1
Amino Acids

By G.C.BARRETT

1 Introduction

The chemistry and biochemistry of the amino acids as represented in the 1992 literature, is covered in this Chapter. The usual policy for this Specialist Periodical Report has been continued, with almost exclusive attention in this Chapter, to the literature covering the natural occurrence, chemistry, and analysis methodology for the amino acids. Routine literature covering the natural distribution of well-known amino acids is excluded.

The discussion offered is brief for most of the papers cited, so that adequate commentary can be offered for papers describing significant advances in synthetic methodology and mechanistically-interesting chemistry. Patent literature is almost wholly excluded but this is easily reached through Section 34 of *Chemical Abstracts*. It is worth noting that the relative number of patents carried in Section 34 of *Chemical Abstracts* is increasing (e.g. Section 34 of *Chem.Abs.*, 1992, Vol.116, Issue No.11 contains 45 patent abstracts, 77 abstracts of papers and reviews), reflecting the perception that amino acids and peptides are capable of returning rich commercial rewards due to their important physiological roles and consequent pharmaceutical status. However, there is no slowing of the flow of journal papers and secondary literature, as far as the amino acids are concerned. The coverage in this Chapter is arranged into sections as used in all previous Volumes of this Specialist Periodical Report, and major Journals and *Chemical Abstracts* (to Volume 118, issue 11) have been scanned to provide the material surveyed here.

2 Textbooks and Reviews

Reviews cover the asymmetric synthesis of unusual amino acids starting from serine or cysteine[1]and the uses of amino acids as chiral synthons in synthesis.[2] A review of selenocysteine, an amino acid that has leapt to prominence as a new addition (codon UGA) to the universal genetic code, has appeared.[3] A plea for consistent representation on paper of chiral formulae, and details of a new method for doing so, has

been published.[4] Several other reviews have appeared, and are listed at the start of appropriate Sections in this Chapter.

3 Naturally Occurring Amino Acids

3.1 *Isolation of Amino Acids from Natural Sources.*

This Section continues to hold a position early in this Chapter even though it would be thought of as a routine aspect of the literature. However, the validity of reports on the presence of amino acids in natural locations is only reliable if it is certain that artefacts are not introduced through extraction procedures. Although the extreme sensitivity of current analytical methods for amino acids enhances confidence in the results obtained for samples, at the same time it enhances the possibility that erroneous conclusions may be reached on the indigeneity of amino acids in natural sources.

Extraction of tyrosine from aqueous solutions using n-butanol is 87% complete after two partitions if the aqueous solution is saturated with an alkali-metal salt.[5] Similar partition leading to separation of amino acid mixtures and enrichment of amino acids in liquid surfactant membranes using tri-n-octylmethylammonium chloride, has been described.[6] After extraction of samples with water, acidic amino acids (aspartic and glutamic acids) may be adsorbed preferentially from the solutions on to acid-treated alumina.[7] A similar principle has been applied to isolate glutamic acid, glycine and lysine sequentially from aqueous solutions using silica-magnesia mixtures, and histidine and lysine using silica-titania mixtures.[8] Isolation of tryptophan from aqueous solutions using the MK-40 cation exchange membrane[9]and the adsorption of this amino acid onto the gel matrix during gel chromatography of amino acid hydrolysates on Bio-Gel P-2 has been described.[10] Tryptophan is the most readily adsorbed from a mixture of amino acids [Gly < Ala < Cys < Val < Met < Pro < Ile < Leu < Tyr < Phe < Trp] from aqueous solutions by benzylsilylated silica gel when the amino acids in the mixture are derivatized as N-acetylamino acid N'-methylamides.[11]

3.2 *Occurrence of Known Amino Acids.*

The unusual amino acids present in mushrooms[12] and the distribution in plant gall tumours and the chemistry of N-(carboxyalkyl)amino acids,[13] have been reviewed. The occurrence and identification of N-carbamyl-β-amino acids in urine has relevance in the monitoring of metabolic processes.[14]

Substantial studies over the years, of cross-linking amino acids in proteins, continue unabated, a representative review this year being the

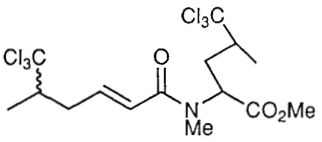
identification of cross-links in cattle hide after maturation.[15] These cross-links are predominantly between histidine and hydroxylysinonorleucine, but the discovery of proteoglycans as a source of bridging sites, is notable.

Other studies identifying the presence of known, but unusual, amino acids in hydrolysates, include alloisoleucine, allothreonine, N-methylphenylalanine, and p-methoxyphenylglycine from the antibiotic xanthostatin,[16]and O-methylserine and αβ-dehydrotryptophan from the cyclic peptide keramamide F from the marine sponge *Theonella.*[17] Herbaceamide (1), from the marine sponge *Dysidea herbacea*, is an N-acylated (2S,4S)-5,5,5-trichloroleucine, adding to the lengthening list of halogenated amino acids found in such organisms.[18] Careful studies have established the presence of D-enantiomers of alanine, serine, and proline in the mouse kidney.[19] Similarly careful studies are obligatory in assessing the common amino acids present in meteorites, and the problem of ensuring the indigeneity of protein amino acids in such sources was recently considered solved, since in test cases, the stable isotope distribution of organic constituents differed from the terrestrial distribution (see Vol. 24, p.2). A salutary warning arises from independent studies, that hydrolysis and derivatization reactions performed on fossils and meteorites can be accompanied by kinetic fractionation, influencing the stable isotope signatures.[20,21] In a particular context,[21]as a dipeptide is progressively hydrolysed the residual unhydrolysed dipeptide is increasingly enriched in ^{13}C and ^{15}N.

3.3 *New Naturally Occurring Amino Acids.*

Close relatives of protein amino acids that have been newly-discovered, are the novel immunomodulator metacyclofilin (2), from *Metarhizium* sp.TA2759 (the structure assigned lacks details of absolute configuration),[22]and the potent insecticide ulosantoin (3) from the marine sponge *Ulosa ruetzleri.*[23] New α-amino acids with heterocyclic side-chains are two analogues (4) and (5) of acromelic acid, from *Clitocybe acromelalga.*[24]Full details have been published[25]of the characteristics of the new amino acids from *Clitocybe acromelalga* L-3-(2-pyrrolyl)alanine (see Vol.24, p.3) and L-3-(2-oxo-5-pyridyl)alanine, as well as their biosynthetic precursor, the already-known stizolobic acid (6). Also from the poisonous mushroom *Clitocybe acromelalga*, another neuroexcitatory α-amino acid L-3-(6-carboxy-2-oxo-4-pyridyl)alanine (7) has been identified.[26] The isoxazolinone (8) from *Streptomyces platensis* A-136 shows antifungal activity against *Candida albicans* and low toxicity against mice.[27]

Greater separation between the amino and carboxy functions is shown in the herbicidal γ-amino acid cis-2-amino-1-hydroxycyclobutane-1-acetic acid (9)[28] from *Streptomyces rochei*, and the new spermine



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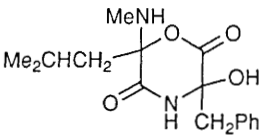

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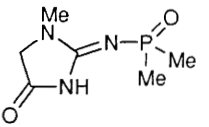

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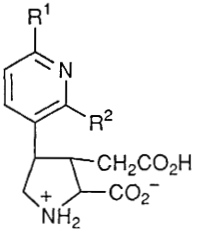
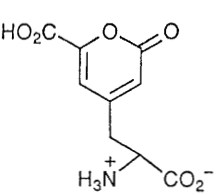


(4; $R^1 = CO_2H$, $R^2 = H$)
(5; $R^1 = H$, $R^2 = CO_2H$)



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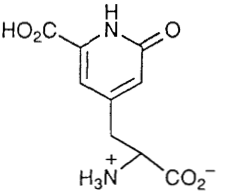

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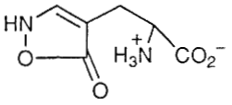

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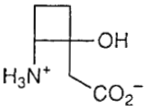

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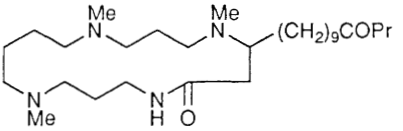
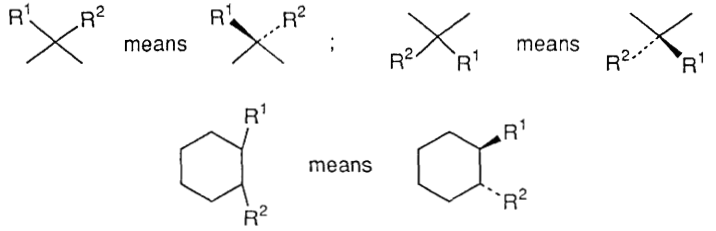


(10)

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

(a) horizontally-ranged atoms, and their bonds, and atoms in rings, are understood to be in the plane of the paper;
(b) atoms and groups attached to these atoms in (a) are ABOVE the page if ranged LEFTWARDS and BELOW the page if ranged RIGHTWARDS;



macrocyclic alkaloid budmunchiamine (10) present in seeds of *Albizia amara*.[29]

3.4 *New Amino Acids from Hydrolysates.*

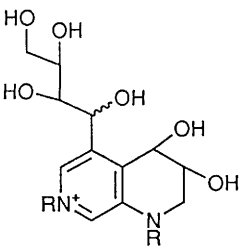
The flow continues unabated, of new discoveries of peptides and related derivatives comprising new amino acids that can be formally considered to be obtained from them by hydrolysis. In the protein cross-linking category, "cyclopentensine" has joined other elastin cross-links and is a condensate of three allysine residues[30] to generate a cyclopentene moiety, unprecedented in crosslinking amino acids. Lysine residues in proteins can provide the amino group required for the Maillard reaction. There is a growing realization that crosslinking may result from an *in vivo* version of this reaction between proteins and carbohydrates (see Vol. 22, p.49), and a model reaction between α-N-acetyl-L-lysine and glucose has been shown to lead to fluorescent compounds [11; R = $-(CH_2)_4CH(NHAc)CO_2H$] that have properties similar to age- and diabetes-related cross-linking moieties in proteins.[31] Simpler analogues (11; R = n-pentyl) were also made in this study, and, like the lysine analogues, the configuration at one chiral centre is still to be determined.

Immunosuppressive lipopeptides, microcolins A and B, from *Lyngba majuscula*, contain N-methylvaline, O-acetyl-D-threonine, N-methylleucine, proline (or hydroxyproline, in the case of microcolin B), and 2-methylpyrrolidin-5-one condensed in that order from the N-terminus. The microcolins carry an N-terminal 2,4-dimethyloctanoyl moiety.[32] Botanical interest predominates in the case of BZR-cotoxin II, the cause of Leaf Spot disease in corn and produced by Bipolaris zeicola race 3 (the factor is a cyclic nonapeptide containing N-methyl δ-hydroxyleucine, 1-aminocyclopropane-1-carboxylic acid, and of γ-methylproline, together with some common amino acids),[33] and in the case of the antimitotic tetrapeptide ustiloxin (12) produced by *Ustilaginoidea vireus* growing on rice plant panicles.[34] The latter compound is related to Phomopsin A, but contains a novel di-amino di-acid carrying a sulphinyl function.

4 Chemical Synthesis and Resolution of Amino Acids

4.1 *General Methods of Synthesis of α-Amino Acids.*

Named preparative methods are as widely used as ever, almost literally "as ever", since they were established many decades ago. Many of the methods described in the next, and later, Sections are also general methods. The Ploechl-Erlenmeyer process based on $Ph_2C{=}NMe$ for alkylation of 2-phenyloxazol-5(4H)-one has been illustrated,[35] and an



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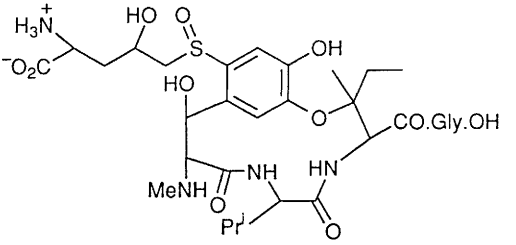

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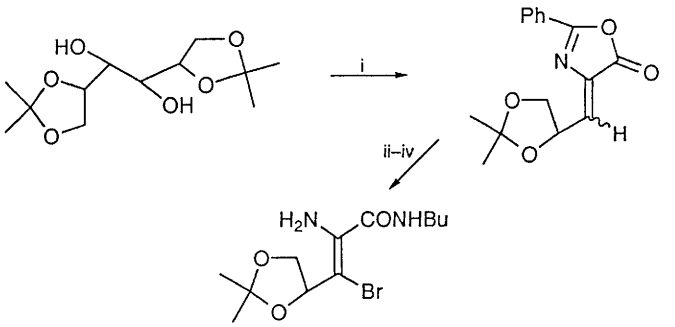
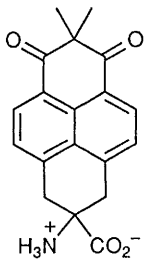


Reagents: i, $Pb(OAc)_4$, Ac_2O, hippuric acid, THF, reflux; ii, $BuNH_2$; iii, Br_2/CH_2Cl_2; iv, DABCO→ more stable *Z*-isomer

Scheme 1



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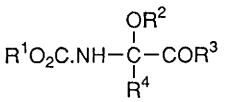

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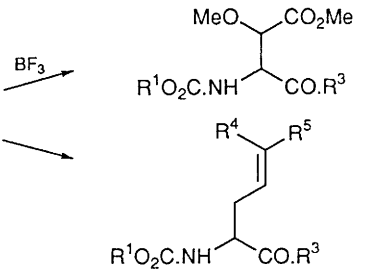
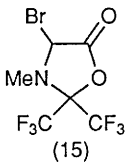


[Ref.53: R^1 = Me; R^2 = Me; R^3 = NMe; R^4 = H, Me
Ref.54: R^1 = H; R^2 = $SiMe_3$; R^3 = NMe; R^4 = H, Me]



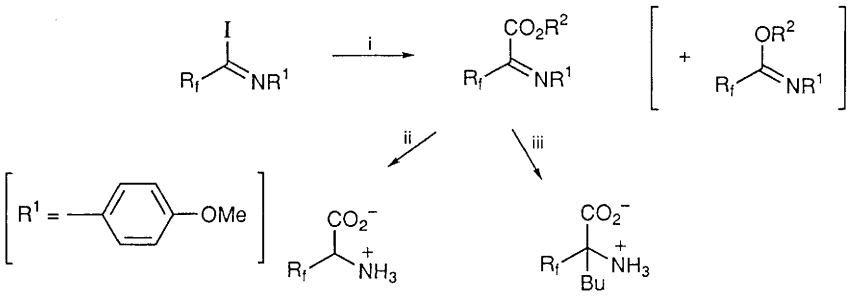
(15)

interesting *in situ* generation of a triose aldehyde for the process using $Pb(OAc)_4$ to cleave a protected hexose derivative (Scheme 1) has been described.[36] The customary concluding step for the process is reduction of the C = C bond but the latter example is designed to lead to β-bromo-αβ-dehydro-amino acids. A related procedure employing 2,5-di-oxopiperazine has been exemplified for a synthesis of phenylalanine, through alkylation with benzaldehyde followed by Zn-acid reduction.[37]

More fundamental processes are at work in carbonylation reactions illustrated for perfluoroalkyl α-amino acids (Scheme 2).[38] A yield of 64% obtained in this study for the preparation of 3,3,3-trifluoro-alanine, compares well with a figure (12%) through the best previous route for this compound. The Strecker synthesis applied to N-alkyl α-amino acids uses a primary amine, HCN, and an aldehyde.[39] The similarly-oriented hydantoin synthesis but using $(NH_4)_2CO_3$, has been used to provide a series of phenylalanine analogues with two substituents in the phenyl moiety.[40]

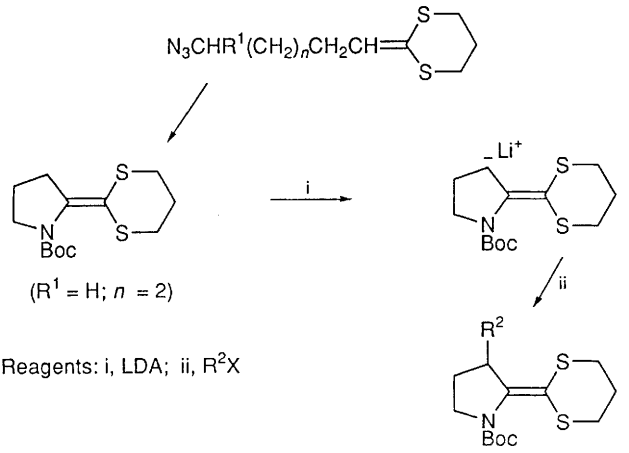
Alkylation of glycine derivatives has expanded in scope from the time-honoured acetamidomalonate synthesis[159,204] to the more recent processes based on the alkylation of glycine Schiff bases, e.g. $Ph_2C{=}NCH_2CO_2Me \rightarrow Ph_2C{=}NCHRCO_2Me$. Schiff base alkylation can be achieved by various strategies after carbanion generation, illustrated by Michael addition to $ArCH{=}CRCO_2Et$ giving 3-arylglutamates,[41] and by the use of nitro-aldols formed from RCH_2NO_2 + $HCHO \rightarrow RCH(NO_2)CH_2OH$ (R = D-xylopyranosyl).[42] The purpose of the last-mentioned study, synthesis of C-glycosyl serines, was achieved after reductive de-nitration of the alkylated Schiff base with Bu_3SnH/AIBN. More conventional alkylation protocols, using alkyl halides, are represented in the synthesis of phenylalanine analogues[43] including α-di-alkylation after NaHDMS de-protonation, leading to the remarkable αα-dialkylated glycines (13; such crowded structures are difficult to prepare through the classical Bucherer-Bergs method).[44] An improved synthesis of α-amino phosphonic acids follows this strategy with $Ph_2C{=}NCH_2P(O)(Bu^iO)_2$.[45] αα-Disubstituted amino acid amides can be prepared by phase-transfer alkylation of benzylidene-amino acid amides $PhCH{=}NCHRCONH_2$.[46]

The most obvious short cut for this alkylation approach for some applications, is to use an N-acylated or N-carbamylated amino acid, i.e. not an ester; thus, Boc-glycine gives the tri-anion with LDA/THF which gives 40-80% yields on alkylation without di-alkylation side-products.[47] Contrary to earlier reports,[48] only two equivalents of strong base (rather than one, which results in N-alkylation) are needed for C-alkylation of methyl hippurate, though it should be noted that the choice of additive



Reagents: i, CO(1 atm), R^2OH/catalytic $Pd_2(dba)_3/CHCl_3$; ii, Zn—AcOH; iii, BuLi then H_2/Pd—C

Scheme 2



Reagents: i, LDA; ii, R^2X

Scheme 3

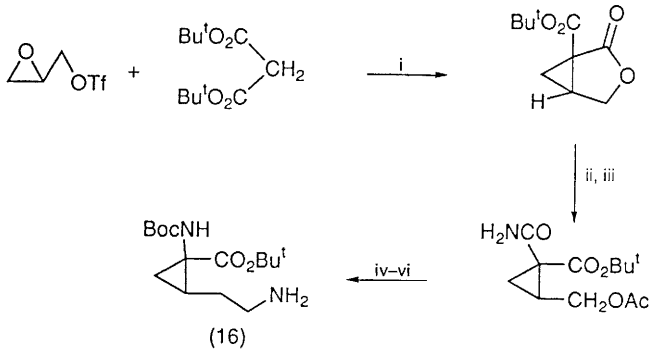
(TMEDA versus HMPA) influences the product composition.[49] The carbanion formed with LDA from Boc-sarcosine ethyl ester, undergoes aldol condensation with acrolein to give predominantly (85%) the anti-isomer.[50]

The special opportunities offered by proline as a synthon are often grasped for the synthesis of substituted prolines (and indeed, in alkaloid synthesis), and a circuitous approach giving 3-substituted prolines through γ-alkylation of 2-aminoketene S,S-acetals after carbanion formation LDA (Scheme 3).[51] Intramolecular azide cycloaddition can provide the pyrrolidinone S,S-acetals and higher homologues (also in Scheme 3).[52]

The alternative approach in which α-hetero-atom-substituted glycines act as cation equivalents continues to be usefully explored. α-Methoxyglycines of various types (14) undergo BF_3-catalysed addition to ester enolates so as to give ββ-disubstituted aspartates,[53] and α-(trimethylsilyl)oxy alanines[54] can be alkylated by allylsilanes with TMSOTf to give γδ-unsaturated α-methyl-α-amino acids. Some dehydroalanine is formed as side-product in the latter study, and further clarification of reaction conditions will be needed if this is to be avoided. A new electrophilic sarcosine synthon (15) has been advocated, and employed in Michaelis-Arbuzov-type synthesis of sarcosines carrying phosphorus-containing side-chains.[55]

αβ-Dehydroamino acids are becoming more attractive synthons for use in α-amino acid synthesis, though of course, as is the case for a number of outcomes of other alkylation methods, they yield racemic products when used for Lewis-acid catalysed α-acylamidoalkylation of furans and anisole.[56] A most promising route, in which N-acetyl dehydro-alanine methyl ester complexed with $Fe(CO)_3$ [*alias* (methyl 2-acetamido acrylate)tricarbonyl iron(0)], treated with MeLi and a tertiary alkyl halide, gives t-leucine and new amino acids with β-branched alkyl side-chains (2-amino-3,3-dimethyl-pentanoic and -hexanoic acids).[57]

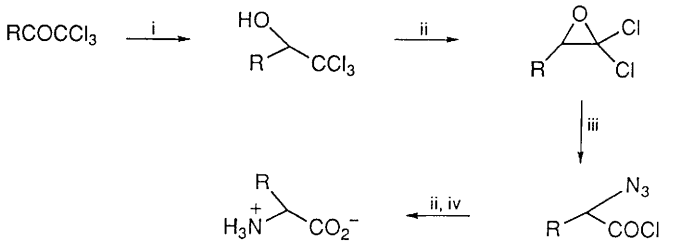
Amination of a range of substrates has long been a favoured approach to α-amino acids, and is exemplified in its classical form using phase-transfer catalysed amination of α-halogeno-esters by Cl_3CONH_2[58] or by $F_3C(CF_2)_nCH_2CH_2NH_2$.[59] Reductive amination of α-keto-acids is also represented in the recent literature.[245] Synthesis of N,N-bis(carbamylated) amino acids can be accomplished using potassium iminodicarboxylates (readers will recognize the formula $Boc_2N^-K^+$ more readily!) with 2-bromo-alkanoates or through a Mitsunobu reaction involving ethyl lactate (cf. also Ref. 78).[60] New-style Hofmann rearrangement leading to amination employs $Pb(OAc)_4$ and Bu^tOH, and is illustrated (Scheme 4) in a synthesis of sterically-constrained surrogates



(16)

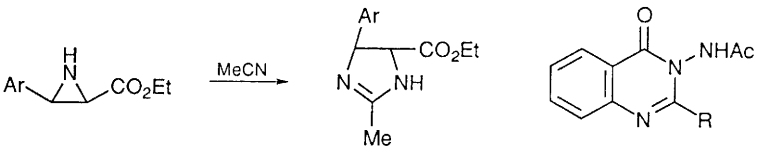
Reagents: i, NaH; ii, NH_3; iii, Ac_2O; iv, $Pb(OAc)_4$ /Bu^tOH; v, Boc_2O; vi, routine elaboration → ornithine and arginine side-chains

