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# The Practice of Ring Constraint in Peptidomimetics Using Bicyclic and Polycyclic Amino Acids

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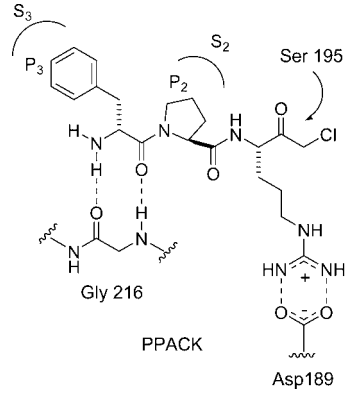
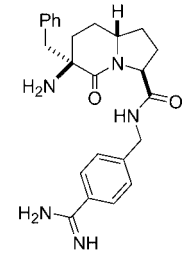
## CONSPECTUS




Constrained mimetic
$IC_{50}$ = 4nM (thrombin)

Medicinal chemistry has witnessed major advances with the discovery of small synthetic molecules that mimic natural peptidic substrates. These small synthetic mimics do not undergo proteolytic degradation, an advantage they hold over their natural counterparts. Small synthetic molecules make up a number of life-saving marketed drugs that inhibit certain physiologically relevant proteases.

The advent of sophisticated instrumental methods, such as X-ray crystallography and high-field NMR, has played a pivotal role in the design of structure-based enzyme inhibitors. Highly stereocontrolled methods of synthesis have led to a variety of functionally diverse molecules that function as peptidomimetics because they have isosteric subunits not affected by proteolytic enzymes. Further studies to optimize biological activity and achieve desirable pharmacokinetic profiles can eventually lead to drug substances.

The practice of constraining natural amino acids like their conformationally rigid counterparts has been highly successful in the design and synthesis of peptidomimetic molecules. With some notable exceptions, structural information gathered from protein X-ray crystallography of therapeutically relevant target enzymes, alone or in complex forms with inhibitor molecules, has been instrumental in the design of peptidomimetics. For example, a significant number have become marketed drugs as antihypertensives and antivirals. Natural products have also been a source of inspiration for the design and synthesis of truncated analogues with the intention of maintaining, or even improving, their biological activities.

However, lower molecular weight peptides are not suitable as therapeutic agents because they are subject to rapid amide proteolysis. They are poorly transported to the brain and rapidly excreted through the liver and kidney. Thus, lower molecular weight peptides are eliminated as potential drug substances in clinical practice. A synthetic peptidomimetic is needed that is resistant to cleavage but maintains its biological activity. Conformationally constrained monocyclic and bicyclic unnatural amino acids can be directly incorporated in a potential inhibitor molecule as part of the design element.

In this Account, we describe our efforts in the synthesis of constrained azacycles that contain proline or pipecolic acid as an integral part of bicyclic and polycyclic amino acids. We devised syntheses of conformationally biased monocyclic, bicyclic, and polycyclic amino acid analogues, into which pharmacologically or structurally relevant functional groups were incorporated. Stereocontrolled reactions for C—C, C—N, and C—O bond formation had to be implemented on appropriately protected amino acid frameworks. A number of these frameworks provided access to functionally diverse scaffolds for further use as core subunits in more elaborated structures. Specific applications as peptidomimetics of natural substrates for relevant enzymes, such as thrombin, were also pursued, resulting in highly active inhibitors *in vitro*.

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## Introduction

It is well-known that lower molecular weight peptides are not suitable as therapeutic agents, despite their remarkable activities in enzymatic or receptor-based assays. Small molecule peptides are subject to rapid amide proteolysis *in vivo*. They are poorly transported to the brain and are rapidly excreted through the liver and kidney, which contribute to their exclusion as drug substances in clinical practice. A synthetic peptidomimetic that is not subject to cleavage while maintaining the biological activity of the original peptide may have distinct advantages as a potential drug substance. A synthetic peptidomimetic may also act as a surrogate of a substructure of a natural peptide substrate in the active site of a proteolytic enzyme that would otherwise cleave the peptide substrate with undesirable physiological effects.[1]

Conformationally constrained monocyclic and bicyclic unnatural amino acids offer opportunities in the synthesis of peptidomimetics by directly incorporating them in a potential inhibitor molecule as part of the design element.[2]

In this regard, proline and pipecolic acid have been excellent building blocks to explore the synthesis of azabicyclic amino acids in the design of targeted peptidomimetics. To this end, we have explored a number of Lewis acid-mediated carbocyclizations of cyclic *N*-benzyloxycarbonyl iminium ions derived from L-pyroglutamic acid and 6-oxopipecolic acid. As a result, we have discovered new methods for the synthesis of 4,5-methanoprolines and 5,6-methanopipecolic acids and their congeners in conjunction with studies of kainic acid analogues. Studies directed toward the inhibition of penicillin-binding proteins and $\beta$-lactamases led us to devise methods to synthesize unusual tricyclic lactams harboring a methano group as one of its rings, also exploiting iminium ion chemistry. X-ray cocrystal structures of serine protease inhibitors isolated from Nature have led to the synthesis of bicyclic amino acids with an indolizidinone or octahydroindole core subunit, based on seldom used carbocyclizations of cyclic *N*-acyloxyiminium ions with tethered olefinic appendages.

In the following sections, we describe our efforts in the synthesis of constrained azacycles that contain proline or pipecolic acid as an integral part of bicyclic and polycyclic amino acids. A common theme is the exploitation of iminium ion chemistry in intramolecular carbocyclization reactions. A short compendium of other functionally useful and novel cyclic amino acids is included in the Supporting Information.

