Natural Occurrence, Syntheses, and Applications of Cyclopropyl-Group-Containing α-Amino Acids. 1. 1-Aminocyclopropanecarboxylic Acid and Other 2,3-Methanoamino Acids

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Contents

1. Introduction

None of the naturally occurring amino acids containing a cyclopropyl group is proteinogenic, but most of them bring about some interesting and important biological activity. This also holds for some of the cyclopropyl analogues of the proteinogenic acids. In addition, both the naturally occurring and the nonnatural cyclopropylamino acids play a unique role as conformationally constrained analogues of proteinogenic amino acids in the synthesis of certain peptide analogues, so-called foldamers and peptide mimetics. Starting with the first synthesis of 1-aminocyclopropanecarboxylic acid (ACC) in 1922,[1] the development of highly efficient synthetic routes to cyclopropylamino acids up to date offers a great challenge for organic chemists. The overwhelming role of cyclopropylamino acids in biologically important processes gave rise to highly interesting discoveries in the field of pharmacology as well as biology.

There are several common terms used for the characterization of cyclopropylamino acids. Besides the rather rarely employed names "cyclopropylogs" and "methanologs", cyclopropylamino acids are often classified as "methanoamino acids". The simplest α-amino acids with a cyclopropyl group are the 2,3-methanoamino acids **1**. Its parent compound **1** (R = H), 1-aminocyclopropanecarboxylic acid, is also known as 2,3-methanoalanine, but it is mostly just called ACC. Generally, the term 2,3-methanoamino acid is only used if the amino acid is derived from a proteinogenic amino acid or is a homoanalogue thereof. Other amino acids bearing an α-cyclopropyl substituent are classified as substituted 1-aminocyclopropanecarboxylic acids. Structures **2** and **3** conform to 3,4- or 4,5-methanoamino acids, respectively, which are established in the literature as cyclopropylglycine and cyclopropylalanine derivatives, too (Figure 1).

Several reviews dealing exclusively or in part with the syntheses and applications of cyclopropyl-group-containing α-amino acids[2−7] as well as β-amino acids[8] have been published in the past, but the vast number of publications concerning 2,3-methanoamino acids, which have appeared especially within the last 10 years, have not been summarized up to date. This article is intended to compile the various syntheses, biological properties, and pharmacological activities of 1-aminocyclopropanecarboxylic acid, the unsubstituted 2,3-methanoamino acid, and substituted derivatives thereof. In order to reflect the main intention of the authors of the original publications, the sections of this review are being arranged according to the methods used for the syntheses of these amino acids, showing the feasibility of a certain method for the preparation of the respective cyclopropyl-group-containing amino acids, as most of them were prepared with no specific biological application in mind.

The relative configurations of the stereogenic centers of cyclopropyl-group-containing α-amino acids are being specified with the (*E*) and (*Z*) descriptors and indicated by wide lines, whereas the *R*/*S* descriptors are used for absolute configurations, which are indicated by wedged lines.

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2. 1-Aminocyclopropanecarboxylic Acid (ACC, 2,3-Methanoalanine)

2.1. Biological and Biochemical Studies Concerning ACC

1-Aminocyclopropanecarboxylic acid (ACC) was first isolated in 1955 by Vähätalo and Virtanen from cowberries.[9] Only 2 years later, it was also found in perry pears and cider apples.[10] Four natural products containing an ACC constituent have been isolated. The nonadepsipeptide BZR-cotoxin II (**4**) is produced by *Bipolaris zeicola race 3* and causes leaf spot disease in corn.[11] Cytotrienins A (**5**) and B (**6**) (Figure 2) isolated from *Streptomyces* sp. induce apoptosis in human Leukemia HL-60 cells,[12,13] and the structurally related antibiotics TMC-135A (**7**) and B (**8**) (Figure 2) exhibit cytotoxic activity.[14] Compound UCF116 [(3*S*,11*S*,12*R*,13*S*)-**9**] (Figure 2) is produced by *Streptomyces* sp., and its farnesyltransferase inhibitory activity presents a potential therapeutic option as an anticancer agent.[15]

In 1978, microorganisms which are able to utilize 1-aminocyclopropanecarboxylic acid were discovered, offering the first insights into the metabolism of ACC.[16,17] One year later, ACC was identified independently by Lürssen and Naumann as well as by Adams and Yang to be an intermediate in the biosynthetic conversion of methionine to ethylene in higher plants.[18,19] Starting with this insight, the role of ACC in the ethylene biosynthesis has been examined extensively within the following 10 years.[20−53] The results of this considerable research have been summarized,[54,55] mainly as parts of reviews about the biosynthesis of ethylene.[56−59]

Parallel to the discovery of ACC to be the direct precursor of the plant hormone ethylene, it was shown that 1-aminocyclopropanecarboxylic acid and numerous derivatives thereof exhibit herbicidal activity and influence plant growth, caused by intervention in the metabolism.[60−67] In addition, very small amounts of ACC bring about body weight gain and promotion of protein synthesis in microorganisms and animals.[68]

1-Aminocyclopropanecarboxylic acid has served as a valuable tool for the characterization and mechanistic studies of the enzymes ACC-synthase,[69−72] ACC-oxidase,[73−76] and ACC-deaminase.[16,77−80] Simple and sensitive methods for the quantitative determination of 1-aminocyclopropanecarboxylic acid have been developed. These assays were based on gas chromatography after liberation of ethylene from ACC with sodium hypochlorite in the presence of mercury(II),[81]

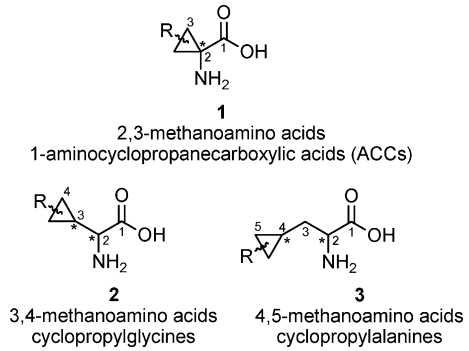


Figure 1. Classification of cyclopropyl-group-containing α-amino acids.

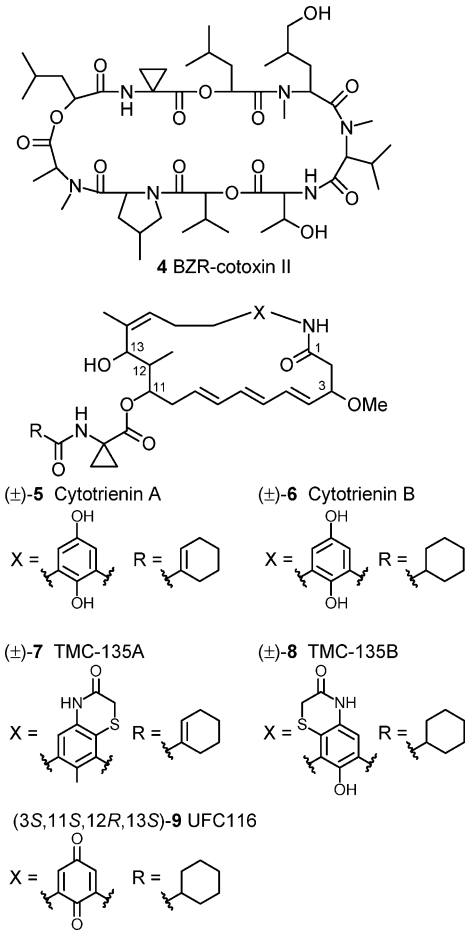


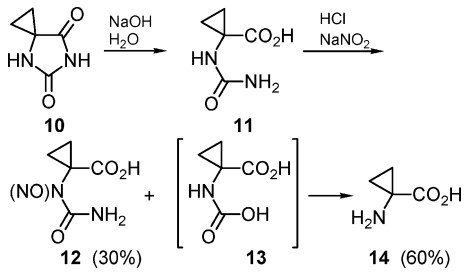
Figure 2. Some natural products containing a 1-aminocyclopropanecarboxylic acid moiety.[11−15]

enzymatic deamination of ACC and estimation of the α-ketobutyrate formed,[82] and mass spectrometric measurements.[83]

2.2. Syntheses of ACC

The first synthesis of 1-aminocyclopropanecarboxylic acid **14**, as published in 1922,[1] was accomplished by alkaline hydrolysis of the spirocyclopropanehydantoin (**10**), which was obtained upon Hofmann degradation of one amide functionality in cyclopropane-1,1-dicarboxamide. Treatment of the resulting hydantoic acid **11** with nitrous acid furnished the *N*-nitroso compound **12** (30%) along with the carbaminic acid **13**, and the latter spontaneously loses carbon dioxide to form ACC **14** in 60% yield (Scheme 1).

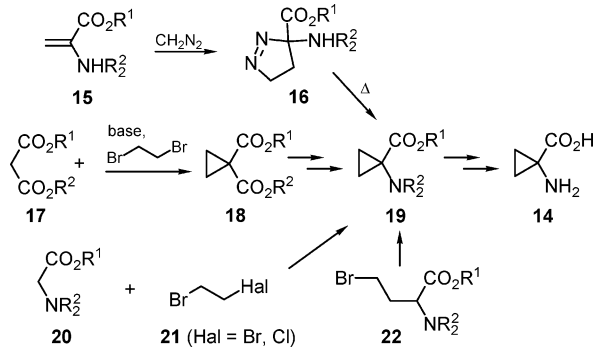
Scheme 1. The First Synthesis of ACC[1]



It took about 20 years until the second synthesis of ACC was achieved by quaternization of (2-dimethylaminoethyl)-acetamidomalonate, hydrolysis, decarboxylation, and γ-elimination of the quaternary ammonium hydroxide.[84] During the course of investigations directed at developing novel syntheses of fluoroamino acids, fluorodehydroxylation of 2-methylserine afforded not only the expected 2-(fluoromethyl)-alanine in 18% yield but also the undesired 1-aminocyclopropanecarboxylic acid hydrochloride in 28% yield.[85]

An early discovered synthetic route, valuable until today, is the "diazo addition method",[86−93] in which diazomethane is added to a 2-aminoacrylic acid derivative **15**, forming a pyrazoline **16**, which can be fragmented thermally with liberation of nitrogen to form the amino acid derivative **19**. This method has been extended to a highly efficient, small scale synthesis of ACC with virtually 100% overall yield (Scheme 2).[94,95] An essentially analogous transformation has been performed using oxosulfonium ylides as the cyclopropanating agents.[92]

Scheme 2. Commonly Used Syntheses of Protected ACC Derivatives: The "Diazo Addition Method",[86−95] Cyclodialkylation of Dialkyl Malonates with Subsequent Conversion of One Ester Group,[96−98] Cyclodialkylation of Enolizable Glycine Equivalents[60,61,99−110] and γ-Dehydrobromination of α-Amino-γ-bromobutyric Acid Derivatives[111−115]



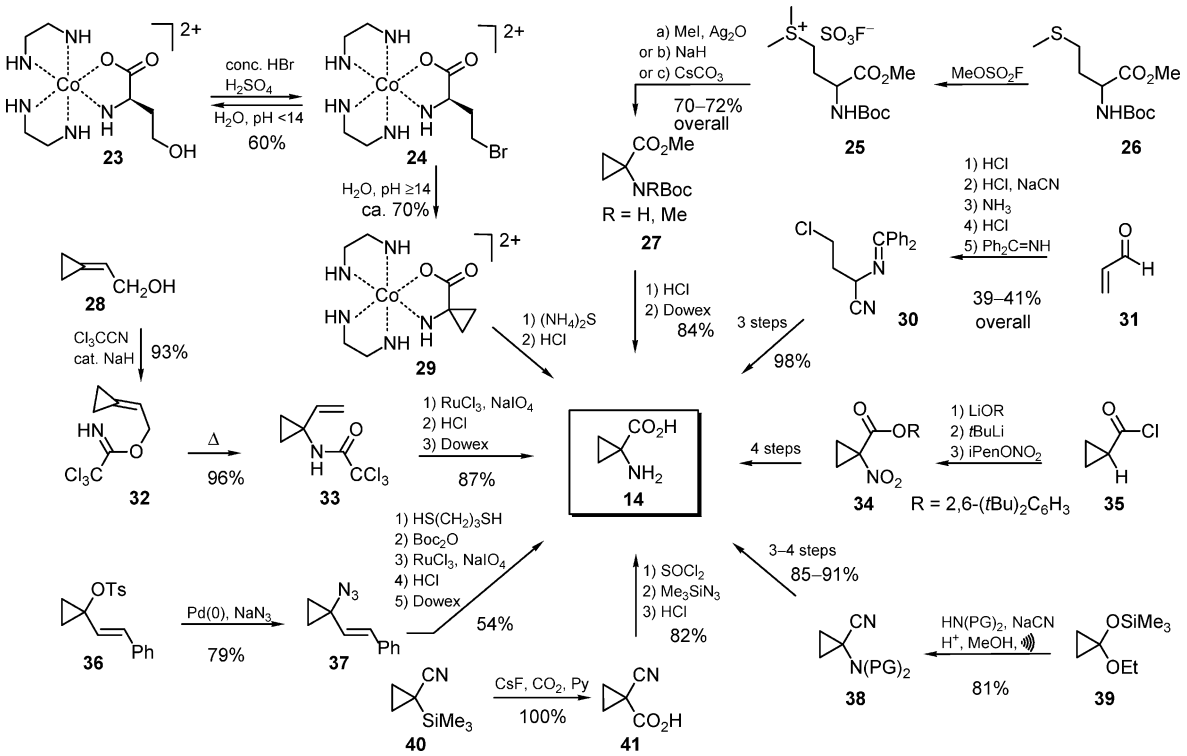
A second frequently utilized and straightforward access to ACC starts with the cyclodialkylation of a dialkyl malonate **17** with 1,2-dibromoethane to yield a dialkyl cyclopropane-1,1-dicarboxylate **18**. The latter can be hydrolyzed to the monoester or directly transformed to the hydrazinocarbonylcyclopropane-1-carboxylic acid, both of which were converted to the monoacid azide, which was in turn subjected to a Curtius degradation.[96,97] Alternatively, the diester **18** by treatment with ammonia can be converted into the corresponding monoamide, and this can then be subjected to Hofmann degradation to yield the ACC derivative **19**.[98]

A commonly practiced variation of this method is the cyclodialkylation of a readily enolized glycine equivalent of type **20** with a 2-bromo-1-haloethane **21**; this saves the conversion of an ester to an amino group. Starting with the synthesis of "the curiosity isocyano-1-ethoxycarbonylcyclopropane" obtained by cyclodialkylation of α-metalated α-isocyanocarboxylic acid esters,[60,61,99−101] this method has found general attention.[102−108] Thus, it was applied toward a solid-phase synthesis of ACC and the synthesis of ACC-containing dipeptides.[109,110] γ-Dehydrobrominations in appropriately *N*-protected alkyl 2-amino-4-bromobutyrates **22** also led to ACC derivatives **19** (Scheme 2).[111−115]

Compared to the "diazo addition method", the cyclodialkylations of **17** or **20** can more easily be scaled up to give larger quantities of ACC **14**.

Since the discovery of ACC as an intermediate in the biosynthesis of ethylene, the demand for convenient and

Scheme 3. Convenient Syntheses of ACC 14 Developed During the Past 25 Years[116,119,121,124−128]



productive syntheses has resulted in numerous novel approaches to this amino acid, which initially was considered a curiosity.

The methyl ester of *N*-Boc-protected methionine **26** can be *S*-methylated with methyl fluorosulfate to the sulfonium salt **25**, which can undergo γ-elimination upon treatment with methyl iodide in the presence of silver oxide or with sodium hydride (or with cesium carbonate) to give the protected ACC derivatives **27** (R = H, Me) in 70−72% overall yield. Compound **27** (R = H) can be deprotected to furnish ACC **14** in its free form (Scheme 3).[116] In a modification of this method toward technical application, a protected methionine derivative was methylated with dimethyl sulfate followed by alkali alkoxide- or potassium carbonate-induced ring closure to the corresponding ACC derivative.[63,117,118]

Another suitable precursor for a convenient and inexpensive access to larger amounts of ACC **14** turned out to be 2-(diphenylmethyleneamino)-4-chlorobutyronitrile (**30**), which can readily be obtained in a five-step synthesis from acrolein (**31**) in up to 41% yield. Compound **30** smoothly undergoes γ-dehydrochlorination to the corresponding cyclopropyl derivative, which, after hydrolysis, furnishes unprotected ACC **14** in almost quantitative yield (Scheme 3).[119,120]

Since the enolate formed upon deprotonation of ethyl cyclopropanecarboxylate undergoes self-condensation, the sterically protected lithium enolate of 2,6-di-*tert*-butylphenylcyclopropanecarboxylate was generated and trapped with heteroatom nucleophiles such as, e.g., isopentyl nitrite, to furnish 2,6-di-*tert*-butylphenyl 1-nitrocyclopropanecarboxylate (**34**) on a preparative scale of up to 100 mmol. Reduction of the nitro group and saponification of the ester function then leads to ACC **14** (Scheme 3).[121]

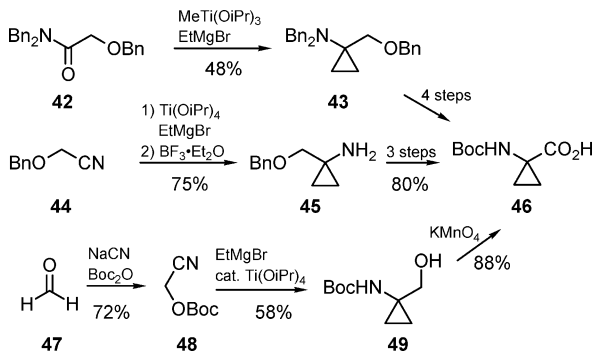
Since cyclopropanone ethyl trimethylsilyl acetal (**39**) is easily available,[122,123] a straightforward synthesis of ACC was realized via the aminocyanocyclopropane **38** obtained by a Strecker reaction under ultrasonication. Hydrolysis and deprotection then led to ACC **14** in high overall yield (Scheme 3).[124] α-Trimethylsilyl-substituted cyclopropane derivatives bearing a strongly electron-withdrawing group, such as the cyano in **40**, can be desilylated with cesium fluoride in the presence of electrophiles to give the corresponding substitution products. With carbon dioxide in pyridine, a quantitative yield of 1-cyanocyclopropanecarboxylic acid (**41**) was obtained, and this could be transformed into the hydrochloride of ACC **14** by Curtius degradation and hydrolysis (Scheme 3).[125]

Palladium(0)-catalyzed nucleophilic substitution with azide of the 1-styrylcyclopropyl tosylate (**36**) regioselectively provided 1-azido-1-styrylcyclopropane (**37**), which also turned out to be a convenient precursor to ACC. Thus, reduction of the azide function in **37** followed by *tert*-butoxycarbonyl protection of the resulting amine and oxidative cleavage of the double bond by in situ generated ruthenium tetroxide, followed by treatment with hydrochloric acid and ion exchange chromatography, yielded ACC **14** (54% overall from **37**, Scheme 3).[126]

The thermal [3,3]-sigmatropic rearrangement (aza-Claisen rearrangement) of the trichloroacetimidate **32**, which can easily be prepared from cyclopropylidenethanol (**28**), provided an easy access to *N*-(1-ethenylcyclopropyl)trichloroacetamide (**33**) in almost quantitative yield. Oxidative cleavage of the double bond and removal of the acetamide moiety under acidic conditions, followed by ion exchange chromatography, furnished free ACC **14** in an excellent overall yield (78%) starting from **28** (Scheme 3).[127]

A very simple, though not inexpensive, synthesis of ACC **14** starts from homoserine via the cobalt(III)bis(ethane-1,2-diamine) [Co(en)$_2$] complex **23**, which acts as a protecting and activating group throughout the synthesis. Bromination of the *O*,*N*-chelated homoserine **23** yields the α-amino-γ-bromobutyrate complex **24**, which, at pH $\geq$ 14, undergoes intramolecular cyclization to form the corresponding complex **29** of ACC, from which ACC **14** can be liberated by treatment with ammonium sulfide (Scheme 3).[128]

Scheme 4. Syntheses of 1-Aminocyclopropanecarboxylic Acid Applying Titanium-Mediated Reductive Cyclopropanations as Key Steps[129−131]



Several syntheses of *N-tert*-butoxycarbonyl-protected 1-aminocyclopropanecarboxylic acid **46** have been performed applying the titanium-mediated cyclopropanation of *N,N*-dialkylcarboxamides or nitriles as a key step. Thus, benzyloxyacetic acid *N,N*-dibenzylamide (**42**) upon treatment with ethylmagnesium bromide in the presence of methyltitanium triisopropoxide gave the (1-benzyloxymethyl)cyclopropylamine **43**. Hydrogenolytic removal of the *N*-benzyl groups, reprotection with an *N-tert*-butoxycarbonyl group, *O*-debenzylation, and final oxidation furnished the protected ACC **46** (Scheme 4).[129]

Benzyloxyacetonitrile (**44**), the benzyl ether of formaldehyde cyanohydrin, when subjected to a titanium-mediated cyclopropanation, led to the cyclopropylamine **45**, which, after protection of the amino group, debenzylation, and oxidation, yielded *N-tert*-butoxycarbonyl-protected ACC **46** (Scheme 4).[130]

An even shorter recently developed synthesis of **46** starts from the *tert*-butyl cyanomethylcarbonate (**48**) obtained in a one-pot operation by trapping the in situ formed cyanhydrin of formaldehyde with di-*tert*-butyl pyrocarbonate. Titanium tetraisopropoxide-mediated reductive cyclopropanation of the cyano group in **48** led to the *N*-Boc-aminoalcohol **49** in 58% yield as the only product, and **49** could be oxidized with potassium permanganate to furnish the *N*-Boc-ACC **46** (Scheme 4).[131]

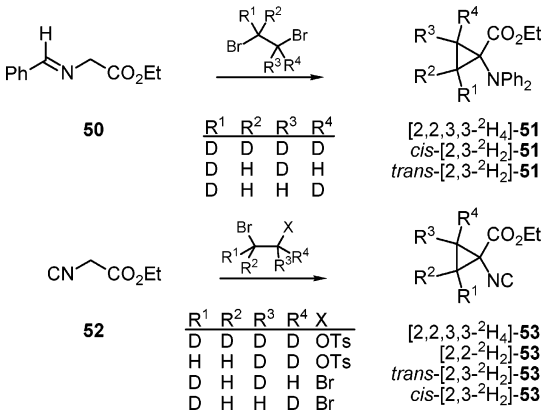
While 1-aminocyclopropanecarboxylic acid (**14**) is commercially available from numerous suppliers, it costs several hundred dollars/euros per 1 g.

2.3. Isotopically Labeled ACC

With regard to the stereochemical course of the metabolic transformations of ACC in the biosynthesis of ethylene, several deuterium-labeled 1-aminocyclopropanecarboxylic acids were synthesized and used in numerous mechanistic studies.

The tetradeuterated 1-aminocyclopropanecarboxylic acid [2,2,3,3-$^2H_4$]-**51** can easily be obtained by cyclodialkylation of the protected glycine ester **50** with 1,2-dibromotetradeuterioethane and subsequent deprotection.[32,34] The same method provides access to racemic *cis*- and *trans*-dideuterated ACC *cis*- and *trans*-[2,3-$^2H_2$]-**51** using *meso*- and *d,l*-1,2-dibromo-1,2-dideuterioethane, respectively, as the alkylating agent. However, the products turned out to be contaminated with up to 49% of residual glycine.[34] An analogous approach to tetradeuterio- as well as any dideuterio-substituted racemic ACC utilizes cyclodialkylation of ethyl 1-isocyanoacetate (**52**) with the accordingly tetra- and

Scheme 5. Syntheses of Racemic Tetra- and Dideuterated ACC[32,34,83,132−134]

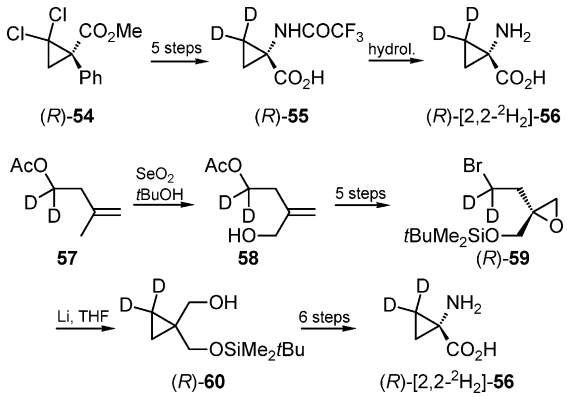


dideuterated 2-bromoethyl tosylate or 1,2-dibromoethane, respectively, followed by final hydrolysis (Scheme 5).[83,132] 2,3-Dideuterated ACC [2,2-$^2H_2$]-**53** was also obtained by 1,3-dipolar cycloaddition of [$^2H_2$]-diazomethane to methyl 2-(acetylamino)acrylate followed by thermolysis (see Scheme 2).[133]

cis-[2,3-$^2H_2$]-ACC in its free form has been applied in studies toward elucidating the stereochemistry of the oxidative degradation of ACC to ethylene, carbon dioxide, and cyanide. Oxidation of unprotected *cis*-[2,3-$^2H_2$]-ACC with hypochlorite yields *cis*-1,2-dideuterioethylene with retention of configuration, whereas oxidation with copper(II) sulfate, potassium permanganate, and dipotassium tetraoxoferrate gave completely scrambled *cis*- and *trans*-dideuterioethylene, reminiscent of the biosynthetic pathway.[134]

A variety of syntheses leading to enantiomerically pure 1-amino-2,2-dideuteriocyclopropane-1-carboxylic acid [(*R*)-[2,2-$^2H_2$]-**56**] have been developed. What has been termed the "Georgia synthesis",[78] started with the optical resolution of 2,2-dichloro-1-phenylcyclopropanecarboxylic acid, followed by reduction of, e.g., the corresponding methyl ester (*R*)-**54** with tri-*n*-butyltin deuteride. Subsequent hydrolysis, Curtius degradation to the amine, purification of the latter as the trifluoroacetamide, and final oxidation with ruthenium(IV) oxide gave the *N*-trifluoroacetylated acid (*R*)-**55**, which could easily be hydrolyzed to (*R*)-[2,2-$^2H_2$]-**56** (Scheme 6). In the so-called "Zürich synthesis" of (*R*)-[2,2-$^2H_2$]-**56**,[78] the deuterated 3-methylbut-3-en-1-yl acetate **57**, prepared from 3-methylbutenoic acid by reduction with $LiAlD_4$ and subsequent acetylation, was oxidized with selenium dioxide and *tert*-butyl hydroperoxide in the allylic position to yield the

Scheme 6. Syntheses of Enantiomerically Pure 1-Amino-2,2-dideuterocyclopropanecarboxylic Acid[78]



alcohol **58**, which was separated by chromatography from the concomittantly formed regioisomer. A five-step sequence consisting of Sharpless enantioselective epoxidation, silyl protection of the hydroxy group, and conversion of the acetate to the bromide gave the epoxide (*R*)-**59**. An intramolecular displacement reaction, initiated by bromine−lithium exchange, furnished the cyclopropane derivative (*R*)-**60**, which could be converted in six additional steps into (*R*)-[2,2-$^2H_2$]-**56** (Scheme 6).

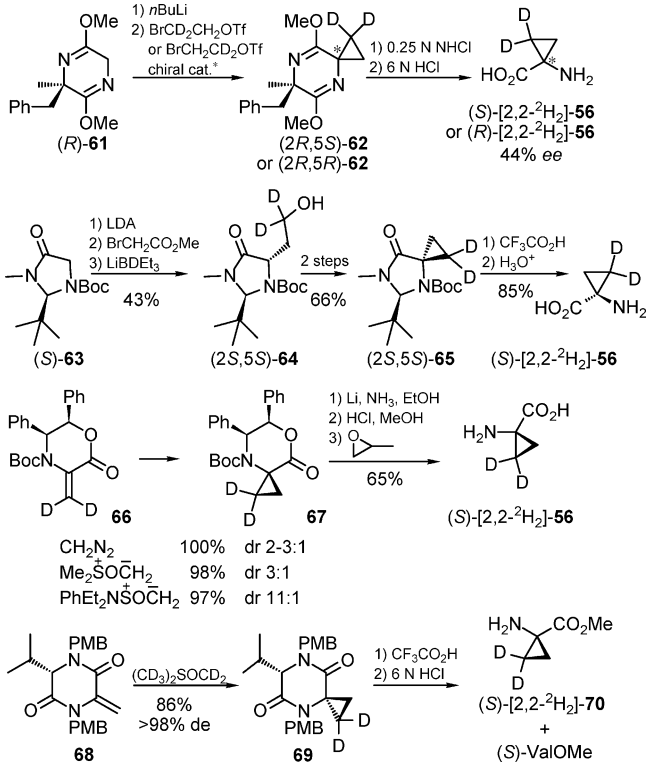
Another access to enantiomerically pure 1-amino-2,2-dideuteriocyclopropanecarboxylic acid [2,2-$^2H_2$]-**56** started with the stepwise cyclodialkylation of the enantiomerically pure chiral bislactim ether (*R*)-**61** with 2-bromoethyl tosylate and subsequent hydrolysis; however, the overall achieved enantiomeric excess was only 44% (Scheme 7).[135]

Alkylation of the commercially available chiral glycine derivative (*S*)-**63** with methyl bromoacetate followed by reduction with lithium triethylborodeuteride gave the 2′,2′-dideuterated alcohol (2*S*,5*S*)-[$^2H_2$]-**64**. Transformation of the hydroxymethyl into a chloromethyl group, subsequent cyclization by intramolecular nucleophilic substitution, and deprotection afforded enantiomerically pure 2,2-disubstituted ACC (*S*)-[2,2-$^2H_2$]-**56** (Scheme 7).[136]

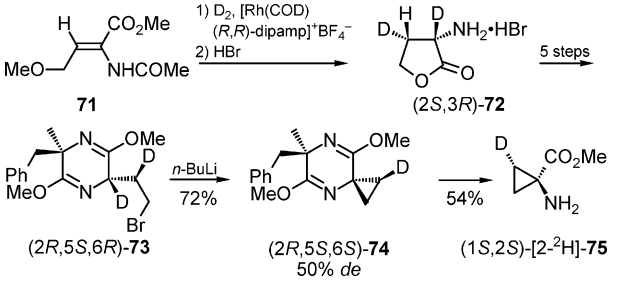
Cyclopropanation of the dideuteriodehydroamino acid **66** with diazomethane or with dimethylsulfoxonium methylide provided the cyclopropane derivative **67** in excellent yield, but with low diastereoselectivity. Switching to [(diethylamino)phenyl]oxosulfonium methylide greatly improved the diastereoselectivity. Final deblocking in three steps liberated (*S*)-[2,2-$^2H_2$]-**56** (Scheme 7).[137]

Cyclopropanation of the *N*-4-methoxybenzyl-protected diketopiperazine **68** with deuterated dimethylsulfoxonium methylide provided the dideuterated diketopiperazine **69** in high yield and with excellent diastereoselectivity. Removal of the *N*-protecting group and hydrolysis gave a mixture of

Scheme 7. Additional Syntheses of Enantiomerically Pure 1-Amino-2,2-dideuteriocyclopropanecarboxylic Acid[135−138]



Scheme 8. Synthesis of Enantiomerically Pure Monodeuterio-substituted ACC[139]



(*S*)-[2,2-$^2H_2$]-**70** and (*S*)-valine methyl ester (Scheme 7), which was further coupled with l-phenylalanine, affording separable dipeptides of the latter and (*S*)-[2,2-$^2H_2$]-**70**.[138]

An asymmetric synthesis of stereospecifically monodeuterated methyl 1-aminocyclopropanecarboxylate (1*S*,2*S*)-[2-^{2}H]-**75** started with the catalyzed addition of deuterium to the double bond in **71** employing a rhodium-(*R*,*R*)-dipamp complex as an asymmetric hydrogenation catalyst. Subsequent hydrolysis gave the corresponding homoserine lactone (2*S*,3*R*)-**72**. Coupling of the latter with a chiral auxiliary and a subsequent four-step transformation to the bislactim ether (2*R*,5*S*,6*R*)-**73** followed by cyclization through intramolecular nucleophilic substitution proceeded with 50% diastereomeric excess and furnished the bislactim ether **74** as the main product. Final hydrolysis led to the monodeuterated ACC (1*S*,2*S*)-[2-^{2}H]-**75** (Scheme 8). When (*S*,*S*)-chiraphos was used as the chiral ligand in the asymmetric deuteration of **71**, the (2*R*,3*S*)-enantiomer of **72** was obtained and could analogously be converted to (1*R*,2*R*)-[2-^{2}H]-**75**.[139]

In addition to the presented deuterium-labeled ACC-derivatives, [1-^{13}C,carboxyl-^{14}C,^{15}N]-1-aminocyclopropanecarboxylic acids have been synthesized by cyclodialkylation of the corresponding [1-^{13}C,1-^{14}C,^{15}N]-glycine equivalents and used for studies of the biosynthetic pathway to azetidine-2-carboxylic acid in *Convallaria majalis*.[140]

