1
Amino Acids

BY GRAHAM C. BARRETT

1 Introduction

The literature of 1996 is covered in this Chapter, which aims to report and appraise newly-published knowledge of the chemistry of amino acids. Biological aspects are given prominence only where the chemical interest is enhanced by explaining the life science context.

Literature citations forming the basis for this Chapter have been obtained from *Chemical Abstracts* (Volume 124, Issue no. 11 to Volume 126, Issue no. 9 inclusive), and from papers consulted in major Journals that have consistently been used by authors of relevant material.

The expanding volume of the relevant literature continues to demand ingenuity in somehow getting a litre of wholesome nourishment into the half-litre pot that this Chapter represents, and restrictions have been placed on citations of the patent literature and material of a more routine nature. Authors who repeat-publish and over-fragment their material are responsible to a significant extent for the ever-increasing number of references for this Chapter, and this Reviewer's conscience rests easily when grouping such papers together without detailed comment on each of them.

As usual, the carboxylic acid grouping is understood to be implied by the term 'amino acid' for the purposes of this Chapter, though interest in boron and phosphorus oxy-acid analogues and also in sulfonic acid analogues, is continuing to grow. Methods applicable for the synthesis of α-aminoalkaneboronic acids (Refs. 65, 146, 147), α-aminoalkanesulfonic acids (Refs. 154, 845), and α-aminoalkanephosphonic acids and other phosphorus oxyacids (Refs. 32, 62, 80, 82, 85, 87, 88, 152, 326, 374, 437, 843) are usually derived from extensions of standard methods in the amino acid field, and representative examples of syntheses of amino oxyacid analogues are described, side-by-side with corresponding methods for amino carboxylic acids, in appropriate locations in this Chapter.

2 Textbooks and Reviews

References collected in this Section do not represent the total coverage for this year, since many reviews are located with their primary literature in appropriate sections in this Chapter.

Amino Acids, Peptides and Proteins, Volume 29

Books on protein analysis and peptide topics inevitably relate to amino acids as well.[1] New books[2] and Conference Proceedings[3] are a continuing support for all those working in this flourishing field, and are especially useful to those entering it for the first time and depending on a general background in organic and biological chemistry. Material presented at Conferences is usually published elsewhere, or is already on its way to the primary literature by the time that the Proceedings Volumes appear, and studies covered in this Chapter are linked only to their journal sources even if accessible also through Conference Proceedings.

Reviews cover the twenty-first amino acid utilized in normal ribosome-mediated protein synthesis, selenocysteine[4] (see also the report[5] on incorporation into proteins by modified *E.coli* of numerous non-natural amino acids), uses of tert-leucine[6] and trans-4-hydroxy-L-proline[7] as chiral starting materials for organic synthesis, (S)-2,3-diaminopropanoic acid,[8] lipidic α-amino acids,[9] chemical modification of amino acid side-chains for studies of protein function,[10] the detection of amino acids in samples collected on Mars,[11] naturally-occurring proline analogues,[12] analysis methods for D-α-amino acids and discussion of their *in vivo* roles,[13] free-radical reactions in the synthesis of amino acids,[14] cation π-binding between aromatic amino acid side-chains in host-guest complexes,[15] synthesis and uses of α-trifluoromethyl-α-amino acids,[16] and L-carnitine biochemistry.[17] As with earlier issues of the 'Methods in Molecular Biology' series, useful material on amino acids science is contained in current Volumes,[18] and the same applies to American Chemical Society Symposia.[19]

3 Naturally Occurring Amino Acids

3.1 Isolation of Amino Acids from Natural Sources – New solutions to problems of winning of amino acids from mixtures, by conventional or novel methods are collected in this Section. Protein hydrolysis is important both in terms of reliability of analytical data, and as a source of certain amino acids on a preparative scale. The recovery of tryptophan (86–88%) from seaweed is considerably better by aqueous alkaline hydrolysis than by mercaptoethanesulfonic acid degradation[20] (though the latter method is claimed to give >90% recovery of tryptophan from proteins when dithioglycollic acid is added[21]). Degradation accompanying conventional acid hydrolysis of a protein is even greater for cysteic acid than for serine.[22] A new enzyme, actinase, that catalyses the hydrolysis at both peptide bonds that anchor a tyrosine residue within a protein, may be widely useful; for example, the tyrosine content (12%) is released from silk through its action.[23]

Further details (see Vol. 28, p. 3) of the application of an emulsion liquid membrane consisting of di-(2-ethylhexyl)phosphoric acid, Span 80, and kerosene, for concentrating alanine from aqueous solutions, have been published.[24] An organic membrane has been formulated for the separation by nanofiltration of arginine, glutamic acid, and serine from an aqueous solution containing 15 amino acids,[25] and N-benzyloxycarbonyl-L-aspartic acid and L-phenylalanine methyl ester hydrochloride can be concentrated and separated from each other in

solutions in organic solvents, by using reverse osmosis membranes.[26] N-Acylation of protein hydrolysates has been claimed[27] to provide easier separation, though the well-known further reactions undergone by N-acylamino acids and acylating agents may create more confusion. A novel approach, temperature-swing chromatography, has been applied to the preparative scale separation of a mixture of arginine, histidine, and lysine.[28] Conventional large-scale ion-exchange purification methods have concentrated on the removal of inorganic impurities from amino acid mixtures.[29]

An effective solvent system for amino acids and their derivatives is dimethylformamide containing a strong acid (TFA, HBF_4, TosOH *etc.*) together with an excess of tertiary amine with pK less than 6 (pyridine is recommended).[30] Derivatization of amino acids, *e.g.* by acylation, is claimed to be feasible in such systems, but it should be appreciated that troublesome side-reactions unique to amino acids would be expected for syntheses carried out in such media.

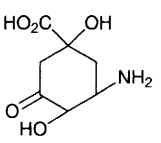
Crystallization techniques leading to pure products are routine final steps in isolations of amino acids from mixtures, and new data are contained in studies of aspartic acid and phenylalanine.[31]

3.2 Occurrence of Known Amino Acids – This section could be very extensive, but it does not include routine papers mentioning familiar amino acids in their predictable locations in the biosphere; therefore, only those papers describing familiar amino acids in unusual locations (extraterrestrial; Ref. 11), or describing more unusual amino acids in natural locations, are considered.

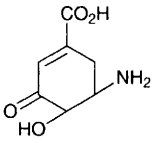
Glycine appears in hydrolysates of bacterial lipopolysaccharides, and is concluded to be an integral constituent.[32] L-Arginine appears in *Coccinellidae subcoccinella-24-punctata* as its N^{α}-quinaldyl derivative,[33] and in the marine ascidian *Leptoclinides dubius* as corresponding p-hydroxybenzoyl and 6-bromo-1H-indolyl-3-carbonyl derivatives;[34] also present are N^{α}-(1H-indolyl-3-carbonyl)-D-arginine, N^{α}-(6-bromo-1H-indolyl-3-carbonyl)-L-histidine, and the rare amino acid L-enduracidin. Assignments of structure to konbamide[35] (from the sea sponge *Theonella sp.*) and related cyclic peptides are shown to be incorrect by synthesis of tryptophan-containing analogues of the proposed peptides, and creation of D- and L-2-bromo-5-hydroxytryptophan residues by NBS bromination.[36] Hypusine [N^{ε}(4-amino-2-hydroxybutyl)-L-lysine] is formed by transfer of the side-chain substituent from spermidine to a lysine residue in a protein.[37]

The opines [α-(N-carboxyalkylamino)alkanoic acids; ten such compounds are uniquely located in 43 crown gall tumours] have been surveyed.[38] N^{ε}-Carboxymethyl-L-lysine is an advanced glycation end-product of proteins *in vivo*, and is thought to arise by reaction with compounds formed by lipid peroxidation since it can be generated *in vitro* by copper-catalysed oxidation of mixtures of proteins with polyunsaturated fatty acids.[39] Crosslinking amino acids released from proteins *in vivo*, that then find their way into clinical samples, are attracting increasing interest since they are thought to be markers of human bodily deterioration; deoxypyridinoline is one of these (a marker for osteoporosis; see also Refs.1048,1075-1078) and its identification in urine together with hydroxyproline has been studied.[40]

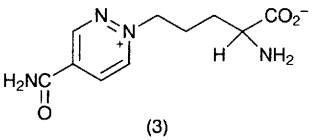
Biosynthesis by *Streptomycetes* of 3-amino-5-hydroxybenzoic acid involves a new variant of the shikimate pathway, since 3,4-dideoxy-4-aminoarabinoheptulosonic acid, 5-deoxy-5-amino-3-dehydroquinic acid (aminoDHQ, 1) and 5-deoxy-5-amino-3-dehydroshikimic acid (2) are present in cultures.[41] Pyridazomycin (3) is biosynthesized from ornithine, glycine, and a C-4 unit.[42] The antimetabolite YS-460 from a *Streptomyces* sp. turns out to be identical with furanomycin.[43] Nostocyclin, from newly-discovered *Nostoc* strains, extends the list of cyclodepsipeptides of cyanobacteria (blue-green algae) that contain the 3-amino-6-hydroxy-2-piperidone moiety.[44]



(1)



(2)



(3)

3.3 New Naturally Occurring Amino Acids – *Neocosmospora vasinfecta* contains (2S,3R,4R,6E)-2-acetylamino-3-hydroxy-4-methyloct-6-enoic acid (structure assigned on the basis of synthesis by aldolization of tert-butyl isocyanoacetate and routine elaboration; Section 4.2).[45]

3.4 New Amino Acids from Hydrolysates – This section covers new amino acids that occur as residues in larger structures that can in principle be broken down by hydrolysis.

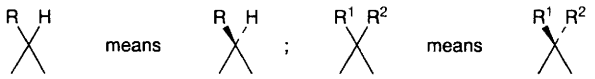
The most prolific growth area under this heading is the group of cyclic dipeptides (*alias* dioxopiperazines), and new examples include diatretol (4; from *Clitocybe diatreta*)[46] and the four cyclotryprostatins (5) from *Aspergillus fumigatus* BM 939 that are responsible for inhibition of cell cycle progression.[47]

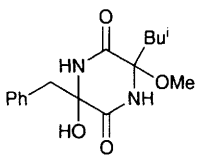
Studies of the fluorescent 'crossline', a lysine residue in proteins that has become post-translationally modified through condensation with D-glucose, have been reported.[48] A di-isotyrosine isolated from hydrolysates of cell walls of tomato cell cultures has been shown to be a biphenyl rather than a diaryl ether.[49]

Of course, the field covered by this section includes acylated amino acids as well as unusual peptides and crosslinked proteins. The first-mentioned of these

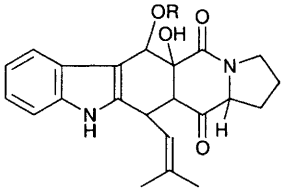
---

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



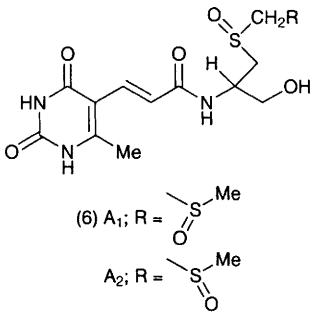


(4)



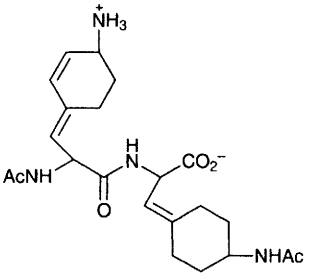
(5) a: R = H
b: R = Me
c: as a, epimeric at OH
d: as c, C=O in place of CH(OR)

classes is represented in the modulators of the proliferation of mammalian cells, the sparoxomycins A1 and A2 (6; these are epimers at the sulfoxide chiral centre).[50] The trypsin inhibitor radiosumin (7), from the blue-green alga *Plectonema radiosum*, contains unsaturated moieties that are novel in the amino acid context,[51] while clathramides A and B (8) are novel bromopyrroles from the

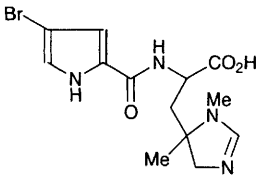


(6) A_1; R =

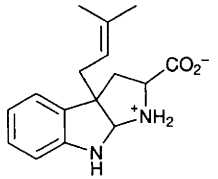
A_2; R =



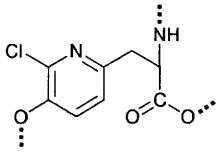
(7)



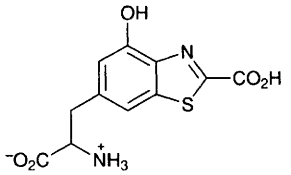
(8)



(9)



(10)



(11)

sponge *Agelas clathrodes*.[52] The chymotrypsin inhibitor oscillatorin (from the toxic freshwater cyanobacterium *Oscillatoria agardhii*) is a cyclic decapeptide that contains 3a-cis-1,2,3,3a,8,8a-hexahydro-3a-(3-methyl-2-butenyl)-pyrrolo[2,3-b]-indole 2-carboxylic acid (9).[53] Progress with the structure determination of kedarcidin has been reported; its incompletely defined chromophore contains partial structure (10).[54]

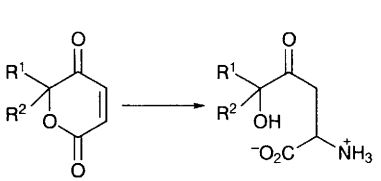
The novel amino acid (11) is released from pheomelanins through alkaline hydrogen peroxide treatment at room temperature.[55]

4 Chemical Synthesis and Resolution of Amino Acids

4.1 General Methods for the Synthesis of α-Amino Acids – Routine methods based on the amination of carbonyl compounds, carboxylation of amines, and alkylation of glycine derivatives continue to provide the main material under this heading.

Significant modifications providing improvements to standard methods are noticeable, and over the years there have been continuous developments, including improved deprotection conditions [alkaline hydrolysis of N-phthaloylglycine and acid hydrolysis of N-(o-carboxybenzoyl)glycine in aqueous organic solvents] for the Gabriel synthesis.[56] Attempted aminolysis of dimethyl 1-bromocyclopropane-1,2-dicarboxylate in methanol gave the methyl ether.[57] Amination through azidolysis of α-halogenonitriles followed by reduction of the azide grouping and hydrolysis of the nitrile is another standard approach, illustrated in this year's literature with 1-halogeno-D-tetra-O-acetylglycopyranosyl cyanides giving monosaccharides carrying amino and carboxy groups at the anomeric carbon.[58] Azidolysis of cyclic carbonates (using NaN_3)[59] or oxiranes (using 1,1,3,3-tetramethylguanidinium azide with a simple transition-metal salt as catalyst)[60] *en route* to trans-1,2-amino alcohols (see also Refs. 125, 128 *etc.*) is the first step in an easy introduction of a primary amine function. Reductive addition of hydrazoic acid to γ-keto-α,β-unsaturated dicarbonyl compounds, *e.g.* lactones (12), offers an alternative approach to this amination protocol.[61] Lithiated cycloalkanephosphonate esters[62] and N-acylmethylanilides[63] have undergone electrophilic azidation (diphenyl phosphorazidate) followed by reduction (H_2/Pd) and hydrolysis, to lead to α-aminoalkanephosphonic acids and α-amino acids, respectively.

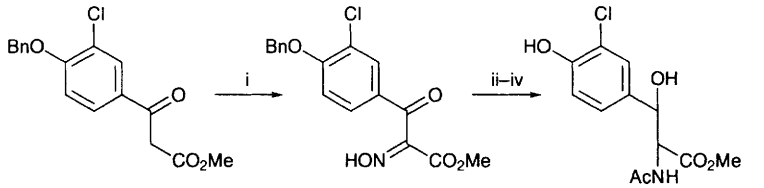
Vinylglycinol has been obtained by Pd(naphthalene)-catalysed amination of butadiene mono-epoxide by phthalimide.[64] α-N-Boc-Aminoalkaneboronate



(12)

esters have been obtained through amination (BocNHNa) of α-halogenoalkaneboronates.[65]

Nitrosation of β-ketoesters (Scheme 1) giving α-oximino-esters, and electrophilic amination of the corresponding α-hydroxy ester with di-tert-butyl azodicarboxylate to give the α-hydrazino β-hydroxy ester, are the initial steps for two standard amination protocols used for the syntheses of the vancomycin constituents, syn- and anti-β-hydroxy 3-chlorotyrosines, respectively.[66] β-Alkoxy-α-oximino-esters have been prepared from oxiranes and hydroxylamine,[67] and easily-prepared α-oximinoalkanephosphonates are readily reduced ($NaBH_4$) to α-aminoalkanephosphonates.[68]



Reagents: i, BuONO, HCl; ii, Zn, AcOH; iii, H_2, 140 bar, $RuBr_2$[(*R*)-MeOBiphep]; iv, H_2/Pd–C

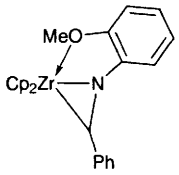
Scheme 1

Another 'named' method also based on amination, the Strecker synthesis, has been used with carbonyl compounds derived from protected D-glyceraldehydes to give (2S,3S)- and (2R,3S)-2-amino-3,4-dihydroxybutanoic acids;[69] the Strecker synthesis gives poor yields when attempting the synthesis of amino acids bearing electron-withdrawing groups such as 4-pyridyl.[70] A close relative of the method is involved in a synthesis of phenylglycine from benzaldehyde, $CHCl_3$, KOH and ammonia; an identical brew has been studied over many years and this time inclusion of β-cyclodextrin in the reaction mixture is shown to generate stereoselectivity (to an extent that is not clear from information in the abstract).[71]

Ugi solid-phase syntheses, one (employing 1-isocyanocyclohexene)[72] giving α-amino acid derivatives *via* a munchnone intermediate, and a related approach[73] giving hydantoin-4-imides in another way (the isocyanide is tethered to the solid phase[74]), have been studied. These are being studied in the context of the generation of combinatorial compound libraries, as is a route to 5-alkoxyhydantoins employing α-hydroxyalkanoylated Merrifield resin ($BnONH_2$ followed by ArNCO).[75] The rich reactivity profile of the munchnone intermediate involved in these studies can be exploited in other ways, *e.g.* 1,3-dipolar cycloadditions with alkynes leading to pyrroles (see also Ref. 72).[76]

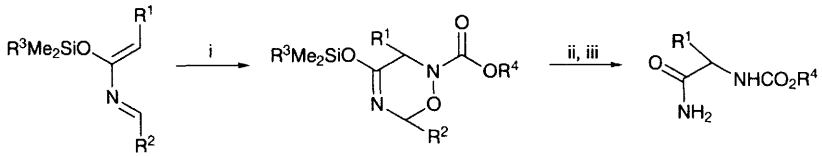
A '5-centre-4-component reaction' (aldehyde, L-amino acid, isocyanide, and alkanol) leads to homochiral 1,1′-iminodicarboxylic acid derivatives.[77] Reactions of chiral imino aziridines (the synthetic equivalent of the condensation of three of the four components of the classical Ugi reaction) with alkanoic acids give N-acylamino acid amides with very little racemization, as well as analogues resulting from Mumm rearrangement.[78] Optically-active zirconaziridines (13) can be

trapped with ethylene carbonate (a 'CO_2 synthon') as they are formed, and the resulting complex generates α-amino-α-methyl esters, or gives phenylglycinamides when isocyanates are added; optically-active substrates generate poor enantioselectivity.[79]



(13)

Amination of keto-acids leading to α-aminoalkylphosphonic acids has been demonstrated, employing benzhydrylamine and reduction of the resulting Schiff base with $K(OAc)_3BH$; a synthesis of phosphohomoserine lactone is included.[80] Amination of azadienes through cycloaddition to arylnitroso compounds (Scheme 2) gives N-arylamino acids through reductive cleavage.[81] Mitsunobu amination of α-hydroxyphosphonates formed from dibenzyl phosphite and aldehydes is an effective route to N-hydroxy-α-aminophosphonates.[82]



Reagents: i, $R^4OCON{=}O$, CH_2Cl_2, r.t.; ii, MeOH; iii, Na–Hg in MeOH

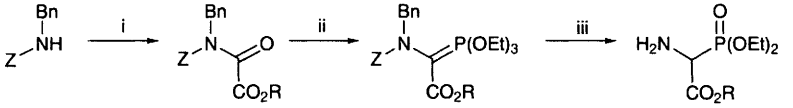
Scheme 2

[3,3]-Trichloroacetimidate rearrangement of mono-protected *syn*-allylic diols leading to allylic amines is followed by successive ozonolysis and Jones oxidation in a standard route to α-amino acids.[83] Full details have been reported for the preparation of trichloroacetimidates.[84]

Carboxylation of amines is rarely used for α-amino acid synthesis, though addition of diphenyl phosphite to an imine to give a diphenyl N-alkyl-α-aminophosphonate illustrates the principle [$DMTO(CH_2)_2N{=}CH_2 \rightarrow DMTO(CH_2)_2NHCH_2P(O)(OPh)_2$; see the coverage of PNAs in the later Section 4.10].[85] Hydrophosphonylation of a cyclic imine is enantioselective when a chiral titanium-diol complex (20 mol%) is used as catalyst.[86] Equivalent phosphonylation of imines by polymer-bound H-phosphonates gives α-aminophosphonates,[87] and polymer-bound imines give α-aminophosphonic acids by reaction with $HP(OTMS)_2$.[88] Amidocarbonylation (acetamide, CO, H_2, with an aldehyde and $PhCCo_3(CO)_9$[89] or with benzyl chloride, to give DL-phenylalanine[90]) and a

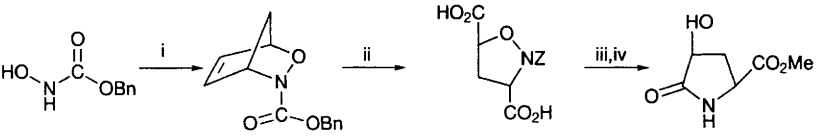
closely-related route to N-α-acylaminophosphonates [$HP(O)(OR^1)_2$ + R^2CHO + R^3X-$CONH_2$][91] have been developed further. Carboxylation and amination are combined in a three-component synthesis of aldehydes, primary amines, and silanes [R^1CHO + R^2NH_2 + Me_3Si-Nu → $R^1CH(NHR^2)$Nu] that leads to β-aminoketones, β-amino esters, or α-aminonitriles,[92] while trifluoromethylated enamino- and imino-esters are formed from an iminophosphorane, TFAA, and an organozinc reagent.[93]

Isocyanoacetates undergo transition metal-catalysed aldolization by ketones to give β-disubstituted β-hydroxy-α-amino acids.[94] Close relatives of keto acids, the oxalylcarbamates $R^1R^2NCOCO_2Et$, give α-diethylphosphonyl-α-amino acids by reaction with triethylphosphite and steps shown in Scheme 3[95] (the later Section 4.7 deals with α-hetero-atom-substituted α-amino acids). α-MethylDOPA has been obtained through an 8-step route from diethyl methylmalonate, Hofmann rearrangement being the key step that introduces the eventual amino group in a synthesis of 2-carbamoyl-2-methyl-3-[3,4-(methylenedioxy)phenyl]propanoic acid.[96] The 1,2-oxazoline formed by hetero-Diels-Alder addition of cyclopentadiene to benzyl N-hydroxycarbamate and oxidation of the adduct *in situ* with tetrabutylammonium periodate, has been used for the synthesis of γ-substituted glutamic acids by hydrogenation and ring opening (Scheme 4), and in principle could be more widely applicable.[97]



Reagents: i, $NaN(TMS)_2$ then $ClCOCO_2R$; ii, $P(OEt)_3$,toluene, reflux 7 h; iii, TMSBr then H_2/Pd–C

Scheme 3



Reagents: i, Bu_4NIO_4 + cyclopentadiene; ii, $KMnO_4/Bu_4NHSO_4$; iii, $Me_3O^+BF_4^-$, Pr^i_2NEt; iv, H_2/Pd–C

Scheme 4

Bucherer-Bergs synthesis (see also Ref. 941) of N^{α}-Fmoc-N^{γ}-Boc-4-aminopiperidine-4-carboxylic acid from the corresponding piperidin-4-one,[98] preparation of αα-dialkylglycine esters through Beckmann rearrangement of correspondingly substituted β-keto-esters,[99] and Schmidt rearrangement of the ethyl αα-dibenzylacetoacetate (14),[100] illustrate further standard methods.

A curious observation, that aldoses react with propylamine, N^{α}-acetyl-L-

(14)

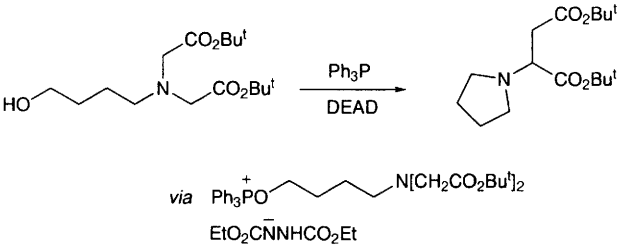
lysine, glycine, or alanine, to give N-propyl alanines and (4S,5R)-5,6-dihydroxy-2-propylamino-γ-hexanolactone, is accounted for by the intervention of methylglyoxal formed through the Maillard reaction (see Section 6.2). This is unlikely to develop into a general amino acid synthesis.[101]

Diethyl acetamidomalonate, the glycine synthon surviving from classical times of amino acid synthesis, is still being given regular employment, leading to protected allylglycines suitable for osmylation by OsO_3, for a synthesis of 5-hydroxy-4-oxonorvaline,[102] and leading to tyrosine analogues,[103] (2S)-amino-3-cyclopropylpropanoic acid,[104] and 2-amino-5,5-dimethylhexanoic acid using 4,4-dimethylpentyl bromide as alkylating agent.[105] A new variant of this route involves alkylation of organo-iron complexes of $EtO_2CCH(NH_2)CO_2(CH_2)_2SiMe_3$, which leads to diastereoisomerically-pure samples.[106] Mono-ethyl acetamidomalonate serves in a corresponding way for the synthesis of α-acylamino-β-ketoesters.[107] Oxazolones are also long-serving synthons, useful for the synthesis of α-hydroxymethyl-phenylglycine and phenylalanine[108] and other αα-dialkylglycines (see Vol. 28, p.23; and Ref. 179).[109]

Glycine Schiff bases, *e.g.* $Ph_2C{=}NCHR^1CO_2R^2$ (R^1 = H; see also Refs. 336, 397) and homologues (R^1 = alkyl), give 4-(phosphonomethyl)phenylalanine and homologues through alkylation,[110] and $Ph_2C{=}NCH_2CN$ (see also Refs.100, 370) has been used similarly. Double alkylation of ethyl cyanoacetate by 1,2-dibromoethane constitutes the crucial step in a synthesis of 1-aminocyclopropane-1-carboxylic acid, successive treatment with aqueous sodium hydroxide, H_2O_2, and Br_2-NaOH generating the required functional groups.[111]

N-Phenylsulfonyl DL-α-bromoglycinate esters undergo nucleophilic substitution with alkylaluminium complexes, to give modest asymmetric induction when homochiral reagents are used.[112] Weakly-activated glycine derivatives participate in aldol reactions: Boc-sarcosine benzyl ester and acetone give N-methyl hydroxy-DL-valine;[113] a protected glycine TMS ketene acetal adds to an aldehyde to give (2- and 6-fluoro-threo-dihydroxyphenyl)serines.[114] Boc-Glycine and excess LDA and alkyl bromides $BrCH_2XCN$ give α-cyanoalkylglycines from which N^{ω}-hydroxyindospicine and p-hydroxyamidinophenylalanine have been prepared [X = $(CH_2)_3$ and p-C_6H_4, respectively].[115] N-(δ-Hydroxybutyl)-N-tert-butyloxcarbonylmethyl-glycine esters undergo unusual intramolecular alkylation (Stevens rearrangement; see also Vol. 27, p. 9, and Ref. 275) under Mitsunobu conditions, so far limited to generating aspartic acid derivatives (Scheme 5).[116]

A wide range of standard approaches to aspartic acid and glutamic acid derivatives, starting from ethyl N-(diphenylmethylidene)glycinate,

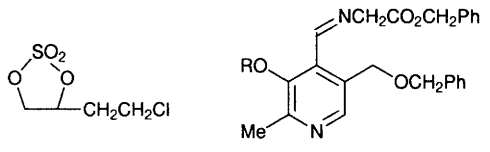


Scheme 5

$Ph_2C{=}NCH_2CO_2Et$, is covered in a paper describing α-alkylation, αα-dialkylation, and phase-transfer-catalysed Michael addition reactions,[117] and alkylation of this Schiff base by methyl 4-bromocrotonate has been optimized for syntheses of 2,3,4-trisubstituted prolines and α-cyclopropylglycines,[118] and 'methanoprolines' through cyclization following alkylation with the cyclic sulfate (15) formed from (S)-butane-1,2,4-triol,[119] and a corresponding route to (1S,2R)-allonorcoronamic acid.[120] α-Alkylation of glycine aldimines formed from novel pyridoxamine models (16) mimics an *in vivo* mechanism and leads to αα-dialkylglycine esters after hydrolysis.[121] α-Vinylation of N-(benzylidene)glycinonitrile using non-activated alkynes under basic conditions has been described.[122] tert-Butyl N-(p-chlorobenzylidene)glycinate gives novel 1,1'-binaphthyl-substituted analogues of aminoisobutyric acid, a new chiral atropisomeric amino acid (a close relative has been prepared from 14, Ref. 100).[123]

Cycloaddition of samarium(III) azomethine ylides to αβ-unsaturated esters (Scheme 6) gives αα-disubstituted-γ-carboxypyroglutamates.[124]

The growth of interest in routes to β-amino alcohols[125] and 1-amino-2,3-diols,[126] also the long-standing awareness of the usefulness of α-aminonitriles,



(15) (16)

Reagents: i, $R^2CH{=}CHCO_2Me$; ii, 1M HCl

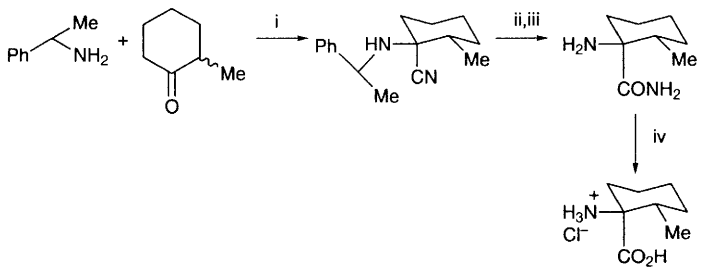
Scheme 6

has generated careful studies of the final stages of their use as precursors of α-amino acids. Kinetics of the selective hydration of the last-mentioned family (alkaline H_2O_2)[127] and oxidative cleavage of aminodiols as a route to lipidic amino acids (Ref.126), have been established. Rearrangement of homochiral dialkylaminomethyloxiranes using TMSOTf gives trans-β-amino alcohols.[128]

4.2 Asymmetric Synthesis of α-Amino Acids – A survey of the general field of asymmetric synthesis[129] includes several methods that are relevant to the amino acid context. Coverage of routes to fluorinated amino acids (Ref. 327) includes reviews of synthesis methods that are also applicable to amino acids more generally. A complete issue of the journal *Amino Acids* has been taken over by reviews of asymmetric synthesis of α-amino acids (*e.g.*, Refs. 9, 131, 225, 327, 369, 432). Uses of chiral auxiliaries or kinetic enzymic resolution to provide homochiral αα-dialkylglycines have been reviewed.[130]

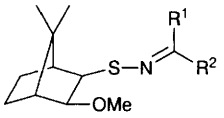
The preceding section of this Chapter mentions classical routes that have been extended to provide asymmetric syntheses, and further examples are provided here. Strecker synthesis catalysed by homochiral dioxopiperazines (cyclo-L-histidyl-L-norarginine and the L-Phe-L-Arg analogue) gives L-amino acids (see also Ref. 998),[131] and alternative asymmetric Strecker syntheses of a vancomycin component from a benzyl-protected isovanillin with trimethylsilyl cyanide and (S)-phenylglycinol,[132] and of all four stereoisomers of 1-amino-2-methylcyclohexanecarboxylic acid [using (S)- or (R)-2-methylbenzylamine; Scheme 7],[133] are notable. A simpler system is represented by hydroxylamination of isobornyl α-cyanoalkanoates using O-(diphenylphosphinyl)hydroxylamine, to give (R)-α-(2-aminomethyl) α-amino acids.[134] Enantiopure sulfinamides ArS(O)N=CHR give best results with diethylaluminium cyanide in Strecker syntheses of L-phenylglycine and L-tert-leucine when 1 equivalent of propan-2-ol is present.[135] (+)-Camphor-derived sulfenimines (17) undergo enantioselective cyanation (TMSCN) *en route* to L-α-amino acids.[136] Chiral α-hydrazinonitriles are formed highly diastereoselectively from chiral α-hydrazones [aliphatic aldehyde condensed with (S)-1-amino-2-methoxymethyl-indoline] through reaction with TMSCN in the presence of diethylaluminium chloride.[137]

Asymmetric electrophilic α-amination using di-tert-butyl azodicarboxylate



Reagents: i, $ZnCl_2$, various solvents; ii, conc. H_2SO_4; iii, H_2/Pd–C; iv, conc. HCl

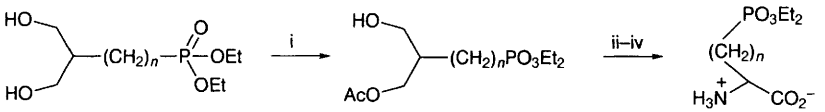
Scheme 7



(17)

with Ph_3P has been illustrated through the conversion of a chiral β-hydroxyester, $Me_2C{=}CHCH_2CH_2CH(OH)CH_2CO_2Me$, into both enantiomers of trans-3-hydroxypipecolic acid.[138] The diol formed by Sharpless asymmetric dihydroxylation of a substituted styrene has been elaborated into the corresponding (R)-phenylglycine component of vancomycin through the same amination procedure.[139]

Uses for proteins in biomimetic amination continue to be demonstrated, this year for a novel system in which an adipocyte lipid-binding protein enclosing a pyridoxamine cofactor has been used for the reductive amination of α-keto-acids.[140] Conventional uses for enzymes in fermentative production of common amino acids is covered in the next Section of this Chapter; unusual asymmetric desymmetrization processes are attracting more interest, not least because such routes can give both enantiomers of the target amino acid. Thus, *cis*-6-hydroxymethylpipecolic acid enantiomers have been obtained through lipase-catalysed partial hydrolysis of *cis*-2,6-bis(acetoxymethyl)-N-benzyloxycarbonyl piperidine,[141] and the reverse process, lipase-catalyzed mono-acylation of 2-(ω-phosphonoalkyl) propane-1,3-diols followed by routine elaboration (Scheme 8), has led to L-α-amino acids carrying aliphatic phosphonate side-chains.[142] Methods established earlier (*e.g.* Vol. 22, p. 30) involving β-methylaspartase bioconversions of alkylfumarates have been used in routes to (2S,3S)-3-methyl- and isopropyl-aspartic acids.[143] A target amino acid for mycestericin D synthesis has been obtained through condensation of benzyloxybutanal with glycine catalysed by L-threonine aldolase, achieved under kinetic control leading to high erythro/threo selectivity.[144]

