α,β-Dehydroamino Acids

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Abstract: Dehydroamino acids are versatile intermediates in organic synthesis and occur as frequent structural motives in natural products and biologically active compounds. This review summarizes recent work (since 1999) on the synthesis, reactions and applications of acyclic and cyclic α,β-dehydroamino acids, α,β-dehydroamino esters, and protected α,β-dehydroamino acids.

1 Introduction

α,β-Dehydroamino acids do not belong to the 20 natural proteinogenic amino acids, but they are found in nature in toxins and antibiotics. They play an important role in the biosynthesis of other non-proteinogenic amino acids and D-amino acids.

In the following, we give an overview of the recent literature on α,β-dehydroamino acids since 1999. For the topics that have not been comprehensively covered in the previous reviews on α,β-dehydroamino acids and α,β-dehydropeptides by Stammer (1982),1 Schmidt (1988),2 and Humphrey and Chamberlin (1997),3 the most important publications before 1999 have been included. Hydrogenation4–8 and cycloaddition reactions9 of α,β-dehydroamino acids are only covered briefly, because both topics were reviewed recently.

2 Synthesis of α,β-Dehydroamino Acids

Non-functionalized parent α,β-dehydroamino acids are enamines and are therefore susceptible to hydrolysis. Upon hydrolysis, ammonia is released and α-ketoacids are formed. Acylated derivatives and α,β-dehydroamino acids that are incorporated into peptides are more stable and can be prepared by several methods.

2.1 By Elimination Reaction

Elimination of water from β-hydroxy-α-amino acids is a well-established route to α,β-dehydroamino acids. This method has been used for the preparation of dehydroalanine (Δ1α) and dehydroaminobutanoate (Δ2α) from serine and threonine. Activation of the hydroxyl group for elimination can be achieved by various reagents, e.g. dichloroacetyl chloride/triethylamine,10 tosyl anhydride/1,4-diazabicyclo[2.2.2]octane (DABCO),11 triphenylphosphine/diethyl azodicarboxylate (DEAD),12 diethylaminosulfur trifluoride (DAST)/N,N-diisopropylethylamine (DIPEA),13 tosyl chloride14–17 and carbodiimide/copper(I) chloride.18 N-Ethyl-N,N'-[3-(dimethylaminomethyl)propyl]carbodiimide/copper(I) chloride conditions have been employed for α,β-dehydroamino acid synthesis in solution and on solid support,19–22 and were used in the synthesis of lantibiotics.23–25 A yield of up to 92% was reported for the elimination with Boc-anhydride and 4-(N,N-dimethylamino)pyridine (DMAP) by Ferreira.24 The anti-selective elimination gives only one of the two possible E/Z isomers (Z from the threo compound), but all amides become Boc-protected under the reaction conditions (Scheme 1).

Another method of stereoselective elimination was described by Wandless:26 the reaction of β-hydroxyamino acids with thionyl chloride gives cyclic sulfamidates. Subsequent elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) proceeds in an anti-periplanar fashion and yields selectively (E)- or (Z)-α,β-dehydroamino acids, depending on the configuration of the β-hydroxyamino ester. The reaction can be performed as a one-pot procedure, and even tertiary alcohols are stereoselectively trans-
formed into α,β-dehydroamino esters. The method is suitable for solid-phase peptide synthesis protocols. Acylation of threonine, dehydration and cleavage from aminomethyl polystyrene resin is possible using a linker developed by Chan.27 Yokokawa and Shioiri use Martin’s sulfuran28 as reagent to selectively dehydrate, for example, threonine in the presence of an O-acyl threonine.29,30 The oxidation of thio31,32 and seleno33,34 amino acids and subsequent thermolysis gives the corresponding dehydroamino acids in very good yields. Miao and Tam used a cysteine thioester ligation to prepare cysteine-containing peptides from unprotected peptide fragments. These compounds were then used as precursors to prepare cyclic and acyclic peptides with α,β-dehydroalanine at the point of ligation (Scheme 2, top).35 The peptide cleavage from the resin and the introduction of the α,β-dehydroalanine in a single step becomes possible with a seleno-linker, introduced by Nakamura (Scheme 2, bottom).36,37

Biographical Sketches

Christoph Bonauer was born in 1975 in Burghausen, Germany. He studied chemistry at the University of Regensburg and completed his diploma in 2000. Supported by a doctorate fellowship from the Fonds der Chemischen Industrie, he investigated heterocyclic peptide mimics for his dissertation in the group of Prof. König. In 2003, he was a JSPS fellow at Kyushu University, Japan, in the group of Prof. Shinkai. He completed his Dr. rer. nat. in 2004 and joined Procter and Gamble, Germany.

Thomas Walenzyk was born 1977 in Rüsselsheim, Germany. He completed his Bachelor of Science with Honours in Chemistry at Murdoch University, Australia, under the supervision of Prof. R. G. F. Giles in 1999. Thereafter, he spent two years working in Clinical Research before taking up a research position in cosmetic science at Merck KGaA, Germany. He completed his Ph.D. in chemistry at the University of Regensburg in the group of Prof. König in 2005, with research interests in organic/inorganic hybrids and the immobilization of biologically active substances. He is currently working as a research scientist at Procter and Gamble, Germany.

Burkhard König received his doctorate in 1991 from the University of Hamburg under the direction of Prof. de Meijere. He continued his scientific education as a postdoctoral fellow with Prof. M. A. Bennett, Canberra, and Prof. B. M. Trost, Stanford. In 1996, he obtained his ‘Habilitation’ at the University of Braunschweig. Since 1999, he is full professor of organic chemistry at the University of Regensburg. His current research interests focus on the development of synthetic receptors for peptide and protein recognition.
An aminohalogenation reaction to \( \alpha,\beta \)-unsaturated esters 3 followed by base treatment yields \( \alpha,\beta \)-dehydroamino esters 5 in moderate to good yields. Both steps are conveniently combined in a one-pot procedure, but only [2.2.2] bicyclic organic bases were found to be effective for the second transformation (Scheme 3).

\[ \text{Scheme 3} \quad \text{One-pot synthesis of } \alpha,\beta \text{-dehydroamino acid derivatives} \]