## 4,5-Methanoprolines and 5,6-Methanopipecolic Acids

$\alpha$-Kainic acid, **1**, is a naturally occurring excitatory amino acid[3] that can be viewed as a constrained L-glutamic acid (Figure 1). As a consequence, we became interested in incorporating a methano bridge[4] in a number of pyrrolidine and piperidine carboxylic acids, as exemplified by structures **2**−**13** to study the effect of ring constraint on the binding to the kainoid receptor. The five-membered pyrrolidine ring in 4,5-*trans*-methano-*N*-Boc-L-proline, **2**, was found to be practically flat in the solid crystalline state (rms = 0.003 Å) (Figure 1).[5] The flattening of the *cis*-isomer **3** was much less pronounced. This topological feature can be further exploited by studying the susceptibility of ring amides to proteloytic enzymes, such as prolidases, as a function of the state of hybridization of the ring nitrogen atom. Compounds **2** and **3** were initially synthesized starting with the L-pyroglutamate ester **14**, by a novel acid-mediated destannylative carbocyclization of stereochemically defined iminium ions **15** and **17** respectively, to give the corresponding 4,5-methano-L-prolinol analogues **16** and **18** (Figure 1A).[5,6] Further steps led to **2** and **3**, which were obtained as crystalline compounds. Extended tethers as in **15b** led to the bicyclic 2,3-trimethylene analogue **19**. The analogous azabicyclo[3.3.0]octane 7-carboxylic acid motif is found in the ACE inhibitor ramipril. A practical method to access the *cis*-acid **3** consisted of a Simmons−Smith cyclopropanation of the *N*-Boc 4,5-ene carbamate ethyl ester derived from L-proline.[6] The 4,5-methano-L-proline 3-acetic acid analogues **4** and **5** were prepared using a free-radical-mediated addition of trimethyltin hydride to an acrylamide appendage and trapping the formed radical by intramolecular conjugate addition to an $\alpha,\beta$-unsaturated ester **20**, which gave the 3,4-*trans*-isomer **21** as the major isomer (Figure 1B).[7] Carbocyclization of **21** and **22** afforded the products **23** and **24**, respectively. Radical cyclization of the extended *trans*-isomer **25** led to the lactam **26** as a single isomer (Figure 1C). Formation of the K enolate and quenching with dibenzyl malonate as a proton source gave the *cis*-isomer **27**. Treatment of the iminium ions prepared from **26** and **27** with trifluoroacetic acid afforded the vinyl cyclopropanes **28** and **29**, respectively. As a result of these studies, we discovered a seldom explored carbocyclization using trimethyltin radical addition to $\alpha,\beta$-unsaturated amides and concomitant Michael-type intramolecular cyclizations with $\alpha,\beta$-unsaturated esters. The methanopyrrolidine and -piperidine acetic acids **6**−**8** and