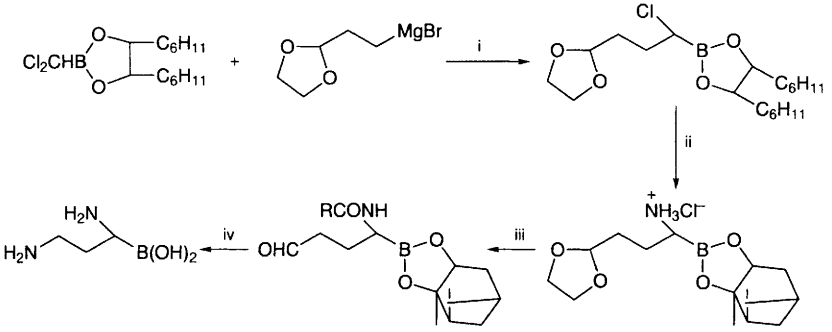


Reagents: i, lipase PS/vinyl acetate/organic solvent; ii, $RuCl_3$–$NaIO_4$; iii, DPPA, Et_3N, BnOH; iv, routine development of functional groups

Scheme 8

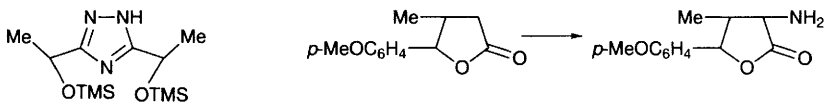
Amination of triflates of α-hydroxyacids by N-benzyl-ω-(alkoxycarbonylamino)alkylamines or N-benzyl-ω-(N-Boc-amino)alkylamines has been studied as a route to N^{α}-(ω-aminoalkyl)amino acids.[145] Amination is the anti-climax of a route to α-amino boronic acids starting with a spectacular elaboration sequence of a chiral boron synthon (Scheme 9);[146] this route uses a (+)-pinanediol-derived

boronic ester, also used in a synthesis of (R)-1,4-diaminobutane-1-boronic acid hydrochloride (an L-ornithine analogue) involving the B-(3-azidopropyl) synthon, and the same ensuing stages.[147] Use of the chiral triazole (18) for enantioselective amination of α-bromo acid esters gives the expected product that can act as a protected synthon, alkylation leading to αα-dialkylglycines.[148] Azidolysis after electrophilic bromination of the TMS enol ether of the butenolide (19) leads to the N-terminal residue of nikkomycins B and B_x.[149]



Reagents: i, $ZnCl_2$; ii, transesterification with (+)-pinanediol; iii, LHMDS, then HCl (3 eq); iv, H_2NOH, then H_2–cat., H_3O^+

Scheme 9



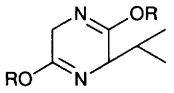
(18) (19)

Addition to imines amounting to the introduction of a carboxylic acid function can be easily biased towards a particular enantiomer, for example using imines of (R)-(+)-camphor to which addition of the 5-methylthiazole carbanion has been demonstrated.[150] Stereocontrolled introduction of a carboxy group into an alkylamine is usually a multistage process, as in the preceding example and in Pummerer rearrangement of homochiral α-(tolylsulfinylmethyl)alkylamines [*e.g.*$TolS(O)CH_2CR^1R^2NHZ \rightarrow HOCH_2CR^1R^2NHZ$][151] (see also Ref. 174). All four stereoisomers of phosphothreonine $MeCH(OH)CH(NH_2)PO_3H_2$ have been prepared from the N-trimethylsilyl lactimine and O-trimethylsilyl diethyl phosphite, and exploiting the inversion accompanying Mitsunobu amination of α-hydroxy-β-silyloxyphosphonate.[152] Addition of an organometallic reagent to the protected benzylimine $BnOCH_2CH(OBn)CH{=}NBn$ prepared from D-glyceraldehyde, and elaboration of the deprotected diol, gives either a D-α-amino acid or a β-amino acid depending on choice of route.[153]

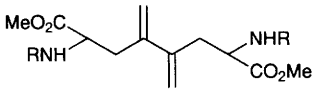
2-Aminoalkanesulfonic acids are best prepared through substitution by sulfite of methanesulfonates of protected 2-aminoalkanols.[154]

(S)-$Ph_2C{=}NCH(CO_2Bu^t)CR(CO_2Me)_2$ (R = H) formed from diethyl malonate and the corresponding Schiff base of acetoxyglycine with $Pd(OAc)_2$/(2S,4S)-BPPM, can be alkylated (R = Me, allyl, benzyl) through a standard phase-transfer catalysis protocol.[155]

The routes that are based on chiral glycine synthons have continued to dominate the current literature covering the asymmetric synthesis of α-amino acids. The Schollkopf bis-lactim ether route provides the following (further examples are covered elsewhere in this Chapter, Refs. 399, 406): all four isomers of 3-(4-chlorophenyl)glutamic acid [alkylation of the (S)-bis-lactim ether (20) through Michael addition to methyl *cis*-4-chlorocinnamate gives a 56:40-mixture of (2R,3S)- and (2*R*,3*R*)-diastereoisomers],[156] the novel bis(amino acid) (21) through $Pd(OAc)_2PPh_3$-catalysed alkylation by 2,3-dibromopropene,[157] 2-alkanethio-3,5-dimethoxy-L-phenylalanine,[158] (2R)-6-Z-amino-2-Boc-amino-hex-4-ynoic acid (a constrained analogue of D-lysine),[159] and 2,3-*anti*-2-amino-3-substituted 4-phosphonobutanoic acids and 2-amino-6-phosphono-4-hexenoic acid through addition to *E*-alkenyl- and 1,3-butadienylphosphonates.[160] A synthesis of (S)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid [(S)-AMPA] involves a novel KF-promoted 1,3-dipolar cycloaddition to give 3-bromo 4-hydroxymethyl-5-methylisoxazole, used in a standard alkylation protocol employing the D-valylglycine-derived bis-lactim ether, (20).[161] L-(p-Borono)phenylalanine has been prepared through this protocol, relying on chymotrypsin resolution for attainment of full homochirality.[162] The D-penicillamine-derived bis-lactim ether offers easier handling and better stereodiscrimination than the standard valine analogue in a synthesis of L-propargylglycine.[163] A brief review of Schollkopf methodology has appeared.[164]



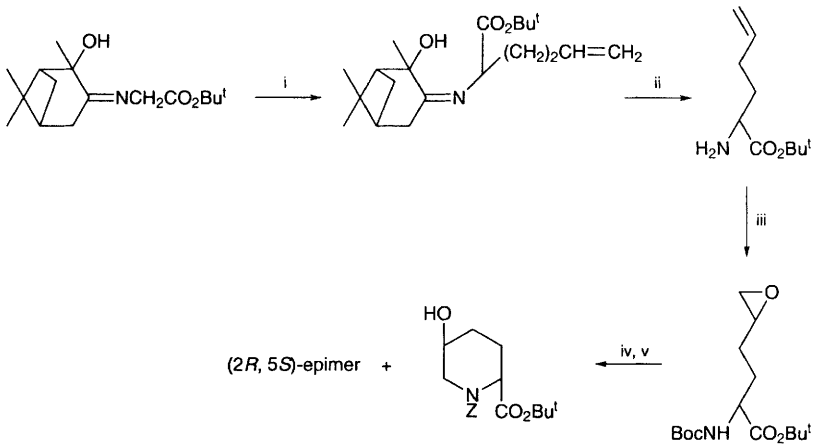
(20)



(21)

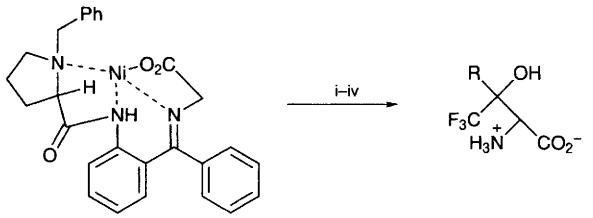
Oppolzer's camphorsultam has served well for the preparation of enantiomers of p-carboranylalanine and 2-methyl o-carboranylalanine,[165] and N-benzyloxyallylglycines[166] (see also Refs. 422, 483), and chiral glycine synthons based similarly on Schiff bases have been used for the synthesis of cis- and trans-5-hydroxy-D-pipecolic acid (Scheme 10).[167] An unusual variation uses *N*-acryloyl (2S)-bornane-10,2-sultam in a 1,3-dipolar cycloaddition to the nitrone (4-$MeOC_6H_4)_2CHN(O){=}CHCO_2Et$, leading to the usual isoxazolidine from which N-Boc-(4S)-4-hydroxy-L-glutamic acid is obtained through routine stages.[168]

A novel approach using a cobalt(III)-chelated glycinate involves the addition of carbanions illustrating "asymmetric transformations of the second kind",[169] and a new chiral Schiff base (Scheme 11; closely shadowing voluminous earlier work by the same research group, using an L-proline-based glycine Schiff base) has been used for the preparation of (2S,3S)-β-hydroxy-β-trifluoromethyl-α-amino acids,[170] and for asymmetric aldol reactions with trifluoromethyl ketones



Reagents: i, LHDMS, $CH_2{=}CH(CH_2)_2I$; ii, H_3O^+; iii, Boc_2O then MCBA; iv, LiBr, then TBDMSCl, then NaH/DMF; v, Bu_4NF, THF

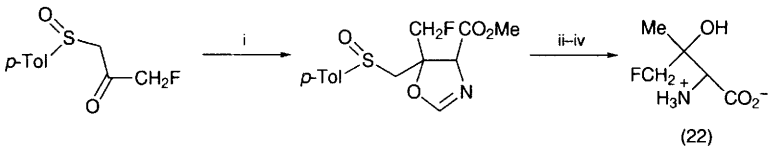
Scheme 10



Reagents: i, CF_3COR/DBU, MeCN; ii, aq. AcOH; iii, HCl/MeOH, iv, Dowex-H^+/NH_4OH

Scheme 11

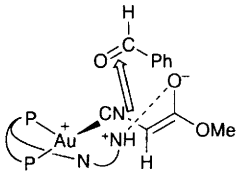
to give (2S,3S)-3-trifluoromethyl-3-alkylserines in 90–98% diastereoisomeric excess.[171] The earlier-established chiral glycinate Schiff base nickel complex just referred to has been used for a synthesis of o-, m-, and p-fluoro-L-phenylalanines through standard methodology.[172] Further novelty is exhibited in the use of the ester of N-benzylideneglycine formed with an (S)-binaphthol, giving predominantly D-amino acids through routine alkylation and work-up.[173] Aldol reactions are not limited to Schiff bases, as in examples in the preceding text, with copper(I)-catalysed addition of (S)-3-fluoro-1-(p-tolylsulfinyl)acetone to methyl isocyanoacetate leading to stereoisomers of 3-fluoromethyl-threonines (Scheme 12;[174] see also Refs. 45, 385). The absolute stereochemistry of one of these products (22 in Scheme 12) was determined by X-ray crystal structure analysis. The stereochemistry of gold(I)-catalysed asymmetric aldolization of isocyanoacetic acids with fluorobenzaldehydes is rationalized as a consequence of *si*-face to *si*-face interaction, as in (23).[175] Palladium(0)-catalysed alkylation of the



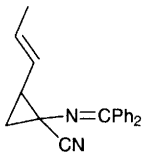
(22)

Reagents: i, $CNCH_2CO_2Me$; ii, H_2O, $CHCl_3$; iii, Raney nickel, methanol buffer pH 5.2; iv, 1 M HCl

Scheme 12



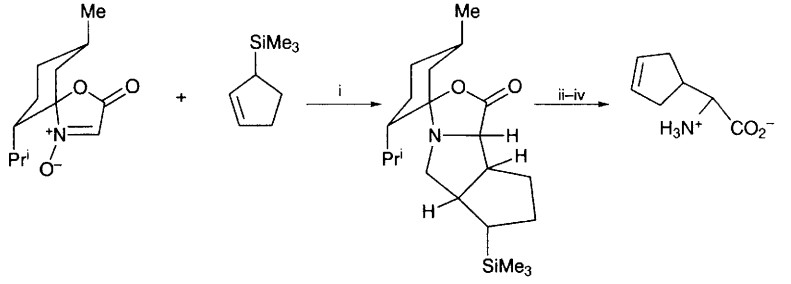
(23)



(24)

carbanion of the achiral Schiff base $Ph_2C{=}NCH_2CN$ with (4S)-1-chloropent-2-en-4-ol, followed by Mitsunobu $S_{N'}$ cyclization, gives the cyclopropane (24).[176]

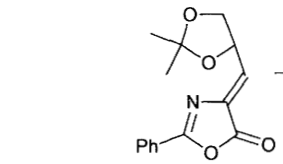
An oxazol-5(4H)-one is essentially a Schiff base of an α-amino acid, and although asymmetric syntheses based on 4-alkylation have been standard practice for many years, a novel approach based on the cycloaddition reactivity of the nitrone of an oxazol-3(2H)-one has been described (Scheme 13), and illustrated for (2S,1'S)-cyclopent-2-enylglycine.[177] An N-mannofuranosyl nitrone added to methylenecyclopropane gives a 4:1-mixture of regioisomeric isoxazolidines, the major product being isomerized in xylene at 137° to give the virginiamycin component (2S)-4-oxopipecolic acid, from which the novel cis-4-hydroxy-analogue was obtained by L-Selectride reduction.[178] Further results from the project directed at asymmetric synthesis of oxazol-5(4H)-ones of (S)-αα-dialkylglycines employing L-phenylalanine cyclohexylimide as recoverable chiral auxiliary (see Vol.28, p. 23, and also Ref. 109) describe the preparation of α-bromomethyl-S-



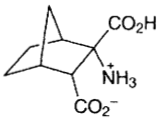
Reagents: i, $BF_3.Et_2O$; ii, OH^-; iii, H_2/Pd; iv, BF_3

Scheme 13

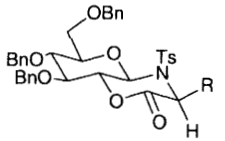
alanine.[179] The (R)-glyceraldehyde-derived oxazol-5(4H)-one (25) has appeared in several papers describing amino acid syntheses, *e.g.* the conformationally-constrained L-aspartic acid analogue (26) obtained from the Diels-Alder adduct with cyclopentadiene,[180] and the corresponding cyclohexenone formed with the Danishefsky diene.[181] Lithium enolates of glucose-derived bicyclic oxazinones (27) are alkylated easily, with high diastereoselectivity but giving only modest reaction yields.[182] A more routine addition pathway is demonstrated in Michael addition of the carbanion of ethyl benzylideneglycinate to trans-$CF_3CH{=}CHCO_2Et$, ensuing cyclization leading to a cis-trans mixture of ethyl 3-trifluoromethylpyroglutamate;[183] further results from this study include the corresponding use of the homochiral Schiff base from tert-butyl glycinate and 2-hydroxypinan-3-one to give the separate enantiomers of the same product. (+)-8-Phenylmenthyl N-benzylideneglycinate has been used for synthesis of eudistomidin B (28) through alkylation with the appropriate chiral iminium ion and showing the expected double diastereodifferentiation.[184] The titanium enolate of the Schiff base formed between ethyl glycinate and (1R,2R,5R)-hydroxypinanone [shown to adopt the (E)-configuration through X-ray crystal analysis] undergoes enantioselective aldol reactions as illustrated by preparations of pure (1R,2S)-chloramphenicol base and of D-allo-threonine.[185] Conventional diastereoselective



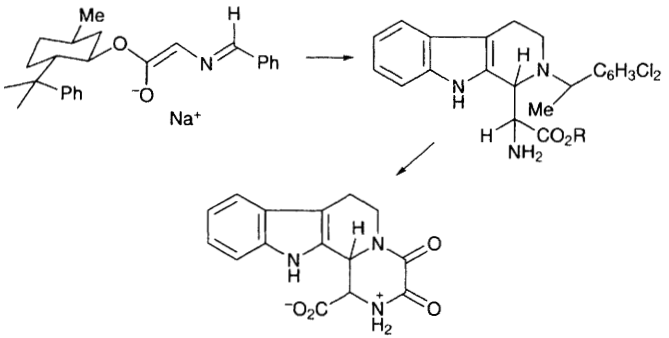
(25)



(26)



(27)

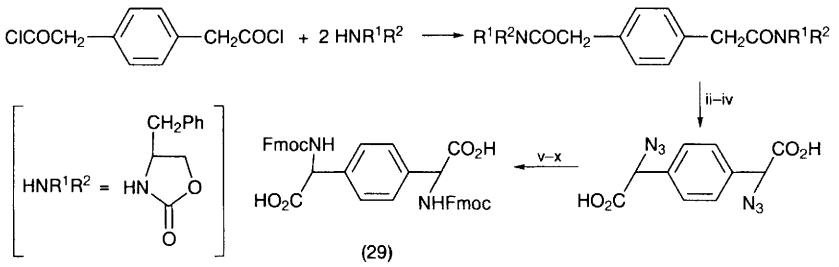


(28)

alkylation (LDA/alkyl halide) of this substrate or its equivalent (thiazol-2-yl in place of the ester function) is described in a project aimed at a mechanistic understanding of the process (two hypotheses are presented),[186] including molecular orbital calculations for three-dimensional details of the alkylation transition state.[187]

A brief review of Seebach methodology (in other words, the use of chiral oxazolidinones and imidazolidinones derived from glycine for the asymmetric synthesis of amino acids) has appeared.[188]

The (R)- and (S)-oxazolidinones introduced by Evans continue to be useful, and new examples prepared from cis-2-amino-3,3-dimethylindan-1-ol through a standard sequence[189] have been described. A general high-yielding route to 4-alkoxycarbonylimidazolidin-2-ones has been established.[190] '(S,S)-Phenylbis(glycine)' (29 and its m-isomer; Scheme 14) have been prepared from (S)-4-benzylox-

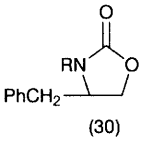


Reagents: i, Bu^nLi, THF,–78 °C; ii, KHDMS, THF; iii, $ArSO_2N_3$; iv, AcOH; v, $SnCl_2$; vi, Boc_2O; vii, LiOH; viii, TFA; ix, HMDS, TMSCl; x, FmocCl

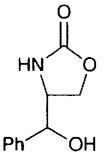
Scheme 14

azolidin-2-one through N-acylation with benzenediacetyl dichlorides and routine steps thereafter,[191] exemplifying this approach. D- and L-Carboranylalanines have been prepared through addition of the same chiral auxiliary to allylcarborane.[192] The synthon was used as the boron enolate of its N-bromoacetyl derivative with 4-fluoro-3-nitrobenzaldehyde to give an amino acid moiety of orienticin C.[193] Azidolysis was used to introduce the amine function and other well-established steps completed these preparations. 3-(4-Hydroxyphenyl)-prolines (conformationally-constrained tyrosine analogues) have been prepared through this standard protocol, with cyclization accomplished at the α-azidoalkanoate stage of the route.[194] Alkylation of the lithium enolate of $Ph_2C{=}NCH_2CO_2Et$ with the N-acylated oxazolidinone (30; R = $BrCF_2CH{=}CHCO$-) and further synthesis stages, gives trans-3,4-difluoromethano-glutamic acid.[195] All four stereoisomers of the highly conformationally constrained amino acid β-isopropylphenylalanine have been prepared from commercially available (4R)- or (4S)-4-phenyloxazolidin-2-one,[196] and an unjustly criticized synthesis of (3R)- and (3S)-piperazic acids from a 5-bromopenta-

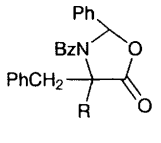
noyloxazolidinone and di-tert-butyl azodicarboxylate has been rigorously authenticated.[197] Related oxazolidinones (31) and (32; R = H) have been used for asymmetric synthesis of β-benzoylaminophenylalanine (an analogue of the taxol side-chain) from (31),[198] and to reveal an unexpected self-addition by-product (32; R = PhCONHCHPh) accompanying alkylation of (32) by diphenylmethyl bromoacetate.[199] α-Methyl-L-phenylalanines carrying halogen substituents in the benzene ring are accessible from the imidazolidinone (33 in Scheme 15).[200] tert-Butyl 1-methyl-2-oxoimidazolidine-4-carboxylate continues to prove interesting in the context of the dynamic kinetic resolution of its 3-(2-bromopropionyl) derivative (see Vol.28, p. 13, and Ref. 532), used for Gabriel synthesis of L- or D-alanine, the outcome depending on the nitrogen nucleophile.[201]



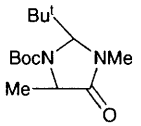
(30)



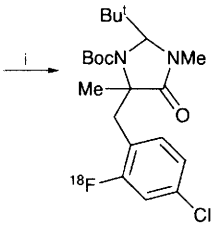
(31)

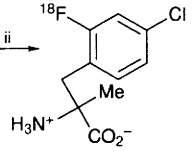


(32)



(33)

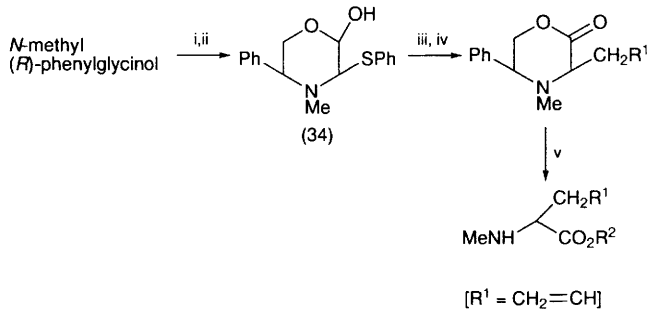




Reagents: i, $ArCH_2I$; ii, H_3O^+

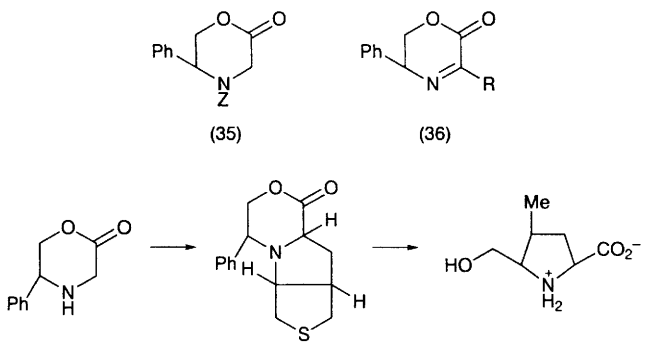
Scheme 15

(R)-Phenylglycinol-derived morpholines, *e.g.* (34) produced by condensation with glyoxal (Scheme 16; R^1 = $CH{=}CH_2$ or $CMe{=}CH_2$),[202] and the more familiar morpholinone (35) formed from ethyl bromoacetate followed by N-protection in a 'one pot' synthesis,[203] are further 'chiral glycine' synthons that have been put to use, the former for a synthesis of N-methyl-D-allylglycine and its homologues. α-Substituted alanines are obtainable through methylation of the morpholinone (36) prepared from (R)-phenylglycinol and an α-keto-ester,[204] a variation on the established use of azomethine ylides generated from this synthon for stereospecific proline synthesis, illustrated most recently for 5-hydroxymethyl-4-methylproline (Scheme 17),[205] and 3,4-dicarboxy-,[206] 2-phenyl-3,4-di(methoxycarbonyl)-[207] and 2-methyl-prolines.[208] Alkylation of the ephedrine-based morpholinone gives (2S,3S,6S)-2,3-methano-2,6-diaminopimelic acids and (2S,3S,6R)- and (2R,3R,6S)-isomers *via* the lithium enolate (37),[209] and N-Fmoc-4-(phosphonodi-

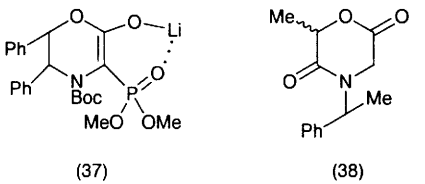


Reagents: i, glyoxal; ii, PhSH; iii, TMSCl, then $CH_2{=}CHCH_2SiMe_3$ + $ZnBr_2$; iv, oxalyl chloride + DMSO; v, routine hydrolysis, hydrogenolysis

Scheme 16



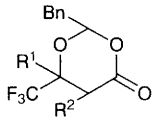
Scheme 17



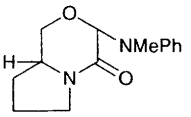
fluoromethyl)-L-phenylalanine has been prepared from the same synthon.[210] Further syntheses of D- or L-amino acids by enantiospecific alkylation of N-[(S)-1-phenylethyl]morpholin-2,5-diones (38) have been published.[211]

The dioxanone (39) has been introduced for α-amino acid synthesis as substrate for amination by BocN=NBoc, and demonstrated for asymmetric synthesis of (2R,3S)- and (2S,3R)-2-amino-3-trifluoromethyl-3-hydroxyalkanoates.[212] A novel synthon (40) shows considerable promise, from the point of view that the L-prolinol moiety can be recycled; further development is needed (moderate optical purity in preparations of N-methyl-L-allylglycine and related L-amino acids).[213]

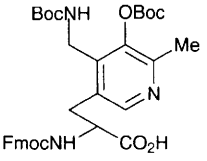
The 'chiral glycinamide' $NH_2CH_2CONMeCHMeCH(OH)Ph$ derived from ψ-ephedrine (see Vol. 28, p.12) continues to show promise, *e.g.* for the synthesis of L-2′-azatyrosine[214] and an amino acid carrying the pyridoxamine moiety (41), noting that hydrolytic removal of the chiral auxiliary needs harsh conditions that cause partial loss of Boc groups.[215] Syntheses of representative D- and L-N-methylamino acids have also been achieved[216] with this approach, with the claim that the chiral auxiliary is easily removed by hydrolysis in hot water or in aqueous dioxane.



(39)



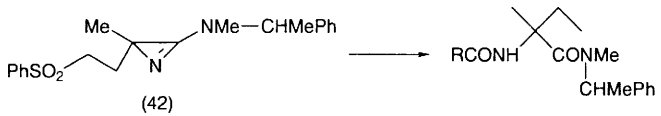
(40)



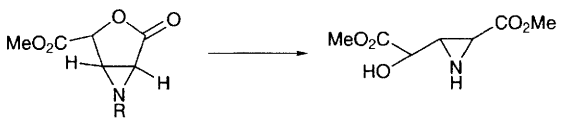
(41)

Claisen rearrangement of chiral allyl esters of N-Boc-glycine leading to β-methyl-D-aspartic acid after oxidation ($RuCl_3/NaIO_4$) of the resulting D-alkenylglycine has extended established methodology (see also Section 4.11).[217]

Other routes employing starting materials with amino and carboxy groups in place, but in a latent form (see also Section 6.3), include chiral azirines [*e.g.* 42, used in a synthesis of L-isovaline, *alias* (S)-α-methyl-α-ethylglycine],[218] and chiral aziridines. The lactone (43; R = Ac) from D-ribose, when treated with BF_3/MeOH, generates the novel 2,3-iminoglutamate (44; the first example of the synthesis of an L-glutamic acid derivative from a carbohydrate) but this treatment gives (4S)-hydroxy-(3S)-methoxy-L-glutamic acid with the analogue (43; R = Z).[219] Examples of the use of the latter class of synthon include a synthesis of αα-disubstituted glycines by nucleophilic ring-opening of 2,2-dialkyl derivatives;[220] analogous syntheses of both α- and β-amino acids using magnesium bromide, sodium iodide or sodium bromide, respectively,[221] and using copper-'catalysed' Grignard reagents.[222] A new enantioselective synthesis of N-arylaziridine-2-carboxylic acids involves addition of N-acyl-N-arylhydroxylamines to tert-butyl acrylate using a quaternary salt of a *Cinchona* alkaloid as phase-transfer catalyst.[223]



(42)

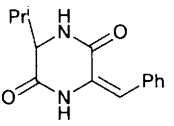


(43) (44)

Chiral α-hydroxy-β-lactams can be made to undergo oxidative rearrangement to give N-carboxyanhydrides of αα-dialkylglycines (see also Vol. 28, p. 19 and Ref. 885).[224]

The usual crop of papers dealing with asymmetric hydrogenation of achiral precursors of α-amino acids provides small improvements here and there, to well-established methodology. A broad review of the hydrogenation of 'dehydro-amino acids' catalysed by homochiral rhodium(I) complexes has appeared,[225] and better than 90% e.e. can be secured with the PROPRAPHOS ligand,[226]and with related catalysts.[227] Another typical example of this approach concentrates on the assessment of other chiral diphosphines, *e.g.* 2,3-bis(silyloxy)-1,4-bis(di-phenylphosphino)butanes, for use as ligands for rhodium(I) hydrogenation catalysts acting on methyl α-acetamidoacrylate; these turn out to be rather unselective in giving 19-23 % enantiomeric excess (e.e.).[228] D-Mannitol-derived chiral diphosphine catalysts generate e.e. of 24 - 80% in this process.[229] The use of Rh^+ complexed to solid-phase supported homochiral peptides carrying phosphine side-chains offers a promising new variant.[230]

A related approach with a long history (and even worse discrimination) is illustrated by the hydrogenation of the oxime of pyruvic acid catalysed by palladium-alumina in the presence of a homochiral alkaloid (best result: 26% e.e. using ephedrine).[231] Where the hydrogenation substrate is chiral, as with the dioxopiperazine (45), good results can be obtained with simple hydrogenation catalysts (*e.g.* 45 → L-threo-product in 91% e.e.) but with extraordinary dependence on structure; thus, hydrogenation of the bis(N-Boc) derivative of (45) gives the L-erythro-derivative in 95% e.e.[232] Reduction of 2-(N-arylimino)-3,3,3-trifluoropropionates by a chiral borane gives (R)-trifluoroalanine in only 62% e.e.[233]



(45)

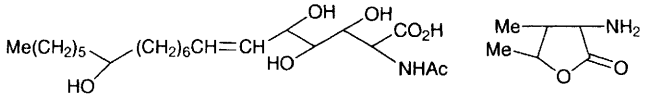
Asymmetric synthesis of *vic*-amino-alcohols, illustrated by oxa-Michael addition of (-)-N-formyl norephedrine to nitroalkenes and $NaBH_4$-Pd/C reduction including removal of the chiral auxiliary,[234] provides close relatives of the amino acids that are useful in synthesis (see also Refs. 125, 126).

4.3 Synthesis of Protein Amino Acids and Other Naturally Occurring α-Amino Acids – A number of papers describing the synthesis of amino acids conforming to this title appear elsewhere in this Chapter, because they are used primarily to demonstrate novel applications of synthetic methodology. This section carries papers that describe applications of established methodology for achieving specific targets.