### 2.2 By Horner–Wadsworth–Emmons and Wittig Reactions

The group of Schmidt and Lieberknecht developed the synthesis of dehydroamino acids using the Horner–Wadsworth–Emmons (HWE) reaction for C–C coupling. The condensation of commercially available \( N \)-acyl dialkoxyphosphoryl glycine ester (7) with aldehydes gives \((Z)\)-dehydroamino acids as the major product in chemical yields ranging from 80% to 95%. Most reactions use DBU or tert-butoxide in dichloromethane at –70 °C as base. The method, in combination with subsequent stereoselective hydrogenation, has recently been applied to drug synthesis. Jorgensen and Gautun were able to prepare isodityrosine (9) by this route in only three steps, with complete Z selectivity of the C=C bond formation in 8 (Scheme 4, top).

\[ \text{Scheme 4} \quad \text{Synthesis of isodityrosine using the commercially available HWE reagent 7; } 40 \text{ synthetic route to } \beta \text{-turn mimic 13 (bottom)} \]

The HWE reaction is the key step in the synthesis of \( \beta \)-turn mimic 13 (Scheme 4, bottom) \(^{41-43}\) and \((S,S)\)- or meso-diaminopimelic acid reported by Hruby. Pyridine-containing amino acids, such as L-azatyrosine (16) were prepared by Adamczyk using the HWE reaction with subsequent hydrogenation (Scheme 5). Similar routes were used for the preparation of \((S)-(-)-\)acromelic acid (17) and \((S)-(-)-\)acromelobinic acid (18). An unusual type of \( \alpha,\beta \)-dehydroamino acid was developed by Cativiela and Su. They prepared \( \alpha,\beta \)-dehydroamino acids with axial chirality using the Erlenmeyer method and oxazolone ring-opening, and later replaced this sequence by the HWE reaction. Racemic 21 (Scheme 6) was obtained in 42% \((R = Me)\) to 85% \((R = CO_2Me)\) yield using a fourfold excess of the keto compound 19.

The HWE reaction allows the synthesis of alkynyl-substituted \( \alpha,\beta \)-dehydroamino acids 14. The stereochemistry of the reaction is determined by the substituents of the phosphoryl glycine ester amino group: A doubly protected (Bz and Cbz) amine leads to the \( E \) isomer, while mono-protected (Boc or Ac) derivatives give the \( Z \) isomer (Table 1).
The synthesis of the sugar amino ester 26 by HWE reaction was reported by Chun (Scheme 7).53 Cyclization leads to the six-membered ring of dideoxynojirimycin, a glucosidase inhibitor.

Kinoshita54 reported a Wittig-type reaction using N-protected α-tosyl glycine ester in the reaction with tributylphosphine, sodium carbonate as base and tetrabutyl ammonium bromide as phase-transfer catalyst to prepare the ylide. The in situ reaction with (R)-isopropylideneglyceraldehyde gave α,β-dehydroamino esters in yields of up to 94% and complete Z selectivity (Scheme 8). The method was applied to the synthesis of (R,R)- and (S,S)-4-hydroxyproline (32).

The solid-phase synthesis of α,β-dehydroamino acids and dehydro-2,5-diketopiperazines was described by Couladouros.55 Using as a key intermediate Schmidt’s phosphonate in solid-supported form, small libraries of dehydro-

2,5-diketopiperazines were prepared with moderate product yield.

A different approach to the synthesis of dipeptides was described by Buck, based on the formation of the NHCHRCONH–CHR’CO bond by carbenoid N–H insertion, rather than the formation of the peptide bond itself.56 Decomposition of triethyl diazophosphonoacetate catalyzed by rhodium(II) acetate in the presence of N-protected amino acid amides 33 gave phosphonates. Subsequent HWE reaction with aldehydes in the presence of DBU led to dehydrodipeptides 34 (Scheme 9).

The classical method for the preparation of dehydroamino acids with aromatic or heteroaromatic rings is the Erlenmeyer synthesis.57 The reaction is possible as a one-pot procedure with an aldehyde, acetylglycine, acetic anhydride and sodium acetate, or a previously prepared 5-(4H)-oxazolone is condensed with the aldehyde in the presence of a base, such as DBU. Ring-opening with alcohols leads to α,β-dehydroamino esters, while aqueous solvents give the free acid. If amino esters or salts of amino acids are used as nucleophiles for the ring-opening, peptides are obtained. The mechanistic investigations of the ring-opening reaction were recently supplemented by a mass spectrometric study conducted by Traldi.58

Ring-opening reactions with acylhydrazines gave the desired N-acyl-α,β-dehydroamino hydrazide (37) only in small amounts. The major product was the triazole 36 (Scheme 10).59

### Table 1 Synthesis of Alkynyl Dehydroamino Esters 242

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<td>Ac</td>
<td>H</td>
<td>47</td>
<td>Z</td>
</tr>
</tbody>
</table>

### Scheme 7 Synthesis of dideoxynojirimycin derivative 28 via α,β-dehydroamino ester 26 obtained from a HWE reaction

### Scheme 8 Synthesis of (S,S)-4-hydroxyproline (32) according to Kinoshita54

### Scheme 9 A carbenoid approach to peptide synthesis56

### 2.3 Erlenmeyer Synthesis and Ring-Opening of Oxazolones

The classical method for the preparation of dehydroamino acids with aromatic or heteroaromatic rings is the Erlenmeyer synthesis.57 The reaction is possible as a one-pot procedure with an aldehyde, acetylglycine, acetic anhydride and sodium acetate, or a previously prepared 5-(4H)-oxazolone is condensed with the aldehyde in the presence of a base, such as DBU. Ring-opening with alcohols leads to α,β-dehydroamino esters, while aqueous solvents give the free acid. If amino esters or salts of amino acids are used as nucleophiles for the ring-opening, peptides are obtained. The mechanistic investigations of the ring-opening reaction were recently supplemented by a mass spectrometric study conducted by Traldi.58

Ring-opening reactions with acylhydrazines gave the desired N-acyl-α,β-dehydroamino hydrazide (37) only in small amounts. The major product was the triazole 36 (Scheme 10).59
2.4 \(\alpha,\beta\)-Dehydroamino Esters from Nitroalkanes

Nagano and Kinoshita report \(\alpha,\beta\)-dehydroamino ester syntheses using nitroalkanes.\(^6\) N-Protected \(\alpha\)-tosylglycine ester (38) was reacted with various nitroalkanes \(^3\) (Scheme 11). The nitroalkane \(\alpha\)-carbon nucleophile attacked the intermediate imine from tosyl elimination. Subsequent DBU-catalyzed elimination of nitric acid tacked the intermediate imine from tosyl elimination. Tended to dipeptides that contain \(\alpha,\beta\)-dehydroamino acids, surprisingly high stereoselectivity.

