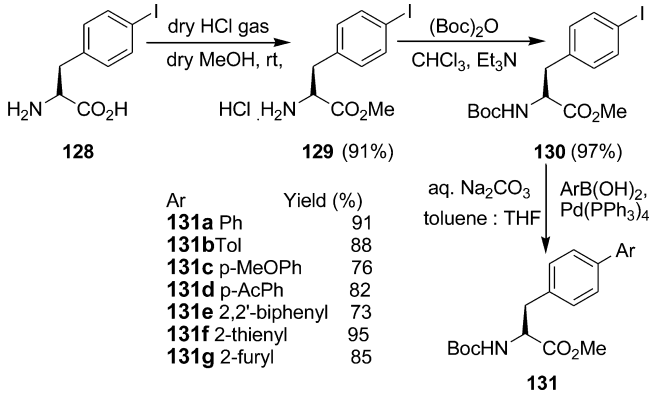
corresponding DA adduct which undergo dehydrogenation under DDQ conditions to give indane-based AAA derivatives **123a–d**.

Later, EM and DA reactions were used to design indanyl glycine derivatives.[90] To this end, five-membered inner-outer ring diene building block **126** containing an AAA moiety (Scheme 33) has been assembled by EM as a key step. Since it is difficult to control the stepwise alkylation with EICA, benzophenone Schiff base **49** has been used as a starting material, which is known to undergo stepwise alkylation under PTC conditions. Propargylation and allylation followed by hydrolysis and acetylation gave the enyne derivative **125** in good yield. Ring-closing enyne metathesis (RCEM) reaction of **125** gave the diene building block **126**. DA reaction of **126** with various dienophiles and subsequent dehydrogenation of the DA adducts with DDQ gave various angularly substituted indanyl glycine derivatives **127a–c**.[91] This strategy based on EM/DA reaction followed by oxidation to generate polycyclic compounds has been utilized by several groups to design intricate and complex targets.[29] The Undheim group also reported the application of EM to generate various diene-containing AAA derivatives.[18b] However, their utility in DA chemistry was not explored.

■ MODIFIED PHENYLALANINE (PHE) DERIVATIVES

A simple approach to obtain modified Phe-based peptides is to incorporate the commercially available 4-iodo-L-phenylalanine **128** into a peptide chain and then perform cross-coupling reaction using the iodine functionality as a handle. Toward this end, the SM cross-coupling reaction of **130** with arylboronic acids gave the modified AAA derivatives (Scheme 34). This

Scheme 34

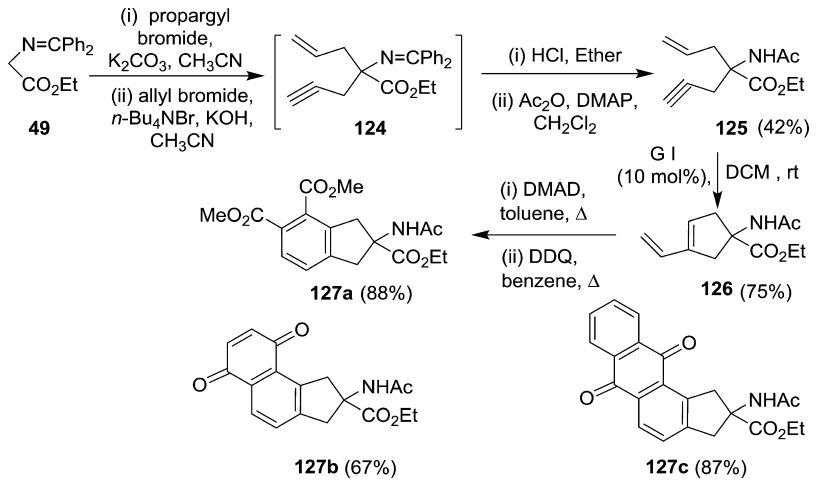


Ar	Yield (%)
131a Ph	91
131b Tol	88
131c p-MeOPh	76
131d p-AcPh	82
131e 2,2'-biphenyl	73
131f 2-thienyl	95
131g 2-furyl	85

methodology gave diverse Phe-based AAA derivative by coupling with various boronic acids. Since, there are more than 1000 boronic acids commercially available, one can easily generate a library of modified Phe derivatives by using this strategy.[92a,b] Moreover, this approach has been used to synthesize aromatic-ring-substituted tyrosine derivatives.[93] Recently, this methodology has been extended to prepare 4-biphenyl-L-phenylalanine, a fluorescent amino acid, and it was incorporated at position 17 and 115 of dihydrofolate reductase (DHFR). These findings have helped in understanding the conformational dynamics associated with inhibitor binding.[92c]

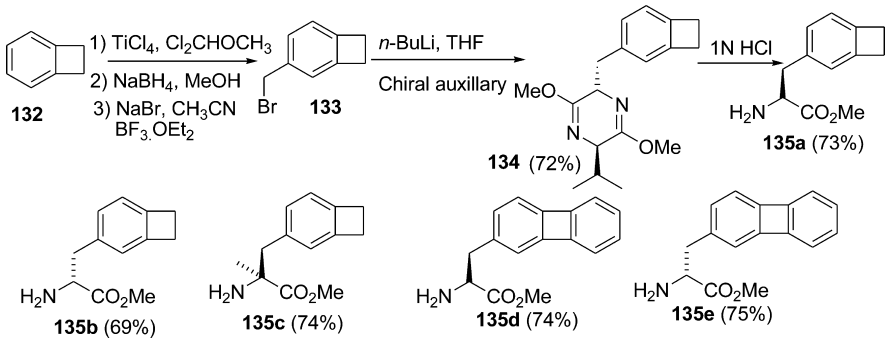
To expand the building block approach, benzocyclobutene (BCB)-based AAA derivatives have been assembled for the first time by alkylation of the Schölkopf chiral auxiliary[18b] with a suitably substituted bromomethyl benzocyclobutene derivative **133**.[94] In this regard, benzocyclobutene **132** was converted to the bromomethyl derivative **133** in a three-step sequence (Scheme 35). Later, the bromide **133** was reacted with the monoanion of Schöllkopf's bis-lactim ether to deliver the

Scheme 33

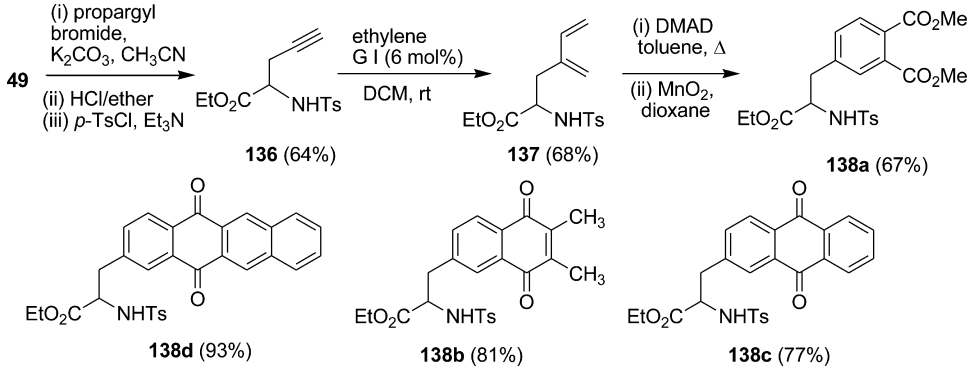


dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288–12313

Scheme 35



Scheme 36



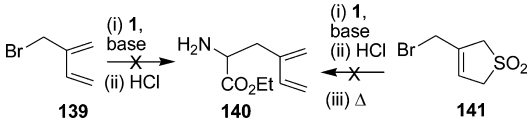
compound **134** with very high diastereoselectivity (>95%). Hydrolysis of **134** with dilute HCl gave the required amino ester **135a**. Further, this methodology has been extended to assemble biphenylene-based AAA derivatives **135d–e**. BCB derivatives are useful because of their ability to undergo the DA chemistry via *o*-xylylene intermediates.[42]

So far, we have prepared the modified Phe based AAA derivatives involving coupling reactions starting with preformed benzene derivatives. However, there are no reports where Phe-based AAA are designed via the building block approach. Therefore, we felt that there is ample opportunity to generate new strategies based on this theme. In this regard, we designed a novel approach by using cross-enyne metathesis (CEM)[95] and DA[96] reaction as key steps. This strategy is unique and has embedded various points for diversification. Therefore, it enables us to generate a library of AAA derivatives, which may not be possible with the other strategies.

Toward this end, the alkyne precursor **136** was assembled starting with the Schiff base **49** via an alkylation, hydrolysis, and protection sequence.[97] Later, the alkyne building block was subjected to CEM with ethylene as a coupling partner to generate the diene **137**. The diene was then treated with various dienophiles such as DMAD, and subsequently, the DA adduct was aromatized to give highly functionalized Phe derivative **138a** in good yield (Scheme 36). In another report, Hiemstra and co-workers[98] prepared an analogue of the diene **137** by using *N*-acyliminium ion chemistry. In this regard, CEM strategy was used to generate various amino acid and peptide-based dienes. Further, Baldwin and co-workers reported a similar diene-containing AAA derivative by using Denmark's coupling as a key step.[99]

Here, it is necessary to mention that the formation of the diene **140** could not be realized by alkylation of ethyl isocyanoacetate **1** with 2-bromomethyl-1,3-butadiene **139** or sulfolene bromide **141** under different reaction conditions (Scheme 37).[100]

Scheme 37



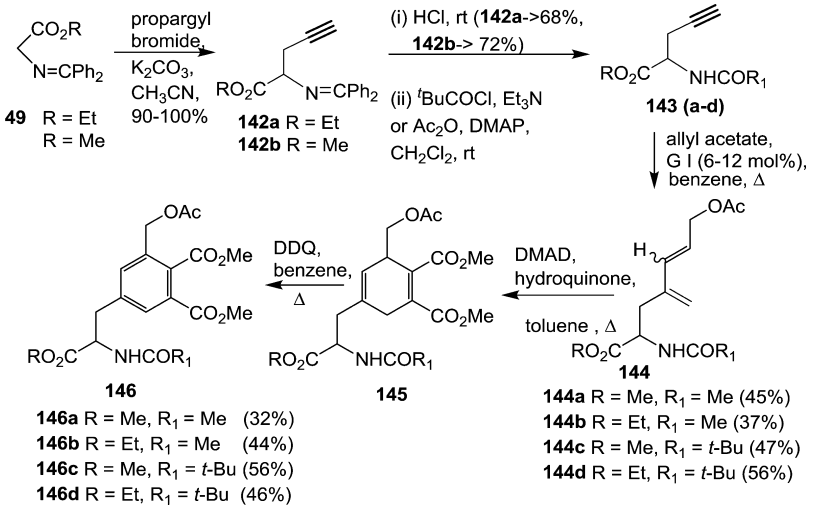
The EM strategy was further expanded to design highly functionalized Phe derivatives. To this end, the alkyne building block **143** was reacted with functionalized ethylene derivative such as allyl acetate in refluxing benzene to give the dienes **144a–d** as a mixture of cis/trans isomers (1:1).[100] The alkyne building block **143** has been used to prepare enol lactones under Cu(I)-catalyzed conditions by Mindt and co-workers.[101]

The acetylenic building blocks **143a–d** containing different *N*-protecting groups were prepared starting with the Schiff base **49** (Scheme 38). Since the cross-enyne metathesis with allyl acetate gave the diene **144a–d** as mixture of cis/trans isomers, no attempts were made to separate the cis/trans isomers. The DA reaction of **144** with DMAD gave the cycloadducts **145a–d**, and then subsequent oxidation of the DA adducts with DDQ gave highly functionalized Phe derivatives **146a–d** in a moderate yield. The CEM reaction was successful with allyl acetate and allyl phenyl ether. It was found that the syntheses of the dienes **144a–d** from the allyl building block containing AAA moiety via CEM with various alkynes was not successful.

