1
Amino Acids

BY GRAHAM C. BARRETT

1 Introduction

The literature of 1999 is covered in this chapter, which aims to report and appraise newly-published chemistry of the amino acids, with some biological aspects covered to provide clarification of the chemical content of particular studies. A few references deal with literature appearing a little earlier (from late 1998) and also into the early part of 2000.

Literature citations forming the basis for this chapter have been found through *Chemical Abstracts* (Volume 130, Issue no. 11 to Volume 132, Issue no. 9 inclusive), and from searches of major journals that are favoured by authors of relevant material.

Excessive fragmention by authors and lax refereeing is responsible to a significant extent for the ever-increasing number of references for this chapter. This chapter's policy for dealing with papers reporting obvious results, is to group such papers together without detailed comment on any of them. Conference proceedings are not covered in detail and the patent literature is excluded.

As usual, the carboxylic acid grouping is understood to be implied by the term 'amino acid' for the purposes of this chapter, though interest in boron and phosphorus oxyacid analogues, and also in sulfonic acid analogues, is continuing to grow. Methods applicable for the synthesis of α-aminoalkaneboronic acids, α-aminoalkanesulfonic acids, and α-aminoalkanephosphonic acids and other phosphorus oxyacids are usually extensions of standard methods in the amino carboxylic acid field, and representative examples of syntheses of amino oxyacid analogues are mixed in with corresponding methods for amino carboxylic acids in appropriate locations in this chapter.

2 Textbooks and Reviews

Most of the relevant material under this heading is mentioned in later sections of this chapter. The following sources are listed here where more general topics within amino acid science are reviewed.

Textbooks covering amino acids to a significant extent include protein reviews,[1] plant amino acids,[2,3] peptides,[4] and metabolism.[5]

Amino Acids, Peptides and Proteins, Volume 32

Reviews have appeared, of roles for D-aspartic acid in animal tissues,[6] glycine transport systems,[7] biotransformations,[8] PNA,[9] and selenocysteine, the twenty-first coded amino acid.[10] Recommended 1- and 3-letter abbreviations for selenocysteine are U and Sec, respectively[11] (a website, http://www.chem.qmw.ac.uk/iupac/Amino Acid/, is available for all current IUPAC IUB amino acid and peptide nomenclature pronouncements).

Some interesting amino acid papers that do not fall naturally into a section in this chapter are located here. The seventh paper in an idiosyncratic series on orismology (the science of defining words) suggests that the trivial amino acid names have an effect in stimulating research.[12] More important is an unexplained finding that amino acid infusion of a patient during general anaesthesia induces thermogenesis and prevents post-operative hypothermia and shivering, and hospitalization may thereby be shortened.[13]

3 Naturally Occurring Amino Acids

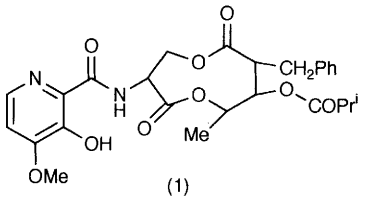
3.1 Occurrence of Known Amino Acids. – This section reports unusual contexts in which known amino acids appear, and these reports can include the most familiar amino acids – glycine as its N-[3-(D-13′-methyltetradecanoyloxy)-15-methylhexadecanoyl] derivative constitutes more than 5% of the lipids of *Cyclobacterium marinus*,[14] and serine appears in UK-2A (1) from *Streptomyces* sp. 517-02.[15] Ethiin (*alias* S-ethyl-L-cysteine sulfoxide) has been found for the first time in alliin.[16] Justiciamide (2), an amide of (2S,4S)-threo-γ-hydroxyglutamic acid found in *Justicia ghiesbreghtiana*, is in the same category of novel derivatives of known amino acids,[17] as is N-acetyl aminomalonic semialdehyde $AcNHCH(CHO)CO_2H$ shown to be the acetyl derivative of the 'lost C_3 fragment' that is a side-product in the biosynthesis of thyroxine (rather than dehydroalanine, as accepted for more than 50 years).[18]

2-Amino-3-cyclopropylbutanoic acid accompanies the known 2-amino-5-chloropent-4-enoic acid in the toxic fungus *Amanita castanopsidis*.[19] (R)-β-DOPA (3) constitutes 2% of the dry weight of the mushroom *Cortinarius violaceus* in the form of its iron(III) complex.[20]

The betaine solorinine (4) previously located in the Canadian lichen *Solorine crocea*, is now shown to be widespread in Pettigeraceae, accompanied in *Pettigera praetextata* by its homologue (NMe_2 instead of NMe_3^+).[21]

Dehydrotryptophan appears in the form of its dioxopiperazine, dipodazine, in *Penicillium dipodomyis* and *Penicillium nalgiovense*.[22] The easy formation of the 2,2′-bi-indole grouping established for the reaction of tryptophan with an aldehyde[23] is seen in the ditryptophan crosslink, a prominent feature of the fascaplysins.[24] Cysteine sulfenic acid occurs in proteins and provides an unusually stable example of this fleeting sulfur functional group.[25]

3.2 New Naturally Occurring Amino Acids. – The claim to have isolated (2,5-dioxo-4-imidazolidinyl)carbamic acid (5) from *Cistanche deserticola Y. C. Ma* requires some reconsideration for the predictable instability of this



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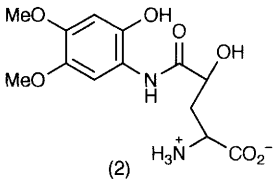

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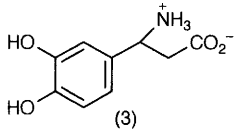

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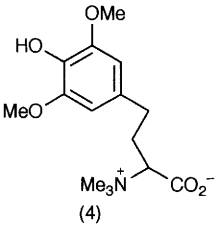

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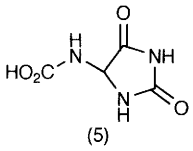

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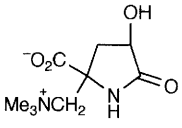

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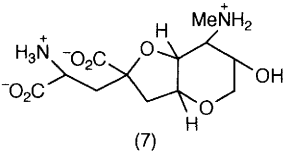

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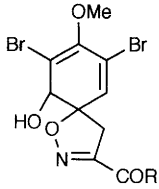

(8) R = $NHCH_2CO(CH_2)_2NHCO_2Me$
(9) R = $NH(CH_2)_2COCH_2NHCO_2Me$

structure (carbamic acids are recognized to be artefacts created during isolation procedures and α-aminoglycine derivatives are easily hydrolysed).[26] Uncertainty should not however surround the claims for dysibetaine (6), a new α,α-disubstituted α-amino acid from the marine sponge *Dysidea herbacea*,[27] and (−)-dysiherbaine (7; see also ref. 268) from the same source.[28] The Caribbean sponge *Plakortis simplex* produces (S)-2-amino-4-ethylpent-4-enoic acid.[29]

Novel bromotyrosine derivatives (8, 9) from the sponge *Aplysina cauliformis* possess cytotoxic properties.[30]

3.3 New Amino Acids from Hydrolysates. – Acylated or amidated versions of new amino acids are covered in this section, whether or not the reported work

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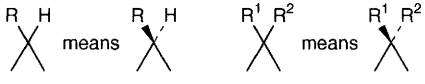
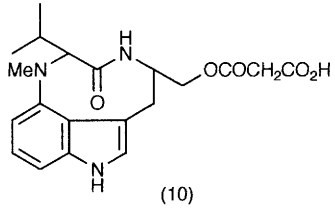
Three-dimensional features of molecules are depicted throughout this Chapter as follows: horizontally-ranged atoms and bonds and ring atoms are to be understood as being in the plane of the paper; substituent atoms and groups attached to these are to be understood to be ABOVE the page if ranged LEFTWARDS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



actually included hydrolysis of the derivatives to the parent compounds. Peptides and depsipeptides are the usual source of these new amino acids, and polyoxypeptins A and B from a *Streptomyces* sp. (which show potent apoptosis-inducing properties) are notable not only in containing (2S,3R)-3-hydroxy-3-methylproline in the former compound, but other unusual amino acids also (3-hydroxyleucine, N-hydroxyvaline, N-hydroxyalanine, piperazic acid, 5- hydroxyhexahydropiperazine-3-carboxylic acid).[31] The cyclic dipeptide (−)-indolactam (10) from *Streptomyces blastmyceticum* has been characterized.[32]

Higher homologous amino acids are well represented. Five ψ-cyclotheonamides (new cyclic peptides from the marine sponge *Theonella swinhoei*), contain α-ketohomoarginine and vinylogous tyrosine moieties, and are effective as serine protease inhibitors.[33] Zelkovamycin from *Streptomyces* sp. 1454-19 is a cyclic peptide containing several unusual features.[34] Aeshynomate (11) is a derivative of a new γ-amino acid from *Aeshynomene indica* L.;[35] calvine (12) with its 2-epimer (13) derives from the ladybird beetle (*Calvia*);[36] and the 11-membered ring (14) is a component of the alga *Sargassum vachellianum*.[37]

Cyclopentenosine (a new trifunctional crosslinking amino acid from elastin hydrolysates) is a cyclopent-2-en-1-one and αβ,γδ-unsaturated aldehyde, and its imine-enamine tautomers and enantiomers, formed from three allysine residues.[38]



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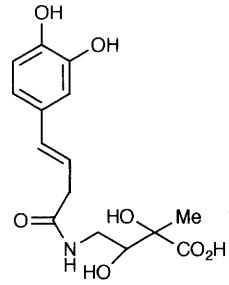

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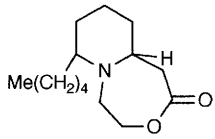
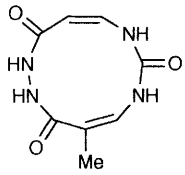


(12)
(13) has the side-chain below the plane of the ring



(14)

4 Chemical Synthesis and Resolution of Amino Acids

Sections 4 and 6.3 of this chapter should be consulted by readers seeking syntheses of particular amino acids, but a considerable degree of cross-referencing has been included to aid searches.

Several reviews of standard syntheses, most of them lacking depth and critical appraisal, have been published: general surveys,[39,40] synthesis of aspartic acid β-semi-aldehyde,[41] uses of β-lactams in syntheses of α- and β-amino acids,[42] synthesis of pipecolic acids and derivatives,[43] synthesis of lipidic amino acids,[44] large-scale synthesis of non-natural amino acids employing enzymes,[45] and syntheses of γ-aminobutyric acid analogues.[46]

Discussion of isotopically-labelled amino acids is distributed throughout this chapter: syntheses of [^{2}H]-,[345,694,847,984] [^{11}C]-,[167,237,374,924] [^{13}C]-,[186,345] [^{15}N]-,[345,353] [^{18}F]-,[236,287,969-972] [^{99m}Tc]-,[932] and [^{128}I]-isotopomers[973] are represented.

Syntheses of phosphorus oxyacids[58,59,71,72,80,142,181,182,218,220,375,407,460,715,721] and sulfur oxyacids[763] are located in sections determined by the underlying functional group chemistry.

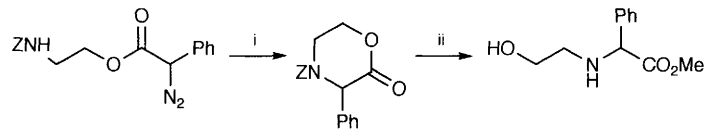
4.1 General Methods for the Synthesis of α-Amino Acids, Including Enantioselective Synthesis. – The various approaches are grouped into conventional categories as in preceding Volumes, and most of the papers are merely listed or given only brief comment where no new methodology is involved.

4.1.1 Amination of Alkanoic Acid Derivatives by Amines and Amine-related Reagents. The standard Gabriel reaction protocol applied to the reaction of fluoroarylamines and methyl α-bromoisovalerate under phase-transfer catalysis conditions yields corresponding N-arylvalines.[47] Another down-to-earth study describes continuous production of glycine from monochloroacetic acid through catalysed ammonolysis.[48] α-Halogeno-α-phenylselenoesters give 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid esters through Lewis acid-catalysed reaction with N-toluene-p-sulfonyl-β-phenylethylamines.[49]

Further examples of aminolysis by benzylamine of α-halogeno-esters $Br(CH_2)_3CHBrCHRCO_2Et$ exploiting kinetic dynamic resolution (Volume 31, p. 7) achieve diastereoisomeric excesses of 98% (and no less than 85%).[50] Reaction of ammonia with chloroform and an aldehyde [$RCHO \rightarrow H_3N^+CHRCO_2^-$] can be guided to favour one enantiomer when β-cyclodextrin is present.[51]

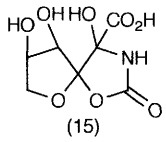
More roundabout, but still simple, amination procedures start with ketones *via* oximes (leading to β-alkoxy-α-amino acids)[52] and insertion of a carbene into an N–H bond (Scheme 1).[53] Diethyl azodicarboxylate as aminating agent for enolates of (S,S)-(+)-pseudoephedrine amides $ArCH_2CONHCHMeCH(OH)Ph$ gives good stereoselectivity.[54]

A review has appeared of amination of silyl enol ethers and glycal derivatives by a nitridomanganese complex.[55] Cyanate as aminating species is featured in conversion of dehydroascorbic acid into (15), an unusual reaction



Reagents: i, $Sc(OTf)_3$, Δ, benzene; ii, H_2–Pd/C, MeOH

Scheme 1



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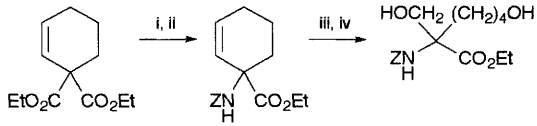
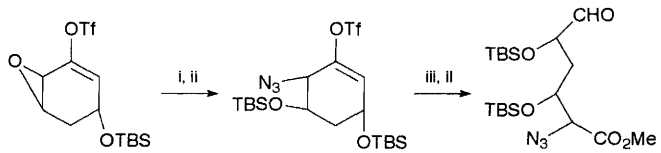


Reagents: i, pig liver esterase; ii, diphenyl phosphoryl azide, NEt_3 then $PhCH_2OH$; iii, O_3/CH_2Cl_2; iv, $NaBH_4$, EtOH

Scheme 2

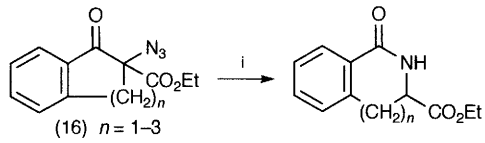
product that releases cyanate when in alkaline solution (this corrects the information in an earlier abstract used to obtain material in Volume 30, p. 5).[56] Prochiral malonates subjected to pig liver esterase-catalysed hydrolysis give half-esters from which an α-hydroxymethyl α-amino acid (*e.g.* the myriocin precursor in Scheme 2) may be obtained using cyanate.[57] Analogous treatment of diisopropyl α-chloroacetoxyphosphonates prepared from aliphatic aldehydes and lipase resolution gives phosphonic acid analogues of coded L-amino acids (valine, leucine, isoleucine, methionine) and α-aminobutyric acid.[58] 1-Amino-2-hydroxypropanephosphonic acid and 1-amino-2-hydroxy-2-phenylethanephosphonic acid have been prepared.[59]

Conversion of methyl α-bromo-esters into corresponding azides *en route* to α-amino acids continues to be a popular approach, radical bromination of carbohydrate C-glycosides giving tetrahydrofuran-based α-amino acids.[60] Preparation of α-azido-esters through epoxide opening (Scheme 3),[61] also applicable to the preparation of α-azidovinyl esters, *e.g.* $Pr^nCH{=}CH(N_3)CO_2Et$ when using diphenyl phosphoroazidate,[62] emphasizes the favoured regioselectivity for the process. α-Azido-β-keto-esters (16 in Scheme 4) undergo Schmidt rearrangement accompanying Bu_3SnH reduction, unusually involving radical intermediates.[63]



Reagents: i, tetramethylguanidinium azide; ii, TBSCl with imidazole; iii, O_3, MeOH then $NaHCO_3$

Scheme 3



(16) $n = 1$–3

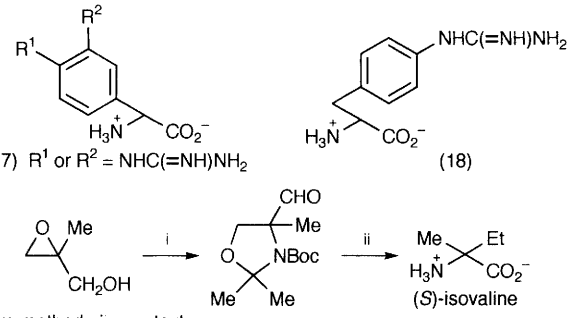
Reagents: i, Bu_3SnH in refluxing benzene

Scheme 4

Asymmetric aminohydroxylation of alkenes gives β-aminoalkanols (*e.g.* the synthesis of the Abbott aminodiol[64]) from which corresponding α-amino acids may be obtained, illustrated in preparations of phenylglycines and phenylalanines (17 and 18 respectively) designed as conformationally restricted L-arginine analogues.[65] The enantioselectivity of the $(DHQ)_2$-AQN aminohydroxylation system is dependent on the structure of the αβ-unsaturated aryl esters which the methodology has been applied.[66] Uses of the reaction have been reviewed.[67]

Aldols from chiral aldehydes and (4-methylphenylthio)nitromethane give oxiranes through oxidation with a metal alkyl peroxide, aminolysis giving α-amino acid thiolesters,[68] also obtainable from N,N-disubstituted 2-amino-alken-2-als $R^1CR^2{=}C(NR^3{}_2)CHO$ through addition of a thiol through an unusual 1,3-shift of the initial 1,2-adduct.[69]

(R)-2-Methylglycidol is the starting point for a synthesis of (S)- and (R)-N-Boc-α-methyl serinal acetonides (Scheme 5), which can be used to prepare (R)-



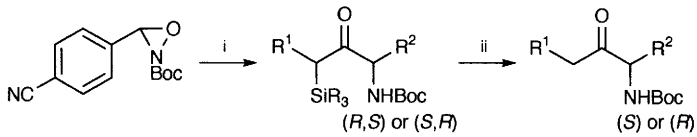
(17) R^1 or R^2 = $NHC(=NH)NH_2$ (18)

(*S*)-isovaline

Reagents: i, literature method; ii, see text

Scheme 5

and (S)-α-methyl-α-amino acids respectively without racemization, through Wittig reaction with $Ph_3P^+Me\ Br^-$ and hydrogenation.[70] Related ring-opening syntheses include conversion of 2-methylaziridine-2-phosphonic acid esters into α-amino-α-methylphosphonic acids (including α-methyl-'phosphono-phenylalanine'),[71] and corresponding use of homochiral N-toluene-p-sulfinylaziridine-2-phosphonates,[72] and reductive opening of homochiral substituted aziridine-2-carboxylates (polymethylhydrosiloxane–Pd/C).[73] A route from β-enamino esters to α-amino-β-esters through reaction with ethyl N-[(4-nitrobenzene-sulfonyl)oxy]carbamate is thought to involve an aziridine intermediate.[74] Conversion of N-Boc-oxaziridines into α-aminoketones proceeds with moderate enantiomeric purity through reaction with α-silyl ketones (Scheme 6).[75]

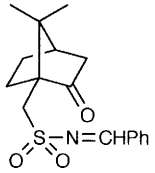


Reagents: i, $R^1CH(SiR_3)COCH_2R^2$, LDA/THF; ii, TBAF, KH_2PO_4, NH_4F, HF/THF

Scheme 6

4.1.2 Carboxylation of Alkylamines and Imines, and Related Methods. Control by the N-protecting group permits (–)-sparteine-catalyzed reaction of $BzlN(SiR_3)CO_2Me$ with EtMeCHLi and carboxylation with CO_2 to give either enantiomer of phenylglycine.[76] Direct asymmetric α-carbalkoxylation of an amine, using an enantiopure carbonate as a chiral CO_2 synthon for ring-opening an achiral zircona-aziridine derived from Cp_2ZrCl_2, exploits the dynamic kinetic resolution principle, and leads to α-amino acid esters in good enantiomeric purity (Volume 29, p. 7).[77]

Reaction of an N-benzylimine with methyl chloroformate gives the corresponding amino acid ester, used for preparation of 9-aminofluorene-9-carboxylic acid[78] and the 4,5-diaza-analogue.[79] Analogous use of a chiral sulfur imine (19 or 20) with a metal phosphite leads to α-amino phosphonic acids.[80] Alkylation at a methylene group adjacent to imine and chiral sulfoxide groupings in $R^1OCH_2C(=NR^2)CH_2S(O)Tol$ offers the opportunity for general α-amino acid synthesis, illustrated for 4-substituted 2-aminoadipic acids.[81]



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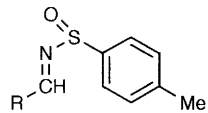
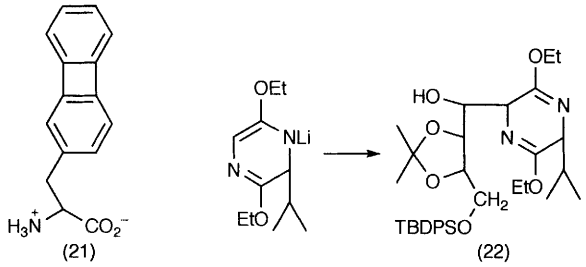


(20)

Alkylation of amines by nitromethane and alkaline permanganate oxidation of the nitromethyl derivative is an indirect carboxylation process that is clearly limited to substrates that can withstand these conditions.[82]

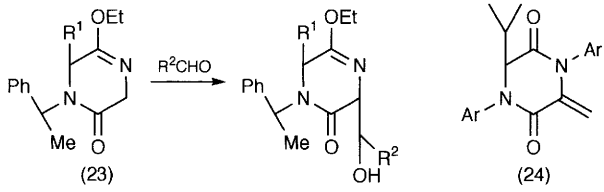
4.1.3 Use of Chiral Synthons in Amino Acid Synthesis. Whereas chiral auxiliaries feature frequently in syntheses of α-amino acids, and are also covered in other sections, some have become identified with routes to amino acids through the names of their creators, and are covered here. Although these synthons are usually glycine derivatives, their use is covered here because papers describing the use of simple glycine derivatives in amino acid synthesis are covered in section 4.1.7.

The standard Schollkopf route employing a cyclized L-valylglycine [an '(R)- or (S)-2-isopropyldiketopiperazine'] or a 3,6-dialkoxy-dihydropiperazine (a 'bislactim ether') derived from it by O-alkylation is illustrated for syntheses of 5-hydroxylysine,[83] 3-(R)- and (S)-carboxyphenyl-(S)-prolines,[84] 2-(3′-alkyl-2′-



(21) (22)

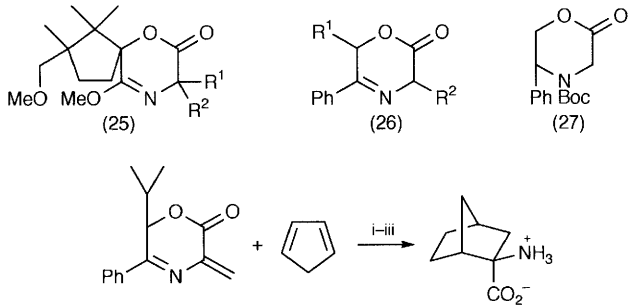
carboxycyclopropyl)glycine,[85] the biphenylene analogue (21) of phenylalanine and its benzocyclobutane analogue,[86] (2S)-2-amino-3-(1H-indol-4-yl) propanoic acid,[87] the β-hydroxy-α-amino acid obtained from (22) using the lithium azaenolate of the bislactim ether, *en route* to 1-deoxygalactostatin,[88] (2S,3R)-β-hydroxy-3′-isopropenyltyrosine,[89] (−)-sparteine-catalysed aldolization of ethyl 3,6-diethoxy-2,5-dihydropyrazine-2-carboxylate in highly enantioselective fashion,[90] use of a 2-(3-trimethylsilylethyn-1-yl) bislactim ether for substituted tryptophan synthesis.[91] Variants of the process are represented in aldolization of the N-[(S)-2-phenylethyl] synthon (23) to give β-hydroxy-α-amino acids[92] and in conjugate addition of organocuprates to the dehydroalanine homologue (3S)-N,N′-bis(p-methoxybenzyl)-3-isopropyl-6-methylenepiperazine-2,5-dione (24).[93] A particularly interesting use of the latter approach establishes moderate to high diastereoselectivity in addition reactions of carbon radical species.[94] The leaving group of the electrophile used in Schollkopf bislactim ether alkylation affects the diastereoselectivity of the process, with diphenyl phosphate best in this context, compared with tosylate and bromide.[95]



(23) (24)

Further interest shown in 6-substituted piperazine-2,3,5-triones has been rewarded with the finding that alkylation by methyl bromoacetate at C-6 accompanies the expected N-alkylation, so opening up a useful synthesis of α,α-disubstituted amino acids.[96]

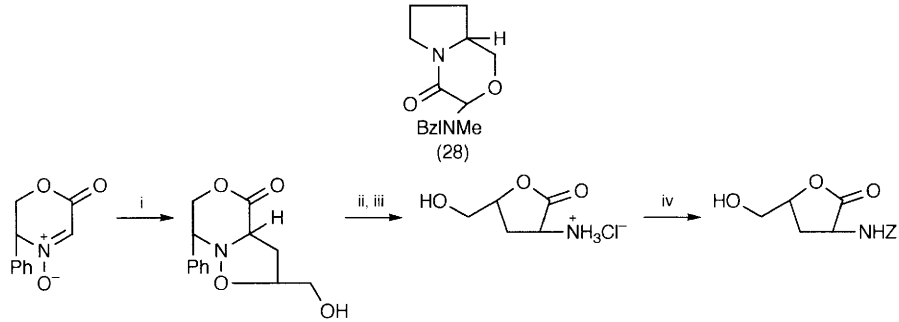
The analogous use of chiral morpholinones continues to develop into novel areas, illustrated with the homochiral synthon (25) used in syntheses of α,α-disubstituted amino acids,[97] and Diels-Alder reactions of a dehydroalanine relative (Scheme 7).[98] (S)-α-Methyl-α-amino acids have been prepared from 3,6-dihydro-2H-1,4-oxazin-2-ones (*i.e.*, 26) through mild phase transfer-catalysed alkylation or allylation.[99] The particular synthon (27) used for preparations of L-[3-^{13}C]phenylalanine and tyrosine (using [α-^{13}C]benzyl bromides made through standard routes from ^{13}CO) is now frequently called Dellaria's oxazinone.[100] L-[α-^{13}C]Aspartic acid has been prepared from the



Reagents: i, MePh, rt for 3h then 2M HCl, H_2–Pd/C; ii, 6M HCl, 150 °C; iii, propylene oxide, EtOH, reflux

Scheme 7

[2-^{13}C]version of this oxazinone (prepared from phenyl [2-^{13}C]bromoacetate and (S)-2-phenylglycinol).[101] The L-proline-derived synthon (28) offers a synthesis of methyl esters of N-methyl-L-α-amino acids through a conventional alkylation and ring cleavage sequence.[102] (R)-5,6-Dihydro-5-phenyl-1,4-oxazin-2-one N-oxide seems to present a useful entry to a clavalanine synthesis intermediate through reaction with allyl alcohol (Scheme 8).[103]

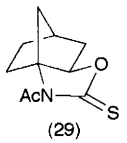


Reagents: i, CH_2=$CHCH_2OH$, $MgBr_2$, $ClCH_2CH_2Cl$; ii, H_2–$Pd(OH)_2$/C; iii, HCl–EtOH; iv, ZCl, aq. $NaHCO_3$

Scheme 8

Oppolzer's camphorsultam is featured in syntheses with glyoxylic acid (ref. 196) and in synthesis of β-amino acids (ref. 427).

