Natural Occurrence, Syntheses, and Applications of Cyclopropyl-Group-Containing α-Amino Acids. 2. 3,4- and 4,5-Methanoamino Acids

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Contents

1. Introduction

One of the reasons that cyclopropyl-group-containing α-amino acids play an outstanding role in biologically important processes, the synthesis of peptide mimetics and modern drug discovery, is their constrained conformational flexibility compared to analogous α-amino acids without the cyclopropyl group. Although all of this essentially started with the first synthesis of 1-aminocyclopropane-1-carboxylic acid (ACC) in 1922,[1] this compound was merely regarded as an interesting structural curiosity. The real interest in the so-called methanoamino acids only began with the discovery that several of them occur as natural products and as such come along with interesting and important biological activities. Ever since, these amino acids have attracted considerable attention of certain biologists and synthetic organic and peptide as well as medicinal chemists. The investigations in this area have been intensified particularly within the last 15 years, when a number of methanoamino acids were found to be valuable entities in pharmacologically relevant compounds. Up to date, several reviews dealing in part[2−4] or exclusively[5−7] with the syntheses and applications of 2,3-methanoamino acids have been published, with the most recent one coming from our own group.[8] Since research toward 3,4- and 4,5-methanoamino acids, also called cyclopropylglycines and cyclopropylalanines, respectively, is the relatively newest area that had attracted little attention until about 20 years ago, its achievements have not been summarized so far. Thus, this review is intented to particularly compile and briefly discuss the biological properties, pharmacological activities, and successful syntheses of these 3,4- and 4,5-methanoamino acids.

2. 3,4-Methanoamino Acids

2.1. Unsubstituted 3,4-Methanoamino Acid (Cyclopropylglycine) and Its Derivatives

Cyclopropylglycine exhibits several interesting biological properties. For example, it was found to act as a noncompetitive inhibitor of *Escherichia coli*, without showing toxic effects in mammalian systems.[9,10] Cyclopropylglycine acts as an alternative substrate for the valyl-transfer ribonucleic

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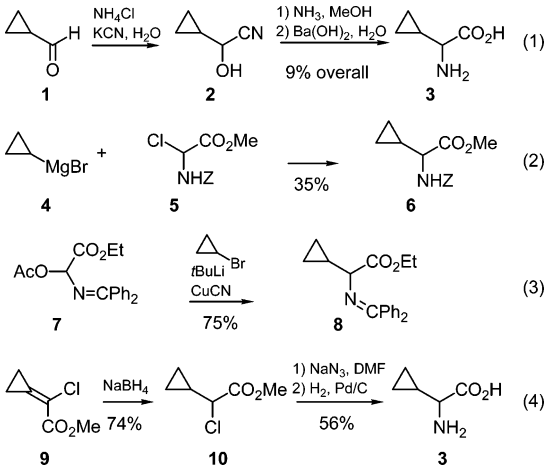
Scheme 1. Syntheses of Racemic Cyclopropylglycine[12−16]



acid (RNA) synthetase; as such, it is more effective than valine itself, and it participates in the adenosine 5′-triphosphate phosphorus-32-phosphate (ATP-$P^{32}P_i$) exchange catalyzed by either valyl-RNA synthetase or leucyl-RNA synthetase.[9,11]

The first synthesis of cyclopropylglycine, originally called α-aminocyclopropylacetic acid, was developed in 1952 with regard to a study of the biological effects of analogues of naturally occurring amino acids. Starting from cyclopropanecarboxaldehyde (**1**), a Strecker synthesis via the cyanohydrine **2** provided access to racemic cyclopropylglycine (**3**) in 9% overall yield (Scheme 1, eq 1). In this context, cyclopropylglycine was found to have a slightly sweet taste.[12]

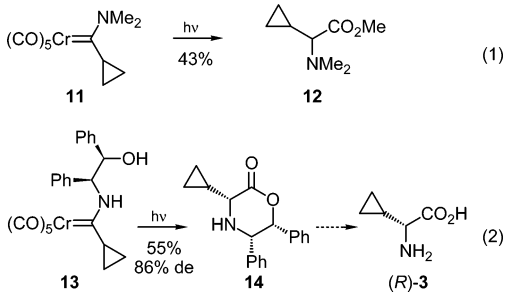
In combination with the design of a synthesis of *β*,*γ*-unsaturated α-amino acids by reaction of electrophilic glycine cation equivalents with Grignard reagents, the racemic *Z*-(benzyloxycarbonyl-) protected methyl cyclopropylglycinate **6** was prepared in a single step from the *Z*-protected methyl amino(chloro)acetate **5** and cyclopropylmagnesium bromide (**4**), albeit in moderate yield only (Scheme 1, eq 2).[13,14] The glycine cation equivalent ethyl 2-acetoxy-2-(diphenylmethylene)aminoacetate (**7**), upon reaction with the cyclopropyl cuprate generated from cyclopropyl bromide with *tert*-butyllithium and cuprous cyanide, furnished the protected cyclopropylglycine **8** in a single operation and good yield (Scheme 1, eq 3).[15] The reaction of a resin-bound glycine cation equivalent, generated by reaction of a resin-bound (acetoxy)-aminoacetate, with the cyclopropylorganoborane generated from cyclopropyllithium and 9-methoxy-9-BBN, was used for a solid-phase synthesis of racemic cyclopropylglycine.[17]

Racemic cyclopropylglycine is also accessible from methyl 2-chloro-2-cyclopropylideneacetate (**9**), which can be reduced with sodium borohydride to methyl 2-chloro-2-cyclopropylacetate (**10**). Nucleophilic substitution of the chlorine in **10** by azide and subsequent catalytic hydrogenation gave unprotected cyclopropylglycine (**3**) (Scheme 1, eq 4).[16]

The synthesis of racemic cyclopropylglycine coordinated to cobalt in the form of its tetramine complex $[Co(NH_3)_4$-CprGly$]^{2+}$ has also been published.[18]

Photolysis of the (dimethylamino)(cyclopropyl)carbenechromium complex **11**, easily available by reaction of *N*,*N*-dimethylcyclopropanecarboxamide with disodium pentacarbonylchromium, furnished methyl *N*,*N*-dimethylcyclopropylglycinate (**12**) (Scheme 2, eq 1).[19] Application of these reaction conditions to the chirally modified (amino)(cyclopropyl)carbenechromium complex **13**, obtained by treatment

Scheme 2. Syntheses of Racemic and Enantiomerically Pure Cyclopropylglycine from Carbenechromium Complexes[19,20]



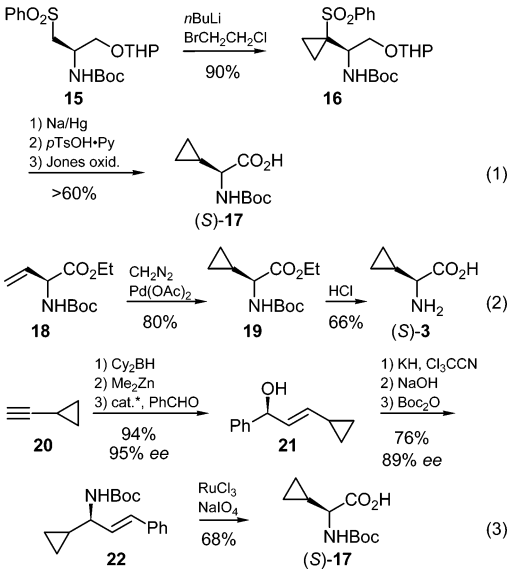
of the corresponding (cyclopropyl)(methoxy)carbenechromium complex with (1*R*,2*S*)-2-amino-1,2-diphenylethanol, afforded the chiral morpholinone derivative **14** in moderate yield with a good diastereomeric excess. Since lactones such as **14** are readily cleaved to free amino acids by hydrogenolysis or lithium in ethanol reduction, this chemistry was claimed to provide a convenient route to (*R*)-cyclopropylglycine (**3**); however, removal of the chiral auxiliary in **14** has not been reported by the authors (Scheme 2, eq 2).[20]

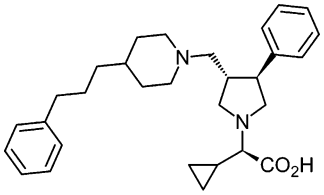
Enantiomerically pure *N*-acetylcyclopropylglycine has been obtained by enzymatic resolution of the corresponding racemate using Acylase I.[21]

In addition, several asymmetric syntheses of cyclopropylglycine have been published. Cyclo-1,1-dialkylation of the phenylsulfonyl-stabilized carbanion, generated from the chiral glycinol building block **15**, with 2-chlorobromoethane gave the cyclopropane derivative **16**, which was further converted by reductive desulfonation, cleavage of the tetrahydropyranyl ether, and oxidation of the resulting primary alcohol to yield *N*-*tert*-butoxycarbonyl-protected (*S*)-cyclopropylglycine (*S*)-**17** (Scheme 3, eq 1). As both enantiomers of the chiral glycinol derivative **15** are available,[22,23] this method offers access to both enantiomers of cyclopropylglycine.[24]

Palladium acetate-catalyzed cyclopropanation with diazomethane of enantiomerically pure ethyl *N*-Boc-vinylglycinate (**18**) provided the corresponding cyclopropylglycine derivative **19**, which was deprotected to furnish (*S*)-**3** (Scheme 3, eq 2).[25]

Scheme 3. Syntheses of Enantiomerically Pure Cyclopropylglycine[24−26]





23

Figure 1. A 2-pyrrolidinylacetic acid derivative featuring a cyclopropylglycine moiety.[27]

Hydroboration of ethynylcyclopropane (**20**) with dicyclohexylborane followed by transmetallation with diethylzinc provided a cyclopropylvinylzinc species which underwent addition to benzaldehyde in the presence of an isoborneol-based chiral catalyst to yield the virtually enantiopure cyclopropylallyl alcohol **21**. Conversion of the latter into its trichloroacetimidate, subsequent [3,3]-sigmatropic rearrangement, and exchange of the trichloroacetyl with an *N-tert*-butoxycarbonyl protecting group yielded the protected allylamine **22** with full retention of the stereochemical information. Oxidative cleavage of **22**, after recrystallization to improve the enantiomeric excess, furnished enantiopure *N-tert*-butoxycarbonyl-protected cyclopropylglycine (*S*)-**17**. As both enantiomers of the chiral catalyst are available, this method offers access to both enantiomers of cyclopropylglycine (Scheme 3, eq 3, only one enantiomer is shown).[26]

The discovery that the β-chemokinine receptor CCR5 is a coreceptor applied by the human immunodeficiency virus (HIV) to gain entry into host cells has sparked the interest in synthesizing small molecules as potential CCR5 antagonists. Within a series of 1,3,4-trisubstituted pyrrolidines, the cyclopropyl(pyrrolidin-1-yl)acetic acid derivative **23** (Figure 1) was prepared and assayed with respect to its antiviral activity. Compared to other pyrrolidine derivatives, however, **23** did not exhibit any adequate activity.[27]

An application of the Ugi four-component reaction to several cyclopropylisonitriles in the presence of cyclopropanecarboxaldehyde, benzylamine (or other primary amines), as well as cyclopropanecarboxylic acid (or other carboxylic acids) provided a series of new dipeptides **24**, each containing a cyclopropylglycine moiety (Figure 2), in yields ranging from 38 to 86%. Several of the dipeptides were very well rigidified and characterized by X-ray crystal structure analysis.[28] These cyclopropyl-group-containing dipeptides, however, have not yet been tested for potential biological activities.

With the intention to unveil selective inhibitors of the peptidylglycine α-hydroxylating monooxygenase (PHM), which were expected to be useful tools in endocrinology, (2*R*)-cyclopropylglycine has been incorporated into the tripeptide **25**, representing a substrate analogue of the naturally occurring tripeptide which contains an unsubstituted glycine moiety (Figure 2). However, the tripeptide **25** proved to act as a poor competitive inhibitor for PHM only.[29]

In order to develop new combined as well as selective antagonists for the Endothelin-1 (ET-1) receptor subtypes, ET_A and ET_B, a variety of peptide analogues of known antagonists have been designed and investigated with respect to their pharmacological characteristics. Among these analogues were several cyclopropylglycine-containing compounds, such as **26** and **27** (Figure 2), which exhibited interesting properties and selectivities toward the ET receptors.[30]

A novel type of oomycete fungicide based on *N*-sulfonyl-amino acid amide mimics has been prepared and assayed

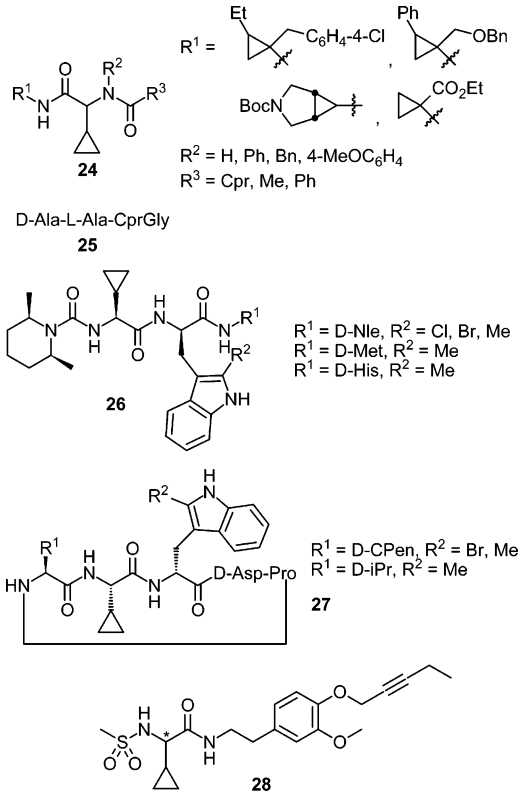


Figure 2. Cyclopropylglycine-containing peptides and peptidomimetics.[29−31]

with respect to its structure−activity relationship, showing that a cyclopropylglycine moiety as in **28** (Figure 2) is tolerated without significantly affecting the fungicidal activity, yet the efficacy was higher for the L- than for the D-enantiomer.[31]

2.2. 2-Amino-2-(1-hydroxycyclopropyl)acetic Acid [(1-Hydroxycyclopropyl)glycine]

Cleomycin **29** is a macrocyclic antitumor agent which belongs to the family of bleomycin−phleomycin antibiotics. Cleomycin **29** contains one unit of (*S*)-cleonine **30**, i.e. 2-amino-2-(1-hydroxycyclopropyl)acetic acid (Figure 3), which can be considered as a 3,3-ethano analogue of serine.[32,33]

An early synthesis of racemic cleonine started with protection of the hydroxy group in cyclopropanone cyanohydrin **31** as an ethoxyethyl ether. Subsequent cautious reduction and hydrolysis afforded the protected aldehyde **32**, which was converted into the aminonitrile **33**. Hydrolysis

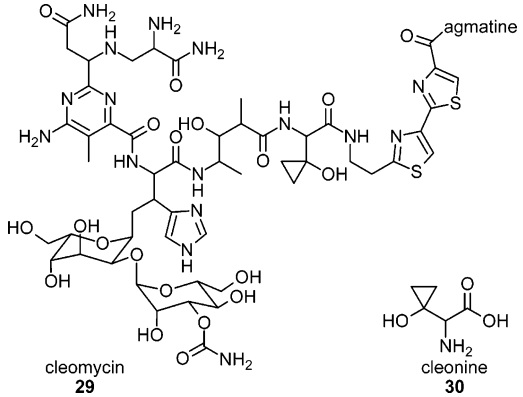
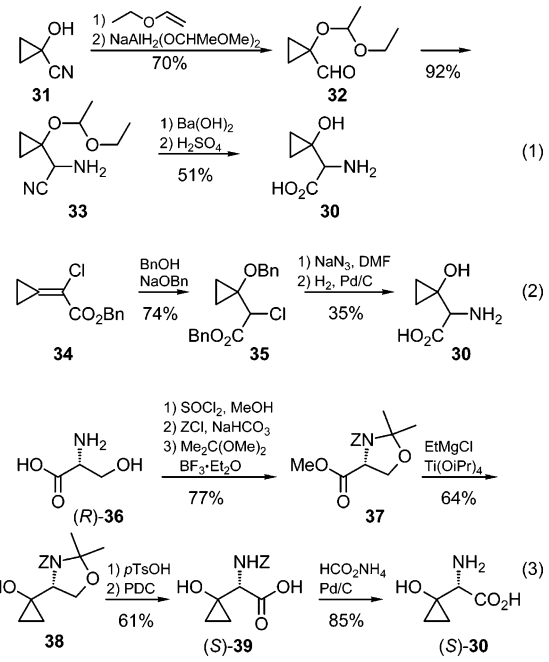


Figure 3. The natural product cleomycin containing the 3,4-methanoamino acid cleonine.[32,33]

Scheme 4. Syntheses of Racemic and Enantiomerically Pure Cleonine[16,32,34]



of the cyano group in **33** and cleavage of the acetal furnished racemic cleonine **30** (Scheme 4, eq 1).[32]

Racemic **30** is also available from benzyl 2-chloro-2-cyclopropylideneacetate (**34**) via the Michael adduct **35** of benzylalcohol formed under base catalysis. Nucleophilic substitution of the chlorine by azide and subsequent hydrogenolysis provided unprotected cleonine **30** (Scheme 4, eq 2).[16]

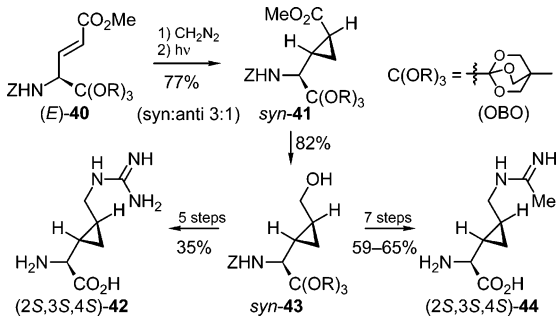
Enantiomerically pure cleonine was prepared starting from the triply protected (*R*)-Z-serine (*R*)-**37**, which is easily available from (*R*)-serine [(*R*)-**36**] by esterification, *Z*-protection of the amino group, and *O,N*-acetalization with acetone dimethyl acetal. Titanium-mediated reductive cyclopropanation of the latter with ethylmagnesium bromide gave rise to the substituted cyclopropanol **38**, the *O,N*-acetal of which was cleaved followed by oxidation of the liberated hydroxymethyl group to furnish the *Z*-protected amino acid (*S*)-**39**. The latter was deprotected to (*S*)-cleonine (*S*)-**30** (Scheme 4, eq 3). In the context of this study, cleonine was also incorporated into a dipeptide with alanine.[34]

The titanium-mediated reductive cyclopropanation of **37** was also carried out in the presence of 1-hexene and the *O*-silyl-protected 1-penten-5-ol as well as 4-phenyl-1-butene, respectively, under ligand exchange conditions, to yield precursors to the 2-butyl-, 2-hydroxylpropyl-, and 2-phenylethyl-substituted analogues of **38** as mixtures of two diastereomers, each of which was further transformed into the corresponding protected 2-substituted cleonine analogue.[34]

2.3. 3,4-Methanoarginine

Arginine and its structural analogues attract considerable attention in the context of nitric oxide synthase (NOS) substrates as well as inhibitors. In order to evaluate the potency and selectivity for human NOS isoform inhibition, conformationally restricted, optically pure *syn*- and *anti*-3,4-methanoarginine were synthesized. 1,3-Dipolar cycloaddition of diazomethane onto the enantiopure (*E*)-dehydroglutamate derivative (*E*)-**40**, obtained by Wittig alkenation of protected serine aldehyde, and subsequent photolytic fragmentation of the formed pyrazoline gave the cyclopropane derivative **41**

Scheme 5. Syntheses of Enantiomerically Pure 3,4-Methanoarginine and a Derivative Thereof (Only Transformations of the *syn*-Isomers Are Shown)[35,36]



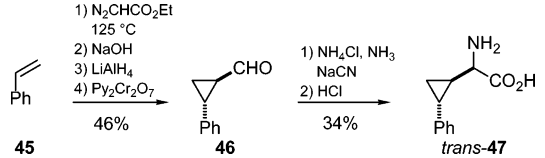
as a separable mixture of two diastereomers. Further conversion of *syn*-**41** by reduction of the carboxyl group afforded the hydroxymethyl derivative *syn*-**43**. Under Mitsunobu-reaction conditions with protected guanidine as the nucleophile, *syn*-**43** gave the protected precursor to 3,4-methanoarginine, which was eventually transformed into *N*-benzyloxycarbonyl-protected (2*S*,3*S*,4*S*)-3,4-methanoarginine **42** (Scheme 5). Alternatively, the hydroxymethyl functionality in *syn*-**43** was converted into an aminomethyl group, and this was subsequently acetimidated. Separation of the diastereomers and removal of the protecting groups furnished the arginine-derived (2*S*,3*S*,4*S*)-3,4-methano-*N*-(1-iminoethyl)-L-ornithine [(2*S*,3*S*,4*S*)-**44**] (Scheme 5). Analogous transformations of *anti*-**43** provided access to (2*S*,3*R*,4*R*)-3,4-methanoarginine [(2*S*,3*R*,4*R*)-**42**] and (2*S*,3*R*,4*R*)-3,4-methano-*N*-(1-iminoethyl)ornithine [(2*S*,3*R*,4*R*)-**44**], respectively.[35,36]

Evaluation of compounds **42** and **44** as potential inhibitors of the three isoforms of nitric oxide synthase determined the arginine derivative (2*S*,3*S*,4*S*)-**42** to be a poor substrate of NOS while the (2*S*,3*R*,4*R*)-isomer of **42** was found to be a poor inhibitor, albeit without any isoform selectivity. Compound (2*S*,3*S*,4*S*)-**44** as well as the (2*S*,3*R*,4*R*)-isomer of **44** exhibited competitive inhibitory activity against NOS in a time-dependent manner, with a selectivity for inducible NOS (iNOS), but not for neuronal (nNOS) or endothelial NOS (eNOS), whereas the (2*S*,3*S*,4*S*)-**44** isomer turned out to be the more potent and selective one.[36]

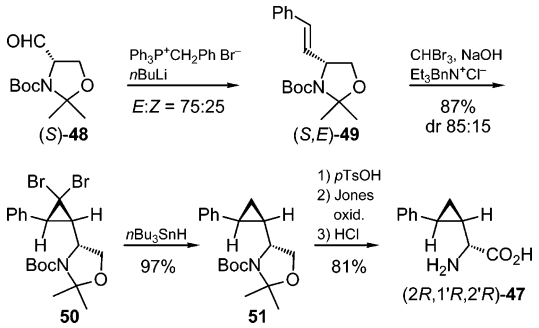
2.4. 3,4-Methanohomophenylalanine [(2-Phenylcyclopropyl)glycine]

An access to racemic *trans*-3,4-methanohomophenylalanine starts with the cyclopropanation of styrene **45** by thermal addition of ethyl diazoacetate to yield ethyl *trans*-2-phenylcyclopropanecarboxylate. Hydrolysis of the latter, reduction to the corresponding hydroxymethyl derivative, and reoxidation led to *trans*-2-phenylcyclopropanecarbaldehyde (**46**), which was converted by a Strecker synthesis to racemic *trans*-3,4-methanohomophenylalanine (**47**) (Scheme 6). The silver(I) peroxydisulfate-induced oxidative decarboxylation of *trans*-3,4-methanohomophenylalanine has served as a chemical model system for reactions catalyzed by monoamine oxidase.[37]

Scheme 6. Preparation of Racemic *trans*-3,4-Methanohomophenylalanine[37]



Scheme 7. Preparation of (2*R*,1′*R*,2′*R*)-3,4-Methanohomophenylalanine[38]

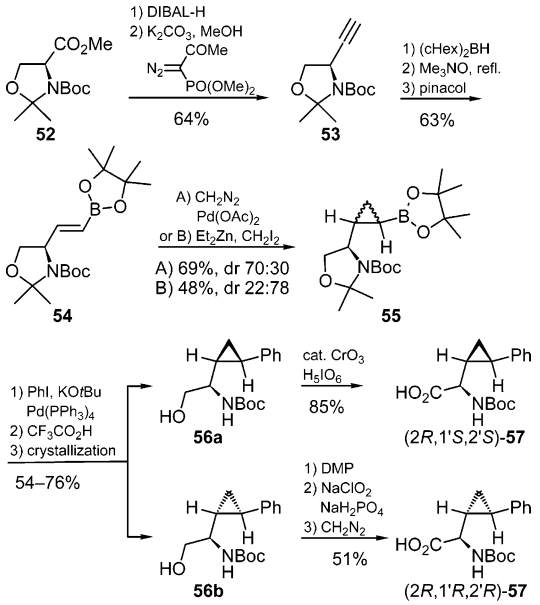


An asymmetric synthesis of 3,4-methanohomophenylalanine started with a Wittig alkenation of the Garner aldehyde (*S*)-**48**, employing the ylide generated from benzyltriphenylphosphonium bromide, to give an easily separable mixture of (*E*)- and (*Z*)-isomers of the corresponding styrene derivative **49**. Subsequent cyclopropanation of the (*E*)-isomer (*S*,*E*)-**49** with bromoform under phase-transfer catalysis provided the corresponding *trans*-disubstituted 1,1-dibromocyclopropane derivatives, the major diastereomer **50** of which was reductively debrominated with tributyltin hydride to yield **51**. Cleavage of the *O*,*N*-acetal, Jones oxidation, and final deprotection led to (2*R*,1′*R*,2′*R*)-3,4-methanophenylalanine [(2*R*,1′*R*,2′*R*)-**47**] (Scheme 7). The same sequence of transformations applied to the (*R*)-enantiomer of **48** gave (2*S*,1′*S*,2′*S*)-**47**.[38]

The synthesis of enantiomerically pure 3,4-methanohomophenylalanine has also been achieved involving a Suzuki coupling of a cyclopropaneboronic acid ester as the key step. Toward that end, the acetonide-protected serine **52** was reduced to the Garner aldehyde **48**, which was directly treated with dimethyl 1-diazo-(2-oxopropyl)phosphonate (Bestmann-Ohira reagent), furnishing the ethynyloxazolidine derivative **53**. The latter was hydroborated with dicyclohexylborane. Subsequent oxidation with trimethylamine *N*-oxide and esterification with pinacol provided the pinacol alkenylboronate **54**, which, by palladium-catalyzed cyclopropanation with diazomethane, afforded an only partially separable mixture of the corresponding diastereomeric cyclopropane derivatives **55**. Cyclopropanation with diiodomethane/diethylzinc proceeded with reversed diastereoselectivity. Palladium-catalyzed Suzuki cross coupling of the obtained mixture with phenyl iodide followed by cleavage of the *O*,*N*-acetal furnished a separable mixture of the diastereomeric primary alcohols **56a** and **56b**. Oxidation of each of the diastereomers to the corresponding acid either in a one-step or in a two-step procedure yielded (2*R*,1′*S*,2′*S*)- and (2*R*,1′*R*,2′*R*)-3,4-methanohomophenylalanine in its *N*-Boc-protected form **57** (Scheme 8).[39]

All four *trans*-isomers of enantiopure 3,4-methanohomophenylalanine and aryl-substituted derivatives thereof were prepared along an enantioselective route starting from (2*E*)-1-(2-furyl)-3-arylprop-2-en-1-ones **58**, which are accessible by cross aldol reactions of acetylfuran with different aromatic aldehydes. Cyclopropanation of **58** with dimethylsulfoxonium ylide yielded the cyclopropyl ketones **59** as single diastereomers, which were stereoselectively transformed into the corresponding (*E*)-oximes (*E*)-**60** or the (*Z*)-oximes (*Z*)-**60**, respectively. Subsequent protection of the hydroxy group as the benzyl ether followed by enantioselective reduction with borane-dimethyl sulfide in the presence of a chiral oxazaborolidine catalyst, generated in situ from borane-

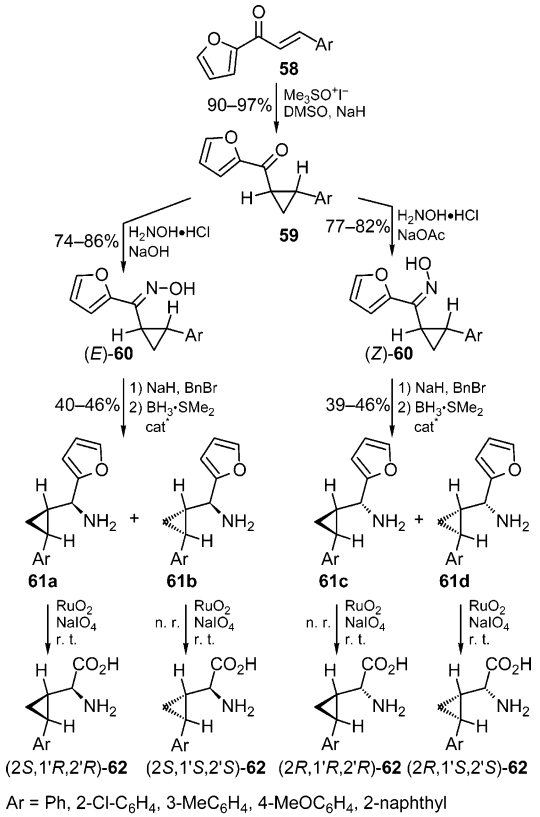
Scheme 8. Synthesis of Enantiopure 3,4-Methanohomophenylalanine[39]



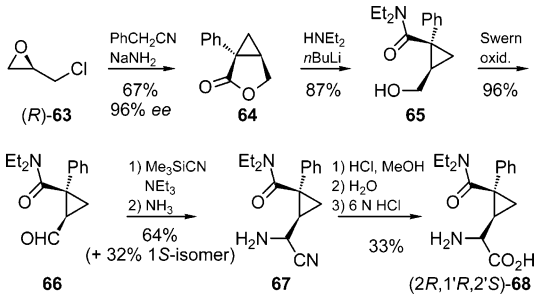
dimethylsulfide and an enantiomerically pure 2-aminoalcohol, provided a separable mixture of (2-arylcyclopropyl)-2-furylmethanemines **61a** and **61b** or **61c** and **61d**, respectively. Oxidative cleavage of the furan ring in each of the four diastereomers with in situ generated ruthenium tetroxide gave the four diastereomeric 3,4-methanohomoarylalanines **62**, each in enantiomerically pure form (Scheme 9).[40]

Milnacipran, (±)-*Z*-2-aminomethyl-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide, is a clinically effective antide-

Scheme 9. Enantioselective Syntheses of *trans*-3,4-Methanohomophenylalanine and Derivatives Thereof[40]



Scheme 10. Synthesis of 4-Diethylaminocarbonyl-3,4-methanophenylalanine[41,42]



pressant due to its competitively inhibiting the re-uptake of serotonin (5-HT) in the central nervous system (CNS). As milnacipran has been found to act also as an *N*-methyl-D-aspartate (NMDA) receptor antagonist, attempts have been made to improve its low affinity toward the NMDA receptor. Among other analogues, the corresponding cyclopropylglycine derivative (2*R*,1′*R*,2′*S*)-**68** was synthesized via the lactone **64**, readily available by reaction of (*R*)-epichlorohydrin (**65**) with deprotonated phenylacetonitrile. Treatment of **64** with lithium diethylamide gave the ring-opened product **65**, which was oxidized to the aldehyde **66**.[41] Conversion of **66** into the cyanohydrin **67** followed by hydrolysis provided the 4-diethylaminocarbonyl-substituted 3,4-methanophenylalanine (2*R*,1′*R*,2′*S*)-**68** (Scheme 10). However, (2*R*,1′*R*,2′*S*)-**68** neither showed affinity toward the NMDA receptor nor acted as a 5-HT uptake inhibitor.[42]

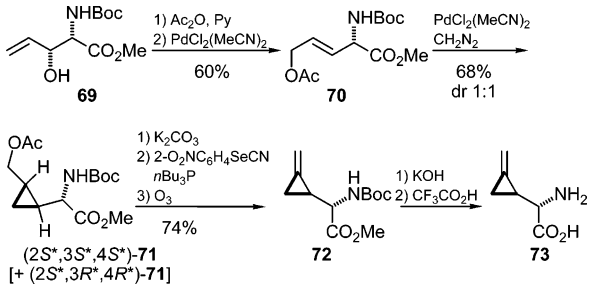
2.5. (2-Methylenecyclopropyl)glycine

(2-Methylenecyclopropyl)glycine (**73**) was first isolated from lychee seeds, *Litchi chinensis*,[43] and later found to also be present in seeds of *Billia hippocastanum* and fruits of *Acer pseudoplatanus*.[44−46] This amino acid is known for its strong hypoglycemic activity due to the ability of its toxic metabolite (2-methylenecyclopropyl)formyl-CoA to block the β-oxidation pathway of fatty acid metabolism.[43,47−49] Besides, **73** was found to exhibit antimutagenic activity spontaneous mutations against *Salmonella typhimurium* TA 100.[50]

Up to now, only one synthesis leading to (2-methylenecyclopropyl)glycine in its racemic form has been published. It starts from the protected *syn*-β-ethenylserine **69**, readily available by selenium oxide or *tert*-butyl hydroperoxide oxidation of the corresponding allylglycine derivative. Palladium-catalyzed [3,3]-sigmatropic rearrangement of the allyl acetate derived from **69** afforded the (acetoxypropenyl)-glycine **70**, which was cyclopropanated with diazomethane under palladium catalysis to provide a separable mixture of (2*S**,3*S**,4*S**)-**71** and (2*S**,3*R**,4*R**)-**71**. Removal of the acetyl group in the (2*S**,3*S**,4*S**)-isomer, subsequent *ortho*-nitrophenylselenenylation of the resulting alcohol with *ortho*-nitrophenylselenenyl cyanide in the presence of tri-*n*-butylphosphine, and oxidative elimination of the selenide residue with ozone yielded the methylenecyclopropane derivative **72**, final hydrolysis and deprotection of which gave a single diastereomer of (2-methylenecyclopropyl)glycine (**73**) (Scheme 11).[51]

In addition to (2-methylenecyclopropyl)glycine itself, the preparation of the fluoro-substituted analogue 2-(2,2-difluoro-3-methylenecyclopropyl)glycine (F_2MCPG) has been described, applying a selenoxide elimination or a difluorocyclopropyl-anion promoted β-elimination of a suitable silyl derivative. Thus, the cyclopropylmethanol derivative

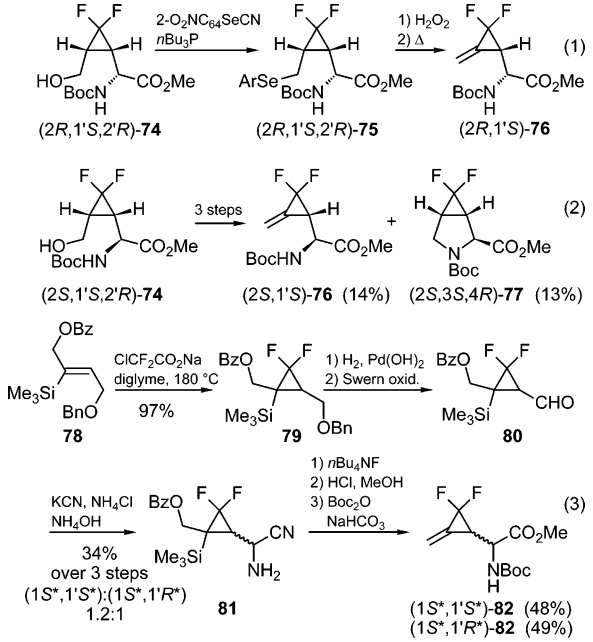
Scheme 11. Synthesis of Racemic (2-Methylenecyclopropyl)glycine[51]



(2*R*,1′*S*,2′*R*)-**74** (obtained in a six-step sequence of transformations from **231**, see section 2.7.4, Scheme 40) was converted to the arylseleno derivative (2*R*,1′*S*,2′*R*)-**75**, which was oxidized to the corresponding selenoxide, and the latter was subsequently thermally eliminated to yield (2*R*,1′*S*)-2-(2,2-difluoro-3-methylenecyclopropyl)glycine in its protected form **76** (Scheme 12, eq 1). Application of this reaction sequence to the (2*S*,1′*S*,2′*R*)-isomer of **74** afforded a mixture of the desired protected (2*S*,1′*S*)-2-(2,2-difluoro-3-methylenecyclopropyl)glycine **76** and the bicyclic 1′,1′-difluoromethanoproline derivative (2*S*,3*S*,4*R*)-**77** (Scheme 12, eq 2).[52]