Scheme 4



Reagents: i, $(1,2\text{-}C_6H_4O_2)BH$, (*S*)–Oxazaborolidine catalyst; ii, OH^-; iii, N_3^-; iv, H_2/Pd–C

Scheme 5



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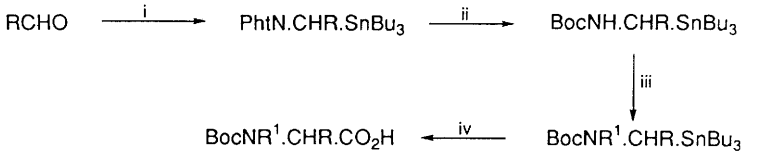
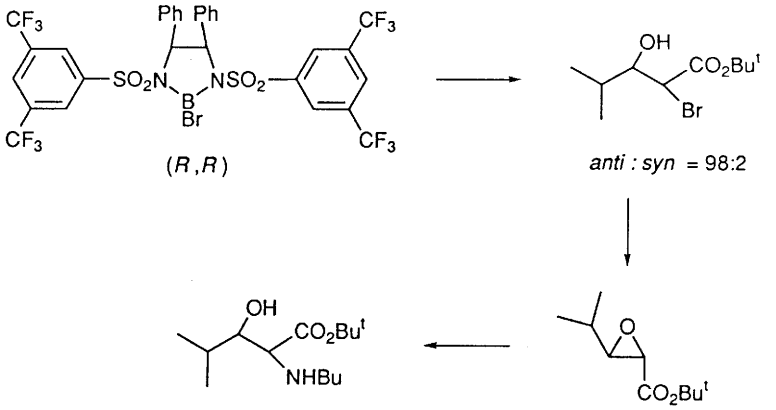


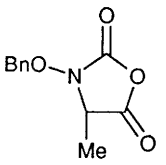
Reagents: i, Bu_3SnLi/ phthalimide /PPh_3 /DEAD; ii, routine deprotection–re-protection; iii, R^1X; iv, BuLi, then CO_2

Scheme 6



Reagents: i, $BrCH_2CO_2Bu^t$; ii, $Pr^i.CHO$; iii, base; iv, $BuNH_2$

Scheme 7



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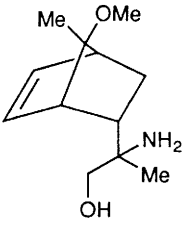

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for ornithine and arginine starting from a homochiral glycidyl triflate and di-t-butyl malonate.[61] The same approach leads to all four stereoisomers of a constrained methionine [16; CH_2SMe in place of $(CH_2)_nNH_2$].[62] Palladium(II)-catalysed Overman rearrangement of homochiral trichloroacetimidates $Cl_3CC(=NH)OCHRCH=CHCH_2OTBDPS$, yields (E)-βγ-unsaturated α-amino acids via optically-pure mono-protected allyldiols $Cl_3CCONHCH(OTBDPS)CH=CHR$ in this particular case.[63] Amination of trichloromethyl carbinols, formed from trichloromethyl ketones, provides the basis of a new enantioselective synthesis of α-amino acids,[64] illustrated (Scheme 5) for t-butylglycine (*alias* t-leucine). A convenient synthesis of trichloromethyl ketones needed for this purpose, has been published.[65] Phthalimides yield Boc-α-amino-organostannanes (Scheme 6), formed by Sn-Li exchange with BuLi, that are configurationally stable at very low temperatures (−95°/10 minutes) but suffer significant racemization at −78° and −55°.[66] An amino acid synthesis emerges from this work on the basis of carboxylation (CO_2) after carbanion formation. Ring-opening of aziridines, e.g. those formed from electron-rich alkenes (such as $MeCH=CHCO_2Me$) and $HN(OMe)_2$/TMSOTf, from which the N-methoxy group can be reductively removed with Na/NH_3,[67] give correspondingly-substituted amino acids. For example, 3-arylaziridine-2-carboxylic esters (17) give 3-chloro- and 3-benzenethio-phenylalanines when treated with HCl and with PhSH respectively,[68] and the trans-3-hexyl analogue reacts similarly,[69] as well as being shown to undergo ring-expansion with MeCN to give the corresponding cis-imidazoline-2-carboxylic acid (essentially a 3-aza-proline).

A new amination reagent, 3-acetoxyaminoquinazolinone (18), that seems capable of reacting with a range of carbonyl compounds so as to introduce an α-amino group, has been fully described.[70] Addition of this reagent to enol ethers $CH_2=CHOEt$ giving α-amino aldehydes, and to silyl ketene acetals $R^1R^2C=C(R^3)OSiMe_3$ giving α-amino ketones (R^3 = alkyl) and acids (R^3 = OMe), offers a valuable route to these compounds, since the N-N bond in the adduct is easily reductively cleaved (SmI_2) and the reagent is then easily regenerated.

4.2 *Asymmetric Synthesis of α-Amino Acids.*

Most of the methods covered in this section are also viable general methods of synthesis of amino acids, but papers are discussed here with exclusive attention to the stereochemical outcome and the way that this is governed by the structural features sought in the synthetic target.

Reviews have appeared of stereoselective syntheses of unusual amino acids,[71] and of arylglycines.[72] A review of the synthesis of chiral

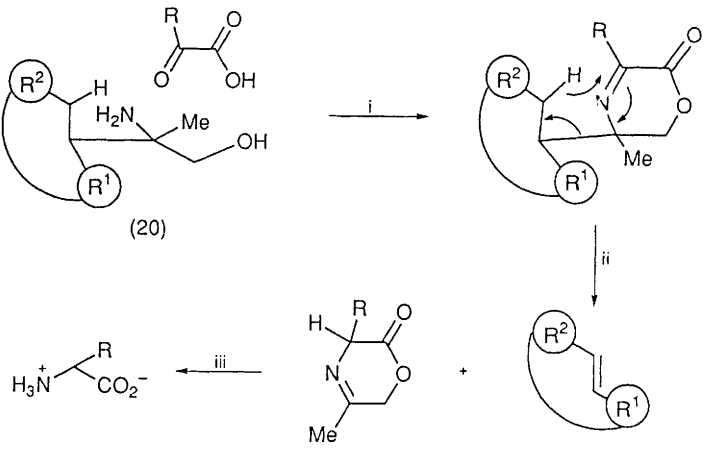
cyanohydrins for use as starting materials in synthesis is relevant to the content of a Chapter on Amino Acids.[73]

An enantioselective version of a standard general method of α-amino acid synthesis is found in a Strecker synthesis of N-[(R)-2-hydroxy-1-phenylethyl]aminonitriles, $HOCH_2CHPhNHCHRCN$, readily elaborated into L-amino acids (R = aryl, Me, Pr^i, Bu^t) and owing their homochirality to the use of (R)-phenylglycinol as a reactant,[74] and transimination-hydrocyanation of O-methoxyisopropyl-(R)-mandelonitrile giving (2R,3R)-β-hydroxy-α-aminonitrile derivatives is a further illustration.[75] Amination of homochiral alkyl α-halogenoalkanoates illustrates an enantiospecific version of a standard method, and there are some unusual variants of this; α-bromoalkanoyl bromides on treatment with a tertiary base, give bromoketenes from which, by addition of a chiral alkanol, the homochiral α-bromoester is obtained. Azide displacement with inversion and routine stages leads to the homochiral α-amino acid, and (R)-pantolactone was used as the chiral alkanol in this study.[76] t-Butyl bromoacetate can participate in diastereoselective aldol reactions (Scheme 7) giving mainly the anti-isomer of a t-butyl α-bromo-β-hydroxyalkanoate.[77] Cyclisation to the chiral oxirane and ring opening with an amine or with azide ion gives the corresponding α-amino-β-hydroxy acid, and the method has been illustrated for a synthesis of (2R,3S)-hydroxyleucine that can be operated on a large scale.

A synthesis of N-benzyloxy-D-alanine anhydride (19) by amination of L-(+)-lactic acid represents relatively routine methodology (cf. also Ref.60),[78] but an unusual amination procedure is based on a new retro-aza-ene reaction; a keto-acid esterified with the (S)-β-aminoethanol (20; abbreviated in Scheme 8) can undergo intramolecular Schiff base formation by cyclization and the ester is liable to thermolysis and acid hydrolysis to give the (R)-α-amino acid.[79] This may not become an established general method because of the complexities but particularly because the chiral auxiliary is not recovered in the process.

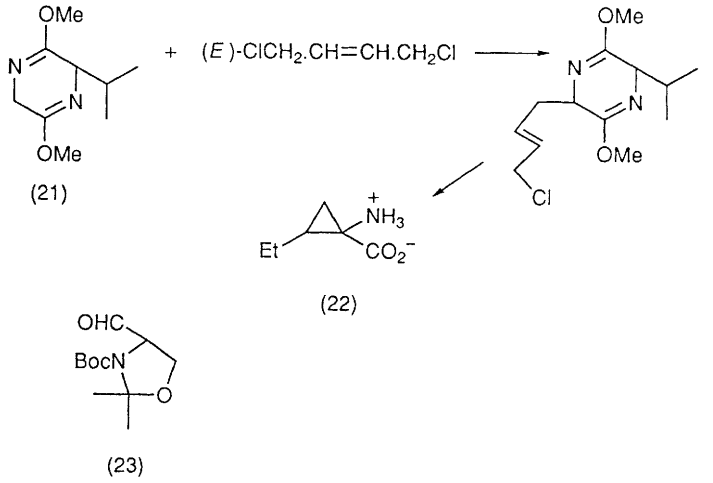
A version of a standard method is seen in phase-transfer alkylation of (S)-aldimine Schiff bases $RCH=NCHMeCO_2Me$.[80]

The use of chiral auxiliaries is more explicit in a number of other enantioselective amino acid synthetic methods that have become standard practice over recent years. Thus, the Schöllkopf bis-lactim ether method continues to gain adherents, as shown in reports of syntheses of (S)-cis- and -trans-crotylglycines using $MeC\equiv CCH_2Br$ as alkylating agent with the lactim ether (21),[81] and analogous applications leading to allocoronamic acid (22) via alkylation with $(E)\text{-}CH_2CH=CHCH_2Cl$/LDA,[82] and 1-benzenesulphonyl-6-methoxy-D-tryptophan methyl ester



Reagents: i, Schiff base formation and esterification; ii, >200 °C; iii, H_3O^+

Scheme 8



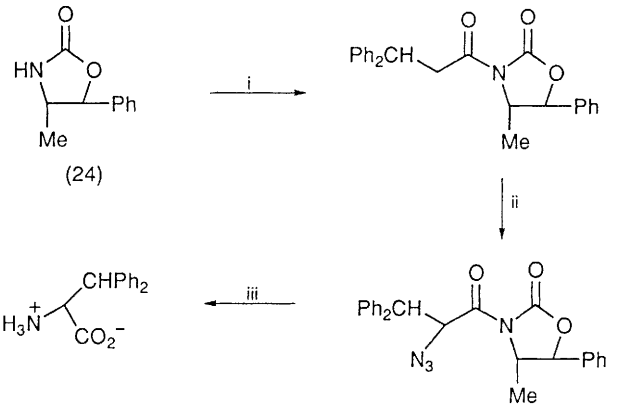
(starting from 6-methoxyindole and generating the relevant alkylating agent from it.[83] In a synthesis of a phenylalanine analogue carrying an N-methyl benzomorpholine moiety in place of phenyl, a claim that the Schöllkopf procedure must be performed in a modified manner to achieve this target in view of the "highly electron-rich side-chain" holds no credibility in view of the lack of comparative data.[84] A thorough assessment of the use of the Schöllkopf procedure in the straightforward (but expensive) way (reactions in MeO^2H and ^2H_2O) for the synthesis of (R)- and (S)-[2-^{2}H]-labelled α-amino acids has appeared.[85]

A use has been explored for the Schöllkopf procedure independently in two laboratories - the synthesis of L,L-di-aminopimelic acid [*alias* (2S,6S)-2,6-di-aminoheptanedioic acid][86] and its meso-diastereoisomer.[87] To attain the synthetic target requires that one of the two eventual chiral centres is located in an alkylating species and that the stereochemistry of the chiral centre that is generated by bis-lactim ether alkylation is controlled by the bis-lactim ether chiral centre. Two-carbon homologation of L-glutamic acid semialdehyde, or the Garner oxazolidine derived from L- or D-serine (23), [-CHO → -CH=CHCHO → -$CH_2CH_2CH_2Br$ or -CH_2CH_2CHO] was followed by routine use of the Schöllkopf procedure. Analogues carrying a 3,4-double bond, or a 4-fluoro- or 3-chloro-substituent, were prepared in one of these studies, in which an improved synthesis of the Garner synthon (23) was reported. The chirality at the 3-chloro-substituent, developed from the hydroxy substituent arising through the use of the aldehyde as alkylating agent, was defined by the enantio- and diastereoselective nature of the aldol addition to the Schöllkopf titanium enolate.

Novel variations of the Schöllkopf procedure include a demonstrated synthesis of L-alanine in 98% diastereoisomeric excess employing cyclo(Gly-L-Ala) carrying an (S)-phenylethyl substituent on each amide nitrogen[88] (perhaps an example of excessive provision of chiral director groups?). The titanated bis-lactim ether (21) undergoes ready Michael addition to nitro-alkenes to give diastereoisomerically pure α-(γ-nitroalkyl) α-amino acids.[89]

Numerous related strategies by which enantioselection can be imposed on an amino acid synthesis by a chiral auxiliary have been proposed and continue to be exemplified. Among the simplest is the 8-phenylmenthyl ester of glycine, which has been shown to undergo free radical bromination (NBS) and (amazingly) with high diastereoselectivity. The products are convertible into L-amino acids by bromide displacement with Grignard reagents.[90]

The Evans amination methodology, in which a chiral oxazolidin-2-one (24) is acylated by an alkanoic acid that is to undergo α-amination



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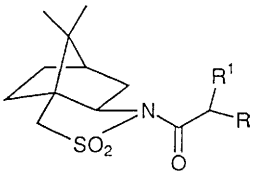
Reagents: i, $Ph_2CH.CH_2.CO_2H/Bu^tCOCl$ + NaH; ii, KHDMS then trisyl azide; iii, $LiOH/H_2O_2$ then H_2/Pd–C

Scheme 9



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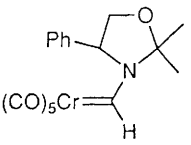

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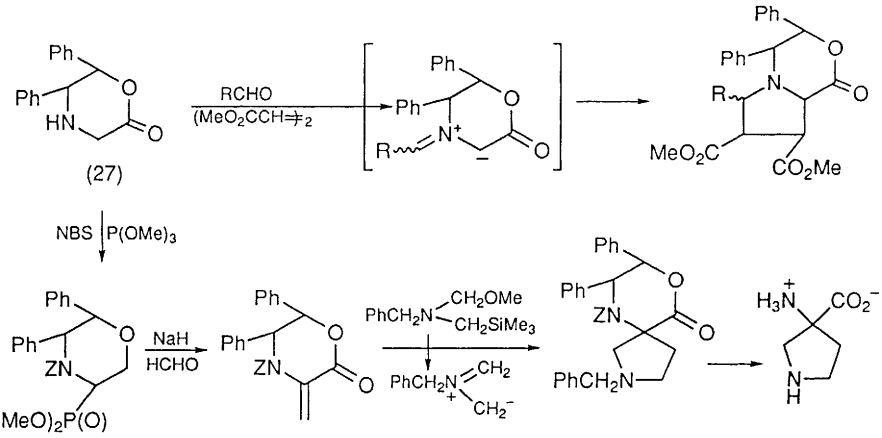


[(Scheme 9) for the synthesis of β-phenyl-(R)-phenylalanine][91] and for a route to either (R)- or (S)-β-methylphenylalanine[92] relies on a similar approach (α-bromination, substitution by azide ion and reduction to the amino group). An oxazolidin-2-one is used as chiral template for setting up the 8S and 9S centres of the unusual amino acid "Adda", using D-aspartic acid.[93] A spectacular use is described, for a synthesis of diphthamide. This amino acid is a residue in EF-2, the protein synthesis elongation factor, and diphthamide has been described as the most complex post-translationally-modified amino acid known in proteins.[94] The synthesis of diphthamide from D-and L-glutamic acids proceeds via an analogue of (24; Ph or $PhCH_2$ in place of Me; H in place of Ph) in the manner of Scheme 9. Further examples have been published, leading to indole-protected β-methyltryptophans from 3-indole-acrylic acid and $MeMgBr/CuBr\text{-}Me_2S$ for alkylation of the resulting N-acyloxazolinone,[95] and to (3S)-and (3R)-piperazic acids by α-hydrazination of N-(5-bromovaleroyl)oxazolinones followed by cyclization.[96]

The principle extends to amination with 1-chloro-1-nitrosocyclohexane, of enolates of N-crotonylsultams (25) formed with $NaN(SiMe_3)_2$. The synthon has been christened a "NH_2^+-equivalent" even though it ws used in this study to give an optically-pure N-hydroxy amino acid.[97] A particularly interesting area of study in which the N-substituent on the eventual amino acid is also homochiral, concerns the oxazolidine carbene Cr complexes (26), which can be regarded as Cr-bound ketenes. These, on photolysis in the presence of ^2H_2O, give (S)/(R)-[2-^{2}H]glycine with good diastereoselectivity.[98] Comparison is made in this study, with the stereoselectivity observed in quenching equivalent ketenes and ester enolates [i.e. R-CH=C=O and R-CH=C(OMe)O$^-$] with ^2H_2O. The same substrate (but with Me in place of H at the carbene C) gives L-alanyl dipeptides with high diastereoselectivity when photolysed in the presence of an L-amino acid ester.[99] The same substrate (but with $O^-Me_4N^+$ in place of H at the carbene C) gives arylglycines with moderate diastereoselectivity via aryl substituted oxazinones when photolysed in (1R,2S)-(-)-2-amino-1,2-diphenylethanol.[100]

The chiral oxazinones mentioned in the preceding paragraph are already familiar as starting materials for enantioselective amino acid synthesis. A route involving a [1,3]-dipolar cycloaddition of diethyl maleate to an azomethine ylide, formed from the saturated 2,3-diphenyl oxazinone (27) and an aldehyde, is highly endoselective, leading to highly-substituted prolines containing up to 4 continuous stereogenic centres.[101] A synthesis of (S)-(-)-cucurbitine, for which no efficient asymmetric synthesis is otherwise available, illustrates the principle of this method using the diphenyloxazinone in the way originally intro-

duced, for a specified synthetic target.[102] The diphenyloxazinone has also been used in an asymmetric synthesis of 2,6-di-aminopimelic acid enantiomers by the same group,[103] and to L-2,7-diaminoheptanoic acid and L-2,8-diaminooctanoic acid (alkylation of the diphenyloxazinone by $I(CH_2)_nI$ and substitution by azide of the ω-iodo atom).[104] (S,S)-2,6-Di-amino-2-hydroxymethylheptanedioic acid has been synthesized from the same oxazinone (27).[105] A related six-membered heterocyclic compound has expanded the horizons of asymmetric synthesis in the β-amino acid field, and is described in the later Section 4.15.

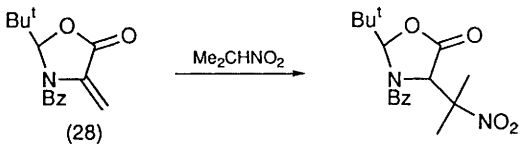
The other homochiral heterocyclic synthons are of the five-membered family, and have also become widely used, particularly the parent oxazolidinone of (28), for the asymmetric synthesis of α-amino acids. Nitronates, e.g. $Me_2C^-NO_2\ K^+$, undergo Michael addition to the methylidene derivative of (28) to give an 84:16-mixture of diastereo-isomers.[106] The method offers a convenient entry to amino acids with β-substituted-alkyl side-chains, based upon the easy reductive cleavage of the nitro group (see also preceding Section 4.1: General Methods of Synthesis). The corresponding imidazolone formed from L-methionine and converted into the vinylglycine analogue (by $NaIO_4$ then pyrolysis) has been used to prepare avicin analogues by 1,3-dipolar cycloaddition to nitrile oxides.[107]

The chiral imidazolidinone (29) has been used in a further example of the "alkylation of chiral heterocycle" approach to asymmetric synthesis of α-amino acids, this time of enantiomers of the NMDA antagonist 2-amino-5-(phosphonomethyl)[1,1'-biphenyl]-3-propanoic acid (*alias* 3'-phosphonomethyl-5'-phenylphenylalanine).[108] This paper includes a preparative procedure for the 2-isopropyl analogue of (29), with glycine, methylamine, isobutyraldehyde and Boc_2O as essential ingredients.