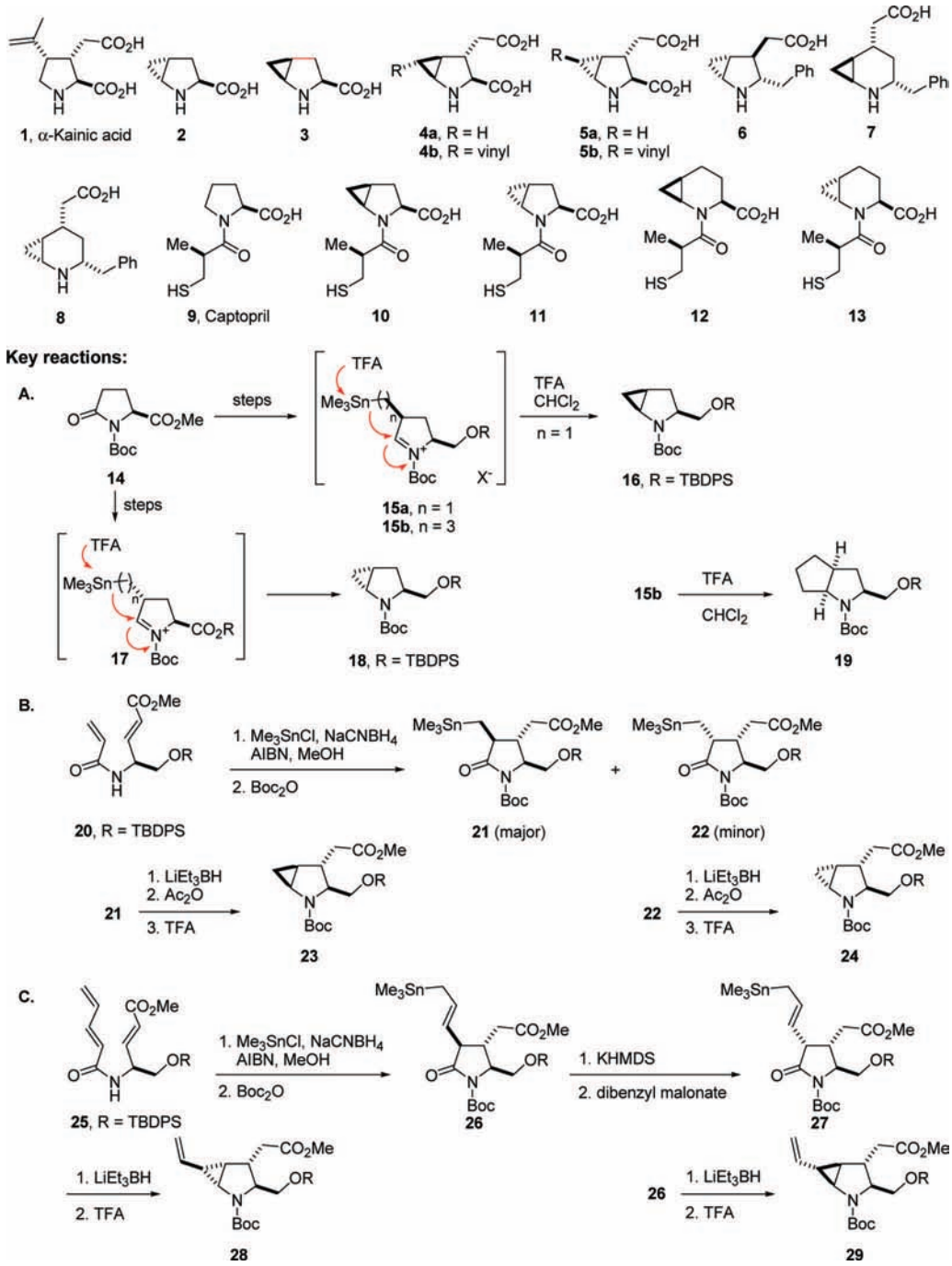



**FIGURE 1.** 4,5-Methanoproline, -prolinol, and -pyrrolidine, and 5,6-methanopiperidine carboxylic acids.

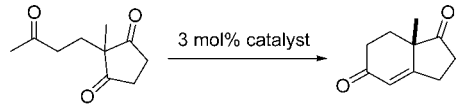
**10**−**13** were prepared in enantiomerically pure form using the carbocyclization−destannylation method described above (Figure 1).

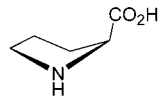
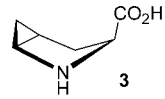
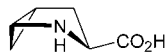
To the best of our knowledge, the formation of cyclopropanes and cyclopentanes from the intramolecular carbocyclizations of $\omega$-trimethylstannyl alkyl appendages onto *N*-acyloxyiminium ions under anhydrous acid-mediated conditions were unprecedented at the time of our studies. Methano analogues of the potent ACE inhibitor captopril **9**, represented by compounds **10**−**13** were found to be equally active against the enzyme[6] regardless of the orientation of the methano bridge. On the other hand, the vinyl analogues **4b** and **5b** were devoid of kainoid receptor activity. *cis*- and *trans*-4,5-Methano-L-prolines were found to be preferred inhibitors of the enzyme dipeptidyl peptidase.[8]

## 4,5-Methanoprolines as Organocatalysts

The utility of proline as an organocatalyst has been popularized in recent years after literally three decades since Hajos

**TABLE 1.** Intramolecular Aldol Reaction with Proline and 4,5-Methanoproline Catalysts




| catalyst | time (h) | yield (%) | ee (%) |
|---|---|---|---|
|  | 48 | 98 | 95 |
|  **3** | 140 | 86[a] | 93 |
|  **2** | 125 | 67[b] | 83 |

[a] 14% starting material recovered. [b] 28% starting material recovered.

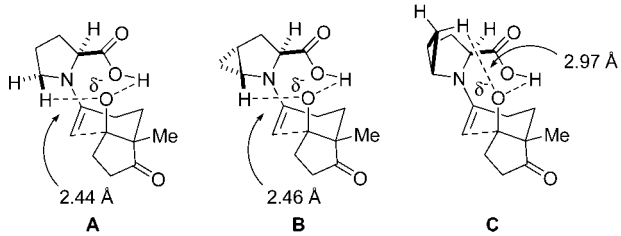



**FIGURE 2.** *Anti*-enamine transition state models showing electrostatic interactions with the developing alkoxide charge.

and Parrish[9] and Eder, Sauer, and Wiechert[10] independently described their landmark studies of intramolecular aldol reactions.[11]

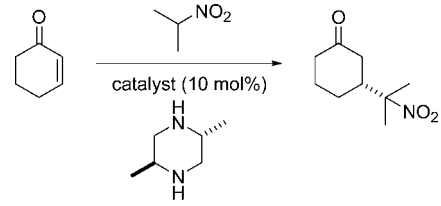
In collaboration with Houk and Cheong, we reported that when *cis*-4,5-methano-L-proline was used as a catalyst, it was equal to L-proline in enantioselectivity but had a much slower rate (Table 1). The *trans*-isomer was less enantioselective.[12]

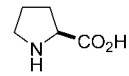
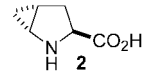
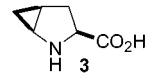
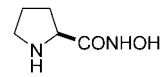
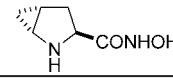
Initially, it was proposed that the C5 methine hydrogen, having a *cis*-relationship to the carboxyl group in the *anti*-enamine intermediate, was involved in a stabilizing $NCH^{\delta+}-O^{\delta-}$ electrostatic interaction in the transition state model **A** (Figure 2).[13]

Only in the *trans*-4,5-methano-L-proline enamine **B** can such a stabilization be realized. An interaction with the cyclopropyl methylene hydrogen can be envisaged, albeit at a longer distance, as depicted in **C**.[12]

The differences in enantioselectivities were attributed to the degrees to which each diastereomeric transition state satisfied the necessary condition for planarity of the iminium ion. Calculations showed that the *anti*-transition structures of the *cis*-isomer have a planar iminium ion compared with a pyramidalized one in the *syn*-counterparts. In contrast, the *trans*-isomer is more pyramidalized. There is less energy difference

**TABLE 2.** Addition of 2-Nitropropane to 2-Cyclohexenone in the Presence of Proline and 4,5-Methanoprolines




| catalyst | ee (%) | yield (%) |
|---|---|---|
|  | 89 | 83 |
|  **2** | 99 | 92 |
|  **3** | 75 | 52 |
|  | 75 | 78 |
|  | 81 | 65 |

between *syn*- and *anti*-enamine/iminium ion structures in the *trans*-isomer ($\Delta H^{\ddagger} = 1.2$ kcal), compared with the *cis* ($\Delta H^{\ddagger} = 2.2$ kcal). Thus, the *cis*-isomer prefers the planar enamine. The naturally pyramidalized enamine in the *trans*-isomer requires less geometric distortion to reach the *syn* pyramidalized iminium transition states. The $NCH^{\delta+}-O^{\delta-}$ electrostatic interaction in the *trans*-isomer provides some gain in stabilizing the *anti*-enamine structure **B**, hence the observation of good enantioselectivity (Table 1). However, the more facile planar *anti*-enamine to *anti*-iminium ion structures favor the *cis*-isomer.

