1
Amino Acids

BY GRAHAM C. BARRETT

1 Introduction

The science of amino acids described here is based mainly on the literature of 1997. Criteria used for structuring this Chapter in all preceding Volumes of this Specialist Periodical Report have been used again for defining the papers chosen for citation here.

Thus, advances in the chemistry of the amino acids, and biological aspects impinging on their chemistry, have been the preoccupation for this Chapter, with routine aspects being excluded from consideration. Even so, the year-on-year increase in the number of papers eligible for inclusion here has continued, and has required a certain amount of restraint and retrenchment in the layout of this Chapter, with merging of some Sections.

Most of the papers cited here are the rewards of scanning the major Journals, and of scanning *Chemical Abstracts* (Issue 10 of Volume 126, up to and including Issue 9 of Volume 128).

2 Textbooks and Reviews

Monographs providing detailed coverage of enantioselective synthesis of β-amino acids[1] and protein sequence determination[2] have appeared; the latter contains a range of chapters relevant to the analysis of amino acids.[3] A text[4] that is aimed at advanced undergraduate and postgraduate students will also assist those active in amino acid and peptide research in chemical, biochemical, pharmaceutical and related research areas.

The biochemistry of L-arginine, and the context of this amino acid in biology, has been reviewed.[5] A survey of methods for the enantioselective synthesis of chiral drugs[6] also covers amino acid synthesis protocols. The occurrence of D-amino acids in free form (particularly D-serine and D-aspartic acid in human brain[7]) and in naturally-occurring peptides[8] has been reviewed, and the literature dealing with hypusine (a post-translationally modified L-lysine derivative) has been surveyed.[9] Other reviews cover the biosynthesis and metabolism of those amino acids (isoleucine, threonine, methionine and lysine) that derive from aspartic acid in higher plants,[10] the amino acid composition of bacterial and mammalian cells,[11] and the natural provenance of dihydroxyprolines.[12]

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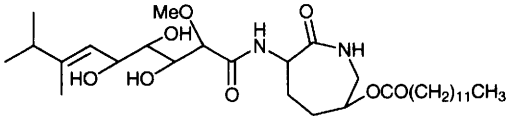
3 Naturally Occurring Amino Acids

3.1 Occurrence of Known Amino Acids – Leaving until later (Section 5.6) some citations that were traditionally placed here (*e.g.*, papers describing unusual results from preparative-scale isolation of amino acids from mixtures), the non-routine literature describes three further N^G,N^G-permethyl arginines in ribonucleoprotein,[13] N-acetyl-L-aspartic acid and N-acetyl-L-histidine as components of the vertebrate nervous system[14] and in the eye lens of goldfish and rats,[15] N-(17-hydroxylinolenoyl)-L-glutamine, known as volicitin, in a secretion of the caterpillars of beet armyworm that attracts predators,[16] four new N-acyl 2-methylene-β-alanine methyl esters (hurghamides A – D, from a Red Sea sponge *Hippospongia*),[17] and five new bengamides (*e.g.* 1) from the New Caledonian sponge *Jaspis carteri*.[18] Further information has been provided on S-methyl-L-methionine salts, with the suggestion that this widely-distributed cellular species (vitamin U) probably acts to diminish lipid peroxidation and monoamine oxidase activity.[19] New data on the neurotoxicity of domoic acid have been reported.[20]

Norvaline has been incorporated into leucine positions in recombinant human haemoglobin expressed in *Escherichia coli*, probably through mis-aminoacylation of $tRNA^{Leu}$ (norleucine is misincorporated in similar circumstances in place of methionine).[21] The tryptophan residue in the cardioexcitatory tripeptide amide H-Asn-Trp-Phe-NH_2 from *Aplysia kurodai* heart tissue is of the D-configuration (the all-L tripeptide amide is much less physiologically active).[22]

A continuing fascination is the occurrence of common amino acids in extraterrestrial samples, and the implications of the report[23] that small excesses of L-amino acids have been found in the Murchison meteorite have been considered.[24] The result is confirmed independently, and stable isotope analysis



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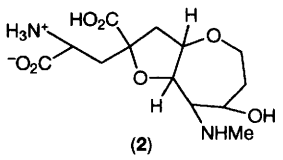

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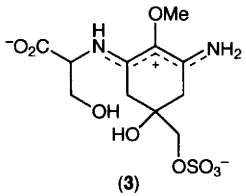

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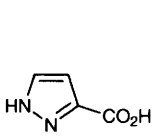
Three-dimensional features of molecules are depicted throughout this chapter as follows: Horizontally-ranged atoms and bonds, and ring atoms, are to be understood as being in the plane of the paper; substituent atoms and groups attached to these are to be understood to be ABOVE the page if ranged LEFTWARDS and BELOW the page if ranged RIGHTWARDS:

indicates that the amino acids are not terrestrial contaminants.[25] The amino acids involved include 2-amino-2,3-dimethylpentanoic acid (α-methylisoleucine; the 'L-enantiomers' among the four possible stereoisomers exist in 7.0 and 9.1% excess, respectively). However, other amino acids are present as racemates (aminoisobutyric acid, norvaline, isovaline and α-methylnorvaline). This might be interpreted to show that what Bada calls 'asymmetric influences' were at work on organic reactions occurring in prebiotic times.

The delivery of amino acids and other extraterrestrial compounds was an incidental feature of the catastrophe that wiped out the dinosaurs and most other species in the Cretaceous – Tertiary era. The same result is implied in the theory that is increasingly gaining support: the encounter of Earth with a giant molecular cloud (which better explains the lowered oxygen levels seen in amber-entombed contemporary air samples and lack of amino acids carrying oxygenated functional groups).[26]

3.2 New Naturally Occurring Amino Acids – The cis-fused hexahydro[3,2-b]pyran (2) that is reminiscent of domoic acid in its neurotoxic effects is a new dysherbaine from the Micronesian sponge *Dysidea herbacea*.[27] One of two palythines (3 and homologue CHMeOH in place of CH_2OH), new UV-B absorbing amino acids of the mycosporin family extracted from a reef-building coral *Stylophora pistillata*,[28] is the sulfate ester of one of the compounds present in *Pocillopora eydouxi*.[29] New mycosporin-like amino acids have been found in the Antarctic sea urchin *Sterechinus neumayeri*.[30] The first report of pyrazoles as natural products (4; and its 4-methyl homologue) concerns the sponge *Tedania anhelans*.[31]



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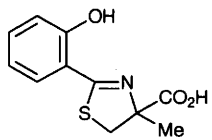

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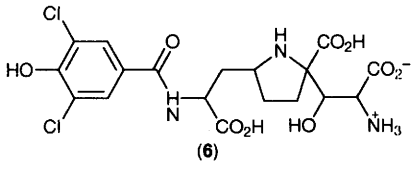
4-Methylaeruginoic acid (5) is a new cytotoxic imino acid from *Streptomyces* KCTC 9303.[32] *Eupenicillium shearii* PF1191 produces kaitocephalin (6; information on stereochemical features not yet available), a novel glutamate receptor antagonist that is a potent suppressor of kainate toxicity.[33] 1-Amino-3-methylcyclobutanecarboxylic acid has been identified in seeds of *Atelia glazioviana Baillon*, though without information on its stereochemistry.[34]

Cycasindene (7; see also Ref. 974) and cycasthioamide (8) have been found, together with eight known 'non-protein amino acids', in seeds of *Cycas revoluta* Thunb.[35] Fruiting bodies of *Clavulinopsis helvola* contain cis-DL-2-amino-3(cis),5-hexadienoic acid.[36] Root bark of *Calotropis gigantea* produces giganticine (9) which functions as an insect antifeedant.[37]

3.3 New Amino Acids from Hydrolysates – *Dysidea herbacea* contains (10), composed of two unusual α-amino acids, and is accompanied by a closely related



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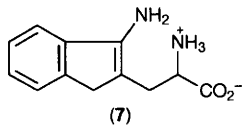

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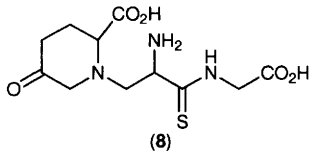

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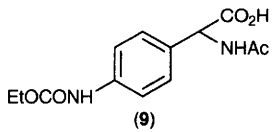

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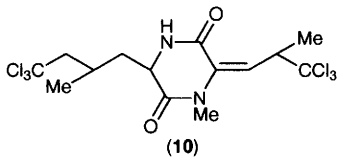
dioxopiperazine ($CHCl_2$ in place of CCl_3),[38] also found as the bis-N-methyl homologue dysamide D (10, NMe in place of NH, >$CHCH_2$- in place of >C=CH-), in *Dysidea fragilis*.[39] (-)-Phenylahistin, (11), from *Aspergillus ustus*, is a prenylated dehydrohistidine derivative.[40] A review[41] covers the identification of β-(methylthio)aspartic acid as a novel post-translationally modified amino acid in ribosomal protein S12 from *E. coli*.

Oscillaginin B, a tetrapeptide from the freshwater toxic cyanobacterium *Oscillatoria agardhii* contains the new amino acid, 3-amino-10-chloro-2-hydroxydecanoic acid.[42] Fischerellin B [(3R,5S)-3-methyl-5(E)-pentadec-5-ene-7,9-diynyl)pyrrolidin-2-one], a new algicide from the cyanobacterium *Fischerella muscicola*, is the lactam of a δ-amino acid.[43]



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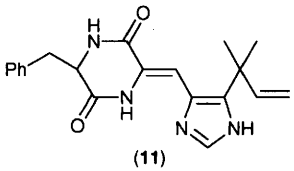

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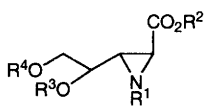
4 Chemical Synthesis and Resolution of Amino Acids

General reviews of amino acid synthesis are located in the appropriate subsections of this Chapter. More specific reviews relate to preparations of coded α-amino acids labelled with stable isotopes (^2H, ^{13}C, ^{15}N, and ^{18}O).[44] Examples throughout this Chapter describe preparations and uses of amino acids labelled with ^2H (Refs. 51, 221, 539, 543, 553, 566, 576, 584, 586, 806, 967), ^{11}C (Refs.113, 162, 805, 839), ^{13}C (Refs. 219, 221, 229, 442, 443, 538, 586, 781), ^{15}N (Refs. 228, 229, 442, 444, 547, 966), ^{17}O (Ref. 586), ^{18}F (Refs. 162, 260, 261, 913), ^{35}S (Ref. 893), ^{77}Se (Ref. 832) and iodine isotopes (Ref. 910). Preparations of aminoboronic and aminophosphonic acids are likewise scattered through Section 4, rather than grouped together as in recent previous Volumes.

4.1 General Methods for the Synthesis of α-Amino Acids, including Enantioselective Synthesis – *4.1.1 Amination of Alkanoic Acid Derivatives by Amines and Amine-related Reagents.* – These processes provide reliable routes to α-amino acids in many cases. They are illustrated in their simplest form in the conversion of chiral α-bromoacrylates into cis- and trans-1H-aziridinecarboxylates (12) through Michael-type reactions with ammonia,[45] and in the synthesis of methyl aziridine-2-carboxylate from methyl 3-(2,2,2-trimethylhydrazino)propionate bromide through N-N-bond cleavage;[46] in the reaction of dehydroascorbic acid with cyanate to give the amino acid carbamate (13) present in *Solanum tuberosum*;[47] and for the rhodium(II) acetate-catalysed decomposition of diazoacetates in the presence of compounds containing N-H groups [α-phenyl diazoacetate or $PhC(N_2)P(O)(OMe)_2$ giving N-substituted phenylglycines or corresponding phosphonates respectively].[48] 2-(N-Trifluoroacetylamino)alkanoic acids are formed from trifluoroacetamide and a 2-bromoalkanoate in the presence of a base, using phase-transfer catalysis.[49]

Some simple nitrogen species that are suitable for the task are indicated in these preceding examples. Azidolysis is also convenient, an interesting example starting with α-alkenyl N-Boc oxazolidines and leading *via* an epoxy-bromocyclocarbocation (formed by reaction with NBS) to β-aminoalkanols through azidolysis, and completed through routine elaboration.[50] Epoxidation of E-but-2-en-1-ol with tert-BuO_2H using L-(+)-di-isopropyl tartrate – titanium isopropoxide, followed by C^2H_3Li-LiI opening, mesylation, and azidolysis are the main steps in a synthesis of (2S,3S)-4,4,4-[$^2H_3$]valine,[51] and mesylate displacement by azide is also featured in a route to (2S,1′S,2′S)-2-(carboxycyclopropyl)glycine (see also Ref 271).[52] The L-lysine keto-amide derivative $BocNH(CH_2)_4CH(NH_2)CO$-$CONHPh$[53] has been prepared similarly by oxirane ring-opening azidolysis, and nucleophilic opening of the epoxide formed from 4-TBSO-$C_6H_4CH(OH)$-$CH{=}CH_2$ is the crucial step in a synthesis of (2S,3R)-β-hydroxytyrosine.[54] A new procedure for the reductive transformation of azido esters into N-Boc-amino acid derivatives using $Pd(OH)_2$-C, $EtSi_3H$ and Boc_2O in ethanol has been outlined.[55] Mitsunobu azidolysis of the homochiral secondary alcohol $TolS(O)CH_2$-$CH(OH)CH_2F$ followed by sulfoxide cleavage through non-oxidative Pummerer rearrangement gives 3-fluoro-D-alanine.[56]



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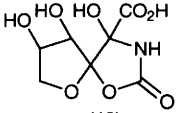

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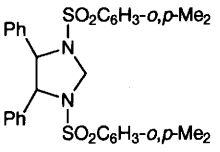


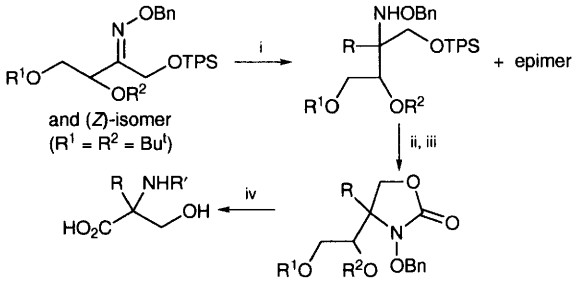
(14)

(Ethoxycarbonyl)nitrene, produced through photolysis *in situ* of ethyl azidoformate, reacts with β-silylated silyl ketene acetals $RCH(SiMe_2Ph)CH{=}C$-$(OMe)OSiMe_2Bu^t$ to give preferentially anti-β-silylated α-N-(ethoxycarbonylamino) esters.[57] Full details are available[58] describing the preparation of

N-substituted 3-alkyl-aspartic acids (Vol. 29, p. 13) through conjugate addition of amines to fumaric acid under catalysis by β-methylaspartase.

Enantioselective electrophilic amination by di-tert-butyl azodicarboxylate (S:R-ratios ranging from 90:10 to 95:5) of an achiral N-acyloxazolidin-2-one (*cf.* Scheme 5; H in place of Ph and R), is efficiently catalysed by (14), prepared from the bis-sulfonamide and dimethylmagnesium.[59] The use of this amination reagent, applied to preparation of α-amino-β-hydroxy acids from β-hydroxyester enolates, has been reviewed.[60] Palladium(0)-catalysed allylic amination of homochiral allyl acetates by simple amines, followed by oxidation, gives arylglycines and glutamic acid derivatives.[61]

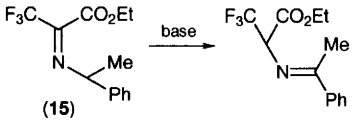
Oxime ethers of 2-furyl ketones $BzlON{=}CR^1R^2$ (R^2 = 2-furyl) undergo enantioselective alkylation with a homochiral boron complex, the furan moiety providing the carboxy group in the final stage of a novel α-amino acid synthesis (a route whose expense may be justified in certain circumstances).[62] A more straightforward method (see also Ref. 879) uses an O-benzyloxime (α-alkylation using an organolithium compound leading to αα-dialkylglycines; Scheme 1).[63]



Reagents: i, RLi; ii, TBAF; iii, carbonyldi-imidazole; iv, routine processing of 1,2-diol

Scheme 1

The (R)-O-(1-phenylbutyl) ether of cinnamaldoxime has provided the substrate for alkylation using an organolithium compound in a diastereoselective synthesis of α-amino acids.[64] A proton shift induced by NEt_3 in the homochiral imine (15) starts a route to βββ-trifluoro-L-alanine.[65] Nitrones formed from aldoximes (*e.g.* from the protected L-gulose oxime, 16 in Scheme 2) have served in a synthesis of the N-terminal component of Nikkomycin Bz.[66]



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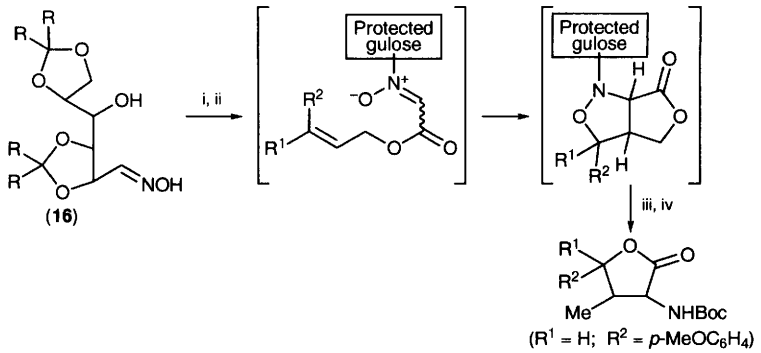
A common feature of many of the preceding examples is their dependence on a supply of halogeno-acids and analogues, and a route to α-halogeno-amides from αα-dicyanoepoxides by reaction with a tertiary amine hydrohalide is notable.[67] Mitsunobu condensation of $Me_3Si(CH_2)_2SO_2NHCO_2Bu^t$ and a chiral cyano-



Reagents: i, methyl glyoxylate hemiacetal, toluene, reflux; ii, (*E*)-*p*-methoxycinnamyl alcohol; iii, $Mo(CO)_6$, 1% HCl-MeCN; iv, MsCl then NaI, $Bu^n{}_3SnH$ after $NH_2 \rightarrow$ NHBoc

Scheme 2

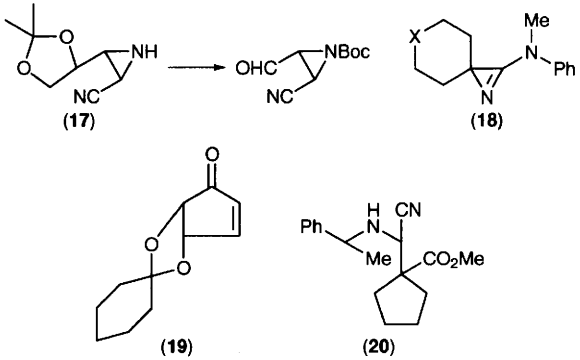
hydrin provides protected α-amino nitriles that are readily converted into α-amino acids.[68]

Electrophilic amination of chiral amide cuprates [from RCH_2COX (X = chiral amide moiety) with nBuLi/CuCN] by lithium tert-butyl N-tosyloxycarbamate illustrates further the improving prospects for carbamates as amination reagents in amino acid synthesis.[69] Benzyl carbamate serves in a route to 1-(Z-amino)-2-arylmethyl phosphinates ZNHCHArP(O)(Ph)R through condensation with ArCHO and dichlorophenylphosphine with acetyl chloride,[70,71] and in an equivalent route to phosphonates using an alkoxydichlorophosphine;[72] phenyl α-(Z-amino)benzyl phosphonates ZNHCHArP(O)(OH)OPh are obtained similarly.[73]

N-(Arene- or methanesulfonyl)aziridinecarboxylates formed as above (see also Refs. 281, 282) can undergo PdL_4-catalysed isomerization (L = ligand) as detailed in a study of five sets of four stereoisomers.[74] The expected higher stability of chiral alkyl (2E)-4,5-cis-(2E)-products, compared with their isomers, was established in this study. β-Erythro-substituted aspartic acids can be obtained through stereospecific nucleophilic ring-opening of dimethyl aziridine-2,3-dicarboxylates,[75] and hydrogenolysis of an aziridine to give (2S,3S)-(-)-3-methylphenylalanine has been described (Ref. 281). tert-Butyl (2R,3R)-2-cyano-3-formylaziridine-1-carboxylate has been obtained from the glyceraldehyde acetonide (17).[76] Further examples of ring-opening of 2H-azirin-3-amines (18; formed from N-methylanilides using $LiNPr^i{}_2$/DPPCl), *e.g.* with PhCOSH, leading to heterocyclic α-amino acid derivatives, have been reported (*cf.* Vol. 29, pp. 6, 22).[77]

Both syn- and anti-β-methyl-L-phenylalanines have been prepared starting from (2S,3S)-2,3-epoxy-3-phenylpropan-1-ol, ring-opening with $Me_2CuCNLi_2$, then mesylation and azidolysis being followed by routine functional group development.[78]

The classical Strecker and Bucherer-Bergs syntheses are also amination processes, illustrated for the former in preparations of (R)-N-Boc-3,5-dichloro-4-methoxyphenylglycine,[79] and for the latter with syntheses of '3-phosphonocyclo-

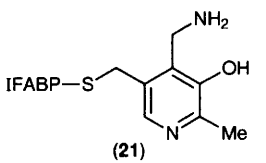


(17) (18) (19) (20)

butyl amino acids' (*i.e.* 1-amino-3-diethylphosphonocyclobutane-1-carboxylates) from the corresponding cyclobutanone.[80] (+)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (a potent and selective Group 2 mGluR agonist) has been prepared by cyclopropanation of cyclopentenone (19) and Bucherer-Bergs synthesis.[81] 4-Aminocyclohexanones have been converted into N,N'-Boc-hydantoins by the Bucherer-Bergs procedure followed by treatment with Boc_2O,[82] also the basis of preparations of 1-aminocycloalkanecarboxylic acids (see also Section 4.4) and α-methyl-(4-carboxyphenyl)glycine.[83]

The asymmetric Strecker synthesis has been illustrated in an intramolecular version[84] for syntheses of both enantiomers of α-benzyl and α-carboxymethyl-serine, and for an improved synthesis of 'L-cyclopentylaspartic acid' [(S)-1-(2α-aminocarboxymethyl)-1-carboxycyclopentane] *via* the (S)-α-methylbenzylamino nitrile (20) on a large scale.[85]

The amination by pyridoxamine of an α-keto acid is a classical biogenetic route to amino acids, a fact that has stimulated a search for a laboratory equivalent, seen in the generation of glutamic acid using the pyridine reagent (21) covalently bound to the cysteine residue (Cys-60) of intestinal fatty acid-binding protein IFABP (*cf.* Vol. 29, p.13).[86] The amination rate is 62 times faster than that effected by pyridoxamine itself. Amination of α-keto-acids has also been illustrated for tert-leucine with an adaptation of the Leuckart reaction (Scheme 3),[87] and for syntheses of vinylglycines using a modified Mannich reaction (Scheme 4)[88] and α-aryl and α-heteroarylglycines.[89]



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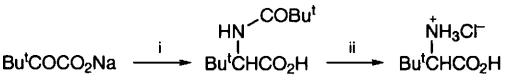
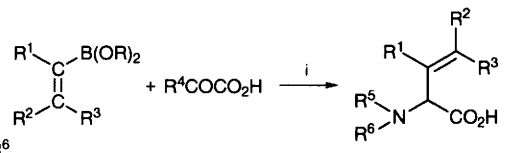
'Multicomponent reactions' employing amination reactions, used in α-amino acid synthesis (the Strecker synthesis, and Ugi and amidocarbonylation routes, amongst others covered later in this Section), have been reviewed.[90]



Reagents: i, $NH_4^+HCO_2^-/HCO_2H$, reflux; ii, 6M HCl, reflux

Scheme 3



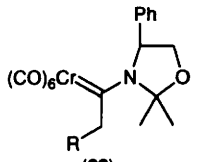
Reagent: i, R^5NHR^6

Scheme 4

The catalytic asymmetric aminohydroxylation of alkenes developed by Sharpless and co-workers (used in a synthesis of phenylisoserine;[91] see Vol. 29, p. 46 and Section 4.15, Refs. 400-403) has been reviewed;[92] this route provides aminoalkanols that are readily converted into α-amino acids, as illustrated with a synthesis of (S)-1-naphthylglycine *via* a homochiral 2,3-dihydroxyalkylamine.[93] Another enantioselective approach giving 3-amino-1,2-diols starts with a glyceraldehyde-derived α-alkoxynitrone (a relative of 16, see Scheme 2), and its arylation with a Grignard reagent in the presence of $ZnBr_2$ and Et_2AlCl.[94]

4.1.2 Carboxylation of Alkylamines and Imines, and Related Methods – Addition of 2-lithiofuran or 2-lithiothiazole to a sugar nitrone is essentially a carboxylation process as in the examples at the end of the preceding section;[95] this approach has been reviewed.[96] Attack of the 3-alkoxy-1-cyanopropene carbanion on a chloroformate is another hidden example of carboxylation,[97] and the classic route is illustrated by carboxylation by CO_2 after lithiation of a benzylamine. This leads to (R)-phenylglycines when (-)-sparteine is part of the reagent system (see also Ref. 329).[98] Use of (-)-sparteine – lithium carbanion pairs in enantioselective synthesis has been reviewed.[99]

A further example of carboxylation *via* chromium carbene complexes (Vol. 28, pp. 7, 15) employing a homochiral N-alkyloxazolidine has been published, illustrating alkylation (22; R = H to R = allyl, *etc*) and photolysis in the presence of a phenol to give the corresponding aryl ester.[100]



(22)

Achiral N-(mesitylsulfonyl)imines add homochiral α-bromovinyl-lithium species to give α-amino acid methyl esters with better than 95% e.e., after ozonolysis in methanol: MesN=CHR → MesNHCHRCBr=CR^{1}R^2 →

$MesNHCHRCO_2Me$.[101] The asymmetric synthesis of amines $NH_2CHR^1R^3$ by nucleophilic 1,2-addition of metal reagents R^3ML to imines $R^1CH{=}NR^2$ has been reviewed.[102] Equivalent syntheses of amino phosphonic acids include addition of hypophosphorous acid H_3PO_2 to an aldoxime, and mild oxidation of the resulting aminophosphinic acid.[103] An asymmetric synthesis of α-aminophosphonic esters has exploited the addition of a metal phosphite to the chiral sulfinamide $TolS(O)N{=}CHAr$.[104]

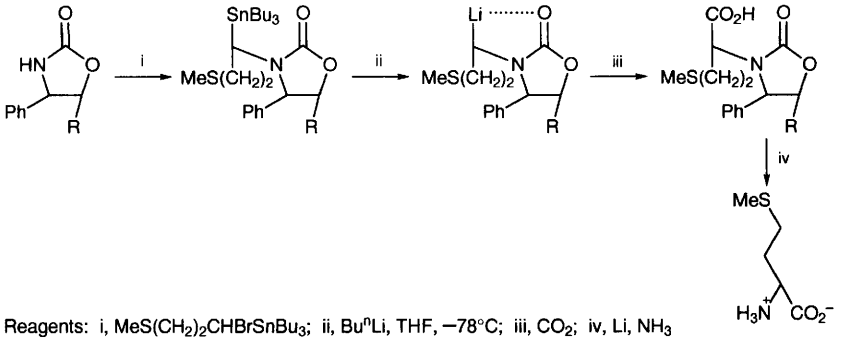
Conversion of a phthalimidoketene $PhtNCR{=}C{=}O$ into the corresponding ester through addition to (R)-pantolactone generates a new chiral centre with good e.e. favouring the L amino acid;[105] this opens up a new deracemization protocol for N-phthaloyl-DL-amino acids.

