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Cyclic amino acid derivatives

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1. Introduction

Conformationally constrained amino acids (AAs) have been the focus of both synthetic and medicinal chemistry, particularly as they apply to the design of novel peptides.[1] Rigidified cyclic amino acids (CAAs) have also played an important role in drug design and development[2] where they exert conformational constraints while maintaining the hydrophobic character of the linear alkyl chains.[3] Thus, the incorporation of CAAs into peptides or peptidomimetics induce conformational restrictions and provide important structural effects. Furthermore, CAAs in peptide surrogates have been used for structural and biomechanistic investigation as well as for probing the structural requirements of receptor-bound ligand conformations. This report provides an overview of the preparation of conformationally constrained CAAs and their derivatives.

Keywords: cyclic amino acids; α-amino acid; β-amino acid; γ-amino acid; heterocycle; synthesis; preparation.

Abbreviations: AAs, amino acids; ACHC, aminocyclohexanecarboxylic acid; ACPC, aminocyclopenatnecarboxylic acid; ACPD, aminocyclopentanedicarboxylic acid; AIBN, 2,2′-azobisisobutyronitrile; BDP, bis(dimethylaluminum)propane-1,3-dithiolate; Bn, benzyl; Boc, *tert*-butyloxycarbonyl; CAA, cyclic amino acid; Cbz, carbonyloxybenzyl; DCC, 1,3-dicyclohexylcarbodiimide; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD, diethyl azodicarboxylate; DHCGA, 2,3-dehydrocycloglutamic acid; DIC, diisopropylcarbodiimide; DMAP, 4-dimethylaminopyridine; DME, dimethoxyethane; DMF, dimethylformamide; DMSO, dimethylsulfoxide; DPPA, diphenylphosphorylazide; EAA, excitatory amino acid; EtOAc, ethyl acetate; Fmoc, 9-fluorenylmethoxycarbonyl; GABA, γ-aminobutyric acid; HATU, *o*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HMPB, 4-(4-hydroxymethyl-3-methoxyphenoxy)-butyric acid; HOAT, 1-hydroxy-7-azabenzotriazole; HOBT, 1-hydroxybenzotrizole; HOSU, *N*-hydroxysuccinimide; LDA, lithium diisopropylamide; LTMP, lithium 2,2,6,6-tetramethylpiperidine; MBHA resin, 4-methyl benzhydrylamine resin; MCPBA, *m*-chloroperoxybenzoic acid; Ms, methanesulfonyl; NMO, 4-methylmorphoine *N*-oxide; PEG, polyethyleneglycol; PLE, pig liver esterase; RCM, ring closing metathesis; TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMSCl, trimethylsilylchloride; Ts, *p*-toluenesulfonyl.

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2. α-AA derivatives

2.1. Cyclopropane AA derivatives

The cyclopropane ring system is particularly interesting because it affects the chemical and biological properties in peptides through significant conformational restrictions in the AA residues. They are found in a wide class of naturally occurring products, and synthetic 2,3-methanoamino acids are structurally related to those cyclopropane AAs found in proteins. Racemic 2,3-methanoamino acids (**4**) have been synthesized by several methods as reviewed by Stammer[4] and Alami.[5] These methods include (i) dialkylation of glycine or malonate derivatives (**1**) with ethylene dibromide or its equivalent, (ii) 1,3-dipolar cycloaddition of diazomethane on β-substituted acrylic acid derivatives (**3**) to

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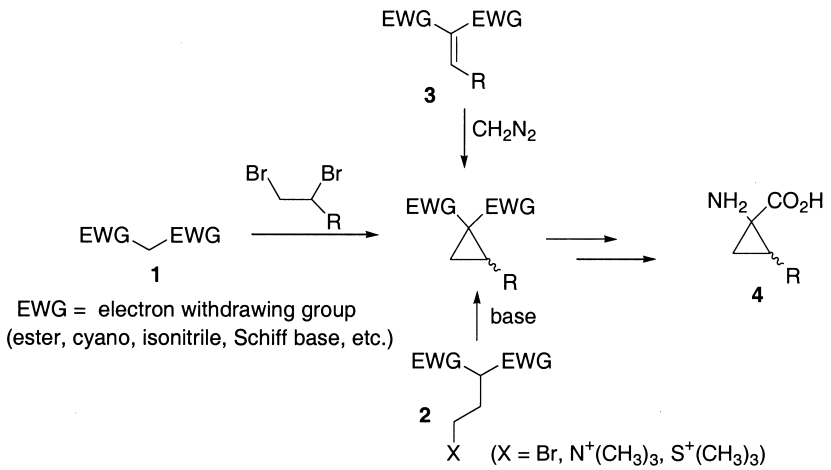


Scheme 1.

form pyrazolines, and (iii) intramolecular cyclization of γ-substituted α-amino butyric acid derivatives (**2**) (Scheme 1).

Optically active 2,3-methanoamino acids and their derivatives have also been synthesized using chiral auxiliaries, including Schölkopf's bislactim ethers,[6] Husson's 1,3-oxazolidine,[7] and the diketopiperazine auxiliary.[8] At the same time, many side-chain functionalized 2,3-methanoamino acids have also been prepared from optically pure lactones or D-mannitol. Some representative 2,3-methanoamino acid derivatives are shown in Figs. 1 and 2; Burgess reviewed these approaches in detail.[9]

New chiral 2,3-methanoamino acids with extended side-chains were prepared from cyclopropane chiron **6**, which was synthesized from diol **5**.[10] Thus, diol **5** was reacted with thionyl chloride to give a cyclic sulfite, which was oxidized into a cyclic sulfate and then reacted with diethyl malonate to afford chiron **6**. Selective hydrolysis of the less hindered ester in **6** followed by Curtius rearrangement and hydrogenolysis afforded Boc-protected amino alcohol **7**. From this intermediate, several Boc-protected 2,3-methanoamino acid derivatives (**8**–**10**) were prepared following the sequences shown in Scheme 2.

2,3-Methanoamino acids were also synthesized diastereoselectively via the one pot palladium(0)-catalyzed alkylation and S'_N cyclization of 1,4-dichlorobut-2-ene by the benzophenone Schiff base of aminoacetonitrile (Scheme 3).[11] After palladium(0)-catalyzed alkylation of (*E*,*Z*)-1,4-dichlorobut-2-ene by the Schiff base anion, the reaction proceeded to the π-allyl palladium intermediate **11**. The S'_N cyclization of the π-allyl palladium intermediate **11** was completely stereoselective, affording the sterically favorable **12** (de=100%) with a *syn* relationship between the ethyl and nitrile groups. Diimide reduction of the ethenyl substituent followed by acid hydrolysis provided racemic coronamic acid (**13**).

This tandem reaction was also attempted using chiral (4*S*)-1-chloropent-2-en-4-ol.[12] Thus, palladium(0)-catalyzed alkylation of this allylic chloride by the Schiff base followed by S'_N cyclization under Mitsunobu conditions afforded **14** diastereoselectively (88% de). Diimide reduction of **14** followed by hydrolysis provided (1*S*,2*S*)-homo-coronamic acid (**15**) in 84% ee (Scheme 4).

Chiral imine (−)-**16** has also been utilized in the preparation of 2,3-methanoamino acid precursors as outlined in Scheme 5.[13] The starting imine (−)-**16** was prepared by the condensation of (−)-(1*S*,2*S*,5*S*)-2-hydroxy-3-pinanone[14] with aminoacetonitrile in the presence of BF_3–etherate in

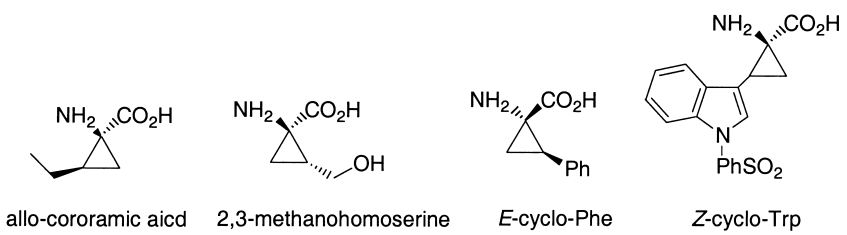


Figure 1. 2,3-Methanoamino acids from chiral auxiliaries.

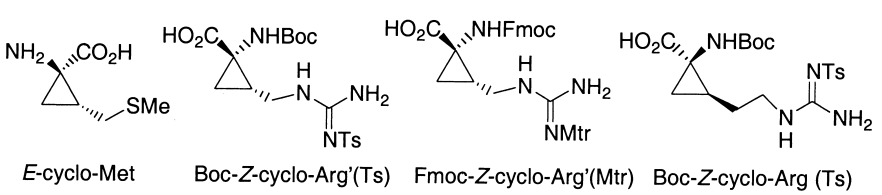
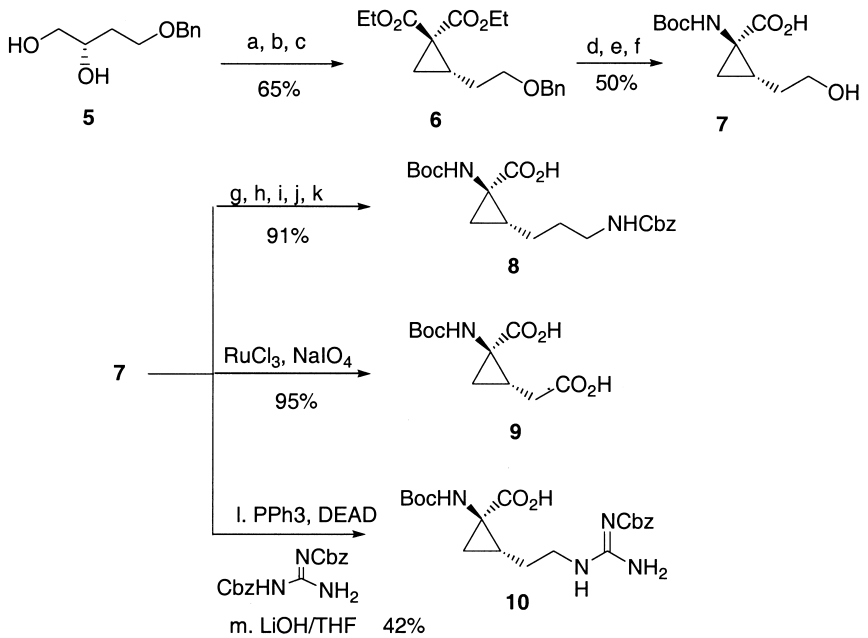
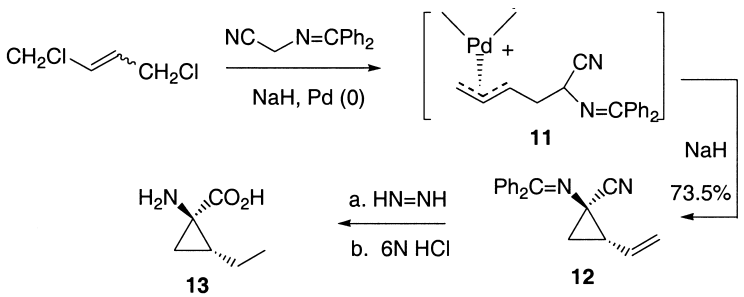


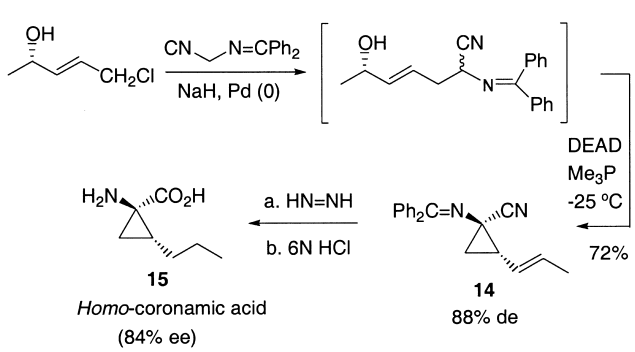
Figure 2. Side-chain functionalized 2,3-methanoamino acids from lactones or D-mannitol.



Scheme 2. (a) $SOCl_2$; (b) $RuCl_3$, $NaIO_4$; (c) diethyl malonate, NaH; (d) KOH/EtOH; (e) $N_3PO(OPh)_2$, Et_3N; (f) H_2, Pd/C; (g) MsCl, Et_3N; (h) NaCN/DMF; (i) NaOH/MeOH; (j) Ra/Ni, NH_4OH; (k) CbzCl, Na_2CO_3.



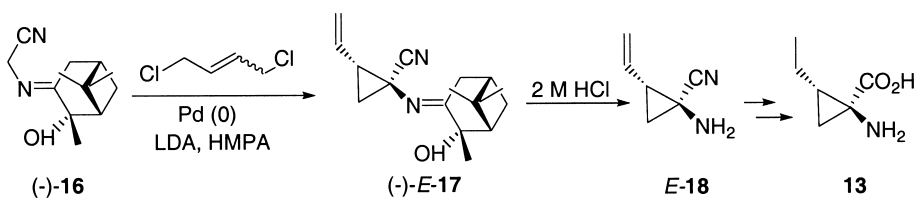
Scheme 3.



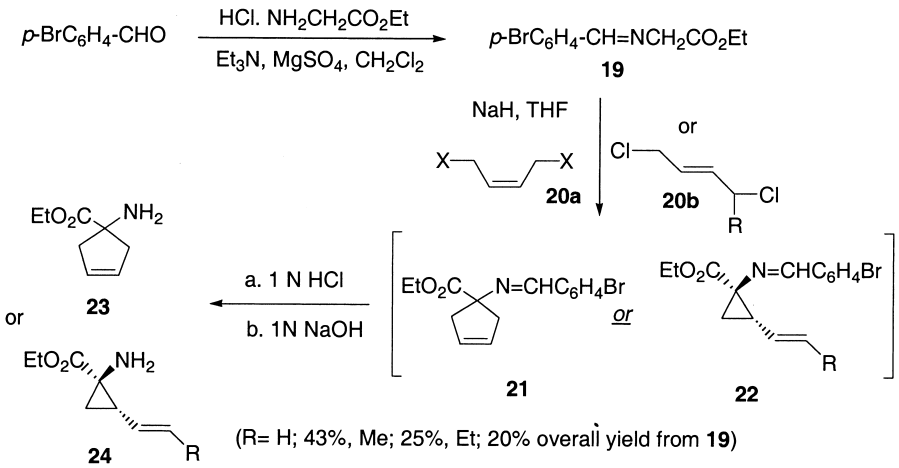
Scheme 4.

benzene. Asymmetric palladium(0)-catalyzed alkylation followed by S_N' cyclization afforded diastereochemically pure (−)-*E*-**17** in 70% yield. Subsequent hydrolysis provided 1-amino-2-vinylcyclopropanecarbonitrile *E*-**18** with 2.4% ee. The same reaction from (+)-**16** gave the diastereochemically pure precursor (+)-*E*-**17** in 70% yield and subsequently provided *E*-**18** with 13.5% ee. Pd(0)-induced reversible ring opening[15] of the vinylcyclopropane moiety appears to be responsible for the low enantiomeric excesses obtained.

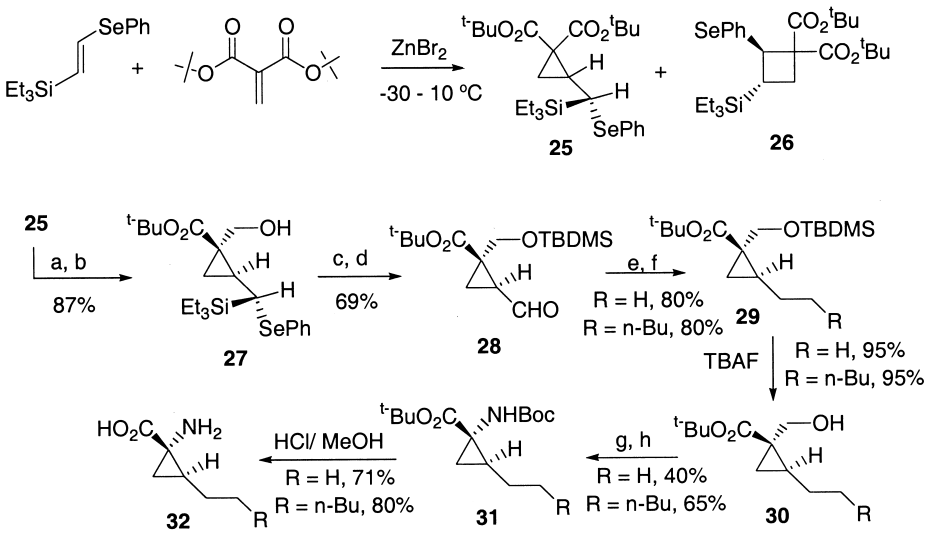
Kurth recently reported the regio- and diastereoselective synthesis of 2,3-methano amino esters from 4-bromobenzaldehyde Schiff base without palladium catalyst.[16] By



Scheme 5.



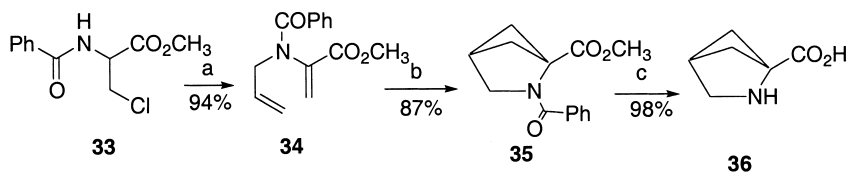
Scheme 6.



