1
Amino Acids

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1 Introduction

This year's literature on the chemistry and biochemistry of amino acids provides further proof of the ever-increasing rate of accumulation of new knowledge of these compounds. This expansion calls for increasing constraints on space allocated for the areas reviewed in this Chapter, which, as in earlier Volumes of this Specialist Periodical Report, emphasises papers covering the occurrence, chemistry and analysis of amino acids. Further narrowing is imposed within this context, only partial coverage being possible from what is judged to be routine literature. Biological areas such as the natural distribution and metabolism of well-known amino acids, for example, are not covered.

Patent literature is almost wholly excluded (but this is easily reached, mostly through Sections 16 and 34 of Chemical Abstracts). The Chapter is organised into a sequence of sections as used in all previous Volumes of this Specialist Periodical Report. Major Journals and Chemical Abstracts (to Volume 114, issue 11) have been scanned for the material to be reviewed.

2 Textbooks and Reviews

Textbook coverage of amino acids within plant biochemistry[1] and biosynthesis[2] has appeared, as has a review of the taste properties (particularly sweetness) of amino acids.[3] A clinical use for assay of 3-methylhistidine in urine, as a marker for skeletal muscle protein degradation, is discussed in a review of this amino acid.[4] Reviews of γ-carboxyglutamic acid[5] and selenocysteine[6] have appeared, in the latter case giving the background to the claimed discovery of the gene for its tRNA. Cyclopropane-based amino acids ("2,3- and 3,4-methano-amino acids") have been reviewed.[7] Numerous other reviews of aspects of amino

acid science have been published during the year under review, and references are located in the relevant sections of this Chapter.

A five-year retrospective survey on amino acids science[9] has been published in the first issue of a new Journal "Amino Acids" (Springer Verlag, Vienna and New York) whose well-justified launch includes in its first Volume, abstracts of papers that were presented at the Second International Congress on Amino Acids and Analogues, Vienna, August 1991.

3 Naturally Occurring Amino Acids

3.1 Isolation of Amino Acids from Natural Sources.- Isolation of amino acids has a simple requirement, to be sustained by proper practice, that the integrity of the amino acid in the extract is preserved. The well-known problem - losses of certain amino acids during protein hydrolysis - has been controlled in many cases by improvements in protocols. Classical 6M-hydrochloric acid hydrolysis procedures can give good recovery of tryptophan if tryptamine is included in the hydrolysis cocktail,[9] or if 3% phenol is added.[10] However, comparisons with standards show that more than 20% destruction of tryptophan must still be expected even when using these additives, though there is some improvement in the recovery of methionine and carboxymethylcysteine in these methods. Microwave irradiation of hydrolysis mixtures helps,[11] and vapour phase hydrolysis (7M-hydrochloric acid containing 10% trifluoroacetic acid, 20% thioglycollic acid, and indole)[12] can give up to 75% recovery of tryptophan.

An extraordinary physical property - adsorption of the $N^{\alpha}N^{\epsilon}$-bis(naphthalene-2,3-dicarboxaldehyde) derivative of lysine on to glass - is not shared by the N^{α}-mono-tagged amino acid.[13] Thus, reductive alkylation of proteins (N^{ϵ}-amino groups → NN-dimethylamino) is recommended before acid hydrolysis, to avoid this "loss" of lysine residues in this increasingly popular derivatization method through this unexpected way.

Methanesulphonic acid (115°, 22h)[14] continues to gain adherents for acid hydrolysis of proteins.

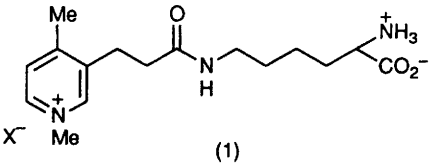
Care taken in preparative h.p.l.c. operations in processing aqueous extracts from fossil bones are described.[15] Errors due to contamination are minimized if all collagen analyses are based on a single bone sample. An aqueous two-phase system (water - aqueous polyethyleneglycol) has been advocated for isolation of amino acids from fermentation broth.[16]

3.2 New Natural Amino Acids.- Derivatives of protein amino acids that owe their exceptional biological activity to the overall structure of the derivative, with the amino acid moiety being merely the passive "carrier" of the derivatizing group, are not unusual. Amphikeumin (1) is an example of this class; it is a synomone, since it mediates partner-recognition between sea anemones and anemone-fish (and the fact that these words end in "-mone" is purely coincidental - synomone and pheromone, for example, have the same etymological base).[17] The range of extraordinary natural thioamides present in roots of radish (takuan) has grown, one of the new ones being the tryptophan derivative (2), presumed to be formed from L-tryptophan and 4-methylthiobut-3-enyl isothiocyanate.[18] The vinyl sulphide =CH-SMe in place of the tryptophanyl moiety[19] and the corresponding vinyl ether[20] are further examples.

A more complex heterocyclic system, though with equally suggestive biosynthetic origins, is represented in L-lupinic acid (3), isolated from the racemic amide through use of the aminopeptidase from Pseudomonas putida.[21]

A new antifungal antibiotic (4) has had all its structural features verified through X-ray analysis of its N-(N-phenylthiocarbamoyl-L-phenylalanyl) derivative.[22] "Pyrrolams" (5) and (6) are new simple pyrrolizidine alkaloids (from Streptomyces olivaceus) that can be recognized as cyclized proline homologues [but the absolute configuration in one case is (R), which might imply that proline itself is not on the biosynthetic pathway].[23] Amino alcohols are near relatives of amino acids, and as such, deserve brief mention in this section of this Chapter; xestoaminols A - C [B is (2S)-aminotetradeca-11,13-dien-(3R)-ol, and A and C are its dihydro- and tetrahydro-derivatives, respectively] have been isolated from a Fijian sponge Xestospongia sp.,[24] and are positional isomers of compounds reported from similar sources in 1989.

3.3 New Amino Acids from Hydrolyzates.- The meaning intended to be conveyed by the title of this section, is the discovery of new groupings in larger structures that would, in principle, be released as a new amino acid by hydrolysis (in principle rather than necessarily in practice). A new penta-functional crosslinking amino acid, allodesmosine, has been identified in bovine ligamentum nuchae elastin. It is a pyridinium salt like its well-known near-relative crosslinking amino acid, desmosine, and arises by further processing of the reduced aldol condensation product of two allysine, and one lysine, residues in the protein.[25] Pulcherosine (7) is a new trifunctional crosslinking amino acid from the fertilization envelope of the sea urchin embryo.[26] It occurs alongside the other major tyrosine-derived crosslinks, di-



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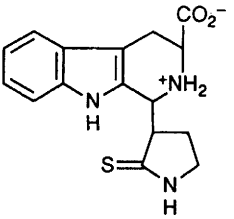

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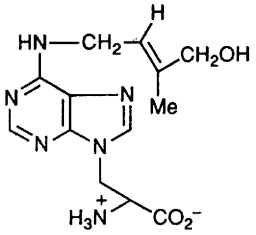

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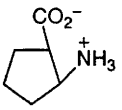

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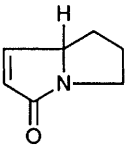

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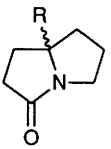
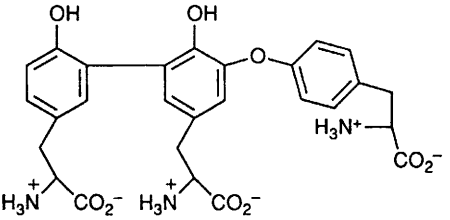


(6) R = OH, OMe, OCHMe, Et

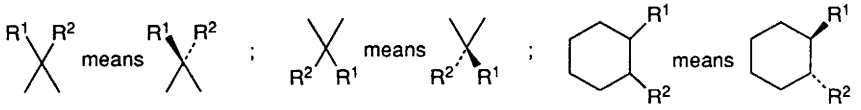


(7)

Three-dimensional features at chiral centres of structures depicted throughout this Chapter follow the convention:

(a) horizontally-ranged atoms, and their bonds, and ring atoms are understood to be in the plane of the paper;

(b) atoms and groups attached to these are ABOVE the page if ranged LEFTWARDS and BELOW the page if ranged RIGHTWARDS



tyrosine and tri-tyrosine. β-Aminoglutaric acid ("β-Glu") is a constituent of marine methanogenic bacteria.[27]

4 Chemical Synthesis and Resolution of Amino Acids

4.1 General Methods for the Synthesis of α-Amino Acids.- The reworking of a promising reaction through time, until it becomes established to be more generally applicable, is recorded in several papers relevant to this Section. Also, the well-known general methods are shown to continue to hold their own through further examples of non-routine character, many of these examples being mentioned elsewhere in this Chapter - particularly in the next section 'Asymmetric Synthesis'.

An α-halogenoglycine in a protected form is a useful synthon for α-amino acid synthesis, nucleophilic substitution by alkynyltin reagents $Bu_3SnC{\equiv}CR$ giving βγ-alkynylglycines.[28] The free alkynyl amino acids formed by deprotection were found in this study to be very labile but trapping experiments demonstrated that they had indeed been formed. N-Benzoyl-α-bromoglycine methyl ester readily undergoes nucleophilic substitution by side-chain functional groups in protected cysteines, serines, and threonines to give novel "cross-linking amino acids"[29] (by which is meant, compounds with the potential for synthesizing peptides as models for cross-linked proteins). The N,O- and N,S-acetal structures formed in this way are relatively easily hydrolyzed, though the cysteine derivatives seem to show stability sufficient for some applications. N-Acetyl bromoglycine methyl ester has been used for a synthesis of L-2-amino-4-methoxy-*cis*-but-3-enoic acid by reaction with $MeO.CH{=}CHLi$.[30] An alternative diethyl acetamidomalonate synthesis was reported later by the same workers [via the dimethylacetal of $HCO.CH_2.C(CO_2Et)_2NHAc$ → (E)-$MeOCH{=}CH.CH(NH_2)CO_2H$, or → $MeOCH(OCOMe).CH_2.CH(NH_2)CO_2H$ → (Z)-$MeOCH{=}CH.CH(NH_2)CO_2H$].[31]

The equivalent α-acetoxyglycines, e.g. $Ph_2C{=}NCH(OAc).CO_2R$, on condensation with malonate anions give protected β-carboxyaspartates.[32] α-Keto-acid methyl esters can be condensed with benzyl carbamate to give protected αβ-unsaturated α-amino acids[33] available also through Wittig condensation of aldehydes with α-phosphono-glycines [e.g. RCHO + $ZNHCH(PO_3Et_2).CH(NH_2)CO_2Me$] or from base-catalyzed eliminations from β-halogeno- or β-acetoxy-α-amino acids. An alternative amination procedure is illustrated in the condensation of diethyl azodicarboxylate with lithium dienolates; full details in support of the preliminary communication of this work (Vol.22, p.7) stress the

importance of choice of catalyst, tin salts giving α-amination products while germanium salts yield Y-amino acids.[34]

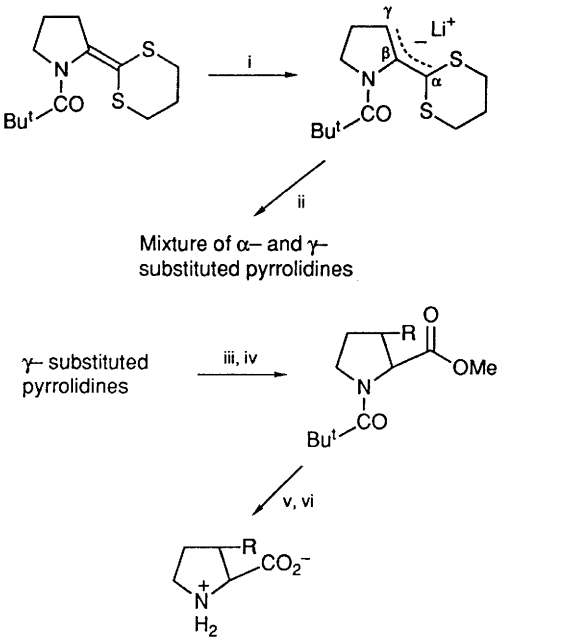
Oxalic acid mono-amide, $H_2N.CO.CO_2H$, should be an α-cationic glycine equivalent suitable for Wittig olefination, and the preparation of a suitably protected form of it has been described, starting from oxalyl chloride, through reaction with t-butanol and collidine - benzophenone imine.[35]

Further details (see Vol.22, p.7) are available[36] of the preparation of α-acylamino nitriles from Mannich-type condensation of benzotriazole with an aldehyde and an amide to give the substituted benzotriazole $R^1CONH.CHR^2.Bt$ which gives the α-acylaminonitrile with an alkali metal cyanide. Conditions are used that should permit a variety of functions within the aldehyde component to survive the reaction and subsequent hydrolysis of the nitrile to an α-amino acid. The same intermediate is involved in a preparation of α-substituted acyl aminals when NH_2 is used in place of cyanide.[37]

The Ugi four-component condensation has been used in an extraordinary "high-pressure mode" in which highly-hindered amino acids are constructed in the form of their N-(Z-L-valyl) derivatives [Z-L-Val-OH + $Ph.CH_2.NH_2$ + R^1_2CO + $CN.CH_2.CO_2R^2$ → $Z\text{-}L\text{-}Val.N(CH_2Ph).CR^1_2.CO\text{-}Gly\text{-}OR^2$].[38]

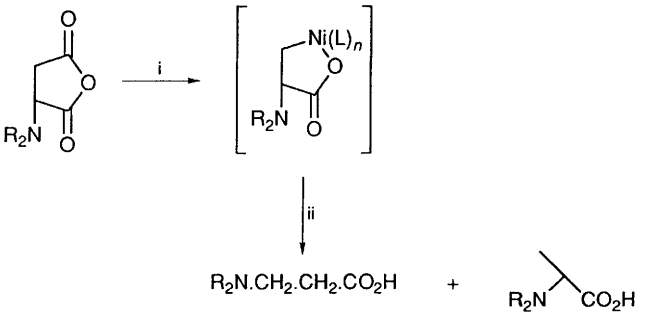
Alkylation of diethyl acetamidomalonate, using N-ferrocenylmethyl trimethylammonium iodide and NaOEt (reflux 45h to give N-acetyl β-ferrocenylalanine ethyl ester after work-up),[39] or using long-chain halogenoalkanes,[40] illustrate standard malonate applications. Improved routes to cis- and trans-3-substituted prolines[41] (condensation of diethyl acetamidomalonate with an αβ-unsaturated aldehyde, and routine elaboration of the resulting 3-substituted 5-hydroxyproline) have been described. A similar approach provides 4-hydroxyproline[42] and proline itself in a route involving reduction of the Michael adduct and cyclization of the derived toluene-p-sulphonate.[43] A new 3-substituted proline synthesis (Scheme 1) depends on the propensity of ketene dithioacetals for carbanion formation[44] and has been developed further for its potential in asymmetric synthesis (next Section, 4.2).

Similar alkylation procedures underpin other general methods, for example the phase-transfer catalyzed alkylation of $Ph_2C{=}N.CHR.CN$ with variously-substituted benzyl bromides followed by routine work-up.[45] A chiral phase transfer catalyst has been used with little success (as far as enantiomeric discrimination is concerned) in catalyzed alkylation of $Ph_2C{=}N.CH_2.CO_2Et$.[46] The other type of Schiff base, e.g. $R^1N{=}CH.CO_2R^2$, gives C-alkylation products with Reformatzky reagents RZnBr.[47] A different alkylation principle is involved in the conversion of the isocyanide $CN.C(CO_2Et){=}CMe_2$ into 1-amino-2,2-dimethylcyclopropane carboxylic acid using trimethylsulphonium iodide and sodium hydride.[48]



Reagents: i, LDA, –78°C; ii, RX; iii, BF_3–Et_2O, then aq. K_2CO_3; iv, NaOMe; v, aq. NaOH; vi, aq. TFA, reflux 2h

Scheme 1



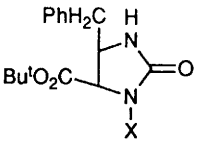
Reagents: i, Ni(cyclo-octadienyl)L_2/THF/heat; ii, H_3O^+

Scheme 2

Exploitation of side-chain functionalized amino acids as synthons for preparing other amino acids has continued to develop into useful general methods in some cases, and many new examples could be created from efficient reactions performed on amino acid side-chains (see Section 6.3). N-Benzyloxycarbonyl-L-vinylglycine methyl ester, for which there are now reliable methods of synthesis not anticipated in the early days, is open to use in this way,[49] [CH_2=CH.CH(NHZ)CO_2Me → R'CH_2CHR²CH(NHZ)CO_2Me] and so, also, are N-protected aspartic and glutamic anhydrides, proposed as synthons for alanines from an observation that oxidative addition and decarbonylation processes result from heating in THF with nickel complexes (Scheme 2).[50] Alkylation of the protected aspartic acid β-ester enolate[51] and their condensation with aldehydes so as to give βγ-unsaturated α-amino acids,[52] is fully described. A route from a protected L-aspartic acid to 2,3-diamino-4-phenylbutanoic acid via Curtius degradation of (8) involves benzylation of the β-carbanion with benzyl bromide, a process that is said to show higher diastereoselectivity than some analogous processes.[53] Organocuprates react with DL-4-iodo-2-(t-butyloxcarbonylamino)-butanoates to give heterocyclic side-chain analogues, while the corresponding use of chiral imines (9) leads to a satisfactory excess of the L-enantiomer.[54]

The Strecker synthesis, applied to 1-amino-2,2-dialkylcyclopropane-carboxylic acids, depends on the survival of the halogeno-alkyl moiety at the stage of preparation of the α-aminonitrile from the aldehyde $ClCH_2$.CR'R².CHO.[55,56] An analogous route involves cyclopropane ring-closure of an α-chloro-imine ClCR'R².C(=NR)R³.[57] A one-carbon homologation of aldehydes using (phenylthio)nitromethane is analogous to the Strecker synthesis but is claimed to be superior, especially for sensitive multifunctional synthesis targets such as the glycosylamino acid, polyoxin C (Scheme 3).[58] A quite different route to this compound uses the "penaldic acid equivalent", viz. 5-formyl N-butoxycarbonyl 2,2-dimethyl oxazolidinone (from L-serine) as protected amino acid moiety on which the glycoside moiety is constructed.[59]

Bucherer-Bergs synthesis of 1-aminocyclohex-2-ene-1,3-dicarboxylic acid from the corresponding cyclohexenone has been reported,[60] and this hydantoin alkylation route has also been used in a large-scale synthesis of phenylalanine (hydantoin is condensed with PhCHO).[61] No "General Methods" section on amino acids would be complete without mention of the azlactone synthesis, in which alkylation of 2-phenyloxazolin-5(4H)-one, generated in situ from hippuric acid, has led to "the 1- and 2-naphthol analogues of tyrosine", i.e. β-(4- and 6-hydroxy-1-naphthyl)alanines.[62]



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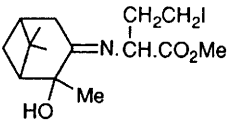

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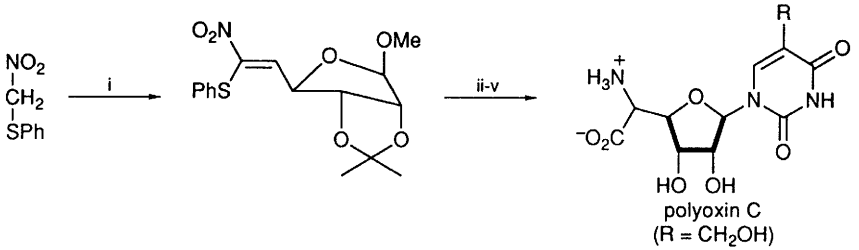
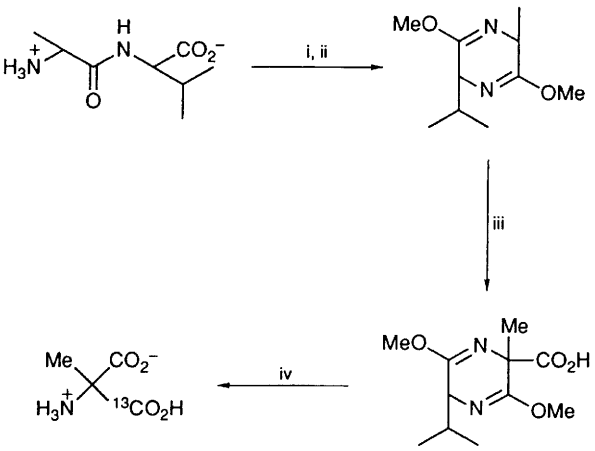


polyoxin C
(R = CH_2OH)

Reagents: i, Corresponding ribose-aldehyde; ii, KOTMS then MeOH [$NO_2C(SPh)=CH- \rightarrow HO(COSPh)CH-$]; iii, Tf_2O; COSPh → CO_2Me; iv, NaN_3; v, —OMe → uracil

Scheme 3



Reagents: All standard (see Vol. 22, p. 7) *e.g.*, i, ii, cyclization, $Me_3O^+BF_4^-$; iii, alkylation; iv, hydrolysis

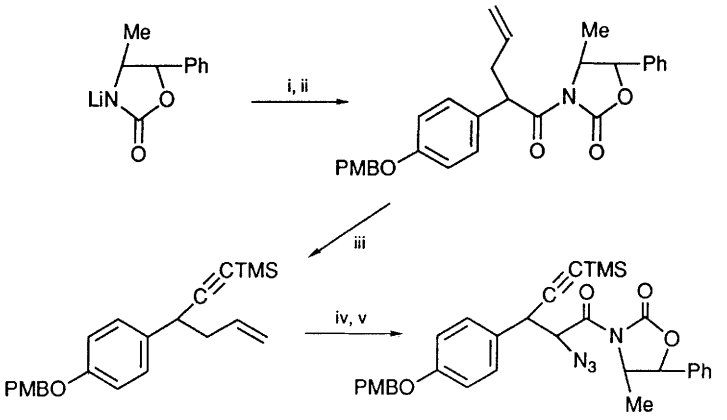
Scheme 4

4.2 Asymmetric Synthesis of α-Amino Acids.- Following on the 'General Methods' approach of the preceding Section, there are many well-developed general asymmetric synthesis routes to α-amino acids. These include direct extensions of some of those methods mentioned in the preceding Section - e.g. the Strecker synthesis of cyanohydrins catalyzed by the dioxopiperazine derived from L-phenylalanyl-L-histidine[63] - while other methods are more distantly related. Some of these have become fully explored, as seems to be the case with the Schöllkopf bis-lactim ether approach (exemplified in Scheme 4 for a synthesis, from the bis-lactim ether derived from L-alanyl-L-valine, of (2R)- and (2S)-[1-^{13}C]-2-amino-2-methylmalonic acid)[64] and they require less space this year since they have been illustrated often in this Section in preceding Volumes.

Good yields of homochiral α-amino acid esters are routinely formed by photolysis of chiral chromium aminocarbene complexes (formed from a tertiary amide and $Na_2Cr(CO)_5$ with TMSCl) in solution in an appropriate alkanol.[65] Homochiral β-lactams are formed similarly through reaction of these complexes with imines.[66] The topic continues to be well-reviewed[67,68] (see also Vol.22, p.8).