The conversion of β-amino acids into α-amino acids [β-lactams give N-carboxylic amino acid anhydrides (Vol. 29, pp.23, 74) through NaOCl/TEMPO oxidation] has always been recognised to be limited in scope, since it is dependent on the supply of homochiral starting materials of known stereochemistry that are stable to the reaction conditions, but a further application, a tert-leucine synthesis, shows that good yields are obtainable.[106]

4.1.3 Use of Chiral Auxiliaries in Amino Acid Synthesis – Under this heading, established methods are included in which a homochiral grouping (N-acyl, ester, or aminoacylamide, *etc*) is released for re-use, in principle, at the end of an α-amino acid synthesis. Evans' oxazolidinones fall in this category, and their applications have been reviewed.[107] Typical examples include its use *via* azides, for syntheses of the four stereoisomers of β-methyl-3-(2′-naphthyl)alanine,[108] β-isopropylphenylalanine,[109] β-isopropyltyrosine,[110] and β-isopropyl-2′,6′-dimethyltyrosines[111] in the same approach already described in numerous papers from the Hruby group; the same method is used for the synthesis of 3-aminocarbonylmethylprolines (as glutamine mimetics).[112] Untypical examples include a route to L-methionine (Scheme 5) that can be completed in less that 40 minutes, so is potentially useful for the production of α-amino acids labelled in their carboxy group with ^{11}C.[113] A resin-tethered oxazolidinone has been used for α-hydroxy acid synthesis.[114] The indeno-oxazolidine (23) contributes efficient diastereoselection to the Wittig rearrangement of its N-allyloxyacetyl derivative, the resulting allylic α-hydroxy acid being converted into an amino acid through azidolysis and ensuing manipulations.[115] A route to L-proline involves allylation of the enolate of (S)-1-benzyloxycarbonyl-2-tert-butyl-3-methyl-1,3-imidazolin-4-one, hydroboration of the C=C bond and cyclization.[116] Double alkylation with (Z)-3-chloro-2-chloromethylprop-1-ene gives (24) and (25) from which (-)-baikiain and (-)-4-methyleneproline respectively were obtained in high yield.[117]

The related (4R,5S)-imidazolin-2-one may be N-acryloylated through an improved protocol employing DABCO as base.[118] Diastereoselective ring expansion of an N-(N′-acylaziridin)oyl moiety linked to this homochiral imidazolin-2-one, to give an oxazoline, is the basis of a route that provides homochiral β-hydroxy-α-amino acids.[119]

Oppolzer's camphorsultam continues to be used, *e.g.* for syntheses of enantiomers of amino acids bearing o- and p-carboranyl substituents in side-chains,[120] of

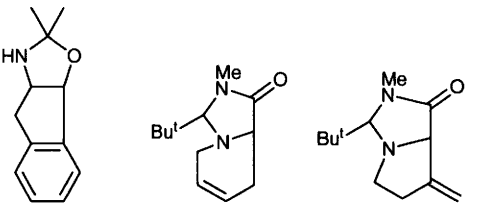


Reagents: i, $MeS(CH_2)_2CHBrSnBu_3$; ii, Bu^nLi, THF, −78°C; iii, CO_2; iv, Li, NH_3

Scheme 5

L-2,3,5,6-tetrafluoro-4-(phosphonomethyl)phenylalanine and L-4-(phosphonodifluoromethyl)phenylalanine,[121] and L-(6,7-dimethoxy-4-coumaryl)alanine (Scheme 6).[122] In a typical application, the sultam formed from glyoxylic acid oxime ether RON=CHCOX* (X* = sultam chiral auxiliary linked through N) undergoes highly diastereoselective radical addition ($RI/Bu_3SnH/Et_3B$) to give D-α-amino acids after standard functional group modifications.[123]

Details have been provided for routes employing ψ-ephedrine;[124] it is N-acylated in high yield and enolates of the resulting amides undergo highly diastereoselective alkylation (as described in Vol. 29, p. 22). Decagram quantities of L-prenylglycine (needed for conversion into Seebach's oxazolidinone) have been prepared using ψ-ephedrine glycinamide in this cost-effective route.[125] The early Seebach methodology based on an L-proline-derived auxiliary, given the label 'self-regulation of chirality', has been reviewed.[126]



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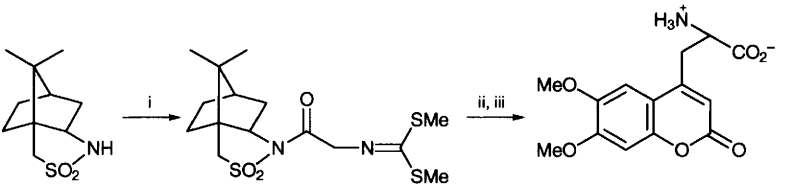
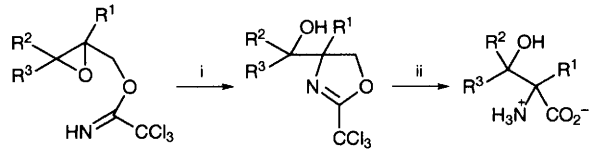


Reagent: i, $(MeS)_2C{=}NCH_2CO_2H$, unspecified coupling protocol; ii, BuLi, then 4-chloromethyl-6,7-dimethoxycoumarin; iii, H_3O^+, then aq. LiOH, then neutralisation

Scheme 6

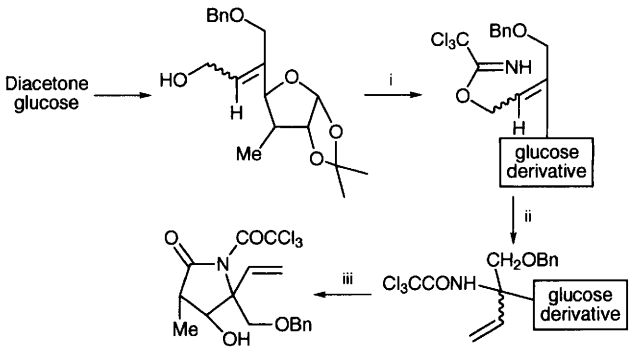
4.1.4 Use of Rearrangements Generating a Carbon–Nitrogen Bond – Rearrangement of trichloroacetimidates provides the stereochemical security associated with an electrocyclization process, and a clear example (Scheme 7) illustrates the preparation of α-substituted serines in good yields.[127] A new synthesis of (+)-myriocin illustrates the value of this rearrangement in routes to αα-disubstituted glycines.[128] A synthesis of (+)-lactacystin (Scheme 8) starts from D-glucose so as to generate the correct stereochemistry in the α-substituted α-amino acid moiety[129] (routes to this compound published in 1992-1994 differ in principle, since they all start from another amino acid).

A process used for the synthesis of α-allyl α-amino acids involves α-allylation of a homochiral α-cyanoalkanoate $R^1CH(CN)CO_2R^2$ followed by Curtius rearrangement with preservation of the initial stereochemistry.[130]



Reagents: i, Lewis acid, Et_2AlCl; ii, hydrolysis, then $CH_2OH \rightarrow CO_2H$

Scheme 7

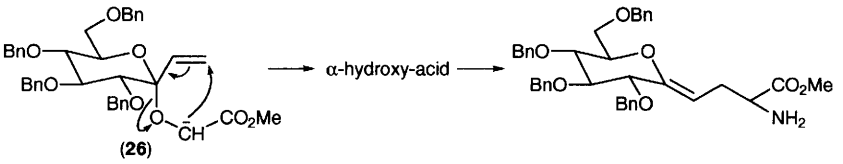


Reagents: i, NaH, then Cl_3CCN; ii, 140 °C, toluene; iii, H_3O^+ then aq. $NaIO_4$, then CrO_3–acetone

Scheme 8

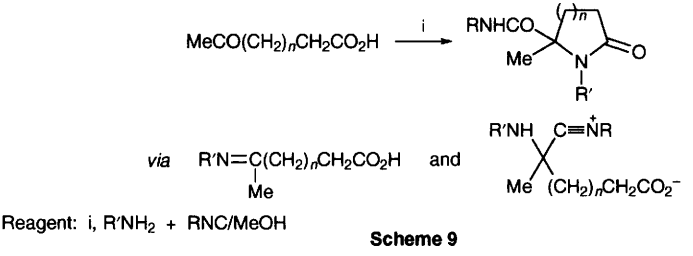
4.1.5 Other Rearrangements - [2,3]-Wittig rearrangement of a 1-vinylglycoside (26) is the essential step in a synthesis of a β-glycosidylalanine (obtained through amination of the intermediate hydroxyacid), useful as a C-analogue of β-D-glucopyranosylserine.[131]

4.1.6 Amidocarbonylation and Related Processes – The scope of this approach, reviewed recently,[132] is seen in a route from an alkene $RCH{=}CH_2$ with acetamide and CO to give α-(N-acetylamino)alkanoic acids $RCH_2CH_2CH(NHAc)CO_2H$ (R = C_8, C_{10}, C_{12}); the sodium salts have commercial uses since they yield viscous



aqueous solutions.[133] N-Acetylphenylalanines are formed from the aldehyde with acetamide and CO in a reducing atmosphere (H_2-DIPHOS with a cobalt carbonyl catalyst).[134] Palladium complexes catalyse the condensation of aldehydes and amides with carbon monoxide to give N-acylamino acids in good yields (99% for the synthesis of valine).[135]

The scope of the Ugi 'four-component condensation' in combinatorial synthesis, leading to amino acid derivatives (see Vol. 29, p.7), has been extended.[136] The same chemistry (without the combinatorial context) has been used for β-lactam synthesis,[137] and includes an intramolecular three-component version (Scheme 9) suitable for the synthesis of 7- and 8-membered lactams.[138] A so-called Ugi 'five-component condensation' uses an alkanol, an amine, an aldehyde, an isocyanide, and CO_2, COS, or CS_2 as oxidized carbon source, and leads to N-protected α-amino acid amides $R^1O_2CNR^2CHR^3CONHR^4$.[139]



Scheme 9

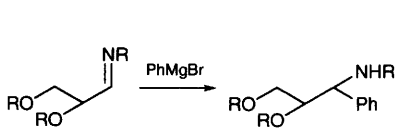
4.1.7 From Glycine Derivatives – The most familiar textbook example under this heading concerns alkylation of diethyl acetamidomalonate, $AcNHCH(CO_2Et)_2$, although conducting this approach with simpler glycine derivatives is now more common. It has been used for syntheses of β-(2-anthraquinolinyl)alanine,[140] 4-fluoro-3-nitrophenylalanine and its 3-fluoro-4-nitro-isomer (see also Ref. 326),[141] and DL-3-(2-furyl)-alanine.[142]

The new chiral atropisomeric αα-disubstituted glycine, α-(1,1'-binaphthylmethyl)-α-methylglycine and its biphenylmethyl analogue, have been prepared from a Schiff base of glycine tert-butyl ester, $4\text{-Cl-}C_6H_4\text{-}C{=}NCH_2CO_2Bu^t$.[143] Corresponding synthesis of a biphenyl-based amino acid has been reported.[144] The 1,1-bis(alkylthio)methylideneglycine esters $(RS)_2C{=}NCHR^1R^2$, have a long history of service in this context, recent acylation studies revealing their further possibilities in synthesis of α-alkyl-β-hydroxy-α-amino acids[145,146] (see also Scheme 6). The α-aminonitrile derivative $Ph_2C{=}NCH_2CN$ has been used for the

synthesis of 2-amino-6-hydroxyalk-4-enoic acids,[147] and as substrate for the preparation of γ-substituted vinyl phosphonates through Pd(0)-catalysed alkylation by CH_2=CHCH(OCO_2Me)P(O)($OR)_2$ (also used for preparation of carboxylates in an analogous route).[148] Alkylation of Ph_2C=NCH_2CO_2Me by fluoroalkyl bromides $RCHFCH_2Br$ gives α-amino-γ-fluoroalkanoic acids,[149] while double alkylation of PhCH=NCH_2CO_2Et (at the α-carbon and at nitrogen) gives 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives when an o-xylylene dibromide is used.[150] Enantioselective alkylation can be effected (67 – 94% e.e.) using a *Cinchona* alkaloid-derived quaternary ammonium salt as phase transfer catalyst[151] or by conducting the alkylation in a homochiral reverse micelle medium.[152]

Esterification of these glycine Schiff bases to solid supports gives substrates that can be αα-di-alkylated in the usual way,[153] and mono-α-alkylated by unactivated alkyl halides.[154]

Numerous further examples of applications of glycine Schiff base synthons appear in this year's literature, as they have in all preceding Volumes, and for use in the preparation of aminodiols through addition of phenylmagnesium bromide to (27) with total diastereoselectivity leading to either (R)- or (S)-phenylglycine depending on the reaction conditions;[155] the same synthon has been used to prepare (2R)-4-oxopipecolic acid from the Danishefsky diene (see also Ref. 290) and L-vinylglycine using vinylmagnesium bromide,[156] and L- or D-trans-β-hydroxypipecolic acid through addition to 2-furyl TBS ether.[157] The long-established alkylation of the nickel(II) complex of an L- or D-prolyl-N-aryl-ideneglycine Schiff base (*cf.* Vol. 29, p. 15) has been used for the synthesis of L- and D-ββ-diphenylalanines,[158] (2S,4R)-4-methylglutamic acid [through Michael addition to methyl methacrylate catalysed by the chiral phosphine (4R,5R)-TADDOL, (28)],[159] (2S,3S)-3-trifluoromethylpyroglutamic acid,[160] and 3-per-fluoroalkyl-2,3-diamino acids.[161] Careful kinetic studies have shown that a five-minute alkylation by a substituted benzyl halide using acetone as solvent leads to satisfactory product yield and good diastereoselectivity, so the process is therefore suitable for the preparation of amino acids labelled with short-lived radio-isotopes (specifically, [β-^{11}C]-L-DOPA and [6-^{18}F]-L-DOPA).[162]



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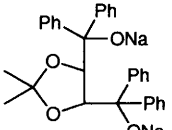
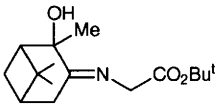


(28)

The homochiral Schiff base (29) is well suited to asymmetric amino acid synthesis, alkylation using $ICH_2CHMeOSiMe_3$ and standard elaboration giving L-γ-hydroxynorvaline.[163] The equivalent camphorsulfonamide Schiff base can be alkylated with representative halides and usually gives (S)-α-amino acids [but benzyl halides give (R)-products] and e.e.s are only moderate.[164]

An unusual glycine-related imine, MeC(OEt)=$NCH(CO_2Me)_2$, *i.e.* an imidate,

has been used in β-hydroxy-α-amino acid synthesis through its propensity to undergo cycloaddition to aldehydes to give oxazolines.[165] An isocyanoacetic acid derivative is at first sight the prototypical glycine imine, but although this is oversimplifying its structure, it behaves as an imine with aldehydes to give oxazolines (and thence to α-amino-β-hydroxyacids).[166] Methyl isocyanoacetate forms oxazolines through reaction with ketones, but its diastereoselectivity is a more subtle detail that has been probed to establish the control exerted that is by transition metal catalysts and base.[167] Isocyanoacetates undergo double alkylation by a quinoxalylxylylene dibromide under solid-liquid phase-transfer catalysis, to give (30),[168] a protocol applied to other 1,2-bis(bromomethyl)arenes.[169] p-Boronophenylalanine has been prepared from ethyl isocyanoacetate.[170]



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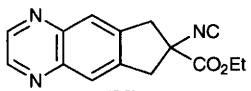
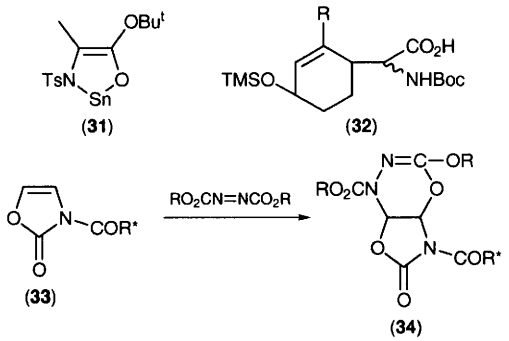


(30)

Protected α-bromoglycine offers access to nucleophilic attack; thus, anionic organotransition metal compounds react with α-bromoglycines to open up access to new organometallic amino acids.[171] Related glycine derivatives behave as nucleophilic synthons in standard amino acid syntheses, and α-acetoxyglycine deserves to be more widely used; thus a reasonable level of deracemization accompanies $Pd(OAc)_2$/(+)-BINAP-catalysed alkylation of its N-diphenylmethylidene ester $Ph_2C{=}NCH(OAc)CO_2Me$ by malonate anions to give β-carboxy-L-aspartates.[172] Organozinc reagents Ar_2Zn react with the protected acetoxyglycine in an efficient α-arylglycine synthesis,[173] and α-triazolylglycines are formed from α-amino-α-azidoglycine esters through cycloaddition of alkynes.[174] α-Hydroxyglycine is referred to in Refs. 88, 89. The new α-(toluene-p-sulfonyl)glycine derivative, $BocNMeCHTsCO_2Et$, is amenable to α-allylation, followed by reductive removal of the toluene-p-sulfonyl group (Mg/MeOH).[175] The phosphonate $BocNHCH[P(O)(OMe)_2]CO_2Me$ condenses with a homochiral aldehyde, illustrated for an efficient synthesis of C-galactosyl-L-serine using tetra-O-acetyl-D-galactopyranosylacetaldehyde, and Rh[DuPHOS]-catalysed hydrogenation of the intermediate αβ-dehydroamino acid.[176]

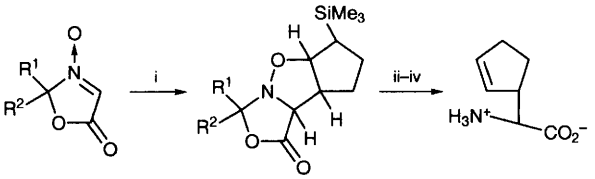
Phase-transfer catalysed alkylation of glycine derivatives,[177] and the wider range of alkylation, Michael addition, and aldolization of enolates,[178] have been reviewed. Deprotonation of N-(toluene-p-sulfonylamino)alkanoates with an excess of LDA and subsequent transmetallation with tin chloride probably results in the formation of the chelated enolate (31), which readily undergoes aldolization and gives trihydroxypipecolates (*alias* 'azasugars'), through addition to a protected aldotetrose followed by Mitsunobu ring closure.[179]

Claisen rearrangement of glycine enolates of homochiral diols provides an unusual example of a well-established process, leading to the cyclohexenylglycine (32) with chiral centres located with known configuration.[180] Enolates from $Ph_2C{=}NCH_2CO_2Me$ or $Bn_2NCH_2CO_2Bu^t$ and LDA have also been employed in



a synthesis of α-glycosyl α-amino acids (*cf* Ref. 131) through addition to an α-D-ribohexofuranos-3-ulose.[181]

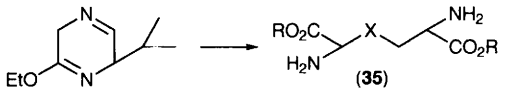
Oxazolones continue to hold their place as glycine derivatives that are amenable to C-alkylation (*cf* Ref. 920), illustrated by reaction of 4-ethoxycarbonyl-2-phenyl-oxazol-5(4H)-one with aryl-lead triacetates and with (E)-styryl-lead triacetates, to give α-aryl- and α-vinylglycines.[182,183] N-[cis-2-Alkoxy-1-apocamphanecarbonyl]oxazol-2-ones (33) undergo [4 + 2]-cycloaddition with dialkyl azodicarboxylates to give (34) and its isomer, from which α-amino acids and α-amino aldehydes are obtained by ring-opening and functional group manipulation.[184] Oxazol-4-one N-oxides formed from homochiral cyclic ketones through cycloaddition to nitrosoketene represent a distant relative of glycine that is a willing partner in cycloaddition reactions, leading to cyclopentenylglycines for example (Scheme 10).[185]



Reagents: i, 1-trimethylsilylcyclopent-2-ene, BF_3–Et_2O; ii, aq. $NaHCO_3$, Amberlite IRC–50; iii, H_2, Pd–C; iv, BF_3–Et_2O, Dowex 50W–X4

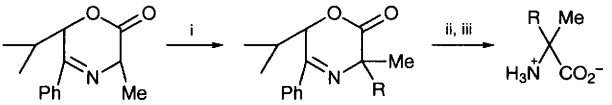
Scheme 10

Homochiral 2,5-diethoxy-3-isopropylpiperazine, now the favoured substrate for the Schollkopf amino acid synthesis, amounts to another hidden form of a glycine Schiff base. Further examples of bis(amino acid)s have been synthesized, *e.g.* diaminosuberic acid and analogues [35; X = -CH=CH- or -CH(OH)-CH(OH)-],[186] analogues with X = (Z)- or (E)-CR=CH-,[187] and with X = -CH=CH-,[188] and (35; X = substituted thiophen groupings),[189] typically using diiodoalkanes and -arenes with Pd-CuI for alkylating the Schollkopf synthon. (2S,9R)-2,9-Diaminododecanedioic acid has been prepared (using the higher order bislactim ether lithium cyanocuprate for creation of the first chiral centre,



(35)

and using Evans oxazolidinone methodology to introduce the second),[190] and similar manipulation of (S)-4-benzyloxazolidin-2-one has provided cyclopropane bis(glycine)s (35; X = cyclopropyl).[191] Use of the Schollkopf synthon provides D-(4α-cyanophenyl)alanine,[192] and 5-, 6-, or 7-membered ring 1-aminocycloalkanecarboxylic acids,[193] 1-amino-2-hydroxycyclopent-3-enoic acid,[194] also other 1-aminocycloalkene-1-carboxylic acids[195] through ruthenium(II)-catalysed ring-closing metathesis with alkenes. Alkylation by a brominated 3-methyl-6-methoxyindole to give the appropriate tryptophan is a key step in an enantiospecific total synthesis of tryprostatin A,[196] and a broad range of brominated tryptophans has been prepared in this way,[197] also 6-methoxytryptophans.[198] Face-selective 1,6-addition to 1E,3E-butadienylphosphonates opens up access to 2,3-anti-4E-2-amino-6-phosphonohexenoic acid derivatives.[199]

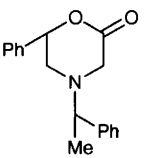


Reagents: i, K_2CO_3, RBr, TBAB, MeCN, r.t., or allylic carbonate/[$Pd(PPh_3)_4$]-dppe; ii, 6M HCl, 150 °C; iii, propylene oxide/EtOH

Scheme 11

Homochiral oxazin-2-ones, *e.g.* the (3R,6R)-3-methyloxazinone shown in Scheme 11, although little used so far for analogous asymmetric syntheses, have been shown to undergo diastereoselective alkylation to give (R)-α-substituted alanines.[200] Further uses for the related (5R)-phenyloxazin-3-one include cycloadditions of derived 1,3-oxazolium-4-olates to give enantiopure αβ-dihydroxy acids.[201] (3R,5R)-3,5-Diphenylmorpholinone undergoes Michael addition to methyl acrylate and its homologues, to give 3-substituted-2-phenylprolines after processing of the adduct,[202] and N-Z-4,5-diphenyl-tetrahydro-oxazin-2-one has been used in a synthesis of L-m-tyrosine.[203] The N-[(R)-1-phenylethyl] tetrahydro-oxazin-2-one (36) has been used in syntheses of α-substituted phenylglycines.[204]

The synthesis of methyl esters of acid-sensitive or highly-hindered α-amino acids from 1-Boc-2-tert-butyl-4-methoxy-2,5-dihydroimidazoles (37) succeeds in part because work-up following their alkylation calls only for mild conditions.[205]



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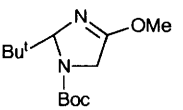
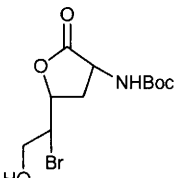


(37)

4.1.8 From 'Dehydro-amino acid' Derivatives – Theoretical aspects [molecular orbital calculations providing evidence for rhodium(I)/N-alkenylamide/phosphine complexes for homogeneous catalysis of the hydrogenation of N-acylaminoacrylates[206]] and synthesis objectives [asymmetric hydrogenation of 1-(formamido)alkenyl phosphonates[207]] represent interests that have been pursued for many years; the general topic has been reviewed.[208] The last-mentioned study employs (S)-BINAP-ruthenium(II) compounds that are typical of the highly-enantioselective catalysts on which attention is currently focussed. A new C_2-symmetric biphosphine, [2,2]PHANEPHOS, has been proposed for Rh-catalysed hydrogenations leading to 91 – 99.6% e.e. when applied to 2-aminoacrylates,[209] while the well-established Rh-DIPAMP system is favoured for synthesis of homochiral ferrocene-bridged bis(alanine).[210] A novel chiral Rh catalyst involving a bicyclo[3.2.0]heptane has been advocated and used in a synthesis of D-phenylalanines with high e.e.[211] Asymmetric hydrogenation [Rh/(R,R)-EtDuPHOS] of αγ-dienamide esters $R^1CH{=}CR^2CH{=}C(NHAc)CO_2Me$ formed by Suzuki cross-coupling and Horner-Emmons reactions gives the L-α-amino acid $R^1CH{=}CR^2CH_2CH(NHAc)CO_2Me$; for R^1 = $TBSOCH_2$, R^2 = H, a route to (+)-bulgecinine has been opened up *via* (38).[212]



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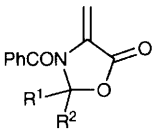


(39)

Diastereoselective Michael addition of azomethine ylides derived from $Ph_2C{=}NCH_2CO_2R$ (or from the corresponding Schiff base formed between camphor and glycine tert-butyl ester) to the 4-methylene oxazolidin-5-one (39) has been used in a synthesis of all four stereoisomers of 4-benzamidopyroglutamic acid,[213] and the same intermediate leads through PPh_3-catalysed cycloaddition to allenes, to 1-amino-2- and -3-carboxycyclopent-2- and -3-ene-1-carboxylic acids, of interest as conformationally-restricted L-glutamic acid analogues.[214] A simpler alkylation procedure, $CrCl_3$-Fe-catalysed reaction of a perfluoroalkyl iodide with methyl α-acetamidoacrylate, gives corresponding α-aminoalkanoates.[215]

4.2 Synthesis of Protein Amino Acids and other Naturally Occurring α-Amino Acids – As an extension of the preceding Section, this concentrates on synthesis targets that either require modification of general synthesis methods, or require an individually tailored synthesis strategy.

The literature describing enzymic synthesis of common protein amino acids is already substantial, and is augmented in the current literature by accounts of production scale methods for L-cysteine (immobilized *Pseudomonas* M-38),[216] L-aspartic acid (immobilized *Brevibacterium flavum* and *E. coli* using ammonium

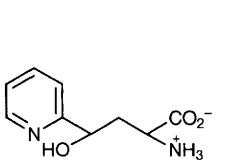
fumarate *via* L-malic acid),[217] L-lysine (*Corynebacterium glutamicum*),[218] L-[3-^{13}C]serine from [^{13}C]formaldehyde using L-serine hydroxymethyltransferase and tetrahydrofolate,[219] hyperproduction of L-threonine (modified *E. coli* that shows impaired threonine uptake),[220] L-[3-^{13}C]- and -[3-^{2}H]phenylalanine and leucine (*Brevibacterium methylicum* in $^{13}C^{2}H_3OH$ – $^{2}H_2O$),[221] L-tryptophan (genetically-modified *E. coli* that shows elevated tryptophan synthetase activity),[222] and a novel approach to L-β-aryl-α-alanines using red yeast cells (*Rhodotorula rubra* and *Rhodotorula glutinis*) with ammonia and a trans-β-arylacrylic acid.[223] An aminoacylase from *Bacillus thermoglucosidius* converts α-(chloracetamido)cinnamic acid into phenylpyruvic acid, which is a substrate for phenylalanine dehydrogenase and accounts for the production of L-phenylalanine by this organism.[224] Close relatives of the protein amino acids include S-adenosyl-L-methionine, prepared on a large scale from methionine using an *E. coli* strain.[225]

α-Keto-acids are substrates for the production of D-glutamic acid, D-phenylalanine, and D-tyrosine, based on a D-amino acid transferase/alanine racemase/L-alanine dehydrogenase/formate dehydrogenase system.[226] Reductive amination of α-keto-acids catalysed by leucine or phenylalanine dehydrogenase can give L- or D-amino acids together with L-α-hydroxy acids.[227] Homologation of ethyl (S)-lactate and development to $MeCH(OMOM)COCO_2H$ gives a substrate that is converted into the [^{15}N]-L-threonine derivative using leucine dehydrogenase, and to the allothreonine analogue from the appropriate precursor.[228] [1,2-$^{13}C_2$; ^{15}N]-L-Serine is formed through the action of serine hydroxymethyltransferase on the labelled glycine, and tryptophan synthase leads to the labelled L-tryptophan.[229] Recombinant D- and L-threonine aldolases effect the conversion of aliphatic aldehydes into erythro-β-hydroxy-α-amino acids, and aromatic aldehydes into their threo-analogues (syntheses of 3-hydroxyleucine, γ-benzyloxy- and γ-benzyloxymethylthreonines, and polyoxamic acid, are notable).[230]

Synthesis of (40), the N-terminal amino acid of Nikkomycins K_x and K_z, has employed a pyruvate aldolase-catalysed condensation of 2-pyridinecarboxaldehyde, pyruvic acid, and CO_2.[231]

Uses of transaminases, and of asymmetric hydrogenation of acylamidocinnamic acid derivatives, in commercial scale synthesis of non-natural amino acids, have been reviewed.[232] Reviews of the production of amino acids by methanol-utilizing bacteria[233] and more general production methods,[234] and of enzymic hydroxy-L-proline production,[235] have appeared, and also a review of enzymic synthesis methods used in an Edinburgh laboratory,[236] and more general review coverage,[237] including a broad general survey of the enzymology of amino acid production.[238] Access to this largely biotechnological field, for which only representative citations are given here, is facilitated by *Chemical Abstracts, Section 16: Fermentation and Bioindustrial Chemistry.*

A synthesis of D- and L-enantiomers of threonine and also their allo-isomers is based on an ingenious BF_3-catalysed hetero-Diels-Alder reaction of acetaldehyde with the azadiene (41) and its epimers.[239] Synthesis *via* DL-trans-4,5-dihydro-5-(4-methoxyphenyl)-4-methylisoxazoline-5-carboxylic acid, involving an acylase resolution stage, of (2S,3S,4S)-4-(4-acetoxyphenyl)-2-amino-3-methylbutan-4-



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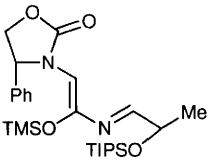
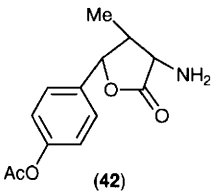


(41)

olide (42), a precursor for the unusual amino acid present in Nikkomycin B [also Refs. 66, 824 for other syntheses of Nikkomycin constituents] has been described.[240] Renewed interest in the synthesis of 'MeBmt', the N-methyl-L-threonine derivative that is a component of cyclosporins, is justified if shorter routes can be found that also allow analogues to be targetted; the syn-(2R)-amino-1,3,4-butanetriol derivative (43), accessible from D-isoascorbic acid, has been converted smoothly into the MeBmt precursor (44).[241] For new syntheses by manipulation of threonines, see Ref. 841. The protected component needed for preparing one of the unusual amino acids in microsclerodermins has been synthesized by incorporating a number of strategies newly introduced in this field, namely the use of a nitrone moiety and of a 2-furyl moiety that become the amino and carboxy group, respectively, in the synthesis target (Scheme 12).[242]



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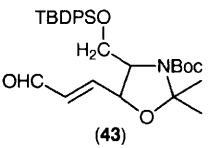

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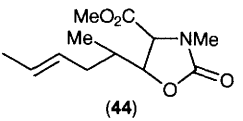