The use of enzymes and whole-cell techniques for the synthesis of familiar amino acids is an inescapable feature of this section, year after year, but only

representative citations for this commercially-important topic can be accommodated in the space available. Reviews cover the production of threonine and lysine from a *Corynebacterium* sp. and a *Brevibacterium* sp.,[235] of L-lysine and other L-amino acids using mutants of *Bacillus methanolicus*,[236] of L-tryptophan from glucose using *E. coli* engineered with the *Enterobacter aerogenes* tryptophanase gene,[237]and microbiological production of L-tyrosine.[238] A general review has appeared,[239] and the use of methanol-utilizing bacteria in this context has been surveyed.[240] New results in this category include L-serine formation from methanol and glycine acted upon by *Methylobacterium* sp. MN43,[241] and a study of parameters determining optimum L-phenylalanine formation by *E. coli* AT2471.[242] The *E. coli* mutant W1485lip2 that generates pyruvic acid has been transformed for use for L-tryptophan production when presented with ammonia and indole,[243] and reductive amination of pyruvic acid employing a NADH regeneration system and alanine dehydrogenase (or the leucine equivalent) has been accomplished.[244] Methyl L-phenylalaninate is an unusual outcome from phenol-ammonia lyase-containing cells of *Rhodotorula glutinis*.[245]

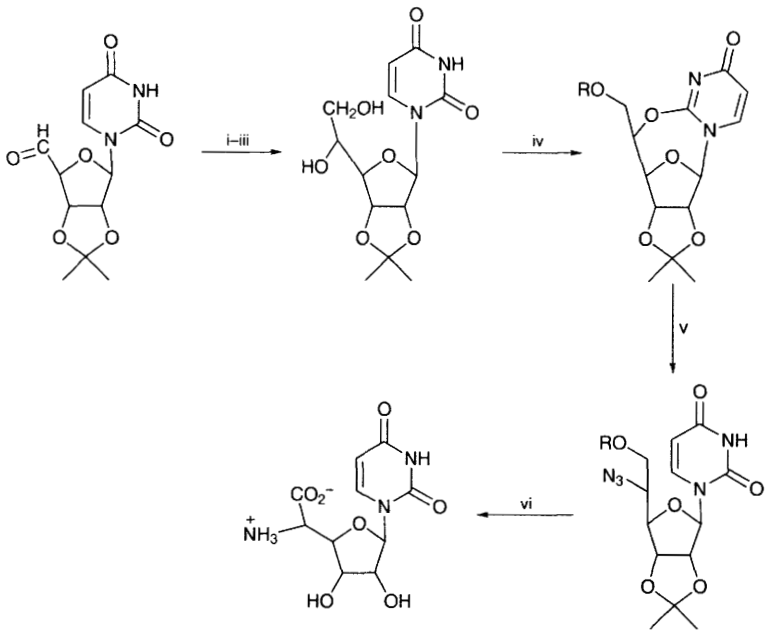
Sphingofungin D (46; the N-acetyl derivative of asperfungin) has been obtained from myo-inositol and (R)-epoxyoctane, thus establishing the (R)-configuration at C-14 based on secure understanding of the stereochemical basis of this nucleophilic ring-opening process.[246] (+)-Polyoxamic acid also offers a challenge for exploring synthesis methodology, and the modest selectivity that often accompanies deracemization of acyclic allyl esters *via* π-allylpalladium intermediates does not cause complications in a route to (E)-4,5-epoxypent-2-en-1-ol, ring-opening with phthalimide being followed by dihydroxylation and established steps.[247] Two new stereoselective syntheses of characteristic metabolites of *Quararibea funebris* have been based on the lactone of (2S,3S,4R)-γ-hydroxyisoleucine (47), including amination of β-angelicalactone.[248]



(46) (47)

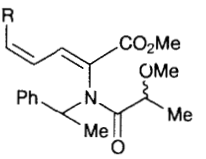
An ingenious strategy for placing an amino acid moiety with correct stereochemistry appears in a synthesis of uracil polyoxin C (Scheme 18).[249] Other natural amino acids with heterocyclic side-chains, (S)-β-pyrazolylalanine and (S)-quisqualic acid, are both conveniently accessible from (S)-tert-butyloxycarbonylaziridine-2-carboxylate through nucleophilic ring opening.[250]

Natural cyclic α-imino acids regularly targetted for synthesis include L-proline, for which a new route from N-protected L-2-amino-5-bromopentanoic acid esters prepared from L-glutamic acid, and a similar approach to 1-aminocyclopropanecarboxylic acid, starting from 2-aminobutanoic acid, has been described.[251] Both enantiomers of cis-4-hydroxyproline have been obtained by double iodocyclization of the diene (48) prepared from the (6R)- and (6S)-forms of N-[(S)-1-



Reagents; i, $AcCN_2P(O)(OMe)_2$; ii, H_2/Pd–C; iii, AD-mix-d; iv, O-protection, then DBU/DMF/70 °C; v, NaN_3; vi, routine steps

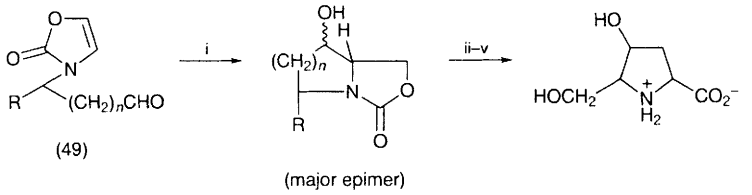
Scheme 18



(48)

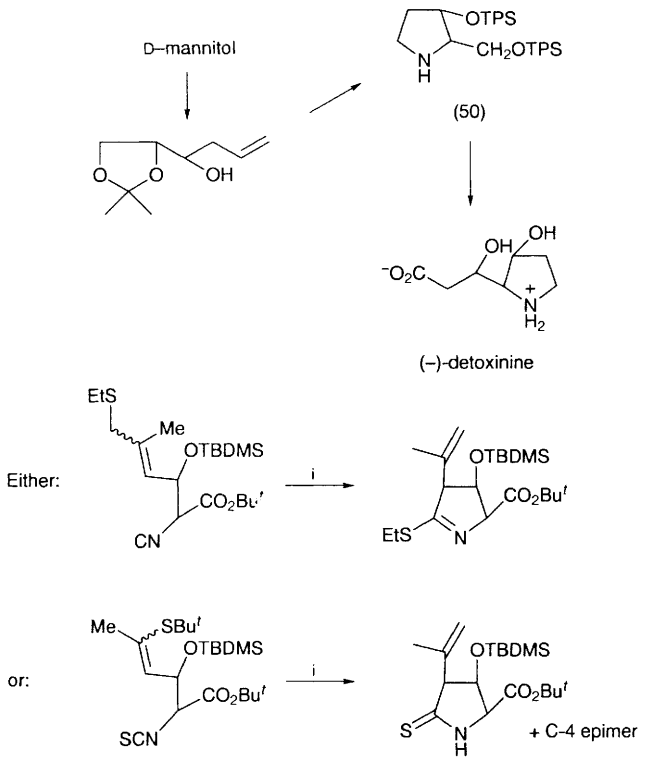
phenylethyl]-6-methylmorpholin-2,5-dione (see also Ref. 211),[252] and a corresponding approach to (+)- and (-)-bulgecinines has been described.[253] An alternative synthesis of (+)-bulgecinine starts with the O-stannyl ketal of the N-substituted oxazolin-2-one (49 in Scheme 19).[254] cis- and trans-3-Hydroxy-D-prolines and (+)-detoxinine (the non-natural isomer) have been synthesized from D-mannitol (see also Ref. 307) *via* (50).[255]

A broadly-applicable route to prolines based on thiol-mediated free radical isomerization has been worked out (Scheme 20)[256] that generates all the structural features of α-kainic acid, except the 3-carboxymethyl group. Extension of this route introduces this feature by intramolecular alkylation *via* a cyclic sulfone involving the isopropenyl group.[257] Trimethylstannyl radical carbocyclization of a diene (51) derived from L-serine, leading to a 2,3-trans-/3,4-cis- and 2,3-trans-/3,4-



Reagents; i, Bu_3SnH/AIBN, reflux 5h; ii, TBSCl [for $n = 1$, R = $PhCH_2OCH_2$]; iii, H_2/Pd–C; iv, $RuCl_3$–$NaIO_4$; v, NaOH in 10% aq. EtOH

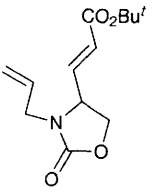
Scheme 19



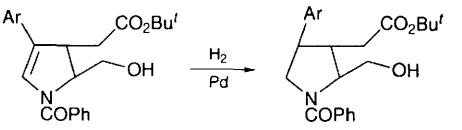
Reagents; i, Bu_3SnH/AIBN

Scheme 20

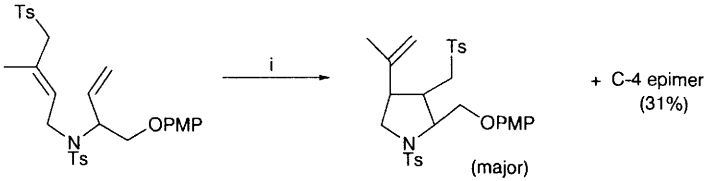
trans- mixture of isomers (2.8:1) in high yield and favouring the natural stereochemistry, has been used for syntheses of (-)-α-kainic acid and (+)-α-allokainic acid.[258] Hydroxyl group-directed heterogeneous catalytic hydrogenation of an enamide (52) establishes the cis-C-3/C-4 stereochemistry in a route to acromelic acid analogues.[259] Stereocontrol is a well-established feature of carbocyclizations, and this step is a feature of a high-yield route to kainoids (Scheme 21) using N,N-



(51)



(52)



Reagents: i, TsSePh (0.15 equiv.), *hν*, C_6H_6

Scheme 21

di-allyl-N-toluene-p-sulfonylamines.[260] The synthesis of kainoids has been reviewed.[261]

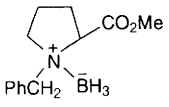
4.4 Synthesis of α-Alkyl Analogues of Protein Amino Acids and of Other Natural α-Amino Acids – This section expands year by year, seeming to suggest a growing interest in these particular homologues of the protein amino acids. The derivatives have their own importance, particularly in enzyme inhibition studies, and synthetic methods undergoing establishment for access to α-amino acids in general are often easily extended to their α-alkyl analogues, as illustrated in preceding sections of this Chapter as well as with papers collected here. Results from Ohfune's group on routes to αα-dialkylglycines have been reviewed.[262]

Several projects described in the preceding sections covering general synthesis methods, include αα-dialkylglycine syntheses. α-Methyl serine, needed for the synthesis of the novel immunomodulator (+)-conagenin, has been obtained through different routes: Katsuki-Sharpless oxidation of methallyl alcohol to give (S)-2-methylglycidol, and rearrangement of the derived trichloroacetimidate,[263] and by an application of the Schollkopf procedure.[264] α-Methylphenylalanine and α-methyl-β-phenylserine have been prepared through ring-opening of N-(toluene-p-sulfinyl)aziridine-2-carboxylic acid.[265]

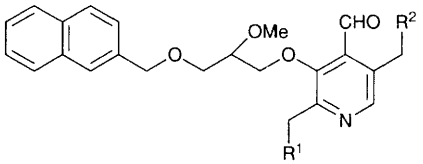
Direct α-alkylation of an α-amino acid derivative is a common approach. The most familiar commercially-available derivatives are often the least satisfactory for this purpose, as seen in carbanion generation from N-Boc hydroxy-L-proline by LDA followed by reaction with an alkyl halide, resulting in only 20% diastereoisomer excesses and modest yields.[266] An extraordinary set of results has been collected for α-benzylation of methyl N-benzyl-L-prolinate in the presence of BH_3-Me_2S [the (S)-product is favoured (54% yield) by the simplest benzylation protocols but with LDA/18-crown-6/HMPA, the (R)-enantiomer is formed], including an X-ray crystal analysis of the intermediate (53).[267]

Electrochemical α′-methoxylation (see also Refs. 882, 883), substitution to give an α′-phenylthio group, α-methylation and reductive removal of the phenylthio group has been used to prepare non-racemic α-methyl-proline and α-methyl-pipecolic acid.[268]

An effective substrate is an imidazolinone from (R)-4-hydroxyphenylglycine (C-2-epimer of 33; N-benzoyl, R = 4-$PhCH_2O$-C_6H_4-), providing the basis for the synthesis of (S)-(+)-α-methyl-(4-carboxyphenyl)glycine;[269] the same target, studied independently from the point of view of establishment of its absolute configuration through X-ray crystal analysis,[270] was obtained by resolution of the racemate through N-(L-leucin)ylation and anion exchange separation of the resulting diastereoisomers followed by hydrolysis. Asymmetric alkylation of α-amino acid esters by use of a novel pyridoxal model (54) carrying a chiral ionophore (the Na^+ ion plays an important role) has been reported.[271]



(53)



(54) R^1–R^2 = (*S*)-$S(CH_2)_5S$–

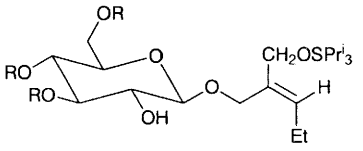
α-Halogenomethylated protein amino acids are a subject of interest in several laboratories, as potential inhibitors of certain enzymes. Their synthesis is therefore bringing out some ingeneous approaches; thus, regioselective alkylation of imines $XCF_2CH(=NCO_2R)CO_2Me$ provides α-chlorodifluoromethyl- and α-bromodifluoromethyl-α-amino acid esters,[272] while addition of HCN to homochiral enamines $TolS(O)CH=C(CHF_2)NH_2$ has been used to start syntheses of (R)-α-difluoromethylalanine and (S)-α-difluoromethylserine.[273] Both enantiomers of α-trifluoromethylbutyrine have been prepared in the same way from homochiral alkyl p-tolylsulfoxides.[274] Methyl 3,3,3-trifluoro-2-diazopropionate, in the presence of catalytic amounts of copper and di-rhodium tetra-acetate, forms ammonium ylides with amines and amides that undergo [1,2]-Stevens rearrangement (see also Ref. 116) to give α-trifluoromethyl-N,N-dialkylamino acid esters.[275]

4.5 Synthesis of α-Amino Acids Carrying Alkyl Side-Chains, and Cyclic Analogues – This section is devoted for the most part, to the synthesis of near analogues of familiar natural α-amino acids. A variety of differing motives underlies the choice of targets.

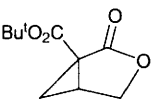
L-tert-Leucine is gaining in importance as a chiral auxiliary (Ref. 6) and its preparation by reductive amination of trimethylpyruvate esters with leucine dehydrogenase can become a continuous process when NADH that is required is regenerated by formate dehydrogenase.[276]

'Methano' analogues of the protein amino acids have served well as conformationally-restricted models for structure-activity studies, and a general approach employing stereoselective cyclopropanation (Et_2Zn/CH_2I_2) of a D-glucose-derived chiral auxiliary (55) has been described (amination is achieved by a Curtius rearrangement at a late stage).[277] A new route to '(-)-(Z)-2,3-methano-L-glutamic acid', *i.e.* a stereoisomer of 1-amino-2-carboxymethyl cyclopropanecarboxylic acid, has been described, proceeding *via* cyclopropanation of a D-glyceraldehyde-derived aminopentenoate to a protected (-)-(Z)-cycloaspartic acid derivative, and final Arndt-Eistert chain extension.[278] The same approach provides (-)-isomers of allocoronamic acid, allonorcoronamic acid, (Z)-2,3-methanohomoserine, and (Z)-2,3-methanomethionine.[279] Three stereoisomers of N-protected 2,3-methanomethionine have been prepared through conventional methods suitable for large-scale production, two from (S)-1-O-benzylglycerol, the other through ammonolysis of the malonate (56).[280] 2,3-Methanophenylalanine, prepared by cyclopropanation of the protected dehydro-amino acid, adds a further example to the list.[281] A mixture of cis/trans 2,3-methanotryptophans has been obtained by cyclopropanation of the corresponding azlactone,[282] and 2,3-methanopipecolic acid has been prepared through (3-chloropropylcyclopropan)ation of methyl N-benzylideneglycinate followed by cyclization.[283] An alternative route to methano-pipecolates[284] and methano-kainoids[285] exploits the recently acquired understanding of relevant radical cyclization methodology (*cf* Ref. 258), and is based on cyclization of trimethylstannyl radicals attached through a methylene group to suitably structured acrylates and acrylamides.

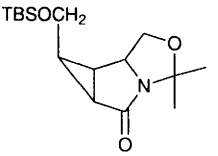
Carboxycyclopropyl-L-glycines, *alias* 3,4-methano-L-glutamic acids, have been generated from the pyroglutamate derivative (57).[286] The general synthesis of 1-aminocyclopropane-1-carboxylic acids, a subject that has been reviewed,[287] has also been developed strongly, in fulfilment of the interest in conformationally-restricted amino acids that has attracted several groups to the 'methano-amino acids'. Cyclopropanation of the oxazinone derivative (58) using the Corey ylide $CH_2{}^-S^+(O)Me_2$ gives access to 1-amino-2-alkylcyclopropanecarboxylic acids.[288] Further examples include a synthesis of (2S,1'S,2'S,3'R)-2-(2'-phenyl-3'-carboxycycloprop-1'-yl)glycine, which is a potent glutamate receptor antagonist,[289] and a synthesis of all sixteen stereoisomers of 2-(2'-carboxy-3'-phenylcyclopropyl)glycine starting from the racemic aldehyde.[290] The first example of a [1,1,1]-propellane analogue (59), which incorporates the structural feature of linearity of the side-chain carboxy group with the chiral centre, has been reported.[291]



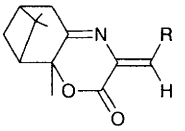
(55)



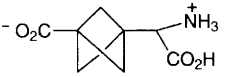
(56)



(57)

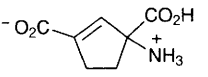


(58)

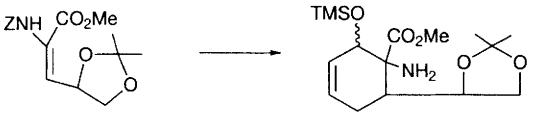


(59)

Tri-anions created from cyclopent-1-ene-1,3-dicarboxylic acids have been aminated with chloramine, to give the corresponding βγ-unsaturated-α-amino acids (60).[292] Four 1-amino-2-phenyl-1-cyclohexanecarboxylic acids have been prepared through asymmetric Diels-Alder addition of 1,3-butadiene to chiral (E)-2-cyanocinnamates, and their N-acryloyl derivatives used in Diels-Alder reactions with cyclopentadiene; poor diastereoselectivity was shown.[293] Diels-Alder reactions of the 'dehydroamino acid' derivatives [61; or the equivalent oxazolin-5(4H)-one][294] and a homochiral 2-substituted 4-methylideneoxazolidinone[295] lead to the 1-aminocyclohexene-1-carboxylic acid (62) and a bicyclo[2.2.2]octane analogue. An analogous bicyclo[2.2.1]heptane (63) has been prepared.[296]



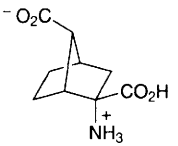
(60)



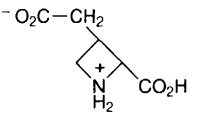
(61) (62)

This Section in all preceding Volumes has reflected the prominent role given in current research to aziridinecarboxylic acids, azetidinecarboxylic acids, and other analogues of proline and pipecolic acid, and their importance continues to be reflected in novel synthetic approaches. Aziridination of αβ-unsaturated esters by ethoxycarbonylnitrene, generated by α-elimination from 4-NO_2-$C_6H_4SO_2ONH$-CO_2Et using CaO, gives good yields;[297] and even higher yields of the same products have been claimed from the interaction of hexahydro-1,3,5-triazines and alkyldiazoacetates in the presence of tin(IV) chloride, though rather poor diastereoselectivity is achieved using N-[(S)-1-phenylethyl]triazines.[298]

General synthesis protocols have been illustrated leading to trans-2-carboxy-

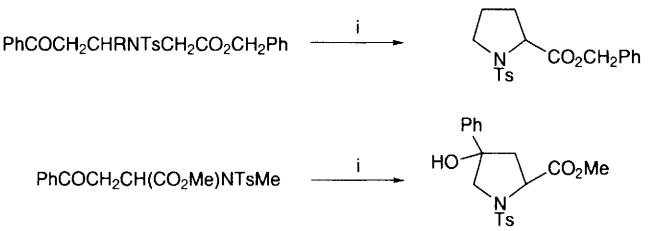


(63)



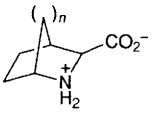
(64)

azetidine-3-acetic acid (64), its diastereoisomers, and homologues,[299] to 4-hydroxy-4-phenyl-L-proline and other hydroxyprolines (Scheme 22),[300] and to highly functionalized 2-methylthio-Δ^1-pyrroline-5-carboxylic acid esters, the latter being formed through diastereoselective 1,3-dipolar cycloaddition of samarium(III)-azomethine ylides $(MeS)_2NCR{=}CH(OSm)OEt$ to αβ-unsaturated esters (as in Scheme 6, Ref. 124).[301] Resin-bound αβ-unsaturated carbonyl compounds have been converted into substituted prolines through cycloaddition to methyl N-benzylideneglycinate, and released from the solid phase by trifluoroacetic acid after N-acylation.[302] The same outcome has been accomplished with a resin-bound azomethine ylide adding to maleimide, a process cryptically described as a 'three-component 1,3-dipolar cycloaddition'.[303] Trifluoromethyl azomethine ylides formed from N-trifluorothioacetyl pyrrolidine have been added to αβ-unsaturated esters and analogues to give bicyclic proline analogues with nitrogen at the ring junction;[304] isomeric bicyclic proline analogues may be prepared by Birch reduction of O-methyl-L-tyrosines, followed by acid-catalysed aminocyclization, giving cis-6-hydroxyoctahydroindole-2-carboxylic acid.[305] Yet another type of bicyclic proline analogue (65) is accessible through cycloaddition of cyclopentadiene or cyclohexadiene to the chiral iminium ion derived from (+)-1-phenylethylamine with freshly prepared benzyl glyoxylate $PhCH_2O_2CCHO$, followed by hydrogenation (H_2/Pd-C).[306]

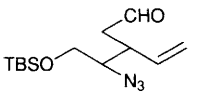


Reagents: i, *hν*

Scheme 22



(65)



(66)

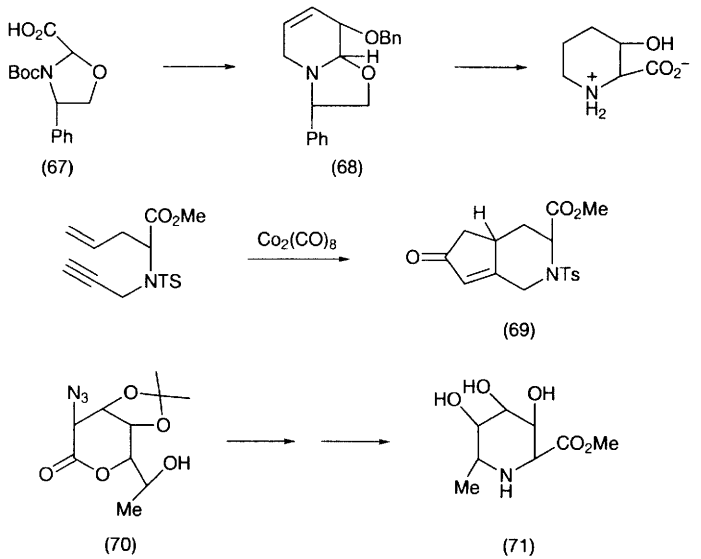
D-Mannitol has been developed into γ-azido-aldehydes (66; see also Ref. 255) and iminophosphoranes derived from them undergo Staudinger - aza-Wittig

cyclization under mild conditions to give 3-, 3,5- and 3,4,5-substituted D-prolines.[307]

7-Azabicycloheptane-based amino acids have been prepared by transannular alkylation of 5-bromoethylproline prepared from L-glutamic acid.[308]

3-Carboxypipecolic acids (*i.e.* piperidine-2,3-dicarboxylic acids) can be accessed by aza-annulation of enamino esters of a morpholinone of (S)-phenylglycinol (*cf* 34), using acryloyl chloride or a homologous alk-2-enoyl halide.[309] (2S,3S)-3-Hydroxy analogues have been obtained from the (R)-phenylglycinol-derived oxazolidine-2-carboxylate (67) *via* (68),[310] and racemic 3-methyl- and ethyl-pipecolate esters have been obtained from the triflate of commercially-available 3-hydroxypyridine-2-carboxylic acid through Pd-catalysed cross-coupling.[311] Bicyclic pipecolates, *e.g.* (69) have been prepared through an unusual intramolecular Pauson-Khand reaction (either solution or solid-phase modes) applied to intermediates prepared from either (S)-allylglycine or RS-propargylglycine.[312] The readily available[313] L-rhamnose-derived azidolactone (70) leads to trihydroxypipecolic acids, *e.g.* (71),[314] and has also been used to prepare spirohydantoins and spirodioxopiperazines joined at the anomeric position, through HOBr oxidation (Ref. 313). (2S,4R)- and (2R,4S)-4-Hydroxypipecolic acid lactones are formed (60:40) through iminium ion cyclization of the N-(3-butenyl)-(S)-α-methylbenzylamine adduct.[315] A short synthesis of β-amino-alkanols based on the pipecolic acid structure exploits the spontaneous cyclization, after deprotection, of the products of Sharpless asymmetric epoxidation of 7-N-phthalimidohept-2-enols.[316]

Cyclization of hydrazones of α-keto acid esters, or δ-hydrazinopentanoates, provides 6-substituted perhydropyridazine-3-carboxylic acid esters.[317]



4.6 Models for Prebiotic Synthesis of Amino Acids – Some 40 years after the classic Miller-Urey experiment, which remains the inspiration for most of the ensuing research, this topic continues to generate new information, illustrated with the formation of amino acids in a $N_2/H_2O/CH_4$ mixture bombarded with high energy protons (a major constituent of cosmic radiation).[318] A review has appeared.[319]

A study using UV radiation (254 nm) acting on allyl alcohol in aqueous ammonium hydroxide illustrates the mild energy requirements established in recent years that lead to the generation of amino acids in organic - inorganic media. No fewer than ten aliphatic protein amino acids have been formed in this particular reaction mixture, together with 2-amino-2-methylpropanoic acid and β-alanine.[320] Formaldehyde and HCN are more plausible prebiotic building blocks and lead to amino acids and other organic compounds now known to be essential to life. Aspartic acid, alanine and valine, together with adenine and other heterocyclic compounds, are formed *via* diaminomaleonitrile in this system. A role for montmorillonite as a template for bringing these reactants together has been strongly advocated.[321]

The current interest in deep sea hydrothermal vents as the prebiotic, and presumably continuing, source of amino acids, has been reviewed.[322]

4.7 Synthesis of α-Alkoxy-α-Amino Acids, and Analogous α-Hetero-atom Substituted α-Amino Acids – Protected α-hydroxy- and α-alkoxy-α-amino acids are intermediates in syntheses of hetero-atom analogues, for example the preparation of N-Fmoc-α-(tert-butyloxycarbonylamino)-glycine from Fmoc carbamate, glyoxylic acid, and tert-butyl carbamate.[323] N-Alkyl analogues may be prepared through amination of the protected α-hydroxyglycine in the same way, or through amination (using BocNHR + NBS) of the α-alkylthioglycine $FmocNRCH(SPr^i)CO_2H$ prepared from the corresponding α-hydroxyglycine derivative.[324] H_2SO_4-Catalyzed O-alkylation of methyl N-Z-α-hydroxyglycinate has been achieved (see Refs. 882, 883), and remarkably, this aminal can be saponified to give an N-protected intermediate suitable for use in peptide synthesis.[325]

The condensation of oxalyl carbamate with triethyl phosphite gives the phosphorane $BzlO_2CN(Bzl)C(CO_2R)=P(OEt)_3$ from which α-diethylphosphonylglycine esters $H_2NCH[P(O)(OEt)_2]CO_2R$ are readily obtained through phosphorus functional group conversion (Me_3SiBr or HBr/AcOH) and hydrogenolysis (H_2-Pd/C).[326] α-Diethylphosphonylglycine derivatives are useful in synthesis (Refs. 95, 355, 370).

Section 4.4 carries some further examples of the preparation and use of α-alkoxy-α-amino acid derivatives.

4.8 Synthesis of α-(ω-Halogeno-alkyl)-α-Amino Acids – The year has been a prolific one in this field, producing a crop of reviews of the general field of fluorinated amino acids,[327] of fluorinated amino acid precursors of amine neurotransmitters,[328] and of γ-fluoro-α-amino acids.[329] (S,S)-δ-(Fluoromethyl)-ornithine has received attention in a review[330] that acknowledges the importance

of this compound as an ornithine aminotransferase inhibitor. Numerous papers in this Symposium Volume are of broader interest in amino acid synthesis, for example a detailed coverage of the use of asymmetric aldol reactions leading to enantiopure amino acids,[331] and routes to fluorinated cyclopropanes for use in the preparation of 'fluoromethano'-amino acids[332] (see also Section 4.5).

Fluorination of ethyl N-acetyl-DL-leucinate using CF_3OF causes γ-fluorination of the side-chain, as well as the expected formation of the N-fluoramide.[333] Indirect routes leading to (2S,3S)- and (2S,3R)-3-fluoroaspartic acids start with esters of D-tartaric acid, aminolysis of the derived epoxide followed by substitution with retention of the hydroxy group using Et_2NSF_3, to give the former target, and fluoride ring-opening of the cyclic sulfate of tartaric acid, followed by substitution with inversion of the triflated hydroxy group by azide providing the diastereoisomer.[334]

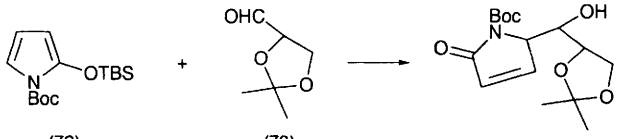
A synthesis of methyl (S)-hexafluorovalinate has been established, in which (R)-(+)-1-phenylethylamine undergoes anti-Michael addition to $(F_3C)_2C{=}CHCO_2Me$. This gives a 52:48-mixture of diastereoisomers from which the (S,R)-hydrochloride fortunately happens to crystallize.[335] Michael addition of the ethyl benzylideneglycinate anion to 3-chloro-4,4,4-trifluorocrotonate, and routine ensuing steps, has led to diethyl 3-(trifluoromethyl)-DL-glutamate.[336]

4,4-Difluoro-DL-glutamic acid has been prepared through aldol addition of ethyl nitroacetate to the ethyl hemiacetal of a difluorinated aldehyde,[337] and the procedure has also been used to give the 3,3-difluoro-analogue.[338] The activation of the side-chain function by the neighbouring fluorine atoms in the 4,4-difluoro-compound allows selective conversions to be implemented to give the glutamine and ornithine analogues.[339]

4.9 Synthesis of α-(ω-Hydroxyalkyl)-α-Amino Acids – Approaches to the synthesis of the archetypal members of this family, serine and threonine, and analogues, are mentioned elsewhere in this Chapter (Sections 4.2, 6.3).

A review has appeared of asymmetric syntheses of β-hydroxy-α-amino acids through aminolysis of chiral epoxy-acids, including the synthesis of the cyclosporin constituent MeBmt using methylamine in this reaction.[340]

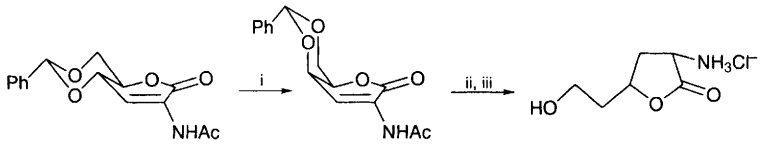
The broad principles of aldolization of glycine and its analogues, to give β-hydroxy-α-amino acids, have become well entrenched in current methodology. These principles have been illustrated further in an exploration of routes to anti-α-alkyl-7-hydroxy-α-amino acids from chelated metal enolates formed from N-protected alanine, ethylglycine, valine, or phenylalanine by treatment with LDA and a metal salt.[341] The pyrrole (72) is a hidden form of glycine (though it is better viewed as a four-carbon synthon of wider applicability in organic synthesis), and its aldolization with the increasingly useful glyceraldehyde synthon (73; *cf* also 61) forms the basis for a synthesis of both enantiomers of trans-2,3-cis-3,4-dihydroxyproline.[342] A different route to these imino acids has already been described (Vol. 21, p. 29). Corresponding aldolization of Grignard reagents with the Garner aldehyde (a close relative of 73; see 121, and Section 6.3) leads to β-hydroxy-α-amino acids with only moderate asymmetric induction.[343]



(72) (73)

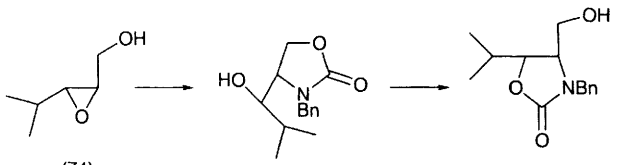
γ-Hydroxy-α-amino acids are formed through 1,3-dipolar cycloaddition of alkenes to nitrones $BnN^{+}(O^{-})=CHCO_2H$; this gives cis-isoxazolidines when the reactants are mixed at room temperature, but gives trans-isomers when triethylamine is also present.[344]

Routes to specific targets are often endowed with particularly interesting synthetic features, or may arise serendipitously from a quite different objective. The syntheses of (2S,4R,5R)-4,5,6-trihydroxynorleucine and of 5-hydroxynorvaline that have been described starting from D-glucosamine, involve precursors derived from an unusual rearrangement of a 5,6-dihydro-2-pyrone (Scheme 23).[345] The key steps in a valuable enantioselective route to βω-dihydroxyalkyl amino acids are Sharpless asymmetric dihydroxylation of αβ-unsaturated esters, 4-nitrobenzenesulfonylation of the more acidic α-hydroxy group, and azidolysis.[346] The same approach to allo-threonine and other β-hydroxy-α-amino acids, *via* azidolysis of the cyclic sulfate of the dihydroxylation product, has been shown to be viable on a large scale.[347] A new asymmetric route to all four isomers of 3-hydroxyleucine (needed for a synthesis of lactacystin) involves conversion of the appropriate homochiral epoxide (*e.g.* 74) into an oxazolidinone with BnNCO, and isomerization.[348]



Reagents: i, $SnCl_4$; ii, H_2/Pd–C; iii, 2M HCl, 100 °C, 12 h

Scheme 23



(74)

4.10 Synthesis of N-Substituted α-Amino Acids – This has become more than a routine topic, with only the opines (Ref. 38) previously offering a high point of interest. N-Aminoalkylglycines carrying one or other of the four nucleobases

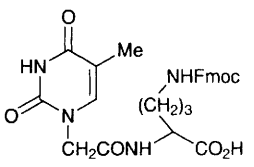
linked to the nitrogen atom have generated interest as precursors of peptide analogues of nucleic acids [known as 'peptide nucleic acids' (PNAs); the topic has been reviewed[349]].

Unremarkable chemistry is involved in the preparation of PNAs suitable for solid-phase synthesis [$H_2N(CH_2)_2NHCH_2CO_2H \rightarrow$4-methoxytrityl-$NH(CH_2)_2N(COCH_2X)CH_2CO_2H$; X = nucleobase].[350,351] The synthesis of homologues (carrying the nucleobase at the β-position of the N-ethyl group) has been reported,[352] and thymine-based PNAs prepared from L-lysine, serine, glutamic acid, aspartic acid, and isoleucine, $H_2N(CH_2)_2N(COCH_2T)CHRCO_2H$ (T = thymin-1-yl), have been described.[353]

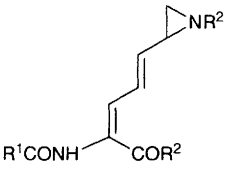
N-Protected L- and D-ornithine carrying a thymine-bearing side-chain to provide PNAs of alternative structures (75) have been prepared and found to be suitable for routine peptide synthesis.[354]

4.11 Synthesis of α-Amino Acids Carrying Unsaturated Aliphatic Side-Chains – Citations of papers describing syntheses of amino acids in this category can also be found in the later Section 6.2 if another amino acid is used as the starting material. However, uses of glycine synthons are dealt with here, since they are fundamental to many classical amino acid syntheses.

Amino acids with olefinic side-chains continue to be prepared in all their familiar forms, though with new substitution patterns; αβ-unsaturated amino acids ('dehydro-amino acids') are represented by dienes (76), formed for use in an azinomycin synthesis from a dialkoxyphosphonylglycine through Horner-Emmons condensation with an aldehyde,[355] and 2-amino-3,3-difluoropropeno-ates, $CF_2=C(NRAr)CO_2Et$ (R = alkyl), prepared from the imino ester $CF_3C(=NAr)CO_2Et$ (Ar = p-MeO-C_6H_4) by treatment with organometallic reagents.[356] (E)-N-Acetyl-dehydrotryptophan ethyl ester and its Z-isomer have been prepared through condensation of indole with ethyl α-nitro-β-ethoxyacrylate $EtOCH=C(NO_2)CO_2Et$ and ensuing steps, as a 1:1-mixture that was separated by flash chromatography.[357] Configurational assignment rested on interpretation of ^{1}H-NMR spectra; the Z-isomer was established by this study to be formed by the incubation of N-acetyl-L-tryptophan ethyl ester with L-tryptophan 2′,3′-oxidase.