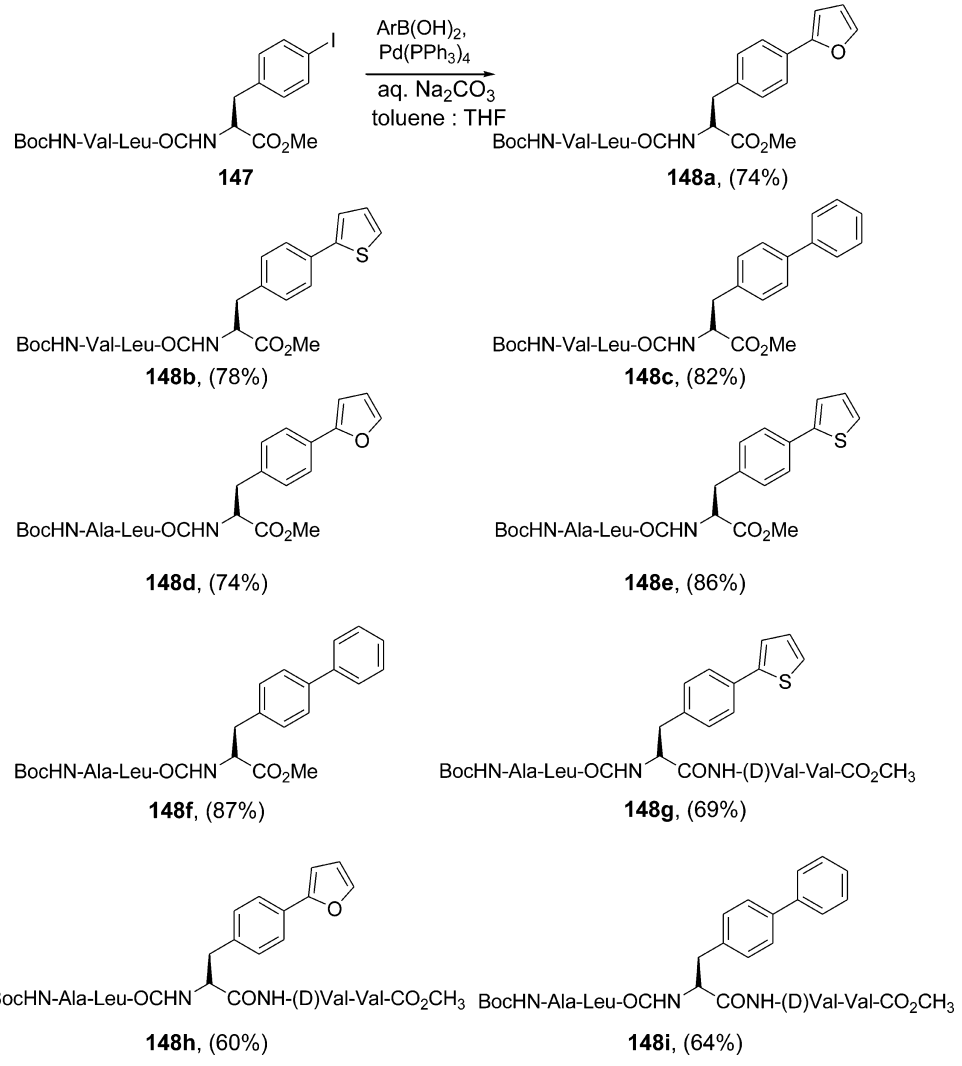
Toward the modification of Phe peptides, the required precursors were prepared by using carbodiimide-mediated peptide-coupling strategy. Then, the SM coupling with these peptides was realized using the conditions developed with Phe-

dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288–12313

Scheme 38



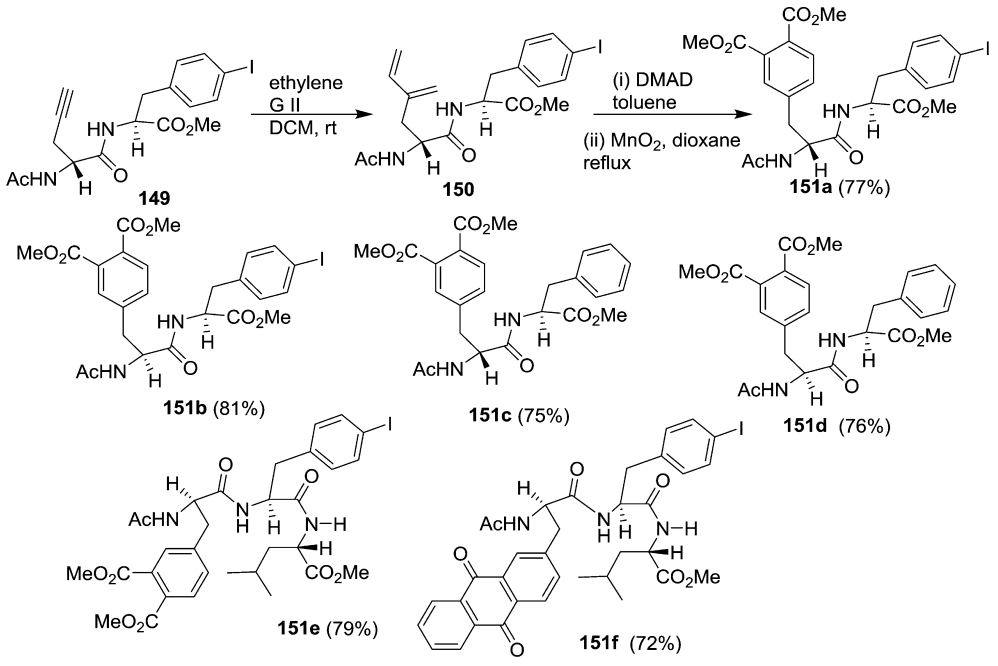
Scheme 39



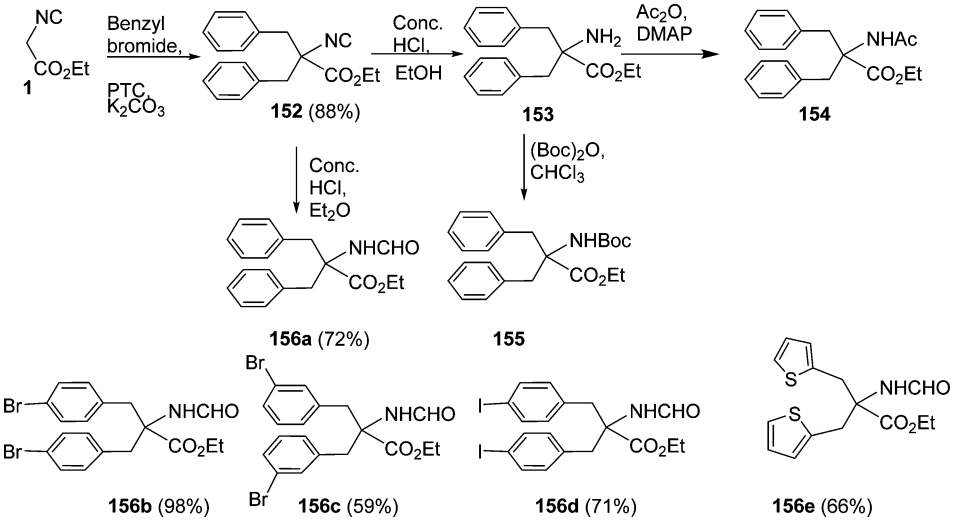
based AAA derivatives, and the coupling products were obtained in good yield (Scheme 39).[92] The methodology delivered a range of modified Phe analogues **148a–i** which may be useful to design various biologically active peptides and also suitable for developing combinatorial synthesis of peptidomimetics. Recently, this methodology has been extended toward the synthesis of peptide dimers,[102] regioselective postsynthetic iodination of Phe peptides,[103] protein modification,[104] solid-

dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288–12313

Scheme 40



Scheme 41



phase peptide modification,[105] C-arylation of tryptophan residues,[106] arylation of Phe and Tyr side chain by SM coupling in water,[107] and SM reaction of *N*-protected 4-iodo Phe linked isoxazoles.[108] Recently, SM coupling was used to synthesize biaryl cyclic peptides by Planas and co-workers.[109]

We also tested the idea of generating phenyl ring by CEM–DA approach with peptides. In this regard, the alkyne-based peptide building block **149** containing alkyne was assembled from diethyl acetamidomalonate **22**. The alkyne **149** was then subjected to CEM with ethylene as a cross-metathesis partner to generate the diene **150** which on treatment with DMAD, followed by aromatization with MnO_2, gave the desired modified Phe-based peptide **151a** (Scheme 40).[110] This strategy was further extended to tripeptides, and the DA reaction was also tested with 1,4-napthaquinone to establish the generality and the diversity of this approach.

■ DIBENZYLGLYCINE (DBZG) AND ITS DERIVATIVES

The Dbzg[111] is an interesting variant of α-aminoisobutyric acid (Aib). Incorporation of Dbzg in a peptide chain not only imparts rigidity to the peptide backbone but also act as a useful handle to study the $\pi-\pi$ interactions. Synthesis of densely functionalized Dbzg derivatives is a difficult task by the Bucherer–Bergs method or the Ugi three-component procedure or the Schmidt rearrangement method. Thus, we have explored a general and useful methodology for the preparation of Dbzg derivatives by dialkylation of EICA **1** with various benzylbromides.

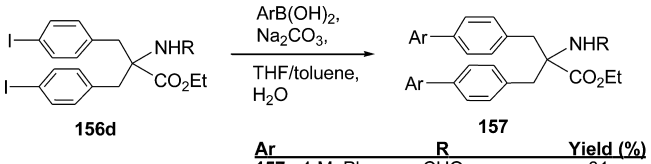
After considerable amount of experimentation, we found that compound **1** can be alkylated under PTC conditions with benzyl bromide to give Dbzg derivative **152** in high yield (Scheme 41). Later, hydrolysis and acetylation of the free amino group gave the acetylated product **154**. This reaction also works well with other benzylbromides (**156b–e**). Here,

dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288–12313

the acetylated product was contaminated with *N*-formyl derivatives **156a**. The formylated impurity is derived during the hydrolysis step, and it was carried out in the subsequent steps. This problem has been resolved by converting the isonitrile derivative **152** to *N*-formyl derivative **156a** by acid hydrolysis in aprotic solvent. Having formyl derivative of Dbz in pure form, efforts were directed toward the SM reaction. All of the coupling products (**157a**–**h**) were obtained in good yield. We have also prepared the *N*-Boc-protected derivatives as they are important in peptide chemistry.