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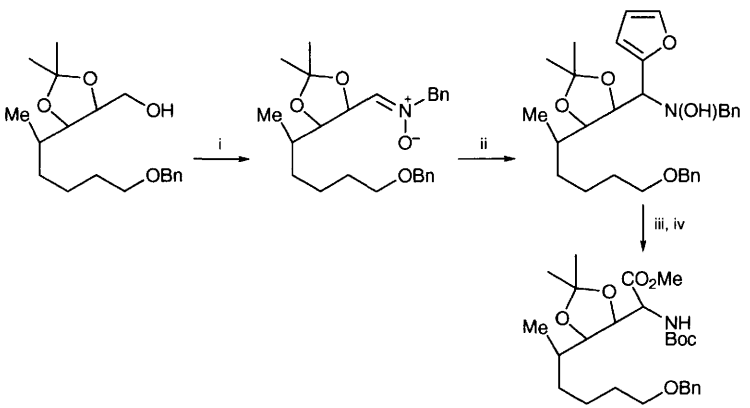


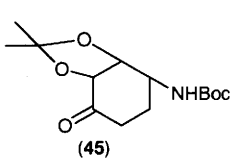
Reagents: i, $(COCl)_2$, DMSO, then BnNHOH; ii, 2-furyl-lithium/Et_2AlCl;
iii, separate epimers, react with $TiCl_3/H_2O$ then Boc_2O; iv, RuO_2, then MeI

Scheme 12

Total synthesis as the means of determining the absolute configuration of radiosumin, shown to be (S), has required the establishment of a synthesis of 2-amino-3-(4-amino-2-cyclohexylidene)propanoic acid and its cyclohexene analogue; the phosphonate $MeON{=}C(CO_2Me)CH_2PO(OMe)_2$ was condensed with the cyclohexanone (45) to give an intermediate from which both target amino acids were obtained.[243]

D- and L-Proline have been prepared starting from D-glucono-1,5-lactone *via* the D-erythrohexonate ester (46) through azide substitution, reductive cyclization into the pyrrolidine, and generation of the carboxy group.[244]

Kainoid synthesis is an area of vigorous exploration, in a search for appropriate methodology leading particularly to neuro-active analogues of these natural proline derivatives. Papers from research groups who have already established their interest in this field cover the introduction of substituents into trans-4-hydroxy-L-proline, giving correctly oriented C-3- and C-4-substituted kainoids.[245] Enamine alkylation for introduction of a C-3 carboxymethyl grouping, conversion into the 4-oxoproline, and subjecting this to Grignard addition or Pd(0)-catalysed cross-coupling to introduce C-4-aryl substituents, gives the useful intermediate (47), whose scope as a starting point for synthetic manipulations has been explored in related studies.[246]



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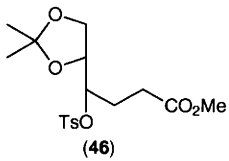

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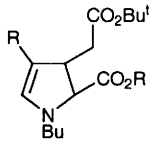

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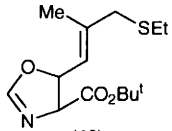

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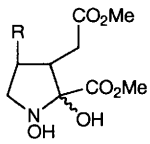
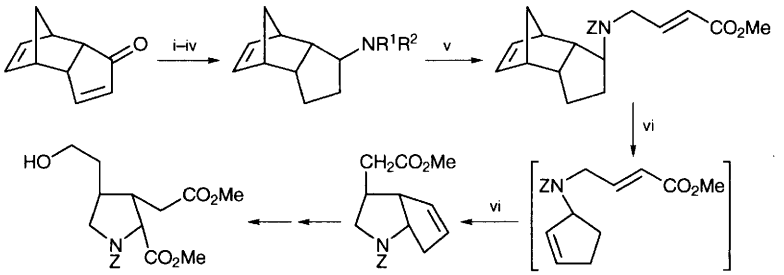


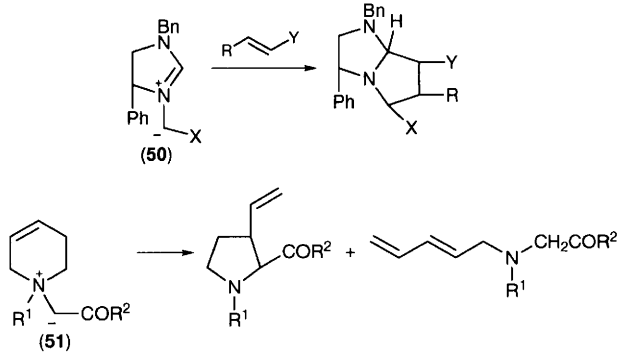
(49)

Bachi's proline ring-construction approach [Vol. 29, p. 25; alkylation of tert-butyl isocyanoacetate by 4-(ethylthio)-3-methylbut-2-enal catalysed by 10 mol $(C_6H_{11}NC)_2AuBF_4$/chiral bis(diphenylphosphino)ferrocene] has provided the oxazoline (48) from which (-)-kainic acid was obtained through standard functional group elaboration.[247] A proline ring-construction starting with Mitsunobu alkylation of (S)-$CH_2{=}CH(NHTs)CH_2OCH_2OMe$ with $PhSCH_2CMe{=}CH\text{-}CH_2OH$ and a subsequent thiyl radical addition – cyclization – elimination sequence has also provided (-)-kainic acid.[248] Racemic kainic acid analogues have been obtained through Michael addition of dimethyl α-ketoglutarate to 2-methoxy-β-nitrostyrene, taking advantage of the favourable 14:1 anti:syn mixture of adducts from which the cis-trans target stereochemistry (49) was achieved through reduction of the nitro group followed by cyclization.[249] The route to (-)-kainic acid *via* the Diels-Alder cycloadduct of a (+)-norcamphor synthon (Vol.

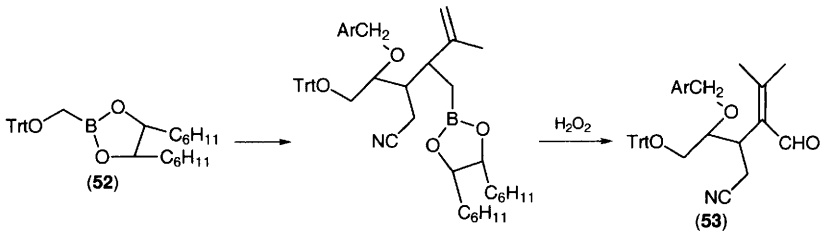


Reagents: i, Zn/AcOH–EtOH, reflux; ii, $NaBH_4$–MeOH; iii, DPPA; iv, $LiAlH_4 \rightarrow R^1 = R^2 = H$; v, $BrCH_2CH{=}CHCO_2Me$ then ZCl/NaH/DMF; vi, PhOPh, reflux 60 min

Scheme 13

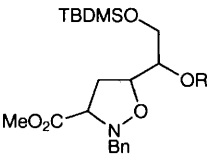


21, p. 15) has been explored further,[250] and a new stereocontrolled route to (-)-kainic acid from the same research group employs concurrent retro-Diels-Alder and intramolecular ene reactions of the optically pure ketodicyclopentadiene shown in Scheme 13.[251] Trisubstituted pyrrolidines including kainoids are accessible from intramolecular cycloadditions of homochiral azomethine ylides (50).[252] [3,2]-Sigmatropic rearrangements of didehydropiperidinium ylides (51) can give acceptable yields of disubstituted proline derivatives as ring-contraction products although the route is seriously devalued by competing elimination.[253] Stepwise additions of dihalogenomethyl-lithium to the homochiral boronic acid ester (52) gave the aldehyde (53) on H_2O_2 cleavage of the C-B bond, rather than the expected sec-kainic acid.[254]



Kainic acid analogues with the isopropenyl moiety replaced by the $CF_3C(N_2)CO$- group should prove valuable probes for tissue studies aimed at mapping kainoid receptors.[255] The same objective has stimulated studies of 1,3-cycloaddition of $PhCH_2N(O)=CHCO_2Me$ to (Z)-(2-X-C_6H_4)$CH=CHCH_2$-CO_2Me for a preparation of oxa-analogues[256] (for aza-analogues, see Ref. 879).

(-)-Bulgecinine has been prepared (see also Section 6.3, Ref. 859) together with three of its isomers from the 1,3-dipolar cycloadduct (54) of N-benzyl α-methoxycarbonyl methanamine N-oxide with the homochiral allylic alcohol (R)-$H_2C=CHCH_2CH(OH)CH_2OSiPh_2Bu^t$.[257]



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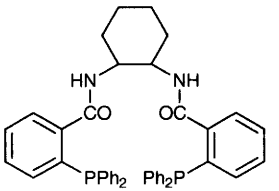

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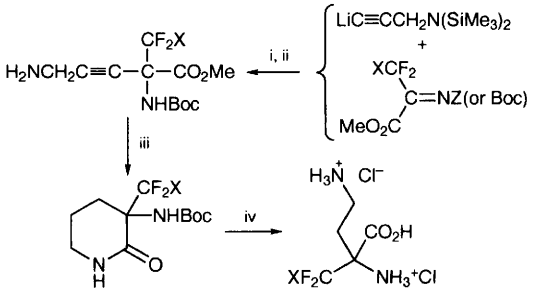
4.3 Synthesis of α-Alkyl-α-Amino Acids – Standard general methods leading to these compounds are reliable, and, apart from the importance of the targets as potential enzyme inhibitors, points of interest are mostly to be found in difficulties in synthesis, associated with steric hindrance. The applications for the synthesis of α-alkyl-α-amino acids, of the Schollkopf, Strecker, and Seebach methods (see examples in Sections 4.1, 4.2) have been reviewed,[258] and a review of the general topic has appeared.[259]

The Seebach imidazolidin-4-one, as its 3,5-dimethyl derivative, has been applied to the synthesis of [^{18}F]fluoro-α-methyl-L-phenylalanines,[260] and 2- and 3-[^{18}F]fluoro-α-methyl-L-tyrosines have been prepared.[261] Alkylation of DL-4-methyl-2-phenyloxazol-5(4H)-one with 3-acetoxycyclohexene is highly stereospecific when catalysed by $[(\eta^3\text{-}C_3H_5PdCl)_2]$ in the presence of the chiral ligand (55; 8.7:1 d.e.),[262] applicable also for a synthesis of serine analogues using $PhCH=CHCH_2CH(OAc)_2$ as alkylating agent. The N-(2-cyanopropionyl) derivative of the sultam introduced by Oppolzer undergoes efficient diastereoselective alkylation with methyl bromoacetate to provide (S)-α-methyl-aspartic acid.[263] N-2-Alkenylsultams act as dipolarophiles towards diazomethylsilanes Me_3SiCHN_2, to give α-alkyl-azaprolines.[264]

The direct α-alkylation of an amino acid is rarely used because of the need for full protection, but ethyl N-Boc-N-methyl-L-phenylalaninate meets this criterion and lithium 2,2,6,6-tetramethylpiperidide and methyl iodide at -78 °C brings about α-methylation with retention of chirality (82% e.e.).[265] Protected (R)-4-hydroxyphenylglycine similarly gives the α-methyl analogue,[266] and so does L-tryptophan, protected by conversion into bis-N-benzyloxycarbonyl tetrahydropyrrolo[2,3-b]indole-2(S)-carboxylic acid methyl ester.[267] The L-proline-derived

Seebach oxazolidinone undergoes α-alkylation by α,α′-dibromo-m-xylene to provide a novel ligand for a tetraprolinate dirhodium catalyst.[268]

Imines are more easily alkylated, illustrated in a new efficient synthesis of α-difluoromethyl- and α-trifluoromethyl-ornithines (Scheme 14) in which a synthon carrying the latent side-chain of the named amino acid reacts with a halogenomethylimine.[269] This alternative approach is also needed for the large-scale preparation of α-phenyl-α-amino acids, *viz.* phase-transfer-catalysed α-allylation of N-benzylidene-DL-phenylglycine, then successive resolution using an esterase (but better results were obtained using the *Ochrobactrum anthropi* amidase; see also Ref. 471), hydroboration and Mitsunobu cyclization to give (R)-α-phenylproline.[270]

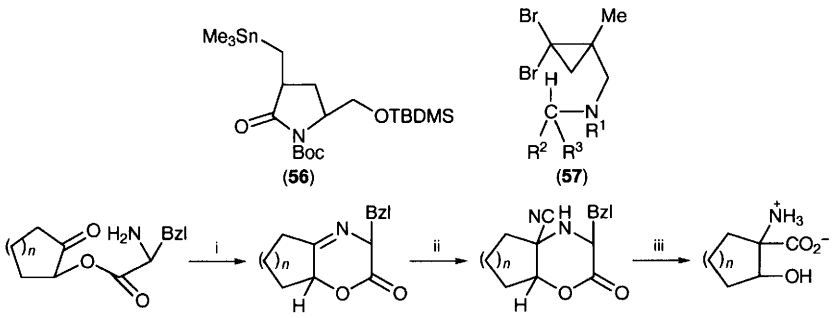


Reagents: i, −78 °C → r.t.; ii, aq. HCl; iii, H_2, Pd/C–MeOH; iv, 6M HCl

Scheme 14

4.4 Synthesis of α-Amino Acids Carrying Alkyl Side-chains, and Cyclic Analogues – The synthesis of close analogues of the aliphatic protein amino acids, as well as alicyclic and saturated heterocyclic examples, is surveyed here (see also Section 6.3); but several studies, mentioned earlier under the heading of general methods of synthesis, also extend to non-protein amino acids.

'Methano-amino acids', perhaps better described as α-cyclopropylglycines and their homologues, are of continuing interest as conformationally-constrained analogues of familiar protein amino acids. Synthesis methodology is straightforward for (2S,1′S,2′S)-(2-carboxycyclopropyl)glycine (oxazolidinone method)[271] and its α-methyl homologue,[272,273] and (S)-2-amino-2-methyl-4-phosphonobutanoic acid, following routes already applied (Vol. 29, p. 29) to the synthesis of these targets as glutamic acid mimics, isotype-selective agonists of metatropic glutamate receptors (see also Refs. 52, 81). (2S,3R,4S)-4,5-Methanoproline and the corresponding 5,6-methanopipecolic acid enantiomer have been prepared by a novel intramolecular cyclopropanation of iminium ions, *e.g.* from L-pyroglutaminol to give the former *via* (56),[274] and by intramolecular insertion into C-H bonds five atoms distant from a tertiary amine function (*cf.* 57).[275] 2-Fluoro-1-aminocyclopropane-1-carboxylic acid has been prepared by cyclopropanation of the fluoroacrylate followed by standard manipulations (ester → NH_2; aryl moiety → CO_2H).[276]



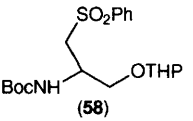
Reagents: i, base; ii, NH_4CN, aq. MeOH; iii, H_2/Pd then hydrolysis

Scheme 15

1-Aminocyclobutanecarboxylic acid carrying the 2-[1,7-dicarba-closo-dodecaboran(12)-1-yl]ethyl substituent has been prepared for its potential in neutron capture therapy, using the hydantoin general synthesis applied to the corresponding cyclobutanone.[277] Synthesis of 2-hydroxy-1-aminocycloalkanecarboxylic acids, designed as conformationally-restricted serine analogues, has involved a novel intramolecular Strecker procedure (Scheme 15).[278] Further examples of these types of conformationally-restricted analogues of common amino acids have been prepared by exploiting the dienophilic character of 2-phenyl-4-alkylideneoxazol-5(4H)-ones (Vol. 29, p. 18; *cf* also Ref. 290).[279] 1-Aminocyclohexanecarboxylic acids constructed in this way carry substituents with known stereochemical relationships to each other, as illustrated for the synthesis of (1R,3R,6R)-1-amino-3-hydroxy-6-phenylcyclohexane-1-carboxylic acid and its enantiomer.[280]

Synthesis of (2S,3R)-3,3-disubstituted aziridine-2-carboxylic acids through highly selective syn-addition of MeMgBr to enantiopure ethyl 3-phenyl 2H-azirinecarboxylate,[281] and of dimethyl (R)-2-methylaziridine-1,2-dicarboxylate [from the (R)-epoxide prepared from $MeO_2CNHCH_2CMe{=}CH_2$ through chloroperoxidase-mediated asymmetric epoxidation],[282] has been reported.

trans-3-Substituted prolines have featured in a number of papers in which novel routes are explored. Homochiral sulfone (58) condensed with 2-bromoethyl triflate gives cis- and trans-3-allyl prolines.[283] Cyclization of a zinc enolate with a non-activated alkene favours cis-diastereoisomers (Scheme 16), a route demonstrated in a synthesis of proline analogues of methionine and valine [*e.g.* (2S,3S)- and (2S,3R)-3-(methylsulfanylmethyl)pyrrolidine-2-carboxylic acid].[284] A parallel study building on Normant's preceding work with zinc enolates, introducing zinc-ene-allenes, has also been published.[285] [2 + 2]-Cycloaddition of N-benzyloxycarbonylpyrrolid-2-ene to dichloroketene gives the expected dichlorocyclobutanone, from which 3-substituted prolines were obtained (diazomethane ring expansion or ozonolysis of the derived enol acetate).[286] 4,5-Dehydro-L-proline gives 4,5-disubstituted homologues through this route. C_2-Symmetric pyrrolidine-2,5-dicarboxylates and -2,3,4,5-tetracarboxylates have been prepared through 1,3-dipolar cycloadditions to azomethine ylides.[287]



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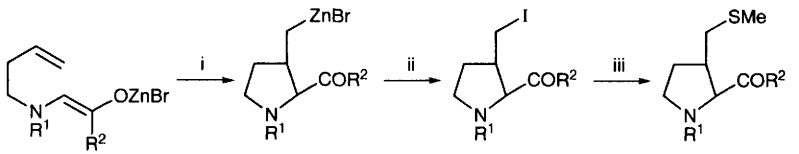
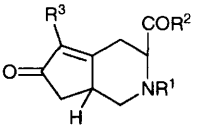


Reagents: i, −90 °C → r.t.; ii, I_2; iii, MeSNa, DMF (R^1 = benzyl, with R^2 = ethoxy, menthyloxy, phenylmenthyloxy, and camphorsultam; R^1 = (−)-α-methylbenzyl, with R^2 = ethoxy)

Scheme 16

3-Phenyl-4,5-benzoprolines (more correctly, cis- and trans-3-phenylindoline 2-carboxamides) have been prepared from indoles as representatives of conformationally constrained phenylalanines, the route being easily generalized to provide correspondingly constrained analogues of other protein amino acids.[288]



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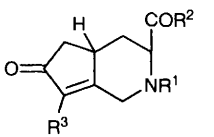

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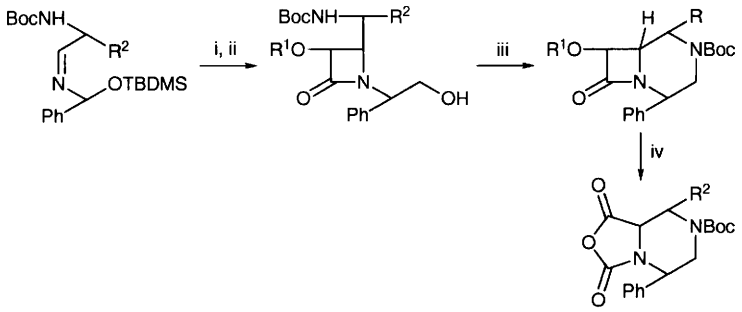
Isomeric pipecolic acids (59) and (60) have been prepared through intramolecular Pauson-Khand cyclization,[289] and a Diels-Alder route (*cf.* also Ref. 290) involving the Danishefsky diene leads from the D-glyceraldehyde-derived imine $PhCH_2N{=}CHCH(OCH_2Ph)CH_2OCH_2Ph$ to (2R)-4-oxopipecolic acid (see also Ref. 156).[290] Intramolecular addition of allylsilanes to iminium salts $CH_2{=}N^+CHRCH_2OH\ X^-$ formed between a homochiral β-aminoalkanol and glyoxal starts a route to 3,4-functionalized pipecolic acids.[291] A more traditional route starting from 3-hydroxypyridine-2-carboxylic acid or quinolinic anhydride gives corresponding substituted pipecolic acids in racemic form.[292]

Piperazine-2-carboxylic acids are reached through a lengthy route starting from an acyclic N-Boc-α-amino imines (Scheme 17), including a β-lactam → N-aminocarboxylic anhydride stage (*cf.* Ref. 106).[293]

4.5 Models for Prebiotic Synthesis of Amino Acids – Theories of prebiotic amino acid synthesis have been reviewed,[294] and a limited description of this chemistry has been published.[295]

Irradiation (254 nm) of a propene – ammonia mixture in dry and aqueous environments would have been thought to generate amino acid mixtures, based on more than forty years of similar studies, but we are told that the four nucleic acid bases adenine, guanine, thymidine and uracil are formed.[296] Recent examples



Reagents: i, R^1OCH_2COCl, NEt_3; ii, TBAF; iii, MsCl, Et_3N then TFA, then Boc_2O; iv, NaOCl, TEMPO or P_2O_5–DMSO followed by *m*-CPBA

Scheme 17

of the expected outcome include the formation of amino acids from $CH_4 - NH_4X - H_2O$ at 260-325 °C to simulate undersea thermal vent conditions;[297] some amino acids decompose under these conditions, but it has been reasoned[298] that the particular environment in hydrothermal vents protects amino acids and that laboratory models are misleading, since glycine, alanine and glutamic acid have been found in an outflow from the Okinawa Trough. Amino acids are formed from $CO - N_2 - H_2$ in a magneto-plasma dynamic arc jet,[299] and from $CH_4 - N_2 - CO - H_2O$ under spark discharge or irradiation with high energy particles.[300] The last-mentioned study, intended to simulate primitive planetary environments, shows that high yields of amino acids, as well as uracil and imidazole, are formed through the irradiation process, suggesting that cosmic-ray induced synthesis was important in this context in prebiotic times.

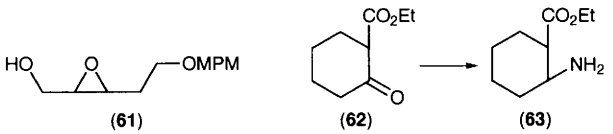
4.6 Synthesis of α-(ω-Halogeno-alkyl)-α-Amino Acids – Alkylation of a homochiral imidazolidin-4-one (*cf.* Section 4.1) has formed the basis of a synthesis of (2S,3S)-4-fluorothreonine.[301] 5,5,5,5′,5′,5′-Hexafluoro-L-leucine has been prepared starting from hexafluoroacetone, giving $(CF_3)_2CHCH_2COCO_2Et$ with ethyl bromopyruvate, baker's yeast reduction introducing the required homochirality preceding routine aminolysis.[302] (-)-4,4,4,4′,4′,4′-Hexafluoro-D-valine has been prepared from $(CF_3)_2C{=}CHCO_2Bn$ through Michael addition of (R)-$PhCHMeNH_2$ as the crucial step, incidentally correcting an earlier assignment of configuration to the (-)-isomer obtained in this way.[303]

These illustrate uses of standard asymmetric synthesis methods, and the modest diastereoselectivity sometimes achieved; in a further example, condensation of 1-bromo-2-fluoroalkenes with glycine ester imines derived from R-(+)-camphor has given seven homologous α-fluoroalkyl-α-amino acids, (R)-(-)-2-amino-4-fluorobutanoate being obtained in 32% e.e.[304] Preparations of 3-fluoroalanine (Ref. 56) and 3,3,3-trifluoroalanine (Ref. 65) are discussed elsewhere.

4.7 Synthesis of α-(ω-Hydroxyalkyl)-α-Amino Acids – Reviews include the use of aldonolactones in the asymmetric synthesis of hydroxyamino acids,[305] and routes to O-glycosyl-α-amino acids.[306]

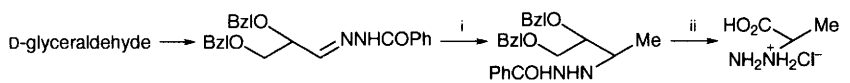
Familiar aldol alkylation and epoxide ring-opening alkylation processes have been used for access to α-amino acids carrying β-hydroxyalkyl side-chains. Thus, the essential step in a synthesis of (2S,3R)-β-hydroxyornithine involves amination of the epoxide (61) with benzyl isocyanate.[307] An alternative approach with hydroxy groups in place from the start is offered by carbohydrate-based synthons, as with the D-glyceraldehyde nitrone (*cf.* Scheme 2; *cf.* Ref. 94) converted into a propargylhydroxylamine with LiC ≡CSiMe$_3$, thence to the dioxolanylglycine, a protected form of a β-hydroxy-α-amino acid.[308] All stereoisomers of β-hydroxynorvaline have been synthesized, each using an oxazolidinone enantiomer (*cf.* Scheme 5; BzlOCH$_2$ in place of Ph, CH$_2$CH$_2$R in place of R; stereochemistry as appropriate to the target stereoisomer).[309]

The net change L-valine → (2S,3S)-γ-hydroxy-L-valine has been accomplished, exploiting 1,2-asymmetric induction occurring in anti-Markovnikov hydrobromination of βγ-dehydro-L-valine.[310] Through this synthesis, identity with the amino acid occurring naturally in leaves and stems of *Kalanchoe diagremonitana* was established.



(61) (62) (63)

4.8 Synthesis of N-Substituted α-Amino Acids – Preparation of N-alkylamino acids has been reviewed.[311] A standard reductive N-alkylation route has provided N$^{\alpha}$-ω-(Y-alkyl)-α-amino acids (Y = RS, RNH, or HO$_2$C);[312] where a benzylamine is employed for reductive amination of keto-acid derivatives, hydrogenolysis of the resulting N-benzylamino acid is one of the standard amino acid synthesis protocols, and where (R)-PhCHMeNH$_2$ is used, then useful stereocontrol may be achieved (62) → (63).[313] α-Hydrazino acids feature in a continuing study (a preparation of α-hydrazinopropanoic acid is shown in Scheme 18).[314]



Reagents: i, MeMgBr, CeCl$_3$; ii, successively, Boc$_2$O, H$_2$/Pd(OH)$_2$, RuCl$_3$/NaIO$_4$, then H$_3$O$^+$Cl$^-$

Scheme 18

The extraordinary generation of N-propylamides of glycine and alanine from reaction mixtures comprising glucose or ribose with propylamine has been studied further[315] [but the essential basis of this process has already been established (Vol. 29, p. 9].

Interest continues in the preparation of peptides (PNAs; first reported in 1991),[316] made through condensation of (N-aminoethyl)glycines that carry N-(pyrimidin-1-yl)alkanoyl and N-(purin-1-yl)alkanoyl or related groups. A paper describing current work with these compounds advocates Mmt-N-protection.[317] Interactions of PNAs with nucleic acids, and some mimicking of the behaviour of DNA by PNAs, have provided new understanding of certain properties of these biologically-important natural products, and PNAs have been advocated for a role as primordial genetic material.[318]

Monomers needed for this purpose have been synthesized by various means, and a Mitsunobu approach with N-Boc-N-(2-hydroxyethyl)glycine methyl ester as substrate has been disclosed.[319]

4.9 Synthesis of α-Amino Acids Carrying Unsaturated Aliphatic Side-Chains – 'Dehydro-amino acids', *alias* αβ-unsaturated α-amino acids (see also Section 4.1 and Refs. 176, 813), are easily prepared from imines $(MeS)_2C{=}NCH_2CO_2R$ through addition to electron-deficient alkynes,[320] and addition of nucleophiles to conjugated alkynoates (*e.g.*, phthalimide to alkyl propiolates) in the presence of PPh_3 is a practical new alternative.[321] Formation of dehydroamino acids from pyruvic acid through condensation with benzyl carbamate, then N-acylation with bromoacetyl bromide, illustrates a classical approach.[322]

Amination of γ-silylated αβ-unsaturated esters using ethyl N-[(4-nitrobenzenesulfonyl)oxy]-carbamate gives βγ-unsaturated α-amino acid esters, *e.g.* $CH_2{=}CHCMe(CO_2Me)NHCO_2Et$.[323]

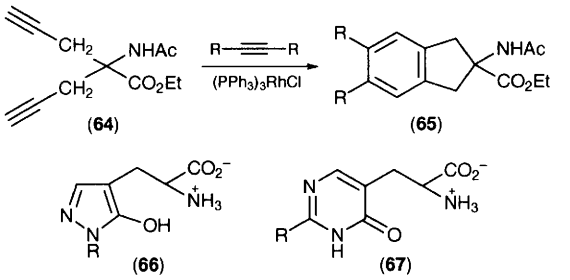
The synthesis of γδ-unsaturated α-amino acids, in ways other than direct allylation of glycines, can involve chelate – enolate Claisen rearrangement of alkenyl esters,[324] or use of unsaturated organozinc reagents with N-(phenylsulfano)imines $PhSN{=}CHCO_2Me$ to give $CH_2{=}CHCH_2CH(NHSPh)CO_2Me$.[325] α,β-γ,δ-Unsaturated amino acids have been described (Ref. 812).

