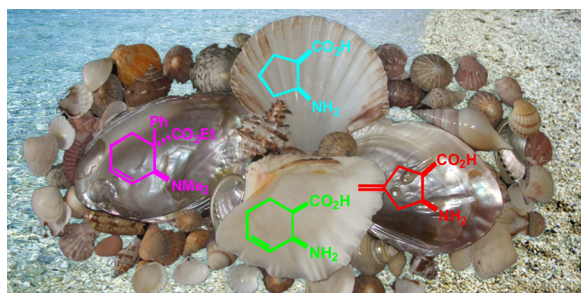# Synthesis of Carbocyclic and Heterocyclic β-Aminocarboxylic Acids

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CONTENTS

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]
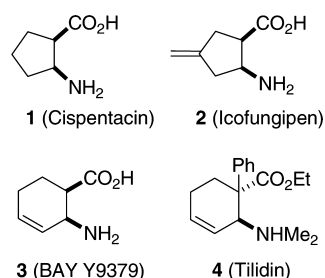
Figure 1. β-Amino acid drugs.

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*, 2001[1a]), 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 comprehesive, 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 approches 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
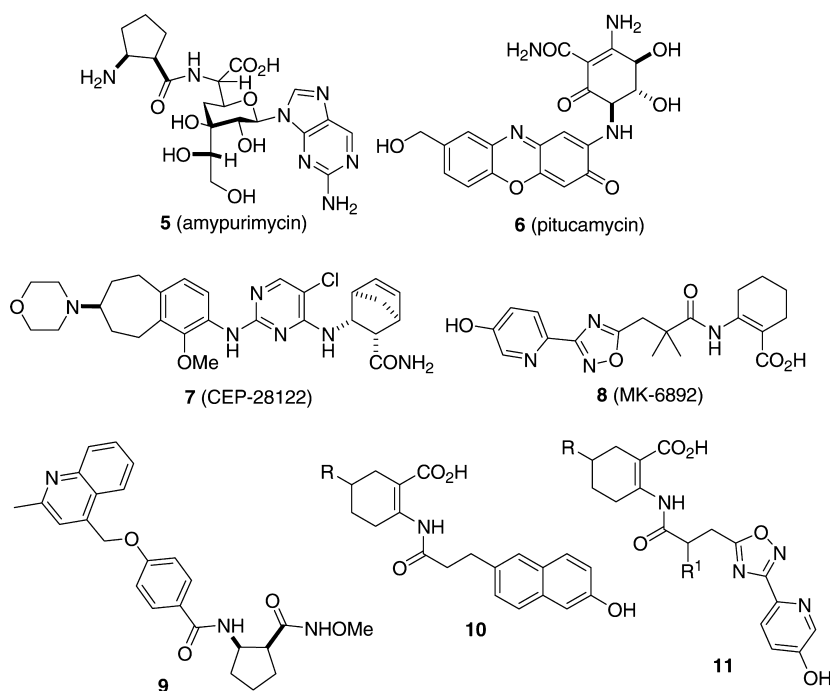

Figure 2. Pharmacologically active β-amino acid derivatives.

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.
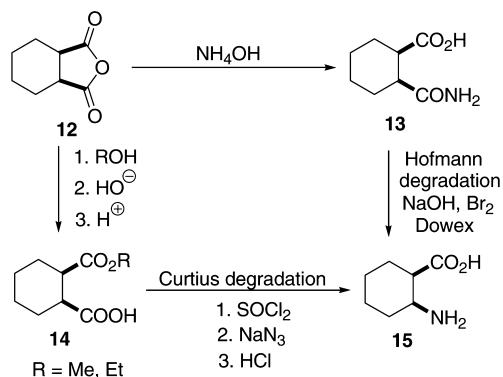
2. CARBOCYCLIC β-AMINO ACIDS

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-aminocyclohexanecarboxylic acid is based on the transformation of hexahydrophthalic anhydride (12) by amidation and Hofmann degradation of the resulting amide (13) to the corresponding β-aminocyclohexanecarboxylic acid 15.[1a]

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

Scheme 1. Syntheses of Carbocyclic β-Amino Acids via Hofmann or Curtius Degradation

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-aminocyclohexenecarboxylic 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
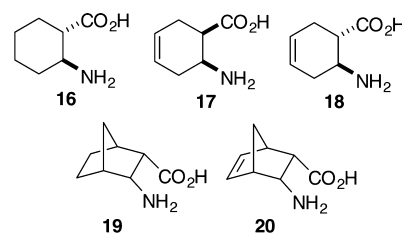
Figure 3. Several carbocyclic β-amino acids.

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
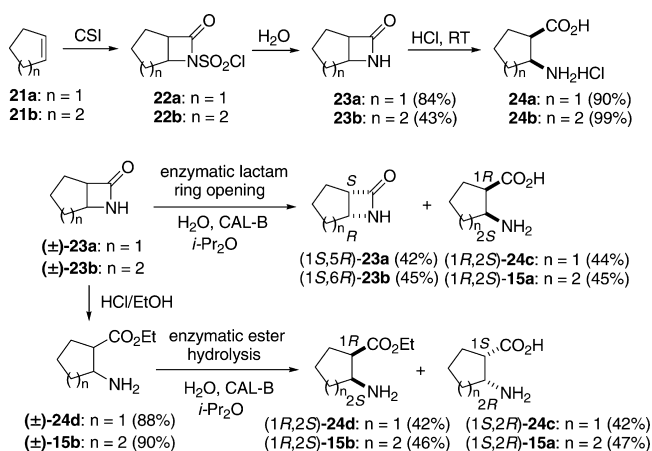
Bicyclic β-lactam ring-opening by hydrolysis or ethanolysis has been extended toward the synthesis of enantiomerically pure carbocyclic β-amino acids. Enzyme-catalyzed lactam ring-opening of racemic azetidinone (23a,b) resulted in the enantiomerically pure unreacted lactam and the corresponding alicyclic *cis-β-amino acid* enantiomer (15a, 24c). The amino acid enantiomers (15a, 24c) were prepared by an alternative route: enzymatic hydrolysis of the racemic carbocyclic 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−s]

This lactam opening method has been efficiently used for the preparation of a series of derivatives such as the β-aminocyclohexene (17) or cyclopentenecarboxylic (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
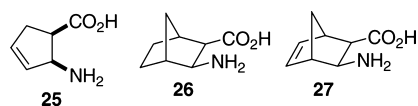
Figure 4. Carbocyclic β-amino acids derived from β-lactams.

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. Carbocyclic β-Amino Acids from β-Keto Esters. Carbocyclic β-keto esters, conveniently synthetized 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. Reductive amination of cyclic β-keto esters is a suitable method for the synthesis of carbocyclic 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

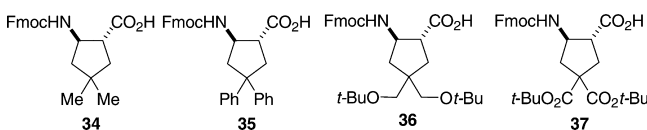**Scheme 3. Synthesis of a *trans*-β-Amino Acid from the Corresponding β-Oxo Ester by Reductive Amination**
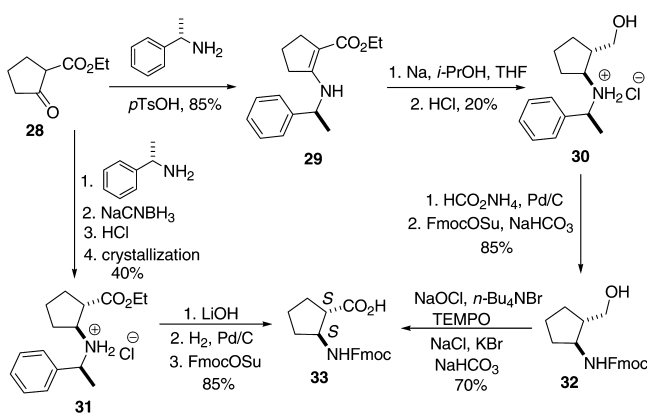
with (S)-α-methylbenzylamine to furnish enamine derivative **29** in high yield. Reduction of **29** with Na in *i*-PrOH led to *trans*-amino alcohol **30**, which was converted by removal of the chiral auxiliary, N-Fmoc protection, and oxidation to *trans*-amino acid enantiomer **33**.[6]

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).[6]

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 disubstituted cyclic β-amino acids **34**−**37** (Figure 5).

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

octanecarboxylic acids was reported by Tang et al.[8] Their method was based on the catalytic asymmetric hydrogenation of enamines and, in contrast with the earlier strategies (see Scheme 3), led to *cis*-β-aminocarboxylates. A Ru catalyst and a chiral phosphine ligand were used to convert enamine **38** cis-selectively to *cis*-aminocyclopentane or cyclohexane ester **39** in 99% ee (Scheme 4).

Scheme 4. Syntheses of Carbocyclic β-Amino Esters by Cis-Selective Catalytic Reduction of Enamines
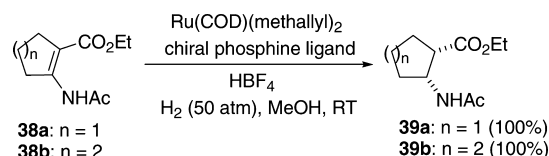
From *cis*-amino esters **39**, the trans counterparts could be easily synthetized by epimerization at C-1 with NaOEt.[8] New Rh complexes were used for the asymmetric hydrogenation of β-acetamido dehydroamino acid derivatives by Wu et al.[9a] Yu et al. have synthetized novel β-sulfonamidocyclopentanecarbox-ylates by using Pd(OCOCF₃)₂/chiral diphosphine ligand systems for the enantioselective hydrogenation of cyclic β-arylsulfonamido acrylates.[9b] Developments relating to the large-scale applicability of the asymmetric hydrogenation of dehydroamino acids were reported by Enthaler et al.[10] Novel chiral phospine ligands were used in multi-10-g scale reactions, and up to 94% ee was achieved.[10]

Enantiomerically pure β-(4-fluorobenzyl)aminocyclo-pentanecarboxylate (**41**) (Scheme 5) is a precursor of the

Scheme 5. Syntheses of *cis*- and *trans*-β-Amino Esters by Reduction of Enamines with NaBH₃OAc
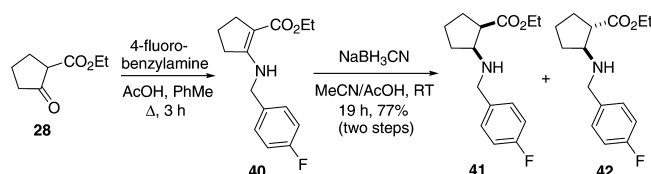
biologically interesting compound HCV NS5B,[11] known as a polymerase inhibitor. β-Keto ester transformation through the enamine was applied for the synthesis of racemic **41**. In this case, reductive amination of **28** with 4-fluorobenzylamine and NaBH₃CN furnished racemic *cis*-amino carboxylates **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 benzyloxymethyl-containing keto ester **44** by reductive amination (Scheme 6).[2a]

2.1.2. Carbocyclic β-Amino Acids by Metathesis. Carbocyclic 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

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

Scheme 6. Synthesis of Exomethylenic β-Aminocyclopentanecarboxylic Acid by Reductive Amination

Scheme 7. Syntheses of *trans*-β-Aminocycloalkenecarboxylates from α,β-Unsaturated Esters

unsaturated acyclic esters afforded acyclic dieno amino esters **49** and **50** (for the conjugate addition to α,β-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 β-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 β-amino acid enantiomers were synthetized from enantiomerically pure α-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 β-amino ester enantiomers (Scheme 8).[12b]

Scheme 8. Syntheses of *trans*-β-Aminocycloalkenecarboxylates from S-Methionine and R-Allylglycine

β-Lactams can be easily transformed to the corresponding β-amino acids by lactam ring-opening. Dienes possessing a β-lactam framework (**57**) were converted thro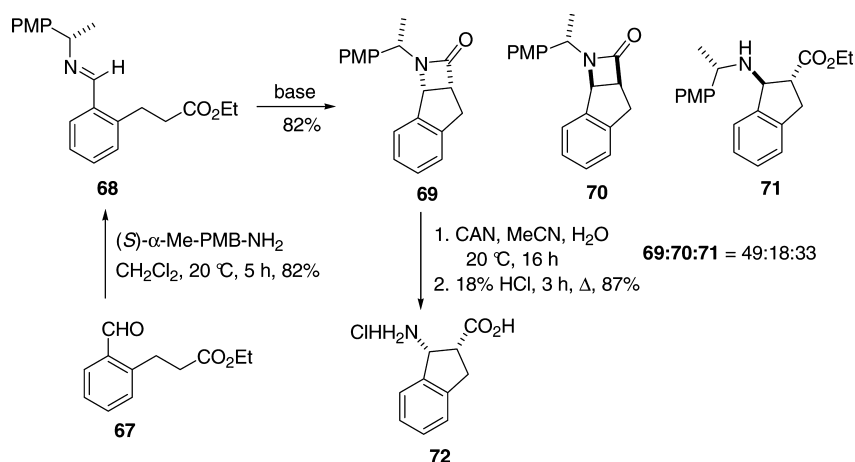ugh acyclic β-amino acid derivatives **58** by intramolecular ring-closing metathesis to afford unsaturated carbocyclic *trans*-β-amino esters (**59**). The configurations of the stereocenters in the starting lactam **57** were not affected during the process, which resulted in five- or six-membered *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 β-amino acids. A general method for the synthesis of difluorinated

Scheme 9. Syntheses of *trans*-β-Aminocycloalkanecarboxylic Acids from Diene β-Lactams

Scheme 10. Syntheses of Difluorinated β-Aminocycloalkanecarboxylates from Fluorinated Imidoyl Chlorides

Scheme 11. Synthesis of Benzo-Fused Cispentacin from Imino Esters

β-aminocyclopentane-, cyclohexane-, and cycloheptanecarboxylic acids via a cross-metathesis reaction as key step was developed by Fustero et al.[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 phenylmenthyl ester (the cross-metathesis product) and subsequent hydrogenation gave the corresponding enantiomerically pure cyclic cis-amino ester.[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.[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 synthetized.[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 transpentacin 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).[15]

A recent method involving ring-closing metathesis was developed by Davis et al. Addition of unsaturated carboxylic acid derivative 76 to p-toluenesulfinylimine 75 with a C−C

Scheme 12. Synthesis of Bicyclic β-Lactam from Imino Esters
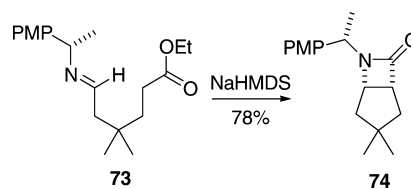
Scheme 13. Syntheses of *cis-β*-Aminocycloalkanecarboxylates from Unsaturated Sulfinimines and Weinreb Amide
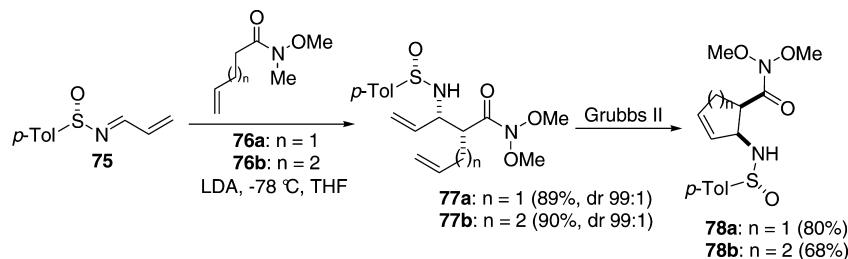
double bond furnished syn (dr > 99:1) dieno amino carboxylic acid derivative **77**, whose ring-closing metathesis afforded the corresponding five- or six-membered carbocyclic *cis-β*-amino acid derivative (Scheme 13). The relative configuration of the chiral C-centers in **77**, resulting from the syn-selective 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*-unsaturated carboxylate 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*-amino ester derivative **81**, which, after removal of the chiral auxiliary by hydrogenolysis, provided *cis*-2-aminocyclopentanecarboxylic acid enantiomer (**82**) in 98% ee (Scheme 14).[17b,104]

Scheme 14. Synthesis of Cispentacin from *α,β*-Unsaturated Esters and Lithium Amides
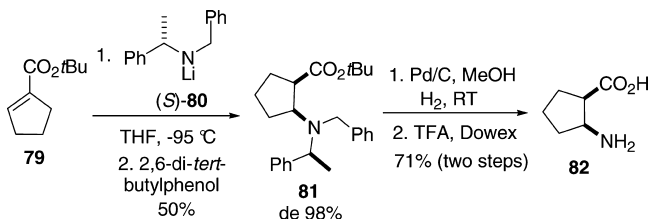
An important advantage of this strategy is its ready applicability for the preparation of alkyl-substituted analogs of cispentacin in enantiomerically pure form. Davies et al. further extended this methodology.

tert-Butyl 3-methylcyclopentenecarboxylate 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 synthetized 5-alkyl-substituted cispentacins. Addition of chiral amide (*S*)-**80** to 5-isopropyl-, 5-phenyl-, and 5-
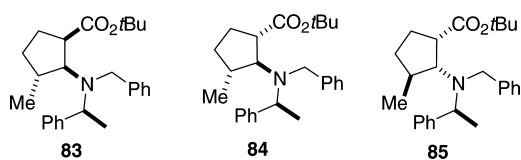

Figure 6. Structures of methyl-substituted cispentacin and trans-pentacin synthetized by lithium amide conjugate addition.

tert-butylcyclopentenecarboxylates 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-carboxymethyl-cyclopentanecarboxylate stereoisomers were synthetized 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-enecarboxylate (**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 (1*R*,2*S*,5*S*)- and (1*S*,2*R*,5*R*)-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 transpentacin 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**.

Scheme 15. Syntheses of Aminocyclopentanedicarboxylic Acids by Lithium Amide Addition to Diene Carboxylates
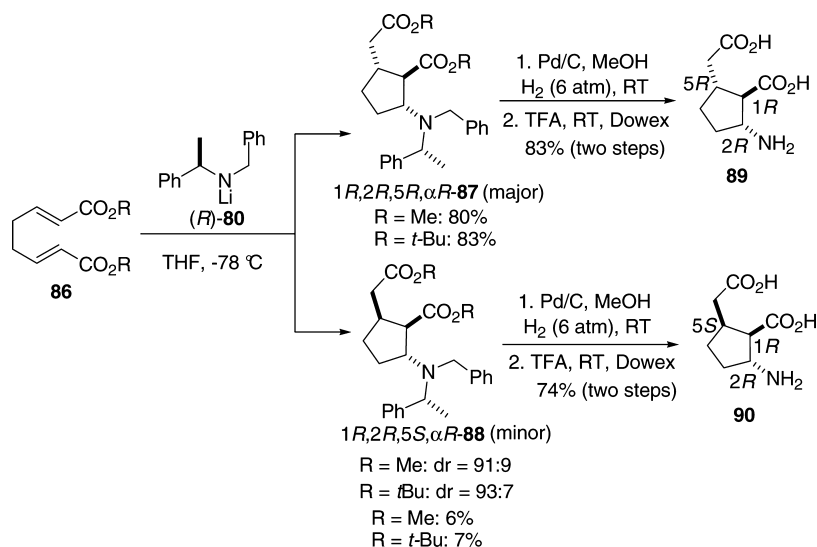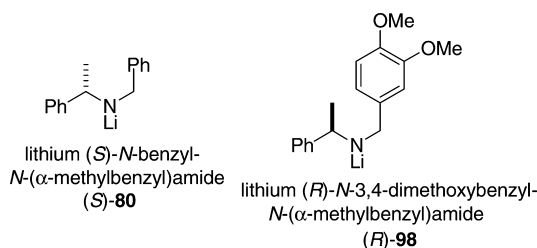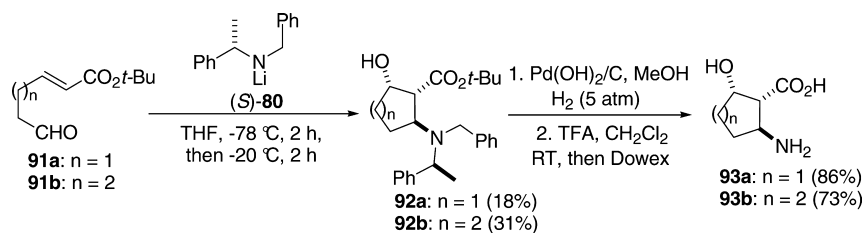

Scheme 16. Syntheses of Hydroxylated β-Aminocycloalkanecarboxylic Acids by Lithium Amide Addition to Unsaturated Oxo Esters

Figure 7. Structures of chiral lithium amides.

Figure 8. Methyl-substituted cispentacins synthetized by chiral lithium amide conjugate addition.

Removal of the chiral auxiliary, *N*-protection, and ester hydrolysis gave transpentacin enantiomer **102** (Scheme 18).[25]

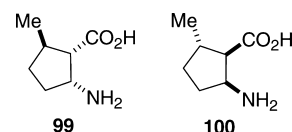The double Michael conjugate addition outlined in Scheme 15 was efficiently further developed by Ozeki et al. for the synthesis of functionalized β-aminocycloalkanecarboxylates with multiple chiral centers by the addition of different aldehydes. Analogously to the process presented in Scheme 15, addition 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

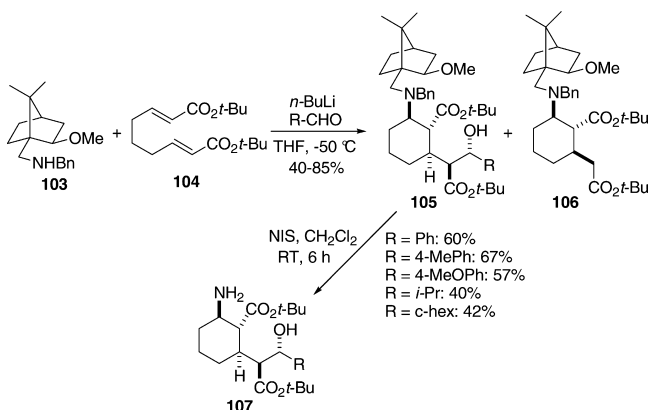**Scheme 17. Addition of Lithium Amides to Phenylthio α,β-Unsaturated Esters**
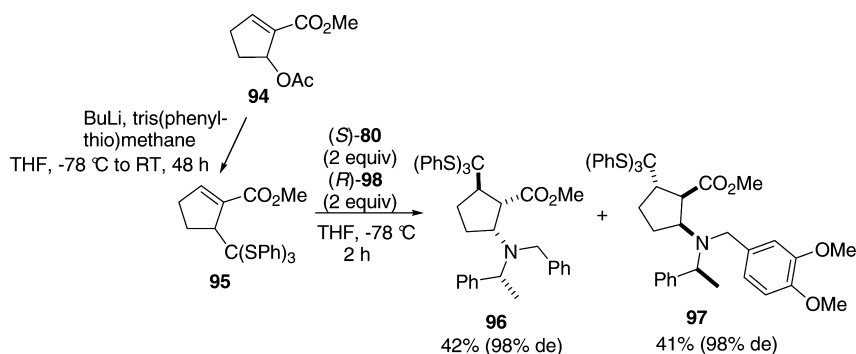
Scheme 18. Synthesis of Z-Protected Transpentacin by Chiral Lithium Amide Conjugate Addition
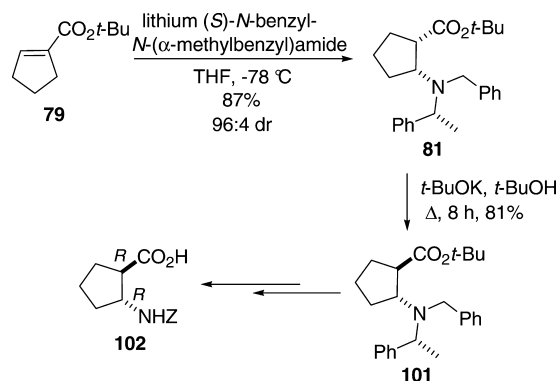
Scheme 19. Synthesis of Functionalized *tert*-Butyl β-Aminocyclohexanecarboxylate by Conjugate Addition of Chiral Amine to Unsaturated Diesters

**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 butadienecarbamate **108** to acrylate **109** provided a mixture of two cycloadducts, *cis-* and *trans*-2-amino-3-cyclohexenecarboxylates **110** and **111**, in a ratio of 4:1.

