1

Amino Acids

BY GRAHAM C. BARRETT

1 Introduction

The literature of 1998 relating to the amino acids is covered in this Chapter, which is based on the chemistry literature mainly, and on related biological studies. The format used in all preceding Volumes of this Specialist Periodical Report is adopted. Some economies, introduced last year to save space, are continued. These do not affect the depth of coverage, but there are fewer sub-headings so that some topics, previously grouped on their own, have been combined more economically with other material.

Literature coverage is based on information from *Chemical Abstracts* (Issue 10 of Volume 128 to Issue 9 of Volume 130 inclusive), and scanning the major Journals. The literature continues to expand. The accusation[1] that much of the primary scientific literature is of declining quality could be recast in less provocative language so as to become more acceptable (in the context of the present Chapter: the accusation could be 'too many fragmented reports, too many papers describing predictable outcomes of well-known reactions and obvious properties of amino acids'); but nevertheless, most of the new experimental detail published on amino acids is actually needed by researchers.

2 Textbooks and Reviews

A recent monograph deals with the synthesis of derivatives of amino acids.[2] Reviews covering synthesis include: uses of L-amino acids in synthesis,[3] uses of L-pyroglutamic acid for the synthesis of alkaloids and other natural products.[4] Further reviews covering synthesis, reactions and properties of amino acids are located in appropriate sub-sections of this Chapter.

Mycosporins[5] and excitatory amino acids,[6] occurrence and physiological role of D-amino acids,[7] and L-cysteine metabolism and toxicity[8] have been reviewed.

The nomenclature of amino acids and their approved abbreviations have been surveyed.[9]

Amino Acids, Peptides and Proteins, Volume 31

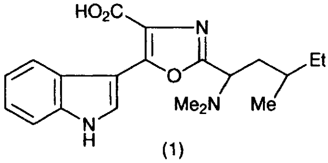
3 Naturally Occurring Amino Acids

3.1 Occurrence of Known Amino Acids – Among the non-routine topics that this Section covers, is the location of amino acids in extra-terrestrial samples, bones and fossils. The significance of amino acids as biomarkers indicative of life early in the Earth's history has been reviewed,[10] and the uncertainty in the use of ^{14}C data for dating bone samples through their γ-carboxyglutamic acid and α-carboxyglycine (*alias* aminomalonate) content has been emphasised.[11]

The other main area under this heading, the identification of known amino acids in live organisms, is similarly restricted here to non-routine examples: the high levels of L-DOPA in seeds of *Stizolobium aterrima*[12] and the presence of *cis*-3-hydroxy-N-methyl-L-proline in the South Australian marine sponge *Dendrilla.*[13]

Unusual known amino acids condensed with other compounds to give representatives of the usual families of natural products include D-proline-containing dioxopiperazines in the sponge *Calyx CF podatypa* for which a correction has been published.[14] N^{ε}-[(R)-(1-Carboxyethyl)]-L-lysine in the form of its N^{α}-(D-glucuronoyl) derivative in *Providencia alcalifaciens 023*,[15] γ-glutamyl-S-ethenylcysteine in seeds of the Narbon bean (*Vicia narbonensis*; breakdown products of this isopeptide are responsible for the repulsive odour associated with its germination),[16] and 1-aminocyclopropanecarboxylic acid in the *Streptomyces* sp. metabolite cytotrienin A,[17] provide further examples. Unusual modifications of common amino acids in peptides include D-tryptophan as a constituent of contryphans present in the venom of fish-hunting cone-snails *Conus radiatus*,[18] and 6-chloro-N-methyl-L-tryptophan and N-methyl-L-tryptophan as constituents of keramamides K and L respectively, from *Theonella* sp.[19] The novel indole alkaloid martefragin A (1) present in the red alga *Martensia fragilis*, is the result of an unusual *in vivo* elaboration process applied to N^{α}-L-isoleucyl-L-tryptophan.[20]

3.2 New Naturally Occurring Amino Acids – Previously-known (2RS)-2-amino-4,5-hexadienoic acid and (2S)-2-amino-4-hexynoic acid accompany new natural products (2R)-2-amino-6-hydroxy-4-hexynoic acid and (2S)-2-amino-5-chloro-5-hexenoic acid in fruit bodies of *Amanita miculifera*.[21] A novel lysine



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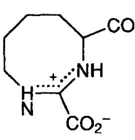

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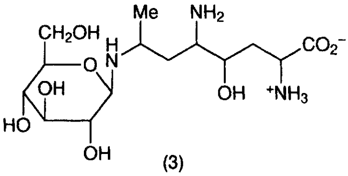

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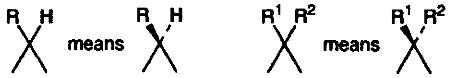
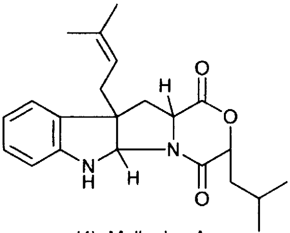
Three-dimensional features of molecules are depicted throughout this Chapter as follows: horizontally-ranged atoms and bonds and ring atoms are to be understood as being in the plane of the paper; substituent atoms and groups attached to these are to be understood to be ABOVE the page if ranged LEFTWARDS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



relative (2) has been identified in the Micronesian marine sponge *Axinyssa terpnis*.[22] Ascaulitoxin is an unusual phytotoxic bis(amino acid) N-glucoside (3) that has been isolated from *Ascochyta caulina*.[23]

3.3 New Amino Acids from Hydrolysates – As usual, this section collects papers that describe reports of new amino acids condensed with other compounds: into dioxopiperazines, *e.g.* mollenines A and B (4) from the sclerotoid ascostromata of *Eupenicillium molle*,[24] and into peptides: the potent trypsin inhibitor, dehydroradiosumin (5) from the freshwater cyanobacterium *Anabaena cylindrica*,[25] eurypamide A and three related cyclic tripeptides in the Palauan sponge *Microciona eurypa*, containing iodotyrosine and (2S,3S,4R)-3,4-dihydroxyarginine,[26] cyclolinopeptide CLX from linseed that contains N-methyl-4-aminoproline,[27] hibispeptin A (6) from the root bark of *Hibiscus syriacus*, that contains a novel homophenylalanine derivative (stereochemistry not yet defined),[28] and 3-amino-6-hydroxystearic acid in nostofungicidine from the terrestrial blue-green alga *Nostoc commune*.[29]



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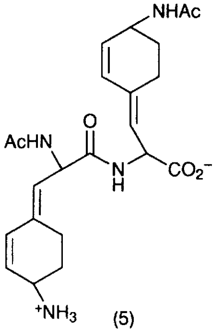

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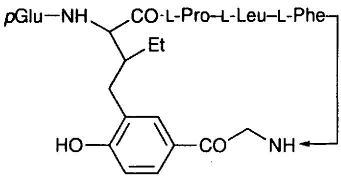

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(2S,3R)-3-Hydroxy-3-methylproline is a new natural product, a component together with other unusual α-amino acids of the carcinoma apoptosis-inducing polyoxypeptin.[30]

A novel protein crosslink found in bovine dentin, together with dihydroxylysinonorleucine and hydroxylysylpyridinoline, consists of a pyrroleninone carrying three amino groups and three carboxy groups.[31]

4 Chemical Synthesis and Resolution of Amino Acids

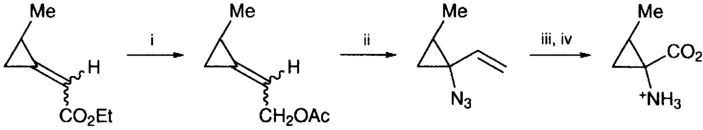
This Section is subdivided so as to collect current papers describing new examples of applications of each of the major general amino acid synthesis approaches. These methods are mostly well-established, though many improvements are to be found in the small print of these papers. Some newly-introduced synthesis methods are described.

As in last year's Volume, syntheses of isotopically-labelled coded amino acids are not collected in a separate subsection, but are spread throughout the Chapter: ^{2}H, Refs. 98, 370, 599, 945, 946, 1034, 1097; ^{3}H, Ref. 1105; ^{11}C, Ref. 161; ^{13}C, Refs. 122, 124, 126, 131, 599, 1098; ^{14}C, Refs. 123, 1105; ^{15}N, Refs. 122, 124, 131, 160, 235; ^{18}O, Ref. 599; ^{18}F, Refs. 1011, 1038; ^{128}I, Ref. 1035.

General reviews of synthesis methods applied to α-amino acids have appeared: asymmetric synthesis,[32] general strategies of synthesis of α-amino acids and α-methyl-α-amino acids,[33] use of sulfinimines in asymmetric synthesis,[34] 2-(α-aminoalkyl)thiazoles as masked α-aminoaldehydes,[35] and use of the Mitsunobu reaction.[36]

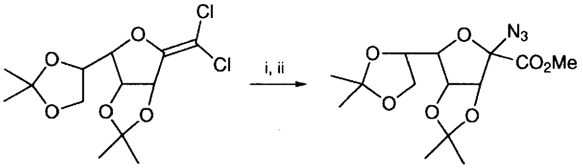
4.1 General Methods for the Synthesis of α-Amino Acids, Including Enantioselective Synthesis – *4.1.1 Amination of Alkanoic Acid Derivatives by Amines and Amine-related Reagents* – Descriptions of simple syntheses of common amino acids are to be found in the recent literature, and some of these emerge from the continuing fascination of prebiotic amino acid synthesis (Section 4.5). α-Phenylglycine, $H_3N^+CHPhCO_2^-$, is formed from the reaction of phenylacetic acid with Br_2 and NH_3,[37] and 3,5-dihydroxy-4-methoxybenzaldehyde leads on to the correspondingly-substituted phenylglycine through reaction with ammonia and toluene-p-sulfonyl cyanide (Strecker synthesis, see also Section 4.1.6).[38]

Palladium(0)-catalysed azidation of (2S)-1-ethoxycarbonylmethylidine-2-methylcyclopropanes is a notable feature of a route to (−)-(1R,2S)-norcoronamic acid (Scheme 1).[39] Similar treatment of the α-chloroester formed by m-chloroperbenzoic acid oxidation of sugar-derived dichloroalkenes (Scheme 2) makes use of a remarkably simple C=O → >$CHCO_2Me$ procedure.[40]



Reagents: i, DIBAL-H, then Ac_2O, NEt_3, DMAP; ii, LnPd(0), NaN_3; iii, $HS(CH_2)_3SH$, then Boc_2O; iv, $RuCl_3$, $NaIO_4$ and routine work-up

Scheme 1



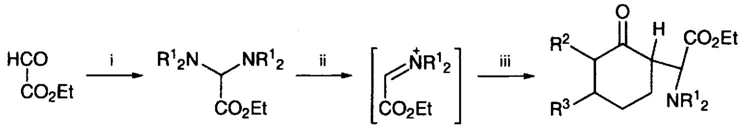
Reagents: i, *m*-chloroperbenzoic acid, CH_2Cl_2, hydroquinone; ii, NaN_3, dry DMF

Scheme 2

Resin-tethered N-chloroacetyl arylamides[41] and bromoacetates[42] have been converted into N-alkyl glycines (for use in the synthesis of 'peptoids') through successive reaction with an amine and an acylating agent.

Nitrenes are seldom used in routine synthesis for amination, potential hazards possibly being a deterrent, but low yields are another factor, seen in the FeCl$_2$-catalysed amination of ketene acetals by Boc-azide.[43]

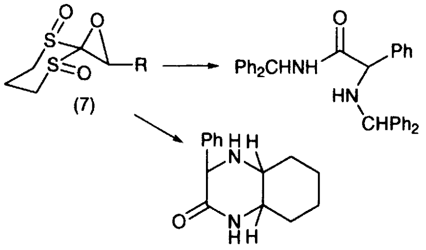
Amination of aldehydes to give imines has long been a reliable method of introducing a nitrogen function as a substituent on a carbon chain, and in the special case of glyoxylic acid some useful amino acid syntheses have been established. One-pot processes starting with this step can be developed in a number of ways depending on other reagents; the formation of a ternary iminium salt (Scheme 3) from the intermediate aminal is a key step in the synthesis of syn,anti- or anti,syn-δ-hydroxy-α-amino acids.[44] Some inspired reasoning in mechanistic organic chemistry is needed to explain how *cis*-2-butenedial held at 435 K for 6 h in aqueous ammonia is converted into aspartic acid.[45]



Reagents: i, R$^1{}_2$NH; ii, AcCl; iii, substituted cyclohexanone, reflux 3 h

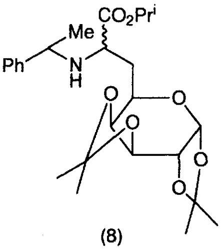
Scheme 3

Homochiral bis(sulfinyl)oxiranes (7) are masked forms of ketones that can be aminated to give α-amino acid amides, announced as a new asymmetric synthesis.[46]



Amination of 3-nosyloxy-2-ketoesters with methyl carbamate and reduction of the resulting 4-alkoxycarbonyloxazolin-2-ones gives α-amino acid esters, but hydrogenation is sluggish.[47] Reductive amination of α-ketoesters represents a one-pot introduction of an alkylamino group without isolation of the intermediate imine, and treatment of simple pyruvates with Na(OAc)$_3$BH and phenylethylamine,[48] and similar treatment of structurally complex homologues (protected α-D-galactohexodialdo-1,5-pyranoses → 8) has been described.[49] The trifluoroalanine analogue CF$_3$CH(NHR^1)P(O)(OR^2)$_2$ has been prepared in this way.[50] (p-Methoxybenzoyl)acrylic acid PhCH$_2$COCH=CHCO$_2$H adds (S)-phenylethylamine to give the L-homophenylalanine derivative in poor diastereoisomeric excess (ca 10%), but gives enantiomerically pure product through equilibration, presumably involving dynamic resolution.[51]

β-Keto-esters undergoing α-oximation and reduction to the α-amino-β-keto-



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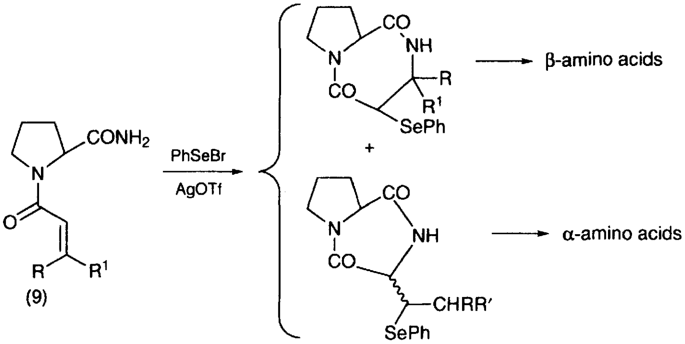
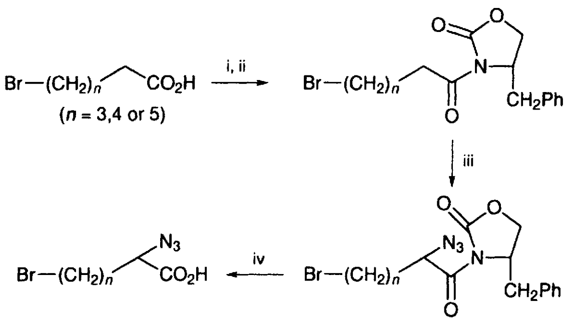
ester stage, and then asymmetric hydrogenation, have been converted into syn- and or anti-β-hydroxy α-amino acids, *e.g.* $Pht(CH_2)_3CH(OH)CH(NH_2)CO_2H$.[52] Exploitation of dynamic kinetic resolution in the last step led to a quantitative yield of the syn-isomer, (2S,3R)-3-hydroxylysine, after deprotection.

'Intramolecular amination' gives a title to the phenylselenium-induced lactamization of N^{α}-(alk-2-enoyl) L-prolinamides (9) to give both α- and β-amino acids with modest stereoselection.[53]



Introduction of the azido group into (2S,R_S)-1-(p-tolylsulfinyl)-butan-2-ol (NaN_3, PPh_3, CBr_4) and the equivalent Mitsunobu reaction with diethyl azodicarboxylate (see also Ref. 911), gives enantiomerically pure β-aminoalkanols after routine functional group changes.[54] Serine C-glucoside analogues that have an α-azido group masquerading as a protected amino group have been prepared from 1-vinyl-D-glucosides by stereoselective [2,3]Wittig rearrangement (Vol. 30, p. 12).[55]

The Evans approach to amino acids *via* amination procedures applied to N-acyloxazolidinones is illustrated in a synthesis of synthetically-useful ω-bromo-(2S)-azido acids (Scheme 4),[56] and a further example of the same approach, used many times by Hruby's group (Vol. 30, p. 10), giving four 2-amino-3,3-diarylpropanoic acids.[57] C-Linked isosteres of α- and β-glycoconjugates carrying the serine moiety have been prepared by electrophilic amination of the enolate of the Evans chiral oxazolidinone.[58] A study of the conversion of the azido function into the Boc-amino group using the Stau-



Reagents: i, Et$_3$N, Bu^{t}COCl; ii, Bu^{n}Li, (*S*)-(−)-4-benzyloxazolidin-2-one; iii, KHDMS, trisyl azide in AcOH; iv, LiOH, aq H$_2$O$_2$

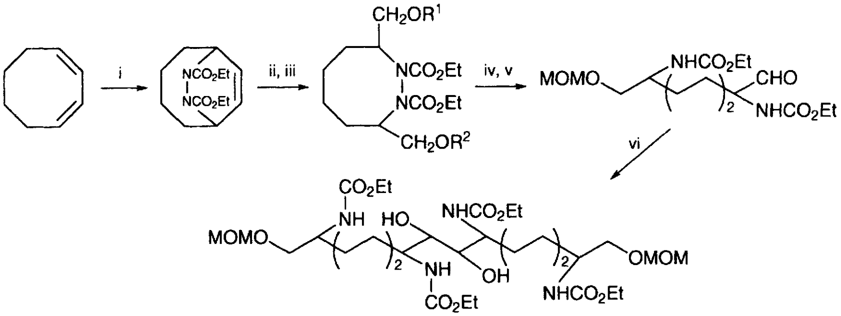
Scheme 4

dinger reaction (PBu$_3$ in the presence of Boc$_2$O) has concentrated particularly on the side-reaction leading to ureas.[59] The work of Evans and Nelson (1997, Vol. 30, p. 6) based on magnesium bis(sulfonamide) complexes as catalysts for merged enolization and amination of N-acyloxazolidinones has been surveyed,[60,61] and a new cleavage method has been introduced that exchanges the chiral auxiliary for an alcohol moiety using lanthanum(III) iodide in an alcohol at room temperature.[62] New data on dynamic kinetic resolution of α-haloacyl imidazolidinones accompanying amination have been collected.[63]

Chiral 4-substituted-5,5-diaryloxazolidin-2-ones[64] and benzosultams[65] are readily N-acylated and can be used in the Evans way, azidation occurring with better than 95% diastereoselectivity and, no doubt, capable of improvement. For further applications of Evans methodology in the amino acids context see Refs. 142, 206, 335, 461, and 819.

A protected cyanohydrin, ROCH$_2$CN, has appeared to be an attractive starting point for αα-disubstituted glycine synthesis for many years, through double nucleophilic addition to the triple bond, and this reaction with Grignard reagents has now been found to be promoted by titanium isopropoxide.[66]

The enantioselective aminohydroxylation procedure improved recently by Sharpless has been shown to be a valuable stage on a route from alkenes to α-amino acids, *e.g.* conversion of styrenes into (R)- and (S)-N-benzyloxycarbonyl- or tert-butoxycarbonyl-arylglycinols,[67] and the use of other alkyl carbamates in this way,[68] and oxidation of the products to the corresponding arylglycine derivatives. Regioselection in aminohydroxylation of cinnamate esters can be reversed to give phenylserines if *Cinchona* alkaloid ligands with an anthraquinone core are used, or to give isoserines if the usual phthalazine ligands are used;[69] adenine N-chloro-N-sodio salts are also suitable.[70] The classic alternative route for aminohydroxylation of alkenes, *via* epoxides, is illustrated with aluminium azide as reagent.[71] Oxidation of homochiral α-amino-β-hydroxyalkanes with CrO$_3$ does not cause racemization.[72] Oxazolines, readily prepared from α-amino-β-hydroxyalkanes, have uses in enantioselective α-amino acid synthesis, and these uses have been reviewed.[73] Alkyl carbamates have been employed for aminohydroxylation of styrenes. Conju-



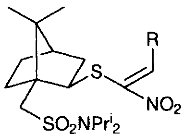
Reagents: i, Diethyl azodicarboxylate, *hν*; ii, O_3; iii, $NaBH_4$; iv, Li–NH_3; v, selective O-protection, oxalyl chloride–DMSO; vi, pinacol formation using $[V_2Cl_3(thf)_6]_2\,[ZnCl_6]$

Scheme 5

gated dienes can be aminated through cycloaddition to diethyl azodicarboxylate, a particular example studied this year being 1,3-cyclo-octadiene;[74] much interest in this study lies in the development of the resulting adduct into α-amino aldehydes and other useful products (Scheme 5). The bis(α-amino acid)s formed through pinacol formation are particularly notable.

Nitroalkenes are also valuable sources of α-amino acids through nucleophilic addition routes, rendered enantioselective when attached to a homochiral grouping; a (+)-camphorsulfonamide gives (10) through addition to a nitronate, and this is easily converted into the α-amino acid thiolester by ozonolysis.[75] Further work has been reported, on addition of the potassium salt of (R)- or (S)-4-phenyl-2-oxazolidinone to nitroalkenes, followed by oxidative conversion into nitromethyl into carboxyl and oxazolidinone cleavage, giving D- and L-amino acids respectively.[76]

α-Ethoxycarbonylaziridines are conveniently prepared from αβ-unsaturated esters, *e.g.* using $PhI{=}NSO_2Ar$,[77] and syntheses of α-amino acid develop from these intermediates through a variety of ways; for example through nucleophilic ring opening as in the preparation of D-α-(3-phenylpropyl)glycine[78] and D-homophenylalanine[79] using the aziridine (11) prepared from D-mannitol; preparation of α-hydroxymethylserine derivatives (12) and (13);[80] and D-phenylalaninol by hydrogenolysis.[81]



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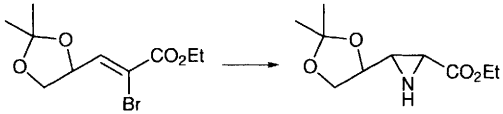

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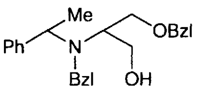

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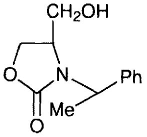

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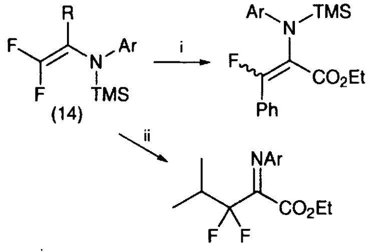
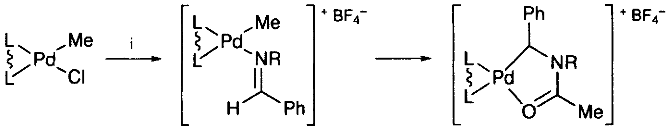
4.1.2 Carboxylation of Alkylamines and Imines, and Related Methods – Processing of N-TMS-N-aryl enamines (14; Scheme 6) gives αβ-dehydroamino acids and α-carboxyimines.[82] The insertion of imines into acyl-palladium bonds was achieved (Scheme 7), but the intended outcome, a new synthesis of amino acid amides, was not realized.[83]



Reagents: i, PhLi (1.5 equiv.); ii, Pr^{i}I (10 equiv.), BEt$_3$

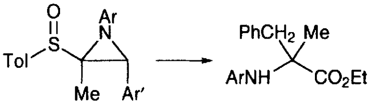
Scheme 6



Reagents: i, CO (3,4 bar)

Scheme 7

α-Amino acid thiolesters R^{1}NHCHR^{2}COSPh can be obtained by trifluoroacetic anhydride-induced Pummerer rearrangement of 3,N-disubstituted 4-phenylsulfinyl-β-sultams.[84] Homochiral toluene-p-sulfinylaziridines (15) have been carboxylated with ethyl chloroformate, the products being further developed, *e.g.* into N-phenyl S-α-methylphenylalaninate.[85]



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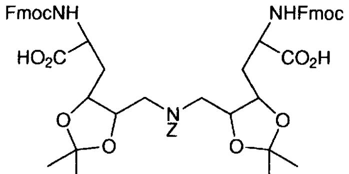
4.1.3 Use of Chiral Synthons in Amino Acid Synthesis – The use of the Schollkopf approach has continued on a broader basis, due to the exploration of modified homochiral dioxopiperazines for the purpose. Standard applications of the Schollkopf method include syntheses of 'αα′-bis(glycine)s', *i.e.* R^{1}O$_2$CCR^2(NHR^3)-R-CR^2(NHR^3)CO$_2$R^1 where -R- is an alkyl chain [R^2 = Me, R = H],[86] leading to (2R,5R)-2,5-diaminohexane-1,6-dioic acid,[87] (2S,7S)-2,7-diamino-octane-1,6-dioic acid, the dicarba-analogue of L-cystine,[88] and a di(hydroxylysine) analogue (16),[89] and syntheses of R- and S-p-(4-hydroxybenzoyl)phenylalanines,[90] 3′,5′-dimethoxy-2-mercaptophenylalanines and heteroarylphenylalanines synthesized in support of an imbricatine synthesis,[91] 2,6-dibromo-L-tyrosine,[92] and 2-isopropenyl-L-tryptophan.[93] 1-Amino-



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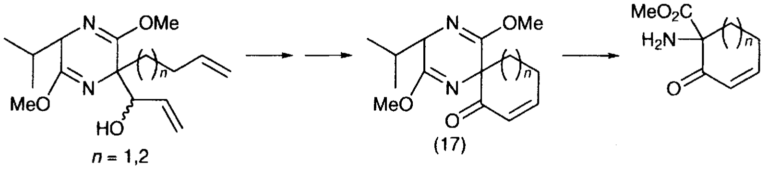
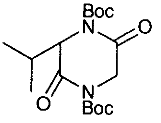
cycloalkenoic acids emerge from alkenylation of a bis(lactim) ether followed by ruthenium(I)-catalysed cycloisomerization, applied to 3-hydroxymethyl[94] and 2-alkenylcarbonyl analogues,[95] leading to (*e.g.* 17), and 1-amino-4-hydroxycyclohex-3-enoic acids.[96] Pd-Catalyzed Heck cyclization of bromodienes derived from the Schollkopf synthon[97] is an equivalent process.



