1
Amino Acids

By GRAHAM C.BARRETT

1 Introduction

The 1993 literature covering the chemistry and biochemistry of the amino acids, is dealt with in this Chapter. The approach taken in all previous Volumes of this Specialist Periodical Report continues to be relevant, and therefore the coverage in this 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 almost wholly 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. The coverage in this Chapter is arranged into sections as used in all previous Volumes of this Specialist Periodical Report, and major Journals and *Chemical Abstracts* [to Volume 120 (1994), issue 11] have been scanned to provide the material surveyed here. Where it is helpful to refer to earlier Volumes of this Specialist Periodical Report, the formula "(Vol. XX, p. YY)" is used.

For most of the papers cited, description is brief so that adequate commentary can be offered for particular papers describing significant advances in synthetic and analytical methodology, with mechanistically-interesting chemistry being given prominence.

2 Textbooks and Reviews

IUPAC/IUB Nomenclature Recommendations ("Nomenclature and Symbolism for Amino Acids and Peptides, 1983"; see Vol.16 of this Specialist Periodical Report, p.387) have recently been seen to contain three errors (one, in the systematic name for leucotriene D; another, the omission of indication of cyclization through side-chains in the peptide Ala-Thr-Gly-Asp-Gly; and the third, a typographical error),[1] and textbook representations of more subtle stereochemical details of protein amino acids are almost always erroneous.[2] Broad coverage of the recent literature on the chemistry of the amino acids has appeared in a classic organic chemistry series.[3]

Reviews have appeared covering synthetic applications of L- or D-amino

acid esters as chiral auxiliaries,[4] properties and synthesis of 1-aminocyclopropanecarboxylic acids,[5] uses of α-amino-β-hydroxy acids in the total synthesis of aminosugars,[6] synthesis of non-natural amino acids,[7] uses of pyroglutamic acid in the synthesis of near relatives,[8] the reaction of aldehydes with tryptophan giving toxic derivatives (causing eosinophilia-myalgia syndrome; see Vol. 24, p. 58),[9] and the role of β-methylamino-L-alanine in neurodegenerative disorders.[10] The effects of thiol-containing amino acids and peptides in interacting with food toxicants, has been reviewed.[11] Many relevant reviews have appeared in a Conference Volume, including the origin of life and the role of amino acids,[12] recent advances in the biochemistry of amino acids,[13] post-translationally-modified amino acids as constituents of proteins,[14] aldosine (a new crosslink in collagen and in elastin) and oxodesmosine (a new crosslink present in elastin, derived from deaminated lysine residues of tropelastin)[15] and the presence of o-bromophenylalanine in sea urchin eggs, in free form and as its m- and p-isomers in peptides, and bromohistidine in the same source.[16]

3 Naturally Occurring Amino Acids

3.1 Isolation of Amino Acids from Natural Sources

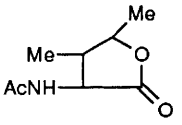
All fermentative processes for the production of amino acids involve routine isolation of the product; or the separation of mixtures of amino acids, as the concluding stage, but this section does not cover this topic, it is intended to deal with rather more subtle aspects, particularly those unexpected outcomes of otherwise straightforward techniques.

Protein hydrolysates may deliver partly-racemized components, which can be eliminated (< 0.002%) through partial chemical hydrolysis (6M HCl/15 min/80-90°C) followed by enzyme-catalysed lysis, first by pronase at 50°C during 12-16h, then leucine aminopeptidase and peptidyl D-amino acid hydrolase during 24h.[17] Microwave heating completes 6M HCl hydrolysis of proteins within 10-20 min as the first stage in an automated protein analysis system.[18] Cystine-containing proteins yield cysteine when subjected to reductive hydrolysis (6M HCl/110°C/0.1% phenol/5% thioglycollic acid/18h), and special attention has been given to ion-exchange chromatographic separation of cysteine from proline in such hydrolysates.[19]

Isolation in the form of its lactam, of γ-(N-propylamino)but-3-enoic acid, employs matrix–solid phase dispersion.[20] Advantages of displacement ion-exchange chromatography of amino acid mixtures have been reviewed, and persuasively illustrated for the preparative-scale separation of valine from isoleucine by displacement with aqueous ammonia from strong acid cation exchangers.[21] On a production scale, a multi-stage fluidized ion exchange bed has been described for amino acid separation.[22]

3.2 Occurrence of Known Amino Acids

This Section is restricted to unusual and/or significant results, to the exclusion of the vast continuing literature covering the familiar amino acids.



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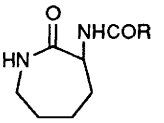
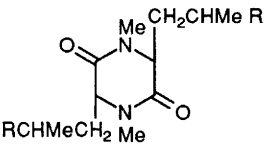
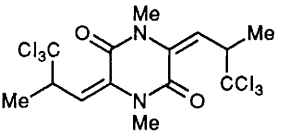


(2)

Caprolactin A:
R = $-(CH_2)_5CHMe_2$
Caprolactin B:
R = $-(CH_2)_4CHMeEt$



(3; R = $-CHCl_2$ or $-CCl_3$)



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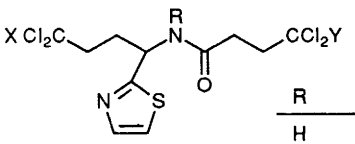

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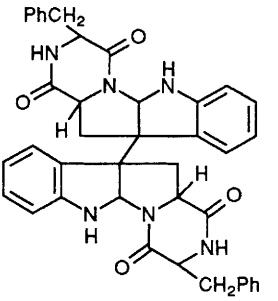
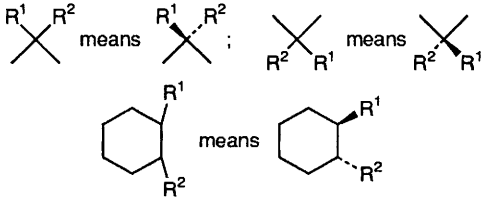
R	X	Y
H	Cl	Cl
Me	Cl	Cl
Me	Cl	H
H	Cl	H
Me	H	H



(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:

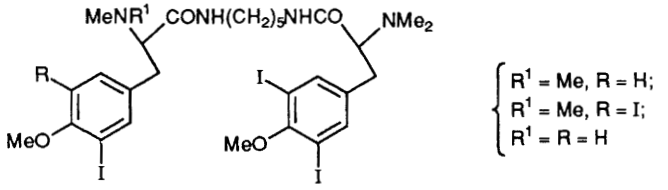


The family of aplyorines, potent anti-tumour compounds from the sea hare *Aplysia kurodai*, carry esterified NN-dimethylserine O-methyl ether and NN-dimethylglycine within their structures.[23] The aerial parts of *Desmodium styracifolium* contain desmodilactone (1).[24] Arthonin, a lichen metabolite of *Arthonia endlicheri*, has been formulated as the ester of N-benzoyl leucinol with N-benzoyl-L-isoleucine, while isoarthonin is the corresponding amide.[25] Further newly-located, though known, compounds have been established in that far more familiar plant source, garlic, now seen to contain the glycoside (-)-N-(1'-deoxy-1'-β-D-fructofuranosyl)-S-allyl-L-cysteine sulfoxide as well as (+)-S-allyl-, (+)-S-methyl-, and (+)-S-(trans-1-propenyl)-L-cysteine sulfoxide.[26] It is comforting to those who enjoy this food accessory, and seek medical rather than aesthetic reasons to justify its inclusion in their diet, that the glycoside showed some inhibition of platelet aggregation *in vitro*. 4-Chloro-L-tryptophan has been located[27] in immature seeds of *Pisum sativum*, and accompanied by its N-malonyl derivative (formerly assigned the D-configuration). Other stereochemical re-assignments concern the polyoxin constituent polyoximic acid (whose side-chain has the cis-configuration rather than trans),[151] and anticapsin (whose C-4 configuration is S).[28]

Protein constituents arising through post-translational modifications have been surveyed (see also reviews cited in Section 2).[29] These include glycosylated, phosphorylated, and sulfated derivatives of well-known protein amino acids, and desmosine, allo-desmosine, hydroxylysylpyridinoline, 3-hydroxypyridinium compounds, cyclopentenosine, and other modified lysines, dityrosine, and the novel tyrosine-derived pulcherosine. o-Tyrosine and the aromatic ether, dityrosine, arise in proteins during radiolysis and through H_2O_2/Cu^{++} oxidation,[30] and evidently survive long storage, since dityrosine has been identified in the collagen content of the Dead Sea Scrolls.[31] Lysinoalanine formation has been reviewed.[32]

3.3 New Naturally Occurring Amino Acids

Previously unknown close relatives of the familiar α-amino acids include the antifungal antibiotic β-cyano-glutamic acid, from *Streptomyces* sp. K749-42, particularly effective against *Candida albicans*,[33] and N^2-(2-carboxyethyl)-arginine and N^2-(2-carboxyethyl)-3-hydroxyarginine, produced by a blocked mutant of *Streptomyces clavuligerus* dclH65.[34] The novel arginines are possibly intermediates in the biosynthesis of clavulanic acid. Caprolactins A and B (2) are new caprolactams from an unidentified gram-positive bacterium, showing anti-viral and cytotoxic properties.[35] Another common type of cyclized aliphatic amino acid is the di-oxopiperazine family, represented in dysamides A-C (3) and corresponding dehydro-amino acid analogue (4) from the marine sponge *Dysidea fragilis*,[36] and in corresponding compounds from *Tolypocladium* sp., in which α-(methylthio)glycine and O-(3-methylbut-2-enyl)-α-(methylthio)-D-tyrosine are condensed together,[37] and dysideathiazole (5), in which the α-carboxy group has been modified to the thiazole moiety, from *Dysidea herbacea*.[38] The previously-known N^1-methyl albonoursin, a weakly antibiotic factor from a *Streptomyces* sp. from perennial rye grass,[39] and the C_1-symmetric WIN 64821



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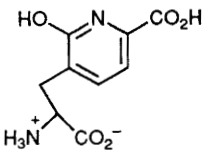

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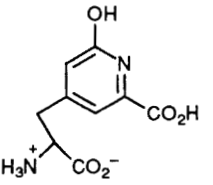

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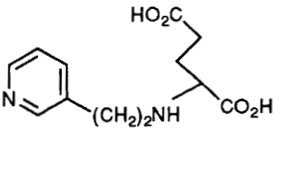

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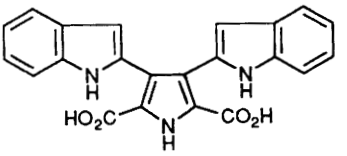

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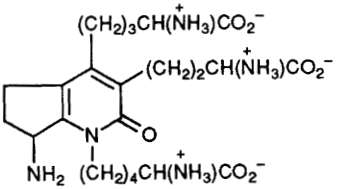

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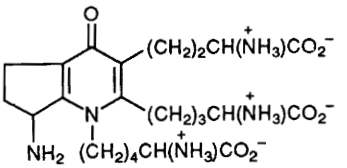

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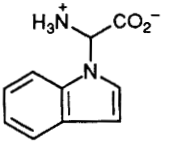

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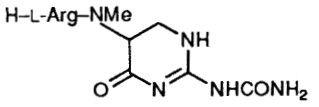

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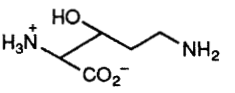


(16)

(6), a new competitive antagonist for Substance P, from *Aspergillus*,[40] have been reported.

Other new aromatic and heteroaromatic α-amino acids (unusually abundant in this year's literature), are the tyrosine derivatives (7) from *Aplidium* sp. (colonial ascidians),[41] and pyridyl-L-alanines (8, 9) and -L-glutamic acid (10) from *Clitocybe acromelalga*, whose existence is consistent with the proposed biogenesis of acromelic acids.[42] threo-β-Hydroxy-L-histidine has appeared as a component of a new pyoverdine-type siderophore (Vol.24, p.5) from the culture filtrate of *Pseudomonas fluorescens* 244, functioning as a bidentate ligand for ferric ions.[43] Chromopyrrolic acid (11) from a *Chromobacterium violaceum* mutant, is a new tryptophan metabolite.[44]

3.4 New Amino Acids from Hydrolysates

This section encompasses natural products from which new amino acids can be released by hydrolysis or similarly simple chemistry.

Two new crosslinking α-amino acids, oxodesmosine (12) and iso-oxodesmosine (13), from bovine aorta elastin, contain the oxopyridine moiety but are otherwise closely similar to the well-known desmosines from the same source.[45] These are probably metabolic intermediates *en route* to the major pyridinium crosslinks of elastin.

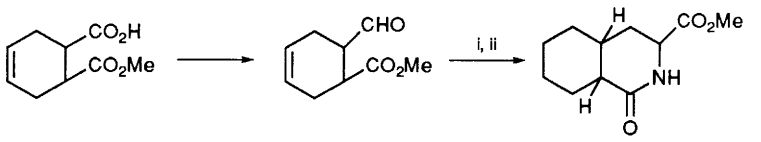
Novel amino acid residues with nitrogen functional groups in side-chains have been reported; the novel α-aminoglycine derivative (14) in lyciumins A-D, cyclic peptides from *Lycium chinense Mill.* (Solonaceae)[46] and the unusual component of the dipeptide antibiotic TAN-1057A (15) isolated from *Flexibacter* sp. PK-74.[47] The oxidative ozonolysis product of cylindramide, a novel cytotoxic tetramic acid lactam from the marine sponge *Halichondria cylindrata*, has been shown to include (2S,3S)-erythro-β-hydroxy-L-ornithine (16).[48]

New β-amino acids have been reported, (2S,3R)-2-methyl-3-aminopentanoic acid as a component of the cyclic depsipeptide metabolite majusculamide C from the alga *Lyngba majuscula*,[49] and a complex β-tyrosine constituent of Antibiotic C-1027.[50] Dolastatin D, a new depsipeptide from *Dolabella auricularia*, contains (2R,3R)-3-amino-2-methylbutanoic acid, not previously found in Nature.[51]

4 Chemical Synthesis and Resolution of Amino Acids

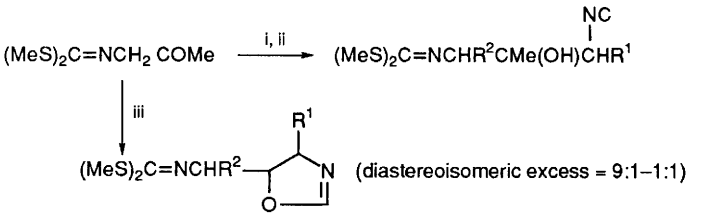
4.1 General Methods for the Synthesis of α-Amino Acids

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. 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, asymmetric synthesis methods are nearly always "general methods of synthesis" too, and so are reactions by which one amino acid is used as starting material for the



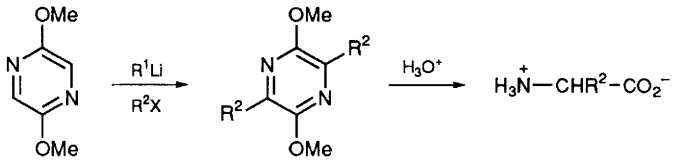
Reagents: i, PhCH=NCH=C(OMe)OLi; ii, H_2/Pd

Scheme 1



Reagents: i, R^1CH_2NC, $KOBu^t$/THF; ii, MeOH; iii, $CNCH_2CO_2Et$

Scheme 2



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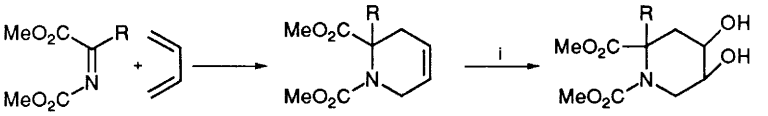


Reagent: i, OsO_4

Scheme 3

synthesis of another (these reactions are mostly covered in the later Section 6.3: Specific Reactions of Amino Acids).

The acetamidomalonate synthesis [$AcNHCH(CO_2Et)_2$ + RX → $AcNHCR(CO_2Et)_2$ → $H_3N^+CHRCO_2^-$] remains the most popular of the glycine alkylation methods, described in the recent literature. Examples of novel variants include new synthesis of 5-bromotryptophan (from 5-bromo-3-methylindole, after N^{im}-benzenesulfonylation and conversion into the bromide with NBS),[52] similar preparation of 3-(carbazol-2- or -3-yl)-DL-alanines from 2- or 3-methylcarbazoles,[53] and Mn(III) acetate-induced addition of conjugated alkenes.[54] The recent literature has many illustrations of forays by Chinese workers into phase-transfer-catalysed examples of this process.[55] N-Boc-L-(2-Bromoallyl)glycine has been prepared by the acetamidomalonate method.[56] The related formamidomalonate route has led to a carboranyl-substituted phenylalanine through alkylation by a 1,2-dicarba-*closo*dodecaborane-substituted benzyl bromide.[57] Ref.162 describes a similar use of isocyano-acetates, and uses for α-bromoglycine are continuing to be favoured (e.g. Ref.189).

Preparation of α-acylamino-β-oxocarboxylic acid esters can be achieved through the above route [$AcNHCH(CO_2Et)_2$ + RCOX + 2 BuLi][58] and also through acylation of glycine Schiff bases [$PhCH=NCH_2CO_2Me$ + RCOX + $KOBu^t$] (see also Refs.169, 208).[59] This is the basis of several related syntheses, both of a simple nature (alkylation by an alkyl halide is complete in 1 minute by a microwave-mediated solid-liquid phase-transfer-catalysed system without solvent),[60] and for more complex targets (Scheme 1).[61] Di-alkylation of the Schiff bases is easier than has been supposed under phase-transfer catalysis.[62] The analogous imines $(MeS)_2C=NCH_2CO_2Me$ undergo alkylation by isonitriles (Scheme 2) with an unusual outcome.[63] Hidden versions of the same procedure include alkylation of 2,5-dimethoxypiperazines (17) derived from glycine methyl ester.[64] The last-mentioned route is illustrated through a "difficult" synthesis, of t-leucine ($H_3N^+CHBu^tCO_2^-$).

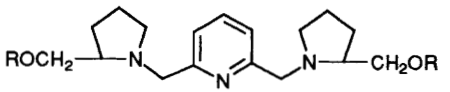
The other version of imine alkylation that can be envisaged for α-amino acid synthesis [alkylation of $R^1N=CHCO_2R^2$ + RZnBr → $R^1N=CRCO_2R^2$ (R^1 = Me_3SiOCH_2CHEt-)[65]] has also been put to use. An aza-Diels-Alder process using an aldimine (Scheme 3) starts a route to (±)-baikiain.[66] The applications of the nucleophilic alkylation of imines for the synthesis of uncommon amino acids has been reviewed.[67]

Hippuric acid alkylation, *via* its cyclized form [2-phenyloxazol-5(4H)-one], using 4-formyl(2,2'-bipyridine)[68] or 3,4-dimethoxybenzaldehyde,[69] provides 2-amino-3-(2,2'-bipyridin-4-yl)propanoic acid and DOPA, respectively.

The hydantoin synthesis (see also Refs. 168, 233) is particularly suited to the preparation of -α-disubstituted α-amino acids, illustrated for the preparation of geometrical isomers (the trans-isomer receives its first synthesis) of 1-amino-1,2-cyclopentanedicarboxylic acid fortuitously facilitated by epimerization during the hydrolysis of the Bucherer-Bergs reaction product.[70]

The Strecker synthesis is represented in later Sections (Refs. 78, 161, 270).

Amination procedures continue to come into their own, illustrated by azidolysis of methanesulfonyloxy-amides,[71] and of 1-alkenylcyclopropyl toluene-



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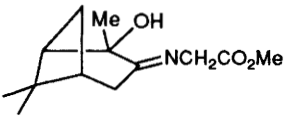

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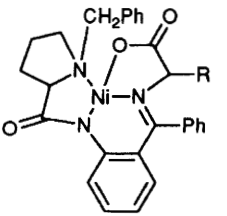

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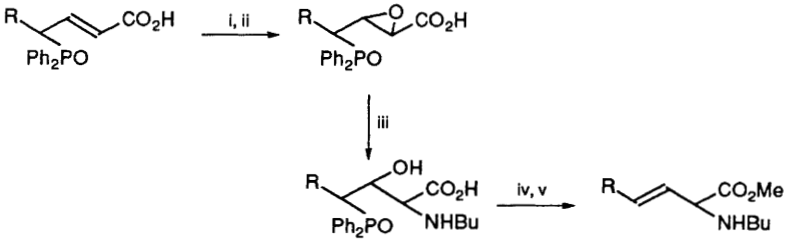
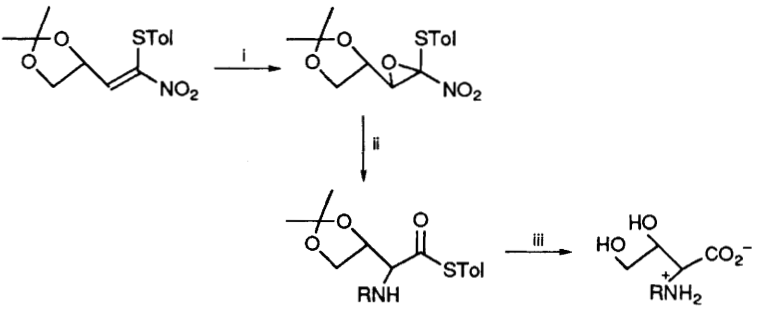


Reagents: i, $Bu^tOOH/Ti(OPr^i)_4$; ii, $RuO_4/NaIO_4$; iii, $BuNH_2$; iv, KOH; v, CH_2N_2

Scheme 4



Reagents: i, $Li^+ {}^-OOBu^t$ ⟶ *syn* ; KH-Bu^tOOH ⟶ *anti* (preferentially);
ii, RNH_2; iii, H_3O^+

Scheme 5

p-sulfonates [Pd(0)-catalysed, leading to "2,3-methano-amino acids", *alias* 1-aminocyclopropane carboxylic acids; see later Section 4.5][72] and reductive amination of glyceric acid (Ru-Pd/C) to give serine.[73] An extraordinary amination procedure using a molybdenum nitride complex, trans-[MoCl(N)$(Ph_2PCH_2CH_2PPh_2)_2$], has been used to prepare correspondingly-complexed glycine and alanine ester ylides by reaction with α-iodoalkanoates, the amino acid ester being released by electrochemical Mo-N cleavage.[74] Pd(0)-Catalysed amination of allyl acetates [RCH=CHCH(OAc)R' → RCH=CHCH(NR_2)R' → $MeO_2CCH(NR_2)R$] followed by ozonolysis at -78°C in MeOH gives methyl esters of α-amino acids.[74a] Many more examples of amination, and of other general methods of amino acid synthesis (e.g. the Gabriel synthesis[97, 272]), are located in the following section.

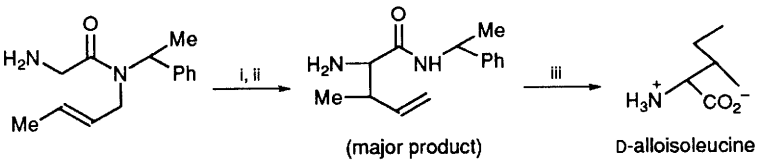
4.2 Asymmetric Synthesis of α-Amino Acids

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 re-presented here in "asymmetric versions".

In the last-mentioned category, amination reactions in the presence of homochiral species are represented in a synthesis of L-phenylalanine from phenylpyruvic acid and a mixed ligand copper(II) Schiff base complex formed between pyridoxamine and (18),[75] and in a simple, intriguing synthesis (RCHO + $CHCl_3$ + aqueous NH_3 in the presence of β-cyclodextrin)[76] with enantiomeric excesses at a disappointing level (2.6% for L-phenylglycine and 28.2% in favour of D-phenylalanine) and unpredictable direction of the stereochemical bias.

