Synthesis of Carbocyclic and Heterocyclic β-Aminocarboxylic Acids

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1. INTRODUCTION

In consequence of their biological effects, conformationally constrained carbocyclic β-amino acids have generated great interest among synthetic and medicinal chemists in the past 2 decades, and they have become a hot topic in organic and bioorganic chemistry. These compounds are found in natural products and antibiotics. They are also considered important precursors for pharmacologically interesting β-lactams and other bioactive compounds. Certain carbocyclic β-amino acids, e.g., cispentacin (1), icofungipen (2), and BAY Y9379 (3), possess noteworthy antifungal or antibacterial activities, while tilidin (4), a phenyl-substituted cyclohexene amino ester, is an analgetic (Figure 1).1,2a–d

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Carbocyclic β-amino acids are also important elements in many products with interesting pharmacological potential. Several of them are depicted in Figure 2. Amipurimycin (5) and pitucamycin (6), containing five- and six-membered carbocyclic β-amino acid moieties, are antibiotics, while compounds 7–11 possess enzyme-inhibitory and antitumoral activities.2e−k Since these compounds may be applied as building blocks in peptide synthesis, the incorporation of novel conformationally restricted β-amino acids into peptides, and especially foldamers, has attracted considerable interest from the aspect of the preparation of peptide-based drug molecules with high biological potential.3,4 As a result of the immense progress made in the field of carbocyclic β-amino acids, a high number of original papers and reviews (around 200) have been published on this topic in the past 10 years. Since the most recent comprehensive survey of the synthesis and chemistry of β-aminocycloalkanecarboxylic acids was published over a decade ago (Chemical Reviews, 20011a), we consider that there is a great need for an updated coverage of the subsequent relevant synthetic advances, particularly those concerning the synthesis of such derivatives in enantiomerically pure form, together with other important chemical aspects in this developing area of organic and medicinal chemistry.

Besides these carbocyclic compounds, conformationally rigid cyclic β-amino acids containing a heteroatom (nitrogen or oxygen) in the ring and with the carboxylic and the extracyclic amino functions attached to stereogenic C-centers on the skeleton have likewise received significant attention in recent years as a result of their biological importance, and chemical interest in these medicinally relevant molecules has increased rapidly.5 Despite the rising number of publications on these heterocyclic β-amino acids (almost 200 references in the past 15 years), no comprehensive, systematic overview has appeared, so far, on the syntheses and applications of this valuable class of compounds in the field of amino acids. Accordingly, a comprehensive description of the synthetic routes with an account of the main biological activities appears highly necessary.

A considerable number of syntheses of carbocyclic and heterocyclic β-amino acid derivatives in racemic forms and many methods for their preparation in enantiomerically pure form have been reported in recent years. Intensive research has focused on their transformations to heterocycles, peptides, or other bioactive derivatives. The aim of the present review is to survey the results on this exciting and intensive area of development in the framework of cyclic β-amino acids.

The review begins with a presentation of the results achieved in the past decade in the field of carbocyclic derivatives. Relevant synthetic routes will be given toward the preparation of the largest family of these derivatives, i.e., the five- and six-membered carbocyclic amino acids, followed by an account of the smaller and then the larger ring analogs. The syntheses in general will be described for the racemic substances, unless asymmetric approaches or enantioselective preparations are presented, for which the product will be mentioned as enantiomerically pure; in the latter case, either absolute configurations or sign of the optical rotations will be given. Since the functionalized cyclic β-amino acids have attracted increasing attention in

Figure 1. β-Amino acid drugs.

Figure 2. Pharmacologically active β-amino acid derivatives.
recent years, the most interesting procedures for the syntheses of these derivatives will also be presented.

The second part of the review will be devoted to the heterocyclic β-amino acids with carboxyl and extracyclic amino functions attached to stereogenic C-centers of the ring, followed by a structural organization depending on the nature of the heteroatom and the ring size. Each part deals with the chemical approaches toward the synthesis of these heterocyclic amino acids, including the enantiomers, and their transformations to other important bioactive substances, evaluated in terms of applicability, usefulness, and limitations.

Besides the synthetic aspects, each section will provide representative information on the biological importance and applications of these interesting β-amino acids. The final concluding remarks will briefly discuss the perspectives for future research.

In view of the lack of any other comprehensive coverage of the recent results on carbocyclic and heterocyclic β-amino acids, a systematic review of their preparations and biological effects is likely to be of great interest to a wide range of synthetic chemists and biochemists.

2. CARBOCYCLIC β-AMINO ACIDS

2.1. Syntheses of Five- or Six-Membered Carbocyclic β-Amino Acids

The syntheses of cyclic β-amino acids have aroused considerable interest in the past 2 decades as a result of their presence in pharmacologically active compounds, other biologically relevant products, and important peptides. The largest and most important groups of cyclic amino acids are those with five- or six-membered rings. One general mode of access to β-aminoacyclohexanecarboxylic acid is based on the transformation of hexahydrophthalic anhydride (12) by amidation and Hofmann degradation of the resulting amide (13) to the corresponding β-aminoacyclohexanecarboxylic acid 15.1a

In an alternative route, Curtius degradation of the half-ester 14 derived from anhydride 12 gives amino acid 15 (Scheme 1).

The above synthetic protocol has been applied effectively for the preparation of other related cyclic β-amino acids, such as 16, the trans counterpart of 15, 2-aminoacyclohexanecarboxylic acids 17 and 18, and the bicyclic di-endo-β-amino acids 19 and 20 (Figure 3).

Another rapid and simple procedure for the synthesis of five- or six-membered cyclic β-amino acids consists of the ring-opening transformation of bicyclic β-lactams (23) derived from cycloalkenes (21a,b) by the cycloaddition of chlorosulfonyl isocyanate (CSI) (Scheme 2). A full list of the abbreviations used is to be found at the end of this review.

Scheme 2. Syntheses of Carbocyclic β-Amino Acids in Racemic or Enantiomerically Pure Form via β-Lactam Opening

Bicyclic β-lactam ring-opening by hydrolysis or ethanololysis has been extended toward the synthesis of enantiomerically pure carbocyclic β-amino acids. Enzyme-catalyzed lactam ring-opening of racemic azetidinone (23a,b) resulted in the enantiomerically pure unreacted lactam and the corresponding alicyclic cis-β-amino acid enantiomer (15a, 24c). The amino acid enantiomers (15a, 24c) were prepared by an alternative route: enzymatic hydrolysis of the racemic bicyclic β-amino esters (15b, 24d), during which the racemic ester afforded the optically pure β-amino acid and the unreacted β-amino ester enantiomer. The latter procedure (see Scheme 2) allowed the preparation of trans-β-amino acids. Both enzymatic resolution methodologies furnish saturated alicyclic β-amino acid enantiomers with different ring sizes, and their counterparts with a C–C double bond in the ring.1i

This lactam opening method has been efficiently used for the preparation of a series of derivatives such as the β-aminoacyclohexene (17) or cyclopentencarboxylic (25) acids and for the synthesis of bicyclic di-exo derivatives 26 or 27 (Figure 4).1a

Although the routes presented above for the preparation of cyclic β-amino acids are efficient and simple methods with high

Figure 3. Several carbocyclic β-amino acids.

Figure 4. Carbocyclic β-amino acids derived from β-lactams.
overall yields and low costs that are applicable on a large scale, they suffer from certain limitations: they afford only racemates or they are not applicable for the synthesis of a large variety of substituted derivatives.

2.1.1. Carboxyclic β-Amino Acids from β-Keto Esters. Carboxyclic β-keto esters, conveniently synthesized by the Dieckmann condensation of acyclic diesters, are readily available precursors for the preparation of five- or six-membered cyclic β-amino acids. Cyclic β-amino carboxylates are synthetized by the reduction of oximes or enamines formed from the corresponding β-keto esters. R educative amination of cyclic β-keto esters is a suitable method for the synthesis of carboxyclic β-amino acids in enantiomerically pure form. Protected amino acid enantiomer 33 was prepared from five-membered keto ester 28 by using (S)-α-methylbenzylamine as chiral auxiliary (Scheme 3). Cyclic keto ester 28 was reacted with (S)-α-methylbenzylamine to furnish enamine derivative 29 in high yield. Reduction of 29 with Na in i-PrOH led to trans-amino alcohol 30, which was converted by removal of the chiral auxiliary, N-Fmoc protection, and oxidation to trans-amino acid enantiomer 33.5

An alternative simplified route has been described with the same chiral auxiliary. The enamine resulting from the reaction of keto ester 28 and (S)-α-methylbenzylamine was reduced with NaCNBH3 to give trans-β-amino ester 31. Ester hydrolysis, removal of the chiral auxiliary, and N-Fmoc protection led to amino acid 33 (Scheme 3).

Gellman et al. applied this method to prepare enantiomerically pure 4,4-disubstituted derivatives of trans-β-amino-cyclopentanecarboxylic acids.7 The 4,4-disubstituted β-keto esters were reacted with (R)-α-methylbenzylamine and the resulting enamines were reduced with NaCNBH3. The diastereomeric mixture of trans- amino esters was separated by chromatography, followed by transformation to the corresponding substituted cyclic β-amino acids 34–37 (Figure 5).

A general approach for the asymmetric synthesis of β-amino-cyclopentane-, cyclohexane-, cycloheptane-, and cyclo-

Figure 5. Structures of several alicyclic trans-β-amino acids.

From cis-amino esters 39, the trans counterparts could be easily synthetized by epimerization at C-1 with NaOEt.8 New Rh complexes were used for the asymmetric hydrogenation of β-acetamido dehydroamino acid derivatives by Wu et al.8b Yu et al. have synthetized novel β-sulfonamidocyclopentanecarboxylates by using Pd(OCCF3)2/chiral diphosphine ligand systems for the enantioselective hydrogenation of cyclic β-arylsulfonamido acrylates.9 Developments relating to the large-scale applicability of the asymmetric hydrogenation of dehydroamino acids were reported by Enthaler et al.9 Novel chiral phosphine ligands were used in multi-10-g scale reactions, and up to 94% ee was achieved.10

Enantiomerically pure β-(4-fluorobenzyl)amino-cyclopentanecarboxylate (41) (Scheme 5) is a precursor of the biologically interesting compound HCV NS5B,11 known as a polymerase inhibitor. β-Keto ester transformation through the enamine was applied for the synthesis of racemic 41. In this case, reductive amination of 28 with 4-fluorobenzylamine and NaBH4CN furnished racemic cis-amino carboxylates 41, together with minor amounts of trans derivative 42 (Scheme 5).

Resolution of racemic 41 with (S)-(−)-mandelic acid afforded the enantiomerically pure compounds.11

Reductive amination of β-keto esters is a suitable method also for the synthesis of functionalized racemic carbocyclic β-amino acids. An icofungipen (for the structure, see 2) analog 48 with an exocyclic methylene unit has been prepared in seven steps from the benzylloxymethyl-containing keto ester 44 by reductive amination (Scheme 6).2a

2.1.2. Carboxyclic β-Amino Acids by Metathesis. Carboxyclic β-amino acids can be prepared from acyclic β-amino acid derivatives by ring-closing metathesis. An important advantage of this methodology is that it gives cyclic β-amino acids whose olefinic bond may be functionalized to yield novel substituted derivatives. Chiral lithium amide addition to various

Scheme 3. Synthesis of a trans-β-Amino Acid from the Corresponding β-Oxo Ester by Reductive Amination

Scheme 4. Syntheses of Carboxyclic β-Amino Esters by Cis-Selective Catalytic Reduction of Enamines

Scheme 5. Syntheses of cis- and trans-β-Amino Esters by Reduction of Enamines with NaBH4OAc
unsaturated acyclic esters afforded acyclic dieno amino esters 49 and 50 (for the conjugate addition to \(\alpha,\beta\)-unsaturated esters, see also section 2.1.3), generating two stereogenic centers. These unsaturated amino esters were transformed by ring-closing metathesis with a Ru alkylidene catalyst to the corresponding \(\beta\)-aminocycloalkene esters 51 and 52 (Scheme 7). The configuration of the chiral centers in 49 and 50 determined the trans stereochemistry in the carbocyclic products 51 and 52.\(^{12a}\)

Unsaturated cyclic \(\beta\)-amino acid enantiomers were synthesized from enantiomerically pure \(\alpha\)-amino acids via a ring closure metathesis as key step.

The transformation of (S)-methionine or (R)-allylglycine involving allylation and the Arndt–Eistert reaction resulted in amino ester 53 or 55, which under ring-closing metathesis conditions furnished the corresponding five- or six-membered cyclic \(\beta\)-amino ester enantiomers (Scheme 8).\(^{12b}\)

\(\beta\)-Lactams can be easily transformed to the corresponding \(\beta\)-amino acids by lactam ring-opening. Dienes possessing a \(\beta\)-lactam framework (57) were converted through acyclic \(\beta\)-amino acid derivatives 58 by intramolecular ring-closing metathesis to afford unsaturated carbocyclic trans-\(\beta\)-amino esters (59). The configurations of the stereocenters in the starting lactam 57 were not affected during the process, which resulted in five- or six-membered trans-amino acid enantiomers 60 after removal of the chiral auxiliary (Scheme 9).\(^{13}\)

The synthetic protocol based on metathesis offered an opportunity for the preparation of functionalized carbocyclic \(\beta\)-amino acids. A general method for the synthesis of difluorinated

**Scheme 6. Synthesis of Exomethylenic \(\beta\)-Aminocyclopentanecarboxylic Acid by Reductive Amination**

**Scheme 7. Syntheses of trans-\(\beta\)-Aminocycloalkenecarboxylates from \(\alpha,\beta\)-Unsaturated Esters**

**Scheme 8. Syntheses of trans-\(\beta\)-Aminocycloalkenecarboxylates from S-Methionine and R-Allylglycine**

**Scheme 9. Syntheses of trans-\(\beta\)-Aminocycloalkenecarboxylic Acids from Diene \(\beta\)-Lactams**
β-aminocyclopentane-, cyclohexane-, and cycloheptanecarboxylic acids via a cross-metathesis reaction as key step was developed by Fustero et al.\textsuperscript{14} The cross-metathesis of geminal difluorinated imidoyl chlorides (61) with ethyl acrylate to give 62 was followed by saturation of the olefinic bond to difluorinated imino ester 63, intramolecular base-mediated ring closure of which furnished the corresponding difluorinated cyclic β-amino ester 64 (Scheme 10). Catalytic hydrogenation of 64 resulted in racemic difluorinated five- or six-membered cis-β-aminocycloalkanecarboxylates (66).

The above synthetic strategy was extended to the preparation of enantiopure difluorinated β-amino ester. This was accomplished by using (−)-8-phenylmenthol as chiral auxiliary. LDA-mediated ring closure of the phenylmethyl ester (the cross-metathesis product) and subsequent hydrogenation gave the corresponding enantiomerically pure cyclic cis-β-amino ester.\textsuperscript{14a}

The cross-metathesis of imidoyl chlorides with unsaturated esters, such as pent-4-enoate or but-3-enoates, was later extended by the same research group to the preparation of cyclic difluorinated β-amino acid enantiomers with various ring sizes.\textsuperscript{14b}

A method relatively similar to the above-described enolate addition to imidoyl chlorides involved the intramolecular cyclization of imines and ester enolates, when benzo-fused cispentacins were synthesized.\textsuperscript{15}

The chiral imine 68, derived from 67, underwent intramolecular addition in the presence of various bases. The reaction with LiHMDS (lithium hexamethyldisilylamide) or KHMDS at room temperature resulted in β-lactam stereoisomers 69 and 70 and benzofused transpentacinet derivative 71 in a ratio of 49:18:33 or 30:31:39 (Scheme 11). When the addition was carried out with NaHMDS, only the lactams were detected in a ratio of 77:23. Moreover, at −40 °C in the presence of a crown ether catalyst, excellent selectivity (69:70 99:1) was attained. Compound 69 was readily transformed by chiral auxiliary removal and lactam opening to the corresponding enantiomerically pure benzo-fused cispentacin 72 (Scheme 11).