(17)

The bis(N-Boc)-piperazinedione (18) has been used in a synthesis of [2,3-$^2H_2$]-labelled erythro-β-hydroxy-α-amino acids through aldol addition, elimination and catalysed deuteriation;[98] use of the standard Schollkopf methodology (no Boc protection on nitrogen) gives the corresponding threo isomers. Mono-N-Boc-piperazinone (19) is a new homochiral alanine template that has been advocated for the synthesis of α-methyl-α-amino acids, giving better than 94% diastereoisomeric excess.[99]



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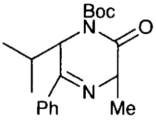
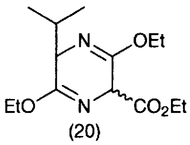


(19)

A use for ethyl (6S)-6-isopropyl-2,5-diethoxy-dihydropyrazine-3-carboxylate (20) in syntheses of α-alkylserines through alkylation with an alkyl halide[100] or with an aldehyde[101] provides a valuable new variation. These are mostly based on bis-lactim ethers derived from 3-isopropylpiperazine-2,5-dione (for which a reliable 45 g scale synthesis has been worked out, also a synthesis of the monomethyl ether for the first time[102]). Alkylation of a related mono-ethyl ether, N-[(S)- or (R)-α-phenylethyl]oxazinone (21) offers a satisfactory enantioselective route to α-methyl-α-alkylglycines.[103] A related derivative, (S)-3-isopropyl-N,N-di-(p-methoxybenzyl)piperazine-2,5-dione (22) has been shown to allow oxidative removal of the N-substituents, and to favour trans-alkylation leading to better than 90% diastereoisomeric excess;[104] similar use of this synthon has been illustrated in syntheses of both enantiomers of phenylalanine,[105] and in a broad range of similar applications.[106] N-(L-Prolyl)amino-



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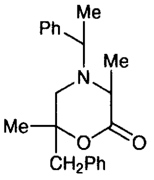

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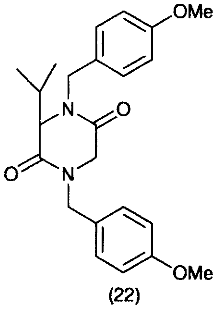

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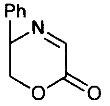
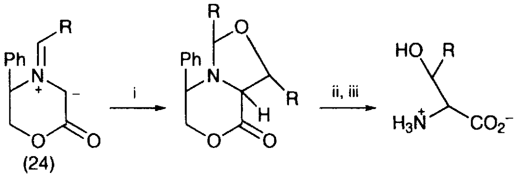


(23)

malonate is the source of methoxycarbonylpiperazin-2,5-dione which gives 3-methoxypiperazin-2,5-dione by electrochemical methoxylative decarboxylation; this is a useful new synthon whose potential has been demonstrated in a synthesis of D-allylglycine.[107]

Structurally-related homochiral morpholinones (*e.g.* 23) can be synthesized carrying a range of substituents, due to the easy availability of β-aminoalkanols used for their preparation. Standard methodology is illustrated in Lewis acid-catalysed alkylation by Grignard reagents,[108] and in synthesis of α-methyl-α-amino acids from the 3-methyl-5-isopropyl analogue.[109] A broader use of (5S)-phenylmorpholin-2-ones lies in prior conversion into iminium salts (24) formed with aldehydes (Scheme 8).[110] In the latter case, excess aldehyde leads to β-hydroxy-α-amino acids in good yield, and this approach has been used in a synthesis of (+)-(2S,3S,4S)-polyoxamic acid from (S)-glyceraldehyde.[111] The use of aldimines, instead, gives secure knowledge of stereochemistry for the product of cycloaddition; the cleavage product of an adduct formed in this way is a threo-(2S,3R)-3-aryl-2,3-diaminoalkanoic acid.[112]



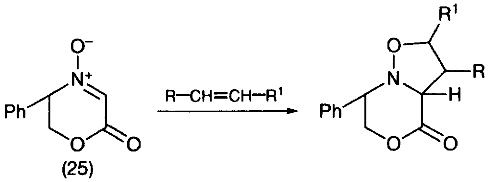
Reagents: i, RCHO (2 equiv.); ii, H_2–$Pd(OH)_2$, TFA (1 equiv.); iii, ion-exchange chromatography

Scheme 8

(5S,6R)-N-Benzyloxycarbonyl-5,6-diphenylmorpholin-3-one (see also Ref. 911) has been applied to a preparation of (S)-α-methylasparagine through alkylation using a glycine enolate (see Section 4.1.7) as reactant,[113] and through another standard approach, aldolization, to give diastereoisomeric β-hydroxpipecolic acids.[114] Standard practice with this synthon has also been illustrated in a synthesis of p-(carboxydifluoromethyl)-L-tyrosine.[115] A related 5,6-disubstituted morpholinone has been used in an interesting study of alkylation *via* alkyl radicals at −40 °C, a process that shows complete stereocontrol; in contrast, the cycloaddition of this synthon to the homochiral imine

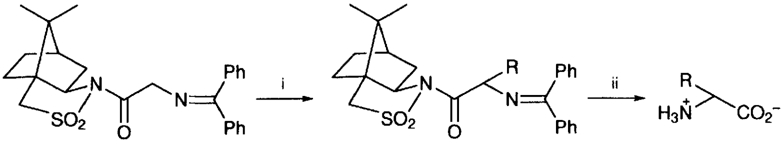
(E,S)-$MeO_2CCH{=}NCHMePh$ gives a 70:30-mixture of diastereoisomers.[116] 3-Methoxymorpholin-2,5-diones have been prepared from (S)-α-hydroxyacids and dimethyl aminomalonate and electrochemical methoxylation of the product after decarboxylation, and used in the standard way as a cationic glycine equivalent.[117] The related route from the sodium salt of an amino acid with a homochiral α-hydroxyacid ester *via* an N-(α-hydroxyacyl)amino acid ester is completed by cyclization in an aprotic acid medium.[118]

The nitrone (25), prepared by direct oxidation of the morpholinone, offers a different α-alkylation opportunity through 1,3-addition to an alkene, and leads to γ-oxygenated amino acids.[119]



(25)

The Oppolzer camphorsultam has many supporters, new and old, who have applied it for enantioselective syntheses of N-Boc-N-methyl-(p-benzoyl)-L-phenylalanine,[120] highly-fluorinated L-(S)-2-amino-3-(7-methoxycoumarin-4-yl)propanoic acids,[121] [1-^{13}C]-, [2-^{13}C]-, and [^{15}N]-labelled L-amino acids,[122] D-[3-^{14}C]phenylalanine,[123] and L-[^{13}C, ^{15}N]prolines.[124] Phase-transfer catalysis of alkylation of the (2R)-bornane-derived 10,2-sultam amide (Scheme 9) has proved to be highly diastereoselective (better than 97% d.e.).[125] Other uses for chiral glycine equivalents include preparations of [^{13}C]-labelled L-β-arylalanines from corresponding [^{13}C]-labelled aralkyl halides.[126]



Reagents: i, RBr, K_2CO_3, catalytic Bu_4NBr; ii, 2.5 M LiOH, then bring to pH 2

Scheme 9

4.1.4 Use of Rearrangements Generating a Carbon–Nitrogen Bond – Trichloroacetimidate esters are the essential intermediates in the [3,3]-sigmatropic rearrangement route, *e.g.* to *cis*-5-phenylproline from (R)-mandelic acid methyl ester protected as the MOM ether.[127]

Beckmann rearrangement of tosylated oximes of homochiral acyclic β-ketoesters is advocated for a synthesis of αα-disubstituted glycines, although it is already well-documented in this context.[128] The Curtius rearrangement appears several times in this Chapter (Refs. 268, 289, 290, 434), and has been used in the conversion of cyclopent-3-ene-1,1-dicarboxylic acid into 1-aminocyclopent-3-ene 1-carboxylic acid *en route* to 1-aminocyclopentane-1,3-dicarboxylic acid,[129] and epoxysilyl ethers *via* isomeric aldehydes into S-α-methylphenylglycine.[130]

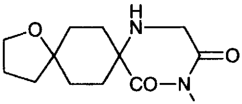
$Na^{13}CN$ and $NaC^{15}N$ have been used to prepare substrates for Neber rearrangements leading to [1-^{13}C]- and [1-^{15}N]-DL-homophenylalanine, employing conventional methodology.[131]

4.1.5 Other Rearrangements – Claisen rearrangements of allyl glycinates have been covered in this Section in previous Volumes of this Specialist Periodical Report, and current papers (Refs. 215-217) develop the same theme.

4.1.6 Amidocarbonylation and Related Multicomponent Processes – Catalysts for the synthesis of N-acetylamino acids from an aldehyde, acetamide, and carbon monoxide[132] have been investigated methodically, and the $PdBr_2$–LiBr–H_2SO_4 cocktail has proved to be the best.[133] Of course, the classic Bucherer–Bergs synthesis employing an aldehyde, ammonium carbonate, and sodium cyanide is a three-component synthesis, and has been applied to give a high yield of phenylglycine from benzaldehyde,[134] and to give ββ-disubstituted tryptophans, *via* hydantoins.[135] Combinatorial synthesis of hydantoins continues to be attractive for the preparation of libraries containing potentially useful lead compounds,[136] with resin-bound ketimines being used in a versatile approach.[137] [For other Strecker syntheses see Refs. 138, 141, and 142.] Since scandium triflate-catalysed Strecker-type reactions with aldehydes, amines and $SnBu_3CN$ give α-amino nitriles in both organic and aqueous media, they have been described (stretching commonly-understood definitions somewhat) as an environmentally-friendly route to amino acids.[138] An aldehyde, together with (S)-α-methylbenzylamine, and TMSCN in LPDE gives predominantly S-α-aminonitriles.[139] Development of earlier work on asymmetric Strecker synthesis covers catalysis by the homochiral dioxopiperazine, cyclo(D-His-D-Phe) (Vol. 29, pp. 12, 82);[140] the use of a chiral sulfinimine ArCH=NSOAr for the Strecker synthesis of a vancomycin component has been reported.[141] (S)-Phenylglycinol is the component that makes a Strecker synthesis of N-Boc-D-[3,5-bis(isopropyloxy)-4-methoxyphenyl]glycine diastereoselective.[142] Double asymmetric synthesis is illustrated in the use of homochiral amine and (2S)-methylcyclopropane methyl hemiacetal in a synthesis of (1R,2S)-(+)-allonorcoronamic acid.[143] Better than 80% e.e. has been achieved for the first time using this approach with N-allylbenzamidine.[144]

Other ‘multicomponent’ amino acid syntheses include the Ugi four-component condensation (4CC), which is undergoing something of a revitalization. The mechanistic basis of this method has been reviewed,[145] and an application leading to a 2,6-dioxopiperazine (26) has been reported, employing an amino acid as the amine component leading to the derivative of a different amino acid.[146] A 4CC approach to 2-oxopiperazines uses an N-(2-aminoethyl) N-Boc-N-alkylamine with the usual three other reactants.[147] Synthesis of α-methyl-α-amino acids through the 4CC route in solution and in solid-phase (combinatorial synthesis) modes has been described,[148] including a polymeric amine on which isocyanoacetamide and a carboxylic acid were condensed.[149]

Rapid access to metalloproteinase inhibitors (27) is possible through the 4CC synthesis.[150] A variant of this has been described as a five-component condensation, the 4CC synthesis being followed in the same pot by hydroxylaminolysis.[151] Protected D-glucosyl isonitrile syntheses do not inject diastereoselectivity into the process when used in the Ugi amino acid synthesis.[152]



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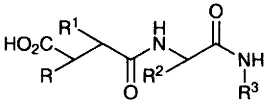


(27)

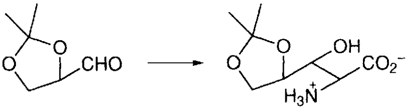
Further results have been reported for the formation of anti-β-aminoalkanols from alkenyl or arylboronic acids by condensation with a primary amine and an α-hydroxyaldehyde or α-hydroxydioxolane (Vol. 30, p. 8), and ruthenium(IV) oxidation into amino acids.[153]

4.1.7 From Glycine Derivatives and from Imines of Glyoxylic Acid Derivatives – These two families of compounds, $\mathrm{R^1NHCH_2CO_2R^2}$ and $\mathrm{R^1N{=}CHCO_2R^2}$ respectively, are so closely related in their applicability to α-amino acid synthesis that there is some logic in collecting their uses under the same heading.

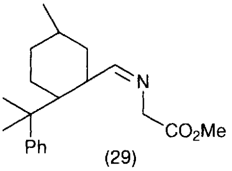
The classic amino acid synthesis based on C-alkylation of diethyl acetamidomalonate[154] has been used for the preparation of N-acetyl-β-(2-naphthyl)-alanine ethyl ester,[155] and perdeuterioglycine.[156] Diethyl formamidomalonate has been used to prepare substituted β-aminoalanines $\mathrm{R^1R^2NHCH_2CH(NH_2)CO_2H}$, the acid hydrolysis step needed to release the amino acid product needing to be conducted below 30 °C with this substrate.[157] Diethyl 2-phthalimidomalonate and diethyl 2-nitromalonate were 2-formylethylated successfully.[158] *erythro*-3-Phenylglutamic acid diethyl ester emerges from NaOEt-catalysed Michael addition of diethyl benzylidenemalonate to diethyl acetamidomalonate.[159] Alkylation of an analogous [^{15}N]glycine synthon has been employed in a synthesis of [α-^{15}N]-DL-tryptophan,[160] and an analogous route to [β-^{11}C]-L-DOPA is based on alkylation by [α-^{11}C]-3,4-dimethoxybenzyl bromide.[161]

Aldolization of glycine by 4-acetamidobenzaldehyde using a pyridoxal-mediated abzyme system is a development of knowledge of the mode of action of L-threonine aldolase,[162] which catalyses the addition of α-adeninyl- and α-guaninylacetaldehyde to glycine.[163] D-Threonine aldolase catalyses the aldolization of glycine by the protected glyceraldehyde, giving the (2R,3R,4R)-product (28; 0.2% solutions in organic solvents form gels), mixed with its epimer (which does not share this property).[164]

C-Alkylation of alkoxycarbonylmethyl imines $\mathrm{Ph_2C{=}NCH_2CO_2Bu^t}$ [165,166] is a well-established synthesis approach to α-amino acids, and has been used for preparations of 2-amino-4-fluoroprop-4-enoic acid[167] (the alanine homologue has been used to prepare γ-fluoroalkyl-α-methyl-α-amino acids[168]), *cis*-


(28)

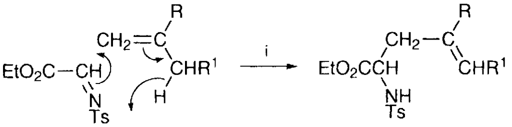
2,3-dialkylpyroglutamic acid esters,[169] and, in resin-bound form, Michael addition to give libraries of glutamic acid analogues.[170] Alkylation using a neutral non-ionic phosphazene base and chiral quaternary ammonium salt derived from a *Cinchona* alkaloid is highly enantioselective.[171] Allylation followed by tandem Michael-Dieckmann cyclization gives a 4-ethoxycarbonyl pyrrolidin-3-one *en route* to substituted quinolines.[172] High enantioselectivity accompanies cinchonidinium salt-catalysed alkylation.[173] The advantages of this glycine derivative, compared with ethyl nitroacetate, for Pd-mediated coupling with 2,6-dibromo-1,6-dienes, cycloisomerization of the resulting 1,6-enynes giving bicyclic and tricyclic αα-disubstituted glycines, have been established;[174] nevertheless, nitroacetates are versatile glycine synthons, suitable for dehydroamino acid synthesis and open to alkylation with organozinc reagents.[175] A version of this glycine imine carrying a novel chiral auxiliary (29) is advocated for the synthesis of D-α-amino acids (from 29) or L-α-amino acids (from the epimer of 29).[176] Through an uneventful application of standard reactions, the analogous Schiff base of (+)-(R,R,R)-hydroxypinanone has led to (2R,3R)-m-chloro-3-hydroxytyrosine (a vancomycin and aridicin A component)[177] and to R-2′-methyltryptophan,[178] and underwent diastereoselective aldolization to start a synthesis of sulfobacin (independently prepared from cysteine, see Ref. 1011).[179]


(29)

The long-established Schiff base complex formed between an o-substituted benzophenone and L-prolylglycine and a nickel(II) salt has been used in newer forms, *e.g.* the L-alanine homologue to prepare α-methyl-α-amino acids [L- and D-α-(3,4-dichlorophenyl)-α-methylalanine;[180] α-methyl-D-phenylalanine, D-β-allylglycine and α-allyl-D-alanine;[181] other homologues through phase transfer-catalysed alkylation employing (4R,5R)- or (4S,5S)-2,2-dimethyl–tetraphenyl-1,3-dioxolane-4,5-dimethanol, *alias* TADDOL[182]]. L,L-2,4-Diaminoglutaric acid has been prepared through Michael addition to dehydroalanine.[183] Use of homochiral sodium alkoxides to catalyse the Michael addition of methyl methacrylate with an achiral Schiff base of this family, formed from glycine and N-(2-pyridylcarbonyl)-o-aminobenzophenone, gives 4-methylglutamic acid with moderate enantioselectivity.[184] Use of this synthon continues to attract other research groups, and C-alkenylation using allyl or propargyl bromides, followed by hydroboration of the resulting ω-unsaturated α-amino acid derivatives has led to ω-boronoalkyl-α-amino acids.[185]

Isocyanoacetates are occasionally used for α-amino acid synthesis, bis(α-alkylation) with 2,3-di(2-iodoethyl)buta-1,3-diene giving 3,4-dimethylenecyclopentane-1-carboxylic acid after the usual isocyanide-to-amino group conversion.[186]

The first enantioselective imino-ene reaction shown in Scheme 10 (see also Ref. 190) is capable of providing amino acids of high optical purity.[187] The (−)-8-phenylmenthylglyoxylate has been used similarly.[188] The N-toluene-p-sulfonylimine $TsN{=}CHCO_2Et$ can be C-alkylated diastereoselectively and enantioselectively by an enol silane when catalysis by (S)-BINAP-$CuClO_4(MeCN)_2$ is employed;[189] a preference for (R)-Tol-BINAP has been expressed for alkylation of this imine by an alkene $R^1C({=}CH_2)CH_2R^2$ to give a γδ-unsaturated (S)-α-amino acid $TsNHCH(CH_2CR^1{=}CHR^2)CO_2H$.[190] The imine from (R)-phenylglycinol and glyoxal carrying an N-(6-trimethylsilyl-hex-4-enyl) side-chain moiety yields a transient iminium ion that undergoes intramolecular addition to give methyl *cis*- or *trans*-3-vinyl-(R)-pipecolinate.[191] Imines formed from glyoxylate esters $HCOCO_2R + RNH_2 \rightarrow RN{=}CHCO_2R$ can be alkylated using enol silyl ethers $Me_3SiOCR{=}CH_2$ and lead to γ-oxoalkylglycines in better than 90% e.e. when a chiral palladium(II) species is employed as catalyst,[192] and undergo Diels-Alder addition (R = MeOCH=CH-) to give N-aryltetrahydropyridin-4-one 3-carboxylates in high enentiomeric excess when catalysed with a homochiral Lewis acid.[193] Chiral glyoxylate ester imines undergo Staudinger β-lactam synthesis (to give 3-substituted azetidin-2-one-4-carboxylic acids).[194]



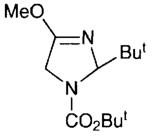
Reagents: i, (*R*)-Tol-BINAP, Cu-bis(MeCN) perchlorate, $PhCF_3$, room temp.

Scheme 10

The dianion of ethyl Z-glycinate has been used in a synthesis of 3-alkoxycarbonylisoquinolin-2-one through condensation with an alkyl o-formylbenzoate.[195] Ethyl 2-phthalimidoacetate undergoes alkylation to give the corresponding α-amino acid derivative with no better than 59.5% enantioselectivity when catalysed by chiral reverse micelles,[196] but wide variation (20–98%) in the outcome with phenylalanine synthesized through the alkylation of hippuric acid (1R,2S)-2-arylcyclohexyl esters, depending on the nature of the aryl group, has been reported.[197] An unusual intramolecular cyclization, N-Boc-N-(o-bromobenzyl)-glycine N′-allylamide to pyrrolidin-2-one by Bu_3SnH–1,1′-azobis(cyclohexanecarbonitrile), relies on formation of a glycinyl radical intermediate.[198]

Hippuric acid coupled to (1S,2R)-1-amino-indan-2-ol provides a chiral glycine equivalent that gives D-amino acids in 90–99% d.e. through alkylation of its enolate.[199]

Oxazolidinones and dihydroimidazoles have been resolved over chiral stationary phases using the moving bed technique,[200] and the newly-prepared dihydroimidazole (30) has been resolved by chromatography over a polysaccharide stationary phase.[201] The new chiral glycine derivative (30) undergoes diastereoselective alkylation with an alkyl halide after lithiation;[202] a valuable feature is the mild release of the amino acid product after the alkylation stage, so that acid-sensitive functional groups are not affected. Alkylation of a differently-conceived chiral glycine derivative, the oxazolidine (31), prepared from (S)-phenylglycinol, is described in a preliminary study.[203] Its use in aldol reactions after lithiation and reaction of the enolate with an aldehyde is notable in giving β-hydroxy-α-amino acids with anti-selectivity.[204]



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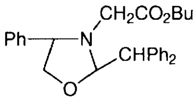
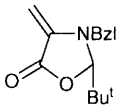


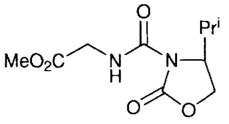
(31)

The dehydroalanine synthon (32) continues to be a useful substrate for addition reactions that lead to L-α-amino acids with extended side-chains (Vol. 30, p. 18; see also Refs. 295, 319), and an extraordinary use has been reported: photoinduced radical addition of alkanols and ethers leading to homoserine derivatives.[205] A difficulty arises when this synthon is used for these targets, since epimerization accompanies cleavage when the product is hydrolysed to the amino acid.



(32)

The ureide (33) formed from methyl glycinate and the Evans oxazolidinone undergoes allylation under radical conditions (allyltributyltin, AIBN, −50 °C) with excellent stereocontrol exerted by the presence of $ZnCl_2$-Et_2O to give D-allylglycine with 93 : 7-diastereoselectivity.[206] The glycine synthon (34) that incorporates the analogous imidazolidinone as an amide function is also well suited for L-α-amino acid synthesis.[207] A review has appeared covering the uses of chiral imidazolidinones in asymmetric synthesis.[208]



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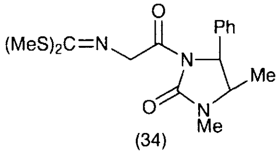
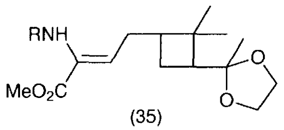


(34)

α-Heteroatom-substituted glycinates $RNHCH[P(O)(OMe)_2]CO_2Me$ have been regularly used for dehydro-amino acid synthesis (*cf.* Section 4.9) through Wittig olefination with a chiral aldehyde, as for the preparation of novel cyclobutanes (35),[209] and with acetaldehyde (developed *via* the β-bromoalkyl amino acid into a substituted dehydrotryptophan).[210] A 3-pyrrolylalanine synthesis also uses this route.[211] Synthesis of the cyclopropylglycine (36)



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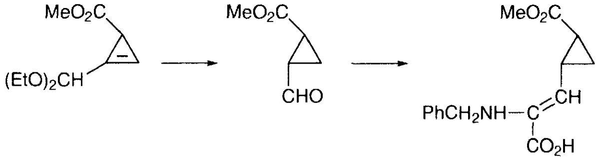
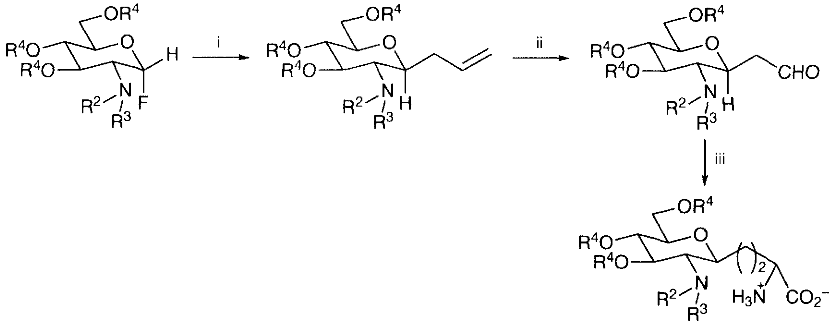


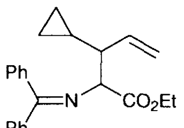
(36)

illustrates the enantioselectivity that accompanies hydrogenation of the cyclopropene, controlled by the 2R-methyl group.[212] An extended route (Scheme 11) to C-glucopyranosyl-D- and L-serines demonstrates the construction of an extended aliphatic side-chain through the Wittig synthesis strategy.[213] The α-glycinylzinc chloride $Ph_2C=NCH(CO_2Et)ZnCl$ undergoes palladium(0)-catalysed cross-coupling with substituted bicyclopropylidenes and bromomethylenecyclopropane to give α-(alkadienyl)glycines (37).[214]



Reagents: i, $Me_3SiCH_2CH=CH_2$, $BF_3{\cdot}Et_2O$; ii, O_3; iii, Wittig synthesis, then H_2–Pd

Scheme 11



(37)

Allyl glycinates can undergo [3,3]-sigmatropic rearrangement, delivering the appropriate unsaturated side-chain onto the glycine methylene group. The topic has had tediously fragmented exposure in the recent literature (Vol. 30, p. 29) but the process provides unsaturated amino acids (see also Section 4.9) with predictable stereochemistry.[215,216] Its scope has been broadened to encompass the rearrangement of allyl ethers into γ-keto-α-amino acids [$XNHCH_2CO_2CHRC(OMEM)=CF_2 \rightarrow XNHCH(CF_2COCH_2R)CO_2H$].[217] 2-Trichloromethyl-imidazole has been prepared from glycinal dimethyl acetal $H_2NCH_2CH(OMe)_2$.[218]

4.1.8 From Dehydro-amino Acid Derivatives – In addition to examples mentioned elsewhere in this Chapter, a number of non-routine studies cover enantioselective synthesis of α-amino acids from achiral α-aminoacrylates. These studies focus mainly on chiral phosphines as ligands for rhodium(I)-catalysed hydrogenation, such as CARAPHOS, which is less effective in this context[219] than other well-known diphosphines[220] such as DIPAMP,[221] and PROPRAPHOS.[222] Good stereoselectivity is seen for (S,S)-1,2-bis(alkylmethylphosphino)ethanes,[223] (R,R)-ethyl-DuPHOS,[224] and hydroxy-DIOP.[225] Other less familiar ligands include homochiral phosphaferrocenes[226] and the air-stable FERRIPHOS series,[227] and an aminophosphine phosphinite prepared from (1S,2R)-1,2-diphenyl-2-aminoethanol.[228] An alternative approach using a phosphinite, $[Rh(COD)_2]BF_4$, has the benefit of high stereoselectivity;[229] this system has been used also for corresponding synthesis of β-aminoalkanols from MOMOCH = CRNHAc.[230]

The rhodium(I)-(S,S)-PrTRAP complex has been used to catalyse the hydrogenation of the unfamiliar substrate, ethyl (E)-αβ-bis(N-acylamino)-acrylate, to provide the corresponding (2S,3R)-2,3-diamino-alkanoic acid derivative.[231]

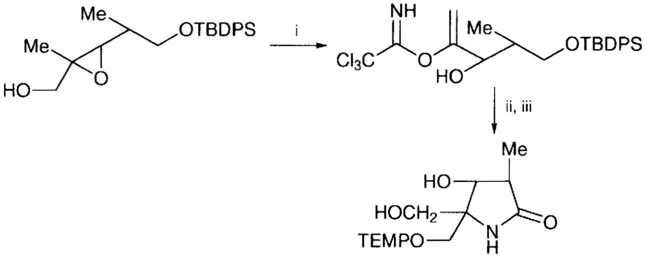
This topic is well-served with reviews.[232]

4.2 Synthesis of Protein Amino Acids and Other Naturally Occurring α-Amino Acids – Reports of enzyme-catalysed syntheses leading to familiar L-α-amino acids provide a large part of this Section, and, as usual, the literature coverage is not exhaustive on biotechnological aspects, but describes selected non-routine studies. This literature on biosynthesis studies also extends to bacterial and other whole-cell processes, but studies involving plants and higher organisms are not covered in this Chapter.

Alanine dehydrogenase (conversion of pyruvate into L-alanine) is usefully combined with glucose dehydrogenase so that NADH regeneration can accompany continuous production.[233] The classic route to L-DOPA using mushroom tyrosinase-catalysed oxidation of tyrosine can be improved by immobilizing the enzyme on chemically-modified nylon[6.6] membranes.[234] Immobilized aspartase features in a synthesis of [^{15}N]aspartic acid from a dialkyl fumarate and $^{15}NH_4OH$,[235] and this route and a whole-cell alternative based on L-aspartate-β-decarboxylase has also been developed.[236] A whole-cell approach to L-DOPA production by use of *Stizolobium hassjoo* cell culture has been described,[237] and the use of *Corynebacterium glutamicum* has been shown to be appropriate for L-lysine production.[238]

Reviews cover uses of transaminases for large-scale production of non-natural α-amino acids,[239] enzyme-catalysed manufacture of L-phenylalanine,[240] production of D-α-amino acids from hydantoins using N-carbamyl-D-amino acid aminohydrolase,[241] processes leading to L-α-amino acids base on Coryneform bacteria,[242] and plant sources as the basis for amino acid production.[243]

Routine literature covering the laboratory synthesis of common naturally-occurring α-amino acids is dealt with in other sections of this Chapter. New syntheses of more complex examples have been reported for sphingofungins B and F [tin(II)-catalysed asymmetric aldol addition],[244] an alternative route to sphingofungin F through asymmetric alkylation of an azlactone catalysed by a recently-introduced homochiral palladium complex (Vol. 30, p. 23),[245] and for lactacystin (see also Refs. 479, 480; and Vol. 30, p. 12). A route[246] to the last-mentioned cysteine derivative is notable for a doubly-diastereoselective Mukaiyama aldol coupling of a chiral tertiary α-aminoaldehyde with an achiral silyl enol ether to give the required antiselectivity, and a route to the precursor aminoalkanol for lactacystin (Scheme 12) employs a trichloracetimidate ester for the amination step.[247]

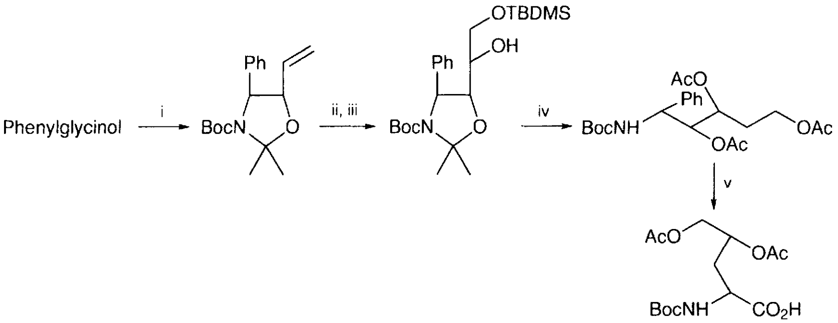


Reagents: i, LDA/thf, then Cl_3CCN; ii, $Hg(OTf)_2$, K_2CO_3, then aq. KBr; iii, functional group adjustment followed by conc. HCl/Zn

Scheme 12

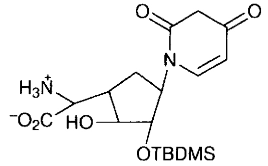
Polyoxamic acid is available through a relatively short synthesis based on manipulation of N-Boc-R-phenylglycinol (Scheme 13; see also Ref. 931).[248] Improved routes to an intermediate suitable for uracil polyoxin C synthesis,[249] and to carbocyclic analogues (38),[250] include carefully worked-out stages calling for mild conditions. Also noteworthy are new synthesis approaches to nicotianamine and 2′-deoxymugineic acid,[251] (2S,4S)-γ-hydroxynorvaline (a constituent of the Boletus toxin),[252] (2S,4R,5S)-piperidine-2,4,5-tricarboxylic acid from the poisonous mushroom *Clitocybe acromelalga*,[253] Actinomycin Z_1 constituents (2R,3R,5R)- and (2S,3S,5S)-3-hydroxy-5-methylpiperidine-2-carboxylic acids,[254] and the N-terminal amino acid residue of nikkomycin B.[255]

Synthesis studies for kainic acid, and kainoids generally, have featured in the literature over several years. New work deals with ketyl radical cyclization onto an enecarbamate derived from L-pyroglutamic acid to introduce the C-4



Reagents: i, routine stages; ii, AD-mix-β; iii, TBDMSCl, imidazole, DMAP;
iv, Bu_4NF/thf. then Ac_2O/DMAP; v, $RuCl_3$–$NaIO_4$

Scheme 13



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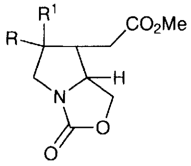
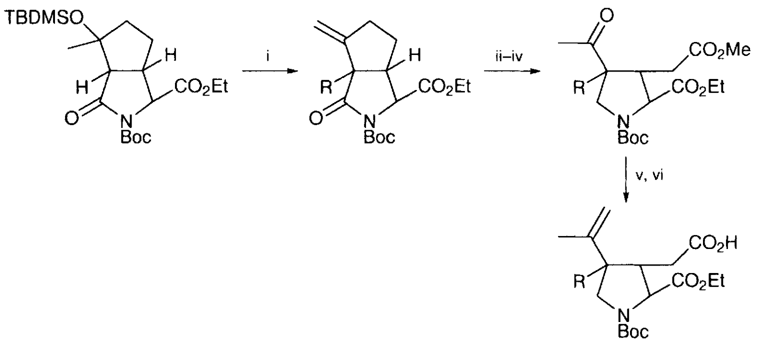


(39)

substituent on the pyrrolidine framework,[256] and an alternative approach to racemic 4-substituted kainic acids (Scheme 14)[257] with variants that lead to (−)-kainic acid[258] that also start from L-pyroglutamic acid. A route to an established key intermediate (39) for a (+)-α-allokainic acid synthesis has been established.[259] The synthesis strategy for (−)-α-kainic acid used by Bachi's group (Vol. 30, p. 21) has been reviewed.[260] Full reports of acromelic acid A and alloacromelic acid A syntheses, and an approach to acromelic acid B through palladium(0)-catalysed cross-coupling to C-4-catechol precursor and pyridones, have appeared;[261] a biomimetic approach was followed similar to that leading to stizolobic acid (Vol. 30, p. 70) that was used earlier by this research group.



