The Chemistry of 2-Aminocycloalkanecarboxylic Acids

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Contents

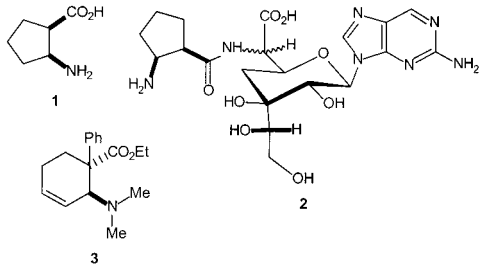
Ferenc Fülöp was born in Szank, Hungary, in 1952. He received his MSc in Chemistry in 1975 and his PhD in 1979, from József Attila University, Szeged, Hungary, under the supervision of Professor Gábor Bernáth. He spent almost two years as a postdoctoral fellow in Turku, Finland, and three months in Bonn, Germany, working in the fields of heterocyclic and structural chemistry. In 1990, he received his DSc from the Hungarian Academy of Sciences in Budapest. After different teaching positions, he was appointed full professor at the Institute of Pharmaceutical Chemistry in 1991, and since 1998 has been head of the Institute. He has a wide range of research interests in heterocyclic chemistry, including isoquinolines and fused skeleton saturated 1,3-heterocycles. His studies on the ring-chain tautomerism of 1,3-oxazines and oxazolidines in the 1990s led to interesting results. His recent activities have focused on the use of amino alcohols and amino acids in enzymatic transformations, asymmetric syntheses, and combinatorial chemistry, with a view to the development of pharmacologically active compounds.

I. Introduction

Although of less importance than their α-analogues, *β*-amino acids are also present in peptides and different heterocycles, and their free forms and derivatives exhibit interesting pharmacological effects. The chemistry and pharmacology of *β*-amino acids have been widely reviewed,[1−8] but in these works the alicyclic derivatives are mentioned only marginally.

Investigations on the alicyclic *β*-amino acids have so far undergone two considerable impulses. A decade ago, (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid **1** ((1*R*,2*S*)-2-ACPC; cispentacin), an antifungal antibiotic, was isolated independently by two Japanese groups from *Bacillus cereus*[9,10] and *Streptomyces setonii*.[11,12] *cis*-2-ACPC[13] is also a component of the antibiotic amipurimycin.[14] Amipurimycin **2**, isolated from *Streptomyces novoguineensis*, is strongly active both in vitro and in vivo against *Pyricularia oryzae*, the organism responsible for rice blast disease. It is also active in vitro against *Alternaria kikuchiana* and *Helminthosporium sigmoideum var. irregulare*. Amipurimycin **2** contains a nucleic base attached to the anomeric carbon of a branched-chain deoxy sugar. The chain is extended by a dipeptide containing *cis*-2-ACPC.[15−17]

Chart 1



The second impulse in the chemistry of 2-aminocycloalkanecarboxylic acids (2-ACACs) was recently

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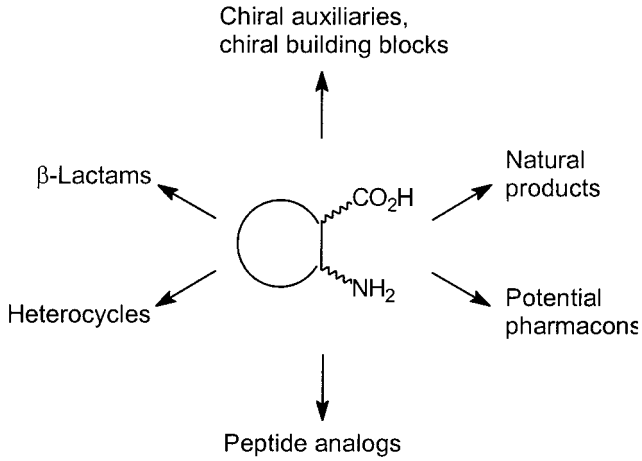
Scheme 1



generated by Gellman et al.[18,19] The research groups of Seebach and Gellman have in parallel published pioneering reports on oligopeptide chains that can fold into a stable helical structure.[20−24] Gellman's group synthesized and investigated[18,19] *trans*-2-ACPC and *trans*-2-aminocyclohexanecarboxylic acid (*trans*-2-ACHC) oligomers. It was clearly demonstrated that, as an example, the hexamer of *trans*-2-ACHC displays a helical conformation that involves 14-membered rings.

Among the synthetic derivatives, Tilidine **3**, a cyclic β-amino acid derivative, ethyl (±)-*trans*-2-(dimethylamino)-1-phenyl-3-cyclohexene-1-carboxylate hydrochloride, is an opioid analgesic used in therapy to control moderate to severe pain.[25,26] (In the Schemes, for simplicity only one of the enantiomeric forms of the racemates is shown.)

Besides their own pharmacological activity, the alicyclic β-amino acids can be used as building blocks for the preparation of modified (unnatural) analogues of biologically active peptides. By insertion of an alicyclic β-amino acid in place of an α-amino acid of a naturally occurring pharmacologically active peptide, the activity or the effect can be modified. By means of such an exchange, the stabilities of the natural peptides can be increased since the β peptides are resistant to enzymatic degradation.[4] The difference in ring size allows modification of the conformations of the peptides. Such investigations are applied for determination of the fine structures of receptors. On the other hand, cyclic β-amino acids can be used as starting substances of different heterocycles, potential pharmacons, for the synthesis of natural products or analogues, and also as building blocks in drug research. Their enantiomerically pure forms can serve as chiral auxiliaries or additives (Scheme 1). Their use in combinatorial chemistry is also in progress.

Because of the natural occurrence and the biological activity, interest in chemical investigations of the alicyclic β-amino acids has rapidly increased. A number of new synthetic strategies, involving transformations to heterocycles or to peptides and peptidomimetics, have been developed. New syntheses have also been developed and protected by patents (e.g., refs 27−31). The aim of this work is to summarize the results in this intensively developing field of research.

II. Syntheses of 2-Aminocycloalkanecarboxylic Acids

A. 2-Aminocyclopentane- and 2-Aminocyclohexanecarboxylic Acids

Among the cyclic β-amino acids, the most widely investigated derivatives are the five- and six-membered derivatives. This is probably due to the relation to anthranilic acid and to the natural occurrence mentioned in the introduction and also stems from the relatively simple synthetic pathways.

1. Syntheses of the Racemic Compounds

a. By Selective Reduction. The selective reduction of anthranilic acid in amyl alcohol with sodium to produce *trans*-2-ACHC has been known for more than a hundred years and is sometimes still applied.[32] When anthranilic acid is reduced over Adams catalyst in acetic acid or over a Rh−Al catalyst, the main product is *cis*-ACPC.[32,33] When colloidal ruthenium was used under hydrogen pressure, the cis−trans isomer ratio was 6:1.[34]

Later, a number of more stereoselective methods were applied to obtain five- or six-membered β-amino acids by the reduction of oximes[35] or enamines,[36−39] which can easily be prepared, e.g., from the corresponding cyclic β-ketoesters. In the early procedures, the main product was in most cases the corresponding cis isomer, but the diastereomeric ratios have been given only rarely. In many cases, it is not possible to prepare the products in diastereomerically pure form; they may contain 5−15% of the other isomer.[40] After further transformations, the minor component may perhaps be lost.

In the past few years, the selective reductive aminations of β-ketoesters via enamines have revealed the accurate ratios of cis and trans diastereomers[41−44] (*de* ranges from 60 to 90%).

b. Syntheses from 1,2-Dicarboxylic Acid Derivatives by Rearrangements. A number of diastereomerically pure 1,2-dicarboxylic anhydrides are commercially available or can easily be prepared by the Diels−Alder reaction of butadiene and maleic anhydride. The resulting tetrahydroanthranilic anhydride is readily reducible to the hexahydro analogue. The first selective synthesis of *cis*-2-ACHC **6** was performed from anhydride **4** after amidation, followed by Hofmann degradation with hypobromite.[40,45,46] This protocol was used to prepare a number of homologues and analogues, e.g. *cis*-2-ACPC,[45,47] *cis*- and *trans*-2-amino-4-cyclohexenecarboxylic acid,[48] *diendo*-3-aminobicyclo[2.2.1hept-5-enecarboxylic acid,[49] 3-*endo*-amino-5-*exo*-phenylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid,[50] and *cis*-3-aminobicyclo[2.2.2]octane-2-carboxylic acid.[51] In cases of double bond-containing derivatives, modified Hofmann degradation with hypochlorite has been applied to avoid bromine addition. After Hofmann degradation, ion-exchange chromatographic purification is the method usually applied, but in some cases

the purification was achieved through the ester[46] or the *N*-acyl derivative.[49] An electrochemically induced Hofmann degradation was also successfully performed from **5**, under neutral conditions.[52]

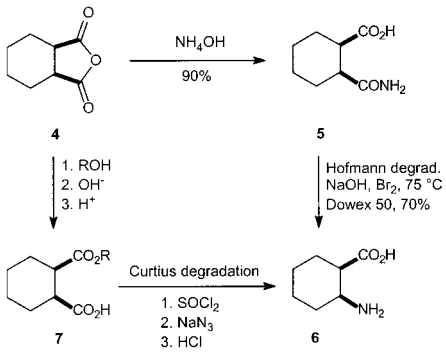
Anhydride **4** can be esterified and selectively monohydrolyzed to **7,** which is a suitable starting substance after Curtius degradation for the production of 2-ACACs.[51,53−55] This method is widely applied for the preparation of enantiomerically pure amino acids since the desymmetrization of diesters is a relatively easy process (see later). Curtius degradation has been found to be broadly applicable for the solid-phase synthesis of cyclic β-amino acid derivatives.[56] The synthesis of an antifungal drug candidate BAY 10-8888, (1*R*,2*S*)-2-amino-4-methylenecyclopentanecarboxylic acid, was also performed via Curtius degradation, where the desymmetrization was mediated by one equivalent of quinine.[57]

Lossen rearrangements of *cis*-*N*-phenylsulfonyloxyhexahydrophthalimide and of the corresponding *di-endo* norbornane and norbornene derivatives have been successfully performed in aqueous sodium hydroxide, resulting in good yields of the benzenesulfonates of the corresponding amino acids.[58]

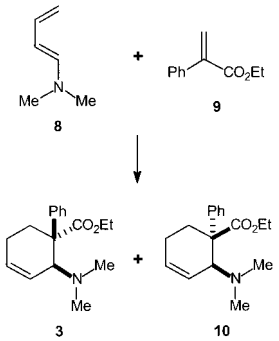
c. Michael Additions to Cycloalkenecarboxylic Acids. *trans*-2-ACPC and *trans*-2-ACHC can be obtained selectively in moderate yields by Michael addition of ammonia to 1-cyclopentene- or 1-cyclohexenecarboxylic acid at 150−170 °C in an autoclave.[40,45,47] In the Michael addition to 1-cyclopentenecarboxylic acid, Connor and Ross reported the isolation of *cis*-2-ACPC besides the main trans acid.[59] Later, in the same reaction there was no mention of formation of the cis product.[47,60] Methylamine addition to 1-cyclohexenecarboxylic acid at 140−160 °C, yielded *trans*-2-(methylamino)cyclohexanecarboxylic acid in 51% yield after 48 h.[61] The addition of aniline or benzylamine to 1-cycloalkenecarboxylic acids resulted in *N*-substituted-*trans*-2-(substituted amino)-cycloalkanecarboxamides in moderate yields.[62] Addition of substituted benzylamine to methyl 1-cyclohexenecarboxylate proved unsuccessful under a wide variety of conditions.[43] All four stereoisomers of diethyl 2-aminocyclohexane-1,4-dicarboxylate were prepared from ethyl 4-cyano-3-cyclohexenecarboxylate by ammonia addition, followed by hydrolysis and esterification.[63] The addition led to an aziridine intermediate and finally gave the cis amino ester. Intramolecular addition of an alkenyl-substituted cyclopropylamine, followed by oxidative cyclopropane cleavage, furnished a bicyclic β-amino ester.[64]

d. Diels−Alder Reactions. Satzinger reported the 1,4-cycloaddition reaction of *trans*-1-(dimethylamino)-1,3-butadiene **8** with ethyl atropate **9**, which resulted in a mixture of diastereomers **3** and **10** in 1:3 ratio, the minor product being the currently clinically applied analgesic Tilidine[53,65] **3** (Scheme 3). The reaction became generally used and has been utilized for a wide variety of substituents on both the diene and the dienophile side. Depending on the substituents, the reaction can shift in the *endo* or *exo* direction, and sometimes high diastereoselectivities can be attained. With the aid of this reaction, a number of polysubstituted 2-amino-3-cycloalkenecarboxylates have been prepared.[66−69]

Scheme 2



Scheme 3

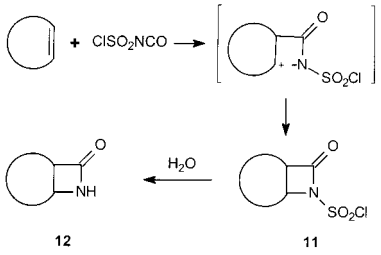


The Diels−Alder strategy has been utilized to prepare a number of β-amino acid derivatives by the reaction of cyclopentadiene with ethyl nitrocrotonates, followed by reduction,[70] or from cyclopentadiene with dimethyl acetamidofumarate and further dienes.[71,72] The intramolecular Diels−Alder reactions of dienamines with acrylates occur readily to produce *cis*- and *trans*-fused bicyclic β-amino acid derivatives.[73]

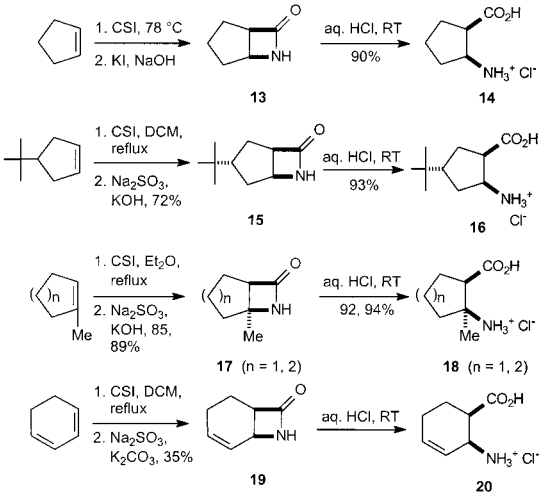
e. Syntheses from β-Lactams. Although β-amino acids are well-known as precursors of β-lactams,[74−76] the reverse route, i.e., the β-lactam → β-amino acid transformation, is one of the most often used strategies[77] for cyclic β-amino acid synthesis. The discovery and exceptionally easy 1,2-dipolar cycloaddition of chlorosulfonyl isocyanate (CSI) to different cycloalkenes has become a well-known route for the synthesis of cycloalkane-fused β-lactams[78−80] and for alicyclic β-amino acids, after hydrochloric acid treatment of lactams.[81−83] The best-known solvents in the CSI addition reaction are dichloromethane (DCM) and diethyl ether; the reaction temperature ranges from −78 °C to reflux temperature. The addition always takes places regio- and stereoselectively, in accordance with the Markovnikov orientation rule. The *N*-chlorosulfonyl derivatives **11** are often isolable in the reaction (Scheme 4). For their reductive−hydrolytic decomposition to lactams **12**, the most often used reagent compositions are sodium sulfite and potassium hydroxide or benzenethiol, pyridine and water.