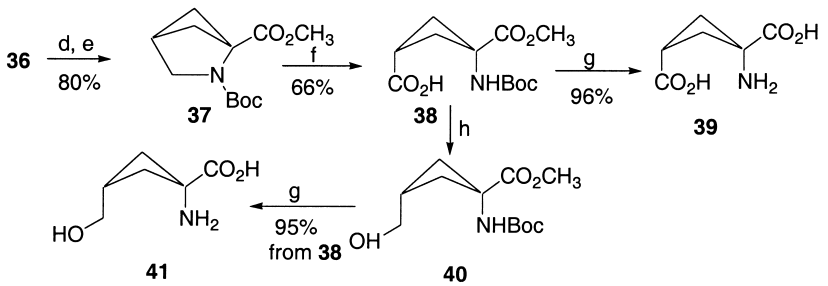
Scheme 7. (a) $LiAlH_4$; (b) $NaBH_4$; (c) TBDMSCl, imidazole, CH_2Cl_2; (d) $NaIO_4$, THF/H_2O; (e) $Ph_3P{=}CHR$; (f) HN=NH; (g) $RuCl_3$–$NaIO_4$; (h) DPPA, ^{t}BuOH.

modifying bis-electrophile **20b**, 1-amino-2-vinyl cyclopropane carboxylate ester derivatives **24** were synthesized with the amine and vinyl moieties *trans* to each other (Scheme 6). The complete *trans* diastereoselectivity results from transition-state selectivity in the ring closing step where the energy difference between the *cis* and *trans* geometries for the imine and vinyl substituents is energetically favorable for *trans*-**22**. When *cis*-1,4-dichloro-2-butene **20a** (X=Cl) was employed as the alkylating agent, only 1-aminocyclopent-3-ene-1-carboxylate **23** was obtained. On the other hand, *cis*-1,4-dimesyl-2-butene **20a** (X=OMs) delivered both **23** and **24** (**23**/**24**=1:2).

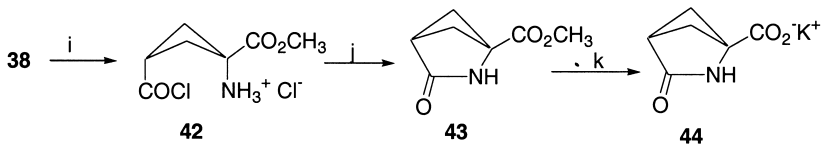
2,3-Methanoamino acids have also been synthesized by utilization of the [2+1] cycloaddition reaction of 1-seleno-2-silylethenes (Scheme 7).[17] This approach to the cyclopropane ring derives from a selenium-stabilized 1,2-silicon migration process.[18] Thus, the reaction of 1-(phenylseleno)-2-(triethylsilyl)ethane and di-*tert*-butyl methylenemalonate afforded the selenium- and silicon-containing cyclopane **25** along with cyclobutane byproduct **26** (**25**/**26**=7:3, 90–98% yield). Stereoselective reduction of the less hindered ester functional group *trans*to the (phenylseleno)(triethylsilyl)-methyl group and alcohol protection provided the primary alcohol derivative **27**. Subsequent oxidation afforded aldehyde **28** and Wittig reaction followed by diimide reduction gave synthetic intermediate **29** (R=H). Sequential deprotection of the TBDMS group, oxidation, and Curtius



Scheme 8. (a) THF/^{t}BuOK, allyl bromide; (b) $h\nu$, acetophenone; (c) 6N HCl.



Scheme 9. (d) $(Boc)_2O$, NaOH; (e) CH_2N_2/Et_2O; (f) RuO_4; (g) HCl/H_2O; (h) BH_3/THF.



Scheme 10. (i) $SOCl_2/CH_2Cl_2$; (j) Et_3N/CH_2Cl_2; (k) K_2CO_3, MeOH, H_2O.

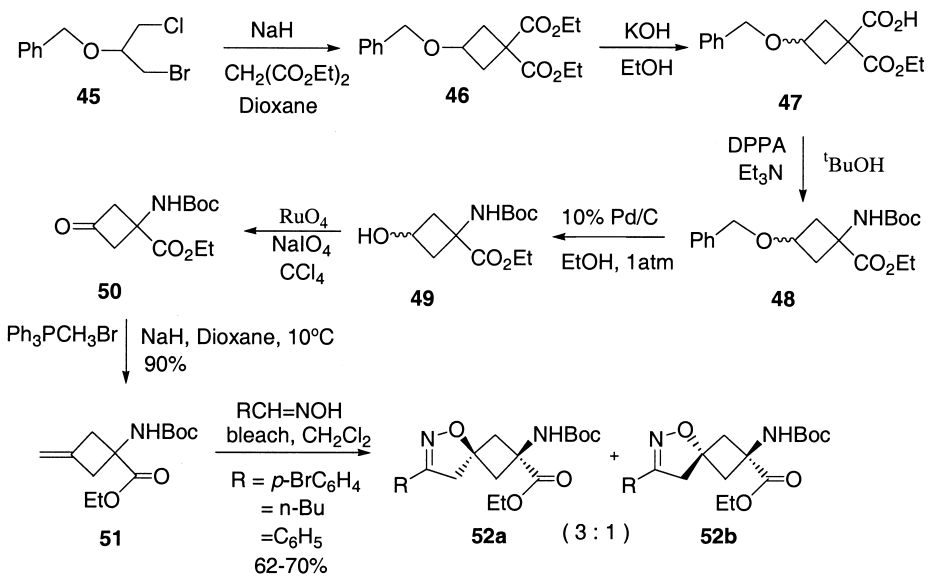
rearrangement afforded Boc-protected coronamic acid **31** (R=H), which was finally deprotected and hydrolyzed to provide racemic coronamic acid **32** (R=H). This method provides a general approach to (*E*)-2-alkyl-1-aminocyclopropane-1-carboxylic acid derivatives.

2.2. Cyclobutane AA derivatives

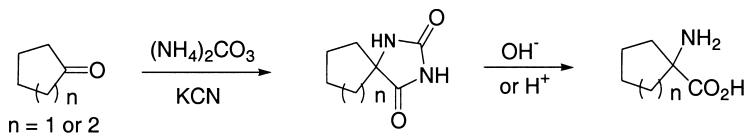
Natural cyclobutane AAs,[19] like 2,4-methanoproline **36**, 2,4-methanoglutamic acid **39**, and their derivatives **41** and **44**, have been synthesized from methyl 2-benzamido-3-chloropropionate **33** (Schemes 8–10).[20] Starting material **33** was made from serine by known methods[21] and converted to azahexdiene **34** in one pot by sequential dehydrohalogenation and amide allylation. Irradiation of **34** with a medium pressure Hanovia lamp afforded the desired photoproduct **35**, which was hydrolyzed to give natural cyclobutane AA **36** (Scheme 8).

To obtain 2,4-methanoglutamic acid (**39**), oxidation precursor **37** was prepared from AA **36** by Boc protection followed by diazomethane esterification. Oxidation of **37** with ruthenium tetraoxide using Sharpless conditions[22] provided acid **38**, which was hydrolyzed to deliver natural 2,4-methanoglutamic acid (**39**). Hydroxy AA **41** was obtained by reduction of carboxylic acid **38** followed by ester hydrolysis (Scheme 9). On the other hand, 2,4-methanopyroglutamic acid (**44**) was synthesized by ring closure of acid **38** using thionyl chloride followed by ester hydrolysis (Scheme 10).

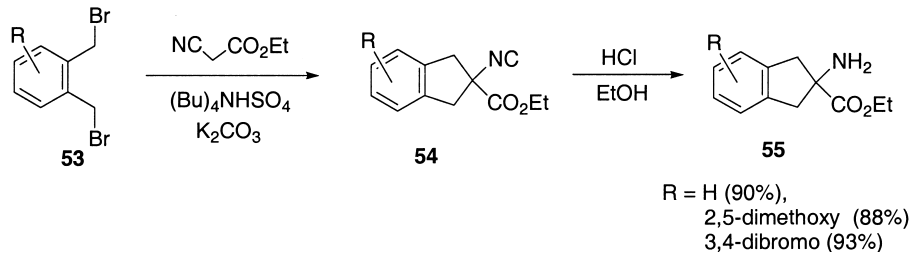
The synthesis of several Boc-protected cyclobutane amino esters which incorporate isoxazoline heterocycles (e.g. **52**) has been reported by Kurth (Scheme 11).[23] Bis-alkylation of diethylmalonate with 1,3-dihalopropane **45**[24] afforded the cyclobutane skeleton **46**, which was partially hydrolyzed to mono acid **47**. Subsequent Curtius rearrangement followed



Scheme 11.



Scheme 12.



Scheme 13.

by deprotection of the benzyl ether provided Boc-protected hydroxy cyclobutane amino ester **49**. Oxidation to ketone **50** followed by Wittig olefination afforded *exo*-methylene substituted Boc-protected amino ester **51**. At this point, diastereoselective nitrile oxide 1,3-dipolar cycloaddition to the methylene moiety provided several isoxazoline-containing Boc-protected cyclobutane amino esters **52**. The diastereoselectivity arises from intermolecular hydrogen bonding between the Boc-NH and the incoming nitrile oxide dipole.

2.3. Cyclopentane, cyclohexane, and higher membered CAA derivatives

Simple 5- or 6-membered CAA have been synthesized by the Bucherer–Bergs method.[25] Here a cyclic ketone is

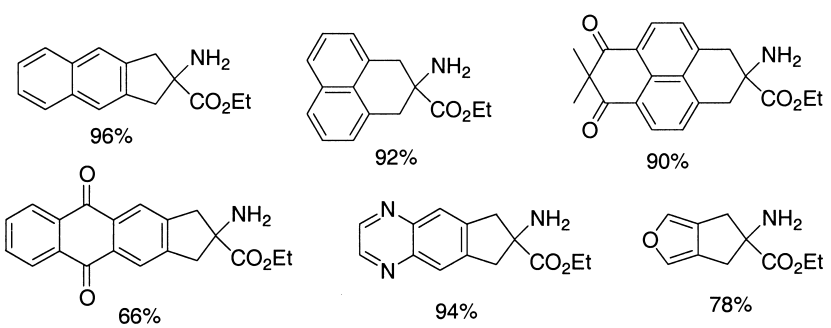
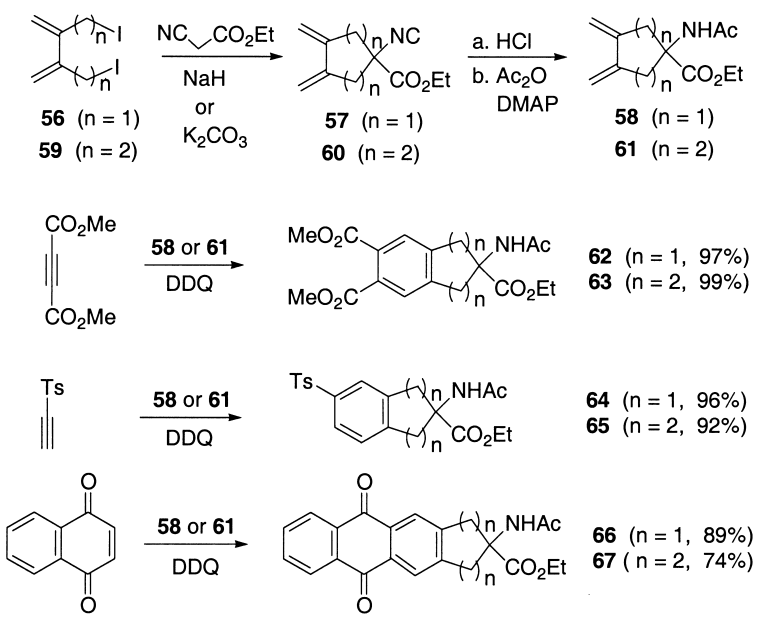
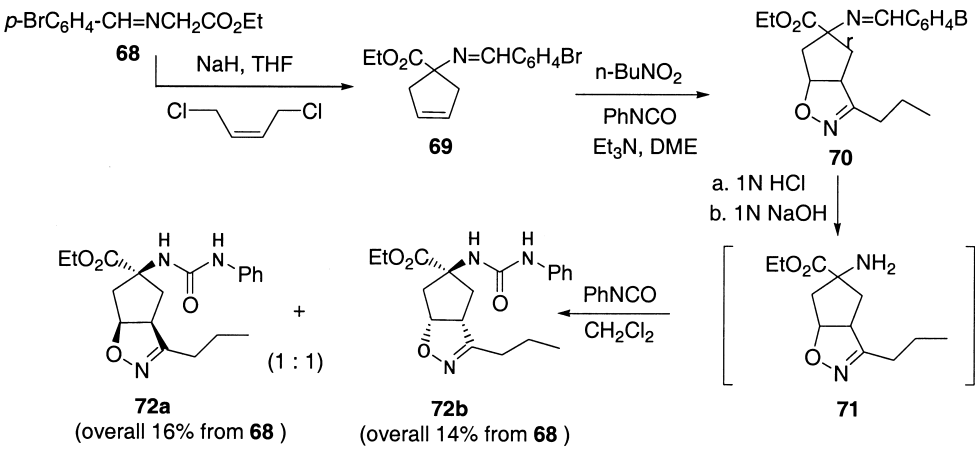


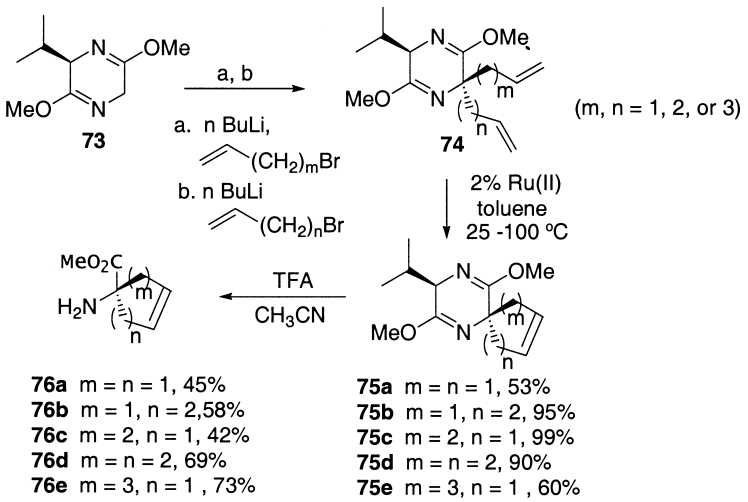
Figure 3.



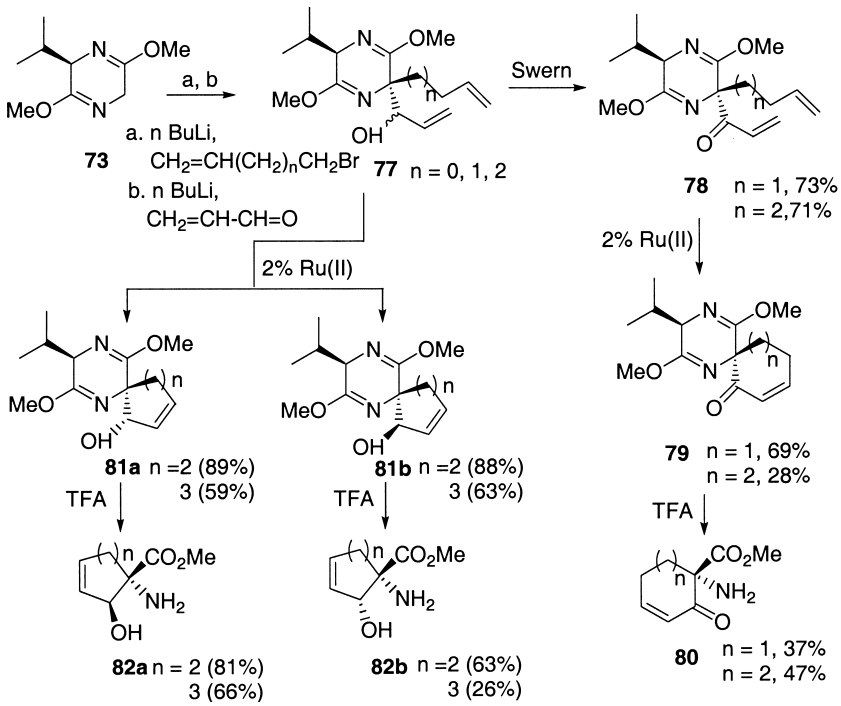
Scheme 14.



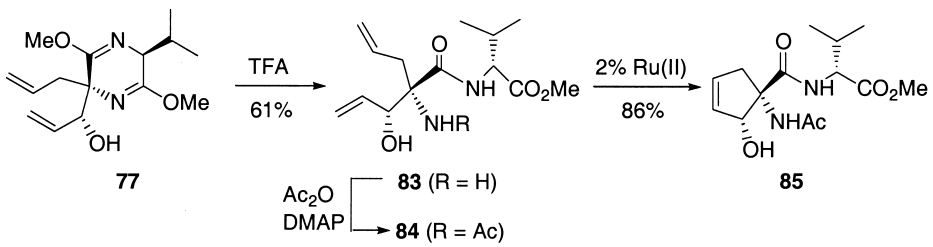
Scheme 15.



Scheme 16.



Scheme 17.