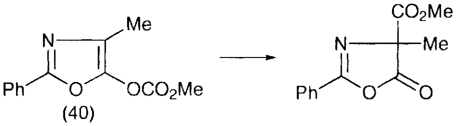
Reagents: i, LiHDMS, RX; ii, TFA, then Boc_2O/DMAP; iii, DIBAL-H, then $Et_3SiH/BF_3{\cdot}Et_2O$;
iv, OsO_4, $NaIO_4$; v, $Ph_3P{=}CH_2$; vi, Jones oxidation followed by deprotection

Scheme 14

Pride of place for the synthesis of an amino acid-based natural product this year must be the vancomycin aglycone (see also Refs. 373, 374);[262] extensive work on amino acid syntheses in recent years has provided the foundation for this achievement.

4.3 Synthesis of α-Alkyl α-Amino Acids – Many of the general methods of α-amino acid synthesis are applicable for the synthesis of their α-alkyl homologues, and applications in this context have been mentioned in the preceding section. A review has appeared.[263]

Rearrangement of 4-methyl-5-alkoxycarbonyloxyoxazoles (40) has been known for many years and seems ideally suited for the synthesis of α-methyl-α-amino acids and homologues, given the extensive experience of the use of oxazol-5(4H)-ones in amino acid synthesis and the effective catalysis of the rearrangement by the iron(III) complex of 4-pyrrolidinopyrindene.[264] Standard practice is illustrated in the formation of (41) as major product (8.7:1) through reaction of 4-methyl-2-phenyloxazol-5(4H)-one with 3-acetoxycyclohexene and a chiral palladium catalyst.[265] Ethylation of (2R,4S)- or (2S,4S)-diphenyloxazolidin-5-one gives enantiomers of α-ethyl-α-phenylglycine,[266] and a similar use of the 4-ferrocenyl analogue, prepared in better than 98% e.e. from ferrocenecarbaldehyde and sodium L-alaninate followed by reaction with pivaloyl chloride, gives (R)-α-methyl-α-amino acids.[267]



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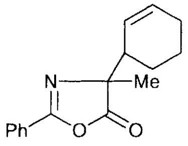

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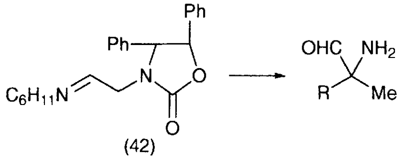
Close analogies of standard methods covered in the preceding section are also seen in the alkylation of (1S,2R,4R)-10-isobornylsulfamoylisobornyl 2-cyanopropionate to give αα-dialkyl-α-cyanoesters, and then to (S)-α-methylserinal acetonide through Curtius rearrangement,[268] a route to α-methyl-α-aminoalkanals from an N-alkenylated oxazolidin-2-one (42),[269] a morpholinone-based route to α-alkyl-α-amino acids involving trans-induction,[270] trans-alkylation of 1-benzoyl-2S-isopropyl-4-methoxy-6S-carbomethoxy-1,2,5,6-pyrimidine to give an α-alkyl-2S-aspartic acid with regeneration of the initial S-configuration,[271] Sharpless asymmetric dihydroxylation to generate two chiral centres in one step, leading to α-methylthreonine and αβ-dimethylcysteines,[272] alkylation of chelated enolates of N-protected alanine esters [best results with tin(II) enolates of the N-arylsulfonylated amino acid],[273] alkylation of the homochiral N-toluene-p-sulfinylimine of ethyl trifluoromethylpyruvate



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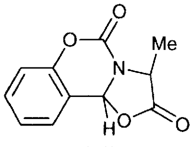
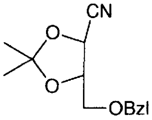


(43)

giving α-trifluoromethyl-α-amino acids with high enantioselectivity,[274] and alkylation of the tricyclic oxazolidinone (43) formed from the N-salicylaldehyde Schiff base of L-alanine, to give R-α-methyltryptophan.[275] α-Methyl- and α-benzyl-quisqualic acids have been synthesized.[276]

Individual tailoring of a route to suit a particular synthetic target is illustrated in highly diastereoselective addition of an alkyllithium to the chiral oxime ether derived from erythrulose to give (R)-(−)-2-methylserine and its (S)-enantiomer, (R)-(+)-2-phenylserine and (R)-(−)-2-butylserine.[277] Sequential nucleophilic additions to the tartaric acid-derived nitrile (44) give imines *en route* to αα-dialkylglycines.[278]



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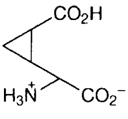
4.4 Synthesis of α-Amino Acids Carrying Alkyl Side-chains, and Cyclic Analogues – This section is in essence little different from the preceding two sections, because it covers standard methods of synthesis of α-amino acids; but the complexity of the synthesis target often constrains the choice of synthesis route and determines strategy in certain cases. Major subdivisions of this section are falling into place through the increasing interest in pharmacological properties of conformationally-constrained versions of the common amino acids; (a) α-cyclopropylglycines; (b) 1-aminocycloalkanecarboxylic acids and homologues, and (c) saturated nitrogen heterocycles carrying one or more carboxy-groups.

4.4.1 α-Cyclopropylglycines and Higher Homologues – Synthesis of stereoisomers of α-(2-carboxycyclopropyl)glycine (45) through previously developed furyl moieties as latent carboxy groups.[280] The latter study has several other noteworthy synthesis features, such as introduction of the amine function by way of an oxime ether and its reduction catalysed by a chiral oxazaborolidine to give the D- or L-product. Relatives of this glutamate analogue have also featured in numerous other synthesis studies: the phosphonoglycine analogue (46) prepared by alkylation of the phosphonoglycine Schiff base (47) with ethyl bromocrotonate followed by cyclopropanation;[281] and 2-(2-carboxy-3′,3′-difluorocyclopropyl)glycine prepared from (R)-2,3-O-isopropylideneglyceraldehyde.[282] αα-Dialkylglycines in this category, such as α-alkyl-α-(2-carboxy-3′-substituted cyclopropyl)glycines[283] include the extraordinary tritiated derivative (48).[284] Extraordinary in another way is (S)-2-(4′-carboxycubyl)glycine (49), a new selective metabotropic glutamate receptor antagonist.[285] (2S,1′S,2′S)- and (2S,1′S,2′R)-2-(2-carboxycyclobutyl)glycines have been prepared through [2+2]photocycloaddition applied to a homochiral αβ-unsaturated-γ-lactam.[286]



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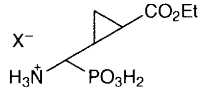

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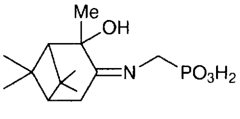

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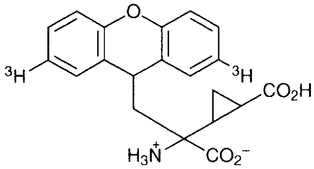

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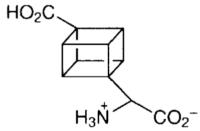
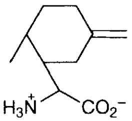


(49)

More flexibility is offered by the α-(substituted α-cyclohexyl)glycine (50) prepared through [4 + 2]cycloaddition to the widely-useful chiral oxazolidine synthon (51).[287] Relatively rigid analogues of N^{α}-(1-iminoethyl)-L-ornithine eight in number (including 52 and 53), have been prepared.[288]



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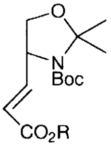

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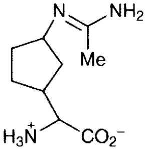

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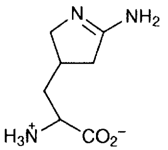

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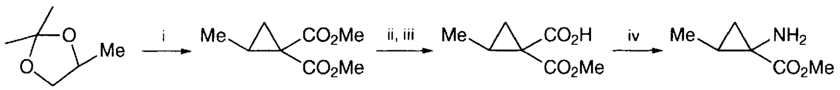
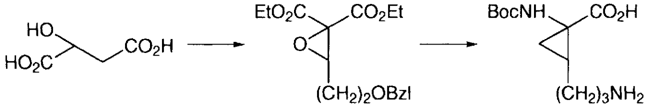
4.4.2 1-Aminocyclopropanecarboxylic Acids – ‘2,3-Methano-amino acids’, *alias*



Reagents: i, $CH_2(CO_2Me)_2$, NaH; ii, mild hydrolysis; iii, resolution as (–)-brucine salt; iv, Curtius rearrangement

Scheme 15

acids. New syntheses have been reported based on Curtius rearrangements; with cyclopropane-1,1-dicarboxylic acid[289] for 1-ACA, enantiomerically-pure 1,2-propanediols as starting point for the preparation of norcoronamic acids from 2-methyl-1-methoxycarbonylcyclopropanecarboxylic acid (Scheme 15),[290] and L-malic acid as the starting point for 2,3-methanoglutamic acid, 2,3-methanoarginine and trans-N-Boc-N-Z-2,3-methano-L-lysine (55, *via* 54).[291] Alternative syntheses of 1-ACA are routine.[292] Cyclopropanation of aldol condensation products of the chiral glycine equivalent 3,6-dihydro-2H-

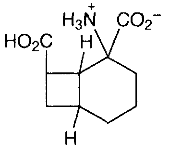


L-Malic acid (54) (55)

1,4-oxazin-2-one has provided new syntheses of 1-ACA and (–)-allo-norcoronamic and (–)-allo-coronamic acids[293] (see also Refs. 39, 143), and careful assessment of the best catalyst metal complex–ligand cocktail for cyclopropanation leading to 3-phenyl-2,3-methanophenylalanine has been described.[294] Cyclopropanation studies have been reported for 4-methylene-2-phenyloxazolidin-5-one, leading to a mixture of three diastereoisomers when ethyl or t-butyl (dimethylsulfuranylidene)acetate is used as reagent.[295] An erratum referring to an earlier publication on this topic has been published.[296] Chiral imines formed between (–)- or (+)-1-hydroxypinanones and aminoacetonitrile give 1-amino-2-vinylcyclopropanenitrile in no more than 32% e.e. when reacted with (E)- or (Z)-1,4-dichlorobut-2-ene catalysed by a palladium(0)-(R)- or (S)-BINAP complex.[297]

4.4.3 Higher Aminocycloalkanecarboxylic Acids and Saturated Heterocyclic Analogues – 1-Aminocyclopentane-1-carboxylic acids (56) represent a novel glutamate mimic, prepared through a lengthy route including a photoaddition stage.[298] Four racemates of 1-amino-4-hydroxy-2-phenylcyclohexane-1-carboxylic acid emerge from Diels-Alder addition to 4-methylene-2-phenyloxazolidin-5-one and ensuing routine elaboration,[299] and synthesis of (1R,2R)- and (1S,2S)-1-amino-2-phenylcyclohexane-1-carboxylic acids uses an earlier method (Vol. 25, p. 53) and includes a conventional resolution step.[300]

Readily-available azidolactones serve as starting materials for the synthesis dine-1-oxyl-4-amino-4-carboxylic acid[303] (the latter is used as a nitroxide spin-labelled amino acid in radical reaction studies[304]).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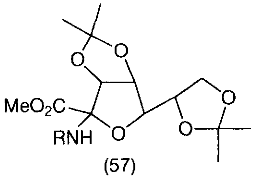
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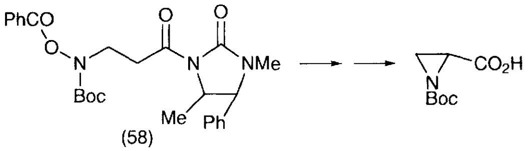
4.4.4 Aziridinecarboxylic Acids and Azetidinecarboxylic Acids – Conjugate addition of N-Boc-O-benzoylhydroxylamine to an αβ-unsaturated acid that has been amidated with the chiral imidazolidin-2-one (58), followed by NaH-induced cyclization, gives the N-Boc-aziridinecarboxamide.[305] The simplest access to aziridinecarboxylic acids is the Gabriel-Cromwell reaction of a primary amine with a 2-bromoacrylate, shown to work well in this context.[306] tert-Butyl 2H-azirine-3-carboxylate, prepared from tert-butyl acrylate ($CH_2{=}CHCO_2Bu^t \rightarrow BrCH_2CHBrCO_2Bu^t \rightarrow N_3CH_2CHN_3CO_2Bu^t \rightarrow CH_2{=}CN_3CO_2Bu^t$ (59), proved to be usable over a period of two hours for Diels-Alder additions leading to other amino acids.[307]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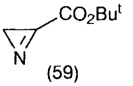
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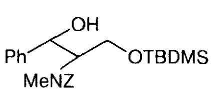
Photocyclization (60) → (61) followed by stages that amount to standard methodology, leads to (2R)- and (2S)-azetidine-2-carboxylic acids.[308] α-Amino-γ-chloroalkanoate esters lead either to N-alkyl-3,3-dimethylazetidine-2-carboxylate esters through $NaBH_3(CN)$ reduction of α-N-alkylimines in refluxing methanol, or to 1-(N-alkylamino)-2,2-dimethylcyclopropane-1-carboxylic acid esters by 1,3-dehydrochlorination.[309]

Diazirinecarboxylic acid esters, prepared from amidines by HOCl oxidation, are useful carbene sources but do not show particular potential for amino acid synthesis.[310]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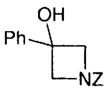
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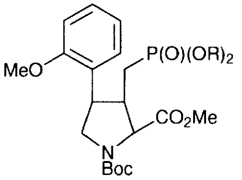
4.4.5 Pyrrolidine- and Piperidine-carboxylic Acids and Analogues – New syntheses of 4,5-methano-L-proline[311] and its near relative 2,4-methanopyrrolidine-2,4-dicarboxylic acid, prepared through a [2 + 2]photocyclization route and designed as a glutamate analogue,[312] are accompanied in the recent literature by routes to kainoid analogues (62)[313] and (63).[314] The last-mentioned examples involve radical cyclization of an αβ-unsaturated phosphonate, and chain-extension of pinanediol[(trityloxy)methyl]boronate with $LiCHCl_2$ and ensuing H_2O_2 oxidation (in very low yield) respectively. (2S,3R,4R)-Diaminoproline is reached from ascorbic acid through conventional amination and functional group development,[315] and (2S,3S)-3-hydroxyproline likewise from L-malic acid, cyanide displacement of the methoxy group of an α-methoxypyrrolidine being a key step.[316]



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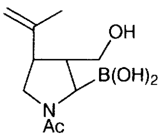
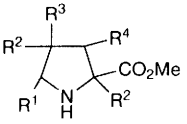


(63)

A long route to (2S,4R)-4-carboxyproline starts from the L-cysteine-derived sulfone $BocN(Bzl)CH(CH_2OBzl)CH_2SO_2Ph$ and builds the requisite carbon chain on nitrogen.[317]

(E)-Nitroalkenes participate in [3 + 2]cycloaddition to azomethine ylides derived *in situ* from Schiff bases of methyl glycinate and homologues $R^1CH{=}NCHR^2CO_2Me$ to give 4-nitroprolines, $LiClO_4$ catalysis giving the endo isomer (64), and AgOAc catalysis favouring exo-addition.[318] Further examples of 1,3-dipolar cycloaddition of these Schiff bases to 4-methylene-2-phenyloxazolidin-5-one demonstrate effective stereocontrol of this route to highly functionalized prolines, now leading to all four stereoisomers of 4-benzamidoproline.[319] This process can be carried out with a tethered dipolarophile and an azomethine ylide.[320] Thermal [3 + 2]cycloaddition of glyoxylate imines $BzlON{=}CHCO_2R$ to protected alkylidenecyclopropanones gives 4,5-substituted prolines, though without offering any obvious generality to the route (Scheme 16).[321] Cycloaddition of [60]fullerene with a glycine Schiff base[322] and resolution through derivatization with a homochiral isocyanate[323] gives enantiopure fullerene-fused prolines; pipecolic acid derivatives (65) are obtained similarly using an azadiene.[324] Fullerene-amino acid reaction products have been reviewed.[325]



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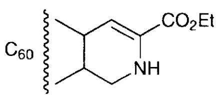

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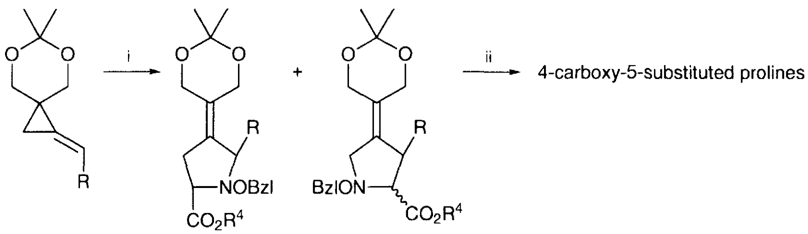


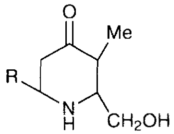
Reagents: i, $BzlON{=}CHCO_2R^4$, 100 °C, 4 h; ii, H_3O^+

Scheme 16

Highly-substituted prolines are the inevitable outcome of developing a carboxy substituent on a Boc-protected 2,5-imino-D-glucitol.[326] Polyhydroxylated prolines are accessible from previously-reported azidolactones.[327]

New α-trifluoromethylprolines and pipecolic acids have been prepared in various proportions from $CH_2{=}CHCH_2NR^1C(CF_3)[(CH_2)_2CH{=}CH_2]\text{-}CO_2Me$ through ruthenium-catalysed ring-closing metathesis.[328] Another cyclization route to prolines, C-H insertion by chiral ester diazoanilides $R^*O_2CC(N_2)\text{-}CON(Bzl)Ar$ [R^* = 2-(1-naphthyl)norbornyl] to give 4-substituted pyrrolidinones, has been illustrated in a synthesis of trans-4-cyclohexyl-L-proline.[329] 4-Alkylpipecolinates can be prepared from 1-acylpyridinium salts through phenyldimethylsilylmethylation, rearrangement, and subsequent oxidative desilylation.[330] Enantiopure 4-piperidinones (66), formed by cycloaddition of chiral 2-aminodienes with imines, have been developed into pipecolic acid derivatives.[331]

Enecarbamates (67) have been developed into β-hydroxy-prolines and -pipecolic acids through epoxidation and cyanohydrin stages.[332]



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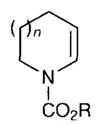

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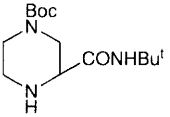
Imidazolidine-2-carboxylic acid has been prepared in orthogonally protected form from N-Boc-N′-Fmoc-ethylenediamine and glyoxylic acid as a new proline surrogate,[333] and the tetrahydropiperazinecarboxylic acid amide (68) has been prepared by a lengthy route involving asymmetric hydrogenation at the last stage.[334] (3S,5S)-5-Hydroxypiperazic acid, *i.e.* 5-hydroxy-hexahydropyridazine-3-carboxylic acid, has been prepared by the Evans procedure and



(68)

building on a D-mannitol moiety; this provides material more economically than the current route that calls for a resolution step.[335] Reviews cover piperazic acids[336] and use of the aza-Achmatowicz reaction for the preparation of amides of furan-2-carboxylic acid as starting materials for the synthesis of unusual amino acids.[337]

4.5 Models for Prebiotic Synthesis of Amino Acids – Conventional studies, in which gas mixtures subjected to high energy irradiation generate amino acids, show no signs of losing their fascination. A novel twist to this work is the search for technology for 'fixing' unwanted atmospheric carbon dioxide, and the formation of amino acids, nucleic acid bases, and organic acids through UV irradiation (shorter wavelength than 280 nm) of gaseous moist ammonium carbonate at 80 °C over a magnesium salt is noteworthy.[338] This reaction pathway presumably involves oxalic and oxamic acids. An extraordinary result, which is contradicted by all previous reports of the same experiment, claims that precursors of non-racemic alanine and aspartic acid (15% excess of the L-enantiomer) are formed by synchrotron irradiation of a N_2–CO_2–H_2O mixture.[339] An amorphous film deposited in a reaction vessel containing carbon monoxide and nitrogen held in high energy plasma[340] or irradiated with high energy particles[341] releases amino acids when exposed later to a cold moist atmosphere.

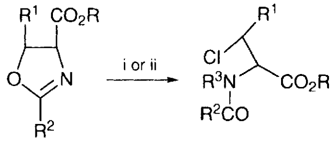
Most of these studies in the past have attempted to model the chemistry of the atmosphere of prebiotic Earth, but events at the surface of the geosphere are also of interest, such as the conversion of aqueous formaldehyde mixed with HCN and NH_3 into α-hydroxyacetonitrile and α-aminoacetonitrile.[342] At first sight the unfavourable equilibrium (99.9:0.1) that is generated is not suited to explain the prebiotic genesis of amino acids, but further processes available only to the latter product (conversion into α-amino acid amides; their reaction with CO_2 to give hydantoins) will shift the equilibrium so that conversion is eventually complete. Prebiotic production of N-carbamoylamino acids is easily envisaged, and so is their generation in space on ice particles under UV irradiation[343] and on carbon powder suspended in a hydrogen–nitrogen mixture (15:85) bombarded with high energy particles.[344] Another study of a role for aqueous formaldehyde that leads to glyoxal sees the generation of alanine and homoserine under mild conditions from ammonia in the presence of a thiol as catalyst.[345] Solid sodium acetate bombarded with high energy nitrogen ions accumulates organic cyanides and releases amino acids through hydrolysis.[346]

Hydrothermal vents on the ocean floor are the currently-favoured environment for prebiotic amino acid synthesis; a persistent objection, that amino acids generated there would be degraded at the high temperatures, has been addressed. The moderately reducing environment that this represents, means that the reaction energetics are as favourable on the sea floor at 100 °C as they are at 18 °C in the oxidizing conditions at the sea surface.[347]

Better focussing of experiments in support of these ideas would be achieved if reliable parameters for young Earth's surface composition could be established. Numerous contributions to a recent Conference have addressed this aspect.[348]

4.6 Synthesis of α-(ω-Halogenoalkyl)-α-Amino Acids – Fluorinated analogues of the common amino acids have been featured regularly in this Section over the years, and also elsewhere in this Chapter. ββ-Difluoro-L-methionine, -L-homocysteine, and -L-homoserine have been prepared starting from 5,6-O-isopropylidene-L-isoascorbic acid,[349] and hexafluoro-L-valine[350] and -leucine[351] have been obtained through a more traditional route (hexafluoroacetone and ethyl bromopyruvate for the latter case in seven steps, including enantioselective reduction of $(CF_3)_2CHCH_2COCO_2Et$).

Novel reagents for the conversion of oxazolines into β-chloro- or iodo-α-amino acids (Scheme 17) are described, giving new life to a well known route from β-hydroxy acids to halogeno-analogues.[352]

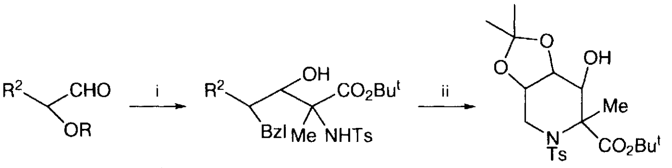


Reagents: i, ROCOCl; ii, NaI, EtCOCl → I in place of Cl

Scheme 17

4.7 Synthesis of α-(ω-Hydroxyalkyl)-α-Amino Acids – The family of β-hydroxy-α-amino acids includes several natural products, not only serine and threonine, and (2R,3R)-p-chloro-3-hydroxytyrosine is also one of the important members, since it is a vancomycin constituent. A synthesis with a conventional basis starts from the α-azido acid derivative $ArCOCH(N_3)CO_2Et$ and exploits the propensity of Baker's yeast to deliver the anti-β-hydroxy-α-azidoester with better than 90%.e.e.[353] Hydrogenation of β-trialkylsilyloxy- and -pivaloyloxy-α-acetamidoacrylates catalysed by a standard rhodium(I)–chiral diphosphine complex offers an alternative enantioselective strategy.[354]

Aldol condensation of an aldose with the anion of a protected glycine or other amino acid is an extension of the standard α-hydroxy-α-amino acid synthesis that facilitates access to polyhydroxylated homologues (Scheme 18).[355] A route from D-mannitol *via* 2-isoxazoline N-oxides also leads to these compounds, including α-alkyl homologues.[356]



Reagents: i, $TsNHCHMeCO_2Bu^t$, LDA, MX_n; ii, H_2–Pd, then DEAD, PPh_3

Scheme 18

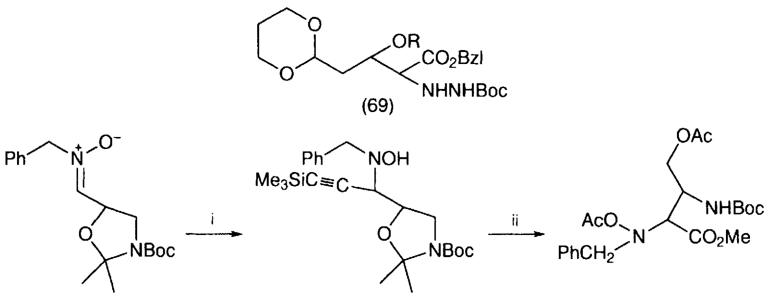
A route from an oxazoline-4-carboxylic ester to a β-hydroxy-α-amino acid (6 M hydrochloric acid at 80–100 °C),[357] reverses a standard heterocyclic synthesis but is a viable general synthesis method since oxazolines can be obtained in other ways, and are open to substitution and manipulation of functional groups.

(4R)-4-Hydroxy-(2S)-amino acids have become more easily available with the finding that kynureninase-catalysis is more generally applicable for transaldolization than the single case of kynurenine added to a simple aldehyde.[358]

4.8 Synthesis of N-Substituted α-Amino Acids – Coverage of routine N-substitution reactions of amino acids will be found in Section 6.2.2, and this section is concerned with reaction strategies by which a modified amino group is introduced into a nitrogen-free alkanoic acid synthon.

N-Boc-Hydrazino acids (69), precursors for (3S,4S)-4-hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylic acid,[359,360] and 2-(hydroxyimino)propanohydroxamic acid (HONHCHMeCONHOH), have been prepared by routine methods.[361] The last-mentioned compound is a more effective chelating agent than alanine towards copper(II) and nickel(II) ions.

Further examples (see also Refs. 442, 443) of the use of the N-hydroxyglycine cation equivalent (70, and its equivalent synthon, 82) in the synthesis of diastereoisomerically-pure N-hydroxyacids have been reported (Scheme 19).[362,363]

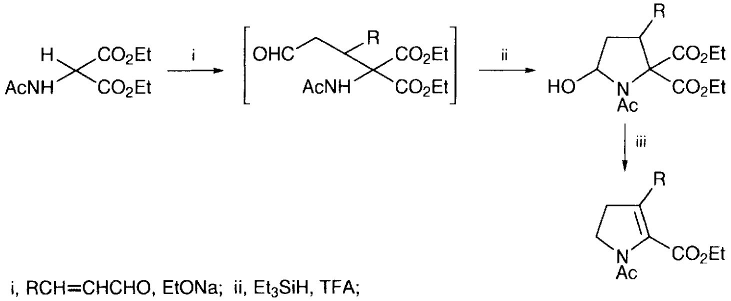


(70)

Reagents: i, $LiC{\equiv}CSiMe_3$; ii, $C{\equiv}C \rightarrow CHCO_2Me$

Scheme 19

4.9 Synthesis of α-Amino Acids Carrying Unsaturated Aliphatic Side-chains – New synthesis approaches to 'dehydroamino acids', *alias* α-aminoacrylic acid $H_2NC(=CH_2)CO_2H$ and homologues, are reported occasionally, also unusual outcomes of standard syntheses. Dehydration of N-protected β-hydroxy-α-amino acid esters using Boc_2O and DMAP gives N-protected N-Boc-dehydroalanines.[364] Oxidative decarboxylation of mono-ethyl acetamidomalonates [by lead(IV) acetate with copper(II) acetate; see Vol. 11, p. 25] has been used to prepare dehydroamino acids, with a specifically useful outcome in a preparation of a series of 3-substituted 2,3-dehydroprolines (Scheme 20).[365]



Reagents: i, RCH=CHCHO, EtONa; ii, Et_3SiH, TFA;
iii, aq. NaOH (1 equiv.), then $Pb(OAc)_4$–$Cu(OAc)_2$, py, DMF

Scheme 20

2-Substituted 4-alkylidene-oxazolin-5-ones created on a solid phase can be released by aminolysis giving libraries of N-acyl dehydroamino acid N′-alkylamides.[366] Reactions of glycinate anions and α-heteroatom-substituted glycinates $RNHCH(XR)CO_2R$ that lead to 'dehydroamino acids' are covered in Section 4.1.7.