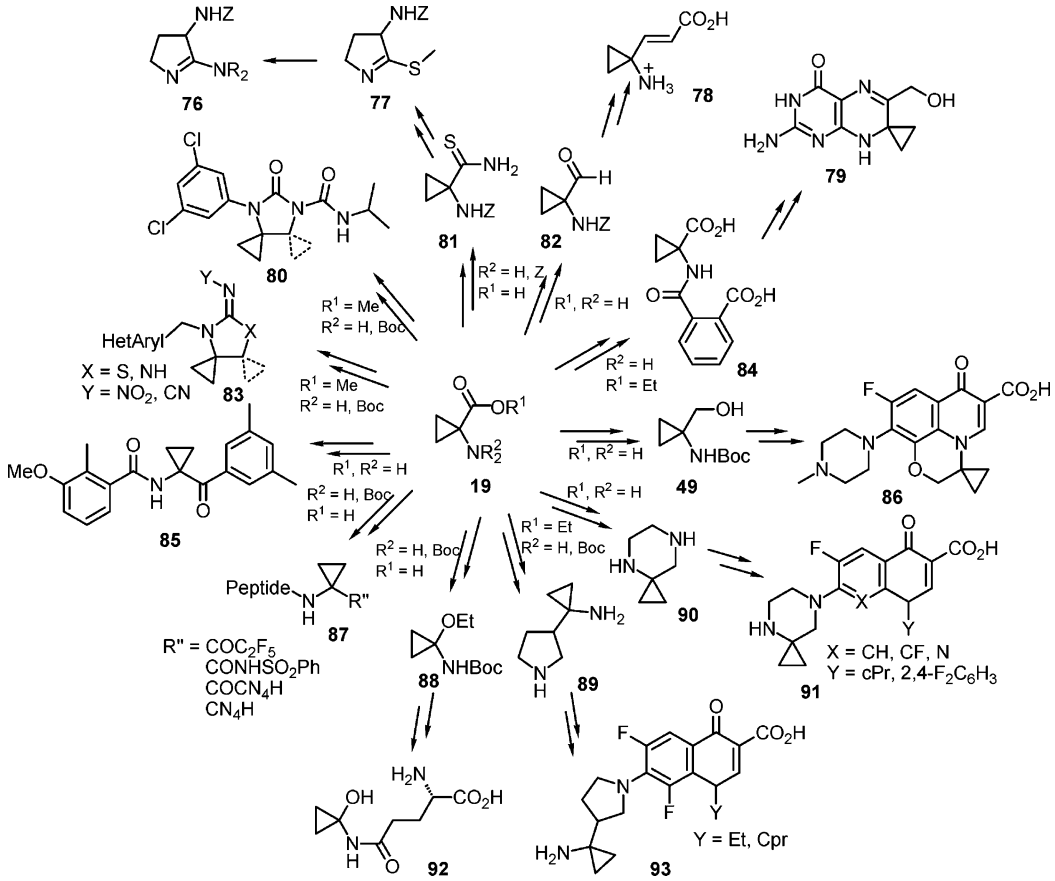
2.4. Biological Activities of ACC

Studies of the pharmacological and toxicological properties of a series of derivatives and analogues of 1-aminocyclopentane-1-carboxylic acid disclosed that 1-aminocyclopropanecarboxylic acid (ACC) (**14**) had no significant tumor growth inhibitory activity.[141]

Oxazolone-protected 1-aminocyclopropanecarboxylic acid has been shown to be a submicromolar inhibitor of viruses of the *Herpes viridae* family, exhibiting high potency against the herpes simplex virus 2 (HSV-2) protease and rather low potency against human cytomegalovirus (HCMV) protease.[142]

In 1988, 1-aminocyclopropanecarboxylic acid (**14**) was first reported to mimic the effect of glycine on the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors, indicating that ACC is a potent agonist on the NMDA-receptor channel.[143] These results were confirmed by others.[144] Probing the action of ACC as a potential agonist by both neurochemical and electrophysiological studies exhibited characteristics consistent with it being a partial agonist on the glycine modulatory site of the NMDA receptor.[145,146] With the discovery of these properties, the applications of ACC for further pharmacological studies of the previously rarely examined NMDA receptor were triggered. Thus, ACC was found to show, at least in animal models, a certain activity as an antidepressant and anxiolytic compound.[147,148]

Scheme 9. Applications of ACC as a Valuable Starting Material for the Synthesis of Various Biologically Active Compounds[115,158−170]



Due to the zwitterionic character of ACC, limiting penetration and bioavailability,[149] the ACC methyl ester upon oral application turned out to be more potent than ACC in its free form, suggesting that 1-aminocyclopropanecarboxylates might constitute a new class of antidepressant and anxiolytic agents.[150] Chronic administration of ACC resulted in a desensitization of the *N*-methyl-D-aspartate receptor complex, indicating that acute treatment with ACC might be a novel, highly efficient means of ameliorating the consequences of neuronal degeneration, such as ischemia, caused by excititoxic phenomena.[151] However, the observed loss in effectiveness, although reversible, diminished the possibility that this glycinergic ligand might be of general use as a clinically useful antidepressant.[152] One of the most pronounced effects of ACC is its capability to block morphine tolerance on the μ- and δ-opioid receptor complex. As ACC is relatively free of side effects, it might be a valuable tool in the use of opioid analgetics.[153]

Besides ACC itself, the *N*-phenyl- and several *N*-alkyl-substituted derivatives have been tested for their activity at the glycine binding site of the NMDA receptor complex. Several of the evaluated compounds were able to activate the receptor, and *N*-methyl-1-aminocyclopropanecarboxylic acid turned out to exhibit remarkable activity as a selective partial agonist. It was therefore claimed to be an acknowledged lead for the development of therapeutics.[154]

A variety of *N*-substituted 1-aminocyclopropanecarboxylic acid derivatives were found to stimulate fruit loosening and fruit drop, to act as defoliants,[155,156] and to exihibit fungicidal as well as herbicidal activity.[157]

2.5. Applications of ACC in the Synthesis of Biologically Active Compounds

With the discovery and development of reasonably efficient and convenient syntheses of 1-aminocyclopropanecarboxylic acid (see section 2.2), the use of ACC in its protected or free form as a valuable starting material for further transformations into other biologically active compounds began.

γ-Aminobutyric acid aminotransferase (γ-Abu-T) is an important target in the design of anticonvulsant drugs. (*E*)-3-(1-Aminocyclopropyl)-2-propenoic acid (**78**) was prepared as an analogue of the inactivator of γ-Abu-T in seven steps from ACC (Scheme 9). This cyclopropyl derivative, however, was found not to be a competitive inhibitor of the enzyme.[158]

Pteridine derivatives, which act as inhibitors of dehydrofolate reductase, are typical drugs for the treatment of bacterial and protozoal infections. The spirocyclopropanepteridine **79** was synthesized from the ethyl ester of ACC via the phthalic acid monoamide **84** and shown to be the first mechanism-based time-dependent inhibitor of both mammalian and bacterial dehydrofolate reductase (Scheme 9).[159−161]

ACC served as the starting material for the synthesis of the conformationally restricted 1-cyclopropylquinolone **86** as well as the analogues **91** and **93** of the lead structure with a cyclopropyl moiety in the 7-amino group (Scheme 9). These compounds were found to exhibit DNA gyrase inhibitor activity and in vivo antibacterial potency. However, the activities were lower or at best comparable to those of the well-established structural analogues Ciprofloxacin and Ofloxacin, respectively.[162−164]

Coprin **92**, a toxine of the edible and palatable inky cap mushroom *Coprinus atramentarius*, is known to cause a severe oversensitivity to ethanol after its consumption, as it efficiently inhibits the enzyme acetaldehyde dehydrogenase. One exercized synthesis of Coprin **92** proceeds via the hemiaminal **88**, which is readily obtainable from ACC (Scheme 9).[115]

Promising antiviral drugs to control Hepatitis C infections are inhibitors of the nonstructural protein 3 (NS3). Potential synthetic inhibitors of the NS3 protease are based on the native system containing a hexapeptide. ACC has been used as the starting material in the synthesis of numerous cyclopropyl-group-containing analogues **87** (Scheme 9). All of these compounds showed NS3-protease inhibitory activity, opening a promising way for new therapies against Hepatitis C virus infections.[165]

With regard to improving the potency of α-acylaminoketones as Ecdysone agonists for the control of gene expression, cyclic derivatives were synthesized. However, the biological activity decreased sharply with decreasing ring size, making the cyclopropane analogue **85** the last effective one (Scheme 9).[166]

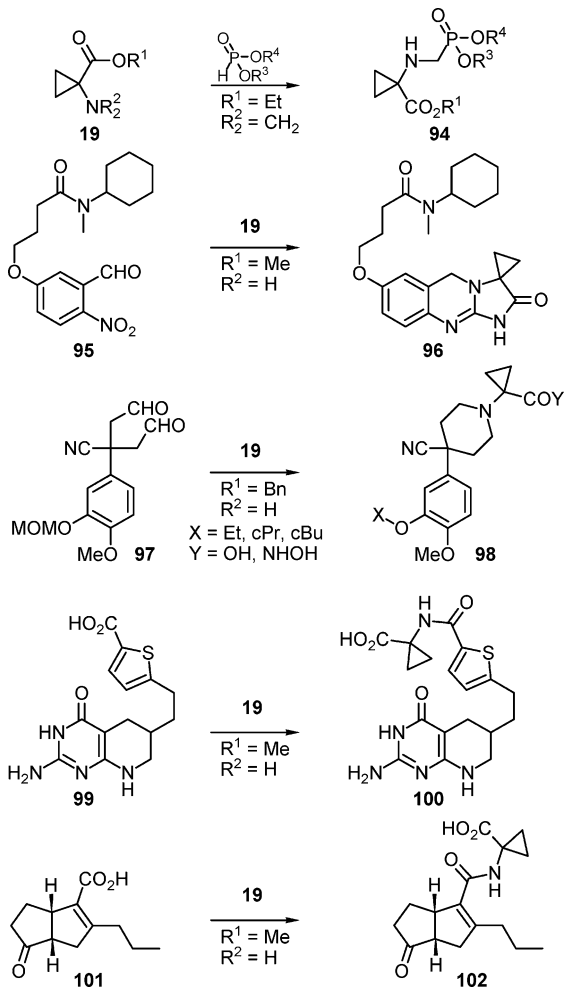
Imidacloprid and Thiacloprid are highly effective insecticides finding worldwide application in crop protection. In order to study the influence of spirocyclopropane-annelation upon the biological activity, spirocyclopropanated analogues **83** (Scheme 9) were synthesized and turned out to be of comparable potency as the original compounds.[167,168] With the same concept in mind, spirocyclopropanated analogues **80** (Scheme 9) of the fungicide Iprodione were prepared; however, their biological activity was minimal.[169]

The cyclopropylketiminium ion rearrangement (Cloke rearrangement) has been applied in the synthesis of a number of pyrrolidine-containing alkaloids, requiring ready access to substituted 2,3-diaminodihydropyrroles **76**. ACC can easily be converted into its thioamide **81**, and this undergoes rearrangement to the corresponding 3-amino-2-methylthiodihydropyrrole **77**, in which the methylthio group can subsequently be substituted with various amines to afford the desired 2,3-diaminohydropyrroles **76** (Scheme 9).[170]

Besides these applications as a precious multifunctional intermediate in organic synthesis, 1-aminocyclopropanecarboxylic acid itself has been incorporated into biologically active compounds. Since *N*-(phosphonomethyl)glycine derivatives possess herbicidal and growth regulating properties, the structurally interesting cyclopropane analogues **94** were prepared by addition of diethyl phosphite to the methyleneamino ethyl ester of ACC followed by selective, partial hydrolysis to yield **94** (R^1 = Et, R^3 = R^4 = H or R^1 = R^2 = Na, R^3 = Et) or complete hydrolysis to furnish **94** (R^1 = R^3 = R^4 = H) (Scheme 10). However, the obtained *N*-phosphonomethyl-substituted 1-aminocyclopropanecarboxylic acid derivatives **94** did not exhibit any herbicidal or growth regulating activity.[171]

Within a series of analogues of cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE) inhibitors, the spirocyclopropanated compound **96** was synthesized using ACC as a building block. This ACC-containing PDE-inhibitor turned out to be less efficient than similar compounds without the ACC unit.[172] Phosphodiesterase type 4 (PDE4) inhibitors attract considerable attention as antiinflammatory agents for the treatment of asthma and rheumatoid arthritis. A biological evaluation of ACC-containing analogues **98** of the clinically used orally administered, active

Scheme 10. Incorporation of ACC into Potentially Biologically Active Compounds[171−175]



PDE4-inhibitor Ariflo shows them to have lost their inhibiting activity at least partially (Scheme 10).[173]

ACC has been used for the synthesis of **100**, a conformationally constrained analogue of tetrahydrofolic acid derived antitumor agents; however, compound **100** did not exhibit significant cell growth inhibitory activity (Scheme 10).[174]

In addition, ACC has been condensed with a conformationally restricted bicyclic analogue **101** of jasmonic acid, giving a conjugate **102**, which exhibits only slightly weaker potato cell expansion-inducing activity than the jasmonic acid standard (Scheme 10).[175]

2.6. Applications of ACC in Peptide Chemistry

In 1981, 1-aminocyclopropanecarboxylic acid (**14**) was introduced into peptide chemistry for the first time, starting with the synthesis of the protected ACC-containing dipeptide **103** and the *N*-adamantyl-substituted tetrapeptide **104** as an enkephalin analogue (Figure 3) in order to compare the steric requirement of the cyclopropyl with that of a methyl group in the analogous tetrapeptide containing the nonproteinogenic 2-methylalanine moiety.[176,177]

Besides standard peptide coupling conditions, three rather unusual methods have been used for the synthesis of peptides incorporating an ACC moiety: Three ACC-containing dipeptides **105** were prepared by regioselective cyclodialkylation of dipeptides containing a C-terminal aminoacetonitrile

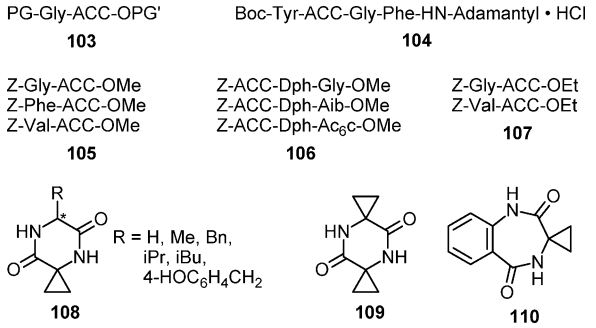


Figure 3. ACC-containing peptides.[109,176−180,189−192]

residue, with ethylene sulfate, and subsequent hydrolysis.[109] An interesting approach to the tripeptides **106** consisting of α,α-diphenylglycine (Dph), ACC, and either glycine, 2-aminoisobutyric acid (Aib), or 1-aminocyclohexane-1-carboxylic acid (Ac_6c) is by a modified Ugi-four-component reaction.[178] Additionally, the ACC-containing dipeptides **107** have been synthesized from 1-azidocyclopropanecarboxylic acid and glycine by a self-regulating redox process using diphenyl diselenide (Figure 3).[179,180]

The conformational preferences of 1-aminocyclopropanecarboxylic acid homopeptides have been studied extensively by computations,[181,182] IR and NMR spectroscopy,[181] as well as X-ray diffraction.[183] Peptides incorporating one ACC unit have been explored by ab initio and semiempirical computational methods[184,185] as well as experimentally by X-ray structure analyses.[186−188] All of these investigations have shown that the conformational space of ACC-peptides is quite peculiar and differs from that of regular peptides by very unusually restricted ϕ- and ψ-torsion angles and a propensity to fold into α- and 3_{10}-helices. These conformational specialties offer a powerful design tool for the generation of structurally defined peptides as conformational probes and bioactive agents.

The smallest possible cyclic dipeptides, the 2,5-diketopiperazines (DKPs), have found widespread attention. The 2,5-diketopiperazine of type **108** consisting of one unit of 1-aminocyclopropanecarboxylic acid and L- as well as D-phenylalanine has been examined by NMR spectroscopy in order to develop a method to distinguish between the enantiotopic methylene groups of ACC.[189] Along with other symmetrically substituted 2,5-diketopiperazines derived from 1-aminocycloalkanecarboxylic acids, the DKP **109** (Figure 3), consisting of two ACC moieties, has been synthesized in order to determine its crystal structure.[190] Numerous diketopiperazines **108** (Figure 3) with one ACC subunit and a proteinogenic α-amino acid as the second component were prepared and tested for their potential proliferative or antiproliferative activity on human embryo as well as on HL60 leukemia cells, but they were found to be inactive.[191] The diketodiazepine (benzodiazepinedione) **110** (Figure 3), derived from one unit of ACC and a 2-aminobenzoic acid moiety, was prepared as a 1,4-analogue of the tranquilizer diazepam.[192]

The discovery that l-aspartyl-l-phenylalanine methyl ester has a very sweet taste has led to numerous investigations of aspartyl peptides as potential artificial sweeteners. Intensive research in the area of 1-aminocyclopropanecarboxylic acid esters as dipeptide sweeteners determined numerous l-aspartyl-1-aminocyclopropanecarboxylic acid esters **111** (Figure 4) to have a sweet taste of up to 300 times stronger than that of sucrose.[193−195]

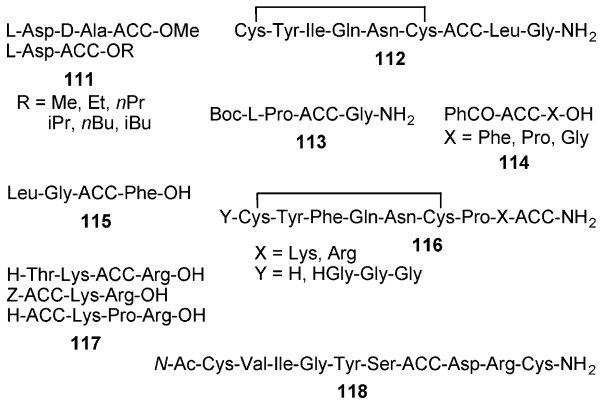


Figure 4. Additional ACC-containing peptides.[193−205]

The analogue **112** (Figure 4) of the nonapeptide oxytocin, in which proline in position 7 was replaced by ACC, has been synthesized. This analogue showed a lower biological activity than the original oxytocin and had a different uterotonic and galactogogic activity.[196] In addition, ACC-containing analogues **113** (Figure 4) of the tripeptide amide tail of oxytocin have been synthesized and examined with regard to their conformational behavior.[197]

Dipeptides **114** and tetrapeptide **115** (Figure 4) containing an ACC moiety as well as various derivatives thereof were found to be potent inhibitors of Carboxypeptidase A.[198−202]

Incorporation of ACC in position 9 in nonapeptides derived from lysine- or argininevasopressin furnished selectively acting antidiuretic agonists **116** (Figure 4), but with low potency and no effect on the central nervous system (CNS).[203] ACC was also introduced into the tetrapeptide Tuftsin, substituting the threonine and/or the proline moiety,[204] and into the epidermal growth factor (EGF) sequence 33−42,[205] yet the biological activity of these analogues **117** and **118** (Figure 4) has not been described.

Among a number of other unnatural amino acids, ACC could successfully be incorporated as the 164 residue in T4 lysozyme, demonstrating the capability of the *Escheria coli* protein biosynthetic machinery to tolerate a wide range of backbone and side-chain substitution patterns.[206]

Inhibitors of the neutral endopeptidase (NEP) and the angiotensin-I converting enzyme (ACE) are clinically applied in the treatment of hypertension and congestive heart failure. A potent inhibitor of NEP and ACE is an α-thiodipeptide **119** (Figure 5), containing ACC as the central building block.[207] The interaction and selectivity of the heptapeptide deltorphin with the δ- and μ-opioid receptor depends on the properties of the side chains of its amino acids and can be influenced by the introduction of ACC, as shown in the two examples **120** (Figure 5).[208] Spiroindane-annelated growth hormone secretagogue **121** (Figure 5), with an ACC side chain, exhibits only very low activities.[209]

L-Prolyl-L-leucinyl-glycinamide is a tripeptide present in the central nervous system (CNS) which modulates dopaminergic neurotransmission. Substitution of glycine in this by an ACC moiety furnishes an analogue **122**, and further rigidification gives an analogue **123** (Figure 5). Both compounds increase the binding affinity of an agonist to the dopamine D_2 receptor, an effect which is postulated to be useful in the treatment of extrapyramidal motoric disorders such as Parkinson's disease and depression.[188]

Cyclic peptides **124** (Figure 5) with peptide nucleic acid (PNA) side chains containing ACC moieties have been

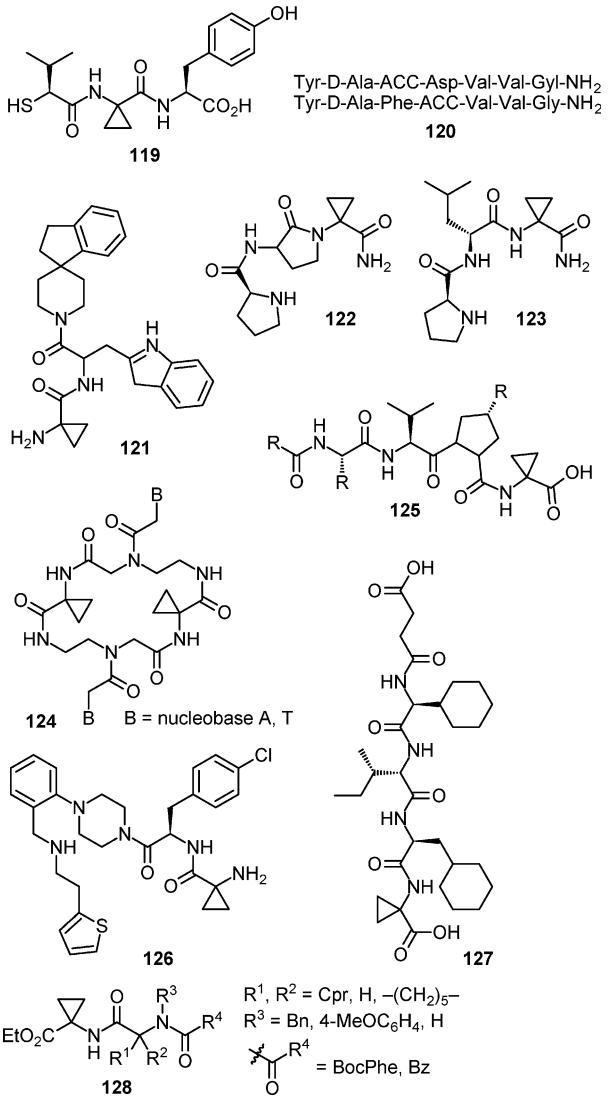
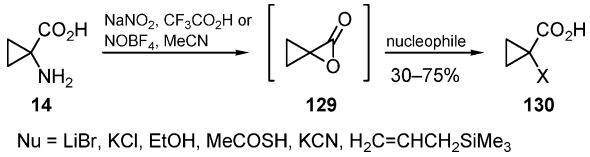


Figure 5. Even more ACC-containing peptides.[188,207−215,218]

synthesized in order to increase the rigidity of the ring, which might improve the stacking properties into nanotubular structures.[210] ACC has been incorporated into several highly potent tetra- and hexapeptide analogues **125** and **126** of NS3-protease inhibitors (Figure 5; see also section 2.5),[211−215] and the binding characteristics of one of these analogues have been studied by nuclear magnetic resonance.[216] ACC has attracted attention as a turn-inducing linker with chelating ability in the solid-phase synthesis of sensors for protein kinase activity.[217] In the context of investigations directed toward the development of potent and selective antagonists of the human melanocortin receptor 4 (MC4) as potential drugs for the treatment of obesity and cachexia, ACC has been used as a scaffold for the dipeptide side chain of piperazinylbenzylamines, giving an MC4-ligand **127** (Figure 5), yet with low potency.[218]

Employing the previously reported ethyl 1-isocyanocyclopropanecarboxylate[99] in an Ugi-four-component reaction with cyclopropanecarbaldehyde or cyclohexanone as the carbonyl component, benzylamine, *p*-methoxyaniline, or ammonia as the amine, and cyclopropanecarboxylic acid or *N*-Boc-penylalanine or benzoic acid as the fourth component, five different dipeptides **128**, all with an ethyl 1-aminocyclopropanecarboxylate terminus, were obtained in yields

Scheme 11. Diazotation of ACC[222]



ranging from 38 to 86%. Two of these were structurally characterized by X-ray diffractometry.[219]

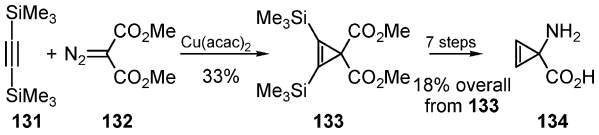
2.7. Miscellaneous

In order to study the regioselectivity in the catalytic hydrogenolysis of 1-aminocyclopropanecarboxylic acid and its methyl ester, these compounds were hydrogenated over palladium on charcoal. The ring-bond cleavage upon hydrogenolysis of the acid in water or methanol turned out to be nonselective, as it occurred across both the C^1-C^2 and C^2-C^3 bonds almost in a 1:1 ratio. In aqueous ammonia, mainly the C^1-C^2 and, in acetic acid, mainly the C^2-C^3 bond was cleaved. In the case of the methyl ester, the C^1-C^2 bond could selectively be hydrogenolyzed in hexane and methanol, whereas the C^2-C^3 bond was cleaved in acetic acid.[220]

Decarboxylation of ACC in its free form and of several protected derivatives was examined, and under certain conditions, the cyclopropane ring was shown to survive. The decarboxylation reactions provide a new entry to cyclopropanone derivatives.[221]

Upon diazotation of ACC **14**, the α-lactone 1-oxaspiropentane-2-one (**129**) is formed as a reactive intermediate, which can be trapped with nucleophiles, furnishing 1-substituted cyclopropanecarboxylic acid derivatives **130** that are otherwise difficult to obtain (Scheme 11).[222]

Scheme 12. Synthesis of 1-Aminocycloprop-2-ene-1-carboxylic Acid[223]



The unsaturated analogue of 1-aminocyclopropanecarboxylic acid has been synthesized in nine steps starting from bis(trimethylsilyl)acetylene (**131**). Addition of dimethyl diazomalonate (**132**) in the presence of cupric acetylacetonate furnished dimethyl 1,2-bis(trimethylsilyl)cyclopropene-3,3-dicarboxylate (**133**), which, by protiodesilylation, monohydrolysis, and subsequent Curtius degradation, was converted into 1-aminocycloprop-2-ene-1-carboxylic acid (**134**) (Scheme 12).[223]

3. Substituted 2,3-Methanoamino Acids

3.1. Biological and Biochemical Studies of Substituted 2,3-Methanoamino Acids

Several substituted 2,3-methanoamino acids themselves or as constituents of natural products have been found in nature. Among these compounds, the plant toxin coronatine plays an outstanding role. Coronatine was first isolated in 1977 from *Pseudomonas coronafacience* var. *atropurpurea* and was found to induce chlorosis on leaves of the Italian ryegrass,[224] to expand potato cells, and to inhibit root elongation of wheat.[225,226] Shortly thereafter, a toxin causing

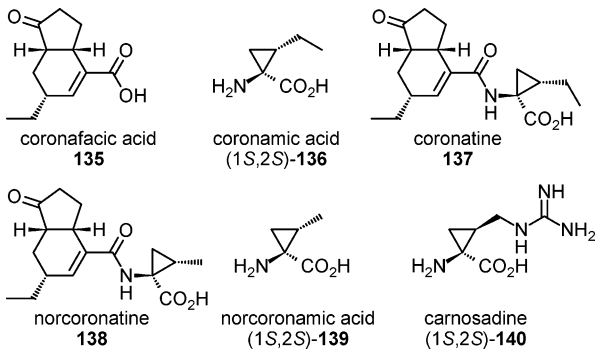


Figure 6. Coronatine and its biosynthetic precursors as well as the natural amino acid carnosadine.

chlorosis in bean as well as soybean leaves was isolated from *Pseudomonas syringae* pv. *glycinea* and was also characterized as coronatine.[226,227] On the basis of its spectroscopic data and X-ray crystallographic analysis, coronatine could be identified as consisting of two fragments bound to each other by an amide linkage, and the two are coronafacic acid **135** and (−)-coronamic acid **136**.[228] Partial total synthesis of coronatine from natural coronafacic acid and enantiomerically pure synthetic (1*R*,2*R*)-coronamic acid along with ORD measurements were used to determine the absolute configuration of the natural product,[229] but this original assignment was later disproved by the same group and corrected as being that of **137**, i.e. 1*S*,2*S*-configured, by enzymatic methods and X-ray structure analysis (Figure 6).[230]

In order to probe the active site of coronatine **137**, analogues in which the coronamic acid moiety was replaced by its stereoisomers, by ACC, and by other amino acids were synthesized and tested to establish a structure−activity relationship. In this context, the configuration at the α-carbon atom as well as the presence of the alkyl group in the amino acid moiety proved to be important for the physiological activity, and the cyclopropane ring turned out to be indispensable. However, among all examined analogues, coronatine itself was the most active compound.[231] Coronatine stimulates the production of ethylene in bean leaf discs, and in analogy to the chlorosis effect, the intact coronatine molecule is necessary for ethylene production, as its hydrolysis products do not trigger these effects.[232] It could be shown that ethylene emitted from plant tissues exposed to coronatine is of plant origin and results from coronatine-induced increased biosynthesis of ACC from methionine rather than from the breakdown of coronatine itself.[233]

The biosynthesis of the phytotoxine coronatine has been clarified to proceed by condensation of coronafacic acid **135** and coronamic acid (1*S*,2*S*)-**136** derived from L-isoleucine with the intermediacy of L-*allo*-isoleucine.[234−239] Norcoronatine, the coronatine analogue incorporating a norcoronamic acid moiety **139** instead of the coronamic acid residue, has been isolated as a minor ingredient,[240] and the absolute configuration of coronamic acid derived from coronatine has been established as 1*S*,2*S* (Figure 6).[241]

Coronatine has been identified as a structural analogue of the octadecanoic acid precursors of the cyclopentanoid jasmonic acid. Just like this, coronatine is able to act as a powerful signal-inducing molecule in higher plants involved in defense against pathogene attack,[242] and it exhibits biological activities similar to or even more pronounced than those of jasmonic acid.[243] Just as jasmonic acid, coronatine is able to induce emission of volatile compounds from leaves

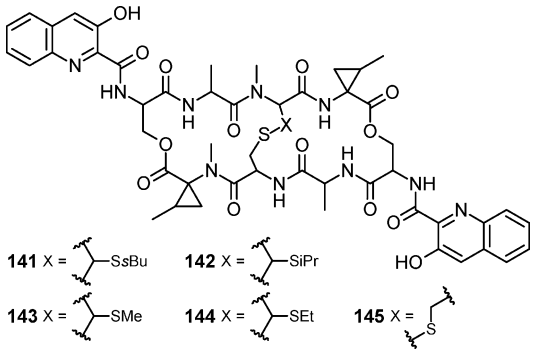


Figure 7. Norcoronamic acid-containing natural products.[250−253]

of numerous plants, suggesting an interesting perspective for the induction of valuable aroma components.[244]

After the development of a practical synthesis for all four stereoisomers of coronamic acid,[245] the first asymmetric total synthesis of coronatine **137** was completed by peptide coupling of (+)-coronamic acid **136** with coronafacic acid **135** (which had been constructed starting from (*R*)-4-acetoxy-2-cyclopent-1-one as a chiral building block by an intramolecular 1,6-conjugate addition as the key step).[246,247]

In 1984, the α-amino acid carnosadine **140** was isolated from the red algae *Grateloupia carnosa*.[248] The structure was unequivocally established to be 1-amino-2-guanidinomethylcyclopropanecarboxylic acid, and the absolute configuration of the natural product was confirmed by enantioselective total synthesis to be 1*S*,2*S* (Figure 6).[249]

Norcoronamic acid has been found to be a constituent of natural products belonging to the quinomycin family. Thus, a norcoronamic acid moiety is incorporated in the antimicrobial antibiotic UK-63052 complex, consisting of mainly the three components **141**−**143** (Figure 7), isolated from *Streptomyces braegensis* subsp. *japonicus*,[250,251] and in the depsipeptides SW-163C (**144**) and SW-163E (**145**), which have potent *in vitro* antitumor activity against various tumor cell lines and *in vivo* activity against murine leukemia.[252,253]

Several substituted 1-aminocyclopropanecarboxylic acids have been applied for the characterization and mechanistic studies of the pyridoxalphosphate (PLP) dependent enzyme ACC deaminase. In this context, it was shown that, among the four stereoisomers of coronamic acid, only the (+)-(1*S*,2*S*)-isomer **136** turned out to be a substrate for ACC deaminase.[254] Besides 1-amino-2-methylenecyclopropanecarboxylic acid (**146**), which was shown to be an irreversible inhibitor of ACC deaminase,[255,256] racemic 2,3-methanovaline (**147**) and racemic (*Z*)- as well as (1*S*,2*S*)-norcoronamic acid **139** were investigated (Figure 8).[256,257]

Coronamic acid **136** and its stereoisomers,[258,259] (1*R*,2*S*)-*allo*-norcoronamic acid **136**[260] and its 3-deuterated derivative [3-^{2}H]-**136**,[261] all four diastereoisomers of racemic 1-amino-2,3-dimethylcyclopropane-1-carboxylic acid (**148**),[262] (2*S*,3*R*)-2,3-methanohomoserine (**149**),[263] 1-amino-2-cyclopropylcyclopropanecarboxylic acid (**150**),[264,265] and 2,3-methanoproline (**151**)[266,267] have been applied in biochemical studies aimed at the elucidation of ethylene biosynthesis and the understanding of the senescence of flowers (Figure 8, see also section 2.1).

3.2. Syntheses of Substituted 2,3-Methanoamino Acids

By now, an enormous variety of synthetic routes providing access to substituted 2,3-methanoamino acids have been

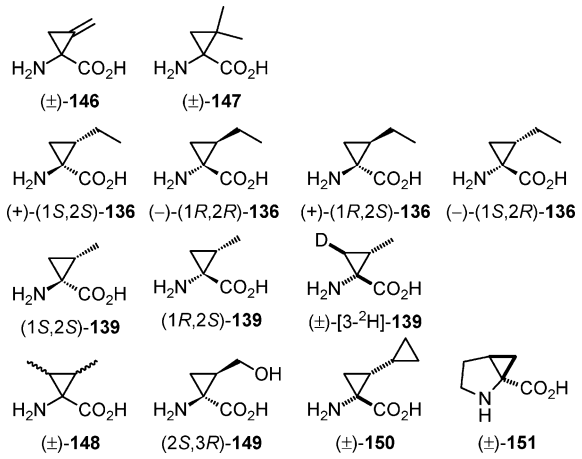


Figure 8. 2-Substituted 1-aminocyclopropanecarboxylic acids employed in studies of ACC deaminase and ethylene biosynthesis.