2.5 Schöllkopf Formylamino-methylation

The Schöllkopf formylamino-methylation procedure allows the efficient and completely Z-stereoselective preparation of 3-substituted ethyl (Z)-4,4,4-trifluoro-2-formylamino-2-butoanoates (42) starting from ethyl isocyanatoacetate and various trifluoromethyl ketones (Scheme 12).\(^6\) The special electronic and steric effects of the trifluoromethyl substituent are the cause for the surprisingly high stereoselectivity.

2.6 Synthesis of Cyclic \(\alpha,\beta\)-Dehydroamino Acids

Chiral cyclic \(\alpha,\beta\)-dehydroamino esters or amides are suitable starting materials for many reactions. The compounds shown in Figure 1 have been used recently.

Cyclic \(\alpha,\beta\)-dehydroamino acids have found their main applications in cyclopropanation reactions, Diels–Alder reactions, radical additions and hydrogenations.

Figure 1 Chiral cyclic dehydroamino acid derivatives used in recent syntheses

The compound class \(^4\) was obtained by condensation of methylcysteine with the corresponding aldehyde (such as benzaldehyde or pivalaldehyde), addition of an activated acyl protective group (such as benzylchloride, Cbz-chloride or acetyl bromide), oxidation with Oxone, elimination using DBU, and elimination using BuLi.\(^6\) The stereoisomers could be separated at the stage of the saturated oxazolidin-5-one sulfoxides, prior to the elimination reaction. Thereby, cis,trans mixtures of 81:19 (PG = benzoyl, \(R^1 = t\)-But), 6:94 (PG = benzoyl, \(R^2 = Ph\)) and 8:92 (PG = Ac, \(R^2 = Ph\)) in overall yields of 49%, 28% and 23%, respectively, were obtained. An alternative synthetic route, starting from the saturated alanine oxazolidinone, used bromination followed by dehydrohalogenation.

The \(\alpha,\beta\)-dehydroamino ester derivative 44 was obtained from a commercially available glycinate precursor by a Horner–Emmons reaction. The synthesis of the required phosphonate ester used N-bromosuccinimide in carbon tetrachloride and trimethylphosphite in 86% yield. The subsequent base-mediated coupling with aldehydes gave compounds (E)-44 in yields of 82–100%. Isobutyraldehyde coupled in only 19% yield.

The precursor of 45, 3-isopropyl-2,5-piperazinedione, is commercially available. The compound was nitrogen-protected with Boc2O/DMAP (82%) and condensed with benzaldehyde (100%, \(Z:E = 84:16\)) or 2-methylpropanal (82%, \(Z:E = 71:11\)) in the presence of potassium tert-butoxide, whereby the Boc-group on N-1 was cleaved. Protection with either Boc (to 45) or Ac is possible. Other aldehydes gave condensation products in yields between 55% and 92%, leading preferentially to the Z configuration. Reactions using acetyl protective groups gave similar yields. A different method for the synthesis of 3-isopropyl-6-methylidene-2,5-piperazinedione (45, \(R = H\)) is the dehydration of the cyclic diamide of valine and serine.

The synthesis of diketopiperazone 46 started with oxazolidinones and proline. The ring closure of the intermediate product with acetic anhydride gave the required diketopiperazone.
A series of piperazines of type 45 and 46 was obtained by a different synthetic route with an overall yield of 65% to 83% and mainly Z-configured products (E:Z = 8.92 to 5.95).77 The N-protected benzyl ester of the corresponding amino acid (49 in Scheme 13; Val for 45, Pro for 46) and 2-oxocarbonylic acid 50 were coupled with diisopropylcarbodiimide (DIC) and subsequently cyclized with ammonium acetate. Both the oxazolinone method78 and the oxocarbonylic acid method77 are suitable for solid-phase synthesis to generate a multitude of piperazine derivatives in combinatorial chemistry strategies.

Scheme 13 Synthesis of diketopiperazines77

Compounds of type 46 can also be prepared using a HWE reaction.79,80 The required phosphono diketopiperazine was obtained from Cbz-protected phosphonoglycine and proline benzylester in two steps in 87% yield. The reaction with aldehydes and potassium tert-butoxide yielded dehydrodiketopiperazine 46 (PG = H) in more than 80% yield and in E:Z ratios from 30:70 up to 2:98.

Compound 47 was obtained by esterification of 2-hydroxy-3-pinanone with Boc-glycine, subsequent deprotection and spontaneous cyclization.81 Condensation with aldehydes in tetrahydrofuran/potassium –78 °C gives the (R = CH₃, C₂H₅) in 85% yield.82

An aldol reaction or a reaction with an Eschenmoser salt gave rise to compounds 48. The cyclic glycine precursors came from the coupling of Boc-glycine with 2-hydroxysteroidalphenone (X = O),83–86 or 2-amino-sterolphenone (X = NBoc),86–88 deprotection and cyclization with HCl and Me₂N, and, in the case of X = NBoc, another Boc protection. Overall yields of 56% and 78%, respectively, were obtained. The reaction with aldehydes under solid–liquid phase-transfer conditions using potassium carbonate and tetra-n-butylammonium bromide in dichloromethane gave the product in 50–64% yield and Z:E ratios >96:4 (X = O), or 47–88% yield and Z:E ratios >98:2 (X = NBoc). Similarly, the authors described, in the case of X = NBoc, the condensation with acetone in 50% yield and the reaction to the dimethyleamine derivative (R = NMe₂) in 96% yield. The reaction with the Eschenmoser salt (N,N-dimethylmethyleneammonium iodide) gave 48 (R = H) in 60% (X = O) and 88% (X = NBoc) yields, respectively.

3 Reactions of α,β-Dehydroamino Acids and Esters

3.1 Halogenation

van der Donk and Zhou88–91 investigated the fluorination of dehydroalanine. In four steps, the authors converted Fmoc-protected dehydroalanine diphenylmethyl ester 53 (Scheme 14) into the corresponding fluorinated derivative 58 as a mixture of E and Z isomers. The Boc-protected benzyl ester as starting material gave the cyclized compound 59 as a side product in 15% yield. β-Fluoro dehydropeptides underwent clean nucleophilic substitution via an addition–elimination mechanism with retention of the E:Z ratio. The authors illustrated this in the substitution reaction with p-methoxyxiphenol.

