Synthesis of 1,3-Diene-Containing alpha-Amino Acids and Peptides via N-Acyliminium Ions

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Chapter 1

Unsaturated α-amino acids: isolation and synthesis

1.1 Introduction

Apart from the twenty proteinogenic amino acids (the “usual” amino acids) there is a growing number of natural but unusual α-amino acids, which have gained increasing attention in recent years. Due to the progress in enzyme engineering, a few of these amino acids can now be incorporated into enzymes and other proteins. Although the exact biological relevance of these amino acids is unknown, they are believed to play a role in the defense against predators, either as toxin or as an intermediary metabolite.

The interest in amino acids is fed by the growing desire of biologists and material scientists to implement these compounds in larger peptide structures to provide handles for tissue engineering and other complex syntheses. Besides that, they can be used for the isolation and identification of enzymes in certain enzymatic processes. When enantiomerically pure, they add to the chiral pool as well. Olefinic and acetylenic α-amino acids (Figure 1.1) constitute a large sub-class of amino acids. Due to their unsaturated nature, these α-amino acids are valuable synthetic building blocks in (organic) chemistry. Synthetic applications of these amino acids have been described in two recent reviews.

Figure 1.1

This thesis focuses on the synthesis of olefinic amino acids, and α-dienyl α-H amino acids in particular (e.g. 1), some of which have been isolated from natural sources. Therefore this introductory chapter describes the synthesis and biological activity of naturally occurring α-vinylic, α-allylic and α-propargylic amino acids (2, 3 and 4 respectively, Figure 1.1). Amino acids with more than one carbon atom between the amino acid backbone and the unsaturation as well as quaternary α-olefinic amino acids represent both a structurally and functionally distinct class of amino acids. Because of their irrelevance to the research described in this thesis, they will remain untouched throughout this discussion. An overview of the related α-dienyl amino acids will be given in Chapter 2.
1.2 Naturally occurring α-vinylc amino acids

1.2.1 α-Vinylglycine

The first amino acid to be discussed in this chapter is α-vinylglycine (2, Figure 1.2), which has the olefinic moiety directly attached to the α-carbon. The (R)-enantiomer of this amino acid is known to be produced by the mushroom Rhodophyllus nidorosus. Its antipode (S)-vinylglycine has not been isolated from biological sources yet, but has been shown to be generated in the active site of various pyridoxal phosphate (PLP) enzymes, for example during the conversion of homoserine to threonine. Both (R)- and (S)-vinylglycine display a broad spectrum of biological activity such as inhibition of several transaminases, peptide α-hydroxylating enzyme and nifS gene product inactivation, and via a radical pathway, flavo-enzyme L-amino acid oxidase inactivation. Most interestingly, α-vinylglycine has served as a template for the development of Vigabatrin, a drug which inhibits gamma-aminobutyric acid transaminase (GABA-T), and is used for the treatment of epileptic seizures.

Three years after the first racemic synthesis of α-vinylglycine by Baldwin et al., the first asymmetric synthesis of vinylglycine was published by Afzali-Ardakani and Rapoport. In this synthesis (Scheme 1.1) (S)-methionine methyl ester (5) was first oxidized, after which the resulting sulfoxide 6 was pyrolyzed under reduced pressure to give the desired (S)-vinylglycine 2 in 99% enantiomeric excess (ee). Later on Griesbeck and co-workers used a photofragmentation approach to convert a derivative of 6 (N-phthaloyl) to vinylglycine. Many other enantioselective syntheses of vinylglycine use optically active amino acids as starting chiron, such as homoserine, glutamic acid and serine. Besides amino acids, also Garner’s aldehyde and D-mannitol have been used as chiral building block for the synthesis of 2.
While the above syntheses use enantiopure starting materials, several enantioselective procedures have also been developed for the synthesis of vinylglycines. Among those are methods that make use of a chiral auxiliary such as Schöllkopf’s chiral glycine enolate bis-lactim ether and involve quenching of a lithium enolate with a chiral acid. Catalytic asymmetric syntheses have been reported by Trost, who uses a Pd(0)-mediated allylic amination with butadiene monoepoxide, and Berkowitz who employs a Ni(0)-mediated allylic amination for the synthesis of a 4-vinylloxazolin-2-one intermediate.