Addition of the potassium salt of (R)- or (S)-4-phenyloxazolidin-2-one to monosubstituted nitroalkenes proceeds with good diastereoselectivity.[104] Further applications have been reported for the camphor-derived oxazolinethione (29) that has been advocated for Ti-mediated bromination and aldolization [Ac- → $Pr^iCH(OH)CHBrCO$-] followed by conventional azidolysis and generation of a primary amino group.[105] Extension of the Evans methodology, in which the aldolization step is followed by displacement of the chiral auxiliary to give the corresponding Weinreb amide followed by Mitsunobu inversion, has been illustrated with an efficient synthesis of a D-erythro-β-methylaspartic acid analogue (the 'amino portion' of the β-amino acid ADDA; see ref. 241).[106] A new synthesis of oxazolidin-2-ones uses 1,2-aminoalkanols



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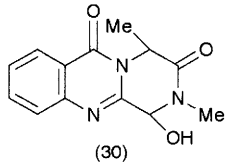
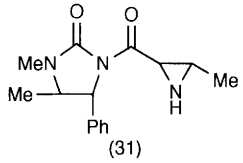


(30)

and electrochemically-generated tetraethylammonium peroxydicarbonate, but yields are modest.[107] Further experience has been reported, of applications of N-acyl-5,5-dimethyloxazolidin-2-ones (42) as chiral synthons.[108,250]

(1S)-1-Hydroxy-(4S)-2,4-dimethyl-2,4-dihydro-(1H)-pyrazino[2,1-*b*]quinazoline-3,6-dione (30) is an effective new chiral electrophilic glycine synthon.[109]

4.1.4 Use of Rearrangements Generating a Carbon–Nitrogen Bond. Ring-expansion of chiral N-(α-aminoacyl)aziridine-2-carboximides (31) in highly regio- and stereoselective fashion gives oxazolines from which threonine dipeptides are obtained by mild hydrolysis.[110] This route has been used to prepare (2R,3S)- and (2S,3R)-β-hydroxyphenylalanine from a corresponding carboximide.[111] Uses of the Schmidt rearrangement (ref. 62) and of the Curtius rearrangement (refs. 391, 430, 455, 459, and 794) are covered elsewhere in this chapter.



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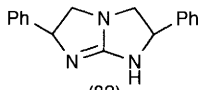
4.1.5 Other Rearrangements. Intramolecular proton transfer after carbonyl group excitation through UV irradiation leads to formation of biradicals from amidoketones. These undergo highly diastereoselective ring closure to give α-amino acids.[112]

4.1.6 Amidocarbonylation and Related Multicomponent Processes. Simple syntheses of particular amino acids are covered later in Section 4.5; marginally less primitive routes are represented by preparations of phenylglycine from benzaldehyde, KOH, NH_4OH, and $CHCl_3$[113] and from glyoxylic acid, MeCN, benzene, acetic anhydride, and H_2SO_4.[114] The former of these studies included β-cyclodextrin in the reagent cocktail but the Abstracts source of this information does not indicate the enantiomeric excess achieved.

Amidocarbonylation, the use of carbon monoxide in conjunction with a nitrile and an aldehyde for the preparation of N-acyl α-amino acids, depends on effective palladium catalysis, and work in Beller's laboratory over many years (Volume 31, p. 13) has achieved good results,[115] an easily-performed Pd/C-catalysed conversion involving a mixture of amide, aldehyde, CO, LiBr, and

1% H_2SO_4.[116] The corresponding preparation of hydantoins by the palladium-catalysed carbonylation of a mixture of an aldehyde and a urea is a new development.[117]

Standard multicomponent approaches are represented in the Strecker synthesis (review, ref. 118) leading from aldehydes to optically-pure α-arylglycines *via* α-aminonitriles when (R)- or (S)-2-amino-2-phenylethanol is used as amine component,[119] and to α-methyl-α-arylglycines from methyl ketones when (R)-phenylglycinol is used.[120] An asymmetric Strecker synthesis of α-substituted and α,γ-disubstituted glutamic acids is based on involvement of (S)-phenylglycinol as esterifying agent for a γ-keto-acid.[121] All four isomers of 1-amino-2-hydroxycyclohexanecarboxylic acid[122] have been prepared analogously using (R)- or (S)-2-phenylethylamine as amine component, leading to 87–98% enantiomeric excesses; a practical observation in this study, that cleavage of a benzyl–nitrogen bond was accomplished by concentrated sulfuric acid, should be worth following up. An asymmetric Strecker synthesis of D-alloisoleucine is based on the easy availability of (S)-2-methyl-1-butanol,[123] and further use of the chiral sulfinimide $TolSONH_2$ (see also ref. 72) has been demonstrated for synthesis of syn- and anti-β-fluoro-α-amino acids.[124] A different approach to the 'asymmetric Strecker synthesis' is the use of a chiral catalyst for mediating the condensation of reactants, exemplified by (32) for the process $PhCH{=}NCHPh_2 \rightarrow PhCH(CN)NHCHPh_2 \rightarrow$ D-phenylglycine,[125] and by a Ti-tripeptide Schiff base complex.[126] Better than 80% yields of aminonitriles with over 99% enantiomeric excess have been achieved in the last-mentioned study. α-Amino aldehydes have been converted into aminonitriles, and these have been proposed for wider use in synthesis as a protected form of their sensitive parents; they can also be put through the standard Strecker reaction to give corresponding α-amino acids.[127]



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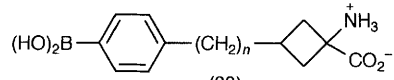
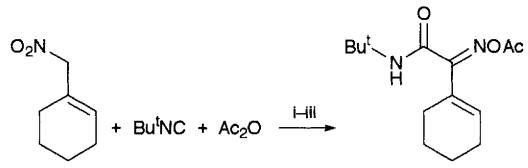


(33)

Synthesis of (33) from the corresponding cyclobutanone illustrates established Bucherer-Bergs methodology.[128] The 'three-component boronic acid Mannich reaction' introduced by Petasis (Volume 31, p. 14), accomplished by mixing an alkenylboronic acid $PhCH{=}CHB(OH)_3$, an amine $BocNHCH_2CH_2NH_2$, and an aldehyde (glyoxylic acid) at room temperature in methanol or dichloromethane, gives $PhCH{=}CHCH(CO_2H)NHCH_2CH_2NH_2$ in 88% yield.[129]

Further development of the Ugi four-component (4CC) condensation is described in synthesis of PNA monomers;[130] in the use of (β-isocyanoethyl) alkyl carbonates $CNCMe_2CHOCO_2R$ so as to lead to N-acyl α-amino acid esters and avoid the troublesome conversion of secondary amide to ester needed in the standard Ugi route;[131] in the use of ethyl glyoxylate,[132] and using an N-Boc-α-amino aldehyde.[133] The first example of a multi-component

condensation using a nitro-compound, an isocyanide and acylating agent (Scheme 9) giving α-oximino-amides, has been reported.[134] An otherwise routine Ugi 4CC uses microwave assistance in an application of solid-phase methodology.[135] An erratum[136] withdraws a claim[137] to have accomplished the first asymmetric Ugi 4CC-synthesis, through use of protected galactosylamine or arabinosylamine and o-isocyanobenzyl alcohol tri n-butylsilyl ether, in view of a prior demonstration by Kunz and Pfrengle (Volume 21, p. 7).

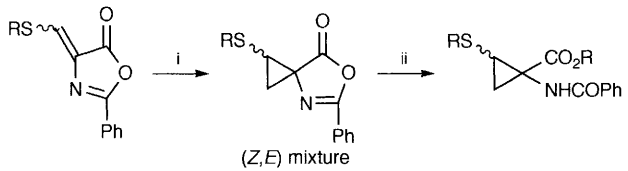


Reagents: i, MePh, NEt_3, 12 h; ii, evaporate; iii, chromatography over SiO_2

Scheme 9

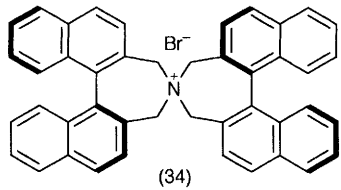
4.1.7 From Glycine Derivatives and from Imines of Glyoxylic Acid Derivatives. Diethyl acetamidomalonate is one of the longest-used glycine synthons, and used in routes to L-azatyrosine (alkylation by 5-hydroxy-2-bromomethylpyridine O-benzenesulfonate, and completed with an enzymic resolution),[138] to aryl-substituted 1,2,3,4-tetrahydroisoquinolin-3-carboxylic acids designed as conformationally restrained phenylalanine analogues (alkylation by α,α-dibromo-4-nitro-o-xylene and routine ensuing steps),[139] and to N-acetyl β-trifluoromethyltryptophan.[140] D- and L-β-(Pyrid-4-yl)alanine have been prepared by this route with resolution through enzymic hydrolysis of the intermediate ethyl 2-acetamido-3-(pyrid-4-yl)propionate.[141]

Equally long in use, the azlactone synthesis employing a 2-substituted oxazol-5(4H)-one as alkylation substrate has served for routes to α-(triphenylphosphanyl)glycine,[142] and 2-alkyl- and 2-arylsulfanyl-1-aminocyclopropanecarboxylic acids (Scheme 10).[143] A standard feature of the azlactone synthesis is the ring-opening step, brought about by simple nucleophiles [ethanolysis of 4-(N,N-dimethylaminomethylidene)oxazolones with NaOEt in EtOH[144]] and continuing efforts are being made to turn this into an enantioselective operation [(−)-cinchonine in MeOH giving (S)-benzoylamino acid methyl esters with 10–33% e.e.,[145] while corresponding preparation of N-benzoylamino acid isopropyl esters using titanium (R,R)-TADDOLates based on the kinetic resolution principle achieves better than 95% e.e. after recrystallization of the products[146]].



Reagents: i, CH_2N_2 (excess), 1–3 h, Et_2O; ii, EtOH, DMAP

Scheme 10



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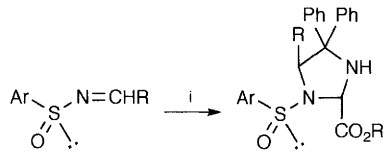
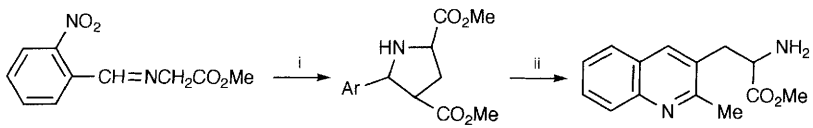
Benzophenone-derived Schiff bases $Ph_2C{=}NCH_2CO_2R$ and N-benzylideneglycines are major contributors to amino acid synthesis and their chiral phase transfer-catalysed alkylation has become one of the most attractive options, especially (−)-cinchonidine-catalysed alkylation of the tert-butyl ester[147] [review ref. 148; work with N-anthracenylmethyl dihydrocinchonidinium bromide (achieving better than 95% e.e.),[149] and similarly enantioselective aldolization;[150] corresponding use of the C_2-symmetric chiral quaternary ammonium salt (34) has been described[151]]. When this procedure is applied to Schiff bases bonded to Wang resin, either enantiomer of the target amino acids can be obtained though e.e. are somewhat modest (51–89%) using cinchonine or tetra-alkylammonium salts of cinchonidine.[152] Amino acid syntheses that do not aspire to enantioselectivity have been described for propargylglycine[153] and its homologues,[154] and dimethylaminomethylidene glycines.[155] Michael addition to acrylates catalyzed by N,N′-bis[(S)-phenylethyl]guanidine leads to no better than 30% e.e.[156] Enolates of these Schiff bases are reactive ambident 1,3-dipoles when O-palladated, participating readily in [2 + 3]cycloaddition reactions leading to proline analogues.[157] Tris(polypyridyl)ruthenium(I) complexes are efficient phase transfer catalysts for alkylation of these glycine Schiff bases.[158] A rhenium tetracarbonyl – glycine ester Schiff base tetrafluoroborate gives an enolate complex after deprotonation, and its substitution behaviour has been explored.[159] Chiral p-tolylsulfinimides yield diastereoisomerically pure N-sulfinyl imidazolidines through cycloaddition to diphenylmethylideneglycine Schiff base enolates (Scheme 11).[160] The equivalent process with o-nitrobenzylideneglycinates is illustrated in a route to β-(quinolin-3-yl)-alanines (Scheme 12).[161]



Reagents: i, $Ph_2C{=}NCH_2CO_2R$ with LDA

Scheme 11

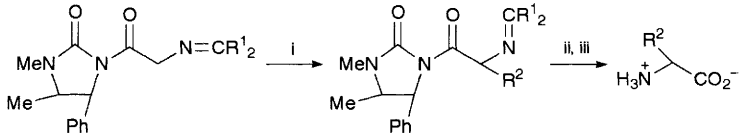


Reagents: i, $MeCOCH{=}CH_2$, DBU, AgOAc in MeCN; ii, H_2–Pd/C

Scheme 12

Alkylation of pyridoxal Schiff bases of amino acid esters, where the pyridoxal grouping carries an ionophoric (Li^+ or Na^+) chiral glyceryl side-chain, shows useful stereoselectivity.[162]

Aza-allyl carbanions formed from N-alkylideneglycinates by lithiation are versatile synthons for the general preparation of α-amino acids,[163] a recent application being the preparation of Z-γ-substituted α,β-dehydroglutamic acids.[164]



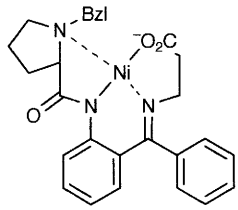
Reagents: i, R^2hal or an acrylic ester/DBU or BEMP; ii, 0·5M HCl then K_2CO_3; iii, LiOH in THF–H_2O then Dowex chromatography

Scheme 13

The alternative approach to asymmetric alkylation of glycine Schiff bases depends on incorporation of a chiral auxiliary, and representative (S)-α-amino acids have been prepared from chiral amides (Scheme 13; R^1 = SMe or Ph)[165] and from (R)-(+)-camphor-based glycine or alanine ester imines (3-bromo-2-fluoropropene as alkylating agent yielding (R)-2-amino-4-fluoropent-4-enoic acid from which 2-amino-4-oxopentanoic acid was obtained by drastic hydrolysis[166]). Preparation of [3-^{11}C]-L-alanine requires a protocol that can be completed within the hour from the moment of generation of [^{11}C]methyl iodide, and benefits from using the well-established glycyl-L-proline Schiff base nickel(II) complex (35).[167] Further results from extensive series of reports of this protocol have been published,[168] and a standard application for the synthesis of (2S,3S)-3-methyl- and 3-trifluoromethyl-pyroglutamic acids[169] and (2S,3S)-3-methyl-3-trifluoromethyl- and (2S,3S,4R)-3-trifluoromethyl-4-methyl-pyroglutamic acids[170] extends the interest of Hruby's group in the synthesis of side-chain methyl homologues of common amino acids. An unusual metallated glycine Schiff base [36; R = H→R = CH(OH)R^1] (see ref. 159) has been used in conventional aldolization followed by mild acid hydrolysis (10% hydrochloric acid) to lead to β-hydroxy-α-amino acids.[171]

N-Acylglycine esters [hippurate esters of *trans*-2-phenylcyclohexanol;[172] N-Boc-, N-Z-, or N-(toluene-p-sulfonyl)glycine tert-butyl esters[173]] must survive deprotonation by a powerful base prior to alkylation, the formation of chelated enolates by use of LiHMDS–$ZnCl_2$ being an effective prelude to allylation in the last-mentioned study, and for alkylation through Michael addition of a chiral alkoxyalkenylcarbene chromium(0) complex in a synthesis of 3-substituted glutamic acids [*e.g.*, 3-(furan-3-yl)-L-glutamic acid from 37; R = (−)-phenylmenthyloxy].[174] R,R-(−)-ψ-Ephedrine-modified glycinamide now has the credential of an *Organic Syntheses* protocol (synthesis of L-allylglycine[175]) and continuing improvements in the use of this synthon, and simplification of the methodology of alkylation, have been established.[176]

α-Heteroatom-substituted glycine derivatives are increasingly popular as



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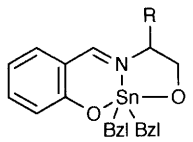

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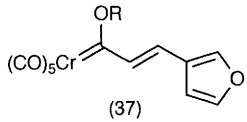

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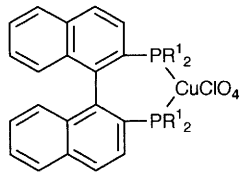

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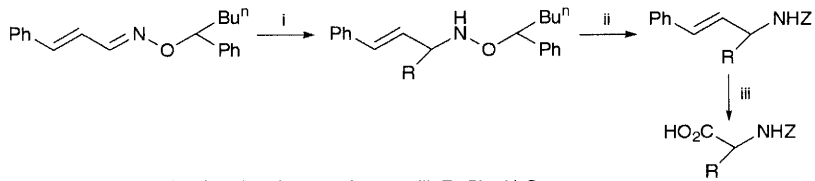
alkylation substrates; protected α-bromoglycine undergoes alkylation with a nitroalkane anion,[177] and asymmetric alkylation of 2-aza-allyl acetates $Ph_2C{=}NCH(OAc)CO_2R$ with a dialkyl sodiomalonate gives 3-carboxy-L-aspartic acid with better than 93% e.e. with a chiral Pd-catalyst or with (S)-BINAP in MeCN.[178] A similarly effective use of the chiral copper(I) Lewis acid complex (38) in mediating the first examples of asymmetric alkylation of α-alkoxyglycinates has been reported,[179] optimization leading to yields in the 73–93% range and e.e. 70–96%.[180] α-Phosphonoglycine derivatives have been used for the preparation from aldehydes of isoquinoline-3-carboxylates[181] and (E)-pyrrolidin-2-ylideneglycinates[182] (see also refs. 142, 218).

More distant glycine relatives are regularly used for the synthesis of α-amino acids, including azidoacetic acid esters (aldolization illustrated with a synthesis of N-Boc-phenylserines[183]) and (R)-o-(1-phenylbutyl)cinnamaldoxime whose benzylidene moiety serves as a latent carboxy group (Scheme 14).[184] α,β-Unsaturated esters prepared from methyl nitroacetate through Knoevenagel



Reagents: i, RM; ii, routine functional group change; iii, $RuCl_3$–HIO_4

Scheme 14

condensation with aldehydes undergo asymmetric conjugate addition with dialkylzinc reagents,[185] and the doubly [^{13}C]-labelled form of the synthon gives labelled amino acids through routine elaboration of this route.[186] Modest diastereoselectivity is shown when carbohydrate-derived 2-nitropropionates are homologated by $S_{RN}1$ reactions.[187] The nitrone $^{-}O\text{-}N^{+}{\equiv}CCO_2Et$ is admittedly a remote glycine synthon but functions as such in a preparation of

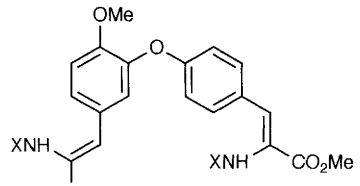
all four stereoisomers of 4-hydroxy-4-methylglutamic acid through cycloaddition to ethyl acrylate followed by *Aspergillus oryzae* protease-catalysed hydrolysis and routine workup.[188] Condensation of cyanoformates $N{\equiv}CCO_2R$ with active methylene compounds has been used in dehydroamino acid synthesis.[189]

Glyoxylic acid and its derivatives give α-carboxyimines $R^1N{=}CR^2CO_2R^3$ that have become increasingly used in α-amino acid synthesis. The usual protocol is *in situ* generation of the imine or the related iminium salt, as in the synthesis of α-aryl-α-amino acid esters from a primary amine, glyoxylate ester, and 1H-benzotriazole,[190] (R)-(−)-thiazolidine-2-carboxylic acid from cysteamine and glyoxylic acid with (2R,3R)-tartaric acid,[191] and similar involvement of a nitroalkane to give β-nitro-α-amino acids.[192] Radical additions to glyoxylate imines have given fascinating results, being effected by O_2–Et_2Zn[193] or Et_3B–RI (to glyoxylic oxime ethers $BzlON{=}CHCO_2Me$ formed from methyl 2-hydroxy-2-methoxyacetate, the hemiacetal of methyl glyoxylate, and benzyloxyamine,[194] also carried out on oxime ethers anchored to a solid phase[195]). Zinc-mediated asymmetric addition of allylic halides to the camphorsultam derivative of glyoxylic acid O-benzyl oxime gives L-azetidine-2-carboxylic acid and its (3R)-phenyl-, naphthyl-, and isopropyl homologues.[196] An alternative use of a standard chiral synthon is seen in a stereoselective Mannich-type reaction of the N-(benzyloxyacetyl)-derivative of the Evans oxazolidinone to $CF_3C(=NZ)CO_2Et$, to give predominantly (91%) the anti-adduct *en route* to D-erythro-β-hydroxy-α-trifluoromethylaspartic acid.[197]

Further results (Volume 31, p. 16) on the ene reaction catalyzed by chiral copper(I) complexes ($CuPF_6$-BINAP) of N-toluene-p-sulfonylimines of glyoxylates with alkenes[198] or allylstannanes[199] have been published, and the asymmetric version of this catalytic aminoalkylation procedure has been reviewed.[200] Furfural can be considered to be a latent form of glyoxylic acid, and the imine formed with (S)-valinol, protected as the O-trimethylsilyl ether, readily undergoes alkylation by organometallic species, the target N-protected amino acid being released by oxidation of the furyl moiety to the carboxy group.[201]

4.1.8 From Dehydro-amino Acid Derivatives. Progress towards effective procedures for the asymmetric hydrogenation of 'α,β-dehydro-α-amino acids', *alias* 2-aminoacrylic acid homologues $R^1R^2C{=}C(NHR^3)CO_2R^4$, continues to depend on catalyst design. Very low enantiomeric excesses result from heterogeneous-catalysed hydrogenation of aminocinnamic acid derivatives in the presence of (−)-cinchonidine or another alkaloid,[202] and for a homochiral bicycloheptanediol-derived phosphine,[203] while 99.9% e.e. has been claimed for a homogeneous-catalysed version of the procedure using protected dehydro-α-amino acids with a water-soluble chiral biphosphinite ligand;[204] a parallel claim for this first water-soluble ligand has appeared, demonstrating a similar performance.[205] Rhodium catalysts carrying a ferrocenyl diaminophosphine ligand,[206] recently-reported rhodium phosphinite complexes,[207] 1,2,5,6-di-isopropylidene-3,4-bis(diphenylphosphino)-D-mannitol[208] and a

closely similar ligand,[209] give almost the same result as does Rh-1,2,5-triphenylphospholane,[210] and 1,2-bis(isopropylmethylphosphino)benzene,[211] while a poly(acrylic acid) supported rhodium(I)/phosphine-catalysed hydrogenation of acetamidocinnamic acid achieves 89% e.e.[212] As in earlier years, there are numerous routine reports on this topic, either repeating existing knowledge or providing modest new results (a new tridentate phosphine ligand gives no better than 70% e.e.[213]). Particular L-amino acids that have been prepared in this way include β-branched allylglycines,[214] thienyl and furyl analogues of phenylalanine,[215] isodityrosines from (39),[216] (S)-2-quinolinylalanine,[217] and bis(glycine)s from (40).[218]



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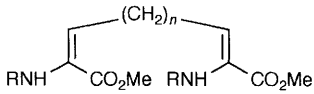

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Dehydro-β-acetamidoalkanols and near relatives give similar results in standard asymmetric hydrogenation protocols.[219]

Enamidophosphonates $AcNHC(=CH_2)P(O)(OMe)_2$ have been investigated as substrates for homogeneous asymmetric hydrogenation, with preliminary results suggesting that phosphorus oxyacids will generally follow the pattern of their carbon analogues as would be expected.[220]

The equivalent asymmetric alkylation through conjugate addition of a Grignard reagent or organocuprate to (S)-2-acetamidoacrylic acid ethoxycarbonyl phenylmethyl ester has been thoroughly investigated.[221] Addition of pyrrole or indole to a chiral 3-alkylidene-dioxopiperazine catalysed by HBr is a useful route to 2-alkyl-tryptophans and pyrrol-2-yl analogues but is troubled by C=C migration,[222] and radical addition (alkylmercury chloride/$NaBH_4$) to polymer-supported 2-acetamidoacrylic acid gives modest yields (49–60%).[223]

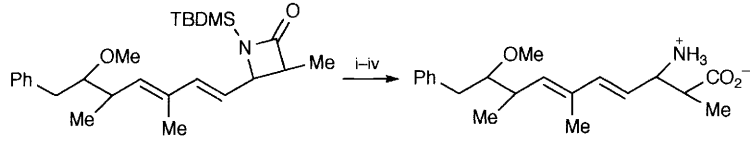
4.2 Synthesis of Protein Amino Acids and other Well-known Naturally Occurring Amino Acids. – The synthesis of coded α-amino acids as targets for trying out new or modified general protocols has been illustrated in the preceding section, and the use of readily available α-amino acids for the synthesis of other amino acids is covered in Section 6.3.Thus, this Section is restricted to (*a*) biotechnological production of coded α-amino acids, and (*b*) synthesis of unusual α-amino acids.