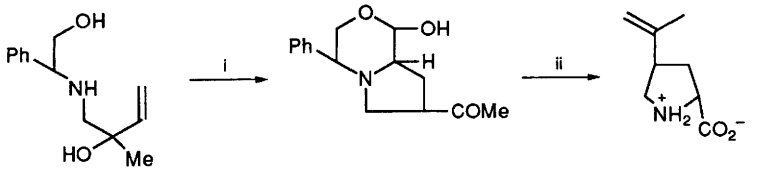
The conventional aldol synthesis of β-hydroxyalkyl-α-amino acids is given an asymmetric bias in an example (PhCHO + glycine → β-phenylserine) conducted in the presence of chiral supramolecular assemblies $[Me(CH_2)_{15}]_2NCO$-Ala-$NHCO(CH_2)_5N^+Me_3$ X^-/N,N-bis(hexadecyl)pyridoxal/Zn^{2+}].[77]

A one-pot asymmetric Strecker synthesis uses a chiral primary amine [RCHMeNH_2 (R = Ph or 2-naphthyl) or 1-amino tetra-O-pivaloyl-D-galactose] as aminating agent with 2,2-dimethylcyclopropane hemiacetal as masked aldehyde, in a synthesis of 2,3-methanovalines in high enantiomeric excess,[78a] and a very similar principle underlies the use of a homochiral α-aminonitrile formed by using a monoterpene ketone as a relay in an otherwise conventional Strecker synthesis of D-α-amino acids from aldehydes.[78b] Other amination reactions of homochiral species leading to homochiral α-amino acids, in which the chirality of the substrate is "transferred" to the α-carbon atom, are increasingly attracting new adherents, for example the route (Scheme 4) starting with an allyl alcohol.[79] Other examples of the genre include nucleophilic epoxidation and aminolysis (Scheme 5)[80] involving treatment of the homochiral epoxide from an allyl alcohol with BocNH_2 and $RuCl_3/NaIO_4$ oxidation of the resulting glycol to give the Boc-amino acid.[81] Aza-Claisen rearrangements (Scheme 6) exemplified in a synthesis of D-alloisoleucine, show excellent syn:anti (98:2) and facial (89:11) selectivities,[82] and an aza-Cope rearrangement combined with Mannich cyclization (Scheme



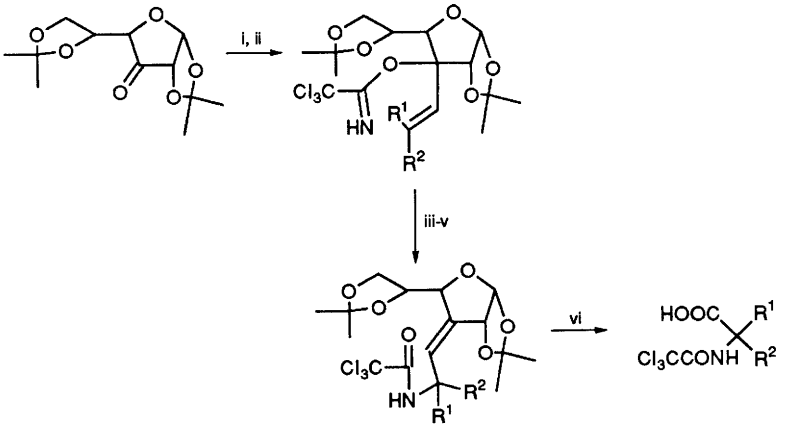
Reagents: i, LHDMS/–78 °C, ii, Δ; iii, H_2/Pd-C, then H_3O^+

Scheme 6



Reagents: i; OHCCHO; ii, H_2/Pd-C

Scheme 7



Reagents: i, $HC{\equiv}C^-M^+$; ii, TMSCl, then MeI/BuLi; desilylate; iii, $LiAlH_4$; iv, H_2O; v, Overman protocol; vi, Sharpless oxidation

Scheme 8

7),[83] yield 3-substituted prolines. The Overman rearrangement has been used (Scheme 8) for asymmetric synthesis of D- and L-alanine and chirally deuteriated glycine,[84] and for D-valine and for a more ambitious purpose in a synthesis of thymin polyoxin C.[85]

The nitrone from D-glyceraldehyde [CHO → $C{=}N^{+}(O^{-})CH_2Ph$], protected as the isopropylidene derivative, reacts with a 2-metallated thiazole to give the corresponding α-(N-benzyl-N-hydroxyaminoalkyl)thiazole. This is the basis of an interesting α-amino acid synthesis, since the thiazole grouping is readily degraded to the required carboxy group; 4-O-benzyl-2,3-isopropylidene-L-threose used in this way leads through routine subsequent steps to 5-O-carbamoylpolyoxamic acid [$H_2NCO_2CH_2CH(OH)CH(OH)CH(NH_2)CO_2H$].[86] It is possible to start with a racemic α-bromoalkanoic acid, aminolysis of the derived (R)-pantolactone esters giving homochiral α-amino acid esters; the reaction appears to incorporate a kinetic resolution so leading to efficient delivery of one enantiomer, though this may need verification.[87] An "asymmetric Gabriel synthesis" has been performed with bornyl esters of 2-bromoalkanoic acids.[97] Enolates of N-acyl sultams undergo stereobiased hydroxyamination [$R^1CH_2CONR^2R^3$ → $R^1CH(NROH)CONR^2R^3$, where $-NR^2R^3$ is an isobornylsultam moiety].[88]

An approach using the same principle, applied to the alkylation of glycine derivatives carrying chiral auxiliaries, continues to find favour, illustrated in the successive bromination (NBS) (Vol.25, p.15) and reduction (Bu_3Sn^2H or (Bu_3SnH) of (-)-8-phenylmenthyl esters of Boc-glycine or Boc-2,2-dideuterioglycine to give both (S)- and (R)-2-^{2}H-glycine in 90% optical yields.[89] (-)-Menthyl N-Boc-α-bromoglycinate acts as radical source in reacting with $Co(Acac)_2$ to give α-(acetylaceton-3-yl)glycine, on which, various five-membered heterocyclic side-chains were constructed, and from which, L-norvaline was obtained to demonstrate the potential of the method.[90]

Both enantiomers of 2-amino-2-methylbutanoic acid ("isovaline") are available through diastereoselective alkylation of (1S,2R,4R)-10-dicyclohexylsulfamoyl isobornyl esters of cyanoacetic acid.[91] The same moiety attached as an amide to N-benzylideneglycine provides the template for synthesis of L-α-(indan-1-yl)glycine and L-α-(benz[*f*]indan-1-yl)glycine.[92] Schiff bases formed between glycine methyl ester and a chiral amine undergo diastereoselective alkylation and aldol reactions, the latter principle illustrated in aldolization of (19) with protected ribose or galactose in the first asymmetric synthesis of glycosyl-β-hydroxy-(S)-α-amino acid esters.[93] The related alkylation of chiral Schiff bases has been thoroughly studied by Belokon's group in the context of the nickel(II) prolylglycine complex (20) and its prolylalanine analogue, with new results for the preparation of fluorinated (S)-phenylalanines in greater than 90% enantioselectivity,[94] and of (S)-2-amino-4-phosphonobutyric acid and (S)-2-amino-5-phosphonovaleric acid.[95] Conference Reports covering this work have appeared.[96] Further examples (see Vol.25, p.20 and preceding Volumes) of the "double asymmetric induction" procedure, in which phase-transfer-catalysed alkylation of a glycine ester Schiff base in which amino and carboxy groups both carry homochiral substituents, have been published.[97,98]

Glycine Schiff bases yield azomethine ylides with DBU/AgOAc, that add

to chiral enones to yield homochiral prolines (Scheme 9).[99] $SnCl_4$-catalysed asymmetric ene reactions involving (-)-8-phenylmenthyl esters of glycine imines, give L-enantiomers (21) preferentially, considered to be due to blockage of the *re*-face of the imine by the phenyl group.[100]

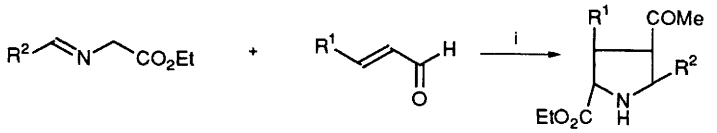
The Schollkopf piperazinedione alkylation procedure, and its more recent variants, are used year after year both by the originators and increasingly by others. The original form of the procedure is now used less for asymmetric synthesis of α-amino acids, but the acetylated synthon (22 in Scheme 10) shows wider usefulness, for example in allowing α-bromination (NBS)[101] and in facilitating aldolization with PhCHO *en route* to 2,3-methanophenylalanine methyl ester.[102] An extraordinary variant involving alkylation (RBr/LiHDMS/THF) of the analogous bis[N-(S)-phenylethyl]-(3S)-3-methyl piperazinedione gives better than 98% diastereoisomeric excess in up to 96% reaction yields.[103] Curiously, the (3R)-epimer performs less well. The bis-lactim ether used in a popular variant of this procedure was chosen for syntheses of β-trimethylsilyl-D-alanine (Scheme 11),[104] L-2-amino-4-phosphonobutanoic acid (see also Ref.255),[105] and anticapsin.[29] The mild conditions (aqueous TFA) for ring-opening with release of the amino acid in the form of its ester were exploited in a synthesis of D-phenylalanine benzyl ester (better than 95% enantiomeric excess).[106]

The continuing interest in enantioselective homogeneous-catalysed hydrogenation of α,β-unsaturated α-amino acids has been demonstrated recently in results for enantiomeric excesses of a modest level (43% for N-benzoyl-L-phenylalanine ethyl ester using H_2/BICHEP-Ru(II) complexes[107] to very high levels with related chiral phosphines for cinnamates with Rh complexes[108,109] or Rh or Ni analogues[110] and analogous acylamino(thienyl)acrylic acids,[111] and ferrocenylalanine[112] using Rh-chiral phosphine complexes. Rh-Cyclo-octadiene complexes catalyse asymmetric hydrogenation of N-acyl dehydro-amino acids when in the presence of 2,3-bis(O-diphenylphosphinyl)-D-glucose ethers.[113] The general topic has been reviewed.[114]

Extending the principle to β-keto-esters through subjecting them to asymmetric hydrogenation (chiral Ru complexes) and amination with di-t-butyl azodicarboxylate leads to anti-N-Boc-α-hydrazino-β-hydroxyesters (23).[115] Cyclic α-hydrazino acids are formed diastereoselectively, by aza-Diels-Alder addition (Vol.25, p.17) of azodicarboxylates to homochiral esters ROCH=CHCH=$CHCO_2R'$ (R' = tetra-O-acetyl-D-glucopyranos-1-yl).[116]

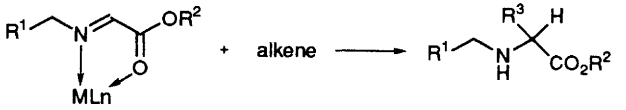
Nucleophilic addition to chiral imines provides a near analogy to the hydrogenation process, but previous results have not been as encouraging as those (90-96% enantiomeric excess) for additions of organolithium or Grignard reagents ($CeCl_3$ catalysis) to (24).[117] Reductive cleavage (Raney nickel) leading to D-alanine is used to illustrate an asymmetric synthesis.

The uses of Evans' chiral oxazolidin-2-ones in the asymmetric synthesis of amino acids have been illustrated in a synthesis of all stereoisomers of O-methyl 2',β-dimethyltyrosine incorporating some beneficial modifications (Scheme 12) to the usual procedure.[118] The same methodology has been used for β-methyltyrosine and has been described as incorporating an asymmetric Michael-like 1,4-



Reagent: i, AgOAc, DBU

Scheme 9



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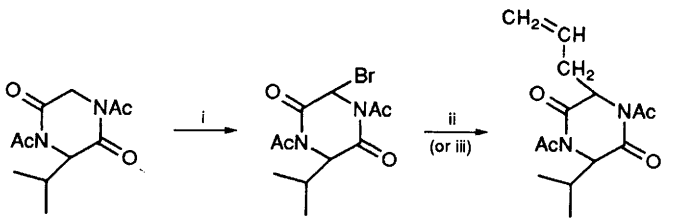
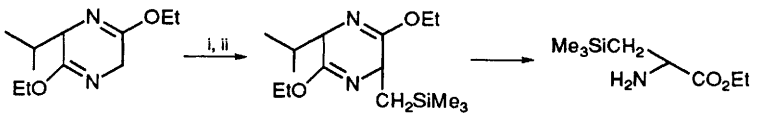


(22)

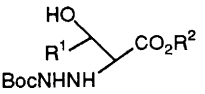
Reagents: i, NBS; ii, $CH_2{=}CHCH_2SnBu^n{}_3$; iii, $^2H_2/PdCl_2 \longrightarrow {}^2H$ in place of $CH_2{=}CH\text{-}CH_2$

Scheme 10



Reagents: i, BuLi; ii, Me_3SiCH_2Cl

Scheme 11



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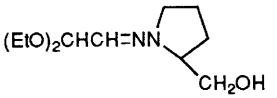
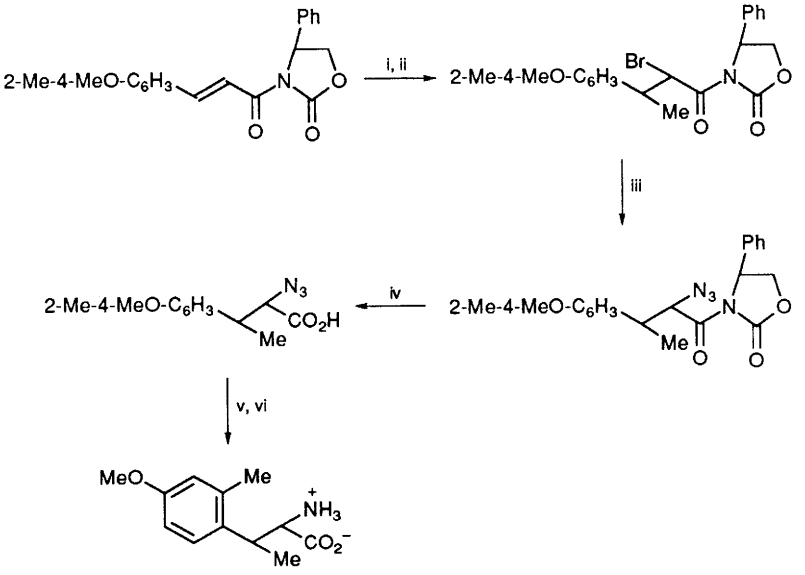


(24)



erythro -L-isomer

Reagents: i, MeMgBr,CuBr.SMe_2; ii, NBS; iii, tetramethylguanidinium azide; iv, LiOH, H_2O; v, Pd-C/H_2; vi, ion exchange chromatography

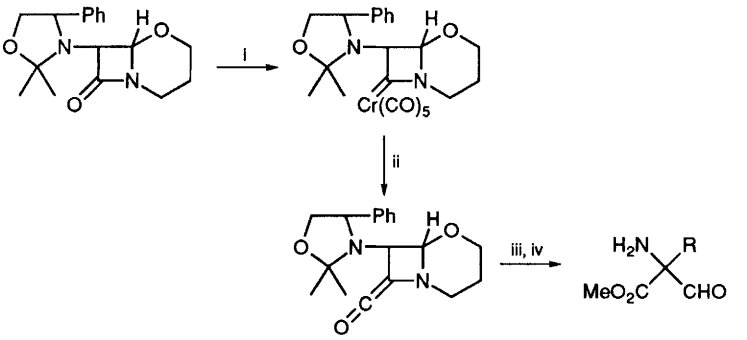
Scheme 12

addition.[119] Rather more complicated versions of the procedure are involved in useful asymmetric syntheses of α-alkyl-, -alkenyl-, and -alkynyl-α-amino acids (Scheme 13) through photolytic rearrangement (Vol.25, p.17) of oxazolidine carbene Cr complexes,[120] and in syntheses of polychlorinated threonines (Scheme 14), including the previously known (2S,3S)-4,4-dichloro-2-amino-3-hydroxybutanoic acid.[121] The four stereoisomers of 3-hydroxyleucine have been synthesized starting with Sharpless oxidation of (E)-4-methylpent-2-en-1-ol and $PhCH_2NCO$-induced epoxide opening to give the 4-(2-hydroxy-3-methylpropyl)-N-benzyloxazolidin-2-one.[122] An interesting feature of this synthesis, concluded by Jones' oxidation (leading to recyclization to 4-carboxy-5-isopropyloxazolidinone) and de-protection, is the propensity towards epimerization of the intermediate oxazolidinone. Synthesis of the pyrimidoblamic sub-unit of bleomycin A_2 has been modelled by stereocontrolled introduction of the C-2 acetamidomethyl side-chain through alkylation of the stannous (Z)-enolate of the oxazolidin-2-one (25).[123] The "chiral vinyl anion" equivalent, (S)-$MeOCH_2CH_2OCH_2OCHMeCH=CBr_2$, has been used to convert an imine 1,3,5-$Me_3SO_2C_6H_2N=CHR$ into the corresponding homochiral α-amino aldehyde 1,3,5-$Me_3SO_2C_6H_2NHCHRCHO$, for the purpose of synthesis of homochiral oxazolidin-2-ones (26; R^1 = 2,4,6-$Me_3C_6H_2$-, R^2 = CMe_2CO_2Me).[124]

An "Org.Synth." has been published[125] for the standard method for exploitation of oxazolidin-5-ones in this area, based on the earliest report on the introduction of the method[126] The "dehydro-alanine" oxazolidin-5-one (27) undergoes gem-dimethylcyclopropanation with $Ph_3P=CMe_2$ to give unequal proportions of (S)- and (R)-"methanovaline" (*alias* 2,2-dimethyl-1-aminocyclopropane-1-carboxylic acid).[127]

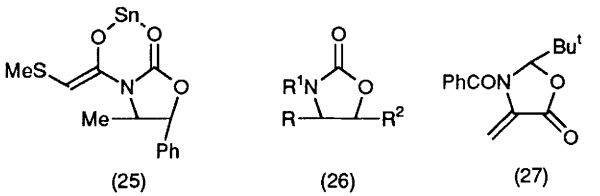
Corresponding uses for imidazolidinones (28 in Scheme 15)[128] and pyrrolidines (29 in Scheme 16)[129] indicate the value of five-membered heterocycles as chiral auxiliaries. Further results (Vol.24, p.12) for the $Hg(OTFA)_2$-catalysed cyclization of homochiral amidals to 2,5-trans-imidazolin-4-ones in a synthesis of D-α-amino adipic acid illustrate the potential of this method.[130] The six-membered analogues have already established a competitive foothold in the same area of applications, with morpholin-2-ones being employed in the enantioselective synthesis of α-alkyl-α-amino acids[131] and in continuing studies (see Vol. 25. p.36) of applications of the cycloaddition reactivity of their derived azomethine ylides with alkenals and alkynals, for the synthesis of prolines of high enantiomeric purity.[132] 2-Substituted pipecolic acids have been synthesised from chiral morpholin-2,5-diones prepared using a chiral α-hydroxyacid (30 in Scheme 17).[133]

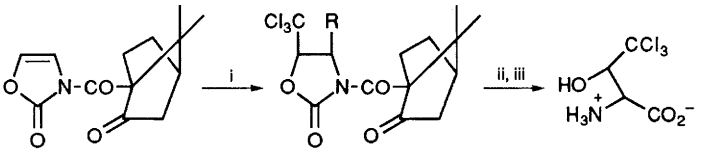
Applications of enzymes for the synthesis of α-amino acids can extend beyond the fermentative production methods used for the production of the familiar coded amino acids, covered in the next Section. This small topic area is represented in the recent literature by lipase-catalysed hydrolysis of (±)-3-benzyloxy-4-hydroxy-Δ^2-isoxazoline butyrate and conventional work-up to provide cycloserine enantiomers,[134] and (R)- and (S)-oxynitrilase-catalysed enantioselective addition of HCN to aldehydes, with incomplete enantioselectivity in forming the cyanohydrins, from which α-amino acids are easily accessible.



Reagents: i, $Cr(CO)_6$; ii, *hν*; iii, MeOH; iv, H_2/Pd-C

Scheme 13

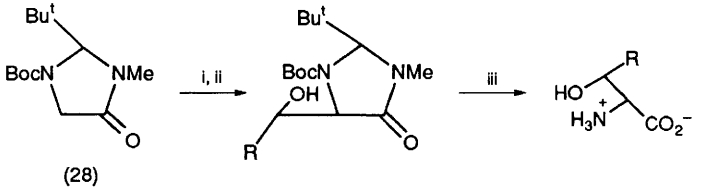




(4*S*, 5*R*) + (4*R*, 5*S*)

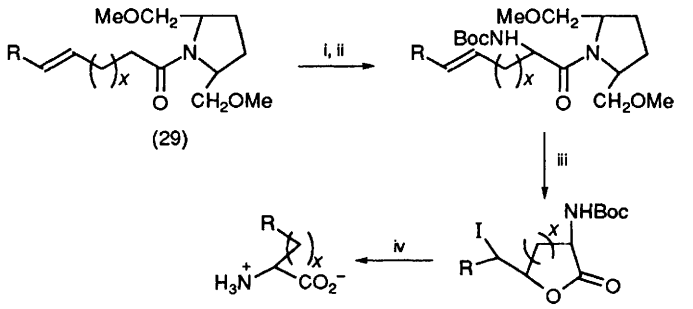
Reagents: i, CCl_4 or CCl_3Br/radical initiator; ii, separate diastereoisomers; iii, H_3O^+

Scheme 14



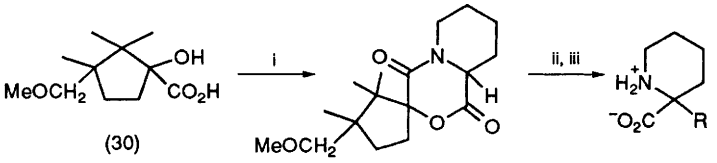
Reagents; i, RCOCl; ii, $LiBHEt_3$; iii, H_3O^+

Scheme 15



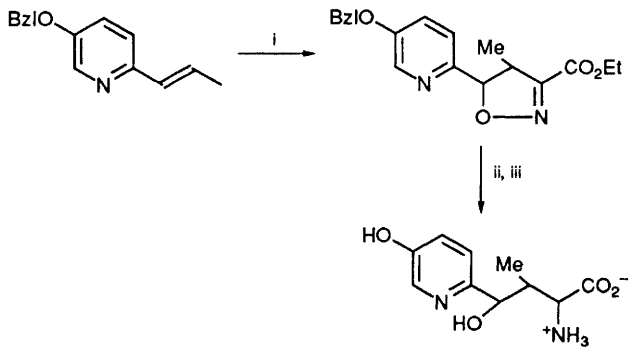
Reagents: i, I_2-Collidine; ii, $BocNH_2$; iii, I_2-EtOH/H_2O; iv, Zn/THF, then routine deprotection steps

Scheme 16



Reagents: i, condense with pipecolic acid; ii, R^1Li; iii, RBr

Scheme 17



Reagents: i, (*Z*)-$EtO_2CCCl{=}NOH$; ii, Zn, Cu/AcOH; iii, deprotection

Scheme 18

Improved optical yields result from the presence of organic solvents in the reaction media.[135]

4.3 Synthesis of Protein Amino Acids and Other Naturally Occurring α-Amino Acids

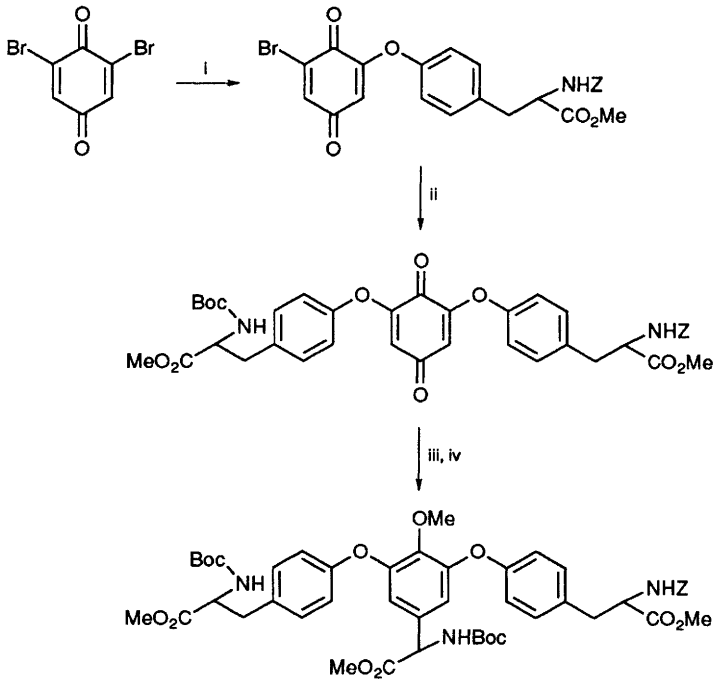
This Section concentrates on laboratory synthesis, but fermentative production of the familiar protein amino acids and near relatives constitutes its opening paragraph, as it has done over recent years and with an ever more perfunctory coverage of the burgeoning literature, now mostly emanating from Pacific Rim countries. This topic has an increasingly routine nature but the full literature can be easily accessed through Section 16: Fermentations and Bioindustrial Chemistry of *Chemical Abstracts*. Some contributions in a recent text deal with this area, represented by a review of membrane bioreactors for the production of L-amino acids,[136] production of L-lysine by asymmetric transformation of α-amino-ε-caprolactam,[137] production of homochiral protein amino acids through the use of aminotransferases,[138] and a review of methods for the production of natural and non-natural homochiral amino acids.[139] Production of L-DOPA continues to be an active area of research, with descriptions of interesting routes from catechol, pyruvate, and ammonia, one using *Escherichia coli* into which had been cloned the gene encoding tyrosine phenol-lyase from *Erwineia herbicola*[140] and the other, an economical and high yielding route using polyphenol oxidase from banana leaf.[141] *Escherichia coli* accomplishes the conversion of pyrrol-1-ine 2-carboxylic acid into L-proline.[142]

Simple syntheses have been described for threonine (copper glycinate and acetaldehyde)[143] glutamic acid (from cyclopentadiene by successive addition of HCl, ozonolysis, ammonolysis, and hydrolysis).[144] A convenient synthesis of L-α-amino-adipic acid starts with (S)-hexahydro-3-phthalimido-2H-azepin-2-one.[145]

A new synthesis (Scheme 18) of the pyridyl γ-hydroxy-α-aminobutanoic acid component of Nikkomycin Z, has been developed by authors who were unable to reproduce a nitrile oxide addition step in a previous synthesis.[146] Further syntheses of antibiotic components include the bicyclo-C,D,E-diphenyl ether component of vancomycin (Scheme 19)[147] and the component ISP-1 (*alias* myriocin or thermozymocodin) of a recently-isolated immunosuppressant (Scheme 20).[148]

