1
Amino Acids

By G.C. BARRETT

1 Introduction

The 1994 literature covering the amino acids, from the point of view of their chemistry and biochemistry, is dealt with in this Chapter. The approach adopted is identical to that used in all previous Volumes of this Specialist Periodical Report. The Chapter concentrates on the literature covering the natural occurrence, chemistry, and analysis methodology for amino acids. Routine literature covering the natural distribution of well-known amino acids is excluded. Patent literature deals with material that also finds its way into the conventional literature, and is therefore excluded from this Chapter. It is easily reached through the appropriate sections of *Chemical Abstracts* (Section 34 in particular).

The flow of Journal papers and secondary literature continues to accelerate, as far as the amino acids are concerned, and papers have been collected for this Chapter from major Journals and from *Chemical Abstracts* [to Volume 122 (1995), issue 9]. Where it is helpful to refer to earlier Volumes of this Specialist Periodical Report, the formula '(see Vol. 23, p. 3)' is used.

Most of the papers cited are only briefly described, so that adequate commentary can be offered for particular papers presenting significant advances in synthetic and analytical methodology relating to the amino acids, with mechanistically-interesting chemistry being given prominence.

The coverage adopts the usual meaning of the term 'amino acids', i.e. aminoalkanoic acids $H_3N^+(R^1R^2C)_nCO_2^-$. Many conceivable structural types (for example, benzene derivatives carrying amino and carboxy groups) are excluded. Representative citations are offered, of analogues in which the carboxy group is replaced by a phosphorus oxyacid equivalent, H_3N^+-$(R^1R^2C)_n$-$P(O)(OH)(O^-)$,[1-4] e.g. (1S,2S)-phosphothreonine,[4] have important research applications; even the boron analogue $R_3N{\cdot}(BHR^1)_n$-CO_2R may hold some similar promise.[5]

2 Textbooks and Reviews

A substantial source of information on instrumental and analytical protocols[6] includes material on the amino acids. A similarly thorough coverage of topics in the synthesis of amino acids has been published.[7]

Several reviews will be found in appropriate sections of this Chapter, though others of a more general nature are collected here; these cover α-aminoisobutyric acid,[8] carboranylalanine in neutron capture therapy,[9] cyclopropane-based amino acids,[10] 1-aminocyclopropanecarboxylic acid synthesis,[11] cyclobutane-based amino acids,[12] synthesis of heterocyclic amino acids,[13] uses of amino acid esters as chiral auxiliaries in organic synthesis,[14] uses of α-amino acids in aminosugar synthesis,[15] and stereochemical details of metabolic reactions of amino acids.[16]

3 Naturally Occurring Amino Acids

3.1 Isolation of Amino Acids from Natural Sources – All fermentative processes for the production of amino acids require routine isolation of the product, and, like the production of amino acids through protein hydrolysis, the separation of mixtures is a common concluding stage to the process. This section is intended to select some less routine aspects of the isolation of amino acids, particularly those unexpected outcomes of otherwise straightforward procedures.

Protein hydrolysis is most commonly accomplished using hydrochloric or methanesulfonic acids, but several alternative protocols have been suggested; mercaptoethanesulfonic acid (160-180°) has been found to be effective.[17]

Continuous concentration of amino acids using a liquid emulsion membrane with a cation extractant, di-2-ethylhexylphosphoric acid, has been described.[18] Preparative chromatographic isolation (gel filtration and partition) of pyridinoline[19] and of hydroxylysyl- and lysyl-pyridinolines[20] from biological fluids, and preparative chromatography of benzyl esters of basic amino acids[21] and N-benzyloxycarbonyl amino acids (Z-amino acids)[22] illustrate standard methods.

3.2 Occurrence of Known Amino Acids – Where common amino acids are found in meteorites, and in ancient fossils, an obvious first question, but one only recently addressed in a rational scientific manner, is: is the amino acid indigenous or has it been introduced subsequently? Further studies (see Vol.25, p.3) based on sensitive GC-MS isotope-analytical techniques confirm the indigeneity of amino acids through identical $\delta^{13}C$ and $\delta^{15}N$ values for D- and L-enantiomers of a particular amino acid in thoroughly-cleaned 7000–10^5 y samples, and in Pleistocene fossils.[23] Quaternary land snails given more detailed study[24] confirm this diagnostic test as far as neutral amino acids are concerned, but differing $\delta^{13}C$ values for D- and L-enantiomers of aspartic and glutamic acids introduce an element of doubt; presumably these amino acids as constituents of shell protein are subject to more complex diagenesis.

Contemporary natural sources that have been shown to contain unusually interesting, though known, amino acids include D-aspartic acid (supplied by intestinal bacteria) in appreciable quantities in *Octopus vulgaris*,[25] the antimicrobial and antioxidant N-(p-coumaryl)pipecolic acid in rhizomes of *Cirsium brevicaule*.[26] Both D- and L-tert-leucine appear, together with D-kynurenine, as constituents of discodermin E, from the marine sponge *Discodermia kiiensis*.[27] α-Methylcysteine appears in condensed form in the cryoprotective agent

thiazohalostatin (1) from *Actinomadura*.[28] Another peptide from *Verticillium coccosporum* has been discovered to contain 2-amino-8-oxo-9-hydroxydecanoic acid.[29]

The presence of β-alanine in *Clitocybe acromelalga*, as its L-glutamide derivative[30] adds another natural location to those already established for this β-amino acid. γ-Hydroxy-L-glutamic acid occurs in bulbs of *Hemerocallis longituba* in the form of the amide, longitubanine (2; R = OH).[31]

Synthetic cis-4-methylproline is physically different from the compound located over the years in various natural sources, calling for some reconsideration of the structural assignments.[32]

The assessment of crosslinks that develop *in vivo* in proteins of higher species, as a result of ageing or disease, has become an important diagnostic criterion, and pyridinium crosslinks[33] and dityrosine crosslinks have been identified in bovine thyroglobulin.[34]

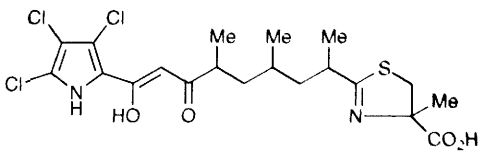
3.3 New Naturally Occurring Amino Acids – Mycestericins from *Mycelia sterilia* are potent immunosuppressants that have been shown to be hydroxylated α-hydroxymethyl-α-aminoalkanoic acids (3–5) of extraordinary types.[35] Another new acyclic aliphatic α-amino acid also owes its fascination to the functional group that it contains, the first natural azoxy-containing antifungal agent, L-azoxybacilin (6), from *Bacillus cereus* NR2991.[36] Sphingofungins (7) are a new family of antifungal metabolites from *Aspergillus fumigatus* ATCC 20857.[37] New opines (8)[38] and piperidine 2,4,5-tricarboxylic acid (9), are further metabolites from *Clitocybe acromelalga*[39] (see also Ref.30). Five new compounds (e.g., 10 and stereoisomers) related to domoic acid have been isolated from mussels.[40]

3.4 New Amino Acids from Hydrolysates – γ-Hydroxy-tert-leucine is a constituent of polytheonamides A-C from the marine sponge *Theonella swinhoei*,[41] and Zwittermicin A from *Bacillus cereus* is (11).[42] The other new amino acids are mostly lactams condensed into more complex structures; the 2,5-dihydrofuryl-γ-lactams, fulvanines D and E (12), (13) from *Hemerocallis fulva*,[43] anchinopeptolides B–D (14) from the sponge *Anchinoe tenacior*,[44] the antibiotic magnesidin A (15) from *Vibrio gazogenes*,[45] and the novel siderophore vibrioferrin (16) that develops in *Vibrio parahaemolyticus* in response to limitation of Fe in the culture fluid.[46]

4 Chemical Synthesis and Resolution of Amino Acids

4.1 General Methods for the Synthesis of α-Amino Acids – The term 'general methods' has been attached to a group of reactions that have become familiar through use for many years; these are covered in this Section as far as the α-amino acids are concerned.

Relatively few novel ideas have been introduced under this heading in recent years, and those that have, have been concerned with the burgeoning area of 'Asymmetric Synthesis'. Although given a Section of their own in this Chapter



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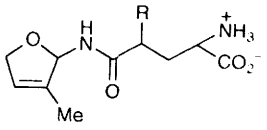

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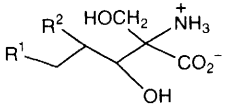
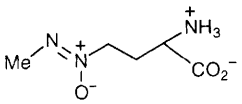


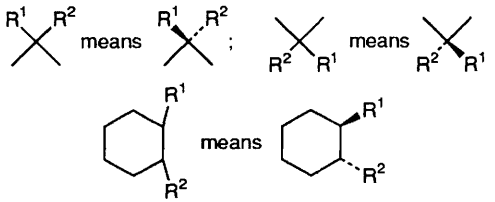
(3) R^1 = (*E*,*E*, *R*)-CH=CH$(CH_2)_4$CH=CHCH(OH)$(CH_2)_5$Me, R^2 = OH
(4) R^1 = (*E*)-CH=CH$(CH_2)_6$CH(OH)$(CH_2)_5$Me; R^2 = OH
(5) R^1 = $(CH_2)_8CO(CH_2)_5$Me; R^2 = OH; or R^1 = (*E*)- CH=CH
or R^1 = (*E*)-CH=CH$(CH_2)_6CO(CH_2)_5$Me; R^2 = H

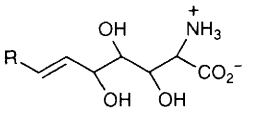


(6)

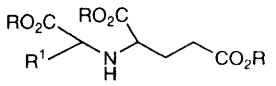
Three-dimensional features at chiral centres of structures depicted in this chapter follow the convention:–

(a) horizontally-ranged atoms, and their bonds, and atoms in rings, are understood to be in the plane of the paper;
(b) atoms and groups attached to these atoms in (a) are ABOVE the page if ranged LEFTWARDS and BELOW the page if ranged RIGHTWARDS:

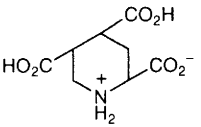




(7) R = $(CH_2)_6CH(OH)(CH_2)_5Me$ and
N-acetylated, for Sphingofungin D;
N-non-acetylated, for Sphingofungin B;
NH_3^+ replaced by $NHC(=NH)NH_2$ for Sphingofungin A



(8) R^1 = Pr^i, Bu^i, or Bu^s



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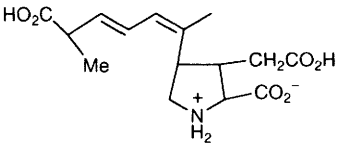

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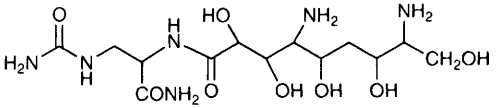

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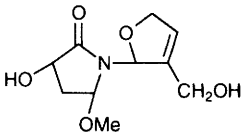

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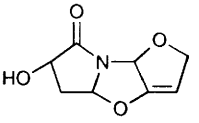

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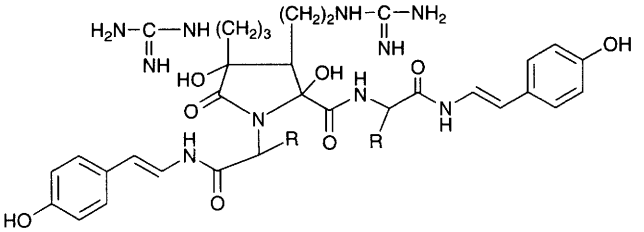
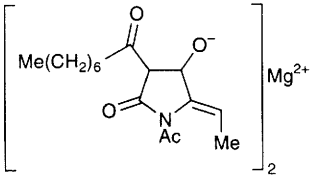


(14) various R



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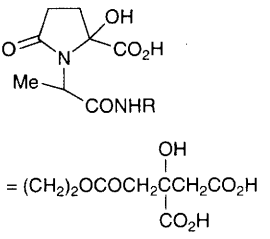
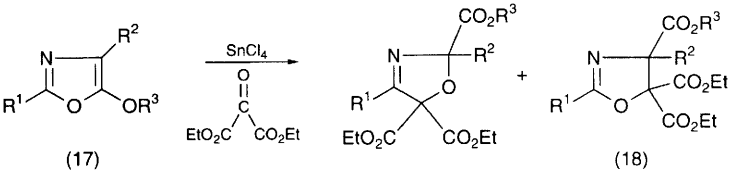


(16) R = $(CH_2)_2OCOCH_2\overset{OH}{\overset{|}{C}}(CH_2CO_2H)CO_2H$



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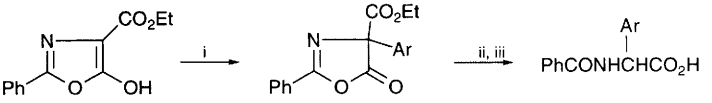


Reagents: i, $ArPb(OAc)_3$; ii, NaOH in EtOH–H_2O; iii, H_3O^+

Scheme 1

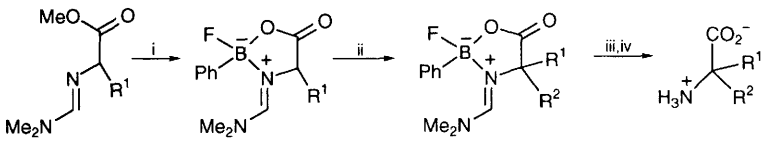
(Section 4.2), asymmetric synthesis methods are nearly always 'general methods of synthesis' too. Other general reactions by which one amino acid is used as starting material for the synthesis of another, are mostly covered in the later Section 6.3 (Specific Reactions of Amino Acids).

Long-established methods continue to be revisited as reliable routes, and many of these are used in syntheses of labelled amino acids (see Section 4.15). The alkylation of diethyl phthalimidomalonate (see Refs.166,256) and diethyl acetamidomalonate (see also Refs.254,258), e.g. for a synthesis of 2-amino-7,7-dimethyloctanoic and 2-amino-8,8-dimethylnonanoic acids,[47] and the alkylation of oxazolones, e.g. in an aspartic acid synthesis (17 → 18),[48] in a synthesis of α-amino-β-phosphonopropionic acid,[49] and in an arylglycine synthesis (Scheme 1)[50] and corresponding vinylglycine synthesis,[51] are typical long-established methods. Rearranged dimers that are well-known (usually unwanted) side-products from oxazolone alkylation, can be hydrolysed to give α-alkyl-α-amino acids.[52] Addition of a thiol to 4-benzylidene-2-methyloxazolone, followed by routine work-up, gives a threo/erythro-mixture of N-acetyl S-(p-methylbenzyl)-β-phenylcysteine methyl ester.[53] A novel variant of the oxazolone procedure is represented in the conversion of a 4,4-bis(isopropylthio)oxazolone into amides or peptides, and its chlorinolysis (SO_2Cl_2) to give halogenoglycine derivatives that are easily converted into other amino acids through halogen substitution.[54]

These two general methods are essentially glycine alkylation procedures; other routes in this category include alkylation of glycine Schiff bases (phase-transfer catalysed alkylation of $PhCH=NCH_2CO_2Me$ → phenylalanine, mediated by microwave energy),[55] and corresponding syntheses of leucine, serine and aspartic acid,[56] Michael additions, of $(R^1O)_2P(O)CH=CH_2$[57] and a two-step alkylation (by $R^1CH=CRCH_2Br$ then γ-elimination of Br) to give α-cyclopropylglycines.[58] Similar approaches employing N-phenacyl-N-benzylglycine[59] and N-(ω-chloroalkyl)-N-Boc-glycine[60] as starting materials lead to azetidinecarboxylic acids and higher homologues. The corresponding use of N-oxides of glycine Schiff bases to prepare α-(N-hydroxyamino) acids,[61] and of α-amidinoalkanoates (Scheme 2)[62] have a good deal in common, mechanistically.

The [3,3]-rearrangement of N-protected glycine allyl esters (19 → 20)[63] exemplifies an alternative glycine alkylation process that has been well studied from the 1960's.

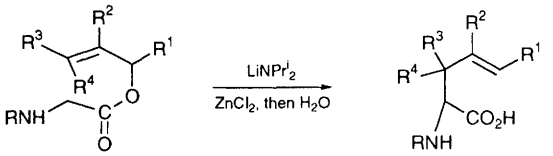
Alkylation of α-halogenoglycine synthons (Scheme 3) is significantly facilitated by $ZnCl_2$, indicating a radical mechanism where the catalyst is both a radical initiator and chelates the substrate.[64] Copper(I)-catalysed Cl-transfer radical cyclization of N-(alk-3-enyl)-α-chloroglycines gives prolines *via* 2-aza-5-alken-1-yl radicals.[65] A similar study of the generation of the glycine α-radical formed by stannanes from α-bromo-, -benzyloxycarbonyloxy-, and -methoxy-glycine derivatives, and its alkanesulfenylation with disulfides, has been described.[66] Xanthates $MeO_2CNHCH(S_2COEt)CO_2Me$ similarly yield radicals that add to alkenes to offer a valuable new general amino acid synthesis.[67] N-Protected α-hydroxyglycine esters are readily substituted, illustrated this year in a preparation of (p-vinylphenyl)glycine.[68] α-Acetoxy analogues have been employed in syntheses of vinylglycine[69] and propargyl homologues.[70]



(+ epimer at B)

Reagents: i, $K^+ PhBF_3^-/Me_3SiCl$; ii, $KOBu^t$, R^2hal; iii, refluxing MeOH; iv, ethylenediamine / MeOH

Scheme 2



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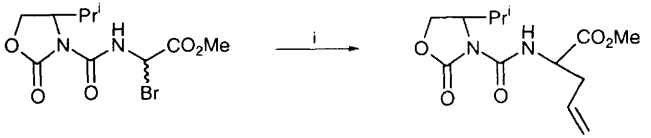


Reagents: i, $CH_2CH{=}CHSnBu_3$, $ZnCl_2.OEt_2$

Scheme 3

Isocyanoacetates $CNCH_2CO_2R$ (see also Ref.255) perform well in aldol additions that show high diastereoselectivity to provide β-hydroxy-α-amino acids.[71] α-Nitroacetates are readily alkylated, Michael addition of allyl acrylate followed by reductive cyclization giving N-hydroxy-pyroglutamate derivatives.[72]

Amination processes leading to amino acids constitute an established group of general methods that have been exemplified this year by some of the oldest variants: reductive amination of α-ketocarboxylic acids using NH_3/Raney nickel,[73] and of methyl (1S,2R,3R)-3-hydroxy-2-methoxycyclohexanecarboxylate;[74] ammonolysis or methylaminolysis of t-butyl bromoacetate,[75] and the corresponding process with diethyl bis(2-methylthioethyl)malonate.[76] Addition of ammonia, primary amines, or hydroxylamine to substituted fumaric acids leads to corresponding aspartic acid analogues,[77] and corresponding Michael addition of N-acylisoureas (formed from a carbodi-imide and a carboxylic acid) to methyl hydrogen maleate to give N-carbamylaspartic acids.[78] Further examples (see Vol. 26) of the formation of cyclic hydrazino-acids through cycloaddition of dienes to azodicarboxylates, have been published[79] (see also Ref.199). Condensation of a primary amine ($TiCl_4$) with a γ-chloro-α-ketoester to give a γ-chloro-α-iminoester is followed by cyclization to give a 1-amino-2,2-dialkylcyclopropanecarboxylic acid.[80]

Several examples of azidation, of enolates[81] and of α-methoxyacrylonitriles (giving α-azidonitrates),[82] have been described as stages in α-amino acid syntheses. Diazonium salts are electrophilic α-aminating agents towards esters in the form of their ketene silyl ketals, yielding α-azo- or -hydrazono-esters which on hydrogenation yield α-amino acid esters.[83] Use of an alkyl sulfenimine $R_2S{=}NH$ as aminating agent towards a latent nucleophilic carboxy group equivalent has been given a preliminary assessment.[84]

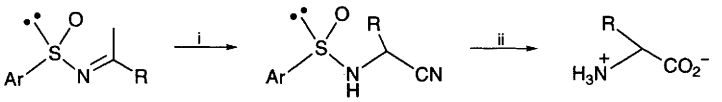
Amination through Stevens rearrangement of transient ammonium ylides formed between amines and diazoketones or diazoesters gives α-aminoketones or α-amino esters, respectively, in one step.[85]

Amidocarbonylation – the introduction of both amino and carboxy groups in a one-pot process – has been illustrated in an N-acetylglycine synthesis (paraformaldehyde, CO, and H_2, with a cobalt-phosphine catalyst),[86] and the distantly-related equivalent process from aldehydes and $CHCl_3$ continues to be studied.[87]

Introduction of the carboxy function into a protected amine, to lead to the corresponding α-amino acid, can be accomplished in certain cases, e.g. by the oxidation of a phenyl group (C_6H_5- → -CO_2H) using RuO_4.[88]

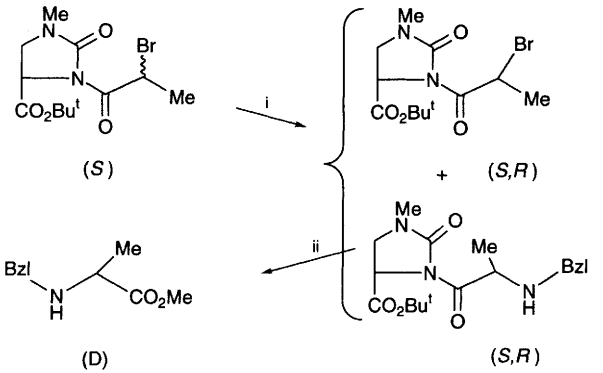
'Modifications to an amino acid side-chain' could be described as a general method of amino acid synthesis, although examples of this approach constitute a somewhat miscellaneous collection and are mostly located later in this Chapter (Section 6.3). However, an interesting set of procedures for the alkylation of the dehydro-alanine derivative methyl 2-acetamidoacrylate)tricarbonyliron(0), has been described,[89] leading to βββ-tri-alkyl amino acids through successive treatment with 2 eq MeLi and an alkyl halide (see also Vol.25, p.9).

Contraction of a β-amino acid backbone could also be described as a general synthesis method for α-amino acids, and further examples (see Vol.24, p.8) of the conversion of α-keto-β-lactams into α-amino acid N-carboxylic acid anhydrides



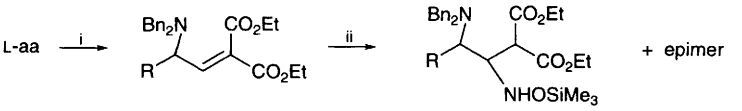
Reagents: i, Et_2AlCN; ii, 6M HCl, reflux

Scheme 4



Reagents: i, $PhCH_2NH_2$, K_2CO_3, CH_2Cl_2, r.t. 40 h; ii, NaOMe/ MeOH

Scheme 5



Reagents: i, established methods; ii, $Me_3SiNHOSiMe_3/CH_2Cl_2$, 22 °C, 18h

Scheme 6

have been accomplished by Baeyer-Villiger oxidation,[90] a process that is applicable to homochiral substrates, leading to β-alkylserine N-carboxylic anhydrides.[91] The method has been also been illustrated in a synthesis of (R)-α,β-di-amino-γ-hydroxyacid N-carboxylic anhydrides from β-lactams.[92]

4.2 Asymmetric Synthesis of α-Amino Acids – Activity in this area continues to increase, both in the provision of new methodology and in the development of established methods, including well-known standard general methods of synthesis, some of which are described in the preceding section, and revisited here in 'asymmetric versions'.

Two thorough reviews cover the overall topic[93,94] and another review deals with asymmetric synthesis of '2,3-methano'-amino acids (i.e., 1-aminocyclopropanecarboxylic acids).[95]

Modifications of standard general methods of α-amino acid synthesis are represented in a Strecker procedure employing a chiral ketone as catalyst for the equilibration of aminonitriles $R^1R^2C(CN)NHCHRCN$,[96] and in an equivalent process using homochiral sulfinimines (illustrated for the (S_S)-configuration in Scheme 4).[97]

Amination reactions incorporating kinetic resolution (Scheme 5),[98] and related hydroxylamination (Scheme 6),[99] illustrate further standard methods.