Cycloaddition-dimerization of a glycine Schiff base (involving its azomethine ylide tautomer $R^1CH{=}NH^+CH^-CO_2R^2$) gives a 1-(alkoxycarbonylmethyl)imidazolinecarboxylic acid that fragments in basic media into α-dehydroamino acid (R^1 = alkenyl or aryl).[367]

Elimination brought about with threonine methyl ester using acetic anhydride–pyridine at reflux not surprisingly causes N-bis(acetylation), but perhaps unexpectedly leads to a single geometric isomer (Z)-$Ac_2NC(CO_2Me){=}CHMe$.[368]

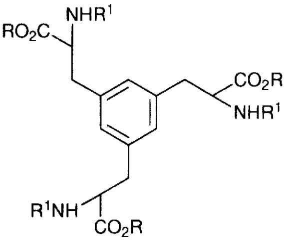
Description of a synthesis of L-vinylglycine using previously reported methods omitted four citations that should have been acknowledged.[369] Stereospecifically ^{2}H-labelled D-propargylglycine has been obtained from nucleophilic cleavage of N-Pmc-aziridinecarboxylic acid with propargyllithium.[370]

An α-(γδ-unsaturated aliphatic) side-chain is introduced into an N-protected amino acid by Claisen rearrangement of its enynol ester, induced by forming its lithium enolate.[371] Polyhydroxylated homologues have been prepared by the same strategy.[372]

4.10 Synthesis of α-Amino Acids with Aromatic or Heteroaromatic Groupings in Side-chains – The literature on this topic is split between synthesis starting from the familiar coded amino acids under this heading (this is dealt with in Section 6.3), and applications of the standard general amino acid synthesis strategies.

Some notable achievements do justice to the importance of synthesis targets under this heading, none outshining the total synthesis of vancomycin and eromomycin aglycones.[373] This has required the synthesis of some unusual α-amino acids as described in earlier Volumes of this Specialist Periodical Report, often by standard methods but applied within demanding structural constraints (for example, the enantioselective synthesis of the three atropisomeric amino acid fragments).[374]

Typical syntheses are illustrated with phenyltris(alanine)s [71; Horner-Wadsworth-Emmons olefination or Heck coupling to connect glycine units, followed by H_2–rhodium(I)/DUPHOS reduction of the resulting tris(dehydroamino acid)],[375] 4-tert-butylphenylalanine (Ref. 154), (R)- and (S)-3,5-dinitro-o-tyrosine by routine synthesis and enzymic resolution,[376] 3′-amino-L-tyrosine,[377] 4-(4′,4′-diphenylbutyl)glutamic acid,[378] naphthyl-substituted N-toluene-p-sulfonylphenylglycines,[379] amidrazonophenylalanine (N-substituted p-aminoamidinophenylalanine N′-methylcyclohexylamide)[380] and other o-, m-, and p-amidinophenylalanine amides showing potential as novel thrombin inhibitors,[381] α-methylphenylalanine 4′-phosphonic acid and the cyclic relative (72) as analogues of α-methyl-3-carboxyphenylalanine,[382] and p-boronophenylserine and o-carboranylmethyl-3-hydroxytyrosine, prepared from an isocyanoglycine synthon.[383] The binaphthyl (73) and its epimer[384] add new examples of axially chiral bis(α-amino acid)s (Vol. 30, p. 13). 4′-(Diphenylphosphonomethyl)- and 4′-diethylphosphonodifluoromethyl-phenylalanines and β-amino acid homologues have been prepared from 2-benzyl-1,3-propanediols carrying the phosphorus groupings, by lipase-catalysed hydrolysis of the di-acetate, and routine amination steps (DPPA or HN_3 and reduction).[385]



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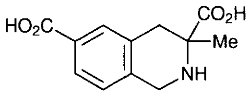
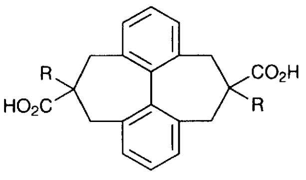


(72)

The interest in α-amino acids carrying heteroaromatic groupings as attachments to aliphatic side-chains lies either in their pharmacological potential, or in their use as monomers for the synthesis of peptide nucleic acids (PNAs). α-Amino acids carrying isoxazolyl side chains (74) have been prepared as analogues of AMPA, extending a series of publications that has appeared over several years.[386] α-Substituted-α-(β-triazolylmethyl)glycines have been prepared through cycloaddition of alkynes to 2-phenyl-4-azidomethyloxazoline,



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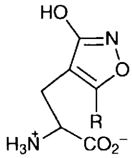
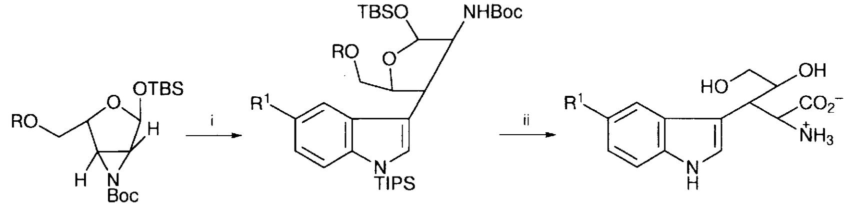


(74)

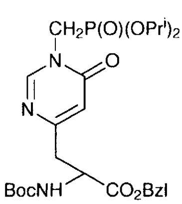
followed by ring opening and oxidation ($CH_2OH \rightarrow CO_2H$).[387] β-Tetrazolyl analogues have been prepared through addition of 5-aryltetrazoles to N-benzyloxycarbonyl dehydroalanine methyl ester.[388] Other analogues include ring-halogenated histidines starting from imidazoles,[389] β-hydroxy-β-(N′-toluene-p-sulfonylpyrrol-3-yl)alanine, *alias* 3-deaza-β-hydroxyhistidine, using a glycine anion synthon approach, or its Wittig equivalent.[390] Pictet-Spengler cyclization of these products with aldehydes gives pyrrolo[2,3-*c*]tetrahydropyridine-5-carboxylic acid esters which on aromatization with Pd-C give 6-azaindoles. β-Substituted tryptophans have been prepared through ring-opening of 2,3-aziridinotetrahydrofurans with indoles, and elaboration of the reaction products (Scheme 21).[391]



Reagents: i, see text; H_3O^+, then oxidation

Scheme 21

Six-membered heteroaromatic groupings have been introduced into amino acid side-chains using β-iodoalanine (75; by palladium-catalysed condensation with a pyridone triflate),[392] with 4,4′-dimethyl-2,2′-bipyridyl to prepare 2-amino-3-(4′-methyl-2,2′-bipyridin-4-yl)propanoic acid,[393] and similarly straightforward routes to (S)-2-Fmoc-amino-3-(oxin-2-yl)propanoic acid and (S)-2-Fmoc-amino-3-(oxin-5-yl)propanoic acid as fluorescent 8-hydroxyquinolines.[394] Greater spacing of the heteroaryl grouping from the glycine moiety is seen in butyrines carrying a nucleobase at the γ-position (76, and



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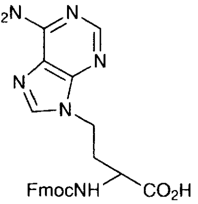
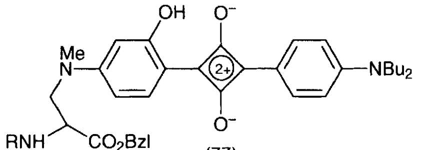


(76)

three analogues with the other nucleobases), for which improved syntheses are reported,[395] and in (S)-2-amino-6-(7′,8′-dimethylisoalloxazin-10′-yl)hexanoic acid and homologues, synthesized for study as riboflavin analogues.[396] The nucleobase-containing compounds are near relatives of monomers used to prepare PNAs,[397] and new examples of these based on proline carrying a nucleobase at its 4-position have been described.[398]

4.11 Synthesis of α-Amino Acids Carrying Amino Groups, and Related Nitrogen Functional Groups, in Aliphatic Side-chains – β-Aminoalkyl-α-amino acids have become permanent inhabitants of this section, and new syntheses include conversion of tert-butyl crotonates into 2,3-diaminobutanoates through Sharpless asymmetric aminohydroxylation,[399] aminolysis of cyclic sulfamidates and thiohydrolysis of the resulting α-aminosulfamic acids,[400] and Grignard addition to β-aminonitrones derived from L-serine, leading to (2R,3S)- and (2R,3R)-3-substituted αβ-diamino acids.[401] Approaches to novel diamino acid derivatives have led to the squarylium dye (77),[402] and to the L-arginine analogue $H_2NC(=NH)NH(CH_2)_3CH(NHR)B(OH)_2$.[403]



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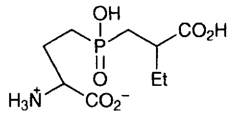

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4.12 Synthesis of α-Amino Acids Carrying Silicon Functional Groups in Aliphatic Side-chains – A synthesis of γ-silyl-α-amino acids involves a standard development of the aldehyde function of the Garner aldehyde (123) by silylcupration of its ethynyl analogue.[404]

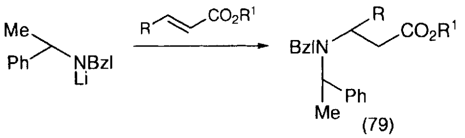
4.13 Synthesis of α-Amino Acids Carrying Phosphorus Functional Groups in Aliphatic Side-chains – Mention has been made, in other Sections, of reports of common amino acids functionalized with phosphorus oxyacid groupings, including analogues in which the carboxy group is replaced [*e.g.* $HO_2C(CH_2)_nCH(NHAc)P(O)(OPh)_2$ as analogues of aspartic and glutamic acids[405]]. The transition state analogue inhibitor (78) of *E. coli* α-glutamylcysteine synthetase is a particularly interesting example of newer thinking in this area.[406]

4.14 Synthesis of α-Amino Acids Carrying Sulfur-, Selenium-, or Tellurium-containing Aliphatic Side-chains – Protected ω-mercapto-α-amino acids have been obtained from ω-bromo-α-azido acids by displacement using a sulfur nucleophile, followed by tin(II) chloride reduction.[407] Derivatives conferring lipophilic properties on S-adenosyl-L-methionine have been prepared.[408]

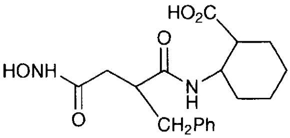
Sulfinamide and sulfone analogues of (78) were included in the synthesis study referred to in the preceding Section (Ref. 406).

4.15 Synthesis of β-Amino Acids and Higher Homologous Amino Acids – Reviews under this heading include α-hydroxy-β-amino acids.[409]

Asymmetric amination of achiral αβ-unsaturated esters by lithium (S)- or (R)-N-benzyl-N-α-methylbenzylamide continues to serve well for the synthesis of N,N-disubstituted β-amino acid esters (79),[410] including D-β-phenylalanine tert-butyl ester (a constituent of moiramide B and andrimid).[411] Chiral lithium


(79)

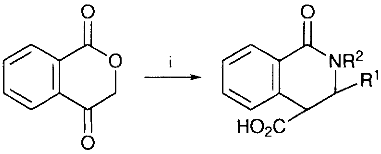
amide bases that are useful in this context have been reviewed,[412] the choice of base for the synthesis of both stereoisomers of β-homothreonine,[413] and other anti-α-alkyl-β-amino acids, by this strategy being (R)-N-(1-phenylethyl)-N-(trimethylsilyl)amine or a homochiral amidocuprate.[414] N-(α-Methylbenzyl)-N-3,4-dimethoxybenzylamine used in this protocol offers the opportunity for selective deprotection.[415] A nine-step route based on this amination approach, to a 2-aminocyclohexanecarboxylic acid derivative, the kelatorphan-like enkephalinase inhibitor (80), starts with tert-butyl cyclohex-1-ene-1-carboxylate,[416] and the same approach provides an essential intermediate in a synthesis of tussilagine and isotussilagine.[417] Another method for asymmetric amination of achiral αβ-unsaturated esters is illustrated with formula 9, Ref. 53.


(80)

αβ-Unsaturated pyrazolamides RCH=CHCONR^{1}R^2 (R^{1}R^2=3,5-dimethylpyrazolyl residue) add O-benzylhydroxylamine with high enantioselectivity when a chiral Lewis acid catalyst is used, prepared from MgBr$_2$.Et$_2$O and a chiral bis(oxazolyl)cyclopropane.[418]

Conventional amination of lipase-resolved syn-2,3-dihydroxy-3-phenylpropanoic acid enantiomers by conventional bromination–azidation and epoxyacid pathways gives (2R,3S)-phenylisoserine.[419] 1,2-Dihydroxyindane-2-carboxylic acid esters can be selectively benzylated and substituted by azide, and processed to give the β-aminoindanecarboxylic acid, designed as a conformationally constrained phenylisoserine.[420] Amination *via* azides leading to β-amino acids is also illustrated in Ref. 385.

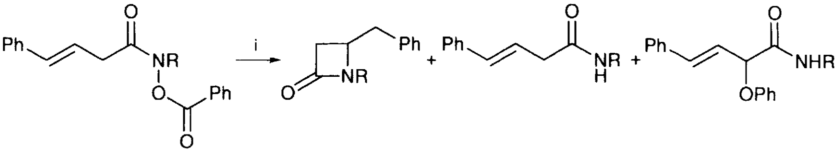
Lewis acid-promoted addition of chiral imines to enol ethers CH$_2$=C(OEt)-OSiMe$_2$Bu^t to generate an additional chiral centre leads to (R,R)-β-amino acid esters, although the corresponding process with 1,3-oxazolidines derived from (R)-phenylglycinol yields (R,S)-products.[421] A solid phase version of this process, but with achiral tethered imines, has been explored.[422] Homochiral oxazolidinones used in this way with αβ-unsaturated esters for enantioselective β-amino acid synthesis are, in effect, recyclable chiral reagents.[423] Homochiral N-sulfinylimines (S)-RS(=O)N=CHPh add to the lithium dienolate of methyl propen-3-oate to give (E)-α-ethylidene-α-amino acid esters *via* a cis/trans mixture of the α-vinyl isomer.[424] Catalysis by ZnCl$_2$, ZnBr$_2$, or ScF$_3$ leads to this outcome, although catalysis is not necessary but absence of catalyst results in the formation of the β-(N-arylsulfinylamino)-α-ethylidenealkanoic acid ester. o-(Nitrophenyl)imines and the lithium enolate of methyl isobutyrate combine to give a β-aryl-αα-dimethyl-β-alanine that is a potentially UV-cleavable resin linker for solid-phase synthesis.[425] Preparations of β-aminoaldehydes *via* β-(toluene-p-sulfinylamino)alkanoate esters prepared in this way, and chain extension to δ-amino acid derivatives, emphasise the usefulness of imines in β-amino acid synthesis.[426] The equivalent Mannich-type process, in which an aldehyde, an amine, and the silyl enol ether are combined under indium trichloride catalysis, proceeds in moderate to good yields and leads to β-aminoketones with simple enol ethers.[427] A mixture of aldehyde, amine and homophthalic anhydride with a Lewis acid catalyst gives a trans-isoquinolonic acid (Scheme 22).[428] C-Acylation of imines with N,N′-carbonyldi-imidazole gives β-enamino acid derivatives [$R^2C(=NR^1)CH_3 \rightarrow R^2C(NHR^1)=CH\text{-}COIm$].[429] Imines are reactants for standard β-lactam syntheses; their preparation in immobilized form and conversion into β-lactams is only the start of the problem with solid-phase synthesis but removal of the product from the polymer under acidic and basic conditions has been successful.[430] In what has been described as a new three-component condensation, β-(N-acylamino)-aldehydes $R^1CONHCH(CH_2R^2)CHR^2CHO$ are formed from a primary amide, two equivalents of an aldehyde, and a strong acid catalyst (CF_3SO_3H);[431] this seems to be anything but new, since it is described by the imine alkylation process illustrated in the preceding examples.



Reagents: i, R^1CHO/R^2NH_2, MeCN, Na_2SO_4, $BF_3{\cdot}Et_2O$

Scheme 22

A radical cyclization pathway (Scheme 23) transforms O-benzoylhydroxamic acids into β-lactams,[432] but the other reaction products formed 75% of the total so there is room for improvement. The 'β-lactam synthon method' for β-amino acid synthesis has been illustrated by highly stereoselective alkylation of 3-trialkylsilyloxy-β-lactams that leads to α-methylisoserines.[433]

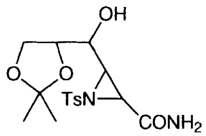


Reagents: i, Bu_3SnH, AIBN

Scheme 23

Attack of N-(benzyloxycarbonylaminomethyl)benzotriazole, an electrophilic aminomethyl synthon, on enolates of chiral 3-acyl-1,3-oxazolidin-2-ones gives 3-aminopropanoic acid derivatives; an alternative approach is to apply the Curtius rearrangement to the same substrate.[434] Dimethylformamide diethyl acetal condenses with α-heteroarylacetic acid esters under microwave irradiation, to give N,N-dimethyl eneamine esters that are readily converted into αβ-unsaturated β-amino acid esters by reaction with a primary amine.[435]

Alternative asymmetric amination approaches to β-amino acids include aminohydroxylation, *e.g.* of (E)-vinylphosphonates $RCH=CHPO_3Et_2$, offering α-hydroxy-β-amino phosphonic acids in moderate e.e.,[436] and a synthesis of (3R)-amino-(2S)-hydroxyheptanoic acid.[437] N-Toluene-p-sulfonyl-aziridine has been identified as an intermediate in a route from N,N-dimethylcinnamide to phenylisoserine using this methodology,[438] and aziridinecarboxylic acid derivatives (81) have been used as starting points in routes to 3-amino-2,3-dideoxyhexonic acids.[439] Palladium(0)-catalysed cyclization of (S)-$PhCH(NHBz)CH=CHCH_2OAc$ (from L-phenylglycinal) gives (4S,5R)-2,4-diphenyloxazoline-5-carboxylic acid, a precursor for the stereoisomer of phenylisoserine component of taxol.[440]



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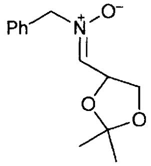

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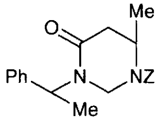


(83)

Diastereoselective addition of allylmagnesium bromide to an O-(1-phenylbutyl)aldoxime is a promising method for preparation of a range of protected β-amino acids.[441] The equivalent process with the homochiral nitrone (82) leads to (2S,3R)- and (2S,3S)-3-phenylisoserine after appropriate functional group development, the choice of Lewis acid in the initial addition step determining the stereochemical outcome.[442] Addition of the same nitrone to excess O-methyl-O-tert-butyldimethylsilyl ketene acetal provides entry to the βγ-diamino acid series.[443] Enantioselective and diastereoselective synthesis of syn-β-amino-α-hydroxy acids occurs through addition of toluene-p-sulfonyl isocyanide to chiral α-hydroxy-βγ-unsaturated esters.[444] More conventional amination strategies include: reaction of 3-perfluoroalkyl-3-fluoroprop-2-enoate esters by amines or sodium azide followed by hydrogenation to give fluorine-substituted β-alanines;[445] four-step conversion of β-hydroxy acids with retention of configuration at an α-chiral centre, and inversion at a β-centre;[446] biomimetic transamination (ethyl 2-methyl-3-keto-4,4,4-trifluorobutanoate → 2-methyl-3-amino-4,4,4-trifluorobutanoate).[447] Independent accounts have appeared detailing the use of ammonium acetate–malonic acid as reagent for the conversion of tertiary aldehydes into β-alkyl-β-amino acids [$R^1R^2R^3CHO \rightarrow R^1C(R^2R^3)CH_2CO_2H$],[448] and of benzaldehyde into 3-benzoylamino-3-phenylpropanoic acid [used in a preparation of (2R,3S)-

phenylisoserine involving enzymatic resolution and α-iodination (with LiHDMS and I_2) as key steps].[449]

Carboxylation of amines is relatively easy for the preparation of β- and higher homologous amino acids, through cyanohydrin formation of homochiral α-aminoalkanals [(S)-NN-dibenzylphenylalaninal gives (2S,3S)-3-amino-2-hydroxy-4-phenylbutanoic acid;[450] KCN–acyl halide gives α-acyloxy-β-amino acids[451]]. N-Boc-Phenylglycinal adds diethyl phosphite in a moderately diastereoselective fashion to give diethyl 2-N-(Boc-amino)-1-hydroxy-2-phenylethyl phosphonate, a practical benefit being the ease of separation of syn- and anti-isomers by fractional crystallization.[452] α-Trialkylsilyl-β-amino acids are unusually easily desilylated in aqueous media, attributed to anchimeric assistance by amino and carbonyl functions.[453]

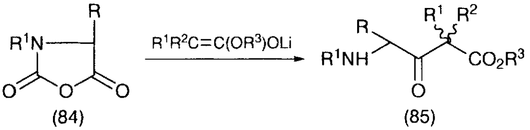
Ethyl cyanoacetate is a ready-made source of αα-disubstituted β-amino acids, bis-alkylation by 2,2′-bis(bromomethyl)-1,1′-biphenyl followed by $NaBH_4$–$CoCl_2$ selective reduction of the cyano group leading to αα-disubstituted β-amino acids possessing axial chirality.[454] Allylindium reagents give enamines $RO_2CCR{=}C(NH_2)CH_2CH{=}CH_2$.[455] α-Aminonitriles are also suitably- activated in this context, reaction with Reformatzky reagents giving β-amino esters, β-lactams, tertiary amines and cinnamic acid derivatives in an apparently wayward process that can be controlled to give the β-amino esters exclusively.[456] α-Aminoalkylbenzotriazoles, prepared from an aldehyde, an amine and benzotriazole, react with Reformatzky reagents derived from ethyl bromofluoroacetates to give α-fluoro-β-amino acid esters.[457] Acylation of tolyl cyanide $PhCH_2CN$ by the chloroformate of Oppolzer's (S)-sultam and routine ensuing steps leads to (S)-$BocNHCH_2CHPhCO_2H$.[458] Another illustration of the use of the tetrahydropyrimidinone chiral synthon (83), prepared from 3-aminobutanoic acid, has been presented; its 5-halogeno-derivative has been used in preparations of enantiomerically pure threonine and allothreonine.[459]

Standard practice is also represented in Arndt-Eistert homologation of N-protected α-amino acids.[460] More than 20 repetitive papers have appeared on this topic in the last four years, including three more. One of the current papers[461] compares the Arndt-Eistert strategy with Evans amination; another[462] deals with the ultrasound-mediated Wolff rearrangement approach. Instead of Wolff rearrangement, an α-amino acid diazoketone can be treated with N,O-dimethylhydroxylamine to give a β-amino acid dimethylhydroxamate.[463] Lossen rearrangement of alkyl succinimidyl carbonates in basic buffers leads to the corresponding β-alanines.[464] Rearrangement of alkoxycarbonylmethyl iminoethers $ArN{=}CR^FOCH_2CO_2R$ gives β-perfluoroalkyl isoserines, through a promising new general method.[465]

Sequential Birch reduction, 3-alkylation, and catalytic hydrogenation of pyrrole-3-carboxylic acid derivatives give β-substituted β-prolines.[466]

The term 'the γ-amino acids' first brings to mind GABA (γ-aminobutyric acid) and statine as standing at the head of the list, and while the former does not normally stimulate any particular synthesis interest, the latter certainly does. Reductive alkylation of (S)-O-tert-butyldimethylsilyl malimide has been established as the key step in a new synthesis of (3S,4R)-statine,[467] and other non-general routes are available for syntheses of *cis*- and *trans*-(3-substituted vinyl)-γ-aminobutyric acids [by Claisen rearrangement of phthalimides $PhtCH_2CHCR^3CHOHR^2$, or by Wittig synthesis starting from 3-formyl-4-phthalimidobutanoic acid],[468] and a synthesis of a GABA analogue [the photogenerated Barton ester radical from N-Fmoc-α-aminoisobutyric acid, trapped by methyl acrylate, gives $FmocNHCMe_2CH_2CH(SPy)CO_2Me$].[469] Allylic acetates $Ph_2C{=}CHCH(OAc)R$ subjected to palladium-catalysed substitution by methyl cyanoacetate, followed by functional group development, offer an entry to α-substituted GABAs.[470] The useful (−)-isomer of carnitine can be obtained from its (+)-isomer (ca 64% at equilibrium) through the use of d- or l-carnitine dehydrogenases from *Agrobacterium* sp.525a.[471] A short synthesis of another γ-amino acid with physiological activity, R-(−)-baclofen, starts with p-(2-aminoethyl)chlorobenzene, N-malonylation and conversion into the α-diazoester preceding enantioselective ring closure by C-H insertion through the influence of dirhodium(II) tetrakis[(S)-N-phthaloyl tert-leucinate].[472] (S)-Vigabatrin $H_3N^+CH(CH{=}CH_2)(CH_2)_2CO_2^-$ has been synthesized from butane-1,4-diol, the laborious nature of the route following determination by the authors to use the Sharpless aminohydroxylation.[473] (S,S)-4-Amino-3-hydroxy-5-phenylpentanoic acid has been prepared from 4-benzyl-5-vinyloxazoline, formed from the oxazolidin-2-one derived from L-phenylalanine.[474] γ-Amino α-keto-esters $ZNHCHRCH_2COCO_2R'$, prepared from L-α-amino acids *via* β-amino acids, lead to 4-amino-2-hydroxyacids through standard steps including lipase and oxidoreductase resolution to generate the required stereochemistry at C-2.[475]

L-α-Amino acids serve as starting materials for homochiral γ-aminoalkynoic acid esters from aldehydes, through a Corey-Fuchs route -CHO → $-CH{=}CBr_2$ → $-C{\equiv}CCO_2Me$.[476] Urethane-protected N-carboxyanhydrides (UNCAs; see also Ref. 761) give α-alkyl-γ-amino-β-ketoesters through condensation with lithium enolates (84 → 85),[477] and give β-amino α-ketoesters with cyanomethyltriphenylphosphonium chloride.[478] Lactacystin is composed of a cysteine and γ-lactam fragment, and an analogue of the latter has been prepared from a lithium enolate $Me_2C{=}C(OMe)OLi$ and the protected amino aldehyde (86; see Ref. 246),[479] or through a route starting from condensation



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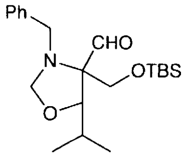
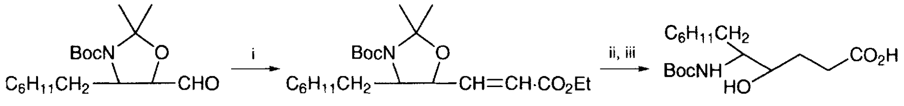


(86)

of DL-dimethyl isopropenylmethylmalonate with methyl N-4-methoxybenzylglycinate.[480] Other classical organic synthesis procedures are seen in Beckmann ring expansion of dichloroketene – chiral enol ether cycloadducts, to give the lactone of (3S,4S)-4-amino-3-hydroxy-5-phenylpentanoic acid,[481] and ring expansion of β-lactams to γ-lactams with trimethylsilyldiazomethane anion and photolytic Wolff rearrangement.[482]

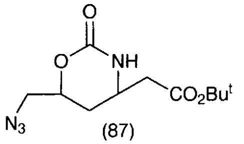
γ-Amino acids are prototypical dipeptide mimetics, and replacement of the amide bond of a dipeptide by various isosteres is covered elsewhere in this Specialist Periodical Report. αβ-Unsaturated δ-amino acids $PhNHCHArCH_2CR{=}CHCO_2H$, prepared from an imine and a 1,1-di(trimethylsilyloxy)-buta-1,3-diene,[483] are one step removed from being described as a dipeptide mimetic, and so are the compounds resulting from a novel 1,6-amino addition reaction to naphthalene followed by electrophilic alkylation.[484] (3R,4S)-3-Tri-isopropylsiloxy-N-Boc-β-lactams start pathways to 4-hydroxy-, 3,4-dihydroxy-, and 3-amino-4-hydroxy-5-amino acids,[485] also obtained from oxazolidine-5-carbaldehydes (Scheme 24).[486] Homochiral vinylogous N-MTS-aziridinecarboxylic acids carrying amino acid side-chains undergo ring-opening with TFA to give substituted 5-aminopent-3-enoic acids closely mimicking dipeptides in both structure and stereochemistry.[487] Conformational constraint is introduced by incorporating part of the carbon chain of a δ-amino acid into a cycloalkane grouping, as in piperidine-4-acetic acids[488] and 3-aminomethyl-5-substituted cyclohexanecarboxylic acids.[489] N-Fmoc-2-carboxybenzylamine justifies mention here (since anthranilic acids and related aromatic amino acids are not covered in this Chapter) but only on the basis that it has been proposed as a β-turn-inducing residue for peptide synthesis.[490]



Reagents: i, Ph_3PCHCO_2Et; ii, H_2–Pd/C, then *p*-TsOH, EtOH; iii, *p*-TsOH, thf

Scheme 24

Greater separation of amino and carboxy functions is becoming easier to arrange, with ring-closing metathesis reactions of amides $CH_2{=}CH(CH_2)_nCONH(CH_2)_mCH{=}CH_2$ becoming well established (14-membered lactams;[491] lactams of βγ-unsaturated δ-amino acids, from the allylamine prepared from L-phenylalaninal;[492] see also Refs. 907-915, Section 6.3). Other methods are used for 6-aminoalkanoic acids and derivatives, *e.g.* the negamycin synthesis intermediate (87) prepared using the L-malic acid-derived synthon (88),[493] the 8-aminononanoic acid, and 9-, and 10-amino homologues that are components of polyazamacrolides in the defence secretion of the ladybird beetle *Epilachna borealis*,[494] the 6-amino-4,6-deoxyheptopyranuronic acid constituent of amipurimycin,[495] 5-aminomethyltetrahydrofuran-1-carboxylic acids (89; given the name C-glycosyl sugar amino acid derivatives) that open up the synthesis of peptide analogues with a pseudopolysaccharide backbone.[496]



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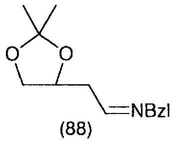

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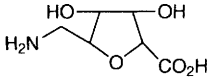

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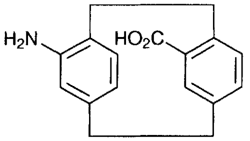

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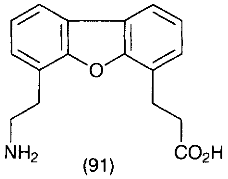
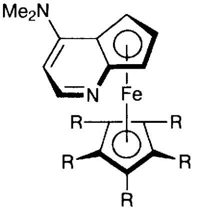


(91)

Compounds with amino and carboxy groups separated over an aromatic ring system, *e.g.* the homochiral [2.2]paracyclophane (90)[497] and the proposed protein β-turn moiety (91),[498] have been prepared.

