1
Amino Acids

BY GRAHAM C. BARRETT

1 Introduction

The literature of the amino acids for 1995 is reviewed in this Chapter, aiming particularly at thorough coverage of developments in chemical and analytical areas. Although the literature covering routine biological studies of common amino acids is excluded, the more innovative biological and pharmaceutical work is covered. Scrutiny of the hard copy literature (the major journals, and *Chemical Abstracts* from issue 11 of Vol 122 to issue 9 of Vol 124 inclusive) has provided the citations that make up the Chapter.

Continuity with preceding Volumes of this Specialist Periodical Report has been a prime consideration, so the Chapter has been sub-divided in the style used in all previous Volumes in this series. The device '(see p. XX, Vol YY)' that is used in this Chapter provides reference back to preceding Volumes, and helps the reader to keep track of important amino acid topics that have been developing over the years.

This Report has acknowledged in recent Volumes, that the term 'amino acids' has numerous meanings, but that the almost exclusive emphasis of this Chapter is on the α-aminoalkanoic acids. The reason for acknowledging this is the rising interest in the study of amino acids incorporating other oxyacid functions, particularly phosphorus analogues of the common aminoalkanoic acids. Short sections are included in this Chapter, on this topic, even though coverage must be

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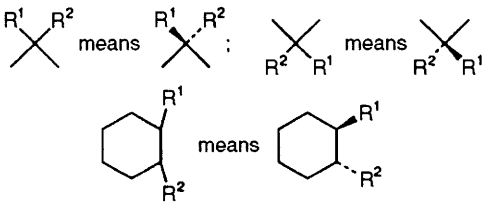
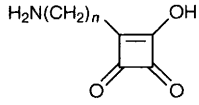
Three-dimensional features at chiral centres of structures depicted in this chapter follow the convention:–

(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:





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selective in order that the literature of aminoalkanoic acids may receive thorough treatment. The unusually acidic 3-hydroxy-3-cyclobuten-1,2-dione grouping, established to be a bio-isostere of the carboxy group, has stimulated the synthesis of the corresponding amino acid analogues (1).[1]

2 Textbooks and Reviews

Several recent textbooks give either partial[2,3] or exclusive[4] coverage of amino acid topics. A symposium report[5] covers a wide range of recent studies on amino acids in higher plants.

Reviews have appeared covering derivatives of natural amino acids as radioprotectants,[6] and industrial aspects of the uses of amino acids.[7] The unusual amino acids hypusine [N^{ε}-(4-amino-2-hydroxybutyl)-L-lysine],[8] ovothiols (mercaptohistidines),[9] and the pyridinolines[10] have been reviewed from the point of view of their occurrence; members of the last-mentioned family, particularly pyridinoline itself and deoxypyridinoline, that derive from collagen breakdown, are present in urine at levels related to bone resorption activity, and these levels may be used as an osteoporosis index for individual patients (see also Ref. 849). The occurrence in proteins of the fluorescent crosslinking amino acid, pentosidine, has been reviewed;[11] its formation accompanies glycoxidation *in vivo*, and it accumulates at a greatly accelerated rate in uraemic patients; thus it is linked with the ageing process, and this suggests that its accumulation can be used as a diagnostic indicator. A review[12] covers the extensive literature on the non-natural amino acid threo-dihydroxyphenylserine, whose importance lies with the fact that it undergoes L-aromatic amino acid decarboxylase-catalyzed decarboxylation to give neurally-active norepinephrine.

Other recent reviews are more appropriately located in later Sections of this Chapter.

3 Naturally Occurring Amino Acids

The work described in this Section concentrates mainly on new amino acids, and on the more unusual of the known amino acids discovered in previously-unknown natural compounds.

3.1 Isolation of Amino Acids from Natural Sources – If reliable results are to emerge from such endeavours, then reliable methods of isolation of individual amino acids from complex mixtures are needed. This section has been introduced

into this Chapter in recent years as a collection point for citations on apparently routine current work that often includes salutary warnings of sources of error and contamination. Analytical and preparative scale purification of amino acids is covered in later sections of this Chapter.

A commercial cation exchange resin has been found[13] to be contaminated with several common amino acids (e.g. leucine: 260 pmol ml^{-1}resin). It is a mixed blessing, that there is no satisfactory method of clearing this background, which could have serious consequences for the reliable quantitation of amino acids in at trace levels if released by the resin into analytical samples. Concentration of solutions of amino acids can be achieved using ion exchange membranes,[14] and ion exchange chromatography has been used for large-scale purification of phenylalanine.[15] Other purification procedures with a similar context, for phenylalanine (continuous emulsion liquid membrane separation),[16] and for the separation of isoleucine from valine (kerosene – D_2EHPA partition),[17] rely on different physical principles. The extraction of phenylalanine and tyrosine from aqueous solutions, using hydrophilic solvents, has been precisely formulated,[18] a resource that may help in the work-up of complex amino acid mixtures. Milligram scale preparative HPLC allows the isolation of pure (96-99%) individual amino acids from mixtures, as their N-benzyloxycarbonyl derivatives.[19] The recovery (68-89%) of amino acids from mixtures in this way should surely be capable of improvement.

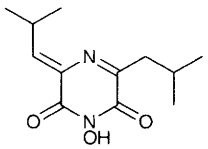
3.2 Occurrence of Known Amino Acids – Selection for this section is limited by excluding routine work with common amino acids; but the identification of αα-dialkyl α-amino acids in geological samples (they are minor components),[20] of common amino acids in resinous and other non-protein materials used by artists,[21] and in amber-entombed insects,[22] seem to be eminently worthy of mention. Samples for the last-mentioned study were aged from <100 y to 130×10^6y; the interpretation of amino acid racemization data determined for these samples would have given much younger ages; racemization rates for common amino acids must suffer retardation by the amber environment by a factor greater than 10^4.

Streptomyces akiyoshiensis cultures accumulate N-acetyl-L-DOPA,[23] which is shown in this study not to be involved in the biosynthesis of 5-hydroxy-4-oxo-L-norvaline (the major metabolite of this bacterium). Fungal and other plant sources shown to contain unusual amino acids include *Tricoloma muscarium* (ibotenic acid; the first report of this isoxazole derivative in a mushroom not belonging to the genus *Amanita*),[24] *Ateleia glazioviana Baillon*, a tree that is insect-repellent and toxic to cattle (1-aminocyclobutane-1,3-dicarboxylic acid and δ-acetylornithine),[25] and roots of *Glycyrrhiza yunnanensis* (NNN-trimethyl tryptophan betaine).[26]

Rhizocticins A, B, and D contain (Z)-L-2-amino-5-phosphonopent-3-enoic acid,[27] an α-amino acid already described to be a component of plumbemycins but thought to be of the D-configuration in these members of the latter family, whose structures are now in need of correction as far as absolute configuration is concerned. Structures have been established for new microcystins, which contain

2-aminobuten-2-oic acid.[28] Cyanobacteria (blue-green algae) are already known to produce bioactive cyclic peptides, and new examples are: anabaenopeptins A and B (*Anabaena flos-aquae* NRC 525-17) that contain, together with other common L-amino acids, D-lysine, N-methyl-L-alanine and homo-L-tyrosine;[29] and the cyclic depsipeptide oscillapeptin (*Oscillatoria agardhii* NIES-204)[30] together with the cyclic hexapeptide oscillamide Y,[31] which contain homotyrosine and N,O-dimethyl-L-tyrosine (in the former case) and N-methyl-L-alanine (in the latter case) amongst other constituents. The dioxopiperazine, flutimide (2) has been isolated from a new fungus *Delitschia confertaspora*.[32]

The rapidly accumulating literature covering the discovery of D-enantiomers



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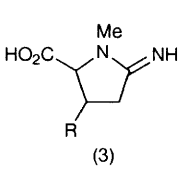
of the common amino acids in natural sources is illustrated for D-serine in rat brain and D-aspartic acid in peripheral organs[33] (see Ref. 897 for the identification of D-amino acids in serum samples). The occurrence of D-aspartic acid in proteins, and the broader picture concerning *in vivo* racemization of amino acids, have been reviewed.[34] D-Alanine occurs in free form in 15 out of 24 species of marine micro-algae.[35]

3.3 New Naturally Occurring Amino Acids – New aliphatic α-amino acids include (2S,3S,4R)-β-hydroxy-γ-methyl glutamic acid and its (2S,3R,4R)-epimer (together with pipecolic acid and 5-hydroxypipecolic acid) in seeds of *Gymnocladus* dioicus (see also Ref. 828),[36] (S)-cis-2-amino-5-chloropent-4-enoic acid in *Amanita vergineoides*,[37] (2S)-2-amino-5-chloro-4-hydroxyhex-5-enoic acid from *Amanita gymnopus* fruit bodies (together with (2S)-2-aminohex-5-enoic acid a first natural occurrence of an amino acid already known in the laboratory and (2S)-2-aminohexa-4,5-dienoic acid and (2S)-2-aminohex-5-ynoic acid).[38] The pyroglutamic acid relatives (3; R = OH, or H), found in *Streptomyces sp. SA-3501*, have been christened pyrostatins A and B, respectively; they have potential importance due to their role as inhibitors of N-acetyl β-glucosaminidase.[39]

New natural aromatic and heteroaromatic α-amino acids include purealidins J – R [nine new bromotyrosine derivatives, e.g. (4) and (5), from *Psammaplusilla purea*, an Okinawan marine sponge],[40] and the cysteine derivative (6) from *Streptomyces SB212305*.[41] A new mycosporin-like amino acid (7) from the reef-building corals *Pocillopora damicornis* and *Stylophora pistillata* contains methylamine in place of the glycine moiety usually seen in the mycosporins.[42]

The novel β-amino acid (S)-3-amino-5-mercatopropionic acid (8) occurs in caledonin (from the marine tunicate *Didemnun rodriguesi*),[43] while the higher



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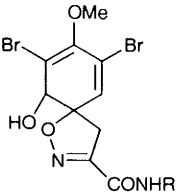

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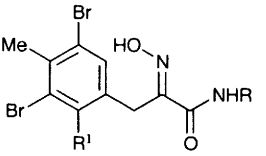

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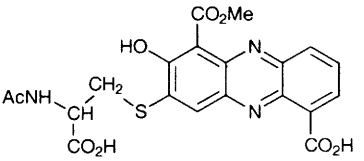

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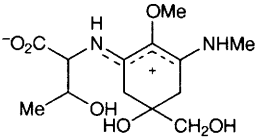

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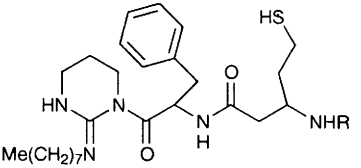

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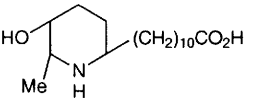

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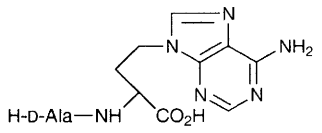
homologue (9) is one of four new piperidine alkaloids from leaf extracts of *Cassia leptophylla*.[44]

3.4 New Amino Acids from Hydrolysates – The title of this Section, though cumbersome, adequately accommodates details of work through which the presence of new amino acids bound up into amides of varying structures, and esters and close analogues, has been revealed.

The dipeptide (10) incorporating a novel adenine derivative has been isolated from the fungus *Taloromyces* NK 374200.[45] 2-Oxohistidine has been established to be a constituent of oxidatively-modified proteins,[46] and β-hydroxyhistidine is only one extraordinary feature of exochelin MN (11), the extracellular siderophore from *Mycobacterium neoaurum* that transports iron into *Mycobacterium leprae*.[47] Phosphocysteine is a constituent of a PTS-protein from *Staphyllococcus carnosus*.[48] A β-hydroxy-γ-chloroproline residue is a notable feature of the cyclic pentapeptide astin I (from *Aster tataricus* roots),[49] while trans-2,3-cis-3,4-dihydroxyproline (12) occurs repeatedly in the sequence of the byssus protein from the marine mussel *Mytilus edulis*.[50] The trichlorovaline subunit present in dysidenin (13) from the marine sponge *Dysidea herbacea* is also represented in a novel chlorinated ketide amino acid, herbamide A (14), from the same source.[51]



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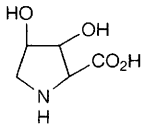

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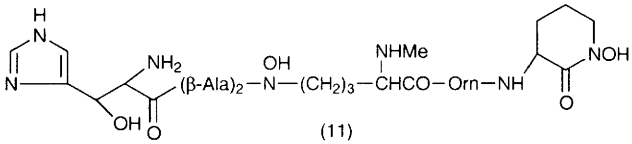

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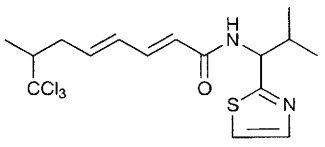

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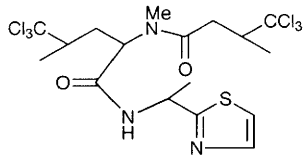

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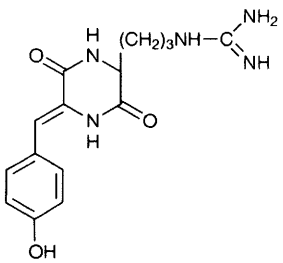
A new metabolite of the cyclosporin-producing fungus *Tolypocladium terricola* is identical with cyclosporin D except for the presence in this cyclic peptide, of hydroperoxy-MeBmt (i.e. 3-hydroxy-7-hydroperoxy-4-methyl-2-methylamino-5E-octenoic acid).[52]

Dioxopiperazine-2,5-diones (*alias* cyclic dipeptides) have featured in this section over the years, and have continued to show increasingly surprising structures, and they often have useful medicinal properties. Recent examples range from the dehydrotyrosine derivative (15) (together with new pipecolic acid derivatives) from the sponge *Anthosigmella aff. raromicrosclera*,[53] the tryptophan derivatives maremycins A and B (16) from a marine *Streptomyces sp.*,[54] leptosins K, K_1, and K_2,[55] and tryprostatins A and B (17; R = H, OMe, respectively) from *Aspergillus fumigatus BM939*.[56] Dehydrogenated derivatives macrophominol (18)



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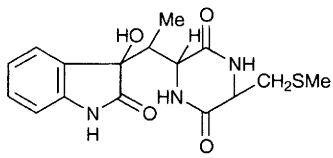

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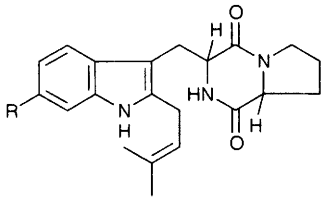

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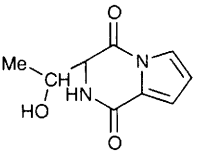

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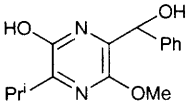

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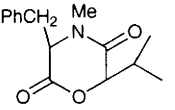

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from *Macrophomina phaseolina,*[57] terezines A – D (19) from *Sporormiella teretispora,*[58] and the morpholin-2,5-dione bassiatin (20) from *Beauveria bassiana K-717*[59] are notable new naturally-occurring amino acid derivatives.

4 Chemical Synthesis and Resolution of Amino Acids

4.1 General Methods for the Synthesis of α-Amino Acids – The methods that have been used for many years are well trusted, and sufficiently broad in their scope to accommodate new and current needs. However, innovation in organic synthesis continues at its usual rapid pace within the amino acids field, as elsewhere, and some new ideas (as well as fresh-looking results that are in fact extensions of existing knowledge) have been a feature of this Section over recent years. The elaboration of side-chains of the readily available α-amino acids is increasingly being chosen for the synthesis of other amino acids, and this literature is covered in a later Section (Section 6.3; Specific Reactions of Amino Acids).

Advances in methodology are more noticeable in aspects of asymmetric synthesis (see next Section), and in some cases these can also be considered to be advances in general methods of synthesis.

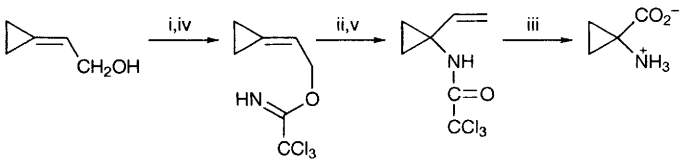
Reviews have appeared covering α-cation equivalents of amino acids[60] and the 1994 literature on the synthesis of amino acids, amides, and peptides.[61] Synthesis of α-amino acids from higher fatty acids,[62] and synthesis through photolysis of chromium(II)-carbene complexes in the presence of nucleophiles (see Vol 27, p. 15, and Ref. 118 for further examples), have been reviewed.[63]

Standard routes illustrated in the 1995 literature are the Bucherer-Bergs synthesis (αα-disubstituted α-amino acids from 3-substituted cyclopentanones;[64] see also Ref. 718) and its near relative seen in the preparation of phenylglycine from $PhCHO/CHCl_3/NH_3$ in aqueous NaOH containing Bu_4NBr.[65] The Ugi

synthesis continues to provide a direct approach in suitable cases (Refs. 258, 295). The Strecker synthesis has been used for the preparation of 3,5-dimethoxyphenylglycine constituents of vancomycins.[66] α-Bromo-substitution (CBr_4) of the 2-methoxycarbonylpyran α-proton can be readily achieved after anion formation using lithium bis(trimethylsilyl)amide, if substituents elsewhere in the ring place this proton in the equatorial plane; ensuing azidolysis and reduction to the αα-disubstituted glycine proceeds normally.[67] Substitution of triflate by azide, and elaboration into α-substituted α-amino acids, has also been used in this study of the preparation of glucofuranose- and glucopyranose-based hydantoins[68] and related dioxopiperazines[69] as analogues of the potent herbicide, hydantocidin.

Conversion of chiral α-hydroxy acid derivatives into amino acid analogues can be accomplished by the Mitsunobu protocol, illustrated this year for N-alkylation of 2-(trichloroethyloxycarbonylamino)thiazole by ethyl (S)-lactate.[70]

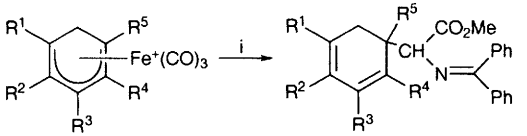
There are numerous examples elsewhere in this Chapter, of applications of classical rearrangements that deliver a nitrogen grouping to carbon, in a manner appropriate for amino acid synthesis [Curtius (e.g. Refs. 183, 207, 287), Hofmann (Ref. 265), Beckmann (Ref. 423) and Schmidt rearrangements among others], and a further example of the aza-Claisen rearrangement of an allyl trichloroacetimidate has offered a new entry to 1-amino cyclopropanecarboxylic acids (Scheme 1).[71]



Reagents: i, Cl_3CCN,NaH; ii, 100 °/toluene, 48 h; iii, aq $NaIO_4$, $RuCl_3$; iv, alternatively *p*-$MeOC_6H_4CCl{=}NH$; v, alternatively, $PdCl_2(PhCN)_2$

Scheme 1

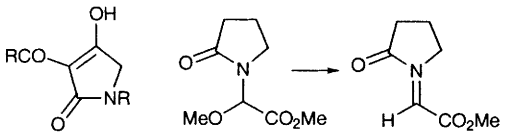
Examples of alkylation of familiar glycine synthons illustrating general routes are found in the phase-transfer catalyzed alkylation of diethyl acetamidomalonate with weakly electrophilic alkyl halides[72] [see also Ref. 296; diethyl formamidomalonate (Ref. 286) and ethyl acetamidocyanoacetate (Ref. 285) have also been used for similar purposes], phase transfer-catalyzed Michael anti-addition of $(MeS)_2C{=}NCH_2CO_2R^1$ to αβ-unsaturated esters[73] (see also Ref.132), and alkylation of $Ph_2C{=}NCH_2CO_2R$ with cyclohexadienyliron π-complexes (Scheme 2)[74] and with 1,ω-dichloroalkanes [giving bis(α-amino acids)].[75] Condensation of diazoacetylglycine methyl ester with an aldehyde, and Bu_4NF cyclization of the resulting β-keto-amides, gives a 3-acyltetramic acid (21; these can be categorized in other ways, as cyclized δ-amino acids for example).[76] Alkylation of the α-bromoglycine derivative $R^1R^2NCHBrCO_2R^3$ by alkyl nitronates gives α-halogeno-, β-nitro-, and αβ-dehydro-amino acid derivatives.[77] Ammonia reacts with methyl N-benzoyl-2-bromoglycinate to yield trimethyl



Reagents: i, $Ph_2C{=}NCH_2CO_2Me$, then LDA

Scheme 2

2,2′,2″-nitrilotris[2-(benzoylamino)acetate] as a 6:1-mixture of diastereoisomers, which can be separated by crystallization.[78] α-Methoxyglycine derivatives (*alias* glyoxylic acid – amine adducts) continue to reappear in different applications, e.g. the 2-pyrrolidinone adduct (22) or its pyroglutamic acid analogue, that is susceptible to arylation *via* its N-acyliminium ion (Scheme 3).[79] An example of an unfamiliar glycine synthon is carbethoxyformonitrile oxide, used as Michael donor to alkylate a vinyl ester in a synthesis of the racemic form of the natural sweetener, monatin (Scheme 4).[80]



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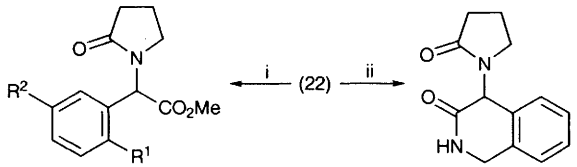
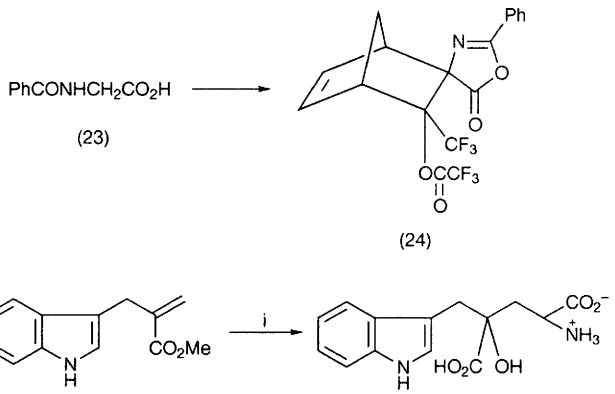
The oxazolone (*alias* azlactone) route, based on alkylation at C-4 of a 2-substituted oxazol-5(4H)-one obtained by dehydrative cyclisation of an N-acyl-α-amino acid, has been used for the synthesis of γ-(1,2,4-triazin-5-yl)butyrines,[81] β-phosphonioethylglycines $[R^1CONHCR^2(CO_2R^3)CH_2CH_2PPh_3{}^+Br^-]$[82] and novel open-chain and constrained tyrosine analogues (see Refs. 191,192). Hippuric acid undergoes unconventional alkylation with trifluoroacetic anhydride and cyclopentadiene (23→24).[83]



Reagents: i, H_2SO_4, $R^1C_6H_4R^2$; ii, $PhCH_2NH_2$, then methanesulfonic acid, 6 days

Scheme 3

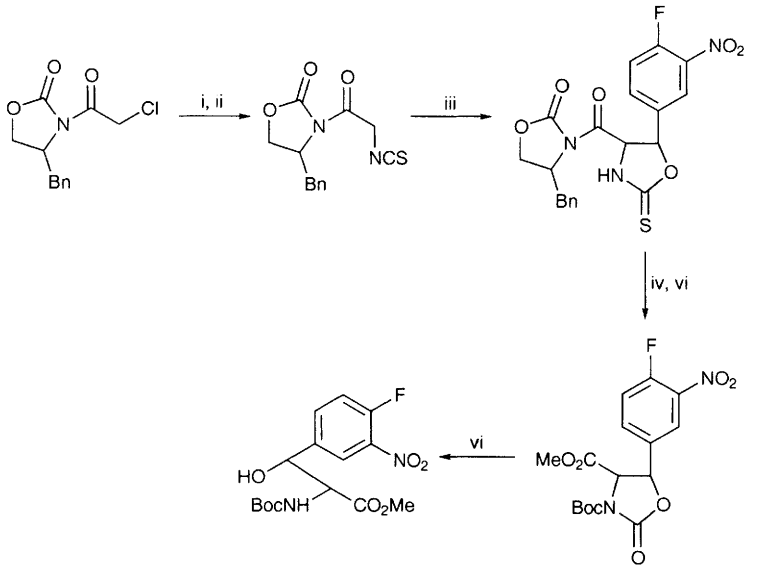


Reagent: i, $EtO_2CCOCNO$, then hydrolysis

Scheme 4

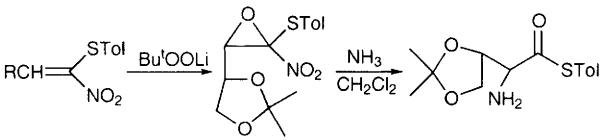
4.2 Asymmetric Synthesis of α-Amino Acids – The 1995 literature covering the asymmetric synthesis of α-amino acids mainly amounts to a consolidation of existing methods, though the modifications introduced by some workers when revisiting established protocols occasionally provide valuable steps forward.