Reviews have appeared covering fermentative production of coded α-amino acids,[224] L-alanine,[225] L-lysine,[226] L-threonine,[227] and D-amino acids,[228] enzymic production of L-threonine and L-allothreonine from 3-substituted 2-oxobutanoic acids using leucine dehydrogenase,[229] D-phenylalanine and D-tyrosine, also from corresponding α-keto acids but by a more roundabout route (glutamate racemase, D-amino acid transferase, glutamate dehydro-

genase, formate dehydrogenase),[230] and L-2-aminobutanoic acid (transamination from threonine or aspartic acid to 2-oxobutanoic acid by recombinant *E. coli* K12).[231] A preparation of (2S,4R)-4-propylglutamic acid from the α-keto acid is efficiently mediated by glutamic oxalacetic transaminase.[232]

Aliphatic coded α-amino acids have featured in several studies, L-isoleucine being produced from *E. coli* engineered to carry a modified threonine deaminase,[233] and similarly from strains of *Corynebacterium glutamicum*.[234] Tyrosine-specific enzymes have been involved in commercial production of L-DOPA (tyrosine phenol-lyase),[235] and 6-[^{18}F]fluoro-L-DOPA (β-tyrosinase with 4-[^{18}F]fluorocatechol and pyruvic acid).[236] The special requirement of rapid reactions is accommodated in preparations of L-[β-^{11}C]-L-DOPA and L-[β-^{11}C]-5-hydroxytryptophan from L-[β-^{11}C]-DL-alanine catalysed by immobilized L-alanine racemase, D-amino acid oxidase, and β-tyrosinase or β-tryptophanase.[237]

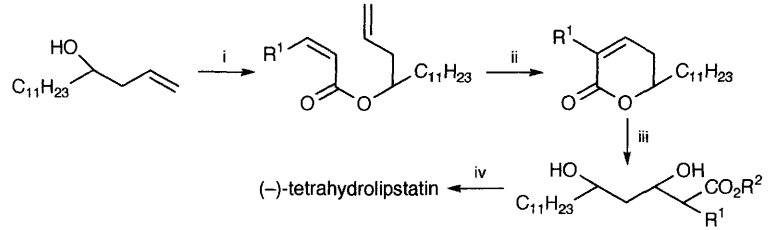
Bacterial hydantoinases and carbamoylases are establishing a prominent role in large scale amino acid production;[238] immobilized *Pseudomonas putida* has been applied for production of D-5-(p-hydroxyphenyl)hydantoin,[239] and recombinant *E. coli* D-hydantoinase can be used to give N-carbamoyl D-(4-hydroxyphenyl)glycine.[240]



Reagents: i, KF, MeOH; ii, Boc_2O; iii, LiOH then HCl, EtOAc; iv, $NH_4^+HCO_2^-$

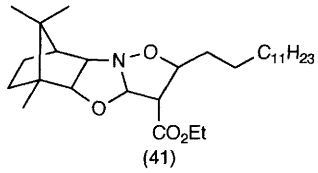
Scheme 15

The more exotic natural amino acids continue to attract novel synthesis methodology, applied to the β-amino acid ADDA (Scheme 15; see also ref. 106),[241] D,L-hypoglycine A [α-amino-β-(methylenecyclopropyl)propionic acid, through ^{i}PrMgBr/Ti(O^iPr)$_4$-mediated addition of ethyl acetate to vinylacetaldehyde diethyl acetal, followed by amination];[242] D,L-coronamic and norcoronamic acids from (E)-methanohomoserine, from which the (1S,2R)-form and allonorcoronamic acids were obtained, though in modest yields;[243] enantiopure aminopolyols and polyoxamic acid derivatives through ring-opening of ethyl *cis*- and *trans*-3-(1′,3′-dioxolan-4′-yl)aziridine-2-carboxylates;[244] (+)-polyoxins J and L from 4-O-tert-butyldiphenylsilyl-2,3-isopropylidene-L-threose [vinylmagnesium bromide followed by Ac_2O/py giving the crucial protected substrate $ROCH_2CH(OPG)CH(OPG)CH(OAc)CH{=}CH_2$ for azidolysis and routine elaboration[245]]; (−)-tetrahydrolipstatin (an N-formyl-L-leucine ester) through olefin metathesis of an acrylate ester (Scheme 16;[246] a differently-conceived synthesis has been reported[247]), and through a [2 + 3]nitrone cycloaddition leading to intermediate (41);[248] the cyclosporin constituent 'MeBmt' [(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-methylamino-oct-6-enoic acid] from a chiral auxiliary acylated by a 2,2-dichlorohex-4-enoyl moiety, treated with Et_3B–$(Me_3Si)_3SiH$,[249] an approach used also with the newly-introduced



Reagents: i, $R^1CH{=}CHCOCl$, Et_3N, DMAP; ii, $(PCy_3)_2Cl_2Ru{=}CHPh$, $Ti(OPr^i)_4$; iii, H_2O_2–NaOH then $(PhSe)_2$, $NaBH_4$; iv, β-lactone formation, coupling with Z–L–Leu–OH, exchange Z for formyl

Scheme 16



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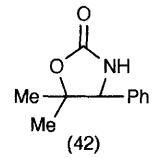

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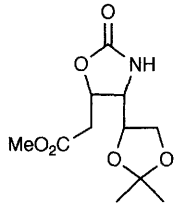

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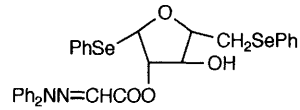

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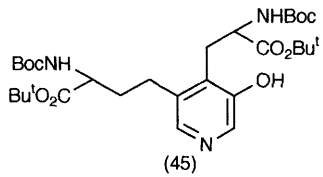
equivalent Evans-type chiral auxiliary (42) from D-phenylglycine, N-acylated with but-2-enoic acid followed by introduction of the n-heptyl group in excellent e.e. *en route* to aplysillamide B (see also ref. 108).[250] All these amino acids have been synthesis targets in recent years, as have (−)-detoxinine [newly synthesized from L-ascorbic acid *via* (43)[251]], and (+)-furanomycin [prepared from L-xylose, with radical cyclization of (44) as a key step[252]].

Recognition of the importance of polyfunctional protein crosslinks (+)-pyridinoline and its deoxy homologue has stimulated further exploration of routes for their synthesis (see Volume 30, p. 30), from Boc-L-glutamic acid α-tert-butyl ester *via* tert-butyl (2S)-2-(Boc-amino)-4-(2-oxiranyl)butanoate,[253] *via* (45),[254] or from tert-butyl (2S)-2-(Boc-amino)-6-aminohexanoate.[255] A route to the 3-hydroxypyridinium salt, (+)-deoxypyridinoline, starts from the pyridine (46) that is conveniently obtained from Vitamin B_6;[256] an alternative



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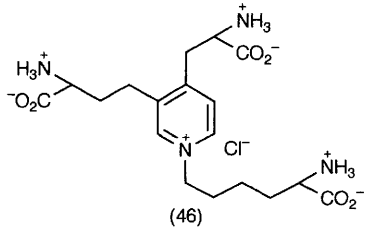
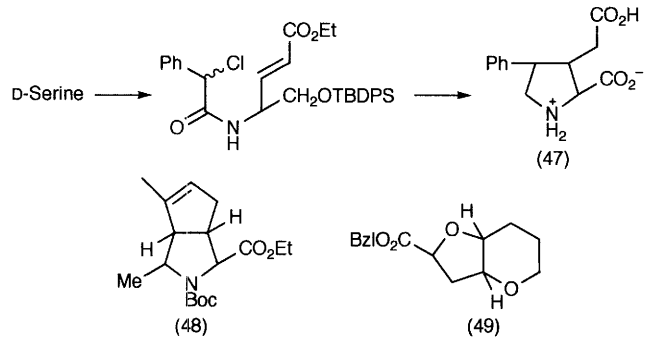


(46)

biomimetic synthesis uses protected L-lysine and L-glutamic acid.[257] A synthesis of the pyridinium crosslink, pentosidine, from tert-butyl (2S)-2-(Boc-amino)-6-iodohexanoate and an N^{δ}-(imidazopyridyl)ornithine, has been described (see ref. 939).[258]

Further kainoid synthesis routes have been established (for a review see ref. 259), mostly continuing to address the main problems of setting up appropriate stereochemical parameters of the three substituents on the tetrahydropyrrole framework in an ever more efficient manner. (−)-α-Kainic acid arises from titanium-mediated diene metallabicyclization of $PhOCH_2CR^1{=}CHCH_2NBzl\text{-}CHR^2CH{=}CH_2$ (prepared from an L-serine-derived aldehyde; see Section 6.3),[260] and from L-pyroglutamic acid *via* ketyl radical cyclization on to an enecarbamate so as to deliver the C-4 substituent.[261] D-Serine provides a starting point for a synthesis of phenyl allokainoid (47) employing a radical cyclization,[262] and addition of 3-trimethylsilylcyclopentene and to a phenylaziridine ensures correct relative stereochemistry in a synthesis of racemic phenylkainic acid.[263] A related route from L-pyroglutamic acid to 5α- and 5β-substituted kainic acids involves stereoselective nucleophilic substitution of the N-acyliminium ion of (48) by organocopper reagents.[264]



(+)-α-alloKainic acid has featured as the target in routes from a D-serine-derived alkynylenone, reaction with Et_3Al being followed by palladium-catalysed allylic carbonate reductive transposition,[265] and from L-serine by $Rh_2(OAc)_4$-catalysed CH insertion of an α-diazoacetamide tethered to (S)-4-(buten-3-yl)-2,2-dimethyl-1,3-oxazolidine.[266]

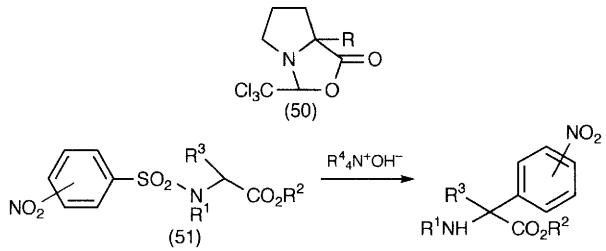
4-Arylkainic acids can be obtained by a highly stereoselective Michael addition reaction of dimethyl 2-oxoglutarate with a nitrostyrene, followed by reduction of the nitro-group, deoxygenation, and epimerization.[267]

Analogues of the neuroexcitatory amino acid dysiherbaine (7), lacking hydroxy and N-methyl groups, have been synthesized from the Garner aldehyde and the lithium enolate of ester (49).[268]

4.3 Synthesis of α-Alkyl α-Amino Acids – The particular interest in α-methyl analogues of the coded L-amino acids has extended to more general types of structure under this heading (see also refs. 96, 99). The classical synthesis

routes (hydantoin and Bucherer-Bergs syntheses) have given good service for preparing racemic forms of these derivatives. These methods are less successful for the preparation of enantioselective modifications of α-alkyl α-amino acids, and uses of modifications of the chiral synthons and chiral auxiliaries that have already been covered in this chapter (Section 4.1.3) provide the main strategy. Alkylation of chiral 1,4-benzodiazepin-2,5-diones formed from N-methylisatoic anhydride and (S)-phenylethylamine,[269] benzylation of Schiff bases of alanine esters catalysed by (R)-2-hydroxy-2′-amino-1,1′-binaphthyl (up to 68% e.e.)[270] or by sodium (R,R)-TADDOLate.[271]

Alkylation of α-amino acid derivatives provides a more direct route to α-alkyl homologues, but usually requires substantial activation of the α-carbon [homologation of 2-(trichloromethyl)oxazolidinone (50; R=H→R = alkyl)];[272] or other special characteristics as with N-alkyl N-(o- or p-nitrophenyl)sulfonyl-amino acid esters (51) which undergo intramolecular arylation through a N–C rearrangement, though not the Stevens-type route previously assigned to the process.[273] The lithium enolate of methyl N-Boc-O-TBDPS-hydroxyprolinate undergoes alkylation by an alkyl halide in good yield only when excess HMPA is used (10 eq.), and stereoselectivity depends on the reagent and the N-protecting group.[274] S_N1 Nucleophilic cleavage of cyclic sulfamidates derived from an α-alkyl serine should be a versatile new general approach to α-alkyl-α-amino acids.[275]



4.4 Synthesis of α-Amino Acids Carrying Alkyl Side-chains, and Cyclic Analogues. – The synthesis of 'non-natural α-amino acids', most of which are designed either for their potential physiological activity or for use in peptide synthesis, is covered in this section if general synthesis methods are used for their preparation. Examples synthesized from readily available amino acids are mostly covered later in Section 6.3.

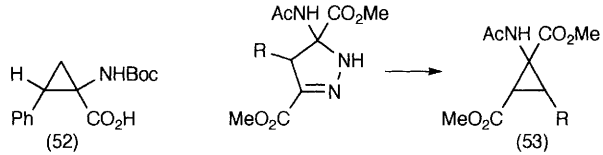
The long-running interest in amino acids with side-chains carrying a cycloalkyl moiety is based on their potential as conformationally-constrained versions of physiologically-active amino acids. Of the many options available, cyclopropyl analogues of coded α-amino acids continue to attract attention. These compounds have their own trivial names ['2,3-methanophenylalanines' (52) and three stereoisomers, have been prepared by well-established routes and separated by chromatography over polysaccharide-derived chiral stationary phases[276]].

Conformationally-constrained analogues of phenylalanine, tyrosine, trypto-

phan, and histidine have been reviewed.[277] The (1S,2S)-cyclopropane precursors of these compounds have been prepared by palladium(0)-catalysed alkylation and S_N1 cyclization of 1,4-dichlorobut-2-ene using deprotonated α-substituted alkanenitriles, d.e.s from 88–100% having been achieved.[278] A traditional route has been developed to constrained aspartic acids (53), involving ring-contraction of 4,5-dihydro-1H-pyrazoles in boiling DMF with loss of N_2,[279] and another familar concept is represented in $KOBu^t$ mediated cyclization of substituted β-chloroethyl aminoacetonitriles, *e.g.* $ClCH_2CMe_2CH(NH_2)CN$.[280] Routes such as that to (+)-R-1-amino-2,2-difluorocyclopropane-1-carboxylic acid through cyclopropanation of $CH_2{=}C(CH_2OAc)_2$ and lipase-catalysed desymmetrization, and routine ensuing steps, involve good stereochemical control.[281]

Homologous cyclopropylglycines ['3,4-methanophenylalanines' – (54) and near relatives] are also of considerable interest as mimetics of natural neuroactive amino acids, (2R,1′S,2′R,3′S)-2-(2′-carboxy-3′-phenylcyclopropyl)glycine being a potent antagonist for the metabotropic glutamate receptor,[282] synthesized by standard methods such as that leading to (2R,1′R,2′R,3′R)-2-(2′,3′-dicarboxycyclopropyl)glycine [reaction of ethyl (dimethylsulfuranylidene) acetate with (55) prepared from (S)-glyceraldehyde].[283]

Azaspiropentanecarboxamides (56) prepared from methyl 2-chloro-2-cyclopropylidene acetate and a primary amine followed by $NaH–NEt_3$ cyclization,[284] and racemic bicyclopropylidenyl- and methylenespiropentyl-substituted alanines prepared from the corresponding substituted methanols (with I_2) as alkylating agents towards ethyl N-benzylideneglycine,[285] represent a novel alternative type of peptide mimetic.



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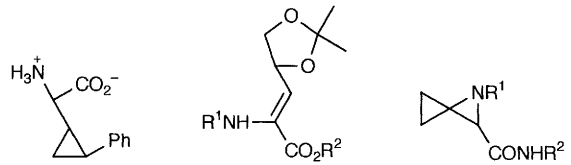
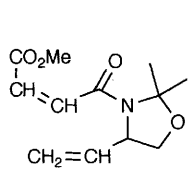


(54) (55) (56)

(2S,1′R,2′S,3′S)-2-(2′,3′-Dicarboxycyclobutyl)glycine and its (2S,1′R,2′R,3′S)-isomer have been prepared from 3-azabicyclo[3.1.1]heptan-2-ones that result from intramolecular photocycloaddition of (57).[286] Simpler cyclobutanes, 1-amino-3-fluorocyclobutane-1-carboxylic acid and its [^{18}F] isotopomer have been prepared for brain tumour imaging through positron emission tomography.[287]

Novel bicyclic glutamic acid analogues (58) and (59) have been prepared from cyclohexane-1,4-dicarboxylic acids through conventional alicylic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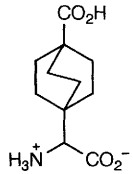
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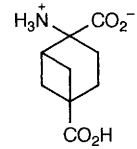
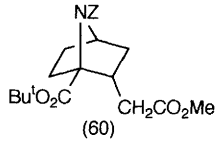

(59)

methodology and use of the Corey-Link amino acid synthesis [$CO_2Me \rightarrow CHO \rightarrow CH(OH)CCl_3 \rightarrow CH(NH_3^+)CO_2^-$].[288] Substituted 1-amino-2-hydroxycyclohexane-1-carboxylic acids are accessible from 4-chloromethyleneoxazol-5(4H)-ones through $EtAlCl_2$-mediated cycloaddition to butadienes followed by replacement of Cl by OH.[289]

Synthesis of new proline analogues, a prominent interest over the years because of the importance of post-translationally modified natural products, and of excitatory amino acids (kainoids and related compounds), continues with 1-amino-(2R,4R)-4-aminopyrrolidine-2,4-dicarboxylic acid,[290] other 4-substituted prolines [from (R)-BocNHCH(CH_2OH)$CHSO_2Ph$ with (2R)-2,3-isopropylideneglyceraldehyde;[291] 3-substituted prolines by $ZnBr_2$ cyclization of enolates of alkyl N-but-3-enyl-N-(S)-phenylethylglycinates[292]], (2S,3R,4R)-3,4-dihydroxyproline[293] and diastereoisomers prepared through lengthy routes from D-ribonolactone[294] and from D-gulonolactone.[295] Numerous bicyclic prolines have been prepared by conventional cycloaddition processes: the glutamic acid analogue (60) *via* the pyrrolidine (61) from L-serine,[296] (−)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid and the 2-thia-analogue as potent Group II metabotropic glutamate receptor agonists,[297] azabicycloheptanes [(62) and its enantiomer],[298] intramolecular aziridine–allylsilane cyclization to give (63),[299] [3+2]cycloaddition of (−)-8-phenylmenthol-derived Fischer carbene complexes with diazomethane derivatives to give Δ^2-pyrazolinecarbenes as precursors (64) to 5-azaprolines,[300] $TiCl_4$-mediated addition of 3-vinylindoles to the iminium ion precursor $MeOCH_2N(CO_2Et)CH(CO_2Et)_2$ giving 3-indolylprolines,[301] and the spiro-diamino acid (65), useful as a template for combinatorial chemistry.[302] Competitive intramolecular substitution occurring in a route to a cyclopropylglycine gives the bicyclic proline [(66) in Scheme 17] as side-product.[303]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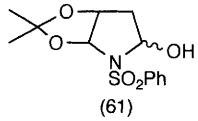
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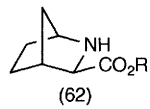
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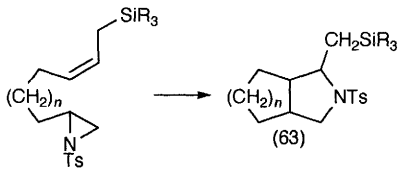
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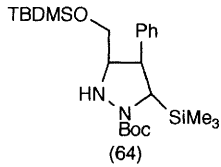
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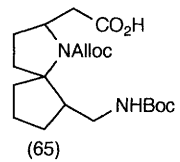
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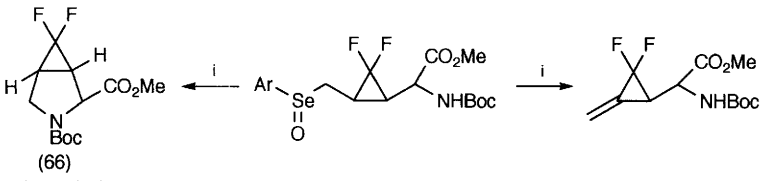
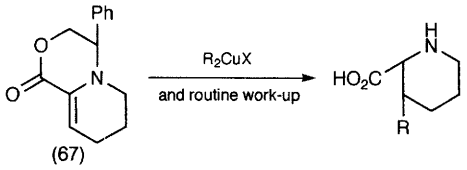


(66)

Reagent: i, pyrolysis

Scheme 17

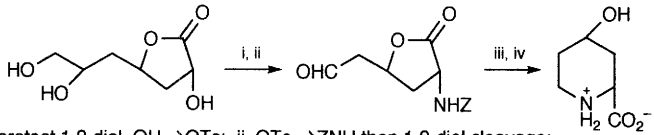


(67)

3-Alkylpipecolic acids have been prepared by an extension of the homochiral morpholinone methodology (Section 4.1.3) to (67).[304]

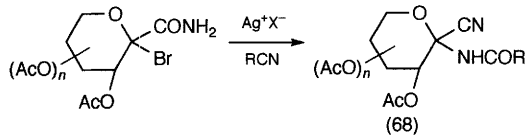
Opportunistic syntheses of unusual amino acids from alkaloids over the years are now extended to quincorine and quincoridine, oxidation giving the corresponding bicyclic aminodicarboxylic acid.[305] Another non-general example is provided in Birch reduction of N-Boc-pyrrole-2- and 3-carboxylates[306] and analogous amides.[307] 3,4-Dehydro-proline analogues and β-prolines are formed, with good diastereoselectivity when homochiral esters were employed, and when a chiral acid was used for protonation at the quenching stage of the process. Electroreduction of pyridine-dicarboxylic acids gives dihydro- and tetrahydro-analogues.[308]

Advances in enantioselective synthesis of pipecolic acid analogues have been recorded for (2R,4S)-4-hydroxypipecolic acid and its (2S,4R)-isomer (Scheme 18),[309] and for both enantiomers of *cis*-6-(hydroxymethyl)-pipecolic acid and its *cis,cis*-4-hydroxy-analogue.[310]



Reagents: i, protect 1,2-diol, OH→OTs; ii, OTs→ZNH then 1,2-diol cleavage; iii, CHO→ CH_2OMs then OH^-; iv, H_2–Pd/C

Scheme 18



(68)

Anomeric amino acid derivatives have been prepared from C-(1-bromo-1-deoxy-D-glycopyranosyl)formamides *via* 1-cyano-analogues (68).[311]

A routine preparation of 7-phenylazo-1,2,3,4-tetrahydroisoquinoline-3-car-

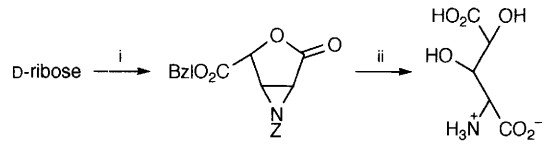
boxylic acid has been published,[312] and the Ph_4PCl-mediated Heck reaction is now becoming a regular means of using bromoarenes to prepare complex amino acids, illustrated with 1,2,3,4,5,6-hexahydro-3-benzazocine-2-carboxylic acid and 2,3,4,5,6,7-hexahydro-1H-3-benzazonine-2-carboxylic acid.[313]

4.5 Models for Prebiotic Synthesis of Amino Acids. – The feedback from evolving theories which informs new thinking has been evident over the years (for reviews of current ideas see refs. 314–317). There is an increasing volume of work on this topic, some of which extends traditional studies (synthesis of amino acids from a $CO/N_2/H_2O$ mixture at 1 atm pressure under 1–2 KeV X-irradiation;[318] or in a magnetoplasma dynamic arc jet[319]). Many of the reports are for or against a new idea, as with a role for thermophiles,[320] opposition to the claimed reduction of CO_2 by the $FeS\text{-}H_2S/FeS_2$ redox couple that is required by simple amino acid-forming reactions (the reducing power of this couple decreases drastically with rising temperature, so undersea hydrothermal vents seem to be an unlikely prebiotic source for amino acids),[321] and continuing support for stereoselective UV photolysis of interstellar dust by circularly-polarized synchrotron radiation from neutron stars.[322] The excess of the L-enantiomer for some amino acid constituents of the Murchison meteorite (ref. 1119) is considered to support the last-mentioned controversial hypothesis. Interstellar dust as the basis of UV photochemical amino acid production has been supported.[323] This paper describes millimeter array spectroscopic observation of glycine in the dense cloud from which Sagittarius B2 is forming, and provides a puzzle because the gas-phase chemistry associated with amino acid production is considered to be unlikely in dense clouds. But UV photolysis of interstellar ice grains is more likely, and therefore asteroids and comets are ruled out as prebiotic delivery vehicles to Earth for amino acids.

Maintaining a plausible scenario for terrestrial prebiotic amino acid synthesis calls for consideration of mineral surfaces as likely catalysts, and the topic has been reviewed.[324]

4.6 Synthesis of α-(ω-Halogenoalkyl)-α-Amino Acids. – The standard synthesis methods have been applied to compounds under this heading, such as D,L-α-aminoperfluoroalkanoic acids $R(CH_2)_{n-1}CH(NH_3^+)CO_2^-$ ($R = C_6F_{13}$, C_8F_{17}; $n = 3$, 10),[325] and α-bis(fluoromethyl)glycine.[326] Similar applications are described in refs. 124, 281, 303. Direct fluorination of a protected pyroglutaminol leading to 4,4-difluoro-L-glutamic acid using N-fluorobenzenesulfonimide is unusually simple.[327]

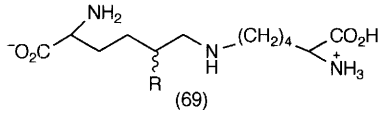
4.7 Synthesis of α-(ω-Hydroxyalkyl)-α-Amino Acids. – Numerous examples of compounds of this structural class have been prepared by routine methods (Section 4.1, see also refs. 66, 68, 92, 105, 171, 877). More unusual synthesis routes are represented: leading to the four stereoisomers of β-hydroxyhistidine;[328] D- and L-cycloserine derivatives prepared by solid-phase methodology;[329] and a route from D-ribose to (3S,4S)-dihydroxy-L-glutamic acid (Scheme 19).[330]



Reagents: i, literature method; ii, $BF_3.Et_2O/PhCH_2OH$; iii, H_2—$Pd(OH)_2/C$

Scheme 19

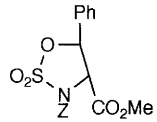
4.8 Synthesis of N-Substituted α-Amino Acids. – The conversion of primary amines into N-substituted versions is covered in relation to amino acids in Section 6.3, while side-chains carrying nitrogen functional groups are collected here. Crosslinking of proteins through a secondary amine is represented in lysinonorleucine (69; R = H) and its 5-hydroxy analogue (69; R = OH), for which a conventional synthesis has been reported.[331]



(69)

The substantial topic of protein nucleic acids (PNAs) continues to expand, based on the availability by synthesis of N-(β-purinyl and -pyrimidinyl) alanines (reviews: refs. 9, 332).

4.9 Synthesis of α-Amino Acids Carrying Unsaturated Aliphatic Side-chains. – α,β-Unsaturated α-amino acids are accessible through DBU-mediated elimination from sulfamidites (70) with $SOCl_2$ in CH_2Cl_2 to give *cis*-alkenes,[333] and through cobalt hexacarbonyl-mediated acylation of an alkyne $RC{\equiv}CCO_2H$ and Curtius development of the carboxy group into NHZ and ceric ammonium nitrate oxidation, which unexpectedly provides a 3-substituted N-alkoxycarbonyl-2,3-dehydro-aspartic acid anhydride.[334] The azlactone synthesis with 4-methylcyclohexanone followed by resolution (reaction with L-phenylalanine cyclohexylamide and separation of the diastereoisomeric dipeptides) gives an α,β-dehydroamino acid that owes its optical activity to the cyclohexyl chiral centre.[335]



(70)

Further conventional elimination procedures are represented in a synthesis of β,γ-dehydro-L-valine from γ-(phenylselenyl)-L-isoleucine[336] and in new examples of rearrangements of allyl glycinates to allylglycines [$R^1NHCH_2CO_2$-$CH_2CH{=}CHR^2 \rightarrow R^1NHCH(CHR^2CH{=}CH_2)CO_2H$] with stereochemical control

through the presence of R^1 = L-α-aminoacyl.[337] Separation of isomers of 2-amino-3-methylpent-4-enoic acid prepared in this way, using L-aminoacylase and L-amino acid oxidase, provides the (2S,3R)-diastereoisomer, hydrogenation completing an efficient route to L-alloisoleucine.[338] A nitrosoketene from Meldrum's acid has been used in a synthesis of allylglycine and cyclopentenylglycine through [1,3]cycloaddition of the derived cyclic nitrone to alkenes.[339]

Unsaturated homologues of α-aminopimelic acid $HO_2CC(=CH_2)$-$(CH_2)_3CH(NH_3^+)CO_2^-$ and $HO_2CCH=CH(CH_2)_2CH(NH_3^+)CO_2^-$ have been prepared for use as reversible inhibitors of meso-diaminopimelic acid D-dehydrogenase, from aspartic and glutamic acids *via* side-chain aldehydes, by an S_H2' allylstannane coupling [$MeO_2CC(=CH_2)CH_2SnPh_3$ + $I(CH_2)_2CH$-$(NHR^1)CO_2R^2$] and a Wittig synthesis, respectively.[340]

4.10 Synthesis of α-Amino Acids with Aromatic or Heteroaromatic Groupings in Side-chains. – This remains an active topic because of the opportunities offered by aryl and heteroaryl moieties for synthetic modifications, giving access to isotopically-labelled amino acids and analogues of physiologically active substrates.