4.10 Synthesis of α-Amino Acids with Aromatic or Heteroaromatic Groupings in Side-chains – Members of the phenylalanine family continue to attract interest through their pharmacological importance, and standard synthesis protocols have been used [4-fluoro-3-nitro-DL-phenylalanine from acetamidomalonate (see also Ref. 141),[326] alkylation of glycine benzophenone imine $Ph_2C{=}NCH_2CO_2Et$ by (4-pinacolylborono)benzyl bromide,[327] and for preparations of N-Boc tyrosine methyl ether carrying various 3′-substituents[328]]. (N-Boc-Aminomethyl)arenes have been elaborated into α-, β-, and γ-aryl amino acids through asymmetric lithiation induced by (-)-sparteine (see also Refs. 95, 96), *via* $Ar^1N(Boc)CH(SnMe_3)Ar^2$.[329] Diphenylalanine derivatives $AcNHCH(CO_2Me)CRPh_2$ and analogues in which the two phenyl groups are linked by aliphatic chains $-(CH_2)_n-$, have attracted interest in view of their 'crowded' side-chains,[330] and conformational constraint has been designed into the general β-arylalanine structure through radical cyclization of N-(o-iodophenyloxymethyl)-N-Boc-dehydroalanine to produce 2,3,4,5-tetrahydro-1H-3-benzazepine-2-carboxylic acid and its benzazocine and benzazonine analogues[331] and 8- and 9-membered ring homologues.[332] Similar objectives lie behind the preparations of 1-amino-1-carboxyindane

5-phosphonic acid and the analogous 3-amino-tetrahydrochroman-3,6-dicarboxylic acid[333] and isoindolinones.[334] A novel approach employing the αα-bis(propargyl)glycine (64), leading to 2-amino-2-carboxyindanes (65), required the discovery of the optimum glycine synthon towards bis(propargyl)ation; that turned out to be ethyl isocyanoacetate.[335]

A constrained tyrosine has been prepared (three-carbon aliphatic chains join one o-position to the β-C, and join the other o-position to the nitrogen atom) for its potential value as a constituent of analogues of biologically-active peptides.[336]

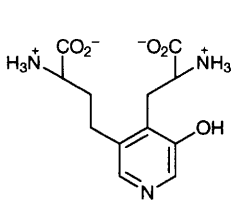
Hydantoin and oxazolone protocols have been applied to the preparation of L-thienylalanines *via* microbial transamination of 2-hydroxy-3-thienylacrylic acid with L-aspartic acid as amino group donor.[337] Bucherer-Bergs synthesis of benz[f]tryptophan from the corresponding formylmethyl N^{in}-allyl benzindole is straightforward.[338] N^{in}-Fmoc-2-Phenyltryptophan has been prepared on a multigram scale from 3-diethylaminoethyl-2-phenylindole through condensation with ethyl nitroacetate,[339] and (7-carboxyindol-3- and -4-yl)glycines have been prepared through alkylation of glycine cation equivalents $BzNHCH(OMe)CO_2Me$ and $Ph_2C{=}NCH(OAc)CO_2Et$.[340]



γ-Tetrazolyl α-aminobutyric acid[341] and related β-heteroaryl alanines (66) and (67) have been prepared, the last-mentioned examples through the 'ring-switching' approach starting from pyroglutamates (Vol. 28, p. 34).[342] The preparation of β-heteroaryl alanines has been reviewed.[343] Analogues of 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (a long-studied neuroactive agent) have been synthesised through established methods (Vol. 29, p.38; Vol. 28, p. 33).[344]

The first total synthesis of the protein cross-linking amino acids deoxypyridinoline and hydroxypyridinoline *via* the 3-hydroxypyridine (68) has provided reliable standards for the development of a diagnostic kit that can be used for monitoring the onset of osteoporosis.[345]

Stimulated by growing interest in PNAs (Section 4.8), the synthesis of N-Fmoc-amino acids carrying a nucleobase in the side-chain has been explored, starting with γ-benzyl Boc-L-glutamate and proceeding *via* the protected 2-amino-4-bromobutanoic acid.[346] A similar approach provides N-Boc-4-(pyrimidin-1-yl)-L-prolines and related γ-amino acid derivatives.[347] ω-(Pyrimidin-4-yl)-α-aminoalkanoic acids, including L-lathyrine, have been prepared through condensation of amidines with alkynyl ketones derived from α-amino acids.[348]



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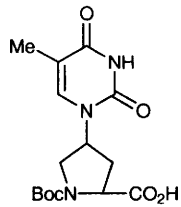

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4.11 Synthesis of α-Amino Acids Carrying Amino Groups, and Related Nitrogen Functional Groups, in Aliphatic Side-chains – Schiff bases of ethyl glycinate $Ph_2C{=}NCH_2CO_2Et$ are readily alkylated by imines [with $ArCH{=}NAr \rightarrow Ph_2C{=}NCH(CHArNHAr)CO_2Et$],[349] and undergo oxidative dimerization [with $I_2 \rightarrow$ protected threo-3-aminoaspartic acid][350] to lead to members of the aminomethylglycine family. The nickel(II) – benzophenone-L-proline Schiff base (Section 4.1.7) derived from dehydroalanine undergoes Michael addition with amines to give (S)-αβ-diamino acid derivatives (see also Ref. 405).[351]

3-{(4′-Mercaptophenyl)amino}alanine and 4′-mercaptophenylalanine have been prepared from N-trityl-L-serine (Mitsunobu condensation) and L-phenylalanine (p-chlorosulfonylation followed by Sn-HCl reduction), respectively.[352]

4.12 Synthesis of α-Amino Acids Carrying Sulfur-, Selenium-, or Tellurium-containing Side-chains – Several new sulfur-containing amino acids have been prepared (including examples described in Section 6.3). (2S,4S,6S)-4-Hydroxy-5-phenylsulfinylnorvaline has been prepared starting from N-Boc-(S)-allylglycine through bromolactonization, sulfide formation, and routine concluding steps, as a model for a synthesis of the unusual amino acid in ustiloxins A and B.[353]

L- and D-β-(Phenylseleno)alanines have been prepared from β-lactones derived from L- and D-serine, respectively, and used for dehydroalanine synthesis based on oxidative elimination of the phenylseleno group.[354]

4.13 Synthesis of α-Amino Acids Carrying Silicon Functional Groups in Side-chains – Three new silicon-containing DL-amino acids $MeR_2SiCH_2C(NHAc)(CN)CO_2Et$ and corresponding hydantoins have been prepared (see also Ref. 464) through alkylation of ethyl α-(acetamido)cyanoacetate.[355]

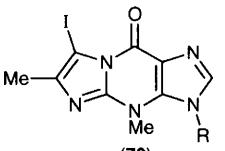
p-Trimethylsilyl-L-phenylalanine enantiomers are available through conventional synthesis and resolution (Ref. 467).

4.14 Synthesis of α-Amino Acids Carrying Phosphorus Functional Groups in Side-chains – Many of the amino acids of this category that are of current interest are phenylalanine derivatives with phosphorus functional groups as arene substituents, and these are prepared from the parent protein amino acid and dealt with in Section 6.3.

The phosphonium salt (S)-$Ph_3P^+CH_2CH(CO_2^-)NHCO_2Me$ serves in efficient

Wittig-type condensations, *e.g.* with (70; R = D-ribofuranosyl moiety), initiating routes for syntheses of ribofuranosylwybutines.[356]

2-Amino-5-phosphonylpentanoic acid [$Ph_2C{=}NCH_2CO_2Et$/BSA/Pd(0)/ethyl (3-acetoxyalk-1-enyl)phosphonate],[357] phosphinothricine and other glutamic acid analogues,[358] and the glutamic acid analogue $HO_2CCH(NH_3^+)CH_2CF_2(PO_3H^-)$[359] have been prepared through standard alkylation protocols applied to synthons derived from glycine and from other simple α-amino acids.



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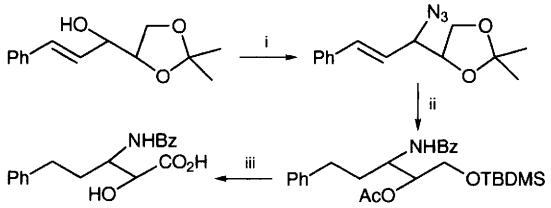
4.15 Synthesis of β-Amino Acids and Higher Homologous Amino Acids – The surge of interest in higher homologues of the α-amino acids has clearly not slowed down. New natural examples of the family, and new syntheses, have been described in the recent literature

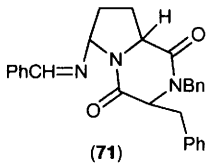
Reviews of addition of homochiral lithium amides to Michael acceptors have appeared,[360,361] and this approach has been used to prepare homochiral N-propargyl- or -allyl-β-amino esters $PhCHMeN(CH_2R)CHR^1CHR^2CO_2R^3$.[362] New examples of Michael acceptors are [S-(E)]- and [R-(E)]-2-[(4-methylphenyl)-sulfinyl]-3-phenylprop-2-enoic acid 1,1-dimethylethyl ester, including SmI_2-mediated reductive elimination of the sulfur function after addition of nitrogen nucleophiles (ammonia, piperazine).[363] Dimethyl 2-phenylselenofumarate readily participates in Michael addition reactions with amines, giving 3-amino-2-phenyl-selenosuccinates in high yields with complete regio- and stereo-selectivity.[364] Ti(IV)-Catalysed Michael addition of O-benzylhydroxylamine to homochiral αβ-unsaturated N-acyl-1,3-oxazolidinones generates disappointing e.e. (up to 42%).[365] Processing of an L-arabinose-derived dioxolane (Scheme 19) gives a vinylogue of phenylisoserine, and the isomeric δ-amino acid $PhCH(NHBz)CH(OH)CH{=}CHCO_2H$ with corresponding stereochemistry was also prepared in this study (from methyl glycidate, generation of the amino alcohol moiety, then chain extension from the ester grouping) through a route employing familiar methodology.[366] Further examples have been described, of the preparation of β-amino acids *via* hydrazines formed between TMS-SAMP and an ω-halogeno-αβ-unsaturated ester (Scheme 20).[367] Opportunities have been established for Ugi condensations in the synthesis of β- and higher amino acids (Refs. 137, 138).

Introduction of two new chiral centres is a feature of Zn-catalysed addition of bis-O-trimethylsilyl ketene acetals $R^1CH{=}C(OSiMe_3)_2$ to N-galactosylimines to produce β-amino acids.[368] This approach based on the Mannich reaction has been carried out with $Me_2C{=}C(OMe)OSiMe_3$ and an imine carrying a novel



Reagents: i, TPP, DEAD, DPPA; ii, iii, standard functional group transformations (7 steps)

Scheme 19



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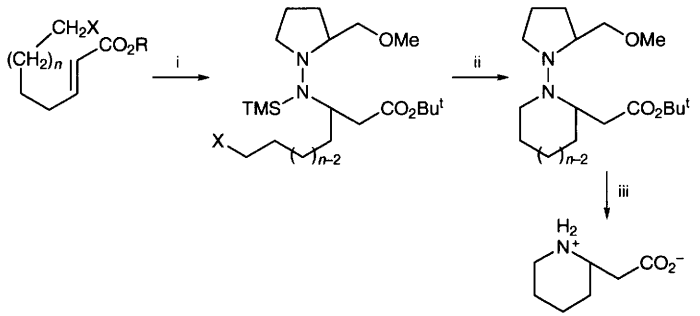
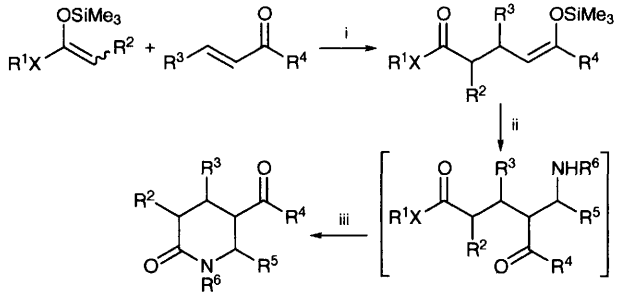


Reagents: i, TMS–SAMP, Bu^{n}Li, THF, −78 °C; ii, SiO_2–EtOAc, then NaI–K_2CO_3/MeOH at reflux; iii, Raney Ni–MeOH, then 6M HCl, followed by Dowex 50WX8–200

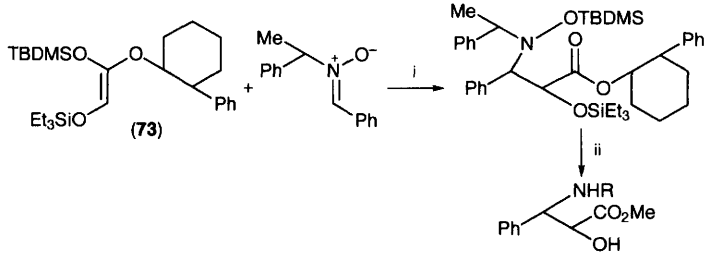
Scheme 20

chiral auxiliary (71), in the presence of $ZnCl_2$, to give (S)-3-amino-3-phenyl-2,2-dimethylpropanoic acid after acid hydrolysis.[369] The usual β-lactam synthesis involving a ketene and an imine ($Bu^tO_2CCH{=}NC_6H_4$-p-OMe + BnOCH=C=O; *cf.* Scheme 17) has been chosen as a route to benzyl N-Boc-isoserinates;[370] the general topic of applications of β-lactams in syntheses of amino acids has been reviewed.[371] Where silyl enolates (72; Michael adducts of ester equivalents with αβ-unsaturated carbonyl compounds) are used in additions to imines, then β-alkoxycarbonyl-δ-lactams are formed (Scheme 21).[372] Homochiral silyl enolates (73) add to homochiral nitrones to give excellent e.e. (98%) in a novel β-phenylisoserine synthesis (Scheme 22).[373] An organoselenium-induced cyclization of an N-acryloyl-L-prolinamide (Scheme 23) may become a valuable general asymmetric synthesis of β-amino acids (as well as to α-amino acids), but formation of unwanted elimination by-products is difficult to control, and routes with fewer steps are not seriously challenged at the moment.[374]



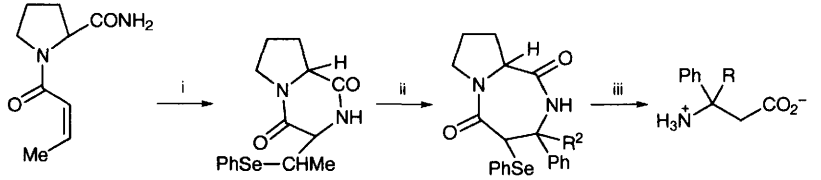
Reagents: i, $SbCl_5$–$Sn(OTf)_2$; ii, $R^5CH{=}NR^6$, $Sc(OTf)_3$, −78 °C; iii, $Hg(OTFA)_2$

Scheme 21



Reagents: i, ZnI_2; ii, functional group development

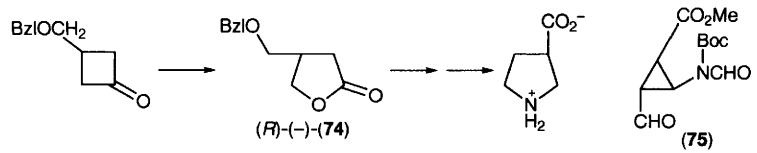
Scheme 22



Reagents: i, PhSeBr, AgOTf, MeCN; ii, $NiCl_2$; iii, $NaBH_4$

Scheme 23

Fluorinated imidoyl chlorides $R_FCCl{=}NR$ condense with lithium enolates of aliphatic esters to give β-enamino esters,[375] and β-amino-αβ-unsaturated alkanoic acid esters are easily prepared by the little-used Blaise reaction (sonicated RCN + $BrCH_2CO_2Et$ in the presence of Zn powder and ZnO → $NH_2CR{=}CHCO_2Et$).[376] These readily undergo α-alkylation since they are substrates for Michael additions to α-methyl-, α-acetoxy-, or α-acetamido-acrylates;[377] condensation with maleic anhydride gives 3-carboxymethyl-4,5-dehydropyrrolid-2-ones.[378] Eschenmoser condensation of N-[(S)-1-phenylethyl)]pyrrolidin-2-thione with ethyl bromoalkanoate/PPh_3 gives the corresponding Z-β-enamino ester that gives the (1R,2R)-α-alkylhomoproline derivative either through catalytic hydrogenation



followed by α-alkylation of the β-unsubstituted derivative,[379] or through catalytic hydrogenation of the α-alkyl α-enamino ester.[380]

A rare example of microbial help in a β-amino acid synthesis is featured in the formation of both β-proline enantiomers *via* (R)-(-)-(74) starting with the racemic cyclobutanone.[381] Amination of cinnamoylamides through epoxidation [polyaniline-supported cobalt(II)-salen complex/O_2] and anilinolysis gives anti-phenylisoserine derivatives in a one-pot procedure,[382] also applied to a synthesis of (-)-bestatin[383] revealing extraordinary control over the stereochemical outcome by the p-substituent of the aromatic ring.[384]

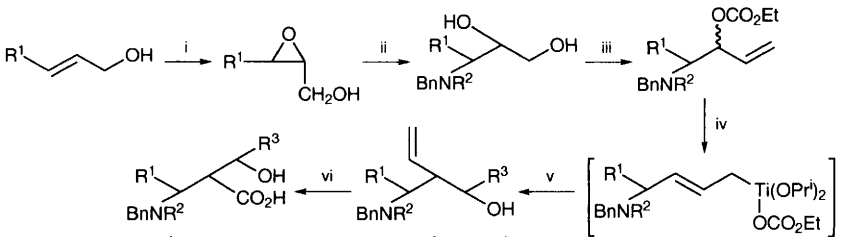
Cyclopropanation of N-Boc-pyrrole by methyl diazoacetate in an improved procedure, followed by ozonolysis and reductive work-up, gives the β-amino acid aldehyde (75) as a single stereoisomer.[385] Homochiral 3-amino-2,2-dimethylcyclobutanecarboxylic acids have been prepared by Curtius rearrangement of the half ester of the corresponding cyclobutanedicarboxylic acid using $(PhO)_2P(O)N_3$,[386] similarly employed for amination of the product of cyclopropanation of tert-butyl cinnamate using the anion of chloromethylphosphonamide to give enantiopure 2-amino-3-phenylcyclopropanephosphonic acid.[387] All four stereoisomers of 2-aminocyclopentanecarboxylic acid have been prepared starting from readily-available enantiomers of 3,4-dimethoxycarbonylcyclopentanone and resolution with (+)- or (-)-ephedrine of amination products at the end of the reaction path.[388] The synthesis of methyl (2S,3S)-3-amino-2-methyl-7-octynoate, a component of onchidin, and the (2R,3R)-diastereoisomer, have been synthesized *via* the β-lactam formed by amination of the corresponding β-hydroxy acid prepared by the Evans route (Section 4.1.3).[389]

Homologation of N-Boc- or N-Z-L-proline by diazomethane-silver benzoate gives excellent yields,[390] and the same applies to the preparation of N-Fmoc β-amino acids[391] including their *in situ* generation during a solid-phase β-peptide synthesis.[392] Homologation of α-amino acids into β-amino acids (see also Ref. 534) has been reviewed.[393] Another classical approach, the easy alkylation of ethyl cyanoacetate followed by reduction of the cyano group, has been used for the synthesis of α-alkyl-β-alanines (see Ref. 166).

cis-4-Hydroxypiperidine-3-carboxylic acid, prepared as the racemate by the reduction of the readily available ketone (a literature account suggesting that baker's yeast reduction was highly enantio- and diastereo-specific could not be confirmed), was used in combinatorial synthesis of bioisosteric carbohydrate mimetics.[394] Cocaine and related tropane alkaloids are not overlooked as sources of cyclic β-amino acids, and N-Fmoc derivatives of tropanes, stripped of certain functional groups, have been described.[395] Elaboration of the Diels-Alder adduct of N-Boc-pyrrole with methyl 3-bromopropiolate has given similarly useful

substrates,[396] and 4-alkylidene homologues have been prepared by the corresponding [4 + 2]-cycloaddition to allenic esters.[397]

3-Amino-2-hydroxyalkanoic acids are easily prepared through aldolization of α-aminoalkanals, and since these are available from α-amino acids and their sensitivity is now well understood, the overall process amounts to the conversion of an α-amino acid into a homologous β-amino acid.[398] The sulfur analogues, β-amino-α-mercaptoalkanoic acids, can be prepared best by p-methoxybenzylsulfenylation of β-amino acid enolates using (2,4-dinitro-C_6H_3)$SSCH_2$(C_6H_4-4-OMe) and replacing the p-methoxybenzyl protecting group as required.[399] The aminohydroxylation procedure introduced by Sharpless continues to offer valuable stereochemical control, shown as applied to methyl (E)-cinnamate (Vol. 29, p. 46; see also Ref. 91),[400] and a route to (2R,3S)-3-(N-toluene-p-sulfonylamino)-4-cyclohexyl-2-hydroxyalkanoic acids from the corresponding αβ-unsaturated esters is another simple example[401] (see Ref. 91 for a synthesis of phenylisoserine using this procedure). The drawback, the need to cleave a sulfonamide to release the amino acid, is less of a problem now that improved methods are available for this step, but the corresponding process with an N-halogenocarbamate sodium salts[402] should prove more convenient. An unusual development of Sharpless epoxides into β-amino acid derivatives *via* 3-amino-1,2-diols involves a chiral allyltitanium intermediate (Scheme 24).[403]

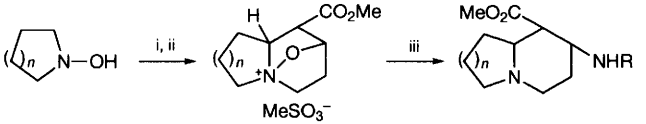


Reagents: i, $Ti(OPr^i)_4$/L-(+)-DIPT/TBHP; ii, $BnNHR^2$, $Ti(OPr^i)_4$;
iii, $NaIO_4$, $H_2C{=}CHMgBr$, $ClCO_2Et$/Py; iv, $Ti(OPr^i)_4$, Pr^iMgCl; v, R^3CHO; vi, O_3

Scheme 24

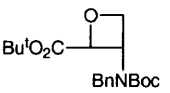
Nucleophilic attack at C-2 of N-toluene-p-sulfinylaziridine 2-carboxylic esters is a relatively rare event (C-3 attack is more usual), and is accomplished, with ring-opening, using $LiAlH_4$. It is highly stereoselective, oxidative manipulation of the products giving α-methyl-β-amino acids.[404] β-Lactams have been found suitable for the preparation of 2,3-diaminoalkanoic acids, in a programme with particular emphasis on the synthesis of analogues of taxol.[405] Other ring-opening processes are essential steps in syntheses of 4-aminopiperidine-3-carboxylic esters (Scheme 25).[406] Approaches to novel α-cyclopentyl (S)-isoserines have been explored, featuring ring-opening of an appropriate epoxide with (R)-α-methylbenzylamine.[407] Poly(L-leucine)-catalysed asymmetric epoxidation of trans-αβ-unsaturated ketones by urea-H_2O_2 in THF with DBU and aminolysis of the homochiral product gives (2R,3S)-β-phenylisoserine.[408] syn-β-Amino-α-hydroxyacids have been prepared through conversion of homochiral α-hydroxy-βγ-

unsaturated esters into allylic carbamates using TosNCO, and their iodocyclization into trans-4,5-disubstituted oxazolidin-2-ones, followed by reductive deiodination.[409] The antibiotic β-amino acid oxetin (76 without protecting groups) has been synthesized as its racemate through Paterno-Buchi cycloaddition of the enecarbamate CH_2=CHN(Bn)CO_2Bu^t to Bu^tO_2COH.[410]



Reagents: i, [O] → nitrone; ii, [1,3]dipolar cycloaddition to alkadienoate; iii, DABCO, RNH_2

Scheme 25



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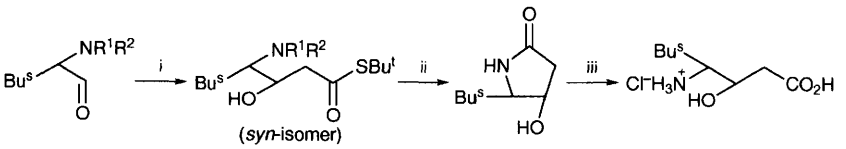
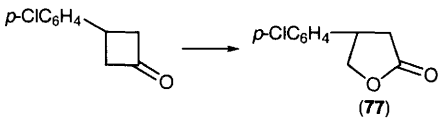
(3R,5R)-3,6-Diamino-5-hydroxyhexanoic acid, the β-amino acid constituent of (+)-negamycin, has been prepared through a route employing mandelonitrile lyase (further details not provided in the abstract source of this information).[411] Further details have been given of the synthesis of N-Boc-Adda from L-serine and (S)-phenyl-lactic acid (see Vol. 29, p. 43),[412] and a new synthesis of N-Boc-(2S,3S,8S,9S)-Adda, employing Pd(0)-catalysed cross-coupling of a syn-homopropargylic ether to a secondary allylic amine bearing an (E)-vinyl iodide, has been reported (see Ref. 768 for a synthesis from an α-amino aldehyde).[413]

γ-Amino acids continue to be almost exclusively synonymous with statines, as seen in a survey of the literature on amino acid synthesis. A route to these from 3-keto-esters,[414] and other pathways from α-aminoalkanals, through aldolization (Scheme 26),[415] through reaction with 3-methylglutaconate to give 2-substituted statines, $RCH(NBn_2)CH(CO_2Me)CMe{=}CHCO_2Me$,[416] and through syn-selective allyl- or vinyl-magnesium bromide addition [L-leucinal → (-)-N-Boc-statine and (-)-N-Boc-norstatine],[417] feature new developments in synthetic methodology. Other familiar examples of γ-amino acids that continue to attract synthetic interest are (R)-carnitine [see also Vol. 29, p. 48; prepared from (R)-4-trichloromethyloxetan-2-one *via* ethyl (R)-3-hydroxy-4-chlorobutanoate formed through hydrogenolytic ring-opening,[418] from R-(-)-epichlorhydrin by reaction with CH_2=$CHMgBr/CuBr$ and subsequent processing,[419] and from trans-crotonobetaine using *E.coli* 044 K74[420]], racemic baclofen [H_2N-CH_2CH(4-Cl-C_6H_4)CH_2CO_2H, from the [2 + 2]-cycloadduct of dichloroketene with an alkene],[421] R-(-)-baclofen [seven-step route with *Cunninghamella echinulata*-mediated generation of the (3R)-chlorophenyl-lactone (77), by Baeyer-Villiger oxidation of a racemic precursor, as a key step],[422] (-)-detoxinine [prepared in a novel way starting from dichlorodi-isopropylsilane (Scheme 27)],[423] and (S)-vigabatrin after deprotection of CH_2=$CHCH(NHBoc)CH_2CH_2CO_2Me$ [from



Reagents: i, $[(menthyl)_2CH_2]_2BCl$ [from (+)-menthone] → $CH_2=C(SBu^t)OB[(menthyl)CH_2]_2$; ii, $NH_4^+HCO^-/Pd$; iii, $H_3O^+Cl^-$

Scheme 26



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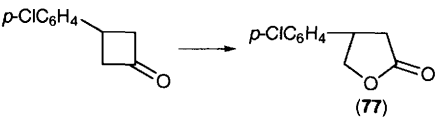

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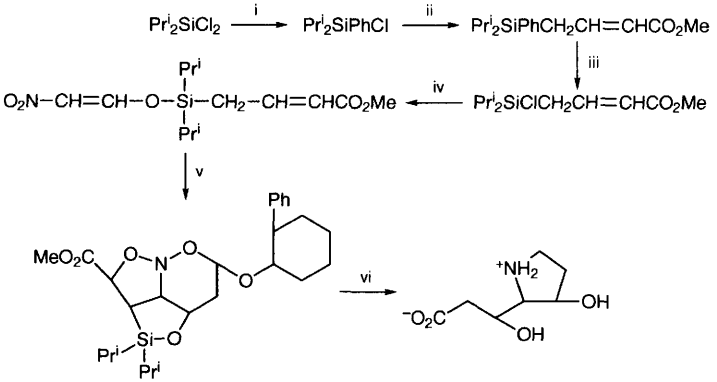
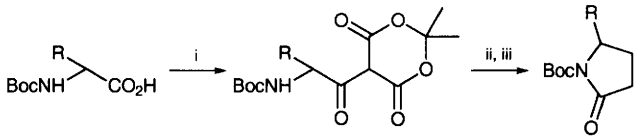


Reagents: i, 1 eq. PhLi; ii, Li, CuCN, $ICH_2CH=CHCO_2Me$; iii, HCl, $CHCl_3$; iv, $KOCH=CHNO_2$; v, (−)-(2-phenylcyclohexyl) vinyl ether; vi, routine hydrolysis

Scheme 27

(E)-5-phenyl-2-penten-1-ol *via* Sharpless oxidation and oxidative conversion of the phenyl group into CO_2H].[424]

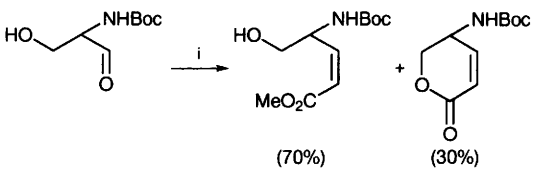
3-Aminocyclopentanecarboxylic acids bearing a 5-[pyrimidin- or purin-1-ylacetyl] grouping have been described (Ref. 347), and δ-amino acid analogues have been synthesized, in each of which the cyclopentane ring is replaced by a glucosamine moiety carrying one of the four nucleobases.[425] Conformationally-restricted β-hydroxy-γ-amino acids have been prepared by Diels-Alder addition to an N-acryloylcamphorsultam [*cf.* Scheme 6, $CH_2=CHCO$- in place of $(MeS)_2C=CHCO$-; for a synthesis of (3S,2S,1S)-3-amino-2-hydroxycyclohexane-1-carboxylic acid].[426]



Reagents; i, Meldrum's acid; ii, $Na(OAc)_3BH$; iii, $\Delta(-CO_2)$

Scheme 28

Simple homologation of α-amino acid esters (DIBALH then $Ph_3P{=}CHCO_2R$ followed by H_2/Pd-C) to γ-amino acid esters, and introduction of an α-substituent through enolate alkylation, offers an attractive route to γ-amino acids (which may not be applicable if sensitive functional groups are present in the target amino acid).[427] Another standard route in which an N-Boc-L-α-amino acid is condensed with Meldrum's acid leads to γ-lactams (Scheme 28).[428] A frequently-used homologation from the Garner aldehyde (see Section 6.3) involves condensation with the bistrifluoroethyl phosphonate $(CF_3CH_2O)_2P(O)CHMeCO_2Me$ to give γ-amino αβ-unsaturated esters which prove to be amenable to Os-catalysed dihydroxylation.[429] An alternative route to these substrates starts with the addition of lithiated tert-butyl or ethyl propiolates to nitrones $R^1CH{=}N^+R^2O^-$ [→ $R^2N(OH)CHR^1C{\equiv}CCO_2R$ → $R^2NHCHR^1CH_2CH_2CO_2R$ *etc*].[430] Horner-Wadsworth-Emmons alkene synthesis from α-amino-β-hydroxyalkanals involves Z-selectivity when bis(trifluoroethyl)phosphonates are used (Scheme 29).[431]

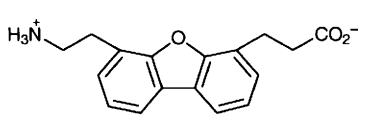


Reagents: i, $(F_3CCH_2O)_2P(O)CH_2CO_2Me$, LiCl, DBU

Scheme 29

Carbon-carbon bond forming syntheses are illustrated by radical cyclization of bromodifluoroacetyl allylamines $BrCF_2CONR^1CH_2CH{=}CHR^2$ to give γ-lactams.[432] γ- and δ-Lactam synthesis is also covered in Ref. 138.