Chiral oxazolines (30 in Scheme 10) are intermediates in a distant relative of the Strecker synthesis, and provide D-amino acid esters from aldehydes via corresponding α-aminonitriles.[109]

Routes to prolines and pipecolic acids based on ene-iminium ion cyclizations that undergo a cationic aza-Cope rearrangement, proceed with complete stereoselectivity, and have been used in syntheses of (R,R)-4-(1-hydroxy-1-methylethyl)proline (31) for example.[110] Further details have been published relating to applications of aza-Diels-Alder reactions in asymmetric synthesis of pipecolic acids.[111]

Schiff bases of glycine esters, in which the Schiff base moiety alone is the chiral director, continue to provide a template for alkylation, in studies of links between structure and diastereoselectivity. A long-standing interest in nickel(II) (S)-2-[N-(benzylprolyl)amino] benzophenone



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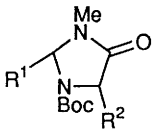

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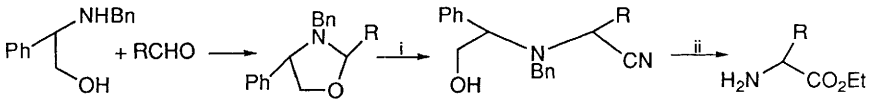

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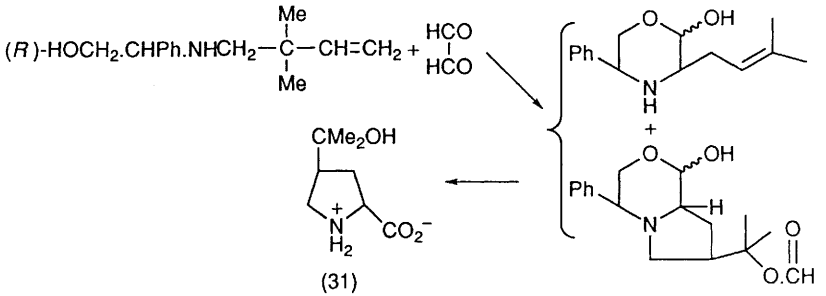
Reagents: i, Et_2AlCN; ii, EtOH; iii, $H_2/Pd–C$

Scheme 10



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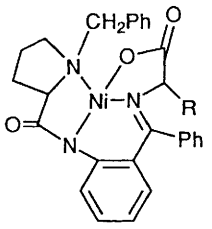

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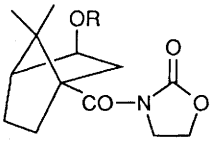

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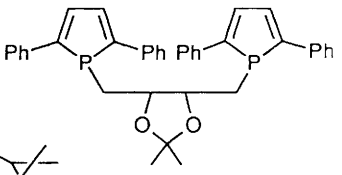

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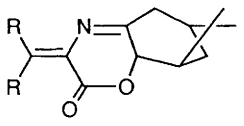


(35)

(32; R = H) has been indulged again, this year's literature describing its alkylation leading to syntheses of novel (S)-α-amino acids with phosphinate ester side-chains (e.g. -$CH_2CH_2P(Me)(O)OH$) with about 90% diastereoselectivity,[112] to (2R,3S)- and (2S,3R)-β-(4-methoxytetrafluorophenyl)serine and β-(pentafluorophenyl)serine,[113] and to propargylglycine (92% d.e.).[114] New variants of the process include the use of its β-alanine homologue for enantioselective β-amino acid synthesis [PhCHO → a mixture of (2S,3S)- and (2S,3R)-$PhCH(OH)CH(CH_2NH_2)CO_2H$].[115]

The "double asymmetric induction" principle in which both the Schiff base AND the ester moiety are chiral directors now has a considerable volume of literature behind it (Vol. 24, p.10). (R)-α-Amino acids form in 73 - 100% e.e. when (+)-camphorimines of (−)-menthylglycinate undergo alkylation,[116] and a wider range of e.e. values accompanies the exchange of the ester moiety for its (+)-enantiomer.[117] It is difficult to see any trends in the data, especially when faced with numerous other reports for alkylation of analogues containing achiral ester moieties; e.g. D-phenylalanine is formed in 99% e.e. when the imine formed between camphor-10-di-isopropylsulphonamide and glycine t-butyl ester is alkylated in the same protocol as for the preceding examples in this paragraph.[118]

N-[(1S)-2-Alkoxy-1-apocamphanecarbonyl)-2-oxazolones (33) provide different opportunities for asymmetric synthesis, but a similar principle is involved to that underlying the Evans and Seebach methodologies. Asymmetric cycloaddition to azines RN=NR and elaboration of the adduct by stereospecific substitution with organocuprates establishes this as a useful chiral synthon for amino acids, though the scope and limitations of the method are yet to be explored.[119]

A further approach to asymmetric synthesis, asymmetric hydrogenation and alkylation of αβ-unsaturated α-amino acid derivatives, continues to be thoroughly studied with similar objectives to the themes developed over the years. 2-Acetamidoacrylates (Z)-$R^1NH.C(=CHR^2)CO_2R^3$ undergo hydrogenation in solutions containing chiral phosphines complexed to Rh(II)-"Propraphos" → fluorinated phenylalanines,[120] -chiral aminophosphine - phosphinite → β-furylalanines,[121] -(3R,4R)-3,4-bis(diphenylphosphino)tetrahydrofuran (easily prepared from tartaric acid) → various substituted alanines, 54-97% e.e.,[122] -(R,R)-DIPPOP (34) → various substituted alanines,[123] → various substituted phenylalanines, with e.e. enhanced through the presence of detergents (SDS or Triton X-100).[124] Chiral phosphines complexed to Ru(II) exert similar roles; five-co-ordinate Ru(II)-binap complex → various substituted alanines, with a notable effect of

temperature on e.e. (at 70°, <70% e.e.; at 50°, 96% e.e.);[125] (R,R)-[dipamp-Ru(II)(2-methylallyl)$_2$] for reduction of the ketone function in α-acetylglycine to allothreonine.[126]

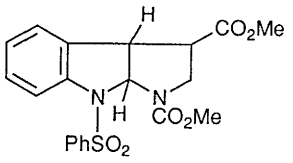
The same objective can be approached through Pd/C-catalysed hydrogenation of chiral Schiff bases of acetamidoacrylates, e.g. (35), gives better than 95% diastereofacial discrimination in favour of the (S)-β-substituted alanine (the same result is obtained by reduction with L-Selectride).[127] While little (44%) or no d.e. is observed in mixed cuprate (PhMgBr/CuI) alkylation of homochiral esters (Z)-$R^1NHC(=CHR^2)CO_2R^3$ [R^3 = (−)-menthyl],[128] higher order cuprates give β-substituted tryptophans with the L-tryptophan-derived synthon (36).[129]

Enzyme-assisted aldol condensation between glycine and an aldehyde is one of the areas where an approach to asymmetric synthesis of amino acids can be contemplated, but hydroxymethyltransferase shows very little ability to determine homochirality at the side-chain chiral centre.[130]

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

Several instances of the use of naturally-occurring α-amino acids as synthesis targets have been described in the preceding sections, and this section deals with specifically-designed syntheses. The usual opening topic of this section, fermentative production of the protein amino acids, is given less thorough coverage this year, citations being restricted to a key review (particularly of the production of glutamic acid, lysine, phenylalanine, and aspartic acid),[131] and indicative primary papers (reductive amination of pyruvate by alanine dehydrogenase to give L-alanine;[132] production of phenylalanine analogues by amination of cinnamates catalysed by the yeast *Rhodotorula glutinis*;[133] and methods using free and immobilized *Corynebacterium glutamicum* cells for L-lysine production.[134]

Natural cyclopropane-based α-amino acids tackled recently, include 1-aminocyclopropanecarboxylic acid (ACC), obtained in near-quantitative yield by cyclopropanation of a dehydroalanine Schiff base $Ph_2C=NC(=CH_2)CO_2Me$ using CH_2N_2,[135] and (+)-(1R,2S)-allocoronamic acid obtained through similar cyclopropanation of a chiral alkylidenedioxopiperazine (37).[136] A different, but still classical, route leads to N-Boc-ACC benzyl ester, elaborated for a synthesis of the the *Coprinus atramentarius* toxins coprine and O-ethylcoprine from L-glutamic acid.[137] An asymmetric total synthesis of individual diastereoisomers of hypoglycin A employs Sharpless oxidation of the appropriate



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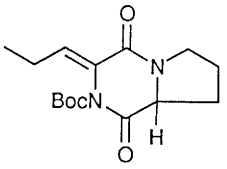

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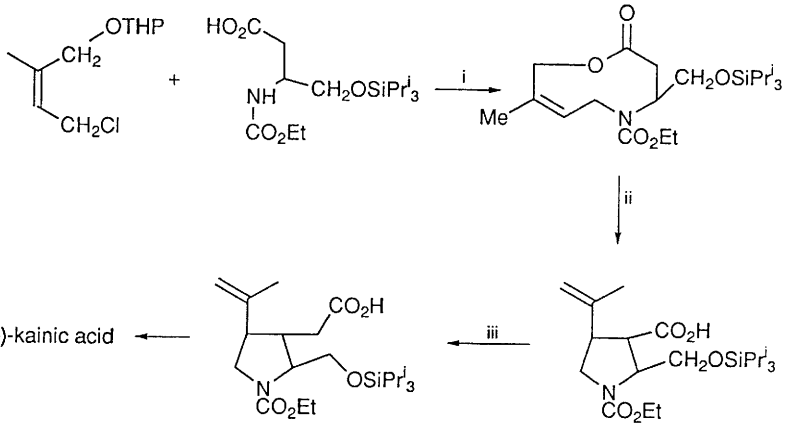
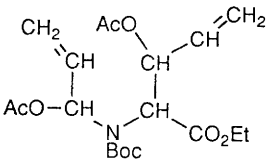


Reagents: i, BuLi/THF/N_2/–70 °C; then deprotection and intramolecular esterification; ii, LDA/BuLi/–100 °C→r.t.; iii, Arndt-Eistert homologation, then routine functional group manipulation

Scheme 11

(38)



(39)

alkene to open up access to the chiral methylenecyclopropane moiety.[138] The readily-available (2R,3R)-epoxysuccinic acid (38) has been elaborated into the γ-azetidinyl-β-hydroxy-α-amino acid related to mugineic acid by Shioiri's group,[139] for whom (2R,3R)-2,3-epoxycinnamyl alcohol has seemed a better starting point in a later study culminating in syntheses of mugineic acid[140] 3-epi-hydroxymugineic acid, and distichonic acid (the azetidine-ring opened analogue).[141]

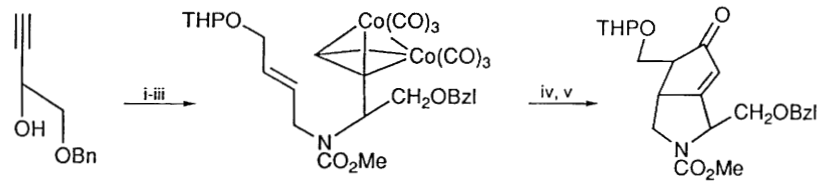
The kainoids and their relatives, like several of the preceding examples, have important, even spectacular, physiological properties that justify the unflagging interest in their synthesis.

Recent papers describing synthesis in this area are mostly extensions or consummations of earlier strategies. The stereochemical requirements as far as relative configurations are concerned, determine that the crop of recent papers, with one exception, exemplify the most obvious approach, in which the eventual substituted proline ring is formed from an acyclic precursor. The exception is the enolate Claisen route from a cyclic β-amino acid derived from L-aspartic acid (Scheme 11)[142] and the other reports relate to intramolecular ene-carbocyclization of (39), obtained by elaboration of N-Boc α-(acetoxyallyl)glycine ethyl ester[143] intramolecular Pauson-Khand ring formation (Scheme 12)[144] and tandem Michael addition (Scheme 13).[145] A previously-established route has been extended to provide a pair of acromelic acid A analogues (40), one of which (n = 0) is as potent in its physiological properties as kainic acid, while the other (n = 1) is inactive.[146]

A new synthesis of (−)-bulgecine uses the increasingly-popular chiral epoxide methodology (Scheme 14).[147] The first synthesis of the non-protein amino acid form the mushroom *Lycoperdon perlatum* involves the SmI_2-mediated formation of a spirolactone at C-4 of 4-hydroxyproline (Scheme 15).[148]

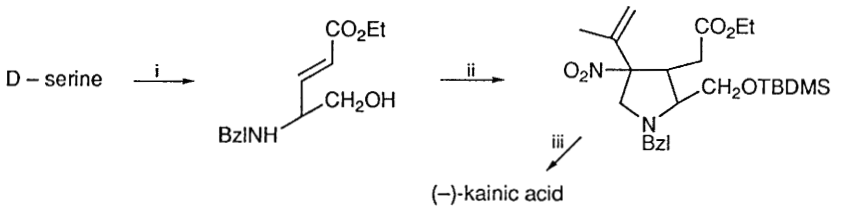
In spite of the vigorous activity surrounding the synthesis of the L-threonine derivative "MeBmt" [*alias* (2S,3R,4R,6E)-3-hydroxy-4-methyl-2-methylamino-6-octenoic acid], the unusual amino acid residue in cyclosporin, only one paper has appeared (Ref. 71 on p. 8, Vol. 20) reporting the synthesis of "MeBma", its C-9 analogue that is epimeric at the chiral centre carrying the hydroxy group. Another expedition along this path is shown in Scheme 16.[149]

Natural amino acids with unusual aromatic side-chains of the O-aryl ether variety, as are found in the ristomycins, offer formidable problems of synthesis. Continuing attempts to simplify the condensation of polyfunctional benzene derivatives through benzene moieties, include a study of the phenoxide-chloroarene-$Mn(CO)_3$ system, with aryl ether formation being followed by alkylation by a chiral glycine enolate to lead



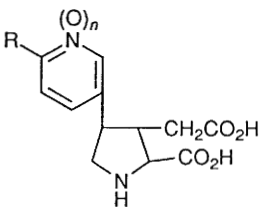
Reagents: i, PhtH, ($Pr^iO_2C.N{=}N$)$_2$ /Ph_3P; ii, $NH_2.NH_2$ then $MeO_2C.Cl$;
iii, routine development; iv, Pauson-Khand reaction;
v, $LiAlH_4$, followed by iii→(–)-kainic acid

Scheme 12



Reagents: i, six steps; ii, $H_2C{=}CMe.C(NO_2){=}CH_2$;
iii, Pd(0)/$HCOO^-NH_4^+$, followed by routine steps→(–)-kainic acid

Scheme 13



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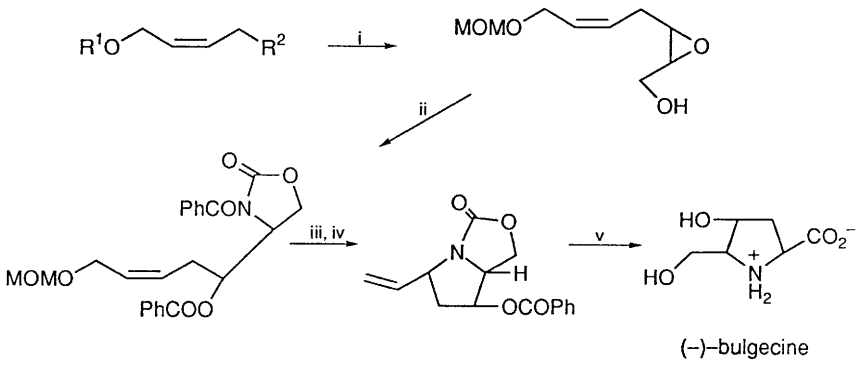
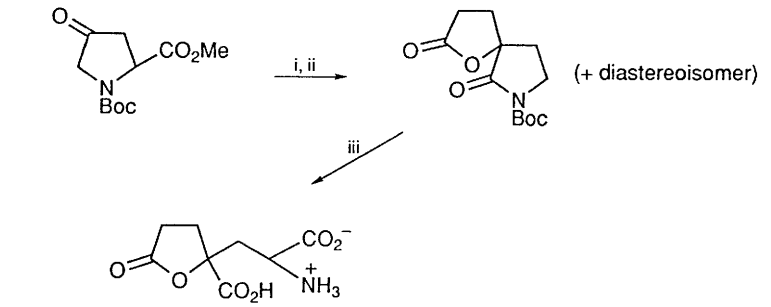


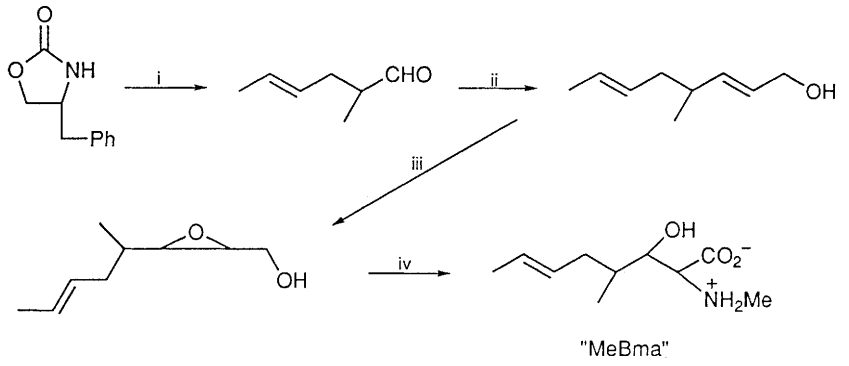
Reagents: i, several steps; ii, Ph.CO.NCO; iii, H_3O^+, deprotection; iv, β–elimination; v, O_3 and $KMnO_4$

Scheme 14



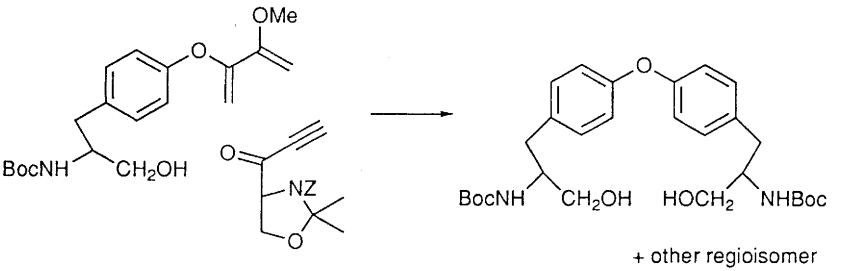
Reagents: i, $CH_2{=}CHCO_2Me/SmI_2$; ii, $RuO_2/NaIO_4$; iii, separate, reflux 6M HCl/12h

Scheme 15

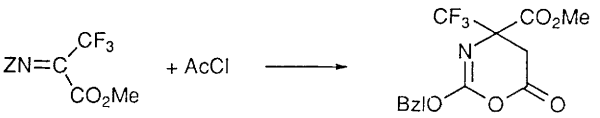


Reagents: i, Evans methodology (*Tetrahedron Lett.*, 1987, **28**, 39);
ii, $(MeO)_2P(O)CH_2CO_2Me/BuLi$, then DIBAL;
iii, $Bu^tOOH/Ti(OPr^i)_4$/L-(+)-DET; iv, PDC then $MeNH_2$

Scheme 16



Scheme 17



(41)

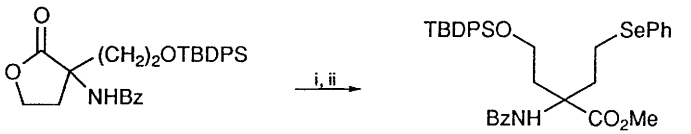
to protected ristomycinic acid derivatives in high optical purity.[150] Another approach avoids the condensation by starting with an appropriate alkenyl ether of Boc-L-tyrosine and forming the other arene ring through a Diels-Alder strategy (Scheme 17; see also Vol. 24, p.18). This leads to a 1:1-mixture of the required isomer, (S,S)-isodityrosinol accompanied by the the meta-isomer.[151]

4.4 *α-Alkyl Analogues of Protein Amino Acids.*

Important pharmaceutical roles are arising for these derivatives, associated with the irreversible enzyme inhibitory activity of some of them, and novel synthetic approaches are being established. Some material under this heading will be found in preceding sections, and elsewhere, in this Chapter. Thus, a general asymmetric α-amino acid synthesis based on alkylation of a homochiral imidazolinone has served to provide enantiomers of α-methylserine, elaboration through standard methods [$-CH_2OH \rightarrow -CH_2Cl \rightarrow -CH_2py^+$] giving the pyridiniomethyl analogue.[152] A quite different approach applied to the preparation of α-methylaspartic acid, is the alkylation with retention of configuration of the hexahydropyrrolo[2,3-*b*]indole easily obtainable from a tryptophan enantiomer, followed by degradation of the indole moiety ($NaIO_4$/$RuCl_3$).[153] A more fundamental approach to assembling the α-substituted aspartic acid framework exploits the dual categorization of this amino acid as a member of both α- and β-amino acid families, by conversion of the imine $ZN=C(CF_3)CO_2Me$ into the oxazinone (41) followed by nucleophilic ring-opening[154] (see also Vol. 22, p.22 for an exact precedent for this work).

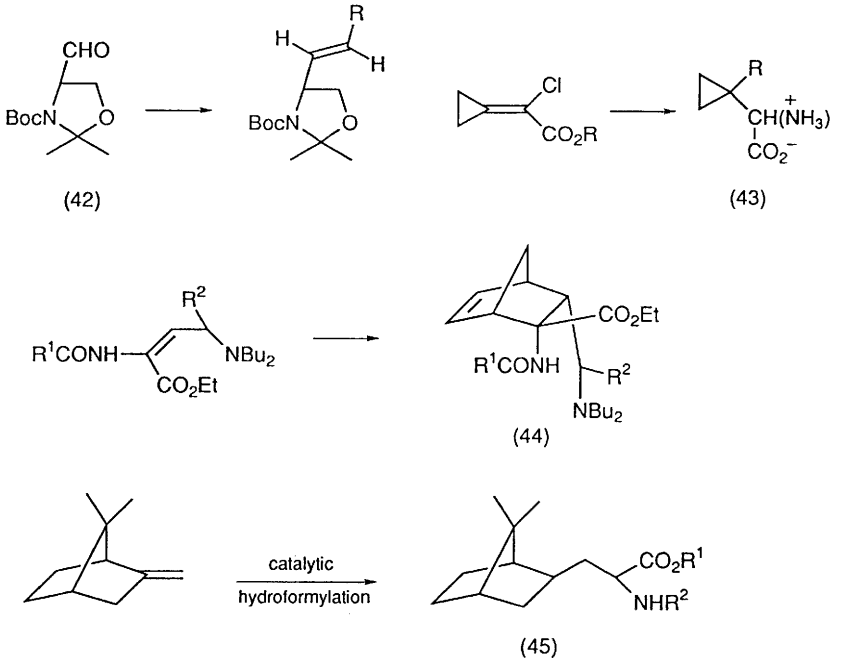
An unexpected entry to α-[2-(phenylseleno)ethyl]-α-amino acids was discovered through attempted PhSeSePh/$NaBH(OMe)_3$/DMF reduction (thought of as "$NaPhSeBH_3$" reduction) of N-benzoyl homoserine lactone (Scheme 18).[155] There is no competing lactone reduction in this process.

Ornithine derivatives are crucially important in the context of the opening sentence of this section, and absolute configurations have been assigned by X-ray crystal analysis and by classical chemical correlation methods to enantiomers of irreversible inactivators of decarboxylases, namely, α-chlorofluoromethyl derivatives of this amino acid and of glutamic acid and m-tyrosine.[156] α-Methylornithine enantiomers have been converted into L-(+)- and D-(−)-α-methylarginines through standard side-chain functional group elaboration using $ZN=C(SMe)NHZ$.[157]



Reagents: i, $(PhSe)_2$, $NaBH(OMe)_3$/DMF/60 °C; ii, CH_2N_2, H_3O^+

Scheme 18



4.5 *Synthesis of C-Alkyl and Substituted C-Alkyl α-Amino Acids and Cyclic Analogues.*

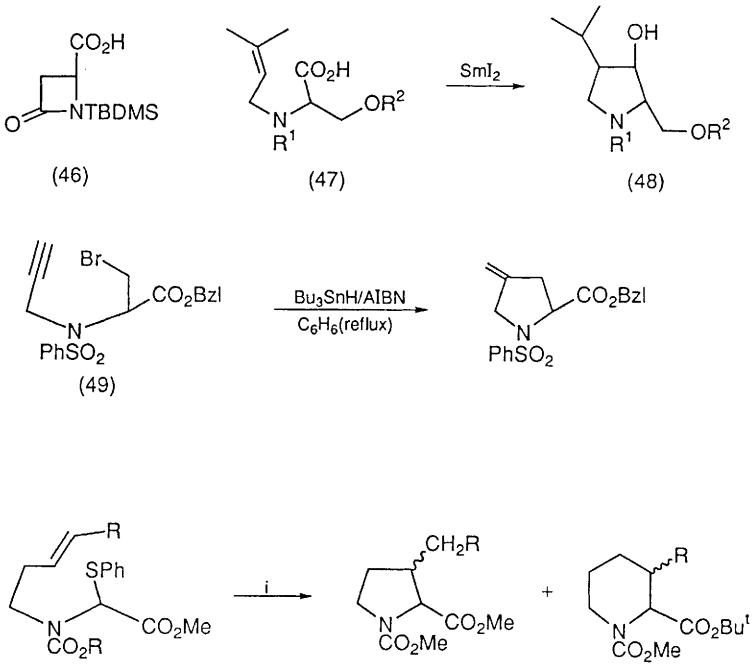
This is a Section intended to give refuge to papers covering both close analogues of protein amino acids, and to more distant structural relatives that are of aliphatic, alicyclic, or saturated heterocyclic types. Again, some papers that might have been included here, because they are covered by this description will be found in a preceding section instead.