In this manner, starting from the corresponding cycloalkene, a number of homologue and analogue alicyclic β-amino acids have been prepared, such as *cis*-2-ACPC[84] **14**, (1*S**,2*R**,4*S**)-2-amino-4-*tert*-butylcyclopentanecarboxylic acid[85] **16**, *cis*-2-amino-2-

Scheme 4



Scheme 5



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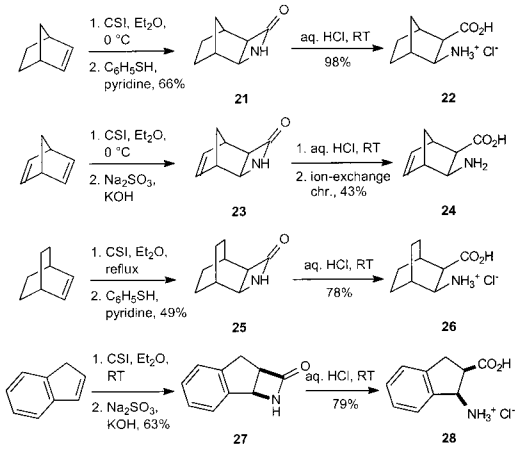
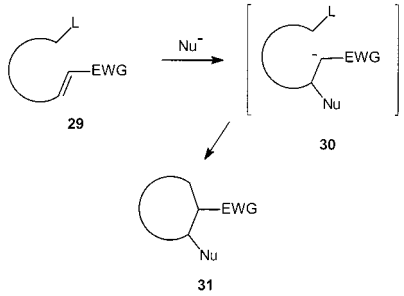


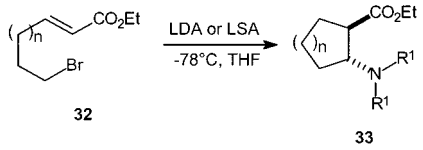
methylcyclopentanecarboxylic acid and *cis*-2-amino-2-methylcyclohexanecarboxylic acid[86] **18**, *cis*-2-amino-3-cyclohexenecarboxylic acid[87,88] **20**, 3-*exo*-aminobicyclo[2.2.1]heptane-2-*exo*-carboxylic acid[81] **22**, 3-*exo*-aminobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid[89] **24**, 3-*exo*-aminobicyclo[2.2.2]octane-2-*exo*-carboxylic acid[81] **26** and *cis*-1-aminoindane-2-carboxylic acid[90] **28** (Schemes 5 and 6).

The hydrochloric acid ring opening of β-lactams results in amino acid hydrochlorides in an exothermic reaction. For preparation of the free amino acids, treatment with a large excess of silver oxide[84] or propylene oxide can be used. Ion-exchange chromatography was later found to be a more suitable method. The ring opening of β-lactams with alcoholic hydrogen chloride results in the corresponding esters;[90,91] with ammonia or alkylamines, the corresponding aminocarboxamides can also be prepared.[92,93]

Scheme 7



Scheme 8



Ring opening of *N*-substituted lactams gives *N*-substituted amino acid derivatives.[94] The ring opening of activated β-lactams has led to a possibility of their direct use in peptide synthesis.[95]

f. Miscellaneous. From among the variety of miscellaneous syntheses of five- and six-membered β-amino acids, the most interesting and probably most widely applicable is the MIRC reaction[96] (Michael initiated ring closure). The reaction scheme can easily be rationalized according to Scheme 7. From *E*-ω-haloalkene carboxylates **32** with lithium diisopropylamide (LDA) or lithium *N*-benzyl-*N*-trimethylsilylamide (LSA), the corresponding cyclic trans-β-amino esters **33** were formed in good yields[96,97] (Scheme 8). LSA was also successfully used for the synthesis of further substituted analogues.[98] Both LDA and LSA are useful nucleophiles for cyclization based on tandem conjugate addition−intramolecular alkylation that results in the thermodynamically more stable steroisomer.[97]

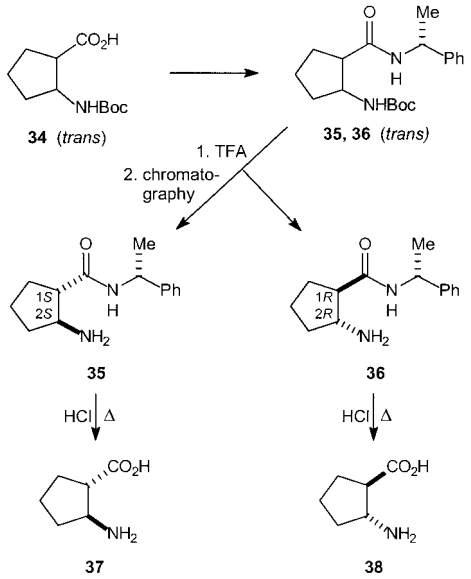
The geometric isomers of 1-amino-1,2-cyclopentanedicarboxylic acid were prepared and successfully separated as the hydrolysis products of 2-cyclopentanecarboxylic acid-5,5′-hydantoin. The hydantoin ester was simply prepared from ethyl 2-oxocyclopentanecarboxylate and potassium cyanide.[99]

In further syntheses, alicyclic β-amino acids have been prepared by other ring opening reactions[100,101] or skeletal rearrangements.[102,103]

2. Resolutions of the Racemates by Diastereomer Separation

The first resolution of *N*-benzoyl-*cis*-2-ACHC was performed by diastereomeric salt formation with cinchonine by Armarego.[103] At the same time, the trans counterpart was resolved with L-ephedrine by Nohira et al.[104] Resolution of racemic *cis*-2-ACPC was reported only after the isolation of natural cispentacin. Konishi et al.[9] resolved racemic Z-protected *cis*-2-ACPC by fractional crystallization of the salt formed with (+)-dehydroabietylamine. Yamazaki et al.[60] resolved the Boc-protected *cis*-2-ACPC racemate with (−)-ephedrine. The resulting salt was fractionally crystallized from ethyl acetate/diethyl ether.

Scheme 9



Ethyl (±)-*trans*-2-(dimethylamino)-1-phenyl-3-cyclohexene-1-carboxylate (Tilidine) was resolved with dibenzoyltartaric acid by Satzinger.[53]

Seed-induced enantioselective crystallization was also performed on *trans*-2-benzamidocyclohexanecarboxylic acid.[105,106] It is interesting that both *cis*- and *trans*-2-benzamidocyclohexanecarboxylic acid were successfully used for the separation of racemic bases by diastereomeric pair formation.[107,108]

By means of diastereomeric pair formation, *cis*- and *trans*-2-ACPC were resolved. Kawabata et al.[12] separated methyl (±)-*N*-(Boc-L-phenylalanyl)-*cis*-2-aminocyclopentanecarboxylate diastereomers by fractional crystallization from ethyl acetate. Edman degradation of the separated isomers, followed by deprotection, acid hydrolysis, and desalting with anion-exchange resin, gave enantiomerically pure (1*S*,2*R*)- and (1*R*,2*S*)-2-ACPC.

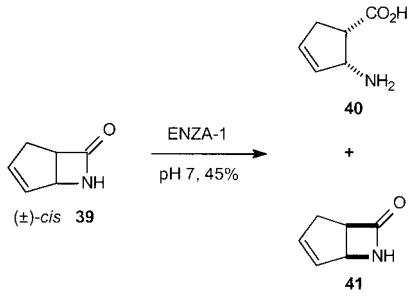
The enantiomers of *trans*-2-ACPC were separated by Yamazaki et al.[60] The Boc-protected racemic amino acid was coupled with *R*-(+)-α-methylbenzylamine by use of a mixed anhydride (Scheme 9). The diastereomers **35** and **36** were separated by silica gel column chromatography after removal of the acid-labile Boc group. The absolute configuration was proved by X-ray diffraction of **36**. The amino acid enantiomers **37** and **38** were obtained after strong acid treatment of **35** and **36**, and anion-exchange desalting of the product.[60]

A very similar method was used for separation of the Z-protected cis carboxamide diastereomers formed with (+)-(*R*)-α-methylbenzylamine. The diastereomers were easily separated by flash chromatography.[109]

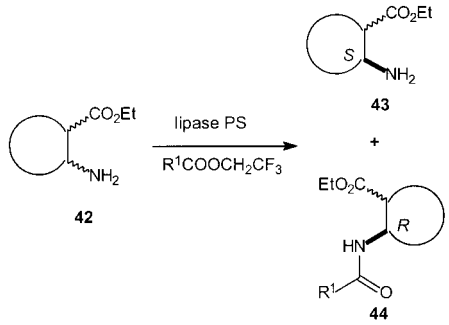
3. Biocatalyzed Transformations, Enzymatic Resolutions

There are only a few methods for the direct enzymatic separation of 2-ACAC acid enantiomers. In this section, the enzymatic processes that allow separation of the various precursors of the target derivatives will also be discussed.

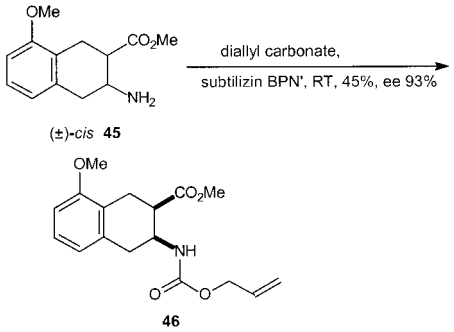
Scheme 10



Scheme 11



Scheme 12

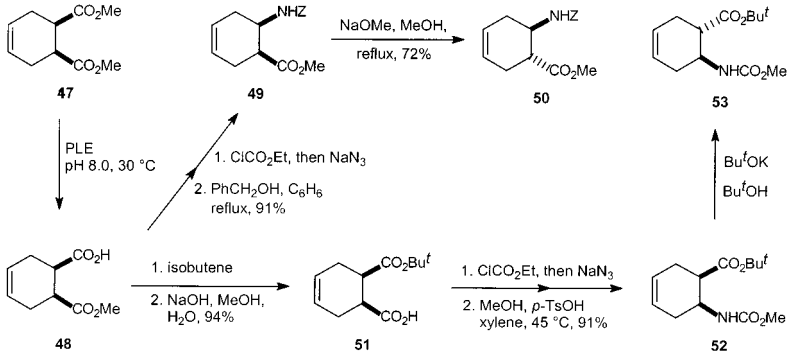


Highly enantioselective hydrolysis of 6-azabicyclo-[3.2.0]hept-3-en-7-one **39** was achieved by using a whole cell preparation of ENZA-1 (*Rhodococcus equi*).[110−112] The hydrolysis selectively gave the amino acid **40** (96% *ee*). The recovered lactam **41** (Scheme 10) was reduced and then hydrolyzed to cispentacin. It is noteworthy that ENZA-1 exhibited only poor hydrolytic activity toward the reduced form of (±)-cis **39**.

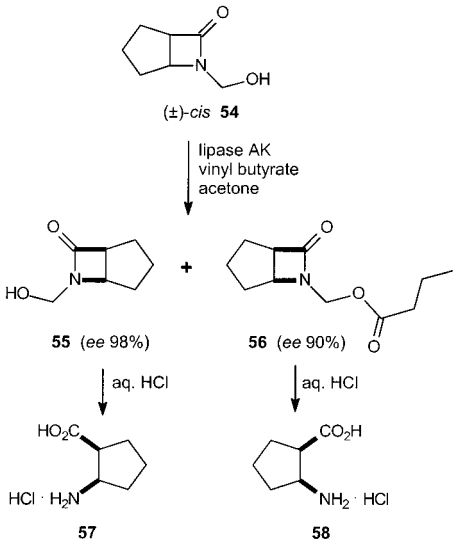
Kanerva et al.[113] resolved ethyl esters of 10 alicyclic β-aminocarboxylic acids by lipase catalysis in organic solvents. The resolutions were based on acylation of the amino group of **42** at the *R*-stereogenic center with various 2,2,2-trifluoroethyl esters (Scheme 11). An unexceptional enantioselectivity enhancement was observed when 2,2,2-trifluoroethyl chloroacetate was used with lipase PS catalysis. With this method, all four enantiomers of 2-ACPC, 2-ACHC, and 2-amino-4-cyclohexenecarboxylic acids, and enantiomers of *diendo*- and *diexo*-3-aminobicyclo[2.2.1]-heptane- and -heptenecarboxylic acids were prepared.[113]

Diallyl carbonate proved to be an excellent agent for the acylation of amino ester **45** when it was reacted in a phosphate buffer at pH 8.0 for 85 h, and gave **46** with 93% *ee*, without hydrolysis of the ester.