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

(4 + 2)-Cycloaddition has been efficiently utilized for the preparation of enantiomerically pure β-amino acids. Unsaturated nitro ester **114** bearing a pyrrolidinone moiety as chiral auxiliary was subjected to cycloaddition with 1,3-cyclohexadiene to furnish bicyclic β-nitro ester **115**. Nitro group reduction, followed by removal of the chiral auxiliary by hydrolysis, gave enantiopure amino acid **117** (Scheme 21).[28]

Cycloaddition is not only a powerful technique for the ring construction but may also be used for the functionalization of molecules. In order to prepare cyclic β-amino acids, both the carboxylic and amino groups can be introduced onto the

Scheme 20. Syntheses of Racemic β-Aminocyclohexenecarboxylic Acids by Diels−Alder Cycloaddition
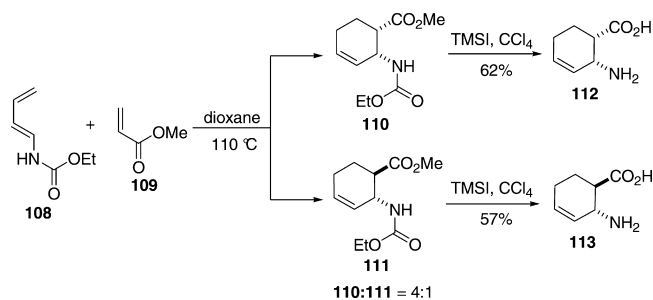
skeleton of a cycloalkane by 1,3-dipolar nitrone cycloaddition. A nitrone generated from aldehyde **118** and chiral (*R*)-*N*-hydroxyphenylglycinol **119** by intramolecular addition in the presence of MgBr$_2$ and *i*-PrOH furnished isoxazolidine **120** with high cis diastereoselectivity (diastereoisomeric ratio 96:4) (Scheme 22). Cycloadduct **120** was readily converted to cispentacin **121**.[29]

Nitrones generated from the enantiomerically pure unsaturated dithioacetal **122** were also efficiently used for the synthesis of cyclic β-amino acid enantiomers. Isoxazolidine **123** was formed as a single diastereoisomer (Scheme 23).

Reductive cleavage of the N−O bond and removal of the dithioacetal moiety followed by debenzylation resulted in (1*R*,2*S*)-cispentacin (**1**).[30a]

Intramolecular nitrone cycloaddition was the key step in the synthesis of cyclopentanecarboxylic acid via an intermediate isoxazolidine derivative. Enantiomerically pure unsaturated aldehyde **125** was readily transformed with *N*-benzylhydroxylamine through the corresponding nitrone **126** to isoxazolidine **127**. Reductive heterocycle cleavage followed by *N*-Boc protection gave amino alcohol **129** (Scheme 24).

Under oxidative conditions, **129** was transformed to a phenyl-substituted enantiopure cyclopentane β-amino acid (**130**).[30b]

2.1.5. Carbocyclic β-Amino Acids by Desymmetrization of *meso*-Anhydrides. In general, an asymmetric synthesis suffers from limitations with regard to the possibility of the large-scale preparation of the required enantiomerically pure substances. Desymmetrization of the readily available *meso*-anhydrides allows large-scale work. Mittendorf et al. prepared amino acid **2** (icofungipen) in high enantiomeric excess by using the desymmetrization procedure.[31]
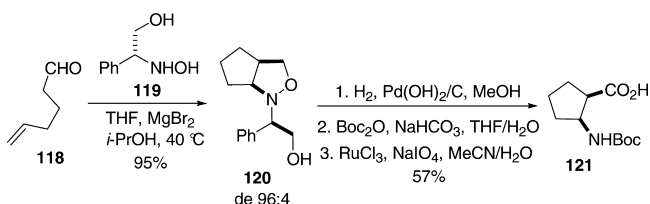
Alcoholysis of anhydride **132** (derived from acid **131**) with cinnamyl alcohol in the presence of a stoichiometric amount of quinine furnished hemiester **133**. Curtius rearrangement followed by Pd-catalyzed ester and amine deprotection afforded amino acid enantiomer **2** (Scheme 25).

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 Hamersak et al. by quinine-mediated desymmetrization of the corresponding racemic anhydride, followed by a Curtius reaction.[33]

tandem Michael−aldol reaction. After chromatographic separation, removal of the chiral auxiliary in **105** resulted in the enantiomerically pure, functionalized β-amino acid derivative **107** (Scheme 19).[26]

Scheme 21. Synthesis of Bicyclic β-Amino Acid Enantiomerically Pure 117 through Cycloaddition of an Unsaturated Nitro Ester and 1,3-Cyclohexadiene
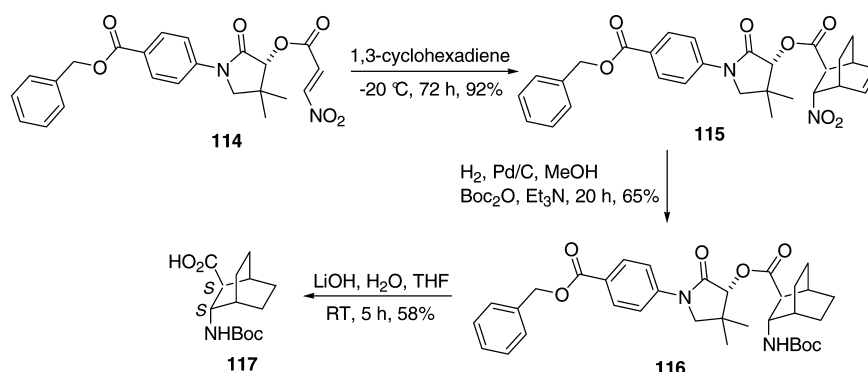
Scheme 22. Synthesis of Cispentacin from a Bicyclic Isoxazolidine


Scheme 23. Synthesis of Cispentacin Enantiomer 1 from an Enantiomerically Pure Ketene Dithioacetal
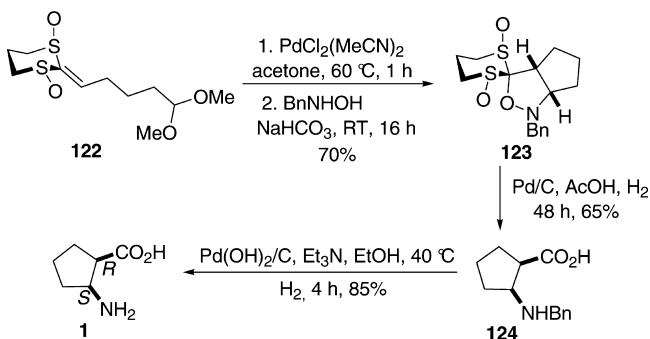
Anhydride **132** was isomerized to its endo derivative **135**, which was next subjected to alcoholysis in the presence of quinine, giving hemiesters **136** and **137** in a ratio of 3:7 (Scheme 26). These esters could not be separated, but their conversion by the Curtius rearrangement afforded the separable amino ester stereoisomers **138** and **139**. Deprotection of the
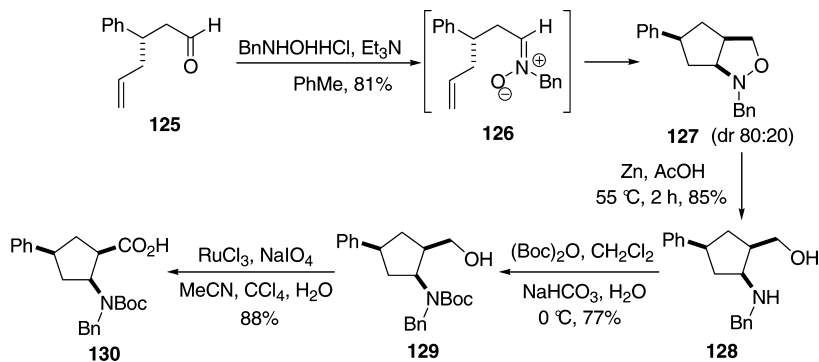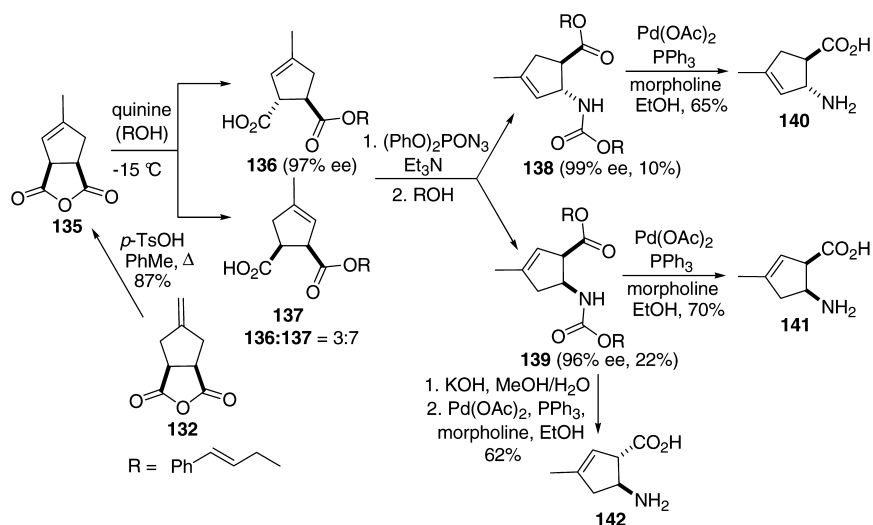
Scheme 25. Synthesis of Icofungipen
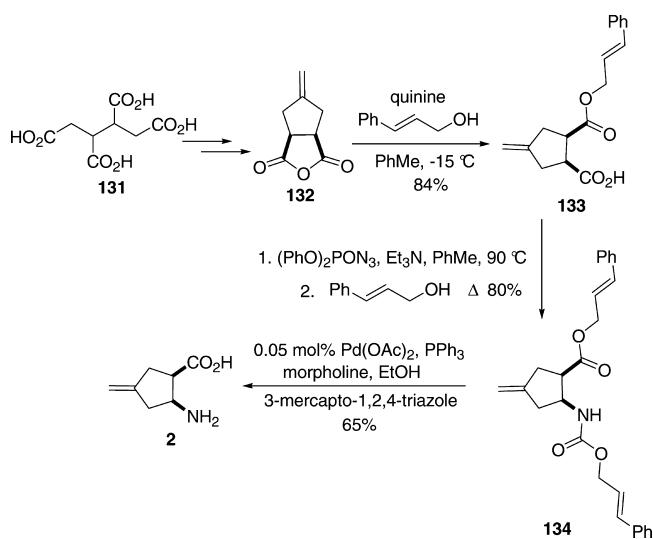
ester and amino functions resulted in β-amino acid enantiomers **140** and **141** in 99% and 96% ee. Base-mediated isomerization of **139** furnished novel stereoisomer **142** in 96% ee (Scheme 26).

The fourth stereoisomer (**144**) was obtained by exo–endo isomerization of the enantiomerically pure icofungipen (**2**) with trimethylsilyl chloride (TMSCl) and NaI (Scheme 27).[33]

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

**Scheme 24. Synthesis of a Phenyl-Substituted Cispentacin Derivative**

**Scheme 26. Syntheses of Icofungipen Isomers from a *meso*-Anhydride**

**Scheme 27. Synthesis of an Icofungipen Analog by Isomerization of Icofungipen**
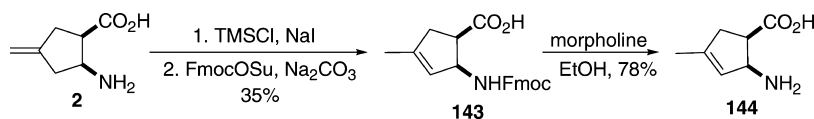
of readily available chiral monoterpenes. The method widely used for the synthesis of bicyclic β-lactams by CSI addition is the key step, involving the C−C double bond transformation of these natural sources for the synthesis of monoterpene-based β-amino acids. By starting from different monoterpenes, a series of cyclic β-amino acids were synthetized. For example, treatment of α-pinene (**145**) with CSI led regio- and stereoselectively to β-lactam **146**, the N-Boc protection and lactam opening of which resulted in carbocyclic β-amino acid enantiomer **148** (Scheme 28).[34]

Scheme 28. Chiral β-Amino Acids Derived from α-Pinene
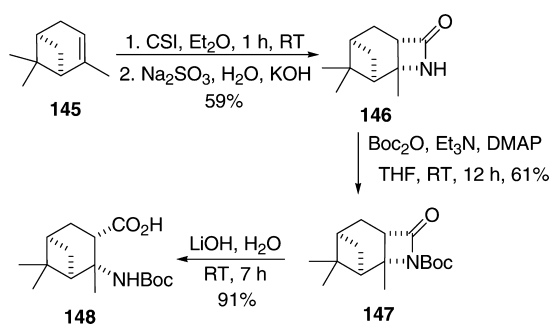
Another monoterpene isomer of **145**, δ-pinene, also underwent CSI addition regio- and stereoselectively to give the corresponding β-lactam **149**, which was next converted to the δ-pinene-based β-amino acid **150** (Figure 9).[35]
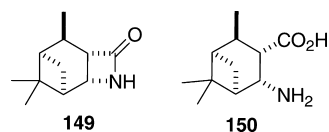
Figure 9. Structures of a α-pinene-derived β-lactam and β-amino acid.

Through application of a similar strategy, enantiomerically pure β-amino acid **152** was easily prepared from the readily available (+)-3-carene. The corresponding β-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]
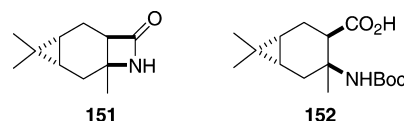
Figure 10. Structures of a β-lactam and a β-amino acid derived from (+)-3-carene.

In contrast with the above CSI additions to various monoterpenes, the addition to (+)-2-carene (**153**) was not regioselective and gave β-lactam isomers **154** and **155** in a ratio of 3:2 (Scheme 29). After separation by crystallization, these β-lactams were converted to the corresponding amino acids **156** and **157**.[37]

Another readily accessible starting material for the preparation of carbocyclic β-amino acid is chiral (−)-apopi-

Scheme 29. Syntheses of β-Amino Acids from (+)-2-Carene
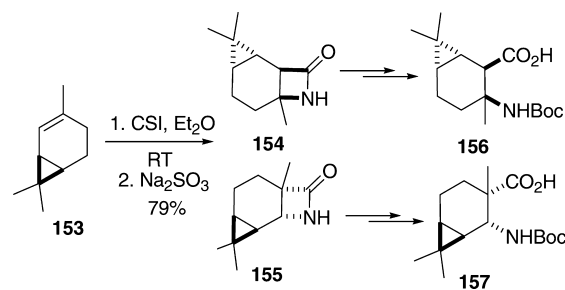
nene, prepared from commercially available (−)-myrtenal. Regio- and stereoselective CSI addition followed by lactam opening afforded enantiomerically pure lactam and amino acid **158** and **159** (Figure 11).[38]
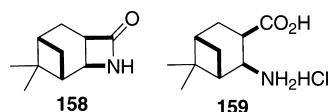
Figure 11. Structures of a β-lactam and a β-amino acid derived from (−)-apopinene.

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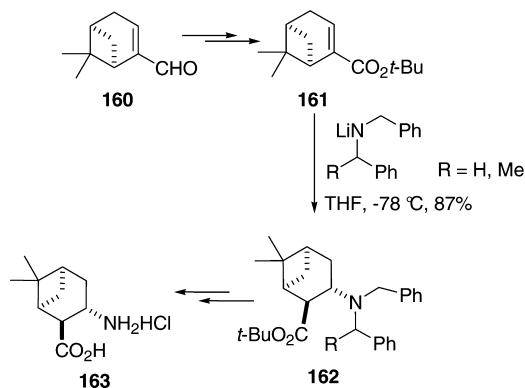
Scheme 30. Synthesis of a β-Amino Acid from (+)-Myrtenal

2.1.7. Miscellaneous. The Strecker reaction is a well-known general approach for the synthesis of α-amino acids. Enantiomerically pure carbocyclic α,β-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 hydrolyis. Through removal of the chiral auxiliary and amide hydrolysis, the amide stereoisomers obtained (**167** and **168**) afforded the corresponding α,β-diaminocyclohexanecarboxylic acids **169** and **170** with an ee of 99% (Scheme 31).[40]

The syntheses of all four enantiomers of cis- and trans-2-aminocyclohexanecarboxylic 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-aminocyclohexanecarboxylic 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 cispentacin **184** (Scheme 33).[42] Via this procedure, various carbocyclic β-amino acids and heterocyclic analogs of cispentacin 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-*

Scheme 31. Syntheses of α,β-Diaminocyclohexanecarboxylic Acids by the Strecker Reaction of Imines
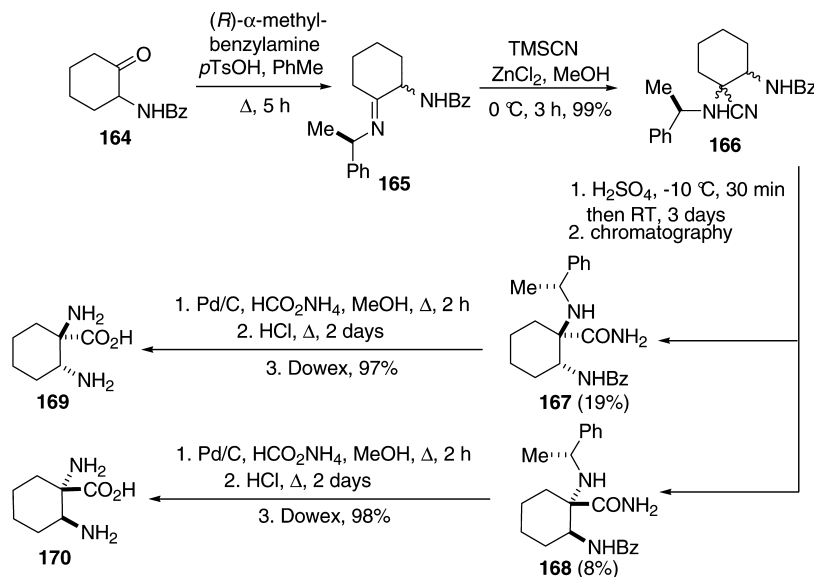
Scheme 32. Precursors for Cyclohexane β-Amino Acids from Benzopyrimidinones
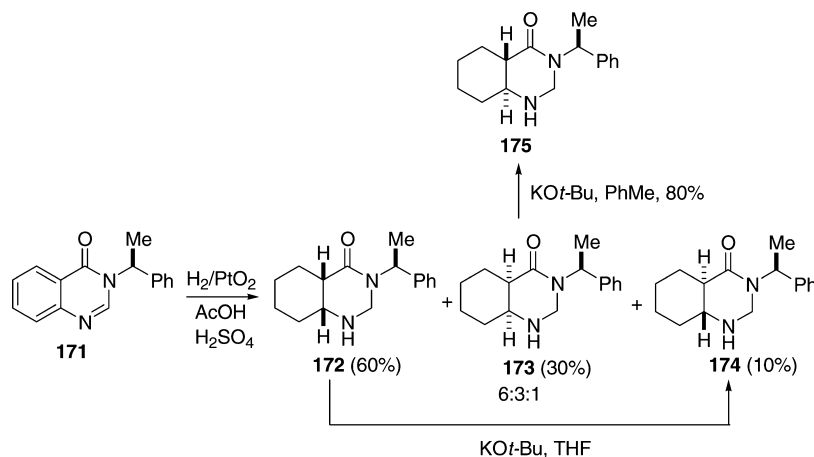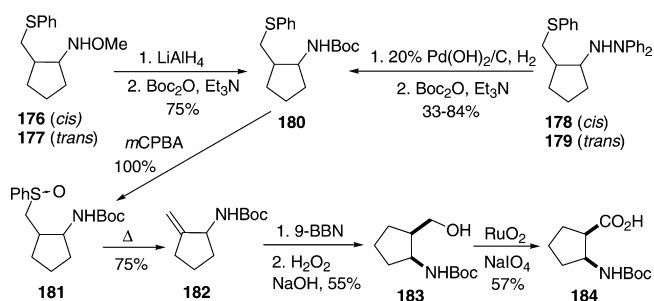

**Scheme 33. Synthesis of Cispentacin by Radical Cyclization of Amino Sulfanilic Compounds**

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 NaIO$_4$ with a catalytic amount of RuO$_2$, and esterification afforded transpentacin derivative **188** (Scheme 34).[43]

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

As conformationally rigid compounds, β-aminocyclopropane-carboxylic 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

Scheme 34. Synthesis of Methyl *trans*-β-Aminocyclohexanecarboxylate by Hydrozirconization of Unsaturated Oxazolidines
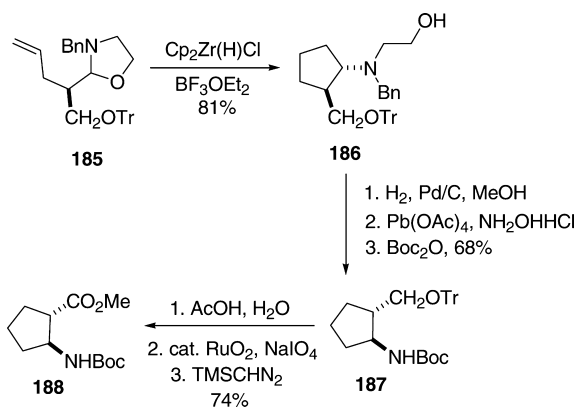
stability.[44] The most common synthesis of β-aminocyclopropanecarboxylic acid derivatives involves the addition of a carbene analog such as diazomethane or a diazocarboxylate to a C−C double bond.[44] Another method consists of the intramolecular ring closure (Michael-induced ring closure) of β-amino-γ-iodocarboxylates 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 35. Syntheses of Methyl-Substituted Cyclopropane β-Amino Acids
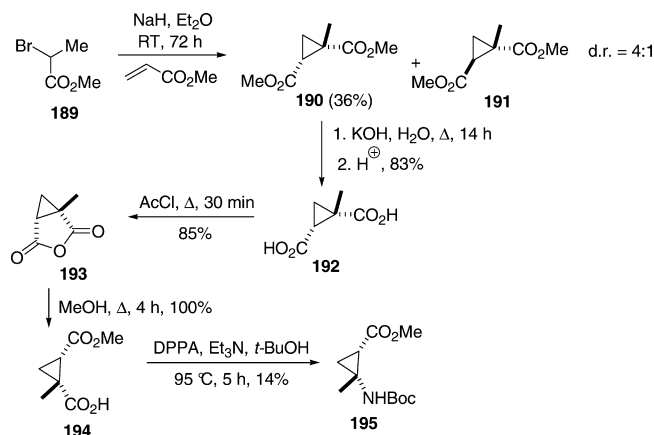
Another easy route to β-aminocyclopropanecarboxylates starts from 2-bromocyclopropanecarboxylic ester **196** through a bromide secondary amide exchange by substitution in the presence of base and crown ether catalyst to give amino acid derivative **197** (Scheme 36).[46]

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 (1*S*,2*R*)- and (1*R*,2*S*)-β-aminocyclobutanecarboxylic acids **203** and **204** by using a chiral uracil mimic **198**. The

Scheme 36. Syntheses of Racemic Cyclopropane β-Amino Acids from Bromocyclopropanecarboxylic Esters

R[1] = Me, nPr, iPr, nBu, tBu, Ph
R[2] = Me, nBu, iPr, tBu
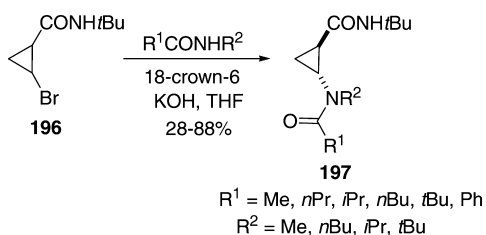
photocycloaddition of ethylene to **198** afforded a mixture of cis-annelated cycloadduct diastereomers **199** and **200**. This mixture could be separated by chromatography; subsequent transformations, finally involving heterocyclic ring hydrolysis, led to cyclobutane amino acid enantiomers **203** and **204** in overall yields of 33% and 20%, with an ee value of >97% (Scheme 37).[48]

Scheme 37. Syntheses of Cyclobutane β-Amino Acid Enantiomers from a Chiral Uracil Derivative
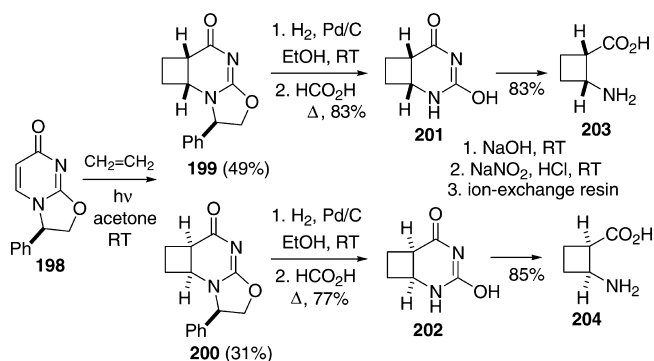
Starting from the chiral uracil derivative, the same research group prepared all four stereoisomers of 2-aminocyclobutane-carboxylic acid enantiomers, by using a similar synthetic strategy involving photochemical (2 + 2)-cycloaddition and isomerization of the cis- to the trans-β-amino acid.[49] The incorporation of cyclobutane cis-β-amino acids into pep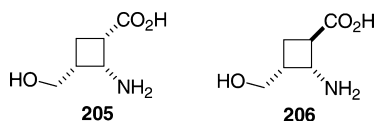tides has also been reported.[50] This technique of cycloaddition of an olefinic bond into the uracil derivative has been successfully applied for the preparation of hydroxymethylated β-amino-cyclobutanecarboxylic acid stereoisomers **205** and **206** (Figure 12).[51]


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-

Scheme 38. Synthesis of cis-Cyclobutane β-Amino Acid via a Curtius Rearrangement
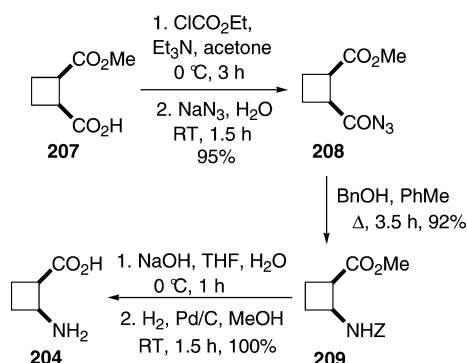
methylbenzylamine as chiral auxiliary, which on reaction with cis-amino acid **210** afforded diastereoisomers **211** and **212** in a ratio of 1:1. These two compounds were separated by chromatography, and then, after removal of the chiral auxiliary, the resulting amides were converted to cis-β-aminocyclobuta-necarboxylic 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]

Scheme 39. Preparation of Enantiomerically Pure Cyclobutane β-Amino Acids by Resolution of the Racemic Compound
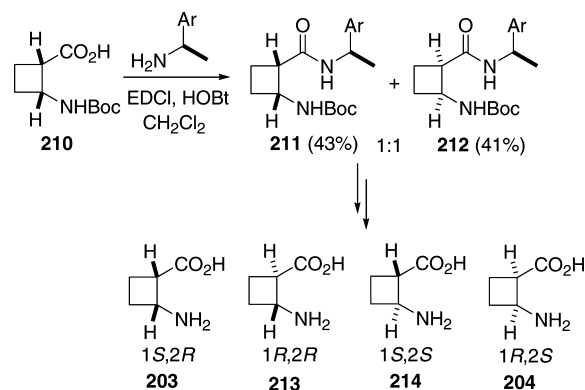
As a general method for the synthesis of cyclic α,β-diaminocarboxylic acids (Scheme 28), the Strecker synthesis was efficiently used for the preparation of this type of compound containing a cyclobutane ring. For this purpose, aminocyclobutanone was first reacted with (S)-α-methylbenzyl-amine to give 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 devel-oped 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.