Dehydroamino acids are brominated in their β-position when treated with N-bromosuccinimide and triethylamine in dichloromethane. The nitrogen-protecting group controls the stereochemistry. Acetyl92 or methoxy carbonyl93,94 dehydroalanine gave the Z isomer, while the Boc-protected compounds yielded the E isomer.95 α,β-Dehydroamino acids with β-substitution, such as ΔAbu, gave mixtures of E and Z isomers92,95,96 with preference for the Z configuration. The iodination of ΔAbu with N-iodosuccinimide and triethylamine or DABCO was more selective, with an Z:E ratio of more than 94:6.96

Scheme 14 Fluorination of ΔAla according to Zhou.90,91 Dpm = diphenylmethyl.

3.2 Nucleophilic Addition

Ferreira97–99 investigated Michael addition reactions to ΔAla and ΔAbu in detail. The yields were only good when there were two electron-withdrawing substituents on the α,β-dehydroamino ester nitrogen atom. Nitrogen nucleophiles, such as pyrazole, imidazole or 7-azaindole, under-
went addition to (Boc)$\text{2}-\Delta$Ala-OMe in up to 99% yield (Scheme 15). For indoles, the reaction yield depended on the acidity of the nucleophile: unsubstituted indole gave 49% of the addition product, the slightly more acidic 3-formylindole gave 99% yield, and the less acidic 3-methylindole or carbazole showed no addition reaction.100 Thio nucleophiles, such as thiophenol, methyl thioacetate and 4-bromothiophenol, reacted readily with (Boc)$\text{2}-\Delta$Ala-OMe. The choice of the nitrogen-protecting group is important with these nucleophiles. Benzoyl or benzyloxy-carbonyl protecting groups were partially cleaved, diminishing the reaction yield by producing unreactive Boc-$\Delta$Ala-OMe.

Scheme 15 Heterocyclic $\beta$-substituted alanine derivatives from (Boc)$\text{2}-\Delta$Ala-OMe

N,N-Disubstituted $\alpha,\beta$-dehydroamino ester 63, with one tosyl protective group, showed a different product distribution.101–104 Depending on the reaction conditions, elimination or rearrangement of the tosyl group was observed after nucleophile addition, giving either the $\beta$-substituted dehydroamino ester 67 or the $\beta$-tolylsulfinate-substituted dehydroamino ester 66 (Scheme 16). Elimination of the $p$-toluenesulfonyl group (64 to 67) could be suppressed by using chloroform as solvent. With some thio nucleophiles, only product 67 was obtained. Carbon nucleophiles, derived from 62, were exceptional and cyclized after addition by tosyl displacement to give 65. The addition of nitrogen or oxygen nucleophiles to 66 yielded $\alpha,\alpha$-disubstituted amino esters 68 and 69, while sulfur nucleophiles displaced the toluenesulfonyl substituent and gave again 67.

Scheme 16 Michael addition reactions to Ts-$\Delta$Ala(N-Boc)-OMe

Pyne used a stereoselective Michael addition of carbon nucleophiles to 43 to synthesize 4-benzamidopyroglutamates106 and prolines.107 From the addition of the benzophenone glycine-tert-butylester imine (71) (Scheme 17) to 70 using DBU and lithium bromide in tetrahydrofuran at $-78{\text{°C}}$, the authors obtained Michael adduct 72 in 65% yield with control of the two new stereocenters and a diastereoselectivity of 97:3. Cleaving the oxazolidinone ring and spontaneous recyclization gave tert-butyl-4-(S)-benzamido-(R)-pyroglutamate (73) in 88% yield. Variation of the oxazolidinone ring and the attacking nucleophile led to three other stereoisomers in similar yields, but lower diastereoselectivities.

Enamine 75 added to 74 in tetrahydrofuran at $-20{\text{°C}}$ in a preferentially cis manner with a diastereoselectivity of 83:17. The cis product 76 was purified by chromatography. Subsequent acidic ring-opening of the oxazolidinone ring and the spontaneous recyclization (99%), hydrogenation (89%, $\text{dr} = 96:4$) and deprotonation gave cis-5-isopropylproline (77). The enamines of cyclopentanone and cyclohexanone added to 74 only with poor diastereoselectivites.

The organocuprate addition to 78 in tetrahydrofuran at $-78{\text{°C}}$ gave the cis product in high yields of 88–92% and >95% diastereomeric excess (Scheme 18).108 After deprotection and ring-opening, Bull obtained a mixture of valine and the desired amino acid, which was separated using an ion-exchange column.

Addition to the $\alpha$-carbon of 80 was made possible by HBr catalysis (Scheme 19). Jin and Liebscher109 achieved, by this method, the addition of heteroarenes such as pyrrol and indole, in medium to high yields and good stereoselectivities. However, as a side reaction, the double bond isomerizes; this was also observed with compound 45,110
3.3 Radical Addition Reactions

Sutherland and Vederas used the conjugate addition of radicals derived from diacyloxyiodobenzenes to α,β-dehydroamino esters.\textsuperscript{111} They obtained new analogues of diaminopimelic acid by radical decomposition of bis[(2S)-N-benzylxycarbonyl-2-aminopentan-5-carboxy-1-methyl ester]iodobenzene followed by decarboxylation and subsequent conjugate addition to protected α,β-dehydroamino acids. Interestingly, the unsaturated addition products were obtained from hydrogen abstraction in yields of 50% and had to be converted into the desired saturated products by hydrogenation with [(COD)Rh[(R,R)-Et-DuPHOS]]BF₄.

Sibi\textsuperscript{112} reported a different strategy for an enantioselective radical addition reaction to an α,β-dehydroamino ester. Tributyltin hydride was used as a H-atom donor, and reaction with a complex of magnesium perchlorate and a chiral bisoxazoline ligand gave product 84 with up to 85% ee (Scheme 20).