With greater separation of amino and carboxy functions, appropriate synthetic methodology becomes more mundane, and general syntheses do not exist. A synthesis is individually tailored to give access to the particular target, as with 2-[4-(2′-aminoethyl)-6-dibenzofuran-2-yl]propanoic acid (78)[433] and sialyl sugar amino acids (starting from neuraminic acid),[434] a conversion of unprotected D-pentono-1,4-lactones into 5-amino-5-deoxy-D-pentonolactams by manipulating the primary alkanol function (CH_2OH → CH_2Br → CH_2N_3 → CH_2NH_2),[435] and aminomethylthiophen-1-carboxylic acids.[436] The synthesis of conformationally-constrained 3-amino-1-aza-2-oxobicycloalkanecarboxylic acids (*e.g.* 79) through standard methods (such as the Schollkopf synthesis, Section 4.1) has been reviewed.[437] Interesting approaches are still available to be explored, *e.g.*



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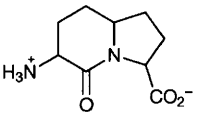

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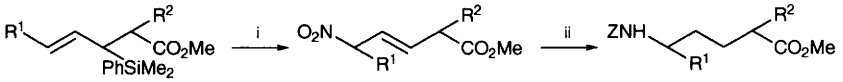
nitration as a means of introducing the δ-amino function into homochiral (E)-crotyl silanes (Scheme 30).[438] 5-(Z-Amino)-2-alkyl-4-hydroxyalkanoic acids have been prepared through condensation of an N-Z-L-α-amino acid with 2-triflyloxy-esters (see also Ref. 414),[439] and δ-amino-βγ-unsaturated alkanoates, *e.g.* $Me_2CHCH(NHMts)CH{=}CHCH(CH_2Ph)CO_2Me$, have been obtained from 4-(aziridin-2-yl)acrylates.[440]



Reagents: i, $NO_2^+BF_4^-$; ii, functional group development

Scheme 30

α-Sulfenylation of 2-(ω-benzenesulfonylaminoalkyl)-1,3-oxazolines gives ω-benzenesulfonylamino-α-(methylthio)alkanoic acids.[441]

An erratum has been published[442] relating to an account of the synthesis of 4-[^{13}C]-, 5-[^{13}C]-, and [^{15}N]-labelled 5-aminolaevulinic acid, currently of interest as a substrate for porphyrin biosynthesis whose photoactivation in tumours is a promising therapeutic approach. A simple condensation of the acid chloride of labelled phthalimidoglycine with the zinc homoenolate of ethyl propionate constitutes this synthesis, and a similar approach giving [2,3-$^{13}C_2$]-5-aminolaevulinic acid uses ethyl [1,2-$^{13}C_2$]bromoacetate.[443] Potassium [^{15}N]phthalimide reacts with tetrahydrofuranyl bromide to give the aminofuran derivative that yields [^{15}N]-labelled 5-aminolaevulinic acid through RuO_4 oxidation.[444]

These δ-amino acids, and the 'δ-nucleo-amino acids' formed by alkylation of protected L-serinols or L-homoserinols with bromoacetates followed by Mitsunobu introduction of thymidine or uracil to give $H_2NCH(CH_2base)$-$CH_2OCHRCO_2H$ and its homologue,[445] or by amination by azidolysis of δ-hydroxy β-(β′-adeninylalkylidene)alkanoic esters and thymidinyl analogues,[446] fall in the category of dipeptide mimetics which are covered in a later Chapter in this Volume.

4.16 Resolution of DL-Amino Acids – Techniques for the separation of enantiomeric amino acids from a racemic mixture fall into several clearly defined categories. Classical laboratory resolution methods are illustrated by separation by fractional crystallization of diastereoisomeric salts formed between N-pivaloyl-DL-tert-leucine with (S)-α-methylbenzylamine for a route to (R)-tert-leucine (Ref. 87), similarly for DL-α-methyl-(4-carboxyphenyl)glycine (Ref. 83), 2-methylamino-3-phenylpropanoic acid (using mandelic acid; Ref. 448), and a synthesis of all stereoisomers of 2-aminocyclopentanecarboxylic acid [(+)- and

(-)-ephedrine, in Ref. 388]. There are cases where a D- or L-amino acid derivative is used for the formation of diastereoisomer mixtures, and of course these operations can be used in reverse for the resolution of DL-amino acids; examples are separations accomplished after the acylation of oxidized Cleland's reagent by N-Boc-L-phenylalanine,[447] combination of (RS)-2-chloro-3-phenylpropanoic acid with ethyl L-phenylalaninate,[448] and of (RS)-2-substituted ω-phenylalkanoic acids with methyl (S)-phenylglycinate,[449] and the corresponding use of an L-β-(N-trimethylammonio)alkanol bromide for efficient resolution of 2,2′-dihydroxy-1,1′-binaphthyl.[450]

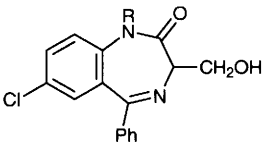
A retroracemization procedure in which a DL-amino acid is condensed with a (S)-2-[(N-alkylprolyl)amino]benzophenone in the presence of nickel(II) nitrate releases the (S)-enantiomer through hydrolysis (*cf.* Ref. 158) in 55-99% e.e.[451] A corresponding deracemization procedure employs an N-phthaloyl-DL-amino acid and (R)-pantolactone (Ref. 105).

The fortuitous preferential crystallization of one enantiomer (initiation of crystallization through seeding with the required enantiomer of the particular target amino acid, or even with an enantiomer of a structurally-related compound) lends itself to large-scale operation. A review has appeared,[452] and recent examples give practical details for DL-methionine hydrochloride,[453] (2RS,3SR)-2-amino-3-chlorobutanoic acid hydrochloride,[454] and DL-α-amino-γ-butyrolactone hydrochloride.[455]

The use of enzymes continues to occupy a prominent place in any list of current resolution options, and is illustrated in the current literature for catalysis of enantioselective hydrolysis: ethyl N-acetyl DL-3-aminobutyrate using lipase from *Candida antartica*,[456] rice bran lipase for a variety of N-acetyl DL-amino acid esters,[457] *Aspergillus niger* lipase for N-protected amino acid esters,[458] long-chain alkyl esters of non-protein amino acids using a microbial protease,[459] also used for syntheses of a Nikkomycin B constituent (Ref. 240) and (S)-4-fluoro-3-nitrophenylalanine (Ref. 326, and resolved using subtilisin, Ref. 141), diethyl acetamidomalonate using α-chymotrypsin to give the (+)-mono-ester (probably the R-enantiomer).[460] α-Chymotrypsin immobilized on Aphron[461] or on porous silica[462] is effective for the continuous-flow resolution of methyl DL-phenylalaninate. The resolution of N-chloroacetyl-DL-7-azatryptophan by carboxypeptidase A,[463] and N-acetyl-DL-(3-trimethylsilyl)alanine using hog kidney acylase (also used for N-acetyl-O-benzylthreonines; Ref. 841) and N-acetyl-DL-(p-trimethylsilyl)phenylalanine using an N-carbamoyl amino acid amidohydrolase[464] (see also Ref. 467) have been described.

A wide variety of sulfur- and selenium-containing N-acetyl-DL-amino acids are substrates for acylase I from *Aspergillus oryzae*[465] (a useful review covers aminoacylase resolution of N-acetyl-DL-amino acids and corresponding use of D-hydantoinases[466]). Acylase resolution (see also Ref. 806) of N-acetyl-β-(2-anthraquinolinyl)alanine has been reported (Ref. 140). N-Carbamoyl-D-amino acid amidohydrolase contained in cell-free extracts of *Blastobacter* sp. A17p-4 catalyses the enantioselective hydrolysis of N-carbamoyl-DL-(p-trimethylsilyl)-phenylalanine.[467] Hydantoins of numerous DL-arylglycines have been shown to be substrates of D-hydantoinase from various bacteria.[468] The peptide amidases

from *Citrus sinensis* and *Stenotrophomonas maltophilia* are effective in the resolution of N-acetyl-DL-amino acid amides[469] (see also Ref. 877 for a use of *Penicillium* amidase, and Ref. 815 for an application of *Pseudomonas putida* amidase). A whole-cell approach exploiting the amidase content of selected bacteria delivers (S)-amino acids with accompanying racemization (in other words, kinetic resolution) when applied to piperidine- and piperazine-2-carboxamides,[470] and the amidase of *Ochrobacterium anthropi* (see also Ref. 270) has been applied to racemic threo-amides to obtain 4-methylthio- and 4-methysulfonyl-(2S,3R)-3-phenylserines.[471] The reverse approach is illustrated in enantioselective N-α-phenylacetylation of amino acids using immobilized penicillin G acylase,[472] and acetylation by p-nitrophenyl acetate of an amino acid anion catalysed by β-cyclodextrin,[473] formation of N-acetyl-D-3-amino-3-phenylpropanoic acid by processing of the racemate by cell-free extracts of *Streptomyces neyagawaensis* SL-387,[474] and O-acetylation of (80) with kinetic resolution, catalysed by immobilized *Mucor miehei* lipase at 60 °C, leading to D- and L-serine after workup.[475]



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Antibody-catalysed enantioselective hydrolysis of N-benzyloxycarbonyl-DL-amino acid esters has been reviewed.[476]

A series of papers is appearing dealing with the production of D-amino acids, through the destruction of the L-enantiomer in a racemate by bacterial action (DL-methionine; *e.g. Proteus vulgaris*).[477] In the case of the production of D-lysine, the starting point was the L-enantiomer, with *Comamonas testosteroni* emerging from exploration of numerous species as the favoured agent for digestion of the racemate created by prior chemical racemization.[478] Biocatalytic deracemization (*i.e.* enzyme-mediated dynamic resolution and stereoinversion of easily racemized amino acid derivatives, such as oxazolones and thiazolones) has been reviewed.[479]

Chromatographic and related physical techniques continue to show improving potential when applied to preparative-scale separation of enantiomers.[480] Classical resolution methods associated with classical chiral stationary phases (CSPs), *e.g.* cellulose for the resolution of all the protein amino acids and representative N-dinitrophenyl derivatives,[481] polymer-supported bovine serum albumin (BSA) as stationary phase for the resolution of N-substituted DL-amino acids,[482] and apoenzymes immobilized in a porous polymer membrane[483] for enantioselective transport of amino acid derivatives, and a related ultrafiltration application of BSA for the resolution of DL-tryptophan[484] have been illustrated. Novel CSPs include (R)-phenylglycine-derivatized poly(siloxane)s [efficient separation of N-(3,5-dinitrobenzoyl)-DL-α-amino acid amides],[485] (1→6)-2,5-anhydro-3,4-di-O-

methyl-D-glucitol attached to silica gel for efficient resolution of bulky DL-amino acids (tryptophan and phenylglycine),[486] and CSPs employing the ligand exchange principle, also for use with underivatized amino acids.[487] Uses of CSPs in analytical resolution are covered in parts of Section 7 of this Chapter.

Molecule-imprinted CSPs have been described: cellulose acetate imprinted with Boc-L-glutamic acid shows preferential permeation by L-glutamic acid;[488] methacrylic acid – trimethylolpropane trimethacrylate copolymer imprinted with Boc-L-phenylalanine successfully resolves Boc-DL-phenylalanine;[489] poly(methacrylate)s imprinted with L-phenylalanine anilide have functioned in the capillary electrophoresis mode for resolution of amino acids.[490] Polymers imprinted with N-Boc-L-alanine, -phenylalanine, or -glutamic acid, favour passage of the D-enantiomer of N-Boc-DL-phenylalanine, though with low efficiency, thought to provide evidence of homogeneity of binding sites.[491] The results achieved by chromatography over molecule-imprinted polymers, *e.g.* resolution of DL-amino acids in aqueous buffers,[492] have been reviewed.[493] Such media, prepared by polymerization of an achiral monomer, copper(II) N-(4-vinylbenzyl)iminodiacetic acid, and an amino acid template with ethyleneglycol – dimethylmethacrylate as crosslinking agent, then grafting on to silica gel, give good results with DL-phenylalanine but no resolution was achieved for DL-alanine.[494]

Polymeric membranes bearing the tetrapeptide Asp(OChex)-Ile-Asp(OChex)-Glu(OBzl)O-CH_2- (*i.e.* covalently-bonded through its C-terminal carboxy group), that have been imprinted by Boc-D- or L-tryptophan, allow L-amino acids to permeate preferentially, under electrodialysis conditions.[495] L-Tryptophan has been shown to permeate a (+)-poly{2-[dimethyl(10-pinanyl)silyl]norbornadiene} membrane more readily than its D-enantiomer,[496] and a similar result has been found for membranes made from poly(γ-benzyl-L-glutamate) carrying poly(oxyethylene) side-chains, the polymer adopting a right-handed α-helical conformation.[497] A chiral emulsion liquid membrane [copper(II) N-decyl-L-hydroxyproline in hexanol – decane] offers accelerated transport of D-phenylalanine from the racemate.[498]

Two-phase liquid-liquid extraction is enantioselective when a carbamoylquinine is included in the phase containing an N-protected DL-α-amino acid derivative.[499]

Speculation on mechanisms through which the L-enantiomeric amino acids came to predominate from presumed prebiotic racemic mixtures has featured in this Section over the years, and the mirror-symmetry breaking hypothesis[500] and the broader range of theories[501] will be familiar to regular readers. Surveys across a range of disciplines are published in a Conference Proceedings Volume.[502] Among the ideas with a more recent origin reviewed in the last-mentioned article, the interaction of chiral radiation (*e.g.* circularly-polarized light in the ultraviolet wavelength region) with DL-amino acids at a water-air interface of the prebiotic oceans continues to be developed; electrochemical reduction of phenylglyoxylic acid oxime in magnetic fields has been shown to deliver product with no e.e.;[503] synchrotron grazing incidence X-ray diffraction reveals that amphiphilic DL-amino acid monolayers on water or aqueous glycine separate into islands of opposite chirality.[504] The role of circularly-polarized synchrotron radiation, and

means by which a small initial enantiomer imbalance might have been amplified, are covered in a recent review.[505]

5 Physico-chemical Studies of Amino Acids

5.1 X-Ray Crystal Analysis of Amino Acids and their Derivatives – Amino acids that have received attention this year are: glycine – urea (1:1),[506] L-arginine perchlorate,[507] L-arginine phosphate, deuteriated in guanidino, amino and carboxy groups,[508] L-threonine at 12 K,[509] L-proline hydrate at 100 K,[510] α-methyl-L-proline hydrate,[511] DL-lysine oxalate and its L-form,[512] L-tyrosine perchlorate,[513] L-phenylalanine (S)-mandelate and the D(S)-diastereoisomer of this salt,[514] L-phenylalanine hemisulfate hydrate,[515] O-phospho-L-tyrosine,[516] L-histidine oxalate and the corresponding racemate,[517] (+)-α-methyl-4-carboxyphenylglycine (assigned the S-configuration),[518] [(2′R,4′S)-3′-benzoyl-4′-benzyl-5′-oxo-2′-phenyloxazolidin-4′-yl)]acetic acid and its (2′S,4′R)-analogue carrying 3′-acetyl in place of benzoyl,[519] and 5,7-dichlorokynurenic acid hydrate.[520]

X-ray data collected for amino acid and peptide derivatives have been reviewed.[521] New data for amino acid derivatives cover hexamethyl-L-cystine,[522] L-leucinamide,[523] N-acetyl-L-isoleucinamide and its sarcosine analogue,[524] N-acetyl-L-glutamic acid,[525] N-dodecanoyl-L-serine monohydrate,[526] N-trichloroacetyl-DL- and L-valine and trichloroacetates of these amino acids,[527] N^{α}-pyruvoyl-L-methionine and its copper(II) complex (binding of the metal ion is established to involve the α-keto-amide moiety),[528] the N-Boc-L-phenylalanine – pyridine complex,[529] methyl (R)-α-methylphenylalaninate hydrochloride,[530] 2-alkoxyoxazol-5(4H)-ones,[531] symmetrical anhydrides of N-benzyloxycarbonyl αα-dialkylglycines (of interest through revealing intramolecular interactions between urethane NH and phenyl groups),[532] DL-phenylalanine N-carboxy-anhydride,[533] methyl N-Fmoc homo-β-(S)-leucinate,[534] and (4R,5S)-3-[(2R,3S)-3-hydroxy-2-methyl-7-octynoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one.[535]

Several of these studies reach conclusions through incorporating data from spectroscopic techniques (*e.g.*, Raman – IR, Ref. 529).

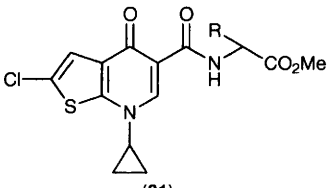
5.2 Nuclear Magnetic Resonance Spectrometry – The usual focus for this section, the frontier science featuring newer instrumental methods and unusual contexts, is illustrated by *in vivo* studies for non-invasive estimations of N-acetyl-L-aspartic acid by ^{1}H-NMR,[536] and for glutamic acid and glutamine (midfield ^{1}H-NMR for quantitative analysis based on areas of α- and β-proton resonances),[537] and the inverse spin-echo difference estimation of the ^{13}C-content of ^{13}C-enriched glutamic acid.[538]

Conventional studies include kinetics of ^{1}H-^{2}H-exchange for the α-protons of protonated methyl glycinate in $^{2}H_2O$.[539] Conformational outcomes from studies employing ^{1}H and ^{13}C-NMR are reported for α-, β- and γ-methylglutamic acids and cyclopentyl and cyclohexyl analogues,[540] kainic acid in water,[541] 2-(carboxycyclopropyl)glycines,[542] sodium N-dodecanoyl-N-methylglycinate (a Z/E-mixture in $^{2}H_2O$),[543] substituted 2,3-diaminopropenoic acid esters,[544] and 1-(N-

acylamino)adamantane-1-carboxylic acid amides.[545] Rotational barriers about C-N bonds for N-α-acylamino acid N′-methylamides have been derived from ^{15}N-NMR spectra,[546] and ^{1}H-^{15}N dipolar coupling studies have been reported for [^{15}N]-tryptophan and π-[^{15}N]-histidine.[547] Solid state studies of amino acids (^{13}C-NMR)[548] and amides of L-amino acids have been described in several recent papers employing ^{1}H-NMR (L-leucinamide,[549] L-alaninamide[550]) and joint NMR-X-ray analysis of L-leucinamide (Ref. 523). ^{13}C-NMR Spectra of amides of N-formyl-alanine, valine, and isoleucine have been reported.[551] As an illustration of a halfway stage between solid-state and solution-phase NMR, 2D J-resolved NMR spectra provide excellent results for N-protected amino acids attached to DMF-swollen Wang resin.[552] ^{19}F-NMR Spectra for N-trifluoroacetyl-amino acids in poly(γ-benzyl-L-glutamate), a chiral liquid crystal medium, show split resonances from which D:L-ratios can be calculated;[553] the equivalent methodology in other branches of NMR [^{2}H-NMR of N-(C^2H_3CO)-derivatives and earlier ^{1}H-NMR applications; see also Ref. 449)] is already well-established.

β-Cyclodextrin-entrapped N-dansyl-L- or -D-leucine,[554] and the enantioselectivity of D-mannitol-based crown ethers towards DL-amino acid esters[555] are examples of structural studies depending on standard NMR instrumentation.

5.3 Optical Rotatory Dispersion and Circular Dichroism – Little new has emerged in this topic area, and what there is [*e.g.* solvent-dependent CD of chromophore-substituted amino acid esters (81)[556]] derives from well-established principles. CD Features are generated within achiral poly(4-carboxyphenylacetylene) when in contact with solutions of homochiral amines and aminoalkanols,[557] and similarly for L- or D-amino acids complexed by achiral gadolinium(III) porphyrins.[558] The last-mentioned study also describes the extraction of the amino acid from aqueous media into a dichloromethane solution of the ligand, and emphasises the secure correlation observed between sign of Cotton effect and absolute configuration of the amino acid.



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5.4 Mass Spectrometry – Research activity centred on underivatized amino acids demonstrates state-of-the-art MS methodology. Time-of-flight plasma desorption studies of L-valine and L-leucine revealing the formation of ionic heteroclusters through gas-phase intermolecular reactions,[559] specifically identified to involve pairing in all four chiral combinations when pairs of amino acids are involved (*e.g.* the trimer formed from amino acids A and B → A_2BH^+ → ABH^+ + A_2H^+).[560] Chiral discrimination energies of 0.4 – 4 kJ mol^{-1} derived

from these data can be exploited to allow amino acid enantiomers to be distinguished by mass spectrometry, due to the basicity differences they exhibit when their dimers form part of gas-phase cluster ions. Complexes of α-amino acids with copper(I) ions survive into the gas phase.[561] Related laser desorption MS of tryptophan has provided internal energy data,[562] and has produced evidence of a stable ground state zwitterion structure for arginine through binding energy measurements on gas-phase dimers.[563]

Creation has been established of metastable ions $[MH - CO_2H_2]^+$ from leucine and isoleucine,[564] $[M + H]^+$ ions arising through electrospray MS of strongly basic solutions of amino acids, and $[M - H]^-$ ions from strongly acidic solutions,[565] and of $[M + {}^2H]^+$ ions from amino acids using C^2H_4 and $(C^2H_3)_2CO$ as ionization reagents in CIMS.[566] Consideration of fragment ions in the latter case has demonstrated scrambling of protons (in other words, high proton mobility).

Nickel(II) salt – aliphatic amino acid mixtures behave similarly to corresponding mixtures with copper(II) salts, in yielding $[M + Ni]^+$ ions through FABMS but $[Ni(M-H)M]^+$ ions through electrospray ionization.[567]

Reaction products in the gas phase from cysteine, Me_2Cl^+ and $MeOCH_2^+$ are shown by MS to include S-methylcysteine and N-methylcysteine.[568]

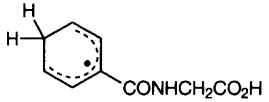
Electrospray ionization mass spectra of PTHs have been fully characterised;[569] three fragmentation pathways have been established for the $[M-H]^-$ ion formed from the PTH of phenylalanine.[570]

5.5 Other Spectroscopic Studies of Amino Acids – Identification of reaction products by routine spectrometric methods is occasionally mentioned elsewhere in this Chapter, but this section is reserved for more unusual studies. These include FTIR study of the effect of glycine and alanine on the water structure of their aqueous solutions,[571] FTIR estimation of self-association of N-Boc-L-α-amino acids in CCl_4[572] and IR-Raman study of amino acids at 18 K over the frequency range 400 – 3800 cm^{-1},[573] non-ionized glycine in a low-temperature argon matrix,[574] and corresponding vibrational spectra for α- and β-alanine,[575] [^{2}H]-doped glycine hydrochloride,[576] N-acetyl-αβ-dehydro-amino acid N′-methylamides,[577] fullerene – amino acid reaction products (see also Ref. 598),[578] and polarized Raman analysis of the vibrational coupling of water of hydration with the amide-I band of N-acetylglycine,[579] UV resonance Raman study of domoic acid,[580] and Raman and ^{1}H-NMR demonstration of the effectiveness of non-polar side-chains in enhancement of water structure by amino acids.[581] Surface-enhanced Raman spectra have been determined for L-phenylalanine,[582] and similarly for GABA,[583] using silver-colloid solutions. An inelastic coherent neutron scattering study augmented by IR-Raman data has been reported for N-[^{2}H]-L-isoleucine.[584]

Further development has been reported of an application of absorption millimetre spectroscopy at 31.42 GHz (see Vol. 29, p.60) in the establishment of a hydrophobicity scale for amino acids.[585]

Electron spin resonance (ESR) spectrometry of UV-irradiated [^{2}H]-, [^{13}C]-, [^{17}O]-labelled tyrosine has allowed the mapping of π-electron spin-density of the neutral phenoxy radical in frozen alkaline solution,[586] and ESR of X-irradiated

single crystals of hippuric acid has demonstrated decarboxylation (formation of carbon centred radicals $PhCONHC^{\cdot}H_2$) and hydrogen radical addition to the phenyl group to give (82).[587] Identification of radicals formed in X-ray-irradiated solid L-alanine has been reported,[588] and ESR properties of this amino acid are also described in support of *in vivo* radiation dosimetry, in a paper[589] that is representative of group of related studies described in a Conference Proceedings volume.



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5.6 Other Physico-chemical Studies of Amino Acids – This Section has settled into a number of sub-sections that are retained in the order in which they have been presented in recent Volumes, but topic areas now deserve to be highlighted through specific sub-headings.

5.6.1 Measurements for Amino Acid Solutions. – Continuation of major studies, into the calorimetry of ternary aqueous systems to establish pairwise cross-interaction coefficients for α-amino acid solutes,[590] enthalpies of interaction of some alkali-metal halides[591] and ammonium methanoate[592] with α-amino acids, appear side-by-side with papers of a less substantial nature (those cited here, are representative of a much larger literature), on solute interactions between NaCl and KCl with glycine, DL-alanine, DL-valine, and DL-leucine in water (Vol. 29, p. 60),[593] with D- and L-serine,[594] of NaCl and $NaNO_3$ with DL-threonine[595] and with glycine and DL-methionine,[596] effects of temperature and pH on the solubilities of common L-α-amino acids,[597] the degree of self-association in water of the remarkably water-soluble fullerene[60] – amino acid adducts (see also Refs. 578, 802, 942, 943),[598] and complex permittivity values for glycine and valine in aqueous organic solvents.[599] Differential scanning calorimetry of aqueous proline over the temperature range -60 °C to 20 °C has been carried out in pursuit of an explanation for the low temperature dependence of the high solubility of this imino acid in water.[600]

Isolated accounts have been published on hydration heat capacities for amino acids in their zwitterionic form,[601] activity coefficients for amino acids through vapour pressure measurements on aqueous solutions,[602] partition coefficients and solubility data for glycine in butan-1-ol – ethanol – water mixtures[603] and in dextran – poly(ethyleneglycol) – water,[604] and distribution of L-tryptophan in aqueous di-(2-ethylhexyl)phosphoric acid – hexane (Vol. 29, p. 2; *cf.* also Ref. 628),[605] de-protonation constants for seleno-DL-cystine and seleno-DL-methionine by potentiometry,[606] dissociation constants for amino acids in dioxan – water at 298 K,[607] apparent molar volumes of ω-amino acids in aqueous guanidine hydrochloride,[608] partial molal volumes of solutions of α-amino acids

in aqueous urea at different temperatures,[609] and partial molal volumes and adiabatic compressibilities of N-acetyl-DL-serinamide and the threonine analogue in aqueous media.[610] Further results for hydrophobicity measurements on amino acids in aqueous media have been obtained using a multichannel taste sensor (Vol. 27, p. 49).[611] Amino acids complexed to metal ions, $M(aa)_n$, where M = Co, Cr, Rh, are well salted-in to water by simple salts.[612]

The explanation for an increase in specific rotation with dielectric constant of the solvent, noted for N-methacryloyl-L-leucine methyl ester,[613] is of continuing interest. Chemiluminescence is generated by adding H_2O_2 and ethidium bromide to aqueous solutions of L-aspartic and L-glutamic acids,[614] and glycine and L-asparagine.[615]

Proline at high concentrations (greater than 4M) prevents the precipitation of lysozyme from aqueous solutions by trichloroacetic acid (the classical protocol for protein isolation from aqueous media).[616] Although this, and the finding that L-histidine cleaves RNA, but not DNA,[617] are isolated observations of a semi-quantitative nature, they deserve to be recorded in the thorough review of amino acid science that this Chapter attempts to offer. L-Seryl-L-histidine cleaves DNA, but its N^{α}-(O,O-di-isopropyl)phosphoryl derivative is less effective in this respect.[618]

5.6.2 Measurements for Solid Amino Acids. – Differential scanning calorimetry of water-containing samples of DL-2-aminobutanoic acid and DL-norleucine have revealed series of similar phase transitions.[619] The optical activity of crystalline L-aspartic acid has been assessed.[620]

5.6.3 Amino Acid Adsorption and Transport Phenomena. – These topics also relate to studies that are described elsewhere in this Chapter, of chromatographic separations (Section 7.5, 7.6) and resolution (Section 4.16) of amino acids. A major topic area is illustrated in a study of the mechanism of adsorption of glutamic acid to a weakly basic ion-exchange resin,[621] of alanine to boehmite,[622] and variation with sodium chloride concentration of the uptake of leucine and phenylalanine by a strong cation exchanger.[623]

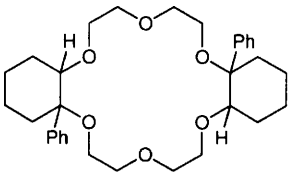
Another topic that is receiving much attention, for its *in vivo* role as well as for its practical applications, is transport of amino acids through membranes: separation of nine different amino acids on the basis of their differing electrostatic attraction for groupings built into a nanofiltration membrane;[624] a similar role for plasticized cellulose triacetate membranes containing large amounts of a quaternary ammonium salt (effectively a supported liquid membrane);[625] transfer of tryptophan and lysine through an impregnated liquid membrane using a strong acid,[626] and of tryptophan hydrochloride through PTFE-supported liquid membranes containing macrocyclic carriers;[627] and extraction of amino acids using PVF-supported liquid membrane with di-(2-ethylhexyl)phosphoric acid as carrier (*cf.* Ref. 605).[628] Transport properties for amino acids through a chitosan membrane have been reviewed,[629] and a review of amino acid transport by crown ethers has appeared.[630]

Size-exclusion chromatographic separation of amino acid mixtures has re-

vealed unexpected behaviour for tryptophan, ascribed to adsorption equilibria involving the stationary phase,[631] and L-thyroxine binding to human serum albumin as column chromatographic medium has been noted.[632] Chelated metal ion affinity chromatographic separation of amino acids and peptides using a Sephadex G10 medium modified by successive reaction with epichlorhydrin and copper(II) iminodiacetate has been described, separation depending on the differing stabilities of the copper(II) complexes of the amino acids.[633] Optimised preparative ion-exchange separation of a mixture of nine amino acids depends on simpler principles.[634]

5.6.4 Host–Guest Studies with Amino Acids – A series of supramolecular complexes between ammonium salts of L-α-amino acids and 2,3,11,12-bis[4-(11-aminoundecanoyl)benzo]-18-crown-6 has been described,[635] and the binding of alkylammonium salts of acids to 18-crown-6 hosts in water – 1,2-dichloroethane mixtures has been correlated with structure.[636] Molecular orbital calculations for relative binding free energies (*i.e.* enantioselectivities) for complexes of ammonium salts of amino acids with synthetic ionophores,[637] and for binding of methyl L-alaninate and L-alanine N′-methylamide to podand ionophore hosts and to C_3-symmetric receptors[638] have been reported.