Addition of difluorocarbene to the alkene **78** yielded the 1-benzoyloxymethyl-1-(trimethylsilyl-3,3-difluorocyclopropylmethyl benzyl ether **79**. Debenzylation and Swern oxidation of the latter gave the aldehyde **80**, which was further converted by a Strecker reaction to furnish a separable mixture of two diastereomeric aminonitriles **81**. Each diastereomer of **81** was subjected to a fluoride-induced Peterson-type β-elimination to yield the corresponding methylenecyclopropane derivative. Methanolysis of the cyano group and final protection of the amino function furnished *N*-*tert*-butoxycarbonyl-protected (2*S**,1′*S**)- and (2*S**,1′*R**)-2-(2,2-difluoro-3-methylenecyclopropyl)glycine **82** (Scheme 12, eq 3).[53]

Scheme 12. Synthesis of 2-(2,2-Difluoro-3-methylenecyclopropyl)glycine[52,53]

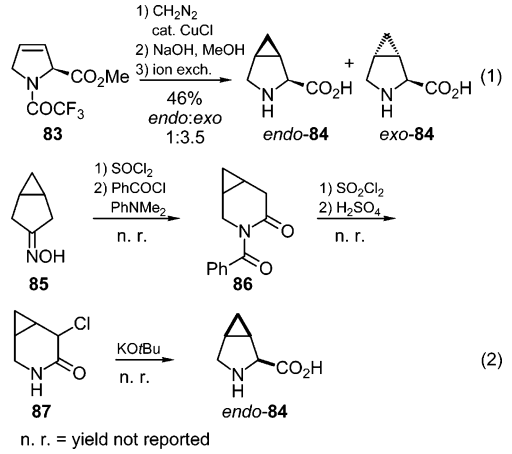


2.6. 3,4-Methanoproline

endo-3,4-Methanoproline (*endo*-**84**)[54]—sometimes wrongly referred to as *cis*-3,4-methanoproline in the literature—was isolated from seeds of *Aesculus parviflora*,[55] from *Ephedra foeminea*, and from *Ephedra foliata*[56] along with, what probably is its biogenetic precursor, (2-carboxycyclopropyl)-glycine (see section 2.7), suggesting a biogenetic relationship akin to the one existing between proline and glutamic acid. The conformation of 3,4-methanoproline has been determined by nuclear magnetic resonance studies and X-ray crystal structure analysis to be that of a flat boat.[57,58]

The first synthesis of the 3,4-methanoprolines *endo*-**84** and *exo*-**84** was completed by cuprous chloride-catalyzed cyclopropanation of protected 3,4-dehydro-L-proline **83** with diazomethane, furnishing a 1:3.5 mixture of *endo*- and *exo*-**84** (Scheme 13, eq 1).[58] The separation of the *endo*- and *exo*-isomers was achieved by selective crystallization of suitable derivatives.[59]

Scheme 13. Syntheses of Racemic 3,4-Methanoproline[58,60]

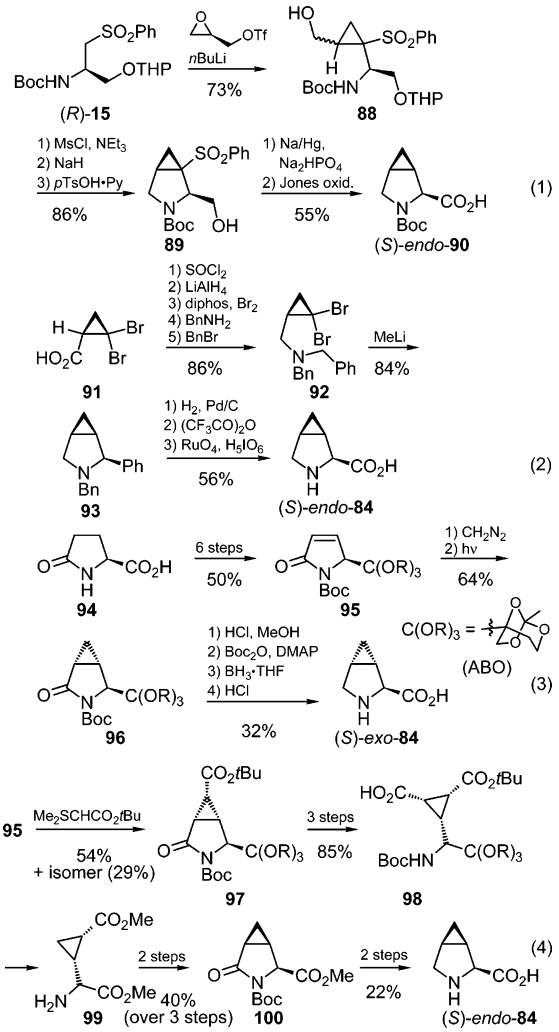


Racemic *endo*-3,4-methanoproline (*endo*-**84**) has also been synthesized starting with a Beckmann rearrangement of 3-hydroxyiminobicyclo[3.1.0]hexane (**85**), initiated by thionyl chloride, and subsequent benzoylation to give the bicyclic *δ*-lactam **86**. Chlorination of the latter, removal of the *N*-benzoyl group, and Favorski-type ring contraction of the resulting **87** by treatment with potassium *tert*-butoxide then gave racemic *endo*-3,4-methanoproline (*endo*-**84**) (Scheme 13, eq 2).[60]

Several stereoselective approaches to enantiomerically pure 3,4-methanoprolines **84** have been developed. Thus, cyclo-1,1-dialkylation of the chiral enantiopure protected amino-hydroxypropyl phenyl sulfone (*R*)-**15** with oxiran-2-ylmethyl triflate provided the cyclopropane derivative **88**, the mesylate of which was subjected to a base-induced cyclization. Subsequent cleavage of the tetrahydropyranyl ether in the resulting **89**, reductive removal of the sulfonyl group, and, finally, Jones oxidation gave rise to *N*-*tert*-butoxycarbonyl-protected enantiomerically pure (*S*)-*endo*-3,4-methano-L-proline (*S*)-*endo*-**90** (Scheme 14, eq 1).[61]

Enantiopure 2,2-dibromo-1-cyclopropanecarboxylic acid (**91**), obtained by oxidative cleavage of the vinyl group in 1,1-dibromo-2-vinylcyclopropane and subsequent optical resolution, was converted into its acid chloride. The latter was reduced to the corresponding alcohol, which was transformed to the bromide, and this in turn was first substituted with benzylamine, and then the amino group was further benzylated with benzyl bromide. Treatment of

Scheme 14. Enantioselective Syntheses of Enantiomerically Pure 3,4-Methanoprolines[61−63]



1-(dibenzylamino)methyl-2,2-dibromocyclopropane (**92**) with methyllithium generated a cyclopropylidene which underwent insertion into the C−H-bond adjacent to the nitrogen atom to give the *endo*-configured *N*-benzyl-2-phenyl-3-azabicyclo-[3.1.0]hexane (**93**). Ruthenium tetroxide-mediated oxidative degradation of the phenyl group completed the synthesis of (*S*)-*endo*-3,4-methanoproline (**84**) (Scheme 14, eq 2). Applying the same sequence of transformations starting from 2,2-dibromo-1-methylcyclopropanecarboxylic acid provided (*S*)-*endo*-3,4-methano-4-methylproline.[62]

A stereocontrolled approach to (*S*)-*endo*- as well as (*S*)-*exo*-3,4-methanoproline (**84**) has been developed employing the 3,4-didehydropyroglutamate derivative **95** as an enantiopure precursor. The latter was assembled in six steps starting from L-pyroglutamic acid (**94**), involving the installation of the 2,7,8-trioxabicyclo[3.2.1]octyl orthoester (ABO) moiety as a protected carboxyl group, subsequent phenylselenylation, and oxidative deselenylation in order to establish the double bond. Cyclopropanation of the thus obtained **95** by 1,3-dipolar cycloaddition of diazomethane followed by photochemical ring contraction led to the *endo*-configured protected 4-oxo-3-azabicyclo[3.1.0]hexanecarboxylic acid derivative **96**. Cleavage of the ABO group by acid-catalyzed methanolysis, chemoselective reduction of the lactam carbonyl group, and final deprotection of the amino acid functionality furnished enantiomerically pure (*S*)-*exo*-3,4-methanoproline [(*S*)-*exo*-**84**] (Scheme 14, eq 3). When the

cyclopropanation of **95** was carried out with *tert*-butyl dimethylsulfuranylideneacetate, a separable mixture of the *exo,endo*-**97** and the corresponding *exo,exo*-**97** was obtained. Chemoselective ring opening of the lactam in **97** offered access to the *all-cis*-trisubstituted cyclopropane derivative **98**, which, upon treatment with methanolic acid and subsequent Barton decarboxylation, gave protected *cis*-(2-methoxycarbonylcyclopropyl)glycine **99**. Ensuing intramolecular lactamization yielded the *endo*-isomer of the methyl 4-oxo-3-azabicyclo[3.1.0]hexanecarboxylate **100**, which was further converted by chemoselective reduction of the lactam carbonyl group and final liberation of the amino acid functionality to provide (*S*)-*endo*-3,4-methanoproline [(*S*)-*endo*-**84**] (Scheme 14, eq 4).[63] *endo*-3,4-Methanoproline (*endo*-**84**) has also been accessed by base-catalyzed epimerization of the *N*-acylated *exo*-isomer.[64]

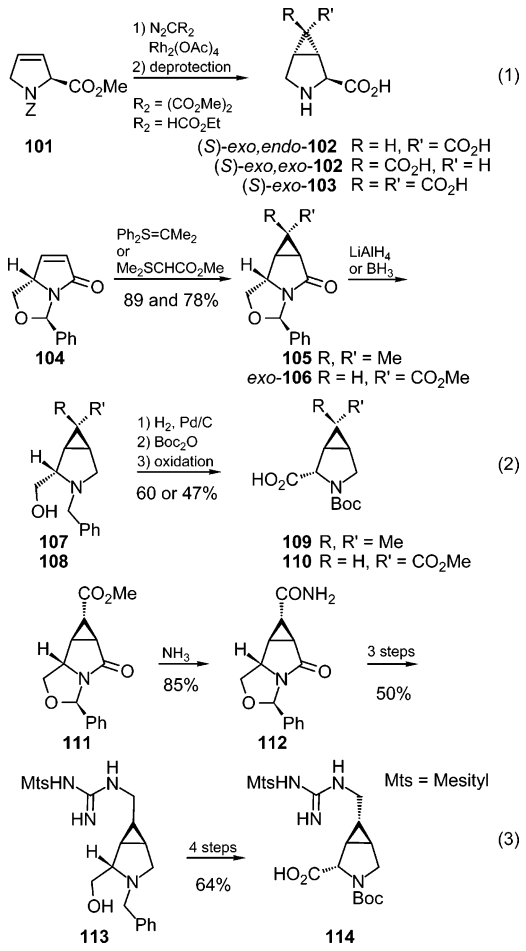
(*S*)-*endo*-3,4-Methanoproline [(*S*)-*endo*-**84**] in its boat conformation was associated with its properties to act as a powerful competitor for proline in, for example, the permease system.[58] A mixture of *endo*- and *exo*-3,4-methanoproline in their racemic forms and their salts have been investigated as potential chemical control agents in the production of hybrid wheats, and as thus, they have been applied for the sterilization of male anthers in plants, in particular in small grain cereals.[65]

Amides of 3,4-methanoproline have been condensed with a variety of amino acids and subsequently dehydratized to furnish the corresponding methanoprolinonitrile dipeptide mimetics. Biological evaluation of the latter for the inhibition of the *N*-terminal sequence-specific serine protease dipeptidyl peptidase IV (DPP-IV), which plays a key role in the degradation of glucose-stimulated insulin secretion and as thus in the treatment of type 2 diabetes, showed that mimetics having incorporated an (*S*)-*endo*-3,4-methanoproline moiety can act as highly potent DPP-IV inhibitors with enhanced stabilities in solution.[66]

Besides 3,4-methanoproline (**84**) itself, several 1′-substituted analogues have been synthesized. Thus, the protected (*S*)-3,4-didehydroproline derivative **101**, prepared from *trans*-4-hydroxy-(*S*)-proline,[67] was cyclopropanated with ethyl diazoacetate in the presence of dirhodium tetraacetate, furnishing a mixture of protected (*S*)-*exo,endo*- and (*S*)-*exo,endo*-(1′-carboxy-3,4-methano)prolines which were deprotected to yield the corresponding free amino acids (*S*)-*exo,endo*-**102** and (*S*)-*exo,exo*-**102** (Scheme 15, eq 1). The two diastereomers of (*R*)-*exo*-(1′-carboxy-3,4-methano)-proline (*R*)-*exo,endo*-**102** and (*R*)-*exo,exo*-**102** were also synthesized according to the same protocol. Application of dimethyl diazomalonate instead of ethyl diazoacetate provided access to (*S*)-*exo*-(1′,1′-dicarboxy-3,4-methano)proline [(*S*)-*exo*-**103**] (Scheme 15, eq 1). All of the thus synthesized methanoprolines were evaluated with respect to their activity toward ionotropic and metabotropic glutamate receptors, but none of the four diastereomers of **102** exhibited any remarkable activity. In contrast, (*S*)-*exo*-(1′,1′-dicarboxy-3,4-methano)proline [(*S*)-*exo*-**103**] showed good neuroprotective activity in a concentration-dependent manner when evaluated against *N*-methyl-D-aspartate (NMDA) and kainate (KA) induced toxicity in cultured cortical neurons.[68,69]

The unsaturated pyroglutamic acid-derived lactam **104**, accessible from the corresponding saturated derivative, was cyclopropanated with diphenylsulfonium isopropylide to yield the tricyclic product **105**. Reductive cleavage of the *O,N*-acetal provided **107**; exchange of the *N*-protecting group

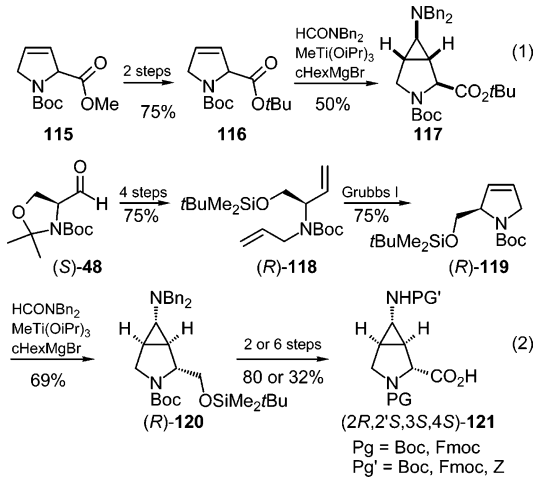
Scheme 15. Syntheses of 1′-Substituted 3,4-Methanoproline Derivatives[68−71]



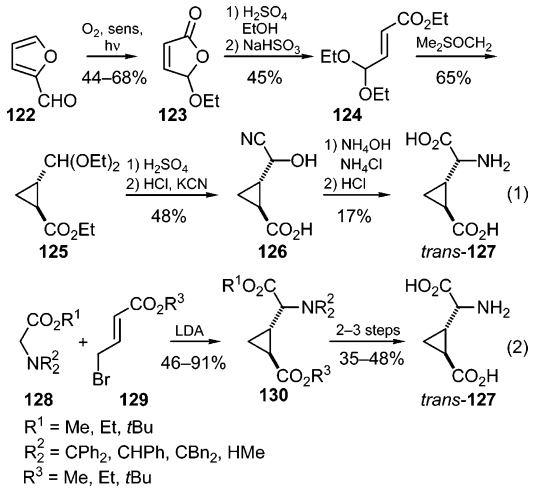
and subsequent Jones oxidation of the alcohol gave the protected *exo*-(1′,1′-dimethyl-3,4-methano)proline **109** (Scheme 15, eq 2).[70,71] Upon cyclopropanation of **104** with dimethylsulfonium methoxycarbonylmethylide, the tricycle **106** was obtained as a mixture of *exo*- and *endo*-isomers (R = CO_2-Me, R′ = H, structure not shown). Further conversion of *exo*-**106**, in analogy to that of **105**, yielded the protected *exo*-(1′-carboxy-3,4-methano)proline **110** (Scheme 15, eq 2). Tripeptides of **109** as well as of **110** have been synthesized, and their conformations have been analyzed by NMR and molecular modeling studies.[70,72] In addition, the tricycle **111** has been converted into the bicyclic arginine analogue **114** by aminolysis to the amide **112**, subsequent reduction to the amine and cleavage of the *O,N*-acetal, solid-phase guanidinylation of the (1′-aminomethyl-3,4-methano)proline, introduction of a mesityl (Mts) group on the guadinyl moiety, and final oxidation (Scheme 15, eq 3).[71] Several different 1′-guanidinylmethyl-substituted 3,4-methanoproline derivatives corresponding to **114** with different substituents on the guanidine moiety were incorporated into two model pentapeptides.[73]

Adopting a published procedure, *N*-Boc-2,5-didehydropyrrole was converted into racemic methyl 3,4-didehydroprolinate (**115**),[74] and this was converted to the *tert*-butyl ester **116** in order to protect that particular carbonyl functionality against attack of the organometallic reagent in the subsequent titanium-mediated reductive aminocyclopropanation with *N,N*-dibenzylformamide. This transformation proceeded diastereoselectively, yielding the racemic protected 3,4-(aminomethano)proline (Amp) **117**. Applying the same

Scheme 16. Syntheses of Some More 1′-Substituted 3,4-Methanoproline Derivatives[75,76]



Scheme 17. Syntheses of Racemic *trans*-(2-Carboxycyclopropyl)glycine[80−85]



sequence of transformations to the enantiomerically pure *tert*-butyl ester (2*S*)-**116**, obtained from *trans*-4-hydroxy-L-proline,[67] gave virtually enantiomerically pure 3,4-(aminomethano)proline in its protected form (2*S*)-**117** (Scheme 16, eq 1), and the latter was incorporated into model tripeptides containing glycine, alanine, and phenylalanine moieties.[75]

An access to enantiomerically pure 3,4-(aminomethano)-proline (**121**) equipped with various protecting groups has been developed starting from the readily available Garner aldehyde (*S*)-**48**.[77] Wittig alkenation of the latter, cleavage of the *O*,*N*-dimethyl acetal, and subsequent silyl-protection of the hydroxy function followed by *N*-allylation afforded the allylvinylglycinol derivative (*R*)-**118**. Ring-closing cross metathesis of (*R*)-**118** to the 3,4-dehydroprolinol derivative (*R*)-**119** and subsequent titanium-mediated aminocyclopropanation with *N*,*N*-dibenzylformamide gave the protected 3,4-(aminomethano)prolinol derivative (*R*)-**120** as a single diastereomer. The latter served as a versatile starting material for the introduction of various *N*,*N*′-protecting groups before final Jones oxidation to the corresponding amino acid (2*R*,2′*S*,3*S*,4*S*)-**121** (Scheme 16, eq 2). In addition, the diketopiperazine consisting of two units of protected 3,4-(aminomethano)proline has been prepared and incorporated into foldamers based on γ-Amp units.[76]

2.7. 3,4-Methanoglutamic Acid and Its Derivatives

2.7.1. (2-Carboxycyclopropyl)glycine

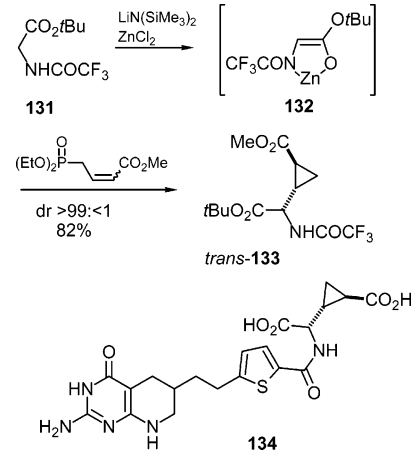
cis-(2-Carboxycyclopropyl)glycine (*cis*-**127**) was isolated from seeds of *Aesculus parviflora* and was found to be a potent inhibitor of the growth of mung bean seedlings. As this inhibition could not be reversed by supply of either glutamic acid or proline, it was concluded that *cis*-**127** does not interfere with the biosynthetic action of glutamic acid.[55] *trans*-(2-Carboxycyclopropyl)glycine (*trans*-**127**) was found to be present in *Blighia sapida* seeds along with the dipeptide γ-L-glutamyl-*trans*-2-L-(2-carboxycyclopropyl)glycine.[55,78] Three diastereomers of (2-carboxycyclopropyl)glycine have been isolated from *Ephedra altissima* and were characterized to be the two *cis*-isomers (2*S*,1′*S*,2′*R*)- and (2*S*,1′*R*,2′*S*)-(2-carboxycyclopropyl)glycine as well as the *trans*-isomer (2*S*,1′*S*,2′*S*)-(2-carboxycyclopropyl)glycine.[56,79]

Several accesses to *trans*-**127** in its racemic form have been developed. Thus, the dihydrofuranone **123** obtained by photooxidation of 2-fururaldehyde (**122**) was converted into ethyl 4,4-diethoxybut-2-enoate (**124**), which turned out to be a suitable starting material for the preparation of ethyl *trans*-2-(diethoxymethyl)cyclopropanecarboxylate (**125**). The latter was obtained from **124** by cyclopropanation with dimethylsulfoxonium methylide. Subsequent cleavage of the acetal to the corresponding aldehyde followed by cyanohydrin formation, conversion of the hydroxyl into an amino group, and final hydrolysis furnished racemic *trans*-(2-carboxycyclopropyl)glycine (*trans*-**127**) (Scheme 17, eq 1).[80]

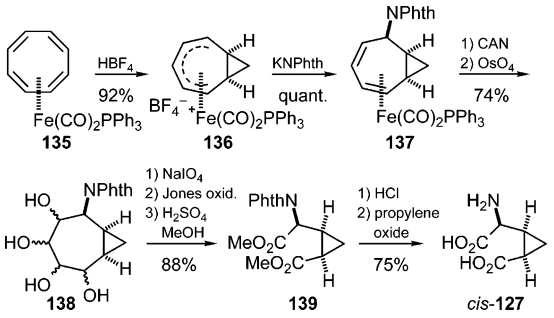
A second *trans*-diastereoselective access to (2-carboxycyclopropyl)glycine **127** was realized by a so-called MIRC (Michael-induced ring closure) sequence. Thus, the enolates of several differently protected glycinates **128** were added to a number of alkyl (2*E*)-4-bromobut-2-enoates **129** to yield, after *trans*-selective cyclizations, the correspondingly protected *trans*-(2-carboxycyclopropyl)glycine derivatives **130**, several of which could be fully deprotected to *trans*-**127** (Scheme 17, eq 2).[81−85]

In a variant of this MIRC-type reaction, *tert*-butyl *N*-trifluoroacetylglycinate (**131**) was deprotonated with lithium bis(trimethylsilyl)amide in the presence of zinc chloride, whereupon the chelated zinc (*Z*)-glycinate enolate **132** was formed. Subsequent trapping of the latter with methyl (*Z*)-4-(diethoxyphosphonyl)but-2-enoate as an electrophile af-

Scheme 18. Synthesis of Racemic *trans*-(2-Carboxycyclopropyl)glycine via a Chelated Zinc Enolate of *t*-Butyl *N*-trifluoroacetylglycinate[86]



Scheme 19. Preparation of *cis*-(2-Carboxycyclopropyl)-glycine Employing Organoiron Chemistry[88]



forded the protected *trans*-(2-carboxycyclopropyl)glycine derivative **133** with excellent *trans*-diastereoselectivity (Scheme 18). The same product **133** was obtained when the reaction was performed using the 4-bromo-(2*E*)-butenoate instead of the (*Z*)-4-phosphonylbutenoate, albeit in poorer yield and with lower diastereoselectivity (Scheme 18).[86]

Compound **134** with a *trans*-(2-carboxylcyclopropyl)-glycine moiety attached in a peptide manner has been synthesized as a conformationally constrained analogue of tetrahydrofolic acid-derived antitumor agents. However, **134** did not exhibit any significant cell growth inhibitory activity (Scheme 18).[87]

cis-(2-Carboxycyclopropyl)glycine (*cis*-**127**) has been prepared employing some organoiron chemistry. Protonation of dicarbonyl(cyclooctatetraene)(triphenylphosphine)iron (**135**) afforded the bicyclo[5.1.0]octadienyliron tetrafluoroborate **136** as a single diasteromer. Reaction of **136** with potassium phthalimide gave the phthalimido-substituted complex **137**, from which the ligand was liberated by oxidation with ceric ammonium nitrate and further hydroxylated with osmium tetroxide to furnish the tetrol **138** as a mixture of two unidentified diastereomers. Subsequent twofold glycol cleavage, Jones oxidation, and esterification afforded the protected *cis*-(2-carboxycyclopropyl)glycine **139**, which could be deprotected to the free amino acid *cis*-**127** (Scheme 19).[88] An asymmetric variant of this methodology using an iron complex analogous to **135**, but endowed with a chiral (−)-neomenthyldiphenylphosphine instead of the triphenylphosphine ligand, was tested; however, the enantiomeric excess in the final product *cis*-**127** was only 38%.[89]

L-Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS), acting through either ligand-gated ion channels, the ionotropic receptors (subclasses: *N*-methyl-D-aspartate NMDA, kainate KA, and α-amino-5-hydroxy-3-methyl-4-isoxazole propionic acid AMPA), or G-protein coupled, metabotropic receptors (subclasses: group I with mGluR 1 and 5, group II with mGluR 2 and 3, and group III with mGluR 4, 6, 7, and 8). Interaction with these receptors is envisaged as a potential target for the treatment of CNS disorders, such as Alzheimers or Parkinsons, for example, requiring intensive studies of the specific task of each receptor subtype.

In view of the discovery that L-glutamic acid adopts a specific conformation during its neurobiological interaction with the receptors of some neurons, the conformationally restricted form of glutamine, (2-carboxycyclopropyl)glycine, was considered to be a valuable tool in the study of mammalian glutamate receptors, as each of the eight possible L- and D-isomers mimics a specific conformation of glutamate, represented by either the extended forms CCG-I and II or the folded forms CCG-III and IV (Figure 4, only the

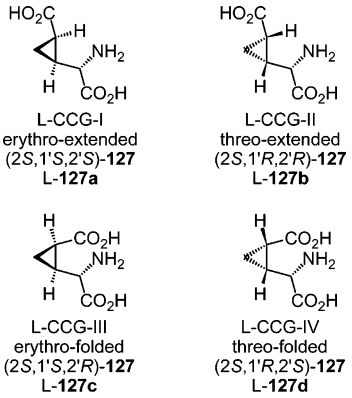


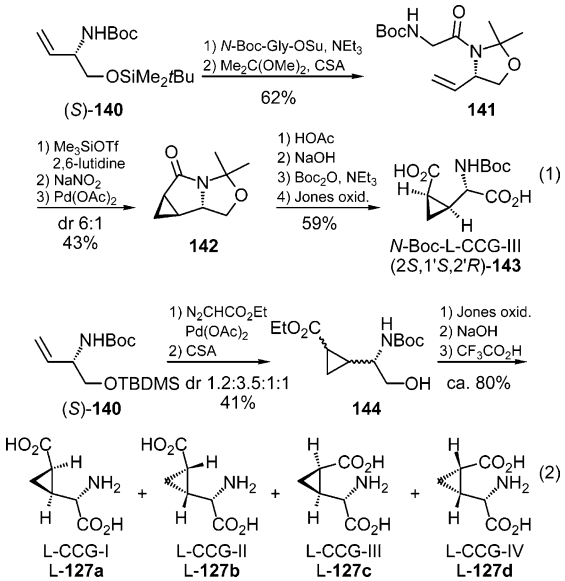
Figure 4. Chemical structures and configurations of L-CCG-I through -IV.

structures of the L-isomers are depicted). Thus, a stereoselective access to each L- as well as D-configured isomer of 2-(carboxycyclopropyl)glycine L-CCG I−IV L-**127a**−**d** and D-CCG I−IV D-**127a**−**d** was indispensable and, consequently, has attracted and still is attracting considerable attention.

The first synthesis of enantiomerically pure L-CCGs started with a peptide coupling and acetalization of the protected (*S*)-vinylglycinol (*S*)-**140**, offering access to the chirally modified glycinamide derivative **141**. Removal of the *tert*-butoxycarbonyl group, subsequent transformation of the α-aminoamide into the corresponding α-diazoamide, and palladium-catalyzed intramolecular cyclopropanation furnished the tricyclic product **142** as the major diastereomer in a separable mixture with a minor diastereomer. Further cleavage of the *O*,*N*-acetal, hydrolysis of the amide, protection of the resulting amine, and Jones oxidation yielded L-CCG-III in its *N*-*tert*-butoxycarbonyl-protected form (2*S*,1′*S*,2′*R*)-**143** (Scheme 20, eq 1).[90,91]

When the vinylglycinol derivative (*S*)-**140** was subjected to an intermolecular cyclopropanation with ethyl diazoacetate, a mixture of all four possible diastereomeric cycloadducts **144** was obtained, the *trans*-isomers of which could be separated after removal of the silyl-protecting group and the *cis*-isomers after δ-lactonization. Subsequent Jones

Scheme 20. Syntheses of L-CCG-I through -IV Starting from Protected Vinylglycinol[90,91]



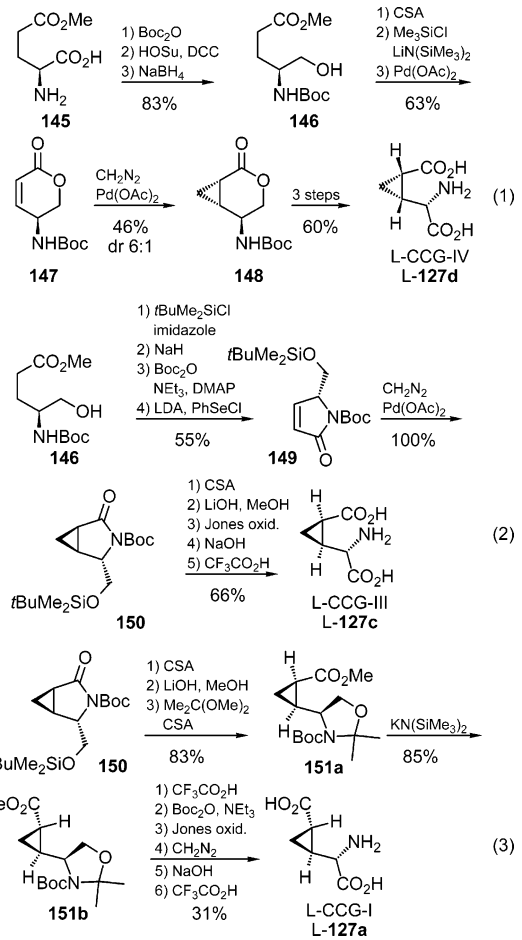
oxidation and removal of the protecting groups of all isomers completed an access to each diastereomer of L-CCG-I−IV **127a**−**d** based on a non-stereoselective method (Scheme 20, eq 2).[90,91]

An enantioselective approach to L-CCG-IV starts with the conversion of the glutamic acid half ester **145** into methyl (*N*-Boc-4-amino)-5-hydroxypentanoate (**146**) by *N*-protection and chemoselective reduction of the carboxylic acid function. Lactonization followed by transformation into the α,β-unsaturated lactone **147** provided a suitable material for a palladium-catalyzed cyclopropanation with diazomethane. The thus obtained bicyclic lactone **148** was hydrolyzed and further transformed by esterification, Jones oxidation, and removal of the protecting groups to yield L-CCG-IV in its free form L-**127d** (Scheme 21, eq 1).[92]

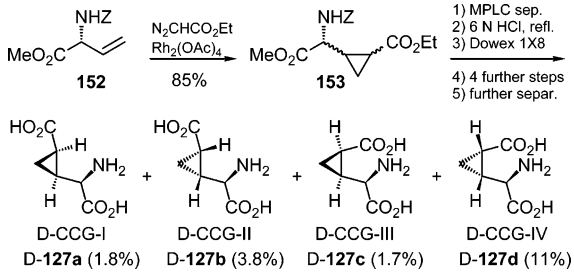
On the other hand, silyl protection of methyl (*N*-Boc-4-amino)-5-hydroxypentanoate (**146**), lactamization, *N*-reprotection, and formal dehydration produced the α,β-unsaturated lactam **149** as an adequate substrate for palladium-catalyzed cyclopropanation with diazomethane to provide the bicyclic lactam **150**. Removal of the silyl group, methanolysis of the amide, oxidation of the hydroxymethyl group, and removal of the protecting groups afforded L-CCG-III in its free form L-**127c** (Scheme 21, eq 2).[92]

Alternatively, the lactam **150** after removal of the silyl group was reprotected as the *O*,*N*-acetonide and the latter subjected to methanolysis to furnish the cyclopropane derivative **151a**. The α-cyclopropyl ester enolate generated from **151a** with potassium bis(trimethylsilyl)amide, upon

Scheme 21. Stereoselective Approach to L-CCG-I, -III, and -IV Starting from L-Glutamic Acid[92,93]



Scheme 22. Nonstereoselective Synthesis of D-CCG-I through -IV by Cyclopropanation of Protected Vinylglycine with Ethyl Diazoacetate[94]



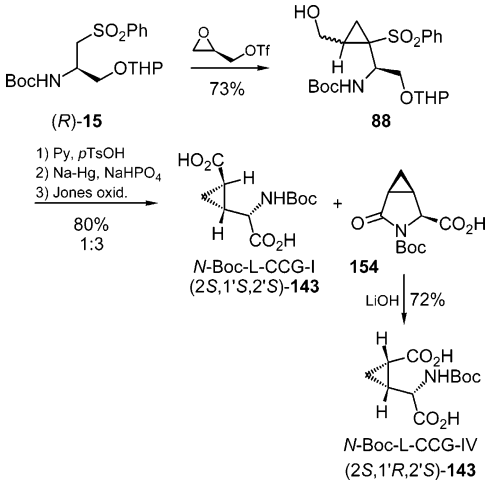
reprotonation, had undergone complete inversion to give the epimer **151b**. Further transformations including Jones oxidation and removal of the protecting groups provided L-CCG-I in its free form L-**127a** (Scheme 21, eq 3).[93]

Dirhodium tetraacetate-catalyzed cyclopropanation of the protected vinylglycine **152** with ethyl diazoacetate furnished a mixture of all four possible diastereomers of the protected (2-carboxycyclopropyl)glycine **153** which could be separated into a mixture of the two *cis*- as well as a mixture of the *trans*-isomers by medium-pressure liquid chromatography (Scheme 22). Further separation into each single diastereomer D-**127a**−**d** was successful after derivatization of the mixtures with (*R*)-2-phenylglycinol.[94]

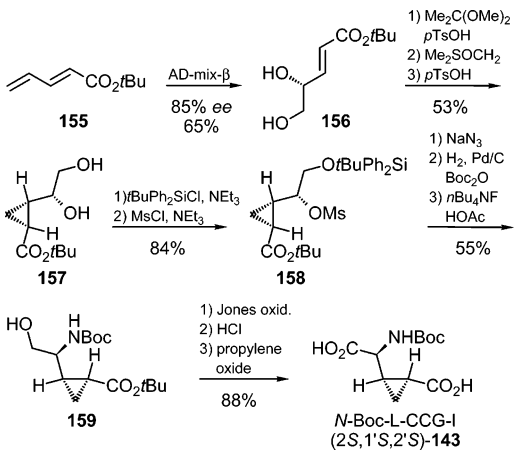
An enantioselective synthesis of L-CCG-IV was accomplished by cyclo-1,1-dialkylation of the enantiomerically pure protected 2-amino-3-hydroxypropyl phenyl sulfone (*R*)-**15** with (*R*)-oxiran-2-ylmethyl triflate, providing the cyclopropane derivative **88**, which was subjected to removal of the tetrahydropyranyl group followed by reductive desulfonylation and Jones oxidation to afford a mixture of *N*-*tert*-butyoxycarbonyl-protected L-CCG-I (2*S*,1′*S*,2′*R*)-**143** and the 3-aza-4-oxobicyclo[3.1.0]hexane derivative **154**, which could easily be separated by crystallization. Hydrolysis of the bicyclic amide **154** led to *N*-protected L-CCG-IV (2*S*,1′*R*,2′*S*)-**143** (Scheme 23).[61]