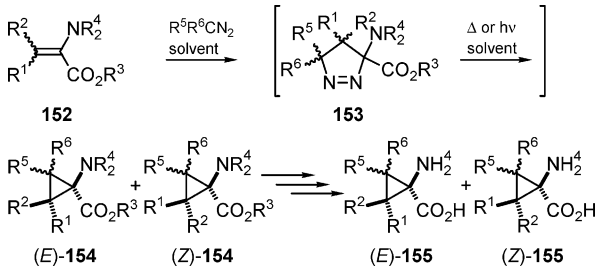
explored. Nevertheless, a generally applicable method is still lacking. Thus, especially the development of routes leading to stereodefined substituted 2,3-methanoamino acids is still attracting considerable attention.

Based on the number of previous publications, the addition of 1,3-dipoles such as diazomethane (see section 3.2.1) and sulfonium (or other) ylides (see section 3.2.2) to 2-aminoacrylic acid derivatives, also called dehydroamino acids, or derivatives thereof, respectively, has most frequently been applied toward the synthesis of substituted 2,3-methanoamino acids. Several enantioselective variations thereof, making use of chiral auxiliaries, chiral starting materials, chiral catalysts, or optical resolution have been investigated. Another often applied protocol has been the cyclodialkylation of malonic acid derivatives with suitable biselectrophiles followed by degradation of one acid moiety to an amino group (see section 3.2.3). A straightforward modification of this principle is the cyclodialkylation of nucleophilic glycine anion equivalents (see section 3.2.4). For both routes, practical asymmetric variants have been explored. In addition, numerous newer and individually developed syntheses of substituted 2,3-methanoamino acids have been explored (see section 3.2.5).

3.2.1. Syntheses Applying 1,3-Dipolar Cycloadditions of Diazomethane and Its Derivatives as Key Steps

The most often applied key step in the synthesis of appropriate precursors to 2-substituted 1-aminocyclopropanecarboxylic acids is the 1,3-dipolar cycloaddition of diazomethane or derivatives thereof, respectively, to substituted protected 2-aminoacrylates **152**, providing an aminopyrazolinecarboxylate **153**. The latter may be formed either as an unstable intermediate which spontaneously cleaves off nitrogen with ring contraction to the corresponding 1-aminocyclopropanecarboxylic acid derivatives (*E*)- and (*Z*)-**154** or as a stable product which can be fragmented with ring contraction by thermolysis or photolysis to yield the corresponding diastereomeric cyclopropane derivatives (*E*)- and (*Z*)-**154**.[268] Depending on the stereochemical information in the starting material as well as on the reaction conditions, the product of such a 1,3-dipolar cycloaddition can be produced diastereoselectively, but also as a mixture of diastereomers, which can often be separated by simple column chromatography. With almost any substituent, the obtained products **154** have been further functionalized, partially or fully deprotected to the corresponding diastereomeric free amino acids (*E*)- and (*Z*)-**155** (Scheme 13).

Scheme 13. 1,3-Dipolar Cycloadditions of Diazomethane and Substituted Diazomethanes to 2-Aminoacrylic Acid Derivatives 152. the (*E*)- and (*Z*)-Notation is Based on the Relationship of R^1 to the Amino Substituent[268]



The most frequently used protecting group for the amino and at the same time the acid function is an oxazolinone or a thiazolinone group, respectively. 1,3-Dipolar cycloaddition of diazomethane to such a methylene-substituted heterocycle **156** (X = O) or **157** (X = S) furnishes directly the diastereomeric spirocyclopropanated compounds **158** (X = O) and **159** (X = S), without formation of an isolable pyrazole. In most cases, these derivatives can easily be transformed into the corresponding deprotected (*E*)- and (*Z*)-configured amino acids **160**. (Scheme 14).

Starting in 1937 with the discovery that oxazolinone-protected 2-(5-methoxycarbonyl-2,4-dimethylpyrrol-3-yl)-aminoacrylic acid and the (1-acetylindol-2-yl)-substituted analogue upon exposure to diazomethane furnished the correspondingly 2-substituted oxazolinone-protected 1-aminocyclopropanecarboxylic acids **158** (Table 1, entries 1 and 2),[269] several other 2-hetaryl-substituted spirocyclopropanated oxazolinones (*E*)- and (*Z*)-**158** (R^1 = heteroaryl), and from them the corresponding 2-substituted 1-aminocyclopropanecarboxylic acids **160** have been prepared (entries 3−6).[89,270,271] Since then, especially aryl-substituted compounds (*E*)- and (*Z*)-**158** (R^1 = aryl) have been investigated (entries 8−50),[272−283] but also methyl- (entries 51−53),[279,281] halo- (entries 54−58),[284−286] acyloxy- (entries 59 and 60),[286] and organothio-substituted (entries 61−64)[287] spirocyclopropanated oxazolinones (*E*)- and (*Z*)-**158** have been synthesized. Starting from only one diastereomer of **156**, the stereochemical information is often lost during the cyclopropanation sequence; however, under certain reaction conditions, diastereomerically pure cyclopropanation products could be obtained in moderate yields (Table 1).

In analogy to the oxazolone chemistry, the 1,3-dipolar cycloaddition of diazomethane to substituted alkylidenethia-

Scheme 14. 1,3-Dipolar Cycloaddition of Diazomethane to Oxazolinone- or Thiazolinone-protected 2-Aminoacrylic Acid Derivatives 156 or 157, Respectively (for Further Details See Tables 1 and 2)

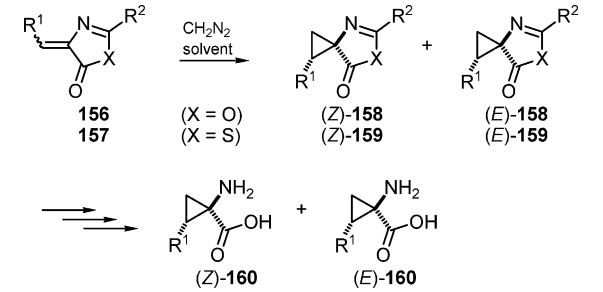
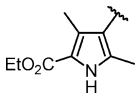


Table 1. Spirocyclopropanated Oxazolinones 158 Obtained by 1,3-Dipolar Cycloaddition of Diazomethane to 2-Aminoacrylic Acid Derivatives 156 (See Scheme 14)

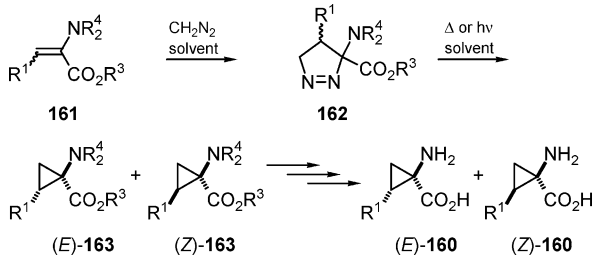
entry	config **156**	R^1	R^2	solvent	yield (%)/ *E*/*Z*-ratio	ref
1	(*E*/*Z*)		Ph	MeOH	n.r./n.r.[a−c]	269
2	(*E*/*Z*)	3-(1-acetylindolyl)	Ph	MeOH	n.r./n.r.[b,c]	269
3	(*Z*)	3-(1-acetylindolyl)	Ph	Et_2O	46/only (*Z*)	270
4	(*E*)	3-(1-acetylindolyl)	Ph	Et_2O	81/only (*E*)	270
5	(*E*/*Z*)	4-(1-acetylimidazolyl)	Ph	$CHCl_3$	19/n.r.[b]	271
6	(*E*/*Z*)	4-(1,3-diphenylpyrazolyl)	Ph	C_6H_6	80/n.r.[b]	89
7	(*Z*)	4*H*-chromen-4-one-3-yl	Ph	CH_2Cl_2	20/only (*Z*)	272
8	(*E*/*Z*)	1,2-$(OCH_2O)C_6H_3$	Ph	dioxane	n.r./n.r.[b]	273
9	(*E*/*Z*)	Ph	Me	dioxane	n.r./n.r.[b]	273
10	(*Z*)	Ph	Ph	dioxane	40/n.r.[b]	274, 275
11	(*E*/*Z*)	Ph	4-NO_2Ph	dioxane	65/n.r.[b]	274, 275
12	(*E*/*Z*)	Ph	Ph	$CHCl_3$	39/n.r.[b]	276
13	(*Z*)	Ph	Ph	CH_2Cl_2	31/n.r.[b]	277
14	(*E*)	Ph	Ph	CH_2Cl_2	54/n.r.[b]	277
15	(*E*)	Ph	Ph	Et_2O or C_6H_6	65−70/3.3−3.7:1	278
16	(*Z*)	Ph	Ph	Et_2O or C_6H_6	65−70/3.3−4:1	278
17	(*Z*)	Ph	Me	Et_2O or C_6H_6	40/1:1	278
18	(*Z*)	Ph	3-HO_2CPh	CH_2Cl_2	33/only (*Z*)	279
19	(*Z*)	Ph	Ph	THF	42/3:11	280
20	(*E*)	Ph	Ph	THF	73/55:18	280
21	(*Z*)	Ph	Me	THF	13/4:9	280
22	(*Z*)	Ph	Ph	CCl_4	70/3:11	280
23	(*Z*)	Ph	Ph	DMF	36/2:7	280
24	(*E*)	Ph	Ph	C_6H_6	50/only (*E*)	281
25	(*Z*)	Ph	Ph	C_6H_6	45/only (*Z*)	281
26	(*E*/*Z*)	4-MeC_6H_4	Ph	dioxane	n.r./n.r.[b]	273
27	(*E*/*Z*)	4-MeC_6H_4	Ph	dioxane	50/n.r.[b]	274, 275
28	(*E*)	4-MeC_6H_4	Ph	C_6H_6	40/only (*E*)	281
29	(*Z*)	4-MeC_6H_4	Ph	C_6H_6	60/only (*Z*)	281
30	(*Z*)	4-$MeOC_6H_4$	Ph	$CHCl_3$	53/only (*Z*)	282
31	(*E*/*Z*)	4-$MeOC_6H_4$	Ph	$CHCl_3$	35/n.r.[b]	274, 275
32	(*E*)	4-$MeOC_6H_4$	Ph	C_6H_6	50/only (*E*)	281
33	(*Z*)	4-$MeOC_6H_4$	Ph	C_6H_6	55/only (*Z*)	281
34	(*E*)	3-$MeOC_6H_4$	Ph	C_6H_6	30/only (*E*)	281
35	(*Z*)	3,4-$(MeO)_2C_6H_3$	$Fe(CO)_3$butadien-1-yl	CH_2Cl_2	<73/>4.8:1	283
36	(*E*/*Z*)	4-ClC_6H_4	Ph	dioxane	n.r./n.r.[b]	273
37	(*E*)	4-ClC_6H_4	Ph	C_6H_6	50/only (*E*)	281
38	(*Z*)	4-ClC_6H_4	Ph	C_6H_6	50/only (*Z*)	281
39	(*E*)	2-ClC_6H_4	Ph	C_6H_6	50/only (*E*)	281
40	(*Z*)	4-$AcOC_6H_4$	Ph	$CHCl_3$	38/only (*Z*)	282
41	(*E*/*Z*)	4-$AcOC_6H_4$	Ph	dioxane	60/n.r.[b]	274, 275
42	(*E*/*Z*)	3-$AcOC_6H_4$	Ph	dioxane	50/n.r.[b]	274, 275
43	(*Z*)	4-AcO-3,5-$I_2C_6H_2$	Ph	$CHCl_3$	50/only (*Z*)	282
44	(*Z*)	4-MeO-3,5-$I_2C_6H_2$	Ph	$CHCl_3$	55/only (*Z*)	282
45	(*Z*)	4-(4-AcOPhO)-3,5-$I_2C_6H_2$	Ph	$CHCl_3$	29/only (*Z*)	282
46	(*Z*)	4-(4-MeOPhO)-3,5-$I_2C_6H_2$	Ph	$CHCl_3$	32/only (*Z*)	282
47	(*E*/*Z*)	3-MeO-4-$AcOC_6H_3$	Ph	dioxane	35/n.r.[b]	274, 275
48	(*E*/*Z*)	3,4-$(AcO)_2C_6H_3$	Ph	$CHCl_3$	50/n.r.[b]	274, 275
49	(*E*/*Z*)	3,4-$(AcO)_2C_6H_3$	Me−C═CHPh	$CHCl_3$	45/n.r.[b]	276
50	(*E*/*Z*)	4-$NO_2C_6H_4$	Ph	dioxane	40/n.r.[b]	274, 275
51	(*Z*)	Me	Ph	Et_2O or C_6H_6	60/1:1	278
52	(*E*)	Me	Ph	C_6H_6	25/only (*E*)	281
53	(*Z*)	Me	Ph	C_6H_6	25/only (*Z*)	281
54	(*E*)	Cl	Ph	CH_2Cl_2	75/11:1	284
55	(*E*)	Br	Ph	Et_2O	21/4:17[d]	285
56	(*E*)	Cl	Ph	n.r.[b]	73/53:20	286
57	(*E*)	Br	Ph	n.r.[b]	17.5/1:6	286
58	(*Z*)	I	Ph	n.r.[b]	0/−[e]	286
58	(*Z*)	OAc	Ph	n.r.[b]	76/21:17	286
60	(*Z*)	OPiv	Ph	n.r.[b]	73/30:43	286
61	(*Z*)	SMe	Ph	CH_2Cl_2	70/1:3	287
62	(*Z*)	SPh	Ph	CH_2Cl_2	73/1:3	287
63	(*Z*)	SBn	Ph	CH_2Cl_2	54/1:5	287
64	(*Z*)	$SCPh_3$	Ph	CH_2Cl_2	67/1:3	287

[a] The acid functionality was transformed into the corresponding methyl ester during the reaction. [b] n.r. = not reported. [c] The oxazolinone ring underwent opening during the reaction. [d] Additionally, the rearrangement product 2-bromomethyl-1-aminocyclopropanecarboxylic acid was formed (51%, *E*/*Z* 1:1). [e] Only the rearrangement product 2-iodomethyl-1-aminocyclopropanecarboxylic acid was formed (76%, *E*/*Z* 1.2:1).

Table 2. Spirocyclopropanated Thiazolinones 159 Obtained by 1,3-Dipolar Cycloaddition of Diazomethane to 2-Aminoacrylic Acid Derivatives 157 (See Scheme 14)

entry	config **157**	R^1	R^2	solvent	yield (%)/ *E*/*Z*-ratio	ref
1	(*Z*)	Ph	SBn	C_6H_6	45/only (*Z*)	288
2	(*Z*)	4-MeC_6H_4	SBn	C_6H_6	45/only (*Z*)	288
3	(*Z*)	3-$MeOC_6H_4$	SBn	C_6H_6	45/only (*Z*)	288
4	(*Z*)	4-$MeOC_6H_4$	SBn	C_6H_6	45/only (*Z*)	288
5	(*Z*)	3-Cl	SBn	C_6H_6	30/only (*Z*)	288
6	(*Z*)	4-Cl	SBn	C_6H_6	35/only (*Z*)	288
7	(*Z*)	Ph	OBn	C_6H_6	30/only (*Z*)	288
8	(*Z*)	4-$MeOC_6H_4$	OBn	C_6H_6	25/only (*Z*)	288
9	(*Z*)	4-Cl	OBn	C_6H_6	40/only (*Z*)	288
10	(*Z*)	4-$AcOC_6H_4$	Ph	C_6H_6	54/only (*Z*)	289

Scheme 15. 1,3-Dipolar Cycloaddition of Diazomethane to 2-Aminoacrylic Acid Derivatives 161 Separately Protected on the Amino and Carboxyl Function (for Further Details See Table 3)



zolinones **157** furnished spirocyclopropanated thiazolinone compounds (*E*)- and (*Z*)-**159**. In contrast to the corresponding cyclopropanations of oxazolinones, thiazolinones are generally converted without loss of the stereochemical information; however, so far, only (*Z*)-configured alkylidenethiazolinones have been synthesized and cyclopropanated (Table 2).[288,289]

In almost all cases, the obtained spirocyclopropanated oxazolinones or thiazolinones, respectively, were further functionalized or transformed in generally high yields into the corresponding (*Z*)-isomer **160** of the free amino acid. Protected, racemic 2,3-methanophenylalanine (entry 14) has been resolved by fractional crystallization of its brucine salt, giving rise to (−)-(2*S*)- and (+)-(2*R*)-2,3-methanophenylalanine.[290]

In addition to the described cyclopropanation sequences of oxazolinone-protected 3-monosubstituted 2-aminoacrylic acids, one example of an analogous reaction using a corresponding 3,3-disubstituted derivative is known. Thus, the 4-isopropylidene-substituted oxazolinone was converted with diazomethane to yield the protected 1-amino-2,2-dimethylcyclopropanecarboxylic acid.[291]

When the amino and the acid function of the 2-aminoacrylic acid derivative are protected separately and not in a heterocyclic form as in **161**, the corresponding initially formed pyrazoline **162** in most cases can be isolated. To achieve ring contraction, the pyrazoline **162** has to be subjected to irradiation or thermolysis. The 1,3-dipolar cycloaddition as well as the ring contraction proceeds with retention of the stereochemical information and affords in moderate to almost quantitative yields the desired diastereomeric 2,3-methanoamino acid derivatives **163** (Scheme 15, Table 3).[89,91,249,266,267,292−299]

Besides simple deprotection of almost any of the protected derivatives **163** to the corresponding (*E*)- or (*Z*)-configured amino acids **160**, the dimethyl (*Z*)-2,3-methanoglutamic acid derivative thus obtained (entries 6 and 7) has been used for further transformations. Thus, the ω-carboxyl was Hofmann degraded to an amino group. Subsequent coupling with (*R*)-(+)-1-phenylethylamine gave two diastereomers which were separated, and then both guanidinylated and deprotected, affording enantiopure naturally occurring (1*S*,2*S*)-carnosadine and its enantiomer, (1*R*,2*R*)-carnosadine **140**.[249] Additionally, (*Z*)-2,3-methanoglutamic acid was submitted to hydrogenolysis, upon which an intramolecular cyclization to 2,3-methanopyroglutamic acid took place.[293] This racemic mixture was coupled with either L- or D-leucinamide, and the obtained diastereomers were separated by crystallization. Final hydrolysis afforded enantiopure (−)-(2*S*,3*S*)- or (+)-(2*R*,3*R*)-2,3-methanopyroglutamic acid, respectively.[300]

Table 3. Protected 2,3-Methanoamino Acids (*E*)- and (*Z*)-163 Obtained by 1,3-Dipolar Cycloaddition of Diazomethane to 2-Aminoacrylic Acid Derivatives 161 and Subsequent Ring Contraction of the Pyrazolines 162 (See Scheme 15)

entry	config **161**	R^1	NR_2^4	R^3	solvent/yield (%) **162**	cond/yield (%)/*E*/*Z*-ratio **163**	ref
1	(*E*/*Z*)	Me	NHCOPh	Me	not isol.	dioxane/80/n.r.[a]	89
2	(*Z*)	Me	N_3	Et	Et_2O/90	Δ, CCl_4/57/1:4	91
3	(*Z*)	Me	N=CPh_2	Me	CH_2Cl_2/52	Δ, CCl_4/100/3:7 or *hν*/100/6:4	301
4	(*E*)	Me	N=CPh_2	Me	CH_2Cl_2/86	Δ, CCl_4/100/3:1 or *hν*/100/only (*E*)	301
5	(*Z*)	Ph	N_3	Et	Et_2O/48	Δ, CCl_4/22/n.r.[a]	91
6	(*Z*)	Ph	N=CPh_2	Me	CH_2Cl_2/30	Δ, CCl_4/100/n.r.[a] or *hν*/100/only (*Z*)	301
7	(*E*)	Ph	N=CPh_2	Me	CH_2Cl_2/45	Δ, CCl_4/100/n.r.[a] or *hν*/100/only (*E*)	301
8	(*Z*)	Et	N_3	Me	Et_2O/n.r.[a]	Δ, CCl_4/61/>90%	91
9	(*Z*)	Et	NHCOPh	Me	CH_2Cl_2/n.r.[a]	*hν*, C_6H_6/41/only (*Z*)	292
10	(*Z*)	CH_2CO_2H[b]	NHZ	H	MeOH/100	Δ, toluene/71/only (*Z*) or *hν*, toluene/78/only (*Z*)	249
11	(*Z*)	CH_2CO_2H[b]	NHZ	H	CH_2Cl_2/n.r.[a]	*hν*, CH_2Cl_2/98/only (*Z*)	267, 293, 294
12	(*Z*)	CH_2CO_2Et	NHCOPh	Et	$CHCl_3$/n.r.[a]	*hν*, Et_2O, C_6H_6/78/only (*Z*)	295
13	(*E*)	Ph	NHCOPh	Me	$CHCl_3$/100	Δ, $HO(CH_2)_2OH$/82/only (*E*)	296, 297
14	(*E*)	Ph	NHCOPh	Me	not isol.	Δ, glycerol/96/only (*E*)	298
15	(*E*)	4-MeOPh	NHCOPh	Me	$CHCl_3$/n.r.[a]	Δ, glycerol/90/only (*E*)	298
16	(*E*)	4-MePh	NHCOPh	Me	$CHCl_3$/n.r.[a]	Δ, glycerol/90/only (*E*)	298
17	(*E*)	4-ClPh	NHCOPh	Me	$CHCl_3$/n.r.[a]	Δ, glycerol/95/only (*E*)	298
18	(*E*)	2-thienyl	NHCOPh	Me	$CHCl_3$/n.r.[a]	Δ, glycerol/90/only (*E*)	298
19	(*E*)	3-thienyl	NHCOPh	Me	$CHCl_3$/n.r.[a]	Δ, glycerol/92/only (*E*)	298
20	(*Z*)	$-CH_2CH_2NHZ$		*t*Bu	CH_2Cl_2/n.r.[a]	*hν*, CH_2Cl_2/65/only (*Z*)	259
21	(*Z*)	$CH_2PO(OEt)_2$	NHZ	Me	Et_2O/67	*hν*, $CHCl_3$/74/only (*Z*)	299
22	(*E*)	$CH_2PO(OEt)_2$	NHZ	Me	Et_2O/88	*hν*, $CHCl_3$/54/only (*E*)	299

[a] n.r. = not reported. [b] The acid functionality of the side chain was transformed to the methyl ester under the reaction conditions.

Table 4. Protected 1-Aminocyclopropanecarboxylic Acids 154 Obtained by 1,3-Dipolar Cycloaddition of Substituted Diazomethanes to 2-Aminoacrylic Acid Derivatives 152 and Subsequent Ring Contraction of the Pyrazolines 153 (See Scheme 13)

entry	**152**	R^1	R^2	R^3	NR_2^4	R^5	R^6	solvent/yield (%) **154**	cond/yield (%)/ rel config **154**	ref
1	(*E*/*Z*)	Ph	H	N=C(Ph)−		Me	H	not isol.	dioxane/n.r./n.r.[a]	273
2	(*Z*)	H	Ph	N=C(Ph)−		Ph	Ph	not isol.	C_6H_6/70/n.r.[a]	303, 304
3	(*Z*)	H	Ph	N=C(Me)−		Ph	Ph	not isol.	C_6H_6/n.r./n.r.[a]	303, 304
4	(*E*)	Ph	Me	N=C(Ph)−		Ph	Ph	not isol.	C_6H_6/n.r./n.r.[a]	303, 304
5	n.r.[a]	4-ClC_6H_4	H	N=C(Ph)−		Ph	Ph	not isol.	n.r.[a]	304
6	n.r.[a]	4-$MeOC_6H_4$	H	N=C(Ph)−		Ph	Ph	not isol.	n.r.[a]	304
7	(*E*/*Z*)	−$(CH_2)_4$−		N=C(Ph)−		Ph	Ph	not isol.	C_6H_6/n.r./n.r.[a]	303
8	(*E*/*Z*)	−$(CH_2)_5$−		N=C(Ph)−		Ph	Ph	not isol.	C_6H_6/n.r./n.r.[a]	303
9	(*E*/*Z*)	4-(1,3-diphenyl-pyrazolyl)	H	N=C(Ph)−		Ph	Ph	not isol.	xylene/80/n.r.[a]	89
10	(*Z*)	H	Ph	N=C(Ph)−		Ph	H	not isol.	toluene/87/only (2*Z*,3*E*)	305
11	(*Z*)	H	4-$MeOC_6H_4$	N=C(Ph)−		Ph	H	not isol.	toluene/91/only (2*Z*,3*E*)	305
12	(*Z*)	H	4-ClC_6H_4	N=C(Ph)−		Ph	H	not isol.	toluene/85/only (2*Z*,3*E*)	305
13	(*Z*)	H	4-$O_2NC_6H_4$	N=C(Ph)−		Ph	H	not isol.	toluene/89/only (2*Z*,3*E*)	305
14	(*Z*)	H	2-furyl	N=C(Ph)−		Ph	H	not. isol.	toluene/78/only (2*Z*,3*E*)	305
15		H	H	4-$O_2NC_6H_4$	NHBoc	Me	H	Et_2O/96	Δ, toluene/94/only (*E*)	90
16		H	H	4-$O_2NC_6H_4$	NHBoc	Et	H	Et_2O/59	Δ, toluene/77/only (*E*)	90
17		H	H	4-$O_2NC_6H_4$	NHBoc	iPr	H	Et_2O/98	Δ, toluene/95/only (*E*)	90
18		H	H	4-$O_2NC_6H_4$	NHBoc	Ph	H	Et_2O/92	Δ, toluene/n.r./only (*E*)	90
19		H	H	4-$O_2NC_6H_4$	NHBoc	Me	Me	Et_2O/63	Δ, toluene/88/−	306
20		H	H	4-$O_2NC_6H_4$	NHBoc	Me	Me	CH_2Cl_2/74.5	Δ, C_6H_6/91/mixture	306
21		H	H	4-$O_2NC_6H_4$	NHBoc	EtO_2C	H	not isol.	toluene/35/69:31	307
22		H	H	4-$O_2NC_6H_4$	NHBoc	H_2C=CH−	H	not isol.	toluene/38/71:29	307
23		H	H	4-$O_2NC_6H_4$	NHBoc	Ph_2C=CH−[b]	H	not isol.	toluene/88/67:33	307
24		H	H	4-$O_2NC_6H_4$	NHZ	iPr	H	CH_2Cl_2/74.5	*hν*, toluene/42.7/only (*E*)	306
25		H	H	Me	$NBoc_2$	Ph_2C=CH−[b]	H	not isol.	toluene, 100/72:28	307
26		H	H	4-$O_2NC_6H_4$	$NBoc_2$	Ph_2C=CH−[b]	H	not isol.	toluene/42/55:45	307
27		H	H	Me	NC=Ph_2	Me	H	EtOAc/∼100	EtOAc/∼100/1:1	92
28		H	H	Me	NC=$(SMe)_2$	Me	H	EtOAc/∼100	EtOAc/∼100/1:3	92
29		H	H	Me	NC=Ph_2	Ph	H	not isol.	toluene/96/1:1.2	92
30		H	H	Me	NC=$(SMe)_2$	Ph	H	not isol.	toluene/∼100/1.1:1	92
31		H	H	Me	NC=Ph_2	iPr	H	not isol.	CH_2Cl_2/82/1:1	301
32		H	H	Me	NHAc	MeO_2C	H	not isol.	$CHCl_3$/70/n.r.[a]	93, 308
33		H	H	Me	NHAc	MeO_2C	H	not isol.	CH_2Cl_2/10−30/1:2−3.3	309−311
34		H	H	Me	NHAc	EtO_2C	H	not isol.	$CHCl_3$/70/n.r.[a]	93
35		H	H	Me	NHAc	EtO_2C	H	not isol.	CH_2Cl_2/10−68/1:2−3.3	308−310, 312
36		H	H	Et	NHAc	EtO_2C	H	not isol.	n.r.[a]/12.5/only (*Z*)	313
37	(*E*/*Z*)	Ph	H	Me	NHAc	MeO_2C	H	n.r.[a]/40	Δ, DMF/40/only *trans*[c]	311, 314

[a] n.r. = not reported. [b] Prepared in situ from *p*-toluenesulfonyl-(3,3-diphenyl-2-propenal)hydrazone sodium salt. [c] The authors did not define the notation "*trans*".

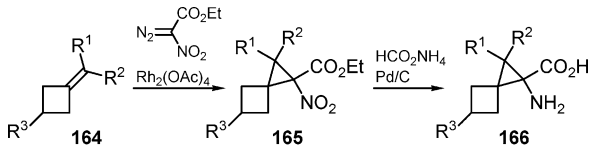
In addition to the 1,3-dipolar cycloadditions of diazomethane described above, diazomethane has also been used for the cyclopropanation of oxazolidinone-protected 1,4-dihydroquinoline-2-carboxylic acid, giving rise to methyl tetrahydro[1a*H*]cyclopropa[*b*]quinoline-1a-carboxylate.[302]

Besides diazomethane itself, diverse substituted diazomethanes have been applied in 1,3-dipolar cycloadditions to 2-aminoacrylic acid derivatives in various protected forms. Utilizing these compounds, 1-substituted, 1,1- as well as 1,2-disubstituted, and also tri- as well as tetrasubstituted 1-aminocyclopropanecarboxylic acid derivatives have been prepared in moderate and up to quantitative yields (Table 4).[89,90,93,273,303−314] Almost all of the obtained compounds were deprotected to the free amino acids, and in addition, the 2,2-diphenylvinyl-substituted 1-aminocyclopropanecarboxylic acid derivatives (Table 4, entries 23, 25, and 26) served as the starting materials for the synthesis of (phosphonoamino)-carbonyl- and difluoro(phosphono)acetyl-substituted 1-aminocyclopropanecarboxylic acid.[307,315]

Oxazolinone-protected racemic 1-amino-2,3-diphenylcyclopropanecarboxylic acid (entry 10) was resolved by HPLC on a chiral column after conversion into the corresponding *N*-Boc-protected methyl carboxylate to yield (2*R*,3*R*)- and (2*S*,3*S*)-1-amino-2,3-diphenylcyclopropanecarboxylic acid.[316]

A straightforward approach to 2,3-methanoamino acid esters has been developed employing a rhodium-catalyzed cyclopropanation of alkenes with the readily available alkyl nitrodiazoacetates. The thus obtained 1-nitrocyclopropanecarboxylates can be considered as protected amino acid equivalents, from which the amino acids can be liberated by selective reduction of the nitro group and subsequent hydrolysis.