Enzymatic kinetic resolutions were successfully applied to vinylglycine 2. Very early on Friis et al. subjected (R,S)-2 to fermentation with Baker’s yeast to give (R)-2 in 39% yield and 82% ee. An interesting route consists of the synthesis of racemic vinylglycine via a Neber rearrangement of N-chloroimide 8, followed by a papain-mediated esterification in a biphasic system to give (S)-2 (Scheme 1.2).

Scheme 1.2

1.2.2 β-Substituted α-vinylc amino acids

Three β-substituted vinylglycine derivatives have been isolated from natural sources (Figure 1.3). 3,4-Didehydrovaline 10 is a constituent of the 13-membered macrocycle phomopsin A, which was isolated from Phomopsis leptostromiformis. Vinylglycine derivative 11 was found in Lactarius helvus and Philadelphus coronarius from which also its γ-glutamyl dipeptide 12 was isolated. Finally, β-methylene-norleucine 13 was obtained from the isolates of Amanita vaginata. None of these amino acids have been prepared synthetically, nor is there any information about their biological activity.

Figure 1.3
1.2.3 γ-Substituted α-vinylc amino acids

As is shown in Figure 1.4, some interesting γ-substituted α-vinylc amino acids have been isolated from biological sources. All these amino acids have extra hetero-atoms in the side chain, while some of them have the enol ether substructure (14 – 16).

![Figure 1.4](image)

Isolated from *Pseudomonas aeruginosa*, *E*-4-methoxyvinylglycine 14 was the first amino acid to be discovered with an enol ether functionality.42,43 This amino acid was shown to inhibit several enzymes.14,44-48 A completely stereoselective method for the synthesis of 14 has not been developed yet. The compound is either isolated as a mixture of *E/Z*- or (*R/S*)-isomers. Separation is achieved via column chromatography (*E/Z*) followed by an enzymatic resolution (*R/S*).49-51

Amino acid 15 was found in the fermentation broth of *Streptomyces sp.*,52 and was reported to inhibit cystalysin53 and several lyases.52,54,55 More important, 15 inhibits 1-aminocyclopropane-1-carboxylate (ACC) synthase, the enzyme responsible for plant ethylene biosynthesis.56 Because of this, 15 has seen wide application as a fruit ripening inhibitor. Nevertheless, only one synthesis of 15 has been reported.51

![Scheme 1.3](image)
The most structurally complex member of the enol ether subfamily of the α-vinyllic amino acids is rhizobitoxine 16. Rhizobitoxine is produced by bacteria, such as *Rhizobium japonica*57-59 and *Pseudomonas andropogonis*.60 This amino acid inhibits cystathionine β-lyase,59,61 decreases hydrogenase biosynthesis62 and, like 15, inhibits ACC synthase.63 The only synthesis of rhizobitoxine (16) was published by Keith and coworkers,64 and is depicted in Scheme 1.3. The key transformation is a Pd(II)-mediated *trans*-vinyl etherification between methoxy vinylglycine 22 and serinol 23. Protected rhizobitoxine (24) was obtained as a 1:1 mixture of E/Z-isomers which could be separated via column chromatography. The Z-isomer was resubjected to the palladium conditions to give 24 in a 3:2 E/Z-ratio. Overall 24 could be obtained in 11% yield starting from 21.

Bis-homo glutamic acid derivative 17 (Figure 1.4) was isolated from the fronds and rhizomes of *Asplenium unilaterale* and *A. wilfordii*.65,66 No synthesis has been reported, and nothing is known about its biological activity.

The naturally occurring phosphonate amino acid Z-2-Amino-5-phosphono-3-pentenoic acid (Z-APPA, 18) is a constituent of the dipeptide rhizocotics67,68 and tripeptide plumbemycins67,69 which were isolated from *Bacillus subtilis* and *Streptomyces* sp. respectively. Amino acid 18 is an irreversible inactivator of threonine synthase from *E. coli*.70 Two fully stereoselective syntheses are published for its isomer E-APPA,71,72 while a third synthesis reports the isolation of a 1:1 mixture of E/Z-APPA.73

The four related amino acids 19a-d were found as amino acid constituents in radiosumin A (19a,b) and B (19c,d), isolated from the cyanobacteria *Plectonema radiosum*74,75 and *Microcystis aeruginosa*,76 respectively. Besides their biological activity as trypsin inhibitor, nothing is known about this densely functionalized family of amino acids.