A stereoselective synthesis of L-CCG-I began with the *tert*-butyl (*E*)-pentadienoate (**155**), prepared from acrolein and *tert*-butyl 2-triphenylphosphoranylideneacetate, which was subjected to a Sharpless asymmetric dihydroxylation to produce the diol **156** with a high enantiomeric excess. Acetal protection of the vicinal diol, subsequent cyclopropanation

Scheme 23. Enantioselective Syntheses of L-CCG-I and L-CCG-IV Starting from an Enantiopure Protected 2-Amino-3-hydroxypropyl Phenyl Sulfone[61]



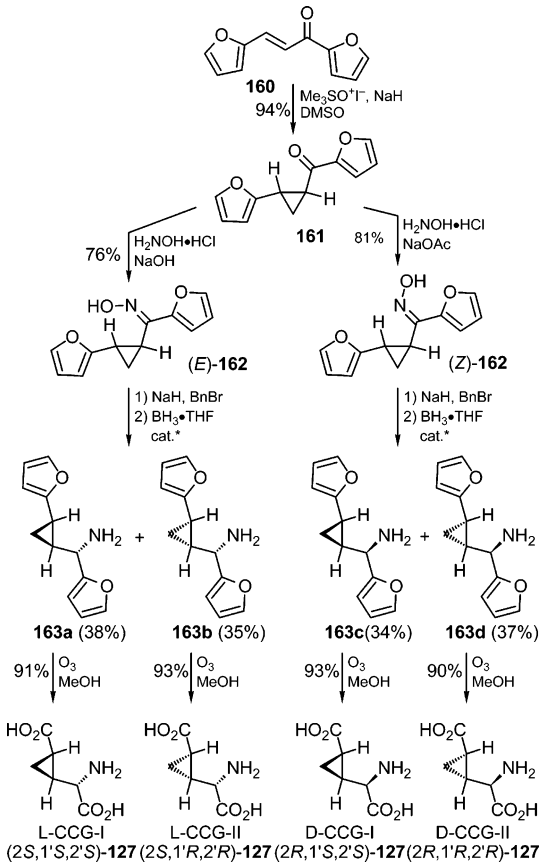
Scheme 24. Stereoselective Synthesis of L-CCG-I Applying a Sharpless Asymmetric Dihydroxylation as the Key Step[95]



using dimethylsulfoxonium methylide, and reliberation of the diol furnished the cyclopropane derivative **157**. Selective protection of the primary hydroxy function was successful with a sterically demanding silyl chloride. Subsequent mesylation of the secondary hydroxy group and substitution of the mesylate in the resulting **158** by an azide group, reduction of the latter to an amino substituent, and removal of the silyl group provided the protected amino alcohol **159**. Final Jones oxidation and hydrolysis afforded the desired *N*-protected L-CCG-I (2*S*,1′*S*,2′*S*)-**143** (Scheme 24).[95]

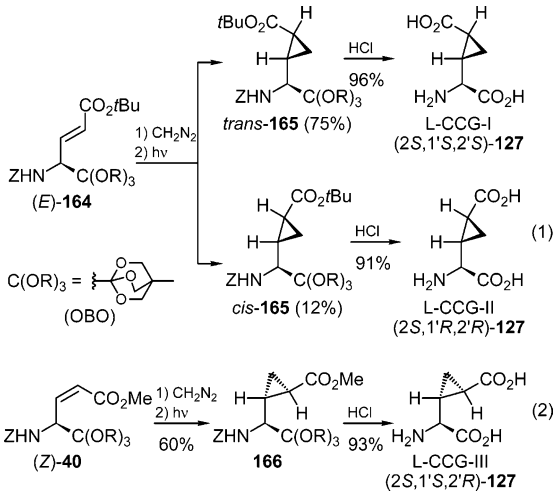
An enantioselective route to all four *trans*-isomers of (2-carboxycyclopropyl)glycine, L- as well as D-CCG-I and -II, started from (*E*)-1,3-di(2-furyl)propenone (**160**), which was synthesized from furfural and 2-acetylfuran. Treatment of

Scheme 25. Synthesis of L- and D-CCG-I and -II Employing Enantioselective Reduction of Oxime Ethers as a Key Step[96]



the enone **160** with dimethylsulfoxonium methylide yielded the cyclopropyl ketone **161**, which was selectively converted into the (*E*)-oxime (*E*)-**162** or the (*Z*)-oxime (*Z*)-**162**. Subsequent *O*-benzylation provided *O*-benzyloximes which could be reduced enantioselectively with borane-tetrahydrofuran in the presence of chiral oxazaborolidine catalysts generated in situ from borane-tetrahydrofuran and different enantiopure amino alcohols. Thus, reduction of the (*E*)-oxime (*E*)-**162** afforded a separable mixture of the enantiopure diastereomeric amines **163a** and **163b**, which were further transformed to L-CCG-I (2*S*,1′*S*,2′*S*)-**127** and L-CCG-II (2*S*,1′*R*,2′*R*)-**127**, respectively, by ozonolysis with workup under oxidative conditions. The analogous reaction sequence applied to the (*Z*)-oxime (*Z*)-**162** gave D-CCG-I (2*R*,1′*S*,2′*S*)-**127** and D-CCG-II (2*R*,1′*R*,2′*R*)-**127** (Scheme 25).[96]

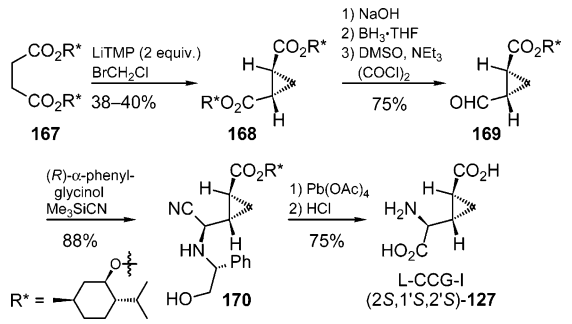
Scheme 26. A Concise Synthesis of L-CCG-I through -III Applying 1,3-Dipolar Cycloadditions of Diazomethane onto Enantiopure 3,4-Didehydroglutamate Derivatives[97]



A concise synthesis of L-CCG-I to -III has been developed based on the stereochemical control of a 1,3-dipolar cycloaddition of diazomethane onto enantiopure L-3,4-didehydroglutamate derivatives (*E*)-**164** and (*Z*)-**40**, which were prepared by stereoselective Wittig alkenation of protected L-serine aldehyde endowed with the bulky 4-methyl-2,6,7-trioxabicyclo[2.2.2]octyl (OBO) orthoester group. Addition of diazomethane to (*E*)-**164** and subsequent photolysis gave a separable mixture of the *trans*- and *cis*-1,2-disubstituted cyclopropane derivatives *trans*-**165** and *cis*-**165**, hydrolysis of which gave rise to L-CCG-I (2*S*,1′*S*,2′*S*)-**127** or L-CCG-II (2*S*,1′*R*,2′*R*)-**127**, respectively (Scheme 26, eq 1). In contrast, cyclopropanation of the (*Z*)-configured acrylate (*Z*)-**40** under the same conditions yielded the cyclopropane derivative **166** as a single diastereomer which was eventually hydrolyzed to L-CCG-III (2*S*,1′*S*,2′*R*)-**127** (Scheme 26, eq 2).[97]

A stereoselective preparation of L-CCG I started with the vicinal cyclodialkylation of the successively generated bis-enolate of (−)-dimenthyl succinate **167** with bromochloromethane in the presence of lithium tetramethylpiperidide to yield (−)-dimenthyl cyclopropane-1,2-dicarboxylate (**168**) with two well-defined stereogenic centers.[98] Partial hydrolysis, chemoselective reduction of the thus obtained monoacid to the primary alcohol, and reoxidation to the corresponding aldehyde gave menthyl 2-formylcyclopropanecarboxylate (**169**). Derivatization utilizing (*R*)-α-phenylglycinol as a chiral auxiliary followed by conversion of the resulting Schiff base into the nitrile provided **170**, which was subjected to

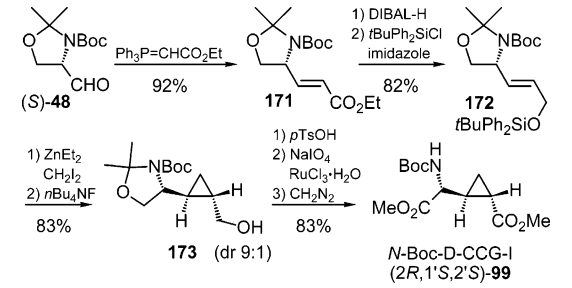
Scheme 27. Preparation of L-CCG-I from (−)-Dimenthyl Succinate[99]



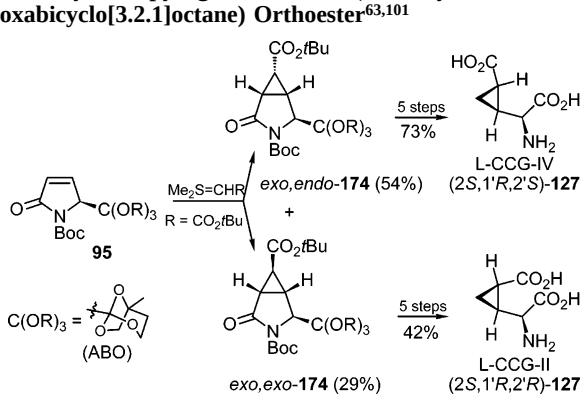
oxidative cleavage and final hydrolysis, yielding L-CCG-I (2*S*,1′*S*,2′*S*)-**127** (Scheme 27).[99]

On the other hand, protected D-CCG-I was synthesized from the readily available enantiopure Garner aldehyde (*S*)-**48**, which, by Wittig alkenation with (ethoxycarbonylmethylene)triphenylphosphorane, provided the ethyl 4-amino-5-hydroxy-(2*E*)-pentenoate derivative **171**. The latter was reduced to the allyl alcohol, and this in turn was protected as the silyl ether **172**. Simmons−Smith-type cyclopropanation with diiodomethane/diethylzinc and removal of the silyl group afforded the cyclopropane derivative (2*R*,1′*S*,2′*S*)-**173** as the major isomer in a separable mixture with the (2*R*,1′*R*,2′*R*)-diastereomer. Hydrolysis of the *O*,*N*-acetal in (2*R*,1′*S*,2′*S*)-**173**, subsequent oxidation of the two hydroxymethyl groups, and final esterification furnished the dimethyl ester of D-CCG-I in its *N*-*tert*-butoxycarbonyl-protected form (2*R*,1′*S*,2′*S*)-**99**-Boc (Scheme 28).[100] The *N*-*tert*-butoxycarbonyl-protected dimethyl ester of L-CCG-III (2*R*,2′*S*,2′*S*)-**99** was also synthesized as an intermediate en route to (*S*)-*endo*-3,4-methano-L-proline [(*S*)-*endo*-**84**] (see section 2.6, Scheme 14), which was converted into its fully deprotected form (2*R*,2′*S*,2′*S*)-**127** by acid hydrolysis.[63,101]

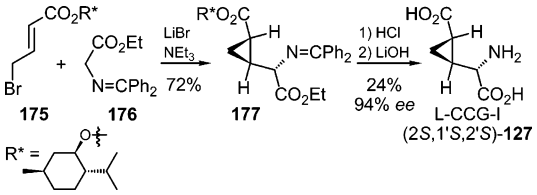
Scheme 28. Synthesis of Protected D-CCG-I Employing a Simmons−Smith-Type Cyclopropanation on a Chirally Modified Allyl Alcohol Derivative[100]



Scheme 29. An Approach to L-CCG-II and L-CCG-IV Applying a Stereocontrolled Cyclopropanantion of the 3,4-Didehydro-L-pyroglutamic ABO (5-Methyl-2,7,8-trioxabicyclo[3.2.1]octane) Orthoester[63,101]



Scheme 30. Synthesis of L-CCG-I by a Michael-Induced Ring Closure (MIRC) Reaction[102]



The cyclopropanation of the enantiopure 3,4-didehydro-4-pyroglutamine orthoester **95** with *tert*-butyl dimethylsulfuranylideneacetate provided the 3-aza-4-oxabicyclo[3.1.0]-hexanedicarboxylic acid derivative **174** as a separable mixture of the two diastereomers *exo*,*endo*-**174** and *exo*,*exo*-**174**. Chemoselective ring opening of the lactam in **174**, subsequent Barton decarboxylation, and final hydrolysis gave rise to L-CCG-IV (2*S*,1′*R*,2′*S*)-**127** starting from *exo*,*endo*-**174** and L-CCG-II (2*S*,1′*R*,2′*R*)-**127** from *exo*,*exo*-**174**, repectively (Scheme 29).[63,101]

A Michael-induced ring closure (MIRC) reaction of the glycinate enolate generated from ethyl (diphenylmethyleneamino)acetate (**176**) with the enantiopure (−)-menthyl 4-bromocrotonate (**175**) furnished the cyclopropane derivative **177** as a single diastereomer. Successive acid- and base-catalyzed hydrolysis of the ester and Schiff-base functionalities led to enantiomerically pure L-CCG-I (2*S*,1′*S*,2′*S*)-**127** (Scheme 30).[102]

In contrast, an analogous MIRC reaction carried out with an (*R*)-camphor-derived imine of *tert*-butyl glycinate and methyl (2*E*)-4-bromobut-2-enoate gave a mixture of four, only partially separable diastereomers of the corresponding cyclopropyl derivative.[103]

Different diastereomeric (2-carboxycyclopropyl)glycines in enantiopure form have played an important role in a variety of pharmacological investigations and studies concerning the involvement of the neurotransmitter L-glutamate and glutamate receptors in integrative brain functions of the mammalian central nervous system (CNS).

Thus, submission of L-CCG-I−IV to a neurobiological assay with β-hydroxy-L-glutamate-sensitive neurons induced a variety of depolarizing effects and indicated a conformation−activity relationship between the L-glutamate analogues, as only the folded forms L-CCG-III and L-CCG-IV were recognized by the *N*-methyl-D-aspartate (NMDA) receptor, and the extended conformers L-CCG-I and L-CCG-II were recognized by the metabotropic receptor. The folded isomers L-CCG-III and IV as well as all four D-CCG-isomers were classified as NMDA receptor agonists, as their effects were almost completely blocked by several NMDA receptor antagonists whereas both L-CCG-IV as well as D-CCG-II exhibited an about five times higher depolarizing effect than NMDA itself.[90,91,104,105]

All four isomers of D-CCG were evaluated with respect to their affinity toward the three subclasses of ionotropic glutamate receptors. In these studies, D-CCG-III was shown to be the most selective NMDA receptor agonist up to date, with an affinity of almost a magnitude higher than that of the prototypic agonist L-glutamate.[94] This, to a certain extent, contradicts earlier reports.[104,105]

L-CCG-I was assumed to exhibit agonist activity at metabotropic glutamate receptors,[105] which, by detailed

studies of its electrophysical action, was later proven to be true.[106,107] Further analysis of the agonist properties at the metabotropic receptor subclasses mGluR1, mGluR2, and mGluR4 of all eight CCG isomers revealed that L-CCG-II exhibits affinities for mGluR1 and mGluR2 receptor subtypes only, whereas L-CCG-I showed agonist properties toward all three of the examined receptor subtypes. Although, in the first instance, L-CCG-I was claimed to be a potent and selective agonist for mGluR2 with a potency of more than an order greater than the one of glutamate itself,[108] L-CCG-I was subsequently proven to activate principally all mGluR subtypes, albeit with different potencies and an up to ten times higher activity than that of glutamate itself. Thus, L-CCG-I has served as a pharmacological tool for distinguishing and examining metabotropic glutamate receptor subtypes.[109−113]

A significant increase in the intracellular Ca^{2+} ion concentration was induced by L-CCG-IV, making L-CCG-IV a more than 100 times more potent elevator of the Ca^{2+} ion concentration than NMDA. Additionally, L-CCG-IV was found to exhibit morphological and biochemical neurotoxicity.[114,115]

Among the four L-isomers investigated, L-CCG-III was shown to be a potent competitive inhibitor of glutamate uptake in neurons and glial cells of the mammalian central nervous system, whereas L-CCG-IV exhibited only a weak inhibition, and the extended forms L-CCG-I and II were inactive.[116] In studies directed toward the characterization of sodium-dependent L-[^{3}H]-glutamate transport in the cerebellum and the cortex, L-CCG-II was identified to be the most potent and selective inhibitor of transport activity in the cerebellum. L-CCG-I also suppressed this activity, albeit with lower potency than that of L-CCG-II.[117]

2.7.2. (2,3-Dicarboxycyclopropyl)glycine

With the intention to improve the pharmacological properties of 2-(2-carboxycyclopropyl)glycine, the extended and folded conformations were unified in one molecule, leading to stereodefined 2-(2,3-dicarboxycyclopropyl)glycines. Thus, a hybridization of L-CCG-I and L-CCG-IV is resembled by L-DCG-1/4, later called L-DCG-IV, and the hybrid of L-CCG-II and L-CCG-III corresponds to L-DCG-2/3 (Figure 5).

The first ever developed access to L-DCG-IV suffered from the burden of requiring more than 20 steps with poor overall yield. The Garner aldehyde (*R*)-**48** as a readily available enantiopure starting material was subjected to a stereoelective Wittig alkenation with methyl [bis(trifluoroethoxy)phosphoryl]acetate, to yield the corresponding (*Z*)-alkene. Subsequent reduction of the methoxycarbonyl to a hydroxymethyl functionality, cleavage of the *O*,*N*-acetal, peptide coupling with *N*-Boc-protected glycine, reintroduction of the acetonide moiety, and silyl protection of the allyl alcohol functionality afforded the intermediate (*Z*)-**179** with a (*Z*)-configured double bond. Chemoselective removal of the *N*-*tert*-butoxycarbonyl group and diazotation of the resulting α-amino-

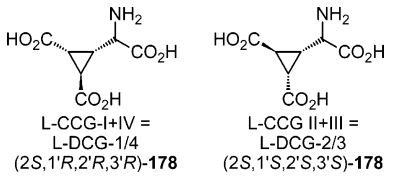
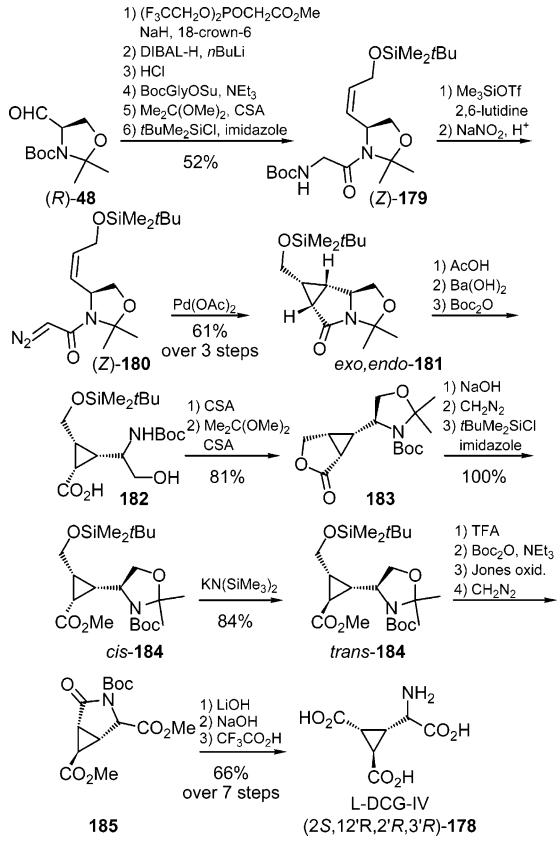


Figure 5. Chemical structures and configurations of the hybrids L-DCG-1/4 (L-DCG-IV) and L-DCG-2/3.

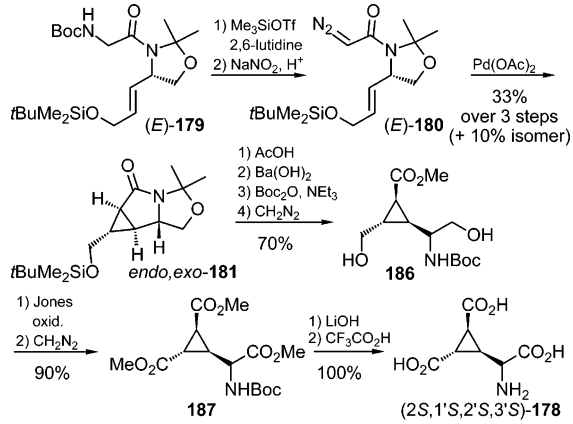
Scheme 31. The First Synthesis of (2*S*,1′*R*,2′*R*,3′*R*)-2-(2,3-Dicarboxycyclopropyl)glycine, L-DCG-IV[118,119]



amide furnished the α-diazoamide (*Z*)-**180**, which, upon treatment with palladium acetate, yielded the *exo*,*endo*-3-aza-4-oxobicyclo[3.1.0]hexane derivate *exo*,*endo*-**181**, albeit in a separable mixture with the corresponding *endo*,*endo*-product (ratio 3.3:1). Cleavage of the *O*,*N*-acetal in *exo*,*endo*-**181**, hydrolysis of the lactam, and protection of the thus liberated amino and hydroxy functionalities afforded the cyclopropane derivative **182**,[118] which was further transformed into the acetonide *cis*-**184** via the lactone **183**. The methyl cyclopropanemonocarboxylate *cis*-**184** with its *O*,*N*-acetal moiety could be epimerized at C-2′ under catalysis of potassium bis(trimethylsilyl)amide. Simultaneous removal of the *O*,*N*-acetonide as well as the silyl group ensued, and subsequent Jones oxidation of the two hydroxymethyl groups was accompanied by formation of the corresponding γ-lactam, which was isolated as the dimethyl ester **185**. Hydrolytic opening of the lactam moiety followed by stepwise removal of the protecting groups completed the first access to L-DCG-IV in its fully unprotected form (2*S*,1′*R*,2′*R*,3′*R*)-**178** (Scheme 31).[119]

When the Garner aldehyde (*R*)-**48** was submitted to a Wittig reaction using methyl [bis(2,2,2-trifluoroethoxy)-phosphoryl]acetate, the (*E*)-alkene corresponding to the precursor to (*Z*)-**179** was obtained and could be further transformed analogously to the intermediate (*E*)-**179** to provide access to the α-diazoamide (*E*)-**180**. Palladium acetate-catalyzed intramolecular cyclopropanation of (*E*)-**180** gave the *endo*,*exo*-3-aza-4-oxobicyclo[3.1.0]hexane derivative *endo*,*exo*-**181** in a separable mixture with the corresponding *exo*,*exo*-isomer. Subsequent removal of the protecting groups and hydrolysis of the lactam afforded the corresponding cyclopropanemonocarboxylic acid, which was

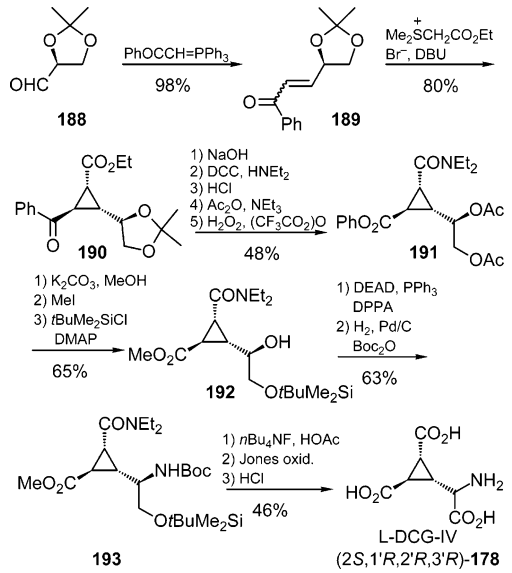
Scheme 32. The First Synthesis of (2*S*,1′*S*,2′*S*,3′*S*)-2-(2,3-Dicarboxycyclopropyl)glycine[118,119]



isolated as the methyl ester in its *N*-*tert*-butoxycarbonyl-protected form **186**.[118] Subsequent Jones oxidation and esterification furnished **187**, which, upon hydrolysis, gave rise to the (2*S*,1′*S*,2′*S*,3′*S*)-isomer of 2-(2,3-dicarboxycyclopropyl)glycine **178** (Scheme 32).[119]

The preparation of L-DCG-IV has also been accomplished by applying a stereocontrolled cyclopropanation of an enone derived from (*S*)-glyceraldehyde acetonide. Toward that end, a mixture of the (*E*)- and (*Z*)-isomers of the enone **189** was prepared by a Wittig alkenation of (*S*)-glyceraldehyde acetonide (**188**) with 1-phenyl-2-(trimethylphosphoranylidene)ethanone. Cyclopropanation of this mixture with ethyl (dimethylsulfuranylidene)acetate produced the cyclopropanecarboxylate **190** as a single diastereomer. To avoid lactonization at a later stage, the ester group of **190** was transformed into an amide by hydrolysis and condensation with diethylamine. After replacement of the acetonide on the vicinal diol by two acetyl groups, the phenyl ketone could be transformed to a phenyl ester by Baeyer−Villiger oxidation to yield **191**. Hydrolysis of the acetoxy groups as well as the phenyl ester, reaction with iodomethane, and protection of the primary hydroxy function as a silyl ether afforded the trisubstituted cyclopropane derivative **192**. This secondary alcohol was subjected to a Mitsunobu reaction to introduce an azide functionality, which was subsequently reduced to

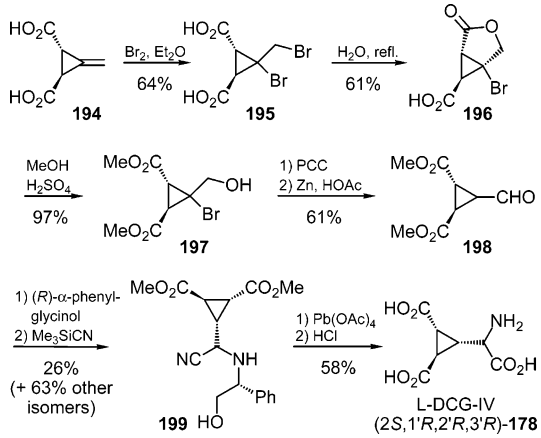
Scheme 33. Synthesis of L-DCG-IV by Cyclopropanation of an Enone Derived from (*S*)-Glyceraldehyde Acetonide[120,121]



an amino group, and the product was isolated in its *N*-*tert*-butoxycarbonyl-protected form **193**. Removal of the silyl protecting group, Jones oxidation, and final hydrolysis gave rise to L-DCG-IV (2*S*,1′*R*,2′*R*,3′*R*)-**178** (Scheme 33).[120,121]

A comparably short synthesis of L-DCG-IV has been accomplished starting from enantiopure Feist's acid **194**.[122] Bromination of **194** and reaction of the resulting dibromide **195** with water gave the bromolactone **196**. Transesterification of the lactone moiety in **196** with methanol under acid catalysis led to the alcohol **197**. Oxidation of the latter to the corresponding α-bromoaldehyde and subsequent reductive dehalogenation furnished dimethyl 3-formylcyclopropane-*trans*-1,2-dicarboxylate (**198**), which was submitted to a diastereoselective Strecker synthesis involving the condensation of **198** with (*R*)-α-phenylglycinol to induce the (*S*)-configuration at the thus newly formed stereocenter. However, a mixture of four aminonitriles was obtained, from which the isomer **199** was separated and subjected to oxidative cleavage as well as subsequent hydrolysis to yield L-DCG-IV in its free form (2*S*,1′*R*,2′*R*,3′*R*)-**178** (Scheme 34).[123]

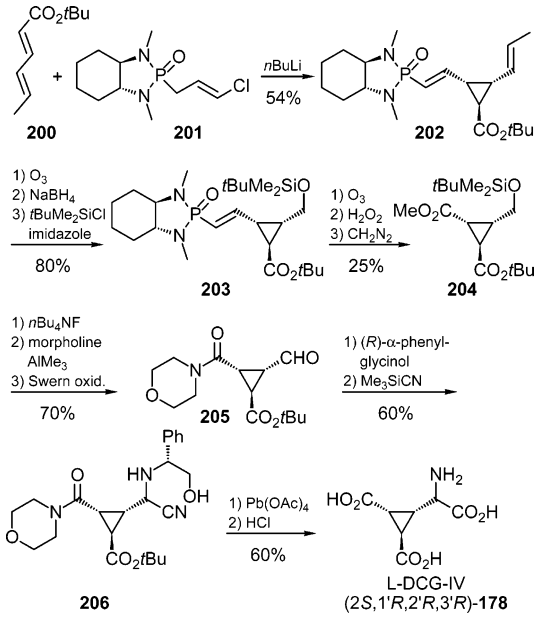
Scheme 34. Preparation of L-DCG-IV Starting from Feist's Acid[123]



L-DCG-IV has also been prepared by applying a highly stereocontrolled conjugate 1,4-addition of the carbenoid, generated by deprotonation of the (*E*)-chloroallylphosphonamide **201** with *n*-butyllithium, onto *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate (**200**) to yield the cyclopropane derivative **202** as a single diastereomer. Regioselective ozonolysis of its (*E*)-propenyl side chain with reductive workup led to the corresponding cyclopropylcarbinol, which was protected as its silyl ether **203**. A second ozonolysis of the phosphorylethenyl moiety with oxidative workup produced the corresponding acid, which was isolated as its methyl ester **204**. Removal of the silyl protecting group led to cyclization to the corresponding lactone, which was subjected to ring opening with Weinreb's reagent to provide a hydroxymethyl-substituted cyclopropanecarboxylic acid morpholinide. The latter was oxidized under Swern conditions to the aldehyde **205**. A diastereoselective Strecker synthesis with **205** in the presence of (*R*)-α-phenylglycinol gave the aminonitrile **206**, which was submitted to oxidative cleavage and subsequent hydrolysis to yield L-DCG-IV (2*S*,1′*R*,2′*R*,3′*R*)-**178** (Scheme 35). This synthesis was claimed to be applicable for the preparation of L-DCG-IV on a large scale.[124]

Since L-DCG-IV unifies the structural features of L-CCG-I and -IV (see section 2.7.1), it was expected to act as a mixed

Scheme 35. A Large Scale Preparation of L-DCG-IV[124]



agonist for both the metabotropic and the *N*-methyl-D-aspartate (NMDA) receptor. Indeed, the first electrophysiological experiments with L-DCG-IV revealed a depolarizing effect due to activation of the NMDA receptor, albeit higher than the one of glutamate but lower than the one of NMDA itself. Additionally, L-DCG-IV depressed monosynaptic excitation, leading to expectations of metabotropic agonist effects of about ten times higher potency than the one of L-CCG-I.[119,125] This suggestion was supported by the dramatic enhancement of quisqualate-stimulated phosphoinositite hydrolysis.[126,127]

L-DCG-IV was found to activate metabotropic glutamate (mGlu) receptors negatively coupled to adenylate cyclase, classified as group II and III receptors, and thus acted as one of the most potent inhibitors of forskolin-stimulated cyclic adenosine monophosphate formation.[128] Closer studies revealed L-DCG-IV to be a potent and selective agonist for group II mGlu receptors only, consisting of the mGluR2 and the mGluR3 subclasses.[112,129]

In analogy to 2-(carboxycyclopropyl)glycine (see section 2.7.1), L-DCG-IV turned out to be a tool of enormous value in the exploration of metabotropic glutamate receptors, leading for example to the discovery that the sensitivity of mGlu receptor agonists was decreasing in due course.[130] Thus, L-DCG-IV was applied to investigate the role of mGlu receptors in the olfactory system,[129,131] recovery from halothane anesthesia,[132] the regulation of CA1 pyramidal cell excitability,[133] mGlu receptor modulation of voltage-gated Ca^{2+} channels,[134] and the role of mGlu subreceptors in motoric behavior.[135]

L-DCG-IV was shown to exhibit a protective effect against excitoxic neuronal death induced by exposure to NMDA, suggesting a corresponding neuroprotective role for mGluR2 or mGluR3 receptors and the possible application of L-DCG-IV for the therapy of neurodegenerative disorders.[136−140] L-CCG-IV also revealed neuroprotective properties against intraventricular kainate. In this context, L-DCG-IV was shown to act as an anticonvulsive agent,[141] and this feature was later investigated in detail, establishing the remarkable potency of L-DCG-IV in controlling seizure activity by its modulatory action on neuronal glutamate release.[142]

The capability of L-DCG-IV to act as an NMDA receptor agonist was further investigated in detail. As the activation of the NMDA receptor required a certain concentration of L-DCG-IV, it was concluded that L-DCG-IV can be applied for the study of metabotropic glutamate receptors only as the concentration is kept below the one activating NMDA receptors.[143]

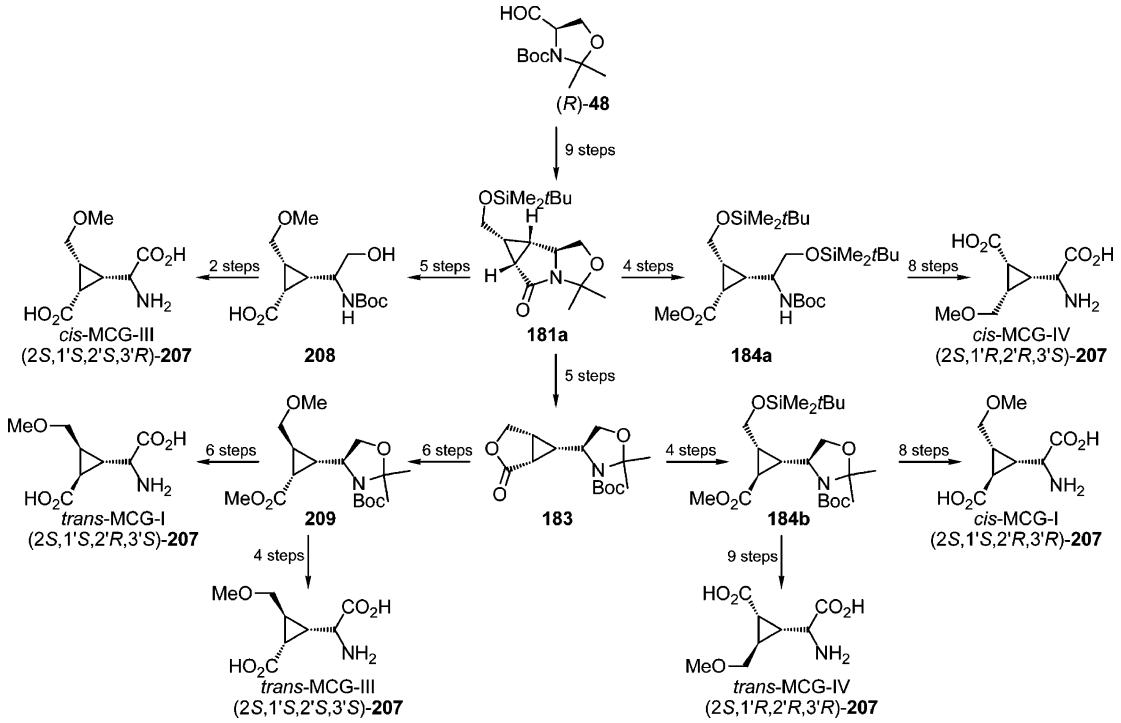
Upon examination of its neurotoxicity, L-DCG-IV was found to cause repetitive seizure and selective neuronal damage, possibly due to the synergistic activation of mGlu receptors and NMDA receptors.[144] L-DCG-IV turned out to be one of the most potent antagonists at group III mGlu receptors, consisting of the mGluR4, -6, -7, and -8 subreceptors, known so far.[145]

2.7.3. [2-Carboxy-3-(methoxymethyl)cyclopropyl]glycine and [2-Carboxy-3-(hydroxymethyl)cyclopropyl]glycine