Several examples of the alkylation of glycine derivatives can be grouped together: Michael addition of $MeCH(CN)CO_2Me$ to vinyl ketones or acrolein catalysed by a Rh(I)-chiral phosphine complex, giving (R)-$RCOCH_2CH_2CHMe(CN)CO_2Me$ in 83–93% e.e. and thence to (R)-α-methyl-α-amino acids through routine elaboration;[100] stereoselective alkylation of glycine Schiff bases $Ph_2C{=}NCH_2CO_2Bu^t$ using active methylene compounds and a (-)-cinchonidine-derived chiral catalyst;[101] aldolization of glycine with PhCHO, catalysed by supramolecular bilayer assemblies containing L-alanine–lipid peptides with pyridoxal and Cu(II) salts, to give (S)-β-phenylserine in modest enantiomeric excess;[102] alkylation of (-)-menthyl N-acetyl α-bromoglycine by allyltrimethylsilane catalysed by $ZnCl_2$ to give (S)-(+)-norvaline after hydrogenation (see also Scheme 3);[103] for a synthesis of (-)-menthyl N-acetyl α-hydroxyglycine by this research group using (-)-menthyl glyoxalate + $MeCONH_2$, see Ref. 104.

Addition of a glycine enolate to the carbonyl group of α-D-ribohexofuranos-3-ulose gives the corresponding (S)-α-(glycos-2-yl)glycine.[105] The asymmetric benzylation of the carbanion from (-)-menthyl hippurate and similar glycine derivatives carrying chiral auxiliary groups, although thoroughly researched over many years, was recently found to be unsuccessful when only one equivalent of base is used.[106] In a broad study, the diastereoselectivity of this process was shown to be dependent upon the amount of additives and the nature of the N-acyl group and of the chiral ester. Alkylation of homochiral glycinamides gives generally good diastereoselectivity.[107] N-Boc-2-(tert-Butyldiethylsilyloxy)pyrrole is a glycine equivalent that underges aldol addition to homochiral aldehydes (Scheme 7) to give α-(polyhydroxyalkyl)-α-amino acids.[108]

Further conventional approaches are described for phase transfer-catalysed Gabriel synthesis employing (-)-bornyl α-bromoalkanoates (optical purities from

1.7–47%);[109] rather worse results are obtained in this reaction with various heterogeneous phase-transfer catalysts.[110] The conversion of lithium (1S,2R,4R)-10-dicyclohexylsulfamylisobornyl-2-cyano-3,3-diphenyl propanoate into ββ-diphenyl-α-methylalanine (21 → 22) involves a Curtius rearrangement.[111] A related approach for a synthesis of (S)-3,4-dichlorophenylalanine[112] is completed by a subtilisin resolution (see Section 4.17) in view of the disappointing optical purity of the product of the synthesis.

Photochemical amination of chiral silyl enol esters (23 in Scheme 8) has been illustrated in a synthesis of erythro-β-methyl-L-phenylalanine.[113]

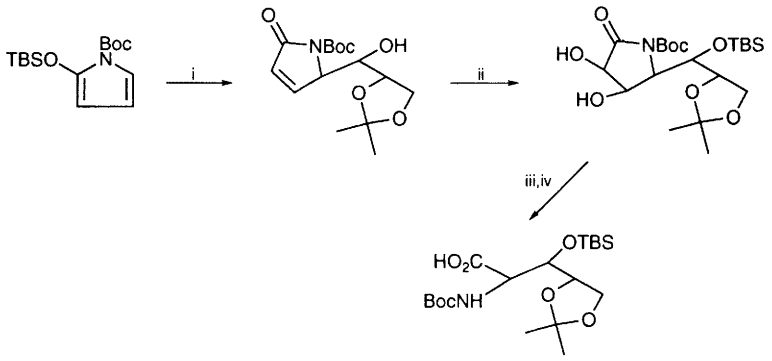
The Schollkopf bis-lactim ether synthesis continues in use (see also Ref.260) for the asymmetric synthesis of 2-amino-3-methyl-4-phosphonobutanoic acids,[114] 3-fluoro-4-nitro-L-phenylalanine,[115] bicyclic lactams,[116] and (2S,3R)-3-methylglutamic acid.[117] Alkylation of L-valine-derived piperazine-2,5-diones (24) followed by hydrolysis leads predominantly to (S)-α-amino acids.[118]

The S-configuration is induced by the chiral grouping in the substrate, during the hydrogenation of N-formyl-(Z)-dehydro-βββ-trifluorobutyrine (-)-menthyl ester (25 → 26).[119] The other main interest in the asymmetric hydrogenation of dehydro-amino acid derivatives over the years has concentrated on achiral substrates, and on the development of improved asymmetric hydrogenation catalysts. A clear enhancement of enantioselectivity (e.e.'s of L-amino acids up to 99%) accompanies the incorporation of electron-donating aromatic substituents in vic-diarylphosphonites derived from carbohydrates, as the chiral moiety in a Rh(I)-chiral phosphine catalyst.[120] The role of the protecting groups in cinnamates subjected to this procedure has been assessed.[121]

The main focus of development of synthetic methodology continues to be the use of heterocyclic chiral auxiliaries, most of which have been favoured for several years now. Predominantly (2R)-syn-β-substituted serines are formed (d.e. 84–100%) when the Ni(II) complex of the Schiff base of N-benzyl-L-proline o-benzoylanilide is aldolized by m-fluorobenzaldehyde or by a fluorine-substituted alkanal.[122] Alkylation of the Schiff base using alkyl halides[123] illustrates the approach employed by this research group for many years, though they have now established aldolization of the chiral Schiff base (27) by aldehydes to be an efficient (better than 90% e.e.) alternative route to substituted serines.[124] Use of this synthon in a synthesis of the photoactivatable 4′-(1-azi-2,2,2-trifluoroethyl)-L-phenylalanine has been described as extremely efficient.[125]

N-Acryloyl and -crotonoyl-camphorsultams can be used for the synthesis of stereodefined aziridine-2-carboxylic acids through bromination, dehydrobromination, and aminolysis stages.[126] Construction of a cyclopropane ring on the well-known aminoalkenyl synthon R*-CH = C(NHZ)CO_2Me [R*-CH is the (S)-glyceraldehyde moiety] and subsequent processing gives (1S,2R)-1-amino-2-vinylcyclopropanecarboxylic acid (*alias* γδ-dehydro-allocaoronamic acid).[127]

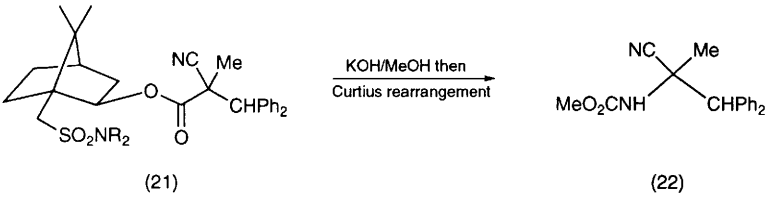
The use of chiral N-acyloxazolidinones in various contexts (see also Ref.64) continues to give excellent results, illustrated in the synthesis of (-)-pyrimidoblamic acid (Scheme 9) the early stages being based on [4 + 2]-cycloaddition of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine to 1-(dibenzylamino)-1-propyne);[128] β-branched phenylalanines;[129] tryptophans;[130] and αβ-dimethyl-1,2,3,4-tetrahy-



protected 4-*epi*-polyoxamic acid

Reagents: i, *0,0*-isopropylidene-(*R*)-2,3-dihydroxypropanal, $SnCl_4$, Et_2O;
ii, $KMnO_4$, CH_2Cl_2; iii, LiOH, THF, then $NaIO_4$; iv, $NaIO_4$, RuO_2

Scheme 7



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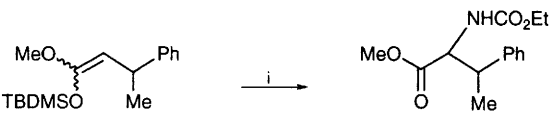

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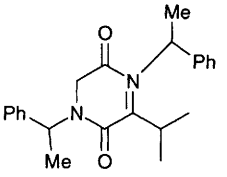
Reagents: i, ethyl azidoformate, *hv*

Scheme 8



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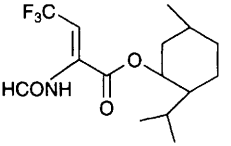

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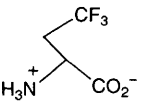

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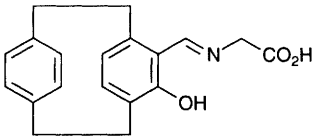

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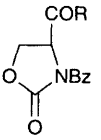

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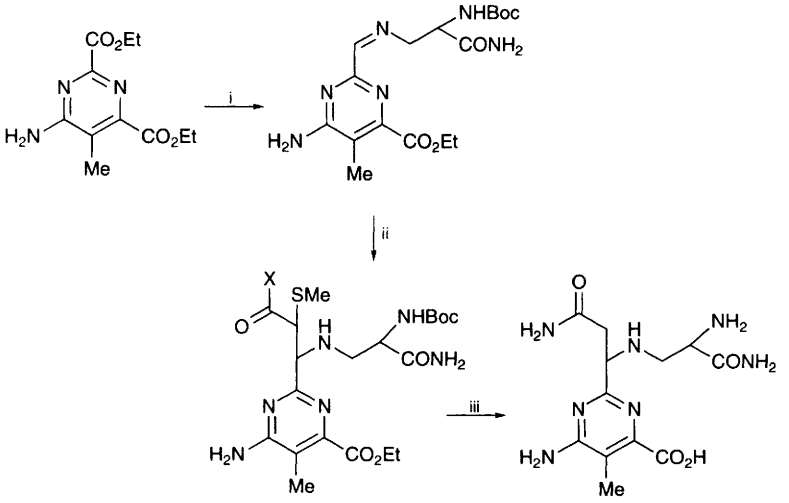


Reagents: i, $CO_2Et \longrightarrow CHO$ + Boc-Asp derivative; ii, Evans Sn^{II} enolate; iii, Bu_3SnH then HCl.EtOAc

Scheme 9

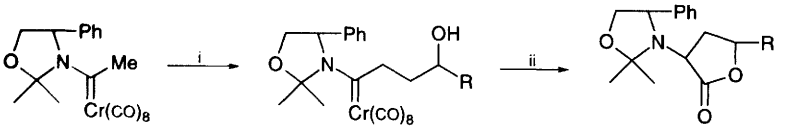
droisoquinoline-3-carboxylic acids;[131] homoserine analogues (using the alternative Karady/Seebach oxazolidinone approach);[132] and (2S,3S)-threoninol and related compounds using the (R)-glycidol-derived oxazolidinone (28).[133] Homologous chiral heterocycles used in similar ways include oxaziridines [reaction with copper(I) salts to give products of N-centred radicals leading to cis-5-benzyl-D-proline].[134] cis-4,5-Disubstituted oxazolidin-2-ones are epimerized at C-5 *via* a N/C-5 di-anion.[135] Piperazinones carrying a homochiral N-substituent[136] provide a new variant of the well-established imidazolidin-5-one.[137] An alternative to the oxazolidinones is the lactam (28; $-CH_2-$ in place of ring -O-), shown to be a useful chiral auxiliary.[138] N-Acylated 5-substituted 3,3-dimethyl-2-pyrrolidinones created in this study have been used in illustrative asymmetric syntheses.[139]

Routes based on recently-developed variants include the synthesis of γ-hydroxy-α-amino acids, illustrated for (+)-bulgecinine, based on aldolization of the Cr(0)-modified acyloxazolidinone (Scheme 10; see Vol.26, p.16),[140] a highly-diastereoselective aldol reaction of a Cr(0)-complexed benzaldehyde derivative starting a synthesis of (29), an analogue of the N-terminal amino acid of nikkomycin B,[141] synthesis of (2S,1'S,2'S)-2-(carboxycyclopropyl)glycine from the serine-derived oxazolidine (e.g. compound 107),[142] and a synthesis of (2S)-N-benzoyl 2-t-butyl-4-methylene-oxazolidin-5-one (Vol,26, p.16) for use in asymmetric synthesis, by bromination (Br_2/hv) of the L-alanine-derived heterocycle, then dehydrobromination (NaI),[143] and synthesis of (2R,3S)- and (2S,3R)-precursors (30 and epimer, respectively; Scheme 11) illustrated for syntheses of β-methyl analogues of protein amino acids (Phe, Tyr, and His analogues; see also Vol.26, p.13).[144]

Alkylation of new heterocyclic 'chiral glycine derivatives' prepared from glycinamide (Scheme 12) follows the oxazolidinone philosophy,[145] and hydrogenation of homochiral 3-ethyl-5-phenyl-3,4-didehydro morpholinones (see Vol.26, p.16) has led to (R)- and (S)-2-aminobutanoic acids from 2-oxobutanoic acid.[146]

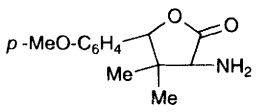
Particular examples, illustrating new synthons that are capable of being used in asymmetric syntheses more generally, have been reported; thus, the furan-2-one synthon (31), obtained from D-glucosamine, has been used in a synthesis of 4-hydroxy-L-pipecolic acid,[147] and D-glucosamine has been used in a preparation of Boc-L-serinal through periodate cleavage.[148] D-Mannosamine is a starting material for a synthesis of sphingofungin D (7; Scheme 13).[149] Kinetic resolution induced by L-(+)-di-isopropyl tartrate accompanies $Bu^tOOH/Ti(O^iPr)_4$ oxidation of α-furanylamines (32 → 33 + 34) and ozonolysis of the residual L-α-furanylamine leads to the N-toluene-p-sulfonyl L-amino acid.[150] Unconventional asymmetric synthesis of amino acids features a homochiral α-amino acid as chiral auxiliary to generate an enantiomer of γ-hydroglutamic acid,[151] 'ring-contraction' of 5-isonitroso-2,2-dimethyl-1,3-dioxan-4,6-dione through refluxing with ketones *via* a nitrosoketene (Scheme 14), cycloaddition to alkenes and routine elaboration yielding L-α-amino acids,[152] while ring-expansion is involved in a 4-oxoproline synthesis from a homochiral azetidinonecarboxylic acid (Scheme 15).[153]

4.3 Synthesis of Protein Amino Acids and Other Naturally Occurring α-Amino Acids – This section continues the coverage of α-amino acid synthesis, showing



Reagents: i, BuLi, RCHO; ii, *hν*, CO[–Cr(CO)$_6$]

Scheme 10



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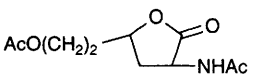

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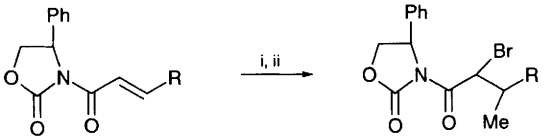

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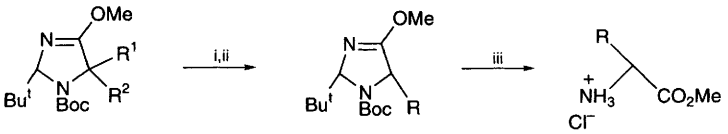
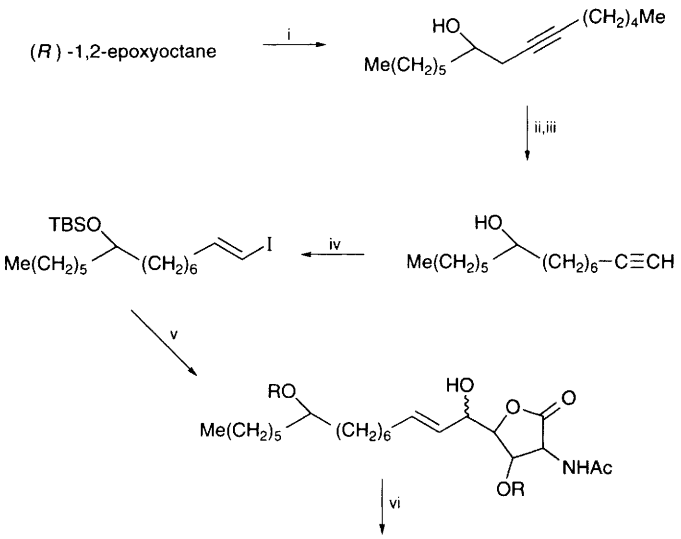
Reagents: i, MeMgBr–CuBr.SMe$_2$; ii, NBS

Scheme 11



Reagents: i, LDA/THF,–78 °C; ii, RX; iii, TFA/CH_2Cl_2 then 0.2M HCl

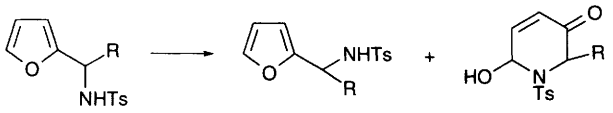
Scheme 12



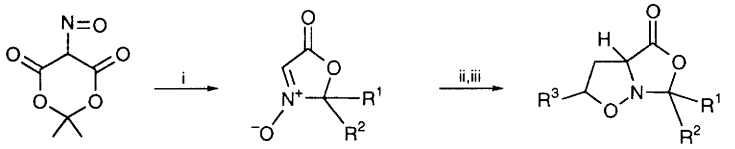
sphingofungin D (7)

Reagents: i, 1-heptyne, BuLi, $BF_3.OEt_2$; ii, Li, Bu^tOK, $H_2N(CH_2)_3NH_2$;
iii, $EtO_2C–N=N–CO_2Et$, Ph_3P, $PhCO_2H$ then TBSCl;
iv, Bu_3SnH, AIBN then I_2; v, synthon from *N*-acetyl-D-mannosamine, $CrCl_2/NiCl_2$/DMSO; vi, routine steps

Scheme 13

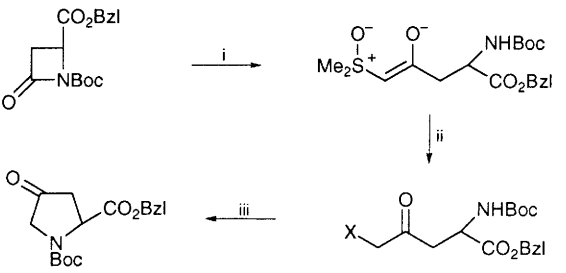


(32) (33) (34)



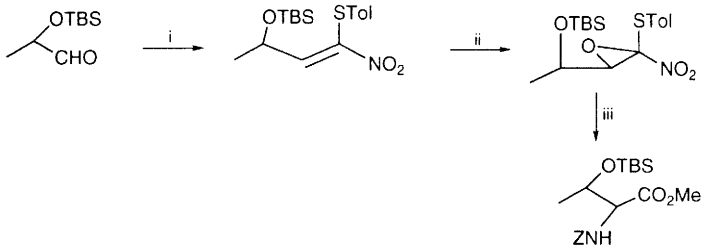
Reagents: i, R^1COR^2, reflux; ii, $R^3CH=CH_2$;
iii, ⟶ α-amino acid by aq. $NaHCO_3$, then H_2/5% Pd–C

Scheme 14



Reagents: i, Me_2SOCH_2, DMSO; ii, HX; iii, ML_n(cat.)

Scheme 15



Reagents: i, $TolSCH_2NO_2$, then $MeSO_2Cl$, ii, Bu^tCOOK; iii, NH_3 then ZCl

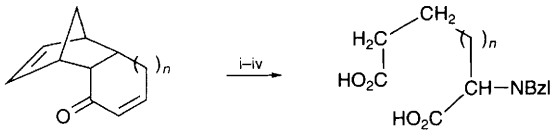
Scheme 16

applications of current methodology for the synthesis of natural products. Choice of route is usually tailored to the particular synthesis target, though alternative approaches are occasionally compared.

The usual crop from the primary literature dealing with aspects of fermentative production of the common amino acids [L-lysine using *Corynebacterium glutamicum*;[154] L-aspartic acid using intact coryneform *Brevibacterium flavum* MJ-233;[155] L-threonine using *Brevibacterium lactofermentum*;[156] L-phenylalanine methyl ester from methyl trans-cinnamate using phenylalanine ammonia lyase;[157] L-DOPA using a cell suspension culture of *Mucuna pruriens*;[158] and D-amino acids from enzymic hydrolysis of hydantoins by whole cells of *Agrobacterium radiobacter*[159]] is supplemented by reviews [production of amino acids using genetically-engineered *Serratia marcescens*;[160] using aminopeptidases and aminoamidases;[161] using hydantoinases;[162] L-aspartic acid using immobilized microorganisms;[163] and L-DOPA using tyrosine phenol lyase[164]]. Details of routine studies of the biosynthesis of amino acids in plants have not been collected in this Chapter over the years, though there has been the custom to mention unusual studies, e.g. the enzymic synthesis of β-substituted alanines in plants,[165] and of 5-hydroxy-4-oxo-L-norvaline in *Streptomyces akiyoshiensis*.[166]

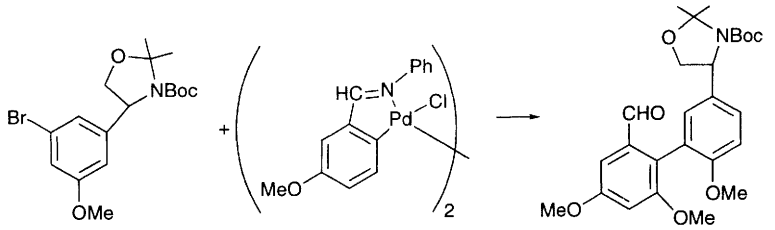
A new synthesis of D-alloisoleucine from (S)-2-methylbutanol[167] compares favourably with two standard procedures, *viz.* inversion at C-2 of L-isoleucine and racemization of N-acetyl-L-isoleucine and resolution with hog acylase. New syntheses of protected D-threonine and L-allo-threonine[168] employ a little-used general method of α-amino acid synthesis (Scheme 16). Extraordinary syntheses of L-glutamic acid and L-α-aminoadipic acid[169] use chiral equivalents of cyclopentadienone and cyclohexadienone respectively (Scheme 17).