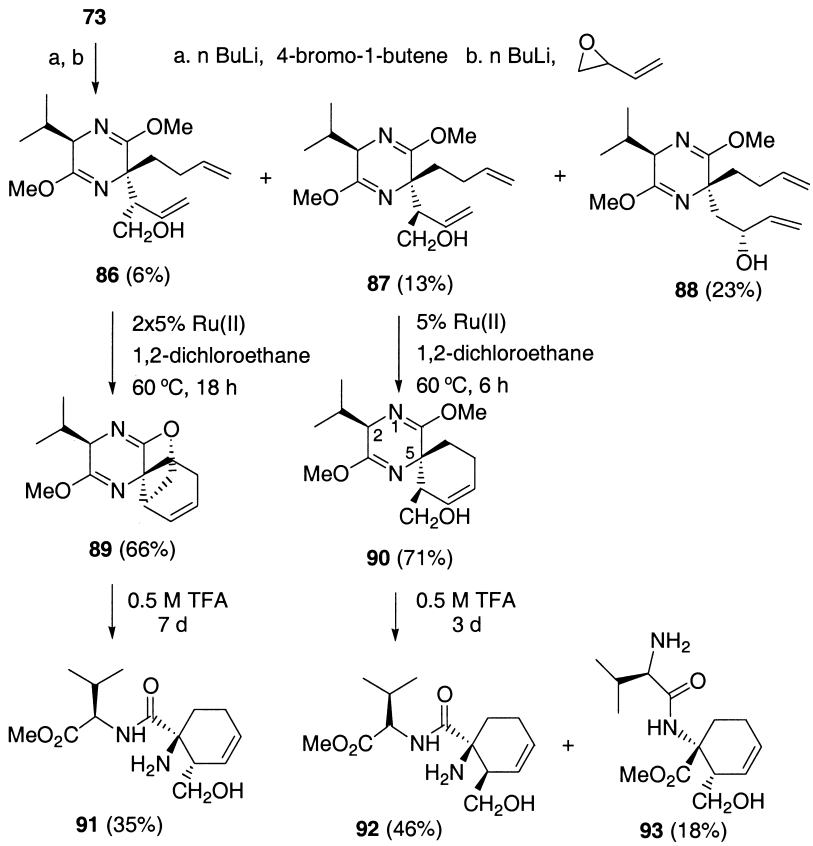
Scheme 18.

converted into its spirohydantoin in the presence of potassium cyanide and ammonium carbonate. Base [$Ba(OH)_2$, 140°C] or acid [60% H_2SO_4, 140°C] hydrolysis of the spirohydantoin then affords the CAA (Scheme 12).

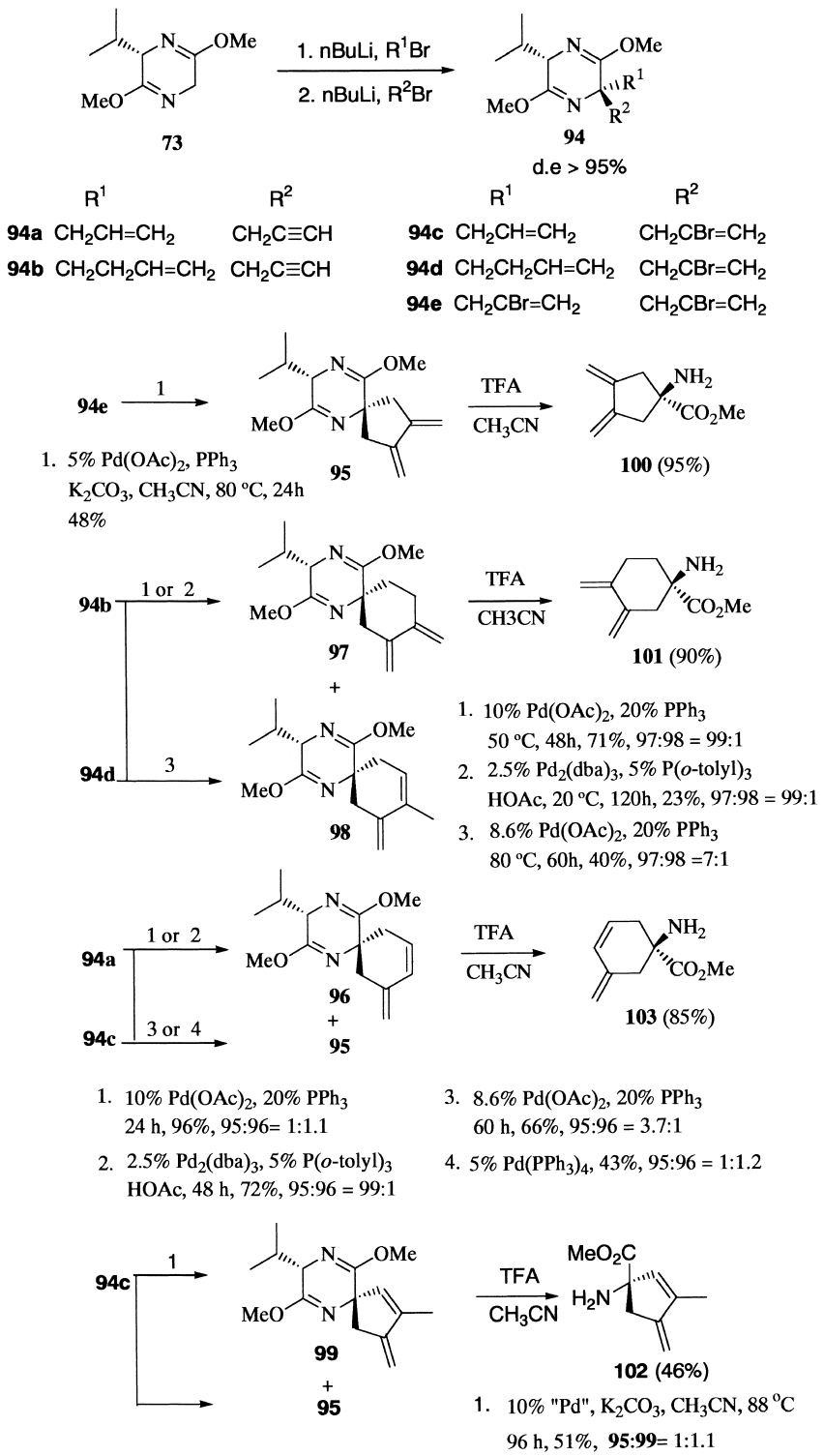
O'Donnell has established methodology for CAA synthesis by alkylation of the Schiff base of glycine ester in the presence of a phase-transfer catalyst.[26] To probe the binding pockets of Phe[7] (S_7) and Phe[8] (S_8), two important aromatic residues for pharmacological properties of substance P (SP), several 2-indanyl-glycine derivatives were synthesized by Chassaing et al.[27] Using ethyl cyanoacetate as a glycine equivalent, indan-based unnatural CAA derivatives have also been synthesized under phase-transfer catalysis conditions by Kotha et al.[28] Thus, ethyl cyanoacetate was bis-alkylated with dibromo-*o*-xylene derivative **53** in the presence of base (K_2CO_3) and PTC catalyst (tetrabutylammonium hydrogen sulfate) to afford isonitrlie derivatives **54**. These isonitrile derivatives were subsequently hydrolyzed (HCl/EtOH) to give cyclic amino esters **55** (Scheme 13). Following the same reaction sequence, naphthalene, anthraquinone, quinxaline, and furan derived cyclic amino esters were synthesized from their isonitrile precursors **54** (Fig. 3).

Another approach to indan-based CAA derivatives employs 1,2-exomethylene dienes (Scheme 14).[29] Starting dienes **58** and **61** were prepared from iodo derivatives **56** and **59**, respectively, and reaction of these dienes with several dienophiles and subsequent aromatization resulted in 5- and 7-membered CAA derivatives (**62**–**67**). These reactions were carried out by reacting the diene and dienophile in benzene at ambient temperature, followed by DDQ[30] treatment in benzene by reflux.

Isoxazoline-incorporated cyclopentane amino esters **71** have been synthesized by alkylation of the 4-bromobenzaldehyde Schiff base of glycine with *cis*-1,4-dichloro-2-butene (Scheme 15).[31] Subsequent 1,3-dipolar cycloaddition reaction to the alkene in **69** followed by hydrolysis



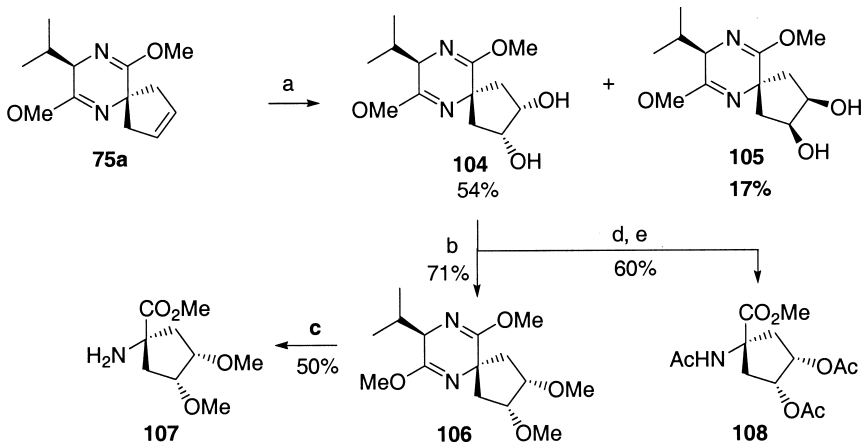
Scheme 19.



Scheme 20.

of the imine in **70** afforded isoxazoline-incorporated cyclopentane amino esters **71**, which were isolated as regioisomeric ureas **72**.

The preparation of unique and conformationally constrained α-AAs from the Grubbs ring closing metathesis (RCM) reaction has been reported (Scheme 16).[32] Substrates (**74**) for the RCM reactions were synthesized in a stepwise manner by use of Schöllkopf methodology employing the chiral auxiliary (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine.[33] The alkylations were carried out by lithiation and alkylation using allyl bromide, 4-bromo-1-butene, and 5-bromo-1-pentene. While the monoalkylated bislactim ether was obtained in 75–96% diastereomeric excess, the subsequent dialkylated product **74** was obtained in 95% de; a consequence of differential steric effects that the second alkylating agent experiences as it approaches the carbanionic center at the 5-position. Five to seven-membered



Scheme 21. (a) 1.0 mol% OsO_4, NMO; (b) NaH, MeI, DMF/THF; (c) 0.1 M TFA; (d) 0.1 M TFA; (e) Ac_2O, DMAP, CH_2Cl_2.

rings **75** were synthesized via RCM reaction, but the 8-membered derivative was not obtained. Schöllkopf bislactim ethers were readily hydrolyzed by 0.2 M trifluoroacetic acid to afford unsaturated cyclic amino esters **76**.

α,β-Unsaturated hydroxy or oxo derivatives of α-CAA **80** or **82** were also synthesized from bislactim ether **73** (Scheme 17).[34] For the synthesis of oxo derivative **80**, substrate **73** was monoalkylated, then employed in an aldol condensation to afford a mixture of aldols (**77**; n=1 or 2). The selectivity at the α-aldol carbon was moderate, but the aldol reaction of **73** with acrolein has been reported to result in high stereoselectivity.[35] Oxo substrate **78** (for 6- to 7-membered ring) was synthesized by Swern oxidation of the allylic alcohol. Subsequent RCM and acid hydrolysis provided 5- to 7- membered cyclic amino esters **80**.

The keto moiety seems to have little electronic influence to either substrate and the yields are mostly dependent upon conformational preferences in the two substrates. For the preparation of hydroxy derivatives **82**, aldols **77** (n=1 or 2) were cyclized via RCM to afford cyclized products **81** which, upon hydrolytic cleavage with TFA, afforded **82**. However, efforts to obtain 5-membered rings were not successful. Another attempt to hydrolyze **77** (n=0) prior to the cyclization resulted in the dipeptide **83**, which was protected as an *N*-acetyl derivative to afford **84**. RCM reaction of **84** finally provided the 5-membered serine analogue **85** as a dipeptide (Scheme 18).

Hydroxymethylated α-CAA derivatives were also synthesized employing vinyloxirane as the alkylating agent (Scheme 19).[36] By stepwise alkylation of bislactim ether **73** with 4-bromo-1-butene and vinyloxirane (in the presence of BF_3–etherate), hydroxymethyl derivatives **86** and **87** were obtained. Due to steric hindrance, differences between the lithiated homoallyl bislactim ether and the more substituted carbon of the epoxide, attack at the less substituted epoxide carbon predominated, resulting in the β-hydroxy derivative **88**.[37] Cyclization of **86** and **87** via RCM reaction afforded tricyclic spirane **89** and hydroxymethyl heterospirane **90**, respectively. Tricyclic spirane **89** was obtained via a re-esterification with expulsion of methanol under the RCM reaction conditions. Due to steric congestion in the bislactim-spiranes, a partial hydrolytic cleavage with ring opening of the bislactim ether at the 3,4-positions or 1,6-lactim positions delivered dipeptides **92** and **93**, respectively. However, in the cleavage of tricyclic spirane **89**, only the dipeptide **91** was obtained from hydrolysis in the 3,4-lactim position.

Undheim et al. also synthesized α-CAAs via a palladium mediated cyclization.[38] Thus, bislactim was stepwise alkylated to afford several diene and enyne substrates (Scheme 20). Employing a Heck reaction delivered 3,4-dimethylene derivative **95** from dibromide **94e**. Substrates carrying a butenyl alkene substituent (**94b** and **94d**) afforded 3,4-dimethylenecyclohexane **97** almost exclusively via competitive 6-*exo* and 6-*endo* Heck reactions. Substrates **94a** and **94c** delivered 3,4-dimethylenecyclopentane 4-ene and 5-mehtylenecyclohex-3-ene **96** via both 5-*exo* and 6-*endo* cyclizations in an intramolecular Heck reaction. The product ratio was dependent upon reaction conditions. On the other hand, the acetate-bridged palladacycle[39] [available

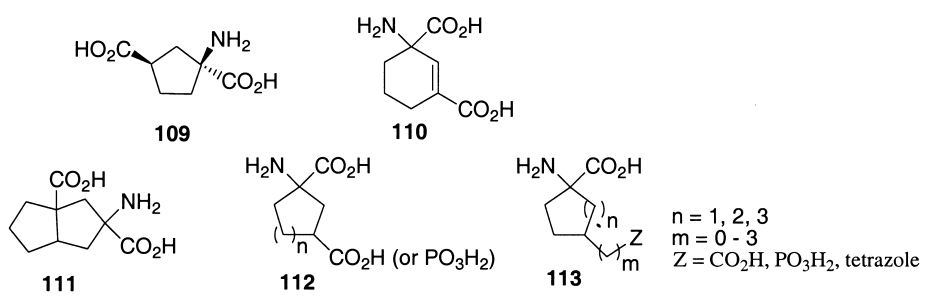
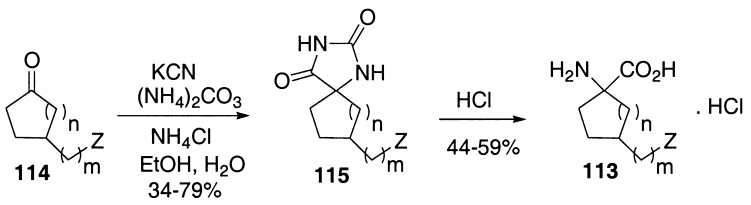


Figure 4.



Scheme 22.

from the reaction of $Pd(OAc)_2$ with tri-*o*-tolylphosphane] converted **94c** into **95** and **99** in almost the same ratio (**95/99**=1:1.1).

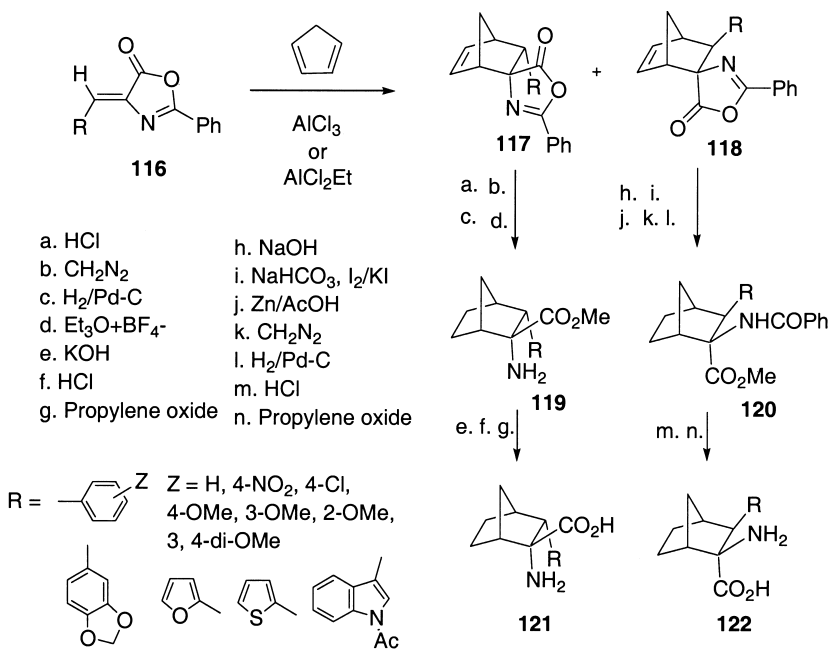
Conformationally constrained vicinally dihydroxylated CAAs, prepared as rigidified analogs of serine or homoserine, were prepared via the streoselective methodology outlined in Scheme 21.[40] Spirocycloalkene **75a** was oxidized to dihydroxy products **104** and **105** (the ratio, 3:1). Hydrolytic cleavage of the pyrazine ring using 0.1 M TFA in aqueous acetonitrile afforded the highly water soluble methyl amino ester. Consequently, this substrate was isolated as either its dimethoxy analog **106** or its triacetylated AA ester derivative **108**.