In order to gain further insights into the structure−activity relationship of glutamate receptors, a synthetic access to the ether derivative of 2-(2,3-dicarboxycyclopropyl)glycine DCG (**178**) (see section 2.7.2), in the form of 2-[2-carboxy-3-(methoxymethyl)cyclopropyl]glycine MCG, has been examined. For the preparation of the *cis*- as well as *trans*-isomers of MCG, the 4,6-bis(hydroxymethyl)-3-azabicyclo[3.1.0]-hexane-2-one in its protected form **181a**, available from the Garner aldehyde (*R*)-**48** via the (*Z*)-alkene (*Z*)-**179** (see section 2.7.2, Scheme 31), served as a suitable starting material.[118] *cis*-MCG-III (2*S*,1′*S*,2′*S*,3′*R*)-**208** was prepared from the tricycle **181a** by removal of the silyl group and *O*-methylation of the free hydroxy group, followed by cleavage of the acetonide, hydrolysis of the lactam, and protection of the amino function as the *tert*-butoxycarbonyl derivative **208**. Jones oxidation of the carbinol functionality in **208** and deprotection of the amino group led to *cis*-MCG-III (2*S*,1′*S*,2′*S*,3′*R*)-**207** (Scheme 36). If instead the acetonide in the tricycle **181a** was cleaved first, silyl protection of the hydroxy group and *N*-*tert*-butoxycarbonyl protection of the thus liberated amino group followed by hydrolysis of the lactam provided access to the cyclopropane derivative **184a**. Reduction of the methoxycarbonyl group in **184a** and methylation of the resulting carbinol as well as cleavage of both silyl ethers and Jones oxidation of the resulting diol gave the corresponding diacid, which was isolated as its dimethyl ester. A three-step hydrolysis completed the transformation of **184a** into *cis*-MCG-IV (2*S*,1′*R*,2′*R*,3′*S*)-**207** (Scheme 36).[118,146]

Access to other isomers of MCG was gained by conversion of the tricycle **181a** into the lactone **183** (see section 2.7.2, Scheme 31), which served as a versatile building block for further transformations.[118] Hydrolysis of its lactone moiety followed by esterification of the thus obtained acid functionality and oxidation of the carbinol to the corresponding aldehyde was accomplished. Subsequent epimerization of this stereogenic center, re-reduction to the alcohol, and final methylation yielded the cyclopropane derivative **209**. Reduction of the methoxycarbonyl moiety of the latter to a carbinol, subsequent reoxidation to the corresponding aldehyde, and epimerization at the neighboring stereogenic center furnished a cyclopropane derivative which was further oxidized and converted by an additional three steps into *trans*-MCG-I (2*S*,1′*S*,2′*R*,3′*S*)-**207** (Scheme 36).[93,146] Alternatively, the cyclopropane derivative **209** was submitted to cleavage of the *O*,*N*-acetonide and hydrolysis of the ester. Subsequent Jones oxidation and liberation of the amino group afforded *trans*-MCG-III (2*S*,1′*S*,2′*S*,3′*S*)-**207** (Scheme 36).[146]

Scheme 36. Preparation of Enantiomerically Pure 2-[2-Carboxy-3-(methoxymethyl)cyclopropyl]glycine[93,118,146]



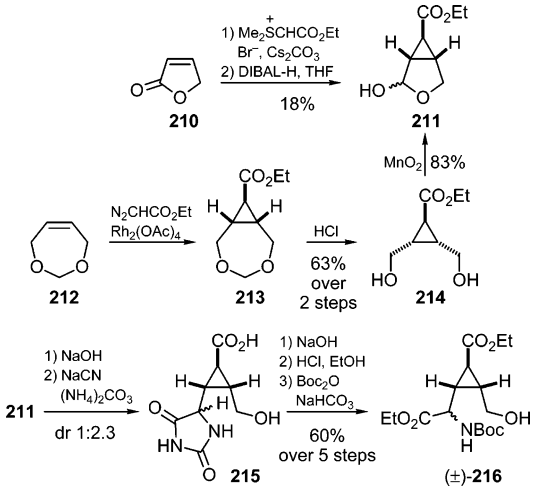
When the lactone in **183** was hydrolyzed, the resulting acid functionality was subsequently esterified, and the hydroxy group was protected as a silyl ether, the stereogenic center bearing the ester substituent could successfully be epimerized to provide the cyclopropane derivative **184b** (see section 2.7.2, Scheme 31). Removal of the silyl-protecting group in **184b** and methylation of the thus liberated hydroxy group afforded a compound which was further transformed, in an additional six steps involving Jones oxidation and removal of the protecting groups, into *cis*-MCG-I (2*S*,1′*S*,2′*R*,3′*R*)-**207** (Scheme 36).[93,146] Additionally, the methyl ester functionality in the cyclopropane derivative **184b** was reduced to the corresponding carbinol, which was subsequently methylated. Removal of the silyl-protecting group, oxidation of the liberated carbinol to the acid, isolated as the methyl ester, and a further four-step transformation consisting of the removal of all protecting groups and Jones oxidation led to *trans*-MCG-IV (2*S*,1′*R*,2′*R*,3′*R*)-**207** (Scheme 36).[146]

Upon pharmacological evaluation of the prepared 2-[2-carboxy-3-(methoxymethyl)cyclopropyl]glycines, *trans*-MCG-IV was found to activate the kainate (KA) receptor with a depolarizing effect as potent as the one of kainic acid itself. In contrast, *cis*-MCG-IV exhibited agonist properties toward the *N*-methyl-D-aspartate (NMDA) receptor with half of the activity of L-CCG-IV. Both, *cis*- and *trans*-MCG-I turned out to be potent agonists of metabotropic glutamate receptors, with no activity toward ionotropic glutamate receptors, whereas the potency of *trans*-MCG-I was about two times higher than the one of *cis*-MCG-I and equal to the one of L-CCG-I.[118,146−148] *trans*-MCG-III was found to inhibit the L-[^{3}H]-glutamate transport selectively in the cerebellum.[117]

Characterization of 3′-benzyloxymethyl-substituted 2-(2-carboxycyclopropyl)glycine derivatives analogous to *trans*-MCG-IV revealed a similar pharmacological profile, albeit generally of lower potency.[149]

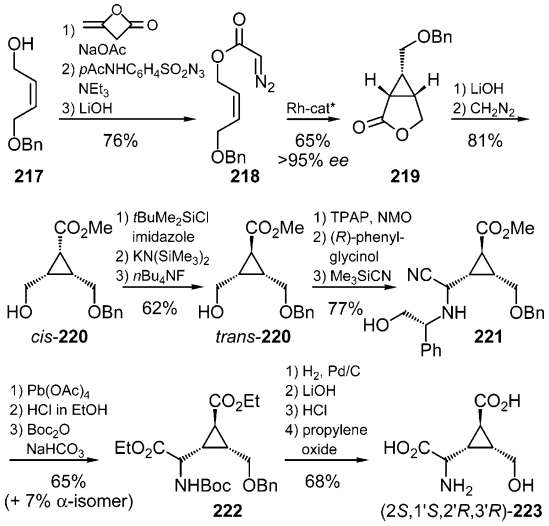
With the intention to investigate a potential glutamate receptor ligand having the possibility of acting as both a hydrogen bond donor as well as an acceptor, 3′-hydroxymethyl-substituted 2-(2-carboxycyclopropyl)glycine was synthesized. In view of the interesting pharmacological properties of *cis*-MCG-I,[147] the analogous (2*S*,1′*S*,2′*R*,3′*R*)-isomer was envisaged. The chosen starting material, the lactol **211**, was available from furan-2(5*H*)-one (**210**) by cyclopropanation with ethyl (dimethylsulfuranylidene)acetate and subsequent chemoselective reduction of the thus obtained bicyclic lactone. The lactol **211** was also accessible in a better yield by the rhodium-catalyzed, diastereoselective cyclopropanation of *cis*-4,7-dihydro-1,3-dioxepin (**212**) with ethyl diazoacetate, subsequent cleavage of the bicyclic acetal **213**, and mild oxidation of the diol with manganese dioxide. As the further transformation of **211** by Strecker reaction proceeded with low diastereoselectivity for the nondesired diastereomer only, a Bucherer−Berg reaction was employed in order to introduce the amino group, and this yielded the hydantoin **215** as a mixture of two diastereomers. Hydrolysis

Scheme 37. Synthesis of Racemic 2-(2-Carboxy-3-hydroxymethylcyclopropyl)glycine[150]



of this mixture, subsequent esterification, and *N*-protection provided racemic *N*-Boc-2-(2-carboxy-3-hydroxymethylcyclopropyl)glycine (**216**) as a separable mixture of two diastereomers (Scheme 37), the major of which was the (2*S*,1′*S**,2′*R**,3′*R**)-isomer. The latter was successfully resolved by HPLC on a chiral column, before the protecting groups were removed finally.[150]

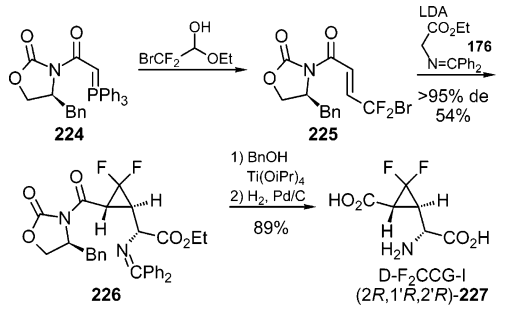
Scheme 38. Enantioselective Synthesis of (2*S*,1′*S*,2′*R*,3′*R*)-2-(2-Carboxy-3-hydroxymethylcyclopropyl)glycine[150]



A reported enantioselective approach to (2*S*,1′*S*,2′*R*,3′*R*)-2-(2-carboxy-3-hydroxymethylcyclopropyl)glycine (**223**) started with the preparation of *cis*-4-benzyloxy-2-butenyl diazoacetate (**218**) obtained from *cis*-4-benzyloxy-2-buten-1-ol (**217**) and diketene. Intramolecular cyclopropanation of **218** in the presence of a chirally derivatized rhodium catalyst afforded virtually enantiomerically pure bicyclic lactone **219**. Subsequent hydrolysis and esterification led to the *all-cis*-1,2,3-trisubstituted cyclopropane derivative *cis*-**220**, a suitable compound for epimerization adjacent to the methoxycarbonyl moiety after silyl protection of the hydroxy group. In the thus obtained epimer *trans*-**220**, the hydroxymethyl was oxidized to an aldehyde group, and the aldehyde was subjected to an enantioselective Strecker synthesis employing (*R*)-(−)-α-phenylglycinol as the chiral inducing agent. Oxidative cleavage of the resulting **221**, hydrolysis, and *N*-protection gave *N*-Boc-2-(2-carboxy-3-hydroxymethylcyclopropyl)glycine **222** in protected form, and this was converted in an additional four steps to the free amino acid (2*S*,1′*S*,2′*R*,3′*R*)-**223** (Scheme 38).[150]

Racemic as well as enantiomerically pure 2-(2-carboxy-3-hydroxymethylcyclopropyl)glycine were evaluated with respect to their properties as metabotropic glutamate receptor ligands. Whereas the (2*R*,1′*R*,2′*S*,3′*S*)-isomer [(−)-isomer] turned out to be inactive, the (2*S*,1′*S*,2′*R*,3′*R*)-isomer [(+)-isomer] exhibited agonist-like affinity toward metabotropic group II receptors mGluR2 and -3 with a 90-fold higher potency than that of L-CCG-I, and toward metabotropic group III receptors mGluR6 and -8 with a 40-fold higher potency than L-CCG-I, suggesting that the presence of the hydroxymethyl group significantly enhances the population of the active conformation. As such, (+)-**223** was the most potent cyclopropylglycine known so far for mGluR2, -3, -6, and -8 receptors, and it has been shown to be orally active in models for anxiety and psychosis.[150]

Scheme 39. Synthesis of (2*R*,1′*R*,2′*R*)-2-(2-Carboxy-3,3-difluorocyclopropyl)glycine D-F2CCG-I[151]



2.7.4. (2-Carboxy-3,3-difluorocyclopropyl)glycine [3,4-(Difluoromethano)glutamic Acid]

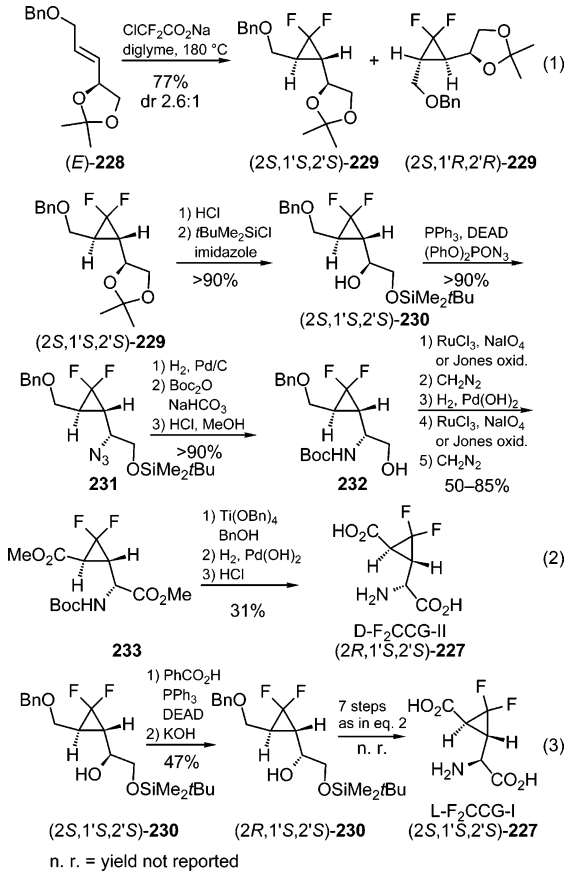
Substitution of the two hydrogen atoms at the 3′-position in 2-(carboxycyclopropyl)glycine by fluorine was expected to influence the pharmacological activity by further restricting the possible conformations of the molecule and increasing the C,H-acidity at the cyclopropyl group. In order to be able to study the properties of 2-(2-carboxy-3,3-difluorocyclopropyl)glycine (F_2CCG), stereoselective approaches to F_2-CCG were developed.

Wittig alkenation of the ethyl hemiacetal of bromodifluoroacetaldehyde with the phosphorane **224** gave the oxazilidinone-protected (*E*)-4-bromo-4,4-difluorobut-2-enamide **225**. Submission of this Michael acceptor endowed with a chiral auxiliary to a MIRC reaction with the enolate of ethyl (diphenylmethyleneamino)acetate (**176**) afforded the *gem*-difluorocyclopropane derivative **226** virtually as a single diastereomer. Titanium tetraisopropoxide-catalyzed transformation of the carbamate and the ethyl ester moiety in **226** to the corresponding dibenzyl ester and subsequent hydrogenolysis completed the synthesis of D-F_2CCG-I in its fully deprotected form (2*R*,1′*R*,2′*R*)-**227** (Scheme 39).[151]

Starting from the (*E*)- or the (*Z*)-isomer of the trisprotected pent-3-ene-1,2,5-triol **228**, accessible by stereoselective Wittig alkenation of (*R*)-2,3-*O*-isopropylideneglyceraldehyde as the chiral precursor, all eight stereoisomers of F_2CCG were made available.

Difluorocarbene addition to (*E*)-**228** afforded a readily separable mixture of the diastereomeric difluorocyclopropanes (2*S*,1′*S*,2′*S*)-**229** and (2*S*,1′*R*,2′*R*)-**229** (Scheme 40, eq 1). The isomer (2*S*,1′*S*,2′*S*)-**229** was further converted by cleavage of the acetonide and silyl protection of the primary hydroxy group to the cyclopropane derivative (2*S*,1′*S*,2′*S*)-**230**. By a Mitsunobu reaction, the latter was transformed to the azide **231**, which was subsequently reduced to the corresponding amine followed by *N*-protection and cleavage of the silyl ether. As a single step oxidation of the dialcohol prepared by debenzylation of **232** failed, the oxidation was performed in two steps, the first one on the monoprotected alcohol **232** with intermediate esterification of the monoacid, debenzylation, oxidation, and esterification again to finally afford the desired amino diacid as its dimethyl ester **233**. Complete deprotection of **233** succeeded by titanium tetrabenzyloxide-catalyzed transesterification, subsequent hydrogenolysis of the dibenzyl ester, and final treatment with acid, furnishing D-F_2CCG-II (2*R*,1′*S*,2′*S*)-**227** (Scheme 40, eq 2). When the cyclopropane derivative (2*S*,1′*S*,2′*S*)-**230** was first subjected to a Mitsunobu reaction with hydroxide as the nucleophile, the diastereomer (2*R*,1′*S*,2′*S*)-**230** with inverted configuration at C-2′ was obtained, and it was subsequently

Scheme 40. Synthesis of D- and L-F_2CCG-I and -II[152]



transformed into L-F_2CCG-I (2*S*,1′*S*,2′*S*)-**227** (Scheme 40, eq 3), applying the same reaction sequence as described above.

Analogous procedures, but utilizing the (2*S*,1′*R*,2′*R*)-isomer of the cyclopropane derivative **229**, offered access to L-F_2CCG-II (2*S*,1′*R*,2′*R*)-**227** and D-F_2CCG-I (2*R*,1′*R*,2′*R*)-**227** (not shown).

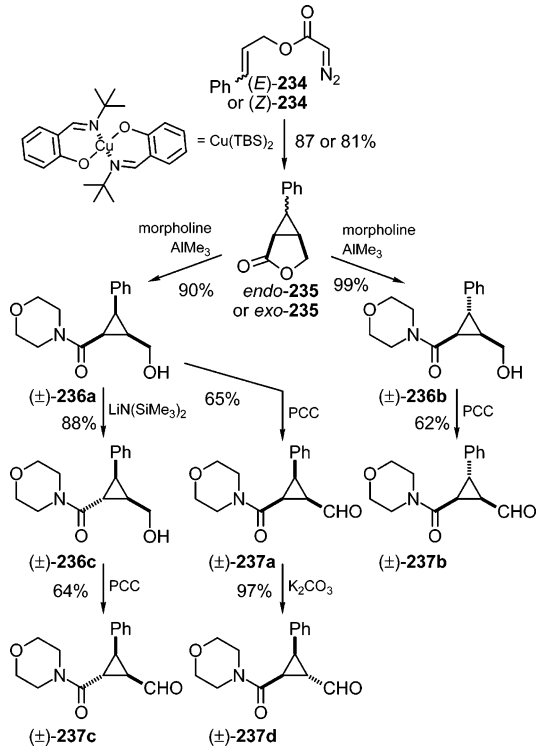
Application of the same transformations as carried out with the (*E*)-isomer of the protected triol (*E*)-**228** toward the syntheses of D- and L-F_2CCG-I and -II to the (*Z*)-isomer of **228** stereoselectively led to D- and L-F_2CCG-III and -IV, albeit via a bicyclic β-lactam intermediate.[152]

Pharmacological evaluation of the eight stereoisomers of F_2CCG revealed that their properties corresponded in the broadest sense to the ones of CCG (see section 2.7.1). It is noteworthy that the potency of L-F_2CCG-I to activate group II metabotropic glutamine receptors is about three times higher than that of L-CCG-I. The most distinctive pharmacological change achieved by the introduction of two fluorines was that L-F_2CCG-III did not exhibit the inhibitory action of L-CCG-III upon Na^+-dependent glutamate uptake.[152,153]

2.7.5. (2-Carboxy-3-phenylcyclopropyl)glycine

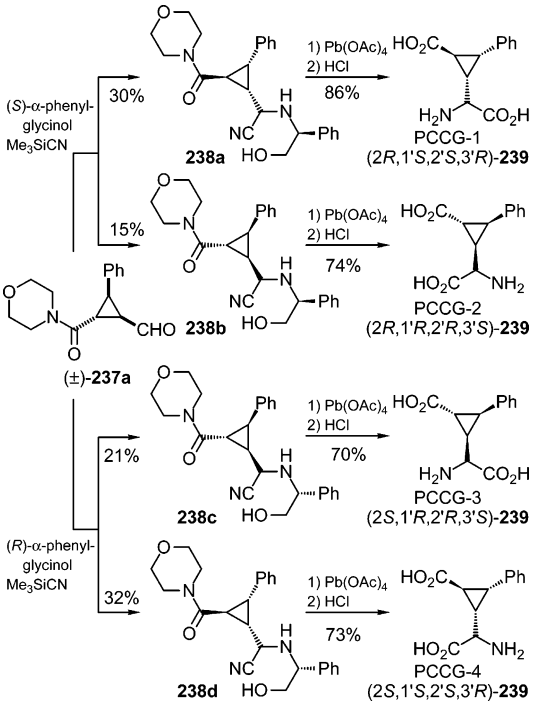
All 16 stereoisomers of 2-(2-carboxy-3-phenylcyclopropyl)glycine have been synthesized from the four diastereomers of racemic 2-(morpholin-4-ylcarbonyl)-3-phenylcyclopropanecarbaldehydes (**237**). A copper(II)-induced intramolecular cyclopropanation of either the (*E*)- or the (*Z*)-isomer of the phenylallyl diazoacetate (**234**) led to the bicyclic lactones *endo*-**235** and *exo*-**235**, respectively. Treatment of the *endo*-lactone **235** with morpholine and trimethylaluminum (Weinreb's reagent) gave the 2-morpholinocarbonylcyclopropylmethanol (±)-**236a**, which could be oxidized to the aldehyde (±)-**237a**. Base-induced epimerization of (±)-**237a** offered access to the diastereomeric aldehyde (±)-**237d**. Alternatively, the morpholinocarbonyl-substituted cyclopropylmethanol (±)-**236a** was selectively epimerized adjacent to the morpholinocarbonyl moiety to yield (±)-**236c**, which was oxidized to the aldehyde **237c**. Treatment of the *exo*-configured bicyclic lactone *exo*-**235** with Weinreb's reagent led to the corresponding cyclopropylmethanol (±)-**236b**, which was oxidized to the aldehyde (±)-**237b** (Scheme 41). Having all four diastereomers of racemic 2-(morpholin-4-ylcarbonyl)-3-phenylcyclopropanecarboxaldehyde [(±)-**237**] in hand, each of them was subjected to a diastereoselective Strecker reaction involving the condensation of the aldehyde with either (*R*)- or (*S*)-α-phenylglycinol. Nucleophilic addition of cyanide to each of the thus obtained Schiff bases afforded a separable mixture of diastereomeric aminonitriles **238a** and **238b** or **238c** and **238d**, respectively. Oxidative cleavage of the latter and final hydrolysis provided access to all 16 stereoisomers of 2-(2-carboxy-3-phenylcyclopropyl)glycine (**239**) (Scheme 42, only the conversion of the aldehyde (±)-**237a** to PCCG-1 through -4 is depicted, whereas the identical transformations of (±)-**237b** to PCCG-5 through -8, (±)-**237c** to PCCG-9 through -12, and (±)-**237d** to PCCG-13 through -16 are not shown).[154]

Scheme 41. Synthesis of All Four Diastereomers of Racemic 2-(Morpholin-4-ylcarbonyl)-3-phenylcyclopropanecarboxaldehyde as Precursors to All Sixteen Stereoisomeric 2-(2-Carboxy-3-phenylcyclopropyl)glycines (See Scheme 42)[154]



In addition to the described enantiodivergent approach to all stereoisomers of PCCG starting from the corresponding racemic aldehydes, asymmetric syntheses of PCCG-4 (2*S*,1′*S*,2′*S*,3′*R*)-**239** as well as PCCG-13 (2*R*,1′*S*,2′*R*,3′*S*)-**239** have been developed. Thus, PCCG-4 (2*S*,1′*S*,2′*S*,3′*R*)-**239** was obtained by intramolecular cyclopropanation of (*Z*)-3-phenylprop-2-enyl diazoacetate [(*Z*)-**234**] in the presence of a chiral rhodium catalyst, furnishing the bicyclic lactone

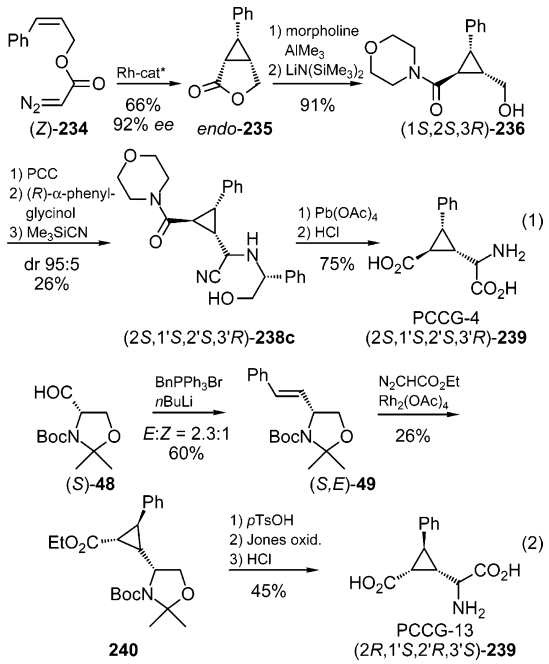
Scheme 42. Conversion of Racemic 2-(Morpholin-4-ylcarbonyl)-3-phenylcyclopropanecarboxaldehydes into Enantiopure 2-(2-Carboxy-3-phenylcyclopropyl)glycines[154]



endo-**235** in high enantiomeric purity. Employing the same sequence of transformations as described above (see Schemes 41 and 42), namely lactone opening to the corresponding morpholinocarbonyl-substituted cyclopropylmethanol followed by epimerization to the cyclopropane derivative (1*S*,2*S*,3*R*)-**236**, subsequent oxidation to the corresponding aldehyde, diastereoselective Strecker reaction in the presence of (*R*)-α-phenylglycinol, oxidative cleavage, and final hydrolysis, provided enantiomerically pure PCCG-4 (2*S*,1′*S*,2′*S*,3′*R*)-**239** (Scheme 43, eq 1).[155]

Wittig alkenation of the Garner aldehyde (*S*)-**48** with the ylide from benzyltriphenylphosphonium bromide gave a separable mixture of the corresponding (*E*)- and (*Z*)-styrene derivative **49**. Rhodium-catalyzed cyclopropanation of the (*E*)-isomer (*S*,*E*)-**49** with ethyl diazoacetate provided the cyclopropane derivative **240** as a single diastereomer. Removal of the acetal moiety in **240** followed by Jones oxidation and hydrolysis gave rise to PCCG-13 (2*R*,1′*S*,2′*R*,3′*S*)-**239** (Scheme 43, eq 2).[156]

Scheme 43. Asymmetric Syntheses of PCCG-4 and -13[155,156]



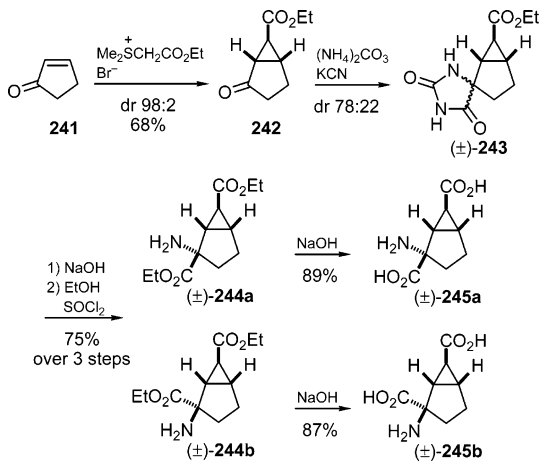
The pharmacological characterization of all 16 stereoisomers of 2-(2-carboxy-3-phenylcyclopropyl)glycine showed that this "stereolibrary" is endowed with a peculiar pharmacological profile: PCCG-2 and PCCG-3 exhibited mentionable agonist properties at the kainate receptor, whereas PCCG-9 and PCCG-11 weakly interacted with the *N*-methyl-D-aspartate receptor. PCCG-5, -10, and -12 inhibited the Ca^{2+}-dependent glutamate transport system.[154] PCCG-13 turned out to be the first potent and selective competitive antagonist for metabotropic glutamate receptors coupled to the activity of phospholipase D (PLD) activation.[156,157] Intensive examination of the interaction of PCCG-4 with metabotropic glutamate receptors revealed that PCCG-4 exhibited a remarkably high antagonist activity at mGluR2 without significant effects at other receptors, making it the most potent and selective mGluR2 antagonist reported until then.[154,158] As thus, PCCG-4 reduced neuroprotection caused by L-CCG-I and L-DCG-IV.[140] PCCG-4 created a significant increase of glutamate output in striatal dialysate, suggesting that selective ligands for mGluR2s affect the function of caudate neurons and might find application in treatment of motoric disorders.[159]

2.7.6. 2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid and Analogues

With the intention to prove that a fully extended glutamate backbone is required for optimal group II metabotropic glutamate receptor protein−ligand interaction, several amino acids have been designed in which the glutamic acid moiety is incorporated into a bicyclo[3.1.0]hexane skeleton.

An efficient synthesis of unsubstituted 2-aminobicyclo-[3.1.0]hexane-2,6-dicarboxylic acid started with the carboxycyclopropanation of cyclopenten-3-one (**241**), utilizing ethyl (dimethylsulfuranylidene)acetate, to yield, under optimized conditions, the ethyl 2-oxobicyclo[3.1.0]hexane-6-carboxylate (**242**) as a single diastereomer. The ketone **242** was then subjected to hydantoin formation under Bucherer−Berg conditions, whereupon a mixture of the two possible diastereomers of (±)-**243** was obtained. The latter was either

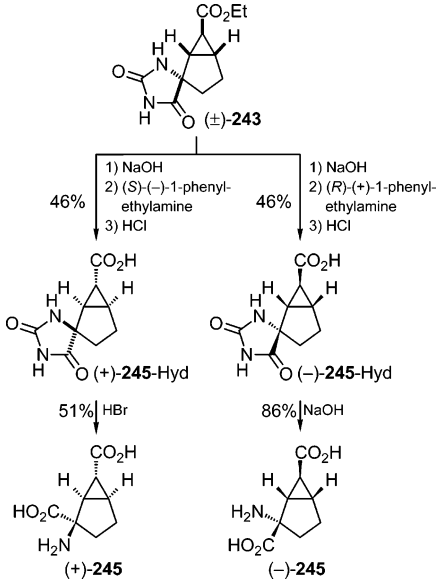
Scheme 44. Synthesis of Racemic 2-Aminobicyclo-[3.1.0]hexane-2,6-dicarboxylic Acids[160]



separated or used as a mixture for subsequent hydrolysis and esterification in order to give the two separable diastereomers of the protected amino acid diethyl esters (±)-**244a** and (±)-**244b**. Final hydrolysis provided the two target 2-aminobicyclo-[3.1.0]hexane-2,6-dicarboxylic acids in their racemic forms (±)-**245a** and (±)-**245b**, respectively (Scheme 44).[160]

When, instead, the hydantoin (±)-**243** was hydrolyzed and then treated with either (*S*)-(−)- or (*R*)-(+)-1-phenylethylamine, optical resolution was achieved, and the resulting hydantoins (+)-**245**-Hyd and (−)-**245**-Hyd could be hydrolyzed to yield enantiomerically pure 2-aminobicyclo[3.1.0]-hexane-2,6-dicarboxylic acids (+)-**245** and (−)-**245**, respectively (Scheme 45).[160]

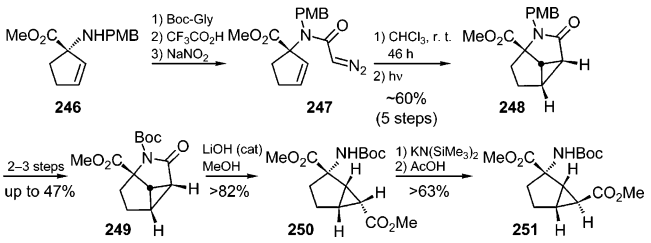
Scheme 45. Optical Resolution of (±)-2-Aminobicyclo-[3.1.0]hexane-2,6-dicarboxylic Acid[160]



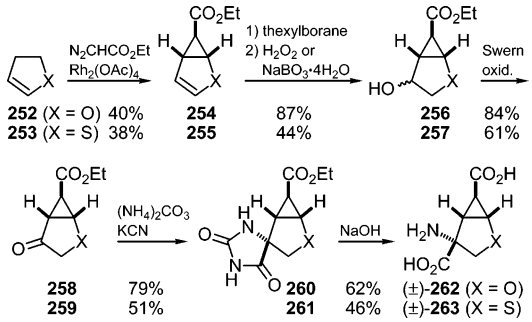
An enantioselective synthesis of the appropriate stereoisomer of **242**, the precursor to (+)-**245**, and thus formally (+)-**245** itself has been achieved with the application of a chirally modified ester-stabilized sulfonium ylide.[161] Prior to that, the only stereocontrolled synthesis of (+)-**245** had been completed starting from the enantiomerically pure 3,4-didehydroamino acid ester **246** (Scheme 46).[162] The *p*-methoxybenzyl-protected ester **246** was coupled with *N*-Boc-protected glycine, and the *N*-Boc group was cleaved off with trifluoroacetic acid. Diazotation of the amino group then gave the α-diazoamide, which, upon standing at ambient temperature, underwent an intramolecular 1,3-dipolar cycloaddition to yield a tricyclic pyrazoline. Photolysis of the latter furnished the tricyclic lactam **248**, in which the *N*-PMB group was modified to an *N*-Boc protecting group before methanolysis was carried out to give the diester **250**. Inversion of the stereogenic center adjacent to the methoxycarbonyl group on the cyclopropane ring was carried out by treatment with potassium bis(trimethylsilyl)amide and reprotonation. Finally, all protecting groups were removed from **251** to yield enantiomerically pure (+)-**245**.[162]

The pharmacological evaluation showed that racemic as well as the (+)-enantiomer of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (**245**) were exceptionally potent agonists at group II metabotropic glutamate receptors, possessing no activity at other receptor subtypes. Detailed characterization of the (+)-enantiomer, referring to LY354740, revealed that it closely mimicked the biologically active conformation

Scheme 46. Enantioselective Synthesis of (+)-2-Amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic Acid from an Enantiomerically Pure Substrate[162]



Scheme 47. Syntheses of Racemic 4-Amino-2-oxa- and 4-Amino-2-thiabicyclo[3.1.0]hexane-4,5-dicarboxylic Acid[165]



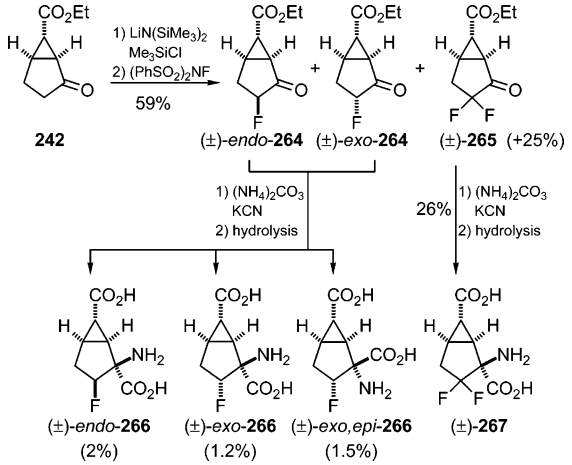
of glutamate. As such, it was able to interact with human metabotropic glutamate receptors as a highly potent, efficacious, and selective group II receptor agonist, making it the first orally applicable selective group II mGluR agonist described so far and a promising tool in treatments of anxiety and other central nervous system-related disorders in humans.[160,163,164]

Encouraged by this success, several structurally related analogues of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid were prepared, and their pharmacological profile was established. The rhodium-catalyzed carboxycyclopropanation of either the furan **252** or the thiophene **253** with ethyl diazoacetate afforded the cyclopropane-annelated heterocycles **254** and **255**, respectively. Hydroboration/oxidation across the double bond and subsequent Swern oxidation of the resulting carbinols **256** and **257**, respectively, furnished the heterobicyclic ketones **258** and **259**, respectively. Conversion of the carbonyl group to the corresponding spiroannelated hydantoin functionality turned out to be diastereoselective, giving the hydantoins **260** and **261**, respectively, which were finally hydrolyzed to racemic 4-amino-2-oxabicyclo[3.1.0]hexane-4,5-dicarboxylic acid [(±)-**262**] and 4-amino-2-thiabicyclo[3.1.0]hexane-4,5-dicarboxylic acid [(±)-**263**], respectively (Scheme 47). Optical resolution of (±)-**262** and (±)-**263** was achieved by selective crystallization of either the (*R*)- or the (*S*)-2-phenylglycinol salts (see Scheme 45 for an essentially analogous resolution of (±)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid).[165]

Compounds (−)-**262**, also called LY379268 and (−)-**263**, corresponding to LY389795, exhibited agonist activity at group II metabotropic glutamate receptors of even higher potency than that of the lead structure **245** without the heteroatom in the bicyclic ring system; however, the effects were not totally specific, as each of them also activated the group I mGluR subtypes 6 and 8 at higher concentrations.[165]

In order to further improve the pharmacological properties of the bicyclic glutamate analogues, the introduction of fluorine atoms was envisaged, expecting essentially no steric, but an interesting electronic change within the molecule.