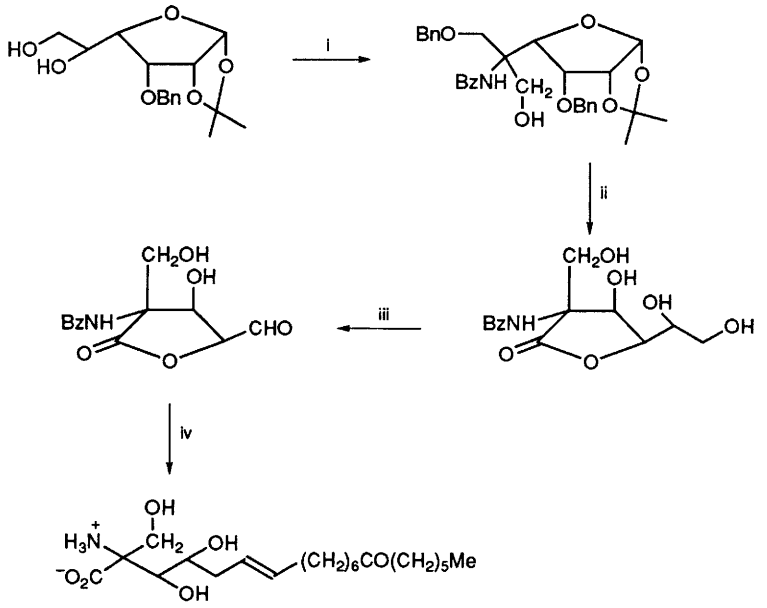
Alicyclic α-amino acids that derive from natural sources include ring sizes from 3 to 6 in this year's literature, which at the small ring end, is represented by 3-(trans-2'-nitrocyclopropyl)alanine (a constituent of the peptide lactone hormaomycin). The (±)-compound has been synthesized in three steps from t-butyl acrylate, and the (1'S,2'R)- and (1'R,2'R)-isomers (31 in Scheme 21) synthesized in six steps from (S)-2,3-isopropylidene glyceraldehyde.[149] Carnosadine (32) has been prepared from the corresponding cyclopropylmethanol.[150]

A notable synthesis from D-serine O-t-butyldiphenylsilyl ether, of cis-polyoximic acid (Scheme 22), now known to be the natural isomer after a correction of the literature, has been reported.[151] The non-natural (-)-isomer of polyoxamic acid has been synthesized starting from the N-benzyl β-lactam (33).[152] A rearrangement in a synthesis (Scheme 23) of (+)-monomorine, an



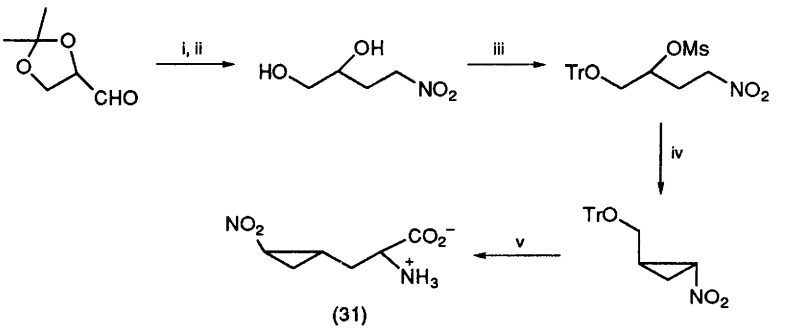
Reagents: i, ii, protected L-tyrosine/6 eq. KF/DMF/90 °C; iii, $Na_2S_2O_4$, selective conversion of OH to $-CH{=}CH_2$; iv, $CH{=}CH_2 \longrightarrow$ L-$MeO_2CCHNHBoc$ by standard methods

Scheme 19



Reagents: i, extended sequence of standard functional group manipulations; ii, $RuCl_3/NaIO_4$; iii, iv, *J.Chem. Soc., Perkin Trans. 1,* 1983, 1613

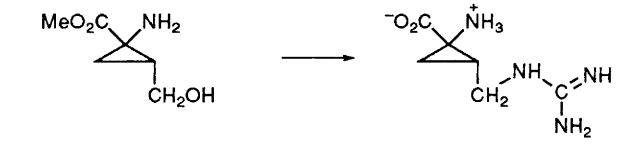
Scheme 20



(31)

Reagents: i, $MeNO_2/KF$, then Ac_2O/DMAP and $NaBH_4$; ii, TsOH; iii, OH group protection; iv, Na_2CO_3–toluene/110 °C/15h; v, $-CH_2OTr \longrightarrow CH_2Br$, then $Ph_2C{=}NCH_2CH_2CO_2Bu^t$/BuLi and routine deprotection

Scheme 21



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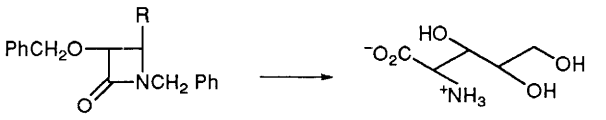
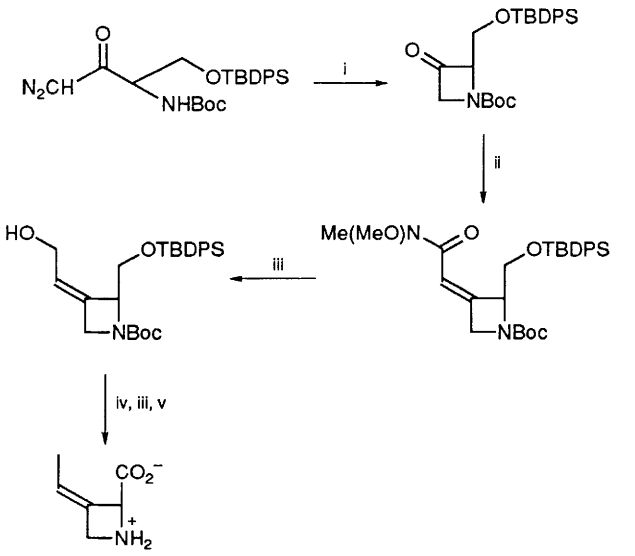
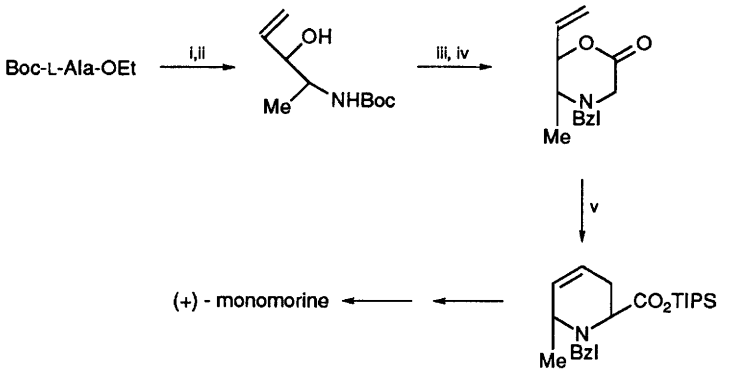


(33; R = D-mannitol residue) (–)-polyoxamic acid



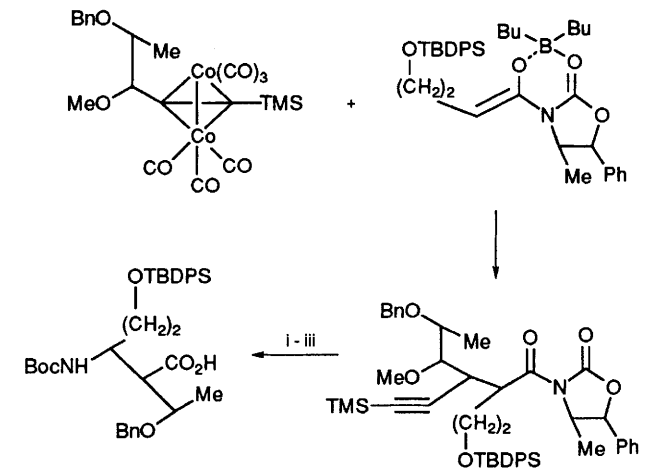
Reagents: i, $Rh_2(OAc)_4$; ii, NaH, (*N*-methoxy-*N*-methyl)-2-(triphenylphosphoranylidene) acetamide ⟶ *trans*:*cis* = 11:89; iii, *cis* ⟶ $LiAlH_4$; iv, CBr_4, PPh_3; v, remove TBDPS, Jones' reagent, remove Boc

Scheme 22



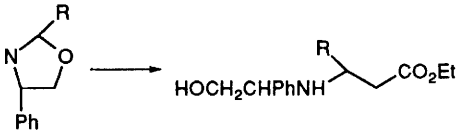
Reagents: i, DIBAL-H; ii, CH_2=CHMgCl; iii, protecting group changes; iv, $BrCH_2CO_2Ph$; v, TIPS-OTf

Scheme 23



Reagents: i, H_2O; ii, Curtius (DPPA/Bu^{t}OH) degradation;
iii, $-C\equiv C- \longrightarrow -CO_2H$ with $OsO_4/NaIO_4$

Scheme 39



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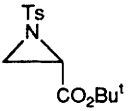

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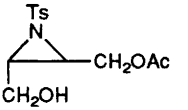

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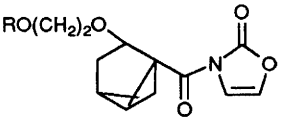

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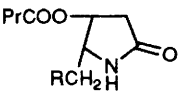

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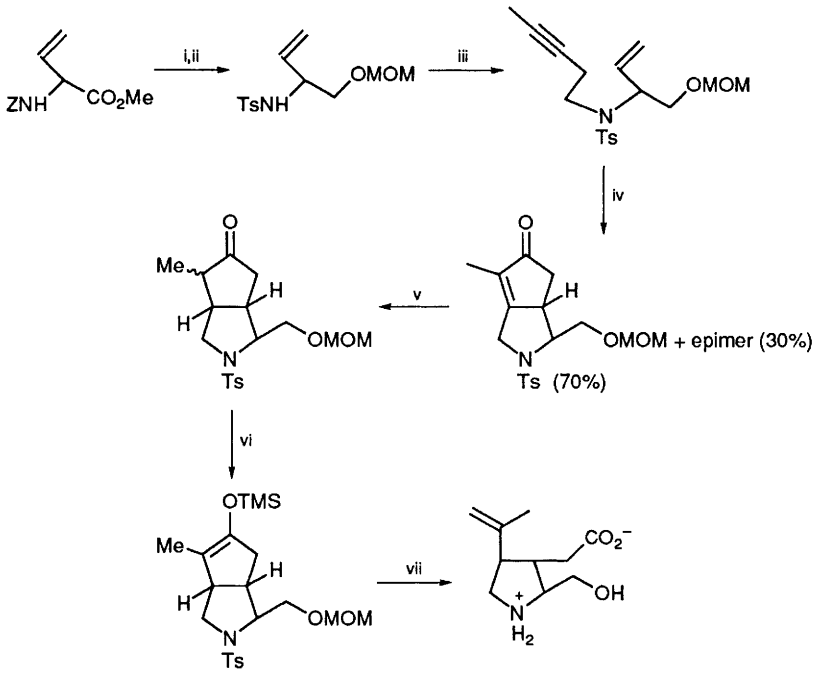
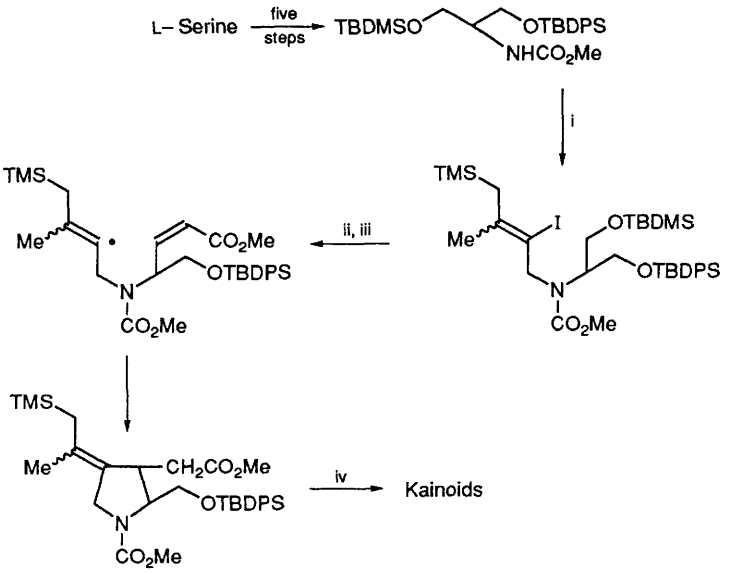


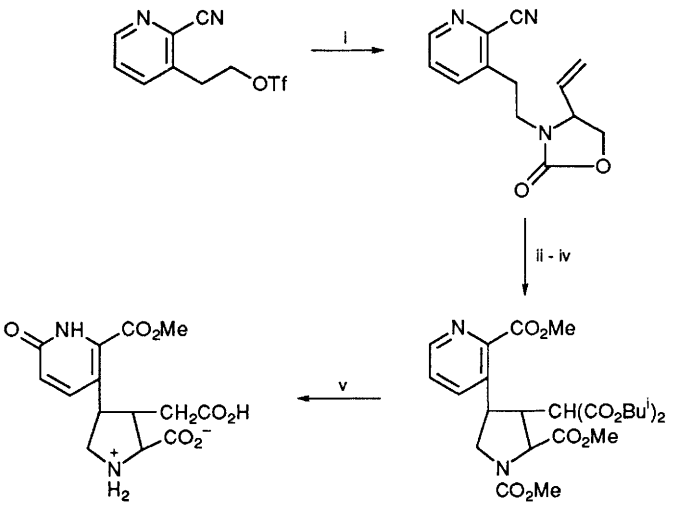
Reagents: i, $CO_2Me \longrightarrow CH_2OH$; ii, protecting group introductions and changes; iii, $MeC{\equiv}CCH_2CH_2Br$; iv, $Co_2(CO)_8/CH_2Cl_2$; v, H_2/Pd on epimer mixture; vi, $FeCl_3$/EtMgBr/TMSCl on major isomer; vii, followed by routine development $\longrightarrow$ (–)-kainic acid

Scheme 24



Reagents: i, $TMSC(Me)=CICH_2I$ (from $TMSCH_2CMe=C=CH_2$);
ii, deprotection, TsOH, [O], $(CF_3CH_2O)_2P(O)CH_2CO_2Me$
iii, Bu_3SnH/AIBN; iv, protodesilylation, then complete deprotection

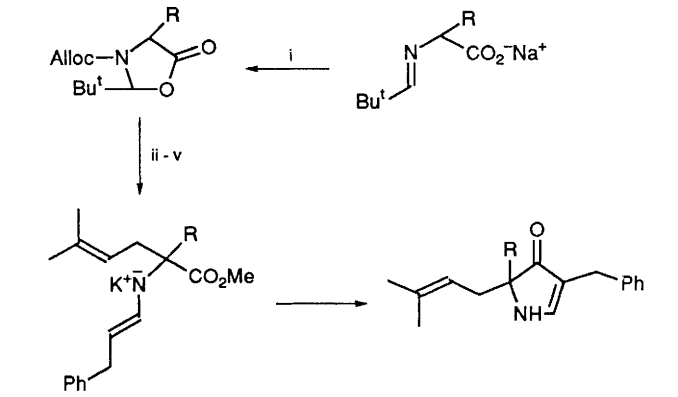
Scheme 25



acromelic acid B

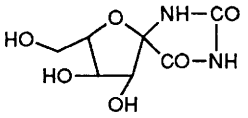
Reagents: i, L-vinylglycinol-derived oxazolidin-2-one;
ii, $-CH{=}CH_2 \longrightarrow -CH(CO_2Bu^i)_2$; iii, $-CN \longrightarrow -CHO$ *etc*.;
iv, MeONa; v, established methods

Scheme 26



Reagents: i, AllocCl; ii, KHDMS; iii, $Me_2C{=}CHCH_2Br$; iv, $Pd(PPh_3)_4$;
v, $Ph(CH_2)CHO$ then ii

Scheme 27



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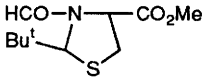

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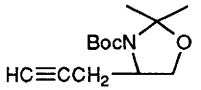

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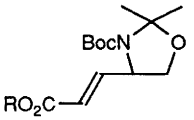

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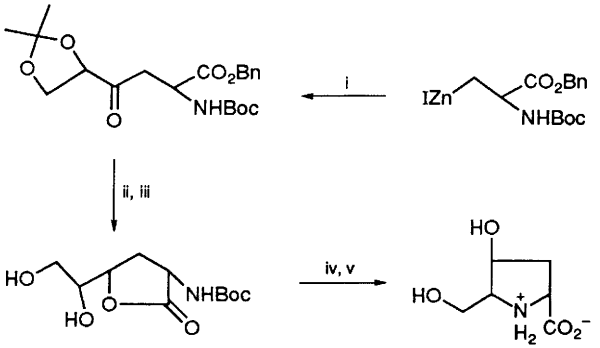
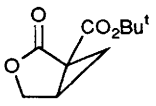


(+) - bulgecinine

Reagents: i, (*R*) - isopropylideneglyceryl chloride/Pd(0); ii, L - Selectride; iii, I_2/MeOH; iv, TBDMSCl; v, steps established earlier (*Tetrahedron*, 1987, **43**, 423)

Scheme 28



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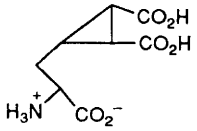


(39)

$HCONHCMe(SiMe_3)CO_2Et$, and α-acetoxyglycine analogues, yield highly electrophilic iminium ions by electrochemical oxidation, that react with allylsilanes and silyl ethers to give novel α,α'-disubstituted glycines.[170] A notable inclusion in the list of amino acids prepared in this way is the α-phenyl family.

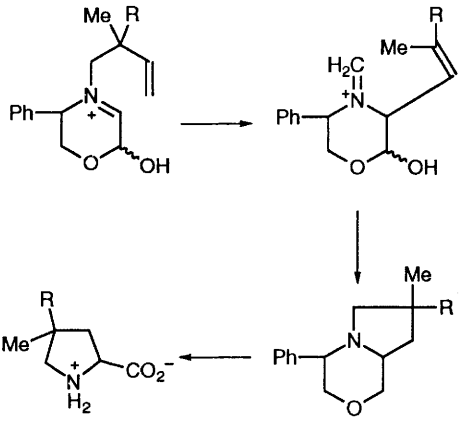
4.5 Synthesis of α-Amino Acids Carrying Alkyl Side-chains, and Cyclic Analogues

Close structural analogues of the aliphatic protein amino acids are collected here, together with alicyclic analogues.

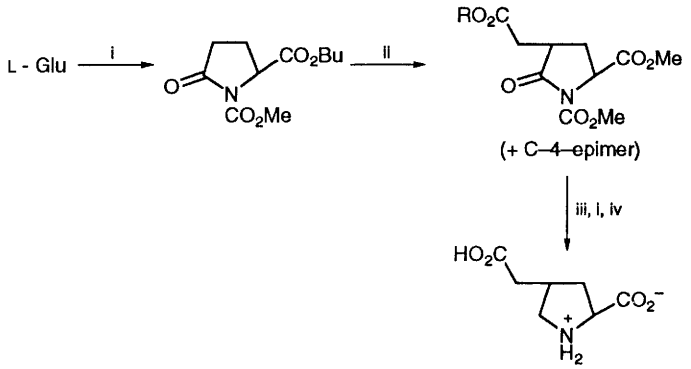
Acyclic α-amino acids fulfilling the title of this Section include new types of 4,4-disubstituted L-glutamic acids (4-methylene-, 4,4-dimethyl-, and the cyclopropyl analogue incorporating C-4, prepared as conformationally constrained L-glutamic acid analogues from Boc-L-aspartic acid γ-benzyl ester *via* (36), which is subjected to aminocarbonylation.[171] Three diastereoisomers of L-2-(2-carboxy-4-methylenecyclopentyl)glycine have been prepared (one of which is a potent kainoid receptor agonist), through the use of chiral oxazolines (37) and similar heterocyclic auxiliaries, starting with alkylation by 2-[(trimethylsilyl)methyl]prop-2-en-1-yl acetate.[172] More pedestrian syntheses of 4-methyl- and 4-ethyl-L-glutamic acids from corresponding glutaric acids are mediated by glutamic oxalacetic aminotransferase.[173] Further synthetic targets for the L-serine-derived zinc reagent shown in Scheme 28 include α-(4-oxo-alkyl)-α-amino acids (elaborated into (+)-bulgecinine precursors),[174] and alkylation of the synthon by $C_6H_5{}^+Fe(CO)_3\ PF_6^-$ gives cyclohexadienylalanine;[175] reactions with chloroformates[176] and with acyl chlorides and allylic chlorides[177] have also been described, the last-mentioned study covering uses of the glutamic acid-derived organocopper analogue. The γ-oxoalkyl α-amino acids have been approached in another way, from nucleophilic ring-opening of activated chiral α-alkoxycarbonyl β-lactams by $Me_2S^+(O)CH_2^-$, by lithiated sulfones, or by $Bu_2Cu(CN)Li_2$.[178]

α-Amino acids with alicylic structures in the side-chains continue to attract attention as conformationally-constrained mimics of the physiological action of the familiar acyclic protein amino acids, and the lactone (38) is a useful cyclopropyl chiron for the synthesis of 2,3-methano-amino acids[179] (several other recent papers describe synthesis of members of this class: Refs. 72, 78, 102, 342). A simple synthesis of 1-aminocylopropanecarboxylic acid starts with the conversion of a chelated homoserine into 2-amino-4-bromobutyrate.[180] Further potential glutamic acid agonists, (39) and its stereoisomer with reversed chirality for the ring CO_2H groups, have been prepared following the synthetic methodology reported earlier by the same workers (Vol. 24, p.22).[181] Alkenoic esters prepared from (1S,2R)-PhCHRCHPhOH [cleavable by $Pb(OAc)_4$], have been used for the preparation of (1S,2R)-1-amino-2-phenylcyclopropane carboxylic acid.[182]

Cyclic α-imino acids, the family of alicyclic α-amino acids that enclose the amino group as a member of the ring, are represented in a synthesis of (-)-trans-azetidine-2,4-dicarboxylic acid,[183] in a synthesis of 5,5-dimethyl-DL-proline (prepared by addition of HCN to 5,5-dimethylpyrrolideine N-oxide,[184] and in an interesting aza-Cope rearrangement process (Scheme 29).[185] A more conventional proline synthesis employs L-pyroglutamic acid (Scheme 30).[186]



Scheme 29



Reagents: i, conventional methodology; ii, LiHDMS/$BrCH_2CO_2R$; iii, separate epimers; iv, deprotection

Scheme 30

Six-membered ring α-imino acids approached through unusual routes include 4- and 5-substituted (S)-pipecolic acids, formed by ring-expansion of 4-oxo-L-proline with N_2CHCO_2Et.[187] The 4-oxopipecolic acids on reduction and sulfation give homochiral products exhibiting potent NMDA receptor agonist activity. NMDA Antagonism is shown by 3-(β)-phosphonoalkyl-substituted pipecolic acids prepared by established methodology.[188] Aza-Diels–Alder cycloaddition methods providing pipecolic acid derivatives involve N-camphorsulfonylimines $RSO_2N=CHCO_2Et$ (prepared from the corresponding α-bromoglycine derivative) with Danishefsky's diene,[189] and N-arylidene α,β-dehydro-α-amino acid esters $ArCH=NCH(=CH_2)CO_2Me$ (prepared by either a long-known method from cysteine methyl ester, or from serine methyl ester) with electron-deficient alkenes (an interesting aza-Cope rearrangement concludes one of these syntheses).[190]

Conventional Diels-Alder addition of cyclopentadiene to either isomer of 4-benzylidene-2-phenyloxazol-5(4H)-one provides all four racemates of 2-amino-3-phenylnorbornane-2-carboxylic acids.[191]

4.6 Models for Prebiotic Synthesis of Amino Acids

Conventional studies of the formation of α-amino acids in activated mixtures of simple compounds [A2]aqueous ammonium acetate subjected to high energy LET particle [$^{10}B(n,\alpha)^7Li$] irradiation, or ^{60}Co-γ-irradiation, giving aspartic acid, serine, glycine, alanine, valine, β-alanine and γ-aminobutyric acid, etc),[192] or UV irradiation of a gaseous mixture of H_2 and HCN,[193] as reported in this Section over the years, are accompanied by results of investigations into intermediate stages involved in abiotic synthesis of the starting compounds. Formation in the early non-reducing atmosphere, of ammonia or fixed-nitrogen compounds required by theories of prebiotic α-amino acid synthesis, must have proceeded *via* nitric oxide, thence to nitrous and nitric acids whose reduction in water at pH 7.3 at temperatures above 25°C can be accounted for by the oxidation of ferrous salts to ferric compounds.[194]

Aqueous solutions of ammonia and 2-aminopropionitrile, a putative alanine precursor plausibly formed in an HCN-containing atmosphere, react to give 2,2'-iminodipropionitrile, N-(cyanoethyl)alaninamide, and alanine. 3-Aminopropionitrile reacts similarly to give β-alanine, among other products.[195]

4.7 Synthesis of α-Alkoxy-α-Amino Acids and Analogous α-Heteroatom-substituted α-Amino Acids

Several papers have appeared dealing with members of the easily-prepared α-hydroxyglycine family and analogues that are also mentioned in other sections of this Chapter. N-Z-[-(Diethoxyphosphonyl)]glycine has been prepared from Z-α-hydroxyglycine (i.e. ZNH_2 + $OHCCO_2H$) using $PCl_5/P(OEt)_3$, and deprotection and Schiff base formation have been demonstrated.[196]

Growing interest in protected α-aminoglycines (Scheme 31) and sulfur analogues for use in peptide synthesis is supported by relevant preparative methods.[197]

4.8 Synthesis of α-Halogenoalkyl α-Amino Acids

Amino acids carrying fluoroalkyl side chains have yielded rewarding results as far as their enzyme inhibitory properties are concerned, and their synthesis continues to be studied, in some cases providing novel mechanistic insights.