(75)



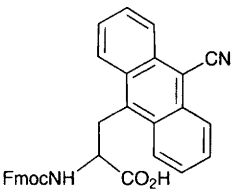
(76)

α-Chlorovinyl- and α-bromovinyl-α-amino acids have been prepared from N-trifluoroacetyl α-vinyl analogues through additions of benzeneselenyl chloride or bromide, respectively, and pyrolytic elimination of the derived sulfoxides.[358]

Further work on the ester enolate Claisen rearrangement route[359] has been published (see also Ref. 217, and Vol. 28, p. 16) extending its use to the preparation of polyhydroxylated γδ-unsaturated amino acids,[360] and to βγ- and γδ-unsaturated amino acids when starting with allyl esters of dehydroamino acids.[361] The route leads satisfactorily to α-alkyl-γδ-unsaturated amino acids starting from a variety of α-amino acids,[362] and to sterically-demanding targets (including demonstration of diastereo- and enantioselectivity when the reactant was used in the form of a metal chelate including quinine).[363] Allenic side-chains can be introduced through the equivalent route, involving the rearrangement of propargylic esters.[364] Alternative routes have been explored, including highly enantioselective allylation of oximes of α-ketoesters $BnON{=}CR^1CO_2R^2$, for the preparation of allylglycine and its homologues, including the α-methyl-α-amino acid.[365]

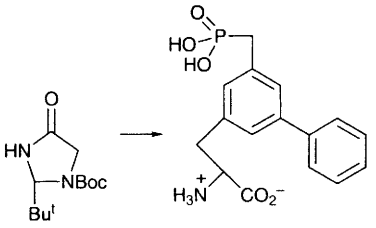
The synthesis of ethynylglycine, and of other βγ-alkynyl-α-amino acids, has been reviewed.[366] 'δ-Acetylenic amino acids' have been obtained through Pd-mediated Heck-type arylation and by Simmons-Smith homologation of terminal alkynes for use in alkylation of N-benzylideneglycine esters.[367]

4.12 Synthesis of α-Amino Acids with Aromatic or Heteroaromatic Groupings in Side-Chains – Common amino acids carrying functional groups in side-chains continue to serve as starting materials for the preparation of aryl and heteroaryl analogues, and current examples are covered later in Section 6.2. More fundamental approaches include enzymatic synthesis (tyrosine phenol-lyase) of fluorinated tyrosines from fluorophenols and ammonium pyruvate,[368] and laboratory syntheses of tyrosine analogues using diethyl formamidomalonate.[369] A new synthesis of 3,4-dimethoxyphenylalanine (a fluorescence quenching amino acid) and a synthesis of the fluorescent cyanophenanthrene analogue ('Flu'; 77) have been described, through alkylation of $Ph_2C{=}NCH_2CO_2Bu^t$.[370] Cobalt-mediated alkylation of (4R)- and (4S)-3-acetoacetyl-4-benzyloxazolidin-2-ones [30 → MeCOCHRCOX → AcNHCHRCOX *via* Schmidt rearrangement of the azidoamide], using alkyl halides that are known to react through radical intermediates, such as benzylic halides, has been used to prepare enantiopure diphenylmethyl, fluoren-9-yl, and adamant-1-yl glycines.[371] Corresponding use of the imidazolidinone chiral auxiliary is illustrated in a route to the biphenyl side-chain (78).[372]



(77)

Increasing effort is being put in to the discovery of amino acids that affect NMDA receptors, and modification of the aromatic side-chains of common



(78)

amino acids has led to useful lead compounds. A modified di-iodotyrosine (79) provides a new example;[373] the phosphonate analogue of L-phenylalanine, $PhCH_2CH(NHCOPh)P(O)(OMe)_2$[374] and (2S,4S)-2-amino-4-(4,4-diphenylbutyl)-pentane-1,5-dioic acid[375] are among several other amino acids cited in this section that were prepared for their pharmacological potential. Many more analogues prepared from phenylalanine, tyrosine and tryptophan are listed in Section 6.3.

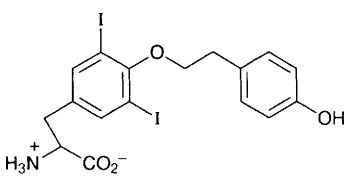
The synthesis of novel excitatory amino acids carrying isoxazolyl side-chains for use in related receptor studies has continued to develop using established methodology (see Vol. 28, p. 33), with 2-amino-4-(3-hydroxy-5-methylisoxazol-4-yl)butanoic acid emerging as a highly selective metabotropic compound at the $mGlu_6$ receptor.[376] The thymine derivative (80) is an 'alanine PNA' (see Section 4.10) prepared from the L-serine-derived β-lactone.[377]

Syntheses of other heteroaromatic relatives include (81) and (82) as powerful bidentate ligands for metal ions, *e.g.* for zinc(II),[378] and the thiatryptophan (83), prepared by Pd-mediated Heck cyclization of the benzoyloxime ether of ethyl (E)-2-oxo-5-bromo-3-pentenoate.[379] (S,S)-Pyridin-2,6-diyl bis(alanines) (84) have been prepared from 2,6-pyridine dicarbaldehyde through Horner-Emmons condensation with a protected dialkoxyphosphonylglycine followed by asymmetric hydrogenation $[H_2/Rh\{(COD)(R,R\text{-}DIPAMP)\}BF_4]$, after finding that double Heck coupling with Boc-amino acrylate esters was unsuccessful.[380] A synthesis of N^{in}-methyl-7-azatryptophan starts with the readily available amino acid.[381] cis- and trans-2,3-Methanotryptophans feature in an application of oxazolones in amino acid synthesis (Ref. 282).

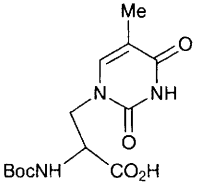
Indoline 2,2-biscarboxylates (85) have been prepared from diethyl bromomalonate and o-bromomethyl-N-trifluoroacetylanilines.[382]

4.13 Synthesis of α-(N-Hydroxyamino) Acids – A number of papers discussed in other Sections deal with these compounds which are usually prepared from α-oximino esters (Refs. 379, 424).

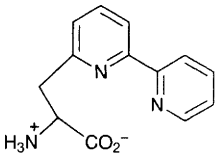
4.14 Synthesis of α-Amino Acids Carrying Aminoalkyl Groups, and Related Nitrogen Functional Groups, in Side-chains – β-(Phenylamino)-phenylalanine has been prepared as a mixture of diastereoisomers through condensation of trans-2-oxo-1,5-diphenyl-4-imidazolidineamide (*cf* 30; NH in place of ring O, CO_2H at C-4) with N-benzylideneaniline, followed by hydrolysis.[383] In a similar way to a



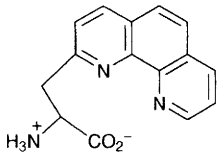
(79)



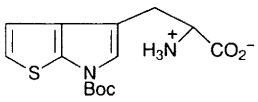
(80)



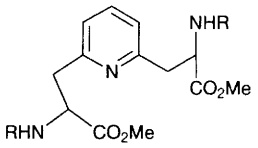
(81)



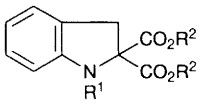
(82)



(83)



(84)



(85)

standard synthesis of β-hydroxy-α-amino acids, amino analogues have been prepared from methyl isocyanoacetate by AuCl(cyclohexylisocyanide) catalysed addition to imines.[384]

α-Amino-β-lactams are formed as a mixture of isomers from triethylamine-induced condensation of tetrachlorophthalimidoacetyl chloride with an imine, but the trans-isomer predominates under microwave irradiation.[385] Another use for these synthons, for peptide synthesis, has been explored.[386]

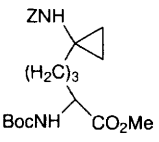
The L-lysine analogue (86) has been prepared from N-Boc-2,2-dimethyl-5-(3-hydroxypropyl)oxazolidine through a lengthy sequence of functional group manipulations from the hydroxy group, notable for a phosphonate-promoted cyclopropanation of the $Et_2O_3PCH(CO_2Et)CH_2CH_2CH_2$ side-chain.[387] An arginine analogue $R^1N{=}C(NH_2)NH(CH_2)_3CH(NH_2)P(O)(OH)R^2$ has been prepared in a search for novel nitric oxide synthase inhibitors.[388]

Further details have been published of a nitrogen analogue of S-adenosylmethionine (Vol. 28, p. 34) that has been prepared from L-glutamic acid and D-adenosine.[389]

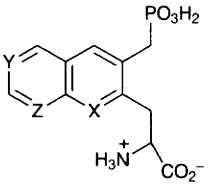
4.15 Synthesis of α-Amino Acids Carrying Sulfur-, Selenium- or Tellurium-containing Side-chains – (2R,3R)-3-Mercaptoaspartic acid is readily obtained through sulfenylation of a protected β-aspartyl enolate dianion using a novel reagent, 4-methylphenyl 2,4-dimethoxybenzylthiosulfonate.[390]

A classical route to seleno- and telluro-methionines, based on ring-opening of DL-2-(acetylamino)butyrolactone with MeSeLi or MeTeLi, employs aminoacylase resolution to obtain enantiomerically-pure samples.[391]

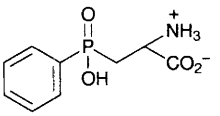
4.16 Synthesis of α-Amino Acids Carrying Phosphorus Functional Groups in Side-chains – A synthesis that exemplifies recent interests in the evaluation of potential competitive NMDA antagonists has led to α-amino acids carrying alkanephosphonate side-chains modified with arene and heteroarene spacers (87, X, Y, Z = N or CH; and the benzofuran analogue).[392] The kynurenine analogues (88) carrying phosphinic acid or methyl phosphinate functional groups in place of the keto-group have been described.[393] A typical route to N-Boc- and N-Fmoc 4-[diethyl phosphono(difluoromethyl)]-L-phenylalanine using the β-iodoalanine organozinc synthon (see also Section 6.3, especially Refs. 923-925) employs Pd-mediated coupling to the appropriate iodoarene.[394]



(86)



(87)



(88)

Silylation of the phenolic function of tyrosine and its analogues is recommended prior to diethyl phosphite - CBr_4 treatment leading to O-phosphotyrosines.[395]

The 4-(phosphonomethyl)pipecolic acid (89), formed through standard olefin - iminium ion cyclization protocol, is a potent and specific NMDA antagonist.[396]

4.17 Synthesis of α-Amino Acids Carrying Boron Functional Groups in Side-chains – Standard routes to DL-o-carboranylalanine and its tyrosine and phenylalanine analogues have been illustrated and developed.[397] The aliphatic compound was obtained by building the carboranyl function on to the N-benzylidene propargylglycine side-chain and the others were prepared by alkylation of the Schiff base with the appropriate benzyl bromide. Curtius rearrangement of 1,12-bis(hydroxycarbonyl)-p-carborane in tert-butanol gives the p-(N-Boc-amino) polyhedral-p-carborane,[398] and other standard routes are Schollkopf synthesis of (S)-5-[2-methyl-1,2-dicarba-closo-dodecaboran(12)-1-yl]-2-aminopentanoic acid[399] and Pd-mediated coupling of iodophenylboronic acid with the L-serine-derived β-lactone to give 4-borono-L-phenylalanine.[400]

An alternative aldolization route using ethyl isocyanoacetate with 4-[1,2-dicarbadodecaboran(12)-1-ylmethoxy]benzaldehyde has led to the corresponding 3-hydroxytyrosine analogue,[401] and p-boronophenylserine (90) has been prepared in the same way.[402]

4.18 Synthesis of Isotopically Labelled α-Amino Acids – The importance of these compounds is, as ever, to satisfy the need for materials either for metabolic and mechanistic studies in the laboratory and *in vivo*, or for clinical investigations. Their synthesis has been reviewed.[403]

Derivatives are listed in order of increasing relative atomic mass of the label. The well-established unpredictability of direct [^{1}H]–[^{2}H]-exchange resulting from drastic treatment of solutions of amino acids in ^2H_2O is further revealed in results for mixtures kept at 400°C and 390 bar pressure.[404] Rapid exchange of the α-proton occurs, but decarboxylation and failure to achieve exchange elsewhere in the molecule limits the value of this approach; a similar outcome, but with racemization and destruction of side-chain functional groups, accompanies attempted exchange in alkaline media under the same conditions.[405] More appropriate access to non-racemic α-[^{2}H]-labelled α-amino acids uses a chiral dioxopiperazine, and, as with deuteriation of 3,4-dehydro-L-proline and routine elaboration to give (2S,3S,4R)-[3,4-$^2H_2$]glutamic acid, also places the label with known stereochemistry.[406]

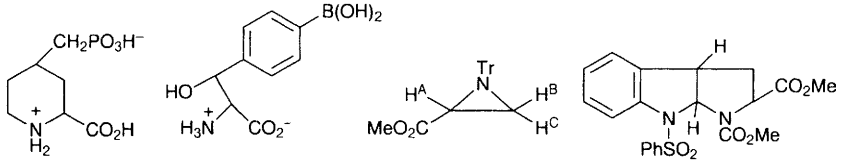
Enzyme-catalysed processes are also appropriate in some cases, and bacterial tryptophan synthase seems to offer a breakthrough for the preparation of α-[^{2}H]-labelled L-enantiomers of alanine, serine, methionine, phenylalanine, asparagine and glutamine, as well as tryptophan.[407] An alternative classical route involving exchange of the α-proton by acetylation and ^2H_2O quenching followed by acylase resolution has been used for preparations of 2S-[2-^{2}H]-tryptophan and -kynurenine.[408] Routes to 2S-O-phosphohomoserine and its [2-^{2}H]- and [3-^{2}H]-isotopomers announced earlier (see Vol. 28, p. 37) and starting from 2S-[2-^{2}H]aspartic acid, have been fully described.[409]

Detailed information is given for the preparation of stereospecifically-[^{2}H]-labelled aziridines (91) starting from corresponding (2S)-isoserines.[410] These products are useful in the synthesis of a variety of β-[^{2}H]-labelled α-amino acids with securely-known stereochemistry. Earlier reports (see Vol. 28, p. 37) are now backed up with full details of routes to (2S,4S)-5,5′-dihydroxy-[5,5-$^2H_2$]leucine and its (2S,4R)-epimer starting with either L-pyroglutamic acid or with 4-hydroxy-L-proline,[411] and the route to (2S,4R)-[5,5,5-$^2H_3$]leucine from L-pyroglutamic acid.[412]

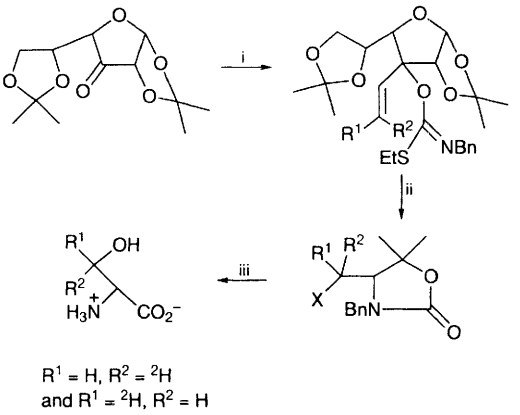
An alternative preparation of chirally β-[^{2}H]-labelled α-amino acids using diacetone-D-glucos-3-ulose has led to (3R)- and (3S)-[3-^{2}H]-(2S)-serine (Scheme 24).[413] More routine syntheses include preparations of [$^2H_9$]- and [$^2H_6$]lysines from [$^2H_{10}$]cyclohexanone through polyphosphoric acid-induced rearrangement of the oxime.[414]

^{11}C-Labelled amino acids are of value in clinical tomography, and synthetic methodology needed to provide them may seem routine, because it is chosen on the basis of reliability, and, above all, a need for speed imposed by the short half-life of the label, and depends on the particular ^{11}C-labelled intermediates available. Nevertheless, these syntheses offer a challenge, to provide a fascinating exercise in economy of time and motion in the laboratory; synthesis of ^{11}C- and ^{18}F-labelled amino acids has been reviewed.[415] Simple acetylation to give α-N-(1-[^{11}C]acetyl)aminoisobutyric acid,[416] and esterification by [^{11}C]methyl iodide to

give N^{ω}-nitro-L-arginine [^{11}C]methyl ester (to be used for *in vivo* studies of this nitric oxide synthase inhibitor),[417] is in contrast to a more central role for the same reactant in classical amino acid synthesis in routes to [^{11}C]aminoisobutyric acid[418]and to α-[^{11}C]methyl-L-tryptophan.[419] The last-mentioned preparation from the well-established tryptophan synthon (92), involving the successive generation of its anion with LDA, deprotection (TFA and alkaline hydrolysis), and HPLC purification, occupied 30-35 minutes.



(89) (90) (91) (92)



R^1 = H, R^2 = ^{2}H
and R^1 = ^{2}H, R^2 = H

Reagents: i, $R^1R^2C{=}CHMgBr$, then $EtSCCl{=}NBn$; ii, Br^+, H_3O^+, then X = Br → X = OH; iii, [O], H_3O^+

Scheme 24

Standard oxazolidinone methodology has been used for syntheses of 3-[^{14}C]-(2S,3R)-2-amino-3-(3,4-dihydroxyphenyl)-3-hydroxypropanoic acid ('L-DOPS'),[420] and of (3R)-[4-$^2H_3$]valine, L-[^{15}N]isoleucine and L-[^{15}N]alloisoleucine[421] (involving enzymic asymmetric amination of intermediate keto acids in the latter study). Oppolzer's camphorsultam auxiliary has been used for the preparation of L-[1,2-$^{13}C_2$]amino acids,[422] and when acylated by the $(MeS)_2C{=}^{15}N^{13}CHR^{13}CO$-grouping and subjected to familiar manipulations, has (for the first time, it is claimed) provided L-amino acids labelled with ^{2}H, ^{13}C, and ^{15}N.[423] Hydroxyamino acids have been prepared through Zn/H^+ reduction of the [^{15}N]oxime of the N-acylcamphorsultam.[424] Standard protocol for the

conversion of glutamic acid into lysine employing $Na^{13}CN$ has given the [6-^{13}C]isotopomer.[425]

The CNS imaging agent (S)-(2-[^{18}F]fluoro-4,5-dihydroxyphenyl)-2-methyl-L-alanine has been obtained from the corresponding acetophenone,[426] and 6-[^{18}F]fluoro-O-pivaloyl-L-DOPA has been prepared, using [^{18}F]acetyl hypofluorite, for similar metabolic studies;[427] in this preparation, 2,6-[^{18}F]difluoro-L-DOPA is a significant side-product.[428] The preparation of α-methyl-p-chloro-o-[^{18}F]fluorophenylalanine has been described in an earlier Section (Ref. 200).

Nucleophilic aromatic substitution of N-trifluoroacetyl 6-trifluoroacetoxymercurio-L-DOPA ethyl ester forms the basis of a preparation of 6-[^{125}I]iodo-L-DOPA.[429]

A synthesis of [^{75}Se]selenomethionine[430] has been claimed as a 'first', but the route was established many years ago (Vol. 25, p. 44).

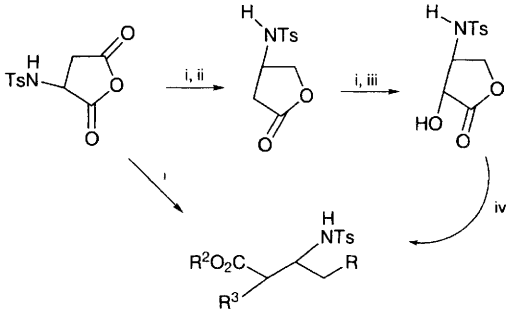
4.19 Synthesis of β-Amino Acids and Higher Homologous Amino Acids – Reviews of routes to β-amino acids and their α-substituted homologues,[431] and of stereoselective syntheses of β-amino acids,[432,433] have appeared.

Routes from α-amino acids have continued to be attractive, especially for the synthesis of β-amino acids carrying an α-chiral centre. A lengthy and rather routine approach from N-Fmoc- or N-Boc-L-α-amino acids *via* the α-amino aldehyde and the propargyl alcohol to give XNHCHRCH(OH)C≡CH (further protected as the tetrahydropyranyl ether) followed by generation of the carboxy group has been explored.[434] Homologation of α-Z-amino aldehydes into α-benzeneselenyl-β-amino aldehydes provides opportunities for further homologation to give amino oxiranes and δ-amino acids,[435] and aldolization of α-Boc-amino aldehydes with 4-isopropyloxazol-5(4H)-one (a nucleophilic aldehyde equivalent) gives β-amino-α-hydroxyalkanoic acids.[436] Diethyl 2-amino-1-hydroxy-3-phenylpropylphosphonate has been obtained by the addition of diethyl phosphite to an N-protected L-phenylalaninal.[437]

Diazomethyl esters of α-amino acids have long been used (Wolff rearrangement) for homologation, and have been newly studied for conversion into β-amino acid esters through rearrangement using silver benzoate in the presence of triethylamine and a nucleophile (*e.g.* $HOCH_2CH_2CMe_2OH$).[438]

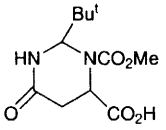
L-Aspartic acid is a special case in this context, being both an α- and β-amino acid; elaboration of its α-carboxy group (see also Section 6.3) into a particular α-substituent is illustrated for a range of syntheses of (R)-3-aminobutanoic acids (Scheme 25), including the preparation of 2-hydroxy-analogues through electrophilic hydroxylation.[439] A route to (R)-3-amino-4-phenylbutyric acid involves a more straightforward use of aspartic acid, as the carbonyl component in Friedel-Crafts acylation of benzene.[440] D-Asparagine, converted into the nitrile $Bn_2NCH(CH_2OH)CHRCN$, leads to αβ-disubstituted β-amino acids.[441] The preparation from L-asparagine and pivaldehyde of the general purpose β-amino acid synthon (93) has been carefully worked out.[442] Alkylation of (93; H in place of CO_2H, PhCO in place of CO_2Me) gives β-substituted β-alanines.[443]

Among acyclic natural α-amino acids, the pre-eminent synthetic challenge remains ADDA, and a new synthesis combines (S,S,E)-$PhCH_2CH(OMe)CH$-



Reagents: i, $NaBH_4$; ii, LDA, TMSCl; iii, NaHDMS, $PhSO_2N$(O)$CHPh$; iv, TMSI, then R_2CuLi

Scheme 25



(93)

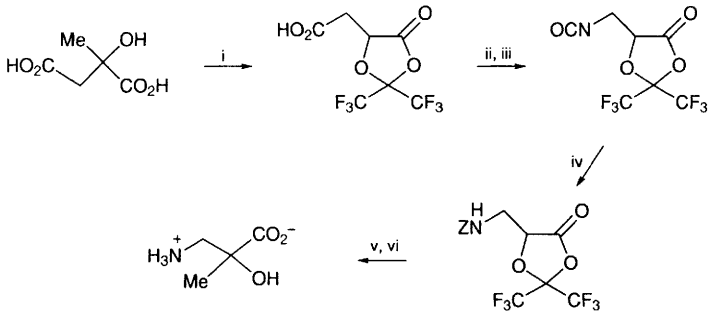
MeCH=CMeI, prepared from (S)-lactic acid, and (S,S,E)-Me_3SnCH=CHCH(NHBoc)CHMeCO_2Me prepared from D-aspartic acid, in a $[Cl_2PdMeCN)_2]$-catalysed cross-coupling reaction.[444] An equivalent route from $PhCH_2CH$(OMe)CHMeCH=CMe$CH_2P^+Ph_3$ Br^- and OHCCH(NHBoc)CHMe-CO_2Me has been reported.[445] A quite different approach[446] starts from D-glucose and places the β-amino acid moiety into the molecule at the last stage through development of the carboxy group from the acetal of a 4-aminopyran.

Routes to β-amino acids from other α-amino acids are covered in the later Section 6.3.

A variety of other β-alanine synthons is being developed, *e.g.* the isocyanate prepared from (S)-(+)-citramalic acid, as used in the preparation of (S)-α-methylisoserine derivatives (Scheme 26).[447] More distant relatives of β-alanine such as the protected syn-2R-amino-1,3,4-triol (94) obtained from D-iso-ascorbic acid,[448] and the anti-α-aminoalkyl epoxides (95)[449] are being evaluated; the latter synthons are particularly useful as cationic β-aminoalkanol equivalents, and have been prepared independently[450] from 5-chloromethyl-4-methoxyoxazolidin-2-one. β-Aminonitriles, *e.g.* that formed from the β-azidonitrile derived from glucosamine,[451] are also latent β-amino acids.

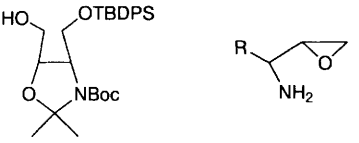
The construction of more complex structures, achieved by starting with a β-amino acid, is covered mostly in the later Section 6.3.

The other synthesis approaches to β-amino acids can be grouped together on the basis of (i) β-amination of a carbonyl compound -C-C-COR ('N + C_3



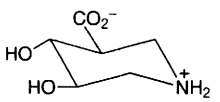
Reagents: i, $(CF_3)_2CO$, DMSO; ii, $SOCl_2$; iii, $TMSN_3$/toluene/80 °C; iv,BnOH, $CHCl_3$; v, H_2O, Pr^iOH; vi, H_2/Pd–C

Scheme 26



(94) (95)

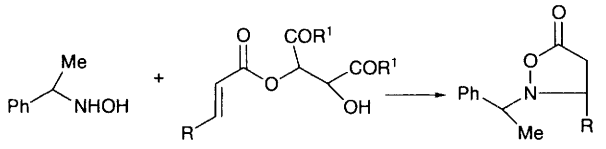
condensation'; see also Refs.80, 92), (ii) β-carboxylation of an ethylamine (-N-C-C- + 'CO_2'), or (iii) condensation of N-C + C-C units. The simplest approach to amination is represented by azidolysis of anhydrides of β-chloro-acids, and routine development to give the amino group.[452] Greater complexity is seen in the development from the primary azide formed from D-arabinose, through numerous stages to the new glucuronic acid-based iminosugar (96), a pipecolic acid isomer that is a potent β-glucuronidase inhibitor.[453] Conversion of an acid chloride of thiomalic acid into an isocyanate and routine conversion into carbamates yields DL-isocysteine.[454] (S)-2-(Aminomethyl)butanedioic acid has been prepared through stereoselective alkylation of the sodium enolate of an Evans acyloxazolidinone (30; R = vinyl or 3,4-dimethoxyphenyl group) with methyl bromoacetate, followed by oxidation of R into carboxyl, then Curtius rearrangement.[455]



(96)

Diastereoselective conjugate addition of lithium (α-methylbenzyl)benzylamide to αβ-unsaturated esters has been illustrated further, for syntheses of the δ-hydroxy-β-lysine constituent of negamycin[456] and of (2S,3S)- and (2R,3S)-2,3-

diaminobutanoic acids.[457] Other amination processes are represented in hydroxyamination of an αβ-unsaturated ester (Scheme 27),[458] and asymmetric aminohydroxylation of alkenes, *e.g.* ethyl trans-crotonate with chloramine-T/$K_2OsO_2(OH)_4$/dihydroquinine/phthalazine gives ethyl (2R,3S)-N-(toluene-p-sulfonyl)-3-amino-2-hydroxybutanoate in 74% e.e.[459] The viability of this route has been realized through recently-disclosed mild de-sulfonylation conditions. Biomimetic Miller cyclization of a β-hydroxy acid O-methyl hydroxamate into an N-methoxy-β-lactam,[460] biomimetic base-catalysed transamination of fluorinated β-keto-esters with benzylamine to give β-fluoroalkyl-β-amino acids,[461] and a related approach to give syn-β-amino-α-hydroxyacids starting from βγ-unsaturated α-ketoesters[462] have been reported.



Scheme 27

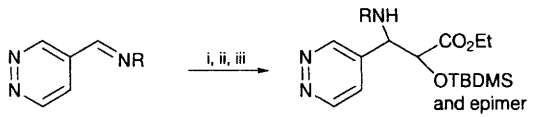
β-Enamino esters can be reduced to α-amino esters using sodium triacetoxyboron hydride in acetic acid, with good diastereoselectivity and enantioselectivity if the N-substituent is a homochiral grouping.[463] Reduction of homochiral α-hydroxy-βγ-unsaturated nitriles (formed through R-oxynitrilase-catalysed addition of HCN to αβ-unsaturated aldehydes) gives α-hydroxy-β-amino acids, as illustrated in a synthesis of isoserines.[464] Direct hydroxylation of enolates of N-substituted 3-amino-3-phenylpropionate, to give the taxol component (2R,3S)-3-phenylisoserine, can be accomplished using the oxodiperoxymolybdenum-pyridine-HMPA complex,[465] and the same target has been attained both through the equivalent aminolysis of epoxides formed from cinnamates using the cobalt(III)-DMG - O_2 reagent,[466] and through the longer route from homochiral trans-epoxy ester to anti-bromohydrin (using $MgBr_2$ etherate) followed by azidolysis.[467] L-Isoserinal has been prepared from the N-benzylimine of D-glyceraldehyde acetonide (73).[468] 1-Arylthio-1-nitroalkenes formed from α-Boc-amino aldehydes and (4-tolylthio)nitromethane are converted into 5-carboxy-oxazolidin-2-ones (instead of the expected epoxides), using lithium tert-butyl peroxide.[469] These are protected forms of anti-α-hydroxy-β-amino acids; the diastereoisomeric pair derived from 3-amino-2-hydroxyvaleric acid has been separated into threo and erythro forms,[470] and their relative stereochemistry assigned through interpretation of ^{1}H-NMR spectra. The threo-isomer was used for the determination of absolute configuration of the 3-amino-2-oxovaleric acid constituent of poststatin [established to be (S)], through resolution and assignment to it of (2R,3S)-configuration, followed by oxidation and comparison with the natural material.

Wacker aminocarbonylation (synchronous carboxylation and intramolecular amination of an alkene) has been applied for a synthesis of cyclic β-amino acids (Scheme 28).[471]

Reagents: i, $PdCl_2$, $CuCl_2$, CO, methyl orthoacetate

Scheme 28

Imines can be condensed with silyl enolates, a process illustrated in a route to isoserines that also emphasizes the need for a separation step when particular stereoisomers are required (Scheme 29),[472] and this well-established general route has been reduced to its simplest form, the condensation of an aldehyde, a chiral amine, and silyl enolate using $Yb(OTf)_3$ as catalyst.[473] Good diastereoselectivity accompanies the use of methyl L-valinate in this route, which is equivalent to the $Yb(OTf)_3$-catalysed addition of N-(α-aminoalkyl)benzotriazoles to silyl enolates.[474] Simple enol ethers $F_2C{=}CROMe$ react with N-acyliminium ions $R^1CH{=}N^+HCO_2Et$ [formed from $R^1CH(NHCO_2Et)_2$ with Tf_2O] to give β-amino-α,α-difluoroketones,[475] and a similar use of an imine is described in Ref. 153. Bromoacetates of chiral alcohols condense easily with imines under the influence of activated zinc, with high diastereoselectivity in certain cases.[476] Achiral trimethylsilylimines ArCH=NTMS add chiral boron enolates derived from the boron reagent Men_2BBr [Men = menth-2-yl from (+)-menthone] and an α-halothioacetate XCH_2COSBu^t to give α-halo-β-amino thioesters and used for a synthesis of hydroxymethylaziridines.[477] β-Amino thioesters are obtainable also from polymer-supported thioketene silyl acetals and imines through scandium triflate catalysis.[478] Nucleophilic ring-opening of N-tosyl aziridines gives a mixture of β- and γ-amino acids.[479]



Reagents; i, TBDMSO−CH=C(OEt)OTBDMS; ii, $ZnCl_2$; iii, crystallization

Scheme 29

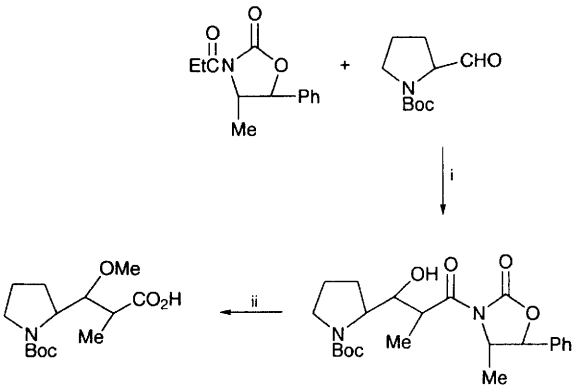
Standard β-lactam synthesis using $(4\text{-}MeOC_6H_4)N{=}CHCF_3$ and the ketene $PhCH_2OCH{=}C{=}O$ leads on to a preparation of methyl syn-3-trifluoromethylisoserinate.[480]

3-Aminoalkanols are prime synthesis targets for uses outside the amino acid field, but routes to them can also serve for β-amino acid synthesis. An example is the synthesis of 1-TBDMS ethers of protected syn- and anti-3-aminoalkane-1,2-diols, selective deprotection and oxidation of the anti-isomer giving (2R,3S)-3-phenylisoserine.[481] Pig liver esterase de-symmetrization of $ZNHCH(CO_2Me)_2$

and tert-butyl esterification of the resulting carboxy group gives (R)-β-lysine after elaboration of the CO_2Me group ($CO_2Me \rightarrow CH_2OH \rightarrow CH_2CN \rightarrow CH_2CH_2NH_2$).[482] A similar chain extension has been exemplified for the standard Oppolzer camphorsultam protocol [$R^*O_2CCH(OAc)CN \rightarrow R^*O_2CCMe(OH)CH_2NH_2$; R* = (1S,2R,4R)-1-dicyclohexylsulfamoylisobornyl residue] for a synthesis of (2R)-α-methylisoserine.[483] A route to 3-aminoalkanols through Michael addition of nitrones $R^1CH{=}NR^2{=}O$ to allyl sulfones $CF_3CH{=}CHCH_2SO_2Ph$ proceeds *via* 5-trifluoromethyl isoxazolidines.[484]

A synthesis of (R)-carnitine from $ClCH_2CO_2Et$ (Grignard addition, reduction, amination) employs dibenzoyl (+)-tartaric acid for resolution,[485] and amine analogues have been prepared through azidolysis of (R)-carnitine β-lactam.[486]

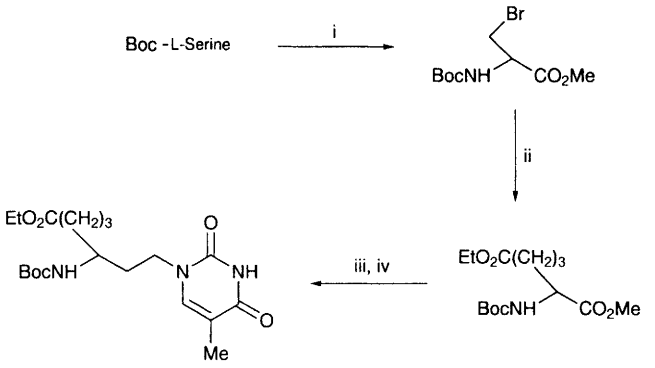
As with other homologues, routes to homochiral γ-amino acids that start from D- or L-α-amino acids should be among the first to be considered. An effective route to dolaproline starting from (S)-prolinal (Scheme 30) illustrates a standard approach, involving Bu_2BOTf-catalysed condensation with a homochiral oxazo-



Reagents: i, Bu_2BOTf, NEt_3; ii, routine steps

Scheme 30

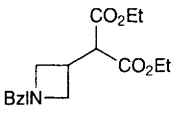
lidinone (*cf* 30)[487] and a protected L-isoleucinal has been condensed similarly with N-[(methylthio)acetyl]oxazolidinone to start a route to dolaisoleucine (3R,4S,5S)-EtCHMeCH(NHR)CH(OMe)CH_2CO_2H.[488] Chiral β-amino alcohols condense with lactams to give 2-(ω-aminoalkyl)oxazolines that may be α-alkylated to give enantiomerically-pure ω-amino acids,[489] although another approach[490] employs (R)-phenylglycinol to generate 2-(β-cyanoalkyl)oxazolines *via* 2-alkenyl analogues, and then $LiAlH_4$ reduction and hydrolysis (the oxazoline C-2 becomes the carboxy group) leading to (S)-4-amino-3-methylbutanoic acid (β-methyl-GABA).[491] Other examples of similar uses of α-amino acid-derived synthons are dealt with in Section 6.3. Arndt-Eistert homologation of β-amino acids prepared from Boc-L-serine (Scheme 31) has been used to prepare new PNAs (see Section 4.10).[492]