Scheme 48. Preparation of Racemic 2-Amino-3-fluoro- and 2-Amino-3,3-difluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid[166]

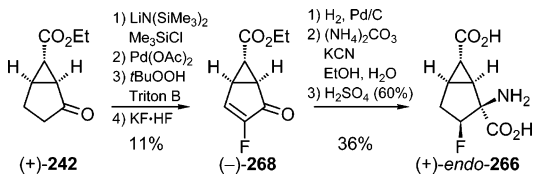


Thus, the racemic 4-oxobicyclo[3.1.0]hexane-6-carboxylate (±)-**242** (see Scheme 44) was converted to its silyl enol ether, and this was then fluorinated with *N*-fluorobenzenesulfonamide, yielding an inseparable mixture of the diastereomeric *endo*- and *exo*-3-fluoro-2-oxobicyclo[3.1.0]hexanecarboxylates (±)-*endo*-**264** and (±)-*exo*-**264** as well as the 3,3-difluoro derivative (±)-**265**. Submission of the mixture of 3-monofluorinated diastereomers *endo*- and *exo*-**264** to hydantoin formation afforded three separable hydantoins which were hydrolyzed to the corresponding diastereomeric 2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acids [(±)-*endo*-**266**], [(±)-*exo*-**266**], and [(±)-*exo,epi*-**266**]. Similarly, the 3,3-difluorinated ketone (±)-**265** was converted to 2-amino-3,3-difluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid [(±)-**267**] (Scheme 48).[166]

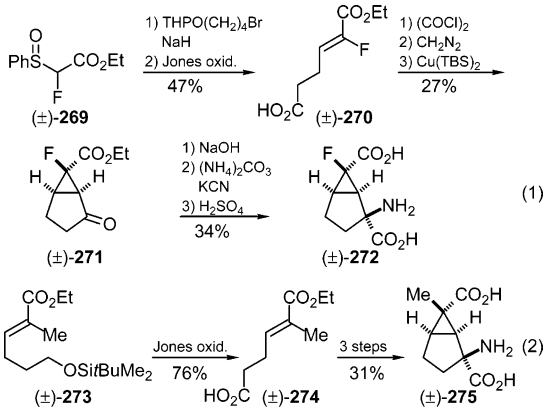
Optically pure *endo*-**266** was obtained by derivatization of its hydantoin salt with (*R*)-(+)-1-phenylethylamine (see Scheme 45 for an analogous resolution of (±)-2-aminobicyclo-[3.1.0]hexane-2,6-dicarboxylic acid). Additionally, enantiomerically pure (+)-*endo*-**266** was prepared from (+)-**242**, obtained by HPLC separation of (±)-**242** on a chiral column, subsequent stereoselective epoxidation of the silyl enol ether of (+)-**242**, and eventually fluorination to the key intermediate (−)-**268**. Catalytic hydrogenation of this fluorobicyclohexenone occurred stereoselectively, yielding, after diastereoselective hydantoin formation and final hydrolysis, the enantiopure (+)-2-amino-3-*endo*-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid [(+)-*endo*-**266**] (Scheme 49). Following this procedure, but carrying out the hydrogenolysis with tritium gas, the radiolabeled [^{3}H]-(+)-*endo*-**266** was prepared.[166]

The pharmacological characterization of 2-amino-3-*endo*-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (*endo*-**266**) revealed that the racemic compound exhibited high agonist activity at mGlu2 receptors which was demonstrated to be highly stereoselective, as the (+)-enantiomer turned out to

Scheme 49. Preparation of (+)-2-Amino-3-*endo*-fluorobicyclo-[3.1.0]hexane-2,6-dicarboxylic Acid[166]



Scheme 50. Synthesis of Racemic 6-Fluoro- and 6-Methyl-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid[166]



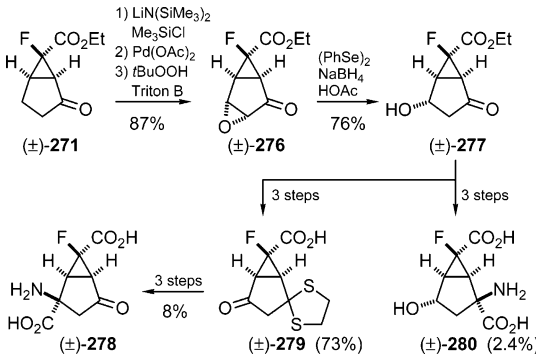
be about 90 times more potent than the (−)-enantiomer of *endo*-**266**. As (+)-*endo*-**266** also showed agonist activity on mGlu3, but not on any other receptors, it was claimed to be a selective agonist for group II metabotropic glutamate receptors. Conspicuously, the diastereomer (±)-*endo,epi*-**266** was only negligibly potent, and neither the racemic mixture of the diastereomer (±)-*exo*-**266** nor the difluoro-substituted derivative (±)-**267** exhibited any agonist or antagonist activity at group II mGluRs. Additionally, compound (+)-*endo*-**266** was found to inhibit phencyclidine (PCP) induced head-waving behavior and hyperactivity, suggesting, in view of its oral bioavailability, an application in the treatment of schizophrenia.[166]

With the objective to introduce a fluorine atom at the C-6 of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid, ethyl phenylsulfinylfluoroacetate [(±)-**269**] was stereoselectively coupled with THP-protected 4-bromobutanol, and the product was subjected to Jones oxidation conditions to yield the monoester of (*E*)-2-fluorohex-2-enedioic acid (±)-**270**. Activation of the acid functionality as the acid chloride, reaction with diazomethane, and conversion of the resulting diazoketone by intramolecular cyclopropanation in the presence of bis(*N*-*tert*-butylsalicylaldimine)copper(II) [Cu(TBS)$_2$] furnished the 2-oxobicyclo[3.1.0]hexanecarboxylate (±)-**271**, which, upon ester hydrolysis, hydantoin formation under Bucherer−Berg conditions, and final hydrolysis led to (±)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid in its free form (±)-**272** (Scheme 49, eq 1). Optically pure (+)-**272** and (−)-**272**, respectively, were obtained by resolution of (±)-**271** by HPLC on a chiral column and subsequent conversion of each enantiomer in analogy to the racemic derivative. Applying the same sequence of transformations to the methyl-substituted monoester hex-2-enedioic acid (±)-**273** furnished (±)-2-amino-6-methylbicyclo[3.1.0]hexane-2,6-dicarboxylic acid (±)-**275** (Scheme 50, eq 2).[166]

In analogy to the 3-fluoro-substituted compound **266**, the racemic mixture of the 6-fluoro-substituted derivative (±)-**272** demonstrated high agonist activity on group II metabotropic glutamate receptors which was found to be about 67 times higher for the (+)-enantiomer than for the (−)-enantiomer of **272** at mGluR2s. In contrast, the analogous 6-methyl-substituted bicyclic compound **275** was completely inactive.[166]

The oxobicyclo[3.1.0]hexanecarboxylate (±)-**271** (see Scheme 50) also served as a suitable starting material for the preparation of 4-hydroxy- **280** as well as 4-oxo-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (**278**),

Scheme 51. Preparation of Racemic (±)-4-Hydroxy- and (±)-4-Oxo-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid[166]



respectively. Conversion of (±)-**271** into its silyl enol ether and stereoselective epoxidation gave the epoxide (±)-**276**, which could regiospecifically be reduced to the hydroxyl derivative (±)-**277**. Hydrolysis of the ester functionality of the latter, hydantoin formation under Bucherer−Berg conditions, and final hydrolysis provided (±)-**280** (Scheme 51). Alternatively, compound (±)-**277** was transformed into the thioacetal (±)-**279** before it was submitted to hydrolysis, hydantoin formation, and removal of all protecting groups to yield (±)-**278** (Scheme 51).[166]

Optically pure (+)-**278** and (−)-**278**, respectively, were accessible either by derivatization of the hydantoin derived from (±)-**279** with (*R*)-(+)-1-phenylethylamine, separation, and subsequent hydrolysis or by resolution of (±)-**271** by HPLC on a chiral column and subsequent transformation of each enantiomer in an essentially analogous manner as described for the racemic compound.[166]

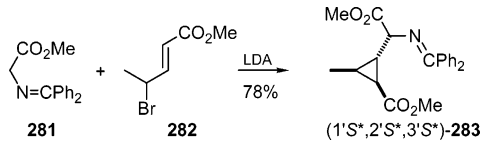
Whereas the incorporation of the hydroxyl group at C-4 did not significantly enhance the agonist potency on group II mGluRs compared to that of the 4-unsubstituted compound **272**, introduction of the carbonyl group significantly increased the potency while maintaining the selectivity. Furthermore, in analogy to compound (+)-*endo*-**266** without the carbonyl functionality, the orally active (+)-enantiomer of **278** was found to strongly antagonize phencyclidine (PCP) induced head-waving behavior and hyperactivity, suggesting its application in the treatment of schizophrenia.[166]

2.7.7. (3-Alkyl-2-carboxycyclopropyl)glycines

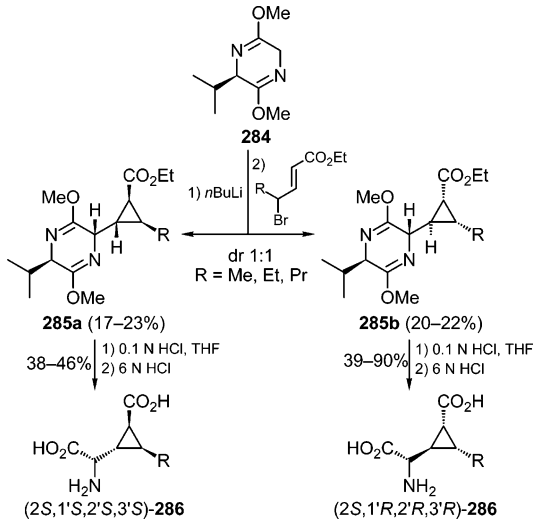
2-(2-Carboxy-3-methylcyclopropyl)glycine in its racemic form has been prepared by a Michael-induced ring closure (MIRC) reaction of the glycine anion equivalent formed by deprotonation of **281**, with methyl (*E*)-4-bromopent-2-enoate (**282**). This provided the (1′*S**,2′*S**,3′*S**)-isomer as a single diastereomer in its protected form **283** (Scheme 52).[81]

MIRC reaction of the anion generated from the chiral bislactim ether **284** with racemic 4-alkyl-4-bromobut-2-enoates led to the diastereomeric cyclopropanecarboxylate derivatives **285a** and **285b**, having identical relative configurations at all three stereogenic centers on the cyclopropane ring and the same absolute configuration at C-5. A stepwise hydrolysis of each of these stereoisomers led to (2*S*,1′*S*,2′*S*,3′*S*)-**286** and (2*S*,1′*R*,2′*R*,3′*R*)-**286**, respectively, having a methyl, ethyl, or propyl substituent at C-3 of the cyclopropane ring, respectively (Scheme 53).[167]

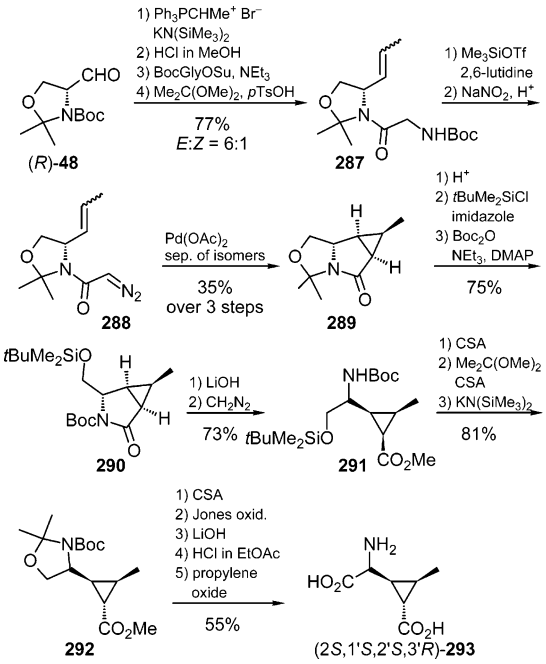
Scheme 52. Synthesis of Protected (1′*S,2′*S**,3′*S**)-2-(2-Carboxy-3-alkylcyclopropyl)glycine[81]**



Scheme 53. Synthesis of 2-(3-Alkyl-2-carboxycyclopropyl)glycines[167]



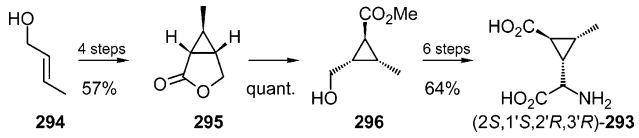
Scheme 54. Preparation of (2*S*,1′*S*,2′*S*,3′*R*)-2-(2-Carboxy-3-methylcyclopropyl)glycine[168]



Wittig alkenation of the Garner aldehyde (*R*)-**48** with the ylide generated from ethyl(triphenyl)phosphonium bromide gave the corresponding 4-propenyl-substituted oxazolidine derivative as a mixture of (*E*)- and (*Z*)-isomers, from which the protecting groups were removed. Subsequent coupling with *N*-Boc-protected glycine and reintroduction of the acetonide protection provided the *N*-Boc-glycyloxazolidine **287**. Chemoselective removal of the *N*-*tert*-butoxycarbonyl group and diazotation of the resulting amine furnished the diazoamide **288**, which, by palladium acetate-catalyzed intramolecular cyclopropanation and separation of the major diastereomer, yielded the tricyclic compound **289**. Cleavage of the *O*,*N*-acetonide and subsequent protection of the hydroxy as well as the amino group led to the *N*-Boc-γ-

lactam **290**. The latter was hydrolyzed to the corresponding acid, which was isolated as the methyl ester **291**. Removal of the silyl group and reintroduction of the acetonide gave a suitable material for epimerization to the isomer **292**. A final five-step transformation involving removal of the protecting groups and Jones oxidation furnished (2*S*,1′*S*,2′*S*,3′*R*)-2-(2-carboxy-3-methylcyclopropyl)glycine in its free form **293** (Scheme 54).[168]

Scheme 55. Preparation of (2*S*,1′*S*,2′*R*,3′*R*)-2-(2-carboxy-3-methylcyclopropyl)glycine[168]

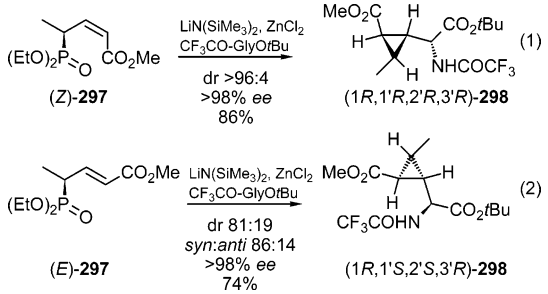


Employing essentially the same sequence of transformations as described for the preparation of (2*S*,1′*S*,2′*R*,3′*R*)-2-(2-carboxy-3-hydroxymethylcyclopropyl)glycine (**223**) (see section 2.7.3, Scheme 38), (2*S*,1′*S*,2′*R*,3′*R*)-2-(2-carboxy-3-methylcyclopropyl)glycine (**293**) was synthesized. Thus, (*E*)-but-2-en-1-ol (**294**) was converted to the cyclopropane-annelated lactone **295**. This was subsequently hydrolyzed, and the resulting acid was esterified to provide the disubstituted methyl cyclopropanecarboxylate **296**. Subsequent oxidation of the hydroxymethyl group to the aldehyde, diastereoselective Strecker reaction employing (*R*)-(−)-α-phenylglycinol, further oxidative cleavage, and hydrolysis gave rise to (2*S*,1′*S*,2′*R*,3′*R*)-2-(2-carboxy-3-methylcyclopropyl)glycine (**293**) (Scheme 55; for a detailed description, see section 2.7.3 and Scheme 38).[168]

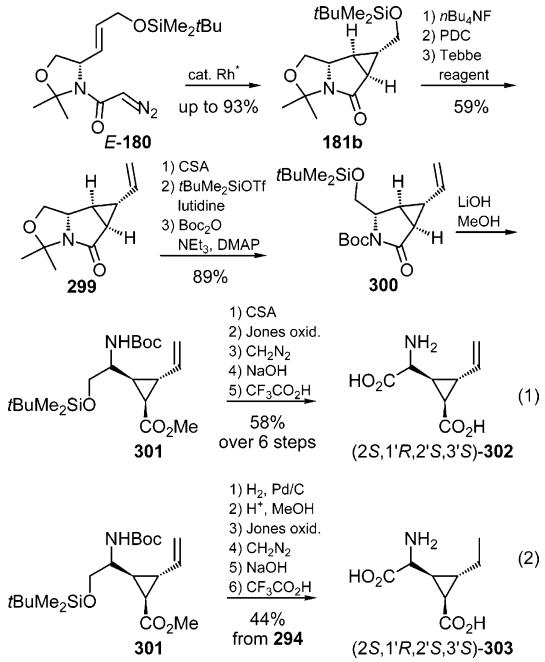
Enantiomerically pure protected 3-methyl-2-(2-carboxycyclopropyl)glycine has also been prepared by applying a Michael-induced ring closure (MIRC) reaction on a protected glycinate enolate in the presence of a zinc salt (for the intermediately formed chelated glycine ester zinc enolate, see section 2.7.1 and Scheme 18). When the reaction was carried out using the (*Z*)-isomer of the chiral phosphonyl-substituted pent-2-enoate **297** as the Michael acceptor, virtually diastereomerically as well as enantiomerically pure protected (1*R*,1′*R*,2′*R*,3′*R*)-2-(2-carboxy-3-methylcyclopropyl)glycine **298** was obtained. When, instead, the corresponding (*Z*)-pentenoate was employed, a mixture of four diastereomers was obtained, from which (1*R*,1′*S*,2′*S*,3′*R*)-**298** was isolated as the major product (Scheme 56).[86]

The pharmacological evaluation of the affinity of 2-(2-carboxy-3-methylcyclopropyl)glycine toward metabotropic glutamate receptors revealed that the (2*S*,1′*S*,2′*R*,3′*R*)-isomer was only slightly active, whereas the (2*S*,1′*S*,2′*S*,3′*R*)-isomer turned out to be not only a highly active and selective group II mGluR agonist but also an orally active compound in

Scheme 56. Preparation of Enantiopure 2-(2-Carboxy-3-methylcyclopropyl)glycines by MIRC Reactions[86]



Scheme 57. Synthesis of 3′-Vinyl- and 3′-Ethyl-2-(2-carboxycyclopropyl)glycine[169]



models for anxiety with remarkably high potency due to its good bioavailability.[168]

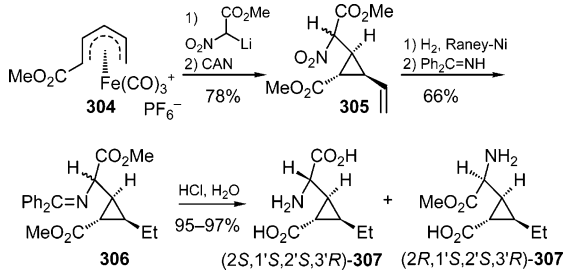
When the cyclopropanation of the (*E*)-4-aminopent-2-ene-1,5-diol derivative (*E*)-**180** was carried out in the presence of a rhodium instead of a palladium catalyst (see section 2.7.2, Scheme 32), the stereochemical outcome was reversed, and the *endo*-**181b** instead of the *exo*-adduct *exo*-**181a** was isolated. Subsequent removal of the silyl-protecting group in **181b** was followed by oxidation of the obtained hydroxymethyl group to the corresponding aldehyde, and this in turn was methylenated with Tebbe's reagent to yield the vinyl derivative **299**. Cleavage of the *O*,*N*-acetonide in **299** and protection of the hydroxy as well as the amino group provided the bicyclic lactam **300**, which was hydrolytically opened to afford **301**. A subsequent five-step transformation involving removal of the protecting groups and Jones oxidation gave (1*S*,1′*R*,2′*S*,3′*S*)-2-(2-carboxy-3-vinylcyclopropyl)glycine (**302**) (Scheme 57, eq 1).[169]

When in **301** the vinyl was hydrogenated to an ethyl group before removal of the protecting groups and Jones oxidation, (1*S*,1′*R*,2′*S*,3′*S*)-2-(2-carboxy-3-ethylcyclopropyl)glycine (**303**) was obtained (Scheme 57, eq 2).[169]

Characterization of (1*S*,1′*R*,2′*S*,3′*S*)-**302** and (1*S*,1′*R*,2′*S*,3′*S*)-**303** as ionotropic glutamate receptor ligands showed that both compounds exhibited only weak affinity toward these receptors; nevertheless, the vinyl-substituted glutamate analogue (1*S*,1′*R*,2′*S*,3′*S*)-**302** was characterized as a mixed agonist of non-NMDA type with a depolarizing potency almost as high as the one of NMDA or KA, and (1*S*,1′*R*,2′*S*,3′*S*)-**303** was found to act as a mixed NMDA-type agonist.[169]

Enantiomerically pure 3′-ethyl-substituted 2-(2-carboxycyclopropyl)glycine has been synthesized by employing the enantiopure tricarbonyl-(1-methoxycarbonylpentadienyl)iron tetrafluoroborate (**304**) and the lithium enolate of methyl nitroacetate with subsequent oxidative cleavage of the resulting tricarbonyl(diene)iron complex to lead to the vinylcyclopropane derivative **305** as a mixture of diastereomers. Reduction of both the vinyl as well as the nitro group, with Raney nickel and protection of the thus obtained amine

Scheme 58. Synthesis of Enantiomerically Pure 2-(2-Carboxy-3-ethylcyclopropyl)glycine[170,171]



as the diphenylmethyleneamino derivative, furnished a separable mixture of the two diastereomers of **306**. Hydrolysis of each of these provided (2*S*,1′*S*,2′*S*,3′*R*)- and (2*R*,1′*S*,2′*S*,3′*R*)-2-(2-carboxy-3-ethylcyclopropyl)glycine **307**, respectively (Scheme 58). Starting from the racemic iron complex **304**, the corresponding racemic 2-(2-carboxy-3-ethylcyclopropyl)-glycines were obtained.[170,171]

The enone **308**, prepared by Wittig alkenation of the Garner-aldehyde (*S*)-**48** with 1-phenyl-2-(triphenylphosphoranylidene)ethanone, upon reaction with ethyl (dimethylsulfuranylidene)acetate provided the disubstituted cyclopropanecarboxylate **309** as a separable mixture with two other diastereomers. Reduction of the phenyl ketone moiety by catalytic hydrogenation afforded the corresponding benzyl derivative, which was subjected to cleavage of the *O*,*N*-acetal and subsequent Jones oxidation. Final hydrolysis yielded 2-(3-benzyl-2-carboxycyclopropyl)glycine (**310**) as the (2*R*,1′*R*,2′*R*,3′*R*)-stereoisomer (Scheme 59).[172]

Applying an analogous reaction sequence as described for the synthesis of enantiomerically pure PCCG-4 (2*S*,1′*S*,2′*S*,3′*R*)-**239** (see section 2.7.5, Scheme 43) to 9-xanthenylmethyl- and 9-xanthenylethyl-substituted allyl diazoacetate, respectively, provided (1*S*,1′*S*,2′*S*,3′*R*)-2-(2-carboxy-3-xanthenylmethylcyclopropyl)glycine (**311**) and (1*S*,1′*S*,2′*S*,3′*R*)-2-(2-carboxy-3-xanthenylethylcyclopropyl)-glycine (**312**) (Figure 6). Evaluation of these compounds as metabotropic glutamate receptor ligands showed that both compounds selectively exhibited antagonist activity toward

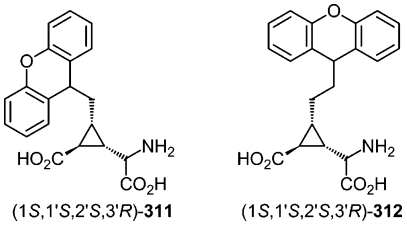
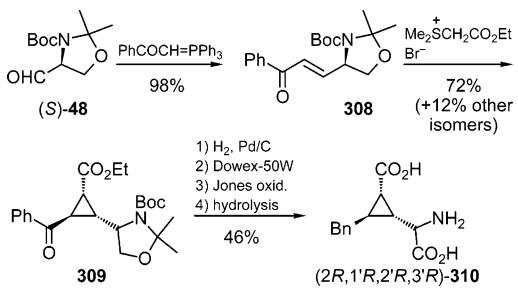
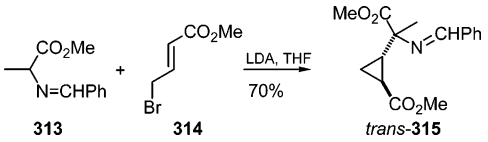


Figure 6. Structures of 3-xanthenylmethyl- and 3-xanthenylethyl-substituted 2-(2-carboxycyclopropyl)glycine.[173]

Scheme 59. Preparation of (2*R*,1′*R*,2′*R*,3′*R*)-2-(3-Benzyl-2-carboxycyclopropyl)glycine[172]



Scheme 60. Preparation of Racemic *trans*-2-Methyl-2-(carboxycyclopropyl)glycine[81]



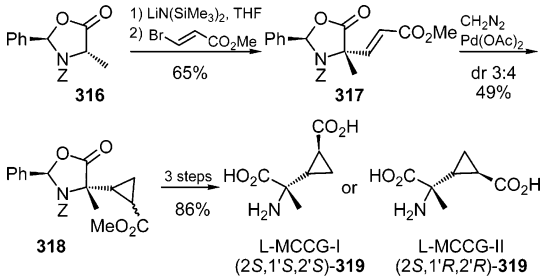
group II mGluRs, with (1*S*,1′*S*,2′*S*,3′*R*)-**311** being the more potent ligand.[173]

2.7.8. 2-Substituted (2-Carboxycyclopropyl)glycines

A Michael-induced ring closure (MIRC) reaction of the protected alanine **313** with methyl (2*E*)-4-bromobut-2-enoate (**314**) yielded racemic 2-methyl-2-(carboxycyclopropyl)-glycine in its protected form *trans*-**315** (Scheme 60).[81]

The chiral *trans*-2-phenyloxazolidinone **316**, easily available from L-alanine, served as the starting material for the preparation of enantiopure 2-methyl-2-(carboxycyclopropyl)-glycine. Michael addition of the enolate of **316** to methyl (*E*)-3-bromopropenoate gave the α,β-unsaturated ester **317**. Palladium-catalyzed cyclopropanation of the latter with diazomethane led to the cyclopropane derivative **318** as a separable mixture of two diastereomers. Stepwise hydrolysis of each of these furnished the 2-methyl-2-(carboxycyclopropyl)glycines L-MCCG-I (2*S*,1′*S*,2′*S*)-**319** and L-MCCG-II (2*S*,1′*R*,2′*R*)-**319**, respectively (Scheme 61).[174]

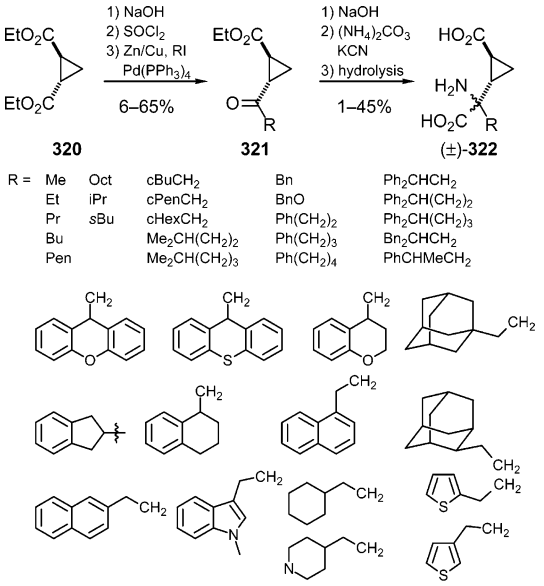
Scheme 61. Synthesis of Stereodefined 2-Methyl-2-(carboxycyclopropyl)glycine[174]



In analogy to L-CCG-I, L-MCCG-I was found to exhibit selective affinity for group II metabotropic glutamate receptors, but interestingly, the additional α-methyl group caused this compound to be an antagonist rather than an agonist.[175,176] Studies directed toward the characterization of antagonists of mGluR2 and -4 revealed L-MCCG-I to be the most potent antagonist for mGluR2 known to date, with no activity at mGluR4.[177] Thus, L-MCCG-I was able to antagonize the antiseizure activity of L-CCG-I and DCG-IV.[142,178] However, concomitantly L-MCCG-I behaved as a partial agonist at group II metabotropic receptors, limiting its usefulness as a metabotropic glutamate receptor antagonist.[112,179]

In order to study the antagonist properties of α-substituted 2-(carboxycyclopropyl)glycine in detail, a whole series of these compounds was synthesized by a general approach. Thus, the C_2-symmetric diethyl cyclopropanedicarboxylate (**320**) was hydrolyzed to the monoester, and the acid then converted into the corresponding acid chloride, which, upon zinc- or copper-mediated, palladium-catalyzed coupling with various alkyl iodides, afforded the alkyl cyclopropyl ketones **321**. Hydrolysis of their ester function, hydantoin formation under Bucherer−Berg conditions, and final hydrolysis of the hydantoin furnished α-substituted 2-(carboxycyclopropyl)-

Scheme 62. Preparation of α-Alkyl-Substituted 2-(Carboxycyclopropyl)glycines[180]



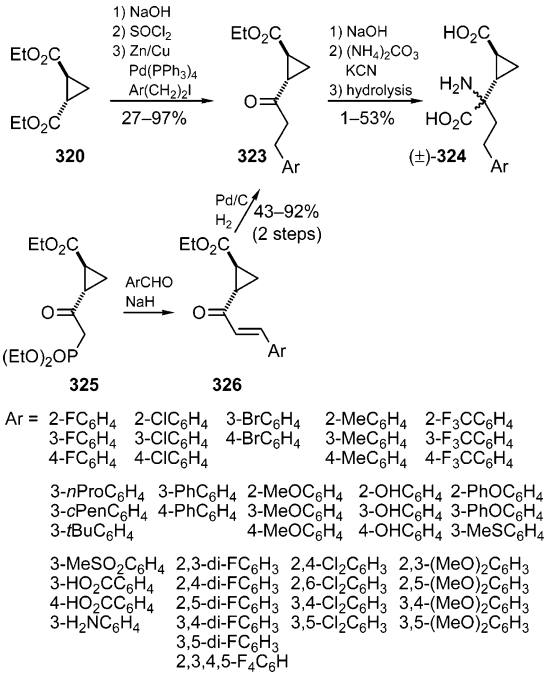
glycines **322**, however, as mixtures of two diastereomeric pairs of enantiomers (Scheme 62).[180]

Studies concerning the structure−activity relationship of these isomeric mixtures showed that other simple alkyl substituents did not lead to any significant change of the affinity in comparison with the α-methyl-substituted compound **319**, but phenylethyl and diphenylethyl substituents were beneficial. The affinity of the diphenylethyl-substituted derivative could further be enhanced by linking the two phenyl groups with a heteroatom as in the tricyclic xanthylmethyl and thioxanthylmethyl groups. Among the numerous evaluated substrates, only the amino acids with these two substituents were able to distinguish between the group II subreceptors mGluR2 and mGluR3, both being 13−16 times more potent at mGluR2. Generally, α-xanthylmethyl-substituted 2-(carboxycyclopropyl)glycine turned out to be about 50 times more active than the analogous α-methyl-substituted compound **319**.[180] The pharmacological profile of 2-xanthylmethyl-2-(carboxycyclopropyl)glycine, referring to LY341495, was further studied in detail, supporting its nanomolar potency for mGluR2 and -3, but also revealing its only slightly lower potency for mGluR8 and its micromolar activity for mGluR7 as well as its low potency for any other metabotropic glutamate receptor subtypes and no activity toward ionotropic glutamate receptors.[181] As such, LY341495 has served as a valuable tool in the discovery of a new putative metabotropic glutamate receptor.[182]

Additionally, a tritiated version of 2-xanthylmethyl-2-(carboxycyclopropyl)glycine has been synthesized in order to be employed in the activity studies.[183]

With the intention to further increase the affinity toward group II metabotropic glutamate receptors, the effects of substitution on the aromatic ring of 2-phenylethyl-2-(carboxycyclopropyl)glycine were explored. The desired mixtures of four stereoisomers of the compounds (±)-**324** were prepared by hydantoin formation and subsequent hydrolysis of the ketoester intermediate **323**, which was available either as described above (see Scheme 62), by palladium-catalyzed coupling of the monoacid chloride derived from **320** with a substituted 2-phenylethylzincate, or by Horner−Emmons alkenation of substituted benzaldehydes with the phosphonate **325** followed by hydrogenation of the enones **326** (Scheme

Scheme 63. Synthesis of α-(2-Arylethyl)-2-(carboxycyclopropyl)glycines[184]



63). It turned out that *meta*- but not *ortho*- or *para*-substitution on the aromatic ring in (±)-**324** with a variety of electron-donating as well as electron-withdrawing substituents caused an increase in affinity, with the exception that the *para*-fluoro-substituted derivative was the most potent compound of all the monosubstituted ones.[184]

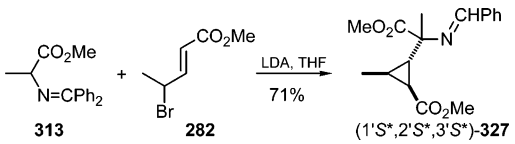
2-Diphenylethyl-, 2-xanthylmethyl-, and 2-(3-methylphenyl)ethyl-2-(2-carboxycyclopropyl)glycine were resolved into their four constituent stereoisomers, and the affinity as well as antagonist activity toward group II mGluRs was found to reside solely in the (2*S*,1′*S*,2′*S*)-isomers, consistent with the affinity of L-CCG-I (2*S*,1′*S*,2′*S*)-**127**. Among the assayed compounds, 2-xanthylmethyl(carboxycyclopropyl)glycine turned out to be the most potent one, showing high plasma levels and ready penetration into the brain, but unfortunately only limited bioavailability.[184]

2.7.9. 2-Alkyl-(3-alkyl-2-carboxycyclopropyl)glycines

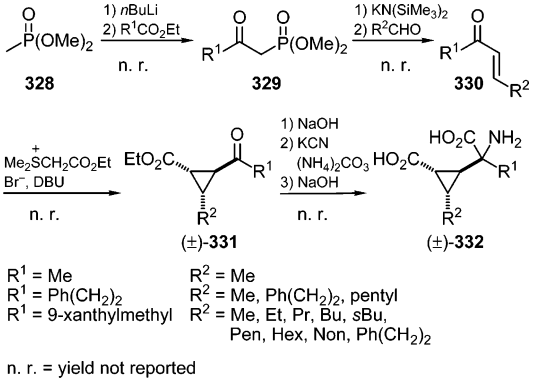
In analogy to the preparation of 2-(2-carboxy-3-methylcyclopropyl)glycine (see section 2.7.7, Scheme 52), Michael-induced ring closure (MIRC) reaction of the protected alanine **313** with methyl (2*E*)-4-bromopent-2-enoate (**282**) furnished racemic 2-methyl-2-(2-carboxy-3-methylcyclopropyl)glycine as the *trans*,*cis*,*trans*-isomer (1′*S*,2′*S*,3′*S*)-**327** (Scheme 64).[81]

In order to synthesize a whole range of differently 2,3′-disubstituted 2-(2-carboxycyclopropyl)glycines, the α,*β*-unsaturated carbonyl compounds **330** were conceived as suitable precursors. Preparation of the latter was accomplished by conversion of dimethyl methylphosphonate (**328**) into the corresponding 2-oxoalkylphosphonates **329** and subsequent Horner−Emmons reaction with the respective

Scheme 64. Synthesis of *trans*,*cis*,*trans*-2-Methyl-2-(2-carboxy-3-methylcyclopropyl)glycine[81]



Scheme 65. Preparation of 2-Alkyl-(3-alkyl-2-carboxycyclopropyl)glycines[185]