Stereoselective synthesis of vicinal *cis*-dihydroxy-1-aminocyclohexane-carboxylic acid methyl esters and their methoxy analogs were also prepared in a manner similar to that described in Scheme 21. High stereoselectivity was obtained for the 6-membered ring analogs of **104** and **105** (14:1, respectively).

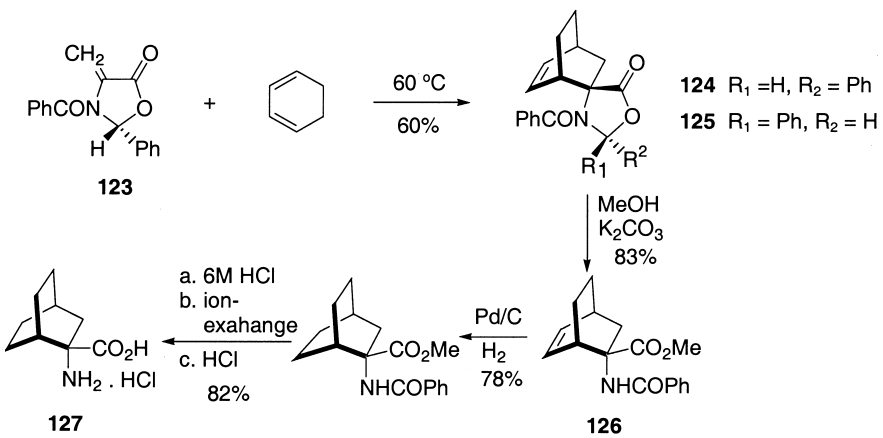
1-Aminocyclopentane-1,3-dicarboxylate (*trans*-ACPD) **109**[41] is known to activate the metabotropic receptor, one of several EAA (excitatory AA) receptors. To probe for potential activity against that receptor, several α-CAAs with a second acidic group were synthesized (Fig. 4). For example, 1-amino-2-cyclohexene-1,3-dicarboxylic acid (DHCGA) **110**,[42] an unsaturated cyclic analog of glutamic acid, was prepared from 3-carboxy-4-cyclohexenone by a Bucherer–Bergs reaction. Conformationally constrained ACPD analogs **111**[43] were synthesized from (±)-1-phenyl-bicyclo[3,3,0]octan-3,7-dione.[44] On the other hand, cyclopentane- and cyclohexane-derived analogs of glutamic acid **112** were obtained from the corresponding 3-keto-cycloalkyl carboxylic acids by a combination of microbial and chemical methods.[45]

To expand the scope of substituents in **112**, Nájera[46] synthesized several α-CAAs **113** with a second acidic group (carboxylic acid, phosphonic or tetrazole group) attached to 5-, 6-, or 7-membered ring skeletons (Scheme 22). Thus, cyclic ketones **114**[46] were subjected to Bucherer–Bergs reaction to afford spirohydantoins **115**. Upon hydrolysis, these provided AA hydrochlorides **113**.

The Diels–Alder reaction provides another useful route to CAA derivatives. Use of 2-phenyl-4-benzyliden-5(4*H*)-oxazolone **116** as dienophile in the Diels–Alder reaction of several dienes affords various cyclic analogs of pharmacologically interesting natural AAs **121** and **122** (Scheme 23).[47] In particular, 2-aminobicyclo[2,2,1]heptane-2-carboxylic acid has been used to evaluate the transport of AAs with hydrophobic side-chains.[48] 5(4*H*)-Oxazolones **116** were synthesized by the Erlenmeyer–Plochl method[49] where the *endo*/*exo* ratio (**117/118**)



Scheme 23.



Scheme 24.

was found to be independent of the nature of the substituents.

The spiroxazolone mixture (**117** and **118**) was separated by an iodolactonization procedure (steps h and i). Methyl esters **119** and **120** were then obtained by esterification with diazomethane followed by hydrogenation using 10% palladium on carbon. The benzamide group in **120** was hydrolyzed with 6N HCl and the free AA **122** was obtained by treatment of the resulting HCl salt with propylene oxide.

(+)-(2*S*)-2-Aminobicyclo[2,2,2]-octane-2-carboxylic acid **127**, a homologue of **121**, was also synthesized[50] in a study to selectively perturb the levels of neutral AAs in the cerebral cortex. Thus, the Diels–Alder reaction of chiral oxazolidinone **123** and cyclohexadiene afforded diastereomers **124** and **125** which, upon methanolysis, provided ester **126** as a single diastereomer. Diastereomer **125** came from a thermally induced C-2 epimerization of **124** during the Diels–Alder reaction.[51] Subsequent hydrogenation of **126** followed by acid hydrolysis finally delivered the hydrochloride salt **127** (Scheme 24).

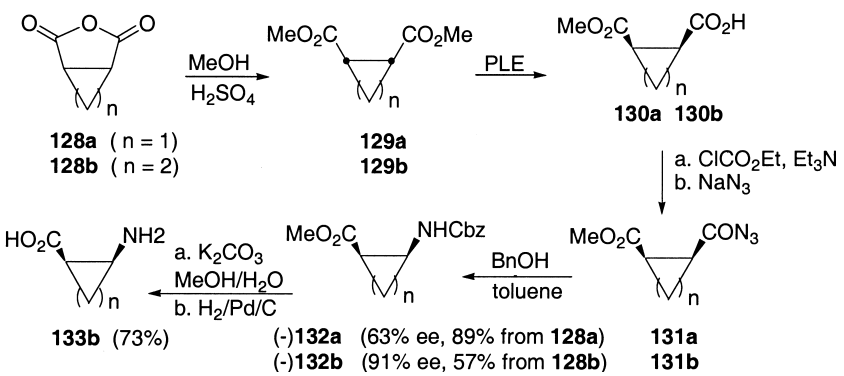
3. β-AA derivatives

β-AAs are a widespread class of non-proteinogenic AAs which are found in nature both in free form and in peptides. They are also important elements in some well known enzyme inhibitors, statins, and the anticancer agent taxol.[52] As probes of both structural effects and properties, conformationally constrained α- and β-AAs have been widely employed in peptide synthesis.[53]

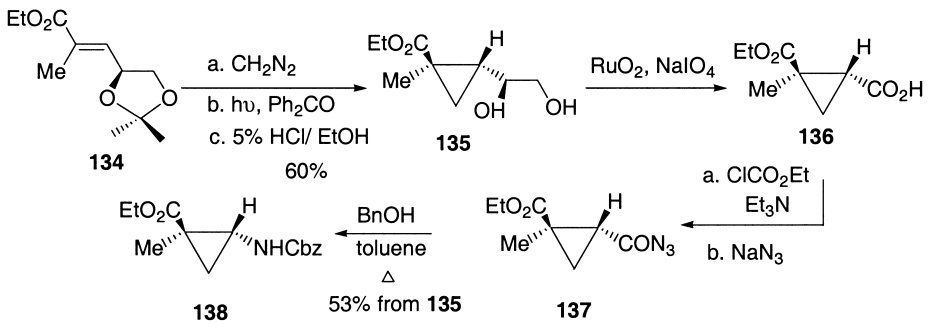
Maleic anhyrides (**128**) have been used as starting materials in the enantioselecive synthesis of β-CAAs and afford enantiomeric cyclopropane and cyclobutane β-AA derivatives **132** through a chemoenzymatic approach (Scheme 25).[54] Thus, Fisher esterification of anhydrides afford *meso* diesters **129**, which were chemoselectively hydrolyzed by pig liver esterase (PLE) to provide hemiesters **130**.[55] Subsequent synthesis of acyl azides followed by Curtius rearrangement in the presence of benzyl alcohol afforded enantiomeric *N*-Cbz protected amino esters **132**. Hydrolysis and deprotection of **132b** (n=2) delivered 2-aminocyclobutanecarboxylic acids **133b**.

Enantiomerically pure ethyl (1*R*,2*R*)-2-*N*-(benzyloxycarbonylamino)-2-methyl-1-cyclopropane carboxylate **138** was synthesized from the unsaturated ester **134** (Scheme 26).[54] Thus, Wittig–Horner reaction of D-glyceraldehyde with a suitable phosphonate provided the starting ester **134**.[56] A highly stereoselective 1,3-dipolar cycloaddition reaction[57] of **134** followed by photolysis of the resulting pyrazoline and subsequent hydrolysis of the acetonide delivered cyclopropane derivative **135** in 60% overall yield. Oxidation of the diol afforded acid **136**. Its conversion to acyl azide **137**, followed by Curtius rearrangement, provided **138** in 53% overall yield from diol **135**.

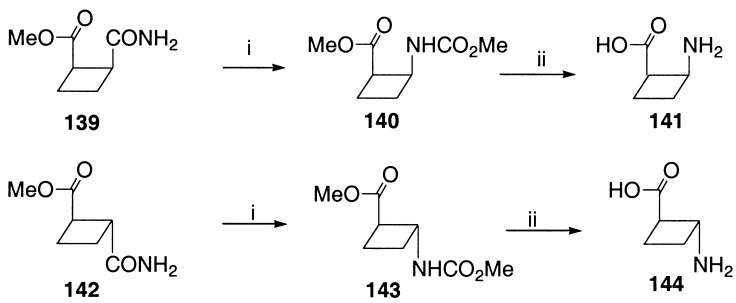
2-Aminocyclobutanecarboxylic acids, which lack the 'GABA structural element', were synthesized following



Scheme 25.



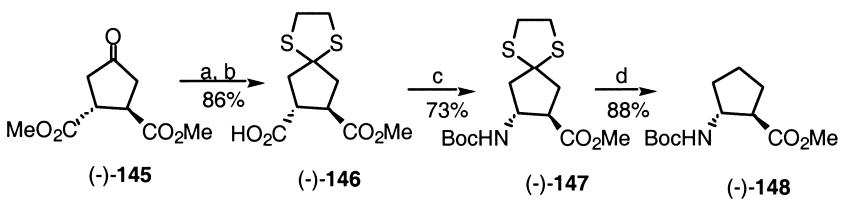
Scheme 26.



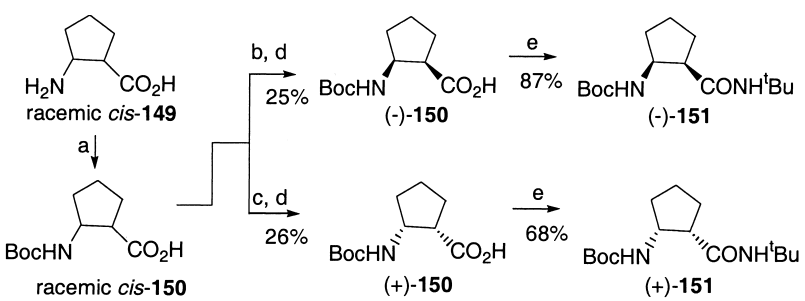
Scheme 27. (i) $Pb(OAc)_4$/MeOH/toluene; (ii) (a) NaOH/EtOH, (b) H+.

the reaction sequences in Scheme 27.[58] Thus, starting *cis*- and *trans*-amido esters (**139** and **142**)[59] underwent lead tetraacetate induced rearrangement to carbamates **140** and **143**, respectively. These were hydrolyzed to provide *cis*- and *trans*-2-aminocyclobutanecarboxylic acids **141** (56% yield) and **144** (66% yield), respectively.

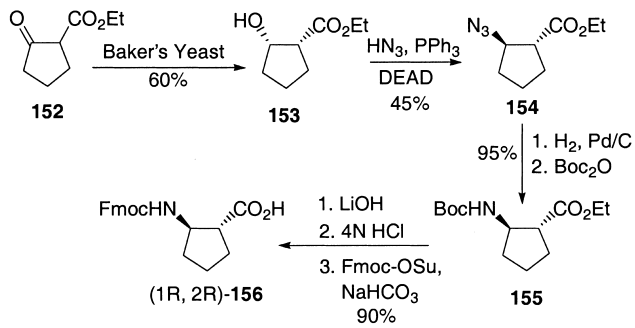
2-Aminocyclopentanecarboxylic acids (ACPC) and their derivatives have shown a wide range of interesting biological activities. It is known that 2-aminocyclopentanecarboxylic acid containing oligomers adopt a helical conformation[60] and their β-peptide displays interesting antibiotic activity.[61] As for the 5-membered cyclic β-aminoacid derivatives, enantiomerically pure *trans* ACPC esters (−)-**148** and (+)-**148** were prepared from chiral ketones (−)-**145** and (+)-**145**, respectively (Scheme 28). These AA derivatives were synthesized as replacements for proline in potential HIV protease inhibitors containing a hydroxyethylamine dipeptide isostere.[62] Thus, the ketone moiety in (−)-**145** was protected and the diester was monohydrolyzed to afford thioketal **146**, which underwent Curtius rearrangement to provide Boc protected amino



Scheme 28. (a) $HSCH_2CH_2SH$, $SnCl_4$; (b) NaOH; (c) DPPA, Et_3N, ^tBuOH; (d) Raney Nickel/MeOH.



Scheme 29. (a) $(Boc)_2O$, $NaHCO_3$, THF/H_2O; (b) (+)-ephedrine, EtOAc, crystallization; (c) (−)-ephedrine, EtOAc, crystallization; (d) 1 M $NaHSO_4$; (e) *tert*-butylamine, HOBt, EDC.



Scheme 30.

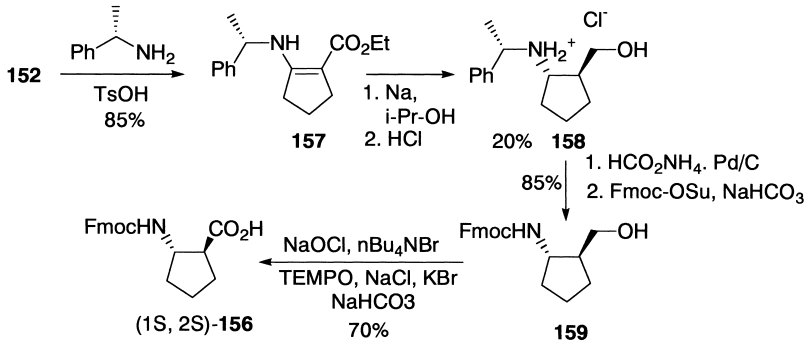
ester (−)-**147**. Reduction of the thioketal using Raney nickel gave Boc protected *trans* 2-aminocyclopentanecarboxylic ester (−)-**148** in 88% yield. Enantiomer (+)-**148** was likewise synthesized from (+)-**145** following the same sequences shown in Scheme 28.

Enantiomerically pure *cis*-ACPC esters (−)-**151** and (+)-**151** were prepared from racemic *cis*-2-ACPC **149**, which was synthesized by a known method[63] (Scheme 29). Boc protection of the starting amine afforded racemic *cis*-**150**, and subsequent resolution by chiral ephedrine delivered each acid **150** in high enantiomeric excess. The carboxylic acid moiety of each antipode was coupled with *tert*-butylamine to deliver the two derivatized enantiomers **151**.

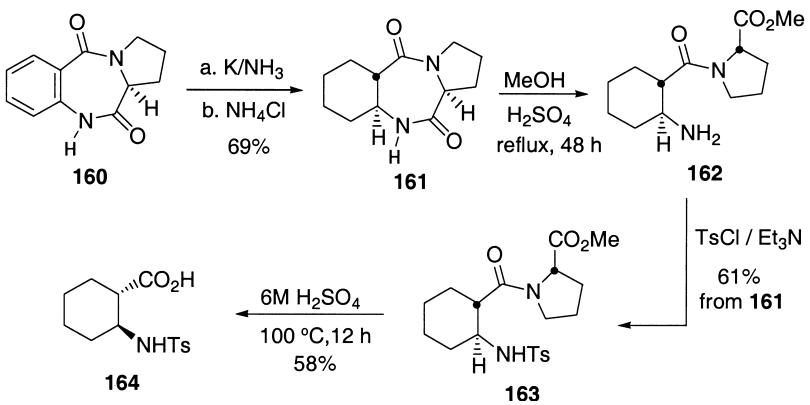
On the other hand, pure Fmoc protected *trans*-2-ACPC **156** was prepared from ethyl 2-oxocyclopentanecarboxylate (Scheme 30).[64] Cyclic β-ketoester **152** was converted into (1*R*,2*S*)-2-hydroxycyclopentanecarboxylate **153** via Baker's yeast reduction. Mitsunobu reaction of **153** with HN_3, followed by reduction and Boc protection, afforded *trans* 2-aminocyclopentanecarboxylic ester **155**. Subsequent hydrolysis and Fmoc protection provided (1*R*,2*R*)-Fmoc-ACPC **156**.

For the other enantiomer, ketoester **152** was reacted with (*S*)-α-methylbenzylamine to give enamine **157**, which was reduced to γ-amino alcohol **158**. Removal of the chiral auxiliary followed by Fmoc protection afforded protected γ-amino alcohol **159**, which was oxidized to provide (1*S*,2*S*)-Fmoc-ACPC **156** (Scheme 31). The development of these synthetic routes to the two enantiomers of Fmoc-ACPC should facilitate the investigations of conformational and biological properties of 12-helical β-peptides.