α,α-Disubstituted amino esters 87 were prepared by a free-radical-mediated tandem reaction of α,β-dehydroamino ester derivatives with a π-allyl palladium complex (Scheme 21).\textsuperscript{113–115}

The groups of Beckwith\textsuperscript{116,117} and Jones\textsuperscript{66} reported radical additions to oxazolidinones. Beckwith investigated the resulting diastereoselectivities in the addition of alkyliodides in benzene using tributyl tin and azobis(isobutyronitrile) under UV radiation. The authors reported a \textit{trans} selectivity in the addition to 43a (PG = benzyol) with a diastereoselectivity of 71:29 (with methyliodide) up to >88:12 (with tert-butyliodide and cyclohexyl iodide) in yields of 60–73%. \textit{Cis} selectivity was observed with other nitrogen-protecting groups, such as carbamates (Table 2, entries 1–3) or benzylacetamides. Suarez\textsuperscript{118} reported the Zn–Cu–ultrasound-induced addition of alkyl iodides to benzyl-protected oxazolidinones. This method improved the yield of the cyclohexyl iodide.
addition to 91%. The reaction was less selective (diastereoselectivity 91:9) than that reported by Beckwith, but avoided the use of tin or mercury compounds (see Table 2, entry 4).

Jones\textsuperscript{66,119} used the radical addition in the synthesis of monomers of peptide nucleic acids (PNAs) and added both pyrimidine and purine bases to an oxazolidinone acceptor (Scheme 22).

![Scheme 22](image)

Jones\textsuperscript{66,119} used the radical addition in the synthesis of monomers of peptide nucleic acids (PNAs) and added both pyrimidine and purine bases to an oxazolidinone acceptor (Scheme 22).

Pyne and Schafer investigated other sources of radicals.\textsuperscript{120} The photochemically induced radical addition of alcohols and ethers to chiral oxazolidinones was found to give only poor yields of up to 55%, with mostly low diastereoselectivity. Only isopropanol and selected ethers reacted diastereoselectively.

Chai\textsuperscript{121} adopted Beckwith’s conditions for the addition to diketopiperazines analogous to \(45\), but with a methyl group in place of the sterically demanding isopropyl group (Table 2, entry 5). The yields of the reactions were lower with 37–77%. Depending on the nitrogen-protecting group and the attacking radical, selectivities can be high. The reactions of the diacetylated diketopiperazine with cyclohexylidide, isopropylidide, tert-butylidide and benzylidide gave exclusively the cis product (entry 5, Table 2).

In the attempted synthesis of diaminopirinic acid by Sutherland and Vederas\textsuperscript{111} the addition of radicals from diacetoxyiodobenzene to acyclic dehydroalanine and to cyclic compounds such as 44 (PG = Boc) and 43a (PG = Cbz) was studied. However, the desired products were not obtained.

### 3.4 Sonogashira Coupling Reactions

The Sonogashira coupling of brominated dehydroalanine was reported by Miossec.\textsuperscript{94} (Z)-β-Bromo dehydroalanine 94 reacted, with retention of the double-bond configuration, with terminal alkynes (Scheme 23), while acetylene gave 77% of a bis-coupling product. Sonogashira cross-couplings of α,β-dehydroamino acid derivatives with phenylacetylenes gave fluorescent products.\textsuperscript{122}

In the synthesis of the vasopeptidase inhibitor BMS-189921\textsuperscript{123} the Sonogashira reaction of a bromo α,β-dehydroamino ester was used as a key step to build the carbon skeleton and to introduce the required functional groups.

![Scheme 23](image)

### Table 2 Radical Additions to Cyclic α,β-Dehydroamino Ester Derivatives

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<th>Entry</th>
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<td>3</td>
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<td>(C_6H_5I, Zn, CuI, EtOH, H_2O, ultrasound)</td>
<td>94</td>
<td>91:9</td>
<td>118</td>
</tr>
<tr>
<td>5</td>
<td>45 (Me instead of i-Pr) PG = Me, R = H</td>
<td>(C_6H_5HgCl, NaBH_4)</td>
<td>49</td>
<td>100:0</td>
<td>121</td>
</tr>
</tbody>
</table>
3.5 Suzuki Coupling Reactions

Burk tested the Suzuki coupling as an alternative vinylic C–C coupling method on α,β-dehydroamino acids.92 Mild conditions were sufficient, such that no ester hydrolysis occurred and the stereochemistry of the double bond was maintained. Using palladium acetate (10 mol%) and two equivalents of sodium carbonate in ethanol at 50–55 °C, the authors achieved good to very good product yields (Table 3).

Hoerrner et al. used this method96 to synthesize β-(2R,3S)-methyltryptophane, as did Queiroz to synthesize sulfur analogues of dehydrotryptophane (Figure 2).95,124,125 In addition, the preparation of new β,β-bis(benzo[b]thienyl)dehydroalanines became possible by a double Suzuki coupling using dibromo-α,β-dehydroalanine (Scheme 24).126,127

This coupling was also used by Zhang42,43 as a key step in their synthesis of β-turn mimetics 108–110 (Figure 3).

### Table 3  Suzuki Coupling Using α,β-Dehydroamino Acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>Configuration of 105</th>
<th>R2</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Z</td>
<td>Bn</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>Z</td>
<td>Ph</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Z</td>
<td>t-Bu</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Z</td>
<td>n-hex</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>E</td>
<td>Ph</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>E</td>
<td>n-hex</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Z</td>
<td>Ph</td>
<td>67</td>
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<tr>
<td>8</td>
<td>Z</td>
<td>n-hex</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Et</td>
<td>E</td>
<td>Ph</td>
<td>78</td>
</tr>
<tr>
<td>10</td>
<td>E</td>
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<td>76</td>
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<td>73</td>
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<tr>
<td>12</td>
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<tr>
<td>13</td>
<td>i-Pr</td>
<td>E</td>
<td>Ph</td>
<td>40</td>
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<tr>
<td>14</td>
<td>E</td>
<td>n-hex</td>
<td>44a</td>
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</tr>
<tr>
<td>15</td>
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<td>0b</td>
<td></td>
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<td>16</td>
<td>Z</td>
<td>n-hex</td>
<td>74c</td>
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<tr>
<td>17</td>
<td>Bn</td>
<td>E</td>
<td>Ph</td>
<td>83</td>
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<tr>
<td>18</td>
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<td>t-Bu</td>
<td>85</td>
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<tr>
<td>19</td>
<td>E</td>
<td>n-hex</td>
<td>85</td>
<td></td>
</tr>
<tr>
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<td>Z</td>
<td>Bn</td>
<td>63d</td>
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<td>Z</td>
<td>Ph</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Z</td>
<td>n-hex</td>
<td>88</td>
<td></td>
</tr>
</tbody>
</table>

a Mixture of 105 and 107; yield interpolated from 1H NMR spectrum.
b 1,4-Diphenylbutadiene (82%) and 105 (17%) obtained.
c With isomerization of configuration of 105; 1:1 mixture.
d With 20 mol% Pd(OAc)2, 70% yield.