β-Iodo-alanine is becoming established as a useful synthon, when converted into its organozinc derivative, for development of side-chain aliphatic features, such as 4-oxo-alkyl (reaction with RCOCl) and 3-arylalkyl (reaction with an aryl iodide).[158] An uninformative abstract (*Chem.Abs.*, 1992, **117**, 112003) has to be blamed for lack of details relating to syntheses of DL-2-amino-5,5-dimethylhexanoic acid and -6,6-dimethylheptanoic acid as their N-acetyl methyl esters and employing t-butyl chloride (presumably a version of the acetamidomalonate synthesis).[159]

Side-chain alicyclic structures may be built on to acyclic side-chains of amino acid synthons in a variety of ways for a variety of purposes - ethyl diazoacetate to a protected D-allylglycine to give D-2-amino-4,5-methano-adipates that show NMDA receptor activity;[160] αβ-methano-valine, -phenylalanine, and -alanine by treatment of N-phthaloyl β-bromo amino acids with NaH,[161] DL-(E)- and (Z)-2,3-methano-m-tyrosines (potent L-aromatic amino acid decarboxylase inhibitors, by similarly classical methods from mono-ethyl malonate,[162] and (E)-α-[2-phenyl(or ethyl)cyclopropyl]glycines by diastereoisomeric dibromocyclopropanation of the alkene derived from the D-serine synthon (42; cf, 23) followed by reductive debromination.[163] A novel and efficient route to these cyclopropanated side-chains starts with the dehydro-alanine imine $(MeS)_2C{=}NC(=CH_2)CO_2Me$ and involves its cyclopropanation with diazomethane.[164] The only recent study within this family of compound, involving amination of a substrate that already has the cyclopropane moiety built in to it, has been directed at syntheses of natural cyclopropylglycines (43; R = Me), including cleomin (43; R = OH).[165]

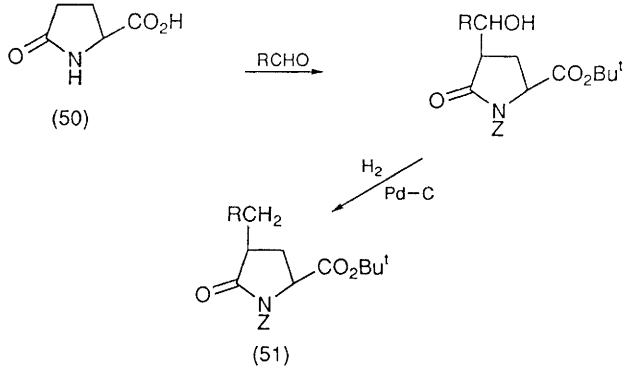
Cognate areas in which alicyclic side-chains are constructed analogously, are covered in cycloadditions to chiral αβ-dehydro-amino acid derivatives (e.g. 44), including diazomethane cyclopropanation,[166] and a synthesis of the (+)-fenchane derivative (45), which is 2200 times sweeter than sucrose.[167] Improved syntheses are reported for β-cyclohexyl-L-aspartic acid and γ-cyclohexyl-L-glutamic acid in protected forms.[168]

Alkylation of N-TBDMS-azetidinone-4-carboxylates (*alias* β-lactam-4-carboxylates; 46) through standard LDA/alkyl halide protocols



Reagents: i, Bu_3SnH, AIBN

Scheme 19



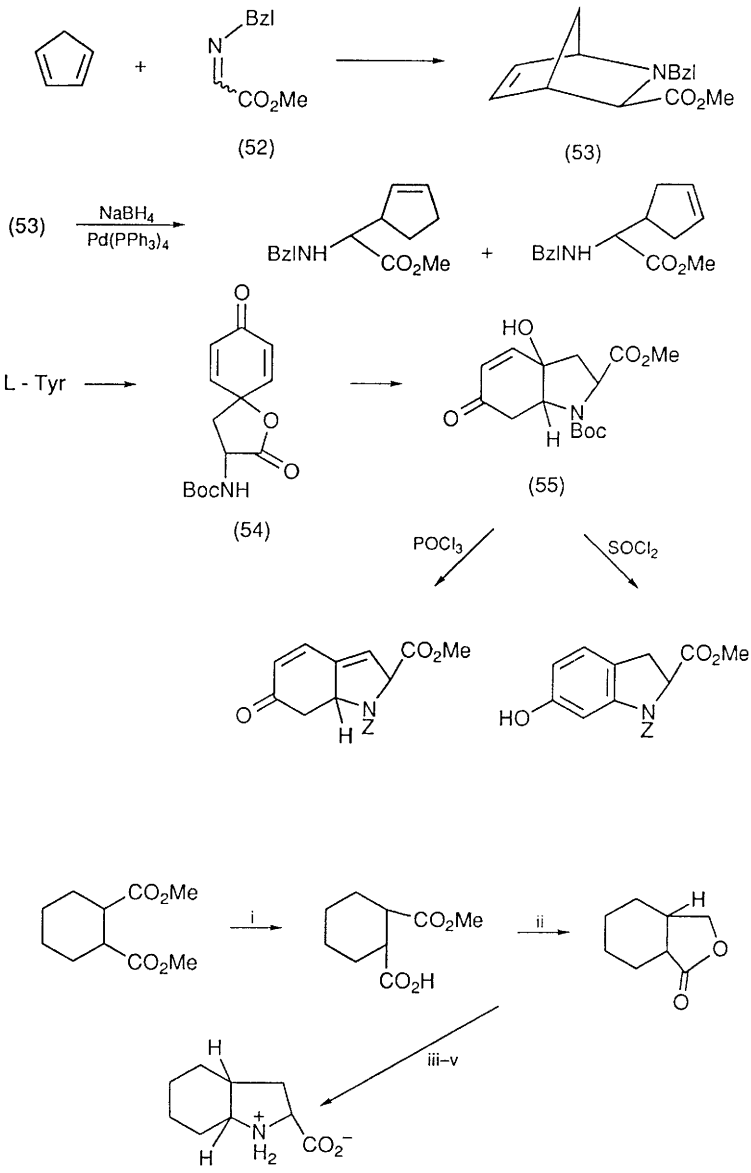
gives anti-oriented products from which (2S,3R)-3-alkylaspartic acids can be obtained.[169] (2RS,E)-3-Ethylidene azetidine-2-carboxylic acid (*alias* racemic polyoximic acid) has been prepared through $Rh(OAc)_4$-catalysed cyclization of $BocNHCH_2COCN_2CO_2Bu^t$ followed by Wittig alkenylation with $PhSCOCH=PPh_3$ and routine elaboration.[170]

α-Imino acids are of ever-increasing interest, and some syntheses of members of the proline and pipecolic acid families of natural origin have been mentioned in the preceding sections. N-Alkenylserine derivatives have been shown to undergo ring-closure with oxophilic samarium(II) species (47 → 48),[171] and analogous starting materials are employed in Bu_3SnH/AIBN cyclisation of N-alkenyl α-(phenylthio)glycine esters (Scheme 19).[172] The minor competing 6-endo-cyclization mode was observed in some cases in this study, leading to pipecolic acid isomers, but not in the 5-exo-dig radical cyclisation of the L-serine-derived substrate (49) put through the same reagent treatment.[173]

Traditional routes to substituted prolines include uses for pyroglutamic acid enantiomers (aldolization after Li enolate generation; 50 → 51),[174] Diels-Alder reactions of N-benzylimines (52 → 53),[175] and routes to bicyclic prolines, one exploiting the L-tyrosine functional groups (54 → 55),[176] and the other following the "magic meso" philosophy that is currently intriguing several research groups and has been used for the preparation of the ACE inhibitor Trandolapril (Scheme 20).[177]

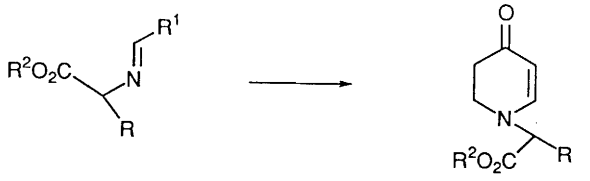
Syntheses within the pipecolic acid family (see also Refs.110,111), that approach the target through conventional cycloaddition strategies employing imines, include the use of Danishefsky's diene with an N-alkylidene L-amino acid ester (56 → 57),[178] and a similarly-oriented study using $RCH=CR^1C(OSiMe_2R^2)=CH_2$ + $R^3N=C(CO_2R^4)_2$ in which the outcome of the cycloaddition contradicts earlier claims.[179] The cyclohexenones resulting from these reactions can be elaborated further through their C=C grouping to give trans-3-substituted-4-oxo-L-pipecolic acids.[180] The hitherto unsuspected propensity for Schiff bases of αβ-dehydroamino acids $ArCH=NC(CO_2Me)=CH_2$ to undergo dimerization has now become a reality (Scheme 21), with the benefit of leading to new types of mono- and bicyclic α-amino acids.[181]

A different pattern of substitution arises from the cyclisation of derivatized 1-aminobut-3-en-2-ols, obtained from N-Boc-L-alanine and providing the N-methyl-L-pipecolic acid analogue (58).[182] An alternative cyclization strategy is involved in rhodium(II) diacetate catalysed NH insertion of L-glutamic acid-based diazoketones (59 → 60).[183]



Reagents: i, Pig liver esterase; ii, $NaAlH_2Et_2$/toluene
iii, isomerize ring junction stereochemistry (MeONa)
iv, NH_3, Beckmann rearrangement; v, HCHO/KCN then H_3O^+

Scheme 20



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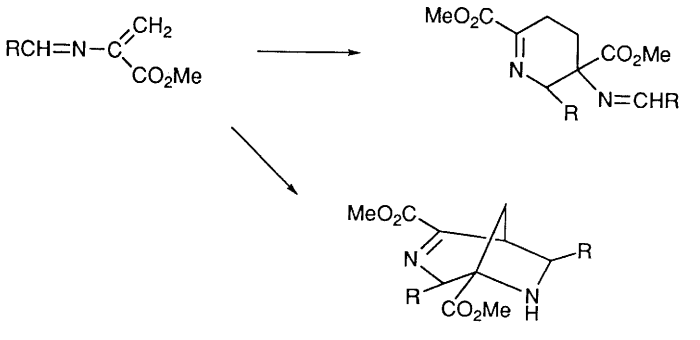
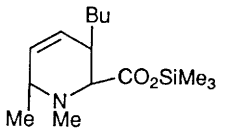


Scheme 21



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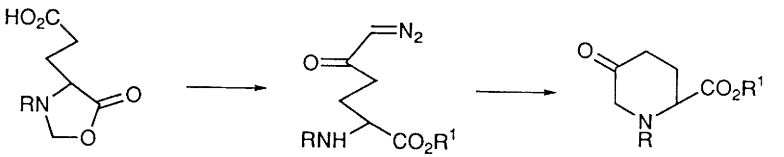


(59) (60)

4.6 *Models for Prebiotic Synthesis of Amino Acids.*

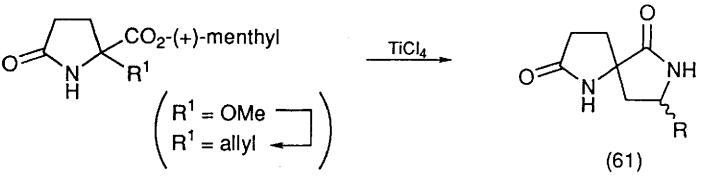
It is many Volumes ago in this Series that the *deja-vu* nature was suggested, of papers still appearing then as now, describing laboratory modelling of the presumed chance environmental synthesis of protein amino acids from simple atmosphere components and an energy source. However, the picture has certainly taken a wider perspective, and has become more detailed, as the years have gone by, even though the general approach to the underlying chemistry has remained the same. In particular, the discovery of nucleic acid components[184] and carbohydrates[185] in the laboratory soups has been a useful outcome, as well as establishing the role of HCN and opening up its organic chemistry a little more.

The former[184] of these two studies has established the intermediacy of oxalic acid and/or oxamic acid in the formation of amino acids and nucleic acid bases during u.v. photolysis (<280 nm, $> -80°$) of aqueous $(NH_4)_2CO_3$ in the presence ofMg^{2+} salts. In the latter study, conditions mimicking ash-gaseous volcanic clouds were shown to generate glucose, mannose, ribose, and deoxyribose, and (although not mentioned in the abstract of this paper) presumably also traces of amino acids. Unusually high concentrations of 4-aminoisobutyric acid and of DL-isovaline are found at the Cretaceous/Tertiary (K/T) boundary at Sterns Klint, Denmark. Intrusion of magma into a coal bed has been speculated to give the simple gases needed to synthesize hydantoins from which these amino acids could have formed.[186]

Simulated hydrothermal conditions (submarine volcanic vents) are underlying experiments exploring the latest thinking on the origin of life, and the high temperature (150°) and reducing conditions (pH $\sim$ 7) applied to HCHO, NH_3, HCN, and H_2O mixtures in contact with mineral surfaces yield a range of amino acids with a similar profile to that obtained in traditional electric spark discharge experiments, but with higher relative yields of amino acids other than glycine.[187] Bombardment of $CO/N_2/H_2O$ mixtures with 2.8-40 MeV protons to yield HCN and amino acids is claimed to show that cosmic radiation is a more effective energy source in this area than electric spark discharge.[188]

4.7 *α-Alkoxy α-Amino Acids.*

The anodic oxidation of α-imino acids in alkanol solvents has been known for some years now, to lead to α-alkoxy analogues. A recent extension of this methodology to L-pyroglutamic acid (+)-menthyl ester and substitution of the α-methoxy group by reaction with allyltrimethylsilane and $TiCl_4$, gives a 2:1-mixture of diastereoisomers of spiro-compound (61).[189]



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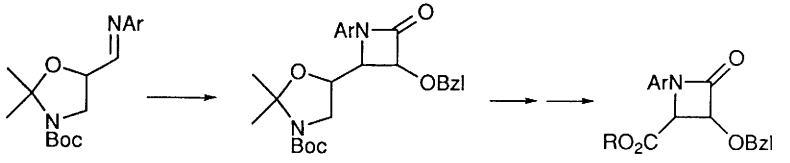

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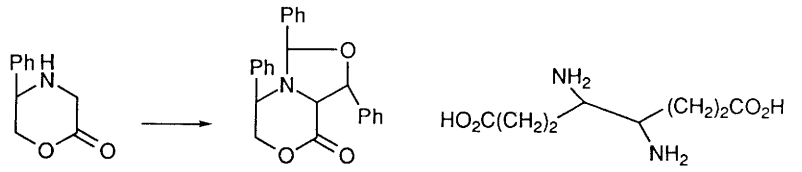
(64) (65)



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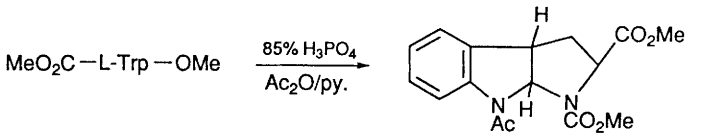


(69)

α-Benzyloxy- and -methoxyglycines are more stable than corresponding bromides, but undergo analogous substitution reactions and are thus more convenient for such processing; e.g. reaction with Sn_2Bu_6 and a disulphide RSSR gives α-(alkanethio)glycines.[190]

4.8 *α-(Halogenoalkyl) α-Amino Acids.*

In noting that synthetic work starting in a routine way with β-bromoalanine and related compounds has been cited in preceding sections of this Chapter, this section covers papers more centrally concerned with the halogenoalkyl amino acids as final targets. 4-Fluoroglutamic acid is a representative illustration of the attraction of such compounds, not in their own right but as potential enzyme inhibitors or otherwise capable of disrupting certain metabolic processes. The stereospecific route to this compound requires the hydroxypyroglutamic acid as precursor, to be substituted with inversion by diethylaminosulphur trifluoride.[191] This work follows pioneering work by Hudlicky[192] (see Vol. 23, p.26) which is discussed in Ref. 191.

4.9 *α-(Hydroxyalkyl) α-Amino Acids.*

Several examples of aldol reactions with glycine carbanions or equivalents have been described in preceding pages, and these and others like them collected here, lead to β-hydroxy-α-amino acids. N^{τ}-Trityl β-hydroxy-L-histidine has been prepared by the oxazolid-2-one method using the trityl 4-formylimidazole[193] and β-hydroxyaspartates via β-lactam formation from the Garner oxazoline derived from L-serine (62 → 63).[194] An interesting trimethylsilylated homoserine lactone analogue has been prepared.[195]

The elaboration of simple monosaccharide derivatives into hydroxylated amino acids continues to offer particularly convenient access to prolines (64 from D-xylonolactone → 65).[196]

The versatile chiral glycine synthon (66) has recently shown even more versatility in the synthetic applications of the stable azomethine ylides (67) formed from it. The previously-established uses flow from cycloadditions, but if excess aldehyde is used in the preparation of the ylide, then adducts transformable into β-hydroxy-α-amino acids are formed in the absence of dipolarophile.[197]

4.10 *α-Amino Acids with Aminoalkyl Side-Chains.*

An increasing number of studies under this heading is reflected in entries in a number of other Sections in this Chapter (Refs. 86, 87, 104, 105, for example). Typical studies to be described here, must start with a heroic preparation of L-(+)-2,4-di-aminobutanoic acid, by refluxing L-

glutamic acid with NaN_3 and H_2SO_4,[198] followed by a more controlled synthesis of (S,S)-2,3-di-aminobutanoic acid, the constituent of antimycins and cirratiomycins.[199] The latter synthesis starts with N-Boc-L-threonine, via the 1,3-diol and exploiting the propensity of TBSCl/DMAP to silylate the primary alcohol function selectively; mesylation of the other function, and displacement by azide, completes the process. An interesting preparation of di-amino di-acids (68) uses the known 1,4,6-tri-O-acetyl-2-azido-2,3-dideoxy-3-nitro-α-D-glucose.[200]

4.11 *α-Amino Acids with Unsaturated Side-Chains.*

A number of examples of alkenylation of α-functionalized glycine synthons has been reported in the current literature, viz. S_N1-substitution of N-alkoxycarbonyl α-methoxyglycinamide by allylsilanes mediated by BF_3,[201] and Wittig-Horner reaction of $Me_2O_3PCH(NHR)CO_2Me$ with R^1OCH_2CHO to give (E)-vinyl ethers[202] and protected (E)-αβ-dide-hydro-amino acids more generally.[203] Acetamidomalonate routes to propargylglycines, and the homologation of the products through $Pd(PPh_3)_4$-mediated reactions with aryl and vinyl halides or triflates ($-CH_2C{\equiv}CH{\rightarrow}-CH_2C{\equiv}CR$) without racemization, have been described.[204] A synthesis of 5-methoxy-N-methoxy-L-proline methyl ester and its reaction with bis(trimethylsilyl)acetylene/$TiCl_4$ to give cis- and trans-5-vinyl-L-proline, and analogous carbanion substitution reactions to give the 5-ethynyl analogues, as well as a synthesis of 4-methylene-L-proline from the 4-oxo-compound, have been described.[205]

A standard synthesis of αβ-dehydroalanine and its butyrine analogue through dehydration of protected serines and threonines respectively, has been improved through the use of diethylchlorophosphate [$(EtO)_2P(O)Cl$] and NaH in THF.[206]

The first of many potential uses for a new L-serine-derived Zn-Cu reagent, $IZn(CN)CuCH_2CH(NHBoc)CO_2Bzl$, prepared from the protected iodo-alanine by reaction first with the Zn-Cu couple, then with Knochel's soluble copper salt CuCN,2LiCl, has been chosen to be homologation by reaction with an allyl halide, or other allylic electrophile.[207]

Manipulation of the products of these syntheses is feasible in several ways, such as (E)- → (Z)-isomerization by acid, base or radical catalysis,[203] and other examples of re-location of the site of unsaturation described in a later Section (6.3: Specific Reactions of Amino Acids) extends the synthetic usefulness of these compounds.

4.12 *α-Amino Acids with Aromatic and Heteroaromatic Side-Chains.*

A major feature over the years, has been the collection of papers describing syntheses of near-relatives of the protein amino acid

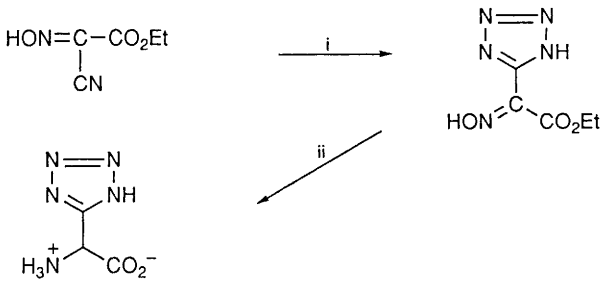
representatives conforming to the title of this Section. The significance of the work carried out lies only occasionally in the synthetic details, but more in the potential physiological properties, particularly towards the NMDA receptor, of the amino acids.

Standard general methods (e.g. bis-lactim ether alkylation,[208] Pd-catalysed cross-coupling of an aryl iodide with methyl 2-acetamidoacrylate[209]) have been illustrated for syntheses of N-Boc p-dimethylphosphonomethyl-L-phenylalanine[208] (see also[210] for this and for p-sulpho- and -carboxy and -N-hydroxycarboxamido-L-phenylalanines, and see[211] for o-, m-, and p-phosphonomethyl-, o-, m-, and p-sulphomethyl-, m-carboxymethyl- and m-N-hydroxycarboxamidomethyl-L-phenylalanines (and some cyclohexylalanine analogues), and see[212] for syntheses of 6-fluoroDOPA and its potential metabolites. Pd-Catalysed cross-coupling reactions have been explored, so as to develop methods for the connection of relevant aryl moieties, viz. (R)-4-hydroxyphenylglycine and (S)-3,5-dihydroxyphenylglycine, seen in vancomycin.[213]

Some general methods related to those of the preceding paragraph have proved satisfactory for syntheses of tryptophan analogues, viz. $EtAlCl_2$-catalysed Michael-type addition of indoles to Schiff bases of αβ-dehydroalanine, $Ph_2C{=}NC(=CH_2)CO_2Me$,[214] and (−)-(R)-7-aza-tryptophan through alkylation [-100°/HMPA/THF/$KN(SiMe_3)_2$] of the (+)-camphor imine of glycine t-butyl ester.[215] A 5-cyano-L-tryptophan synthesis employs a protected L-tryptophan (69) as starting material and proceeds via the 5-bromo-analogue (NBS/AcOH).[216]

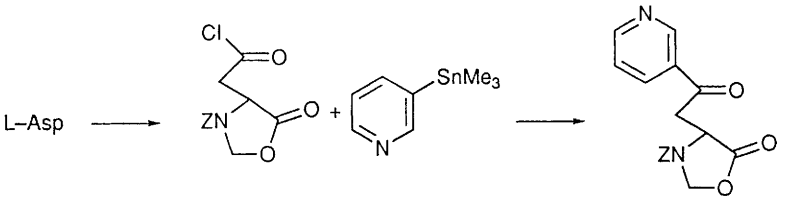
N^{τ}-Alkylation of L-histidine using 2-chloro-1-methoxymethylindole starts a short synthesis of the amino acid residue present in moroidin.[217] Non-protein natural amino acids with heteroaromatic side-chains often possess spectacular physiological properties, represented in this year's literature by analogues of homoibotenic acid and of its isoxazole variant,[218] that include potent agonists tested for NMDA receptor activity. Quisqualic acid analogues tested for, but ineffective in, sensitizing cell neurons to depolarization by L-2-amino-4-phosphonobutanoic acid, involve replacement of the isoxazole moiety by the maleimide ring and other simple five-membered heterocycles.[219] However, DL-[tetrazol-5-yl]glycine, prepared using a rarely-used but specifically appropriate glycine equivalent (Scheme 22),[220] is a highly potent NMDA agonist. (2S)-Nicotinylalanine (in Scheme 23) has been prepared through an unusual L-aspartic acid synthon in which the β-carboxy group is liberated for activation as the acid chloride. The product shows promise as a new neuroprotecting agent.[221]

Analogues of DOPA and methylDOPA in which the catechol moiety is replaced by analogous benzimidazole and benzotriazole group-



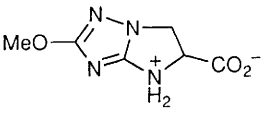
Reagents: i, NaN_3/DMF; ii, H_2/Pt

Scheme 22



Reagents: i, $PdCl_2(PPh_3)_2$; ii, deprotection, H_3O^+

Scheme 23



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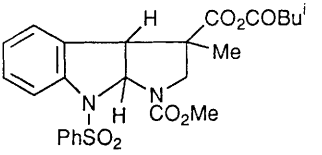

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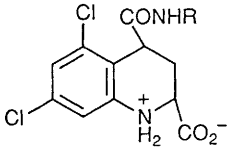

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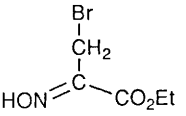

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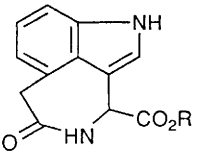

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ings have been prepared through routine application of standard methods.[222]

Increasing interest is being shown in sterically-constrained analogues of these aromatic and heteroaromatic amino acids, in which the common alanyl moiety is connected through nitrogen to the aromatic or heteroaromatic grouping. From one structural viewpoint, these are proline, or occasionally pipecolic acid, derivatives, and it seems that the interest in them for their potential physiological properties may be the result of empirical thinking-compounds that fuse the structural details of two classes of neuroactive α-amino- and -imino acids might themselves show some valuable properties. Distant proline relatives include the triazole (70) formed from the 5-bromo-1,2,4-triazole and methyl N-benzylaziridinecarboxylate,[223] and the unusually stable mixed carboxylic carbonic anhydride (71) formed from N^{im}-benzenesulphonyl-L-tryptophan after cyclisation through established methods.[224] trans-2-Carboxy-5,7-dichloro-4-amido-1,2,3,4-tetrahydroquinolines (72)[225] and analogous compounds derived from kynurenic acid[226] have been considered useful compounds with which to explore the NMDA receptor (glycine site) in a search for antagonists. (R)- and (S)-1,2,3,4-Tetrahydro-6,7-dihydroxy-1-methylisoquinoline-1-carboxylic acids (metabolic precursors of (R)-salsinol in humans) have been synthesized through standard isoquinoline methodology, and their absolute configurations have been established.[227] The cyclic tryptophan derivative (74) has arisen from studies of tryptophan synthesis using indole and the β-bromoalanine synthon (73).[228]

4.13 *N-Substituted α-Amino Acids.*

A long-established method for preparing N-methyl amino acid esters, condensation with formaldehyde followed by reduction, has been accomplished using Et_3SiH/TFA for the reduction step and now understood to proceed via the iminium ion.[229] Side-chain N-alkylated arginines have become important again, this time in the context of potential nitric oxide synthase inhibitors, as described in the work of Olken and Marletta[230] on N^G-allyl- and -cyclopropyl-L-arginine (reviewed by Feldman).[231] Synthesis of these compounds is straightforward from ornithine, the requisite amidinating agent being prepared through the sequence BzNCS→BzNHCSCHR (R = allyl or cyclopropyl) → S-alkyl, followed by established methodology.