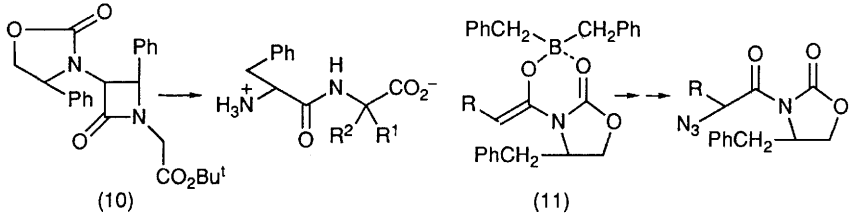
Chiral saturated heterocycles have occupied a firm niche in this Section, as vehicles for asymmetric synthesis of α-amino acids. Evans' methodology based on lithiated (4R,5S)-4-methyl-5-phenyloxazolidinone has been used for a synthesis of (+)-(2S,3S)-ethynyltyrosine (Scheme 5)[69] and an analogous oxazolidinone underpins the asymmetric double alkylation of the glycine derivative (10) en route to homochiral N-(L-phenylalanyl)amino acids.[70] L-Serine gives the same chiral heterocyclic system carrying a 4-methoxycarbonyl grouping, christened a nucleophilic L-alaninol synthon since conversion into the Wittig reagent and condensation with aldehydes [$CO_2Me \rightarrow -CH_2P^+Ph_3\ I^- \rightarrow HOCH_2CH(NHBoc)CH{=}CHR$ as a result of ring-opening] occurs readily and with high stereoselectivity.[71] Bromination (N-bromosuccinimide) of dibenzylboron enolates (11) derived from N-alkanoyl 4-benzyloxazolidin-2-ones, followed by electrophilic azidation (tetramethylguanidinium azide) gives (R)- or (S)-α-azidoalkanoic acids.[72] The more convenient potassium enolate reacting with 2,4,6-tri-isopropylphenylsulphonyl azide is better than 90% diastereoselective (but dependent on the nature of the acylating grouping).

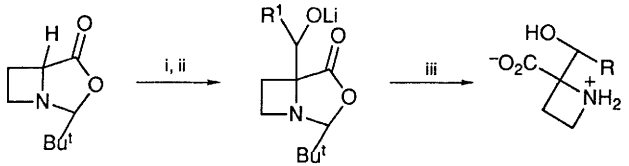
The alternative chiral oxazolidinone (a cyclic acetal) continues to be studied (cf. Vol.22, p. 12),[73] this year in a bicyclic form (Scheme 6) in which the focus of interest is the racemization that accompanies alkylation of the exocyclic enolate by electrophiles. A methylene derivative (12) of Seebach's choice of oxazolidinone is susceptible to diastereoselective free radical addition leading to β-extended alanines.[74] A route from L-cysteine to the (2R)-thiazoline (13; R =



Reagents: i, 4-(4′-$MeOC_6H_4$–)$OC_6H_4CH_2CO_2H$, 0°C; ii, NaHDMS, then allyl bromide;
iii, $LiAlH_4$, then successively $COCl_2$/DMSO, Et_3N, CBr_4/PPh_3, Bu^tLi, TMSCl;
iv, O_3, then $NaClO_2$;
v, Bu^tOCOCl, Li salt of (4*S*, 5*R*)-4-methyl-5-phenyloxazolidinone, $ArSO_2N_3$

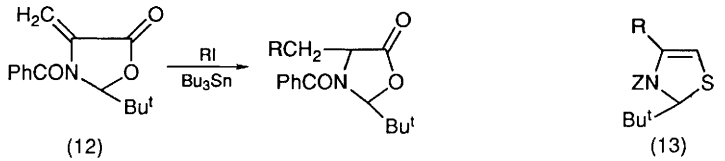
Scheme 5





Reagents: i, $LiNR_2$; ii, R^1CHO; iii, H_2O, H_3O^+

Scheme 6



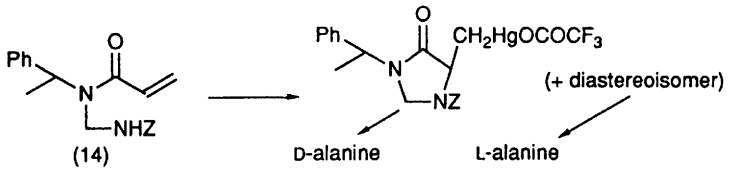
CO_2R), useful in this context (see Vol. 22, p.10 for uses of the equivalent oxazoline) has been described.[75]

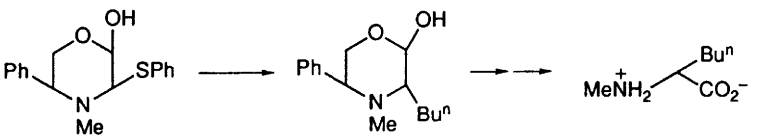
The analogous imidazolinones have also been used in asymmetric synthesis of amino acids, illustrated further for $Hg(OCOCF_3)_2$ cyclization of the chiral amidal (14) formed from 1,3,5-tri-(S)-phenylethylhexahydrotriazine and acryloyl chloride.[76]

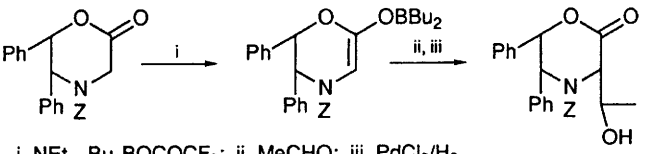
Six-membered chiral glycine-cation equivalents have been supplemented usefully[77,cf.,78] by a phenylthio-substituted oxazine (15) that shows propensity towards substitution either with inversion (by Bu^nCu) or with retention (Bu^nZnI). This behaviour has been seen in several similar cases before, and continues to defy rationalization. Williams' oxazinone (Scheme 7), converted into the boron enolate and alkylated with acetaldehyde, yields L-allothreonine on work-up,[79] thus showing the opposite stereoselectivity from that of the corresponding reaction undergone by Seebach's imidazolinones. Enantiomeric excesses between 82 and 94% are reported for C-arylglycines prepared by either Friedel-Crafts or cuprate couplings with the bromo-oxazinone (16).[80]

A new chiral imine approach uses the hydrazone (17 in Scheme 8); and 100% diastereoselectivity is claimed for a representative L-alanine synthesis employing it.[81]

Small-ring chiral synthons complete this crop of related routes. Ammonolysis of chiral oxiranes (resulting from Sharpless oxidation of crotyl and allyl alcohols) gives L- and D-allothreonines and (S)- and (R)-isoserines, respectively,[82] and a similar methodology is involved in the synthesis of (2S,3S)- and (2R,3R)-3-hydroxyleucine (Scheme 9).[83] Turning things on their heads, an aziridine-2-carboxylate prepared from D-threonine serves as starting material for alkylation by an N-alkylindole (catalyzed by BF_3–OEt_2) to give (αR,βR)-1,β-dimethyltryptophan (Scheme 10).[84] The same approach using the C2-symmetric diethyl N-toluene-p-sulphonyl aziridine-2,3-dicarboxylates prepared from (+)- and (-)-tartaric acids yields products formally derived from the β-cation of L- and D-aspartic acid respectively, through nucleophilic ring-opening (with $LiCuMe_2$ to give homochiral β-methyl aspartates, for example).[85] Natural (2S,3R)-tartaric acid serves as starting material in a straightforward synthesis of (2S,3R)-N-Boc-3-benzyloxyaspartate.[86] Other 'carbohydrate-based' asymmetric syntheses are more interesting; N-Boc D-glucosamine through successive $NaBH_4$ reduction and $NaIO_4$ oxidation gives L-serinal (in its stable polymeric form in aqueous solution) from which D-dehydroglutamic acid was prepared through aldehyde processing (-CHO → -CH=CHCOR).[87] Di-acetoneglucose yields (2S,3R,4R)-3,4-dihydroxyproline (and the route can be adapted to give the corresponding pipecolic acid) through azidolysis of the protected methyl acetal, to give (18), and hydrogenation of the separate α- and β-anomers.[88] A similar exploitation

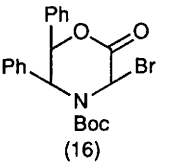


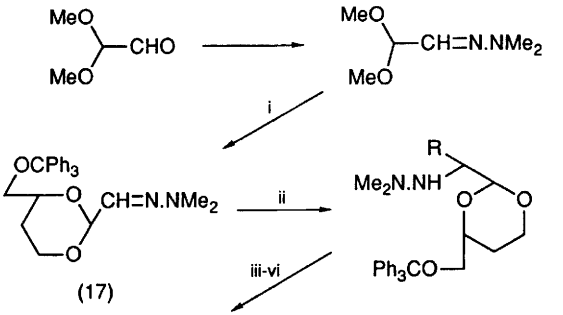




Reagents: i, NEt_3, $Bu_2BOCOCF_3$; ii, MeCHO; iii, $PdCl_2/H_2$

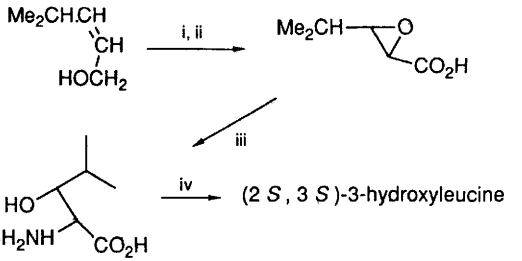
Scheme 7





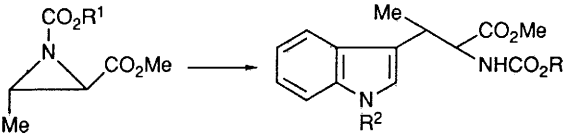
Reagents: i, (*S*)-$HO.CH(CH_2OH)CH_2OH$, Ph_3CCl; ii, RLi; iii, H_2/Ni; iv, phthaloylation; v, HOCl; vi, NH_2NH_2

Scheme 8

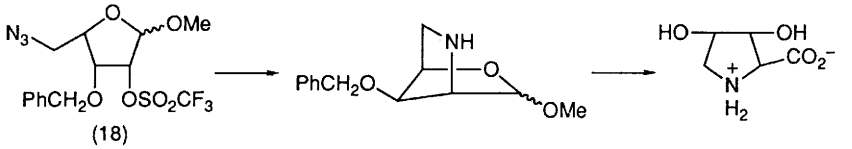


Reagents: i, Sharpless oxidation; ii, RuO_4; iii, $PhCH_2NH_2$; iv, H_2/Ni

Scheme 9



Scheme 10



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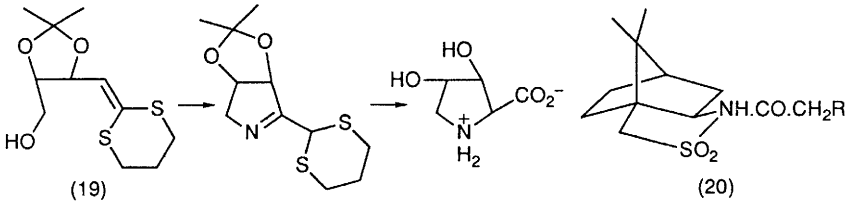

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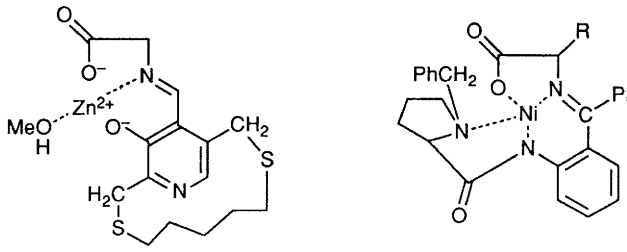


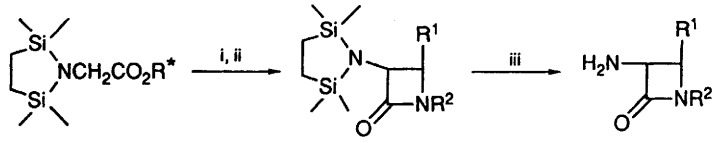
(21) (22)

of azide chemistry, leading to (2S,3S,4R)-3,4-dihydroxyproline, introduces a very promising use for chiral ketene dithioacetals (19; cf. Scheme 1).[89] In the latter example, the routine conversion OH → N_3 is followed by intramolecular cycloaddition.

Asymmetric alkylation of a glycine derivative, implicit in some of the preceding examples, continues to offer an attractive route to homochiral α-amino acids. A striking example leading to α-amino-β-lactams (Scheme 11) that has a famous ancestor in a total synthesis of penicillins and cephalosporins, is also a hidden illustration of a chiral synthesis of β-amino acids.[90] In this case, a chiral ester moiety R* induces the enantioselectivity, and needs to be chosen through trial and error so as to give maximum enantiomeric excess in any particular case.

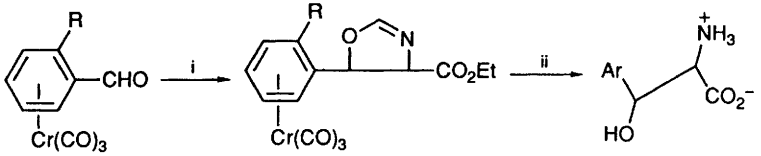
Oppolzer's bornanesultamylglycine (20; cf. Vol.22, pp.12,13) has found a new compatible reagent, 1-chloro-1-nitrosocyclohexane, to carry out amination of its enolate, so as to offer N-hydroxyamino acids as well as its original purpose, asymmetric synthesis of the amino acids themselves, obtained through Zn^{2+}/aqueous acid reduction of the hydroxylamines.[91] Chirality in the Schiff base moiety of glycine imines is a more favoured, and probably a better, choice within this approach. Examples range from the simplest glycine Schiff bases (see previous Volumes of this Report) to conformationally rigid (and therefore more complex) cases. The latter category is illustrated by the chiral pyridoxal-like pyridinophane Zn complex (21), used for aldol condensations leading to α-amino-β-hydroxy acids giving 27-77% enantiomeric excess[92] and benzylation giving substituted phenylalanines.[93] A similar application for Ni^{2+} complexes of Schiff bases (22) formed between glycine (22; R = H) or alanine (22, R = Me) and (S)-N-(N-benzylprolyl)aminobenzophenone has been developed over several years, this year for o-, m- and p-fluorophenylalanines and their α-methyl analogues[94] and for allo-isomers of β-substituted (S)-2-aminobutanoic acids.[95] Nucleophilic substitution of bromoglycine complexes (22; R = Br) by diethyl malonate or n-C_4H_9ZnCl gives L-aspartic acid (80% e.e.) and L-norleucine (68% e.e.) respectively.[96] Chiral arylaldehyde-$Cr(CO)_3$ complexes add to the glycine equivalent, ethyl isocyanoacetate,[97] accomplishing an asymmetric aldol reaction (Scheme 12) that is effectively the same route as that leading to α,γ-diamino-β-hydroxycarboxylic acids using (S)-dibenzylaminoalkanals with ethyl isocyanoacetate,[98] via the same oxazoline intermediate.

A near relative of glycine alkylation, providing a new principle in enantioselective amino acid synthesis, is based on nucleophilic ring-opening of 1-nitrocyclopropanecarboxylic acid salts. With an L-amino acid methyl ester the route gives 4-(α-methoxycarbonylalkylamino)-2-nitroalkanoic acids,[99] which on reduction with Zn/AcOH in the presence



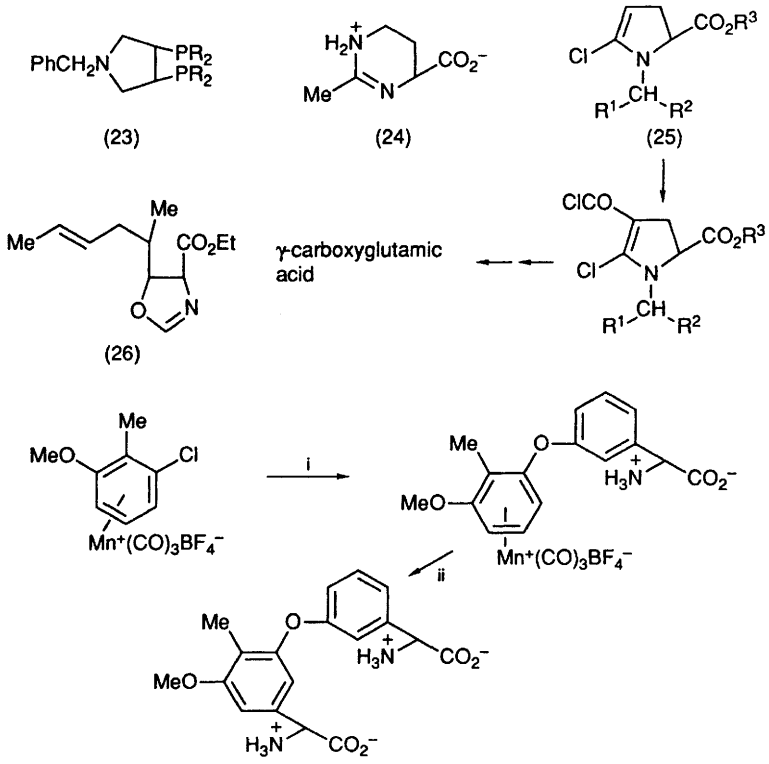
Reagents: i, LDA; ii, $R^1CH{=}NR^2$; iii, H_2O

Scheme 11



Reagents: i, $CN.CH_2.CO_2Et$; ii, ArCHO

Scheme 12



Reagents: i, *N*-Boc-(*S*)-(3-hydroxyphenyl)glycine; ii, Schöllkopf alkylation (*cf.* Scheme 4)

Scheme 13

of acetic anhydride gives the corresponding L-amino acid in moderate enantiomeric excess.

"Asymmetric hydrogenation" of α-acylamido-cinnamic acids using rhodium - chiral phosphine catalysts, is a long-ongoing interest of several research groups. This can be very effective in terms of high enantioselectivity, with up to 87% enantiomeric excess being achieved with mineral-supported catalysts,[100] and better in other cases[101] (e.g. 95% e.e. in synthesis of dihydroxyphenylalanines).[102] The role of the approach pathway of hydrogen is important in determining stereoselectivity, and relatively rigid chiral phosphines, e.g. (23), seem to have a particularly effective role. The contribution of molecular graphics in determining structural features in the catalyst, that allow only that pathway that must lead to the desired enantiomer, has been reviewed.[103] This essentially expands the report by the same author cited last year (Vol.22, p.10).

4.3 Synthesis of Protein Amino Acids and Other Naturally Occurring α-Amino Acids.- Examples of amino acids synthesis under this heading can also be found elsewhere in this Chapter, particularly in the preceding two sections. However, enzymatic methods and laboratory synthesis of the more unusual natural amino acids are reserved for this Section.

Reviews have appeared of microbial and enzymatic production of L-tryptophan,[104] of L-lysine and L-glutamic acid (use of L-lysine oxidase from Trichoderma viride, and L-glutamic acid oxidase from Streptomyces sp., respectively),[105] and of D-amino acids.[106] Representative papers cover bioreactors with NH_3 or urea as nitrogen source, for the production of branched side-chain L-amino acids,[107] production of L-lysine with methionine and threonine double auxotrophic mutants from Bacillus megaterium,[108] and use of the same means for L-alanine and L-valine production.[109]

A Volume entitled "Biochemical Engineering 6" includes several papers dealing with fermentative production of amino acids, covering L-aspartic acid,[110] L-phenylalanine (use of Escherichia coli),[111] and fermentative production of D-amino acids from DL-hydantoins.[112] The use of hydantoins in this context for the synthesis of L-amino acids continues to develop, with Arthrobacter showing the appetite for the task of L-tryptophan production.[113,114] Enzymatic conversion of DL-hydantoins into L-amino acids has been reviewed,[115] and a thoughtful exposition on the production of either D- or L-amino acids from hydantoins in this way concentrates on the three enzymes involved.[116] D-Glyceric acid provides a substrate for the synthesis of L-serine by successive operation of glyoxylate reductase and alanine dehydrogenase.[117] Reductive amination of phenylpyruvic acid by

phenylalanine dehydrogenase from Bacillus sphaericus, and the more general involvement of this system in L-amino acids synthesis has been explored.[118]

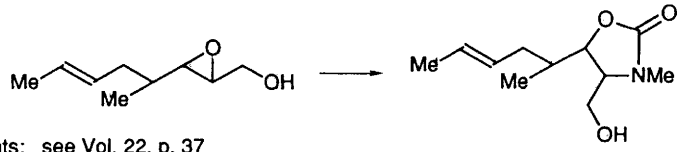
Non-protein amino acids D-p-hydroxyphenylglycine (from the action of Agribacterium sp. on the appropriate DL-hydantoin),[119] L-DOPA (tyrosinase from A. terreus 104),[120] S-adenosyl-DL-homocysteine, (Saccharomyces cerevisiae cells transformed with a plasmid containing an ethionine resistance gene),[121] and S-adenosyl-L-methionine[122] are also accessible by enzymatic methods. A Tolypocladium inflatum mutant has been reported to accumulate MeBmT, i.e. (4R)-4-[(E)-2-butenyl)-4,N-dimethyl-L-threonine.[123]

No attempt is made in this Chapter to cover the literature of the more academic aspects of the biosynthesis of amino acids, though a note on the origins of ectoine (24) from phosphorylated L-aspartic acid in Ectothiorhodospira halochloris and Halomonas elongata catches one's interest.[124]

An improved β-carboxyaspartic acid synthesis based on alkylation by sodium dibenzyl malonate,[125] and another efficient γ-carboxylation of protected (S)-pyroglutamate via the γ-enolate have been reported.[126] N-Benzhydryl-L-pyroglutamic esters give α-chloro-enamines (25) with phosgene, from which γ-carboxyglutamic acid can be obtained.[127] A concise route to L-phenylalanine from (R)-epichlorhydrin is available.[128] Laboratory synthesis of thyroxine and tri-iodothyronine has been reviewed.[129] More sophistication is needed, based on organomanganese chemistry, for the synthesis of a deoxy-ristomycinic acid derivative (Scheme 13),[130] in which the α-amino acid formation step uses the standard Schöllkopf asymmetric synthesis methodology (cf. Scheme 4).

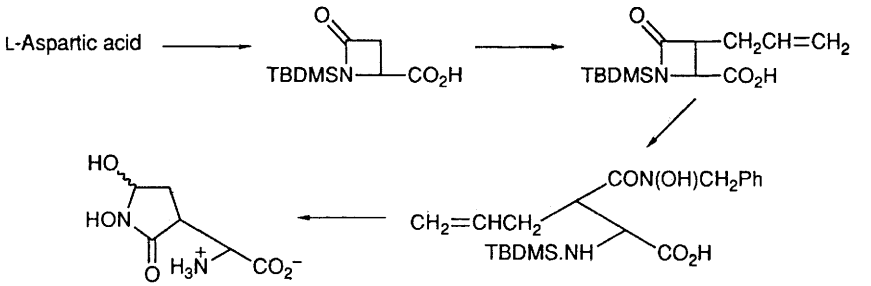
The remaining examples in this section will be recognized by faithful readers as even more challenging synthetic targets that have already featured in these reviews. Other similarly-daunting natural amino acids that will come into readers' minds will be found in a later section where they fall within the β-amino-and-higher acid category.