Scheme 13



Scheme 14



The unreacted substrate was not isolated in this reaction[114] (Scheme 12).

An excellent and elegant method was developed by Ohno et al.[74,115,116] for the synthesis of all four enantiomers of 2-amino-4-cyclohexenecarboxylic acid. The key step in the synthesis is the pig liver esterase-catalyzed desymmetrization of *meso* diester **47.** The hydrolysis proceeded very smoothly in pH 8.0 phosphate buffer and acetone at 30 °C, with *ee* 96% on a multi-hundred gram scale. The half-ester **48** with *R* configuration at the carboxyl function was transformed to the Z-protected amino ester with ethyl chloroformate, followed by sodium azide treatment, and a Curtius rearrangement resulted in amino ester **49**. Sodium methoxide isomerization of cis ester **49** gave trans ester **50** in 72% yield (Scheme 13).

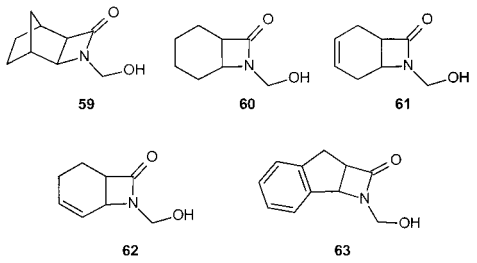
When the acid function of **48** was esterified with isobutene, followed by selective hydrolysis of the methyl ester, the monoester with an *S* configuration at the carboxyl function was formed. This was transformed to cis and trans amino esters **52** and **53** by the same synthetic route (Scheme 13).

The main advantage of the desymmetrization of *meso* esters is that, instead of the 50% yield of the resolutions here, the yield is up to 100%, and the desymmetrized half ester can be transformed to all four enantiomers. Desymmetrization can also be performed excellently by nonenzymatic routes.[117−119]

A highly enantioselective enzymatic acylation was observed for *N*-hydroxymethylated *β*-lactam **54**, which was prepared from the corresponding *β*-lactam with paraformaldehyde by sonication. Lipase AK-catalyzed butyrylation with vinyl butyrate in acetone gave the readily separable azetidinones **55** and **56** with 98 and 90% *ee*, respectively, after 2.7 h at room temperature. Hydrolysis of *β*-lactams **55** and **56** resulted in both enantiomers **57** and **58** of *cis*-2-ACPC[120] (Scheme 14).

By the same pathway, a number of hydroxymethylated *β*-lactams have been acylated enantioselectively. The optimal enzymes, acylating agents, solvents, reaction times, and enantiomeric ratios (*E*) of the acylations were as follows: **59**,[120] lipase AK, vinyl butyrate, acetone, 3.5 h, $E = 62$; **60**,[88] lipase PS, vinyl butyrate, acetone, 5 h, $E > 200$; **61**,[88] lipase PS, vinyl butyrate, acetone, 5 h, $E > 200$; **62**,[88] lipase PS, vinyl butyrate, acetone, 5 h, $E > 200$; and **63**,[90] lipase AK, vinyl butyrate, THF, 2.5 h, $E > 200$. In all cases, *β*-lactam enantiomers were hydrolyzed to the corresponding alicyclic amino acid enantiomers.

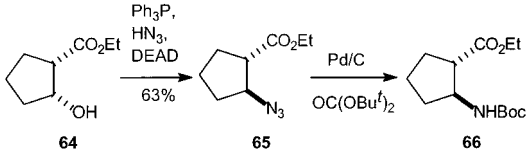
Chart 2



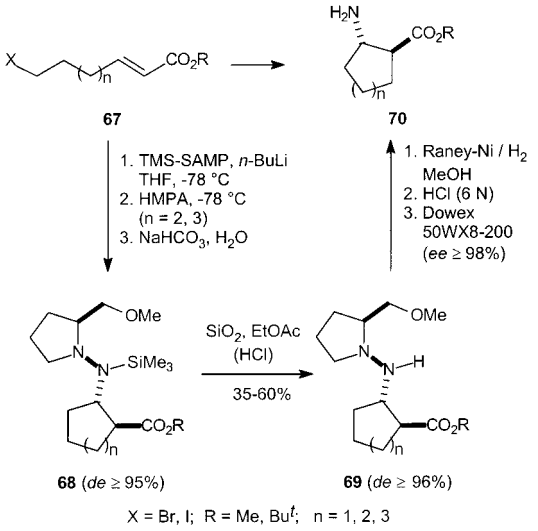
The enantiomerically pure hydroxy ester **64** is readily available by yeast-mediated reduction of ethyl 2-oxocyclopentanecarboxylate. Treatment of **64** with hydrazoic acid under Mitsunobu conditions resulted in inversion and gave the azide **65,** which was reduced in the presence of di-*tert*-butyl dicarbonate to give the Boc-protected ester **66** (Scheme 15). Ester hydrolysis with lithium hydroxide gave the corresponding acid as single enantiomer.[121]

Lipase PS-catalyzed transesterification of 2-(*tert*-butyldimethysilyloxymethyl)-cyclopentanol with vi-

Scheme 15



Scheme 16



nyl acetate in *tert*-butyl methyl ether furnished the corresponding enantiomerically pure ester and the alcohol. Using simple functional group transformations (four steps), including the Mitsunobu reaction, Theil et al.[122] developed a method for the chemoenzymatic synthesis of both enantiomers of *cis*-2-ACPC.

Noteberg et al.[123] devised a simple four-step synthesis of both enantiomers of *trans*-2-ACPC. The key starting components, bis(methoxycarbonyl)cyclopentanone enantiomers, are readily available in high enantiomeric purity by enzymatic resolution.[124] After monohydrolysis and Curtius rearrangement, followed by removal of the oxo group, *trans*-2-ACPC enantiomers were obtained in good overall yield.

4. Enantioselective Syntheses

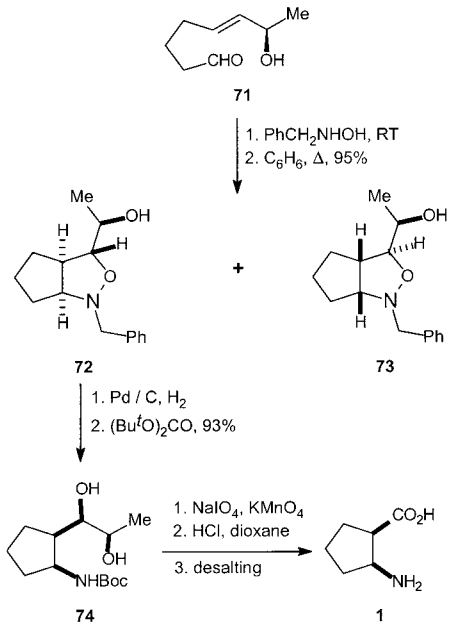
Homologues of (1*S*,2*S*)-*trans*-ACACs **70** have been prepared in a relatively short pathway by Enders et al.[125] By addition of the chiral ammonia equivalent lithiated (*S*)-(−)-2-methoxymethyl-1-trimethylsilylaminopyrrolidine (TMS-SAMP) to *ω*-halo-substituted enoate **67**, followed by the MIRC reaction, **68** was formed with 96−98% diastereoselectivity (Scheme 16). After desilylation, reductive *N*−*N* bond cleavage and hydrolysis of the ester and desalting with ion-exchange chromatography, **70** was obtained.[125,126]

The asymmetric synthesis of methyl (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-indenecarboxylate was reported to occur when the MIRC reaction was used with lithium (*R*)-(α-methylbenzyl)benzylamide as chiral nucleophile.[127] Asymmetric induction in the MIRC reaction has also been described with the use of chiral haloester auxiliaries.[96]

Konoshu and Oida described[128] a simple, but long enantioselective protocol from (*R*)-aldehyde **71**. It was transformed with *N*-benzylhydroxylamine to the nitrone, which underwent intramolecular cycloaddition to yield isoxazolidine **72** with high diastereoselectivity (**72**:**73** = 15:1). The cycloadduct **72** was transformed into natural cispentacin **1** in four steps: ring opening, protection, oxidation, and removal of the protecting group (Scheme 17).

Michael addition of a chiral amine to a cycloalkenecarboxylic acid derivative controls the new ste-

Scheme 17

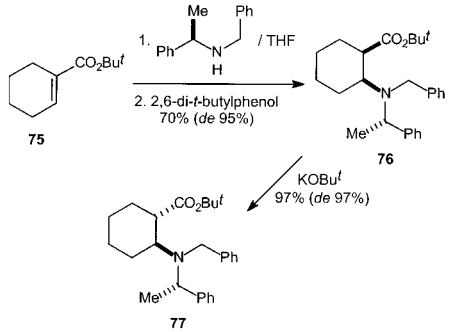


reogenic center[129,130] and is therefore suitable for the enantioselective synthesis of 2-ACHC. Davies et al.[131] made elegant use of this reaction, which is based in practice on the high diastereofacial control. Addition of lithium (*S*)-(α-methylbenzyl)benzylamide to *tert*-butyl 1-cyclohexenecarboxylate **75** at −95 °C, followed by quenching with 2,6-di-*tert*-butylphenol, gave **76** in 96−98% diastereomeric excess. Compound **76** was debenzylated by catalytic hydrogenation, and acidic hydrolysis was then afforded (1*R*,2*S*)-2-ACHC (Scheme 18).

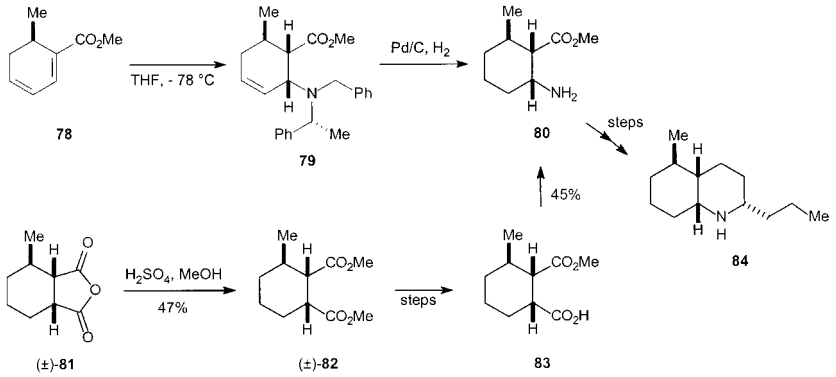
Compound **76** was easily isomerized to its C-1 epimer **77**, which after the above protocol gave (1*S*,2*S*)-2-ACHC in 97% diastereomeric excess.[131] A similar protocol was repeated with lithium (*R*)-(α-methylbenzyl)benzylamide enantiomer, and with the five membered systems, too, affording all four enantiomers of 2-ACHC and 2-ACPC.[131−133]

A versatile formal synthesis of (−)-pumiliotoxin C **84** has been achieved in six steps with an overall yield of 61%. The key step was the addition of lithium (*R*)-(α-methylbenzyl)benzylamide to methyl (*R*)-2-methyl-1,3-cyclohexadienecarboxylate **78**, derived from (*R*)-pulegone. After debenzylation, an advanced intermediate *β*-amino ester **80** toward pumiliotoxin C was formed.[134] By addition of the above chiral lithium amide to dimethyl (*E*,*E*)-octa- or -nonadienedioate,

Scheme 18



Scheme 19



by a diasteroselective domino reaction cyclic β-aminodicarboxylic acid derivatives have been prepared.[135] A similar tandem conjugate addition with menthyl ester has likewise been performed.[136]

An alternative synthetic pathway to amino ester **80** and after several steps to (−)-pumiliotoxin C **84** is shown also in Scheme 19. The synthesis starts from the readily available racemic anhydride **81**. After esterification and selective hydrolysis the single enantiomer **83** was obtained. This was transformed to amino ester **80** by diphenylphosphoryl azide-mediated Curtius degradation. Ester **80** was transformed to (−)-pumiliotoxin C **84** in several steps.[54,137] (+)-Pumiliotoxin C was also synthesized from pyrrolobenzodiazepine-5−11-dione via a cyclic β-amino acid intermediate.[138,139]

Another chiral natural substance, (+)- and (−)-α-pinene, is also a suitable starting substance for chiral cyclic β-amino acids. Chlorosulfonyl isocyanate underwent regio- and stereospecific addition to (+)- or (−)-α-pinene to give the enantiomerically pure β-lactams, which were converted with ethanolic HCl to enantiomers of ethyl 2-aminopinane-3-carboxylate (*ee* > 99%).[140]

A convenient route to enantiomerically enriched cyclic β-amino esters is the selective reduction of enantiopure β-enamino esters. Both enantiomers of α-methylbenzylamine are widely used to form β-enamino esters from β-ketoesters. Their reduction with sodium triacetoxyborohydride occurs with good diastereoselectivity. After separation of the diastereomers, the benzyl group can be removed by hydrogenolysis, giving the enantiomerically enriched β-amino esters.[141−143]

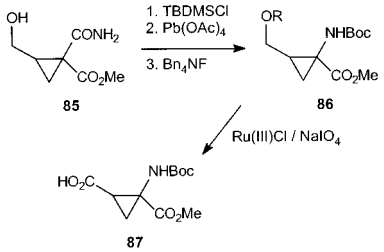
Further various enantioselective syntheses of differently substituted derivatives have also been described.[144−148]

B. Syntheses of Small Ring 2-Aminocarboxylic Acids

1. 2-Aminocyclopropanecarboxylic Acids

The unprotected β-aminocyclopropanecarboxylic acids are unknown to date, in consequence of the well-known tendency of donor acceptor-substituted cyclopropanes to undergo rapid ring opening reactions.[149] On the other hand, β-aminocyclopropanecarboxylic acids are the conformationally most rigid

Scheme 20



cycloalkyl bridged β-alanine derivatives and are therefore of special interest.[150]

The Curtius and Hofmann degradations that are widely applied for higher-membered analogues are also applicable for three-membered systems, with some modifications.