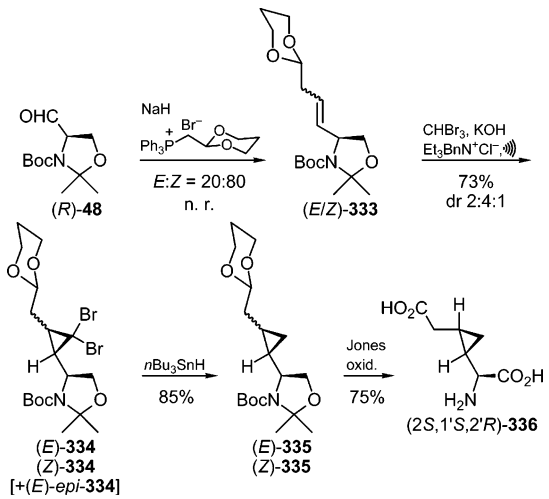
aldehydes. Stereoselective cyclopropanation of the alkenones **330** utilizing ethyl (dimethylsulfuranylidene)acetate led to the corresponding cyclopropane derivatives, which were isolated each as the single diastereomer **331**. Hydrolysis of the ester moiety, subsequent hydantoin formation under Bucherer−Berg conditions, and final hydrolysis of the hydantoin led to the 2-alkyl-2-(3-alkyl-2-carboxycyclopropyl)glycines **332**, each of which was obtained as a mixture of four stereoisomers (Scheme 65).[185]

All of the thus prepared compounds were evaluated as ligands for metabotropic glutamate receptors. In this context, antagonist activity for all compounds toward group II receptors was indicated with a generally 10−50 times higher potency for mGluR2 compared to mGluR3 and the highest affinity for the xanthylmethyl-substituted derivatives. Additionally, general antagonist activities toward group III receptors were demonstrated with a preference for the mGlu8 subreceptor. With the exception of the 9-xanthylmethyl-substituted derivatives endowed with a 3′-hexyl and 3′-nonyl substituent, respectively, none of the evaluated compounds exhibited any significant antagonist activities toward group I receptors.[185]

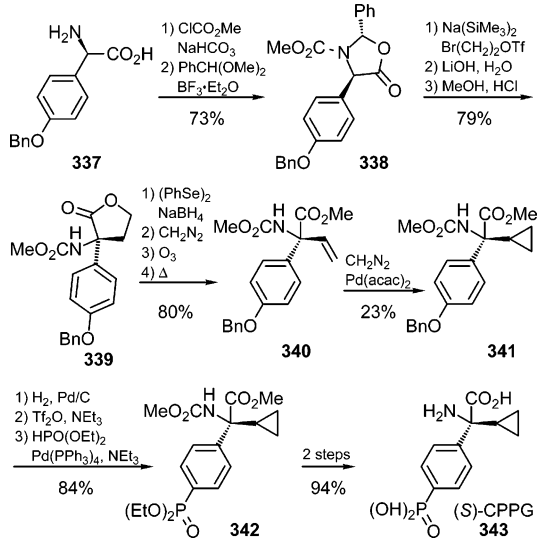
2.7.10. 3,4-Methanohomoglutamic Acid [(2-Carboxymethylcyclopropyl)glycine]

The naturally occurring *trans*-2-(2-carboxymethylcyclopropyl)glycine (**336**) was first isolated from *Blighia unijugata*.[186] A stereoselective synthesis of this amino acid started

Scheme 66. Preparation of (2*S*,1′*S*,2′*R*)-2-(2-Carboxymethylcyclopropyl)glycine[188]



Scheme 67. Synthesis of (*S*)-2-Cyclopropyl-4-phosphonophenylglycine[189]



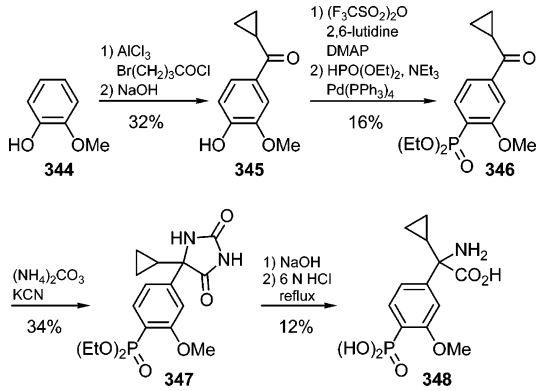
with a Wittig alkenation of the Garner aldehyde (*R*)-**48** with the ylide from 2-(2,3-dioxan-2-yl)ethylidenetriphenylphosphonium bromide to yield a mixture of the (*E*)- and (*Z*)-isomers of the corresponding alkene **333**. Dibromocyclopropanation under phase-transfer catalysis conditions furnished a mixture of three diastereomers of the dibromocyclopropane derivative **334**, which was identified to consist of the (*Z*)-isomer (*Z*)-**334** as well as the two (*E*)-isomers (*E*)-**334** and (*E*)-*epi*-**334** with the opposite configuration on the cyclopropane ring (structure not shown).[187] One of the three could be picked out, and reductive debromination of the remaining mixture of two diastereomers afforded the cyclopropanes (*E*)-**335** and (*Z*)-**335**, which were easily separated by chromatography. Jones oxidation of (*E*)-**335** provided (2*S*,1′*S*,2′*R*)-**336**, which was identified to be the naturally occurring stereoisomer (Scheme 66).[188]

2.8. 2-Cyclopropyl-2-(4-phosphonophenyl)glycine

With the objective of preparing (*S*)-2-cyclopropyl-2-(4-phosphonophenyl)glycine [(*S*)-**343**], the amino group of (*R*)-2-(4-benzyloxyphenyl)glycine (**337**) was protected as the carbamate and the latter was treated with benzaldehyde dimethyl acetal under boron trifluoride catalysis to yield the *trans*-disubstituted oxazolidinone **338**. Stereoselective alkylation of the enolate derived from **338** with 2-bromoethyl triflate gave the corresponding 4-(2-bromoethyl) derivative, which was further converted to the aminolactone **339**. Nucleophilic ring opening of **339** with in situ generated sodium phenylselenide, and esterification with diazomethane, oxidation with ozone to the selenoxide, and subsequent thermal elimination of benzeneselenenic acid led to the α-ethenylglycine derivative **340**, cyclopropanation of which with diazomethane in the presence of a palladium acetylacetonate produced the cyclopropylglycine derivative **341**. Hydrogenolytic removal of the benzyl group, transformation of the liberated hydroxy function into a better leaving group, and eventual palladium-catalyzed phosphonation yielded the desired cyclopropylglycine in its protected form **342**. Final hydrolysis of the latter in two steps led to enantiomerically pure 2-cyclopropyl-2-(4-phosphonophenyl)glycine in its fully deprotected form (*S*)-CPPG **343** (Scheme 67).[189]

2-Cyclopropyl-2-(4-phosphonophenyl)glycine in its racemic form (±)-**343** was found to be a potent glutamate

Scheme 68. Synthesis of Racemic 2-Cyclopropyl-2-(3-methoxy-4-phosphonophenyl)glycine[192]



receptor antagonist toward metabotropic group II and group III receptors with a 30-fold selectivity for group III receptors, a negligible activity at group I receptors, and no activity at ionotropic receptors.[190−192]

The analogous 2-cyclopropyl-2-(3-methoxy-4-phosphonophenyl)glycine (**348**) was synthesized from guaiacol **344**, starting with its acylation with 4-bromobutyryl chloride in the presence of aluminum trichloride, initiating a Fries rearrangement to the corresponding butyrophenone, which cyclized to the aryl cyclopropyl ketone **345** upon treatment with base. Triflation of the latter followed by palladium-catalyzed phosphonation afforded the (4-phosphonophenyl)-substituted analogue **346**. Hydantoin formation under Bucherer−Berg conditions gave the arylcyclopropylhydantoin **347**, which was subsequently hydrolyzed to 2-cyclopropyl-2-(3-methoxy-4-phosphonophenyl)glycine (**348**) (Scheme 68).[192]

Compound **348** was evaluated with respect to its pharmacological properties on metabotropic glutamate receptors and showed neither agonist nor antagonist activities.[192]

Among other α-aryl-substituted cyclopropylglycines, the antagonist activity of (±)-α-cyclopropyl-4-carboxyphenylglycine at group I metabotropic glutamate receptors was studied, and it turned out to be more effective toward mGluR5 than toward mGluR1, but generally weak compared to other antagonists; however, its synthesis has not been described in detail.[193]

2.9. Other Substituted 3,4-Methanoamino Acids

In 1979, the so-called substance SF-1835 was isolated from the fermentation broth of *Streptomyces zaomyceticus*. SF-1835 exhibited antimicrobial activity against *Xanthomonas* species and was effective in controlling bacterial leaf blight of rice plants under greenhouse conditions.[194] The antimicrobial activity was antagonized by L-proline, suggesting a bioactivity as an antimetabolite of L-proline. The structure of SF-1835 was elucidated to be that of (3*S*)-2-azabicyclo-[2.1.0]pentane-3-carboxylic acid (**349**) (Figure 7), a highly strained and thereby reactive bicyclic analogue of proline.[195]

Besides 3,4-methano analogues of proteinogenic or non-proteinogenic naturally occurring amino acids, numerous synthetic cyclopropylglycines endowed with a variety of substituents on the cyclopropane ring have been prepared.

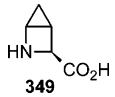


Figure 7. (3*S*)-2-Azabicyclo[2.1.0]pentane-3-carboxylic acid.

A convenient general approach to such amino acids has been elaborated starting from the readily available alkyl 2-chloro-2-cyclopropylideneacetate **356**,[196] acting as a Michael acceptor.

Reaction of dimethyl- and diethylamine as well as piperidine with the unsubstituted as well as di-, tri-, and tetramethyl-substituted alkyl 2-chloro-2-cyclopropylideneacetates **356** led to several 3-amino-substituted cyclopropylglycine derivatives **352** in a single step in moderate to good yields (Scheme 69).[197]

Several monosubstituted cyclopropylideneacetates **356** (R^2-R^4 = H) were treated with (4*S*,5*R*)-4,5-diphenyl-1,3-oxazilidin-2-one to yield the respective Michael adducts **357** with excellent *trans*-selectivities (with respect to the newly introduced substituents on the three-membered ring). Subsequent reductive dehalogenation of the separated diastereomers, enolate formation, introduction of an amino group equivalent by electrophilic azide transfer, hydrogenolytic removal of the chiral auxiliary along with reduction of the azido to an amino group, and final hydrolysis afforded diastereomerically and enantiomerically pure 4-substituted 3-amino-3,4-methanoamino acids **358** (Scheme 69).[198,199]

According to this method, unsubstituted methyl or benzyl 2-chloro-2-cyclopropylideneacetate **356** (R^1-R^4 = H, R^5 = Bn) was converted with nucleophiles, providing 1′-substituted 2-chloro-2-cyclopropylacetates **360**. Substitution of the chlorine with azide and mild deprotection led to 1′-methyl-, 1′-amino-, 1′-hydroxy-, 1′-methoxycarbonylmethyl-, and 1′-methylthio-substituted 2-cyclopropylglycines **363** (Scheme 69).[16] Upon reduction of 2′-benzyloxymethyl-substituted benzyl 2-chloro-2-cyclopropylideneacetate **356** (R^1 = $BnOCH_2$, R^2-R^4 = H), a benzyloxymethyl-substituted cyclopropane derivative analogous to **360** was obtained (Nu = H), which was further transformed into the 4-hydroxymethyl-3,4-methanoamino acid.[16]

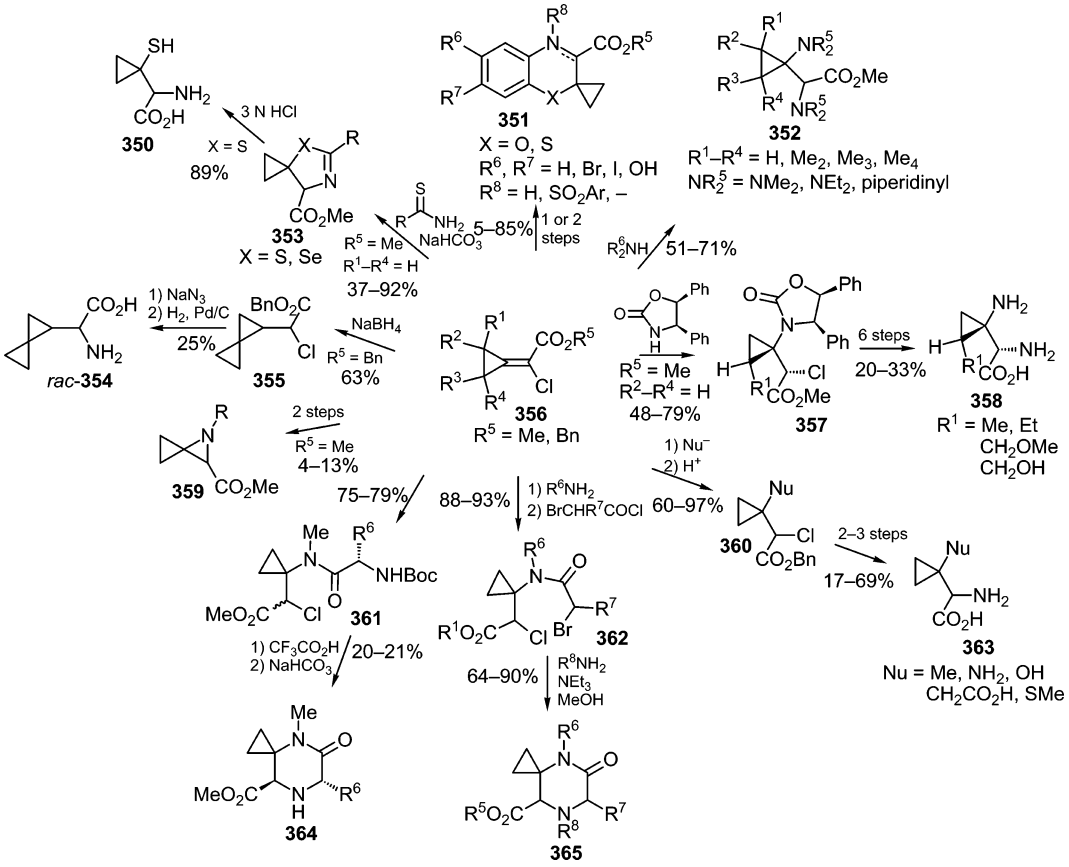
Unsubstituted methyl or benzyl 2-chloro-2-cyclopropylideneacetate **356** (R^1-R^4 = H) was treated with primary amines, and the obtained Michael adducts were coupled with bromoacetyl chloride to yield bromochloro-substituted acylaminoesters **362**, which, by treatment with a primary amine, underwent twofold nucleophilic substitution with ring closure to furnish the *N*,*N*′-substituted spirocyclopropanated 4-oxopiperazinecarboxylates **365** with an incorporated cyclopropylglycine moiety (Scheme 69). An analogous sequence of transformations, yet with the incorporation of chiral amino acids, led to enantiomerically pure 5-substituted 4-oxopiperazinecarboxylates **364** via the separable diastereomeric dipeptides **361** (Scheme 69). Compounds **364** were further transformed into octahydro[2*H*]pyrazino[1,2-a]pyrazines as conformationally restricted tetrapeptide mimics.[200]

The highly strained methyl *N*-benzyl-1-azaspiropentane-2-carboxylate **359** was also accessed from methyl 2-chloro-2-cyclopropylideneacetate **356** (R^1-R^4 = H) (Scheme 69), albeit in rather low yield.[201]

Racemic spiropentylglycine (*rac*-**354**) was obtained by reduction of benzyl 2-chloro-2-spiropentylideneacetate (**356**) (R^1-R^2 = CH_2-CH_2, R^3, R^4 = H, R^5 = Bn), nucleophilic substitution of the chlorine **355** with azide, and hydrogenolytic deprotection (Scheme 69).[202]

Thiocarboxamides and thioureas as well as selenoamides were also found to easily undergo Michael additions onto alkyl 2-chloro-2-cyclopropylideneacetates **356**, with the sulfur or selenium, respectively, attacking as the nucleophilic moiety, and subsequent intramolecular substitution to afford

Scheme 69. Syntheses of Substituted 3,4-Methanoamino Acids Starting from Alkyl 2-Chloro-2-cyclopropylideneacetates[16,197,199−206]



spirocyclopropane-annelated thiazoline- and selenazolinecarboxylates **361**, respectively, formally incorporating a 3,4-methanoamino acid moiety.[203,204] Hydrolysis was performed for the sulfur-containing compound, providing (1′-mercaptocyclopropyl)glycine (**350**), formally a 3-mercapto-3,4-methanoamino acid and a thioanalogue of cleonine **30** (Scheme 69).[203]

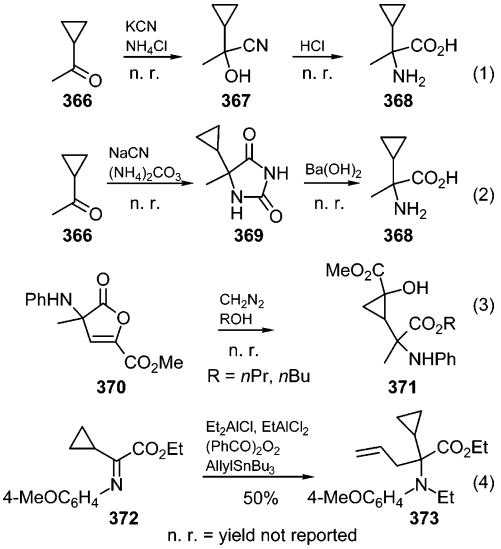
Additionally, diverse heterocycles **351** which formally comprise a 3-mercapto- or 3-hydroxy-3,4-methanoamino acid unit were prepared starting from alkyl 2-chloro-2-cyclopropylideneacetates **356** ($R^1-R^4 = H$) (Scheme 69).[205]

Various individual approaches to substituted cyclopropylglycine derivatives have also been developed.

2-Cyclopropyl-2-methylaminoacetic acid (**368**), also called 2-cyclopropylalanine, corresponding to 2-methylcyclopropylglycine, has been synthesized from cyclopropyl methyl ketone (**366**) via the cyanohydrin **367** by applying a Strecker-type synthesis (Scheme 70, eq 1). Along with the synthesis of 1-aminocyclopropane-1-carboxylic acid (see Part 1, section 2.2),[8] this preparation, dating from 1922,[1] represents the first synthesis of a cyclopropane-containing amino acid.[207]

Again starting from cyclopropyl methyl ketone (**366**), 2-cyclopropylalanine (**368**) has also been obtained via the corresponding hydantoin **369** (Scheme 70, eq 2).[208] In this context, the amino acid **368** has been incorporated into a glycyl-dipeptide.[209] In conjunction with a survey of α,α-disubstituted phthalimidoacetamides as anticonvulsant agents, the phthalimidoylation of cyclopropylmethylaminoacetic acid **368** has been studied.[210] Following an analogous hydantoin formation and hydrolysis, but starting with 1-(1-methylcyclopropyl) methyl ketone, 2-(1-methylcyclopropyl)alanine

Scheme 70. Syntheses of 2-Substituted Cyclopropylglycine Derivatives[207−209,212,213]

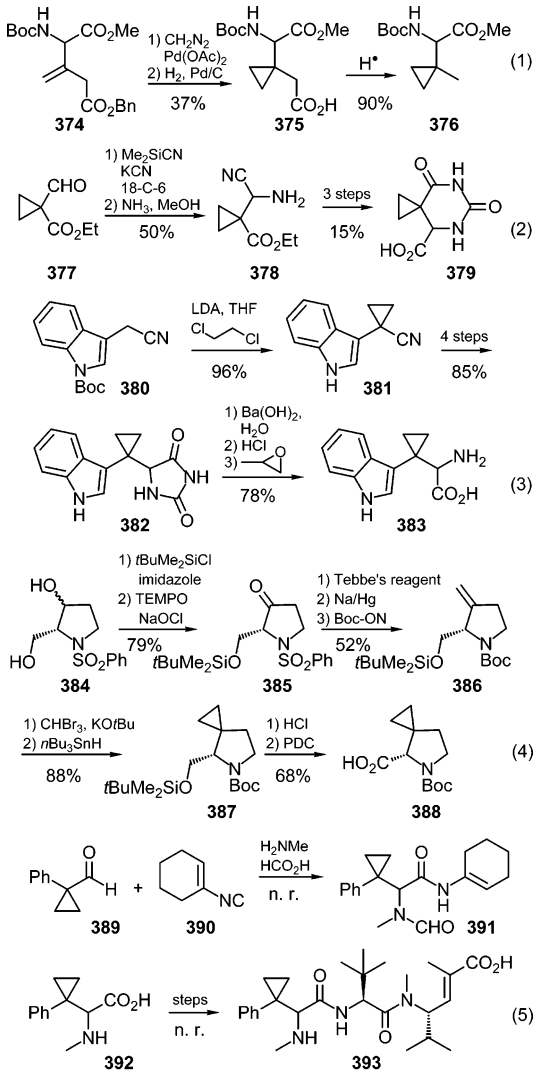


was synthesized. Upon biological examination of the latter, an expected toxicity against *Escherichia coli* could not be verified.[211]

The enol lactone **370** reacted with diazomethane in an alcoholic solvent to yield 2-(2-carboxy-2-hydroxycyclopropyl)alanine in its protected form **371**; the latter represents a substituted 2-methyl-2-cyclopropylglycine derivative (Scheme 70, eq 3).[212]

In the context of a study toward the reactivity of α-imino esters, a synthesis of α,α-disubstituted amino acids has been

Scheme 71. Syntheses of 1′-Substituted Cyclopropylglycine Derivatives[217−220]



discovered, performing a sequential *N*-alkylation and *C*-allylation reaction of α-imino esters using organoaluminum reagents and allyltributyltin. Application of these reaction conditions to the cyclopropyl-substituted imino ester **372** furnished the 2-allylcyclopropylglycine derivative **373** (Scheme 70, eq 4).[213]

(*S*)-2-(1-Methylcyclopropyl)glycine was isolated from the culture broth of *Micromonospora miyakonensis* sp. nov. and was found to exhibit antimicrobial activity against *Escherichia coli* on a synthetic medium.[214,215] Protected racemic 2-(1-methylcyclopropyl)glycine has been prepared starting with the 1,3-dipolar cycloaddition of diazomethane to the protected 3-methyleneglutamate **374**, a 3,4-dehydroamino acid derivative.[216] Subsequent hydrogenolytic cleavage of the benzyloxycarbonyl group afforded protected 2-(1-carboxymethylcyclopropyl)glycine **375**, corresponding to a 3,3-ethano analogue of protected glutamic acid which, upon homolytic decarboxylation, furnished methyl *N*-Boc-(1-methylcyclopropyl)glycinate (**376**) (Scheme 71, eq 1).[217]

The inhibition of dihydroorotate dehydrogenase (DHOD) has been identified as a significant target for chemotherapy, especially of parasitic diseases. 5-Spirocyclopropanedihydroorotic acid **379**, which represents a direct substrate analogue of DHOD, was expected to exhibit interesting activity as an activator or as an irreversible inhibitor of DHOD. Submitting ethyl 1-formylcyclopropane-1-carboxylate (**377**) to Strecker conditions gave the aminonitrile **378**. Transformation of its amino into a urea functionality, cyclization to the cyanopyrimidindione, and final hydrolysis gave rise to 5-spirocyclopropanedihydroorotic acid **379** (Scheme 71, eq 2). However, the biological activity of **379** has not been reported yet.[218]

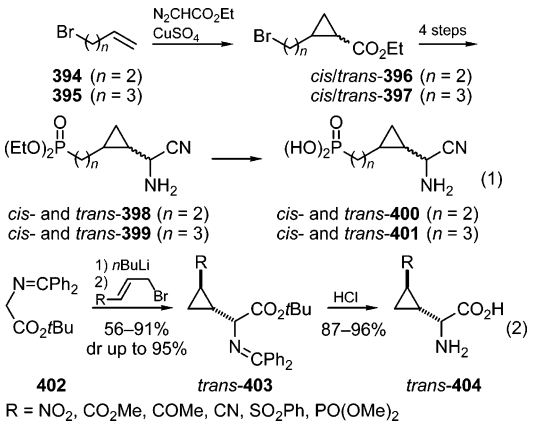
Within a study directed toward the synthesis of conformationally constrained analogues of trypthophane, the cyclopropyl derivative **383** was synthesized. Protected indolylacetonitrile **380** was 2,2-dialkylated with 1,3-dichloroethane, furnishing 3-(1-cyanocyclopropyl)indole (**381**). Reduction of the cyano to an imino group and subsequent hydrolysis afforded the corresponding aldehyde, which was further converted into the hydantoin **382**. Hydrolysis of the latter provided 2-[1-(1*H*-indol-3-yl)cyclopropyl]glycine (**383**), corresponding to a tryptophane analogue with a 1,1-disubstituted cyclopropane moiety (Scheme 71, eq 3).[219]

3-Spirocyclopropanated proline **388** was accessible from *N*-phenylsulfonyl-2-hydroxymethyl-3-hydroxypyrrolidine (**384**). Selective protection of the primary hydroxy group in **384** as a silyl ether and oxidation of the secondary alcohol provided the pyrrolidinone **385**. Methylenation of this ketone with Tebbe's reagent, reductive removal of the *N*-sulfonyl, and replacement with a *tert*-butoxycarbonyl group yielded the *N*-Boc-3-methylenepyrrolidine (**386**). The latter was dibromocyclopropanated, and the two bromines were removed from the resulting dibromocyclopropane by reduction with tri-*n*-butyltin hydride. Eventual desilylation and oxidation of the alcohol furnished the protected 3-spirocyclopropanated proline **388** (Scheme 71, eq 4). The latter has been incorporated into the tetrapeptide Z-Gly-Phe-X-GlyOEt, which was tested as a substrate analogue and a mechanistic probe for the human prolyl 4-hydroxylase-catalyzed hydroxylation reaction and turned out to be neither an inhibitor nor a substrate of the enzyme.[221]

Applying the Ugi four-component reaction, condensation of 1-phenylcyclopropanecarbaldehyde (**389**), 1-isocyanocyclohexene (**390**), methylamine, and formic acid, provided the *N*-formyldipeptide **391**, which was hydrolyzed to *N*-methyl-(1-phenylcyclopropyl)glycine (**392**), an analogue of phenylalanine with a 1,1-disubstituted cyclopropane moiety (Scheme 71, eq 5). The *N*-methyl(1′-phenylcyclopropyl)-glycine **392** was used to prepare the peptidomimetic **393** (Scheme 71, eq 5), representing an analogue of the natural product Hemiasterlin, which induces microtubule depolymerization and mitotic arrest in cells. Among a variety of other analogues of Hemiasterlin, the peptidomimetic **393** was evaluated with respect to its effects on microtubule polymerization as well as its in vitro and in vivo anticancer activity. It showed excellent inhibition of microtubule polymerization, yet its cytotoxicity was significantly lower than that of other analogues.[220]

In order to obtain 2′-phosphonoalkyl-substituted cyclopropylglycine derivatives, 4-bromo-1-butene (**394**) and 5-bromo-1-pentene (**395**) were cyclopropanated with ethyl diazoacetate under copper catalysis to provide **396** and **397**. Separation of the *cis*- and *trans*-isomers, their transformations into the corresponding aldehydes, and Arbuzov and subsequent Strecker reactions afforded the aminonitriles *cis*- and *trans*-**398** as well as *cis*- and *trans*-**399**. Final hydrolysis gave rise to *cis*- and *trans*-2-phosphonoethyl- and (2-phosphono-

Scheme 72. Syntheses of 2′-Substituted Cyclopropylglycines[84,222]

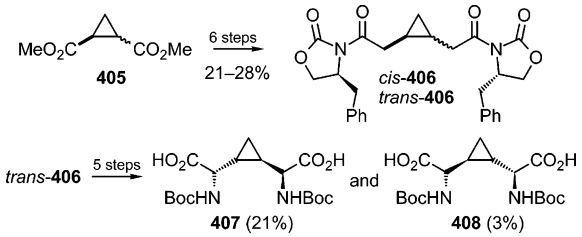


propylcyclopropyl)glycine in their free forms *cis*- and *trans*-**400** as well as *cis*- and *trans*-**401**, respectively, each of them as a mixture of four stereoisomers (Scheme 72, eq 1). The four compounds *cis*- and *trans*-**400** as well as *cis*- and *trans*-**401** were assessed with respect to their biological activities as *N*-methyl-D-aspartate (NMDA) receptor antagonists. Yet, none of these 2′-phosphonoalkyl-substituted cyclopropylglycines exhibited any antagonist activity; however, *cis*-**401** manifested agonist-like activity at the NMDA receptor and as such represents the only example of an ω-phosphonoamino acid with inverted efficacy at the NMDA receptor.[222]

Diastereomerically pure substituted cyclopropylglycines endowed with an electron-withdrawing group in the 2′-position were prepared by Michael-induced ring closure (MIRC) reaction of the enolate of the protected glycine **402** with several appropriately 1-substituted (*E*)-3-bromopropenes to yield the *trans*-diastereomers *trans*-**403**, which eventually were deprotected to 2′-substituted cyclopropylglycines *trans*-**404** in their free form (Scheme 72, eq 2). The nitro-substituted derivative was further reduced to 2,4-diamino-3,4-methanobutanoic acid. Application of this method to (*E*)-3-bromo-2-methyl-1-nitroprop-1-ene furnished 2-(1-methyl-2-nitrocyclopropyl)glycine.[84]

With the aim to link two glycine residues with conformationally rigid two-carbon bridges between the α- and α'-positions, *trans*-cyclopropane-1,2-bisglycine (**407**) was prepared in a stereoselective manner. Thus, a *cis*/*trans* mixture of dimethyl cyclopropane-1,2-dicarboxylate (**405**) was reduced to the corresponding mixture of diols, and the diastereomers were separated. Conversion of the *cis*- and the *trans*-diols to the corresponding dibromide, subsequent nucleophilic substitution with cyanide, hydrolysis of the resulting bisnitrile, conversion of the diacid into the bisacid chloride, and acylation of (*S*)-4-benzyl-2-oxazolidinone with each of the diastereomeric diacid dichlorides gave the diastereomeric bisamides *cis*- and *trans*-**406**, respectively. Introduction of the two amino functionalities was accomplished by electrophilic azidation of the bisenolate of, for example, *trans*-**406**, whereupon two diastereoisomers were obtained as a separable mixture. Subsequent reduction of the azide functionalities, twofold *N*-*tert*-butoxycarbonyl protection, and hydrolytic removal of the chiral auxiliaries afforded protected (1*R*,2*R*)-1,2-bis[(2*S*)-amino]cyclopropanediacetic acid **407** and (1*S*,2*S*)-1,2-bis[(2*S*)-amino]cyclopropanediacetic acid **408** (cyclopropane-*trans*-1,2-bisglycine) (Scheme 73).[223]

Scheme 73. Stereoselective Synthesis of Protected Cyclopropane-*trans*-1,2-bisglycine[223]



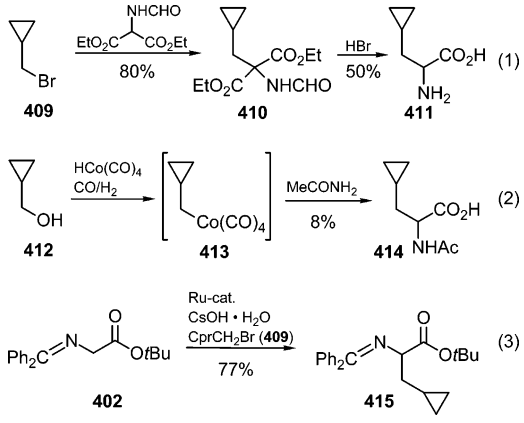
3. 4,5-Methanoamino Acids

3.1. 3-Cyclopropylalanine, the Unsubstituted 4,5-Methanoamino Acid

In 1986, an antifungal amino acid, which was found to inhibit the spore germination of *Pyricularia oryzae*, causing rice blast disease, was isolated from the mushroom *Amanita virgineoides* Bas. Its structure was elucidated as (*S*)-2-amino-3-cyclopropylpropionic acid (**411**), equivalent to (*S*)-3-cyclopropylalanine.[224] Racemic 3-cyclopropylalanine was found to have potent antibacterial activity against a certain strain of *Escherichia coli*.[225]

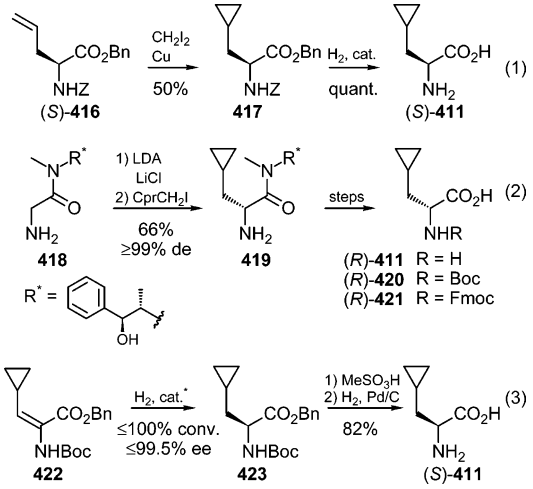
3-Cyclopropylalanine in its racemic form was first synthesized in 1955 from cyclopropylmethyl bromide (**409**), readily available by conversion of cyclopropylmethanol. Alkylation of diethyl formamidomalonate with **409** furnished **410**, which, upon hydrolysis and decarboxylation, afforded 3-cyclopropylalanine (**411**) in its free form (Scheme 74, eq 1). During this investigation, 3-cyclopropylalanine was found to have a sweet taste.[225] Following the same procedure, but using 2-(acetylamino)malonate, *N*-acetylcyclopropylalanine (**414**) was prepared.[226] The latter was also obtained from cyclopropylmethanol (**412**) by cobalt-mediated amidocarbonylation via the tetracarbonyl(cyclopropylmethyl)cobalt σ-complex **413**, albeit in rather low yield (Scheme 74, eq 2).[227]

Scheme 74. Syntheses of Racemic 3-Cyclopropylalanine[225,227−229]



Racemic 3-cyclopropylalanine in its protected form **415** has also been made available by alkylation of the enolate of the protected glycine **402** with cyclopropylmethyl bromide (**409**) in the presence of cesium hydroxide and a catalytic amount of a ruthenium(II)−polypyridyl complex as a phase transfer catalyst (Scheme 74, eq 3).[228] Application of a chiral allyl(anthracenylmethyl)cinchonidinium bromide as a phase

Scheme 75. Syntheses of Enantiomerically Pure 3-Cyclopropylalanine[224,231−234]



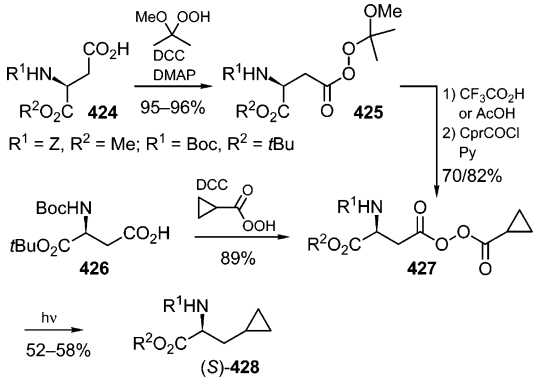
transfer catalyst in the alkylation of **402** offered access to highly enantioenriched protected cyclopropylalanine **415**.[229]

Enzymatic resolution of racemic *N*-trifluoroacetyl- and *N*-acetylcyclopropylalanine has been achieved with an acylase.[21,226,230] An asymmetric synthesis of protected (*S*)-3-cyclopropylalanine **417** was accomplished by cyclopropanation of protected (*S*)-allylglycine (*S*)-**416** with diiodomethane in the presence of copper powder. Subsequent hydrolysis of **417** furnished (*S*)-3-cyclopropylalanine in its free form (*S*)-**411** (Scheme 75, eq 1).[224]