This ring-closing method was also applied for the preparation of dimethyl-substituted cispentacin. Imino ester 73, obtained from 4,4-dimethylcyclohexanone, readily afforded β-lactam 74 with high diastereoselectivity (dr 97:3) by intramolecular nucleophilic addition (Scheme 12).\textsuperscript{15}

A recent method involving ring-closing metathesis was developed by Davis et al. Addition of unsaturated carboxylic acid derivative 76 to p-toluenesulfonylimine 75 with a C–C
double bond furnished syn (dr > 99:1) dieno amino carboxylic acid derivative 77, whose ring-closing metathesis afforded the corresponding five- or six-membered carbocyclic cis-β-amino acid derivative (Scheme 13). The relative configuration of the chiral C-centers in 77, resulting from the syn-selective addition between 75 and 76, determined the cis stereochemistry in the carbocyclic product 78.16

2.1.3. Carbocyclic β-Amino Acids by Amino Group Conjugate Addition. α,β-Unsaturated carbocyclic acid derivatives are excellent starting materials for the synthesis of cyclic β-amino acids.17a

Stereoselective conjugate addition of an amine nucleophile derivative to an α,β-ununsaturated carbocycle is an efficient strategy for access to five- or six-membered cyclic β-amino acids. Chiral lithium amides such as (S)-80 have been used as chiral ammonia equivalents for this purpose. Addition of (S)-80 to ester 79 led completely stereoselectively to cis-α-amino ester derivative 81, which, after removal of the chiral auxiliary by hydrolysis, provided cis-2-aminoacyclohexanecarboxylic acid enantiomer (82) in 98% ee (Scheme 14).17b,104

Scheme 14. Synthesis of Cispentacin from α,β-Unsaturated Esters and Lithium Amides

An important advantage of this strategy is its ready applicability for the preparation of alkyl-substituted analogs of cispentacin in enantiomerically pure form. Davies et al. further extended this methodology.

tert-Butyl 3-methylcyclopentanecarboxylate was used as starting material for the preparation of 3-methyl-substituted cispentacin enantiomers (83–85; Figure 6) in 98% ee.18

By using the conjugate addition technique, the same research group also synthesized 5-alkyl-substituted cispentacins. Addition of chiral amide (S)-80 to 5-isopropyl-, 5-phenyl-, and 5-

tert-butylcyclopentanecarboxylates led with a high degree of stereoselectivity to the major derivatives with the amine trans to the 5-alkyl group. Removal of the chiral auxiliary and subsequent ester hydrolysis afforded 5-substituted cispentacins in 98% ee.19

Conjugate addition proved to be a suitable method also for the synthesis of various other functionalized cyclic β-amino acid derivatives. Starting from diene 86, 2-amino-5-carboxymethylcyclopentanecarboxylate stereoisomers were synthesized by the addition of lithium amide (R)-80. Addition products 87 and 88 resulting from the reaction of 86 and (R)-80 were separated by column chromatography.

Removal of the chiral auxiliary and subsequent ester hydrolysis afforded optically active amino diacids 89 and 90 with ee up to 99% (Scheme 15).20

This functionalization strategy was extended to the preparation of cyclohexane analogs. Starting from a diene dicarboxylate, conjugate addition followed by ring closure by using chiral lithium amide (S)-80 proceeded with high diastereoselectivity to give the corresponding aminocyclohexanecarboxylates.21

Hydroxy-functionalized cyclopentane or cyclohexane β-amino acids were prepared by applying the conjugate addition–ring closure procedure. Unsaturated formyl carboxylates (91) served as suitable starting materials for this purpose. Similarly to the transformations presented above, enantiomerically pure 5- and 6-hydroxylated cyclopentane- and cyclohexanecarboxylic acids (93) were obtained (Scheme 16).21

The parallel kinetic resolution of substituted unsaturated esters is an interesting application of chiral amide conjugate addition. Addition of a 1:1 mixture of a pseudoenantiomeric mixture of (S)-80 and (R)-98 (Figure 7) to racemic 5-tris(phenylthio)methylcyclopent-1-ene carboxylate (95, derived from 94) provided tris(phenylthio)amino ester derivatives 96 and 97 with de higher than 98% (Scheme 17).

After chromatographic separation, 96 and 97 were subjected to Raney Ni reductive desulfurization to furnish 5-methyl-substituted derivatives. Hydrogenolysis and ester hydrolysis gave (1R,2S,5S)- and (1S,2R,5R)-5-methylcispentacin (99 and 100) in 98% ee (Figure 8; for 5-alkyl-substituted cispentacins, see also ref 19).22

The parallel kinetic resolution strategy based on conjugate addition was efficiently used for the preparation of 6-methyl-substituted β-aminocyclohexanecarboxylic acid enantiomers 23 and 3-alkyl-substituted cispentacin enantiomers.24

Chiral lithium amide (80) addition to unsaturated cyclic esters (79; Scheme 14) provided cis-β-amino ester 81, while the N-protected transient cispentacin could be easily prepared by epimerization of 81 at C-1 with base. On treatment with t-BuOK, 81 led to the corresponding trans derivative 101.
Removal of the chiral auxiliary, N-protection, and ester hydrolysis gave transpentacin enantiomer 102 (Scheme 18).

The double Michael conjugate addition outlined in Scheme 15 was efficiently further developed by Ozeki et al. for the synthesis of functionalized β-aminocycloalkanecarboxylic acids with multiple chiral centers by the addition of different aldehydes. Analogously to the process presented in Scheme 15, addition of amino alcohol derivative 103 as chiral auxiliary to diene 104 gave the corresponding amino dicarboxylate 106. However, in the presence of an aldehyde, the reaction led not only to 106 but also to 105, formed in a yield of 6–45% by a...
2.1.4. Carbocyclic β-Amino Acids by Cycloaddition. Diels–Alder cycloaddition is a widely used as an efficient method for the construction of a cyclic compound with new stereogenic centers and can also be applied for the synthesis of cyclic β-amino acids. Addition of butadiene carbamate 108 to acrylate 109 provided a mixture of two cycloadducts, cis- and trans-2-amino-3-cyclohexene carboxylates 110 and 111, in a ratio of 4:1.

Diastereoisomers 110 and 111 were separated by chromatography, and treatment with trimethylsilylamine (TMSI) furnished racemic cis- and trans-cyclohexene amino acids 112 and 113 (Scheme 20). 27

Scheme 18. Synthesis of Z-Protected Transpentacin by Chiral Lithium Amide Conjugate Addition

Scheme 19. Synthesis of Functionalized tert-Butyl β-Aminocyclohexane-carboxylate by Conjugate Addition of Chiral Amine to Unsaturated Diesters

Scheme 20. Syntheses of Racemic β-Aminocyclohexene-carboxylic Acids by Diels–Alder Cycloaddition

The general applicability of desymmetrization was demonstrated by Bolm et al. Desymmetrization of easily accessible meso-anhydrides by cinchona-mediated ring-opening with benzyl alcohol afforded different hemiesters with high enantioselectivities. These hemiesters were transformed to enantiomerically pure cyclopentane, norbornane, or norbornene β-amino acids. 32

Four enantiomerically pure endo isomers of icofungipen (2) were prepared by Harmers et al. by quinine-mediated desymmetrization of the corresponding racemic anhydride, followed by a Curtius reaction. 33
Scheme 21. Synthesis of Bicyclic β-Amino Acid Enantiomerically Pure 117 through Cycloaddition of an Unsaturated Nitro Ester and 1,3-Cyclohexadiene

Scheme 22. Synthesis of Cispentacin from a Bicyclic Isoxazolidine

Scheme 23. Synthesis of Cispentacin Enantiomer 1 from an Enantiomerically Pure Ketene Dithioacetal

Scheme 24. Synthesis of a Phenyl-Substituted Cispentacin Derivative

Scheme 25. Synthesis of Icofungipen

Anhydride 132 was isomerized to its endo derivative 135, which was next subjected to alcoholysis in the presence of quinine, giving hemiesters 136 and 137 in a ratio of 3:7 (Scheme 26). These esters could not be separated, but their conversion by the Curtius rearrangement afforded the separable amino ester stereoisomers 138 and 139. Deprotection of the ester and amino functions resulted in β-amino acid enantiomers 140 and 141 in 99% and 96% ee. Base-mediated isomerization of 139 furnished novel stereoisomer 142 in 96% ee (Scheme 26).

The fourth stereoisomer (144) was obtained by exo−endo isomerization of the enantiomerically pure icofungipen (2) with trimethylsilyl chloride (TMSCl) and NaI (Scheme 27).

2.1.6. Carbocyclic β-Amino Acids from Natural Sources. An efficient and convenient means of access to optically pure carbocyclic β-amino acids is the transformation
of readily available chiral monoterpenes. The method widely used for the synthesis of bicyclic \(\beta\)-lactams by CSI addition is the key step, involving the C–C double bond transformation of these natural sources for the synthesis of monoterpene-based \(\beta\)-amino acids. By starting from different monoterpenes, a series of cyclic \(\beta\)-amino acids were synthesized. For example, treatment of \(\alpha\)-pinene (145) with CSI led regio- and stereoselectively to \(\beta\)-lactam 146, the N-Boc protection and lactam opening of which resulted in carbocyclic \(\beta\)-amino acid enantiomer 148 (Scheme 28).34

Another monoterpene isomer of 145, \(\delta\)-pinene, also underwent CSI addition regio- and stereoselectively to give the corresponding \(\beta\)-lactam 149, which was next converted to the \(\delta\)-pinene-based \(\beta\)-amino acid 150 (Figure 9).35

Through application of a similar strategy, enantiomerically pure \(\beta\)-amino acid 152 was easily prepared from the readily available \((+)-3\)-carene. The corresponding \(\beta\)-lactam 151 was produced regio- and stereoselectively by the addition of CSI, and subsequent N-Boc protection followed by lactam opening furnished optically active 152 (Figure 10).36

In contrast with the above CSI additions to various monoterpenes, the addition to \((+)-2\)-carene (153) was not regioselective and gave \(\beta\)-lactam isomers 154 and 155 in a ratio of 3:2 (Scheme 29). After separation by crystallization, these \(\beta\)-lactams were converted to the corresponding amino acids 156 and 157.37

Another readily accessible starting material for the preparation of carbocyclic \(\beta\)-amino acid is chiral \((-)-apopi-
nene, prepared from commercially available (−)-myrtenal. Regio- and stereoselective CSI addition followed by lactam opening afforded enantiomerically pure lactam and amino acid 158 and 159 (Figure 11). 38

![Figure 11. Structures of a β-lactam and a β-amino acid derived from (−)-apopinene.](image)

As a convenient chiral natural source, (+)-myrtenal (160) was also efficiently used for the synthesis of cyclic β-amino acid enantiomers. Michael lithium amide trans-selective addition (for conjugate amine addition, see section 2.1.3) to ester 161 (derived from 160) gave 162, the debenzylation and ester hydrolysis of which led to a novel monoterpene-based trans-β-amino acid (163) in enantiomerically pure form (Scheme 30). 39

![Scheme 30. Synthesis of a β-Amino Acid from (+)-Myrtenal](image)

**2.1.7. Miscellaneous.** The Strecker reaction is a well-known general approach for the synthesis of α-amino acids. Enantiomerically pure carbocyclic αβ-diamino acid derivatives could be prepared with this method by reacting (R)-α-methylbenzylamine with amino ketone 164. Cyanide addition to the resulting imine 165 led to a mixture of diastereoisomers 166, which were separated by column chromatography after nitrile hydrolysis. Through removal of the chiral auxiliary and amide hydrolysis, the amide stereoisomers obtained (167 and 168) afforded the corresponding αβ-diaminocyclohexanecarboxylic acids 169 and 170 with an ee of 99% (Scheme 31). 40

The syntheses of all four enantiomers of cis- and trans-2-amino-cyclohexanecarboxylic acids were achieved from enantiomerically pure quinazolinone 171. Diastereoselective hydrogenation of 171 with PtO2 provided octahydroquinazolinone diastereoisomers 172, 173, and 174 in a ratio of 6:3:1. Cis-annelated derivatives 172 and 173 could be isomerized with KOt-Bu to give the corresponding trans-fused derivatives 174 and 175. Subsequently, all four octahydroquinazolinones (172–175) were converted by ring-opening with HCl, followed by ion-exchange chromatography, to furnish the corresponding two cis- and two trans-2-amino-cyclohexanecarboxylic acid enantiomers (Scheme 32). 41

Carbocyclic β-amino acids have also been synthetized through the radical addition–cyclization of sulfanilic compounds. Cyclization was achieved from oximes or hydrazones with thiophenol and AIBN as radical initiator, furnishing diastereomeric mixtures of 176 and 177 and of 178 and 179 in ratios of 3:3:1 and 2:1, respectively. The diastereomeric mixtures 176, 177 and 178, 179 were next transformed to the Boc-protected amine diastereomers 180, which were converted through sulfoxide 181 by pyrolysis to the cyclic exomethylene derivative 182. Hydroboration of the C−C double bond gave cis-amino alcohol 183 with high regio- and diastereoselectivity. In the last step, oxidation of 183 led to the Boc-protected cis-pentacin 184 (Scheme 33). 42 Via this procedure, various carbocyclic β-amino acids and heterocyclic analogs of cis-pentacin were synthetized, these examples revealing the great advantage of this method.

A relatively new approach to transpentacin was presented by Joosten et al. A highly trans-diastereoselective tandem hydrozirconation and Lewis acid-promoted cyclization of oxazolidines with an unsaturated side chain (185) furnished trans-
cyclopentane amino alcohol 186, which was next converted by debenzylation, oxidative cleavage, and Boc protection to amino alcohol 187. Removal of the O-protecting group, alcohol oxidation with NaIO₄ with a catalytic amount of RuO₂, and esterification afforded transpentacin derivative 188 (Scheme 34).43

2.2. Syntheses of Small-Ring Carbocyclic β-Amino Acids

As conformationally rigid compounds, β-aminocyclopropanecarboxylic acids are considered very attractive building elements for the synthesis of novel peptides. However, in consequence of their instability and high reactivity, they have only limited usage. In general, only the protected derivatives exhibit stability.44 The most common synthesis of β-aminocyclopropanecarboxylic acid derivatives involves the addition of a carbene analog such as diazomethane or a diazocarboxylate to a C–C double bond.44 Another method consists of the intramolecular ring closure (Michael-induced ring closure) of β-amino-γ-iodocarboxylates to cyclopropane amino esters.45 Carboxylate-substituted cyclopropanes may be constructed by the reaction of α-bromocarboxylate 189 with methyl acrylate. This reaction provided diastereomers 190 and 191 in a ratio of 4:1. After hydrolysis and treatment with AcCl, diester 190 furnished anhydride 193, which was then converted by esterification and Curtius rearrangement to the Boc-protected β-aminocyclopropane ester 195 (Scheme 35).45a

Scheme 32. Precursors for Cyclohexane β-Amino Acids from Benzopyrimidinones

Another easy route to β-aminocyclopropanecarboxylates starts from 2-bromocyclopropanecarboxylic ester 196 through a bromide secondary amide exchange by substitution in the presence of base and crown ether catalyst to give amino acid derivative 197 (Scheme 36).46

Although the building block potential in peptide synthesis of β-aminocyclobutanecarboxylic acids as conformationally rigid compounds is known, only a few such syntheses have been reported.47 Aitken et al. developed an efficient procedure for the synthesis of (1S,2R)- and (1R,2S)-β-aminocyclobutanecarboxylic acids 203 and 204 by using a chiral uracil mimic 198. The
photocycloaddition of ethylene to 198 afforded a mixture of cis-annelated cycloadduct diastereomers 199 and 200. This mixture could be separated by chromatography; subsequent transformations, finally involving heterocyclic ring hydrolysis, led to cyclobutane amino acid enantiomers 203 and 204 in overall yields of 33% and 20%, with an ee value of >97% (Scheme 37).48

Starting from the chiral uracil derivative, the same research group prepared all four stereoisomers of 2-aminocyclobutane-carboxylic acid enantiomers, by using a similar synthetic strategy involving photochemical (2 + 2)-cycloaddition and isomerization of the cis- to the trans-β-amino acid.49 The incorporation of cyclobutane cis-β-amino acids into peptides has also been reported.50 This technique of cycloaddition of an olefinic bond into the uracil derivative has been successfully applied for the preparation of hydroxymethylated β-amino-cyclobutanecarboxylic acid stereoisomers 205 and 206 (Figure 12).51

Figure 12. Hydroxylated cyclobutane β-amino acid stereoisomers.