Among α-amino acids, syntheses of the cyclosporin component MeBmT [(4R)-4-[(E)-2-butenyl)-4,N-dimethyl-L-threonine] are being achieved in fewer steps than the marathon accomplishments of previous years (see Vol.22, p.37). Gold(I)-chiral ferrocenylphosphine catalysis of the aldol reaction between (2R,4E)-MeCH=CHCH$_2$CH(Me)CHO and ethyl isocyanoacetate gives the oxazoline (26) carrying the appropriate stereochemistry. Two further steps to reach the target, constitutes the shortest synthesis (so far) of this α-amino acid.[131] A "chiral epoxide" methodology (Scheme 14) involving base-catalyzed rearrangement of β-hydroxyurethanes, has been used to synthesise a 3-hydroxy-MeBmT



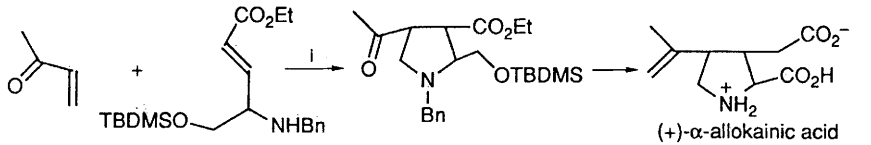
Reagents: see Vol. 22, p. 37

Scheme 14



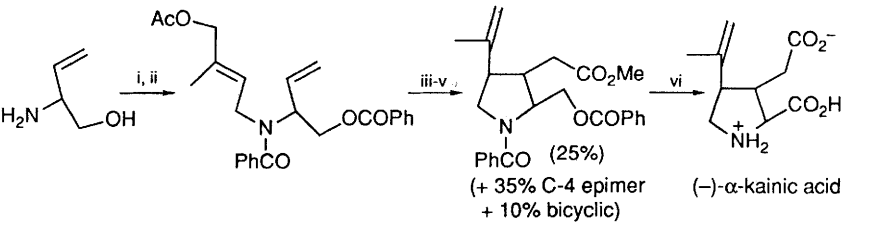
Reagents: as noted in text

Scheme 15



Reagents: i, reactants in EtOH, 15 days; or, with catalytic tetramethylguanidine or, in two separate stages (a) $FeCl_3$, (b) tetramethylguanidine (90% yield)

Scheme 16



Reagents: i, $AcO.CH_2.CMe{=}CH.CH_2Cl$; ii, $PhCOCl$; iii, $Pd(DBA)_2$, PPh_3, CO, AcOH, 80°C;
iv, hydrolysis, then CH_2N_2;
v, repeat of conditions (iii), but with higher pressure (3 atm.) of CO;
vi, routine elaboration

Scheme 17

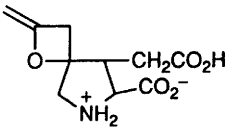
stereoisomer,[132] and analogously for the synthesis of the δ-oxygenated analogue from (4S,2Z)-$PhCH_2OCH_2$.CHMe.CH=CH.CO_2Me.[133]

Several examples of the use of protein amino acids with side-chain functional groups, for the synthesis of more complex non-protein amino acids, emphasise the growing importance of this approach. Indeed, some examples have been included in a preceding section (4.1 General Methods of Synthesis of Amino Acids) since they could be judged to have entered into this category. A synthesis, from L-aspartic acid, of de-alanylalahopcin, the non-protein moiety of the dipeptide, has been described (Scheme 15).[134] Notable features are the diastereoselective alkylation of the azetidinone and thiolate-catalyzed ring opening with benzylhydroxylamine via the readily aminolyzed thiolester.

Protected L-pyroglutamic acid is efficiently alkylated in terms both of yield and trans-stereoselectivity, after Y-anion formation using $LiNPr^i_2$ or $LiNBu^t_2$ in THF.[135] A not-too-distant relative is Bulgecin C, for which the first total synthesis is reported, starting from (2S,4R)-hydroxyproline.[136] This synthesis exploits the electrochemical methoxylation of the protected hydroxyproline acetate and ensuing routine elaboration. Syntheses of kainic acids start from a protected serine, employing Co(II)-mediated radical cyclization of a derived halide already well-established by Baldwin's group, in a route leading to (-)-α-kainic acid,[137] and tandem Michael reaction methodology [leading to (+)-α-allokainic acid; Scheme 16] in another study.[138] Pd(0)-mediated alkene-insertion and carbonylation (Scheme 17)[139] has been described. The Michael route is notable in being a one-pot process that generates three chiral centres in one stage.

Members of the kainoid family (kainic acid, acromelic acids, domoic acid) share the ability to inflict marked depolarization effects on L-glutamate receptors, and syntheses of analogues are very much of interest in exploring structure-activity relationships. Synthesis of analogues has been reported,[140] simple analogues of acromelic acid (o-hydroxyphenyl in place of 3-pyridonyl; see Vol.22, p.15) being more highly active agonists of kainic acids than any natural kainoid. Scheme 18 outlines this synthesis, starting from L-vinylglycinol. In another account, synthesis of a novel oxetane-containing analogue of kainic acid (27) is described, synthesized starting from kainic acid, with allylic hydroxylation proceeding with complete retention at C-4.[141] Loss of affinity for glutamate receptors accompanies this structural change.

A synthesis of the Y-azetidinyl-β-hydroxy-α-amino acid moiety of mugineic acid starts with (R)-glyceric acid,[142] converted into (28) through an earlier-established sequence (Vol.21, p.20) and then elaborated stereospecifically into the serinal derivative (29). The extraordinary antibiotic duocarmycin A (30; from Streptomyces sp.) and related pyrindamycins A and B have been synthesized through



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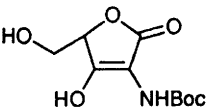

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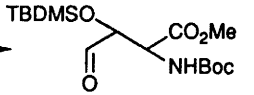

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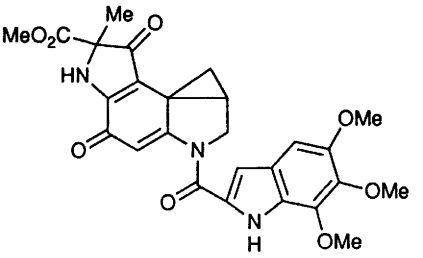

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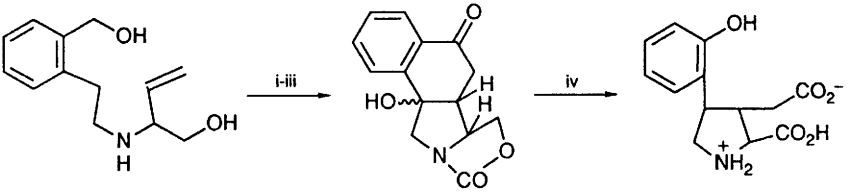
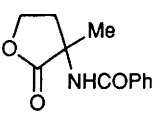


Reagents: i, Z.Cl, K_2CO_3, then KOH, MeOH; ii, MnO_2 (-CH_2OH→ -CHO); iii, *h* ν, then MnO_2; iv, routine elaboration

Scheme 18



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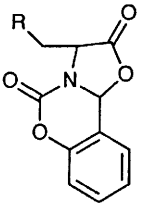


(32)

Reagents: i, α-glucosyl bromide + $ZnBr_2$; ii, H_2O

Scheme 19

constructing the amino acid moiety on to an NH_2 group carrying the rest of the structure using MeCHBr.CO_2Me.[143]

4.4 α-Alkyl and Aryl Analogues of Protein Amino Acids.- These are important as potential disruptors of metabolic processes, whether in their own right or as components of peptides. They can be prepared through certain standard routes - e.g. by Strecker synthesis from ketones - or through α-alkylation of a protein amino acid derivative. Recent examples in the latter category are the conversion of N-benzoyl-DL-alanine methyl ester into α-methyl homoserine lactone (31) through di-anion formation and reaction with ethylene oxide,[144] (nucleophilic ring-opening by $PhSe^-$ is followed by β-elimination to give the α-vinyl alanine derivative), and catalytic phase transfer alkylation of an alanine Schiff base ester by an imidazolylmethyl acetate (or the alternative methylation of the histidine Schiff base) to give α-methylhistidine.[145]

An N-protected tryptophan methyl ester survives the conditions of alkylation if the indole nitrogen atom is also Boc-blocked, demonstrated by α-anion formation from the isocyano analogue, using LDA, and reaction with an alkyl bromide.[146] N^{in}-Alkylation competes with α-alkylation in Michael additions to N-benzylidene tryptophan methyl ester.[147]

Stereoselective double alkylation of some of the chiral synthons covered in the earlier Section, 4.2 "Asymmetric Synthesis", is already well-researched, but a new example is an interesting resurrection of the chiral oxazolidinone (32) formed between an amino acid, salicyaldehyde and phosgene emphasises the fact that these saturated heterocycles are not newly-discovered synthons.[148] Stereoselective alkylation after anion formation [lithium bis(trimethylsilylamide] is efficient in the modest number of cases tried.

Further work has been reported from Burger's group, extending their methodology for preparation of trifluoromethyl amino acids (see Vol.22, p.25). α-Alkynyl "trifluoro-alanines" are available through Grignard alkynylation of CF_3.C(=NZ).CO_2R (or corresponding use of NaC≡CR),[149] and ω-carboxyalkyl analogues have been prepared through routine elaboration of corresponding ω-alkenyl analogues.[150] New 2-phenyl-4-(α-arylalkyl)-4-trifluoromethyl oxazolones,[151] and the 4-methyl-4-(α-hydroxybenzyl) analogue (threo:erythro = 3:1)[152] have been described, as have analogous oxazinones[153] from which the respective α-trifluoromethyl or α-methyl α-amino acids could be secured through aqueous acid hydrolysis.

An interesting series of α-substituted α-amino acids becomes available through the establishment of an α-C-glucosylation route using ketene acetals and α-glucosyl bromide/$ZnBr_2$,[154] (Scheme 19). There is no reference to asymmetric induction in this study.

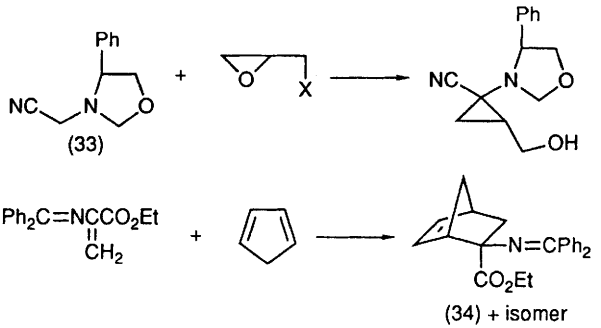
Selective monophenylation of active methylene compounds in the synthesis of α-phenyl-α-amino acids (the work of M.J.O'Donnell's group) has been reviewed.[155] α-Arylamino acids are formed in good yield by treating Schiff bases with (arene)halotricarbonylchromium(II) complexes.[156]

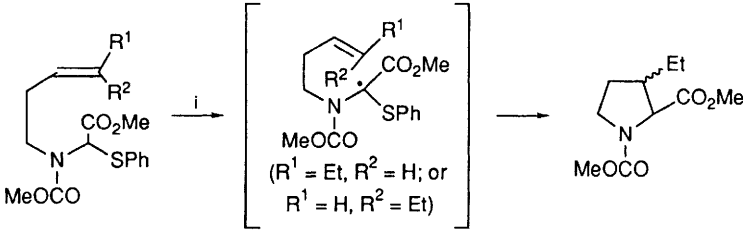
4.5 α-Amino Acids Carrying Alkyl Side-Chains, and Cyclic Analogues.- This section is intended to be the repository for papers covering the synthesis of aliphatic non-protein α-amino acids lacking side-chain functional groups, and has become more and more concerned with alicyclic representatives (amino function outside the ring). Saturated heterocyclic examples including proline analogues (amino function within the ring) are also covered here.

(1R,2S)- and (1S,2R)-1-Amino-2-hydroxymethylcyclopropanecarboxylic acids have been prepared through cycloalkylation of dimethyl malonate with epichlorhydrin (the nucleophile attacks the epoxide in preference to displacing the halogen), followed by a classical Hofmann rearrangement to deliver the α-amino group and separation of diastereoisomers.[157] Epichlorhydrin, or alternatively, glycidyl triflate, has also been used for alkylation of the chiral aminonitrile synthon (33) to give two of the four possible diastereoisomers of 2,3-methanohomoserine, separated by conventional crystallization.[158] 1-Amino-2-oxo-3-oxabicyclo[3.1.0]hexane, the lactonized isomer of the amino acid just mentioned, has been synthesized through cyclization of the carbenoid derived thermolytically from an alkyl allyl diazomalonate $RO_2C.CN_2.CO_2.CH_2.CH{=}CH_2$, followed by selective elaboration of the alkyl ester function (RO_2C- → HO_2C- → H_2N- with diphenylphosphoryl azide).[159] The other approach to preparing conformationally-constrained analogues of protein amino acids is to place the cyclopropyl ring one carbon further away from the "glycine moiety", as in (2R, 3S, 4R)-α-carboxycyclopropylglycine, alias "D-cyclopropylglutamic acid".[160] This synthesis was achieved through dirhodium(II) tetra-acetate catalyzed thermal decomposition of ethyl diazoacetate in the presence of Z-D-vinylglycine methyl ester. A similar approach using photolysis of diazomethane, has been used for the preparation of 2,3-methanoproline.[161]

Geometrical isomers of 4-guanidinocyclohexylglycine (proposed as arginine analogues), have been prepared through standard methods.[162] Pyroglutamic acid processing (→ N-Boc (S)-pyroglutaminol, and alkylation) gives (2S,4S)- and (2S,4R)-$HO_2C.CH(NH_2).CH_2.CH(CO_2H)(CH_2)_nPh$, (n = 1,3,5), as 4-substituted glutamic acid analogues for neuroexcitatory activity studies.[163]

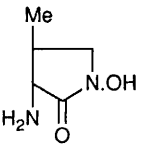
The four stereoisomers of 3-phenyl-1H-aziridinecarboxylic acid are the outcome of a route starting with racemic ethyl (E)-2-





Reagents: i, Bu_3SnH/azo-bis-isobutyronitrile, toluene, 80°C/N_2

Scheme 20



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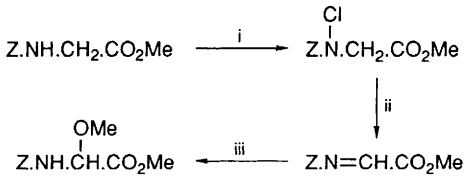
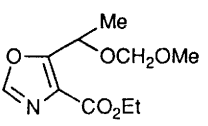


Reagents: i, Bu^{t}OCl; ii, base; iii, NaOMe, MeOH

Scheme 21



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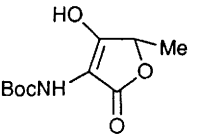


(37)

phenyloxiranecarboxylate, prepared by Darzens reaction between benzaldehyde and ethyl chloroacetate,[164] azidolysis after resolution, and cyclization with Ph_3P.

Like the corresponding cyclopropanes, azetidine-2,4-dicarboxylic acid[165] and its 4-alkyl analogues[166] are of considerable interest as potential agonists of N-methyl-D-aspartate receptors. There are no particular targets justifying the synthesis of "norbornane amino acids" (34) other than a useful extension of Diels-Alder methodology.[167]

Prolines and pipecolic acids have been prepared through cyclization of the C2-radical of 1-methoxycarbonyl-2-aza-5-hexenyl phenyl sulphides (Scheme 20).[168] Photocyclization of αω-di-amino acids giving prolines and pipecolic acids involves what has been called an aqueous semi-conductor suspension (water/TiO_2 or CdS/PtO_2).[169] Less spectacular syntheses of pipecolic acids are based on processing of substituted 2-cyanopyridines formed from pyridines by N-oxidation followed by Me_3SiCN.[170]

A near relative to these classes is the pyrrolidinone (35), a potent glycine and N-methyl-D-aspartic acid receptor antagonist that has been synthesized through a well-planned stereoselective route.[171]

4.6 Prebiotic Synthesis of Amino Acids.- The simple-chemical-mixture/sophisticated-energy-source combination that has been the main feature of this section over the years is repeated in a variety of ways. Sixteen amino acids are present in the sputtered material when graphite is bombarded by high energy molecular beams in which the elements hydrogen, nitrogen and oxygen are represented.[172] A similar experiment involves 3 MeV proton irradiation (van de Graaff generator) of an atmosphere of carbon monoxide and nitrogen over water, which produces various amino acids (and imidazole) during 2 - 5 h.[173] From this result, it is reasoned that cosmic radiation and/or solar flares should be considered to have a place in theories of the origins of life.

Higher up the pathway leading to amino acids - or so the originators of these experiments presumably speculate - are carboxylic acids, which through high-pressure explosive amination using ammonium carbonate or ammonium hydrogen carbonate (no further information in the abstract of this paper) form glycine, phenylalanine and aspartic acid.[174] A similar treatment of ^{14}C-methylamine through catalyzed carboxylation with CO_2 gives glycine, glutamic acid, and β-alanine,[175] the radiolabel allowing conclusions to be drawn to the effect that CO_2 only contributes the carboxyl carbon; and that glycine was the precursor of the other two amino acids. KrF Excimer laser irradiation of ethylamine in aqueous HCl results in stepwise oxidation to give ethanolamine and glycine, through cleavage of water into H and OH radicals.[176] The maximum *yield*

of glycine is poor at 10%, but is of a level that suggests that the results of serendipitous experiments of this type may feature in future production processes that create a cocktail of more or less useful organic chemicals (though probably not for the production of amino acids!).

Erythrose and formamidine, both known to be formed in prebiotic conditions, have been shown to react to give imidazole-4-acetaldehyde.[177] Since HCN and NH_3 (required for Strecker amino acid synthesis) were also abundant at prebiotic times, the formation of histidine in 3.5% yield through presenting these compounds to the erythrose - formamidine reaction mixture is a convincing proposal for the genesis of this amino acid.

4.7 α-Alkoxy α-Amino Acids.- α-Hetero-atom substituted glycine derivatives continue to play a useful role in amino acid synthesis. Examples have been mentioned earlier in this Chapter, and protected α-alkoxy α-amino acids achieved the status of carving out their own Section in this Chapter some years ago as a result of their simple electrochemical synthesis. A new synthesis of α-methoxyglycine from the N-chloro derivative of Z.Gly.OMe has been described (Scheme 21).[178]

4.8 Halogeno-alkyl α-Amino Acids.- All the examples in this Section this year concern fluorine-substituted protein amino acids - which is not to be interpreted as saying that no other halogeno-alkyl amino acids have been prepared in ways that are chemically-interesting, but that (unlike the fluorinated compounds) these others are intermediates en route to amino acids that are mentioned elsewhere in this Chapter.

Syntheses of fluorinated amino acids[179] and more specifically, α-(β-fluoroalkyl) α-amino acids[180] have been reviewed. (-)-D-erythro- and (+)-L-threo-4-fluoroglutamic acids have been prepared from trans- and cis-4-hydroxyprolines, respectively, through substitution of OH by F after N-acetylation and esterification, followed by RuO_4 oxidation to the pyroglutamate.[181] 4,4-Difluoroglutamic acid has been prepared through Michael addition of a 2,2-difluoroketene silyl acetal [$F_2C{=}C(OMe)OSiR_3$ from $F_2CI.CO_2Me$] to a homochiral N-propenoyl 5-benzyloxazolidin-2-one (cf. Scheme 5),[182] and a simpler version of the same methodology was used to prepare Ph.CONH.CH_2.CF_2.CH_2.CHO for use in a Strecker synthesis of 5,5-difluoro-lysine. 5-Fluoro-L-lysine is accessible from L-homoserine and ethyl bromofluoroacetate through a Horner-Emmons reaction.[183]

More direct fluorination approaches in which fierce reagents are presented to protected amino acids usually cause multiple and untargeted substitution, as with the reaction of XeF_2 with N-trifluoroacetyl S-benzyl cysteine.[184] Monofluorination of the benzyl

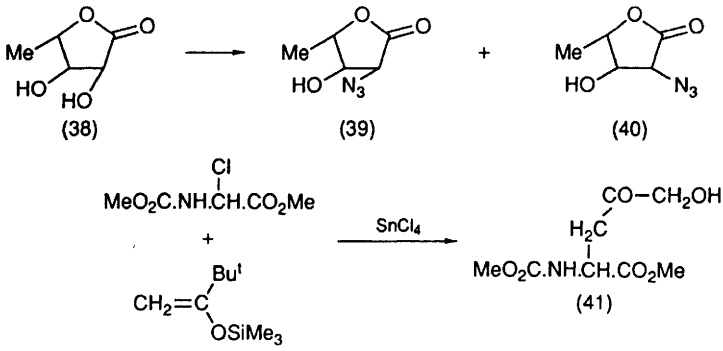
methylene group, and substitution of the benzylthio-group, accompany the formation of a useful protected β-fluorocysteine, which over 24 h spontaneously eliminates HF to give the mixed Z/E-dehydrocysteine derivative.

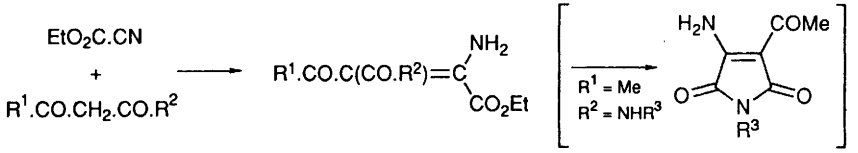
4.9 α-(ω-Hydroxyalkyl) α-Amino Acids.- There are many examples of syntheses of α-(β-hydroxyalkyl) α-amino acids, not least because there are several important natural compounds of this family (and for this reason, this year's crop of examples will be found in other sections of this Chapter). An interesting use of enzymes is seen in preliminary results for the synthesis of these compounds through the aldol reaction of an aldehyde with glycine catalyzed by aldolase enzymes extracted rabbit liver and corn seedlings.[166] The alternative stereoselective synthesis methodology for this process is represented in the Zn(II) or Cu(II)-catalyzed aldolization of a homochiral glycine imine [derived from (1R)-3-hydroxymethylbornan-2-one for this study], reaction with benzaldehyde giving β-phenylserine diastereoisomers.