Further, we have studied the SM reaction with the *N*-Boc derivative (Scheme 42).[112] The Cativiela group has assembled

Scheme 42



Ar	R	Yield (%)
157a 4-MePh	CHO	81
	Boc	73
157b 4-MeOPh	CHO	86
	Boc	96
157c 4-AcPh	CHO	68
	Boc	72
157d Ph	CHO	72
157e 4-CHOPh	Boc	54
157f 2-thienyl	CHO	93
157g 2-furyl	CHO	92
157h 2-benzothienyl	Boc	79

Dbzg by using this methodology and further incorporated Dbzg in place of Phe in gramicidin S to prepare various analogues of gramicidin S and evaluated their antibiotic activity.[113]

To design AAA derivatives containing a cyclophane unit by RCM reaction as a key step, diallyl compound **160a** was considered as a suitable precursor. As a model substrate, we next prepared the allylated aromatic-AAA derivatives **159** by Pd-catalyzed cross-coupling reaction between aromatic halide and allylboronic acid pinacol cyclic ester in presence of CsF.[114] It is worth mentioning that Stille coupling with allyltri-*n*-butyltin in the presence of Pd(0)/THF did not deliver allylated product **159** in a clean fashion. Since the Suzuki coupling is known to avoid such problems, we tried to introduce allyl group using the commercially available allyl boronic ester. The presence of CsF was found to be important for the success of the SM coupling. The allylation methodology works with various aryl iodides and bromides (Scheme 43).[115] We feel that the allylation protocol is a better alternative to the traditional 9-borabicyclo[3.3.1]nonane (9-BBN)-mediated SM coupling.[116] We have also synthesized divinyl compound **160b** in connection with our interest preparing cyclophane containing AAA derivatives. However, our attempts to realize RCM were not successful. Further, this allylation condition has been used by Kozlowski and co-workers for the synthesis of diallylated intermediate **164** during the preparation of perylenequinone natural products **165** (Scheme 44).[117]

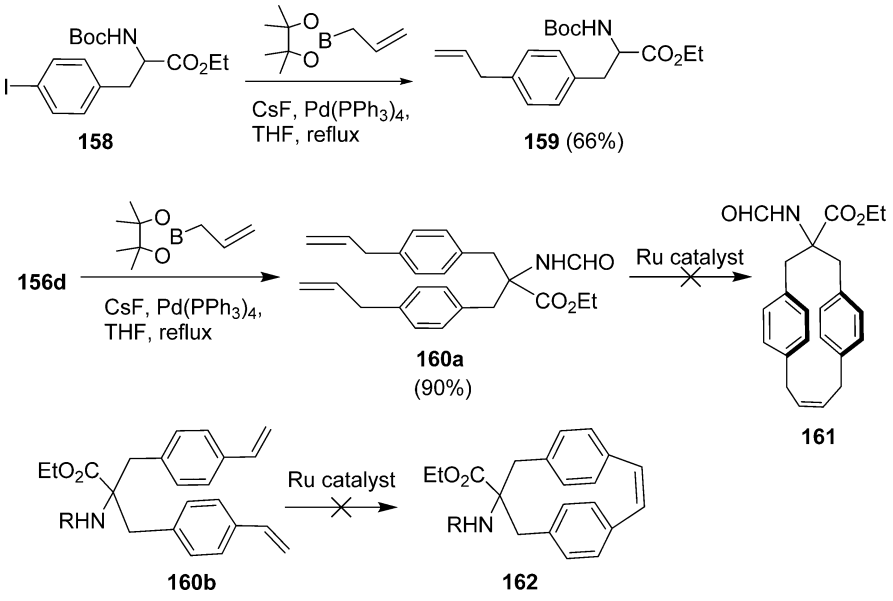
Podestá and group have shown that the allylation protocol is applicable to a wide range of organic substrates.[118] This allylation strategy has been used for the synthesis of natural product pochonin J.[119]

In view of the various applications of benzcyclobutene derivatives in organic synthesis and polymer chemistry,[42] we have synthesized dibenzocyclobutenylglycine derivatives **169** (Scheme 45).[120] Attempts to convert these benzocyclobutene derivatives to cyclophane-based unusual amino acid derivative **170** under flash vacuum pyrolysis (FVP) conditions were not successful.

■ MULTIARMED AAA DERIVATIVES

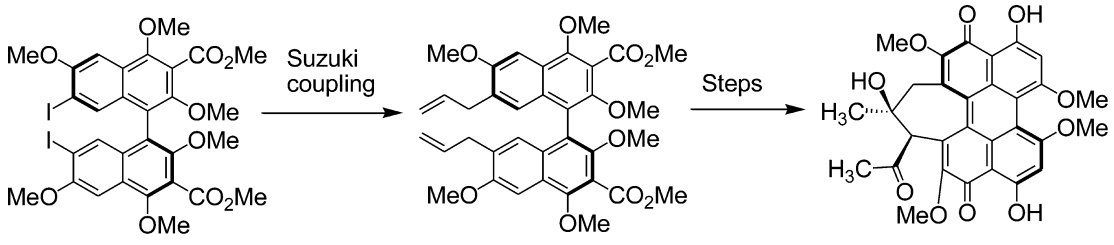
Bis-armed-α-amino acids (BAAAs) are key structural elements present in antibiotics that disrupt microbial cell wall synthesis, and they are useful to stabilize structure of proteins in bacteria and plants.[121] Various BAAA derivatives are also used as helix–turn–helix (HTH) motif of DNA-binding proteins.[122] Also, BAAA derivatives are known to be versatile ligands for the chelation with appropriate metal and the complex thus formed can be used as a chiral catalyst in asymmetric synthesis.[123] Therefore, we explored the synthesis of bis- as well as multiarmed AAA derivatives.

