SYNTHESES OF β,γ-UNSATURATED α-AMINO ACIDS

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A review article about synthetic procedures to α-amino acids with multiple bond at β,γ-position which have been developed so far. Attention is also paid to the title syntheses of optically active products.

1. INTRODUCTION

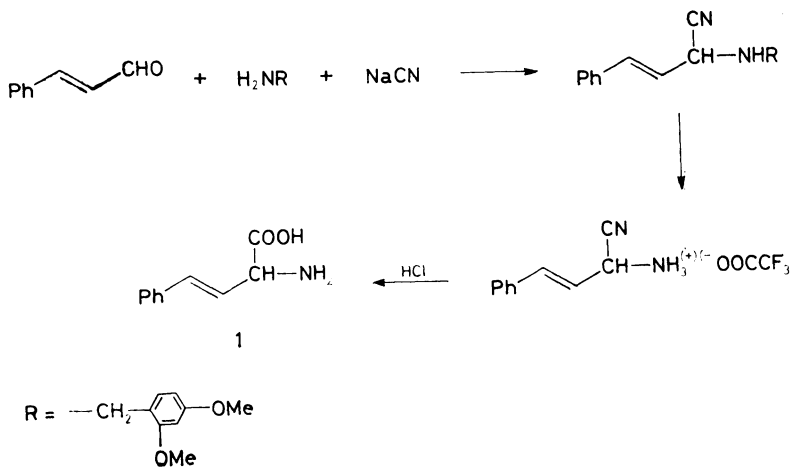
The synthesis of β,γ-unsaturated α-amino acids represents an interesting area of chemistry of compounds with antibiotic effects. They include, first of all, inhibitors of enzymes which metabolize amino acids (ornithine decarboxylase, alanine racemase, glutamate transaminase, aspartate transaminase, β-cystathionase). Unsaturated amino acids also enable preparation of tritium-labelled amino acids and peptides by addition of tritium to the multiple bonds.

The aim of this paper is to give a survey of described syntheses of α-amino acids with a multiple bond at the β,γ-position and a hydrogen atom at α-position. Syntheses of these amino acids (in contrast to their α-alkylated derivatives) are often complicated by rearrangement of double bond to α,β-position and by an increased tendency to racemization.

2. SYNTHESES OF β,γ-UNSATURATED α-AMINO ACIDS

2.1. *Strecker Synthesis*

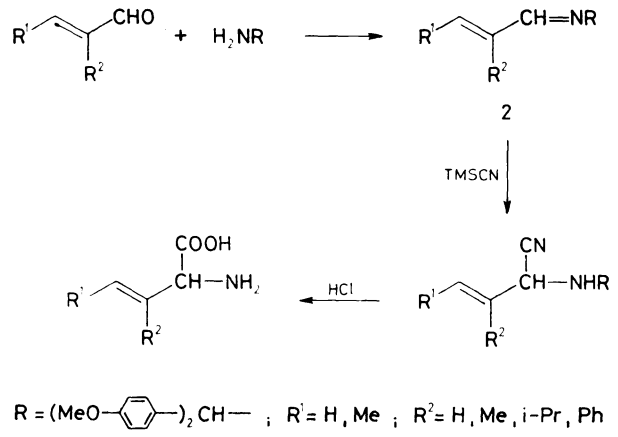
The Stecker synthesis represents a general procedure for preparation of 2-amino acids which, in principle, is applicable to 3,4-didehydro-2-amino acids, too. Thus e.g. Hines et al.[1] developed a synthesis of (*E*)-2-amino-4-phenyl-3-butenoic acid (**1**) making use of 2,4-dimethoxybenzyl protective group (Scheme 1, yield 39%).



SCHEME 1

Comparison with the further-given examples of syntheses shows that conjugation of the double bond with an aromatic ring contributes to relative successfulness of the Strecker synthesis by stabilizing the double bond position. The corresponding aliphatic unsaturated aldehydes give complex mixtures under conditions of the Strecker synthesis, the nature of the side products being not discussed in literature. Thus e.g. the synthesis of 2-amino-3-ethyl-3-butenoic acid from 2-ethyl-2-propenal (NH_4Cl, KCN) reported by Levenberg[2] gave a yield of 0·4%. Without giving the yield, Cahil et al.[3] described the synthesis of (*E*)-2-amino-3-methyl-3-pentenoic acid from (*E*)-2-methyl-2-butenal (NH_4Cl, NaCN). 2-Amino-3-butenoic acid was prepared from acrolein[4] (NH_4, KCN) in the yield of 1·1%. The preparation of 2-amino-2-(2-cyclohexenyl)acetic acid from 1-cyclohexenecarbaldehyde is described in patent literature: *1*) NH_4Cl, NaCN, yield 25% (ref.[5]); *2*) $(NH_4)_2CO_3$, KCN, yield 27% (ref.[6]). Relatively successful (27% yield) was the synthesis of (*E*)-2-amino-3-methyl-3-pentenoic acid from (*E*)-2-methyl-2-butenal ($AcONH_4$, KCN, EtOH) described by Greenlee[7].

The last paper mentioned[7] also gives a modified Strecker synthesis for preparation of other 3,4-didehydro-2-amino acids with overall yields as high as 50% (Scheme 2). The synthesis is based on the addition of trimethylsilyl cyanide (TMSCN) to a pre-



SCHEME 2

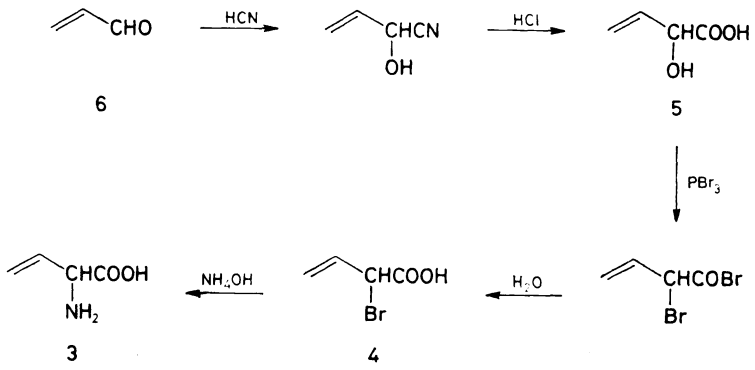
-synthetized unsaturated aldimine **2**. 4,4'-Dimethoxybenzhydryl group proved useful in protecting the imino group. The reaction of starting *E* isomers of aldehydes gave less than 5% of the *Z* product in all the cases. The application of TMSCN significantly favours the 1,2-addition to the detriment of the 1,4-addition to the conjugated system of double bonds in aldimine as it follows from ref.[8], whereby the synthesis course is markedly positively affected. A limitation of the method mentioned consists in impossibility of preparation of 4,4-disubstituted 3,4-didehydro-2-amino acids, since acid hydrolysis of the corresponding aminonitrile produces the respective γ-lactone. The following amino acids were prepared by the procedure given in Scheme 2 (yield): D,L-(*E*)-2-amino-3-heptenoic acid (45%), D,L-(*E* + *Z*)-2-amino-3-pentenoic acid (*E*/*Z* = 95/5; 48%), D,L-(*E*)-2-amino-3-methyl-3-pentenoic acid (44%), D,L-2--amino-3-butenoic acid (7%), D,L-(*E*)-2-amino-4-phenyl-3-butenoic acid (15%). Later the method was applied by Thornberry et al.[9] to the synthesis of 2-amino-3-fluoro-3--butenoic acid from 2-fluoro-2-propenal (25%).

2.2. *Reactions of Ammonia with 2-Halogeno-3,4-didehydroacids*

Friis et al.[4] described syntheses of 2-amino-3-butenoic acid (**3**) from ethyl 2-bromo-3--butenoate. The highest yield (6·6%) was obtained from the reaction of the bromo derivative **4** with concentrated aqueous ammonia at −5°C. Rando[10] synthetized 2-amino-3-butenoic acid (**3**) in the yield of 50%, starting (in contrast to Friis[4]) from

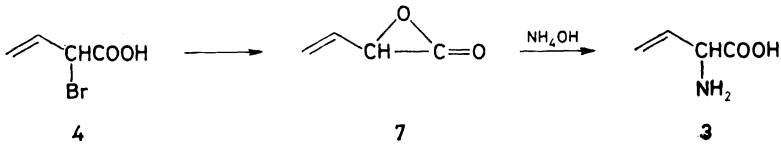
free 2-bromo-3-butenoic acid (**4**). Rando[11] also mentioned a synthesis of (*E*)-2,5--diamino-3-pentenoic acid from 2,5-dihydroxy-3-pentenoic acid without giving the reaction intermediates and yields.

Baldwin et al.[12] published a synthesis of 2-amino-3-butenoic acid (**3**) from 2--hydroxy-3-butenoic acid (**5**) with the yield of 26% (Scheme 3). The starting hydroxy



SCHEME 3

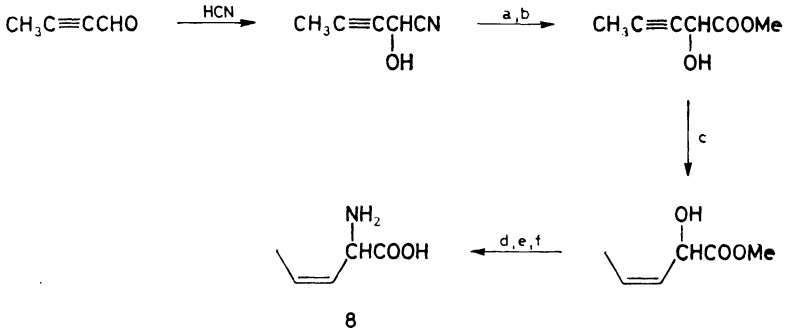
acid was prepared from acrolein (**6**) with a yield of 37%. The authors state that on submitting ethyl 2-bromo-3-butenoate (instead of the free acid) to action of ammonia they obtained a complex reaction mixture with ethyl 2-amino-2-butenoate as the main component, wherefrom they conclude that the reaction of ammonia with acid **4** goes via α-lactone **7** (Scheme 4). (*E*)-2-Amino-3-pentenoic acid was prepared



SCHEME 4

analogously (Scheme 3) from crotonaldehyde[13,14] with a yield of 21%. The *Z* isomer of amino acid **8** was obtained by Johnston et al.[14] from 2-butinal by the reaction sequence given in Scheme 5 in an overall yield of 5%.

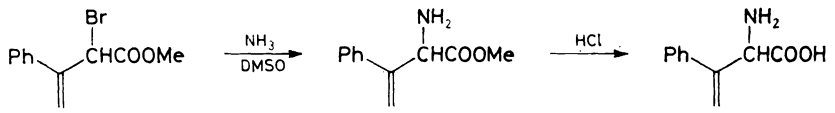
Chari et al.[15] (Scheme 6), when synthetizing 2-amino-3-phenyl-3-butenoic acid (**9**), carried out the substitution of bromine atom by amino group in dimethyl sulfoxide medium. They state that this procedure restricts the extent of side reactions due to the acidity of hydrogen atom at α-position. The satisfactory reaction yield (55%) certainly is a consequence of stabilization of the double bond position by conjugation with the aromatic nucleus.



8

a) HCl ; b) CH_2N_2 ; c) H_2,Lindlar catalyst ; d) NaOH ; e) PBr_3 ; f) NH_4OH

SCHEME 5



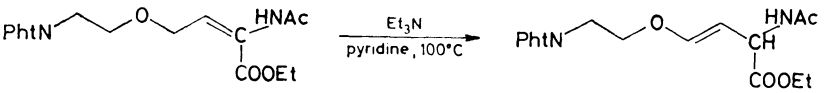
9

SCHEME 6

2.3. *Rearrangement of Double Bond from* 2,3-*Position*

2,3-Didehydro derivatives of 2-amino acids are relatively well accessible, viz. predominantly by elimination reactions. Hence in suitable cases there seems to be a possibility of their application to syntheses of 3,4-didehydro-2-amino acids by the so-called deconjugation reactions.