Ortuno et al. synthetized enantiomers of cis-β-amino-cyclobutanecarboxylic acids from the enantiomerically pure hemiester 207, which was prepared by desymmetrization of meso-cyclobutane-1,2-dicarboxylic acid methyl ester. The synthetic protocol involved Curtius rearrangements of azidocarbonyl esters as the key step (Scheme 38). The opposite enantiomer of 204 was also prepared from hemiester 207.52

A novel approach for the preparation of cis- and trans-β-aminocyclobutanecarboxylic acid enantiomers used (R)-α-methylbenzylamine as chiral auxiliary, which on reaction with cis-amino acid 210 afforded diastereoisomers 211 and 212 in a ratio of 1:1. These two compounds were separated by chromatography, and then, after removal of the chiral auxiliary, the resulting amides were converted to cis-β-aminocyclobutanecarboxylic acid enantiomers 203 and 204. On treatment with NaOH, the amide intermediates underwent epimerization to yield the corresponding trans-β-amino acid enantiomers 213 and 214 (Scheme 39).53

As a general method for the synthesis of cyclic αβ-diaminocarboxylic acids (Scheme 28), the Strecker synthesis was efficiently used for the preparation of this type of compound containing a cyclobutane ring. For this purpose, aminocyclobutanone was first reacted with (S)-α-α-methylbenzylamine to give two of the four possible imine diastereoisomers (E/Z), which were transformed as a mixture without isolation on treatment with NaCN to give 216 and 217. After separation by chromatography, these derivatives were converted by chiral auxiliary removal and nitrile hydrolysis to cyclobutane amino acid enantiomers 218 and 219 (Scheme 40).54

The desymmetrization protocol of meso-anhydrides developed by Bolm et al. (section 2.1.5) also permitted the synthesis of enantiomerically pure cyclobutane β-amino acids.32

2.3. Syntheses of Carbocyclic β-Amino Acids with Larger Ring Systems

Although less abundant than the five- or six-membered derivatives, the larger-ring analogs of carbocyclic β-amino acids may be accessed by using several synthetic methods.
Although a good number of generally applicable and efficient methods are available for the synthesis of five- and six-membered cyclic trans-β-amino acids, there are fewer examples of the synthesis of analogs with larger ring systems, such as cycloheptane or cyclooctane derivatives.

A general procedure for the preparation of carbocyclic β-amino acids containing a larger than six-membered ring system is analogous to that for the five- or six-membered counterparts. It consists of the cycloaddition of CSI to carbocycles with one or two C=C double bonds in the ring. The addition of CSI to cyclooctene or 1,5-cyclooctadiene, for example, proceeded via the corresponding β-lactams to yield the racemic eight-membered cis-β-amino acids 220 and 221 (Figure 13).1a Analogously, 12-membered counterparts have been synthesized by using a similar protocol.15

Another method for the preparation of cycloheptane β-amino acid is based on catalytic asymmetric hydrogenation of the corresponding cyclic enamines (e.g., 222), affording cis-β-aminocarboxylate 223 (ee 80%). A Ru catalyst and a chiral phosphine ligand were used in this reaction (Scheme 41).8

A difluorinated cycloheptane cis-β-amino ester (230) was prepared from the cross-metathesis product 229 in several steps by C=C double bond saturation and ring closure via base-promoted Cl displacement as the key step (Scheme 43).12b Lithium amide conjugate addition to α,β-unsaturated esters (see section 2.1.3) was efficiently extended for the synthesis of cyclic cis-β-amino acids with larger ring systems. Thus, chiral lithium amide addition to 231 gave 232, which after deprotection led to the cyclooctane cyclic β-amino acid enantiomer 220 (Scheme 45), while from the diene derivative the corresponding cyclooctene β-amino ester was analogously obtained.56

A simple synthesis of seven- or eight-membered trans-β-amino acids from the readily available cis-2-hydroxycycloalkanecarboxylates (233) involves substitution of the hydroxy group with azide by inversion via the tosylates (234), which results in trans-2-azidocarboxylates 235. Azide reduction followed by ester hydrolysis afforded the corresponding cycloheptane and cyclooctane trans-β-amino acids 237a and 237b (Scheme 46). The method was also extended to the synthesis of the enantiomerically pure materials, starting from the enantiomerically pure esters (233) obtained by enzymatic resolution of the racemates.57

Access to seven-membered cyclic β-amino acid derivatives was achieved by ring-closing metathesis (for five- or six-membered analogs, see Scheme 7) of diolefinic intermediate 224 (derived from αβ-unsaturated esters and chiral amides), the result being the corresponding trans-β-amino cycloheptene ester 225, in which the olefinic bond is at a two C-atom distance from to the amine moiety (Scheme 42).12a

Ring-closing metathesis of 226 (derived from optically pure serine) was the key step for the synthesis of trans-β-aminocycloheptene ester enantiomer 227, in which the C=C double bond is at a three C-atom distance from the carbamate group (Scheme 43).12b

A difluorinated cycloheptane cis-β-amino ester (230) was prepared from the cross-metathesis product 229 in several steps by C=C double bond saturation and ring closure via base-promoted Cl displacement as the key step (Scheme 43).12b

Lithium amide conjugate addition to α,β-unsaturated esters (see section 2.1.3) was efficiently extended for the synthesis of cyclic cis-β-amino acids with larger ring systems. Thus, chiral lithium amide addition to 231 gave 232, which after deprotection led to the cyclooctane cyclic β-amino acid enantiomer 220 (Scheme 45), while from the diene derivative the corresponding cyclooctene β-amino ester was analogously obtained.56

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Scheme 40. Syntheses of Cyclobutane αβ-Diamino Acids

Scheme 41. Synthesis of a cis-Cycloheptane β-Amino Ester from the Corresponding Enamine

Scheme 42. Synthesis of a Cycloheptene β-Amino Ester by Metathesis

Scheme 43. Synthesis of a Cycloheptene β-Amino Ester from S-Serine

Figure 13. Cyclooctane and cyclooctene β-amino acids.
2.4. Synthesis of Functionalized Carbocyclic β-Amino Acids

Highly functionalized carbocyclic amino acids have aroused considerable interest in the past 10 years. Introduction of a functional group (e.g., hydroxy, azido, amino, fluoro) into the carbocycle of an amino acid may have a major influence on its biological activity and on the pharmacological properties of the subsequent peptides.

Some representative compounds, such as oryzoxymycin (238),1 peramivir (239),58 or Tamiflu (240),59 exhibit strong antiviral, antifungal, or antibacterial activities (Figure 14). Modified derivatives and other multisubstituted cyclohexane amino acids60 have recently been the focus of interest in synthetic and medicinal chemistry in view of their enormous pharmacological potential.

An increasing number of highly functionalized carbocyclic β-amino acids derivatives (analogs of Tamiflu) have been synthetized and investigated as potential antiviral agents in recent years (Figure 15).61

2.4.1. Syntheses of Functionalized Cyclic β-Amino Acids by C−C Double Bond Functionalization.

One main route to multisubstituted carbocyclic β-amino acids is based on the selective functionalization of their ring C−C double bond (Figures 3 and 4 contain several examples of starting materials). The most important methods involving these strategies are presented briefly in this section.

2.4.1.1. Functionalization via Selective Iodolactonization.

A method widely used for the regio- and stereoselective functionalization of carbocyclic β-amino acids consists of the iodolactonization of N-Boc-protected amino acids. For example, on treatment with KI/I2 in the presence of NaHCO3, cis-2-aminocyclohexane carboxylic acid 245 gave iodolactone 246 regio- and stereoselectively. Reductive deiodination with nBu3SnH, followed by lactone ring-opening and N-deprotection under acid catalysis, selectively furnished all-cis-S-hydroxylated β-aminocyclohexanecarboxylic acid 248 (Scheme 47).62

Figure 14. Some bioactive highly functionalized cyclic amino acids.

Figure 15. Structures of β-amino acid-modified Tamiflu analogs.
This method allowed the preparation of other regio- and stereoisomers of a series of other hydroxylated alicyclic β-amino acids.63

The iodolactonization procedure was easily applicable for the synthesis of hydroxylated carbocyclic β-amino esters with a C–C double bond in their ring. For example, iodolactone 246, obtained from 245 by treatment with DBU as base, was transformed by HI elimination to unsaturated lactone 249, which in the presence of NaOEt in EtOH at 0 °C gave all-cis-cyclohexene β-amino ester 250 (Scheme 48).64

Starting from 1,4-cyclohexadiene- or 1,3-cyclohexadiene-derived bicyclic lactams, the above methodology based on iodolactonization, HI elimination, and subsequent lactone ring-opening was successfully used for the synthesis of other hydroxylated β-amino cyclohexencarboxylates (Figure 16).64,65

The ring C–C double bond of hydroxylated cyclic β-amino acids offers a possibility for further selective functionalizations, leading to the synthesis of different highly functionalized bioactive compounds. Thus, all-cis-methyl 5-hydroxy-2-amino-cyclohexene carboxylate was used as a precursor in the synthesis of the antibiotic Fortamycine.66

The hydroxy function selectively attached to the carbocycle of a β-amino acid may also be transformed to a series of other functional groups. Hydroxylated amino ester 255 was easily converted via mesylation, followed by meslyoxy group substitution with azide and reduction, to orthogonally protected diaminocyclohexencarboxylate stereoisomers 257 and 258 (Scheme 49).67

Stereo- and regioselective hydroxylation and hydroxy–azide interconversion were the key steps for the synthesis of other orthogonally protected diaminocyclohexencarboxylic acid stereoisomers (259 and 260) (Figure 17).68

Because of the considerable importance of fluorinated organic molecules, and especially of fluorinated amino acids, in the area of medicinal chemistry and drug research, much effort has been devoted to the synthesis of fluorinated cyclic β-amino acids. By using organic fluorinated agents such as diethylaminosulfur trifluoride (DAST) or bis(2-methoxyethyl)-aminosulfur trifluoride (Deoxo-Fluor), a hydroxy–fluorine interconversion can be effected. Hydroxylated β-amino acids are excellent, readily available precursors for this purpose. Thus, on treatment with DAST, 3-hydroxylated cyclohexene β-amino ester 253 reacted via an S_N2′ mechanism to give 5-fluoro-2-amino cyclohexencarboxylate 262, while the corresponding saturated derivative 261 underwent inversion under similar conditions and yielded 3-fluorinated β-amino cyclohexencarboxylic ester 263 (Scheme 50).65

As discussed earlier (Scheme 10), geminal difluorinated cyclic β-amino acids have been synthetized efficiently from difluorinated imidoyl chloride synthons by metathesis as key step. However, the hydroxylated β-amino cyclohexencarboxylic esters presented above (Figure 16) could be used not only for the synthesis of monofluorinated compounds but also for the direct preparation of difluorinated amino esters via the corresponding oxo derivatives. For example, oxidation of the hydroxy group in hydroxylated amino ester 261 gave rise to oxo ester 264, which on treatment with Deoxo-Fluor underwent fluorination to furnish difluorinated amino ester 265 (Scheme 51).65

Both of the above approaches for the synthesis of mono- or difluorinated 2-amino cyclohexencarboxylates were also ex-
cellent methods for the synthesis of a series of other novel fluorine-containing six-membered cyclic $\beta$-amino acid regio- and stereoisomers, from either 1,3-cyclohexadiene- or 1,4-cyclohexadiene-derived bicyclic $\beta$-lactam through selective iodolactonization and hydroxylation followed by hydroxy-fluorine or oxo-fluorine exchange.65,69

The regio- and stereoselective iodolactonization offered an opportunity for the selective preparation of epoxycyclohexane $\beta$-amino acids.70 As an example, iodolactone 267 derived from amino acid 266 under basic conditions took part in lactone opening, followed by intramolecular iodine displacement with a hydroxyl group, and easily furnished epoxy amino acid 268 (Scheme 52), which would otherwise have not been possible to synthetize by the direct epoxidation of 266 with peracids.70

2.4.1.2. Functionalization via Selective Iodo oxazinone and Iodo oxazoline Formation. Another method in which the key step is the functionalization of the C–C ring double bond of a cyclic $\beta$-amino acid derivative with iodine or N-iodosuccinimide (NIS), followed by intramolecular nucleophilic ring closure, is iodo oxazinination or iodo oxazoline formation. In contrast with iodolactone formation, in this type of functionalization the starting materials are the N-protected amino esters, in which the absence of the carboxylate nucleophile leads to the carbamate O-atom functioning as a nucleophilic center. Another efficient route for the synthesis of hydroxylated $\beta$-amino cyclohexanecarboxylic acids was based on iodo oxazinination.

Amino ester 269 reacted with NIS to give oxazinone derivative 270 regio- and stereoselectively. After dehalogenation with nBu$_3$SnH, followed by simultaneous oxazinone opening and ester hydrolysis in the presence of aqueous HCl, this heterocyclic derivative afforded 4-hydroxylated 2-amino cyclohexanecarboxylic acid 272 (Scheme 53).62,71 The particular benefit of the iodo oxazinination method in comparison with iodolactonization (where 5-hydroxylated derivatives were formed) lay in the possibility of the preparation of a 4-hydroxylated cyclohexanecarboxylic amino acid.

When the starting derivative contained an amide function instead of a carbamate group, the above procedure involved not iodo oxazinone nor iodo oxazolinone, but oxazine or oxazoline formation. Thus, on treatment with N-bromosuccinimide (NBS), amino ester 273 provided bromooxazoline 274, which was next converted to hydroxylated $\beta$-aminocyclopentanecarboxylic acid 276 (Scheme 54).72

The iodo oxazinination and iodo oxazolination method was readily utilized for the synthesis of a series of other hydroxylated five- and six-membered carbocyclic amino acid regio- and stereoisomers and for bicyclic norbornane derivatives.63

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A novel route to hydroxylated cyclohexane $\beta$-amino acids, based on selective oxazoline formation, though not with electrophile (iodine)-induced cyclization, started from trichloro imidate 277. A base-initiated ring closure by a Michael addition afforded oxazolines 278 (cis:trans = 73:27). A novel route to hydroxylated cyclohexane $\beta$-amino acids, based on selective oxazoline formation, though not with electrophile (iodine)-induced cyclization, started from trichloroimidate 277. A base-initiated ring closure by a Michael addition afforded oxazolines 278 (cis:trans = 73:27). The oxazoline stereoisomers were separated by chromatography and submitted to acidic ring-opening to give 3-hydroxylated $\beta$-aminocyclopentanecarboxylic acid derivatives 279–281 (Scheme 55). With the use of this strategy, hydroxylated five-membered carbocyclic $\beta$-amino acids were also prepared.73

Scheme 50. Syntheses of Fluorinated Cyclohexane 2-Aminocarboxylates

Scheme 51. Synthesis of a Difluorinated 2-Aminocyclohexane Amino Ester

Scheme 52. Synthesis of an Epoxy Amino Acid with a Cyclohexane Skeleton

Scheme 53. Synthesis of a 4-Hydroxylated 2-Aminocyclohexanecarboxylic Acid via Iodo oxazinone Formation

Scheme 54. Synthesis of a 3-Hydroxylated 2-Aminocyclopentanecarboxylic Acid

Scheme 55. Synthesis of a 3-Hydroxylated 2-Aminocyclopentanecarboxylic Acid
2.4.1.3. Functionalization via Selective Iodolactamization.
Campbell et al. reported a special functionalization procedure for cyclohexenecarboxylic acid derivative 282, based on regio- and stereoselective iodolactamization. On treatment with nBuLi and I2, N-protected amide 282 furnished iodolactam 283. Subsequent reductive deiodination and lactam opening resulted in the orthogonally protected cyclohexane diamino alcohol 285 (Scheme 56).74

2.4.1.4. Functionalization via Stereoselective Epoxidation and Regioselective Oxirane Opening. Another broadly applicable and successful method for the synthesis of highly functionalized carbocyclic β-amino acids starts with stereoselective epoxidation of the ring C–C double bond, followed by regioselective oxirane ring-opening. In 2003, Steel and co-workers reported the enantioselective synthesis of a hydroxylated carbocyclic β-amino acid derivative, the antibiotic oryzoxymycin ([–]-238). Enantioselective hydrolysis (pig liver esterase, PLE) and ring-opening under basic conditions of a β-amino ester with an oxabicyclic framework (286) led to hydroxylated amino acid enantiomers 287 and 288 in an approximate ratio of 1:1. Enantiomer 287 was the intermediate for the preparation of ([–]-oryzoxymycin (Scheme 57).75 Other stereoisomers and saturated counterparts of 287 were prepared analogously.76

The hydroxylated β-amino esters synthetized by the above procedures were subjected to epoxidation by the same group of authors. For example, the selective oxidation of 287 with m-chloroperbenzoic acid (mCPBA) in CH2Cl2 gave epoxymino ester diastereoisomers 289:290 in a ratio of 9:1 (77%), whereas in the more polar solvent MeCN the ratio of the products was 1:2 (95%) (Scheme 58). After separation of the two diastereoisomers (289 and 290), under catalytic hydrogenation conditions they participated in simultaneous olefinic bond saturation and oxirane opening in the presence of Ac2O to result in diacetoxylated β-amino esters 291 and 292.