In another example of organocatalytic reaction, we studied the addition of 2-nitropropane to 2-cyclohexenone in the presence of L-proline and the achiral 2,6-dimethylpiperazine as an additive.[14] (*R*)-3-(2-Nitropropyl)cyclohexanone was obtained with an ee of 93%. Originally, Yamaguchi and coworkers[15] had achieved a 59% ee with Rb prolinate (Table 2).

Surprisingly, *trans*-4,5-methano-L-proline **2** led to an adduct with 99% ee,[16] while the *cis*-isomer **3** was much less efficient (75% ee). We have rationalized these results based on a combination of effects. The boat forms of the *cis*-isomer **3** will be subject to severe 1,3-A strain placing the carboxyl group in a pseudoaxial orientation. This will result in a steric clash with the *cis*-cyclopropane group. *trans*-Methano-L-proline is more favored to form the intermediate iminium ion in this case.

It is also of interest that the hydroxamic acid analogues of L-proline and *trans*-4,5-methano-L-proline **2** were also reason-

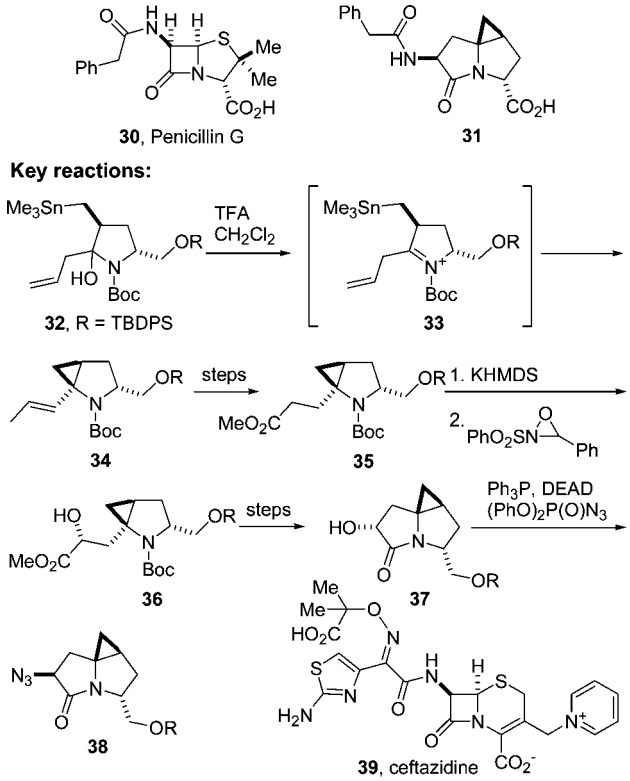



**FIGURE 3.** Tricyclic $\beta$-lactam surrogates.

ably efficient catalysts in the Michael additions reaction, albeit at much slower rates (Table 2). In an effort to probe the effect of chirality associated with the additive, we used (*S*,*S*)-2,6-diisopropyl piperazine. However, the ee of the adducts remained unchanged in comparison to the achiral *trans*-2,6-dimethyl piperazine.[17]

## Methanopyrrolizidinone Amino Carboxylic Acids

Penicillin G (**30**), the quintessential $\beta$-lactam antibiotic, has been the subject of intensive studies on several fronts since its discovery (Figure 3). New generations of therapeutically important penams, penems, and carbapenems are now available and widely used to combat infections.

In an effort to introduce strain that could approximate the mode of action of the bicyclic $\beta$-lactams, we proposed the tricyclic $\gamma$-lactam carbapenam congener **31** (Figure 3).[18,19] Acid-mediated destannylative carbocyclization of the iminium ion **33** generated from **32** gave **34** with migration of the double bond. Further manipulation of the olefinic tether led to the extended ester **35**, which was converted to the α-hydroxy ester **36** by stereoselective enolate hydroxylation.[20] Lactam formation yielded **37**, which was converted to the inverted azide **38** by a Mitsunobu reaction. Although the tricyclic penicillin G surrogate **31** was devoid of antibacterial activity of its