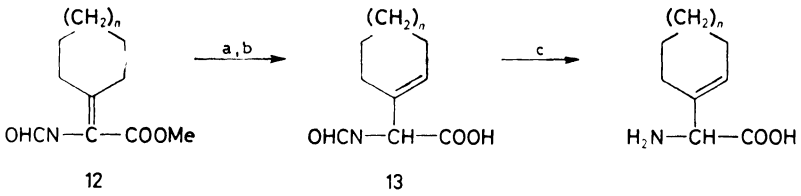
Keith et al.[16] described the synthesis of (*E*)-2-amino-4-(2-aminoethoxy)-3-butenoic acid by isomerization of the 2,3-unsaturated derivative **10** to enol ether **11** (Scheme 7)



10 11

SCHEME 7

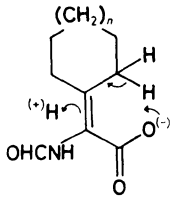
by action of triethylamine at enhanced temperatures. The synthesis utilizes the fact that a double bond is stabilized more effectively in enol ether than it is by conjugation with an ester function.



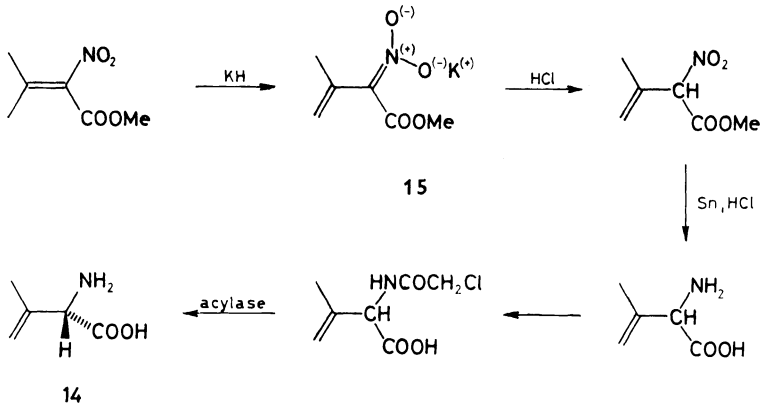
$n = 0, 1, 2, 3, 7$
a) KOH ; b) HCl, 0°C ; c) HCl, 50°C

SCHEME 8

Nunami et al.[17] (Scheme 8) made use of a rearrangement of double bond of alkylideneformamidoacetates **12** to 3,4-position taking place during saponification of the ester group (2M KOH in methanol at 50°C or in THF–H_2O at 25°C). On the basis of results of studies of rearrangement of double bond the authors suggest the cyclic reaction mechanism presented in Scheme 9. They successfully prepared several



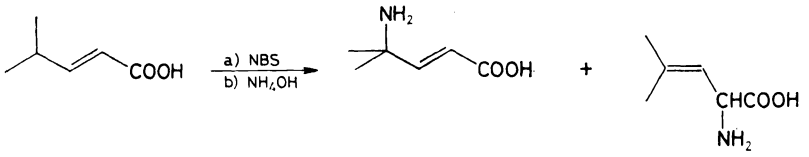
SCHEME 9



SCHEME 10

cycloalkenyl derivatives of glycine in high yields 80–90% (**12** → **13**). Among the aliphatic amino acids only 2-amino-3-methyl-3-butenoic acid was prepared in this way (this compound is often denoted as isodehydrovaline). The saponification in this case takes the desired course in a THF–H_2O system (yield 42%). If methanol is used as the solvent, the main product is the 2-amino-3-methoxy-3-methylbutanoic acid formed by the Michael addition.

Baldwin et al.[12] (Scheme 10) published a synthesis of L-2-amino-3-methyl-3-butenoic acid (**14**) by the deconjugation reaction of potassium salt of aci-tautomer of methyl 2-nitro-3,3-dimethylacrylate (**15**) in the overall yield of 8%.



16 17

SCHEME 11

Allan[18] described the formation of 2-amino-4-methyl-3-pentenoic acid (**17**) as an easily separable side product in a preparation of 4-amino-4-methyl-2-pentenoic acid (**16**). The yields of this two-step synthesis are 16% and 24%, respectively (Scheme 11).

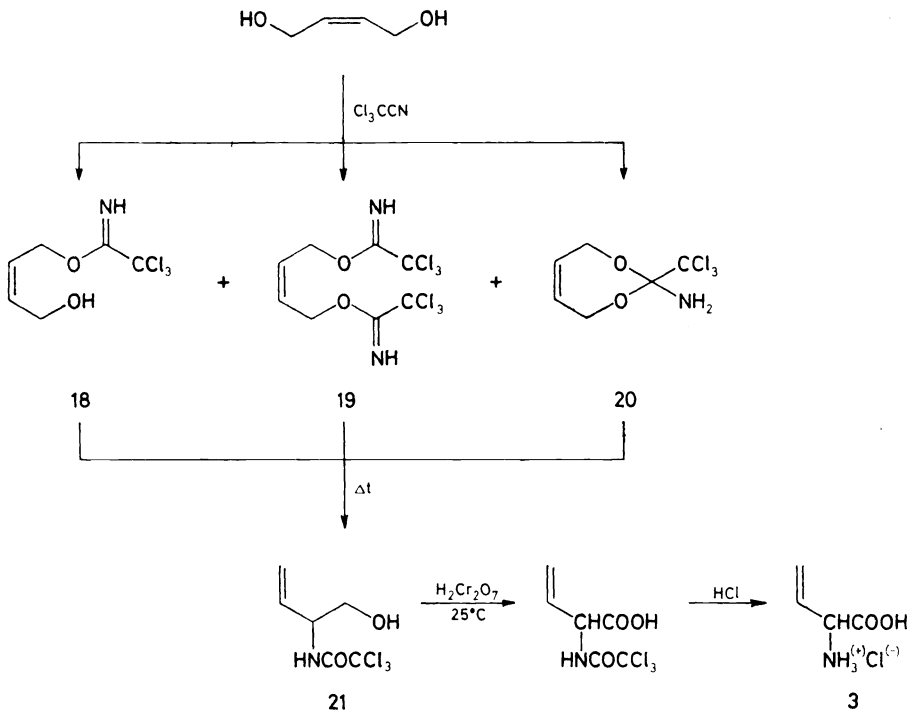
2.4. *Molecular Rearrangement*

Vyas et al.[19] (Scheme 12) described the synthesis of 2-amino-3-butenoic acid (**3**) based on a thermal rearrangement of the imino derivative **18** or **19** or that of 4,7-dihydro-1,3-dioxepine derivative **20** to the trichloroacetamide derivative **21**. The conditions of this thermal rearrangement were studied on the isolated derivatives **18**, **19**, **20**, but the synthesis is feasible also with a raw mixture of the derivatives mentioned. The overall yield of this synthesis starting from (*Z*)-2-butene-1,4-diol is 26%.

Campbell et al.[20] (Scheme 13) utilized the thermal rearrangement of trichloromethylimido derivative **22** for a synthesis of lactone of *R*- and *S*-(*Z*)-2-trichloroacetyl-5-hydroxy-3-pentenoic acids **23** (yield 61%).

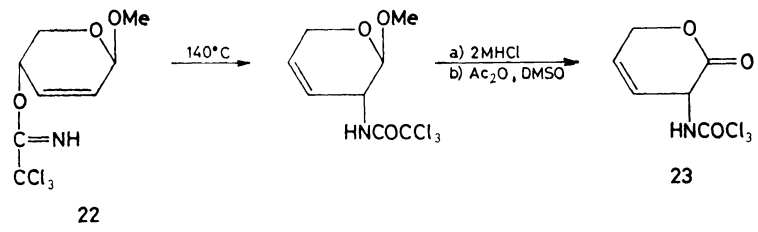
Fitzner et al.[21] prepared a number of methyl esters of N-alkoxykarbonyl-3,4-didehydro-2-amino acids **24** based on the oxidative amidation of phenylalkylselenides **25** with subsequent rearrangement (Scheme 14). In this case the choice of the base appeared to be significant. An attempt at the application of triethylamine instead of diisopropylamine led to formation of the 2,3-didehydro derivatives. A drawback of this synthesis lies in that the starting phenylalkyl selenides are not easily accessible.

The said process was applied to preparations of racemic N-alkoxycarbonyl esters of the following amino acids (yield): 2-amino-3-butenoic acid (66%), (*E*)-2-amino-3-



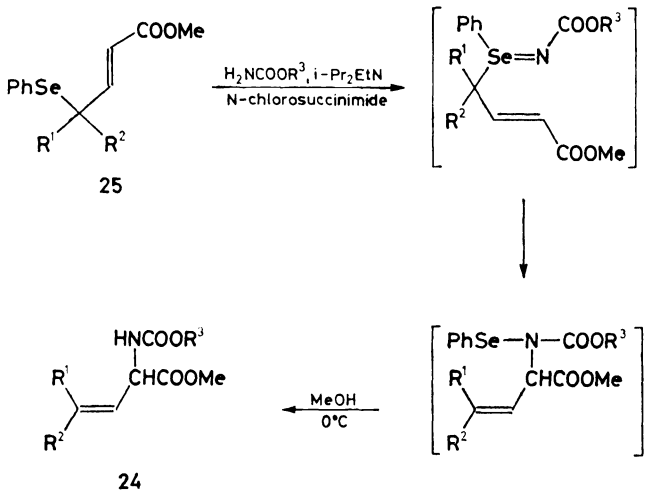
SCHEME 12

-pentenoic acid (72%), 2-amino-4-methyl-3-pentenoic acid (32%), 2-amino-3-cyclohexylidenepropanoic acid (12%).



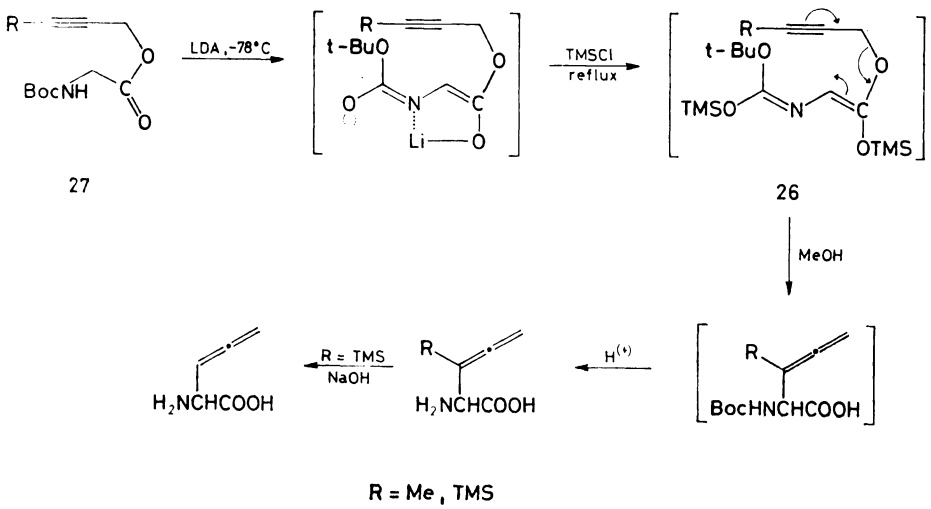
SCHEME 13

Castelhano et al.[22] described syntheses of 2-allenyl-2-amino acids by the so-called Ireland–Claisen rearrangement of the silylenolether **26** which is formed by deprotonation and subsequent silylation of the starting 2-butinyl N-Boc-glycinate **27** (Scheme



SCHEME 14

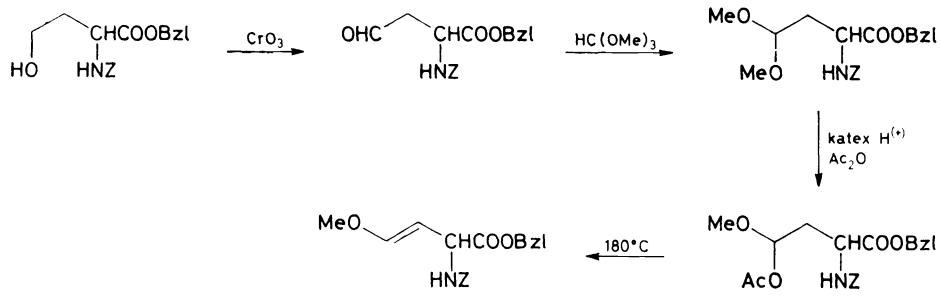
15). 2-Amino-3,4-pentadienoic acid was prepared with a yield of 5% and 2-amino-3--methyl-3,4-pentadienoic acid with a yield of 20%.