An alternative procedure to iodolactonization and iodooxazinization (see earlier) for the selective introduction of a hydroxy group onto the skeleton of a cyclic β-amino acid consists of stereoselective ring C–C double bond epoxidation, followed by regioselective oxirane opening. Thanks to the H-bonding directing effect of the carbamate, treatment of trans-amino ester 297 with mCPBA cis-stereoselectively afforded...
epoxy derivative 298, in which the oxirane ring and the carbamate at C-2 are in a cis stereochemical arrangement. Compound 298 reacted with NaBH₄ (as a hydride source) to undergo regioselective oxirane opening, leading to 5-hydroxylated 2-aminocyclohexanecarboxylate 299, the ester hydrolysis and N-deprotection of which afforded hydroxylated amino acid 300 (Scheme 60).≤8

Scheme 60. Synthesis of a Hydroxylated β-Amino Acid via Selective Epoxidation and Oxirane Opening

The crucial step in the synthesis of other hydroxylated cyclic β-amino acids was cis-selective epoxidation, followed by regioselective oxirane opening. Thus, under conditions similar to those described in Scheme 60, ethyl cis-2-benzyloxycarbonylaminoctenecarboxylate, a stereoisomer of 297, led selectively to all-cis-4-hydroxylated 2-aminocyclohexanecarboxylic acid and its C-1 epimer.≤9 These hydroxylated amino acids were also prepared in enantiomerically pure form. The starting enantiomerically pure cyclohexene amino acid was obtained by enzymatic hydrolysis or the corresponding bicyclic lactam opening reaction, followed by esterification and N-protection. On application of the same processes as for the racemic compounds, the desired hydroxylated cyclohexane β-amino acid enantiomers were finally obtained.≤8,≤9

Not only cis-selective but also trans-selective epoxidation can be efficiently utilized for the stereo- and regioselective hydroxylation of carbocyclic β-amino acids. Epoxidation of the olefinic bond of N-protected bicyclic lactam 301 was achieved stereoselectively with opposite selectivity, with the formation of trans-epoxy derivative 302, in which the oxirane and carbamate are in a trans steric arrangement. Lactam ring-opening with NaΟEt under different conditions provided epoxy amino ester 303 and its C-1 epimer 304, the oxirane opening of which under reductive conditions with NaBH₄ permitted the preparation of other novel hydroxylated cyclohexane β-amino acid derivatives (305 and 306) (Scheme 61).≤9

Scheme 61. Syntheses of Hydroxylated β-Amino Acids via Selective Epoxidation and Oxirane Opening

Selective epoxidation proved to be an efficient method not only for hydroxylation but also for the introduction of other functional groups onto the carbocycle of a β-amino acid. Three useful epoxy β-amino ester stereoisomer intermediates (307–309) for this purpose were prepared from 2-aminocyclopentene-carboxylic acid or from a cyclopentadiene-derived bicyclic β-lactam by means of epoxidation based on opposite selectivities (Figure 18).≤80

Figure 18. Structures of epoxy β-aminocyclopentanecarboxylates.

These epoxy amino esters were then subjected to azidolysis with NaN₃, resulting regioselectively in the corresponding 4-azido-substituted β-amino esters 310–313 (Figure 19).≤80 These compounds can be regarded as orthogonally protected ββββ-diaminocarboxylic acid derivatives.

Figure 19. Structures of Azido β-Aminocyclopentanecarboxylates.

The enantiomers of the above azido esters were also prepared by starting from the corresponding enantiopure cyclopentene β-amino acid, which was prepared by enzymatic resolution of its bicyclic β-lactam precursor.≤80

An optically active 1,2,3-triazole-substituted cispentacin derivative was synthesized when azido amino ester 310 was reacted with symmetrical diethyl acetylenedicarboxylate through an azide−alkyne 1,3-dipolar cycloaddition. The reaction took place readily in refluxing EtOH to give enantiopure 314 (Scheme 62). Analogously, azido esters stereoisomers 311–313 were converted to the corresponding triazole-functionalized cyclopentane β-amino acid derivatives.≤81

Other 1,2,3-triazole-substituted cispentacins were synthesized when the earlier prepared azido cyclopentane amino esters were reacted with unsymmetrical acetylenes. Thus, the reaction of azido ester 310 with ethyl propiolate (R₁ = CO₂Et, R₂ = H) under thermal conditions without the addition of a Cu(I)
catalyst furnished 1,4-disubstituted 1,2,3-triazole derivative 315 regioselectively. With other acetylenes, however, when R1 = Pr or Ph and R2 = H, the reaction proceeded with CuI to give 1,4-disubstituted triazole derivatives 316 and 317 regioselectively (Scheme 62).82

Azidolysis of epoxycyclohexane β-amino ester 318 in the presence of NH4Cl proceeded smoothly to a 5-azido ester 319 by 100% regioselectively (Scheme 63). However, when AlCl3 was used as additive in this reaction, the coordinating ability of Al and the diaxial preferred conformations during the oxirane opening of the epoxycyclohexane meant that the reaction gave rise to a mixture of azido ester regioisomers 319 and 320 in a ratio of 1:1.83 These were separated and isolated by chromatography (Scheme 63).83

A nitrile function can be introduced on the carbocycle of a β-amino acid by starting from epoxy amino esters. Thus, treatment with Et2AlCN epoxide 318 furnished two regioisomers, the 4- and 5-nitrile-substituted products, in a ratio of approximately 2.5:1.83 However, when epoxide 321 underwent oxirane opening under similar conditions, 322 was formed 100% regioselectively (Scheme 64).83

A series of other novel nitrile- and azide-functionalized cyclohexane amino ester regio- and stereoisomers have been synthetized in racemic and enantiomerically pure form.85

2.4.1.5. Functionalization via Stereoselective Dihydroxylation. Hydrolysis of optically active cis-α-amino acid derivative 323, benzyl esterification, and cis-dihydroxylation in the presence of OsO4 resulted in dihydroxylated β-amino ester 324, in which the two hydroxy groups are oriented trans to the ester and carbamate functions. Transformation of Diels-Alder cycloadduct 325 by formyl group oxidation, benzyl ester formation, and dihydroxylation furnished the same amino ester 324 (Scheme 65).84

Dihydroxylation of cis-2-amino cyclopentanecarboxylic ester 329 with NMO/OsO4 proceeded stereoselectively with the formation of dihydroxy amino ester 330, in which the two hydroxy groups are in a trans relationship with the ester and carbamate. Simultaneous N-deprotection and ester hydrolysis under acidic conditions led to dihydroxylated cispentacin 331. In contrast, dihydroxylation of trans-amino ester 332, which was obtained by epimerization of 329 at C-1 with NaOEt, resulted stereoselectively in dihydroxylated amino ester 333, in which both hydroxy functions are oriented cis to the carbamate. Ester hydrolysis and Boc protection in acidic medium gave dihydroxylated transpentacin 334, a stereoisomer of 331 (Scheme 67).72

The above dihydroxylated cyclopentane β-amino acids were also prepared in enantiomerically pure form. Starting from the racemic bicyclic β-lactam, enzymatic lactam opening and then esterification and N-Boc protection led to optically pure amino ester 329. Following the synthetic steps presented in Scheme 67, enantiomerically pure dihydroxylated amino acids were accessed.72

Analogously to the methodology presented above, various dihydroxylated cyclohexane β-amino acid regio- and stereoisomers were also synthetized by OsO4-catalyzed dihydroxylation.85 The vicinal dihydroxylated carbocyclic β-amino-
carboxylic esters proved to be valuable synths for the preparation of N-heterocyclic \( \beta \)-amino acid derivatives (see sections 3.1.3.5 and 3.1.4).

2.4.1.6. Functionalization via 1,3-Dipolar Cycloaddition. 1,3-Dipolar cycloaddition of nitriles to a C–C double bond is a widely used efficient method for the construction of an isoxazoline skeleton and has also been utilized for functionalization of the olefinic bond of carboxylic \( \beta \)-amino acids. Isoxazoline-fused cispentacins were synthesized by this methodology. Addition of nitrile oxide generated from nitroethane with \( \text{Boc}_2\text{O}/\text{DMAP} \) to ethyl cis-2-amino cyclohexanecarboxylate (329) yielded three of the four possible regio- and stereoisomers, 335, 336 and 337, in a ratio of 6:1:0.7 (Scheme 68). These compounds were separated and isolated by means of chromatography.

However, when the reaction was carried out under similar conditions with ethyl trans-2-amino cyclopentene carboxylate, the C-1 epimer of 329, the cycloaddition was 100% selective, furnishing only one cycloaddition product, which could also be prepared by epimerization of the minor derivative 337.87 Moreover, cycloaddition to 329 with the nitrile oxide generated from \( \text{PhNCO} \) and \( \text{Et}_3\text{N} \) resulted 100% regio- and stereoselectively in isoxazoline-fused derivative 335.87

The synthetic procedure designated to obtain isoxazoline-fused cispentacin derivatives was extended to the preparation of the enantiomerically pure substances. Enzymatic lactam opening of the racemic bicyclic \( \beta \)-lactam, followed by esterification and N-protection, afforded optically pure amino ester 329, which was next submitted to dipolar cycloaddition, leading to optically pure isoxazoline-fused cispentacins.87

The enormous advantage of the dipolar cycloaddition of nitrile oxide to cycloalkene \( \beta \)-amino acids lies in the opportunity for the selective preparation of highly functionalized derivatives of this class of compounds by isoxazoline ring transformation. When subjected to heterocycle opening under reductive conditions with concomitant imine hydrolysis in the presence of \( \text{HCO}_2\text{NH}_4 \) and Pd/C as catalyst, isoxazoline-fused cispentacin derivative 335 afforded oxo amino ester 338 (Scheme 69).88

2.4.2. Several Relevant Routes to Functionalized Cyclic \( \beta \)-Amino Acids Other Than Functionalization of the Ring C–C Double Bond. Functionalized carboxylic \( \beta \)-amino acids have not only been obtained by transformation of the ring C–C double bond. The most relevant other routes were mentioned earlier in connection with the most general approaches to this class of compounds.2a,7,14,15,20 Polyhydroxylated alicyclic \( \beta \)-amino acid stereoisomers were prepared in enantiomerically pure form from optically pure nitrohexofuranoses in eight or nine steps.89 A didymolysis of \( \alpha,\beta \)-epoxy cyclohexanecarboxylates in a metal-catalyzed one-pot reaction afforded cyclohexane \( \alpha \)-hydroxy-\( \beta \)-amino acids.90 Another route to substituted alicyclic \( \beta \)-amino acids is based on a stereocentered three-component reaction. The CAN-catalyzed one-pot reactions between alkyamines, \( \beta \)-keto esters, and chalcones gave cis-4,5-disubstituted 2-amino cyclohexanecarboxylates.91

3. CYCLIC \( \beta \)-AMINO ACIDS WITH A HETERATOM IN THE RING

Although slightly less abundant than their carboxylic analogs, the heterocyclic \( \beta \)-amino acids are an interesting class of derivatives because of their important biological activities, and an ever-increasing number of publications have appeared on these compounds during the past 10 years. As an example, the four-membered cyclic \( \beta \)-amino acid with an \( O \) atom in the ring, \((2R,3S)-3\)-amino oxetane-2-carboxylic acid or oxetin \((344)\), exhibits antibiotic and herbicidal activity (Figure 21).92

The unsubstituted \( \beta \)-amino acid with a pyrrolidine framework (APC, 345; Figure 21) has been used in combination with ACP (\( \beta \)-amino cyclo pentanecarboxylic acid) as a building element in the construction of novel peptides with antimicrobial activities.93 A number of the functionalized pyrrolidine-based \( \beta \)-amino acids (e.g., 346) are known to be efficient TACE inhibitors and also display antitumoral activity (see ref 94 and references cited therein).

Scheme 68. Syntheses of Isoxazoline-Fused Cispentacin Derivatives

Scheme 69. Reduction of an Isoxazoline-Fused Cispentacin Derivative

Scheme 70. Formation of a Highly Functionalized Cispentacin Derivative from an Isoxazoline-Fused Precursor

Figure 20. Structures of highly functionalized cispentacin derivatives.
Other heterocyclic \( \beta \)-amino acids (Figure 22; see also section 3.2.3.2) are key elements in many bioactive products. Some of them are nucleoside-based antibiotics, e.g., blasticidin S (347), gougerotin (348), and chryscandin (349) (see ref 95 and references cited therein). The pyran-based \( \beta \)-amino acids have been gaining in importance as analogs of the antiviral agent zanamivir (350; Figure 22; see also section 3.2.3.3).28

**3.1. Syntheses of Cyclic \( \beta \)-Amino Acids**

Among the large number of synthetic methods available for the preparation of heterocyclic \( \beta \)-amino acids in which the carboxylic and the amino functions are connected to stereogenic C-centers, several are analogous to procedures already described for their carbocyclic counterparts, but many transformations are specific methods that depend on the heteroatom (N or O) and the ring size.

### 3.1.1. Three- and Four-Membered \( N \)-Containing Cyclic \( \beta \)-Amino Acids

Analogously to the cyclopropane \( \beta \)-amino acids, the heterocyclic substances containing an N atom are unstable derivatives, which in general tend to serve as intermediates for the preparation of other derivatives. Thus, addition of ethyl \( N \)-(4-nitrobenzenesulfonyl)oxy)carbamate (NsONHCO\(_2\)Et) to unsaturated amino esters 351 leads to an aziridine intermediate 352, which readily undergoes hydrolysis to give oxo amino ester 353 (Scheme 71).97

Azirine carboxylate 354 has been used as an alkylating agent for different amines. When 354 was treated with amines in the presence of Na\(_2\)CO\(_3\), the products were aziridine amino carboxylates 355, which could be easily transformed to various other derivatives (Scheme 72).29

**Scheme 71. Transformation of an Aziridine \( \beta \)-Amino Acid Intermediate**

![Scheme 71](image)

**Scheme 72. Three-Membered \( N \)-Heterocyclic \( \beta \)-Amino Acids**

![Scheme 72](image)

\( \beta \)-Amino acids containing the four-membered azetidinone skeleton are elements of peptide-based antitumoral antibiotics, e.g., deoxybouvardin (a bicyclic hexapeptide) analogs. Azetidinone amino ester enantiomer 362 was prepared from chiral oxazolidinone 356, which was converted in a Staudinger reaction to \( \beta \)-lactam derivative 358. Ozonolysis and formyl group reduction gave 359, which was subjected to reductive conditions, N-protection, hydroxymethyl oxidation, and esterification to furnish 362 (Scheme 73).99

Et\(_2\)AlCl-promoted coupling of imine 363, followed by ring closure of the syn and anti adduct mixture of 364 in the presence of i-PrMgBr, resulted in a mixture of trans- and cis-azetidinone \( \beta \)-amino carboxylates, 365 and 366 (Scheme 74).100

Four-membered \( N \)-heterocyclic \( \beta \)-amino acid derivatives have been synthesized from \( \alpha \)-amino-\( \beta \)-\( \gamma \)-aziridino esters by an aziridine ring-opening ring-closure protocol. When heated in MeCN in the presence of Et\(_3\)N, aziridinone derivatives 367, obtained by the addition of glycine esters to \( \alpha \)-chlorosulfonylmines followed by imine reduction,101 furnished azetidine \( \beta \)-amino esters 368 (Scheme 75).5a

The asymmetric version of this method starts from the optically active \( \alpha \)-chlorinated toluenesulfinimine, which reacts with glycine esters via aziridine derivative 369 to give azetidine \( \beta \)-amino acid enantiomer 370 (Scheme 75).5b

### 3.1.2. Five-Membered \( N \)-Containing Cyclic \( \beta \)-Amino Acids

In contrast with the three- and four-membered heterocyclic \( \beta \)-amino acids, the five-membered \( N \)-heterocyclic \( \beta \)-amino acids comprise a large group of compounds. Accordingly, the range of synthetic methods applied to access this class of products is far wider. The following sections will describe the most generally applicable synthetic routes, together with several special methodologies.

#### 3.1.2.1. Synthesis by Amino Group Conjugate Addition

The procedure discussed in section 2.1.3 for amino group conjugate addition to unsaturated carbocyclic esters is also an efficient general method for the construction of five-membered \( N \)-heterocyclic \( \beta \)-amino acids. N-Heterocyclic unsaturated ester 371, prepared by reductive deoxygenation of the corresponding oxo ester, was a suitable starting compound for this purpose. Michael addition of \((R)\)-\( \alpha \)-methylbenzylamine to \( \alpha \)-unsatu-

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**Figure 21.** Some bioactive heterocyclic \( \beta \)-amino acids.