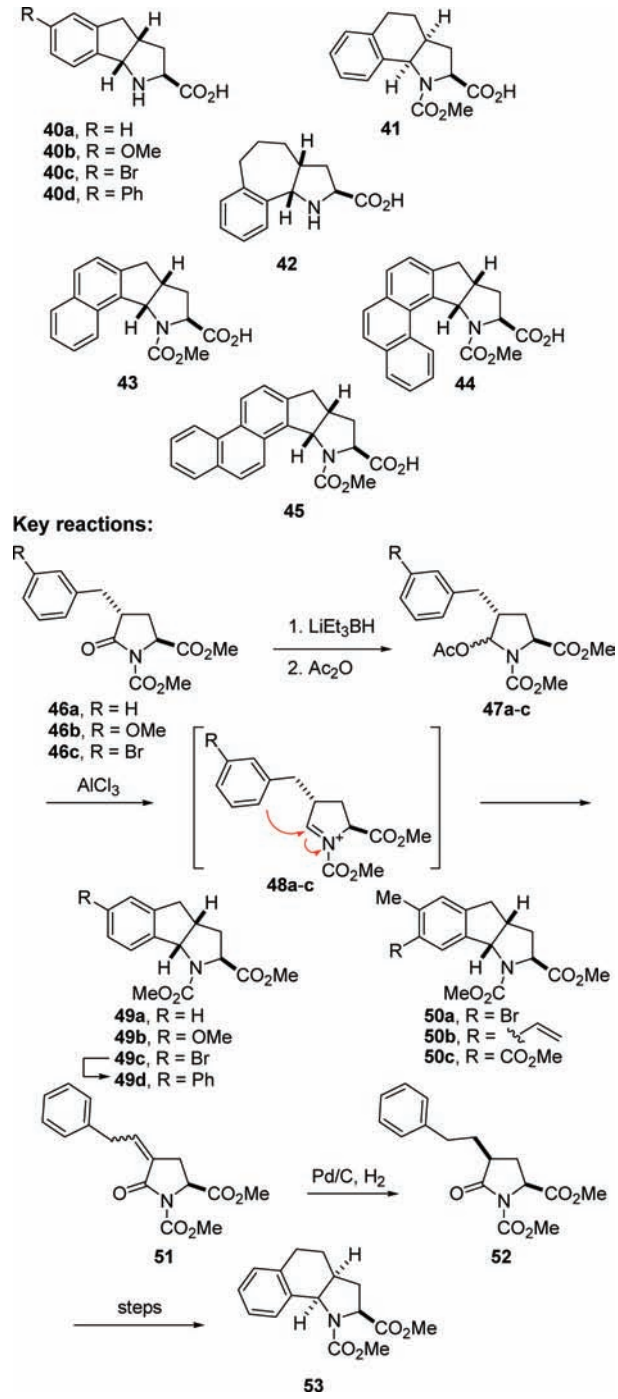



**FIGURE 4.** Conformationally constrained polycyclic analogues of proline.

own, it enhanced the activity of ceftazidine **39**, as measured by its minimum inhibitory concentration (MIC) against some $\beta$-lactamase producing organisms. It would be interesting to devise synthetic methods toward the highly strained hypothetical $\beta$-lactam congener of **31**.

## 4,5-Polycyclic Prolines

Conformationally constrained polycyclic analogues of proline can be accessed through intramolecular Friedel–Crafts-type

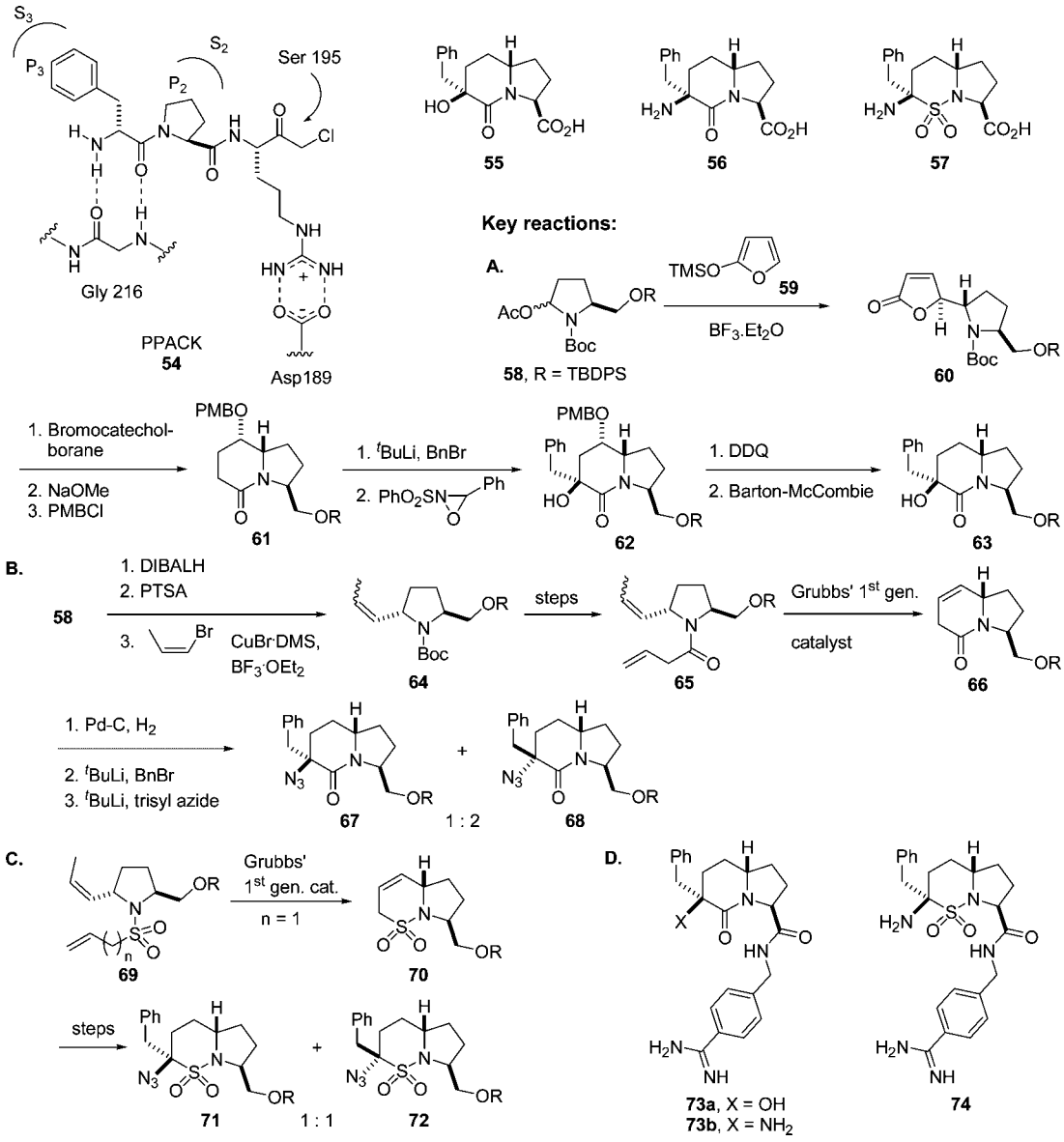



**FIGURE 5.** Constrained analogues of a Phe-Pro-Arg sequence in PPACK.

carbocyclizations from iminium ion intermediates (Figure 4).[21] A variety of architectures represented by the prototypes **40a**−**d** and **41**−**45** are easily assembled from C4 arylalkylated intermediates, available from *N*-methoxycarbonyl methyl L-pyroglutamates **46a**−**c**.