The laboratory synthesis of 'MeBmt', the threonine derivative present in cyclosporin, has been reviewed.[170] A new synthesis in four steps[171] from (2Z,4R)-4-methyloct-6-yn-2-en-1-ol (Sharpless epoxidation and ring-opening with $MeNH_2$ are the essential steps), offers an improvement on the heroic multistage first synthesis of MeBmt (see Vol.17, p.8). A synthesis of 2-amino-4-hydroxy-3,3-dimethylbutyric acid (alias pantonine) from 3-chloro-2,2-dimethylpropanol,[172] β-hydroxyhomoserine (an intermediate in mugeneic acid syntheses) in 12 steps[173] from cis-2-butene-1,4-diol, (2S,3R)-2-amino-4-hydroxyadipic acid (a constituent of theonellamide F) by asymmetric reduction of the corresponding β-ketoester obtained from L-aspartic acid,[174] quisqualic acid from L-serine *via* the Garner aldehyde (107, R = H; -CHO → -CH=NOH → $-CH_2N(OH)CONHCO_2Et$, etc),[175] stizolobic acid through a biomimetic route starting with a catechol aldehyde,[176] and the alicyclic relatives anticapsin and bacilysin starting with a Diels-Alder adduct of dehydroalanine with O-TMS-cyclohexadienol,[177] In the last-mentioned study, independent confirmation is provided that the previously announced stereochemistry of anticapsin requires revision [it has the (S)-configuration at C-4; see Vol.26, p.4]. Construction of the side-chain of arogenic acid, (γS)-β-(1-carboxy-4-hydroxy-2,5-cyclohexadien-1-yl)-L-alanine, is conveniently achieved through Michael addition of the anion of methyl 1,4-dihydrobenzoate to methyl N-acetyldehydroalaninate.[178] Further exploration of routes to vancomycinic acid precursors (35)[179,180] and polyoxamic acid (36; a synthesis involving



Reagents: i, $-CH{=}CH \longrightarrow -CH_2-CH_2-$; ii, $BzlNH_2$; iii, $NaBH_4$; iv, $NaIO_4$, $RuCl_4$

Scheme 17



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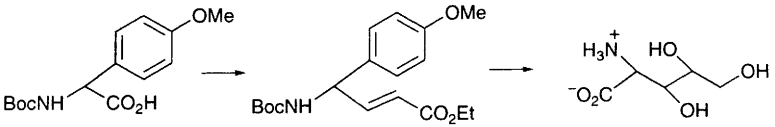

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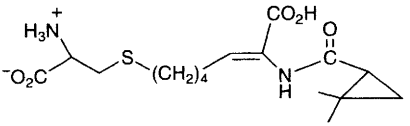


(37)

$-C_6H_5 \rightarrow -CO_2H$)[181] has been reported. The same method of generating a carboxy group appears in a synthesis from α-aryl-β-alanines, of 2′-deoxymugineic acid and nicotianamine.[182] Complex synthetic targets are also represented in cilastatin (37), constructed from L-cysteine, 7-bromo-2-oxoheptanoic acid, and (+)-(S)-2,2-dimethylcyclopropanecarboxylic acid.[183] The synthesis of several other cyclopropanes [trans-α-2-(carboxymethyl)cyclopropyl]glycine from *Blighia unijugata*, synthesized by dibromocyclopropanation of (38) prepared from D-serine;[184] all four stereoisomers of carnosadine (39; a set of constrained arginines, see Vol.26, p.19);[185] (1R,2S)- and (1S,2S)-dehydrocoronamic acids from dimethyl 2-vinylcyclopropanedicarboxylic acid (selectively hydrolysed by successive treatment with two esterases with different regioselectivities) then routine introduction of the amino group through the Curtius rearrangement[186]] have been described. Full details (see Vol.25, p.21) of a synthesis of (2S,4R)- and (2S,4S)-diastereoisomers of hypoglycin A have been described, incorporating a Sharpless epoxidation stage in an asymmetric methylenecyclopropane synthesis.[187]

(2R,3S)-3-Hydroxylysine has been synthesized through Hayashi's chiral ferroceno-gold catalysed oxazoline formation from 4-phthalimidobutanal and methyl isocyanoacetate, and the (2S,3R)-enantiomer through a route incorporating a Sharpless cis-hydroxylation.[188]

Total synthesis of the azetidinecarboxylic acid derivative, mugineic acid (40, X = H; equally correctly described either as a β-hydroxyornithine derivative or an α-hydroxy-GABA derivative) (see Vol.25, p.23)[189] and its 3-epi-hydroxy-derivative (40; X = OH)[190] involve a common intermediate (41). The latter report also describes the synthesis of distichonic acid A, and 2′-hydroxynicotinamine.

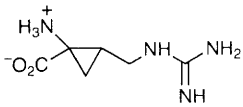
Naturally-occurring proline derivatives of continuing interest, the kainoids and bulgecinine, have been synthesized by new routes. Condensation of glyoxal with the (R)-phenylglycinol derivative (42) proceeds *via* a cyclic iminium ion that undergoes tandem aza-Cope–Michael reactions *en route* to (-)-α-allokainic acid.[191] A six-step route to DL-kainic acid (43 in Scheme 18) uses a similar reaction sequence to set up the ring system with the correct relative stereochemistry.[192] Further details have been published[193] of a synthesis of (-)-α-kainic acid employing a ring construction step based on the Pauson-Khand reaction (see Vol.26, p.24) and the same research group has reported an effective synthesis of α-allokainic acid (Scheme 19).[194] A short, efficient route to 4-arylkainoids starts with trans-4-hydroxy-L-proline.[195] Radical cyclization of a protected L-serinal (44) is at the heart of an elegant synthesis of (+)-bulgecinine,[196] also reached through reduction of appropriately substituted 2-amino-4-oxoalkanoic acids (45; somewhat capricious stereoselectivity is involved in the reduction).[197] Clavalanine and erythro-4-hydroxyornithine were also prepared from the same starting material in this study.

A route to (S)-(-)-pipecolic acid (46 → 47) employing the chiral oxazolidine approach is also capable of extension to the synthesis of 2- and 6-alkyl analogues.[198]

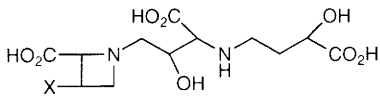
'PCA', an unusual hydrazino acid that is a constituent of the Luzopeptins, has been synthesized by the condensation of di-t-butyl azodicarboxylate with the di-anion of $(MeO)_2CHCH_2CH(OH)CH_2CO_2Et$ (see also Ref.79).[199]


Boc
N
O
O
O
H_3N^+
^-O_2C
CO_2H

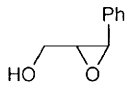
(38)


H_3N^+
^-O_2C
NH
NH_2
NH

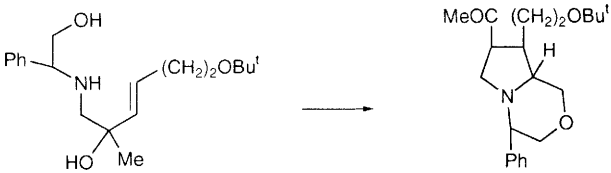
(39)


HO_2C
OH
HO_2C
N
N
H
CO_2H
X
OH

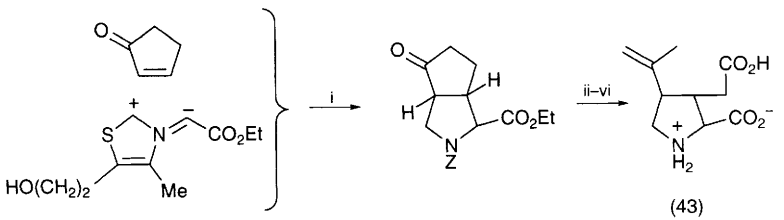
(40)


Ph
HO
O

(41)


OH
Ph
NH
$(CH_2)_2OBu^t$
HO
Me
MeOC
$(CH_2)_2OBu^t$
H
N
O
Ph

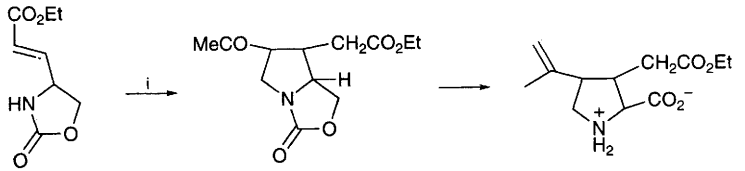
(42)



(43)

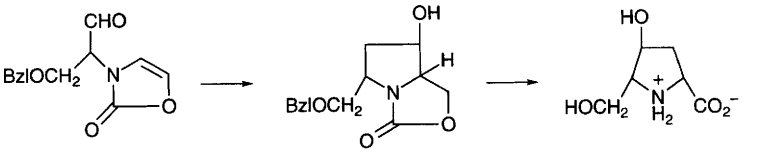
Reagents; i, Et_3N, MeCN, r.t., then $SnBu_3H$/AIBN, ZCl; ii, MeLi, $TiCl_4$; iii, $BF_3.Et_2O$; iv, oxidative ring-opening (RuO_2/$NaIO_4$); v, $CH_2{=}PPh_3$ or CH_2I_2/Zn; vi, separate diastereoisomers then OH^-, ion exchange

Scheme 18



Reagents: i, $MeCOCH{=}CH_2$; ii, $CH_2{=}PPh_2$

Scheme 19



(44)

(+)-bulgecinine

4.4 Synthesis of α-Alkyl Analogues of Protein Amino Acids – The synthesis of homochiral examples of known absolute configuration of this class of substituted α-amino acid has been considered to be a difficult enterprise, but the extraordinary fact that a configurationally-stable anion can be generated from N-Boc-N-methyl-L-phenylalanine using Li 2,2,6,6-tetramethylpiperidide opens the door to α-alkyl analogues.[200]

The conventional approach, α-methylation of a Schiff base of a protein amino acid, is illustrated in a synthesis of α-methylhomocysteine (Scheme 20).[201] α-Allylation of pipecolic acid and ensuing steps yield the α-(2-alkoxycarbonyl)ethyl analogue.[202] The hydantoin route is often inappropriate, because of the drastic conditions needed to release the amino acid, but 3-(toluene-p-sulfonyl)hydantoins carrying adenine and thymidine side-chains are easily hydrolysed to give the corresponding amino acids, in dilute alkali at slightly elevated temperatures.[203]

Grignard addition to fluoroacetonitrile followed by routine stages gives α-fluoromethylglutamic acid, whose cyclization leading to the glutamate racemase inhibitor, aziridinoglutamate, has been worked out.[204]

The need for resolution is avoided in the chiral oxazolidinone approach, used for a synthesis of (S)-2-methylproline,[205] although the oxazolidinone hydrolysis step that completes the procedure can be simplified.[206] (S)-α-2-Aminoethylmethionine has been obtained in 18% yield from the 5-(methylthioethyl)oxazolidinone, through enolate alkylation with $BrCH_2CN$ and routine elaboration.[207]

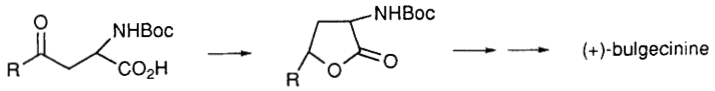
Stereoselective alkylation of isobornyl 2-cyanopropanoate is exemplified with syntheses of α-methyl-L- and D-tryptophan[208] and α-methyl-D- and -L-phenylalanine.[209]

αβ-Di-alkylaspartic acids are readily obtained *via* β-lactams prepared from Schiff bases $ArN=CRCO_2Me$ and ketenes.[210]

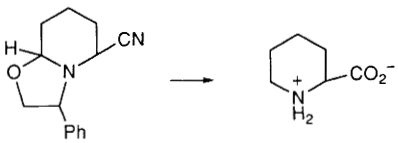
4.5 Synthesis of α-Amino Acids Carrying Alkyl Side-Chains, and Cyclic Analogues – With the proviso that 'use of one α-amino acid for the synthesis of another' is covered in the later Section 6.3 (Specific Reactions of Amino Acids) papers collected here deal with approaches to aliphatic synthetic targets from other starting points.

(S)-2-Aminosuberic acid has been prepared from $(E)\text{-}CH_2=CH(CH_2)_5CH=CHCH_2OH$ through asymmetric epoxidation, ring-opening with benzhydrylamine, and oxidative cleavage.[211] Other amination processes include Curtius rearrangement (diphenyl phosphoroazidate) of selectively-hydrolysed 2,2-dialkylcyclopropane-1,1-dicarboxylic acid esters,[212] and ring-closure of 2,5-dibromoadipic acid (R)-pantolactone esters using benzylamine to give trans-pyrrolidine-2,5-dicarboxylic acids.[213] 1,2-trans-Placing of NH_2 and OH in a 1,2-trans relationship on cyclopentadiene (AcOOH then NH_3/MeOH) and *Candida antarctica* resolution starts a route to (2S,3R)-3-hydroxyproline.[214] An unusual synthesis of 3-phenyl-3-hydroxyproline from an N-benzoylethyl-N-toluene-p-sulfonylglycinamide involves photochemical cyclization.[215]

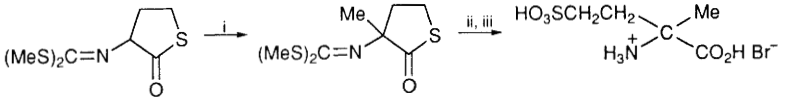
Carboxylation of 4-(hydroxymethyl)pyridine through reaction of its O-trimethylsilyl-N-oxide with Me_3SiCN and saturation of the ring leads to the 4-substituted piperidine-2-carboxylic acid.[216] Hydrogenation of dimethyl



(45)

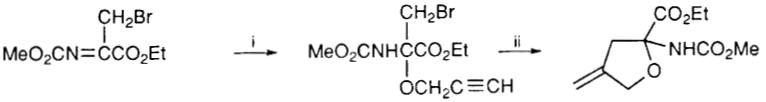


(46) (47)



Reagents: i, base, MeI; ii, aq. HCl; iii, Br_2, H_2O

Scheme 20



Reagents: i, $HOCH_2C{\equiv}CH$, $(PPh_3)_4Pd/CuI$; ii, $Bu_3SnH/AIBN$

Scheme 21

3,5-pyridinedicarboxylate provides a 1:1 cis-trans mixture of piperidine dicarboxylic acids.[217]

4.6 Models for Prebiotic Synthesis of Amino Acids – Conventional studies under this heading continue much as they have done for many years, represented by $CO_2/CO/N_2/H_2O$ mixtures subjected to electric discharge (giving 6 protein amino acids, glycine predominating, and 2 non-protein amino acids when CO is abundant),[218] and by ^{60}Co γ-irradiated aqueous glycine (Asp, Ser, Thr, and Glu, and $MeNH_2$ + $EtNH_2$ formed from reaction of a glycine radical with glycine breakdown products).[219]

Current speculation, that deep oceans were the sites of the origin of life, is helped by confirmation (hydrothermal synthesis; Vol. 25, p.34) of the generation of amino acids from $C_2H_2/H_2O/O_2/H_2/(NH_4)_2CO_3$ mixtures at 200-275°.[220]

4.7 Synthesis of α-Alkoxy α-Amino Acids, and Analogous α-Heteroatom-substituted α-Amino Acids – Asymmetric synthesis of (R)-α-sulfenylglycine has been achieved by the reaction of MeSSMe with 2-hydroxypinan-3-one Schiff bases.[221]

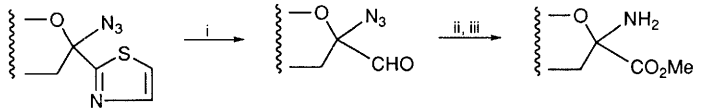
Fmoc-α-Methoxyglycine has been prepared by addition of Fmoc-carbamate to glyoxylic acid, then O-methylation by $MeOH/H^+$.[222] Anodic α-methoxylation of α-amino acids has become a routine step in many synthetic applications (notably, substitution by alkyl groups), and illustrated with asparagine and serine derivatives[223] and proline.[224]

Independent studies were aimed at the provision of anomeric tetrahydrofuranosyl amino acids and pyranosyl analogues (Scheme 21)[225] (Scheme 22)[226] within the context of analogues of the herbicide (+)-hydantocidin, whose short synthesis (see Vol.26, p.24) from β-D-ribofuranosyl amide results from fortuitous α-bromo β-amide formation and treatment with silver cyanate.[227]

Several examples of the uses in synthesis, of glycine derivatives conforming to the title of this section, are cited elsewhere in this Chapter.

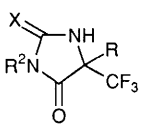
4.8 Synthesis of α-(ω-Halogeno-alkyl) α-Amino Acids – A review has appeared describing Ukrainian work on the synthesis of fluorine-containing amino acids.[228] A well-established route to ββ-difluoroalanine from $ZNHCH(CHF_2)CH=CH_2$ through oxidation to generate the carboxy group, has been rendered a practical proposition through an efficient synthesis[229] of $H_2NCH(CHF_2)SEt.HBr$. α-(Fluoromethyl)-β-fluoroalanine, an important intracell pH indicator, can be prepared in 44% overall yield from 1,3-difluoropropan-2-ol, through application of standard methods [1,3-difluoroacetone → $(FCH_2)C=NCHPhCH_2OH$ → $(FCH_2)CH(CN)NH_2$ using TMSCN].[230] α-Trifluoromethyl-α-amino acids are readily obtainable from imidazolidin-2,5-diones (48).[231] β-Difluoromethyl-m-tyrosine has been prepared through an uneventful Evans oxazolidinone synthesis.[232]

(2S,4S)-5-Fluoroleucine has been synthesized from L-pyroglutamic acid through diastereoselective methylation, followed by less stereochemically-demanding steps.[233]

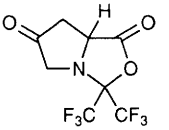


Reagents: i, TfOMe, then $NaBH_4$ and $HgCl_2$; ii, Ag_2O then CH_2N_2; iii, H_2–Pd/C

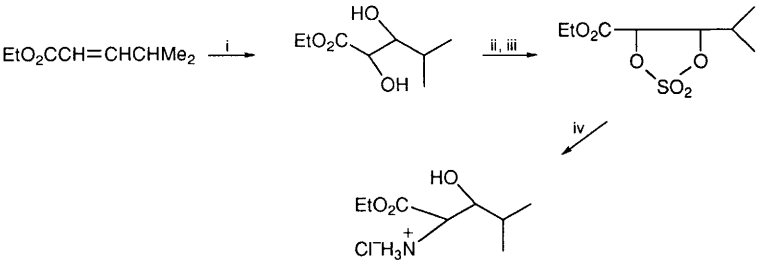
Scheme 22



(48) X = O or S



(49)



Reagents: i, Sharpless dihydroxylation; ii, $SOCl_2$; iii, $NaIO_4/RuCl_3$; iv, NaN_3 and reduction

Scheme 23

trans-4-Fluoro-L-pipecolic acid and the 4,4-difluoro-analogue have been prepared from di(ethylamino)sulfur tetrafluoride and the oxazolidinone (49), available from L-aspartic acid;[234] and (2R,5R)-5-chloropipecolic acid has been obtained by elaboration of the readily-available N-methoxycarbonyl (S)-5-TBDMSoxy-2-oxo-piperidine.[235]

Examples of side-chain halogenation of amino acid derivatives are to be found in the later Section 6.3, though it could be noted here, that 4-alkyl-5-ethoxyoxazoles (easily prepared from N-acylamino acids) are useful substrates for perfluorination.[236]

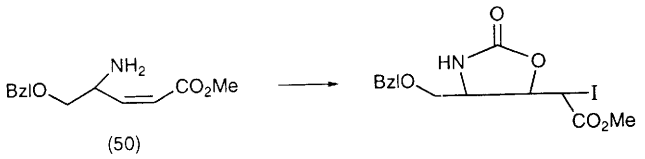
4.9 Synthesis of α-(ω-Hydroxyalkyl) α-Amino Acids – Hydroxylation of alkenes leading to hydroxyalkyl side-chains is represented in a number of different strategies. Where the α-amino acid moiety is in place, as with L-vinylglycine [$CH_2=CHCH(NH_2)CO_2H$], then 1,2-dihydroxylation using OsO_4 yields hydroxythreonine stereospecifically.[237] In a similar approach, 1-aminocyclohexene-1-carboxylic acids, formed from 4-arylideneoxazolin-5-ones by Diels-Alder addition to dienes, give iodohydrins that yield γ-hydroxy-α-amino acids through reductive dehalogenation and hydrolysis.[238] Protected aspartic acid enolates provide (3R)- and (3S)-hydroxy-L-aspartates through treatment with electrophilic hydroxylating agents.[239]

Grafting the α-amino acid moiety on to a hydroxylated structure is illustrated in a new synthesis of C-α-D-glucosyl-α-amino acids starting with a protected 1-allyl-1-deoxyglucose, then Sharpless epoxidation, selective mesylation, tritylation, and azidolysis and routine elaboration.[240] A similar approach leading to (2S,3S)- and (2R,3R)-3-hydroxyleucine (Scheme 23) also succeeds because of favourable regioselectivity.[241] Mercury(II) oxide oxidation of D-glucosamine gives D-glucosaminic acid, and straightforward replacement of the 3-hydroxy group by H, giving (2S,4S,5R)-4,5,6-trihydroxynorleucine.[242] Monosaccharide-derived azidolactones continue to serve (see Vol. 26, p.33) as starting materials for tetrahydroxy-1-aminocyclopentane- and cyclohexanecarboxylic acids with unambiguous control of stereochemistry.[243] threo-3-Hydroxy-L-glutamic acid[244] and (2S,3R)-3-hydroxyornithine[245] have been prepared through a highly stereoselective iodocyclocarbamation of the chiral alkene (50) obtained from O-benzyl-L-serine.

4.10 Synthesis of α-(ω-Amino-alkyl) α-Amino Acids – The synthesis of isoxazolidin-5-ones, and their use in the synthesis of β-amino- and β-(N-hydroxylamino)-alanines, has been described.[246] Substitution of aminating agent for hydroxylating agent in a process described in the preceding section[239] has been successful in leading to (3R)- and (3S)-amino-L-aspartates.

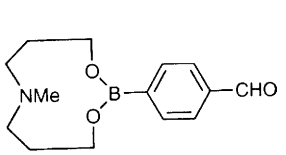
4.11 Synthesis of α-Amino Acids Carrying Unsaturated Aliphatic Side-Chains – As usual, there is interest in each of the categories covered by the heading of this Section: the αβ-unsaturated-α-amino acids, *alias* 'dehydro-amino acids', are constituents of natural peptides, while they and their homologues (vinyl- and allyl-glycine) are increasingly valuable in synthesis.

Protected dehydroalanine is easily formed from serine derivatives, treatment of



(50)

(51) (52)



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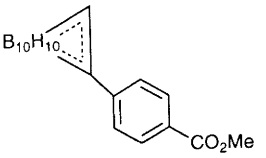
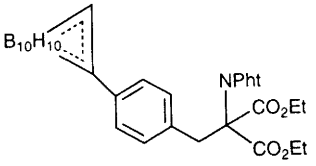


(54)



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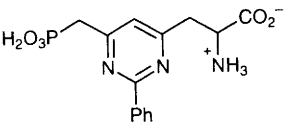


(56)

Z-Ser(OTs)OEt with $Bu_4NI/NaOH$ being currently recommended.[247] The potassium salt of N-acetyl α-(diethylphosphonyl)glycine condenses readily with aldehydes, exemplified in the synthesis of dehydro-amino acids carrying long side chains, (E)- or (Z)-$EtO_2CC(NHAc)=CHCH_2(CH_2)_nCO_2Me$.[248] N-Acyl-2,3-dehydro-2-amino acid esters result from perrhenate-catalysed decomposition of α-azido acid esters in solution in organic solvents containing an acyl chloride.[249]

A general synthesis of αβ-dehydroamino acids from a glycine derivative is exemplified with the preparation and hydrolysis of 4-alkylaminomethylenethiazol-5-ones.[250] The reaction sequence from the aldehyde (51) formed from D-arabinose and L-serine, to the highly functionalized dehydroamino acid (52) postulated to be a constituent of azinomycins, includes a Wittig condensation with a glycylphosphonate.[251]

An αβ-dehydroamino acid with an extended side-chain, methyl (-)-(Z)-2-(Z-amino)-4,5-cyclopropane-hex-2-enoate has been prepared through manipulation of functional groups on 5-(t-butyldimethylsilyloxy)furan-2(5H)-one.[252] A more routine approach to such systems is Michael addition to a protected dehydroalanine, which offers convenient access to (Z)-dehydrotryptophans through $PdCl_2$/NaOAc-AcOH catalysed reaction with indoles (see also Refs.177,178).[253]

4.12 Synthesis of α-Amino Acids with Aromatic or Heteroaromatic Groupings in Side Chains – Increasing interest in the therapeutic use of common amino acids capable of neutron capture when carrying appropriate substituents has encouraged studies in the synthesis of organic boron derivatives (see also Refs.9,868). Standard methods have been applied for the synthesis of o- and m-borono-L-phenylalanines. Grignard reaction of o- and m-bromotoluene with $B(OMe)_3$ and functionalization so that alkylation of diethyl acetamidomalonate can be carried out, was followed by α-chymotrypsin resolution.[254] p-Borono-DL-phenylalanine and -DL-phenylserine were prepared by aldolization of methylisocyanoacetate using the aldehyde (53).[255] A series of papers has appeared, describing the synthesis of phenylalanines substituted in the phenyl moiety by carboranyl groupings. One of these starts with methyl p-bromobenzoate *via* p-$(HC\equiv C)$-$C_6H_4CO_2Me$ + decaborane → (54), and reaction of the derived benzyl bromide with diethyl phthalimidomalonate → (55).[256] Other standard methods are represented, e.g.[257] the elaboration of an allyl chain carrying a carboranylphenyl grouping, into the acyl group of a chiral N-acyloxazolidinone (*cf.* Section 4.2).