A preparation of the oxazoline (36) from ethyl isocyanoacetate and (S)-$MeOCH_2$.OCHMe.CO_2Me and its use as a chiral β-hydroxy-α-amino acid synthon has been described.[166] For example, reaction with diphenyl phosphorazidate and NaH and routine steps, leads to lactone (37) that yields a mixture of γ-hydroxynorvaline diastereoisomers on hydrogenation. A more stereoselective route to the same target employs (38), derived from D-ribolactone, as starting material,[167] proceeding through azides (39) and (40). More routine methods underlie the syntheses of γ-hydroxyvalines (modified Erlenmeyer synthesis) and δ-hydroxyleucine and δ-hydroxyisoleucine (Michael addition).[168]

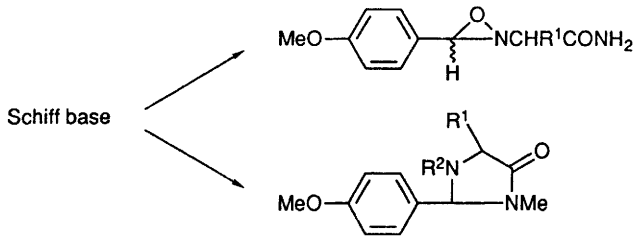
Lewis acid-catalyzed coupling of N-methoxycarbonyl chloroglycine methyl ester with a silyl enol ether has been used for the synthesis of the antitubercular/antifungal 5-hydroxy-4-oxo-norvaline (41).[169]

4.10 α-Amino Acids Carrying Unsaturated Side Chains.- 2-Aminoalken-2-oic acids ("αβ-dehydro-amino acids") call for simple methods in the simplest cases [condensation of secondary amines + pyruvate esters catalyzed by $AsCl_3$;[130] dehydration with di-isopropylcarbodi-imide/Cu(I)Cl of β-hydroxy-N-diphenylmethyleneamino acids;[131] and condensation of EtO_2CCN with a 1,3-dicarbonyl compound (Scheme 22)[132]] but more sophisticated procedures are needed for polyfunctional examples. 4-Bromo-N-tosylindoles add to N-protected α-amino acrylates under $PdCl_2$ catalysis to give dehydro-tryptophans, though a side-reaction due to benzo-substitution is troublesome.[133] A similar approach gives β-vinyl and β-aryl dehydro-amino acids, using vinyl and aryl triflates as reagents and methyl α-acetamidoacrylate as substrate under Pd(II) catalysis.[134]

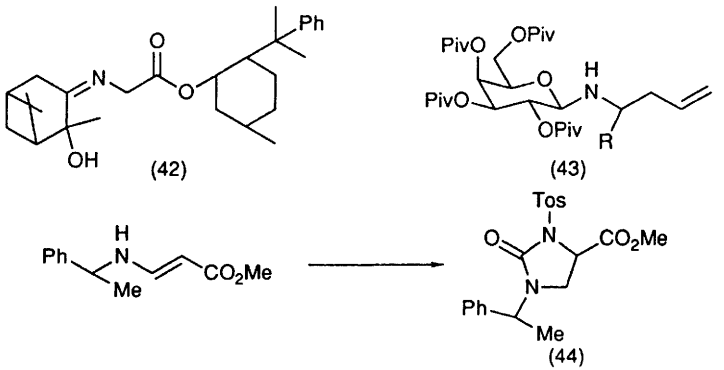




Scheme 22



Scheme 23



An interesting observation, that oxidative dehydrogenation of α-aminoacidato complexes of cobalt(II), viz. $[Co(en)_2(aa)]^{2+}$, is brought about by $SOCl_2$, could be exploitable for a practical synthesis of αβ-dehydroamino acids through rearrangement of the resulting imines $HN{=}CRCO_2H$.[195]

An effective synthesis of N-benzyloxycarbonyl L-vinylglycine methyl ester from the L-methionine derivative is based on facile elimination following conversion to the sulphoxide.[196] Other 3,4-dehydroamino acids synthesized recently include (Z)-3,4-dehydronorvaline and the (E,Z)-3,4-dehydro-ornithine and 2,5-di-aminopimelic acid analogues, through addition of Grignard reagents to diethyl acetyliminomalonate.[197]

γδ-Unsaturated amino acids have been prepared through the substitution of a protected α-chloro- or α-methoxyglycine with an allylsilane.[198]

The first synthesis of an ethynylglycine derivative has been achieved through substitution of N-acetyl α-chloroglycine diphenylmethyl ester and $Me_3SiC{\equiv}CSnBu_3$ followed by deblocking.[199]

4.11 Aromatic and Heteroaromatic α-Amino Acids.- As is the case for other nearby sections in this Chapter, covering particular side-chains, relevant information will also be found in the later section 'Specific Reactions', where reactions at the side-chain of one of the well-known aromatic or heteroaromatic amino acids are described that can produce a new addition to the same family. General methods for amino acid synthesis have also been applied, for example to the preparation of α-amino phenylacetonitrile $H_2N,CHPh,CN$, from which phenylglycinamide may be prepared through HCl - mercaptoethanol treatment in THF.[200]

Carbalkoxyalkylation - replacement of the OH group of a hydroxyphenylalanine - has been demonstrated through reaction of a protected tyrosine triflate with an acrylate ester catalyzed with $(Ph_3P)_2PdCl_2$, followed by hydrogenation.[201]

A 1975 preparation of L-homohistidine has been improved through the use of formamidine acetate and NH_3 in the final imidazole-forming stage.[202] The next higher homologue, but with the imidazole moiety linked through nitrogen, i.e. δ-(1-imidazolyl)norvaline, has been synthesized as an arginine analogue.[203] A photo-activatable heteroaromatic amino acid analogue, 2'-diazo-histidine, has been synthesized as its N^{α}-Boc methyl ester using routine imidazole chemistry through the 2'-amino histidine.[204]

4.12 N-Substituted α-Amino Acids.- This section serves here for unusually-modified amino or imino groups; protection or transient modification as part of a reaction pathway is either covered in the

later Section 'General Reactions' or excluded from the Chapter if its details are routine.

N^{α}-Hydroxy-L-amino acid amides are conveniently prepared from oxaziridines produced by oxidation of the Schiff base (Scheme 23), or (as second best) from N^{α}-oxidation of the imidazolidinone formed from the Schiff base.[205]

An alternative synthesis of N^{α}-benzyloxycarbonyl-N^{δ}-hydroxy-L-ornithine methyl ester has been announced, in which the N^{δ}-acetyl derivative is reacted with benzoyl peroxide.[206]

4.13 α-Amino Acids Containing Sulphur, Selenium, or Tellurium.- There is one citation for each element, as it happens, for this year's review. 2'-Arylthio-L-histidines have been prepared[207] for use in peptide synthesis. A routine selenomethionine synthesis uses MeSeH and an α-protected-amino γ-butyrolactone or α-protected-amino methyl cyclopropanecarboxylate,[208] while telluromethionine is available in the same way (α-amino-γ-butyrolactone + LiTeMe).[209]

4.14 Phosphorus-Containing α-Amino Acids.- As is the tradition of this Chapter, α-amino acids in which the carboxy group is replaced by a phosphorus oxy-acid group, are not covered (nor are amino-sulphonic, amino-boronic etc, acids). Where a phosphorus side-chain function is involved, as in the obviously-important competitive glutamate antagonist (at the N-methyl-D-aspartic acid complex), (R)-4-oxo-5-phosphono-norvaline,[210] there is every reason to put such information side-by-side with that on other amino-carboxylic acids. The synthesis of this compound from D-aspartic acid in six relatively straightforward steps, via the ketone $RCH_2.CO.CH_2.PO_3H_2$, is described in this paper.

The racemic homologue, E-2-amino-5-phosphonopenten-3-oic acid, E-$HO_2C.CH(NH_2).CH{=}CH.CH_2.PO_3H_2$, has been synthesized from the unsaturated β-acetoxynorvaline $EtO_2C.CH(NHBoc)CH(OAc)CH.CH{=}CH_2$ through Pd(II)-catalyzed [3,3]-sigmatropic rearrangement followed by elaboration to the phosphonic acid.[211]

Enantiomerically-pure D- and L-2-amino-3-phosphonopropanoic acid has been prepared from the homochiral Boc-serine α-lactones and $(MeO)_3P$.[212] Phosphinothricin and analogues have been prepared by Michaelis-Becker alkylation of $R^1R^2P(O)H$ by acetylaminolactams.[213]

4.15 Labelled Amino Acids.- This is the repository for papers that demonstrate the use of reliable standard methods of amino acid synthesis in the context of isotopically-labelled compounds. Given the high cost of intermediates, whether in terms of cash or in investment of effort, in many of the examples in this section, the reader seeking

an optimized preparative procedure would do well to consult these papers to see how the last available milligram might be extracted from an amino acid synthesis. As usual for this Section, labelled amino acids are grouped in order of increasing atomic number (and subdivided in order of increasing relative atomic mass) of the labelled atom(s).

Simple α-^{2}H-labelling of protein L-amino acids has been claimed using tryptophanase-containing whole cells of E.coli B/1t7-A in $^{2}H_2O$.[214] Variously ^{2}H- and ^{13}C-labelled indoles have been included in fermentative production of L-tryptophans leading to six different isotopomers.[215] An alternative approach to the same objective is pyridoxal-catalyzed α-^{1}H - ^{2}H exchange with inversion of configuration, demonstrated for valine.[216] ^{2}H - I Exchange brought about for N-acetyl 3,5-di-iodotyrosinamide depends on parameters such as the nature of the catalyst used, and the protocol followed.[217] ^{2}H-Exchange both sides of the sulphur atom in D-methionine has been accomplished using $NaO^{2}H$ with the sulphonium salt, followed by mercaptoacetic acid reduction.[218] Use of the recently-established methionine elimination permitted the extension of this route to the preparation of D-[4-$^{2}H_2$]vinylglycine.

Routes to [3,4-$^{3}H_2$]-1-aminocyclopropane-1-carboxylic acid by tritium addition (Pd/C catalyzed) to the corresponding cyclopropene,[219] and to [4,5-$^{3}H_2$]-DL-leucine and -isoleucine (using the acetamidomalonate synthesis) and to [2,3,4,5-$^{3}H_4$]-DL-proline (pyrrole/$(NH_4)_2CO_3$ followed by $^{3}H_2$-Pd/C)[220] use standard methods.

^{11}C-Labelling continues to be a strong feature of this section, with its own fascination associated with the need for deft chemical operations as a result of the short half-life of this isotope. It has extra interest also, generated by a controversy[221] over the value of direct recoil ^{11}C-labelling of L-valine and 2-aminobutanoic acid, with retention of chirality, by brehmstrahlung from a 65 MeV linear electron accelerator.[222] This results in ^{11}C-atom insertion, and in reply, it was acknowledged[223] that useful radioactivity levels may not be achieved in this way. Other papers follow the conventional pathway in applying procedures occupying less than one hour, from generation of $^{11}CO_2$ or H^{11}CN to the finished product, such as the double chiral induction process using the glycine Schiff base (42) for a synthesis of [β-^{11}C]-L-alanine employing $^{11}CH_3Li$,[224] and the alkylation of Belikov's nickel-complexed chiral Schiff base (22) with $^{11}CO_2$ as starting point for the synthesis of alkylating agents for preparation of β-^{11}C-labelled amino acids.[225] Enzyme-catalyzed routes seem to be entering Langstroem's thinking, with [β-^{11}C]-L-serine as target, starting with $^{11}CO_2$, en route to $^{11}CH_3OH$ and H^{11}CHO via N^5,N^{10}-[^{11}C]methylenetetrahydrofolate (1 - 2% yield within 50 - 65 min after preparation of $^{11}CO_2$).[226] Enzymatic conversion of DL-[3-^{11}C]alanine (formed from $^{11}CO_2$ → $^{11}CH_3I$ + $Ph_2C{=}N.CH_2.CO_2Bu^t$), into L-[β-^{11}C]tryptophan and its 5-hydroxy-

derivative, has been described,[227] so also have [β-^{11}C]-L-tyrosine and -DOPA.[228] A multi-enzyme synthesis of ^{11}C-carboxy group-labelled tyrosine, DOPA, tryptophan, and 5-hydroxytryptophan from H^{11}CN,[229] and of 1-[^{11}C]-DL-homocysteine thiolactone using $^{11}CO_2$ and α-lithiated S-tetrahydropyranyl-thiopropyl isonitrile,[230] has been described. L-[5-^{11}C]Ornithine has been prepared through processing the K^{11}CN - γ-bromohomoserine lactone reaction product.[231]

[ε-^{13}C]-L-α-Amino-adipic acid and five of its isotopomers, variously labelled with ^{13}C, ^{15}N, and ^{2}H in δ and ε positions, have been synthesized through the Schöllkopf bis-lactim ether procedure (Scheme 4) with the use of K^{13}CN and routine elaboration, as far as the ^{13}C isotope is concerned.[232] [1,2-$^{13}C_2$]Lysine has been prepared by Co-catalyzed hydroformylation of 3-cyanopropene using ^{13}CO and CH_3CONH_2, via 5-cyano-2-acetamidopentanoic acid (some 4-cyano-2-acetamido-3-methylbutanoic acid is also formed).[233] Another of the protein amino acids is represented among the ^{13}C-labelled group of papers this year, in the form of [2-^{13}C]-DL-glutamic acid (DABCO-catalyzed addition of diethyl [2-^{13}C]acetamidomalonate to methylacrylate),[234] and both enantiomers of the non-protein [1-^{13}C]-2-amino-2-methylmalonic acid by straightforward means.[235] The last-mentioned preparation was the means by which stereospecific decarboxylation of this malonic acid derivative was demonstrated to involve the 2-pro-R-carboxy group in the biogenesis of D-alanine.

A lengthy synthesis involving a resolution with (-)-N-methylephedrine at its final stage to give [2-^{14}C]-L-glutamic acid, has been detailed.[236] It starts from sodium [2-^{14}C]acetate, which is converted into ethyl [2-^{14}C]-2-bromoacetate for reaction with the morpholine enamine of ethyl pyruvate, to give diethyl [4-^{14}C]-2-oxoglutarate. $LiAlH_4$ Reduction of the oxime, and resolution, completes the synthesis. 5-Amino-[4-^{14}C]laevulinic acid has been prepared,[237] a key step being the Pd(0)-catalyzed coupling of 2-phthaloylamino-[1-^{14}C]acetyl chloride (from K^{14}CN) to $EtO_2C.CH_2.CH_2.ZnI$. [2,3-^{14}C]-1-Aminocyclopropanecarboxylic acid is produced in low yield from $Br^{14}CH_2.{}^{14}CH_2Br$ and $NC.CH_2.CO_2Et$.[238]

Enzymatic methods enter again, and particularly logically, into the labelled amino acid field for syntheses of [^{15}N]-L-phenylalanine and [^{15}N]-L-tyrosine, employing [^{15}N]-ammonia and glutamic or pyruvic acids.[239] A synthesis of the neurotoxin $Me^{15}NH.CH_2.CH(NH_2)CO_2H$ from N-acetyldehydroalanine and [^{15}N]-methylamine uses the enzyme acylase I in the traditional end-of-synthesis manner for resolution.[240]

The synthesis of [^{18}F]-substitution products of m-tyrosine[241] and of 6-trifluoroacetoxymercuriDOPA[242] leads to mixtures of 2-, 4- and 6-mono-[^{18}F]-fluoro-m-tyrosines, and [^{18}F]-6-fluoroDOPA, respectively, when [^{18}F]-acetyl hypofluorite is the reagent. The latter product has been prepared through an alternative route,[243] based on displacement by $^{18}F^-$ +

crown ether of the nitro group in 3,4-dimethoxybenzaldehyde or 6-nitropiperonal, followed by a standard azlactone synthesis.

DL-[^{35}S]Cysteine has been obtained through addition of [^{35}S]-thioacetic acid to α-acetamido-acrylic acid followed by routine deprotection and purification.[244] L-[^{35}S]homocysteine thiolactone is also accessible through standard methods.[245]

L-6-[^{123}I]Iodo-m-tyrosine is formed through the reaction of Chloramine-T - $^{123}I_2$ with L-m-tyrosine,[246] while $^{123}I^-$ - Br exchange involving 6-bromoDOPA is particularly simple (35 min at 97°, pH 4).[247] In this latter study, a process was worked out for iodo-demercuration of a mercuriDOPA derivative based on I_2 composed of the normal iodine isotope. Similar approaches form the bases of syntheses of 3-[^{123}I]iodo-D-tyrosine[248] and of 3-(4'-[^{125}I]-iodophenyl)-4-aminobutyric acid, a radioactive analogue of Baclofen.[249]

4,16 β- and Higher Amino Acids.- This Section continues to expand, illustrating the growing importance of amino acids in which a larger separation of amino and carboxy functions is involved. Much of the expansion is associated with their importance as constituents of biologically-active natural products, and the interest in synthesis of peptide analogues.

Standard methods to β-amino acids, undergoing development, include Michael addition of primary or secondary amines to silyl acrylates $R^1R^2NH + CH_2{=}CHCO_2SiMe_3$.[250] and the equivalent process, addition of imines to ketene silylacetals catalyzed by FeI_2 or trityl hexachloro-antimonate.[251] Addition of the N-dialkylamino group of 1-(N-dialkylamino)benzotriazoles to ketene silylacetals leading to the same outcome, has been reported.[252] Use of N-(α-alkoxycarbonylalkyl)benzotriazoles in a general β-amino acid ester synthesis, based on Reformatzky reagents, has been described.[253] The overall sequence α-amino acid → β-amino acid is represented in the regio- and stereoselective conversion of chiral N-toluene-p-sulphonylaziridines (prepared from L-α-amino acids) using cyanotrimethylsilane.[254,255 also 256]

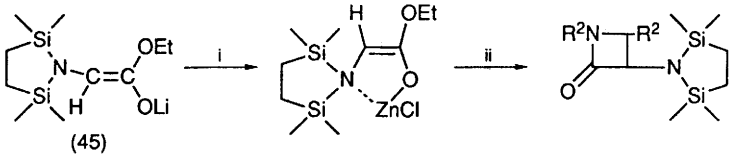
L-Asparagine serves in a general synthesis of enantiomerically pure β-amino acids, via β-cyano-alanine, thence to the methanesulphonate $(PhCH_2)_2NCH(CH_2.CN)CH_2.OMes$ which is subjected to substitution by a lithium dialkylcuprate.[255] Alternative ways in which an enantiospecific route can be organized include condensation of 3-methyl-1-nitrobutane with (-)-8-phenylmenthyl glyoxalate (KF in THF) to give a mixture of diastereoisomers including 77% of that needed for processing so as to give (2S,3R)-3-amino-2-hydroxy-5-methylhexanoic acid,[256] and (a rare example of the citation of a patent in this Chapter) a synthesis of β-amino-α-hydroxyalkanoic acids from a malic acid enantiomer.[257] Chiral

homoallylamines, e.g. (43) formed by diastereoselective addition of the familiar (see Vol.22, pp.15, 34) chiral tetra-O-pivaloylaminopyranose to allyl trimethylsilane, are cleaved by aqueous acid, to give (S)-β-phenyl-β-alanine in this particular example after $KMnO_4$ oxidation at the alkene function.[258] Transfer of chirality observed[259] to accompany DBU-catalyzed rearrangement of imines $CF_3CPh{=}NCHMePh \rightarrow CF_3CHPhN{=}CMePh$ is to be investigated for the synthesis of α-substituted β-amino acid analogues, initial experiments indicating that a much higher temperature (225°) is required for the β-amino acid synthesis than in the satisfactorily-demonstrated case (120°). Another chirality transfer is seen in the addition of toluene-p-sulphonyl isocyanide to (S)-PhCHMe.NH.CH=CH.CO_2Me, which provides $Me_3N^+.CH_2.CH(NHTos).CH_2.CO_2^-$ via the intramolecular Michael adduct (44).[260]

Improvements in syntheses of azetidin-2-ones (alias β-lactams) amount to improved β-amino acid syntheses, and provide in some cases useful exploitation of glycine and other α-amino acid synthons. The glycine ester-derived enolate (45) undergoes $ZnCl_2$-catalyzed addition to imines in the conventional way (Scheme 24).[261] (2R,3S)- and (2S,3R)-3-Amino-2-hydroxyalkanoic acids have been prepared from methyl (R)- and -(S)-mandelate, respectively, through [2 + 2]-cycloaddition of the derived chiral imines $PhCH(OR')CH{=}NR_2$ to benzyloxyketene (from $PhCH_2O.CH_2.COCl$ + NEt_3).[262] 3-Trimethylsilyloxyazetidin-2-ones and α-alkylidene-β-lactams, prepared from α-bromo-esters and azetidin-2,3-diones[263] have been used in stereoselective syntheses of α-hydroxy-β-amino acid constituents of the peptide antibiotics taxol and bestatin.[264]

For γ-amino acids, an equivalent process to those seen in the preceding paragraphs [$MeNO_2$ + $CH_2{=}C(CF_3)CO_2Bu \rightarrow NO_2.CH_2.CH_2.CH(CF_3)CO_2Bu$] leads to 2-trifluoromethyl-4-aminobutanoic acid[265] or to 3-alkyl analogues.[266] (R)- and (S)-4-Amino-3-methylbutanoic acids have been prepared through a route starting with enantioselective hydrolysis (pig liver esterase) of dimethyl 3-methylglutarate to give methyl (R)-3-methylglutarate, followed by the conversion of the ester group into NH_2 with one portion, and conversion $CO_2H \rightarrow NH_2$ for the other.[267] α-Methoxy-γ-lactams (46) undergo substitution with 1,3-dicarbonyl compounds and other active methylene compounds to give γ-aminoalkanoic acids.[268] Stereoselective $NaBH_4$ reduction of the Boc-L-valine-derived allyl ketone BocNH.CHPr^i.CO.CH_2.CH=CH_2 is the crucial step in a synthesis of (3S,4S)-BocNMe.CPr^i.CH(OMe)CH_2CO_2H.[269]

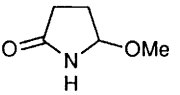
The statine synthesis industry is in ever-expanding mood, with new papers describing methods that run over well-used tracks. L-Malic acid has been used as a starting point in two independent routes, both through the chiral pyrrolidin-1,5-dione (47 in Scheme 25) and depending on regioselective carbonyl addition.[270,271] Similar strategy for a stereospecific synthesis of (-)-(3S,4S)-statine based on tetramic acid



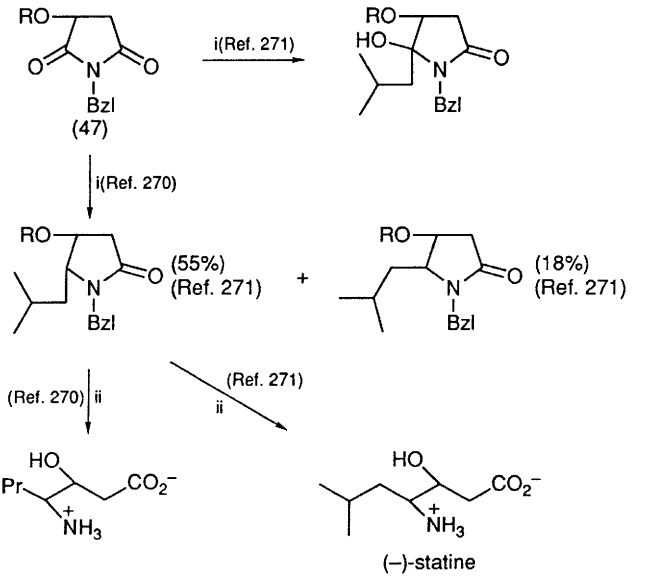
(45)

Reaction: [(45) is formed using LDA in THF at –78°C]
i, $ZnCl_2$; ii, $R^1N{=}CHR^2$

Scheme 24



(46)