Scheme 40. Syntheses of Cyclobutane α,β-Diamino Acids
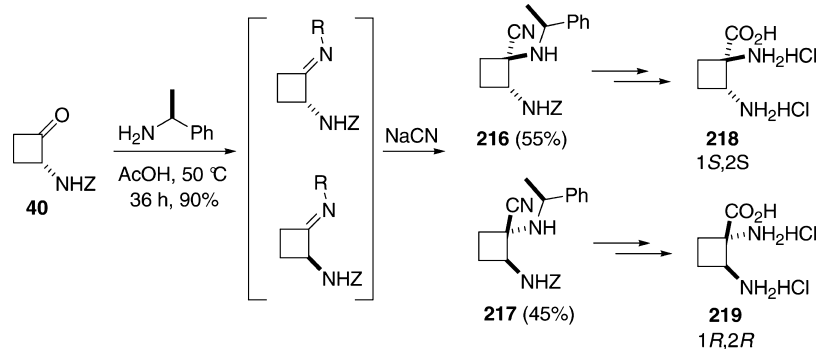
Although a good number of generally applicable and efficient methods are available for the synthesis of five- and six-membered cyclic *trans-β-amino* acids, there are fewer examples of the synthesis of analogs with larger ring systems, such as cycloheptane or cyclooctane derivatives.

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 o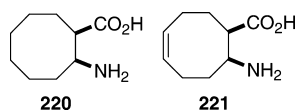r two C−C double bonds in the ring. The addition of CSI to cyclooctene or 1,5-cyclooctadiene, for example, proceeded via the corresponding β-lactams to yield the racemic eight-membered *cis-β-amino* acids **220** and **221** (Figure 13).[1a]

**Figure 13.** Cyclooctane and cyclooctene β-amino acids.

Analogously, 12-membered counterparts have been synthetized by using a similar protocol.[55]

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]

Scheme 41. Synthesis of a *cis*-Cycloheptane β-Amino Ester from the Corresponding Enamine
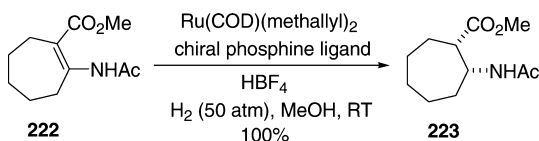
Access to seven-membered cyclic β-amino acid derivatives was achieved by ring-closing metathesis (for five- or six-membered analogs, see Scheme 7) of diolefinic intermediate **224** (derived from α,β-unsaturated esters and chiral amides), the result being the corresponding *trans-β-amino* cycloheptene 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

Scheme 42. Synthesis of a Cycloheptene β-Amino Ester by Metathesis
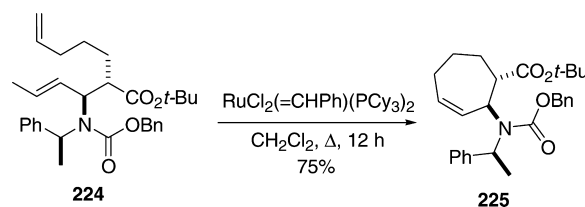
double bond is at a three C-atom distance from the carbamate group (Scheme 43).[12b]

Scheme 43. Synthesis of a Cycloheptene β-Amino Ester from S-Serine
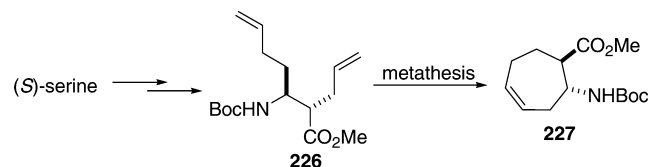
A difluorinated cycloheptane *cis-β-amino* ester (**230**) was prepared from the cross-metathesis product **229** in several steps by C−C double bond saturation and ring closure via base-promoted Cl displacement as the key step (Scheme 44; see also Scheme 10).[14]

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]

Scheme 44. Synthesis of a Difluorinated Cycloheptane β-Amino Ester
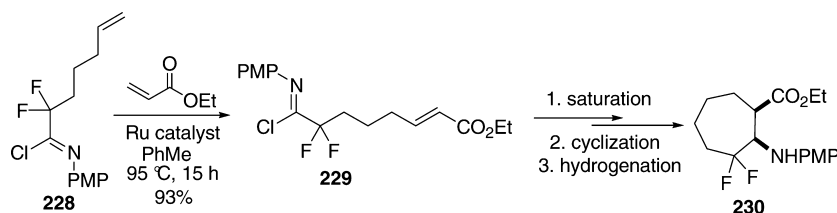
Scheme 45. Synthesis of Enantiopure *cis*-Cyclooctane β-Amino Acid by Conjugate Addition to the Corresponding Unsaturated Ester
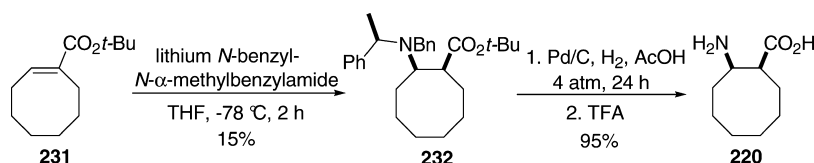
Scheme 46. Syntheses of *trans*-Cyclooctane and Cycloheptane β-Amino Acids
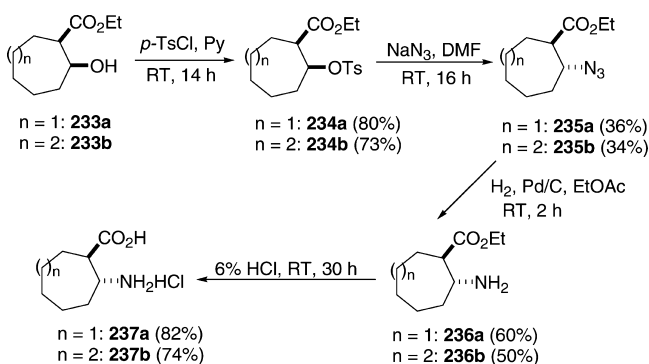
2.4. Synthesis of Functionalized Carbocyclic β-Amino Acids

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

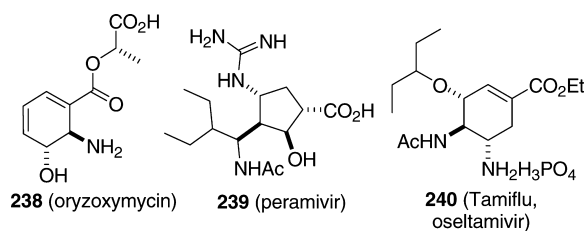**Figure 14.** Some bioactive highly functionalized cyclic amino acids.

antiviral, antifungal, or antibacterial activities (Figure 14). Modified derivatives and other multisubstituted cyclohexane amino acids[60] 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]
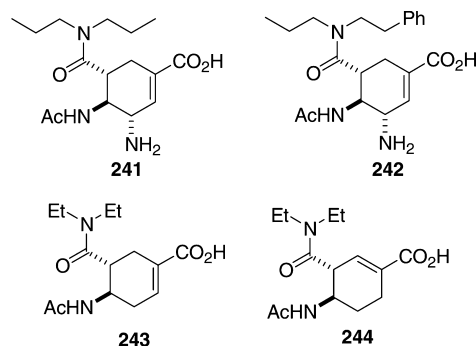
Figure 15. Structures of β-amino acid-modified Tamiflu analogs.

Whereas numerous highly substituted derivatives of cyclic α- or γ-amino acids with interesting biological activities have been synthetized and investigated, the functionalized β-amino acids have received less attention. However, due to their pharmacological potential, an increasing number of publications are now being devoted to these carbocyclic β-amino acids. The aim of this section is to summarize the most relevant synthetic techniques for access to these compounds.

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/I$_2$ in the presence of NaHCO$_3$, *cis*-2-aminocyclohexenecarboxylic acid **245** gave iodolactone **246** regio- and stereoselectively. Reductive deiodination with *n*Bu$_3$SnH, followed by lactone ring-opening and *N*-deprotection under acid catalysis, selectively furnished *all-cis*-5-hydroxylated β-aminocylohexanecarboxylic acid **248** (Scheme 47).[62]

1131

dx.doi.org/10.1021/cr300454h | *Chem. Rev.* 2014, 114, 1116−1169

Scheme 47. Synthesis of 5-Hydroxylated 2-Aminocyclohexanecarboxylic Acid via Iodolactonization
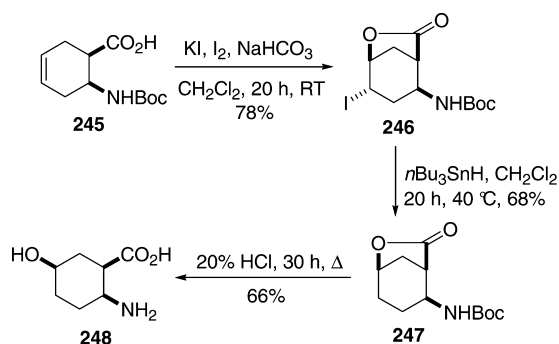
This method allowed the preparation of other regio- and stereoisomers of a series of other hydroxylated alicyclic β-amino acids.[63]

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-aminocyclohexenecarboxylates (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-cyclohexenecarboxylate 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 mesyloxy group substitution with azide and reduction, to orthogonally protected diaminocyclohexanecarboxylate 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 diaminocyclohexanecarboxylic 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

Figure 16. Structures of hydroxylated 2-aminocyclohexenecarboxylates.

Scheme 49. Synthesis of an Orthogonally Protected 2,5-Diaminocyclohexanecarboxylic Ester
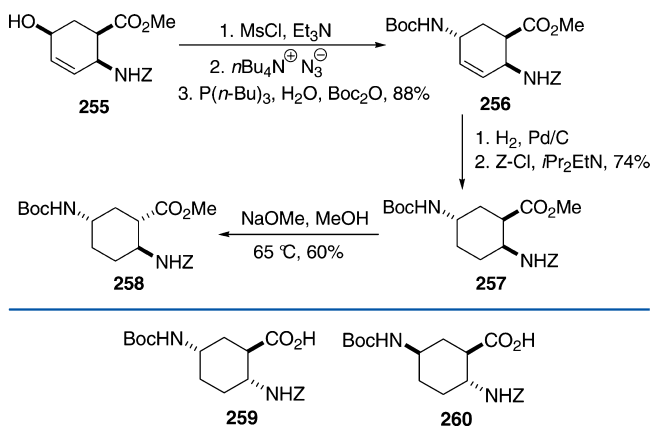
Figure 17. Structures of orthogonally protected 2,5-diaminocyclohexanecarboxylic esters.

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-aminocyclohexenecarboxylate **262**, while the corresponding saturated derivative **261** underwent inversion under similar conditions and yielded 3-fluorinated β-aminocyclohexanecarboxylic 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-aminocyclohexanecarboxylic 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-aminocyclohexanecarboxylates were also ex-

Scheme 48. Synthesis of a 5-Hydroxylated Cyclohexene Amino Ester via Iodolactonization

Scheme 50. Syntheses of Fluorinated Cyclohexane 2-Aminocarboxylates
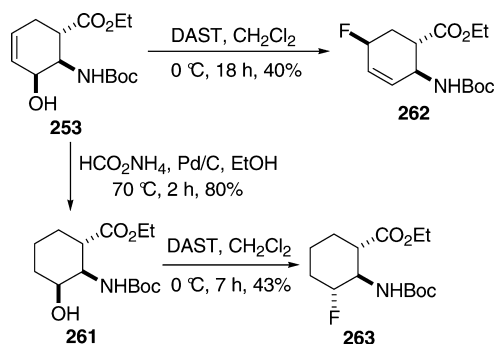
Scheme 51. Synthesis of a Difluorinated 2-Aminocyclohexane Amino Ester
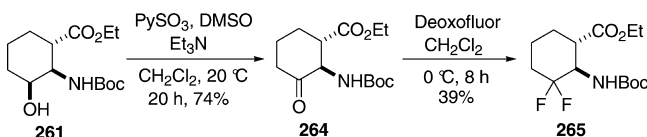
cellent methods for the synthesis of a series of other novel fluorine-containing six-membered cyclic β-amino acid regio- and stereoisomers, from either 1,3-cyclohexadiene- or 1,4-cyclohexadiene-derived bicyclic β-lactam through selective iodolactonization and hydroxylation followed by hydroxy–fluorine or oxo–fluorine exchange.[65,69]

The regio- and stereoselective iodolactonization offered an opportunity for the selective preparation of epoxycyclohexane β-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]

Scheme 52. Synthesis of an Epoxy Amino Acid with a Cyclohexane Skeleton
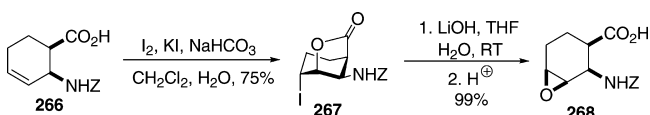
2.4.1.2. Functionalization via Selective Iodooxazinone and Iodooxazoline Formation. Another method in which the key step is the functionalization of the C–C ring double bond of a cyclic β-amino acid derivative with iodine or N-iodosuccinimide (NIS), followed by intramolecular nucleophilic ring closure, is iodooxazination or iodooxazoline 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 β-aminocyclohexanecarboxylic acids was based on iodooxazine formation.

Amino ester **269** reacted with NIS to give oxazinone derivative **270** regio- and stereoselectively. After dehalogenation with *n*Bu₃SnH, followed by simultaneous oxazinone opening and ester hydrolysis in the presence of aqueous HCl,

this heterocyclic derivative afforded 4-hydroxylated 2-amino-cylohexancarboxylic acid **272** (Scheme 53).[62,71] The particular

Scheme 53. Synthesis of a 4-Hydroxylated 2-Aminocyclohexanecarboxylic Acid via Iodooxazinone Formation
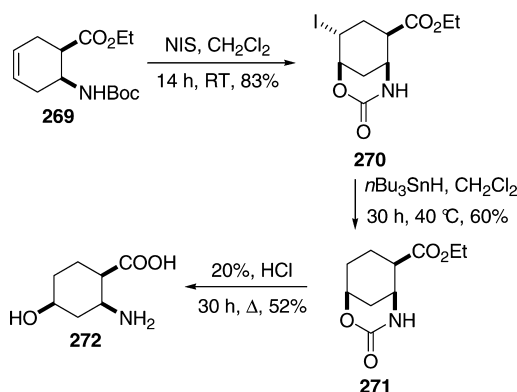
benefit of the iodooxazination method in comparison with iodolactonization (where 5-hydroxylated derivatives were formed) lay in the possibility of the preparation of a 4-hydroxylated cyclohexanecarboxylic amino acid.

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

Scheme 54. Synthesis of a 3-Hydroxylated 2-Aminocyclopentanecarboxylic Acid
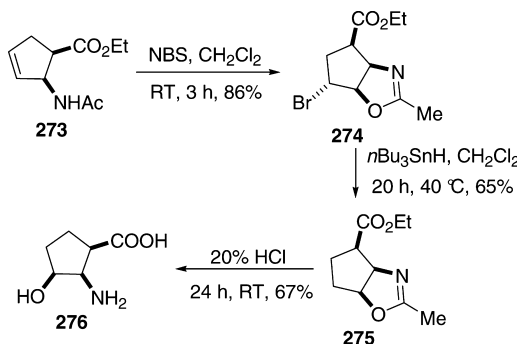
The iodooxazination and iodooxazolination method was readily utilized for the synthesis of a series of other hydroxylated five- and six-membered carbocyclic amino acid regio- and stereoisomers and for bicyclic norbornane derivatives.[63]

A novel route to hydroxylated cyclohexane β-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 β-aminocyclohexanecarboxylic acid derivatives **279–281** (Scheme 55). With the use of this strategy, hydroxylated five-membered carbocyclic β-amino acids were also prepared.[73]

Scheme 55. Syntheses of Hydroxylated 2-Aminocyclohexanecarboxylates via Oxazoline Formation
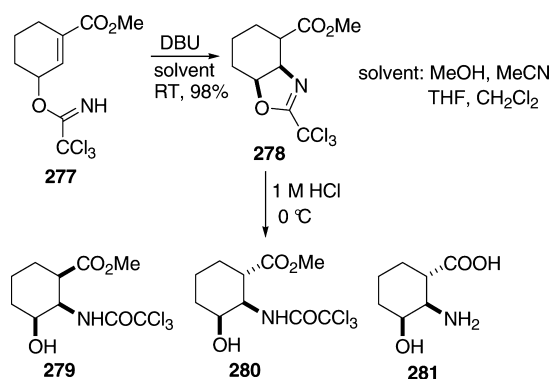
2.4.1.3. Functionalization via Selective Iodolactamization. Campbell et al. reported a special functionalization procedure for cyclohexenecarboxylic acid derivative **282**, based on regio- and stereoselective iodolactamization. On treatment with *n*BuLi and I$_2$, *N*-protected amide **282** furnished iodolactam **283**. Subsequent reductive deiodination and lactam opening resulted in the orthogonally protected cyclohexane diamino alcohol **285** (Scheme 56).[74]

Scheme 56. Iodolactamization of a β-Aminocyclohexenecarboxylate
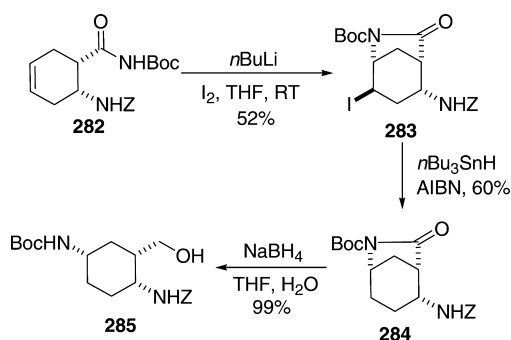
2.4.1.4. Functionalization via Stereoselective Epoxidation and Regioselective Oxirane Opening. Another broadly applicable and successful method for the synthesis of highly functionalized carbocyclic β-amino acids starts with stereoselective epoxidation of the ring C–C double bond, followed by regioselective 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 (*m*CPBA) in CH$_2$Cl$_2$ gave epoxyamino ester diastereoisomers **289**:**290** in a ratio of 9:1 (77%), whereas in the more polar solvent MeCN the ratio of the products was
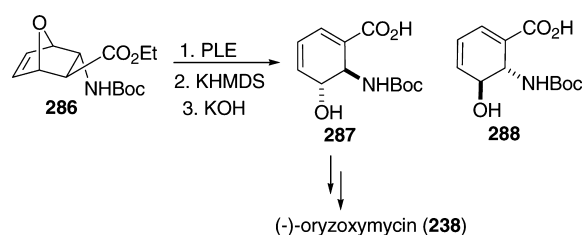
Scheme 57. Syntheses of Hydroxylated β-Aminocyclohexadienecarboxylic Acids

1:2 (95%) (Scheme 58). After separation of the two diastereoisomers (**289** and **290**), under catalytic hydrogenation

Scheme 58. Syntheses of Acetoxylated β-Aminocyclohexanecarboxylates
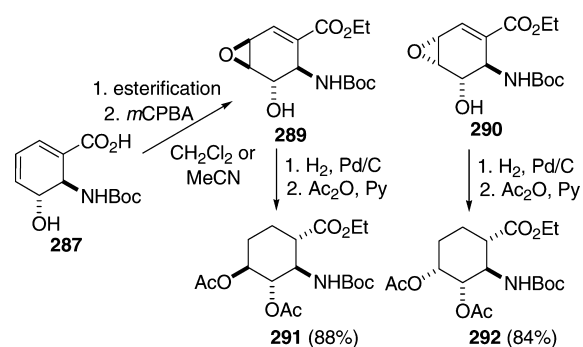
conditions they participated in simultaneous olefinic bond saturation and oxirane opening in the presence of Ac$_2$O to result in diacetoxylated β-amino esters **291** and **292**[77]

Formation of a polyacetoxylated cyclohexane β-amino ester was reported by the same group of authors: epoxidation of **293** (derived from the di-exo analog of **286** by treatment with BF$_3$·OEt$_2$ in Ac$_2$O) as the key step proceeded cis-selectively as concerns the carbamate to give **294** as the major isomer (**294**:**295** = 9:1). Compound **294** was next submitted to oxirane opening by hydrolysis under acidic conditions, followed by acetylation to furnish **296** (Scheme 59).[77]

Scheme 59. Synthesis of a Polyacetoxylated β-Aminocyclohexanecarboxylic Ester
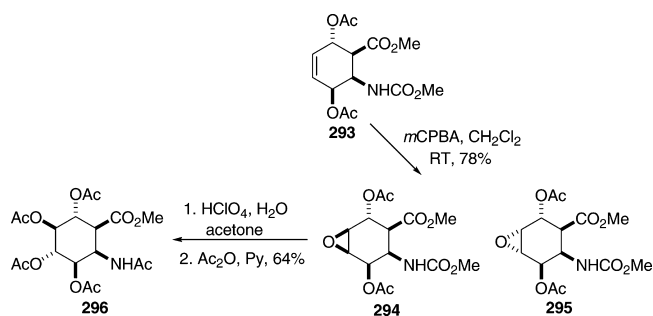
An alternative procedure to iodolactonization and iodoox-azination (see earlier) for the selective introduction of a hydroxy group onto the skeleton of a cyclic β-amino acid consists of stereoselective ring C–C double bond epoxidation, followed by regioselective oxirane opening. Thanks to the H-bonding directing effect of the carbamate, treatment of *trans*-amino ester **297** with *m*CPBA 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 NaBH$_4$ (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).[78]

Scheme 60. Synthesis of a Hydroxylated β-Amino Acid via Selective Epoxidation and Oxirane Opening
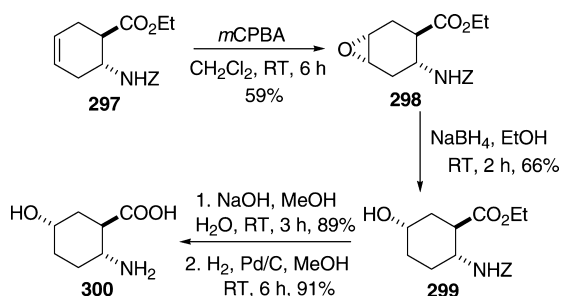
The crucial step in the synthesis of other hydroxylated cyclic β-amino acids was cis-selective epoxidation, followed by regioselective oxirane opening. Thus, under conditions similar to those described in Scheme 60, ethyl *cis*-2-benzyloxycarbonylaminocyclohexenecarboxylate, a stereoisomer of **297**, led selectively to *all-cis*-4-hydroxylated 2-aminocyclohexanecarboxylic acid and its C-1 epimer.[79] 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.[78,79]

Not only cis-selective but also trans-selective epoxidation can be efficiently utilized for the stereo- and regioselective hydroxylation of carbocyclic 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 NaOEt under different conditions provided epoxy amino ester **303** and its C-1 epimer **304**, the oxirane opening of which under reductive conditions with NaBH$_4$ permitted the preparation of other novel hydroxylated cyclohexane β-amino acid derivatives (**305** and **306**) (Scheme 61).[79]
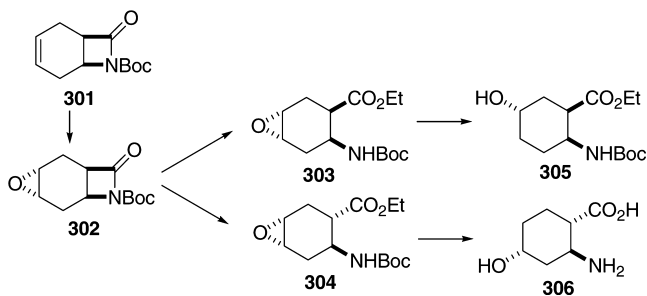
Scheme 61. Syntheses of Hydroxylated β-Amino Acids via Selective Epoxidation and Oxirane Opening

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-aminocyclopentenecarboxylic acid or from a cyclopentadiene-derived bicyclic β-lactam by means of epoxidation based on opposite selectivities (Figure 18).[80]
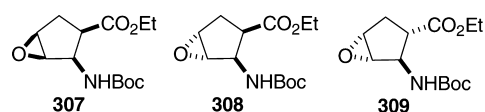
Figure 18. Structures of epoxy β-aminocyclopentanecarboxylates.