A γ-fluorine substituent increases the propensity for 1,4-addition during the ammonolysis of α,β-unsaturated α-bromobutenoic acid esters, leading to aziridines and lowering the yields of the intended reaction product, the trans-β,γ-unsaturated γ-fluoroalkyl-α-amino acids.[198] New fluorinated analogues of (S)-norvaline (4,4-difluoro-, 4,4,5,5,5-pentafluoro-) and of (S)-norleucine (5,5-difluoro-, 5,5,6,6,6-pentafluoro-, and 4,4,5,5,6,6,6-heptafluoro-) have been prepared by standard methods,[199] also illustrated for the synthesis of a 1:1-mixture of (2S,4S)- and (2S,4R)-5,5,5-trifluoroleucine from 5,5,5-trifluoro-4-methyl-2-oxo-pentanoic acid by enzymatic transamination using *Alcaligenes faecalis* IAM 1015.[200]

A review of synthetic approaches to 4-fluoroglutamic acid,[201] and methods for the preparation and separation of cis- and trans-4-fluoropyroglutamic acid, have been published.[202] All four stereoisomers of 4-fluoroglutamic acid are accessible from (-)-trans-4-hydroxy-L-proline through inversion at C-4 (Ph_3P/DEAD), substitution of the hydroxy group by diethylaminosulfur trifluoride, and RuO_4 ring-opening.[203] DL-3,3-Difluoroglutamic acid is accessible from 3-hydroxyprolinol in a very similar way.[204] 4,4-Difluoro-L-arginine has been prepared from Boc-D-serine *via* the Garner aldehyde (37; CHO in place of -CH=CHCO$_2$R) through reaction with ethyl bromodifluoroacetate and routine elaboration to incorporate the guanidine grouping.[205] A combination of side-chain fluorination and phosphonation to provide potential pharmacological activity is involved in 4-phosphono(difluoromethyl)-DL-phenylalanine, a target reached through a synthesis starting from 4-(diethoxymethyl)benzaldehyde and its reaction with ethyl α-azido-acetate.[206] A protected L-tyrosine O-trifluoroacetate is the starting material in an independent synthesis of the L-analogue, involving carbonylation [CO/Pd(OAc)$_2$], conversion into the triethoxyphosphonylcarbonyl-L-phenylalanine, and fluorination with diethylaminosulfur trifluoride.[207]

4.9 Synthesis of α-(ω-Hydroxyalkyl) α-Amino Acids

This, one of the particularly variegated families of modified α-amino acids, is accessible through a range of mechanistically-interesting synthesis methods. β-Hydroxyalkyl-α-amino acids are easily prepared from glycine derivatives by aldol reactions using aliphatic aldehydes unless steric hindrance is involved; in which case, titanium enolates formed through transmetallation of lithium enolates using dichloro-di-isopropoxy-titanium are useful. They react well with N-alkylideneglycine esters preferentially yielding the anti-isomer under kinetic control, and have provided anti-2R-products with glycinamides in which the amide moiety is a chiral oxazoline.[208] Separable mixtures of diastereoisomeric racemates of β-hydroxyalkyl-α-amino acids are obtained when glycine enolates [$Cl_3CCONRCH_2CO_2Me + CF_3SO_3SiMe_3 \rightarrow Cl_3CCONRCH{=}C(OMe)OSiMe_3$] react with aldehydes.[209]

Ethylene oxide is a valuable vinyl cation equivalent for use in the synthesis of γ-hydroxyalkyl-α-amino acids through alkylation of di-anions formed from N-benzoylglycine esters using LDA (Scheme 32),[210] and thence to α-vinyl-α-amino acids. Nitrogen functions can be introduced stereoselectively into D-ribonolactone to yield 4,5-dihydroxy-D-erythro-norvaline and 4,5-dihydroxy-L-threo-norvaline.[211] Monosaccharide derivatives (40) and (41) have been used in sophisticated syntheses of hydroxylated 1-aminocyclopentanecarboxylic acids[212] and furan analogues,[213] the routes incorporating mechanistically-interesting ring-contractions.

N-Z-O-TBS-L-Serinal yields (5S)-Z-amino-(4R)-hydroxy-6-TBSO-hex-1-ene through highly stereoselective addition of allyltrimethylsilane, elaboration giving (2R,3S)-3-hydroxyproline.[214]

N-Protected L-aspartic acid α-esters are useful starting points in the synthesis of α-(ω-hydroxyalkyl)-α-amino acids, through subjecting them to side-chain elaboration, and they have been used in a synthesis of RI-331 [(-)-5-hydroxy-4-oxo-L-norvaline];[215] and in a similar way using hexafluoroacetone as protecting agent for both amino and α-carboxy groups.[216] 2-Amino-5,6-dihydroxy-5-(acetamidomethyl)hexanoic acid is an interesting putative biosynthetic precursor of oxapenam antibiotics, that has now been established to be represented by (42) through synthesis from N-Z-β-iodo-L-alanine by free-radical alkylation with $HOCH_2C(=CH_2)CH_2SnR_3$, followed by Sharpless epoxidation and routine elaboration.[217]

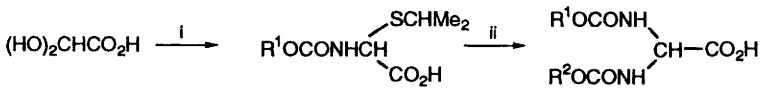
4.10 Synthesis of α-Amino Acids with Unsaturated Aliphatic Side-chains

In addition to standard methods of synthesis involving elimination reactions [of α-vinylglycine, Ref.210 and preparation from L-methionine *via* the sulfoxide[218] and of α,β-dehydroamino acids, $(MeS)_2C=NC(CO_2Me)=CHR$ starting from β-hydroxy-α-amino acids,[219]], some unusual approaches provide useful new methodology. (2S,3S)-2-Amino-3-methylpent-4-ynoic acid has been prepared starting with 3-chlorobut-1-yne,[220] and the serine-derived organozinc synthon (cf.Refs.174-177) has proved useful *via* transmetallation [→ $IZn(CN)CuCH_2CH(NHBoc)CO_2Bn$] for synthesis of allenic amino acids through reaction with toluene-p-sulfonyloxymethyl alkynes $RC\equiv CCHR'OTs$.[221]

α-Allylglycine has been prepared from methionine by the application of the Ramberg-Baecklund rearrangement.[222]

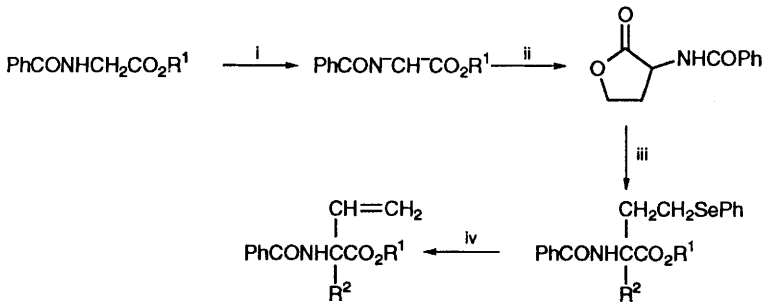
4.11 Synthesis of α-Amino Acids with Aromatic or Heteroaromatic Groupings in Side-chains

Active research topics providing routes to near relatives of the aromatic and heteroaromatic protein amino acids are reported in several recent papers collected here. Standard methodology for the preparation of phenylalanine analogues is illustrated in a route to 3'-azidotyrosine employing 3-azidophenol, pyruvic acid, and tyrosine phenol-lyase.[223] Preparations of conformationally-constrained L-phenylalanine analogues, one using Evans' methodology,[224] and



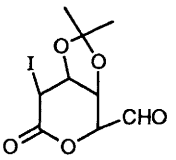
Reagents: i, R^1OCONH_2, Me_2CHSH; ii, R^2OCONH_2/NBS

Scheme 31

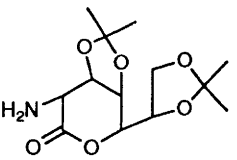


Reagents: i, LDA; ii, ethylene oxide; iii, LDA, R^2X, then $(PhSe)_2$/$NaBH(OMe)_2$; iv, O_3, R^1OH_2, Δ

Scheme 32



(40)



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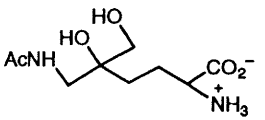

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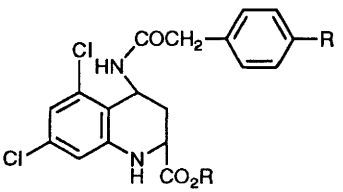


(43)

another developing existing routes to trans-2-carboxy-4-substituted tetrahydroquinolines (43) that are showing promise as glycine-site NMDA antagonists (see also Vol.25, p.40).[225] Simple transformations through nucleophilic substitution of p-iodophenylalanine derivatives lead to new phenyl-modified analogues, e.g. p-(tri-n-butylstannyl)phenylalanine.[226] A new synthesis of actinoidic acid (44; $H_3N^+CHCO_2^-$ in place of CHO) involves an efficient biphenyl-forming step (44 + 45 → 46) followed by Strecker synthesis.[227]

Tryptophan analogues continue to predominate in the heteroaromatic category, with new examples prepared through familiar routes. L-4-Aza-tryptophans are accessible through the condensation of a 4-aza-indole with serine, mediated by tryptophan synthase,[228] and chlorotryptophans have been prepared similarly,[229] while N-1- and C-2-substituted tryptophans, and 5-substituted analogues, are available from the corresponding indoles through alkylation by $BrCH_2C(=NOH)CO_2Et$ and conventional elaboration.[230] Pd-Catalysed annulation of substituted 2-iodoanilines with δ-silylated propargylglycines gives substituted tryptophans.[231] α-Substituted 5-hydroxytryptophans have been obtained through alkylation of homochiral pyrroloindoles (Vol.25, p.40) (LDA, bromoalkane) with retention of configuration.[232] 1,2,3,4-Tetrahydro-2-amino-2-carboxycyclopent[*b*]indole is a new conformationally-constrained tryptophan analogue prepared through the hydantoin synthesis from the corresponding ketone.[233]

Side-chain pyridinium salt moieties are accessible from the corresponding β-(pyrid-3-yl)alanines through alkylation using a halogenoalkane in the presence of Ag_2O.[234] A general route to such β-(heteroaryl)alanines has been fully documented for the case of N-Z-β-(pyrazol-1-yl)-L-alanine, prepared from N-Z-L-serine through conversion (Ph_3P/DEAD) into the β-lactone.[235] Boc-L-Serine methyl ester has been converted into novel amino acid nucleosides *via* its methylthiomethyl ether followed by reaction with silylated N-benzoyl purine and pyrimidine bases.[236] Vederas' 1988 route to these compounds using N-Boc-L-serine-β-lactone continues to be used by others.[237]

Further examples have been provided of preparative methods leading to new β-(heteroaryl)alanines and homologues containing two or more nitrogen atoms. β-[(3-Phosphonoalkyl)quinoxalin-2-yl]alanines[238] present a familiar general disposition of functional groups (47) for potential NMDA receptor affinity. γ-(3,5-Dimethylpyrimidin-2-onyl)-L-butyrine has been prepared from L-glutamic acid *via* the corresponding ureide.[239] ω-(Tetrazol-5-yl)alkyl analogues have been prepared as potential NMDA antagonists,[240] and trans-4-(tetrazol-5-yl)-L-proline (LY300020) has been announced as a novel systematically-active AMPA agonist, prepared from N-Z-hydroxy-L-proline *via* nucleophilic displacement by CN^- on the O-toluene-p-sulfonyl derivative followed by tetrazole construction with Bu_3SnN_3.[241]

3-(Thiazol-4-yl)alanines and selenium analogues have been prepared by conventional Hantzsch synthesis from 2,2-bis(trifluoromethyl)-4-(3-bromo-2-oxopropyl)-1,3-oxazolidin-5-one, readily obtained from aspartic acid protected by condensation with hexafluoroacetone.[242] Thiazol-2- and 4-yl analogues and homologues have been reported independently.[243]

4.12 Synthesis of α-Aminoalkyl α-Amino Acids

Derivatives of the basic protein amino acids showing useful pharmacological potential include the cyclized ornithine derivative (48), already known to act as a partial agonist of the glycine site of the NMDA receptor. A series of β-substituted analogues has been prepared by the previously-established methodology.[244] Ring-opening by hydroxylaminolysis, of the pyrrolid-1-ine carboxylic acid obtainable from hydroxy-L-proline, gives the oxime of the α-keto-acid corresponding to (4R)-hydroxyornithine.[245] One-pot Schiff base alkylation and amination of (Z)-$AcOCH_2CH=CHCH_2OCO_2Et$ by BocONHBoc or Me_2NH, respectively, gives 1,4-adducts with $Ph_2C=NCH_2CO_2Et$ from which, by hydrogenation, DL-N^6-hydroxylysine and DL-laminine can be obtained.[246] The same target, but the L-(+)-enantiomer, has been synthesized starting from L-allylglycine, through a sequence resulting in hydroxymethylation at C-5.[247]

Mitsunobu processing of N-Fmoc-L-threonine and -allo-L-threonine N-Boc-hydrazides, giving (2S,3R)- and (2S,3S)-N^{α}-Fmoc-N^{β}-Boc-α,β-diamino acids, can be operated on a multigram scale.[248] The greater confidence with which α-amino aldehydes are being used is illustrated in a synthesis of homochiral 2,4-di-amino acids (49 → 50).[249]

4.13 Synthesis of α-Amino Acids Carrying Sulfur- or Selenium-containing Side-chains

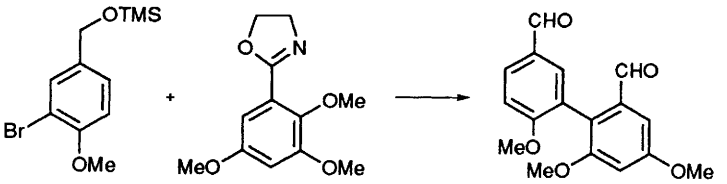
Cysteine homologues $RNHCH_2S(CH_2)_2CH(NH_2)CO_2H$ and $MeS(CH_2)_3CH(NH_2)CO_2H$ that are, from another point of view, also lysine and methionine analogues respectively, are accessible from L-methionine by Na/NH_3 cleavage and S-alkylation by $AcNHCH_2OH$, and from L-ornithine through nucleophilic substitution of the derived pyridinium salt by methanethiolate.[250]

Isothiazolidine-1,1-dioxide 3-carboxylic acid[251] can also be viewed in two ways; as a proline analogue or as a homocysteine analogue. A near analogue (51) has been unintentionally prepared, in addition to the expected sulfonamide, through reaction of aspartic acid diesters with arenesulfonyl chlorides.[252]

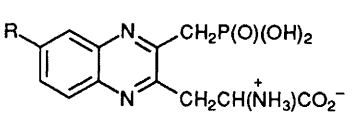
4.14 Synthesis of α-Phosphonoalkyl α-Amino Acids and α-Amino Acids Carrying Other Phosphorus Functional Groups in Side-chains

Representing the simplest trivalent phosphorus derivatives, N-protected 3-(triphosphonio)alanine esters are valuable in synthesis for preparing "vinylglycines" with high optical purity through ylide formation and reaction with carbonyl compounds [with PhCHO → (S,E)-$PhCH=CHCH(NHR)CO_2R'$].[253]

Another simple representative of this family, (2R)-2-amino-5-phosphonopentanoic acid, is available through an interesting new route from (S)-serinal that involves addition of the trimethylsilylethyne carbanion, dehydration-rearrangement to the allene, and (after reductive de-silylation) routine completion of the synthesis.[254] Its near relative, (E)-$H_2O_3PCH_2CH=CHCH(NH_2)CO_2H$, a constituent of plumbemicine, has been prepared through standard bislactim ether methodology or from ethyl 3-ethenyloxazoline 4-carboxylate.[255] The 4-oxo analogue of (2R)-2-amino-5-phosphonohexanoic acid has also generated interest as a receptor antagonist, and homologues carrying methyl substituents at other



(44) (45) (46)



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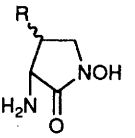

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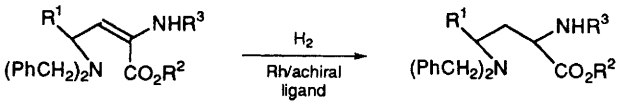


(49) (50)

(51) (52)

side chain locations, have been prepared (they are less strongly bound to receptors).[256]

Synthesis of (4'-phosphonodifluoromethyl)phenylalanines has been covered in the earlier Section 4.8.

Intense synthesis activity must be an accurate description of work leading to the identification and stereospecific synthesis of (2R,4R,5S)-2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid, the potent, selective, and competitive NMDA antagonist (52), previously prepared in admixture with other stereoisomers (NPC 12626). An efficient nine-step synthesis incorporates the hydantoin method to construct the α-amino acid moiety on the 4,5-bis(carboxymethyl) cyclohexene monomethyl ester.[257]

4.15 Synthesis of Isotopically Labelled α-Amino Acids

Direct synthesis of ^{2}H-labelled α-amino acids based on enzyme-catalysed exchange in ^2H_2O represents the simplest approach, and as illustrated in experiments with *Escherichia coli* cystathionine γ-synthase, can be operated on a gram scale with several protein amino acids.[258] The procedure is most effective with arginine, glutamic acid, histidine, homoserine, and lysine; less so for asparagine, glutamine, methionine, ornithine, and S-methylcysteine; and of insignificant use for other amino acids. Some β-exchange can also be detected. Improved chemical catalytic exchange methods (better than 95% exchange) have been described as applied to syntheses of [2,3,5,6-$^2H_4$]tyrosine and [2,3,4,5,6-$^2H_5$]phenylalanine, as part of an account of new syntheses that include [2,3,5,6-$^2H_4$]phenylalanine and [2,3,6,7-$^2H_4$]tryptophan.[259] ^{2}H–^{1}H Exchange kinetics in ^2H_2O–^{2}HCl and ^2H_2O–$^2H_2SO_4$ for L-phenylalanine, L-tyrosine, and L-tryptophan, and for [2,4,5,6,7-$^2H_5$]L-tryptophan and [3,5-$^2H_2$]L-tyrosine in aqueous HCl, yield activation energies for direct exchange at various atoms in these amino acids.[260]

Stereospecific syntheses in the ^{2}H-labelling category have been reported for (2S,3R)-[3-^{2}H]-3-methylaspartic acid,[261] and for (2S,3S)-[2,3-$^2H_2$]-L-ornithine and (2S,3R)-[3-^{2}H]-L-ornithine, by asymmetric homogeneous-catalysed reduction [(R)-Rh-Prophos] of the protected α,β-dehydro-α-amino acid PhCONHC(CO_2Me)=CR$(CH_2)_2$NPht.[262] Labelled pyroglutamic acids formed by intramolecular ketene trapping in diazomethyl ketones originating in labelled glutamic acids, can be reduced (BH_3-Me_2S) to (2S,3S)-[3-^{2}H]- and (2S,3R)-[2,3-$^2H_2$]prolines[263]

Tritiated analogues of GABA and β-phenylGABA, respectively, can be secured either through addition of $^3H_2$ to PhtNCH$_2$C≡CCO_2Me, catalysed by tris(triphenylphosphinerhodium(I) chloride, and work-up to give (E)- and (Z)-$H_2NC^3H=C^3HCO_2H$,[264] or by Pd/C-catalysed addition of $^3H_2$ to the homochiral ester PhtNCH$_2$CPh=CHCO_2R.[265]

Among carbon isotopes, the most interesting synthetic challenges are provided by the need to introduce the short-lived ^{11}C label within the shortest possible time. There have been many impressive successes in this respect, reviewed recently.[266] New results include an interesting route to α-[3-^{11}C]aminoisobutyric acid (Scheme 33) with an unusual N-protection strategy,[267] and independent reports on the preparation of [^{11}C]-L-methionine[268] and its DL-analogue.[269]

Strecker methodology leading to DL-[1-^{13}C]valine from isobutyraldehyde and K^{13}CN followed by resolution using a D-amino acid oxidase–branched amino acid aminotransferase enzyme cocktail illustrates a typical approach to a simple case.[270] L-Glutamic acid can be prepared carrying ^{13}C at any position through enzyme-mediated syntheses employing appropriately-labelled pyruvic acid, acetic acid, and sodium bicarbonate.[271] ^{14}C-Vigabatrin has been synthesized.[320]

Multiple labelling is carried out increasingly confidently, illustrated by a one-pot preparation of DL-[2-^{15}N,5-^{13}C]glutamic acid from 2-bromobutyrolactone using potassium [^{15}N]phthalimide and K^{13}CN,[272] L-[3,4-$^{13}C_2$]proline and L-[^{15}N]proline from correspondingly-labelled L-glutamic acids *via* the appropriate 5-oxo-L-prolines (reduction of the amide grouping *via* the thioamide using Bu_3SnH).[273] Stereoselective synthesis and applications of L-[^{15}N]- and -[^{13}C]-amino acids, prepared either from labelled L-serines produced through bacterial synthesis, or using 1-chloro-1-nitrosocyclohexane as electrophilic amination agent for chiral enolates, has been reviewed.[274]

^{15}N-Enriched amino acids can be prepared through use of a coupled enzyme system, e.g. $(^{15}NH_4)_2SO_4$ with α-ketoglutaric acid and glutamate dehydrogenase.[275] Direct chemical synthesis of labelled asparagine and glutamine, based on [^{15}N]ammonolysis of the benzyl esters of the N-Boc-amino acids, is straightforward.[276]

^{18}F is another short-lived isotope whose properties lead to important medical uses when it is incorporated into an α-amino acid. The topic has been reviewed.[277] The chemistry of fluorination and the need for relatively swift working, in view of the short half-life of the isotope, lead to choice of the tyrosine family as substrates, and there have been new syntheses in this category. 6-[^{18}F]- and 4-[^{18}F]Fluoro-m-tyrosines have been prepared through ^{18}F-destannylation (using [^{18}F]$^{18}F_2$ and [^{18}F]acetyl hypofluorite), of (3'-acetoxy-5'-trimethylstannyl)-phenylalanine, protected as its N-trifluoroacetyl ethyl ester derivative.[278] 6-[^{18}F]Fluoro-L-DOPA is accessible (in 110 minutes' reaction time) from 6-nitroveratraldehyde, subjected to nucleophilic [^{18}F]fluorination and further elaboration into 2-[^{18}F]fluoro-4,5-dimethoxybenzyl bromide and presentation to the Li enolate of the 1-(S)-camphorimine of glycine t-butyl ester or (S)-(-)-1-Boc-2-butyl-3-methyl-4-imidazolidinone, giving *ca.*85% enantiomeric excess.[279]

6-[^{77}Br]BromoDOPA is accessible through direct bromination of DOPA.[280]

4.16 Synthesis of β-Amino Acids and Higher Homologous Amino Acids

Arndt-Eistert homologation is a standard general approach in this area, and bearing in mind the easy availability of α-amino acids, it is used for the synthesis of β-amino acids more often than for the higher homologues. Its use is illustrated for homologation of cis-4-hydroxy-L-proline (Scheme 34).[281] A new approach to homologation of α-amino acids in which derived ketones are subjected to the Wittig reaction followed by diastereoselective hydroboration, oxidation and de-protection [MBzlNTsCHR'C(=CH_2)R → MBzlNTsCHR' $CHRCO_2H$] has been investigated.[282] A novel diastereoselective rearrangement

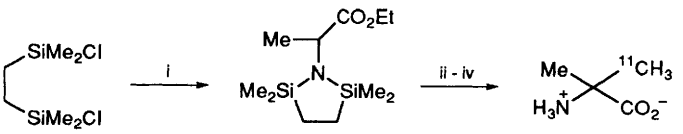
of O-prop-1-enyl α-N-acyl(methylamino)alkyl ethers, leading to β-(acyl-N-methylamino)aldehydes (Scheme 35) amounts to a synthesis of a β-amino acid from an equivalent α-amino acid.[283] A use of α-N-Boc-amino aldehydes for the synthesis of β-(N-Boc-amino)-α-keto acids employs 2-trimethylsilylthiazole to supply the extra carbon atom, through the formation of the aldol-type adduct, the corresponding 2-(β-N-Boc-amino-α-hydroxy)thiazole.[284] Selective reduction of the cyano-group of 1-cyanocyclopropanecarboxylic acid benzyl ester has provided the 1-aminomethyl analogue, required for study as a mechanism-based inactivating agent for mono-amine oxidase.[285]

The addition reactivity of imines has been as useful for β-amino acid synthesis as for the preparation of their α-amino acid analogues, though with the unique benefit of being able to base the method on mild Lewis acid-catalysed addition of ketene acetals (Scheme 36).[286] With the inclusion of vinylic ketene acetals in one of these studies, it was possible to demonstrate the effectiveness of the method for the synthesis of δ-amino acids.