(–)-statine

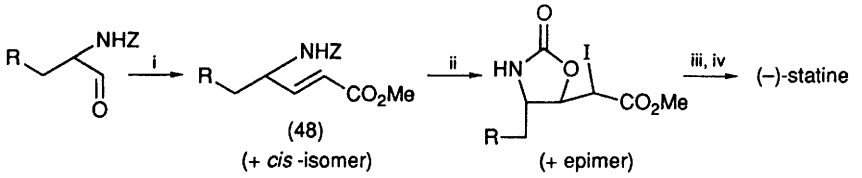
Reagents: (Ref. 271) i, $CH_2{=}CMeCH_2MgBr$; ii, dehydration, then H_2/Pd-C in CH_2Cl_2;
(Ref. 270) i, (R = H) → (R = Ac), $NaBH_4$, allyltrimethylsilane,
H_2/Pd (→ Pr^n in place of Pr^i)

Scheme 25

chemistry through the same intermediate has been demonstrated.[272] Diastereoselective $TiCl_4$-catalyzed allyl-metal addition to (S)-α-Boc-aminoalkanals[273] follows earlier precedent (Vol. 22, p.34) and involves erythro/threo ratios favouring the natural amino acid. (-)-Statine is also accessible from an (S)-α-Boc-aminoalkanal through Horner-Emmons reaction to give the cis-trans alkene (48 in Scheme 26) which is then subjected to "iodocyclocarbamation" and simple further processing.[274] The cyclic carbamate technology that is being increasingly used (Vol. 22, pp.19, 53) has been fully written up, and illustrated with a statine synthesis (Scheme 27).[275]

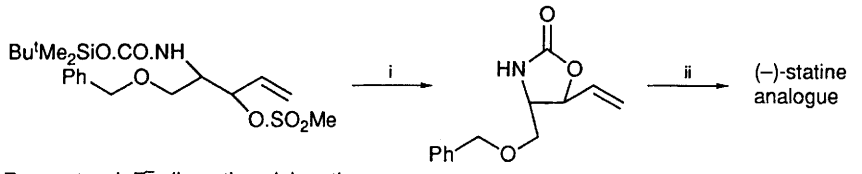
Alternative ways of inducing the correct stereochemistry at the C-3 chiral centre are available, one somewhat cumbersome method using (S)-phenylethylamine for reductive amination of isobutyl 2,5-dimethoxyphenyl ketone and depending on Birch reduction of the aryl moiety followed by ozonolysis to give $Pr^iCH(NHBoc)CO.CH_2.CO.Me$ calling for further routine processing.[276] The all-S diastereoisomers of statine and cyclohexylstatine are formed in a highly diastereoselective (94:6) aldol route involving an (S)-α-isopropoxycarbonylaminoalkanal with O-methyl-O-trimethylsilylketene acetal.[277] This is described by its originators as "the most practical synthetic route" to these compounds, a phrase that will be used more often to justify future statine papers, now that so many effective routes are available. A paper from the same group could even be seen as challenging the claim, involving $CeCl_3$-catalyzed stereoselective Grignard addition to the imine derived from (2S,3S)-tartaric acid in a synthesis of the corresponding (2R,3S)-3-amino-2-hydroxyalkanoic acid, alias cyclohexylnorstatine (Scheme 28),[278] the same product as obtained starting from L-phenylalanine in a route established by these workers to prepare the aldehyde of its cyclohexyl analogue in the form of its N-isopropoxycarbonyl derivative; the route includes a highly diastereoselective acetoxycyanohydrin formation step.[279] A correspondingly simple route to the same target starts with N-Boc-L-phenylalaninal.[280] A chiral thioacetamide PhCHMe.NH.CS.Me has been used to start a statine synthesis through Michael addition of its carbanion (Bu^nLi) to acrolein, followed by diastereoisomer separation and stereoselective iodolactamization (Scheme 29).[281]

"Isostatine", in which another chiral centre is created as an isopropyl methyl group is moved to C-5, is nevertheless an easier synthetic challenge since Fmoc-D-alloisoleucine offers a convenient starting point, either in the form of the methyl ester[282] or as the acid chloride.[283] Full details in the former paper include a synthesis of D-alloisoleucine from L-isoleucine (5 steps) as well as the 6 further steps needed for reaching (3S,4R,5S)-isostatine; the other paper covers the simpler acylation of $LiCH_2.CO_2Bu^t$, KBH_4 reduction and flash



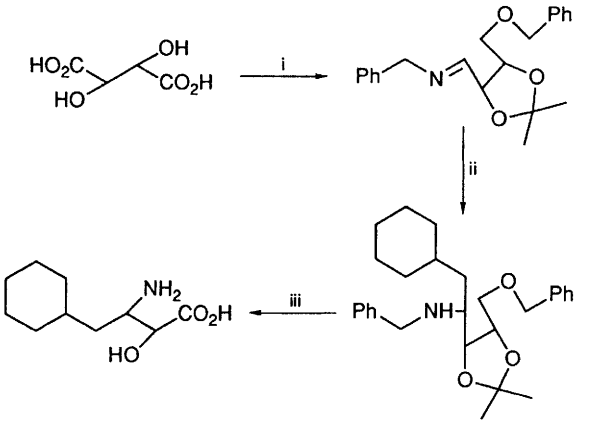
Reagents: i, $(MeO)_2POCH_2CO_2Me/NaH$; ii, $I_2/MeCN$; iii, $Bu^n{}_3SnH$; iv, alkaline hydrolysis

Scheme 26



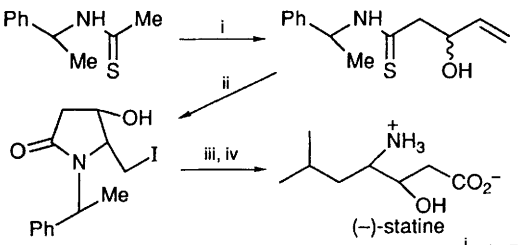
Reagents: i, F^-; ii, routine elaboration

Scheme 27



Reagents: i, known sequence; ii, $C_6H_{11}CH_2MgX$, $CeCl_3$; iii, deprotection, *etc.*

Scheme 28



Reagents: i, Bu^nLi, acrolein; ii, resolve, then MeI, then I_2; iii, $I \rightarrow Pr^i$; H_2/Pd; iv, hydrolysis

Scheme 29

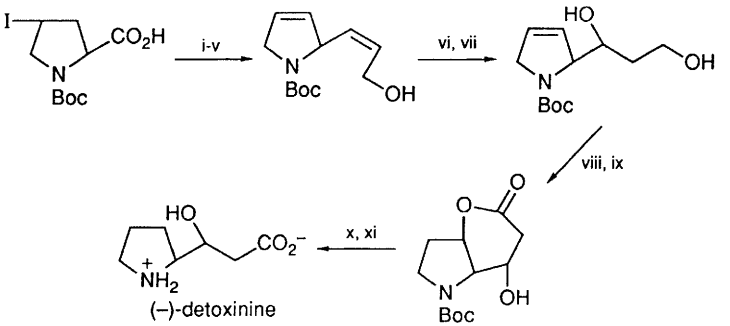
chromatographic separation stages, and also explores the corresponding use of Fmoc-L-leucine in a statine synthesis.

The earlier-mentioned use of cyanotrimethylsilane[284] for cyanohydrin formation from an N-protected α-amino-aldehyde is also used in a one-pot anti-diastereoselective route to β-amino-α-hydroxyesters for bestatin and amastatin synthesis,[284] also in a route to corresponding formyl anion synthons (thiazole moiety in place of the ester function) when 2-trimethylsilylthiazole is used in place of the cyanide.[285]

More complex natural β-amino acids are covered in a (−)-detoxinine synthesis (already the subject of three total syntheses), starting from N-Boc-(2S,4S)-4-iodoproline methyl ester, easily prepared from 4-hydroxyproline, and proceeding through highly diastereoselective stages (Scheme 30),[286] and a synthesis of "ADDA" [(2S,3S,8S,9S)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid] starting from the (2S,3R)-epoxide of 4-benzyloxy-cis-2-buten-1-ol in which all chiral centres are generated with the correct configurations (Scheme 31).[287]

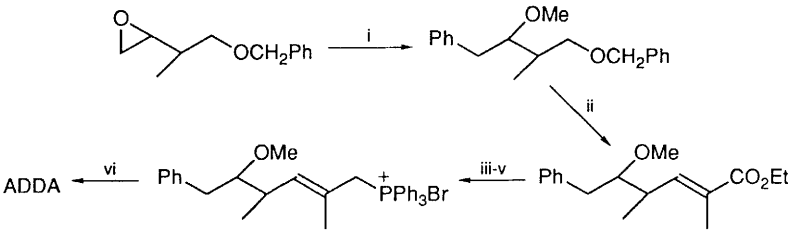
γ-Amino acids result from carboxylation of lithiated di-allylamines (Scheme 32).[288] Both enantiomers of carnitine $Me_3N^+.CH_2.CH(OH).CH_2.CO_2^-$ (the L-isomer is often referred to as Vitamin B_T) have been synthesized from malic acid, through relatively straightforward functional group transformations.[289] Other γ-amino acids also requiring more than a little skill for their synthesis include "(R)-GABOB" - alias (R)-γ-amino β-hydroxybutyric acid - for which several efficient syntheses have been reported. Claisen condensation (lithium diethylamide) of N-benzyloxycarbonylglycinal with $(R)\text{-}MeCO_2CHPhC(OH)Ph_2$ occurs with induction of the correct stereochemistry (Scheme 33).[290] A route from $CH_2{=}CHCH_2CONHCH_2Ph$ to the γ-lactam [a substituted (R)-GABOB] exploits a chiral phenylethylamine for the induction of the correct stereochemistry, and of course, the route equally conveniently provides (S)-GABOB.[291] (+)-Tartaric acid is the starting point in another (R)-GABOB synthesis.[292]

δ-Amino acids are of increasing interest since they provide dipeptide isosteres for routes to peptide analogues. γ-Keto-δ-amino acids ("ketomethylene pseudopeptides" in the jargon of peptide analogues), have been synthesised through an efficient route.(Scheme 34).[293] Bamberger cleavage of ethyl 3-(4-imidazolyl)butanoate (see Vol.22, p.37) using (−)-menthyl chloroformate gives the 3,4-di-aminobutanoates as their carbamates though not particularly high enantioselectivity, a process applicable also to L-histidine methyl ester.[294] Naturally-processed dipeptides incorporating thiazole moieties are, from one point of view, peptide analogues, and a synthesis of the thiazole (49)[295] is properly located in this section since it is effectively a dipeptide derivative and at the same time, a δ-amino acid derivative.



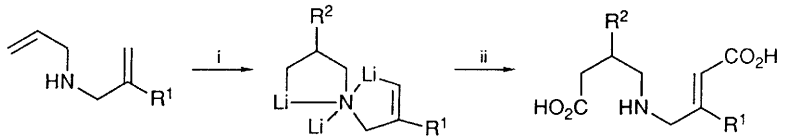
Reagent: i, $NaBH_4$-LiCl; ii, $COCl_2$/DMSO; iii, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$; iv, DIBALH; v, PhSeNa; vi, MCPBA, then diastereoisomer mixture is separated; vii, *syn* -isomer reduced with Red-AL ®; viii, Pt-O_2; ix, Br_2-EtOH; x, Bu_3SnH; xi, TFA and work up

Scheme 30



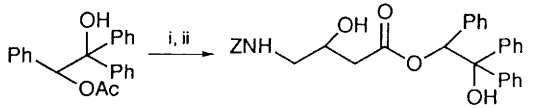
Reagents: i, PhMgBr/CuI, then NaH/MeI; ii, Pd/C; H_2, then $COCl_2$/DMSO, then $Ph_3P{=}CMe.CO_2Et$; iii, DIBALH; iv, CBr_4/PPh_3; v, PPh_3/MeCN; vi, Bu^nLi, then condensation with modified C-1 to C-4 segment of ADDA (in the form of the C-4 aldehyde), followed by routine elaboration

Scheme 31



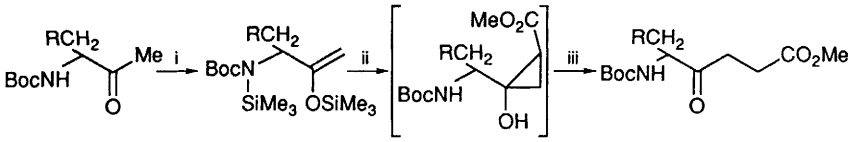
Reagents: i, RLi; ii, CO_2

Scheme 32



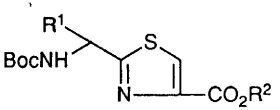
Reagents: i, LDA; ii, Z.NH.CH_2.CHO

Scheme 33

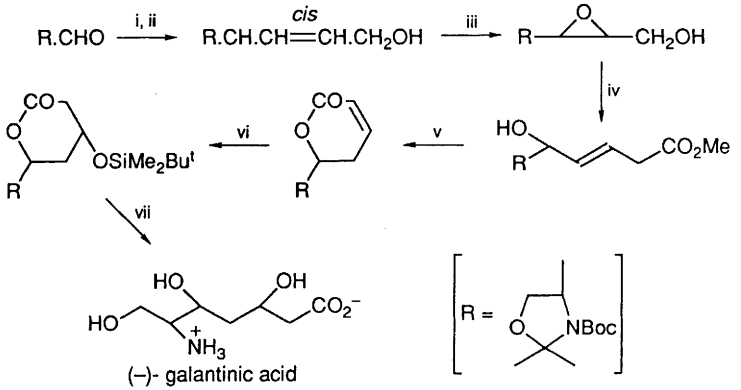


Reagent: i, LDA, Me_3SiCl; ii, N_2CHCO_2Me, $Cu(acac)_2$; iii, $Bu_4N^+F^-$

Scheme 34



(49)



Reagents: i, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH; ii, Bu^i_2AlH; iii, MCPBA;
iv, $COCl_2$/DMSO, then Ph_3PCHCO_2Me; v, DBU; benzene, reflux;
vi, Bu^tOOH (→ oxirane) then PhSeH, TFAA/DMSO, NH_3-BH_3, $TfOSiMe_2Bu^t$;
vii, TFA-CH_2Cl_2

Scheme 35

A synthesis supporting a revised structure for (-)-galantinic acid has been described (Scheme 35).[296] This does not invalidate another synthesis[297] so far as its strategy is concerned, which is based on the chiral oxazolidin-2-one methodology mentioned earlier. A point of interest in this strategy[297] is the substitution of a 4-phenylthio group on the oxazolidinone by photochemical radical allylation.

Qualifying for last mention in this section, organized as it is in order of increasing separation of amino and carboxy functions, is the synthesis of cis-12-amino-9-octadecenoic acid methyl ester and derivatives, using standard functional group transformations.[298]

4.17 Resolution of DL-Amino Acids.- The main subsections of this topic remain under active investigation, and are described here as in preceding Volumes. Although resolution through chromatographic and other physical principles is included here, it is also covered in analytical terms in the later sections covering t.l.c., g.l.c., and h.p.l.c.

Classical non-enzymatic methods of resolution of DL-amino acids involve diastereoisomer salt formation (mentioned at appropriate points elsewhere in this Chapter - refs. 48, 188, are representative), or conversion into diastereoisomeric derivatives, an unusual example this year being the esterification of N-phthaloyl-β-phenyl-γ-aminobutyric acid with (R)-(-)-pantolactone.[299] A review has appeared covering the resolution of multigram quantities of enantiomer mixtures.[300]

Crystallization of the reaction mixture from DL-phenylalanine + [Cr(L-Phe)$_2$(NCS)(OH$_2$)] [i.e. aqua(isothiocyanato)bis(L-phenylalaninato)chromium] from ethanol gives successive crops of [Cr(L-Phe)$_2$(NH$_2$CS-D-Phe)(OH$_2$)] + [*fac*)-(-)$_{546}$-[Cr(L-Phe)$_3$],[301] thus achieving resolution of the DL-amino acid. Other crystallization processes based on physical phenomena, are continuing to be studied, and a Symposium Volume has been dedicated to this topic.[302] Two papers from this source deal with batch crystallization purification of L-isoleucine[303] and with growth rate and impurity occlusion in crystals of S-carboxymethyl-D-cysteine from solutions of the seeded supersaturated racemate.[304] An extension the latter study describes the promotion of crystallization of S-carboxymethyl-L-cysteine from aqueous solutions through addition of NaCl or KCl.[305] Four papers from Shiraiwa's group fall within the latter area, one dealing with the "replacing crystallization" principle and illustrated for DL-threonine solutions containing L-proline as optically-active co-solute.[306] D-Threonine of 91% optical purity crystallizes out to the extent of 78% of that available, and L-threonine crystallizes from the mother-liquors. A merging of two classical resolution methods is represented in asymmetric transformation, in which transient, racemizable

intermediates are formed as one diastereoisomeric salt crystallizes out; illustrated for (RS)-N-methyl-2-phenylglycine/aldehyde/(S)-camphor-10-sulphonic acid[307] and for the corresponding system based on (R)-α-methylbenzylamine/N-acetyl-(RS)-2-phenylglycine[308] and the 4-hydroxyphenyl analogue.[309]

An example of more interest in synthesis concerns the epimerization of β-methyl L-aspartate by heating in solution in MeCN with salicylaldehyde and (-)-PhCHMe.SO_3H, relying on the fact that the salt of the D-isomer is practically insoluble.[310]

Aminolysis of oxazolones with L-phenylalanine methyl ester continues to be studied for what is essentially an asymmetric transformation process, current results establishing that triethylamine usefully augments diastereoselectivity by increasing both racemization and reaction rates.[311] *Reductive aminolysis of 4-alkylidene-oxazolones* ("azlactones") in this way gives only 9 - 27% diastereoisomeric excesses of the D,L-dipeptide ester,[312] and little better using (R)-phenylglycine methyl ester.[313] Further results (Vol.22, p.53) concerning the asymmetric induction that accompanies the aminolysis of 2-phenyloxazolones with an L-amino acid ester[314] confirm the predominance of the D,L-dipeptide derivative in the product, even in a polar solvent, with an influence of temperature inconsistent with that reported by Benoiton ten years previously.[315]

A continuing high level of interest in uses for enzymes for "resolution" of DL-amino acids is partly explained by the growing awareness of methods by which their selectivity can be "broadened" considerably. A review of resolution by enzymes emphasizes the mechanistic organic chemistry of the process.[316] A novel demonstration of the classical use of enzymes for the present purpose is the conversion DL-histidine → D-histidine + histamine,[317] while other papers cover applications in which moderately successful processes are achieved for compounds somewhat different from the enzymes' natural substrates; such as methyl, ethyl, or butyl esters of amino acids (modest stereoselectivity using Sulfolobus solfataricus whole cells trapped in calcium alginate),[318] and Pseudomonas whole cells used for the liberation of L-cysteine from DL-thiazolidine-4-carboxylic acid.[319] A notable feature of the last-mentioned study is the inclusion of hydroxylamine to prevent further enzyme-catalyzed changes, so making this a viable process. The first illustration of the formation of D-amino acid N-alkylamides in this way from a DL-amino acid ester and immobilized D-amino acid peptidase has been reported.[320] Although no microbial methods yet exist for the isolation of L-methionine from its racemate, the process can be achieved in better than 95% yield and better than 99% enantiomeric excess by a roundabout method (via α-oxo-γ-methyl thiobutyrate) in which a cocktail containing *D-amino acid*

oxidase, catalase, leucine dehydrogenase, and formate dehydrogenase are employed.[321] Of academic interest, perhaps, is the fact that this useful method is successful also with alanine and leucine, but more important is the implication that it is applicable to any leucine dehydrogenase substrate.

The lipase-catalyzed n-butanolysis in di-isopropyl ether, of 2-phenyl-4-methyloxazol-5(4H)-one with in situ racemization of the oxazolone so as to give N-benzoyl-L-alanine n-butyl ester[322] has successfully passed referees' attention to enter the literature, though the principle was well-established many years ago for thiazolones, using trypsin.[323]

Methyl N-acetyl phenylserinate and threoninate are "resolved" by α-chymotrypsin, subtilisin, or bromelain.[324] The last-mentioned enzyme shares the preference of α-chymotrypsin for the (R)-enantiomer of the esters of phenylserine.[324] Various kinetic and structural parameters relating to the resolution of N-acetylphenylalanine ethyl ester by α-chymotrypsin have been considered.[325] A production method for L-phenylalanine[61] employs chymotrypsin resolution.