![Figure 1.5](image)

1.2.4 β,γ-Substituted α-vinyllic amino acids

The last three α-vinyllic amino acids discussed in this paragraph are β,γ-substituted (Figure 1.5). Amino acids 25 and 26 were isolated together from the mushroom *Bankera fuligineoalba*,77 while glutamic acid analogue 27 was found in *Streptomyces viridogenes*.78 Recently it was found from [15N]- and [13C]-labeled studies that the biosynthesis of 27 originates from glutamic acid or proline. The results also suggest that chlorination does not occur via a radical mechanism, but rather indicate that a FADH2-dependent halogenase is involved.79
1.3 Naturally occurring \(\alpha\)-allylic amino acids

1.3.1 \(\alpha\)-Allylglycine

Among the naturally occurring \(\alpha\)-allylic amino acids, the simplest and probably most widely studied member of the family is \(\alpha\)-allylglycine 3 itself (Figure 1.6). Natural sources for the \((R)\)-enantiomer have not been disclosed yet, but the \((S)\)-enantiomer has been isolated from the Japanese mushrooms *Amanita pseudophorphyria*80 and *A. abrupta*81 in 1985 and 1986, respectively. Until then, allylglycine 3 was a synthetic antibiotic, known to inhibit the growth of *Escherichia coli* and *Saccharomyces cerevisiae*.82 Later findings showed 3 as an inhibitor of glutamate decarboxylase and a \(\gamma\)-aminobutyric acid (GABA) antagonist.83 It is used to induce convulsions in experiments on animals. Allylglycine also inhibits protein synthesis in brain and liver mitochondria and in nerve endings.84

\[
\text{3 (S)-2-aminopent-4-enoic acid}
\]

\[
\text{L-allylglycine}
\]

\[
\text{Amanita pseudophorphyria}
\]

\[
\text{Amanita abrupta}
\]

Figure 1.6

The first synthesis of racemic allylglycine was described as early as 1908.85 This method is, although slightly modified still the method of choice for the (large scale) synthesis of racemic allylglycine, and other synthetic amino acids. It consists of the \(\alpha\)-deprotonation of diethyl 2-formamidomalonate 29 with a base, usually NaH or NaOH (Scheme 1.4), followed by the addition of an electrophile, in this case allyl bromide. The resulting diethyl 2-allyl-2-formamidomalonate 30 undergoes hydrolysis and decarboxylation under acidic conditions to provide the desired amino acid 3. Although other methods are available,86,87 they can not compete with this short and efficient synthesis.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{N} \\
\text{C} & \quad \text{O} \\
\text{O} & \quad \text{Et} \\
\text{Et} & \quad \text{Et}
\end{align*}
\]

1) base

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{N} \\
\text{C} & \quad \text{O} \\
\text{O} & \quad \text{Et} \\
\text{Et} & \quad \text{Et}
\end{align*}
\]

2) allyl bromide

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{N} \\
\text{C} & \quad \text{O} \\
\text{O} & \quad \text{Et} \\
\text{Et} & \quad \text{Et}
\end{align*}
\]

aq, HCl

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{N} \\
\text{C} & \quad \text{O} \\
\text{O} & \quad \text{Et} \\
\text{Et} & \quad \text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 & \quad \text{COO} \\
\text{HO} & \quad 
\end{align*}
\]

Scheme 1.4

Allylglycine has served as model substrate in the development of many asymmetric methods and therefore a wide variety of methods is available for the enantioselective synthesis of either \((R)\) or \((S)\)-3. The starting point of many protocols is the addition of an allyl
source to a glycine derivative substituted with a chiral auxiliary on the N- or C-terminus, or both. Although good ee’s are obtained, the need to cleave and recycle the auxiliaries makes these methods less attractive. A convenient procedure was developed by O’Donnell in which an enantiopure phase transfer catalyst (PTC) is used for the addition of an allyl source to a Schiff-base like 7 (Scheme 1.5). Many different PTC’s have been developed, among which cinchona alkaloid and binaphthyl derivatives. In this way, (R) and (S)-3 have been prepared in over 90% yield and up to 97% ee.