Scheme 43

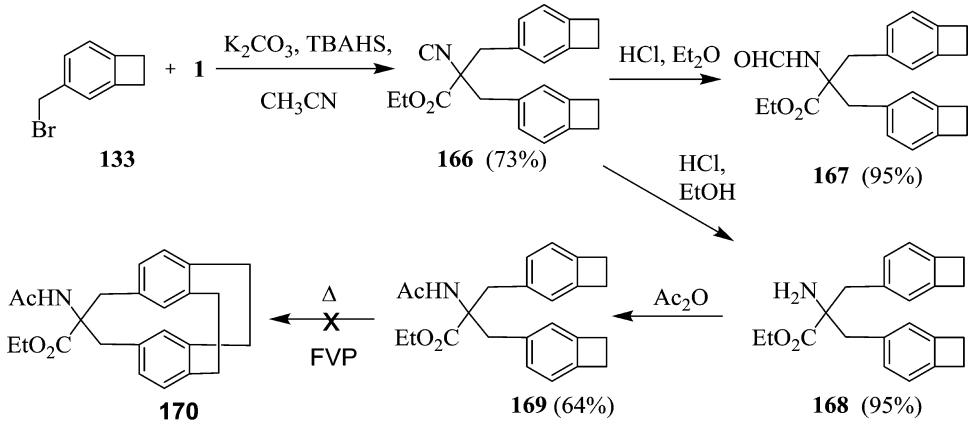


dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288–12313

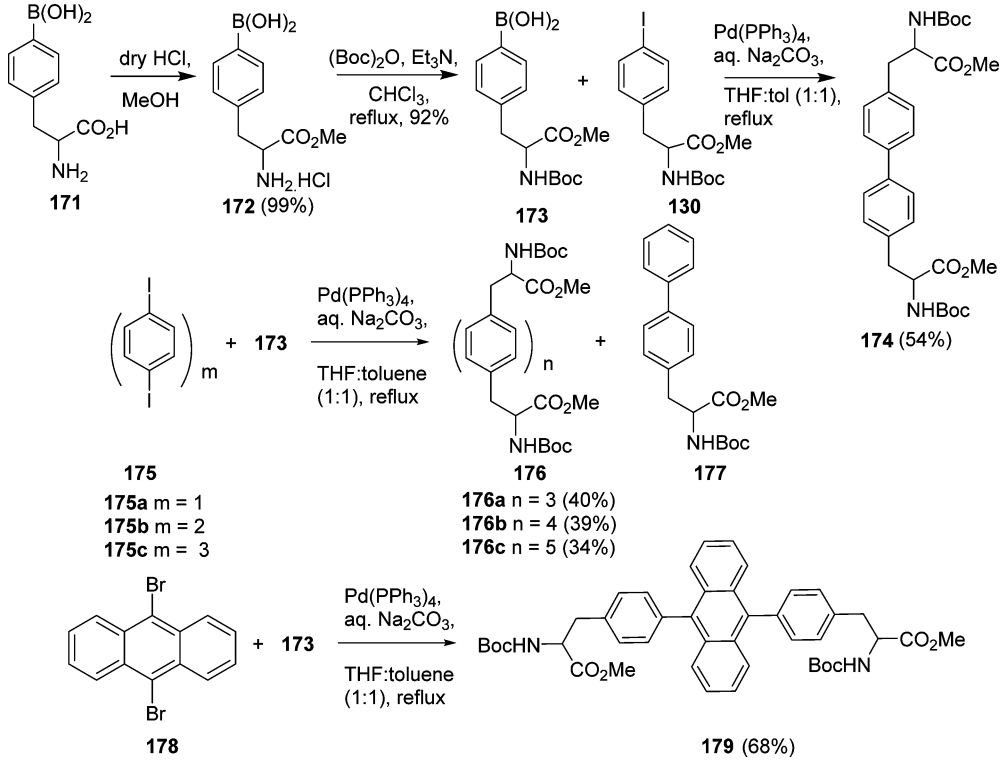
Scheme 44



Scheme 45



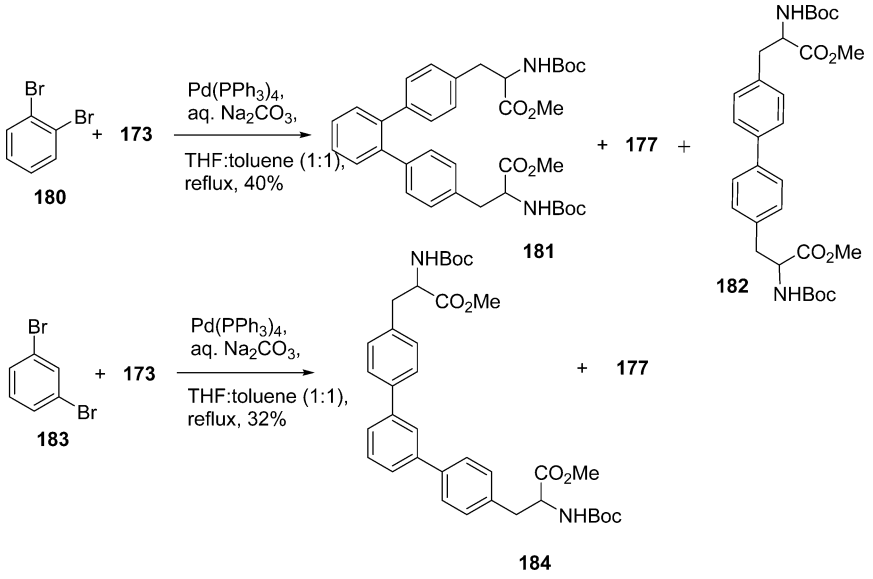
Scheme 46



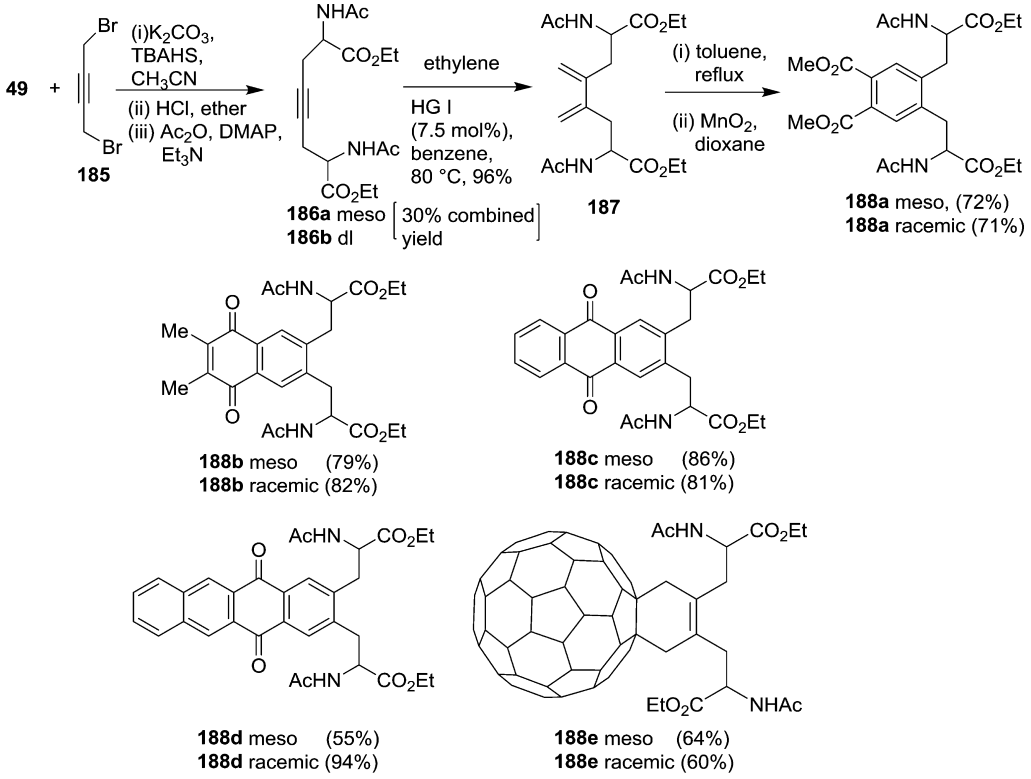
Commercially available DL-4-boronophenylalanine **171** appears to be a potential candidate to design BAAA derivatives via the SM reaction. The carboxylic group of **171** was protected as a methyl ester under acidic conditions to give the compound **172**, which was reacted with Boc-anhydride to deliver the *N*-Boc-protected boronic acid derivative **173** (Scheme 46).[124] 4-Iodophenylalanine derivative **130** was then coupled with the boronic acid **173** to generate the biphenyl derivative **174** in 54% yield. We also found that ethyl isocyanoacetate is useful to design BAAA derivatives similar to **174** using PTC conditions

dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288−12313

Scheme 47



Scheme 48



starting with the corresponding biphenyl based dibromo compounds. When the boronic acid **173** was subjected to SM reaction under Pd(0) conditions with 1,4-diiodobenzene **175a** (m = 1), the coupling product **176a** (n = 3) was obtained in 40% isolated yield along with the scrambled product **177** (26%). Similarly, when 4,4′-diiodobiphenyl **175b** (m = 2) and the diiodide **175c** were subjected to the SM reaction with **173**, the cross-coupling products **176b** (n = 4) and **176c** (n = 5) were isolated in 39% and 34% yields, respectively. Along similar lines, bis-armed anthracene-based AAA derivative **179** was also prepared. It is interesting to note that these anthracene derivatives exhibit interesting fluorescent properties.

The above methodology was then extended to the synthesis of angular BAAA derivatives. In this regard, 1,2-dibromobenzene **180** and 1,3-dibromobenzene **183** were coupled with the boronic acid derivative **173** to deliver the corresponding *o*-terphenyl BAAA derivative **181** and *m*-terphenyl BAAA derivative **184** in 40% and 32% yields, respectively (Scheme 47).[124]

Later on, CEM followed by a DA reaction and aromatization sequence has been used for the synthesis of BAAAs.[97] Thus, the 1,4-dibromo-2-butyne **185** was reacted with Schiff base **49**, and the product was hydrolyzed and protected to obtain the desired alkyne **186** as a mixture of *meso* and *dl* isomers (Scheme 48).

dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288−12313

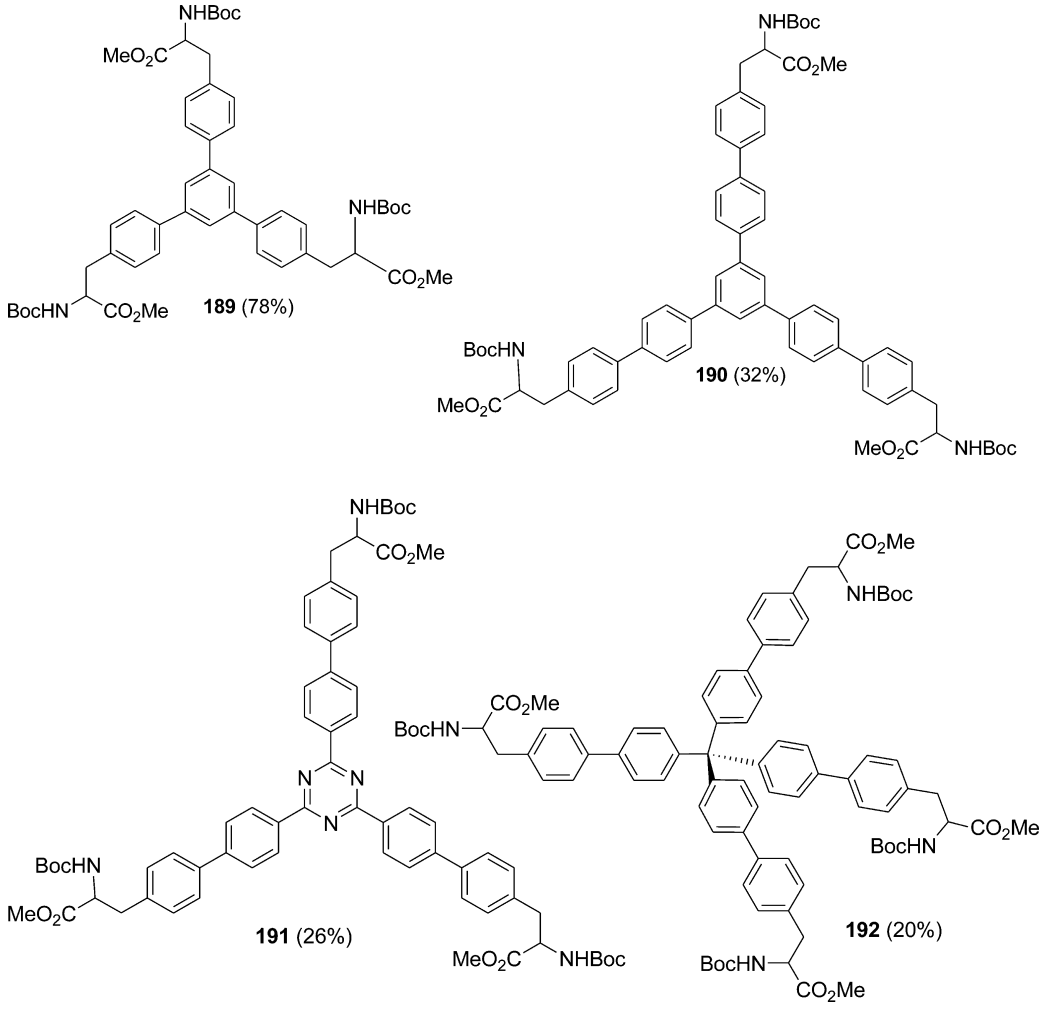
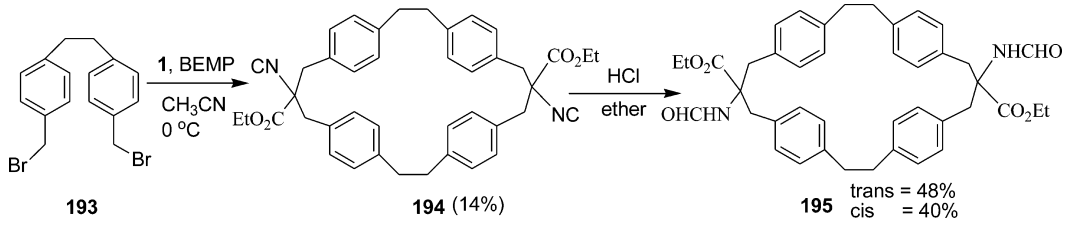


Figure 7. Multiarmed AAA derivatives synthesized.

Scheme 49



After careful separation the *meso* isomer was subjected to CEM reaction under ethylene atmosphere. The DA reaction of these dienes with various dienophiles followed by aromatization delivered highly functionalized Phe derivatives (**188a−e**). Similarly, starting with *dl* isomer, various Phe derivatives (**188a−e**) were prepared. Also, one can visualize that these AAA derivatives **188a−e** can be called as carba- analogous to cystine. The Suzuki coupling strategy has been also extended to tris- and tetra-armed AAA derivatives (**189−192**), which are useful building blocks for peptide dendrimers (Figure 7).[125]

■ MISCELLANEOUS AAA DERIVATIVES

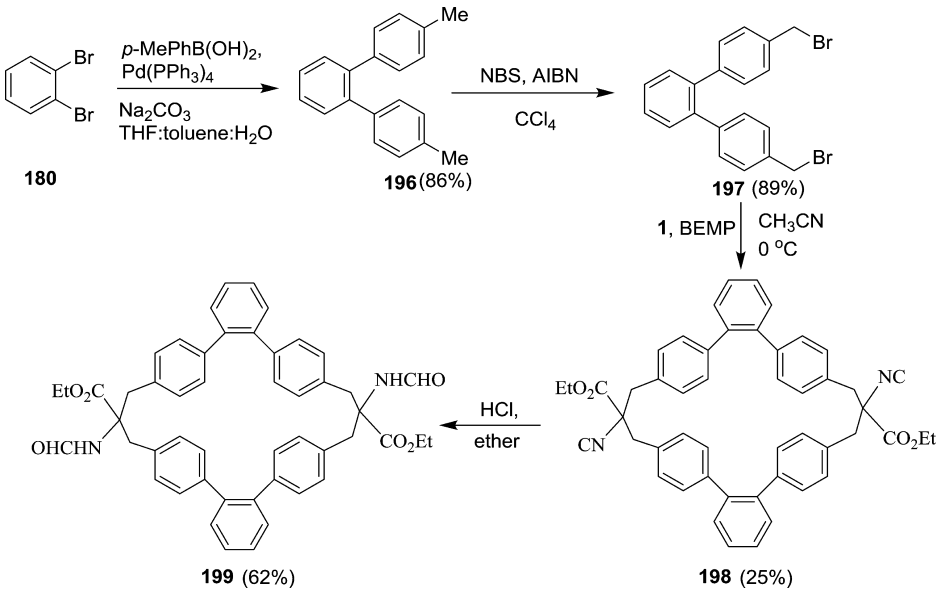
A macrocyclic cyclophane-based unusual α-AAA derivative **195** was assembled by coupling of EICA (**1**) with 1,2-bis(4-bromomethylphenyl)ethane under basic conditions. Later, acid hydrolysis of **194** afforded the cyclophane-based AAA derivative **195** as an isomeric mixture (Scheme 49).[126]