A practical method for the synthesis of a variety of D- and L-amino acids employs an asymmetric alkylation of the pseudoephedrine glycinamide **418** as the key step. Thus, alkylation of **418** with cyclopropylmethyl iodide afforded the amide **419** in good yield and with excellent diastereoselectivity. Hydrolysis of the pseudoephedrine amide **419** furnished (*R*)-3-cyclopropylalanine, which was isolated either in its free form (*R*)-**411** or as the protected derivatives (*R*)-**420** and (*R*)-**421**, respectively (Scheme 75, eq 2).[231−233]

Enantiomerically pure 3-cyclopropylalanine has also been made available by asymmetric hydrogenation of the *N*-Boc-aminoacrylic acid derivative **422**. Among the tested chiral catalysts, a rhodium complex with a phosphine−aminophosphine-substituted ferrocene (BoPhoz) ligand turned out to be the most efficient one providing access to virtually enantiomerically pure protected (*S*)-3-cyclopropylalanine (*S*)-**423**, which was eventually converted into its free form (*S*)-**411** (Scheme 75, eq 3).[234]

Scheme 76. Preparation of Optically Pure Protected (*S*)-3-Cyclopropylalanine by Photolysis of a Diacyl Peroxide[235]



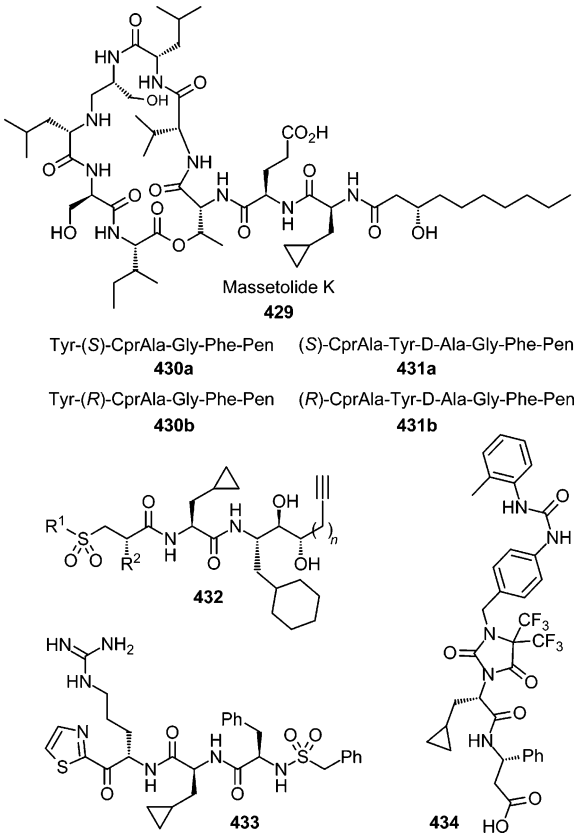


Figure 8. Cyclopropylalanine-containing peptides and peptidomimetics.[230,237−241]

Additionally, enantiomerically pure (*S*)-3-cyclopropylalanine in its protected forms (*S*)-**428** has been obtained by photolysis of the diacyl peroxide **427**, which was prepared from the protected aspartic acid **424** by condensation with 2-methoxyprop-2-yl hydroperoxide, subsequent cleavage of the resulting perester **425**, and acylation of the latter with cyclopropylcarbonyl chloride. Alternatively, **427** was prepared by coupling of the protected aspartic acid **426** with cyclopropanepercarboxylic acid (Scheme 76).[235]

3-Cyclopropylalanine has been used in feeding experiments to elucidate the biosynthesis of the antimycobacterial cyclic depsipeptides called massetolides, which were isolated from cultures of *Pseudomonas* sp. Massetolide K **429** (Figure 8) represented the first complex peptide containing a 3-cyclopropylalanine moiety.[236]

Cyclopropylalanine has also been incorporated into four analogues of enkephalin, resulting in the pentapeptides **430a** and **430b** and the hexapeptides **431a** and **431b** (Figure 8). Each of these cyclopropylalanine-containing analogues was found to be a full agonist on the guinea pig ileum (GPI). Peptide **431a** exhibitited agonist activity also on rat vas deferens (RVD), whereas **430b** turned out to act as a mixed partial agonist−antagonist.[230]

Diol derivatives generally characterized as having one propargyl and one aryl- or alkylsulfonyl terminus as well as an incorporated 3-cyclopropylalanine moiety as depicted in **432** (Figure 8) have turned out to be useful as renin inhibitors for the treatment of hypertension.[237]

A series of α-ketothiazoles were prepared by applying a polymer-assisted solution-phase synthesis and were screened with respect to their potency and selectivity on tissue factor VIIa and other enzymes affecting coagulation. Among the evaluated compounds was the α-ketothiazole **433** (Figure

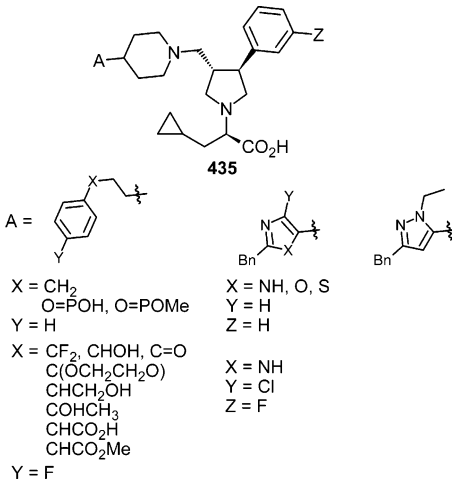


Figure 9. Cyclopropylalanine-containing pyrrolidine derivatives.[27,242−244]

8), with an incorporated cyclopropylalanine moiety. Compound **433** exhibited activity on tissue factor VIIa; however, its potency as well as its selectivity were rather moderate.[238]

3-Cyclopropylalanine bound to bis(trifluoromethyl)-substituted hydantoin has served as a versatile building block for the synthesis of the peptidomimetic **434** (Figure 8). Compound **434** was shown to act as a highly potent antagonist at the very late antigen-4 receptor (VL4), offering interesting options for the treatment of inflammatory diseases such as asthma, rheumatoid arthritis, and multiple sclerosis.[239−241]

In analogy to cyclopropylglycine (see section 2.1, Figure 1), 3-cyclopropylalanine has been incorporated into 1,3,4-trisubstituted pyrrolidine derivatives **435** (Figure 9), which were evaluated as β-chemokinine receptor antagonists in order to act as potent and selective antivirals against the human immunodeficiency virus (HIV). The cyclopropylalanine-containing derivatives **435** all showed a significant and some even an excellent antiviral activity with concomitantly approved pharmacokinetic properties.[27,242−244]

With the intention to develop new pharmaceuticals with enhanced antiinfective properties, modified peptide nucleic acid (PNA) molecules bound to a peptide by a cyclopropylalanine linker have been prepared.[245]

3.2. Hypoglycine

In 1954, two toxic components named hypoglycine A and B were first isolated from the ripe and especially the unripe fruits of *Blighia sapida*, also known as ackee fruits, which are a very common diet in Jamaica.[246] Several improved methods for the isolation of hypoglycine A and B have been described.[247−250] Later on, hypoglycine A and B were also isolated from seeds of *Billia hippocastanum* and fruits of *Acer pseudoplatanus* along with their lower homologue α-(2-methylenecyclopropyl)glycine (see section 2.5).[44−46]

Hypoglycine A and B were found to entail the so-called Jamaican vomiting sickness, a local disease caused by severe hypoglycemia in the form of very low blood glucose and almost absent liver glycogen values, ending lethal without therapeutic administration of glucose. Subsequent extensive studies of the biological activities, the pharmacological properties, as well as the biosynthesis and biochemistry of hypoglycine have disclosed that the toxicity of hypoglycine is the result of its metabolization to (methylenecyclopropyl)-acetate or (methylenecyclopropyl)acetyl-CoA, respectively, which suppresses the oxidation of fatty acids by inhibition

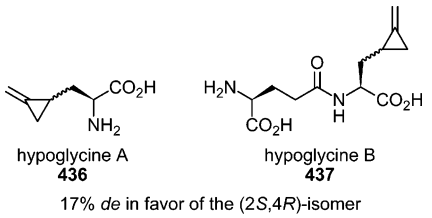


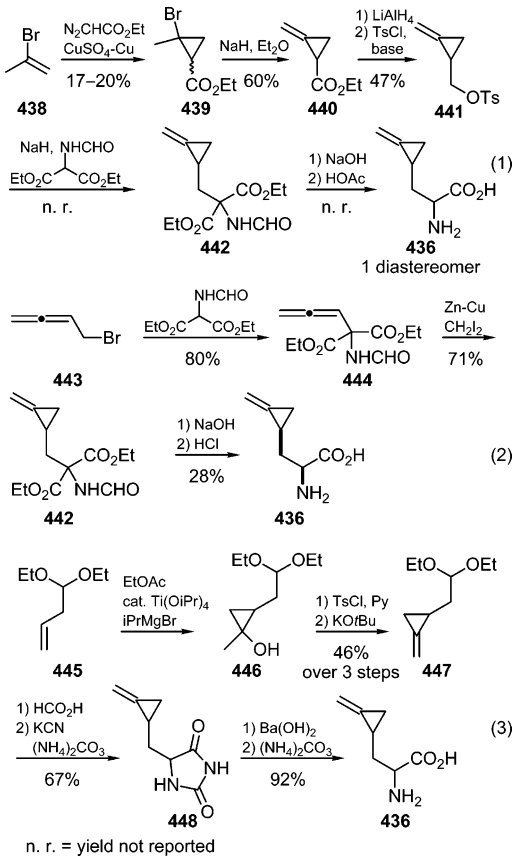
Figure 10. Hypoglycine A and B.

of acyl-CoA dehydrogenase.[246−248,251−270] Besides, hypoglycine A was found to be an antimutagene against spontaneous mutation of *Salmonella typhimurium* TA 100.[47,50] The lipid-lowering agent clofibrate was found to partially protect against hypoglycine A toxicity.[271,272]

Starting with the determination of its molecular formula,[273] several research groups simultaneously elucidated the constitution of hypoglycine A to be 3-(2-methylenecyclopropyl)-alanine, also referred to as α-amino(methylenecyclopropyl)-propionic acid.[249,255,274−278] The configuration of the α-carbon was evidenced to be 2*S*,[249,255] and after an originally wrong assignment for the γ-carbon atom to have (*S*)-configuration, natural hypoglycine A **436** (Figure 10) was proven to be a diastereomeric mixture of the (2*S*,4*R*)- and the (2*S*,4*S*)-isomer with 17% diastereomeric excess in favor of the (2*S*,4*R*)-isomer (Figure 10).[266,267] Hypoglycine B was shown to be the γ-L-glutamyl dipeptide **437** (Figure 10).[273,279,280]

Several synthetic approaches to racemic hypoglycine A have been developed. Thus, cyclopropanation of 2-bromopropene (**438**) with ethyl diazoacetate under copper catalysis gave ethyl 2-bromo-2-methylcyclopropanecarboxylate (**439**), which was dehydrobrominated to ethyl 2-methylenecyclopropanecarboxylate (**440**). The ester was reduced to the corresponding alcohol, the latter was converted to the

Scheme 77. Syntheses of Racemic Hypoglycine A[282,285−287]



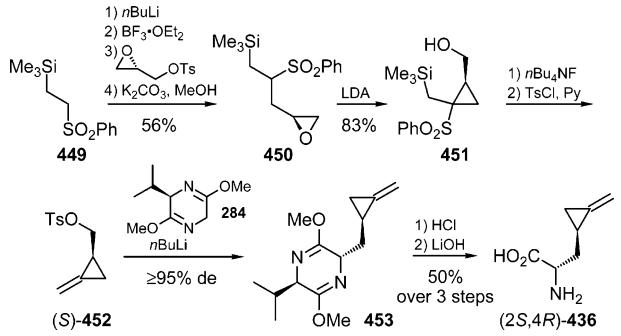
tosylate **441**, and this in turn was used to alkylate diethyl *N*-formylaminomalonate to yield **442**. Hydrolysis and decarboxylaton of the latter provided a single diastereomer of hypoglycine A **436**, the relative configuration of which was not assigned (Scheme 77, eq 1).[281,282]

The synthesis of racemic hypoglycine A was also achieved starting with the alkylation of diethyl formylaminomalonate with 4-bromobuta-1,2-diene (**443**), accessible by reaction of propargyl alcohol with triphenylphosphite dibromide,[283,284] to yield diethyl buta-1,2-dien-3-yl(formylamino)malonate (**444**). Simmons−Smith cyclopropanation of **444** occurred regioselectively at the more highly substituted double bond, affording **442**. Hydrolysis and decarboxylation gave the (*R**,*R**)-diastereomer of hypoglycine A **436**, which was wrongly considered to have the same configuration as the natural product (Scheme 77, eq 2).[285,286]

Another synthesis of racemic hypoglycine A started with the titanium-catalyzed hydroxymethylcyclopropanation of vinylacetaldehyde diethyl acetal (**445**) with isopropylmagnesium bromide in the presence of ethyl acetate. The thus obtained cyclopropanol **446** was tosylated and the tosylate eliminated to the methylenecyclopropane derivative **447**. The transformation of the acetal to an amino acid moiety was performed via the corresponding hydantoin **448**, which was finally hydrolyzed to furnish hypoglycine A **436** in an overall yield of 28% (Scheme 77, eq 3).[287]

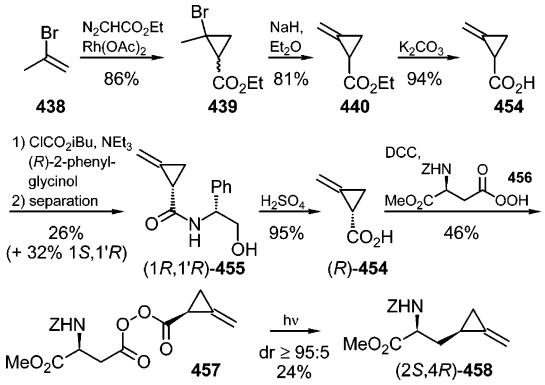
Racemic hypoglycine A has been coupled with L-glutamic acid to furnish the γ-L-glutamyl-hypoglycine A dipeptide, hypoglycine B.[288,289]

Scheme 78. Synthesis of Enantiomerically Pure Hypoglycine A (Only the Preparation of the (2*S*,4*R*)-Isomer Is Depicted)[290,291]



Until today, only two synthetic accesses to enantiomerically pure hypoglycine A have been published. Thus, reaction of the tosylate of enantiomerically pure oxiran-2-ylmethanol (glycidol), accessible by Sharpless asymmetric epoxidation of allyl alcohol and subsequent tosylation, with the anion generated from (trimethylsilylethyl)phenylsulfone (**449**) gave a β-hydroxy-substituted tosylate which upon treatment with base was converted to the epoxide **450**. Subsequent treatment with lithium diisopropylamide afforded the (hydroxymethylcyclopropyl)phenylsulfone **451**, which upon fluoride-induced desilylation/elimination and subsequent tosylation gave the (2-methylenecyclopropyl)methyl tosylate (**452**). Substitution of this tosylate with the deprotonated enantiopure bislactim ether **284** as a chirally derivatized glycine anion equivalent yielded the alkylated bislactim ether **453**, which was hydrolyzed in two steps to hypoglycine A **436**. When the alkylation of **284** was carried out with the pure (*S*)- and (*R*)-enantiomers of **452**, respectively, the corresponding intermediates **453** and final products **436** were virtually enantiomerically pure (Scheme 78). Even with the racemic tosylate

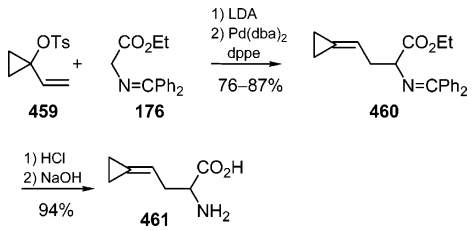
Scheme 79. Synthesis of Enantiomerically Pure Hypoglycine A Employing Photolysis of a Diacyl Peroxide as a Key Step[235]



452, a certain degree of kinetic resolution was observed in the alkylation of the bislactim ether **284**, resulting in a 20% diastereomeric excess in favor of the (*R*)-configured stereogenic center in the three-membered ring, and this ratio corresponds almost exactly to the diastereomeric ratio in the natural product.[290,291]

Treatment of 2-bromopropene (**438**) with ethyl diazoacetate in the presence of dirhodium tetraacetate gave ethyl 2-bromo-2-methylcyclopropanecarboxylate (**439**) in a significantly higher yield than the same cyclopropanation in the presence of a copper catalyst (see Scheme 77, eq 1). Dehydrobromination of **439** to ethyl 2-methylenecyclopropanecarboxylate (**440**) and subsequent hydrolysis led to the acid **454**. Derivatization of the latter with (*R*)-2-phenylglycinol gave a separable mixture of the corresponding amides, the diastereomer **455** of which was hydrolyzed to enantiomerically pure 2-methylenecyclopropanecarboxylic acid [(*R*)-(**454**)].[268] Coupling of (*R*)-**454** with the peracid **456** (see section 3.1, Scheme 76 for its preparation) led to the diacyl peroxide **457**, and photolysis of **457** diastereoselectively gave (2*S*,4*R*)-hypoglycine in its protected form **458** (Scheme 79).[235]

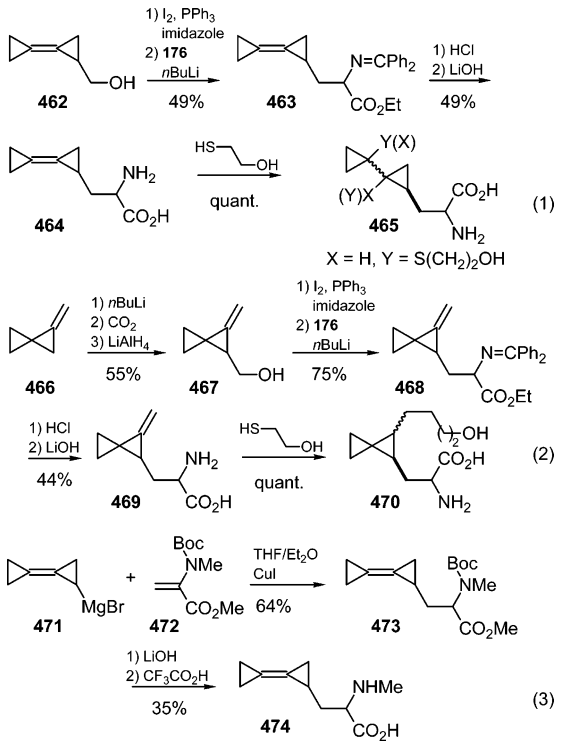
Scheme 80. An Isomer of Hypoglycine A[292]



The protected 3-cyclopropylidenealanine **460**, representing an interesting constitutional isomer of hypoglycine A, was obtained by palladium-catalyzed allylation of the enolate of ethyl (diphenylmethyleneamino)acetate (**176**) (O'Donnel's glycine equivalent) with 1-ethenylcyclopropyl tosylate (**459**) and subsequent hydrolysis (Scheme 80).[292] Enantiomerically pure (*S*)-isohypoglycine (*S*)-**461** has been prepared employing a glycine anion equivalent analogous to **176** chirally modified with a camphorsultam moiety.[293]

Additionally, the hypoglycine analogue **464** with a bicyclopropylidene instead of the methylenecyclopropane moiety has been synthesized. Thus, bicyclopropylidenylmethanol (**462**) was converted into the corresponding iodide, and this in turn was used to alkylate the enolate of O'Donnell's glycine equivalent **176** to provide **463**. Subsequent depro-

Scheme 81. Syntheses of Cyclopropyl-Group-Containing Analogues of Hypoglycine[294,295]



tection of the latter led to 3-(1,1′-bicyclopropyliden-2-yl)-alanine (**464**) (Scheme 81, eq 1).[294] An essentially analogous set of transformations of (2-methylenespiropentyl)methanol (**467**), easily accessible from methylenespiropentane (**466**) by deprotonation, reaction with carbon dioxide, and reduction, led to 3-(2-methylenespiropent-1-yl)alanine (**469**) (Scheme 81, eq 2).[294]

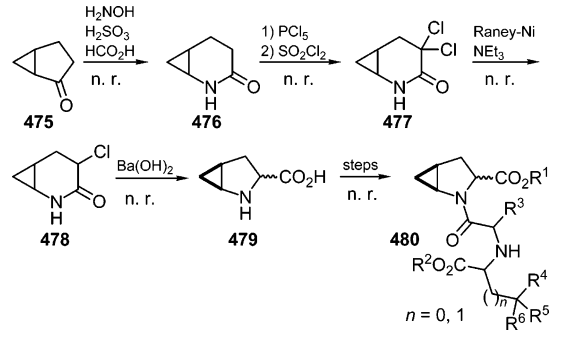
Both amino acids **464** and **469**, like unsubstituted bicyclopropylidene and methylenespiropentane, underwent facile addition of thiols (Scheme 81, eqs 1 and 2).[295] The products **465** and **470** resulting from such additions of 2-hydroxyethanethiol are interesting functionally substituted 3-cyclopropylalanines as well.

The *N*-methyl derivative of **464** was obtained by Cu(I)-catalyzed addition of bicyclopropylindenylmagnesium bromide (**471**) across the α-acylaminoacrylate **472** to afford the protected derivative **473**. Deprotection of the latter furnished 3-(1,1′-bicyclopropyliden-2-yl)methylalanine (**474**) (Scheme 81, eq 3).[294]

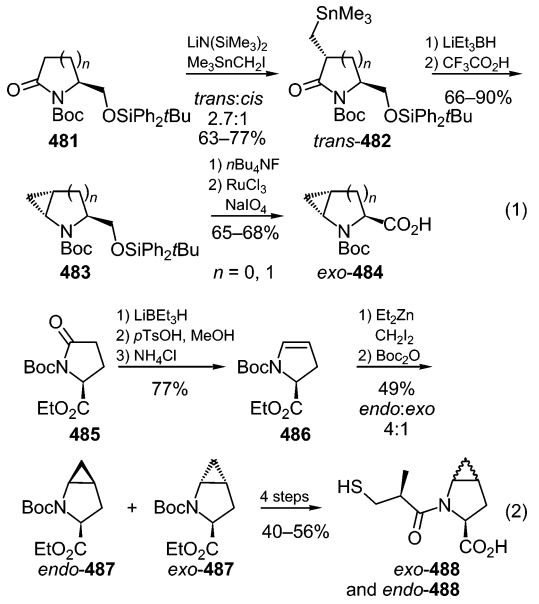
3.3. 4,5-Methanoproline

4,5-Methanoproline in its racemic form has been prepared from bicyclo[3.1.0]hexan-2-one (**475**) in a sequence starting

Scheme 82. Syntheses of an *endo*/*exo* Mixture of 4,5-Methanoproline and Its Incorporation into Peptides[296]



Scheme 83. Syntheses of 4,5-Methanoproline[297,298]



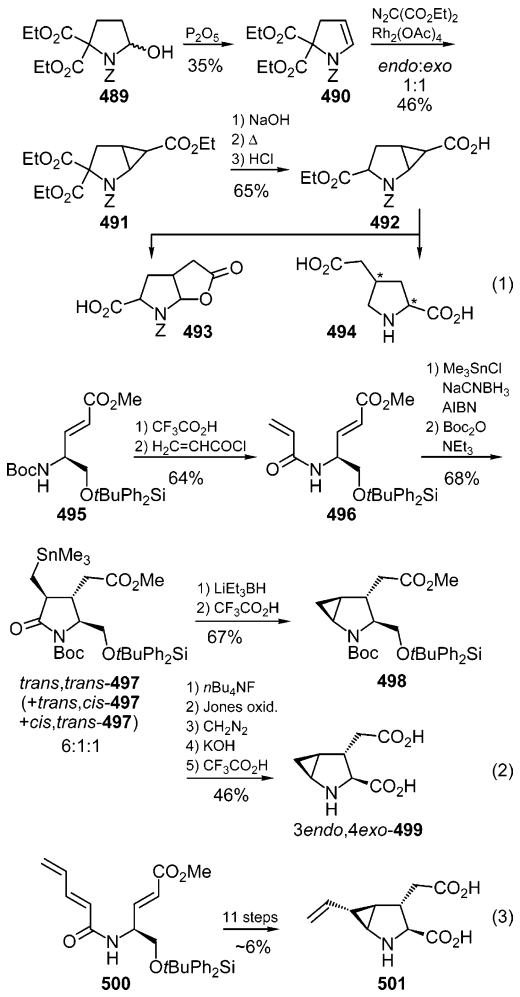
with a Beckmann rearrangement of the oxime of **475** to yield the bicyclic δ-lactam **476**. Twofold chlorination of the latter, partial reductive dechlorination with Raney nickel of the resulting 4,4-dichlorinated product **477**, and Favorski rearrangement of **478** furnished 4,5-methanoproline (**479**) as a mixture of the *endo*- and *exo*-diastereomers, which could be separated after *N*-acylation with benzyl chloroformate. 4,5-Methanoproline (**479**) has been incorporated into dipeptides of type **480** (Scheme 82), which turned out to be potent antihypertensive agents and strong inhibitors of the angiotensin converting enzyme (ACE).[296]

Enantiomerically pure 4,5-methanoproline (**479**) has been made available from the γ-lactam **481** ($n = 1$), which was stannylmethylated to give the pyrrolidin-2-one derivative *trans*-**482** ($n = 1$) in a mixture with its *cis*-diastereomer. Further conversion of each of the diastereomers by reduction of the carbonyl group and acid-induced intramolecular cyclization yielded the 2-azabicyclo[3.1.0]hexane derivative **483** ($n = 1$), the hydroxymethyl group of which was desilylated and finally oxidized to provide *N*-*tert*-butoxycarbonyl-protected *exo*-4,5-methanoproline (*exo*-**484**) or *endo*-4,5-methanoproline (*endo*-**484**), respectively (Scheme 83, eq 1, only the synthesis of the *exo*-isomer is depicted).[297]

A second expedient route to protected enantiomerically pure 4,5-methanoproline has been developed starting with protected L-pyroglutamic acid **485**. Thus, reduction of its carbonyl group, subsequent conversion to the methoxy hemiaminal carbamate, and elimination of methanol gave ethyl 4,5-dehydroprolinate **486**, Simmons−Smith cyclopropanation of which followed by protection of the amino functionality yielded protected 4,5-methanoproline **487** as an easily separable mixture of the *endo*- and the *exo*-diastereomer (Scheme 83, eq 2). In order to prepare conformationally constrained analogues of the angiotensin converting enzyme (ACE) inhibitor captopril, used for treatment of hypertension, the *endo*- as well as the *exo*-isomers of the 4,5-methanoproline derivative **487** were further converted to the dipeptides **488** (Scheme 83, eq 2). The latter indeed turned out to be highly potent inhibitors of ACE, even surpassing captopril itself.[298]

4,5-Methanoproline was found to catalyze the Hajos−Parrish−Eder−Sauer−Wiechert reaction. The fact that the

Scheme 84. Syntheses of Substituted 4,5-Methanoproline Derivatives[300−302]



endo-isomer exhibits a higher acceleration and selectivity (86% yield, 93% *ee*) than the *exo*-isomer (67% yield, 83% *ee*) has been interpreted on the basis of density functional theory (B3LYP) computations.[299]

In analogy to 3,4-methanoproline (**84**) (see section 2.6), the 4,5-methanoproline derivative **487** was transformed into methanoprolinenitrile dipeptide mimetics. The latter were found to act as highly potent DPP-IV inhibitors with enhanced solution stability, when they had an L-*endo*-4,5-methanoproline moiety incorporated.[66]

A synthesis of racemic 1′-carboxy-4,5-methanoproline has been accomplished starting with diethyl 5-hydroxypyrrolidine-2,2-dicarboxylate (**489**) prepared from diethyl *N*-benzyloxycarbonylaminomalonate and acrolein. Dehydration of **489** afforded the corresponding diethyl dihydropyrrole-2,2-dicarboxylate **490**. Rhodium-catalyzed cyclopropanation with ethyl diazoacetate yielded the 2-azabicyclo[3.1.0]hexane-2,2,6-tricarboxylate **491** as a mixture of the *endo*- and *exo*-isomers which was partially hydrolyzed and decarboxylated to give the protected 2′-carboxy-4,5-methanoproline **492**. This amino acid was further transformed into 1′-carboxy-4-carboxymethylpyrrolidin-5-ol lactone **493** and was also applied as a suitable starting material for the synthesis of all four diastereomers of 4-(carboxymethyl)proline (**494**) (Scheme 84, eq 1).[300,301]

With the intention to develop new congeners of α-kainic acid as probes of glutamate receptors, enantiomerically pure 3-carboxymethyl-4,5-methanoproline derivatives have been prepared. Thus, the protected 4-amino-5-hydroxypentenoate **495**, easily accessible from D-serine, after removal of the *N*-Boc group, was acylated with acryloyl chloride to yield the amido-1,6-diene **496**, which was treated with in situ generated trimethyltin hydride, leading to a separable mixture of three diastereomeric pyrrolidinones **497**. Further transformation of the major isomer *trans,trans*-**497** by reduction to the *O,N*-hemiacetal and treatment of the latter with acid led to the 2-azabicyclo[3.1.0]hexane derivative **498**. This was desilylated, the hydroxymethyl group was oxidized, and the ester as well as the carbamate moiety were hydrolyzed to yield 3-(carboxymethyl)-4,5-methanoproline in its fully deprotected form **499** (Scheme 84, eq 2). The minor isomer *trans,cis*-**497** was converted in the same manner to provide the corresponding 3-carboxymethyl-4,5-methanoproline *trans,cis*-**499**. Application of the same sequence of transformations to the amidotriene **500** led to the 2′-vinyl-substituted 3-carboxymethyl-4,5-methanoproline **501** (Scheme 84, eq 3). Biological tests of these 4,5-methanoproline analogues **499** and **501** with respect to their binding affinities to ionotropic glutamate receptors showed neither significant antagonist nor agonist properties.[302]

3.4. 5-Nitro-4,5-methanonorvaline [3-(2-Nitrocyclopropyl)alanine] and Analogues

In 1989, a peptide lactone consisting of eight amino acid residues was isolated from *Streptomyces griseoflavus* strain W 384, and its constitution was assigned.[303] It was termed hormaomycin and found to have an interesting broad spectrum of biological activities ranging from specific antibacterial properties and in vitro antimalaria activity to its action as a signal substance for streptomycetes including the producing strain.[303−305] Hormaomycin proved to be the only natural product known up to date having incorporated the unusual amino acid 3-(*trans*-2-nitrocyclopropyl)alanine.[306] Subsequently, the structure including the absolute configuration of hormaomycin has been fully assigned to be **502** (Figure 11),[307] and the biosynthetic pathway of 3-(*trans*-2-nitrocyclopropyl)alanine from lysine has partially been clarified.[308]

To date, two synthetic strategies toward *trans*-3-(2-nitrocyclopropyl)alanine have been pursued, both utilizing *trans*-3-(2-nitrocyclopropyl)methanol as a key intermediate. Following the first one, enantiomerically pure *trans*-3-(2-nitrocyclopropyl)methanol (**505**) was prepared starting from readily available enantiopure 2,3-*O*-isopropylideneglyceraldehyde (**188**), which was transformed into 4-nitrobutane-1,2-diol (**503**) by a one-pot reductive nitromethylation and subsequent cleavage of the acetal group. Selective protection

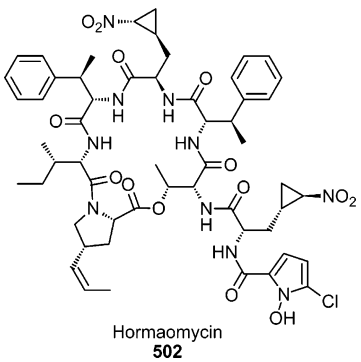
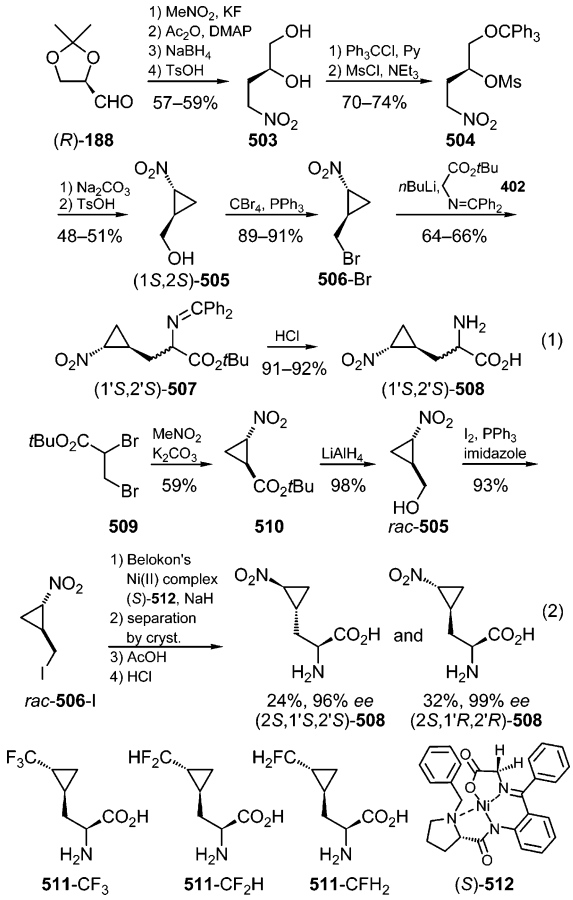


Figure 11. The natural product hormaomycin containing two diastereomeric moieties of *trans*-3-(2-nitrocyclopropyl)alanine.