### Scheme 24  Double Suzuki coupling to dibromo-α,β-dehydroanline followed by palladium-catalyzed cyclization

### Figure 2  (S)-Dehydrotryptophane derivatives prepared by Queiroz95,124,125

### Figure 3  β-Turn mimetics synthesized by Zhang42,43
3.6 Ring-Closing Metathesis (RCM)

This popular C–C coupling method was recently utilized for α,β-dehydroamino acids by Manzoni.\textsuperscript{128} Ring-closing metathesis with a second-generation Grubbs catalyst (112) gave bicyclic 6- and 7-membered-ring lactams 113 (Table 4). The authors explained the ring contraction to a six-membered ring side product (entry 3) with an isomerization of the double bond prior to RCM.

| Table 4 Ring-Closing Metathesis of α,β-Dehydroamino Acids\textsuperscript{128} |
|-----------------|-----------------|-----------------|-----------------|
| Entry | PG n | Conditions | Yield (%) |
| 1    | Ac 1 | 20 °C, 5 h, CH₂Cl₂ | 89  |
| 2    | Cbz 1 | 20 °C, 24 h, CH₂Cl₂ | 81  |
| 3    | Ac 2 | 100 °C, 72 h, toluene | 53a |

a The product from entry 1 (14%) was also obtained.

3.7 Cycloadditions

Cycloaddition reactions of α,β-dehydroamino acids include Diels–Alder reactions, cyclopropanations, and 1,3-dipolar cycloadditions. Cativiela and Diaz-de-Villegas reviewed the use of these reactions to generate quaternary amino acids in detail.\textsuperscript{9} Therefore, we discuss these aspects only briefly and focus on the more recent work.

3.7.1 Diels–Alder Reactions

The Diels–Alder reaction of α,β-dehydroalanine derivatives with 1,3-butadiene was first investigated by Horikawa in 1980.\textsuperscript{129} The acylated ester yielded, at 90 °C in toluene, or at room temperature in CCl₄ with AlCl₃ or FeCl₃ in ether, 62–79% of a mixture of the exo and endo product (60:40). The methoxy carbonyl-protected ester gave exclusively the exo product in 56% yield. Bueno explained this exo selectivity by invoking secondary interactions of the acetamido group.\textsuperscript{130}

Hydroxycyclohexane-α-amino carboxylic acids are of interest as analogues of serine (120) and homoserine (121), as they are conformationally restricted and are related to biological functions. The same is true for compound 123, an achiral proline analogue (Scheme 25).

These compounds were synthesized using a Diels–Alder reaction of α,β-dehydroamino acid 114 with dienes, such as 1-methoxy-1,3-butadiene (117) or Danishefsky’s diene, (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (115) (Scheme 25).\textsuperscript{131–133} The Diels–Alder reaction with 115 in dioxane yielded the product with an exo:endo selectivity of 90:10. The reaction with 117 produced two stereoisomers, corresponding to endo selectivity: the 1,2-adduct 118 and the 1,3-adduct 119, in a ratio of 9:1. The exo adducts were not observed. The further conversion of 118 or 116 gave 120 as a racemic mixture that was then purified by enantiomeric separation techniques. Compounds 122 and 123 were prepared from 116 by subsequent transformations.

Scheme 25 Cyclohexane amino carboxylic acids 120–123\textsuperscript{131–133} prepared by Diels–Alder reactions of α,β-dehydroamino acids

The influence of different nitrogen-protecting groups on the Diels–Alder reaction with 1-(trimethylsilyloxy)cyclohexa-1,3-diene (124) was investigated by Crossley and Stamford (Table 5).\textsuperscript{134,135}

| Table 5 Effect of Nitrogen-Protecting Groups on the Diels–Alder Reaction\textsuperscript{134,135} |
|-----------------|-----------------|-----------------|-----------------|
| Entry | R¹ | R² | R³ | Conditions | Yield (%) | exo:endo |
| 1    | Me | Phth |  | 150 °C, 48 h | 51  | 64:36 |
| 2    | Bz | Cbz | H | 120 °C, 24 h | 72  | 40:60 |
| 3    | Bz | Boc | H | 140 °C, 78 h | 48  | 36:64 |
| 4    | Bz | CF₃CO | H | 75 °C, 4 h | 56  | 33:67 |
| 6    | Me | Ac | H | 120 °C, 20 h | 21  | 28:72 |

Burkett and Chai used a polymer-bound Fmoc-α,β-dehydroalanine for Diels–Alder reactions and obtained yields of approximately 50% and an exo selectivity of up to 80:20. With other dienes, such as cyclohexadiene or acy-
cyclic dienes, then *endo* and *exo* selectivities obtained were different.\textsuperscript{36}

The reaction of 1,3-dienylocobaloxime complexes was investigated by Chai.\textsuperscript{131} However, only poor yields were obtained in the Diels–Alder reaction with N-protected α,β-dehydroalanine esters. Higher yields were achieved with methyldiene piperazinediones, as cyclic α,β-dehydroalanine derivate and oxazolones.\textsuperscript{138–140}

Burkett and Chai investigated the dependence of the Diels–Alder reaction of diketopiperazines on different protecting groups and chiral substituents.\textsuperscript{74} The *exo* product, as one of four possible reaction products with cyclopentadiene, was obtained preferentially (*exo:endo* ratios of 55:45 to 93:7) and the substituents controlled the *Re* or *Si* attack. Najera achieved almost complete *endo* selectivity with compounds 48, 53,83–88 Cyclopentadiene and 1-methoxy-cyclohexadiene reacted with 48 (X = O) smoothly at room temperature to give isolated product yields of 55% and 66%, respectively. Six hours at 90 °C were required for the reaction with cyclohexadiene, which gave product in 49% isolated yield. The product ratios, of one *endo* product to the other three isomers, were 85:15, 94:6 and 88:12. However, for the reaction with cyclohexadiene, the authors could only determine that it gave an *endo* product, but the absolute stereochemistry was uncertain. Higher selectivities were achieved with compound 48 (X = NBoc). The reaction of cyclopentadiene (room temperature, one day, 42% yield) and cyclohexadiene (room temperature, six days, 95% yield) gave only the *endo* product as one of four possible isomers, whereas for the reaction with 1-methoxy-1,3-butanediene (50 °C, one day), a 67:33 mixture of *endo* (or trans) and *exo* (or cis) products was obtained in a yield of 66%. Cycloaddition products of cyclohexadiene and cyclopentadiene were subsequently deprotected to give the bicyclic amino acids, such as 2-aminobicyclo[2.2.2]octane-2-carboxylate and 2-aminobicyclo[2.2.1]heptane-2-carboxylate.