Preferential binding of the L-enantiomer of an amino acid ester hydrochloride by a chiral crown ether (83) prepared from (R,R)-1-phenyl-1,2-cyclohexanol occurs with low enantioselectivity (14 – 26%),[639] as is also the case for (84), acting as host for aromatic amino acids,[640] and for N-protected amino acids interacting with chiral C_3-symmetric cage-like receptors [(S,S,S)-(+)-85] that carry convergent helically-oriented amide binding sites (Vol. 29, p. 61).[641] Rather better results are achieved with Z-DL-glutamic acid using sapphyrin derivatives [porphyrin-CO-X-CO-porphyrin; X = (1S,2S)-1,2-bisamidocyclohexane][642] and for underivatized amino acids with ammonium 2,3,11,12-bis[4-(10-aminodecylcarbo-



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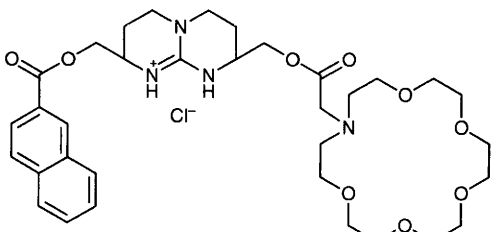

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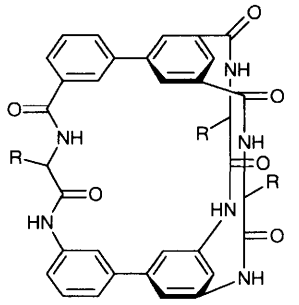

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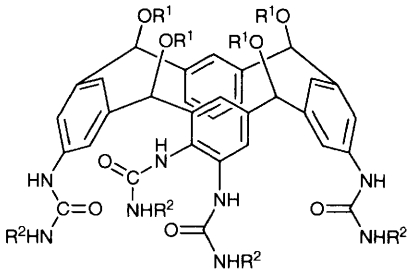
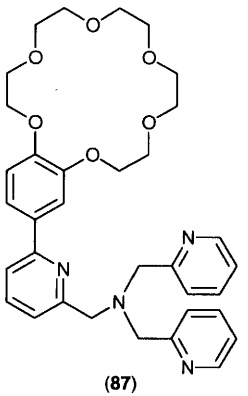
nyl)]benzo-18-crown-6[643] and β-cyclodextrin derivatives (*e.g.* L:D = 33:1 for leucine).[644] The 6-O-monophosphate of β-cyclodextrin shows moderate to good enantioselectivity in favouring complex formation with the D-enantiomer when presented with a racemic amino acid;[645] thermodynamic stability constants of amino acid – cyclodextrin complexation[646] and of complexation of amino acids with mono-[6-(1-pyridinio)-6-deoxy]-α- and γ-cyclodextrins[647] and anilino-β-cyclodextrin analogues[648] have been reported. The association of a copper(II) β-cyclodextrin complex with aromatic amino acids,[649] and the enhanced fluorescence, with intensity in proportion to the concentration of an amino acid in the same solution, of the copper(II) complex of a dansyl-diethylenetriamine-modified β-cyclodextrin,[650] have been described.

Calix[4]arene-based α-aminophosphonates exhibit remarkable selectivity as carriers for membrane transport of the zwitterionic form of aromatic amino acids,[651] and calix[4]arene dimers (86) and amino acid derivatives form homochiral capsules.[652] The binding profile of the novel host (87) for a series of amino acid guests indicates that the two binding sites are 6.5 angstroms apart.[653]



(86)

One of these hosts (84), specific for aromatic amino acids, carries a chiral bicyclic guanidine moiety, and a remarkable opposite to this is seen in the arene $[4\text{-}\{(MeO)P(O)_2CH_2C_6H_4\}_2X]^{2-}$ $[Bu_4N]_2$ (X = S, O, *etc.*) that binds to guanidines (especially to N- and C-amide-protected arginines), exactly analogous to the 'arginine fork' postulated for RNA-protein recognition in the AIDS virus.[654]



(87)

Competition between N-Z-amino acids for a novel host (zinc acetate – N-methylmesoporphyrin-II basket with a xylylene-diamide 'handle') favours Z-glycine, but in $CHCl_3$ – water those guests carrying hydrophilic side-chains are preferred.[655]

5.7 Molecular Orbital Calculations for Amino Acids – The unremitting flow of papers describing molecular orbital calculations chosen to simulate the behaviour of an amino acid residue in a polypeptide continues with N-formyl-L-phenylalaninamide,[656] the N-acetyl amino acid N-methylamides of L-alanine,[657] αα-dialkylglycines,[658] valine,[659] asparagine,[660] cis- and trans-2,3-methanomethionines,[661] and phenylalanine analogues with crowded side-chains (Ref. 330), the main differences from previous studies being the gas-phase or solution context of the molecule under scrutiny. Adsorption binding energies of amino acids to ionophores have been calculated (Refs. 637, 638).

Calculated conformational equilibria for N-acetyl alanine-, leucine-, and glutamine-N-methylamides at the water – hexane interface have been presented,[662] and data for N-acetyl-L-prolinamide have been compared with calculations for the free imino acid.[663] The eight most stable conformers of N-methylglycine have been identified, in parallel with similar calculations for the NN-dimethyl analogue.[664] Conformational studies for the glycine zwitterion in aqueous solution[665] and in the gas phase,[666] and corresponding treatment for the L-alanine zwitterion,[667] methyl 2-acetamidoacrylate, and energy calculations for the N-acylimine – enamide tautomers of this compound,[668] kainic acid (Ref. 541), and 2-(carboxycyclopropyl)glycine (Ref. 542) exemplify the thermodynamics context to which MO calculations can contribute (for a review see Ref. 669). This context is also a feature of intramolecular proton transfer within glycine in aqueous solution[670] and the related topic of the proton affinity of protonated glycine,[671] conformational energies of glycine and dithioglycine,[672] free energies of hydration of the coded amino acids in their zwitterionic form,[673] hydration structures of N-acetyl-L-leucinamide and its glutamine analogue,[674] glutamic acid – water interactions,[675] energetics of the conversion of L-arginine into its

N^G-hydroxy derivative,[676] absolute affinities of α-amino acids for copper(I) ions in the gas phase,[677] and Raman vibrational frequencies for L-asparagine[678] and for L-glutamine hydrate.[679] Calculations of standard molal thermodynamic properties of L-α-amino acids at elevated temperatures and pressures underpin a practical purpose, illustrated with effects on lysine and arginine, which exist in aqueous solutions at pH 7 at 25 °C almost entirely as protonated species, but are calculated to be 50% dissociated at 125 °C under pressure.[680] Electron – ion interactional potentials of amino acids have been correlated with physical properties such as hydrophobicity.[681]

Solvent accessibility offered by aromatic side-chains in water-organic solvent mixtures,[682] and similar studies of tryptophan,[683] have been featured in recent papers.

Amino acid radicals receiving attention include glycine in aqueous solutions in relation to their ESR characteristics,[684] tyrosine,[685] and the protonated tryptophyl radical cation $TrpH^{+\cdot}$.[686] The energetics of hydrogen transfer between amino acids in the presence of radicals has been considered.[687]

6 Chemical Studies of Amino Acids

6.1 Racemization – Complete racemization of amino acids liberated during protein hydrolysis occurs using 4M $Ba(OH)_2$ as reagent at 110 °C for 48 h.[688]

Racemization rates for aspartic acid at 60, 80, and 100 °C have been determined, and lead to an activation energy 29.1 kcal mol^{-1} for the process. The stimulus for this work was the derivation of a racemization rate for ambient 12.5 °C, so that age could be determined for a sample of colonial anemone *Gerardia* collected alive at 630 m depth in the sea off the Bahamas.[689] The figure was 250 ± 70 y, on the basis of the D/L-ratio for aspartic acid in samples taken from innermost and outer layers of the trunk, and, not surprisingly, was more readily believed than a radiocarbon date 1800 y.

Such figures derived from amino acid racemization data have become less respected; however, protein at constant temperature, and avoiding turnover through its life cycle, should provide credible data for a living organism. Abstracts of papers given at a Conference 'Perspectives on Amino Acid and Protein Geochemistry', published in Issue 3 of Volume 15 (1998) of the journal *Amino Acids*, include a large number of dating applications. A survey of principles and applications of amino acid racemization dating includes appropriate warnings of sources of inaccuracy,[690] and of course, errors will be introduced where there is uncertainty about the circumstances in which the samples have been placed; for example, stereoinversion at the aspartic acid residue at position 151 of αA-crystallin from human eye lens is a result of UV-B irradiation, but no changes occur in UV-A light.[691] Improved protein recovery from fossils and animal bones, and protocols for preparation of N-alkoxycarbonyl derivatives of methyl and ethyl esters for GLC estimations of aspartic acid obtained from the protein hydrolysates have been described.[692]

6.2 General Reactions of Amino Acids

6.2.1 Thermal Stability of Amino Acids – Isolated observations on this topic have been recorded over the years, but the greater interest in this topic, now that amino acids have been found in samples from extraterrestrial sources and from high temperature vents on the ocean floor, is revealing a lack of disciplined knowledge.

Contradictory claims that simple amino acids have been sublimed unchanged (Ref. 25), and that they self-condense through such treatment (Refs. 784, 786, 787), should be seen with a comment that the undersea vent scenario might make it unreliable to reason from laboratory analogies (Ref. 301). Results from earlier literature under this heading are summarised in Ref. 693.

6.2.2 Reactions at the Amino Group – Replacement of hydrogen at the amino group by simple species (kinetics of N-chlorination by N-chlorosuccinimide[694]) continues a long-running study (Vol. 29, p. 64). A mechanistic study of N-nitrosation of amino acids has been reported.[695]

Replacement of the amino group by halogen with retention of configuration, following the standard protocol, has been applied to D-methionine[696] and δ-phthalimido-L- or D-ornithine[697] for syntheses starting from homochiral amino acids. Conversion of an α-amino acid ester into an α-isocyanoalkanoate avoiding the use of phosgene has been described (DMAP- Boc_2O),[698] and a route to tert-butoxycarbamates from benzamides and acetamides (*e.g.*, AcNHR → AcNBocR → BocNHR) has been described.[699]

N-Acylation by standard procedures has provided N-(benzotriazol-1-ylcarbonyl)amino acids.[700] Lipases catalyse long-chain acylation of L-serine and L-lysine derivatives,[701] and aqueous thioacetic acid, acting as an oxidizing agent, catalyses the acetylation of phenylalanine and leucine, suggesting a primordial role for this compound.[702] Acylation occurs readily in compressed monolayers containing long-chain thioesters of N-acetylglycine and glycine-N′-alkylamides $H_2NCH_2CONH(CH_2)_{15}Me$.[703]

Reaction of an amino acid ester with bis(4-nitrophenyl) carbonate gives hydantoins as well as the expected NN′-carbonyl bis(amino acid ester)s.[704] Removal of the Boc group using BF_3-etherate in CH_2Cl_2 in the presence of molecular sieves requires only room temperature conditions;[705] removal of N-allyloxycarbonyl protection employs $Pd(PPh_3)_4$ – $PhSiH_3$.[706] The preparation of N-Fmoc-amino acids and their use in peptide synthesis has been reviewed.[707] Preparation of N-Fmoc-N-(2-hydroxy-4-methoxybenzyl)amino acids avoiding the formation of N,O-bis(Fmoc) side-products has been described.[708]

Sulfenamides have been prepared with the purpose of generating aminyl radicals through treatment with Bu_3SnH/AIBN.[709] N-Phosphonylation is a clean process when a catalytic amount of 1H-tetrazole accompanies a phosphonyl dichloride in the reagent mixture, since unwanted replacement of both chlorine atoms in sequential reactions with an alcohol and an amino acid is avoided.[710]

N-Silylation of a Boc-amino acid using a silyl triflate in dichloromethane at 0 °C has been described as 'protection of a protecting group', to emphasise the

point that the acidity of the carbamate proton can frustrate synthetic operations elsewhere in the molecule (see also Ref. 724).[711] Unexpected N-acetylation of the N-Fmoc-group of Fmoc-L-seryl and threonyl glycosides has been noted during standard protocols aimed at acetylation of the glucosamine moiety.[712]

N-(α-Picolinoyl)amino acids and peptides prepared from them, are easily deprotected by electrochemical reduction.[713] α-Chloroethyl chloroformate in methanol can be used to debenzylate NN-dialkyl-N-benzylamines.[714]

Schiff base formation is usually routine, and reaction of sn-1-palmitoyl- or stearoyl-2-(9-oxo-nonanoyl)glycerophosphocholine with amino acids is worthy of mention in the context of the unusual reagent.[715]

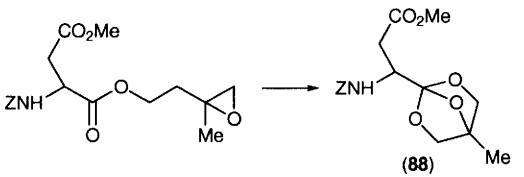
N-Alkylation of amino acids by carbene insertion into an N-H bond (Z_2C: + $RNH_2 \rightarrow RNH\text{-}CHZ_2$) can be accompanied by β-alkylation and ammonium ylide formation; existing knowledge on this topic has been reviewed,[716] and the process applied to an N-protected amino acid amide has been advocated as a new peptide synthesis approach ($R^1NHCHR^2CONH_2 + EtO_2CC(=N_2)P(O)(OEt)_2/Rh_2(OAc)_4$/toluene $\rightarrow R^1NHCHR^2CONHCH[P(O)(OEt)_2]$).[717] Preparation of N-methylamino acids on a solid support uses the Fukuyama method [(2-nitrobenzenesulfonylation, Mitsunobu methylation or the equivalent using MeI/K_2CO_3, and removal of the sulfonyl protecting group with PhSNa in DMF],[718] also applied to 4-nitrobenzenesulfonamides but in normal solution media.[719] Alkylation procedures have been described that are appropriate for the preparation of N-(ferrocenyl)amino acids,[720] N-[(R)-1-phenylethyl]phenylalanine and N-(3,4,5-trihydroxyphenyl)glycine,[721] N-(homoallylic)-amino acids (from a Schiff base using an allylindium reagent),[722] N-(arylation) using a substituted fluorobenzene,[723] N-(2-hydroxy-4-methoxybenzylation) through reaction with the corresponding aldehyde, followed by $NaBH_4$ reduction, and preparation of their N-Fmoc derivatives after O-protection using trimethylsilyl chloride (see also Ref. 711),[724] N-alkylation (benzophenone Schiff base, HCHO or other alkanal, $NaBH_3CN$),[725] N-vinylidenation (addition of Cl_2C: to a benzophenone Schiff base to generate a dichloroaziridine, then ring opening and dechlorination).[726] Use of the Mitsunobu reaction for the N-monoalkylation of amino acid esters after N-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)ation has been demonstrated.[727] N-Methylation of an N-Boc-amino acid after NaH deprotonation can be accomplished using methyl iodide (Ref. 767).

N^{α}-Alkylation of glycinamide using an alkyl bromide is an essential stage in peptoid synthesis, and repetitive use of an N-alkylation – bromoacetylation sequence has provided peptoid oligomers carrying N-acetylglucosamine residues.[728] N-Benzhydrylation of methyl pyroglutamate using benzhydryl chloride requires prior N-trimethylsilylation and triflic acid catalysis.[729]

A particular form of N-alkylation of amino acids *via* Schiff bases is represented in the Maillard reaction.[730]

N-Oxide formation from an amino acid is a highly stereoselective process; the unusually stable products (see also Vol. 28, p. 59) from N-benzylpipecolic acid and its analogues have been assigned relative configuration through X-ray crystal analysis.[731]

6.2.3 Reactions at the Carboxy Group – Formation of methyl esters has been reported when methanolic plant extracts (*Inga punctata foliar*) containing hydroxypipecolic acids are purified over a cation exchange resin.[732] Improvements to conventional esterification procedures have eased the preparation of tert-butyl esters (only tert-BuOH, anhydrous $MgSO_4$, and H_2SO_4 are needed, though lengthy reaction times in stoppered vessels are involved; the procedure also converts OH groups into tert-butyl ethers).[733] Secondary alkyl esters can be prepared from Z-L-amino acids in organic solvents using a Celite-immobilized proteinase or lipase, but 3 – 4 days reaction times are needed to secure yields around 70%.[734] Amidation of an N-protected amino acid by an alkylamine uses Boc_2O – pyridine (Ref. 698 describes a different outcome with Boc_2O-DMAP) described in a paper that contributes further to the voluminous preceding literature on this process (Vol. 28, p. 62).[735] Preparation of N-Z-amino acid ortho-esters (88) has been accomplished through $Cp_2(Cl)Zr^+$-catalysed rearrangement of 3,4-epoxyalkyl esters.[736]

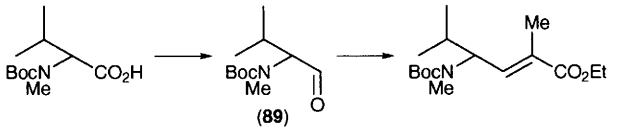


(88)

β-(Trimethylsilyl)ethoxymethyl esters can be cleaved using magnesium bromide etherate.[737] Pd/C-Catalysed hydrogenolysis of benzyl esters can be accomplished while preserving 4-methoxybenzyl ethers intact, if conducted in the presence of pyridine.[738]

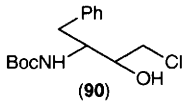
Reactions at the carbonyl group of an amino acid ester may be influenced considerably by the adjacent structural features, as in the reaction of organolithium reagents with methyl N-(phenylfluorenyl) pyroglutamate to give corresponding ketones, ascribed to unusual stabilization of the tetrahedral intermediate [$R^1CO_2Me + R^2Li \rightarrow R^1CR^2(OLi)Me$].[739] Regioselectivity of attack by an aniline on N-protected aspartic and glutamic acid anhydrides is dependent upon the solvent used.[740] Ketones can be formed on solid supports by reaction of the Weinreb amide RCON(Me)OMe with Grignard reagents,[741] also an intermediate in chain extension, *via* the α-aminoaldehyde (89) in a route to γ-amino-αβ-unsaturated esters.[742] An unusual twist is provided by coupling of γ-amino αβ-unsaturated acids to a solid support for use in peptide synthesis, terminated by ozonolysis to release peptide C-terminal aldehydes.[743] Condensation of an α-amino acid ester with $CH_2=C(OLi)OBu^t$ gives a β-ketoester,[744] and formation of α-ketoamides from homologation of the carboxy group proceeds *via* the acyl-cyanophosphorane intermediate $RCOC(=PPh_3)CN$.[745]

α-Amino bromomethyl ketones can be prepared from N-alkoxycarbonylamino acid esters, avoiding the use of diazomethane, through the Kowalski procedure (iodochloromethane and LDA), and have been used in α-aminoalkyl epoxide synthesis on a large scale.[746] α-Aminoalkyl chloromethyl ketones are claimed to



(89)

provide the best entry to α-aminoalkyl epoxides through stereoselective reduction,[747] although 3-Boc-aminoalkane-1,2-diols provide the same product through a modified Mitsunobu reaction.[748] Diastereoselective reduction of the chloromethyl ketone from Boc-L-phenylalanine using *Streptomyces nodosus* SC13149 gives the alkanol (90).[749] Amino acid diazoketones, (S)-$R^1R^2NCHRCOCHN_2$, form ketenes on photofragmentation that may be trapped *in situ* with an aldimine to yield an aminoalkyl-β-lactam.[750] Vinyl ketones $BocNHCHR^1COCH{=}CHR^2$ give aminodiol dipeptide isosteres through enantioselective reduction of the carbonyl group followed by aminohydroxylation of the C=C bond[751] and dimerization of methyl ketones $Bn_2NCH(CH_2Ph)COCH_3$ has been accomplished by copper(II) reagents acting on the sodium enolate.[752]



(90)

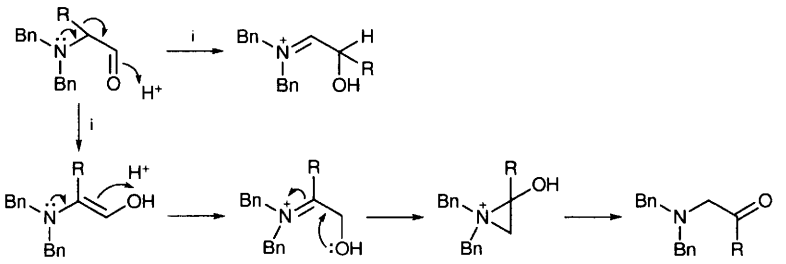
Fmoc-L-phenylalanyl fluoride can be used for O-aminoacylation of oligonucleotides after protection of phosphate groups by β-cyanoethylation.[753]

Tertiary amide enolates derived from amino acids are being used increasingly in general synthesis because of their propensity to electrophilic attack, and the simplest of these processes is re-protonation, illustrated to be enantioselective for an N^{α}-(alkoxycarbonyl)pipecolic acid amide when a chiral amine is used as proton source.[754] Cleavage of secondary amides is effected by N-nitrosation followed by treatment with lithium hydroperoxide and reduction with sodium sulfite.[755] Sodamide – MeCN converts an N,N-dibenzylamino acid ester into the cyanomethyl ketone, a useful source of enaminones $Bn_2NCHR^1CO{-}CH{=}CR^2NH_2$ that are accessed through addition of excess Grignard reagent R^2MgCl.[756]

Reduction of the carboxy group of an amino acid to the aldehyde provides a useful synthesis intermediate, and sets the stage for further functional group elaboration. The DIBAL-H reagent is often used for this conversion, but better results may be achieved in some cases (N-Boc-S,O-isopropylidene-L-serinal from L-serine methyl ester) through lithium aluminium hydride reduction to the primary alcohol, followed by Swern oxidation (methodology already published; Vol. 27, p. 64).[757] The use of DIBAL-H with N-Boc-β-aminonitriles gives N-Boc-β-aminoaldehydes (*e.g.* 89) after the usual work-up.[758] Acetals [*e.g.* (R)-$BocNHCHMeCH(OMe)_2$] derived from these aldehydes can be converted into homoallylic aminoalkanols (R)-$BocNHCHMeCH(OH)CH_2CH{=}CH_2$, syn:anti = 68:32) with tetra-allyltin – TFA,[759] while reductive allylation of amino acids with

diallylborane gives 1,1-diallyl-2-aminoalkanols (useful as substrates for iodocyclization to 3-allylpyrrolidines).[760] The N-substituent of an N-protected amino aldehyde has a considerable effect on the stereochemical outcome of three-carbon elongation using allylmetal reagents.[761] No such complication arises in the case of one-carbon homologation by $Sm(0)/CH_2I_2$ [-CHO → -CH(OH)CH_2I].[762]

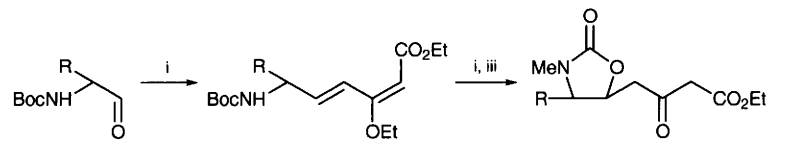
Boc-α-Aminoaldehydes (*e.g.* 89) have been employed in azapeptide synthesis (condensation with an acylhydrazide and reduction of the C=N bond),[763] and feature in an unusual rearrangement to give ketones, presumed to involve either a 1,2-alkyl shift followed by a 1,2-hydrogen shift, or an equivalent process (Scheme 31).[764] Further examples of synthesis applications for α-aminoaldehydes include



Reagent: i, SiO_2 or pyH^+OAc^-

Scheme 31

syn-aldolization to give α-aminoalkyl epoxides,[765] condensation of N-phosphonyl derivatives with a chiral phosphonate $(RO)_2P(O)CH_2CO_2R^*$ [R* = (-)-menthyl] leading to stereoisomer mixtures as a result of easy epimerization at the α-carbon atom.[766] Similar condensation with a 2-ethoxy-(3-ethoxycarbonylallylidene)triphenylphosphorane gives 6-Boc-amino-3-ethoxy-2,4-hexadienoates, used in a synthesis of homochiral N-methyl-oxazolidinones (Scheme 32) through cyclization after N-methylation.[767] Aldolization with (R,E)-crotylsilanes and their S-enantiomers, $MeCH{=}CR^1CH(SiMe_2Ph)CH_2CO_2Me$, leads to 7-(Boc-amino)alk-3-enoates (Ref. 413).[768] Boc-α-Aminoaldehydes react with an allylindium reagent to give allyl alcohols with very modest stereoselectivity.[769]



Reagents: i, $Ph_3P{=}CHC(OEt){=}CHCO_2Et$, THF, r.t., 24 h; ii, NaH, DMF, then MeI;
iii, H_2SO_4–SiO_2/CH_2Cl_2

Scheme 32

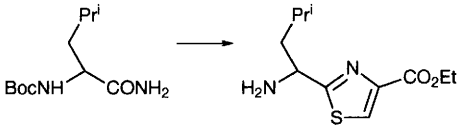
Radical cyclization of N-allyl-α- and -β-aminoaldehydes using Bu_3SnH/AIBN in boiling benzene (*cf.* Ref. 817) leads to hydroxypyrrolidines and hydroxypiperidines.[770]

N-Protected (S)-β-aminoalkanols, prepared from L-amino acids, have nu-

merous uses in their own right, and conversion into corresponding bromoalkanes and attachment through the ether linkage to 3,5-dihydroxybenzoic acid or gallic acid followed by acylation of the amino groups after deprotection, followed by repetition of these steps a number of times, gives highly divergent dendrimers.[771]

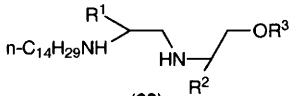
Hypotaurine $H_2NCH_2CH_2SO_2H$ is a special case of an amino acid with an acid group at low oxidation level, and therefore shows the expected tendency to disproportionate into taurine, cysteamine, and cystamine.[772]

Esters of L-proline undergo Curtius rearrangement to give isocyanates,[773] and acylnitroso dienophiles can be generated *in situ* through oxidation by $NaIO_4$, of N-protected amino acid hydroxamates (S)-Boc-NHCHMeCONHOH.[774] Amino acid amides can be developed through the carbonyl group *via* thioamides into thiazolecarboxylates (91)[775] and into analogous oxazoles[776] as dipeptide surrogates, through standard methods.