α,β-Unsaturated β-amino acids are produced by "allylic" acylation of imines by carbonyldi-imidazole [$R^1N{=}CR^2CH_2R^3 + Im_2CO \rightarrow R^1NHCR^2{=}CR^3COIm$],[287] and base isomerization of N-benzylimines of β-fluoroalkyl-β-keto-esters gives high yields of corresponding N-benzylidene β-amino acid esters.[288] Addition of malononitriles to imines [$RCH(CN)_2 + R'N{=}CHAr \rightarrow R'NHCHArCR(CN)_2$] calls for high pressures.[289]

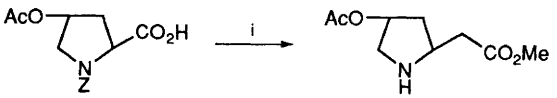
The growth in interest in enantioselective methods for β-amino acid synthesis is now very noticeable. The recent literature includes descriptions of several new procedures as well as extensions of methods used in the asymmetric synthesis of α-amino acids. The imine addition theme is given an interesting variation in a synthesis of (R)-β-amino acids using (S)-prolinol-based hydrazones that can be alkylated by an organometallic reagent (Scheme 37). The synthesis target is released by reductive N-N cleavage followed by ozonolysis.[290] 99% Diastereoisomeric excess is claimed in the addition of a chiral imine (Scheme 36; R^2 = (R)-PhChMe-, R^1 = Ph) to silyl acetals mediated by an *in situ*-generated homochiral borate complex.[291] The Staudinger reaction (ketene + imine → β-lactam) applied to the homochiral imines $ArCH{=}NCHMePh$ with $AcOCH_2COCl/NEt_3$ gives an unequal mixture of cis-adducts from which, after separation and HCl ring opening, phenylisoserine esters are obtained.[292] A similar approach using the homochiral Evans-Sjogren ketene (from an $N\text{-}ClCOCH_2$-oxazolidin-2-one) has been used.[293]

Asymmetric Michael addition has been used previously in the β-amino acid field, usually to establish chirality at the β-carbon atom. Addition of lithium (R)-(–methylbenzyl)benzylamide to t-butyl cinnamate and its 2-methyl analogue gives β-phenylalanine (95% e.e.) and its α-methyl homologue, as well as corresponding β-lactams.[294] Addition of a chiral azepine to t-butyl crotonate followed by hydrogenolysis gives a mixture of erythro- and threo-α-substituted β-amino acid esters,[295] while addition of lithium enolates to homochiral 2-aminomethyl acrylates (53) is exceptionally effective (better than 99% diastereoselectivity) in establishing α-chirality.[296] It would be interesting to see the method extended to acrylates carrying a homochiral 2-(aminoalkyl) grouping, with or without the



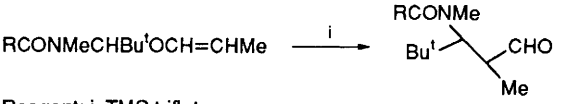
Reagents: i, L–alanine; ii, BuLi + 2,2,6,6 - tetramethylpiperidine; iii, $^{11}CH_3I$; iv, 5M aq. HCl

Scheme 33



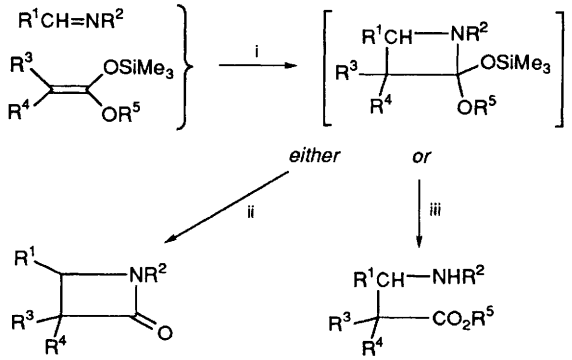
Reagents: i, Bu^iOCOCl, NMM; ii, CH_2N_2; iii, BzOAg/MeOH, 40 °C; iv, deprotect

Scheme 34



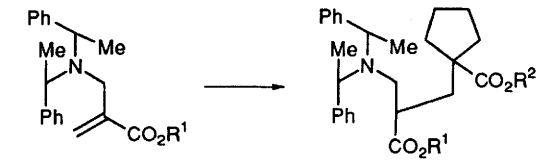
Reagent: i, TMS triflate

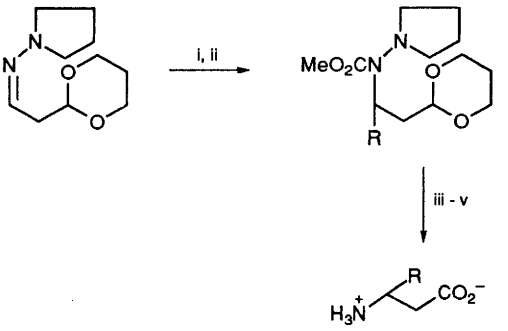
Scheme 35



Reagents: i, metal salt of Lewis acid coated on dry montmorillonite; ii, $-R^5OM$; iii, H_2O

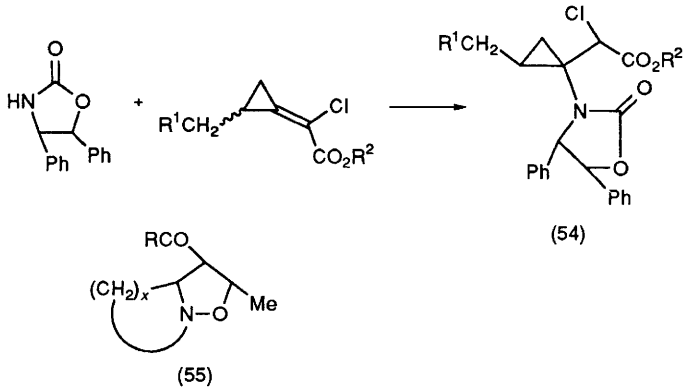
Scheme 36





Reagents: i, RM; ii, MeO_2CCl; iii, [H](N—N cleavage); iv, O_3; v, deprotection

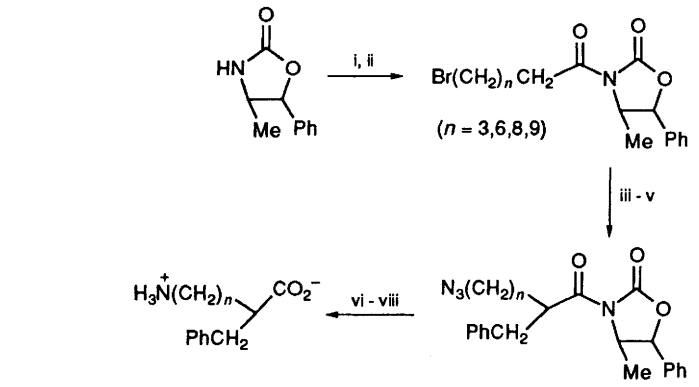
Scheme 37



homochiral N-substituents. Michael addition through the nitrogen atom of homochiral oxazolidin-2-ones to α-cyclopropylidene α-chloroacetates in the presence of 10 mol% KH, mediated by an 18-6-crown ether, yields β-amino acids carrying a β-cyclopropyl function (54).[297] Lewis acid catalysed 1,4-addition of O-benzylhydroxylamine to N-(alk-2-enoyl)oxazolidin-2-ones is a similar example of the genre, leading to homochiral α-substituted β-alanines, with a curious dependence of stereochemical pathway on the Lewis acid ($TiCl_4$ and Me_2AlCl provide opposite diastereoselectivity).[298] I_2 catalysed 1,3-dipolar addition of cyclic nitrones to homochiral bornane-1,2-sultam esters of crotonic acid gives β-amino acid derivatives (55) with high diastereoselectivity, from which piperidine and pyrrolidine alkaloids, (+)-sedridine and (+)-hygroline respectively, were obtained by further elaboration.[299] Intramolecular nitrone–alkene cycloaddition involving homochiral $PhCH_2N^+(O^-)=CH(CH_2)_3CH=CHR$ [R = (S)-CHMeOH] yields the naturally-occurring β-amino acid cis-pentacin, after hydrogenolysis and oxidative elaboration of the cycloadduct.[300] Acryloyl chloride $CH_2=CHCOCl$ reacts through the Michael addition pathway in aza-annulation of enamines formed between $BuNH_2$ and β-ketoesters to give δ-lactam epimer mixtures,[301] and a straightforward Michael reaction gives β-amino-β-(pyrimidin-5-yl)propanoic esters.[302]

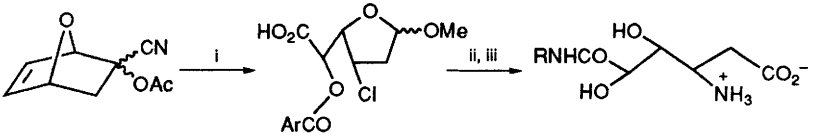
Several research groups have established the merits of Evans methodology for the asymmetric synthesis of β-amino acids using chiral oxazolidin-2-ones (already illustrated in this Section to put stereochemical bias on to the Michael addition route). The acylation–azidation–alkylation sequence shown in Scheme 38 is not quite the way things are done for α-amino acid synthesis![303] The Nicholas reaction applied to boron enolates of N-acyloxazolidin-2-ones (Scheme 39) leads to excellent diastereoselectivity.[304] The closely-related approach employing alkylation (LDA/MeI or $PhCH_2X$) of (S)-1-benzoyl-3,6-dimethylperhydropyrimidin-4-one (prepared by cyclization of the Schiff base of (S)-3-aminobutanoic acid)[305] is a hidden form of a general approach in which one homochiral β-amino acid is used to synthesize another, also illustrated in uses for L-aspartic acid *via* its N-toluene-p-sulfonyl anhydride and thence *via* the protected 4-iodo-3-amino acid synthon to (R)-γ-alkyl-β-amino acids[306] and their α-hydroxy-analogues.[307] This route,[306] which can be operated on a multigram scale, exploits regioselective $NaBH_4$ reduction of the anhydride, Me_3SiI lactone cleavage, and substitution of the iodo-atom by R_2CuLi, leading to (R)-γ-alkyl-β-amino acids after somewhat fierce de-toluene-p-sulfonylation process (refluxing in 47% aq HBr/PhOH). (R)-S-Methylcysteine is used as starting material for a homochiral 4-methylene-oxazolidin-5-one, from which 1-aminobicyclo[2.2.1]heptane-2-carboxylic acids can be prepared through Diels-Alder addition.[308] C-2-Alkylation of the homochiral N,O-acetal (56) using $Bu_3SnCH_2CO_2Et$ followed by $Pb(OAc)_4$ cleavage of the resulting N-[(S)-1-phenyl-2-hydroxyethyl] β-amino acid, is offered as a new enantioselective approach to these amino acids.[309]

Nucleophilic ring-opening of N-toluene-p-sulfonylaziridines (57) using a Grignard reagent with CuBr-SMe_2/THF-HMPA has been established to give modest (0–55%) yields of (R)-N-toluene-p-sulfonyl-β-amino acids.[310] The aziridines can be prepared from an L-serine ester in seven steps. Chiral aziridines (58)



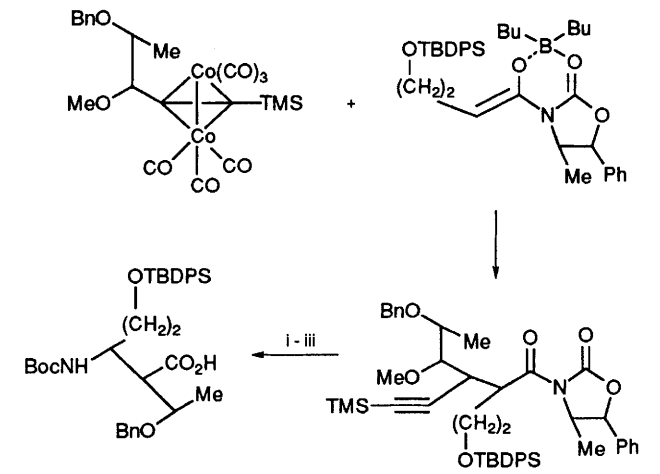
Reagents: i, BuLi; ii, $Br(CH_2)_n CH_2COCl$; iii, NaN_3/DMF; iv, $NaN(SiMe_3)_2$; v, $PhCH_2Br$; vi, [H]; vii, $PhCH_2OLi/PhCH_2OH$; viii, various protection-deprotection steps

Scheme 38



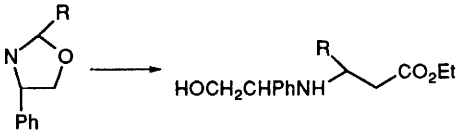
Reagents: i, MeOH – Cl_2; ii, NH_3, iii, [O]

Scheme 40

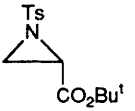


Reagents: i, H_2O; ii, Curtius (DPPA/Bu^{t}OH) degradation;
iii, $-C\equiv C- \longrightarrow -CO_2H$ with $OsO_4/NaIO_4$

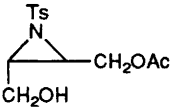
Scheme 39



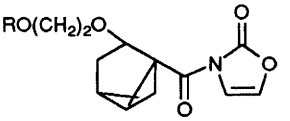
(56)



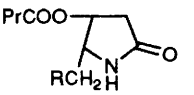
(57)



(58)



(59)



(60)

have been used to synthesize enantiomers of $ZNHCH(CH_2Ph)CH(OH)CO_2Me$, which are key intermediates for bestatin synthesis.[311] The use of lipase for enantioselective transesterification of methyl trans-β-phenylglycidate and successive ring-opening with HBr, azidolysis, and routine elaboration provides the (2R,3S)-enantiomer of the taxol side-chain, phenylisoserine.[312]

Corresponding ring-opening processes are well-established for azetidinones, the interest residing as much in the methods of synthesis of the four-membered rings as in the β-amino acids. Recent examples are C-4-alkylation, using titanium enolates, of azetidinones formed by cycloaddition of chiral imines derived from (S)-mandelic aldehyde or (R)-glyceraldehyde,[313] and C-4-deuteriation of homochiral 3-trimethylsilyl-4-phenylthio-azetidinones leading to stereospecifically-C-3-deuteriated β-alanines.[314]

Azidolysis of the methanesulfonate of homochiral 4-hydroxy-3-methylhex-1-enes, and alkene → CO_2H conversion, provides (2R,3R)- and (2R,3S)-isomers of 3-amino-2-methylpentanoic acid, verifying through comparison with moieties from majusculamide C and dolastatins that these contain the (2S,3R)-isomer.[315]

Unusual synthesis methods for β-amino acids, whose course is determined by the particular synthetic target, have been described for a synthesis of N-alkylamides of the β-amino acid component of the gastroprotective agent AI-77B (Scheme 40),[316] and for (+)-megamycin and its 5-epimer [a fifteen-step synthesis involving Pd(II)-assisted alkylation of a homochiral ene carbamate followed by carbonylative coupling to a trialkylvinyltin].[317] The (9R)-isomer of the 3-amino-10-phenyl-2,5,9-trihydroxydecanoic acid known as "Ahda" has been synthesized by a route starting with a C-C bond-forming step involving the appropriate aldehyde and $(MeO)_2P(O)CH_2COCH_2CH(NHBoc)CH(OR)CH_2OR$.[318] A C-C bond-forming step is involved (N^{α}-Boc-N^{δ}-Z-ornithine + ethyl lithioacetate) in a synthesis of (2R,3S)-3-amino-2-carboxymethylpiperidine.[319]

γ-Amino acids are of increasing general interest because of pseudopeptide field, and for the growing number of members of the family contributing useful physiological properties. Standard methods are illustrated for ^{14}C-vigabatrin (4-amino-5-hexenoic acid), prepared from 5-hydroxymethyl-pyrrolidin-2-one toluene-p-sulfonate and $Na^{14}CN$, and reduction of the nitrile in the presence of Me_2NH.[320] and the natural (S)-isomer, synthesized from either L-glutamic acid through elaborating the α-carboxy group (→ $-CH_2OH$ → $-CHO$ → $-CH=CH_2$)[321] or from D-methionine through a similar sequence but using $(EtO)_2P(O)CH_2CO_2Et$ for the Wittig reaction step, and converting the methylthioethyl side chain into the vinyl moiety.[322]

Vinylogous α-amino acid esters, $R_2NCHR'CH=CHCO_2Et$, undergo Michael addition ($MeNO_2$/DBU) to give β-substituted γ-amino acid esters.[323] A useful route to a synthon for homochiral vinylogous esters involves homogeneous metal-mediated hydroformylation (CO, H_2) of (R)-2-t-butyloxazoline.[324]

(R)-(-)-Baclofen has been prepared by Evans' methodology (cf. Scheme 12) through alkylation of the chiral enolate with $BrCH_2CO_2Bu^t$ and routine elaboration.[325]

(R)-(-)-GABOB (γ-amino-β-hydroxybutyric acid) and (R)-carnitine have been prepared by catalytic asymmetric dihydroxylation of allyl bromide using

$K_3Fe(CN)_6/K_2OsO_2(OH)_4$ in the presence of a dihydroquinidine-derived ligand, conversion of primary OH to CN, and routine elaboration.[326] A more traditional approach to GABOB and to isoserine involves enzymatic kinetic resolution of acetylated racemates formed from cyanohydrins $EtO_2C(CH_2)_nCH(OH)CN$.[327]

A new homologation employs the aluminium acetals that have recently been discovered as intermediates in the low temperature DIBAL reduction of esters; these add to silylketene acetals and allylstannanes in the presence of a Lewis acid, to give γ-amino-β-hydroxy esters.[328]

As in recent years, considerable interest is being sustained in statine synthesis, including routes leading also to stereoisomers and analogues. The chiral synthon (59) is amenable to electrophilic addition [59; R = Me + Br_2/ $MeC(OMe)_3$ → N-substituted (4S,5S)-4-bromo-5-methoxyoxazolidin-2-one → allyl replacing Br with retention of configuration using $CH_2=CHCH_2SnMe_3$/ hν],[329] and Ru(II)-catalysed intramolecular cycloaddition [59; R = $COCHR^1R^2$, R^1 = R^2 = Cl or F],[330] giving enantiomerically-pure products.

Other statine syntheses have been developed; using pyrrolidin-2-ones (60) prepared from methyl (E)-4-chloro-3-methoxybut-2-enoate and incorporating lipase-mediated kinetic resolution,[331] using (4R,5S)-oxazolidin-2-ones (61) prepared in 8 steps from D-glucosamine, leading to natural statine and analogues,[332] or using tetramic acids (62) prepared from (S)-4-N-Z-3-oxo-alkanoate esters through DMAP-catalysed cyclization, and used in a syn-statine synthesis.[333] Pd-Catalysed [3.3]-sigmatropic rearrangement of trichloroacetimidates prepared from homochiral vinylogous α-amino acid esters through reduction [$-CO_2Et$ → $-CH_2OH$ → $-CH_2OC(=NH)CCl_3$] leads to 3-aminodeoxystatines.[334]

N-Protected L-serine and (S)-prolinol undergo DABCO-catalysed Baylis-Hillman addition to methyl acrylate *en route* to the novel sphingosine analogue (63).[335] The increasing use of homochiral aldoses for amino acid synthesis is illustrated in the use of the protected furanose (64) in stereospecific azidolysis and elaboration into 2,3-dihydroxy-4-aminobutanoic acid and its 5-aminopentanoic acid analogue.[336] L-Glutamine acts as starting material for a synthesis of 1-aminoalkyl-4-carboxy-3,4,5,6-tetrahydropyrimidines, pyoverdin constituents that are formally δ-amino acids.[337] Homochiral 5-amino-2-hydroxy-4-oxoalkanoic acid derivatives have been prepared starting from L-α-amino acid-derived Δ^2-1,2-oxazetidines.[338]

All four stereoisomers of 2-methyl-4-hydroxy-5-aminopentanoic acid are obtainable from D- or L-glutamic acids *via* the lactone (65) and its enantiomer;[339a] 5-amino-4-hydroxyalkanoic acids and 3-amino-2-hydroxyalkanoic acids can be approached starting from D-isoascorbic acid.[339b] Synthesis of δ-phthalimido-γ-keto esters has been illustrated in a specific case, employing methyl 3-iodo-2-methylbutanoate and the acid chloride of phthalimido-L-phenylalanine.[340]

New homochiral 7-aminoalkanoic acids are accessible in the form of N-protected δ-amino-γ-lactones, from analogues of (65), through toluene-p-sulfonylation, azidolysis, and conventional elaboration.[341]

4.17 Resolution of DL-α-Amino Acids, and Assignments of Absolute Configuration to Enantiomers of α-Amino Acids

The increasing number of papers on this topic collected here for discussion, include several that are cross-referenced to other sections of this Chapter, since resolution is often a routine terminal step in a synthesis route.

Conventional procedures based on diastereoisomeric derivatives have been used for 2,3-methanopyroglutamic acid (salt formation with L- or D-leucinamide).[342] Correlation of the enantiomers with 2,3-methanoproline, whose absolute configuration was previously established by X-ray crystallography, shows that (-)-2,3-methanopyroglutamic acid is the (2S,3S)-isomer. New variants of this classical resolution procedure include O-benzyl derivatives of (S)-(+)- and (R)-(-)-2-aminobutan-1-ol (resolution of N-acetyl α-phenylglycine and α-(4-hydroxyphenyl)glycine),[343] and moderately-effective mutual resolution of amino acids (81% and 74% enantiomeric excesses, respectively, for phenylalanine and α-phenylglycine) and mandelic acid complexed with Cu(II) ions.[344] Resolution of α-methyltryptophan by co-ordination to Co[(R,R)-N,N-di(2-picolyl-1R,2R-diaminocyclohexane] has been described.[345]

Studies of the underlying physical basis of resolution using these principles are illustrated by an estimation of interactive forces between enantiomers (L- + D-pairs of alanine and phenylalanine have lower energy than L-L- and D-D-pairs).[346] This study has also demonstrated enantiomeric molecular recognition between 4-nitrobenzoylamino acids and N-butyroylvaline t-butylamide. A detailed X-ray study of interactions at the molecular level between one of the classical resolving alkaloids, brucine, and N-phthaloyl threo-β-hydroxy-D- or -L-leucine, reveal hydrogen-bonding between the carboxy and hydroxy groups and the methoxyindole moiety of the alkaloid, as well as electrostatic and van der Waals interactions.[347]

Asymmetric transformations of a traditional nature involve tartaric acid and salicylaldehyde [applied to (R,S)-1,3-thiazane-4-carboxylic acid and leading to enantiomers of homocysteine],[348] and carboxylic acid-catalysed racemization and asymmetric transformation of "unwanted" enantiomers formed during resolution of (R,S)-N-methyl-2-phenylglycine with (1S)-camphor-10-sulfonic acid and of N-ethyl-N-methyl-2-phenylglycine with (R)-phenylethylamine.[349]

Growing interest in the use of homochiral macrocyclic hosts for the resolution of amino acids and derivatives has been reviewed.[350] Research papers illustrating well-established principles concentrate on acetylated and methylated cyclodextrins,[351] a homochiral 18,6-crown ether synthesized from D-mannose,[352] and 36-membered ring pseudopeptides prepared from alternating glycine and (2S,3'S)-4-methyl-2-(2'-oxo-3'-isobutyl-1'-piperazinyl)pentanoic acid moieties.[353] The last-mentioned study includes 24- and 27-membered ring analogues, which are more effective than the larger ring in the resolution of (R,S)-alanine N-methylanilides. Similarly exquisite tailoring of the helicity of the tetrakis (o-aminophenyl)porphyrin ring by connecting the amino groups through different bis(acyl) chains is rewarded with significant chiral recognition in the formation of 1:1-adducts of Zn complexes with amino acid esters.[354] Proline (S)- or (R)-phenylethylamides and (S)- or (R)-lactate esters respond enantio- and diastereo-

selectively to new examples (see Vol.25, p.54) of conformationally homogeneous host podand receptors (66 and hexacyclic analogues) by undergoing enantiopreferential complexation and partition into chloroform.[355]

Selective transport of L-enantiomers of phenylglycine, phenylalanine, and tryptophan has been observed through membranes prepared through crosslinking of poly[γ-(2-chloroethyl)-L-glutamic acid] with diethylenetriamine.[356] Similar discrimination occurs in crown ether-mediated transport of amino acids through supported liquid membranes containing o-nitrophenyl octyl ether.[357]

Chromatographic separations of racemic mixtures based on heterogeneous processes based particularly on the chiral stationary phase (CSP) approach, continue to be studied in detail. The notion of "entangled pairs" has been advanced for enantiodiscriminating interactions between racemic solutes in aqueous media with CSPs using N-(undec-10-enoyl)-L-valine t-butylamide and N-(hex-5-enoyl)-L-valine t-butylamide.[358] Equally subtle design leading to chiral brush-type CSPs has been described, providing unexpected consequences; the separation efficiency and even the order of elution of enantiomers are temperature-dependent.[359] Conventional applications of commercially-available Chirasil-Val CSPs and oligopeptide analogues, continue to be described in the research literature.[360] α-Cyclodextrin dodecabenzoate-modified silica gel has been advocated for chromatographic resolution of p-nitrophenyl esters of Z-amino acids.[361] Insoluble proteins offer readily-available chiral surfaces, and immobilized human serum albumin has been studied in this context for the resolution of DL-tryptophan.[362] In establishing baseline resolution in the HPLC mode in less than 2 min elution time, these workers found that the L-enantiomer binds to the indole site of the protein while the D-enantiomer has no interaction with this site but is attracted indirectly to the warfarin site.