5-Fluoro-D- and L-DOPAs and ^{18}F-analogues have been prepared starting from 5-nitrovanillin, through the acetamidomalonate route and Balz-Schiemann substitution of a diazonium group by fluorine, followed by chromatographic resolution.[258] 6-Fluoro-L-DOPA and its 3-O-methyl derivative have also been obtained by standard synthetic methods.[259]

Homochiral bis-amino acid diaryl ethers exist in natural products, and O-arylation of tyrosine derivatives employing fluoroarenes has been established using suitably mild reaction conditions.[260]

Simple heteroaromatic side-chains are represented in β-(2-pyridyl)-L-alanine, prepared from 3-(2-pyridyl)acrylic acid through catalysis by L-phenylalanine

ammonialyase (present in *Rhodotorula rubra* mycelium);[261] and in the pyrimidine isostere (56) of the potent NMDA antagonist, SDZ EAB 515,[262] synthesized by alkylation of $Ph_2C=NCH_2CO_2Me$. β-Isoxazol-4-yl-L-alanines are potent NMDA agonists, and further synthetic studies (see Vol.25, p.38) have been described of homologues (57 and 58),[263] AMPA and 4-methylhomoibotenic acid have been prepared through cycloaddition of suitably substituted bromonitrile oxides to alkynes.[264] Resolution using (-)-phenylethylamine and absolute configurational assignment by X-ray crystal analysis is included in one of these preparations.[263]

A related alanine derivative that carries a β-heterocyclic moiety is the neurally-active quisqualic acid. Conformationally-constrained analogues have been synthesized, using standard methods.[265] The homochiral α-amino acid (59) carrying a thiazoline side-chain was obtained by a novel manipulation of the penicillin nucleus.[266]

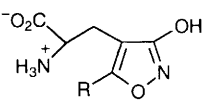
β-Substituted tryptophans (see also Refs.129-131, 144, in Section 4.2) have been obtained by Lewis-acid catalysed ring-opening by indoles, of the aziridine (60). Opposing regioselectivities are observed; the lactone (61, from 60, RR^1 = O) leads to β-amino acids, and the acetal (60, R = H, R^1 = OTBDMS) yields (62) from which β-substituted tryptophans were obtained.[267] erythro-β-Alkylated tryptophans can be obtained by conjugate addition to (63) formed from the tryptophan derivative (64) that Crich's research group has been establishing as a valuable synthon in recent years.[268] 3,4-Bridged tryptophans (65) are, likewise, obtained starting from tryptophan itself, *via* 4-bromodehydrotryptophan and cyclization of the derived 4-bromo-α-propenyl-DL-tryptophan.[269] Other 3,4-cyclized tryptophan analogues formed with the α-amino group through an isoleucyl bridge[270] are members of a family of conformationally constrained amino acids that includes potential protein kinase C modulators.

These analogues support a wide range of pharmacological studies that reflect the importance of derivatives of the parent amino acid, and the fact that N-ethyl-L-tryptophan benzyl ester is a weak antagonist at the Substance P(NK_1) receptor has stimulated the synthesis of indole-substituted analogues [N-acetyl-L-(3′,5′-di-trifluoromethyl)tryptophan was found to be particularly effective] by standard methods.[271] An efficient synthesis of 5-azidotryptophan[272] employs a standard route, starting from 5-nitroindole.

4.13 Synthesis of α-Amino Acids Carrying Sulfur- or Selenium-containing Side Chains – This class of amino acid is gaining further importance, since certain sulfur functional groups react with nitric oxide. L-Thiocitrulline (readily prepared from L-ornithine) and its S-methyl derivative, and L-homothiocitrulline, are potent inhibitors of nitric oxide synthase, and presumably owe this property to their structural similarity with arginine analogues.[273]

Conventional synthetic strategies are involved in the synthesis of S-alkyl-L-cysteines[274] (see also Ref.53) and of the conformationally-constrained L-methionine (66) obtained by elaboration of the Diels-Alder adduct of 5-norbornen-2-ol with a protected dehydroalanine.[275]

L-(+)-Selenomethionine has been prepared from L-homoserine lactone and MeSeLi.[276]



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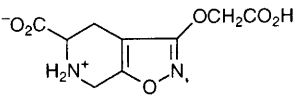

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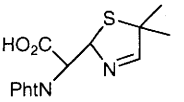

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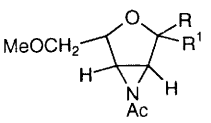

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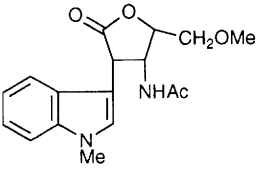

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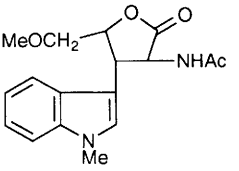

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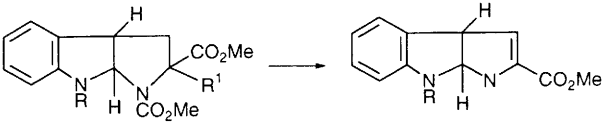

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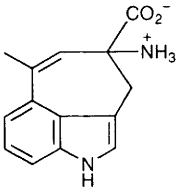

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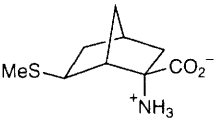

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4.14 Synthesis of α-Amino Acids Carrying Phosphorus Functional Groups in Side Chains – Main areas of interest in compounds of this class, as distant isosteres of some common amino acids, are being sustained by current research (see also Refs.99,114), e.g. into the synthesis of (R)-4-oxo-5-phosphononorvaline, $H_2O_3PCH_2COCH_2CH(N^+H_3)CO_2^-$ (a selective NMDA glutamate site antagonist) in four steps from D-aspartic acid.[277] Stereoselective synthesis of L-phosphinothricin [$MeP(O)(OH)CH_2CH_2CH(NH_2)CO_2H$], present in the herbicide 'glufosinate-ammonium', has been reviewed.[278] The (αα-difluoroalkyl)phosphonate analogue of phosphoserine has been synthesized starting from O-benzyl-N-Boc-L-serine.[279] 1-(Z-Amino)-5-(Boc-amino)-pentylphosphinic acid, an isostere of lysine, has been synthesized from 3,4-dihydro-(2H)-pyran.[280]

Phosphonate-bridged phenylalanine derivatives (67) that are capable of selective de-protection so that they can be incorporated into peptides have been synthesized from the corresponding p-iodo-L-phenylalanines (an improved synthesis of this amino acid has been worked out), through Pd-catalysed coupling.[281] The phosphonotyrosine isostere N-Fmoc-4-phosphono(difluoromethyl)-L-phenylalanine, has been prepared from the organozinc reagent from β-iodoalanine together with the requisite iodoarene,[282] and independently from the methyl ester of its diethylphosphonate.[283] N-Boc-(4′-dimethylphosphonomethyl)-L-phenylalanine (68) has been obtained through a route that employs the iodarene-organozinc reagent C-C-bond-forming methodology.[284]

4.15 Synthesis of Isotopically Labelled Amino Acids – All the familiar isotopes featured under this heading over the years are represented in the current literature. ^{2}H-Labelled protein amino acids, intended to assist biosynthetic studies, often call for the most ingenious synthetic strategies, as illustrated by (2S,4S)- and (2S,4R)-[5,5,5-$^2H_3$]leucine. The route starts from (R)-pulegone → [2-^{2}H]citronellal → [5,5,5-$^2H_3$]isovaleric acid (through de-carbonylation using Wilkinson's catalyst followed by oxidation), then follows standard steps.[285] Labelled aziridines (69; prepared from labelled malates, starting with fumarates/fumarase or by enzymic amination) serve as starting materials for syntheses of stereospecifically-[^{2}H]-labelled D-serine, D-cystine, and β-chloro-D-alanine, through nucleophilic ring-opening.[286] Synthesis of labelled D-(prop-2-ynyl)glycine (70) follows an identical strategy using a carbanion as nucleophile.[287]

Regiospecific labelling of the aromatic ring in phenylalanine is achieved by treating a protected tyrosine tetrazolyl ether or its o- or m-isomer, with ^2H_2O.[288]

The development of established methods (see Vol. 26, p.38) allowing the preparation of ^{2}H-L-glutamic acid, and ^{2}H-, ^{13}C- and ^{15}N-L-glutamic acids, on a gram scale from 2-oxoglutaric acid, includes several points of interest; e.g. the involvement of glutamate dehydrogenase with ^2H_2O as solvent, for C-3- and C-4-labelling, and exchange at C-4 by equilibration in 20% ^{2}HCl-^2H_2O.[289] A related approach to ^{13}C- and ^{15}N-L-alanine using alanine dehydrogenase, and to other ^{15}N-L-α-amino acids, includes full experimental detail.[290]

^{11}C-Labelled amino acids are accessible only through super-rapid methods of synthesis (and equipment ensuring the safety of operators), due to the short

half-life of the isotope, but this requirement has not only been met satisfactorily over recent years, but with sufficient leeway to permit purification to be included in the cycle. Thus, a 45-minute process (including HPLC purification) serves for the preparation of [β-^{11}C]-p-chloro-L-phenylalanine from 4-Cl-C_6H_4-$^{11}CH_2Br$ and the Li enolate of a chiral imidazolinone (see Scheme 5, Section 4.2) followed by hydrolysis.[291] The special reactivity of the L-tryptophan-derived bis(N-methoxycarbonyl)hexahydropyrrolo[2,3-*b*]indole (64, *cf.* Ref.137) allows rapid alkylation by $^{11}CH_3I$ *en route* to [α-$^{11}CH_3$]-L-tryptophan and its N-carboxylic anhydride.[292] The use of the Anatech RB-86 robotic synthesizer permits rapid synthesis of [1-^{11}C]-L-tyrosine from the analogous isocyanide[293] (see Vol.19, p.20) and of [CH_3-^{11}C]-L-methionine through robot-controlled methylation of homocysteine lactone.[294]

α-[^{14}C]Methyl-L-tryptophan has been prepared by methylation of the Li enolate of a Schiff base of an L-tryptophan, followed by enzymic resolution.[295] and by similar processing of the L-tryptophan-derived bis(N-methoxycarbonyl)-hexahydropyrrolo[2,3-*b*]indole (64).[296] The α-[^{3}H]methyl-analogue was also prepared in the latter study.

The simplest amino acid syntheses leading to labelled glycines, amination of [^{13}C]bromoacetic acid esters with $Boc_2{}^{15}N^-K^+$[297] and carboxylation of BocN-$MeCH_2SnBu_3$ with $^{14}CO_2$ after lithiation with MeLi,[298] are typical of numerous syntheses of labelled protein amino acids over the years, a further example being ^{15}N-[$^2H_3$]acetyl-L-aspartic acid as a standard for isotope dilution GC-MS analysis of N-acetyl-L-aspartic acid in urine.[299] The glycine isotopomers were used for spectroscopic assignments.[297]

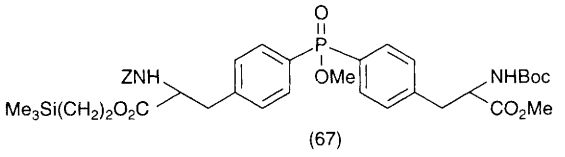
[^{18}F]-Labelled amino acids, e.g. β-[^{18}F]fluoro-alanine[300] provide useful substrates for *in vivo* drug delivery and similar diagnostic studies, a popular substrate being 6-[^{18}F]fluoro-L-DOPA, whose 3-O-methyl derivative has been prepared by fluorodestannylation of the corresponding stannylated DOPA.[301]

Saccharomyces cerevisiae mediates the synthesis of L-[^{35}S]cysteine and -methionine from $Na_2{}^{35}SO_4$.[302]

Aromatic iodination of tyrosine, by either the Chloramine-T/I_2 or analogous Iodogen methods, is a standard preparation of 2,5-di-iodotyrosine, and has been applied for [^{125}I]-labelling of α-methyl-L-tyrosine.[303]

4.16 Synthesis of β-Amino Acids and Higher Homologous Amino Acids – Extraordinary growth of interest in this topic is evident in the current literature. The driving force, apart from the usual mechanistic interest in novel bond-forming processes, must be the importance of the isolated examples of natural amino acids, amides and peptides within this category; perhaps also the intuitive expectation that many more physiologically-active natural β-amino acids are waiting to be discovered.

A major proportion of these studies now concerns stereoselective synthesis, and recent work with β-amino acids has been reviewed from this point of view.[304] Some general methods are extensions of those used for the stereoselective synthesis of α-amino acids, such as the C-5-aldolization[305] and C-5-alkylation[306] of six-membered chiral perhydropyrimidino-4-ones (Scheme 24) and alkylation at



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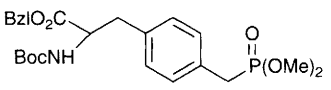

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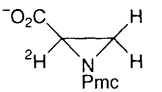

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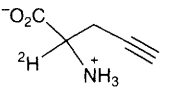

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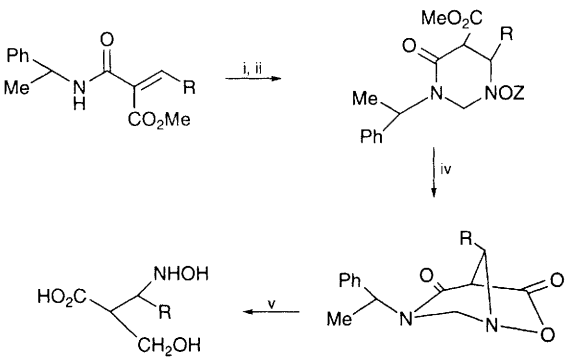
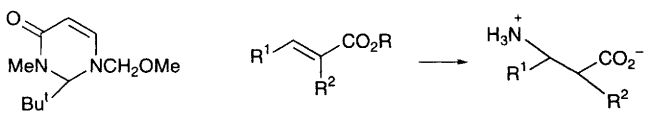


Reagents: i, NH_2OH, then ZCl/NaOH; ii, $(CH_2O)_n$, TsOH; iii, remove Z, then LiHDMS; iv, Amberlyst H-15; v, $LiAlH_4$, then H_3O^+

Scheme 24



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C-6 of unsaturated analogues (71),[307] addition of chiral imines [(S)-PhCHMeN=CHR to (E)- or (Z)-α-silyloxyketene acetals mediated by chiral boron reagents,[308] or $^{-}CH_2CO_2Me$ to (+)-(S)-p-tolylS(O)N=CHPh to give (R)-3-amino-3-phenylpropanoic acid,[309] addition of the highly syn-stereoselective nitrogen nucleophile (R)-PhCHMeNLiCH_2Ph to alkyl cinnamates (72 → 73)[310] and anti-addition to crotonates;[311] the reasons for high stereoselectivity in the latter approach have been discussed.[312] The adducts can be further alkylated with excellent stereoselectivity, and an example of this is included in the novel establishment of an asymmetric Michael addition of a homochiral magnesium amide (R)-PhCHMeN(MgBr)CH_2Ph.[313] A further example of a synthetic target that has been achieved through asymmetric Michael reactions is (2S,3R)-2-methyl-3-aminopentanoic acid [(R)-PhCHMeNLiCH_2Ph + t-butyl (E)-2-methyl-penten-2-oate].[314]

Amination of ethyl 2-methyl-4,4,4-trifluoroacetoacetate using benzylamine and appropriate further steps (including penicillin acylase resolution – the (R)-enantiomer is most readily hydrolysed) forms the basis of a synthesis of all four stereoisomers of α-methyl-β-trifluoromethyl-β-alanine.[315] The [1,3]-proton shift at the heart of this process can be biased by (-)-cinchonidine to give enantiomerically-enriched (R)-β-fluoroalkyl-β-amino acid derivatives (up to 36% e.e.).[316] A similar approach is seen in the addition of benzylamine to ethyl (R)-trans-4,5-O-isopropylidene-4,5-dihydroxy-2-pentenoate (Scheme 25),[317] and in the addition of phthalimide salts to imides of chiral imidazolidinones.[318] An interesting alkylation process $NO_2CH_2CH_2CO_2Bu^t$ → $NO_2CH[CH(OH)CH_2F]CH_2CO_2Bu^t$ uses 2-fluoroethanol/$COCl_2$.[317] α-(o-Hydroxyphenyl)-β-alanines are available through the addition of $(Me_3Si)_2N^-Li^+$ to coumarins.[319] Homochiral N-diphenylamino-3-amino-1,2-diols formed by aminolysis of epoxyalkanols can be converted into β-amino acids *via* allylamines.[320] Reductive dimethylamination of αβ-unsaturated acids has been described.[321] β-Amination of 3-hydroxycyclobutanecarboxylate esters through treatment with carbonyldi-imidazole and sodium azide involves an acylnitrene insertion step.[322]

Nucleophilic addition to imines ($PhCH=NSO_2R$ + $BrZnCH_2CO_2Bu^t$ → $H_2NCHPhCH_2CO_2H$)[323] and the related process with N-acyl-α-methoxyamines[324] illustrate one general approach to β-amino acid synthesis, while 1,2-cyanohydroxylation of alkenes by nitrile-imines [$EtO_2CC\equiv N^+N^-CH_2Ph$ → 3-carboxypyrazolines → $RCH(CH_2CN)NHCH_2Ph$][325] provides an alternative amination pathway. Hydrogenation of homochiral aziridine-2-carboxylates over 3 days gives β-amino acid esters.[326]

Further syntheses of N-benzoyl-(2R,3S)-3-phenylisoserine methyl ester, the derivatized side-chain moiety of taxol, have been described, one[327] employing conventional synthesis and resolution, while the other incorporates yeast-catalysed reduction to introduce a second chiral centre into (S)-phenylglycine-derived acyl cyanides $PhCH(NH_2)COCN$.[328] Diastereoselective reduction of N-protected β-amino-α-ketoacids has been achieved, by H_2/RuCl/(R)-BINAP for the preparation of L-isoserine,[329] and employing microbial reduction for the preparation of (2R,3S)-(-)-phenylisoserine.[330] Although oxazolones offer standard routes to α-amino acids, exploitation of their reactivity at C-2 in a β-amino acid synthesis has

also been realized (Scheme 26).[331] This amounts to one-carbon homologation of an aldehyde, also achieved using nitromethane; the ensuing conversion ($-CH_2NO_2 \rightarrow -CO_2H$) involves drastic conditions (12M HCl,100°,46 h) but is nevertheless appropriate for an erythro-phenylnorstatine synthesis.[332]

Examples of the extension of standard practice in the α-amino acid field are: alkylation of β-alanine carrying two chiral auxiliary groups, *viz.* N-(hydroxypinanylidene)-β-alanine (-)-menthyl ester;[333] hydrogenation (H_2/Pd) of 3-aryl-2-aminomethacrylic esters $BocN^iPrCH_2C(=CHAr)CO_2Me$ gives racemic β-amino acid esters.[334] An asymmetric Diels-Alder approach gives the fused-ring didemnin analogues (74).[335] Ireland enolate-Claisen rearrangement of β-alanine allyl esters, (E)- and (Z)-$RCH=CHCH_2O_2CCH_2CH_2NR^1R^2$, leads to α-alkyl-β-amino acids (75 and 76).[336] Alkylation α- to the carboxy group of a β-amino acid derivative through the aldol route allows versatile chain extension.[337]

Amidiniomycin (77) has been synthesized from norbornylene via meso cis-dicarbomethoxycyclopentane; the route depends on enzymic discrimination between enantiotopic ester groups for its success.[338] A synthesis of (2S,3R)-3-amino-2-hydroxyalkanoic acids by amination of (78) may require a broader study if, as claimed, it is to be accepted as a 'general' synthetic route.[339]

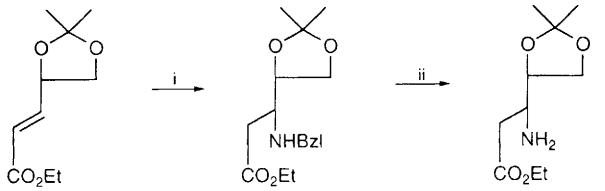
Syntheses starting with an α-amino acid include Wolff rearrangement of the diazomethylketone derived from an N-protected α-amino acid[340] followed by diazo-transfer and oxidation (dimethyl dioxirane) to give N-protected β-amino α-keto-esters without racemization. Homologation, through the Wolff procedure, of protected L-arginine gives dipeptides when irradiation is performed in the presence of an amino acid ester.[341] One-carbon homologation of α-amino acids, by their conversion into 2-(2-aminoalkyl)thiazoles followed by hydrolytic thiazole cleavage and further elaboration (*cf* Scheme 22, Ref. 226) has been demonstrated to give α-hydroxy-β-amino aldehydes and acids.[342]

Schmidt rearrangement of cis-1-carboxy-2-carbomethoxy-bicyclo[2.2.1]heptene gives the corresponding β-amino acid ester.[343]

Unprecedented syntheses of mechanistic interest have been described, by which unique β-amino acid targets have been attained (e.g. 79), by ring-contraction of tetrahydroisoquinoline alkaloids after lithiation,[344] and (80) from the 2-(β-naphthyl)oxazoline (81) by direct amination and alkylation followed by hydrolysis.[345]

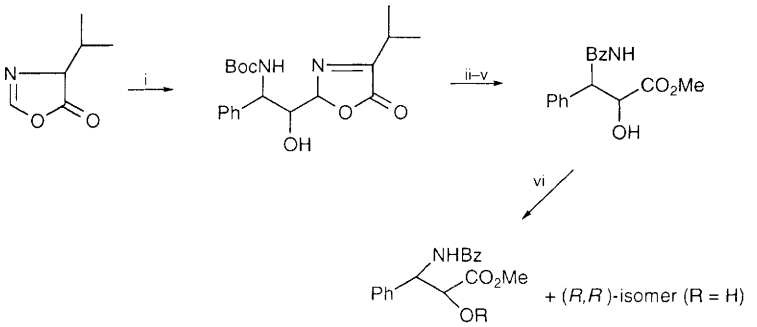
Ozonolysis of N-ethoxycarbonyl-2,3-dihydropyrroles in methanol gives the corresponding N-formyl-N-ethoxycarbonyl-β-amino acid methyl esters; the well-known oxidative ring-opening of 1,2,3,4-tetrahydropyridines to give 5-aminoalkanals is also explored further in this study.[346]

An extension of the amination approach leading to β-amino acids has been established. A tandem conjugate addition–hydroxylation protocol[347] using (S)-$PhCHMeNLiCH_2Ph$ and [(+)-camphorsulfonyl]oxaziridine leads to homochiral 3-amino-2-hydroxyalkanoic acids (82; R = Ph, *alias* allophenylnorstatine, a component of the HIV-protease inhibitor kynostatin);[348] and to (83; R = hexyl, *alias* microginin).[349] Both (2R,3R)- and (2S,3R)-diastereoisomers of the last-mentioned example were prepared, establishing the latter to be the absolute configuration of the natural ACE inhibitor. (3S,4S)-Statine and its isomers are



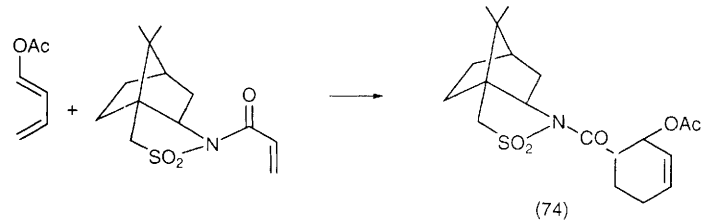
Reagents: i, $BzlNH_2$; ii, H_2, Pd/C, EtOH

Scheme 25



Reagents: i, Boc-phenylglycinal; ii, Et_3N; iii, 6M-HCl, 110 °C, 12 h;
iv. $SOCl_2$; v, BzCl; vi, *Pseudomonas fluorescens*, vinyl acetate

Scheme 26



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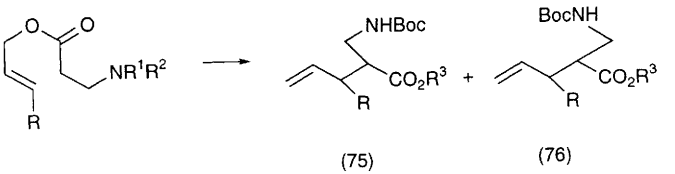

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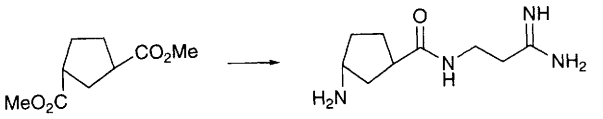