4.14 *Sulphur Containing α-Amino Acids.*

The most familiar of the α-amino acids under this heading, cysteine and its post-translationally modified derivatives, are featured in this

year's crop of citations that are not without interest even though exploring familiar and otherwise thoroughly-studied amino acids.

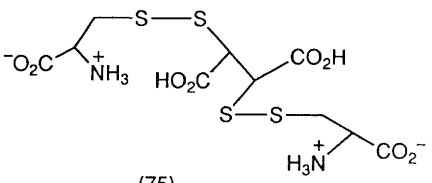
A preparation of S-alkylcysteine homologues involving AIBN-catalysed addition of thiols to (R)- or (S)-allylglycine is accompanied by only a small degree of racemisation.[232] Enantioselective synthesis of (2R;3S)- and (2R,3R)-3-phenylcysteine derivatives has been accomplished in this general way.[233] Preparations of N-Boc-S-trifluoromethyl-DL-cysteine,[234] and of D-(β-ureidoethyl)-cysteine and -homocysteine, involve routine methodology.[235] The last-mentioned preparation involves hydantoin formation and *Agrobacterium radiobacter* resolution.

A synthesis of meso-lanthionine calls for a rather more subtle strategy than at first sight would appear to be needed. Temporary linking of two cysteine molecules of opposite configuration through their carboxy-groups, then disulphide formation, has been achieved through esterifying N-Z-D-cysteine with N-Boc-S-trityl-L-cysteine 2-hydroxyethyl ester (DCCI/DMAP) followed by $PhI(OAc)_2$ oxidation. The functional group transformation disulphide → sulphide was achieved in the usual way with $(Et_2N)_3P$ in DMF.[236] The bis-cysteine disulphide of meso-dimercaptosuccinic acid (75) may be the form in which dimercaptosuccinic acid (a metal-binding agent) is excreted by mammals.[237]

4.15 *Phosphorus Containing α-Amino Acids.*

There is a steady interest in amino acid analogues in which the carboxy group is replaced by a phosphorus oxy-acid group, but the policy for this Specialist Periodical Report continues to exclude these and other carboxy group substitutions. However, the presence of a phosphorus oxy-acid moiety in an amino acid side-chain does render that amino acid open to consideration for inclusion in this Section. Indeed, there is growing interest in such compounds, both for synthetic applications (see preceding Section 4.1) and for their potential physiological activity.

Treatment of the serine-derived β-lactone (76) with dimethyl trimethylsilylphosphite gives β-(dimethylphosphonyl)-L-alanine in a protected form suitable for use in peptide synthesis.[238] The homologous γ-(dimethylphosphonyl)butyrine has been approached by elaboration of the side-chain carboxy group of N-Boc-L-aspartic acid α-t-butyl ester → CH_2OH → CHO by TEMPO-catalysed NOCl oxidation, and dimethyl trimethylsilylphosphate treatment[239] and alternatively, by asymmetric amination of $Et_2O_3PCH_2CH_2COCO_2Et$ with (1S,2R)-$PhCH(OH)CHPhNH_2$.[240] L-Aspartic acid is the source of phosphinothricin, $MeP(O)(OH)CH_2CH_2CH(NH_2)CO_2H$, in protected form, based on conversion into an N-protected L-homoserine lactone, ring-opening



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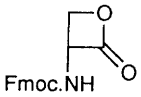

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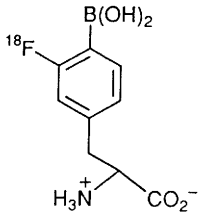

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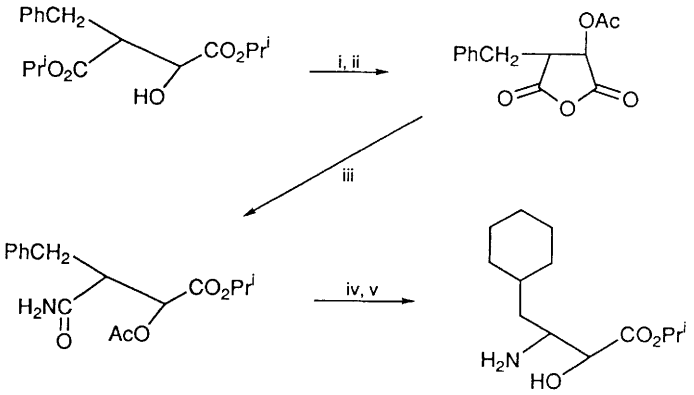


Reagents: i, KOH–aq. THF; ii, AcCl; iii, Pr^iOH; iv, 1 eq. NH_3, then $Pb(OAc)_4$–Bu^tOH; v, HCl–Pr^iOH, then H_2–Rh/C

Scheme 24

with HCl to give the β-chlorobutyrine, and reaction with $MeP(OEt)_2$,[241] An alternative starting point for this compound is a protected L-vinylglycine, prepared from L-methionine or L-glutamic acid in established ways.[242] The phosphinic acid analogue of kainic acid in which the γ-carboxy group is replaced, has been synthesized by Michael addition to $HC{\equiv}CPO_3Et_2$ of the (1S,2S,5S)-2-hydroxypinanone - glycine Schiff base, N-alkenylation with $BrCH_2CH{=}CMe_2$ an ene cyclisation through established methodology.[243]

4.16 *Synthesis of Labelled Amino Acids.*

The reports collected for this Section all concern α-amino acids, except for one citation for the preparation of ^{13}N-labelled GABA (from $^{13}NH_3$ + tri-isopropylbutenoate).[244] Taking the papers in order of increasing atomic number of the labelled atom(s), [4-$^2H_3$]-3-methylbutyraldehyde acetal has been prepared from crotonaldehyde via 3-bromobutanal and C^2H_3MgI, and used in preparations of [5-$^2H_3$]leucine and [4-$^2H_3$]valine.[245] Isotope exchange processes with amino acids themselves, selectively with ^2H-ethanoic acid/0.05 eq.PhCHO to give better than 99.5% α-exchange[246] and general exchange (solid L-alanine/$^3H_2$ with retention of configuration see Vol.24, p.31).[247] Selective deuteriation by ^1H-^2H exchange at C-3 and C-5 of a ^{15}N-labelled DL-γ-keto-ornithine, $H_2{}^{15}NCH_2COCH_2CH(NH_2)CO_2H$, gives multiply-labelled DL-histidine after construction of the imidazole ring.[248] Further transformations in this study include enzymic resolution, C-5'-^2H → ^1H-exchange by boiling water, use of $NaSC^{15}N$ as a variation in the imidazole contruction step leading to the multiply-labelled 2'-mercapto-histidine, and degradation of the labelled histidines into corresponding L-aspartic acids. Similar multiple labelling including an approach from methyl N-benzylidene (4-methoxyphenyl)alaninate to α-C^3H_3-tyrosine with ^{11}C- and ^{14}C-variants at the α-position, has been described.[249]

^{11}C-Labelled amino acids have important clinical applications but must be prepared and used on a very short timescale because of the short half-life of the isotope and the need for operator protection. Ingenious modifications to standard amino acid syntheses have been explored over the years, and the modified Bucherer-Strecker route has been improved in this respect by remote control equipment[250] and by reduced reaction times achieved by using microwave irradiation.[251] A synthesis of DL-[1-^{11}C]Tyrosine established in this study was achieved in about 1/15 to 1/20 of the previous best time, leading to 70-100% higher radioactive emission. α-[^{11}C]Methyl tryptophan and the corresponding methyl ester have been prepared from the N-benzylidene derivatives by LDA deprotonation and alkylation with [^{11}C]methyl iodide.[252] Within the 50-

minute preparation time reported for the [1-^{11}C]acetyl derivative of leukotriene E_4, *alias* (5S)-hydroxy-(6R)-(N-[1-^{11}C]acetylcysteinyl)-7,9-trans-11,14-cis-eicosatetraenoic acid, most of the initial radioactivity (originating in $Me^{11}COCl$) will have decayed.[253]

Preparations of the six possible N-Boc-[^{13}C]glycines, with and without [^{15}N]-labelling, have been achieved by amination of the corresponding alkyl bromoacetates.[254] Syntheses of L-[4-^{13}C]- and L-[3,4-$^{13}C_2$]aspartic acids from L-serine and L-[3-^{13}C]serine respectively, via $K^{13}CN$ opening of the derived β-lactones, have been developed.[255] [1-^{14}C]-1-Aminocyclopropane-1-carboxylic acid is available from $Ba^{14}CO_3$ via the arylideneglycine $4\text{-}BrC_6H_4CH{=}NCH_2{}^{14}CO_2H$ through cyclopropane ring construction with $BrCH_2CH_2Br$.[256] The burgeoning interest in carboranylation of amino acids for clinical investigations is illustrated in a synthesis of Me_3NBH_2CO-[^{14}C]phenylalanine methyl ester from the labelled amino acid ester with Me_3N-carboxyborane/$Ph_3P/CCl_4/Et_3N$/MeCN.[257]

A review has appeared of the preparation of 6-[^{18}F]fluoroDOPA, discussing the non-regioselective nature of electrophilic fluorination, and comparison with regioselective fluoro-demetallation and nucleophilic substitution routes.[258] Direct fluorination of 3-O-methylDOPA gives 2- and 6-[^{18}F]fluoroDOPAs.[259] The [^{18}F]DOPA analogue (77) shows good uptake in melanoma tissue, and is a promising positron emission tomography tracer for melanoma imaging.[260]

A description of upscaling an existing route (see Vol.20, p.26) to L-[^{75}Se]selenomethionine, and remote handling conditions to give a high level of radioactivity in the product, have been described.[261]

4.17 *Synthesis of β-Amino Acids, and Higher Homologous Amino Acids.*

The startling increase in the number of papers in this area is a reflection of the increasing level of interest in the amino acid field as a whole, but it certainly represents larger proportional growth in recent times. Taken with the growing interest in oligopeptide isosteres (covered later in this Specialist Periodical Report), compounds that can reasonably be categorized as higher homologous amino acids, the rate of development of interest seems remarkable.

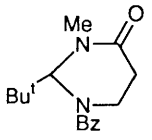
Simple routes with original features, leading to β-amino acids, continue to be explored, such as α-amidoalkylation of esters [$PhCH_2CO_2Bu^t + PhCON{=}CHPh \rightarrow PhCONHCHPhCHPhCO_2Bu^t$],[262] and by an unusually facile oxidative C–N cleavage reaction of polyamines (the first example of such a cleavage reaction), e.g. diethylenetriamine $H_2N(CH_2)_2NH(CH_2)_2NH_2$, mediated by the rhenium(V) nitrido complex $ReNCl_2(PPh_3)_2$.[263] Buried within a new

stereoselective nor-C-statine synthesis (Scheme 24)(the 15-year-old route is not suitable for large-scale operation) from malic acid esters, is the traditional Hofmann rearrangement approach to β-amino acids in a novel $Pb(OAc)_4$-mediated form.[264]

The other β-amino acid syntheses culled from the recent literature are developments of asymmetric syntheses based on methods or principles established relatively recently. Evans' methodology starting with an N-bromoacetyloxazolidin-2-one (cf. 24) leads to N-protected β-phenylisoserine, given as a representative application, in a highly stereoselective route.[265] An oxazolin-2-one intermediate arises in a new synthesis of the (2S,3R)-α-hydroxy-β-amino acid (−)-bestatin but not as a chiral synthon; it is formed by elaboration of diethyl L-maleate and its formation involves a Curtius rearrangement of the acyl azide of a β-hydroxy-acid.[266] Some other stereoselective β-amino acid syntheses use L-aspartic acid as chiral auxiliary, e.g. a route to the 3-aminohex-2-ene-1,6-dioic acid moiety present in the potent gastroprotective agent AI-77-B, via a protected L-aspartic α-semialdehyde,[267] but most of the current papers employ chiral heterocyclic synthons. The presently-favoured example is the (S)-tetrahydropyrimidin-4-one (78) from L-asparagine, that gives (R)-α-methyl-β-alanine as a result of highly stereoselective trans alkylation with MeI after lithiation.[268] The synthon is prepared via the dihydropyrimidin-4-one (79), which can also yield β-amino acids through Pd-catalysed conjugate addition of aryl iodides.[269] Chromatographic resolution of β-alanine cyclic acetals (78), and of glycine analogues (80) has been achieved over silica gel coated with a copolymer of ethyl N-acryloyl-L-phenylalaninate.[270] The 6-methyl homologue of (78), prepared from enantiomers of 3-aminobutanoic acid, has also been submitted to the same alkylation procedure for synthesis of (2R,3R)- and (2S,3S)-2-substituted 3-aminobutanoic acids.[271] The need to resolve DL-3-aminobutanoic acid to create the chiral 6-methyl synthon is avoided if the N-[(S)-phenylethyl] analogue of compound (78, lacking t-butyl), formed by Hg-mediated cyclization of βγ-unsaturated amidals,[272] is used (see Vol. 24, p.6). These synthons are also amenable to highly stereoselective trans-alkylation.[273]

A conversion of a protected β-alanine into α-(2-hydroxyalkyl) analogues through classical aldolization has been illustrated for the reaction of $BocNMeCH_2CH_2CO_2Et$ with benzaldehyde, to give an erythro/threo mixture of products.[274]

An oxygen near-analogue of (78) has been involved in an unusual asymmetric synthesis of β-amino acid esters (Scheme 25) starting with amidals of (R)- or (S)-phenylglycinol.[275] A Reformatzky reagent brings about ring-expansion and retains 60-92% of the initial homochirality in



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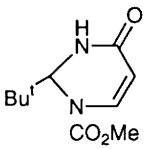

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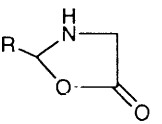

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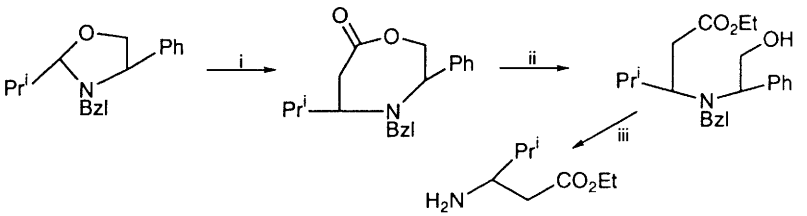
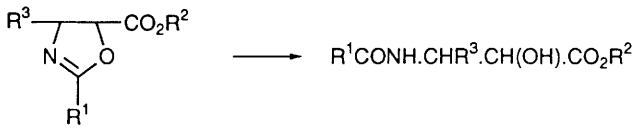


Reagents: i, $BrZnCH_2CO_2Et/Et_2O/35$ °C; ii, sat. HCl in EtOH;
iii, H_2–Pd/C

Scheme 25



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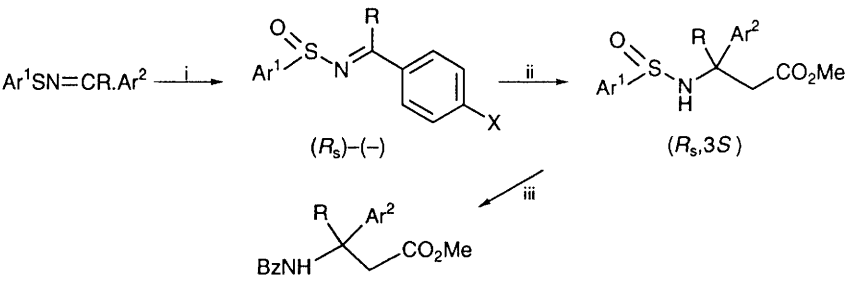


Reagents: i, chiral oxaziridine; ii, $CH_2{=}C(OLi)OMe$;
iii, TFA, then PhCOCl

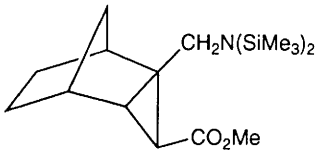
Scheme 26

leading to the product. Ring-opening of oxiranes by nitriles gives oxazolines (81) that are readily hydrolysed to provide a general synthesis of α-hydroxy-β-amino acids.[276] Corresponding oxazolines (81; R^1 = Ph; R^3 = CH_2OTs, H in place of CO_2Me) undergo nucleophilic substitution with CN^- in a variant of a standard route from α- to β-amino acids that is achieved by aqueous acid hydrolysis of the resulting β-aminonitriles.[277] Chiral oxaziridines are not themselves the synthons in an asymmetric synthesis developed to β-amino acids, but the means of converting prochiral sulphenimines into homochiral sulphinimines that provide the β-amino group through addition to a lithium enolate (Scheme 26).[278] The method, for which the diastereoselectivity was not high, was illustrated further in a synthesis of the (2R)-hydroxy-(3S)-amino-alkanoic acid moiety of taxol. Azetidinones that are obtainable from non-amino acid sources continue to be valuable sources of β-amino acids, and full details are available (see Vol.24, p.34) of the [2 + 2]cycloaddition of benzyloxyketene with a chiral imine from methyl (R)- or (S)-mandelates, exemplified in the preparation of (2R,3S)- and (2S,3R)-3-amino-2-hydroxybutanoic acids, components of a renin inhibitor, and of bestatin, respectively.[279] N-Tosylaldimines undergo $TiBr_4$-mediated condensation with ketene trimethylsilyl acetals $RCH=C(OSiMe_3)_2$ to give anti-β-amino acid derivatives with 92% diastereoselectivity.[280]

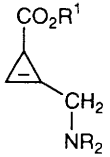
More conventional syntheses, against the background of established standard methods, include extensions of α-amino aldehydes in highly diastereoselective aldol reactions leading to the γ-hydroxy-β-amino acid "Aboa" ($p\text{-}BrC_6H_4CH=CHCMe=CHCH(OH)CH(NH_3^+)\text{-}CH_2CO_2^-$, a constituent of theonellamide F),[281] and (2R,3S)-3-amino-4-cyclohexyl-2-hydroxybutanoic acid and the 4-phenyl analogue, and their (2S,3R)-diastereoisomers.[282]

Diastereoselective synthesis of β-oxygenated γ-amino acids and γ-oxygenated δ-amino acids has been reviewed.[283] Hydroxylated γ-amino acids calling for a relatively simple stereoselective route, such as (S)-(−)-4-amino-2-hydroxybutanoic acid,[284] and (R)-erythro-4-amino-3-hydroxybutanoic acid,[285] have been prepared by Baker's yeast-catalysed reduction of the corresponding oxo-analogues in suitably protected form. The last-mentioned protected product was needed in syntheses of sperabillin C and (R)-GABOB (the β-hydroxylated version of the neurotransmitter, GABA, *alias* γ-aminobutyric acid). Another synthesis of (R)-(−)-GABOB is based on aminolysis in 89% enantiomeric excess, of the chiral oxirane (82) formed from $BrCH_2CHO$ and allyl(di-isocamphenyl)borane.[286] The GABA analogue synthesis field is very actively cultivated at the moment, with routes to (S)-γ-acetylenic-[287] and -trans-γ-butenyl-GABAs, using phthalimide for Mitsunobu amination,

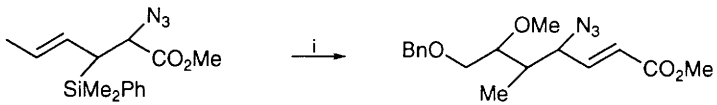
(82)



(83)

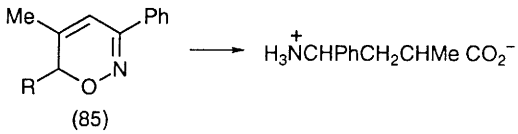


(84)

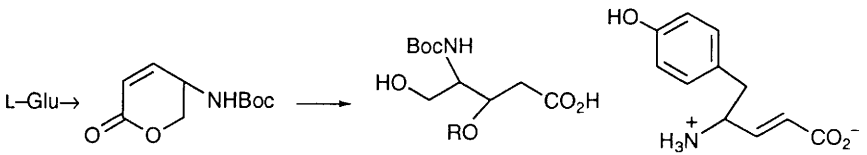


Reagents: i, $BnOCH_2CH(OMe)_2$, TMSOTf

Scheme 27



(85)



(86) (87)