(91)

Kinetics have been determined for copper(I) or zinc-catalysed hydrolysis of alanyl ethyl phosphate, viewed as an analogue of an aminoacyl adenylate.[777] Catalysed enantioselective ester hydrolysis has been a long-running topic in the amino acid field, and this year there are further results from enantioselective hydrolysis of p-nitrophenyl N-dodecanoyl-D- or L-phenylalaninate catalysed by L-histidine-containing surfactants (Z-L-Phe-L-His-L-Leu-OH can generate almost 100% discrimination).[778] A new approach is the involvement of lipophilic homochiral ligands (92) in cationic aggregates [*e.g.*, of cetyltrimethylammonium bromide containing a copper(II) salt], which generates remarkably high enantioselectivity (11 to 35-fold).[779] N-(β-Hydroxyethyl)amino acid amides are unusually easily hydrolysed, due to participation by the hydroxy group of the N-substituent, and therefore they are easily aminolysed and are activated towards peptide bond formation under mild conditions.[780]

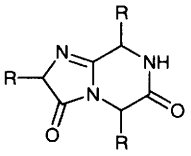


(92)

Peroxyl radical attack on [1-^{13}C]leucine has been shown to lead to decarboxylation but also to several products in which the carboxy group is retained, notably 3-methylbutanoic acid.[781]

6.2.4 Reactions at both Amino and Carboxy Groups – Self-condensation of amino acids in concentrated salt solutions (Vol. 28, p. 64) has been established to be a

remarkably simple pathway to peptides, that may have relevance to prebiotic synthesis. Studies of this topic by the pioneers have moved on to specific protocols; *e.g.* alanine and glycine subjected to wetting-drying sequences at 80 °C on alumina, silica, montmorillonite, or hectorite leads to dioxopiperazinediones with the first two minerals but to longer oligopeptides with the second two.[782] Exploration of sequence preferences (those amino acids that self-condense with ease, or condense with other amino acids in mixtures, and those that do not) has also featured in recent studies.[783] Other research groups are studying mechanistic details [kinetics for the copper(II) acetate – glycine – alanine system].[784] Structure-reactivity relationships may emerge for this process from future studies along these lines. Carbonyldi-imidazole accomplishes the oligomerization of L-aspartic acid, L-glutamic acid, and O-phospho-L-serine in aqueous solution in a most efficient manner,[785] as seen for the self-condensation of glycine in an aqueous suspension of zeolite and kaolinite, presumed to occur *via* dioxopiperazine.[786] Sublimation of simple amino acids alanine, valine, leucine, or α-aminoisobutyric acid over silica at 230-250 °C under reduced pressure gives dioxopiperazines and the surprising homologues (93) and (94).[787]



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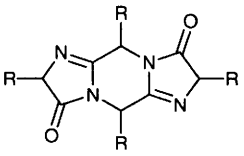
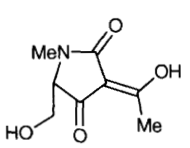


(94)

Solid amino acid mixtures bombarded with high energy particles, simulating cosmic ray irradiation, accumulate peptides,[788] a result that is easier to understand than the claimed formation of peptides when the frequency corresponding to the cyclotronic frequencies of amino acids matches that of an irradiating alternating magnetic field combined with electric fields.[789]

Homochiral aziridines obtained from (R)- and (S)-norvaline through successive $LiBH_4$ reduction, O-toluene-p-sulfonylation, and K_2CO_3-mediated cyclization, have been used in an epilachnene synthesis to establish the absolute stereochemistry of the natural azamacrolide from *Epilachna varivestis*.[790] N-Methyl-L-serine has been converted into (95), a tetramic acid analogue of physarobinic acid from *Physarum polycephalum*.[791] Several other uses of amino acids in heterocyclic synthesis are well-established, illustrated this year for syntheses from L-prolinol of the oxazolone (96) and its imines and sulfur analogues,[792] dioxopiperazines from differently-protected aspartic acids,[793] the morpholinone (97) from N-alkyl N-acetylamino acids treated with trifluoroacetic anhydride and pyridine,[794] and oxidized lipid – amino acid reaction products 1-methyl-4-pentyl-1,4-dihydropyridine-3,5-dicarbaldehyde, 1-(5-amino-1-carboxypentyl)pyrrole, and N-Z-1(3)-[1-(formylmethyl)]hexyl-L-histidine.[795] Extraordinary reaction products [98; R = $CH_2OP(O)(OH)O^-$, equal amounts of (R,R)- and (S,S)-isomers], arise from copper(II)-mediated reactions of L-amino acids with pyridoxal 5-phosphate.[796]

A standard synthesis of hydantoins appears in a solid-support version,[797] and



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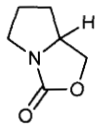

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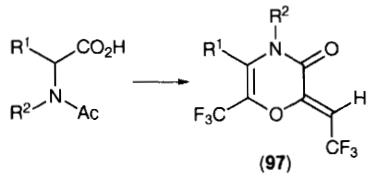

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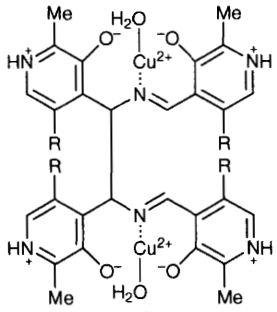


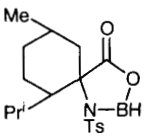
(98)

amino acid, acetyl chloride, and trimethylsilyl isothiocyanate reaction mixture gives authentic standards for the revived peptide sequencing method in which the C-terminal residue is converted by cleavage into a thiohydantoin.[798]

Several simple protocols are available that bring about the protection of both amino and carboxy groups of an α-amino acid in one step, though BF_3-etherate condensation must be one of the easiest practical operations of this type. It has been used in an improved procedure for side-chain protection of serine and threonine.[799] The N-toluene-p-sulfonyl derivative of the menthol-derived amino acid reacts with BH_3-THF in nitroethane at 45 °C during 1 h to give the Lewis acid (99; Masumune's catalyst) whose use in asymmetric aldol reactions is illustrated in this work.[800]

An unusual incorporation of an amino acid to form a di-aza-crown ether has been developed, using L-threoninol and di(2-chloroethyl) ether; the route was simple to operate because the secondary alcohol function did not require protection.[801]

[60]Fullerene derivatives of amino acids (Vol. 29, p. 73) have been prepared efficiently, and their properties surveyed; these include one outstanding characteristic, their surprisingly high water-solubility (see also Sections 5.5, 5.6.1).[802] The spiroheterocycle (100) emerges after 20 h from a [60]fullerene – DL-valine –



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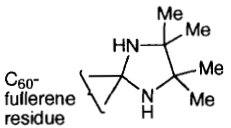


(100)

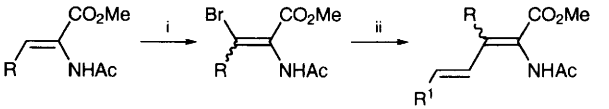
4,4,5,5-tetramethylimidazoline-2-thione mixture in refluxing chlorobenzene under nitrogen.[803] The mechanism proposed seems unlikely, since it requires a carbene intermediate (whose generation in the absence of the fullerene was not tested, but whose presence should be readily demonstrable).

6.2.5 Reactions at the α-Carbon Atom of α- and β-Amino Acids – Nickel peroxide oxidation of N-benzoylamino acids involves N-C^{α} bond cleavage since benzamide is formed in high yield.[804] α-Methylation (MeI/LDA) of ethyl N-benzylidene-β-alaninate and work-up can be achieved sufficiently rapidly to allow production and use of [^{11}C]-β-aminoisobutyric acid within the short time of life of the isotope.[805] α-Proton – ^{2}H-exchange through the classical N-acetylation – cyclization – $^{2}H_2O$ hydrolysis sequence (see also Ref. 539) followed by acylase resolution, gives 2S-[2-^{2}H]kynurenine, also obtained from L-[2-^{2}H]tyrosine, prepared analogously, by ozonolysis.[806]

6.3 Specific Reactions of Amino Acids – Reactions of amino acid side-chains, or reactions that involve amino and carboxy groups as well as side-chains, are covered in this Section. The former category predominates in the literature, reflecting the widespread use of common amino acids as starting materials for the synthesis of other amino acids.

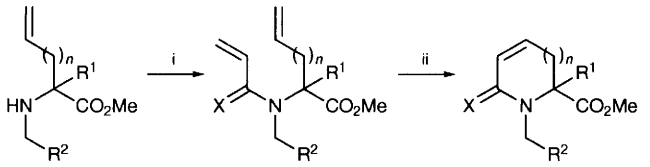
Saturated aliphatic side-chains offer few opportunities for structural modifications, or for the introduction of functional groups, though fenugreek seedlings accomplish the 4-hydroxylation of L-isoleucine, requiring iron(II) salts, ascorbate, 2-oxoglutarate and oxygen (thus implicating a dioxygenase in the process).[807] Industrial-scale conversion of proline into trans-4-hydroxy- and cis-3-hydroxy-L-prolines by *E. coli* proline hydroxylase has been reviewed.[808] Kolbe electrolysis of orthogonally-protected amino acid mixtures gives 2,5-di-aminoadipic acid, 2,6-di-aminopimelic acid, 2,5-di-aminoadipic acid, and 2,7-di-aminosuberic acid.[809]

Unsaturated aliphatic hydrocarbon side-chains offer much scope for functional group elaboration, illustrated for methyl (R,S)-2-(N-diphenylmethylidene)amino-pent-4-ynoate (hydrostannation of give regioisomeric tributylvinylstannane mixtures,[810] nucleophilic addition of N- and C-protected serine, cysteine, and lysine[811]) and coupling of vinylboronic acids to (Z)-β-alkenamide esters *via* a palladium acetate-catalysed Suzuki reaction (Scheme 33) to give α,β-γ,δ-unsaturated amino acids[812] and a simpler version in which indoles are coupled with ethyl α-acetamidoacrylate to give αβ-dehydrotryptophans[813] and cyclopropanation of this substrate with ethyl diazoacetate,[814] ring-closure of N-allyl-α-alkenylglycines through ruthenium-catalysed olefin metathesis to give highly-



Reagents: i, NBS/CH_2Cl_2, then NEt_3; ii, *trans*-$R^1CH{=}CHB(OH)_2$, $Pd(OAc)_2$, Na_2CO_3

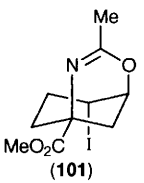
Scheme 33



Reagents: i, CH_2=CHCOCl or CH_2=$CHCH_2$Br/base; ii, $Ru(Pcy_3)_2Cl_2$, CH_2Cl_2, reflux

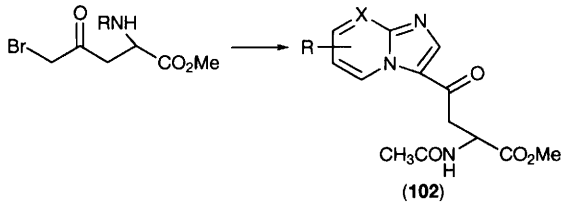
Scheme 34

functionalized 6-and 7-membered ring amino acids (Scheme 34),[815] analogous intermolecular metathesis of homoallylglycine derivatives with aryl- and alkylalkenes using 5 mol% $Cl_2(PCy_3)_2Ru$=CHPh to give modest yields,[816] and diastereoselective cyclization to pyroglutamates of radicals derived from N-bromoacetyl-N-benzylaminoacrylates (esterified with a chiral alkanol) by treatment with AIBN-Bu_3SnH (*cf.* Ref. 770).[817] Catalysed deuteriation of 3,4-dehydroproline and RuO_2 – $NaIO_4$ oxidation gives the 3,4-labelled pyroglutamic acid which by $LiEt_3H$ and Et_3Ge^2H reduction results in (2S,3S,4R,5S)-[3,4,5-$^2H_3$]proline.[818] Pd-Catalysed reaction of dimethyl esters of N-Boc-kainic acid with aryl halides leads to (E)-vinylic substitution products.[819] Manipulation of the alkene moiety of N-acetylaminocyclohex-3-ene carboxylic acid gave (101) from which exo-3-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylic acid, a new conformationally-constrained 4-hydroxyproline analogue, was prepared.[820]



(101)

α-(ω-Halogenoalkyl)-α-amino acids also provide useful synthesis intermediates for a wide range of applications, the routine use shown in the conversion of β-bromoarylalanines into β-hydroxy-analogues concealing a good deal of mechanistic interest.[821] The organozinc synthon IZn(NC)$CuCH_2CH(CO_2R)$NHBoc, derived from β-iodo-L-alanine, is particularly valuable; for example in Pd-catalysed conversion into (2S,6S)-4-oxo-2,6-diaminopimelic acid or through reaction with functionalized aryl iodides, into L-kynurenine;[822] also its use with (η^3-allyl)tetracarbonyl salts to give, for example, $PhSO_2CH$=$CHCHMeCH_2CH$-(CO_2R)NHBoc, epoxidation and Zn-TMSCl-mediated cyclization giving 4,5-disubstituted pipecolic acids.[823] Diastereoselective methylation of 4-oxohomophenylalanine $ZNHCH(CO_2R)CH_2COPh$, formed from the same organozinc synthon, gives the anti-isomer from which all stereoisomers of a Nikkomycin B constituent, 2-amino-3-hydroxy-4-phenylbutanolide, were obtained by appropriate manipulation[824] (see also Ref. 240). 5-Bromo-4-oxonorvaline gives azatryptophans (102; X = N, CH, CR; *cf.* Vol. 28, p. 70) through condensation with pyridinyl- and pyrimidinyl-formamidines,[825] and (S)-2-amino-4-bromobutanoic



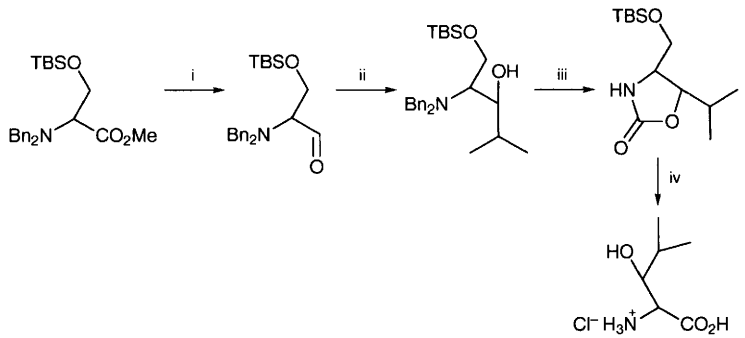
(102)

acid (formed from N-Boc-L-homoserine) has been used to construct α-amino acids each carrying one of the four DNA bases in the side-chain.[826]

α-(ω-Hydroxyalkyl)glycines, particularly the prototype β-hydroxyalkylglycine, L-serine, have featured in a rich variety of syntheses in recent years. However, novel pathways are rare; one such pathway is the conversion of nitrate esters of N,C-protected β-hydroxyalkyl-α-amino acids into alkoxy radicals on treatment with tributyltin hydride, from which α-C-centred radicals develop through β-scission.[827] The oxidation pathway from serine to dehydroserine has been established (the dehydration product, dehydroalanine, was the invariable end result of previous attempts) through a careful study of dimethyl sulfoxide – toluene-p-sulfonyl chloride oxidation. The (E)-enol toluene-p-sulfonate was the predominant product.[828] Enol triflates of 3,4-dehydroprolines from 4-hydroxy-prolines are more easily prepared *via* N-(9-phenylfluorenyl)-4-oxoprolines.[829]

The β-lactone of an N-protected L-serine can be opened by soft nucleophiles, as illustrated in a synthesis of S-prenylated L-cysteines.[830] More conventional leaving groups, found in O-mesylates or the β-iodo-alanine derived from N-trityl serine, or homologues derived from threonine or allothreonine, have been employed in intermediates used for syntheses of lanthionines and related cysteine derivatives[831] and L-selenocystine and its [^{77}Se]- and tellurium analogues;[832] in a preparation of γγ′-di-tert-butyl N-Fmoc-γ-carboxy-L-glutamate;[833] and in preparations of β-pyridylalanines using 2-, 3-, and 4-bromopyridines.[834] Mitsunobu processing of a protected serine (*cf.* Ref. 352) is now commonplace. Cycloserine (an isoxazolidinone formed from D-serinamide), undergoes changes in aqueous solutions to form β-(aminoxy)-D-alanine and its cyclic dipeptide (*i.e.* the dioxopiperazine), as demonstrated by IR studies.[835] Side-chain protection of serine through strong acid-catalysed addition of isobutene has a long history of use, but the surprising demonstration that N-Fmoc- or N-Z-serine pentafluorophenyl esters are appropriate substrates for this reaction will be a welcome short cut, lessening the expense of materials for peptide synthesis.[836] O-Alkylation with a primary alkyl bromide is more difficult but has been accomplished in moderate to good yields over 17 h at room temperature using finely-ground KOH – Aliquat 336.[837] Glycosidation of methyl N-acyl-L-serinates by p-nitrophenyl-D-galactose employing a glycosidase from *Aspergillus oryzae* has been demonstrated,[838] and a representative example of enzymatic hydroxy-group replacement has led to (S)-2,4-diamino[4-^{11}C]butanoic acid after reduction of the intermediate cyanide.[839]

Another example to add to the list of syntheses starting from D-serine, in which the hydroxymethyl side-chain becomes the carboxy group of an amino acid of the L-configurational series, concerns (2S,3S)-β-hydroxyleucine (Scheme 35).[840]

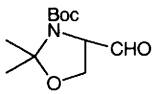


Reagents: i, $LiBH_4$ then Swern oxidation; ii, Pr^iMgCl; iii, $Pd(OH)_2$–H_2 then carbonyl di-imidazole/DMAP; iv, KF, Jones oxidation and conc. HCl

Scheme 35

The oxazolone formed by cyclization of N-acetyl-O-benzyl-L-threonine is easily epimerized and the hydrolysed product mixture can be resolved using hog kidney acylase I, offering an overall conversion into separate samples of N-acetyl-O-benzyl allo-D-threonine and its L-isomer.[841]

The N,O-protected L-serine derivative (103; the Garner aldehyde) continues to be chosen for syntheses of other α-amino acids: N-Boc-D-albizzine (104), *via* the protected (R)-2,3-diaminopropanol;[842] (2R,4R)-2,4-diaminoglutaric acids *via* the



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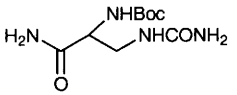
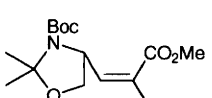


(104)

α-aminoacrylate (105);[843] (2S,3S)- and (2S,3R)-m-prenyl-β-hydroxytyrosine present in a novel cyclic heptapeptide from *Aspergillus flavipes*;[844] a maduropeptin moiety;[845] (2S,3S,4R)-phytosphingosine;[846] penaresidin A and related azetidine alkaloids;[847] and the D-O-E segment of vancomycin.[848] For a new synthesis of the Garner aldehyde, see Ref. 902. Conversion of the aldehyde group into ethynyl (-CHO → -C≡CH) is already well-known and is exploited in a number of these examples, including simple elongation of this carbon chain through Pd-catalysed coupling with aryl and vinyl halides.[849] Unusual control of the stereochemistry of propargylation of the Garner aldehyde with LiC≡C-CH_2OTBS ($SnCl_4$ and HMPA favour syn- and anti-products, respectively) has been noticed.[850] The nitrone (106; *cf.* ref 91, 311) derived from L-serine *via* the



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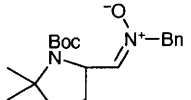

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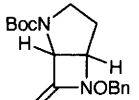


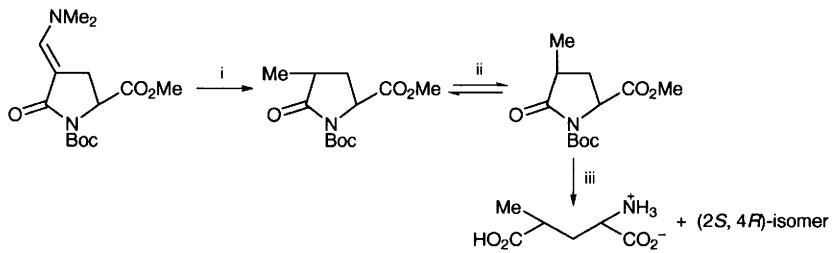
(107)

Garner aldehyde has proved useful in 2,3-diaminobutanoic acid synthesis[851] (another use for the Garner aldehyde is described in Ref. 429).

Suitably-protected cis-4-hydroxy-D-proline, elaborated into (2R,4R)-4-amino-pyrrolidine-2,4-dicarboxylic acid through a Bucherer-Bergs synthesis, generates a novel mGluR6 receptor antagonist.[852] trans-3-Hydroxy-L-proline hydroxamate has been cyclized to the β-lactam (107) through the Mitsunobu reaction,[853] as precursor to sulfams and sulfates (SO_3H and OSO_3H respectively, in place of OBn; potential β-lactamase inhibitors).

3-Hydroxyaspartic acid diastereoisomers are intermediates in the route from tartaric acid esters to (2R,3R)- and (2R,3S)-3-hydroxyaspartic acid β-hydroxamates.[854]

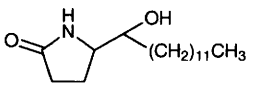
Aspartic and glutamic acids are represented in either acyclic forms or in one of several cyclized forms in synthesis applications: routes to 2-substituted-4-methylene-L-glutamic acids either through alkylation of the 4-methylene-L-pyroglutamate anion or through methylenation after alkylation of ethyl L-pyroglutamate;[855] conversion of tert-butyl 4-dimethylaminoalkylidene-N-Boc-pyroglutamate into chain-extended forms (NMe_2 → H, Me, Et, Ph, C≡CH, $CH{=}CH_2$ with DIBAL-H or a Grignard reagent),[856] conversion of L-pyroglutamic acid into (2S,4S)- and (2S,4R)-4-methylglutamic acid (Scheme 36);[857]



Reagents: i, H_2, Pd–C; ii, KCN, DMF; iii, LiOH, Pr^iOH, then HCl–AcOH and ion-exchange neutralization

Scheme 36

extension of the carboxy group of L-pyroglutamic acid to provide aza-muricatacin (108 and epimer at the side-chain chiral centre), an analogue of the hydroxybutanolide from *Annona muricata*;[858] a synthesis of (-)-bulgecinine (*cf.* Ref. 212) from L-pyroglutaminol[859] and from L-aspartic acid *via* a diazoketone [side-chain = $EtO_2CC(N_2)COCH_2$] (see also Vol. 29, p. 79),[860] and generation of ketones including 4-oxo-L-pipecolic acid from L-aspartic acid (Scheme 37).[861] Introduction of alkyl groups using trialkylaluminium reagents into the 5-position of pyroglutamic acid does not cause ring opening, so hydrogenation (Pt/C) leading to cis-5-alkylprolines can then be accomplished with secure knowledge of



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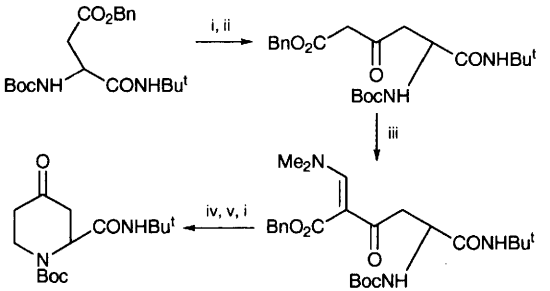
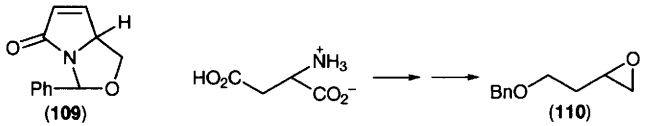


Reagents: i, H_2–Pd/C; ii, carbonyldi-imidazole, $(BnO_2CCH_2CO_2)_2Mg$; iii, DMF–dimethylacetal; iv, HCl; v, Boc_2O/DIPEA

Scheme 37

the stereochemistry of the product.[862] Adapting the carbonyl functions of L-pyroglutamic acid ($CO_2H \rightarrow CH_2OTBDPS$; $>C=O \rightarrow >CH\text{-}CHO$] gives a building block for a synthesis of trans-threo-trans-threo-trans-terpyrrolidine, needed for the preparation of potential hosts for molecular recognition studies.[863] Uses for the 3,4-dehydropyroglutaminol synthon (109) include β-amination (though this is a reluctant process in the absence of activating substituents),[864] and conversion into (2S,3R,4S)-epoxyproline *en route* to (2S,3S,4R)-epiminoproline *via* the azido-alcohol.[865] Addition of the imine PhCH=NTs to the enolate derived from the ring carbonyl group of pyroglutamic acid gives the 4-(1′-toluene-p-sulfonylamido)benzyl derivative.[866] A synthesis of spiroacetals from the Tephritid fruit-fly (particularly *Bactrocera*) uses aspartic acid to create the (R)-epoxide (110) through successive brominative deamination with retention of configuration, and borane reduction of the carboxy groups preceding epoxide formation.[867] Further examples include Hofmann rearrangement of N^{α}-protected asparagines to provide β-amino-L-alanine (*alias* 2,3-diaminopropanoic acid),[868] the use of dimethyl (4S,5S)-1-benzyl-2-oxo-3-(9′-phenylfluoren-9′-yl)imidazolone-4,5-dicarboxylate derived from L-aspartic acid for chemoselective ester manipulation to give the γ-hydroxy-α,β-diaminoalkyl functionality required for a component of streptothricin antibiotics;[869] synthesis of (E)- and (Z)-2-amino-4-phenylbut-3-enoic acids (*alias* styrylglycines) from L- and D-aspartic acids respectively.[870]

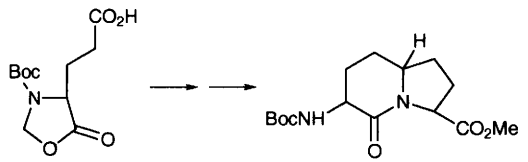


(109) **(110)**

L-β-Aspartic semialdehyde has been used for access to 4-oxo-L-norvaline through homologation with diazomethane.[871] A synthesis of the hydrochloride of the α-semialdehyde has been reported, by ozonolysis of 3-amino-3-vinylpropanoic acid formed from 4-acetoxy-azetidin-2-one[872] and the L-glutamic acid-derived aldehyde, $Boc_2NCH(CO_2Me)CH_2CH_2CHO$, forms the basis for a synth-

esis of C-glycosidic amino acid through aldolization by a glycoside di-anion.[873] An analogous species, formed by ozonolysis of the Birch reduction product of L-phenylalanine, has been condensed with 3-amino-5-oxo-4-phenyl-2,5-dihydroisoxazole to give β-(isoxazolo[2,3-a]pyrimidin-4-yl)-L-alanine.[874]

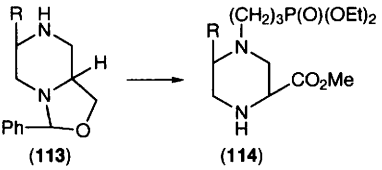
L-Glutamic acid protected at both NH_2 and α-carboxy groups through conversion into the oxazolidinone (111) is transformed into the azabicyclononane derivative (112) through Claisen condensation with the lithium enolate of Z-Glu(OBn)OMe and ensuing tandem cyclization.[875]



(111) (112)

Lysine and other α-(ω-aminoalkyl)-α-amino acids in various protected forms have proved to be effective starting materials in syntheses of unusual α-amino acids: L-homoglutamine by oxidation of N^{ε}-Z-L-lysine;[876] (2S,5S)-5-(fluoromethyl)ornithine from (2S,4S)-diaminoadipic acid;[877] N^{γ}-alkylation of the protected 2-(hydroxymethyl)piperazine (113) *en route* to piperazinic acid analogues (114);[878] preparation of homochiral dihydroimidazoles (115) from corresponding β-aminoglutamic acids;[879] and preparation from L-2,4-diaminobutanoic acid, of an amino acid with an adenine-carrying side-chain.[880] The novel N^{ω}-(monomethoxytrityl) group has been advocated for N-protection of an aminoalkyl side-chain, with the advantage of mild cleavage (dichloroacetic and chloroacetic acids) and easy work-up.[881]

A novel protein crosslinking site, threosidine (116), is generated through



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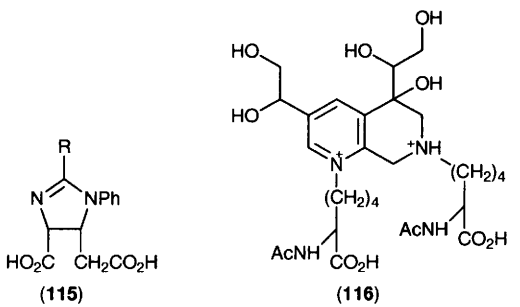


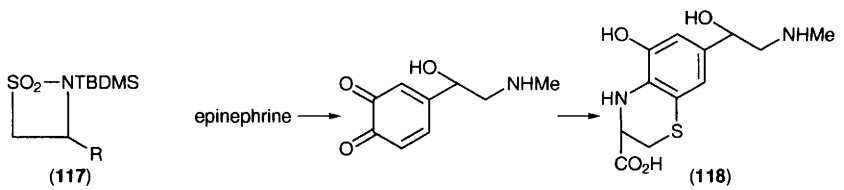
(115) (116)

condensation of N^{α}-acetyl-L-lysine with D-threose.[882] Condensation of lysine protected at α-NH_2 and carboxy groups, with malondialdehyde and 4-hydroxy-non-2-enal (formed *in vivo* through oxidation of polyunsaturated fatty acids) followed by $NaBH_4$ reduction, provides N^{ε}-propyl derivatives (*cf.* Vol. 29, pp. 81, 82).[883] 1-(N^{α}-Hippuryl-lysyl)-2-hydroxy-2-pentyl-3-(N^{α}-hippuryl-lysylimino)-1,2-dihydropyrrole is the fluorescent product formed from 4-hydroxynon-2-enal and N^{α}-hippuryl-lysine in phosphate buffer at neutral pH, thus identifying the site of attack of this lipid degradation product in proteins as a lysine residue.[884] In a related process, N^{α}-Boc-L-arginine reacts with methylglyoxal to form the novel fluorescent derivative, N^{δ}-(5-hydroxy-4,6-dimethylpyrimidin-2-yl)-L-ornithine, also formed by reactions of arginine derivatives with various sugars and with ascorbic acid, thus providing a clue to damage caused to proteins by this compound.[885] Bis(N-Boc)-protection of the arginine side-chain guanidine becomes more attractive as a result of the effectiveness of $SnCl_4$ as deprotecting reagent.[886]