4.16 Resolution of DL-Amino Acids – The following subsections segregate the topics dealt with in this Section, as in previous Volumes. Care has been taken to cross-reference where papers described elsewhere in this Chapter include resolution as an aspect of synthetic work.

4.16.1 Diastereoisomeric Derivatization and Diastereoisomeric Salt Formation – Classical procedures are represented by DL-leucine–S-(-)-1-phenylethanesulfonic acid mixtures crystallized from MeCN–MeOH (to give the less-soluble L-amino acid salt) or from MeCN–water (to give the less-soluble D-amino acid salt monohydrate);[499] by ethyl DL-methioninate–N-acetyl-D-methionine (less-soluble D,D-salt);[500] by binaphthyl-based 1-aminocycloheptane-1-carboxylic acids showing axial chirality, resolved using L-phenylalanine cyclohexylamide;[501] and by 2-(aminomethyl)cyclopropane-1-carboxylic acids resolved as (R)-pantolactone derivatives.[502] In reverse, the resolution of a DL-alkylamine using N-acetyl-L-leucine may be noted.[503] Kinetic resolution procedures have been employed: methyl DL-4-chlorophenylalaninate–(2S,3S)-tartaric acid–salicylaldehyde from which the derivatized D-amino acid ester crystallizes;[504] the planar-chiral DMAP (92) induces equilibration of 2,4-disubstituted oxazolin-5(4H)-ones with modest e.e.;[505] novel chiral cation exchange resins accomplish the kinetic resolution of cyclic amino acid derivatives.[506] A review covers resolution of amino acids based on asymmetric transformation.[507]



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4.16.2 Enzyme-catalysed Enantioselective Reactions of Amino Acid Derivatives

The propensity of familiar enzymes for handling reactions of non-protein amino acids almost as well as they deal with their normal substrates has enhanced the practical value of this 'resolution' strategy.

Penicillin G acylase-catalysed acylation of the L-enantiomer in DL-phenylglycine is exploited for production of D-phenylglycine,[508] and *Aspergillus* acylase has been applied analogously to the resolution of 7-azatryptophan[509] (see also Refs. 37, 38). An acylase-derivatized medium for use in a centrifugal partition chromatographic mode has been illustrated with N-acetyl-DL-amino acids.[510]

Porcine kidney acylase accepts N-acetyl 4′-substituted (RS)-phenylalanines as substrates.[511] *Candida antarctica* B lipase catalyses the amidation by ammonia of methyl DL-phenylglycinate (47% conversion) giving D-phenylglycinamide in 78% e.e. when the strategy of *in situ* racemization by pyridoxal is employed to maximize the conversion.[512] Substituted DL-hydantoins are accepted as substrates by papain, hydrolysis leading to L-α-amino acids *via* N-carbamoyl derivatives.[513] The more usual protocol with these compounds is demonstrated by conversion by *Agrobacterium tumefaciens* of a DL-p-hydroxyphenylhydantoin into D-p-hydroxyphenylglycine; this involves the cooperation of a racemase, a D-hydantoinase, and an unusual D-selective N-carbamoylamino acid amidohydrolase.[514] In a distantly-related kinetic resolution procedure leading to N-benzyloxycarbonyl-D- and L-serines, acetylation–equilibration of DL-3-(hydroxymethyl)-1,4-benzodiazepin-2-ones has been mediated by immobilized *Mucor miehei* lipase (see Vol. 30, p. 42).[515] A more conventional procedure is represented by the immobilized chymotrypsin–methyl DL-phenylalaninate system.[516]

4.16.3 Chromatographic Resolution, and Applications of Other Physical Methods for Resolution of DL-*Amino Acid Derivatives* – Newer variations of standard practice are represented by resolution of DL-tryptophan by passage through a porous hollow-fibre membrane in which immobilization of bovine serum albumin has been accomplished using glutaraldehyde,[517] similar results with DL-phenylalanine,[518] and resolution of N-Boc- and -Z-DL-amino acids over a chiral stationary phase (CSP), *viz.* Chiralpak AS.[519] A chiral crown ether stationary phase has been used with modest results for the resolution of cyclic β-amino acids.[520] CSPs have been reviewed.[521]

The binding mechanism for a CSP carrying N-(3,5-dinitrophenyl)-R-phenylglycine[522] and for another standard CSP [(N-3,5-dinitrobenzoyl)-L-leucine as chiral discriminator][523] involves hydrogen bonding and π-stacking interactions; typical applications of CSPs of this type involves resolution of N-(3,5-dimethoxybenzoyl)-DL-amino acid NN-diethylamides over a new CSP derived from (S)-N-(3,5-dinitrobenzoyl)-L-leucine N-phenyl-N-alkylamide [alkyl = $(CH_2)_3Si(OEt)_3$].[524] Reversing the structural features of stationary phase and substrate, resolution of N-(3,5-dinitrobenzoyl-DL-amino acid amides over silica gel derivatized with (R)-4-hydroxyphenylglycine has been demonstrated.[525] Aminopropylsilica derivatized with N-(3,5-dichloro-s-triazinyl)-L-proline tert-butyl ester serves to resolve DL-amino acids as copper(II) complexes on the ligand-exchange chromatography principle.[526] A novel extension of this to ligand-exchange adsorbents imprinted with a polymerizable copper(II) complex of the L-enantiomer of the amino acid to be resolved has been described in an *ACS Symposium Volume* devoted to the topical polymer-imprinting technology.[527] A review of molecule-imprinted polymers for use in analysis has appeared,[528] recent developments including efficient resolution of methyl DL-tryptophanate,[529] and DL-phenylalanine anilides.[530] The principle extends to molecule-imprinted membranes, polymers grafted with the tetrapeptide H-Asp(O-cyclohexyl)-Val-Asn-Glu(O-Bzl)-CH_2-,[531] or with H-Glu(O-Bzl)-Glu-Lys(4-Cl-Z)-Leu-CH_2- (imprinted with N^{α}-acetyl-L-tryptophan or its N-Boc analogue),[532] which preferentially retain the print isomer and therefore allow the opposite enantiomer to migrate faster. A poly(pyrrole)–poly(vinyl alcohol) colloidal dispersion imprinted with Z-L-aspartic acid preferentially incorporates the D-enantiomer from DL-glutamic acid.[533]

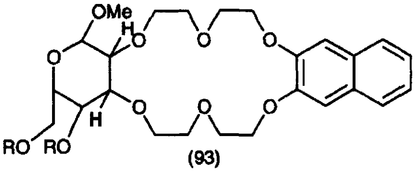
Enantioselective permeation of amino acid perchlorates through a solid membrane formed by grafting (1→6)-2,5-anhydro-3,4-di-O-methyl-D-glucitol on to poly(acrylonitrile) uniformly favours faster permeation by the D-enantiomer, relative rate differences being highest for phenylglycine, lowest for tryptophan. The separation mechanism seems to involve molecular size as a major factor, but best results are not impressive (up to 75% e.e. achieved for phenylglycine).[534]

DL-Kynurenine has been resolved by high speed countercurrent chromatography;[535] other liquid–liquid media capable of resolution of amino acids include chiral liquid membranes.[536]

4.16.4 Host – Guest Resolution – This topic is also covered in Section 7.5, but papers are located here if exploitation of the phenomenon in terms of resolution is involved.

Pronounced enantioselection towards DL-amino acids, in their zwitterionic forms or as K or Na salts, is seen when chiral naphtho-18-crown-6-ethers (93) and aza-analogues derived from α-methyl D-mannopyranoside are contained within a supported liquid membrane separating aqueous media.[537] Protonated heptakis(6-amino-6-deoxy)-β-cyclodextrin binds the anionic form of L-enantiomer of N-acetyl-L-tryptophan, -phenylalanine, -leucine, or -valine more strongly than the D-enantiomer,[538] and permethylated cyclofructans similarly discriminate enantiomers of DL-amino acid ester hydrochlorides.[539]

4.16.5 Prebiotic Resolution of DL-Amino Acids – Mechanisms accounting for the presumed predominance of the L-amino acids, destined to be built into proteins at the start of life processes on this planet (and perhaps elsewhere), have largely featured enantioselective destruction, *e.g.* by asymmetric photolysis,[540] or by differential interaction of elementary particles with individual enantiomers.[541] A new idea, that a net natural chiral right-handed helical force field produced by the Earth's orbital chirality could make 'right-handed enantiomers' more stable than their 'left-handed' forms, is asserted to have



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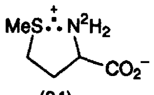

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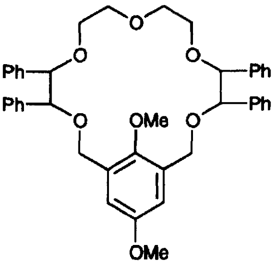

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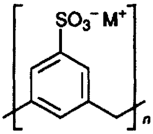

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experimental support (though apparently based on a cyclic argument).[542] Parity-violating energy differences between L- and D-enantiomers of a chiral molecule continue to be claimed to underly the favoured survival of L-amino acids, stabilized by the weak nuclear force.[543]

Selection by RNA of the L-enantiomer from a DL-amino acid, when undergoing aminoacylation *in vitro*, requires the system to be constrained on a surface that mimics a prebiotic monolayer;[544] stereochemical parameters for aminoacylation of RNA have been reviewed.[545]

5 Physico-chemical Studies of Amino Acids

5.1 X-Ray Crystal Analysis of Amino Acids and their Derivatives – Amino acids and their derivatives are covered, in that order, in this Section; a review has appeared of supramolecular networks in amino acid crystals and co-crystals.[546] The continual re-examination of the common amino acids usually accompanies advances in instrumentation or technique, and the ‘accelerated’ X-ray crystal analysis of DL-proline monohydrate is a significant example,[547] as is DL-aspartic acid at 20 K.[548] More routine work concerns D-phenylglycine hydrochloride,[549] oxalic acid salts of DL- and of L-arginine,[550] maleic acid salts of DL- and of L-arginine,[551] the (1:1)-salt of L-histidine with 4,5-imidazoledicarboxylic acid, and the corresponding L-lysine salt,[552] the (1:1)-salt of L-serine with squaric acid[553] and bis(L-asparaginium) hydrogen squarate monohydrate,[554] ibotenic acid,[555] and L-carnitine L-tartrate.[556] The electron charge density distribution in X-ray crystal structure of DL-proline hydrate and DL-aspartic acid hydrate has been used to support a discussion of quantum topological theory.[557]

Derivatives assessed by X-ray crystal analysis are mostly chosen so as to be of interest in a biological or a laboratory synthesis context: O-phospho-L-tyrosine,[558] N-(3,5-di-tert-butyl-4-oxo-1-phenyl-2,5-cyclohexadien-1-yl)-L-isoleucine methyl ester,[559] HOBt, HOAt, and HOOBr esters of N-protected L-amino acids,[560] N-Boc-N-benzylglycine,[561] and N-acetyl-L-prolinamide.[562] The objective of the last-mentioned study (as in several other cases; Section 5.7) was comparison of data with conformational information obtained through molecular-orbital calculations. Alkylamines can be chosen to prepare salts of N,N'-oxalylbis(phenylglycine)s that will crystallize either as monolayers or as bilayers.[563]

5.2 Nuclear Magnetic Resonance Spectrometry – Instrumental advances continue to give new leases of life to ^{1}H-NMR spectrometry, with a 2D-study of L-glutamine to reveal cross-relaxation between non-equivalent protons of the side-chain NH_2 group,[564] chemical shift and coupling constant data for L-glutamic acid and L-glutamine in ^2H_2O at p^{2}H 6.6,[565] CRAMPS data for amino acid crystals to give an accurate measure of the effect of surrounding magnetic variations on ^{1}H chemical shifts,[566] data for polycrystalline aromatic amino acids revealing ^{1}H magnetic relaxation and molecular motion at 270–450 K.[567] Data for tert-butyl N-acetyl-L-prolinate and fulleroproline[568] and for N-acetyl-L-proline N'-methylamide and the corresponding 4-hydroxyproline and 3,3-dimethylproline analogues[569] are aimed at better understanding of the factors that determine the position of the *cis–trans* equilibrium for the amide bond. The influence of solvent on the position of the tautomeric equilibrium for N,N-dimethylglycine has been assessed.[570] Detailed NMR analysis of β-alanine and piperidine-3-carboxylic acid (nipecotic acid) has been published.[571]

Remarkable instrumental sensitivity has been developed for the estimation of N-acetylaspartic acid in excised[572] and *in situ* brain tissue.[573] The problem of peak overlap that undermines *in vivo* analysis of taurine by ^{1}H NMR can be solved by double quantum filtration.[574]

Commercial samples of glycine can contain both α- and γ-glycine polymorphs, which can be detected through their differing ^{13}C NMR shielding parameters and dynamic properties.[575] Other non-routine NMR studies involving heavier nuclei include ^{31}P NMR estimation of pH-dependent interactions of O-phosphoserine and -tyrosine with aluminium(III) ions.[576]

A 2-centre 3-electron-bonded radical cation (94) has been identified by NMR-CIDNP as the intermediate in the photo-oxidation of methionine in ^2H_2O–4-carboxybenzophenone.[577]

^{1}H-NMR assignment of absolute configuration to amines derivatized with 1-fluoro-2,4-dinitrophenyl-5-(R)-phenylethylamine relies on chemical shift values (see also Ref. 1157).[578]

5.3 Optical Rotatory Dispersion and Circular Dichroism – Spectra of L-methionine reveal low-lying transitions at ca 262 and 285 nm; this new result from a CD and MCD study has been explained in terms of singlet–triplet transitions from the highest filled orbital of a sulfur lone pair.[579]

5.4 Mass Spectrometry – Useful spectra are obtained for underivatized amino acids by CIMS with acetone as reagent, showing $[M+H]^+$, $[M+43]^+$ and $[M+59]^+$ ions,[580] and with dimethyl ether as reagent, showing abundant $[M+13]^+$ and $[M+45]^+$ ions, with $[M+91]^+$ ions being most abundant for serine and threonine.[581] Electrospray mass spectra of threonine or its methyl ester proceed *via* the $[M+H-H_2O]^+$ ion, which is now shown to be a protonated aziridine (protonated hydroxy group, not protonated amino group) rather than dehydrobutyrine as previously supposed.[582] Measurement of ionization energy for 19 L-α-amino acids[583] and collection of data on gas-phase basicities/proton affinities for a broad range of amino acids[584] illustrate routine mass spectrometry studies.

Notable results are being obtained through mass spectrometry of host–guest complexes. β-Cyclodextrin–amino acid complexes give informative spectra,[585] and the fact that the exchange reaction of these complexes that occurs with protonated alkylamines shows different rates for D-amino acid complexes compared with their L-amino acid analogues is a fine demonstration of the information available through modern mass spectrometry.[586] Mass spectra of amino acid complexes formed between the crown ether (95) and L- and D-amino acids[587] and complexes formed with ^{2}H-labelled hosts offer access to useful analytical information, *e.g.* the determination of e.e. data for partly-racemic amino acid samples.[588] The applications of this measurable chiral discrimination towards amino acids and their ester hydrochlorides, arising from the work of Sawada's research group, have been reviewed.[589]

More conventional studies with derivatized amino acids also include access to notable structural information through mass spectrometry: unequivocal distinction between N^{τ}- and N^{π}-substituted histidines solves a long-standing problem;[590] distinction between leucine and isoleucine through liquid secondary-ion mass spectrometry of N-acyl derivatives based on the greater relative abundance of $[M+H-(H_2O+CO)]^+$ ions shown by isoleucine;[591] and new information on the mechanism of fragmentation during electrospray mass spectrometry of phenylthiohydantoins derived from α-amino acids.[592] Mass spectra of protonated α-methyl and β-methyl monoesters of aspartic acid have been interpreted in detail.[593]

5.5 Other Spectroscopic Studies of Amino Acids – Increasing numbers of amino acid topics are being identified for infrared spectroscopic study: single crystal L-histidine dihydrogen orthophosphate[594] and corresponding study of glycine, β-alanine, L-histidine, and DL-tryptophan single crystals;[595] non-ionized glycine and its ^{2}H-isotopomer isolated in a low temperature argon matrix[596] and corresponding study of L-alanine;[597] vibrational dynamics study of L-alanine;[598] assignment of vibrational modes for tyrosine through painstaking ^{2}H, ^{13}C, and ^{18}O labelling.[599] The frontier science in this area is infrared cavity ringdown laser absorption spectroscopy, used to show that arginine exists as its neutral tautomer in a supersonic molecular beam.[600] Dissociation kinetics of a dimeric form of protonated methyl N-acetyl-L-alaninate have been determined by black body IR radiative dissociation.[601] N-Boc-L-α-Amino acids (as solids and as CCl_4 solutions) have been studied by near IR spectroscopy.[602] Fourier transform IR (FTIR) spectra of αβ-dehydroamino acids[603] and their N-acetyl N′-methylamides[604] have been interpreted to determine aspects of conformation. FTIR reflection–absorption studies of amphiphilic N-octadecanoyl-L-alanine have revealed the adoption of a regular chiral arrangement for the derivative, when in the form of a surface monolayer.[605] The temperature dependence of chiral discrimination in an N-hexadecanoyl-L-alanine monolayer, when it overlays an aqueous zinc(II) salt solution, is particularly clear.[606]

IR-Raman studies are also flourishing, dealing with DL-aspartic acid nitrate monohydrate,[607] acid and alkali salts of glycine,[608] β-alanine,[609] and N-acetyl-L-cysteine and -cystine.[610] Polarized IR-Raman studies are still searching for soluble tasks; gaining the data is routine, *e.g.* for L-threonine crystal samples,[611] but interpretation is problematic.

Microwave spectra for L-prolinamide have been interpreted in terms of conformational equilibria.[612]

Dissociation constants for tyrosine in aqueous media at different ionic strengths have been determined by the standard use of UV spectroscopy.[613] More demanding UV studies deal with assessment of radical formation from short-lived N-chloroamino acids, assisted by EPR data,[614] and UV–resonance Raman spectroscopy of tryptophan and other indoles.[615]

Higher energy radiation produces radicals from glycine (EPR study after 30 keV ion bombardment),[616] and generates photoelectron spectra of representative α-amino acids through X-irradiation.[617]

5.6 Other Physico-chemical Studies of Amino Acids – Sub-sections follow that break up a substantial body of literature into logical topic areas. Selection of papers for citation has not been particularly severe, although much repetitive data-gathering needing only simple equipment can be discerned in the papers cited (especially in the first of the following topic areas). The results may well lead to what can be useful insights.

5.6.1 Measurements for Amino Acid Solutions – Effects of solute on the solubility in aqueous media of DL-α-aminobutyric acid,[618] of glycine,[619] of DL-serine compared with L-serine,[620] L-arginine phosphate,[621] of amino acids in aqueous acetonitrile[622] and in aqueous DMF,[623] and extensions of this field of study[624] can be interpreted in terms of apparent molar volumes, isentropic compressibilities, and activity coefficients. Enthalpies of solution for alanine in aqueous NaBr, KBr, and KI at 298.15 K have been determined.[625] A study of the solubilization of amino acids in cationic reversed micelles has a more practical aim.[626]

Solubility data for argon in aqueous amino acids solutions provide interaction coefficients for the solute pairs.[627] Other solute interaction studies involving amino acids include cytosine as a partner,[628] and further development of the extraordinary evidence for chiral recognition by certain N-acetylamino acids (leucine and proline; but not alanine, valine, methionine, or aspartic acid) from calorimetric and nuclear relaxation time mesurements.[629] The results show that interaction energies for DL-pairs differ from those for LL-pairs, thus demonstrating chiral recognition. Calorimetry provides date for enthalpy of transfer of glycine, L-alanine, L-serine and L-proline from water to aqueous glucose at 298.15 K.[630]

Molar volume data have been obtained for aqueous glycine, alanine, and valine[631] and the first two of these amino acids together with β-alanine in aqueous dimethyl sulfoxide,[632] from viscosity coefficients; a related study for aqueous guanidine hydrochloride solutions has been published.[633] Volume properties for glycine have been determined using a new vibrating tub densimeter,[634] and ultrasonic velocity and absorption determinations provide adiabatic compressibilities for glycine, L-alanine, and L-proline.[635]

Dissociation constant data continue to be collected, and redetermined in some cases (first and second dissociation constants for glutamic acid in aqueous media at 298.15 K)[636] for comparison with calculated values.[637] A related study provides the proton binding isotherm for glutamic acid.[638] All the conceivable changes of parameters for such measurements inevitably lead to new data, as in the determination of the variations with ionic strength of acid–base equilibrium constants for glycine in aqueous $NaClO_4$, KCl, and KBr.[639]

5.6.2 Measurements and Studies for Solid Amino Acids – Enthalpies of combustion and formation for enantiomers and racemic forms of aspartic acid[640] and thermal stability data for the same samples and for alanine[641] have been obtained by thermogravimetry and differential thermal analysis. Heat capacities of amino acids, peptides and proteins have been reviewed.[642]

Crystallization studies (L-phenylalanine seeds enhance the growth of an L-glutamic acid polymorph from the racemate;[643] seeding by L-lysine, but not D-lysine, has the same effect[644]) and non-linear optical properties (L-arginine hydrobromide monohydrate[645]) are topics of continuing interest.

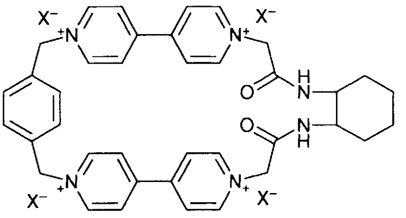
5.6.3 Amino Acid Adsorption and Transport Phenomena – Thermodynamics of adsorption of amino acids to silica,[646] and separation and purification of amino acids[647] have been reviewed. Determination of equilibrium isotherms for adsorption of DL-phenylalanine to polymeric adsorbents[648] and adsorption of L-lysine to a strong acid ion-exchanger,[649] and theory aspects for ion exchange and adsorptive parametric pumping for the separation of amino acid mixtures[650] illustrate more fundamental studies, while practical aspects are also covered: use of histidine as a dipolar eluent in comparison with 2,3-diaminopropanoic acid for the chromatography of alkali and alkaline earth cations;[651] isothermal supersaturation of a sulfonic acid cation exchange resin in its hydrogen ion form, by passage of a solution of the sodium salt of an amino acid.[652] The recovery of amino acids from aqueous media by ion exchange has been reviewed.[653]

A flow injection technique has been applied to the determination of diffusion coefficients of glycine, alanine, and proline.[654] Partition of amino acids within a two-phase aqueous poly(ethyleneglycol)–aqueous dipotassium hydrogen phosphate medium,[655] and within a toluene–water–organic acid system,[656] are described in studies that develop a long-running theme. Membrane transport of amino acids is also a well-established topic of study, with nanofiltration (charged amino acids through inorganic membranes[657] and ultrafiltration membranes[658]), permeability of a cation exchanger membrane for leucine,[659] and electrodialysis through bipolar membranes as an amino acid extraction technique.[660] Liquid membranes through which anionic carrier-mediated transport of L-valine can be accomplished feature in the system 1-decanol–bis(2-ethylhexyl)phosphate–water[661] and for reverse micelles of bis(2-ethylhexyl) sulfosuccinate, studied for their potential in selective transport of tryptophan and p-iodophenylalanine.[662] Sulfonate cation exchange in this fashion has been applied to other amino acids.[663]

5.6.4 Host–Guest Studies with Amino Acids – Some of the transport studies of the type described in the preceding section have included crown ethers as complexing agents for amino acids. An example is the role of 18-crown ether-6 in facilitating amino acid transport into chlorinated solvents from water.[664] A crown ether-functionalized nickel salicylaldimine complex [18-crown-6-Ni-(tert-Bu)$_4$-salphen] is effective in transporting amino acids from an aqueous acid phase through a chloroform membrane to pure water,[665] and crown ether complexation assists the partition of amino acids across bi- and triphasic systems.[666] A C_2-symmetric bis(18-crown-6) analogue of Troger's base shows moderate enantioselective discrimination towards dimethyl cystinate.[667] Several of these crown ether studies are supported by the collection of fundamental data for binding constants through tritration calorimetry [cryptand(2.2.2) and amino acids in methanol;[668] effect of guanidinium compounds on crown ether–amino acid complexation[669]]. Guanidine-modified cyclodextrins have proved to be effective hosts for tyrosine and O-phosphotyrosine.[670]

Calix[4]arene derivatives continue to prove their potential in this area, and have shown this in a spectacular way; (S)-1,1′-bi-2-naphthyl- and bis(indophenol)-derived calix[4]crown ethers are chromogenic hosts, showing naked eye-detectable chiral recognition of optically-active amines and derivatized amino acids.[671] D-Amino acids (alanine, valine, leucine, tryptophan) induce surface area changes, into monolayers of chiral lipophilic calix[4]resorcinarenes carrying (S)-α-phenylethyl or (1R,2S)-norephedrinyl groupings, that differ from the changes induced by their L-enantiomers.[672] Interaction of a series of calixarenesulfonates (96) with arginine and lysine has been assessed using ^{1}H NMR.[673]

Pyridinium cyclophanes (97) show three times greater binding efficiency towards methyl L-tryptophanate than its D-enantiomer.[674] A zinc complex of a porphyrin carrying an L-threonine grouping exhibits significant chiral recognition towards phenylalanine esters.[675] Novel chiral receptors (98 and its analogue with 1,2-cyclohexyl in place of the 1,2-diphenylethyl moiety) show enantioselective binding of amino acid derivatives.[676] A chiral receptor of a different type, the multichannel taste sensor reported in previous Volumes



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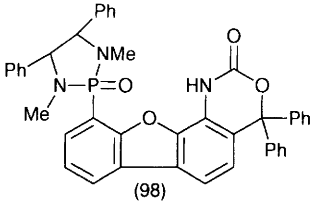

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(Vol. 30, p. 48), has been used to quantify the taste of bitter amino acids[677] and to distinguish D-tryptophan from its L-enantiomer through impedance measurements.[678]

5.6.5 Miscellaneous Physical and Conformational Studies – Methods for determining bond energies for the 20 common amino acids have been reviewed,[679] and existing indices that rank the propensities of these amino acids for conferring β-sheet[680] and α- and β-structures[681] on proteins have been developed further. Conformational characteristics of gem-diamino acids and aminomalonic acids have been reviewed.[682]

Aggregation by the toluene-p-sulfonate of ethyl L-leucinate, leading to gel formation in non-polar solvents, has been visualized at the molecular level as one particular chiral arrangement chosen from a large number of possibilities.[683]

5.7 Molecular Orbital Calculations for Amino Acids – A monograph collects reviews on several topics allied to the applications of molecular orbital (MO) calculations in conformational analysis of amino acids.[684] The primary literature on this topic continues the long series of papers covering gaseous protonated glycine conformers[685] (the general topic of N- versus O-protonation of amino acids in the gas phase,[686,687] as well as N to O proton transfer,[688] has been considered), and an overview of glycine conformations has been published.[689] Intramolecular proton transfer for aqueous glycine[690,691] and an extension of this to include glycine and alanine zwitterions[692] and the stabilization of the alanine zwitterion by four water molecules[693] illustrate MO studies for amino acids in the solution phase. Protonated methionine and its sulfoxide and sulfone have been given similar MO treatment,[694] and the same research group has computed effective charges and proton affinity at carbon atoms in α-amino acids.[695] Interactions of cations with side-chain groupings in the common amino acids have been assessed,[696] and interactions of amino acids with chiral stationary phases (see Sections 4.16.3 and 7.5) have been computed and compared with NMR data.[697]

Considerable effort continues to be expended on calculations of vibrational parameters for the glycine zwitterion,[698] cysteine and serine zwitterions,[699] cysteine and serine hydrochlorides,[700] cysteine and serine zwitterions,[701] and aqueous glutamine.[702] The structure and magnetic properties of glycine radicals in aqueous media at various pH values have been assessed.[703]

Near-edge X-ray absorption features for glycine, phenylalanine, histidine, tyrosine, and tryptophan,[704] and calculated relevant X-ray CD features,[705] have been reported.

Amino acid derivatives have been given MO treatment, continuing the study of N-acylamino acid amides to model the conformational situation of amino acid residues in proteins. Calculations for N-formyl-L-alanine amide[706] and N-formyl-L-serine amide[707] have been presented, similarly for N-acetyl-L-alanine N'-methylamide and its leucine and glutamine analogues.[708] The latter study is unusual since it deals with the conformational behaviour of these derivatives at the water–hexane interface. Calculated conformations of N-acetyl-L-alanine N'-methylamide in homogeneous media concentrate on effects of solvent,[709,710] and on Raman spectroscopic characteristics, vacuum-CD, and Raman optical activity.[711] Calculations for geometrical isomers of N-acetyl 1-aminocyclohexanecarboxylic acid N'-methylamide and its cyclobutane homologue have concentrated on conformational behaviour.[712] N-Thioacetylglycine N'-methylamide conformations revealed through MO calculations continue a study of simple isosteres of the N-acetylamino acid methylamides.[713]

A rare application of MO methods to model a reaction (decomposition of N-chloroamino acids in aqueous media) has been published.[714]

6 Chemical Studies of Amino Acids

6.1 Racemization – Fundamental laboratory assessment of mechanistic details of amino acid racemization is not represented this year, but the dating of fossils continues to be carried out through exploitation of the known kinetics. The ways in which the assumptions involved in applying this method are often overstretched is also becoming better appreciated.