The indanoproline analogues **40a**−**c** were prepared from the corresponding **46a**−**c** by reduction of the lactam carbonyl with Super hydride and acetylation to **47a**−**c**. Treatment with $AlCl_3$ led through the intermediate iminium ions **48a**−**c** to the indano-L-proline analogues **49a**−**c**. The 4-bromobenzyl analogue **49c** could be phenylated by application of a Suzuki−Miyaura coupling with phenylboronic acid to give **49d**. The *trans*-analogues **42**−**45** could be prepared in a similar way using the appropriate benzylic halides. The bromo analogue **50a** was a substrate for Pd-catalyzed vinylation and methoxycarbonylation to give **50b** and **50c**, respectively. However, for the less reactive phenylethyl halides, which were prone to elimination during the enolate alkylations, we opted for the *cis*-diastereomer **41**. Thus, treatment of *N*-carbomethoxy methyl L-pyroglutamate with phenylacetaldehyde followed by elimination, gave the mixture of *E*- and *Z*-olefins **51**, which upon catalytic hydrogenation afforded the *cis*-phenylethyl lactam analogue **52**. Following the same Friedel−Crafts alkylation of the corresponding iminium ion led to the all *cis*-tricyclic analogue **53**. The free amino acids and their *N*-Boc or *N*-methoxycarbonyl derivatives were obtained by hydrolysis of the esters. The syntheses were initiated with the *N*-methoxycarbonyl pyroglutamates because they were found to be more compatible with the use of $AlCl_3$. Other Lewis acids ($BF_3$. $Et_2O$, $SnCl_4$, $TiCl_4$, $Me_3Al$) were not as effective as $AlCl_3$.

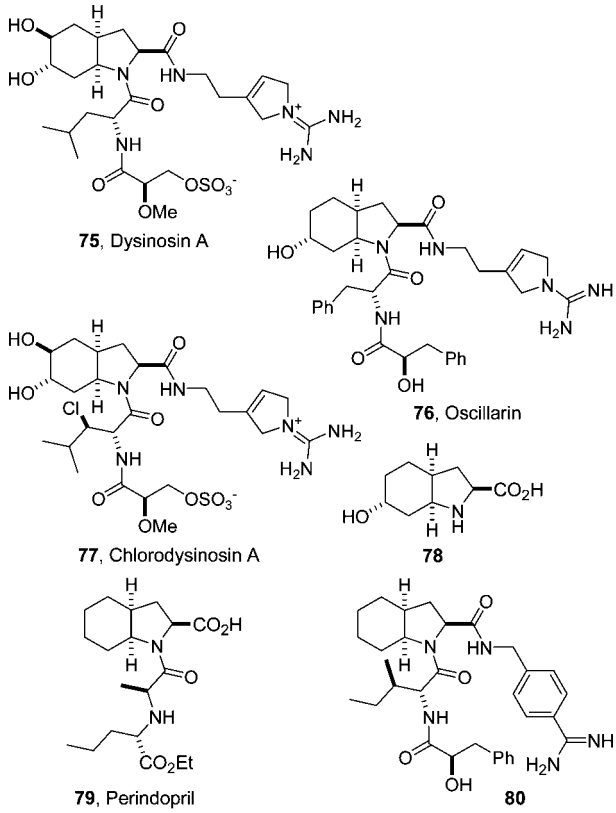



**FIGURE 6.** Structures of selected aeruginosins containing a 2-carboxy octahydroindole core.

A number of analogues were amenable to single-crystal X-ray analysis. The overall topologies of these polycyclic analogues offer opportunities for the study of intercalation in DNA among other interesting applications, such as nucleating motifs for the construction of helical arrays.[22]

## Amino Indolizidinone Carboxylic Acids

The chloromethyl ketone analogue of the tripeptide Phe-Pro-Arg, **54** (PPACK), has been known to be a potent irreversible inhibitor of the enzyme thrombin.[23] On the basis of information provided by the X-ray cocrystal structure of PPACK and molecular modeling, we proposed to study constrained analogues corresponding to an indolizidinone core represented by **55**, **56**,[24] and the sultam **57** (Figure 5).[25]