Similarly, we reported the synthesis of macrocyclic cyclophane-based AAA derivative **199**. In this regard, SM coupling was performed with 1,2-dibromobenzene **180** with *p*-methylphenylboronic acid to deliver *o*-terphenyl derivative **196**. Further benzylic bromination of **196** gave the dibromide **197**. Treatment of the dibromide **197** under basic conditions [2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)] afforded **198** as an isomeric mixture. This mixture **198** on acid hydrolysis afforded the *N*-formylcyclophane derivative **199** (Scheme 50).[127]

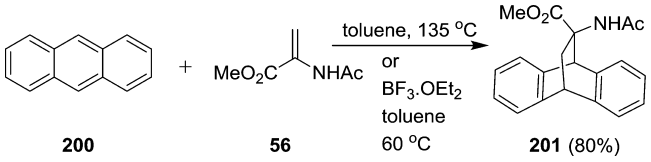
In another event, DA chemistry was applied to methyl-2-acetamidoacrylate **57** and anthracene **200** to generate a highly constrained AAA derivative **201** (Scheme 51).[128] Later, similar compounds were prepared as useful candidates for biological

dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288−12313

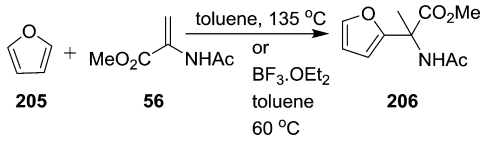
Scheme 50



Scheme 51



Scheme 53



activity and also main theme in international patents.[129] In 2005, Yang and co-workers extended this methodology to the synthesis of 9-substituted anthracene-based AAAs (Scheme 52).[130] In this case, they isolated *meta* product **203** as the major isomer under different reaction conditions. These AAA derivatives have been used in peptidomimetics.[131] However, furan **205**, when reacted with **57**, gave the Friedel–Craft type of product **206** (Scheme 53) instead of the expected DA product.[128] In another report, the Cativiela group has reported the synthesis of amino acids α-methyl-α-(4-methoxyphenyl)-glycine **209** by using a Lewis acid catalyzed Friedel–Crafts reaction (Scheme 54).[132]

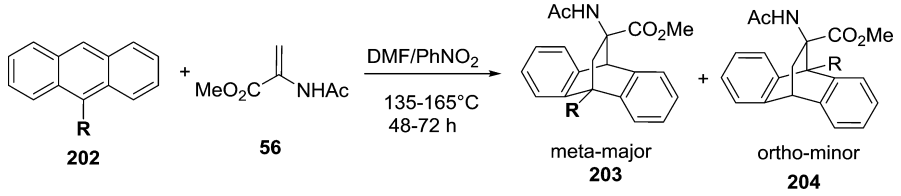
The 7-membered outer ring diene moiety **214** was prepared involving double ortho-ester Claisen rearrangement as a key step. Reduction, tosylation, and iodination of **210** gave the diiodo compound **212** through the formation of the compound **211**. Bis-alkylation of EICA (**1**) with the diiodo compound **212** under PTC conditions gave the required coupling product **213**, which was immediately hydrolyzed to the corresponding amino ester, and converted to the *N*-acetyl derivative **214** (Scheme 55).[89] Later, application of DA chemistry with various dienophiles followed by aromatization sequence with DDQ gave nonproteinogenic AAA derivative **215a–c**. It is worth mentioning that very few examples are available in the literature for the synthesis of cyclic AAA derivatives via the DA approach due to the lack of availability of synthetic methods to assemble the diene or dienophile components containing AAA building blocks.[133,134]

In continuation with our interest in peptide modifications,[10] we have conceived a short synthetic route to triazole-containing peptides by Cu-catalyzed Huisgen cycloadditions (click chemistry) as a key step. Initially, we tested this idea with simple monoalkynes. In this regard, the monoalkyne **216** was reacted with phenyl azide **217** to optimize the reaction conditions for Cu-catalyzed cycloaddition to obtain the triazole-based peptide **218** (Scheme 56). Later, a library of mono- and ditriazole-based peptidiomimetics were assembled by using the above strategy. The triazole-based peptide was found to be a selective and sensitive fluorescence chemosensor for zinc ions.[135] Some of these molecules are also found to be useful candidates as mammalian sterile 20 kinase inhibitors.[136]

CONCLUSIONS

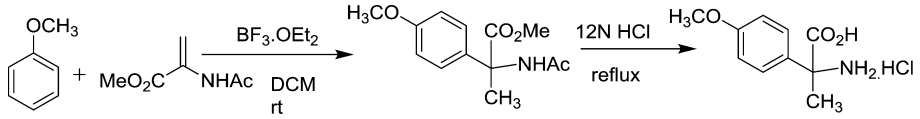
We have developed several useful stratagies to unusual amino acids and peptides based on a building block approach. Our

Scheme 52

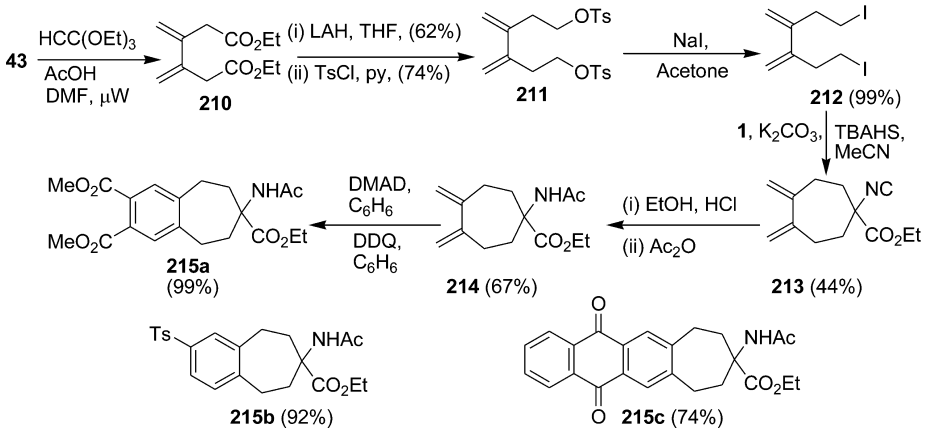


dx.doi.org/10.1021/jo4020722 | J. Org. Chem. 2013, 78, 12288–12313

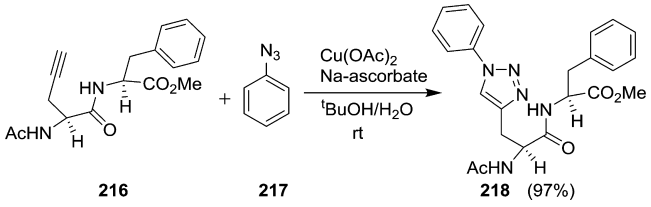
Scheme 54



Scheme 55



Scheme 56



diversity-oriented approach has delivered various constrained analogues of Phe with varied steric and electronic properties. In addition, we prepared several polycyclics, carbocyclics, heterocyclics, and macrocyclics containing an AAA moiety. In this regard, we have used several olefin metathesis protocols (e.g., RCM, EM, RCEM), [2 + 2 + 2] cycloaddition, DA reaction, and Suzuki coupling to expand the diversity of unusual amino acids and peptides. In some cases, we have used rongalite to generate the required DA precursors. Our strategies involve several points for diversification and are also capable of generating a library of diverse structures. It is worth mentioning here that this is all one can hope to achieve during a diversity-oriented approach.[137] The synthetic method described here involves atom economy, and in some cases redox economy and step economy have been incorporated. These methods can deliver valuable compounds for bioorganic studies. Lessons learned during the development of these synthetic methods will enable us to create new and additional chemical space which in turn will help to create peptidomimetics with extended diversity. Moreover, these new tools provide opportunitiues to design miracle peptide drugs.

AUTHOR INFORMATION

Corresponding Author

*E-mail: srk@chem.iitb.ac.in. Tel: +91 22 25767160. Fax: +91 22 25767152.

Notes

The authors declare no competing financial interest.

Biography

Prof. Sambasivarao Kotha received his Ph.D. at the University of Hyderabad in 1985. He joined IIT-Bombay in 1994 as an assistant professor and was promoted to professor in 2001. At present he holds the Pramod Chaudhari Chair Professor for Green Chemistry and Industrial Biotechnology. He was a recipient of the B. M. Birla prize in Chemical Sciences, the Professor N. S. Narasimhan endowment award, the CRSI bronze medal, the Bhagyatara National award, and the Professor S. C. Bhattacharya award for research excellence. He is a member of the editorial boards for *Indian J. Chem., Sec-B*, *J. Amino Acids*, *Catal. J.*, and *Eur. J. Org. Chem.* He is also an elected Fellow of the National Academy of Sciences, India, The Indian Academy of Sciences, and the Royal Society of Chemistry. Recently, he was awarded the J. C. Bose National Fellowship from DST and the Professor Y. T. Thathachari Award from Bhramara Trust. His research interests include the development of new synthetic methods.

ACKNOWLEDGMENTS

We thank DST, CSIR, for their financial support. D.G. and A.S.C. thank UGC and CSIR, New Delhi, respectively, for the award of scholarships. S.K. thanks the DST for the award of a J. C. Bose fellowship. We thank Dr. D. Deodhar for his help in preparing the manuscript. S.K. thanks his past and present

M.Sc., Ph.D., and post-doctoral students (~80) for their valuable contributions. He also thanks his wife Chandra and daughters Leela and Pallavi for their constant support and understanding.