Scheme 1.5

Enzymatic resolution is a different option for obtaining both enantiomers of 3. Among the enzymes used are Porcine Kidney Acylase I, α-Chymotrypsin (esterase) and an amidase from Pseudomonas putida (Scheme 1.6). The amidase from P. putida first hydrolyzes one of the amino acid amide enantiomers into the desired amino acid with high selectivity. Then the unreactive substrate enantiomer is converted into its Schiff base (see Chapter 4.4) which allows for the separation of (S)-3 and (R)-33. After hydrolysis of (R)-33 by a second enzyme (Rhodococcus erythropolis) both allylglycine antipodes can be obtained in high yield and more than 99.5% ee (Scheme 1.6). The group of LeMaster reported the conversion of racemic allylglycine into the (S)-product. In this method a D-amino acid oxidase was coupled with an aminotransferase using L-glutamate as the substrate (nitrogen source) for the transferase. Using this elegant system, (S)-3 could be obtained in 61% yield and 98.5% ee.

Scheme 1.6
1.3.2 Alkyl-substituted α-allylic amino acids

Besides the parent compound 3, nature has developed a wide spectrum of substituted allylglycine based unusual amino acids, of which the alkyl substituted ones are depicted in Figure 1.7. The 2-ethyl-substituted allylglycine 34 has only recently been isolated from the sponge Plukortis simplex,106 a year after the synthesis of its N-acetyl derivative.107 Via a double bond isomerization 34 is structurally related to amino acid 35. This toxic amino acid was first isolated together with its γ-glutamyl dipeptide 36 from Aesculus californica108,109 and later also appeared to be present in the endosperm of the fruit of this species.110

![Figure 1.7](image)

Compound 35 has been reported to have antibiotic properties111 and could serve as a phenylalanine surrogate.109 The racemic synthesis of 35 was easily achieved by the addition of (E)-1-bromo-2-methyl-2-butene to acetamidomalonic or acetamidocynoacetic ester.109,111,112 By virtue of [13C]-labeling experiments 35 was shown to originate from isoleucine via a series of biotransformations.113,114 The group of Dardenne isolated prenyl derivative 37 from the mushroom Leucocortinarius bulbiger (Figure 1.7) in 1968.115 Although nothing is known about its biological properties, it has served as a target substrate in many asymmetric syntheses. Besides its racemic synthesis in 1971,116 stereoselective syntheses based on chiral auxiliaries,88,117,118 chiral hydrogenation (38 to 39, Scheme 1.7)119 and construction from chiral starting materials (39 from 40),120,119 have been reported.

![Scheme 1.7](image)
1.3.3 ε-Hydroxy-substituted α-allylic amino acids

Not surprising, allylglycine derivative 41 (Figure 1.8) was isolated from the same source as the structurally related unsaturated amino acid 35.\(^{108,109}\) It is believed that both amino acids are part of the biosynthetic pathway towards hypoglycin A (44, Figure 1.8), a very toxic amino acid which was first isolated from Blighia sapida.\(^{121}\) In the same way 42, isolated from the seed of Blighia umiagata,\(^{122}\) can be regarded as the hydroxylated analogue of 37. Like allylglycine 2 itself, chlorohydroxyamino acid 43 was found in the mushroom Amonita abrupta.\(^{123}\) This amino acid is believed to be formed by the addition of chlorohydrin to 2-amino-4,5-hexadienoic acid (see Chapter 2) which is also present in the same mushroom. Although these three allylic alcohols are structurally intriguing amino acids, no biological properties or syntheses have been reported to date. It has to be noted, however, that the aqueous extract of Amonita abrupta is highly toxic,\(^{81}\) so 43 should be treated with precaution.