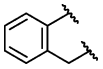
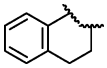
Scheme 16. Synthesis of Oligocyclic 1-Aminocyclopropanecarboxylic Acids by Rhodium-catalyzed Cyclopropanation with Ethyl Nitrodiazoacetate of Alkylidenecyclobutanes and Subsequent Reduction of the Nitro Group[317]



R^1	R^2	R^3	%	%
H	H	H	89	56
−$(CH_2)_3$−		H	59	62
H	H	CO_2Me	78	53

For example, three different methylenecyclobutanes **164** were treated with ethyl nitrodiazoacetate in the presence of catalytic amounts of dirhodium tetraacetate to furnish ethyl 1-nitrospiro[2.3]hexanecarboxylates **165** in good yields

Table 5. 1-Aminocyclopropanecarboxylates 169 Obtained by Rhodium-catalyzed Cyclopropanation of Alkenes with Alkyl Nitrodiazoacetates and Subsequent Reduction of the Nitro Group (See Scheme 17)[318]

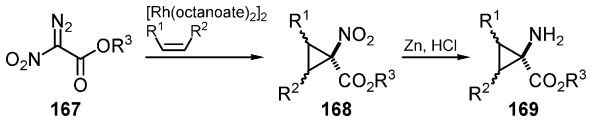
entry	R^1	R^2	R^3	yield (%) **168**	ratio (*E*/*Z*) or (*exo*/*endo*)	yield (%) **169**
1	Ph	H	Et	90	93:7	49−77
2	1-naphthyl	H	Me	86	95:5	76
3	3-*t*BuPh$_2$SiOC$_6$H$_4$	H	Me	92	92:8	74
4	4-ClC$_6$H$_4$	H	Me	87	91:9	76
5	PhCH$_2$CH$_2$	H	Me	70	53:47	93
6	−(CH$_2$)$_3$−		Bn	81	87:13	88
7	−(CH$_2$)$_4$−		Me	55	88:12	74
8	−(CH$_2$)$_5$−		Bn	39	86:14	87
9	−(CH$_2$)$_6$−		Bn	66	80:20	>99
10	−(CH$_2$)$_7$−		Bn	71	74:26	94
11			Et	79	97:3	79
12			Me	84	97:3	86

(59−89%). Reduction of the nitro group by catalytic hydrogenation with ammonium formate in the presence of palladium on carbon and subsequent hydrolysis smoothly gave the corresponding free amino acids **166**, the isolation of which, however, turned out to be rather difficult, and thus provided only moderate yields of **166** (Scheme 16).[317]

In an essentially analogous transformation, various 1-substituted and cyclic 1,2-disubstituted alkenes were converted with alkyl nitrodiazoacetates **167** in the presence of a dirhodium tetracarboxylate catalyst, affording 1-nitrocyclopropanecarboxylates **168** in moderate to high yields with moderate to excellent diastereoselectivities. Reduction of the nitro function with zinc in the presence of hydrochloric acid turned out to be a suitable way to obtain 1-aminocyclopropanecarboxylates **169** in high yields (Scheme 17, Table 5).[318]

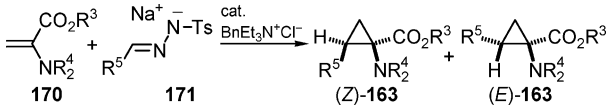
Even more variously substituted alkyl 1-nitrocyclopropanecarboxylates have been prepared by rhodium-catalyzed cyclopropanation of the correspondingly substituted alkenes with alkyl nitrodiazoacetates, yet their reduction to the corresponding substituted 1-aminocyclopropanecarboxylates has not explicitly been reported.[319,320]

Scheme 17. Rhodium-catalyzed Cyclopropanation of Alkenes with Alkyl Nitrodiazoacetates and Subsequent Transformation of the 1-Nitro- to the 1-Aminocyclopropanecarboxylates[318]



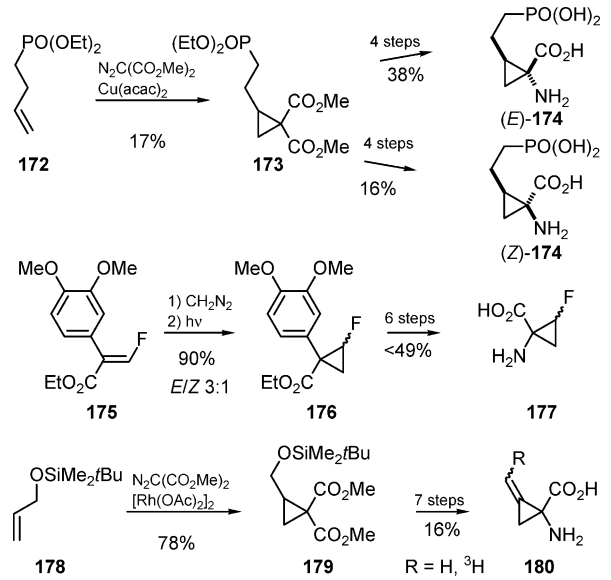
Diastereomerically enriched protected 2,3-methanoamino acids were synthesized by 1,3-dipolar cycloaddition of substituted diazomethanes in situ generated from tosylhydrazone sodium salts **171**, to dehydroamino acids **170** (Scheme 18). In the presence of the phase transfer catalyst benzyltriethylammonium chloride, the reaction predominantly produced the (*E*)-isomers **163** of the 1-aminocyclopropanecarboxylates. In contrast, in the presence of a transition metal catalyst such as dirhodium tetraacetate or *meso*-tetraphenylporphyriniron(III) chloride (ClFeTPP), the (*Z*)-isomers **163** were formed predominantly (Table 6, only results of optimized reactions are shown).[321]

Scheme 18. Cyclopropanations of 2,3-Dehydroamino Acid Derivatives with Substituted Diazomethanes, Generated in Situ from Tosylhydrazone Salts[321]



Instead of cyclopropanating 2-aminoacrylic acid derivatives with diazomethane or substituted analogues, non-aminosubstituted alkenes have been cyclopropanated with dialkyl diazomalonates, and subsequently one of the two acid moieties in the resulting cyclopropane-1,1-dicarboxylates after partial hydrolysis has been degraded to lead to the corresponding 1-aminocyclopropanecarboxylic acids. According to this method, diethyl 3-butenylphosphonate (**172**) was transformed into the cyclopropanedicarboxylate **173**. Subsequently, either **173** was monohydrolyzed, the obtained half ester was directly degraded, and the product was deprotected to the (*E*)-1-amino-2-[2-(diethoxyphosphonyl)-ethyl]cyclopropanecarboxylic acid [(*E*)-**174**] or **173** was first transformed into the corresponding methyl (hydrazinocarbonyl)cyclopropanecarboxylate and the latter was then degraded via the azide to produce (*Z*)-**174** (Scheme 19).[322]

Scheme 19. 1,3-Dipolar Cycloadditions of Diazomethane Derivatives to Non-aminosubstituted Dipolarophiles and Subsequent Transformations to 1-Aminocyclopropanecarboxylic Acids[256,322,323]



1,3-Dipolar cycloaddition of diazomethane to the 2-aryl-3-fluoroacrylate **175** gave the corresponding pyrazoline, which upon photolysis furnished the 1-aryl-2-fluorocyclopropanecarboxylate **176** as a mixture of diastereomers. Curtius degradation, oxidative fragmentation of the dimethoxyphenyl moiety, and final deprotection gave **177**, the first fluoro-substituted 2,3-methanoamino acid reported so far (Scheme 19).[323]

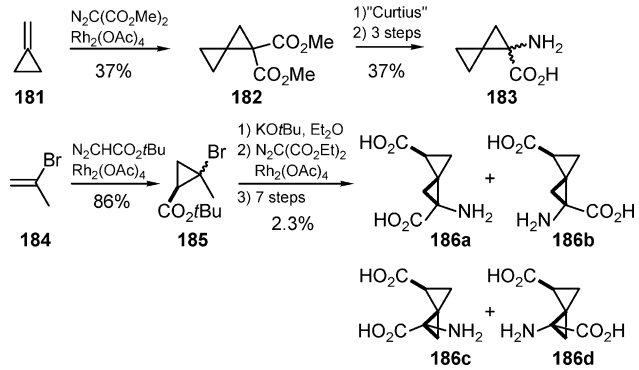
Cyclopropanation under dirhodium tetraacetate catalysis of the silyl-protected allyl alcohol **178** with dimethyl diazomalonate furnished the 2-(silyloxymethyl)cyclopropane-1,1-dicarboxylate **179**, which was converted either into unlabeled 1-amino-2-methylenecyclopropanecarboxylic acid (**180**) or into the tritium-labeled analogue [^{3}H]-**180** (Scheme 19).[256]

Table 6. 1-Aminocyclopropanecarboxylates 163 Obtained by Cyclopropanations of 1,2-Dehydroamino Acid Derivatives with Substituted Diazomethanes Generated in Situ from Tosylhydrazone Salts (See Scheme 18)

entry	R^3	R^4, R^4	R^5	yield (%) **163**	ratio (*E*/*Z*)	cat. (1 mol %)
1	Me	H, Boc	Ph	68	94:6	
2	Me	H, Boc	Ph	79	36:64	ClFeTPP
3	Me	H, Boc	Ph	12	49:51	$Rh_2(OAc)_4$
4	PNB	H, Boc	Ph	80	95:5	
5	PNB	H, Boc	Ph	73	43:57	ClFeTPP
6	Me	H, Ac	Ph	48	85:15	
7	Me	H, Ac	Ph	84	19:81	ClFeTPP
8	PNB	H, Boc	4-$MeOC_6H_4$	72	95:5	
9	PNB	H, Boc	4-$MeOC_6H_4$	52	12:88	ClFeTPP
10	PNB	H, Boc	4-MeC_6H_4	52	89:11	
11	PNB	H, Boc	4-MeC_6H_4	49	14:86	ClFeTPP
12	PNB	H, Boc	4-FC_6H_4	62	87:13	
13	PNB	H, Boc	4-FC_6H_4	82	15:85	ClFeTPP
14	PNB	H, Boc	4-*t*$BuMe_2SiOC_6H_4$	47	96:4	
15	PNB	H, Boc	4- *t*$BuMe_2SiOC_6H_4$	44	16:84	ClFeTPP
16	PNB	H, Boc	$Ph_2C{=}CH-$	76	66:34	
17	PNB	H, Boc	$Ph_2C{=}CH-$	82	8:92	ClFeTPP
18	PNB	H, Boc	$H_2C{=}CH-$	36	72:28	

A simple access to racemic 1-aminospiropentanecarboxylic acid (**183**) was developed by rhodium-catalyzed cyclopropanation of methylenecyclopropane (**181**) with dimethyl diazomalonate to yield dimethyl spiropentane-1,1-dicarboxylate (**182**). Subsequent monohydrolysis, Curtius degradation of the half ester, and final hydrolysis gave 1-aminospiropentanecarboxylic acid (**183**) (Scheme 20).[324]

Scheme 20. Some More 1,3-Dipolar Cycloadditions of Diazomethane Derivatives to Non-aminosubstituted Dipolarophiles and Subsequent Transformations to 1-Aminocyclopropanecarboxylic Acids[324,325]

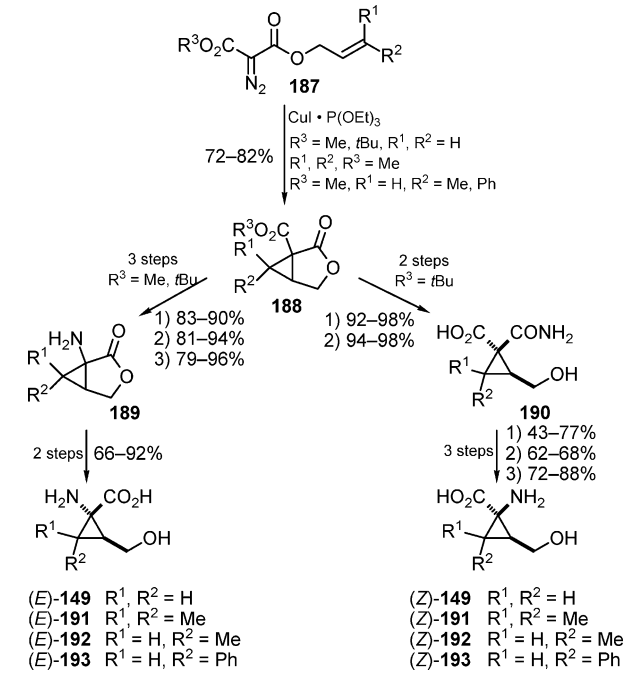


Two of the four diastereomers of 1-aminospiropentane-1,4-dicarboxylic acid (**186**) have been prepared diastereoselectively starting from 2-bromopropene (**184**). Both three-membered rings were built up by dirhodium tetraacetate-catalyzed cyclopropanations of double bonds with *tert*-butyl diazoacetate and diethyl diazomalonate, respectively (Scheme 20).[325] The typical sequence of transformations of the thus obtained tri-*tert*-butyl spiropentane-1,1,4-tricarboxylate then led to the two diastereomers **186a** and **186b**. The other two, i.e., **186c** and **186d**, were prepared along a similar route starting from (2-methylenecyclopropyl)methanol (sequence not shown).[325]

A copper(I)-catalyzed intramolecular cyclopropanation of the allyl group in allyl alkyl diazomalonates **187**, accessible by base-catalyzed diazo group transfer from tosyl azide to alkyl allyl malonates, provided the bicyclic cyclopropane derivatives **188**. Cleavage of the *tert*-butyl ester moiety in **188**-*t*Bu, Curtius degradation of the monoacid, and liberation of the amino group led to substituted 2,3-methanohomoserine lactones **189**.[326,327] Hydrolysis of the lactones **189** furnished (*E*)-2,3-methanohomoserine [(*E*)-**149**], (*E*)-1-amino-3-(hydroxymethyl)-2,2-dimethylcyclopropanecarboxylic acid [(*E*)-**191**], (*E*)-1-amino-2-(hydroxymethyl)-3-methylcyclopropanecarboxylic acid [(*E*)-**192**], and (*E*)-1-amino-2-(hydroxymethyl)-3-phenylcyclopropanecarboxylic acid [(*E*)-**193**]. Upon treatment of the lactones **188** with ammonia, the 2-(hydroxymethyl)cyclopropanecarboxamides **190** were obtained. Hofmann degradation of these and final hydrolysis afforded the (*Z*)-isomers (*Z*)-**149** and (*Z*)-**191**−(*Z*)-**193** (Scheme 21).[327]

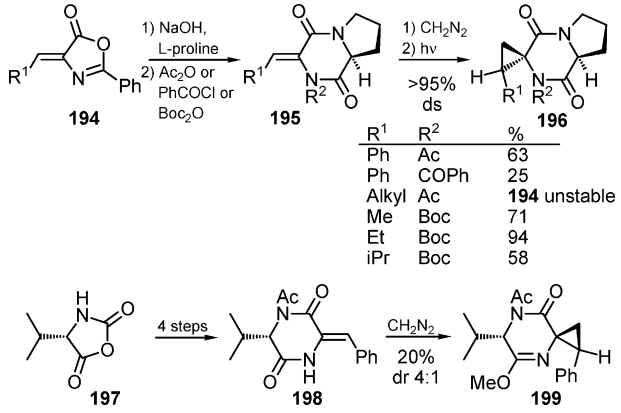
Several enantioselective variants of cyclopropanations with diazomethane and derivatives thereof to yield suitable 1-aminocyclopropanecarboxylic acid precursors are known. In these, the stereochemical information is introduced either by use of a chiral starting material, by the help of a chiral auxiliary, or by use of a chiral catalyst in the cyclopropanation step.

Scheme 21. Intramolecular Cyclopropanation of Allyl Diazomalonates and Subsequent Transformations to 2-(Hydroxymethyl)-1-aminocyclopropanecarboxylic Acids[326,327]



As chiral auxiliaries, diketopiperazines have proved to be of value. Thus, the (*Z*)-configured alkylidenediketopiperazine **195** obtained by treatment of the corresponding alkylideneoxazolones **194** with l-proline reacted with diazomethane to yield the corresponding pyrazolines virtually as single diastereomers (ds > 95%). Photolysis of the latter produced the spirocyclopropanated diketopiperazines **196**, which could easily be hydrolyzed to the corresponding free 1-aminocyclopropanecarboxylic acids. Not only could the enantiopure 2-phenyl-1-aminocyclopropanecarboxylic acid derivative **196** (R^1 = Ph) be prepared by this methodology,[328,329] but also the 2-alkyl-substituted analogues **196** (R^1 = Alk).[329,330] An analogous transformation of the diketopiperazine **198** prepared from the oxazolidinedione **197** furnished the spirocyclopropanated heterocycle **199**, albeit in low yield and with moderate diastereoselectivity only (Scheme 22).[331,332]

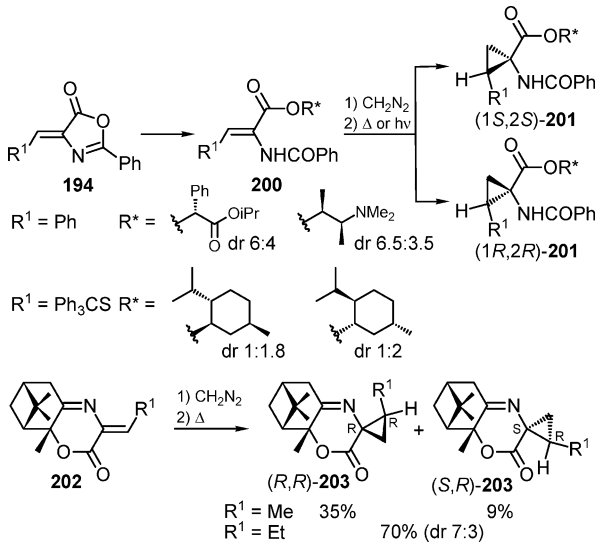
Scheme 22. Enantioselective Syntheses of 2-Substituted 1-Aminocyclopropanecarboxylic Acids by Cyclopropanation with Diazomethane of Starting Materials Containing Chiral Auxiliaries[329−332]



Racemate cleavage of the oxazolone **194** with (*R*)-isopropyl mandelate, (−)-*N*-methylephedrine, or (+)- or (−)-menthol, respectively, gave the enantiomerically pure chiral (*N*-acylamino)acrylates **200**, which reacted with diazomethane to give easily separable mixtures of the corresponding diastereomeric pyrazolines. Ring contraction of the latter either by heating or by irradiation furnished the two diasteromers (1*S*,2*S*)- and (1*R*,2*R*)-**201**, from which the chiral auxiliary could easily be removed to give *N*-protected 2-phenyl-[328,329] and 2-tritylsulfanyl-substituted[333] 1-aminocyclopropanecarboxylic acids, respectively (Scheme 23). Upon treatment of the dehydroamino acid derivative **202**, endowed with a pinane moiety, with diazomethane and subsequent heating, the diastereomeric spirocyclopropanated heterocycles (*R*,*R*)- and (*S*,*R*)-**203** were obtained. The methyl-substituted diastereomers **203** (R^1 = Me) were separable; the ethyl-substituted derivatives **203** (R^1 = Et) were not. Hydrolysis furnished the corresponding free amino acids, albeit only in low yields (Scheme 23).[334]

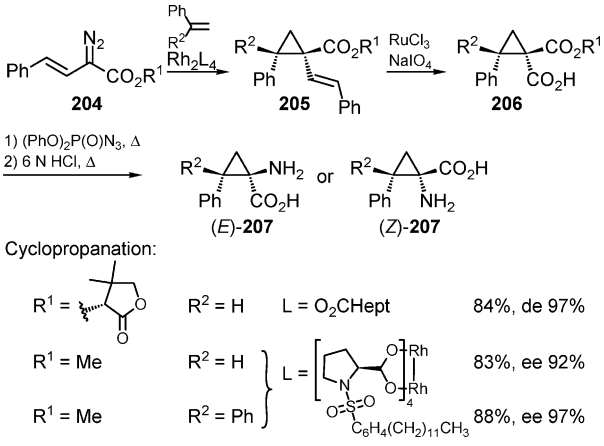
The chiral auxiliary can also be introduced into the diazomethane derivative. Thus, the metalcarbene generated from the diazoester **204** derived from the chiral 2-hydroxypantholactone [R^1 = 5-(4,4-dimethyldihydrofuranon-2-yl)], in the presence of dirhodium tetraoctanoate, was added to styrene as well as to 1,1-diphenylethylene, to yield the corresponding 1-alkenylcyclopropanecarboxylates **205**. With the proper choice of the rhodium catalyst, high chemical yields and diastereoselectivities of up to 97% have been achieved (Scheme 24).[335] It is more economical, though, to

Scheme 23. Some More Enantioselective Syntheses of 2-Substituted 1-Aminocyclopropanecarboxylic Acids by Cyclopropanation with Diazomethane of Starting Materials Containing Chiral Auxiliaries[328,329,333,334]



bring the chirality in with the rhodium catalyst. Screening of a variety of chiral ligands for the cyclopropanation reaction of styrene as well as 1,1-diphenylethylene with **204** (R^1 = Me) proved a [(dodecylphenyl)sulfonyl]proline derivative to be the most effective ligand with respect to the yields as well as diastereomeric excesses obtainable.[336,337] Oxidative cleavage of the styryl group in the cyclopropane derivative **205** gave cyclopropane-1,1-dicarboxylic acid monoesters **206**. Subsequent Curtius degradation and deprotection furnished the (*Z*)-configured 1-aminocylopropanecarboxylic acids (*Z*)-**207**, whereas esterification and subsequent selective monohydrolysis, Curtius degradation, and hydrolysis again gave rise to (*E*)-**207**.[335−337]

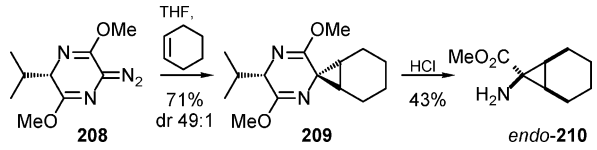
Scheme 24. Enantioselective Syntheses of 2-Substituted 1-Aminocyclopropanecarboxylic Acids by Cyclopropanation Using a Chiral Diazomethane Derivative or a Chiral Rhodium Catalyst.[335−337] The (*E*)- and (*Z*)-Configuration Refer to Orientation of the Phenyl Relative to the Amino Substituent.



The bislactim ether derived from the diketopiperazines formed from one unit of valine and one unit of glycine was converted with tosyl azide to the diazo derivative **208**, which served as a carbene transfer reagent. When **208** was generated in tetrahydrofuran, and the solution was then transferred into excess cyclohexene kept at ambient temperature, the spiroan-

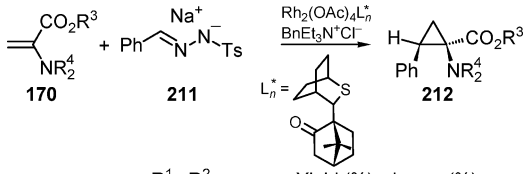
nelated bicyclo[4.1.0]heptane derivative **209** was formed. The latter, upon hydrolysis, produced diastereomerically pure methyl *endo*-7-aminobicyclo[4.1.0]heptane-7-carboxylate (**210**) (Scheme 25).[338]

Scheme 25. Diastereoselective Synthesis of Methyl 7-Aminobicyclo[4.1.0]heptane-7-carboxylate by Cyclopropanation with a Bislactim Ether-derived Chiral Diazomethane Derivative[338]



Highly enantioenriched (2*S*,3*S*)-2,3-methanophenylalanine was synthesized by cyclopropanation of α-(acylamino)-acrylates **170** with phenyldiazomethane, in situ generated from the benzaldehyde tosylhydrazone sodium salt **211**, under catalysis of dirhodium tetraacetate, chirally modified with a 1-(2-thiabicyclo[2.2.2]oct-3-yl)-7,7-dimethylbicyclo-[2.2.1]heptane-2-one ligand, and subsequent deprotection of the resulting **212** (Scheme 26).[339]

Scheme 26. Enantioselective Synthesis of (2*S*,3*S*)-2,3-Methanophenylalanine by Cyclopropanation of α-(Acylamino)acrylates with Phenyldiazomethane in Situ Generated from the Benzaldehyde Tosylhydrazone Sodium Salt[339]



R^1	R^2_2	Yield (%)	dr	ee (%)
Et	succinimide	55%	7:1	91%
Me	Boc_2	72%	6:1	92%

An efficient and highly stereocontrolled approach to enantiopure 3-substituted 2,3-methanoamino acids starts with the condensation of D-glyceraldehyde (**213**) as the chiral building block with the amino(methoxycarbonyl)-substituted phosphonate **214** to produce the (*Z*)-configured α-(acylamino)acrylate derivatives **215**, even on a multigram scale.[340] 1,3-Dipolar cycloaddition of diazomethane to **215** gave the diastereomerically pure corresponding (*Z*)-pyrazolines,[341] which were photolyzed to provide diastereomerically pure 1-aminocyclopropanecarboxylic acid derivatives **216** in quantitative yield over both steps in the best case (Scheme 27).[342] Attempts to prepare the corresponding (*E*)-isomer were also undertaken; however, in the best case so far reported, the conditions of the condensation step could be changed in such a way that it gave a separable mixture of (*E*)- and (*Z*)-product in a ratio of 4:6 in favor of the (*Z*)-isomer.[342,343]

Hydrolysis of the acetonide **216** afforded a quantitative yield of the diol **217**, which, in a variety of subsequent transformations, could be converted to the enantiomerically pure 3-substituted 2,3-methanoamino acids (1*S*,2*R*)-**136**, (1*S*,2*R*)-**223**, (1*S*,2*R*)-**149**, (1*S*,2*R*)-**139**, and (1*S*,2*R*)-**230**. Thus, reductive elimination from **217**, by first forming the thiocarbonate with thiocarbonyldiimidazole (TCDI) and subsequently treating it with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (DMPDAP), furnished the 2-vinyl-substituted 1-aminocyclopropanecarboxylic acid derivative **218**,[340] which was hydrogenated and fully deprotected to give (−)-(1*S*,2*R*)-*allo*-coronamic acid **136** in 37% overall yield.[344] On the other hand, oxidative cleavage of the 1,2-dihydroxyethyl group in **217** using a catalytic amount of ruthenium tetroxide in the presence of sodium periodate led to the protected 2,3-methanoaspartic acid monoester **220**,[344] which could be converted to the acid chloride **221**. Arndt-Eistert chain elongation of the latter and subsequent deprotection furnished (2*S*,3*R*)-2,3-methanoglutamic acid (**223**) in 33% overall yield.[345] Alternatively, treatment of the diol **217** with sodium periodate provided the cyclopropanecarbaldehyde **224**, which was reduced to the hydroxymethyl derivative **225**. Final deprotection of **225** furnished (2*S*,3*R*)-2,3-methanohomoserine (**149**) in 54% overall yield.[344,346] Eventually, the protected hydroxymethyl derivative **225** could be converted to the mesylate **226**, which in turn was reduced and deprotected to provide (−)-(1*S*,2*R*)-*allo*-norcoronamic acid **139** in 55% overall yield.[343] The mesylate **226** also underwent Finkelstein reaction to the iodide **227**, which was transformed by a nucleophilic substitution to the methylthio derivative **229**. Final deprotection of **229** yielded (2*S*,3*R*)-2,3-methanomethionine (**230**) in 37% overall yield (Scheme 27).[343]

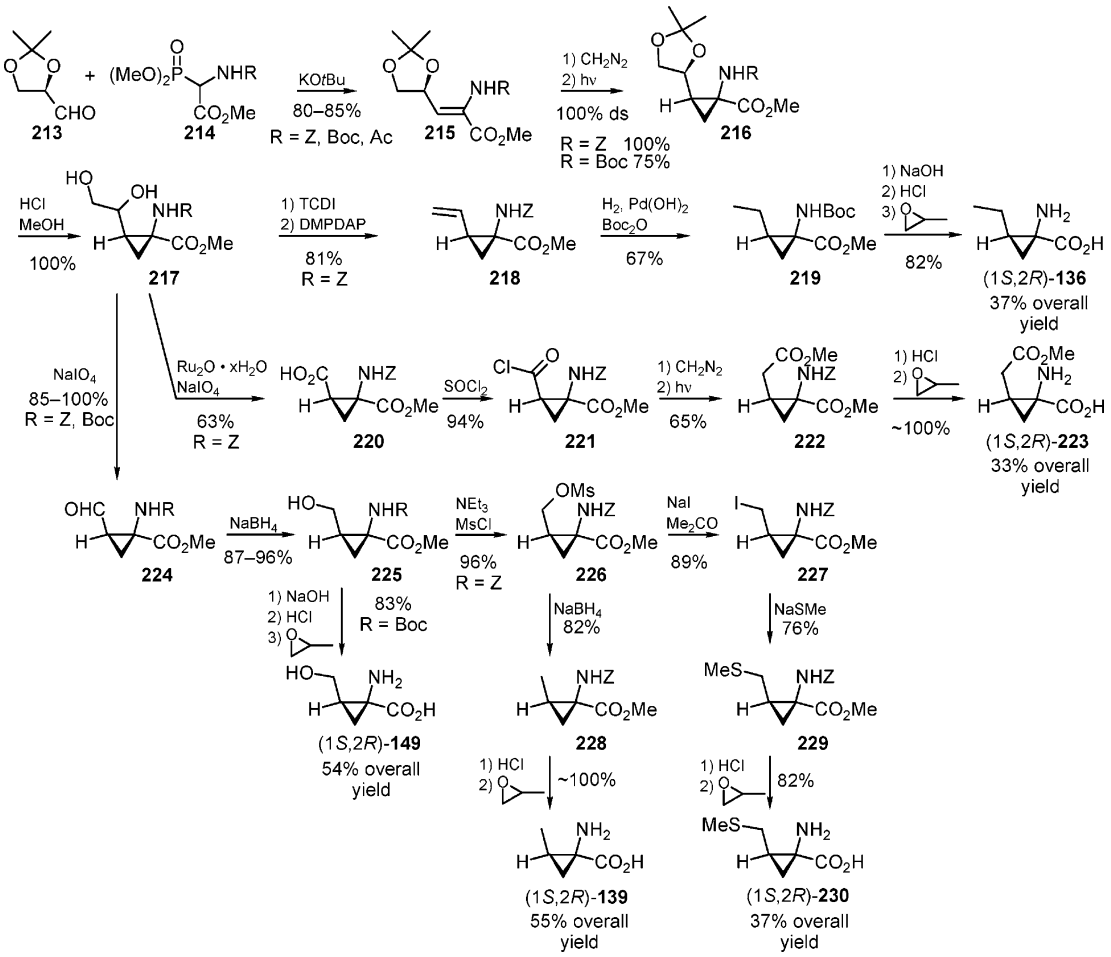
The protected (2*S*,3*R*)-2,3-methanohomoserine **231** and the (1*S*,2*R*)-2-formylcyclopropane-1-carboxylate **233** thus prepared have also been employed in further transformations. As a variety of cyclopropyl-group-containing nucleosides exhibit interesting biological properties, the nucleoside mimetic with a 1-aminocyclopropylmethanol moiety was synthesized in enantiomerically pure form using the protected (2*S*,3*R*)-2,3-methanohomoserine **231** as a suitable starting material (Scheme 28). The antiviral and antitumor activities of **232** were planned to be tested but have not been reported yet.[347]

C_{60}-Fullerenes endowed with a 1-aminocyclopropanecarboxylic acid functionality were prepared from the protected (1*S*,2*R*)-2-formyl-1-aminocyclopropanecarboxylate **233**, which was covalently attached to [60]fullerene by way of the [60]-fulleropyrrolidine **234** and -isoxazoline **235** (Scheme 28).[348]

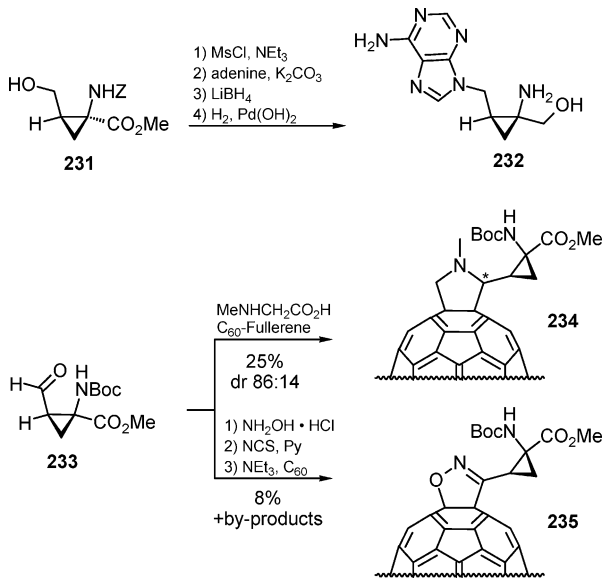
Another enantioselective approach to 3-substituted 2,3-methanoamino acids started with the 1,3-dipolar cycloaddition of diazomethane to the chirally modified oxazolinone-protected α-aminoacrylate derivative **236**. Cyclopropanation of **236** with diazomethane furnished four spirocyclopropane derivatives, namely a pair each of the (*E*)- and (*Z*)-isomers along with a minor product[349] resulting from diazomethane-mediated C-2 methylation.[350] All of these products were extensively analyzed by mass spectrometry.[351] Under optimized conditions, the cyclopropanation of **236** occurred with reasonably high (*E*/*Z*) and (*R*/*S*) diastereoselectivities to give (*R*,*S*,*S*)-**237** as the major stereoisomer in 73% isolated yield (Scheme 28).[350,352] The analogous transformation of the corresponding (*R*,*E*)-**236** has also been investigated, and the origin of the high diastereofacial selectivities in the (*Z*)- as well as (*E*)-series was discussed on the basis of computational results.[353]

Methanolysis of the oxazolinone **237**, hydrolysis of the acetonide, and subsequent oxidative cleavage of the 1,2-dihydroxyethyl group furnished the cyclopropanecarbaldehyde **238**, which proved useful for further transformations. Wittig alkenylations provided various alkenyl-substituted 1-aminocyclopropanecarboxylic acid derivatives **240**−**243**, which were hydrogenated to afford the correspondingly substituted 2-ethyl-1-aminocyclopropanecarboxylic acid de-

Scheme 27. Enantioselective Syntheses of 2,3-Methanoamino Acids by 1,3-Dipolar Cycloadditions of Diazomethane of the Chirally Modified α-(Acylamino)acrylate 177 and Subsequent Transformations[340−345]



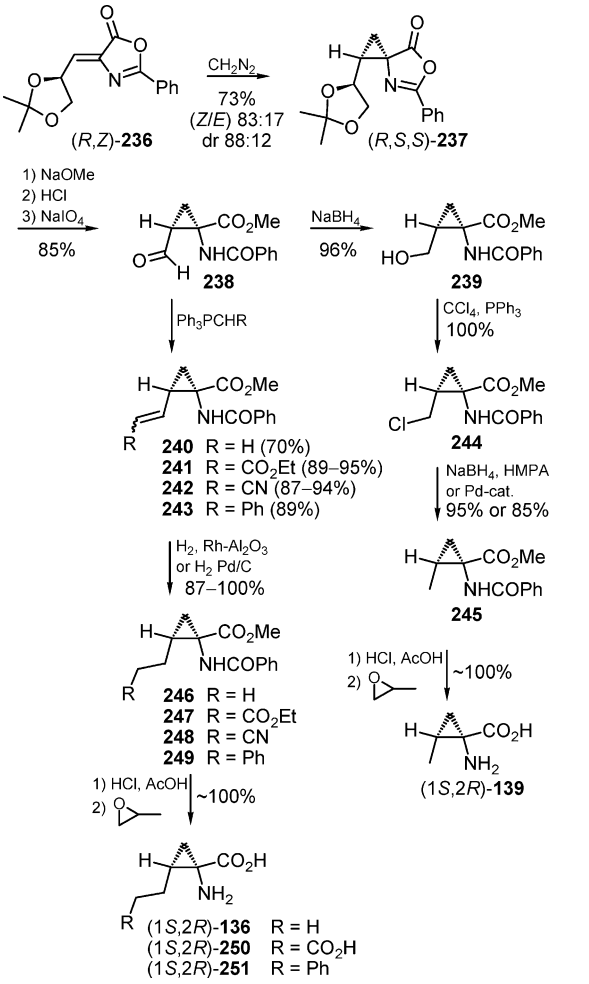
Scheme 28. Further Transformation of (2*S*,3*R*)-2,3-Methanohomoserine and (1*S*,2*R*)-2-Formylaminocyclopropanecarboxylate[347,348]



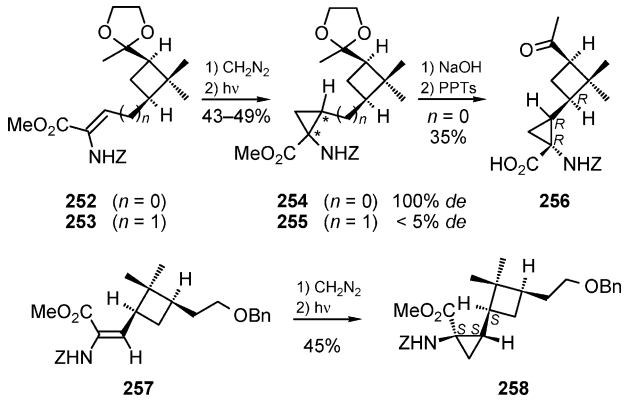
rivatives **246**−**249**. Deprotection of the ethyl-substituted derivative **246** furnished (−)-(1*S*,2*R*)-*allo*-coronamic acid **136** in 38% overall yield,[352] whereas hydrolysis of the protected ethoxycarbonyl- and cyanoethyl-substituted derivatives **247** and **248** led to (1*S*,2*R*)-homoglutamic acid (**250**). Alternatively, (2*S*,3*R*)-**250** was obtained by oxidative degradation of the phenylethyl-substituted derivative **249** and final deprotection. Simple cleavage of the protecting groups in **249** gave (1*S*,2*R*)-1-amino-2-(2-phenylethyl)cyclopropanecarboxylic acid (**251**).[354] Additionally, the formyl group in **238** has been reduced to provide the hydroxymethyl compound **239**, which could easily be converted to the corresponding chloromethyl derivative **244**. Reductive removal of the chlorine in **244** with sodium borohydride or by hydrogenolysis and final deprotection led to (−)-(1*S*,2*R*)-*allo*-norcoronamic acid **139** (Scheme 29).[355]

The cyclobutyl- and cyclobutylmethyl-substituted α-(acylamino)acrylates **252**, **253**, and **257**, prepared in enantiomerically pure form from (−)-α-pinene and (−)-verbenone, respectively,[356,357] were also cyclopropanated by 1,3-dipolar cycloaddition of diazomethane and photolytic ring contraction of the resulting pyrazolines. The substituted cyclobutyl moiety plays the role of a chiral inducer, the efficiency of which strongly depends on the proximity of the double bond and the nearest stereogenic center in the cyclobutane ring. Thus, cyclopropanation of **253** ($n = 1$) led to the corresponding cyclopropane derivative **255** with a diastereomeric excess of <5%, whereas cyclopropanation of **252** ($n = 0$) furnished a virtually diastereomerically pure product **254**, which was further converted into the partially deprotected cyclobutyl-substituted 1-aminocyclopropanecarboxylic acid derivative **256** as a single enantiomer. An analogous cyclopropanation of the α-(acylamino)acrylate **257** gave the cyclobutyl-substituted 1-aminocyclopropanecarboxylic acid

Scheme 29. Enantioselective Syntheses of Various 3-Substituted 2,3-Methanoamino Acid Derivatives by Cyclopropanation with Diazomethane of Chirally Modified 4-Alkylideneoxazolinone 236 and Subsequent Transformations[350,352,353,355]



Scheme 30. Stereoselective Syntheses of Cyclobutyl-substituted 1-Aminocycloproanecarboxylic Acid Derivatives[358]

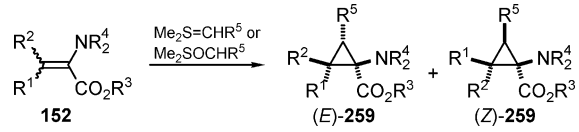


derivative **258** with the opposite configurations of both stereocenters in the cyclopropane ring (Scheme 30).[358]

3.2.2. Syntheses by Addition of Ylides to Michael Acceptors

The addition of ylides to α,β-unsaturated carboxylic acid derivatives provides a second synthetic route to substituted 2,3-methanoamino acids. The most frequently used ylides are sulfonium and oxosulfonium ylides, which have found application in the synthesis of racemic as well as enantiomerically pure 3-substituted 2,3-methanoamino acids. In addition, iodonium and phosphonium ylides have been employed.