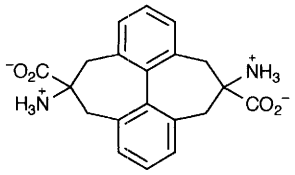
Further reviews commemorating last year's vancomycin syntheses (Volume 31, p. 32) have appeared;[341,342] one covers the synthesis of the amino acid building blocks,[343] and the other describes the route used by Boger[344] (see also ref. 877).

Synthesis of ^{13}C-, ^{15}N-, ^{2}H-isotopomers of L-phenylalanine and L-tyrosine in any chosen combination of labelling atoms in various positions in the molecule calls for construction of the aromatic moiety from 1,6-disubstituted hexatrienes and application of standard amino acid syntheis protocols.[345] 4-Substituted phenylglycines continue to provide attractive synthesis targets for pharmacological studies, *e.g.* (R,S)-4-phosphonophenylglycine as a potent and selective Group III metabotropic glutamate receptor agonist, reached through routine methods.[346] Phenylalanines of similar potential include 4-(carboxymethyl)- and 4-(carboxydifluoromethyl)-,[347] p-porphyrinyl-,[348]

Other modified phenylalanines reported, are: β-hydroxy-β-(fluoronitrophenyl)alanines,[349] the biphenyl-based bisamino acids (71) and (72),[350] (2S,3R)-β-methyltyrosine (tyrosine phenol lyase in a notable application to a non-natural substrate).[351]

Tryptophan synthase can be used analogously, for preparations from L-serine of furano- and selenophenyl- analogues of tryptophans (73–75),[352] while standard chemical synthesis leads to racemic α-[^{15}N]-tryptophan (from [^{15}N]-glycine *via* the hydantoin, condensed with indole-3-aldehyde and Al-Ni/H_2O reduction of the resulting dehydrotryptophan)[353] and an analogous preparation of dihydrotryptophan.[354]

A standard ibotenic acid synthesis modified to allow N^{α}-alkyl derivatives of this isoxazolylglycine to be prepared[355] has given samples for testing for metabotropic glutamate receptor activity. Thiazole, imidazole, and oxazole-containing amino acids[356] and 'biheterocyclic' amino acids have been built from protected α-azidoglycine and homologues by [1,3]cycloadditions.[357]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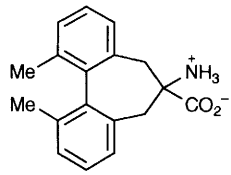
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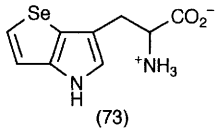
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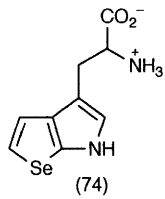
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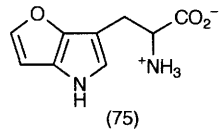
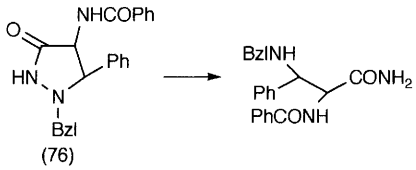

(75)

Numerous β-(heteroaryl)alanines have been prepared (see also refs. 138, 139, 160), often intended as analogues of common amino acids [4′-phospho-2′-furyl)-L-alanine as an N^{im}-phosphohistidine mimic;[358] N-benzoyl-(2R,3R)-3-phenyl-3-(pyrazol-1-yl)-L-alanine,[359] D,L- and L-β-(6,7-dimethoxy-4-coumaryl)alanine[360]] but also including natural products [pyrimidin-4-yl substituted amino acids, one of which is L-lathyrine, prepared from amidines and alkynyl ketones[361]]. Michael addition of heterocyclic nucleophiles to a protected dehydroalanine gives β-(1,2,4-triazol-1-yl)alanine and others of the same type.[362] Standard methods for this class of amino acid are illustrated in condensation of 2-Boc-amino-5-bromopentanoic acid with imidazoles and 1,2,4-triazoles[363] and Lewis acid-catalysed condensation of the β-alanylzinc synthon $BocNHCH(CO_2H)CH_2ZnI$ with an aryl iodide (for the preparation of C-glycosylated tyrosines).[364]

4.11 Synthesis of α-Amino Acids Carrying Amino Groups, and Related Nitrogen Functional Groups, in Aliphatic Side-chains. – Most of the current examples under this heading have been prepared through standard protocols, aldolization of $(MeS)_2C{=}NCMe(COR)CO_2Et$ with an α-metallated ethyl isocyanoacetate leading to syn,syn- and syn,anti-ONN′-protected 2,4-diamino-3-hydroxyglutaric acids.[365] A similar reaction of RCH=NTs and ethyl isocyanoacetate catalysed by Me_2SAuCl with a chiral ferrocenylphosphine gives (4R,5R)- and (4S,5S)-imidazol-2-ines, from which corresponding homochiral 2,3-diaminoalkanoic acids were obtained by hydrolysis and 2,3-diaminoalkanols through reduction.[366] The Garner aldehyde approach to tri-amino acids (-CHO→-$CH_2NRCH_2CH_2NHBoc$) was found to be too cumbersome in comparison with a conventional sequence *via* asparagine and diaminopropanoic acid.[367]

(4R,5R)-4-Benzoylamino-5-phenyl-3-pyrazolidinone (76) has provided a family of 3-alkylaminophenylalanines[368] and heteroaryl analogues[369] through condensation with carbonyl compounds followed by Raney nickel reduction.

Conformationally-constrained arginine analogues, $H_2NC(=NH)NHCH_2$-$CH{=}CHCH(NH_2)CO_2H$ (E- and Z-isomers) and the N-(n-propyl) and keto



homologues (C=O in place of CH_2), and (m-guanidinophenyl)glycine, have been prepared.[370]

A long-running project is reported on, describing syntheses of the tertiary amine and quaternary ammonium analogues of S-adenosylmethionine (NMe and N^+Me_2 in place of SMe^+).[371]

4.12 Synthesis of α-Amino Acids Carrying Boron Functional Groups in Side-chains. – The long-studied o-carboranylalanine [3-{1,2-dicarba-*closo*-dodecaboran(12)-1-yl}-2-aminopropanoic acid] spontaneously fragments to *nido*-carboranylalanine containing the dodecahydro-7,8-dicarba-nido-undecaborate(1 –) cage with loss of a boron atom.[372]

4.13 Synthesis of α-Amino Acids Carrying Silicon Functional Groups in Side-chains. – A novel vinylsilane-containing amino acid has been prepared for use in a conventional pipecolic acid synthesis involving N-acyliminium ion cyclization.[373]

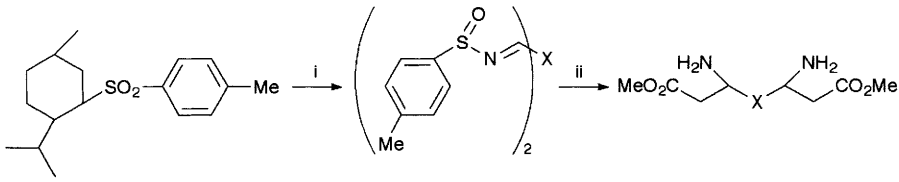
4.14 Synthesis of α-Amino Acids Carrying Phosphorus Functional Groups in Side-chains. – Main examples under this heading are covered elsewhere in this chapter (Section 4.10; *e.g.* ref. 346) reflecting the importance of phenylalanines carrying phosphorus functional groups in the aryl moiety, and uses of phosphonoglycines in synthesis (refs. 142, 181, 182, 218, 721).

4.15 Synthesis of α-Amino Acids Carrying Sulfur-, Selenium-, or Tellurium-containing Side-chains. – [^{11}C-Methyl]methionine is available within 15 minutes from $^{11}CH_3SH$ and O-acetyl-L-homocysteine, through efficient catalysis by γ-cyano-α-aminobutyric acid synthase.[374] The phosphinic acid analogue of methionine has been described[375] (see also ref. 143).

S-Neopentyl cysteic and homocysteic acids have been prepared to provide isosteric sulfonate analogues of aspartic and glutamic acids, respectively.[376]

4.16 Synthesis of β-Amino Acids and Higher Homologous Amino Acids. – Reviews of preparations of β-amino acids and β-lactams through addition of lithium amides to α,β-unsaturated carbonyl compounds,[377] of enantioselective synthesis of β-amino acids,[378] and of statines[379] have been published. β-Amino acid synthesis has been reviewed from a chemical process perspective.[380]

Several synthesis strategies that are standard in the α-amino acid series are also routine for higher homologues, particularly the newer amination methods,



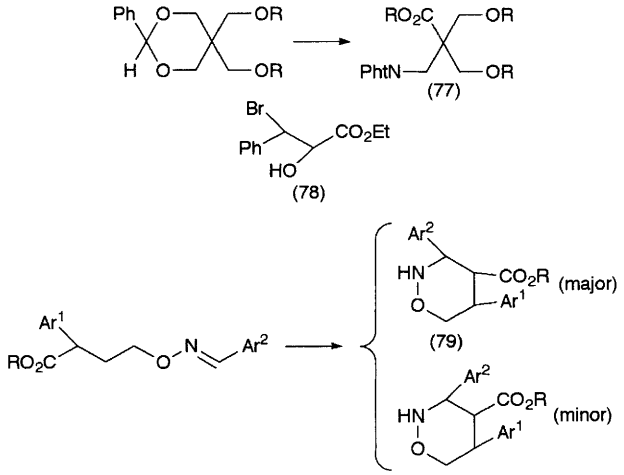
Reagents: i, $LiN(SiMe_3)_2$, OHC–X–CHO; ii, $MeOC(=CH_2)ONa$ then H_2O

Scheme 20

an unusual example featuring bis-imines (Scheme 20).[381] Amination of methyl nicotinylacetate with (S)-α-phenylethylamine gives enantiomerically-enriched (S)-3-amino-3-(pyrid-3-yl)propanoate after work-up.[382] More conventional examples involve enantioselective addition of (S)-α-phenylethylamine and other chiral amines to (E)-$PhCOCH{=}CHCO_2Et$,[383] a lithium (R)-(α-methylbenzyl)allylamide to isopropyl (E,E)-hepta-2,5-dienoate *en route* to the highly-functionalized β-amino acid constituent of sperabillins B and D,[384] hydrazoic acid to α,β-unsaturated imides catalysed by chiral (salen)Al(III) complexes,[385] sulfinylimines (formed from chiral 2-methylpropanesulfinamide with a carbonyl compound) to lithium or titanium enolates[386] and ytterbium(III)-catalysed addition of toluene-p-sulfinylimines to lithium (α-carboxyvinyl)cuprates,[387] N-acyloxyiminium ions (formed from nitrones with acyl halides) to chiral enolates,[388] nitrones to achiral N-crotonyl-1,3-oxazolidin-2-ones catalysed by chiral ytterbium(III) complexes.[389] Amination can be effected *via* β-nitro-acid derivatives, as in a route to enantiomerically-pure alkyl *cis*- and *trans*-2-aminocyclohexanecarboxylates starting from Diels-Alder adducts from nitroalkenes and 2-aminodienes.[390] The conformationally-constrained β-amino acid (−)-(1R,2S)-2-aminocyclobutane-1-carboxylic acid has been prepared from *cis*-cyclobutane-1,2-carboxylic acid anhydride through pig liver esterase-catalysed hydrolysis and Curtius rearrangement of the resulting half-ester.[391] Condensation of aldimines with silyl enolates catalysed by a Zr-(R,R)-bis(naphthol)methane complex gives substituted β-amino acid esters with high e.e.[392]

No attempt at asymmetric bias is involved in the addition of an imidoyl chloride to a lithium ester enolate to give fluorinated β-enaminoesters, ZnI_2/$NaBH_4$ reduction giving syn-β-amino-β-(fluoroalkyl)-α-methylalkanoate esters,[393] or in addition of metallated 2-alkyloxazolines, -thiazolines and imidazolines to alkanenitriles [het-CH^-R^1 Li^+ + $R^2CN \rightarrow NH_2CR^2{=}CR^1$-het] to give precursors of β-enamino acids.[394] Development of one of the functional groups of a malononitrile into a carboxy group *via* an oxazoline, while the other nitrile becomes an aminomethyl group,[395] and an alternative approach to the same substrate,[396] is a variation on this theme. β-Phthalimido-α,α-disubstituted alkanoic acids (77) have been prepared from O-benzylidene-pentaerythritol.[397] Poly(aniline)-supported cobalt(I) acetate catalyses the condensation of methyl acetoacetate, an aldehyde, and acetonitrile followed by reduction (synthesis of β-aryl homo-isothreonines).[398]

Gabriel syntheses have led to (S)-N-benzoyl 3-phenylisoserine from the



bromo compound (78),[399] and to the racemate from benzaldehyde, ethyl chloroacetate and ammonia (*via* trans ethyl 3-phenylglycidate),[400] and to (3S)-amino-(2R)-methylbutanoic acid through amination of a bromolactonization product formed using S-(−)-N-methoxypyrrolidinecarboxamide as chiral auxiliary.[401] Substitution reactions leading to methyl 3-aryl-3-(piperidin-1-yl) propionates[402] and 3-aryl-3-hydroxylaminopropionates,[403] and addition of Reformatzky reagents to aldimines, have been reported.[404]

Ring opening of *trans*-3-substituted aziridine-2-carboxylic acids has been established as an efficient route to anti-α-substituted-β-amino acids, and the route can include *Candida antarctica* lipase resolution.[405] SmI_2-Mediated cleavage of aziridines simplifies their use in β-amino acid synthesis.[406] Ring opening of (R)-diethyl oxiranephosphonate by benzylamine and hydrogenolysis gives (R)-2-amino-1-hydroxyethanephosphonic acid.[407] An O-alkyl oxime has been used to give a 9:1-mixture of 1,2-oxazine (79) and its diastereoisomer, ring-opening and recyclization giving the substituted β-proline ABT-627.[408] Other β-proline syntheses are initiated by [3+2]cycloaddition of N-tosylimines to 2-alkynoates and allenoates,[409] Pd-mediated addition of propargylamines to Michael acceptors,[410] and $ZnCl_2$-mediated asymmetric Michael-type annulation of the (R)-phenylethylamine enaminoesters $MeO_2CCH{=}C(NR)CH_2CH_2CH{=}CO_2Me$.[411] Dihydroxylated β-pipecolic acids have been prepared from the readily-available Dieckmann adduct 3-ethoxycarbonylpiperidin-4-one, chloromethyl ethers reacting with the derived dianion and effecting 5-alkoxymethylation, opening up a new route to azasugars.[412] A less flexible route to β-pipecolic acids is based on diastereoface-selective asymmetric addition to chiral 1,4-dihydropyridines derived from nicotinic acid amides.[413]

Further preparations of α-substituted-β-amino acids include hydroxyalkyl compounds $R^1CH_2NHCH_2CH(CO_2Me)CH(OH)R$[414] and $TsNHCH_2C(OH)(CO_2Me)CH(OH)R$[415] prepared from Baylis-Hillman adducts (see also ref. 416), while anti-α-hydroxy-α-alkyl-β-amino acids are available through alkyl-

ation of *trans*-oxazoline-5-carboxylic acids (formed by iodocyclization of alkyl 3-benzoylaminoalkanoates[417]) followed by ring-opening and resolution using penicillin G acylase.[418]

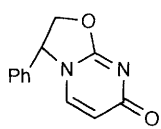
The trichloroacetimidate rearrangement applied to PhCH=CHCH(OH)-CH_2OH gives N-benzoyl-(2R,3S)-phenylisoserine methyl ester after development of functional groups.[419] An unusual rhodium(II)-induced decarboxylative rearrangement of diazoalkyl urethanes $TsNHCO_2CHRC(N_2)CO_2Et$ gives enamines ($TsNHCR{=}CHCO_2Et$ or its isomer).[420]

Chiral synthons leading to β-amino acids are similar to those used for α-amino acid asymmetric synthesis; the (S)-phenylglycinol-derived heterocycle (80) undergoes alkylation with organocopper reagents[421] and its near-relative ($-CR^1R^2CH_2-$ in place of -CH=CH-) gives α-methyl-β-amino acids through enolate alkylation with electrophiles.[422] The related tetrahydropyrimidinone (81) prepared from L-asparagine is a convenient source of α-dialkyl-β-amino acids (R = H→R = alkyl; further alkylation can be effected),[423] and its methoxytetrahydropyrimidine analogue has been used for a synthesis of α-alkylaspartic acids.[424] Manipulation of this synthon into lithium enaminates (lithiated dihydropyrimidines) gives a substrate that readily undergoes electrophilic substitution to give α-branched β-amino acid esters.[425] Enantioselective α-alkylation of acyclic lithium amide enolates is facilitated by a novel chiral pentamine ligand.[426]

Camphorsultam derivatives of oxime ethers, *i.e.* N-(β-oximino)acyl derivatives of the Oppolzer auxiliary, undergo addition of alkyl radicals to give α,β-dialkyl-β-amino acids.[427] An N-acyl chiral ephedrine-derived imidazolidinone, another auxiliary that is familiar through its use for the asymmetric synthesis of α-amino acids, has been applied to β-amino acid synthesis, through addition of $PhCH{=}NSO_2Tol$ to its titanium enolate [RCH_2CON-Imid→PhCH(NHTs)CHRCO-Imid],[428] and titanium[429] and sodium[430] enolates of chiral N-acyloxazolidinone imides have been applied similarly, giving modest (60%) d.e., the former in reaction with α-alkoxyamines (*e.g.*, 2-ethoxypiperidines), the latter in reaction with tert-butyl bromoacetate to give β-substituted β-amino acids through application of the Curtius rearrangement protocol.

Highly enantioselective hydrogenation of (E)-β-acylaminoacrylates to give β-amino acids has been achieved using standard homogeneous catalysis protocols (Rh/MeDuPhos),[431] and amination [(R)-(+)-N-benzyl-α-methylbenzylamine/BuLi] of the equivalent substrate (a substituted cinnamic acid) has been used for synthesis of the β-tyrosine moiety of C-1027.[432] These β-amino acid precursors are available from sulfonyl imines and activated bisaminals.[433]

Synthesis of β-amino acids starting from α-amino acids is a continuously developing approach, and could even be described as over-developed in areas that have been well researched already (*e.g.*, Arndt-Eistert homologation of α-amino acid derivatives *via* N-protected α-aminoacyldiazomethanes[434]). α-Amino acids are used to prepare UNCAs (Volume 29, p. 72, Volume 31, p. 55) that have been used in a preparation of β-amino-α-hydroxy acids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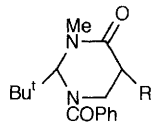
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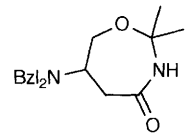
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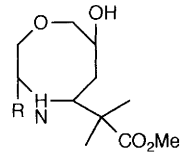
(norstatines) *via* the ketoacetylenic homologue.[435] A different homologation ($CO_2H \rightarrow CH_2OH \rightarrow CH_2CN$ *etc.*) has been used to prepare homophenylalanine.[436] L-Aspartic acid is a readily-available β-amino acid whose α-carboxy-group is adaptable to suit certain synthesis objectives, as for (2S,3R)-3-Z-amino-4-phenyl-2-hydroxybutanoic acid [prepared *via* (4S,5R)-2-benzyloxy-5-phenyloxazoline-4-acetate] as a constituent of (−)-bestatin[437] and the 6-amino-oxazepin-4-one (82), intended for use as a conformationally-restricted β-amino acid.[438] Chiral β-amino alcohols (originating in L-α-amino acids) are the starting point for the uneventful preparation of cyclic β-amino acids (83).[439] Direct α-hydroxylation of an N-protected (3S)-amino-alkanoic acid as its metal enolate provides a diastereoisomer mixture,[440] and homophenylalanines are conveniently prepared from β-amidozinc reagents $IZnCH_2CH(NHBoc)CH_2CO_2Me$ through coupling with an aryl iodide (in DMF to suppress a β-elimination side-reaction), and substitution of the Zn–Cu analogue by allylic halides.[441] *trans*-Cinnamyl alcohol has been elaborated into (S,S)-2-aminomethylcyclopropane-1-carboxylic acid through conventional functional group manipulations.[442]

The γ-amino acid family includes several members that are important for their physiological properties, and the most effective general synthesis strategies can be classified into different addition processes [aldimines to cinnamates to give 4-amino-3,4-diarylbutanoic acids,[443] allylamines with methyl chloroformate mediated by BuLi-(−)-sparteine to give (S)-2-substituted 4-aminobutanoic acids or ring-opening of equivalent β-lactams to give the (R)-enantiomer,[444] (S)-N-Boc-α-aminoaldehydes to triphenylphosphoranes $Ph_3P{=}CR^2CO_2Et$ to give $BocNHCHR^1CH{=}CR^2CO_2Et$[445] and a similar route to (Z)- and (E)-4-amino-2-(trifluoromethyl)-but-2-enoic acid from N,N-bis-Boc-glycinal and ethyl 2,2-dichloro-3,3,3-trifluoropropionate using Reformatzky conditions followed by reductive elimination[446]].

Special cases are also represented, N-allyl α-bromoamides leading to 3-aza-2-oxo-bicyclo[3.1.0]hexanes that give *cis*-2,3-methanoGABAs by reductive ring-opening (Li-NH_3).[447] Chain extension by C-acylation of Meldrum's acid by an N-protected amino acid activated with isopropenyl chloroformate leads to γ- and δ-amino-β-keto-esters [*e.g.* $RNHCH(CO_2R^1)CH_2COCH_2CO_2R^2$].[448]

Oxazolidinones are prepared from α-amino acids (*e.g.* 84), homologated using a Wittig reaction ($>C{=}O \rightarrow >C{=}CHCO_2Et$) in a diastereoselective synthesis of (3S,4S)- and (3R,4S)-4-methylamino-3-hydroxy-5-phenylpentanoic acid (N-methyl-AHPPA), a constituent of the cyclic depsipeptide hapalosin and of statine;[449] a different synthesis approach starts from (2R,3R)-2,3-epoxy-4-phenylbutan-1-ol.[450] Glycine crotyl ester $CF_3CONHCH_2CO_2CH_2CH{=}CHMe$ subjected to (−)-quinine-catalysed Claisen rearrange-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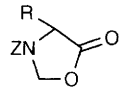
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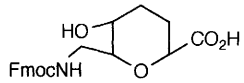
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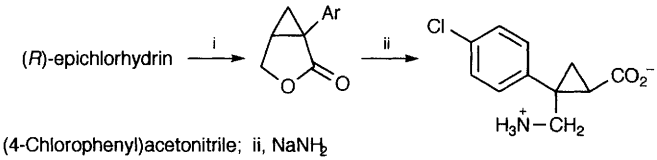
ment (Volume 31, p. 32) and two-carbon homologation ($CO_2H \rightarrow COCH_2CO_2Et$) gives isostatine,[451] and homologation of the Weinreb amide of N-Boc-L-leucine ($CO_2H \rightarrow COC{\equiv}CSiMe_3$) followed by borane reduction mediated by a chiral oxazaborolidine leads to statine; the route can be adapted to provide norstatine.[452] Synthesis of all four stereoisomers of 4-amino-3-hydroxy-2-methylpentanoic acid [one of which is a constituent of bleomycin A_2 and the (2R,3S,4S)-isomer is present in the marine toxin janolusimide] depends on crotylboration of N-Boc-L- or D-alaninal as the crucial step.[453] N-Z-α-(p-Tolyl)thio-trifluoroalaninal, (R)- or (S)-ZNHCMe[S(p-MeC_6H_4)]CHO, starts an aldolization route to syn-γ-amino-γ-trifluoromethyl-β-hydroxybutyric acid, as an alternative to 'non-oxidative Pummerer rearrangement' employing an α-lithiosulfoxide as a chiral hydroxyalkyl equivalent.[454] Simpler homochiral γ-amino-β-hydroxybutyric acids (such as the γ-benzyl homologue that is present in hapalosin) have been prepared through aldolization of (4S)-benzyl-3-(3-phenylpropanoyl)-1,3-oxazolidin-2-one with acrolein followed by Curtius rearrangement and generation of the carboxy group by oxidation of the C=C grouping.[455]

Development of methods for the synthesis of pyrrolidin-2-ones has had a long history, but asymmetric synthesis has been studied only relatively recently, with new examples illustrating the options available [*e.g.* (S)-malic acid→(S)-$HOCH_2CH(OH)CO_2Me$→(S)-4-hydroxypyrrolidin-2-one;[456] N-(3-ethoxycarbonylprop-2-enyl)-N-methoxycarbonylacetyl-(S)-phenylethylamine converted into the pyrrolidin-2-one or into the tetrahydropyridine (the direction of cyclization being controlled by the reaction conditions) *en route* to diastereoisomers of 2-aminomethylcyclobutane-1-carboxylic acid;[457] (−)-sparteine-catalysed addition of an alkyl carbamate-derived cuprate to an allenic ester $Bu^tOCON(CH_2R)_2$ + $R^1CH{=}C{=}CHCO_2Et$[458]]. The equivalent (S)-3-hydroxy-γ-butyrolactone has been used as starting material for (R)-4-amino-3-hydroxybutanoic acid (GABOB) and (R)-3-hydroxy-4-trimethylaminobutanoic acid [(R)-carnitine] *via* a 4-cyanobutanoate ester prepared as source of the 4-aminobutyronitrile through Curtius rearrangement.[459] The classical carnitine synthesis from (R)-(−)-epichlorhydrin has been adapted to provide phosphocarnitine.[460] 3-Trimethylammonio-2-hydroxycyclohexanecarboxylic acid stereoisomers have been synthesized as conformationally constrained carnitine analogues.[461] Other familiar γ-amino acids or their analogues have been synthesized: GABA, by use of immobilized *E. coli* fed on waste from L-glutamic acid production,[462] (R)-(−)-baclofen through [2 + 2]cycloaddition of 4-chlorostyrene to dichloroketen and ensuing functional group development,[463] and baclofen analogues (Scheme 21).[464] Pentafluorophenyl 4-(Fmoc-



Reagents: i, (4-Chlorophenyl)acetonitrile; ii, $NaNH_2$

Scheme 21

amino)-N-methylpyrrole-2-carboxylate[465] is representative of a class of γ-amino acids not reviewed exhaustively here, but mention of them is appropriate since such compounds are used in syntheses of peptide mimetics.