Direct applications of some of the general methods of DL-α-amino acid synthesis covered in the preceding Section, so as to give an α-amino acid enantiomer, continue to be studied. One such example is a highly diastereoselective Strecker synthesis employing α-phenylglycinol as chiral auxiliary.[84] This procedure has also been used for a synthesis of the 3,4,5-trihydroxyphenylglycine moiety of vancomycin.[85] The same paper describes a chiral auxiliary approach (see later discussion) to the vancomycin constituent (2S,3R)-β-(4-fluoro-3-nitro)-phenylserine in which the appropriate aldehyde is reacted with a chiral isothiocyanate (Scheme 5). α-Aminonitriles serve as starting material in some versions of the Strecker synthesis, and have been prepared by addition of trimethylsilyl cyanide to a chiral nitrone with essentially total syn-stereoselectivity.[86] Further illustration by way of a stereocontrolled Strecker synthesis, in which ammonia is reacted with 2-(arylthio)-2-nitro-oxiranes to give α-amino thioesters in good yield, has been published.[87] The examples of synthesis targets given, β-hydroxy-α-amino acids and α-amino dicarboxylic acids, include the γ-hydroxythreonine derivative (25) and polyoxamic acid. Intramolecular amidoalkylation of 2- or 3-vinyl- or phenylsiloxyaminoacetals, occurring after their conversion into imines or iminium ions with Lewis acids, has been exploited for syntheses of Z-allo-L-threonine and N-ethoxycarbonyl anti-γ-hydroxy-DL-norvaline.[88] N-Alkyl α-amino acids have been obtained through reductive alkylation of optically-pure α-azido acids using bromodimethylborane.[89] This exemplifies a fresh approach to the standard synthesis of amino acids involving amination of a halide, in this



Reagents: i, NaN_3, Bu_4NHSO_4, $CH_2Cl_2 - H_2O$; ii, CS_2, PPh_3; iii, $Sn(OTf)_2$, base, 4-fluoro-3-nitrobenzaldehyde; iv, MeMgBr, then Boc_2O/DMAP; v, H_2O_2; vi, $CsCO_3$, MeOH

Scheme 5

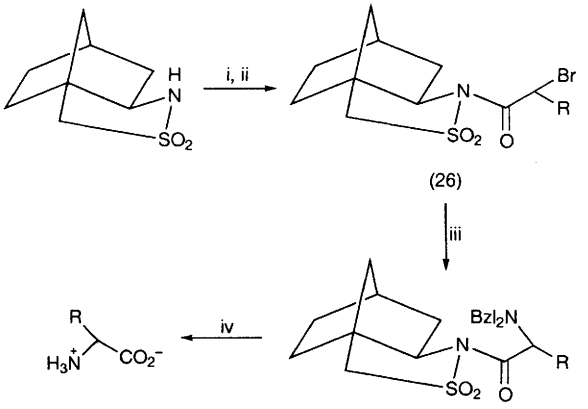


R = (*S*)-dioxolanyl (25)

example taking advantage of newly-introduced reagents. This is also seen in α-stannylation of optically-active enecarbamates with tri-alkylstannyl chlorides, after α-lithiation, then palladium-catalyzed coupling with an acid chloride to give an α-keto enecarbamate, or carboxylation ($BuLi/CO_2$) to give an optically active carbamatoacrylate, leading to an enantiomer of an α-amino acid through addition of a Grignard reagent.[90] Enantiospecific carboxylation using CO_2 is a rare event in the laboratory, and has been accomplished with N-Boc-N-methyl-benzylamine after enantioselective deprotonation with the Bu^sLi/(-)-sparteine complex, to give Boc-N-methyl-D-phenylglycine.[91]

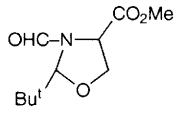
Uses of 'chiral glycine' derivatives continue to provide the greatest volume of literature in this area, with 8-(-)-phenylmenthyl N-Boc-α-bromoglycinate acting as substrate for S_H2' alkylation by allyl tri-n-butylstannanes, a process that

incorporates high diastereoselectivity.[92] Conjugate addition of a chiral glycine synthon [the bis-lactim ether lithium salt; see (30) in Scheme 11] to β-substituted vinyl sulfones starts a route to threo-(2S,3R)- or erythro-(2S,3S)-3-methylphenylalanine and tryptophan.[93] (R,R)-(-)- and (S,S)-(+)-Pseudoephedrine-derivatized glycinamides have been prepared[94] and used[95] for asymmetric synthesis of L- and D-amino acids respectively, through highly diastereoselective alkylation. Surprisingly, there is no need to protect the functional groups in these glycinamides, but it is not obvious why substantial N- and O-alkylation does not accompany the intended C-alkylation. α-Benzamidocinnamic esters of N-methylephedrine or of mandelic acid[96] have been shown to undergo highly diastereoselective alkylation. In the last-mentioned example, the alkylation step took the form of pyrazoline ring formation with diazomethane, and ensuing pyrolysis to give (1R,2R)-, (1S,2S)- or (1S,2R)-1-amino-2-phenyl- or alkyl-cyclopropanecarboxylic acids. Several other established substrates have been employed in this approach, and Oppolzer's chiral sultam has become increasingly popular (see also Refs. 97, 98, 101, 193, 194, 334); starting from DL-α-bromoalkanoic acids (see also Ref. 106). α-Amino acids have been secured in diastereoisomerically-enriched form from this synthon *via* α-bromoamides after nucleophilic substitution by dibenzylamine (Scheme 6).[97] More conventional use of this lactam (26 in Scheme 6; H in place of Br) is illustrated in Pd-catalyzed allylation by $R^5R^3C{=}CR^4CR^1R^2OR$ in a preparation of α-allyl-α-amino acids[98] and in the preparation of the currently-in-vogue (p-phosphonomethyl)-L-phenylalanines (see also Section 4.12).[99] The fully-protected methyl (2S,4R)-oxazolidine-4-carboxylate (27) has been used for a synthesis of components of mycestericins E and G,[100] and using Seebach's imidazolidin-4-one approach for the synthesis of β-{1,2-dicarba-closo-dodecaborane(12)cage}-substituted alanines [the (S)-config-



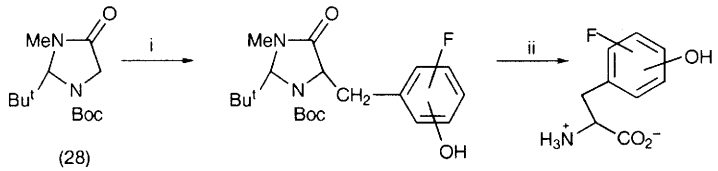
Reagents: i, TMSCl, then NEt_3; ii, RCHBrCOCl, $CuCl_2$; iii, 10 equiv. BzI_2NH; H_2/Pd–C, and hydrolysis

Scheme 6



(27)

uration was assigned to the (+)-enantiomers that were obtained in e.e. >98%].[101] 1-Benzoyl-2-alkyl-3-(1′-(R)- or (S)-methylbenzyl)imidazolidin-4-ones have been shown to undergo highly-diastereoselective alkylation, leading to corresponding α-amino acids by acid hydrolysis.[102] Alkylation of this synthon with heteroaryl halides gives the corresponding α-amino acids.[103] The 2-tert-butyl imidazolidin-4-one [(28) in Scheme 7; it has become abbreviated '(S)-Boc-BMI'] has been used for syntheses of (S)-2- and 4-fluoro-m-tyrosine and of fluoro-tyrosine.[104] A new chiral auxiliary to add to this family is tert-butyl 2-tert-butyl-5,5-dimethyl-4-oxoimidazolidine-1-carboxylate, prepared from L-alanine, α-aminoisobutyric acid and pivaldehyde,[105] and used in syntheses of hindered α-alkyl α-amino acids.



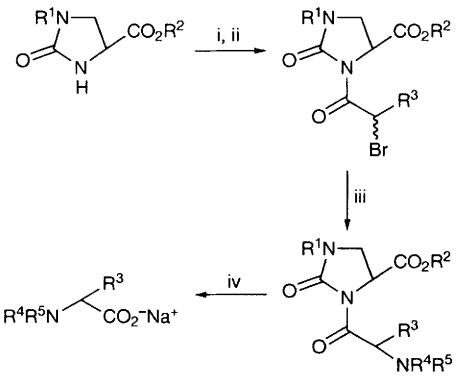
(28)

Reagents: i, F,OH-C_6H_3-CH_2Br, base; ii, hydrolysis

Scheme 7

A variant of this procedure, employing an N^1-alkylimidazolidin-2-one-4-carboxylic acid as novel chiral auxiliary, has been used for stereospecific amination of the derived N-[α-bromoacylated] derivative (Scheme 8), a useful feature being the dynamic kinetic resolution due to epimerization at the side-chain chiral centre that accompanies the amination step, enhancing the yield of the favoured diastereoisomer in some cases,[106] and this feature has been given a particularly thoughtful study for the corresponding auxiliary (S)-tert-butyl 1-methylimidazolidin-2-one-4-carboxylate[107] from which N-benzyl L-amino acids could be prepared after N-acylation by a DL-α-bromoacyl chloride.

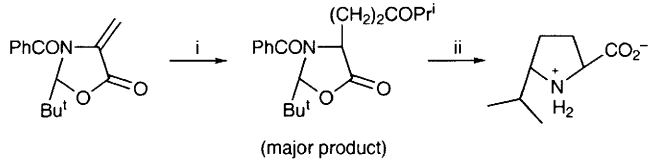
The related oxazolidin-2-one approach is illustrated by syntheses of N^{α}-Fmoc-N^{ε}-Boc-α-methyl-D-ornithine using the oxazolidinone prepared from Z-L-alanine.[108] Preparation of an appropriate oxazolidinone involves potentially hazardous borane reduction and the intermediacy of water-soluble amino alcohols, thus reducing the yields, and these drawbacks are avoided in a thoroughly researched protocol for the synthesis of the (4R)-(-)-phenyloxazolidinone from D-phenylglycine.[109] 4-Diphenylmethyl oxazolidin-2-one is another new chiral auxiliary given thorough testing through representative protocols.[110] A useful variant leading to β-substituted alanines has been given further study leading to (5R,2S)- and (5R,2R)-5-isopropylprolines through conjugate addition



Reagents: i, KOBu^t, THF, –50 °C; ii, $R^3CHBrCOBr$; iii, R^4R^5NH; iv, MeONa, MeOH

Scheme 8

of enamines (Scheme 9).[111] 1,3-Dipolar cycloaddition to this chiral synthon of azomethine ylides derived from N-benzylidene-amino acid esters leads to polyfunctional 2,3-disubstituted prolines of high enantiomeric purity.[112] Use of the norleucine-derived oxazolidinone with N-bromomethylphthalimide as alkylating agent has given (S)-α-aminomethyl-norleucine.[113] Diastereoselective radical addition to these methyleneoxazolidinones is favoured by certain N-protecting groups, and for certain radical species.[114]



(major product)

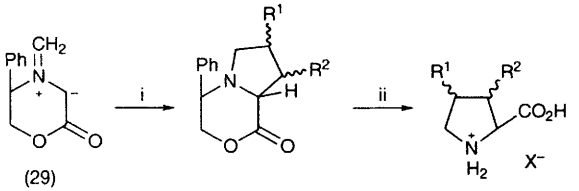
Reagents: i,  , 16 h, RT; ii, Reflux, 6M HCl, then H_2/Pd–C

Scheme 9

The N-acylation of homochiral oxazolidinones, pioneered by Evans (see also Refs. 324, 384) and used by Hruby's group (e.g. to prepare all four isomers of β-methyl-2′,6′-dimethylphenylalanine[115]), has been thoroughly exemplified in preceding Volumes of this Specialist Periodical Report; as has Hruby's work, already committed to the literature in detailed preliminary communications for this compound, and for syntheses by his group of β-methyl-phenylalanine[116] and β-methyl-2′,6′-dimethyltyrosine.[117] Further details of the photolysis of the homochiral N-[(pentacarbonyl)chromium(II)ketene]-oxazolidinone (see also Ref.

63) in the presence of free amines and free, highly-hindered amino acids, leading to amino acid amides, have been given.[118]

Analogous use of the Williams chiral glycine template, benzyl (2R,3S)-2,3-diphenyl-6-oxomorpholine-4-carboxylate, has been reported (see also Ref. 289),[119] also a synthesis of γ-carboxy-L-glutamic acid in excellent (>99%) enantiomeric excess through Michael addition to di tert-butyl methylenemalonate (this paper also provides details of a synthesis of the morpholinone from benzoin oxime).[120] A simpler analogue of this chiral auxiliary (29 in Scheme 10), readily available from (S)-2-phenylglycinol, has served in a chiral synthesis of functionalized prolines through cycloadditions to the derived azomethine ylide.[121] Enantio-



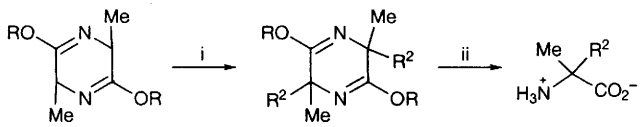
(29)

Reagents: i, $R^1CH{=}CHR^2$; ii, H_2/Pd-C, H_3O^+

Scheme 10

selective synthesis of arylglycines from arylacetic acids proceeds *via* the chiral oxazoline formed with (R)-(-)-2-aminobutanol, but leads only to low optical yields (5-10%).[122]

The piperazinedione prototype that paved the way for all these heterocyclic chiral auxiliaries is illustrated for a synthesis of α-trifluoromethyl-α-amino acids, starting from the 3-hydroxy-3-trifluoromethylpiperazinone.[123] It is now more often seen in the form of its bis-lactim ether derivative (30 in Scheme 11); a typical use (see also Refs. 128, 174, 291, 294, 323, 335, 336, 350) is demonstrated in the preparation of α-methyl-D-serine and its homologues[124] and of L-(-)-6-chloro-5-hydroxytryptophan (a constituent of keramamide A) and its D-(+)-enantiomer,[125] as well as 2-bromo-7-hydroxy-L-tryptophan (a constituent of konbamide and jaspamide).[126] Radical addition to (S)-3-methyl-6-methylene-piperazine-2,5-dione is accompanied by excellent diastereofacial selection,[127] and this may become a favoured method if the product yields can be raised.

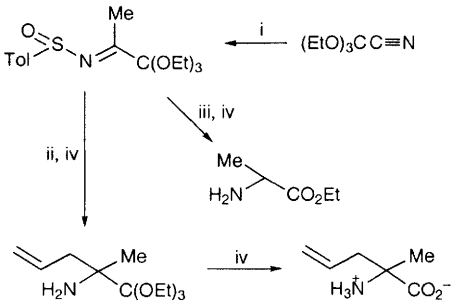


(30)

Reagents: i, R^2X, various catalysts; ii, H_3O^+

Scheme 11

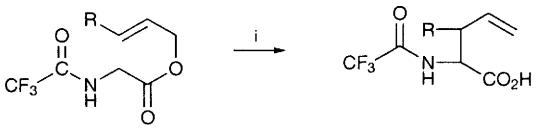
New routes to homochiral α-amino acids based on additions to imines involve the sulfinamide moiety as enantioselector (Scheme 12),[128] and a more conventional approach is offered by the cyanosilylation of imines derived from (S)-TBDMS-lactaldehyde, leading to threonine,[129] and by asymmetric reduction [2-(N-arylimino)-3,3,3-trifluoropropanoic acid esters by the (S)-oxazaborolidine – catechol – borane system],[130] and asymmetric hydrophosphonylation [catalyzed



Reagents: i, MeLi, (+)-*R*-[(−)-menthyl]toluene-*p*-sulfinate; ii, $CH_2{=}CHCH_2$ MgBr; iii, 9-BBN (stereoselective reduction); iv, TFA, H_2O–MeCN

Scheme 12

by La/K-BINOL complexes, to give α-aminophosphonates in 96% e.e.].[131] The presence of a chiral ester component in a glycine-derived imine represents one of the longest-running substrates for the synthesis of homochiral α-amino acids, illustrated with surprising results for 8-phenylmenthyl esters [$(MeS)_2C{=}NCH_2CO_2R$; there is a non-asymmetric version of this process described in the preceding Section, by the same authors (Ref. 73)]; the enolate undergoes alkylation leading to the (S)-α-amino acid series when an alkyl halide – Bu^tOK system is employed, but to the (R)-series when using an alkyl triflate with LDA or tert-butyllithium.[132] Where the ester moiety is derived from a chiral allyl alcohol, Claisen rearrangement (Scheme 13) leads to either one of two possible homochiral outcomes depending on the catalyst used [quinine leads to (2R,3S)-allylglycines as shown in the Scheme, while quinidine leads to the (2S,3R)-series].[133] α-Cyanoalkanoates derived from (1S,2S,4R)-10-(dicyclohexylsulfa-

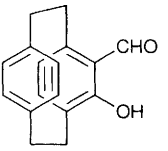


Reagents: i, $LiN(SiMe_3)_2$, quinine

Scheme 13

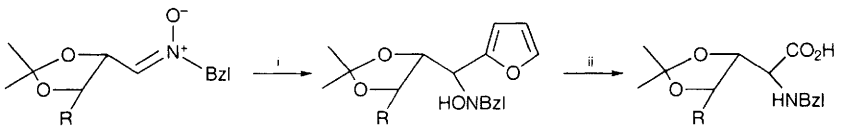
moyl)isoborneol undergo highly diastereoselective alkylation, Curtius rearrangement of the products leading, for example, to (R)-α-methylvaline and to (R)-α-phenyl-α-amino acids.[134] Schiff bases of α-aminonitriles carrying a chiral β-chloroalkyl side-chain can be cyclized with 100% stereoselectivity to 1-aminocyclopropanecarboxylic acids using a mild base (K_2CO_3).[135]

Almost equally long-running in the present context are the Schiff bases derived from N-benzyl-L-prolyl o-aminobenzaldehyde and glycine (see Vol 27, p. 12, and earlier Volumes) which can participate as their nickel(II) complexes in aldol reactions leading to syn-(2S)- and syn-(2R)-β-alkylserines,[136] and as Michael donors towards ethenesulfonate esters leading to fluorinated esters of (S)-homocysteic acid.[137] A novel variant is radical addition to the dehydroalanine version of this Schiff base, radical formation being initiated by 2,2′-azabutyronitrile and tributyltin hydride.[138] The resolution of the aldehyde (31) *via* the Schiff base formed with (R)-α-phenylethylamine, and its use for amino acid synthesis in



(31)

analogous alkylations, leads to β-hydroxy-α-amino acids and α-methylphenylalanine in 45-98% enantiomeric excess (see also Vol 27, p. 12).[139] The Schiff base N-oxides (Scheme 14), available from homochiral α-alkoxyaldehydes, can be carboxylated using α-lithiated furan as a masked form of the carboxy group.[140] A 2-silylated pyrrole, N-Boc-2-TBDMS-pyrrole is a masked glycine anion analogue,

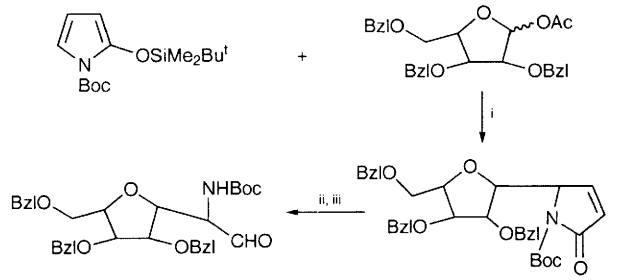


Reagents: i, α-Lithiofuran; ii, $TiCl_3$; then RuO_4

Scheme 14

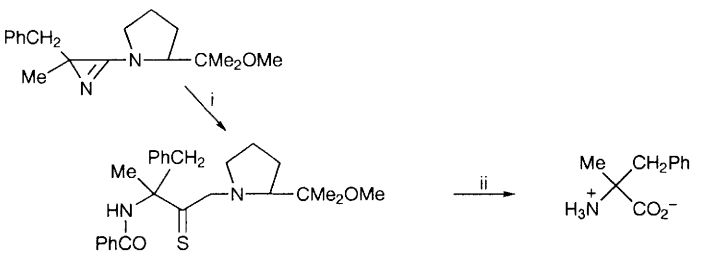
used for diastereospecific α-C-glycosylation of α-C-arabinofuranosylglycine (Scheme 15),[141] and in a synthesis of β-hydroxy-α-amino acids.[142]

Pd-Catalyzed allylation of achiral α-phthalimidoacetates can lead to surprisingly high enantiomeric purity (96% e.e.) when a chiral ligand is incorporated into the catalyst.[143] Ring-opening of a homochiral azirine (Scheme 16)[144] provides an α-methylphenylalanine enantiomer using a sulfur nucleophile, while



Reagents: i, Trityl perchlorate, 0 → 20 °C during 48h; ii, $KMnO_4$, 18-crown-6-ether, then $NaIO_4$; iii, 1M-LiOH/THF (to be followed by $NaClO_2$: CHO → CO_2H)

Scheme 15



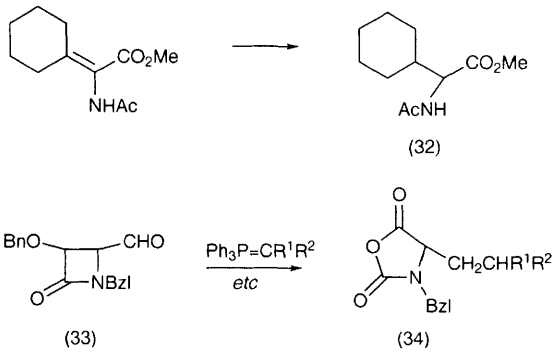
Reagents: i, PhCOSH, Et_2O; ii, H_2O_2, H_3O^+

Scheme 16

ring-opening of (S)-(-)-N-acetyl-2-methoxycarbonylaziridine[145] using a Broensted acid (or using a nucleophile in the presence of a Lewis acid) gives a mixture of α- and β-amino acid derivatives. Excellent regiospecificity has been found, giving optically-pure α-amino acids where the substrate carries one chiral centre, in ring-opening of toluene-p-sulfonylaziridine-2-carboxylic acid salts by carbon nucleophiles.[146] Lithium trimethylsilylacetylide alone, among the nucleophiles studied, led to a high yield of the target α-amino acid (as opposed to an α-amino acid – β-amino acid mixture) when the aziridine carried two chiral centres.

Uses for enzymes are continually being found for the synthesis of unusual amino acids (uses in synthesis of protein amino acids are covered in the next Section), recent examples being preparations of (S)-3-(2-chlorophenyl)- and (S)-(3-hydroxyphenyl)alanine from corresponding 3-arylacrylates, ammonia, and red yeast,[147] and hydration of α-aminonitriles catalyzed by immobilized pronase, to give a mixture of L-α-amino acid and D-α-amino acid amide.[148]

Enantioselective catalytic hydrogenation of α-amino acrylic acid derivatives, a



long-running topic of study that continues to turn up novel features, has nearly reached its peak of perfection in delivering a 99.5% enantiomeric excess of α-cyclohexylglycine (32) using supercritical carbon dioxide as solvent.[149] Better than 96% e.e. is secured for such β-branched compounds using benzene as solvent (H_2 at 90 psi pressure, Me-DuPHOS-Rh catalyst),[150] and the important role played by solvent is well appreciated, seen especially in Rh(II)/achiral phosphine-catalyzed hydrogenation of menthyl α-(N-benzamido)cinnamate.[151] Hydrogenation of enamides catalyzed by the last-mentioned catalyst leads to amino acid derivatives suitable for use in palladium-catalyzed cross-coupling reactions.[152] Rhodium(II)-catalyzed hydrogenation of α-acetamidoacrylates leads to 77-88% e.e. when trans-chelating chiral diphosphine ligands are incorporated into the catalyst,[153] and 86-93% e.e. has been reported for a closely-related system.[154] D- and L-β-(Heteroaryl)alanines have been prepared through Rh(II)/chiral diphosphine-catalyzed hydrogenation of appropriate αβ-dehydro-amino acids.[155] A broad range of rhodium(II)-chiral phosphine-catalyzed hydrogenation studies of αβ-dehydro-amino acids is reaching its culmination.[156] Asymmetric hydrogenation of methyl tetrahydropyrazine-2-carboxylate and the N-tert-butylamide, catalyzed by a Rh(II)/chiral biphosphine, leads to the corresponding (S)-piperazic acid derivatives needed for an HIV protease inhibitor synthesis (Indinavir).[157] Conventional (H_2/Pd-C) hydrogenation of 'dehydroamino acids' in the form of dipeptides prepared with L-proline N-methylamide is accompanied with high enantiomeric bias, as illustrated in a synthesis of (R)-neopentylglycine.[158]

The contraction of a β-amino acid enantiomer to give an α-amino acid is not too exaggerated a description of the route from the 'β-alaninyl cation equivalent' (33) *via* Wittig olefination, MCPBA oxidation and Baeyer-Villiger rearrangement to give the α-amino acid after hydrolysis of (34).[159]

4.3 Synthesis of Protein Amino Acids and other Naturally Occurring α-Amino Acids – The structural features present in individual α-amino acids of natural origin offer a particularly stringent challenge, in some cases, to test the available synthetic methods, while in other cases, structural features are benign but still

offer attractive targets to test synthetic methodology since the properties of the products are so well understood. Syntheses of natural α-amino acids of these types are also described in the preceding two Sections and in later Sections, especially in Section 6.3.

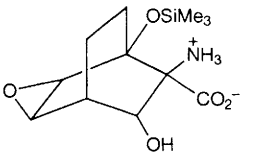
As usual, enzymic catalysis blithely ignores stringent challenges when exploited in syntheses of natural α-amino acids relevant to the specificity of particular enzymes, and representative citations from the rapidly expanding literature on this topic deal with L-tyrosine and its 2- and 3-fluoro-, 3,5-difluoro-, 2-chloro-, 2-methyl- and 3-methyl-derivatives prepared from ammonium pyruvate and the appropriate phenol using *Citrobacter intermedius*, a source of tyrosine phenol-lyase;[160] with L-phenylalanine from N-acetamidocinnamic acid, using a *Corynebacterium sp.*;[161] with L-tryptophan using *Corynebacterium* mutants;[162] and with a hydrogenase – glutamate dehydrogenase cocktail for the reductive amination of 2-oxoglutaric acid to give L-glutamic acid.[163] [^{15}N]-L-Valine can be produced from [^{15}N]-ammonium sulfate through the agency of *Corynebacterium pekinense*.[164] Section 16 of *Chemical Abstracts*: Fermentation and Bioindustrial Chemistry (and other Sections also, Section 10: Microbial, Algal, and Fungal Biochemistry in particular) give access to the full literature (including the patent literature) on this topic, which can only be hinted at here. A review of the production of microbial amino acids using heterotrophic bacteria has appeared.[165]

Glutamic acid, alanine and glycine are generated in low yield in aqueous solutions of corresponding keto-acids, ammonia and reducing agents,[166] and the keto-acids required for the genesis of branched-chain amino acids are suggested to evolve through reductive carboxylation of alkanoic acids.[167] This extends the scope of the prebiotic scenario (see the later Section 4.6) by demonstrating that the usual assumption, the need for some energy source with such reactions to make them plausible prebiotic drivers along the road to Life, is not necessarily valid. Photolysis of lactic acid and ammonia in a cadmium(II) sulfide suspension generates alanine (see also Refs. 608, 730).[168] A laboratory synthesis that is closer to the biogenetic pathway is reflected in the enantioselective generation of threonine and allothreonine from glycine and acetaldehyde, catalyzed by a synthetic cyclophane-embedded pyridoxal (see also Ref. 301).[169]

Stereoselective syntheses of peptide constituents (2S,3R)-3-hydroxyleucine (from lysobactin),[170] of (2R,1'R,2'R)-3-(trans-2'-nitrocyclopropyl)alanine (from hormaomycin) and its 2S-epimer (also present in hormaomycin),[171] of (4R)-4-[(E)-2-butenyl]-4-(NN-dimethyl)-L-threonine (*alias* '4MeBmt' from cyclosporin),[172] and of (3S,4S)-4-hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylic acid (from luzopeptin A)[173] demonstrate representative current methodology. Full details (see Vol 27, p. 19) of a stereocontrolled synthesis using the bis-lactim ether auxiliary have been published of the recently-revised structure for anticapsin,[174] as well as details of retroaldolization of (35) with Bu_4NF to give some near-relatives of anticapsin;[175] and a further synthesis of 'Adda' starting from L-threonine, have been described.[176] Asymmetric total synthesis of the potent immunosuppressive agent ISP-I (*alias* myriocin or thermozymocidin) has been accomplished without recourse to aldoses or ketoses as chiral starting points;[177]

instead, the optimum method for aldolization of the bis-lactim ether synthon was found that successfully introduced the long-chain moiety with the correct stereochemistry. That simple statement hides a considerable amount of development of the reaction conditions needed for understanding the factors determining diastereoselection in this synthesis, and in the synthesis of α-hydroxyalkyl-L-serine.[178]

Cyclopropyl side-chains have been built on to chiral α-aminopentenoates[179] and on to the azlactone (36),[180] in routes to (-)-allocoronamic acid, (-)- '2,3-methanohomoserine' and methyl (2S,3R)-1-aminocyclopropane-1,2-dicarboxy-



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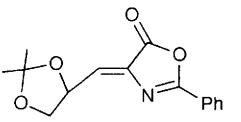
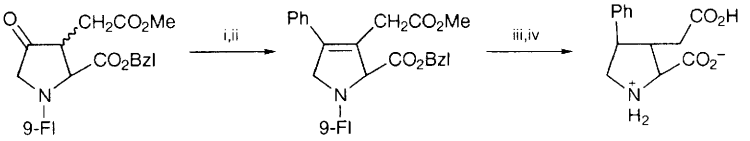


(36)

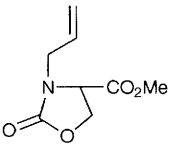
late ('cyclo-Asp-OMe'; Ref. 179); and to (-)-(1S,2R)-allonorcoronamic acid (Ref. 180). D-Glyceraldehyde-derived starting materials were used in these syntheses. (1S,2S)-Coronamic acid and its enantiomer, and (1S,2S)-norcoronamic acid have been obtained through a route involving diastereoselective cyclization of 2-(benzylideneamino)-4-chlorobutyronitriles,[181] and all four stereoisomers of coronamic acid have emerged from another classical synthesis starting from enantiomers of the cyclic sulfate of butan-1,2-diol, used for alkylation of the dibenzyl malonate anion; this stage is followed by partial hydrolysis and Curtius rearrangement.[182] All four stereoisomers of '2,3-methanoleucine' starting from (R)- or (S)-2-hydroxy-3-methylbutan-1-ol, have been prepared from D- and L-valine.[183] The cyclopropane moiety was created from the derived cyclic sulfate through reaction with dimethyl malonate or with dimethyl gluconate, Curtius rearrangement giving (E)- and Z-products respectively. N-Boc-cis-(2S,3R,4S)-'3,4-Methanoproline' and N-Boc-(2S,3R,4S)-'3,4-methanoglutamic acid' have been synthesized by a six-step route starting with condensation of the anion of N-Boc-β-(benzenesulfonyl)-L-alaninol tetrahydropyranyl ether with (2R)-glycidyl triflate.[184] A related approach to stereoisomers of '2,3-methanoglutamine' employs cyclopropane analogues of a γ-lactone and of an α-alkylated malonate to arrive at the requisite cis and trans stereochemistry, respectively, through cautious and traditional functional group development.[185]

The kainic acid family continues to attract attention, and synthesis at its simpler level in this area is represented for arylkainoids (of interest as simple analogues of acromelic acid); phenyl-[186] and substituted phenyl-kainoids[187] have been synthesized, with (2S)-benzyl 4-oxo-N-[9-(9-phenylfluorenyl)]prolinate serving as starting material in one of these routes (Scheme 17). D-Serine starts a route to conformationally restricted kainic acid analogues, *via* the derived N-allyl-5-tert-butoxycarbonylvinyl-lactone (37).[188] Acromelic acid analogues and their C-4 epimers have been reached, starting from trans-4-hydroxy-L-proline



Reagents: i, $KN(SiMe_3)_2$, Tf_2NPh; ii, $PhB(OH)_2$, $(Ph_3P)_4Pd$; iii, NaOH, EtOH; iv, H_2–Pd/C

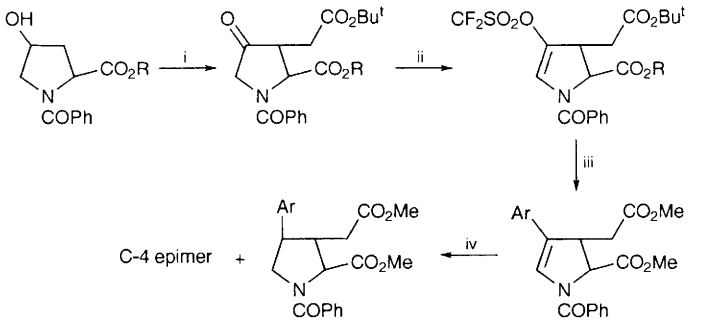
Scheme 17



(37)

through a short and versatile route (Scheme 18) that is suitable for larger scale synthesis.[189]

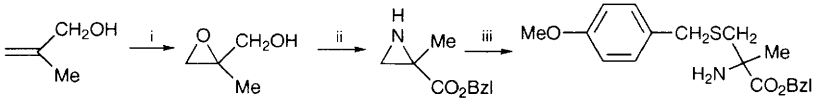
4.4 Synthesis of α-Alkyl Analogues of Protein Amino Acids – The topic is gaining in importance since, among other reasons, it meets the demand for pharmaceutically-active compounds destined to join the high-profile examples recently publicised (α-difluoromethylornithine has emerged as an anti-cancer agent). Together with papers mentioned elsewhere (in preceding Sections of this Chapter) that have described syntheses of α-alkyl-α-amino acids and alicyclic analogues, the current overall picture is completed with a number of papers collected here.