![Figure 1.8](image)

1.3.4 Chlorinated α-allylic amino acids

Besides (Z)-2-amino-5-chloro-6-hydroxyhex-4-enoic acid 43, four other chlorinated allylic amino acids have been isolated from various Amanita species (Figure 1.9). Among those are three different regioisomeric chloro-allylglycines 45 – 47. The δ-(S,Z)-isomer 45 was found in A. virgineoides\(^{124}\) while the racemate was isolated from A. castanopsidis Hongo.\(^{125}\) Its (E)-isomer 46 was isolated from A. cokeri in 2002.\(^{126}\) Both amino acids have been synthesized as racemates using the acetamido malonic ester method. They were mostly prepared as (E,Z)-mixtures.\(^{127-129}\) Only one stereoselective synthesis is known.\(^{130}\) Until now, no enantioselective synthesis has been reported. The amino acids 45 and 46 do not appear to be very toxic. From a series of toxicological studies, 45 has only been found to inhibit the root elongation in lettuce seedlings.\(^{125,126}\) The third regioisomer γ-chloroallylglycine 47 was found in A. pseudoporphyria Hongo, and has only been synthesized as a racemate by the reaction of 2,3-dichloropropene with formylamino malonic acid diethyl ester.\(^{130,131}\) Unfortunately, 47 has not been tested for biological activities.

![Figure 1.9](image)
Finally, (S,Z)-2-amino-5-chlorohex-4-enoic acid 48 was found in *A. solitaria*.\textsuperscript{132} As was the case with 43, 2-amino-4,5-hexadienoic acid (Chapter 2) was also found in large amounts in this mushroom. Therefore, the authors believe that 48 is the product of hydrochloride addition to this allene. Besides racemic synthesis via the usual acetamidomalonate alkylation route,\textsuperscript{132} 48 has also been found as the isomerized product after the addition of HCl to homo-propargylglycine.\textsuperscript{133}

1.3.5 \(\gamma\)-Methyleneglutamic acid derivatives

Remarkably enough, until now only one \(\beta\)-substituted allylglycine derivative has been isolated. In 1974 the group of Dardenne reported the isolation of 2(S),3(S)-3-hydroxy-4-methyleneglutamic acid 49 from the seeds of *Gleditsia caspica* (Figure 1.10).\textsuperscript{134} To the best of our knowledge, no synthesis of this highly functionalized amino acid has been reported. However, 49 is a member of a group of \(\gamma\)-methylene-substituted glutamic acid derivatives (Figure 1.10).

![Figure 1.10](image)

The naturally most abundant of this series of unusual amino acids is *L*-\(\gamma\)-methyleneglutamic acid 50, which has been identified in more than 20 different species of plants, mushrooms and fungi.\textsuperscript{135-139} It has been shown to exhibit strong CNS inhibitory action,\textsuperscript{140,141} and in peptides, to inhibit the vitamin K mediated \(\gamma\)-carboxylation of glutamic acid, which is important in the blood clotting process.\textsuperscript{142}

![Scheme 1.8](image)

Both racemic\textsuperscript{143} and enantioselective syntheses\textsuperscript{144,145} of 50 have been published. The enantioselective method depicted in Scheme 1.8 was also used for the synthesis of 52 and 53, and provides a general synthesis for amino acid displaying this \(\alpha,\beta\)-unsaturated acid
moiety.\textsuperscript{144} Of these last two amino acids, propylidene derivative \textit{53} is the most rare with only one natural source known,\textsuperscript{136} while \textit{52} was isolated from about a dozen natural sources.\textsuperscript{135,136,138,139} The double bond in \textit{52} and \textit{53} was determined to have the \textit{E}-configuration.\textsuperscript{146} Finally, glutamine derivative \textit{51} was isolated from five natural sources,\textsuperscript{138,147,148} and has been synthesized only once,\textsuperscript{149} a few years after its first isolation from \textit{Arachis hypogaea}.