SCHEME 15

2.5. *Elimination Reactions*

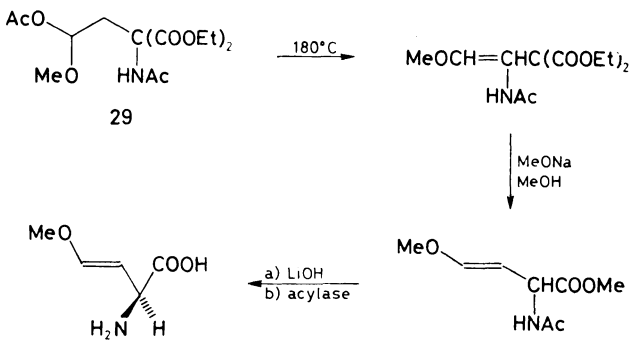
Keith et al.[23] (Scheme 16) described a synthesis of benzyl 2-benzyloxycarbonylamino -4-methoxy-3-butenoate (**28**) from 2-amino-4-hydroxybutanoic acid with the overal



28

SCHEME 16

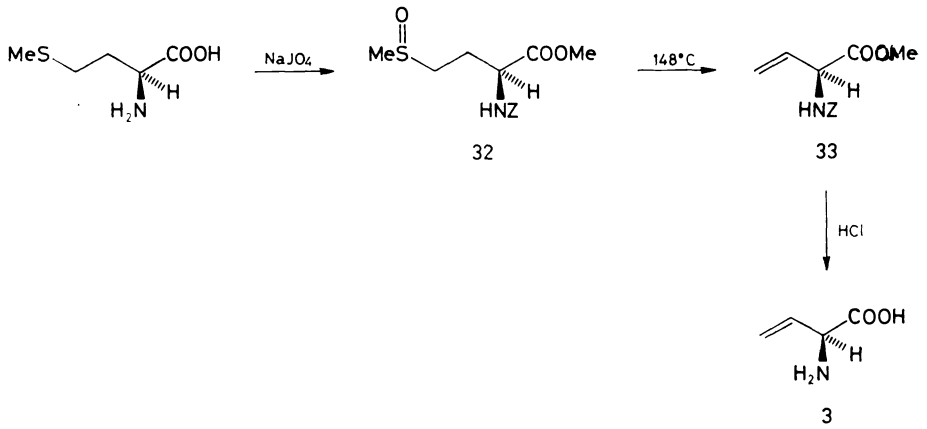
yield of 14% and the isomer ratio $E/Z = 3/2$. A later modification[24] of this synthesis uses the pyrolysis of the malonate derivative **29** (Scheme 17). The (*E*)-N-acetyl derivative of amino acid **30** separated from a mixture of geometrical isomers by means of chromatography on silica gel was – after hydrolysis of the ester group – submitted to enzymatic resolution, which gave L-(*E*)-2-amino-4-methoxy-3-butenoic acid (**31**) in the total yield of 22%.



SCHEME 17

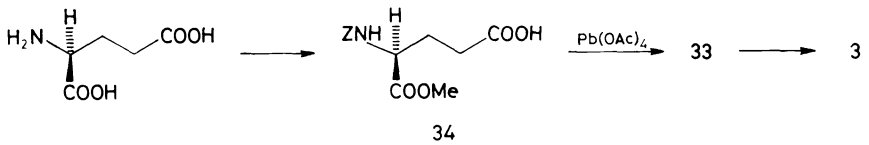
The β-elimination reaction was used advantageously as the key step of a number of syntheses of 2-amino-3-butenoic acid (vinylglycine) (**3**). Ardakani et al.[25] prepared L-2-amino-3-butenoic acid (**3**) from L-methionine in an overall yield of 57% (Scheme

18). The double bond is introduced into the molecule by the thermal *syn*-elimination of sulfoxide **32**. The authors pointed out that bases (even as weak ones as triethylamine) caused a rapid isomerization of the ester **33** to the α,β-unsaturated compound. A certain improvement of yield in this synthesis was achieved by Meffre et al.[26] who carried out the pyrolysis of sulfoxide **32** in the presence of calcium carbonate.



SCHEME 18

A modification of the above-mentioned procedure based also on the pyrolysis of sulfoxide was suggested by Weber et al.[27]: the carboxylic group and amino group are blocked by formation of oxazolidin-5-one.

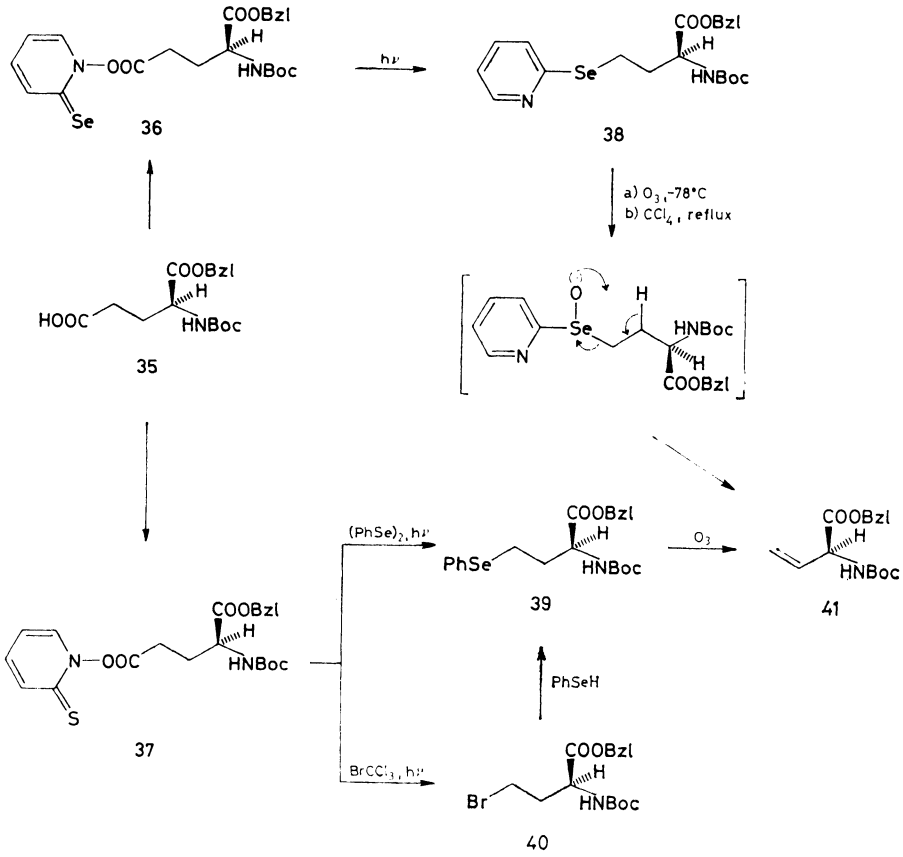


SCHEME 19

Another synthesis[28] (Scheme 19) starts from L-glutamic acid and gives L-2-amino-3-butenoic acid (**3**) in a yield of 50%. The monomethyl ester **34**, on boiling in benzene with lead tetraacetate and catalytic amount of cupric acetate, splits off formic acid to give the desired protected amino acid **33**.

Other procedures adopting L-glutamic acid for synthesis of L-2-amino-3-butenoic acid (**3**) were developed by Barton et al.[29,30] (Scheme 20). The starting 1-benzyl ester of N-Boc-L-glutamic acid **35** was activated as a mixed anhydride and was left

to react with N-hydroxy-2-selenopyridine or N-hydroxy-2-thiopyridine. Photolysis of the esters **36**, **37** formed generates the radical $^{\bullet}CH_2CH_2C(BocNH)COOBzl$ which – according to the reaction conditions – provides the compounds **38**, **39**, or **40**.

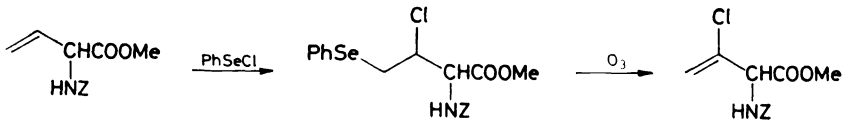


SCHEME 20

The seleno derivatives **38**, **39**, finally, were degraded by oxidation (a *syn*-elimination of pyridylselenoxide or phenylselenoxide) to give the protected L-2-amino-3-butenoic acid **41**. The synthetic procedures going via the derivative **38** or **40** give the product **41** in a yield of 45%. The last pathway via the derivative **39** gives a yield as high as 80%. However, the syntheses have the drawback in that they necessitate the (unpleasant) manipulation with selenium compounds.

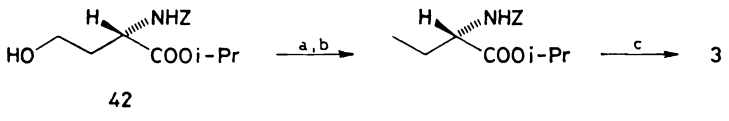
Thornberry et al.[9] (Scheme 21) applied the elimination of phenylselenoxide to

transformations of D- and L-2-amino-3-butenoic acids into D- and L-2-amino-3--chloro-3-butenoic acids, respectively (15% yields).



SCHEME 21

Pellicciari et al.[31] prepared L-2-amino-3-butenoic acid (**3**) from the protected derivative of L-2-amino-4-hydroxybutanoic acid **42** (L or D) by oxidation elimination (Scheme 22).

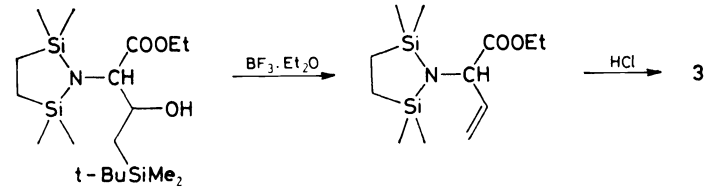


42

a) *o*-$NO_2PhSeCN$, Bu_3P; b) H_2O_2; c) HCl

SCHEME 22

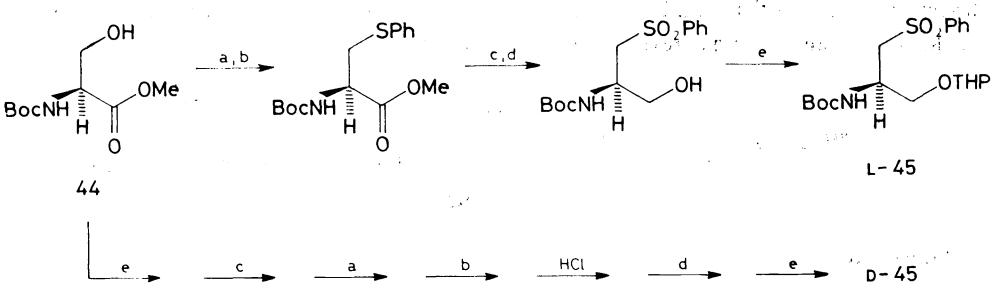
Hurdlík et al.[32] described a relatively complex synthesis of 2-amino-3-butenoic acid (**3**) by the β-elimination of 3-hydroxy ester **43** (Scheme 23) with a yield of 48%.