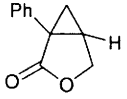
Reagents: i, CBr_4, PPh_3; ii, Vitamin B_{12a}/ethyl acrylate; iii, $CO_2Me \longrightarrow COCHN_2 \longrightarrow (CH_2)_2Br$; iv, thymine

Scheme 31

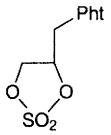
γ-Amino acids have been synthesized through other straightforward approaches, such as a route from epichlorhydrin, to azetidin-3-ylacetic acid *via* the malonate (97),[493] and to the NMDA receptor antagonist milnacipran *via* the lactone (98) formed with phenylacetonitrile using $LiNEt_2$ in THF followed by azidolysis and hydrogenation ($CH_2OH \rightarrow CH_2NH_2$; similarly in Ref. 452).[494] Electrochemical reduction of oximes of 2-hydroxy-4-oxoalkanoic acids gives the corresponding γ-amino acids.[495] A new synthesis of the CNS-active drug vigabatrin (γ-vinylGABA) employs phthalimide for asymmetric amination of butadiene mono-epoxide based on differentiation within a π-allylpalladium complex, and homologation by malonate of the resulting 2-phthalimidobut-3-en-1-ol.[496] An efficient GABOB synthesis from D-mannitol arises from subjecting the 3-aminopropan-1,2-diol synthon (99) to ring-opening by cyanide.[497] Another chiral auxiliary approach involves the Evans N-acyloxazolidinone (30; see also Ref. 192),



(97)



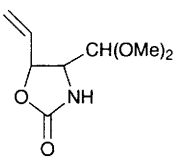
(98)



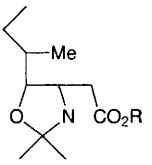
(99)

cyanomethylation giving 2-substituted 4-aminobutanoic acids through the conversion $R \rightarrow NH_2$.[498] An approach to γ-amino-β-ketophosphonic acids is described in Ref. 843. The D-glucosamine-derived starting material (100) has provided a lengthy entry to calyculin constituents, *viz.* (2S,3S)-dihydroxy-(4S)-amino acids,[499] and to other threo-β-hydroxy-γ-amino acids such as (3S,4S)-statine and (3S,4S)-AHPPA.[500] This approach bears comparison with the route from anti-3-aminoalkane-1,2-diols to syn- or anti-β-hydroxy-γ-amino acids, with asymmetric

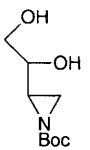
epoxidation of allylic alcohols as a key step, and Ti-promoted oxirane-opening, as illustrated with a cyclohexylstatine synthesis,[501] and with further statine syntheses by the same research group using essentially the same approach (nucleophilic opening of a chiral oxirane). Thus, cyclohexylnorstatine was obtained from either (E)-4-cyclohexylbut-2-en-1-ol,[502] or (S)-2-methylbutan-1-ol *via* the oxazolidine (101).[503] An equivalent use of the homochiral N-Boc-aziridine (102) has been illustrated for the synthesis of statines and analogues,[504] also formed by alkylation of imines formed from (R) or (S)-1-phenylethylamine with (S)-$HOCH_2$-CH(OBn)CHO.[505] Further results from azaenolate α-alkylation or nucleophilic addition to a homochiral hydrazone (Vol. 28, p. 44) include a statine synthesis.[506] Hydrogenation of chiral tetramic acids formed by dicyclohexylcarbodi-imide-induced condensation of N-protected α-amino acids with Meldrum's acid gives homochiral cyclic statines.[507] The products formed from the rhodium carbenoid formed from the decomposition of the glycine-derived diazo-acetoacetamide $MeO_2CCH_2N(Ac)COC(N_2)CO_2Me$ include N-acetyl isopyroglutamates.[508]



(100)

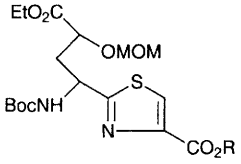


(101)

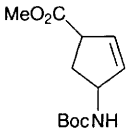


(102)

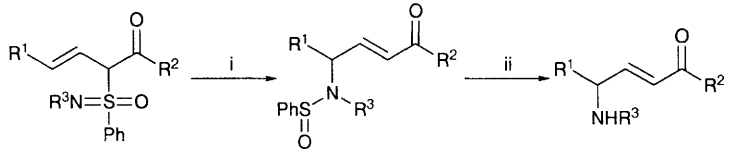
Cycloaddition of chiral enol ethers to dichloroketene, then Beckmann ring expansion to give a γ-lactam, offers an alternative approach to β-hydroxy-γ-amino acids, and has been developed into a (-)-statine synthesis.[509] A synthesis of the α-hydroxy-γ-amino acid fragment (103) of nosiheptide starts from L-pyroglutaminol.[510] Chiral αβ-acetylenic γ-amino acids and GABA analogues have been prepared either through pyrolysis of chiral aminoacyl phosphorus ylides $R^1O_2CNR^3CHR^2COC(=PPh_3)CO_2Et$,[511] or from (S)-N-Boc-amino aldehydes through the Corey-Fuchs protocol.[512] Palladium(0)-catalysed rearrangement of allylic sulfoximines leads to αβ-alkenyl γ-amino acids (Scheme 32), though the route has been established only for racemic substrates;[513] a Ru-catalysed metathesis process (Scheme 33) is a spectacular route to these compounds.[514] The starting point (104) for the synthesis of carbanucleoside analogues has been prepared by asymmetric Pd-mediated desymmetrization of meso-cyclopent-2-ene-1,4-diols and functional group incorporation into the cis-isomer.[515]



(103)



(104)



Reagents: i, $Pd(PPh_3)_4$, THF; ii, MeOH with trace of NEt_3

Scheme 32

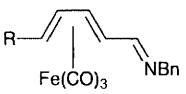
($FmCH_2$ = ferrocenylmethyl)

Reagents: i, $Ph_2C{=}CHCH{=}RuCl_2(PCy)_3$, benzene; ii, TFA, CH_2Cl_2; iii, $Et_3O^+BF_4^-$; iv, 0.4M HCl

Scheme 33

γ-Lactams are featured in a study of penicillin and cephalosporin analogues,[516] and have been built in to analogues of conformationally-constrained peptides.[517]

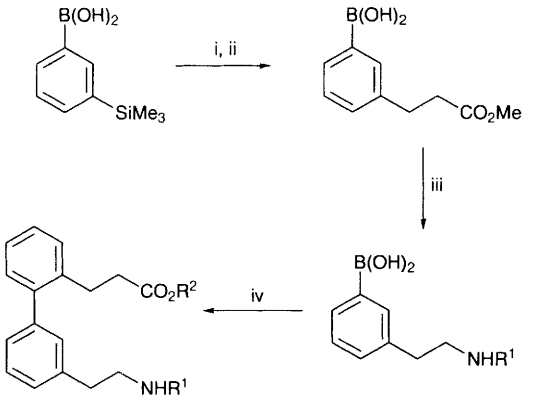
In the δ-amino acids context too, α-amino acids are valuable starting materials for the synthesis of their higher homologues, as illustrated in the cycloaddition to methyl acrylate of nitrile oxides formed *in situ* from N-protected α-amino aldehyde oximes, followed by acidolysis of the resulting isoxazoline to give δ-amino-αβ-unsaturated-γ-oxoesters $BocNHCHRCOCH{=}CHCO_2Me$.[518] (S)-5-Benzyl-5-amino-Z-pent-3-enoic acid is available from L-phenylalaninal by routine Horner-Emmons condensation[519] and by other homologation approaches (Ref. 435), including allylmagnesium bromide homologation of the Weinreb amide of L-phenylalanine, and then routine steps.[520] 1-Iminobutadiene-$Fe(CO)_3$ complexes (105) are Schiff bases, and may be alkylated at the imine carbon atom in the way that is so useful in α-amino acid synthesis; the resulting N-(butadienyl)amines have been elaborated into δ-amino acids.[521]



(105)

Chain extension of propargylamine with ethylene oxide, followed by oxidation, gives 5-aminopent-3-ynoic acid,[522] and hetero Diels-Alder reaction between 1,3-bis(tert-butyldimethylsilyloxy)-2-azabuta-1,3-diene and [60]fullerene gives the expected δ-valerolactam [*i.e.* a [60]fulleropiperidone].[523]

Miscellaneous examples of syntheses of ω-amino acids include amination by acylnitrene insertion leading to 1-amino-2-hydroxybicyclo[2.2.1]heptane-7-carboxylic acids.[524] Synthesis of biphenyl-based amino acids (Scheme 34) is a notable example of current practice in manipulations of benzene ring functional groups.[525]



Reagents: i, —$SiMe_3$ ⟶ —I ⟶ —CH=$CHCO_2Me$ by standard protocols; ii, H_2/Pd; iii, Curtius rearrangement (phosphoroazidate method); iv; Et *o*-bromocinnamate

Scheme 34

4.20 Resolution of DL-Amino Acids – Classical resolution procedures applied to DL-amino acids fall into the categories (i) preferential crystallization from racemates, and crystallization from a mixture of diastereoisomeric salts formed either with a homochiral acid or with a homochiral base; (ii) separation of a diastereoisomer mixture formed through derivatization with a homochiral reagent; (iii) chromatographic resolution and related processes; (iv) enantioselective hydrolysis, or a similar process, catalysed by enzymes or by other homochiral species. Categories (iii) and (iv) continue to be emphasized in the non-routine literature.

The solid form of (RS)-2-amino-3-chloropropanoic acid is a conglomerate, whereas its hydrochloride crystallizes as a racemic compound and is therefore resolvable through the preferential crystallization technique.[526] Separation by fractional crystallization, of salts formed with L-tyrosine hydrazide, has proved to be satisfactory for the resolution of DL-o- and p-fluorophenylalanines as their N-benzoyl derivatives,[527] and DL-pipecolic acid has been resolved through fractional crystallization of chiral Pd complexes.[528] (-)-Cinchonidine and (-)-quinine have been used for the resolution of DL-α-(hydroxymethyl)-phenylglycine and DL-α-(hydroxymethyl)-phenylalanine, respectively (Ref. 108). Diastereoisomeric derivatives formed between DL-α-amino acids and a salicylaldehyde carrying an optically-active 3-substituent are easily separated by conventional chromatography of their copper(II), zinc(II), or nickel(II) chelates.[529] Total

conversion of DL-phenylglycine into the (R)-enantiomer can be accomplished through conversion into a ketene and diastereoselective addition to (R)-pantolactone followed by transesterification and hydrazinolysis, though side-reactions will undermine the process with many common α-amino acids carrying functional groups in side-chains, and N-phthaloyl protection is necessary.[530] Chiral trans-dioxoruthenium(VI) porphyrins effect oxidation of DL-amino acid esters; the resulting achiral imines enter the complex and are accompanied by one enantiomer of the initial substrate.[531]

Dynamic resolution continues to attract interest (Vol. 28, p. 13; see also Ref. 201) with further examples based on N-(2-bromopropionyl)-(4R,5S)-1,5-dimethyl-4-phenylimidazolidin-2-one (total equilibration within the N-substituent by Bu_4NBr in favour of the R-configuration),[532] and epimerization of (S)-2-(2-Z-aminoisovaleroyl)-4-benzyloxazol-5(4H)-one.[533]

Proteolytic enzyme-catalysed hydrolysis continues to be widely used, discrimination between enantiomers being shown by subtilisin with phenylglycine ethyl ester;[534] α-chymotrypsin with β-(pyrid-2-yl)alanine[535] and (p-borono)phenylalanine (Ref. 162), with esters of azatyrosine [*i.e.* β-(3-hydroxypyrid-5-yl)alanine],[536] and with ethyl trans-3-(trifluoromethyl)pyroglutamate.[537] Anhydrous organic solvents can supply a suitable medium for protease-catalysed transesterification of N-trifluoroacetyl-DL-phenylalanine 2,2,2-trifluoroethyl ester with propan-1-ol,[538] and for papain-catalysed enantioselective hydrolysis of protected DL-4-carboxyglutamic acid esters[539] or conversion of the free acid into dipeptides.[540] Corresponding media used for CLEC-subtilisin with a range of amino acids and racemic alkylamines give protected L-aminoacyl-(S)-alkylamides.[541]

Aminoacylases can achieve the same outcome through enantioselective deacylation, illustrated for stereoisomer mixtures of 4-fluoroglutamic acid after separation of the erythro- and threo-DL-diastereoisomers,[542] and for amides of N-phenylacetyl anti-α-alkyl-β-amino acids using immobilized penicillin G acylase[543] (see also Ref. 408). Enantioselective pent-4-enoylation of racemic amino-alkanols catalysed by a serine acylase also accomplishes the same outcome.[544] A review has appeared covering results relevant to this area, covering also the use of a new N-acylamino acid racemase.[545] Another review covers exploitation for amino acid resolution of the amidase and aminopeptidase activity of *Pseudomonas patida*, *Mycobacterium neoaurum*, and *Ochrobactum anthropi*.[546] An aminoacylase together with a serine protease is advocated for the formation of L-ω-esters from α-N-acetylaminoalkanedioic acid diesters.[547] The promising results established for the exploitation of hydantoinases in this context are further illustrated with immobilized recombinant *E.coli*,[548] *Pseudomonas desmolyticum*,[549] and *Bacillus stearothermophilus* SD-1,[550] as used for the enantioselective hydrolysis of DL-hydantoins to give N-carbamyl-D-(p-hydroxyphenyl)glycine.

Lipases are also emerging as strong contenders for the resolution of amino acids in the form of their alkyl esters,[551] and are effective in organic solvents with alicyclic β-amino acids.[552] Transesterification of (1RS,2SR)-(2-TBDMS-oxymethyl)cyclopentanol with vinyl acetate benefits from lipase catalysis is followed by amination for a synthesis of both enantiomers of cis-pentacin [(1R,2S)- and (1S,2R)-2-aminocyclopentane-1-carboxylic acids]; the enzyme-catalysed kinetic

resolution approach is featured in this route.[553] Porcine pancreatic lipase has been found to be the most satisfactory lipase for the resolution of ethyl DL-2-amino-4-phenylbutyrate.[554]

An attractive practical proposition is offered by lipase- or α-chymotrypsin-catalysed hydrolysis of Schiff bases of DL-amino acids in aqueous MeCN (5:95).[555] The L-amino acid precipitates out, and more than half the initial amount of L-enantiomer can be obtained, as expected on the basis of asymmetric transformation.

β-Cyclodextrin-catalysed hydrolysis of DL-tryptophan isopropyl ester involves very restricted enantioselectivity, in leading to a predominance of the L-enantiomer.[556]

A widening variety of resolution techniques is being developed, based on physical interactions resulting in discrimination between enantiomers when they encounter chiral heterogeneous media. The classical test compound for such techniques applied to underivatized amino acids is DL-tryptophan; the L-enantiomer shows preferential transport through a (+)-poly[1-{dimethyl(10-pinanyl)silyl}prop-1-yne] membrane[557] and through an analogous homochiral supramolecular polymer membrane based on a poly(N-isopropylacrylamide) backbone.[558] Membranes formed from a cellulose acetate membrane carrying monoterpenes,[559] and membranes made from an acrylonitrile - styrene copolymer carrying a covalently-bonded all-L-tetrapeptide, have been studied; in the former case, dialysis and ultrafiltration rates are enhanced for the L-enantiomer for DL-tryptophan solutions, and in the latter case, the electrodialysis rate of N-acetyl-DL-tryptophan is enhanced for the L-enantiomer.[560] Porous poly(ethene) membranes have been rendered homochiral through grafting an epoxyalkylvinyl monomer, followed by reaction with an L-amino acid.[561] Following a long tradition exploiting natural homochiral materials as chromatographic media, the glycopeptide antibiotic teicoplanin has been used for the resolution of non-derivatized amino acids,[562] and polysaccharides and other CSPs are effective for the resolution of tryptophan derivatives.[563]

Molecule-imprinted polymers have continued to show promise for enantio-selection (and therefore, resolution of racemates), when the imprinting species is a homochiral amino acid derivative; the topic has been reviewed.[564] However, their use for the construction of membranes and chromatographic media still lacks a clear rationale that links the structure of the imprint with the structure undergoing chiral recognition. Thus, polymers prepared with monomers carrying the tetrapeptide H-Asp(O-cyclohexyl)-Ile-Asp(O-cyclohexyl)-Glu(O-Bzl)-OCH_2-grouping with Boc-L-tryptophan present from the start of the polymerization show preferential retention of several L-amino acids of diverse structural types (not only tryptophan, but also phenylalanine, alanine, arginine, and glutamic acid).[565] Polymers imprinted with this peptide permit D-tryptophan to pass more rapidly than its L-enantiomer.[566] Polymer-imprinting with antibody mimics has given CSPs showing enantiomer discrimination for amino acids.[567]

A report that ultrafiltration enhanced by chiral micelles effects the separation of amino acid enantiomers has required a correction to be published.[568]

More conventional chiral stationary phases (CSPs) applied to amino acid

resolution have been prepared; those carrying covalently-bonded L-proline-3,5-dimethylanilide and analogues,[569] and used for the chromatographic resolution of N-(3,5-dinitrobenzoyl)-DL-amino acid esters, appear to owe their high efficacy to 1:1-complex formation between the chiral moiety of the CSP and the L-enantiomer of the solute.[570] This arrangement in reverse, *i.e.* the CSP carries N-(3,5-dinitrobenzoyl)-(R)-phenylglycine linked to a polymer through the $-O(CH_2)_3SiMe_2O-$ linkage, is an effective medium for resolving DL-amino acid esters and amides[571] [a correction has been published[572] concerning preparative resolution using a hollow fibre membrane carrying N-(1-naphthyl)-L-leucine as chiral selector]. CSPs have been prepared either by bonding aminopropylsilica to Marfey's reagent followed by capping unreacted amino groups by N-trifluoroacetylation, or by reaction with the closely-related reagent, N-5-(1-fluoro-2,4-dinitrophenyl)-L-phenylalanine tert-butyl ester and capping with butanoyl chloride after ester cleavage;[573] these show good discrimination between enantiomers of N-(2,4-dinitrophenyl)- and N-(3,5-dinitrobenzoyl)amino acid esters.

Lipids bonded to L-glutamic acid form highly oriented gels in benzene, and elution with water when N-dansyl-DL-phenylalanine is trapped in the gel causes the preferential release of the L-enantiomer.[574] Cyanuric chloride has already been established (Vol. 28, p.76) to be a useful, cheap compound to develop into a homochiral reagent, and has now shown its potential as a medium on which to build a CSP, through substitution of a chlorine atom by aminolysis with L-valinamide, for use in the resolution of N-dansyl-DL-amino acids.[575] Porous cross-linked poly(vinyl alcohol) carrying covalently-bonded L-proline-based groupings is an effective medium after complexation with copper(II) ions, for ligand-exchange chromatographic resolution of DL-amino acids.[576]

Common chromatographic media to which chiral species are adsorbed offer simple alternative CSPs for amino acid resolution, though the empirical nature of knowledge of their mode of action makes them attractive only to those with a predilection for gambling. (1→6)-2,5-Anhydro-3,4-di-O-methyl-D-glucitol adsorbed on silica gel is a good prospect as a CSP for the resolution of DL-amino acid salts,[577] and N-carboxymethyl-N-dodecyl-L-leucinol sodium salt[578] or copper(II) - N-octyl-(S)-phenylalanine N′-octylamide,[579] adsorbed on reversed phase C-18 silica gel, are effective in the resolution of free DL-amino acids and their esters and amides, using the ligand exchange chromatography principle.

The remaining topic under this heading, the mechanisms by which prebiotic enantioselection can be explained, continues to enjoy a loyal following, with well-worn themes that are rarely put to rest as a result of having waited in vain for experimental support. A review of mechanisms proposed under this heading suggests[580] that the order of events could not have been the generation of chiral polymers followed by their influence on racemic amino acids. Current themes and their practitioners have appeared in print.[581] A broad review of current theories has been published,[582] and a hybrid theory combining the parity violation mechanism with the long-respected Frank model has been considered.[583] Mirror symmetry-breaking ideas (see Vol. 28, p. 50) that invoke putative, unimaginably small, energy differences between enantiomers due to parity violation, as an explanation, may perhaps never be substantiated in the laboratory,[584] and energy

differences for β-decay electrons of opposite symmetry resulting from parity violation have been ruled out for frequently-observed spontaneous resolution by crystallization under racemization conditions; this study describes a bromo-fluoro-1,4-benzodiazepino-oxazole as a new example of this phenomenon that has led to high e.e. values, and stereoselective autocatalysis offers the best explanation for the result. Conventional concepts of the kinetics of enantioselective processes are an alternative explanation that has been considered within the mirror symmetry-breaking approach.[585] The enantioselection mechanism depending on a low temperature phase transition proposed for amino acids has been reviewed.[586]

5 Physico-chemical Studies of Amino Acids

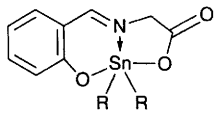
5.1 X-Ray Crystal Analysis of Amino Acids and Their Derivatives – Crystal structure details for many familiar L-(α-amino acids have been reinvestigated, and this adds to the impression that there has been a deluge of papers in this topic area. Structures have been determined at 120 K for L-isoleucine,[587] L-leucine,[588] L-cysteine,[589] DL-valine,[590] DL-norleucine (β-form),[591] and L-methionine and L-valine.[592] A new study of DL-glutamine has been reported.[593] An inelastic neutron scattering study of L-leucine[594] continues a series of similar applications of the technique, which has also been used in an investigation of samples in aqueous media to give direct evidence for a modified solvent stucture within the hydration shell of a hydrophobic amino acid.[595]

Salts of common amino acids have been studied: sarcosine sulfate,[596] L-argininium hydrogen squarate,[597] (R)-(-)-1-phenylglycinium hydrogen squarate,[598] picrates of DL-arginine, L-arginine, L-lysine, and L-ornithine,[599] arenesulfonates of glycine, L-alanine, and L-serine,[600] and amino acids with sulfonated azo dyes.[601]

Amino acid complexes have been studied: L-histidine - glyoxylic acid,[602] L-glutamic acid - 2-methylimidazole (1:1),[603] and sarcosine - sucrose (1:1).[604]

Amino acid derivatives have been studied: O-phospho-L- and -DL-threonine (structure comparisons with corresponding serine derivatives),[605] N-Boc-L-phenylglycine,[606] N-Boc-L-alanine,[607] N-benzyloxycarbonyl-L-serine tert-butyl ester,[608] N-acetyl (S)-isovaline methylamide,[609] ethyl N-(isopropylcarbamoyl-methoxyphosphonyl)-L-phenylalanine,[610] and L-histidine methyl ester dihydrochloride.[611]

Derivatives with structures more remote from the amino acids themselves have been subjected to X-ray crystal analysis so as to verify structures involved in reaction pathways, including amino acid synthesis routes. These are represented by (1S,6R,9S)-6-benzamido-9-hydroxymethyl-8-oxabicyclo[4.3.0]non-3-en-7-one,[612] (3RS,6SR,1'RS)-6-tert-butyl 3,6-dihydro-5-methoxy-3-methyl-3-(3-oxocyclohexyl)-2H-1,4-oxazin-2-one (verified as the structure of an intermediate in an α-methyl α-amino acid synthesis),[613] and novel five-coordinate tin(II)-amino acid derivatives, bicycloazastannoxides (106).[614] Recent controversy (*cf* Ref. 870) concerning the correct structure for the product formed from L-tryptophan and



(106)

pyrroloquinolinequinone (PQQ) has been settled by an X-ray structure determination showing the product to be an imidazolopyrroloquinoline (116).[615] X-ray data for proteins has been analyzed leading to comparisons of local structures with predicted conformations for individual amino acids.[616]

5.2 Nuclear Magnetic Resonance Spectrometry – Papers reviewed here cover either studies that employ more sophisticated instrumental techniques with amino acids, or studies yielding information that is of a non-routine nature.

Solid-state NMR data for crystalline amino acids providing rotation rates for the amino group show the dominant role of hydrogen bonding.[617] The same technique allows solid state molecular motion around carbon atoms within Boc-L-alanine to be quantified, and establishes heteronuclear dipolar coupling constants; the particular help that magic-angle spinning data can offer is demonstrated in this study.[618] ^{2}H-Spin-lattice relaxation times permit motion within the $N^{2}H_3$ group of labelled L-alanine to be assessed.[619] Deuteriated glycine samples have been assessed in a ^{2}H -^{1}H-cross-polarization kinetics study,[620] and determination of torsion angles Ψ for solid amino acids through a 2D-double quantum NMR study, has called for doubly-^{13}C-labelled amino acids.[621] High sensitivity INADEQUATE data for ethyl [N,N,O-$^{2}H_3$]-DL-tyrosinate has been converted into more conventional ^{13}C-^{13}C format.[622]

Triple resonance measurements can be exploited for direct NMR identification of certain amino acid types - those that lack $^{13}C^{\beta}$ - $^{13}C^{\gamma}$ coupling (glycine, alanine, cysteine, serine) and those for which C^{γ}-resonances are well-separated from other spectral features (aspartic acid, asparagine, phenylalanine, etc.).[623]

The relative stereochemistry of kainoids (3,4-disubstituted prolines) can be determined through ^{1}H-NMR in $^{2}H_2O$, concentrating on the resonances of the protons at C-2 and C-4; the 2,3-trans configuration is indicated when the resonance for H-2 appears at greater than 4.2 ppm in the p^{2}H-range 3 - 8.[624] ^{1}H-NMR chemical shift data has been interpreted to give information on intramolecular hydrogen bonding for amino acids.[625] Conformational information for glutamic acid and a series of its homologues carrying methyl groups at C-3 and C-4, and the 4-methylene derivative, has been obtained through interpretation of ^{1}H- and ^{13}C-NMR data and compared with molecular orbital calculations,[626] also applied to stereoisomers of aminocyclopentane-1,3-dicarboxylic acid.[627] A useful compilation has been published of ^{13}C-NMR data determined for the 20 common coded amino acids in a uniform sample environment (25°C, phosphate buffer, pH 7.3).[628]

NMR study of derivatives is an effective source of information on the solution behaviour of amino acids, *e.g.* the stabilization of the syn-rotamer of carbamate

derivatives of an α-amino acid by intramolecular hydrogen bonding with the carboxy group.[629] Suitably chosen derivatives give useful insights into peptide and protein behaviour, and determinations of cis-trans isomer ratios for the amide grouping of N-acetyl-L-proline N′-methylamide, and its cis and trans-5-tert-butyl homologues,[630] and of intramolecular hydrogen bonding within Me_2N-$CO(CH_2)_2CO$-Gly-NHMe and $Me_2NCO(CH_2)_3CO$-Gly-NHMe,[631] also benefit from FTIR data. Bis(amino acid) derivatives formed by acylation of representative amino acid esters (valine, phenylalanine, and proline) by 1,1′-ferrocenedicarboxylic acid adopt an intramolecularly hydrogen-bonded structure, as revealed by NMR and IR data.[632]

Determination of enantiomer ratios for amino acids by NMR methods already has a lengthy list of methods that exploit traditional physical principles, and new variants of these are the ^{1}H-NMR data for (R)-O-aryl lactic acid amides,[633] and ^{1}H- and ^{13}C-NMR data for C2-chiral palladium complexes [(2S,3S)-2,3-diaminobutanepalladium(aminoacidato)] dinitrates[634] of the target DL-amino acid sample. Another axially-chiral derivatization agent, 1,1′-binaphthalene-8,8′-diol, has been proposed for the determination, based on ^{1}H- and ^{13}C NMR, of absolute configuration of α-chiral carboxylic acids (see also Ref. 706).[635]

5.3 Optical Rotatory Dispersion and Circular Dichroism – As in other areas where new instrumental developments show their potential through dramatic extensions to existing knowledge, polarimetry is a newly-emerging and highly sensitive technique. The optical activity of crystalline L-glutamic acid has been determined[636] to establish solid state rotatory powers, including the temperature dependence of gyration tensor components, through the use of a high accuracy polarimeter. Instrumental details of a high sensitivity polarimeter, based on the magneto-optical principle and using a He-Ne laser monochromatic light source, have been published.[637]

Standard CD spectrometers have continued to give data that may be interpreted in terms of the absolute configuration of amino acids after derivatization so as to introduce a grouping that absorbs light in the accessible UV wavelength region, such as Pd(dmba)(acac), giving Cotton effects centred at 265-280 and 305-320 nm, with signs characteristic of absolute configuration, after complexation with α-amino acids.[638] A helical chirality characteristic of absolute configuration is induced into zinc biliverdin derivatives through complexation with an enantiomer of an α-amino acid ester, as revealed by CD and NMR data (M-helicity corresponds with the L-configuration).[639]

Information concerning solution conformations has been deduced from Raman optical activity data for N-acetyl-L-alanine N-methylamide.[640]

5.4 Mass Spectrometry – Only in the last few years has the non-routine literature on this topic shifted from an almost exclusive coverage of amino acid derivatives, to concentrate largely on the amino acids themselves. This is mainly due to the emergence of new ionization methods, but the delay is partly due to a lingering respect for the received wisdom that amino acids are involatile and therefore not suitable for mass spectrometry.

Evidence for aggregation of amino acid molecules ejected into the gas phase continues to accumulate; thus, tryptophan clusters of up to 5 molecules form during seeded supersonic expansion and ionization through laser desorption.[641] Although, at first sight, it is not surprising that no differences were found through this technique between data for L-, D-, and DL-tryptophan, it was a valid study in view of the different solid-state structures adopted by certain racemates in comparison with their enantiomers.[642] Individual molecules within heterogeneous clusters formed by mixed amino acid samples in the gas phase have been shown to participate in proton transfer reactions.[643] Kinetic energy release associated with the separation of a protonated dimer of an amino acid into protonated and neutral monomers has been evaluated.[644] The facility offered by mass spectrometry to study molecular complexes in the gas phase has been applied to determine the stoichiometry of αβ-cyclodextrin - protonated tryptophan complexes,[645] and a demonstration[646] (supporting a conclusion derived from ^{1}H-NMR data) that permethylated cyclodextrins complex preferentially (5:1) with the D-enantiomer of the methyl esters of phenylalanine or tryptophan. Complex formation between aluminium(III) salts, glycerol, and amino acids has been established by FAB-MS,[647] and gas-phase reactions of copper(I) and iron(I) ions with protein amino acids have been shown to be most prevalent with those that carry non-polar side-chains, suggesting that the ionized carboxy group is the prime reaction site.[648] Protonated nitric oxide reacts with glycine, alanine, and valine, and their N-methyl homologues, to produce the $[M-H]^+$ ion through hydride abstraction, which leads to iminium ions by loss of HNO_2 and CO.[649] Alkylation of glycine by ethylenehalonium ions $(CH_2)_2X^+$ (X = Cl, Br) has been observed in a similar study.[650]

Protonation of amino acids has been a long-running study and has promoted joint mass spectrometry - molecular orbital calculation studies, seen in a study of proton transfer from protonated glycinamide,[651] and to histidine, lysine, and their di- and tripeptides.[652] Protonated amino acids formed in the gas phase generate metastable ions that release H_2O and CO fragments.[653]

Although applied to less-common amino acids, mass spectrometric studies of L-cysteinylDOPA,[654] fluorinated β-hydroxy-β-phenylserines,[655] and the cross-linking amino acids pyridinoline and deoxypyridinoline[656] employ standard instruments. The last-mentioned study involves the continuous liquid flow/liquid secondary ion-ionization technique, and illustrates the high sensitivity of mass spectrometry to permit analysis at the 100 pmol level of these clinically-important amino acid markers (see also Refs. 663, 1049).

Standard derivatization protocols have been applied in the numerous papers in this year's literature, describing structure assignments using basic instrumentation. This topic is not covered thoroughly here because of its generally routine nature, but mechanistically-interesting results are illustrated by a structure assignment to the very intense *m/z* 171 ion generated by a modified McLafferty rearrangement of N-dansylamino acids and their methyl esters,[657] and a new fragmentation mechanism for leucine (as its N-heptafluorobutyryl isobutyl ester), assisted by the parallel study of the [1-^{13}C]isotopomer.[658] $[M-H]^-$ ions generated for N-phenylthiohydantoins are a reliable basis for characterization purposes.[659]

5.5 Other Spectroscopic Studies of Amino Acids – Infrared and Raman spectroscopy papers can only justify citation here if they are of exceptional interest from the point of view of either developing instrumentation, or new interpretations. While a vibrational frequency assessment of L-proline through FTIR - Raman study would be, by now, considered to be routine,[660] the use of photoacoustic FTIR for monitoring solid-phase reactions [four reaction steps from resin-bound S-benzyl-N-Boc-L-cysteine to resin-bound N-(p-cyanobenzoyl)-dehydroalanine] is a new application.[661] For other FTIR studies, see Refs. 630, 631. Three Raman tensors have been deduced from polarized Raman spectra of single crystals of N-acetyl-L-tryptophan.[662] Assistance in amino acid structural assignments given by IR studies is referred to in Refs. 607 and 632.