1.3.6 Cyclic $\alpha$-allylic amino acids

A structurally somewhat different class of naturally occurring unsaturated amino acids are the cyclic $\alpha$-allylic amino acids (Scheme 1.9). This class can be divided in two subclasses: amino acids having the double bond positioned endocyclic and exocyclic. Perhaps the most intriguing cyclic amino acid is the cyclopropylglycine \textit{57} and its $\gamma$-glutamyl dipeptide \textit{58}. While \textit{57} was isolated from \textit{Litchi chinensis},\textsuperscript{150} dipeptide \textit{58} was isolated from \textit{Acer pseudoplatanus}.\textsuperscript{151} Both compounds were found together in \textit{Billia hippocastanum}.\textsuperscript{152} This methylenecyclopropyl amino acids belongs to a larger subfamily, all containing this special moiety, only differing in the spacer between the amino acid backbone and the cyclopropyl group. All these molecules are highly toxic, of which hypoglycin A (\textit{44}, Figure 1.8) and its $\gamma$-glutamyl dipeptide hypoglycin B are the most infamous. They are known to cause Jamaican vomiting sickness, and ultimately death. In rats, \textit{57} was shown to be equally toxic as hypoglycin A.\textsuperscript{150} Despite (or perhaps because) its biological activity, only one synthesis of \textit{57} is known.\textsuperscript{153}

![Scheme 1.9](image)

The opposite is true for 4-methyleneproline \textit{59}. Isolated as a racemate from \textit{Eriobotrya japonica} and \textit{Raphiolepis indica},\textsuperscript{154-156} it has been synthesized many times. At first to confirm the proposed structure of the isolate,\textsuperscript{157,158} later for its biological properties \textsuperscript{159,160} and as a test substrate for the development of new synthetic methodologies. One of the shortest routes goes via the commercially available 4-hydroxyproline. Oxidation to the corresponding ketone followed by a Wittig reaction gives the desired 4-methyleneproline \textit{59}.\textsuperscript{160} Other syntheses go via a radical mechanism\textsuperscript{161} or start from pyroglutamic acid\textsuperscript{162} or from Seebach’s imidazolidinones.\textsuperscript{163} In the latter procedure (Scheme 1.10), imidazolidinone \textit{62} (prepared from pivaldehyde and 2-amino-$N$-methylacetamide followed by a resolution with a chiral acid)\textsuperscript{164} was treated with LDA and 3-chloro-2-(chloromethyl)prop-1-ene. After TFA induced
liberation, the free nitrogen substitutes the allylic chloride to give bicyclic product 63. Hydrolysis of 63 gave the desired 4-methylene proline 59 in 33% yield and 90% ee.

Scheme 1.10

The six-membered cyclic amino acid (S)-baikiain, 60, was first isolated from the bark of *Baikiaea plurijuga* in 1950. Later it was also found in *Caesalpinia tinctoria*, mushrooms and many (red) algae. Many syntheses have been described, some of them racemic, most of them enantioselective. A recent review by Kadouri-Puchot and Comesse about piperolic acid derivatives describes several syntheses of baikiain. One of the syntheses consists of a palladium-catalyzed coupling between sulfonamide 64 and benzyloxyallene 65 providing N,O-acetal 66 (Scheme 1.11). Grubbs I catalyzed ring closure (67) and an N-sulfonyliminium ion reduction to 68 established the baikiain ring. Although no extensive toxicological studies have been undertaken, baikiain was shown to have antibiotic properties, as well as activity as an amnesic agent.

β-Hydroxy-substituted baikiain 61 was isolated from the toxic mushroom *Russula subnigricans* together with baikiain itself in 1987. Except for one (partial) synthesis little is known about this natural product.

Scheme 1.11

1.4 Naturally occurring α-propargylic amino acids

1.4.1 α-Propargylglycine

The parent compound of all α-propargylic amino acids, (S)-2-aminopent-4-yne acid, or *L*-propargylglycine (4, Figure 1.11) was isolated from the mushroom *Amanita*
unsaturated α-amino acids: isolation and synthesis

*pseudoporphyria* (Figure 1.11) and the fermentation broth of *Streptomyces* sp. Propargylglycine has been studied intensively for its biological activities. It strongly inhibits the growth of *Saccharomyces cerevisiae*, but less strongly that of *Escherichia coli*. Further, it inhibits amylase synthesis and inactivates the pyridoxal phosphate dependent enzymes. Also the phenomenon of specific disintegration of *Hydra japonica* by treatment with 4 was reported.