A review has appeared of applications of L-cysteine as a D-amino acid synthon;[887] these applications are mostly obvious extensions of the well-known uses of L-serine in this respect. One of the many reactions in which L-cysteine behaves differently from serine is its ready formation of an L-thiazolidine-4-carboxylic acid with a carbonyl compound, now shown to be facilitated by microwave radiation.[888] Another growth area of research has developed around sulfur-containing amino acids through the need to identify likely *in vivo* associates for nitric oxide and other nitrogen oxides. Studies of cysteine in this context include determination of the kinetics of nitrosation of L-cysteine, and related reactions,[889] and properties of S-nitrosothiols (for a review see Ref. 890). For S-nitroso-N-acetylcysteine and its penicillamine analogue, the apparently greater thermal stability of the latter is ascribed to steric repression of disulfide formation and therefore, presumably, recapture of nitric oxide.[891] The reversibility of S-nitrosation has been demonstrated through reduction of copper(II) species by S-nitrosothiols.[892]

[^{35}S]-Labelled (S)-homocysteine and L-methionine have been prepared from O-acetyl-(S)-homoserine through (S)-homoserine sulfhydrylase-catalysed thiol exchange with $H_2{}^{35}S$.[893]

Studies of cysteine chemistry leading to sulfur heterocycles cover the formation of the α-sultam (117) and its potential in synthesis,[894] uses in trapping sensitive o-quinones (*e.g.* from epinephrine through mild oxidation → 118),[895] photocyclization of methyl N-phthaloylcysteinate to the benzazepin-1,5-dione and other species,[896] and oxidative consequences of attack by the superoxide radical on N-acetylcysteine.[897]



(117) (118)

Cysteine selenotrisulfide has been prepared through the reaction of L-cysteine with sodium selenite in acid solutions.[898] Cobalt-assisted cleavage of disulfide bonds, *e.g.* conversion of N-acetyl-L-cystine to S-alkyl-, -aryl- or -acyl-mercapturic acids, has been established using Zn together with a trace of $CoCl_2$, and an organic halide.[899] One-electron oxidation potentials of α-carbon-centred radicals of cysteine methyl ester, cystine, and related amino acids have been determined to throw light on their redox chemistry.[900] Spontaneous oxidation of methionine in samples prepared for analysis has not been sufficiently recognized as a source of underestimation of this amino acid; the effects on the generation of methionine sulfoxide, of co-solutes and other factors present in physiological samples have been intelligently established through an HPLC study of OPA-mercaptoethanol condensation products.[901] The L-methionine side-chain provides the aldehyde function of the D-Garner aldehyde in a synthesis from the N-Boc-amino acid, through oxidative elimination after reduction of the carboxy function and cyclization with $Me_2C(OMe)_2/BF_3$.[902]

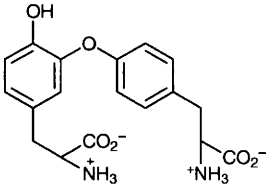
Phenylalanine side-chain modifications (see also Section 4.10) originating in the electrophilic substitution chemistry of benzene are illustrated in preparations of p-(N-thioaroylamino)-L-phenylalanines,[903] of o- and p-phosphinophenyl derivatives of glycine and alanine through nucleophilic phosphination of 2- and 4-fluorophenylglycine and -alanine with PhP(R)K (R = Me, Ph).[904] p-(Chlorosulfonyl)ation is described in Ref. 352. L-4-(Phosphonofluoromethyl)phenylalanine has been obtained similarly, through substitution of L-p-iodophenylalanine.[905] Pd-Catalysed Stille cross-coupling of methyl N-Boc-4-(trimethylstannyl)-L-phenylalaninate with aryl and vinyl iodides and triflates gives 4-aryl and 4-vinyl homologues.[906]

Tyrosine side-chain protection through (2-adamantyloxycarbonyl)ation of its copper complex has been advocated.[907] (2,4-Dimethylpent-3-yloxycarbonyl)ation of Boc-L-tyrosine gives a suitably protected intermediate for peptide synthesis since the group is stable towards piperidine but completely cleaved by HF,[908] and O-[bis(2-cyanoethyl)thiophosphonyl]ation has been effected using a phosphoramidite, catalysed by 1H-tetrazole.[909]

Tyrosine is the source of 4-iodo-L-phenylalanine, through reaction with NaI and Chloramine-T in aqueous media at pH 7, a procedure applied to give the [^{131}I] and [^{123}I]isotopomers,[910] and the iodo-compound lies along a pathway to 4-ethynyl-L-phenylalanine through application of the Heck reaction.[911] De-amination and de-iodination accompanying the formation of various radicals is the fate of this amino acid through irradiation in aqueous media.[912] [^{18}F]Acetyl hypofluorite is the key reactant in routes to 6-[^{18}F]fluoro-L-m-tyrosine and its 2-[^{18}F]-isomer, also the 6-[^{18}F]fluoro-β-fluoromethylene homologue.[913] Reimer-Tiemann formylation of N-Boc-L-tyrosine and application of the Dakin reaction leads to m-hydroxy-O-benzyl-L-tyrosine.[914] 3-Nitrotyrosine formation from the amino acid, together with nitrous and nitric acids, with peroxonitrous acid has been shown through ^{15}N-CIDNP NMR to involve radical intermediates.[915]

(S,S)-Isodityrosine (119) has been prepared from methyl Boc-L-tyrosinate, after conversion into the m-iodo analogue followed by Pd-catalysed coupling with N-Boc-β-iodo-L-alanine.[916] Horseradish peroxidase mediates the C-O-

coupling of dibromo- and dichloro-tyrosines to give substituted isodityrosines.[917] Biomimetic oxidative coupling of ethyl N-acetyl-3,5-di-iodo-L-tyrosinate *via* the usual aryloxydienone intermediate gives N-acetyl-L-thyroxine,[918] also obtained from the unprotected di-iodotyrosine through reaction with epoxide (120) formed from the corresponding benzyl alcohol by sodium bismuthate oxidation.[919]



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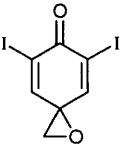
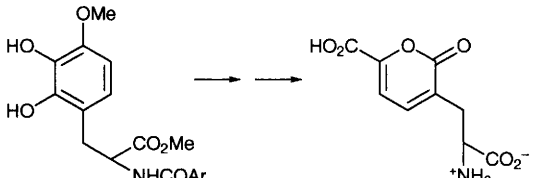


(120)

Oxidative cleavage of the catechol moiety of the DOPA analogue (121) prepared by Erlenmeyer and Schollkopf syntheses gave the muconate, followed by recyclization to give stizolobinic acid in a biomimetic route.[920]



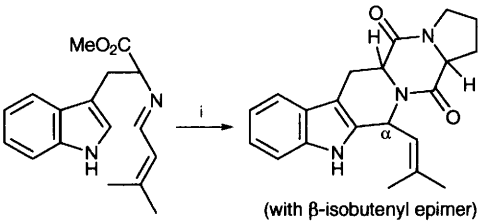
(121)

N-Acyl-α-arylglycines owe their presence in diagnostic kits to their role as chemiluminescence substrates, peroxidase-catalysed oxidation by hydrogen peroxide leading to 3-acylaminobenzo[b,d]furan-2(3H)-ones.[921]

Histidine side-chain protection that restrains interference by the imidazole moiety in the various operations involved in peptide synthesis is accomplished by N^{π}-(2-adamantyloxymethyl)ation[922] or N^{π}- and N^{τ}-allylation,[923] these groups being increasingly used in other contexts, and in the latter case offering the convenience of Pd-mediated cleavage. Full protection of L-histidine is mandatory for the introduction of an α-alkyl group using species generated by silver(I)-catalysed radical decarboxylative oxidation of an alkanoic acid in the presence of ammonium persulfate in 10% sulfuric acid.[924] During esterification of N^{α}-acetyl-L-histidine with diazomethane, some 1′-methylation is observed,[925] but a careful study of N^{τ}-(4-nitrophenyl)ation and H_2/Pd-C cleavage does not substantiate the claim that N^{τ}-N^{π}-migration occurs.[926] N^{α}-Acetylhistidine undergoes nucleophilic addition to catecholamines through its side-chain nitrogen atoms, to give C-2 and C-6 adducts,[927] an observation that will have significance in *in vivo* processes.

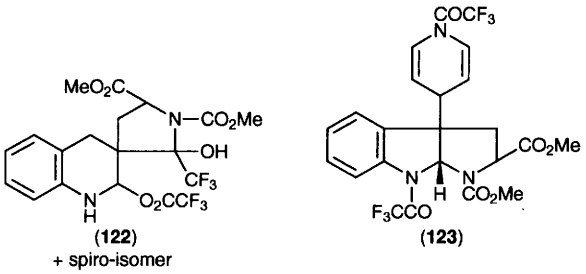
Tryptophan side-chain chemistry provides a rich mixture of indole substitution processes, including intramolecular cyclization to the aliphatic moiety. Photochemical versions of these processes are covered in the next Section, while Pictet-

Spengler condensations continue to be predominant in the solution chemistry of tryptophan, leading to indole alkaloids[928] and oxindole alkaloids[929] (proceeding *via* different tetracyclic ketone intermediates), and leading to the pentacyclic fumitremorgin cell cycle inhibitors through a different pathway (Scheme 38).[930] Adding pyridine to the previously-studied N-methoxycarbonyl-L-tryptophanate – trifluoroacetic anhydride reaction mixture leads to further new products (122 and its stereoisomer) and (123) as well as a trifluoroacetylated indole derivative.[931] TFA Dimerization of tryptophan derivatives generates δ_1, δ_1'-trans-indolines.[932] Oxidation of tryptophan by H_2O_2 gives the known products oxindolylalanine > 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylic acid, > N-formylkynurenine > dioxindolylalanine > kynurenine > 5-hydroxytryptophan (there are some surprises in the order of yields of reaction products).[933] γ-Irradiation gives the same major product, with N-formylkynurenine and 4-, 5-, 6-, and 7-hydroxylated tryptophans.[934] Oxidation by the dibromine radical anion or by peroxidase-catalysed processes has been studied with particular reference to the involvement of oxygen and superoxide.[935]



Reagent: i, Fmoc-L-Pro-Cl/py, then piperidine–CH_2Cl_2

Scheme 38



6.4 Effects of Electromagnetic Radiation on Amino Acids – Much of the current chemistry of tyrosine and tryptophan falls into this category, but photochemical and related consequences for an increasing range of common amino acids are being studied.

Photodecomposition of aliphatic amino acids in water at 248 nm[936] and 266 nm[937] is a result of two-photon excitation of water so as to generate radicals that are the effective reagents in the process. Four dipeptides formed from valine and

methionine undergo efficient peptide bond cleavage under irradiation at 193 nm.[938]

Radicals are formed by irradiation of L-alanine with a 3.4 MeV/amu ^{59}Co ion beam,[939] and the radical anion $MeCH{\cdot}CO_2^-$ formed in this way can be detected by its extraordinary UV absorption characteristics (λ_{max} 350 nm, (1100 $M^{-1}cm^{-1}$).[940] UV-Irradiated aqueous amino acids in contact with TiO_2 fragment into ammonia, nitrates, and CO_2, somewhat whimsically called photocatalysed mineralization,[941] while photolysis of [C_{60}]fullerenes with ethyl L-alaninate and acetaldehyde or iminodiacetic esters gives fulleropyrrolidines (*cf.* Vol. 29, p.73);[942] methyl esters of morpholino- and piperidino-acetic acids lead to analogous products while the free acids undergo decarboxylation to give dialkylaminomethylfullerenes.[943] Selective destruction of L-alanine and L-aspartic acid by ionizing radiation, reported previously, is unexpectedly prevented by glycine, thought to be due to the reaction of the glycine α-radical with alanine to regenerate the more stable alanine α-radical.[944]

A review of the extensive use of 5-aminolaevulinic acid in photodynamic therapy of cancer has been published,[945] focussing on underlying mechanisms (the wider literature from the medical perspective cannot be accommodated here).

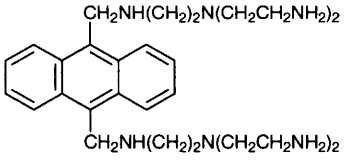
Aromatic and heteroaromatic acids provide substrates for all the various branches of photochemistry, represented by pyridinoline and deoxypyridinoline (effects of UV, visible, X-ray and γ-irradiation),[946] β-homotyrosine (fluorescence characteristics),[947] histidine [fluorescence quenching through binding to the di-zinc(II) complex of the fluorophore (124)],[948] and phosphorescence of tryptophan, tyrosine, phenylalanine, proline, and histidine (the latter three amino acids generate only about one-hundredth of the emission of tryptophan).[949]

Tryptophan studies cover generation of its neutral radical through 355 nm laser flash photolysis in the presence of N-hydroxypyridin-2-thione;[950] photosensitized oxidation in Triton X-100 micelles[951] and by singlet oxygen or electron transfer pathways;[952] fluorescence characteristics of L-tryptophan and N^{α}-acetyl-L-tryptophanamide in micelles;[953] and photoexcited triplet states studied by spin-lattice relaxation with respect to the influence of solvent and salts.[954] N-Nitroso-L-tryptophan, S-nitrosothiols, and other nitric oxide derivatives can be analysed by chemiluminescence spectroscopy after photolysis.[955]

7 Analytical Methods

7.1 Introduction – General reviews cover amino acid analysis[956] and peptide and protein hydrolysis.[957] Occasionally, there are papers that cover all standard analytical methods from the point of view of one particular amino acid, and that has arisen in the current literature for homocysteine[958,959] and tryptophan.[960] In one of these broad studies,[956] data on the variation in performance of different laboratories on homocysteine analysis have been considered.

7.2 Gas-liquid Chromatography – Results have appeared from conventional protocols followed for mixtures: of N(O,S)-isobutyloxycarbonyl derivatives of



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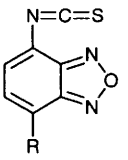

(125)

amino acid methyl esters[961] (including the use of N- and P-selective detectors[962]), of N(O) pentafluorobenzil derivatives of amino acid pentafluorobenzyl esters,[963] and of N-ethoxycarbonylamino acid ethyl esters from hydrolysates of samples of oil paintings.[964]

The mass spectrometer as detector is an essential feature of analyses of ^{13}C-enriched leucine, isoleucine, and valine mixtures, rendered suitable for GLC through derivatization with o-phenylenediamine after conversion into α-keto-acids using L-leucine dehydrogenase.[965] The GC-MS combination has also been applied to estimating the [^{15}N]amino acid content of samples derivatized as their N-trifluoroacetyl isopropyl esters,[966] for N-heptafluorobutyroyl pentafluorobenzyl esters of N(O)-TMS-amino acids using [^{13}C],[^{2}H]-labelled amino acid standards,[967] for dansyl- and Z-[^{13}C, ^{2}H]-labelled amino acids,[221] for N-perfluoroacyl alkyl esters using CH_4-CIMS, shown to generate [M+H], [M+C_2H_5], and [M+H−C_3H_6] ions,[968] and for amino acid mixtures in the form of their N-ethoxycarbonyl trifluoroethyl esters.[969] Considerable care has been taken to develop a one-step derivatization protocol [N(O,S)]-ethoxycarbonylation and ethyl esterification using ethyl chloroformate, applied for stable isotope analysis of amino acids.[970]

Particular amino acids targeted in GC-MS analysis include S-carboxymethyl-L-cysteine,[971] 3-chlorotyrosine aiming at attomole sensitivity for human tissue samples,[972] eight known pipecolic acids in plants,[973] and non-protein amino acids in cycad seeds (including the previously-reported species-specific cycasindene, see also Ref. 35).[974]

Estimation of D:L-ratios for amino acids has been achieved through GLC over a CSP similar to Chirasil-Val, though more sensitive, of samples derivatized as N-pivaloyl methyl esters,[975] and for trifluoroethyl esters of N- and N,O-isobutoxycarbonyl derivatives for separations over Chirasil-D-Val for serine and threonine have been reported.[976]

7.3 Ion-exchange Chromatography – Most amino acids analysers are now based on HPLC instrumentation (Section 7.5), and the ninhydrin reagent protocol is still favoured, *e.g.* for homocysteine;[977] a new ion-exchange analyzer based on traditional lines has been described.[978] Exploration of continuous rotating annular chromatography technique for cation-exchange separation of amino acid mixtures has been reported;[979] another novel technique for continuous monitoring of eluate containing underivatized amino acids is based on evaporative light-scattering.[980]

7.4 Thin-layer Chromatography – A review[981] covers estimation of D:L-ratios for derivatized amino acids using TLC plates impregnated, for example,[982] with (1R,3R,5R)-2-azabicyclo[3.3.0]octane-3-carboxylic acid.

7.5 High-performance Liquid Chromatography – Studies under this heading, dealing with mixtures of amino acids, are grouped together, first in the category of conventional approaches to the analysis of free amino acids and derivatized samples, then into various categories of modified stationary phases.

Amino acids such as iodo- and di-iodotyrosine, tri-iodothyronine, and thyroxine[983] are well-suited to an HPLC analysis protocol that employs a UV or fluorescence detector, and so are histidine and its 1- and 3-methyl derivatives in muscle (analysed after OPA derivatization),[984] dityrosine in spinal fluid (λ_{exc} 285 nm, λ_{em} 410 nm)[985] and in plasma proteins and haemoglobin,[986] pyridinoline and its deoxy-homologue,[987] and hydroxylysylpyridinoline and its lysyl analogue.[988] The Beckman Cross-Links kit for HPLC analyis of pyridinoline and its deoxy-homologue is superior to others and HPLC is an attractive alternative to immunoassays.[989] The preceding group of analyses of protein crosslinking amino acids is joined by desmosine (from elastin),[990] and histidinohydroxylysinonorleucine (after Fmoc derivatization), a more recently discovered trifunctional collagen crosslink.[991] These are markers for osteoporosis and other afflictions, and another amino acid of this type is N-phenylpropionylglycine, whose presence in urine indicates the level of medium-chain acyl coenzyme A dehydrogenase deficiency.[992] Quantitation at 412 nm has been achieved for cysteine and N-acetylcysteine after post-column reaction with 5,5α-dithiobis(2-nitrobenzoic acid), a classical derivatization reagent for thiols.[993]

A lengthy procedure for hydroxyproline estimation employs nitrous acid deamination of primary amino acids, extraction of N-nitrosoimino acids into ethyl ethanoate, de-nitrosation with HBr, then derivatization with dabsyl chloride and HPLC analysis.[994] A sensitive procedure for the HPLC analysis of L-DOPA and its 3-O-methyl derivative in blood platelets employs electrochemical detection.[995]

Unusual analytes or techniques are illustrated in estimation of S-adenosyl-L-methionine in blood,[996] microwave-induced plasma MS as detector system for HPLC of S-(2-aminoethyl)-cysteine, cystathionine, and lanthionine,[997] and seleno-amino acids[998] (including ICP-MS for analysis of selenocysteine, selenomethionine, and methylselenocysteine in yeast[999]) and N^G-dimethyl-L-arginine in blood plasma.[1000]

Derivatization intended to raise the sensitivity of amino acid analysis, at the same time calling for simplified HPLC instrumentation, remains the standard approach. N-Fmoc amino acids[1001] (see also Ref. 988) are well established fluorescent derivatives, whose use has been extended to diastereoisomer formation through treatment of enantiomer mixtures of amino acids with N-Fmoc-L-amino acid N-carboxyanhydrides prior to HPLC analysis for determination of their D:L-ratios.[1002] Fluoresceamine derivatives[1003] are not completely out of fashion, and benzoxadiazolyl derivatives are definitely in favour (derivatization of homocysteine using 7-fluorobenzo-2-oxa-1,3-diazole-4-sulfonate; other exam-

ples are scattered throughout Section 7).[1004] PTC-Amino acids give reliable results (Ref. 11).

New proposals for sensitive fluorescent derivatives include N-(3-indolylacetyl)-amino acids,[1005] N-(acridin-9-yl)amino acids,[1006] 2-(4-hydrazinocarbonylphenyl)-4,5-diphenylimidazole-derivatized carnitines,[1007] and Schiff bases formed with 3-(4-carboxybenzoyl)quinoline-2-carboxaldehyde.[1008]

OPA Derivatives formed between amino acids and an o-phthaldialdehyde – thiol reagent cocktail (3-mercaptopropionic acid has been advocated[1009]) have been chosen for analyses of glutamine,[1010] the NO synthase-related basic amino acids (N^{ω}-hydroxy-L-arginine, L-arginine, and its mono- and di-methyl derivatives),[1011] N-methylated lysines,[1012] argininosuccinic acid,[1013] neurotransmitter amino acids,[1014] and amino acid mixtures in physiological samples.[1015] The 5-aminolaevulinic acid – OPA derivative has been determined at trace levels through electrochemical detection.[1016] A noticeable increase in interest in 6-aminoquinolylamino acids (AQC-amino acids formed by the AccQ-Tag procedure[1017]) follows from their high sensitivity (from 12 fmol for threonine to 1.8 pmol for tryptophan[1018]) based on measurements at the fluorescence maximum 395 nm (λ_{exc} 250 nm) for derivatives separated over C_{18} silica using the ion-pair elution technique. The derivatization reagent, 6-aminoquinolyl N-hydroxysuccinimidylcarbamate, causes no complications in the interpretation of a chromatogram, when a quaternary eluent system is used,[1019] and a measure of its efficiency is shown in improved separation of 24 derivatized amino acids in 45 minutes.[1020]

An amino acid is released at each cycle of an Edman sequence determination of a polypeptide as a 2-anilinothiazol-5(4H)-one, and instead of conversion into a phenylthiohydantoin (PTH), its reaction with 4-aminofluorescein at one cycle, and with aminotetramethylrhodamine at the next, generates considerably simplified interpretations of HPLC traces.[1021] Non-fluorescent PTHs and dansylamino acids have been detected by indirect time-resolved fluorescence generated by the inclusion of europium(III) chelates to the eluent.[1022] Determination of D:L-ratios for PTHs has been accomplished through HPLC using mobile phases containing various chiral selectors,[1023] while the normal PTH analysis protocol in which no discrimination of enantiomers is intended, is employed in an improved system,[1024] and in a sensitive estimation of 1-aminocyclopropanecarboxylic acid in plant tissues.[1025] This employs MS detection, as does an even more sensitive protocol based on 4-(3-pyridinylmethylaminocarboxypropyl)PTHs.[1026] Diastereoisomer-forming derivatization has been explored using a series of p-substituted heteroaryl isothiocyanates (125),[1027] and using 1-fluoro-2,4-dinitrophenyl-5-L-alaninamide (the advanced Marfey reagent)[1028] and HPLC separation. In the former case, the purpose was to find a derivatizing isothiocyanate that did not introduce racemization, and an electron-donating p-substituent was found to be effective. The Marfey reagent study showed that the LL-diastereoisomer is not always eluted ahead of the LD-isomer. A chiral isothiocyanate is more effective for the estimation of D:L-ratios and the fluorescent reagent (-)-4-(3-isothiocyanatopyrrolidin-1-yl)-7-(N,N-dimethylaminosulfonyl)-2-oxabenzo-1,3-diazole has been advocated.[1029]

Commercial chiral stationary phases (CSPs) of the Pirkle type have been used

to estimate D-amino acid trace contaminants in L-amino acid samples derivatized by 4-fluoro-7-nitro-2,1,3-benzoxadiazole.[1030] Experimental CSPs include porous graphite coated with an N-substituted L-phenylalanine,[1031] and human serum albumin for HPLC of dansylamino acids.[1032] C_{18}-Silica coated with N,S-dioctyl-D-penicillamine as a chiral ligand-exchange phase for complexing with copper(II) ions and providing excellent resolution of amino acid enantiomers,[1033] and graphite coated with an N-substituted L-proline as chiral selector has been compared with other CSPs for ligand-exchange separation of enantiomers of amino acids.[1034] A quinine carbamate-based chiral anion exchanger has been explored for the resolution of DNP-amino acids.[1035] Mercaptopropylsilica gel derivatized with a benzamide, $-CH_2CH_2O\text{-}p\text{-}C_6H_4\text{-}CONR^1R^2$, in which NR^1R^2 is a homochiral 3,4-diaminopyrrolidinamide,[1036] has been used as a novel CSP for the HPLC resolution of DL-β-amino acid esters.[1037] Imprinted polymers for HPLC or CZE resolution of aromatic DL-amino acids have been reviewed,[1038] and the broader field of enantiomer HPLC separation over homochiral polymers has been surveyed.[1039]

Dansylamino acids can be resolved using hydroxypropyl-β-cyclodextrin as chiral selector.[1040] Systems based on cyclodextrins, for the estimation of enantiomer ratios using HPLC with electrochemical detection have been reviewed,[1041] and a brief but broader review[1042] has also appeared.

7.6 Capillary Zone Electrophoresis (CZE) and Related Analytical Methods – Textbook support for CZE and related techniques reflects their value in separation of mixtures for analysis.[1043] The subject has been reviewed.[1044]

Dramatic illustrations continue to appear: the separation and identification of a mixture of 12 amino acids and 9 carbohydrates, employing amperometric detection after separation,[1045] and estimation of the glutamic acid content of a single cell by quantifying the laser-induced fluorescence of NADH generated by passage, after CZE separation, through a column carrying glutamate dehydrogenase and glutamate-pyruvate transaminase.[1046]

In appropriate cases, UV quantitation is used for CZE of underivatized amino acids: oxidation products of tyrosine and DOPA,[1047] S-adenosyl-L-homocysteine,[1048] and indirect means in which a salicylate or benzoate is used as a UV-absorbing buffer additive.[1049] But the usual approach is the same as for HPLC analysis, *i.e.* derivatization prior to separation, and the same general emphasis on a few derivatization protocols applies to both techniques. Thus, recent studies have involved 6-aminoquinolinylamino acids,[1050] PTHs (CZE),[1051] PTHs of 3- and 4-hydroxyproline after clearing primary amines using OPA (MEKC),[1052] fluorescein TH of glutamic acid,[1053] OPA-chiral thiol derivatives (MEKC),[1054] naphthalene-2,3-dicarbaldehyde derivatives of aspartic and glutamic acids,[1055] 1-methoxycarbonylindolizine-3,5-dicarbaldehyde derivatized amino acids,[1056] 4-aminosulfonyl-7-fluoro-2,1,3-benzoxadiazole as derivatization reagent for homocysteine and other thiols (worse results were obtained using ammonium 4-aminosulfonyl-7-fluoro-2,1,3-benzoxadiazole-4-sulfonate),[1057] and DNP derivatives (magnesium, cadmium and zinc salt additives offer better separations).[1058] The inclusion of a cyclodextrin in the buffer enhances the fluorescence of NDA-

derivatized glutamic and aspartic acids and therefore increases the sensitivity of CZE analysis of these amino acids.[1059]

Fluorescein THs have been detected at 10 zmol levels (*i.e.* 10^{-20} mol) using CZE.[1060]

The resolution of DL-amino acids on the analytical scale by CZE techniques has been reviewed.[1061] Chiral stationary phases are applicable to CZE and the related MEKC and MECC techniques, with AQC-DL-amino acids,[1062] dansyl-DL-amino acids,[1063] and 7-nitro-2-oxabenzo-1,3-diazolyl-DL-amino acids,[1064] the last-mentioned being resolved using heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin in the buffer. Chiral separations (MEKC) employing hydroxypropyl-β-cyclodextrins as buffer additives have been reviewed.[1065] The alternative derivatization approach, generation of diastereoisomers, has been illustrated with the use of the OPA – chiral thiol reagent system for aspartic and glutamic acids (tetra-O-acetyl-1-thio-β-D-glucopyranose was the best co-reagent).[1066] Creation of molecule-imprinted polymers for CZE resolution of enantiomers has been explored, using L-phenylalanine anilide as print molecule, and methacrylic acid and 2-vinylpyridine as monomers.[1067]

7.7 Assays for Specific Amino Acids – Colorimetric procedures based on established principles allow estimation of hydroxyproline at trace levels,[1068] and the use of spectrophotometric enzymic assays is also standard practice, *e.g.* for GABA in plant samples[1069] and glutamic acid in tissue through deamination using glutamic dehydrogenase, followed by derivatization by formazan formation.[1070] An unusual approach, using TLC with a stationary phase carrying *Agrobacterium tumefaciens* harbouring lac2 fused to a gene that is regulated by autoinduction, has been applied to the characterization of N-acyl-L-homoserine lactones in biological samples.[1071]

The trend shown in the literature, on which this Section is based, continues towards the development of sensors designed for the quantification of individual amino acids in physiological samples. A chemiluminescence-generating system centred on an immobilized D-amino acid oxidase has been described for estimating the D-enantiomer content of samples of coded amino acids.[1072] New technology for amino acid oxidase electrodes based on iridium-dispersed carbon paste media allows estimations of amino acids in solutions down to 10^{-5} M,[1073] and immobilization on an oxygen electrode of the L-amino acid oxidase present in *Vipera ammodyter* venom extracts provides a novel amperometric sensor for L-amino acids.[1074] Immobilized glutamate oxidase using a hydrogen peroxide electrode permits quantitation of L-glutamic acid, L-glutamine, and GABA,[1075] and more sophistication is introduced into this system when a calixarene ammonium ionophore is incorporated.[1076] Analogous estimation of L-glutamine requires a mixed L-glutamate oxidase – glutaminase electrode.[1077]

L-Phenylalanine generates a response from an immobilized L-phenylalanine dehydrogenase sensor in a flow injection system,[1078] also the basis of corresponding macroelectrodes for L-alanine, L-serine, L-aspartic acid, and L-arginine[1079] and miniaturized versions of these.[1080] A carbon paste electrode carrying tyrosinase, salicylate hydroxylase, and L-phenylalanine dehydrogenase serves for

the assay of L-phenylalanine based on the quantitation of NADH produced.[1081] An amperometric assay for L-glutamic acid is based on use of an immobilized thermophilic L-glutamate dehydrogenase electrode.[1082]

The benefits of flow-injection amperometry have been exploited in a biosensor carrying tryptophan 2-mono-oxygenase for analysis of L-tryptophan or L-phenylalanine.[1083] The first on-line sensor for GABA employs glutamate oxidase and catalase immobilized on a glassy carbon electrode together with bovine serum albumin and horseradish peroxidase.[1084]

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