![Figure 21](image)

**Figure 22.** Several bioactive compounds with a \( \beta \)-amino acid element in their structure.

![Figure 22](image)
rated ester 371 afforded a trans-amino ester derivative containing a pyrrolidine ring, 372. After removal of the chiral auxiliary by reductive methods, amino ester enantiomer 373 was obtained (Scheme 76).102

β-Aminopyrrolidinecarboxylic acid (APC) and β-amino-cyclopentanecarboxylic acid (ACPC) have been used as building residues for the construction of β-peptide oligomers.93,103

Scheme 75. Syntheses of β-Amino Acid Derivatives Containing an Azetidine Skeleton

Scheme 76. Synthesis of Pyrrolidine β-Amino Esters by Conjugate Addition to an Unsaturated Ester

A rather interesting process with regard to the products of conjugate addition was observed when lithium dibenzylamide was added to unsaturated tert-butyl ester 377. Ester 377 was obtained by the Michael addition-condensation of glycine ester 374 and reaction with tert-butyl acrylate, via the corresponding enolate 375. In contrast with the addition of (R)-α-methylbenzylamine (see Scheme 76), treatment of 377 with lithium dibenzylamide at −78 °C yielded the cis-amino ester derivative 378 as the major product, along with pyrroline (379) and pyrrole (380) compounds as minor derivatives (Scheme 77).104 Such cis-selective addition was also observed when lithium (S)-N-benzyl-N-α-methylbenzylamide was added to ester 381, with the formation of β-amino acid derivative 382. The trans counterpart 383 could be readily prepared by the isomerization of 382 at C-1 in the presence of t-BuOK in refluxing t-BuOH. Reductive removal of the chiral auxiliary and ester deprotection in both 382 and 383 led to the pyrrolidine β-amino acid enantiomers cis-384 and trans-385 (Scheme 78).104
These heterocyclic β-amino acids are themselves bioactive derivatives; for example, cis-4-aminopyrrolidine-3-carboxylic acid (384) is a GABA (γ-aminobutyric acid) receptor, while cis-N-Boc-4-aminopyrrolidine-3-carboxylic acid (386) is a modest influenza neuraminidase inhibitor. They additionally serve as precursors for the synthesis of other important active influenza neuraminidase inhibitors, such as 387 (Figure 23).104

Amine conjugate addition to α,β-unsaturated esters was also efficiently applied for the synthesis of pyrrolidine β-amino acids. Unsaturated amino ester 388 underwent Michael addition on reaction with chiral amine 389, leading to products 390 and 391 in a ratio of 1:1, which were separated by chromatography. Cleavage of the trichloroacetyl group under basic conditions, esterification with diazomethane, and oxidative removal of the chiral auxiliary resulted in β-amino ester enantiomer 392, containing a γ-lactam skeleton (Scheme 79).105

The same research group utilized analogous methods to prepare other pyrrolidinone-based β-amino acid stereoisomers as conformationally restricted analogs of aspartic acid and peptidomimetics for the synthesis of novel β-foldamers.106

Enantiomerically pure 1-oxyl-2,2,5,5-tetramethylpyrrolidine-carboxylic acids were also synthetized as spin-labeled β-amino acids (399 and 400) by a conjugate addition procedure. αβ-Unsaturated nitrile 394 derived from amide 393 underwent NH₃ addition to give racemic amino nitrile 395, in which the amino and nitrile functions are in a trans relationship. Nitrile hydrolysis and amine protection with Fmoc furnished amino acid 396. This was next reacted with the chiral (R)-2,2-dihydroxy-1,1′-binaphthyl in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and DMAP to afford amino ester diastereomers 397 and 398, which were separated and isolated by means of chromatography. Next, removal of the chiral auxiliary by basic hydrolysis, N-Fmoc protection, and esterification with 7-aza-1-hydroxy-1,2,3-benzotriazole (HOAt), N-methylmorpholine (NMM), and EDC resulted in amino ester enantiomers 399 and 400 (Scheme 80).107

3.1.2.2. Syntheses by Cycloaddition. Intramolecular 1,3-dipolar nitrone cycloaddition to an chiral ketene dithioacetal
dioxide was the crucial step for the preparation of pyrrolidine \(\beta\)-amino acids. Amino acetal 403, containing a formyl moiety, derived from 401 by allylation and oxidative C–C bond cleavage, was reacted with chiral phosphonate 404 to give 405. Treatment of 405 with \(\rho\)-TsOH and \(N\)-benzylhydroxylamine (BnNHOH) led through the corresponding nitrone intermediate by intramolecular 1,3-dipolar cycloaddition to isoxazolidine-fused pyrrolidine derivative 406. Under reductive conditions, with isoxazolidine opening, followed by removal of the \(N\)-protecting groups, 406 furnished the \(N\)-heterocyclic amino acid enantiomer 408 (Scheme 81).108

The construction of an isoxazolidine-fused pyrrolidine ring via intramolecular nitroene 1,3-dipolar cycloaddition was the key step in the synthesis of orthogonally protected amino acid enantiomer 413. Unsaturated aldehyde 409 was reacted with chiral hydroxylamine derivative 410 via nitrone formation to obtain isoxazolidine diastereoisomers 411 and 412 regioselectively in a ratio of 96:4. After separation from the minor derivative, hydrogenolysis of 411, \(N\)-protection, and oxidation provided pyrrolidine \(\beta\)-amino acid enantiomer 413 (Scheme 82).108

The pyrrolidine skeleton of \(N\)-heterocyclic \(\beta\)-amino acids can be efficiently created by azo-methinylide (3 + 2)-cycloaddition of benzylglycine to benzyl methyl maleate (414). \(N\)-Benzyglycine and paraformaldehyde were reacted with ester 414 to obtain 415, the debenylation and \(N\)-Boc protection of which resulted in its half-ester. Curtius rearrangement of this gave pyrrolidine \(\beta\)-amino ester 416, which was next coupled with carboxylic acid derivative 417 to furnish ester 418. \(N\)-Boc deprotection of 418 and its conversion to hydroxymic acid afforded 419, a selective inhibitor of the TNF-\(\alpha\) converting enzyme (Scheme 83).2k A series of similar bioactive products

Scheme 80. Syntheses of 1-Oxypyrrolidine \(\beta\)-Amino Acids

Scheme 81. Synthesis of a cis\(\beta\)-Amino Acid Containing a Pyrrolidine Core from Ketene Dithioacetal Dioxide
containing a pyrrolidine \( \beta \)-amino acid element have also been synthetized and investigated.\(^{109} \)

### 3.1.2.3. Syntheses from \( \beta \)-Keto Esters

Alicyclic \( \beta \)-oxo esters are convenient starting compounds for preparation of the corresponding five- or six-membered \( \beta \)-amino acids (see section 2.1.1). Cyclic \( \beta \)-oxo esters with an \( N \) atom in the ring are also suitable precursors for the preparation of \( N \)-heterocyclic \( \beta \)-amino acids. This is one of the most common routes to this class of compounds. Amination of enolate \(^{420} \) (prepared as presented in Scheme 77) with benzylamine and AcOH in MeOH furnished enamino ester \(^{421} \), the cis-selective reduction of which with NaBH\(_4\) provided pyrrolidine \( \beta \)-amino ester \(^{422} \), in which the ester and amino functions are in a cis relationship. This compound could be readily converted to an orthogonally protected amino acid \(^{424} \) (Scheme 84).\(^{110} \)

Various pyrrolidine \( \beta \)-amino acid analogs that behave as neuramidase inhibitors have been synthetized by the \( \beta \)-keto ester reduction methodology.\(^{60b,110} \)

The asymmetric variation of the \( \beta \)-keto ester transformation procedure for the preparation of \( \beta \)-amino acids containing a pyrrolidine ring was efficiently applied by Gellman and co-workers for the synthesis of these compounds in optically pure form. N-Cyclic oxo ester \(^{425} \) was reacted with \((R)-(\pm)-\alpha\)-methylbenzylamine to give enamine \(^{426} \), the reduction of which proceeded trans-selectively and led to trans-\( \beta \)-amino ester derivative \(^{427} \). Ester hydrolysis of \(^{427} \), chiral auxiliary removal, and \( N \)-Fmoc protection furnished the optically pure, orthogonally protected pyrrolidine \( \beta \)-amino ester \(^{429} \) (Scheme 85).\(^{111} \)
Similar transformations were performed by starting from 420, with (S)-(-)-α-methylbenzylamine as chiral auxiliary.6 The chiral N-heterocyclic β-amino acid was applied for the synthesis of peptide oligomers in combination with its carbocyclic analog or with nucleoside β-amino acid analogs.112 Pyrrolidine β-amino acids with an attached carbohydrate were incorporated into peptide sequences with 2-amino-cyclopentanecarboxylic acid (ACPC), forming a 12-helical foldamer in aqueous solution. Amino ester 427, synthesized from the corresponding oxo ester, was converted to 430 by ethyl ester hydrolysis, benzyl ester formation, Boc-deprotection, and N-sulfonamide formation. The sugar moiety was attached to 430 in a cross-metathesis reaction with unsaturated monosaccharide 431 (Scheme 86).113

Scheme 86. Synthesis of a Pyrrolidine β-Amino Acid with a Carbohydrate Moiety

N-Aryl β-enamino esters based on a pyrrolidine skeleton, synthetized by reductive amination of the corresponding β-oxo esters, were described as intermediates for the preparation of different carboxylic esters containing the pyrrolol[3,2-b]-quinoline ring system.114 Besides the use of a chiral auxiliary (Schemes 85 and 86), the asymmetric syntheses of pyrrolidine β-amino acids can also be achieved by enantioselective reduction of β-enamino esters 433 with a Ru catalyst in the presence of a chiral phosphine ligand (see Scheme 4 for carbocyclic analogs). The reduction of enamine 433 resulted in optically pure 434 with an ee value of 95% (Scheme 87).8

3.1.2.4. Syntheses by Intramolecular Radical Cyclization. Sulfanyl radical addition—cyclization of oxime ethers linked to alkenes through an N atom (435) yielded cis- and trans-cyclized products 436 and 437 in a ratio of 3:1. After separation of these diastereoisomers, trans isomer 437 was subjected to N-Boc protection and oxidation with mCPBA to give sulfoxide derivative 439. Acidic hydrolysis of 439 next afforded aldehyde 440, whose formyl moiety was oxidized to give the corresponding ester 441. Cleavage of the oxime ether, followed by ester hydrolysis and N-Boc deprotection, led to β-amino acid 442 (Scheme 88).42

The above intramolecular radical cyclization protocol has likewise been used to synthetize other novel substituted pyrrolidine β-amino acids.42

3.1.2.5. Syntheses from Hydroxylated Proline Precursors. Optimally active hydroxylated prolines are efficient and important precursors for the preparation of pyrrolidine β-amino acids in enantiomerically pure form. After N-Cbz protection, benzyl ester formation, and elimination via the tosylate, trans-4-hydroxy-L-proline (443) furnished the unsaturated proline derivative 444. This was next subjected to C=C double bond functionalization through epoxidation with mCPBA, to give cis- and trans-epoxy derivatives 445 and 446 in an approximate ratio of 1:2, which were separated by chromatography. When reacted with NaN₃, epoxy amino ester 445 underwent oxirane ring-opening to furnish azido esters 447 and 448 in a ratio of 1:2, the two regiosomers likewise being separated and isolated by chromatography. Reductive azido group transformation of 447 readily yielded trans-β-amino acid enantiomer 449 (Scheme 89).115 It is noteworthy that azidolysis of 446 led exclusively to a 4-azido derivative, which did not afford a pyrrolidine β-amino acid.

However, the readily available trans-3-hydroxy-L-proline offered a possibility for the preparation of other stereoisomers of pyrrolidine β-amino acid derivatives. When treated with diphenylphosphoryl azide (DPPA), PPh₃, and diethyl azodicarbonyl (DEAD), ester 452 derived from hydroxyproline 451 under Mitsunobu reaction conditions underwent inversion to afford the cis-3-azidoproline methyl ester 453, which can be regarded as an orthogonally protected β-amino acid derivative (Scheme 90).116

The synthesis of trans-3-azido proline methyl ester 456, a stereoisomer of 453, was accomplished from N-Boc-protected trans-3-hydroxy-L-proline 452 by double inversion. Ester formation (454) with inversion under Mitsunobu conditions with 4-nitrobenzoic acid, followed by ester cleavage with NaNO₂, led to cis-3-hydroxyproline methyl ester 455, which underwent hydroxy–azide exchange with inversion in a Mitsunobu reaction to give azido ester 456 (Scheme 91).116

An alternative route to a cis-hydroxyproline derivative, a precursor of trans-aminoprolines, was described by Gellman and co-workers from keto ester 457. The baker’s yeast-catalyzed reduction of 457 cis-selectively furnished hydroxy ester 458, which was readily transformed by hydroxy–azide exchange, followed by reduction of the azido group, to the corresponding optically pure trans-β-aminoproline derivative 459 (Scheme 92).117

The 3-aminoproline derivatives are important precursors for the synthesis of other bioactive compounds, such as the arginine-containing dipeptide amide 460. Amidation of hydroxyproline 460 by carboxylic group activation with isobutyl chloroformate (IBCF) and N-methylmorpholine (NMM), followed by ammonolysis, furnished 461. A double inversion Mitsunobu reaction and azidolysis, followed by reduction, led to β-amino acid derivative 463, the coupling of which with Boc-protected nitroarginine yielded dipeptide 464 (Scheme 93).118
3.1.2.6. Syntheses from Carbohydrate Derivative Precursors. Enantiomerically pure functionalized β-aminoproline derivatives have been synthesized from bicyclic hydroxylated pyrrolidine-fused β-lactam 465, derived from ascorbic acid in 10 steps. The hydroxy group of 465 was converted to a benzoyl-protected amino function to give lactam derivative 466. Azetidinone ring-opening followed by esterification with CH₂N₂ resulted in orthogonally protected methyl β,γ-diaminopyrrolidinecarboxylate 467 (Scheme 94).¹¹⁹

An alternative route to 3-aminoproline derivatives from ascorbic acid was described by Pfeifer et al. (see also section 3.1.2.5). Bicyclic β-lactam 465 was subjected to hydroxy group removal by transformation to the corresponding triflate, followed by reduction with NaBH₄ to give 468. Oxidative removal of the 2,4-dimethoxybenzyl (DMB) group and subsequent N-Boc protection furnished azetidinone 469. Base-catalyzed lactam opening, removal of the Z group by...
hydrogenolysis, and N-Fmoc protection afforded heterocyclic \( \beta \)-amino acid derivative 470 (Scheme 95). \(^{120}\)

### Scheme 95. Synthesis of an Orthogonally Protected Pyrrolidine \( \beta \)-Amino Acid Derived from Ascorbic Acid

\( \beta \)-Lactam 465 was a suitable precursor for the preparation of 4-hydroxylated 3-aminoproline derivatives, which were then transformed to various highly substituted pyrrolidine derivatives with pharmacological potential (Figure 24). \(^{121}\)

3.1.2.7. Syntheses by Curtius Rearrangement of Heterocyclic Dicarboxylates. The five-membered \( N \)-heterocyclic dicarboxylates are excellent precursors for the synthesis of the corresponding \( \beta \)-amino acid derivatives. The key step in these transformations is the Curtius rearrangement of one carboxylic function to the requisite NHZ moiety. One approach to pyrrolidine dicarboxylates was based on dipolar cycloaddition of the azomethine ylide of benzylglycine to benzyl methyl maleate, followed by the sequences presented in Scheme 83, which resulted in the five \( N \)-heterocyclic \( \beta \)-amino acid derivatives. Another route to pyrrolidine dicarboxylic esters (476) started from azetidinone carboxylic acid 475. Removal of the benzhydryl group of 476, followed by Curtius rearrangement of acyl azide 478, furnished 3-aminoproline derivative 479 (Scheme 96). \(^{122}\)

Another pyrrolidine \( \beta \)-amino acid regioisomer was prepared from half-ester 480 via the Curtius reaction to give 481. Compound 481 served as a precursor of functionalized aminopyrrolidine 482, a known factor Xa inhibitor (Scheme 97). \(^{123}\)

3.1.3. Six-Membered \( N \)-Containing Cyclic \( \beta \)-Amino Acids. The main synthetic methods available for the preparation of six-membered \( N \)-heterocyclic \( \beta \)-amino acids exhibit similarities with those presented for the carbocyclic or five-membered \( N \)-containing cyclic derivatives.