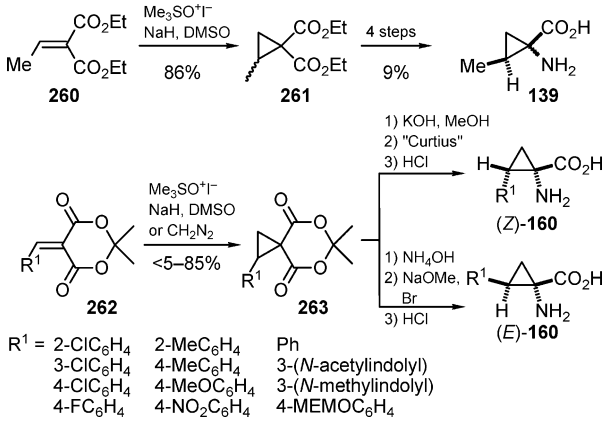
Scheme 31. Syntheses of 2,3-Methanoamino Acids by Michael Addition of Sulfonium and Sulfoxonium Ylides to α-Aminoacrylates 152 (for Details See Table 6). The (*E*)- and (*Z*)-Notation Is Based on the Steric Relationship of R^1 with Respect to the Amino Substituent.



The addition of sulfonium and sulfoxonium ylides to protected α-aminoacrylate derivatives **152** afforded 1-aminocyclopropanecarboxylic acid derivatives **259** in moderate to high yields with moderate to often excellent diastereomeric excesses, both depending on the reaction temperature (Scheme 31, Table 7).[92,102,257,359−361] Many of the derivatives **259** could easily be converted into the corresponding free amino acids. Protected racemic 2,3-methanovaline (entry 1) has been resolved by fractional crystallization of its (−)-quinine salt, giving rise to (−)-(*S*)- and (+)-(*R*)-2,3-methanovaline.[362]

Reaction of dimethylsulfoxonium methylide with diethyl 2-ethylidenemalonate (**260**) provided diethyl 2-methylcyclopropane-1,1-dicarboxylate (**261**), which, upon monohydrolysis, Hofmann degradation of the half ester, and final deprotection, readily gave racemic coronamic acid **139** (Scheme 32).[133]

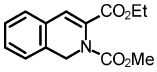
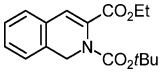
Scheme 32. Michael Addition of Dimethylsulfoxonium Methylide to Alkylidenemalonates and Subsequent Transformations of the Adducts to 1-Aminocyclopropanecarboxylic Acids[133,364,365]



Addition of dimethylsulfoxonium methylide to a variety of (arylmethylene)malonic acid derivatives **262** furnished the corresponding spirocyclopropanated compounds **263**.[364,365] A comparative study showed that these reactions generally gave significantly higher yields of products **263** than the cyclopropanation of the same substrates with diazomethane.[364] Depending on further treatment of compounds **263**, 3-substituted 2,3-methanoamino acids were obtained either as the (*Z*)-isomer (*Z*)-**160** or the (*E*)-isomer (*E*)-**160** (Scheme 32).[364,365]

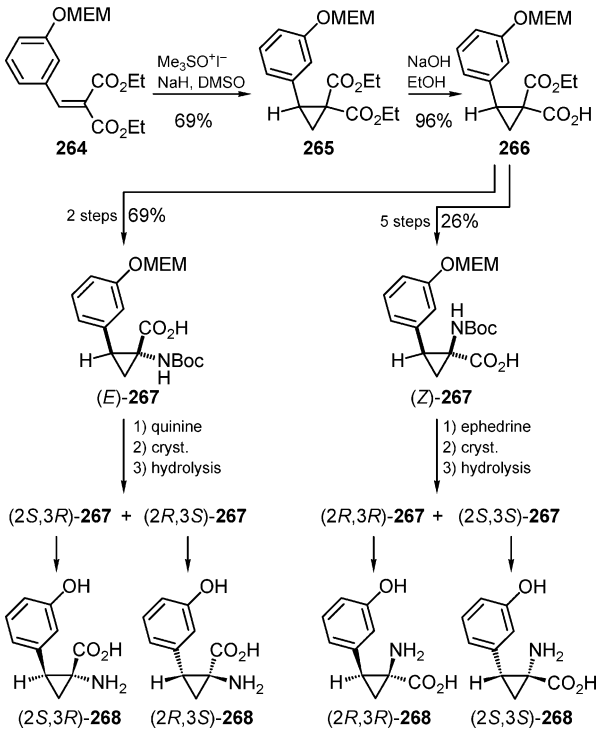
Both, racemic (*E*)- and (*Z*)-2,3-methano-*m*-tyrosine were synthesized from (methoxyethoxy)methyl (MOM)-protected 3-(4-hydroxybenzylidene)malonate **264**, readily available by

Table 7. Protected 2,3-Substituted 1-Aminocyclopropanecarboxylic Acids (*E*)- and (*Z*)-259 Obtained by Michael Additions of Sulfonium and Sulfoxonium Ylides to α-Aminoacrylates 152 (See Scheme 31)

entry	(*E*/*Z*)-ratio **152**	R^1	R^2	NR_2^4	R^3	ylide	yield (%)/ (*E*/*Z*)-ratio **259**	ref
1		Me	Me	N=C	Et	Me_2SOCH_2	55−71/−	102, 257, 362
2		Et	Et	N=C	Et	Me_2SOCH_2	71/−	102
3		−$(CH_2)_5$−		N=C	Et	Me_2SOCH_2	51/−	102
4	1:5	iPr	H	N=C	Et	Me_2SOCH_2	79/*E*>*Z*	102
5		Ph	Ph	N=C	Et	Me_2SOCH_2	>5/−	102
6	1:2.6	Ph	H	N=C	Et	Me_2SOCH_2	83/40:1	102
7	(*Z*)	Ph	H	N=C(Ph)−		$Me_2SCHCOPh$	max. 84.5/up to 1:13[a]	359
8	(*Z*)	4-AcOPh	H	N=C(Ph)−		$Me_2SCHCOPh$	max. 57.5/up to 1:1.7[a,b]	359
9	(*Z*)	PhCH=CH	H	N=C(Ph)−		$Me_2SCHCOPh$	max. 49/up to only (*Z*)[a,b]	359
10	(*Z*)	2-furyl	H	N=C(Ph)−		$Me_2SCHCOPh$	57/1:11.7	359
11	(*Z*)	3-(1-acetylindolyl)	H	N=C(Ph)−		$Me_2SCHCOPh$	49/only (*Z*)	359
12		Me	Me	N=C(Ph)−		$Me_2SCHCOPh$	83.5/1:2.7	359
13		−$(CH_2)_5$−		N=C(Ph)−		$Me_2SCHCOPh$	84	360
14		−$(CH_2)_6$−		N=C(Ph)−		$Me_2SCHCOPh$	35	360
15		−$(CH_2)_5$−		N=C(Ph)−		Me_2SCHCO_2Et	97	360
16	(*E*)	PhCH=CH−	H	N=C(Ph)−		$Me_2SCHCPhCHCO_2Et$	4/only (*E*)	360
17		H	H	N=CPh_2	Me	$PhNEt_2SOCHCH_3$	93−96/up to 2:98[a]	92
18		H	H	N=$C(SMe)_2$	Me	$PhNEt_2SOCHCH_3$	70−92/up to 4:96[a]	92
19	(*Z*)	4-MeC_6H_4	H	N=C	Et	Me_2SOCH_2	52/mixture	361
20	(*Z*)	 [c]				Me_2SOCH_2	80/only (*Z*)	363
21	(*Z*)	 [c]				Me_2SOCH_2	81/only (*Z*)	363

[a] The yield and the diastereomeric ratio decreased with increasing temperature. [b] Additionally, up to 50% of the product with a cleaved oxazolinone ring was isolated (R^3 = H, NR_2^4 = NHCOPh). [c] The complete starting material **152** is depicted.

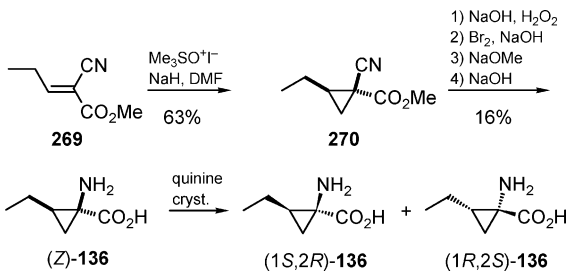
Scheme 33. Synthesis of All Four Stereoisomers of 2,3-Methano-*m*-tyrosine by Addition of Dimethylsulfoxonium Methylide to Protected (3-Hydroxybenzylidene)malonate[366]



Knoevenagel condensation of 2-MOM-protected 3-hydroxybenzaldehyde. Cyclopropanation of **264** with dimethyloxosulfonium methylide furnished the cyclopropane-1,1-dicarboxylate **265**, which was hydrolyzed to the monoester **266**. Curtius degradation of the carboxylic acid moiety in **266** and subsequent hydrolysis of the ester gave protected (*E*)-2,3-methano-*m*-tyrosine (*E*)-**267**, which was either deprotected in order to yield (*E*)-2,3-methano-*m*-tyrosine or resolved by crystallization of its quinine salt before removal of the protecting groups in order to give (2*S*,3*R*)- and (2*R*,3*S*)-2,3-methano-*m*-tyrosine (2*S*,3*R*)-**268** and (2*R*,3*S*)-**268**, respectively. In contrast, conversion of the monoester **266** into its hydrazide before nitrosation, subsequent degradation, and hydrolysis led to (*Z*)-2,3-methano-*m*-tyrosine (*Z*)-**267**, which was also deprotected or resolved by crystallization of its ephedrine salt to furnish (2*R*,3*R*)- and (2*S*,3*S*)-2,3-methano-*m*-tyrosine (2*R*,3*R*)-**268** and (2*S*,3*S*)-**268**, respectively, after removal of the protecting groups (Scheme 33).[366]

Racemic *allo*-coronamic acid was synthesized by cyclopropanation with the dimethyloxosulfonium methylide of methyl (2*E*)-2-cyano-2-penteneoate (**269**) obtained by condensation of propionaldehyde with methyl cyanoacetate. Hofmann degradation and final hydrolysis yielded the desired amino acid **136**. Racemic *allo*-coronamic acid **136** was resolved through its quinine salt to provide (+)-(1*S*,2*R*)- and (−)-(1*R*,2*S*)-*allo*-coronamic acid (*Z*)-**136** (Scheme 34).[367]

Scheme 34. Synthesis and Deracemization of *allo*-Coronamic Acid by Cyclopropanation of Methyl (2*E*)-2-Cyano-2-penteneoate with Dimethylsulfoxonium Methylide[367]

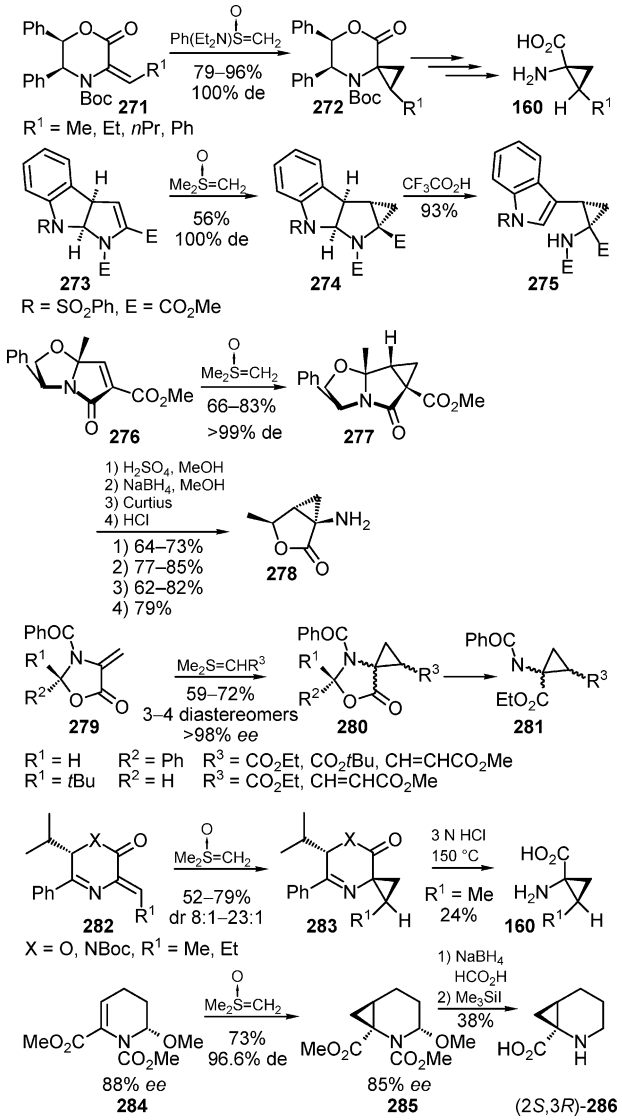


Several asymmetric variants of the addition of sulfur ylides to α,β-unsaturated carboxylic acid derivatives have been

developed, in which the stereochemistry is controlled either by introduction of a chiral auxiliary or by utilization of a chiral starting material.

Thus, cyclopropanation of the chiral α,β-dehydroamino acid derivative **271** with dimethylsulfoxonium methylide afforded the corresponding cyclopropylamino acid derivatives in high yield, but as a mixture of two diastereomers. Switching to [(diethylamino)phenyl]oxosulfonium ylide greatly improved the diastereoselectivities, providing protected amino acids **272** in high yields, which could easily be converted to the corresponding free 2,3-methanoamino acids **160** (Scheme 35).[137,368]

Scheme 35. Asymmetric Syntheses of 2,3-Methanoaamino Acids by Cyclopropanation of Chirally Modified α-(Acylamino)acrylic Acid Derivatives with Sulfur Ylides[137,369−376]



Treatment of the chiral tetrahydropyrroloindole **273** with dimethylsulfoxonium methylide gave the tetracyclic heterocycle **274** as a single diastereomer. Due to the significant strain in **274**, it easily undergoes ring opening to the enantiopure 2,3-methanotryptophane derivative **275** upon treatment with trifluoroacetic acid (Scheme 35).[369,370]

Cyclopropanation of the enantiopure bicyclic lactam **276** followed by methanolysis of the *O*,*N*-acetal, reduction of the ketone with concomitant lactone formation, and subsequent Curtius degradation of the remaining ester after hydrolysis led to the enantiopure bicyclic aminolactone **278** (Scheme 35).[371]

The chiral methyleneoxazolidinones **279** were converted with (dimethylsulfanylidene)acetates or -butenoates, respectively, to give a mixture of three to four diastereomers of the corresponding spirocyclopropane derivatives **280**, which were transformed to the ring-opened products **281**. An attempted hydrolysis of **281** ($R^3 = CO_2Et$) did not succeed, as the cyclopropane ring did not survive the hydrolysis conditions (Scheme 35).[372]

Cyclopropanation of the chiral α,β-dehydroamino acid derivative **282** with dimethylsulfoxonium methylide diastereoselectively furnished the cyclopropane derivatives **283**.[373−375] Hydrolysis of the latter proceeded smoothly in the case of the aminolactone (X = O)[373,374] but led to decomposition or low yields of the corresponding free amino acids **160** in the case of the diketopiperazine derivative **282** ($R^1 = NHBoc$)[375] (Scheme 35).

The optically active 2,3-didehydropipecolinic acid derivative **284** was diastereoselectively transformed into the heterobicycle **285**, which, by reduction and subsequent hydrolysis, was converted to (2*S*,3*R*)-2,3-methanopipecolinic acid [(2*S*,3*R*)-**286**] (Scheme 35).[376]

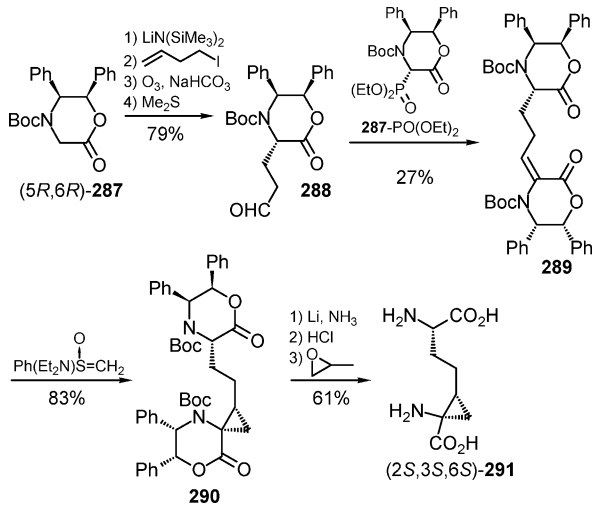
In order to avoid the formation of a diastereomeric mixture in the cyclopropanation of the α,β-didehydroamino acid derivative **202** bearing a chiral pinane moiety (see Scheme 23), diazomethane was replaced by dimethylsulfoxonium methylide. As desired, only one diastereomer was formed, and it could be identified as the (*Z*)-isomer (*R*,*R*)-**203**. The alkyl-substituted spirocyclopropane compounds **203** could be hydrolyzed to give low yields of the corresponding free 1-aminocyclopropanecarboxylic acids; however, hydrolysis of aryl-substituted compounds **203** failed completely.[377]

With the intention to develop a large-scale synthesis of the 1-aminocyclopropanecarboxylic acid precursor **216** avoiding diazomethane (see Scheme 27), the α,β-dehydroamino acid derivative **215** was cyclopropanated with sulfur ylides. (Diethylamino)phenyloxosulfonium methylide proved to be a suitable alternative for diazomethane with respect to the achieved diastereoselectivities.[378]

An asymmetric synthesis of 2,3-methano-2,6-diaminopimelic acids **291** started with the alkylation of the lithium enolate of the optically pure glycine derivative **287** with 4-iodo-1-butene, ozonolysis of the double bond, and reductive (with dimethyl sulfide) workup to yield the aldehyde **288**. Emmons−Horner−Wadsworth alkenation of **288** with the phosphonate ester **287**-$PO(OEt)_2$ prepared from the enolate of (5*R*,6*R*)-**287**[137] provided the (*E*)-alkene **289** as a single diastereomer. When **289** was treated with [(diethylamino)-phenyl]oxosulfonium methylide, the cyclopropane derivative **290** was obtained, again as a single diastereomer. Removal of the chiral auxiliary from **291** by dissolving-metal reduction and removal of the Boc-protective group afforded 2,3-methano-2,6-diaminopimelic acids **291**. Depending on the enantiomer of **287** and **287**-$PO(OEt)_2$ used, the syntheses of (2*S*,3*S*,6*S*)-**291**, (2*S*,3*S*,6*R*)-**291**, and (2*R*,3*R*,6*S*)-**291**, respectively, were accomplished (Scheme 36).[379]

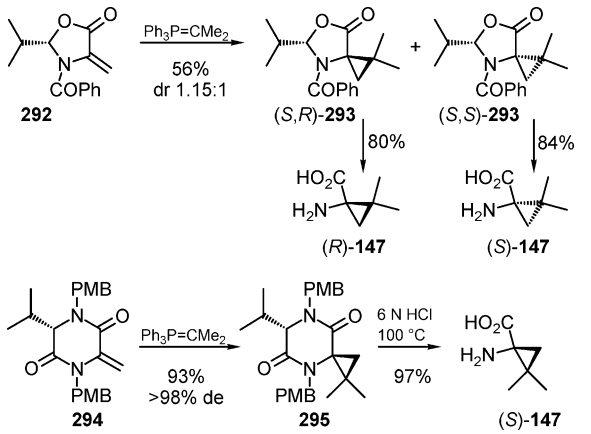
Utilization of isopropylidenetriphenylphosphorane for the cyclopropanation of the chiral α,β-didehydroamino acid derivative **292** led to a separable mixture of the diastereomeric spirocyclopropanated oxazolidinone derivatives (*S*,*R*)-**293** and (*S*,*S*)-**293**. Hydrolysis of the latter furnished enantiomerically pure 2,3-methanovalines [(*R*)-**147**] and [(*S*)-

Scheme 36. Enantioselective Synthesis of 2,3-Methano-2,6-diaminopimelic Acid.[379] Only the Synthesis of the (2*S*,3*S*,6*S*)-Enantiomer of 291 Is Depicted



147].[380] Analogously, the chiral methylenediketopiperazine **294** was diastereoselectively converted into the spirocyclopropanated derivative **295**, which could be hydrolyzed to (*S*)-2,3-methanovaline [(*S*)-**147**] (Scheme 37).[138]

Scheme 37. Asymmetric Syntheses of 2,3-Methanovaline by Cyclopropanation of Chiral α-Aminoacrylic Acid Derivatives with Phosphorus Ylides[138,380]



An efficient and expedient access to 2,3-methanoamino acids was developed by addition of (alkoxycarbonyl)-nitrocarbenes to alkenes and subsequent reduction of the nitro group. Toward that end, iodonium ylides generated in situ from nitroacetates and bis(acetoxy)iodobenzene, in the presence of a rhodium catalyst, were found to offer a safe alternative to nitrodiazoacetates as metalcarbene precursors. The corresponding nitrocyclopropanecarboxylates **168** (see Scheme 17) were formed in only slightly lower yields with comparable diastereoselectivities.[318,381]

3.2.3. Syntheses by Cyclodialkylation of Malonic Acid Derivatives and Subsequent Degradation to the Amino Acid

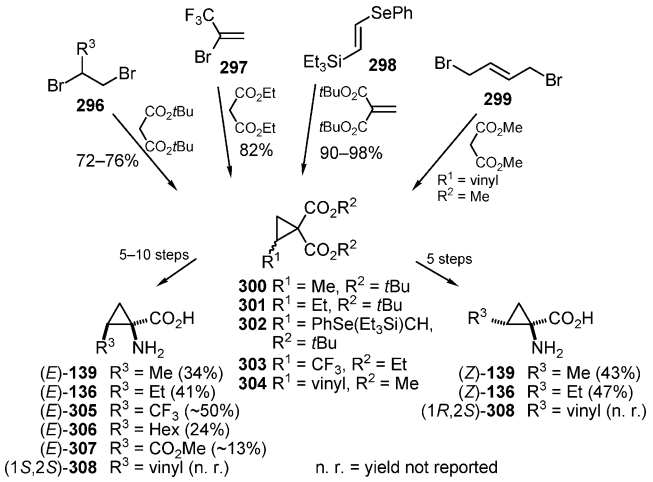
A large-scale synthesis of racemic mixtures of methyl- and ethyl-substituted 1-aminocyclopropanecarboxylic acids was accomplished by initial cyclodialkylation of di-*tert*-butyl malonate with 1,2-dibromopropane **296** (R^3 = Me) or 1,2-dibromobutane **296** (R^3 = Et), respectively. Stereoselective transformation of one of the two *tert*-butoxycarbonyl functions into an amino group in the thus obtained cyclopropane-1,1-dicarboxylates **300** and **301** completed the access to either (*E*)-norcoronamic acid (*E*)-**139** and (*E*)-coronamic acid (*E*)-**136** or the corresponding (*Z*)-isomers (*Z*)-**139** and (*Z*)-**136** (Scheme 38).[318] The racemic mixture of norcoronamic acid was enzymatically resolved using Porcine Kidney Acylase I to give enantiomerically pure (+)-(1*S*,2*S*)- and (−)-(1*R*,2*R*)-norcoronamic acid. *allo*-Coronamic and *allo*-norcoronamic acid were resolved by esterification with *S*-(+)-2-hydroxy-2-phenylacetic acid, crystallization of the thus obtained diastereomers, and final hydrolysis to furnish (−)-(1*S*,2*R*)- and (+)-(1*R*,2*S*)-*allo*-coronamic acid **136** and (−)-(1*S*,2*R*)- and (+)-(1*R*,2*S*)-*allo*-norcoronamic acid **139**, respectively.[382]

An analogous transformation employing labeled *meso*- and D,L-1-deuterio-1,2-dibromopropane or -butane, respectively, provided regiospecifically 2-alkyl-3-deuterio-1-aminocyclopropanecarboxylic acids.[383]

Racemic (*E*)-trifluoromethyl-substituted norcoronamic acid (*E*)-**305** was obtained by reaction of 2-bromo-3,3,3-trifluoropropene (**297**) with diethyl malonate and selective conversion of the (*E*)-positioned ester to an amino group (Scheme 38).[384]

The reaction of 1-phenylselenenyl-2-triethylsilylethene (**298**) with di-*tert*-butyl methylenemalonate in the presence of a Lewis acid provided the highly functionalized cyclopropane derivative **302**. This was stereoselectively transformed into racemic (*E*)-2,3-methanoaspartic acid (*E*)-**307** [isolated as Boc-Asp(OMe)-O*t*Bu], into coronamic acid (*E*)-**136**, and into (*E*)-1-amino-2-hexylcyclopropane-1-carboxylic acid [(*E*)-**306**] (Scheme 38).[385]

Scheme 38. Various 2-Substituted Dialkyl Cyclopropane-1,1-dicarboxylates and Their Transformations into 2-Substituted 1-Aminocyclopropanecarboxylic Acids[382−387]



The real strength of the synthesis of 2,3-methanoamino acids via cyclodialkylation products of dialkyl malonates lies in a number of interesting asymmetric versions which make use of enzymatic degradation either of a suitable intermediate or of a chiral auxiliary or a chiral starting material, respectively.

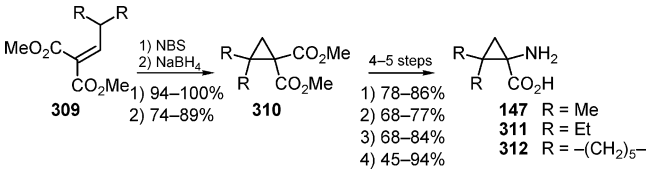
Thus, dimethyl 2-methylcyclopropane-1,1-dicarboxylate (**300**) was subjected to the action of two enzymes, pig liver esterase (PLE) and an esterase (E 30.000) from bacterial origin, and depending on the order of steps, all four stereoisomers of norcoronamic acid **139** were obtained.[386]

The syntheses of (1*R*,2*S*)- and (1*S*,2*S*)-2-vinyl-1-aminocyclopropanecarboxylic acids [(1*R*,2*S*)-**308**] and [(1*S*,2*S*)-**308**]

were accomplished starting with the cyclodialkylation of dimethyl malonate with 1,4-dibromobut-2-ene. The thus obtained racemic mixture of prochiral dimethyl 2-vinylcyclopropanedicarboxylate (**304**) was successfully resolved on a large scale by successive use of two esterases with different diastereoselectivities. Conventional carboxylic acid degradation then led to (1*R*,2*S*)- and (1*S*,2*S*)-vinyl-1-aminocyclopropanecarboxylic acids [(1*R*,2*S*)-**308**] and [(1*S*,2*S*)-**308**] (Scheme 38).[387]

Dimethyl 2,2-dialkylcyclopropane-1,1-dicarboxylates **310** were prepared from alkylidenemalonates **309** by allylic bromination and subsequent Michael-induced ring closure (MIRC) reaction. Selective hydrolysis of one ester functionality in **310** followed by Curtius degradation of the monoacid and hydrolysis of the remaining ester completed a straightforward access to racemic 2,3-methanovaline (**147**), 2,3-ethylnorvaline (**311**), and 1-aminospiro[2.4]heptane-1-carboxylic acid (**312**) (Scheme 39).[388] When dimethyl 2,2-dimethylcyclopropane-1,1-dicarboxylate (**310**) (R = Me) was first converted to the corresponding bis(trifluoroethyl) ester, an enzymatic desymmetrization by esterase-mediated monohydrolysis could be achieved. Subsequent degradation then led to virtually enantiopure (*S*)-2,3-methanovaline [(*S*)-**147**].[389]

Scheme 39. Synthesis of 1-Amino-2,2-dialkylcyclopropane-1-carboxylic Acids from Alkylidenemalonates[388,389]



Asymmetric syntheses of a variety of 2,3-methanoamino acids have been achieved using substituted ethylene sulfates **316**−**320** (Scheme 40) as chiral enantiopure starting materials, since sulfates **316**−**320** are generally easily available as both enantiomers and on a large scale by conversion of the underlying chiral diol with thionyl chloride followed by oxidation. This route offers a practical way to synthesize all four stereoisomers of 2,3-methanoamino acids.