Reagents: i, $RuO_2/NaIO_4$, then pyrrolidine, then $BrCH_2CO_2Bu^t$; ii, $LiN(SiMe_3)_2$, then $PhN(SO_2CF_3)_2$; iii, $ArB(OH)_2/Pd(PPh_3)_4$; iv, Et_3SiH

Scheme 18

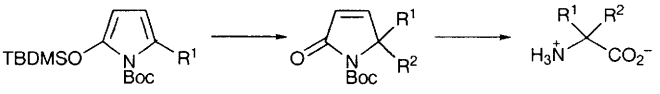
A standard application of methyl acetoacetate, ethyl nitroacetate and ethyl N-(diphenylmethylene)glycinate as anionic glycine equivalents for the synthesis of bicyclic and tricyclic αα-disubstituted glycines,[190] and a standard oxazolone 4-alkylation procedure[191,192] to generate (R)- and (S)-enantiomers of α-methylglutamic acid, α-methylaspartic acid and α-isobutylaspartic acid, illustrate routine methods in this area. One of these routes from Obrecht's group employs L-phenylalanine cyclohexylamide for resolution through aminolysis of the substituted oxazolone and separation of the resulting diastereoisomer mixture. Methylation of $ClC_6H_4CH{=}NCHRCOS^*$ (S* = Oppolzer's camphorsultam chiral auxiliary) employing methyl iodide with a strong base has received a detailed study[193] (see also Refs. 97, 98), and the equivalent substrate ($MeS_2C{=}$ in place of $ClC_6H_4CH{=}$) has been given wide-ranging application including ω-haloalkylation with assistance from phase-transfer catalysis and ultrasound irradiation.[194] Esters formed between benzoylalanine and chiral alcohols are readily alkylated after chiral di-anion generation using LDA, in an enantiospecific approach; the (-)-8-phenylmenthyl esters offer the highest diastereofacial bias to the di-anion, judging by the results obtained.[195] Chiral aziridines (Scheme 19) have been used in a lengthy route to α-methylcysteines.[196]



Reagents; i, Bu^tOOH, (D)-DET, $Ti(OPr^i)_4$; ii, NaN_3, then $OH \rightarrow OMs$, $CH_2OH \rightarrow CO_2Bzl$, and base; iii, $BF_3{\cdot}Et_2O$, *p*-$MeO\text{-}C_6H_4CH_2SH$, CH_2Cl_2

Scheme 19

An extension of the 2-silyloxypyrrole method (see Refs. 141, 142), based on double γ-alkylation *en route* to αα-disubstituted glycines (Scheme 20),[197] and efficient alkylation of α-iminoesters derived from α-amino acids by condensation with a novel pyridoxal-5′-phosphate model carrying a Li^+ ionophore,[198] have been employed. The oxazolidin-4-one chiral auxiliary (Section 4.2) offers a route to α-alkyl analogues of protein amino acids if the auxiliary is synthesized with one of the two required α-alkyl groups already in place; this strategy has been used in a synthesis of α-methyl-L-tryptophan (starting from L-tryptophan)[199] and (R)-α-methyl-phenylalanine (starting with L-alanine, and employing a novel



Reagents: generally as in Scheme 15

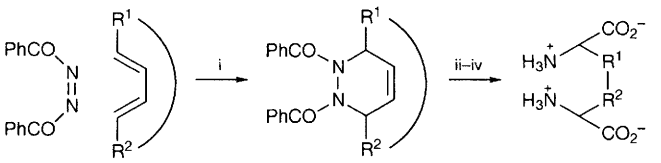
Scheme 20

2-ferrocenyl-substituted chiral oxazolidinone).[200] All isomers of α-methyl-L-serine and α-methyl-L-threonine have been prepared, representing a further stage of Ohfune's long synthesis quest through analogues of the protein amino acids.[201] More innovative procedures have been described, one employing a Pummerer rearrangement *en route* to (S)-α-trifluoromethylserine,[202] another involving conversion of 2-methyl-2-vinyl-3-alkyloxiranes (prepared the Sharpless-Katsuki way) through 1,2-alkyl migration with inversion of configuration into 2-methyl-2-vinylalkanals, followed by functional group manipulation to give (R)-α-methyl-phenylalanine and N-protected α-methyl-α-aminoaldehydes.[203] Chiral N-(β-trimethylsilylethanesulfonyl)aziridinemethanol prepared from (S)-(-)-2-methyl-glycidol (cf. Ref. 196) undergoes nucleophilic ring-opening to give (S)-(+)-α-methyl-serine.[204]

4.5 Synthesis of α-Amino Acids Carrying Alkyl Side-Chains, and Cyclic Analogues – This section catches those papers covering synthesis of aliphatic α-amino acids that do not qualify for location elsewhere in this Chapter, although the synthesis targets are frequently very close structural relatives of the common α-amino acids. Indeed, one common objective for work described here, is the synthesis of analogues of biologically important compounds; the overwhelming emphasis in the recent literature, on alicyclic compounds in this category, reflects the growing interest in the synthesis of conformationally-constrained analogues for biological testing.

Acyclic examples include the synthesis of all four diastereoisomers of 4-methyl glutamic acid.[205] An extraordinary route illustrated for the synthesis of meso-αω-di-amino-dicarboxylic acids (Scheme 21) is largely limited in scope by its dependence on the supply of appropriately substituted dienes, and it remains to be seen whether a particularly useful potential application of this method, the synthesis of αα′-dialkylated analogues, can be achieved.[206]

A continuing flow of new routes to cyclopropane-based amino acids, adding to

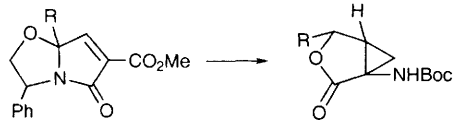


Reagents: i, CCl_4; ii, RuO_2(cat.) aq $NaIO_4$; iii, 6M HCl–AcoH/100 °C, iv, H_2/Pt

Scheme 21

those studies discussed in preceding Sections, includes cyclopropanation of the fused oxazolidinone (38) followed by removal of the chiral auxiliary and Curtius rearrangement.[207] The preparation of 1-aminocyclobutane-1,3-dicarboxylic acids involving degradation of benzenesulfonylbicyclobutanes has been thoroughly documented,[208] and cis- and trans-3-substituted-1-aminocyclobutane-1-car-

boxylic acids are covered, including 3-(2'-phosphonoethyl) derivatives that are effective at the NMDA receptor.[209] This work includes a synthesis of 3-hydroxymethyl-1-aminocyclobutane-1-carboxylic acid; 4-carboxymethyl-1-aminocyclobutane-1,3-dicarboxylic acid has been obtained through a standard hydantoin synthesis employing bicyclo[3.2.0]heptan-2-one followed by oxidative ring-opening.[210] X-Ray structure determination was employed to assign relative configuration to this product. 3-Aminobicyclo[3.3.0]octane-1,3-dicarboxylic acid (39) has been obtained through a lengthy sequence from readily available diketone (40).[211]



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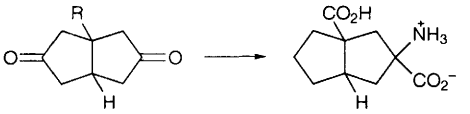
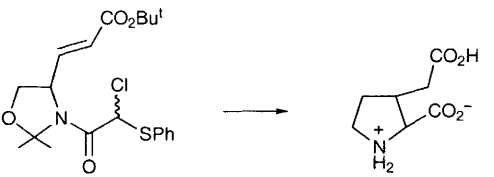


(40) (39)

(S)-1-Phenylethylamine acts as chiral auxiliary as well as nitrogen donor in a route to (R,R)-azetidine-2,4-dicarboxylic acid.[212]

Numerous avenues to substituted prolines are represented in the recent literature:- a general route illustrated by cyclization of 5-(N-phosphinyloxy-amino)valerate esters after generation of the α-anion;[213] a route to (2S,3R)-3-carboxyproline and its 3-amino analogue through stereospecific alkylation of (4S)-N-(TBDMS)-azetidin-2-one-4-carboxylic acid in several ways, best through the use of the cyclic sulfate of ethyleneglycol and elaboration of the resulting β-hydroxyethylated substrate;[214] to 4-hydroxy-3-phenylproline through hydration and hydrolysis of 1-acetyl-2,2-diethoxycarbonyl-2,3-dihydro-3-phenyl-1H-pyrrole;[215] to methyl 3-amino-3-pyrrolidine 3-carboxylate *via* addition of acrylates to the azomethine ylide formed from $PhCH_2N(CH_2OBu)CH_2SiMe_3$, *en route* to cucurbitine;[216] to the simple kainic acid analogue (41);[217] and to

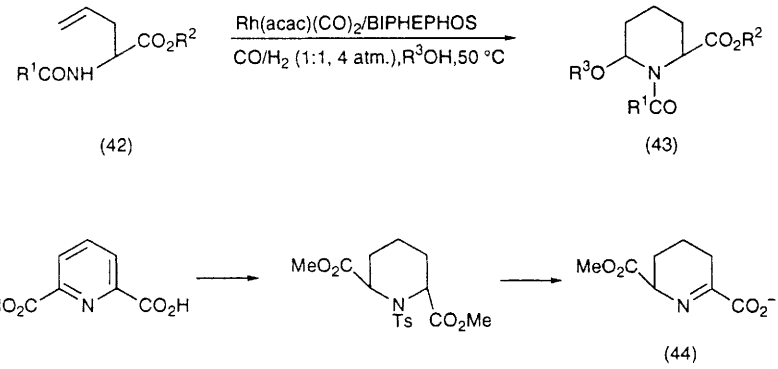


(41)

substituted pyrrolidinecarboxylic acids starting from Diels-Alder adducts of maleic anhydride with alkadienes.[218] Methyl L-prolinate has been used as chiral reagent for ring-opening of meso-norbornene-derived anhydrides, leading to amido acids with excellent levels of asymmetric induction, and thence to valuable synthons.[219]

Bicyclic proline analogues can be constructed through methylenation of pyrrolines using ethyl diazoacetate/Rh(II) tetra-acetate, an approach used with 3,4-dehydroproline[220] and with 2,3-dihydropyrrole-2,2-dicarboxylic acid.[221] Instead of having the proline moiety in place as with these two examples, the synthesis target can be approached by building on to a cyclic template, as in the cycloaddition of ethyl glyoxylate to the azomethine ylide derived from (S)-5-phenylmorpholin-2-one (see also Vol 27, p. 15).[222] Of course, the Diels-Alder addition fits into this category, and has been illustrated again for the addition of cyclopentadiene to a chiral glycine imine, (R)-PhCHMeN=CHCO$_2$Bzl, to give conformationally-constrained proline analogues after hydrogenolysis (cleavage of the chiral auxiliary) and hydrogenation of the C=C bond.[223] [60]Fullerene undergoes 1,3-dipolar cycloaddition to N-benzylideneglycine methyl ester to provide the fullerene-fused 5-phenylproline ester,[224] while C-N bond breaking accompanies the corresponding reaction with sarcosine esters, yielding both fullerene-pyrrolidines and methanofullerenes.[225]

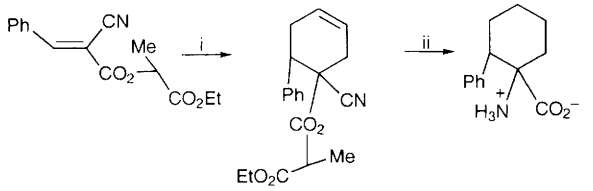
6-Alkoxy-5,6-dehydropipecolic acid esters have been prepared from allylglycine esters through an intramolecular cyclohydrocarbonylation sequence (42 → 43).[226] Conversion of pyridine-2,6-dicarboxylic acid (dipicolinic acid) into dimethyl cis-piperidine-2,6-dicarboxylate, and further conversion into the racemic methylpyrrolidinedicarboxylate (44), could be described as an approximate



(42) (43) (44)

reversal of a common biosynthetic pathway;[227] a similar approach to cis-6-hydroxymethylpipecolic acid involves catalytic hydrogenation of 6-hydroxymethylpyridine-2-carboxylic acid.[228] Aza-Diels-Alder routes, one employing the 8-phenylmenthyl ester of (R)-PhCHMeN=CHCO$_2$H,[229] and another example (heterogeneous catalyzed) employing the (-)-menthyl ester of an N-acetyl-αβ-dehydroamino acid,[230] lead to pipecolic acid derivatives. The double chiral

tagging approach, illustrated in one of these studies, has been used before in unrelated amino acid syntheses but not to such a spectacular outcome as far as diastereoisomeric excess (>95%) is concerned. In a different asymmetric Diels-Alder approach [in which two new chiral centres, 1S and 2R, are generated when butadiene reacts with a chiral (E)-2-cyanocinnamate ester formed with (S)-ethyl lactate], the adduct is converted into 1-amino-2-phenyl-1-cyclohexanecarboxylic acids by routine functional group transformations (Scheme 22).[231] Diels-Alder addition [Danishefsky's diene to (Z)-4-benzylidene 2-phenyloxazol-5(4H)-one]



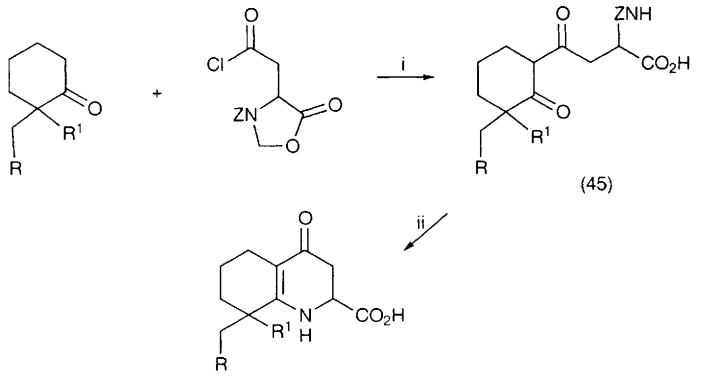
Reagents: i, butadiene, $TiCl_4$, CH_2Cl_2; ii, H_2–Pd/C, then Curtius rearrangement, and CN→CO_2H

Scheme 22

followed by standard operations gives 1-amino-4-hydroxycyclohexane-1-carboxylic acid from which exo-2-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid, a new constrained proline analogue, was obtained by intramolecular cyclization.[232] N-Protected 2-keto-aziridines react with Ph_3PCH_2 and BuLi,[233] with the same outcome seen for aza-[2,3]-Wittig rearrangements of N-tert-butoxycarbonylmethyl vinylaziridines, giving cis-2-substituted 3,4-dehydropipecolic esters (preserving stereochemistry for homochiral examples);[234] carboxy group manipulations and cyclization leads to indolizidines. The alternative thermal homodienyl-[1,5]-hydrogen shift of the same aziridines can also be brought about quantitatively, to give N-alkylglycine Schiff bases, and consideration has been given to the effects of substituents on these processes.[235]

cis-(2R,3S)- and trans-(2S,3S)-Piperidine-2,3-dicarboxylic acids are of interest as cyclic analogues of N-methyl-D-aspartic acid, and have been synthesized from the morpholinone obtained by condensation of (2S)-phenylglycinol with dimethyl acetylenedicarboxylate followed by annulation with acryloyl chloride, and straightforward steps thereafter.[236]

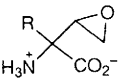
Synthesis of saturated heterocyclic analogues of common amino acids provides another minor component to complete this section, with cyclization of 4-oxo-alkanoic acids (45 in Scheme 23) yielding quinolinic acid analogues.[237] Bischler-Napieralski cyclization of an N-acyl-(L)-3,4-dimethoxyphenylalanine attached to chloromethylated poly(styrene) resin has been investigated;[238] reduction with $NaBH_3CN$ was successful in providing resin-bound 1-substituted isoquinolinic acids, which could be stripped from the resin in the usual way. A synthesis of free



Reagents: i, Mesityl-Li, –78°C, then 1M KOH; ii, HCO_2^- NH_4^+, Pd–C

Scheme 23

α-oxiranyl α-amino acids (46) from Z-DL-vinylglycine through MCPBA oxidation, or *via* the derived diol, is notable.[239]



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4.6 Models for Prebiotic Synthesis of Amino Acids – Standard themes continue to be played or this topic, updated from time to time by new ideas. This year, further account is taken of the proposed genesis of amino acids in submarine thermal vents, an idea that has been undermined by the claims that 'amino acids are irreversibly destroyed at 240°' and that quasi-equilibrium calculations, advanced by others to give credence to experimental observations, are not applicable to high temperature systems involving organic compounds such as amino acids.[240] What is controversial then, is the paper showing that the thermodynamics of the Strecker reaction running at $\geq$400° are in favour of the abiotic synthesis of amino acids in thermal vents,[241] but pyrolysis studies of amino acids over many years have shown that simple α-amino acids can be recovered from self-condensation products formed at these temperatures.[242] α-Amino acids are indeed formed in simulated thermal vent environments;[243] this article also reviews other proposals for the abiotic synthesis of amino acids. Another experiment in which high energy plasma and heterogeneous salt interfaces act on the standard $CH_4/NH_3/H_2O$ mixture, to mimic the marine system, has found the usual products including amino acids, but also polycyclic aromatic compounds including azulenes and long-chain alkanes.[244]

The role of elementary particles in driving the enantioselective synthesis of amino acids has been reviewed.[245] Irradiation at 10K by high energy protons (to simulate cosmic radiation) of aqueous $CO/CH_4/NH_3/H_2O$ mixtures (the likely composition of cometary ice) generates glycine and alanine,[246] a result also achieved using mildly oxidized gas mixtures.[247]

The role of ferrous sulfide (pyrite) in mediating such reactions is, not surprisingly, controversial. Amino acid synthesis does not occur in systems where $CO_2$is reduced by ferrous sulfide + H_2S (a strongly reducing combination) in a reverse citric acid cycle;[248] however, reductive amination of α-ketoacids can be accomplished in a system in which oxidative formation of pyrite is occurring, and involves CO_2 as catalyst.[249] The roles of different prebiotic raw materials, with special emphasis on minerals, has been reviewed.[250]

4.7 Synthesis of α-Alkoxy α-Amino Acids and Analogous α-Hetero-atom Substituted α-Amino Acids – The applications of α-methoxy α-amino acids (Refs. 79, 427) and α-bromo-analogues (Ref. 77), seem to have been more important this year than the routine methods by which they are synthesized.

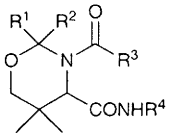
4.8 Synthesis of α-(ω-Halogenoalkyl) α-Amino Acids – A review of synthetic methods has been published as part of a major treatise on fluorinated amino acids.[251]

Fluorination (F_2) of 4-alkylidene-oxazolin-5(4H)-ones and alkaline hydrolysis of the difluorinated adducts gives β-fluoro-α-keto-acids that can be returned to the α-amino-acid family through standard reductive amination to β-fluoro-α-amino-acids.[252] Claisen rearrangement of trifluoromethyl allyl ethers $RCH{=}CHCH_2OCCl(CF_3)CO_2R^1$ gives δε-unsaturated ββ-difluoro-α-keto-esters $CH_2{=}CHCHRCF_2COCO_2R^1$ that can be elaborated into the ββ-difluoro-α-amino-acids through standard reductive amination methods ($NH_3/NaBH_4$).[253]

Simple ω-iodo-α-aminoalkanoic acids, such as β-iodoalanine, continue to show useful applications in synthesis (e.g. Refs. 288, 707). Reliable synthetic methods have been described for higher homologues.[254]

4.9 Synthesis of α-(ω-Hydroxyalkyl)-α-Amino Acids – One of the simplest modifications of a glycine anion, through aldol addition, results in α-(α-hydroxyalkyl)ation and has been regularly featured in the literature. Together with citations in other Sections of this Chapter concerned with simple synthetic applications of aldol reactions (e.g. Section 4.2), the recent crop of papers collected here concentrates especially on stereochemical aspects of aldolization. syn- or anti-Selectivity is shown in the formation of α-amino-β-hydroxyacid esters in this reaction, applied to ethyl N-methyl-N-benzylglycinate and its borane adduct,[255] while titanium enolates of N-benzyloxycarbonylamino acid esters yield alkyl anti-α-amino-(β-hydroxy)alkanoates, best results accruing for bulky aldehydes reacting with sterically-hindered amino acid derivatives.[256]

Homoserine and structural analogues have been laboriously synthesized (homoserine betaines in nine steps from ethyleneglycol[257]) and innovatively synthesized *via* 1,3-oxazines, either through the Ugi reaction applied to 3-



(47)

hydroxy-2,2-dimethylpropanal[258] giving (47), or from a dihydro-1,3-oxazine, giving 1-amino-3-hydroxycyclohexane-1-carboxylic acid as a conformationally constrained homoserine analogue.[259]

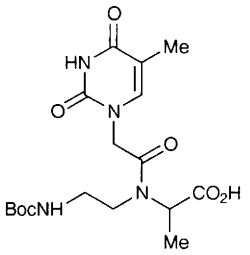
L-Threonine aldolase (*Candida humicola*) has been shown to be relatively unspecific, in catalyzing the addition of a wide variety of aldehydes to glycine to give L-α-amino-β-hydroxy acids; however, it is dismissive of the need to deliver a particular configuration at the β-chiral centre.[260] The same protocol has been used for a synthesis of (2S,3R)-2-amino-3-hydroxybutyrolactone starting from glycine.[261]

4.10 Synthesis of N-Substituted α-Amino Acids - This Section may seem unnecessary, since routine preparations of these derivatives starting from amino acids are located in the later Section 6.2. However, it is appropriate to provide space to cover syntheses from other starting materials, and to acknowledge the growing importance of studies of modified peptides, e.g. those that mimic polynucleotides (these mimics are known as 'PNA's) which has called for the supply of appropriate amino acids for their synthesis. One example is N-(2-Boc-aminoethyl)-N-(thymin-1-yl)acetyl-L-alanine (48) that is synthesized in a straightforward way starting from alanine.[262] Benzyl N-Boc 4-bromo-2-aminobutanoate, prepared from α-benzyl N-Boc-glutamate *via* photolysis of the 1-hydroxy-2-thiopyridyl ester in CCl_3Br, reacts readily with the nucleotide bases adenine, thymine, cytosine or guanine to give useful building blocks[263] for PNA synthesis.[264]

Novel building blocks for PNAs with an N-(aminomethyl)-β-alanine backbone ('retro-inverso PNA') have been synthesized by a route starting with a Hofmann rearrangement [$H_2NCOCH_2NH(COCH_2B)CH_2CH_2CO_2Et \rightarrow H_2NCH_2NH(CO\text{-}CH_2B)CH_2CH_2CO_2Et$; where B is one of the polynucleotide bases].[265]

Modified peptides now known as peptoids, are prepared from N-substituted glycines; a synthesis of one member of the peptoid family calls for N-Fmoc-protected amino acids, prepared from ethyl bromoacetate, aminolyzed by alkylamines representing Phe, Leu, Lys(Boc) and Met side-chains, was then saponified and converted into the Fmoc derivative (to give 'Fmoc-NPhe-OH', etc; 49) in preparation for standard solution-phase peptide synthesis.[266]

4.11 Synthesis of α-Amino Acids Carrying Unsaturated Aliphatic Side-Chains – The 'dehydro-amino acids' are the simplest representatives of this class, and one of the most easily synthesized and also useful in general amino acid synthesis



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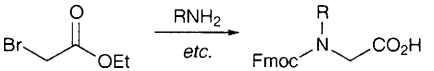
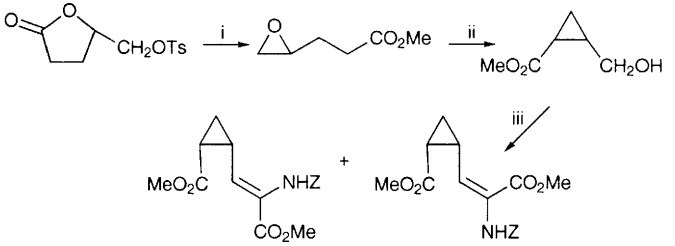


(49)

(Refs. 81, 305), despite lacking the α-chiral centre. These are easily prepared through condensation of an aldehyde or ketone corresponding to the intended side-chain with an anionic glycine synthon, usually an oxazol-5-(4H)-one, and $(MeO)_2P(O)CH(NHZ)CO_2R^1$ is a useful alternative synthon, used in a synthesis of cyclopropylmethyleneglycines (Scheme 24).[267] β-Hydroxy α-amino acids are efficiently dehydrated to 'dehydro-amino acids' using dichloroacetyl chloride and a tertiary amine.[268] 2-Azidoacrylates undergo per-rhenate-catalyzed decomposition in $ClCO_2CCl_3$ or $COCl_2$ followed by NEt_3-induced dehydrochlorination, to give 2-isocyanoatoalken-2-oates.[269]



Reagents: i, MeONa, MeOH; ii, 1.2 equiv. LDA, THF, – 50 °C; iii, CrO_3–py, then $(MeO)_2P(O)CH(NHZ)CO_2Me$

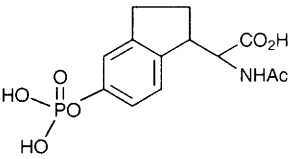
Scheme 24

Vinylglycine represents the archetypal βγ-unsaturated α-amino acid, and has been newly synthesized by Neber rearrangement of the chloroimidate derived from allyl cyanide.[270] This method is successful for the synthesis of (E)-2-aminopent-3-enoic acid and its 3-methyl homologue. Even more importance is acquired for vinylglycine through this work, since it can be used to synthesize other amino acids (see Refs. 239, 710, 711). Mitsunobu synthesis by the condensation of phthalimide with chiral secondary allylic alcohols and (R)-isopropylideneglyceraldehyde leads to βγ-unsaturated α-amino acids [the use of ethyl (S)-lactate in the process leads to αβ-unsaturated γ-amino acids].[271] (E)- and (Z)-β-(Fluoromethylene)-substituted m-tyrosines have been prepared (see also

Ref. 281) and resolved, with configurational details settled through considerable effort (CD and X-ray analysis).[272] Vinylglycine homologues have been prepared starting from homochiral 5-vinyl oxazolidin-2-ones, effectively a protected form of the parent amino acid that can tolerate chain extension by organocuprates.[273]

α-Substituted (E)-βγ-dehydroglutamic acids have been prepared through establishing a simple Michael-type addition process between N-diphenylmethyleneglycine ethyl ester and ethyl propiolate.[274] The initial mixture of E- and Z-adducts was easily separated on the basis of 3,4-dehydropyroglutamate formation by the Z-isomer during work-up.