Figure 24. Several bioactive, highly substituted pyrrolidine derivatives synthetized from 4-hydroxylated 3-aminoproline derivatives.
3.1.3.1. Syntheses from β-Keto Esters. β-Ketopiperidine carboxylates are suitable starting materials for the synthesis by reductive amination of six-membered β-amino acids in racemic or enantiomerically pure form (see sections 3.1.1 and 3.1.2.3 for alicyclic and N-heterocyclic five-membered analogs). Thus, treatment of β-oxopiperidine ester 483 with AcOH/NaH resulted in a mixture of two dicarboxylate stereoisomers 487. Its reduction under different experimental conditions afforded stereoisomers 488 and 489, the best selectivity being achieved with NaBH(OAc)3/TFA at −45 °C (488:489 = 28:1). The cis isomer 488 could be separated from the minor trans one 489 by means of chromatography (Scheme 98).124

As presented earlier for the carbocyclic and the five-membered N-cyclic analogs, the reductive amination methodology can also be extended to the synthesis of the enantiomers, by using optically active amines as chiral auxiliaries. Reaction of ester 486 with (R)-1-phenylethylamine provided enaminocarbonyl ester 487. Its reduction under different experimental conditions afforded stereoisomers 488 and 489, the best selectivity being achieved with NaBH(OAc)3/TFA at −45 °C (488:489 = 28:1). The cis isomer 488 could be separated from the minor trans one 489 by means of chromatography (Scheme 99).125

Another asymmetric version of the above reaction with inverse stereoselectivity was reported by Gellman and co-workers. Upon treatment with (R)-1-phenylethylamine, ethyl ester 490 gave enamine 491. Reduction of 491 with NaBH4 resulted in a mixture of trans- and cis-piperidine β-amino esters in a trans:cis ratio of 4:1. Isomerization of the cis derivative from the mixture afforded trans-β-amino ester 492, and removal of the chiral auxiliary by transfer hydrogenolysis, ester hydrolysis, and N-Fmoc protection resulted in amino acid 493, which can be used as a chiral building block in the synthesis of peptide oligomers (Scheme 100).126

Reduction of the chiral enamine derived from 4-oxopiperidine-3-carboxylic acid methyl ester (494) was performed 100% cis-selectively with the use of NaBH(OAc)3, to yield 488 (Scheme 101).127

Similar experiments involving cis-selective enamine reduction were executed by starting from the regioisomer methyl 3-oxopiperidine-4-carboxylate (496). Reductive removal of the chiral auxiliary in 488 and 497 furnished piperidine β-amino ester regioisomers 495 and 498 (Schemes 101 and 102).127

Highly cis-selective reduction of piperidine enamine esters was attained with NaBH(OAc)3, by using the CoCl2 and (S)-2,2′-2-p-tolylphosphino)-1,1′-binaphthyl ((S)-TolBINAP) catalyst system.127,128

Spin-labeled chiral β-amino acids in the form of nitroxide free radicals have important applications in medicinal chemistry as spin labels, oxidizing agents, antioxidants, etc. The six-membered azaheterocyclic β-amino acids have also been synthesized by reductive amination of β-keto esters (for the five-membered analogs, see Scheme 80) and investigated as components in the synthesis of β-hexapeptides. Oxo ester 500 (prepared from ketone 499 by treatment with CO2 under basic conditions, followed by esterification) reacted with (R)-α-methylbenzylamine to yield 501. Reduction of 501 with NaCNBH3 resulted in a mixture of two cis-β-amino ester diastereoisomers, which were separated by crystallization to provide pure 502 and 503 (Scheme 103).129

The cis-β-amino acid nitroxide derivatives were then prepared by removal of the chiral auxiliary and N-Fmoc protection.129 The trans isomer was obtained by epimerization under basic conditions.129,130

3.1.3.2. Syntheses by Amino Group Conjugate Addition. Amino group conjugate addition to α,β-unsaturated carboxylic esters as a general method for the synthesis of cyclic β-amino acid derivatives (e.g., carboxylic β-amino acids, described in section 2.1.3, or five-membered N-heterocyclic β-amino acids, presented in section 3.1.2.1) may also be applied for the construction of β-amino acids with a six-membered N-heterocyclic framework. Dialkylation of benzylamine with unsaturated bromoester 504 resulted in diester 506, which on treatment with chiral (S)-N-benzyl-N-α-methylbenzylamide by Michael conjugate addition provided piperidine amino dicarboxylic ester stereoisomers 507 and 508 in a ratio of approximately 9:1 (Scheme 104). The stereoisomers were separated by chromatography and, after removal of the chiral auxiliary by hydrogenolysis, gave the corresponding piperidine β-amino esters.21

3.1.3.3. Syntheses by One-Pot Multicomponent Reaction. Six-membered N-heterocyclic β-amino acid derivatives may be prepared by a rather novel and special one-pot multicomponent reaction approach. 4-Methylbenzaldehyde, aniline, and methyl acetate in the presence of I2 in MeOH underwent one-pot multicomponent reaction (MCR) to afford highly functionalized piperidine 509 (Scheme 105).131 However, the carboxylic

Scheme 96. Synthesis of a Pyrrolidine cis-β-Amino Ester by Curtius Rearrangement

Scheme 97. Synthesis of a trans-Pyrrolidine β-Amino Ester by Curtius Rearrangement
and amino functions in this product are not connected to stereogenic carbon centers.

The above method could be generalized by using different aldehydes and anilines, when the transformation was carried out in the presence of Zr derivatives.132

3.1.3.4. Syntheses by Intramolecular Michael Addition to Piperidine Carboxylates. Intramolecular conjugate addition of trichloroimidates to a piperidine α,β-unsaturated ester led to highly functionalized six-membered N-heterocyclic β-amino acids. Thus, unsaturated ester 510 was reacted with trichloroacetonitrile in an intramolecular Michael addition to give oxazoline derivative 511 (Scheme 106). In the presence of p-TsOH, pyridine, and H2O, 511 underwent hydrolysis with oxazoline opening to furnish stereoisomers 512 and 513 in a ratio of 9:1. After their separation, 512 and 513 were easily converted by reduction of the trichloroacetate group, followed by ester and amino group deprotection, to highly functionalized piperidine β-amino acids 514 and 515 (Scheme 106).133

Other bioactive L-iduronic acid-type 1-N-imino sugar derivatives similar to 514 have been demonstrated to possess enzyme inhibitory and antimetastatic activity. A synthetic protocol to a related compound is presented in Scheme 107.

Unsaturated ester 516 was reacted with Cl3CCN via an intramolecular Michael addition followed by oxazoline opening to give 518. After reductive cleavage of the Cl3CCO group followed by guanylation of the free amino function and ester deprotection, the novel highly functionalized piperidine β-amino acid 521 was obtained (Scheme 107).5c

3.1.3.5. Syntheses from Carbocyclic β-Amino Esters by an Oxidative Ring-Opening−Reductive Ring-Closure Protocol. β-Amino esters with a piperidine skeleton have been prepared from their five-membered unsaturated carbocyclic analogs. Dihydroxylated amino ester enantiomer 330, prepared as presented in section 2.4.1.5 by OsO4-catalyzed dihydroxylation, was a suitable starting material for this purpose. Amino ester enantiomer (+)-330 underwent oxidative C−C bond cleavage with NaIO4. The dialdehyde intermediate formed in the presence of benzylamine and NaCNBH3 participated in reductive ring closure to afford the corresponding piperidine β-amino ester enantiomer (+)-522 (Scheme 108).3c

Amino ester (−)-333, a stereoisomer of 330, was transformed analogously in a similar protocol to furnish ethyl trans-β-aminopiperidincarboxylate (−)-523 (Scheme 108).3c
Scheme 102. Synthesis of Enantiomerically Pure Piperidine \( \beta \)-Amino Ester by Reductive Amination of the Corresponding Keto Ester

\[
\text{CO}_2\text{Me} \quad \begin{array}{c}
1. (R)-\alpha\text{-methylbenzylamine} \\
\text{Yb}(OTf)_3, \text{C}_6\text{H}_6, \Delta \\
2. \text{NaBH}_4(\text{Oac})_3, \text{AcOH} \\
\text{MeCN}, 0 \degree \text{C}
\end{array}
\]

\[
\text{Boc} \quad 496 \quad \text{NH} \quad 497 \quad \text{H}_2, \text{Pd(OH)}_2/C, \text{AcOH} \\
\text{HCl, EIOH} \quad \text{MeCN}, 0 \degree \text{C} \quad \text{MeCN}, 0 \degree \text{C}
\]

\[
\text{CO}_2\text{Me} \quad \begin{array}{c}
1. \text{MeOH, } \text{HCl, EIOH} \\
\text{MeCN}, 0 \degree \text{C} \quad \text{MeCN}, 0 \degree \text{C}
\end{array}
\]

\[
\text{NH} \quad 498 \quad \text{HCl, EIOH}
\]

3.1.4. \textit{N}-Containing Cyclic \( \beta \)-Amino Acids with Larger Ring Systems. The oxidative cleavage of dihydroxylated carbocyclic \( \beta \)-amino esters, followed by ring closure with reductive amination, was efficiently applied for the synthesis of seven-membered \( N \)-containing heterocyclic \( \beta \)-amino acids. Thus, on treatment with \( \text{NaIO}_4 \) and then with benzylamine and \( \text{NaCNBH}_3 \), 3,4-dihydroxylated ethyl 2-aminocyclohexane-carboxylate enantiomer 524 yielded azepane \( \beta \)-amino ester 525 in optically pure form. Epimerization of 525 with \( \text{NaOEt} \) readily provided the trans stereoisomer 526 (Scheme 109).\textsuperscript{5d}

Another azepane \( \beta \)-amino ester, a regioisomer of 526, could be prepared from ethyl 4,5-dihydroxylated 2-aminocyclohexancarboxylate 527. Oxidative ring-opening of enantiomer \((-\)-)527, followed by reductive amination and ring closure, gave azepane enantiomer \((-\)-)528, a regioisomer of 525, whose epimerization led to its trans stereoisomer \((+)-529 \) (Scheme 110).\textsuperscript{5d}

\( N \)-Containing bicyclic \( \beta \)-amino esters were easily prepared from norbornene amino esters 530 or 534 by using the above procedure. Dihydroxylation of \( \text{di-exo-norbornene ester} \) 530, followed by oxidative ring cleavage and ring closure under reductive amination conditions, provided bicyclic \( \beta \)-amino ester 533 (Scheme 111). Similarly, transformation of \( \text{di-endo-dihydroxy derivative} \) 534 afforded a mixture of two isomers, the desired 536 and the earlier prepared 533, which probably resulted from enolization of the dialdehyde intermediate. After separation, 536 underwent epimerization to give stereoisomer 537 (Scheme 112).\textsuperscript{5e}

3.2. Syntheses of Cyclic \( \beta \)-Amino Acids with an \( \text{O} \) Atom in the Ring

The most abundant of the \( \text{O} \)-containing cyclic \( \beta \)-amino acids are those containing an oxetane, tetrahydrofuran, or pyran ring system. Accordingly, this chapter will focus on the syntheses of such four-, five-, and six-membered \( \text{O} \)-heterocyclic derivatives. In contrast with the carbocyclic and \( \text{N} \)-heterocyclic analogs, far fewer general synthetic methods are available for the synthesis of these classes of compounds. For this reason, syntheses will be described for the most representative of these compounds.

3.2.1. Four-Membered \( \text{O} \)-Containing Cyclic \( \beta \)-Amino Acids. Isolation of the four-membered \( \text{O} \)-heterocyclic \( \beta \)-amino acid antibiotic oxetin (344; Figure 21)\textsuperscript{92} led to appreciable interest in the synthesis of functionalized oxetane \( \beta \)-amino acid derivatives. The main procedure for the preparation of oxetane \( \beta \)-amino acids starts from various monosaccharides and results after a number of steps in optically pure target compounds. For example, \( \text{l-ramnose} \) can be converted to hydroxylated ester 539 containing an oxacyclobutane ring in four steps. The hydroxyl group of ester 539 was converted via triflate 540 by inversion with \( \text{NaN}_3 \) to \( \text{cis-azido ester} \) 541. Transformation of triflate 540 by treatment with \( \text{F}_3\text{CCO}_2\text{Cs} \) in butanone yielded cis-hydroxylated ester 542, which by hydroxy–azide exchange afforded trans-azido ester enantiomer 543. Both cis- and trans-azido ester stereoisomers 541 and 543 are orthogonally protected oxetane \( \beta \)-amino esters (Scheme 113).\textsuperscript{5s}

Methyl-substituted oxetane \( \beta \)-azido esters have been prepared from \( \text{\textit{o-xylene}} \). Bromomethyl ester 545, derived from monosaccharide \textsuperscript{544} in five steps, was reduced with \( \text{Me}_3\text{SiH} \) to yield 546. This underwent benzyl ester hydrolysis to give hydroxylated ester 547, which was finally converted to methyl-substituted oxetane \( \text{cis-\beta-azido ester} \) 548 (Scheme 114).\textsuperscript{136}

By means of the above procedures, several other substituted oxetane \( \beta \)-amino acids have been synthesized in optically pure form (Figure 25).\textsuperscript{133a,c,137}
Not only carbohydrates but also optically pure α-amino acid derivatives are suitable precursors for oxetane β-amino acids. One synthetic pathway started from optically pure tritylserine (553), which was transformed with the coupling agent BOP [(benzotriazol-1-yl)oxytris(dimethylamino)phosphonium hexafluorophosphate] to a lactone intermediate, the methylation and oxidation of which resulted in spiro compound 554. Reduction of 554 with diisobutylaluminium hydride (DI-BALH) produced oxirane-ring-opened stereoisomers 555 and 556 in a ratio of 2:1, which were then separated (Scheme 115).

After O-protection by acetylation, followed by N-protecting group exchange for Boc, amino alcohol 555 afforded 557. Following deacetylation, 557 was then subjected to hydroxymethyl group oxidation and N-deprotection to yield β-amino acid enantiomer 560 (Scheme 116).

### 3.2.2. Five-Membered O-Containing Cyclic β-Amino Acids
Among the five-membered 0-heterocyclic β-amino acids, the largest groups, the sugar amino acids (SAAs) and the nucleoside amino acid (NAAs), are biologically important products.

#### 3.2.2.1. Sugar Amino Acids (furanoid β-amino acids)
The sugar amino acids are carbohydrate derivatives bearing both
amino and carboxylic acid functionalities. They are versatile glyco- or peptidomimetics of value as conformationally rigid building blocks in the construction of novel peptides (Figure 26).\textsuperscript{2a,139}

A number of furanoid $\beta$-amino acids (e.g., \textsuperscript{561} and \textsuperscript{562}) possess noteworthy antifungal activities.\textsuperscript{2a}

A series of conformationally rigid enantiomerically pure sugar $\beta$-amino acid stereoisomers has been synthesized and investigated as bioactive derivatives and also in peptide chemistry, forming an important bridge between carbohydrates and proteins (Figure 27).\textsuperscript{140}

The synthesis of sugar $\beta$-amino acids starts from different enantiomerically pure carbohydrate derivatives and leads to optically pure target products.

The preparation of conformationally rigid glutamate analog lactone $\beta$-amino ester \textsuperscript{574} was accomplished from optically pure ribofuranose derivative \textsuperscript{570} (methyl 5-O-trityl-$\beta$-D-ribofuranoside). The key steps in the synthesis were hydroxy–azide exchange at C-3, followed by oxidation of the hydroxymethyl moiety with NaIO\textsubscript{4} in the presence of RuCl\textsubscript{3}. The compound obtained, \textsuperscript{572}, was next converted by

---

Scheme 110. Syntheses of \textit{cis}- and \textit{trans}-Azepane $\beta$-Amino Ester Enantiomers from a Carbocyclic Precursor by a Ring-Enlargement Procedure

\begin{align*}
\text{Scheme 111. Synthesis of an Azabicyclic $\beta$-Amino Ester from a Carbocyclic Precursor by Ring Enlargement}\\
\text{Scheme 112. Syntheses of Azabicyclic $\beta$-Amino Esters from a Carbocyclic Precursor by Ring Opening–Ring Closure}\\
\text{Scheme 113. Syntheses of Hydroxylated Oxetane $\beta$-Amino Esters from L-Rhamnose}
\end{align*}

---

Figure 25. Structures of some substituted oxetane $\beta$-amino acids.
Scheme 115. Syntheses of Oxetane Amino Alcohol Stereoisomers

Scheme 116. Synthesis of a trans-Oxetane β-Amino Acid from the Corresponding Amino Alcohol

Figure 26. Structures of bioactive tetrahydrofuran β-amino acids.

Figure 27. Some hydroxylated tetrahydrofuran β-amino acid stereo-isomers.

intramolecular aziridination followed by aziridine opening with EtSH to furnish the required heterocyclic β-amino ester derivative glutamate analog 574 (Scheme 117).141

Glucosamine derivative 575 (2-amino-2,6-dideoxy-α-D-glucopyranoside) was the starting material for the synthesis of lactone β-amino acid 579. Oxidative ring contraction of 575 afforded carboxysulfonamide derivatives 576 and 577 in a ratio of approximately 1:1. After separation of the two isomers, removal of the sulfonyl group from 576 in the presence of Li in liquid NH₃ afforded furan β-amino acid derivative 578, which, after ether cleavage and glycosidic hydroxy group oxidation, provided 579. β-Amino acid derivative 579 was the precursor in the synthesis of the antibiotic thienamycin (Scheme 118).142

Furanoid β-azido esters derivatives as five-membered O-heterocyclic-protected β-amino acids served as precursors of functionalized O-heterocyclic β-amino acids, which were key elements in the construction of various linear or cyclic peptide oligomers with antiproliferative and multidrug-resistance activities.