Other absorption spectroscopy studies that have yielded significant results, range from simple established techniques to sophisticated new methods; careful accumulation of accurate data for the standardization of analytical assays of pyridinoline and deoxpyridinoline (see also Refs. 656, 1049) based on UV absorption at 295 and 325 nm (ε values 5490 and 5785 L mol^{-1} cm^{-1} respectively for the former crosslinking amino acid, and 5160 and 5290 for the latter);[663] and absorption millimetre spectroscopy data at 31.42 GHz for solid samples of 19 amino acids, to reveal details of their hydration behaviour.[664] Solvatochromic parameters determined for N,N-dimethylvaline have been used to evaluate populations of zwitterionic tautomers in different solvents.[665]

ESR Spectra of glycine, DL-serine, DL-asparagine, and L-glutamic acid γ-irradiated at room temperature have filled gaps in the substantial literature on radical formation in solid amino acids.[666] Spectra of γ-irradiated hydrochlorides of methyl L-valinate and L-leucinate are best interpreted in terms of the location of the unpaired electron on the carbon atom adjacent to the isopropyl group.[667]

5.6 Physico-chemical Studies of Amino Acids – The simplest physico-chemical measurements for amino acids are usually made for their own sake, but also with the knowledge that improved understanding of their behaviour (in aqueous solutions in particular) will inevitably have some significance in the context of the living cell. Representative data in this category are partial molar volumes and isentropic compressibilities of aqueous solutions of N-acetyl amino acid amides,[668] and activity coefficients of amino acids in aqueous electrolytes[669] (determined by electrochemical methods with superior accuracy in comparison with standard techniques;[670] see also Ref. 725). Protonation constants have been reported for alanine,[671] and the effects of sodium dodecyl sulfonate on protonation equilibria of L-glutamic acid and L-ornithine have been determined.[672] Thermodynamic parameters have been collected, giving standard enthalpies of formation for ethyl NN-diethylalaninate and methyl and n-propyl N,N-dimethyl-aminoisobutyrate.[673] Enthalpies of sublimation and heat capacities have been determined for N-acetylamino acid amides.[674]

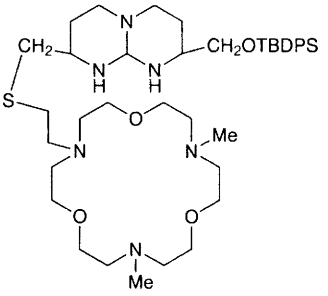
Intermolecular interactions involving amino acids continue to provide a major emphasis in this Section; calorimetric data giving a measure of hydrophobic interactions for N-acetylamino acids as a function of structure have been determined for binary aqueous solutions,[675] and further information has been

published[676] in this context for interactions between enantiomers of amino acids. Complexation constants have been determined for supramolecular aromatic amino acids with cyclodextrin - copper,[677] and for L-alanine β-naphthylamide hydrobromide with methyl β-cyclodextrin (by ultrafiltration).[678] Favourable interactions account for the 12,000 times stronger binding of L-arginine to RNA aptamers compared with the D-enantiomer,[679] for selective binding of amino acids to yeast tRNA in solutions at high ionic strength,[680] for enhancement by amino acids of pyrene - β-cyclodextrin binding,[681] and for binding to 1-(N-benzylamino)cyclopentyl O,O-diamylphosphonate.[682] In the latter case, the interaction accounts for the transport of amino acids across a Teflon matrix that has been impregnated with a solution of the aminophosphonate in o-nitrophenyl octyl ether, and similar explanations surround the transport of protonated amino acids by macrocyclic ligands[683] and transport of lipophilic lanthanide tris(β-diketonate) - valine and leucine complexes across CH_2Cl_2 membranes under neutral conditions,[684] enantioselective transport of amino acids across polymer membranes impregnated with a homochiral crown ether,[685] partition of amino acids in an aqueous two-phase system containing poly(ethylene glycol), with sodium sulfate, and mild surfactants[686]or in the same medium with dextran,[687] or on an ethylene oxide - propylene oxide copolymer,[688] and ordered aggregation of N-acylamino acid amphiphiles (*e.g.* N-stearoyl-L-valine) at liquid air interfaces.[689] The widely-used cationic surfactant, cetyltrimethylammonium bromide, showed only weak binding to 11 amino acids from an extensive series tested by TLC.[690] Free energy of adsorption data for amino acids at a hydrophobic and a hydrophilic surface (surprisingly, leucine is more strongly adsorbed than serine),[691] and for amino acids to silica[692] and to porous polymeric adsorbents[693] have been determined.

Classical separation procedures, such as the presentation of amino acids in aqueous ethanol to a weak acid cation exchanger, involve sorption as a major contributory mechanism.[694] The kinetics parameters for the DL-lysine - Amberlite IRA420 interaction have been evaluated,[695] and similar studies have involved Amberlite IR120[696] and a cellulose-based ion exchanger.[697] Partitioning of amino acids in water - butan-1-ol[698]and in other water - partially miscible alkanol mixtures[699] and assessing the distribution of the solute, gives considerable insight into structural factors that determine the magnitude of the ternary interactions involved. Enthalpic interaction coefficient data for amino acid - β-cyclodextrin complexes reveal the involvement of three different types of stabilizing interactions,[700] and similar detail is provided by interfacial tension measurements at the benzene - water interface for solutions of alanine, valine, leucine, and phenylalanine in the presence and absence of β-cyclodextrin.[701] The inclusion of the alkyl side-chain within the host, β-cyclodextrin, is claimed to contribute significantly towards the constructive interaction.

Host - guest interaction studies are well-represented again this year, with enantiospecific recognition of N-benzyloxycarbonylglutamic acid shown by chiral cage-like C_3-symmetric receptors,[702] and of aromatic amino acids in water or N-acetylamino acids in organic solvents, shown by cyclobis(paraquat - p-phenylene), a π-electron-deficient tetracationic cyclophane.[703] Discrimination to the

extent of 74% e.e. is found for a homo-oxacalix[3]arene - amino acid ester system[704] whereas a lower value (40% e.e. with phenylalanine) is shown for amino acid zwitterions enclosed by the chiral crown ether (107).[705] An axially-chiral derivatization agent, 1,1′-binaphthalene-8,8′-diol, has been found to bind a variety of amines and α-amino acids with significant chiral recognition (see also Ref. 635).[706] In a particularly thorough study of supramolecular bio-organometallic hosts, [(η^5-pentamethylcyclopentadienyl-rhodium(I)]-nucleobase, -nucleoside, and -nucleotide cyclic trimer complexes, it has been found that π - π interactions and hydrophobic interactions, as well as hydrogen bonding, contribute to the favoured complexation of L-enantiomers from aqueous solutions of DL-amino acids.[707]



(107)

A clear indication of the complete shift from one structural type of aggregate to another is contained in the finding that long-chain bis(N-acyl)amides Z-Phe-NH(CH_2)$_{12}$NH-Phe-Z form gels, while analogues Z-Phe-NH(CH_2)$_3$Me form fibrils.[708] Information of this type obtained in the laboratory will contribute new insight into the nature of molecular interactions within the living cell, *e.g.* the conformational change induced into BkdR (the activator of the inducible bkd operon of *Pseudomonas putida*) by branched-chain L-amino acids.[709] Helix-forming propensities of basic αω-diamino acids, as constituents of peptides, increase with increasing length of the side-chain.[710]

Data from several routine optical measurements have been reported for single crystals of L-alanine.[711]

5.7 Molecular Orbital Calculations and Theoretical Studies for Amino Acids – Studies dwelling on continuing interests, concerned with conformational aspects in particular, have provided most of the papers in this Section over the years. A widening of the range of applications for molecular orbital calculations, and a significant increase in the number of studies published, is discernable.

Conformational calculations for N-formyl-L-serinamide[712] concentrate on backbone torsion angles, while a more extensive coverage under the same heading is provided for N-acetyl-N′-methyl-α-methyl-β-L-aspartamide[713] and other N-acetyl-N′-methyl-α-amino acid amides[714] including the 1-aminocyclo-

hexa-2,5-diene-1-carboxylic acid derivative[715] and the alanine derivative.[716] Models for solvation around the amino acid derivative are the particular concern of the last-mentioned study, also a feature of other studies [polarizing effect of the medium on conformations of amino acids;[717] structure of the (1:1)-glycine - water complex[718]].

The increasing proportion of papers dealing with underivatized α-amino acids is clearly a trend, covering electrostatic potential maps,[719] alanine in the gas phase,[720] proton - proton interactions for L-leucine and L-isoleucine,[721] and further development of the connectivity index proposed for the common protein amino acids.[722] Twenty stable conformations are predicted for β-alanine on the basis of calculations using standard protocols.[723]

Physical characteristics of amino acids and their common derivatives have been assessed through molecular orbital calculations: crystal lattice energies of amino acid hydrohalides,[724] activity coefficients of amino acids in water (see also Refs. 669, 670),[725] electronic spectral features of glycine and N-acetylglycine,[726] vibrational frequencies for L-proline and hydroxy-L-proline[727] and for L-asparagine,[728] and FTIR/Raman characteristics of alanine.[729] The structure of a glycine radical and its calculated ESR characteristics have been considered in relation to experimental values.[730] Certain conformers predicted for glycine and alanine have not been found in ultrasonic jet spectroscopy studies, and this is thought to be due to selective conformational relaxation of these conformers into lower energy species during spectroscopic study.[731]

Examples of applications of calculations for the solution of mechanistic problems include unimolecular decomposition of N-chloroglycine[732] and of anions of other N-chloro-amino acids,[733] and the C-H acidity of succinimides derived from N-acyl-L-aspartic acids.[734] The impetus for the last-mentioned study lies in the well-known enigma concerning the enhanced propensity for racemization shown by aspartic acid and asparagine residues in peptides.

There are several methods of determining helicity leagues for the twenty coded amino acids, reflecting their tendency, as constituents of peptides and proteins, to promote helix formation, and three of these methods have been critically appraised.[735] One helicity-ranking method has been considered in detail.[736] A review of the predominant conformations available to individual amino acids, together with a controversial approach in which structural and functional distinction of amino acids, one from another, in terms of atomic number and nucleon number, has appeared.[737]

6 Chemical Studies of Amino Acids

6.1 Racemization – Racemization of free amino acids is a topic with clearly-defined strands of continuing interest, mostly connected with kinetics and mechanism, with racemization rates for constituents in protein hydrolysates featuring strongly. A salutary lesson relevant to the preparation of analytical samples, that solid D- or L-leucine suffers racemization within a few minutes when powdered in a planetary gear mill,[738] extends a few earlier examples of

the same sort, though some of these reports have been shown to be non-reproducible.

Loyalty is shown by several research groups to particular problems, one stemming from stereoinversion at aspartic acid residues in fossil proteins, and in proteins with no turnover in living organisms. Thus, αA-and αB-crystallins of human eye lens are known to undergo residue-specific racemization at aspartyl residues, and the ensuing conformational changes result in insolubilization and this is connected with the development of cataracts.[739] A kinetic study of this process in a series of synthetic peptides, chosen as models for the crystallins, has shown that racemization rates are strongly dependent on the sequence neighbouring the aspartyl residue.[740] Human teeth also offer a reproducible protein sample, dentin, usually of reliable age, and careful attention to analytical details has featured in recent papers describing aspartyl racemization studies.[741] Retrievable DNA in ancient tissue samples showing a D/L-ratio >0.08 for their aspartic acid content cannot be endogenous, a conclusion based on the degraded DNA content of unadulterated samples.[742]

An increased racemization rate can be expected for aspartyl residues in fossil proteins, undermining the reliability of amino acid racemization data, if microbial degradation is one of the diagenetic processes at work.[743] Standard analytical procedures have been set out for assessing high levels of racemization of C-terminal aspartic acid[744] and of Fmoc-S-trityl-L-cysteine[745] during solid-phase peptide synthesis.

Deliberate laboratory racemization of L-amino acids has been practised for many years for the provision of D-isomers, exploiting the easy stereoinversion at C-4 of certain five-membered heterocyclic compounds enclosing the -NH-CHR-CO- grouping. Hydantoins belong to this family, and deuteriation rates vary widely within a series, showing the control exerted by the 5-substituent on the rate of the underlying S_E2 push-pull mechanism.[746] Homochiral thiazol-5(4H)-ones produced either through cyclization of N-thioacyl and N-alkylthiocarbamoyl-L-α-amino acids, or from peptides through sequencing chemistry (Edman and related methods), are racemized by trifluoroacetic acid but not by BF_3.[747]

6.2 General Reactions of Amino Acids – Papers are grouped under three main headings: (a) reactions at the amino group, (b) reactions at the carboxy group, (c) reactions involving both amino and carboxy groups. Papers covering (d) reactions at the α-carbon atom of α-amino acids are collected next, followed by (e) reactions of β- and higher homologous amino acids.

6.2.1 Reactions at the Amino Group – Mechanistic interest in the N-halogenation of amino acids and the synthetic implications of some ensuing processes have continued to feature in the literature. The repetitious nature of these papers, from more than one research group, illustrates the advertiser's technique - since so much is arriving in the literature on a narrow topic, it must be an important topic! - and others are attracted to it. Kinetic parameters of the N-bromination of amino acids using N-bromosuccinimide have been determined.[748] Rates of base-

induced elimination from N-halogeno-α-amino acids in aqueous media are determined significantly by the structure of the side-chains (see also Ref. 733).[749] The reactions lead on to give hydrolysis products, aldehydes and/or ketones and ammonia and/or primary amines in near-neutral conditions, or α-keto acids in basic media.[750] In support of earlier conclusions, decarboxylative dechlorination of N-chloroalanine is a concerted fragmentation process in aqueous media.[751] N-Bromoamino acid anions show a clear absorption maximum centred at 290 nm and this has facilitated the determination of kinetic aspects of the E_2 elimination that is characteristic of these species.[752]

Another routine area that continues to generate a large number of papers on the oxidation of amino acids can only be hinted at here, *e.g.* a significant rate-enhancing role exerted by chloride and sulfate ions on chloramine-T oxidations in aqueous solutions.[753]

Displacement of the amino group of D-serine by bromine (HBr, $NaNO_2$) initiates a route to (S,S)-3-prolylazetidin-2-one.[754]

Acylation reactions of amino acids of unusual interest are represented in photoinduced N-phenylacetylation through UV irradiation of 2'-disubstituted diazoacetophenones $ArCHN_2$ in the presence of amino acid esters,[755] highly selective acetylation (of primary amines in the presence of secondary amines) using N-acetyl-N-acyl-3'-aminoquinazolinones,[756] and enzymic acylation/deacylation [a classical 'resolution' technique for amino acids (Section 4.21; most of the year's papers are covered there)]. But enzymic N-alkylation is unusual, and is illustrated for opine synthesis from an L-amino acid and pyruvic acid using an opine dehydrogenase from *Arthrobacter*.[757] N-Formylation of an amino acid ester hydrochloride can be brought about using cyanomethyl formate.[758] A thorough assessment of conditions for N-phenylacetylation of L-tyrosine ethyl ester using ethyl phenylacetate and penicillin amidase in a benzene - aqueous salt medium has been published,[759] and the N-tetrachlorophthaloyl protecting group (removed with ethylenediamine) has been advocated.[760]

Mild conditions have been established for N-sulfonylation, effective for γ-substituted glutamates without risk of pyroglutamate formation.[761]

Naturally-occurring 3-oxohexanoyl-L-homoserine lactone can be prepared in moderate yield from the two components through the dicyclohexylcarbodiimide - hydroxybenzotriazole procedure,[762] and a solid-supported carbodiimide has been used to couple Mosher's acid to homochiral amines and amino acids.[763]

N-Alkoxycarbonylation would be thought of as an optimized procedure, in view of the wide use made of the resulting N-protected amino acids, but improved results for preparations of N-Fmoc derivatives using Fmoc-Cl can be secured, using a borate buffer (pH 11.4), with a reaction time of 40 minutes at room temperature.[764] Even histidine and tyrosine, normally needing special care, are derivatized efficiently through this procedure. N-Benzyloxycarbonylation using ZCl with DMAP in $ClCH_2CH_2Cl$ illustrates beneficial inverse phase-transfer catalysis[765] in simple cases, but the severe conditions that are needed (ZCl or Boc_2O/LiHDMS/THF/−78°C) for N-protection of pyroglutamate esters[766] might be expected to generate side-products. Introduction of the Boc-group into α-alkylprolines and sterically-hindered αα-disubstituted glycines using Boc_2O is

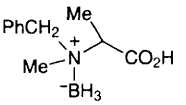
best accomplished in MeCN, but requires tetramethylammonium hydroxide to achieve solution, and four days for good yields![767]

New acid-labile N-alkoxycarbonyl groups [*e.g.* H_2C=CMeCONHCH$_2$C-Me$_2$(OCO)-] have been proposed.[768]

Removal of the Boc-group is the subject of even more papers this year: for side-chain tryptophan selective deprotection, silica gel under reduced pressure;[769] for removal in the presence of silyl ethers, saturated HCl in ethyl acetate;[770] for universal Boc removal, cerium(VI) ammonium nitrate catalysis in MeCN,[771] silicon tetrachloride with excess phenol in CH_2Cl_2,[772] or tin(IV) chloride in organic solvents (this avoids disruption of any thioamide groupings in the same molecule).[773] The removal of the increasingly widely-used N-Alloc-grouping using water-soluble palladium(0) catalysts has been reviewed.[774]

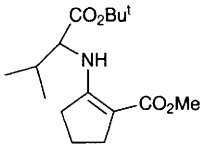
Pd/Cu-Catalysed N-arylation reactions, using aryl halides, give enantiomerically-pure products when L- or D-amino acids are used;[775] nucleophilic addition of amino acid butyl esters through nitrogen to quinones represents an alternative arylation procedure.[776] The preferred N-mono-methylation procedure for primary and secondary amines involves condensation with formaldehyde, followed by reduction, to ensure freedom from over-alkylation; use of microwave irradiation using formic acid as reaction medium is beneficial.[777] Fmoc-Amino acids are conveniently N-methylated by reaction with formaldehyde followed by reduction with triethylsilane,[778] while TFA-sensitive N-(2-hydroxy-4-methoxy)-benzyl Fmoc-amino acids are best prepared through attaching the amino acid to a chlorotrityl resin, conversion into the Schiff base, and $NaBH_3(CN)$ reduction.[779] The general alkylation process [RCHO/$NaBH_3(CN)$] leading to higher homologous N-alkylamino acids has been applied to amino acid amides.[780] Using $NaB(OAc)_3H$ for the reduction stage is claimed to lead to fewer problems.[781] In the presence of heteroaromatic acid amides, formaldehyde reacts with amino acid esters to give N-amidomethyl derivatives,[782] and an amino acid, an aldehyde, an isocyanide, and an alkanol react to give 1,1′-iminodicarboxylic acid derivatives.[783] Reductive alkylation of 5-aminopentanoic acid with N-Boc-piperidin-4-one is an essential stage of a semi-synthesis of the anti-tumour agent irinotecan.[784]

The borane adduct (108) of methyl L-alaninate has been separated from its epimer, and shown to undergo stereoselective α-alkylation in up to 82% e.e.[785]



(108)

Enamines (109) formed from β-ketoesters with tert-butyl L-alaninate are representative of valuable intermediates in synthesis (*e.g.* of non-racemic acids[786]), and methyl N-(benzylidene)-L-valinate serves for the synthesis of R,S- or S,S-secondary homoallylic amines (the stereochemistry depending on the



(109)

nature of the allylmetal reagent used for addition to the imine moiety).[787] Near relatives, the homochiral azomethine ylides $XCH^-RN^+{=}CHY$, *e.g.* from (R)- or (S)-phenylglycine,[788] are even more versatile through their 1,3-dipolar cycloaddition reactivity, giving optically active pyrroloimidazoles.

The Maillard reaction, and associated reactions, continue to provide new products from the interactions of amino acids with carbohydrates (even though the reaction dates from 1912). These reactions (see also Refs. 101, 994) are increasingly recognized as having important roles *in vivo*, including higher organisms, as well as in food science and related areas, and the Maillard reaction has been reviewed[789] specifically from the human physiology perspective. The formation of Amadori rearrangement products, 1-(N-alkylamino)-1-deoxy-2-ketoses, through reductive amination of aldehydes by amino acids, has been demonstrated,[790] and the fructose - benzyl L-tyrosinate product has been studied.[791] The formation of Amadori compounds, an early stage in Maillard processes, has been shown to be reversible, thermolysis of N-(1-deoxy-D-fructopyranos-1-yl)-L-proline giving aldoses (identified after conversion of the reaction mixture into per-O-trimethylsilyl ethers).[792] α-N-Acetyl-L-lysinamide reacts with glucose in the usual Maillard fashion, but a product derived from two amino acid molecules and one glucose molecule is also formed, indicating that a search for a new protein crosslink could be worthwhile.[793] A 1,4,5-trideoxy-1-(N-alkylamino)-2,3-hexulos-4-ene formed from an Amadori product by double dehydration has been targeted in synthetic work, since its cyclization under physiological conditions may be relevant to protein crosslinking.[794]

The de-sulfonylation of protected amides has presented formidable problems, but a Bu_3SnH-AIBN induced radical reaction that requires neutral conditions (boiling toluene) is likely to be widely used. Since those working in the amino acid field could be main users, the method needs to be illustrated with more than just the one example used in this study.[795]

N-Phosphorothio-L-leucine derivatives $ROP(O)(S)NHCH(Bu^s)CONH_2$ that carry a chiral phosphorus centre have been prepared as individual stereoisomers,[796] and reactions with uridine of N-(O,O-di-isopropyl)phosphoryl-L-threonine have permitted the construction of a nucleotide at the N-substituent.[797]

Z-Protected guanidino acids have been prepared from amino acids, trimethylsilyl chloride, NEt_3, $ZNHC(SMe){=}NZ$ in CH_2Cl_2,[798] and from the more useful mono-Mtr- or Pmc-protected analogues using essentially the same method.[799] Amidines $R^1R^2NCSN{=}CPhNHCHRCO_2Me$ have been prepared from amino acids using the chloroimidate as reagent.[800]

Incorporation of the amino group into heterocyclic structures is the result of

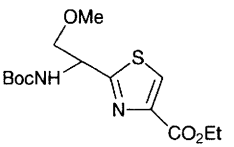
condensation of amino acid esters with tetrahydro-2,5-dimethoxyfuran {giving 1-(1H-pyrrolyl) derivatives}[801] and with 2-(formylmethyl)cyclohexanone.[802] Racemization to the extent of 9 - 18% occurs during the formation of the pyrroles, when acetic acid is used as reaction medium, probably because of N-acetylation and side-reactions that generate the oxazol-5(4H)-one, but problems can be avoided by the use of other solvents.

The photolysis of α-N-phthalimido acids (see Vol. 28, p. 63) has been reviewed.[803] Radical attack has been established to occur at nitrogen using ferrate(V) species formed from K_2FeO_4 and ethanol at pH 10, in contrast to the behaviour of hydroxyl radicals, which preferentially attack side-chain functions in methionine and phenylalanine.[804]

6.2.2 Reactions at the carboxy group – The compliant character of acid halides derived from suitably N-protected amino acids is now clearly established, and Fmoc-L-amino acid chlorides and fluorides have been reviewed from the points of view of their preparations and uses.[805] The fluorides of severely hindered amino acids have been prepared and used in peptide synthesis;[806] diethylaminosulfur tetrafluoride shows superior characteristics as reagent for their preparation.[807]

N-Trityl-O-methyl D- or L-serine has been converted into the corresponding thiazole (110) with preservation of stereochemistry, changing from carboxy group *via* ester, aldehyde and alkanol functions; these steps illustrate standard interconversions that are applicable to all N-protected amino acids.[808] The route is a reversal of a newly-developing standard synthesis of amino acids in which C-2 of a thiazole becomes the carboxy group of the target amino acid (see Ref. 186). The 2-aminothiazol-5-yl analogue has been prepared *via* a diazoketone.[809] N-Benzyl imino acid esters condense with cysteamine in the presence of $Bu^i{}_3Al$ to give 2-(α-iminoalkyl)thiazolines.[810]

Decarboxylation is a stage of the classic colour-forming reaction of amino



(110)

acids that employs ninhydrin as oxidant. Certain solvents (DMSO; methyl Cellosolverm) enhance the colour intensity more than variations in other reaction parameters (pH, temperature, presence of hydrindantin or ascorbic acid).[811] Decarbonylation of N,N-disubstituted-αα-disubstituted glycines through thermal elimination of their acid chlorides (- CO, - HCl) has been illustrated with a pipecolic acid derivative, and offers a route to enamides *via* acyliminium ions.[812] A more involved approach to the replacement of the carboxy group of an amino

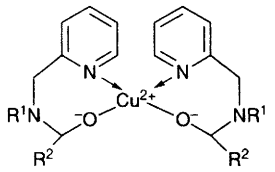
acid (>$CHCO_2H$ →>$CMeCONH_2$→>CMeNHR) has been illustrated with 3-carboxypiperidine (nipecotic acid).[813]

Thiol esters may be prepared in high yields from acids and thiols using ethyl 3-(dimethylamino)propylcarbodiimide on a solid support.[814] Amino acid 'active esters' (still in favour as aminoacylating agents) include pentafluorophenyl esters, prepared from unprotected amino acids using pentafluorophenyl trifluoroacetate, acetate, or corresponding carbamates, and simultaneously providing N-protection,[815] and hydroxybenzotriazolyl esters, used after isolation of their stable rearranged amides for the preparation of tert-butyl esters of N-tritylamino acids, and β-lactones of serine and threonine.[816] N-Benzhydrylglycolamide esters proposed for carboxy group protection, can be cleaved using either Bu_4NF in MeCN or DMF, or by hydrolysis by K_2CO_3 in aqueous DMF.[817] The 3-methylpent-3-yl grouping has been advocated for side-chain carboxy group protection of aspartic acid (*cf.* Vol. 28, p.69).[818]

Conversion of N-protected α-amino phosphonic acids into monoesters is efficiently brought about using peptide synthesis coupling agents BroP or TPyClU and an alkanol.[819]

Reactions of amino acid esters include conversion of alkyl esters of tyrosine and o-tyrosine into oximes through sodium tungstate-H_2O_2 or dimethyldioxirane oxidation, for use in the synthesis of marine sponge metabolites.[820] Conventional ammonolysis in toluene or water converts methyl esters of the familiar aromatic amino acids into amides;[821] this apparently simple process has usually been considered to be open to serious losses through side-reactions, and no doubt a later paper will give further details on this aspect.

Non-enzymic enantioselective hydrolysis studies of N-protected DL-amino acid p-nitrophenyl esters are of interest in a number of contexts, with a search for solutions to mechanistic problems being a predominant theme in studies of cationic micelles, containing copper(II)-complexes of the homochiral N-(pyrid-2-ylmethyl)-β-aminoethanols (111),[822] or various hexapeptides.[823] Transition metal salts promote the hydrolysis of alanine decyl ester in a reversed micelle environment.[824] Novel water-soluble crosslinked polymers imprinted with the transition state analogue (±)-phenyl 1-benzyloxycarbonylamino-3-methylpentyl phosphonate, but rendered capable of enantioselection through carrying L-histidine moieties and quaternary tetra-alkylammonium groups, have been shown to favour the L-enantiomer when presented with p-nitrophenyl N-benzyloxycarbonyl-DL-leucinate.[825]

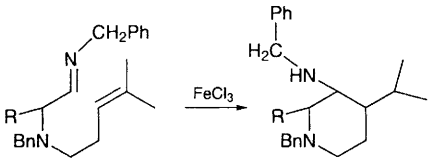


(111)

Preparative aspects, linking to the essential role of ester cleavage as a stage of selective deprotection of amino acids in organic synthesis, are represented in the use of bis(tributyltin)oxide for cleavage of methyl, benzyl, and phenacyl esters linked to resins,[826] and $CF_3SO_3SiMe_3$ for cleavage of tert-butyl esters while leaving tert-butyl ethers unaffected.[827]

Glycine dimethylacetal has had a rare use, providing access to the enol ether AcNHCH=CHOMe used as dienophile for the synthesis of novel pyran-based β-amino acids as enzyme inhibitors.[828]

α-Amino aldehydes are well established starting materials in broad areas of synthesis, and the preparation of this sensitive species is now a matter of routine, *e.g.* by $LiAlH_4$ reduction of Weinreb amides (preceding Horner-Emmons homologation to $=CHCO_2Et$ then on to 'aminoalkoxyoxiranes'[829]) Preparation of argininals from Boc N^{γ}-nitro-L-arginine, then to $BocNHCHR^1CONMeOMe$ and reduction, is another example.[830] Aldol reactions of the products are useful for carbon chain extension (see Section 4.19), and under some reaction conditions, pyrroles are at the end of the reaction path;[831] the 2-vinylpyrrolidine formed from ethyl Z-L-prolinate *via* the aldehyde has been elaborated by bromofluorination (NBS/Bu_4NF/HF) and dehydrobromination into the 1-fluorovinyl analogue.[832] A formal hetero-ene reaction is illustrated in the Lewis acid-catalysed cyclization of N-[2-(3-pentenylaminoethylidene] benzeneamines of aminoaldehydes prepared from methyl alaninate, leucinate, and phenylalaninate (112) into 3-amino-2,4-dialkylpiperidines (113).[833] Vinyl magnesium bromide



(112) (113)

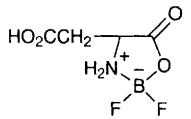
generates vinyl ketones that have been elaborated into corresponding oxiranes in a route to novel protease inhibitors.[834] The aldol reactions of α-amino aldehydes with nitroalkanes mediated by Bu_4NF proceed with high anti-anti diastereoselectivity to provide useful trifunctional compounds $Bn_2NCHR^1CH(OH)$-CHR^2NO_2.[835] Reduction of the carboxy group of an acylated proline is very straightforward (conversion into ester, then DIBALH reduction) as illustrated in conversions of the aldehyde function into the diethyl dithioacetal and (less believably) into the thioaldehyde.[836] Reduction to the aldehyde *via* the primary alcohol has been the preferred route for some workers; BH_3-SMe_2 then $COCl_2$ - DMSO and NEt_3, of Boc-L-proline or -pipecolic acid;[837] BH_3-SMe_2 then py/SO_3 for Boc-L-proline;[838] $LiAlH_4$ then $COCl_2$ - DMSO and NEt_3 for N,N-dibenzyl-L-phenylalanine.[839] Zinc borohydride is needed in only stoichiometric amounts for reduction of amino acids to 2-aminoalkanols, though reflux in THF during 5 hours is required.[840] α-Amino ketones have become favoured starting materials

for chain extension through Horner-Emmons alkenation (see also Ref. 829), with some control over the Z/E-isomer ratio being available through choice of reagent.[841] β-Ketoesters $BocNHCHRCOCH_2CO_2Et$ may be prepared from a Boc-amino acid and the lithium salt of ethyl acetate, through the involvement of carbonyl di-imidazole,[842] and γ-amino-β-ketophosphonates $Bn_2NCHRCOCH_2P(O)(OMe)_2$ are formed analogously from the benzyl ester and the lithium salt of dimethyl methanephosphonate.[843]

Sodium or lithium borohydride reduction of the carboxy group of the common amino acids, after esterification, leads to primary alcohols. Serine presents an annoying problem insofar as loss of chirality is ensured unless the side-chain hydroxy group is derivatized; the TBDMS group or oxazoline formation fulfil this role satisfactorily.[844] Reduction of Boc-amino acid esters by $LiBH_4$ gives the corresponding alcohols; conversions from derived methanesulfonates ($CH_2OMs \rightarrow CH_2Cl \rightarrow CH_2SO_3^-Na^+$) gives 2-substituted taurines.[845] Good yields of alkanols are obtained through reduction of mixed carbonic anhydrides with $NaBH_4$ and for the conversion of these into aldehydes through periodinane oxidation (*e.g.*[846] β-benzyl N-Boc-D-aspartate; see also syntheses of ADDA, Refs. 444-446, 510).

The natural protein kinase inhibitor balanol contains the β-amino alcohol moiety, and combinatorial solid-phase synthesis of simple analogues from Fmoc-β-amino alcohols has been reported.[847] Prolinol and pyroglutaminol have been used in a pyrrolizidine synthesis [(-)-heliotridane].[848] A wide variety of established uses of these compounds in synthesis is extended by condensation of homochiral examples with dimethyl acetylenedicarboxylate to give, after ozonolysis, morpholine 2,3-diones of potential value in asymmetric synthesis.[849] Phosphinamides prepared from L-prolinol are effective partners in asymmetric reductions of ketones by borane.[850]

6.2.3 Reactions involving both amino and carboxy groups – The easy selective esterification of side-chain carboxy groups in aspartic and glutamic acids has been used as a demonstration of the usefulness of B,B-difluoroboroxazolidinones (114) for protecting both amino and α-carboxy groups (Vol. 26, p. 62); side-chain tert-butyl esters of these amino acids were obtained through H_3PO_4-catalysed addition to isobutene after mixing the amino acid with BF_3-Et_2O.[851] Condensation of amino acids with hexafluoroacetone achieves the same outcome (*i.e.* masking both amino and carboxy groups of an amino acid in the form of an easily-cleaved heterocycle), and also usefully activates the carboxy group so that aminoacylation can be brought about (of amines, *e.g.* for an aspartame synthesis).[852] N-(9-Phenylfluoren-9-yl)amino acid oxazolidinones give



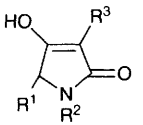
(114)

aminoketones by reaction with organolithium reagents, with negligible racemization.[853]

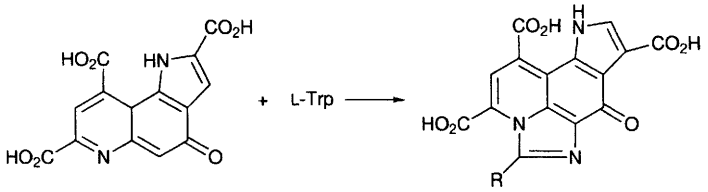
The powerful acylation reactivity shown by N-carboxyanhydrides (NCAs) was established in the earliest days of polymer chemistry, and their uses in peptide synthesis were recognized from the 1960s but were resisted by most practitioners. A new synthesis of NCAs under mild conditions *via* an α-isocyanato acid involves nitrosation ($NO + O_2$) of N-carbamyl-L- or D-amino acids.[854] Preparations and uses of N-alkoxycarbonyl-NCAs (UNCAs; now accepted as having overcome some of the problems associated with uses of NCAs in synthesis) have been reviewed,[855] and new results include the preparation of γ-amino-β-ketoesters through condensation of UNCAs with the lithium enolate of ethyl acetate,[856] alkanolysis to give N-protected amino acid esters,[857] and the formation of N-urethane-protected 3,5-dialkyl-3-aminopyrrolidin-2,4-diones under the influence of base.[858] Acyl analogues of these compounds have been known for more than 50 years as self-acylation products of 2-alkyl- or aryl-oxazol-5(4H)-ones, and an independent study providing the same information has been published.[859]

Uses of amino acids in the preparation of heterocyclic compounds,[860] and for the preparation of chiral auxiliaries for use in asymmetric synthesis,[861] have been reviewed.