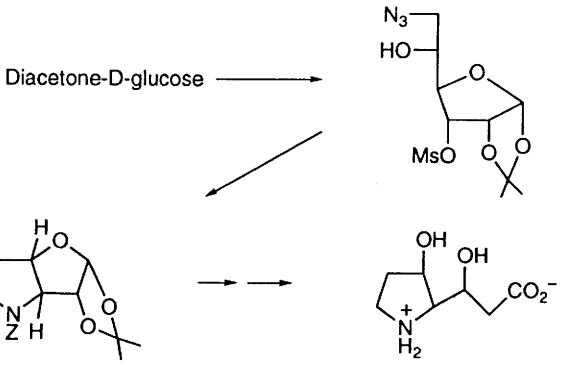
e.g. of (R,E)-$Me_3SiC{\equiv}CCH{=}CHCH(OH)(CH_2)_3OSiPh_2Bu^t$ followed by functional group elaboration in the latter case.[288] VinylGABA (4-aminohex-5-enoic acid) has been obtained from L-glutamic acid (itself a γ-amino acid as well as an α-amino acid) in 33% overall yield in six relatively routine steps. One of the steps applied to the pyroglutamate intermediate in this synthesis involves a novel alkenyl protecting group to permit the conversion to (S)-2-oxopyrrolidine-5-carboxaldehyde.[289] α-Methylene-β-hydroxy-GABA derivatives are easily available by aldolization of an acrylate ester with an α-amino aldehyde.[290] Diels-Alder synthesis of the rather remote GABA analogue (83) uses the cyclopropene (84) formed by $Rh_2(OAc)_4$-catalysed cyclopropenation of $HC{\equiv}CCH_2N(SiMe_3)_2$ with an alkyl diazoacetate.[291]

Some new approaches to γ-amino acids have been studied. Stereospecific allylic azide isomerization offers a way of inter-relating the α- and γ-amino acid series, since this process accompanies the attempted alkylation of α-azido-βγ-unsaturated esters (Scheme 27) by acetals.[292] Only low diastereoselectivity is shown, however, in the outcome of hydrogenation (H_2/Pd), and functional group elaboration, of chiral 3-phenyl-6H-1,2-oxazines (85).[293]

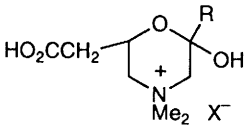
Synthesis studies for other γ-amino acids with significant biological importance have been reported. "MeBmt" analogues (86), prepared starting with L-glutamic acid[294]are obtained in 53–100% yields with diastereoisomer ratios 73:27–99:1. Statine syntheses are being pursued currently, mainly as vehicles for exploring interesting synthetic methodologies, as in a new route to β-hydroxy-γ-amino acids starting with Sharpless oxidation of 3-hydroxy-5-methylhex-1-ene.[295] The 8 possible isostatine isomers [the natural compound is (3S,4R,5S)] have been prepared from the 4 isomeric isoleucinals/allo-isoleucinals by reaction with ethyl lithioacetate.[296] A similar use of an α-amino aldehyde arises in the synthesis of the D-tyrosine relative (87) that is a constituent of cyclotheonamide A.[297] Full details of the elaboration of (R)-2-hydroxy-3-phenylpropanoic acid into statine have been supplied.[298]

At least five syntheses have been reported for detoxinine (88), a constituent of (−)-detoxin D_1, to which is added a sixth new stereospecific synthesis (based on a modification of an earlier route).[299]

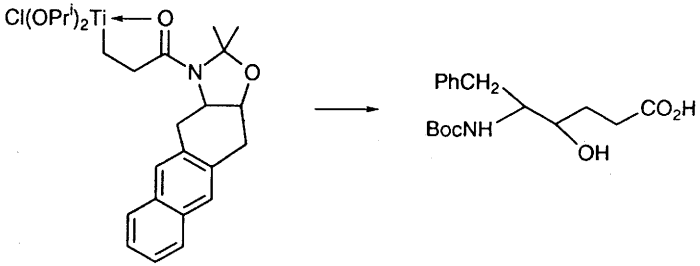
Syntheses from monosaccharide derivatives are appropriate in the (R)-carnitine area [two simple syntheses from D-galactono-1.4-lactone (see also Vol. 24, p.33)],[300] and analogues (89) of this compound have been synthesized as potential carnitine acyltransferase inhibitors.[301] An efficient (R)-carnitine synthesis employs microbial "resolution" of (RS)-2,3-dichloropropan-1-ol to the derived homochiral oxirane (as in Scheme 4, with Cl in place of OTf) followed by routine steps.[302]


Diacetone-D-glucose
N3
HO
MsO
OH
OH
CO2−
N
H2
H
O
N
Z H

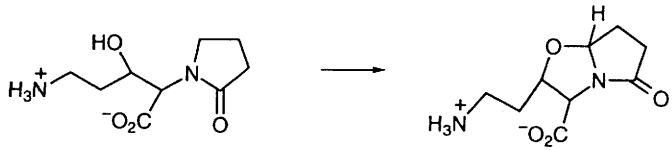
(88)


HO2CCH2
R
OH
N
Me2
X−

(89)


Cl(OPri)2Ti
O
N
O
PhCH2
BocNH
CO2H
OH

(90)


HO
H3N
N
−O2C
O
H
O
N
O
H3N
−O2C

(91)

Aldolization of N-Boc-L-phenylalaninal with the chiral Ti-enolate (90) is the first step in a synthesis of δ-amino acids.[303] The cyclization of the γ-lactam of proclavaminic acid into (91) and the aminoethylidene analogue is an unusual though doubtless, non-general, conversion of one δ-amino acid into another.[304]

Monosaccharide elaboration is also involved in a synthesis of the γ-amino acid destomic acid (92) from Bu^tPh_2SiO-protected Z-L-serinal.[305] The use of the same starting material in the synthesis of anhydrogalantinic acid is also described in this paper.

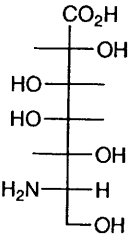
4.18 *Resolution of DL α-Amino Acids.*

Again as in previous Volumes, this topic is separated into preparative resolution, details of which are carried here; and analytical resolutions (even though they use the same chromatographic and other separation principles), which are described in the later Analytical Sections 7.2.–7.5.

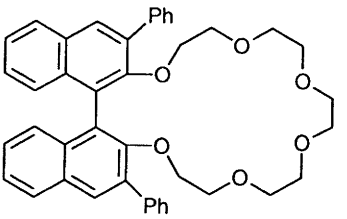
Preparative chromatographic resolution employing chiral stationary phases has been reviewed,[306] and a Symposium account touching on prebiotic and environmental resolution of DL-amino acids, has appeared.[307]

The rapidly growing area under this heading is the exploitation of physical chiral recognition principles in heterogeneous systems, for resolution of DL-amino acids and their derivatives. At its simplest level, a successful approach is the passage of a solution through a column of porous, insoluble material to which is adsorbed, or bonded, a homochiral amino acid derivative. (R)-N-(2-Naphthyl)alanine is such a derivative, thought to offer preferential hydrophobic interactions towards one enantiomer of a solute, rather than the other.[308] Other "Pirkle CSPs" include N-(3,5-dinitrobenzoyl)amino acid derivatives, and a series of 15 N-(3,5-dinitrobenzoyl)dipeptide esters,[309] and N-(3,5-dinitrobenzamides of α-aminophosphonates[310] have been resolved on four different CSPs. An L-amino acid-glutaraldehyde "condensate" introduced into a poly(sulphone) membrane matrix was permeable to D-phenylalanine in preference to its L-enantiomer.[311]

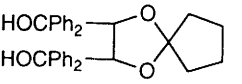
A recent fascinating development (see Vol.24, p.39) has been the use of "imprinted" polymers to promote chiral recognition, and a clever extension of this, combining two different strands of chiral recognition science, has been the generation of "chiral catalytic cavities" in silica gel, using Z-L-alanine N-benzylamide, then to use this material for selective 2,4-dinitrophenolysis of the L-enantiomer of benzoic N-Z-alanine anhydride.[312] The distantly-related principle of "replacing crystallization" has been illustrated for the seeding of a saturated solution or melt


CO2H
OH
HO
HO
OH
H2N
H
OH

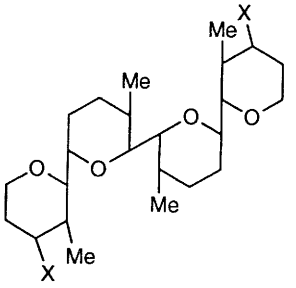
(92)


Ph
O
O
O
O
O
O
Ph

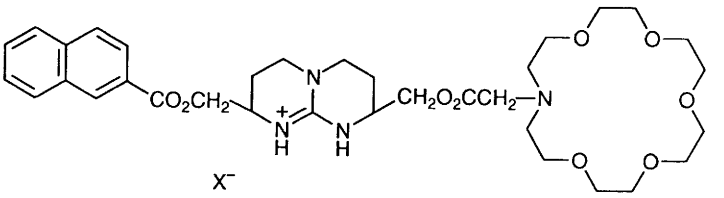
(93)


HOCPh2
HOCPh2
O
O

(94)


X
Me
Me
O
O
O
O
O
Me
Me
X

(95)


CO2CH2
N
+
N
H
N
H
CH2O2CCH2
N
O
O
O
O
O
O
X−

(96)

of (RS)-thiazolidine-4-carboxylic acid with L-isoleucine or L-cysteine [to cause crystallization of the (R)-enantiomer, and with other L-amino acids to bring out the (S)-enantiomer].[313]

Classical examples of the conventional resolution approach based on differential solubility of diastereoisomeric salts or derivatives include 4-(tetrazolylmethyl)pipecolic acids (di-p-toluyltartaric acid)[314] DL-amino acids generally (N-protected aspartame; salts with the D-amino acids are less soluble),[315] N-Z-α-methoxyglycine (D- or L-phenylalaninol, or (1S,2S)-2-amino-1-phenylpropane-1,3-diol),[316] and salts with quinine or ephedrine.[162] 5,5-Di-alkylhydantoins derivatized with (S)-(−)-phenylethyl isocyanate have been separated by medium pressure liquid chromatography, followed by hydrolysis into homochiral α-alkyl-α-amino acids,[317] and DL-α-alkyl-α-amino acids have been resolved by coupling as benzoyl derivatives to L-phenylalanine NN-dimethylamides or L-phenylalanyl-L-phenylalanine NN-dimethylamides.[318]

Methods involving enantioselective transport across liquid interfaces, especially involving liquid membranes entrapping a chiral amino acid-complexing agent, are prominently represented in the recent literature. The crown ether (93) is central to one of these studies.[319] The passage of L-phenylalanine from a solution of racemate, into a liquid membrane containing a chiral cation complexing agent, is assisted by di-(2-ethylhexyl)phosphoric acid as carrier.[320] A variant of this approach is to entrap an enzyme in the liquid membrane. When such a membrane is adjacent to a solution of DL-phenylalanine ethyl ester, the separation of enantiomers through the hydrolysis of one of them has been demonstrated.[321]

Solid-phase versions of this principle are illustrated in the intercalation of layered α-$Zr(HPO_4)_2$ by the chiral selector cation 3,5-dinitrobenzoyl-L-Leu-$NHCH_2CH_2NMe_3^+$, which selectively binds methyl N-(2-naphthyl)-L-alaninate from a solution of the racemate in MeCN,[322] and in the use of microporous hollow fibres involving a poly(vinyl alcohol) barrier, that permits the preferential passage of L-leucine from a stationary aqueous solution of the racemate through to a flowing octan-1-ol solution of N-dodecyl-L-hydroxyproline.[323]

Solution studies involving familiar enantioselective chiral host-guest systems have continued. Natural chiral pool constituents, of course, offer convenient starting points, and complexes of amine salts with crown-type chiral ionophore receptors from the monensin family have been studied.[324] X-Ray analysis of complexation of tartaric acid-derived hosts (e.g. 94) with amino acid esters shows that hydrogen bonding interactions are important in the chiral selection.[325] Such studies of the origins of the chiral recognition are becoming more common, as in

n.m.r. studies of the L-tryptophan - cyclodextrin complex that indicate that the protonated amino group does not contribute to the binding.[326] Unmodified and methylated cyclodextrins show the ability to complex selectively with enantiomers of N-dansyl amino acids, and this underlies the enantiomeric analysis of these derivatives by capillary zone electrophoresis.[327]

Conformationally homogeneous podand ionophores (95) have been thoroughly studied for enantioselective complex formation with enantiomers of amino acid ester cations, and other ammonium ions.[328] Those ionophores with hydroxy functions (95; X = OH) were much more effective than (95; X = H) with enantioselectivities expressed (in organic chemists' terms!) as 0.8 - 1.4 kCal mol^{-1}. The ion-encapsulating host (96) strongly (40%) favours complexation with L-enantiomers of phenylalanine and tryptophan from neutral solutions of racemates, but showed no discrimination towards valine enantiomers.[329]

Applications of enzymes for the delivery of particular amino acid enantiomers from racemates - the overall outcome is resolution, but the process can hardly be called resolution! - are expanding considerably, with the use of enzymes outside the protease and aminopeptidase areas for the purpose. Thus, microbial lipases catalyse the enantioselective hydrolysis of Z-DL-amino acid methyl esters, in the same manner as subtilisin,[330] and pancreatic lipase and a lipase from *Aspergillus niger* perform similarly with 2-phenyloxazol-5(4H)-ones.[331] DL-α-Methyl-α-amino acids can be "resolved" in this classical manner, using a lipase from *Candida lipolytica*[332] (see also Ref.62), and alcalase catalyses the hydrolysis of N-acetyl-DL-amino acid esters in aqueous organic solvents,[333] an enzyme used in the same way with the unsaturated methionine analogue (Z)-MeSCH = CHCH(NHAc)CO_2R.[334]

More conventional enzyme applications (see also Ref.248) are described in a larger number of papers than usual, in some of which the resolution step is an incidental routine detail while in others, there is some novelty to the study. Subtilisin Carlsberg esterase (see also Ref.210) has been used in a prototype liquid membrane-entrapped-in-hollow-fibre reactor (described above in this Section) for continuous flow enantioselective hydrolysis of isopropyl DL-phenylalaninate.[335] The enzymatic resolution of non-protein amino acids is attracting more interest, and serine proteases have been shown to be capable of mediating the kinetic resolution of DL-DOPA ethyl ester in organic solvents,[336] while in this area, the protease from *Bacillus subtilis* is more effective than that from *Aspergillus oryzae*.[337] A further example of the toleration by enzymes of unusual experimental conditions, now that their usefulness in organic media is well-established, is the conversion of DL-proline into L-proline

in better than 98% yield by D-amino acid oxidase and $NaBH_4$.[338] The process involves the conversion of D-proline into Δ^1-pyrroline-2-carboxylic acid, which is immediately reduced to DL-proline, thus effecting a novel kinetic resolution process. For a use of L-amino acid oxidase, see Ref. 43, and for uses of acylases, see Refs. 39 and 167. Delivery of L-tyrosine in high optical purity by α-chymotrypsin-catalysed hydrolysis of DL-tyrosine ethyl ester in largely organic media is a significant observation.[339]

Whole-cell processes include *Candida maltosa*/DL-alanine → D-alanine,[340] *Rhodococcus rhodochrons* PA34/DL-α-aminonitriles → L-amino acids,[341] and immobilized enzyme studies [poly(acrylate)-amino-acylase/N-acetyl-DL-methionine].[342] Resolution of 5-alkylhydantoins using *Agrobacterium radiobacter* continues to be a convenient variation of these approaches.[234]

A review has appeared of chemo-enzymic synthesis of amino acids, and the stereoselective hydrolysis of DL-amino acid amides by an aminopeptidase from *Pseudomonas putida* and by an amidase from *Mycobacterium neoaurum*[343] (see also Ref.46).

Speculation on resolution mechanisms operating on DL-amino acids in prebiotic times (and, presumably, still operating) continues to be published when backed up by experimental observations. Familiar aspects represented this year concern the stereoselective bias in favour of L-isomers accompanying de-amination of aqueous aspartic and glutamic acids over sodium montmorillonite at pH 6,[344] and reversible redistribution of L- and D-valine in the surface layer of an aqueous solution under non-equilibrium conditions.[345] The exact context of this claim is not clear from the information in the abstract, and neither is its relevance to the present dominance of L-amino acids in life processes, in suggesting that the ocean-air interface is selective in favour of one enantiomer rather than the other.

5 Physico-chemical Studies of Amino Acids

5.1 *X-Ray Crystal Structure Analysis of α-Amino Acids.*

Most of the recent papers cover the protein amino acids in derivatized forms: bis(glycine)HBr (i.e., $^+H_3NCH_2CO_2^-$ $^+H_3NCH_2CO_2H$ Br^-; a re-investigation),[346] bis(N-Boc)glycine N′-methoxy N′-methylamide,[347] N-Boc-D-alanine benzylamide,[348] N^β-hydroxy-DL-asparagine monohydrate,[349] ammonium L-glutamate monohydrate,[350] sodium DL-glutamate monohydrate,[351] potassium L-glutamate monohydrate,[352] propanediamine complexed with L-glutamic and with DL-glutamic acids,[353] Z-L-prolinamide,[354] di-L-phenylalani-

nium sulphate monohydrate,[355] L-phenylalaninium formate,[356] and N-Boc-L-phenylalanine benzyl ester.[357]

Unusual amino acids subjected to X-ray crystal analysis include two αα-disubstituted glycines (as their N-carboxyanhydrides),[358] L-azetidine-2-carboxylic acid (as its N-Boc derivative),[359] and indospicine hydrochloride monohydrate.[360]

5.2 *Nuclear Magnetic Resonance Spectrometry.*

The role of n.m.r. spectrometry in revealing finer structural details is exemplified well in carefully-devised experiments reported in the current literature. The complex formation that occurs through adding L-Chirasil-Val to solutions of enantiomers of N-trifluoroacetylamino acid methyl esters in CCl_4 is revealed in chemical shift non-equivalence in both ^{1}H-n.m.r. and in ^{19}F-n.m.r.[361] Weak hydrogen bonding interactions involving the amide proton are identified for N-acetyl-DL-valine through ^{2}H-n.m.r. spectrometry of a series of isotopically-labelled compounds.[362] Less ambitious studies are represented in the collection of ^{1}H-n.m.r. data for mono- and di-fluorotryptophans,[363] and in ^{13}C-n.m.r. assessment through lanthanide shift studies, of conformational information for L-lysine in solution.[364] Similar conformational objectives for L-leucine in its cationic and anionic forms have been achieved through interpretation of n.m.r. spin-spin coupling constants and nuclear Overhauser effect data.[365]

CP/MAS ^{13}C-n.m.r. spectra of crystalline L-leucine and DL-leucine show considerable differences, including a different order of peaks in some cases, with well-known solution spectra of these amino acids.[366]

^{14}N-N.m.r. spectra for 19 amino acids in various protonated/deprotonated forms have been published.[367] This technique has shown its potential for providing structural information, in a measurement of rate constants for H-exchange involving glycine, proline and aspartic acid in aqueous solutions.[368]

Peak separation of 0.099 ppm is seen in ^{31}P-n.m.r. of diastereoisomeric phosphinamides formed between (S,S)-$(EtCHMeO)_2P(O)H$ and DL-alanine, permitting the establishment of a novel method of estimating enantiomer excesses for amino acids that compares well with results from analogous α-chloropropionyl chloride derivatization and polarimetric quantitation.[369]

5.3 *Optical Rotatory Dispersion and Circular Dichroism.*

These techniques, or at least, circular dichroism spectrometry (c.d.), are occasionally combined with other physical methods for routine structural and stereochemical assignments to amino acids, as in an

exploration of interactions between β-cyclodextrin as host and 2,4-dinitrophenyl-D- or -L-valine as guest.[370]

Pioneering studies of vibrational Raman optical activity continue to use homochiral amino acids as models, and more data have been accumulated of the back-scattered absorption features of L-alanine as a function of pH.[371]

5.4 *Mass Spectrometry of α-Amino Acids and Related Gas Phase Studies.*

This and the neighbouring Sections of this Chapter have been steadily declining in scope in relative terms, as some of the techniques become established and therefore routine in nature. The newer ionization techniques are yielding new information, as in the positive plasma desorption mass spectra for the 20 common amino acids,[372] and corresponding positive and negative ion mass spectra for N-acetylcysteine and a number of its biologically-important S-alkylated derivatives.[373]

Collection of gas-phase proton affinity data interests several research groups, one study relating to arginine by determining dissociation rates of protonated dimers,[374] another[375] relating accumulated rate data with adiabatic ionization energies obtained from photoelectron spectra.[376] A theoretical study relating to glycine[377] has appeared. Fourier transform ion cyclotron resonance spectrometry provides proton affinities for the 20 common amino acids that point to intramolecular hydrogen bonding in the gas phase in the cases of lysine and glutamic acid.[378]

5.5 *Other Spectrometric Studies of α-Amino Acids.*

Excluding routine spectrometric measurements that are incidental to the main thrust of amino acid studies, there are relatively few papers calling for discussion here.

Fourier transform-i.r. studies of N-Boc sarcosine methylamide show that equilibria between seven-membered ring intramolecular hydrogen bonded structures, and extended conformations are very sensitive to solvent characteristics, e.g. hexane versus CCl_4.[379] A similar study with N-Boc proline methylamide [380] shows the greater propensity in this case towards the intramolecularly hydrogen-bonded conformation.