43

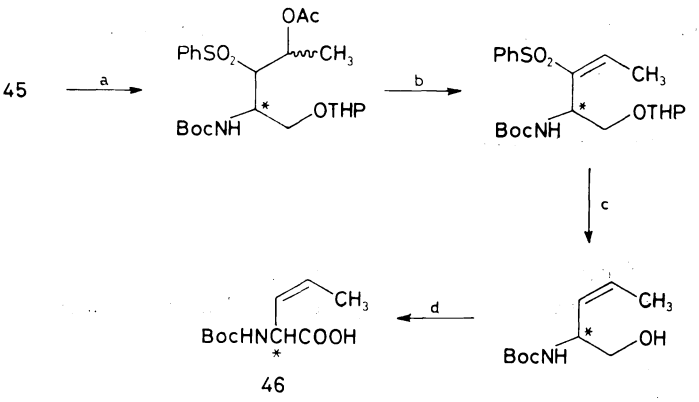
SCHEME 23

Methyl ester of N-tert-butoxycarbonyl-L-serine **44** was adopted by Sasaki et al.[33] for the preparation of both L and D enantiomers of N-Boc-(*Z*)-2-amino-3-pentenoic acid **46** by the procedures described in Schemes 24 and 25. The chiral synthon **45** was obtained in the form of both the D and L enantiomers depending on the order of the transformation reactions. The yield of the synthesis proper (Scheme 25) of the unsaturated amino acid (**45** → **46**) based on stereoselective synthesis of olefins by reduction of easily accessible vinyl sulfones with sodium dithionite was 23%.



a) tosylchlorid ; b) NaSPh ; c) $NaBH_4$; d) 3-chloroperoxybenzoic acid ; e) tetrahydropyran

SCHEME 24

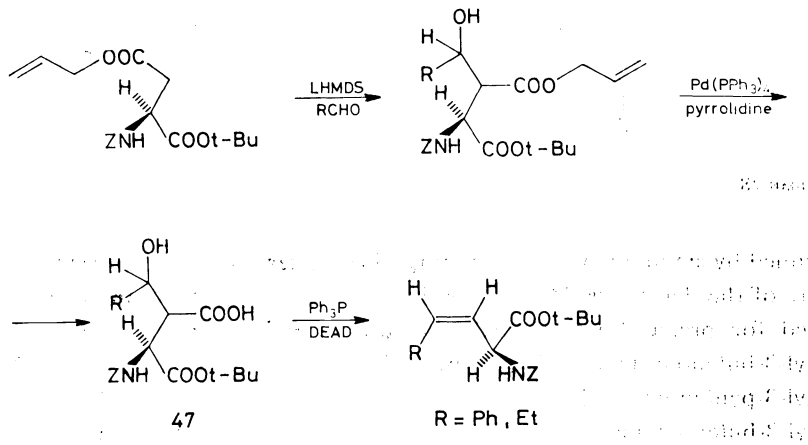


a) BuLi , CH_3CHO , Ac_2O ; b) NaOH , Et_2O , 25°C ; c) $Na_2S_2O_4$;
d) pyridiniumchlorochromate , 25°C

SCHEME 25

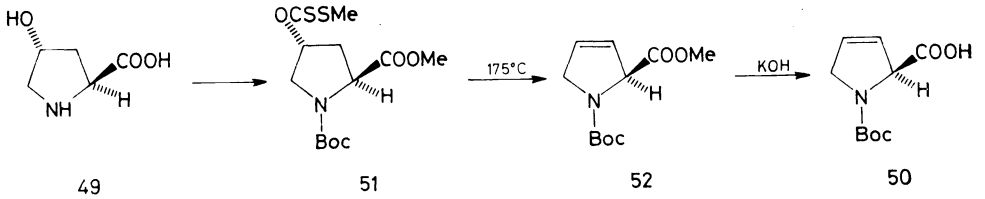
The synthetic procedure to 3,4-didehydro-2-amino acids making use of aspartic acid as the chiral synthon was developed by Baldwin et al.[34] (Scheme 26). The double bond was introduced into the molecule by the decarboxylation-dehydration of the β-hydroxy ester **47** by action of the adduct of triphenylphosphine and diethyl azodicarboxylate (DEAD). This procedure was applied to the syntheses of (L)-2--amino-4-phenyl-3-butenoic acid (5·3%) and (L)-2-amino-(Z)-3-hexenoic acid (29%).

A β-elimination seems also to be applicable to the preparation of L-3-pyrroline-2--carboxylic acid (L-3,4-didehydroproline) (**48**) from the easily available (2*S*,4*R*)-4--hydroxyproline (**49**). Although Robertson and Witkop[35] write about considerable



SCHEME 26

efforts which they made in order to carry out this transformation – without the desired results, later attempts were successful. Thus Dormoy et al.[36] (Scheme 27)

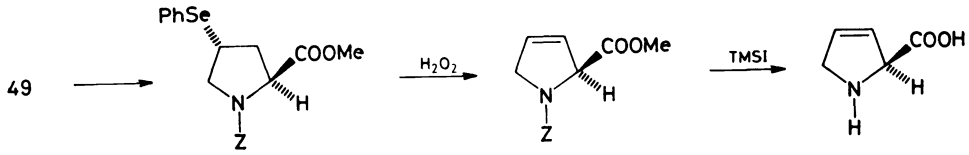


SCHEME 27

described the preparation of L-N-Boc-3-pyrroline-2-carboxylic acid (**50**) by means of the Chugaev pyrolysis of dithiocarbonate **51**; the yield related to methyl ester of N-Boc-L-4-hydroxyproline was 40%. A noteworthy step here is the basic hydrolysis of ester **52** in aqueous dioxane (1 : 1) proceeding – according to the authors – without racemization.

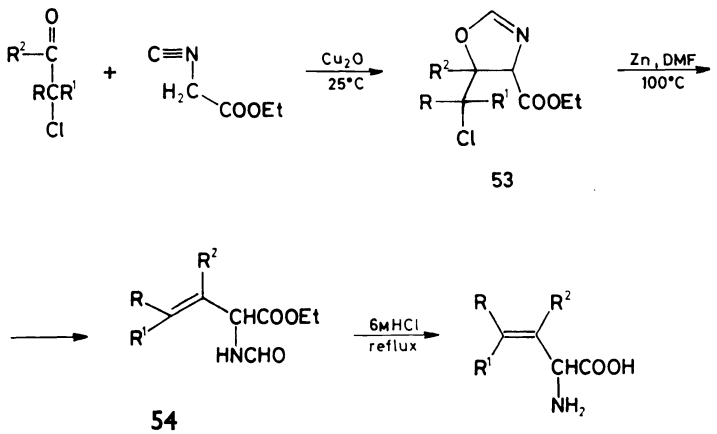
Rüget and Benn[37] (Scheme 28) described a synthesis of L-3-pyrroline-2-carboxylic acid (**48**) from (2*S*,4*R*)-4-hydroxyproline (**49**) based on the elimination of phenyl-selenoxide. Trimethylsilyl iodide proved useful in removing the protecting groups. The overall yield of the synthesis is 50%.

A relatively general method of preparation of 3,4-didehydro-2-amino acids starting from the corresponding α-chlorocarbonyl compounds was described by Heinzer et al.[38] (Scheme 29). It is based on the elimination of chlorine with zinc from 5-(1-chloroalkyl)-4-ethoxycarbonyl-2-oxazoline derivatives **53**, which is ac-



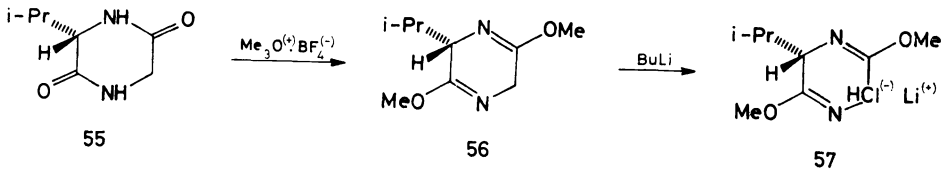
SCHEME 28

companied by simultaneous ring opening of the heterocycle. A side reaction produces isomers of the derivative **54** with the double bond at 2,3-position. The method was adopted for preparations of the following racemic products (yield): 2-amino-3--methyl-3-butenoic acid (22%), 2-amino-3-ethyl-3-butenoic acid (24%), 2-amino-3--methyl-3-pentenoic acid (20%), (*E*)-2-amino-3-hexenoic acid (18%), 2-amino-3--phenyl-3-butenoic acid (22%). The apparent versatility of this method is restricted by availability of the respective α-chlorocarbonyl compound and by the necessity to optimize the reaction conditions according to the chloro ketone used.



SCHEME 29

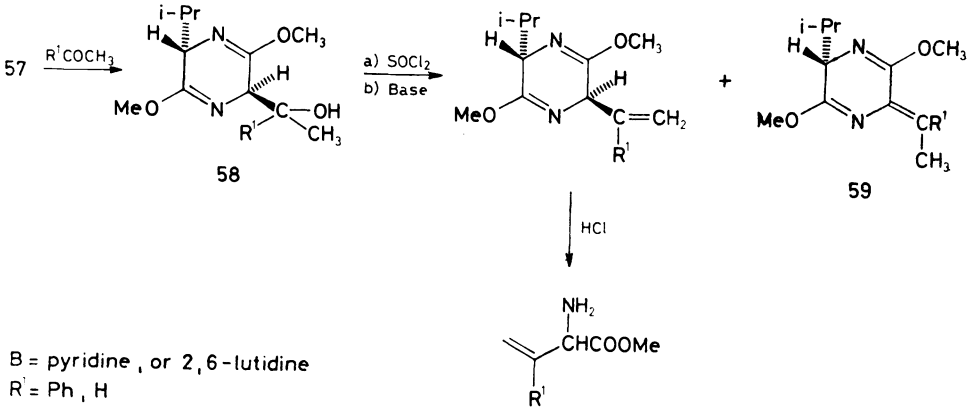
Angst[39] succeeded in making the elimination (**53** → **54**) reaction conditions milder when he found that the reaction is catalyzed either by vitamine B_{12} in dimethylformamide medium or by its partially degraded (more lipophilic) derivative – cobester in tetrahydrofurane medium. With both the catalysts the reaction proceeds at room temperature. In this way it was possible to prepare D,L-2-amino-3-methylenepentanedioic acid (3-methylene-D,L-glutamic acid) with a yield of 42% (related to the oxazoline derivative) as well as D,L-2-amino-3-methylenebutanedioic (3-methylene-D,L-aspartic) acid in a yield of 32% (related to the starting α-chlorocarbonyl compound).