More familiar heterocyclic structures are represented in studies leading to novel reaction products; these include 5-(tert-butyloxycarbonyl)oxy-oxazoles formed from N-acylamino acids and $(Boc)_2O$,[862] and 2-alkyloxy-oxazol-5(4H)-ones formed through milder cyclization conditions.[863] A Pictet-Spengler-like reaction, with interesting stereochemical details, of a 4-arylideneoxazol-5(4H)-one (an 'azlactone') with trans-(2-aminocycloalkyl)indoles opens up a route to tetrahydro-β-carbolines;[864] photodecarbonylation of 'azlactones' leads to trappable ketenimines, though this is wavelength-dependent, mild conditions causing only Z/E-isomerization.[865] Several Diels-Alder reactions have been reported for the chiral 'azlactone' (25; Refs. 180, 181), including the Danishefsky diene as a substrate, and uses for the resulting 1-aminocyclohex-2-ene 1-carboxylic acid derivatives.[866] N-Substituted 4-(aminomethylene)oxazol-5(4H)-ones provide 3-aminopyridino-4-ones when condensed with cyclic ketones,[867] and a distantly-related intramolecular cyclization *via* a mesoionic oxazol-5(4H)-one provides 4-oxo-4,5,6,7-tetrahydroindoles.[868] Homochiral tetramic acids (115) are formed through the condensation of succinimido esters of N-alkoxycarbonyl-L-amino acids with active methylene compounds.[869] The long-standing acceptance of another structure for the L-tryptophan - pyrroloquinolinequinone condensation product appears to have been put to rest (see also Ref. 615), with an imidazolo-



(115)



(116) R = indol-3-yl-$(CH_2)_n$; n = 0, 1

pyrroloquinoline structure (116) now assigned, and discovery of another two co-products (116; R = indol-3-yl and indol-3-ylmethyl).[870]

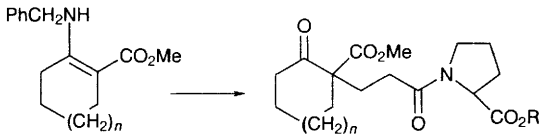
Hydantoins have been prepared by attaching an amino acid to a solid-phase benzyloxycarbonylation reagent, followed by amidation and cyclization causing detachment from the resin.[871] Adducts are formed between C_{60} and amino acid derivatives at 110-120°, but further details are not given in the *Chem. Abstr.* source of this citation;[872] however, the results no doubt correspond with reports of the formation of fulleroprolines *via* azomethine ylides[873] (also formed from glycine ethyl ester, thermally, whereas the 5-alkoxycarbonylproline analogue is formed photochemically[874]); fulleropyrrolidines have been obtained from amino acid Schiff bases *via* azomethine ylides.[875] 4-Hydroxypyrrolidin-2-ones formed from N-protected amino acids and Meldrum's acid give corresponding Δ^3-pyrrolin-2-ones as main products when preparation of O-Boc derivatives was attempted.[876] Pyrazino[2,3-e]-1,4-diazepines have been prepared through an intramolecular aza-Wittig reaction following condensation of 3-aminopyrazine-2-carboxylic acid with an α-amino acid ester, then generation of an iminophosphorane intermediate.[877]

Common L-α-amino acids have been incorporated with $NbCl_5$ or $TaCl_5$ to generate Diels-Alder catalysts, with a 2:1-ratio successfully bringing about good enantioselectivity in representative examples.[878]

The other main topic covering reactions in which both amino and carboxy groups are involved is the polymerization of amino acids to give oligo- and polypeptides. The process can be strongly accelerated by heterogeneous surfaces, *e.g.* clay minerals,[879,880] and by less subtle means, *e.g.* thermal condensation of aspartic acid - proline mixtures.[881] These studies continue a long tradition relating to interests in putative prebiotic processes, and since the product distribution resulting from thermal polymerization of amino acid mixtures is often less-than-random, these are anything but routine studies.

6.2.4 Reactions at the α-Carbon Atom of α-Amino Acids – Electrochemical α-methoxylation is one of the few synthetically feasible operations under this heading, and a thorough review has appeared[882] that also covers anodic methoxylative decarboxylation of amino acid derivatives (the Hofer–Moest reaction) to give homochiral building blocks for amino acid synthesis through diastereoselective amidoalkylation (see also Section 4.7). Boc-L-Proline methyl ester has been α′-methoxylated in this way with simple equipment[883] (see also Ref. 268).

6.2.5 Reactions Specific to β- and Higher Homologous Amino Acids – Excluding papers describing reactions at amino or carboxy groups, that are performed with higher homologues in just the same way as for the α-amino acids, the particular interest under this heading lies with uses of β-lactams and β-lactones for the synthesis of other amino acids. Uses of β-lactams for asymmetric synthesis of non-protein α-amino acids have been reviewed,[884] and further examples of Baeyer-Villiger oxidation of α-hydroxy-β-lactams to NCAs have been described[885] (see also Ref. 224). The last-mentioned study describes one-pot TEMPO conversions giving members of the threonine and azathreonine families. $TiCl_4$-Catalysed alkylation of enamines (117) by N-acryloyl-L-proline esters proceeds with high diastereoselectivity.[886] The conversion of the homologue $PhCH_2OCH_2CH(NHZ)CH{=}CHCO_2Me$, formed from L-serine,[887] into threo-aminoalcohols by iodine-mediated cyclocarbamation has been described,[888] and an analogue tethered to a solid phase has been converted into 2-oxotetrahydropiperazines.[889]



(117)

Some reactions of β- and higher homologous amino acids fall into this Section on the basis of reactions at amino and carboxy groups, and other papers are discussed in the next Section. An example is (R)-4-trimethylammonio-3-chloro-butanoic acid, uneventfully prepared starting from (S)-carnitine (an otherwise useless industrial by-product) and converted into the corresponding enantiomerically-pure β-lactone, from which substituted (R)-carnitines have been prepared through aminolysis (see also Ref. 486).[890]

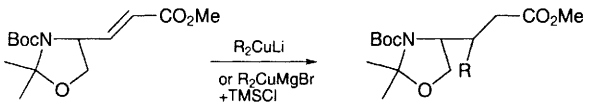
6.3 Specific Reactions of Amino Acids – As usual, this Section covers reactions of side-chains of the common amino acids, and therefore implicitly includes the use of one amino acid to synthesize another.

An extraordinary observation, that aromatic hydroxylation may be achieved through directing a blowtorch at the surface of an aqueous solution of phenylglycine or a homologue, is considered to be consistent with the intermediacy of hydroxy radicals.[891]

ω-Halogenoalkyl side-chains can be generated by direct halogenation of the common aliphatic amino acids, but reliable samples are usually prepared in other ways, *e.g.* β-halogenoalanines from serine (represented by the organozinc reagent $BocNHCH(CO_2Me)CH_2ZnI$, whose use in synthesis is illustrated by coupling with 4-iodoquinoline[892] - see also Refs. 924, 925). However, β-bromo-L-valine is accessible from L-valine, and has been used for S_N2-reaction studies to reveal neighbouring group participation by an amide

function, favouring substitution to give the β-hydroxy compound at the expense of E_2 elimination.[893]

β-Bromination of protected dehydroamino acids can be accomplished using N-bromosuccinimide, and β-acetoxylation occurs with lead tetra-acetate; the products appear to be quite stable and amenable to controlled use in synthesis, and hydrolysis and oxazolone formation, and other manipulations, have been described.[894] Bromination of methyl N-formyl-αβ-dehydroalaninate, $HCONHC(=CH_2)CO_2Me$, in this way is Z-selective.[895] Cyclization of N-(α-halogenoacetyl)-αβ-dehydroalanines with Bu_3SnH in boiling toluene gives pyroglutamic acid through a radical cyclization mechanism, best results being secured with dichloro- and trichloroacetamides,[896] and iminophosphoranes of αβ-dehydrotryptophans are easily cyclized with benzylglyoxal and decarboxylated to give eudistomins T and S, and xestomanzamine A.[897] Irradiation (>280 nm) of N-acetyl αβ-dehydro-(4-chlorophenyl)alanine esters yields 1-azetidine carboxylic acid amides and isoquinolines through 1,5-acetyl shifts.[898] 1,3-Butadiene and a chiral 2-acetamidoacrylate provide (1S,3R)-1-amino-3-hydroxycyclohexane-1-carboxylic acid through Diels-Alder addition followed by a directed hydroxylation.[899] Elaboration of the unsaturated grouping in chiral γ-amino-αβ-unsaturated esters (118) with dialkyl or diaryl cuprates leads to the corresponding β-substituted γ-amino esters with high syn-stereoselectivity, and further reactions (potassium enolate + trisyl azide; oxaziridine oxidation; Mitsunobu inversion) have been performed with clear stereochemical control.[900] Optimized procedures have been established (choice of N-protecting group; optimum Sharpless catalyst) for asymmetric dihydroxylation of chiral γ-amino-αβ-unsaturated esters.[901] N-Toluene-p-sulfinyl cis-(Z)-2-phenyl-1-(2-methoxycarbonylethenyl)aziridines exposed to $Pd(PPh_3)_4$ give the (E)-isomers through Pd-mediated ring opening.[902]

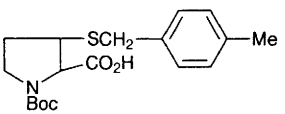


(118)

Methyl vinylglycinate and allylglycinate undergo chemo- and regioselective hydroboration by diorganoboranes, leading to homoserines, δ-hydroxynorvaline, and corresponding 2-amino-4- and 5-boronoalkanoic acids.[903] β-Acetoxyallylglycine esters undergo Pd(II)-catalysed rearrangement into δ-hydroxy-βγ-unsaturated analogues.[904] Where the side-chain C=C grouping is several atoms removed from the amino and carboxy groups of an α-amino acid, its reactions are more typical of a simple alkene, as illustrated in $OsCl_3$-catalysed oxidation to α-ketols $R^1R^2C(OH)CO(CH_2)_nCH(NHR^3)CO_2R^4$, a process used in a synthesis of (S)-5-hydroxy-4-oxonorvaline.[905] Allenic side-chains are dihydroxylated with OsO_4 to give regioisomeric α-ketols (erroneously formulated in this paper).[906] The cyclic anhydride of 4-methyleneglutamic acid yields Diels-Alder adducts with 2,3-dimethylbuta-1,3-diene,[907] and cyclopropane construction on to protected 3,4-

dehydro-L-prolines can be brought about through rhodium(II) acetate-catalysed reaction with dimethyl diazomalonate.[908]

The first synthesis of homochiral βγ-alkynylglycines $H_2NCH(C(CR)CO_2H$ has been described,[909] through elaboration of the CH_2OH function illustrating one of an increasing number of uses for synthons based on L-serine. tert-Butyldimethylsilyl ethers of N-protected serine esters can be cleaved selectively using 1% I_2 in methanol.[910] N-Fmoc-O-[(benzyloxy)hydroxyphosphinyl]-L-serine and threonine have been prepared using a new phosphite-forming reagent, $^iPr_2NP(OBn)(OCH_2CCl_3)$.[911] N-Acetylation of most amino acids in the presence of an alkali metal cyanate (the Schlack-Kumpf reaction) leads to 2-acetylaminohydantoins, and with serine and threonine gives the N-acetylthiohydantoins of cysteine and β-methylcysteine respectively when ammonium thiocyanate is used.[912] This finding is the latest in a long history of the use of β-hydroxy-α-amino acids for the synthesis of their sulfur analogues, and needs rigorous proof of stereochemical details for the case of threonine. Conversion of the TBDMS ether of cis-3-hydroxy-L-prolinol into N-Boc-3-(4-methylbenzyl)thio-L-proline (119) with inversion of configuration follows established mechanistic principles.[913] N-Thioalkanoyl and alkanoyl-α-amino β-hydroxy acids have been cyclized to thiazolines and oxazolines respectively using poly-(ethyleneglycol)-supported Burgess reagent.[914] Chiral bis-oxazolines have been prepared from Z-D-serine methyl ester through carboxy group manipulation ($CO_2Me \rightarrow CMe_2OH \rightarrow CMe_2OTMS$) and N-deprotection and bis-N-acylation with dimethylmalonyl chloride, and used as ligands for incorporation into copper(I) triflate catalysts in the crucial asymmetric intramolecular cyclopropanation step in a phorbol synthesis.[915] Conversion of L-serine into enantiomers of 3-hydroxy-4-nitroprolinols, as potential enzyme inhibitors, involves distinctive routes with routine functional group transformations preceding tandem Michael-Henry condensation with nitroethene.[916]



(119)

A convenient preparation of allo-L-threonine from Boc-L-threonine based on traditional Walden inversion chemistry has been described.[917] Substitution of the hydroxy group of β-hydroxy-α-amino acids can be accomplished in numerous ways, additional to those just described, Mitsunobu sulfonation with inversion being an effective way of converting hydroxy-L-proline (as its N-benzoyl methyl ester) into its non-natural stereoisomer.[918] Intramolecular Mitsunobu lactonization of N-trityl trans-4-hydroxy-L-proline and ring opening with methanol gives cis-4-hydroxy-L-proline methyl ester,[919] while N-toluene-p-sulfonylserine tert-butyl ester gives tert-butyl aziridine-2-carboxylate through Mitsunobu processing.[920] Mitsunobu reactions with L-serine esters are free from side-reactions leading to dehydroalanine derivatives when phenylfluorenyl- and trityl-N-protec-

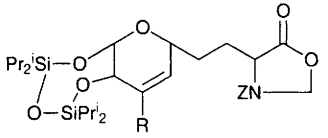
tion is used.[921] Side-chain protection (TBDMS) of (2S,3S)-3-hydroxyleucine is appropriate when it is used as its N-Fmoc acid chloride in synthesis of an A83586C fragment.[922]

N-Trityl-3-iodoalanine methyl ester, prepared from serine, can be used to prepare γ-functionalized amino acids through substitution of the halogen by malonate nucleophiles.[923] Aziridinecarboxylates are major side-products of this process, to the extent of 5 - 50%. The derived alkylzinc iodide $BocNHCH(CH_2ZnI)CO_2Me$ has been coupled with 1-iodoferrocene, catalysed by palladium(0) species.[924] C-3 and C-1 Adducts (*e.g.* 120) formed by β-face attack, have been obtained through the reaction with protected glucals of the alkylzinc iodide reagent derived from butyrine.[925]

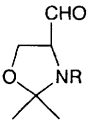
N-Boc-(2S,3S,4R,4E)-2-Amino-3-hydroxy-4-methylocten-6-oic acid and N-Boc-(2S,4R)-2-amino-4-methylhexanoic acid have been prepared from the acetonide of D-serine aldehyde, which functions as a formylglycine equivalent, through $TiCl_4$-catalysed alkylation with (E)-crotylsilane and elaboration of the ethene grouping.[926] The enantiomeric Garner aldehyde derived from L-serine (121) continues to prove its worth in broad areas of organic synthesis, though the topics covered here are mostly syntheses of amino acids and near relatives. The corresponding methyl ester reacts with lithiated diethyl difluoromethylphosphonate to give β-(αα-difluoromethyl)phosphonate analogues of L-phosphoserine, L-phosphothreonine, and L-phospho-allothreonine after converting the β-hydroxy function into H,[927] and with N-benzoylglycine methyl ester, followed by hydrogenation of the resulting dehydroamino acid derivative, to give meso-2,4-diaminoglutaric acid.[928] ω-Aminosphingosine analogues have been obtained through aldolization of (121),[929] and another sphingosine synthesis from a masked form of serine, *viz* an aziridinecarboxylic acid, has been described; (2R,3R)-N-toluene-p-sulfinyl 2-alken-1-ylaziridinecarboxylate esters subjected to hydrolysis cause threo ring-opening, while, remarkably, TFAA gives the natural D-erythro-sphingosine.[930]

Homoserine has been used for a reliable L-vinylglycine synthesis ($NaBH_4$/PhSeSePh for Z-L-homoserine lactone cleavage;[931] and photoelimination from N-phthaloyl esters of homoserine and other γ-functionalized α-amino acids[932]), and in a versatile synthesis of α-substituted β-amino acids (the hydroxyethyl side-chain becomes the eventual carboxymethyl moiety).[933]

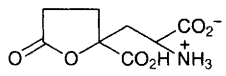
4-Hydroxy-L-proline has been used for the preparation of N-α-benzoyl-cis-4-amino-L-proline through standard steps ($OMs \rightarrow N_3 \rightarrow NH_2$);[934] the 4-mercapto analogue has been prepared through intramolecular cyclization of the same intermediate mesylate after conversion of the carboxy group into thiolcarboxylate.[935] Substitution with retention of configuration has been explored for the synthesis of acromelic acid analogues from 4-toluene-p-sulfonyloxyproline using lithium diaryl cuprates,[936] while (2S,3R,4S)-3-carboxymethyl-4-phenylproline is best prepared *via* 3,4-dehydroproline through manganese(III) acetate-catalysed oxidative radical addition of a monoalkyl malonate.[937] 4-Hydroxyproline starts the first synthesis of lycoperdic acid (122) through samarium iodide-mediated alkylation with methyl acrylate to give the proline-based spiro-γ-lactone as a mixture of epimers, followed by RuO_4-$NaIO_4$ oxidation to the pyroglutamate



(120)



(121)



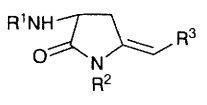
(122)

and ring cleavage.[938] Decarboxylation of 4-hydroxy-L-proline (cyclohexanol, cyclohex-2-en-1-one, 160°C, 4 h) gives (R)-3-hydroxypyrrolidine for use in a (-)-retronecanol synthesis.[939]

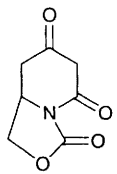
4-Oxo-L-proline undergoes regioselective enolization after N-phenylfluorenylation, permitting alkylation leading to β-alkylprolines,[940] and Bucherer-Bergs synthesis (see also Ref. 98) and other elaboration steps to give (2R,4S)-4-amino-4-carboxy-2-alkylpyrrolidines.[941] Chiral pyrrolidines are also accessible from 5-oxo-L-prolines (*i.e.* L-pyroglutamates) in a similar way.[942]

The di-anion of (3S,2R)-3-hydroxyproline ethyl ester has been alkylated with a variety of alkyl halides with net retention of configuration to give the α-alkylated hydroxyprolines, contributing part of the structure of microbial metabolites paraherquamide A and lactacystin.[943]

Aspartic and glutamic acid derivatives rival serine analogues for their potential applicability in amino acid synthesis, and this topic is reviewed here and also in Section 4.19. Of course, these compounds are also useful in organic synthesis outside the amino acid field, but no attempt is made here to cover this wider area in a thorough manner. Bulky esters have proved useful as β-protecting groups of aspartic acid, in minimizing the commonly-observed side reaction for aspartic acid synthons that leads to aspartimides, and 2,4-dimethyl-3-pentyl esters have been successful in this context.[944] The aspartimide derivative (123) has been used for the synthesis of 2-amino-4-oxoalkanoic acids.[945] α-Methyl Z-L-asparaginate and the glutamine analogue can be selectively hydrolysed at the amide group by tert-butyl nitrite in refluxing MeCN,[946] and used in a synthesis of pipecolic acid. Aspartic acid derivatives are involved in syntheses of the natural β-amino acid, ADDA (see Refs. 444-446), one of a number of fragments required for a convergent synthesis of microcystins and nodularins (a new approach to β-methyl-L-aspartic acid derivatives is also included in this study).[947] These preceding examples, like other β-amino acid syntheses from aspartic acid covered in Section 4.19, exploit the fact that aspartic acid is both an α- and a β-amino acid. L-Asparagine has been used to prepare the oxazolidinone (124) for use in

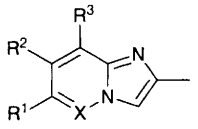


(123)

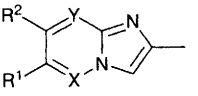


(124)

the preparation of substituted pipecolic acids (better prepared from lysine; see later),[948] and to prepare the tetrahydropyrimidinone (93) that provides a starting material for a synthesis of (R)- and (S)-α-alkyl-β-amino acids.[949] (R)-Isoserine, prepared from D-asparagine, leads to the analogue of the Garner aldehyde (121; $Me_3SnCH{=}CH$- in place of CHO) for syntheses of Caramel Colour III derivatives as potential immunomodulators.[950] Since many further applications of this type can be expected, simple modifications to the aspartyl side-chain will extend the range of synthetic targets that can be addressed. N-Protected (S)- and (R)-2,3-diaminopropanals have been prepared from L- and D-aspartic acids, respectively.[951] The elusive L-aspartic acid semialdehyde is best prepared through hydrolysis of its enol ether, (S)-2-amino-4-methoxybut-3-enoic acid.[952] The equally problematical L-aspartic acid β-chloride has been prepared in the form of its 2,2-difluoromethyloxazolidinone (*cf* Scheme 26; in other words, aspartic acid doubly protected by condensation with hexafluoroacetone), and used through Stille coupling to prepare γ-oxo-α-amino acids (4-oxo-ornithine, and 5-hydroxy-4-oxo-L-norvaline).[953] A preparation of 2-amino-4-oxobutanoic acid, from which both enantiomers of 2-amino-4,4-dichlorobutanoic acid (armentomycin) and its fluorine analogues have been prepared, has used similarly-protected aspartic acid intermediates.[954] The novel electrophilic sulfenylating agent, 2,4-dimethoxybenzyl p-toluenethiolsulfonate, has been used to generate thiols bearing an acid-labile S-protecting group, as illustrated in the preparation of (2R,3R)-3-mercaptoaspartic acid through attack by the side-chain anion of protected L-aspartic acid.[955] The heterocyclic side-chains (125) and (126) have been built on to the β-carboxy group of phthaloyl DL-aspartic acid.[956]

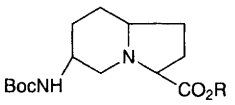


(125)

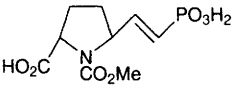


(126)

Glutamates employed in similar ways are the starting point for syntheses of 5-tert-butyl-L-proline (from γ-methyl 9-phenylfluorenyl-L-glutamate after γ-lithiation and reaction with pivaloyl chloride, then cyclization);[957] of indolizidine amino acids (127; through a similar cyclization of glutamate-derived β-keto-esters);[958] of γ-benzyl-substituted L-pyroglutamates [through palladium(0)-catalysed cross-coupling of ethyl (2S,4S)-4-(4-bromobenzyl) N-Boc-pyroglutamate with various organostannanes];[959] of δ-substituted prolines, including the δ-phosphonalkyl derivative (128), viewed as a conformationally-restricted analogue



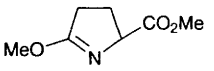
(127)



(128)

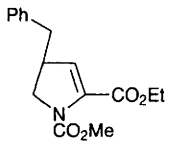
of (R)-2-amino-7-phosphonoheptanoic acid;[960] of condensed 5-arylpyrrolidin-2-ones [from the acyliminium salt of N-(N′-acetyl-N′-arylaminomethyl)pyroglutamyl chlorides formed under Friedel-Crafts conditions];[961] of substituted pipecolic acids *en route* to homopipecolic acids including streptolutine;[962] and of L-indospicine, (S)-6-amidino-2-aminohexanoic acid.[963]

For the preparation of apparently simple pyroglutamate derivatives, unusual measures are sometimes needed for best results; thus, it is claimed to be advisable to start with the imino ether (129) in order to prepare N-(4-nitrobenzyl)pyroglutamate.[964] The straightforward N-alkylation procedure with alkyl chlorides in THF is satisfactory for pyroglutamate esters, however, if a strong base (NaH) is used.[965] An unusual use as chiral auxiliary is shown in Diels-Alder additions of N-alka-1,3-dienyl-L-pyroglutamates with nitroso compounds.[966]

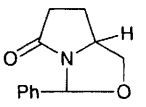


(129)

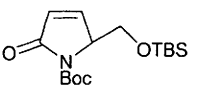
The ring carbonyl function plays a role in a group of uses of pyroglutamates; the protected dehydroprolinate (130; see Vol. 28, p.66), prepared from pyroglutamic acid, has been used for highly diastereoselective Michael reactions leading to all-trans-3,4-disubstituted prolines.[967] 4-Substituted 2,3-methanoprolines have also been prepared in this study, from the same starting material. 4,4-Dialkylation can be accomplished *via* the pyroglutaminol aminal (131).[968] The pyroglutamate synthon (132) derived from L-glutamic acid, and the D-serine-derived synthon (133), have been used for a synthesis of the four stereoisomers of β-benzylglutamic acid, and their β-methallyl and β-isobutyl analogues.[969]



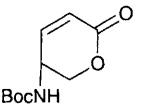
(130)



(131)



(132)



(133)

α-Acyl-N-acylglycinamides tethered to a solid phase provide a library of imidazoles through treatment with ammonium acetate.[970] The side-chain aldehyde function in methyl (1S,2R)-2-formyl-1-benzoylaminocyclopropane-1-carboxylate has been extended through standard Horner-Emmons chain extension to provide a glutamic acid homologue ($CHO \rightarrow CH_2CH_2CO_2H$),[971] and the sulfur analogue (121; S in place of ring O) of the Garner aldehyde, prepared from L-cysteine in four steps, has given segments needed for a total synthesis of curacin A through a similar chain extension.[972]

S-Nitroso L-cysteine is of enhanced interest due to the roles established for nitric oxide (though is clear that S-nitrosothiols cannot serve as *in vivo* carriers of

NO species[973]). Its formation from the two fragments is catalysed by iron(0) or by iron(II) ions,[974] more plausibly the latter species, under anaerobic conditions at neutral pH.[975] S-Nitroso-L-cysteine is stable in aqueous media within the pH range 1 - 5, and indeed is considerably more stable in higher pH solutions than previously assumed;[976] the mechanism of fragmentation into its constituents crucially involves catalysis by copper(I) species,[977] and catalysis by transition metal ions more generally.[978] Peroxynitrite ions, formed *in vivo* by reaction between superoxide and nitric oxide free radicals, can bring about cleavage of DNA and can cause protein peroxidation. The sulfur amino acids offer protection by intercepting the oxidant, but more effective still in this role are selenocysteine and selenomethionine[979] (rapidly oxidized by peroxynitrite, but only to the selenoxide[980]). In contrast with the well-known outcome for methionine, oxidation of selenomethionine with H_2O_2 in the presence of cyanogen bromide gives 2-amino-4-butyrolactone through C-Se cleavage of an unusual intermediate, Se,Se-dihydroxyselenomethionine, releasing either methaneseleninic acid or MeSeCN.[981] Fe(III)-Catalyzed oxidation of S-(aminoethyl)cysteine ketimine, a compound of long-standing interest as the product of deamination of S-aminoethylcysteine, generates radical intermediates *en route* to known products.[982]

Sulfoxides from protected S-(p-tolyl)-L-cysteine undergo highly stereospecific S_N2-type displacement of sulfinyl by OH under Pummerer reactions conditions to give threonine derivatives,[983] and protected L-methionine sulfoxides and sulfones have been cyclized with sure stereochemistry to give amino ketones and related compounds after Ramberg-Backlund rearrangement or Raney nickel desulfurization of intermediates.[984]

More conventional studies, invoking the high nucleophilicity of the thiol side-chain function, have focussed on the formation of S-α-glycosides of N-phthaloyl-L-cysteine esters using simple glycosylating agents.[985] Caesium carbonate-catalysed Michael addition of allyl Fmoc-L-cysteinate to methyl Boc-dehydroalaninate gives a protected lanthionine,[986] and analogous additions to dopaminequinone lead mainly to C-5 adducts with C-2 adducts as minor side-products.[987] Mixed disulfide formation can be achieved using $MeSO_2SCH_2$-CH_2OH as sulfenylating agent.[988] Substitution of the methionine side-chain function by bromine gives a valuable synthesis intermediate that has been used in reactions with purines (adenine, *etc.*) to give α-(β-purinylethyl)-α-amino acids.[989] Rearrangement of S-(purin-6-yl)cysteine gives the N-substituted amino acid.[990] Conversion of the side-chain of α-allyl-L-methionine (constructed *via* an oxazolidinone) into the sulfonium salt is a crucial step in a synthesis of α-aminolactams.[991]

Lysine derivatives give fluorescent 2-hydroxy-1,2-dihydropyrrolin-3-ones with aliphatic aldehydes and peroxides (Vol. 25, p.5), but so do simple aliphatic amines; therefore, the generation of fluorescence cannot be used as a reliable marker for protein degradation caused by ageing.[992] The generation of a 4-methylimidazolium salt by reaction of 1,3-di-N^{α}-hippuryl-L-lysine with methylglyoxal has been established; this must now be considered to be a potential protein modification reaction[993] (see also Vol.28, p.66). The crosslinking amino

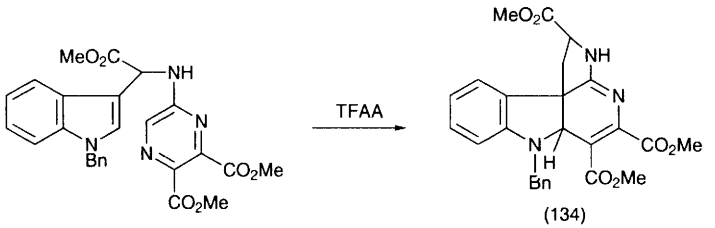
acid pentosidine is formed in mixtures of ribose, lysine and arginine, together with 'penK$_2$', a crosslink found in ribose-treated proteins and formed by characteristic Maillard processing,[994] identical with a protein constituent reported earlier.[995] The lysine side-chain is implicated in the formation of an imidazolium crosslink with stoichiometry 1:2, through model reactions of N-protected amino acids with methylglyoxal, though arginine forms a pyrimidine with this compound, in a 1:1-addition process.[996] Also in the context of cell reactions, L-lysine α-aminotransferase has been shown to catalyse the first of two steps involved in the conversion of L-lysine into L-ε-aminoadipic acid.[997] Hofmann rearrangement of resin-bound aminoacyl-L-glutamine gave the corresponding (S)-2,4-diaminobutanoic acid derivative which on guanylation gave L-norarginine in the form of its dioxopiperazine (for its use as catalyst for asymmetric Strecker reactions, see Ref. 131).[998] Guanidinylation of the ornithine side-chain contained in a macrocyclic peptide has been described.[999]

The chemistry of N$^{\omega}$-hydroxy-L-arginine, topically interesting in view of the search for nitric oxide sources *in vivo*, has been reviewed.[1000] The kinetics of degradation, under physiological conditions, of the nitric oxide synthase inhibitors N^{G}-nitro-L-arginine and its methyl ester have been determined, establishing the first step for the degradation of the ester to be conversion into the free acid.[1001]

Crystallization of N$^{\alpha}$-Z-L-histidine hydrazide from water gives 2-oxo-1,3,7-triazabicyclo[4.3.0]nona-6,8-diene-4-carboxyhydrazide,[1002] through a well-known reaction of the histidine side-chain. This example is based on a surprising cyclization involving the N-protecting group, and the compound contains a ring system that is amenable to alkylation followed by ring-opening, to give 1'-alkyl-L-histidines.[1003] Isolation from proteins of amino acids modified only at histidine indicates that 4-hydroxynon-2-enal (known to react with this side-chain; see Vol. 28, p. 72) reacts solely at this site.[1004] 3-Methylhistidine can be isolated from acid-hydrolysed urine proteins but decomposition is significant if the temperature exceeds 120°.[1005]

Cyclic tautomers of tryptophan have been useful in syntheses of analogues, and their preparation and behaviour have been reviewed.[1006] Epimerization in acid, of one of the best known of these tautomers (represented by cis-1,3-disubstituted N$^{\beta}$-benzyl-1,2,3,4-tetrahydro-β-carbolines), has been shown to involve C-1 - N-2 bond scission.[1007] Studies of oxidation and inhibition of oxidation have been prominent with tryptophan, and copper chelation has been shown to protect the amino acid from the effects of pro-oxidant systems containing copper ascorbate.[1008] 5-Hydroxytryptophan gives the 2-bromo compound through electrophilic bromination,[1009] and electro-oxidation in the presence of glutathione gives not only 4-S-glutathioninyl-5-hydroxytryptophan but also 7-S-glutathioninyltryptophan-4,5-dione, the latter being formed through nucleophilic addition of thiolate to the oxidized amino acid.[1010] Schiff bases of L-tryptophan give enaminones through Mannich-Michael condensation with electron-rich siloxydienes, *en route* to highly functionalized indoloquinolizines (as in yohimbine and reserpine alkaloids).[1011] Ergot alkaloids are constructed by linking through C-4 of the indole portion of tryptophan to the glycine moiety,

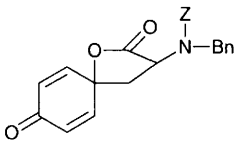
and the Heck reaction has supplied the crucial means of accomplishing this in a synthesis of chanoclavine-I from 4-bromotryptophan.[1012] Intramolecular cycloaddition of an N-triazinyl-L-tryptophan employing trifluoroacetic anhydride provides a single diastereoisomer (134),[1013] while the more familiar cyclization involving aldehydes in the Pictet-Spengler reaction gives β-carbolines from abrine (N-methyl-L-tryptophan).[1014]



(134)

Protection of the indole grouping of tryptophan, to avoid ring-substituted side-products in synthesis, has been studied for a range of substituents in place of the N^{in}-proton, with cyclohexyloxycarbonyl proving the best in terms of stability and removeability.[1015]

Standard aromatic substitution reactions shown by L-tyrosine (see also Section 4.12) include iodination by I_2 to give the expected 3-iodotyrosine, using a liquid membrane system (I_2, KI in an aqueous phase separated from aqueous tyrosine by a solution of a crown ether in dichloroethane).[1016] Alkoxylation (BF_3/MeOH) of the L-tyrosine synthon (135) gives the 2,4-dimethoxyphenylalanine.[1017] L-Phenylalanine, p-substituted with a vicinal tricarbonyl moiety (-COCOCO$_2$R), has been prepared from Z-L-tyrosine benzyl ester through routine steps after substitution of the derived triflate with tert-butyl acrylate;[1018] this triflate also features in preparations of 4-carboxy- and 4-methoxycarbonyl-L-phenylalanines through Pd(0)-catalysed carbonylation reactions,[1019] and analogous diphenylphosphinylation.[1020] Aldol addition to p-formyl-L-phenylalanine starts a satisfactory route to L- and D-(p-phosphonofluoromethyl)-phenylalanines.[1021] Conversion of protected 3-chloro-L-tyrosine into vancomycin diaryl ether sub-units has been worked out through mild Ru-complex catalysis[1022] as an alternative to thallium(III) nitrate oxidation to form the oxygen bridge within a dipeptide formed from modified L-tyrosines.[1023] 4-Nitrophenylalanine has been used to prepare the 4-(oxomalonylamino) analogue,[1024] and to prepare 4-bis(2-hydroxyethyl)amino-L-phenylalanine for N-aminoacylation (at the latest possible stage) to allow construction of N-aminoacyl-melphalans through



(135)

replacement of OH by Cl.[1025] Pd-Mediated tert-butylthiolysis of N-Boc-4-iodo-L-phenylalanine gives a protected L-thiotyrosine.[1026] Hydrogenation of L-phenylalanine (H_2/Adams catalyst) starts a route to (S)-2-(N,N-dibenzylamino)-3-cyclohexan-1-ol, chain extension giving a core mimetic for a classic renin inhibitor.[1027]

4′-O-(Carboxymethyl)ation of trichloroethyl N-Boc-L-tyrosinate,[1028] 4′-O-(laevulinoyl)ation (then tethering to a solid phase, $NaBH_4$ deprotection and incorporation into oligonucleotides),[1029] and 4′-O-(2-fluoromalonyl)ation,[1030] have been accomplished.