3.7.2 Cyclopropanations and 1,3-Dipolar Cycloadditions

The synthesis of cyclopropane amino acids\textsuperscript{9} by the addition of diazo compounds has been studied intensively. Recent work focused on practical aspects of the cyclopropanation and handling of the diaco compounds. Due to the toxicity and ease of decomposition of the diazo compounds, *in situ* release followed by transition-metal-catalyzed reaction is advantageous. Anisimova\textsuperscript{141} showed that in the reaction of diazo esters with N-acetyl α,β-dehydroamino esters in the presence of Rh$_2$(OAc)$_2$, only 10% of the cyclopropane amino ester is produced. Nevertheless, Cox and Aggarwal\textsuperscript{142–144} succeeded in the stereoselective cyclopropanation by *in situ* release of the diazo compound from tosylhydrazonium salts with and without transition-metal catalysts. The reaction without catalyst yielded mainly the *E*-configured product 131, while the reaction catalyzed by the iron porphyrin (ClFeTPP) gave the *Z*-configured product 130 (Table 6).

The in situ reaction of protected α,β-dehydroamino acids with derivatives of vinyl Diazomethane led to vinyl cyclopropanes via a [3+2] dipolar cycloaddition followed by dinitrogen extrusion.\textsuperscript{145,146} Oxidative cleavage of the vinyl moiety then gave directly the protected cyclopropane aspartic acid derivatives.

1,3-Dipolar cycloadditions of azomethylenides to 43a and 43b yielded spiro compounds and, after ring-opening, highly functionalized proline derivatives.\textsuperscript{145,146} The azomethylenides were generated in situ from imines of benzaldehyde and various amino esters by addition of a base (DBU or Et$_3$N) and a metal salt (LiBr or AgOAc). Selectivities and yields obtained with 43a were higher than those for 43b.

Cycloadditions of nitrones to 43,\textsuperscript{147} and nitrile oxides to 43,\textsuperscript{148,149} and 45\textsuperscript{148} were also investigated.

The synthesis of conformationally hindered cyclopentylglutamates by Pyne\textsuperscript{149,150} (Scheme 26) utilized a [3+2] cycloaddition. α,β-Dehydroamino ester 132 reacted with ylide 133, which was prepared in situ from an allene or alkyne precursor by phosphine addition.

The use of a stabilized sulfur ylide improved the cyclopropanation yields of 43,\textsuperscript{151} The reaction of 43b with ethyl- or tert-butylmethylsulfonylaluminum acetate at 0 °C gave product yields of around 55%, with selectivities of 90:10 for one of the four possible diastereomers. Selectivities were lower with 43a, and with an allyl derivative of the ylide.

Bunuel\textsuperscript{152} used phosphorylides for the cyclopropanation of 45 (PG = PMB). For symmetrical ylides, such as isopropylidene triphenylphosphorane, one of the two possible diastereomers is formed in up to 93% with a diastereomeric ratio of >98:2. Unsymmetrical ylides were less selective. The reaction with benzylidiazomethane gave two of four diastereomers.

Compound 48 (R = Me or Et) was cyclopanonated by Najera\textsuperscript{83–88} using Corey’s dimethylsulfonoxonium methylyde. In the case of X = O, the authors obtained 52% (dr = 89:11) or 63% (dr = 91:9) yield of the product, and, after ring-opening, 60% of (∼)-allo-norcoronamic acid or 67% of (∼)-norcoronamic acid, respectively. In the case of
X = NBoc, 81% (dr = 92:8) or 82% (dr = 96:4) product yields were obtained; however, the ring-opening gave only 24% of (–)-allo-norcoronamic acid and failed completely for the (–)-coronamic acid.

3.8 Epoxidation

Liebscher investigated the stereoselective oxidation of \( \text{46}_{153,154} \) Compounds with an acyl protective group on nitrogen were successfully epoxidized in moderate to high yields (56–95%) and more than 95:5 dr with dimethyloxirane at room temperature (Scheme 27). However, the subsequent conversion of the compounds to allo-threonyl diastereomers by hydrolytic cleavage of the oxiranes \( \text{136} \) failed because of epimerization. The authors described a detour via ring-opening of the oxiranes in boiling toluene with a catalytic amount of \( p \)-toluenesulfonic acid. Ketones \( \text{137} \) were subsequently reduced to alcohols \( \text{138} \) with high selectivities of 70:30 to 92:8. Cleavage of the piperazine ring in 6 N HCl gave allo-threonine in an optical purity of 88% ee.

3.9 Hydrogenation

Chiral cyclic \( \alpha,\beta \)-dehydroamino acids have been hydrogenated stereoselectively without the use of chiral-ligand catalysts. Nishiyama prepared various 2,3-dideuterated L-threo and L-erythro amino acids from \( \text{45} \) (Table 7).\(^{71,72,155} \) The hydrogenations of alkyldiene- and arylidene-diketopiperazines of type \( \text{46} \) were investigated by Bycroft and Lee\(^{156} \) and Poisel and Schmidt.\(^{157} \) The hydrogenation reactions showed a chiral induction of more than 90%.
The hydrogenation of 47 (R = CH₃, C₂H₅, Ph, 3,4-dimethoxyphenyl) with hydrogen and Pd/C proceeded in yields of 63–75% and de values of up to 95%. The subsequent acidic release of the amino acid yielded 85–93% of the product, with retention of configuration.