The conclusion that a human tooth dated ca. 3000 BC by ^{14}C methods must have been from a 34 year old individual, based on the D:L-ratio 0.1948 for its aspartic acid content, relies on the assumption that the sample remained at ambient temperature 12.5 °C in the meantime.[715] Fossil bone studies have frequently resorted to amino acid racemization dating, and a useful check on a date obtained in this way is obtained from cystine, methionine and tyrosine levels, which show reduction with time, relative to levels of the other protein amino acids.[716] Dating of younger bone collagen samples has benefited from improved methods of determining enantiomer ratios.[717]

6.2 General Reactions of Amino Acids – The main topics under this heading, which deal with reactions at amino and carboxy groups and at the α-carbon atom of amino acids, fall conveniently into a number of separate sub-sections. The chemistry reviewed here is restricted to coverage of non-routine information, but includes simple new protocols where these offer practical benefits.

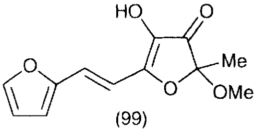
6.2.1 Thermal Stability of Amino Acids – A somewhat obscure title, but intended to cover changes, if any, brought about in amino acids through high temperatures. The starting point is the claim that amino acids sublime under partial vacuum at elevated temperatures with racemization or decomposition;[718] this is important in view of the long series of reports stating the opposite that have appeared in the literature over the years. It is further claimed that the trifunctional compounds aspartic acid and serine can be sublimed out from geological and fossil samples, just as well as glycine, alanine, α-aminoisobutyric acid, and valine.

The state of an amino acid sample may determine the effects caused by high temperatures; the formation of short peptides by heating solid amino acid mixtures to 270 °C at 58.6 MPa pressure is assisted by inorganic additives,[719] while glycine in suspension in glycerine at 175–180 °C is almost quantitatively dimerized with loss of water into the cyclic dipeptide, dioxopiperazine.[720] Cyclic dipeptides are formed (ignoring low molecular weight volatile products) by heating alanine and α-aminoisobutyric acid under nitrogen at 500 °C.[721] The isolated yield is 68% for the former but only 1% for the latter because it suffers decarboxylation and loss of isopropylamine to give bicyclic amidines. Valine and leucine held at 500 °C under nitrogen are recovered unchanged to the extent of 10% for the former, and 2% for the latter, releasing alkanoic acids, primary and secondary amides and hydrantoins as well as the other products mentioned above.[722] Amino acids vapourized at 270 °C in the presence of silica gel and pulverized basaltic lava yield bicyclic and tricyclic amidines and cyclic dipeptides, the essential events being dehydrogenation, loss of alkyl groups and dehydration together with significant racemization.[723]

Amino acids chosen for exposure to space conditions on the BIOPAN-1 mission, as samples free from additives, and adsorbed on to clay, were glycine and the mainly racemic amino acids alanine, leucine, valine, aspartic acid, and glutamic acid (as found in the Murchison meteorite); L-tyrosine was also included.[724] There were no detectable D-enantiomers formed, and no other decomposition except partial degradation of aspartic acid and glutamic acid in those samples that were in the free form.

6.2.2 Reactions at the Amino Group – N-Chlorination of amino acids continues to head this subsection to which several research groups have devoted themselves. Decomposition of the products follow unimolecular kinetics[725] and specific attention has been given in this context to N-chlorovaline and N-chloronorvaline.[726] Another oxidative process at nitrogen that has been studied in depth is attack on the glycine anion by methyl and hydroxy radicals, and by the isopropanol carbon-centred radical.[727] Classical deamination protocols are represented for preparation of hydroxy esters from D-leucine[728] and (R)-2-bromo-5-phthalimidopentanoic acid from N^{δ}-phthalimido-L-ornithine[729] by diazotization, and the conversion of D-phenylalanine into phenylpyruvic acid by a co-immobilized mixture of D-amino acid oxidase and catalase.[730]

The Maillard reaction is another topic that continues to receive in-depth study. It is easy to ascribe this interest to the physiological importance of the reaction, as well as its role in food chemistry, but the fact that the mechanistic challenge that it offers has been only superficially addressed means that there is considerable scope for turning out some worthwhile new knowledge. Reviews from several active research groups published in a Royal Society of Chemistry monograph can be checked for their content through *Chemical Abstracts* (see also Refs. 731, 735, 1020); a typical study is the reaction of glycine with glyoxal that leads to 3-carboxymethyl-1-(2-carboxyethyl)imidazole as well as to Strecker degradation products of the amino acid.[731] Over extended reaction times, a glycine–glucose mixture at physiological temperatures in aqueous media at physiological pH, becomes brown through formation of melanoidins;[732] different amino acids undergo glycation at different rates with galactose under such conditions.[733] Coloured compounds including (99) are



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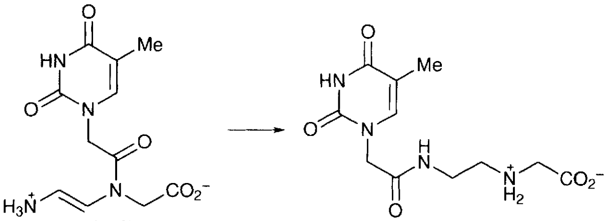
formed from N-(1-deoxy-D-fructos-1-yl)-L-proline and furan-2-carboxaldehyde (but not from the corresponding L-alanine derivative);[734] these early products in a representative Maillard process arise from acetylformoin, an important intermediate that offers different reaction pathways to other initially-formed compounds. Fluorescent compounds generated from 3-deoxyglucosone, itself derived from initially-formed Amadori compounds, are the result of reactions with arginine and lysine in Maillard processes.[735] Chemiluminescence developed in glycine–glucose solutions (Vol. 30, p. 48) has been studied further.[736]

N-Acylation of amino acids catalysed by 4-dimethylaminopyridine, and reversal of this process, has been reviewed.[737] The use of sodium 2-ethylhexanoate as nonpolar solvent-soluble base in Schotten-Baumann acylation of amino acid amides is beneficial.[738] Enzyme-mediated N-acylation of L-methionine (hog kidney and intestinal aminoacylase) is successful with a range of short-chain alkanoic acids.[739] An unusual approach to N-formylation of an α-amino acid ester [from the Schiff base $Bu^tCH{=}NCHR^1CO_2R^2$, *via* the oxaziridine (m-chloroperbenzoic acid) and iron(III) sulfate hexahydrate ring-opening] involves non-basic conditions that might be advantageous in certain cases.[740] Intramolecular acyl transfer (100 → 101) occurs slowly (half-life 34



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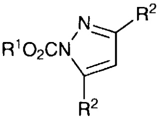
days at pH 11) and must be guarded against in the use of these N-acyl-N-(2-aminoethyl)glycines in PNA synthesis.[741]

Resin-tethered N-acylamino acids in which the acyl groups carry an electron-withdrawing group in the α-position have been cleaved from the polymer in the form of a tetramic acid,[742] while 3-acyltetramic acids formed similarly are released from the solid phase under very mild conditions (1 eq KOH in MeOH).[743] N-Alkylamino acids esterified to a solid phase condense with N-α-ketoacylaminoacids to provide a library of (Z)-3-alkylidene-2,5-dioxopiperazines.[744]

3-Chloro-3-(dimethoxyphosphoryl)-1(3H)-isobenzofuranone reacts with amino acids at room temperature to give phthalimido-acids in good yield.[745] Improved selectivity is claimed in optimized procedures for preparations of α-phthalimido and -benzyloxycarbonyl-protected L-arginine.[746]

N-Alkoxycarbonylation using the N-alkoxycarbonylpyrazole (102) tolerates an aqueous medium and does not cause racemization;[747] a preparation of



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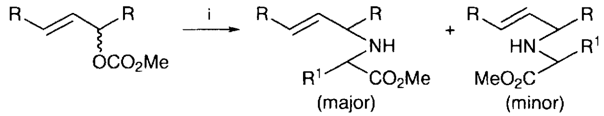
Fmoc-amino acids under neutral anhydrous conditions is a little more roundabout (first, reflux the amino acid with N-methyl-N-trimethylsilyl-trifluoroacetamide, add N-Fmoc-succinimide and then desilylate the product with methanol).[748] Selective Boc-protection of piperazinecarboxylic acid can be accomplished with Boc$_2$O at pH 11.5, the second imino group being arenesulfonylated in the usual way with di-isopropylethylamine as base.[749] N-Alkoxycarbonylation[750] and N-acylation[751] of amino acids with a chloroformate or acyl chloride, respectively, is accelerated by the presence of activated zinc. A novel chiral tetra-O-benzylglucosyloxycarbonyl group can be introduced *via* the isocyanato acid ester, and removed under mild conditions using α- and β-glucosidase, after hydrogenolysis of the benzyl groups;[752] another unusual N-protecting group, o-nitromandelyloxycarbonyl, has been shown to be removed from L-glutamic acid by UV irradiation.[753] Acetyl chloride in methanol generates hydrogen chloride that cleaves the N-protecting group from Boc-amino acids; esterification of the carboxy group occurs at the same time.[754] Other new Boc-deprotection procedures include sodium iodide in neutral aqueous media,[755] microwave irradiation of the derivatives adsorbed on silica gel alone[756] and with one equivalent of aluminium chloride,[757] and reaction with Yb(OTf)$_3$ on silica gel.[758] Resin-tethered Boc-peptides that are sensitive to TFA can be deprotected by trimethylsilyl triflate–2,6-lutidine.[759] Fmoc-amino acids tethered to peptide synthesis resin have been converted into N-Boc analogues by either KF with tert-Boc-S-2-mercapto-4,6-dimethylpyrimidine or KF–Boc$_2$O.[760]

UNCAs (see also Ref. 477) react with Grignard reagents to give N-benzyloxycarbonyl-N-acylamino acids, but several side-products are also formed.[761]

N-[2-(N-Protected amino)thioalkanoyl]phthalimides are efficient selective N-thioacylating agents towards β-aminoalkanols, though they are ineffective with hindered amines.[762] Ureas, both symmetrical and unsymmetrical, have been prepared from amino acids using 1,1′-carbonylbis(benzotriazole), in solution and solid phase modes.[763]

N-Arylsulfonyl derivatives are easily prepared represented in the combinatorial synthesis mode for libraries of derivatized L-phenylalanine amides.[764] Toluene-p-sulfonyl group removal from such derivatives has presented a greater problem until recently, and another procedure, but limited to β-amino-α-hydroxyalkanoic esters since it depends on neighbouring group participation by the ester group, involves isopropylidenation with acetone dimethyl acetal–toluene-p-sulfonic acid in toluene at 70 °C (4–6 h).[765] N-Phosphorylation through phosphoramidite–amine exchange in the presence of 1-tetrazole is rapid and efficient,[766] and N-(N-methylaminothiomethanephosphonyl) derivatives show promise, after cyclization, for use in thiopeptide synthesis.[767] A practical N-(di-isopropylphosphoryl)ation procedure involves NaOCl, di-isopropyl phosphite, and NaOH.[768]

N-Arylation occurs without racemization, using aryl halides with copper(I) iodide as catalyst.[769] Mono- and dimethoxytritylation,[770] and protection of an amino acid with hexafluoroacetone prior to N-monomethylation (MeCl with Et_3SiH and TFA)[771] or analogous N-phosphinomethylation,[772] have been described. A two-step strategy from an N-Boc- or -Z-amino acid *via* reduction of the oxazolidinone formed with paraformaldehyde gives optically-pure N-methylamino acids (see Ref. 857 for a standard preparation of an oxazolidinone that is the intermediate in this process).[773] N-Benzyl-N-Boc-amino acid esters have been converted into homochiral 2,6-*cis*-disubstituted piperidines, *via* 1,5-aminoalkenols $BzlNHCHR^1CH{=}CHCH_2CH(OH)R^2$.[774] Diastereoselective N-alkylation of α-amino acid esters in which a new chiral centre is created in the resulting alkyl group has been worked out (Scheme 25).[775,776]

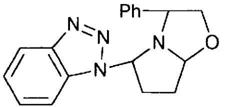


Reagents: *i*, L-amino acid, $[\eta^3\text{-}C_3H_5PdCl]_2$, Et_3N, CH_2Cl_2, room temp.

Scheme 25

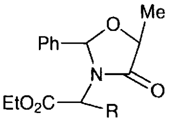
N-(β-Boc-Aminoethyl)-N-acyl-α-amino acids in which the acyl group carries a nucleobase have been prepared by successive reductive alkylation [$BocNHCH_2CHO$, $NaBH_3(CN)$] and acylation, to give monomers for the preparation of functionalized PNAs.[777]

2,5-Dimethoxyfuran reacts with (S)-phenylglycinol and benzotriazole to give (4S,5R)-5-(benzotriazol-1-yl)-4-phenyl[1,2-a]oxazolopyrrolidine (103) which is easily substituted by Grignard reagents and cleaved to give homochiral 2,5-



(103)

disubstituted pyrrolidines.[778] An oxazolidinone (104) from o-bromobenzaldehyde, S-lactic acid, and an L-α-amino acid is amenable to radical substitution to give methyl 2-[tributylstannyl)methyl]propenoate after hydrolysis, with modest stereocontrol.[779]



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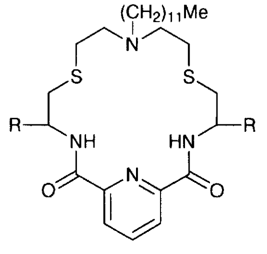

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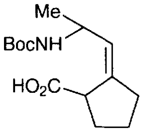

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Esters of N-toluene-p-sulfonyl- and -trifluoroacetylamino acids are readily N-allylated using allyl carbonate and a palladium(0) catalyst.[780] N-(3-Pyridazinamin-3-yl)amino acids are formed with 4-cyano-3-chloropyridazines and removal of the cyano group by catalytic hydrogenolysis (the results are only given for two amino acids, and the hydrogenolysis was not demonstrated).[781] Reductive amination of tert-butyl glycinate with glyoxylic acid, and functional group development to the aldehyde $HCOCH_2N(Boc)CH_2CO_2Bu^t$, provides the starting material for a synthesis of a C-glycosylated peptoid building block through condensation with the aldehyde grouping.[782] The equivalent Michael addition process also leads to the most stable diastereoisomer, illustrated for the addition of isopropyl L-alaninate to ω-nitrostyrene.[783] An unusual version of this category of N-alkylation reaction (amino acids add to 1,2-naphthoquinone-4-sulfonic acid to give coloured derivatives, λ_{max} 480 nm) employs the reagent immobilized on an ion-exchange resin.[784] Bearing in mind the current interest in photosensitized reactions, including amino acids, the observation that their photoalkylation can be brought about by benzophenone is important.[785]

N-Amination is a viable option now that N-Boc-3-trichloromethyloxaziridine has been shown to react much faster than aryl analogues to give N^β-*Boc*-hydrazino-acids, including N^β-Boc-N^β-benzyl-L-glutamic acid, suitable for the preparation of S-piperazic acid and its dihydro-analogue.[786] Bis-Boc-$[^{15}N_2]$Hydrazine converted into di-tert-butyl azodicarboxylate and thence into $[^{15}N_2]$-S-piperazic acid illustrates standard methodology.[787]

6.2.3 Reactions at the Carboxy Group – Esterification of amino acids can be accomplished in high yield through stirring a suspension in an alkanol over

Amberlyst-15 cation exchange resin in the hydrogen form,[788] or using 2,2-dimethoxypropane, methanol, and a catalytic amount of HCl, the advantage of the latter method being that it is selective for alkanoic acids in the presence of aromatic acid functions.[789] For N-protected amino acids, use of an 2-phenylisopropyl or tert-butyl trichloroacetimidate is advocated, especially useful with β-hydroxy-α-amino acids.[790] Esterification of Boc-glycine to poly-(ethylene glycol), Boc removal, and Schiff base formation have been monitored by ESI-mass spectrometry.[791] Carbodi-imide-mediated esterification of Boc-L-tryptophan to 4-hydroxythiophenol-linked resin and Pictet-Spengler construction of a library of tetrahydro-β-carbolines is followed by release from the resin by a primary amine (see also Ref. 1060).[792] Polymer-bound HOBt mediates the preparation of N-hydroxysuccinimide esters of N-Boc-L-proline.[793]

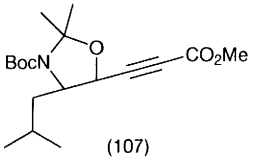
α-Chymotrypsin-catalysed transesterification of methyl L-tyrosinate gives the fructosyl ester in 63% yield.[794] Fullereneproline esters in toluene can be transesterified by 2,2,2-trifluoroethyl esters of palmitic and butyric acids, using lipases.[795] Porcine liver esterase catalyses the hydrolysis of the pro-S ester group of diethyl α-alkyl-α-(benzyloxycarbonylamino)malonates and enantiodivergent reduction gives α-substituted D-serines.[796] The other major enantioselective reaction topic, ester hydrolysis (but without enzyme catalysis), is represented by lipophilic macrocyclic ligands (105) as catalysts, mediating the hydrolysis of long-chain alkyl esters,[797] and copper(II) complexes of homochiral ligands[798] and sugar-derived surfactants such as N-dodecylmaltobionamide[799] mediating the hydrolysis of p-nitrophenyl esters. Mechanistic aspects are at the heart of these studies (aspects of the field have been reviewed[800]); the general complexity of the topic is illustrated in the last-mentioned research, where it was shown that enhanced enantioselectivity is observed when the pH is changed rapidly at the start of a reaction. Ester hydrolysis protocols ignoring this stereochemical aspect are: lanthanide-ion catalysis of the hydrolysis of simple esters of amino acid derivatives,[801] polymers bearing pyridine side-chains complexed to copper(II) ions as catalysts for the hydrolysis of p-nitrophenyl esters of N-protected α, β, and γ-amino acids,[802] arylpalladium complexes [Pd($C_6H_4CHMeNMe_2$)Cl(py)] as catalyst for the hydrolysis of Z-leucine p-nitrophenyl esters,[803]and enhancement of the hydrolysis of ethyl glycinate by CTAB micelles.[804] Transesterification of simple esters leading to hindered esters is catalysed by titanium(IV) ethoxide.[805] Aminolysis of hydroquinone esters of N-protected amino acids is assisted by a bivalent metal oxidant.[806]

Acyl fluorides formed by the reaction of N-tritylamino acids with cyanuric fluoride are already established as powerful acylating agents, and in a broad study their reduction (-COF → -CH_2OH), chain extension *via* a phosphorane (→ TrNHCHRCF=$CMeCO_2Me$), and conversion into the trifluoromethyl ketone using Ruppert's reagent, has been demonstrated.[807] Comparison of reactivity of these fluorides with corresponding chlorides has revealed the effectiveness of the chlorides of N-arenesulfonylamino acids, but not the fluorides, for acylation of hindered amines.[808] The use of Fmoc-amino acid chlorides for amination is better assisted by zinc dust rather than an organic base,[809] and the use of Fmoc-α-aminoisobutyroyl chloride for the synthesis of peptides of this highly hindered amino acid uses the potassium salt of hydroxybenzotriazole as co-reactant.[810] Aminolysis of N-protected amino acid esters by amino acids can be usefully mediated by $AlMe_3$.[811] β-Ketoester formation involves reaction of the activated carboxy group with the allyl acetate anion.[812]

Reductive processes applied to the carboxy group and its derivatives typically involve $NaBH_4$–LiCl, applied to protected serine[813] and to amino acids adsorbed on Amberlyst -15 cation exchange resin suspended in THF,[814] to lead to β-amino-alcohols. Fmoc-Amino acids treated to $NaBH_4$ reduction and then Swern oxidation after conversion into the mixed anhydride, or $LiAlH_4$ reduction of Weinreb amides Fmoc-aa-CONMeOMe (-aa- = amino acid residue), give β-amino-aldehydes.[815] Simple N-protected amino acid amides are reduced to amines by BH_3 in a route to spermines starting from β-alanine,[816] but hindered N-phenylethylhomoproline esters could not be reduced by DIBAL-H.[817] The mixed anhydride grouping introduced by isobutyl chloroformate into β-tert-butyl N-Boc-L-aspartate is selectively reduced with $NaBH_4$ to hydroxymethyl.[818]

Reduction of L-tyrosine by BH_3–Me_2S starts a preparation of an oxazolidinone destined to be N-acylated and anchored to a solid phase for use in Evans-type synthesis.[819] N-Protected L-phenylalaninal, and other amino acid aldehydes, can be condensed with a resin-bound Wittig reagent, built upon by normal peptide synthesis and then released as a peptide aldehyde by ozonolysis;[820,821] milder conditions will be needed to make this into a general method. Sodium borohydride reduction of the α-HOBt ester of β-benzyl aspartate gives a quantitative yield of the primary alcohol.[822] Different hydride reagents have been compared in a search for a clean procedure for the reduction of aspartic and glutamic Weinreb amides to aldehydes, leading to the conclusion that $LiAl(O^tBu)_3H$ or the tris(3-ethyl-3-pentyloxy) analogue are best (see also Ref. 957).[823] Condensation of the Weinreb amide of NN-dibenzyl-L-alanine with iodocyclopentene and elaboration leading to the vinylogous amino acid (106) has been reported.[824] N-Benzyloxycarbonyl-L-proline gives the prolinal derivative by the equivalent BH_3–Me_2S reduction followed by either Swern or Dess-Martin periodinane oxidation.[825] The $NaBH_4$–LiCl reagent can reduce an ester grouping in the presence of an α-azido group, thus opening up some novel possibilities for the synthesis of modified amino acids.[826] N-Acyl- or N-thioacyl-N-methyl-α-amino acid esters are fully reduced by $NaBH_4$ in MeOH but the simpler N-H compounds are not.[827] An N-hydroxymethyl group, introduced by treating a Boc-amino acid with formaldehyde, stabilizes the N-Boc-amino acid aldehyde formed by reduction by DIBAL-H, especially against racemization.[828] [See also Refs. 774, 958 for related uses of DIBAL-H.]

The prolinal above has been used to prepare S-(pyrrolidin-2-yl)alkenes, and N-Boc-N-benzyl-L-phenylalaninal has been converted into a 95:5 mixture of $BocN(Bzl)CHBzlCH_2CH{=}CH_2$ and $BocN(Bzl)CHBzlCH{=}CHCH_3$ *via* the



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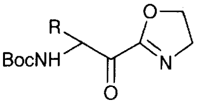

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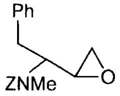


(109)

carbonate $BocN(Bzl)CHBzlCH(OCH_2CO_2Et)CH{=}CH_2$.[829] N-Boc-L-leucinal provides the means of chain construction for a homochiral dihydroisocoumarin through cycloaddition of the acetylenic ester (107) to a substituted cyclohexadiene, and elaboration of the adduct.[830] [See also Ref. 476 for conversion of an amino aldehyde into a α-amino-alkynoic acid.]

Mitsunobu reactions with N-protected β-aminoalkanols, giving O-acyl derivatives, are best conducted by replacing triphenylphosphine with 1,2-bis(diphenylphosphino)ethane.[831]

Carbonyl attack by nucleophiles of other types is represented in several studies. trans-Alkenation is effected with a pathway starting with lithiated benzylic or allylic benzotriazoles ($BtCLiR \rightarrow BtCRCOR' \rightarrow RCH{=}CHR'$).[832] Reactions of N-protected amino acids esterified to a solid-phase with aqueous hydroxylamine give corresponding hydroxaminic acids[833] (these have been used as the source of homochiral acylnitroso compounds for use in Diels-Alder addition reactions leading to isoxazolidines[834]), and solution reactions of esters with α-lithiated isocyanides give N-protected 5-(β-aminoethyl)oxazoles.[835] The equivalent process, reaction of Fmoc-amino acid amides with diazo-esters $RCOC({=}N_2)CO_2Me$, gives 2-(β-aminoalkyl)-4-methoxycarbonyl-5-substituted oxazoles.[836] Pyrazoles and isoxazoles have been prepared from α-aminoalkyl trimethylsilylethynyl *via* β-diethylaminoethenyl ketones.[837] Further examples of solid phase Ugi reactions that convert Boc-amino acids into libraries of dioxopiperazines, with the beneficial use of cyclohexenyl isonitrile, have been reported;[838] the same chemistry has been explored in the solution mode,[839] and L-homoserine gives N-carbamoylmethyl-α-aminobutyrolactones.[840] α-Hydroxy-β-Boc-amino acid N′-(2-hydroxyethyl)amides have been converted into oxazolines and thence into α-Boc-amino keto-oxazolines (108) by standard methods.[841] Polymeric aryl hydrazines acylated by an N-protected amino acid, are oxidized to nitrogen and nitrobenzene by mild oxidants, in the process of releasing the attached moiety after combinatorial or peptide synthesis operations.[842] Diazoketones derived from N-toluene-p-sulfonyl-α- and β-amino acids can react through several different pathways, but the β-amino acid derivatives give 5-substituted pyrrolidinones in excellent yields under the conditions of the Wolff rearrangement.[843]

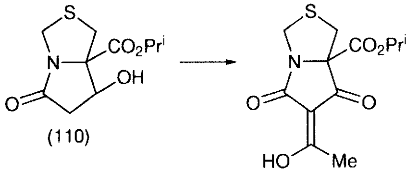
Decarboxylation and electron transfer cyclization have all been established as outcomes for photolysis of N-phthaloylamino acids, and elimination occurs with cysteine derivatives.[844] Formation of phthalimido-substituted radicals from N-phthaloyl-O-tri-isopropylsilyl-DL-threonine by UV-irradiation after conversion into the Barton ester.[845] Decarboxylation of leucine by hydroxy radicals generated from the iron(II)–porphyrin–H_2O_2 reagent system,[846] and formation of CO_2, NH_3, and alkanoic acids through electrochemical oxidation,[847] are further examples of the results of more drastic treatment of amino acids and their derivatives.

α-Aminoketones are acquiring new uses in synthesis, and enantiopure samples have been prepared through Al-Hg reduction of γ-amino-β-ketosulfones generated through condensation of an N-protected α-amino acid ester with Li_2CHSO_2Tol, followed by alkylation.[848] Treatment of an imidazolide derived from an α-Boc-amino acid, with excess Grignard reagent in the presence of a copper(I) salt, provides a general route to α-aminoketones,[849] as does palladium-catalysed reaction of N-Z-amino acid thiolesters with organozinc reagents.[850] Diazoketones (S)-PhtNCHBu^{i}COCH = N_2 have provided the first example for this class of compound, of rhodium-catalysed intramolecular C-H insertion.[851] The *threo*-N-methyl-N-benzyloxycarbonyl-L-phenylalanine-derived oxirane (109) has been prepared through established routes; from the bromoketone, or through epoxidation.[852]

6.2.4 Reactions at both Amino and Carboxy Groups – This section mostly covers routes from amino acids to heterocyclic compounds, concentrating on less routine work and leaving β-lactams for coverage elsewhere in this Specialist Periodical Report [except for mention of new examples of the route from β-amino acids to α-amino acids: oxidative ring-expansion of 3-hydroxy-β-lactams to give N-carboxyanhydrides (NCAs) of polyhydroxylated α-amino acids[853]]. Boc-NCAs are also easily prepared from α-amino acids and are effective acylating agents towards alkanols as well as their well-known use in peptide synthesis; sugars in various degrees of protection are aminoacylated by them.[854] Metallacyclic oxidative addition products from NCAs with zerovalent nickel complexes have been described.[855] Other non-routine lactamization studies are published for macrocyclic lactams, which can be formed from 6-amino-7-hydroxyoct-5-enoic acid by way of a ring-contraction rearrangement of the lactone.[856]

Oxazolidin-2-one formation from an α-N-Fmoc-amino acid with formaldehyde is straightforward, and modest improvements are represented in the mild conditions associated with catalysis by $BF_3.Et_2O$ or toluene-p-sulfonic acid on silica gel (see also Ref. 773).[857] An unusual version of this is seen in the sequence (110) to (111), occurring with retention of configuration.[858] More results have been reported for the conversion of 3-(acylamino)benzo[b]furan-2(3H)-ones into 3-arylthio-substituted versions that is accompanied by visible chemiluminescence (see Vol. 30, p. 70).[859]

As usual, this section is dominated by work on oxazoles and oxazolones, the



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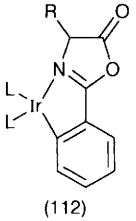
(111)

former class being accessible as their 5-trifluoromethyl derivatives, from N-acylamino acids in trifluoroacetic anhydride–pyridine,[860] a reaction medium that promotes an anomalous Dakin-West reaction with an N-(alkoxycarbonyl)proline leading *via* the mesoionic oxazol-5-one to 4-trifluoroacetyl-2,3-dihydropyrroles.[861] 4-Trifluoroacetyl-1,3-oxazolium-5-olates formed from N-alkyl-N-acylglycines with trifluoroacetic anhydride are opened by O-nucleophiles at C-5, and by N-nucleophiles at C-2;[862] phenylhydrazine gives trifluoromethyl-substituted pyrazoles and 1,2,4-triazines.[863] Novel 2-phenyloxazol-5(4H)-one complexes (112) have been prepared.[864] Mesoionic oxazol-4-ones ('isomunchnones') are formed by rhodium(II) catalysed cyclization of α-diazoimides $AcN(CHRMe)COC(=N_2)CO_2Me$, trapped through additions to dipolarophiles.[865] Oxazoles are formed from the related rhodium(II)-mediated condensation of diazomalonates $(RO_2C)_2C{=}N_2$ with amino acids; amides R^1CONH_2 give N-acylaminomalonates $(RO_2C)_2CH(CH_2)_2CONHCH(CO_2R)_2$.[866] Further results for coloured 2-arylaminothiazol-5(4H)-ones,[867] and the formation of thiohydantoins *via* oxazol-5(4H)-ones by successive treatment of an α-Boc-amino acid with isobutyl chloroformate and trimethylsilyl isothiocyanate,[868] have been published.