Prominent bands in polarized Raman spectra, claimed to be useful markers for the amino acids phenylalanine, tyrosine and tryptophan, have been studied further.[381] In a similar vein, new bands and revisions of earlier assignments are reported for Raman spectra of glycine in the solid state, in water, and in ^2H_2O.[382] Vibrational spectra (i.r. absorption

and Raman scattering) of L-amino acids have been measured over the range 10 - 400 cm^{-1}.[383]

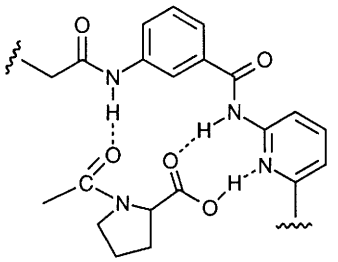
Continuation of sophisticated laser-induced fluorescence spectrometry of phenylalanine and tyrosine in a supersonic jet has been justified by the important results already obtained, since spectral features can be assigned by this technique to each of the several conformations present. No support was obtained of intramolecular exciplex formation in these samples, in contrast to earlier claims for tryptophan.[384] A single crystal electron spin-echo envelope modulation study of copper(II)-doped L-histidine hydrochloride has provided values for ^{14}N hyperfine and quadrupole coupling tensors for this compound.[385]

5.6 *Other Physico-Chemical Studies.*

The ability of low levels of amino acids to modify considerably, the structure of aqueous solutions, is well-known. They play a natural cryoprotectant role, by their ability to depress the freezing point of such solutions which is crucially important biologically (and also useful in food processing), and studied recently for glutamine in aqueous solutions modelling cell fluids.[386] Glycine, sarcosine, NN-dimethylglycine, and glycine betaines have been studied for their role in preventing leakage from liposomes after freezing and thawing.[387]

Further unusual properties of solutions of amino acid derivatives are coming to light, in the gel-like nature seen in certain cases, for example. Fibrous aggregates are a feature of the gels formed at low temperatures by N-acyl-L-aspartic acids with long-chain (C_{12}-C_{18}) alkanoyl groups in neutral aqueous solutions, and by N-dodecanoyl-β-alanine (but not by N-dodecanoyl-L-glutamic acid).[388] A most extraordinary example in this area is the thermoreversible hard gel that forms on cooling a 1% solution of Z-L-alanine 4-hexadecanoyl-2-nitrophenyl ester, in methanol or in cyclohexane.[389] The nature of the intramolecular interactions involved in such cases is assumed to be predominantly hydrogen-bonding, but N-dodecanoylhistidine methyl ester forms a complex with dodecyl dihydrogen phosphate in $CHCl_3$ that must involve both hydrogen bonding and ion-pair interactions.[390] Efficient hydrogen bonding occurs between N-acetyl amino acids and a model (97) for the vancomycin-D-alanyl-D-alanine interaction.[391]

Calorimetric studies with amino acids include glycine dissociation in aqueous glucose over the temperature range 5–45°,[392] enthalpy of protonation of glycine in water,[393] thermogravimetry and differential scanning calorimetry of amino acids,[394] and further measurements of enthalpies of dilution of solutions of glycine in binary solvent



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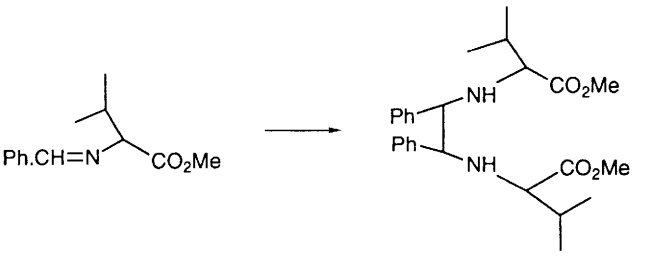

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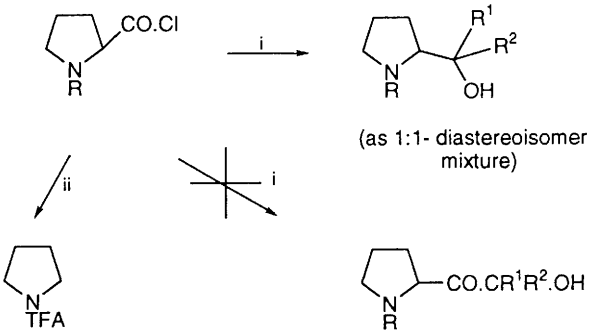


Reagents: i, $R^1.CO.R^2$ /SmI_2/THF; ii, conditions as in i, but R = TFA

Scheme 28

mixtures.[395] Microscopic protonation constants have been determined for 10 amino acids related to tyrosine; values for the basicities of the amino and phenolate groups in these compounds have been interpreted in terms of the roles of other structural features.[396] A molecular connectivity model has been applied for calculating the isoelectronic points of amino acids,[397] and for assessing atomic charges on atoms of second row elements when present in amino acids.[398]

Apparent molar volumes correlate well with computed van der Waals and molecular volumes for 17 amino acids.[399] Dipole moment data for L-threonine in water confirm the existence of a solvent - solute interaction,[400] and corresponding data for L-tyrosine have shown the existence of the dihydrated zwitterion in aqueous solutions.[401]

2,4-Dinitrophenyl-L-amino acid derivatives R-X-$OCH_2C{\equiv}CC{\equiv}CCH_2O$-X-R (R-X = dnp-L-amino acyl), otherwise viewed as chiral acetylenes, have been prepared as potential non-linear optical materials.[402]

5.7 *Molecular Orbital Calculations for α-Amino Acids.*

A relatively larger proportion of papers than usual under this heading deals with calculations for the amino acids themselves, rather than for their simple derivatives.

Calculations for glycine that attend to both charge distribution and conformational features[403] establish the point that a zwitterionic structure is not adopted by glycine in the gas phase. Calculations for vibrational modes for neutral glycine in its ground state give deformation frequencies that are in good agreement with experimental i.r. spectra.[404] Calculations for glycine force fields have been carried out,[405] and extension of the gas-phase scenario for glycine to its C-, N-, and O-methylated analogues has been described.[406]

The motion of methyl and protonated amino groups in the L-alanine crystal,[407] and the broader conformational dynamics of the L-tryptophan molecule,[408] have been quantified on a theoretical basis.

The N-acetyl-L-amino acid N-methylamide approach that has been such a familiar part of this topic, since it is used to probe the behaviour of an amino acid as a residue in a protein, continues with comparisons of calculations for the L-alanine representative for the gas phase compared with aqueous solutions, to assess solvent-solute interactions.[409] Calculations aimed at the assessment of helicogenic properties, or otherwise, of the side-chains of the protein amino acids, have been reviewed.[410] Conformational deductions based on calculations previously (1983) presented for N-acetyl-L-phenylalanine N′-(4-acetylphenyl)amide have been revised on the basis of current MM2 methodology.[411]

Many of the studies described in the preceding paragraphs are aimed at useful extensions of understanding of the ways in which amino acids perform in chemical and physical contexts, but two further papers indicate the two extremes encompassed by the topic of this Section. In one, a very specific interest is addressed by conformational calculations for N-acryloyl-L-phenylalanine methyl ester and its alanine analogue, to explain the observed asymmetric induction in their Diels-Alder additions to cyclopentadiene;[412] in the other study, an outcome of much broader relevance arises from calculations suggesting the existence of a weak hydrogen bond between a methyl group and a negatively-charged oxygen atom in creatinine and in its competitive inhibitor, N-carbamoylsarcosine.[413]

6 Chemical Studies of Amino Acids

6.1 *Racemization.*

The scope of recent studies encompasses familiar themes, though with rather fewer racemization studies taking place overall.

Reviews have appeared covering the dating of fossils through the measurement of the extent of racemization of indigenous amino acids.[414,415] A similar use of racemization data in the broader area of geochronology is covered in one of these reviews.[415] Indigenous aspartic acid has racemized relatively faster than the other protein amino acids in ancient mollusc shells, within the range 2–5% per century (depending on ambient temperature and other environmental factors) and enantiomeric analysis of the aspartic acid content has been advocated for dating purposes in this fossil area.[416] However, isoleucine epimerization continues in favour for the purpose, especially for workers with interests in fossils at the older end of the age range; ostrich egg shells retain proteinaceous material over more than 10 million years,[417] the date given to samples from the Border Cave in South Africa. A salutary warning has been given that estimates of isoleucine epimerization may be open to a systematic error. A standard amino acid derivatization reaction (o-phthaldialdehyde-β-mercaptoethanol; see Section 7.4) occurs at different rates with isoleucine and allo-isoleucine (Ile > alloIle), and incorrect ratios can be obtained by incomplete derivatization.[418]

Laboratory studies of amino acid racemization are usually performed for specific preparative purposes, such as the asymmetric transformation of L-histidine into its enantiomer by salicylaldehyde Schiff base formation using (2R,3R)-tartaric acid in acetic acid, followed by hydrolysis,[419] and in assessing the causes of epimer formation in peptide synthesis. In the latter category, racemization of an N-

substituted L-proline phenacyl ester by 1-hydroxybenzotriazole[420] contravenes the standard dogma that this acidic compound is generally protective against racemization when used as an additive in the aminolysis of active esters (the other compound in this study is a member of that class).

More fundamental aspects are explored in the determination of absolute rate constants for acid- and base-catalysed racemization of representative amino acids in the pH range 0.53 - 10.35 (i.e. the rate constants for each of the three, or more, ionic species of amino acids).[421] Results - a massive arithmetical problem solved with the help of simplex optimization computer analysis - are consistent with the classic Neuberger mechanism requiring α-proton abstraction. Racemization rates for N-acetyl-L-tyrosine, phenylalanine, 4-hydroxyphenylglycine, phenylglycine and alanine using (RS)-α-methylbenzylamine as base catalyst have been determined.[422] An interesting but subsidiary aspect of this study is the demonstration of asymmetric transformation of 4-hydroxyphenylglycine by (R)-α-methylbenzylamine, a subtle weak acid-weak base interaction presumably being the underlying explanation of this phenomenon.

6.2 *General Reactions of Amino Acids.*

Reactions involving the amino and carboxy functions, and the α-carbon atom, of the amino acids are covered in this Section, while reactions involving mainly the side chain are covered in the following Section 6.3: Specific Reactions of Amino Acids.

Though amino acids are generally regarded as stable towards routine handling, chemical changes can be inflicted on amino acids thermally, and such changes are subject to catalysis. The extraordinary ease of polymerization brought about in aqueous solutions by copper(II) salts (see Vol. 24, p. 47) is given continuing attention.[423] $CuCl^{+}(H_2O)_n$ ions acting in concert with $Na^{+}(H_2O)_n$ ions (ions with incomplete hydration shells), are considered to be responsible for accepting water liberated in the self-condensation of amino acids in 0.5M copper(II) chloride in aqueous 5M NaCl. Corresponding self-condensation of L-aspartic acid in the presence of metal ions at 200° during 2 hours is claimed to lead to polymer mixtures.[424] Thermal decarboxylation of L-ornithine to give putrescine is brought about by heating in aqueous solution in the absence of oxygen.[425]

Reliable protocols for the preparation of tetra-n-butylammonium salts of amino acids that are soluble in organic solvents (e.g. dichloromethane), have been published.[426]

Reactions at the amino group are often pursued with an eye on the

biological roles of the amino acids, as well as on the uses in synthesis of N-protected amino acids. The biological context frequently implies condensation with aldehydes and the ensuing reactions of the resulting Schiff bases; in the food science area this means primarily the Maillard reaction, with its multitudes of eventual condensation products. Amino- and hydroxyethylpyridines, imidazoles and cyanopyrroles are formed through condensation of aspartic acid or asparagine and glucose,[427] and more than 50 different indoles are formed between tryptophan and glucose, xylose, or furfurals at 220°.[428] Fructose-methionine Amadori compounds give methioninal on heating, with pyridines, pyrazoles, pyrroles, and furans, some retaining the methylthioethyl side chain.[429] Similar cysteine - carbohydrate systems have been studied under milder conditions, to establish the primary formation of the corresponding thiazolidine carboxylic acid, which decomposes through two pathways, one via the classical Amadori compound; and that the level of browning and the development of meat flavour are in proportion to the concentration of the thiazolidinecarboxylic acid.[430] Also on a more descriptive note, but probably of considerable significance in nutritional contexts, is the observation that glucose-amino acid reaction products have anti-oxidant properties.[431] L-Lysine reacts with the lipid oxidation product, (E)-4,5-epoxyheptanal, under microwave irradiation to give Schiff bases, thence to browning reaction products; a role is thus demonstrated for oxidized lipids in non-enzymic browning processes.[432] With importance in another biological context, the Schiff bases formed between retinal and amino acids continue to stimulate chemical studies, and their demonstrated formation in reversed micelles also reflects the growing interest in performing organic reactions in unusual media.[433] A curious reductive dimerization process has been illustrated with N-benzylidene-L-valine methyl ester (Zn/MsOH/THF/−50°) to induce mainly the (R,R)-stereochemistry in the newly-created chiral centres (98).[434] The substantial body of papers already published on the kinetics of N-chlorination in aqueous solutions, is added to this year with demonstrations of a rate-determining Cl transfer to nitrogen from hypochlorite ion in alkaline media.[435] Decomposition of N-halogeno-amino acids follows first order kinetics.[436,437]

Replacements of the α-amino group by other nitrogen-containing groups are described for the preparation of isocyanates (amino acid esters with phosgene in toluene under mild conditions),[438] and of azides via α-hydroxy esters and their O-(p-nitrobenzenesulphonyl) derivatives without racemization.[439]

The replacement of an N-Z protecting group by Boc is accomplished by catalytic transfer hydrogenation of the Z-amino acid in the

presence of $(Boc)_2O$,[440] while the one-pot conversion of an amino acid into its N-Boc methyl ester has been accomplished by Fischer esterification followed without purification by reaction with $(Boc)_2O$.[441] A new base-labile N-protecting group, N-2-(2,4-dinitrophenyl)ethoxycarbonyl, has been advocated.[442]

Functional group modifications to the carboxy group of amino acids can be divided into the topics that are familiar to readers of this section over the years. Reduction of amino acids to amino alcohols, once seeming so difficult, is accomplished by $NaBH_4$-H_2SO_4 (1:1),[443] presumably relying on the generation of B_2H_6 *in situ*. $LiAlH_4$ in THF, followed by py-SO_3, is an effective sequence for overall reduction of Z-amino acids to Z-amino alcohols.[444] An alternative way of converting α-amino alcohols to α-amino aldehydes without racemization, employs TEMPO oxidation (NaOCl/2,2,6,6-tetramethylpiperidin-N-oxyl). [445] Little or no racemization accompanies electrochemical reduction leading to α-amino aldehydes.[446] In this method, a Z-L-amino acid is electrolysed at -30° in the presence of PPh_3 under nitrogen with $HPPh_3^+$ ClO_4^-. Another illustration of a standard preparation of α-amino aldehydes [R.CON(OMe)Me → RCHO with $LiAlH_4$] has been published in a preparation of the N-Boc β-cyclohexylalanine aldehyde for use in statine syntheses.[447] Aldehydes prepared in these ways have become important intermediates for carbon-carbon bond-forming processes mentioned in a number of contexts earlier in this Chapter, and used outside the amino acid field e.g. to prepare chiral allylsilanes [BocNHCHRCHO → (Z)-BocNHCH=CHMe → (Z)-BocNHCHRCH=$CHCH_2SiMe_3$].[448] N-Acyl-L-prolinols prepared from corresponding esters using $NaBH_4$-MeOH also represents standard practice.[449]

Thiazol-2-yl ketones BocNZCH(CH_2Ph)COR show further uses in synthesis.[450] The thiazolylketone moiety can be converted into an α-hydroxyaldehyde [-COR → -CH(OH)CHO], from which by standard C-C bond-forming operations, an overall synthesis of δ-amino acid esters can be defined.

N-Protected α-amino acid chlorides and fluorides are proving useful in synthesis after evidence has accumulated, showing that they have sufficient stability to survive the procedures involved in their preparation. Oxalyl chloride has been used for this purpose, with N-ethoxycarbonyl α-amino acids,[451] and N-TFA- or -Fmoc-L-prolyl chlorides have been useful in chain extension to alkanols (Scheme 28) by reductive condensation with ketones mediated by SmI_2.[452]

Amide formation from N-protected amino acids with amines has been accomplished, using standard peptide coupling reagents BOPCl and

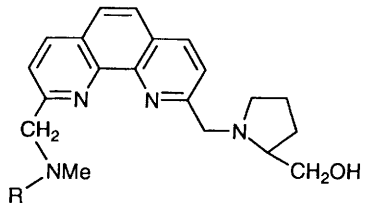
TBTU[453] and with crystalline ammonium salts of 3-hydroxy-1,2,3-benzotriazin-4(3H)-one with N-hydroxysuccinimide.[454]

N-Protected α-amino acid amides can be O-alkylated with trialkyloxonium tetrafluoroborates to give iminium salts that undergo thiohydrolysis to give thionesters, $R^1NHCHR^2CSOR^3$, without racemization.[455] Corresponding dithioesters are prepared from N-protected α-amino nitriles in the time-honoured way [RCN → $RCSNH_2$ → $RC(SMe)=NH_{2+}\ X^-$ → RCSSR'].[456]

There are relatively few novel esterification studies, but an increasing number of enantioselective hydrolysis projects. L-Aspartic acid gives the di(trimethylsilyl) di-ester by refluxing with excess trimethylsilazane, and ways of preparing N-protected derivatives of the diester have been established.[457] An interesting study of relative rates of acylation of 5'-AMP by N-acetyl-D-amino acids reveals faster rates than for L-enantiomers, particularly so for β-branched amino acids valine and isoleucine, with generally decreasing rate differences as the hydrophobicity of the side-chain decreases.[458]

The simplest catalyst system so far studied, in which rate differences are seen for the hydrolysis of enantiomeric amino acid esters, is a combination of an L- or D-amino acid with a metal oxide (ZnO, γ-Al_2O_3, or SiO_2).[459] Further examples (see Vol.24, p.52) involving chiral catalysts within micelles, N-Z-L-Phe-L-His-L-Leu-OH for example,[460,461] for such studies with L-phenylalanine p-nitrophenyl ester, have been published, and the chiral ligand (99) contained in mixed micelles has been applied to the same purpose.[462] In the last-mentioned study, the presence of metal ions Zn, Co, Cu, or Ni, only slightly enhances the catalytic effect of the organic ligand. Outside the enantioselective hydrolysis area, transition metal ions are good catalysts for the hydrolysis of amino acid esters, and their effect is enhanced by certain ligands.[463] Reactivity studies of conventional types have been applied to determine rates of aminolysis of Z-amino acid N-hydroxysuccinimide esters[464] and a series of N-phthaloyl-L-phenylalanine 2-substituted indan-1,3-dione enol esters [highest acylation reactivity was shown by the 2-(4-fluorophenyl) compound].[465]

Oxidation studies continue for common amino acids with conventional oxidants [serine/Tl-$HClO_4$ oxidation catalysed by Ru(III) > Os(VIII) > Nd(III)],[466] [aspartic acid/Bi(V)-$HClO_4$ oxidation → HO_2CCH_2CHO].[467] Other oxidative decarboxylative processes leading to aldehydes have been established for oxidation at the Pt anode of aqueous solutions at pH = 1 and pH = 13, of α-, β-, and γ-aminobutanoic acids.[468] Peroxydisulphate ($S_2O_8^-$) oxidation of 2,2(phenylcyclopropyl)glycine catalysed by silver picolinate gives 2-hydroxy-5-phenylte-



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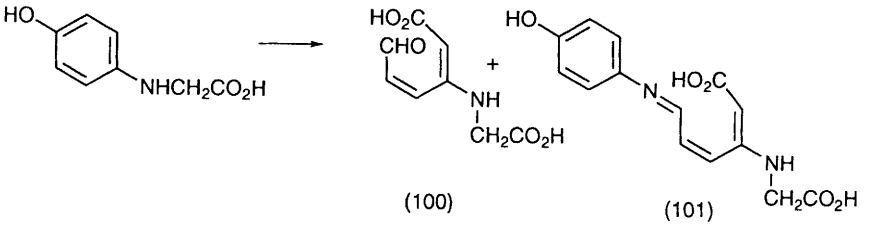

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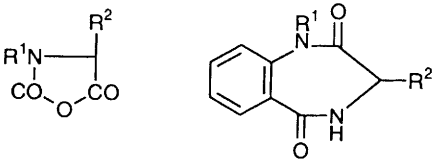

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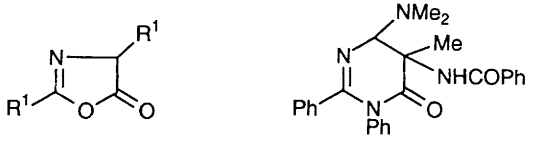

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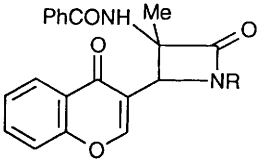

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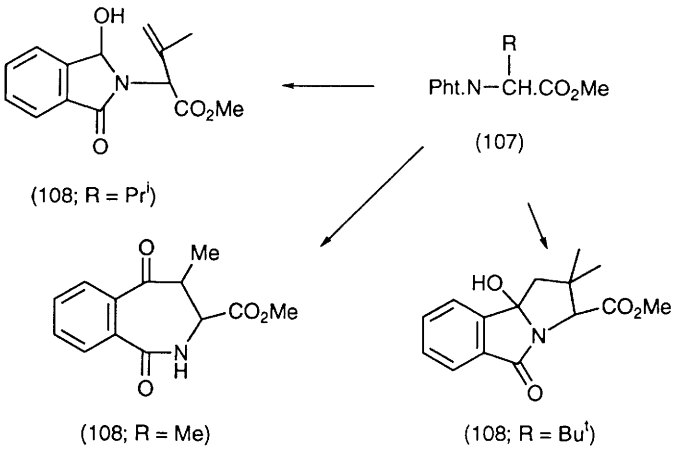
trahydrofuran, via an α-amino radical intermediate.[469] Further studies of oxidative de-aldolization and oxazolopyrroloquinoline formation through reactions of co-enzyme PQQ with amino acids have been reported.[470] More extensive changes accompany the tyrosinase-catalysed oxidation of N-(4-hydroxyphenyl)glycine (→ 100 + 101).[471]

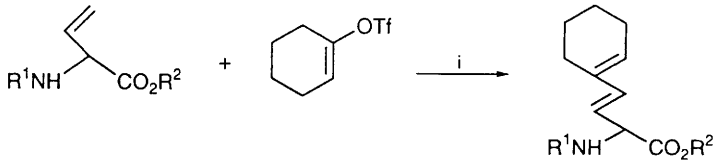
Heterocyclic compounds feature substantially in every year's literature dealing with the general reactions of amino acids, and one of the classes given much attention in earlier times, the N-carboxylic amino acid anhydrides (NCAs, 102) has been revisited by several groups. One valuable new synthesis starts with N-Boc-L-amino acids, using PCl_3.[472] Others use triphosgene/NEt_3,[473] $SOCl_2$ (with Z-α-trifluoromethyl-α-amino acids),[474] or PyBrOP or PyClOP with N-Boc-N-methyl-L-amino acids[475] for the cyclization. N,N-Bis(Boc)- or N-Boc-N-Z-L-amino acids react with $SOCl_2$/DMF to give N-Boc- or N-Z-L-NCAs, respectively, but react with cyanuric fluoride to give the corresponding acid fluorides.[476] NCAs react with N-Boc-anthranilic acid to give 1,4-benzodiazepine-2,5-diones (103),[472] and in addition to the well-known exploitation of their acylation reactivity in peptide synthesis, they participate in Friedel-Crafts reactions without racemization under standard conditions.[477]

Oxazol-5(4H)-ones (104) represent another class of five-membered heterocyclic compound that is readily accessible from N-acyl-α-amino acids, and their reactions usually preserve intact, the α-aminoacyl residue -NHCHRCO-. They are prepared using simple cyclization reagents, though the synthesis of an optically-active oxazol-5(4H)-one by treatment of L-tryptophan with trifluoroacetic anhydride is an interesting exception to a rule, precedents suggesting that the oxazol-5(2H)-one tautomer is usually favoured by the 2-trifluoromethyl substituent.[478] This work was published previously in preliminary form.[479] Diazadienes react with 4-methyl-2-phenyloxazol-5(4H)-one to give dihydropyrimidin-6-ones (105),[480] and 3-(aryliminomethyl)chromones undergo cycloaddition with oxazolones to give azetidinones (106).[481] 4-Alkylidene-oxazol-5-ones are implicated in reactions of N-acetyl αβ-dehydro-α-amino acids, which give poor yields during attempted formation of amides through standard peptide coupling methodologies.[482]

6.3 *Specific Reactions of Amino Acids.*

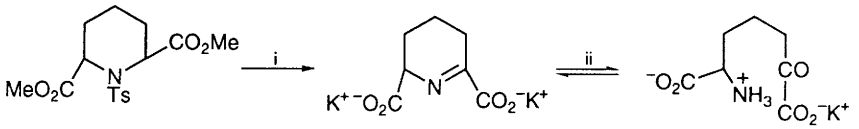
This Section deals with reactions involving primarily the side-chains of the more common amino acids. The outcome is often a synthetic route to another amino acid (but biosynthetic studies are not covered here), and many of the examples discussed in earlier "Synthesis" sections (in Sections 4.1–4.16) could have been located here instead.





Reagents: i, Pd–Heck coupling

Scheme 29



Reagents: i, H_3O^+, bring to near-neutral pH; ii, spontaneous ring-opening in aq. soln.