55 56 57

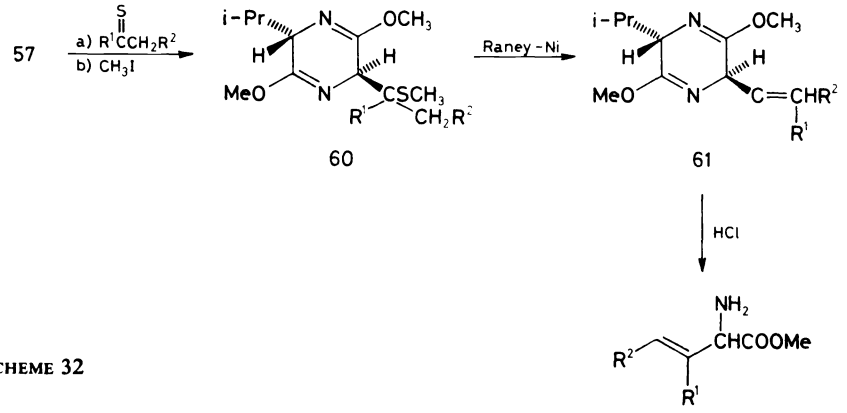
SCHEME 30

Elimination reactions were also utilized in asymmetric syntheses of D-3,4-dide-hydro-2-amino acids (Schöllkopf et al.[40,41]). These syntheses start from the 2,5--dioxopiperazine **55** (Scheme 30) prepared from L-valine and glycine. The dioxo-piperazine **55** is transformed into the bis-lactim ether **56** whose lithium salt **57** reacts subsequently with a ketone (Scheme 31), a thioketone (Scheme 32), or with 2-((di-



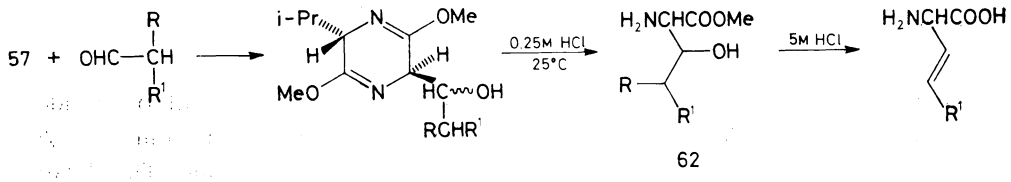
B = pyridine, or 2,6-lutidine
R' = Ph, H

SCHEME 31



SCHEME 32

methyl-tert-butyl)silyl)alkanal (Scheme 33). There takes place a nucleophilic addition of anion of the heterocycle to the carbonyl (thiocarbonyl) carbon atom. The bond formed between the 3-carbon atom of the ring and the carbon atom carrying the hydroxyl (or SH) group preferently adopts *trans*-configuration with respect to



R = Si(t-Bu)Me$_2$

SCHEME 33

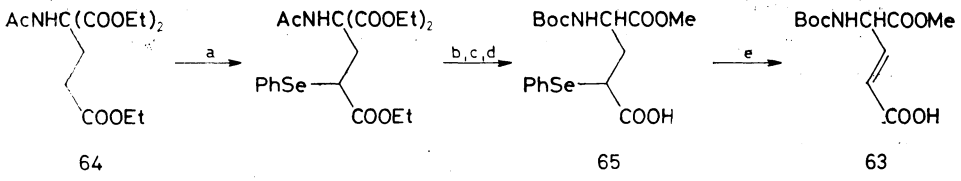
the 6-isopropyl group. The addition proceeds with asymmetric induction, the enantiomer purity of the product being above 95%. The addition to methyl phenyl ketone and to acetaldehyde gave the respective hydroxy derivatives **58** (Scheme 31) whose dehydration and deprotection gave methyl D-2-amino-3-phenyl-3-butenoate (yield 50% related to bis-lactim **56**) and methyl D-2-amino-3-butenoate (yield is not given), respectively. The dehydration of the hydroxy derivative **58** partially produces the undesirable isomer **59** and, therefore, two alternative procedures were developed for syntheses of other amino acids.

The thio derivative **60** was prepared by the addition of lithium salt **57** to thioketone (Scheme 32) and by subsequent methylation of the thiol formed. The required olefin **61** was prepared at first by the usual procedure, i.e. transformation of the thio derivative **60** into the sulfonium salt (CH_3I) and subsequent pyrolysis. It was, however, surprising to find that the attempt at hydrodesulfurization (Raney Ni, boiling EtOH) of the thio derivative **60** led to the Hofmann olefin **61**, the yield being higher than that of the pyrolysis of sulfonium salt. The following products were prepared in this way (the yields are related to the bis-lactim ether **56**): D-2-amino-3-ethyl-3--pentenoic acid (35%), D-2-amino-2-(1-cyclohexenyl)acetic acid (21%).

A synthesis was developed which utilizes the addition of anion of the lithium salt **57** to 2-((dimethyl-tert-butyl)-silyl)alkanal (Scheme 33). The applications of this method are limited by the stability of the intermediate **62** which is unstable in the case of 4,4-dialkyl derivatives. The method was adopted in syntheses of the following products (the yields are related to the bis-lactim ether **56**): D-2-amino-3-pentenoic acid (32%), D-2-amino-3-butenoic acid (25%).

Schöllkopf and Schröder[42] also made an attempt to apply the last method mentioned to the synthesis of 2-amino-3-pentenedioic (3,4-didehydroglutamic) acid, but they were unsuccessful because of the strong inclination of the double bond to re-

arrange to the 2,3-position; similar attempts made by Kishida et al.[43] and by Tolman[44] failed, too. Bory et al.[45], however, succeeded in preparation (Scheme 34) of



64 65 63

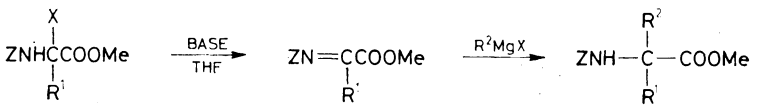
a) LDA, Ph_2Se, -78°C ; b) 6M HCl, reflux ; c) Boc_2O ; d) CH_2N_2, -78°C ; e) H_2O_2, 0°C

SCHEME 34

1-methyl ester of D,L-(*E*)-2-tert-butoxycarbonylamino-3-pentenedioic acid (**63**), i.e. a protected derivative of 3,4-didehydroglutamic acid, by oxidative elimination reaction in an overall yield of 1·4%. The starting derivative of pentanedioate **64** was prepared by the Michael addition of acrylate to acetamidomalonate. The efforts directed to selective esterification of the α-carboxyl group were unsuccessful, and the isomer **65** was isolated chromatographically from a mixture of the mono-and dimethyl esters. The double bond was introduced into the molecule by the elimination of phenylselenoxide from compound **65**. It was, however, impossible to obtain the parent acid. The authors also studied the kinetics of rearrangement of the double bond of methyl ester **63** to the 2,3-position in the medium of phosphate buffer. The half-life of the transformation was only 6 min at pH 7·0.

2.6. *Synthetic Applications of Unsaturated Organo-Metallics*

The reaction is based on the addition of organo-metallic reagents to the acylimino-malonate **66** prepared in situ (Scheme 35, $R^1 = COOCH_3$) or to the iminoacetate



67 66 68

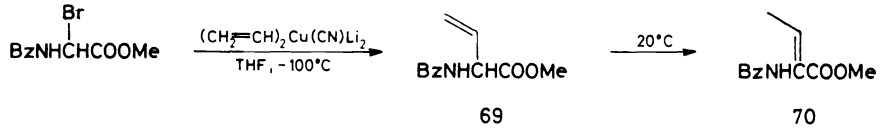
SCHEME 35

derivative **66** (R^1 = H). The imino derivatives are produced from the corresponding halogenated derivatives **67** by dehydrohalogenation by action of an excess of the organo-metallic agent or by addition of amine. In order to suppress the side reactions,

viz. the addition to ester carbonyl group, dimerization or radical reduction, low reaction temperatures (−100°C or −78°C) are used for the additions of organo--metallics to C=N bond.

Castelhano et al.[46] described reactions of vinylic Grignard reagents with the methyl N-benzyloxycarbonyliminoacetate prepared in situ which were used for syntheses of methyl esters of the following N-benzyloxycarbonyl acids: 2-amino-3--butenoic, 2-amino-3-methyl-3-butenoic, (*E*,*Z*)-2-amino-3-methyl-3-pentenoic, (*E*)-2--amino-3-hexenoic, (*E*)-2-amino-4-phenyl-3-butenoic, and 2-amino-3,4,4-trifluoro-3--butenoic. The authors report the yields in the range of 55−65%.

Münster et al.[47] added Grignard reagents to tert-butyl N-(tert-butoxycarbonyl)-iminoacetate. In this way they prepared (after removing the protecting groups from the reaction product) 2-amino-3-butenoic acid with a yield of 72%. Moreover, the same authors studied the addition reactions of other organo-metallic agents with acyliminoacetate and published a paper[48] stating that the Grignard reagents give only low yields in a number of cases. The best results were obtained with application of organo-copper compounds of the type $R_2Cu(CN)Li_2$. Methyl 2-(benzamido)-3--butenoate **69** (Scheme 36, yield 50%) is the only derivative with a 3,4-double bond

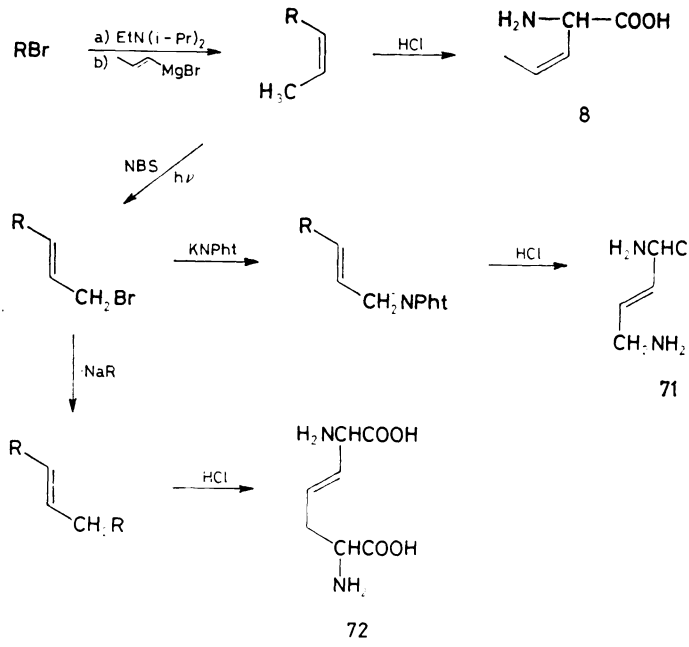


69 70

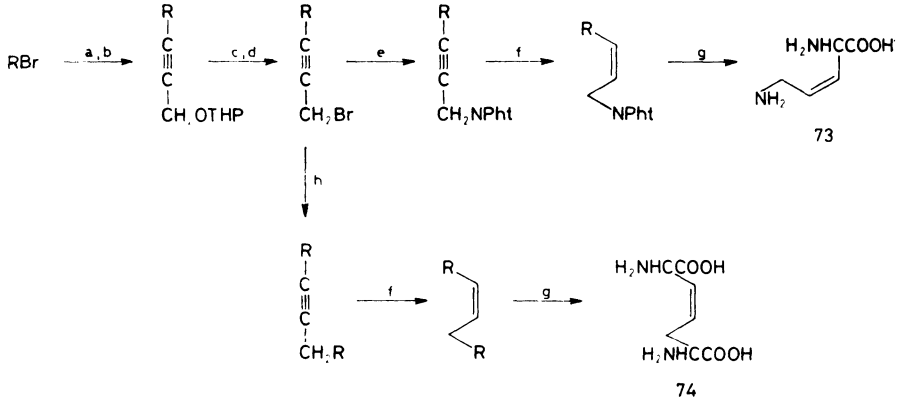
SCHEME 36

prepared so far in the way mentioned; the parent amino acid was not obtained from the ester. The authors point out two interesting facts: (i) The application of organo-copper compounds of the type mentioned gave satisfactory results in the reactions with methyl 2-acetamido-2-bromoacetate where – according to the authors – the reaction with Grinard reagents fails. (Havlíček[49] applied the addition of 1-propenylmagnesium bromide to methyl acetiminomalonate and obtained the required 2-acetamido-3-pentenoate in a yield of only 10%). (ii) If the reaction mixture (after the addition of vinylic organo-copper compound to benzimidomalonate) was decomposed at room temperature, the double bond migrated to give the 2,3-didehydro derivative **70**; if the decomposition was carried out at −100°C, no rearrangement took place and the expected 3,4-unsaturated ester **69** was formed.