Scheme 85. Syntheses of *trans*-3-(2-Nitrocyclopropyl)-alanine[309−311]



of the primary hydroxy function as a trityl ether and transformation of the secondary hydroxy group into a mesylate as a better leaving group afforded **504**, which, by a stereoselectively occurring γ-dehydromesylation, gave the corresponding *trans*-configured cyclopropyl derivative. Upon cleavage of the trityl ether, enantiopure *trans*-3-(2-nitrocyclopropyl)methanol (**505**) was obtained. Conversion of the latter to the bromide **506**-Br and substitution of the bromide with the lithium enolate of the glycine anion equivalent *tert*-butyl (diphenylmethyleneamino)acetate (**402**) provided protected *trans*-3-(2-nitrocyclopropyl)alanine **507**, which was further transformed into its fully deprotected form **508**. Depending on the enantiomer of the glyceraldehyde derivative **188** used, either the (1′*S*,2′*S*)- or the (1′*R*,2′*R*)-isomer of *trans*-3-(2-nitrocyclopropyl)alanine (**508**) was obtained, however, both as inseparable mixtures of diastereomers (Scheme 85, eq 1, only the synthesis of the (1′*S*,2′*S*)-isomer is depicted).[309,310]

trans-3-(2-Nitrocyclopropyl)methanol (**506**) in its racemic form is more easily accessible than the pure enantiomer. The bromine adduct **509** of *tert*-butyl acrylate was converted to *tert*-butyl *trans*-2-nitrocyclopropanecarboxylate (**510**) by base-induced 1,2-dehydrobromination, Michael addition of nitromethane, and 1,3-dehydrobromination. Chemoselective reduction of the ester group in **510** provided racemic *trans*-3-(2-nitrocyclopropyl)methanol (*rac*-**505**).[310,311] Subsequent treatment of *rac*-**505** with iodine/triphenylphosphine in the presence of imidazole furnished racemic *trans*-1-(iodomethyl)-2-nitrocyclopropane *rac*-**506**-I, which was employed to alkylate the enolate of the chirally masked glycine moiety in the (*S*)- and (*R*)-configurated Belokon nickel(II) complex **512**, respectively. A notable difference in the solubility between the diastereomeric product complexes facilitated their separation by crystallization. Subsequent decomposition of the complexes, purification by ion exchange chromatography, and crystallization provided access to all four stereoisomers of *trans*-3-(2-nitrocyclopropyl)alanine (**508**) in virtually enantiopure form (Scheme 85, eq 2, only the syntheses of the (2*S*,1′*S*,2′*S*)- and the (2*S*,1′*R*,2′*R*)-isomers are depicted).[311]

When the reduction of *tert*-butyl 2-nitrocyclopropanecarboxylate (**510**) was carried out with lithium aluminum deuteride, (2-nitrocyclopropyl)dideuteriomethanol [$^2H_2$]-**505** was obtained, and this could further be converted into racemic 3,3-dideuterio-*trans*-3-(2-nitrocyclopropyl)alanine ([$^2H_2$]-**508**).[312]

Once productive syntheses of enantiomerically pure 3-(2-nitrocyclopropyl)alanines **508** had been established, the first total synthesis of the depsioctapeptide hormaomycin could be completed.[313]

Employing essentially the same key steps as in the most advanced synthesis of **508**,[311] all four stereoisomers of *trans*-(2-trifluoromethylcyclopropyl)alanine (**511**-CF_3), *trans*-(2-difluoromethylcyclopropyl)alanine (**511**-CF_2H), and *trans*-(2-fluoromethylcyclopropyl)alanine (**511**-CFH_2) were prepared from the correspondingly substituted cyclopropylmethanols, for incorporation into hormaomycin analogues.[314]

3.5. 4,5-Methanoornithine [3-(2-Aminocyclopropyl)alanine]

Belactosin A **513** was isolated from a fermentation broth of *Streptomyces* sp. UCK 14 along with belactosin B **514** (Figure 12), a product apparently stemming from β-lactone cleavage and belactosine C, an analogue of **513** without a cyclopropyl group).[315] Belactosin A was found to be a potent proteasome inhibitor and to mediate cell-cycle progression by acting on cyclin-dependent kinase complexes which have been reported to be present in various tumors, whereas belactosin B turned out to be inactive. Thus, belactosin A exhibited *in vitro* antiproliferative and antitumor activity and a weak *in vivo* activity which could significantly be enhanced by esterification of the carboxylic acid moiety.[315−318]

A particularly interesting feature of belactosins A and B is the presence of the unique *trans*-3-(2-aminocyclopropyl)-alanine as the central constituent. The first synthesis of this amino acid has been accomplished using racemic *trans*-3-(2-nitrocyclopropyl)methanol (*rac*-**505**) (for its preparation see section 3.4, Scheme 85) as the key intermediate. Hydrogenation of the nitro alcohol **505** gave the amino alcohol **515**, which was converted into its protected form **516**, and this was subsequently transformed into the iodide **517** of limited stability. Alkylation of a glycine anion

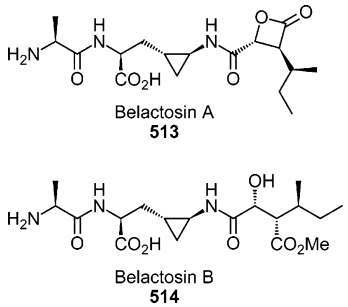
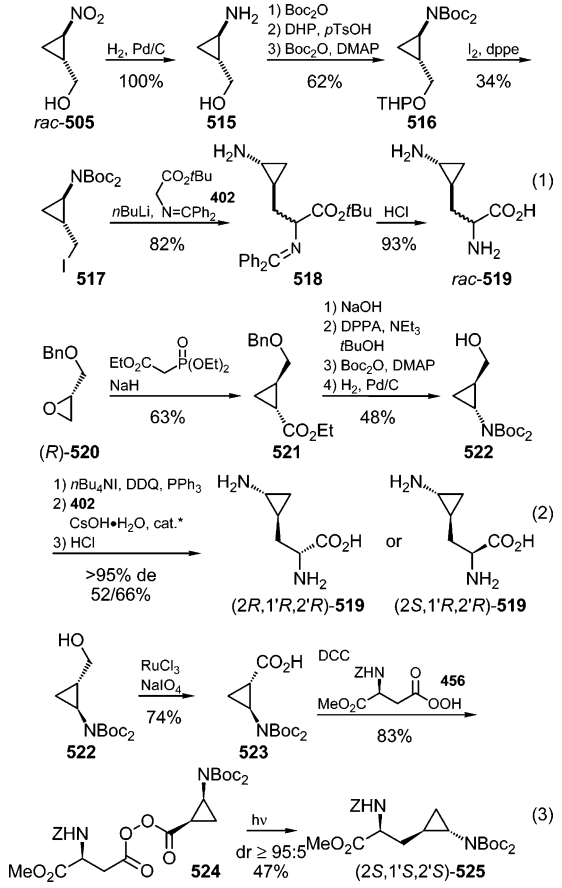


Figure 12. The natural products belactosin A and B containing a 3-(2-aminocyclopropyl)alanine moiety.

Scheme 86. Syntheses of *trans*-3-(2-Aminocyclopropyl)-alanine[235,319,320]



equivalent with the iodide **517** and subsequent removal of all protecting groups furnished racemic *trans*-3-(2-aminocyclopropyl)alanine (*rac*-**519**) isolated as a mixture of two diastereomers resulting from the lack of stereocontrol for the newly formed stereogenic center at the α-carbon atom in **519** (Scheme 86, eq 1).[319] As (nitrocyclopropyl)methanol (**505**) is also available in enantiomerically pure form,[310,319] this preparation offers an approach to enantiopure *trans*-3-(2-aminocyclopropyl)alanine (**519**), however, as a mixture of two diastereomers. An analogous transformation of 3,3-dideuterio-(2-nitrocyclopropyl)methanol ([$^2H_2$]-**505**) obtained by reduction of *tert*-butyl 2-nitrocyclopropanecarboxylate (**510**) with lithium aluminum deuteride provided access to 3,3-dideutero-*trans*-3-(2-aminocyclopropyl)alanine.[312]

A fully stereocontrolled synthesis of *trans*-3-(2-aminocyclopropyl)alanine (**519**) has been achieved starting with a Horner−Wadsworth−Emmons cyclopropanation of the enantiopure glycidol benzyl ether (*R*)-**520** to provide ethyl 2-(benzyloxymethyl)cyclopropanecarboxylate (**521**). Hydrolysis of the ester group in the latter followed by Curtius degradation of the acid, bis-*N*-*tert*-butoxyoxycarbonyl protection, and removal of the benzyl group afforded (1′*R*,2′*R*)-(aminocyclopropyl)methanol in its protected form **522**. Transformation of the latter to the iodide and application of this to alkylate the O'Donnell glycine anion equivalent **402** in the presence of a chiral cinchonidinium or cinchonium catalyst, respectively, led to control of the configuration at the α-carbon atom, and after hydrolytic removal of all protecting groups, virtually enantiopure (2*R*,1′*R*,2′*R*)- or (2*S*,1′*R*,2′*R*)-3-(2-aminocyclopropyl)alanine (**519**), respectively, depending on the catalyst used, was obtained (Scheme 86, eq 2).[320]

Besides, the protected (1′*R*,2′*R*)-(aminocyclopropyl)methanol **522** could be oxidized to the corresponding 2-aminocyclopropanecarboxylic acid **523**, which was used for a dicyclohexylcarbodiimide-mediated coupling with the aspartic acid-derived peracid **456** (see section 3.1, Scheme 79 for an analogous preparation), providing the diacyl peroxide **524**. Photolysis of **524** afforded optically pure, protected (2*S*,1′*S*,2′*S*)-3-(2-aminocyclopropyl)alanine **525** (Scheme 86, eq 3) in a mixture with *O*-[(2-aminocyclopropyl)carbonyl]-serine (41%, structure not depicted).[235] All four stereoisomers of *trans*-3-(2-aminocyclopropyl)alanine (**519**) have been synthesized from the corresponding (2*S*,1′*S*,2′*S*)-, (2*S*,1′*R*,2′*R*)-, (2*R*,1′*S*,2′*S*)-, and (2*R*,1′*R*,2′*R*)-3-(2-nitrocyclopropyl)alanines (**508**), respectively, (see section 3.5) by catalytic hydrogenation (91−95% yield, 96−99% *ee*).[321]

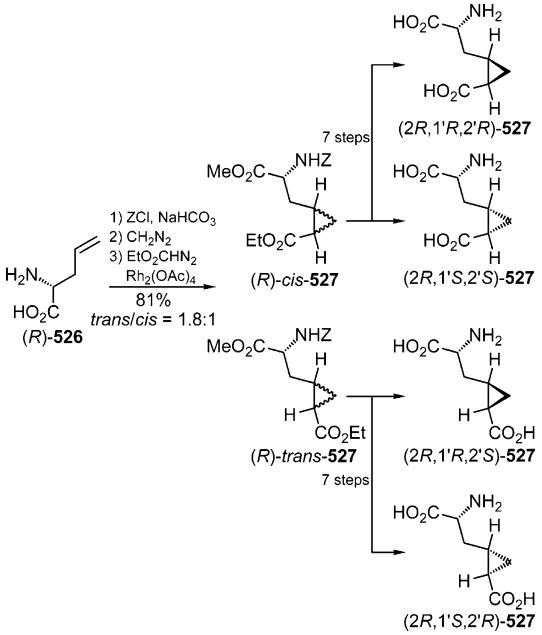
trans-3-(2-Aminocyclopropyl)alanine (**519**) and an appropriately protected alanyl peptide of it have served as the key building blocks in the two so far developed total syntheses of belactosin A.[322,323] In addition, *trans*-3-(2-aminocyclopropyl)alanine (**519**) has been used for feeding experiments with *Streptomyces griseoflavus* strain W384, in which it turned out not to be a suitable substrate for hormaomycin synthetase.[312]

3.6. 3,4-Methanoglutamic Acid and Derivatives

3.6.1. 4,5-Methanohomoglutamic Acid [3-(2-Carboxycyclopropyl)alanine]

A synthetic route to all four diastereomers of D-3-(2-carboxycyclopropyl)alanine started with protection of the amino group and esterification of D-allylglycine [(*R*)-**526**]. Subsequent rhodium-catalyzed cyclopropanation using ethyl diazoacetate provided a mixture of all four possible diastereomers, the *trans*- and *cis*-isomers (*R*)-*trans*-**527** and (*R*)-*cis*-**527**, which could be separated by chromatography. Further separation of the two *trans*- or *cis*-isomers required a seven-step transformation, involving conversion into a paraform-aldehyde-derived oxazilidinone and derivatization with *R*-(−)-α-phenylglycinol in order to obtain a separable mixture of diastereomers finally leading to all four stereoisomers of **527** in diastereomerically and enantiomerically pure form (Scheme 87).[324]

Scheme 87. Synthesis of 3-(2-Carboxycyclopropyl)alanine[324]



A pharmacological evaluation of **527** toward ionotropic glutamate receptors showed that, out of the four diastereomers, the (2*R*,1′*S*,2′*S*)-isomer as well as both *trans*-isomers of **527** exhibited agonist-type properties at the *N*-methyl-D-aspartate (NMDA) binding site whereas the (2*R*,1′*R*,2′*R*)-isomer acted as an antagonist. All of the four stereoisomers interacted weakly with the kainate (KA) binding site, but none of them with the α-amino-5-hydroxy-3-methyl-4-isoazole propionic acid (AMPA) binding site.[324]

In this context, mixtures of *trans*- and *cis*-isomers of L- as well as D-3-(2-carboxycyclopropyl)alanine have been prepared and studied with respect to their interaction with ionotropic glutamate receptors, too.[325]

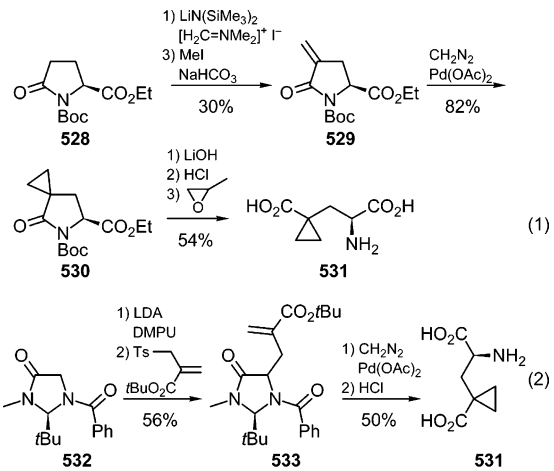
3-(2-Carboxycyclopropyl)alanine (**527**) has also been prepared, in better overall yield, by alkylation of O'Donnell's glycine equivalent with methyl 2-(iodomethyl)cyclopropanecarboxylate and subsequent hydrolysis (see Scheme 86, eq 1, for an analogous sequence employing an (aminocyclopropyl)methyl iodide).[312] Both, 3-(2-carboxycyclopropyl)-alanine (**527**) as well as 3-(2-methoxycarbonylcyclopropyl)-alanine have been incorporated into Hormaomycin analogues by precursor-directed biosynthesis.[312]

3.6.2. 4,4-Ethanoglutamic Acid [3-(1-Carboxycyclopropyl)-alanine]

A remarkably short synthesis of enantiomerically pure 3-(1-carboxycyclopropyl)alanine has been developed starting from protected pyroglutamate **528**. Thus, the lithium lactam enolate of **528** was first treated with Eschenmoser's salt to yield the corresponding 4-(dimethylamino)methylpyroglutamate, which was transformed with methyl iodide to the quaternary ammonium salt, and the latter was subjected to Hofmann elimination to furnish the protected 4-methylenepyroglutamate **529**. Palladium acetate-catalyzed cyclopropanation of **529** with diazomethane yielded *N*-*tert*-butoxycarbonyl-protected spirocyclopropanated ethyl pyroglutamic acid **530**, which was fully hydrolyzed to 3-(1-carboxycyclopropyl)alanine (**531**) (Scheme 88, eq 1).[326] Partial hydrolysis of *N*-*tert*-butoxycarbonyl-protected spirocyclopropanated *tert*-butyl pyroglutamic acid prepared in analogy to **530** has also been described.[327] Additionally, the cyclopropanation of protected 4-benzylidenepyroglutamic acid has been examined and was found to give a mixture of all four diastereomers of (2-phenylspirocyclopropane)pyroglutamic acid derivatives.[327]

Compound **531** has also been prepared starting from the commercially available enantiopure glycine derivative **532**, the lithium enolate of which underwent a diastereoselective reaction with *tert*-butyl 2-(tosylmethyl)acrylate to yield compound **533**. Subsequent cyclopropanation with diazomethane in the presence of palladium acetate and final hydrolysis gave rise to 3-(1-carboxycyclopropyl)alanine (**531**) in its fully deprotected form (Scheme 88, eq 2).[326]

Scheme 88. Syntheses of 3-(1-Carboxycyclopropyl)alanine[326]

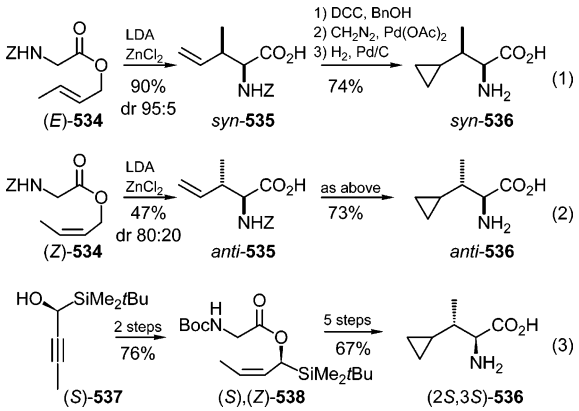


3.7. Other Substituted 4,5-Methanoamino Acids

During a search for novel plant growth regulators in the mushroom *Amanita castanopsidis* Hongo, employing a lettuce seedling assay, 2-amino-3-cyclopropylbutanoic acid (**536**) (Scheme 89) was isolated, and its absolute configuration at the α-carbon was determined to be 2*S* by CD spectroscopy.[328] Later on, **536** was reported to be present also in *Amanita cokeri*.[329] Growth experiments pointed out the capability of **536** to substantially inhibit root elongation in lettuce seedlings, while hypocotyls elongation and germination stayed unaffected.[328] Besides, **536** was found to be toxic to the fungus *Cercospora kikuchii*, the arthropod *Oncopeltus fasciatus*, and the bacteria *Agrobacterium tumefaciens*, *Erwinia amylovora*, and *Xanthomonas campestris*. As toxicity to bacteria was reversible by addition of isoleucine, 2-amino-3-cyclopropylbutanoic acid (**536**) was considered to be an isoleucine antimetabolite.[330]

The configuration of the naturally occurring **536** has been assigned as 2*S*,3*S* through its diastereo- and enantioselective synthesis employing a chelate−enolate Claisen rearrangement as the key step. Thus, [3,3]-sigmatropic rearrangement of the (*E*)- or (*Z*)-prop-1-enylglycinates **534**, respectively, gave either the *syn*- or the *anti*-diastereomer of the 1-methylallylglycine derivative **535**, each of which was submitted to palladium acetate-catalyzed cyclopropanation of its double bond with diazomethane. Subsequent hydrolysis afforded *syn*- and *anti*-2-amino-3-cyclopropylbutanoic acid **536**, respectively (Scheme 89, eqs 1 and 2).[331]

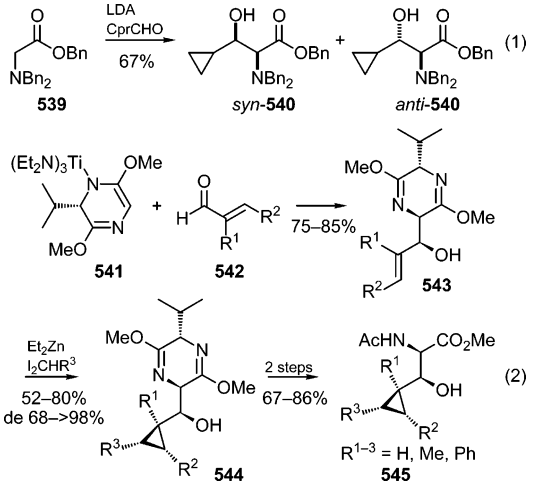
Scheme 89. Syntheses of 2-Amino-3-cyclopropylbutanoic Acid[331]



An enantioselective synthesis of (2*S*,3*S*)-**536** has been accomplished by silyl-assisted[3,3]-sigmatropic rearrangement of the enantiopure 1-silyl-substituted (2*Z*)-but-2-enylglycinate (*S*),(*Z*)-**538** obtained by esterification of glycine with the (*S*)-propargyl alcohol **537** and reduction of the triple to a double bond. Concurrent removal of the protecting groups, cyclopropanation, and hydrolysis yielded virtually enantiomerically pure (2*S*,3*S*)-2-amino-3-cyclopropylbutanoic acid [(2*S*,3*S*)-**536**], the configuration of which was found to be identical to that of the natural product (Scheme 89, eq 3).[331]

A one-step synthesis of protected 3-cyclopropylserine in its racemic form has been achieved by reaction of the lithium

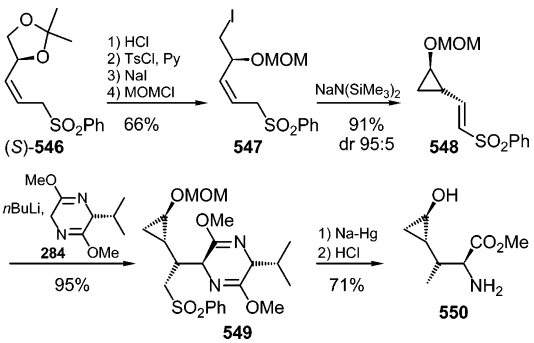
Scheme 90. Syntheses of 3-Cyclopropylserine Derivatives[332−335]



enolate of benzyl *N*,*N*-dibenzylglycinate (**539**) with cyclopropanecarbaldehyde, providing a separable mixture of the *syn*- and the *anti*-diastereomers of benzyl *N*,*N*-dibenzyl-3-cyclopropylserinate (**540**) (Scheme 90, eq 1). The diastereomeric mixture of **540** served as the starting material for the synthesis of protected cyclopropylalaninol, the kinetic resolution of which was studied by applying the (−)-sparteine-controlled deprotonation−reprotonation sequence.[332]

The titanium-coordinated 2,5-dihydropyrazine **541** derived from the corresponding lithum-coordinated 2,5-dihydropyrazine turned out to be a versatile template for the synthesis of several 3-cyclopropylserine derivatives endowed with substituents on the cyclopropyl moiety. The intermediate **541** can easily be prepared by regioselective deprotonation of the corresponding 2,5-dihydropiperazine with *n*-butyllithium and subsequent transmetallation. Employing this so-called "bislactim ether method", the titanium reagent **541** was treated with α,β-unsaturated aldehydes **542**, which underwent 1,2-addition to each give a single diastereomer of the 2,1′-*syn*-adduct **543**. Cyclopropanation of the latter with diiodomethane or diiodophenylmethane in the presence of diethylzinc proceeded with moderate to excellent diastereoselectivities and led to the corresponding cyclopropane derivatives **544** with up to three newly created stereogenic centers. Hydrolysis of compounds **544** subsequent to *O*-acetylation afforded *N*-acetylated methyl 2-amino-4,5-methano-3-hydroxyalkanoates **545**, each obtained in virtually enantiomerically pure form after recrystallization (Scheme 90, eq 2).[333−335]

Scheme 91. Synthesis of Enantiomerically Pure 5-Hydroxy-4,5-methanoisoleucine[336]

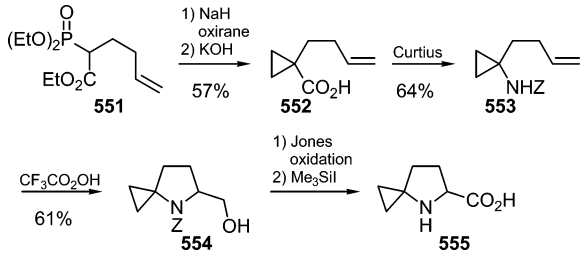


A synthetic access to 5-hydroxy-4,5-methanoisoleucine starts from the enantiopure allyl sulfone (*S*)-**546**. Cleavage of the acetal moiety in the latter, tosylation of the primary hydroxy function, conversion of the tosylate to an iodide, and protection of the secondary hydroxy group gave the allylsulfone **547**. Subsequent base-induced ring closure diastereoselectively provided the *trans*-1,2-disubstituted cyclopropane derivative **548**, which underwent Michael addition of the lithiated enantiopure bislactim ether **284** to form **549** with virtually complete diastereoselectivity. Reductive removal of the sulfonyl group from **549** and subsequent hydrolysis completed the preparation of enantiomerically pure 5-hydroxy-4,5-methanoisoleucine isolated as its methyl ester **550** (Scheme 91). The energetically favored minimum energy conformation of **550** in its fully deprotected form has been shown to mimic the pharmacologically relevant extended conformation of glutamate; however, pharmacological characterization of 5-hydroxy-4,5-methanoisoleucine has not been described yet.[336]

4. Miscellaneous

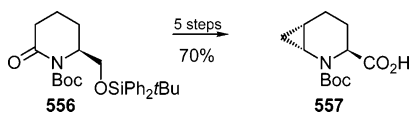
With regard to the synthesis of an inhibitor and a mechanistic probe of prolyl 4-hydroxylase, the 5-spirocyclopropanated proline **555** was synthesized with the spirocyclopropane to serve as a free radical clock. Toward that end, the phosphonohex-5-enoate **551**, available by alkylation of triethyl phosphonoacetate with 4-bromo-1-butene, was transformed to 1-(3-butenyl)cyclopropanecarboxylic acid (**552**) by reaction with oxirane, according to a Horner−Emmons procedure and subsequent hydrolysis. Curtius degradation of the acid functionality furnished 1-(3-butenyl)-aminocyclopropane **553**, isolated in its benzyloxycarbonyl-protected form **553**. Formation of the pyrrolidine ring was achieved upon epoxidation of **553** with trifluoroperacetic acid to yield the 2-spirocyclopropanated 5-hydroxymethylpyrrolidine **554**. Final Jones oxidation of the hydroxymethyl to the carboxylic acid functionality and deprotection of the amino function afforded the 5-spirocyclopropanated proline **555** (Scheme 92).[337]

Scheme 92. Syntheses of 5-Spirocyclopropanated Proline[221,337]



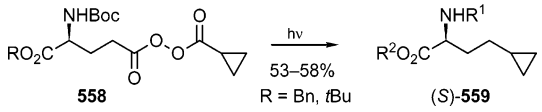
Applying the synthetic sequence used for 3,4-methanoproline (**484**), starting from the lactam **483** (see section 3.3, Scheme 83, eq 1), to the corresponding ring-expanded lactam **556** provided access to the *N*-Boc protected 5,6-methanopipecolic acid **557** (Scheme 93).[297]

Scheme 93. Preparation of 5,6-Methanopipecolic Acid[297]



Following an analogous set of transformations as described for the synthesis of the protected cyclopropylalanine **426** from the diacyl peroxide **427** (see section 3.1, Scheme 76), the glutamic acid-derived diacyl peroxide **558** was prepared

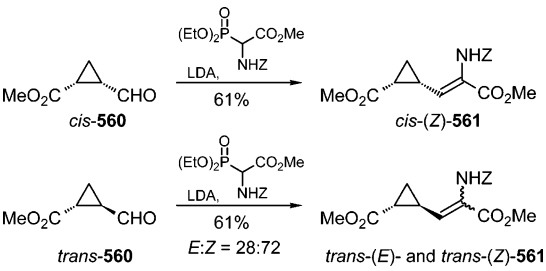
Scheme 94. Preparation of 5,6-Methanonorleucine[235]



and photolyzed to yield 5,6-methanonorleucine (2-amino-4-cyclopropylbutanoic acid) (**559**) (Scheme 94).[235]

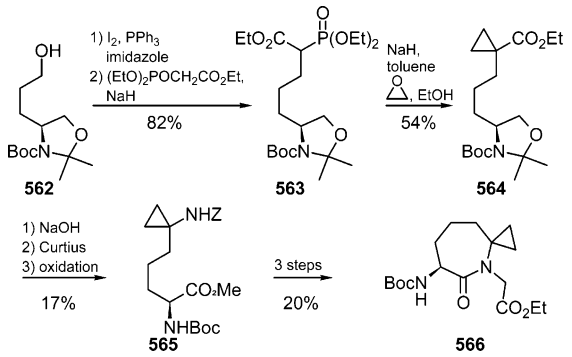
Three diastereomeric cyclopropyl-group-containing Z-protected 2,3-dehydroamino acids have been prepared by Horner−Wadsworth−Emmons alkenation of methyl 2-formylcyclopropanecarboxylate (**560**) with methyl (*Z*)-amino(diethoxyphosphono)acetate. The condensation with the *cis*-configured aldehyde *cis*-**560** gave the *cis*-(*Z*)-configured cyclopropane-containing dehydroamino acid *cis*-(*Z*)-**561** diastereoselectively, whereas *trans*-**560** afforded a mixture of *trans*-(*E*)- and *trans*-(*Z*)-**561** (Scheme 95).[338,339]

Scheme 95. Stereoselective Synthesis of Cyclopropyl-Containing 2,3-Dehydroamino Acid[338,339]



The orthogonally protected 6,6-ethanolysine **565** corresponding to 5-(1-aminocyclopropyl)norvaline, a cyclopropyl-group-containing analogue of lysine, has been prepared from the 4-(3-hydroxypropyl)oxazolidinone **562** derived from glutamic acid. The alcohol was transformed to the iodide and the latter used to alkylate triethyl phosphonoacetate to furnish phosphonoacetate **563**, which was used to cyclopropanate oxirane and yield the correspondingly 1-substituted ethyl cyclopropanecarboxylate. Subsequent hydrolysis of the ethyl ester, Curtius degradation of the acid to the amine, isolated in its *Z*-protected form, and oxidation of the liberated hydroxymethyl to a carboxyl group afforded 5-(1-aminocyclopropyl)norvaline in its protected form **565** (Scheme 96). This lysine analogue was cyclized and further functionalized to the spirocyclopropanated α-amino-ϵ-caprolactam derivative **566** (Scheme 96), which can be regarded as a conformationally constrained dipeptide surrogate.[340]

Scheme 96. Steroselective Synthesis of a Cyclopropyl Analogue of Lysine, a Cyclopropyl-Group-Containing α,ϵ-Diamino Acid, and an ϵ-Caprolactam Derived from It[340]



The outstanding antibacterial activity of penicillins and cephalosporins has initiated numerous investigations focusing on chemical modifications of such azetidinone antibiotics. In this context, several β-lactams, which formally imply a substituted 3,4-methanoamino acid moiety, were synthesized and to some extent investigated with respect to their biological activities.

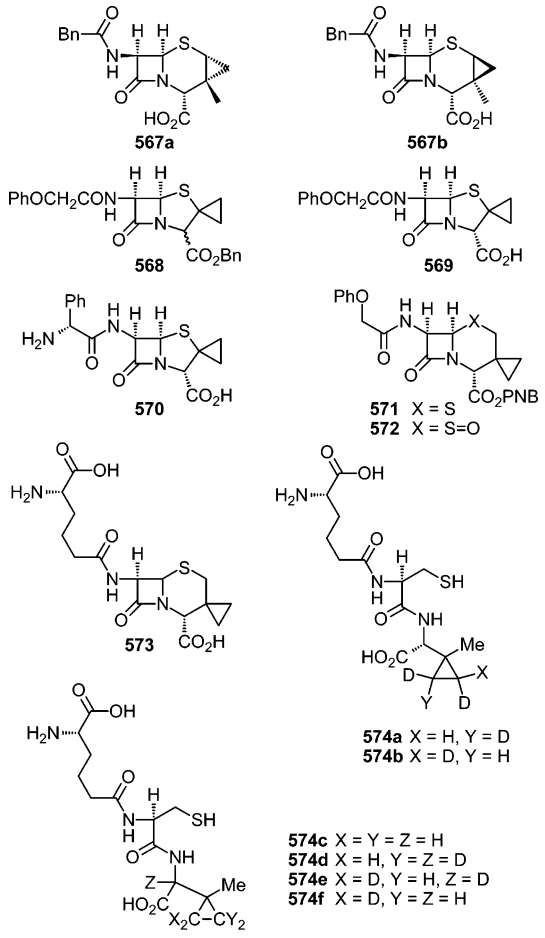


Figure 13. Cephalosporin analogues (cephams) and penicillin analogues (penams) with an incorporated 3,4-methanoamino acid moiety.[341−347]

Among these compounds, the cephalosporin analogue **567a** and its epimer **567b** have also been inaccurately referred to as 2,3-methylenecephams (Figure 13). Compounds **567a** and **567b** both exhibited activities against *Staphylococcus aureus*, *Bacillus subtilus*, *Sarcina lutea*, *Proteus vulgari*, and *Escherichia coli*, and the diastereomer **567b** consistently showed slightly better activity.[341]

The spirocyclopropanated analogue **568** of penicillin was prepared as a mixture of C-3 epimers. The (3*S*)-stereoisomer of these was further transformed into the free acid **569** as well as the derivative **570** (Figure 13). The antibacterial activity of the acid **569** was found to be comparable to that of penicillin V. The penam analogue **570** had activities against Gram-positive and Gram-negative bacteria similar to that of ampicillin while being slightly more stable than ampicillin toward staphylococcal β-lactamase, indicated by a superior activity against *Staphylococcus aureus*.[342] Additionally, the spirocyclopropanated cephalosporins **571** and **572** (Figure 13) have been synthesized; however, their biological activities have not been reported yet.[343]

The spirocyclopropanated cephalosporin analogue **573** (Figure 13) was prepared and evaluated as a substrate for deacetoxy-deacetylcephalosporin C synthetase. In this context, compound **573** was shown to be the first example of a

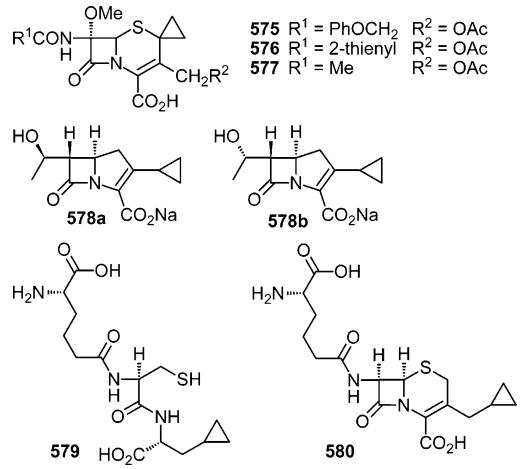


Figure 14. Cephalosporin analogues (cephams) and penicillin analogues (penams) with an incorporated 4,5- or 5,6-methanoamino acid moiety.[344,348−350]

cyclopropyl-group-containing cephalosporin which served as a substrate for a non-heme Fe^{II}/α-ketoglutarate dependent oxygenase.[344]

With the intention to provide evidence for an insertion−homolysis mechanism for the carbon−sulfur bond formation in penicillin biosynthesis, stereospecifically labeled tripeptides **574a**−**f** (Figure 13) were prepared and incubated with isopenicillin N synthetase. These experiments support the stepwise and ultimately radicaloid nature of the carbon−sulfur bond formation in the process of the second ring closure of penicillin biosynthesis.[345−347]

Besides β-lactams which imply a substituted 3,4-methanoamino acid moiety, several β-lactams formally having incorporated a 4,5-methanoamino acid moiety were synthesized and evaluated with respect to their biological activities. Thus, the spirocyclopropanated cephalosporin analogues **575**−**577** (Figure 14) were prepared and claimed to be biologically active; however, these activities have not been specified.[348]

The synthetic cyclopropyl-group-containing carbapenam **578a** and its epimer **578b** (Figure 14) both showed significant antibacterial activities against Gram-positive and Gram-negative microorganisms, with **578a** being the more potent one.[349]

The tripeptide **579** (Figure 14) was prepared for incubation with isopenicillin N synthetase to prove the hypothesis that a carbon-centered free radical or an equivalent iron-carbon bonded intermediate is involved in the carbon−sulfur bond formation during the penicillin biosynthesis.[350]

Additionally, one example of a cephalosporin which has formally incorporated a 5,6-methanoamino acid moiety is known. Thus, the cepham **580** (Figure 14) was synthesized and tested as a substrate for deacetoxy-deacetylcephalosporin C synthetase, but was shown not to interact with the enzyme.[344]

A series of tricyclic oxopyrrolizidinecarboxylic acids have been synthesized as mimics of carbapenems and carbapenams. Among these derivatives were the cyclopropane-annelated compounds **581**−**584** (Figure 15), which formally correspond to a γ-lactam containing a 4,5-methanoamino acid. The oxopyrrolizidinecarboxylic acids **581**−**584** did not show any antibacterial activity when tested on a panel of bacterial strains, but the antibacterial activity of the antibiotic ceftazidine against some β-lactamase producing strains was improved in the presence of the carbapenam and carbapenem mimics **581**−**584**.[351]

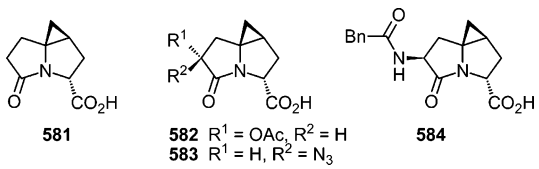


Figure 15. Tricyclic oxopyrrolizidinecarboxylic acids as carbapenam and carbapenem mimics.[351]

5. Conclusions

Hypoglycine A, first isolated from ackee fruits and identified some 50 years ago, represents the first 4,5-methanoamino acid ever found in nature. Fifteen years later, the first 3,4-methanoamino acid was isolated from lychee seeds in the form of 3,4-methanoproline, and since then, more than ten naturally occurring 3,4- and 4,5-methanoamino acids have been identified.

Concomitantly with the isolation of hypoglycine A, the first synthesis of a 3,4-methanoamino acid was performed by the preparation of cyclopropylglycine, but until about 20 years ago, the syntheses of both 3,4- and 4,5-methanoamino acids rarely stirred the interest of organic and medicinal chemists. This situation changed dramatically with the discovery of the outstanding pharmacological properties of 3,4- and 4,5-methanoamino acids, the most remarkable example of which is the detection of 2-(2-carboxycyclopropyl)glycine to act as a potent glutamate receptor ligand. As represented by a vast number of publications, this discovery evoked enormous efforts toward the development of convenient syntheses of 3,4- and 4,5-methanoamino acids in their racemic and particularly in their enantiomerically pure forms. Thus, syntheses of a whole range of stereodefined, structurally rather complicated 3,4- and 4,5-methanoamino acids bearing several functionalities have been accomplished. However, up to date their preparations often imply multistep reaction sequences and require individual approaches for different stereoisomers or time-consuming separations preventing large scale syntheses.

Thus, 3,4- and 4,5-methanoamino acids have been elevated from nature-made structural curiosities via synthetic challenges for organic preparative chemists to highly valuable pharmacological tools. The applications of these entities and structural principles in drug discovery will certainly pose further challenges and offer chances for medicinal and synthetic organic chemists in the near and possibly longer future.

6. Acknowledgments

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