Csuk and Scholz prepared *N*-Boc-protected methyl 2-aminocyclopropanecarboxylate from dimethyl 1,2-cyclopropanedicarboxylate, which is easily obtainable from methyl acrylate and methyl chloroacetate. Pig liver esterase-catalyzed selective hydrolysis afforded the (1*S*,2*R*) monoester with *ee* > 99%. Curtius degradation of the carboxyl moiety with diphenylphosphoryl azide in the presence of *tert*-butyl alcohol gave the desired *N*-Boc-protected methyl 2-aminocyclopropanecarboxylate.[151] The synthesis was also performed from the racemic monoester.[152] The cyclopropane derivatives were used for the synthesis of carbocyclic cyclopropanoid nucleoside analogues.[151−153] With the Curtius degradation, other methods too have been developed, resulting in differently protected aminocyclopropanecarboxylic acid derivatives.[154−157]

The synthesis shown in Scheme 20 is based on the Hofmann rearrangement of a protected cyclopropane-1,1-dicarboxylate. The free hydroxyl group of alcohol **85** was protected as silyl ether, and the resulting intermediate was subjected to Hofmann degradation with $Pb(OAc)_4$ in *tert*-butyl alcohol. Removal of the *O*-protecting group, followed by oxidation, resulted in the *N*-Boc-protected amino acid **87**.[158]

Another strategy with which to synthesize 2,3-methanoaspartic acid is by oxidation of the correspondingly substituted derivatives on the side-chain.[159,160] With dimethyloxosulfonium methylide, substituted thymines gave 2,4-diazabicyclo[4.1.0]-heptane-3,5-diones (cyclothymines), sodium hydroxide hydrolysis of which resulted in the corresponding

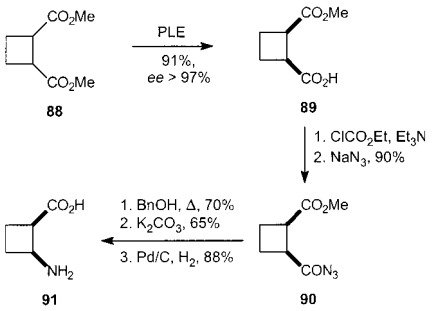
cis-2-ureidocyclopropanecarboxylic acids in excellent overall yields.[161]

1-[*N*,*N*-bis(Trimethylsilyl)amino]-1-propene can be cyclopropanated with methyl diazoacetate with copper(II)-acetylacetonate catalysis to afford the corresponding bis(trimethylsilylated) cyclopropanecarboxylate.[162] This amino acid has been incorporated into a dipeptide via CsF-mediated condensation with *N*-tosylated phenylalanine chloride.[163] The reaction of *N*-protected methyleneglycinates with ethyl diazoacetate in the presence of copper complexes gave the cyclopropanated amino diacids.[164]

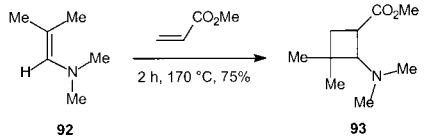
Cyclopropanation of *N*-protected pyrrole or furans with methyl diazoacetate, with copper(II) triflate and phenylhydrazine as catalyst, proceeds efficiently to furnish bicyclic adduct. Ring cleavage of these adducts by reductive ozonolysis and subsequent oxidation yields β-aminocyclopropanedicarboxylic acids.[149,165] Kinetic enzymatic resolution of the direct precursor bicyclic adduct was successful with pig liver esterase.[166] Lithiathion of *N*-Boc-*N*-alkylcyclopropylamines in the β position, followed by dimethyl carbonate treatment gave methyl 2-aminocyclopropanecarboxylates in yields over 60%.[167]

Although the inherent instability of free β-aminocyclopropanecarboxylic acid is known, a two-step synthesis of dimethyl 1-aminocyclopropane-1,2-dicarboxylate from dimethyl 1-bromo-1,2-cyclopropanedicarboxylate with potassium hexamethyldisilazane in liquid ammonia at −78 °C has been described.[168] It was later clearly proved by Taylor that the product was not the desired amino ester, but dimethyl 1-methoxycyclopropane-1,2-dicarboxylate.[169]

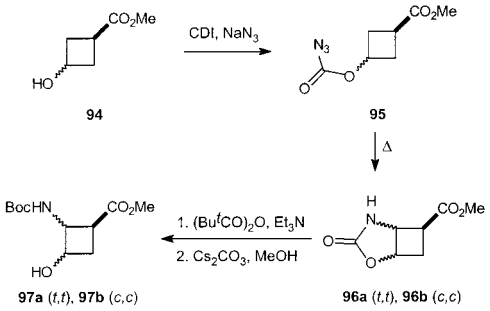
Scheme 21



Scheme 22



Scheme 23



2. 2-Aminocyclobutanecarboxylic Acids

As compared to β-aminocyclopropanecarboxylic acids, the four-membered homologues are more stable and the basic unsubstituted representatives are known. Curtius and Hofmann degradations are widely applied for the synthesis of four-membered systems.

As early as in 1972, *cis*- and *trans*-2-carbomethoxycyclobutanecarboxamide were smoothly rearranged with lead tetraacetate in methanol to the corresponding carbamates. The Hofmann hypohalide reaction failed with both three- and four-membered monoamides.[170] Later, the carbamates were hydrolyzed with sodium hydroxide, resulting after ion-exchange chromatography in the free racemic *cis*- and *trans*-2-aminocyclobutanecarboxylic acids.[171]

The Curtius rearrangement of methyl *trans*-2-chloroformylcyclobutanecarboxylate with sodium azide, followed by benzyl alcohol treatment, gave the Z-protected methyl *trans*-2-aminocyclobutanecarboxylate in excellent overall yield.[154] A stereoselective synthesis of (1*R*,2*S*)-2-aminocyclobutanecarboxylic acid was also performed by Ortuno et al.,[157,172] using the Curtius rearrangement (Scheme 21). Pig liver esterase-catalyzed desymmetrization of **88** gave monoester **89** with *ee* > 97%.[172] The Curtius rearrangement was performed in a stepwise manner by treatment of **89** with ethyl chloroformate followed by triethylamine. Heating in toluene with benzyl alcohol decomposed the resulting azide **90**. Hydrolysis and deprotection resulted in the free amino acid **90** with *ee* 91%. The hydrolysis step is crucial because of the easy epimerization of the product.[157,172]

Cycloaddition of isobutenylamine **92** with electrophilic olefins such as methyl acrylate gave β-aminocyclobutanecarboxylate **93** as early as in 1961[173] (Scheme 22). This reaction afforded the possibility of a wide variety of substitution on the cyclobutane ring.[174,175] Ring opening, ring enlargement, and side-chain reactions of this kind of product have also been studied.[176,177] Allylamines react with acryl esters in the presence of ruthenium complexes and *N*-methylpiperidine at 70 °C for 2 h, to give cyclobutane β-amino acid derivatives of **93**[178] up to 85% yield.

Reductive cleavage of thymine and thymidine dimers gave cyclobutane β-amino acid derivatives.[161,179] Cyclobutane-fused β-lactam ring opening also resulted in cyclobutane β-amino acid derivatives.[180]

An interesting new strategy was developed by Hansen et al.,[181] based on azidoformate ring closure to cyclobutane (Scheme 23). A mixture of *cis*- and *trans*-3-hydroxycyclobutanecarboxylates **94** was transformed to azidoformates **95** and was thermally cyclized to oxazolidinone **92**. The cis and trans isomers were separated in this phase; then, after Boc protection and careful cleavage of the carbamate moiety, 3-hydroxy-substituted β-aminocyclobutanecarboxylate isomers **97a** and **97b** were obtained. They were transferred to dipeptides and incorporated into a longer peptide sequence.[181]

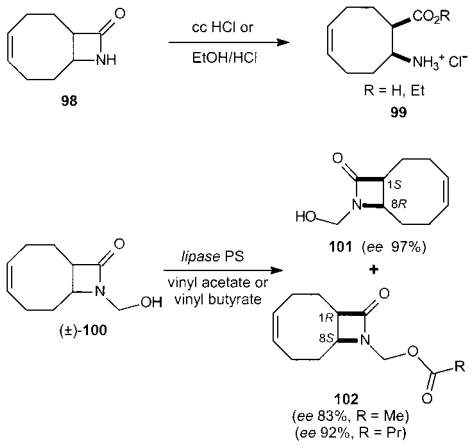
C. Syntheses of 2-Aminocycloheptanecarboxylic Acids and Larger Ring Analogues

Very few examples are available of the synthesis of cyclic β-amino acids with seven-membered or larger rings. Of the basic unsubstituted amino acids, only *cis*- and *trans*-2-aminocycloheptanecarboxylic acid and *cis*-2-aminocyclooctanecarboxylic acid are known.

cis-2-Aminocycloheptanecarboxylic acid has been prepared in a similar way to the six-membered analog: by Hofmann degradation of the monoamide obtained from cycloheptane-1,2-dicarboxylic anhydride. The trans counterpart was prepared from 1-cycloheptenecarboxylic acid by ammonia addition.[182] Further *N*-substituted trans derivatives were obtained from Z-protected amino acids with mixed anhydride methods, using isobutyl chloroformate and the corresponding amine, or by benzylamine addition to 1-cycloheptenecarboxylic acid.[62,183] The MIRC reaction of methyl or ethyl (*E*)-8-halo-2-octanoate has furnished *N*-substituted trans amino esters.[96,97] The MIRC reaction has also been successfully used for the preparation of (1*S*,2*S*)-2-aminocycloheptanecarboxylic acid, with SAMP as chiral ammonia equivalent.[125] A mixture of ethyl *cis*- and *trans*-2-amino-5-cycloheptenecarboxylates has been prepared from the corresponding ketoester with sodium cyanoborohydride in the presence of ammonium nitrate.[184] A polysubstituted 2-aminocycloheptanecarboxylic acid was synthesized from the corresponding cycloheptene by CSI addition resulting in a β-lactam, followed by 12% hydrochloric acid treatment.[185]

From racemic 9-azabicyclo[6.2.0]dec-4-en-10-one **98**, obtained from cyclooctadiene by CSI addition and ring opening with cc HCl or ethanolic HCl, *cis*-2-aminocyclooct-5-enecarboxylic acid and the corresponding ethyl ester have been prepared. Cyclohexene-mediated transfer hydrogenation led to the saturated analogues of **99**. The racemic hydroxymethylated lactam **100** was resolved through lipase PS-catalyzed acetylation with *S* selectivity, resulting in lactam enantiomers **101** and **102** (Scheme 24). The ethanolic HCl treatment of **101** and **102** gave ethyl 2-aminocyclooct-5-enecarboxylate hydrochloride enantiomers, which were reduced to ethyl 2-aminocyclooctanecarboxylate hydrochloride enantiomers.[186] The synthesized substances are potential starting compounds in anatoxin-*a* synthesis.

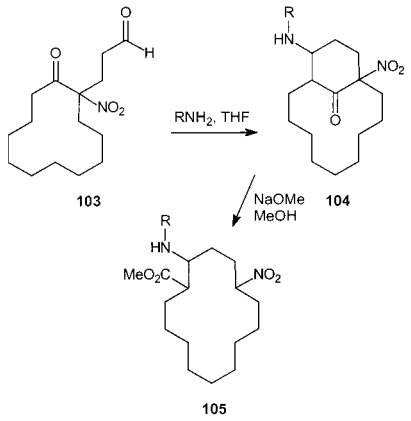
Scheme 24



The addition of CSI to cyclononadiene resulted in the corresponding lactam, which was hydrolyzed and reduced to 2-aminocyclononanecarboxylic acid hydrochloride.[187] The configuration of the reduced amino acid was not determined.

Methyl 5-nitro-2-alkylaminocyclotetradecanecarboxylates **105** (R = *n*-C_3H_7, *n*-C_5H_{11}, CH_2Ph) have been prepared in over 50% overall yields by treatment of aldehyde **103** with amine followed by sodium methoxide[188] (Scheme 25). The relative configurations were not determined.

Scheme 25



III. Transformations

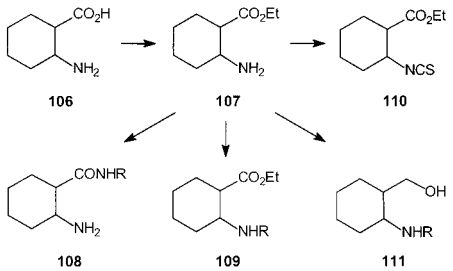
A. General Reactions, Characterizations

A number of simple transformations on the amino and carboxyl functions of cyclic β-amino acids have been carried out under practically the same conditions as for α-amino acids. Examples are shown on 2-ACHC **106** in Scheme 26.

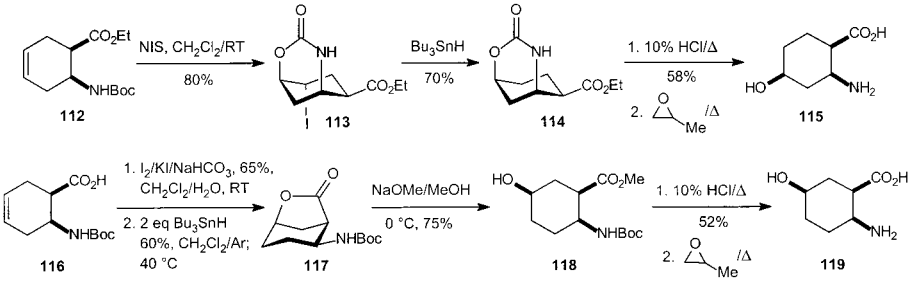
For esterification of the carboxyl function, besides the acid-catalyzed reflux with an alcohol,[189] the best procedure is the use of thionyl chloride and absolute alcohol at −5 to −10 °C (see e.g., refs 190, 191).