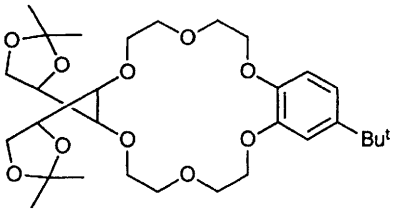
Preparative chromatographic resolution of DL-amino acids follows established methods, some of recent origin, such as use of "chirally imprinted" polymers, and others of almost antique character but of immense value, such as resolution over cellulose. The imprint generated by copolymerizing L-tyrosinyl acrylate with a large excess of vinylbenzene, followed by hydrolysis in hot aqueous NaOH to remove the optically-active ester group, binds D-4-aminophenylalanine ethyl ester in preference to its L-enantiomer, maximum selectivity from a range of experiments being 1.35:1.[326] Methacrylate analogues[327] similarly imprinted using L-amino acid anilides are found to be efficient in resolution of DL-amino acids, not restricted to the imprinting amino acid. Other chiral polymers prepared similarly, but leaving the amino acid residue in place and attached, have been used as chiral stationary phases; specifically, (R)-N-(3,5-dinitrobenzoyl)phenylglycine-derivatized polymers,[328] (S)-N-(3,5-dinitrobenzoyl)tyrosine analogues,[329] similarly-formed mixed DL-N-(3,5-dinitrobenzoyl)valine methyl ester/(S)-2-(phenylcarbamoyloxy)propionic acid n-butylamide-derivatized polymers,[330] and silica gel treated with $ClSiMe_2CH_2CH_2NHCHPhCONHPr$, formed from Me_2SiCl_2 and N-acryloyl (R)-phenylglycine n-propylamide.[331] Much debate can be noted, on the mode of action of these polymers in discriminating between enantiomers, and one of these papers describes direct spectroscopic evidence for a chiral recognition mechanism that had been proposed earlier.[332] A crosslinked polystyrene + chiral di-amine or L-proline + a Cu(II) salt combination has been used for chromatographic resolution of DL-amino acids.[333] β-Cyclodextrin incorporated into silica gel acts as chiral discriminator in displacement chromatography of

dansyl-DL-amino acids,[334] as it does when incorporated into gels for isoelectric focussing on immobilized pH gradients.[335] 2-Amino-ω-phosphono-alkanoic acid enantiomers are rather inefficiently resolved using simple crown ether-based chiral stationary phases,[336] though the more formidable crown ether (50) incorporated into C-18 silica[337] is more successful for the resolution of DL-α-amino acids. (R,R)-(-)-NN'-trans-1,2-dicyclohexyl-hexanediamine is a suitable chiral selector for the resolution of DL-amino acids and their dansyl derivatives.[338] Proteins have been advocated as chiral selectors for large-scale resolution of DL-amino acids by centrifugal partition chromatography.[339]

The ligand exchange principle, in which discrimination is exerted through competitive interactions involving an achiral stationary phase and a mobile phase containing a copper(II) - derivatized-L-amino acid complex, works well for preparative resolution of DL-amino acids.[340] Dansyl-DL-amino acids have been resolved in this way, using copper(II) - mixed o-, m-, and p-xylenyl-L-prolinates,[341] and the related "continuous counter-current fractional extraction" technique, using a two-phase system prepared from aqueous butan-1-ol and copper(II) - N-(n-dodecanoyl)-L-hydroxyproline results in a concentration of the D-isomer in the upper (organic-enriched) layer when applied to DL-valine.[342]

Returning to the long-standing method, cellulose chromatography, referred to in the opening paragraphs of this Section, the effects of salts and of added methanol, on the resolution of 5-methyl-DL-tryptophan in aqueous media, has been investigated.[343] [^{14}C]-Labelled phenylalanine and methionine have been resolved efficiently (greater than 99% optical purity) through cellulose column chromatography,[344] and N-protected DL-amino acid esters have been resolved over 6-cellulose tris(phenylcarbamate)s and 5-amylose tris(phenylcarbamate)s, the L-enantiomer emerging first.[345]

Somewhat obscure calculations are purported to demonstrate that amorphous cellulose shows 1% discrimination between the alanine enantiomers as far as the energetics of attractive forces are concerned,[346] and adsorption of L-alanine on kaolinite has been shown through SCF calculations to be favoured, relative to adsorption of the D-isomer, by 0.14 and 0.04 kJ mol^{-1} for the positive ion and for the zwitterion, respectively.[347] Interestingly, these microscopic energy differences are many orders of magnitude greater than the energy difference between amino acid enantiomers that arises from the "electroweak" parity-violating energy difference. There is some connection between the purpose of these calculations, and theories of prebiotic "resolution" of DL-amino acids, for which reviews[348] and further experimental studies have been published. In this latter category, "resolution" through the differential destruction of



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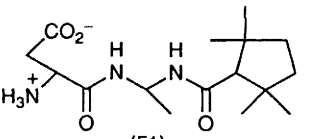

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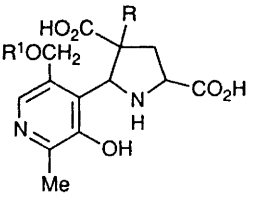

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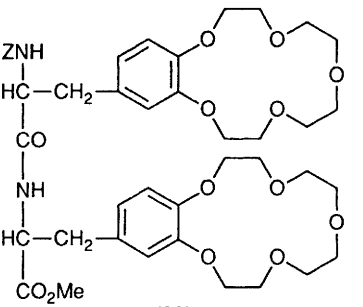

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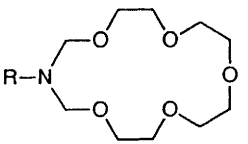
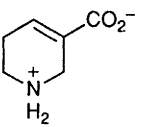


[(54) R = Z.Gly, Z.Phg-Gly, or MeO.CO.CHPh-Gly]



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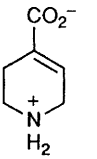

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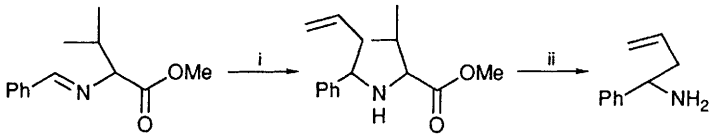
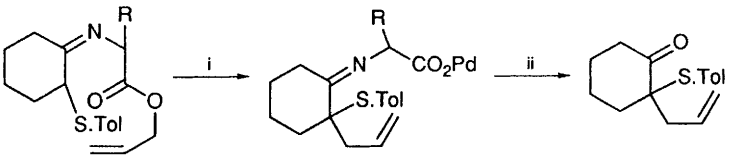


(+ 5% diastereoisomer)

Reagents: i, $CH_2{=}CHCH_2Br/TiCl_4$ (catalytic amount); ii, OH^-, then e^-

Scheme 36



Reagents: i, $Pd(0)Ac_2$; ii, hydrolysis

Scheme 37

enantiomers of an amino acid has long been speculated to accompany high-energy β-irradiation and positron annihilation. The analysis by pulse-height spectroscopy, of Cerenkov radiation emitted as β-particles pass through enantiomerically-pure samples, verifies that chiral electrons actually do distinguish between molecules of opposite chirality.[349]

5 Physico-Chemical Studies of Amino Acids

5.1 Crystal Structures of Amino Acids and Their Derivatives.- With one or two exceptions where some commentary is added, studies are merely listed as having been reported.

Protein amino acids subjected to X-ray crystal analysis are L-serine, L-cysteine, and L-cystine,[350] potassium hydrogen L-glutamate monohydrate,[351] strontium L-aspartate trihydrate and barium L-aspartate trihydrate,[352] L-asparagine monohydrate,[353] DL-lysine mono- and di-hydrochlorides,[354] DL-arginine acetate hydrate and DL-lysine acetate,[355] DL-arginine hemisuccinate dihydrate and the corresponding L-arginine salt,[356] and DL-arginine DL-glutamate hydrate and the corresponding DL-aspartate salt.[357] Compared with the L-arginine and L-lysine acetates, the DL-salts show quite different crystal structures as far as their hydrogen bonding patterns are concerned, a fact that the authors speculate might be of relevance to the prebiotic ascendancy of the L-amino acids.

N-Methyl-D-aspartic acid hydrate is an important natural protein amino acid derivative that has been included in this year's published X-ray work,[358] as has L-lanthionine.[359] X-Ray studies on derivatives that are more familiar in laboratory synthetic operations or molecular orbital studies include N-trityl-L-4-hydroxyproline methyl ester,[360] N-phenylacetyl-L-aspartic acid,[361] various N-acylureas of N-benzyloxycarbonyl-L-valine,[362] N-acetyl-DL-methionine and its calcium salt,[363] α-(N-acetylamino)-α-n-butylnorleucine,[364] and N$^{\alpha}$-acetyl-N-methyl-L-tryptophanamide.[365]

The crystal structure of the intensely sweet L-aspartamide (51), an inverso-dipeptide derivative from one structural point of view, has been reported.[366]

5.2 Nuclear Magnetic Resonance Spectrometry.- A spectacular application, 2D-COSY ^{1}H-n.m.r. assignments to cerebral metabolites L-alanine, N-acetyl-L-aspartic acid, L-aspartic acid, γ-aminobutyric acid, and L-glutamic acid, has been achieved for a living animal using

a surface coil probe.[367] Other n.m.r. papers published this year can hardly live up to that, but are worthy in their own right.

^{1}H-N.m.r. studies continue to provide practical analytical support for amino acid studies, as in assignments of absolute configuration to α-methyl α-amino acids through detection of the precise chemical shift for the methyl proton resonances in aqueous solutions containing the chiral lanthanoid shift reagent 1,2-propanediamine tetra-acetato europium(III).[368] The resonance for the (S)-enantiomer is upfield relative to that of its (R)-isomer. The enantiomeric purity of N-Boc N-methyl α-amino acid methyl esters can be assessed through Eu(hfc)$_3$-induced shift separation of the Boc and N-methyl signals.[369]

Phenacyl esters of Boc-proline, prepared from the imino acid in a one-pot procedure, exist in solutions in a 1:1-cis:trans mixture.[370] Magnetic asymmetry is revealed for the phenacyl group in this study. Similar cis:trans-mixtures occur for 3-benzamido-2-piperidonecarboxylic acid, which adopts a distorted chair conformation in dimethyl sulphoxide-$^2H_6$.[371] Higher up the sophistication scale, conformational assignments have been made to N-benzoyl-L-phenylalanine through combined rotation and multiple pulse ^{1}H-n.m.r. (CRAMPS).[372] N.m.r. spectra of N-acetyl N'-methylamides of aliphatic amino acids, a well-studied category of compound for molecular orbital calculations, have been analyzed after specific ^{13}C-labelling of the carbonyl carbon atom, in terms of the dependence of $^3J_{HNC\alpha H}/^3J_{C'NC\alpha H}$ values on the dihedral angle Ø.[373] The dihedral angle increases regularly with increasing side-chain bulk.

^{1}H-N.m.r. data show that caffeine stacks in a parallel ("pack of cards") fashion with L-tryptophan in a 1:1-ratio in aqueous solutions (as it does with several other more-or-less two-dimensional heteroaromatic species).[374] Establishment of the existence of intermolecular structuring of this sort, both between different molecules and between two or more identical molecules, is a continuing feature of n.m.r. studies of amino acids that has been extended to mono- and di-thiocarbonyl analogues of methylamides of N-acylamino acids and dipeptides.[375] The intramolecular hydrogen bonding patterns in N$^\alpha$-thioacetylproline methylamide have been located through a combination of i.r., ^{1}H- and ^{13}C-n.m.r. in this study.

^{13}C-N.m.r. spectra of strategically-^{13}C-labelled L-lysine[232] have established the correct assignments for β- (31.2 ppm) and δ- and ε- (27.6 ppm) side-chain resonances hitherto thought to be the other way round. Synchronous ^{13}C-/^{15}N-n.m.r. monitoring has been used to follow the metabolism of [1-^{13}C,^{15}N]glycine on whole liver cells, through the development of serine resonances.[376] In CP-MAS ^{13}C-n.m.r. of polycrystalline L-leucine, the splitting of the β-carbon resonance is due to site differences in the $P2_1$ unit cell, not to long range residual

dipolar ^{14}N - ^{13}C coupling.[377] ^{17}O-N.m.r. spectrometry has also been applied to polycrystalline L-leucine with a view to establishing hydrogen bonding patterns.[378] A more familiar ^{17}O-n.m.r. application in the amino acids field is the measurement of spin-lattice relaxation times T_1 for $H_2{}^{17}O$, as a function of structure for apolar amino acid solutes and various physical parameters of the solutes.[379]

^{19}F-N.m.r. data for 1:1-inclusion complexes of N-trifluoroacetyl-D- and -L-4-fluorophenylalanines and -phenylalanines with cyclomaltahexaose (alias α-cyclodextrin) have been reported, contributing to understanding of the penetration and relative geometry of the aryl moiety into the cavity of the host.[380]

5.3 Optical Rotatory Dispersion and Circular Dichroism.- A careful study of the c.d. of L-phenylalanine, compared with that of (R)-3-amino-4-phenylbutanoic acid, has been reported.[381] The two compounds, though of the same configurational family, show oppositely-signed ^1L_a Cotton effects associated with the phenyl chromophore, and caution is advocated for empirical configurational assignments based on the sign of a 200 - 400 nm Cotton effect developed in a phenyl chromophore perturbed by a β-chiral centre.

5.4 Mass Spectrometry.- Excluding routine results, and leaving analytical studies such as g.l.c. - m.s. of derivatized amino acids to a later section, results cited here relate to pioneering m.s. studies of the amino acids and their significant reactions.

Negative ion m.s. of deprotonated amino acids have been interpreted in terms of specific H^+ transfers to carboxylate anions followed by simple fragmentation processes through ion complexes.[382] Positive ion m.s. studies for 2-amino-alken-2-oic acids ("dehydro-amino acids") have been reported.[383]

DL-γ-Carboxyglutamic acid reacts with pyridoxal phosphate in water to give (52; R = H or CO_2H), identified by FAB-m.s. more conveniently than other derivatives and therefore proposed to have potential analytical value.[384]

5.5 Other Physico-chemical Studies.- Spectroscopic studies, using techniques in addition to those (n.m.r., o.r.d./c.d., and m.s.) specifically located in sections preceding this one, continue to be applied in amino acids science, but are either too routine to deserve citation here, or arise in isolated, pioneering, papers; and are therefore discussed here. Photo-electron He(I)- and He(II)-spectroscopic studies of N-acetyl dehydroalanine methylamide[385] with objectives in conformational assignments, and i.r. and p.e. spectroscopy of glycine, L-alanine and β-alanine on a copper surface[386]

have been reported. U.v. Resonance Raman saturation spectroscopy, a new technique concentrating on relaxation measurements with associated vibrational band resolution, has contributed a new aspect to the very substantial body of Raman data on tryptophan and its derivatives,[387] together with data on u.v. resonance Raman excitation profiles of this amino acid.[388] Sub-picosecond fluorescence anisotropy of tryptophan in water,[389] and the underlying cause of oscillating absorption and fluorescence of tyrosine in water,[390] have been studied.

As with some of the papers mentioned in the preceding paragraph, many of the papers located in this section are aimed at providing information of use in understanding the reaction behaviour and particularly, aspects of the physiological properties of amino acids. This is particularly clear with adsorption and other more obvious transport properties, such as calorimetric studies yielding heats of dilution, from which chiral interactions involving protonated amino acids in aqueous hydrochloric acid may be deduced.[391] Dilution enthalpies thus obtained are identical for such solutions containing only one enantiomer or containing both enantiomers of an amino acid. Therefore, the recently uncovered evidence that there is a greater attraction between an L- and a D-enantiomer of an amino acid in aqueous solution than between two enantiomers of the same configuration is deduced to involve the zwitterionic forms of the amino acids. Enthalpies of dilution of solutions of N-acetyl N'-methylamides of D- and L-amino acids with alkyl side-chains[392] and for L-serine, L-threonine, and hydroxy-L-proline and their enantiomers.[393] The same data have been collected for glycine, alanine, valine, leucine, proline, sarcosine, and N-methyl-alanine in aqueous media,[394] (see also ref. 395) confirming that interaction between an L-amino acid derivative with its D-enantiomer is significantly less exothermic than that between two identical molecules. L-Phenylalanine – α-cyclodextrin inclusion complexation[396] has been studied, and thermodynamic data relating to 298.15K, for stable 1:1-amino acid : "Cryptand 222" complexes[397] formed in methanol have been reported. Within this same topic area, but with quite a different objective, is the thermoenergetic identification of enantiomers, through study by n.m.r. and differential scanning calorimetry, of D- or L-amino acid:sodium chloride:water eutectic mixtures.[398] The abstract source of this information leaves the scientific basis of this study unfathomable. Hydrophobic interactions have been shown to be the basis of complexation of amino acids by the water-soluble porphyrin, 5,10,15,20-tetrakis(4-sulphonatophenyl)-21H,23H-porphine.[399]

New clarity is provided for mechanisms of amino acid transport by demonstrations of the effectiveness of the chiral 15-crown-5-ether (53)[400] and of lariat-type ligands (54)[401] in carrying protected DL-amino

acids through CH_2Cl_2 and $CHCl_3$ membranes, respectively. Potassium salts of dipeptides were also suitable passengers in the latter study, in which the L-enantiomers of Z-amino acids were favoured, though minimal enantioselection was observed in the former study. Studies of this type can lead to useful practical advances, through establishing means by which amino acids can be taken into organic solutions. At the extreme limit of this process is the solubilization of tryptophan and proline in ethane and propane through the use of reverse micelles in the supercritical fluids,[402] while the possibility of enriched concentrations of amino acids at phase interfaces through adsorptive bubble separation in aqueous media by foam flotation has been theoretically modelled.[403] Concentration of amino acids at interfaces, detected by oriented crystallization,[404] may have important implications. Liquid emulsion membranes have been devised for the separation and concentration of amino acids using di-(2-ethylhexyl)phosphoric acid as cation carrier.[405] At another level of thinking, helical bilayer membranes can be formed from L-glutamic acid derivatized with bis(dodecylamide) groups.[406]

Adsorption of amino acids and their derivatives from solutions has been studied for hydroxylapatite (aspartic acid, lysine, alanine; see also Vol.22, p.2),[407] for silica gel (glutamine, methionine, phenylalanine, and tryptophan),[408] and for an aminocarboxy-cellulose-based ampholyte.[409] The object in these studies has a practical preparative side to it, and the preferential adsorption of one enantiomer of an amino acid has been a topic of long-standing study in relation to prebiotic chemistry (see also Section 4.17 Resolution of DL-Amino Acids). Adsorption isotherms of N-benzoyl D- and L-alanine at different temperatures allow enthalpy of adsorption data to be established. For a protein, these data give support to a bimodal retention mechanism for the enantioselection.[410]

More academic studies concern relationships between structure and pK values, for α-trifluoromethyl-α-amino acids (lowering of pK values for CO_2H and NH_3^+ groups).[411] L-Alaninehydroxamic acid shows a higher pK value for its NH_3^+ group than for its other acidic group, but the order is reversed for the corresponding *β*-alanine derivative.[412] As well as the usual potentiometric methods, ^{13}C-n.m.r. data were also employed in this study. Routine evaluation of acidity constants of amino acids[413] and dissociation constants of DL-amino acids in aqueous dioxan (cf. Vol.22, p.45, ref.298) has been reported.[414] Activity coefficient data confirming the destabilization of an amino acid through transfer from water to aqueous alcohols.[415] A purely theoretical study has been completed, modelling the effects of temperature and of pH on the solubility of an amino acid in water, with reference to activity coefficient data.[416]

5.6 Molecular Orbital Calculations.- Theoretical studies dealing with amino acids fall into categories of conformational analysis on the one hand, and calculations of physical parameters on the other. The conformational theme continues to dominate this group of papers, with protein amino acids being represented as zwitterions in the gas phase (glycine, alanine, and serine),[417] and in less specific situations (L-cysteine,[418] and L-arginine and its des-amino analogues[419]). Atom-centred partial charges have been calculated for amino acids.[420]

Conformations of amino acid residues in peptides and proteins are modelled by N-acetylamino acid methylamides, and new calculations of conformational energies have been reported.[421] N-Formyl-L-serinamide has been treated in a similar way.[422] Calculations of entropy and solvent effects on conformational energies have been reported for some conformations of N-acetylalanylglycinamide,[423] and for hydration energies of the twelve lowest energy conformations of N-acetylalanine methylamide.[424]

These same methods and objectives have been applied to non-protein amino acids too, dealing with the identification of the most stable conformation for L-2,4-di-aminobutanoic acid[425] and β-alanine.[426] Conformational calculations for γ-aminobutyric acid have been matched with those for two compounds that inhibit its neurotransmission properties [guvacine (55) and isoguvacine (56)].[427]

A summary has appeared of molecular dynamics simulation of the conformational behaviour of dityrosine in an attempt to account for its non-exponential fluorescence decay.[428] Calculated energy barriers relating to the diphenyl moiety of thyroxine are in qualitative agreement with those measured from n.m.r. data.[429]

6 Chemical Studies

6.1 Racemization.- Microwave irradiation of solutions of isoleucine and phenylalanine in acetic acid leads to quantitative racemization.[430] Slow acetylation of amino acids in acetic acid was established long ago, and it remains unclear how these results should be interpreted. The racemization of L-proline as a component in milk subjected to microwave treatment is a cause of anxiety because D-proline is known to be toxic.[431] Rate studies have been reported showing the effect of neighbouring functional groups on the racemization of βγ-unsaturated amino acids in acetic acid.[432] (E)-2,4-Di-aminobuten-3-oic acid racemizes somewhat faster than its N^4-benzyloxycarbonyl derivative, but both racemize at rates several orders of magnitude faster than 3,4-dehydrovaline. All these racemize more readily than ornithine and

norvaline. The pH - rate profile for the racemization of L-5-benzylhydantoin demonstrates catalysis by hydroxide ion.[433]

L-Phenylalanine, -leucine, -isoleucine, and -tyrosine subjected to high pressure (several GPa) at ambient temperatures, undergo substantial racemization.[434] Positive catalysis by minerals used as supports for the amino acids is observed, with silica gel and alumina inducing the greatest rate enhancements. Results such as these fuel the controversy over applications of racemization levels of amino acids in fossils as a date index, but those proponents of the method can point to careful calibration of their results that tends to promote their credibility. An interesting example is the finding that ancient eggshell samples for the African ostrich (Struthio camelus) retain their indigenous organic matrix, and their L-isoleucine:D-alloisoleucine ratio can be used to date Pleistocene archaeological sites.[435] Fossil bones from two sealed catacombs in Rome dating to the 4th Century BC provide ideal samples for calibrating the L-aspartic acid racemization scale, since constant temperature and humidity conditions have prevailed, and the sites are presumed to be free from human contamination. Relatively high D-aspartic acid content was found, showing that bone collagen decomposes and racemizes faster in conditions of high humidity.[436] A new study (see Vol.22, p.47) of the dating of human remains through the D-aspartic acid content of dental collagen (alias dentin) based on teeth from 18th and 19th Century burials gives good agreement with known interment dates.[437] A feature of this study, from the point of view of analytical chemistry, is an improved derivatization procedure using D-leucine N-carboxyanhydride, to provide the diastereoisomer mixture from which D:L-aspartic acid ratios are obtained. The amino acids in tooth enamel of a 230,000 y fossil (from the Hexian-Man site, Anhui Province, China) show a quite different profile from that of a modern mammal tooth,[438] implying that caution is required in interpreting amino acid data in any context for very old fossils.

6.2 General Reactions of Amino Acids.- Reactions at the amino and carboxy groups (or at both) are covered in this section; the following section is devoted to papers that deal exclusively with side-chain processing.

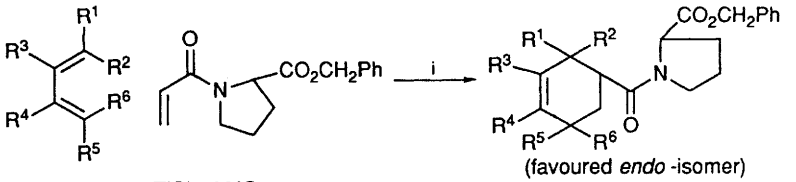
Thermal decomposition of amino acids has featured in this section in earlier years, the interest being in the nature of the pyrolysis products. A current example is the formation of pyrroline-2,5-dione and its 3-methyl and 3,4-dimethyl analogues when aspartic acid is maintained at 220° at 10 mm Hg pressure under nitrogen.[439] Asparagine behaves similarly but seems to undergo degradation at a slower rate. A study by thermogravimetry and differential scanning calorimetry of the

thermal stability of representative amino acids has been completed, with no product information.[440] At a more energetic level, irradiation of alanine with 200 KeV helium and argon ions leads to breakdown into H_2, NH_3, CO_2 and hydrocarbons.[441]

Solubilization of amino acids in organic solvents has been claimed for tetrabutylammonium salts formed by evaporating aqueous solutions of amino acids neutralized with tetrabutylammonium hydroxide.[442] Perhaps this is a good example of a short communication providing too few details, since attempts by some of us to reproduce the results are not successful.