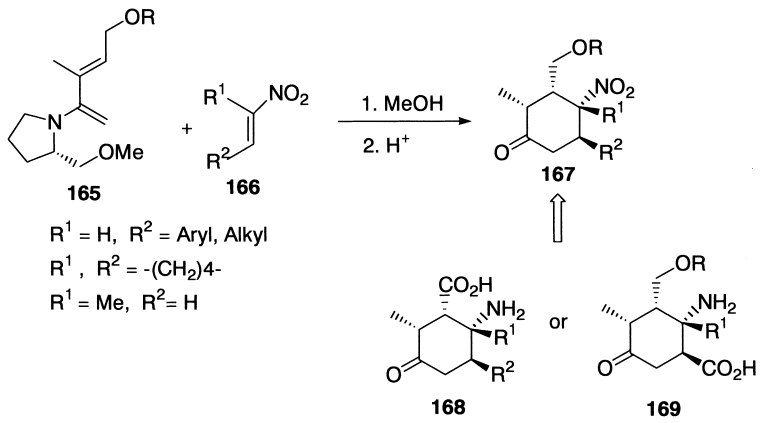
Racemic 2-aminocyclohexanecarboxylic acids (ACHC) were prepared either from anthranilic acid by the action of sodium in isoamyl alcohol[65] or from the reaction of 1-cyclohexene-1-carboxylic acid with ammonium hydroxide.[66] Pure *trans*-ACHC[67] was prepared by resolving the quinine salt of *N*-benzoyl-*trans*-ACHC:[68] the tetramer and the hexamer of this β-AA are known to have helical conformations with 14-membered-ring hydrogen bonds between a carbonyl oxygen and the amide proton of the second residue from the N-terminus. Asymmetric synthesis of a *trans*-ACHC derivative[69] was accomplished from pyrrolobenzodiazepine-5,11-dione (Scheme 32). Thus,



Scheme 31.



Scheme 32.



Scheme 33.

alkali metal reduction of **160** in ammonia afforded dione **161**, which underwent methanolysis to provide **162**. Tosylation of the free amine to give **163**, followed by hydrolysis, gave (+)-*trans*-ACHC derivative **164** in 58% yield.

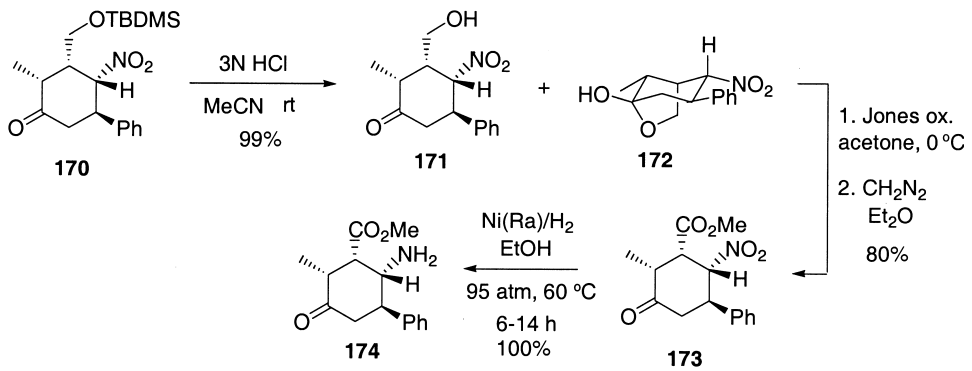
Enantiomerically pure substituted *cis*- and *trans*-2-aminocyclohexanecarboxylic esters **168** and **169** have been synthesized by Barluenga from 4-nitrocyclohexanones **167**.[70] These nitrocyclohexanones were derived from asymmetric cycloadditions of 2-aminodienes **165** and nitroolefins **166** (Scheme 33).

For the synthesis of the *cis*-βAA derivative, the hydroxy group of **170** was deprotected under acidic conditions to afford nitro hydroxy ketone **171** together with its hemiketal **172**. Jones oxidation of the mixture followed by diazomethane esterification provided nitroester **173** as a single compound. Subsequent hydrogenation of the nitro group using Raney nickel delivered *cis*-β-amino ester **174** in 80% overall yield (Scheme 34).

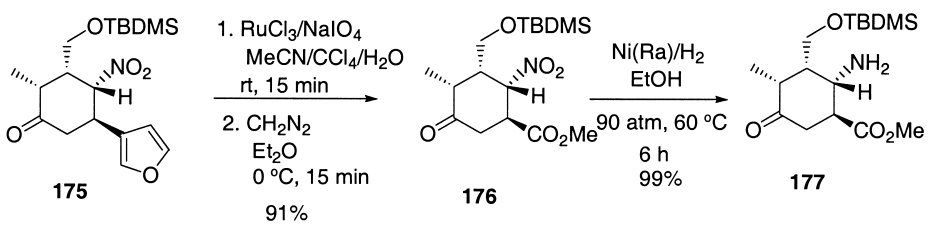
As for the *trans* derivative, starting material **175**, derived from β-(3-furyl)nitroethylene, was employed. Thus, oxidation[71] of the furan ring followed by diazomethane esterification provided β-nitro ester **176**. Reduction of the nitro group afforded *trans*-β-amino ester **177** in 91% overall yield (Scheme 35).

4. γ-AA derivatives

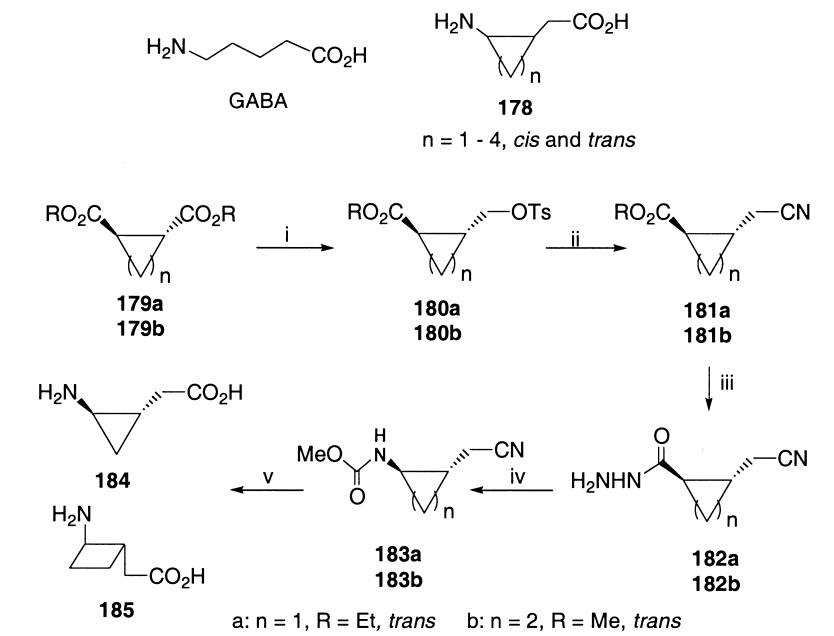
2-Aminocycloalkylacetic acids **178**, with their restricted rotation about the C(3) and C(4) atoms, have been synthesized[72] as analogs of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Thus, cyclopropane (**184**) and cyclobutane analogs (**185**) were prepared from readily available diesters **179a**[73] and **179b**,[74] respectively. Sequential partial diester hydrolysis, acid to alcohol reduction, and tosylation of the resulting alcohols delivered tosylates **180a** and **180b**. Upon treatment with potassium cyanide, nitriles **181a** and **181b** were obtained. These were converted into acid hydrazides (**182a** and **182b**)[75] which in



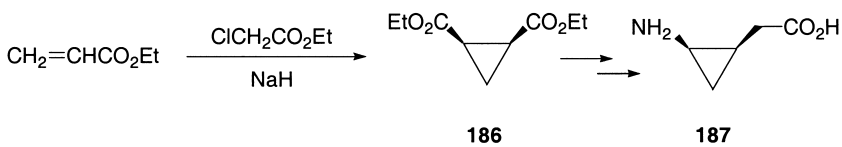
Scheme 34.



Scheme 35.



Scheme 36. (i) NaOH/EtOH, then BH_3·THF/Et_2O, then TSCl/pyridine; (ii) KCN/DMSO; (iii) hydrazine/EtOH; (iv) $NaNO_2$, then heating, then MeOH; (v) NaOH/EtOH.



Scheme 37.

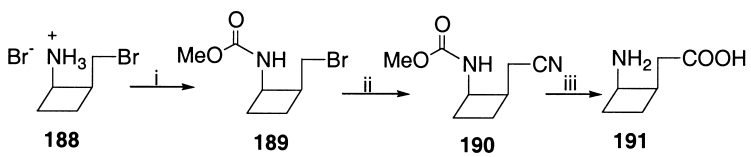
turn delivered carbamates (**183a** and **183b**) via Curtius rearrangement. Carbamate hydrolysis finally provided the *trans*-AAs **184** and **185** (Scheme 36). The *cis*-cyclopropane derivative **187**[73] was synthesized from *cis*-diester **186** following the same sequences as in Scheme 36 (Scheme 37).

On the other hand, *cis* cyclobutane derivative **191** was prepared from the bromomethyl derivative **188**.[73] However, treatment of compound **188** with potassium cyanide resulted in cleavage of the cyclobutane ring to generate an iminium ion. To prevent this, the amine functional group was protected as the carbamate (**189**) and subsequent introduction of the nitrile group proceeded smoothly to provide **190**. Upon hydrolysis of **190**, the desired *cis*-γ-aminobutyric acid **191** was obtained (Scheme 38).

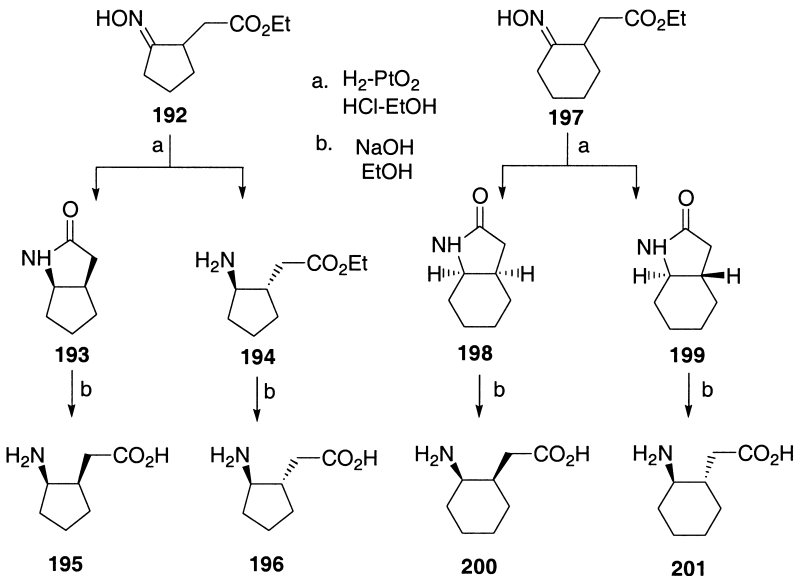
cis- and *trans*-Cyclopentyl and cyclohexyl AAs were synthesized from oximes (Scheme 39). For cyclopentyl derivatives, oxime **192** was hydrogenated over platinum oxide in ethanolic HCl to afford *cis*-lactam **193** and the *trans*-amino ester **194**, which were subsequently hydrolyzed to provide the *cis*- and *trans*-AAs **195** and **196**, respectively. The same method was applied to the synthesis of the cyclohexyl AAs. Thus, both *cis*- and *trans*-lactams were obtained from hydrogenation of the starting oxime **197**. Hydrolysis of these lactams yielded AAs **200** and **201**, respectively.

2-(Aminomethyl)cycloalkanecarboxylic acids **205** were also synthesized to restrict bond rotation about the C(2)–C(3)bond of GABA (Scheme 40).[76] In this work, the synthesis of *trans*-cyclopropyl and cyclobutyl amino-acid **205a** and **205b** starts from the Gabriel reaction of tosylates **202** with potassium phthalimide. Dephthaloylation followed by hydrolysis afforded the desired *trans* products **205**, which proved to be potent in GABA receptor binding studies. The synthesis of *cis*-cycloalkylamino acids were accomplished by reaction of lactones **206**[73] with potassium phthalimide followed by dephthaloylation (Scheme 41).

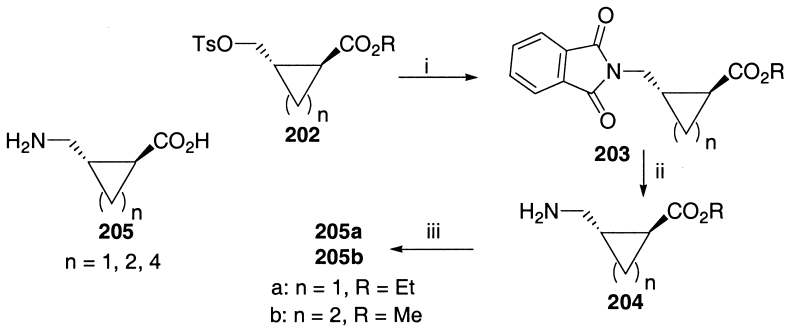
Optically active *N*-protected 1,3-cyclobutane AAs **213** and ent-**213** were synthesized from α-pinene (Scheme 42);[77]



Scheme 38. (i) $ClCO_2Me$/pyridine/Et_2O; (ii) KCN/DMSO; (iii) NaOH/EtOH.



Scheme 39.



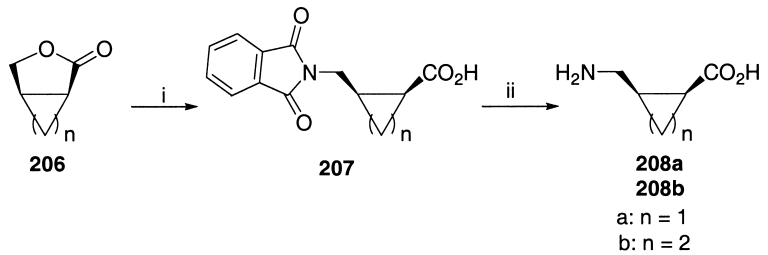
Scheme 40. (i) Potassium phthalimide/DMF; (ii) $MeNH_2$/EtOH; (iii) NaOH/EtOH.

these AAs have potential applications in designed peptidomimetics. The starting material, verbenone, obtained from allylic oxidation of (+)-α-pinene, was oxidatively cleaved to afford keto-acid **209**. Subsequent benzylation followed by the haloform reaction delivered acid **211**, which underwent Curtius rearrangement to provide Boc-protected amine **212**. Debenzylation by hydrogenolysis finally afforded *N*-protected AA **213** which is suitable for peptide synthesis. To obtain its enantiomer, ent-**213**, Curtius rearrangement was performed first to give compound **214** and subsequent haloform reaction provided ent-**213**.

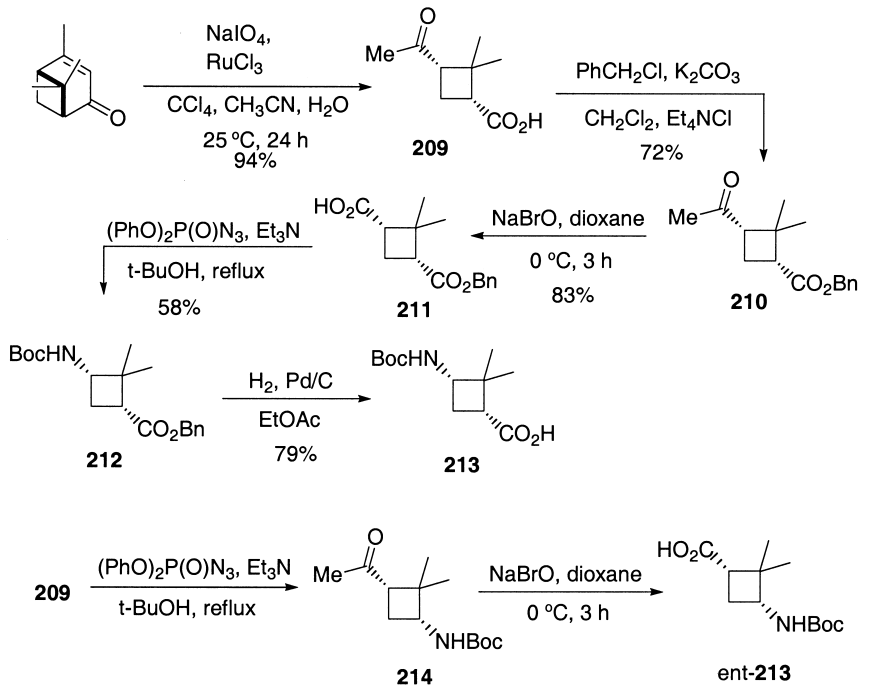
The more flexible cyclobutane AA derivative **216** was synthesized directly from (+)-α-pinene and without oxidation to verbenone (Scheme 43). Thus, oxidation of (+)-α-pinene gave ketoacid **215**, which underwent sequential Curtius and haloform reactions to provide *N*-protected AA derivative **216**. These AAs (ent-**213** and **216**) were converted into their FMOC protected AAs for solid-phase peptide/peptidomimetic syntheses.[78]

5. CAA derivatives with the amine group inside the cyclic system

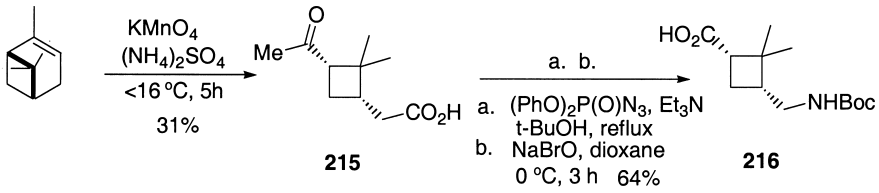
Aziridine-2-carboxylic acids are important components for the preparation of a variety of conformationally constrained peptidomimetic building blocks. These chiral aziridines are also key intermediates in the asymmetric synthesis of α-methyl cysteine, α,β-dimethylcysteines and



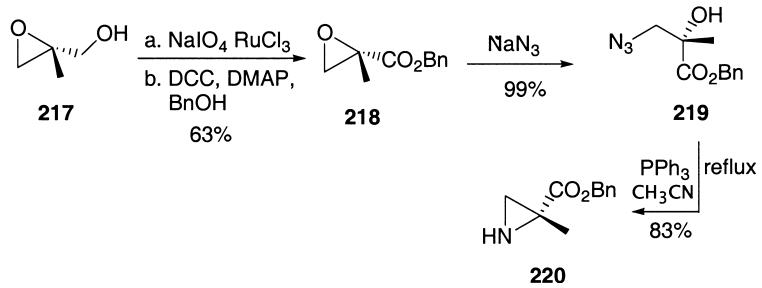
Scheme 41. (i) Potassium phthalimide/DMF; (ii) $MeNH_2$/EtOH.