The recent excitement (Vol.25, p.51) generated by molecularly-imprinted stationary phases seems to have subsided as measured by the volume of the associated literature, but no doubt much is going on in research laboratories in view of the potential benefits. An indication that the potential of such phases in related areas is being recognized, is the finding that a silica-alumina surface imprinted with bis(N-benzyloxycarbonyl-L-alanyl)amine, $(Z\text{-L-Ala})_2NH$, exhibits discrimination towards L-, D-, and meso-isomers of the structurally similar anhydride $(Z\text{-Ala})_2O$.[363]

The preferential crystallization technique has been established as a simple, effective large-scale method for the separation of an enantiomer from a racemic amino acid, and the range of examples susceptible to this technique is being steadily extended over the years; the accessibility of D-allo-threonine in this way has been established recently.[364]

Enzyme-catalysed enantioselective hydrolysis and related processes with DL-amino acid derivatives are casually referred to as "resolution", though in many instances only one enantiomer of the racemate is accessible. α-Chymotrypsin continues to be a popular choice in this context, with studies of DL-phenylalanine esters in a liquid/liquid/solid three-phase system indicative of the potential of large-scale working.[365] Studies include α-chymotrypsin-catalysed hydrolysis of α-alkenyl-DL-α-amino acid esters.[366] N-benzylidene DL-amino acid

esters,[367] and β-(isoxazol-4-yl)-DL-alanine esters[368] represent more conventional laboratory studies. In contrast to proteases, carbonic anhydrase-catalysed hydrolysis of N-acetyl DL-amino acid esters favours the D-enantiomer.[369] Penicillin acylase-catalysed hydrolysis has been applied to N-phenylacetyl derivatives of threo-β-(4-fluorophenyl)serine and (2-, 3-, or 4-fluoro- and 2,3,4,5,6-pentafluorophenyl)alanines[370] and to N-phenylacetyl-DL-β-amino acids[371] and to analogous γ-ethynyl-, γ-allenyl-, and γ-vinylGABAs.[372] D-Aminoacylase from *Alcaligenes faecalis* releases D-enantiomers from N-benzoyl- and -benzyloxycarbonyl-DL-amino acids,[373] while the more common aminoacylases, immobilized by bonding to alginate, effectively catalyse the hydrolysis of the L-enantiomer of N-acetyl DL-phenylalanine.[374]

Lipase-catalysed hydrolysis (see also Refs.312, 331) has been used with fluorinated 3-acetoxy-2-(methoxyimino)butanoates, syntheses of enantiomers of mono-, di-, and tri-fluorothreonines and allo-threonines being completed by hydrogenation of the methoxyimino group.[375] Non-protein amino acids, derivatized as 2,2,2-trifluoroethyl esters, can be resolved by lipase in organic solvents by enantioselective transesterification with methanol.[376] A combination of lipase (from *Pseudomonas cepaeia*) for ring-opening of oxazol-5(4H)-ones and thiazol-5(4H)-ones into N-benzoyl- and -thiobenzoyl-L-amino acids, and protease-catalysed kinetic resolution, is advocated for efficient production of L-amino acids.[377]

Exploitation of the propensity of alcalase to tolerate organic solvents as operating medium is seen in its use as catalyst for the hydrolysis of DL-amino acid esters, leading to precipitation of the L-enantiomer.[378] High enantiomeric excess and effective use of the technique with several "unnatural" amino acids is dependent upon the lowest possible water content in the medium consistent with a reasonable reaction rate.

The use of *Arthrobacter* D-amidase for the preparation of D-alanine from DL-alaninamide has been described.[379]

Conversion of L-glutamic acid into D-glutamic acid qualifies for inclusion in this Section of this Chapter. Successive reactions of glutamate racemase (from *Lactobacillus brevis* ATCC 8287) and glutamate decarboxylase (to break down any remaining L-glutamic acid) can be operated efficiently on a large scale.[380]

Whole-bacteria applications have been described for the conversion of DL-5-substituted hydantoins into L-amino acids using *Pseudomonas* sp.strain NS671,[381] and for soil bacteria immobilized in poly(acrylamide), acting on the same substrate to give D-9-hydroxyphenyl)glycine.[382] A common problem in such processes is the inefficiency associated with the consumption by the bacteria of the released amino acids, but the method is viable for the production of L-methionine.

The evolution of the L-amino acids over geological time is a topic under the heading of "resolution" that has been a source of speculation informed by advances in physics and in organic chemistry for many years. One approach–the preferential destruction of D-amino acids in racemates–has been encapsulated as the Vester-Ulbricht theory, and another claim[383] that positron annihilation brings about this result in crystalline leucine must be balanced against the many

opposite assertions in the recent literature. Chiral amplification over time, of any microscopic bias in the L:D-ratio, is also the subject of speculation, and a modification of the respected Frank hypothesis has been proposed.[384] The hypothesis proposes that two types of reaction are involved, autocatalytic generation of L- and D-amino acids and an interaction between them by which they eliminate each other, and it has been suggested that instead of both steps being irreversible, the first step could be considered reversible. The racemization process that opposes the effect of any chiral amplification mechanism, has been considered[385] within the context of the open-chain non-equilibrium model proposed by Kondepudi and Nelson.[386]

Keeping all options open, the prior genesis of homochiral carbohydrates could explain the predominance of L-amino acids on the basis of "hetero-pairing"–as known for many years, the complexing of L-amino acids with nucleic acids involving D-ribose is energetically more favourable than L–L (and D–D) complexation.[387]

5 Physico-chemical Studies of Amino Acids

5.1 X-Ray Crystal Structure Analysis of Amino Acids and Their Derivatives

Although the usual style for this section continues, with papers that report factual material predominating over studies with a deeper penetration, there are some more interesting insights than usual in this year's literature.

Structures for amino acids themselves and their salts have been reported for diglycine hydrochloride,[388] DL-proline hemisuccinate,[389] L-leucine nitrate,[390] sodium cysteine-S-sulfonate,[391] the copper(II) chloride complex of 3,5-di-iodo-L-tyrosine,[392] abrine (*alias* N-methyol-L-tryptophan),[393] and GABA.[394] L-Alanine crystals involve a strong hydrogen bond and significant methyl-methyl interactions, as determined by coherent inelastic neutron scattering data which also provide a measure of vibrational details on a picosecond timescale.[395] Comparison of X-ray details for L-tryptophan picrate and its DL-tryptophan analogue reveals three different sorts of indole–picric acid stacking modes.[396] X-Ray study of DL-histidine–succinic acid (1:3) crystals into which aqueous MeCN is diffused adopt DL-histidine hemisuccinate dihydrate stoichiometry in contrast to the L-histidine system in which the trihydrate is the final state.[397]

N-Substituted amino acids reported on recently are N-di-t-butoxy-carbonyl-L-alanine,[398] N-acetyl-L-homocarnosine monohydrate,[399] N-Z-DL-2-amino-4-phosphonobutanoic acid monohydrate,[400] and N^2-toluene-p-sulfonyl-L-glutamine.[401] N-Substituted amino acid esters (N-diphenylmethylene-L-threonine methyl ester,[402] N-acetyl-L-tyrosine ethyl ester monohydrate,[403] N-phthaloyl β-phenylserine methyl ester [shown to be the (2S,3R)-isomer],[404] and N-t-butoxy-carbonyl-L-valine N-hydroxysuccinimide ester[405] have been studied.

5.2 Nuclear Magnetic Resonance Spectroscopy

Those papers under this heading that are aimed at more than routine data-collecting are given space here. ^{1}H-NMR spectra for Boc-L-valine N-acylurea in

DMSO-$^2H_6$ reveal an intramolecularly hydrogen-bonded ureide NH proton,[406] while studies of pH-dependent chemical shifts for N-acetyl-L-aspartic acid suggest that awareness of the phenomena observed could avoid mistaken interpretations of spectra of similar solutes.[407] In particular, the corresponding signals for N-acetyl-L-aspartic acid overlap those of acetate at pH 4.7, but in more acidic solutions the acetate signals are further downfield. Another well-established principle underlies the use of ^{1}H-NMR in assessing the optical purity of α-N-Boc-amino aldehydes through the slightly differing chemical shift of the Boc resonance seen for each diastereoisomer for semicarbazones formed with (S)-PhCHMeNHCONHNH$_2$.[408]

More common practice now, is to call upon interpretations of NMR spectra derived from two or more nuclei to obtain secure information, for example the 56:44 ratio of conformers of trans-4-hydroxy-N-Fmoc-L-proline in solution determined through ^{1}H–^{13}C studies,[409] and the likelihood of indole ring distortion in 4-methyltryptophan in 0.1M NaO^{2}H/C^{2}H$_3$O^{2}H.[410] A combination of ^{1}H–^{13}C NMR with molecular orbital calculations and X-ray crystallographic analysis has led to identification of an exclusive chair conformation for 1-aminocyclohexane-1,3-dicarboxylic acid diastereoisomers.[411] Routine stereochemical information can be obtained by NMR measurements through the Mosher approach, derivatization with (S)-[methoxy(trifluoromethyl)phenylacetyl] chloride,[412] and Eu(hfc)$_3$ shift studies, illustrated for the latter case for enantiomeric purity determinations with N-phthaloyl 2-cyanoglycine.[413]

Applications of ^{3}H-NMR to tritiated amino acids have been reviewed.[414]

^{13}C-NMR has been applied to a precise determination of ^{14}N/^{15}N equilibrium isotope effects on the acid-base chemistry of the amino group of amino acids in solutions, through determining chemical shift data for the carboxyl carbon atom as a function of pH.[415] Sophisticated applications of solid state ^{13}C-NMR are becoming more frequent, with correlations of protonation state with shielding of the carboxy groups in microcrystalline amino acids,[416] studies of inter- and intramolecular interactions in crystalline amino acids in which the asymmetric unit cell contains three L-isomers and one D-isomer,[417] and measurements of ^{13}C-chemical shift anisotropies of solid amino acids involving spinning side band separation of protonated and non-protonated carbon atoms in slow spinning conditions *via* dipolar dephasing.[418] The interpretations of NMR spectra for nitrogen nuclei in amino acids remain divided between the acquisition of fundamental physical data, such as the quadrupole coupling tensor for the ^{14}N nucleus in a single crystal of L-alanine by the overtone NMR approach,[419] and their use for establishing particular structural features, such as the existence of individual tautomeric forms of histidine in aqueous ethanol at −55°C, with only a very weak hydrogen bond between the π-NH group and the α-amino group (previously claimed to be a more significant structural feature).[420]

^{31}P-NMR features of phosphonamides (67, for the L-amino acid) formed by derivatization of partly-resolved amino acid esters, provide accurate estimates of enantiomer ratios.[421]

5.3 Optical Rotatory Dispersion and Circular Dichroism

Those early applications of these complementary techniques that were used to assign absolute configuration to amino acids, based on the sign of a particular Cotton effect, are now rarely used. The revised geometry for polyoximic acid (Scheme 22) does not query the absolute configuration originally assigned by o.r.d. methods. The unique spectroscopic basis of the techniques can be exploited to follow the course of a chemical change, as in the case of electrochemical oxidation of L-tryptophan.[422]

Architectural features of complex systems, and changes occurring within them, can also be picked out, as for the identification, based on the large positive CD centred at 213–215 nm, of micellar aggregation of N-palmitoyl- and N-stearoyl-L-serines in aqueous solutions.[423] The CD arising through coupled amide chromophores in a regular array around the micelle surface, is largely lost by disintegrating the micelles in 50% aqueous ethanol. A different explanation has been given for the same strong CD feature, seen for methanol solutions of N-dodecanoyl derivatives of L-glutamic acid and L-valine, together with a smaller negative CD peak at 240 nm.[424] These results are now interpreted to indicate dimerisation (supported by IR evidence) and the presence of two different rotamers, and in this respect these workers have replaced a previous interpretation involving hydrogen bonding between carboxy groups and NH moieties.

5.4 Mass Spectrometry

All the papers from the 1993 literature discussed here deal with spectra generated for the amino acids themselves using the more sophisticated instrumental variants. Interpretation of spectra obtained for derivatized amino acids through standard ionization techniques now generally amounts to a routine exercise, and papers covering this approach are mostly excluded from this review.

^{252}Cf-Plasma desorption MS of glycine–alkali metal salt mixtures [425] and of mixtures of 3, 4, or 5 amino acids,[426] in both positive ion and negative ion modes, have been interpreted. Strong MH^+ and $[M - H]^-$ parent ions are formed. The negative ion mode responds most easily to interpretation. Plasma desorption MS provides more prominent parent ions with a range of energies, and compares favourably with ammonia and methane CIMS for the leucine-and-isoleucine test case.[427]

Aqueous solutions of amino acids, sampled by the atmospheric pressure electrospray technique, yield positive ions in intensity order alanine, leucine threonine, serine, aspartic acid, glutamic acid.[428]

Cycloalkane-based β-amino acids have been shown to conform to the general pattern for primary amines in favouring α-cleavage at nitrogen after ionization in the mass spectrometer.[429]

Techniques leading to significant fragmentation can occasionally provide useful stereochemical information, as revealed in an interesting FAB-MS distinction between the N-benzyloxycarbonyl derivatives of γ-hydroxyornithine diastereoisomers due to the faster side-chain dehydration shown by the negative ion of the threo-isomer.[430]

5.5 Other Spectrometric Studies of Amino Acids

This section exists to acknowledge the variety of relevant work on amino acids involving spectrometric techniques in addition to those already covered in preceding sections, but again, excludes routine material.

Rotational spectra for alanine have been interpreted in terms of dipole moment data showing the presence of two conformers corresponding to those already demonstrated for glycine.[431] Another example of extensions of earlier work describes IR spectra of CCl_4 solutions containing N-Boc-L-proline N-methylamide and phenol, interpreted to reveal the formation of hydrogen-bonded complexes involving the amide carbonyl group.[432]

At first sight, ESR spectra of $CaCO_3$ and hydroxyapatite doped with amino acids represents a routine study in giving the expected signals for radicals derived through side-chain cleavage.[433] However, the septet for isopropyl radicals derived from L-valine is accompanied by signals for the t-butyl radical, indicating the involvement of potentially interesting heterogeneous chemistry. More conventional ESR research is illustrated by monitoring ^2H–^1H exchange processes occurring in a γ-irradiated single crystal of L-alanine.[434]

Electronic absorption spectra of analogues of phenylalanine and tyrosine constrained within a supersonic jet have been obtained using laser-induced fluorescence measurements.[435]

5.6 Other Physico-chemical Studies of Amino Acids

A number of novel strands of research have developed in recent years under this heading, and most of them continue to be pursued. Membranes capable of penetration by amino acids have been of considerable interest, especially when they show enantioselective transport properties (see the earlier Section 4.17 Resolution), and a novel twist is shown in a property of some membranes to allow the transport, by ε-Schiff bases formed between N^{α}-Z-L-lysine methyl ester and copper(II) or nickel(II)-3-substituted salicylaldehydes, of Li, Na, K, Cs, Ca and ammonium ions.[436] Gels made up of micellar rods and vesicular tubules form from aqueous solutions of L-lysine derivatives $H_3N^+CH[(CH_2)_4NHCO(CH_2)_{11}NH_2]CO_2^-$.[437]

Thermodynamic data accumulated over recent years, feature enthalpies of solution of amino acids in the 0.005–0.07 mol Kg^{-1} concentration range,[438] enthalpies of dilution of aqueous solutions of β-alanine, α-aminobutyric acid, γ-aminobutyric acid, ε-aminocaproic acid, α-aminovaleric acid, and threonine,[439] and enthalpic pairwise interaction coefficients of N-acetyl-L-leucinamide and N-acetylglycinamide in concentrated aqueous tetramethylurea and in urea.[440] The last-mentioned study indicates structure-dependent coefficients, suggesting that protein denaturation in these media is a complex process. Calorimetric studies have been extended to amino acids with heteroatoms in their side-chains.[441]

Partial molar characteristics (apparent molar volumes, apparent compressibilities, etc) have been determined for aqueous solutions of glycine and alanine under high pressures, by ultrasound methods.[442] More conventional studies have been reported for apparent molar volumes of amino acids in aqueous solutions of

varying KCl concentrations,[443] for limiting partial molar volumes obtained from density measurements of aliphatic amino acids in water containing various admixtures of HCl and NaOH,[444] and for partial molal isothermal compressibilities of glycine and alanine in aqueous solution.[445]

On a simpler conceptual level, the cryoprotectant role of amino acids *in vivo* is reflected in studies of aqueous glycine in canine renal tubules,[446] and separations of amino acid mixtures are represented in measurements of crystal growth kinetics of L-alanine from solutions containing L-phenylalanine or L-leucine.[447]

Hydrophobicity values for tryptophan deduced from partition coefficient data, and hydrophilicity and lipophilicity values for the same amino acid determined from vapour-to-solvent coefficients, have been reported.[448]

Stability constant data for proton- and metal-ion-complexation equilibria for aliphatic amino acids have been reviewed,[449] accompanying new data for mixed ligand complexes of lysine + aspartic acid, lysine + succinic acid, and glycine + malonic acid.[450]

The effect of ionic strength on the acid-base stoichiometric ratios for L-valine[451] has been determined, as has the role of urea (1–8 mol dm^{-3}) in suppressing the first ionization constant of amino acids.[452] Fingers have been wagged at those who draw titration curves incorrectly for amino acids to show the change of charge distribution as a function of pH–graphs can be mis-shapen, or the axis of the graph can be mis-labelled.[453] The extraordinary development of scanning tunneling microscopy has been extended in the amino acid field with visualization of individual molecules of glycine, alanine and phenylalanine adsorbed on graphite.[454]

5.7 Molecular Orbital Calculations for α-Amino Acids

As usual, the papers collected for this section defy tidy classification, although all are aimed in one way or another at assisting understanding of amino acid structures and properties.

Extensions have been published to a series of papers (Vol.25, p.60) advocating a molecular connectivity model for describing physico-chemical properties of α-amino acids.[455]

Conformational assignments and energies of intramolecular interactive forces are frequently represented in papers under this heading, and N-formyl L-valinamide[456] and other N-formyl amino acid amides[457] and N-acetyl-L-alanin-amide[458] have received detailed attention in this context. *Ab initio* IGLO (individual guage for localized orbitals) calculations for N-acetylglycine N-methylamide have been aimed at relating isotropic ^{13}C chemical shifts to putative conformations.[459] These amino acid derivatives are obviously chosen as models for residues in proteins, so that meaningful statements about the behaviour of amino acids in this context may be made, but more direct models have been used, to assess the effect of change of configuration on the phenylalanine residue at the active site of thermolysin,[460] and to assess the influence of neighbouring side-chains on particular amino acid residues in proteins.[461]

For the amino acids themselves, calculations have been reported for

interaction energies of the 20 coded amino acids,[462] for ground state geometries and energies of first excited singlet states of phenylalanine and tyrosine,[463] and for hydrophobicity characteristics derived from calculations of electrostatic fields at points on the van der Waals surfaces of amino acids.[464]

Calculated proton affinities of lysine and histidine show the considerably higher relative basicity of lysine.[465]

6 Chemical Studies of Amino Acids

6.1 Racemization

A 1989 report that racemization accompanies microwave heating of aqueous L-proline solutions (Vol.23, p.51) has been disputed repeatedly, and most recently through experiments involving aqueous solutions of L-alanine, L-glutamic acid and L-proline. These are unchanged after 30 min heating either on a hotplate or in a microwave oven.[466] Much more drastic treatment, ^{60}Co γ-irradiation, of L- or D-leucine, or DL-leucine, fails to cause racemization even though some degradation occurs, into H_2, CO_2, and NH_3.[467]

Time-honoured methods for bringing about amino acid racemization depend upon derivatization, such as dissolution of esters in ketones containing acetic acid; the best reagent is acetone containing 15% acetic acid.[468] Hydantoins are readily racemized through contact with an anion exchange resin (Q-Sepharose) at pH 6–13.5.[469]

Little that is new, has appeared in the scientific literature covering fossil dating through measurement of enantiomer ratios of indigenous amino acids.[470]

6.2 General Reactions of Amino Acids

This substantial section of this Chapter deals with reactions involving (a) the amino group; (b) the carboxy group; (c) both amino and carboxy groups. Reactions at the α-carbon atom of α-amino acids have mostly been covered in earlier sections covering synthetic methods. The next section 6.3, covers reactions involving amino acid side-chains.

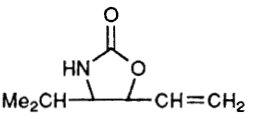
One of the simplest reactions at the amino group, often taking place without being appreciated as such, is carbamate formation in solutions of amino acids and peptides ($H_3N^+CHRCO_2^- + CO_2 \rightarrow H^+ + {}^-O_2CNHCHRCO_2H$).[471] However, amino acids with $pK_a > 9.5$ do not form significant amounts of carbamate in neutral aqueous solutions. Another simple reaction, N-chlorination, continues to receive detailed mechanistic study (Vol.25, p.63), recent results indicating that protonation of N-chloro-α-amino acids takes place at lower pH than previously thought ($pK_a < 1$ for the -NHCl moiety) and that this step is crucial in promoting the decomposition of these species.[472] The decomposition of N-chloro-glutamic acid and of N-chloro-threonine is a first order process, and is independent of pH over the range 5–10.[473]

N-Oxide formation with N-benzyl-L-prolinamide is completely diastereo-selective.[474] N-Alkoxycarbonyl oxaziridines are effective new electrophilic

aminating agents, bringing about the conversion of amino acids (as tetra-alkylammonium salts) and their esters into N-alkoxycarbonylhydrazino acids.[475]

Reductive alkylation of α-imino acids, e.g. L-proline, is the outcome of reaction with ketones in the presence of H_2/Pd-C [$HNR^+CHR'CO_2^-$ + MeCOR → (S,S)-$RCHMeNH^+CHRCO_2^-$].[476] This recipe is involved in a classic Z-protecting group removal procedure, and is responsible for inadvertent N-methylation in H_2/Pd-C/MeOH treatment of Z-amino acids due to Pd-catalysed oxidation of solvent to formaldehyde.[477] This side-reaction can be avoided by including at least 5% water in the solvent, or changing solvent to isopropanol (or, of course, by ensuring the absence of oxygen!). The Pictet-Spengler reaction is well-known for the preparation of isoquinolines from indolylethylamines, and when applied to a mixture of an aldehyde and an N-[2-(indol-3-yl)ethyl]-L-amino acid ester, it results in enantiospecific ring closure on the secondary amine.[478] Mono-N-methylation of amino acids can be accomplished by cyanoborohydride reduction of N-(o-nitrobenzylidene)amino acid esters followed by photolytic cleavage at 350nm.[479] The same process is used to cleave N-(o-nitrobenzyl)amino acid amides.[480] bis-N-Alkylation of (4'-nitrophenyl)alanine by $BrCH_2CH_2N(CH_2CO_2R)_2$ has been reported.[481] Release of the homochiral β-amino-β-phenylalkanoic acid ester from the product of a classical asymmetric synthesis protocol (→ $EtO_2CCH_2CHPhNHCHPhCH_2OH$ → $EtO_2CH_2CHPhNH_2$) would be accomplished by hydrogenation were it not for the bis(benzyl)amine character of the compound. An alternative $Pb(OAc)_4$ cleavage procedure is effective, without causing racemization.[482] Removal of N-benzenesulfonyl or -toluene-p-sulfonyl groups from alanine or phenylalanine has been long known to be achievable electrochemically, and a recent study throws light on the nature of the three cathodic reduction steps that are involved.[483]

A large crop of papers covering amino acids carrying familiar N-acyl and similar groups has emerged in the 1993 literature. N-Stearoyl-, -oleyl-, and -ricinoleyl-L-leucines have been prepared as potential antibacterial agents.[484] N-Boc amino acids can be prepared through acylation of amino acid salts by Boc-imidazole.[485] The recently disclosed bis-N-Boc amino acids can be converted into their N-Boc analogues by $Mg(ClO_4)_2$/MeCN, and this leaves the t-butyl ester moiety unaffected when applied to $(Boc)_2$-aspartic acid β-t-butyl ester α-methyl ester.[486] Solid phase N-(9-fluorenacetyl)ation of amino acids on a hydrophobic polymeric support has been explored,[487] and insignificant effects have been established, of constituents (salts, buffers, surfactants) in the reaction medium on the course of N-(9-fluorenylmethoxycarbonyl)ation (by Fmoc-Cl), N-phenylthiocarbamoylation, and cyanoisoindole formation (by naphthalene-1,2-dicarboxaldehyde/CN^-).[488] Replacement of N-Fmoc by N-Z in good yield can be achieved for the protected amino acids, by using N-Z-5-norbornene-2,3-dicarboximide/KF/Et_3N.[489] Optically-pure N-Fmoc amino acids can be obtained by mild [$Ti(OPr^i)_4$] cleavage of N-acylsultams where the acyl group is $(MeS)_2C$=NCHRCO-.[490] Rapid (5 min) N-allyloxycarbonyl group cleavage from N-Alloc-amino acids can be accomplished by Pd(0)-catalysed allyl transfer to diethylamine, and even the most severely hindered cases (e.g. N-Alloc-N-Boc-anilines) are cleaved within 45 min.[491]



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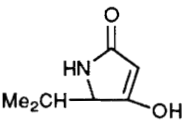

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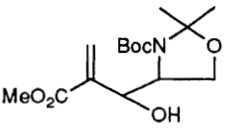

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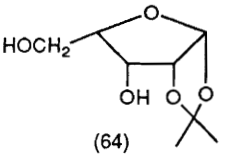

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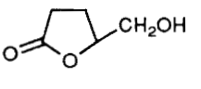

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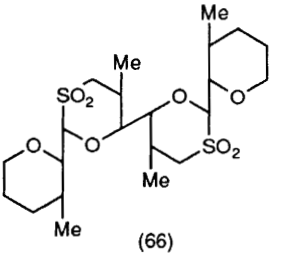

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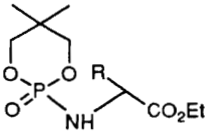

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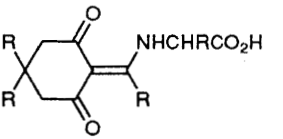

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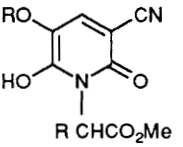

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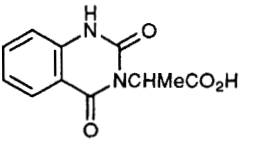

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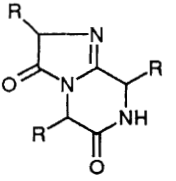

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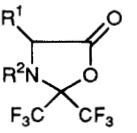

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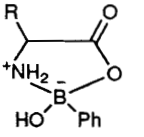


(73)

An N-protection strategy, enamine formation (→ 68 and methyl homologues, deprotected by hydrazine at room temperature)[492] is particularly useful in peptide synthesis since it provides a compatible side-chain protection strategy for lysine.[493] Enamines $MeCOCMe=CMeNHCHRCO_2Me$ have been prepared from a mixture of 1,3-diketone, amino acid ester hydrochloride, and KF in dry conditions, under microwave irradiation.[494] The 3-(3',6'-dioxo-2',4',5'-trimethylcyclohexa-1',4'-diene)-3,3-dimethylpropanoyl grouping used as an N-protecting group leads to redox-sensitive, coloured derivatives, that can be deprotected by aqueous sodium dithionite.[495]

New examples of reactions at nitrogen, that result in this function becoming enclosed within a heterocyclic ring, have been described for methoxymethylene malononitrile (→ 69)[496] and o-methoxycarbonylphenyl isocyanate(→ 70).[497]

Enzyme-catalysed de-amination of amino acids is represented here by unusual examples, (R,S)-2-methyl- and (S)-2,2-dimethyl-1-aminocyclopropanecarboxylic acid (by bacterial ACC deaminase),[498] and N^{γ}-Z-L-lysine to give the α-hydroxy acid (by L-amino acid oxidase from *Providencia alcalifaciens* together with L-2-hydroxyisocaproate dehydrogenase).[499]

Reactions at the carboxy group of an amino acid generate at least as much research interest as the corresponding processes at the amino group, and new methods have been reported, as well as the development of established methods. Tetra-n-butylammonium salt formation has been adopted as both a useful solubilizing technique for taking up amino acids into organic solvents, and as a transient carboxyl protection strategy, and further practical details have been published on the procedure.[500] Sodium L-prolinate–borane complexes have been advocated [501] for asymmetric reduction of aromatic ketones, though they are not so effective as the NN'-dibenzoyl-L,L-cystine–$LiBH_4$–ROH complex. Recently the stability and usefulness of suitably N-protected amino acid fluorides was established, and N-bis(Boc)amino acid fluorides have been added to the list.[502] They are prepared using cyanuric fluoride in CH_2Cl_2/py from −30 to −20°C.