Homologation of baclofen to 5-amino-4-(p-chlorophenyl)-pentanoic acid and preparation of the 3-aryl isomer by ring-opening of the corresponding piperidinone has been reported,[466] indicative of conventional access to δ-amino acids. N-Protected α-aminoaldehydes continue to provide the most popular starting materials for this class of amino acid, In-mediated coupling with an alkyl 2-bromomethylacrylate giving mainly syn-homoallyl alcohols without racemization *en route* to aminoalkyl-substituted α-methylene-γ-butyrolactones[467] that act as substrates for C- and O-nucleophiles (*e.g.* cyanide delivered by trimethylsilyl cyanide[468]). An extraordinary double alkylation of an α,β-unsaturated imine with a keten silyl acetal and allyltributyl stannane, giving a δ-amino acid derivative $R^1NHCH(CH_2CH{=}CH_2)CH_2CHR^2CMe_2CO_2Et$, has been reported.[469] Other standard synthesis protocols have provided substituted 5-(Z-amino)pentanals $ZNHCH(^iPr)COCH_2CH(CH_2Ph)CHO$,[470] δ-aminolaevulinic acid,[471] and partially deoxygenated aminogluconic acids (85 and its isomers).[472] Homologation of α-amino acids into δ-amino acids *via* ketosulfones is a standard protocol (*e.g.*, ref. 786). 6-Amino-2-substituted hexanoic acids have been prepared from lysine *via* the triflate of 6-amino-2-hydroxyhexanoic acid,[473] and an excellent new synthesis of galantinic acid starts with L-serine, employing an oxazolidine-based strategy with chain elongation steps that are familiar through the many applications in synthesis of the Garner aldehyde (Section 6.3).[474]

4.17 Resolution of D,L-Amino Acids. – Classical procedures based on separation of enantiomers or diastereoisomers by crystallization, and amplification of enantiomer ratios by asymmetric transformations, continue to be applied. The former category is illustrated in the phenomenon of preferential crystallization of one enantiomer from stirred D,L-glutamic acid containing small amounts of L- or D-lysine (leading to 10% e.e. for crops of crystals produced in the first 30 min but 0% thereafter[475]) and of (R)- or (S)-1,4-thiazane-3-carboxylic acid from S-(2-chloroethyl)-D,L-cysteine.[476] Esters formed from D,L-bromo-acids and (R)- or (S)-3-hydroxy-4,4-dimethyl-1-phenylpyrrolidin-2-one under dynamic kinetic resolution, ensuing Gabriel synthesis with phthalimide giving corresponding phthaloylamino acids (resolution of D,L-phthaloylamino acids with these esters is also described).[477] Resolution of α-aminonitriles through asymmetric transformation using (R)-mandelic acid–amygdalin exploits the Dimroth principle.[478]

A useful practical demonstration that sensitive N-protected α-heteroatom-substituted glycines can be resolved by fractional crystallization of their (+)-(1S,2S)-2-amino-1-phenylpropane-1,3-diol salts or (+)- or (−)-menthol esters has been reported for N-protected D,L-2-alkoxyglycines.[479]

Enzyme-mediated resolutions are applicable to near relatives as well as to the common α-amino acids, and there are further indications of the scope for broadened specificities accompanying modified reaction conditions. Uses of esterases in this context have been reviewed,[480] and enantioselective hydrolysis of methyl D,L-phenylalaninate by pancreatin in toluene-water mixtures[481] and of dimethyl D,L-2-aminosuberate by papain in aqueous DMF or by subtilisin in acetonitrile with minimum water content[482] indicate the general approach. Increasing interest in the use of readily-available alcalase is being shown, with hydrolysis of familiar amino acid esters under physiological conditions[483] and, specifically, methyl D,L-phenylalaninate.[484] Carboxypeptidase A acting on the N-trifluoroacetyl derivative of β-methyl-D,L-tryptophan[485] and the reverse process with D,L-valine undergoing enantioselective acetylation mediated by immobilized L-aminoacylase[486] (see also ref. 338) are further examples of classical methods, as are uses of penicillin G acylase (refs. 20, 418, 736), lipases (refs. 58, 405) and chymotrypsin (ref. 138). Enantioselective conversion of the D-enantiomer of a D,L-hydantoin into the corresponding N-carbamoyl-D-amino acid[487] is now regularly used, also conveniently operated with an immobilized form of D-hydantoinase.[488] A new approach illustrated with the resolution of D,L-threo-β-[4-(methylthio)phenyl]serine is based on the use of D-threonine aldolase from an *Arthrobacter* sp.[489]

Chromatographic resolution has continued to develop into more efficient versions. N-Boc- and -Z-D,L-α-amino acids can be resolved by elution over polysaccharide-based chiral stationary phases (CSPs),[490] N-(3,5-dinitrobenzoyl)-D,L-α-amino acid esters over homochiral phenylurea derivatives,[491] dansylamino acids over immobilized bovine serum albumin[492] and human serum albumin,[493] N-Boc-D,L-amino acids[494] and N-methylamino acids[495] over a teicoplanin-based CSP, amino acid esters[496] and N-protected amino acids[497] over immobilized α-chymotrypsin. Some of these studies use an underivatized amino acid, always D,L-tryptophan (a particularly convenient test species as used in the classical demonstration of enantiomer discrimination by natural homochiral species such as cellulose) with immobilized bovine serum albumin,[498,499] and bovine serum albumin membranes.[500] β-Cyclodextrin and its heptakis(3-O-methyl) derivative,[501] and L-tryptophanamide covalently bonded to β-cyclodextrin,[502] are examples of CSPs in one of the most active research categories; β-cyclodextrin-bonded CSPs are more effective for enantiomer resolution of N-benzoylamino acids compared with other common derivatives.[503] Synthetic CSPs are ever more sophisticated in concept, with ruthenium-porphyrin complexes carrying (S)- or (R)-α-methoxy-α-(trifluoromethyl)phenylacetyl residues on each side of the porphyrin plane,[504] α-(acetamidopyridyl)binaphthalenes bridged by but-2-yne-1,4-diyl- or 1,4- xylylene moieties,[505] quinine immobilized on 3-mercaptopropyl-silica gel (greater chiral discrimination compared with the N-Boc-quinine analogue),[506] and Crownpak

CR(+)®, an ODS matrix coated with a chiral crown ether applicable to resolution of hydrophobic amino acids.[507] The best known approach with CSPs based on dinitrophenyl derivatives has been extended to N-acylated L-proline anilides.[508] Separate enantiomers of D,L-N-(2,4-dinitrophenyl)amino acids assemble in chloroform–water mixtures containing a lipophilic 2′-deoxyguanosine derivative.[509]

The use of polymeric CSPs that have been imprinted by a homochiral additive during their preparation has broadened considerably, with membranes imprinted with protected L,L,L-tripeptides showing enhanced recognition of the L-enantiomer during adsorption of N^{α}-acetyl-D,L-tryptophan.[510] Corresponding adsorbents have been prepared from octadecyltrichlorosilane and indium and tin oxides[511] and sugar acrylates imprinted with Z-L-aspartic acid (and recognising the imprint),[512] imprinted acrylamide–methacrylic acid–vinylpyridine copolymers,[513] crosslinked poly(alkene)s (imprinting with L-phenylalanine leads to good chiral discrimination),[514] poly(acrylate)s (imprinting with Boc-L-phenylalanine and recognizing the imprint when adenine and 2-aminopyridine are incorporated in the polymer).[515] Further studies from other pioneers in this area (Volume 31, p. 44) employ common poly(alkene) polymers studied after imprinting with Boc-L-tryptophan,[516] and D-phenylalanine.[517] Nylon-6 imprinted with L-glutamine was found to show enhanced adsorption for the imprint in comparison with its enantiomer,[518] and cellulose acetate membranes imprinted with Z-D-glutamic acid allowed the D-enantiomer to permeate preferentially when presented with D,L-glutamic acid.[519] Poly(aniline) imprinted with (R)-camphorsulfonic acid adsorbs L-phenylalanine but not its enantiomer.[520]

The explanation for the enantiomeric imbalance in the amino acids originating in living organisms on Planet Earth has settled down to a few distinct categories of speculation, each with a considerable volume of literature.[521] Prebiotic (and current) delivery of extraterrestrial amino acids that have undergone enantioselective photodecomposition having been subjected to circularly-polarized infrared radiation is a favoured theory,[522] and radiolysis and radioracemization considered to have been verified in some laboratories for solid D- or L-leucine has been extended to representative oligo(L-leucine)s and poly(L-leucine)s.[523] Calculations of the parity-violating energy shift for L-valine support its small energy advantage relative to its enantiomer, thus giving more credence to both the electroweak energy theory and the Salam phase-transition theory as the basis for the predominance of the L-enantiomers of the α-amino acids.[524]

5 Physico-chemical Studies of Amino Acids

5.1 X-Ray Crystal Analysis of Amino Acids and Their Derivatives. – Crystal structure analysis data have been reported for amino acids [hexagonal L-cystine (electron density determination),[525] D,L-cysteine,[526] L-asparagine hydrate, D,L-glutamic acid hydrate, D,L-serine, and L-threonine (fast diffraction

using synchrotron radiation giving charge density distribution),[527] D,L-histidine,[528] 6-fluoroDOPA monohydrate[529]], amino acid salts [mono-L-alaninium nitrate,[530] mono-β-alaninium nitrate,[531] L-argininium diphenylacetate,[532] L-cysteinium L-tartrate monohydrate[533]], 1:1-amino acid–amino acid pairs [L-valine or L-leucine co-crystallized with D-2-aminobutanoic acid, D-2-aminopentanoic acid, or D-methionine,[534] L-isoleucine co-crystallized with each of seven D-amino acids,[535] D-norleucine co-crystallized with each of a number of L-amino acids[536]], derivatized amino acids [ethyl N-acetyl-L-tyrosinate (charge density study),[537] methyl D-phenylglycinate perchlorate–18-crown-6 complex,[538] N-benzenesulfonyl-D-glutamic acid,[539] N-(cytosinyl)-L-tyrosine,[540] N-[3-(cytosin-1-yl)propionyl]-L-isoleucine,[541] methyl N-ferrocenylglycinate,[542] 2-(toluene-p-sulfonylamino)- and -methylamino-butanoic acid fluorides and the corresponding 2-methylpropanoic acid derivatives,[543] N-trityl- and N-(9-phenylfluorenyl)-N-carbonylamino acid anhydrides (NCAs)[544]], and N-Boc-β-alanine N′-methylamide.[545]

5.2 Nuclear Magnetic Resonance Spectrometry. – Conventional studies cover ^{1}H-NMR of solid tyrosine derivatives (alone and mixed with L-leucinamide),[546] and N-acetyl-D-aspartic acid[547] and other amino acids assessed by ^{1}H-NMR *in vivo*.[548] N-Acetyl α-amino acid esters[549] and N-acyl (4R,2S)-4-amino-2,4-dimethylbutanoic acid,[550] N-(p-tolyl)- and N,N-dimethylglycines,[551] α-tert-butyl β-benzyl N-(p-chlorobiphenylsulfonyl)-3-allylaspartate,[552] and kainic acid[553] have yielded ^{1}H-NMR data, used to assess intramolecular hydrogen bonding, relative stereochemistry, and conformational equilibria.

Determination of enantiomeric excess data for amino acids has been reported for weakly acidic solutions containing the lanthanum(III) N,N,N′,N′-tetrakis(2-pyridinylmethyl)-(R)-propylenediamine complex[554] and a similar approach using (R)-(+)-[{Pd(η^5-C_5H_5)Fe(η^5-C_5H_3CMe=NAr)}(μ-Cl)]$_2$.[555] ^{1}H-NMRdata for (R)- or (S)-N-Boc-phenylglycyl derivatives of α-substituted primary amines $R^1R^2CHNH_2$ can be used for the same objective, also the reverse approach in which an amine of known absolute configuration provides the amides from amino acids whose enantiomeric excess values are required.[556]

Complete assignments of ^{13}C-NMR resonances have been deduced for N-(alkanoyl)- and N-(3-oxoalkanoyl)-L-homoserine lactones.[557]

Decay of ^{1}H-^{15}N-NMR 2-spin order data for L-tryptophan provides information on exchange kinetics for indole protons with water,[558] while more fundamental instrumental aspects leading to resolution enhancement have been established through ^{15}N-NMR of [per-^{15}N]L-arginine hydrochloride.[559]

^{31}P-NMR monitoring of aminoacylation of 5′-adenosine monophosphate by amino acids using standard condensation reagents illustrates one of the simplest uses of routine NMR spectroscopy.[560]

^{77}Se-NMR data for ^{77}Se-enriched L,L-selenocystine[561] and D,L-selenomethionine[562] have been determined.

5.3 Optical Rotatory Dispersion and Circular Dichroism. – Current options for deducing structural information from CD data are well shown for

L-histidine, at the membrane–water interface with phosphatidylcholine. The sign of the Cotton effect developed in the imidazole chromophore has been interpreted in terms of structure of the ion-pair that forms at the interface.[563]

CD data obtained with more conventional systems, [Pd(dmba)(acac)] complexes [dmba = 2-{(dimethylamino)methyl}phenyl-Cl],[564] Mo, Rh, or Ru complexes $[M_2(O_2CR)_4]^{n+}\ X^{n-}$ (molybdenum complexes give two Cotton effects in the 300–400 nm region; the other complexes give features at wavelengths up to 600 nm),[565] and copper(II) complexes of N,N-dialkylamino acids,[566] have been used in traditional applications of CD for the assignment of absolute configuration to amino acids. The last-mentioned study is notable for having demonstrated the acquisition of this information with only microgram quantities of an amino acid.

5.4 Mass Spectrometry. – As discussed in the adjacent sections, spectroscopic instrumentation continues to be applied to amino acids and their derivatives in both routine and pioneering contexts. MS study of underivatized amino acids currently falls in both these contexts, acknowledging the tailoring of ion sources to the special needs of amino acid studies. Glycine cations are accompanied by anions as a result of mild ionization, shown in a study aimed at correlating experimental data with molecular orbital calculations of bond cleavage.[567] Collision neutralization of the α-glycine cation leads to the corresponding radical which is stable on the microsecond time scale.[568] Features in the MS of sodiated and caesiated glycine and arginine indicate that sodium ions are solvated by both amino and carboxy groups, but caesium ions are solvated only by the carboxy group.[569] A long-standing problem, the differentiation of leucine from isoleucine by MS, succumbs to standard electrospray ionization MS when the respective $[M-H]^-$ ions, *m/z* 130, are separated on the basis of asymmetric waveform ion mobility, to allow quantitation of a mixture of one equivalent of either amino acid in the presence of 625 equivalents of the other.[570] Photoionization of ion beam-desorbed amino acids using femtosecond laser pulses at 195 nm and 260 nm has been studied, leading to decarboxylated ions at the shorter wavelength (except for tyrosine and tryptophan, from which the side-chain cation is produced by α-cleavage).[571] Chemical ionization MS of amino acids using dimethyl ether as reagent has been reviewed;[572] use of 2-methoxyethanol generates $[M+H]^+$, $[M+13]^+$, $[M+27]^+$, and $[M+77]^+$ from amino acids, with the first and last of these being the most abundant.[573]

Unashamedly routine applications of MS to amino acid analysis have appeared for homocysteine (after stable isotope dilution with $[^2H_8]$homocystine),[574] and mono- and dihydroxypipecolic acids in plant samples (negative ion MS–MS).[575]

MS spectra of amino acid derivatives are determined either to support analytical studies, or for extending the scope of newly-developing instrumental techniques. In the former category, MALDI-TOF data have been secured for N-acetylcysteine–1,4-dihydronaphthalene adducts,[576] MALDI-PSD and electrospray data for thionopeptides (thermal chain cleavage at the thioamide

residue),[577] electrospray ionization mass spectra for PTHs[578] and N-terminal analysis of peptides through PTH generation from PTC-peptides.[579] Valine and its naphthylamide, nitroanilide, N-dansyl, and PTH derivatives have been studied by laser-desorption MS, from which the benefits of derivatization for reliable analysis are demonstrated.[580] Estimation of the (N^{ε}-trimethyl)lysine content of human serum by MS using a salt of the methyl ester suffers interference from homoarginine due to coincident relative molecular mass, a problem that is avoided by derivatization with acetylacetone or by acetylation.[581] L-Amino acid methyl ester salts are incorporated better than their enantiomers into matrices of D-mannose, D-galactose, or D-glucose, and SIMS data for the resulting complexes can be used for optical purity determination of partly racemic amino acids.[582] Chiral recognition is established through FABMS of chiral crown ether complexes[583] and spiroacetal polyether complexes[584] of amino acid derivatives. These astonishing results are matched by MS of 1:1-amino acid–β-cyclodextrin complexes, determined after conventional electrospray ionization.[585] Collision-induced dissociation spectra of protonated trimers of amino acids formed by electrospray ionization in the presence of Boc-L- or D-phenylalanine, Boc-L-proline or O-benzyl Boc-L-serine, have been interpreted in terms of chiral recognition.[586]

Some of the mild ionization methods are applied to samples evaporated on to metal surfaces, and Li and Na binding energies of N-acetylamino acids have been determined to provide insight into factors affecting release of ions into the gas phase.[587]

5.5 Other Spectroscopic Studies of Amino Acids. – This, something of a catch-all section for spectroscopic data of amino acids not covered in preceding sections, has expanded in recent volumes because of simplified instrumentation for some classical and newer techniques. Fourier transform infrared data for glycine[588] and valine[589] in an argon matrix have proved to be a convenient means of demonstrating the proportions of the three predominant conformers in the former case and their interconversion through UV irradiation, and in the latter case the first observation of the non-ionized tautomer. Low temperature IR study of D,L-serine has been reported,[590] and familiar laboratory IR spectroscopic protocols have been applied to arginine and its derivatives,[591] to L-alanine,[592] and to the establishment of dimers in CCl_4 solutions of Boc-L-phenylalanine.[593]

IR-Raman spectroscopic studies of D,L-histidinium dinitrate and L-histidinium sulfamate,[594] L-asparagine monohydrate,[595] complexes of N-benzoyl-L- and D-leucine with β-cyclodextrin,[596] and L-tryptophan in KBr,[597] represent standard data-gathering applications, while surface-enhanced Raman scattering data for lysine adsorbed on gold colloid,[598] α,ω-diamino acids adsorbed on gold and silver surfaces,[599] and representative amino acids adsorbed on an electrochemically-roughened silver surface[600] provide information on structural and conformational aspects.

Microwave spectra of [^{18}O]-glycine[601] and alaninamide isotopomers[602] have been interpreted in terms of distributions of conformations.

ESR spectroscopy, the indispensible support of studies of mechanism in radical chemistry, has revealed attack by the hydroxyl radical at the α-carbon atom of glycine and side-chain H-abstraction with other amino acids,[603] and formation of transient radicals from histidine through reaction with hydroxyl radicals generated in the titanium(III)–H_2O_2 system.[604] Autoxidation of methyl 4-(N-hydroxyamino)-N-toluene-p-sulfonyl-L-prolinate has been shown to generate aminoxy radicals.[605] ESR monitoring of X-irradiated L-alanine reveals the formation of the well-known deamination product $MeC{\cdot}HCO_2H$ at room temperature but at higher temperatures another stable radical tends to predominate.[606]

Vibronic spectra of tyrosine and tryptophan in helium droplets at 0.38 K (determination of electron energy levels)[607] and electron diffraction of gaseous L-alanine (rotational constants and evidence for the adoption of the neutral tautomeric form) have been reported.[608]

5.6 Physico-chemical Studies of Amino Acids. – Sub-sections introduced recently for this chapter continue to provide a rational grouping of topics in this category. Some areas are relevant to an understanding of certain roles of amino acids in living systems, while other topics are routine. The development of the Amino Acid Index (a database for various physicochemical and biochemical properties of amino acids and pairs of amino acids) has been described.[609]

5.6.1 Measurements for Amino Acid Solutions. Solutions of familiar α-amino acids have featured in studies in which measurements are made leading to apparent molar volumes[610-615] (including viscosity-B coefficients,[610,613] and compressibility data[614-616]) standard molar enthalpies of solution and dilution,[617] enthalpic interaction[618,619] and pairwise enthalpic interaction coefficients[620] and activity coefficients.[621] ω-Amino acids are featured in a study in which apparent molar volumes have been determined.[622] Equivalent conductance data for amino acid mixtures in water have been interpreted to reveal side-chain interactions in certain amino acid pairs.[623]

Traditional study of the solubility of common aliphatic amino acids in aqueous $NaNO_3$ or KNO_3 shows no sign of coming to an end.[624] Solubility of one amino acid of a pair in aqueous media increases as the concentration of the other increases,[625] an observation that does not stand up to scrutiny in all combinations of L-cystine, L-tyrosine, L-leucine, or glycine with another amino acid.[626] Factors governing the solubility of amino acids in cationic reversed micelles have been investigated.[627] Of practical value is attainment of 0.2–3M solutions of amino acids in a water-free aprotic system [DMF, tertiary base, CF_3CO_2Na, $Ba(ClO_4)_2$, $Ca(ClO_4)_2$, $NaClO_4$, BaI_2, or $Ca(NO_3)_2$].[628]

Ion-exchange equilibria for amino acids in conventional separation systems have been the subject of thermodynamic modelling[629] and data for equilibria involving amino acids with a liquid sulfonic acid ion exchange medium have been obtained.[630]

Dissociation constants of amino acids have been determined for solutions in

aqueous isopropanol[631] and in aqueous dioxan,[632] and their protonation constants in aqueous dioxan.[633] An assessment has been made of the variation in the values for L-leucine as a function of ionic strength.[634]

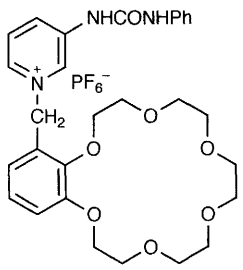
N-Hexadecyl Z-L-phenylalaninamides show remarkable gel-forming properties in organic solvents.[635]

5.6.2 Measurements for Solid Amino Acids. Finely-dispersed L-alanine undergoes a phase transition at 170 K as revealed by phonon echo signal data.[636] Combustion energy data determinations for 13 amino acids have been reported.[637]

5.6.3 Amino Acid Adsorption and Transport Phenomena. Partition of amino acids between immiscible organic and aqueous phases[638] has practical importance in various contexts, *e.g.* in continuous resolution of D,L-isoleucine by countercurrent fractional extraction using an enantioselective two-phase system.[639] A long-running study (Volume 30, p. 47) of the distribution of L-phenylalanine in aqueous di(2-ethylhexyl)phosphoric acid–octane[640] has developed into a study of transport of this amino acid,[641] L-histidine,[642] and L-glutamic acid[643] through corresponding emulsion membranes.

In a study that models an aspect of *in vivo* cellular behaviour, partition coefficients have been measured for amino acids in an aqueous two-phase system developed from dextran, poly(ethylene/glycol), and water.[644] Transport of amino acids through membranes is the other major interest in this category, again with an understanding of *in vivo* systems as the objective, and (−)-menthol- and (−)-nopol-derived mono- and dialkyl phosphates, phosphites, and phosphinites have been established to act as carriers of aromatic amino acids through supported liquid membranes but showing only low or moderate enantioselectivity.[645] A similar study using heteropolysiloxane membranes carrying chiral complexants has demonstrated facilitated transport of the L-enantiomer from D,L-phenylalanine through a pH gradient.[646] Studies of the effects of pH on interfacial transport of amino acids through a cation exchange resin have been reviewed.[647]

5.6.4 Host–Guest Studies with Amino Acids. Refinement of the understanding of the design of cage structures that act as receptors for amino acids follows from the establishment of a widening range of efficient host–guest systems, and there is no lack of new examples in the recent literature. The familiar structural types are not neglected, and recent studies cover 18-crown-6 in water–1,2-dichloroethane[648] and dibenzo-18-crown-6[649] as the means of switching amino acids into the organic phase. Substituted analogues (86)[650] and (87)[651] achieve the same result with neutral aqueous solutions and chloroform, by presenting attachment points for carboxylate and protonated amino groups of amino acids in their zwitterionic form. 5-(2-Carboxyphenyl)-10,15,20-triphenylporphyrins carrying homochiral substituents show selective recognition of amino acid esters,[652] and water-soluble porphyrins that act in this way with amino acids seem particularly promising.[653] Microcalorimetric studies show



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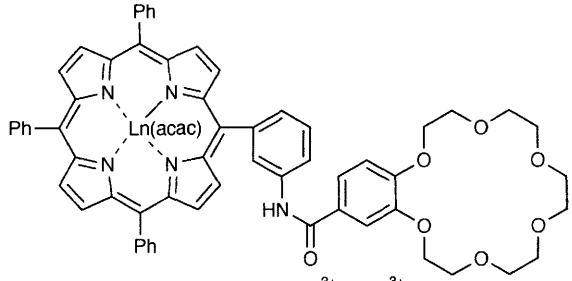
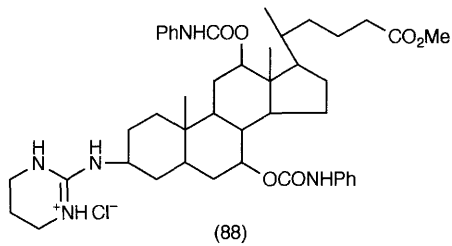


(87) Ln = Er^{3+} or Gd^{3+}



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efficient binding of p-sulfonatocalix[*n*]arenes ($n = 4,6,8$) to lysine and arginine in water,[654] supported by ^{1}H-NMR titration experiments,[655] with rigid peptidocalix[4]arenes showing improved binding characteristics for amino acids[656] and glycyl- and histidyl-calix[4]arenes showing useful complexation of cobalt(II) ions.[657] 5-(Guanidiniocarbonyl)-N-ethylpyrrole-2-carboxamide shows a propensity to bind α-(N-acetylamino) acids in 40% aqueous dimethyl sulfoxide,[658] and guanidinium-substituted cholic acid hosts (88) mediate the extraction of α-(N-acylamino) acids into chloroform from water, showing e.e. approaching 80%.[659] Weak complex formation in water between adenine and non-polar aliphatic amino acids, and stronger binding of polar and aromatic amino acids, is revealed in a thermometric study.[660]

Poly(vinyl alcohol) membranes substituted with β-cyclodextrin have been prepared, showing moderately enantioselective permeation by α-amino acids (improved to 25.4% e.e. with D,L-tryptophan after O-acetylation of the membrane).[661] An erratum[662] draws attention to misleading spectroscopic data concealing the use of impure samples of mono-[6-(m-toluidinyl)-6-deoxy]-β-cyclodextrin (Volume 30, p. 50) in host–guest studies, developed further by the same research group for organoselenium-modified β-cyclodextrins carrying an aromatic grouping.[663] Comparison of the relative effectiveness of L- and D-dansyl-L-leucine-modified β- and γ-cyclodextrins as hosts for amino acids and their derivatives,[664] and chiral recognition properties towards dansylamino acids of a β-cyclodextrin capped by an L-alanyl-crown(3)-L-alanine,[665] have been reported.