Methyl-, ethyl-, and isopropyl-substituted sulfates **316**−**318** were used to cyclodialkylate dialkyl (R^2 = Me, Bn) malonate enolates to furnish protected dialkyl cyclopropanedicarboxylates **321**−**323**. Monohydrolysis and subsequent Curtius degradation of the monoacids from these compounds gave the corresponding protected 2,3-methanoamino acids **336**−**338** (path A, Scheme 40), which were deprotected to yield (1*R*,2*R*)-norcoronamic acid [(1*R*,2*R*)-**139**],[390] (1*R*,2*R*)-coronamic acid [(1*R*,2*R*)-**136**],[245] and (2*R*,3*R*)-2,3-methanoleucine [(2*R*,3*R*)-**335**] (Scheme 40).[391,392] A modification of the hydrolysis and degradation led to the corresponding (1*S*,2*R*)-isomers of coronamic acid (1*S*,2*R*)-**136** and (2*S*,3*R*)-2,3-methanoleucine, the latter of which was isolated in its *N*-benzyloxycarbonyl-protected form (2*S*,3*R*)-**313** (path B, Scheme 40).[245,392]

When benzyloxymethyl- **319** or benzyloxyethyl-substituted ethylene sulfates **320** were used for the cyclodialkylation of malonate enolates (R^2 = Me, Et), the versatile intermediates **324** and **325** for further transformations were obtained. Thus, Curtius degradation of the monoacid obtained by partial hydrolysis of the benzyloxymethyl-substituted derivative **324** furnished the corresponding protected (2*R*,3*R*)-2,3-methanohomoserine [(2*R*,3*R*)-**339**] (path A, Scheme 40). Hydrogenolysis and mesylation of the protected (2*R*,3*R*)-2,3-methanohomoserine [(2*R*,3*R*)-**339**], subsequent reaction with methanethiolate, and deprotection gave (2*R*,3*R*)-2,3-methanomethionine [(2*R*,3*R*)-**230**],[393] whereas mesylation followed by cyanation and subsequent oxidation led, depending on the oxidation conditions, to (2*R*,3*R*)-2,3-methanoglutamine [(2*R*,3*R*)-**341**] or (2*R*,3*R*)-2,3-methanoglutamic acid [(2*R*,3*R*)-**342**].[394] Additionally, the hydroxymethyl function in the (2*R*,3*R*)-2,3-methanohomoserine derivative (2*R*,3*R*)-**327** was converted into an azidomethyl group which could be guanidinylated to yield guanidinylmethyl-substituted (1*R*,2*R*)-1-aminocyclopropane-1-carboxylic acid (1*R*,2*R*)-**343** (Scheme 40).[395]

Curtius degradation of the monoacid from the benzyloxyethyl-substituted derivative **325** afforded protected (2*R*,3*R*)-5-hydroxy-2,3-methanonorvaline (2*R*,3*R*)-**340** (path A, Scheme 40). Hydrogenolysis of **340**, mesylation, and substitution of the mesylate with cyanide furnished a nitrile which was reduced to yield the protected (2*R*,3*R*)-2,3-methanolysine (2*R*,3*R*)-**344**.[396] Alternatively, (2*R*,3*R*)-5-hydroxy-2,3-methanonorvaline, obtained by hydrogenolysis of **341**, was oxidized to (2*R*,3*R*)-2,3-methanoglutamic acid [(2*R*,3*R*)-**345**] or converted into protected (2*R*,3*R*)-2,3-methanoarginine [(2*R*,3*R*)-**346**] by a Mitsunobu reaction (Scheme 40).[396]

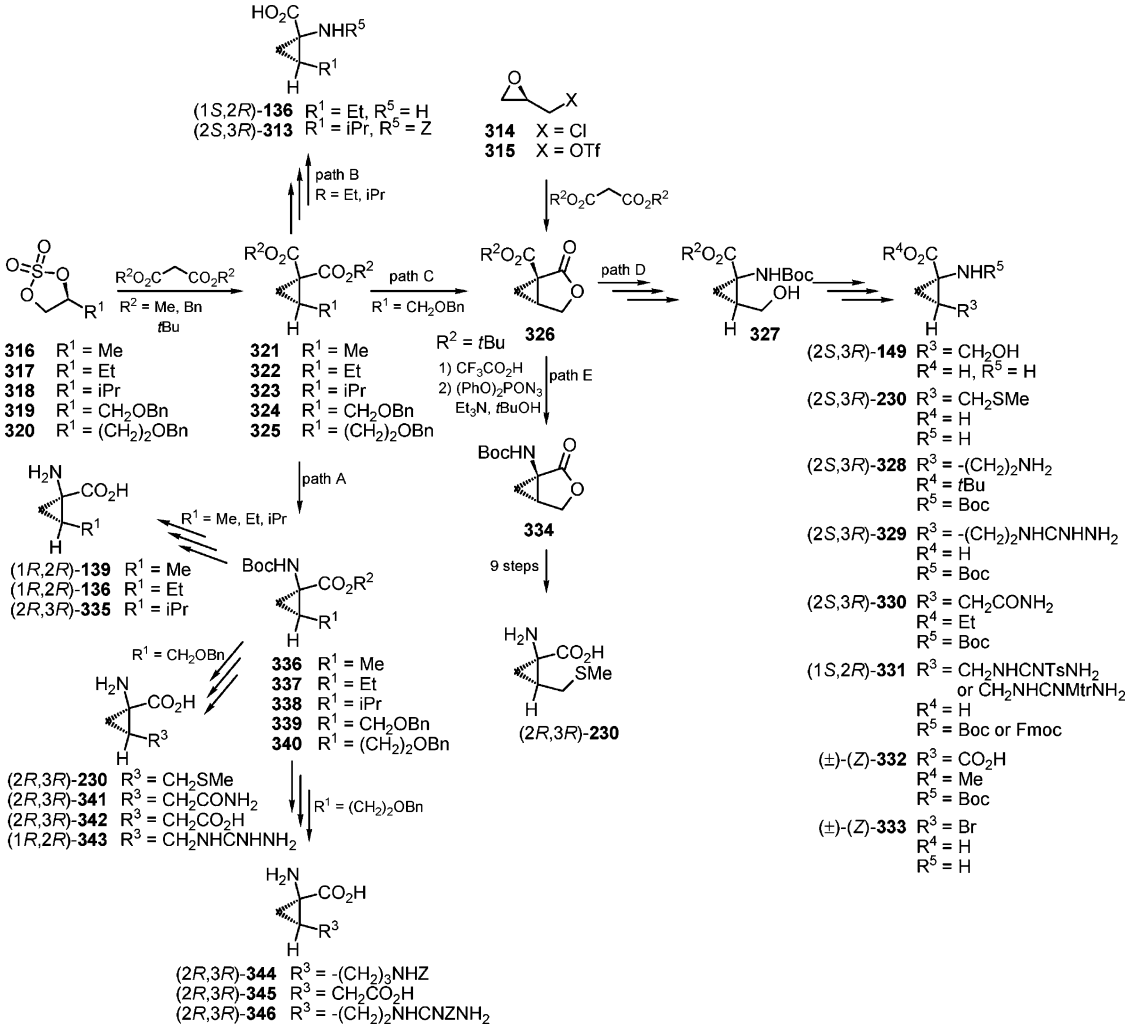
An interesting route to virtually enantiomerically pure 2,3-methanoamino acids utilizes the lactone **326** as a chiral building block, which was synthesized either by cyclodialkylation with subsequent intramolecular transesterification of dialkyl malonate enolates with epichlorohydrin **314** or its triflate analogue **315**,[263,397] or by cyclization of the benzyloxymethyl-substituted cyclopropane-1,1-dicarboxylate **324**.[398] Aminolysis of **326** and subsequent Hofmann degradation of the resulting hydroxymethyl-substituted cyclopropanecarboxamide gave enantiopure protected (2*S*,3*R*)-2,3-methanohomoserine (2*S*,3*R*)-**327** (path D), which was either deprotected to yield (2*S*,3*R*)-2,3-methanohomoserine [(2*S*,3*R*)-**149**] in its free form,[263] or used for further transformations. Thus, mesylation of (2*S*,3*R*)-**327**, subsequent reaction with methanethiolate, and deprotection furnished (2*S*,3*R*)-2,3-methanomethionine [(2*S*,3*R*)-**230**],[393,397] whereas mesylation, nucleophilic substitution with cyanide, and catalytic hydrogenation of the resulting nitrile gave protected (2*S*,3*R*)-2,3-methanoornithine (2*S*,3*R*)-**328**, which was further converted to the protected (2*S*,3*R*)-2,3-methanoarginine (2*S*,3*R*)-**329**.[399] The intermediately formed nitrile was also partially hydrolyzed to the amide to yield the protected (2*S*,3*R*)-2,3-methanoglutamine **330** (Scheme 40).[394]

Furthermore, the hydroxy function in the protected (2*S*,3*R*)-2,3-methanohomoserine (2*S*,3*R*)-**327** was substituted by azide and the azido group was further transformed to a guanidinyl function to provide the protected guanidinylmethyl-substituted (1*S*,2*R*)-1-aminocyclopropanecarboxylic acid (1*S*,2*R*)-**331**, which constitutes the natural product carnosadine (Scheme 40).[395]

Oxidation of the protected racemic (*Z*)-2,3-methanohomoserine (*Z*)-**327** afforded protected (*Z*)-2,3-methanoasparagine (*Z*)-**332**, which was further converted into protected (*Z*)-2-bromo-1-aminocyclopropanecarboxylic acid (*Z*)-**333** (Scheme 40).[400]

(2*R*,3*R*)-2,3-Methanomethionine [(2*R*,3*R*)-**230**] was also prepared via the amino-substituted lactone **334** obtained by Curtius degradation of the acid liberated from the *tert*-butoxycarbonyl-substituted lactone **326** (R^2 = *t*Bu), followed by a nine-step sequence (path E, Scheme 40).[397]

Scheme 40. Asymmetric Syntheses of 2,3-Methanoamino Acids by Reaction of Substituted Ethylene Sulfates with Malonic Acid Derivatives and Subsequent Transformations. (The Depicted Sequences Show Only One Enantiomer, Although the Indicated Steps Were Often Performed with Both Enantiomers).[245,263,390−400]

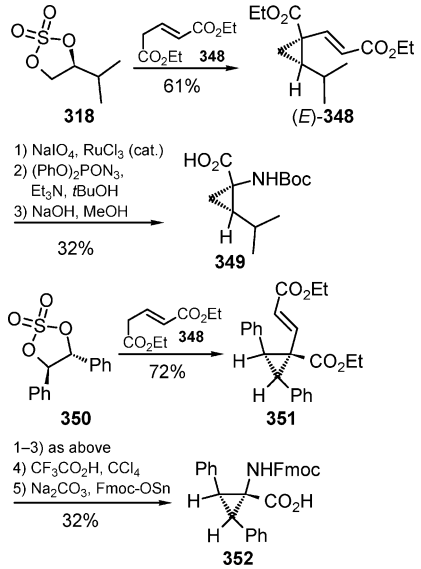


Besides the cyclodialkylation of dialkyl malonates with substituted ethylene sulfates, the isopropyl-substituted ethylene sulfate **318** was also employed to cyclodialkylate the enolate of diethyl *trans*-pent-2-ene-1,5-dioate (diethyl glutaconate) (**348**), giving rise to the cyclopropane derivative (*E*)-**348**, which was separated from the concomitantly formed (*Z*)-**348**. Oxidation of (*E*)-**348** with in situ generated ruthenium tetroxide, subsequent Curtius degradation of the monoacid, and hydrolysis of the ester moiety yielded the protected (2*S*,3*R*)-2,3-methanoleucine (2*S*,3*R*)-**349** (Scheme 41).[391]

An analogous transformation employing the diphenyl-substituted ethylene sulfate **350** as the chiral starting material led to *N*-Boc-protected (2*S*,3*S*)-1-amino-2,3-diphenylcyclopropane-1-carboxylic acid, which was further converted into the corresponding Fmoc-protected derivative **352**.[401]

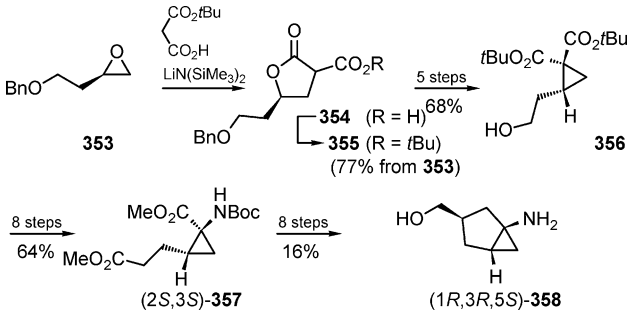
A reported synthesis of protected (2*S*,3*S*)-2,3-methanohomoglutamic acid (2*S*,3*S*)-**357** starts with treatment of enantiomerically pure (benzyloxyethyl)oxirane (**353**) with the dianion of mono-*tert*-butyl malonate to provide the lactone **354**. In a six-step sequence involving esterification with *tert*-butyl alcohol in the presence of dicyclohexyl carbodiimide to **355**, hydrolysis of the lactone, repeated esterification, and ring closure, the di-*tert*-butyl cyclopropanedicarboxylate **356** was prepared. A further eight-step transformation including a Curtius degradation gave rise to protected (2*S*,3*S*)-2,3-

Scheme 41. Reaction between Substituted Ethylene Sulfates and Diethyl Glutaconate and Subsequent Transformations to 1-Aminocyclopropanecarboxylic Acids[391,401]



methanohomoglutamic acid (2*S*,3*S*)-**357**. The latter was eventually converted into (1*R*,3*R*,5*S*)-1-aminobicyclo[3.1.0]-hex-3-ylmethanol [(1*R*,3*R*,5*S*)-**358**], which was considered

Scheme 42. Asymmetric Synthesis of Protected Methanohomoglutamic Acid and Further Transformation into a Precursor to Nucleosides with Carbocyclic Sugar Mimics[402]



to be a valuable precursor for nucleoside analogues with carboxylic sugar mimics (Scheme 42).[402]

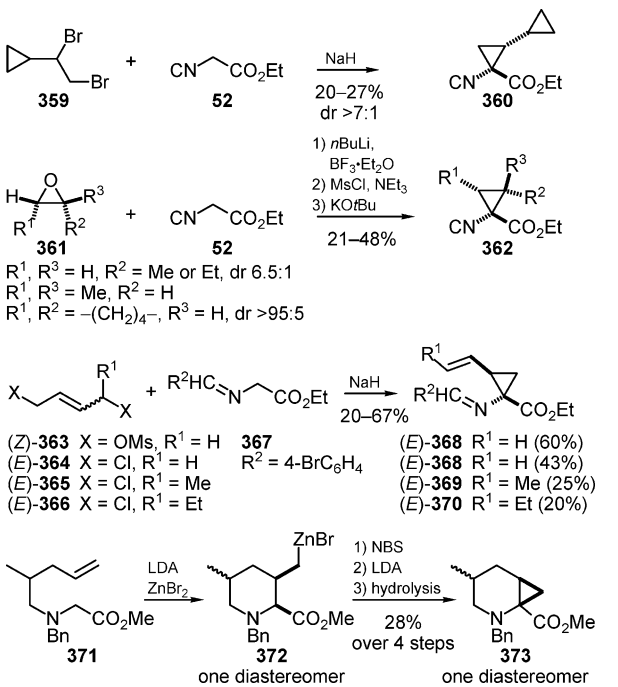
3.2.4. Synthesis by Cyclodialkylation of Nucleophilic Glycine Equivalents

A straightforward approach to substituted 2,3-methanoamino acid derivatives is also by cyclodialkylation of an appropiate nucleophilic glycine equivalent, which can often be achieved with high to excellent diastereoselectivities.

For example, the reaction of (1,2-dibromoethyl)cyclopropane (**359**) with ethyl isocyanoacetate (**52**) furnished the 3-cyclopropyl-2,3-methanoalanine derivative **360**, which could be deprotected to yield 1-amino-2-cyclopropylcyclopropanecarboxylic acid in its free form (Scheme 43).[264] Ethyl isocyanoacetate (**52**) also reacted with various alkyloxiranes **361**. In a sequence of several steps involving ring opening of the epoxide, mesylation of the intermediately formed alcohol, and diastereoselective cyclization, 2-alkyl- and 2,3-dialkyl-substituted 1-aminocyclopropanecarboxylic acid derivatives **362** were obtained (Scheme 43), and these could easily be transformed into their fully deprotected forms.[107]

In analogy to the cyclodialkylation of dialkyl malonate enolates with cyclic sulfates from vicinal diols (see Scheme 40), the isocyanoacetate **52** was cyclodialkylated with epibromohydrine to give an isocyano-substituted bicyclic lactone derivative analogous to **326** (see Scheme 40) which could be ring-opened to protected 2,3-methanohomoserine **327**, however in negligibly low yields.[285]

Scheme 43. Diastereoselective Cyclodialkylation of Nucleophilic Glycine Anion Equivalents[107,264,285,403,405]

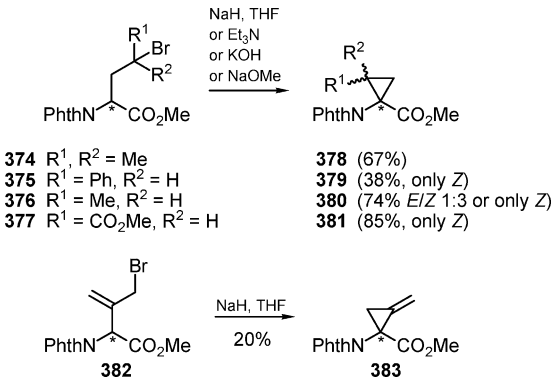


The synthesis of vinyl-, 1-propenyl-, and 1-butenyl-substituted (*E*)-1-aminocyclopropanecarboxylic acids (*E*)-**368**−(*E*)-**370** was achieved by diastereoselective cyclodialkylation of the enolate of the protected glycine ester **367** with 1,4-bis(methanesulfonyloxy)-(2*Z*)-butene [(*Z*)-**363**] or 1,4-dichloro-(2*E*)-butene derivatives **364**−**366** (Scheme 43).[403] The vinyl-substituted derivative (*E*)-**368** thus obtained has been applied in the solid-phase synthesis of hydantoin- and isoxazoline-containing heterocycles.[404]

Deprotonation of methyl *N*-benzyl-(2-methyl-4-pentenyl)-glycinate (**371**), prepared by reaction of the underlying amine with methyl bromoacetate, with lithium diisopropylamide followed by transmetallation to the corresponding zinc enolate, upon warming-up gave the piperidinylmethylzinc derivative **372** as a single diastereomer. The latter, upon hydrolysis and bromination as well as final treatment with base, furnished a single diastereomer of the 2,3-methanopiperidine-2-carboxylic acid derivative **373** (Scheme 43).[405]

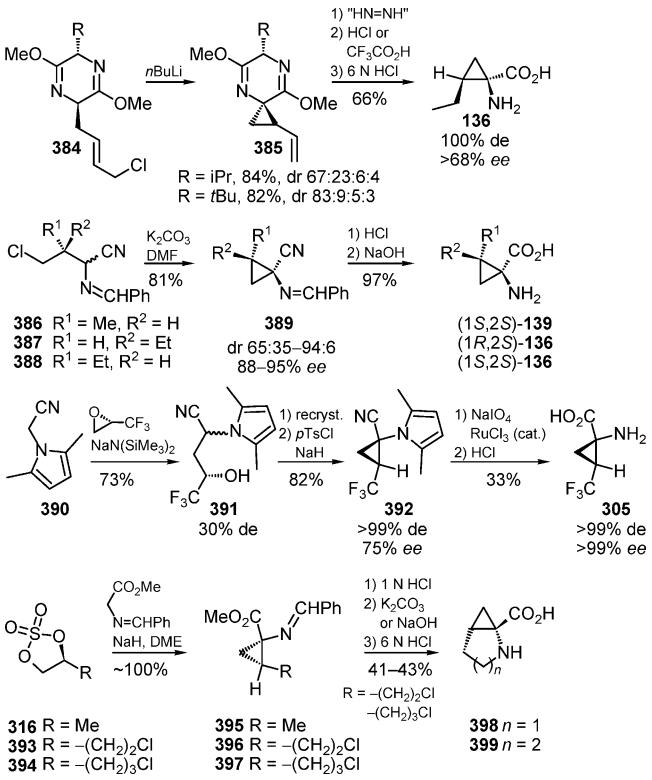
Protected forms of racemic 2,3-methanovaline **378**, (*Z*)-2,3-methanophenylalanine (*Z*)-**379**, norcoronamic acid (*Z*)-**380**, and (*Z*)-aspartic acid (*Z*)-**381** were prepared by base-induced cyclization of the corresponding γ-bromo-substituted amino acid derivatives **374**−**377** (Scheme 44), which had been synthesized by regioselective bromination of the correspondingly protected underlying amino acids leucine, homophenylalanine, norvaline, and glutamic acid.[406,407] An anlogous transformation of the brominated β,γ-didehydrovaline derivative **382** afforded the protected 1-amino-2-methylenecyclopropanecarboxylic acid **383** (Scheme 44).[408] According to this method, enantiopure 2,3-methanovaline was obtained by introduction of an additional stereocenter into the *N*-phthaloyl protecting group (Scheme 44).[409]

Scheme 44. Base-induced Cyclizations of 2-Bromoethyl-substituted Protected Glycine Esters[406−409]

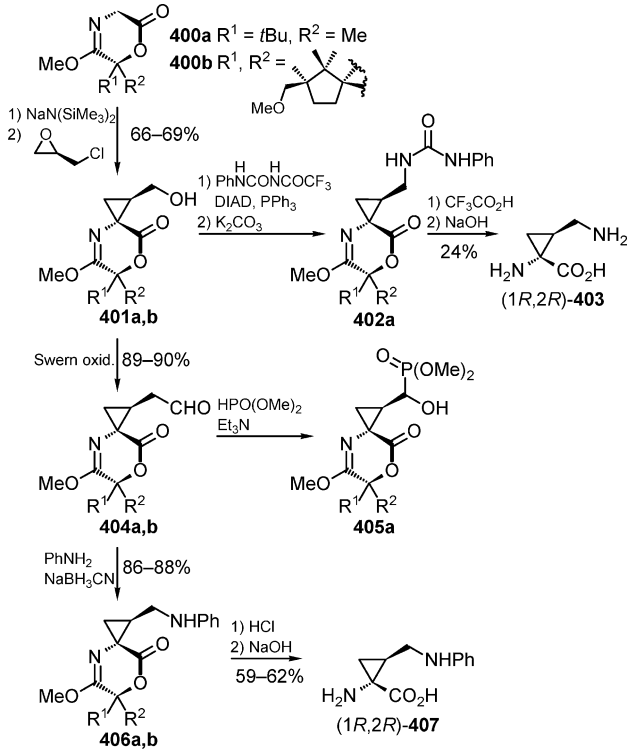


A variety of asymmetric versions for the cyclodialkylation of nucleophilic glycine equivalents have been developed. The bislactim ethers of a valine-glycine- or a *tert*-leucine-glycine-diketopiperazine were monoalkylated with *trans*-1,4-dichloro-2-butene to give the (*E*)-chlorobutenyl derivative **384**. Subsequent base-induced intramolecular alkylation furnished a mixture of four diastereomeric vinylspirocyclopropane derivatives, from which the major component with the relative configuration as depicted in **385** was isolated in pure form. Diimide reduction of the vinyl group and hydrolytic cleavage of the two lactim ether moieties yielded (1*R*,2*S*)-

Scheme 45. Asymmetric Syntheses of 2,3-Methanoamino Acids Employing Glycine Enolate Equivalents[410−416]



Scheme 46. Asymmetric Syntheses of 2,3-Methanoalanine Derivatives from Chirally Derivatized 5-Methoxy-1,4-oxazin-2-one Derivatives[418−420]



allo-coronamic acid (1*R*,2*S*)-**136** with excellent diastereoselectivity, but only moderate enantioselectivity (Scheme 45).[410]

Other suitable building blocks for a convenient route to stereodefined coronamic and norcoronamic acid turned out to be the corresponding stereodefined 3-substituted protected 2-amino-4-chlorobutyronitriles **386**−**388**. Base-induced cyclization of **386**−**388** proceeded with moderate to high diastereoselectivities to the corresponding cyclopropyl derivatives **389**. Separation of the diastereomers and final hydrolysis led to (1*S*,2*S*)-norcoronamic (1*S*,2*S*)-**139**, (1*R*,2*S*)-*allo*-coronamic acid (1*R*,2*S*)-**136**, and (1*S*,2*S*)-coronamic acid (1*S*,2*S*)-**136** with enantiomeric excesses of 88−95% (Scheme 45).[411,412]

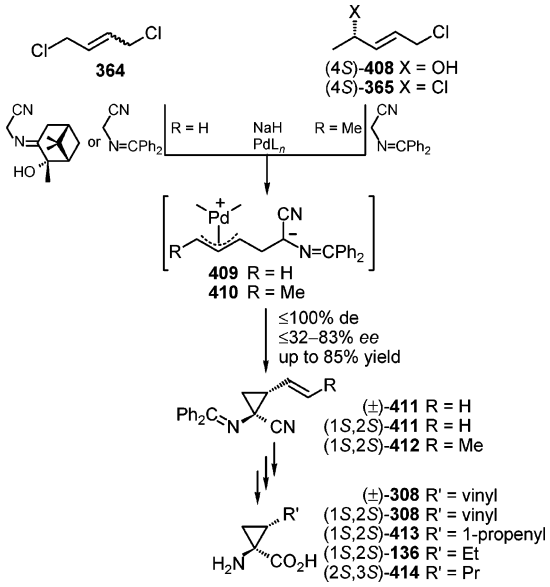
An approach to (1*S*,2*R*)-trifluoronorcoronamic acid (1*S*,2*R*)-**305** is based on a cyclization of the optically active α-amino-γ-hydroxynitrile **391**, which was prepared by reaction of (2,5-dimethylpyrrolyl)acetonitrile (**390**) as a glycine equivalent, with enantiomerically enriched (75% *ee*) trifluoromethyloxirane. A highly diastereoselective cyclization of **391** yielded the cyclopropane derivative **392**. Oxidative degradation of the pyrrole ring and hydrolysis of the cyano group gave enantiopure (1*S*,2*R*)-trifluoronorcoronamic acid (1*S*,2*R*)-**305** (Scheme 45).[413]

In analogy to the cyclodialkylation of dialkyl malonate enolates with enantiopure chiral ethylene sulfates **316** and **393**−**394**, the latter were used to prepare the protected 1-aminocyclopropanecarboxylates **395**−**397** employing cyclodialkylations of protected glycine ester enolates. In the cases of the chloroethyl- and chloropropyl-substituted derivatives **396** and **397**, respectively, the corresponding *N*-deprotected derivatives were further cyclized before final complete deprotection completed the synthesis of (−)-(2*S*,3*R*)-2,3-methanoproline [(2*S*,3*R*)-**398**] and (−)-(2*S*,3*R*)-2,3-methanopipecolic acid [(2*S*,3*R*)-**399**] (also called: 2,3-methanopiperidine-2-carboxylic acid or 2,3-methanohomoproline), respectively (Scheme 45).[414,415] Deprotection of the methyl-substituted derivative **395** furnished virtually enantiopure (−)-(1*S*,2*R*)-*allo*-norcoronamic acid.[416] In an interesting variation of this reaction sequence, the racemic methyl-substituted ethylene sulfate **316** was diastereoselectively transformed with Belokon's nickel(II) complex, an enantiomerically pure masked glycine enolate equivalent. Depending on which enantiomer of Belokon's complex was used, either the (1*S*,2*R*)- or (1*R*,2*S*)-enantiomer of *allo*-coronamic acid could be obtained.[417]

Cyclodialkylation of the chirally modified 5-methoxy-1,4-oxazin-2-one derivatives **400a**,**b** with (*R*)-epichlorohydrine furnished 2,3-methanohomoserine derivatives **401a**,**b** as single diastereomers (Scheme 46), which were either cleaved to afford (2*R*,3*R*)-2,3-methanohomoserine [(2*R*,3*R*)-**149**] (see Figure 8) or used for further transformations.[418,419] Thus, the hydroxy group in the hydroxymethyl side chain of **401a** was substituted with *N*-phenylurea to yield **402a**. All attempts to cleave off the chiral auxiliary in **402a**, leaving the *N*-phenylureylmethyl side chain still intact, only led to the (1*R*,2*R*)-1-amino-2-aminomethylcyclopropanecarboxylic acid [(1*R*,2*R*)-**403**].[419] The same chiral auxiliary in the 1-amino-2-phenylaminomethylcyclopropanecarboxylic acids **406a**,**b**, obtained by Swern oxidation of **401a**,**b** to the aldehyde **404a**,**b** and subsequent reductive amination, could also be cleaved off to furnish (1*R*,2*R*)-1-amino-2-(anilinomethyl)-cyclopropanecarboxylic acid [(1*R*,2*R*)-**407**].[418] Reaction of the aldehyde **404a** with dimethyl phosphite yielded the dimethylphosphonylhydroxymethyl-substituted cyclopropane derivative **405a**, the deprotection of which has not been reported so far (Scheme 46).[420] Some of these syntheses have also been carried out with the (*S*)-enantiomer of epichlorohydrine, providing access to 2,3-methanoamino acids with (2*R*,3*S*)- instead of (2*R*,3*R*)-configuration.

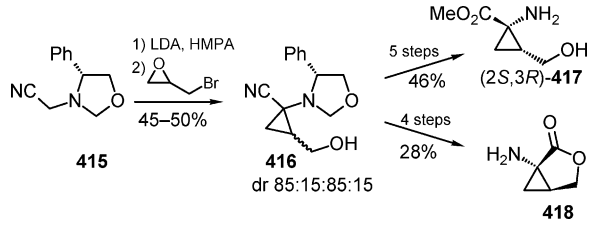
The palladium(0)-catalyzed one-pot sequential alkylation and S_N'-cyclization of (diphenylmethyleneamino)acetonitrile with 1,4-dichloro-2-butene (**364**) provided the racemic (*E*)-3-vinylcyclopropanecarbonitrile **411** diastereoselectively via the π-allylpalladium intermediate **409**.[421,422] Employing a glycine anion equivalent endowed with a pinane moiety as a chiral auxiliary led to negligible enantiomeric excesses, which were improved to 32% at best, by concomitant application of a chiral ligand for the palladium catalyst.[422−424] In contrast, an analogous conversion using (4*S*)-1-chloropent-2-en-4-ol [(4*S*)-**408**] or (4*S*)-1,4-dichloro-2-pentene [(4*S*)-**365**] as chiral starting materials stereoselectively yielded the (*E*)-configured cyclopropane derivative **412** with up to 83% enantiomeric excess.[422,425] Cyclopropyl compounds (±)-(*E*)-**411**, (1*S*,2*S*)-**411**, and (1*S*,2*S*)-**412** were successfully hydrolyzed to provide (±)-(*E*)- and (1*S*,2*S*)-vinyl- and (1*S*,2*S*)-1-propenyl-1-aminocyclopropanecarboxylic acids [(±)-(*E*)-**308**], [(1*S*,2*S*)-**308**], and [(1*S*,2*S*)-**413**]. Alternatively, the alkenyl moieties in the cyclopropane derivatives (1*S*,2*S*)-**411** and (1*S*,2*S*)-**412** were hydrogenated before hydrolysis, whereupon (1*S*,2*S*)-coronamic acid (1*S*,2*S*)-**136** and (2*S*,3*S*)-2,3-methanonorleucine [(2*S*,3*S*)-**414**] were obtained (Scheme 47).[421−425]

Scheme 47. Palladium-catalyzed One-pot Sequential Alkylation and S_N'-Cyclization in the Preparation of 2,3-Methanoamino Acids[421−425]



An interesting asymmetric synthesis of 2,3-methanohomoserine has been accomplished starting from the chirally modified aminoacetonitrile **415** as a chiral starting material (the so-called CN(*R*,*S*) method). Thus, cyclodialkylation of **415** with racemic epibromohydrine gave the aminocyclopropanecarbonitrile **416** as a mixture of two pairs of diastereomers. This mixture served as the starting material for the synthesis of enantioenriched (1*S*,2*R*)-*allo*-coronamic acid (30% *ee*).[426] Separation of this mixture led to the isolation of methyl (2*S*,3*R*)-2,3-methanohomoserinate [(2*S*,3*R*)-**417**] and the bicyclic aminobutyrolactone **418**, formed by intramolecular transesterification of the methyl ester (2*S*,3*S*)-**417**, as the major products (Scheme 48).[427,428] Lactone **418** inevitably underwent a spontaneous cyclodimerization to the corresponding diketopiperazine.[428] After Z-protection of the methyl (2*S*,3*R*)-2,3-methanohomoserinate (2*S*,3*R*)-**417**, its hydroxymethyl was further transformed into an aminomethyl group either in two steps involving a Mitsunobu reaction with phthalimide or in three steps by conversion to a chloride and subsequent nucleophilic substitution with potassium phthalimide, both followed by hydrazinolysis to the amine. Guanidinylation and final hydrolysis led to guanidinylmethyl-substituted (1*S*,2*R*)-1-aminocyclopropanecarboxylic acid (carnosadine) (**140**), in 42−45% yield starting from (2*S*,3*R*)-**417** with >99% enantiomeric excess.[429]

Scheme 48. Synthesis of (2*S*,3*R*)-Methanohomoserine According to the So-called CN(*R*,*S*) Method[426−428]

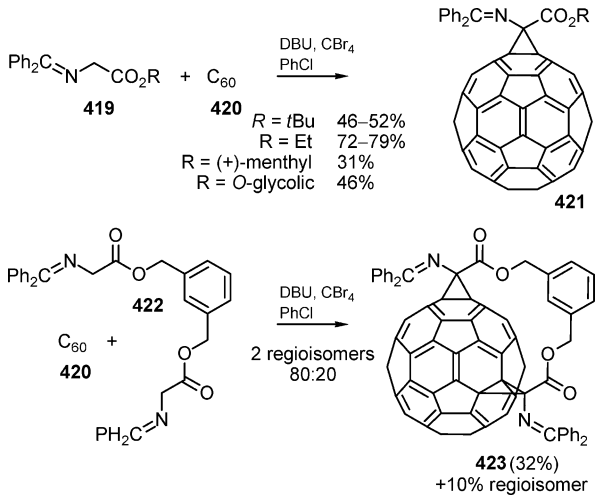


An essentially analogous transformation employing (*N*,*N*-dibenzylamino)acetonitrile as the glycine equivalent, instead of the chiral building block **415**, provided ready access to racemic (*E*)- and (*Z*)-2,3-methanohomoserine.[430]

The reaction of the protected glycine derivatives **419** with [60]fullerene **420** furnished the fullerene derivatives **421** fused with a 1-aminocyclopropanecarboxylic acid moiety (Scheme 49). Whereas all attempts to hydrolyze the derivatives to the free amino acid failed, the cyclopropane ring in **421** could successfully be opened, providing access to 1,2-dihydro[60]fullerylglycine derivatives.[431,432] The bisglycine derivative **422** with a *meta*-disubstituted benzene core was used to create a tethered biscyclopropanation product from [60]fullerene to give predominantly the *trans*-regioisomer **423** besides a minor amount of a *cis*-regioisomer (Scheme 49). In contrast, an analogous biscyclopropanation of C_{60} with the *ortho*-isomer of **422** afforded only two *trans*-regioisomers of the corresponding bis-(aminocylopropanecarboxylate)-annelated [60]fullerene.[432,433] As observed for the attempted deprotection of **421**, hydrolysis of the bifunctional [60]fullerene-annelated aminocyclopropanecarboxylic acid derivatives **421** and **423** also failed. Instead, the cyclopropane ring could only successfully be opened, giving access to 1,2-dihydro[60]fullerylglycine derivatives.[431,432,434]