Acid anhydrides feature in several studies, in a conventional preparation of Fmoc amino acid p-nitroanilides involving isobutyl chloroformate activation [i.e., unsymmetrical (*alias* mixed) anhydride formation] of Fmoc amino acids,[503] and in a corresponding preparation of Z-amino acid active esters.[504] In the course of the last-mentioned study, it was noticed that some mixed anhydrides disproportionate in CH_2Cl_2 during 24h to give the symmetrical anhydride (depending on the alkyl group of the chloroformate) and the amino acid ester.[505] In an alternative but otherwise equally conventional activation of the carboxy group of a Boc amino acid using N-ethyl-N'-(3-dimethylaminopropyl)carbodi-imide, and presentation to p-nitrophenol in an intended conventional esterification protocol, 8–25% of the corresponding dipeptide p-nitrophenyl ester was formed (Boc-aa^1-OH → Boc-aa^1-aa^1-ONP).[506] The side reaction can be prevented by the presence of an equivalent of N-methylmorpholine, and the side reaction is explained by partial Boc breakdown, seen elsewhere (Vol.25, p.67) after cyclization to the 2-t-butyloxyoxazol-5(4H)-one, leading to the amino acid N-carboxyanhydride, an effective acylating agent that reacts with p-nitrophenol and is then in possession

of a free NH_2 group that is acylated by the activated Boc amino acid. Di-alkyl pyrocarbonates in the presence of NEt_3 have been advocated for symmetrical anhydride formation, and esterification of N-protected amino acids.[507]

Esters can be prepared as described in the preceding paragraph and by other time-honoured methods, applied for the in-vogue synthesis of esters using 1,9-(4-hydroxycyclohexano)buckminsterfullerene.[508] A novel method with alkyl trichloroacetimidates $ROC(=NH)CCl_3$ as esterifying agents, has been used to prepare Fmoc amino acid 2-phenylisopropyl esters.[509] These can be cleaved acidolytically under mild conditions so as to leave N-Boc protection and t-butyl ethers and esters unaffected. Butyl esters of Z-amino acids can be prepared by reaction with $Bu^tBr/K_2CO_3/PhCH_2N^+Me_3\ Cl^-$/N,N-dimethylacetamide.[510] Vinyl esters can be prepared through mild oxidation of N-protected amino acid (2-phenylselenenyl)ethyl esters.[511] De-protection of benzyl esters can be accomplished in dry conditions (microwave irradiation of samples on an alumina surface),[512] and phenacyl esters can be cleaved while leaving benzyl and 4-nitrobenzyl esters unaffected, by using tetra-n-butylammonium fluoride hydrate in the presence of 10 equiv 1-octanethiol.[513] Aminoacylimidazoles are capable of more than the well-known mono-esterification of ribonucleotides, since bis(2',3'-diesters) and mixed anhydrides involving phosphate are also formed.[514] The bis(2',3'-diesters) of 5'-AMP are hydrolysed at different rates at different pH, and N-acetyl-L-phenylalanyl diesters are hydrolysed 1.7–2.1 times faster than their D-analogues possibly due to "protection" of the latter by an association with the adenine ring.[515] When N-acetyl-DL-valine is esterified by ribonucleotides, esterification rates are faster for the D-enantiomer.[516] Similar enantioselectivity has been noted frequently with reactions of amino acid esters, and non-polar L-compounds are hydrolysed twice as fast as their D-analogues in the presence of [trans-5,15-bis(2-hydroxyphenyl)-10-[2,6-bis(methoxycarbonylmethyl)phenyl]-2,3,17,18-tetraethylporphyrinato]zinc(II) (though interestingly, the reverse is the case for serine benzyl ester).[517] Aromatic amino acid octadecyl esters undergo polycondensation much more rapidly in the monolayer state.[518] Racemization occurs during the aminolysis of amino acid active esters by amino acid anions in aqueous DMF, i.e. under basic conditions, though the finer details show that the extent of the side reaction is dependent upon the amino acid and on the base used. It is particularly noticeable for valine and $NaHCO_3$, and can be minimized by working with a 50% excess of the amino acid, and with Na_2CO_3 as base.[519] More conventional studies of amino acid esters involve hydrolysis kinetics of phenylalanine methyl ester in comparison with those for aspartame,[520] and ammonolysis through the use of diaminomethane dihydrochloride as a convenient *in situ* ammonia release agent.[521]

Research interests employing amino acid amides often have similar objectives to those described for esters, and an especially notable result is the enzyme-like properties of the synthetic lipids $Me_3N^+(CH_2)_5CO$-L-Ala-$N[(CH_2)_{15}Me]_2\ Br^-/Cu^{2+}$ that catalyse the condensation of DL-serine with indole to favour L-tryptophan as product, when the L-alaninamides are formed into a hybrid bilayer membrane structure.[522]

Reduction of amino acids to 2-amino alkanols with $NaBH_4$–I_2 in THF is

also appropriate for the corresponding process for N-acylamino acids.[523] The direct reduction of L-proline to L-prolinol can be effected in 85% yield with $LiAlH_4$ in THF at 85°C during 3h.[524] $NaBH_4$ Reduction of mixed anhydrides formed from Boc-amino acids gives the corresponding alkanols within a 1h reaction period, and these have been used in a synthesis of homochiral N-Boc-aziridines.[525] Other uses for 2-amino alkanols include a synthesis of α-methyl-amines [L-histidinol → (R)-histamine *via* the chloromethyl analogue and reduction with ammonium formate/Pd-C],[526] and an important role in the preparation of corresponding aldehydes, with Moffatt-Swern oxidation giving good yields of optically-pure products from 2-(Boc-amino)alkanols[527] and applicable also to N-protected N-allylaminoalkanols.[528] Full details of the preparation of Garner's widely-used N,O-protected (S)-serinal (37, CHO in place of $CH=CHCO_2R$) in which DIBAL-H reduction of the protected methyl ester is employed, are available.[529] New methods, illustrated with 3-(N-Boc-amino)-1,2-propanediol giving N-Boc glycinal in 76% yield when cleaved with aqueous KIO_4,[530] and reduction of S-benzyl thioesters with Et_3SiH/Pd-C.[531] The aldehydes can be used in the Wittig alkene synthesis, and thence to a variety of destinations; in a Diels-Alder reaction with Danishefsky's diene to give dihydropyrones,[532] and in an evaluation of a stereospecific synthesis of pyrrolidines and piperidines.[533] A conversion of N-Boc-valine into $BocNHCH(Pr^i)CH=CHCH_2OH$ is notable.[534] Weinraub amides are a convenient source of the aldehydes in particular cases, and preparation and use in pseudopeptide synthesis, of a fully-protected arginine, N^{α}-Boc-Orn[NZC(NHZ)=NH]-NMeOMe,[535] and preparation of bis(N-benzyl)-L-phenylalaninal and its use in the synthesis of (4S,5S)-4-hydroxy-5-amino-6-phenylhexanoic acid,[536] have been described.

γ-Lactams may be obtained by Mg/MeOH treatment of γ-amino acid derivatives $RO_2CNHCHRN^1R^2CH=CHCO_2R^3$ formed in this way.[537]

Amino acid esters react with arylmagnesium halides, to give the expected diarylcarbinols,[538,539] those derived from L-valine methyl ester yielding homochiral 1,2-diamines through routine elaboration.[539] α-Aminoglyoxals have been obtained by reaction of dimethyldioxirane with α-diazoketones derived from amino acids.[540]

Sulfur analogues of the carboxy group are of continuing interest and thiono- and dithio-esters, have been prepared in the conventional manner from nitriles through the Pinner reaction with alkanols and thiols respectively, followed by thiohydrolysis.[541] Reductive acylation of L-α-amino thiocarboxylic acids,[542] and preparations of Boc- or Z-L-amino acid thionimides[543] have featured in recent papers.

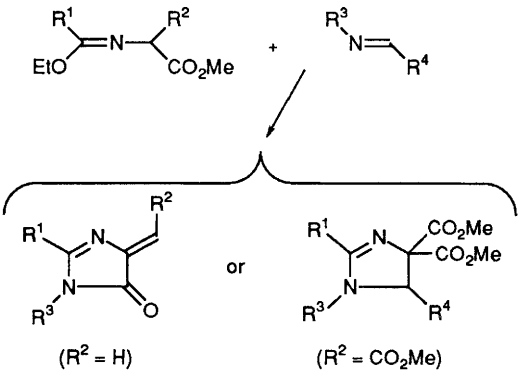
More extensive modification at the carboxy group and the neighbouring α-carbon atom is involved in the numerous oxidative processes that will be familiar to readers of this Chapter over the years. D-Amino acid oxidase reacts slowly with glycine, serine, arginine, histidine, tryptophan, norleucine, and aspartic and glutamic acids. The expected total inability of the enzyme to catalyse the oxidation of L-amino acids has been confirmed in this study.[544] Two citations are offered to represent the numerous mechanistic studies of oxidative decarboxylation of amino acids with simple oxidants (dichloramine-B;[545] N-

bromoacetamide[546]) that continue to appear in the literature. The role of Cu(II), Fe(II), and Mn(II) ions in oxidative modifications of amino acids and proteins has been reviewed.[547] Rates of oxidation of amino acids by the superoxide anion have been measured based on the accompanying chemiluminescence.[548]

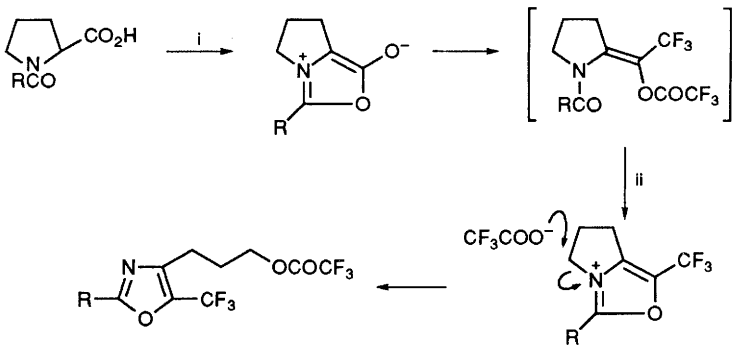
One of the best-known, but only recently properly understood, oxidative decarboxylative modifications of amino acids is that brought about by ninhydrin. Further indications of the synthetic potential of the early azomethine ylide-forming stage of the racemization-free process involving proline or sarcosine are given in the trapping of these transient intermediates by cycloadditions.[549] An account of sensitive colour-forming reactions with ninhydrin and analogues, and corresponding fluorimetric procedures, has been published.[550]

The self-condensation of amino acids takes many pathways, and of course these have considerable importance in geological and biological fields as well as for their essential chemistry. The products of repeated sublimation of simple aliphatic amino acids on to silica and alumina surfaces at 220–240°C have been separated and analysed, and shown to include short peptides, di-oxopiperazines and bi- and tri-cyclic amidines (71) derived from the di-oxopiperazines.[551] Simple additional by-products indicate these products to suffer further degradation.[552] Further results (Vol.25, p.62) for the extraordinary condensation of amino acids into peptides in aqueous solutions with NaCl and $CuCl_2$ have been provided. Successive evaporation and dissolution cycles generate peptides in 1–3 days from glycine, alanine, and aspartic and glutamic acids.[553] Mixtures of glycine, alanine and valine yield mainly N-terminal glycyl dipeptides in the early stages of this process.[554] Rates of formation of multi-component mixtures through heating aspartic acid with proline in aqueous solutions suggest an autocatalytic character to the process.[555] Di-oxopiperazines are formed from 2,2-bis(trifluoromethyl) oxazolidin-5-ones (72) in methanol at room temperature, understood on the basis of the easy hydrolysis of the heterocycle; and the N-carboxymethyl analogues (72; R^2 = $-CH_2CO_2H$) have been prepared from N-carboxymethylamino acids.[556]

Heterocyclic compounds enclosing the -HNCHRCO- moiety are most commonly formed through reactions involving both NH_2 and CO_2H groups of amino acids, and new examples with interesting properties are still being discovered, such as the relatively lipophilic arylboronic acid chelates (73) whose structure, with a little licence, could be categorized as heterocyclic.[557] Imidazolinones are formed through cycloaddition of stabilized ylides derived from Schiff bases of α-amino acids (Scheme 41).[558] N-Acylamino acids often exhibit reactions that are explicable on the basis of initial cyclization to oxazol-5(4H)-ones, as in the case of N-acylproline ring cleavage with trifluoroacetic anhydride (Scheme 42).[559] Undoubtedly, the course of the reaction of N-acylamino acids with the Vilsmeier reagent ($POCl_3$/DMF) leading to (74) and (75) [and (76) from homocysteine thiolactone], can be explained from the same starting point.[560] Reversal of the cyclization is represented in α-chymotrypsin-catalysed hydrolysis of oxazol-5(4H)-ones to N-acyl-L-amino acids,[561] and basic hydrolysis of analogous 2-anilinothiazol-5(4H)-ones to N-phenylthiocarbamoyl amino acids.[562] Hydrogenolytic cleavage of 4-substituted oxazolidin-5-ones using Et_3SiH/

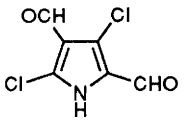


Scheme 41



Reagents: i, TFAA, py., DMAP(trace), 80 °C; ii, $-CF_3COO^-$

Scheme 42



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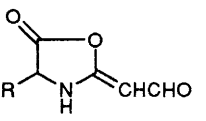

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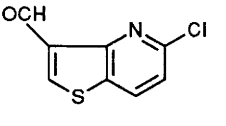


(76)

CF_3CO_2H is a useful, clean, preparation of Z-N-methylamino acids starting from the Z-amino acids (H_2/Pd cleaves the methyl group as well as the Z group).[563]

The Maillard reaction represents a long and complex pathway leading to mixtures of heterocyclic compounds, starting with a Schiff base formed between an α-amino acid and an aldose or ketose. An up-to-date review of the process from the food processing perspective is available,[564] and a representative paper covering the reaction in the physiological context establishes that 2-amino-6-(2-formyl-5-hydroxymethylpyrrol-1-yl)hexanoic acid, *alias* pyrraline, is not a major intermediate or advanced glycation end-product formed from amino acids under physiological conditions, as recently claimed.[565]

β-Amino acids have available to them the monocyclization pathway to azetidinones and this can be brought about using (3-nitropyridyl) dialkyl phosphates[566] or alkylaluminium compounds e.g. Bu^s_3Al.[567] 5-Amino-2-oxo-pentanoic acid exists partly in cyclized form (pyrrol-1-eine-2-carboxylic acid) in aqueous solutions, in proportions dependent upon pH.[568]

6.3 Specific Reactions of Amino Acids.

"The side-chain chemistry of the amino acids" would be a suitable alternative title for this section, and there is some overlap with earlier synthesis sections to the extent that familiar amino acids are chosen increasingly often as the starting point for the synthesis of other amino acids by side-chain modification. Some of this chemistry involves the amino and/or carboxy groups of the amino acids, as well as their side-chains.

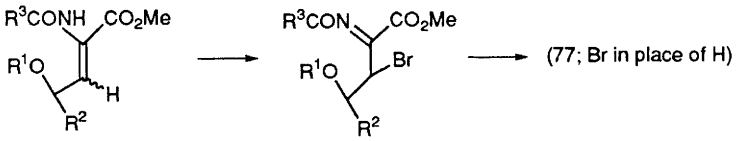
Complete removal of the side-chain could be a way of describing the conversion of protected α-methoxyglycine into highly electrophilic iminium ions [$RO_2CNHCH(OMe)CO_2R' \rightarrow RO_2CNH^+{=}CH(OMe)CO_2R'$] to give versatile glycine cation equivalents that undergo ready alkylation,[569] though α-methoxyglycine and related α-heteroatom-substituted glycines should be appreciated to be a special case. Corresponding alanines react similarly but dehydroalanine formation is a significant side-reaction. Dehydro-amino acid esters, i.e. α,β-unsaturated α-amino acid esters, react stereospecifically with brominating agents to give syn-α-bromo-imines (77 → 78) from which (E)- and (Z)-β-bromo-analogues of the initial reactants can be obtained by base-induced tautomerization.[570]

The side chain ketone function in 3-oxo-L-proline undergoes Baker's yeast-catalysed reduction to give (+)-cis-(2R,3S)-3-hydroxyproline with better than 90% enantiomeric enrichment.[571] Hydroxylation of L-proline catalysed by proline 4-hydroxylase is accomplished with retention of configuration at C-4.[572] The reverse process, the oxidation of the side-chains of the more familiar β-hydroxy-α-amino acids, serine and threonine, to formyl and acetyl respectively, has been accomplished more efficiently than heretofore, after protection of the carboxy groups of the Fmoc-amino acids as the cyclic ortho-ester (79).[573] This useful transformation opens up a further range of applications for synthesising amino acids from serine and threonine (Wittig and similar processes are suggested, and many other functional group transformations could be added), and also allows β-^{2}H labelling. These amino acids are featured in several further citations here as well as in preceding sections of this Chapter, where their uses in

synthesis are described. Full details for the preparation (Ph_3P/DEAD) of the β-lactone of Boc-L-serine have been published.[574] The aziridine obtained by cyclization of Fmoc-L-serine benzyl ester can be opened with 3,4-dimethoxy-6-nitrobenzyl alcohol to give the photo-deprotectable O-aryl serine.[575] Serine methyl ester and benzaldehyde gives a more complex equilibrium mixture[576] of ring–chain tautomers (i.e. Schiff base together with oxazolidines) than previously supposed. The formation of the corresponding N-Boc-oxazolidine from N-Boc-L-serine methyl ester and acetone calls for Mitsunobu reaction conditions.[577] N-Trityl-L-serine methyl ester reacts with thionyl chloride to give the cyclic sulfimidate (80), from which the sulfamidate can be obtained by oxidation.[578] O-Allylation of β-hydroxy-α-amino acids can be accomplished using allyl trichloroacetimidate.[579] *Streptomyces amakusaensis* possesses a novel aldolase that catalyses reverse aldol cleavage of β-hydroxy-α-amino acids.[580]

Aspartic and glutamic acids have many synthetic applications, like the β-hydroxyalkyl-α-amino acids, and again, the reader is directed to other sections in this Chapter so as to access the full coverage of the recent literature on this topic. Glutamic acid α-semialdehyde has been prepared by ozonolysis of γ-vinylGABA, and shown to exist in the cyclic form (81), so explaining its unexpectedly high stability; it can be purified by ion exchange chromatography over Dowex 50W-X8, while α-amino aldehydes are generally considered to need careful handling and storage.[581] Several cyclized forms of aspartic and glutamic acids are useful in synthesis; Z-L-aspartic anhydride has been widely used in aspartame synthesis;[582] the 2,2-bis(trifluoromethyl)oxazolidin-5-one (cf. 72) derived from aspartic acid diazomethyl ketone and used in 4-oxo-L-proline synthesis;[583] and similar oxazolidinone formation allowing the side-chain carboxy group of L-glutamic acid to be elaborated into -COSEt and $-CH(OMe)_2$ *en route* to (+)-porothramycins A and B,[584] and allowing side-chain acid chlorides to be elaborated into sensitive functional groups when the oxazolidinone is protected as the $N\text{-}Cl_3CCH_2OCO$-group (cleaved by Zn/AcOH).[585] Regioselective ring-opening through amide cleavage of N-Boc-pyroglutamic and "-pyroaminoadipic" acid ethyl esters with nucleophiles ROH, RNH_2, $PhCH_2SH$ (KCN catalysis under ultrasound) provides the corresponding γ-carboxy-derivatives.[586]

Enolate di-anions formed with fully protected L-aspartic acid by treatment with $LiN(SiMe_3)_2$ undergo oxygenation by N-(benzenesulfonyl)-3-phenyloxaziridine to give β-hydroxyalkyl-α-amino acids $(2S,3S)\text{-}R^1NHCH(CO_2R^2)CH(OH)CO_2R^3$, while with oxydiperoxymolybdenum in pyridine + HMPT they give the 3R-epimer.[587] Acylation of the corresponding glutamic acid enolate leads to δ-oxoalkyl-α-amino acids *via* decarboxylation of the initially-formed β-keto-esters.[588] An improved synthesis of (S)-α-amino adipic acid δ-methyl ester from L-aspartic acid and its elaboration into homochiral 3-aminocyclopentyl-methanols after Dieckmann cyclization, has been reported.[589] Conversion of L-glutamic acid into its "3,4-didehydro-analogue" in the form of its N-(9-fluoren-9-yl) methyl ester, followed by non-stereoselective methylation ($LiMe_2CuR$) to give 3-methylglutamic acid, and conversion by DIBAL-H reduction, carbamoylation and OsO_4 cleavage into (+)-5-O-carbamoyl polyoxamic acid.[590] 3-Methylaspartic acid has been prepared from DL-glutamic anhydride in



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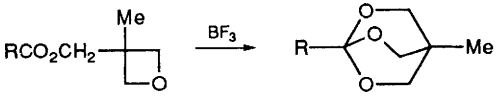

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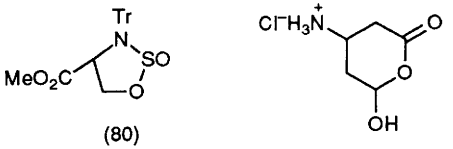

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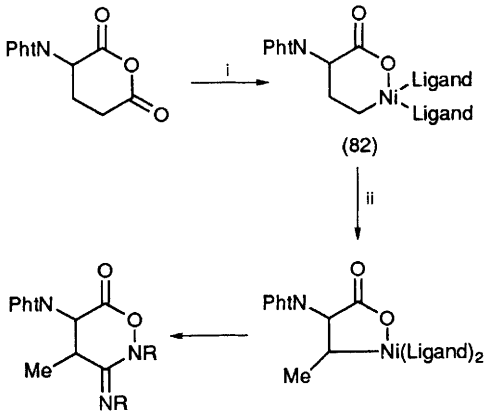


Reagents: i, $Ni(Ligand)_x$, –CO; ii, RNC

Scheme 43

a remarkable ring contraction of the derived nickelacycle (82 in Scheme 43) and further unusual steps for which the metal functions as an activating group.[591] Unexpected cleavage of L-pyroglutamates with the α-sulfinyl carbanion (Scheme 44) creates a number of useful opportunities for the synthesis of other amino acids, illustrated for pyrrolidine-2,5-dicarboxylic acids and 5-hydroxypipecolic acids.[592] Development of earlier success in 4-alkylidenation of pyroglutamates has been reported, leading to three naturally-occurring glutamic acids of this class.[593] N- and Side-chain-protected aspartic and glutamic acids have been converted into β-amino- and γ-amino esters, respectively, by substitution of the tosylated α-carboxy group using organocopper reagents.[594] Several synthesis applications for α-(ω-carboxyalkyl)-α-amino acids have been published during 1993, leading away from the amino acid field, and although brief mention of these is made elsewhere in this Chapter, to the extent that routes start with novel functional group modifications, no attempt is made to cover this area in any thorough way.