The foregoing host types have become well-established by now, and newer ideas are coming forward. Thus, Z-L-alanine and titanium n-butoxide adsorbed on TiO_2 gel give multilayered structures which participate in cycles of solvent extraction and selective binding of the L-enantiomer from solutions

of Z-D,L-alanine (similar examples of 'molecular imprinting' of adsorbents are dealt with in Section 4.17).[666] 'Carbosilane' dendrimers [a 1,3,5-benzenetriamide core substituted at nitrogen with tri(tri-alkylsilylalkyl)silylpropyl groupings] form 1:1-complexes with Fmoc-amino acids in $CHCl_3$, with structure-dependent association constants.[667]

5.7 Molecular Orbital Calculations for Amino Acids. – Calculations for amino acids and their derivatives follow objectives that are familiar from literature coverage in most of the preceding volumes of this series, with occasional extensions into novel areas. For amino acids, outcomes from MO studies of physical properties are: steric and electrostatic properties,[668] solvation parameters derived from atomic radii for constituents of side-chains,[669] densities of aqueous amino acid solutions,[670] absolute proton affinities,[671] charge distribution and molecular electrostatic potentials,[672] conformations (L-alanine[673] and tryptophan[674] in water, side-chain modified L-phenylalanine derivatives,[675] intramolecular interactions of side-chain groupings with the carboxylate anion in arginine[676]), gas-phase tautomerization of sarcosine,[677] spectroscopic data (near-edge X-ray absorption fine structure for cysteine,[678] NMR spectrum of histidine,[679] pH-dependent fluorescence decay of tyrosine and tryptophan[680]). Reactions of amino acids for which experimental data are compared with MO calculations are: high-temperature $^2H_2$–hydroxy-L-proline isotopic exchange,[681] stability and decomposition of stable glycine radicals[682] and L-alanine radicals,[683] and cationized arginine radicals $Arg{\cdot}M^+$ (M = alkali metal ion).[684]

Amino acid derivatives given similar attention are: N-acetylproline N′-methylamide (*cis–trans* isomerism[685]), N-formyl-L-proline N′-methylamide,[686] N-acetylalanine N′-methylamide,[687-689] N-acetyl-L-leucinamide (hydration parameters for comparison with structure determined by neutron scattering),[690] and betaine (crystal structure).[691] Association constants and related parameters have been computed for L-α-amino acid–β-cyclodextrin complexes.[692]

6 Chemical Studies of Amino Acids

6.1 Racemization. – Topics of interest under this heading continue to be researched further, falling mainly into distinct areas: laboratory studies of links between structural features and tendency to racemise; exploitation of racemization kinetics for fossil dating. Protein hydrolysis involves racemization of serine, an unlikely explanation having been advanced[693] that the D-enantiomer is more readily decomposed in the presence of the L-isomer. Further knowledge of the neglected amino acid racemase from *Pseudomonas putida* demonstrates its ineffectiveness with aromatic and acidic amino acids, allowing $^1H - {}^2H$ exchange with retention of configuration for L-phenylalanine and (S)-phenylglycine in ^2H_2O.[694]

The credibility of fossil dating through determination of D:L-ratios of

indigenous amino acids has suffered considerably because corrections to racemization kinetics cannot be computed for catalytic effects of other consituents in the fossil. Amino acids resident in samples for $10^5 - 10^6$ y are totally racemized, and the dating methodology for much younger samples employs those amino acids that are most rapidly racemized. It is these for which new data have been obtained. Thus, aspartic acid racemization applied to bone dating needs to take account of a rapid initial phase which seems to be due to structural changes in the protein (L-asparagine→L-aspartic acid→L-cyclic imide→D-aspartic acid). Although the calculated L:D values are borne out experimentally for the aspartic acid content of proteins at 95–140 °C, the model fails for dentin at 37 °C because the tendency towards cyclic imide formation is conformation dependent and is particularly difficult for this protein and for collagen.[695] For L-isoleucine, whose racemization rate (α-chiral centre) is subject to catalytic effects of unknown origin, it has been suggested that the very slow racemization at the β-chiral centre would be a better basis for dating of fossils.[696] In other words, the method should be restricted to much older fossils than those that have been subjected to the technique recently; this proposal, however, overlooks the fact that the inevitable structural change at the α-chiral centre will affect the kinetics of the racemization process at the β-chiral centre.

Conference reports (ref. 521) include reviews on amino acid racemization and original papers, *e.g.* aspartic acid racemization data for dentin from cave bear fossils, which places the lifetime of the creatures in a wide range of the Pleistocene era.[697]

6.2 General Reactions of Amino Acids. – *6.2.1 Thermal Stability of Amino Acids.* Thermal degradation of amino acids requires investigation, not only for its obvious importance in food science, but also so that problems that arise in amino acid sampling for analysis may be understood. Controversy has arisen over claims that amino acids can be sublimed unchanged (Volume 31, p. 53), since there have been many reports over the years of self-condensation and other changes to amino acids at elevated temperatures. Amino acids on silica gel at 230–250 °C give piperazin-2,5-diones, hexahydroimidazo[1,2-*a*]-pyrazin-3,6-diones and hexahydroimidazo[1,2-*a*]imidazo[1,2-*d*]pyrazin-3,8-diones.[698] Loss of serine and threonine is complete after samples are held for 4 h at 120 °C or for 7 min at 300 °C, leading to pyrazines among other products.[699] Differential thermal analysis and thermogravimetry have been used to study the thermal degradation of α-, β-, and γ-aminobutyric acids and threonine.[700]

6.2.2 Reactions at the Amino Group. The literature on oxidation of amino acids by familiar oxidants continues to be voluminous and too routine to cover here; the policy of previous volumes, to restrict discussion to careful studies with novel oxidant systems, is illustrated by choosing to mention a study of deamination and subsequent decarboxylation of glycine by gold(IV) species, leading to gold(0), glyoxylic acid and ammonium formate.[701] This relatively

standard outcome of oxidation is implicit in the reaction of amino acids with ninhydrin at elevated temperatures, a process which is accelerated in cationic micelles.[702]

Other familiar deamination reactions, aspartate transaminase-mediated equilibration of L-aspartic acid and 2-oxoglutaric acid with L-glutamic acid and oxaloacetic acid (determination of reaction constants),[703] non-stereoselective conversion of α-amino acids into α-hydroxy acids by *Clostridium butyricum*,[704] and inversion of configuration of L-alanine by NAD^+/L-alanine dehydrogenase oxidation, electrochemical regeneration of NAD^+ and reductive amination of pyruvate at the mercury cathode,[705] have been the subject of quantitative studies. The last-mentioned study demonstrates the importance of optimized experimental conditions in making the overall process viable, through circumventing the unfavourable thermodynamics of certain electrochemical steps.

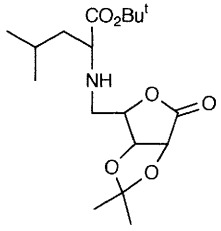
Reductive deamination of α-aminocarbonyl compounds by SmI_2 in THF-HMPA together with a proton source gives the expected result with methyl phenylalaninate, but an unusual outcome in the ring-opening of methyl N-benzylprolinate to give $BzlNH(CH_2)_4CO_2Me$,[706] also seen in reaction of iodine with (diacetoxyiodo)benzene or iodosylbenzene that leads to decarboxylation of pivaloylproline to give $RCONH(CH_2)_3CHO$ through an intermediate N-acyliminum ion.[707]

A permanent feature of this section because of its fascination and importance, studies of the mechanism of the Maillard reaction and its products, continues to reveal surprising new aspects. Thus, L-alanine–pentose or hexose mixtures generate pyrazinium radicals *en route* to conventional Maillard products.[708] Analysis by GLC-MS suggest that the formation of branched-chain alkyl-substituted pyrazines from such mixtures proceeds *via* a Strecker aldehyde.[709] As would be expected, glycosylated amino acids are mild reducing agents and their role in reducing nitrite to nitric oxide under anaerobic conditions[710] may give them an important physiological role. Fully-protected glucosylamino acids formed by Mitsunobu coupling of N-(o-nitrobenzenesulfonyl)amino acids with 2,3,4,6-tetra-O-acetyl-D-glucose, and their Amadori rearrangement products, have been described.[711]

Schiff bases formed between cinnamaldehyde and an L-amino acid ester are equally well viewed as homochiral azadienes, and their complexes with $Fe(CO)_5$ catalyse formation of 4-methoxycyclohexa-1,3-diene-$Fe(CO)_3$ with modest preponderance of the (R)-enantiomer.[712] Schiff bases formed between amino acid esters and a diaryl ketone are readily converted into 1,2-diaryl-2,2-dichloroaziridines through addition of dichlorocarbene,[713] and N-aziridination (solid phase-tethered amino acid reacted with α-bromoacrylates) has been simplified.[714] Azadienes $R^1R^2C{=}CHN{=}CHP(O)(OEt)_3$ can be converted into aziridinephosphonates with diazomethane.[715] Other reactions that involve *in situ* Schiff base formation include monoalkylation [N-ethylation through reaction with acetaldehyde and $NaBH(OAc)_3$,[716] and N-methylation using hexafluoroacetone-protected amino acids[717]]. N-(β-Boc-Aminoalkyl)ation of α-amino acid esters using N-protected α-aminoaldehydes[718] and analogous

N-(β-Fmoc-aminoalkyl)ation with the equivalent α-amino acid S-ethyl thioesters[719] have been developed; in the former case, this step was followed by N-acylation with (thymin-1-yl)acetic acid and related nucleobase moieties, using TBTU as condensing reagent to give four new PNA monomers (see also Section 4.8). In another study, new PNA monomers, one carrying an N-(pyreneacetyl) grouping[720] and others carrying homologated glycine moieties,[721] have been prepared. N-(2,4-Diethoxycarbonylbuta-1,3-dienyl)amino acid esters are formed using ethyl propynoate as reactant.[722] The conversion of amino acids into silapiperidines through reaction with $Ph_2Si(CH_2CH_2OTs)_2$ offers a new selectively-removeable N-protecting group.[723] Diborane-iodine reduction of solid-phase-tethered N-α-acylamino acids gives secondary amines (tethered α-imino acids).[724]

N-Methylation *via* oxazolidinones obtained from α-amino acids, through treatment with $Na(CN)BH_3/TMSCl$[725] is a standard protocol; straightforward amino acid derivatization operations such as these are covered in a new textbook.[726] N-Alkylation of tert-butyl L-leucinate with a pentose triflate gave the derivative (89) which was developed into the 3-aminopiperidin-2-one (90) intended as a seryl-leucine surrogate.[727] The triflate of ethyl (S)-lactate reacts with ethyl L-alaninate in refluxing nitromethane to give the homochiral C_3-triisopropylamine $N(CHMeCO_2Et)_3$.[728] Mannich reactions of amino acids with 3-phenoxychromones have been described.[729]



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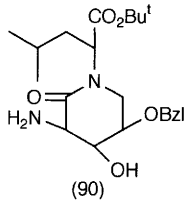

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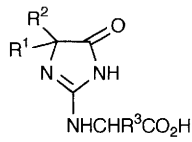

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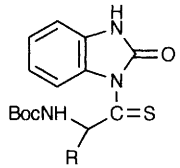
Cyclization of bis(chloromethyl)phenol-formaldehyde tetramers bonded through nitrogen to amino acid methyl esters gives chiral concave calix[*n*]-arenes capable of molecular recognition favouring one enantiomer of a chiral ammonium salt.[730] N-Arylation of amino acids using electron-deficient aryl fluorides is a classical operation that has been extended to 4(6)-mono- and difluoropyrimidinylation through use of 2,4,6-trifluoropyrimidine as reagent.[731] N-(Imidazol-5-on)yl derivatives (91) have been described.[732]

N-Acylation of amino acids serves a range of purposes, particularly the need for reversible N-protection for applications in synthesis. Improved methodology for well-established groupings in this category are: N-formyl [introduced into ethyl N-(ethyl phosphonomethyl)glycinate with triethyl orthoformate],[733] N-trifluoroacetyl (introduced using N-trifluoroacetylsuccinimide),[734] N-acetyl (cleaved with α-chymotrypsin in acetone–alcohol mixtures),[735] N-phenylacetyl (introduction into β-amino acid esters using penicillin G acylase; see also Section 4.17),[736] N-tert-butoxycarbonyl (cleaved with $AlCl_3$;[737] preparation of

tert-butyl N-Boc-S-trityl-L-cysteinate[738]), and N-benzyloxycarbonyl (clean removal using zinc powder in neutral aqueous conditions[739]).

The tri-isopropylsilyloxycarbonyl ('Tsoc') grouping has been advocated for N-protection; it is labile to fluoride ion, so is orthogonal to Boc, Z, and Fmoc in the context of peptide synthesis.[740] N-(Propargyloxycarbonyl)amino acids, originally reported in 1994,[741] are stable to TFA but are cleaved by $Co_2(CO)_8$ in TFA,[742] and are readily cleaved by benzyltriethylammonium tetrathiomolybdate.[743] An N-Z- or N-Boc-sulfonamide $CF_3SO_2NR(p\text{-}CF_3\text{-}C_6H_4)$, R = Z or Boc, is an effective alkoxycarbonylation reagent.[744] The N-[(E)-2-(methylsulfonyl)-3-phenyl-2-propenyloxycarbonyl] (Mspoc) group (introduced using Mspoc-ONSu) is less prone to premature deblocking during peptide synthesis compared with previously-advocated Bspoc and Bsmoc groupings.[745]

N-Acetylation and N-phenylacetylation of PNA monomers has been described, for preparation of corresponding derivatives of the classical DNA mimics.[746] N-Acylation and thioacylation procedures relevant to amino acid analysis are: N-[(S)-(O-acetyl)lactoyl]ation to determine D:L-ratios,[747] N-[β-(Boc-aminoalkyl)thioacyl]ation using (92),[748] phenylthiocarbamoylation[749] and preparation of analogous fluorescent Edman derivatives using 7-[(N,N-dimethylamino)sulfonyl]-2,1,3-benzoxadiazol-4-yl isothiocyanate[750] and (93; R = SO_2Me or SO_2Ph).[751]



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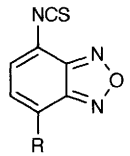

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Allylic carbonates $R^1CH{=}CR^2CH_2OCO_2Et$, carbon monoxide, and $PdCl_2$/dppb react with amino acid esters to give β,γ-unsaturated amides $R^1CH{=}CR^2CH_2CONHR^3$.[752] A classical acylation procedure that is unusual in the amino acid context employs an α-bromoketene (prepared from 3-aryl-2,2-dicyano-oxirane, Li_2NNiBr_4, and Et_3N) leading to N-(α-aryl-α-bromoacetyl)amino acid esters.[753] Other N-acyl derivatives reported in the recent literature are N-(o-carboxybenzoyl)-[754] and N-(o-aminobenzoyl)-[755] L-α-amino acids (the latter showing UV fluorescence properties useful in analysis), and N-acyl-N-hydroxy-L-phenylalanine derivatives,[756] the last-mentioned showing promise as carboxypeptidase A inhibitors. Debenzoylation of N-benzoylamino acid derivatives through N-tert-butyloxycarbonylation followed by $Mg(OMe)_2$ in MeOH at room temperature has been established within a Paclitaxel synthesis.[757]

Photoreactive N-(6-azido-1-oxoindan-4-onyl)amino acids have been prepared for molecular probe studies, for the identification of putative receptors and binding proteins in plants.[758]

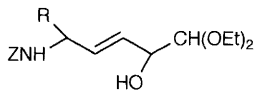
Conversion of amino acids into ureas through reaction of derived isocyanates with amino acid esters,[759] and through a solid phase-tethered i.ocyanato-

acid with simple amines,[760] provides starting materials for potentially effective pharmaceuticals. Decarbamoylation of simple ureas $H_2NCONHCHRCO_2H$ occurs using nitrogen peroxide (or its equivalent; a mixture of nitric oxide and oxygen) in water.[761]

6.2.3 Reactions at the Carboxy Group. Like the preceding section, papers in this category describe a similar mixture of improvements to well-established procedures, as well as novel procedures. The carboxy group of an N-protected amino acid may be displaced by arylation (*e.g.* N-tosylalanine→Ph_2CHMe with benzene and conc H_2SO_4; Volume 31, p. 62)[762] and by a sulfonic acid group [(R)-N-ethoxycarbonyl-D,L-norleucine→2-aminohexanesulfonic acid].[763] Hypotaurine partially disproportionates into taurine, 2-aminoethyl-2-aminoethanethiolsulfonate, and ethanolamine as its solution in hydrochloric acid is evaporated.[764]

Esterification (tert-butyl esters prepared using a di-tert-butyl dicarbonate;[765] methyl esters prepared using a strong acid ion exchange resin suspended in methanol,[766] 9-fluorenylmethyl esters prepared using 9-fluorenylmethylchloroformate;[767] aryl esters from aryl 4-nitrobenzenesulfonates[768]), reduction (CO_2H→CH_2OH using $NaBH_4$-$NiCl_2$ or MoO_3 in water,[769] using $NaBH_4$-cyanuric chloride,[770] *via* pentachlorophenyl esters using $NaBH_4$-I_2 in THF,[771] *via* oxazolidinones using $NaBH_4$,[772] *via* the BuLi–DIBALH 'ate complex' for highly hindered α,α-dialkyl-α-amino acid esters, or using $LiAlH_4$ with persilylated α-benzylhistidine[773]), and further elaboration of the CH_2OH group (→CH_2I→$CH_2CH{=}CH_2$) to convert L-norvaline into the substrate for a Grubbs' ring-closing metathesis synthesis of (S)-(+)-coniine have been reported.[774] Classical Grignard addition to protected serines (CO_2H→CPh_2OH) yields ligands for zinc reagents that have been developed for aldehyde elaborations.[775] Acid chloride preparations [Fmoc-amino acids with bis(trichloromethyl) carbonate[776]] have been studied. N-Protected β-aminoalkanols provide the starting point for the preparation of N-(β-aminoalkyl)amino acid derivatives through Mitsunobu coupling with N-Pmc-amino acid esters.[777]

Partial reduction to give N-protected L-α-aminoaldehydes has become a standard starting point for general organic synthesis, now that initial difficulties in methodology and retaining optical stability of the products have been overcome. An undergraduate exercise proposed to fill five 8-hour laboratory periods starts from L-amino acids and proceeds *via* Z-L-α-aminoaldehydes to products (94) and (95).[778] N-Protected β-amino aldehydes can be prepared



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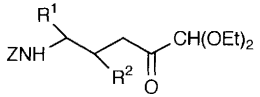

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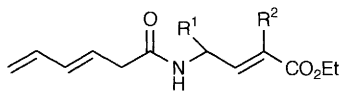


(96)

from α,β-amino acids ($NaBH_4$ reduction of unsymmetrical anhydride, then MnO_2 oxidation) and thence to δ-amino-α,β-unsaturated alkanoates through Wittig homologation.[779]

N-Boc-α-Amino aldehydes (ref. 127) have been converted into (E)-methoxyalkenes BocNHCHRCH=CHOMe and onwards to α-phenylseleno-β-amino aldehydes that can be transformed into epoxides and aziridinecarboxylic acids;[780] into the Diels-Alder substrate (96) through an obvious series of reactions;[781] and two-carbon elongation of an L-serine ester after conversion into an N-tritylaziridinecarboxylate, involving Claisen condensation with the enolate of an alkyl acetate to give the γ-amino-β-ketoester $R^1NHCHR^2COCH_2CO_2R^3$ that opens up synthesis of trisubstituted E-alkenes and N-allylamines.[782] Allylation of protected L-tyrosinal gives a mixture of syn- and anti-2-amino alcohols developed further into β-turn mimetics.[783] Further elaboration of 2,3-epoxyalkanols produced by transformation of the carboxy group of a Boc-amino acid gives 1-cyano-2,3-diols by reaction with diethylaluminium cyanide.[784] A route to erythro-(N-protected α-aminoalkyl)-epoxide that differs from the usual elaboration of an amino acid has been illustrated using $PhCH_2CH(OH)C{\equiv}CTMS$ for preparation of the phenylalanine-related compound used in the production of Saquinavir.[785]

The generation of a ketosulfone by reaction of a protected L-tyrosine ester with the dilithio anion of methyl phenyl sulfone requires two equivalents of reagent.[786] Formation of an ylide [$CO_2H{\rightarrow}COC(=PPh_3)CN$] from a protected L-phenylalanine by coupling to $Ph_3P{=}CCN$ opens up a route to α-keto-amides and peptidic α-hydroxy-amides found in bacterial secondary metabolites phebestin, probestin and bestatin.[787] α-Ketophosphonates can be obtained by Arbuzov reaction of a protected amino acid chloride with triethyl phosphite.[788]

α-Aminoketones can be formed *via* Weinreb amides [$CO_2H{\rightarrow}CONMe(OMe){\rightarrow}COCH_2CH_2Ph$][789] and morpholides;[790] α-(N,N-dibenzylamino) ketones are substrates for stereoselective conversion into tertiary alcohols through non-chelation controlled Grignard type reactions[791] and stereoselective reductive amination.[792] The latter process gives 1,3-diaminoalkanes when applied to β-aminoketones prepared from Weinreb amides of N-protected β-amino acids;[793] an alternative route to these involves Curtius rearrangement [$BocNHCHRCH_2CO_2H{\rightarrow}BocNHCHRCH_2NHCO(Nsu)$].[794] Conversion of N-Boc-β-alanine into N-[3-(N-Boc-amino)thiopropanoyl]phthalimide and thence to ethyl 3-aminodithiopropanoate has been developed using standard thionation protocols.[795] C_2-Symmetrical enantiopure β,β′-diaminoalkyl sulfides have been prepared through a lengthy route starting from α-amino acids.[796]

N-α-(Boc-Amino)acylsilanes $BocNHCHRCOSiMe_2Ph$ offer valuable three-carbon elongation opportunities, those from phenylalanine and isoleucine giving statines through aldol addition and conversion into N-protected β-aminoalkanols.[797] Condensation of $TMSCH_2MgCl/CeCl_3$ with ethyl (R)-β-amino-β-phenylpropionate gives homologue $PhCH(NR^1R^2)CH_2C(=CH_2)CH_2TMS$.[798]

Enantioselective amino acid ester hydrolysis data have been accumulating for many years, and added to by finding up to threefold differentiation between N-protected D- and L-phenylalanine p-nitrophenyl esters in the

presence of (+)-tubocurarine,[799] and similar mediation by chiral metallomicelles [lipophilic copper(II) complexes][800] and N-benzyloxycarbonyl-L-Phe-L-His-L-Leu-OH[801] in the hydrolysis of N-dodecanoyl D- and L-phenylalanine p-nitrophenyl esters.