These epoxy amino esters were then subjected to azidolysis with NaN$_3$, resulting regioselectively in the corresponding 4-azido-substituted β-amino esters **310–313** (Figure 19).[80] These compounds can be regarded as orthogonally protected β,γ-diaminocarboxylic acid derivatives.
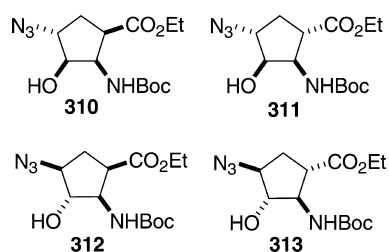
Figure 19. Structures of Azido β-Aminocyclopentanecarboxylates.

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 synthetized when azido amino ester enantiomer **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 synthetized when the earlier prepared azido cyclopentane amino esters were reacted with unsymmetrical acetylenes. Thus, the reaction of azido ester **310** with ethyl propiolate (R^1 = CO$_2$Et, R^2 = H) under thermal conditions without the addition of a Cu(I)

Scheme 62. Syntheses of 1,2,3-Triazole-Substituted Cispentacins via Azide−Alkyne Dipolar Cycloaddition

314: R^1, R^2 = -CO$_2$Et
315: R^1 = CO$_2$Et, R^2 = H
316: R^1 = Pr, R^2 = H
317: R^1 = Ph, R^2 = H
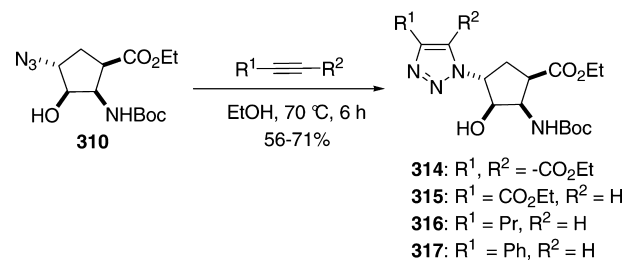
catalyst furnished 1,4-disubstituted 1,2,3-triazole derivative **315** regioselectively. With other acetylenes, however, when R^1 = Pr or Ph and R^2 = H, the reaction proceeded with CuI to give 1,4-disubstituted triazole derivatives **316** and **317** regioselectively (Scheme 62).[82]

Azidolysis of epoxycyclohexane β-amino ester **318** in the presence of NH_4Cl proceeded smoothly to afford 5-azido ester **319** 100% regioselectively (Scheme 63). However, when $AlCl_3$

Scheme 63. Syntheses of Azido β-Aminocyclohexanecarboxylic Esters
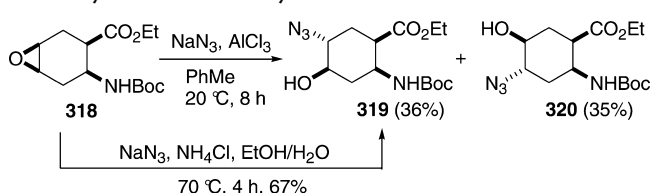
was used as additive in this reaction, the coordinating ability of Al and the diaxial preferred conformations during the oxirane opening of the epoxycyclohexane meant that the reaction gave rise to a mixture of azido ester regioisomers **319** and **320** in a ratio of 1:1; these were separated and isolated 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 Et_2AlCN 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]

Scheme 64. Synthesis of a Nitrile-Substituted β-Amino Ester

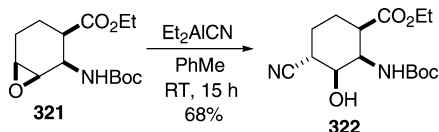A series of other novel nitrile- and azide-functionalized cyclohexane amino ester regio- and stereoisomers have been synthetized in racemic and enantiomerically pure form.[83]

2.4.1.5. Functionalization via Stereoselective Dihydroxylation. Hydrolysis of optically active *cis*-amino acid derivative **323**, benzyl esterification, and cis-dihydroxylation in the presence of OsO_4 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]

Dihydroxylated alicyclic β-amino esters in which the relative steric arrangement of the two hydroxyl groups is trans were

prepared by the same group of authors by hydroxylactonization and lactone opening. Thus, ester hydrolysis of **326**, followed by epoxidation and oxirane opening, yielded hydroxylactone **327** stereo- and regioselectively. Lactone opening with MeOH in the presence of $NaHCO_3$ provided dihydroxylated β-amino ester **328**, in which the hydroxy groups are in a trans steric arrangement (Scheme 66).[84]

Scheme 66. Synthesis of a *trans*-Dihydroxylated β-Aminocyclohexanecarboxylate
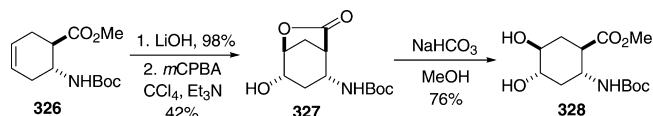
Dihydroxylation of *cis*-2-aminocyclopentenecarboxylic ester **329** with NMO/OsO_4 proceeded stereoselectively with the formation of dihydroxy amino ester **330**, in which the two hydroxy groups are in a trans relationship with the ester and carbamate. Simultanous N-deprotection and ester hydrolysis 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 deprotection in acidic medium gave dihydroxylated transpentacin **334**, a stereoisomer of **331** (Scheme 67).[72]

Scheme 67. Syntheses of Dihydroxylated β-Aminocyclopentanecarboxylic Acids
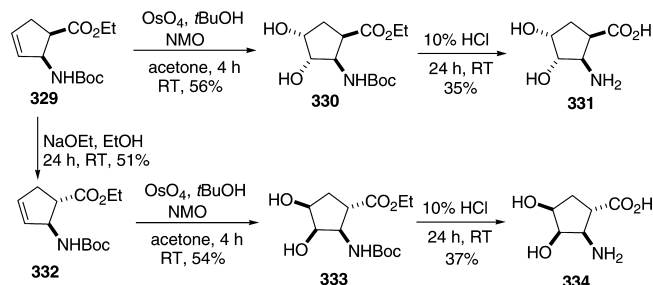
The above dihydroxylated cyclopentane β-amino acids were also prepared in enantiomerically pure form. Starting from the racemic bicyclic β-lactam, enzymatic lactam opening and then esterification and N-Boc protection led to optically pure amino ester **329**. Following the synthetic steps presented in 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 OsO_4-catalyzed dihydroxylation.[85] The vicinal dihydroxylated carbocyclic β-amino-

Scheme 65. Synthesis of a Cis-Dihydroxylated β-Aminocyclohexanecarboxylate
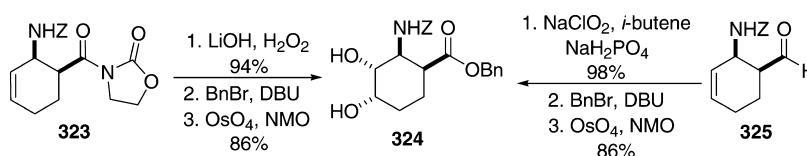
Scheme 68. Syntheses of Isoxazoline-Fused Cispentacin Derivatives
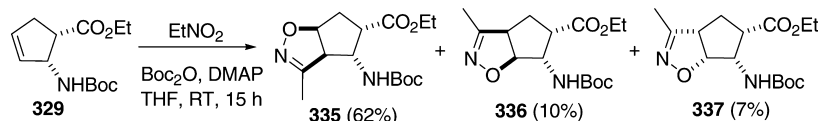
2.4.1.6. Functionalization via 1,3-Dipolar Cycloaddition. 1,3-Dipolar cycloaddition of nitrile oxides to a C—C double bond is a widely used efficient method for the construction of an isoxazoline skeleton and has also been utilized for functionalization of the olefinic bond of carbocyclic β-amino acids. Isoxazoline-fused cispentacins were synthetized by this methodology. Addition of nitrile oxide generated from nitroethane with Boc$_2$O/DMAP to ethyl cis-2-aminocyclohexenecarboxylate (**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.[86]

However, when the reaction was carried out under similar conditions with ethyl trans-2-aminocyclopentenecarboxylate, 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 PhNCO and Et$_3$N resulted 100% regio- and stereo-selectively 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 β-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 β-amino acids lies in the opportunity for the selective preparation of highly function-alized 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 HCO$_2$NH$_4$ and Pd/C as catalyst, isoxazoline-fused cispentacin derivative **335** afforded oxo amino ester **338** (Scheme 69).[88]

Scheme 69. Reduction of an Isoxazoline-Fused Cispentacin Derivative
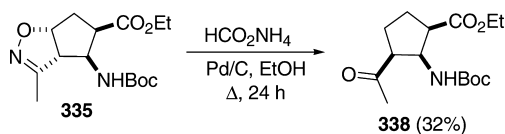

On modification of the reductive conditions to NaBH$_4$/NiCl$_2$, **335** underwent stereoselective isoxazoline opening with the generation of a new stereogenic center to give the highly functionalized cispentacin **339** in good yield (Scheme 70).[88]

The syntheses of several highly functionalized cispentacin stereoisomers (**340**–**343**) were also carried out from other isoxazoline-fused amino ester regio- and stereosiomers (Figure 20).[88]

Scheme 70. Formation of a Highly Functionalized Cispentacin Derivative from an Isoxazoline-Fused Precursor
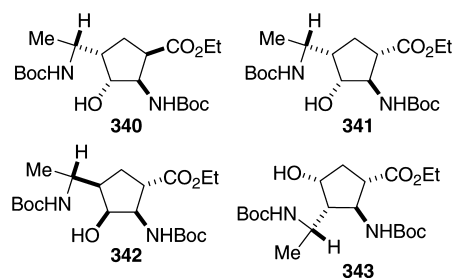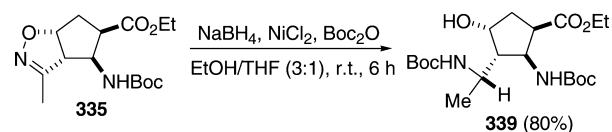
Figure 20. Structures of highly functionalized cispentacin derivatives.

2.4.2. Several Relevant Routes to Functionalized Cyclic β-Amino Acids Other Than Functionalization of the Ring C—C Double Bond. Functionalized carbocyclic β-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] Polyhydroxy-lated alicyclic β-amino acid stereoisomers were prepared in enantiomerically pure form from optically pure nitrohexofuranoses in eight or nine steps.[89] Azidolysis of α,β-epoxycyclohexanecarboxylic acids in a metal-catalyzed one-pot reaction afforded cyclohexane α-hydroxy-β-amino acids.[90] Another route to substituted alicyclic β-amino acids is based on a stereocontrolled three-component reaction. The CAN-catalyzed one-pot reactions between alkylamines, β-keto esters, and chalcones gave cis-4,5-disubstituted 2-aminocyclohexanecarboxylates.[91]

3. CYCLIC β-AMINO ACIDS WITH A HETEROATOM IN THE RING

Although slightly less abundant than their carbocyclic analogs, the heterocyclic β-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 β-amino acid with an O atom in the ring, (2R,3S)-3-aminooxetane-2-carboxylic acid or oxetin (**344**), exhibits antibiotic and herbicidal activity (Figure 21).[92]

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

1137

dx.doi.org/10.1021/cr300454h | Chem. Rev. 2014, 114, 1116−1169
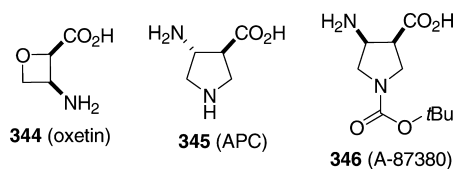
Figure 21. Some bioactive heterocyclic β-amino acids.

Other heterocyclic β-amino acids (Figure 22; see also section 3.2.3.2) are key elements in many bioactive products. Some of
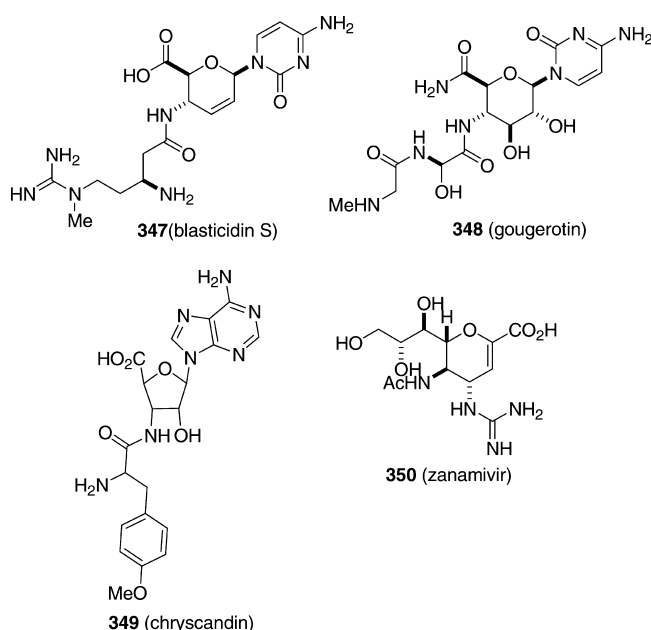
Figure 22. Several bioactive compounds with a β-amino acid element in their structure.

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 β-amino acids have been gaining in importance as analogs of the antiviral agent zanamivir (**350**; Figure 22; see also section 3.2.3.3).[96]

3.1. Syntheses of Cyclic β-Amino Acids with a N Atom in the Ring

Among the large number of synthetic methods available for the preparation of heterocyclic β-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 β-Amino Acids. Analogously to the cyclopropane β-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 ester **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

Scheme 71. Transformation of an Aziridine β-Amino Acid Intermediate
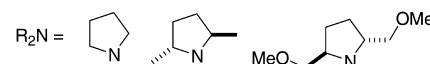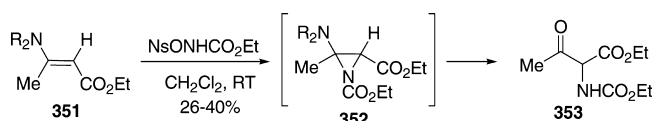
carboxylates **355**, which could be easily transformed to various other derivatives (Scheme 72).[98]

Scheme 72. Three-Membered N-Heterocyclic β-Amino Acids
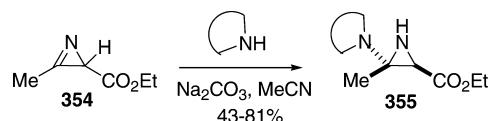
β-Amino acids containing the four-membered azetidinone skeleton are elements of peptide-based antitumoral antibiotics, e.g., deoxybouvardin (a bicyclic hexapeptide) analogs. Azetidinone amino ester enantiomer **362** was prepared from chiral oxazolidinone **356**, which was converted in a Staudinger reaction to β-lactam derivative **358**. Ozonolyis 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 β-amino carboxylates, **365** and **366** (Scheme 74).[100]

Four-membered N-heterocyclic β-amino acid derivatives have been synthetized from α-amino-β,γ-aziridino esters by an aziridine ring-opening ring-closure protocol. When heated in MeCN in the presence of Et$_3$N, aziridine derivatives **367**, obtained by the addition of glycine esters to α-chlorotosylimines followed by imine reduction,[101] furnished azetidine β-amino esters **368** (Scheme 75).[5a]

The asymmetric version of this method starts from the optically active α-chlorinated toluenesulfynimine, which reacts with glycine esters via aziridine derivative **369** to give azetidine β-amino acid enantiomer **370** (Scheme 75).[5b]

3.1.2. Five-Membered N-Containing Cyclic β-Amino Acids. In contrast with the three- and four-membered heterocyclic β-amino acids, the five-membered N-heterocyclic β-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 β-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)-α-methylbenzylamine to α,β-unsatu-

Scheme 73. Synthesis of a β-Amino Acid Containing an Azetidinone Ring
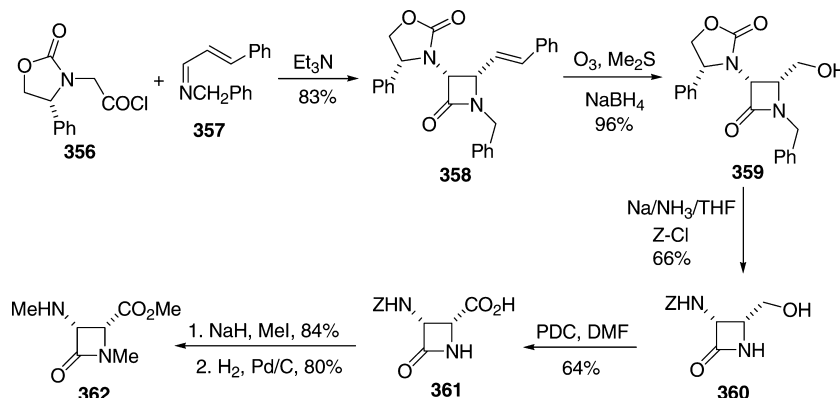
Scheme 74. Syntheses of β-Amino Acid Derivatives Containing an Azetidinone Skeleton
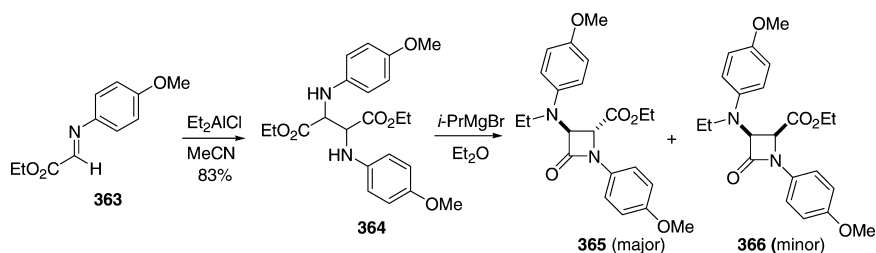
Scheme 75. Syntheses of β-Amino Acid Derivatives Containing an Azetidine Skeleton
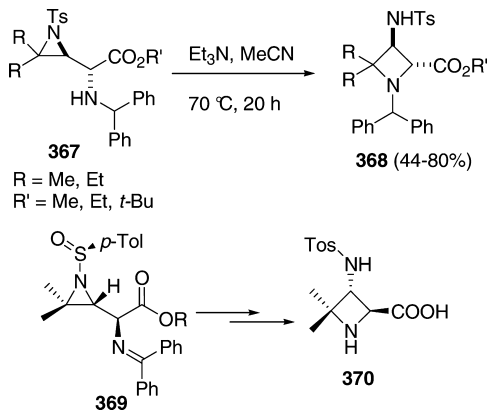
rated ester **371** afforded a *trans*-amino ester derivative containing a pyrrolidine ring, **372**. After removal of the chiral auxiliary by reductive methods, amino ester enantiomer **373** was obtained (Scheme 76).[102]

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 76. Synthesis of Pyrrolidine β-Amino Esters by Conjugate Addition to an Unsaturated Ester
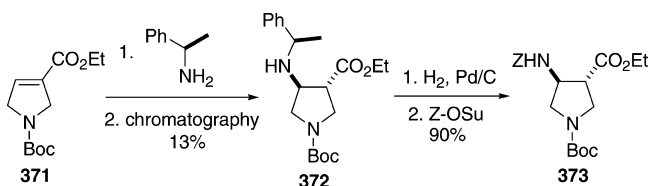
A rather interesting process with regard to the products of conjugate addition was observed when lithium dibenzylamide was added to unsaturated *tert*-butyl ester **377**. Ester **377** was obtained by the Michael addition−condensation of glycine ester **374** and reaction with *tert*-butyl acrylate, 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

Scheme 77. Synthesis of an Orthogonally Protected Pyrrolidine β-Amino Ester via Lithium Amide Addition to an Unsaturated Ester
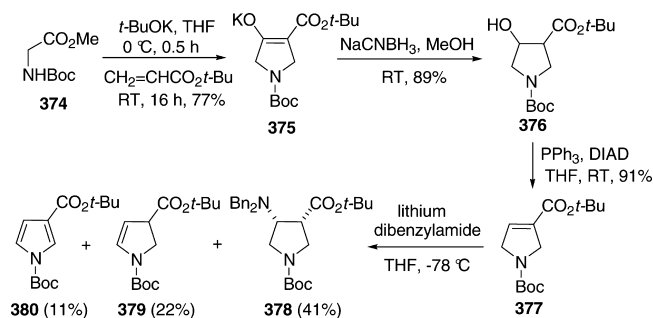
when lithium (*S*)-N-benzyl-N-α-methylbenzylamide was added to ester **381**, with the formation of β-amino acid derivative **382**. The trans counterpart **383** could be readily prepared by the isomerization of **382** at C-1 in the presence of *t*-BuOK in refluxing *t*-BuOH. Reductive removal of the 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]

Scheme 78. Syntheses of *cis*- and *trans*-Pyrrolidine β-Amino Acid Enantiomers by Chiral Lithium Amide Conjugate Addition
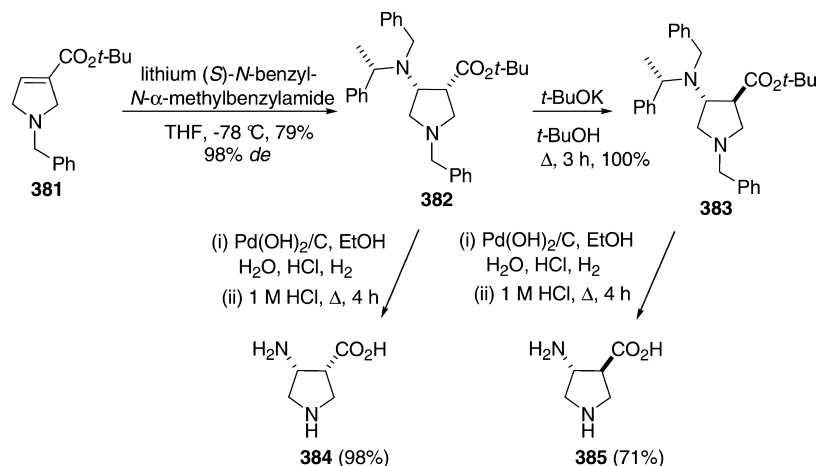
These heterocyclic β-amino acids are themselves bioactive derivatives; for example, *cis*-4-aminopyrrolidine-3-carboxylic acid (**384**) is a GABA (γ-aminobutyric acid) receptor, while *cis*-*N*-Boc-4-aminopyrrolidine-3-carboxylic acid (**386**) is a modest influenza neuraminidase inhibitor. They additionally serve as precursors for the synthesis of other important active influenza neuraminidase inhibitors, such as **387** (Figure 23).[104]
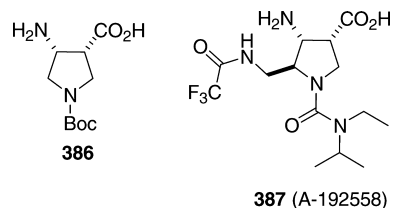
Figure 23. Structures of some bioactive pyrrolidine β-amino acids.