REFERENCES

(1) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699.
(2) (a) Craik, D. J.; Adams, D. *J. Chem. Biol.* **2007**, *2*, 457. (b) Gentilucci, L.; De Marco, R.; Cerisoli, L. *Curr. Pharm. Des.* **2010**, *16*, 3185. (c) Marek, P.; Woys, A. M.; Sutton, K.; Zanni, M. T.; Raleigh, D. P. *Org. Lett.* **2010**, *12*, 4848. (d) Larsen, P. K.; Bundgaard, H. *A Textbook of Drug Design and Development*; Harwood Academic Press: Chur, 1992. (e) Balaram, P. *Curr. Opin. Struct. Biol.* **1992**, 845.
(3) (a) Kotha, S.; Sreenivasachary, N. *Indian J. Chem.* **2001**, *40B*, 763. (b) Diver, S. T.; Giessert, A. *J. Chem. Rev.* **2004**, *104*, 1317. (c) Grubbs, R. H. *Handbook of Metathesis*; Wiley−VCH: Weinheim, 2003; Vols. *1*−3. (d) Cossy, J.; Arseniyadis, S.; Meyer, C. *Metathesis in Natural Product Synthesis*; Wiley−VCH: Weinheim, 2010. (e) Kotha, S.; Dipak, M. K. *Tetrahedron* **2012**, *68*, 397.
(4) Kotha, S.; Sreenivasachary, N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 257.
(5) (a) Casabona, D.; Jiménez, A. I.; Cativiela, C. *Tetrahedron* **2007**, *63*, 5056. (b) Ohwada, T.; Kojima, D.; Kiwada, T.; Futaki, S.; Sugiura, Y.; Yamaguchi, K.; Nishi, Y.; Kobayashi, Y. *Chem.—Eur. J.* **2004**, *10*, 617.
(6) (a) Plé, K.; Haudrechy, A.; Probst, N. P. *Tetrahedron* **2010**, *66*, 5030. (b) Kotha, S.; Krishna, N. G.; Halder, S.; Misra, S. *Org. Biomol. Chem.* **2011**, *9*, 5597.
(7) (a) Conti, P.; De Amici, M.; Di Ventimiglia, S. J.; Stensbøl, T. B.; Madsen, U.; Bräuner-Osborne, H.; Russo, E.; De Sarro, G.; Bruno, G.; De Micheli, C. *J. Med. Chem.* **2003**, *46*, 3102. (b) Roda, G.; Conti, P.; De Amici, M.; He, J.; Polavarapu, P. L.; De Micheli, C. *Tetrahedron: Asymmetry* **2004**, *15*, 3079. (c) Kiss, L.; Nonn, M.; Fülöp, F. *Synthesis* **2012**, 1951.
(8) Brunel, J. M. *Protein Pept. Lett.* **2005**, *12*, 281.
(9) (a) Larionov, O. V.; Kozhushkov, S. I.; de Merijere, A. *Synthesis* **2005**, 158. (b) Casabona, D.; Cativiela, C. *Synthesis* **2006**, 2440.
(10) Kotha, S.; Lahiri, K. *Curr. Med. Chem.* **2005**, *12*, 849.
(11) Kotha, S.; Sreenivasachary, N.; Mohanraja, K.; Durani, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1421.
(12) (a) Lucente, G.; Paradisi, M. P.; Giordano, C.; Sansone, A.; Torino, D.; Spisani, S. *Amino Acids* **2008**, *35*, 329. (b) Whelan, A. N.; Elaridi, J.; Harte, M.; Smith, S. V.; Jackson, W. R.; Robinson, A. J. *Tetrahedron Lett.* **2004**, *45*, 9545.
(13) Kotha, S.; Singh, K. *Tetrahedron Lett.* **2004**, *45*, 9607.
(14) Kotha, S.; Khedkar, P. *Indian J. Chem.* **2007**, *46B*, 975.
(15) Kotha, S.; Singh, K. *Eur. J. Org. Chem.* **2007**, 5909.
(16) Rolfe, A.; Hanson, P. *Chemtracts−Org. Chem.* **2009**, *22*, 200.
(17) Kotha, S.; Bansal, D.; Singh, K.; Banerjee, S. *J. Organomet. Chem.* **2011**, *696*, 1856.
(18) (a) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585. (b) Undheim, K. *Amino Acids* **2008**, *34*, 357. (c) Trabocchi, A. *Amino Acids* **2008**, *34*, 1. (d) Tanaka, M. *Chem. Pharm. Bull.* **2007**, *55*, 349. (e) Park, K.−H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629. (f) Cativiela, C.; Díaz−de−Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645. (g) Gelmi, M. L.; Pocar, D. *Org. Prep. Proc. Int.* **2003**, *35*, 141. (h) Soloshonok, V. A.; Sorochinsky, A. E. *Synthesis* **2010**, 2319. (i) Hong, B.−C.; Sarshar, S. *Org. Prep. Proc. Int.* **1999**, *31*, 1. (j) Kuck, D. *Chem. Rev.* **2006**, *106*, 4885.
(19) (a) Clerc, F. F.; Guitton, J. D.; Fromage, N.; Lelievre, Y.; Duchesne, M.; Tocque, B.; James-Surcouf, E.; Commercon, A.; Becquart, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1779. (b) Klutchko, S.; Blankley, C. J.; Fleming, R. W.; Hinkley, J. M.; Werner, A. E.; Nordin, E.; Holmes, A.; Hoefle, M. L.; Cohen, D. M.; Essenburg, A. E.; Kaplan, H. R. *J. Med. Chem.* **1986**, *29*, 1953. (c) Hanada, M.; Noguchi, T.; Yamaoka, T. *Cancer Sci.* **1998**, *89*, 1055. (d) Mitsuharu, H.; Toshihiro, N.; Takashi, Y. *Cancer Sci.* **2007**, *98*, 447. (e) Ishizumi, K.; Ohashi, N.; Tanno, N. *J. Org. Chem.* **1987**, *52*, 4477. (f) Adamo, I.; Benedetti, F.; Berti, F.; Campaner, P. *Org. Lett.* **2006**, *8*, 51. (g) De Nanteuil, G.; Gloanec, P.; Béguin, S.; Giesen, P. L. A.; Hemker, H. C.; Mennecier, P.; Rupin, A.; Verbeuren, T. J. *J. Med. Chem.* **2006**, *49*, 5047. (h) Ballet, S.; Marczak, E. D.; Feytens, D.; Salvadori, S.; Sasaki, Y.; Abell, A. D.; Lazarus, L. H.; Balboni, G.; Tourwé, D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1610. (i) Ballet, S.; Salvadori, S.; Trapella, C.; Bryant, S. D.; Jinsmaa, Y.; Lazarus, L. H.; Negri, L.; Giannini, E.; Lattanzi, R.; Tourwé, D.; Balboni, G. *J. Med. Chem.* **2006**, *49*, 3990. (j) Cheng, C.; Gallegos, R.; Bridson, G.; Wu, L.; Harbeson, S.; Zelle, R.; Tung, R. *J. Mass Spectrom.* **2013**, *48*, 640. (k) Chen, K. X.; Njoroge, F. G.; Pichardo, J.; Prongay, A.; Butkiewicz, N.; Yao, N.; Madison, V.; Girijavallabhan, V. *J. Med. Chem.* **2006**, *49*, 567. (l) Pfizenmayer, A. J.; Vera, M. D.; Ding, X.; Xiao, D.; Chen, W. C.; Joullié, M. M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3653. (m) Whelan, A. N.; Elaridi, E.; Harte, M.; Smith, S. V.; Jacksonc, W. R.; Robinson, A. J. *Tetrahedron Lett.* **2004**, *45*, 9545.
(20) Torrini, I.; Zecchini, G. P.; Paradisi, M. P.; Lucente, G.; Mastropietro, G.; Gavuzzo, E.; Mazza, F.; Pochetti, G. *Tetrahedron* **1998**, *54*, 165.
(21) (a) Gibson, S. E.; Guillo, N.; Jones, J. O.; Buck, I. M.; Kalindjian, S. B.; Roberts, S.; Tozer, M. J. *Eur. J. Med. Chem.* **2002**, *37*, 379. (b) Mosberg, H. I.; Lomize, A. L.; Wang, C.; Kroona, H.; Heyl, D. L.; Sobczyk-Kojiro, K.; Ma, W.; Mousigian, C.; Porreca, F. *J. Med. Chem.* **1994**, *37*, 4371.
(22) (a) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (b) Kotha, S.; Bansal, D.; Kumar, R. V. *Indian J. Chem.* **2009**, *48B*, 225. For some examples involving synthesis of Tic derivatives, see: (c) Chaturvedula, P. V.; Mercer, S. E.; Guernon, L.; Macor, J. E.; Dubowchik, G. M. *Tetrahedron Lett.* **2010**, *51*, 5588. (d) Kawthekar, R. B.; Chakka, S. K.; Francis, V.; Andersson, P. G.; Kruger, K. G.; Maguire, G. E. M.; Govender, T. *Tetrahedron: Asymmetry* **2010**, *21*, 846. (e) Azukizawa, S.; Kasai, M.; Takahashi, K.; Miike, T.; Kunishiro, K.; Kanda, M.; Mukai, C.; Shirahase, H. *Chem. Pharm. Bull.* **2008**, *56*, 335. (f) Manini, P.; Napolitano, A.; d Ischia, M. *Carbohydr. Res.* **2005**, *340*, 2719. (g) Benz, P.; Wohlgemuth, R. *J. Chem. Technol. Biotechnol.* **2007**, *82*, 1082. (h) Aubry, S.; Pellet-Rostaing, S.; Faure, R.; Lemaire, M. *J. Heterocycl. Chem.* **2006**, *43*, 139. (i) Eustache, J.; de Weghe, P. V.; Le Nouen, D.; Uyehara, H.; Kabuto, C.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4043.
(23) Kotha, S.; Misra, S.; Krishna, N. G.; Devunuri, N.; Hopf, H.; Keecherikunnel, A. *Heterocycles* **2010**, *80*, 847.
(24) Kotha, S.; Misra, S.; Mobin, S. M. *Amino Acids* **2011**, *41*, 933.
(25) Kotha, S.; Sreenivasachary, N. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1413.
(26) Shchetnikov, G. T.; Osipov, S. N.; Bruneau, C.; Dixneuf, P. H. *Synlett* **2008**, 578.
(27) Kotha, S.; Banerjee, S. *Synthesis* **2007**, 1015.
(28) Andraos, J. *The Algebra of Organic Synthesis: Green Metrics, Design Strategy, Route Selection and Optimization*; CRC Press: Boca Raton, 2011.
(29) Kotha, S.; Meshram, M.; Tiwari, A. *Chem. Soc. Rev.* **2009**, *38*, 2065.
(30) Kotha, S.; Sreenivasachary, N. *J. Indian Inst. Sci.* **2001**, *81*, 277.
(31) (a) Kotha, S.; Sreenivasachary, N. *Chem. Commun.* **2000**, 503. (b) Kotha, S.; Sreenivasachary, N. *Eur. J. Org. Chem.* **2001**, 3375.
(32) Stork, G.; Leong, A. Y. W.; Touzin, A. M. *J. Org. Chem.* **1976**, *41*, 3491.
(33) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. *Tetrahedron Lett.* **1978**, *30*, 2641.
(34) (a) Kotha, S.; Kuki, A. *Tetrahedron Lett.* **1992**, *33*, 1565. (b) Kotha, S.; Anglos, D.; Kuki, A. *Tetrahedron Lett.* **1992**, *33*, 1569.
(35) (a) Kaliappan, K. P.; Ravikumar, V. *Org. Biomol. Chem.* **2005**, *3*, 848. (b) Kaliappan, K. P.; Nandurdikar, R. S. *Org. Biomol. Chem.* **2005**, *3*, 3613. (c) Banti, D.; North, M. *Tetrahedron Lett.* **2003**, *44*, 8157. (d) Moreno−Mañas, M.; Pleixats, R.; Santamaria, A. *Synlett* **2001**, 1784. (e) Semeril, D.; Cleran, M.; Bruneau, C.; Dixneuf, P. H. *Adv. Synth. Catal.* **2001**, *343*, 184.
(36) Ockey, D. A.; Lewis, M. A.; Schore, N. E. *Tetrahedron* **2003**, *59*, 5377.