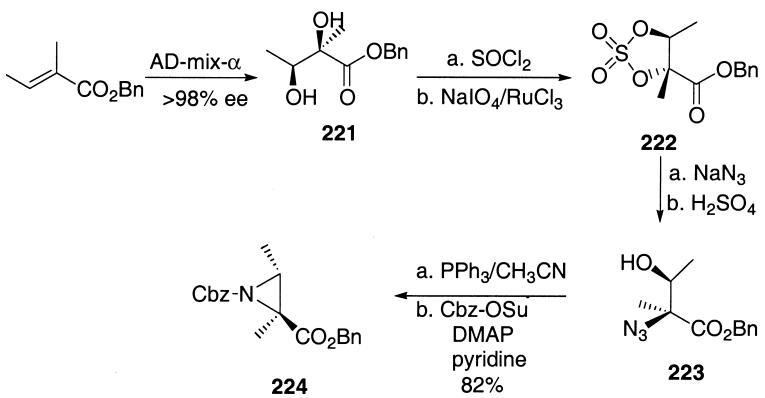
Scheme 42.



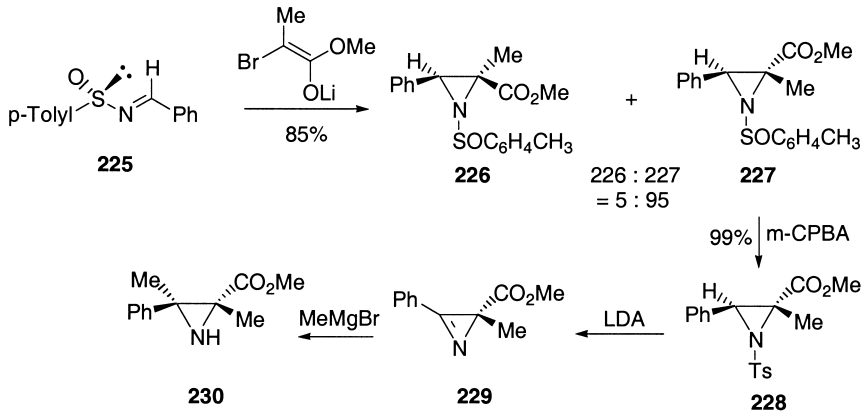
Scheme 43.



Scheme 44.



Scheme 45.



Scheme 46.

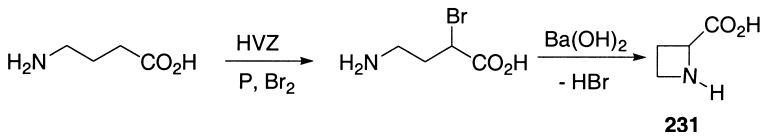
α,β-dimethyltryptophans.[79] The (*R*)-2-methylglycidol **217**, which was obtained from the corresponding allylic alcohol via Sharpless asymmetric epoxidation, was oxidized to the acid. Subsequent formation of benzyl ester **218** followed by ring opening by azide provided azido alcohol **219**. Enantiomerically pure aziridine ester derivative **220** was obtained by refluxing **219** with triphenylphospine (Scheme 44).

Cbz protected aziridne **224**, an important synthon of α,β-dimethylcysteines or α,β-dimethyltryptophans, was synthesized from benzyl tiglate (Scheme 45). Thus, diol **221** was prepared by Sharpless asymmetric dihydroxylation with AD-mix-α. 2,3-Cyclic sulfite formation followed by oxidation afforded cyclic sulfate **222**, which provided α-azido ester **223** by azide substitution followed by acidic hydrolysis. α-Azido ester **223** was then stereospecifically transformed to Cbz protected aziridne **224**.

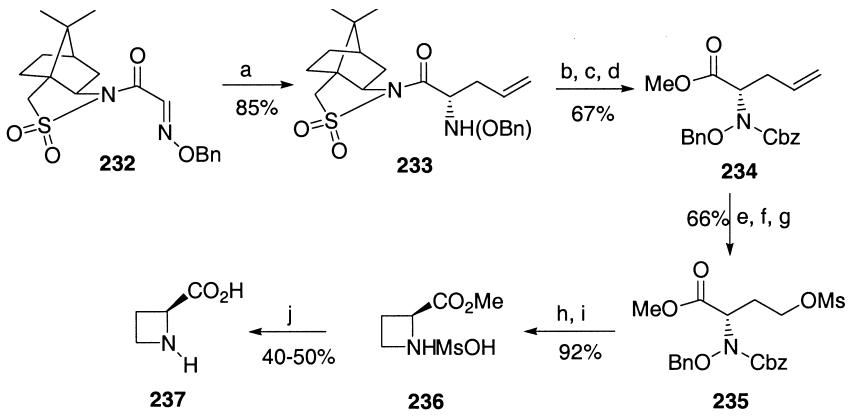
Another substituted aziridine-2-carboxylate (**230**) was synthesized by reaction of (*S*)-(+)-benzylidene-*p*-toluene-sulfinamide **225** with the lithium enolate of methyl α-bromopropionate (Scheme 46). Thus, *trans*-(2*R*,3*S*)-(+)-**227** was obtained as the major product by Darzens-type condensation.[80] Oxidation to compound **227** followed by sequential treatment with LDA and MeMgBr afforded substituted aziridine-2-carboxylate **230**.[81]

Azetidine-2-carboxylic acid was first isolated from *Convallaria majalis* (lily-of-the-valley) in 1955,[82] and also synthesized by Fowden in 1956.[83] It is an important constituent in several natural products[84] and is used for the investigation of secondary structure in unnatural poly-peptides.[85] Fowden synthesized it from γ-aminobutyric acid. Thus, Hell–Volhard–Zelinsky reaction followed by cyclization provided racemic azetidine-2-carboxylic acid **231** in very low yield (Scheme 47). It was also synthesized as a racemate by Cromwell[86] from 2,4-dibromobutyric acid.

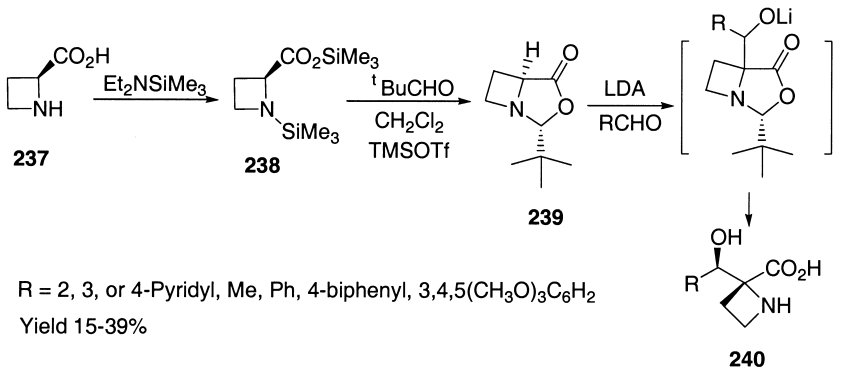
An enantioselective synthesis of L-azetidine-2-carboxylic acid and its derivatives was reported by Hanessian et al. (Scheme 48).[87] In this work, the Oppolzer sultam derivative of glyoxylic acid oxime **232** was reacted with allyl bromide to give chiral allyl glycine **233**. Subsequent hydrolysis of the



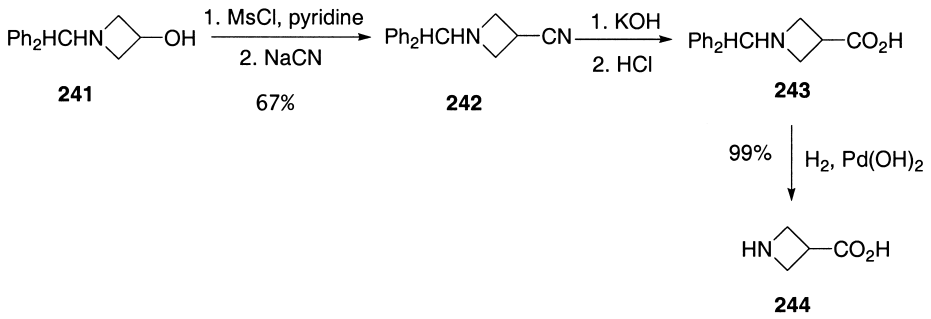
Scheme 47.



Scheme 48. (a) Allyl bromide, Zn, NH_4Cl; (b) LiOH/THF; (c) CH_2N_2–Et_2O, MeOH; (d) Cbz-Cl, $NaHCO_3$; (e) O_3, MeOH; (f) $NaBH_4$; (g) MsCl, pyridine; (h) H_2, 10% Pd/C; (i) $NaHCO_3$; (j) 3N HCl, Dowex.



Scheme 49.



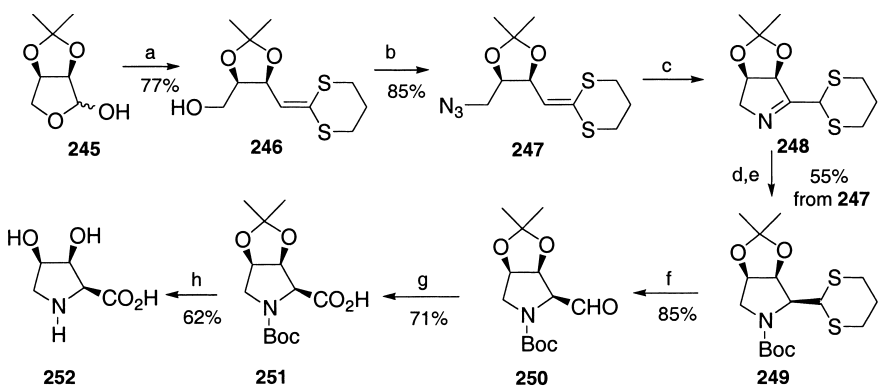
Scheme 50.

chiral auxiliary followed by esterification and Cbz protection afforded the methyl ester **234**. Ozonolysis followed by aldehyde reduction and mesylation delivered mesylate **235**, which was deprotected and cyclized to give L-azetidine-2-carboxylic acid methyl ester **236**. Ester hydrolysis and Dowex purification delivered L-azetidine-2-carboxylic acid **237** in 15% overall yield. Isopropyl, cinnamyl and naphthyl substituted azetidine-2-carboxylic acids were also prepared enantiomerically pure by the same reaction sequences.

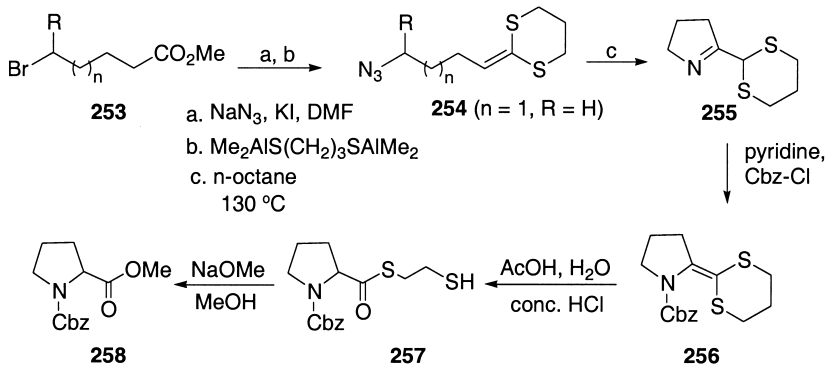
Seebach reported a method for the alkylation of 2-azetidinecarboxylic acid at the 2 position without racemization (Scheme 49).[88] Thus, labile protons in 2-azetidinecarboxylic acid were replaced with trimethylsilyl groups to afford **238**, which in turn reacted with pivalaldehyde to give ester **239**. Treatment of **239** with LDA followed by aldehyde addition provided **240** diastereoselectively (>96% ds).

The synthesis of isomeric azetidine-3-carboxylic acid **244** was also reported (Scheme 50).[89] The starting material, 1-benzhydrylazetidin-3-ol (**241**),[90] was mesylated and then converted into nitrile **242**. Subsequent hydrolysis to give **243**, followed by debenzylation, afforded azetidine-3-carboxylic acid **244** as a racemic mixture.

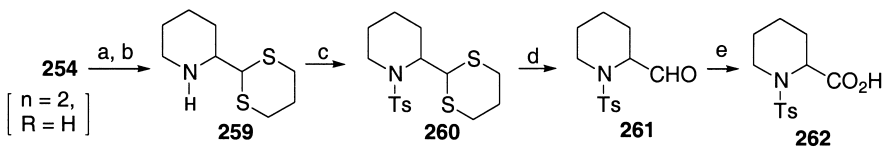
There are numerous approaches to the syntheses of substituted proline derivatives. Proline is known to be the major contributor to the biological activity of several proteins and plays an important role in biological recognition phenomena because of its ability to induce β-turns and initiate the folding of an α-helix.[91] Recently, (2*S*,3*S*,4*R*)-3,4-dihydroxyproline **252**, a known potential glycosidase inhibitor,[92] was synthesized from the azido ketene-*S*,*S*-acetal **247**.[93] Thus, 2,3-*O*-isopropylidene-D-erythrose **245** was converted into **246** by Peterson olefination[94]



Scheme 51. (a) 2-Lithio-2-trimethylsilyl-1,3-dithiane, −78°C to rt; (b) $(PhO)_2PO{\cdot}N_3$, DEAD, Ph_3P; (c) *n*-octane, reflux; (d) $NaBH_4$, MeOH; (e) $(Boc)_2O$, Et_3N; (f) $TI(OCOCF_3)_3$; (g) $NaIO_4$, $RuCl_3$, H_2O; (h) TFA, DOWEX 50x 8-100.



Scheme 52.



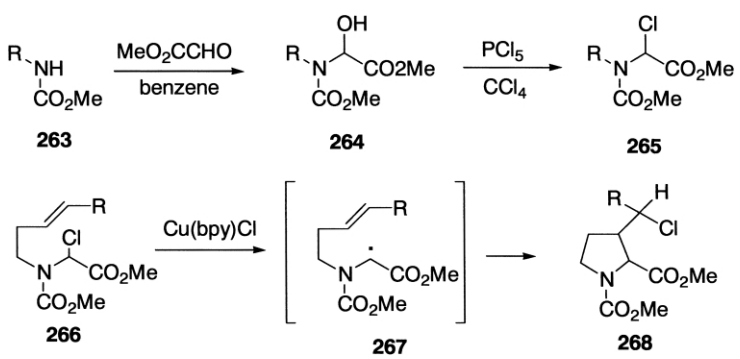
Scheme 53. (a) Octane, 126°C, 24 h; (b) $NaBH_4$; (c) TsCl, pyridine; (d) $PhI(OCOCF_3)_2$; (e) $RuCl_3$, $NaIO_4$, H_2O, CH_3CN.

and the requisite azide functional group was introduced from alcohol in **246** using diphenyl phosphoryl azide. Intramolecular 1,3-dipolar cycloaddition between the ketene-*S*,*S*-acetal and azide moieties was effected by thermolysis to afford 2-amino ketene-*S*,*S*-acetal **248**—a masked substituted proline—which was reduced and then protected to afford Boc derivative **249**. Hydrolysis of the dithioacetal followed by oxidation of the resulting aldehyde **250** delivered the protected AA **251** without epimerization at C-2. Acid-catalyzed cleavage of both acetonide and Boc groups finally provided proline derivative **252** (Scheme 51).

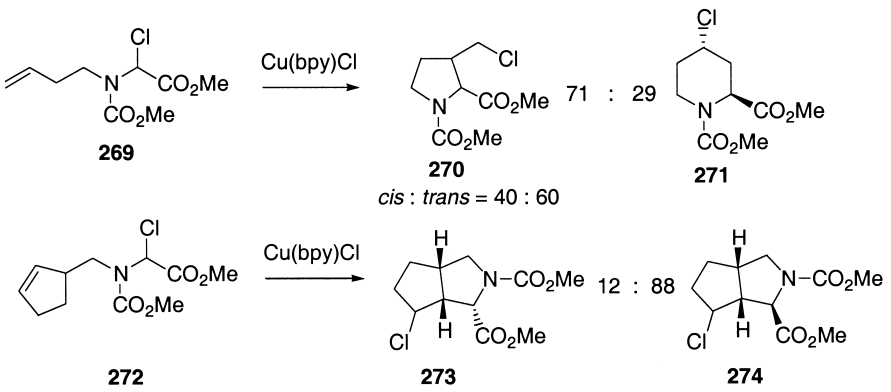
Racemic proline derivative **258** was also synthesized by an intramolecular 1,3-dipolar cycloaddition reaction between ketene-*S*,*S*-acetal and azide.[95] The synthesis of ω-azido ketene-*S*,*S*-acetals **254** starts from bromoester **253** from which the azide functional group can be introduced (Scheme 52). Bis(dimethylaluminum)propane-1,3-dithiolate (BDP)[96] was used to protect ester group in the presence of azide functional moiety and subsequent 1,3-dipolar cycloaddition provided the cyclic imine **255**. N-Acylation gave Cbz-protected 2-amino ketene-*S*,*S*-acetal **256** in 65% overall yield from **254**. Treatment with 50% aqueous acetic acid containing a small amount of concentrated hydrochloric acid afforded acyl sulfide **257** and subsequent sodium methoxide treatment provided racemic proline derivative **258** in 84% overall yield from **256**.