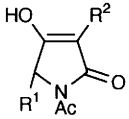
Ammonolysis of methyl D,L-phenylglycinate in tert-butanol at 40 °C catalysed by Novozym 435 (*i.e.*, *Candida antarctica* lipase B) leads to D-phenylglycinamide in 78% e.e. at 46% conversion, pyridoxal-mediated racemization of the unconverted ester contributing to an efficient protocol (but only if operated at −20 °C, when the amide racemises much more slowly than the ester).[802] Not surprisingly, ammonium chloride with an N-protected amino acid and base gives primary amides through a peptide synthesis protocol.[803] A reaction mixture containing an N-protected amino acid, isobutyl chloroformate, and an amine gives amides through a kinetically-controlled process; the disdain with which experienced peptide chemists would dismiss such a protocol is unwarranted since N-tert-butyloxycarbonylation is discovered to be insignificant.[804] Solid phase synthesis of Fmoc-amino acid amides [reductive amination of tethered 4-formyl-3,5-dimethoxyphenoxyvaleric acid (HCO-link-P→R^1NHCH-link-P→R^2CONHR^1CH-link-P→R^2CONHR^1 by conventional protocols] is applicable also to the preparation of sulfonamides[805] (it is presumably suitable for phosphorus acid amides, too). HMDS-Promoted amidation of Boc-L-alanine requires drastic conditions (110 °C) but gives mono-acyl derivatives with di-amines.[806] Condensation of arylalkylamines with N-Z-L-phenylalanine carbamoylmethyl ester is effected by the use of α-chymotrypsin in acetonitrile with low water content,[807] and tyrosinase-mediated cleavage of N-protected amino acid phenylhydrazides offers a novel C-protection strategy.[808] Hydroxylaminolysis of N-protected amino acids leading to N-protected α-aminohydroxamic acids is best accomplished *via* oxazolidinones,[809] for which a simple preparation driven by microwave irradiation has been developed.[810]

6.2.4 Reactions at Both Amino and Carboxy Groups. Heterocyclic synthesis using α-amino acids has been reviewed[811] with special reference to aziridine-2-carboxylic acid and 3-aminoazetidin-2-ones.[812] Standard applications have been illustrated in recent papers, with new details: N-acetyltetramic acids (97) prepared through condensation of N-acetyl-L-α-amino acid N′-hydroxysuccinimidyl esters with malonate anions are only partially racemized;[813] ammonium formate serves as condensing agent for conversion of α-[N,N-di(carboxymethyl)amino] acids into 3,5-dioxopiperazinoalkanecarboxylic acids;[814] α-(N-acylamino) acids attached to a solid phase reduced and then converted into 1,6-disubstituted 2,3-diketodihydropiperazines.[815] Oxazolidinone formation from α-amino acids and trifluoroacetone, a useful one-step protection strategy for both amino and carboxy groups, gives an intermediate iminium species (98) when conducted with N-chloromethylamino acids (prepared from the amino acid, formaldehyde, and $SOCl_2$; [1,3]cycloaddition with alkenes verifies the nature of the intermediate).[816] Dieckmann reaction of adducts of (R)-β-amino esters with methyl acrylate, and hydrogenation of the

resulting enol ethers, gives 2,4,5-trisubstituted piperidines with high diastereoselectivity.[817]

Condensation of tartaric acid with N-benzylaminoalkanols prepared from L-α-amino acids leads to 3-aza-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic acids,[818] and amino acid phenylhydrazides yield hexahydro-1,2,4-triazin-6-ones in aqueous formaldehyde.[819] A longer pathway starting from L-proline leading to the saturated bicyclic system (99) *via* (S)-2-hydroxymethyl-N-Boc-pyrrolidine provides a chiral catalyst for Baylis-Hillman reaction of aldehydes with vinyl ketones.[820]

'N-Carboxyanhydrides' (NCAs; *alias* oxazolidin-2,5-diones), well known for their propensity to polymerise to give oligo- and poly(α-amino acid)s, and for acting as Friedel-Crafts acylating agents towards arenes in the presence of $AlCl_3$,[821] can be formed in less than one hour at room temperature from solid N-carbamoylamino acids (Volume 29, p. 72) in an atmosphere of nitric oxide and oxygen in proportions 4:1.[822] Thiohydantoins are released in the newly-revived C-terminal peptide sequence determination protocol, and standards have been prepared from N-protected amino acids, dicyclohexylcarbodi-imide, and trimethylsilyl isothiocyanate (see also Volume 30, p. 60).[823]



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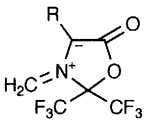

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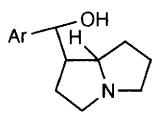

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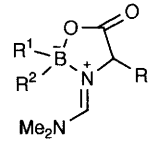


(100)

Oxazaborolidinones (100) can be obtained as a single diastereoisomer by crystallization-induced asymmetric transformation; the stereogenic boron atom resists equilibration on the time-scale of enolate alkylation with iodomethane and other common electrophiles.[824] These heterocycles, derived from homochiral α-amino acids, are employed as chiral catalysts for aldol reactions,[825] and for asymmetric borane reduction of cyclic meso-imides.[826]

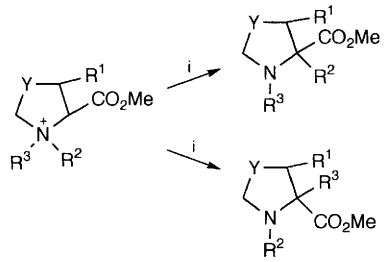
The formation of peptides from amino acid mixtures is becoming a major topic of research, particularly in the context of prebiotic protein synthesis from partly-resolved amino acids (for a review see ref. 827). Most of these studies involve an insoluble inorganic medium as catalyst; clays promote the formation of glycine oligomers but lack the ability to perform similarly with alanine,[828] and clays are therefore established to offer an alternative to salt-induced self-condensation (Volume 31, p. 63) of amino acids.[829] However, oligomerization of glycine has been demonstrated in a flow reactor that simulates a submarine hydrothermal vent but lacks any condensation reagent or metal ion or template catalyst (such as a clay or other mineral).[830] Carbonyl di-imidazole is a condensation reagent that causes oligomerization of L-glutamic acid in water, but not of γ-carboxy-L-glutamic acid, which is oligomerized by magnesium salts and hydroxylapatite.[831]

6.2.5 Reactions at the α-Carbon Atom of α- and β-Amino Acids. Papers under this heading are mostly collected under applications of α-amino acid alkylation

in synthesis (Sections 4.1.5, 4.5, 6.3). Conventional α-alkylation of homochiral β-(pyrrolidin- and piperidin-2-yl)acetates is highly diastereoselective,[832] and α-hydroxylation of β-benzoylamino esters through iodination of the anion (NaHMDS) followed by hydrolysis depends on the intermediacy of a phenyloxazoline.[833] α-Thiocyanation of enamino esters is achieved using 4-chloro-5H-1,2,3-dithiazol-5-one.[834]

6.3 Specific Reactions of Amino Acids. – This section collects papers that deal with structural changes to side-chains of common amino acids, through reactions that often also involve amino or carboxy groups. Procedures in this category can be applied to proteins for modification of side-chains to assist amino acid analysis procedures.[835] A 'Practical Approach' monograph includes protocols for side-chain modifications to several coded L-α-amino acids.[836]

Saturated aliphatic side-chains show a limited range of reactions that result in their functionalization. Oxidation with 3,3-dimethyldioxirane leads mainly to O-insertion into C–H bonds (notably, in the side-chain in preference to the α-CH bond),[837] sodium m-chloroperbenzoate and O_2 can convert benzylic methylene of 1-aminoindane-1-carboxylic acid derivatives to C=O,[838] and proline 3- and 4-hydroxylases mediate the regio- and stereospecific hydroxylation of L-2-azetidinecarboxylate, 3,4-dehydro-L-proline, and L-pipecolic acid.[839] Halogenation is particularly useful since it can open up further synthesis opportunities, such as conversion of protected 4-bromoglutamic acid into heteroatom substitution products, *e.g.* 4-mercaptoglutamic acid.[840] Cyclopropane formation from methyl (S)-N-phthaloyl 4-bromoleucinate *via* the α-methoxyamide that is generated with $NaBH_4$–MeOH to give the protected '2,3-methanovaline',[841] and of '3,4-methano-L-glutamic acid', *alias* L-2-carboxy(2-carboxycyclopropyl)glycine, prepared from the 3,4-dehydro-amino acid orthoester and diazomethane has been reported.[842] Completely stereospecific [1,2]- or [2,3]-shifts occur with ylides generated from N,N-dialkylproline or -threonine derivatives by treatment with Bu^tOK (Scheme 22).[843]

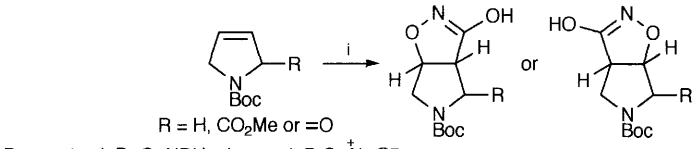


Reagent: i, $KOBu^t$

Scheme 22

α,β-Dehydroalanine prepared on a solid phase exhibits standard Diels-Alder addition behaviour.[844] Methyl N-cinnamyl-N-Z-L-vinylglycinate undergoes sensitized intramolecular [2+2]photoaddition to azabicyloheptanes,[845] and N-

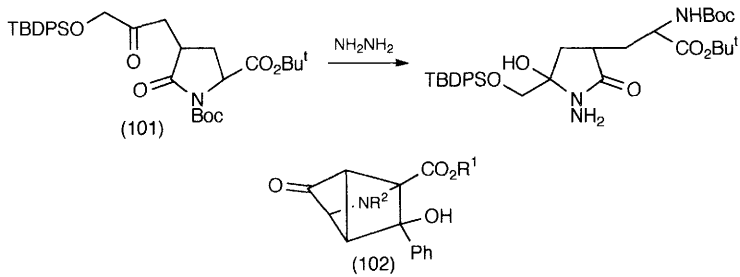
ethynyl-L-allylglycine gives highly functionalized prolines through an intramolecular Pauson-Khand reaction.[846] 3,4-Dehydro-L-proline is one of the most readily accessible alkene analogues of common L-α-amino acids, and is the starting point for preparation of a version of L-proline in which all methylene groups are stereoselectively labelled with ^2H (catalytic deuteriation, RuO_4 oxidation to the labelled pyroglutamate, then syn-selective deuteriation of the derived aminal with Et_3Si^2H-$BF_3.Et_2O$).[847] Cycloaddition of bromonitrile oxide to Δ^3-pyrrolines gives the bicyclic isoxazolinylprolines (Scheme 23),[848,849] one of these studies covering a broad range of substrates (ref. 848) and the other study (ref. 849) proposing the products from dehydroproline as kainate receptor agonists. 1,2-Didehydroproline benzyl ester N-oxide is a source of isoxazolidine and isoxazoline analogues of proline through cycloaddition to alkenes and alkynes respectively.[850]



Scheme 23

Propargylglycine ethyl ester has been subjected to $Rh_2\{(2S)\text{-nepy}\}_4$-catalysed cyclopropenation to give ethyl 2-aminomethylcycloprop-2-ene-1-carboxylate as destined for testing as GABA analogues.[851]

A keto group in an amino acid side-chain activates neighbouring structures towards attack, as in 'ring-switching' conversion of the pyroglutamate analogue (101) into a β-substituted L-alanine.[852] As a consequence of photoactivation, different types of structural change can ensue, as with phenyl ketones derived from L-4-oxoproline giving (102).[853] Baeyer-Villiger oxidation

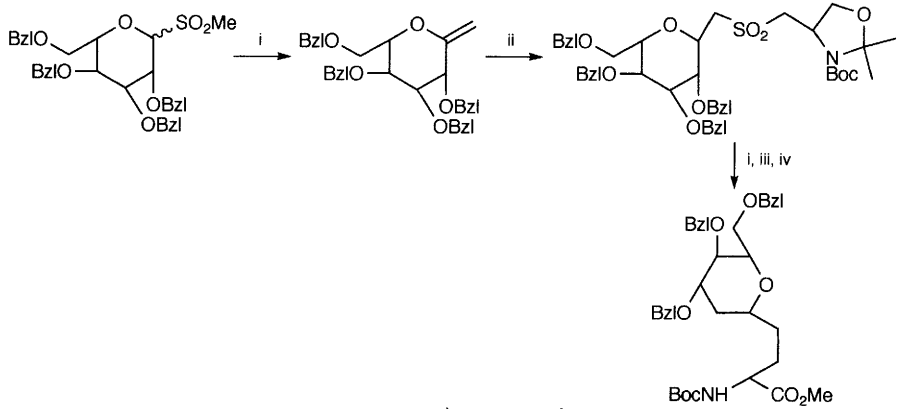


[m-chloroperbenzoic acid catalysed by copper(II) acetate] of this proline derivative gives L-aspartic acid, and prior alkylation adjacent to the keto-group of the substrate delivers β-substituted aspartic acids.[854] tert-Butyl N-Z-4-oxoprolinate undergoes reductive amination with amino acid esters to give (4S)-4-alkylaminoprolines, from which 3-oxo-1,4-diazabicyclo[2.2.1]heptanes have been obtained by cyclization.[855] *trans*-3-Alkylprolines have been prepared by aldolization of the enolate of N-(9-fluoren-9-yl)-4-oxoproline and routine

steps to complete the process.[856] Full reduction of the keto-group in the corresponding aryl ketones using $Et_3SiH/TiCl_4$ establishes syntheses of N-protected 2-amino-4-arylbutanoic acid and 2-amino-5-arylpentanoic acid.[857]

Hydroxyalkyl side-chains generate a profusion of synthesis opportunities, and reviews have appeared of serine derivatives[858] and of N-tritylserine and allothreonine derivatives.[859] O-Glycosylation can be effected through Michael addition of protected serines and threonines to D-galactals,[860] O-prenylation *via* methyl N-Z-aziridinecarboxylate,[861] and O-cyclohexylation *via* the cyclohexenyl ether.[862] Other straightforward manipulations lead to γ-carboxy-D,L-glutamic acid (dehydration to give methyl N-tetrachlorophthaloyl dehydroalaninate, used for Michael addition to a dialkyl malonate),[863] 2,3-disubstituted glutamic acid derivatives through 1,4-addition of the lithium salt of L-threonine-derived 2-phenyl-4-methyloxazoline-5-carboxylate ester to Z-α,β-unsaturated esters,[864] (S)-3,4-dehydroproline (from O-allyl-D-serine),[865] and biomimetic conversion into 4-bromotryptophan (D,L-serine, 4-bromoindole, and *Aspergillus* acylase).[866] Mitsunobu processing of β-hydroxy-α-amino acids to give β-substituted α,β-di-amino acids benefits from the use of cyclic orthoester protection of the carboxy group.[867] L-Serine initiates a route to 3-amino-2-phenylpiperidines including a Substance P antagonist,[868] and D-serine has been used for synthesis of oxazolidinylpiperidines that are starting materials for the preparation of azasugars.[869]

Further uses have been reported for the Garner aldehyde (see also refs. 260, 268, 367), in which the amino group and side-chain function of L- or D-serine are mutually protected through cyclization, and the carboxy group is reduced to aldehyde. An improved synthesis has been published (88% overall yield in four steps)[870] by a group which has developed uses of the (R)-synthon for preparation of C-glycosyl-serines and α-asparagines (Scheme 24)[871] and cross-



Reagents: i, Ramberg–Bäcklund rearrangement; ii, $\diagdown C{=}CH_2 \rightarrow \diagdown CHCH_2I$,

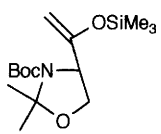
Garner aldehyde $-CHO \rightarrow -CH_2SH$, react with iodomethyl-pyranose then $\diagdown S \rightarrow \diagdown SO_2$;

iii, $TsNHNH_2/NaOAc/85\,°C$; iv, Jones oxidation then CH_2N_2

Scheme 24

coupling of the derived organoborane (side-chain = $CH_2CH_2BR_2$) with vinyl and aryl halides to give novel α-amino acids.[872] A synthesis of β-(tri-O-benzyl-2-deoxygalactopyranosyl)-D-alanine has used the Garner aldehyde with the Wittig reagent of the monosaccharide,[873] an approach used to give α,β-unsaturated ketones (-CHO→-CH=CHCOMe) which after hydrogenation and alkylidenecarbene formation [-CH_2CH_2COMe→-CH_2CH_2C(=C:)Me] and 1,5-C-H insertion gave the isomeric spirocyclopentene from which the '2,5-methanoleucine' derivative could be obtained.[874] An extended route to the manzamine tetracyclic system starts with side-chain aldolization of a Garner aldehyde [-CHO→-(2-ketopiperidin-3-yl)-CH(OH)-], the serine moiety being eventually incorporated into the synthesis target.[875]

The α-methylserine-based Garner aldehyde is illustrated in Scheme 5.[70] The L-threonine-based Garner aldehyde has been converted into the new homo-alanine carbanion equivalent (103) whose use in α-linked C-glycosyl amino acid synthesis (*i.e.*, synthesis of methylene isosteres of O-glycosylserines) has been demonstrated.[876] Uses for preparation of syn- and anti-β-hydroxy-α-amino acids that are constituents of vancomycin involve (R)- and (S)-Garner aldehydes in stereocontrolled arylation.[877] Simple exploration of the chemistry of these synthons gives useful results, such as cyanohydrin formation from HCN in pentan-2-ol with complete stereoselectivity,[878] and fluorination of the N-Boc-Garner aldehyde by diaminosulfur tetrafluoride leading to the extraordinary product (104).[879] Standard reactions allow replacement of aldehyde by novel functional groups, providing the corresponding alkynone (-CHO→-C≡CCOR)[880] as well as the other changes that initiate the applications described in the other papers in this section. Synthesis of sphingosines involves extension of the Garner aldehyde side-chain to $COCH{=}CHC_{13}H_{27}$, and $Zn(BH_4)_2$ reduction,[881] and an equivalent route to the same target has been described.[882]



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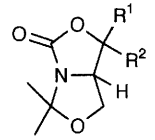
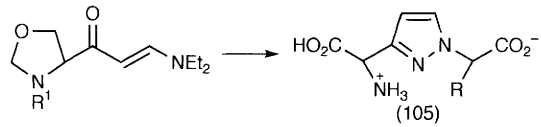


(104) R^1 = F, R^2 = H mixed with R^1 = H, R^2 = F

A related synthon prepared from L-serine, (S)-(+)-4-(2-oxazolidonyl)methyl triphenylphosphinyl iodide, has been engaged in Wittig syntheses with aldehydes to give alkenes, from which β,γ-unsaturated amino alcohols were prepared.[883] L-4-Oxaproline is a little-used synthon, shown to co-operate in some of the typical functional group changes described above (-CO_2H→ -COC≡CTMS *via* the Weinreb amide) to give 1,2-dihydropyrazolyl diacid derivatives (105) by condensation with hydrazino acids $H_2NNHCHRCO_2H$.[884] Routine work as far as the procedures are concerned, but leading to interesting and important synthesis targets, has involved (2S,3R)-threonine [synthesis of enantiomerically-pure piperazine derivatives *via* (106)],[885] L-homoserine [synthesis of novel PNAs, N-Fmoc-δ-amino acids with an ether linkage in the main



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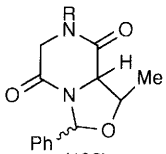

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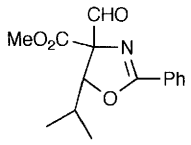
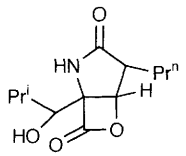


(107)

chain and one of the four nucleobases on a side-chain],[886] and a total synthesis of (+)-lactacystin from (2R,3S)-hydroxyleucine (Volume 31, p. 20) through anti-crotylation of the oxazoline (107).[887] (2S,3S)-N,N-Dibenzyl-hydroxyleucine is liable to cyclize to the protected 3-amino-β-lactone when its carboxy group is activated.[888] A potent analogue (PS-519; 108) of clasto-lactacystin β-lactone has been prepared through a doubly-diastereoselective aldol condensation of oxazoline and aldehyde.[889]

Aspartic and glutamic acids offer a wide range of uses in synthesis, usually aimed at, or proceeding by way of, saturated heterocyclic derivatives. Protected aspartic acid has been used to prepare enantiopure 6-alkylpipecolic acid,[890] N-protected 3- and 4-substituted aminopyrrolidinones,[891] side-chain aryl ketones of aspartimides (from N-acylaspartic anhydrides through Friedel-Crafts arylation) for 1,6-photocyclization to piperidin-2-ones,[892] α-methyl-L-aspartic acid by methylation (MeI-LDA) of the useful synthon (109), prepared from asparagine.[893] D-Aspartic acid is the starting point for a synthesis of allophenylnorstatine, a crucial step being stereoselective hydroxylation of (110).[894] Dianions formed from N-protected dialkyl aspartates undergo 1,2-asymmetric induction during quenching with an electrophile, with preference for the anti-product, but this can be reversed if bulky alkyl groups esters are used.[895] β,β-Dimethylation of dialkyl N-(9-phenylfluorenyl)-D-aspartates and ensuing functional group manipulations provides corresponding new β,β-dimethyl-α-amino acids.[896] Aldolization of the enolate to di-isopropyl squarate followed by easy decarboxylation promoted by the strongly electron-withdrawing squaryl group gives the novel α-amino diacids (111).[897]



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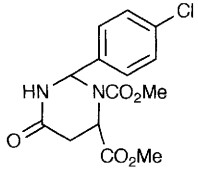

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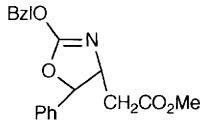

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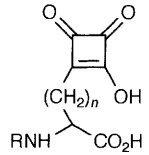
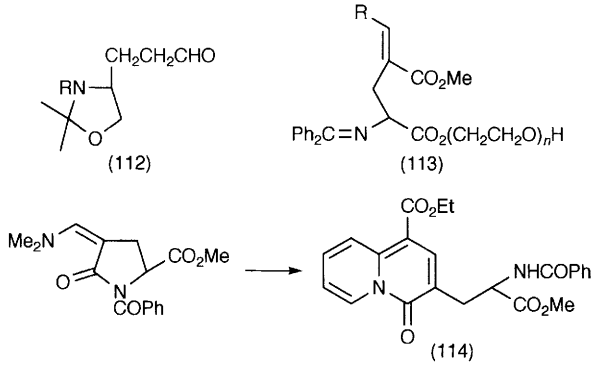


(111)

Novel glycosylated amino acids have been prepared from α-tert-butyl N-Fmoc-aspartate through DCCI-DMAP coupling to C-6 of the glycoside,[898]

and corresponding 2-deoxy-2-fluoroglycosylaspartate and serinates have been described.[899]

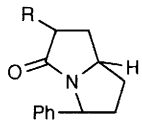
Homologues of the Garner aldehyde can be prepared from any α-amino acid after first reducing the α-carboxy group to CH_2OH, and this has led to (112) by applying standard procedures to a γ-alkyl L-glutamate.[900] Side-chain extension leading to (113; R = H) can be carried further by application of the Heck reaction (*e.g.*, giving 113, R = Ph, using PhI), the poly(ethylene glycol) ester group acting as phase transfer catalyst as well as polymer support for the reactant.[901] Hofmann rearrangement of N^{α}-protected L-glutamine esters to give corresponding N^{α}-protected (2S)-aminobutanoates is a long-known process but its electrochemical variant in trifluoroethanol–MeCN is novel.[902] Side-chain Weinreb amides of solid phase-tethered glutamic acid derivatives have been converted into aldehydes and thence to homologated esters (-CHO→-CH=CHCO$_2$R),[903] and dicyclohexylcarbodi-imide coupling of Z-L-glutamic acid with tryptamine gives the imide, to start a route to indolo[2,3-*a*]-quinolizidines.[904]



Uses of L-pyroglutamic acid in synthesis are well-appreciated (review, see ref. 905). Condensation of its 4-(dimethylamino)methylene derivative with ethyl (pyrid-2-yl)acetate opens up a family of new β-(heteroaryl)-L-alanines (114).[906] C-4-Alkylation can be achieved with O,C-dilithio anions,[907] and N-ethyl N-(*trans*-2-butenoyl)-4,4-dimethylpyroglutamate provides a useful substrate for the study of asymmetric Michael addition reactions.[908] A synthesis of kainic acid starts with L-pyroglutamic acid.[264] Deuteriation of N-Boc-3,4-dehydro-pyroglutamic acid tert-butyl ester gives the (2S,3S,4S)-[3,4-$^2H_2$]isotopomer of this increasingly-used synthon; ring cleavage gives the labelled 2-Boc-amino-5-iodopentanoate, displacement by cyanide ion and reduction providing a route to (2S,3S,4S)-[3,4-$^2H_2$]lysine.[909] Conformationally constrained lysine, ornithine and alanine have been synthesized from pyroglutamic acid *via* the well-established pyroglutaminol derivative (115).[910] Cyclopropanation of the synthon and manipulation of the product has given modified glutamates and arginines,[911] and constrained homoglutamic acids have been prepared by alkylation of the 'Thottathil bicyclic lactam' (115, with saturated lactam ring).[912] The unsaturated 2-amino-adipic acid homologue

(116) has shown similar potential in synthesis, *e.g.* 1,4-addition on treatment with R_2CuLiI_2 and routine work-up giving 2-amino-4-substituted adipic acids.[913]

(S)-Pyroglutaminol derivative (117) has led to a 5-hydroxylated pyrrolidinone, which is structurally related to natural products, *e.g.*, epolactaene and lactacystin,[914] and (S)-pyroglutaminylzinc iodide is suitable for homologation ($-CH_2ZnI \rightarrow -CH_2C{\equiv}CCH_2SiMe_3$) for a new synthesis of (−)-epibatidine.[915] The 3,4-epoxide of (S)-pyroglutaminol has been used in a synthesis of (2S,3S,4R)-3,4-dihydroxyglutamic acid.[916] (S)-1-Benzyl-2-hydroxypyrrolidine derived from pyroglutamic acid has been used to prepare (2S,3S)-3-hydroxy-2-phenylpiperidines.[917]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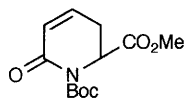
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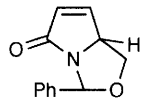
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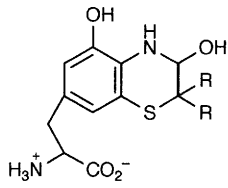

(118)

Reactions at the thiol group of N,C-protected cysteine, leading to djenkolic acid [a consequence of deprotection of the S-dimethylphosphinothioyl derivative using $(Bu_4N)F$],[918] L-felinine (addition to 3-methylcrotonaldehyde, $NaBH_4$ reduction),[919] S-(dihydroxyphenyl)ation and oxidation of the resulting S-cysteinyl-DOPA *via* the 3-hydroxy-3,4-dihydro-1,4-benzothiazine to give (118),[920] S-iminothioethers as intermediates in a mild amidine synthesis (RCN/NH_3/N-acetylcysteine),[921] and formation of (4R)-thiazolidine-2,4-dicarboxylic acid as a mixture of (2R,4R)- and (2S,4R)-diastereoisomers through condensation of L-cysteine with glyoxylic acid in aqueous ethanoic acid at 30 °C,[922] have been described. More routine work deals with preparation of N-Boc-S-alkyl-L-cysteines[923] and S-[^{11}C]methylation.[924] Interest in the last-mentioned preparation lies in practical details for rapid working, involving reactions on C_{18}-Sep-Pak in this case; solid-phase synthesis of 1,4-benzothiazepin-5-ones from resin-bound cysteine with 2-fluoro-5-nitrobenzoic acid is completed with routine steps.[925] S-(Allyloxycarbonylmethyl)ation can be reversed by Pd-catalysed hydrostannolysis using Bu_3SnH.[926,927]

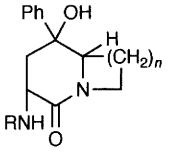
Electrochemical oxidation characteristics of cysteine differ from those of homocysteine because of differences in hydrophobicity and structures of their metal complexes.[928] This explanation may need to be modified in the light of the report that cysteine affects the much slower autoxidation of homocysteine, which is capable of reducing cystine to cysteine.[929] A means of preserving homocysteine-containing clinical samples from oxidative changes, by the addition of 3-deaza-adenosine, has been proposed.[930] Selenocysteine and selenomethionine undergo aerobic decomposition under protein hydrolysis conditions and during ion-exchange purification.[931]

Reaction of S,S′-dibenzyl-N,N′-1,3-propylenediyl bis-L-cysteine with ^{99m}Tc

at pH 12 and further elaboration leads to technetium[99^m]-L,L-propylenedicysteine.[932]

Unexpected flexibility is shown by *Beauveria bassiana* in its conversion of N-phthaloyl D- or L-methionine and -ethionine into the S_S-sulfoxides.[933] Laboratory preparation of sulfoxides of methyl S-methyl N-Z-L-cysteinate and the corresponding methionine using tert-butyl hydroperoxide in supercritical CO_2 has been demonstrated to lead to the anti-isomer.[934] The sulfate anion radical, generated by KrF-laser photolysis (248 nm) of $K_2S_2O_8$, brings about oxidation of methionine and its methyl ester through a 3-electron radical cation intermediate.[935]

S-(Aminoiminomethyl)amides of cysteic and homocysteic acids have been prepared for their potential as mimics of arginine.[936] Ornithine lactams (119, R = TFA or Z; and its epimer as minor product) result from photoinduced ε-H abstraction followed by cyclization of the resulting 1,6-biradicals, from 2-amino-4-oxo-4-phenylbutanoylamines.[937] N^{ω}-Substituted arginine derivatives are effectively prepared from ornithine through mild condensation with $ArSO_2N{=}C(SMe)_2$.[938] A lysine–arginine crosslink develops through reaction of glucose with bovine serum albumin, hydrolysis and isolation giving 2-(5′-carboxypentyl)amino-4-(5′-carboxypentyl)-6,7-dihydroxy-4,5,6,7,8,8a-hexahydroimidazo[4,5-*b*]azepine (120).[939] This shows some instability under the



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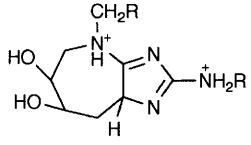
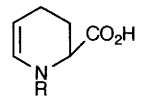