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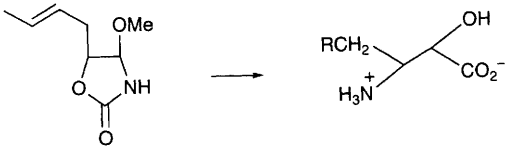

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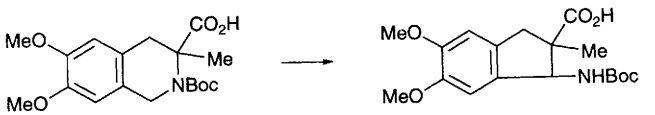

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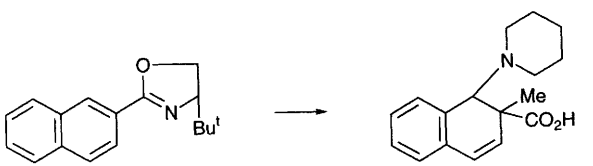

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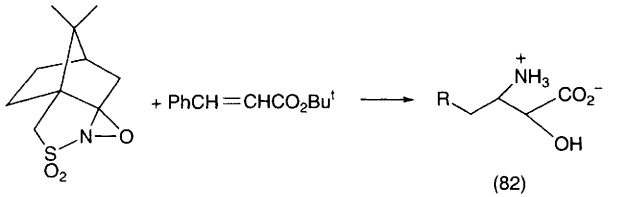
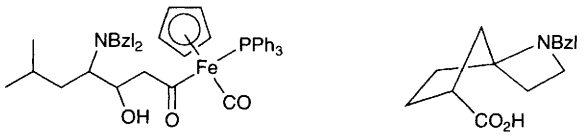
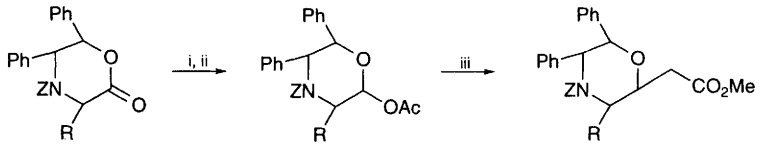






Reagents: i, DIBALH; ii, Ac_2O; iii, $CH_2=C(OMe)OTBDMS$, $ZnBr_2$

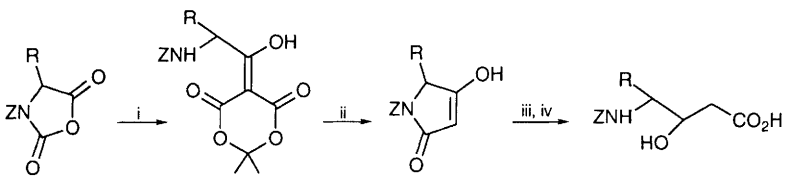
Scheme 27

easily prepared by aldol reactions of a protected L-leucinal, and a highly diastereoselective route has been established employing diethylaluminium enolates derived from $[\eta\text{-}C_5H_5]Fe(CO)(PPh_3)(COMe)$, to give the intermediate (84).[350] Simple alternative routes, addition of lithiated methoxyallene to an N-Boc-aminoalkanal followed by ozonolysis [$BocN(CH_2Ph)CH^iPrCHO \rightarrow BocN(CH_2Ph)CH^iPrCH(OH)C(OMe)=C=CH_2 \rightarrow$ (2S,3S)-norstatine],[351] amination of aldols [N-Boc-aminoalkanal/$PhCH_2CO_2H$ dianion] with $Ph_3P(O)N_3$ and ring-opening of the resulting diastereoisomeric 4,5-disubstituted oxazolidin-2-ones,[352] and azide ring-opening of the appropriate homochiral 2,3-epoxyalkanol, giving statine and its 3-epimer,[353] are typical of routes established over recent years.

A further statine synthesis involves the use of a homochiral oxazinone (Scheme 27) that is alkylated in an unusual way.[354] Similar alkylation of N-protected N-α-amino acid carboxylic anhydrides (NCAs) uses Meldrum's acid (Scheme 28); reduction of the resulting tetramic acids gives statine analogues.[355]

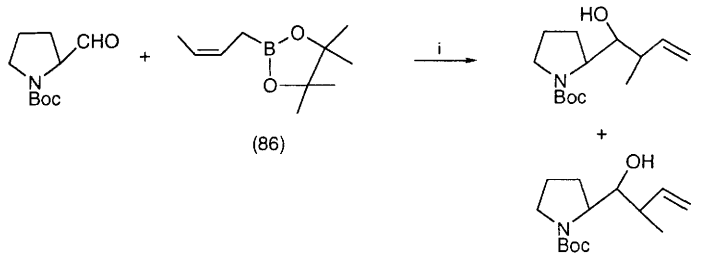
Synthesis of γ- and higher homologous amino acids is studied for much the same reasons that motivate efforts in the α- and β-amino acid area: the provision of authentic samples of biologically-important amino acids and their analogues, and also the growing interest in dipeptide and oligopeptide isosteres that δ-amino acids and higher homologues represent. 'Conformationally-constrained γ-aminobutyric acid' (GABA) is one way of describing the spirobicyclic condensation product (85) of 2-(N-benzylimino)cyclopentanecarboxylic acid with dibromoethane.[356] L-erythro-αβ-dihydroxyGABA and γ-erythronine have been prepared through oxidative degradation of 4-aminopent-1-ene-2,3-diols formed from penta-1,4-dien-3-ol by Sharpless epoxidation followed by amination.[357] Since dolaisoleucine t-butyl ester formed from the aldol adduct from 2-N-methyl-L-isoleucinal and t-butyl glyoxylate is identical with the natural γ-amino acid, the (3R,4S,5S)-stereochemistry can be assigned.[358] Dolaproine, a γ-amino acid from (-)-dolastatin 10, has been assigned the (2S,2'R,3'R)-stereochemistry through examination of the product from a corresponding route from the Boc-L-prolinal/(S)-$HOCPh_2CHPhO_2CEt$ aldol adduct, verified by X-ray crystal analysis.[359] An alternative route to natural dolaproine relies on preferential anti-addition of (Z)-crotylboron reagents (86) to homochiral N-Boc-aminoalkanals (Scheme 29).[360] A simplified route to E/Z-γ-amino acid esters $MeO_2CNHCHRCH=CHCO_2Et$, through a one-pot partial reduction (DIBALH) to the aldehyde and homologation with $(EtO)_2P(O)CHLiCO_2Et$, has been described.[361] Both enantiomers of 4-aminohex-5-enoic acid (vigabatrin) have been prepared in this way, starting with N-Z-L- or -D-methionine methyl ester and concluding with reduction of the double bond and introduction of the terminal alkene group through oxidative elimination of methanesulfinic acid.[362] Wittig reactions of $MeC(=PPh_3)CO_2Me$ (or the corresponding phosphonate) with α-Boc-alaninal gives a 2:1 anti/syn-mixture of 2-methyl-4-aminopentanoic acid derivatives after catalytic hydrogenation.[363]

A variety of routes exist, to lactams of various ring sizes, although their cleavage to give ω-amino acids can be problematical. A study of N-acylated lactams from this point of view has established the use of toluene-p-sulfonic acid



Reagents: i, Meldrum's acid, NEt_3; ii, Δ, AcOEt; iii, $NaBH_4$; iv, NaOH, aq. acetone

Scheme 28



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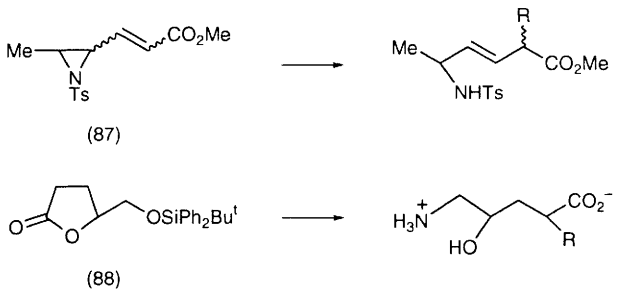
Reagents: i, THF, r.t.

Scheme 29



(87)

(88)

in methanol for the purpose.[364] Oxidation of N-Troc-piperidines with $RuCl_3$/$NaIO_4$ and hydrolysis under unspecified conditions gives 5-aminoalkanoic acids.[365] Pyrrolidin-2-one ring opening is the final stage in a synthesis of 4-amino-2,2-dimethylbutanoic acid.[366] Diastereoselective alkylation of δ-lactams carrying a chiral N-substituent has been established.[367]

A route to δ-amino acids has been established, exemplified by regioselective addition of alkylcopper reagents to each of the four stereoisomers of the N-toluene-p-sulfonylaziridine (87).[368] Analogues [(2R,4S)-5-amino-4-hydroxypentanoic acids] of a particular natural example of this family of amino acid have been synthesized from L-glutamic acid *via* the silylated α-hydroxymethyl-lactone (88).[369] α-N-Boc-Aminoaldehydes yield δ-amino γ-hydroxyacid derivatives through condensation with allylic bromides,[370] as do corresponding methyl ketones through reaction with α-bromoalkanoates.[371] Mitsunobu amination of an allylic alcohol with phthalimide is a step in a route to a δ-aminoalkenoic acid.[372]

4.17 Resolution of DL-Amino Acids – Active development of existing methodology, especially in topic areas under the heading of chromatographic resolution, would be an accurate description of current research. Analytical aspects (determination of enantiomer ratios by chromatographic and related means) are mostly covered in Section 7, and configurational assignments achieved through synthesis strategies are covered in earlier Sections.

Classical laboratory procedures for the resolution of amino acids are represented in diastereoisomeric salt formation with homochiral sulfonic acids.[373] The procedure is usefully complemented by salicylaldehyde-mediated racemization, illustrated by a preparation of D-p-hydroxyphenylglycine.[374] N-Salicylidene- and pyridoxylidene-DL-amino acids have been resolved analogously, through chromatography of derived diastereoisomeric copper chelates.[375] Marfey's reagent can be used both to generate diastereoisomeric derivatives and to assign absolute configuration to individual enantiomers, for example to micricystins.[376] Use has been made of the different rates of condensation of (+)-2-hydroxypinan-3-one with Schiff bases of DL-amino acids, to enrich samples with a particular enantiomer, to the extent of complete resolution in certain cases.[377] Examples of the resolution of higher homologous amino acids in this way are relatively rare, but vigabatrin enantiomers (see preceding Section, Ref.362) have been secured through acylation of 5-vinylpyrrolidin-2-one with (R)-$PhCHMeCO_2H$ and subsequent crystallization.[378]

Resolution of DL-amino acids through preferential crystallization of one enantiomer is underpinned by idiosyncratic physical solid state behaviour; thus, L-phenylalanine crystals added to a DL-glutamic acid sample favour the crystallization of the L-enantiomer, but all attempts failed to achieve the corresponding result using D-phenylalanine.[379] 4-Hydroxyproline assisted the resolution of DL-allothreonine in analogous fashion.[380] Spontaneous resolution under racemizing conditions in prebiotic times was probably not of major importance, either for the origin of enantiomeric imbalance or for the amplification of any microscopic imbalance.[381]

A widening range of both enzymes and non-protein DL-amino acids is being represented in resolution studies. The possibilities have been explored for the use of pronase with non-protein amino acid methyl esters,[382] *Aspergillus niger* lipase for kinetic resolution of pipecolic acid methyl ester,[383] *Candida cylindracea* lipase with aziridinecarboxylates,[384] lipases for α-vinylglycine after reduction,[385] thiol proteases with Z-amino acid methyl esters,[386] subtilisin Carlsberg,[51,112] an amino acid amidase from *Mycobacterium neoaurum* with α,α-disubstituted α-amino acid amides,[387] decanoyl-α-chymotrypsin with N-dodecanoylamino acid p-nitrophenyl esters[388] immobilized *Aspergillus oryzae* aminoacylase with N-acetyl-p-chlorophenylalanine[389] and for continuous column resolution of N-acetyl-DL-methionine,[390] and an aminoacylase from *Streptovercillium olivoreticuli* or penicillin acylase from *E.coli* for preparative-scale resolution of o- and p-fluorophenylglycines.[391] Novel procedures have been studied; one featuring a D-amino acid oxidase/aminotransferase/L-glutamic acid system that converts racemic mixtures of common and non-protein amino acids into the L-enantiomers;[392] another using immobilized enzymes in a tea-bag method, with N-acetylamino acid methyl esters in reverse micellar media;[393] and another establishing the resolution of N-acylamino acids using alcalase in supercritical CO_2.[394] Aldolase from *Streptomyces amakusaensis* catalyses the reverse aldol reaction with (2S,3R)-β-hydroxy-α-amino acids, and therefore provides enantiomers when applied to the racemates.[395]

Most of the current research studies of resolution are based on physical principles, particularly involving chromatographic separation over chiral stationary phases (CSP's). The technique continues to develop rapidly, and reviews have appeared of Pirkle CSP's[396] and preparative-scale resolution by this approach.[397] Long-established examples of CSP'S are represented in recent papers, including cellulose thin-layer chromatography with a cyclodextrin-containing mobile phase, showing additive contributions to discrimination leading to large separation factors for tryptophans.[398] Bovine serum albumin (BSA) achieves the resolution of N-alkanoyl DL-[^{3}H]leucines (the D-enantiomer is more strongly retained and separation factors are strongly dependent upon the solutes in the stationary phase.[399] For the free amino acids in solutions at pH 7.0, the L-enantiomer is more strongly bound to BSA when it is immobilized in the form of a membrane.[400] Cyclodextrins can accomplish the resolution of DL-alanine β-naphthylamide.[401] New examples include β-cyclodextrins to which D- or L-phenylalanine cyanomethyl esters are linked,[402] 6'-(3-aminopropylamino)-6'-deoxycyclomaltaheptaose (which binds L-tryptophan more strongly than β-cyclodextrin),[403] or chiral alcohols immobilized within a poly(ethylene) film (enantioselective transport of amino acids)[404] and 4-vinylpyridine–1-vinylimidazole copolymers imprinted with N-Z-L-aspartic acid (see Vol.26, p.49).[405] Crystals of imprinted D-phenylglycyl-D-phenylglycine formed from solutions containing N-acetyl-L- or D-leucine ethyl ester are capable of enantioselective binding of these solutes.[406] Capillary GLC of N-trifluoroacetyl-DL-amino acid n-butyl esters over L-Phe-tetra-amide CSPs has proved effective in enantiomer ratio determinations.[407] Chromatographic resolution on the ligand-exchange principle is represented in the use of copper(II)-6-deoxy-6-(N-histamino)-β-cyclodextrin

(binding of D-amino acids is favoured),[408] the use of copper(II)- or nickel(II)-N-substituted-L-proline-modified silica gel,[409] and a similar use of (R)-2-amino-alkanol for chiral modification of stationary phases.[410] Results obtained in ligand-exchange resolutions using a range of metal salts have been compared,[411] and the routine method employing a chiral mobile phase additive has been studied for the resolution of fluorine-substituted phenylalanines and phenylglycines.[412]

Permeable membranes have been mentioned in the preceding paragraph, in their role as enantioselective barriers that can form the basis of preparative resolution technology. Membranes to which L-phenylglycine is bonded are more permeable to the D-enantiomer of this amino acid,[413] and hollow-fibre membranes carrying N-(1-naphthyl)-L-leucine have shown promising enantioselectivity.[414] Liquid membranes are particularly promising in this respect, 5-cholesteryl-L-glutamate forming the basis of mixed micelles that preferentially bind the D-enantiomer from solutions of DL-phenylalanine in the presence of copper(II) ions.[415] 1,2,4-Triazole-containing cholesteryl esters offering preferential transport to D-phenylalanine primary alkylammonium salts.[416] Chiral discrimination is also revealed for Langmuir-Blodgett monolayers containing N-palmitoyl-DL-valine and DL-alanine and N-stearoyl-DL-valine, compared with L-analogues,[417] by (cholesteryloxycarbonyl)benzo-18-crown-6 monolayers,[418] and by a variety of emulsion liquid membranes;[419] and several other papers in this Symposium Volume, Ref.419). A promising development is the demonstration of enantiomeric enrichment of derivatized and free amino acids by foam-forming 'chiral collectors'.[420]

A 44-mer RNA that binds L-citrulline and D- or L-arginine has been reported.[421]

Speculation surrounding the methods by which DL-amino acid mixtures, generated in prebiotic times, were supplanted by L-enantiomers has shifted towards the consequences of parity-violating phase transition phenomena (Bose-Einstein condensation activation),[422] a theory advanced by Salam (see Vol. 24, p.40) that he has recently reviewed.[423] Many of the main protagonists in this field have presented their ideas in this publication; favouring either parity-violating energy differences between L- and D-enantiomers of an amino acid,[424,425] through chiral interactions at the ocean-air interface (see Vol.25, p.55),[426] or through spontaneous amplification.[427,428] The emergence of L-amino acids, as a consequence of parity-violating energy differences leading to electroweak neutral currents, has been reviewed more recently[429] by an advocate of an alternative theory (see Vol.26, p.51).

The origin of chirality in amino acids and carbohydrates is suggested to lie in sonically-induced phase transitions; a D- or L-amino acid will eventually accumulate through sonication of a racemic amino acid.[430] A much earlier idea, encapsulated in the Vester-Ulbricht theory, asserts that enantioselective destruction of the D-amino acids occurs more rapidly, relative to their L-enantiomers, under the influence of inherently asymmetric radiation. This has been re-investigated to show that DL-leucine bathed in radiation from a ^{22}Na weak positron source suffers more rapid destruction of its D-enantiomer.[431,432] ESR

study of D- and L-alanine[433] and of D- and L-leucine[434] degraded with ^{90}Sr-^{90}Y β-radiation shows that irradiation generates more radicals in the D-enantiomer, and the Vester-Ulbricht theory is therefore claimed to be given further support. Reviews of origins of chirality and life, giving explanations that make lesser demands on the reader, have appeared.[435,436]

5 Physico-Chemical Studies of Amino Acids

5.1 X-Ray Crystal Structure Analysis of Amino Acids and Their Derivatives – A pattern that has emerged in recent years, the revision of earlier data and determination of structures of new compounds, continues to be represented in the current literature. The fact that X-ray crystallographic instrumentation has become more sophisticated, so that results are more reliable, but also less tedious to obtain, is mainly responsible for the increased activity in this area. Crystal structures for free amino acids have been reported for DL-alanine,[437] DL-arginine (as its dihydrate, formate, and formate dihydrate),[438] L-arginine fluoroborate,[439] L-arginine maleate dihydrate,[440] L-histidine monoacetate,[441] L-histidinium phosphite and a re-investigation of monoclinic L-histidine,[442] and N-methylglycine monohydrogen phosphite.[443]

Crystal structures of amino acids have been surveyed with particular reference to their propensity towards polymorphism.[444]

Derivatives that have been subjected to study are benzyl 2(S)-Boc-amino-4-oxo-6-phenyl-5(E)-hexenoate,[445] DL-valine N-carboxyanhydride,[446] N-monochloracetyl-D-α-methyl-leucine,[447] N-acetyl-L-proline methyl ester, -(4S)-hydroxy-L-proline methyl ester, and -(4S)-fluoro-L-proline methyl ester,[448] N-chlorosulfonyl-L-proline benzyl ester,[449] Z-[(E)-5-(p-nitrobenzyloxycarbonyl-methinyl)]-L-proline t-butyl ester,[450] N-[N-benzyloxycarbonyl-L-1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl]-L-phenylalanine methyl ester,[451] and Boc-L-tryptophan (2-thymin-1-yl)ethyl ester.[452] While crystalline N-acetyl L-proline methyl ester is characterized by a cis-peptide bond, the ring-substituted analogues adopt the trans-configuration.[448]

5.2 Nuclear Magnetic Resonance Spectrometry – An NMR study qualifies for inclusion in this section only if the object of the study involves more than routine support of synthetic studies. Conformational studies are included within this policy, and a familiar example, interpretation of ^{1}H-NMR (as well as IR data) of C^2HCl_3 solutions of N-acetyl-L-proline N-methylamide, provides more reliable conformer ratios based on improved understanding of spectral parameters.[453] Related studies involving chloro-substituted tryptophans[454] and bacoflen analogues [3-(thien-2-yl)- and 3-(furan-2-yl)-γ-aminobutyric acids][455] adopt the common approach of calling for data from both ^{1}H- and ^{13}C-NMR measurements.

Establishment of absolute configuration of α-amino acid enantiomers, and of other α-chiral amines, through interpretation of ^{1}H-NMR data of amides formed with (S)-O-methylmandelic acid,[456] and enantiomeric purity determination of

deuteriated esters of amino acids through ^{2}H-NMR measurements using poly(γ-benzyl-L-glutamate) in CH_2Cl_2 as a chiral lyotropic liquid crystal solvent,[457] are studies that illustrate familiar stereochemical applications of ^{1}H- and ^{2}H-NMR Another analytical application is represented in the estimation of carbamate formation in aqueous solutions of amino acids,[458] while the extraordinary sensitivity of current NMR instrumentation is further illustrated (see Vol.23, p.46) in the detection of glutamic acid, glutamine, and N-acetylaspartic acid in brain tissue.[459] NMR parameters for glycine in frozen aqueous solutions have been collected;[460] values of ^{1}H-NMR spin-lattice and spin-spin relaxation times increase for aqueous solutions of glycine and proline with increases in temperature and concentration.[461] A 'magic angle spinning' study by ^{1}H-NMR of L-alanine has been directed at the assessment of molecular dynamics in the solid state.[462]

^{13}C-NMR studies with similar objectives have been reported; one broad study relates chemical shifts for each carbon atom to torsion angles for N-formyl-L-alanine- and -valine-amides[463] and L-threonine and L-tyrosine,[464] while another study illustrates the usefulness of ^{13}C-NMR measurements for assessing protonation equilibria for ornithine, lysine, and hydroxylysine in aqueous dimethyl sulfoxide.[465] Spectra of N′-alkyl- or aryl-N-carbamyl and their N-nitroso derivatives, have been correlated with structure.[466]

For ^{17}O-NMR, the frontiers continue to be pushed back but gaining results with little general applicability to revealing subtle details of amino acid structures in solutions; for example, further cross-polarized dynamic angle spinning data on ^{17}O-labelled amino acids have been collected.[467] Specialized applications continue, however, for ^{31}P-NMR, with accurate enantiomeric analysis using amides formed from amino acids and the chiral phosphorinane HP(O)(OCHMeCH$_2$NEt$_2$)$_2$,[468] ^{77}Se-NMR data can be used for absolute configurational assignments to amino acids converted into imidazol-2-selenones.[469]

5.3 Optical Rotatory Dispersion and Circular Dichroism – Reports over the years have described the use of these techniques to determine subtle structural details for amino acids, though empirical rules sometimes fail. Thus, the CD spectrum of N$^{\alpha}$-acetyl-L-ornithine and homologues is found to be what the simple rules predict for the D-configuration,[470] and anomalous optical rotation data have been found for N$^{\varepsilon}$-acetyl-L-lysine and N$^{\alpha}$-acetyl-L-lysine.[471] and N$^{\alpha}$-acetyl-L-arginine.[472] Reliable correlation, of CD with absolute configuration, has been established (L-derivatives show positive CD near 310 nm and negative CD at 280–290 nm) for Eu(fod)$_3$ complexes of amino acids[473] and of amino acid esters.[474] The CD features of trinuclear complexes between amino acids and $[M_3O(O_2CCH_3)_6L_3]^{n+}$ (L = water or pyridine, n = 0 or 1) are suitable for the assignment of absolute configuration through the application of a semi-empirical helicity rule.[475]

CD in the Soret wavelength region for solutions of homochiral amino acid derivatives and achiral porphyrins has been ascribed to hydrogen bonding association.[476]

Raman optical activity of amino acids (usually measured as CD) has been

reviewed.[477] This is a topic area that has developed slowly, and its fundamental basis is still being worked out, assisted by studies such as comparisons of measured and calculated Raman CD for L-alanine and its isotopomers.[478]

5.4 Mass Spectrometry – Increased activity associated with the newer instrumental techniques would be an appropriate inference based on the current literature covering mass spectrometric studies of amino acids and derivatives. There is also an awareness that some long-known variants of MS techniques have been under-used, such as negative ion measurement, which gives 'cleaner' spectra for N-(2,4-dinitrophenyl)amino acids,[479] intense $[M-1]^-$ peaks for N-phospho-amino acids,[480] and can allow discrimination between the four γ-hydroxyornithine diastereoisomers after bis(N-benzyloxycarbonylation).[481] Both positive- and negative-ion modes have been applied to generate spectra from free amino acids (glycine, methionine, histidine, and cysteine), the spectra showing prominent $[M-1]^-$ and $[M_2-1]^-$ peaks.[482]

New techniques providing spectra of amino acids themselves include time-of-flight MS of phenylalanine bombarded with 2.5 MeV carbon ions,[483] and pulsed laser-initiated ionization–desorption of tryptophan embedded in rhodamine B and glycerol[484] and of crosslinking amino acids pyridinoline and its deoxy- and glucosylgalactosyl-derivatives.[485] Cluster ion formation from a mixture of two different amino acids in a Na^+-containing matrix has been studied, leading to an Na^+ ion affinity scale for amino acids (a Li^+ affinity scale was constructed similarly).[486] ^1H-^2H-Exchange involving amino acids and CH_3O^2H,[487] and gas-phase proton affinity studies for amino acids, have been the subject of study over several years, applied to glycine and its isotopomers.[488] Corresponding FT-ion cyclotron resonance studies of phenylalanine and its N-methyl- and NN-dimethyl-analogues have been described.[489] Theoretical aspects have been presented, of kinetics of protonation leading to cluster ions $[(\text{amino acid})_2\text{–H}]^+$ in the gas phase.[490] Gas-phase basicities, a subtly-different parameter, have been determined for amino acids[491] with particular attention to lysine and histidine, by the kinetic method.