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. α,β-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-dimethyla-minopropyl)-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

Scheme 79. Synthesis of a Pyrrolidinone *trans*-β-Amino Acid
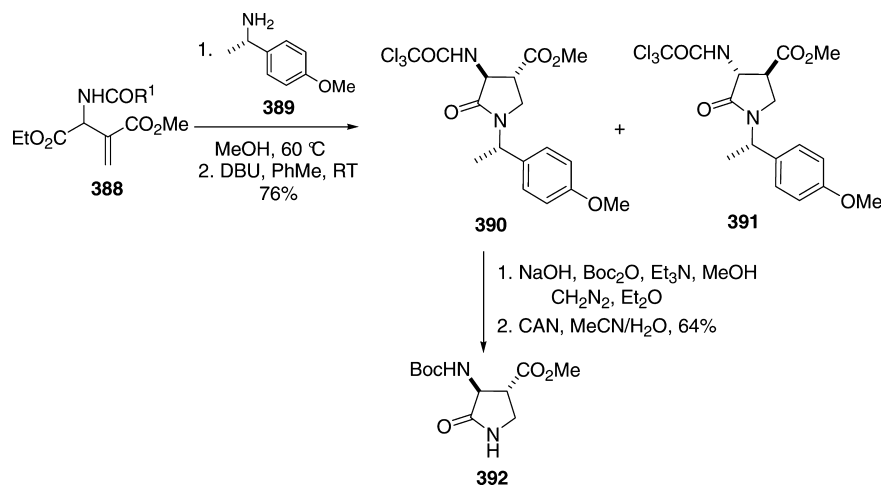
Scheme 80. Syntheses of 1-Oxylpyrrolidine β-Amino Acids
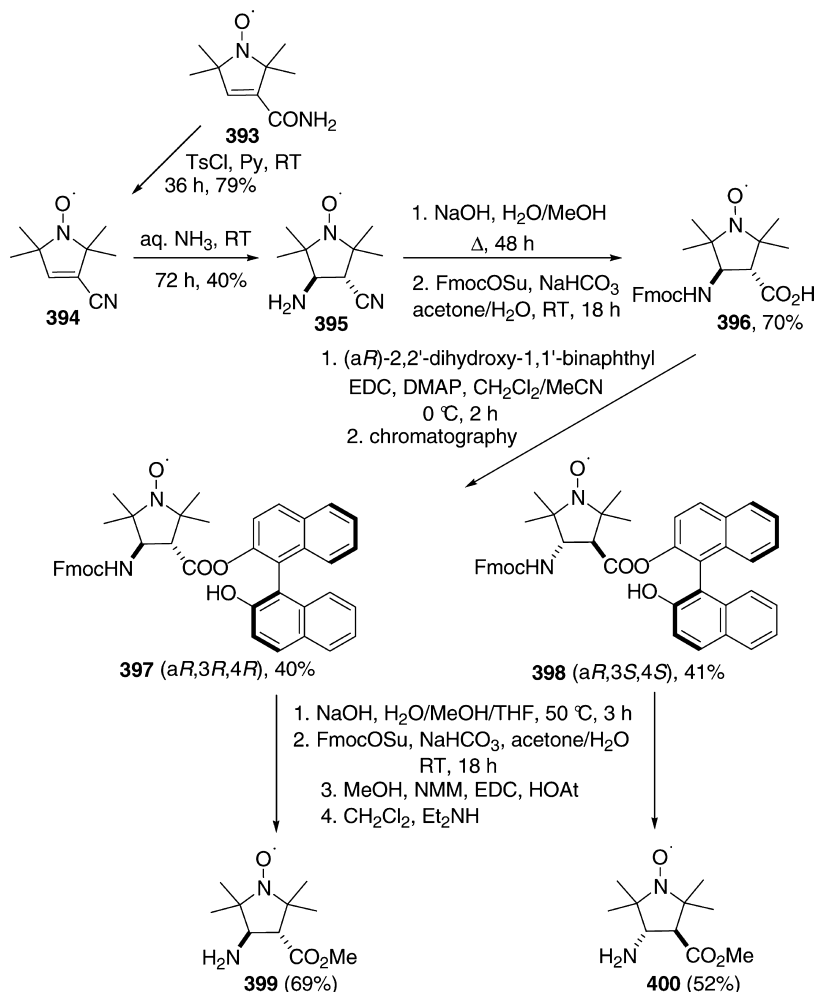
dioxide was the crucial step for the preparation of pyrrolidine β-amino acids. Amino acetal **403**, containing a formyl moiety, derived from **401** by allylation and oxidative C—C bond cleavage, was reacted with chiral phosphonate **404** to give **405**. Treatment of **405** with *p*-TsOH and *N*-benzylhydroxylamine (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).[30a]

The construction of an isoxazolidine-fused pyrrolidine ring via intramolecular nitrone 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 β-amino acid enantiomer **413** (Scheme 82).[108]

The pyrrolidine skeleton of *N*-heterocyclic β-amino acids can be efficiently created by azo-methinylide (3 + 2)-cycloaddition of benzylglycine to benzyl methyl maleate (**414**). *N*-Benzylglycine and paraformaldehyde were reacted with ester **414** to obtain **415**, the debenzylation and *N*-Boc protection of

Scheme 81. Synthesis of a *cis*-β-Amino Acid Containing a Pyrrolidine Core from Ketene Dithioacetal Dioxide
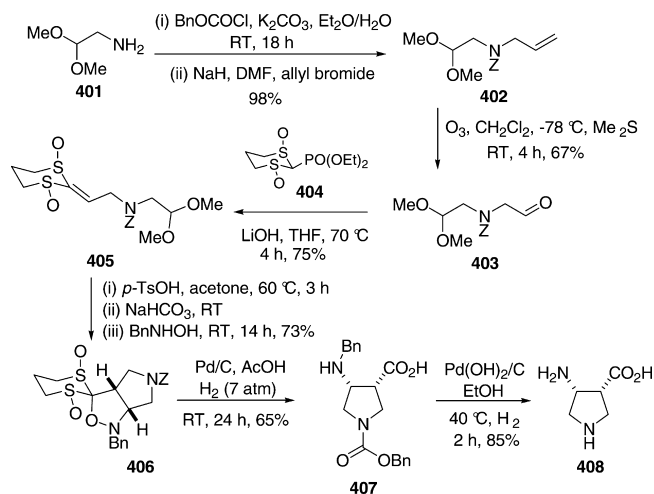
which resulted in its half-ester. Curtius rearrangement of this gave pyrrolidine β-amino ester **416**, which was next coupled with carboxylic acid derivative **417** to furnish ester **418**. *N*-Boc deprotection of **418** and its conversion to hydroxymic acid afforded **419**, a selective inhibitor of the TNF-α converting enzyme (Scheme 83).[2k] A series of similar bioactive products

1141

dx.doi.org/10.1021/cr300454h | Chem. Rev. 2014, 114, 1116−1169

Scheme 82. Synthesis of an Orthogonally Protected Pyrrolidine β-Amino Acid by Intramolecular Cycloaddition in a Nitrone Precursor

Scheme 84. Synthesis of a cis-β-Amino Acid Containing a Pyrrolidine Skeleton from an Oxo Ester

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*)-(+)-α-methylbenzylamine to give enamine **426**, the reduction of which proceeded trans-selectively and led to *trans*-β-amino ester derivative **427**. Ester hydrolysis of **427**, chiral auxiliary removal, and *N*-Fmoc protection furnished the optically pure, orthogonally protected pyrrolidine β-amino ester **429** (Scheme 85).[111]

Scheme 85. Synthesis of a trans-β-Amino Acid Enantiomer Containing a Pyrrolidine Skeleton from an Oxo Ester

containing a pyrrolidine β-amino acid element have also been synthetized and investigated.[109]

3.1.2.3. Syntheses from β-Keto Esters. Alicyclic β-oxo esters are convenient starting compounds for preparation of the corresponding five- or six-membered β-amino acids (see section 2.1.1). Cyclic β-oxo esters with an *N* atom in the ring are also suitable precursors for the preparation of *N*-heterocyclic β-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 β-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).[110a]

Various pyrrolidine β-amino acid analogs that behave as neuramidase inhibitors have been synthetized by the β-keto ester reduction methodology.[60b,110]

The asymmetric variation of the β-keto ester transformation procedure for the preparation of β-amino acids containing a

Scheme 83. Synthesis of a Bioactive Compound Containing a Pyrrolidine β-Amino Acid Element
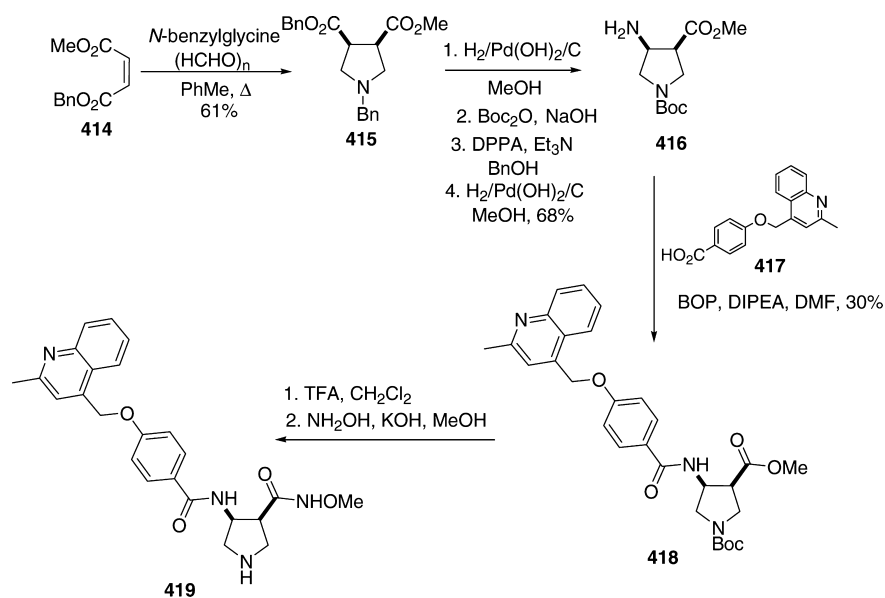
Similar transformations were performed by starting from **420**, with (S)-(−)-α-methylbenzylamine as chiral auxiliary.[6] The chiral N-heterocyclic β-amino acid was applied for the synthesis of peptide oligomers in combination with its carbocyclic analog or with nucleoside β-amino acid analogs.[112]

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**, synthetized 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
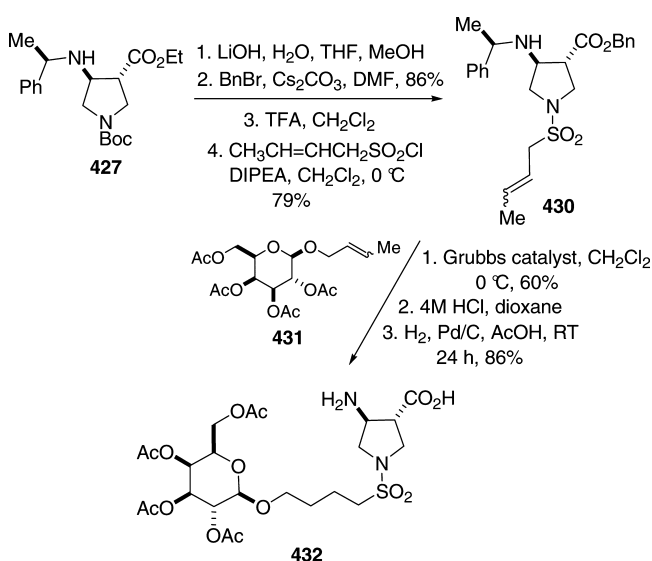
N-Aryl β-enamino esters based on a pyrrolidine skeleton, synthetized by reductive amination of the corresponding β-oxo esters, were described as intermediates for the preparation of different carboxylic esters containing the pyrrolo[3,2-b]-quinoline ring system.[114]

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

Scheme 87. Synthesis of an Orthogonally Protected Pyrrolidine β-Amino Acid from the Corresponding Enamine

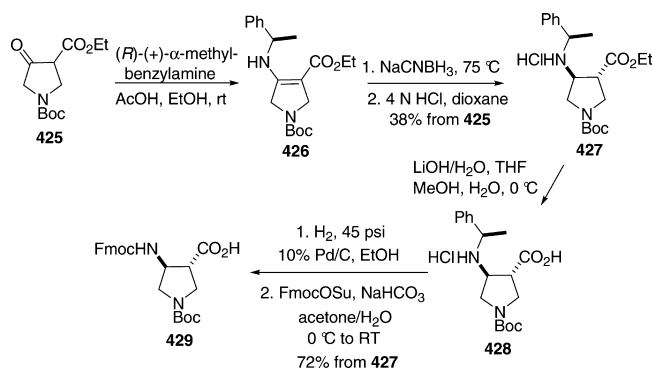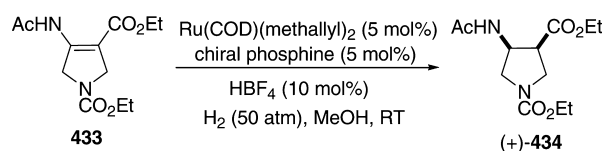of these diastereoisomers, trans isomer **437** was subjected to N-Boc protection and oxidation with mCPBA to give sulfoxide derivative **439**. Acidic hydrolysis of **439** next afforded aldehyde **440**, whose formyl moiety was oxidized to give the corresponding ester **441**. Cleavage of the oxime 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. Optically 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 regioisomers 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 azodicarboxylate (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 NaN₃, 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 **464**. 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]

Scheme 88. Synthesis of a *trans*-Pyrrolidine β-Amino Acid by Radical Cyclization of an Allylamine Derivative
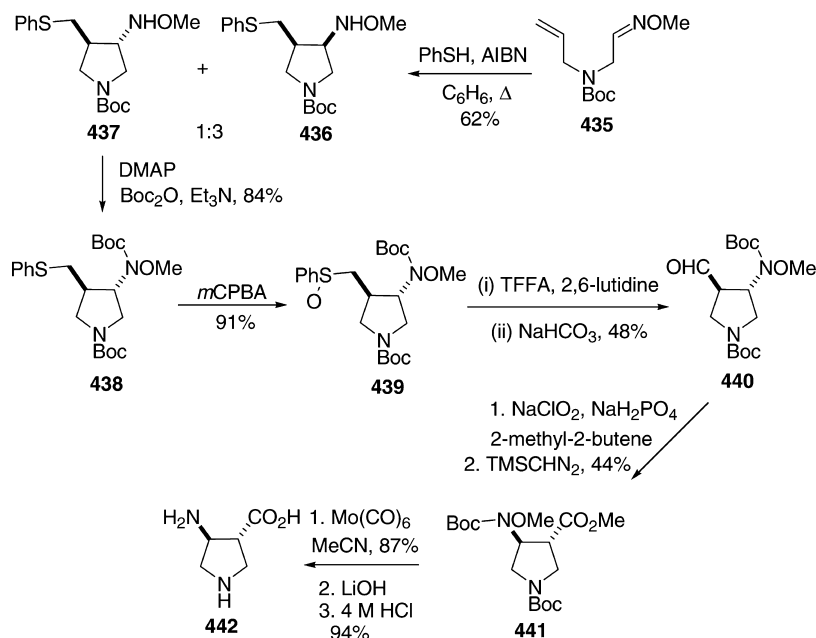
Scheme 89. Syntheses of Hydroxylated Pyrrolidine β-Amino Acid Isomers
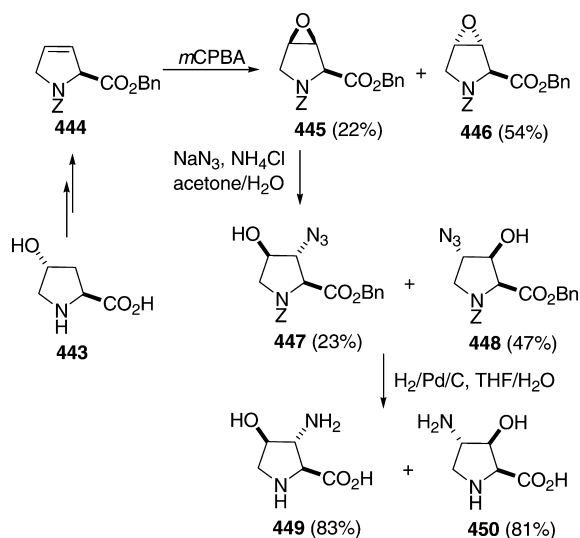
Scheme 90. Synthesis of an Orthogonally Protected Pyrrolidine *cis*-β-Amino Ester from a Hydroxylated Proline
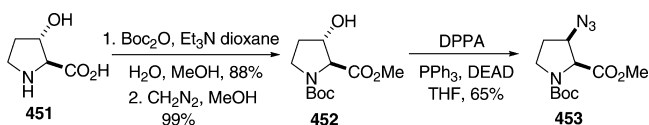
Scheme 91. Synthesis of an Orthogonally Protected Pyrrolidine *trans*-β-Amino Ester from a Hydroxylated Proline Derivative
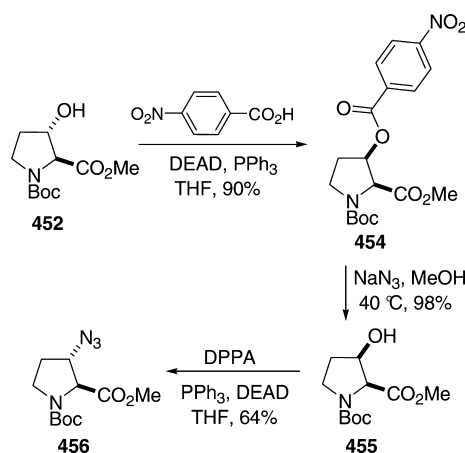
Scheme 92. Synthesis of an Orthogonally Protected Pyrrolidine β-Amino Acid from a Hydroxylated Proline Derivative
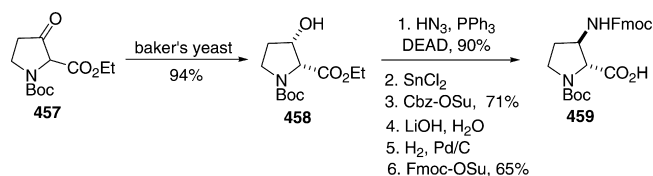
3.1.2.6. Syntheses from Carbohydrate Derivative Precursors. Enantiomerically pure functionalized β-aminoproline derivatives have been synthetized from bicyclic hydroxylated pyrrolidine-fused β-lactam **465**, derived from ascorbic acid in 10 steps. The hydroxy group of **465** was converted to a benzoyl-protected 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

Scheme 93. Synthesis of a Dipeptide Containing a Pyrrolidine β-Amino Acid Element
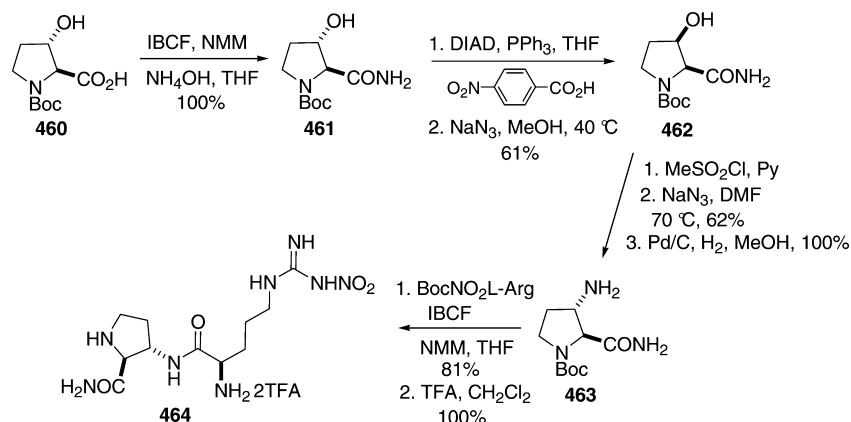
Scheme 94. Synthesis of a Pyrrolidine β,γ-Diamino Ester from Ascorbic Acid
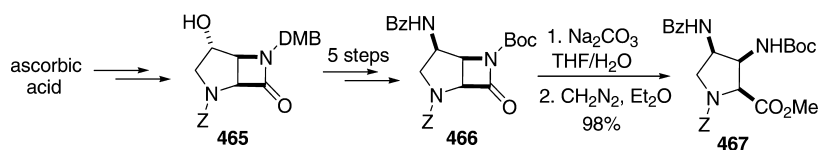
hydrogenolysis, and *N*-Fmoc protection afforded heterocyclic β-amino acid derivative **470** (Scheme 95).[120]

Scheme 95. Synthesis of an Orthogonally Protected Pyrrolidine β-Amino Acid Derived from Ascorbic Acid
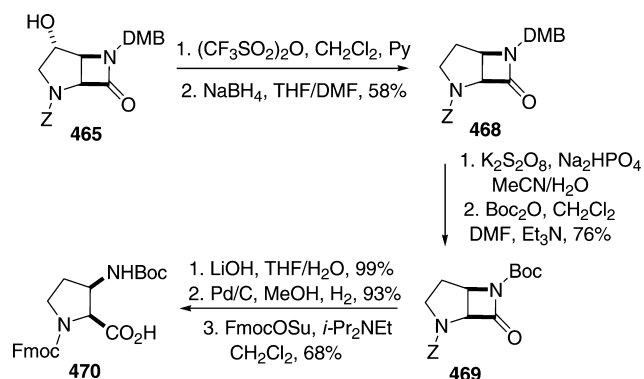
β-Lactam **465** was a suitable precursor for the preparation of 4-hydroxylated 3-aminoproline derivatives, which were then transformed to various highly substituted pyrrolidine derivatives with pharmacological potential (Figure 24).[121]

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 β-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 β-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 β-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 β-Amino Acids. The main synthetic methods available for the preparation of six-membered *N*-heterocyclic β-amino acids exhibit similarities with those presented for the carbocyclic or five-membered *N*-containing cyclic derivatives.
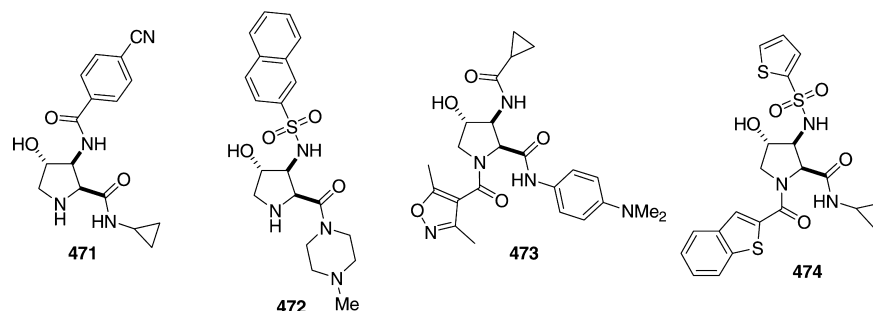
Figure 24. Several bioactive, highly substituted pyrrolidine derivatives synthetized from 4-hydroxylated 3-aminoproline derivatives.