4.12 Synthesis of α-Amino Acids with Aromatic or Heteroaromatic Groupings in Side-Chains – Phenylalanine and tyrosine analogues synthesized through applications of standard methodology include Fmoc-L-p-azidophenylalanine (from L-p-aminophenylalanine),[275] Tyr[P(O)$(NMe_2)_2$]OH as its N-Fmoc derivative[276] (see Vol 27, p. 33); conformationally-constrained analogues of phosphotyrosine (e.g. 50);[277] dimethoxy-L-phenylalanines (a lengthy route starting with chlorocyanoethylation of anisole by 2-chloroacrylonitrile/$TiCl_4$ and routine amination and hydrolysis steps);[278] 2,6-difluoroDOPA (starting from 2,6-difluoroveratraldehyde);[279] and β-(4-diazocyclohexa-2,5-dienonyl)-L-alanines (starting by alkylation of chiral glycine synthons by benzyloxy-nitrobenzyl iodides).[280] 4′-Fluorination of (R)- or (S)-β-(fluoromethylene)-m-tyrosine (see Ref. 272) has been accomplished with AcOF.[281] Ring-substituted α-(4-hydroxyphenyl)-βββ-trifluoro-alanines have been obtained by amination of quinomethides (51),[282] and



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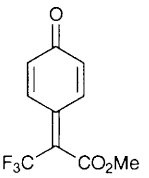
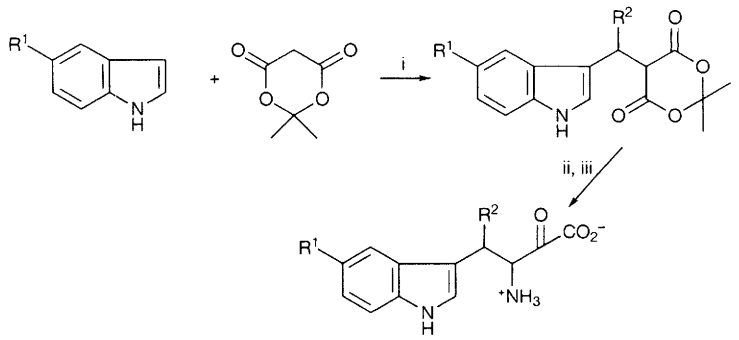


(51)

an 18-crown-6-ether-benzo-substituted L-phenylalanine has been synthesized.[283] Hydroxylation of phenylalanine by H_2O_2 is catalyzed by a remarkable manganese – fluorinated porphyrin, whose effectiveness (and, perhaps, also its selectivity) can be appreciated by the fact that the ring in toluene is also hydroxylated by this system.[284]

Benzo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids represent newcomers to the well-known group of conformationally constrained analogues of phenylalanine, and the three possible versions have been synthesized by alkylation of ethyl acetamidocyanoacetate (see also Refs. 298, 803).[285]

Enantiomerically-pure 4-alkyltryptophans have been prepared through a standard formamidomalonate synthesis, using lithiated N-TIPS-protected gramines as alkylating agents, followed by penicillin G acylase resolution.[286] β-Substituted



Reagents: i, R^2CHO; ii, EtOH, py/80 °C; iii, half-ester → NHZ with DPP (Curtius rearrangement), then $H_2NCOOBzl$; iv, H_2/Pd

Scheme 25

tryptophan esters can be prepared in four steps from indoles, aldehydes and Meldrum's acid (Scheme 25; see also Vol 27, p. 41).[287]

Heteroaromatic targets closely related to protein amino acids have been achieved:- L-β-(5-hydroxy-2-pyridyl)alanine (using the β-iodoalanine synthon $BocNHCH(CH_2I)CO_2Bzl$ by coupling with 5-methoxy-2-iodopyridine followed by BBr_3 deprotection),[288] and 'L-azatyrosine' through standard use of Williams' morpholinone chiral auxiliary;[289] 2-substituted tryptophans [Lewis acid-catalysed Michael addition of 2-substituted indoles to $Ph_2C{=}NC(=CH_2)CO_2R^1$];[290] 5-methoxy-D- and L-tryptophans through standard enantiospecific protocols;[291] thia-analogues of tryptophan (β-3-thieno[2,3-*b*]- and [3,2-*b*]pyrrolyl-L-alanine from thienopyrroles, L-serine, and tryptophan synthase from *Salmonella typhimurium*);[292] and β-(3-N-ethylcarbazolyl)-L-alanine (from the corresponding heteroaryl aldehyde through the Erlenmeyer azlactone synthesis followed by acylase resolution).[293] 3-Methyl-5-(arylthio)-L-histidines have been prepared, as models for the Starfish alkaloid imbricatine, through the bis-lactim ether protocol starting off a 10-step route with 4(5)-bromoimidazole.[294]

Heteroaromatic targets synthesized as analogues of other α-amino acids known to be physiologically-active, include:- the NMDA receptor agonists 2-amino-2-(3-hydroxy-5-methyl-4-isoxazolyl)acetic acid (Ugi synthesis and resolution with cinchonidine),[295] and its racemic 5-isopropyl analogue (acetamidomalonate synthesis);[296] (R)- and (S)-homoibotenic acid (use of Boc-L-phenylalanine as chiral auxiliary);[297] (3SR,4aRS,6SR,8aRS)-6-(1H-tetrazol-5-yl)decahydroisoquinoline-3-carboxylic acid [competitive NMDA and AMPA receptor antagonists {i.e. 2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)acetic acid analogues}, synthesized from 6-formyl-decahydroisoquinoline-3-carboxylic acid];[298] and α-(isoxazol-3-yl)glycine and its isoxazol-5-yl and N-phenylpyrazol-3-yl analogues [ozonolysis of α-(cyclohexa-1,4-dienyl)glycine and construction of the hetero-

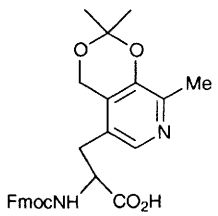
cyclic moiety with hydroxylamine or phenylhydrazine].[299] Synthesis of β-(2-substituted pyrimidin-4-on-5-yl)-L-alanines, shown to possess useful glutamate receptor activity, has followed a 'ring-switching' strategy exemplified earlier, in which a pyroglutamate 4-aldehyde equivalent is converted into a substituted imine, which then opens the pyroglutamate through intramolecular attack at the ring carbonyl group, thus completing a heterocyclization.[300]

In keeping with a theme of a preceding paragraph, where descriptions are given of α-amino acids carrying familiar metabolically-important structures in amino acid side-chains, the 'pyridoxal coenzyme amino acid' (52) has been described (see also Ref.169).[301] The purpose of preparing these amino acids is for their use in peptide synthesis, and in metabolic studies.

4.13 Synthesis of α-(N-Hydroxyamino) Acids – Mitsunobu synthesis involving α-hydroxyacids and N-alkoxycarbonyl-O-alkoxycarbonyl-protected hydroxylamines provides N-hydroxyamino acids in high enantiomeric purity[302] (see also Ref. 380).

4.14 Synthesis of α-Amino Acids Carrying α-(ω-Aminoalkyl) Groups, and Related Nitrogen Functional Groups, in Side-Chains – The contents of this Section overlap considerably with other Sections covering categories of structure with side-chains that extend outwards from the glycine moiety through a nitrogen atom. β-Enamino esters $R^1NHC(SLi)=C(NR_2)CO_2Et$ are formed from the lithium enolate of an NN-diprotected glycine ester and an isothiocyanate,[303] and N^{β}-alkyl diaminopropionic acids are formed by ring opening of tert-butyl N-toluene-p-sulfonylaziridinecarboxylate with a primary amine; treatment of the product with an alkyl iodide in the presence of Cs_2CO_3 creates the selectively N^{α}-alkylated compound.[304]

The addition of nitrogen-centred nucleophiles to dehydroalanine derivatives provides the products of β-addition (leading to β-aminoalkyl α-amino acid derivatives) in competition with α-imine capture.[305] No such competition is seen in the corresponding reaction with methyl 2-acetamidoacrylate catalysed by $FeSO_4$ that leads to β-dialkylamino-α-alanines.[306] An α-amino acid with a 'half-EDTA' side-chain, *viz.* $FmocNHCH[(CH_2)_nN(CH_2CO_2Bu^t)_2]CO_2H$ has been synthesized in a form ready for use in peptide synthesis,[307] and 'azaSAM' (53),



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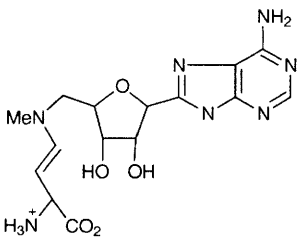


(53)

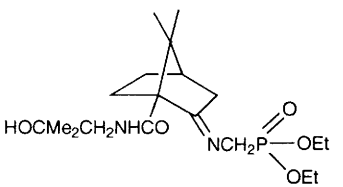
the 5'-methylamino analogue of S-adenosyl-L-methionine, has been synthesized.[308]

Synthesis of the novel natural azoxy compound azoxybacilin (see Vol 27, p.3), starting from α-tert-butyl N-Boc-L-aspartate proceeds *via* the sequence $RCO_2H \rightarrow RCH_2OH \rightarrow RI$ $RN(O)=NMe$, the latter step employing $MeN=NO^-K^+$ as reagent.[309]

4.15 Synthesis of α-Amino Acids Carrying Sulfur- or Selenium-Containing Side-Chains – Most of the published routes claiming the synthesis of felinine (2-amino-7-hydroxy-5,5-dimethyl-4-thiaheptanoic acid) in fact yield the 7,7-dimethyl isomer; the only effective synthesis is a low yield route.[310]

4.16 Synthesis of α-Amino Acids Carrying Phosphorus Functional Groups in Side-Chains, and α-Amino Phosphonic Acids – Whereas common amino acids that are derivatized by phosphorylation are not covered thoroughly in this Chapter [but this year, some citations (Ref. 277) do cover such compounds in passing], the growing importance of alkane- and arene-phosphonates for their potential physiological activity justifies highlighting, through brief separate coverage here.

The asymmetric synthesis of phosphorus analogues of the amino acids has been reviewed.[311] The well-known equivalent of the Strecker synthesis in phosphorus chemistry has been illustrated in a general asymmetric synthesis version, i.e. the preparation of α-amino phosphonic acids from an aldehyde and (R)- or (S)-α-methylbenzylammonium hypophosphate in refluxing ethanol, and bromine water oxidation of the resulting phosphonous acid.[312] (R)- and (S)-2-Amino-5-phosphonopentanoic acids have been prepared through a modified Seebach approach (alkylation of the Li enolate of a chiral imidazolidin-4-one),[313] and the same approach using chiral imidazolidin-4-one 5-phosphonates provides 1,2-diaminoalkane-2-phosphonic acids.[314] Analogous extension of standard practice in the carboxylic acid field is shown in the use of the chiral Schiff base (54),[315] and in stereoselective electrophilic amination of chiral non-racemic α-alkyl



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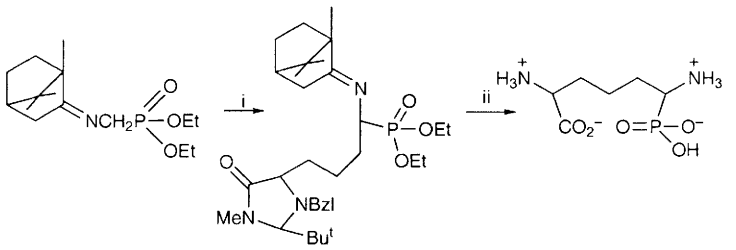
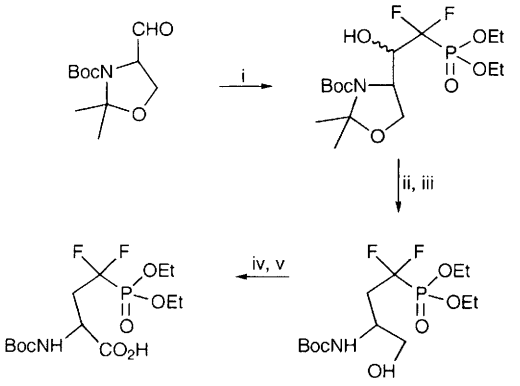
phosphonamides to give α-alkyl-α-aminophosphonic acids.[316] Also, Ru(II)-BINAP-catalyzed hydrogenation of configurationally-labile α-amido β-keto-phosphonic acid esters leads to the (R,R)- or (S,S)-β-hydroxy analogues, the stereochemical outcome indicating the highly enantio- and diastereoselective basis of the process.[317] Synthesis (Scheme 26) and uses of analogues of pimelic acid in which one carboxy group is replaced by the phosphonic acid moiety, have been described.[318]



Reagents: i, BuLi,chiral imidazolidinone; ii, 12 M HCl

Scheme 26

The Garner aldehyde (see also Section 6.3) from D-serine provides the starting point for a synthesis of N-Boc-2(S)-amino-4-(diethylphosphono)-4,4-difluorobutanoic acid (Scheme 27).[319] Synthesis of diphenyl N-(Z-L-α-aminoacyl)pyrrolidine-2-phosphonates, i.e. substituted phosphonic acid analogues of proline, involves cyclization of N-(Z-L-α-aminoacyl)-4-aminobutanal in the presence of $P(OPh)_3$ to give easily separated diastereoisomer mixtures.[320]



Reagents: i, Diethyl difluoromethanephosphonate/LDA/–78 °C; ii, ClCSOPh/DMAP; iii, Bu_3SnH, AIBN; iv, HCl–EtOH; v, $RuCl_3/NaIO_4$

Scheme 27

cis-4-Phosphonomethylpiperidine-2-carboxylic acid has been synthesized from ethyl isonicotinate by reaction with $HCHO/H_2O_2/FeSO_4$.[321] The β-alanine analogue prepared from $PhtNCH_2CH{=}CHP(O)(OEt)CH(OEt)_2$ through catalytic tritiation and deprotection, binds strongly to the GABA-B receptor.[322]

4.17 Synthesis of α-Amino Acids Carrying Boron Functional Groups in Side-Chains, and α-Amino Boronic Acids – (S)-β-(o-Carboranyl)alanine has been synthesized through a standard Schollkopf bis-lactim ether synthesis (see Section 4.2) through propargylation and reaction with 6,9-bis(acetonitrile)carborane, followed by routine work-up.[323]

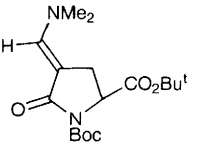
4.18 Synthesis of α-Amino Acids with Silicon Functional Groups in Side-Chains – The Evans oxazolidinone approach (see Section 4.2) is applicable to the preparation of β-trimethylsilyl-L-alanine and $PhSiMe_2$- and $MePh_2Si$- analogues.[324] After uneventful acylation of the chiral auxiliary with $Me_3SiCH_2CH_2$-COCl and analogues, the route involved α-azidation, reduction and cleavage.

4.19 Synthesis of Isotopically Labelled α-Amino Acids – Reviews cover the preparation of ^2H-labelled amino acids[325] and the provision of ^{13}C- and ^{15}N-labelled protein amino acids.[326] A Symposium Proceedings Volume covers most of the salient features concerning the synthesis of labelled amino acids and their current applications,[327] including stereospecific synthesis of ^2H-labelled amino acids[328] (illustrated with D-propynylglycine[329] and ^2H-proline[330]), enzymic synthesis of labelled amino acids[331] and the synthesis of ^{11}C-labelled amino acids[332] including N^{ω}-nitro-L-arginine [^{11}C]methyl ester.[333]

As well as examples given in the preceding paragraph, several other stereospecific syntheses of labelled amino acids have been carried out using standard glycine synthons; thus, alkylation of Oppolzer's camphorsultam (see Section 4.2) and of $Ph_2C{=}NCH_2CO_2R$,[334] base-catalysed deuteriation of the bis-lactim ether chiral auxiliary to give (R)- and (S)- ^2H-labelled α-amino acids[335] and construction of the [^{15}N,$^{13}C_2$]-bis-lactim ether and the corresponding camphorsultam in preparation for the asymmetric synthesis of labelled α-amino acids, e.g. $H_2{}^{15}N{}^{13}CHR{}^{13}CO_2H$.[336] [3-$^2H$]-Labelled phenylalanine stereoisomers have been prepared through deuteriolysis ($^2H_2$/Pd-C) of side-chain brominated phenylalanine derivatives.[337] Catalyzed addition [Pd-C or $RhCl(PPh_3)_3$] of $^2H_2$to dehydroamino acids gives [2,3-$^2H_2$]-labelled α-amino acids,[338] and [1-^{13}C-, 2,3-$^2H_2$]-threo- and erythro-L-α-amino acids have been prepared similarly, involving an enzymic resolution stage. The latter products were used to assist the assignment of ^{13}C-NMR features.[339] L-O-Phosphohomoserine and its two C-3 ^2H-isotopomers have been prepared through standard functional group elaboration of L-aspartic acid and its (2S,3R)- and (2S,3S)-[3-^2H]isotopomers.[340]

Two independent syntheses have been reported of (2S,4S)- and (2S,4R)-[5,5-$^2H_2$]-5,5′-dihydroxyleucine, one from the enaminone (55) from L-pyroglutamic acid [used in a number of previous syntheses of stereospecifically-labelled protein amino acids] through reduction with $NaB(CN)H_3$, and the other involving hydroboronation (disiamylborane) of 4-methyleneproline derivatives.[341] The former route was inefficient though gave the former target, while the latter route was suitable for the latter target. A new synthesis of (2R,3S)-[4-$^2H_3$]valine has been reported.[342] Specific ^3H-labelling of the arene protons of Boc-D-tyrosine in the form of its ethyl ether has been accomplished through iodination – dehalogenation in $^3H_2$[343] (see Ref. 322 for a preparation of tritiated β-aminophosphonic acid).

^{11}C-Labelling continues to stimulate the inventive use of rapid synthetic methods in view of the need to work within the half-life of the isotope (most of the decay occurs in less than one hour). ^{11}C-Labelled alanine has been prepared using $^{11}CH_3I$ for rapid alkylation of N-Boc-3-methyl-4-imidazolidinone (see Section 4.2), and phenylalanine has been prepared in an analogous fashion.[344] $^{11}CH_3I$ has been used for rapid alkylation of L-homocysteine adsorbed on Al_2O_3/KF to give ^{11}C-L-methionine.[345] As an indication of what can be achieved by way of rapid synthesis, this product was ready within 10 minutes after synthesis stages, and including C18-SepPak and alumina SepPak purification. A 40 minute sequence leading to α-[^{11}C]-methyl-L-tryptophan, starting from the enolate of (56), has been described.[346] [2-^{11}C]-α-Aminoisobutyric acid and its N-methyl homologue have been prepared through the Strecker synthesis starting from [^{11}C]-acetone.[347]



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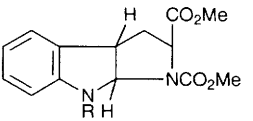

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Alkylation of (S)-N-propanoyl 4-isopropyloxazolidin-2-one and the N-[2-^{13}C]-propanoyl analogue, with $^{13}CH_3I$/NaHMDS and the unlabelled reagent, respectively, gives diastereotopically-^{13}C-labelled L-leucine after routine work-up.[348] The same approach was applied for the synthesis of (2S,4R)-[5,5,5-$^{2}H_3$]leucine.

[2,3-$^{13}C_2$]-4-Hydroxy-L-threonine has been prepared in an 8-step sequence starting from [1,2-$^{13}C_2$]-acetylene, *via* correspondingly labelled 4-benzyloxy-(Z)-but-2-en-1-ol.[349] The relatively much simpler task, synthesis of [2-^{13}C]-labelled amino acids, is exemplified in routes from commercially-available intermediates to [2-^{13}C]-L-lysine (from [2-^{13}C]-glycine through the bis-lactim ether alkylation protocol; see above, and Section 3.2) and to [3,4-$^{13}C_2$]- and [5,6-$^{13}C_2$]-labelled analogues (analogously, from ethyl [1,2-$^{13}C_2$]bromoacetate and [1,2-$^{13}C_2$]acetonitrile, respectively).[350] The same protocol has been used in routes to ^{2}H, ^{13}C- and ^{18}O-labelled L-serine and L-threonine,[351] and to [2′-^{13}C]-, [1′-^{15}N]- and [3′-^{15}N]-L-histidines, though the hard work in these routes was the construction of 1,5-disubstituted imidazoles from labelled toluene-p-sulfonylmethyl isocyanide, 3-phenylpropenal and benzylamine.[352]

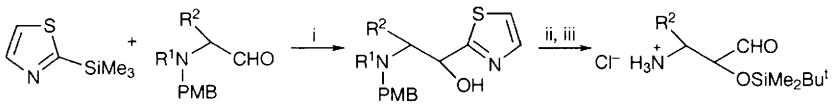
[6-^{14}C]-Vigabatrin, i.e. (RS)-4-aminohex-5-enoic [6-^{14}C]acid, can be obtained through Wittig condensation of 1-(1-butenyl)-2-oxo-5-pyrrolidine carboxaldehyde with methyl[^{14}C] triphenylphosphonium iodide.[353] [U-^{14}C]Glycine has been converted into its N-Z-derivative for use in synthetic operations.[354]

The material in this Section continues to demonstrate the absorption into routine use of asymmetric synthesis methodology employing chiral auxiliaries. The imidazolidinone method has been used for a route to 6-[^{18}F]fluoro-L-DOPA[355] (emphasis is given to the need for care in carrying out the various

stages of this preparation) and the same target has been achieved through the condensation of a chiral methanobenzoxazinone with 3,4-dimethoxy-2-[^{18}F]fluorobenzaldehyde and NaH, followed by L-Selectride-catalyzed hydrogenation.[356]

4.20 Synthesis of β-Amino Acids and Higher Homologous Amino Acids – Reviews of this expanding field cover the general topic of enantioselective synthesis of β-amino acids,[357] and the route involving addition of chiral lithium amides to αβ-unsaturated esters.[358] It is difficult to discern a general falling-into-line behind any particular synthesis method; in this broad area, most of the available methods are being developed successfully.

The Arndt-Eistert homologation of N-alkoxycarbonyl-L-phenylglycine only achieves 9:1-stereoselectivity, while conservation of the initial configuration seems totally assured in the application of this protocol to other L-α-amino acids.[359] This paper also addresses stereoselective α-alkylation of β-amino acids through providing new results. An alternative homologation procedure through the sequence $RCO_2H \rightarrow RCH_2OH \rightarrow RCH_2I \rightarrow RCH_2CN \rightarrow RCH_2CO_2H$ is made somewhat less tedious by the use of polymer-bound triarylphosphine-I_2 complex for one of the steps,[360] and has been employed for the synthesis of several Fmoc, Z and Boc-protected examples.[361] 2-Dibenzylaminobutan-1,4-diol, easily available from L-aspartic acid, is used in the same way, except for the intermediacy of a mesylate in place of the iodide, and has been used for the asymmetric synthesis of representative β-amino acids, including β-proline.[362] Homologation of N-protected α-aminoaldehydes looks more promising as a further use for 2-trimethylsilylthiazole (Scheme 28), giving syn β-aminoalcohols and β-amino-α-



(+25% *syn* -isomer)

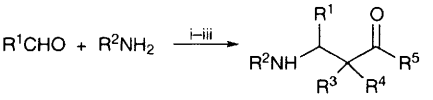
Reagents: i, CH_2Cl_2, –20 °C, then Bu_4NF/THF; ii, Bu^tMe_2SiCl, then CF_3SO_3Me, then $NaBH_4$/MeOH; iii, $HgCl_2$

Scheme 28

hydroxyaldehydes [illustrated for a preparation of (S,S)-3-amino-2-hydroxy-4-phenylbutanol, for use in synthesis of a HIV protease inhibitor] from which β-amino acids may be generated.[363] L-Phenylglycine reacts with the thiazole synthon to lead to the taxol side chain component (2R,3S)-3-phenylisoserine, in the form of its N-benzoyl- and N-Boc-derivatives.[364] Careful study of the chain extension of N-protected α-aminoaldehydes through aldolization with vinyl α-anions derived from acrylic esters has been reported.[365]

The logical deconstructionist view to be taken, in the face of these successful methods, is to bring an aldehyde into touch with an amine together with an

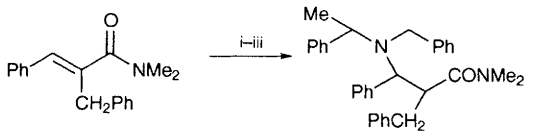
electrophilic synthon that is destined to provide the α-carbon carrying a carboxy group (i.e. a silyl enolate; Scheme 29). In such a way, a one-pot synthesis of β-amino acid esters has emerged after the role for ytterbium(III) triflate as catalyst was established, a method that is also adaptable to β-lactam synthesis.[366] A new, highly regioselective and stereoselective asymmetric oxirane ring-opening brought about with $MgBr_2$ has been established using phenylisoserine as target.[367]



Reagents: i, add $R^3R^4C{=}CR^5OSiMe_3$ after 30 min at room temp.; ii, $Yb(OTf)_3$ 5–10 mol %, CH_2Cl_2; iii, dehydrating agent (molecular sieve 4Å, or $MgSO_4$)

Scheme 29

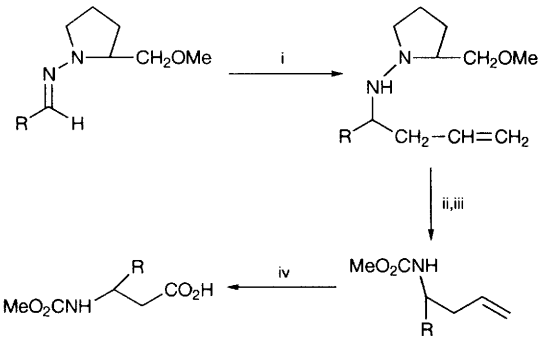
Ytterbium(III) triflate-catalyzed high pressure addition of amines to αβ-unsaturated esters gives moderate to high yields of hindered β-amino esters.[368] Several research groups are extending the general 'asymmetric β-amination of αβ-unsaturated esters or analogues' approach to the synthesis of homochiral β-amino acids in which chiral ammonia equivalents, *viz.* homochiral amidocuprates,[369] the homochiral lithium amides Li (α-S)-(α-methylbenzyl) benzyl allylamide[370,371] and Li α-phenylethylamide,[372] SAMP,[373,374] or TMS-SAMP [(S)-2-methoxymethyl-1-(trimethylsilylamino)pyrrolidine][375,376] are used. Conjugate addition of benzylamine to (S)-5-[(tert-butyl)diphenylsilyloxymethyl]-2(5H)-furanone generated the trans-adduct, a useful synthon for further elaboration by alkylation at C-3 *via* its lithium enolate.[377] High enantioselectivity is achieved in these routes (typical applications are displayed in Schemes 30 and 31), and intermediate enolates can be trapped by quenching with ^2H_2O so as to provide



Reagents: i, (*S*)-[α-Methylbenzyl]benzylamine, ii, $LiNR_2$; iii, H_2–Pd

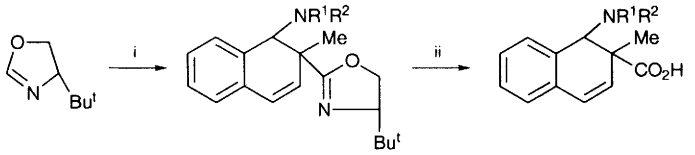
Scheme 30 (ref. 370)

α-^{2}H-β-amino acids (Ref. 369). The use of lithium (α-S)-(α-methylbenzyl)allylamide calls for de-allylation [tris(triphenylphosphine)Rh(I)Cl] to liberate the product (Ref. 371) while the TMS-SAMP procedure ends with N-N cleavage (Ref. 373). The mirror image of this process, carboxylation of enamines, provides an alternative general route, and a veiled form of this has been established in which chiral oxazolines are alkylated (Scheme 32).[378] Another approach to



Reagents: i, Allylcerium chloride, or allyl Grignard reagent; ii, Li/NH_3; iii, MeO_2CCl; iv, O_3

Scheme 31 (Ref.373)



Reagents: i, $LiNR_2$, 2-chloronaphthalene derivative, ii, H_3O^+

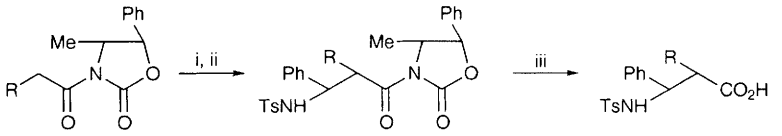
Scheme 32

assembling the components of a target β-amino acid is offered in the Michael-type addition of a carbon radical (alkyl iodide/Bu_3SnH/hν) to α-aminoalkylvinyl esters $ArCH(NHTs)C(=CH_2)CO_2Me$, though syn/anti-ratios are remarkably sensitive to the nature of the o-substituent of the arene moiety.[379]

Michael addition of N-methylhydroxylamine to γ-alkoxy-αβ-unsaturated esters gives β-(N-methyl-N-hydroxyamino) esters.[380]