Treatment of the acetoxy hemiaminal **58** with 2-trimethylsiloxyfuran **59**[26] in the presence of $BF_3$. $Et_2O$ led to **60** as the major isomer (Figure 5A).[24d] Catalytic hydrogenation, ring expansion, and O-protection led to the indolizidinone **61**. Enolate C-benzylation, followed by enolate hydroxylation with the Davis oxaziridine reagent,[20] afforded **62** as the major isomer. Deoxygenation under Barton–McCombie conditions[27] gave **63**. The expected (*S*)-configuration at the hydroxyl-bearing center was corroborated by single-crystal X-ray structures of intermediates, as well as a cocrystal structure with thrombin of the 4-amidino-1-aminomethylphenyl amide analogue of **55** (see below). Although the same method could be followed to prepare the 6-azido analogue, we opted for a ring-closing metathesis[28] route (Figure 5B).[24b] Thus, treatment of **58** with 1-propenyl cuprate in the presence of $BF_3 \cdot Et_2O$ gave the 4-*anti*-product **64**, which was further elaborated to the diene **65**. Cyclization was achieved with the Grubbs first generation catalyst[28] to give **66**. Reduction of the double bond gave the corresponding indolizidinone derivative, which was subjected to sequential C-benzylation and enolate azidation reactions to give a 1:2 mixture of **67** and **68**. Thus, the more sterically demanding azide transfer reagent did not favor the desired (6*S*)-isomer **67**. Nevertheless, the corresponding amino acids could be prepared and tested as their benzamidine amides against thrombin (see below). Having access to 5-propenyl sulfonamide **69**, we prepared the bicyclic sultam **70** using a ring-closing metathesis route (Figure 5C).[25] The product was engaged in sequential enolate alkylation/azidation reactions to give **71** and **72** as a 1:1 mixture of isomers. Five- and seven-membered sultams were also prepared using appropriate tethers (**69**, $n = 0, 2$). As expected, the amino analogue **73b**, exhibited excellent thrombin inhibitory activity *in vitro* ($IC_{50} =$ 4 nM) compared with the hydroxyl analogue **73a** ($IC_{50} = 20$ nM).[24c,25] The sultam congener **74** was 100-fold less active. A cocrystal structure of **73a** revealed the expected interactions with only a small deviation from the binding mode predicted based on molecular modeling.[24d]

In the course of these studies, we converted intermediate **61** to the 6-hydroxy analogue, followed by deprotection of the *O*-silyl group and oxidation to the carboxylic acid. The corresponding benzamidine amide analogue was inactive when tested for inhibition of thrombin *in vitro*. Thus, the axially oriented *O*-PMB group could not occupy the same space as the *C*-benzyl group in **73a**. In another case, we introduced an α-alkyl substituent at C4 of the indolizidinone analogue **73a**, which also contained an α-OMe group at C6. Promising *in vitro* inhibition was observed against thrombin and Factor VIIa (0.21 and 0.42 $\mu$M, respectively). Thus, a hydrophobic chain at C4 may prove to be beneficial for Factor VIIa activity.[24c]

## Amino Octahydroindole Carboxylic Acids

The aeruginosins are a family of marine metabolites found in cyanobacterial algae and sponges.[29] Three new members represented by dysinosin A (**75**),[30] oscillarin (**76**),[31] and chlorodysinosin A (**77**)[32] are shown in Figure 6. The core subunits consist of 2-carboxy 6-hydroxyoctahydroindole ring system (Choi, **78**) or the 5,6-dihydroxy variant. The same perhydroin-

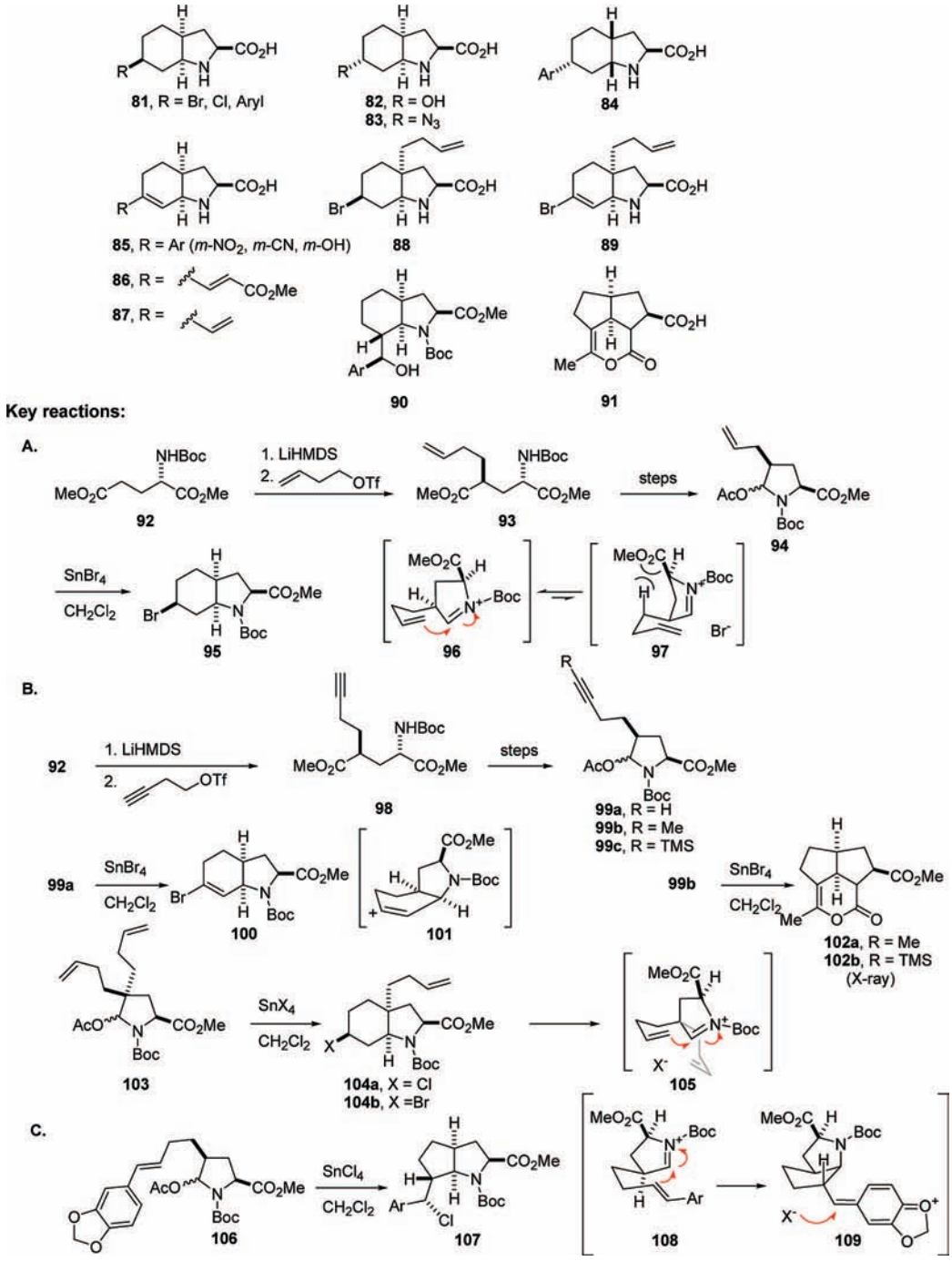



**FIGURE 7.** 2-Carboxyoctahydroindole and related analogues by azonia-Prins cyclization.

dole 2-carboxylic acid motif is present in the synthetic ACE inhibitor perindopril, **79**.[33]