1145

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Scheme 96. Synthesis of a Pyrrolidine cis-β-Amino Ester by Curtius Rearrangement
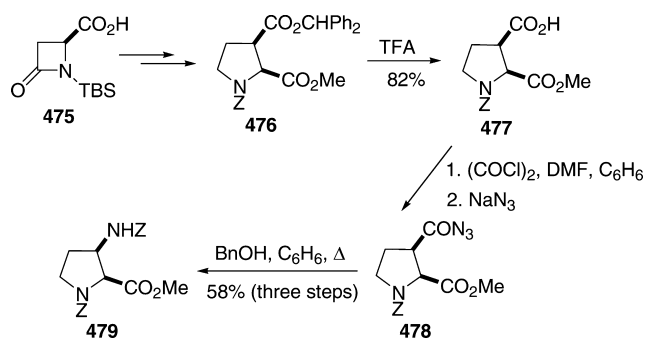
3.1.3.1. Syntheses from β-Keto Esters. β-Ketopiperidine carboxylates are suitable starting materials for the synthesis by reductive amination of six-membered N-cyclic β-amino acids in racemic or enantiomerically pure form (see sections 2.1.1 and 3.1.2.3 for alicyclic and N-heterocyclic five-membered analogs). Thus, treatment of β-oxopiperidine ester **483** with AcONH$_4$ led to ester **484**, which was a precursor of the selective nonpeptide ORL-1 antagonist **485** (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 enamino carboxylic ester **487**. Its reduction under different experimental conditions afforded stereoisomers **488** and **489**, the best selectivity being achieved with NaBH$_4$/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 NaBH$_4$ 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 enamino esters was attained with NaBH(OAc)$_3$ by using the CoCl$_2$ and (S)-(−)-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 synthetized 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 CO$_2$ under basic conditions, followed by esterification) reacted with (R)-α-methylbenzylamine to yield **501**. Reduction of **501** with NaCNBH$_3$ 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., carbocyclic 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 dicarboxylate 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 acetoacetate in the presence of I$_2$ in MeOH underwent one-pot multicomponent reaction (MCR) to afford highly functionalized piperidine **509** (Scheme 105);[131] however, the carboxylic

Scheme 97. Synthesis of a trans-Pyrrolidine β-Amino Ester by Curtius Rearrangement
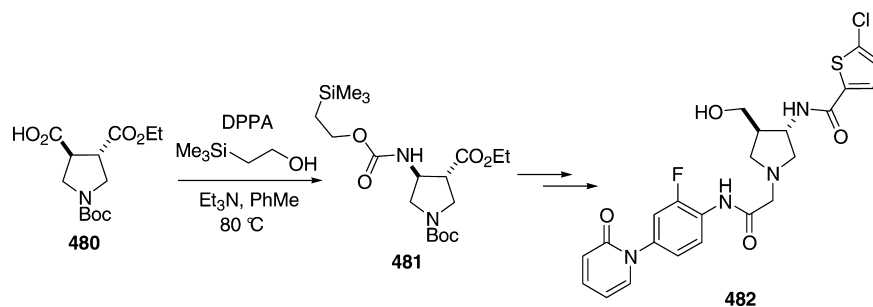
Scheme 98. Synthesis of a Piperidine β-Amino Ester from the Corresponding Oxo Ester
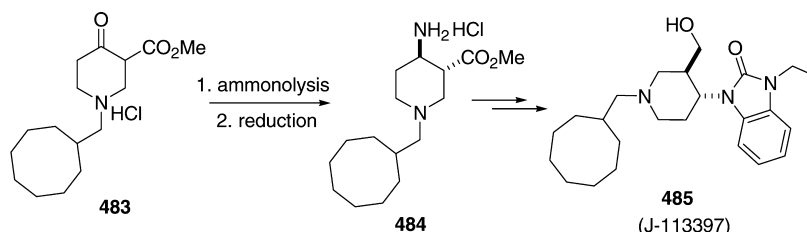
Scheme 99. Syntheses of *cis*- and *trans*-β-Amino Ester Enantiomers Containing a Piperidine Skeleton
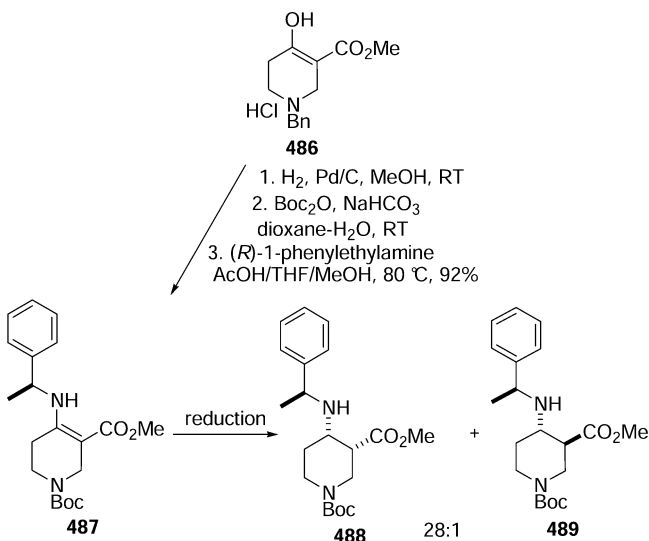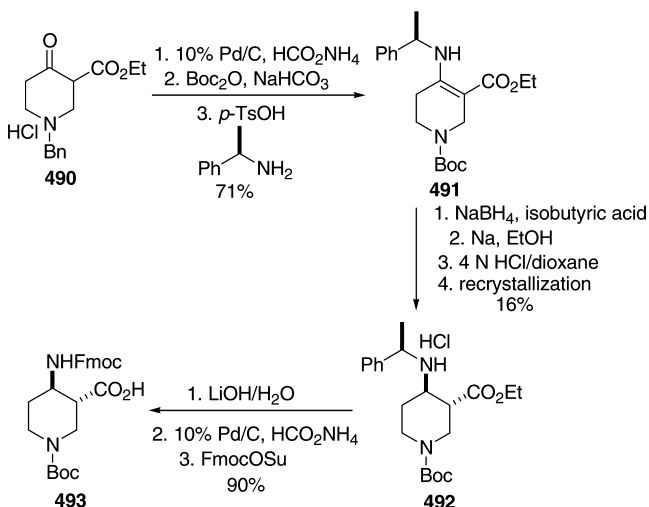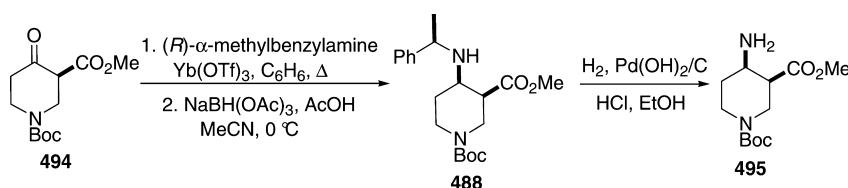
and amino functions in this product are not connected to stereogenic carbon centers.

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 guanylidation of the free amino function and ester deprotection, the novel highly functionalized piperidine β-amino acid **521** was obtained (Scheme 107).[134]

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).[5c]

Amino ester (−)-**333**, a stereoisomer of **330**, was transformed analogously in a similar protocol to furnish ethyl *trans*-β-aminopiperidinecarboxylate (−)-**523** (Scheme 108).[135]

Scheme 100. Synthesis of an Enantiomerically Pure Orthogonally Protected Piperidine β-Amino Acid from the Corresponding Oxo Ester

Scheme 101. Synthesis of a Piperidine β-Amino Ester Enantiomer by Reductive Amination of the Corresponding Oxo Ester

Scheme 102. Synthesis of Enantiomerically Pure Piperidine β-Amino Ester by Reductive Amination of the Corresponding Keto Ester
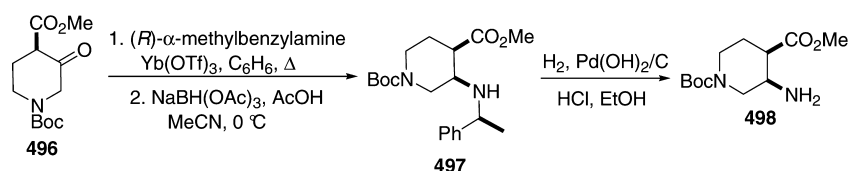
Scheme 103. Syntheses of Chiral β-Amino Acid Nitroxides
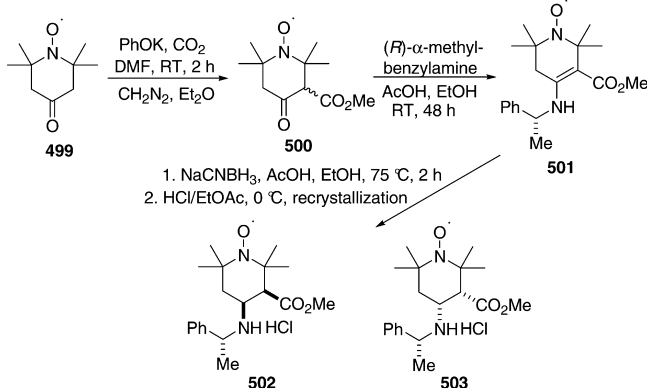
Scheme 104. Syntheses of Piperidine Amino Dicarboxylates by Conjugate Addition to Unsaturated Esters
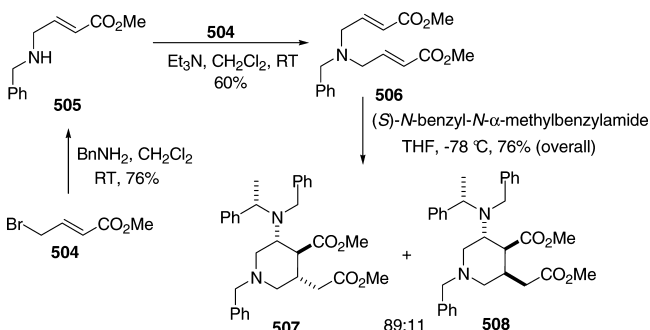
Scheme 105. Synthesis of a Highly Functionalized Piperidine β-Amino Ester in a One-Pot Multicomponent Reaction
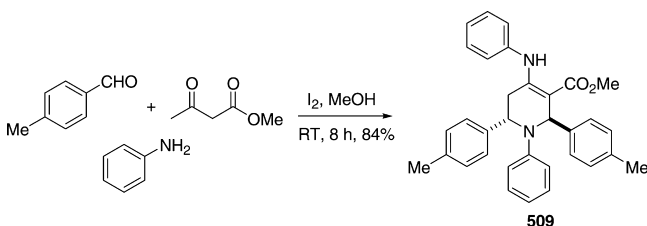
3.1.4. N-Containing Cyclic β-Amino Acids with Larger Ring Systems.

The oxidative cleavage of dihydroxylated carbocyclic β-amino esters, followed by ring closure with reductive amination, was efficiently applied for the synthesis of seven-membered N-containing heterocyclic β-amino acids. Thus, on treatment with $NaIO_4$ and then with benzylamine and $NaCNBH_3$, 3,4-dihydroxylated ethyl 2-aminocyclohexanecarboxylate enantiomer **524** yielded azepane β-amino ester **525** in optically pure form. Epimerization of **525** with NaOEt readily provided the trans stereoisomer **526** (Scheme 109).[5d]

Another azepane β-amino ester, a regioisomer of **526**, could be prepared from ethyl 4,5-dihydroxylated 2-aminocyclohexanecarboxylate **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).[5d]

N-Containing bicyclic β-amino esters were easily prepared from norbornene amino esters **530** or **534** by using the above procedure. Dihydroxylation of di-exo-norbornene ester **530**, followed by oxidative ring cleavage and ring closure under reductive amination conditions, provided bicyclic β-amino ester **533** (Scheme 111).

Similarly, transformation of 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).[5e]

3.2. Syntheses of Cyclic β-Amino Acids with an O Atom in the Ring

The most abundant of the O-containing cyclic β-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 O-heterocyclic derivatives. In contrast with the carbocyclic and 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 O-Containing Cyclic β-Amino Acids.

Isolation of the four-membered O-heterocyclic β-amino acid antibiotic oxetin (**344**; Figure 21)[92] led to appreciable interest in the synthesis of functionalized oxetane β-amino acid derivatives. The main procedure for the preparation of oxetane β-amino acids starts from various monosaccharides and results after a number of steps in optically pure target compounds. For example, L-rhamnose can be converted to hydroxylated ester **539** containing an oxacyclobutane ring in four steps. The hydroxy group of ester **539** was converted via triflate **540** by inversion with NaN_3 to cis-azido ester **541**. Transformation of triflate ester **540** by treatment with F_3CCO_2Cs 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 β-amino esters (Scheme 113).[135]

Methyl-substituted oxetane β-azido esters have been prepared from D-xylose. Bromomethyl ester **545**, derived from monosaccharide **544** in five steps, was reduced with Me_3SiH to yield **546**. This underwent benzoyl ester hydrolysis to give hydroxylated ester **547**, which was finally converted to methyl-substituted oxetane cis-β-azido ester **548** (Scheme 114).[136]

By means of the above procedures, several other substituted oxetane β-amino acids have been synthetized in optically pure form (Figure 25).[135a,c,137]

Scheme 106. Syntheses of Highly Functionalized Piperidine β-Amino Acid Stereoisomers
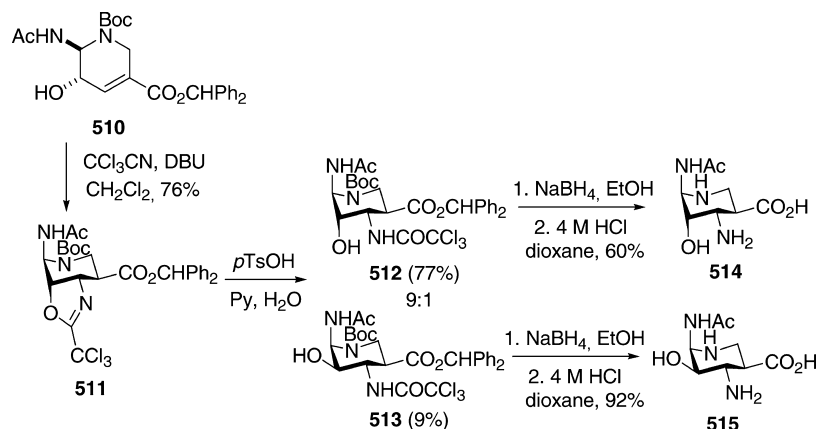
Scheme 107. Synthesis of a Guanylidinated Piperidine β-Amino Acid
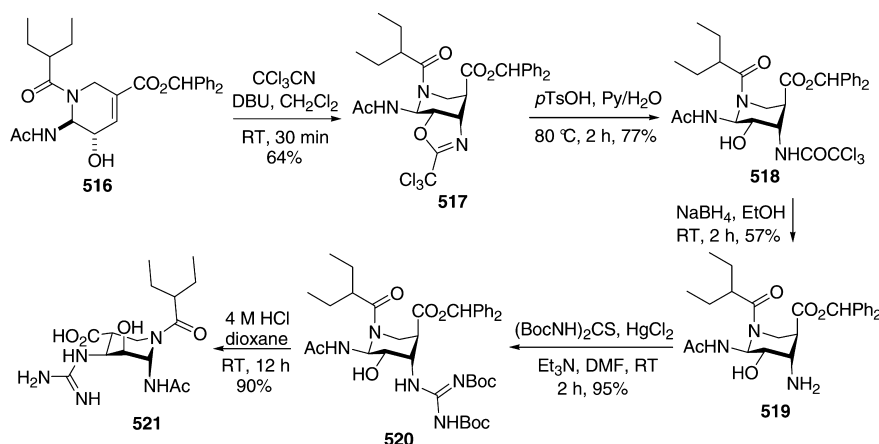
Scheme 108. Syntheses of *cis*- and *trans*-Piperidine β-Amino Esters from a Carbocyclic Precursor by a Ring-Enlargement Procedure
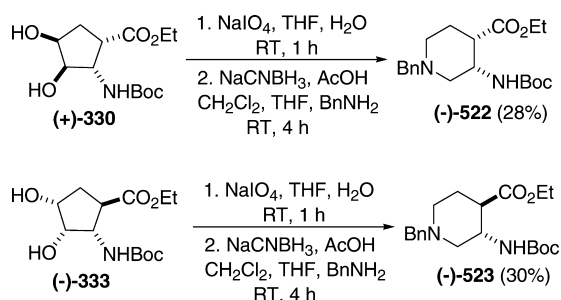
Not only carbohydrates but also optically pure α-amino acid derivatives are suitable precursors for oxetane β-amino acids. One synthetic pathway started from optically pure tritylserine (**553**), which was transformed with the coupling agent BOP

[(benzotriazol-1-yloxytris(dimethylamino)phosphonium hexa-fluorophosphate] to a lactone intermediate, the methylenation 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).[138]

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).[138]

3.2.2. Five-Membered O-Containing Cyclic β-Amino Acids. Among the five-membered o-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

Scheme 109. Syntheses of *cis*- and *trans*-Azepane β-Amino Esters from a Carbocyclic Precursor by a Ring-Enlargement Procedure
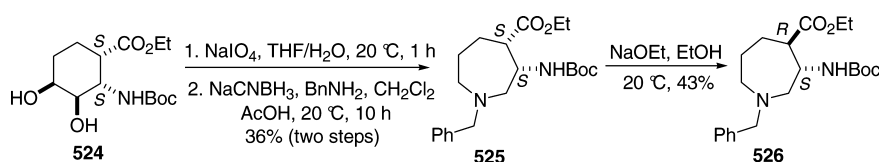
Scheme 110. Syntheses of *cis*- and *trans*-Azepane β-Amino Ester Enantiomers from a Carbocyclic Precursor by a Ring-Enlargement Procedure
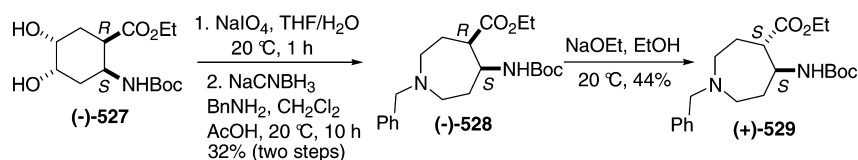
Scheme 111. Synthesis of an Azabicyclic β-Amino Ester from a Carbocyclic Precursor by Ring Enlargement
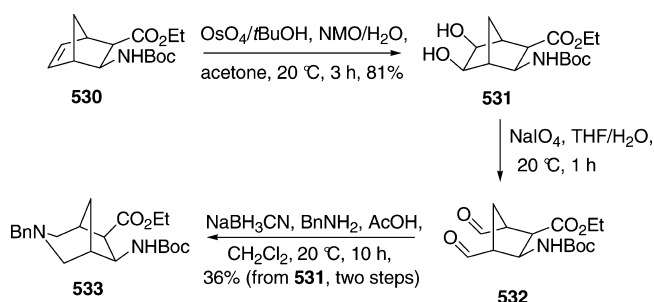
Scheme 112. Syntheses of Azabicyclic β-Amino Esters from a Carbocyclic Precursor by Ring Opening−Ring Closure

Scheme 114. Synthesis of a Methyl-Substituted Oxetane β-Azido Ester from D-Xylose
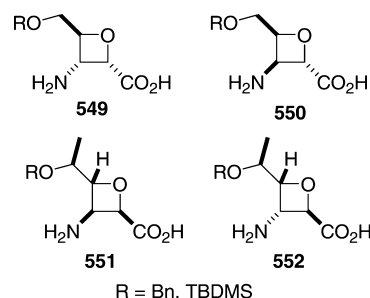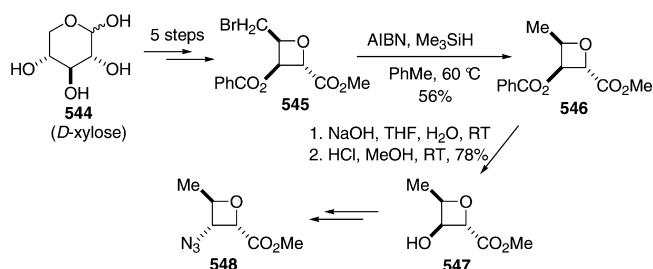
Figure 25. Structures of some substituted oxetane β-amino acids.

chemistry, forming an important bridge between carbohydrates and proteins (Figure 27).[140]

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

The preparation of conformationally rigid glutamate analog lactone β-amino ester **574** was accomplished from optically pure ribofuranose derivative **570** (methyl 5-*O*-trityl-β-D-ribofuranoside). The key steps in the synthesis were hydroxy−azide exchange at C-3, followed by oxidation of the hydroxymethyl moiety with NaIO$_4$ in the presence of RuCl$_3$. The compound obtained, **572**, was next converted by

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).[2a,139]

A number of furanoid β-amino acids (e.g., **561** and **562**) possess noteworthy antifungal activities.[2a]

A series of conformationally rigid enantiomerically pure sugar β-amino acid stereoisomers has been synthetized and investigated as bioactive derivatives and also in peptide

Scheme 113. Syntheses of Hydroxylated Oxetane β-Amino Esters from L-Rhamnose

1150

dx.doi.org/10.1021/cr300454h | Chem. Rev. 2014, 114, 1116−1169
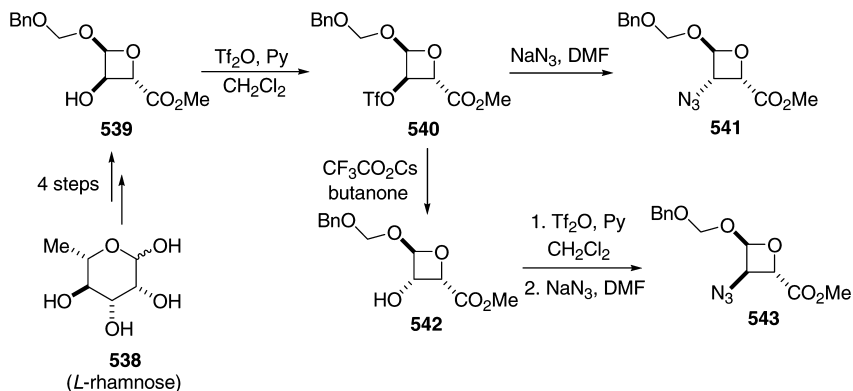
Scheme 115. Syntheses of Oxetane Amino Alcohol Stereoisomers
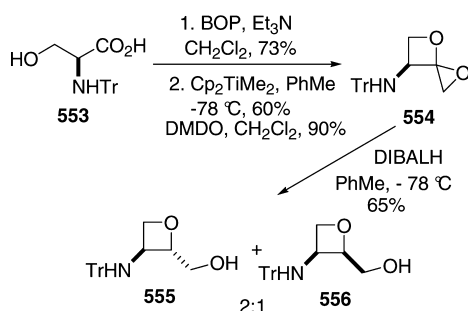
Scheme 116. Synthesis of a *trans*-Oxetane β-Amino Acid from the Corresponding Amino Alcohol
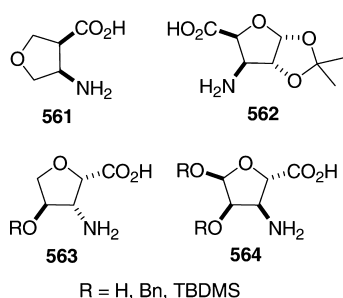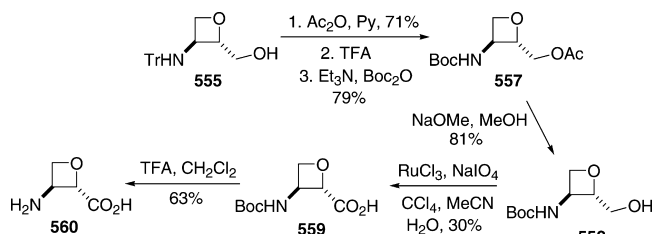
Figure 26. Structures of bioactive tetrahydrofuran β-amino acids.
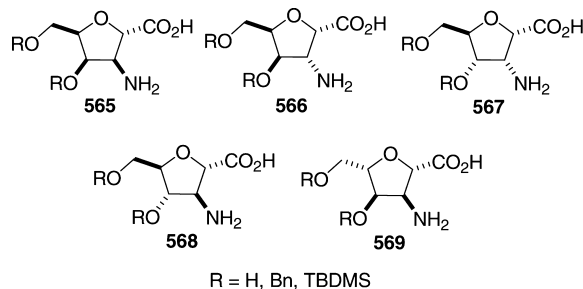
Figure 27. Some hydroxylated tetrahydrofuran β-amino acid stereoisomers.