(120) R = $(CH_2)_3CH(NH_2)CO_2^-$



(121) R = Z or Boc

conditions of acid hydrolysis, perhaps explaining why it has not been isolated in real situations before, but otherwise it behaves similarly to the lysine crosslink pentosidine (see also ref. 258). tert-Butyl (9R,10S,11E,13S)-9,10-epoxy-13-hydroxyoctadec-11-enoate undergoes ring-opening with N-acetyl-lysine 4-methylcoumarin-7-ylamide, and the search is on for products of aminolysis of α,β-unsaturated epoxides by protein-bound lysine.[940] Hippuryl-arginine and -lysine react differently with glyoxal at 40 °C, in the obvious way with the former compound but sluggishly with the lysine side-chain, reaction only occurring significantly at 80 °C to give N^{ε}-(carboxymethyl)lysine in low yield.[941] This lysine derivative has been identified as a constituent of proteins,[942] and the N^{ε}-hexanoyl analogue is formed with hippuryl-lysine by reaction with the lipid hydroperoxide, hydroperoxyoctadeca-1,3-dienoic acid.[943] Similar studies of reactions of lysine-containing peptides with *trans*-2-hexenal have been described,[944] and the crosslink formed between lysine residues in adjacent polypeptide chains, through reaction with (E)-4-hydroxy-2-nonenal, has been confirmed to be a 2-alkyl-2-hydroxy-1,2-dihydropyrrolin-3-one imine.[945]

A new look at these processes involving lysine with oxidized species would

be desirable, in view of the easy hydroperoxydeamination of hydrazino side-chains [prepared from lysine derivatives with N-Boc-3-(4-cyanophenyl)-oxaziridine]. Air oxidation in the presence of bicarbonate ions gives the hydroperoxide, which is readily reduced (*e.g.* with a water-soluble phosphine) to 6-hydroxynorleucine.[946]

Simpler heterocyclic syntheses involving lysine include the N-substituted 5,6-dehydropipecolic acid (121; R = Z or Boc) formed from Z- or Boc-L-lysine with a cell suspension of *Rhodotorula graminis*.[947] (S)- or (R)-2,4-Diamino-butanoic acid gives (3,4,5,6-tetrahydropyrimidinyl)glycines through reaction with imino-ethers derived from glycine, serine or tyrosine.[948] Lysine protection strategies have been optimized over the years as far as the familiar protecting groups are concerned, and reliable recipes for preparation of N^{α}-Z-L-lysine[949] and $N^{\alpha}N^{\varepsilon}$-bis-Boc- and N^{α}-Z- N^{ε}-Boc-L-lysine[950] [*via* the copper(II) complex of N^{ε}-Boc-L-lysine]. Protected arginine cyclic aminals result from $LiAlH_4$ reduction of the arginine Weinreb amide to aldehyde, coupling through the aminal oxygen to a linker unit attached to a solid phase giving a scaffold on which acyl derivatives of the arginine α-amino group were prepared.[951]

Sulfur-containing modifications of the side-chain functional groups of ornithine, citrulline and arginine, *e.g.* (S)-$H_3N^+CH[(CH_2)_3N{=}C(SMe)NHOH]CO_2^-$, have shown promise as nitric oxide synthase inhibitors.[952]

Aromatic groups in amino acid side-chains provide the site for electrophilic substitution, exploited for assorted reasons: assisting analysis, improving cell receptor response, and isotopic labelling are only a few of these. Aqueous phenylalanine gives tyrosine and DOPA through 'heavy ion irradiation' (350 MeV neon ions),[953] and m-tyrosine formation from phenylalanine has been advocated as a sensitive means of detecting hydroxyl radical formation in aqueous media (though this should be followed by diode array or electrochemical devices since HPLC procedures are liable to introduce artifacts).[954] Conversion of DOPA into 6-hydroxyDOPA through use of standard chemical and electrochemical oxidation protocols proceeds *via* dopaquinone.[955] More conventional laboratory substitution protocols have provided 3′-bromo- or iodo-4′-hydroxyphenylglycines,[956] N^{α}-Fmoc-4′-phosphonomethyl-L- and D-phenylalanines,[957] 4′-(diethylphosphonophenylazo)-phenylalanine,[958] 4′-(tert-butylthio)phenylalanine [from 4′-iodo-phenylalanine with Bu^tSH/$Pd_2(dba)_3.CHCl_3$],[959] (S,S)-isodityrosine (coupling of protected L-phenylalanine 4′-boronic acid with 4′-O-benzylDOPA[960] and with aryl halides,[961] and 3-nitrotyrosine (UV absorption at λ_{max} 358 nm).[962] *In vivo* non-enzymic reduction of nitrotyrosine to aminotyrosine involves a haem with thiols.[963] Iodination of aqueous tyrosine in a liquid macrocycle-containing membrane by KI/I_2,[964] and formation of a thymine-tyrosine adduct, 3′-[(1,3-dihydro-2,4-dioxopyrimidin-5-yl)methyl]-L-tyrosine, from L-tyrosine and 5-(hydroxymethyl)uracil *via* radical intermediates,[965] illustrate applications of less familiar procedures. Pd/Cu-Mediated Stille coupling with Me_4Sn after iodination with Barluenga's reagent (Ipy_2BF_4) offers a useful methylation procedure targeted at the phenolic moiety of a tyrosine derivative.[966]

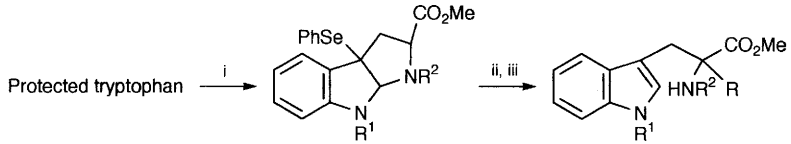
The hydroxy group of '3-hydroxytyrosine' (*i.e.*, 3′-hydroxyphenylalanine) is

the focus of attempts to create the biaryl ether bridge in syntheses of 14-membered macrocycle-containing antibiotics, a new solid-phase S_NAr approach employing an o-nitrofluorophenyl partner offering flexibility.[967]

[^{18}F]Labelling is being explored in several laboratories, providing potential tumour-imaging materials: 3- and 5-[^{18}F]fluoro-L-o-tyrosines (by use of MeO^{18}F)[968] and 5-[^{18}F]fluoroDOPA (by use of H^{18}F /BF_3)[969] from the amino acids themselves, and 6-[^{18}F]fluoro-L-DOPA by [^{18}F]fluorodestannylation with [^{18}F]acetyl hypofluorite in $CFCl_3$,[970] mixture of ring-[^{18}F] and [^{18}F]adducts by [^{18}F]fluorination of (R)- or (S)-(E)-β-fluoromethylene-m-tyrosine,[971] and O-(2-[^{18}F]fluoroethyl)-L-tyrosine.[972] Radio-iodinated α-methyl-L-tyrosine is easily prepared from the amino acid using Chloramine-T/I_2.[973]

Histidine reacts efficiently with the lipid oxidation product hexanal (see lysine above), to give side-chain aminols.[974] Side-chain N-tritylation of protected histidines leads inexorably to the N^{τ}-trityl derivative; the conclusion has been reached[975] that prospects are poor for preparing the N^{π}- trityl isomer that would provide for racemization-free histidylation of a growing peptide chain. However, N^{π}-allyloxycarbonylmethyl protection has been established.[976] Side-chain attachment to a trityl-resin can be a useful prelude to further reactions at histidine functional groups.[977] L-Histidine anions contribute low EES as catalysts for the reduction of carbonyl compounds by a trialkoxysilane.[978]

Tryptophan chemistry that is above the routine level is shown in its reaction with N-phenylselenylphthalimide (Scheme 25), allowing α-alkylation of this



Reagents: i, *N*-phenylselenyl phthalimide; ii, LDA–THF/–78 °C; iii, MeI or *p*-$BrC_6H_4CH_2Br$

Scheme 25

amino acid with inversion of stereochemistry,[979] and in 2′-(α-C-mannosyl)ation using a stannylacetylene as a novel coupling reagent with an aldose.[980] Routes to three types of tetrahydro-β-carbolines to which a 5- or 6-membered heterocycle is attached have been described.[981] Swern oxidation of methyl N-acetyl-L-tryptophanate proceeds *via* a tetrahydro-β-carboline (intramolecular attack of N^{α} on the indole C-2 site) with methylthiomethyl-substituted indoles featuring among the products.[982] The indole moiety of an L-tryptophan derivative undergoes substitution with 1,2-anhydro-3,4,6-tri-O-benzyl-β-D-mannopyranose to give C^2-α-D-[C-mannopyranosyl]-L-tryptophan, a member of a novel sub-class of 'glyco–amino acid'.[983]

6.4 Effects of Electromagnetic Radiation on Amino Acids. – Most of the studies under this heading concern tyrosine and tryptophan, but the usual almost total exclusion of other amino acids is not sustained this year.

Hydroxyl radicals formed by radiolysis of ^2H_2O solutions of amino acids under anaerobic conditions induce ^1H–^2H exchange at C–H bonds to the

extent of 3–8%.[984] N-Centred radicals have been detected in radiolysis or photoionization of aqueous N-phenyl- and N-chloroglycine,[985] while the superoxide radical anion and indole-centred radicals have been detected in corresponding studies of N-acetyltryptophan[986] and three radicals have been generated by γ-irradiation of a single crystal of N-acetyltyrosine.[987]

UV photolysis of N-arenesulfonylamino acids causes sulfonamide cleavage, a promising deprotection option but contradictory results on accompanying structural changes need to be brought into line; the mechanism of the process for N-toluene-p-sulfonylglycine involves intramolecular electron or proton transfer,[988] and the general reaction gives a low return of deprotected amino acids as a result of oxidative decarboxylation.[989] 300 nm Photolysis of N-acetoacetyl-α-amino acid esters gives complex mixtures through Norrish type I reactions (H atom abstraction with concomitant radical cleavage and radical recombination),[990] whereas β-2,2′-dinitrobenzhydryl N-methyl D-aspartate is cleanly cleaved into the free acid.[991] Photolysis of glycine, alanine, and proline, and other common amino acids with functional side-chains (hydroxyproline, arginine, lysine and histidine) that are found in collagen, has been investigated at higher energies (193 nm laser irradiation).[992] Cationic and neutral radicals arise in photo-oxidation of aqueous tryptophan sensitized by $PtCl_6^-$ salts, due to the intervention of Cl_2^- radicals.[993] Intense circularly-polarized irradiation (XeF 351 nm laser source) of threonine and methionine causes deamination and decarboxylation and the D-enantiomers appear to be degraded to a greater degree relative to their L-isomers.[994]

Fluorescence of N-dansyl-S-nitroso-homocysteine is enhanced during its denitrosation by thiols, and this effect can be exploited in a quantitative assay.[995] More conventional fluorescence studies relate to methyl L-tyrosinate {quenching by mesoporphyrin II, 2-[(2-hydroxyethyl)thio]-3-methyl-1,4-naphthoquinone},[996] N-acetyl-L-tyrosinamide (3-photon excitation with 780–855 nm femtosecond titanium sapphire laser),[997] and L-tryptophan [quenching by lanthanum(III) ions,[998] and sensitivity of phosphorescence features to local environment[999] including tryptophan trapped in silica glass[1000]]. Fluorescence features of branched tryptophan derivatives is modified by hydrogen-bonded dendritic microenvironment.[1001] Photoproducts of tryptophan could have roles in light-regulated biosynthesis, since cytochrome P gene expression is affected by their presence.[1002]

7 Analytical Methods

7.1 Introduction. – Reviews spanning several analytical techniques deal with amino acid analysis of proteins,[1003] and applications in amino acid analysis of currently emerging chromatographic and other instrumental methods.[1004] Methods for the analysis of particular amino acids that are diagnostic of metabolic disorders have been intensively studied, and, while pyridinoline and its deoxy-analogue are mentioned in later subsections, there are methods being advocated (immunoassay;[1005] and the rather easier automated chemilumines-

cence assay[1006]) that fall outside the main categories of technique into which this section is divided. 3-Nitrotyrosine has special current interest since it arises in proteins through a pathway starting with nitric oxide.[1007]

7.2 Gas–Liquid Chromatography. – All the conventional methods continue to be developed, with greater confidence in absolute configurational assignments with emphasis on the modification of commercial chiral stationary phases (CSPs). The amino acids of hydrolysed pyoverdins derivatized as N(O,S)-perfluoroacylated alkyl esters and separated over Permabond Chirasil-Val,[1008] and a closely similar study using Chirasil-γ-Dex[1009] and N-trifluoroacetyl selenomethionine isopropyl ester over L-valine butylamide-modified Chirasil-L-Val[1010] illustrate the general style of current work. A new CSP with chiral resorc[4]arene basket-type selector bonded through diamide groups to a dimethyl polysiloxane shows good enantiomer selectivity towards methyl esters of N(O,S)-trifluoroacetylamino acids.[1011]

GLC of N-trifluoroacetyl 2,6-diaminopimelic acid isopropyl esters over Chirasil-L-Val to provide D:L-ratios,[1012] and configurational analysis in the same way, of pipecolic acids in plasma,[1013] of N-aminoethylamino acids after cyclization to piperazin-2-ones with trifluoroacetic anhydride,[1014] employ the standard off-the-peg analytical protocol.

Sulfur-containing amino acids have an above-average share of the papers in this section, due to the clinical relevance of homocysteine monitoring. This amino acid can be analysed together with methionine and cysteine as the N,S-alkoxycarbonyl alkyl esters,[1015] or after S-pyridylethylation with vinylpyridine then tert-butyldimethylsilylation, with ^{2}H- and ^{13}C-labelled analyte as internal standard.[1016] An identical approach has been applied to the analysis of methyl N,S-di-ethoxycarbonylcysteinate,[1017] and to the identification of novel related amino acids in plants (ref. 16).[15]N-Labelled internal standard is appropriate for GLC-MS analysis of S-nitrosocysteine employing $HgCl_2$ cleavage into nitrite and ^{15}N-nitrite.[1018] Spiking with U-^{13}C-labelled amino acids, followed by TBDMS-derivatization, offers a sensitive assay of plasma amino acids.[1019]

Alternative derivatization protocols have been illustrated with GLC analysis of N-carboxymethylserine (as the N,O-diacetyl methyl ester derivative),[1020] 5-hydroxylysine and lysine content of collagen (as the N-trifluoroacetyl n-propyl ester derivative),[1021] GLC-MS analysis of 3-nitrotyrosine as its penta-fluorobenzyl derivative,[1022] tyrosine and substituted tyrosines derivatized using N-methyl-N-(tert-butyldimethylsilyl)trifluoracetamide.[1023]

7.3 Ion-exchange Chromatography. – Some novel variants of classical amino acid analysis protocols are coming to prominence, anion exchange separation followed by amperometric quantitation comparing well with ninhydrin colorimetry.[1024] Interpretation of bimodal integrated amperometric waveforms permit analysis of underivatized amino acids at less than 1 picomole levels,[1025] and carbohydrates do not have to be cleared from samples since they do not interfere.[1026]

Cation-exchange separation of amino acids using evaporative light-

scattering detection offers low sensitivity (more than 200 picomole sample is required).[1027]

7.4 Thin-layer Chromatography. – Enantiomeric analysis of aromatic amino acids is conveniently accomplished on commercially available chiral stationary phases.[1028] The quantitation of L-tyrosine and L-DOPA in samples is feasible when their TLC spots contain more than 0.7 μg and 1.5 μg respectively.[1029]

7.5 High-performance Liquid Chromatography. – Broad-ranging coverage of protein protocols includes reviews of amino acid analysis based on HPLC.[1030] Hydrophobic interaction chromatography has been investigated with amino acids and peptides; amino acids are not retained sufficiently so that useful application of the method is unlikely.[1031] Polymeric stationary phases whose properties are affected by pH and temperature changes, *viz.* irregular poly-(ether)s, have shown merit in separations of amino acids and peptides.[1032]

Underivatized amino acids carrying chromophoric or electrochemically-active groupings are easily detected after HPLC separation, though other detection methods, notably mass spectrometry but also laser-based polarimetry (0.5–50 microgram samples)[1033] and evaporative light-scattering after ion-pair reversed-phase HPLC separation,[1034] are also appropriate (the sensitivity of this detection technique[1035] is 0.5–1 mg mL^{-1}).

Analysis of phenylalanine and tyrosine that exploits their inherent fluorescence (λ_{ex} 215 nm, λ_{em} 283 nm; N-methylphenylalanine as internal standard),[1036] and similar procedures applied to tryptophan and its metabolites,[1037] N-acetyl-S-nitrosocysteine (λ_{max} 333 nm, exploited in an assay for nitrate and nitrite),[1038] S-adenosyl-L-methionine and -L-homocysteine,[1039] tyrosine O-sulfate have been reported.[1040] Electrochemical detection procedures have been applied to a crop of sulfur-containing amino acids: taurine,[1041] S-sulfocysteine,[1042] cysteine and N-acetylcysteine using a novel cobalt ferricyanide electrode,[1043] 5-(S-cysteinyl)DOPA.[1044] Papers covering homocysteine are collected later in this section, together with papers on HPLC analysis of other clinically important amino acids.

Electrochemical detection underpins an HPLC assay of 5-hydroxytryptophan.[1045] An unusual amperometric technique relies on the reaction of electrogenerated bromine species with underivatized amino acids.[1046]

Mass-spectrometric detection allied with HPLC is now a standardized operation, as with phenylalanine and tyrosine quantitation in blood spots based on stable isotope dilution.[1047] The high sensitivity of this method, and its further advantage in yielding spectra that can be interpreted to supply structural information, is underlined by detection for the first time of N′- and 2-(β-D-hexopyranosyl)-L-tryptophans and related conjugates in human urine.[1048]

Ligand exchange HPLC is represented in a use of the copper(II) complex of poly(divinylbenzene)-immobilized L-proline for estimation of D:L-ratios for samples of common amino acids.[1049]

Homocysteine has gained importance as a clinical marker for cardiovascular

disease, and several new studies have led to refined analytical procedures. Classical ion-exchange analysis is not sufficiently sensitive, and relative advantages of the other standard HPLC approaches have been considered,[1050] which has also been coupled with improved analysis of cysteine.[1051-1055] Emphasis has been given to electrochemical detection[1056,1057] and to colorimetry,[1058] with fluorophoric derivatization (use of 7-fluorobenzo-2-oxa-1,3-diazole-4-sulfonamide[1059] and closely-related reagents[1060,1061] to introduce the SBD fluorophore; use of other classical derivatization procedures, *e.g.* to prepare the OPA derivative[1062] or the 7-N,N-dimethylaminobenzenesulfonyl-4-(2,1,3-benzodiazolyl)thiocarbamoyl derivative, λ_{ex} 385 nm, λ_{em} 515 nm[1063]). OPA derivatization has been applied to cysteine after tagging the thiol group with N-(1-pyrenyl)maleimide.[1064]

The levels of pyridinoline and its deoxy-analogue in physiological samples continue to be considered as valuable markers for osteoporosis and bone degradation, and HPLC estimation using established protocols has been reported,[1065-1067] one of the current studies[1068] including another crosslinking amino acid, desmosine, in its assay.

3-Nitrotyrosine is another current target for which HPLC assays have been developed. This trace constituent of modified proteins gives an electrochemical signature permitting its detection with satisfactory sensitivity.[1069] Reviews of methods for analysis of this physiological marker for nitrogen oxides and oxyacids,[1070] together with assays for 3-chlorotyrosine,[1071,1072] N-nitrosoproline,[1073] and 2-oxohistidine,[1074] and glycine betaine,[1075] have been published.

Derivatization of amino acid mixtures and HPLC separation remains the most favoured approach to general amino acid analysis in the absence of special circumstances, and some of the methods chosen most often have been mentioned above for homocysteine. Further examples of analysis as o-phthaldialdehyde (OPA) derivatives, usually relying on fluorescence quantitation, have been published for N-isobutyroyl-D- or L-cysteine,[1076] γ-carboxyglutamic acid,[1077] 2,6-diaminopimelic acid,[1078] isotope-enriched amino acids (mass spectrometric detection),[1079] amino acids in a single human polymorphonuclear leukocyte.[1080] The last-mentioned example underlines the sensitivity of this approach, which can be enhanced by using o-naphthalenedialdehyde as reagent instead of OPA, illustrated for S-adenosylmethionine and -homocysteine.[1081] Careful sample preparation is particularly important with the OPA procedure, and cleansing using a strong cation exchange resin is recommended.[1082]

N-Phenylthiocarbamoylamino acids continue to give good service in this context, illustrated for glutamine analysis (a particularly difficult analytical problem for proteins) using the Pico-Tag protocol, release of the amino acid depending on successive treatment of bovine milk protein with pronase E, aminopeptidase M, and prolidase.[1083] Phosphatidylserine[1084] is another problem amino acid that has been successfully analysed as its PTC derivative, and more general amino acid mixture analyses[1085] have been described that employ this approach. Cyclized PTC-amino acids (*i.e.* PTHs) are supported with a voluminous HPLC literature; their improved analysis benefits from

careful control of gradient and column temperature.[1086] Fluorescent thiohydantoins formed with (R)-(−)-DBD-pyridyl isothiocyanate have proved suitable for the determination of D:L-ratios for amino acid samples.[1087]

Several other fluorescent amino acid derivatives are gaining approval for sensitive HPLC analysis: N-Fmoc (amino acids in Z-DE spots;[1088] detection supported by electrospray MS;[1089] analysis of lysine[1090]). The related procedure employing (+)-1-(9-fluorenyl)ethyl chloroformate as reagent has been used for analysis of the imino acid N-methyl-D-aspartic acid after clearing primary amines from samples by OPA derivatization followed by extraction.[1091] Another amino acid of interest as a cellular constituent and requiring sensitive reliable analysis, D-leucine in rat hippocampus, has been quantified by HPLC over a CSP, at the one femtomole level after derivatization with NBD fluoride.[1092]

Many of the foregoing examples illustrate well-known procedures, and dansyl- and dabsyl-amino acids are also no strangers in this context. The use of the former for analysis of O-(β-1-galactosyl)hydroxylysine in serum[1093] and for demonstrating separation of enantiomers for dansyl-D,L-phenylalanine by HPLC over α-acid glycoprotein,[1094] and of the latter in sensitive amino acid analysis,[1095] indicate current interests in novel chromatographic applications. Newer derivatization reagents that have been advocated, in a search for reliable trace amino acid analysis, are 4-(5,6-dimethoxy-2-phthalimidinyl)-2-methoxyphenylsulfonyl chloride (giving DMS derivatives, λ_{ex} 318 nm, λ_{em} 406 nm, reaching below 5 femtomoles of analyte[1096]) and carbazole-N-(2-methyl)acetyl chloride (giving CMA derivatives, λ_{ex} 335 nm, λ_{em} 360 nm, 10–65 femtomoles of analyte[1097]). The former reagent has been applied to the estimation of as little as 1–5 femtomoles of proline and hydroxyproline in amino acid mixtures after removal of primary amines using OPA (as above).[1098] Results for the analogous use of acridone-N-acetyl chloride have been published.[1099]

Condensation products of amino acids with pyrroloquinoline quinone have been assessed by HPLC with mass spectrometric structure determination.[1100]

7.6 Capillary Zone Electrophoresis (CZE), and Related Analytical Methods. – The topic has settled into established categories of routine amino acid analysis which are closely related, from the point of view of sample preparation and detector response, to HPLC methodology. A review of 1997–8 literature has appeared.[1101]

Free amino acids are amenable to CZE assay [tryptophan, 40 pg sample with detection at 280 nm;[1102] O-phosphorylated serine, threonine and tyrosine;[1103] 3-methylhistidine;[1104] DNA–histidine complexes in isoelectric histidine buffers;[1105] cysteine and homocysteine;[1106,1107] aromatic amino acids[1108]]. Points of interest from these studies include favourable comparison with HPLC assays for homocysteine, and accurate estimation of D:L-ratios when buffers include a chiral additive (cyclodextrin), also seen for ligand exchange CZE [copper(II)–N-alkyl-4-hydroxy-L-proline derivatives], MEKC[1109] [hydroxy-L-proline–surfactant buffers],[1110] and capillary isotacho-

phoresis of N-(2,4-dinitrophenyl)-D,L-norleucine (D:L-ratio determination) with a β-cyclodextrin-containing buffer.[1111] The CZE separation of a mixture of 82 inorganic anions, organic acids including amino acids, and carbohydrates provides a dramatic illustration of the power of the method, though this example depends on the use of highly alkaline buffers so limiting the range of potential applications.[1112] Post-column o-phthaldialdehyde–2-mercaptoethanol treatment allows laser-induced fluorescence quantitation of common amino acids.[1113]

Amino acids have been subjected to standard CZE procedures after derivatization with OPA-2-mercaptoethanol (D:L-ratios for aspartic acid using β-cyclodextrin buffer),[1114] dansyl chloride (D:L-ratios using N-alkoxycarbonyl-L-amino acids as chiral buffer surfactant additive),[1115] fluorescein isothiocyanate (γ-carboxyglutamic acid,[1116] D:L-ratios using β- and γ-cyclodextrins in buffers,[1117] and amines formed by Hofmann rearrangement of N-acetylamino acid amides[1118]), illustrating the two predominant approaches. The last-mentioned derivatives of amino acids extracted from the Murchison meteorite permit sub-attomole quantitation including D:L-ratio determination (SDS-γ-cyclodextrin buffer), when the CZE-on-a-chip technique is applied, and give data closely similar to those already reported (Volume 30, p. 2) for HPLC analysis.[1119] Derivatization efficiency by aliphatic isothiocyanates has been investigated as a function of reaction time, temperature, and other parameters.[1120] PTHs have been detected after CZE separation, through thermo-optical absorbance data,[1121] and analysis of N^{α}-Fmoc derivatives of lysine and methylated lysines separated by two-dimensional electrophoresis has been supported by mass spectrometric detection.[1122]

7.7 Assays for Specific Amino Acids. – Modifications of well-known colorimetric assays have been described, for histidine (coupling with diazotized p-aminoacetophenone followed by electrochemical quantitation),[1123] and for the estimation of a large amount of cysteine in the presence of a small amount of cystine.[1124] For this, a subtractive analysis stage in which an excess of N-ethylmaleimide is added, and unreacted reagent quenched with D,L-homocysteine, is coupled with dithioreitol reduction of cystine and ninhydrin analysis as usual.

The exquisitely specific immunoassay approach to amino acid analysis is not covered routinely in this Specialist Periodical Report. One paper covers a technique showing some breadth of application, in which surface plasmon resonance detection has been applied to an Igs immunosensor mounted on a chiral disc using a competitive antibody assay; this allows differential response of amino acid enantiomers and is a highly sensitive technique.[1125]

Amperometric biosensors of traditional design based on enzymes immobilized on an electrode are dedicated to L-glutamic acid assay (thermophilic L-glutamate dehydrogenase with NADP;[1126] L-glutamate oxidase,[1127] peroxidase with L-glutamate oxidase,[1128] glutamate dehydrogenase and NADH oxidase,[1129] L-glutamate decarboxylase coupled with a CO_2 electrode[1130]), L-alanine/α-ketoglutarate/L-glutamic acid assay (L-alanine aminotransferase

with L-glutamate oxidase, with chemiluminescence exploited as a measure of the H_2O_2 produced[1131]), and L-lysine assay (peroxidase and lysine oxidase[1132]). A flow injection analysis protocol for glutamic acid and glutamine based on L-glutamate dehydrogenase and L-aspartate aminotransferase depends on spectrophotometric quantitation of NADH generated from the analytes.[1133] A review of the literature of 1997 gives thorough coverage of the different categories of amino acid assays using biosensors.[1134]

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