γ-Carboxyglutamic acid reacts with 4-diazobenzenesulfonic acid to give an intensely red compound (λ_{max} 530 nm) resulting from the replacement of both γ-carboxy groups with moieties of the reagent; β-carboxy aspartic acid behaves similarly.[595]

The established side-chain chemistry of lysine and related ω-aminoalkyl α-amino acids is also being extended into new areas, N^{ε}-alkylation by epichlorhydrin being the starting point for a synthesis of naturally-occurring (2S,9R)-hypusine dihydrochloride [Lys($CH_2CH(OH)CH_2CH_2NH_2$] and its (2S,9R)-epimer.[596] N^{α}-Fmoc-N^{ε}-bis(t-Butyloxycarbonylmethyl)lysine and ornithine and diaminopropanoic acid analogues have been synthesized from the protected lysine, ornithine and asparagine, respectively.[597] Selective N^{β}-Boc-protection has been attended to for (S)-2,3-diaminopropanoic acid,[598] and a 100g-scale preparation of N^{ε}-allyloxycarbonyl-L-lysine (85% yield from lysine hydrochloride/Na_2CO_3/$CuCl_2$/allyl chloroformate) as its N^{α}-Fmoc derivative (Fmoc succinimide) has been described.[599] α-[4-N-(Pyridiniobutyl)]-α-amino acids result from the reaction of N^{α}-acetyl-L-lysine with pyrylium salts.[600] Further studies of lysine derivatives carrying redox groupings at the N^{ε}-site (Vol.24, p.58) have been described, the amino acid acting as a vehicle for laser energy conversion by the redox groups (420nm laser pulses generate 1·17 volts energy storage in some cases).[601]

Arginine derivatives that release nitric oxide (other than arginine itself through the action of NO synthase[602,603]) include N^{ε}-nitro-L-arginine and its methyl ester, under the influence of ultraviolet radiation.[604] This may explain the relaxation of smooth muscle that is observed in UV light. The general topic has fascinating physiological implications, and has rejuvenated the study of nitric oxide.[602] The nitric oxide–water system has a short half-life due to oxygenation to nitrite ion (with little or no nitrate ion formed), but the arginine–NO synthase system produces nitrate as well as nitrite if an additional oxidizing species, such as an oxyhaemoprotein, is present.[602]

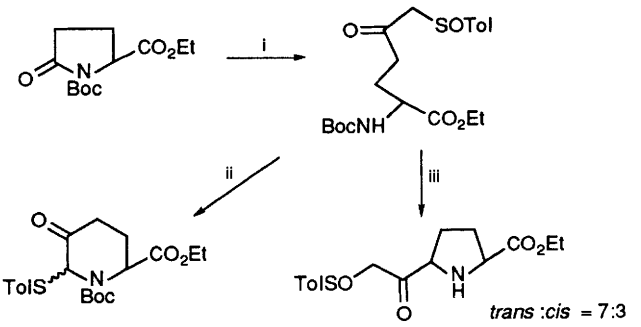
N^{G}-Allyl-L-arginine has been prepared in good yield through the standard general route from L-ornithine using an N-allyl-N'-(pyrazol-1-yl)amidine as

amidinating agent.[605] Side-chain protection for arginine using the 2,2,4,6,7-pentamethyl dihydrobenzofuran-5-sulfonyl group is secure under normal peptide synthesis operations and is more easily removed than current alternative protecting groups.[606] Cleavage of the guanidino group of arginine is the consequence of reaction with N-methyl-N-t-butyldimethylsilyltrifluoroacetamide, leading to TBDMS-ornithine and TBDMS-carbodi-imide.[607]

Cysteine side-chain chemistry continues to undergo development in biological contexts, such as the stereospecific conversion of S-allyl-L-cysteine into the (+)-sulfoxide in culture tissues of *Allium sativum*,[608] and conversion of homocysteine into methionine *via* a non-enzymatic transfer in aqueous solution at pH 7, of a 5-methyl group from the 5-methyltetrahydrofolate model (83) that has a positive charge on N-5.[609] Cysteine esters treated with 3 equiv HNO_2 are de-aminated, as expected, but also caused to cyclise to thiirancarboxylates, presumably *via* the thionitrite.[610] Of relevance in the food science context, cysteine and dihydroxyacetone react to give a large number of volatile products (specifically thiazoles and pyrazines) in proportions dependent on the relative concentrations of reactants and water.[611] Modifications that are restricted to the the environment of the sulfur functional group of members of the cysteine family protected at amino and carboxy groups, have been reported for N-acetylcysteine methyl ester, which acts as a sulfur transfer agent towards carbodi-imides (84 → 85),[612] and for penicillanic acid derivatives which undergo stereospecific oxidation at S with exclusive exchange of protons with ^2H_2O at the adjacent methyl group that is cis to the sulfoxide oxygen atom.[613] Replacement of S-acetamidomethyl-, S-p-methoxybenzyl-, and S-trityl- protecting groups (but not S-benzyl-) from fully protected cysteines, by the S-methylthio-group is achieved using Me_2S^+SMe BF_4^-, a well-known disulfide bond-forming process but novel in this context, that yields protected cysteine derivatives amenable to mild reductive S-deprotection.[614]

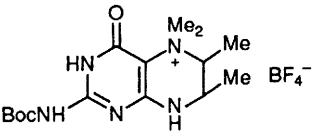
Examples of arene groups undergoing modification have appeared in reports of 4-aminomethylation of protected L-phenylalanine (Cl_3CCONH CH_2OH and H_2SO_4, followed by conc HCl),[615] and phenolic O-[4-(piperidin-4-yl)butyl]ation of trimethylsilyl-protected L-tyrosine *en route* to MK-383, a fibrinogen receptor antagonist.[616] Milder than the usual (48% HBr/AcOH) conditions for demethylation of methoxy-substituted phenylalanines, are needed to avoid racemization; and conc aq HBr + NaI/90°C/2 h is effective.[617] A novel [bis(trifluoroacetoxy)iodo]benzene-mediated oxidative hydroxylation of a protected tyrosinal (86 → 87) is a first step in an aranosin synthesis.[618] Even milder processes are involved in dopaquinone formation from L-tyrosine through catalysed oxidation by immobilized tyrosinase, and its detection through fluorescence generated at 480 nm (λ_{excit} 350 nm) after reaction with 1,2-diphenylethylenediamine,[619] and oxygenation studies of DOPA in aqueous solutions.[620] Identification of 2,4,5-trihydroxyphenylalanine ("TOPA") as an oxygenation product (0.5% yield) and its conversion into a quinone imply that some properties attributed to DOPA may be those of TOPA/TOPAquinone.

N^{α}-Z-Histidine t-butyl ester undergoes Pd(0)-catalysed phenylethynylation at C-4(5) of the imidazole group,[621] a general process that has been used to



Reagents: i, $TolSOCH_2Li$; ii, TFAA/py.; iii, TFA/CH_2Cl_2

Scheme 44



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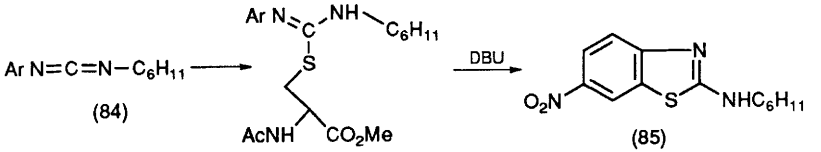

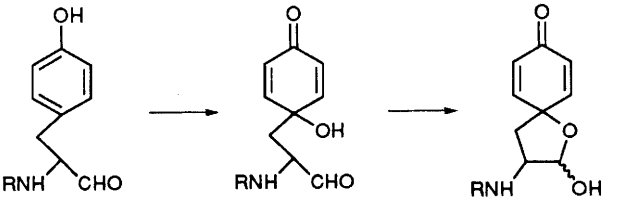

prepare a homologue, diphthine, the major metabolite of diphthamide. Alkanethiols de-iodinate 2'-iodohistidine within 24 h, *via* attack by RS^- on the protonated imidazole.[622] This is thought to account for the limited *in vivo* efficacy of this otherwise promising antimalarial agent.

Regioselective nucleophilic substitution of 1'-hydroxytryptophan in acidic media is the paradoxical result of dissolution in a 10% aqueous sulfuric acid–methanol mixture, leading to 5-methoxy analogues, and offers an attractive model for serotonin synthesis in the central nervous system.[623] Electrophilic substitution at C-5 by NBS is observed during free radical C-3a functionalization of tryptophan (by Br using NBS, by NO_2 and OH using ceric ammonium nitrate) in the form of its N^{in}-benzenesulfonyl hexahydropyrrolo[2,3-*b*]indole methyl ester derivative (Vol.25, p.40).[624] Stereoselective dioxygenolysis of N-acetyl D- or L-tryptophan methyl esters is catalysed by manganese porphyrins bonded to bovine serum albumin.[625] Reactions of tryptophan have been reviewed.[626]

6.4 Effects of Electromagnetic Radiation on Amino Acids

The material traditionally collected here concerns the aromatic and heteroaromatic amino acid side-chains, though some citations that might have been located here have involved additional aspects of chemistry that have caused them to be discussed elsewhere in this Chapter.

Radiolytically-generated hydroxyl and sulfate radicals have been identified as the reagents involved in pulse radiolysis of phenylalanine leading to tyrosine and its isomers.[627] Conversion of L-tryptophan into a hydroperoxide is a well-known example of the role of singlet oxygen, but radiolytic oxygenation has been found to yield two new hydroperoxides where $Cl_3COO^{\bullet}$ can be formed. This adds at C-2 of the indole moiety, and is followed by O_2 addition and formation of the epimeric hydroperoxy-oxindolylalanines.[628] A study showing that chloroform at 0.08% levels, modifies the photolysis of tryptophan to give new products showing intense fluorescence in visible light, may prove to involve the same underlying chemistry.[629] Photolysis of flavin-sensitized tryptophan leads to indole-3-acetaldehyde under anaerobic conditions.[630] There are numerous studies describing the search for new radioprotective agents, and the aromatic amino acids feature frequently in these; a representative citation reports the γ-radiation protection possible with a mixture of hydroxylamine, 2-aminethyl isothiouronium bromide hydrobromide and with 5-hydroxy-L-tryptophan as the major component.[631]

A less common type of study in this category involves two-photon-excited fluorescence excitation spectra using circularly-polarized and linearly-polarized light, for phenylalanine, tyrosine and tryptophan in neutral aqueous solutions.[632] Absorption features in the 440–620 nm wavelength range are observed, corresponding to the familiar one-photon excitation absorption features in the 220–310 nm region. Riboflavin-sensitized photochemistry of tryptophan in visible light has been reviewed.[633]

7 Analytical Methods

7.1 Introduction

Some general reviews have appeared that apply to analysis for particular amino acids in biological samples (homocysteine[634] and tryptophan[635]) and to broader aspects (advances in amino acid analysis[636] and in the analytical chemistry of amino acids, peptides and proteins[637]).

7.2 Gas–Liquid Chromatography

The general theme for the 1993 literature is the continuing development of existing methods (derivatization protocols and instrumental variants). The analysis of a mixture of 22 amino acids over a DB-1 capillary column after derivatization with N-methyl-N-(TBDMS)trifluoroacetamide to give N(O)-TBDMS derivatives, illustrates the generally less time-consuming methodology employed for GLC analysis of amino acids, now used in some laboratories.[638] A similar approach employing ethyl chloroformate in EtOH/py to give N-ethoxycarbonyl amino acid ethyl esters for GC–MS analysis[639] seems to risk the introduction of artifacts due to carboxyl activation by the reagent and competition for reaction at the amino group of an amino acid or amino acid ester, to give derivatized di- and polypeptides. Two-step derivatization procedures are illustrated for proline + hydroxyproline analysis as their N-dimethylthiophosphoryl methyl esters, after OPA treatment of the biological sample to remove primary amines,[640] for O-phospho-serine, -threonine, and -tyrosine in urine hydrolysates, as N-isobutyloxycarbonyl methyl esters,[641] and in the specific case of 1-aminocyclopropanecarboxylic acid (1-ACC) in leaf tissue (preparation of the N-benzoylated propyl ester), and use of capillary-GC with an N/P-sensitive detector.[642] The last-mentioned study describes the development of a reliable protocol, and criticizes an established method for 1-ACC analysis that is subject to interference and lacks internal standards.

Enantiomeric analysis by GC continues to be based on either diastereoisomer formation [(N-menthyloxycarbonyl)ation of amino acid esters[643]] or on the separation of amino acids derivatized in simple ways, over chiral stationary phases (packings coated with N-stearoyl-L-valine t-butylamide for the resolution of N-trifluoracetylamino acid isopropyl esters)[644] and closely-related protocols for general amino acid analysis[645] and specifically for selenomethionine[646]

GABOB analysis (urine samples) by GC–MS is complicated by the fact that it co-elutes with leucine in some standard procedures.[647]

7.3 Thin-layer Chromatography

A paper in the preceding section[642] refers to the considerable expense of GC–MS instrumentation; the increased activity in TLC analysis of amino acids and their derivatives probably reflects this situation. Densitometric quantitation of ninhydrin-developed hydrophilic TLC plates (silica coated with silicic acid) has provided reliable assays of lysine, homoserine and threonine in culture fluids.[648] Amino acids interact with the non-ionic surfactant, nonylphenyl hexa-ethoxylate, a fact established by charge-transfer reversed-phase TLC that has a negligible

effect on the hydrophobicity of amino acids except for cysteine, glutamic acid, glutamine, hydroxyproline, phenylalanine and tyrosine.[649] These results, although puzzling in terms of the particular amino acids that interact and those that do not, illustrates the usefulness of simple methods in obtaining information of wide applicability in amino acid science.

Routine TLC analysis is well-represented in the literature, as usual (e.g., analysis of dansylamino acids[650]) occasionally employing techniques undergoing evaluation as illustrated by the separation of a mixture of 20 PTH's by automated multiple development over silica gel.[651]

Resolution of enantiomer mixtures of derivatized amino acids, employing chiral stationary phases[652] or mobile phase additives (β-cyclodextrin[653] or bovine serum albumin for the analysis of dansylamino acids,[654] continues to be practised.

7.4 High Performance Liquid Chromatography

Some of the derivatization methods encountered in preceding sections are also routinely adopted in HPLC protocols, and the relative merits of the o-phthaldialdehyde/alkanethiol (OPA), N-(fluoren-9-ylmethoxycarbonyl)ation (Fmoc), N-phenylthiocarbamoylation (PTC), and N-dansylation (DNS) methods have been reviewed.[655] HPLC analysis of homocysteine in plasma samples has been reviewed.[656]

HPLC analysis of non-derivatized amino acids (Tyr, His, Phe, Trp) in foods;[657] protein cross-linking amino acids pyridinoline, hydroxylysylpyridinoline, and lysylpyridinoline in urine[658] conventionally involves ion-pair formation with sodium n-heptanesulfonate. Another study describes HPLC analysis of seven major crosslinking amino acids in elastin: desmosine, isodesmosine, allodesmosine, neodesmosine, aldosine, oxodesmosine, and cyclopentenosine.[659]

The sensitivity criteria usually required in amino acid analysis, calls for choice of derivatives with optimised physical characteristics that can be exploited for quantitation. OPA Fluorescence is sufficiently stable to yield good precision with a relative standard deviation of 0.8–7.3% depending on the use of relevant internal or external standards.[660] The presence of cyclodextrins in the mobile phase (a means of exploiting HPLC for the analysis of enantiomer mixtures) affects the fluorescence yield.[661] The protocol has been used for the analysis of tyrosine-O-sulfate (ion-pair variant with t-butylammonium phosphate in the mobile phase),[662] and in other amino acid areas,[663-665] one[665] describing a sample pretreatment procedure that allows proline to be included in the method (which is applicable only to primary amines) through chloramine-T/$NaBH_4$/60°C/11 min treatment that converts the imino acid into 4-aminobutan-1-ol.

Dabsylation of collagen hydrolysates after OPA-blocking of primary amines[666] is capable of extraordinary sensitivity, with hydroxy-L-proline being measureable at femtomole levels with its help.[667] Where radioactive-labelling is distributed between amino acids in physiological samples, the efficiency of HPLC separation with suitable detectors allows their assay in the form of dabsyl derivatives.[668]

7-Chloro-4-nitrobenzo-2-oxa-1,3-diazole, or its 7-fluoro-analogue, has

been used increasingly recently, for derivatization of proline + hydroxyproline in mixtures after OPA blocking of primary amines,[664] or hydroxyproline alone,[669] and for homocysteine analysis.[670] A salutary warning has been published that the derivatization of cysteine by 7-fluoro-4-nitrobenzo-2-oxa-1,3-diazole is reversible in media containing reducing species at basic pH, undermining any quantitation protocol based on the fluorimetric assay using this reaction.[671]

N-Phenylthiocarboamoylation compares well with classical ion-exchange chromatographic analysis for the HPLC estimation of amino acids in plasma,[672] and of protein hydrolysates.[673] Using gas-phase acid hydrolysis, and the Waters Pico-Tag Workstation based on PTC-derivatization, the amino acid content of lysozyme as a typical protein was secured with a 22 min HPLC separation. L-Methionine sulfoxide assay in tissue extracts has been achieved through the sequence ion-exchange, Pico-Tag derivatization and HPLC after derivatization using diethoxymethylene malonate.[674] One-step amino acid derivatization by the new Waters AccQ-Tag Workstation has been described.[675] Traditional PTH analysis[676] and the similar DABTH assay employing HPLC[677] routinely deal with femtomole levels of analyte. Fluorogenic Edman reagents 7-N,N-dimethylaminosulfonyl-4-(2,1,3-benzoxadiazolyl)isothiocyanate and the 7-amino analogue yield amino acid derivatives showing λ_{em} 505 nm for λ_{excit} 385 nm.[678]

Several other derivatization protocols (some well-established, some new) have been reported, and there is perhaps more activity in this area than usual. N-Z-Amino acids,[679] N-acetylamino acid tetra-alkylammonium salts,[680] and amino acid pentafluorobenzyl esters[681] are familiar derivatives that have been studied further, the last-mentioned offering a suitable means of assay for tryptophan at low levels using electron capture detection and negative ion CI-MS. Novel fluorogenic reagents include N-quinolin-6-yl carbamic acid N'-hydroxysuccinimide ester[682] and 2-fluoro-4,5-diphenyloxazole and 2-chloro-4,5-di-(p-N,N-dimethylaminosulfonyl)phenyloxazole, the fluorescence and chemiluminescence from the latter reagent being detectable at 19–64 femtomole levels.[683] Known procedures for specific amino acids include the use of glyoxal (fluorescence generation with tryptophan),[684] and 3-bromopropylamine (for cysteine),[685] and 4,4'-dithiodipyridine (for post-column detection of homocysteine and other thiols).[686] 3'-Methylhistidine analysis has been accomplished through pre-column derivatization (reagent not stated in the abstract of this paper).[687]

The determination of the enantiomeric composition of amino acids in mixtures continues to stimulate the development of known methods, some based on chiral derivatizing agents, (+)-1-(fluoren-9-yl)ethyl chloroformate for amino acids,[688] or N-glycyl-L-(4-nitrophenyl)alanine methyl ester for N-Z-amino acids,[689] others employing chiral stationary phases (cellulose tris(3,5-dimethylphenyl)carbamate for N-protected amino acid esters (N-Z- is better than N-Boc or N-formyl; the L-enantiomer runs fastest),[690] and commercial phases for ligand-exchange HPLC resolution of non-derivatized amino acids (stereoisomers of 2,6-di-aminopimelic acid).[691] A review covers the HPLC resolution of amino acids.[692]

A number of topics in HPLC analysis of amino acids are briefly noted: hydroxylysine glycosides in collagen hydrolysates,[693] S-adenosyl-L-methionine

and its metabolites,[694] serotonin in insect brain tissue (amperometric detection),[695] tyrosine and isoquinoline alkaloids in papaver,[696] and carbidopa in clinical samples (electrochemical detection).[697] HPLC capacity factors have been correlated with Hansch hydrophobic parameters for N-dodecanoylamino acids.[698]

7.5 Fluorimetric Analysis

Much of the material under this heading is located elsewhere in this Section of this Chapter because analytical exploitation is the usual fate for fluorogenic derivatives of amino acids. The fluorescence generated in tryptophan through reaction with aldehydes in mildly acidic media (cf. glyoxal[684]) has been studied in some detail for methoxyacetaldehyde.[699] β-Carboline and 1-methoxymethyl-β-carboline are formed at pH 2.75 in aqueous $NaNO_2$, the intense fluorescence (λ_{em} 450 nm at λ_{excit} 253 nm) being detectable down to 10 picomole levels.

7.6 Other Analytical Methods

The growth area under this heading continues to be capillary zone electrophoresis (CZE), now routinely offering laser-based detection of thiohydantoins at sub-attomole levels,[700] and applicable to chiral separation of derivatized amino acids.[701]

Derivatization protocols for amino acids, and detection techniques, that are used for HPLC and other analytical purposes, are equally valid in the CZE area, as illustrated for laser-induced fluorescence (248 nm) for the detection of Fmoc amino acids (reaching 5×10^{-10} M),[702] and for oxazoles formed by condensation of amino acids with the co-enzyme pyrroloquinolinequinone.[703] Micellar electrokinetic capillary chromatography is an important variant of CZE, used for PTH analysis,[704] and for chiral analysis employing bile salt micelles[705] or β-cyclodextrin (for charged analytes) or carboxymethylethyl-β-cyclodextrin (for neutral analytes).[706]

Absorption spectrophotometry at 440 nm allows simple estimation of the total amino acid content of a mixture reacted with benzoquinone (total protein at 350 nm).[707] Spectrophotometric estimation of phenylalanine in blood samples, on the basis of phenylpyruvate formed by oxidative deamination (phenylalanine dehydrogenase) compares favourably with results from fluorimetry, or other conventional amino acid analysis methods.[708] Asparagine in aqueous solutions develops a colour (λ_{max} 340–350 nm) with ninhydrin that differs from that (λ_{max} 405, 570 nm) for amino acids generally, leading to a simple colorimetric assay that compares favourably with HPLC methods for asparagine.[709] Glutamine colorimetry down to millimolar levels has been established.[710] The violet colour that develops between tyrosine methyl ester and iron(III) salts is the basis of a novel colorimetric assay applicable at 10 nanomolar levels.[711]

A carbon paste electrode impregnated with copper(II) cyclohexylbutyrate has an oxidation peak for copper(0) that is modified by the presence of amino acids in the solution.[712] The increased current taken to achieve the oxidation is proportional to the concentration of the total amino acids, which can thereby be estimated, down to 10^{-6} M levels.

7.7 Assays for Specific Amino Acids

Adding to the methods appropriate for particular amino acids discussed in preceding sections, papers cited here deal mainly with enzymatic methods linked to electrochemical measurements.

An amperometric electrode specific for L-alanine consists of a platinum surface that senses H_2O_2 produced in the presence of aqueous alanine by immobilized alanine aminotransferase and glutamate oxidase.[713] Alanine dehydrogenase and leucine dehydrogenase co-immobilized on chitosan, constitutes an HPLC post-column reactor that catalyses the degradation of alanine, leucine, valine and isoleucine into species amenable to fluorimetric assay.[714] Phenylalanine dehydrogenase, immobilized in a flow sensor, generates NADH from L-phenylalanine that encounters a nylon-immobilized bacterial enzyme capable of creating bioluminescence.[715]

L-Lysine biosensors have been described, one employing a lysine oxidase reactor combined with a fibre-optic H_2O_2 detector incorporating peroxidase and luminol, and capable of dealing with 10^{-6} M levels of analyte,[716] and another based on L-lysine decarboxylase combined with an optical transducer (a membrane carrying a lipophilic tartrate supporting an amine-sensitive dye-light source) for assaying the resulting cadaverine.[717]

Glutamate-sensing systems based on glutamic acid oxidase and other enzymes[718] or on glutamic acid oxidase alone[719] generating H_2O_2 at a Pt electrode in proportion to the concentration of glutamic acid. One of these studies describes ultra-miniaturisation of the sensor,[719] The extension of the amperometric exploitation of glutamic acid oxidase electrodes into glutamine, aspartic acid and aspartame sensing systems has been reviewed.[720] Glutaminase immobilized on an NH_3-sensing electrode constitutes an L-glutamine sensor,[721] while a broader range of analytes can be assayed by a device comprising an amino acid oxidase immobilized on aminated glass cloth and an NH_3-sensitive electrode.[722]

Non-enzymatic assays are involved in the remaining citations in this Section. A labelled L-leucine assay has been described, in which the amino acid is bound to its tRNA in the presence of either added radiolabelled tRNA-Leu and a deficiency of non-radioactive L-leucine, or in the presence of excess non-radioactive L-leucine to correct for other radiolabelled species.[723] This work extends a previously-disclosed method (Vol.25, p.78). A combined glutamine and α-ketoglutarate assay involves ion-exchange separation, o-phenylenediamine derivatization of the ketoglutarate, followed by conversion of the glutamine into ketoglutarate and its estimation as such through absorption spectrophotometry.[724]

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