![Amanita pseudoporphyria](image)

Figure 1.11

Like allylglycine, the first synthesis of 4 was described long before its first isolation from natural sources. In 1949, Gershon et al. used the acetamido malonic ester method for the racemic synthesis of 4. The enantioselective synthesis of propargylglycine has been conducted in many different ways. Most popular are the enzymatic resolutions and the methods employing a chiral auxiliary. One of the methods consists of the addition of glycine to the enantiopure proline-derived amide 69 to form a Schiff base (Scheme 1.12). Chelation by nickel forms a chiral environment, in which the top side of the complex is shielded by the N-benzyl moiety. Addition of propargyl bromide gives adduct 71, which after hydrolysis gives the desired amino acid (S)-4 in 90% yield and 94% ee and liberates the chiral auxiliary that can be re-used.

![Scheme 1.12](image)
1.4.2 Substituted α-propargylic amino acids

In the last half of the 20th century four substituted α-propargylic amino acids have been isolated from natural sources (72 – 75, Figure 1.12). (S)-2-Aminohex-4-ynoic acid 72 was found in *Amanita* sp.\(^{80,133}\) and *Tricholomopsis* sp.\(^{194,195}\) from which also its γ-glutamyl dipeptide was isolated.\(^{196}\) This amino acid seems to exist in several enantiomeric ratios, because the optical rotation of 72 is different in each source. It has been reported earlier that the R:S ratios of amino acids can be dependent on the season as well as on the plant species.\(^{65,66}\) Amino acid 72 was reported to have inhibitory and regulatory effects on ATP:L-methionine S-adenosyltransferase.\(^{197}\) Besides its more or less standard racemic synthesis\(^{195}\) three enantioselective syntheses have been reported. Two of them are enzymatic resolutions (comparable with the synthesis of allylglycine, Scheme 1.6),\(^{104,198}\) the third makes use of the method shown in Scheme 1.12.\(^{199}\)

![Figure 1.12](image)

*Figure 1.12*

The β-hydroxy analogue of propargyl glycine (74) was found in the fungus *Sclerotium rolfsii* in 1977.\(^{200}\) This amino acid was shown to be toxic to New Hampshire chickens (LD\(_{50}\), 150 mg/kg).\(^{200}\) It was prepared by treatment of copper(II)glycinate 79 with propiolaldehyde 80a, providing a diastereomeric mixture of the desired product (Scheme 1.13).\(^{200}\) The same method was used for the synthesis of 75 which was found as a mixture of erythro and threo isomers in *Tricholomopsis rutilans* (Figure 1.12) three years earlier.\(^{202}\) Remarkably, only the erythro isomer of 75 was also isolated as its γ-glutamyl dipeptide 76 from the same organism. Most likely, threo-75 is not a substrate for γ-glutamylpeptidase,\(^{203}\) the enzyme responsible for the formation of the γ-glutamyl dipeptides, whereas erythro-75 is.

The last amino acid to be discussed is (R)-2-amino-6-hydroxyhex-4-ynoic acid 77. This propargylic alcohol was found in the fruiting bodies of *Amanita miculifera*, as reported by Hatanaka *et al.* in 1998.\(^{133}\) The compound was synthesized from formamidomalonate and 1-chloro-but-2-yne-4-ol.\(^{133,174}\) The results of an enzymatic resolution (renal acylase) of its 2-chloroacetamide confirmed the unusual isolation of the R-enantiomer from the mushroom.
Recently (S)-77 has been prepared in a similar manner, using L-acylase.\textsuperscript{204} No biological properties have been reported until now.

![Scheme 1.13](image)

**1.5 Outline of this thesis**

In this chapter the isolation and synthesis of a wide variety of unusual though naturally occurring unsaturated amino acids have been summarized. It is clear that many structurally interesting compounds can be obtained from natural sources, but their synthesis is not always that simple. This thesis details the development of new methodologies for the synthesis of α-amino acids and dipeptides containing an unsaturated moiety on the α-position.

Chapter 2 describes the synthesis of a series of racemic diene-containing α-amino acids, via N-acyliminium ion chemistry, some of them being natural products. In Chapter 3, the methodology described in Chapter 2 is extended to the dipeptide series. Chapter 4 describes the total synthesis of a naturally occurring α-dienic amino acid and its γ-glutamyl dipeptide. This chapter also includes the comparison of several enzymatic systems for the resolution of amino acids. In Chapter 5, a new method is presented for the fast and simple synthesis of 2-substituted piperazines.

**1.6 References**

Chapter 1


Unsaturated α-amino acids: isolation and synthesis