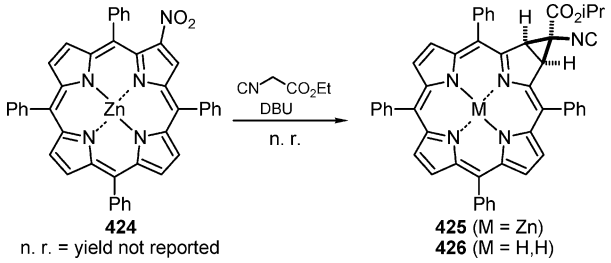
When (2-nitro-5,10,15,20-tetraphenylporphyrinato)zinc(II) **424** was submitted to a Barton−Zard synthesis with ethyl

Scheme 49. Syntheses of [60]Fullerene-annelated 1-Aminocyclopropanecarboxylic Acid Derivatives[431−434]



cyanoacetate as a protected glycine equivalent, the pyrroloporphyrin **425** fused with a cyclopropane ring was obtained, and this was further transformed into the metal-free compound **426** (Scheme 50).[435]

Scheme 50. Synthesis of a Pyrroloporphyrine Fused with a Protected 1-Aminocyclopropanecarboxylic Acid Moiety[435]

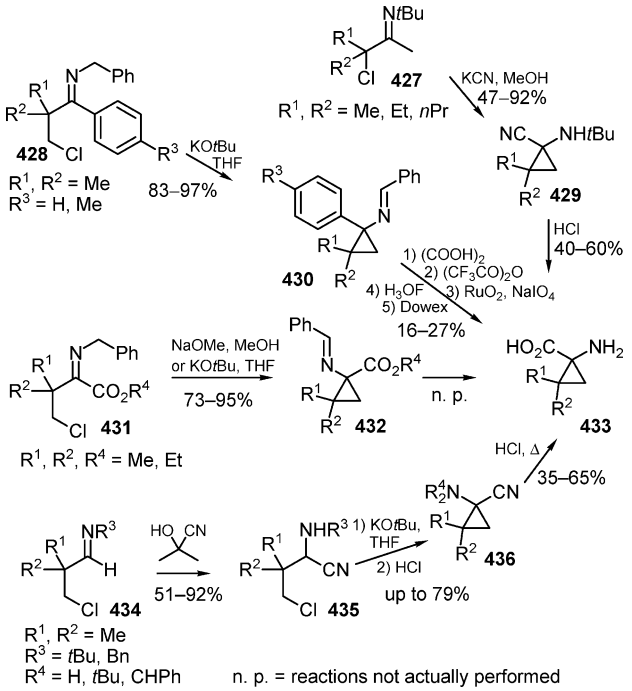


3.2.5. Other Syntheses

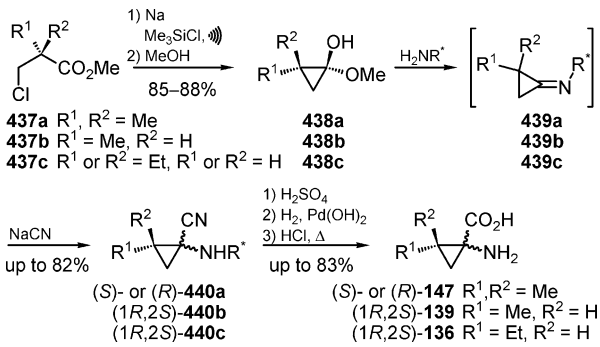
An interesting route to racemic geminally disubstituted 1-aminocyclopropanecarboxylic acids was developed starting from differently substituted chloroimines. Thus, treatment of a dialkyl-substituted α-chloroimine of type **427** with potassium cyanide in methanol led to γ-dehydrochlorination—corresponding to the first step of a Favorski rearrangement of an α-haloketone—with subsequent addition of cyanide to the resulting cyclopropanoneimine to afford the 1-aminocyclopropanecarbonitriles **429**. The latter could be hydrolyzed to the corresponding free amino acids **433**; however, depending on the bulkiness of the alkyl substituents, side reactions such as opening of the cyclopropane ring occurred.[436,437] An alternative synthesis was developed starting from the β-chloroimine **428**, which, by treatment with potassium *tert*-butoxide in tetrahydrofuran, was transformed into 1-aryl-*N*-benzylidenecyclopropylamines **430**. Oxidative degradation of the aromatic ring provided the carboxylic acid function, and final deprotection by simple hydrolysis also led to the geminally disubstituted aminocyclopropanecarboxylic acids **433**.[438,439] In order to shorten the synthetic route, the β-chloroimines **431** endowed with an alkoxycarbonyl substituent were used as starting materials. Their base-induced rearrangement and γ-dehydrochlorination directly led to *N*-benzylidene-1-aminocyclopropanecarboxylic acids **432**, which would easily be convertible to **433** in their free form (Scheme 51).[440] In an interesting variation of this method, β-chloroimines **434** were converted in a Strecker-type reaction to the corresponding α-amino-γ-chlorobutyronitriles **435**, which were, either directly (R = *t*Bu) or after further transformation into an imine (R = CHPh), submitted to a base-induced cyclization to provide **436** before final hydrolysis to **433** (Scheme 51). As compounds **435** also represent glycine anion equivalents, this reaction sequence can also be regarded as a synthesis of 2,2-dialkylcyclopropanecarboxylic acids by cyclodialkylation of a nucleophilic glycine equivalent (see section 3.2.4).[441,442]

2,2-Dimethylcyclopropanone methyl hemiacetal (**438a**), obtained by sodium-induced cyclization of methyl 3-chloro-2,2-dimethylpropionate (**437a**) in the presence of chlorotrimethylsilane under ultrasonication with subsequent methanolysis, has been employed in Strecker reactions with chirally derivatized amines. Depending on the chiral constitution of the amine used, the aminonitriles (*S*)-**440a** or (*R*)-**440a**, formed via the intermediate imines **439a**, were successfully transformed into highly enantioriched (*R*)- or (*S*)-2,3-methanovaline (**147**) (Scheme 52).[443] According to the same procedure, the enantiopure methyl 3-chloro-2-methylpropionate (**437b**) was transformed to the 2-methylcyclopropanone methyl hemiacetal (**438b**)[122,123] and, further, to the aminonitrile (1*R*,2*S*)-**440b**, which furnished the highly enantioenriched (+)-(1*R*,2*S*)-*allo*-norcoronamic acid (1*R*,2*S*)-**139** (Scheme 52).[443]

Scheme 51. Syntheses of Racemic 1-Amino-2,2-dialkylcyclopropanecarboxylic Acids from α- and β-Chloroimines as well as γ-Chloro-α-aminonitriles and -carboxylic Acid Esters[436−442]



Scheme 52. Syntheses of 2-Substituted 2,3-Methanoalanines by Diastereoselective Strecker Reactions of Alkylcyclopropanones in Situ Generated from their Hemiacetals[443,444]

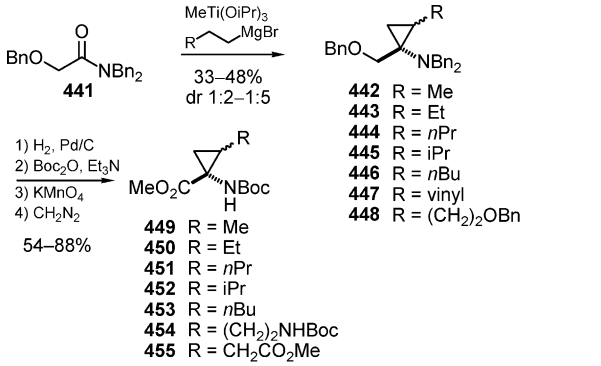


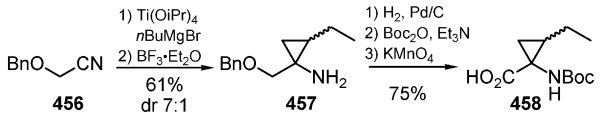
Employing the racemic 2-methyl- and 2-ethylcyclopropanone hemiacetals **438b** and **438c** in a Strecker reaction with chirally derivatized amines led to separable mixtures of diastereomers, which were successfully converted into virtually enantiopure (1*R*,2*S*)- and (1*S*,2*R*)-*allo*-norcoronamic acid **139** and (1*R*,2*S*)- and (1*S*,2*R*)-*allo*-coronamic acid **136**.[444]

The titanium-mediated reductive cyclopropanation of *N*,*N*-dialkylcarboxamides with alkylmagnesium halides provides ready access to a great variety of cyclopropylamines. Thus, transformation of *N*,*N*-dibenzyl-2-benzyloxyacetamide (**441**) with the correspondingly substituted ethylmagnesium bromides furnished 2-alkyl-, 2-vinyl-, and 2-(2-benzyloxyethyl)-

substituted cyclopropylamines **442**−**448**, albeit in only moderate yields and with rather low diastereomeric excesses of only 1:2 to 1:5. Subsequent debenzylation, *N*-reprotection, and oxidation of the hydroxymethyl group in the alkyl-substituted derivatives **442**−**446** gave the protected norcoronamic acid **449**, coronamic acid **450**, 2,3-methanonorleucine **451**, 2,3-methanoleucine **452**, and 1-amino-2-butylcyclopropane-1-carboxylic **453**, respectively. The vinyl-substituted derivative **447** was further transformed to the corresponding aminoethyl-substituted derivative before it was converted to the protected 2,3-methanoornithine **454**. The benzyloxyethyl-substituted derivative **448** was transformed into the 2,3-methanoglutamic acid derivative **455** in a sequence of debenzylation, reprotection, and oxidation (Scheme 53).[129]

Scheme 53. Syntheses of Diastereomeric Mixtures of Various 2-Substituted of 2,3-Methanoamino Acid Derivatives Applying the Titanium-mediated Reductive Cyclopropanation of *N*,*N*-Dibenzyl-2-benzyloxyacetamide and Benzyloxyacetonitrile[129,130]



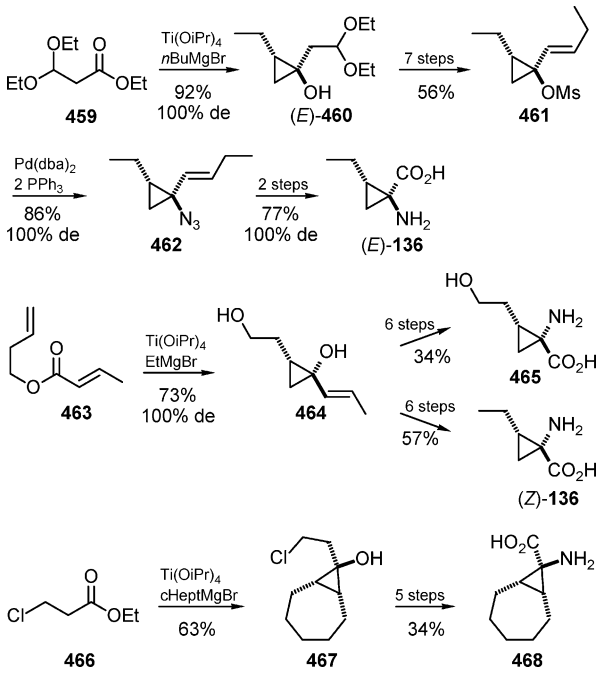


The analogous titanium-mediated reductive cyclopropanation of benzyloxyacetonitrile (**456**) with *n*-butylmagnesium bromide furnished 2-ethyl-1-benzyloxymethylcyclopropylamine (**457**) as a mixture of diastereomers. Protection of the amino group, debenzylation, and final oxidation yielded the protected coronamic acid **458** (Scheme 53).[130]

In contrast to the titanium-mediated cyclopropanation of the carboxamide **441** and the nitrile **456**, the titanium-catalyzed reductive cyclopropanation of ethyl 3,3-diethoxypropanoate **459** with *n*-butylmagnesium bromide proceeded with excellent diastereoselectivity, furnishing the (*E*)-1,2-disubstituted cyclopropanol **460**. The latter, in a seven-step sequence, was stereoselectively transformed into the 1-(1-butenyl)-2-ethylcyclopropyl mesylate (**461**), which, upon palladium(0)-catalyzed retentive substitution with azide, afforded the (*E*)-1,2-disubstituted cyclopropyl azide **462**. Reduction of the azido group and oxidative cleavage of the alkenyl substituent provided (*E*)-coronamic acid **136** (Scheme 54).[445]

A titanium-mediated intramolecular cyclopropanation, initiated with ethylmagnesium bromide, of the butenyl double bond in 3-butenyl (2*E*)-butenoate (**463**) led exclusively to the (*Z*)-isomer of 2-hydroxyethyl-1-(*E*)-propenylcyclopropanol (**464**), which was submitted to palladium(0)-catalyzed azidation followed by reduction and oxidative cleavage of the alkenyl substituent to yield (*Z*)-5-hydroxy-2,3-methanonorvaline [(*Z*)-**465**]. Alternatively, the hydroxyethyl was first transformed into an ethyl substituent and the product then converted to *allo*-coronamic acid (*Z*)-**136** (Scheme 54).[446,447]

Scheme 54. Syntheses of Racemic Substituted 1-Aminocyclopropanecarboxylic Acids Applying the Titanium-mediated Reductive Cyclopropanation of Carboxylic Acid Esters[445−448]



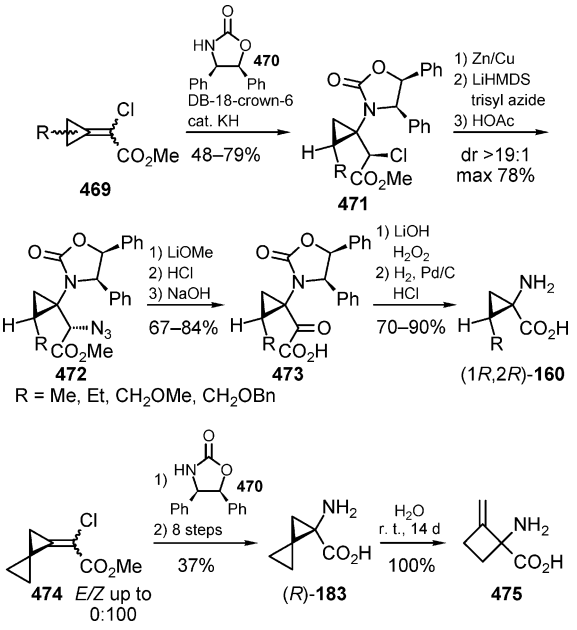
Titanium tetraisopropoxide-catalyzed reductive cyclopropanation of ethyl 3-chloropropanoate (**466**) with cycloheptylmagnesium bromide gave the bicyclic chloroethylcyclopropanol **467** with an *exo*-positioned hydroxy group. Tosylation of the latter and dehydrochlorination furnished a bicyclic vinylcyclopropyl tosylate, which was further transformed as described for **461** and **464**, respectively, into 8-*exo*-aminobicyclo[5.1.0]octane-8-carboxylic acid (**468**) (Scheme 54).[448]

Several enantiomerically pure 2-substituted 1-aminocyclopropanecarboxylic acids have been prepared, starting with an addition of chiral (4*S*,5*R*)-4,5-diphenyloxazolidin-2-one (**470**) to methyl 2-chloro-2-cyclopropylideneacetates **469**, as highly reactive Michael acceptors, yielding the adducts **471** with excellent *trans*-diastereoselectivity. Subsequent reductive dehalogenation, enolization, and electrophilic azidation furnished the α-azidoesters **472**, which were further converted into the corresponding iminoesters, and these in turn were hydrolyzed to the ketoacids **473**. Oxidative decarboxylation and removal of the chiral auxiliary by catalytic hydrogenation furnished (2*R*,3*R*)-2,3-methanoamino acids in their free forms **160** (Scheme 55).[449]

An analogous transformation of methyl 2-chloro-2-spiropentylideneacetate (**474**) provided (*R*)-1-aminospiropentanecarboxylic acid (**183**). The latter turned out to slowly isomerize to 1-amino-2-methylenecyclobutanecarboxylic acid (**475**) upon standing in aqueous solution at ambient temperature (Scheme 55).[324]

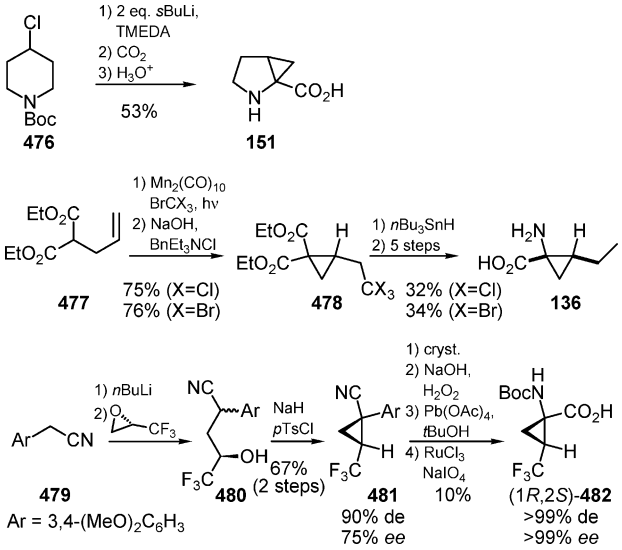
α-Deprotonation of *N*-*tert*-butoxycarbonyl-protected 4-chloropiperidine **476** with *sec*-butyllithium in the presence of tetramethylethylenediamine (TMEDA) was succeeded by an intramolecular nucleophilic displacement with cyclization and α-deprotonation again. The thus formed cyclopropyllithium

Scheme 55. Syntheses of 2-Substituted (1*R*,2*R*)-1-Aminocyclopropanecarboxylic Acids Employing Enantiomerically Pure Michael Donors[324,449]



derivative could be trapped with a variety of electrophiles, including carbon dioxide. Treatment of the product from the latter with acid provided racemic 2,3-methanoproline (**151**) in its free form (Scheme 56).[450]

Scheme 56. Miscellaneous Preparations of 2-Substituted 1-Aminocyclopropanecarboxylic Acid Derivatives[413,450,451]



Irradiation of decacarbonyldimanganese in the presence of carbon tetrabromide or bromotrichloromethane and diethyl allylmalonate (**477**) followed by addition of base gave 2-(2,2,2-trihaloethyl)cyclopropane-1,1-dicarboxylate **478** as a 1:1 mixture of diastereomers. Reductive dehalogenation of **478** with tributyltin hydride afforded diethyl 2-ethylcyclopropane-1,1-dicarboxylate, which was further transformed into coronamic acid **136** by hydrolysis to the half ester, Curtius degradation, and final hydrolysis. The overall yield of this rather short approach to racemic coronamic acid **136** was 27−28% (Scheme 56).[451]

An enantioselective synthesis of (1*R*,2*S*)-trifluoronorcoronamic acid started with the reaction of (3,4-dimethoxyphenyl)acetonitrile (**479**) in the presence of *n*-butyllithium with enantioenriched trifluoromethyloxirane (75% *ee*), furnishing 2-(dimethoxyphenyl)-4-hydroxy-(trifluoromethyl)butyronitrile (**480**), which cyclized to the cyclopropane derivative **481** in the presence of acid. Partial hydrolysis of the cyano group and Hofmann degradation of the resulting amide followed by oxidative degradation of the 3,4-dimethoxyphenyl group gave virtually enantiomerically pure *N*-Boc-protected (1*R*,2*S*)-trifluoronorcoronamic acid (1*R*,2*S*)-**482** (Scheme 56).[413]

Scheme 57. Inter- and Intramolecular Cyclopropanation of Alkenes with Fischer (1-Alkoxycarbonyl-1-dialkylamino)carbenechromium Complexes Leading to 1-Aminocyclopropanecarboxylic Acid Derivatives (for Details See Table 8)[452]

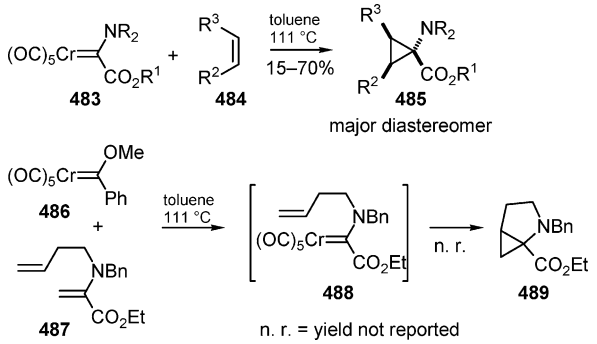
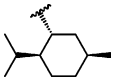


Table 8. 1-Aminocyclopropanecarboxylic Acid Derivatives 485 Obtained by Intermolecular Cyclopropanation of Alkenes with Fischer Dialkylaminocarbene Complexes 483 (See Scheme 57)[452]

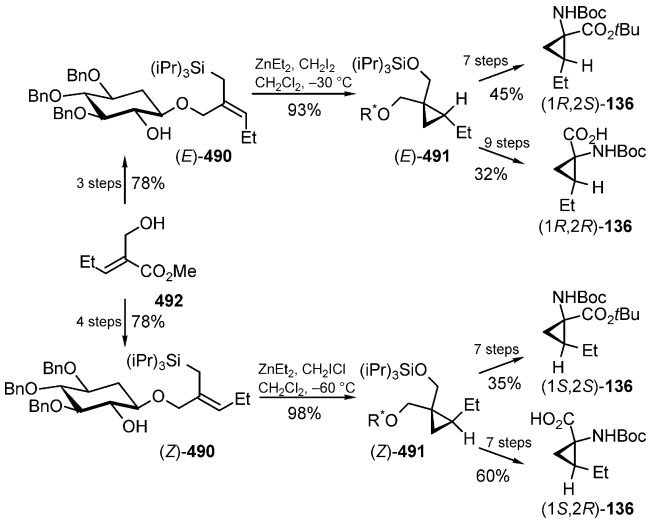
entry	NR_2	R^1	R^2	R^3	de (%)	yield (%)
1	NMe_2	*t*Bu	Ph	H	>95	47
2	NMe_2	*t*Bu	Hex	H	>95	70
3	NMe_2	*t*Bu	CH_2OSiMe_2tBu	H	0	45
4	NMe_2	*t*Bu		H	30	30
5	NBn_2	Me	Ph	H	>95	35
6	morph	Me	Ph	H	>95	70
7	morph	Me		H	>95	69
8	morph	Me	$-(CH_2)_5-$		43	15
9	NMe_2		Ph	H	33[a]	45

[a] In this case, the diastereomeric excess relates to the enantiomeric excess of the (1*R*,2*R*)- over the (1*R*,2*S*)-configured product **485**.

Terminal and (*Z*)-configured internal alkenes undergo cyclopropanation upon reaction with Fischer (1-alkoxycarbonyl-1-dialkylamino)carbenechromium complexes **483**, to provide 1-aminocyclopropanecarboxylic acid derivatives **485** in a single step and, in most cases, with high diastereoselectivity (Scheme 57 and Table 8). The reaction tolerates aryl, alkyl, and nonconjugated alkenyl substituents (Table 8, entries 1−7), but the yield drops drastically when a cyclic alkene such as cycloheptene is employed (entry 8), and trisubstituted double bonds are not cyclopropanated at all under these conditions. Enantiomerically enriched 1-aminocyclopropanecarboxylic acids could also be prepared by employing (−)-menthol esters; however, the diastereomeric excess was only 33% at best (entry 9). A metathesis reaction between the carbene complex **486** and the α,β-didehydroamino acid **487** did not lead to an isolable carbene complex **488**, but directly to the protected 2,3-methanopipecolic acid **489** (2,3-methanopiperidine-2-carboxylic acid, 2,3-metha-

nohomoproline), arising from the intramolecular cyclopropanation of the intermediately formed **488** (Scheme 57).[452]

Scheme 58. Stereocontrolled Syntheses of All Four Stereoisomers of Coronamic Acid by Stereoselective Cyclopropanation of 2-Propylidenepropane-1,3-diol Derivatives with a D-Glucose-derived Chiral Auxiliary[453]

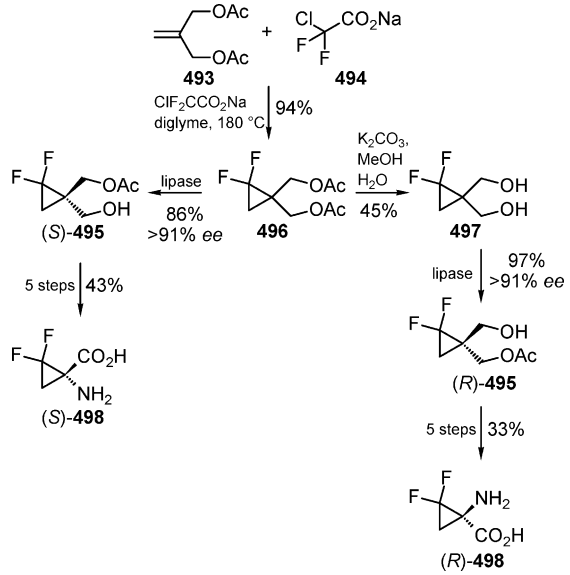


All four stereoisomers of coronamic acid have been prepared by stereoselective cyclopropanation of the 2-propylidenepropane-1,3-diol derivatives (*E*)-**490** and (*Z*)-**490**, bearing a D-glucose-derived chiral auxiliary, and subsequent transformations into both enantiomers of *allo*-coronamic acid (1*R*,2*S*)-**136** and (1*S*,2*R*)-**136** as well as coronamic acid (1*S*,2*S*)-**136** and (1*R*,2*R*)-**136** (Scheme 58).[453] Since other alkyl-substituted allyl alcohols of type **490** were made available,[454,455] this method has been claimed to offer a general approach to all four stereoisomers of various 2,3-methanoamino acids.

Stereocontrolled syntheses of both enantiomers of 1-amino-2,2-difluorocyclopropanecarboxylic acid were accomplished starting with the addition of difluorocarbene, generated from sodium chlorodifluoroacetate (**494**), to 2-methylenepropane-1,3-diol diacetate (**493**), furnishing the prochiral diacetate **496**. Deacetylation of **496** catalyzed by a lipase from *Pseudomonas cepacia* was found to produce the monoacetate (*S*)-**495** with >91% enantiomeric excess. Jones oxidation of the hydroxymethyl group in (*S*)-**495**, subsequent Curtius degradation of the thus generated carboxyl group, hydrolysis of the remaining acetate, a second Jones oxidation, and liberation of the amino group yielded (*S*)-1-amino-2,2-difluorocyclopropanecarboxylic acid [(*S*)-**498**] (Scheme 59). Alternatively, the diacetate **496** was hydrolyzed to the prochiral diol **497**, which was kinetically resolved by lipase-(from *Pseudomonas cepacia*) catalyzed monoacetylation with vinyl acetate to furnish (*R*)-**495** with >91% enantiomeric excess. From the latter, (*R*)-1-amino-2,2-difluorocyclopropanecarboxylic acid [(*R*)-**498**] was obtained following the same sequence as applied for (*S*)-**498** (Scheme 59).[456]

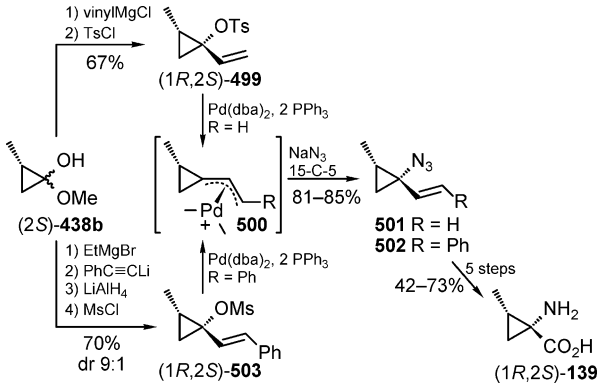
A diastereomeric mixture of 2-methylcyclopropanone methyl hemiacetal [(2*S*)-**438b**], easily available from methyl (2*S*)-3-hydroxy-2-methylpropionate,[123] furnished, upon treatment with vinylmagnesium chloride and subsequent tosylation, (1*R*,2*S*)-2-methyl-1-vinylcyclopropyl tosylate [(1*R*,2*S*)-**499**] as a single enantiomer. Likewise, addition of ethylmagnesium bromide and lithium phenylacetylide to (2*S*)-**438b**, subsequent reduction with lithiumaluminum hydride, and

Scheme 59. Enantioselective Synthesis of (*R*)- and (*S*)-1-Amino-2,2-difluorocyclopropane-1-carboxylic Acid Employing Lipase-catalyzed Desymmetrization of Prochiral Cyclopropane Precursors[457]



mesylation yielded the phenylethenyl-substituted analogue (1*R*,2*S*)-**503** as a 9:1 mixture of diastereomers. Palladium(0)-catalyzed azidation of (1*R*,2*S*)-**499** and (1*R*,2*S*)-**503** via the π-allylpalladium intermediate **500** gave either a single azide (1*R*,2*S*)-**501** or a 96:4 mixture of diastereomeric azides (1*R*,2*S*)-**502** and (1*S*,2*S*)-**502**. Reduction of azides **501** and **502** to the corresponding amines, protection of the respective amino group, oxidative degradation of the vinyl or phenylethenyl substituent, respectively, and *N*-deprotection led to (−)-(1*R*,2*S*)-*allo*-norcoronamic acid (1*R*,2*S*)-**139** with >99% enantiomeric excess (Scheme 60).[458]

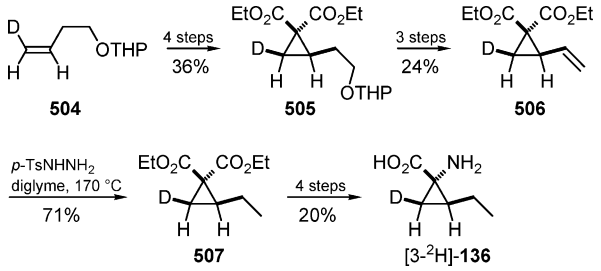
Scheme 60. Synthesis of (1*R*,2*S*)-*allo*-Norcoronamic Acid Employing Palladium(0)-catalyzed Azidation of 1-Alkenylcyclopropyl Sulfonates as a Key Step[458]



A synthesis of 2,3-methanoaspartic acid by base-induced cyclization of dimethyl 2,4-dibromoglutarate with subsequent aminolysis and hydrolysis was reported,[459] but later this was announced to be an error, as 2,3-methanoaspartic acid in its free form turned out to be unstable, probably due to facile ring opening of the donor−acceptor-substituted cyclopropane ring.[457]

A synthesis of racemic 3-deuteriocoronamic acid ([3-^{2}H]-**136**) was achieved starting from the protected 3-deuterio-3-butene-1-ol **504**, obtained by catalytic hydrogenation of the corresponding terminally deuterated alkyne. Thus, a

Scheme 61. Synthesis of 3-Deuteriocoronamic Acid[133]



sulfur-mediated cyclopropanation of **504** with dimethyl disulfide, sulfuryl chloride, and diethyl malonate enolate diastereoselectively gave diethyl 2-(2-tetrahydropyranyloxyethyl)-3-deuteriocyclopropane-1,1-dicarboxylate (**505**). Elimination via an *o*-nitrophenylselenenyl oxide gave the vinyl-substituted derivative **506**, which was subsequently reduced with in situ formed diimide to diethyl 2-ethylcyclopropane-1,1-dicarboxylate (**507**). The latter was further converted by monohydrolysis, Hofmann degradation of the half ester, and removal of the protecting groups into racemic 3-deuteriocoronamic acid ([3-^{2}H]-**136**) (Scheme 61).[133]

3.3. Biological Activities of Substituted 2,3-Methanoamino Acids

Numerous substituted 2,3-methanoamino acids exihibit interesting pharmacological activities. The hydrochloride of 1-acetylimidazolyl-2,3-methanoamino acid (**508**) was found to be an inhibitor of histidine decarboxylase.[271] The 4-(dibromo-4-hydroxyphenoxy)-3,5-diiodophenyl derivative (*E*)-**509** was assayed upon its thyromimetic activity; however, it was found to exhibit only very weak biological activity (approximately 1% of that of thyroxine itself) (Figure 9).[282]

All four stereoisomers of 2,3-methano-*m*-tyrosine (**268**) were shown to be potent 3,4-dihydroxyphenylalanine (DOPA) decarboxylase inhibitors. The (2*R*,3*S*)-isomer turned out to be the most potent one, exhibiting a 45-fold greater inhibition than D-*m*-tyrosine itself.[366] Several substituted (*E*)-phenyl-2,3-methanoamino acids were studied with respect to the kinetics of their interaction with pig kidney DOPA decarboxylase. Among the tested compounds, the (*E*)-3- and (*E*)-4-hydroxy-substituted compounds as well as the (*E*)-3-hydroxy-4-methoxy- and the (*E*)-1-amino-2-(4-hydroxy-3-methoxyphenyl)cyclopropanecarboxylic acids (*E*)-**268** and (*E*)-**510**−(*E*)-**512** (Figure 9) inhibited the enzyme, with an essentially reversible character.[460] Besides, numerous substituted 2,3-methano-3-arylamino acids in their racemic forms were considered to influence the central nervous system and have been found to be useful as ataraxics, antidepressants, and hypotensive agents.[461,462]

Racemic oxazolinone-protected geminally diphenyl-substituted (*E*)-2,3-methanoamino acids (*E*)-**513**−(*E*)-**516** have emerged as potent antibacterials (Figure 9).[303,304]

The racemic (*Z*)-2,3-methanoglutamic acid derivative **517** was utilized in an assay of vitamin K-dependent carboxylase activity. Although **517** turned out to be neither a substrate for, nor an inhibtor of, vitamin K-dependent carboxylase, new insights into the mechanism of carboxylase action were gained (Figure 9).[295]