(37) Günter, M.; Gais, H.-J. *J. Org. Chem.* **2003**, *68*, 8037.
(38) Kotha, S.; Khedkar, P. *Synthesis* **2008**, 2925.
(39) Yamamoto, Y.; Hayashi, H.; Saigoku, T.; Nishiyama, H. *J. Am. Chem. Soc.* **2005**, *127*, 10804.
(40) (a) Snyder, K. R.; Murray, T. F.; DeLander, G. E.; Aldrich, J. V. *J. Med. Chem.* **1993**, *36*, 1100. (b) Oishi, S.; Kang, S. U.; Liu, H.; Zhang, M.; Yang, D.; Deschampsc, J. R.; Burke, T. R., Jr. *Tetrahedron* **2004**, *60*, 2971.
(41) Grunewald, G. L.; Kuttab, S. H.; Pleiss, M. A.; Mangold, J. B.; Soine, P. *J. Med. Chem.* **1980**, *23*, 754.
(42) (a) Mehta, G.; Kotha, S. *Tetrahedron* **2001**, *57*, 625. (b) Segura, J. L.; Martin, N. *Chem. Rev.* **1999**, *99*, 3199. (c) Martin, N.; Seoane, C.; Hanack, M. *Org. Prep. Proc. Int.* **1991**, *23*, 237. (d) Charlton, J. L.; Alauddin, M. M. *Tetrahedron* **1987**, *43*, 2873. (e) Bieber, L. W; Da Silva, M. F. *Molecules* **2001**, *6*, 472.
(43) Kotha, S.; Khedkar, P. *Chem. Rev.* **2012**, *112*, 1650.
(44) (a) Kotha, S.; Ghosh, A. K. *Synthesis* **2004**, 558. (b) Kotha, S.; Thota, G.; Ghosh, A. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1755.
(45) Kotha, S.; Krishna, N. G. *Curr. Sci.* **2011**, *101*, 923.
(46) Silveira, C. C.; Braga, A. L.; Kaufman, T. S.; Lenardão, E. J. *Tetrahedron* **2004**, *60*, 8295.
(47) Ishizumi, K.; Ohashi, N.; Tanno, T. *J. Org. Chem.* **1987**, *52*, 4477.
(48) Ma, D.; Tian, H.; Sun, H.; Kozikowski, A. P.; Pshenichkin, S.; Wroblewski, J. T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1195.
(49) Kotha, S.; Halder, S. *Synlett* **2010**, 337.
(50) (a) Hassner, A.; Namboothiri, I. *Organic Syntheses Based on Name Reactions*; Elsevier: UK, 2012; pp 269; (b) Schollkopf, U.; Meyer, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 629.
(51) (a) Kotha, S.; Brahmachary, E. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2719. (b) Kotha, S.; Brahmachary, E. *J. Org. Chem.* **2000**, *65*, 1359. (c) Kotha, S.; Behera, M. *Indian J. Chem.* **2004**, *43B*, 922.
(52) Damodharan, L.; Shamaladevi, N.; Pattabhi, V.; Behra, M.; Kotha, S. *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **2002**, *58*, 266.
(53) Kotha, S.; Krishna, N. G.; Misra, S.; Khedkar, P. *Synthesis* **2011**, 2945.
(54) Kumaradhas, P.; Gupta, K. R.; Kotha, S.; Brahmachary, E. *Anal. Sci.* **2008**, *24*, 65.
(55) Kotha, S.; Chavan, A. S. *J. Org. Chem.* **2010**, *75*, 4319.
(56) (a) Simpkins, N. S. Sulphones in Organic Synthesis. In *Tetrahedron Organic Chemistry Series*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon: Oxford, U.K., 1993; Vol. *10*. (b) Tanaka, K.; Kaji, A. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C., Eds.; John Wiley & Sons: New York, 1988; p 729.
(57) Kotha, S.; Meshram, M. Presented at JNOST Symposium-IISER Mohali, India, Dec 15−18, 2011. Meshram, M. Ph. D. Thesis, IIT-Bombay, Mumbai, 2013.
(58) Kotha, S.; Misra, S.; Srinivas, V. *Eur. J. Org. Chem.* **2012**, 4052.
(59) Ellis, T. K.; Hochla, V. M.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 4973.
(60) Tanaka, M.; Anan, K.; Demizu, Y.; Kurihara, M.; Doi, M.; Suemune, H. *J. Am. Chem. Soc.* **2005**, *127*, 11570.
(61) Dutot, L.; Wright, K.; Gaucher, A.; Wakselman, M.; Mazaleyrat, J.−P.; De Zotti, M.; Peggion, C.; Formaggio, F.; Toniolo, C. *J. Am. Chem. Soc.* **2008**, *130*, 5986.
(62) Murigi, N. F.; Nichol, G. S.; Mash, E. A. *J. Org. Chem.* **2010**, *75*, 1293.
(63) Lohier, J.-F.; Wright, K.; Peggion, C.; Formaggio, F.; Toniolo, C.; Wakselman, M.; Mazaleyrat, J.-P. *Tetrahedron* **2006**, *62*, 6203.
(64) Taylor, J. B.; Lewis, J. W.; Jacklin, M. *J. Med. Chem.* **1970**, *13*, 1226.
(65) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235.
(66) Kloster, R. A.; Carducci, M. D.; Mash, E. A. *Org. Lett.* **2003**, *5*, 3683.
(67) Weatherhead, R. A.; Carducci, M. D.; Mash, E. A. *J. Org. Chem.* **2009**, *74*, 8773.
(68) Ntirampebura, D.; Jagadish, B.; Nichol, G. S.; Carducci, M. D.; Dawson, A.; Rajapakshe, A.; Oliver, A. G.; Clegg, W.; Harrington, R. W., Jr.; Layne, L.; Margolis, J. I.; Mash, E. A. *Cryst. Growth Des.* **2008**, *8*, 3257.
(69) Lasa, M.; López, P.; Cativiela, C. *Tetrahedron: Asymmetry* **2005**, *16*, 4022.
(70) Kotha, S.; Halder, S.; Lahiri, K. *Synthesis* **2002**, 339.
(71) (a) Kotha, S.; Brahmachary, E.; Kuki, A.; Lang, K.; Anglos, D.; Singaram, B.; Chrisman, W. *Tetrahedron Lett.* **1997**, *38*, 9031 and references cited therein. (b) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: New York, 2001; p 1051. (c) Warren, S. *Solutions Manual to Accompany Organic Chemistry*; Clayden, J., Greeves, N., Warren, S., Wothers, P., Eds.; Oxford University Press: New York, 2001; pp 347.
(72) Staszewska, A.; Stefanowicz, P.; Szewczuk, Z. *Tetrahedron Lett.* **2005**, *46*, 5525.
(73) Kotha, S.; Brahmachary, E. *Indian J. Chem.* **2001**, *40B*, 1.
(74) Wright, K.; Anddad, R.; Lohier, J.-F.; Steinmetz, V.; Wakselman, M.; Mazaleyrat, J.-P.; Formaggio, F.; Peggion, C.; Zotti, M. D.; Keiderling, T. A.; Huang, R.; Toniolo, C. *Eur. J. Org. Chem.* **2008**, 1224.
(75) (a) Kotha, S.; Brahmachary, E. *Bioorg. Med. Chem.* **2002**, *10*, 2291. (b) Kotha, S.; Brahmachary, E. *Tetrahedron Lett.* **1997**, *38*, 3561.
(76) Damodharan, L.; Mohanraja, K.; Kotha, S.; Durani, S.; Pattabhi, V. *Biopolymers* **2001**, *59*, 330.
(77) Hededus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Sausalito, 1999; p 244.
(78) Garcia, L.; Pla-Quintana, A.; Roglans, A. *Org. Biomol. Chem.* **2009**, *7*, 5020.
(79) Senaiar, R. S.; Teske, J. A.; Young, D. D.; Deiters, A. *J. Org. Chem.* **2007**, *72*, 7801.
(80) (a) Yamamoto, Y.; Yamashita, K.; Hotta, T.; Hashimoto, T.; Kikuchi, M.; Nishiyama, H. *Chem.—Asian J.* **2007**, *2*, 1388. (b) Yamamoto, Y.; Hayashi, H. *Tetrahedron* **2007**, *63*, 10149.
(81) (a) Kotha, S.; Ghosh, A. K. *Tetrahedron* **2004**, *60*, 10833. (b) Kotha, S.; Ghosh, A. K. *Tetrahedron Lett.* **2004**, *45*, 2931.
(82) (a) Bianco, A.; Da Ros, T.; Prato, M.; Toniolo, C. *J. Pept. Sci.* **2001**, *7*, 208. (b) Ros, T. D.; Prato, M. *Chem. Commun.* **1999**, 663. (c) Burley, G. A.; Keller, P. A.; Pyne, S. G.; Ball, G. E. *J. Org. Chem.* **2002**, *67*, 8316.
(83) Kotha, S.; Brahmachary, E. *J. Organomet. Chem.* **2004**, *689*, 158.
(84) (a) Tacke, R.; Linoh, H. In *The Chemistry of Organosilicon Compounds*; Patai, R., Rappoport, Z., Eds.; John Wiley: New York, 1989; p 1144. (b) Weidman, B. *Chima* **1992**, *46*, 312. (c) Hughes, A. B. *Amino Acids, Peptides and Proteins in Organic Chemistry*; Wiley−VCH: Weinheim, 2009; pp 261−278.
(85) Seyferth, D.; White, D. L. *J. Am. Chem. Soc.* **1972**, *94*, 3132.
(86) Halder, S. Ph.D. Thesis, IIT−Bombay, 2002.
(87) Kotha, S.; Mohanraja, K.; Durani, S. *Chem. Commun.* **2000**, 1909.
(88) Martin, N.; Altable, M.; Filippone, S.; Martin−Domenech, A. *Synlett* **2007**, 3077.
(89) Kotha, S.; Brahmachary, E.; Sreenivasachary, N. *Tetrahedron Lett.* **1998**, *39*, 4095.
(90) (a) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. *Tetrahedron Lett.* **1998**, *39*, 2805. (b) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. *Eur. J. Org. Chem.* **2001**, 787.
(91) Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*; Oxford University Press: New York, 2012; p 1027.
(92) (a) Kotha, S.; Lahiri, K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2887. (b) Kotha, S.; Lahiri, K. *Biopolymers* **2003**, *69*, 517. (c) Chen, S.; Fahmi, N. F.; Wang, L.; Bhattacharya, L.; Benkovic, S. J.; Hecht, S. M. *J. Am. Chem. Soc.* **2013**, *135*, 12924.
(93) Knör, S.; Laufer, B.; Kessler, H. *J. Org. Chem.* **2006**, *71*, 5625.
(94) (a) Kotha, S.; Sreenivasachary, N.; Halder, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2565. (b) Kotha, S.; Halder, S. *Indian J. Chem.* **2003**, *42B*, 863.
(95) (a) Fischmeister, C.; Bruneau, C. *Beilstein J. Org. Chem.* **2011**, *7*, 156. (b) Castarlenas, R.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H.