During the course of a synthetic program toward the aeruginosins **75**−**77**, we developed highly efficient stereocontrolled methods to prepare 6-substituted 2-carboxy octahydroindoles (**81**−**84**) using an azonia-Prins-type carbocyclization of iminium ions (Figure 7).[34] Related cyclizations provided access to bicyclic and tricyclic congeners **85**−**91**.[35]

Alkylation of the dienolate of **92** with 3-butenyl triflate gave **93** as a single diastereomer (Figure 7A).[34] A three-step sequence afforded the hemiaminal acetate **94**, which upon treatment with $SnBr_4$ in $CH_2Cl_2$ was converted to **95**, obtained as a single diastereomer. This stereochemical outcome was rationalized based on an antiperiplanar attack as shown in **96** rather than a synclinal attack as in **97**. Application of the same protocol with 3-butynyl triflate gave **98**, which was cyclized

via the iminium ion produced from **99a** to the vinylic bromide **100** (Figure 7B). A transient cyclohexenyl-type cation intermediate may be operative, as shown in expression **101**.

When the 4-bis-(4-butenyl) analogue **103** was subjected to the same $SnBr_4$-mediated cyclization, only the α-oriented all-*syn* butenyl side-chain product **104a** (and **104b**, from $SnCl_4$), was formed (Figure 7B). In this case, an antiperiplanar attack is possible from both 4-butenyl tethers (**105**). However, the pathway of cyclization to **104a** (or **104b**) is more favored.[35] 4-Bis-allenyl analogues undergo similar cyclizations. Interestingly, treatment of the 4-methyl-3-butynyl analogue **99b** with $SnBr_4$ gave the tricyclic dihydrooxazinone **102a** (Figure 7B). The methyl ester in **102a** could be cleaved in the presence of LiOH without affecting the cyclic carbamate, thereby offering the possibility for diversification through the carboxyl group. 4-Cinnamyl derivatives such as **106** lead to azacyclic systems containing a chlorine atom with the creation of two new stereogenic centers (**107**) (Figure 7C). We propose an antiperiplanar alignment as in **108**, which undergoes stereocontrolled carbocyclization through the intermediacy of quinonoid motifs such as **109**. The Choi subunit **78** has been incorporated in the structures of hybrid or truncated analogues of aeruginosins[36] as potential inhibitors of the enzyme thrombin. It is of interest that removal of the hydroxyl or diol unit in these analogues in which the natural guanidine P1 unit was replaced by a 4-amidinobenzyl group and the P2 subunit was modified, such as **80** (Figure 6), led to highly potent analogues with low nanomolar *in vitro* inhibition of the enzyme thrombin.[36b] It is therefore possible to prepare highly active non-natural, analogues of the aeruginosins. Furthermore, the replacement of the chlorine atom by a small hydrophobic alkyl group offers an "improvement" over the natural chlorodysinosin A. Clearly, a better fit in the S3 hydrophobic pocket of thrombin may also be accompanied by the removal of some water molecules in these truncated synthetic analogues.[29] Thus, a new generation of synthetic thrombin inhibitors can be envisaged based on the information obtained from the X-ray crystal structure of the natural product in complex with the enzyme.

## Summary

Efforts in our group covering aspects of conformationally constrained amino acids and their chemical modification in the context of peptidomimetic design were highlighted in this Account. Guided by structural information on target enzymes, we devised syntheses of conformationally biased monocyclic, bicyclic, and polycyclic amino acid analogues, in which pharmacologically or structurally relevant functional groups were incorporated. To achieve this objective required the implementation of stereocontrolled C−C, C−N, and C−O bond-forming reactions on appropriately protected amino acid frameworks. A number of these provided access to functionally diverse scaffolds for further use as core subunits in more elaborated structures. Specific applications as peptidomimetics of natural substrates for relevant enzymes such as thrombin were also pursued, resulting in highly active inhibitors *in vitro*.

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**Supporting Information Available.** Compendium of non-natural amino acids. This material is available free of charge via the Internet at http://pubs.acs.org.

BIOGRAPHICAL INFORMATION

**Stephen Hanessian** is the Achaogen Research Chair Professor in the Department of Chemistry at the Université de Montréal. He is the author or coauthor of nearly 500 publications and three monographs and has 42 patents to his credit. He is the recipient of numerous national and international awards, including three honorary doctorates. Since 2000, he has also been affiliated with the Department of Chemistry at University of California, Irvine. He presently also holds joint appointments in the Departments of Pharmaceutical Sciences and Pharmacology at UCI, Irvine. Since 2007, he has been the Director of a new Gateway Graduate Program at UC, Irvine, focusing on synthetic medicinal chemistry, pharmacology, and structural biology. Professor Hanessian's research interests span a wide cross-section of activities that include natural products synthesis, various aspects of medicinal chemistry, organic synthetic methodology, catalysis and asymmetric processes, molecular recognition, carbohydrates and peptides, and computer-assisted synthesis.

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## FOOTNOTES

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