The *N*-unsubstituted or *N*-methyl-substituted carboxamide **108** can be prepared from the ester **107** with methanol containing 25% ammonia or methylamine.[192−194] Further *N*-substituted derivatives of **108** were obtained from Boc- or Z-protected amino acids with a mixed anhydride method, using isobutyl chloroformate and the corresponding amine.[183,195−199] From ester **107** with hydrazine, the hydrazides have been produced.[200] Alkylation of the amino group of β-amino acids can be performed easily: reductive

Scheme 26



Scheme 27



alkylation on the amino group with oxo compounds and sodium borohydride afforded *N*-alkyl-substituted derivatives **109**.[62,201,202] The amino group in **107** was readily transformed to a thiocyanate **108** with thiophosgene in the presence of triethylamine.[203,204] Lithium aluminum hydride reduction can be performed either on the acid **106** or under milder conditions on the ester **107**, or on their *N*-acyl derivatives**,** in diethyl ether or THF, which results in excellent yields of the corresponding amino alcohols **111** (Scheme 26) (see e.g., refs 205−207).

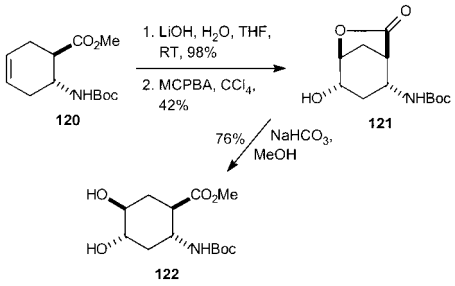
Treatment of *cis*- or *trans*-2-ACPC with $POCl_3$ and subsequent Friedel−Crafts acylation gave the synthetically widely applicable 2-benzoylcyclohexylamine diastereomers.[208] The carboxyl function can also be transformed to aldehyde via reduction to alcohol, followed by Swern oxidation.[209]

By functionalization of the alicyclic ring, a number of further ring-substituted derivatives can be prepared. The double bond in 2-amino-4-cyclohexenecarboxylic acid derivatives offers an excellent possibility to introduce one or two hydroxy groups.[75,210,211] Functionalizations on the ring may lead to pharmaceutically important natural substances such as fortamine,[212] thienamycin,[74] or aminocarba-sugars.[212]

A simple hydroxylation technique resulting selectively in a product hydroxylated in both positions 4 and 5 is shown in Scheme 27. The reaction of *N*-Boc derivative **112** with *N*-iodosuccinimide resulted in bicyclic oxazinone **113**, which was dehalogenated with tributyltin hydride to **114**. Ester **114** was hydrolyzed with dilute hydrochloric acid and desalted with propylene oxide, resulting in the *all-cis* isomer of 2-amino-4-hydroxycyclohexanecarboxylic acid **115**. Stereoselective iodolactonization was the key step in the synthesis of **119**. The reaction of *N*-Boc amino acid **116** with I_2/KI in slightly alkaline medium produced iodolactone, which was reductively dehalogenated to lactone **117**. Alkaline methanolysis gave ester **118,** which was easily converted to the *all-cis* isomer of 2-amino-5-hydroxycyclohexanecarboxylic acid **119**. The syntheses were also performed by starting from the trans counterparts.[213]

When Boc-protected trans ester **120** was hydrolyzed to acid and treated with *m*-chloroperbenzoic acid in situ, cyclization of the epoxide provided the hydroxy lactone **121** as a single diastereomer. Subsequent mild methanolysis led to tetrasubstituted cyclohexane **122**[214] (Scheme 28). Starting from the cis ester, the corresponding trans epoxide has also been synthesized.[215] The hydroxy function on the 2-ACHC derivative was transformed to amine, to

Scheme 28



produce a building block for water-soluble helix-forming β-peptides.[216]

The oxidation of *N*-Boc-protected methyl *diendo*-3-aminobicyclohept-5-ene-2-carboxylate has yielded an aminocyclopentanetricarboxylic acid derivative with *all-cis* substituents. This substance can be used as a scaffold in combinatorial chemistry.[217]

A simple HPLC method was developed for the separation and identification of the (1*S*,2*R*), (1*R*,2*S*), (1*S*,2*S*), and (1*R*,2*R*) enantiomers of 2-ACPC by using precolumn derivatization with the chiral derivatizing reagents *N*-(2,4-dinitro-5-fluorophenyl)-L-alaninamide (Marfey's reagent) and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate.[218] Analogue and homologue derivatives can also be detected by this method.[219,220] A newly developed derivatizing agent DANI, (1*S*,2*S*)-1,3-diacetoxy-1-(4-nitrophenyl)-2-propylisothiocyanate, likewise proved highly applicable for precolumn derivatization.[221] The two enantiomers of cispentacin can be determined in rat urine by reverse-phase HPLC after derivatization with Marfey's reagent.[222] Direct separation of cyclic β-amino acids was performed by using a new chiral stationary phase containing a macrocyclic glycopeptide antibiotic, covalently bonded to silica gel microparticles.[223]

The mass spectral fragmentation of a number of cyclic β-amino acids has been studied under electron ionization by low- and high-resolution, metastable ion analysis and collision-induced dissociation techniques. The major fragmentation pathway for saturated compounds began as an α-cleavage reaction with respect to the nitrogen. For unsaturated compounds, the retro-Diels−Alder reaction is favored.[224]

Physicochemical data such as dielectric increments,[225] partial molar volumes[226] and dissociation,[227] protonation, and complex formation constants[228] have been determined for cyclic β-amino acids. The spontaneous hydrolyses of different esters of cyclic β-amino acids have also been studied kinetically.[229]

Figures 1−10 show perspective views of structures containing a cyclic β-amino acid unit, determined by

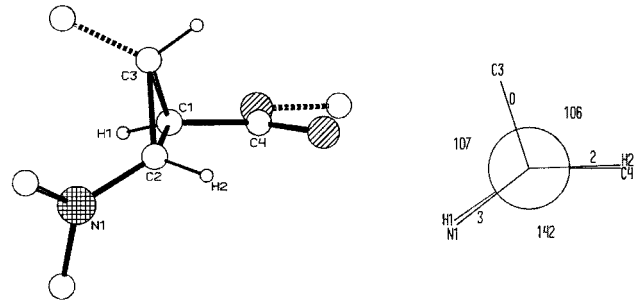


Figure 1. Cyclic β-amino acid unit in methyl 2-formyl-3-[(*N*-*tert*-butoxycarbonyl-*N*-formyl)amino]cyclopropane-1-carboxylate.[165]

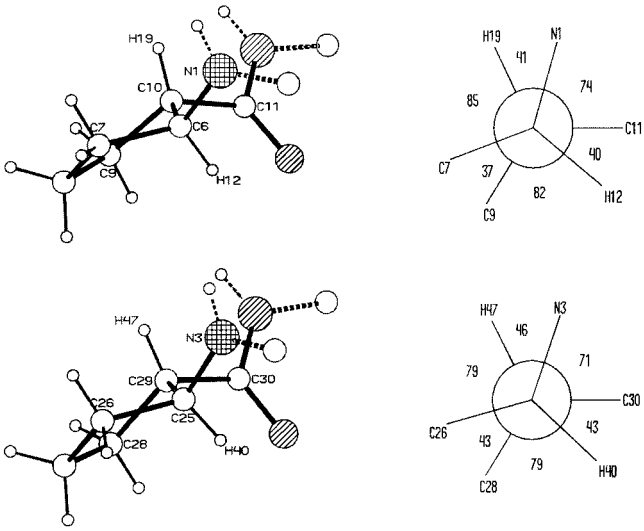


Figure 2. Cyclic β-amino acid unit in *N*-(*tert*-butoxycarbonyl)-(1*R*,2*R*)-2-aminocyclopentanecarbonyl-(*R*)-α-methylbenzylamine.[60]

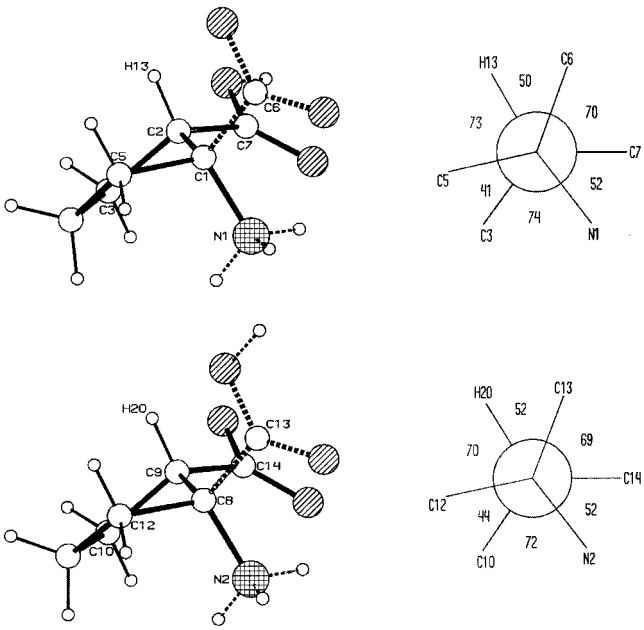


Figure 3. Cyclic β-amino acid unit in *cis*-1-amino-1,2-cyclopentanedicarboxylic acid monohydrate.[99]

X-ray diffraction, together with Newmann projections. The data were collected from the Cambridge Crystallographic Data Centre.[60,90,99,106,136,165,230,276] An

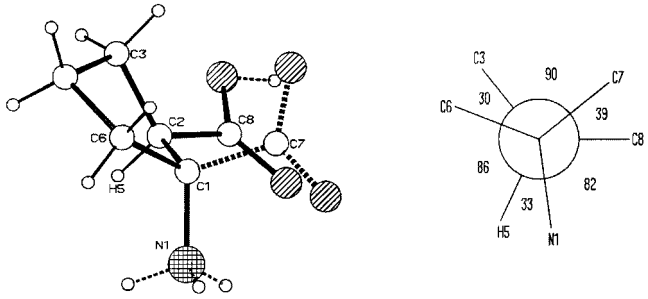


Figure 4. Cyclic β-amino acid unit in *trans*-1-amino-1,2-cyclopentanedicarboxylic acid monohydrate.[99]

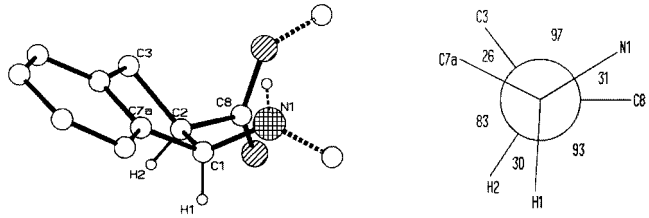


Figure 5. Cyclic β-amino acid unit in ethyl (1*R*,2*R*)-1-[(1′*S*,2′*S*)-1′,3′-diacetoxy-1′-(4′-nitrophenyl)-2′-propylthiocarbamoylamino]indane-2-carboxylate.[90]

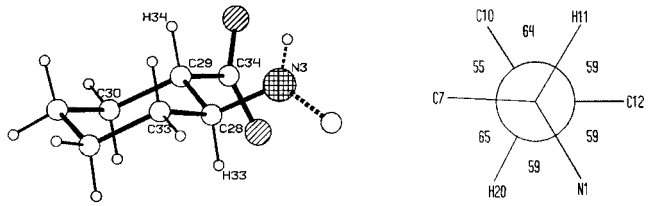


Figure 6. Cyclic β-amino acid unit in quininium *N*-benzoyl-*trans*-2-aminocyclohexanecarboxylate dihydrate.[106]

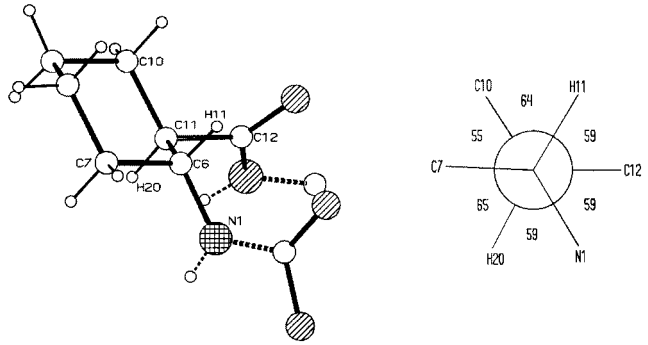


Figure 7. Cyclic β-amino acid unit in benzyl *tert*-butoxycarbonyl-tris(2-aminocyclohexanoyl)-2-aminocyclohexanecarboxylate 1,2-dichloroethane solvate.[106]

attempt has been made to organize the perspective views so that the conformation of the alicyclic ring can be seen. The Newmann projections showing the dihedral angles data are given for C(1)−C(2). When the structures are more complex, only the cyclic β-amino acid unit is given. If symmetry-independent molecules were found in the solid state, both structures are given. When more cyclic β-amino acid units exist in the molecule, the average values are given on the Newmann projections. The data may help in the programmable planning of folded peptide structures and also promote an understanding of the reactivities.