5.5 Other Spectroscopic Studies of Amino Acids – Several projects cited in preceding sections have relied on more than one spectroscopic technique, commonly including IR and other vibrational spectroscopic methods. A remarkably simple positive answer to the question: do diastereoisomeric interactions exist between enantiomers in the solid state? has emerged from IR spectra of L-proline, DL-proline, and of an equimolar mixture of the two, which is not simply the weighted average of the preceding two spectra.[492] The result does not, of course, clarify the nature of these interactions, but much more detail is available through IR studies of glycine in neon, argon, and krypton matrices (three different conformers are established for the first time),[493] and a similar result for proline and ^2H-labelled proline.[494] IR-Raman spectroscopy of solid L-aspartic acid and $^2H_4$- and ^{15}N-isotopomers[495] and of solid L-glutamic acid and $^2H_4$- and ^{15}N-isotopomers[496] yield fundamental vibration modes for these amino acids.

Another familiar interest is revealed in the establishment of intramolecular hydrogen-bonding patterns for derivatives of β- and γ-amino acids through IR study of CH_2Cl_2 solutions.[497]

The rotational spectrum of β-alanine determined in a free-expansion jet spectrometer provides evidence for the existence of the same types of intramolecular interactions within two conformers, as already found in gaseous glycine and alanine.[498]

Photoelectron spectra have been determined for phenylalanine and its N-methyl- and NN-dimethyl-analogues.[489]

5.6 Physico-Chemical Studies of Amino Acids – This section covers useful interpretations, in terms of the behaviour of amino acids, of some simple laboratory measurements. Thus, the solubility behaviour of fourteen amino acids in water as a function of pH and temperature has been considered on the basis of fundamental structural and thermodynamic parameters;[499] solubilities of L-isoleucine, L-leucine, and L-valine in aqueous NaOH increase as the NaOH concentration is increased, then decrease sharply after the 1:1-ratio has been passed.[500] The solubility of the dipeptide derivative Z-L-Asp-L-Phe-OMe (i.e., Z-aspartame) in water containing L-phenylalanine methyl ester shows complex dependence upon concentration, pH and on other parameters, showing that the solutes interact in more ways than simply through ionic attractions and repulsions.[501] Concentrated proline solutions show non-ideal behaviour (freezing point depression and isopiestic data), and this explains the protective effect of proline on enzyme activity (due to the fact that it exerts a role as inert space-filling solute to help maintain a native polypeptide conformation).[502]

The various lipophilicity scales for amino acids have been reviewed,[503] and a new hydrophilicity scale has been proposed based on calculations of solvation parameters.[504] A multi-channel sensor system has been trained to correlate the 'taste' characteristics of amino acids.[505]

Guest–host studies continue (see also Section 4.17), with water-soluble calix-[n]arenes (89; n = 4, 6, 8) that strongly bind amino acid methyl esters into their cavity.[506] The related cyclic tetramer (90),[507] forms 1:1-complexes with aromatic amino acids, and the chiral porphyrin (91) shows enantiodiscrimination towards amino acid esters.[508] The C_2-symmetric chiral porphyrin analogue [92; R = (R)-$CH_2CHMeOH$] is an effective transporter of lithium salts of amino acids through CH_2Cl_2 membranes,[509] and a phenanthroline–copper(I) template supports a bis(2-aminoacylpyridine) receptor that binds Z-L-glutamic acid and other dicarboxylic acids.[510] A similar mechanism accounts for the binding of Z-aspartic acid to an 2-acylaminopyridine-substituted heterocyclic template, to which a broader range of Z-amino acids shows modest binding.[511] Cyclo-oligomers of cylindrical shapes have been synthesized that present amide groups to guest molecules, and show high selectivity towards N-acetylamino acid N′-methylamides.[512] The crown ether (93) has been shown to use its carboxy-group as well as the macrocycle atoms to complex with amino acids.[513]

The enantiomeric discrimination factors that are sought in such studies are being put on a firmer numerical basis, as illustrated for standard molar enthalpies

of binding by cyclodextrins of L- or D-phenylalanine and L-phenylalaninamide. Values have been determined by microcalorimetry, and are independent of configuration.[514] Microcalorimetric data also show that the chiral discrimination of L-ascorbic acid–Fe^{3+} towards enantiomeric α-helical peptides is not exerted towards cysteine enantiomers.[515]

Heterogeneous liquid systems are of growing interest, from the point of view of amino acid transport; systems studied recently (see also Refs.413-419) are basic amino acids/water/$CHCl_3$ + sodium di(2-ethylhexyl)sulfosuccinate[516] organic solvent/water/arylboronic acids + crown ethers,[517] and organic solvent/water/18-crown-6 + picric acid.[518] Reverse micellar extraction of amino acids from aqueous media by di-octyldimethylammonium chloride is sensitive to co-solutes and physical parameters.[519] In the glycine or L-lysine/octyl β-D-glucoside/water systems, from 3 to 7 amino acid molecules can be bound by each molecule of the glucose derivative, resulting in a lowering of its critical micellar concentration.[520]

Equilibria involving transfer of arginine, from solutions containing HCl and NaCl to a cation exchange membrane, have been evaluated.[521] Sorption of amino acids on to ion exchange membranes has been studied.[522]

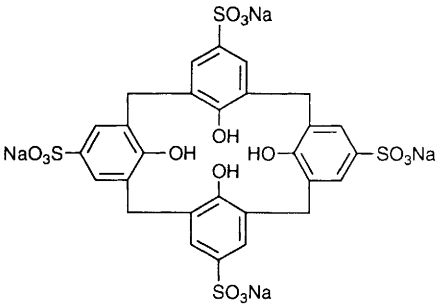
Dipole moment data have been collected for L-cysteine and L-cystine.[523]

A review has appeared covering solute–solute and solute–solvent interactions that occur in solutions of amino acids.[524] The viscosity of a solution of an amino acid has been related to the effects of the solute on water structure,[525] and data have been collected for viscosities of aliphatic α-amino acids in 0.5 and 2M urea.[526] Apparent molar volumes of aliphatic α-amino acids in 0.5 and 2M urea,[527] and of aqueous L-valine, L-isoleucine, and L-leucine[528] have been calculated from densities and volumetric heat capacity data.

Thermodynamic parameters, enthalpies of dilution of L-threonine and L-asparagine,[529] enthalpies of interaction of amino acids and peptides with crown ethers in water,[530] apparent molal heat capacities and volumes of aliphatic α-amino acids at 288–328K,[531] and similar thermal properties of aminopolycarboxylic acid solutions[532] have been collected. Microcalorimetric studies provide enthalpy of dilution data for ternary aqueous solutions that contain glycine, an alkanol, and another α-amino acid.[533]

Electrical measurements for the effects of weak static and alternating low-frequency magnetic fields on current flow through aqueous amino acids[534] and potentiometric titrations leading to protonation constants for glycine in aqueous NaCl[535] and the proton-binding isotherm for glycine[536] have been presented, as have corresponding dissociation constants for L-proline, L-histidine and L-tryptophan.[537] The protonation rates for L-tryptophan in acidic media decrease with increasing pH.[538]

5.7 Molecular Orbital Calculations for Amino Acids – Development of familiar themes under this heading is continuing with calculations of solvation energies of zwitterionic forms of glycine, alanine and serine in different conformations in water,[539] hydration parameters and conformations of N-acetylamino acid methyl esters,[540] and 2-(N-acetylamino)isobutyric acid N-methylamide[541] and of twenty common amino acids substituted in the same way.[542]



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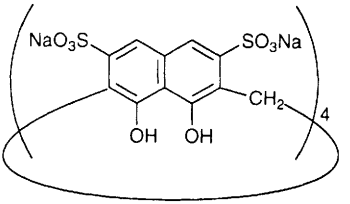

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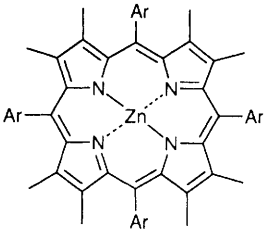

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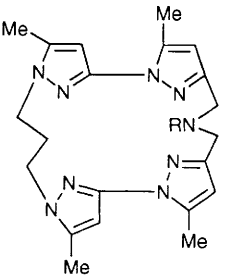

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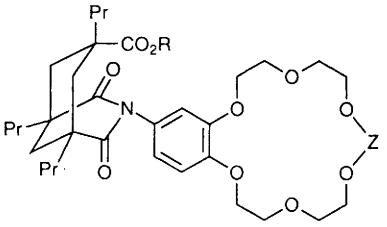

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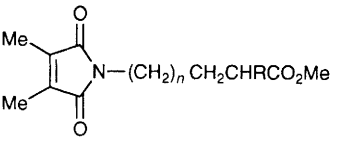

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Quantum mechanical force fields generated by [glycine.nH_2O] supermolecules in basic glycine solutions,[543] electrostatic properties of amino acids modelled using atomic multiple moments,[544] and molecular connectivity models leading to structure–property relationships for amino acids,[545] illustrate another area of computational interest (see also Ref.546).

Spectroscopic data generated through molecular orbital calculations concern vibrational frequencies of three non-ionized conformations of cysteine and serine,[547] chemical shift changes related to dihedral angles for glycine and glycinamide,[548] and gas-phase proton transfer energy values for eight of the protein amino acids.[549] An erratum has been published[550] concerning Ref.461 in Chapter 1 of Vol.26 (p.55).

6 Chemical Studies of Amino Acids

6.1 Racemization – Preparative applications of racemization are covered elsewhere in this Chapter (Section 4; e.g., Ref.167), and the content of papers eligible for discussion in this section is usually limited to a narrow topic, e.g. that the rate of racemization of L-aspartic acid in water at 100° is increased when dimethyl sulfoxide is added.[551]

It has become clear that the dating of fossils based on the presumed constancy of racemization rates of their indigenous amino acids is liable to considerable error because of unspecifiable catalysis, though the basis of a claim, that the kinetics of amino acid racemization are non-linear, is obscure.[552] Application of the method to amber-entombed insects using samples ranging in age from 100 y to 130 × 10^6 y can only provide results matching those of other dating methods if it is assumed that the amber environment retards racemization rates by a factor of greater than 10^4.[553] This, indeed, represents slow racemization and is about the same rate as DNA degradation by de-purination.[554] The dating method applied to *Homo tirolensis* (i.e. the male corpse found in 1991 at a high altitude in the Austrian Tyrol) and also to a specimen of ginger from Egypt, both of the same age (5200 y), in fact gave considerably different age values, and not only that, but the racemization rate in the colder specimen was faster![555] Since o- and di-tyrosine were detected in *Homo tirolensis*, and these are markers for free radical attack on proteins, the authors suggest that the hydroxyl radical formed by sunlight at high altitudes may accelerate amino acid racemization.

6.2 General Reactions of Amino Acids – This Section covers reactions at the amino and carboxy groups (and reactions at both) as well as reactions at the α-carbon atom of α-amino acids $^+H_3NCHRCO_2^-$; the following Section covers reactions of amino acid side-chains R.

Thermolysis of butyrine, 3-amino- and 4-aminobutanoic acids gives many reaction products,[556] while decarboxylation of L-threonine and L-hydroxyproline occurs at 170° in cyclohex-2-enone, giving optically-active β-amino-alkanols.[557] Irradiation of DL-lysine with soft X-rays causes the change of zwitterion to free

base, and decarboxylation leading to 1,5-diaminopentane.[558] Radicals formed by γ-irradiation of DL-threonine[559] and by pyrolysis of DL-serine, DL-threonine and DL-tyrosine at 200–600° for 2-180 min[560] have been studied by ESR. γ-Radiolysis of aqueous phenylalanine leads to tyrosine.[561]

Studies of these types, that often provide essential warnings of sample breakdown to those preparing samples of amino acids for analysis, are few and far between. However, in-depth study of the N-halogenation of amino acids and decomposition of the reaction products, continues to expand (see Vol.26, p.56), with decomposition kinetics being determined for N-chloro-valine,[562] and compared with data for N-chloro-sarcosine, -N-methylalanine, -N-methylvaline, and -proline.[563] N-Bromo-amino acids have been studied.[564] The Grob fragmentation pathway that is followed by these derivatives in aqueous solutions[565] can be promoted by metal alkoxides.[566] N-Nitrosation (N_2O_4/CH_2Cl_2) of α-(acetylamino)acids gives more stable products than hitherto believed, but they fragment in alkaline media to give α-hydroxyacids.[567] Reaction within a Co(III) complex [formed with $K_3\{Co(CO_3)_3\}$] at a pyridoxylidene-amino acid ligand generates an α-hydroxy-α-amino acid.[568] A kinetic study of the nitrosation of imino acids has revealed intramolecular migration of the nitroso group from an intermediate nitrosylcarboxylate formed at high pH.[569]

Conversion of α-amino acids into α-nitro acids employing the powerful oxygen transfer agent HOF.MeCN (formed in aqueous MeCN with F_2) involves racemization.[570]

N-Acylation reactions include formylation of amino acid esters with tri-ethyl orthoformate[571] and conversion of N-formyl-α-trifluoromethyl-α-amino acids into isocyanides.[572] The analogous isocyanates $OCNCR(CF_3)CO_2Me$ and hydrazides are starting materials for the synthesis of azapeptides,[573] and N-acryloyl-L-prolinamides have been prepared for the first time, for use in copolymer preparations.[574] N-Acylation of amino acids using vinyl esters has been advocated[575] (the method is well-known in the literature). N-(L-Maleyl)ation of amino acids (with glycine and proline as exceptions) can be accomplished with the aid of aminopeptidase A.[576] Solid-state N-phthaloylation of amino acids[577] and 3-carboxybenzoylation of DL-alanine using isophthalic acid[578] has been assessed using differential scanning calorimetry. An analogous product (94), previously undetected, emerges from Maillard reactions involving γ-aminobutyric acid, 6-aminocaproic acid, N^{α}-acetyl-L-lysine, and pentoses.[579] Amadori compounds formed at an early stage of the Maillard process, have been generated from D-glucose and α-amino acids, and subjected to FAB-MS and NMR study.[580]

N-[2-(4-Nitrophenyl)sulfonylethoxy)carbonyl]ation of amino acids gives N-protection that can be reversed by bases in aprotic solvents.[581]

Novel N-alkylation of amino acid esters by tricarbonyl(cyclohexadienyl)iron cations,[582] and through high-pressure reaction with oxiranes,[583] together with more traditional reductive alkylation methods using aldehydes (preparation of N-allyl and -propargyl- derivatives,[584] use of PhCHO/NaTeH for preparation of N-benzylamino acids[585]) have been described. The preparation of pure N-methylamino acids by conversion of Z-amino acids into oxazolidinones using

formaldehyde followed by Et_3SiH/TFA reduction ($NaBH_4$ is somewhat less effective)[586] or by the corresponding reaction of N-benzylamino acids with the reduction step accomplished by hydrogenation),[587] follows established methodology. Direct methylation of N-Boc-O-TBDMS-D-tyrosine with MeI/BuLi/-78° seems, however, to proceed uneventfully.[588] Coupling (R)- or (S)-homophenylalanine ethyl ester with lactates gives (R,S)- and (S,R)-N-[(1-ethoxycarbonyl-3-phenyl)propyl]alanine.[589] Procedures have been described for the preparation of N-(9-phenylfluoren-9-yl)-L-alanine and -L-aspartic acid dimethyl ester.[590] Bis-N-alkylation through reductive aminocyclization of L-valine methyl ester with keto-aldehydes is accomplished with high diastereoselectivity (Scheme 30), but with little stereochemical bias for simpler ketones.[591] N-Alkylation of sodium salts of secondary amino acids uses 4-chloro-N-benzylpyridin-2(1H)-one (DMSO, 160–180°).[592]

Following recent results (see Vol.26, p.62) that have established the condensation of amino acids to form peptides in aqueous NaCl by copper salts,[593] another non-enzymic reaction with the same outcome under putative prebiotic conditions has been established. This is based on cyanamide driving the reaction: FeS + $H_2S \rightarrow FeS_2$ (Pyrite) which then brings about the condensation of thioglycollic acid $HSCH_2CO_2H$ so as to activate the amino acid carboxy group for peptide bond formation.[594] A quite different discovery, but connected in its prebiotic relevance, concerns the finding that mixtures of amino acids can exert the catalytic activities shown by β-galactosidase, carbonic anhydrase, and catalase.[595]

Carbamylation of L-aspartic acid[596] and N-(9-acridinylthiocarbamoyl)ation of amino acids[597] have been described, the first of these studies being aimed at establishing the finer details of the biogenesis of dihydro-orotic acid, and the second providing a derivatization protocol that is some 6–22 times faster than phenylthiocarbamoylation, and giving a fluorescent product.

γ-Irradiation of amino acid solutions in the presence of the spin-trap 2-methyl-2-nitrosopropane, gives isolatable t-butylaminoxyl acids $Bu^tN(O\cdot)CHRCO_2H$.[598] The solid-state reaction of p-benzoquinone with amino acids that is accomplished by grinding the mixture, gives a purple solid (λ_{max} 562 nm) that contains free radicals different from those generated when the reactants meet in aqueous solution.[599]

Selective removal of the t-butoxycarbonyl group from N-Boc-amino acid t-butyl esters occurs on treatment with dry HCl in EtOAc; t-butyl ethers also survive the process.[600]

Oxidation of amino acids by peroxomonosulfate in aqueous alkali starts with electrophilic attack at nitrogen to give an imino acid through involvement of the α-CH proton.[601] There are, as usual, numerous papers covering routine oxidation studies of amino acids in the current literature, representative examples dealing with kinetics of chromium(VI)/$HClO_4$ oxidation of alanine, valine, and phenylalanine,[602] and electrolytic oxidation of methionine to its sulfoxide[603] (this study employs carbon, platinum or gold electrodes modified with Langmuir-Blodgett films of stearic acid or N-stearoyl-L-valine, and in the latter case, faster oxidation of the D-enantiomer was observed).

Enhanced colour for the ninhydrin reaction has been reported for 5-arylninhy-

drins.[604] That the enolate ion of Ruhemann's Purple within two five-membered rings of partial anti-aromatic character (as seen in the cyclopentadienyl anion) is the chromophore responsible for the long-wavelength absorption feature is backed up by molecular orbital calculations.[605]

Esterification studies that carry special interest include benzyl ester formation accompanying N-benzyloxycarbonylation, resulting from reaction of excess Z-Cl with α-isopropyl- and α-vinyl-α-amino acids.[606] Also, the formation of aryl esters from N-phenylacetylglycine in the standard fashion (a phenol + dicyclohexylcarbodi-imide + py/TsOH) involves low yields,[607] which can be overcome through an indirect route *via* N-Boc-N-phenylacetylglycine, through esterification followed by Boc removal. N-Boc-Amino acid chloromethyl esters have been prepared using chlorosulfonylmethyl chloride $ClSO_2OCH_2Cl$.[608] The BOP reagent, although little used now in peptide synthesis after its replacement with safer alternatives, is advocated for mild esterification of N- and side-chain protected amino acids.[609] Dicyclohexylcarbodi-imide esterification (catalysed by DMAP) to couple syn-phenylisoserine to baccatin III to form taxol can be effected starting with the derivatized anti-compound.[610] Lipase-catalysed regiospecific esterification of the primary hydroxy group of butyl α-D-glucopyranoside to 2,2,2-trichloroethyl N-Boc-4-aminobutyrate has been reported;[611] lack of space precludes mention of further routine papers covering enzymic esterification of amino acids that are in the current literature.

Ester cleavage from N-acylated amino acid benzyl esters can be achieved using N-bromosuccinimide,[612] or lithium iodide in aprotic non-polar solvents.[613] Lithium iodide also cleaves methyl and tert-butyl esters. Studies of enantioselective hydrolysis of N-protected DL-amino acid esters show no signs of slackening. Remarkably large rate enhancements for the hydrolysis of L-isomers are achieved with careful optimization of salt concentration {[KCl] = 0.03M for the N-dodecanoyl-DL-phenylalanine p-nitrophenyl ester/Z-L-Phe-L-His-L-Leu-OH/di-tetradecyldimethylammonium bromide chiral micelle system}.[614] Similar studies exploring other chiral species have involved (2S)-N-benzyl-N-(long-chain alkyl)-β-aminoalkanols/Cu(II), Zn(II), or Co(II) salts[615] and N-dodecyl-NN-dimethyl 1-octadecylammonium bromide vesicles carrying chiral amine groupings and metal salts.[616] A more conventional approach is represented in subtilisin-mediated transesterification of Z-DL-Ala-ONP with 1-butanol.[617]

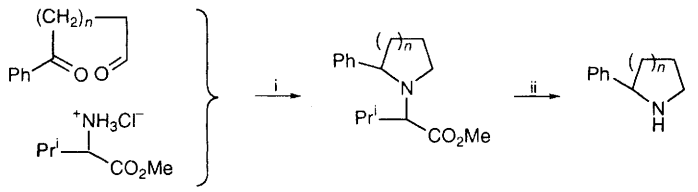
Reduction of the carboxy group of an N-protected α-amino acid to the primary alcohol function ($-CO_2H \rightarrow -CH_2OH$) is occasionally accomplished in a roundabout way, e.g. Boc-L-Val-OMe + RMgBr followed by 1%HF in MeCN,[618] but $BH_3.SMe_2$[619,620] or $LiAlH_4$ reduction[621–623] is straightforward. These last two papers describe the application of Swern oxidation to the alkanols, to give the corresponding aldehydes (see also Ref.624; for the use of $py.SO_3$, see Ref.619), while the conversion of the primary alkanol into iodomethyl (PPh_3/I_2) permits cyclization and further functional group transformations to be performed leading to 3-carboxycyclopentylamines;[625] the homochiral α-aminoalkanals are increasingly valuable in broad areas of organic synthesis, and may be secured in high yield by $LiAl(OBu^t)_3H$ reduction of either Boc-L-amino acid phenyl esters[626] (or the methyl ester of a protected arginine),[627] or Boc-L-amino acid

mixed anhydrides.[628] DIBALH Reduction of diethyl L-aspartic and glutamic acids to aldehydes is α-selective, and if conducted in the presence of a lithium trialkylphosphonoacetate, leads to N-protected γ-amino-αβ-unsaturated dicarboxylic acid esters.[629] Reduction of benzyl aspartates and elaboration of the alkanols to enantiomerically-pure 3-amino and 3,4-diaminoalkanols has been described;[630] conversion of α-(N,N-dibenzylamino)aldehydes into nitriles (-CHO → $-CH_2CN$) and ensuing alkylation and reduction gives 1,3-di-amines.[631] The reduction of the equivalent N-urethane-protected carboxyanhydrides by DIBALH or lithium tris[(3-ethyl-3-pentyl)oxy]aluminium hydride gives high yields without racemization[632] (sodium borohydride reduction gives the protected β-aminoalkanols[633]). Reduction of the Weinreb amide with lithium aluminium hydride gives the aldehyde [$-CO_2H$ → -CONMe(OMe) → -CHO], and ensuing reductive amination with an amino acid ester has been described (→ $-CH_2NHCH_2CO_2Me$),[634] though others have found this last step problematical.[635]

Dissolving metal reduction (Na/refluxing propan-1-ol) of α,α-disubstituted amino acid amides is a new method of obtaining β-aminoalkanols.[636] Conversion of the carboxy group into the acid fluoride is straightforward with NN-bis(alkoxycarbonyl)-L-α-amino acids, without racemization, using cyanuric fluoride; the same starting materials give Boc-N-carboxyanhydrides with the Vilsmeier reagent ($SOCl_2$/DMF)[637,638] Fmoc-amino acid chlorides are reduced [$Bu_3SnH/Pd(PPh_3)_4$] to corresponding aldehydes in rather low yields.[635] Conversion of the carboxy group of L-tryptophan into ketones *via* the Weinreb amide [→ -CONMe(OMe) → $-COCH_2P(O)(OMe)_2$ → -CH = CHAr etc],[639] or the one-step Weinreb-amide-to-vinyl-ketone route using allyl magnesium bromide,[640] conversion of a methyl ketone, formed from a protected phenylalanine in this way, into an isopropyl group,[641] and clean decarbonylation of an α-alkylpipecolic acid using diphenylphosphoroazidate,[642] illustrate further functional group manipulations.