An analogous procedure (reaction of organo-magnesium compound and subsequent decomposition at −78°C) enabled Castelhano et al.[50] to prepare methyl esters of the following 2-benzyloxycarbonylamino-3-alkinoic acids (yield): 3-pentinoic (31%), 3-heptinoic (69%), 3-noninoic (63%), 4-phenyl-3-butinoic (33%). The paper



SCHEME 37



R = —CH(COOEt)2
HNAc

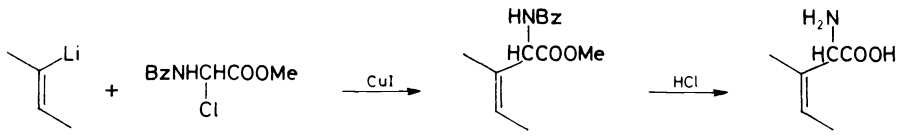
a) $C_2H_5N(i\text{-}Pr)_2$; b) $BrMgC{\equiv}CCH_2OTHP$; c) HCl ; d) Ph_3PBr_2 ; e) PhtNK ; f) H_2, Lindlar catalyst ; g) 5M HCl, reflux

SCHEME 38

gives no information about attempts at preparation of the free acids from the methyl esters.

Havlíček et al.[51] utilized the addition of 1-alkenyl- and 1-alkinylmagnesium bromides to diethyl acetyliminomalonate for syntheses of 3,4-unsaturated 2-amino acids. Making use of a number of stereoselective transformations (Scheme 37, 38) of the unsaturated grouping introduced they prepared (*Z*)-3,4-didehydronorvaline (**8**), (*E*)- and (*Z*)-3,4-didehydroornithine (**71**, **73**), and (*E*)- and (*Z*)-3,4-didehydro--2,6-diaminopimelic acids (**72**, **74**). By enzymatic resolution (acylase I) of the N-acetyl derivatives they obtained the L-enantiomers of (*Z*)-3,4-didehydronorvaline and (*E*)--3,4-didehydroornithine[52].

Cahill[3] prepared (*Z*)-2-amino-3-methyl-3-pentenoic acid (**75**) by a reaction (Scheme 39) of methyl 2-benzamido-2-chloroacetate (**76**) with (*Z*)-2-butenyllithium (**77**) catalyzed with copper(I) iodide. The paper gives no detailed data.

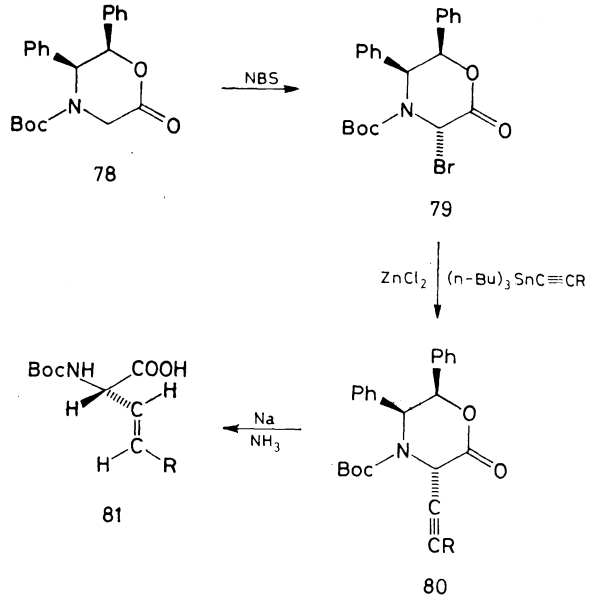


77 76 75

SCHEME 39

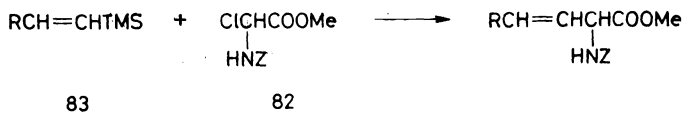
Williams and Zhai[53] published an enantio- and stereoselective (the *E* isomers only were formed) synthesis of 3,4-didehydroamino acids starting from asymmetrical bromomorpholine **78** (Scheme 40). Tributyl(alkinyl)stannium reacts with the bromo derivative **79**, zinc chloride being used as a catalyst. The alkinylmorpholine derivative **80** formed has its alkinyl group in *trans*-position to bulky phenyl groups (enantiomeric purity above 98%). Partial reduction of the triple bond and splitting of the morpholine ring (Na, NH_3, ethanol, $-33°C$) produces the derivative of *trans*-vinylglycine **81**. However, the reduction **80** → **81** is accompanied by partial racemization, hence the enantiomeric purity of the final product is only 55–67%. So far it has been possible to suppress the racemization almost completely in the synthesis of (*E*)-2-amino-3-pentenoic acid using Li instead of Na, but the chemical yield of the whole synthesis decreased to 10%. In other cases the application of Li did not result in any distinct increase of enantiomeric purity. In this way N-Boc derivatives of the following acids were prepared (yield): (*E*)-2-amino-3-pentenoic (48%), (*E*)-2-amino-3--heptenoic (52%), (*E*)-2-amino-3-decenoic (45%).

Angst[39] (Scheme 41) synthetized 3,4-didehydro-2-amino acids by means of an acid-catalyzed reaction ($SnCl_4$ or $AgBF_4$) of methyl 2-benzyloxycarbonylamino-3--chloroacetate (**82**) with *E*- or *Z*-vinylsilanes **83**. In the paper a mechanism is also



SCHEME 40

suggested for the addition of vinyl anion to the benzlyoxycarbonyliminium ion ($ZN^+H{=}CHCOOCH_3$) generated in situ. The hydrolysis of the urethane protecting group was accomplished by means of trimethylsilyl iodide. The following acids were prepared in this way (yield): (*E*)-2-amino-3-octenoic (42%), (*Z*)-2-amino-3-octenoic (39%), (*Z*)-2-amino-3-pentenoic (32%), (*E*)-2-amino-4-phenyl-3-butenoic (52%), (*Z*)-2-amino-4-phenyl-3-butenoic (48%).

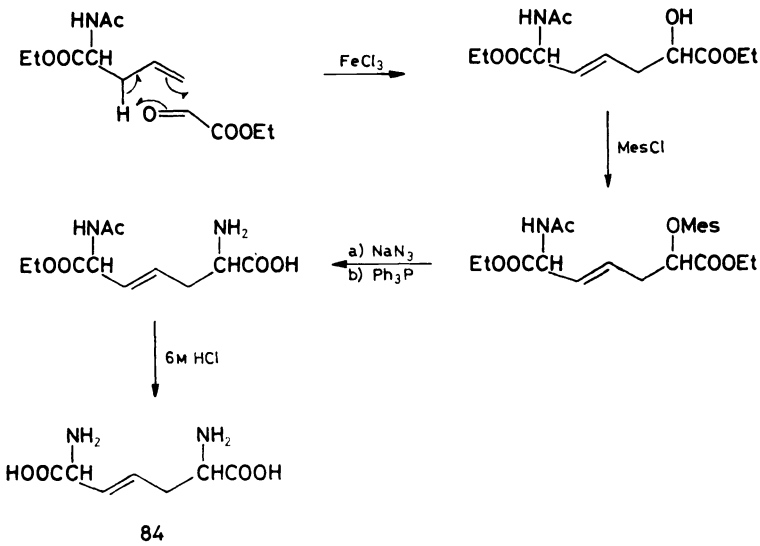


SCHEME 41

2.7. *Other Synthetic Methods*

Agouridas et al.[54,55] adopted the ene reaction (Scheme 42) catalyzed with Lewis acids to prepare (*E*)-2,6-diamino-3-heptenedioic acid (**84**) with the overall yield of 47%. By the same reaction sequence (from the respective substituted starting com-

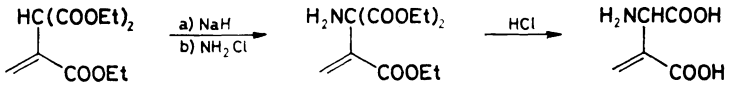
pounds) they also prepared 4-methyl, 2-methyl, and 4-chloro derivatives of (*E*)-2,6--diamino-3-heptenedioic acid as well as (*Z*)-2,6-diamino-4-methyl-3-heptenedioic acid.



84

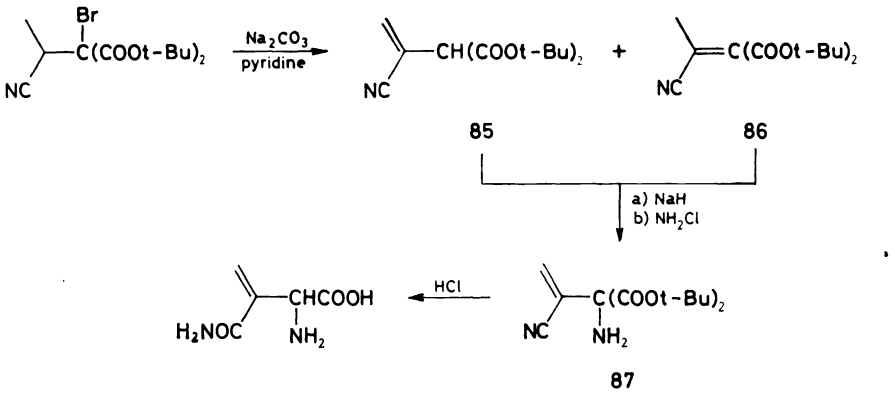
SCHEME 42

Dowd et al.[56] described a synthesis (Scheme 43) of 2-amino-3-methylenebutanedioic (3-methyleneaspartic) acid and also[57] (Scheme 44) of 2-amino-3-carbamoyl-3--butenoic acid (3-methyleneasparagine). The key step consists in the amination of malonate anion with chloramine. In the case of synthesis of 3-methyleneasparagine the deprotonation of both position isomers **85** and **86** and subsequent reaction with chloramine leads to the required 3,4-didehydroderivative **87**. The overall yield of the first synthesis is 46%, that of the second one is 28%.