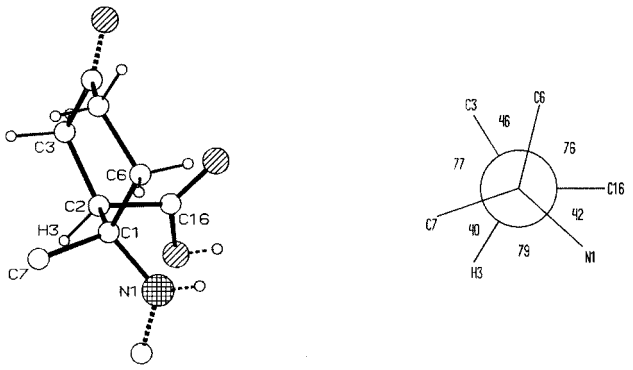


Figure 8. Cyclic β-amino acid unit in (1*R*,2*S*)-2-benzamido-2-methoxycarbonylcyclohexan-5-one-1-carboxylic acid.[230]

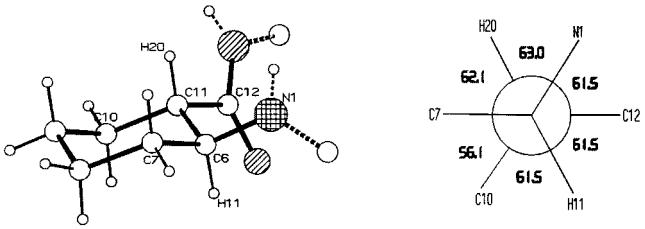


Figure 9. Cyclic β-amino acid unit in benzyl *tert*-butoxycarbonyl-pentakis(2-aminocyclohexanoyl)-2-aminocyclohexanecarboxylate methanol 1,2-dichloroethane solvate.[276]

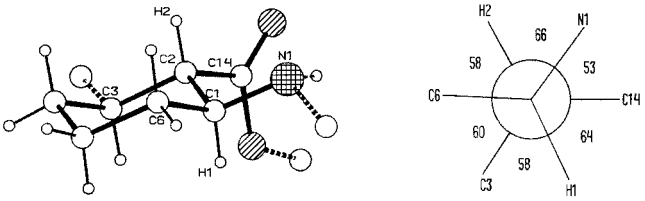


Figure 10. Cyclic β-amino acid unit in (−)-menthyl 3(*S*)-(*N*-benzylamino)-2(*S*)-(−)-menthoxycarbonyl-1(*S*)-cyclohexane-1-acetate.[136]

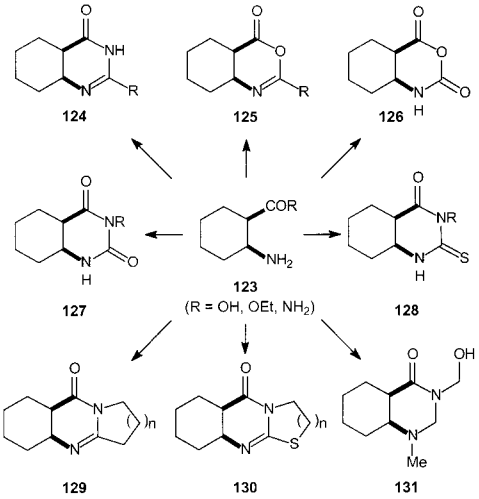
B. Transformations to Heterocyclic Compounds

The synthesis, stereochemistry, and transformations of cyclopentane-, cyclohexane-, cycloheptane-, and cyclooctane-fused 1,3-oxazines, 1,3-thiazines, and pyrimidines have recently been reviewed. Many of these syntheses started from cyclic 2-ACACs or their derivatives[231] and have already been discussed. Accordingly, only the most important and most recently published transformations to heterocycles will be mentioned here. Scheme 29 presents the most important syntheses to 1,3-heterocycles on the example of *cis*-2-ACHC derivatives **123**.

A number of 2-substituted pyrimidinones **124** have been synthesized by reaction of the corresponding β-amino acid **123** (R═OH) or its derivatives (R═OEt, NHR) with imidates, or by the reaction of ortho esters with carboxamide **123** (R═NH_2).[109,193,196,232,233] Of this set of compounds, the racemic 2-(*m*-chlorophenyl)-3,4a,5,6,7,7a-hexahydrocyclopenta[*d*]pyrimidin-4(3*H*)-one (CHINOIN 143) displayed excellent antiinflammatory activity.[234] The ring closure reaction in some cases takes place with epimerization next to the carbonyl group.[109]

Hexahydro-3,1-benzoxazin-4-ones **125** were prepared from *N*-acylated cyclic amino acids, by ring

Scheme 29



closure with $SOCl_2$ or DCC.[235−237] The substances readily react with alcohols and amines to give the corresponding esters or amides. Anhydrides **126** were also prepared from the *N*-Boc-protected amino acid by treatment with $SOCl_2$[238,239] or by hydrolysis of β-isocyanatocarboxylic acid trimethylsilyl esters.[240,241]

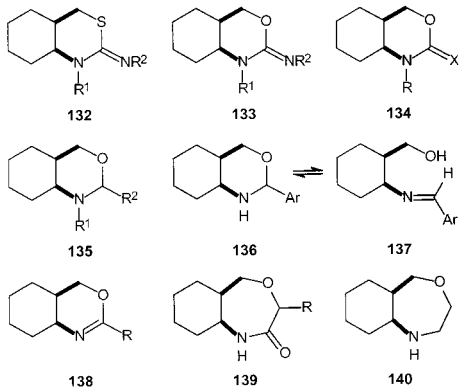
The reactions of amino ester **123** (R═OEt) with potassium cyanate or phosgene afforded pyrimidine-2,4-dione **123**, while those with potassium thiocyanate led to 2-thioxopyrimidin-4-one **128**.[201,242−244] When acid or ester **123** was reacted with phenyl or methyl isothiocyanate or isocyanate, urea or thiourea adducts were formed, which underwent ring closure without difficulty when reacted in the presence of acid or base, resulting in *N*-substituted pyrimidinones **127** and **128**, respectively.[194,201,245] Further derivatives of **127** were prepared from carboxamide **123** (R═NH_2) by cyclization with 1,1′-carbonyldiimidazole.[195,197] An alternative route to **128** involves the treatment of 2-isocyanatocyclopentanecarboxylates with amines.[203,204]

With lactim ethers, acid **123** gave tricycles **129** (*n* = 1−3),[246] while ester **123** related with haloalkyl isothiocyanates to produce sulfur-containing tricycles **130** in a domino cyclization reaction.[247] With a formaldehyde-formic acid mixture, the carboxamide of **123** gave perhydroquinazoline **131**.[248] A number of further transformations of homologous alicyclic amino acids to furnish various heterocycles have been described.[249,250]

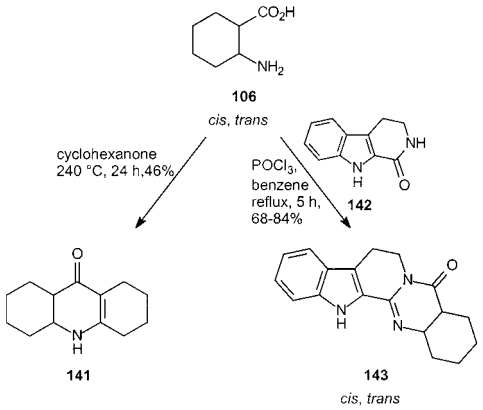
Alicyclic amino alcohols, obtained in a facile way from amino acids by lithium aluminum hydride reduction, are also useful starting substances for different heterocycles.[231] On the example of 2-hydroxymethylcyclohexylamine derived from *cis*-2-ACHC, Chart 3 shows without details some typical representative 1,3-heterocycles **132**−**140** that have been prepared. A number of further transformations of homologue and analogue alicyclic amino alcohols have been carried out to furnish various heterocyclic compounds.[48−50,89,191,202,207,208,251−253]

Ring-chain tautomerism **136** ⇌ **137**, which is a typical process for 1,3-oxazines, has been studied in detail.[254] For a discussion of the ring-chain tautomerism of 1,3-heterocycles derived from alicyclic 1,3-amino alcohols, see, for example, ref 255.

Chart 3



Scheme 30



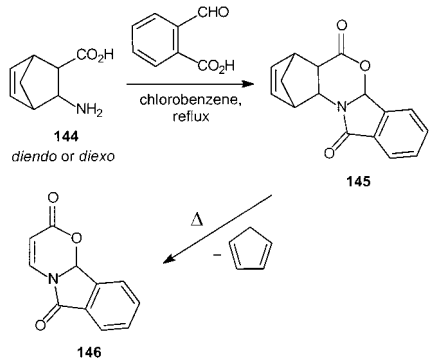
When *cis*-2-ACHC **106** is heated with cyclohexanone to over 200 °C, tricyclic 1,2,3,4,5a,6,7,8,9,9a-decahydroacridone **141** is formed; probably as a consequence of the very high-temperature applied, the fusion configuration in the product is changed to trans.[256] In a similar way, *cis*- and *trans*-hexahydrorutecarpine **143** have been synthesized from 1,2,3,4-tetrahydro-1-oxo-*β*-carboline **142** with *cis*- and *trans*-2-ACHC.[32,189]

Tetracyclic bicyclo[2.2.2]octanyl-1,4-benzodiazepinones have been prepared from *trans*-3-aminobicyclo-[2.2.2]octane-2-carboxylic acid by reaction with 2-fluoronitrobenzenes, followed by reductive cyclization.[257] The sodium borohydride-induced reductive cyclization of a substituted 2-trichloroacetamido-3-cyclopentenecarboxylate resulted in the corresponding unsaturated bicyclic lactam.[258] In the synthesis or decomposition of some more complex alkaloids such as clivonine, clividine, gelsemine, and aflatoxin B, cyclic *β*-amino acids are likewise used.[173,259−261]

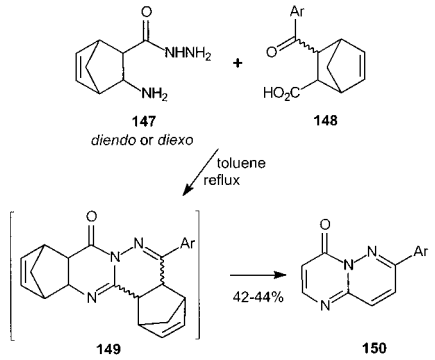
The reactions of 2-carboxybenzaldehyde with amino acids **144** led to the isoindolo[2,1-*a*][3,1]benzoxazines **145**. When heated, **145** undergo retrodiene decomposition by splitting off cyclopentene to give 1,3-oxazino[2,3-*a*]isoindole derivative **146**[262] (Scheme 31).

A number of heteropolycycles containing a pyrimido[1,2-*b*]pyridazine moiety have been obtained from 2-aminocarbohydrazides.[200,263] In the most interesting case, *diendo* or *diexo* hydrazide **147** was reacted with 3-aroylnorbornenecarboxylic acid **148** in boiling toluene and yielded pyrimido[1,2-*b*]pyridazine derivative **150** directly in a double retro Diels−Alder process[263] (Scheme 32). The retro Diels−Alder reaction is typical for *diendo* or *diexo* norbornene-fused heterocyclic systems and provides an easy route and new synthetic strategy for the preparation of heterocycles.[231,263]

Scheme 31



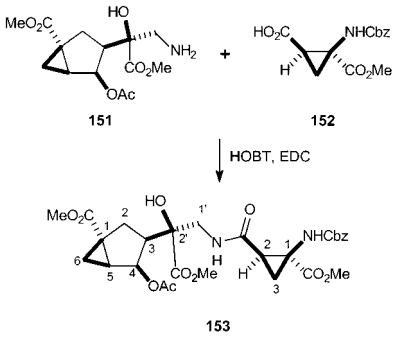
Scheme 32



C. Applications in Peptide Syntheses

Cyclic *β*-amino acids are used as mimetics of some α-amino acids or as newly designed structural units. The standard methods of everyday peptide syntheses can be utilized for the synthesis of peptides containing one or more cyclic *β*-amino acid units. There are examples of both liquid-phase and solid-phase techniques. The customary protecting groups Z, Fmoc, and Boc can readily be applied. The synthesis in most cases starts from the enantiomeric *β*-amino acid, but racemates are often utilized, and, in a certain stage, generally at the end of the synthesis, the diastereomers formed are separated by using HPLC or other techniques. For assignment of the absolute configuration, NOEs and vicinal ^{1}H-^{1}H coupling constants for H−N−C−H groupings can be utilized, for example. In some cases, the diastereomers are not separable. Racemization during the synthesis is not typical. In general, cyclic *β*-amino acids are stronger bases and weaker acids, but do not exhibit any unusual behavior as compared to α-amino acids during peptide syntheses. The only exceptions are cyclopropane derivatives, where the three-membered ring is extremely unstable and sensitive to epimerization at the *N*-substituted stereocenter on the cyclopropane, due to ring opening−ring closure sequences.[264] Of the considerable number of synthetic applications, only a few typical ones are selected for presentation here; the syntheses are discussed in the sequence of increasing ring size of the cyclic *β*-amino acid moiety.

Scheme 33



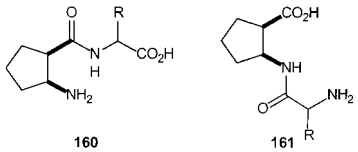
151 152 153

A series of extremely sensitive cyclopropanes have been incorporated to replace the Gly−Gly and Phe−Leu subunits in Leu−enkephalin (H_2N-Tyr−Gly−Gly−Phe−LeuOH), which is believed to bind to opiate receptors in a conformation containing a β-turn.[265] Those derivatives in which cyclopropane has replaced Gly−Gly exhibit only a low micromolar affinity for the μ-receptor. An interesting dipeptide mimetic has been synthesized that contains isoserine and cyclopropane β-amino acid moieties. The last step of the synthesis was the coupling of isoserine **151** with **152** by using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt), resulting in a highly rigid dipeptide surrogate **153**[266] (Scheme 33).