J. Mol. Catal. A: Chem. **2004**, *213*, 31. (c) Mori, M. *J. Mol. Cat. A: Chem.* **2004**, *213*, 73. (d) Tonogakia, K.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 2235. (e) Kummer, D. A.; Brenneman, J. B.; Martin, S. F. *Tetrahedron* **2006**, *62*, 11437. (f) Kotha, S.; Lahiri, K. *Synlett* **2007**, 2767.

(96) (a) Hayashi, Y. *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: New York, 2002. (b) Paquette, L. A. *Comprehensive Organic Synthesis*; Pergmon: Oxford, 1991; Vol. *5*. (c) Carruthers, W. *Tetrahedron Organic Chemistry Series; Vol. 8, Cycloaddition Reactions in Organic Synthesis*; Baldwin, J. E., Magnus, P. D., Ed.; Pergamon: Oxford, 1990.

(97) Kotha, S.; Mandal, K.; Banerjee, S.; Mobin, S. M. *Eur. J. Org. Chem.* **2007**, 1244.

(98) Berkheij, M.; Dijkink, J.; David, O. R. P.; Sonke, T.; Ijzendoorn, D. R.; Blaauw, R. H.; van Maarseveen, J. H.; Schoemaker, H. E. *Eur. J. Org. Chem.* **2008**, 914. For additional references on *N*-acylium ion chemistry, see: (a) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(99) Chen, R.; Lee, V.; Adlington, R. M.; Baldwin, J. E. *Synthesis* **2007**, 113.

(100) (a) Kotha, S.; Halder, S.; Brahmachary, E.; Ganesh, T. *Synlett* **2000**, 853. (b) Kotha, S.; Halder, S.; Brahmachary, E. *Tetrahedron* **2002**, *58*, 9203.

(101) Mindt, T. L.; Schibli, R. *J. Org. Chem.* **2007**, *72*, 10247.

(102) Yoburn, J. C.; Vranken, D. L. V. *Org. Lett.* **2003**, *5*, 2817.

(103) Espuña, G.; Arsequell, G.; Valencia, G.; Barluenga, J.; Alvarez-Gutiérrez, J. M.; Ballesteros, A.; González, J. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 325.

(104) (a) Ojida, A.; Tsutsumi, H.; Kasagi, N.; Hamachi, I. *Tetrahedron Lett.* **2005**, *46*, 3301. (b) Böhrsch, V.; Hackenberger, P. R. *ChemCatChem* **2010**, *2*, 243.

(105) (a) Doan, N.-D.; Bourgault, S.; Létourneau, M.; Fournier, A. *J. Comb. Chem.* **2008**, *10*, 44. (b) Afonso, A.; Rosés, C.; Planas, M.; Feliu, L. *Eur. J. Org. Chem.* **2010**, 1461. (c) Ojida, A.; Tsutsumi, H.; Kasagi, N.; Hamachi, I. *Tetrahedron Lett.* **2005**, *46*, 3301. (d) Limbach, M.; Löweneck, M.; Schreiber, J. V.; Frackenpohl, J.; Seeback, D. *Helv. Chim. Acta* **2006**, *89*, 1427.

(106) Ruiz-Rodriguez, J.; Albericio, F.; Lavilla, R. *Chem.—Eur. J.* **2010**, *16*, 1124.

(107) (a) Vilaró, M.; Arsequell, G.; Valencia, G.; Ballesteros, A.; Barluenga, J. *Org. Lett.* **2008**, *10*, 3243. (b) Gong, Y.; He, W. *Org. Lett.* **2002**, *4*, 3803.

(108) Rajanarendar, E.; Rao, G. M. E. K.; Srinivas, M. *Chin. Chem. Lett.* **2009**, *20*, 1.

(109) Afonso, A.; Lidia, F.; Planas, M. *Tetrahedron* **2011**, *67*, 2238.

(110) Kotha, S.; Goyal, D.; Thota, N.; Srinivas, V. *Eur. J. Org. Chem.* **2012**, 1843.

(111) For earlier references on the synthesis of Dbzg, see: (a) Felkin, H. *Bull. Chim. Fr.* **1959**, 20. (b) Barret, W. H.; Hardy, P. M.; Harrow, T. A.; Rydon, H. N. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2634. (c) Maia, H. L.; Ridge, B.; Rydon, H. N. *J. Chem. Soc., Perkin Trans. 1* **1973**, 98. (d) Ezquerra, J.; Pedregal, C.; Moreno-Manas, M.; Pleixats, R.; Roglans, A. *Tetrahedron Lett.* **1993**, *33*, 8535. (e) Goodson, L. H.; Honigberg, I. L.; Lehman, J. J.; Borton, W. H. *J. Org. Chem.* **1975**, *40*, 953.

(112) (a) Kotha, S.; Behera, M.; Kumar, R. V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 105. (b) Kotha, S.; Behera, M. *J. Peptide Res.* **2004**, *64*, 72. (c) Damodharan, L.; Pattabhi, V.; Behera, M.; Kotha, S. *Acta. Crystallogr. Sect. C: Cryst. Struct. Commun.* **2003**, *59*, 216. (d) Damodharan, L.; Pattabhi, V.; Behera, M.; Kotha, S. *Acta. Crystallogr. Sect. C: Cryst. Struct. Commun.* **2004**, *60*, 527. (e) Damodharan, L.; Pattabhi, V.; Behera, M.; Kotha, S. *J. Mol. Struct.* **2004**, *705*, 101.

(113) Solanas, C.; De La Torre, B. G.; Fernández-Reyes, M.; Santiveri, C. M.; Jiménez, M. A.; Rivas, L.; Jiménez, A. I.; Andreu, D.; Cativiela, C. *J. Med. Chem.* **2010**, *53*, 4119.

(114) Kotha, S.; Behera, M.; Shah, V. R. *Synlett* **2005**, 1877.

(115) Behera, M. *Chemtracts-Org. Chem.* **2009**, *22*, 167.

(116) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(117) O'Brien, E. M.; Morgan, B. J.; Mulrooney, C. A.; Carroll, P. J.; Kozlowski, M. C. *J. Org. Chem.* **2010**, *75*, 57.

(118) Gerbino, D. C.; Mandolesi, S. D.; Schmalz, H.-G.; Podestá, J. C. *Eur. J. Org. Chem.* **2009**, 3964.

(119) Martinez-Solorio, D.; Belmore, K. A.; Jennings, M. P. *J. Org. Chem.* **2011**, *76*, 3898.

(120) Kotha, S.; Halder, S.; Sreenivasachary, N. *ARKIVOC* **2002**, No. vii, 21.

(121) (a) Nieto, M.; Perkins, H. R. *Biochem. J.* **1971**, *124*, 845. (b) Andersen, S. O. *Biochem. Biophys. Acta* **1964**, *93*, 213.

(122) Rose, G. D.; Gierasch, L. M.; Smith, J. A. *Adv. Protein Chem.* **1985**, *37*, 1.

(123) Onescu, R. D. I.; Blom, A.; Frejd, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2369.

(124) (a) Kotha, S.; Shah, V. R.; Halder, S.; Vinodkumar, R.; Lahiri, K. *Amino Acids* **2007**, *32*, 387. (b) Kotha, S.; Shah, V. R.; Mishra, P. P.; Datta, A. *Amino Acids* **2008**, *35*, 169.

(125) Kotha, S.; Shah, V. R. *Amino Acids* **2008**, *35*, 83.

(126) (a) Kotha, S.; Halder, S.; Damodharan, L.; Pattabhi, V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1113. (b) Damodharan, L.; Ibrahim, B. S.; Pattabhi, V.; Halder, S.; Kotha, S. *Acta Crystallogr.* **2002**, *E58*, 1038.

(127) Kotha, S.; Halder, S. *ARKIVOC* **2005**, No. iii, 56.

(128) Kotha, S.; Ghosh, A. K.; Behera, M. *Indian J. Chem.* **2002**, *41B*, 2330.

(129) (a) Duan, J.; Sheppeck, J.; Jiang, B.; Gilmore, J. L. U. S. Patent 2005, US2005176716(A1), Aug 11, 2005. (b) Weinstein, D. S.; Sheppeck, J.; Gilmore, J. L. U. S. Patent 2005, US2005182083(A1) Aug 18, 2005. (c) Sheppeck, J.; Dhar, T. G. M.; Doweyko, L.; Gilmore, J.; Weinstein, D.; Xiao, H.-Y.; Yang, B. V.; Doweyko, A. M. U. S. Patent Appl. Publ. US2006154973(A1), July 13, 2006. (d) Yang, B. V. U. S. Patent Appl. Publ. US2006154962(A1) July 13, 2006.

(130) Yang, B. V.; Doweyko, L. M. *Tetrahedron Lett.* **2005**, *46*, 2857.

(131) Komarov, I. V.; Grigorenko, A. O.; Turov, A. V.; Khilya, V. P. *Russ. Chem. Rev.* **2004**, *73*, 785.

(132) Royo, E.; López, P.; Cativiela, C. *ARKIVOC* **2005**, No. vi, 46.

(133) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. *Tetrahedron* **2001**, *57*, 6261.

(134) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342.

(135) Kotha, S.; Goyal, D.; Banerjee, S.; Datta, A. *Analyst* **2012**, *137*, 2871.

(136) Kotha, S.; Goyal, D.; Bitra, A.; Thota, N.; Kruger, G.; Anand, R. *RSC Adv.* **2013**, *3*, 24447.

(137) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem.* **2004**, *116*, 48; *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (c) Tejedor, D.; Gonzalez-Cruz, D.; Santos-Exposito, A.; Marrero-Tellado, J. J.; Garcia-Tellado, P.; de, A. F. *Chem.—Eur. J.* **2005**, *11*, 3502. (d) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74. (e) Liao, Y.; Hu, Y.; Wu, J.; Zhu, Q.; Donovan, M.; Fathi, R.; Yang, Z. *Curr. Med. Chem.* **2003**, *10*, 2285. (f) Kotha, S.; Mandal, K.; Tiwari, A.; Mobin, S. M. *Chem.—Eur. J.* **2006**, *12*, 8024. (g) Kotha, S.; Lahiri, K. *Eur. J. Org. Chem.* **2007**, 1221. (h) Kotha, S.; Khedkar, P. *Eur. J. Org. Chem.* **2009**, 730. (i) Kotha, S.; Vittal, S. *Synlett* **2011**, 2329. (j) Kotha, S.; Waghule, G. T. *J. Org. Chem.* **2012**, *77*, 6314. (k) Mooberry, S. L.; Hilinski, M. K.; Clark, E. A.; Wender, P. A. *Mol. Pharmaceutics* **2008**, *5*, 829. (l) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40.