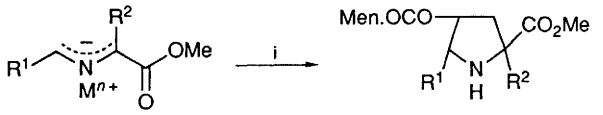
Water-soluble acylating agents p-R.CO.O.C_6H_4.SMe_2^+ $MeSO_4^-$ continue to be advocated (see Vol.21, p.46) for clean N-acylation of amino acids (that is, avoiding the involvement of the carboxy group in mixed anhydride formation, and its consequences).[443] A simple preparation of t-butyl fluoroformate starts from a 1-chloroethyl carbonate - an unusual example of a conversion of an ester into an acid halide.[444] This reagent makes the economics of large-scale preparation of Boc-amino acids more attractive, particularly because of the higher stability of the reagent (it does not react with DMF or DMSO).[445] More familiar acylating agents are used for preparing N$^{\alpha}$-urethanes from L-histidine methyl ester, and this is described in a useful practical account that includes an ion exchange purification procedure for the products.[446]

Other reactions at the amino group include allylation (O-protected tyrosine gives the N,N-diallyl derivative with allyl bromide),[447] and t-butoxycarbonylation [to give N,N-bis(t-butoxycarbonyl)amino acid esters through exhaustive acylation].[448] These bis(Boc)amino acids, converted into active esters, are slow to couple in peptide synthesis and show an enhanced tendency towards hydantoin formation. The NN-bis(diformyl) homologue accompanies N-formylglycine t-butyl ester, when prepared through standard reactions.[449] Stereospecific decarboxylative allylation of N-benzylidene-L-valine methyl ester using allyl bromide catalyzed by $TiCl_4$ with electrolytic cleavage of the valyl chiral residue leads to (S)-2-phenylallylamine (Scheme 36).[450] Stereoselective allylation of aldehydes and ketones can be accomplished through converting the carbonyl compound into its imine with an L- or D-amino acid allyl ester, followed by Pd-catalyzed rearrangement (Scheme 37).[451] There are numerous examples in this year's literature, as in earlier years, of the use of homochiral amino acids in stereoselective synthesis, another example of the type being Lewis acid-catalyzed Diels-Alder reactions (Scheme 38).[452] Reactions under the general heading of N-alkylation include reductive condensation ($NaBH_3CN$) with a ketone, illustrated for "N-menthylation" using menthone,[453] and reaction with malonaldehyde (studied more from the point of view of determining enthalpies of interaction).[454]



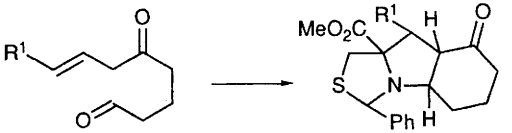
Reagents: i, 1 eq. $TiCl_4$, 20°C

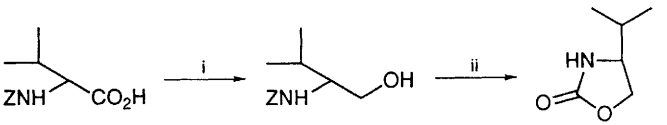
Scheme 38



Reagents: i, menthyl acrylate

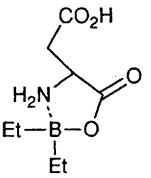
Scheme 39



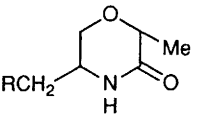


Reagents: i, BH_3-THF; ii, trace Bu^tOK, Δ

Scheme 40



(58)



(59)

A curious pathway is described[455] for the otherwise routine reaction of glycine with 2,4-dinitrochlorobenzene in the presence of $KHCO_3$, followed by nitration to give N-trinitrophenylglycine, purportedly via the N-nitro compound.

Further studies of 1,3-dipolar cycloaddition reactions of amino acid imines continue to reward the research groups responsible for current knowledge of their wide range of synthetic applications. The course of new proline syntheses involving metal ion-catalyzed asymmetric 1,3-dipolar cycloadditions to imines formed with menthyl acrylate, is determined by the metal chosen; Ag(I), Li, and Tl(I) salts direct the reaction to one regioisomer, while Ti(IV) salts give the other (Scheme 39).[456] Similar results and the same conclusion have been described for the cycloaddition of N-titanated azomethine ylides from t-butyl benzylideneamino-acetate to αβ-unsaturated esters, compared with lithium analogues.[457] Very high diastereofacial selectivity is seen in all these processes, with four contiguous chiral centres being generated when αβ-unsaturated esters of optically-active amino acids are used, and after the chiral auxiliary has been removed.[458] Intramolecular cycloaddition of azomethine ylides from 5-oxo-6-heptenals or 4-oxo-5-hexenals and methyl 2-phenylthiazolidine-4-carboxylate illustrates this point, with the formation of (57).[459]

3,4-Dehydroprolines are formed through cycloaddition of arylidene-imines of amino acid esters to alk-2-ynoic esters.[460] Imines formed between 1,8-di-azafluorenone and amino acids proceed along the newly-established ninhydrin pathway via azomethine ylides (Vol.22, p.49) to give a red fluorescent dye, of forensic use for detecting latent fingerprints since it is substantially more sensitive than ninhydrin for this purpose (and for the purposes of mainstream amino acid analysis).[461] Fluorogenic labelling of amino acids at their NH_2 groups can be efficiently accomplished using N-chloroformyl carbazole.[462] An unusual reaction at nitrogen is "borylation"; $R'B{=}NBu^t + NH_2.CHR^2.CO_2R^3 \rightarrow Bu^tNH.BR'.NH.CHR^2.CO_2R^3$.[463]

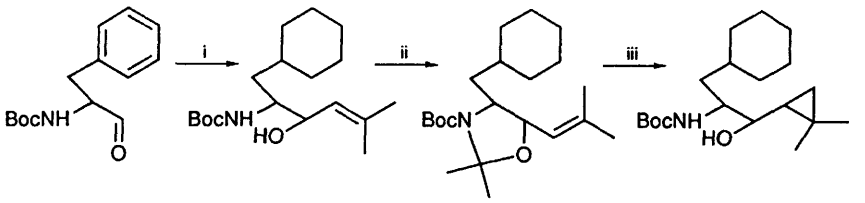
The flexible use of standard N-protecting groups has been extended with new reagents; $ZnBr_2$ in CH_2Cl_2 offers a useful mild means for selective Boc removal from secondary amines,[464] though it is difficult to imagine that familiar methods in use for 60 years for benzyloxycarbonyl group cleavage will be abandoned in favour of a 10 - 36 hour procedure using a 10-fold excess of $BF_3.OEt_2$/EtSH![465]

Oxidation studies of α-amino acids and their derivatives are as voluminous as ever, and while some routine work deserves to be mentioned, what is here is representative of a much larger body of effort. A study of electrogenerated manganese(III) sulphate for oxidation of L-histidine in aqueous H_2SO_4[466] and of alkaline $K_3[Fe(CN)_6]$ oxidation kinetics for lysine, arginine, and histidine have been

described.[467] There are common features in studies of oxidative decarboxylation of amino acids by N-chlorosuccinimide in aqueous alkali,[468] by N-chlorobenzamide in aqueous perchloric acid, catalyzed by Cl^-,[469] and the kinetics of the decomposition of N-chloroamino acids in aqueous solutions (pH 6 - 13).[470] There is considerable preparative value to be had from oxidative decarboxylation of amino acids, shown in a preparation of α-amino phosphonic acids through $Pb(OAc)_4$ treatment followed by reaction with $(MeO)_3P/TiCl_4$; N-acylamino acids give roughly 50:50-mixtures of 1-acylamino-1-acetoxyalkanes and their hydroxy analogues when treated with $Pb(OAc)_4$ in DMF.[471] This process is related to the increasingly-useful anodic oxidation of L-N-acylamino acids in methanol to give 1-methoxy analogues of the lead tetra-acetate reaction products, de-methoxylated by Et_3SiH/Lewis acid to give the corresponding optically-active amine.[472]

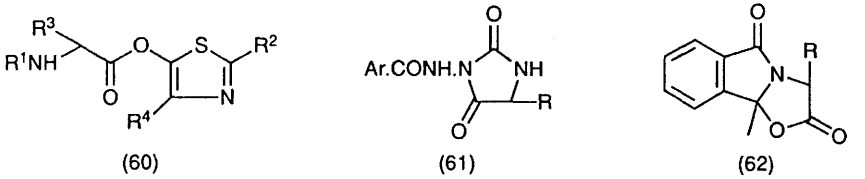
Carboxy-group processing in more explicit forms is seen in racemization-free reduction of esters to alkanols with sodium acetoxyborohydride in dioxan at elevated temperatures,[473] and with di-isobutylaluminium hydride, of a Z-amino acid methyl ester[474] or of an N-benzylidene-amino acid ester,[475] followed by a Grignard reagent to give threo-2-aminoalkanols. This last-mentioned example proceeds via the aldehyde, a class of compound with increasing value in synthesis for which an Organic Syntheses procedure using $LiAlH_4$ for the conversion Boc-L-Leu-NMe.OMe → Boc-L-leucinal *will be found useful*.[476] An improved $LiAlH_4$ reduction of phenylalanine to phenylalaninol has been reported.[523] The Evans chiral auxiliary (S)-4-isopropyloxazolid-2-one (cf. Scheme 40) is easily prepared from Z-L-valine through BH_3-THF reduction to the valinol, followed by thermal cyclization using a trace of Bu^tOK.[477] Selective reduction of the α-carboxy group of L-aspartic acid involves first, formation of the boroxazolidinone (58) with BEt_3 in refluxing THF followed by BH_3-THF reduction at 0°, cyclisation to L-homoserine lactone occurring with HCl.[478] This is a convenient route that is also adaptable for ^2H incorporation. B_2H_6 Reduction of N-Boc L-glutamic acid diethyl ester to the glutaminol provides a synthon for chiral lignan lactones [e.g. (-)-ninokinin].[479] Selective protection of the α-carboxy group of aspartic acid via oxazolidinone formation with formaldehyde allows elaboration of the side-chain carboxy group leading to (S)-2,3-di-aminopropanoic acid via the N-Boc-oxazolidinone.[480]

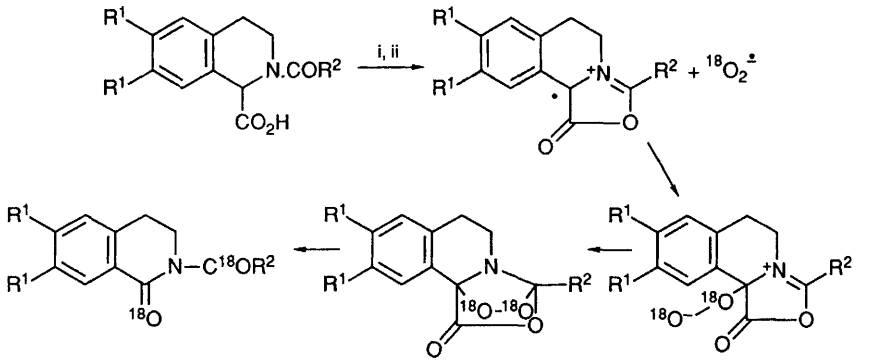
Employment of amino-alkanals in the synthesis of statines and pseudopeptides, among others, has been mentioned earlier in this Chapter, and further illustrations are the use of Boc-L-prolinal in a synthesis of muscarinic agents (starting with -CHO → -CH=CBr_2),[481] a use of Boc-L-phenylalaninal leading to conformationally-restricted transition state analogues (Scheme 41),[482] and stereoselective formation of cyanohydrins, to be converted into homochiral 3-amino-2-



Reagents: i, $Me_2C{=}CHMgBr$; ii, $MeCH{=}CHOMe$; iii, $N_2CH.CO_2Bu^t$

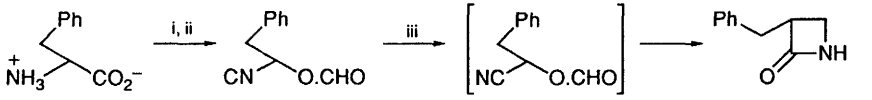
Scheme 41





Reagents: i, DCCI; ii, $^{18}O_2$

Scheme 42



Reagents: i, $LiAlH_4$; ii, $POCl_3$, Pr^i_2NH; iii, 585°C, 10^{-4} Torr

Scheme 43

hydroxyesters via the derived imidate hydrochloride.[483] Reduction with $NaBH_4$ in THF or MeOH, of mixed anhydrides formed from N-protected amino acids, is a convenient route to 2-amino alcohols.[484] Conversion of optically-pure morpholinones (59) formed from N-acylated aminoalkanols, into imino-ethers leads on to ring-opening possibilities (giving depsipeptides) and the process emphasizes that mild cleavage of lactams is practicable.[485] Ethyl N-alkenylpyroglutamates have been subjected to a comparative study showing that reduction with $LiBH_4$ gives poor results, with $LiAlH_4$ – silica gel coming out best.[486]

Renewed interest in uses for N-protected α-aminoacyl halides, particularly in peptide synthesis, has led to further exploration in their preparation. Fmoc-Amino acid fluorides are easily prepared using cyanuric fluoride, a procedure that is compatible with the presence of many side-chain functional groups protected, for example, as their Boc or t-butyl derivatives.[487] Pd-Catalyzed coupling of an N-protected L-prolyl chloride with vinylstannanes provides the corresponding N-protected α-amino αβ-unsaturated ketones.[488] Other types of acylating agents reported in the year under review include triazolides formed between an Fmoc-amino acid and 2,4,6-mesitylenesulphonyl-3-nitro-1,2,4-triazolide (used for coupling the first residue on to a polymer hydroxymethyl group in solid-phase peptide synthesis),[489] imidazolides,[490] and N-acylthiazolidine-2-thiones.[491] Unstable mixed anhydrides formed from N-protected amino acids and isopropenyl chlorocarbonate are effective esterification agents towards alcohols if 4-dimethylaminopyridine is employed as catalyst;[492] and because of this, racemization must be accepted as a side-reaction.

Esters of N-protected amino acids fall into two categories for the purpose of this review; either as acylating agents ("active esters"), or as substrates for mechanistic studies concerning ester hydrolysis or transesterification. In the former category are Fmoc amino acid pentafluorophenyl esters, conveniently prepared using pentafluorophenyl trifluoroacetate,[493] and N-[α-(N'-benzyloxycarbonylaminoacyl)]-N-arylhydroxylamines, for which an N- → O-acyl transfer has been studied as a model for the transformation in vivo of arylamines into "ultimate carcinogens".[494] β-Cyanoethyl esters are little-used as active esters but possibilities are offered for transformations of aspartate derivatives by the sequence Boc.Asp.OCH_2CH_2CN → Boc.Asp(OR).OCH_2CH_2CN → Boc.Asp(OR).OH using piperidine in MeCN for the ester cleavage.[495] Thiolacids are, in their way, activated forms of carboxylic acids, and Z.Ala.SH is a substrate for papain for peptide synthesis (though poor yields are secured with isoleucine and with β-t-butyl aspartate derivatives).[496]

A new class of active esters has been studied as models for the putative oxazolone self-acylation product (60; O in place of ring S, R^1

= R^2, R^3 = R^4), that constitutes a novel racemization mechanism applicable to the methodology of peptide synthesis.[497] Hydrazinolysis of these thiazol-5-yl esters (60) displaces the prochiral leaving group in optically-active form, the first evidence for synchronous proton-capture from the incoming amine by the leaving group in aminolysis of active esters (several authorities[8,9,499] have written the aminolysis mechanism for certain active esters as an electrocyclic process, without evidence). New vinyl esters $ZNH.CHR^1.CO_2.C(=CH_2)CR^2=CH_2$ are obtained by $RuCl_2(PMe_3)$(p-cymene)-catalyzed addition of a Z-amino acid to the corresponding alkyne.[499] Photo-cleavable 2-nitro-4,5-dimethoxybenzyl esters prepared from the corresponding bromide and a Boc-protected neurotransmitter amino acid are of potential value for release at receptor sites.[500]

Acyl migration giving β-(5-hydroxy-4-pivaloyloxyphenyl)-L-alanine accompanies the hydrolysis of the catechol mono-ester of N-pivaloyl-L-DOPA.[501] The rearrangement product exists as an equilibrium mixture with its 3-pivaloyloxy isomer in solution.

Esters of L-DOPA are formed through α-chymotrypsin-catalyzed transesterification in organic solvents, of other amino acid esters; yields no greater than 50% are obtained using various alcohols as acyl acceptors.[502] Accelerated esterification of amino acids has been reported using lipoglycosylated α-chymotrypsin in polar solvents,[503] and esterases of various sorts catalyze the transesterification of N-benzyloxycarbonyl-L-tyrosine p-nitrophenyl ester with methanol.[504] L-Amino acid - ZnO catalysts bias the methanolysis of DL-amino acid active esters in favour of the D-enantiomer.[505]

Continuing a general theme of growing interest in recent years, and implicit from the preceding paragraph, the rate of chiral micelle-catalyzed hydrolysis of N-dodecanoyl-L-phenylalanine p-nitrophenyl ester is more than 19 times faster than for its enantiomer, when co-aggregates of phosphatidylcholine, Triton X-100, and Z-L-Phe-L-His-L-Leu-OH are present.[506] The topic is full of apparent uncertainties; there are remarkable substituent effects when the isomeric nitrophenyl groups are substituted for the generally-used p-isomer,[507] and rates are dependent upon the ionic strength of the medium.[508] The hydrolysis is inhibited by flavanoids present in the micelles.[509] An identical study, though using the β-cyclodextrin - Z-L-His-OH inclusion complex, demonstrated diminished rates though the hydrolysis was enantioselective.[510]

Cyclization reactions via derivatized amino acids, requiring the involvement of both amino and carboxy groups, are represented in the formation of imidazolin-2,4-diones (61) from L-amino acids and 2-phenyl-1,3,4-oxadiazolin-5-ones in m-cresol at 150°C,[511] and in the formation of novel benzo-fused tricyclic oxazolidinones (62) through

condensation of L-amino acids with o-acetylbenzoic acid.[512] The latter study corrects an earlier mis-assignment of an oxazolone structure to these products.[513] 4-Acylation of oxazolones formed between an N-benzoylamino acid and a fluoralkanoic anhydride (the Dakin-West reaction) has been illustrated further as a means of synthesis of N-α-acylaminoalkyl fluoroalkyl ketones through decarboxylation in oxalic acid.[514] Imino acids yield mesoionic oxazolones that are prone to autoxidation; ^{18}O-labelling studies (Scheme 42) have clarified the course of this reaction.[515]

Thiohydantoins are available from N-acylamino acid vinyl esters (as formed from the acid by reaction with Woodward's Reagent K) by condensation with trimethylsilyl thiocyanate in MeCN.[516] N-Alkoxycarbonyl oxazolidin-2,4-diones (alias N-carboxyanhydrides, NCAs), hitherto considered to be somewhat fragile, are accessible through careful operation of a previously-established procedure.[517] An illustrative procedure showing the usefulness of Fmoc-L-leucine-NCA in solid-phase peptide synthesis amounts to a trouble-free derivatization of the Rink resin.

Maillard reactions (condensation of an amino acid with a carbohydrate) involve a more complex pathway than any other amino acid reaction - or more correctly, more complex families of pathways, since the reactions lead to a variety of products. Part of the problem of studying this system lies in the lability of the initial products, and the glycine - glucose reaction buffered at pH 7 has been studied using a trapping technique. Initially-formed aldehydes or ketones give benzimidazoles with o-phenylenediamine, and a lactic acid ester and two furanolactones were identified through their derivatives.[518] The presence of sulphite is said to inhibit the Maillard reaction, but this is loose talk for stating that the system is diverted along another pathway; thus, glycine and glucose give 3,4-dideoxyhexosulose-4-sulphinic acid instead of the normal 3-deoxyhexosulose.[519] S-Alkyl-L-cysteines react with D-glucose to give alkylpyrazines - a common class of Maillard product - and 2,4-bis(propylthio)butanal and an unprecedented 2,4-bis(propylthio)but-2-enal.[520] Of course, numerous other compounds accompany these, and (given the fact that many of the research groups working on this reaction are based in food research) some of these are described as "useful flavour compounds". The tryptophan - glucose system would be expected to involve further complexities, and breakdown of the Amadori rearrangement product that appears early in the pathway (leading to hydroxymethylfurfural, maltol, tryptophan, indole, norharman, and harman) has been subjected to kinetics study at 110° and at 140°.[521] H.p.l.c. study of this Amadori rearrangement product itself shows that various tautomeric carbohydrate moieties are involved (α- and β-furanoses and -pyranoses, as well as

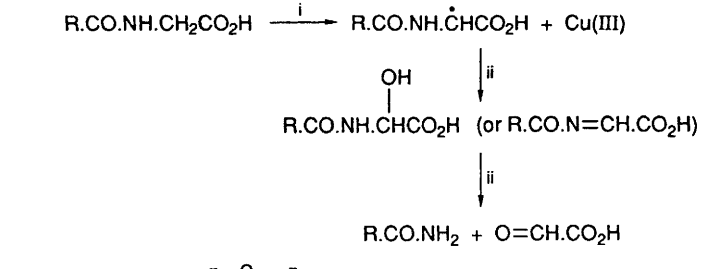
open-chain isomers including ketoses).[522] H.p.l.c. has been brought to bear on the preparative-scale isolation of the major browning compound from the lysine - glucose reaction,[523] and at the opposite end of the scale, capillary zone electrophoresis profiles have been reported for the Maillard reaction products of ribose with glycine, alanine and leucine.[524]

β-Lactams provide the target for much of the research involving β-amino acids, and conversely, their availability through cycloaddition processes provides a useful means for the synthesis of this class of amino acid. The latter aspect has been covered in the earlier section 4.16, and methods for the cyclization of β-amino acids continue to be developed, with ever more unusual reagents ethyl dichlorophosphate and phenylphosphonic dichloride,[525] 1-(methanesulphonyloxy)-6-trifluoromethylbenzotriazole,[526] and diethyl 2-(3-oxo-2,3-dihydro-1,2-benzoisosulphonazoyl) phosphonate.[527]

N-3-(Haloacyl)-α-and β-amino acids $ClCH_2.CRMe.CO-X-OH$ (X = Gly, Val, Trp, or β-alanine) can be cyclized in aqueous NaOH in an unusually facile reaction leading to 3-methyl 3-substituted β-lactams.[528] α-Amino acids provide a chiral source for enantiomerically-pure β-lactams through application of the isonitrile - nitrile rearrangement (Scheme 43); if the intermediates can survive the drastic conditions required (585°C, 10^{-4} Torr), the flash pyrolysis can be performed on 20g batches![529]

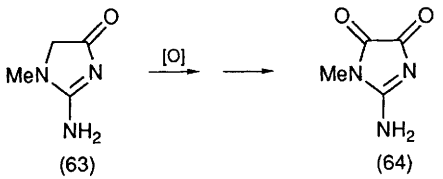
6.3 Specific Reactions of Amino Acids.- The perennial problem (faced particularly in this Section), of grouping material in one part of this Chapter, that could be equally well placed in some other part (or parts), is not solved easily if repetition is to be avoided. Thus, reactions that modify amino acid side-chains amount to the synthesis of one amino acid from another, and could have been described in an earlier "Synthesis" section. However, such work is covered here if it is of a self-contained nature, but reactions that have developed into general synthesis methods are mentioned in the earlier Section 4.1.