Pipecolic acid derivative **262** was also prepared (Scheme 53) from azido ketene-*S*,*S*-acetals **254** (*n*=2, R=H). Thermolysis afforded the cyclic imine which was in turn reduced by $NaBH_4$ to give **259** (58% yield from **254**). The *N*-toluenesulfonyl derivative (**260**) was prepared and its thioacetal functional group was cleaved using $PhI(OCOCF_3)_2$[97] to give aldehyde **261**. Upon oxidation of **261**, pipecolic acid derivative **262** was obtained in 53% overall yield from **260**.

Substituted proline derivatives have also been synthesized by transition metal catalyzed chloride transfer cyclizations of carbon-centered glycine radicals (Scheme 54).[98] The substrates, α-chloroglycine derivatives **265**, are synthesized by the reaction of N-monosubstituted carbamates **263** with methyl glyoxylate. Stable hemiacetals **264** react with PCl_5 to provide the requisite radical precursors **265** (84–100%) which, in the presence of Cu(bpy)Cl, deliver the relatively stable captodative radicals **267** en route to substituted prolines **268**.

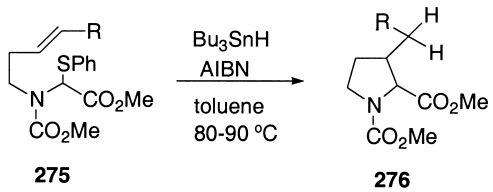


Scheme 54.



Scheme 55.

While monosubstituted alkenes (for example **269**) provided both *exo*-and *endo*-cyclized products (**270** and **271**), disubstituted alkenes (for example **272**) delivered only 5-*exo* cyclized products (**273** and **274**; Scheme 55). Ring size and the *E*/*Z*-nature of double bond have little impact on the stereochemistry of the cyclization. 2,3-*trans*-Substituted pyrrolidines are obtained as the major product because of the preferred quasi-axial orientation of the ester substituent in the reaction's chair-like transition state.[99]



Scheme 56.

Similar results were obtained in the Bu_3SnH-mediated cyclization of α-(phenylthio)glycine derivative **275** to 3-substituted proline derivative **276** (Scheme 56).[100] These reductive cyclizations also provided mainly the 2,3-*trans*-substituted proline derivatives, and the phenylthio analogs of **269** also afforded 6-*endo* cyclization products (**277**–**279**). Electronically unbiased 1,2-disubstituted alkenes afford exclusive 5-*exo* cyclization products (**280**, **281**; Fig. 5).

Use of tin tetrachloride in the cyclization of *N*-(3-alkenyl)-*N*-(methoxycarbonyl)acetoxyglycine ester **282** delivered *trans* 4-chloropipecolic ester **284** as the major product via a cationic π-cyclization reaction (Scheme 57).[101] This transformation is mediated by a rapid cationic aza-Cope of the incipient iminium cation followed by formation of bicyclic dioxycarbenium **283**.

Ellman et al. synthesized C-3 substituted pipecolic acid **290** from the N-allylated AA **289** via sequential ring closing

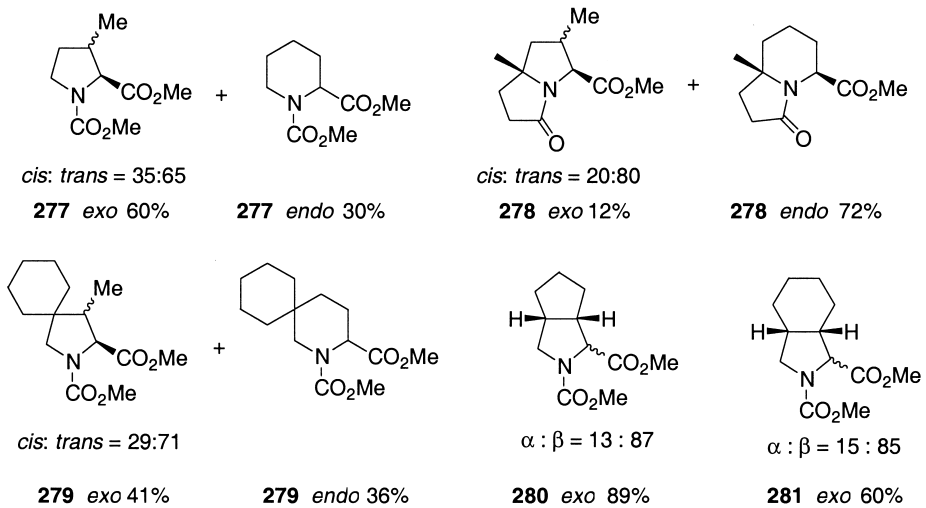
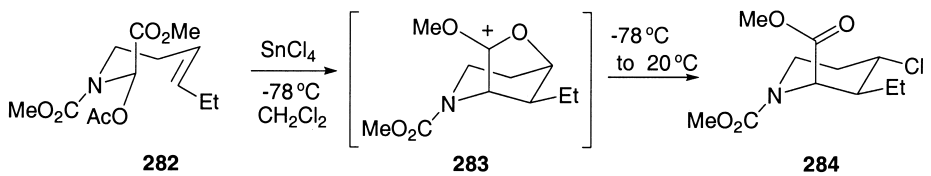
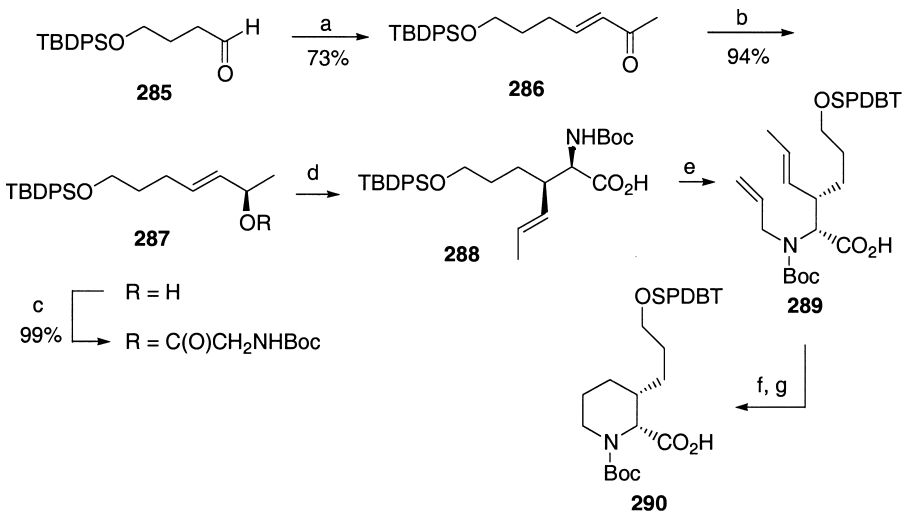


Figure 5.



Scheme 57.



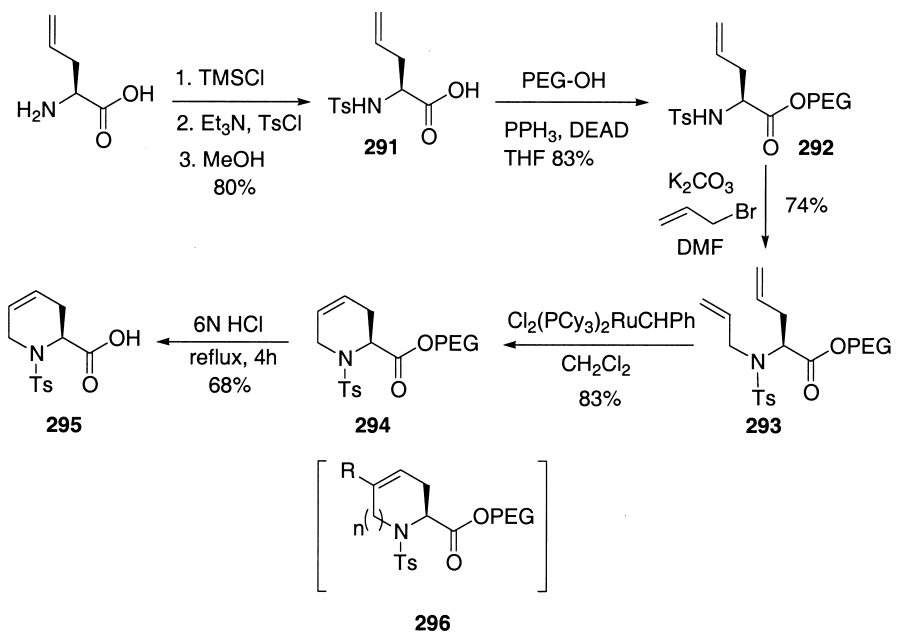
Scheme 58. (a) Acetonyltriphenylphosphonium chloride, Na_2CO_3, dioxane/H_2O reflux, 24 h; (b) catecholborane, CBS-(*S*)-oxazaborolidene, toluene, −78°C; (c) *N*-Boc-Gly, DMAP, DIC, CH_2Cl_2; (d) LDA, THF (−20 to −70°C), then $ZnCl_2$/THF; (e) allyl iodide, NaH, THF; (f) Grubbs catalyst, CH_2Cl_2; (g) 10% Pt/C, H_2, EtOAc, 50 psi.

metathesis and hydrogenation (Scheme 58).[102] Thus, Wittig reaction of aldehyde **285** gave *E*-α,β-unsaturated ketone **286** and subsequent asymmetric reduction of the ketone followed by coupling with *N*-Boc Gly afforded chiral ester **287**. Claisen rearrangement of this ester set the two contiguous stereocenters in AA **288** and selective electrophilic allylation of the Boc-nitrogen in the presence of the carboxylic acid with allyl iodide and NaH in THF gave **289**.

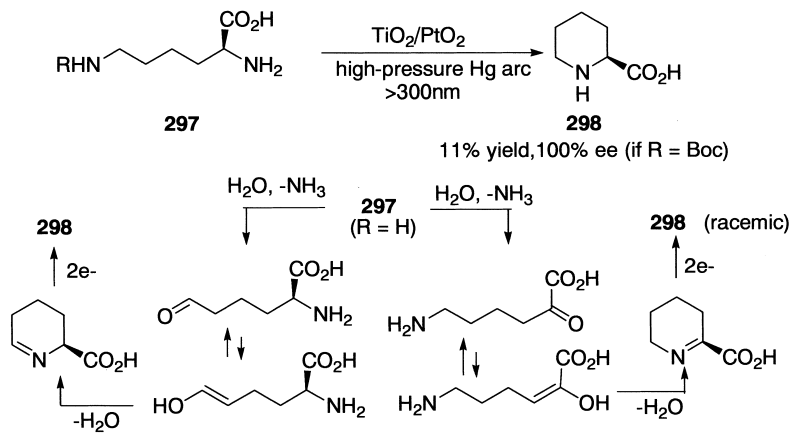
Lamaty et al. synthesized various CAA derivatives—including pipecolic acid derivatives—via RCM on a polyethylene glylcol (PEG) support (Scheme 59).[103] An *N*-tosyl group was used to protect/activate the amino group for N-allylation, but the resulting sulfonamide was sensitive to racemization. Consequently, the mild Mitsunobu reaction was selected to couple **291** with PEG to give **292**. Alkylation followed by RCM (using Grubbs' catalyst) afforded PEG-supported CAA derivative **294**. Acid hydrolysis (6N HCl, reflux 4 h) of PEG-ester **294** delivered AA **295** with no racemization. Other PEG supported CAA derivatives **296** (e.g. R=methyl or vinyl when n=1, and R=H when n=2 or 3) were also prepared by appropriate selection of the alkylating agent.

Chiral pipecolinic acids were also synthesized from α,ω-diamino carboxylic acids by a one-step photocatalytic cyclization[104] (Scheme 60). Thus, L-lysine or its derivatives **297**, when photolized (>300 nm, high-pressure Hg arc) in the presence of catalytic TiO_2/PtO_2, provided pipecolinic acid **298** in 7–43% yields with 13–100% ee. In this reaction, L-lysine undergoes oxidation to give either an α-keto or ω-aldehyde intermediate. Subsequent intramolecular condensation followed by imine reduction provides either an optically pure or a racemic pipecolinic acid.

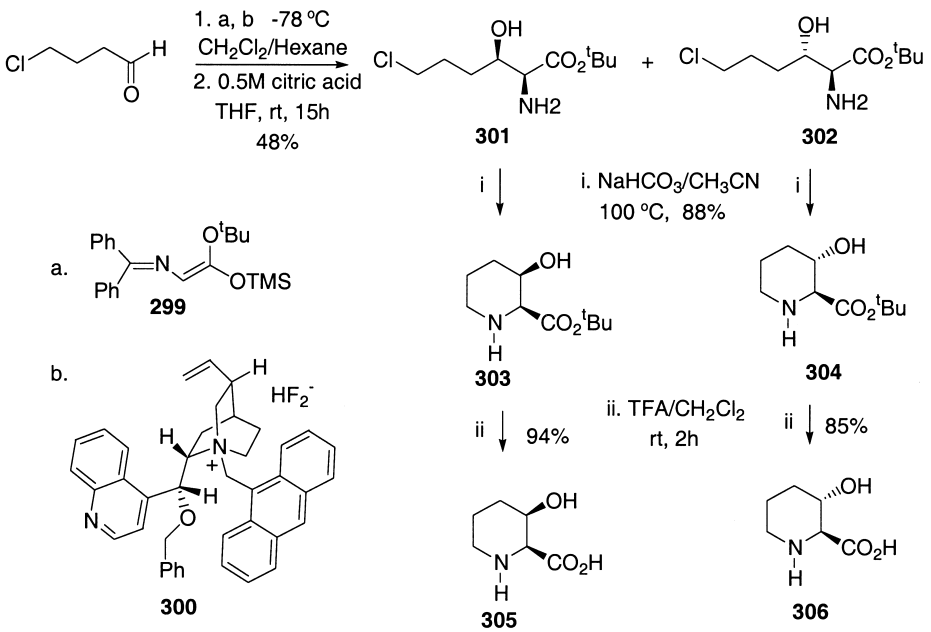
Corey et al. prepared diastereomeric 3-hydroxy-(*S*)-pipecolic



Scheme 59.



Scheme 60.

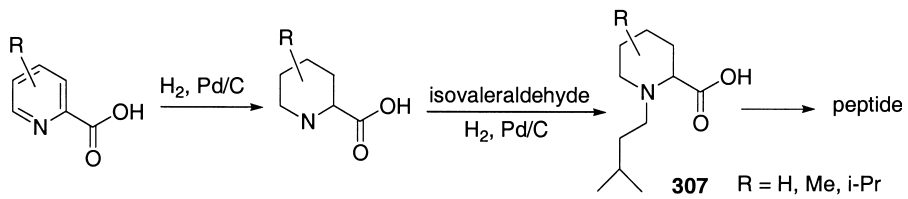


Scheme 61.

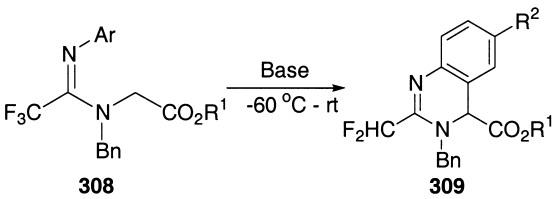
acids **305** and **306** from β-hydroxy-α-amino esters by an aldol coupling reaction (Scheme 61).[105] Thus, aldol coupling of Shiff base **299** with 4-chlorobutyraldehyde in the presence of the chiral quaternary ammonium salt **300** as catalyst produced a 1:1 ratio of *syn* and *anti* adol products **301** and **302**. Subsequent cyclization afforded amino esters **303** and **304**; hydrolysis provided the corresponding pipecolic acids. The highest *syn*/*anti* ratio (13:1) was obtained in the aldol condensation of cyclohexanecarboxaldehyde.

The synthesis of phenylalanine derivatized peptides as novel N-type calcium channel blockers have been prepared from N-alkylated pipecolinic acids, in turn prepared from substituted pyridine-2-carboxylic acids.[106] Thus, reduction of pyridine ring in picolinic acid followed by reductive N-alkylation using, e.g. isovaleraldehyde affords **307** (Scheme 62). Pyridine-3- or -4-substituted carboxylic acid as well as 2-pyrazine carboxylic acid, also afford the corresponding pipecolinic acid or 2-piperidine carboxylic acid derivatives, respectively.

Fluorine-containing AAs have received considerable attention as candidates for peptide modification since



Scheme 62.