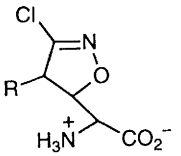
Scheme 30

Manipulations of aliphatic side-chains include photo-isomerization of alkyl α-phthalimido-alkanoates involving an unprecedented double hydrogen transfer (107→108) accompanied by photocyclization to dihydrobenzazepinones,[483] and the use of unsaturated aliphatic side-chains to build heterocyclic systems. N-Protected α-trifluoromethyl-α-alkynyl-α-amino acids (and their α-hydroxy-analogues) add to 1,3-dipoles (nitrile oxides, diazoalkanes, PhN_3) to give corresponding five-membered heterocycles,[484] while αβ-di-amino-αβ-unsaturated acids $Me_2NCH=C(NHBz)CO_2Me$ condense with pyrazolones to give (Z)-β-(pyrazolon-5-yl)-αβ-unsaturated-α-amino acids.[485] Heck couplings between protected L-vinylglycine and aryl and vinyl triflates lead to regioselective, racemization-free, γ-alkenylation (Scheme 29).[486]

Reversible ring-opening follows toluene-p-sulphinic acid elimination from dimethyl meso-N-toluene-p-sulphonylpiperidine-2,6-dicarboxylic acid to give 2,3,4,5-tetrahydrodipicolinic acid, isolated as the potassium salt (Scheme 30), giving an *in vitro* model for the L-lysine biosynthetic pathway followed in bacteria and in fungi.[487] The biosynthesis of avicin (109; R = H) and its 4-hydroxy-analogue (109; R = OH) involves ornithine as primary precursor, rather than glutamic acid or glutamine.[488] Enzyme-catalysed conversion of 5-aminolevulinic acid into porphobilinogen has been contrasted with the formation of pyrazine (110) and pyrrole (111) in the absence of enzyme in some laboratory procedures.[489] A well-known procedure[490] for selective carbamylation of the side-chain amine groups of L-ornithine and L-lysine as their copper(II) complexes, has been fully described.[491]

Ring-opening processes are also a feature of reports of reactions of aromatic and heteroaromatic side-chains, 2,3-bond-cleavage to give (112) occurring when potassium superoxide acts on N-acyl-L-tryptophans [but not when it acts on corresponding tryptophanamides, when dioxindoles (113) are produced].[492] Products of Udenfriend or Fenton hydroxylation of tryptophan (viz., four hydroxytryptophans and oxindole-3-alanine, with N-formylkynurenine) are similar to those obtained by the effects of ionizing radiation on the amino acids in aqueous solutions,[493] while differences arise, comparing Fenton hydroxylation with radiation, with phenylalanine (Fenton → 2-, 3-, and 4-hydroxylation, etc) and tyrosine (Fenton → 2,3- and 3,4-di-hydroxylated products).[494]

Pictet-Spengler reactions of aldehydes with N-diphenylmethyltryptophan isopropyl ester[495] and with di-iodo- or dibromo-L-tyrosines[496] give indolo- (114) and benzo-pipecolic acids (115), respectively. From the point of view of the research interest in preparing these compounds, they can be seen as conformationally-constrained analogues of their parent amino acids. The now notorious L-tryptophan contaminant responsible



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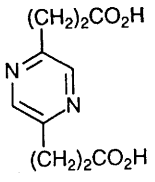

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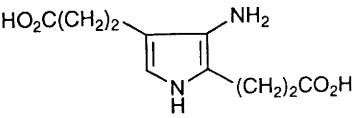

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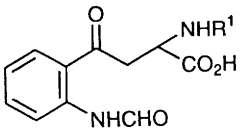

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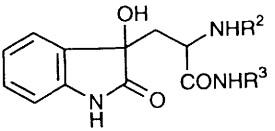

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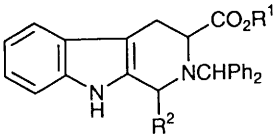

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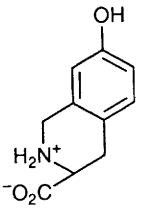

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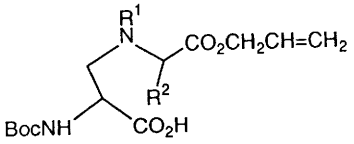

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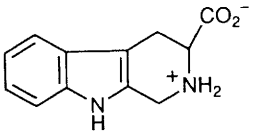

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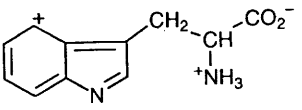

(118)

for an outbreak of eosinophilia myalgia syndrome, 1,1′-ethylidene bis(L-tryptophan), is accompanied by another impurity (UV-5; 0.002g from 150g), "(+)-3-anilino-L-alanine", i.e. (S)-2-amino-3-phenylaminopropanoic acid, presumably introduced during the production process (see Vol.24, p.58).[497]

Protein modification at histidine residues by 4-hydroxynon-2-enal, a lipid peroxidation breakdown product, has been modelled by reactions with N-acetylhistidine,[498] leading after $NaBH_4$ reduction, to N^{π}- and N^{τ}-1,4-dihydroxynonanylhistidines. Lipid hydroperoxides react with tyrosine to give fluorescent 3,3′-dityrosine via radical intermediates.[499]

N-Alkoxycarbonyl derivatives of aspartic acid and glutamic acid give internal anhydrides through carboxy-group activation (using dicyclohexylcarbodi-imide or an alkyl chloroformate), and in no case was a pyroglutamate formed.[500] Pyroglutamic acid derivatives are easily prepared, however, and in protected form this compound is an increasingly valuable synthon, undergoing regioselective nucleophilic ring-opening without racemization.[501] The α-diazoketone of β-t-butyl Z-L-aspartate has been subjected to Wolff rearrangement using silver benzoate, to give the corresponding β-amino acid methyl t-butyl di-ester from which, by selective elaboration at either ester (e.g. by Curtius rearrangement at the methyl ester), (3S)- or (3R)-3,4-di-aminobutanoic acid mono-esters have been obtained.[502] ω-(9-Fluorenylmethyl) esters of aspartic and glutamic acids are formed between the acid and alkanol reactants in THF using HBF_4-OEt_2.[503] Preparations of N-Boc β-aspartyl and γ-glutamyl fluorides have been detailed.[504]

Hydroxyalkyl side-chains of N,C-protected serines and threonines provide sites for O-glycosylation (by a disaccharide derivative, α-D-Xylp-(1→3)-β-D-Glcp,[505] and transglycosylation (from raffinose and lactose, catalysed by α- and β-galactosidases, respectively).[506] Analogous reactions leading to ether phospholipids have been established using a novel phosphite coupling procedure.[507] Methyl N-Z-β-iodoalaninate can be coupled to electron-deficient alkenyl carbohydrates using the Zn/Cu alloy.[508] Cyclization of benzyl N-trityl-L-serine or threonine esters with sulphuryl chloride gives benzyl (2S)-1-trityl-2-aziridinecarboxylate esters or (2S,3S)-1-trityl-3-methyl-2-aziridinecarboxylate esters in excellent yields, something of a breakthrough in achieving this transformation, which seems to be facilitated by the bulky N-substituent.[509] N,O-Acetal formation of L-serine through the hydroxy group, and reduction of the carboxy group of the acetal, provides[510] the Garner aldehyde (23) that has been mentioned in several contexts in this Chapter, all opening up valuable synthetic routes. Another example is reductive amination leading to a product (116) that can be categorized as both an α- or a β-

amino acid derivative.[510] Methyl Z-L-threoninate has been converted into a β-keto-ester analogue through straightforward elaboration.[511] Preparations of t-butyldimethylsilyl ethers of serine and threonine have been described.[512]

Cleavage of t-butyl ethers and esters of hydroxyalkyl amino acids by TFA/CH_2Cl_2 is accompanied by fewer artefacts if Et_3SiH is added to the reaction mixture as carbocation scavenger; this deprotection strategy does not affect Bu^tS, Z, Fmoc, or O- and S-benzyl protection.[513] S-Trifluoromethylation of L-homocysteine can be accomplished using CF_3I in liquid NH_3 under u.v. irradiation,[514] and new S-protection strategies include S-(2,4,6-trimethoxybenzyl)ation (removable with 30% $TFA/CH_2Cl_2/PhOH$),[515] and S-[2-(2,4-dinitrophenyl)ethyl]ation (removable by base).[516]

L-Cysteine easily undergoes autoxidation in solution, and electrochemical reduction of L-cystine has been advocated for its clean preparation in 96% yield.[517] Alkaline aqueous solutions of cystine or homocystine contain various sulphur functional groups (RS^-, RSS^-, and $RSSO_3^-$; R = β-alanyl, γ-butyrinyl, respectively),[518] and slow oxidation of methionine to methionine sulphoxide occurs in solutions containing glucose and copper(II) salts.[519]

6.4 *Effects of Electromagnetic Radiation on Amino Acids.*

This Section deals with non-routine reactions and properties of the more common amino acids when subjected to irradiation. Changes brought about in amino acids as a result of pulse radiolysis in aqueous solutions have been reviewed,[520] and it has been noted that aspartic acid complexed with $Al(OH)_3$ is an effective γ-radiation trap.[521] These reports, and the observation that sunlight photolysis of 0.1M aqueous solutions of aspartic and glutamic acids at pH 7 yields mainly malonic and succinic acids respectively,[522] are relevant to prebiotic and environmental aspects of amino acid science.

Laboratory studies concern the aromatic and heteroaromatic protein amino acids, almost exclusively as in previous years. These studies often call for sophisticated spectrometric techniques, and are aimed more at extending knowledge in general of the interaction of energy with matter, than with interests in the reaction products obtained. Fluorescence studies with N-acetyltyrosinamide in the presence of proton acceptors,[523] and time-resolved fluorescence studies with L,L-dityrosine in aqueous solutions,[524] have been reported. Anthrapyrazoles are novel anti-cancer compounds that are effective agents for photosensitized oxidation of DOPA into o-semiquinone radicals.[525] Tyrosine usefully attenuates the 4-iodophenol-enhanced chemiluminescence assay consis-

tent with its competition with luminol for the aryloxy radicals for which this becomes a sensitive assay system.[526]

Fluorescence studies of phenylalanine, tyrosine, and tryptophan and N-acetyltryptophan amide (193nm and 248nm laser fluorescence spectrometry),[527] of tryptophan,[528] and of the constrained tryptophan (117),[529] follow familiar lines. The last-mentioned study is particularly informative in demonstrating a ^{2}H-isotope effect on the fluorescence yield and its variation as a function of pH and temperature. Flash photolysis of tryptophan in 2,2,2-trifluoroethanol results in transient formation of a cyclohexadienyl-type cation (118) due to photoprotonation of the indole moiety at C-4.[530]

7 Analytical Studies with Amino Acids

7.1 *General.*

Results of a 1989 collaborative study of 43 core amino acid analysis facilities have been reported, in an attempt to measure accuracy and precision in amino acid analysis by various methods.[531] A similar objective has been shared with five laboratories who have co-operated in an independent two-part study to try to improve understanding of factors influencing accuracy and precision.[532]

7.2 *Gas-Liquid Chromatography.*

Many of the derivatization protocols that have been described over the years in this Chapter have been in use again this year. Several papers make little of the routine procedures involved, for preparing and using N- and O-trifluoroacetyl n-butyl esters,[533] N- and O-i-butoxycarbonyl t-butyldimethylsilyl esters,[534] and N-methoxycarbonyl 2′,3′,4′,5′,6′-pentafluorobenzyl esters.[535] The particular analytical context in some of these papers is unusually interesting, e.g. the estimation of hydroxyproline in a few fibres of ancient leather after vapour phase hydrolysis (1:1-HCl/$EtCO_2H$ at 150° during 1 hour)[533] by g.l.c. with mass-spectrometric detection, an instrumental combination also used for 3-methylhistidine estimations in physiological samples.[536]

G.l.c. analysis of cleavage products from peptide sequencing remains a research interest for several groups, especially for ever-lower levels of analyte. Derivatization remains obligatory, 2-anilinothiazol-5(4H)-ones from the Edman degradation procedure being converted by aminolysis into N-phenylthiocarbamoylamino acid 2,2,2-trifluoroethylamides for 180 femtomole level analysis by g.l.c./electron capture detection.[537] N- and O-t-Butyldimethylsilylated methylthiohydantoins

prepared using $^{t}BuSiMe_2CNMeCOCF_3$ have been shown to be of suitable volatility for routine g.l.c. analysis.[538]

Enantiomer ratios for amino acid samples can be estimated by g.l.c., either by passage of samples derivatized as above, over a chiral stationary phase, or by diastereoisomer formation using a chiral derivatization reagent; a new example in the latter category, 2-methoxy-2-trifluoromethylpropanoic acid, has been advocated.[539]

7.3 *Thin-Layer Chromatography.*

Leaving aside the routine use of t.l.c. in support of synthetic and reaction studies, an effective use of two-dimensional t.l.c. to estimate enantiomer ratios (yellow spots after derivatization with Marfey's reagent) of naturally-occurring amino acids, can be cited as an example of out-of-the-ordinary work.[19]

7.4 *Ion-Exchange Chromatography.*

Standard techniques are applicable for the analysis of unusual amino acids, viz. mature and immature crosslinking amino acids in collagen and elastin,[540] and 2,2′-di-aminopimelic acid.[541]

7.5 *High-Performance Liquid Chromatography.*

The predominant approach to amino acid analysis by h.p.l.c. currently involves derivatization of mixtures by one of a number of protocols, followed by separation of the resulting derivatives (the "pre-column derivatization approach"). Reviews of derivatization procedures and appropriate h.p.l.c. methods for the different approaches have been published,[542,543] together with specific coverage of the analysis of amino acids in foods.[544]

The conversion of amino acids into iso-indoles using o-phthaldicarboxaldehyde (OPA) in combination with an alkanethiol continues to be represented in most of the current papers. Although the reaction fails with prolines and other N-alkylamino acids, a "double derivatization approach" in which the OPA-thiol derivatization reaction is followed by Fmoc-chloride derivatization,[545-547] seems very reliable. [Of course, Fmoc-chloride derivatization of amino acid mixtures would convert every amino AND imino acid into derivatives that can be readily separated and quantitated on the basis of their fluorescence, but this approach has not gained popularity]. Among studies using the standard OPA-2-mercaptoethanol protocol, the amino acid content of glycoconjugates[548] describes conventional acid hydrolysate analysis, while identification of di-aminopimelic acid in physiological fluids is aided by the presence of an ion-pairing agent in the mobile phase, sharpening peaks of

nearby co-eluting compounds.[549] An h.p.l.c. analysis explored with 17 of the protein amino acids using ion-pairing additives has been described.[550] Electrochemical detection methods offer lower detection limits (at about the 0.66 picomole level).[551-553] It has been claimed that recent improvements to OPA - thiol derivatization put it on a par with classical ion-exchange separation and post-column ninhydrin analysis of amino acids. An advantage for this method accompanies the use of a chiral alkanethiol, which yields diastereoisomeric mixtures with D/L-amino acid samples and permits enantiomer ratio analysis. This has been seized upon in studies employing D-3-mercaptopropanoic acid[554,555] and other chiral thiols,[556] but particularly N-acetyl-L-cysteine[557] and N-Boc-L-cysteine.[558] The last two studies have particular aspects of interest; one explores automated derivatization by flow injection analysis as well as demonstrating the greater stability of the derivatives prepared using N-acetylcysteine, while the other establishes substantial levels of D-serine in rat brain, but only trace levels of D-alanine and D-aspartic acid.

Cyanobenz[*f*]isoindoles formed analogously using naphthalene-2,3-dicarboxaldehyde with 18 amino acids have been assessed for their electrochemical oxidation characteristics, that permit voltammetric detection.[559] These derivatives are capable of detection at an extremely low level, and are mentioned in this respect in the later Section 7.5. Another recent derivatization method that has become widely used, involves reaction with phenyl isothiocyanate to give N-phenylthiocarbamoyl derivatives (PTC-amino acids). As with other pre-column derivatization methods, it compares well with classical ion exchange analysis, and the derivatives are more stable (unchanged during at least 32 hours) than OPA-thiol condensation products.[560] An application has been described that is routine in terms of the amino acids identified as their PTC-derivatives, but in a spectacular context. Microgram samples from a Renaissance painting (Cosimo Tura's "Annunciation with St Francis and St Maurelius of Toulouse", 1475?) were hydrolysed in acid vapour and analysed to determine whether the painting had an egg tempera base.[561] Amino acids presenting difficulties as far as phenyl isothiocyanate derivatization is concerned, constitute the other papers cited here: N^G-methyl-, N^GN^G-dimethyl- and $N^GN'^G$-dimethylarginines in physiological fluids,[562] hydroxyproline,[563] but particularly cysteine and cystine.[564,565] In acid hydrolysates containing dithioglycollic acid, some problems of identification of cysteine are inevitable; the PTC-derivatives prepared from cysteine and cystine have the same retention time, probably indicating cleavage of the disulphide bond by phenyl isothiocyanate.[565] It is more likely to be due to the formation of the same phenyldithiocarbamate from both amino acids, after disulphide bond

cleavage of cystine; or, possibly, to be due to the formation of the same β-elimination product from both amino acids – see next paragraph.

Phenylthiohydantoins formed through Edman sequencing (they can also be formed from PTC-amino acids) are prone to elimination when the amino acid from which they are derived carries a β-hetero-atom. They are stabilised by allyloxycarbonyl side-chain protection, and such PTHs show clean h.p.l.c. traces in the cases of cysteine, lysine, threonine and tyrosine, but serine, aspartic acid, glutamic acid and arginine show some deprotection while histidine is completely de-protected during the manipulations involved.[566] The PTH of S-(β-amidoethyl)cysteine has been prepared as a standard to assign artefactual h.p.l.c. peaks that have been found to originate in un-polymerized acrylamide present in polyacrylamide gels.[567]

Alternative established derivatization protocols that have been illustrated further this year include dansylation[568] and the related dabsylation (used for estimation of the protein crosslinking amino acid, hypusine, down to 500 femtomole levels),[569] and the more distantly-related thiohydantoins, DABTHs.[570] The N-γ-lysine Schiff base with malondialdehyde has been detected in urine and in enzymic digests of certain foods, and can be assayed at 280nm after Diels-Alder adduct formation with diethyl ethoxymethylene malonate (50°/50 min).[571] A procedure for selenocysteine estimation is based on the fluorescence of its N-(iodoacetylaminoethyl)-5-naphthylamine-1-sulphonyl derivative.[572] Further unfamiliar fluorescence-generating procedures include conversion of N-acetylamino acids into esters with 9-anthryldiazomethane,[573] and formation of the NN-diethyl-2,4-dinitro-5-fluoroaniline-hydroxyproline adduct,[574] Edman cleavage products, the 2-anilinothiazolin-5(4H)-ones, can be detected through fluorescence measurement at the 100 attomole level after aminolysis by 4-aminofluorescein,[575] and almost as effective is aminolysis by *N*-(4-aminohexyl)-*N*-ethylisoluminol and chemiluminescence detection.[576]

Post-column derivatization is a feature of the identification and quantitation of a huge range of amino acids in a test of the Pickering lithium ion gradient mobile phase (ninhydrin colorimetry).[577] ^{3}H-labelling of proteins is assessed by hydrolysis and separation of the resulting amino acids by classical ion-exchange chromatography, then the various fractions are quantitated by OPA fluorimetry and scintillation counting.[578] N^{G}-Methylarginine content of myelin basic protein has been estimated by the same post-column fluorimetry protocol,[579] also used for the quantitation of enantiomer mixtures by separation through the ligand exchange principle using copper(II)-complexed amino acids passing over N-alkyl-L-proline-coated stationary phases.[580,581] The same

principle but using a commercial chiral stationary phase (Chiral-ProCu = S,100) has successfully separated all four isomers of threonine and of β-phenylserine and its o- and p-fluoro-substituted analogues.[582]

Enantiomer quantitation is achieved for N-Boc-amino acids over hydroxypropylated β-cyclodextrin[583] and for dansylamino acids through a switchable two-column system, with one of the columns operating with β-cyclodextrin as a chiral mobile phase additive.[584] Another example of the alternative diastereoisomer-forming derivatization approach has been described, in which chiral monochloro-s-triazines are the reagents,[585] prepared by replacing one chlorine atom of s-trichlorotriazine with 4-aminoazobenzene, and another chlorine atom with L-alanine amide.

Ion-exchange h.p.l.c. procedures are appropriate for certain highly-polar analytes, such as taurine, cysteine-sulphinic acid and cysteic acid,[586] the cyanogen bromide-selenomethionine reaction product,[587] protein cross-linking amino acids pyridinoline and deoxypyridinoline in urine or tissue hydrolysates,[588] and S-adenosyl-L-methionine (after the use of a strong cation exchange sulphonic acid resin for its isolation with other cations from mixtures).[589]

Quantitative h.p.l.c. analysis without derivatization is a feature of a number of studies in the preceding paragraph, and an assay of phenylalanine in dried blood spots by u.v. absorption detection,[590] of photodegradation products of aromatic amino acids by electrochemical detection,[591] and of amino acid pentafluorobenzyl esters at sub-picogram levels by negative ion mass spectrometry.[592]

The expected relationship exists between reversed phase h.p.l.c. retention and structure for a homologous series of aliphatic amino acids, with retention times increasing with molecular mass, while each member of this series shows a lower retention index than its cyclic analogue.[593]

7.6 *Other Analytical Methods.*

Appreciation of the superior separation characteristics of capillary zone electrophoresis (CZE) and related techniques is clear from the growing interest in their use, based on similar derivatization protocols to those established for h.p.l.c.

CZE Analysis of fluoresceamine-derivatized proline and hydroxyproline, (these imino acids give non-fluorescent amino-enones),[594] and of dansylated lysine and valine,[595] have been reported. However, a stunning demonstration has been published, of the sensitivity of naphthalene-2,3-dicarboxaldehyde derivatization (0.8 attomole detection limit for the leucine derivative), using CZE, micellar electrokinetic chromatography (MEKC), and cyclodextrin-modified MEKC (CD-MEKC; 30 minutes

analysis time), with laser-induced fluorescence detection.[596] Chiral separations were established in some cases in this study, by the CD-MEKC technique.

7.7 *Determination of Specific Amino Acids.*

Whereas general analytical methods are, of course, applicable to specific cases, there are uniquely beneficial short cuts available when knowledge is needed of the level of a particular amino acid in a complex mixture. There are limits to this complexity when using specific functional group chemistry, as in an assay of cysteine, homocysteine and cystine in urine based on cyanide - nitroprusside colorimetry (ca. 524nm),[597] and in a specific condensation of lysine with furfuraldehyde that allows this amino acid to be determined in the presence of other di-amino acids,[598] but an assay of 1-aminocyclopropane-1-carboxylic acid in apple juice can be safely based on ethene evolution caused by $NaOCl\text{-}HgCl_2$.[599]

As usual, the predominant theme for this Section lies in the exploitation of enzyme selectivity. A good example of the more recently developed technology is found in estimation of L-leucine in blood, using tRNA/acyl-tRNA synthetase competing with L-[U-^{14}C]leucine and measuring the radioactivity of the acid-insoluble tRNA fraction.[600]

More traditional approaches are being studied, for lysine oxidation to 2-oxo-6-aminocaproate, NH_3, and H_2O_2 catalysed by *Trichoderma viride* L-lysine α-oxidase (O_2 uptake and H_2O_2 generation can be easily measured electrochemically),[601] and a similar L-lysine oxidase-based procedure (chicken kidney tissue) linked to an oxygen electrode.[602] A recently-isolated L-lysine dehydrogenase immobilized on a platinum electrode by gelatin entrapment forms the basis for an amperometric biosensor for L-lysine.[603]

L-Glutamine determination, through the use of glutamine oxidase immobilized by cross-linking to bovine serum albumin deposited on pre-activated nylon,[604] and through the recycling of pink rose petals ("Sonia"; *Rosa hybrida* Hort.: see Vol. 23, p. 70) by attachment to an NH_3 sensor,[605] has been explored further. Immobilized glutamate dehydrogenase acts on L-glutamic acid to liberate the reduced form of NADH that can be assayed through the luminescence generated in a separate sensor, a nylon coil carrying immobilized bacterial bioluminescence-generating enzymes.[606]

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