Diacetone glucose (580) was the starting material for the preparation of enantiomerically pure furanoid β-azido ester stereoisomers, which may be regarded as protected amino esters or precursors of the corresponding β-amino acids. The synthesis is based on hydroxy–azide interconversion, followed by oxidative transformation of the glycosidic hydroxy group. Introduction of the azide onto the carbohydrate was achieved by transformation of its hydroxy function via triacetate in the presence of NaH and NaN₃, followed by acetal deprotection and oxidation of which gave azido acid 581. Diol deprotection with TFA, followed by mild oxidation of the glycosidic hydroxy, yielded lactone 582, which was next transformed by acetal deprotection, triflate substitution, and esterification to cis-β-azido ester 583 (Scheme 119).140a

Other cis- or trans-azidotetrahydrofurancarboxylates presented in Figure 28, stereoisomers of 583 bearing hydroxy and hydroxymethyl groups, have also been synthesized by the same research group.143

L-Arabinose was another carbohydrate that furnished novel optically pure sugar β-azido esters. Ring opening and ring closure of hydroxy lactone 587 (derived from L-arabinose) afforded methyl ester 588, which during transesterification through the corresponding carboxylic acid with AcCl resulted in 589. Hydroxy group protection in compound 589 with tert-butylidiphenylsilyl chloride (TBDPSCI) yielded monoprotected derivatives 590 and 591 in a ratio of approximately 1.3:1. After separation of the two isomers, hydroxy–azide conversion via the triflate in 590 led to β-azido ester enantiomer 592, possessing a protected hydroxy group at C-4 (Scheme 120).144

Another route that led to a sugar azidocarboxylic acid enantiomer started from methyl 3-azido-4,6-O-benzylidene-3-deoxy-α-D-allopyranoside (593). Compound 593, on treatment with diethylaminosulfur trifluoride (DAST) followed by methanolation and acetylation, gave furanoid azido sugar 594, which by ring contraction and subsequent deacetalization and oxidation furnished β-azido ester 595 (Scheme 121).145

An efficient procedure for the preparation of cis- and trans-β-azido esters containing a tetrahydrofurane skeleton was described recently by Pandey et al. Dimethyl acetal derivative 597 (derived from ditosylate sugar synthon 596) underwent intramolecular tosylate displacement to give epoxide derivative 598. Reductive oxirane opening with DIBALH in THF afforded regioisomers 599 and 600 in a ratio of 3:1. When the reaction was performed in CH₂Cl₂, 7:1 selectivity was attained. Subsequently, regioisomers 599 and 600 were separated by means of chromatography (Scheme 122).146

Dimethyl acetal 599 was a suitable starting material for further transformation to tetrahydrofurane β-amino acids. Through the corresponding mesylate and treatment with NaN₃, 599 readily transformed by inversion to 601, the acetal deprotection and oxidation of which gave azido acid 602. Esterification of 602 with CH₃I resulted in cis-β-azido ester 603 (Scheme 123). Its trans counterpart (605) was readily prepared from 604. The synthesis involved oxidation of the hydroxyl function of 599, followed by oxo group reduction, which furnished 604, the cis isomer of 599. Hydroxy–azide
interconversion then afforded the required ω-heterocyclic trans-β-azido ester 605 (Scheme 123).\textsuperscript{146} 

3.2.2.2. Nucleoside β-Amino Acids. In the large field of nucleosides, the nucleoside β-amino acids are of paramount importance as bioactive derivatives. Among them, chryscandin (349; Figure 22), with an adenine nucleobase in its structure, is a well-known antibiotic. An ever-increasing number of compounds of nucleoside β-amino acid type have been reported as selective adenosine A3 agonists; they exhibit cardioprotective effects and, consequently, are used to prevent myocardial ischemic injury. The structures of several such derivatives are shown in Figure 29.\textsuperscript{147,148}

A variety of these derivatives have been utilized as building blocks in the synthesis of oligonucleotides possessing a β-amino acid element.\textsuperscript{147,149}

The most general pathways for the syntheses of nucleoside β-amino acids are those which start from readily available enantiomerically pure carbohydrate derivatives. Besides functionalization with amino and carboxylic groups, these procedures involve creation of the nucleobase by means of different methods. Azido sugar 612, derived from glucose diacetonide, was easily transformed by diol C\texttextsuperscript{-C} bond cleavage, oxidation of the formyl group, and amidation to trans-β-azido amide derivative 613. The latter was next subjected to reaction with an activated purine derivative, which led through the glycosidic hydroxy group to 614, bearing the chloropurine framework. After replacement of the chlorine on the heteroaromatic ring by methylamine, under reductive conditions the azido ester readily furnished the corresponding β-amino amide nucleoside 615 (Scheme 124).\textsuperscript{139h,148}

The synthesis described by Kasinagesan et al. that started from l-xylose involved as key steps coupling of the sugar moiety with silylated purine in the presence of trimethylsilyl triflate (TMSOTf) and oxidation of the hydroxymethyl group. Hydroxy protection of amino sugar 616, followed by acetal cleavage and acetylation, resulted in 618. After coupling with the silylated nucleobase and cleavage of the
hydroxysilyl protecting group, nucleoside 620 was formed. Hydroxymethyl oxidation and amidation of the carboxyl group afforded nucleoside β-amino acid derivative 622 (Scheme 125).\textsuperscript{150}

Aminocarboxylic acid nucleoside 609 was simply synthetized from azidothymidine (AZT; 623) by hydroxymethyl group oxidation and azide reduction (Scheme 126).\textsuperscript{151}

The Fmoc-protected thymidine β-amino acid was investigated as a building block in the construction of peptide oligomers.\textsuperscript{152}
Scheme 124. Synthesis of a Nucleoside $\beta$-Amino Acid Derivative from an Azido Sugar Precursor

Scheme 125. Synthesis of a Nucleoside $\beta$-Amino Acid Derivative from an Amino Sugar Precursor

Scheme 126. Synthesis of an Azidothymidine Analog

Scheme 127. Synthesis of a Tetrahydrofuran $\beta$-Amino Acid from a Functionalized $\beta$-Lactam
The simple and efficient route developed by Leemans et al. for the synthesis of tetrahydrofuran \(\beta\)-amino acids started from \(\beta\)-bromo imine 625 (readily available from aldehyde 624). The construction of functionalized \(\beta\)-lactam 626 by the Staudinger reaction of imine 625 with benzyloxyacetyl chloride in the presence of Et\(_3\)N was the key step in the transformation. Debenzylation of 626, followed by intramolecular nucleophilic substitution of the bromide afforded bicyclic \(\beta\)-lactam 628, the lactam ring-opening of which gave five-membered \(\text{O}\)-hetero-cyclic cis-\(\beta\)-amino ester 629 (Scheme 127).153a

A similar strategy was used by the same group of authors for the synthesis of a nonsubstituted analog of tetrahydrofuran \(\beta\)-amino ester 629. The starting material in the process, a hydroxylated imine, was reacted with phenoxyacetyl chloride to give the corresponding \(\beta\)-lactam, the ring closure of which via its mesylate followed by lactam opening afforded the required \(\text{O}\)-heterocyclic \(\beta\)-amino acid.153b

Amino group conjugate addition (see section 3.1.2.1 for the synthesis of \(N\)-heterocyclic \(\beta\)-amino acids) was also efficiently used for the construction of tetrahydrofuran \(\beta\)-lactam acids. Addition of chiral lithium amides to conjugated unsaturated \(\text{O}\)-heterocyclic carboxylic esters afforded enantiomerically pure \(\text{O}\)-heterocyclic cis- and trans-\(\beta\)-amino acids with high ee.104

An enantiomerically pure tetrahydrofuran \(\beta\)-amino ester was recently synthesized from \(d\)-mannitol. Compound 630 underwent Michael addition with allyl alcohol to yield a mixture of isomers 631 and 632 in a ratio of 4:1. The major isomer was then subjected to intramolecular nitrile oxide cycloaddition to furnish isoxazoline 633 as a mixture of two isomers. On treatment with Li\(\text{AlH}_4\) this mixture gave amino alcohol derivative 634 as the major isomer. 634 was next oxidized to \(\beta\)-amino ester derivative 635. Ketel hydrolysis and diol oxidative cleavage finally afforded tetrahydrofuran amino ester 637 (Scheme 128).154

3.2.3. Six-Membered \(\text{O}\)-Containing Cyclic \(\beta\)-Amino Acids. 3.2.3.1. Syntheses of Sugar Amino Acids. Amino sugars are readily accessible, optically pure starting materials for the synthesis of six-membered \(\beta\)-amino acid sugar derivatives. One main synthetic approach to pyran \(\beta\)-amino acid sugars consists of the transformation of amino sugars to \(\beta\)-amino nitriles, followed by nitrile hydrolysis. Thus, nitrile derivative 639, synthetized from \(d\)-glucosamine 638 by hydrolysis, followed by methanolysis, led through amide 640 to pyran \(\beta\)-amino ester 641. The latter was then transformed to the corresponding \(N\)-Boc-protected \(\beta\)-amino acid derivative 643 (Scheme 129).155

Azido sugar 644, containing a glycosidic trichloroimidate, was reacted with trimethylsilyl cyanide (TMSCN) in the presence of TMSOTf to furnish \(\beta\)-azido nitrile 645, which served as a precursor for the sugar \(\beta\)-amino acid derivative 647 (Scheme 130).156
nitrile 649, which was then easily converted to benzylated sugar amino acid 651 (Scheme 131).  

**Scheme 131. Synthesis of a Pyran β-Amino Acid from an Azido Sugar Precursor**

Compounds such as 647 or 651 are applied as building elements in the synthesis of different carbopeptoid oligomers.  

Azido amino sugars in the form of orthogonally protected sugar diamino acids were synthetized from acetylated sugar β-amino nitrile derivative 652. Decatalization of 652, with subsequent exchange of the more reactive hydroxy group at C-6 to azide, resulted in azido nitrile 654, the methoxymethyl etherification of which, followed by nitrile hydrolysis, yielded azido amino acid 656 (Scheme 132).  

The above synthesis procedure was adopted to prepare peptidomimetics such as the orthogonally protected diamino acids 657 and 658 (Figure 30).  

Sugar azido β-amino acid 661 was synthetized from N-phthaloylamino ester 659 (derived from d-(+)-glucosamine hydrochloride) through a similar azidolysis at C-6 as the key step (Scheme 133).  

EnantiomERICALLY pure amino sugars can be transformed into carbohydrate β-amino acids by lithiation of the corresponding tributyltin derivatives 664, which were prepared from amino sugar 662 via N-CBz protection to give 663, followed by carboxylation of the organometallic intermediate with CO₂ as key steps. After N-CBz protection, benzylated β-glucosamine reacted with SOCl₂ and tributyltin lithium provided 664, which was next subjected to lithiation to organometallic compound 665. The latter reacted with CO₂ to furnish β-amino acid derivative 666, in which the arrangement of the amino and carboxylic groups was trans (Scheme 134). The N-acetylated isomer of 667 was prepared analogously.  

Through a lithiation–carboxylation strategy similar to the method presented above, sugar β-amino acid derivative 671, in which the amino and the carboxylic groups are in the cis arrangement, was synthetized. O-Benzylated N-acetylgalactose 668 was first transformed by inversion at the glycosidic carbon to α-chlorinated derivative 669. Lithiation with n-BuLi afforded the corresponding organometallic derivative 670, which underwent carboxylation to give pyranose β-amino acid derivative 671 (Scheme 135).  

McGarvey et al. reported another approach for the preparation of both cis- and trans-tetrahydropyrane β-amino acid derivatives. For this purpose, alkylidene amino sugar 672 was used as starting material. Dihydroxylation of the C-C double bond with OsO₄, followed by NaIO₄-mediated C-C bond cleavage, afforded aldehyde 673, which in the presence of K₂CO₃ underwent isomerization to yield an equilibrium mixture of epimers 673 and 674 in a ratio of 4:1. Both isomers (with equatorial or axial formyl groups) were oxidized and methylated to afford β-amino ester stereoisomers 675 and 676 (Scheme 136).  

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**Scheme 130. Synthesis of a Pyran β-Amino Acid Derivative from an Azido Sugar Precursor**

**Scheme 132. Synthesis of an Orthogonally Protected Pyran Diamino Acid from an Amino Sugar Precursor**

**Figure 30. Structures of some orthogonally protected pyran diamino acids.**
A number of other sugar β-amino acid stereoisomers (e.g., Figure 31) with a pyranose framework have been reported that are of importance in peptide chemistry (antimicrobial peptides) and in the construction of bioactive oligosaccharides.\textsuperscript{163−165} 3.2.3.2. Syntheses of Nucleoside β-Amino Acids (blasticidin and analogs).

Analogously to the furanose SAAs, besides the pyranose sugar β-amino acids, the nucleoside β-amino acids are of importance as bioactive compounds in medicinal chemistry. Blasticidin S (isolated from \textit{Streptomyces griseochromogenes}) is a known fungicide and antibiotic (347; Figure 22). Other important blastcidin-related nucleoside antibiotics that contain a β-amino moiety include cytomycin (681), cytosinine (682), gougerotin analogs (683), and bagougeramine (684) (Figure 32).\textsuperscript{166}

The syntheses of such derivatives start from readily available optically pure carbohydrates. Protected amino alcohol derived from 2-acetoxy-tri-O-acetyl-D-glucal (685) in seven steps was subjected to hydroxymethyl oxidation and esterification to furnish β-amino ester 687. Removal of the p-methoxyphenyl group followed by acetylation resulted in 688, which was then reacted through its glycosidic hydroxy group with a silylated cytosine derivative to give nucleoside derivative 689. Removal of the trichloroethoxy carbamate (Troc) group and acetylation resulted in two N-glycosidic products, which could be separated. Compound 690 was then transformed into blastcidin S and cytosinine nucleoside antibiotics (Scheme 137).\textsuperscript{167}

A number of blastcidin analogs have been synthetized from azido sugar 691 (derived from \textit{d}-galactose in six steps). Coupling of 691 either with N-acetylcytidine and SnCl\textsubscript{4} or uracil and TMSOTf through its glycosidic acetylated hydroxy group gave the corresponding nucleoside derivative 692. The hydroxymethyl group of 692 was then oxidized to yield the corresponding β-azido carboxylic acid derivative 693, which was subsequently converted to various blastcidin analogs (Scheme 138).\textsuperscript{168}

3.2.3.3. Syntheses of Zanamivir Analogs Containing a β-Amino Acid Moiety. Zanamivir (Relenza) (695), a highly

Scheme 133. Synthesis of a Pyran Azido β-Amino Acid

Scheme 134. Synthesis of a Sugar β-Amino Acid Containing a Pyran Ring from an Aminocarbohydrate

Scheme 135. Synthesis of a Pyran β-Amino Acid from O-Benzylated N-Acetylgalactose

Scheme 136. Synthesis of a Pyran β-Amino Ester from an Alkenyl Sugar Derivative
functionalized six-membered O-heterocyclic amino acid, is an important antiviral agent.\textsuperscript{169}

This bioactive compound has given rise to considerable increasing interest in medicinal chemistry, and a number of analogs and other multifunctionalized O-heterocyclic amino acids have been synthetized and investigated in recent years. Several of these analogs contain a $\beta$-amino acid moiety (Figure 33).\textsuperscript{60,61}

A $\beta$-amino acid-modified zanamivir analog (704) was synthetized in racemic form by Kerrigan et al. Wittig product 700 (derived from 699) underwent cyclization on reaction with nitroethanol to furnish the tetrahydropyran $\beta$-nitro carboxamide derivative 701. Dehydration of 701, followed by nitro group reduction and acetylation, led to the corresponding $\beta$-amino amide derivative 703, the ester hydrolysis of which gave the modified zanamivir target compound 704 (Scheme 139).\textsuperscript{61b}

Another $\beta$-amino acid-modified zanamivir analog was synthetized from azido zanamivir 706 (a precursor of zanamivir). Saponification of 706 with NaOMe, followed by C–C bond cleavage with NaIO$_4$ gave the corresponding aldehyde intermediate, which was subsequently subjected to oxidation and amidation to furnish $\beta$-amino carboxamide 707. Azide reduction of 707 afforded $\beta$-amino acid-modified zanamivir analog 708 (Scheme 140).\textsuperscript{61a}

3.2.3.4. Miscellaneous. Six-membered O-heterocyclic $\beta$-amino acid derivative 714 was utilized as an important synthon in antibiotic chemistry by Hatanaka et al. Its construction involved the cyclization of unsaturated hydroxylated amino ester 711 (prepared by the addition of hydroxy ester 709 to activated imine 710) in the presence of acid to afford pyran $\beta$-amino ester derivative 712. Desulfurization of 712 with AgNO$_3$/Ag$_2$O in MeOH, followed by ester hydrolysis, provided 714, a precursor of the bioactive daunosamine (715) and acosamine (716) (Scheme 141).\textsuperscript{170a}

Other intermediates of 714 for the synthesis of carbapenem antibiotics (thienamycin analogs) were prepared by Ikota et al. from D-glucose\textsuperscript{170b} or for methylcarbapenem derivatives via the corresponding methyl-substituted pyran $\beta$-amino acid intermediates.\textsuperscript{170c–e}

A further lactone $\beta$-amino acid intermediate for access to thienamycin was prepared by Morley et al. from the cycloaddition product of an acyl-nitroso compound and cyclopentadiene, 718. N–O bond cleavage in 718 yielded protected amino cyclopentenone 719, after which C–C double bond functionalization with lithiated trimethylsilyl thioacetal nucleophile and methylation of the active methylene group gave 720. Desilylation with n-Bu$_4$NF afforded 721, which underwent oxidation through its masked formyl function and then esterification to give $\beta$-amino ester derivative 722. Oxidative rearrangement of 722 under Baeyer–Villiger conditions resulted in a $\delta$-lactone $\beta$-amino ester as a precursor for the synthesis of thienamycin (Scheme 142).\textsuperscript{171}

trans-3-Aminopyran-2-carboxylic acid, a building element in the construction of $\alpha/\beta$-peptides, was synthetized from amino alcohol 725 (derived from enantiomerically pure aldehyde 724). The key step in the synthesis was cyclization of diene derivative 726 (prepared from 725 by O-alkylation with allyl

Scheme 137. Synthesis of a Blasticidin S Precursor
bromide) by metathesis, furnishing O-heterocyclic amino alcohol 727. 727 was next converted by protecting group removal to 729, the hydroxymethyl function in which was oxidized by Swern oxidation, followed by treatment with NaClO2, to give the required pyran amino acid 731 (Scheme 143). cis-3-Aminopyran-4-carboxylic acid (737) was synthetized by Duan et al. from unsaturated alcohol 733 through reaction with sodium iodoacetate and MeI. Reduction of the ester intermediate with DIBALH afforded aldehyde 734. Intra-molecular dipolar cycloaddition of the nitrone intermediate obtained from aldehyde 734 led to the key compound, bicyclic isoxazolidine 735. Debenzylation of 735, hydroxymethyl oxidation, and esterification afforded pyran β-amino ester 737 (Scheme 144).<ref> cis-3-Aminopyran-2-carboxylic acid, a regioisomer of amino ester 737, was prepared by the same group from the six-membered O-heterocyclic oxo ester, by means of reductive amination with (R)-α-methylbenzylamine. These heterocyclic β-amino esters were utilized as building elements for the synthesis of a series of products with TACE inhibitor activities. 127,173 </ref>

3.3. Cyclic β-Amino Acids with Other Heteroatoms in the Ring

In comparison with the N- or O-heterocyclic β-amino acids, the number of counterparts containing heteroatoms other than N or O is very low, and only a limited number of publications have dealt with the synthesis of such compounds.