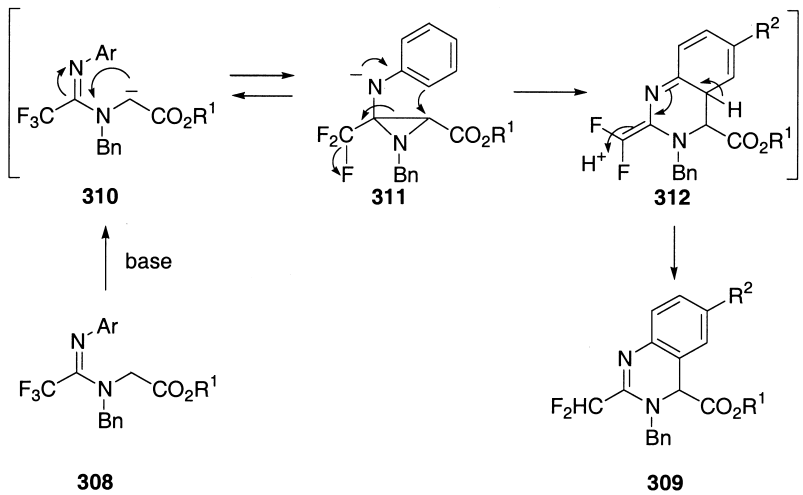
Scheme 63.

lipophilicity and electronegativity in the fluorine-containing moiety may improve drawbacks of peptide drugs; e.g. rapid degradation by proteases and low lipophilicity.[107] Difluoromethylated AAs are important members of the fluorinated family of AAs. Uneyama et al.[108] has reported the synthesis of **309**, a new type of fluorinated CAA, and related esters by an intramolecular defluorinative cyclization under basic conditions (LTMP or *n*-BuLi; Scheme 63). A proposed mechanism for this reaction is depicted in Scheme 64. Thus, intramolecular nucleophilic attack of the carbanion in **310** followed by nucleophilic ring opening of the aziridine in **311** with concomitant defluorination delivers quinazoline **312**. Base-mediated proton migration finally affords quinazolic products **309**. These are new heteroatom substituted AA derivatives which may be candidates for biologically important inhibitors.

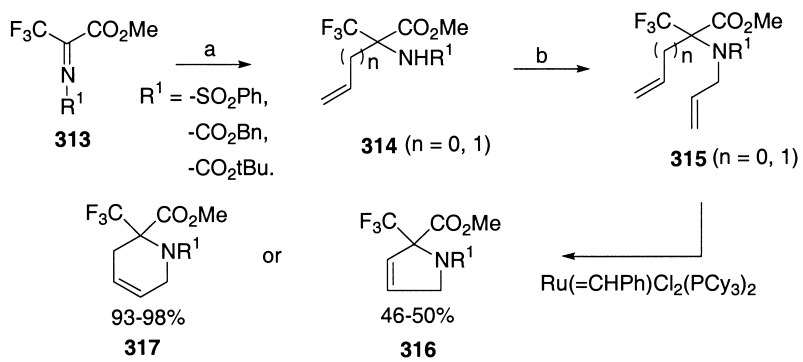
α-Trifluoromethyl substituted dehydroproline **316** and dehydropipecolinic acid **317** were synthesized from α-trifluoromethyl-α-amino esters containing two terminal alkenes **315** by ring closing metathesis (Scheme 65).[109] Thus, imine **313** reacted with vinylmagnesium or allymagnesium bromide to afford **314** and subsequent N-alkylation with allyl bromide gave RCM precursors **315**.

The synthesis of 7-membered α-aminocycloalkane carboxylic acids has been achieved from enantiomerically pure glycine derivatives (*R*)- and (*S*)-*tert*-butyl 2-(*tert*-butyl)-3-methyl-4-oxo-1-imidazolidinecarboxylate (Boc-BMI).[110] Commercially available (*S*)-Boc-BMI **318** was stepwise dialkylated to give geminally 5,5-disubstituted imidazolidinones **320**. TFA deprotection of the Boc group followed by intramolecular cyclization afforded bicyclic derivatives **322**. Subsequent hydrolysis of these cyclized compounds followed by ion-exchange chromatography provided the cyclic amino acids **323** in 70–90% yields (Scheme 66).

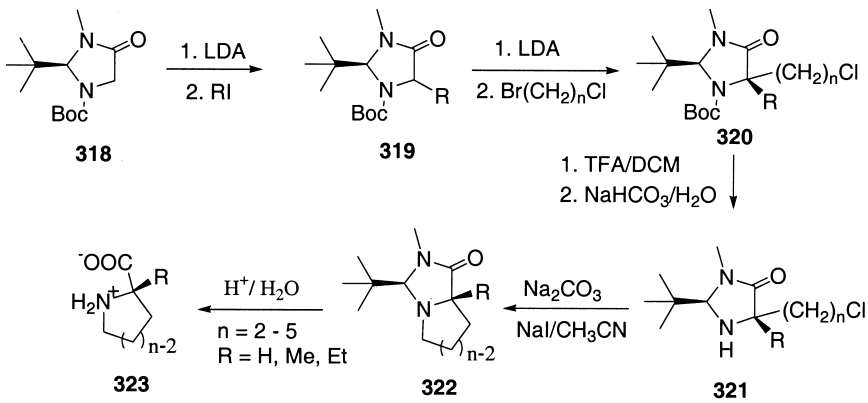
Highly functionalized 7-membered cyclic α-amino acid **330** has also been prepared in the course of the synthesis of (2*S*,4*S*,6*S*)-2-amino-4,6-dihydroxypimelic acid **329** (Scheme 67).[111] Thus, a $SnCl_4$-catalyzed carbonyl-ene



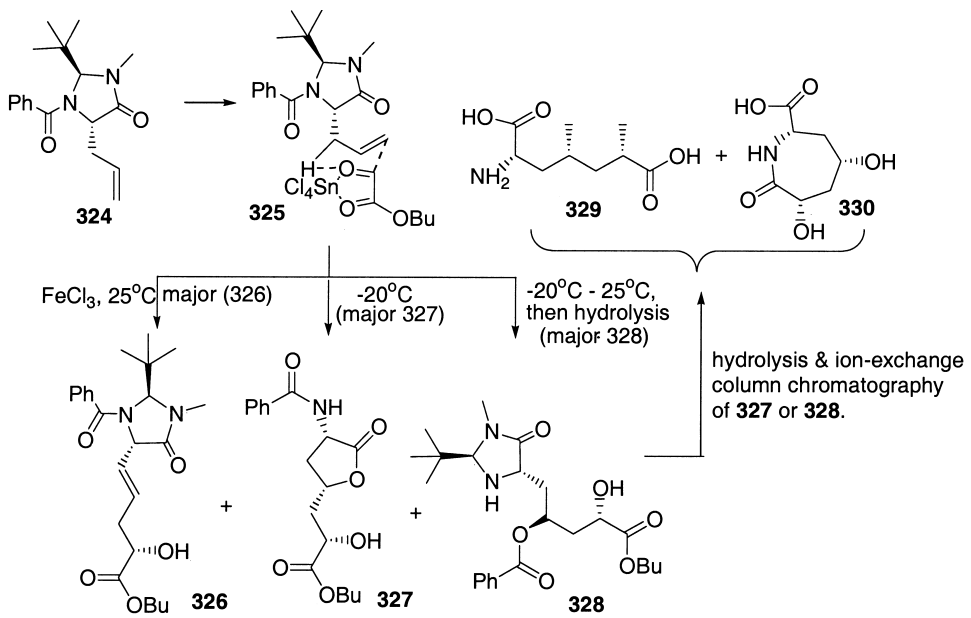
Scheme 64.



Scheme 65. (a) $CH_2{=}CHCH_2MgBr$/THF or $CH_2{=}CHMgBr$/THF, then HCl; (b) NaH, DMF, allyl bromide.



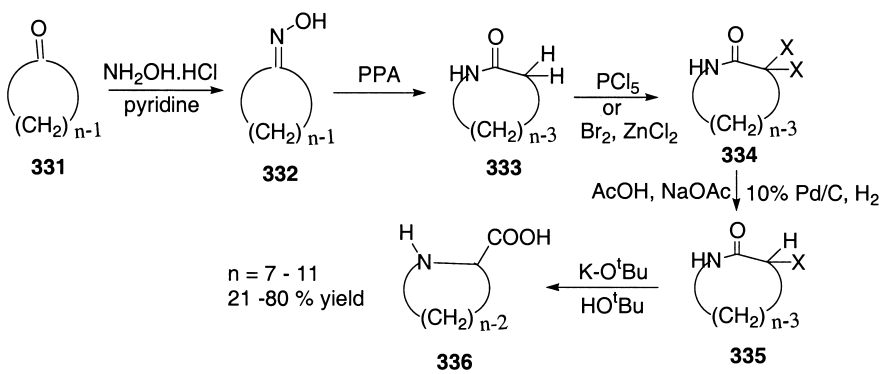
Scheme 66.



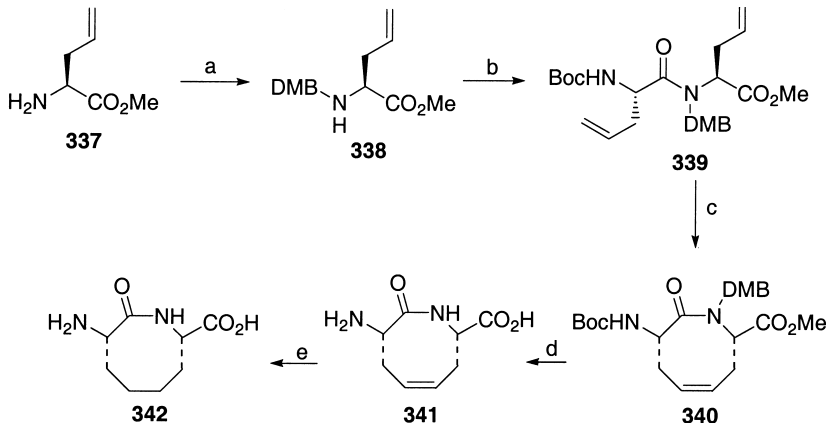
Scheme 67.

reaction of 5-(2-propenyl)-imidazolidinone **324** with butyl glyoxylate resulted in a mixture of ene product **326**, lactone **327**, and rearranged ene product **328**. Via chair-like transition state **325**, the C–C bond is formed by a *re–si* interaction between the allylic double bond and glyoxylate carbonyl group. Acidic hydrolysis of both **327** and **328**, followed by ion exchange chromatography, provided highly functionalized amino acid **329** (74–86%) as well as minor amounts (15%) of 7-membered cyclic α-amino acid **330**.

Favorskii rearrangement[112] of α-halocycloalkanones is another method for the preparation of cyclic α-amino acid derivatives (Scheme 68).[113] Thus, starting cyclic ketones **331** were converted into alicyclic ketoximes **332**, which in turn underwent a Beckmann rearrangement in the presence of polyphosphoric acid (PPA) to afford the corresponding lactams **333**. These lactams were dihalogenated to give α,α-dihalolactams **334**, which were then converted into mono halogenated lactams **335** via catalytic hydrogenolysis.



Scheme 68.



Scheme 69. (a) 2,4-Dimethoxybenzaldehyde, $NaBH(Oac)_3$, >95%; (b) Boc-allylglycine-OH, HATU, HOAT, NEM, 75%; (c) Grubbs catalyst, reflux, DCM, 60 h, 80%; (d) (1) LiOH, $MeOH/H_2O$, quant; (2) 10% TFA, DCM, 3 h; (3) 1N HCl and lyophilize, 78%; (e) Pd/C, H_2, quant.

The homologous series of cyclic α-amino acids **336** were finally obtained through the smooth Favorskii rearrangement of these halolactams.

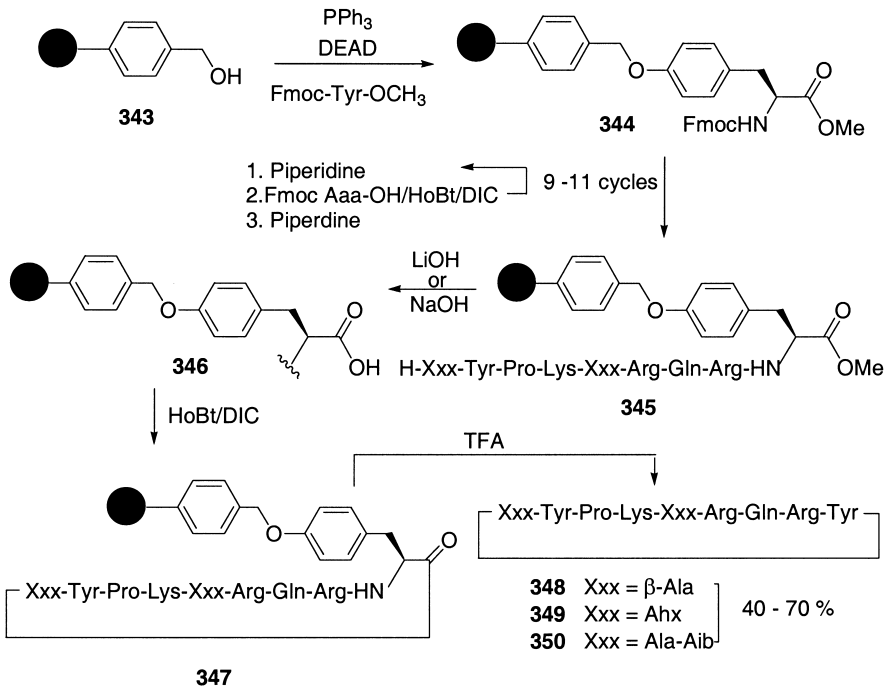
Eight-membered cyclic pseudo-dipeptide **340** has been synthesized using ring closing metathesis (Scheme 69).[114] This 8-membered ring dipeptide may be used as an important scaffold[115] in peptidomimetic research and for studies involving amide self association.[116] The starting material, (*S*)-allylglycine methyl ester **337**, was converted into compound **338** by reductive amination with 2,4-dimethoxybenzaldehyde. Amide bond formation with Boc-(*S*)-allylglycine provided compound **339**, which underwent a RCM reaction to afford protected olefin **340** in 80% yield. Ester hydrolysis (LiOH), followed by deprotection of the Boc and dimethoxybenzyl group, gave pseudo-dipeptide **341**. Reduction of this dipeptide provided saturated pseudo-dipeptide **342** in 60% overall yield from starting material **337**.

Peptide cyclization provides conformationally constrained analogs for probing ligand–receptor interactions and

Table 1. Cyclic peptides synthesized by tyrosine side-chain attachment and resin-bound peptide cyclization

Peptide	AA sequence[a]	Number of backbone atoms
348	Cyclo-(β-Ala-Tyr-Pro-Ser-Lys-β-Ala-Arg-Gln-Arg-**Tyr**)	32
349	Cyclo-(Ahx-Tyr-Pro-Ser-Lys-Ahx-Arg-Gln-Arg-**Tyr**)	38
350	Cyclo-(Ala-Aib-Tyr-Pro-Ser-Lys-Ala-Aib-Arg-Gln-Arg-**Tyr**)	36

[a] The tyrosine side-chain that was attached to the resin is given in bold.



Scheme 70.

structure–activity relationships.[117] Recently, Beck-Sickinger et al. developed a solid-phase synthesis of cyclopeptides by AA side-chain attachment to the resin.[118] Three cyclic analogs of neuropeptides[119] have been synthesized to investigate conformational requirements for receptor affinity and selectivity (Table 1). Thus, HMPB–MBHA resin or Wang resin **343** was coupled with *N*-Fmoc-tyrosine methyl ester by Mitsunobu esterification. Chain assembly of the desired linear peptide methyl ester followed by saponification and subsequent head-to-tail cyclization afforded resin bound cyclic peptide **347**. TFA-mediated resin release gave the targeted cyclic peptides **348**–**350** (Scheme 70).

6. Conclusion

Rigidified α-AAs have played important roles in drug design as well as in the development to effect conformational constraints in peptides. CAA derivatives have been especially interesting targets in peptide-based therapeutics and medicinal chemistry. When incorporated into a peptide chain, these AAs mediate significant changes in peptide conformation, thus facilitating the probe of structural requirements of receptor-bound ligand conformations by affecting the ability of these peptides to fit an enzyme active site. As presented in this review, numerous synthetic methods have been developed to provide a wide range of diverse CAA derivatives.

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Biographical sketch

Kyung-Ho Park was born in 1960 in Kyungpook Cheongdo (Korea). He studied chemistry at Kyungpook National University in Korea (1988), and worked at Korea Research Institute of Chemical Technology (KRICT) until 1995. He obtained his PhD degree on combinatorial synthesis of hydantoins with isoxazoline heterocycle in Professor Mark J. Kurth's group at the University of California, Davis (2000). He joined DuPont CR&D as a research chemist in 2000. His current research interests focus on lead discovery of biologically active small organic molecules as well as new materials via solid-phase combinatorial chemistry.

Mark J. Kurth was born in Iowa in 1953. He received his B.A. degree from the University of Northern Iowa in 1976 where he worked with Professor James G. MacMillan. His PhD degree was from the University of Minnesota (1980) where he worked with Professor Thomas R. Hoye on the total synthesis of brominated marine natural products such aplysistatin. After a postdoctoral study with Professor Wolfgang Oppolzer at the University of Geneva (1980–1981) developing chiral auxiliaries for the Diels–Alder reaction, he joined the chemistry faculty at the University of California/Davis. His current research activities span natural products total synthesis, synthetic methods development, solid-phase organic synthesis and combinatorial chemistry, and polymer synthesis and characterization.