An in situ coupling strategy has been introduced by Reiser et al.,[266] which allows the incorporation of *cis*- and *trans*-β-aminocyclopropanecarboxylic acids into peptide **159** (Scheme 34). The coupling of **155** with *N*-Boc-Gly activated by EDC in the presence of Et_3N was carried out in dichloromethane to keep the epimerization minimal. The tripeptide involving trans substitution has also been synthesized.[264] Another novel strategy has been developed for the synthesis of peptides containing 2,3-methanoaspartic acid, by oxidation of the corresponding 2,3-methanoserine-derived peptides.[160]

Six dipeptide derivatives of (±)-*cis*-2-ACPC have been synthesized to investigate the antifungal activity of cispentacin derivatives. During the syntheses, Z-protected (±)-*cis*-2-ACPC was used, which was activated with isobutyl chloroformate; after coupling and deprotection, the carboxamides **160** were obtained. *N*-Acyl derivatives **161** have been prepared

Chart 4

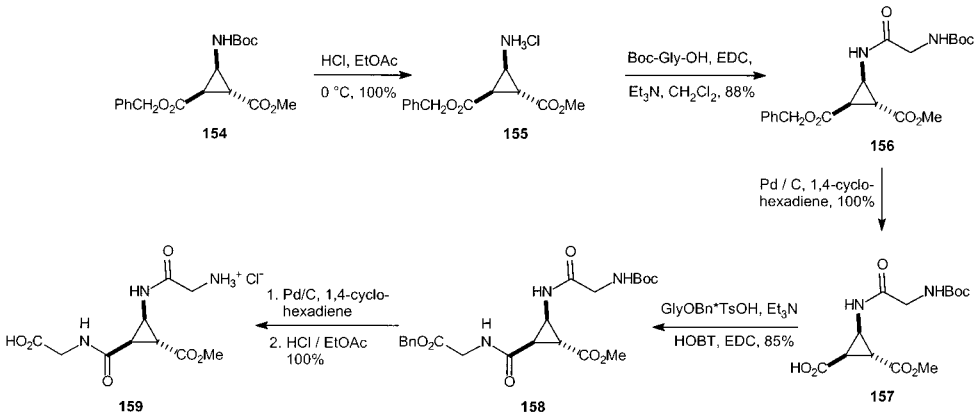


160 161

from the methyl ester of (±)-*cis*-2-ACPC, which was acylated with Boc-amino acid, followed by hydrolysis and deprotection. Gly and Phe were used as α-amino acid component in the synthesis. The diastereomers formed in the syntheses of **160** and **161** were not separated, but in a few cases the syntheses were performed from enantiomeric *cis*-2-ACPC. Both L-Phe derivatives of (1*R*,2*S*)-2-ACPC **160** and **161** exhibited excellent antifungal activity against *Candida albicans*.[267] Goodman et al.[60] investigated the structure−taste relationships of L-aspartyl dipeptides, preparing all four isomers of methyl L-aspartyl-2-aminocyclopentanecarboxylate. The syntheses started from racemic cis and trans Boc-protected ACPC. After esterification, the methyl ester was coupled to *N*-benzyloxycarbonyl-β-benzyl-L-aspartate, HOBt and EDC being used. The diastereomeric pairs were separated by reverse-phase HPLC. The determination of the absolute configuration was based on NMR measurements, but the configuration was also proved by synthesis, starting from the enantiomers of 2-ACPC. In agreement with the results of conformational studies and model calculations, the (1*R*,2*R*) and (1*S*,2*R*) ACPC derivatives have L-shaped conformations and a sweet taste. The (1*S*,2*S*) derivative has a bitter taste, whereas the (1*R*,2*S*) derivative is tasteless, as predicted.[60,268]

Eight morphiceptine analogues (Tyr-(1*R*,2*S*)-ACPC-Phe-Val-NH_2, Tyr-(1*S*,2*R*)-ACPC-Phe-Val-NH_2, Tyr-(1*R*,2*S*)-ACPC-Phe-D-Val-NH_2, Tyr-(1*S*,2*R*)-ACPC-Phe-D-Val-NH_2, Tyr-(1*R*,2*S*)-ACPC-Phe-Pro-NH_2, Tyr-(1*S*,2*R*)-ACPC-Phe-Pro-NH_2, and Tyr-*trans*-ACPC-Phe-Pro-NH_2) containing *cis*- or *trans*-2-ACPC have been synthesized in which the proline in the second position was replaced.[269,270] The syntheses were performed in the solution phase and involved the use of racemic *cis*- or *trans*-2-ACPC, as shown in Figure 11. Pharmacological screening demonstrated that, of the proline analogues, Tyr-(1*R*,2*S*)-ACPC-Phe-Pro-NH_2 was active at both μ- and δ-opiate receptors, with a slight preference for μ-receptors. Of the valine ana-

Scheme 34



154 155 156 157 158 159

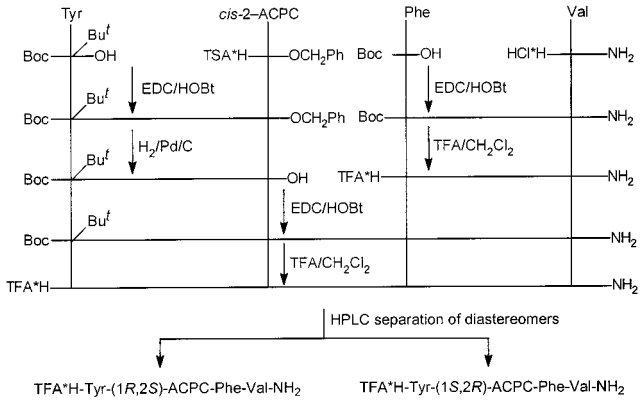


Figure 11. Synthetic scheme for 2-ACPC-containing morphiceptine analogues.

logues, the (1*S*,2*R*) residue-displayed activity at the μ-receptor, but was inactive at the δ-receptor, resulting in a high μ-selectivity. A comparison of the conformational analysis findings and the biological results helped to improve the structure−activity relationship of this important peptide opiate.[269,270]

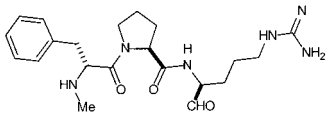
Hydroxamate inhibitors containing cyclic β-amino acids have been synthesized for further characterization of subsite S_2' of both neutral endopeptidase (NEP) and aminopeptidase (APN). *tert*-Butyl esters of racemic *trans*-2-ACPC and *cis*- and *trans*-2-ACHC were used in the syntheses. The diastereomeric products were separated by chromatography on silica gel. All the cyclic β-amino acid-containing compounds synthesized are highly efficient inhibitors of NEP and APN, exhibiting inhibitor activity in the same range.[271]

For investigation of the structural role played by the Phe[11]−Pro[6] bridging region in the cyclic hexapeptide analogue of somatostatin, c[Pro[6]-Phe[7]-D-Trp[8]-Lys[9]-Thr[10]-Phe[11]], a series of cyclic hexapeptide analogues containing 2-ACPC as proline mimetic have been synthesized.[272] In the final step, the diastereomers were separated by preparative HPLC. The synthesized analogues contain a trans amide bond in the bridging region, which leads to the loss of binding activity.[272]

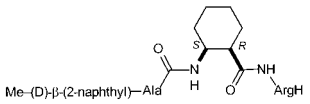
A series of cholecystokinin analogues [Ac-CCK-7: Ac-Tyr(SO_3H)-Met[28]-Gly[29]-Trp-Met-Asp-Phe-NH_2] have been prepared, in which the dipeptide Met[28]−Gly[29] was replaced by unnatural amino acids. The analogue incorporating (1*S*,2*S*)-*trans*-2-ACPC proved highly effective in the binding assays and as an anorectic agent.[121]

cis- and *trans*-ACHC, *cis*- and *trans*-2-amino-4-cyclohexenecarboxylic acid, *diendo*- and *diexo*-3-aminobicycloheptane- and -hept-5-ene-2-carboxylic acid were used to replace D-Ala[2] in the μ-specific opioid peptide dermorphin. The peptides were synthesized by solid-phase techniques, using Boc chemistry; the

Chart 5



162 GYKI 14766



163

couplings were performed with DCC. The pharmacological investigations revealed that insertion of the rigid ring structure in place of D-Ala[2] was in all cases unfavorable for both μ- and δ-binding activity.[273]

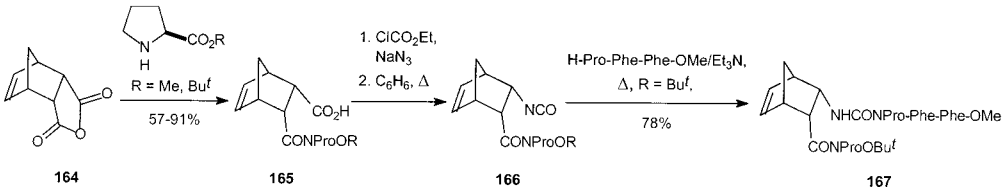
Replacement of the proline residue in GYKI 14766, **162**, with *cis*-2-ACHC gave rise to potent and selective thrombin inhibitors. At the same time, increasing the size of the *N*-terminal side-chain, which was proposed on the basis of model studies, led to the more active and much more selective thrombin inhibitor **163**.[274] A simple and elegant peptide synthesis involves a proline-induced desymmetrization of *endo*-norborn-5-ene-2,3-dicarboxylic anhydride **164** as a key step. Curtius rearrangement on the carboxylic function of **165** generated isocyanate **166**, from which a number of pseudopeptides were prepared. Scheme 35 illustrates only one example. Both peptide chains of **167** can be elongated by standard techniques, and the chains run parallel to one another.[119,275]

A high-affinity antagonist of the Grb2-SH2 domain was found by replacement of asparagine by *cis*-2-amino-3-cyclohexenecarboxylic acid in a selective antagonist, 3-NH_2-Z-*p*Tyr-Ac$_6$c-AsnNH_2, of this SH2 domain.[87] The solid-phase synthesis, based on Fmoc protocol, was used to prepare deltorphin analogues containing cis and trans 2- or 3- or 4-ACHC residues. The compounds prepared showed high resistance to degradation by plasma or brain enzymes.

A new pioneering chapter in peptide chemistry, the use of cyclic β-amino acids, was opened by the fundamental work of Gellman et al.[18,19,106,276−282] and Seebach et al.[21,22] They found that, whereas α-amino acids can adopt the well-known α-helical motif of proteins, β-peptides constructed from carefully chosen β-amino acids can adopt a different, stable helical conformation. Cyclic β-amino acids such as *trans*-2-ACPC and *trans*-2-ACHC can be used to design β-peptides with a very different secondary structure. This demonstrates that, through alteration of the nature of the β-peptide residues, rational control can be exerted over the secondary structure[18,19,106,276−282]

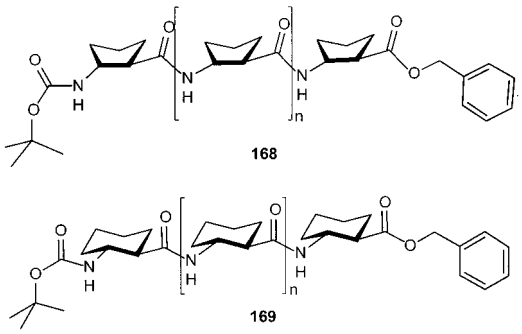
Helix-forming β-amino acid oligomers **168** and **169** were synthesized from enantiomerically pure (*R*,*R*)-

Scheme 35



164 **165** **166** **167**

Chart 6



trans-2-ACPC and (*R*,*R*)-*trans*-2-ACHC. The benzyl esters of Boc-protected amino acids were used, and the couplings were performed in solution with EDC in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP).[106,279] Besides theoretical calculations,[281] the structures were studied in the solid phase (X-ray) and in solution (NMR in pyridine or methanol; CD in methanol). It was clearly demonstrated that, in the solid phase, oligomers of *trans*-2-ACHC display a helical conformation that involves 14-membered ring hydrogen bonds between the carbonyl oxygen and the amide proton of the second residue toward the *N*-terminus. Both the X-ray data and the solution data suggest that the 14-helix is a stable secondary structure for cyclic β-amino acid oligomers (Figure 12). For *trans*-ACPC oligomers, the X-ray results show a helix of interwoven 12-membered ring hydrogen bonds. The solution structures were found to be very similar to those indicated by the X-ray results. The CD data reveal a strong length-dependent conformational preference of the oligomers.[106,279,280]

Water-soluble β-peptides containing pyrrolidine-based residues have a propensity to form 12-helixes.[283] It should be noted that a hairpin conformation (two strands connected via a short loop) is preferred for some peptide oligomers containing analogous heterocyclic β-amino acid residues.[284−286] β-Amino acid foldamers have potent bacteriostatic and bactericidal activity. The foldameric stability of β-peptides may lead to the emergence of a new class of antimicrobial agents.[19]

D. Applications in Combinatorial Chemistry

Although cyclic β-amino acids are often applied as building blocks in the synthesis of potential pharmacons for different areas of therapy,[70,93,209,287−297] they have not yet found equivalent use in the exponentially developing field of combinatorial chemistry. Relatively few papers have been published on them in this respect.

Cyclic β-amino acids have been used in a solid-phase combinatorial synthesis of 1,5-benzodiazepin-2-ones **177**. Scheme 36 presents the example of *cis*-2-ACPC. ArgoGel-Rink resin was used during the synthesis, which was straightforward, the only problem being the poor solubility of β-amino acids in these nonaqueous conditions. The overall yields were over 60%, and the purity was over 95% after RP-HPLC purification[298] (Scheme 36).