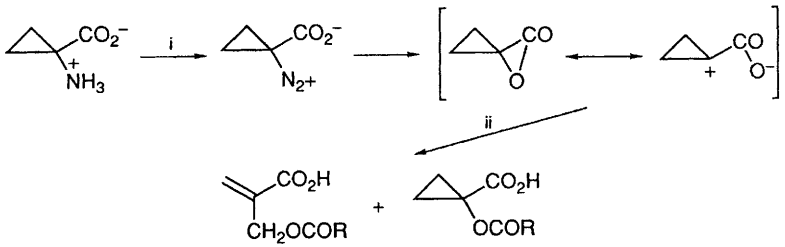
Interesting developments in mild oxidation of acylamino acids as models for the processing that occurs at the C-terminus of a peptide so as to give the amide, have been described for copper(II)-mediated oxidation of N-acylglycines (Scheme 44).[530] The work supports a non-enzymatic oxidative mechanism for peptide amidation that was advocated some time ago.[531] Oxidative processing of the glycine derivative, creatinine (63), to give the ring-opened product $MeNH.C(=NH)NH.CO.CO_2H$ has been re-investigated to assign the correct structure (64) to the re-cyclized intermediate, rather than the isomeric imidazolidinedione structure previously allocated.[532]



Reagents: i, Cu(II) $\xrightarrow{e^-}$ $\xrightarrow{O_2}$ $\xrightarrow{e^-}$ Cu(II)OOH/(IV)=O; ii, H_2O

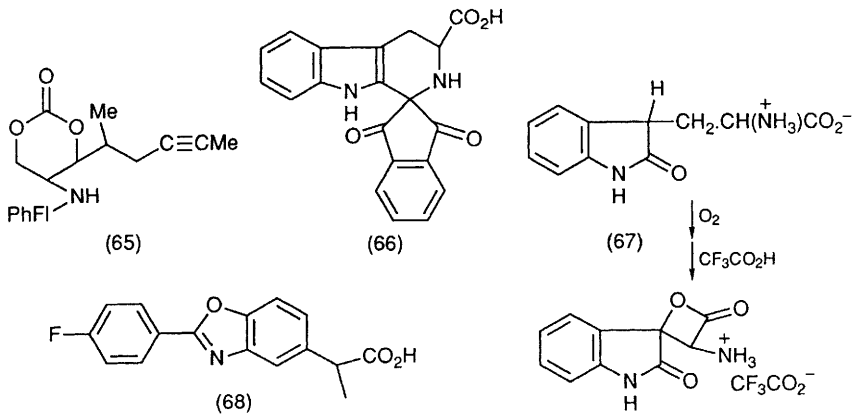
Scheme 44





Reagents: i, $NaNO_2$, RCO_2H, H_2O; ii, RCO_2H

Scheme 45



N-Bromosuccinimide treatment of methyl esters of N-phthaloyl amino acids (leucine, valine, and phenylalanine) followed by $AgNO_3$ in aqueous acetone gives the corresponding β-hydroxy-α-amino acid derivatives with complete diastereoselectivity.[533] Clearly, water is permitted to attack only the less-hindered face of the intermediate carbocation in this process. The same reagent, with protected αβ-dehydroamino acids, gives β-bromo-α-imino acids [$R^1R^2CBr.C(=NCO_2R^3)CO_2R^4$] that are useful in further reactions (if R^1 or R^2 = H), that place a β-heterocyclic structure on the side-chain.[534] There may be a common mechanistic theme underlying this study, and the ability of N-acyldehydroalanines to scavenge superoxide and hydroxyl radicals that leads to their promotion as X-irradation protection agents.[535]

Ring-opening of 1-aminocyclopropanecarboxylic acid that follows diazotization, leads to products of attack by the carboxylic acid used with $NaNO_2$ to provide nitrous acid (Scheme 45).[536] Although the expected product, an α-alkanoyloxymethylacrylic acid, is formed, the retention of configuration in the substitution of $-NH_2$ permits reasonable speculation to be languished on the nature of the intermediate carbocation (a "chimeric zwitterion"?) and gives the first evidence for the existence of the cyclopropyl α-lactone. The ring-closure that occurs through spontaneous hydrolysis of (α-halogenomethyl)-diaminopimelic acid leads to 2-(4-amino-4-carboxybutyl)aziridine, which like other aziridines is a potent irreversible enzyme inhibitor.[537]

Hydroxyalkyl side-chains are represented in cyclization reactions, of L-serine benzyl ester to benzyl (S)-2-aziridinecarboxylate[538] and in the intramolecular Mitsunobu reaction (Ph_3P – diethyl azodicarboxylate) undergone by N-trityl trans-4-hydroxy-L-proline to give the corresponding bicyclic lactone.[539] This is already established as a useful route to the β-lactone from serine, and is used in this study to initiate the route to the cis-hydroxyproline isomer through further routine steps. Boc-D-or -L-serine lactone undergoes ammonolysis to give the corresponding 2,3-diaminopropanoic acids.[540] The α-aminoketone derived from N-phenylfluorenyl-L-serine has been elaborated into the cyclic anhydride (64).[541]

Co-enzyme PQQ, already known to bring about oxidative decarboxylation of acylamino acids to form oxazoles,[542] catalyzes the oxidative fission (de-aldolization) of β-hydroxy-α-amino acids under very mild conditions.[543]

A route from methionine to homoserine is described[544] that conventionally follows sulphonium salt formation with bromoacetic acid and hydrolysis in refluxing aqueous acetic acid. The product is most easily isolated as its lactone, formed using 4M HCl-dioxan. Base-induced ring closure of methylsulphonium salts of N-trityl L-methionine hydroxamide through Me_2S displacement could involve either N or O in the

hydroxyamide moiety as nucleophile. Rather the previously-claimed formation of (S)-4-(N-tritylamino)-1,2-oxazin-3-one (in 3% yield), the product, whose yield can be increased to 34%, is found to be (S)-2-hydroxyimino-3-(N-tritylamino)tetrahydrofuran resulting from nucleophilic attack by carbonyl oxygen.[545]

S-Trimethylacetamido-L-cysteine is easily prepared using N-hydroxymethylpivalamide and trifluoroacetic acid as reagent.[546] Surprisingly, the S-protection is stable to HF but removable by $Hg(OAc)_2$ in TFA or by I_2 in aqueous acetic acid. The high nucleophilicity of the cysteine side-chain function is involved in this reaction, also in a very real analytical problem that explains "losses" of cysteine on polyacrylamide gels through addition to traces of un-polymerized acrylamide.[547] A similar source of loss is through the actions of traces of persulphate (the polymerization initiator) that can both oxidize acrylylamines (used to create a pH gradient) to N-oxides, and cysteine to the sulphonic acid.[548] Cysteine thionitrites continue to be studied (Vol.22, p.59),[549] providing new knowledge of this unusual functional group that may have important physiological functions.

Ammonium persulphate oxidation of L-tyrosine gives only 20% yield of L-DOPA 3-O-sulphate, but this must nevertheless be considered a convenient practical process, considering the difficulties of other standard routes.[550] The fact that photo-oxidation of phenylalanine to o-, m-, and p-tyrosines and DOPA is prevented by radical scavengers and exclusion of oxygen is taken as evidence for the involvement of the hydroxyl radical.[551] Mushroom tyrosinase catalyzed oxidation of α-methylDOPA methyl ester results in iminochrome formation similar to the well-known DOPA - dopachrome conversion. The product is stable at pH 5 but in neutral or slightly alkaline media, it is tautomerized to a quinone methide. These findings strongly support a similar sequence of events as a stage in melanogenesis.[552] Relative iodination rates for tyrosine and di-iodothyronine are roughly 5:1.[553] Diaryl ether analogues of tyrosine have been prepared through aromatic substitution of N-Boc- or N-acetyl-L-methoxytyrosine sodium salt, without racemization, using bis(2-methoxy-5-formylphenyl)iodonium bromide.[554] Similar processing of phenylalanine has been reported, using $ClCH_2OMe/ZnCl_2$.[555]

Peroxomonophosphoric acid brings about the oxidative cleavage of L-tryptophan at pH 0 - 2.5 to give indole-3-acetaldehyde.[556] The ninhydrin reaction, normally an oxidative decarboxylation, gives the condensation product (66) with L-tryptophan, and a kinetics study of this reaction has been reported,[557] also for the corresponding reaction with the DL-amino acid.[558] The cation radical and the neutral radical formed from tryptophan by pulse radiolysis undergo reversible one-electron transfer processes.[559] Indoxylalanine (67) epimerizes at C-3 within 2 - 3 h, and

undergoes C-3 hydroxylation in aqueous NaOH with O_2; easy trifluoroacetic acid cyclization to the oxetanone is notable.[560]

Protection of the arginine side-chain through bis(t-butoxycarbonyl)tetrachlorobenzoylation is reversed through a two step procedure (trifluoroacetic acid, then very dilute acid hydrolysis),[561] a process that should represent a viable competitor for current awkward or expensive protection protocols for the guanidine grouping. Features of the arginine biosynthesis pathway (the urea cycle) have been simulated starting from a protected ornithine, requiring amidation (with nitro-urea) and cyano-ornithine and arginosuccinate synthesis.[562]

Whereas lysine is more nucleophilically reactive in an aqueous buffer relative to cysteine, the order is reversed in a water/oil microemulsion (i.e. a medium of lower polarity).[563]

Rosenmund reduction of acid chlorides of side-chain carboxy groups of Z- or Boc-protected aspartic and glutamic acids after first forming the oxazolidinone from the N-hydroxymethyl compounds is an economical route to the β- and γ-semi-aldehydes.[564] An interesting alternative method for the preparation of glutamic semi-aldehyde employs ozonolysis of a suitably protected 4-vinyl-4-aminobutanoic acid;[565] of no hindrance to the growing use of these aldehydes in synthesis is the fact, shown by n.m.r. data gathered in this study, that hydration of the aldehyde group occurs in solution, and that concentration-dependent dimerization of the hydrate is also prominent.

γ- and δ-Keto-α-amino acids are formed from aspartic and glutamic acids respectively, through the Masamune protocol [$-CO_2H \rightarrow -CO.CH_2.CO_2CH_2CH{=}CH_2 \rightarrow -CO.CR^1R^2.CO_2CH_2CH{=}CH_2 \rightarrow -CO.CHR^1R^2$ with $Pd(PPh_3)_4$].[566] More routine results concerning side-chain fluorenylmethyl esters,[567,568] t-butyl esters (from the amino acids and isobutene, with α-esters as easily-separated side-products,[569] and α-ethyl N-trifluoroacetyl-L-aspartate (formed by hydrogenolysis of the β-benzyl derivative),[570] have been reported. Anodic oxidation of β-enamino-esters derived from pyroglutamic acid (ring $C{=}O \rightarrow C{=}CR^1CO_2R^2$) in methanol gives vinylogous N-acyl-N,O-acetals as a result of replacement of the α-carboxy function by OMe.[571] Melting an alkali metal salt of L-glutamic acid gives L-pyroglutamic acid as an amorphous glass, from which the previously unknown crystalline trihydrate has been obtained through recrystallization from water.[572]

The use of enzymes for selective processing of aspartic acid derivatives has been illustrated in papain-catalyzed hydrolysis, of di-allyl N-benzyloxycarbonyl-L-aspartate to give the β-allyl compound[573] and of an N^{β}-glycosylated Boc-L-asparagine methyl ester to open up the involvement of these sensitive compounds as intermediates for peptide synthesis.[574] Hofmann degradation of asparagine and glutamine with

$PhI(OTFA)_2$ is the basis of efficient syntheses of (S)-Nα-Boc-2,3-di-aminopropanoic acid and -2,4-di-aminopropanoic acid derivatives.[575]

7 Analytical Studies of Amino Acids

7.1 Gas-Liquid Chromatography.- Much of the work is routine application of standard methodology, reported from laboratories that have set up effective systems, especially in conjunction with a mass spectrometry facility.

This is well illustrated by a g.l.c. - m.s. study of $^{12}C:^{13}C$-isotope ratios of amino acids, derivatized as their N-trifluoroacetyl methyl esters.[576] Considerable care is needed to avoid losses in the derivatization of samples, and this paper is excellent reading from this point of view. The same derivatization protocol is applied in analysis of 4-hydroxyproline in collagen samples,[577] and in a thorough study of the homochiral purity of commercial amino acid samples using a Chirasil-Val column.[578] Another common amino acid derivative for g.l.c. analysis is the N-trifluoroacetyl n-butyl ester.[579] An uncommon procedure, used for the analysis of phenylalanine in brain tissue, involves benzoylation and formation of the pentafluorobenzyl ester using dicyclohexylcarbodi-imide and the alcohol.[580]

It goes without saying that this technique is chosen for studies in which sub-nanogram levels of analyte are routinely encountered, and where rapid analysis can also be pointed to as an advantage; both aspects are illustrated in g.l.c. - m.s. of N-heptafluorobutyroylamino acid isobutyl esters.[581] Analysis of phenylalanine, tyrosine and DOPA in a single ventral thoracic nerve cord from the locust (Schistocerca gregaria) established the presence of 194, 347, and 11 ng respectively per sample, through successive conversion of the amino acids into their hexafluoroisopropyl esters and pentafluoropropionylation after azeotroping away with MeCN, the hydrochloric acid used in sample extraction.[582]

G.l.c. is commonly resorted to for the analysis of naturally-derivatized amino acids, such as N-acetylaspartic acid (as its n-butyl ester),[583] and N,N-dimethylglycine (as its ethyl ester).[584]

In view of the crucial importance of clean, quantitative derivatization, it is surprising that one-step processes are little used. However, another look (see Vol.17, p.35) has been taken at 1,3-dichlorotetrafluoroacetone as a derivatization reagent in a g.l.c. - m.s. study of the oxazolidinones formed in this way with glycine, phenylalanine and tyrosine.[585]

7.2 Ion-Exchange Chromatography and Related Techniques.- The classical amino acid analysis protocol is becoming more fully automated (for a review see ref.586) and an auto-hydrolysis - amino acid analysis system has been described.[587] Movement away from the empirical basis of the method is offered in a survey of the theory of strong-acid cation-exchanger equilibria involving amino acids.[588] Free amino acids separated by reversed-phase ion-pair chromatography, have been subjected to post-column derivatization with o-phthaldialdehyde, and estimated fluorimetrically.[589,590]

7.3 Thin-Layer Chromatography.- T.l.c. separation of phosphotyrosine from corresponding serine and threonine phosphates has been described.[591] This contributes useful information on these sensitive derivatives for which mild methods for their release from biologically-important peptides are being sought. It also sets the tone for this section, restricted to less routine studies.

T.l.c. of derivatives of amino acids is covered in reviews of dansyl and dinitrophenylamino acids,[592a] and of the adsorption and partition behaviour of amino acids between a solution and solid in a static relationship compared with the mobile + stationary situation that is the basis of t.l.c. separation.[592b] High-performance t.l.c. quantitative analysis of phenylalanine phenylthiohydantoin has been established with a sensitivity of 0.5 mg L^{-1}.[593]

Chiral t.l.c. has been reviewed (in conjunction with a review of chiral h.p.l.c.).[594] and illustrated for phenylalanine and tyrosine derivatives.[595] Chiral t.l.c., dependent upon chiral solutes in the mobile phase rather than a chiral stationary phase, is particularly effective using the ligand exchange principle, employing copper(II) complexes of diastereoisomeric N-(2-hydroxydodecyl)proline derivatives formed between hydroxy-L-proline and (R,S)-1,2-epoxydodecane are used.[596] N-Benzyloxycarbonyl-L-amino acids are suitable mobile phase components for this approach to t.l.c. resolution of enantiomers.[597]

7.4 High Performance Liquid Chromatography.- A discussion of the relative advantages of pre-column and post-column derivatization[598] is overwhelmingly answered by the sheer volume of work in the former category. If counting papers is a reasonable guide, the o-phthaldialdehyde - thiol protocol for pre-column derivatization has returned to front place, a position it had appeared to lose in the face of competition from N-phenylthiocarbamoyl derivatization.

The typical application of the o-phthaldialdehyde + thiol reagent for amino acid analysis is recorded in papers dealing with tyrosine-O-sulphate,[599] amino acids extracted from dried blood spots by sonication into phosphate-buffered saline,[600] β-amino-isobutyric acid in urine,[601]

N-Bromosuccinimide treatment of methyl esters of N-phthaloyl amino acids (leucine, valine, and phenylalanine) followed by $AgNO_3$ in aqueous acetone gives the corresponding β-hydroxy-α-amino acid derivatives with complete diastereoselectivity.[533] Clearly, water is permitted to attack only the less-hindered face of the intermediate carbocation in this process. The same reagent, with protected αβ-dehydroamino acids, gives β-bromo-α-imino acids [$R^1R^2CBr.C(=NCO_2R^3)CO_2R^4$] that are useful in further reactions (if R^1 or R^2 = H), that place a β-heterocyclic structure on the side-chain.[534] There may be a common mechanistic theme underlying this study, and the ability of N-acyldehydroalanines to scavenge superoxide and hydroxyl radicals that leads to their promotion as X-irradation protection agents.[535]

Ring-opening of 1-aminocyclopropanecarboxylic acid that follows diazotization, leads to products of attack by the carboxylic acid used with $NaNO_2$ to provide nitrous acid (*Scheme* 45).[536] Although the expected product, an α-alkanoyloxymethylacrylic acid, is formed, the retention of configuration in the substitution of $-NH_2$ permits reasonable speculation to be languished on the nature of the intermediate carbocation (a "chimeric zwitterion"?) and gives the first evidence for the existence of the cyclopropyl α-lactone. The ring-closure that occurs through spontaneous hydrolysis of (α-halogenomethyl)-diaminopimelic acid leads to 2-(4-amino-4-carboxybutyl)aziridine, which like other aziridines is a potent irreversible enzyme inhibitor.[537]

Hydroxyalkyl side-chains are represented in cyclization reactions, of L-serine benzyl ester to benzyl (S)-2-aziridinecarboxylate[538] and in the intramolecular Mitsunobu reaction (Ph_3P - diethyl azodicarboxylate) undergone by N-trityl trans-4-hydroxy-L-proline to give the corresponding bicyclic lactone.[539] This is already established as a useful route to the β-lactone from serine, and is used in this study to initiate the route to the cis-hydroxyproline isomer through further routine steps. Boc-D-or -L-serine lactone undergoes ammonolysis to give the corresponding 2,3-diaminopropanoic acids.[540] The α-aminoketone derived from N-(phenylfluorenyl)-L-serine has been elaborated into the cyclic anhydride (65).[541]

Co-enzyme PQQ, already known to bring about oxidative decarboxylation of acylamino acids to form oxazoles,[542] catalyzes the oxidative fission (de-aldolization) of β-hydroxy-α-amino acids under very mild conditions.[543]

A route from methionine to homoserine is described[544] that conventionally follows sulphonium salt formation with bromoacetic acid and hydrolysis in refluxing aqueous acetic acid. The product is most easily isolated as its lactone, formed using 4M HCl-dioxan. Base-induced ring closure of methylsulphonium salts of N-trityl L-methionine hydroxamide through Me_2S displacement could involve either N or O in the

including a prototype automated system, and a review of dabsylamino acids advocating them favourably in relation to other methods.[621]

Specific derivatization is called for in some circumstances, such as for N-benzoylarginine ethyl ester converted into its side-chain N^6-(2-pyrimidinyl) derivative,[622] and similar derivatization of DL-α-difluoromethylarginine with 9,10-phenanthrenequinone.[623] Acylcarnitines have been treated with 4'-bromophenacyl trifluoromethanesulphonate prior to h.p.l.c. analysis.[624] Automated assay of tryptophan and its metabolites has been developed,[625]

Developments in alternative detection methods include chemiluminescence generated by dansylamino acids with H_2O_2 and bis(2,4,6-trichlorophenyl)oxalate,[626] and post-column photochemical derivatization of aromatic amino acids and sulphur-containing amino acids followed by amperometric detection.[627,628] Electrochemical detection as an adjunct of h.p.l.c. analysis of amino acids has been reviewed.[629]

Enantiomeric analysis based on diastereoisomer-forming derivatization has been explored, with sarcosyl-L-phenylalanine methyl ester as reagent for N-benzyloxycarbonyl amino acids[630] and the acid chloride of (S)-flunoxaprofen (68) giving fluorescent derivatives.[631] A well-used system, o-phthaldialdehyde with an N-acyl-L-cysteine, was found to work best, as far as resolution was concerned, with N-isobutyroyl-L-cysteine for the estimation of D-isomers of alanine, aspartic acid, and glutamic acid in yoghourt.[632]

7.5 Fluorimetric Analysis.- This section runs naturally on from fluorescence-forming derivatization in h.p.l.c., but covering wider realms of analysis. Established h.p.l.c. derivatization reagents are used more widely in fluorimetry; o-phthaldialdehyde and naphthalene-2,3-dialdehyde have been reviewed for their potential for femtomole level analysis,[633] with o-phthaldialdehyde being involved in a procedure for the analysis of glycine (1-3 mM) in the presence of glutamic acid (25-100 mM),[634] and in a spectrophotometric total free amino acid assay,[635] and through time-resolved fluorescence of o-phthaldialdehyde - mercaptoethanol adducts prepared to estimate total amino acids in sea-water.[636] The same reagent system has been used for resolution of DL-glutamic acid on a cyclodextrin-bonded stationary phase.[637]

The other function of this Section is to feature the initial explorations in the amino acids field reported for new fluorogenic reagents that may enter the establishment, and 8-methoxy-5-quinolinesulphonyl chloride has been proposed, with modest credentials for this treatment since it shows similar characteristics with the dansyl family.[638]

7.6 Other Analytical Methods.- Pre-eminent now, in this category, is high-performance capillary electrophoresis, recently reviewed so as to cover also h.p.c.e. - m.s.[639] Protocols are being used in h.p.c.e. that are familiar from other areas of amino acid analysis, such as diastereoisomeric derivative formation (Marfey's reagent) for the determination of amino acid enantiomer ratios.[640] While amino acids derivatized with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate are not satisfactorily resolved by h.p.c.e., micellar electrokinetic chromatography in the presence of sodium dodecylsulphate gave excellent results.[641]

Preliminary results have been described for adsorptive stripping voltammetry as a technique for quantitative analysis of phenylthiohydantoins.[642]

The displacement chromatography principle is difficult to set up for individual cases but has useful characteristics as demonstrated for Fmoc-S-trityl-L-cysteine.[643]

7.7 Assays for Specific Amino Acids.- The analysis of L-lysine in amino acid mixtures using four different methods has been reported,[644] use of the amino acid analyzer, spectrophotometrically (ninhydrin or furfural), potentiometric/amperometric, with an enzyme electrode. The last-mentioned approach is of course the predominant feature of this section over the years, and continues to be so, with assays reported for N-acetyl-L-glutamic acid (as activator for carbamoyl phosphate synthetase),[645] L-glutamine (rose petal on ammonia gas sensor)[646] L-lysine (NADH formed with L-lysine dehydrogenase),[647] phenylalanine (NADH-dependent phenylalanine dehydrogenase),[648] and tyrosine and the three branched-chain protein amino acids by a fully-automated multienzyme method.[649] This broadened approach has also been applied in another laboratory to the branched chain amino acids.[650] A review has appeared of analytical approaches to carnitine and its esters.[651] The enzymatic approach using carnitine acetyltransferase has been evaluated using either radioassay or spectrophotometry for quantitation.[652]

The functional group in cysteine that is not shared with any other protein amino acid offers scope for its specific spectrophotometric[653] and amperometric assay.[654]

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