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 NH$_3$ 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 triflate, followed by displacement with NaN$_3$ to give **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 synthetized 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*-butyldiphenylsilyl chloride (TBDPSCl) 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 methanolysis 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 tetrahydrofuran 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 CH$_2$Cl$_2$, 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 tetrahydrofuran β-amino acids. Through the corresponding mesylate and treatment with NaN$_3$, **599** was readily transformed by inversion to **601**, the acetal deprotection and oxidation of which gave azido acid **602**. Esterification of **602** with CH$_2$N$_2$ 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

Scheme 117. Synthesis of a β-Amino Ester Containing a γ-Lactone Skeleton
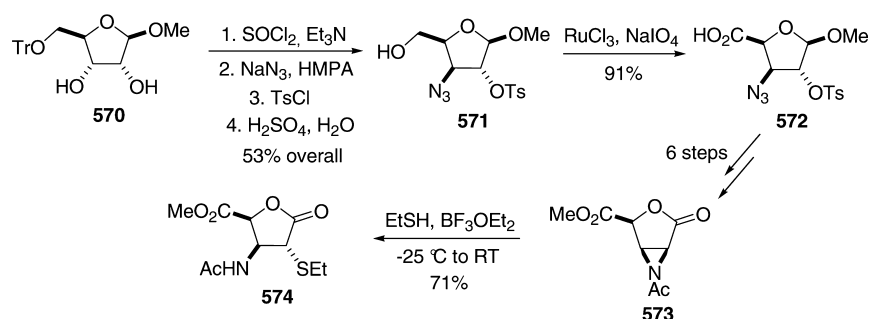
Scheme 118. Synthesis of a Thienamycin Precursor from an Amino Sugar
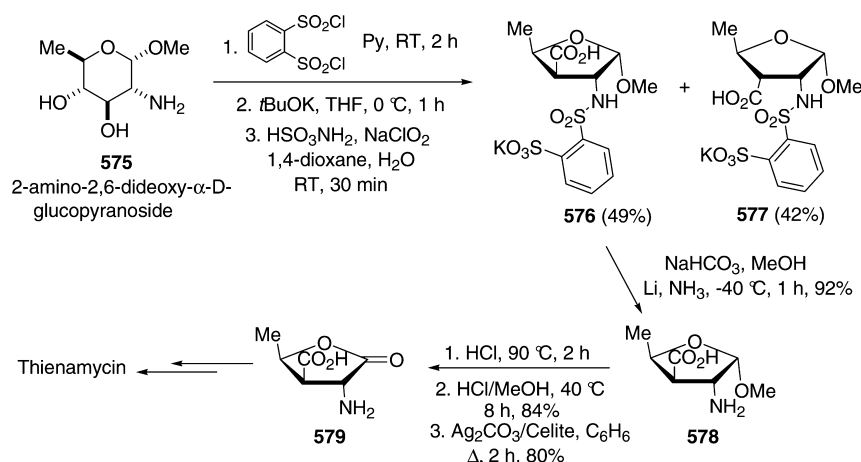
Scheme 119. Synthesis of a Highly Functionalized Tetrahydrofuran β-Azido Ester
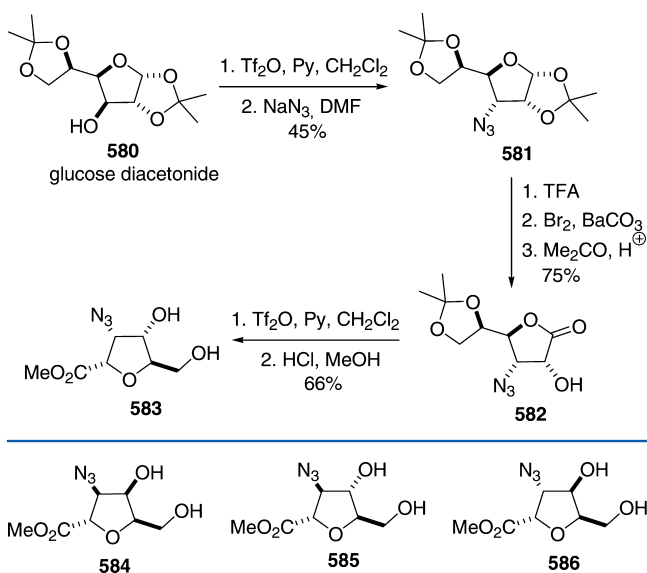
Figure 28. Structures of highly functionalized tetrahydrofuran β-azido esters.

interconversion then afforded the required O-heterocyclic trans-β-azido ester **605** (Scheme 123).[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.[147,148]

A variety of these derivatives have been utilized as building blocks in the synthesis of oligonucleotides possessing a β-amino acid element.[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−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).[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 to a carboxyl function. 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

Scheme 120. Synthesis of a Tetrahydrofuran β-Azido Ester from L-Arabinose
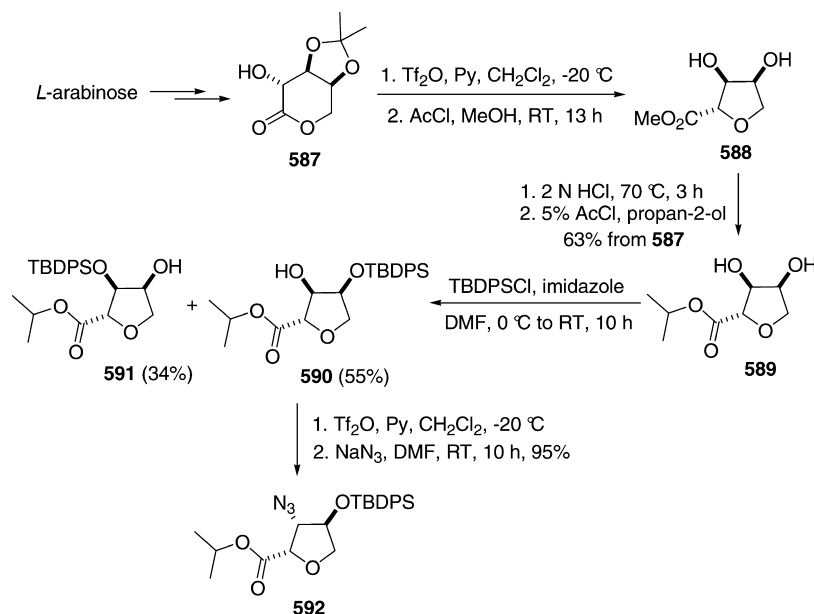
Scheme 121. Synthesis of a Diacetoxylated β-Azido Acid Containing a Tetrahydrofuran Skeleton
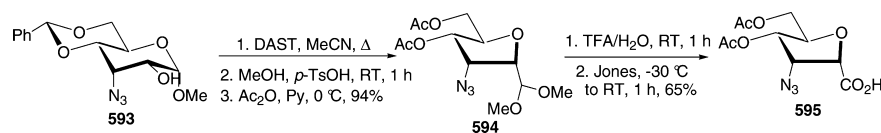
Scheme 122. Syntheses of Functionalized Tetrahydrofuran Regioisomers

Scheme 123. Syntheses of Tetrahydrofuran β-Azido Ester Stereoisomers
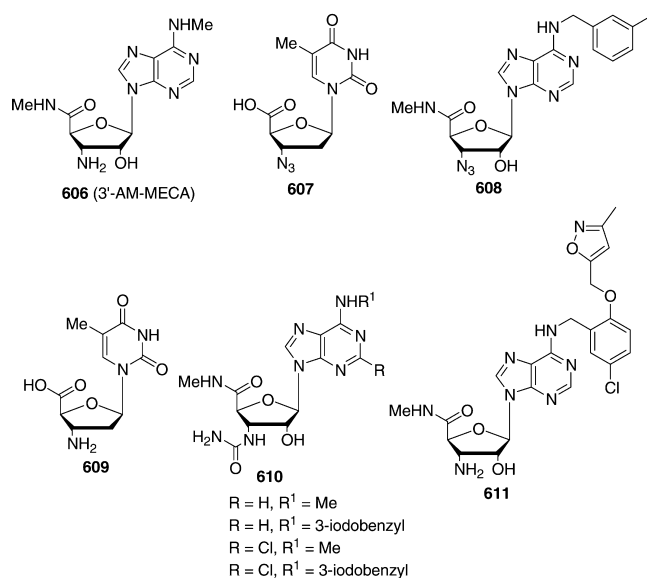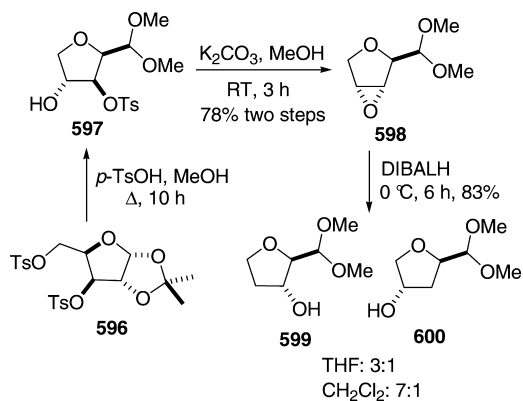
Figure 29. Some bioactive nucleoside β-amino acids.
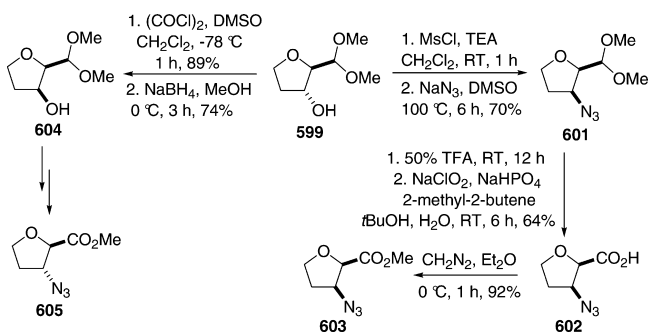
hydroxysilyl protecting group, nucleoside **620** was formed. Hydroxymethyl oxidation and amidation of the carboxyl group afforded nucleoside β-amino acid derivative **622** (Scheme 125).[150]

Aminocarboxylic acid nucleoside **609** was simply synthetized from azidothymidine (AZT; **623**) by hydroxymethyl group oxidation and azide reduction (Scheme 126).[151]

The Fmoc-protected thymidine β-amino acid was investigated as a building block in the construction of peptide oligomers.[152]

1153

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Scheme 124. Synthesis of a Nucleoside β-Amino Acid Derivative from an Azido Sugar Precursor
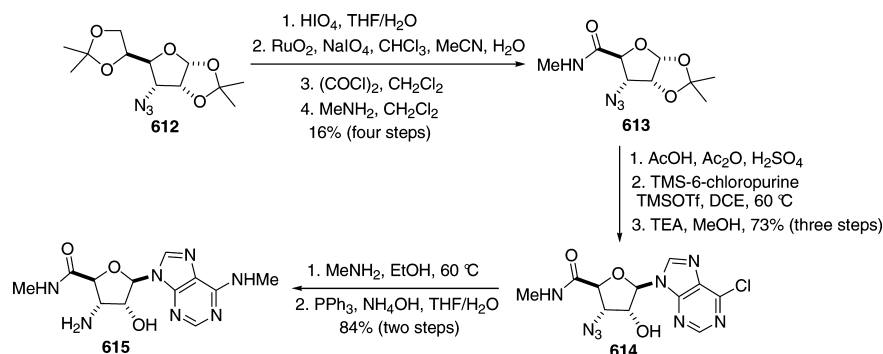
Scheme 125. Synthesis of a Nucleoside β-Amino Acid Derivative from an Amino Sugar Precursor
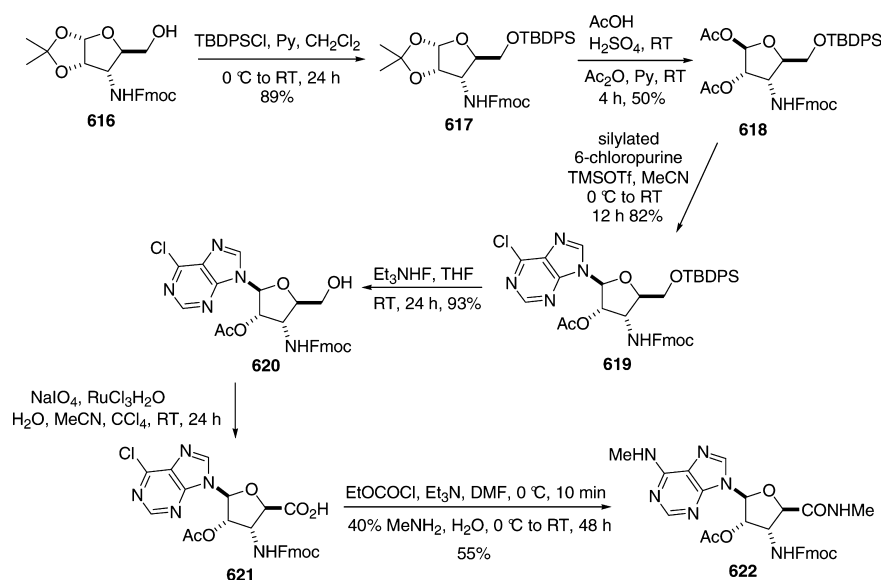
Scheme 126. Synthesis of an Azidothymidine Analog
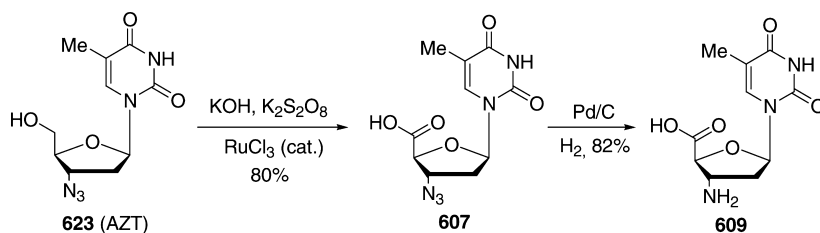
Scheme 127. Synthesis of a Tetrahydrofuran β-Amino Acid from a Functionalized β-Lactam

R = *i*-Pr, *n*-Pr, *c*-Hex, *t*-Bu, 4-MeOPh
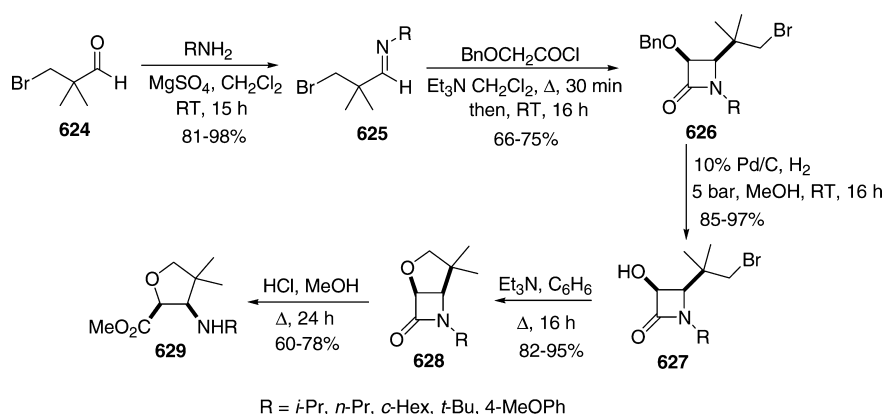
Scheme 128. Synthesis of a Hydroxylated Tetrahydrofuran β-Amino Acid from D-Mannitol
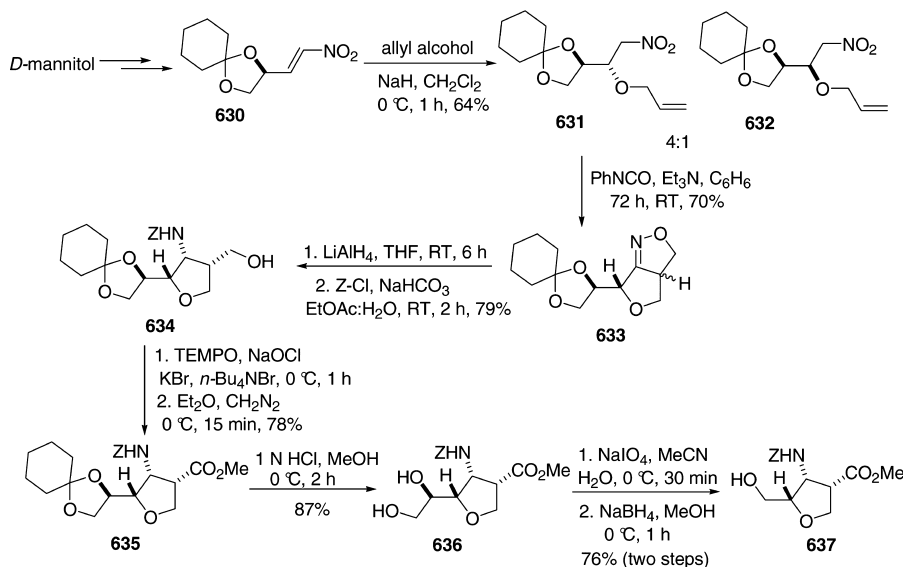
Scheme 129. Synthesis of a Pyran β-Amino Acid from D-Glucosamine
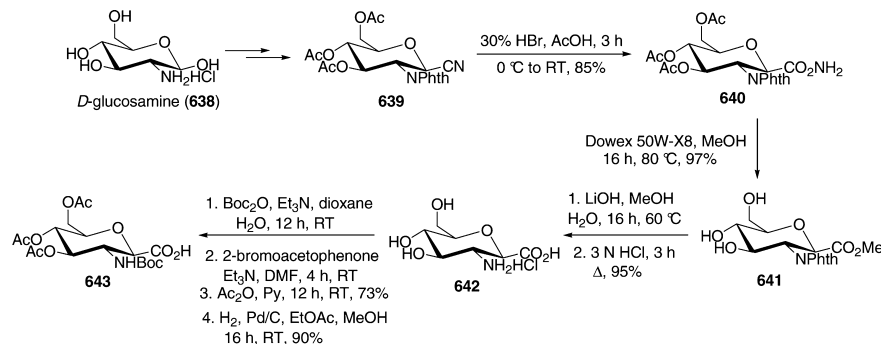
The simple and efficient route developed by Leemans et al. for the synthesis of tetrahydrofuran β-amino acids started from β-bromo imine **625** (readily available from aldehyde **624**). The construction of functionalized β-lactam **626** by the Staudinger reaction of imine **625** with benzyloxyacetyl chloride in the presence of Et₃N was the key step in the transformation. Debenzylation of **626**, followed by intramolecular nucleophilic substitution of the bromide afforded bicyclic β-lactam **628**, the lactam ring-opening of which gave five-membered O-hetero-cyclic cis-β-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 β-amino ester **629**. The starting material in the process, a hydroxylated imine, was reacted with phenoxyacetyl chloride to give the corresponding β-lactam, the ring closure of which via its mesylate followed by lactam opening afforded the required O-heterocyclic β-amino acid.[153b]

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

An enantiomerically pure tetrahydrofuran β-amino ester was recently synthetized from D-mannitol. Compound **630** under-went 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 LiAlH₄, this mixture gave amino alcohol derivative **634** as the major isomer. **634** was next oxidized to β-amino ester derivative **635**. Ketal hydrolysis and diol oxidative cleavage finally afforded tetrahydrofuran amino ester **637** (Scheme 128).[154]

3.2.3. Six-Membered O-Containing Cyclic β-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 β-amino acid sugar derivatives. One main synthetic approach to pyran β-amino acid sugars consists of the transformation of amino sugars to β-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 β-amino ester **641**. The latter was then transformed to the corresponding N-Boc-protected β-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 β-azido nitrile **645**, which served as a precursor for the sugar β-amino acid derivative **647** (Scheme 130).[156]

Through a similar protocol, azido glucose **648** (derived from N-acetylglucosamine) was transformed via the imidate to azido

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

The above synthesis procedure was adopted to prepare peptidomimetics such as the orthogonally protected diamino acids **657** and **658** (Figure 30).[159]

Figure 30. Structures of some orthogonally protected pyran diamino acids.

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).[159]

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 CO_2 as key steps. After N-Cbz protection, benzylated D-glucosamine reacted with $SOCl_2$ and tributyltin lithium provided **664**, which was next subjected to lithiation to organometallic compound **665**. The latter reacted with CO_2 to furnish β-amino acid derivative **666**, in which the arrangement of the amino and carboxylic groups was trans (Scheme 134).[160a] The N-acetylated isomer of **667** was prepared analogously.[160b]

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).[161]

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 OsO_4, followed by $NaIO_4$-mediated C−C bond cleavage, afforded aldehyde **673**, which in the presence of K_2CO_3 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).[162]

nitrile **649**, which was then easily converted to benzylated sugar amino acid **651** (Scheme 131).[157]

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.[156,157]

Azido amino sugars in the form of orthogonally protected sugar diamino acids were synthetized from acetylated sugar β-amino nitrile derivative **652**. Deacetalization 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).[158]

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

Scheme 133. Synthesis of a Pyran Azido β-Amino Acid
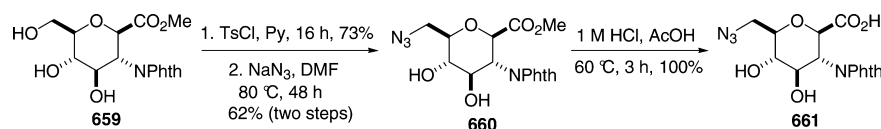
Scheme 134. Synthesis of a Sugar β-Amino Acid Containing a Pyran Ring from an Aminocarbohydrate
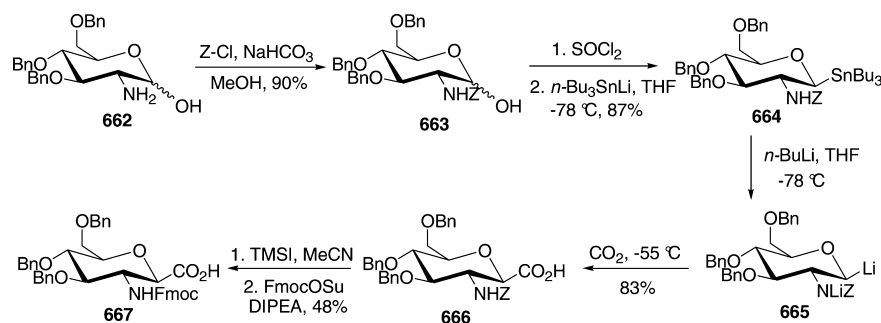
Scheme 135. Synthesis of a Pyran β-Amino Acid from O-Benzylated N-Acetylgalactose
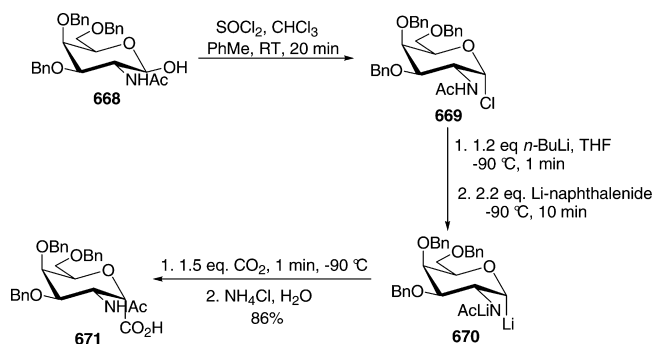
A number of other sugar β-amino acid stereoisomers (e.g., Figure 31) with a pyranose framework have been reported that are of importance in peptide chemistry (antimicrobial peptides) and in the construction of bioactive oligosaccharides.[163−165]

3.2.3.2. Syntheses of Nucleoside β-Amino Acids (blastici-din 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 *Streptomyces griseochro-mogenes*) is a known fungicide and antibiotic (**347**; Figure 22). Other important blasticidin-related nucleoside antibiotics that contain a β-amino moiety include cytomycin (**681**), cytosinine

(**682**), gougerotin analogs (**683**), and bagougeramine (**684**) (Figure 32).[166]

The syntheses of such derivatives start from readily available optically pure carbohydrates. Protected amino alcohol **686** containing a pyran skeleton [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 blasticidin S and cytosinine nucleoside antibiotics (Scheme 137).[167]

A number of blasticidin analogs have been synthetized from azido sugar **691** (derived from D-galactose in six steps). Coupling of **691** either with *N*-acetylcytidine and SnCl4 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 blasticidin analogs (Scheme 138).[168]