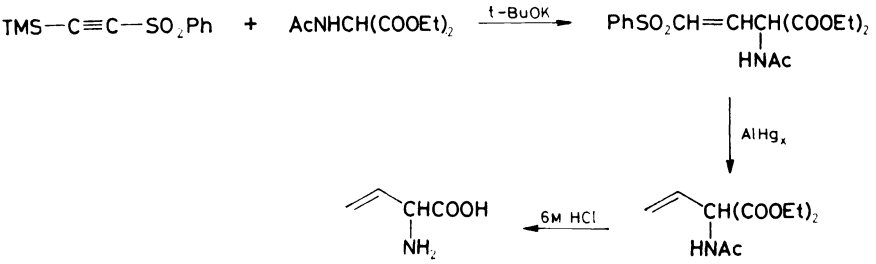
SCHEME 43

Also developed was a synthesis[58] of 2-amino-3-butenoic acid involving – as the key step – the Michael addition of diethyl acetamidomalonate to phenyl 2-(tri-



SCHEME 44

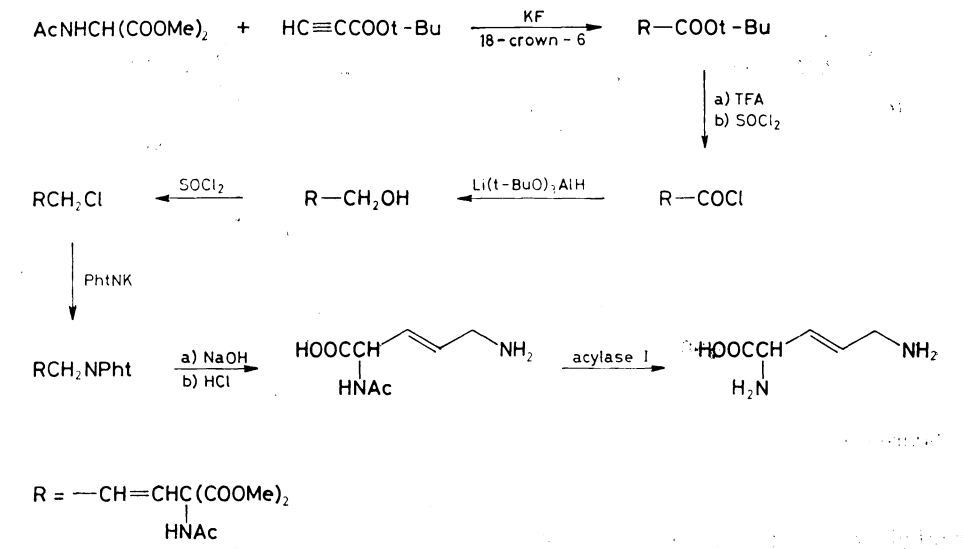
methylsilyl)ethinyl sulfone (Scheme 45) with the overall yield of 48%. The method was also modified for preparation of isomeric deuteriated compounds containing ^2H at 3- and/or 4-positions.



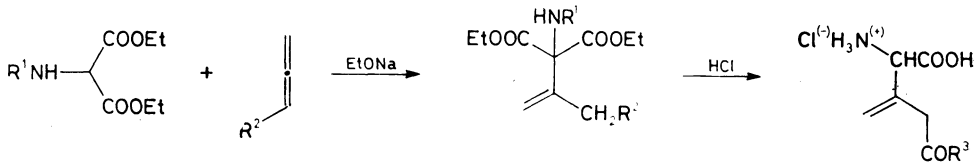
SCHEME 45

A synthesis of L-(*E*)-3,4-didehydroornithine was suggested by Tolman[59] (Scheme 46). It starts from the Michael addition of diethyl acetamidomalonate to tert-butyl propionate. The overall yield of the synthesis is 7·7%.

The Michael addition of a protected aminomalonate to 2,3-butadienoate or cyanoallene (Scheme 47) was used by Paik et al.[60] for a synthesis of 2-amino-3-methylenepentanedioic (3-methylene-D,L-glutamic) acid (yield 55%) and for a synthesis of 2-amino-4-carbamoyl-3-methylenebutanoic acid (3-methylene-D,L-glutamine) (yield 20%).



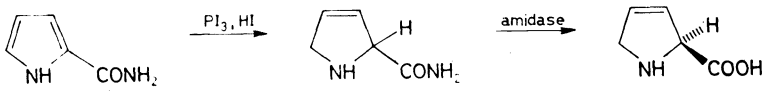
SCHEME 46



1. R^1 = Ac ; R^2 = COOEt ; R^3 = OH
2. R^1 = Boc ; R^2 = CN ; R^3 = NH_2

SCHEME 47

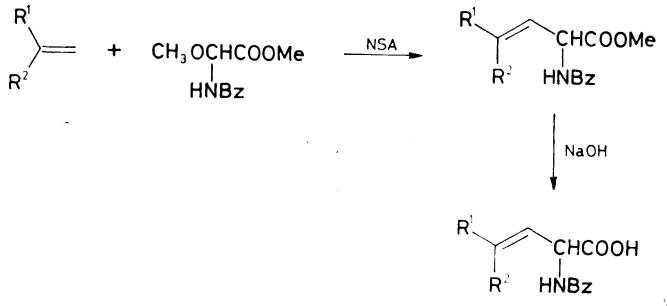
L-3-Pyrroline-2-carboxylic acid (3,4-didehydroproline) was prepared in several cases by partial reduction of pyrrole derivatives. Fischer et al.[61] reduced 2-carbamoylpyrrol with hydrogen iodide as early as in the year 1912. Later this method was refined by Robertson et al.[35], Corbela et al.[62], and Felix et al.[63] (Scheme 48). The resolution was accomplished enzymatically (amidase).



SCHEME 48

Scott et al.[64] carboxylated pyrrol, and reduced the pyrrole-2-carboxylic acid obtained with hydrogen iodide. The resolution was accomplished by crystallization of diastereoisomeric salts of 3,4-didehydroproline with D-tartaric acid. The overall yield of the synthesis was 16%.

Altman et al.[65,66] used the acid-catalyzed reaction of methyl N-benzoyl-2-methoxyglycinate with 1-alkyl-1-arylethylene to prepare a series of 2-benzamido-4-aryl-3,4-didehydro acids (Scheme 49). The applicability of this method is limited to preparations



SCHEME 49

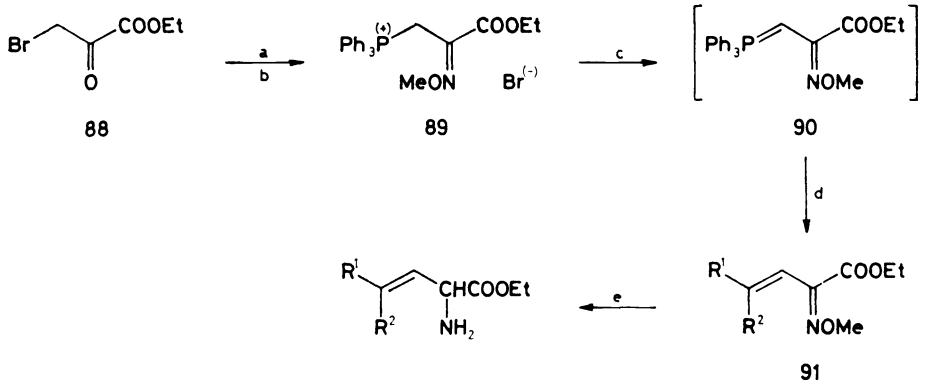
of 4-aryl-3,4-didehydro-2-amino acids, and the products thus prepared include (yield): 2-benzamido-4,4-diphenyl-3-butenoic acid (76%), 2-benzamido-4-phenyl-3--pentenoic acid (25%), 2-benzamido-4-phenyl-3-butenoic acid (42%).

A preparation of 2-amino-2-(1-cyclohexenyl)acetic acid is described in patent literature[67]: The nitrosation of ethyl 2-(1-cyclohexenyl)acetate with isopentyl nitrite gave the corresponding oxime whose reduction with zinc in hydrochloric acid gave ethyl 2-amino-2-(1-cyclohexenyl)acetate. The parent amino acid was obtained by base-catalyzed hydrolysis in the overall yield of 15%.

Finally, also the Wittig synthesis of alkenes was applied successfully to the synthesis of 3,4-didehydro-2-amino acids. Bickel et al.[68] (Scheme 50) started from ethyl 3-bromopyruvate **88** and prepared the O-methyloxime of phosphonium salt **89**. Out of the bases examined for the preparation of the corresponding phosphorane **90**, potassium carbonate in dimethylformamide medium proved to be the most suitable. The phosphorane **90** was left to react with the carbonyl compound chosen, and the O-methyloxime **91** formed was reduced with zinc in formic acid to give ethyl esters of the following acids (yield): (*E*)-2-amino-3-hexenoic (42%), (*E*)-2-amino-5-methyl-3--hexenoic (93%), 2-amino-4-ethyl-3-hexenoic (23%), 2-amino-3-cyclohexylidenepropanoic (30%), 2-amino-3-(4-thiinan)-3-ylidenepropanoic (20%), and 2-amino-4--phenyl-3-butenoic (63%).

Beaulieu et al.[69] developed an enantioselective synthesis (Scheme 51) of D-N^{α}--benzyloxycarbonyl-N^{5}-tert-butoxycarbonyl-2,7-diamino-(*Z*)-heptenoic acid (26%)

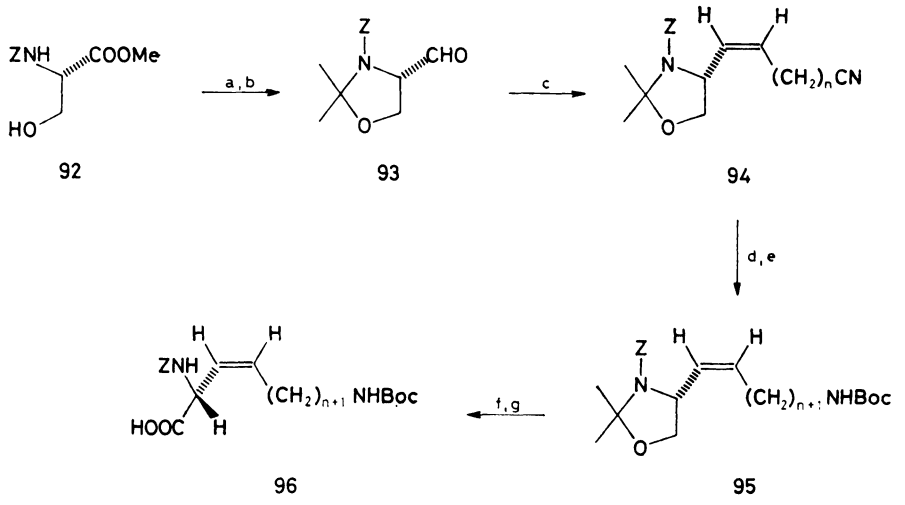
and of D-N^{α}-benzyloxycarbonyl-N^{η}-tert-butoxycarbonyl-2,8-diamino-(Z)-3-octenoic acid (26%) based on the Wittig reaction. Condensation of a protected L-serine **92** with 2,2-dimethoxypropane gave an oxazolidine derivative whose ester group at 3-posi-



88 89 90 91

a) CH_3ONH_2, HCl ; b) Ph_3P, THF, reflux ; c) K_2CO_3, DMF ; d) R^1COR^2 ; e) Zn, HCOOH

SCHEME 50



92 93 94 95 96

a) 2,2-dimethoxypropane, TsOH ; b) diisobutylaluminiumhydride, -78°C ;
c) $Ph_3P{=}CH(CH_2)_nCN$, -78°C → +20°C, n = 2,3 ; d) $NaBH_4$, $CoCl_2$; e) Boc_2O ;
f) TsOH, wet MeOH, reflux ; g) CrO_3

SCHEME 51

tion was reduced to give the aldehyde **93**. The olefinic nitrile **94** formed by the Wittig condensation was selectively reduced. By protecting the amino group the olefin **95** was prepared, and hydrolysis of the 1,3-oxazolidine cycle present therein liberated the corresponding hydroxy derivative. Finally, the Jones oxidation of the hydroxy group gave the above-mentioned protected amino acids **96**. This procedure has a noteworthy feature in that the chiral centre of the starting synthon undergoes the inversion of configuration by oxidation at C-3 and reduction at C-1 during the synthesis.