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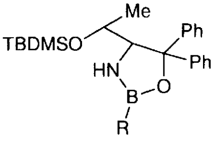
More uses as a chiral reduction catalyst, for the oxazaborolidine (113) prepared from L-threonine,[869] and further examples of boroxazolones (114)[870] and related species, *e.g.* the oxazaborolidinone (115),[871] have been reported.



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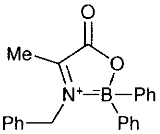

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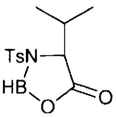

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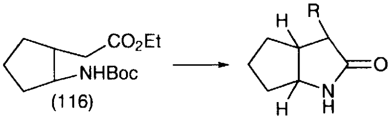
The unexpected displacement of both functional groups from N-toluene-p-sulfonylamino acids by benzene, toluene or p-xylene to give 1,1-diarylalkanes requires long heating at 60–70 °C in the presence of 3 equivalents H_2SO_4,[872] phenylalanine giving 2-arylnaphthalenes.[873] N-Arylsulfonylamino L-acid amides condense with 1,2-dibromoethane to give substituted homochiral oxopiperazines,[874] and larger ring systems can be prepared from β-amino acids as illustrated in a solid-phase synthesis of 1,5-benzodiazepin-2-ones.[875] Hydantoins can be formed by solid-phase reaction of amino acid amides with triphosgene or carbonyldi-imidazole.[876]

The self-condensation of amino acids into dioxopiperazines has been covered in other Sections, and the alternative oligomerization route to generate short peptides under conditions that could have prevailed in the prebiotic environment provides an area of growing interest. Low yields of oligomers are formed from glycine and from glycylglycine adsorbed on silica and alumina through wetting–drying cycles at 80 °C,[877] or on copper(II)-exchanged hectorite.[878] Co-precipitated nickel(II) and iron(II) sulfides suspended in deoxygenated water at 100 °C under a CO–H_2S or MeSH atmosphere provides a more effective system.[879]

The role of other species capable of acting as reagents rather than catalysts features in several related studies. Oligomerization of aspartic acid as its anion in aqueous solution can be brought about by both carbonyldi-imidazole and 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide; for simple α-amino acid anions, the former reagent (but not the latter reagent) is effective, the reverse applying for β-amino acids.[880] The impetus given to this topic was the finding that solution self-condensation of amino acids was induced by high salt concentrations, and development of this in terms of finer details: a glycine–alanine mixture induced to oligomerize by copper(II) salts exhibits 'mutual catalysis'; that is, glycine enhances the formation of alanylalanine through a role for the glycylalanylalanine–copper(II) complex.[881]

The benefits of heterogeneous systems in this context are shown by the finding that β-amino acids yield oligomers on mineral surfaces [*e.g.* formation of poly(β-glutamic acid) on hydroxyapatite] but not in free solutions, under the action of a water-soluble carbodi-imide];[882] similar results were found with negatively-charged α-amino acids (glutamic and aspartic acids and O-phosphotyrosine).[883] Polymerization of amino acids on mineral surfaces has been reviewed.[884]

6.2.5 Reactions at the α-Carbon Atom of α-Amino Acids and Higher Homologues – Alkylation of glycine derivatives is standard synthesis methodology (Section 4.1.7), and routes to α-alkyl-α-amino acids are covered in Section 4.3. Therefore this is a small subsection, dealing with α-alkylation of higher homologues; *e.g.* the γ-amino acid (116) with LiHMDS and allyl or benzyl iodide,[885] and γ-lactams and higher homologues using a chiral tetradentate lithium amide in the presence of LiBr.[886]

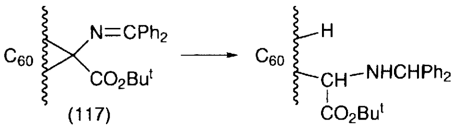


6.3 Specific Reactions of Amino Acids – Reactions involving primarily the side-chains of common amino acids are covered in this section, which is structured as usual – saturated aliphatic groupings, functionalized aliphatic groupings, aromatic and heteroaromatic side-chains.

Few reagents affect the saturated side-chains of alanine, valine and the leucine isomers in controllable ways, but free-radical bromination, when amino and carboxy groups are suitably protected, yields useful synthons whose preparation and uses have been reviewed.[887] α-(β-Iodoalkyl)glycines and γ-iodo-homologues are best prepared from serine, aspartic acid and glutamic acid, respectively; their conversion into zinc and zinc–copper species, and uses of these in the synthesis of other amino acids, has been reviewed.[888] Examples of such uses include routes to α-(ω-arylalkyl)glycines by palladium-mediated coupling to iodoarenes,[889] to halogenoalkenes and acyl halides,[890] and [2,6-bis(ethoxycarbonyl)pyridin-4-yl]-L-alanines.[891] Organocopper synthons formed with Rieke copper are included in these new studies (Ref. 890), and extension of the organozinc species to include modified aspartic and glutamic acids, *viz.* $BocNHCH(CH_2ZnI)(CH_2)_nCO_2Me$ has opened up routes to substituted β- and γ-amino acids.[892] 2-Amino-4-bromobutanoic acid has been subjected to standard nucleophilic substitution protocols to give expected products, including (S)-azetidine-2-carboxylic acid, hitherto difficult to prepare.[893]

Electrochemical 5-methoxylation of methyl N-Boc-L-prolinate followed by allylation (using allysilane–BF_3) is the starting point for further development leading to eight-membered lactams.[894] This intermediate has also been used for one of the many epibatidine syntheses that have been reported this year.[895]

N-Benzhydryl α-fulleren[60]ylglycines are now accessible through a novel cyclopropane ring-opening strategy [DBU and CBr_4 in PhCl, followed by $Na(BH_3)CN$] that is unique to a 'methano[60]fullerene amino acid', the cycloadduct (117).[896]



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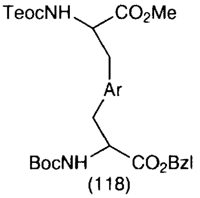
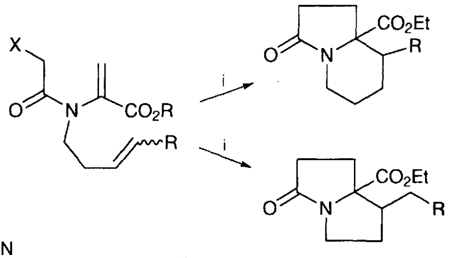
Tautomerization of 'dehydroamino acids', *alias* αβ-unsaturated α-amino acids, accounts for their rapid hydrolysis in neutral aqueous media.[897] Nevertheless, they can be handled without difficulties, *e.g.* in a synthesis of methyl 4-phenylpyroglutamate from N-benzyl-N-α-phenylchloroacetyldehydroalanine through radical intermediates generated by Bu_3SnH-AIBN,[898] in routes to 4-cyanoglutamic acid,[899] to p- and m-phenylenebis(alanine)s (118),[900] and to γ-nitro-α-amino acids by base-catalysed conjugate addition of nitroalkanes,[901]



(118)

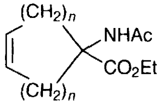
then on to reductive denitration (products of ozonolysis of derived nitronates).[902] N-Acetyl dehydroalanine bound to Wang resin has been shown to undergo Michael addition of 1,2,4-triazole and pyrazole, offering a rapid synthesis of β-heteroaryl-α-amino acids (see also Ref. 998).[903] N-Acyl-N-alk-3-enyl dehydroamino acids participate in tandem radical cyclization to indolizidinones and pyrrolizidinones (Scheme 26).[904]



Reagents: i, Bu_3SnH, AIBN

Scheme 26

N-Benzyloxycarbonyl-L-vinylglycine continues to serve in syntheses of other amino acids through standard routes but using currently-favoured methodologies – preparation of [(E)-(2-arylvinyl)]glycines in high enantiomeric purity, by reaction with an iodoarene catalysed by palladium(II) acetate in aqueous Bu_4N–$NaHCO_3$ at 45 °C.[905] Neither dehydroamino acids nor vinylglycines undergo the Grubbs cross-metathesis reactions shown by allyl- and homoallylglycines with aryl- and alkyl-substituted alkenes mediated by $(Cy_3P)_2Cl_2Ru{=}CHPh$,[906] or $RuCl_2$-mediated ring-closing metathesis of αα-bis(ω-alkenyl)glycine derivatives $AcNHC[(CH_2)_nCH{=}CH_2]CO_2Et$ that leads to 1-aminocycloalken-1-carboxylic acids (119 ; n = 1 or 2),[907,908] proposed for a role as protease inhibitors. The inertness of vinylglycines in this process has been rationalized as a conformation-dependent electronic effect, since N-allyl amides of N-protected vinylglycines were cyclized efficiently.[909] A spectacular Grubbs alkene metathesis route, used for a synthesis of meso-2,6-diaminopimelic acid from the bis(allylglycinate) ester of ethyleneglycol,[910] and for a synthesis of (S,S)-2,7-diaminosuberic acid from the related allylglycine derivative (120),[911,912] also for eneyne metathesis leading to 1-amino-3-vinylcyclohex-3-ene-1-carboxylic acid and related constrained amino acids.[913]



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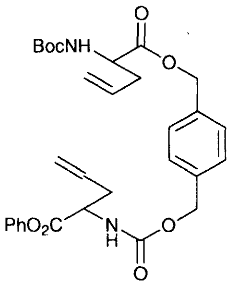

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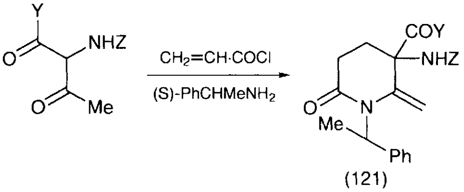
7-Membered ring lactams have been prepared through a high-speed solid phase route in which N-(N-Boc-allylglycinyl)allylamines are subjected to ring-closing metathesis-promoted cleavage as a key step.[914] Iodocyclization of α-allylglycines $TsNH(CO_2Me)CH_2CH{=}CHR$ lacks stereocontrol, leading to *cis*- and *trans*-2,5-disubstituted prolines that undergo aromatization (DBU in DMF) to give corresponding pyrrole 2-carboxylic acids.[915] The equivalent process with alkynylglycines gives 2-substituted-3-iodo-4,5-dehydroprolines.[916] Dihydroxylation (OsO_4–trimethylamine N-oxide) of L-α-allylglycine after routine protection as the N-Boc methyl ester gave *cis*- and *trans*-N-Boc-3-amino-5-hydroxymethyl-γ-lactones.[917] Protected 4,5-dehydro-L-leucine is the source of S-2-aminolevulinic acid through ozonolysis, whose keto-group has been used for development of a glycosylated side-chain through an oxime linkage.[918]

ω-Alkynyl-α-amino acids have been resolved with *Pseudomonas putida* aminopeptidase, and subjected to palladium(0) cyclization to give 5-substituted prolines.[919]

α-(ω-Hydroxyalkyl)glycines, particularly L-serine and L-threonine, provide valuable starting points for routes to a wide variety of synthesis targets. A review has appeared covering uses in synthesis of 4,5-disubstituted oxazolin-2-ones formed from D- and L-serine,[920] an illustration being provided for a synthesis of 1,2-aminoalkanols involving organometallic reagents (cerium, magnesium or lithium).[921] Another route to these compounds from the protected D-serine $Ph_2C{=}NCH(CH_2OTBS)CO_2Me$ also employs organometallic reagents.[922] N-Benzyloxycarbonyl- or -Fmoc-aziridinecarboxylic acid derivatives formed from L-serine undergo $Sc(O_3SCF_3)_3$-mediated opening by arylindoles to give substituted L-tryptophans.[923] An alternative approach to dehydrotryptophan[924] through the reaction of indole in AcOH with (E)-β-(N-methylamino)dehydroalanine, formed from serine, and similar use of the N-dimethylamino-homologue in preparations of β-aryl and -heteroaryl-dehydroalanines,[925] has been developed further. O-Glycosylation at the end of a route to F1α-antigen is accomplished by TMSOTf- or Cp_2ZrCl_2-$AgClO_4$-catalysed condensation with the glycosyl trichloracetimidate or fluoride.[926] Preparation of α-acetylglycine derivatives ZNHCH(COMe)COY from L-threonine opens up a synthesis of δ-lactams by aza-annulation with acrylates (121).[927]



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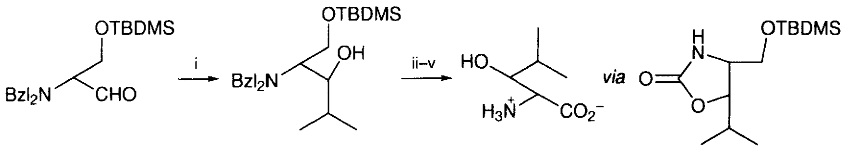
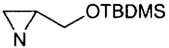
The unique role for D-serine, to offer its side-chain for easy conversion into a carboxy group of a target L-amino acid after functional group changes elsewhere in the molecule, is illustrated in a synthesis of (2S,3S)-β-hydroxy-



Reagents: i, Pr^iMgX or Pr^iCeX; ii, H_2–$Pd(OH)_2$; iii, carbonyldi-imidazole; iv, Jones oxidation; v, conc. HCl

Scheme 27

leucine (Scheme 27).[928] Cyclic ortho-ester protection of the carboxy group of L-serine, giving an homochiral N-protected serinal equivalent, is part of a route to β-disubstituted serines.[929] D-Serine, converted into the aminodiol derivative $TBDMSOCH_2CH(NHBoc)CH(OH)Ph$ (Vol. 30, p. 64), gave chloramphenicol after several routine steps, including p-nitration and dichloroacetylation.[930] The aziridine (122) was prepared by cyclization of protected L-serinol using Ph_3P and di-isopropyl azodicarboxylate, and used for the synthesis of N-Boc-D-amino acids through $CuBr_2.SMe_2$-catalysed opening with Grignard reagents.[931]



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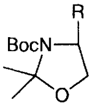
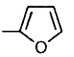
N,O-Protected L-serinals are useful synthons, and $TiCl_4$- or $SnCl_4$-mediated allyltrimethylsilane addition illustrates a typical chain extension operation;[932] the nature of the protecting groups and the Lewis acid used influences the diastereoselectivity of the process. Most of the serine-based syntheses that build structures on to the carboxy-group continue to employ the double N,O-protection strategy represented in the Garner aldehyde (123): demonstrated in routes to (2R)-$F_3CCH_2CH(NHBoc)CO_2H$ (six steps including use of CF_3–TMS for trifluoromethylation),[933] chiral vinyl halides,[934] (2R,3R)-β-hydroxyaspartic acid *via* (124),[935] D-(+)-erythrosphingosine and its (−)-enantiomer *via* (125),[936] alternatively *via* 3-ketosphinganine (126) from the same starting material,[937] β-diphenylphosphinothio-L-alanine,[938] the aminoalkanol $THPOCH_2CH(NH_2)CH(OH)^iPr$ in frangulanine synthesis,[939] and novel isoxazol-3- and -5-ylglycines.[940] This Garner aldehyde was not successfully used in a synthesis of S-2-amino-(Z)-3,5-hexadienoic acid due to the need for oxidative treatment in the final stage, but Lajoie's alternative (N-Boc-L-serinal

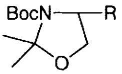


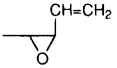
(123) R = CHO

(124) R = CO–


(127) R = COMe

(128) R = $C(=CH_2)OSiMe_3$

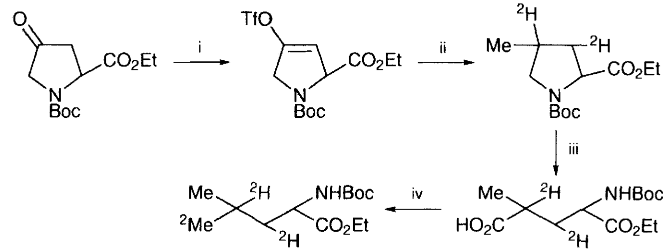


(125) R =


(126) R = $COC_{15}H_{31}$

with the side-chain alkanol protected as an orthoester) was satisfactory.[941] An outing for S-2-(N-Fmoc-amino)-β-lactone, the other main L-serine synthon, has led to a synthesis of the phosphonic acid isostere of L-aspartic acid, $FmocNHCH[CH_2P(O)(OR)_2]CO_2Me$, R = Me or allyl.[942] The threonine analogue of the oxazolidine gives the ketone (127) through chlorochromate oxidation, and this has been used in a multigram synthesis of the silyl enol ether (128), which on condensation with a glycopyranosyl aldehyde gives a 2-amino-5-(β-D-glycopyranosyl)pentanoic acid,[943] and in a route to α- and β-C-galactosylserines.[944]

Hydroxy-L-proline is also a valuable starting material, demonstrated for the synthesis, *via* 3,4-dehydro-L-proline, of L-proline with every methylene group stereospecifically labelled with ^2H,[945] and a synthesis of (2S,3S,4R)-[3,4,5,5,5-$^2H_5$]leucine (Scheme 28),[946] similarly for the synthesis of (2S,3R,4S)-

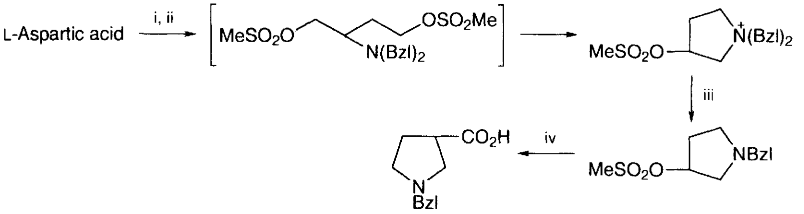


Reagents: i, NaHDMS, Tf_2NPh; ii, Me_2CuMgI, then $^2H_2$–Pt; iii, RuO_4, then LiOH; iv, $CO_2H \rightarrow C^2H_2OH \rightarrow C^2H_2$

Scheme 28

and (2S,3S,4R)-epoxyproline and thence to amino-hydroxyprolines,[947] to *cis*-3,4-dihydroxy-D- and L-prolines, and a first synthesis of (−)-(3S,4R)-dichloroproline,[948] and to 4-fluoro- and 4,4-difluoroprolines.[949] Decarboxylation of hydroxy-L-proline (method not specified) gives R-3-hydroxypyrrolidine.[950] (2S,4S)-2,4-Diaminoglutaric acid has been prepared by RuO_4 oxidation of 4-Boc-aminoproline (available from hydroxy-L-proline) to give the lactam of the target.[951] Use of hydroxyproline in a synthesis of 3-aminopyrrolidines has been described.[952]

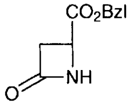
Aspartic acid and asparagine have been subjected to side-chain modifications: synthesis of β-proline (Scheme 29);[953] Hofmann rearrangement of N^{α}-



Reagents: i, BzlBr, K_2CO_3, then $LiAlH_4$; ii, $MeSO_2Cl$; iii, H_2–$Pd(OH)_2$; iv, Cl^-, then NaCN and H_3O^+

Scheme 29

toluene-p-sulfonyl-L-asparagine giving N^{α}-toluene-p-sulfonyl-L-β-aminoalanine;[954] anti-methallylation;[955] and preparation of chiral oxazin-3-ones.[956] Reactions applied to the general class of α-(ω-carboxyalkyl)glycines include selective reduction of ω-esters by DIBAL-H and chain extension through Wittig reactions on the resulting aldehydes (see also Ref. 823),[957] and corresponding reactions of methyl (S)-2-(di-N-Bocamino)-5-oxopentanoate, leading to α-aminoarachidonic acid;[958] development of the β-aldehyde into indolizidine-9-ones;[959] C-glycosylation of a protected L-aspartic β-aldehyde catalysed by SmI_2,[960] selective microbial protease-catalysed hydrolysis of diesters to give ω-methyl, -ethyl, and isopropyl esters;[961] synthesis of 2-amino-4-aryl-4-oxobutanoic acids and higher homologues through condensation with aryl methyl ethers in liquid HF;[962] development of 2-amino-4-oxo-5-phosphonopentanoic acid into the carbon isostere of a N^{β}-glucosyl-L-asparagine;[963] cyclization to homochiral 3-aminopyrrolidines and 3-aminopiperidines.[964] The homochiral azetidinone (129) from L-aspartic acid has been chosen to start a synthesis of xemilofiban through extension of its ester grouping to give ethyl β-ethynyl-β-alaninate,[965] and the N-TBS-relative with an aldehyde function in place of the ester grouping has been used in a synthesis of ADDA derivatives.[966] The β-lactone (130) from L-aspartic acid has been used to alkylate a triazacyclononane to give an amino acid derivative that offers novel opportunities for the synthesis of zinc(II)- and copper(II)-binding peptides.[967]



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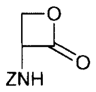

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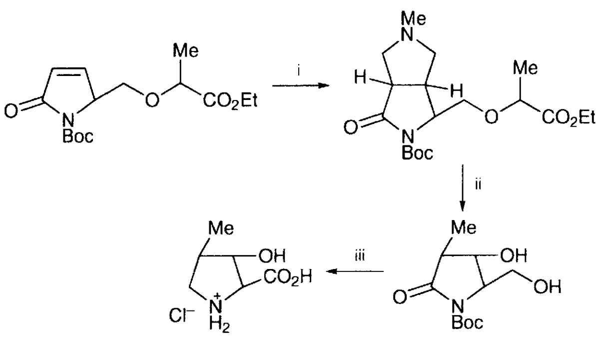
Glutamic acids and their derivatives have been used in Kolbe synthesis of L,L-2,7-diaminosuberic acid,[968] in pyridine synthesis by condensation with alkadienals at 180 °C in aqueous media or in food oils;[969] in Barton radical brominative decarboxylation of α-tert-butyl N-Boc-L-glutamate in syntheses of (2S)- and (2R)-2-amino-4-bromobutanoic acid;[970] in an improved synthesis of (S)-2-amino-5-(aminoxy)pentanoic acid (L-canaline);[971] and in a route to (2R,3R)-3-hydroxyproline.[972]

N-Alkyl-L-pyroglutamic acids have been prepared starting from L-glutamic acid,[973] and amidation of ethyl L- or D-pyroglutamates has been effected with the help of *Candida antarctica* lipase in aqueous media at 60 °C (less than 5 minutes' reaction is needed; at 45 °C the rate for the D-enantiomer is almost unmeasureably slow).[974] Ring cleavage of an N-alkoxycarbonyl pyroglutamate with lithium trimethylsilyldiazomethane provides 6-diazo-5-oxonorleucine.[975]

Uses of L-pyroglutamic acid have been reviewed in the context of the synthesis of amino acids, alkaloids, and antibiotics.[976] New uses for L-pyroglutamic acid include routes to L-α-(3-phenylpropyl)glycine, to L-α-(2-benzyl-3-phenylpropyl)glycine, and *trans*-4-benzyl- and *cis*-5-phenyl-L-prolines.[977] L-Pyroglutaminol continues to develop an independent range of applications, including uses in amino acid synthesis: of the echinocandin constituent



Reagents: i, $MeN^+(O^-)=CH_2$; ii, H_2–$Pd(OH)_2$; iii, functional group development

Scheme 30

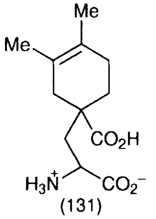
(2S,3S,4S)-3-hydroxy-4-methylproline (Scheme 30);[978] of 3-methoxycarbonylmethyl-4-substituted L-pyroglutamates as conformationally constrained glutamic acid analogues,[979] and (2S,3S)-3-N-(benzylamino)prolinol and (7S,8R)-7-N-(benzylamino)pyrrolizidin-3-one.[980] The corresponding ketone has been rearranged to 2,3-disubstituted piperidines.[981] The lithium enolate of ethyl N-tert-butoxycarbonyl-L-pyroglutamate starts a route to manzamine alkaloids through quenching with ethyl chloroformate.[982]

Alkylation of N-alkoxycarbonyl-L-pyroglutamic acid at C-4 does not invariably lead to the *trans*-stereochemical outcome, but can be encouraged to give pure *cis*-products by judicious choice of reactants and protecting groups;[983] alkylation at C-2 or C-4 is determined by the nature of the N-protecting group, since this determines the site of enolate formation by LiHMDS; the preparation of 2- and 4-indolylmethylglutamic acids provided the results on which this conclusion was based.[984] An alternative approach to *trans*-4-alkenyl glutamic acids and discussion of methods for preparation of stereoisomers has been published.[985] 4-Cyanomethylation of protected L-pyroglutamic acid, ring-opening and recyclization gives epimeric lactams, reduction giving pyrrolidine lysine mimics.[986] 3-Substitution can be accomplished starting with 3,4-dehydropyroglutamates (Ref.169).

(2S)-4-Methyleneglutamic acid is ideally suited to Diels-Alder and 1,4-ionic addition reactions and radical substitution processes, to give side chain-extended homologues (*e.g.* 131).[987]

Higher amino dicarboxylic acids are represented specifically in a review of the cyclization of α-aminoadipic acid to the β-lactam mediated by *Penicillium chrysogenum*,[988] and in the conversion of the hydroxymethyl analogue of this lactam (prepared from L-lysine) into 5-alkyl derivatives.[989]

Reactions at the sulfur atom of the common sulfur-containing amino acids include disulfide formation of protected cysteines, with dimethyl meso-2,3-dimercaptosuccinate,[990] with S-nitrosocysteine,[991] and through photolysis in the presence of a peroxydiphosphate salt (involving a phosphate radical anion).[992] Cystines protected differently at the four functional groups have been prepared using 3-nitropyridinesulfenyl S-activation.[993] Common oxi-



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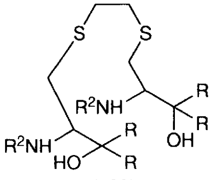

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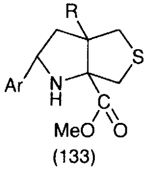

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dizing agents have been assessed for their reactions with DL-cysteine; all modify the thiol grouping but some oxidants cause other changes.[994] S-Alkylation of D- or L-cysteine using bromosuccinic acid enantiomers leading to all four stereoisomers of 2-amino-3-[(1,2-dicarboxyethyl)sulfanyl]propanoic acid has been compared with the alternative route employing mercaptosuccinic acid and 2-amino-3-chloropropanoic acid.[995] S-2,2,2-Trifluoroethylation with the iodonium salt $(CF_3SO_2)_2NI(Ph)CH_2CF_3$[996] can be accomplished in aqueous media. Conventional S-alkylation of N-protected L-cysteine with 1,2-dibromoethane, and Grignard addition leads to C_2-symmetric ligands (132) destined for use in conjunction with metal ions to create novel enantioselective catalysts.[997] S-Alkylation of L-cysteine by Merrifield peptide synthesis resin is the prelude to S-oxidation followed by β-elimination leading to a clean synthesis of dehydroalanine derivatives (see also Ref. 903).[998] The reverse process, nucleophilic addition through sulfur to quinone methides in aqueous media[999] and Michael additions to alkynones,[1000] is also applicable, though more reluctantly, to lysine and serine derivatives.

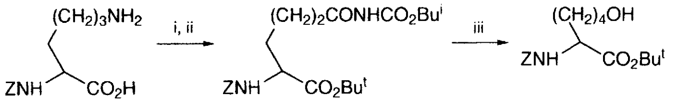
The thiazolidine equivalent of the Garner aldehyde (123; S in place of ring O) has been used in a synthesis of sulfobacins A and B (see also Ref. 179) through aldolization and routine steps.[1001] Ethyl N-formyl-L-cysteinate cyclization by toluene-p-sulfonic acid in boiling toluene gives the (R)-thiazoline-4-carboxylate ester in only 70% e.e.[1002] Cysteine bound through its carboxy group to a resin has been modified at N and S to give a library of thiomorpholin-3-ones after HF cleavage.[1003]

S-Aminoethyl-L-cysteine has been converted through performic acid oxidation into taurine, whereas this reagent gives cysteic acid when applied to cysteine or cystine.[1004] Milder asymmetric S-oxidation of N-Fmoc-S-allyl-L-cysteine [using $Ti(OPr^i)_4$/(−)-diethyl tartrate] gives L-(+)-alliin.[1005] A proposed metabolite of L-histidine catabolism, S-[2-carboxy-1-(1H-imidazol-4-yl)ethyl]-L-cysteine, is a substrate for an enzyme in rat liver homogenate and may have a role in the accumulation of urocanic acid in skin during UV irradiation.[1006] Intramolecular 1,3-cycloaddition of a Schiff base of methyl S-allylcysteinate leads to the bicyclic compound (133).[1007]

L-Methionine shows the standard bivalent sulfur reactions [cyanogen bromide cleavage when bound to peptide synthesis resin, releasing homoserine lactone and adaptable to the generation of a library of analogues;[1008] *Beauveria bassiana* ATCC7159-catalysed oxidation, or H_2O_2 oxidation, of N-phthaloyl-D- or L-methionine to give all four diastereoisomers of the sulfoxide assisted by the ease of separation of the epimers,[1009] and application of H_2O_2 or ozone oxidation for selenoxide formation with DL-selenomethionine;[1010] and conversion of methyl N-Boc-L-methioninate into the [^{18}F]fluoromethyl analogue using XeF_2 with $Bu_4N^{18}F$[1011]] but the *crême brulée* approach (amino acids suffering oxidation by a hydrogen–oxygen flame applied to the surface of an aqueous solution) generates other amino acids in an indiscriminate way (2-aminobutanoic acid, homoserine, and glutamic acid are formed from methionine *via* a side-chain carbon radical intermediate).[1012]

Selective Schiff base formation has been investigated for salicylaldehyde with the diamino acids L-2-amino-3-methylaminopropanoic acid, DL-2,3-diaminopropanoic acid and DL-2,4-diaminobutanoic acid.[1013] Ornithine offers easy access to N^{ω}-alkyl-arginines through reactions with S-alkylisothioureas and iodomethane.[1014] Side-chain tri-alkylsilyl derivatives of N^{α}-Z-arginine react to give the N^{δ},N^{ω}-bis(ethoxycarbonyl) derivative with ethyl chloroformate.[1015]

Lysine studies have mostly concentrated on models for reactions suffered by its side-chain under physiological conditions, but standard nucleophilic reactions of the ε-amino group have also been reported: hydroxy-deamination (Scheme 31),[1016] and side-chain protection (the N-Ddiv group offers improved dimedonyl-type protection[1017]) that is compatible with peptide synthesis protocols. The blue fluorophore (λ_{em} 470 nm) generated between N^{α}-acetyl-L-lysine and 3-deoxyglucosone by condensation of two molecules of each reactant is a furopyrrolopyridinium salt.[1018] A related study of the fluorophores lipofuscin and ceroid formed from N^{α}-acetyl-L-lysine and 4-hydroxy-2-nonenal has identified a sequence of reactions starting from the non-fluorescent 2:1-Michael adduct formed between these reactants, cyclization giving 2-hydroxy-3-imino-1,2-dihydropyrrole.[1019] L-Lysine undergoes N^{ε}-carboxymethylation *via* the Amadori condensation pathway by contact with glyoxal or a reducing sugar (see also Refs. 731, 735);[1020] release of this compound from glycated albumin is greatly accelerated in alkaline media.[1021] Incubation of collagen with glucose under oxidative conditions causes glycation, which eventually leads to the N^{ε}-carboxymethyl-lysine derivative as well as causing oxidative changes to tyrosine (generation of m-tyrosine, dityrosine, DOPA); the hydroperoxides of valine and leucine are also formed.[1022] Protein crosslinking through lysine residues is well-established, a new crosslink involving condensation of N^{ε}-groupings with 4-hydroxy-2-alkenal that is produced by lipid peroxidation.[1023] Malondialdehyde reacts with lysine to give a formyl-substituted dihydropyridine rather than the unstable imidopropene Schiff base previously reported.[1024]

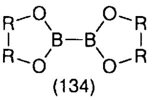


Reagents: i, Bu^iO_2CCl, NaOH, then isobutene, H_2SO_4 (cat.); ii, $NaBrO_3$, RuO_2 (cat.); iii, $NaBH_4$, aq. Pr^iOH

Scheme 31

The phenylglycine family is unique among aromatic α-amino acids in offering an aryl group for transformation into a carboxy group for the synthesis of other α-amino acids, as in a synthesis of (2S,3R)-N-Boc-3-hydroxyglutamic acid[1025] (see also Scheme 13, Ref. 248).