Cyclization of β-aminoalkanols with Ph_2POCl gives N-diphenylphosphinoyl aziridines.[643] Reduction and cyclization of vinylglycine to the oxazolidinone, then N-allylation, can be accomplished in a one-pot process.[644]

The generation of heterocyclization products from N-acylated amino acids continues to attract mechanistic and synthetic interest, focussing on 2-alkoxyoxazol-5(4H)-ones formed from N-alkoxycarbonyl-L-amino acid mixed anhydrides and isopropenyl chloroformate[645] and from analogous symmetrical anhydrides on treatment with NN′-di-isopropylcarbodi-imide.[646] Ureas, e.g. Boc-L-Ala-L-N(Boc)CHMeCON(^{i}Pr)CONH^{i}Pr, are also formed in this process by rearrangement of the symmetric anhydride to the N(Boc)-dipeptide followed by addition to the carbodi-imide. The generation of a mixture of N-acylisourea, symmetrical anhydride and oxazolone through reaction of an N-protected amino acid with a carbodi-imide does not involve significant racemization, which becomes more pronounced when an amine is introduced (as in the normal course of peptide synthesis). As this process continues, it is aminolysis of the anhydride initially, and of the oxazolone at later stages, that introduces racemized products.[647] N-Methylamino acid esters react *via* an oxazolone and/or symmetrical anhydride

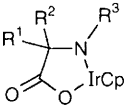


Reagents: i, $NaBH_3CN$ or $NaBH(OAc)_3$; ii, Bu^tOK, and Curtius rearrangement

Scheme 30

Reagents: i, TFAA, Py, 100 °C

Scheme 31



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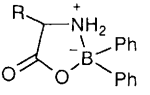

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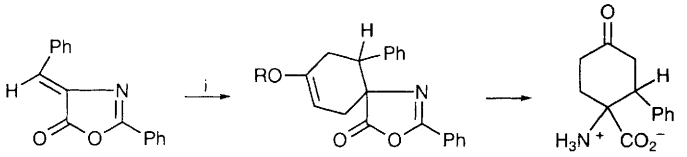


Reagents: i, $CH_2{=}C(OMe)C{=}CH_2$, etc.

Scheme 32

in giving acyloxyphosphonium salts with the currently popular phosphonium peptide-bond-forming reagents PyBrOP and PyClOP (PyBOP reacts sluggishly in this process).[648]

N-Acyl-N-benzylamino acids yield 5-trifluoromethyloxazoles when treated with TFAA/py in benzene (Scheme 31),[649] while N-2-hydroxybenzyl analogues yield tricyclic benzoxazolines.[650] Equilibrium mixtures of thiazolinones, phenylthiocarbamoylamino acids and N-phenylthiohydantoins (PTHs) formed in the Edman peptide sequencing process can be converted into thiazolinones that are amenable to ring-opening with a fluorescent amine.[651] Other interesting five-membered heterocycles include (95), formed from an amino acid and $[Cp^*IrCl(\mu\text{-}Cl)_2]$, and capable of highly diastereoselective ligand complexation[652] and (96) formed from amino acids and diphenylborinic acid (*cf.* Vol.26, p.62).[653]

1,3-Dipolar cycloadditions of amino acid-derived imines illustrated in previous Volumes of this series (see e.g., Vol.23, p.55) continue to provide highly-substituted five-membered heterocycles. Thus, decarboxylation of imines formed from amino acids and alloxan or 1-phenyl-3-methylpyrazolin-4,5-dione gives azomethine ylides that add to maleimides.[654] Highly-substituted homochiral pyrrolidines are formed between N-acryloyl-L-proline benzyl ester and $R^1CH{=}N^+(Li)R^2C^-CO_2Me$.[655] Formation of 3-(3,6-dioxopiperazin-2-yl)propanoic acid from γ-methyl glutamate and glycine ethyl ester[656] exemplifies a familiar six-membered heterocyclic amino acid condensation product, while a more unusual ring-enlargement process (see Vol.25, p.69) accompanies photolysis of N-phthaloyl-L-DOPA methyl ester protected in its side-chain by 3′,4′-methylenation (corresponding treatment of N-phthaloylthreonine and serine methyl esters gives phthaloylglycine through β-fragmentation).[657]

6.3 Specific Reactions of Amino Acids – The conventional use of this section over the years continues in this Volume, covering papers that concentrate mainly on reactions at the side-chain of α-amino acids. By their nature, these processes often amount to the use of one amino acid to synthesize another, and some papers that could have been located here can be found in the earlier synthesis Sections 4.1–4.15.

Side-chain halogenation of aliphatic L-amino acid esters (as their N-phthaloyl derivatives) is stereoselective (particularly so with t-butyl esters), giving (2S,3R)-β-hydroxyphenylalanine after substitution of the bromo-substituent that was introduced using NBS,[658] and 4-bromo-L-glutamates (stereoselectivity not investigated, but the diastereoisomer mixture was easily separated).[659] Fluorination of α-fluoromethyltyrosine with acetyl hypofluorite gives the β-fluoro-analogue.[660] ω-Iodoalkenylglycines $CH_2{=}ClCH_2CH(NHAc)CO_2Et$ undergo Michael-type chain extension with $CH_2{=}CHCO_2Et/Pd(OAc)_2$ to give $EtO_2CCH{=}CHCH{=}CHCH_2CH(NHAc)CO_2Et$.[661] The corresponding reaction occurs with electrophiles, e.g. $(E)\text{-}ICH{=}CHCO_2Et$ with $CH_2{=}C(SnBu_3)CH_2CH(NHAc)CO_2Et$.[662] The organozinc synthon formed from L-glutamic acid (side-chain $-CO_2H \rightarrow -ZnI$) undergoes Pd-catalysed condensation with an aryl iodide to give enantiomerically-pure homophenylalanines,[663]

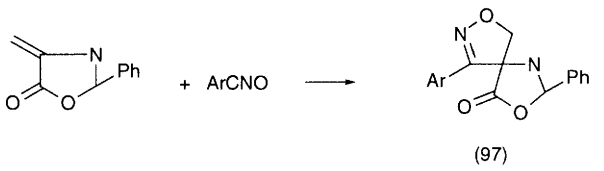
and the equivalent serine-derived synthon[664] reacts with acryloyl chloride, followed either by cyclization to give 4-oxopipecolic acid, or by addition of benzylamine to give 4-oxolysine.[665] Photo-activatable moieties have been added to the isopropenyl and carboxy side-chains of (-)-kainic acid.[666]

Diels-Alder additions of buta-1,3-diene[667] and of Danishefsky's diene [or (E)-PhCH = C(CN)CO_2Me or 2-methoxybuta-1,3-diene][668] to the 2-phenyloxazolone derived from αβ-dehydrophenylalanine (Scheme 32) gives 1-aminocyclohexene-carboxylic acids which can be categorized as conformationally-constrained analogues of common α-amino acids. A heterocyclic version (97) arises by 1,3-dipolar addition of 2,6-dichlorobenzonitrile oxide to 4-methyleneoxazolidin-5-one.[669] Methylenation of the D-glyceraldehyde-derived Z-oxazolone gives a mixture of five cyclopropanes, with the (1S,2R)-derivative as predominant product.[670]

Conventional modifications to the alicyclic moiety of alicyclic α-amino acids include ethylene biosynthesis from 1-aminocyclopropanecarboxylic acid[671] and hydrogenolytic ring-opening of aziridinecarboxylates (98).[672] Studies of saturated heterocyclic imino acids include stereoselective additions of alkylcopper reagents to cyclic acyliminium ions formed from pipecolic acid,[673] and a remarkable ring-expansion (Scheme 33) of 5- and 6-membered members of this class to 8- and 9-membered homologues through the reaction with acetylenic dipolarophiles of azomethine ylides formed with formaldehyde.[674]

Oxidation of urethane-protected L-proline methyl ester to L-pyroglutamic acid with iodosylbenzene/trimethylsilylazide/CH_2Cl_2 also causes 5-substitution (insertion of N_3, Cl, or OH; other substituents and reaction conditions can alter the pattern of reactions).[675] Electrochemical oxidation of L-proline followed by methylcopper addition to give trans-5-methyl-L-proline.[676] 3,4-Dehydro-L-proline (from hydroxy-L-proline) serves as starting material in a route to (2S,3R,4S)-epoxyproline (m-chloroperbenzoic acid) accompanied by its diastereoisomer.[677] The epoxides give an 8.3:1-mixture of 3-methyl-4-hydroxy- and 4-methyl-3-hydroxyprolines through $LiCuMe_2$ ring-opening.[678] Regio- and stereoselective hydroxylation of the enolate of 4-oxoproline is a stage in a route to swainsonine [(2R,3S,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine].[679] Hydroxy-L-proline is also the starting point (conversion into its cis-isomer) in a synthesis of 'de(hydroxymethyl)desulfo-analogues' of the O-sulfonated glycopeptides, bulgecins A, B, and C.[680]

Aromatic side-chain modifications that have been accomplished include the preparation of Boc-L-(4-carboxy)phenylalanine from the corresponding tyrosine O-triflate,[681] preparation of O-glycosylated Fmoc-L-tyrosine pentafluorophenyl esters,[682] anodic oxidation of 3,5-dibromotyrosine methyl ester to generate caremicolin models (99),[683] anodic oxidation or thallium(III) nitrate oxidation and zinc reduction to give isodityrosine and dityrosine derivatives.[684] Electro-oxidation[685] and cyclic voltammetric monitoring of the oxidation[686] of L-DOPA, elaboration of the phenolic side-chain and transesterification of tyrosine, giving L-DOPA esters by combined tyrosinase and α-chymotrypsin treatment,[687] are also reported. 5-S-CysteinylDOPA undergoes oxidation under physiological conditions to give pheomelanins *via* 1,4-benzothiazines.[688] Azide anion radical



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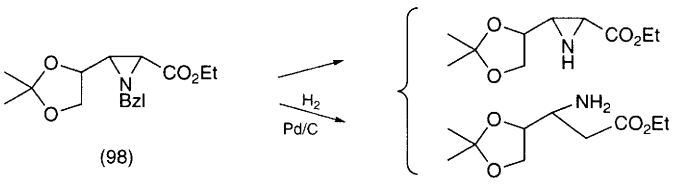

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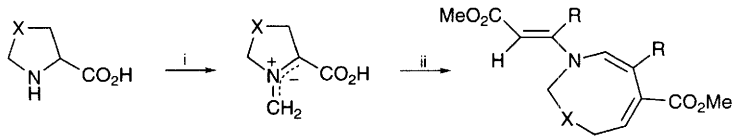
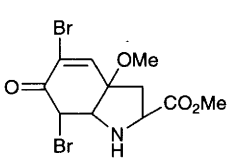


Reagents: i, HCHO; ii, $RC{\equiv}CCO_2Me$

Scheme 33



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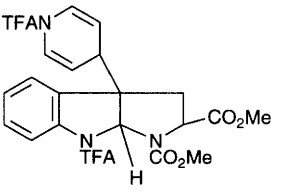


(100)

attack on tyrosine generates the oxygen-centred phenoxide radical, and the eventual reaction product is di-m-tyrosine.[689]

Generation of a fluorescent species (λ_{excit} 320 nm, λ_{em} 392nm) by treatment of tryptophan with nitrous acid has been reported, without speculation or evidence for its structure.[690] X-Ray analysis[691] supports the structure (100) assigned to an N^{im}-trifluoroacetylated reaction product from the reaction of N-methoxycarbonyl-L-tryptophan methyl ester with TFA and pyridine; the minor reaction product (6%)[692] is the all-cis isomer (101; R = H) accompanying 84% of the isomer with inverted ring junction protons, which is the product expected on the basis of existing knowledge of tryptophan cyclic tautomers. Thus, the well-established N^{im}-toluene-p-sulfonyl analogue, which undergoes a highly diastereoselective aldol addition to benzaldehyde after deprotonation with LDA,[693] has appeared in several papers recently (see also Ref.268). The diastereoselectivity of Pictet-Spengler processing of tryptophan esters (RCHO + H_2N- → imine → carbolines) depends on the ester alkyl group.[694] (2-Hydroxyethylthio)-substitution at positions 2 and 7 of the indole moiety of tryptophan by treatment with $Hg(OAc)_2$ followed by mercaptoethanol explains a side-reaction observed during peptide synthesis.[695]

Histidine chemistry described in the current literature covers a 1:1:1-adduct involving the imidazole moiety of the N^{α}-acetylamino acid, with malondialdehyde and an alkanal (but no reaction in the absence of the alkanal),[696] formation of a Michael-type adduct N-Z-1(3)-(1′-formylmethyl)hexyl-L-histidine as a model for attack on proteins by lipid breakdown products,[697] and β-attack by hydroquinone on a protected histidine to give the β-(2,3-dihydroxyphenyl) homologue.[698] S-[2-Carboxy-1-(1H-imidazol-4-yl)ethyl]-3-thiolactic acid is a new histidine metabolite isolated from urine; it has been synthesized from the cysteine adduct through HNO_2 de-amination.[699]

Arndt-Eistert homologation of (2S,3S)-3-methylaspartic acid giving (2S,3R)-3-methylglutamic acid competes favourably with a bis(lactim ether) synthesis.[117] Rapoport-type alkylation of aspartic acid-derived enolates gives syn- or anti-2,3-pyrrolidinedicarboxylic acids,[700] also independently prepared in essentially the same way;[701] the same conformationally-constrained aspartic acid analogues have been synthesized from the glutamic acid-derived synthon (102).[702] α-tert-Butyl-γ-methyl N-Z-glutamate gives the γ-anion with lithium hexamethyldisilazide, which is a convenient source of γ-substituted glutamic acids through reaction with electrophiles.[703] The protected N-hydroxyornithine analogue $FmocNHCH(CO_2H)CH_2CH_2CHRNHOCH_2CH_2SiMe_3$ emerges from a synthesis starting with L-glutamic acid (side-chain $-CO_2H$ → -CH=NOTBDMS) and cyclized *via* the N-hydroxysuccinimide ester to give $N^{\alpha}N^{\delta}$-protected N^{δ}-hydroxycyclo-ornithine and its homologue.[704] 2-Indolylmethyl ketone formation through the side-chain carboxy group of aspartic acid provides the novel sweet compound monatin after stereospecific conversion of the side-chain carbonyl group into $-C(OH)(CO_2H)-$.[705]

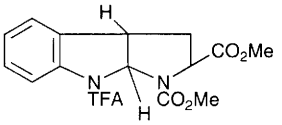
Protected L-pyroglutamic acid continues to be one of the most frequently-used chiral synthons in general organic chemistry, and no less so as starting material for the preparation of other amino acids. 4,4-Di-substitution can be accomplished

after LiHDMA de-protonation,[706] 4-Methylenation and -cyclopropanation have been described, either *via* the 4-(dimethylaminomethyl)pyroglutamate formed from the lithium enolate of a pyroglutamate and Eschenmoser's salt, or through an imidazolidinone synthesis (see Section 4.2; introduction of a $BuO_2CC(=CH_2)CH_2$- group).[707] Independently, the same route has been followed by other workers, but with some different minor details.[708] Reduction of the lactam carbonyl group of pyroglutamates to $-CH_2-$, leaving other reducible functions intact, proceeds *via* the hemiaminal (successively, $LiEt_3BH$ and $SiEt_3H/BF_3.Et_2O$).[709] The hemiaminal was reacted with stabilized phosphonates to give products of Wittig synthesis that were isolated as 5-substituted prolines (103 → 104; trans:cis = 5:1) through cyclization of the intermediate alkene.[710] L-Pyroglutaminol methoxymethyl ether has been used to synthesize (+)-1,8-di-epi- and (-)-1-episwainsonine through construction of a piperidine ring on NH and ether functions, and manipulation of the pyrrolidine functional groups.[711]

Pyroglutamic acid-derived synthons used in large-scale synthetic enterprises include (105; manzamine A);[712] and (106 and its epoxide; natural polyhydroxylated pyrrolidines).[713] The L-pyroglutamate-derived synthon (106) can be subjected to stereoselective epoxidation to give (2S,3S)-3-hydroxyproline from which ($-CO_2H$ → $-CH_2OH$) castanodiol can be obtained,[714] and (2S,3S)-3-methylproline and (2S,3R)-3-phenylproline were prepared similarly.[715] Pyroglutaminyl chloride (from oxalyl chloride and TMS-pyroGlu)[716] and its N-Fmoc derivative (from Fmoc-L-glutamic acid *via* the dichloride formed using $SOCl_2$) have been obtained.[717]

N^{β}-Glycosylated asparagines may be prepared by reaction of Fmoc-L-α-aspartic esters with a glycosyl azide under the influence of Et_3P/CH_2Cl_2.[718] N^{β}-Aralkyl-protected asparagines and glutamines can be cleaved by boron tris(trifluoroacetate) in TFA/AcOH.[719] A route to aspartic acid β-semi-aldehyde, based on ozonolysis of a protected allylglycine, avoids less satisfactory steps in routes from aspartic acid itself.[720] Low yields when reducing the acid chloride (30%) were encountered, however, in a route ($-CO_2H$ → $-COCl$ → $-CHO$) from α-methyl Z-L-aspartate, but could be improved when the reduction was performed in the presence of palladium.[721] Development of the N-acryloyl compound into the conformationally-constrained α-amino acid, 6-oxodecahydroisoquinoline-3-carboxylic acid, is described in this study.[722] The aldehyde was isolated as the dimethyl acetal, a device also used in a related study using glutamic acid γ-semialdehyde,[723] which also features in a synthesis of differentially protected meso-2,6-diaminopimelic acid.[724] Appropriate protection was involved in all these studies, and in the latter route, manipulation of the side chain carboxy group (Wittig homologation etc) of the oxazolidinone was used.

Formation of methyl ethers from protected serines and threonines[725] and benzyl ethers,[726] including benzylation providing precursors to photoactivatable side-chains,[727] follow standard phase transfer alkylation procedures. Routes to 2-acetamido-2-deoxy-β-D-glycosides,[728] corresponding 2-acetamido-galactosides,[729] galactosides,[730] and glycotetraoses[731] have been explored. A cumbersome route from ε-hydroxy-L-norleucine gives homochiral 3-amino-7-substituted azepinones.[732] (2R,3S,4R)-3,4-dihydroxy-2-hydroxymethylpyrrolidine and



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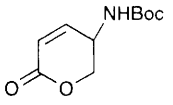

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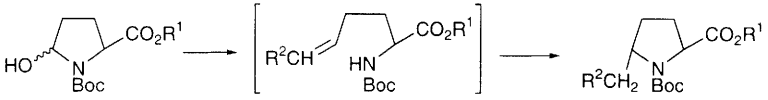

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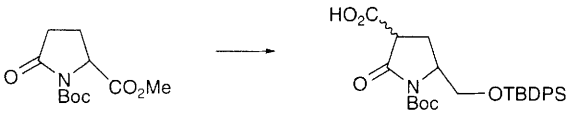

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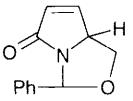

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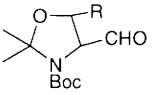

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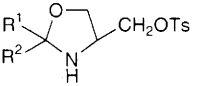
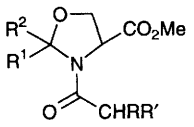


(108)

(2S,3R,4S,5S)-3,4-dihydroxy-2,5-dihydroxymethylpyrrolidine have been prepared from D-serine and D-ribonolactone, respectively.[733]

A number of synthetic opportunities follow from the juxtaposition of amino, carboxy and primary alcohol functions in serine, e.g. a lengthy synthesis of Fmoc-γγ-di-t-butyl-γ-carboxy-L-glutamic acid from D-serine.[734] Here, the carboxy group of the starting material becomes the extended side-chain of the product *via* an aldehyde, and the $-CH_2OH$ side-chain becomes the eventual carboxy group, accounting for the 'L-from-D' nature of the process. The synthetic uses of L-serinal derivatives are proliferating, and two papers report improved syntheses of a protected form, the Garner aldehyde (107; R = H), one route[735] avoiding the need for methyl iodide and benzene and the other, also explored for the threonine homologue (107; R = Me) using an $LiBH_4$ and $COCl_2$/DMSO sequence for the initial stages.[736] D-Threonine gives the corresponding synthon through standard steps.[737] β-Branched α-amino acids have been obtained through the sequence $-CHO \rightarrow -CH(OH)C{\equiv}CH \rightarrow$ bromoallenes.[738] A new electrophilic L-alaninol synthon (108), prepared from L-serine, undergoes nucleophilic substitution by Gilman cuprates or Grignard reagent/CuX complexes.[739] The related N-acylated synthon derived from L-serine (109; R^1 = Bu^t, R^2 = H) gives bicyclic Dieckmann products leading to useful homochiral tetramic acids.[740] N-Z-L-Serine β-lactone reacts with trimethylsilylamines Me_3SiNR_2 primarily by alkyl oxygen cleavage, to give optically-pure β-aminoalanines (certain reaction conditions cause acyl-oxygen cleavage leading to serinamides).[741] The chiral oxazolidinone (110), formed from serine, threonine or cysteine (S in place of ring O) using bis(trichloroethyl) carbonate[742] gives N-allyl derivatives that undergo intramolecular oxime–alkene cycloaddition, to give pyrrolidines.[743] Other ring-closure reactions involving serine include samarium(II) iodide-mediated cyclization of N-allyl-[744] and propargyl-serinals[745] to give 2,3,4-trisubstituted pyrrolidines (111). Access to homochiral 5-alkylpiperazine-2-carboxylic acids (112) is initiated by condensation of L-serine with an α-amino acid.[746]