Synthesis of stereoisomers of 3-amino-2-hydroxydecanoic acid and 3-aminodecanoic acid using the chiral lithium amide strategy, and comparisons of published data for the former β-amino acid (it is the N-terminal amino acid of microginin) with those for the synthesis products, has allowed assignment of the (2S,3R)-configuration to the natural compound.[381] N-Methoxycarbonyl-1-methoxyamines $MeO_2CNHCH(OMe)R$ react with glyoxylic acid derivatives to give syn/anti-mixtures of 3-amino-2-hydroxyalkanoates, appropriate choice of protecting groups allowing control of diastereoselectivity.[382]

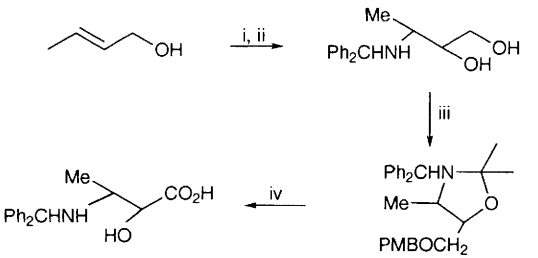
The addition of an α-sulfinyl ester enolate to a benzaldimine carrying an electron-withdrawing group at nitrogen gives a β-amino acid ester in up to 94% e.e., diastereofacial selectivity being widely changeable and determined by the N-



Reagents: i, LDA, −78 °C; ii, PhCH=NTs; iii, H_3O^+

Scheme 33

substituent and additives in the reaction mixture.[383] Lithium and titanium enolates of N-acyloxazolidinones are as useful in β-amino acid synthesis as in their main use in the α-amino acid field, e.g. through addition to imines (Scheme 33). The stereochemical outcome indicates that addition occurs to the *si*-face of the chelated (Z)-enolate.[384] Amidoalkylation of this chiral synthon with 1-(Z-aminomethyl)benzotriazole and routine workup gives (R)-(+)-3-amino-2-phenylpropanoic acid, establishing (by X-ray crystal analysis) the correct absolute configuration for this known compound.[385] Anti-3-amino-2-hydroxybutyrates can be obtained with the aid of the chiral auxiliary anti-$Ph_2CHNHCMe(OH)CH$-MeOH, *via* the oxazolidine derived from it (Scheme 34).[386] Another connection

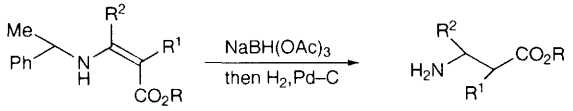


Reagents: i, Bu^tOOH, (D)-DIPT/$Ti(OPr^i)_4$; ii, $Ph_2CHNH_2/Ti(OPr^i)_4$;
iii, PMB-Cl after oxazolidinone formation; iv, H_3O^+ after $CH_2OPMB \rightarrow CO_2H$

Scheme 34

with the α-amino acid field through use of a six-membered analogue of a standard chiral heterocyclic auxiliary (see Section 4.2) is represented in the diastereoselective hydroxylation at C-5, using the camphorsultam-derived oxaziridine, of chiral 6-substituted perhydropyrimidin-4-ones. Enantiomerically pure α-hydroxy-β-amino acids are obtained in this way, illustrated for representative examples,[387] and specifically for preparations of L-isothreonine and D-alloisothreonine[388] and of N-benzoyl-(R,R)-3-phenylisoserine.[389]

Radical cyclization of β-aminoacrylates gives β-proline derivatives.[390] Reduction of homochiral β-enamino esters [N-vinyl (S)-phenylethylamines (57)] using $NaBH(OAc)_3$ gives β-amino acid esters with moderate enantiomeric selectivity.[391]



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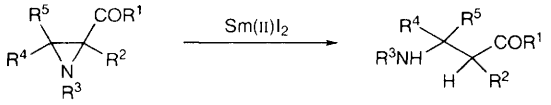
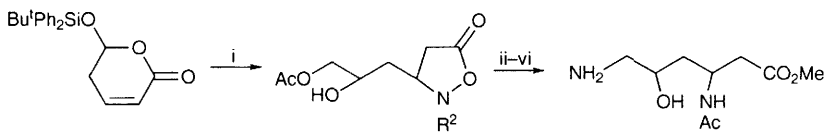


(58)

Small-ring synthons have provided conventional routes to particular targets over the years, and are represented in a synthesis of (2R,3S)-3-phenylisoserine (glycidic ester intermediate),[392] and in oxidative ring-opening of aziridinecarboxylic acids (58).[393] Reductive ring-opening (catalytic hydrogenation) of methyl 3-methyl N-toluene-p-sulfonylaziridine-2-carboxylate gives 3-aminobutanoic acid derivatives, a process that leads to enantiomers when homochiral starting materials (N-α-methylbenzyl and/or non-racemic N-toluene-p-sulfonyl derivatives) are used.[394]

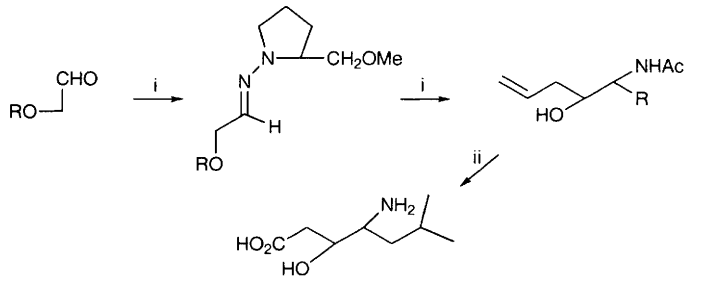
β-Amino acids prepared in other ways include (R)-(+)-β-phenylalanine from (S)-(+)-benzylidene-toluene-p-sulfinimide [S*N=CHPh + CH_2CO_2Me→(S*NH-CHPhCH_2CO_2Me, where S* is the chiral auxiliary],[395] allophenylnorstatine [*alias* (2S,3S)-3-amino-2-hydroxy-4-phenylbutanoic acid] in eight steps from L-phenylalanine,[396] and '(R)-(+)-Boc-iturinic acid-(n-C-14)' [a curious choice of nomenclature, intended to convey the meaning 'the unbranched isomer of iturinic acid', i.e. $Me(CH_2)_{10}CH(NHBoc)CH_2CO_2H$] starting from L-aspartic acid, a key step being organocuprate addition to (S)-BocNHCH(CH_2OTs)CH_2CO_2Bzl.[397] (2S,3R)-3-Amino-2-methylpentanoic acid is conveniently accessible from aspartic acid *via* (3R)-3-N-toluene-p-sulfonylamino-γ-butyrolactone.[398] Further examples of the use of an easily-available amino acid to synthesize a higher homologue are found later in Section 6.3. A synthesis of negamycin lactone *via* the isoxazoline (59 in Scheme 35) starts from D-glucose.[399]



(59)

Reagents: i, R^2NHOH; ii, mesylation; iii, MeOH, K_2CO_3; iv Bu_4NF, repeat ii; v, NaN_3/DMF; vi, H_2, 10% Pd–C

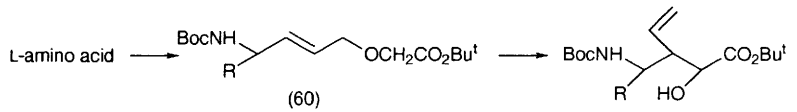
Scheme 35



Reagents: i, SAMP protocol (Scheme 31); ii, O_3

Scheme 36

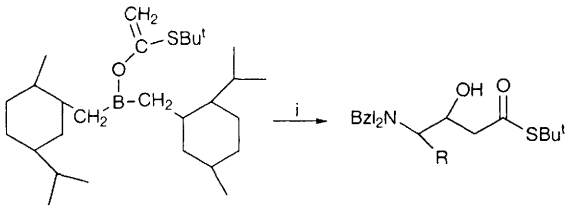
Several important individual examples of free and peptide-bound γ-amino acids provide valid synthetic targets in their own right, irrespective of the general need for reliable synthetic methodology to prepare γ-amino acids to support the burgeoning peptide mimetic field. Some of the current methods are extensions of routes used with lower homologues, such as amination by TMS-SAMP illustrated in an (R,R)-statine synthesis (Scheme 36),[400] and Arndt-Eistert homologation of L-malic acid-derived (S)-N-Boc-2-oxo-oxazolidine-5-carboxylic acid to give (R)-α-hydroxy-γ-aminobutyric acid [(R)-GABOB].[401] Stereoselective Wittig rearrangement of tert-butyl 4-aminoallyloxyacetates (60 in Scheme 37; prepared from L-α-amino acids) leads to α-hydroxy-γ-amino acid esters.[402] Bromination of



Scheme 37

enamines gives an iminium salt [$R_2NCH{=}CR^1R^2 \rightarrow R_2N^+{=}CHCR^1R^2Br$] from which 'αβ-unsaturated GABAs' are obtained by quenching with lithium tert-butyl acetate (see also Ref. 395).[403] Novel lipophilic γ-amino acids (2-amino-methylcyclopropanecarboxylic acids and tricyclic analogues) have been prepared through rhodium(II)-catalyzed cyclopropanation of corresponding alkenes with α-diazoesters N_2CPhCO_2Me and $N_2C(CF_3)CO_2Et$.[404] The formation of azetidin-3-ones from L-α-amino acids *via* corresponding diazoketones has been explored further; reduction of the azetidin-3-ones with complex hydrides or addition of an organometallic reagent leads to γ-amino acids.[405]

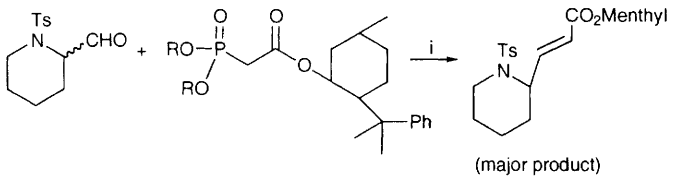
Osmylation of γ-Boc-aminocrotonates has been carried out, routine work-up leading to α-hydroxystatine.[406] N-Aminoacylpyrazoles undergo Reformatzky reaction with β-bromoesters to yield δ-aminated β-ketoesters, from which 4-



Reagents: i, $Bzl_2NCHRCHO$

Scheme 38

(protected amino)-3-oxoalkanoates can be obtained as statine precursors.[407] Stereocontrolled (3S,4S)-statine synthesis from (+)-menthone-derived boron enolates and α-NN-dibenzylamino-aldehydes (Scheme 38)[408] is a notable example of the scope of the aldol family of reactions. DL-α-N-Toluene-p-sulfonylamino aldehydes undergo kinetic dynamic resolution through olefination with a chiral phosphonate in the presence of a slight excess of base (Scheme 39).[409] Much of the interest in an (R)-carnitine synthesis lies in the quinidine-mediated [2 + 2]cycloaddition of keten to chloral that leads to the synthesis intermediate (R)-4-(trichloromethyl)oxetan-2-one.[410]



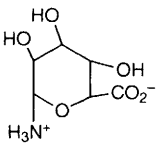
Reagents: i, Slight excess KHMDS

Scheme 39

δ-Amino acids of current interest include baclofen [enantiomers of 4-amino-2-(4-chlorophenyl)butyric acid], accessible from N-toluene-p-sulfonyl-2-(4-chlorophenyl)aziridine *via* ring opening with allylmagnesium bromide and oxidative modification of the allyl group of the resulting pyrrolidin-2-one,[411] also formed from RuO_4 oxidation of dehydroproline formed from trans-4-hydroxy-L-proline,[412] and in enantiomerically pure form through chymotrypsin-catalyzed hydrolysis of dimethyl 3-(4-chlorophenyl)glutarate or through lipase-catalyzed esterification of 2-(4-chlorophenyl)propan-1,3-diol.[413] '(E)-Olefine dipeptide isosteres', i.e. dipeptide mimetics in which the amide grouping is replaced by the (E)-ethene moiety, are also classifiable as αβ-unsaturated δ-amino acids, and a route

(61) (62)

has been established (61→62) involving allylic nitration (NO_2BF_4) of (E)-crotylsilanes followed by reduction.[414] The Overman acetimidate rearrangement route (cf. Scheme 1) is an efficient entry to these αβ-unsaturated δ-amino acids, and has been applied to β-hydroxy γδ-unsaturated acids.[415] Homochiral 4-(α-hydroxyalkyl)-3-(phenyldimethylsilyl)-γ-lactones, which are readily available through stereocontrolled routes, are suitable precursors of αβ-unsaturated δ-amino acids through displacement by azide and ring-opening accompanying desilylation.[416] Hydroxyethylene dipeptide isosteres, i.e. δ-amino-γ-hydroxy acids, have been prepared from α-aminoalkyloxiranes by conversion into homoallylic alcohols $BocNHCHR^1CH(OZ)CH_2CR^2{=}CH_2$ followed by routine elaboration,[417] and from γ-(α-aminoalkyl)lactones prepared from L-glutamic acid.[418] Alkenylaziridines may be prepared by chain extension of β-hydroxy-α-amino acids or from allylic alcohols, and converted into αβ-unsaturated δ-amino acids.[419] The α-carboxy group of L-glutamic acid can, likewise, be extended [after reduction of N-(2,4-dimethoxybenzyl)-L-pyroglutamic acid to the aldehyde] to give 4-amino-5-hexynoic acid.[420] The tetrahydropyran-based amino acids (63) and furan analogues can be viewed, like many other cyclic compounds carrying



(63)

amino and carboxy functions, as conformationally constrained ω-amino acids, and this has attracted interest in their synthesis involving the application of standard operations (azidolysis of sugar-derived epoxides as the crucial step).[421] (S)-5-Aminopiperidin-2-one, which can be categorized as the lactam of either a γ- or a δ-amino acid, has been prepared in enantiomerically pure form from L-pyroglutaminol through ring-opening with methyl carbamate, and amination of the remaining primary hydroxy group through the Mitsunobu method (Ph_3P/diethyl azodicarboxylate).[422]

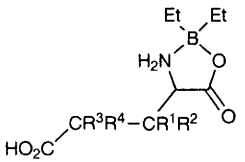
Beckmann rearrangement of alicylic ketones to ω-amino acid salts and then to lactams during workup has a long history, and simple modifications manage to convince Referees of their need for urgent publication (e.g. microwave irradiation of SiO_2-adsorbed reactants, cyclopentanone to cyclododecanone and hydroxylamine-O-sulfonic acid).[423]

4.21 Resolution of DL-Amino Acids – An expanding number of methods for the resolution of DL-amino acids seems to be entering the 'classical' category, due to

the development of new methods over recent years leading to reliable protocols. One of the two archetypal classical non-enzymic resolution protocols, *viz.* formation of diastereoisomeric salts and their separation through crystallization or other physical principles, is regularly represented in this Chapter; this year for DL-amino acids and (-)-1-phenylethanesulfonic acid;[424] for the benzyl ether of (R)-(-)-2-aminobutan-1-ol and the (S)-(+)-enantiomer with N-acyl-DL-phenylglycines and (p-hydroxyphenyl)glycines;[425] and for N-protected α-alkoxyglycines with alkaloids[426] (see also Ref. 295).

When the resolving agent is structurally similar to the enantiomers to be separated, more efficient resolution is achieved because quasi-racemic diastereoisomeric salts are then formed between components of opposite configuration.[427] This is of course, the basis of the long-running preferential co-crystallization method (e.g. D-threonine crystallizes from solutions of its racemate containing L-serine or 4-hydroxy-L-proline[428]), and has also been intuitively felt, and passed on, through generations of organic chemists. However, it is satisfying that the proposal is generally borne out by the results of twelve typical laboratory resolutions, including several common amino acids and their derivatives (described in Ref. 428).

The other archetypal protocol amounts to the conversion of a DL-amino acid into a diastereoisomeric derivative and exploitation of the physical differences between the diastereoisomers; an unusual example is the formation of diastereoisomeric α-boroxazolidinones (64; see also Section 5.1) for the resolution of



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variously α- and β-substituted DL-glutamic acids.[429] The preparation of (R) and (S)-2-(aminomethyl)alanine and 2-(aminomethyl)leucine through reaction of oxazolones of the DL-forms of these amino acids with L-phenylalanine cyclohexylamide also falls within this category (see also Refs.82, 155, 191).[430] Esterification of an N-acyl-DL-amino acid with (+)- or (-)-menthol is also typical (Ref. 426). N-(D- or L-tetrahydro-2-furoyl)ation of DL-amino acid esters gives diastereoisomers that show a difference in boiling points of up to 7°.[431] An inert liquid whose density lies between the densities of a racemate and that of a constituent enantiomer will achieve a separation of the two forms, and L-phenylalanine has been floated off from a mixture with its more dense racemate.[432] This is equivalent to the foam flotation method already described in the recent literature (Vol 27, p. 45).

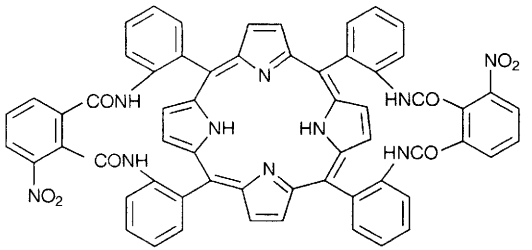
Kinetic resolution of aldehydes, by an asymmetric Wittig-type reaction with chiral 2-phosphonopropionates, has been illustrated for N-toluene-p-sulfonylpipecolic aldehyde.[433]

Enzymes that are shown to be useful in this context are increasing in number and in their diversity. Current standard procedures that represent the culmination of classical methodology for the simplest functional group conversions, illustrated in the use of proteases and lipases for the conversion of DL-amino acid esters into an L-amino acid amide + D-amino acid ester mixture with moderate to high enantioselectivity[434] (D-phenylglycine methyl ester racemizes slowly under these reaction conditions, but enantioselective penicillin G acylase-catalyzed L-mandelylation of DL-phenylglycine and its p-hydroxy analogue seems secure).[435] The use of penicillin G acylase for enantioselective hydrolysis (greater than 95% e.e.) of N-phenylacetyl β-aryl-β-amino acids [(R)-enantiomers are hydrolysed more rapidly][436] is one of several examples of the use of acylases [including also the use of acylase I for the enantioselective hydrolysis of N-acetyl-DL-vinylglycine[437] and the use of aminoacylase for enantioselective acetylation of DL-methionine[438] (see also Refs. 66, 286, 293)]. The use of subtilisin for enantioselective hydrolysis of DL-ββ-difluoro-α-amino acid methyl esters;[439] the use of lipase for enantioselective transesterification of DL-phenylalanine methyl ester with octan-1-ol;[440] and the use of papain for enantioselectively-catalyzed esterification of DL-acids (Ref. 270) illustrate another common approach. A novel procedure is represented in enantioselective alcalase-catalyzed hydrolysis applied to an amino acid ester, parallel with pyridoxal-5-phosphate-catalyzed racemization of the unhydrolysed antipode.[441]

More surprising successes have accrued, for the resolution of representative well-known amino acid pharmaceuticals (aromatic α-methyl-α-amino acids and α-methyl-α-hydrazino acids, using *Candida lipolytica* for ester hydrolysis),[442] and similar results have been secured for αα-disubstituted glycine esters (using *Humicola langinosa*);[443] while the selective hydrolysis of DL-hydantoins so as to liberate D-amino acids (using thermophilic micro-organisms,[444] *Arthrobacter* sp.DSM7330[445] and *Agrobacterium* sp.I-671[446]) represents a more thoroughly-established area. A route to L-tert-leucine from DL-2-phenyl-4-tert-butyloxazolin-5-(4H)-one employs lipozyme present in *Mucor miehei* as catalyst for transesterification with n-butanol, and *Bacillus licheniformis* alcalase for clean hydrolysis, in a new example of the long-established oxazolinone dynamic resolution route.[447]

Destructive 'resolution' procedures, in which the total initial amount of racemate is not returned as separated isomers, are represented by the action of yeast D-amino acid oxidase on a molasses fraction, converting D-α-amino acids into α-keto-acids, to leave L-enantiomers unaffected.[448] An interesting extension of this approach employs genetically-engineered *E.coli* TM93 for the production of D-glutamic acid from its L-enantiomer, involving two successive stages imposed by a glutamate racemase (L→DL) and then enantioselective decarboxylation.[449]

Separations of enantiomers based on chiral recognition principles are represented in a number of papers describing homogeneous solution methods: diastereoselective partition between water and chloroform, of host-guest complexes of phosphorus hexafluorophosphate salts of DL-amino acid esters with poly(1-6)-2,5-anhydro-3,4-di-O-alkyl-D-glucitol,[450] and similar host-guest studies



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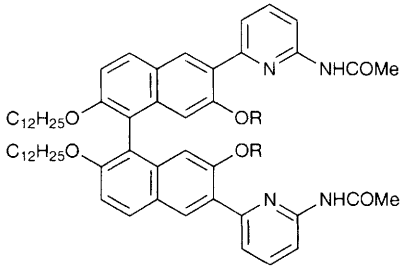

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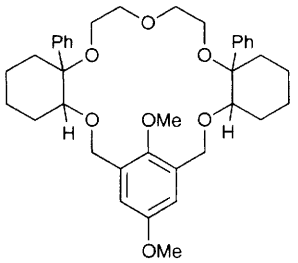

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with an αααα-atropisomer of (65) formed beween meso-tetrakis(o-aminophenyl)-porphyrin and 4-nitroisophthaloyl chloride,[451] and involving Z-aspartic acid, Z-glutamic acid, or Z-kainic acid complexed in C^2HCl_3 with (R)- and (S)-binaphthyls (66);[452] and a FAB-MS evaluation of the host-guest behaviour of the homochiral crown ether (67)[453] (see also Ref. 532). A related NMR study of eleven 1,2-bis(D-hexopyranoside and D-mannitol-derived)-18-crown-6-ethers, showing enantioselection of salts of phenylglycine enantiomers in C^2HCl_3, has been published.[454] Resolution of dinitrobenzoyl-DL-amino acids on a gram scale, by high-speed counter current chromatography using N-decanoyl-L-proline-3,5-dimethylanilide as chiral selector, is a variation of standard chromatographic principles in this area (analogous analytical-scale resolutions are covered in Section 7),[455] and chromatography over poly(acrylate)s imprinted by Boc-L-phenylalanine offers efficient chiral separation of amino acid derivatives[456] (see also Refs. 866, 867). Novel chiral stationary phases (CSPs) have been prepared involving L-phenylalanine or D-phenylglycine residues separated by long spacer units.[457]

Analogous membrane separation studies include ultrafiltration resolution of phenylalanine, tyrosine and tryptophan, employing cellulose acetate derivatized with (-)-menthol;[458] and copper(II)-mediated transport of α-amino acids across a bulk chloroform membrane into aqueous EDTA, by chiral 1,2-diaminoethane derivatives[459] (see also Section 5.4).

Clefts that bind histidine esters tightly are a feature of a homochiral bis(porphyrin) that is structurally a Troger's base analogue, resulting in chiral discrimination between histidine ester enantiomers amounting to 80 – 86% e.e.; only 48% e.e. is achieved with lysine benzyl ester.[460] α-Zirconium phosphate, intercalated by a cationic chiral π-acceptor, selectively binds one enantiomer of 2-naphthyl-DL-alanine methyl ester from solutions.[461]

Speculation about the prebiotic origin of molecular chirality continues to revolve around the effects of the contemporary physical environment on racemic mixtures. 'Symmetry breaking' is the favoured term to refer to the genesis of L-amino acids and D-sugars starting from racemates; lack of rigorous experimental proof for proposed mechanisms[462] is a notable feature of the literature on this topic over many years. The current theme revolving around the parity violation (PV) phenomenon for electroweak interactions,[463] which can be calculated[464] to favour the current scene, has been claimed by Salam (see Vol 24, p. 40) to require that a phase transition will exist at low temperatures that should lead to enantiomeric purity over vast stretches of time. The theory implies that experimental proof will be easier to obtain for the phase transition hypothesis (compared with the difficulty of establishing very small differences in D:L-ratios starting from pure racemates submitted to aggressive radiation treatment), but the vanishingly small energy differences between each enantiomer of a racemate, that PV leads to, may explain why no enantiomeric imbalance could be detected for samples of DL-cystine derivatives held at 0.01K.[465] On the other hand, a specific heat discontinuity found for a single crystal of D-valine held at 272K is not shown by L-valine, and the fact that there is no crystal structure transition for these samples over the temperature range 123 – 293K, is taken to support the conclusion[466] that evidence to support Salam's prediction has become available from this work. Clearly, the failure to try to develop other explanations will cause this conclusion to be queried.

A long-standing critic of the PV hypothesis has continued to maintain that the genesis of molecular chirality in the prebiotic environment must have required the influence of an extra-terrestrial energy source.[467] The proposal, that circularly-polarized UV synchrotron radiation from the neutron star remnants of supernovae caused the enantioselective photolysis of interstellar dust, is based on verified science in all aspects except for decisive laboratory proof of the enantioselective photolysis of amino acid racemates. Some amplification mechanism is required to accompany preferential destruction by radiation of one enantiomer, if a slight chiral excess is to be amplified over time with the extinction of this enantiomer; an amplification mechanism is also needed by other D:L-unbalancing protocols based on the PV hypothesis.[468]

5 Physico-Chemical Studies of Amino Acids

5.1 X-Ray Crystal Analysis of Amino Acids and Their Derivatives – The considerable extent of this topic will be familiar to readers over the years, the sheer volume being partly due to the continual revisiting of particular free amino

acids. Structures for protein amino acids determined recently include DL-proline monohydrate,[469] DL-alanine nitrate,[470] DL-aspartic acid nitrate monohydrate,[471] L-(+)-histidine acetate dihydrate,[472] L-histidine dihydrochloride,[473] anhydrous DL-glutamic acid,[474] DL- and L-lysine formate,[475] ^{1}H and ^{2}H-labelled L-arginine phosphate monohydrate (neutron diffraction),[476] L- and DL-histidine – formic acid complexes[477] and hydrated L-serine – inosine-5′-monophosphate 1:2-complexes.[478] Some of these papers emphasise the hydrogen-bonding features that are revealed, in direct fashion by neutron diffraction, and an unusual version of this approach is used to determine the structure of the hydration sphere surrounding glycine molecules in concentrated (5 mol %) aqueous solution.[479] The overall picture for details of participation of C-H bonds in hydrogen-bonding to oxygen atoms, in a range of molecules including amino acids, has been discussed.[480] Inelastic incoherent neutron scattering of samples of DL- and L-valine,[481] and coherent inelastic neutron scattering features for solid L-alanine,[482] have been assessed. The X-ray structure of the L-proline – 2,5-dihydrobenzoic acid complex provides a rare example of a hydrogen-bonded zwitterion co-crystal, and its non-linear optical properties may be useful in the construction of microelectronic devices (these properties are also shown by other homochiral solids).[483] Re-determination of the structure of DL-norleucine, and observation of changes that occur during heating,[484] of the structure of L-DOPA (for comparison with molecular orbital calculations providing electron distribution),[485] and newly-determined structures for DL-prop-2-ynylglycine,[486] L-nitroarginine monohydrochloride monohydrate,[487] 3-iodo-L-tyrosine methanol solvate[488] and (Z)-β-fluoromethylene-m-tyrosine[489] (see also Refs. 272, 281) cover examples of near relatives of the protein amino acids.

Amino acid derivatives subjected to X-ray crystal analysis include N-benzyloxycarbonylglycine,[490] benzoyl-L-histidine monohydrate,[491] N-[(2R)-bromopropanoyl]-(2S)-proline methyl ester,[492] N-carbamoyl-DL-aspartic acid,[493] NN′-carbonyl bis(L-phenylalanine ethyl ester),[494] N-phthaloyl (E)-α,β-dehydrophenylalanine,[495] the alanine-derived boroxazolidinone (64; Ph in place of Et; Me in place of $CR^1R^2CR^3R^4CO_2H$),[496] (S)-α-ethylphenylalanine N-carboxyanhydride,[497] trans-3-hydroxy-N-methyl-L-proline hydrochloride,[498] methyl N-phenyl-L-tyrosinate,[499] and Boc-N$^\tau$-benzyl-histidine p-nitrobenzyl ester.[500]

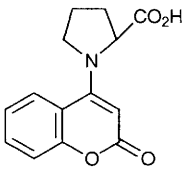
The structure of an unusual condensation product, 1-cyclohexyl-2-cyclohexylaminoimidazol-5(4H)-one, from glycine ethyl ester and dicyclohexylcarbodiimide, has been confirmed by X-ray crystal analysis.[501]

5.2 Nuclear Magnetic Resonance Spectroscopy – Out-of-the-ordinary NMR studies involving amino acids and their derivatives is a rough description of papers selected for this Section, and the term 'out-of-the-ordinary' has been interpreted over the years in this Specialist Periodical Report to cover work with newly-introduced NMR instrumental techniques, and routine techniques applied to structural analysis of unusual substrates.