Amino group conjugate addition to conjugated unsaturated esters is a convenient route for access to S-heterocyclic β-amino acid derivatives (for N-heterocycles, see section 3.1.2.1).

The reaction of ethyl thioglycolate with tert-butyl acrylate in basic medium afforded tert-butyl 4-oxotetrahydrothiophene-3-carboxylate 739, which led via hydroxy ester 740 after dehydration with PPh3 and diisopropyl azodicarboxylate (DIAD) to unsaturated ester 741. Addition of lithium dibenzylamide to 741 provided a mixture of cis- and trans-β-amino ester derivatives 742 and 743 in a ratio of 54:46 in an overall yield of 49% together with isomerized ester 744. On treatment with t-BuOK in t-BuOH, 742 underwent quantitative epimerization to furnish 743 (Scheme 145). The five-membered S-heterocyclic β-amino acid regioisomers depicted in Figure 34 have been investigated as potential antifungal agents.2a Six-membered S-heterocyclic derivatives have been synthesized by Diels–Alder cycloaddition between methyl acrylate (748) and 1-thiobuta-1,3-diene 747. The cycloaddition gave cis- and trans-tetrahydrothiazine β-amino esters 749 and 750 in a ratio of 9:1. In the presence of Zn-, Mg-, or Al-based Lewis acids, cis derivative 749 suffered epimerization to trans derivative 750 (Scheme 146). When chiral oxazolidinone-based unsaturated amines were used in the above reaction, enantiomerically pure products were prepared.174

The synthesis of Si-based heterocyclic derivatives started from Ph2SiCl2 by reaction with vinylmagnesium bromide in the presence of Cp2TiCl2, which afforded heterocyclic compound 751. Azidination of 751 with chloramine-T and phenyltrimethylammonium tribromide (PTAB) resulted in 752. Aziridine opening with EtAlCN provided amino nitrile derivative 753, which was next converted by Boc protection.
and tosyl group removal to 755. Boc protecting group removal and ester hydrolysis in the final step gave the Si-heterocyclic β-amino acid 757 (Scheme 147).

4. SOME RELEVANT BIOLOGICAL PROPERTIES OF CYCLIC β-AMINO ACIDS

Although a description of the synthetic methodologies was the main goal of the present review, the present brief section is intended to offer an insight into the most important biological properties of cyclic β-amino acids, which may be of interest for medicinal chemists.

4.1. Cyclic β-Amino Acids Possessing Antifungal or Antibacterial Properties

Among the most relevant cyclic β-amino acids are those that exhibit antifungal and antibacterial activities. The two most representative compounds in this respect as strong antifungal agents are the five-membered carbocyclic compounds cispentacin (1) (isolated from the culture broth of a Bacillus cereus strain) and icofungipen (2) (active against Candida species). The six-membered unsaturated counterpart BAY Y9379 (3) has been reported to possess similar pharmacological properties. Not only alicyclic but also five-membered heterocyclic
β-amino acids exert antifungal and antibacterial activities. An important class are those with the N-heterocyclic pyrrolidine core (345), including the stereo- and regioisomers 758 and 759. These compounds have been applied as building elements for the construction of antimicrobial peptide oligomers. Among the antifungal β-amino acids with a simple structure similar to that of cispentacin are those with an O (561 and 562) or S (745 and 746) atom in their ring. Several of their substituted derivatives have been reported to possess multidrug-resistance activity. The four-membered O-heterocyclic derivative oxetin (344) (isolated from a fermentation broth of Streptomyces sp. OM-2317), a cyclic β-amino acid with a simple core, is a known antibiotic. Several other six-membered O-heterocyclic analogs (677–680) have been...
incorporated in antimicrobial peptides. A functionalized carbocyclic β-amino derivative containing a hydroxy group and three chiral centers, oryzoxymycin (238) (isolated from a soil sample of *Streptomyces venezuelae* var. oryzoxymyceticus), exhibits moderate activity against *Xanthomonas oryzae*, a Gram-positive bacterium, and has been described as an important antibacterial agent.1 The cyclic β-amino acids are not only pharmacologically active compounds themselves but are also elements in bioactive substances with more complex structures. Thus, amypurimycin (5) and pitucamycin (6), with five- and six-membered carbocyclic β-amino acid moieties, respectively, in their structure are antibiotics.2g−k A large family of bioactive compounds is the nucleoside-based antibiotics, whose structures contain either five- or six-membered O-heterocyclic β-amino acid residues. Chrysandin (349) (produced by *Chrysosporium pannorum* 4629), a peptide-based nucleoside derivative with a 3-aminoctahydrofuran-2-carboxylic acid unit in its structure, expresses strong antifungal and antibacterial activities.95 Antibacterial amino acid nucleosides whose structures include a β-amino acid moiety and a pyran ring have been synthetized in a relatively large number of different derivatives. Among them, the antibiotic blasticidin S (347), isolated from *Streptomyces griseochromogenes*, is probably the most important example. A number of other amino acid nucleoside derivatives, such as gougerotin (isolated from *Streptomyces gougerotii*) and analogs with different functions (348 and 683), cytomycin (681) (produced by *Streptomyces* sp. HKI-0052), cytosinine (682) (hydrolyzed from calf thymus tissues), and bagougeramine A (684) (produced by a strain of *Bacillus circulans*), are antibacterial substances related to blasticidin S.166

4.2. Antiviral Cyclic β-Amino Acids

Besides their antibacterial properties, the other significant pharmacological feature of cyclic β-amino acids is related to their antiviral activities. Investigations on the cyclic β-amino acids in this sense are closely related to their drug counterparts, such as Relenza169 or Tami-flu.59 Some highly substituted cyclohexanecarboxylic β-amino acids, modified analogs of Tami-flu (241−244), have been described to display promising antiviral properties. A number of O-heterocyclic β-amino acid analogs of Relenza (696−698) have also been synthetized and investigated as potent antiviral agents with inhibitory action against influenza virus sialidases.59−61 Five-membered N-heterocyclic β-amino acids are another important class of products that exert antiviral properties. Some of these pyrrolidine β-amino acids, such as 386 (A-87380) or 387 (A-192558), possess influenza neuraminidase inhibitory activity. Through change of the functional moieties either on the amine nitrogen or on the amide nitrogen, a series of other related derivatives (758−761, Figure 35) has been synthetized and investigated as potential influenza neuraminidase inhibitors.104,110

4.3. Cyclic β-Amino Acids with Antitumoral Properties

Although β-amino acids themselves in general do not display antitumoral activity, they are often elements of many...
compounds that do possess this property. Thus, norbornene \( \beta \)-amino acid is an element of CEP-28122 (7), while cyclohexene \( \beta \)-amino acid is a component of MK-6892 (8). Cyclohexene or cyclopentane \( \beta \)-amino acid moieties are found in several other related compounds that exhibit antitumoral properties (9−11). A series of products containing a carbocyclic or heterocyclic \( \beta \)-amino acid residue has been synthetized and evaluated as efficient selective inhibitors of tumor necrosis factor (TNF-\( \alpha \)) converting enzyme (TACE). Apart from those in which there is a carbocyclic \( \beta \)-amino acid (e.g., 9), the most abundant are those with a pyrrolidine \( \beta \)-amino acid framework. Five-membered \( N \)-heterocyclic \( \beta \)-amino acid or hydroxamic acid-containing molecules and related substituted derivatives (41, 42, and 768−767) (Figure 36), for example, are representative molecules of this type. The six-membered \( N \)-heterocyclic \( \beta \)-amino acids and the pyran \( \beta \)-amino acids may also function as elements of molecules with TACE inhibitor activity (e.g., 765). Highly functionalized piperidine \( \beta \)-amino acid derivatives (514, 515, and 768) act as enzyme inhibitors and exhibit antitumoral activity, while pyrrolidine-based \( \beta \)-amino acid derivatives with structures such as 769 behave as dipeptidyl-peptidase IV inhibitors (Figure 37).

4.4. Cyclic \( \beta \)-Amino Acids with Cardioprotective Properties

Nucleoside \( \beta \)-amino acids (606−611) are not only antibacterial agents, but are also used as selective adenosine A3 agonists for the treatment of certain myocardial diseases, for instance, to prevent myocardial ischemic injury. A relatively large number of variously substituted derivatives of these types of compounds have been described in recent years.

5. SUMMARY AND OUTLOOK

As reflected by the increasing number of publications devoted to alicyclic and heterocyclic \( \beta \)-amino acids during the past 15 years, the field is likely to continue to grow in the years to come.
years, this field has become an expanding area in organic and medicinal chemistry. In particular, the biological characteristics of the cyclic β-amino acids as independent molecular entities, together with their usage as precursors of different heterocycles, as chiral auxiliaries in asymmetric syntheses, and as precursors of β-lactams and in foldamer chemistry, have aroused immense interest in chemistry and in drug research, and the synthetic procedures devised for access to these and related derivatives have developed tremendously. The presence of β-amino acid frameworks in various bioactive natural products may be expected to lead to increasing interest in the discovery of novel routes and methodologies for their preparation in enantiomerically pure form. The substituted derivatives of cyclic β-amino acids as analogs of known antiviral agents appear sure to exert a great impact on drug development and the future synthesis of potential bioactive peptides. Novel synthetic pathways to highly functionalized derivatives, e.g., by the selective transformation of ring olefinic bonds with the generation of multiple stereogenic centers, and their conversion via carbocycle-opening procedures, followed by an abundance of functionalization (oxido-reductive techniques, metathesis, etc.), will certainly be topics of enormous interest to synthetic chemists.

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Notes

The authors declare no competing financial interest.

Biographies

Lóránd Kiss graduated with a degree in chemistry in 1997 from the Faculty of Chemistry and Chemical Engineering at Babes-Bolyai University (Cluj-Napoca, Kolozsvár, Romania). He received his Ph.D. in 2002 from the Department of Organic Chemistry at Debrecen University (Debrecen, Hungary) under the supervision of Prof. Sándor Antus, working in the field of the asymmetric syntheses of O-containing heterocyclic natural products. In 2003, he joined the research group of Professor Ferenc Fülöp at the Institute of Pharmaceutical Chemistry, University of Szeged (Szeged, Hungary), where he began to deal with cyclic β-amino acid chemistry. He was a postdoc in the laboratories of Prof. Norbert De Kimpe at Ghent University (Ghent, Belgium), and Prof. Santos Fustero, at the Department of Organic Chemistry, University of Valencia (Valencia, Spain). He is currently a lecturer at the Institute of Pharmaceutical Chemistry, University of Szeged. His recent scientific interest is directed toward the selective functionalization of alicyclic and heterocyclic β-amino acids.

Ferenc Fülöp was born in Szank, Hungary, in 1952. He received his M.Sc. in Chemistry in 1975 and his Ph.D. in 1979, from József Attila University (Szeged, Hungary), under the supervision of Prof. Gábor Bernáth. He was appointed Professor at the Institute of Pharmaceutical Chemistry, University of Szeged (Szeged, Hungary), in 1991, and since 1998 he has been head of the Institute. He is member of the Hungarian Academy of Sciences. He has a wide range of research interests in heterocyclic chemistry, including isoquinolines, saturated 1,3-heterocycles, and the ring–chain tautomerism of 1,3-heterocycles. His recent activities have focused on the use of amino alcohols and β-amino acids in enzymatic transformations, asymmetric syntheses, foldamer construction, and combinatorial chemistry, with a view to the development of pharmacologically active compounds. Since 2009, he has been chairing a European COST Action (CM0803): Functional Peptidomimetic Foldamers: From Unnatural Amino Acids to Self-Assembling Nanomaterials.

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ABBREVIATIONS USED

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ACPC</td>
<td>2-amino-cyclopentanecoxylic acid</td>
</tr>
<tr>
<td>AZT</td>
<td>azido-thymidine</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>BOP</td>
<td>(benzotriazol-1-yl)oxycarbonyl(dimethylamino)-phosphoramide</td>
</tr>
<tr>
<td>CAN</td>
<td>cerium ammonium nitrate</td>
</tr>
<tr>
<td>COD</td>
<td>cyclo-octadiene</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
</tr>
<tr>
<td>CSI</td>
<td>chlorosulfonyle isocyanate</td>
</tr>
<tr>
<td>DAST</td>
<td>diethylaminosulfur trifluoride</td>
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<tr>
<td>Deoxy-Fluor</td>
<td>bis(2-methoxyethyl)aminosulfur trifluoride</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicycloundecene-7-ene</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethylazodicarboxylate</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropylazodicarboxylate</td>
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<tr>
<td>DIBALH</td>
<td>diisobutyalumium hydride</td>
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<tr>
<td>DIPEA</td>
<td>diisopropylethyl amine</td>
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<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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<td>DMB</td>
<td>dimethoxybenzyl</td>
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<tr>
<td>DMDO</td>
<td>dimethylidioxirane</td>
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DMF = N,N-dimethylformamide
DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DPPA = diphenylphosphoryl azide
EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Fmoc = fluorenylmethoxycarbonyl
HMPA = hexamethylphosphoramide
HOAT = 7-aza-1-hydroxy-1,2,3-benzotriazole
IBCF = isobutyl chloroformate
KHMD = potassium hexamethyldisilazide
LDA = lithium diisopropylamide
LiHMDS = lithium hexamethyldisilylamide
HMPA = hexamethylphosphoramide
LiHMDS = lithium hexamethyldisilazide
mCPBA = m-chloroperoxybenzoic acid
Ms = methanesulfonyl
NAAs = nucleoside amino acids
NBS = N-bromosuccinimide
NaHMDs = sodium hexamethyldisilazide
NIS = N-isosuccinimide
NMM = N-methylmorpholine
NMO = N-methylmorpholine N-oxide
Np = p-nitrosulfonyle
PDC = pyridinium dichromate
PLE = pig liver esterase
PMB = p-methoxybenzyl
PMP = p-methoxyphenyl
PTAB = phenytrimethylammonium tribromide
pTs = p-toluenesulfonyl
Py = pyridine
SÁAs = sugar amino acids
TBDDS = tert-butyldimethylsilylethynyl
TEMPO = 2,2,6,6-tetramethylpiperidinyloxy
TF = trifluoromethanesulfonate
TFA = trifluoroacetic acid
TMS = trimethylsilyl
TolBINAP = 2,2′-’-tolylphosphino-1,1′-binaphthyl
Tr = trityl
Troc = trichloroethoxy carbamate
Z = benzylxycarbonyl

REFERENCES


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