(ω-Aminoalkyl)-α-amino acids, notably lysine, are also represented in broader organic synthesis, and the side-chain function has been developed into diazoacetamides $L\text{-}N_2CHCONH(CH_2)_4CH(NH_2)CO_2Et$ that have been added to C_{60}-fullerenes to give a [60]fullerene-fused cyclopropane carrying an amino acid structure.[747] Simpler side-chain modifications are illustrated by the preparation of N^{ε}-(carboxymethyl)-L-lysine and N^{δ}-(carboxymethyl)-L-ornithine through N^{δ}-(carboxyethyl)-L-ornithine synthase-mediated reductive condensation with glyoxylate,[748] and conventional preparations of N^{ε}-Fmoc-L-lysine and N^{δ}-Fmoc-L-ornithine from copper(II) complexes of the amino acids.[749] A more involved sequence (successively, sodium nitroprusside, CBr_4/PPh_3, p-bromoaniline) leads to N^{α}-Z-N^{ε}-(p-bromophenyl)-L-lysine [similarly, to N^{τ}-(p-bromophenyl)-L-histidine from Z-histidine).[750] The ε-amino group of N^{α}-Z-L-lysine methyl ester has been converted (dimethyldioxirane in acetone) into the nitrone [$-NH_2 \rightarrow -N^+(O^-){=}CMe_2$] from which ($H^+$ then Ac_2O) N^{α}-Z-N^{ε}-acetoxy-L-lysine methyl ester was secured.[751] There may be useful analytical applications associated with the finding that the ninhydrin–Fe(III) system reacts specifically



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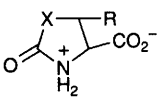

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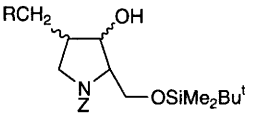

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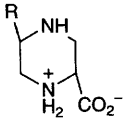

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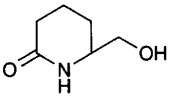

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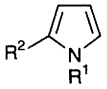

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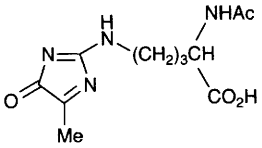

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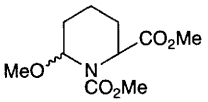

(116)

with lysine at pH 1 (but not with ornithine, arginine, histidine, proline or glycine.[752]

Reactions of the side-chain amino group of lysine, some of them modelling *in vivo* protein behaviour, have been studied. A useful synthon (113) for the synthesis of substituted piperidines, has been prepared in five steps from L-lysine using conventional precedents.[753] With 4,5-epoxy-Z(E)-heptenal (a lipid peroxidation product), lysine gives the pyrroles [114; R^1 = $CH(CO_2H)(CH_2)_4NH_2$ or $(CH_2)_4CH(NH_2)CO_2H$; R^2 = H, CH(OH)Et)] together with the isomeric compounds formed through the α-amino group.[754] With methylglyoxal, reversible glycosylation occurs through conversion of the initially-formed imine into unknown oligomers.[755] The process is irreversible with arginine, giving 4,5-dihydroxy-5-methylimidazolines (115), the imidazolin-4(5)-ones derived from these showing fluorescence (λ_{excit} 320 nm, λ_{em} 398 nm). L-Lysine has been converted into a protected L-α-amino-ε-mercaptohexanoic acid *via* a pyridinium analogue.[756] Anodic oxidation of di-N-methoxycarbonyl-L-lysine methyl ester in methanol gave the α-methoxyoxazolidinone (116) whose stereoselective azidolysis and reduction have provided the first example of an optically-pure α-aminoamine.[757]

Efficient access has been worked out, to N^G-methyl-D- and -L-arginine from the ornithines and $MeNHC(SMe)=NH_2^+$ I^-,[758] and further study of preparations of side-chain protected arginine, either the long way round [synthesis of ω,ω'-bis(urethane)s by N^δ-guanylation of ornithine with bis(urethane)protected 1-guanylpyrazoles],[759] or directly by ω-arenesulfonylation.[760] In the latter study, no improvement on a currently-used protecting group of this family, the Mtr-group, was achieved by the introduction of electron-donating alkyl groups into the aryl moiety. Electro-oxidation of arginine at Pt electrodes liberates nitrate ion through an electron transfer mechanism.[761] This is an interesting result, because it shows that inorganic nitrogen oxides can be released from arginine without the presence of nitric oxide synthase; the bustling activity in the nitric oxide area is illustrated by a synthesis of the NO synthase inhibitor N^ω-hydroxy-N^ω-methyl-L-arginine in 8 steps from N^G-Z-L-arginine.[762]

Tetrahydropyrimidines have been formed from reaction of 2,4-diaminobutyric acid with other amino acids,[763] and related tetrahydropyrimidin-4(1H)-ones have been identified as self-degradation products of bellenamine (R)-$H_2N(CH_2)_3CH(NH_2)CH_2CONHCH_2NH_2$, a β-lysinamide from *Streptococcus nashvillensis* that shows useful immuno-enhancing HIV protease inhibitory action. The formaldehyde needed to generate the reaction products is supplied by hydrolytic cleavage of the $-NHCH_2NH_2$ moiety of the natural product.[764] Methyl 4,5-diaminopentanoate cyclizes to 5-aminomethylpyrrolidinone and 5-aminopiperidinone in dilute aqueous alkali.[765]

The thiol function of cysteine shows important oxidation reactions, illustrated with a kinetic study of photo-oxidation (H_2O_2) of N-acetylcysteine[766] sensitized by N-(9-methylpurin-6-yl)pyridinium salts,[767] and one-electron oxidation by the azide radical anion at pH 10.5 leading to intramolecular proton abstraction and subsequent processes.[768] S-Arenesulfenylation of cysteine derivatives, with the objective of placing a photoactivatable group at sulfur, has been achieved using

the appropriate pyrid-2-yl disulfide.[769] Thiolysis of S-(SCM)cysteine hydrochloride in water gives S-(alkanesulfenyl)cysteines.[770] S-Trifluoromethylation of N,C-protected cysteines has been accomplished,[771] and other S-protection strategies are featured in the current literature: (novel) S-(allyloxycarbonylaminomethyl)ation,[772] and (traditional) benzylation with improved methods for introduction through benzyl cations or $ArCHO/Et_3SiH$.[773] Cyclic ketimine formation from (2-aminoethyl)-L-cysteine mediated by snake venom L-amino acid oxidase[774] parallels the process observed with the cystathionine de-amination product, S-(2-oxo-2-carboxyethyl)-L-homocysteine.[775] The ketimine readily undergoes autoxidation to the sulfoxide.[776] Nitric oxide is released from S-nitrosocysteine under physiological conditions, and there have been several recent studies of the consequences of this, one being the destruction of zinc-sulfur clusters in proteins.[777]

Studies of methionine and other S-alkyl cysteines reflect similar themes. Slow oxidation of S-(2-propenyl)cysteine and its sulfoxide by aqueous nitric oxide,[778] one- and two-electron oxidation of methionine by peroxynitrite HOONO *via* the radical HOONO· (leading first to the sulfoxide and ultimately to the liberation of ethylene),[779] and 2,2'-bipyridinium chlorochromate oxidation of methionine, established by a kinetic study to involve a sulfurane transition state.[780] N-Phthaloyl-L-methionine ethyl ester undergoes the expected reaction with SO_2Cl_2 to give a α-chlorosulfide mixture that yields the aldehyde-containing side-chain on hydrolysis (-CHClSMe → -CHO).[781] S-Phenyl-L-cysteine is best oxidized to the sulfone with magnesium monoperoxyphthalate, giving a versatile synthon for preparations of (S)- or (R)-cycloalkylglycines and prolines and analogues.[782] Facile alkylation α to the sulfone function with stereocontrol is also the basis of the use of the same synthon for syntheses of (2S,3S)- and (2R,3R)-pyrrolidine-2,3-dicarboxylic acids.[783]

6.4 Effects of Electromagnetic Radiation on Amino Acids – The topics covered in this section over the years continue to surface in the literature, which has provided acounts of γ-radiolysis of aqueous tyrosine[784] and 3,5-diiodotyrosine.[785] Photo-oxidation of 5-S-cysteinylDOPA at wavelengths longer than 320 nm gives benzothiazines, whereas cleavage of the aliphatic moiety to yield DOPA is the consequence of irradiation at 280–320 nm.[786] Time-resolved fluorescence of the protein cross-linking amino acid, dityrosine, has been evaluated.[787]

As usual, most of the papers concern tryptophan and its analogues, with investigations of products of photolysis of tryptophan in aqueous solutions,[788] and of quenching of singlet oxygen by aqueous tryptophan (comparisons with tyrosine, histidine, methionine and cysteine were also included in this study).[789] Fluorescence decay studies focus on constrained tryptophan analogues, e.g. 3-amino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid,[790] and on a new reference compound with an ultra-short fluorescence lifetime.[791] Supersonic gas expansion studies of tryptophan and substituted analogues permit the allocation of fluorescence lifetimes to individual conformers.[792] Phosphorescence decay of tryptophan involves energy transfer between individual molecules in the triplet excited

state.[793] Low-temperature UV photolysis of tryptophan yields stable products *via* anion and cation radicals, the products surviving warming to room temperature; they show themselves to be efficient luminescence quenchers.[794]

7 Analytical Methods

7.1 Introduction – Several useful reviews of methods of amino acid analysis have appeared, e.g. analysis of dansylamino acids.[795]

7.2 Gas-Liquid Chromatography – The importance of sample clean-up prior to derivatization and GLC analysis of amino acids has been stressed.[796] Derivatization incorporating an extractive alkylation of amino acids with pentafluorobenzyl bromide followed by N-heptafluorobutyroylation illustrates the greater attention being paid to sample authenticity, prior to GLC analysis incorporating negative ion CI-MS.[797] Similar derivatization approaches employ N(S)-isopropoxycarbonyl methyl esters (sulfur-containing amino acids),[798] and N(O)-isobutoxycarbonyl t-butyldimethylsilyl esters.[799] Alkyl chloroformates can provide a one-step derivatization procedure for amino acids in aqueous solution, to give N-alkoxycarbonylamino acid alkyl esters (the alkyl ester group derives from the breakdown of the chloroformate, but an alcohol is usually added in the reagent cocktail, to ensure complete reaction).[800] Use of a different alcohol, of course, gives more flexibility but also more complications, since ethyl esters are also formed when the $EtOCOCl/CF_3CH_2OH$/pyridine reagent is used.[801]

The stable isotope dilution technique has been employed in the otherwise standard GC-MS analysis of cysteic and homocysteic acids, and cysteinesulfinic and homocysteinesulfinic acids.[802]

Enantiomer separation by GLC has been reviewed.[803] Chiral GLC analysis of N-trifluoroacetylamino acid methyl esters on a 2,6-di-O-butyl-3-O-trifluoroacetyl-γ-cyclodextrin capillary column,[804] and of N-trifluoroacetylamino acid isopropyl esters with Chirasil-L-Val as stationary phase[805] has been accomplished.

7.3 Thin-Layer Chromatography – Routine they may be, but several projects have been reported recently that are useful; comparisons of cellulose with silica gel for their performance in quantitative TLC,[806] a study of resolution of DL-amino acids on borate-gelled guaran-impregnated silica gel[807] and on copper(II)-L-proline-impregnated silica gel[808] from the point of view of the analytical resolution of DL-amino acids. Careful attention to detail is rewarded by reproducible quantitative TLC of lysine, threonine and homoserine.[809]

The preceding studies base their results on conventional ninhydrin colour-formation, though other spray reagents (p-dichlorodicyanobenzoquinone, applicable down to 0.1 μg,[810] and 4-dimethylaminobenzaldehyde (for quantitative TLC of tryptophan)[811] continue to be advocated.

New solvent systems $py\text{-}C_6H_6$ = 2:5:20, $MeOH\text{-}CCl_4$ = 1:20, and $acetone\text{-}CH_2Cl_2$ = 0.3:8, have been suggested for the TLC of PTHs.[812]

7.4 High Performance Liquid Chromatography – Not all the papers cited here deal simply with analytical studies; the chemistry of stationary phases and of derivatization protocols is frequently involved in the reports.

Reviews have appeared of amino acid derivatization,[813] fluorogenic labelling,[814] and derivatization for enantiomeric analysis.[815]

Nearly all HPLC analysis protocols for amino acids call for pre-column derivatization, usually the formation of a N-substituted amino acid mixture from the sample, prior to chromatographic separation and quantitation of the individual components. One commonly-used derivatization protocol is N-phenylthiocarbamoylation (PTC; for a review, see Ref.816), for amino acids in general[817] and arogenic acid (the biogenetic precursor in plants of phenylalanine and tyrosine) in particular,[818] for aspartic and glutamic acids and asparagine,[819] and hydrolysates of proteinaceous material in pollen[820] and in old paintings.[821] Use of the analogous N-butylthiocarbamoylamino acids seems to have no extra justification, though they show excellent chemical stability.[822] 4-(3-Pyridinylmethylaminocarboxypropyl)phenylthiohydantoins, the cyclization-rearrangement products of the correspondingly-substituted PTC-amino acids, have been studied by HPLC-electrospray MS.[823] Conditions for HPLC analysis of PTH mixtures, avoiding reagent-related background peaks, have been established.[824]

N-(Fluoren-9-ylmethoxycarbonyl)amino acids (Fmoc-amino acids) are gradually gaining acceptance for HPLC analysis,[825] reactions following derivatization being avoided by the use of heptylamine to remove excess reagent.[826] A specialized interest is represented in HPLC of Fmoc-(S)-alk(en)yl-L-cysteine sulfoxides in garlic.[827] Analysis of imino acids as Fmoc derivatives after removal of primary amines from samples by conversion into isoindoles (OPA-amino acids) using o-phthaldialdehyde and mercaptoethanol has been represented in analysis of glyphosate (N-phosphonomethylglycine),[828] and in mainstream studies of protein amino acids,[829] including special reference to automated analysis.[830] The OPA-amino acid pre-treatment procedure also allows the estimation of 4-hydroxyproline in biological fluids as its PTC-derivative.[831]

OPA-Derivatization and quantitation of the derivatives continues to be confidently used, and a total time of 17 minutes has been claimed for analysis of an amino acid mixture.[832] It has been used for L-lysine in wheat gliadin proteins,[833] for primary amino acids in rat plasma,[834] and in a rare example of post-column OPA-derivatization of amino acids separated by ion-exchange chromatography.[835] As has been mentioned frequently in the recent literature (see Vol.25, p.75) there is some uncertainty about the reliability of OPA-derivatization because of limited stability of the derivatives, and a study has shown that OPA-amino acid derivatives decompose to the extent of about 6% over 15 h (though their methyl esters reach this point of decay after 8 h).[836] The structurally-related, highly fluorescent, derivatives formed using naphthalene-2,3-dialdehyde continue to be explored.[837]

Comparison of HPLC analyses of D- and L-threo-β-methylphenylalanine by the o-phthaldialdehyde-mercaptopropionic acid method, use of Marfey's reagent (1-fluoro-2,4-dinitrophenyl-5-L-alaninamide), and alkaline acetic anhydride procedures, as well as the use of GLC (N-trifluoroacetyl isobutyl ester) leads to no

particular recommendation.[838] N-Acetylamino acids in urine have been estimated by HPLC with MS detection,[839] whereas derivatization at the carboxy group with 9-anthryldiazomethane has been advocated for the determination of N-acetyl-amino acids released from proteins using proteases.[840] Benzoyl chloride has also been revisited for derivatization, and converts amino acids into 2-phenyl-5-benzoyloxyoxazoles, permitting analysis at the 1 pmol level with the assistance of electrospray MS monitoring.[841] Analysis of kainic acid as either N-(4-azidoben-zoyl)- or N-(4-azidoPTC)-derivatives, has been described.[842]

Dansylation[843] and dabsylation[844] provide stable derivatives and good HPLC separation can be achieved. One of these studies[843] was aimed at verifying the stability of common amino acids in 6M HCl. Analysis by electrospray MS of underivatized basic amino acids and N-hydroxylamino acids is moderately successful, but dansylation gives improved reliability.[845] Dansyl-L-phenylalanine can be detected down to approximately 5×10^{-14} mol levels.[846] 4-Hydroxyproline assay through dabsylation followed by OPA-derivatization provides reproducible results for low levels of analyte.[847]

In a comparison with PTC-derivatization, 6-aminoquinolinyl-N-hydroxysucci-nimide treatment of amino acids (giving AQCamino acids; λ_{max} 248 nm)[848] is clearly superior unless there is a minimal time delay between derivatization and HPLC.[849] Highly fluorescent asymmetric ureas are formed between amino acids and the carbamate of the AQC reagent, and HPLC analysis with their help gives results that compare well with classical ion-exchange analysis.[850] Use of a polymeric reagent carrying this carbamate has been explored.[851]

Post-column derivatization with 1,2-naphthoquinone-4-sulfonate (λ_{max} 305 nm) has been applied to samples separated by ion-pair liquid chromatography.[852]

Particular structural characteristics that allow specific analytical targetting are shown by some common amino acids. This is illustrated for cysteine and homocysteine analysis, conversion into the N-acetyl S-pyridinium derivative,[853] or into derivatives formed with monobromobinane,[854] and derivatization using 7-fluorobenzo-2-oxa-1,3-diazole-4-sulfonate.[855] Non-derivatized samples (electro-chemical detection of cysteine, using a glassy carbon electrode),[856] and of S-adenosyl-L-homocysteine and S-adenosyl-L-methionine by UV detection,[857] have proved to be suitable for analysis. An interesting development for the HPLC ion-exchange analysis of underivatized amino acids exploits the chemiluminescence formed between amino acids and *in situ*-generated $Ru(bipy)_3$.[858] Protocols for HPLC of related amino acids (excitatory amino acids carrying sulfonic and sulfinic acid side-chains),[859] and selenium analogues of sulfur-containing amino acids,[860] have been worked out.

Tryptophan and its 5-hydroxy-derivative in cerebral fluid have been estimated by HPLC with electrochemical detection,[861] and through fluoresence detection (λ_{excit} 302 nm, λ_{em} 340 nm).[862]

Increasing numbers of HPLC studies of crosslinking amino acids reflect the importance of some of them as markers for metabolic disorders. Pyridinoline and its deoxy-analogue have dominated these reports,[863] which describe minor differences in protocol, one of which (use of acetylated pyridinoline as internal standard)[864] needs care so as to minimize its decomposition.[865] Estimation of

aldosine as its oxidative decarboxylation product (Fe^{3+}), 6-(3-pyridyl)piperidine-2-carboxylic acid,[866] and of desmosine and isodesmosine as dansyl derivatives.[867] Analysis of p-boronophenylalanine in tissue is an essential adjunct to studies of the uses of this amino acid in neutron capture therapy.[868]

Estimation of enantiomer ratios for amino acids is most commonly achieved now by modifications of the derivatization methods outlined above. Thus, the use of a homochiral thiol (N-acetyl-L-cysteine[869,870] or N-isobutyroyl-L- or D-cysteine[871,805]) in the OPA procedure permits the complete separation of 18 DL-amino acids. One of these papers[870] describes a dating study concentrating on aspartic acid extracted from dentin, and applicable down to 1 pmol levels. (+)-1-(9-Fluorenyl)ethyl chloroformate similarly yields diastereoisomer mixtures allowing the estimation of D/L-ratios of amino acids in crustacean nerve tissue.[872] A new fluorophore, N-[4-(6-methoxy-2-benzoxazolyl)benzoyl]-L-proline, has been introduced for the same purpose.[873] Protected amino acids for use in peptide synthesis have been derivatized with Marfey's reagent for enantiomeric purity estimations.[874]

The other main approach to HPLC determinations of enantiomer ratios involves the incorporation of chiral species into a silica gel stationary phase (a crown ether, applied to tyrosine and DOPA and analogues),[875] 3-aminopropylated silica gel acylated by 2,4-dinitrobenzoyl-(R)-(1-naphthyl)glycine for the analysis of tryptophan and aspartic acid,[876] tetra-esters of calix[4]arenes bonded to silica gel for the estimation of DL-amino acid esters[877]) and bovine serum albumin bonded to silica gel for the resolution of DL-tryptophan.[878] Pirkle-type columns have been used for enantiomeric analysis of amino acids derivatized with 4-fluoro-7-nitro- or 4-dansyl-7-fluoro-2,1,3-benzoxadiazole, the former reagent giving superior results.[879] 'Chiralcel-OD' [cellulose tris(3,5-dimethylphenyl carbamate)] gives good results for a series of 17 Fmoc-amino acids.[880]

7.5 Fluorimetric Analysis – This section collects miscellaneous exploratory studies that have not been covered elsewhere in this Chapter, such as separation of derivatized amino acids using the fast centrifugal analyser[881] and enhancement of the fluorescence of naphthalene-1,2-dialdehyde-derivatized amino acids by cyclodextrins as mobile phase constituents in HPLC.[882]

7.6 Other Analytical Methods – Clearly, the applications of capillary zone electrophoresis (CZE) and related methods are developing rapidly, as demonstrated by the dedication of a CRC volume to it.[883] There are several applications in the amino acids field.[884–886] One of these studies[885] concentrates on CZE of cysteine and cystine employing electrochemical detection, as does another[886] that also covers a broader range of analytes. Separation of a mixture of 24 dansylamino acids is sharpened by Tween micelles in the liquid phase,[887] and separation of PTHs with good distinction of artefactual peaks has been accomplished.[888] These studies use sample preparation protocols that are familiar from the HPLC field, and this is also seen in use of Fmoc-derivatization for estimation of hydroxyproline in serum after OPA-treatment,[889] enantiomeric

separations of PTHs using N-dodecanoyl-L-serine, -glutamic acid, or -valine micelles,[890] and of dansylamino acids[891] using cyclodextrins as buffer additives,[892] also used for dansyl- and OPA-amino acids.[893] The power of modern methodology is revealed in the estimation, at 140 ppm levels, of the enantiomeric purity of phenylalanine derivatized by 4-fluoro-7-nitrobenz-2,1,3-oxadiazole and separated by CZE with cyclodextrin-containing buffers and using laser-induced (488 nm) fluorescence detection.[894]

Chiral stationary phases are also compatible with CZE enantiomeric purity determination, and mechanistic aspects have been explored.[895] The practice of CZE resolution has been reviewed.[896]

Immunoassay techniques have not been surveyed thoroughly in this Chapter over the years, though attention is drawn to unusual relevant studies such as the estimation of desmosine in biological fluids.[897]

7.7 Assays for Specific Amino Acids – Most of the papers under this heading revolve around enzymatic methods, both in the biosensor category and in flow injection analysis techniques. However, the latter approach can also accommodate standard chemical methods of analysis, such as Chloramine-T oxidation of hydroxyproline to generate a stable colour with Ehrlich's reagent.[898] Photometric estimation of tryptophan depends on the formation of a coloured complex by Fe^{3+}/AcOH/glycollic acid oxidation.[899]

Simultaneous estimation of L-lysine and L-tyrosine based on enzyme-supported flow injection analysis uses two enzyme reactors and a single oxygen electrode.[900] A similar approach accommodates L-alanine and L-phenylalanine, with a flow injection fibre optic biosensor providing the means of quantitation,[901] also for chemiluminescence generated specifically when L-lysine is present, associated with a lysine oxidase/microbial peroxidase membrane.[902] Measurement of oxygen generated in the latter system defines the L-lysine content of a sample.[903]

More conventional biosensor studies also appear in the current literature, often leapfrogging existing technology, but usually adding further illustration of established methods. A 'micro-enzyme sensor', based on immobilized L-amino acid oxidase, has been proposed for the quantitation of L-amino acids in urine,[904] and a combined L- and D-amino acid oxidase version assays total D- and L-amino acids.[905] The immobilization of a peroxidase with a D-amino acid oxidase on an electrode measures D-amino acid concentrations in proportion to H_2O_2 liberated.[906] A process for the electrodeposition of poly(tyramine) on to electrodes provides amino groups through which an L-amino acid oxidase can be immobilized to give satisfactory sensors.[907] An estimation of D-amino acids is based on the formation of D-norleucine by bacterial D-amino acid transaminase coupled with 2-oxohexanoic acid.[908]

The majority of current amino acid–biosensor reports concern L-glutamic acid and its relatives, with immobilized glutamic acid oxidase[909] linked through glutaraldehyde to an aminopropyl-platinized platinum wire, for amperometric measurements.[910] A similar glutarate-immobilized glutamic acid oxidase + glutaminase sensor permits amperometry of glutamic acid and glutamine, which

together with lactic acid can be estimated as a total entity using rhodinized carbon electrodes.[911] The list is completed by an L-glutamic acid + NADH sensor,[912] a glutamic acid decarboxylase-coated electrode,[913] and an L-glutamine sensor comprising kidney slices and an ammonia-sensing electrode.[914]

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