Solid state ^{1}H-NMR data, from which information of proton relaxation and molecular motion in solid amino acids is available, have been presented.[502] Magic angle spinning HQMC and TOCSY ^{13}C-NMR assessment of N$^\alpha$-Fmoc-N$^\varepsilon$-Boc-

L-lysine bonded to solvent-swollen Wang resin, has shown that on-resin monitoring may be achieved during solid-phase peptide and combinatorial synthesis.[503] Rotational-echo double resonance NMR evidence may be interpreted to indicate an extended conformation for [1-^{13}C,^{15}N]acetyl-L-carnitine in the solid state, which contrasts with the folded conformation revealed by X-ray analysis.[504] More routine conformational studies have involved ^{1}H-NMR measurements for solutions of amino acids and nucleotides in $^{2}H_2O$, purporting to derive association constants by fitting changes in chemical shifts for anomeric and ring protons to an isotherm;[505] the strongest associations occurred between coded amino acids and their respective anticodonic nucleotide sequences, a self-fulfilling outcome that does not in itself verify the somewhat tenuous thermodynamic basis of the study. A study of interactions of amino acids with nucleic acids and caffeine calls on a range of techniques.[506] More narrowly-based studies cover Z-N-methylisoleucine derivatives,[507] N-substituted αω-diamino acids[508] and 1-aminocyclopentane-1,3-dicarboxylic acid derivatives (whose importance lies in their potential as glutamic acid analogues).[509] As is often the case with such objectives, X-ray analytical support was obtained for these last-mentioned derivatives. Tautomeric equilibria established by NMR for simple aliphatic NN-dimethylamino acids in $(C^{2}H_3)_2SO$ reveals the predominance of the unionised form.[510]

Continuing themes are represented in photo-CIDNP studies of N-acetyl histidine, tryptophan and tyrosine,[511] and for ^{1}H-NMR assignment of enantiomeric purity to α-amino acids, for which purpose N-coumarinyl-L-proline (68) has been proposed as a new chiral derivatization reagent.[512] Diastereoisomers formed between a racemic chiral acid and (R)- or (S)-phenylglycine methyl ester show sufficiently large differences for chemical shifts for particular protons, to allow assignment of absolute configuration.[513] New chiral NN′-disuccinate ligands (69) formed from (5R)- or (5S)-(menthyloxy)furan-2(5H)-one have been used as complexes with Eu salts to create effective chiral shift reagents for the estimation of D:L-ratios for amino acids.[514]



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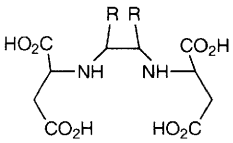

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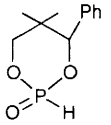

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NMR techniques that deal with higher mass isotopes are featured in an X-ray/^{13}C-MNR study of N-acylated 3-methylaziridine-2-carboxylate esters, showing a 40° tilt in the plane of the amide carbonyl group with respect to the plane of the ring,[515] pH-dependence of the ^{15}N-NMR features of histidine,[516] a study involving ^{1}H-^{15}N-heteronuclear multiple quantum coherence (HMQC) transfer NMR at 200 MHz focussing on the generation of [5-^{15}N]-glutamine after *in vivo* perfusion of $^{15}NH_4^+$into rat brain,[517] ^{19}F-NMR studies of interactions

within complexes of hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin with (RS)-fluorinated amino acid derivatives[518] and an evaluation of ^{13}C- and ^{29}Si-NMR data of trimethylsilyl derivatives of 25 amino acids[519] and analogous TBDMS-amino acids.[520] ^{31}P-NMR has been advocated for providing well-separated signals for diastereoisomers formed from amino acids with the novel chiral derivatization reagent (70).[521]

5.3 Optical Rotatory Dispersion and Circular Dichroism – Further data confirming the anomalous optical rotation behaviour of N^{α}-acyl-L-lysines in water over a wide range of pH (see Vol 27, p.49) have been published.[522] The circular dichroism (CD) characteristics over the wavelength range 200-600 nm, of solutions containing Cu(II) and Ni(II) – L-DOPA complexes can be interpreted to reveal individual stages in the oxidation of the arene chromophore.[523] Among routine assignments of absolute configuration in the recent literature (see also Ref. 272), the interpretation (Ref. 37) of the CD feature at 207 nm indicating the (S)-configuration for cis-2-amino-5-chloropent-4-enoic acid, may be found to be undermined by the mutual influence of the two chromophores absorbing in this wavelength region.

5.4 Mass Spectrometry – The pioneering character assigned to studies of a range of ionization techniques only a few years ago, has been transfigured as they enter into routine laboratory use. FAB and electrospray methods are the most prominent of these newer methods, the former category being represented in a study of phosphoryl derivatives (of 20 common amino acids), in which positive ion analysis is found to be most appropriate for derivatives of the basic amino acids, while negative ion analysis is suitable for the derivatives of the neutral and acidic amino acids, because intense parent ions are produced.[524] Metastable ion fragmentation of cations formed from twelve different copper(I)-amino acids,[525] and a study of molecular radical cations formed from N-toluene-p-sulfonyl-N-alkylamino acid esters embedded in various matrices, have been reported.[526] More fundamental ion-molecule bombardment studies deal with gas-phase protonation of glycine by CH_5^+,[527] and corresponding work with amino acid dimers has been described.[528] Spectra obtained by seeding tryptophan into argon undergoing pulsed supersonic expansion can be linked to particular lowest energy conformations of the amino acid; a straightforward study[529] and a sophisticated version of this approach (IR-laser desorption of tryptophan, and its multiphoton ionization in the gas phase[530]) provide an excellent indication of the application of state-of-the-art MS techniques to fundamental studies of molecules.

Electrospray mass spectrometry of free amino acids can yield isotope ratios for component elements in leucine, arginine and proline, with a standard deviation around 0.1%.[531] This figure was assigned from experiments which yielded accurate diagnostic evidence when amino acid mixtures were spiked with 0.85 mol% of a singly-^{13}C-labelled isotopomer. Further exploitation of the mild nature of electrospray ionization has been reported, leading to spectra for host-guest complexes of amino acids and cyclodextrins.[532]

Other variations of techniques are seen in electron-capture negative ion MS of pentafluorobenzyloxycarbonylamino acids (prominent $[M-181]^-$ ion for the derivatized phenylalanine ethyl ester)[533] and CTC/MS of TBDMS [$^2H_5$]-phenylalanine.[534]

Establishment of absolute configuration for amino acids employing HPLC and mass spectrometry has been addressed, with a modified Marfey derivatization protocol proving useful (with a new reagent, 1-fluoro-2,4-dinitrophenyl-5-L-leucinamide).[535]

5.5 Other Spectroscopic Studies of Amino Acids – Most of the work consigned to this Section deals with frontier-pushing IR/Raman and ESR studies of amino acids and their derivatives. There are other areas of spectroscopic applications, not covered here or in the preceding Sections 5.1-5.4, that have a subsidiary role in analytical applications, and are mentioned later, particularly in parts of Section 7.

Considerable effort has been expended on interpreting IR/Raman data for L-asparagine, employing strategically-labelled substrates (as is typical in such solid-state studies);[536] the straightforwardly-synthesized isotopomer $^2H_3N^+CH(CO_2^-)CH_2CH_2CON^2H_2$, was used in this particular study. Raman-spectroscopic features have been assigned to different conformations of tryptophan through studies including the [2,4,5,6,7-$^2H_5$]isotopomer,[537] and Stark effect fluorescence spectra of this amino acid have been determined.[538] Photoacoustic spectra have been measured for tryptophan.[539]

Structural features of radicals generated in oxidized samples of phenylalanine, tyrosine, histidine and tryptophan have been assigned through combined FTIR and ESR study.[540] The ESR technique continues to provide decisive information concerning the site of high-energy radiation attack on solid samples of simple aliphatic amino acid derivatives, and on the fate of radicals that are generated in this way. Two radicals have been identified by ESR in samples of N-acetyl-DL-alanine subjected to vacuum UV synchrotron radiation, one being the decarboxylated substrate.[541] Similar studies of a range of solid amino acids subjected to pulse radiolysis have been reported.[542] Aromatic side-chains offer the prime site for radical generation through milder radiative treatment, and hydrogen hyperfine interactions have been determined for the tyrosyl radical through ^2H-electron spin echo envelope modulation spectroscopy.[543] ESR spin-stabilization evidence has been acquired pointing to the formation of o-quinones when DOPA methyl ester and α-methylDOPA undergo peroxide oxidation.[544]

Reference has been made in the mass spectrometry section (Ref. 529), to seeding samples into an inert gas undergoing pulsed supersonic expansion, and the fact that data obtained for the gas-phase amino acid can be linked to its lowest energy conformation. In the context of absorption spectra, this approach allows the determination of spectral features that show vibrational, and even rotational, fine structure,[545] and features of detailed rotational spectra obtained in this way for the $^2H_2$, ^{13}C, ^{15}N-isotopomer have been linked to conformers 1 and 2 of glycine, and to conformer 2 for the N,O-$^2H_3$ isotopomer.[546] The electron density distribution in the highest-occupied molecular orbital of the most stable

conformation of glycine has been determined by multichannel electron momentum spectroscopy.[547]

5.6 Physico-Chemical Studies of Amino Acids – Data measured using standard equipment from within the physical chemistry laboratory continue to accumulate, and enlightenment accrues from some of these studies, on the matter of the behaviour of amino acids in solutions. Thus, calorimetric, densimetric and nuclear relaxation time measurements at 25°C for binary and ternary aqueous solutions of amino acids carrying functional groups in side-chains (racemates and enantiomers of lysine, asparagine, glutamine, serine and homoserine) reveal very high differences, compared with simple aliphatic amino acids that lack side-chain functional groups, between homochiral and heterochiral pairwise enthalpic interaction coefficients.[548] In other words, the chiral recognition shown by a homochiral amino acid towards its enantiomer is strongly enhanced by certain functional groups in side-chains. In the same context, calorimetric data have been used to assess the energies of interaction of amino acids (L-phenylalanine, L-tyrosine, L-tryptophan and L-histidine) with α- and β-cyclodextrins.[549] Side-chain transfer free energy values between amino acids and osmolytes (sucrose and sarcosine) have been computed from measurements for binary mixtures as a function of osmolyte concentration,[550] and enthalpies of interaction of glycine with constituents of aqueous solutions containing DMF, formamide and various ureas have been determined.[551] Various thermodynamic characteristics of common amino acids emerge from interpretations of temperature dependence of partial molar volume and adiabatic compressibility data for dilute aqueous solutions[552] and densimetric and heat capacity measurements for aqueous L-asparagine and L-glutamine, and their dipeptides.[553] Details of the thermodynamics of α-chymotrypsin-catalyzed hydrolysis of ethyl N-acetyl-L-phenylalaninate in water and in organic solvents have been described.[554]

Equilibrium constants for the amino acid – hydroxy acid hydrolysis – aminolysis system have been considered in the wider context of the process.[555]

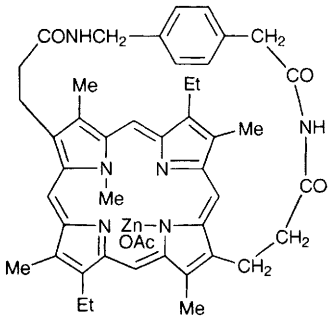
Protonation constants measured for threonine and methionine in aqueous NaCl provide new data that extend the already voluminous literature on this general topic.[556] A down-to-earth exposition[557] shows that three acid-base dissociation constants are needed to calculate the fraction of glycine that is non-ionic in aqueous solutions at the isoelectric point. The effect of micelles on the ionization kinetics of arginine and aspartic acid has been assessed with aid of ultrasonic absorption measurements.[558] Protonation constants of amino acids in salt solutions of various ionic strengths and at various temperatures have been determined.[559]

Hydrophobic parameters and colloidal properties of solutions of N-acylamino acids and their salts have been calculated and compared with data from HPLC,[560] and attention has been given to the means by which the hydrophobicity index for amino acids should be derived.[561] This index is commonly taken to be the value for a particular amino acid, of log $P_{O/W}$(where $P_{O/W}$ is the partition coefficient of derivatized amino acids between water and octan-1-ol), but it has been suggested that retention data for amino acid – o-phthaldialdehyde/N-acetyl-

L-cysteine condensation products (see Section 7.4), as derived by liquid chromatography using micellar eluents, would be a better index (Ref. 561). Four different hydrophobicity scales that have been advocated, based on HPLC data, have been critically assessed.[562] α-Cetylpyridinium bromide has a negligible effect on the hydrophobicity of amino acids in aqueous media, as judged by charge-transfer thin-layer chromatography (the amino acids most affected are alanine, methionine, tryptophan and tyrosine).[563] The large hydrophobicity of phenylalanine is emphasised by its rate-diminishing effect on the hydrolysis of N-acyltriazoles in aqueous media, bearing in mind the rate-enhancing effect of other common amino acids.[564] This general area, the effects of amino acids on other processes, has a literature of its own that can only be hinted at here (e.g. aqueous L-alanine adsorbed from aqueous media on to silica-supported nickel creates a catalyst that brings about asymmetric hydrogenation of methyl acetoacetate[565]). Freezing-point data for aqueous solutions have been interpreted to reveal details of control of local water-structuring by structural features in individual amino acids.[566]

Partition of tryptophan derivatives between sodium dodecanesulfonate micelles and aqueous phases can be assessed easily by UV absorption and fluorescence measurements (fluorescence quenching by succinimide has been noted),[567] and kinetics of mass transfer of tryptophan, partitioned between aqueous solutions and water-in-oil emulsions, have been measured.[568] Partition coefficients have been determined, of amino acids within poly(ethyleneglycol) – aqueous salt solution two-phase systems.[569] Extraction of amino acids from water into CH_2Cl_2 can be achieved through complexation with crown ether – N-methoxy-2,4,6-trinitroanilinium salts,[570] and into $CHCl_3$ by cryptand-2,2,2 analogues.[571] Macrocyclic pseudo-peptides carrying N,N′-ethylene-bridged dipeptide units have been found to show specific transport properties towards salts of amino acid esters across $CHCl_3$ and CH_2Cl_2 – water membranes.[572] New calix[4]arenes carrying carboxymethyl groups have been rendered chiral through coupling to L-phenylalanine, L-phenylglycine or L-tryptophan, and then show chiral recognition towards amino acid esters and Z-amino acids.[573] An optically-pure C_2-symmetric macrobicycle featuring an amidopyridine as a carboxylic acid binding site, and amide functions to provide further hydrogen bonding interactions, is an effective host for binding N-protected amino acids, showing modest chiral differentiation.[574] Highly enantioselective binding of N-Z-, Boc-, 3,5-dinitrobenzoyl- and acetylamino acids is seen for the chiral Zn – porphyrin (71),[575] in which the metal ion binds the carboxylate anion, and the amide groups contribute hydrogen-bonding. Study of the transfer of chiral lanthanide complexes of zwitterionic amino acids from neutral aqueous solutions into CH_2Cl_2 has been described.[576]

Adsorption equilibria involving amino acids have featured in studies of synthetic carbon adsorbents,[577] crosslinked chitosan fibres[578] and talc (which is capable of adsorbing amino acid esters, but not free amino acids).[579] Amino acids are only weakly adsorbed on to silica,[580] but clay to which modified metal complexes are adsorbed is capable of chirality recognition when presented with amino acid derivatives.[581] Blood cell membranes carry about 8% of the total amino acids present in blood.[582] Shifts in membrane potentials measured for



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immobilized γ-globulin membranes accompany the introduction of amino acid solutions into the experimental cell; each amino acid generates a characteristic potential response curve, and a further indication of the possible exploitation of this phenomenon is the finding that potential response curves for the enantiomers of aspartic acid show significant differences.[583]

Sorption and diffusion of DL-tryptophan, DL-phenylalanine and DL-DOPA into divinylbenzene – poly(styrene) resins,[584] and similar non-exchange sorption of amino acids by a weak acid cation exchange resin,[585] have been studied. Ion exchange equilibria involving amino acids have been reviewed,[586] and new work under this heading involves DL-lysine hydrochloride with the ion exchange resin Amberlite IRA-420,[587] and L-glutamic acid with a weakly basic anion exchange resin.[588]

5.7 Molecular Orbital Calculations for Amino Acids – Theoretical studies incorporating molecular orbital calculations provide useful assistance to the interpretation of experimental data in a number of areas of amino acid science, illustrated with ^{13}C-nuclear shielding parameters for solid samples,[589] including solid α-glycine,[590] influence of nearby water molecules on proton transfer energies of glycine and alanine,[591] and verification of the stoichiometry of the dihydrated glycine zwitterion assembly.[592] Other computations for underivatized amino acids include free energy data for transfer of individual amino acid molecules from vapour to water,[593] and consideration of conformational aspects of alanine,[594] glycine and alanine,[595] alanine, serine and lysine,[596] glutamic acid in its non-zwitterionic forms[597] and in its neutral and zwitterionic forms,[598] γ-aminobutyric acid in comparison with β-alanine and glycine,[599] δ-aminopentanoic acid,[600] and ω-amino acids.[601] The structural features of glycine in the gas phase[602] and of the carbon-centred glycine radical in its zwitterionic form,[603] as well as structures and gas phase thermochemistry of glycine and its ions and radicals,[604] have been shown to be a valid focus for molecular orbital calculations.

N-Acetyl-L-amino acid N-methylamides continue to provide the favoured model for calculations of conformational details for individual amino acids in

polypeptides and proteins, and these derivatives of L-alanine[605] and L-proline[606] have been studied this year. Calculations of structural features of complexes of amino acid esters with a porphyrin host have been performed.[607]

6 Chemical Studies of Amino Acids

6.1 Racemization – Major topics under this heading over recent years continue to attract attention, with new themes revealed in papers (see also Refs. 168, 730) on photolytic racemization at wavelengths shorter than 300 nm of L-lysine in the presence of suspended cadmium(II) sulfide particles under anaerobic conditions (L-leucine and L-phenylalanine are also racemized under these conditions, but not L-glutamic acid),[608] and of L-lysine by phosphoric acid and acetic acid.[609]

The extent of racemization of free amino acids under the conditions of acid hydrolysis of peptides (130°; HCl – AcOH = 1:1) has been found to be small for valine (0.1% within 4 hours) and greater (as expected) for aspartic acid (1.5% in 4 hours).[610] This is an important study, confirmed in rather less precise terms for 6M-HCl at 105°,[611] with attention to the effects of other temperatures and acid concentrations, and the effects of irradiation by UV light, etc. As the sensitivity of instrumental analysis methods in this area becomes more and more enhanced, and as statutory requirements for quality control of homochiral pharmaceutical compounds become more stringent, these levels become significant enough to require taking into account when considering the results of routine enantiomeric analysis of samples. This last point provided the stimulus to re-investigate the racemization of L-serine kept in pure water at 100°.[612] In earlier studies, half-life values 400 years for aqueous L-serine at 25°[613] and 4 days at 100°[614] were determined, though the new value (Ref. 612) is 40 days at 100°. Cysteine derivatives protected as alkyl disulfides are easily racemized by 25% piperidine in DMF when the carboxy group is in the form of an ester, but not when it is amidated.[615]

A review has appeared of the post-translational events through which L-amino acids are incorporated into polypeptides as their D-enantiomers, and the role of peptidylaminoacyl L-D-isomerase in some of these processes.[616]

Apart from results for laboratory racemization, and puzzles of a mechanistic nature that arise from them, racemization data obtained by enantiomeric amino acid analysis continue to be exploited in fossil dating (see also Refs. 22, 34). A favoured technique depends on analytical quantitation of L-isoleucine – D-alloisoleucine diastereoisomers, and this has been applied to an eggshell sample of the extinct Pleistocene ratite *Genyornis*, in order to assess variations in ages given by different molecular weight fractions.[617] Results for fossil bones dated in this way have been compared with those obtained through the classical ^{14}C-method,[618] which is not subject to the influences that appear to undermine the amino acid dating method. This is already becoming more than a minor issue, since queries have been surrounding the amino acid racemization dating technique in recent years; thus Otztal Ice Man (the unmolested corpse found at Hauslabjoch, Austrian Tyrol, in September 1991) which has been dated to

4550 ± 27 BC by radiocarbon dating,[619] would have a grossly inaccurate assignment of birthday, based on amino acid data. For younger samples that have been kept in constant conditions, e.g. human tooth cementum, a linear relationship applies for racemization as a function of time.[620]

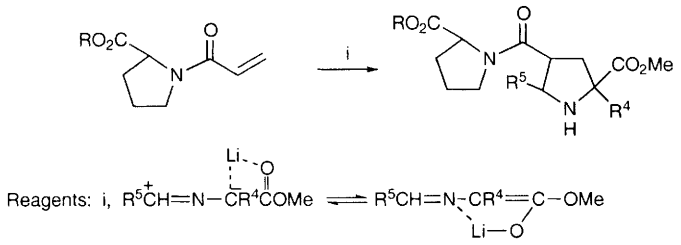
6.2 General Reactions of Amino Acids – Reactions at the amino and carboxy groups of the amino acids are dealt with in this Section as well as reactions at the α-carbon atom of α-amino acids. Although some other papers in this Chapter also qualify for the same narrowly-defined category, these papers are located elsewhere because of priority given to their coverage of another theme.

A long-running project (see Vol 27, p. 53) has established that the oxidative decomposition of alanine, aminoisobutyric acid and proline after N-bromination follows first order kinetics in aqueous alkali.[621] N-Chlorination of optically-active methyl aziridine 2-carboxylates is followed by base-induced elimination to give optically-active 2H-azirine-2-carboxylates, a process that is accompanied by alternative HCl elimination, but Swern oxidation accomplishes the desired change cleanly.[622] Replacement of the amino group by a halogen atom, with retention of configuration, is the best way of preparing homochiral α-halogeno acids, illustrated recently for the conversion of L-isoleucine to (2S,3R)-2-chloro-3-methylpentanoic acid using sodium nitrite and 5M HCl,[623] and for preparing (2S,3R)-2-bromo-3-hydroxybutanoic acid from L-threonine (sodium nitrite and KBr with 1.25M H_2SO_4).[624] The corresponding replacement of the amino group by a hydroxy group employs sodium nitrite and 1.5 equivalents of H_2SO_4 in water.[625] The oxidative decomposition of amino acids by ninhydrin has been shown to offer quantitative release of ammonia, and offers a useful total assay when coupled to an inexpensive flow injection – gas diffusion instrument.[626] Tungstate-catalyzed oxidation of N-alkyl-α-amino acids causes decarboxylation and efficient nitrone formation.[627] Among the vast number of papers on routine oxidative decarboxylation studies of amino acids involving inorganic reagents, is found an account of the first observation of the formation of an initial major reaction product which is neither an aldehyde nor a carboxylic acid. The acetone – potassium peroxymonosulfate reagent used in this work generates dimethyl dioxirane as the effective oxidant.[628] Another component of the classical range of amino acid reactions, the Maillard reaction, has provided yet another fascinating aspect with potential analytical use: the generation of oxygen-dependent chemiluminescence.[629] This, from the 6-aminocaproic acid – D-ribose system, is sufficiently intense to be seen by unassisted eyesight. As far as changes in food are concerned, Maillard degradation of amino acid – carbohydrate mixtures mainly concerns only lysine, histidine and tryptophan.[630] Mechanisms of individual steps in the Maillard reaction have been reviewed[631] (see also Ref. 721). 3-Methylpyrazin-2(1H)-ones are newly-discovered characteristic Maillard reaction products formed from asparagine and monosaccharides.[632] The formation of N-oxides by oxidation of N-benzylprolines is completely diastereoselective;[633] nitrones are formed from esters of the unprotected imino acids when undergoing sodium tungstate-catalyzed oxidation with the urea-hydrogen peroxide complex.[634]

The preparation and reactions of N-acyl-α-amino acids have been reviewed.[635] Reviews in the *ChemTracts* series[636] cover work[637] on the transposition of N-protection; e.g. deprotection of N-allyloxycarbonylamino acids using the Guibe method (tri-n-butyltin hydride as nucleophile; e.g., Ref. 653) in the presence of an active acylating agent; such as Boc-anhydride, to give Boc-amino acids. This becomes a one-step deprotection – coupling procedure leading to peptides when performed in the presence of amino acid pentafluorophenyl esters of amino acids. Palladium(0) – sodium borohydride offers the same de-allylation and protecting group transposition opportunities, as well as the peptide bond-forming option.[638] Palladium(0) – phenyl trihydrosilane or N-methyl-N-(trimethylsilyl)trifluoroacetamide offer effective allyl cleavage protocols.[639] N(O,S)-Isobutyloxycarbonylation of amino acids could become the most favoured protocol as part of the sample preparation procedure for gas-chromatographic analysis of amino acid mixtures, in view of the finding that sonication with isobutoxycarbonyl chloroformate in aqueous alkali completes the derivatization in a matter of seconds.[640] However, the side-reactions (leading to derivatized peptides) of this protocol need to better appreciated. Treatment of an N-alkoxycarbonylamino acid mixed anhydride with a NaH – alkyl chloroformate mixture generates the NN-di(alkoxycarbonyl)amino acid after simple work-up.[641] The bis(N-Boc)amino acids that were studied over several years by several research groups have sustained less interest recently, partly due to some side-reactions and difficulties in preparation; in the latter context, the expected correlation of substrate acidity with ease of introduction of a second Boc grouping catalyzed by 4-dimethylaminopyridine is confirmed, but steric hindrance for some amides does not limit reaction rates as much as might have been expected.[642] N-Acylation of hindered N-alkylamino acids, e.g. $AllocNHCHMeCH_2NHCHBu^iCO_2Me$, is achievable using one of the newer peptide coupling agents, O-(7-azobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.[643]

N-Derivatization of imino acids (L-proline, pipecolic esters) in water has been established to apply to the bismuth(III) chloride – benzotriazole system.[644] Photoinduced Wolff rearrangement (366 nm) of dibenzoyldiazomethane in the presence of an amino acid ester generates the highly electrophilic benzoylketene, which causes N-(α-benzoylphenylacetyl)ation.[645] Mitsunobu processing converts amino acid esters into amidines through use of NN′-bis(benzyloxycarbonyl)acetamidine as reagent,[646] and the α-amino group of lysine has been substituted by a 4-methylbenzylthio-grouping, *via* the pyridinium salt formed through condensation with a pyrylium salt;[647] tryptophan has been converted similarly into pyridinium salts and dihydropyridines, the heteroaromatic nitrogen atom being derived from the α-amino group.[648]

Reliable N-mono-alkylation of amino acids is often achieved only by indirect routes, and the preparation of particular amino acids reversibly derivatized by N-benzylation, e.g. N-tert-butoxycarbonylmethylation of leucine methyl ester using tert-butyl bromoacetate and di-isopropylmethylamine,[649] and preparation of N-(2-hydroxy-4-methoxybenzyl)-L-amino acids, required by some improved peptide synthesis protocols, that illustrate these roundabout routes, have been described.[650] Preparations and uses of NN-dibenzylamino acids and aldehydes have

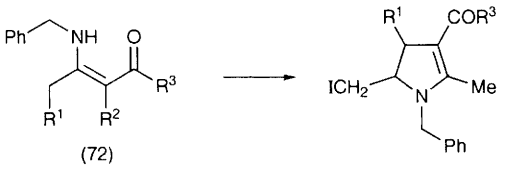


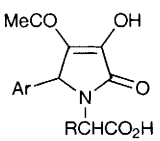
Scheme 40

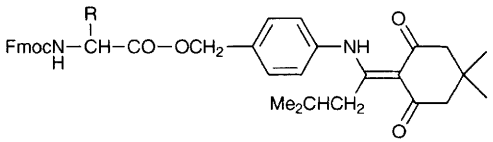
been well-researched already, and further examples have been described.[651] Methylation of glycine by the dimethylchlorinium ion occurs at N and at O in the gas phase (chemical ionization source of a mass spectrometer), while the methoxymethyl cation adds at N under these conditions.[652] Selective deprotection of allylamines using Guibe's palladium(0)/NN-dimethylbarbituric acid/DPPB system, together with 2-mercaptobenzoic acid, has been illustrated for ethyl NN-diallyl L-phenylalaninate.[653]

N-Alkylidenation of amino acids, i.e. Schiff base formation, provides an essential stage of some amino acid synthesis protocols (see Sections 3.1, 3.2), and also extends the uses of amino acids in general organic synthesis, e.g. diastereoselective synthesis of pyrrolidines (Scheme 40).[654] Trimethylorthoformate is an effective dehydrating agent under mild and non-acidic conditions, for imine formation between aldehydes and amino acids.[655] Pyrrolines can be prepared by cyclization of α-alkenyl-β-enamino esters (72),[656] and amino acids react with methyl acetylpyruvate to give pyrrolinones (73).[657] Isoindoles formed from amino acids in reaction with o-phthaldialdehyde/2-mercaptoethanol are of lower stability (as shown by fluorescence decay studies) than those formed from peptides (see also Refs. 20, 658, 874 for studies of this reaction).[658]