Side-chain substitution of protected phenylalanine leading to fluorinated analogues[1026] and to 4′-borono-L-phenylalanine by palladium-catalysed cross-coupling with the diboronate 134; R-R = Me_2C-CMe_2[1027] has been reported; the N-Boc-protected 4′-borono-L-phenylalanine can be converted into 4-aryl-L-phenylalanines.[1028] The latter example illustrates a relatively rare approach to 4'-substituted L-phenylalanines for which L-tyrosine is the more usual starting point. Examples are: 4′-borono-L-phenylalanine prepared by palladium-catalysed cross-coupling with the diboronate 134; R-R = Ph_2C-CPh_2;[1029]



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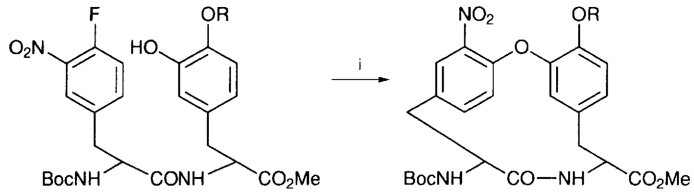
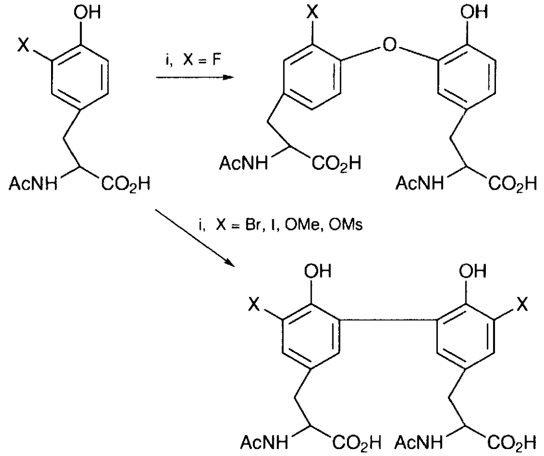
4′-hydroxymethylphenylalanine prepared by palladium-catalysed hydroformylation of methyl O-trifluoromethanesulfonyl-N-Boc-L-tyrosinate followed by $NaBH_4$ reduction;[1030] and a uridinylated analogue FmocPhe[O-P(O)-(OCH_2CH_2CN)(O-uridinyl)OR[1031]]. Photocyclization of dehydronaphthylalanines gives 1,2-dihydrobenzo[f]quinolinones and benzo[f]isoquinoline.[1032]

(R)-4-Hydroxyphenylglycine has been converted through palladium-catalysed substitutions into 4′-phosphonophenyl-, 4′-(tetrazol-5-yl)- and 4′-carboxy-analogues.[1033] Transformations in the aryl moiety of L-tyrosine derivatives, but not at the OH group, include nitration of the $[^2H_4]$-isotopomer to give 3′-nitro-L-$[^2H_3]$tyrosine,[1034] radioiodination (Chloramine-T and $^{128}I_2$),[1035] routes to 4′-(tert-butoxycarbonylmethoxy)-3′-trimethylsilyloxymethoxy-L-phenylalanines and 3′-hydroxy- and -tert-butoxycarbonylmethoxy-analogues,[1036] and more extensive changes to give 3′-aryl-5′-phosphonomethyl-L-phenylalanines.[1037] 3′-Hydroxy- and 3′-nitrotyrosines are employed as starting materials in some of these routes, the former (*i.e.* DOPA) being used also for preparation of 6-$[^{18}F]$fluoroDOPA (by radiofluorodestannylation[1038] and radiofluorodemercuration in a solid phase protocol[1039]). 3′-Nitration and transformation into the 3′-N-acetylamino analogue followed by 6′-nitration and ensuing development leads to 9-substituted 8-membered benzolactams that are important protein kinase C activators.[1040] Intramolecular oxidative coupling of DOPA and 4-fluoro-3-nitrophenylalanine side-chains (Scheme 32)[1041] and mono- and dihalogenated tyrosine using peroxidase (Scheme 33)[1042] has allowed more optimism that current efforts aimed at provision of suitable dityrosines and isodityrosines for syntheses of bastadins 2, 3, and 6 bouvardin will succeed. 4-Hydroxyphenylglycine has been converted into 3,3′-dimers and trimers through treatment with H_2O_2 and horseradish peroxidase.[1043] Simpler oxidative processes with tyrosine itself include the well-known intramolecular attack of the carboxy group on the p-phenolic position,[1044] exploited in synthesis of more complex spirolactams.[1045] DOPA



Reagents: i, NaH, thf

Scheme 32



Reagents: i, horseradish peroxidase, H_2O_2, pH 6.0, then $NaHSO_3$

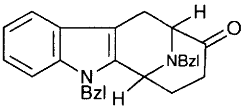
Scheme 33

synthesis is illustrated [hydroxy radicals generated in the iron(II)-EDTA–ascorbic acid cocktail;[1046] horseradish peroxidase-catalysed oxidation enhanced by hydroxycinnamic acid, thus suggesting that tyrosine is substituted *via* its phenoxyl radical[1047]]. Tyrosine partially traps radical intermediates generated in the reaction of peroxynitrite with CO_2.[1048]

Derivatives of tyrosine formed through modification of the phenol group of tyrosine include N-Boc-O-thiophosphono-L-tyrosine[1049] and N-Fmoc-O-(monobenzylphosphono)-L-tyrosine, prepared from its dibenzyl ester.[1050] An arylboronic acid is a suitable reagent for O-arylation of tyrosine and 4-hydroxyphenylglycine;[1051] in the latter case, without the usual problem of racemization. O-Methylation under non-aqueous conditions has been accomplished with dimethyl sulfate and LiOH.[1052] Selectivity in hydrogenolysis of N-benzyloxycarbonyl and nitro-groups on the tyrosine aryl group, leaving O-benzyl in place, can be arranged by having a nitrogen base present.[1053] Reactions of O-(3-pentyl)-tyrosine show that the group offers a new base-resistant side-chain strategy that can be cleaved by HF.[1054]

The mixture of 1- and 3-phosphonylated and 1,3-diphosphonylated histidine derivatives formed by direct reaction was separated by preparative scale chromatography over silica gel.[1055] N^{τ}-Galactosyl-histidine can be reached with the protected glycos-1-yl bromide as reactant.[1056]

Tryptophan reactions are generally well understood, such as Pictet-Spengler condensation with formaldehyde; but two side-products are also formed in this particular process, the N^{in}-hydroxymethylated product and the dimer (two products linked by a CH_2 group through the indole nitrogen atom).[1057] The tetracyclic ketone (135) is easily prepared from methyl D-tryptophanate and starts a synthesis of norsuveoline,[1058] and the hydroxyimidazoindoline ring system of (−)-asperlicin and (−)-asperlicin C has been created from N^{in}-(N-Z-L-leucinyl)-L-tryptophan.[1059] Tryptophan tethered to a solid phase provides the starting point in a synthesis of indolyl diketopiperazine alkaloids,[1060] and conventional solution reactions for a first synthesis of roquefortine D (136) from L-tryptophan and histidine.[1061] δ,δ′-Dimerization through tryptophan side-chains, the result of an acid-catalysed Mannich-type reaction with an aldehyde, can be reversed in ethanolic HCl at 150 °C in the presence of ethanedithiol.[1062] A continuing series of papers (Vol. 30, p. 71) reveals new reaction pathways for N-acylated or N-alkoxycarbonylated tryptophan derivatives; cyclization or dimerization pathways are favoured (Scheme 34), and bi-indoles are formed, depending on the nature of the side-chain nucleophile.[1063] The related process in which a C-terminal tryptophan-containing dipeptide moiety of a longer peptide is cyclized to a dioxopiperazine, is effected by singlet oxygen in the presence of dimethyl sulfide, and is a further example governed by the same principles.[1064] Oxindolylalanine formation following treatment of tryptophan with DMSO with HCl in AcOH has been shown to involve a chlorotryptophan intermediate.[1065]



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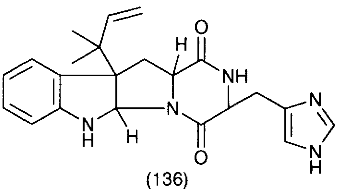

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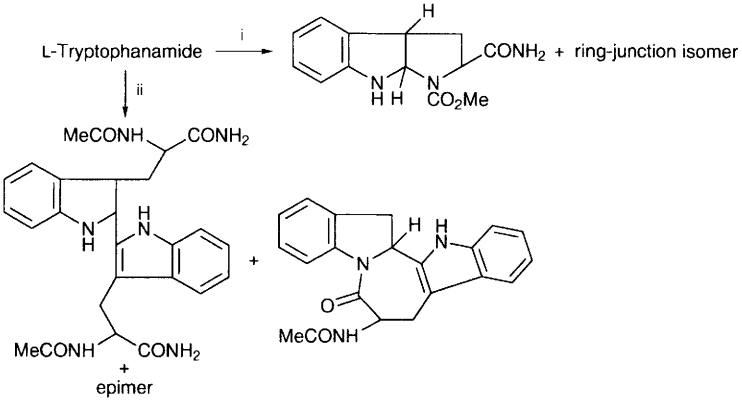


Reagents: i, TFAA, with N^{α}-methoxycarbonyl-L-Trp–NH_2; ii, TFAA, with N^{α}-acetyl-L-Trp–NH_2

Scheme 34

6.4 Effects of Electromagnetic Radiation on Amino Acids – Fluorescence studies centred on tyrosine[1066] and dityrosine[1067] relate the data to molecular rotational dynamics. O-Methyl-β-tyrosine shows substantially different fluorescence features compared with those of tyrosine.[1068] A new approach to interpretation of fluorescence spectra of tyrosine and tryptophan and of other compounds carrying the same chromophores has been reported.[1069] Variations in the steady-state fluorescence of N-acetyl-L-tyrosinamide in the presence of N,N-dimethyl- and N-methyl-acetamide and urea, in four different solvents, imply that the amides are effective in dynamic quenching.[1070] A similar study of the effects of acrylamide and iodides on N-acetyl-L-tryptophanamide fluorescence in propyleneglycol has been carried out,[1071] and a new insight on fluorescence and phosphorescence quenching by oxygen of photoexcited tryptophan in solution is provided by evidence for electron transfer gathered for photoexcitation of the amino acid in the gas phase.[1072] Phosphorescence features of solid tryptophan (λ_{max} 442 nm) differ from those of its 4-, 5-, and 6-fluoro-, and 5-bromo-analogues which show small red and blue shifts.[1073]

5-Hydroxytryptophan fluorescence λ_{max} is insensitive to change of solvent, unlike that of tryptophan or 7-azatryptophan.[1074] Phosphorescence features of 5-hydroxytryptophan have been published.[1075]

Photolysis of proline sensitised by Rose Bengal results in quantitative decarboxylation to give 1-pyrroline.[1076] Similar treatment of N^{α}-acetyltryptophan N′-ethylamide and 5-fluorouracil in water generates the 5-uracilyl cation which gives N^{α}-acetyl-2-(uracil-5-yl)-tryptophan N′-ethylamide and 2-[1-(2-deoxy-β-D-erythro-pentofuranosyl)-uracil-5-yl]-tryptophan N′-ethylamide.[1077] Alanine or glycine photolysed with ascorbic acid and sodium nitrite yields mono-imino- or monohydrasinyl-ascorbyl radicals formed from intermediate Schiff bases.[1078] Curiously, photolysis of phenylalanine with 205 nm right-circularly-polarized light generates alanine; the D:L-ratio is not changed.[1079] Oxidation potentials of carbon-centred radicals formed by photolysis of ethyl cysteinate hydrochloride, dimethyl cystinate dihydrochloride, and N-Boc-proline have been determined.[1080]

Radiation protection afforded by cysteine and its derivatives, and related sulfur compounds, has been reviewed.[1081] Radiolysis and photolysis of amino acids in aqueous media causes the generation of hydroperoxides,[1082] and oxidative degradation accompanying pulse radiolysis of homocysteine thiolactone and its α-methyl homologue is the result of attack by hydrated electrons and hydroxy radicals.[1083] The same species, and hydrogen atoms, are implicated in formation of nitrous oxide and superoxide through pulse radiolysis of aqueous methyl N-acetyltryptophanate, from which the major product is 1-acetyl-2-methoxycarbonyl-3-hydroxy-1,2,3,8,8a-hexahydropyrroloindole.[1084] Pulse radiolysis of ethylenediaminetetraacetic acid gives an N-centred radical cation that slowly rearranges into C-centred radicals.[1085]

Luminescence and resonance Raman scattering[1086] and deamination[1087] of irradiated L-alanine crystals have been investigated, the latter study revealing the formation of a radical, $MeC^{\cdot}HCO_2^-$, that is identical to that formed by pulse radiolysis in aqueous solution. Irradiation of glycine[1088] and threonine[1089] with electrons in the high keV energy region leads to decomposition products that are similar to those seen in radiolysis studies and hot-atom bombardment.

7 Analytical Methods

7.1 Introduction – Several chapters of a recent addition to a standard monograph series are relevant reviews of amino acid analysis methods,[1090] and a review[1091] covers the literature on HPLC and CZE and related methods from 1992. Greater sensitivity that accompanies improved analytical methods requires utmost reliability in sample preparation procedures, and standardization sought for acid hydrolysis of proteins is still not being achieved; for example, microwave heating induces enhanced racemization.[1092] Glycerol added to a protein hydrolysis cocktail leads to under-estimation of aspartic and glutamic acids due to esterification.[1093]

7.2 Gas–Liquid Chromatography – Trimethylsilylation using bis(trimethylsilyl)trifluoroacetamide (Refs. 1092, 1093) is becoming the more widely used derivatization protocol for preparation of samples for GC-MS, including hydrolysates of samples from oil painting binders[1094] and hydroxypipecolic acids from plants (*Inga* species contain eight compounds of this class).[1095] tert-Butyldimethylsilylation offers identification of amino acids in plant leaves at 1–20 ng levels,[1096] and has been used for estimation of ^{2}H-labelled serine and cysteine.[1097]

N-Methoxycarbonyl amino acid esters are also favoured derivatives in recent studies, of [1-^{13}C]valine,[1098] and of pyroglutamic acid.[1099] This last study incorporates a two-column GLC protocol, the second column being a CSP for enantiomer separation prior to MS analysis.

Attomole levels can be assessed for 3-nitrotyrosine after reduction and conversion into the N-heptafluorobutyroyl derivative of its propyl ester,[1100] and N-pentafluoropropionyl analogues of representative amino acids have been employed for enantiomer analysis over L-Chirasil-Val.[1101]

Standard GLC methods for the estimation of homocysteine compare favourably with results of a novel commercial ELISA-based method.[1102]

7.3 Ion-exchange Chromatography – Routine studies using standard amino acid analysis methodology, illustrated for the special case of homocysteine and cysteine in clinical samples,[1103] are not covered. Some standard HPLC analytical protocols employ ion-exchangers as stationary phases, as in the quantitation of glycosylated hydroxylysines as their N-Fmoc derivatives.[1104]

7.4 Thin-layer Chromatography – Advantages of TLC methods still remain clear, for estimation of the enantiomeric purity of ^{14}C and ^{3}H-labelled L-amino acids (as dansyl derivatives with a β-cyclodextrin-containing mobile phase) using reverse isotope dilution analysis,[1105] and for PTH analysis.[1106]

TLC methods for the estimation of lysine, homoserine, and threonine have been reviewed.[1107]

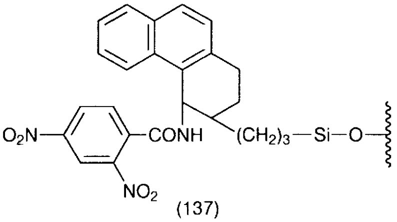
7.5 High-performance Liquid Chromatography – Estimation of components in mixtures of underivatized amino acids separated by HPLC calls for specific structural characteristics in the amino acids to which detectors will respond. These usually rely on UV absorption for aromatic and heteroaromatic compounds (tryptophan and kynurenine,[1108] detection of direct interaction between L-phenylalanine and DNA[1109]) and 3-nitrotyrosine. For the last-mentioned amino acid, of interest for its possible presence in human brain tissue, errors in identification can arise due to other constituents with very similar retention times,[1110] and a new post-column process that is specific for this amino acid, UV photolysis conversion into DOPA, followed by electrochemical detection has been advocated.[1111] Electrochemical detection is already used in HPLC analysis of DOPA-containing samples,[1112] and is also standard practice for homocysteine[1113] and cysteinesulfinic acid and hypotaurine,[1114] and for amino acids in nanolitre samples from brain, as their tert-butyl thiol derivatives.[1115] A special situation allows scintillation counting detection for radiolabelled leucine and phenylalanine.[1116]

The protein crosslinking amino acids that turnover causes to be present in blood and excreted in urine are useful markers of cirrhosis and liver fibrosis (desmosine and hydroxylysylpyridinoline)[1117] and markers of bone formation and resorption[1118] (these include pyridinoline and deoxypyridinoline;[1119] see also Ref. 1191), as well as collagen crosslinks pentosidine and other fluorescent pyridinium-containing amino acids,[1120] have continued to receive special attention.[1121] A notable chemiluminescence detection method for deoxypyridinoline is emerging, and compares well with ELISA.[1122] Carnitine and acylcarnitines are diagnostic markers for inborn errors of fatty acid oxidation, and an HPLC-MS protocol has been developed for their quantitation in physiological samples,[1123,1124] a technique also used to quantitate and identify two side-products in a synthesis of 4′-boronophenylalanine using two different synthesis pathways.[1125] ICP-MS detection for selenium analogues of common amino acids has been demonstrated.[1126]

Amino acids are derivatized prior to HPLC analysis in the majority of cases, to achieve the required sensitivity. The familiar protocols continue to be used; pre-column derivatization using phthaldialdehyde (OPA) with 2-mercaptoethanol (D-phenylalanine in urine,[1127] dimethylated arginines,[1128] and sixteen common amino acids[1129]) or with 3-mercaptopropionic acid (glutamine in rat inestinal mucosa,[1130] representative amino acids,[1131] and histidine using ion-pair HPLC[1132]) remains the most favoured. Results with the OPA–3-mercaptopropionic acid reagent have been compared with those for OPA–N-acetyl-L-cysteine as far as stability of fluorescence of the derivatives are concerned, and both offer reliable quantitation;[1133] the OPA variants work equally well for analysis of aspartic and glutamic acids.[1134] The particular situation for OPA derivatization of N-acetyl-S-ethyl-L-cysteine in urine (after post-column de-acetylation using acylase),[1135] and selenocysteine[1136] and selenomethionine[1137] has been addressed, including, in the last-mentioned study, comparison with the corresponding use of naphthalene-1,2-dialdehyde as reagent (giving more intensely fluorescent derivatives) and β-cyclodextrin as mobile phase additive leading to enantiomer separation.

Fluorescent derivatives are formed using alternative protocols: homocysteine analysis using 7-fluorobenzofurazone-4-sulfonic acid[1138] and an equivalent commercial kit,[1139] 4-fluoro-7-nitro-2,1,3-benzoxadiazole (for analysis of opines),[1140] and new L-proline-substituted members of this class [4-(2-carboxypyrrolidin-1-yl)-7-nitro-2,1,3-benzoxadiazole and its 7-(N,N-dimethylaminosulfonyl) analogue] and the N-methyl-L-alanine relative [4-(N-1-carbethoxethyl-N-methyl)amino-7-nitro-2,1,3-benzoxadiazole and its 7-(N,N-dimethylaminosulfonyl) analogue].[1141] These form diastereoisomeric derivatives with partly racemic samples, to permit the determination of isomer ratios for amino acids with high sensitivity associated with the easily measured fluorescence (λ_{ex} 469 nm; λ_{em} 535 and 569 nm).

N-(2,4-Dinitrophenyl)amino acids (DNP-amino acids) have been used to explore a novel instrumental HPLC technique, toroidal-coil countercurrent flow.[1142] N-Dansyl-DL-amino acids have been resolved using human serum albumin as stationary phase; some benefit is seen in incorporating perchlorate salts in the buffer.[1143] Amino acids carrying standard N-protecting groups (Fmoc, Boc, TFA, Pmc) have been used to test protein-based HPLC stationary phases, including macrocyclic antibiotics.[1144] Synthetic CSPs, *e.g.* silica carrying aromatic substituents as part of a chiral grouping (137),[1145] are also usually tested in the same way, while macrocyclic hosts, a new example being (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid,[1146] have been tried with underivatized amino acids (with poor resolution; though rather better results are achieved with amino acid monoalkylamides). Benzophenone Schiff bases of DL-amino acids can be resolved over [(R,R-Whelk-OI], the L-enantiomer travelling fastest.[1147] Dansylation has been chosen for quantitation of S-methyl-, S-prop-2-enyl- and S-prop-1-enyl-L-cysteine sulfoxides from eight different members of the *Allium* species.[1148] Coloured derivatives formed by dabsylation can be detected at 780 femtomole levels using non-linear laser absorbance detection;[1149] phosphorescence developed by dabsylation of threonine and tyrosine has been assessed for its exploitation in amino acid analysis.[1150] Other conventional fluorophores can be introduced into amino acids using N-(O-succinimidyl)-α-(9-acridine)acetate[1151] or 2-(9-anthryl)ethyl



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chloroformate,[1152] which give tagging groups with fluoresecence characteristics comparable with those of the Fmoc group.

Derivatization through N-phenylthiocarbamoylation by phenyl isothiocyanate seems to require fewer papers to be published on its applications, now that the resulting PTAs have entered routine use for amino acid analysis.[1153] The separation of enantiomers of PTHs formed from PTA-peptides in the Edman sequencing protocol has been accomplished on CSPs to which β-cyclodextrin is bonded;[1154] this requires the use of non-racemizing conditions (BF_3 – HCl/MeOH) for the protocol leading to PTHs. A fluorescence-generating chiral relative, R-(−)-4-(3-isothiocyanatopyrrolidin-1-yl)-7-(N,N-dimethylaminosulfonyl)-2,1,3-benzoxadiazole successfully, amalgamates several of the established fluorophores into one reagent, giving derivatives showing λ_{ex} 460 nm, λ_{em} 550 nm;[1155] the results that are achievable through HPLC of the derivatives were demonstrated for DL-amino acids in yoghourt (11.9% D-glutamic acid, 27.6% D-aspartic acid, and 56.7% D-alanine). The fluorescence-generating reagents (1R,2R)- and (1S,2S)-N-[(2-isothiocyanato)cyclohexyl]-6-methoxy-4-quinolinylamide (λ_{ex} 333 nm, λ_{em} 430 nm) have been introduced for the same purpose.[1156] The classical diastereoisomer-generating Marfey's reagent (1-fluoro-2,4-dinitrophenyl-5-D-leucinamide or the L-enantiomer) has been used in the same way ('advanced Marfey's method') for absolute configurational assignments to amino acids based on elution sequence data[1157] (see also Ref. 578).

Methods for HPLC analysis that are applicable specifically to sulfur and selenium-containing amino acids include bromobimane derivatization of cysteine and homocysteine[1158] and similar fluorophore tagging for a homocysteine assay,[1159] S-pyridinylation of homocysteine,[1160] and S-nitrosation of cysteine and N-acetylcysteine by treatment with excess sodium nitrite.[1161] The nitrosothiols are easily detected, since the chromophore absorbs at 333 nm; or it can be cleaved by a mercury(II) salt, the nitric oxide being trapped with sulfanilamide to give a stable azo-dye.[1162]

7.6 Capillary Zone Electrophoresis (CZE), and Related Analytical Methods – Reviews of capillary electrochromatography [a hybrid of capillary electrophoresis (CE) and HPLC][1163] and chiral CE with respect to its control through inclusion-complexation by chiral selectors[1164] have appeared.

CZE analysis studies of underivatized amino acids include S-[2-carboxy-1-(1-imidazol-4-yl)ethyl]cysteine, a putative histidine metabolite (see Ref. 1006),[1165] cysteine and homocysteine,[1166] and o-, m-, and p-fluoro- and -hydroxy-DL-phenylalanines (by LE-MEKC with copper(II)-4-hydroxy-L-*proline* as chiral selector).[1167]

The range of derivatives that are familiar from HPLC studies are used also in CE analysis. DNP-DL-Amino acids can be analysed rapidly by CZE,[1168] and have been resolved by CZE using cyclic hexapeptides as chiral selectors.[1169] Resolution of dansyl-DL-amino acids, with β-cyclodextrin as chiral selector[1170] and over molecule-imprinted copolymers of vinylpyridine and methacrylic acid,[1171] and dabsyl-amino acids,[1172] are also represented. The last-mentioned study was a test of fibre-optic thermal lens detected that allows working with microlitre volumes, also a feature of the estimation of L-arginine in marine snail neurones at 50 attomole levels after fluoresceamine derivatization.[1173] A mixture of common PTHs can be analysed efficiently through CMEK separation.[1174]

Fluorescent tagging in conjunction with CZE analysis leads to high sensitivity, fluorescamine giving better results than OPA in this respect.[1175] Fluorescein isothiocyanate derivatization of homocysteine generates only modest fluorescence yield in laser-induced fluorescence detection,[1176] a technique used also for quantitation of derivatized glutamic acid and glutamine.[1177] Derivatization with R-(–)-4-(3-isothiocyanatopyrrolidin-1-yl)-7-nitro-2,1,3-benzoxadiazole or its S-(+)-enantiomer permits CZE determination of enantiomer ratios.[1178]

7.7 Other Analytical Methods – Total D-amino acids in plasma can be estimated through treatment of samples with immobilized D-amino acid oxidase followed by measurement of chemiluminescence generated with peroxyoxalate.[1179]

7.8 Assays for Specific Amino Acids – A monograph[1180] and a review of biosensors[1181] cover topics that have provided most of the literature for this Section over the years. Immobilized L-glutamate oxidase and L-glutamate dehydrogenase are at the heart of a novel instrumental configuration for online monitoring of L-glutamic acid production,[1182] a need that has also been met in an independent study leading to a similar biosensor.[1183] Biosensor principles applying to L-glutamic acid and L-glutamine have been outlined,[1184] and two amperometric biosensors responding to L-alanine and pyruvic acid have been developed.[1185] An amperometric biosensor set up for assays of specific L-amino acid can be tuned to discriminate for another L-amino acid through electronic circuit modifications.[1186]

A laboratory version of the chemistry underlying these instruments is seen in an L-glutamic acid assay that employs L-glutamate oxidase and L-glutamic acid–pyruvic acid transaminase leading to α-ketoglutaric acid and H_2O_2, the latter being converted into a chromophoric derivative that is assayed spectrophotometrically.[1187]

An ELISA using monoclonal anti-nitrotyrosine antibodies permitting 3-nitrotyrosine quantitation illustrates another approach to specific amino acid assay.[1188]

Routine colorimetry for cysteine has been used in a novel context, applied after acylase treatment of a cysteine–N-acetylcysteine mixture whose cysteine content was already determined.[1189] The Udenfriend tyrosine fluorimetric assay has been updated,[1190] and chemiluminescence measurements (immunoassay for deoxypyridinoline[1191] and for the DOPA–$KMnO_4$ system[1192]) continue to show valuable characteristics that may lead to robust biosensors and chemical sensors. Fluorescence generated by addition of thiols to maleimides has been related to cysteine concentration.[1193]

Electrochemical detection of nitric oxide released by copper(I)-catalysed homolysis of S-nitrosocysteine employs conventional apparatus that permits quantitative assay of this derivative;[1194] a warning has appeared that nitric oxide microsensors (porphyrinic membranes exploiting oxidative electrochemistry[1195]) respond equally to tyrosine since both species have the same oxidation potential. A graphite paste membrane electrode, used for potentiometric assay of L-proline, has been rendered enantioselective by impregnation with 2-hydroxy-3-trimethylammoniopropyl-β-cyclodextrin.[1196]

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