2.8. *Preparation of Optically Active* 3,4-*Didehydro*-2-*amino Acids*

Kinetic enzymatic resolution was applied to racemates in several cases: acylase I was adopted in the cases of N-chloroacetyl derivative of 2-amino-3-methyl-3-butenoic acid[12] (37%) and N-acetyl derivative of (*E*)-2-amino-4-methoxy-3-butenoic acid[24] (70%). These procedures suffer from a certain drawback in that any sensitive determination of enantioselectivity is missing. In the cases of resolutions of N^{α}-acetyl derivatives of (*Z*)-3,4-didehydronorvaline[52], (*E*)-3,4-didehydroornithine[52], and its N^{δ}-benzyloxycarbonyl derivative[70] using acylase I a decreased enantioselectivity of the enzymatic reaction was observed (GLC determination of enantiomeric purity) as compared with that applied to the corresponding saturated amino acids derivatives. The amidase isolated from pig kidneys was used for resolution of amide of D,L-3,4-didehydroproline[35]. It is advantageous that the amide undergoes racemization at the conditions of the resolution (in contrast to the amino acid formed), hence the yield of resolution reached 75%. However, the enzyme is not available commercially.

The resolution through crystallization of diastereoisomeric salts was described for D,L-3,4-didehydroproline with application of either D-tartaric acid[64] or (*R*)-(+)--methyl-*p*-nitrobenzylamine[63].

Some optically active 3,4-didehydro-2-amino acids were advantageously prepared from optically active precursors – the respective saturated amino acids – with application of stereoselective reactions[9,25–31,33,34,36,37,69] (see parts 2.5. and 2.7.).

At present the attention of synthetic chemists is focused (see refs[39,46,48]) on developing asymmetrical versions of the syntheses. These attempts include also the relatively complex synthesis (developed for the D series) by Schöllkopf et al.[40,41] (see part 2.5.) which, however, produces a mixture of *E* + *Z* isomers. The most recent asymmetrical synthesis by Williams and Zhai[53] (see part 2.6.) has led so far to amino acids with substantially lower optical purity.

2.9. *A Survey of* 3,4-*Didehydro*-2-*amino Acids Described*

D,L-2-Amino-3-butenoic acid[4,7,10,12,19,21,32,46,47,48,58]
L-2-Amino-3-butenoic acid[25,27–31]

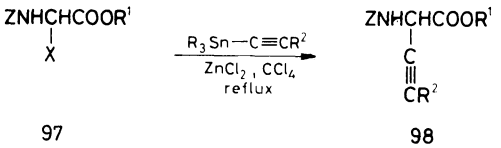
D-2-Amino-3-butenoic acid[40,41]
D,L-2-Amino-3,4,4-trifluoro-3-butenoic acid[46]
D,L-2-Amino-3-fluoro-3-butenoic acid[9]
L-2-Amino-3-chloro-3-butenoic acid[9]
D,L-(*E*)-2-Amino-3-pentenoic acid[7,13,14,53]
D,L-(*Z*)-2-Amino-3-pentenoic acid[14,39,51]
D-(*E* + *Z*)-2-Amino-3-pentenoic acid[41]
L-(*E*)-2-Amino-3-pentenoic acid[53]
L- and D-(*Z*)-2-Amino-3-pentenoic acids[33,52]
D,L-2-Amino-3-methyl-3-butenoic acid[17,38,46]
L-2-Amino-3-methyl-3-butenoic acid[12]
L-3,4-Didehydroproline[35–37,61–64]
D,L-2-Amino-4-methyl-3-pentenoic acid[18,21]
D,L-2-Amino-3-ethyl-3-butenoic acid[2,38]
D,L-(*E*)-2-Amino-3-methyl-3-pentenoic acid[3,7]
D,L-(*Z*)-2-Amino-3-methyl-3-pentenoic acid[3]
D,L-(*E* + *Z*)-2-Amino-3-methyl-3-pentenoic acid[38,46]
D,L-(*E*)-2-Amino-3-hexenoic acid[38,39,46]
L-(*Z*)-2-Amino-3-hexenoic acid[34]
D,L-(*E*)-2-Amino-3-heptenoic acid[7,53]
D-(*E* + *Z*)-2-Amino-3-ethyl-3-pentenoic acid[41]
D,L-(*Z*)-2-Amino-3-octenoic acid[39]
D,L-(*E*)-2-Amino-3-octenoic acid[39]
D,L-(*E*)-2-Amino-3-nonenoic acid[21]
D,L-(*E*)-2-Amino-3-decenoic acid[53]
D,L-2-Amino-2-(1-cycloalkenyl)acetic acids[1,7]
D,L-2-Amino-2-(1-cyclohexenyl)acetic acid[5,6,67]
D-2-Amino-2-(1-cyclohexenyl)acetic acid[41]
D,L-2-Amino-3-cyclohexylidenepropanoic acid[21]
D,L-(*E*)-2-Amino-4-phenyl-3-butenoic acid[1,7,39,46]
D,L-(*Z*)-2-Amino-4-phenyl-3-butenoic acid[39]
L-(*E* + *Z*)-2-Amino-4-phenyl-3-butenoic acid[34]
D,L-2-Amino-3-phenyl-3-butenoic acid[15,38]
D-2-Amino-3-phenyl-3-butenoic acid[40]
L-(*E*)-2-Amino-4-methoxy-3-butenoic acid[24]
D,L-(*E*)-2-Amino-4-(2-aminoethoxy)-3-butenoic acid[16]
D,L-(*E*)-2,5-Diamino-3-pentenoic acid[11,51]
L-(*E*)-2,5-Diamino-3-pentenoic acid[52,59]
D,L-(*Z*)-2,5-Diamino-3-pentenoic acid[51]
D,L-2-Amino-3-methylenebutanedioic acid[56]

D,L-2-Amino-3-carbamoyl-3-butenoic acid[57]
D,L-2-Amino-3-methylenepentanedioic acid[39]
D,L-(*E*)-2,6-Diamino-3-heptenedioic acid[51,55]
D,L-(*E*)-2,6-Diamino-4-methyl-3-heptenedioic acid[55]
D,L-(*E*)-2,6-Diamino-4-chloro-3-heptenedioic acid[55]
D,L-(*E*)-2,6-Diamino-2-methyl-3-heptenedioic acid[55]
D,L-(*Z*)-2,6-Diamino-4-methyl-3-heptenedioic acid[55]
D,L-2-Amino-3-methylenepentanedioic acid[60]
D,L-2-Amino-4-carbamoyl-3-methylenebutanoic acid[60]
D,L-2-Amino-3,4-pentadienoic acid[22]
D,L-2-Amino-3-methyl-3,4-pentadienoic acid[22]
D,L-(*Z*)-2,6-Diamino-3-heptenedioic acid[51]

2.10. 2-*Amino Acids with Triple Bond at* 3,4-*Position*

Castelhano et al.[50] used the reaction of 1-alkinylmagnesium reagents with methyl N-benzyloxycarbonyliminoacetate (see part 2.6.) to prepare methyl esters of the following acids: 3-pentinoic, 3-heptinoic, 3-nonionic, and 4-phenyl-3-butinoic. The paper gives no information about attempts at preparation of the corresponding free amino acids.

A series of completely protected 3,3,4,4-tetradehydro-2-amino acids were prepared by Williams et al.[71] by reactions of 1-alkinyltin(IV) compounds with 2-halogeno-glycinates **97** (Scheme 52). The authors succeeded in isolating either the N-acylated



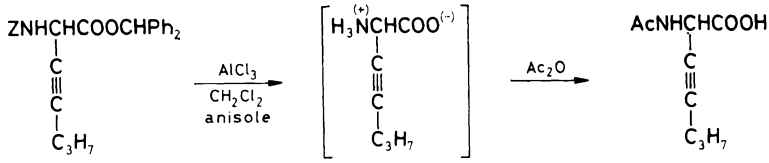
97 98

X = Cl, Br ; R^1 = Me, $CHPh_2$
R^2 = $SiMe_3$, Me, n-Pr, n-Bu, n-Hex, Ph, $CH_2CH_2OSi(Me)_2t$-Bu

SCHEME 52

derivatives (by splitting the benzhydryl esters with trifluoroacetic acid in the presence of anisole) or aminoesters (by splitting off of N-benzyloxycarbonyl group with aluminium trichloride in dichloromethane in the presence of anisole). In spite of large efforts the corresponding free amino acids were not isolated because of their instability. They can be used, however, in situ – in solution – as reaction synthons (Scheme 53). The attempts at splitting off of N-benzyloxycarbonyl group with tri-

methylsilyl iodide resulted in addition of hydrogen iodide and formation of (Z)-4--iodo-3,4-didehydro-2-amino acids.



SCHEME 53

Casara and Metcalf[72] described an unsuccessful attempt at preparation of 2-amino--3-butinoic acid by hydrolysis of the urethane TMS—C≡C—CH($NHCOOC_2H_5$).$COOCH_3$. Both acid- and base-catalyzed hydrolyses gave complex reaction mixtures whose components were not identified. The attempt at selective splitting off of only the urethane protecting group with trimethylsilyl chloride resulted in formation of the allenyl isocyanate TMS—CH=C=C($COOCH_3$)NCO (according to NMR).

Japanese authors[73] isolated an unstable antibiotic from Streptomyces cetenulae. Its acetylation[74] (Ac_2O) gave a stable product which was assigned the structure of N-acetyl derivative of 2-amino-3-butinoic acid. The free amino acid is stable in acidic solutions, being fairly rapidly decomposed in slightly alkaline medium (pH 8) at 4°C.

3. CONCLUSION

The Strecker synthesis of 3,4-didehydro-2-amino acids in its classical arrangement generally gives very low yields. The modified Strecker synthesis (using TMSCN) gives good yields for a number of amino acids except for the 4,4-disubstituted ones.

The reaction of ammonia with 2-halogeno-3,4-didehydrocarboxylic acids gives (in contrast to the analogous reaction with the respectvie esters – according to Baldwin[12]) good yields of the desired products. In spite of that this method has found no wide applications and is not further developed.

The syntheses based on elimination reactions – though not always applicable – enabled preparations of compounds inaccessible by other ways. Their substantial advantage lies in the fact that in suitable cases they enable conversions of optically active saturated amino acids into the respective unsaturated amino acids without racemization. In this field the syntheses by Sazaki et al.[33] and by Baldwin et al.[34] have fairly general applications.

Stereoselective versions of individual reaction steps inclusive of the Wittig reaction which introduce a double bond into a molecule were also utilized by Beaulieu[69] in

syntheses of D-enantiomers of unsaturated amino acids. In principle the procedure is generally applicable.

The applications of unsaturated organo-metallics to syntheses of β,γ-unsaturated α-amino acids represent the approach which is paid the greatest attention at present. The procedure is considerably versatile and, in principle, it enables syntheses of derivatives with both double bond (both *E* and *Z* isomers) and triple bond. At present efforts of many workers are focused on developing the asymmetrical versions of these syntheses. The other synthetic approaches have so far been applied to individual special cases.

4. LIST OF ABBREVIATIONS AND SYMBOLS USED

Ac acetyl, Boc tert-butoxycarbonyl, Bu butyl, t-Bu tert-butyl, Bz benzoyl, Bzl benzyl, DEAD diethyl azodicarboxylate, DMF dimethylformamide, DMSO dimethyl sulfoxide, Et ethyl, LDA lithium diisopropylamide, LHMDS lithium hexamethyldisilylazide, Me methyl, Mes methanesulfonyl, NBS N-bromosuccinimide, NSA 2-naphthalenesulfonic acid, PDCD pyridinium chlorochromate, Ph phenyl, Pht phthaloyl, i-Pr isopropyl, TFA trifluoroacetic acid, THF tetrahydrofurane, THP 2-tetrahydropyranyl, TMS trimethylsilyl, TMSCN trimethylsilyl cyanide, TMSCl trimethylsilyl chloride, TMSI trimethylsilyl iodide, Ts 4-methylbenzenesulfonyl (tosyl), Z benzyloxycarbonyl.

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