Carboxy group manipulations described in the recent literature include all the familiar elaborations of this functional group. Useful modifications and





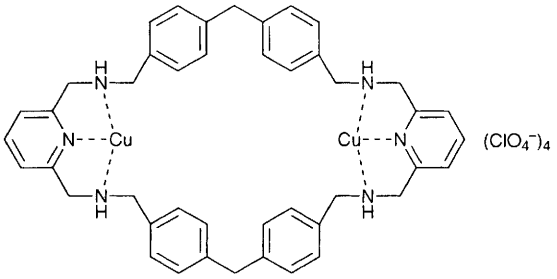


innovative contexts associated with the citations chosen for inclusion, justify the space given here. Reduction to the aldehyde through lithium aluminium hydride reduction of the Weinreb amide [$RCO_2H \rightarrow RCONH(OMe)Me \rightarrow RCHO$] and chain extension through aldolization and standard elaboration is illustrated in a synthesis of keramamide F,[659] and another standard protocol, $NaBH_4/I_2$reduction, has been put to use for the conversion of L-phenylalanine to L-phenylalaninol,[660] *en route* to L-phenylalaninal *via* standard alternative routes. Further results have been reported (see Vol 27, p. 55) on the reduction of N-protected amino acid chlorides to aldehydes using lithium tris(tert-butoxy)aluminium hydride,[661] and further examples have been described of the conversion of N-protected amino acids into amides through the use of di-tert-butyl pyrocarbonate/pyridine/NH_4HCO_3 as condensation reagent.[662] Lithium aluminium hydride reduction of N^{α}-tritylamino acid amides to corresponding amines offers better results for practical reasons than reductions in the presence of other N-protecting groups.[663]

Use of BOP – diethylamine for efficient esterification of Z-L-phenylalanine by methanol has been established;[664] similar reagent systems have not been found to be so effective in the past. Improvements leading to products destined for a role in peptide synthesis include a benefit of phase-transfer catalysis in condensing Boc-L-amino acids with chloromethylpoly(styrene);[665] conversion of Z-L-glutamic acid into a mixture of α- and γ-tert-butyl esters, and separation of the products as their cyclohexylammonium salts;[666] and formation of the pentafluorophenyl ester of Fmoc-L-asparagine using pentafluorophenol with a water soluble carbodi-imide that does not affect the unprotected side-chain.[667] Preparation of N-substituted 4-aminobenzyl esters (74) that fragment readily into the starting acids with 2% hydrazine in aqueous DMF, and therefore provide a useful new protection system for the carboxy group based on the safety-catch principle, has been described.[668] Hetero-Diels-Alder addition to cyclopentadiene, of acylnitroso dienophiles prepared by oxidation of N-protected amino hydroxamic acids, can start routes to other useful products through cleavage of the N – O bond.[669] $Mo(CO)_6$ reduction of the Diels-Alder adducts provides aminocyclopentanols, and Pd-catalyzed allylic substitution of the derived acetates opens up a route to carbocyclic nucleosides or their precursors.[670]

Replacement of the carboxy group by a hydrogen atom is illustrated in a lengthy route to enantiomerically-pure α-methylamines, that involves the transformations [$RCO_2H \rightarrow RCH_2OH \rightarrow RCH_2OMs \rightarrow RCH_2SEt \rightarrow RCH_3$]; the last step features classical Raney nickel reduction, and the route is clearly limited to benign substrates.[671]

Ester hydrolysis studies with novel mechanistic features continue earlier work on systems that promote enantioselectivity. Hydrolysis of the L-enantiomer of N-dodecanoyl-DL-phenylalanine p-nitrophenyl ester by micelles enclosing the peptide Z-L-phenylalaninyl-L-histidyl-L-leucine occurs 77 times faster than that of the D-isomer.[672] Imidazole-appended β-cyclodextrins cause similarly selective enhancement of the hydrolysis of Boc-DL-alanine p-nitrophenyl ester,[673] and an L-histidine-containing polymer has been used in a corresponding way (see Vol 27, p. 55).[674] Clear evidence has been obtained of the cooperation of the two



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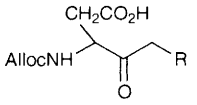
copper atoms complexed by the macrocycle (75), when used as a hydrolysis catalyst for β-alanine p-nitrophenyl ester, but this cooperation does not occur for leucine p-nitrophenyl ester.[675] A water-soluble polymer has been rendered capable of enantioselective hydrolysis of Z-DL-leucine p-nitrophenyl ester through imprinting with Z-L-phenylalanine phosphonate.[676] Nucleophilic cleavage of an N-protected alanine decyl ester can be catalyzed by poly(styrene)-supported ethylenediamine – copper(II).[677] The mimicking of an enzyme, that lies behind some of these studies, still falls behind the achievements of the real thing, especially in the unexpected flexibility shown by familiar enzymes; thus, α-chymotrypsin and subtilisin Carlsberg are effective in organic media (cyclohexane) in catalyzing the transesterification of N-acetylalanine or phenylalanine esters,[678] and porcine liver esterase accomplishes the selective hydrolysis of aspartic acid di-esters into corresponding β-esters.[679]

Preparation of aminoacyl halides has been given new impetus with the finding that their use in peptide synthesis need not be encumbered with side-reactions. New findings for the preparation and uses of N-protected L-pyroglutamyl chlorides[680] (see also Ref. 661) and Fmoc-L-amino acid fluorides[681] have been published.

Photodecarboxylation of N-phthaloylamino acids, in continuation of earlier studies (see Vol 25, p. 69), has led to the discovery that N-{α-[^{2}H]alkyl}phthalimides are formed in this way in ^2H_2O.[682] Decarboxylation is also seen in the photolysis of N-phthaloyl phenylalanine and tyrosine in non-polar solvents,[683] but cis and trans-cinnamic acids are also formed, as well as the benzazepin-1,5-dione in the case of tyrosine by photolysis in MeCN; phthaloylserine and threonine behave similarly, though with a noticeably easy loss of the side-chain.[684]

Other transformations involving the carbonyl moiety of amino acids and their carboxylic acid derivatives include a two-step conversion into hydroxamic esters using organo-aluminium reagent-promoted transamidation (O-benzylhydroxylamine hydrochloride and Et_3Al in benzene) followed by hydrogenation (H_2/Pd-C);[685] and a racemization-free preparation of N-protected α-amino-aldehydes through oxidation of corresponding alkanols with 1,1,1-tris(acetoxy)-1,1-dihydro-1,2-benzo-iodoxol-3(4H)-one ('periodinane').[686] Several papers deal with



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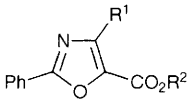

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preparations of α-amino-ketones from α-amino acids, and describe uses of these products; thus, a route to N-allyloxycarbonyl-L-aspartic acid-derived substituted methyl ketones (76) involves the corresponding bromoketone;[687] anions of N-phenylsulfonylamino acids, generated using lithium hydride, are suitable for multigram-scale conversion into ketones through addition of a Grignard reagent;[688] α-aminoalkyl trifluoromethyl ketones are available in excellent yields from oxazolidin-5-ones through cesium fluoride-catalyzed addition of Ruppert's reagent [(trifluoromethyl)trimethylsilane] to the carbonyl group;[689] N-Boc-α-amino ketones are formed efficiently and in high enantiomeric excess through addition of organolithium and Grignard reagents to the pseudoephedrine amide of N-Boc-α-amino acids (see Section 4.2);[690] α-chloro-α'-(dibenzylamino)methyl ketones are the starting material for the highly diastereoselective synthesis *via* reduction and epoxidation, of threo-aminoalkyloxiranes, while a route to erythro-analogues starts with the protected α-amino-aldehyde, which is reacted with *in situ*-generated halomethyllithium.[691] A large-scale preparation of (2S,3S)-N-Boc-3-amino-1,2-epoxy-4-phenylbutane from NN-dibenzyl-L-phenylalaninol proceeds through the classical route *via* aldehyde and chlorohydrin.[692] Preparation of homochiral N-Boc-aminoalkyl oxiranes from anti N-diphenylmethyl-3-amino-1,2-diols has been described;[693] the preparation of protected erythro-α-(aminophenylethyl)oxiranes derived from phenylalanine involves a bromomethyl ketone intermediate,[694] which features as the substrate in a study of their stereoselective reduction by borohydrides to give erythro-Boc-amino alcohols and derived epoxides.[695]

The reactions of amino acids that involve both amino and carboxy groups are maintaining a substantial proportion of the papers selected for this Section, as in previous years. There is more to report this year (see Vol 27, p. 54) on the self-condensation induced in aqueous solutions of amino acids by high concentrations of NaCl and a copper(II) salt, to give peptides.[696,697] The activated species is clearly shown to be the monochlorocuprate(amino acid) complex, and this structural feature is carried through to the products which then continue to undergo condensation that results in chain extension. Stability constants measured for these complexes verify this explanation, since a reaction mixture containing α-, β-, and γ-amino acids tends to generate peptides built up preferentially from α-amino acids, and it is α-amino acids which give the most stable monochlorocuprate(amino acid) complexes.

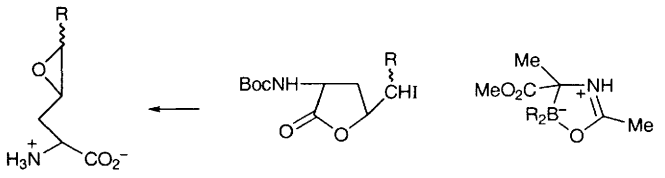
The property of achieving easy cyclization of α-, β-, and γ-amino acids to corresponding lactams is claimed for the N-alkyl-2-benzothiazolylsulfenamide/PPh_3 reagent.[698] Chain extension of the L-proline carboxy group and cyclization of derived N-acetyl- and -propionyl anions gives efficient access to homochiral pyrrolizidines.[699]

The 4,4-disubstituted 2-tert-butoxy-oxazol-5(4H)-one formed by carbodi-imide cyclization of an N-Boc-α-trifluoromethyl-α-amino acid is unusually easily converted into its corresponding N-carboxyanhydride,[700] while corresponding cyclic dipeptides (i.e. dioxopiperazinediones) form unexpectedly easily from the intended preparation of the N-carboxyanhydride of (R)-thiazolidine-4-carboxylic acid.[701] N-Benzoyl-α-amino acids form 2-phenyloxazol-5(4H)-ones easily when treated with a carboxy group-activating reagent, a long known fact but contrasting with the surprising formation of 2-phenyloxazole-5-carboxylic esters (77) in the corresponding reaction with excess oxalyl chloride followed with an alcohol.[702] Esterification accompanies N-ethoxycarbonylation of amino acids treated in MeOH in the presence of K_2CO_3 with ethyl chloroformate,[703] an outcome already established some years ago and explained by the dual role of the reagent (causing carboxyl group activation as well as N-acylation).

6.3 Specific Reactions of Amino Acids – This section covers the reactions of amino acid side-chains that mostly depend on one or both of the amino and carboxy groups being in a protected state. A review covers the uses of amino acids as starting materials for the preparation of enantiopure products.[704]

Among several possible glycine radicals, that in which the unpaired electron is localized on the α-carbon atom is the most stable.[705] A classical radical mechanism accounts for the rearrangement of diethyl 2-acetylamino-2-methylpropanedioate into diethyl 2-acetylaminobutanedioate, that occurs through coordination to a Vitamin B_{12} derivative.[706]

β-Iodo-L-alanine derivatives are proving to be useful synthons, undergoing Pd(0)-catalyzed arylcarbonylation in the form of the derived organozinc reagent RZnI, with an aryl iodide and carbon monoxide (illustrated in a short synthesis of kynurenine).[707] This protocol offers an alternative route to 2-amino-5-oxoalkanoic acids from γ-iodo-L-butyrine derivatives, compounds that are usually approached from the same starting point through reaction with an acyl halide.[708] Carbon-carbon bond formation occurs when the corresponding mixed-metal analogue RCu(CN)ZnI reacts directly with allylic halides and toluene-p-sulfonates.[709] The Heck reaction applied to Z-vinylglycine through reaction with 1-iodo-4-methoxybenzene in DMF in the presence of palladium acetate, illustrates another way of extending the aliphatic side-chain of this useful member of the α-amino acid family.[710] Aza-sugars (i.e. substituted 2-hydroxymethylpyrrolidines) can be synthesized starting from vinylglycine *via* the derived N-allyl 5-vinyloxazolidin-2-one.[711] A route from L-allylglycine and L-crotylglycine derivatives *via* iodolactonisation ends with functionalised 4,5-epoxy-α-amino acids (78),[712] and intramolecular cyclization of βγ-unsaturated acyloxysilanes followed by H_2O_2 ring cleavage are the crucial steps in a route from (S)-3,4-dehydroproline to (2S,3R)-N-Boc-3-hydroxyproline methyl ester.[713] Tributyltin hydride-mediated radical cyclization of N-(α-chloroacetamido) dehydroalanine gives pyroglutamic acid.[714] The amino group is involved, together with the side-chain, when attempted hydroboration of methyl 2-acetamidoacrylate leads to a heterocyclic oxytriorganoborate (79).[715] The nucleophilic character of the α-carbon atom is enhanced in these compounds, as it is in many other heterocyclic compounds



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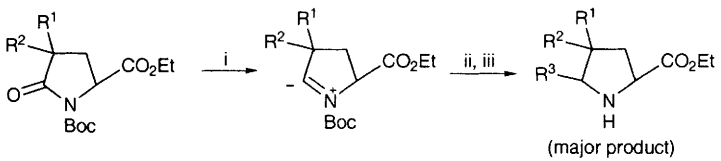
enclosing an α-amino acid moiety, and α-alkylation is possible, though this competes with N-alkylation.[716]

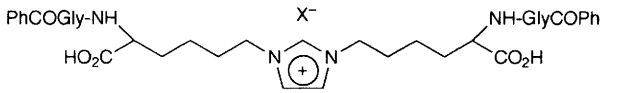
Reactions of cyclic aliphatic α-amino acids most often encountered in this Section over the years are based on proline (and, increasingly often, on pipecolic acid). Natural trans-4-hydroxy-L-proline is used (often, most ingeniously) to synthesize a widening range of substituted prolines, and C-4-inversion to yield the (2S,4R)-epimer has added another useful synthon for this area of synthesis.[717] The spirohydantoin formed from 4-oxoproline through the Bucherer-Bergs amino acid synthesis is easily transformed into 4-amino-4-carboxyproline, and this work has provided all four isomers of this conformationally-constrained glutamic acid analogue.[718] 4-Oxo-L-proline also serves to start a route to the kainoid analogues (2S,3R,4S)-3-benzyl-4-phenylproline and its C-3 epimer.[719] The stereoselective addition of organomagnesium cuprates to the acylium ion from 4,4-disubstituted prolines (Scheme 41) has been developed as a viable stereoselective route to 5-substituted proline analogues.[720]



Reagents: i, $LiBEt_3H$, then TsOH; ii, R^3MgX, CuBr, Me_2S, BF_3–Et_2O; iii, remove Boc

Scheme 41

An N^{α}-protected lysine, namely N^{α}-hippuryl-lysine, reacts with glyoxal to give the bis(4-carboxy-4-hippurylaminobutyl)imidazolium salt (80);[721] this process is an appropriate model for the formation of the Maillard reaction-generated crosslink in proteins, because glyoxal is a retro-aldol cleavage product of many of the common Maillard reaction intermediates (see also Refs. 629-631). There is a quite different course for the reaction between N^{α}-Z-lysine and glyoxal at 37°, which leads to N^{α}-Z,N^{ε}-carboxymethyl-lysine.[722] (E)-4,5-Epoxy-(E)-hept-2-enal, a well-established lipid peroxidation product, gives pyrroles through heating with lysine (see also Ref. 919).[723] Milder conditions for the corresponding reaction of trans-4-hydroxynon-2-enal have confirmed that the Michael addition pathway leads to a 1:2-cyclic hemiaminal with lysine or histidine (formed through the N^{π}-



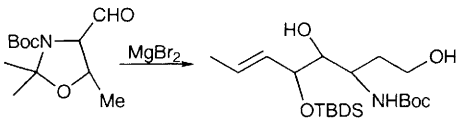
(80)

atom).[724] Thermal rearrangement of (S)- or (R)-hexahydro-1-nitroso-3-phthalimido-2H-azepin-2-one, prepared in known ways from appropriate lysine derivatives, gives the corresponding lactone from which ε-hydroxy- and ε-chloronorleucine enantiomers have been prepared.[725] The side-chain amino group of a protected lysine has been modified to give L-N^{ε}-(1-iminoethyl)lysine, a selective inhibitor of nitric oxide synthase.[726]

Glycosylation of N^{α}-protected β-amino-alanine methyl ester provides a glycosylated 'retro-asparagine', a confusing name if applied to amino and carboxy group derivatives of this isomer, because only one of the three functional groups of derivatives of this protein amino acid is reversed.[727] All diastereoisomers of 2,3-diaminobutanoic acid (*alias* β-aminobutyrine) have emerged from nucleophilic substitution reactions of D- and L-threonine derivatives.[728] Heating N-acetyl-2,4-di-aminobutanoic acid yields ectoine (2,4,5,6-tetrahydro-2-methyl-4-pyrimidinecarboxylic acid).[729] 2,6-Di-aminopimelic acid undergoes photochemical cyclization (λ> 300 nm) into piperidine-2,6-dicarboxylic acid in a deaerated aqueous cadmium(II) sulfide dispersion (see also Refs. 168, 609).[730]

Arginine remains at centre stage because of its importance, among other things, as the source of *in vivo* nitric oxide (released by UV irradiation of squamous cell carcinoma, together with peroxynitrite, ammonia and hydroxylamine),[731] an ESR study of N^{G}-hydroxy-L-arginine revealing that the N-hydroxyguanidine tautomer, not the amino-oxyformamidine form, is the effective source of nitric oxide[732] (addition of hydroxylamine to N^{δ}-cyano N^{α}-Boc-ornithine tert-butyl ester provides the substrate for this study[733]). Methanesulfonylethyloxycarbonyl protection of arginine side-chain nitrogen atoms has been advocated, for easy deprotection and for reliable control of side-reactions originating with arginine during peptide synthesis.[734] Deprotection conditions are mild (aqueous NaOH) for this protection strategy, but analogous Boc side-chain protection has certain benefits, not least for the ease of preparation.[735] Two new close analogues of well-established arenesulfonyl protecting groups (arene = 4-Ph-C_6H_4- or 3-Me_3C-, 4-OMe-C_6H_3-) have been proposed for the arginine side-chain.[736] New details, from the point of view of optimization, of the arginase-catalyzed conversion of arginine into ornithine still come to light.[737]

Preparations of corresponding 4-oxaprolines from serine and threonine enantiomers have familiar precedents,[738] and the well-established, L-serine-derived, Z-α-amino-β-lactone, has been used in a multi-kilogram synthesis of Z-(S-phenyl)-L-cysteine,[739] and in a synthesis of lanthionines through regioselective ring-opening by cysteine derivatives and their ββ-disubstituted analogues.[740] The equally well-appreciated Garner aldehyde obtained from L-serine, and the homologue (81) formed from L-threonine, reacts with γ-oxygenated allylic stannanes through an exclusively syn-selective pathway,[741] and with dimethyl 1-



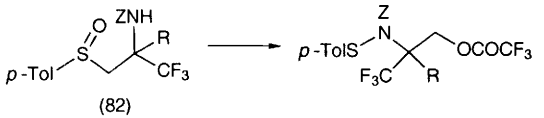
(81)

diazo-2-oxopropyl phosphonate to give N-Boc-D-ethynylglycine[742] and its homologues, through metallation (BuLi) and use as nucleophile towards common organic halides.[743] The Garner aldehyde (see also Ref. 319) is the basis of syntheses of (2R,3S)- and (2R,3R)-phenylserine, (R)-3,3-diphenylserine and (R)-3,3-diphenylalanine, through manipulations of the aldehyde function, and using the original serine side-chain to generate the eventual carboxy group.[744] Further examples of the latter device are seen in a stereoselective synthesis of (2S,3S)-3-hydroxyleucine in which the aldehyde group of a version of the Garner aldehyde is elaborated into the eventual side-chain,[745] and in a synthesis of N-Boc-D-diphenylalanine (*via* the oxazolidin-2-one).[746] The conversion of the aldehyde group into an oxirane through ylide epoxidation,[747] and chain extension through aldolization with $THPO(CH_2)_{13}C{\equiv}CLi$, leads on to a sphingosine analogue suitable for use in acylation of aminated glass beads to be used for the purification of sphingosine kinase.[748] Numerous applications outside the amino acid field (e.g. a route to manzamines)[749] have been found for the Garner aldehyde.

A range of Boc-(S-alkyl)-L-cysteine methyl esters has been obtained through treatment of N-Boc-L-serine methyl ester with disulfide/PBu_3reagents.[750] Mitsunobu processing of N-Boc-L-homoserine benzyl ester with N^3-benzoylthymine provides the corresponding γ-N-heteroarylbutyrine,[751] and the analogous transformation of L-homoserine into L-homocysteine derivatives and into L-2-amino-4-phosphonobutanoic acid[752] emphasises the synthetic usefulness of the ω-hydroxyalkyl-α-amino acids.

Serine and threonine protection as benzyl ethers is retained when hydrogenolysis (H_2/Pd-C) of N-Z-protected benzyl esters of these amino acids is performed in the presence of ammonia, ammonium acetate or pyridine.[753] This will be a useful observation if it can be verified for a wider range of substrates. The tert-butyl ether of Fmoc-L-allothreonine can be prepared more efficiently, through long-established though somewhat drastic methodology (lengthy hydrolytic cleavage of a benzoyl group is needed); inversion of the side-chain chiral centre in this route involves the oxazoline prepared from N-benzoyl L-threonine, and introduction of protecting groups is otherwise straightforward.[754]

Formation of the acid chlorides of serine and threonine calls, not surprisingly, for O- and N-protection through strategies that make stringent demands, and ultimate deprotection after acylation by these synthons must take account of the sensitivity of the β-hydroxy-α-amino acid grouping. Because of this problem associated with unprotected side-chains, N-acetyl 5-chlorocarbonyloxazolidin-2-ones, though not readily purifiable, were studied and were shown to be suitable for introducing serine and threonine residues where standard peptide-forming



(82)

conditions had failed.[755] Conversion of serine derivatives into β-halogeno-alanines by trimethylsilyl halides requires lengthy reflux in MeCN, and fails for the preparation of the fluoro-compound.[756]

O-Glycosylation of α-(ω-hydroxyalkyl)-α-amino acids has generated a sizeable literature, though methods vary from one amino acid to another; a representative example, the preparation of O-glycosylated hydroxy-L-prolines, discusses different approaches and protection strategies.[757]

An alternative route to (S)-2-amino-4-oxo-butanoates (see Refs. 707, 708) involves L-methionine, which requires protection as the phthaloylated methyl ester so that oxidative modifications can be made.[758] The S-p-tolylcysteine sulfoxide (82) undergoes an unusual non-oxidative Pummerer rearrangement with trifluoroacetic anhydride, and (R)- or (S)-α-trifluoromethylserine can be prepared in this way.[759]

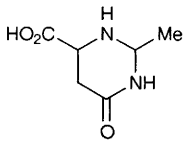
Reactions at the side-chain thiol group in cysteine derivatives are described in papers that deal with kinetics of nitrosothiol formation from N-acetylcysteine and nitric oxide in the presence of oxygen,[760] oxidation of cysteine by copper(II) species and by copper(I) – O_2 adducts,[761] and further studies of the autoxidation of S-aminoethylcysteine ketimine (see Vol 27, p. 67) to give 2,3,6,7-tetrahydro-4H-[1,4]thiazino[2,3-*b*]thiazine, thiomorpholin-3-one and 5,5′,6,6′-tetrahydro-2,2′-dihydroxy-3,3′-bi[(2H)-thiazine].[762] Palladium-catalyzed S-arylation of N-acetyl-L-cysteine methyl ester with an aryl iodide requires mild conditions in leading to moderate to good yields.[763] The reaction of OPA with cysteine-containing proteins at several amino acid residues, in addition to the expected location (the cysteine side-chain), provides a puzzle that will need to be solved if the spectrum of reactivity of this popular reagent (Section 7.5) is to be fully understood.[764] The thiol group in the ovothiols undergoes the expected thiol-disulfide exchange process with glutathione.[765]

The sulfur analogue of the serine-derived Garner aldehyde (see above) has been prepared from cysteine, and used for development of the erstwhile carboxylic acid grouping into a propenyl grouping as part of a synthesis of a model for curacin A.[766]

Aspartic and glutamic acids, and their derivatives, provide the basis of most of the papers in this Section, since valuable synthetic applications originate in the characteristic reactions of the carboxy group and adjacent methylene group in these compounds. Side-chain 2,4-dimethylpent-3-yl ester protection of aspartic acid effectively prevents side-chain involvement (i.e. aspartimide formation) during amidation of the α-carboxy group.[767] Allyl ester protection of the side-chain carboxy group of glutamic acid allows convenient manipulation of the other two functional groups, e.g. to prepare α-tert-butyl N-trityl-L-glutamate.[768] Nucleophilic attack on N-tritylaspartic anhydride occurs at the β-carbonyl

group,[769] to yield asparagines and other familiar derivatives. Elaboration of the side-chain of a protected aspartic acid, leading to N-trifluoroacetyl-5-bromo-4-oxo-norvaline methyl ester and N-trifluoroacetyl-3-formylalanine methyl ester, is uneventful; but the construction of heteroaryl groupings on these modified side-chains, e.g. to give azatryptophan, is notable.[770] However, N-Boc γ-methyl α-tert-butyl-L-glutamate may be elaborated through its side-chain function into the urea (side-chain = $CH_2CH_2NHCONH_2$) *en route* to the corresponding pyrimidinone, built upon the urea nitrogen atoms in the standard way.[771] Asparagine itself can be converted through routine steps *via* a β-homoserine derivative into (S)-3,4-diaminobutanenitriles, through Mitsunobu amination, and thence into 3-aminoGABA.[772] A pathway from Boc-L-glutamine to N^{α}-methyl-arginine and ornithine derivatives proceeds *via* the nitrile.[773] Acetaldehyde reacts with asparagine in aqueous solution at high pH to give the tetrahydropyrimidinone (83; claimed to be novel, but quite well known in the early literature).[774] Side-chain enolates of strategically-protected aspartic acids can be used to synthesise 3-carboxyproline and 5-substituted analogues,[775] and similar manipulation of the L-aspartic acid side-chain after protection using hexafluoroacetone [to give the 2,2-di(trifluoromethyl)oxazolidin-4-one] *en route* to 4-oxopipecolic acid has been described.[776] Sodium borohydride reduction to give cis-4-hydroxy-pipecolic acid and its trans-isomer was also described in this study. α-tert-Butyl Z-L-glutamate gives trans-4-carboxypipecolic acid and a series of analogues, through a route involving electrophilic addition to its γ-enolate.[777] These enolates are formed using lithium bis(trimethylsilyl)amide, and are essentially lithium chelates, a fact that helps to account for the very high diastereoselectivity leading to (2S,4S)- or (2R,4R)-products through electrophilic addition. This was observed in the preceding examples, and with N-(p-nitrobenzoyl)-L- and -D-glutamic diesters.[778] Amidation of Z-L- and D-glutamic diesters catalyzed by the lipase from *Candida antartica* leads to the α-amides with the L-substrates, but to the γ-amides for the D-isomers.[779]

The considerable potential in synthesis already established for pyroglutamic acid and its derivatives continues to be upheld, with syntheses of 4-alkylprolines and 4-alkylglutamic acids by BF_3-catalysed aldolization at C-4 of their lithium enolates[780] and synthesis of (2S,4R)-4-methylglutamic acid,[781] as in the preceding examples. 4-Benzylation in this way, reduction of the ring carbonyl function and functional group manipulation, gives the corresponding 2,3-dehydroproline, a Michael acceptor from which α-allokainic acid analogues were prepared.[782] Aldol reactions with the titanium trichloroenolate of methyl N-ethoxycarbonyl-L-



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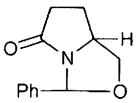

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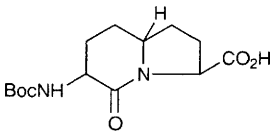


(85)

pyroglutamate give trans-4-(α-hydroxyalkyl)-substituted products, almost exclusively.[783] C-4 Functionalization can be achieved by thio-Claisen rearrangement of S-allylated pyrothioglutamates (5-thioxoprolines) that occurs easily in triethylamine – chloroform;[784] like some other electrophilic C-4 alkylation processes performed with analogous homochiral substrates, this route is not diastereoselective. Carboxy group conversion into the 5-methylisoxazol-2-yl grouping, and modification of other functional groups of (S)-pyroglutamic acid, gives the novel cholinergic channel activator, (S)-3-methyl-5-(1-methyl-2-pyrrolidinyl)isoxazole.[785] Stereocontrolled C-2 functionalization of (S)-pyroglutamic acid can be accomplished by the usual alkylation protocols after conversion into its oxazolidinone with pivalaldehyde.[786] Sulfoxide elimination from a protected pyroglutamic acid derivative leading to 3,4-dehydropyroglutamic acid, starts another pathway that has been trodden before, and illustrated recently for a Diels-Alder addition to cyclopentadiene[787] to give the obvious adduct that is certain to be subjected to further elaboration to provide other amino acids carrying alicyclic structures. A new variation of this approach is illustrated in the use of pyroglutaminol N,O-acetal (84), which can be alkylated following the standard practice with pyroglutamate synthons, and leads to 4,4-disubstituted pyroglutamates after conventional de-acetalization and oxidation.[788] Natural amino acids, and pyroglutamic acid in particular, are increasingly used in syntheses of diverse target natural products and their analogues, outside the amino acid field; thorough coverage of this topic is not justified here. A preparation of long-chain N-acylated pyroglutamates has been described.[789] The efficient routes from tert-butyl N-(9-phenylfluorenyl)-L-γ-methylglutamate to the bicyclic alkaloid analogue (85)[790] and to (2S)-2-amino-3-(3-tert-butyl-5-oxo-2H-isoxazol-4-yl)propanoic acid[791] employ standard methodology.