Racemic 2-phosphonoethyl-substituted 2,3-methanoamino acids (*E*)- and (*Z*)-**174** (Figure 9) were tested with respect to their possible activity as competitive antagonists for the *N*-methyl-D-aspartate (NMDA) receptor; however, they exhibited only weak potency.[322] Racemic (*E*)- and (*Z*)-2-phosphonoethyl-substituted 2,3-methanoamino acids (*E*)- and (*Z*)-**174** were evaluated with respect to their capabilities to block evoked synaptic transmission in specific neuronal pathways of the rat hippocampal slice. Whereas (*E*)- and (*Z*)-**174** were equipotent in the lateral perforant path (LPP), (*E*)-**174** turned out to be much more potent than (*Z*)-**174** in

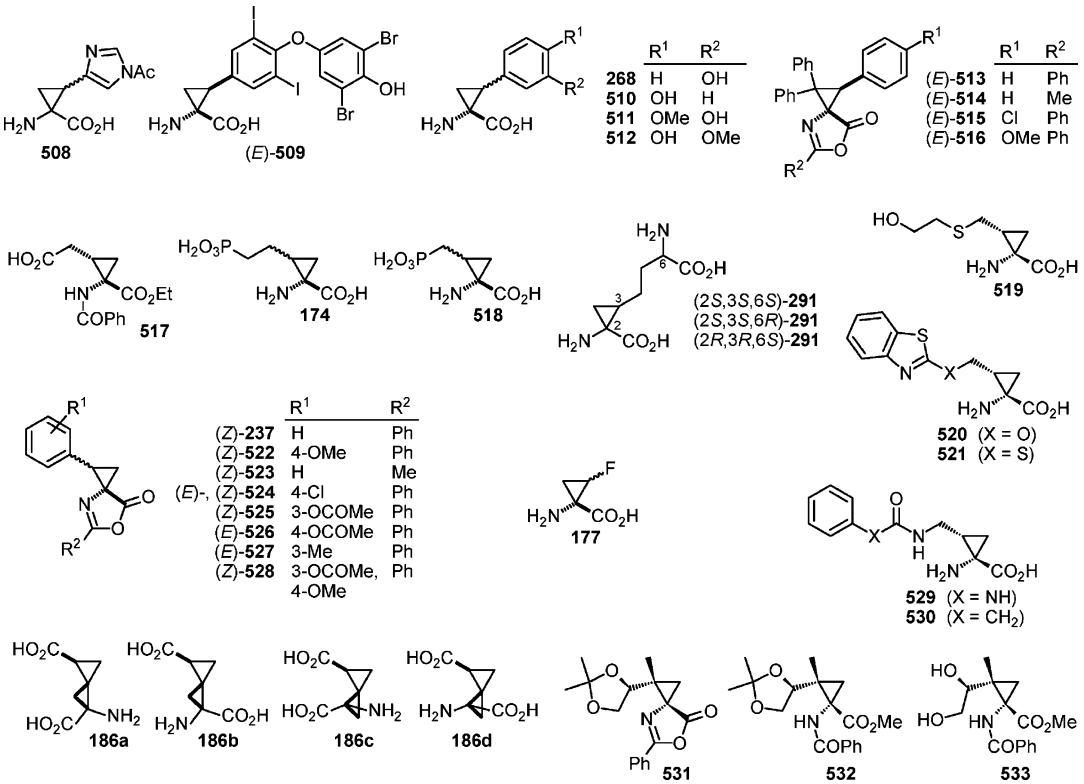


Figure 9. Biologically active substituted 2,3-methanoamino acids.[142,154,271,282,295,322,323,325,349,379,460−462,464]

the medial perforant path (MPP). From these results it could be concluded that the bioactive conformation of the selective glutamate receptor ligand 2-amino-4-phosphonobutanoic acid (AP4) in the LPP is the extended form.[299] Racemic 2-phosphonomethyl-substituted 2,3-methanoamino acids (*E*)- and (*Z*)-**518** were found to exhibit agonist properties toward metabotropic glutamate receptors of type 4a, with (*Z*)-**518** being the more potent one.[463]

Racemic oxazolinone-protected 2-phenyl-2,3-methanoalanines (*Z*)-**237**, (*Z*)-**522**, and (*Z*)-**523** (Figure 9) have been shown to act as submicromolar inhibitors of viruses of the *Herpes viridae* family, such as herpex simplex (HSV) protease and human cytomegalovirus (HCMV) protease. Switching from (*Z*)-**237** to the (*E*)-**237** led to a loss of inhibitory potency for the HSV-2 protease.[142]

Three stereoisomeric 2,3-methano-2,6-diaminopimelic acids [(2*S*,3*S*,6*S*)-**291**], [(2*S*,3*S*,6*R*)-**291**], and [(2*R*,3*R*,6*S*)-**291**] (Figure 9) were synthesized as potential antibacterials applicable as herbicides. While they did not exhibit any antibacterial properties, they were able to mimic 2,6-diaminopimelic acid (DAP) and act as substrates for the DAP-adding enzyme.[379] Racemic 2-fluoro-2,3-methanoamino acids [(*E*)-**177**] and [(*Z*)-**177**] (Figure 9) showed activities comparable to that of the parent 1-aminocyclopropanecarboxylic acid (ACC) at the NMDA receptor.[323] Likewise, compounds (1*S*,2*R*)-**519**−**521**, **529**, and **530** (Figure 9) were examined with respect to their agonist or antagonist activity on the NMDA receptor complex. Whereas 2,3-methanoamino acids (1*S*,2*R*)-**520**, **521**, **529**, and **530** turned out to be ineffective, compound (1*S*,2*R*)-**519** exhibited remarkable activity.[154]

Among a series of various differently substituted spirocyclopropane compounds, oxazolinone-protected 2,3-methano-3-arylamino acids (*E*)- and (*Z*)-**524**, (*Z*)-**525**, (*E*)-**526**, (*E*)-**527**, and (*Z*)-**528** (Figure 9) were evaluated as new antiviral drugs for application as human immunodeficiency virus (HIV) inhibitors. Among these representatives, only compound (*Z*)-**528** showed moderate inhibitory activity in the replication of HIV-1.[464]

All four diastereomers of 1-aminospiropentane-1,4-dicarboxylic acid **186a**−**d** (Figure 9) were tested in a variety of glutamergic receptor assays. A moderate affinity to the NMDA receptor could be observed for compounds **186a** and **186d**, whereas no activity at metabotropic receptors was detected.[325]

The enantiopure compounds **531**−**533** (Figure 9) were evaluated with respect to their cytostatic activity against malignant tumor cell lines. The spirocyclopropanated oxazolinone **531** exhibited the most pronounced antiproliferative activity against murine leukemia and human T-lymphocyte cells. None of the compounds showed appreciable antiviral activity at subtoxic concentrations, except for some very light activity of **531** against cytomegalovirus.[349]

3.4. Applications of Substituted 2,3-Methanoamino Acids in Peptide Synthesis

Numerous substituted 2,3-methanoamino acids have been incorporated into a variety of peptides in order to constrain their conformations by way of the small ϕ- and ψ-torsional angles associated with 2,3-methanoamino acids. In the nomenclature used by peptide chemists, 2,3-methanoamino acids are denoted as $\triangledown^E$AA or $\triangledown^Z$AA, respectively, in which $\triangledown$ is used to symbolize "cyclopropyl" and the superscript indicates the relative configuration on the cyclopropane ring with respect to the amino group. Substituted 2,3-methanoamino acids have usually been incorporated into peptides employing standard peptide coupling techniques. A notable exception is the coupling of (*Z*)-2,3-methano-3-phenylalanine with glycine by a self-regulating redox process using diphenyl diselenide[179,180] or the stereo- as well as chemoselective hydrolysis of compounds **196** and **199** (see Scheme 22) to dipeptides consisting of a 2,3-methano-3-phenylalanine residue and proline or valine, respectively.[329,331]

The first synthesized peptides containing a substituted 2,3-methanoamino acid were enkephalin analogues **534**, with a 2,3-methanophenylalanine ($\triangledown$Phe) residue in position four. In this context, it was shown that the enkephalin analogue **534a**, assembled with a racemic mixture of (*E*)-2,3-methanophenylalanine, had a highly deleterious effect on the ability of the peptide to inhibit muscle contraction, presumably evoked by the (*E*)-configuration of the 1-aminocyclopropanecarboxylic acid moiety.[465] Correspondingly, strong binding affinities were only verified for the peptides **534b** with a (*Z*)-2,3-methanophenylalanine residue,[466] whereas the peptides **534** turned out to be completely inactive in biological assays.[466,467] In contrast, only the (2*R*,3*S*)-isomer of the (*E*)-2,3-methanophenylalanine-enkephalin analogue was found to interact as an antagonist with the δ-receptor in rat brain and, as such, apparently is able to distinguish between the δ-receptors in the central and the peripheral nervous systems, indicating that they are structurally different.[467] The physical properties of all four stereoisomers of **534** were examined, but no correlation between CD spectra and bioactivity could be made.[466] In this context, the absolute configuration of the (+)-$\triangledown^E$Phe moiety was elucidated as being 2*R*,3*S* by X-ray crystallography on the dipeptide (+)-**536** (Figure 10).[468]

With the intention to synthesize salty tasting compounds capable of being substituted for sodium or potassium chloride in baked or cooked food for patients with chronic hypertension or diabetes, the dipeptide **539** consisting of 2,3-methanoornithine and taurine (2-aminoethanesulfonic acid) was prepared (Figure 10).[469]

Intensive research in the area of ester peptides of aminocyclopropanecarboxylic acid as potential dipeptide sweeteners led to the synthesis of all four diastereomers of methyl L-aspartyl-2,3-methanophenylalaninates **535** (Figure 10). In contrast to the corresponding 1-aminocyclopropanecarboxylic acid esters **112** (see section 2.6, Figure 4), all of the four stereoisomers turned out to be tasteless, apparently because of the rigid positioning of the phenyl group incompatible with the aspartam receptor.[470] With the intention to gain further insight into the structure of the aspartam receptor, methyl L-aspartyl-2,3-methanoprolinate **537** was prepared and studied with respect to its conformations. Peptide **537**, independent of the enantiomer of its $\triangledown$Pro residue, had a bitter taste with no indication of sweetness.[471]

Pyroglutamic acid (Glp) is present at the *N*-terminus of the endocrine- and CNS-active thyrotropin releasing hormone (TRH). In order to influence the bioactivity profiles, the scissile Glp-histamine amide bond in TRH was stabilized by replacement of Glp with (*Z*)-2,3-methanopyroglutamic acid. The obtained peptide **540** was conformationally examined, and enzymatic degradation studies showed a sig-

nificantly higher stability of **540** toward pyroglutamate aminopeptidase compared to that of TRH itself (Figure 10).[472]

Chymotrypsin-like proteases have been detected in cancer cells. Inhibitors of chymotrypsin were found to act as an anticarcinogen. With the aim to synthesize new highly specific enzyme inhibitors, dipeptides **541** and **542** containing an (*E*)-2,3-methanophenylalanine residue were conceived. Independent of the incorporated enantiomer of the ∇^EPhe residue, dipeptides **541** and **542** were found to be resistant against chymotrypsin-evoked hydrolysis. Likewise, all compounds were able to inhibit chymotrypsin-induced hydrolysis of ethyl *N*-acetyltyrosinate in a competitive manner, while **541**, having incorporated the (2*R*,3*S*)-enantiomer of 2,3-methanophenylalanine, turned out to be the most potent compound (Figure 10).[473]

2,3-Methanophenylalanine was incorporated in stereodefined analogues **543a,b** and **544** of the tetrapeptide hormone cholecystokinin (CCK). Evaluation of the binding affinity to the CCK-A and B receptors of these analogues illustrated that compound **543b** endowed with an (*E*)-configured 2,3-methanophenylalanine residue is about 100 times more potent than the corresponding compounds **543a** and **544** with (*Z*)-2,3-methanophenylalanine moieties (Figure 10). Compared to CCK itself, **543b** turned out to generally bind less effectively but was endowed with excellent binding affinity and selectivity for the CCK-B receptor.[331,332]

The molluscan neuropeptide FMRFamide has shown antiopiate activity in numerous mammalian test systems. Substitution of the methionine residue by both enantiomers of (*Z*)- as well as of (*E*)-2,3-methanomethionine (**230**) resulted in four diastereomeric peptidomimetics **538a,b** (Figure 10), which exerted a greatly increased antiopiate potency. As analogues **538a** and **b** bound with lower affinity to the corresponding receptor than FMRFamide itself, the higher potency is considered to be an effect of an increased bioavailability.[474,475] Additional substitution of the phenylalanine residue by (2*R*,3*R*)-2,3-methanophenylalanine produced the peptidomimetic **545**, which turned out to be even significantly more potent than the analogues **538a** and **538b** of FMRFa, containing 2,3-methanomethionine alone.[476] The conformations of peptides **538a** and **538b** were explored by NMR and CD spectroscopy. According to these results, the (*E*)- as well as the (*Z*)-2,3-methanomethionine (**230**), when substituted for methionine residues, tend to impart a conformational preference for γ-turns in FMRFa. In this context, the first observation of an element of solution-secondary structure induced by a 2,3-methanoamino acid was made.[477−480] The conformational bias induced by 2,3-methanomethionine has also been explored by quenched molecular dynamics (QMD) computations of the stereodefined tripeptide mimics **546a** and **546b** (Figure 10)[481] and in a comparative study with the analogous α-methylmethionine-containing tripeptides.[482]

Due to its potential biological activity, a highly conformationally constrained, stereodefined isoserine derivative was coupled with both enantiomers of protected (*Z*)-2,3-methanoaspartate to afford the diastereomeric dipeptide surrogates **547**. With the same intention, both enantiomers of the dipeptide surrogate **548** were synthesized (Figure 10).[483,484] However, the biological properties of **547** and **548** have not been reported yet.

The undecapeptide substance P (SP) is a neuropeptide of the tachykinin family widely distributed in the central and peripheral nervous systems. With the intention to study the topography of the binding site of the monoclonal anti-substance P antibody and the NK-1 receptor, a wide range of constrained analogues of substance P were prepared. Among these analogues were the four stereoisomers of (*E*)- and (*Z*)-2,3-methanophenylalanine-substituted compounds **549a** and **549b** (Figure 10). The (*E*)-isomers turned out to exhibit higher affinities than the (*Z*)-isomers; however, none of these compounds was equipotent to SP itself.[485]

Due to the high susceptibility to ring opening of 2,3-methanoasparagine in its free or even partially deprotected form,[457] an indirect route for its incorporation into peptides utilizing a masked form of 2,3-methanoasparagine has been developed. Thus, racemic (Z)-2,3-methanohomoserine (∇Hse) was incorporated into dipeptides **550** and **553** and tripeptides **556**, and the ∇Hse moiety was oxidized to racemic (*Z*)-2,3-methanoasparagine to furnish the corresponding di- and tripeptides **551**, **554**, and **557** (Figure 11).[486]

With the intention to explore the influence of differently configured 2,3-methanophenylalanine moieties on the peptide backbone, the molecular structures of the four diastereomeric model peptides **552a**,**b** (Figure 11) were studied by IR and ^{1}H NMR spectroscopy. All four derivatives turned out to be β-folded with the folding type depending on the configuration of the cyclopropane moiety.[487,488] An analogous study was carried out for model peptides **555**, containing a (2*R*,3*R*)- or a (2*S*,3*S*)-2,3-diphenyl-substituted 1-aminocyclopropane-

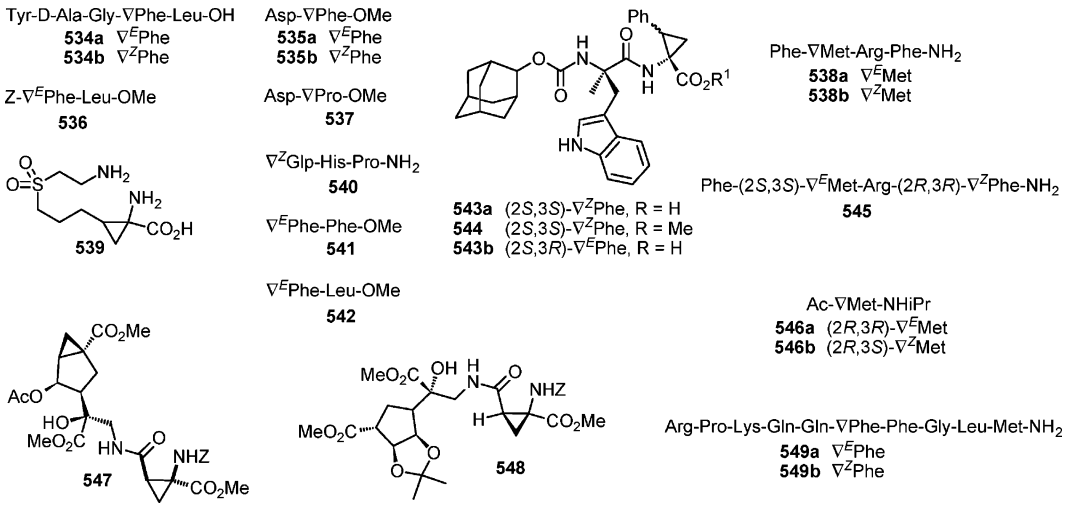


Figure 10. Peptides having incorporated a substituted 2,3-methanoalanine residue.[331,332,465−485]

carboxylic acid residue (▽2,3-diPhe),[489] and for model peptides **558**, containing a 2,3-methanovaline moiety.[291]

The spirocyclopropane-annelated diastereomeric cyclic peptidomimetics **559a**,**b**, containing (2*S*,3*S*)-(*Z*)- and (2*R*,3*S*)-(*E*)-2,3-methanoarginine residues (Figure 11), respectively, were synthesized, and their conformations were explored by a combination of CD and NMR spectroscopy as well as molecular mechanics computations. The obtained results were used to interpret the capability of **559a**,**b** to disrupt the αVβ3-vitronectin and GPIIb/IIIa-fibrinogen interaction, which was shown to be minimal or not ratable at all.[490]

A library of compounds based on the peptide sequence **560** or the anti-opiate peptide **561**, respectively, was prepared, in which all four stereoisomers of 2,3-methanoleucine were incorporated. Binding of the analogues to the μ- and δ-opioid receptor as well as the anti-β-endorphin monoclonal antibody and the neuropeptide FF receptor were examined in reference to the position of the 2,3-methanoleucine moiety.[491]

The *N*-terminal tridecapeptide of RNase has served as a paradigm for conformational studies of short helical peptides. Substitution of arginine by (2*R*,3*S*)- or (2*S*,3*S*)-2,3-methanoarginine was found to stabilize the helical secondary structure in aqueous solution.[492] Replacement of phenylalanine by (2*R*,3*R*)-1-amino-2,3-diphenylcyclopropanecarboxylic acid in RN-24, a derivative of RNase, induced a helical structure which was less perturbed by temperature increases and pH changes than that of RN-24 itself.[401]

Homooligopeptides of (2*R*,3*R*)-1-amino-2,3-diphenylcyclopropanecarboxylic acid were synthesized with the intention to study their conformational behavior. Accordingly, these kinds of peptides are folded into a right-handed, slightly distorted, helical type-III β-turn conformation.[493]

Enantiopure peptidomimetics **562**−**564** (Figure 11) were prepared in order to investigate the conformational biases of the underlying mono- or diphenyl-substituted 2,3-methanoamino acids. The 1,2-disubstituted derivative **564** turned out to be the most rigid one among these analogues. Both the 1,1- as well as the 1,2-diphenyl-substituted derivatives were shown to contain secondary structural elements that were not present in the corresponding monophenyl-substituted derivative.[401,494]

Calpain is a calcium-dependent cystein protease which has been implicated in a number of pathological conditions, such as for example neurological disorders, cataracts, and thrombotic platelet aggregation. In order to study the cellular role of calpain and to find new and selective therapeutic agents, calpain analogues **565a**,**b** (Figure 11) were synthesized, in which the original leucine moiety was replaced by all four stereoisomers of 2,3-methanoleucine. This resulted in an at least 10-fold decrease of calpain I inhibitory activity, but an enhanced selectivity for calpain I over the protease cathepsin B.[495]

In analogy to 1-aminocyclopropanecarboxylic acid (see section 2.6), alkyl- and especially vinyl-substituted 1-aminocyclopropanecarboxylic acids were incorporated in synthetic analogues of the nonstructural protein 3 (NS3). A variety of the obtained linear peptides **566** as well as intramolecularly linked peptides **567** exhibited NS3-protease inhibitory activity and possessed an interesting pharmacological profile, offering a very promising way for new therapies against Hepatitis C virus infections.[214,215,496−504]

3.5. β-Lactams Containing 2,3-Methanoamino Acid Fragments

β-Lactams with a penicillin (penam), a cephalosporin (cepham), or a related skeleton have proven to be of enormous value for the treatment of bacterial infections. Many structural modifications have been made on these scaffolds in order to elucidate their mode of action with regard to finding compounds with better therapeutic properties, including potency, a broader or more selective activity spectrum, and an increased stability toward β-lactamases.

In this context, numerous β-lactams which formally have incorporated a substituted 2,3-methanoamino acid moiety were synthesized and investigated with respect to their biological activities.

Among these compounds were penams, analogues of penicillin, bearing a fused cyclopropane moiety, leading to tricylic β-lactams. Thus, the tricyclic 2,3-methylenepenams **568**−**571** (Figure 12) were synthesized in such a way that the cyclopropane ring was built up by an intramolecular S_N2 reaction.[505,506] Such compounds were further converted by cyclopropane-ring opening reactions into the corresponding cephem derivatives.[507] The *Z*-protected *p*-nitrobenzyl ester **571** has been transformed into the (5*S*)-5-amino-5-carboxypentanoyl-substituted derivative **573** (Figure 12), which was found to be a potent reversible inhibitor of the ring-expansion of penicillin N induced by deacetoxycephalosporin C syn-

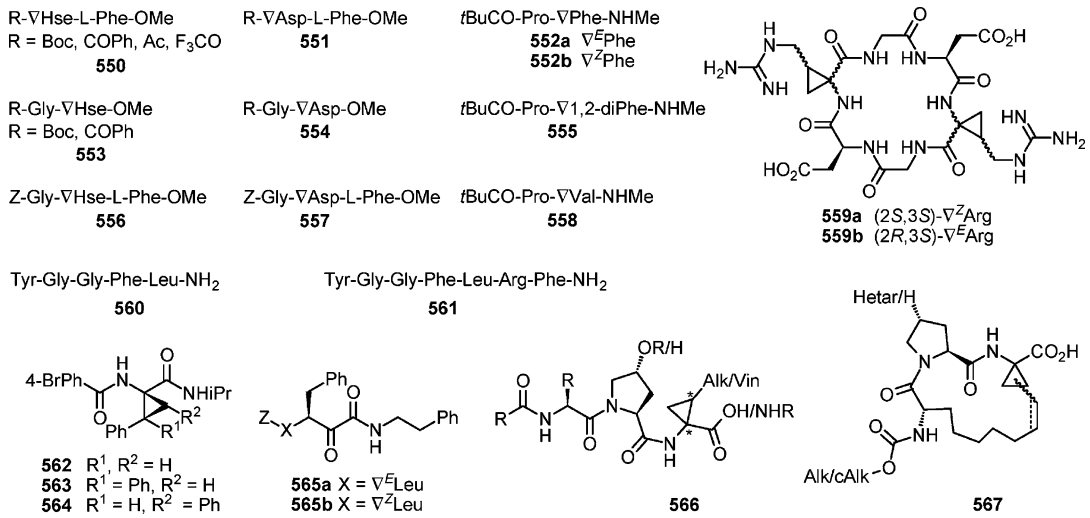


Figure 11. Some more peptides with an incorporated substituted 2,3-methanoamino acid residue.[214,215,291,401,486−491,494−504]

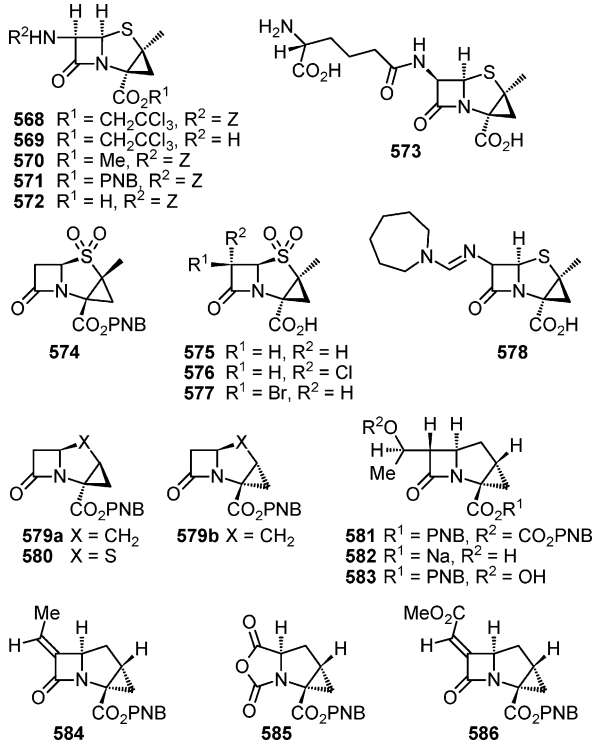


Figure 12. Penicilline analogues (penams) having incorporated a 2,3-methanoamino acid moiety.[505,506,508,510−517]

thetase, but not a substrate of this enzyme.[508] In this context, the reduction of several 2,3-methylenepenam sulfoxides to the corresponding sulfides has been examined extensively.[509]

Besides, compound **571** has been transformed into its partially deprotected form **572** and served as the starting material for the synthesis of the sulfones **574** and **575**−**577** as well as the sulfide **578** (Figure 12).[510−512] The β-lactamase inhibiting properties of **574** were investigated, indicating that β-lactamase recognizes the α-methylenepenam **574** as a cephalosporin and not as a penicillin derivative.[510] The antibacterial potencies of 2,3-methylenepenams **572** and **575**−**578** were tested, and the activities of **572** as well as **578** were shown to be considerably lower than those of their corresponding penam analogues. Despite this, **572** turned out to be a substrate for bacterial β-lactamases and compounds **574**, **576**, as well as **577** exhibited inhibitory activity against β-lactamase.[511]

The diastereomeric carbapenams **579a** and **579b**, the penam **580**, and the carbapenams **581**−**583** (Figure 12) were prepared by 1,3-dipolar cycloaddition of diazomethane to the corresponding carbapenems and subsequent thermolysis of the obtained pyrazolines.[513−515] However, the biological activities of compounds **579**−**583** have not been reported so far. Derivative **583** was submitted to a mesylation−elimination sequence, furnishing the (*E*)-ethylidene-substituted carbapenam **584**, which, upon ozonolysis, afforded the anhydride **585** or the acrylate **586**, depending on the reaction conditions.[516,517]

Besides penams, several cephalosporins with a fused cyclopropane moiety have also been prepared. Thus, the oxadethiacephalosporins **581** and **582** (Figure 13) were synthesized by dichlorocarbene addition to the double bonds of corresponding cephem derivatives. Compound **582** was tested with respect to its antibacterial activity, but it was found to be inactive.[518] The diastereomeric oxacephams **584a** and **584b** as well as the carbacepham **585** were prepared by

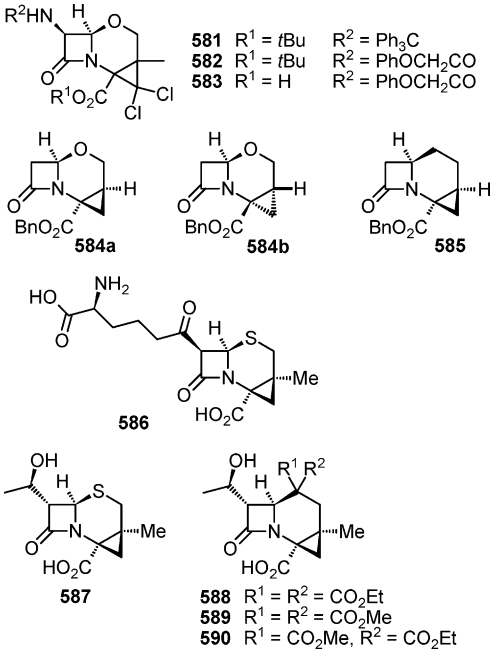


Figure 13. Cephalosporine analogues (cephams) with an incorporated 2,3-methanoamino acid moiety.[518−522]

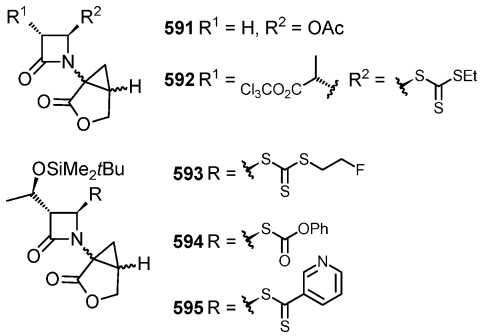


Figure 14. Azetidinones substituted with a 3-oxabicyclo[3.1.0]-hexane-2-one moiety.[523−526]

base-mediated 1,3-elimination in the corresponding iodooxa- and iodocarbahomocephams, respectively, the latter of which were obtained by employing a palladium-catalyzed so-called ene−halogenocyclization.[519,520]

The (5*S*)-5-amino-5-carboxypentanoyl-substituted cepham derivative **586** (Figure 13) was obtained by 1,3-dipolar cycloaddition of diazomethane to the corresponding cephem derivative and elimination of nitrogen from the resulting pyrazoline. Compound **586** was tested as a substrate for deacetoxy-deacetylcephalosporin C synthetase, but it showed no interaction with this enzyme.[521]

The cepham analogue **587** and the carbacepham analogues **588**−**590** (Figure 13) were obtained by an intramolecular cycloaddition of a carbene generated from an oxalimide moiety by treatment with triethylphosphite in refluxing xylene. Compounds **587**−**590** were evaluated for in vitro antibacterial properties and were found to exhibit modest activity against a number of bacterial strains.[522]

An intramolecular cheletropic addition of a carbene generated from an oxalimide moiety to a double bond was also employed in the synthesis of the azetidinones **591** and **592** (Figure 14), having incorporated a 3-oxabicyclo[3.1.0]-hexane-2-one substituent.[523] The analogous derivatives **593**−**595** (Figure 14) were isolated in low to moderate yields as undesired side products in the synthesis of penems.[524−526]

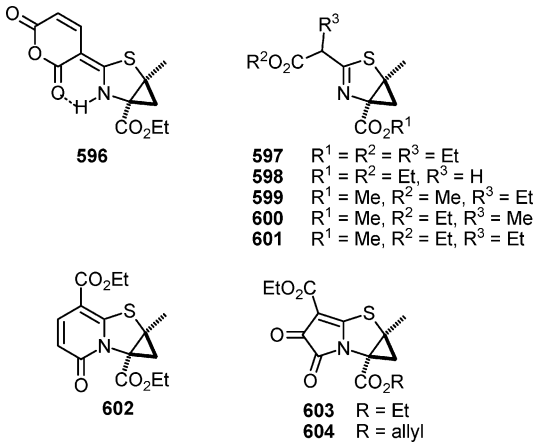


Figure 15. Formal incorporation of 2,3-methanoamino acids into skeletons related to penams and cephams.[527−531]

The biological activities of compounds **591**−**595** have not been reported yet.

Besides the formal incorporation of 2,3-methanoamino acids into penam and cepham systems, several compounds reminiscent of these scaffolds bearing a 2,3-methanoamino acid moiety were synthesized. Among these are the cyclopropane-annelated **596** and **597**−**601** (Figure 15), which were obtained by rearrangement of 1,3-thiazine derivatives upon irradiation.[527,528] The 4,5-methanothiazoline **598** has been converted into the tricyclic compound **602**, which was applied in the mechanistic elucidation of the rearrangement of 2-vinyl-1,3-thiazetidines.[529,530] Additionally, the 4,5-methanothiazoline **598** was used for the preparation of the tricyclic compounds **603**, which represents a γ-lactam analogue of known β-lactamase inhibitors. With the same intention, the analogue **604** was synthesized.[531]

4. Conclusions

As long as 85 years ago, 1-aminocyclopropanecarboxylic acid was synthesized for the first time, and this constituted the very first synthesis of a cyclopropyl-group-containing amino acid. The compound was initially conceived as a structural curiosity, and it took about 50 years until 1-aminocyclopropanecarboxylic acid was found to be the key intermediate in the biosynthesis of the plant hormon ethylene. This discovery then led to a significant demand for convenient syntheses of ACC and its derivatives. Concomitantly, several substituted 2,3-methanoamino acids, such as, for example, coronamic acid, norcoronamic acid, and carnosadine, were found in nature, and the investigation of their biological properties provoked vast synthetic efforts toward this class of compounds lasting until today. To date, an enormous variety of synthetic routes toward 2,3-methanoamino acids in their racemic form have been accessed, among which especially the approaches via 1,3-dipolar cycloaddition of diazomethane and derivatives thereof, the addition of ylides to Michael acceptors, and the cyclodialkylation of malonic acid derivatives as well as nucleophilic glycine equivalents have gained significant importance. Within especially the last 10−15 years, synthetic research has been focused on the development of convenient syntheses of enantiomerically pure substituted 2,3-methanoamino acids, and although remarkable progress has been made, a generally applicable method is still lacking.

Subsequent to the establishment of syntheses, the biological activities of ACC and several of the newly synthesized 2,3-methanoamino acids were investigated, and these studies have revealed them to often exhibit very interesting properties, ranging from being, for example, *N*-methyl-D-aspartate receptor ligands to antidepressants and even antibacterials. In view of the conformational constraints of 2,3-methanoamino acids, they have been incorporated into a variety of peptides. As a consequence of the conformational lock, these peptides were often found to show remarkable pharmacological activities, such as, for example, the recently demonstrated NS3-protease inhibition, which is relevant for the treatment of Hepatitis C infection.

Thus, within the last 85 years, research toward 2,3-methanoamino acids has significantly changed its focus from natural product isolation and structure elucidation via organic synthesis toward pharmacological evaluation. However, especially the latter has certainly not been completed, but is deemed to stimulate further exploitation.

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