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

Scheme 136. Synthesis of a Pyran β-Amino Ester from an Alkenyl Sugar Derivative
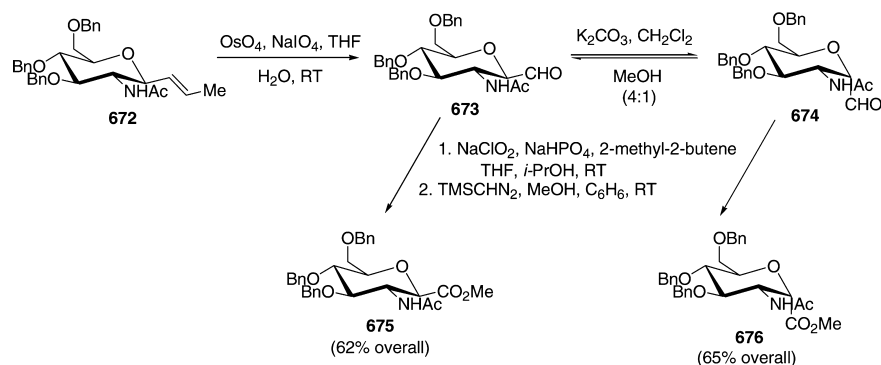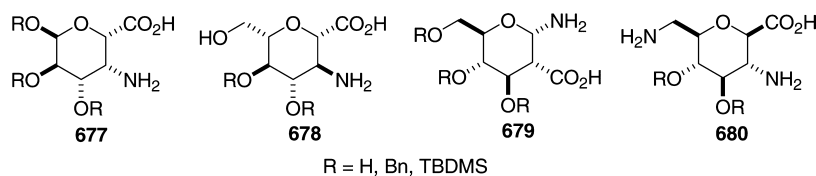
Figure 31. Structures of some bioactive sugar β-amino acids.
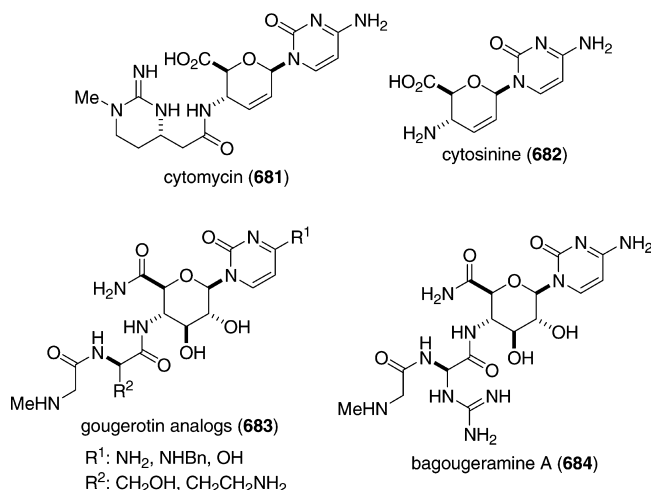
Figure 32. Structures of some nucleoside β-amino acid antibiotics.

functionalized six-membered *O*-heterocyclic amino acid, is an important antiviral agent.[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 β-amino acid moiety (Figure 33).[60,61]

A β-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 β-nitro carboxamide derivative **701**. Dehydration of **701**, followed by nitro group reduction and acetylation, led to the corresponding β-amino amide derivative **703**, the ester hydrolysis of which gave the modified zanamivir target compound **704** (Scheme 139).[61b]

Another β-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 β-amino carboxamide **707**. Azide reduction of **707** afforded β-amino acid-modified zanamivir analog **708** (Scheme 140).[61a]

3.2.3.4. Miscellaneous. Six-membered *O*-heterocyclic β-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 β-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).[170a]

Other intermediates of **714** for the synthesis of carbapenem antibiotics (thienamycin analogs) were prepared by Ikota et al. from D-glucose[170b] or for methylcarbapenem derivatives via the corresponding methyl-substituted pyran β-amino acid intermediates.[170c−e]

A further lactone β-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 β-amino ester derivative **722**. Oxidative rearrangement of **722** under Baeyer−Villiger conditions resulted in a δ-lactone β-amino ester as a precursor for the synthesis of thienamycin (Scheme 142).[171]

trans-3-Aminopyran-2-carboxylic acid, a building element in the construction of α/β-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
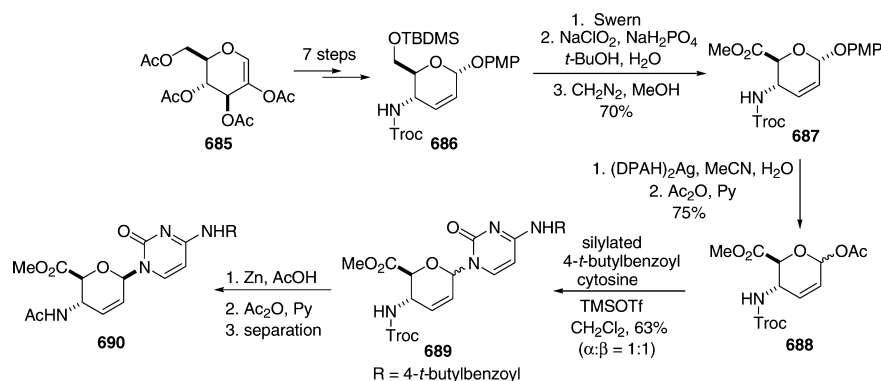
Scheme 138. Synthesis of Blasticidin S Analogs from an Azido Sugar
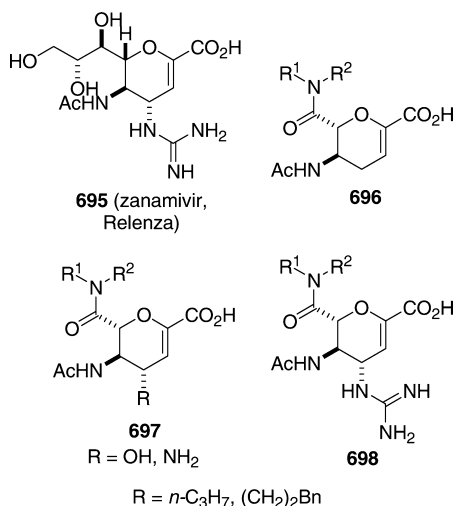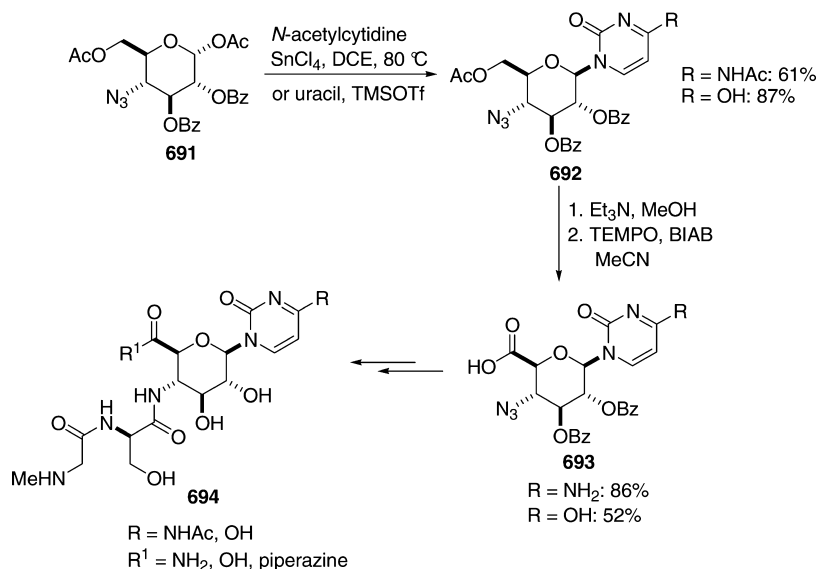
Figure 33. Structures of zanamivir and several β-amino acid-modified zanamivir analogs.

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 NaClO$_2$, to give the required pyran amino acid **731** (Scheme 143).[172]

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**. Intramolecular 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).[127] *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.[173] These heterocyclic β-amino esters were utilized as building elements

for the synthesis of a series of products with TACE inhibitor activities.[127,173]

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 PPh$_3$ and diisopropyl azodicarboxylate (DIAD) to unsaturated ester **741**. Addition of lithium dibenzylamine 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).[104]

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 synthetized 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 Ph$_2$SiCl$_2$ by reaction with vinylmagnesium bromide in the presence of Cp$_2$TiCl$_2$, which afforded heterocyclic compound **751**. Aziridination of **751** with chloramine-T and phenyltrimethylammonium tribromide (PTAB) resulted in **752**. Aziridine opening with Et$_2$AlCN provided amino nitrile derivative **753**, which was next converted by Boc protection

Scheme 139. Synthesis of a Racemic β-Amino Acid-Modified Zanamivir Analog
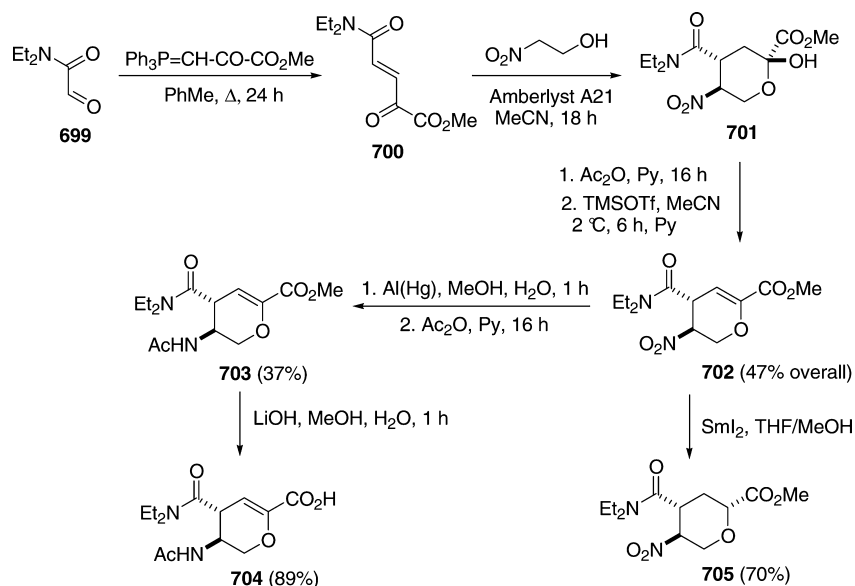
Scheme 140. Synthesis of a Zanamivir Analog Containing a β-Amino Acid
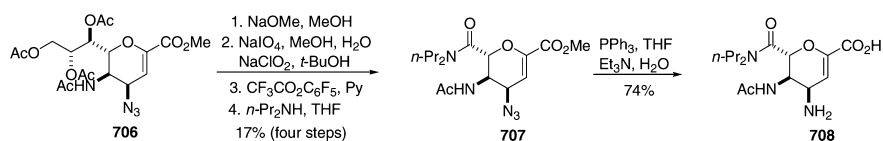
Scheme 141. Synthesis of a Pyran β-Amino Acid As a Precursor of Several Antibiotics
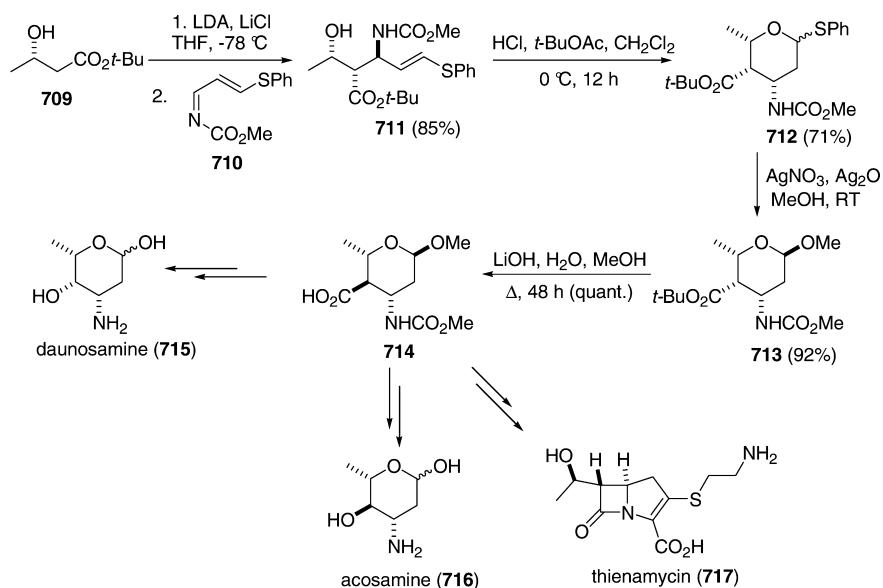
and tosyl group removal to **755**. Boc protecting group removal and ester hydrolysis in the final step gave the *Si*-heterocyclic β-amino acid **757** (Scheme 147).[175]

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[1,2a–e] Not only alicyclic but also five-membered heterocyclic

Scheme 142. Synthesis of a β-Amino Acid Containing a δ-Lactone Ring
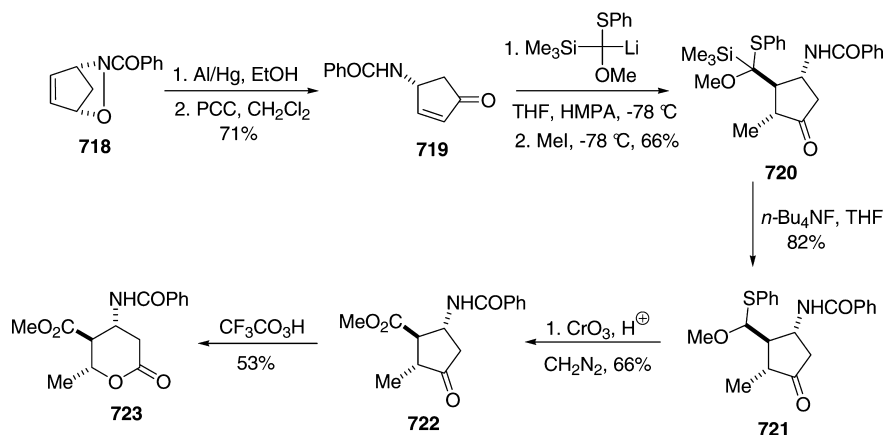
Scheme 143. Synthesis of a Pyran β-Amino Ester from a Diene Ether Derivative
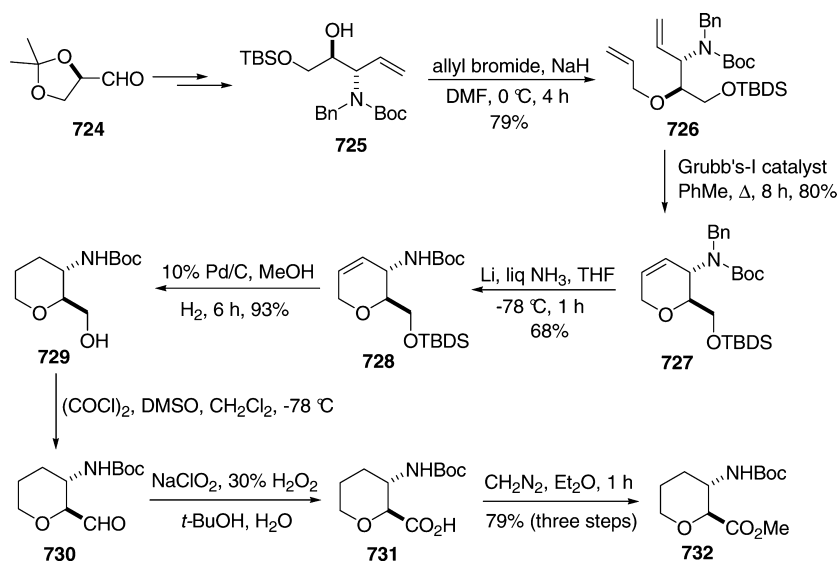
Scheme 144. Synthesis of a Pyran β-Amino Ester from a Pyran-Fused Isoxazolidine
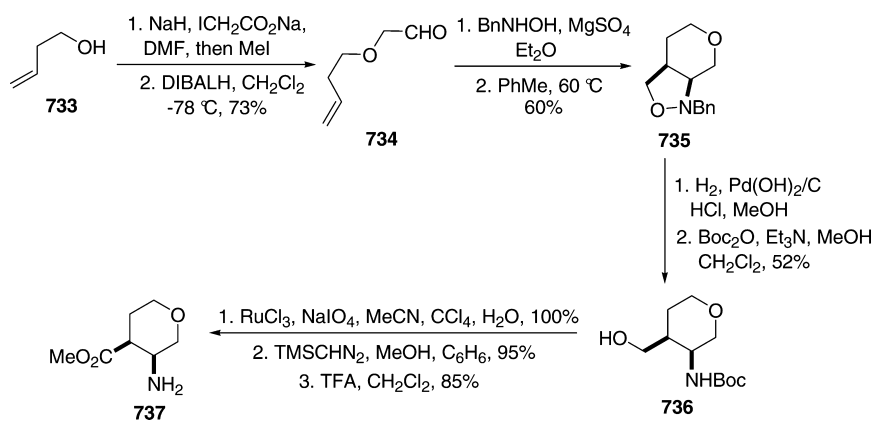
β-amino acids exert antifungal and antibacterial activities. An important class are those with the N-heterocyclic pyrrolidine core (**345**), including the stereo- and regioisomers **758** and **759**.[2a,176] These compounds have been applied as building elements for the construction of antimicrobial peptide oligomers.[93] Among the antifungal β-amino acids with a simple structure similar to that of cispentacin are those with an O (**561**

and **562**)[2a] or S (**745** and **746**)[2a] atom in their ring. Several of their substituted derivatives have been reported to possess multidrug-resistance activity.[139] The four-membered O-hetero-cyclic 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.[92] Several other six-membered O-heterocyclic analogs (**677–680**) have been

Scheme 145. Syntheses of Tetrahydrothiophene β-Amino Esters

Figure 34. Structures of bioactive tetrahydrothiophene β-amino acids.

Scheme 146. Syntheses of Thiopyran β-Amino Esters

compounds is the nucleoside-based antibiotics, whose structures contain either five- or six-membered *O*-heterocyclic β-amino acid residues. Chryscandin (**349**) (produced by *Chrysosporium pannorum* 4629), a peptide-based nucleoside derivative with a 3-aminotetrahydrofuran-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 Relenza[169] or Tamiflu.[59] Some highly substituted cyclohexanecarboxylic β-amino acids, modified analogs of Tamiflu (**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 neuramidase 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 neuramidase 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

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

Scheme 147. Synthesis of a *Si*-Heterocyclic β-Amino Acid

1162

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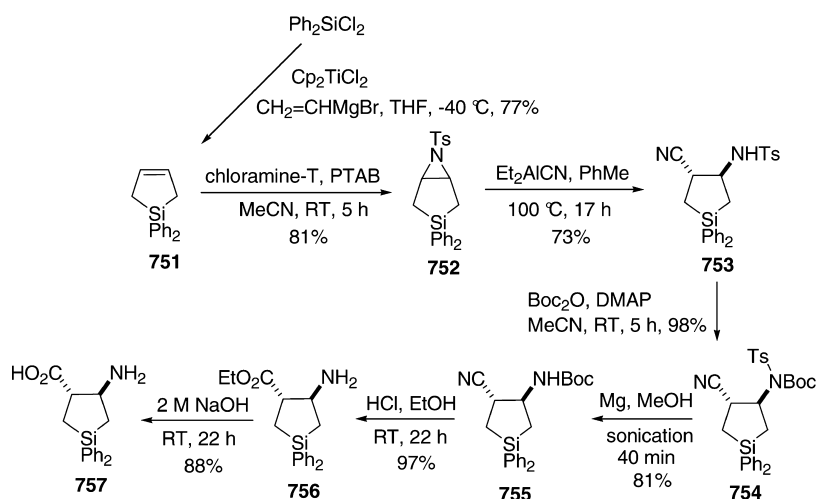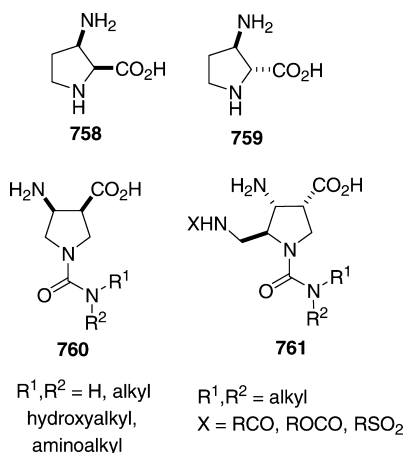
Figure 35. Some pharmacologically important pyrrolidine β-amino acids.

compounds that do possess this property. Thus, norbornene β-amino acid is an element of CEP-28122 (**7**), while cyclohexene β-amino acid is a component of MK-6892 (**8**). Cyclohexene or cyclopentane β-amino acid moieties are found in several other related compounds that exhibit antitumoral properties (**9**–**11**).[2] A series of products containing a carbocyclic or heterocyclic β-amino acid residue has been synthetized and evaluated as efficient selective inhibitors of tumor necrosis factor (TNF-α) converting enzyme (TACE). Apart from those in which there is a carbocyclic β-amino acid (e.g., **9**),[127] the most abundant are those with a pyrrolidine β-amino acid framework. Five-membered N-heterocyclic β-amino acid or hydroximic acid-containing molecules and related substituted derivatives[93,94] **419**[2k] and **762**–**767** (Figure 36), for example, are representative molecules of this type.[109,177]

The six-membered N-heterocyclic β-amino acids and the pyran β-amino acids may also function as elements of molecules with TACE inhibitor activity (e.g., **765**).[127,173,177] Highly functionalized piperidine β-amino acid derivatives (**514**, **515**, and **768**) act as enzyme inhibitors and exhibit antimetastatic activity,[134] while pyrrolidine-based β-amino acid derivatives with structures such as **769** behave as dipeptidyl-peptidase IV inhibitors (Figure 37).[178]
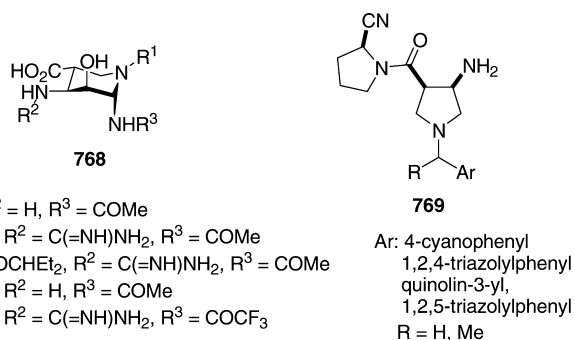
Figure 37. Structures of N-heterocyclic β-amino acids that act as enzyme inhibitors.

4.4. Cyclic β-Amino Acids with Cardioprotective Properties

Nucleoside β-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.[146]

5. SUMMARY AND OUTLOOK

As reflected by the increasing number of publications devoted to alicyclic and heterocyclic β-amino acids during the past 15

Figure 36. Some antitumoral compounds with a heterocyclic β-amino acid element.

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 discovery 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

Loránd 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 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*.

ABBREVIATIONS USED

AIBN = azobisisobutyronitrile
Ac = acetyl
ACPC = 2-aminocyclopentanecarboxylic acid
AZT = azidothymidine
9-BBN = 9-borabicyclo[3.3.1]nonane
Boc = *tert*-butoxycarbonyl
BOP = (benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate
CAL-B = *Candida antarctica* lipase B
CAN = cerium ammonium nitrate
COD = cyclooctadiene
Cp = cyclopentadienyl
CSI = chlorosulfonyl isocyanate
DAST = diethylaminosulfur trifluoride
Deoxo-Fluor = bis(2-methoxyethyl)aminosulfur trifluoride
DBU = 1,8-diazabicycloundec-7-ene
DEAD = diethyldiazodicarboxylate
DIAD = diisopropyldiazodicarboxylate
DIBALH = diisobutylaluminium hydride
DIPEA = diisopropylethyl amine
DMAP = 4-dimethylaminopyridine
DMB = dimethoxybenzyl
DMDO = dimethyldioxirane

DMF = *N*,*N*-dimethylformamide

DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidi-non

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

KHMDS = potassium hexamethyldisilylamide

LDA = lithium diisopropylamide

LiHMDS = lithium hexamethyldisilylamide

*m*CPBA = *m*-chloroperbenzoic acid

Ms = methanesulfonyl

NAAs = nucleoside amino acids

NBS = *N*-bromosuccinimide

NaHMDS = sodium hexamethyldisilylamide

NIS = *N*-iodosuccinimide

NMM = *N*-methylmorpholine

NMO = N-methylmorpholine *N*-oxide

Ns = *p*-nitrosulfonyl

PDC = pyridinium dichromate

PLE = pig liver esterase

PMB = *p*-methoxybenzyl

PMP = *p*-methoxyphenyl

PTAB = phenyltrimethylammonium tribromide

p-Ts = *p*-toluenesulfonyl

Py = pyridine

SAAs = sugar amino acids

TBDMS = *tert*-butyldimethylsilyl

TEMPO = 2,2,6,6-tetramethylpiperidinyloxy

Tf = trifluoromethanesulfonate

TFA = trifluoroacetic acid

TMS = trimethylsilyl

TolBINAP = 2,2′-*p*-tolylphosphino-1,1′-binaphthyl

Tr = trityl

Troc = trichloroethoxy carbamate

Z = benzyloxycarbonyl

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1168

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