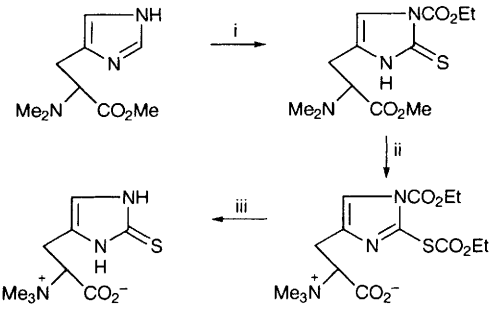
Methyl N-Boc 'pyro-L-aminoadipate' (surely, better named 6-oxopipecolate!) provides 5-alkyl homologues of aminoadipic and pipecolic acids, by stereoselective functionalization in uneventful extensions of the methods used with pyroglutamates, as exemplified in the preceding paragraphs.[792] The (-)-cis-3-hydroxy-6-oxopipecolate analogue features in a route to all four diastereoisomers of 2,6-disubstituted piperidin-3-ol.[793]

Ring contraction and insertion of an isocyanide into a nickelocycle derived from L-glutamic acid anhydride leads to β-methylaspartic acid after functional group conversions (already described in a preliminary communication, Vol 26, p. 67).[794]

Aromatic side-chain construction onto aliphatic amino acids is further illustrated in a synthesis of β-(8-hydroxy-1,4-benzothiazin-6-yl)alanine from S-cysteinylDOPA and H_2O_2 under catalysis by peroxidase.[795] Modifications to existing aromatic moieties in amino acid side-chains are illustrated for the aqueous Heck reaction with arenediazonium salts prepared from 4-aminophenylalanine and 3-aminotyrosine, giving (β-functionalised vinyl) derivatives.[796] L-(O-Malonyl)tyrosine has been prepared as a phosphotyrosine mimic from Fmoc-tyrosine esters by reaction with a di-alkyl α-diazomalonate;[797] further examples of modifications of the tyrosine side-chain are: nitration at pH 5-6 and hydroxylation at pH 2-4, using a peroxynitrite;[798] oxygen-dependent hydroxylation through

γ-radiolysis, effective also with phenylalanine;[799] and m-perfluoroalkylation by a perfluoroalkyl iodide and sodium dithionite.[800] 4-[o,o'-$^3H_2$]Benzoylation of L-phenylalanine can be accomplished through Friedel-Crafts 2,5-dibromobenzoylation followed by ^3H exchange.[801] Breakdown of the phenyl moiety in a protected phenylalanine, through Birch reduction followed by ozonolysis, and condensation of the resulting dialdehyde with appropriate nitrogen derivatives, gives β-isoxazolyl-, (N-phenyl)pyrazolyl-, and pyrazolo[1,5-*a*]pyrimidinyl-alanines.[802] Pictet-Spengler cyclization of 3,3-diphenylalanine is the crucial step in a route to all four isomers of 1,2,3,4-tetrahydro-4-phenylisoquinoline-3-carboxylic acid (see also Ref. 285).[803]

Histidine derivatives have been used in a first synthesis of L-(+)-ergothionene (Scheme 42) that incorporates some useful ring deconstruction – reformation

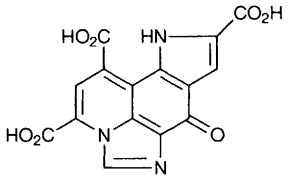


Reagents: i, SCl_2. EtO_2CCl; ii, MeI; iii, deprotection

Scheme 42

operations that will be helpful to others trying to achieve related synthetic objectives (the easy racemization of the betaine, unless acid conditions are used, is noteworthy).[804] Simple imidazole ring modifications include Michael addition to 4-hydroxy-2-nonenal (a lipid peroxidation breakdown product) in confirmation of earlier suggestions that protein modification can occur in this way (see Vol 25, p. 71, and Refs. 805, 919),[805] and N-(O,O-di-isopropyl)phosphorylation of histidine giving derivatives that can cleave supercoiled DNA, a property not shared by either histidine itself, or by its simple dipeptides.[806]

In concentrated H_2SO_4, protonation of L-tryptophan methyl ester occurs at the amino group and also at a ring carbon atom (C-3); then C-5 and C-6 monosulfonation occurs within 2 days, followed by 5,7-, 4,6-, 2,5-, and 2,6-disulfonation.[807] The now notorious toxin, 'peak E', *alias* 1,1'-ethylidene bis(L-tryptophan),[808] that forms in solutions containing the amino acid and acetaldehyde, has been fully documented.[809] 5-Bromocytosine undergoes photochemical coupling with aqueous N^{α}-acetyl-L-tryptophan ethylamide at pH 7, to give the 2-(cytosin-5-yl) derivative.[810] The reaction of an amino acid with the ubiquitous pyrroloquinone PQQ involves decarboxylation, and the side chain is cleaved as a carbanion equivalent; the quinone is converted into an oxazole. A new study of



(86)

this process, using tryptophan, has been shown to give (86) rather than the oxazole isomer previously reported in 1989.[811] Interest in this process has extended to the kinetics of the general PQQ – amino acid reaction, established with the help of CZE monitoring.[812] Acid-catalyzed condensation of N^{α}-Boc-L-tryptophan with aldehydes (the asymmetric Pictet-Spengler reaction) generates trans N^{α}-benzyl-1,2,3,4-tetrahydro-β-carbolines required for syntheses of sarpagine alkaloids, equilibration of the initial cis-trans mixture occurring during removal of the Boc group.[813]

Reactions of the familiar (Vol 25, p. 40; Vol 26, p. 70) N^{im}-benzenesulfonyl hexahydropyrrolo[2,3-*b*]indole methyl ester, formed by cyclization to C-2 through the α-amino group of the corresponding protected tryptophan, now include Barton decarboxylation to give the C^{α}-radical; various reactions illustrate endo face-selective coupling to this radical.[814] Palladium-catalyzed cross-coupling to a 5-iodinated derivative of this cyclic tryptophan has been established as a route to 5-alkyl- and 5-aryl-tryptophans.[815] Tryptophan is the start of numerous biosynthetic pathways, and, not surprisingly, is chosen for equally numerous laboratory syntheses of natural products, e.g. Gyseptin starting from phthaloyl-L-tryptophan methyl ester, a notable step being double oxidative cyclization of the derived dioxopiperazine.[816]

3-Thienylalanine would be a textbook example of an amino acid that an eager research group should find to be worth investigating as an *in vivo* replacement for phenylalanine, and indeed it has been found to be assimilated into protein synthesis by *E.coli*.[817]

6.4 Effects of Electromagnetic Radiation on Amino Acids - Standard photochemical protocols for amino acids under this heading have been used to generate radicals (photochemical decarboxylation of aliphatic amino acids using potassium ferricyanide excited by radiation of wavelengths shorter than 400 nm),[818] and to generate fluorescence (from protoporphyrin IX by δ-aminolaevulinic acid, and potentially useful in medicine for detecting tumours;[819] from dityrosine crosslinks in horse spleen apoferritin using 325nm laser-excitation;[820] or generated in tryptophan and its analogues, interpreted to reveal interactions between the heteroaryl excited state and un-ionised and protonated amino group[821]). Studies of the phosphorescence (i.e. delayed luminescence) of aqueous tryptophan have become possible as a consequence of the availability of sufficiently sensitive detection methods.[822] A 'Proceedings' Volume concentrates on fluorescence studies of protein constituents, e.g.

tryptophan fluorescence in di-octyl sodium sulfosuccinate/iso-octane/buffer reversed micelles.[823]

A rate-enhancing effect has been observed for UV irradiation on the ammonia lyase-induced fragmentation of phenylalanine into trans-cinnamic acid and ammonia.[824]

Rate constants for electron transfer in homogeneous aqueous solutions or within aqueous micelles, between tyrosine or tryptophan and excited states of some sulfonated phthalocyanines, have been determined.[825]

7 Analytical Methods

7.1 Introduction – Reviews of the current status of amino acid analysis have appeared.[826,827]

7.2 Gas-Liquid Chromatography – Fewer papers are appearing under this heading, though not because less use is being made of the method for amino acid analysis; this is a welcome shift away from the repetitive publication of papers describing applications of standard methods, that has been a feature of the analytical literature for amino acids in recent years.

Reliable derivatization protocols [N(O,S)-isobutoxycarbonylation and trimethylsilylation of tert-butyldimethylsilylation] have been illustrated for sample preparation prior to GLC – MS analysis (see Ref. 36). This has provided quantitative data for γ-methylglutamic acid, diastereoisomers of β-hydroxy-γ-methylglutamic acid, and cis- and trans-isomers of 5-hydroxypipecolic acid, as well as constituent protein amino acids, in seeds of *Gymnocladus dioicus*,[828] and for β-methylamino-L-alanine and four non-protein amino acids in *Cycas circinalis*.[829] N(O)-TBDMSylation of amino acids with N-TBDMS-trifluoroacetamide has generated the derivatives of 47 amino acids; their GLC-MS properties compare favourably with those of PTHs, for which extensive data are available and with well-known drawbacks when it comes to definitive identification of some amino acids.[830] N-Ethoxycarbonylation is also a suitable sample derivatization approach.[831]

These methods have continued to be used for the identification of paint binding media in ancient paintings.[832]

A new approach in this area is provided by studies of sample conversion into α-keto acids through digestion with L-amino acid dehydrogenase, derivatization by o-phenylaminediamine yielding stable products.[833] Quantitative analysis of α-amino acids and α-keto acids in human plasma has been explored by GLC – MS, choosing pentafluorobenzyl esterification and N-methoxycarbonylation for sample derivatization.[834]

Enantiomer analysis through separation of derivatized amino acids over chiral stationary phases is also a valuable established application of GLC Modifications to the widely-used Chirasil-Val® stationary phase, through replacement of a proportion of methyl groups of the poly(siloxane) backbone by pentyl and hexyl groups, has been successful in reducing the polarity of the medium, and leading

to shorter retention times for some N(O)-trifluoroacetyl amino acid n-propyl esters.[835]

7.3 Ion-Exchange Chromatography – Papers falling outside the analytical heading have been located elsewhere in this Chapter, and there is some overlap with the HPLC coverage in the later Section 7.5. While there is a considerable volume of routine literature that occasionally provides new material – e.g. shortening of classical analytical protocols by careful choice of buffer constituents,[836] and optimization of the ninhydrin reaction response by deproteinization of samples by passage through a hydroxyapatite cartridge[837] – the non-routine points of interest in the recent literature refer to uncommon analytical targets (underivatized selenium-containing amino acids;[838] diaminopimelic acid;[839] and aspartylglucosamine[840]).

7.4 Thin-Layer Chromatography – Improvements to standard procedures are represented in semi-quantitative assays of amino acids, using mixed natural zeolite and microcrystalline cellulose layers,[841] and using the chromatographic adsorbent RP-18 as stationary phase.[842] Specific attention to the analysis of homocysteine has led to the recommendation that conversion into a disulfide, e.g. through S-(2-hydroxyethylthiol)ation using 2-mercaptoethanol, leads to a reliable assay.[843]

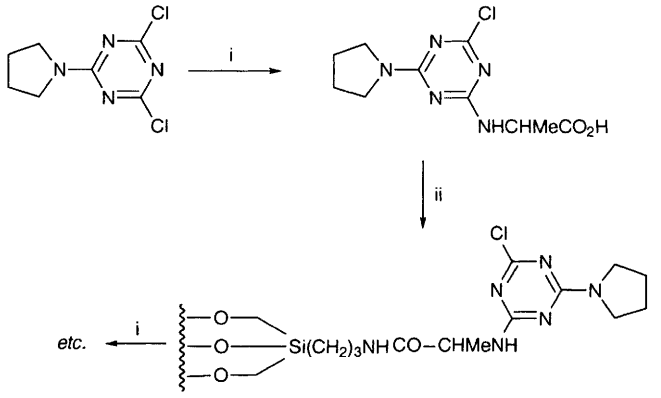
Over-pressured layer chromatography, a simple variant of standard TLC methodology, has been used by the laboratory from which the technique originated, for the separation of betaines of GABA and δ-aminovaleric acid from seaweed extracts.[844]

7.5 High Performance Liquid Chromatography – HPLC methods for the analysis of amino acids[845] and enantiomeric analysis protocols[846] have been reviewed.

An increasing proportion of the published work deals with underivatized amino acids, though this is a distorted reflection of the amount of work actually going on, since some standard derivatization protocols have become routine through regular optimization studies and do not justify further publications. The reason is also ascribable to the advances in instrumentation that favour the analysis of many of the more interesting target amino acids in underivatized form; they have light absorption, electrochemical and other characteristics that permit their detection at low concentrations. Studies cover the crosslinking amino acids desmosine and isodesmosine (detection at 275 nm),[847,848] pyridinoline and deoxypyridinoline (fluorescence and UV absorption; see also Ref. 10),[849] S-adenosyl-L-methionine and S-adenosyl-L-homocysteine (UV absorption at 267 nm),[850] and tyrosine and its 3-amino- and 3-nitro-derivatives (detection at 280 nm),[851] tryptophan (fluorescence,[852] and a similar method for tryptophan in comparison with its neuroactive relatives,[853] or electrochemical detection, and similarly for tyrosine derivatives[854]), ^{11}C-labelled methionine, DOPA and 5-hydroxytryptophan (the need for rapid analysis is met by purification with size-exclusion stationary phases),[855] DOPA and dopachrome,[856] and other protein

amino acids methionine (pulsed electrochemical detection[857] or electrothermal atomic absorption spectroscopy,[858] also applied to selenocystine) and homocysteine (ion chromatography with electrochemical detection).[859] Methionine is retained longer than histidine by poly(acrylamide) containing immobilized silver(I) ions from a buffer at pH less than 5, while the reverse applies at pH 7.[860] Studies of 2-oxo-L-histidine (Ref. 46) and phosphocysteine (Ref. 48), as well as work on the identification of D-amino acids in natural sources (Refs. 33-35), have also been supported by standard HPLC methods.

Determination of enantiomer ratios for amino acids is a continuing interest in increasingly diverse areas, some of which have emerged because the precision and sensitivity of the instrumentation have improved. Newly-proposed CSPs (i.e. stationary phases modified for this application by chiral additives or substitution by chiral groupings) include silica to which L-amino acids are attached (Scheme 43),[861] L-hydroxyproline attached to silica gel[862] and tris-3,5-dimethylphenylcar-



Reagents: i, L-Alanine; ii, *N*-hydroxysuccinimide, aminopropylsilylglass beads

Scheme 43

bamate-derivatized cellulose.[863] Synthesis of poly(siloxane)s carrying N-(3,5-dinitrobenzoyl)-β-amino acid and N-(1-naphthyl)leucine derivatives, and correlation of separation data, has been reported,[864] and optimization of CSP design has been carefully assessed for polymers substituted with chiral N-(1-naphthyl)leucine undecenyl ester and di-n-propylamide groupings.[865] The growing realisation that imprinted polymers are actually capable of doing the job, is emphasised by a growing number of papers from pioneers[866] and new adherents. These CSPs are familiar polymers, prepared from appropriate monomers in the usual way but including a homochiral molecule in the mix that is similar in structure to the analytical target, as illustrated in the trimethylolpropane trimethylacrylate/methacrylic acid copolymer prepared in the presence of a non-racemic dipeptide.[867] A new chiral stationary phase, prepared by attaching an L-tyrosine-

containing cup-shaped macrocycle to γ-mercaptopropylated silica gel, allows separation factors for Boc-DL-amino acids in the range 9 – 43 to be achieved, through elution with organic solvents.[868] An achiral C-18 stationary phase in association with a derivatized β-cyclodextrin component in the eluent[869] achieves the same result, as is the case with a mobile phase containing copper(II) complexes of L-phenylalaninamide used for the analysis of DL-2-hydroxyalkanoic acids.[870]

Standard derivatization methods with occasional new features are described for o-phthaldialdehyde – 3-mercaptopropionic acid (glutamine[871]), and OPA – 2-mercaptoethanol (for arginine and citrulline;[872] and for enantiomer ratio determination with a chiral crown ether-carrying stationary phase[873]). Oppolzer's group has reported a reliable protocol for the determination of D:L-ratios, based on the conversion of analyte into N-[N-(3,5-dinitrobenzoyl)-L-prolyl] derivatives (Ref. 194). Continuation of on-going studies has been described, where the aim has been to detect traces of D-enantiomers in L-amino acids using the OPA – N-isobutyroyl-L-cysteine reagent system[874] (see also Ref. 658; see Ref. 20 for a study of the corresponding OPA – N-acetyl-L-cysteine reagent; these authors found that increasing the time of contact of analyte and reagent from the usual 1–2 min to 15 min achieves enhanced fluorescence). The easy availability of several pharmaceutical amino acid formulations has prompted the need for better quality control of their amino acid ingredients, and some of these products that include racemic amino acids present the same analytical challenge, to establish that the enantiomer ratio is as close to the 50:50 value as is called for to meet the product specification.[875] N-[4-(6-Methoxy-2-benzoxazolyl)]benzoyl-L-phenylalanine or proline have been advocated for use as chiral derivatization reagents for enantiomer analysis of amino acids, through coupling with the 2,2′-dipyridyl disulfide/PPh_3 reagent and HPLC quantitation.[876] A 30 femtomole limit has been assessed for these derivatives ($\lambda_{excitation}$325 nm, $\lambda_{emission}$432 nm).

The effects of concentration and pH on the detector signal intensity have been studied for OPA – 2-mercaptoethanol – amino acid condensation products.[877] An established use for the OPA protocol is based on its exclusive compatibility with primary amino acids; its application to a physiological amino acid mixture, followed by derivatization with Fmoc-chloride[878,879] or DABSYL chloride,[880,881,882] removes primary amino acids from the analysis sample, and heightens the sensitivity of detection for proline and hydroxyproline.

Numerous reports have appeared describing analyses based on DABSYLation (phosphoserine, threonine and tyrosine,[883] amino acids in general,[884] S-sulfocysteine[885]), and on other familiar derivatization schemes: N-phenylthiocarbamoylation (PTC-amino acids in general;[886] S-carboxymethyl- and S-carboxyamidomethyl-cysteine[887]), thiocarbamoylation with a fluorescent chiral isothiocyanate (amino acid enantiomer ratios[888] ; see also Ref. 903) and with 4-(3-pyridinylmethylaminocarboxypropyl)phenyl isothiocyanate,[889] dansylation (amino acid enantiomer ratios through separation of derivatives over cyclodextrin-bonded stationary phases;[890] modification of retention times and enhancement of fluorescence detection, by SDS[891] and by bovine serum albumin[892]), 4-(5,6-dimethoxy-2-phthalimidinyl)phenylsulfonyl derivatives ($\lambda_{excitation}$315 nm,

$\lambda_{emission}$385 nm),[893] dinitrophenylation (4-hydroxypipecolic acid and pipecolic acid in *Acacia* at 100 pmol levels[894]), and preparation of Marfey derivatives (D- and L-phosphoserine in rat brain;[895] enantiomer ratios for protein amino acids[896]) and 7-chloro-4-nitrobenz-2-oxa-1,3-diazole derivatives. The last-mentioned derivatives were prepared from serum samples for analysis over a Pirkle CSP for their D-alanine, D-lysine and D-serine content,[897] and the performance of a variety of other benz-2-oxa-1,3-diazoles was also assessed in this study. In a rare example of post-column derivatization, after separation of enantiomers by ligand exchange chromatography, 7-chloro-4-nitrobenz-2-oxa-1,3-diazole was the chosen reagent.[898]

Specific reactions of side-chain functional groups may be exploited for analytical targetting, as in fluorescent labelling of thiols with N-(1-pyrenyl)maleimide.[899]

7.6 Fluorimetric Analysis – Studies consigned to this section are usually carried out in support of the development of chromatographic and other studies described in surrounding Sections of this Chapter.

N-(Acenaphthene-5-sulfonyl)amino acids show 10 – 25 times greater fluorescence yield compared with their familiar dansyl analogues.[900] Similar explorations of near-relatives of established fluorescent derivatives have been described for naphthalene-2,3-dialdehyde (already well established), its 1-phenyl analogue, and anthracene-2,3-dialdehyde;[901] 7-N,N-dimethylaminosulfonyl-4-(2,1,3-benzodiazolyl)isothiocyanate ($\lambda_{excitation}$387 nm, $\lambda_{emission}$524 nm for arenethiocarbamoyl derivatives of amino acids generated by this reagent)[902] and 4-(3-isothiocyanatopyrrolidin-1-yl)-7-nitro-2,1,3-benzoxadiazole (for fluorescent Edman-type derivatives useful for D:L-ratio determination for amino acids)[903] (see also Ref. 888); and (+)-2-methyl-2β-naphthyl-1,3-benzodioxole-4- and 5-carboxylic acid chlorides ($\lambda_{excitation}$310 nm, $\lambda_{emission}$370 nm for corresponding derivatives of amino acids, with a 0.1 pmol detection limit).[904]

7.7 Capillary Zone Electrophoresis, and Other Analytical Methods – This family of related techniques has developed from its inception in 1988 to a position of considerable importance, a trend that is continuing strongly. Reviews have appeared that give a clear assessment of the scope of current methods.[905,906,907]

The separation by CZE of free amino acids is improved by cyclodextrins as buffer additives.[908] Indirect absorbance detection was used for analyte quantitation in this case, while other studies have employed amperometric detection[909,910] (e.g. selenium-containing amino acids in human milk[911]), electrospray mass spectrometry[912] or post-column derivatization, e.g. by naphthalene-2,3-dialdehyde – 2-mercaptoethanol in a sensitive lysine assay.[913] Samples extracted from rat brain striatum *in vivo* through a microdialysis probe have been assessed for their GABA content by mass spectrometric analysis following CZE separation,[914] and analysis for tryptophan and kynurenine in rat brain samples obtained in the same way can be accomplished at attomole levels.[915]

Many of the standard sample preparation and derivatization procedures have been inherited from HPLC methods, but taking advantage of the greater

sensitivity and resolution that is achievable by CZE; thus, sample preparation by derivatization with naphthalene-2,3-dialdehyde – sodium cyanide (giving N-substituted 1-cyanobenz[*f*]isoindoles) has been illustrated for an assay of α-difluoromethylornithine.[916] PTHs continue to provide a stringent test for CZE methods,[917] seen against the voluminous background of HPLC studies that these derivatives have generated.

The related MEKC technique permits the estimation of tryptophan and related indoles at nanomolar levels based on laser-induced fluorescence detection,[918] and has been applied to the analysis of N^{ε}-pyrrolylnorleucine [the condensation product of lysine with the lipid degradation product, 4,5(E)-epoxy-2(E)-heptenal] after derivatization with diethyl ethoxymethylenemalonate (see also Ref. 724).[919]

CZE of esters of DL-tryptophan in buffers causing them to migrate towards the cathode can become an enantiomer separation procedure if the capillaries are coated with the protein transferrin.[920] The adaptation of CZE techniques for resolution, so as to deliver D:L-ratios, has been taken up enthusiastically; a broad study of the applicability of current derivatization procedures for enantiomeric separation by cyclodextrin-modified CZE, has been described.[921] Enantiomer analysis in the same way, of dansyl-DL-amino acids assisted by β-cyclodextrin[922] and methyl β-cyclodextrin[923] or alkyl glucosides,[924] as buffer additives, and similar studies using a γ-cyclodextrin zinc(II) complex[925] or sodium dodecanoyl-L-amino acid and poly(sodium 10-undecenoyl)-L-valinate micelles (separation of 3,5-dinitrobenzoyl-DL-amino acid isopropyl esters),[926] illustrate clearly-established methods. Amino acid enantiomers derivatized by condensation with 6-aminoquinolyl-N-hydroxysuccinimidyl carbamate have been separated by MEKC by including a synthetic homochiral surfactant in the buffer.[927] Enantiomeric separation of Fmoc-DL-amino acids in a cyclodextrin system has been compared with separation of diastereoisomers formed between DL-amino acids and (-)-fluoren-9-ylethyl chloroformate;[928] this, and an identical study using the enantiomeric reagent (the derivatized L-amino acid travels faster than its D-isomer),[929] favour the latter alternative protocol, which can deliver quantitative data for 3×10^{-10}M levels of analyte.

7.8 Assays for Specific Amino Acids – The growth of this topic is following its well-established direction towards ever more diverse biosensor applications for the detection and quantitative analysis of amino acids (the general topic has been reviewed[930]). However, a number of non-enzymic methods that exploit particular structural characteristics in some common amino acids have been explored; thus, the histidine content of samples can be assessed through differential pulse adsorptive stripping voltammetry[931] and cerium(IV)-generated chemiluminescence from tryptophan in a flow injection system is readily related to the concentration of analyte.[932] Use for the analysis of methionine in rat brain, of specific antibodies raised by injecting rats with methionine-bovine serum albumin conjugates,[933] and of ELISA methods (Ref. 849) are examples of techniques that are outside the general run of papers included in this Section over the years.

Use of an enzyme to generate H_2O_2 from L-α-amino acids, and to use this to

generate chemiluminescence in a flow injection system [leucine dehydrogenase and NADH oxidase co-immobilized on aminated poly(vinyl alcohol) beads][934] gives an illustration of developing methods. To describe a specific case in more detail, delayed chemiluminescence developed in luminol by horseradish peroxidase-generated H_2O_2 formed by copper(II)-catalyzed oxidation of L-cysteine with oxygen, may be measured to provide an estimate of the amount of this particular amino acid in complex mixtures.[935]

More conventional uses for enzymes are described for assays of L-glutamic acid and L-glutamine (immobilized glutaminase;[936] glutaminase *in situ* in kidney cortex tissue or in *E.coli*;[937] L-glutamic acid oxidase;[938,939] an L-glutamic acid oxidase – horseradish peroxidase pair, on a tin oxide surface for amperometric detection[940]) and a combined L-glutamic acid, L-glutamine and D-glucose biosensor.[941] Full details of appropriate methods for attachment of enzymes to micro-electrodes (glutaraldehyde condensation to aminopropylplatinized platinum wire; immobilization in an electropolymerized 1,3-di-aminobenzene film) show that the methods are simple, and this will encourage further expansion of interest in these devices. Construction of an L-tryptophan biosensor through immobilizing tryptophan-2-mono-oxygenase on to silica gel and using this in conjunction with an oxygen electrode,[942] and co-immobilization of D-amino acid oxidase and horseradish peroxidase by glutaraldehyde to bovine albumin[943] are also typical procedures.

Garlic tissue cells contain L-asparaginase, and can be used in conjunction with an ammonia gas electrode for an L-asparagine assay.[944] Innovative instrumental methodology continues to emerge in this area, illustrated by the involvement of a surface acoustic wave conductance sensor to detect the frequency shift as conducting ions are produced from the fragmentation of L-arginine by an arginase and urease mixture.[945]

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