An enantioselective ruthenium-catalyzed hydrogenation of N-sulfonylated ω,β-dehydroamino acids was used to prepare N-sulfonylated amino acids in up to 98% ee in the synthesis of an anthrax lethal factor inhibitor (LFI). This hydrogenation used a chiral Ru catalyst rather than a Rh catalyst that would be typical for acylated ω,β-dehydroamino acids and esters. It was the first report of an asymmetric hydrogenation of a tetrasubstituted ω,β-dehydroamino acid derivative using a Ru catalyst.

Roumestant’s stereoselective synthesis of 4-hydroxyisoleucinelactone (144) used the condensation of the cyclic 2-hydroxy-3-pinanone glycine 141 with butan-2,3-dione (Scheme 28). The resulting E/Z mixture (80:20) of 142 was hydrogenated with H₂ and 10 mol% Pd(OH)₂/C as catalyst, and gave 143 in 64% yield as a single diastereomer. The authors explained the selectivity by invoking an intermediate enolate formation. Hydrogenation of the carbonyl groups and cleavage of the chiral auxiliary yielded (3R,4R,5R)-4-hydroxyisoleucinelactone 144 in an overall yield of 14%.

Additionally, Najera reported the diastereoselective hydrogenation of compound 48 (X = O). In these examples, the imine double bond was hydrogenated, which prohibited the release of the α-amino acid. Only N-methylated α-amino acids could be prepared.

Examples of α,β-Dehydroamino Acids in Natural Products

4.1 β-Lactam Antibiotics

A number of β-lactam antibiotics have an α,β-dehydroamino acid as substructure. These penicillin-like compounds were isolated from natural sources and further developed synthetically to circumvent bacterial resistance against penicillin and other antibiotics.

Among the substances depicted in Figure 4, carbapenems show advantages over the others, including already commercially available drugs. In particular, since the discovery of the thienamycin compound family by Merck, the synthesis of new carbapenem derivatives is the goal of many research groups. Recent reviews summarize the current developments. New carbapenem derivatives have mainly been prepared by the reaction of carbapenem enol phosphate 149 with thiols, by palladium-catalyzed C–C coupling, or by de novo synthesis of the ring skeleton.
4.2 Lantibiotics

The name lantibiotics is derived from the Lanthionine-containing peptide antibiotics. This inhomogeneous group of active substances contains a large number of non-proteinogenic amino acids such as lanthionine, dehydroalanine, dehydrobutyrine and others, some of which contain cyclic thio ether substructures. The antibiotic potential of the substances is based on membrane activation for type I lantibiotics, and on lipid complexation for type II lantibiotics.

4.3 Azinomycins

Azinomycins (150) are antitumor substances and exhibit an in vivo activity against P388 leukaemia in mice. The mechanism of action is based on DNA alkylation by the electrophilic epoxide and aziridine.

Coleman reported the partial (pyrrolidinyl-α,β-dehydroamino acid part) and total synthesis of azinomycins A (150a). Aldehyde 152 (Scheme 29) was coupled in a Horner–Emmons reaction with phosphonate 151. Bromination of the double bond and Pd-catalyzed ring closure completed the synthesis. The synthesis of 150b was published in 2003 by Hashimoto.
The synthesis of azinomycins A and B with an α,β-dehydroamino acid substructure is accomplished by dehydration of threonine. Motuporine, a methyldehydrobutyryne-containing cyclic peptide, which can be isolated from the sponge *Theonella swinhoei*, exhibits *in vitro* cytotoxicity against human cancer cells and inhibits protein phosphatase type 1. Synthetic investigations by Toogood, which failed at the ester hydrolysis of the final product and its purification, utilized the elimination of water from threonine to introduce the α,β-dehydroamino acid. In their study, the authors concluded that the presence of an α,β-dehydroamino acid was not decisive for the compound’s biological activity.

The biological activities of shorter α,β-dehydropeptides have been investigated. L-Glutamyl-α,β-dehydrobutyryne showed some inhibitory activity against γ-glutamyl transpeptidase, a membrane-bound enzyme for the transfer of glutamyl moieties. However, the hypothesized inhibitory activity of tetrapeptides that include an α,β-dehydroamino acid moiety, on the dipeptidyl peptidase cathepsin C, could not be confirmed.

Other cyclic peptides with α,β-dehydroamino acids include kahalalide F and the compound family that includes motuporine, nodularine, and microstmins LA and LR. Kahalalide F is obtained from the green algae *Bryopsis* sp. and is currently in clinical trials as a treatment of prostate cancer. It contains 13 amino acids, a 5-methylhexanoic acid at the N-terminus and a (Z)-dehydrobutyric acid moiety. The introduction of a double bond during the solid-phase synthesis of this depsipeptide is accomplished by dehydration of threonine. Motuporine, a methyldehydrobutyryne-containing cyclic peptide, which can be isolated from the sponge *Theonella swinhoei*, exhibits *in vitro* cytotoxicity against human cancer cells and inhibits protein phosphatase type 1. Synthetic investigations by Toogood, which failed at the ester hydrolysis of the final product and its purification, utilized the elimination of water from threonine to introduce the α,β-dehydroamino acid. In their study, the authors concluded that the presence of an α,β-dehydroamino acid was not decisive for the compound’s biological activity.

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helices or an S-type open structure have also been observed.

Recent work has involved the investigation of the structures of ΔAla, Val, (Z)-β-(1-naphthyl)dehydroalanine, (Z)-β-(1-pyrenyl)dehydroalanine, the conformation of N-acetyl-(E)-dehydrophenylalanine N-methylamide and peptides containing (Z)-β-(3-pyridyl)-α,β-dehydroalanine and the calculation of the structure of various α,β-dehydroamino acids.

The self-association of model peptides and α,β-dehydropeptides has been studied by IR spectroscopy, dipole-moment measurements and computer modeling, which showed that α,β-dehydropeptides have a greater tendency to associate than do their saturated counterparts.

6 Conclusions

The synthetic repertoire by which α,β-dehydroamino acids are accessible has increased significantly in the last years. In particular, the use of α,β-dehydroamino acids as substrates in transition-metal-catalyzed reactions opens new opportunities for their application in synthesis. Cyclic α,β-dehydroamino acids have mainly been applied in cycloaddition reactions, cyclopropanations, radical additions or hydrogenations. The many reported examples clearly demonstrate that α,β-dehydroamino acids, in particular those that are chiral, are useful and versatile intermediates in modern organic synthesis.

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References