A liquid-phase combinatorial library synthesis of 2-thioxopyrimidinones **181** involved the use of methyl

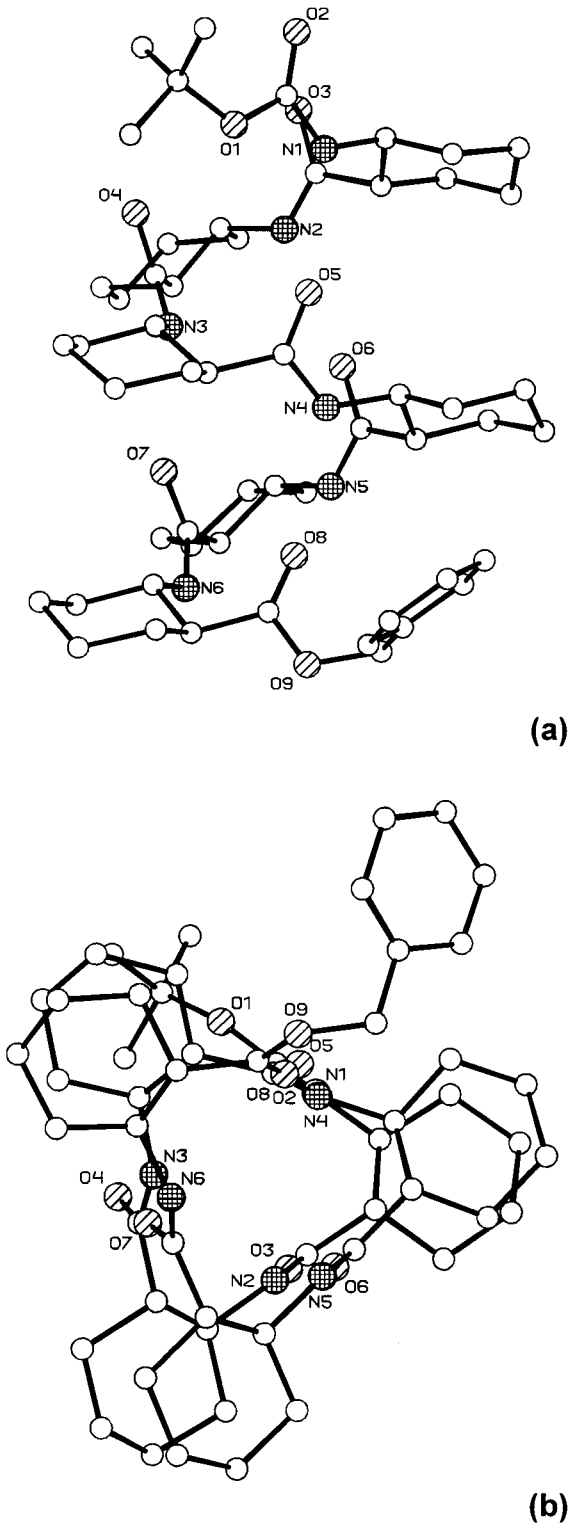
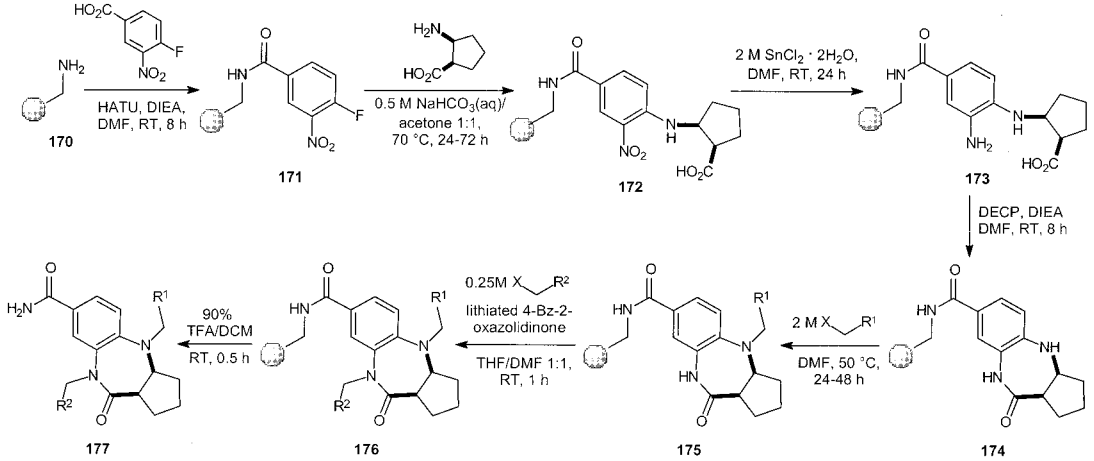


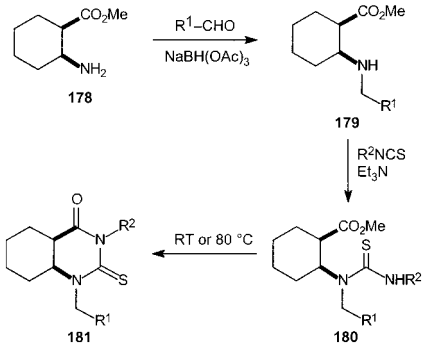
Figure 12. Solid-state structure of *trans*-2-ACHC hexamer **169.** (a) View of one of the three very similar molecules in the asymmetric unit. (b) View of one molecule along the helix axis.[106]

cis-2-aminocyclohexanecarboxylate **178**. Reductive alkylation with aromatic and heteroaromatic aldehydes was carried out on a large scale, and the division of the crude products into portions was followed by reaction with individual isothiocyanates. In some cases, depending on the isothiocyanate, the ring closure proceeded even at room temperature. In the workup procedure, aminomethylated polystyrene

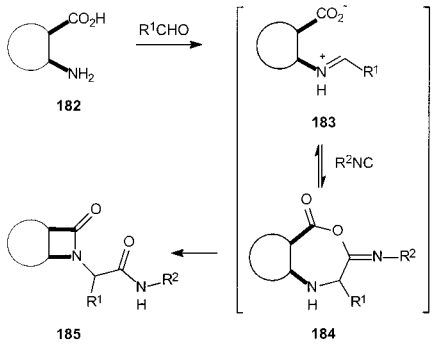
Scheme 36



Scheme 37



Scheme 38



was found to be appropriate for removal of the excess of aldehyde and isothiocyanate.[299]

Patek et al.[217] described the oxidative ring opening of *N*-Boc-protected methyl *diendo*-3-aminobicyclo-[2.2.1]hept-5-ene-2-carboxylate to furnish an amino-tricarboxylic acid. The applicability of solid-phase library synthesis was demonstrated by means of several simple model transformations.[217]

A mixture-based combinatorial synthesis was performed by utilizing the Ugi 4CR reaction. Compounds with a β-lactam backbone were formed when cyclic β-amino acids **182**, aldehydes and isonitriles were reacted by the Ugi reaction (Scheme 38). In the first step, the protonated Schiff base **183** was formed, and subsequent isocyanide addition resulted in azetidinone **185** via an oxazepinone intermediate.

A number of Rubik's cube type of libraries were successfully generated in solution with three different cis-β-amino acids, three different aldehydes and three different isonitriles (Figure 13). The solution-phase libraries were purified by column chromatography. All the compounds in the libraries were identified by MS-MS. After the hydrolytic or ethanolytic ring opening of β-lactams, the corresponding amino acid or ester derivatives were formed.[300]

In this reaction, only *cis*-amino acids were used successfully: *trans*-amino acids failed to cyclize since the magnitude of the ring strain prevents the formation of a *trans*-configurated β-lactam.

In combinatorial chemistry use, it is noteworthy that the ring closures of 1,2-disubstituted cyclohexane, cycloheptane, and cyclooctane derivatives revealed no appreciable differences in the reactivities of the cis and trans isomers in the formation of six-membered 1,3-heterocycles.[231] In contrast, striking differences were observed in the cyclizations of the cis and trans cyclopentane derivatives.[231]

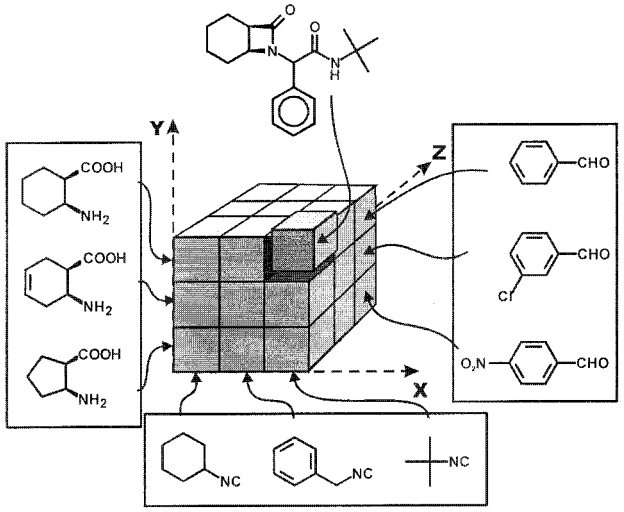
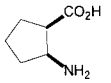
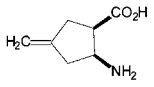


Figure 13. Example of a mixture-based combinatorial library synthesis presented by the Ugi 4CR reaction.

IV. Biological Effects

Ethyl (±)-*trans*-2-(dimethylamino)-1-phenyl-3-cyclohexene-1-carboxylate hydrochloride, Tilidine (Tilidate), is used in therapy as an opioid analgesic (Trade names: Findol, Grüntin, Lucayan, Tilidalor, Tiligetic, Tilitrate, Valomerck, Valoron, Valtran),[25,26] for the control of moderate to severe pain. As a deterrent to

Table 1. Comparison of Activities of Cispentacin and BAY 10-888[8310]

Structure Name	Molecular/Mechanistic activity	*In vitro* antifungal activity (MIC range, μg/ml)	*In vivo* antifungal activity
 Cispentacin	Inhibition of prolyl-tRNA synthetase and protein biosynthesis after concentrative uptake	*Candida* spp.: 8-50 *C. tropicalis*: 6.25->500 *Aspergillus* spp.: >500	100% survival at 20 mg/kg *p.o.* or *s.c.* twice daily in mouse candidiasis model. 100% survival at 50 mg/kg 3 doses in mouse lung candidiasis model. Weak efficacy in systemic *C. neoformans* infection model
 Bay 10-8888	Inhibition of isoleucyl-tRNA synthetase after concentrative uptake	*Candida* spp.: <0.25->32 *Aspergillus* spp.: not active	100% survival at 10 mg/kg *p.o.* twice daily in rat candidiasis model. Efficacy against fluconazole-resistant strains in mouse model of systemic candidiasis

abuse, a combined oral preparation of Tilidine with naloxone is available in some countries. Tilidine is absorbed from the gastrointestinal tract. It is metabolized mainly to nortilidine (ethyl (±)-*trans*-2-methylamino-1-phenyl-3-cyclohexene-1-carboxylate) and bisnortilidine (ethyl (±)-*trans*-2-amino-1-phenyl-3-cyclohexene-1-carboxylate). Nortilidine is responsible for the analgesic activity.[301]

In early studies, a number of amino acid derivatives of cycloalkanes were investigated, among them 2-ACPC, because of the tumor growth-inhibitory activity of 1-ACPC. Significant antitumor activity was exhibited only by compounds closely related to 1-ACPC.[302] Various γ-aminobutyric acid (GABA) analogues, among them *cis*- and *trans*-2-ACPC, were investigated as potential inhibitors of the GABA uptake in brain synaptosomes and in synaptic membrane vesicles.[303,304] *cis*-2-ACPC was found to be a potent inhibitor of the GABA uptake in the synaptosomes. The trans counterpart proved to be half as potent as the cis isomer.[304]

The other important cyclic β-amino acid is the antifungal cispentacin, which has been investigated thoroughly. Cispentacin demonstrated good therapeutic efficacy against a systemic *Candida* infection in mice following either parenteral or oral administration. It was also effective in a systemic infection with *Cryptococcus neoformans*, and in both lung and vaginal infections with *Candida albicans* in mice.[10,12] In acute toxicity experiments in mice, cispentacin did not display any lethality at a dose of 1 mg/kg administered by the iv route or at 1.5 mg/kg following ip or oral administration.[10] Cispentacin and its analogues have a dual mode of action. Cispentacin is rapidly accumulated in fungal cells by active transport via proline and other amino acid permeases, its mechanism of action therefore interfering with amino acid transport and the cellular regulation of the amino acid metabolism.[305−311] When the antifungal activities of certain homologue and analogue derivatives of cispentacin were investigated, it was found that, of the β-amino acids investigated, the five-membered ring derivatives displayed reasonable activities, whereas the cyclohexane and norbornane derivatives had no activity. Although more planar analogues, e.g., BAY 10-8888, which bears an exocyclic methylene group, are more potent, introduction of a double bond into the ring leads to a loss of activity. Several dipeptide derivatives of cispentacin also exhibit potent anti-candida activity, although it is not clear whether they are prodrugs of cispentacin.[267,309−311] The antifungal substance BAY 10-8888, (1*R*,2*S*)-2-amino-4-methylenecyclopentanecarboxylic acid, which blocks protein biosynthesis, is a promising candidate for further clinical development[310−312] (Table 1).

V. Summary and Outlook

The syntheses and transformations of some of the biological features of 2-aminocycloalkanecarboxylic acids have been reviewed. They are unique structures among β-amino acids. The examples presented demonstrate the wide range of their applicability. In the future, rapid progress is expected in some of their syntheses (desymmetrization and biocatalytic transformations). Although a number of reactions have been performed with these compounds, further transformations will almost certainly be of interest and their use as peptidomimetics is of high priority. Their oligopeptides are also expected to widen the fields of both their chemical and pharmacological use. With modifications in their rings, the syntheses of further natural substances may also be expected, and their utilization in combinatorial chemistry may also undergo fast progress.

VI. Acknowledgment

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