6.4 Effects of Electromagnetic Radiation on Amino Acids – Mycosporin-like amino acids (*e.g.* shinorine) present in eggs of the sea urchin *Strongylocentrotus deoebachiensis* are found to exert a photoprotective role against UV damage of cell constituents;[1031] the opposite approach is seen in a study of common UV stabilizers as inhibitors of the photodegradation of tryptophan.[1032] Yet another type of study under this heading is represented by a study of the effect of isoleucine on the fluorescence of aqueous solutions of Schiff bases of pyridoxal and pyridoxal-5′-phosphate.[1033]

The riboflavin-sensitized photolysis of tryptophan and tyrosine has been reviewed;[1034] the process involves radical intermediates and leads to complex mixtures, or to dityrosines, respectively. The discovery that triplet state Rose Bengal inefficiently produces superoxide in aqueous media[1035] will have to be taken into account in the interpretation of the results of many previous studies, *e.g.* factors affecting reaction rates of Rose Bengal-promoted photo-oxidation of alkyl esters of tryptophan.[1036]

Fluorescence of N-acetyl-L-tryptophanamide is a topic of continuing interest (840 nm laser excitation has been investigated[1037]), especially fluorescence decay in reverse micelles (Vol.28, p.74),[1038] similarly for N-acetyl-β-homotyrosine methylamide[1039] and analogous N-acetyl-N′-(ω-diethylaminoalkyl)amides (with consideration of quenching by intramolecular electron transfer).[1040] A sophisticated approach to assessing triplet-state properties of tryptophan, 5-hydroxytryptophan and 7-aza-tryptophan uses optically-detected magnetic resonance in zero applied magnetic field.[1041]

Irradiation of aqueous 5-aminolaevulinic acid at 37°C leads to at least two products, 2,5-(β-carboxyethyl)dihydropyrazine and the corresponding pyrazine.[1042] Some further insights may be gained of the mode of action of this amino acid, widely-used as a photosensitising agent for cancer photochemotherapy[1043] (irradiation at 628 nm[1044]) through laboratory-based studies. Photosubstitution of N-acetyl-DL-2-chlorotyrosine in methanol gives 2-methoxylation (45%), accompanied by intramolecular cyclization to methyl 1-acetyl-6-hydroxyindoline-2-carboxylic acid (35%).[1045] Products of UV irradiation of solid lysine have been separated by gel permeation chromatography and analysed by GLC-MS (the Abstracts source of this citation does not give specific information on the reaction products).[1046]

7 Analytical Methods

7.1 Introduction – A recent text gives background information on the analysis of enantiomer mixtures in amino acid samples.[1047] Specific analytical techniques appropriate for samples from extraterrestrial and deep sea environments, relevant to theories of prebiotic chemical evolution, have been reviewed.[1048] The HPLC analysis of urine for free and total crosslinking amino acids containing the pyridinium grouping (see also Ref. 656) has been reviewed.[1049]

7.2 Gas-Liquid Chromatography – Generally applicable protocols for amino acid analysis by GLC involve derivatization and separation, followed by quantitation of the GLC effluent by conventional detectors, or by MS. More sophistication usually relates to the detection stage, and there is little to report that is particularly new this year. Derivatization of amino acid mixtures as N(O)-ethoxycarbonyl ethyl esters takes less than 10 minutes;[1050] similarly for N(O,S)-isobutoxycarbonyl methyl esters.[1051] N-Acetyl propyl esters have been used for determination of the ^{13}C-content of amino acids,[1052] and TBDMS derivatives for ^{15}N-analysis for wheat protein hydrolysates.[1053] Derivatization as N-benzyloxycarbonyl 2,2,2-trifluoroethyl esters has been advocated for the determination of enantiomer ratios for amino acid samples through separation over Chirasil-Val;[1054] derivatization is not needed for N,N-dimethylamino acids from peptide alkaloid hydrolysates[1055] but N-trifluoroacetyl esters are appropriate for enantiomeric analysis of common amino acids[1056] by GC using modified cyclodextrin CSPs (see also Refs. 741, 744, 745).

Analysis of particular amino acids has been addressed, for studies that aim to solve mechanistic problems or provide physiological information. 5-Hydroxy-2-aminovaleric acid has been proposed as a specific marker for oxidative attack at arginine and proline residues in proteins;[1057] it is formed by reduction of the γ-glutamylsemialdehyde liberated by hydrolysis of oxidized proteins, in trace amounts calling for GLC-MS-SIM analysis. Routine GLC-MS instrumentation supports attention given as in previous years, to the analysis of N-acetyl-aspartic and glutamic acids,[1058] N^{τ}-methylhistidine,[1059] S-(2-aminoethyl)-L-cysteine and other metabolites developed in cystathioninuria,[1060] S-(aminoethyl)cysteine ketimine,[1061] and S-nitroso-L-cysteine.[1062]

7.3 Ion-exchange Chromatography – Standardized protocols continue to be reported but need no discussion here; however, a thoughtful assessment of corrections for losses (or ways of avoiding losses) during sample preparation of amino acid mixtures for ion-exchange analysis, has been published.[1063]

7.4 Thin-layer Chromatography – Though this section is small enough, there are more papers than usual, perhaps reflecting a growing abandonment of snobbery when faced with a choice of this simple technique, applicable to free amino acids, rather than a more esoteric and time-consuming analytical method.

Standard practice is illustrated for the determination of proline and hydro-

xyproline in biological samples,[1064] while more sophistication is needed for fluorescence quantitation of tryptophan, 5-hydroxytryptophan, and their metabolites at 10 - 100 ng levels.[1065] Separation of arginine from citrulline has been described,[1066] and quantitation by densitometry has been applied to a variety of amino acid mixtures.[1067] Derivatization of amino acid mixtures is usually undertaken to facilitate separation and quantitation, and dabsylation is favoured for the estimation of phosphoserine, phosphothreonine, and phosphotyrosine in phosphoprotein hydrolysates,[1068] and for assessment of a multiple-development TLC procedure with dabsylated mixtures of common amino acids.[1069] Separation by TLC of dimethylaminonaphthylazobenzene-thiohydantoins prepared from amino acids has been reported.[1070]

TLC has been used for assessing binding between amino acids and a surfactant (Ref. 690).

7.5 High-performance Liquid Chromatography – Numerous amino acid analysis examples are given in a new monograph.[1071] A review of HPLC methods for amino acid analysis stresses the need for careful sample treatment and precise derivatization protocols.[1072]

In some cases, the analysis is directed at a particular amino acid that can be detected without derivatization, because of some inherent property such as radioactivity {[^{11}C-methyl]-L-methionine[1073]}, fluorescence (3-methylhistidine; λ_{excit} 260nm; $\lambda_{emission}$ 455nm;[1074] tryptophan[1075]), or UV absorption (crosslinking amino acids pentosidine - a marker for diabetes and uremia, though naturally increasing with age,[1076] pyridinoline and deoxypyridinoline in serum,[1077] elastin crosslinks aldosine and cyclopentenosine,[1078] the collagen crosslink lysylpyridinoline in urine;[1079] copper(II) complexes of amino acids at 255 nm;[1080] and 3-nitro-L-tyrosine, formed from tyrosine with NO + superoxide[1081]). Conductivity detection has been chosen for HPLC analysis of meso-alanopine and D-strombine in invertebrate muscle extracts,[1082] and for a phosphoserine assay.[1083]

Overlapping of peaks in the separation of free amino acids can be lessened by ion-pairing additives, and a dual-mode gradient ion-pair HPLC approach has been advocated that includes sodium dodecanesulfonate and perchloric acid in the eluent.[1084] Crown ether-containing phases have been applied for HPLC analysis of neurotransmitter amino acids.[1085]

Pre-column derivatization continues to be the favoured approach for general purpose amino acid analysis (also for MS analyses; see Section 5.4). The o-phthaldialdehyde - mercaptoethanol reagent system has been used with automated equipment for analysis of the glycine/aspartic acid/glutamic acid/taurine/GABA group of neurotransmitters,[1086,1087] and for enantiomer ratio determinations using OPA with a homochiral thiol.[1088] The finding that Beer's Law is obeyed by these OPA-derived isoindoles goes against received wisdom, which states that reproducible fluorescence intensities are dependent upon following rigid protocols.[1089] The more sensitive naphthalenedialdehyde - cyanide equivalent of the OPA protocol has been used for arginine analysis.[1090] Comparison of o-phthaldialdehyde - 3-mercaptopropionic acid with the Fmoc chloride reagent in the automated equipment context has led to indecisiveness in favouring either

one or the other.[1091] 6-Aminoquinolinyl derivatives show similar lowest limits to the OPA or Fmoc analogues.[1092] The OPA procedure continues to be used for clearing primary amines from samples when imino acids are the prime analytical target [*e.g.* proline and hydroxyproline[1093] analysed as their fluorescent 4-(5,6-dimethoxy-2-phthalimidinyl)phenylsulfonyl derivatives, λ_{excit} 315 nm; $\lambda_{emission}$ 385 nm].

The N-phenylthiocarbamoyl derivatives formed from amino acids with phenyl isothiocyanate through the PTA derivatization procedure are claimed to be inferior to benzylthiocarbamoyl analogues, which give better separation characteristics when tested with mixtures of up to 22 amino acids.[1094]

Dabsylation continues to deserve the confidence of long-standing advocates and newcomers, with a use described for the estimation of levels of dityrosine formed through enzyme-catalysed oxidation of tyrosine.[1095] An example of its sensitivity is shown in an application to hydrolysates of electroblotted proteins.[1096] The structurally-related N-(4-phenylazobenzyloxcarbonyl)amino acids have been recommended.[1097]

Dansylamino acids separated efficiently after establishing an appropriate micellar mobile phase, have been detected on the basis of their fluorescence[1098] or chemiluminescence [$Ru(Py)_3^{2+}$/oxalate].[1099] Like fluorescence yield, chemiluminescence intensity is subject to inhibition (the fact that amino acids have this effect on lucigenin[1100] implies that careful assessment of any proposed procedure is necessary). New reagents for amino acid derivatization have been established, indicating a growth point in sensitive fluorimetric amino acid analysis: 1,2-naphthoquinone-4-sulfonic acid,[1101] 7-fluorobenzo-2-oxa-1,3-diazole-4-sulfonic acid[1102,1103] (the homocysteine derivative was found to be highly unstable to light)[1104] and 4-fluoro-7-nitrobenzo-2-oxa-1,3-diazole (for a sensitive assay of 3-nitrotyrosine in human plasma)[1105] have been advocated. Improved protocols for HPLC of Fmoc-amino acids have been worked out,[1106] and a solid-phase 6-aminoquinolinecarbamate has been developed for derivatization of amino acids.[1107] L-Carnitine and its acyl derivatives have provided a test for HPLC analysis using an unusual derivatization protocol through the carboxy group, by dicyclohexylcarbodi-imide coupling to 1-aminoanthracene.[1108]

The determination of enantiomer ratios through HPLC over a chiral stationary phase (CSP; see also Section 5.6) has been developed vigorously (see also Refs. 741, 744, 745), and new commercial products, *e.g.* the β-cyclodextrin-based CSPs Chiradex and Cyclobond I[1109] have appeared. CSPs derived from (S)-1-(1-naphthyl)ethylamine have been evaluated, in cis- and trans-isomeric forms with the trans-form showing best performance.[1110] A CSP carrying L-cysteine has been used for the resolution of dansyl-DL-amino acids with a copper(II) salt in the mobile phase.[1111] The chiral selectivity of N-(tert-butylaminocarbonyl)-(S)-valyl- and (R)-1-(α-naphthyl)ethylaminocarbonylglycyl-aminopropylsilica towards derivatized L- and D-amino acids has been calculated and the results compared with experimental data.[1112]

An alternative approach to the determination of enantiomer ratios, employing chiral derivatizing reagents and HPLC separation of the resulting diastereoisomers, forms the basis of estimations for erythro- and threo-β-methyl-phenyl-

alanine, -tyrosine, and -1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid; comparisons of results obtained with Marfey's reagent, 1-fluoro-2,4-dinitrophenyl-5-alanine amide, with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate are presented.[1113] All amino acids present in Micropeptin 90 are of the L-configuration based on derivatization with Marfey's reagent, or with 1-fluoro-2,4-dinitrophenyl-5-L-leucinamide, and HPLC,[1114] and the same technique has been used to establish the absolute configuration of 3-amino-6-hydroxypiperidin-2-one within aeruginopeptin 228-A.[1115] A new chiral reagent (S)-(+)-2-tert-butyl-2-methyl-1,3-benzodioxole-4-carboxylic acid, gives fluorescent derivatives wth amino acids (λ_{excit} 310nm; $\lambda_{emission}$ 380 nm),[1116] and a further example of a chiral isothiocyanate, (R)-(-)-4-(3-isothiocyanopyrrolidin-1-yl)-7-(NN-dimethylaminosulfonyl)-benz-2-oxa-1,3-diazole, has been advocated for the estimation of D-amino acid content in hydrolysed peptides.[1117] The ligand exchange principle applied to the determination of D:L-ratios for free amino acids is illustrated for HPLC over Zorbax with aqueous L-arginine - copper(II) as eluent,[1118] or the equivalent use of (+)-monoethyl N-(1′-hydroxymethyl)propyl-α-aminobenzylphosphonic acid or (-)-(R)-2-aminobutan-1-ol.[1119]

7.6 Fluorimetric Analysis – In view of the title of this Section, several citations that have been placed elsewhere in this Chapter, particularly from the preceding and next Sections, could have been located here instead. The relative fluorescence yields of members of a series of dansylamino acids have been determined, data that will assist the verification of analytical results employing these derivatives.[1120]

7.7 Capillary Zone Electrophoresis and Other Analytical Methods – The inexorable rise to preeminence of capillary zone electrophoresis (CZE) and related analytical separation techniques over the past decade, justifies its explicit mention in the title of this Section. Applications and sample preparation protocols for HPCE of amino acid mixtures are very much on a par with those used for HPLC, but substantial benefits associated in particular with sensitivity and resolution are available. A review of CZE including amino acid applications has appeared.[1121]

Typical procedures exploring new detection methods are illustrated in CZE analyses of underivatized amino acids: N-nitroso-L-arginine,[1122] identification of amino acids in the haemolymph of the fairy shrimp (UV-laser fluorescence),[1123] and pulsed electrochemical detection.[1124] Derivatives include the phenylthiohydantoin of 3-methylhistidine (UV; more sensitive than the equivalent HPLC protocol),[1125] and quantitative *in vivo* monitoring for aspartic and glutamic acids and other neuroactive amino acids as OPA-β-mercaptoethanol derivatives (laser-induced fluorescence).[1126,1127] CZE Analysis of N-acetyl derivatives of aspartic acid and of α-aminoadipic acid has been described.[1128]

Ligand exchange differentiation permits the separation of a mixture of 11 dansylamino acids by micellar electrokinetic chromatography (MEKC) when copper(II) and NN-di-decyl-β-alanine are part of the running buffer.[1129] N-Dodecanoyloxycarbonyl-L-valine serves as chiral selector for MEKC of 3,5-

dinitrobenzoyl-DL-amino acids.[1130] CZE and MEKC of protected amino acids have been reviewed.[1131]

Exploitation of indirect chemiluminescence generated by copper(II) complexes of amino acids for their detection and quantitation has not proved satisfactory, since copper(II) ions are poor catalysts for the generation of chemiluminescence from the H_2O_2 - luminol reagent; precision is no better than 3 - 6%.[1132]

Resolution of underivatized amino acid enantiomers is achieved by ligand exchange with copper(II) - L-proline or hydroxy-L-proline in the CZE buffer,[1133] and similar use of dextrin 10-sulfopropyl ether as a novel chiral buffer additive has been explored [the CZE basis of the methods is replaced by the MEKC mode with this type of additive].[1134] The detection of 0.1% L-tryptophan in a sample of the D-amino acid has been claimed through the use of a triethanolamine - H_3PO_4 buffer containing α-cyclodextrin.[1135] In a reversal of this protocol, N-p-tert-butylcalix[4]arene tetrakis(acyl-L-alanine tert-butyl ester) is effective for CZE resolution of a non-amino acid racemate.[1136] However, N-derivatization is most commonly employed for such studies and the following have been reported: resolution of a mixture of 12 dansylamino acids by CZE using a β-cyclodextrin (formamide or N-methylformamide is superior to use of a water-based eluent),[1137] of 13 N-{2-(9-anthryl)ethyloxycarbonyl}amino acids using cyclodextrins, by CZE (or, better, by MEKC; only γ-cyclodextrin offered any benefit for the CZE technique),[1138] and for the separation of 2-methyltaurine enantiomers.[1139] n-Octyl β-D-glucopyranoside has been used as pseudo-stationary phase in HPCE resolution studies with N-(alkoxycarbonyl)-DL-amino acids.[1140] A crop of papers has appeared, describing the exploration of a variety of homochiral compounds as chiral selectors for CZE resolution of N-derivatized amino acids. These studies exploit, particularly, the high purity of easily-available clinical products, including vancomycin and ristocetin A,[1141] digitonin or β-escin (resolution of PTHs).[1142] Vancomycin performs better than any cyclodextrin in this respect, when applied to the separation of aminoquinolinylcarbamates prepared from amino acids.[1143]

A range of non-chromatographic electrometric methods offers valuable opportunities for particular situations, often with superior sensitivity and reproducibility compared to established analytical procedures. Thus, a 5 fg limit has been put on electrochemical detection of neurotransmitters,[1144] and 8 ppb using gold ultramicroelectrodes,[1145] and similar results for a nickel-chromium alloy electrode,[1146] for amperometric detection of glycine and other free amino acids in a flowing electrolyte. Amino acids derivatized with 4-chloro-7-nitrobenzofuran have been subjected to cathodic stripping square wave voltammetric analysis,[1147] and the polarographic response given by amino acids has been assessed as $<1\,\mu g\,mL^{-1}$.[1148]

7.8 Assays for Specific Amino Acids – Following the sophistication of the results described in preceding sections, instrumentation covered here is often rudimentary and traditional. However, the specificity often compensates for the loss of sensitivity, such as choramine T conversion of hydroxyproline into pyrrole and its quantitation through Ehrlich reagent colorimetry at 550 nm.[1149] Assay methods have been reviewed for L-arginine and its metabolites, since the central

role of this amino acid in the nitric oxide story has become a matter of special interest.[1150] A silver(I)-based electrode serves the purpose of estimation of cysteine in the presence of cystine,[1151] and an unusual principle has been exploited for the same purpose (inhibition by cysteine of the oxidation of 4-methoxy-1,2-diaminobenzene by H_2O_2/Fe^{3+}).[1152]

The assay methods depending on enzyme specificity have formed the dominant part of this section over the years, and biosensor applications continue to attract new ideas. Tetrathiofulvene-mediated enzyme electrodes (glutamate oxidase + glutaminase)[1153] and a similar L-glutamate assay system (microdialysis probe based on an immobilized enzyme reactor and coated platinum electrode)[1154] represent the advancing field, and ammonium ion-responsive electrodes that have been enzymically sensitized for the analysis of arginine or creatine (immobilized urease, and arginase or creatinase respectively) illustrate the continuing theme of this type assay based on electrochemical measurements.[1155] A system introduced earlier for the analysis of L-phenylalanine and phenylpyruvic acid, using coupled phenylalanine dehydrogenase and glutamine transaminase K, has been rendered 10 times more sensitive for the determination of phenylalanine levels in blood.[1156] Another strand is illustrated by quantitation based on the spectrophotometric determination of NAD that is released through deamination, catalysed by leucine dehydrogenase, of the three branched chain aliphatic amino acids involved in ribosomal protein synthesis.[1157]

References

1 Methods in Protein Analysis, ed. M. Holtzhauer, Springer, Berlin, 1996; Peptide-Based Drug Research, Eds. M.D. Taylor and G.L. Amidon, American Chemical Society, Washington, 1995 (*e.g.* Molecular biology of Amino Acids, R.M.Williamson and D.L.Oxender, p. 3).

2 Methods of Non-α-Amino Acid Synthesis, M.B. Smith, Dekker, New York, 1995; Recent Progress in Excitatory Amino Acid Research, Ed. J. McCall, Academic Press, New York, 1994.

3 Proceedings of the 23rd European Peptide Symposium (1994), Ed. H.L.S. Maia, Escom, Leiden, 1995; Methods in Protein Structure Analysis, Eds. M.Z. Atassi and E. Appella, Plenum, New York, 1995 (*e.g.*, HPLC of glycosylated PTHs, A. Pisano, N.H. Packer, J.W. Redmond, K.L. Williams, and A.A. Gooley, p. 69; Synthesis of the thiohydantoin of proline, J.M. Bailey, O.Tu, G. Issai, and J.E. Shively, p. 13).

4 T.C. Stadtman, *Ann.Rev.Biochem.*, 1996, **65**, 83.

5 T. Hohsaka, Y. Ashizuka, H. Murakami, and M. Sisido, *J.Am.Chem.Soc.*, 1996, **118**, 9778.

6 A.S. Bommarius, M. Schwarm, K. Stingl, M. Kottenhahn, K. Huthmacher, and K. Drauz, *Tetrahedron: Asymmetry*, 1995, **6**, 2851.

7 P. Remuzon, *Tetrahedron*, 1996, **52**, 13803.

8 R. Andruszkiewicz, *Pol.J.Chem.*, 1995, **69**, 1615.

9 G. Kokotos, V. Martin, V. Constantinou-Kokotou, and W.A. Gibbons, *Amino Acids*, 1996, **11**, 329.

10 R. Lundblad, in Proteins Labfax, Ed. N.C. Price, Academic Press, San Diego, 1996, p.287.

11 J.L. Bada and G.D. McDonald, *Anal. Chem.*, 1996, **68**, 668A.
12 A.B. Mauger, *J. Nat. Prod.*, 1996, **59**, 1205.
13 K. Imai, T. Fukushima, T. Santa, H. Homma, K. Hamase, K. Sakai, and M. Kato, *Biomed. Chromatogr.*, 1996, **10**, 303.
14 C.J. Easton, *Chem. Rev.*, 1997, **97**, 53.
15 N.S. Scrutton and A.R.C. Paine, *Biochem. J.*, 1996, **319**, 1.
16 B. Koksch, N. Sewald, H.-D. Jakubke, and K. Burger, *ACS Symp. Ser.*, 1996, **639**, 42.
17 D.P. Knolland and E. Erasmus, *Spectrum*, 1996, **34**, 54 (*Chem. Abs.*, 1996, **124**, 335745).
18 *Methods in Molecular Biology*, (Protein Purification Methods), Ed. S. Doonan, 1996, Vol. 59, Humana, Totowa, NJ; also *Methods in Molecular Biology*, (*e.g.* peptide hydrolysis, I. Davidson, p. 119; pre-column derivatization, G.B. Irvine, p.131; derivatization by ninhydrin, A.J. Smith, p.139; mass spectrometry, F. Greer and H.R. Morris, p.147; 1997, Vol. 64, dansyl-Edman methods, J.M. Walker, p.183; N-dansyl derivatization, J.M. Walker, p.189; HPLC of PTHs, G.A. Grant and M.W. Crankshaw, p. 197; *Methods in Molecular Biology*, 1997, **73** (Neuropeptide Protocols: *e.g.* circular dichroism, L.Otvos, p.153).
19 *ACS Symp. Ser.*, 1996, **641** (Reductions in Organic Synthesis) (*Chem. Abs.*, 1996, **125**, 275974); see also Ref.16.
20 H. Amano and H. Noda, *Fish Sci.*, 1996, **62**, 658 (*Chem. Abs.*, 1996, **125**, 189714).
21 P. Chen and S.-P. Liang, *Shengwu Huaxue Zazhi*, 1996, **12**, 112 (*Chem. Abs.*, 1996, **124**, 225435).
22 A.J. Darragh, D.J. Garrick, P.J. Moughan, and W.H. Hendricks, *Anal. Biochem.*, 1996, **236**, 199.
23 G. Chen, M. Arai, and K. Hirabayashi, *Nippon Sanshigaku Zasshi*, 1996, **65**, 182 (*Chem. Abs.*, 1996, **125**, 165746).
24 J.-Q. Shen, W.-P. Yin, Y.-X. Zhao, and L.-J. Yu, *J. Membr. Sci.*, 1996, **120**, 45.
25 A. Garem, J. Leonit, G. Daufin, and J.L. Maubois, *Lait*, 1996, **76**, 267 (*Chem. Abs.*, 1996, **125**, 162441).
26 K.K. Reddy, T. Kawakatsu, J.B. Snape, and M. Nakajima, *Sep. Sci. Technol.*, 1996, **31**, 1161.
27 A.P. Mikhalkin and V.N. Marshalkin, *Khim. Prom.-st.*, 1996, 20 (*Chem. Abs.*, 1996, **125**, 150735).
28 G. Simon, L. Hanak, G. Grevillot, T. Szanya, and G. Marton, *J. Chromatogr., A*, 1996, **732**, 1.
29 S. Melis, J. Markos, G. Cao, and M. Morbidelli, *Ind. Eng. Chem. Res.*, 1996, **35**, 3629.
30 Y.V. Mitin, *Int. J. Pept. Protein Res.*, 1996, **48**, 374.
31 T. Kawakita, *Nippon Kessho Seicho Gakkaishi*, 1996, **23**, 218 (*Chem. Abs.*, 1996, **125**, 168580).
32 A. Gamian, M. Miszala, E. Katzenellbogen, A. Czarny, T. Zal, and E. Romanowsca, *FEMS Immunol. Med. Microbiol.*, 1996, **13**, 261.
33 S.F. Wang, J.C. Brackman, D. Daloze, J. Pasteels, P. Soelew, N.P. Handjieva, and P. Kalushkov, *Experientia*, 1996, **52**, 668.
34 A. Garcia, M.J. Vazquez, E. Quinoa, R. Riguera, and C. Debitus, *J. Nat. Prod.*, 1996, **59**, 782.
35 J. Kobayashi, M. Sato, T. Muruyama, M. Ishibashi, M.R. Walchi, M. Kanai, J. Shoji, and Y. Ohizumi, *J. Chem. Soc., Chem. Commun.*, 1991, 1050.
36 U. Schmidt and S. Weinbrenner, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1336.

37 M.H. Park, Y.A. Joe, K.R. Kang, Y.B. Lee, and E.C. Wolff, *Amino Acids*, 1996, **10**, 109.
38 L.W. Moore, W.S. Chilton, and M.L. Canfield, *Appl.Environ.Microbiol.*, 1997, **63**, 201.
39 M.-X.Fu, J.R. Requena, A.J. enkins, T.J. Lyons, J.W. Baynes, and S.R. Thorpe, *J.Biol.Chem.*, 1996, **271**, 9982.
40 A. Leino, O. Impivaara, and M. Kaitsaari, *Clin.Chem.*, 1996, **42**, 2037.
41 C.-G. Kim, A. Kirschning, P. Bergon, P. Zhou, E. Su, B. Sauerbrei, S. Ning, Y. Ahn, M. Breuer, E. Leistner, and H.G. Floss, *J.Am.Chem.Soc.*, 1996, **118**, 7486.
42 H. Bockholt, J.M. Beale, and J. Rohr, *Angew.Chem.*, 1994, **106**, 1733.
43 B.-K. Park, *Sanop Misaengmul Hakhoechi*, 1996, **24**, 327 (*Chem.Abs.*, 1996, **125**, 162875).
44 K. Kaya, T. Sano, K.A. Beattie, and G.A. Codd, *Tetrahedron Lett.*, 1996, **37**, 6725.
45 M. Kirihata, Y. Nakao, M. Fukuari, and I. Ichimoto, *Biosci.Biotechnol.Biochem.*, 1995, **59**, 2228.
46 A. Arnone, S. Capelli, G. Nasini, S. Valdo Meille, and O. Vajna De Pava, *Liebigs Ann.*, 1996, 1875.
47 C.-B. Cui, H. Kakeya, and H. Osada, *Tetrahedron*, 1997, **53**, 59.
48 H. Obayashi, K. Nakano, H. Shigeta, M. Yamaguchi, K. Yoshimori, M. Fukui, M. Fujii, Y. Kitagawa, N. Kumura, *et al.*, *Biochem.Biophys.Res.Commun.*, 1996, **226**, 37.
49 J.D. Brady, I.H. Sadler, and S.C. Fry, *Biochem.J.*, 1996, **315**, 323.
50 M. Ukubata, T.-I. Morita, H. Kakeya, K. Kobinata, T. Kudo, and H. Osada, *J.Antibiot.*, 1996, **49**, 396.
51 H. Matsuda, T. Okino, M. Murakami, and K. Yamaguchi, *J.Org.Chem*, 1996, **61**, 8648.
52 F. Cafieri, E. Fattorusso, A. Mangoni, and O. Taglialatela, *Tetrahedron*, 1996, **52**, 13713.
53 T. Sano and K. Kaya, *Tetrahedron Lett.*, 1996, **37**, 6873.
54 M.S. Lee, S.E. Klohr, E.H. Kerns, K.J. Volk, J.E. Leet, D.R. Schroeder, and I.Rosenberg, *J.Mass Spectrom.*, 1996, **31**, 1253.
55 A. Napolitano, M.R. Vicensi, M. D'Ischia, and G. Prota, *Tetrahedron Lett.*, 1996, **37**, 6799.
56 M.N. Khan, *J.Org.Chem*, 1996, **61**, 8063.
57 E.C. Taylor and B. Hu, *Synth.Commun.*, 1996, **26**, 1041.
58 L. Somsak, E. Sos, Z. Gyoergydeak, J.-P. Praly, and G. Descotes, *Tetrahedron*, 1996, **52**, 9121.
59 H.-T. Chang and K.B. Sharpless, *Tetrahedron Lett.*, 1996, **37**, 3219.
60 P. Crotti, V. Di Bussolo, L. Favero, F. Macchia, and M. Pineschi, *Tetrahedron Lett.*, 1996, **37**, 1675.
61 E.A. Couladouros and C.D. Apostolopoulos, *SynLett.*, 1996, 341.
62 C. Gueguen, E. About-Jaudet, N. Collignon, and P. Savignac, *Synth.Commun.*, 1996, **26**, 4131.
63 J.M. Villalgordo, A. Linden, and H. Heimgartner, *Helv.Chim.Acta*, 1996, **79**, 213.
64 B.M. Trost and R.C. Bunt, *Angew.Chem.,Int.Ed. Engl.*, 1996, **35**, 99.
65 P.K. Jadhav and H.-W. Man, *J.Org.Chem*, 1996, **61**, 7951.
66 A. Girard, C. Greck, D. Ferroud, and J.P. Genet, *Tetrahedron Lett.*, 1996, **37**, 7967.
67 S. Boukhris, A. Spuizi, and A. Robert, *Tetrahedron Lett.*, 1996, **37**, 4693.
68 A.S. Demir, C. Tanyeli, O. Sesenoglu, S. Demic, and O.O. Evin, *Tetrahedron Lett.*, 1996, **37**, 407.

69 C. Cativiela, M.D. Diaz De Villegas, J.A. Galvez, and J.L. Garcia, *Tetrahedron*, 1996, **52**, 9563.
70 P.K. Kadaba and L.P. Glavinos, *Heterocycl.Commun.*, 1996, **2**, 81.
71 C. Zhou, D. Yuan, and X. Rugang, *Yingyong Huaxue*, 1996, **13**, 46 (*Chem.Abs.*, 1996, **125**, 168607).
72 A.M. Strocker, T.A. Keating, P.A. Tempest, and R.W. Armstrong, *Tetrahedron Lett.*, 1996, **37**, 1149.
73 P.A. Tempest, S.D. Brown, and R.W. Armstrong, *Angew.Chem.,Int.Ed.Engl.*, 1996, **35**, 640.
74 K.M. Short, B.W. Ching, and A.M.M. Mjalli, *Tetrahedron Lett.*, 1996, **37**, 7489.
75 S. Hanessian and R.-Y. Yang, *Tetrahedron Lett.*, 1996, **37**, 5835.
76 A.M.M. Mjalli, S. Sarshar, and T.J. Baiga, *Tetrahedron Lett.*, 1996, **37**, 2943.
77 A. Demharter, W. Hoerl, E. Herdtweck, and I. Ugi, *Angew.Chem.,Int.Ed.Engl.*, 1996, **35**, 173.
78 H. Quast and S. Aldenkortt, *Chem.-Eur.J.*, 1996, **2**, 462.
79 D.A. Gately and J.R. Norton, *J.Am.Chem.Soc.*, 1996, **118**, 3479.
80 A. Ryglowski and P. Kafarski, *Tetrahedron*, 1996, **52**, 10685; see also A. Ryglowski, R. Lazaro, M.L. Roumestant, and P. Viallefont, *Synth.Commun.*, 1996, **26**, 1739.
81 V. Gouverneur and L.Ghosez, *Tetrahedron*, 1996, **52**, 7585.
82 V. Gouverneur and M.N. Lalloz, *Tetrahedron Lett.*, 1996, **37**, 6331.
83 H. Imogai, Y. Petit, and M. Larcheveque, *Tetrahedron Lett.*, 1996, **37**, 2573.
84 V.J. Patil, *Tetrahedron Lett.*, 1996, **37**, 1481.
85 A.C. van der Laan, R. Stromberg, J.H. van Boom, E. Kuyl-Yeheskiely, V.A. Efimov, and O.G. Chakhmakhcheva, *Tetrahedron Lett.*, 1996, **37**, 7857.
86 H. Groger, Y. Saida, S. Arai, J. Martens, H. Sasai, and M.S hibasaki, *Tetrahedron Lett.*, 1996, **37**, 9291.
87 C. Zhang and A.M.M. Mjalli, *Tetrahedron Lett.*, 1996, **37**, 5457.
88 E.A. Boyd, W.C. Chan, and V.M. Loh, *Tetrahedron Lett.*, 1996, **37**, 1647.
89 J. Zhao, Y. Luo, and H. Fu, *Hebei Gongxueyan Xuebao*, 1995, **24**, 1 (*Chem.Abs.*, 1996, **124**, 233057)
90 J.G. de Vries, R.P. de Boer, M. Hogeweg, and E.E.C.G. Gielens, *J.Org.Chem*, 1996, **61**, 1842.
91 S. Chen and J.K. Coward, *Tetrahedron Lett.*, 1996, **37**, 4335.
92 S. Kobayashi, S. Nagayama, and T. Busujima, *Tetrahedron Lett.*, 1996, **37**, 9221.
93 Y. Shen and S. Gao, *J.Fluorine Chem.*, 1996, **76**, 37.
94 V.A. Soloshonok, A.D. Kacharov, D.V. Avilov, and T. Hayashi, *Tetrahedron Lett.*, 1996, **37**, 7845.
95 M. Seki and K. Matsumoto, *Synthesis*, 1996, 580.
96 S. Jew, S. Yun, and Y. Cho, *Soul Tawhakkyo Yakhak Nonmunjip*, 1994, **19**, 38 (*Chem.Abs.*, 1996, **125**, 168593).
97 L.J. Heinz, W.H.W. Lunn, R.E. Murff, J.W. Paschal, and L.A. Spangle, *J.Org.Chem*, 1996, **61**, 4838.
98 C.L. Wysong, T.S. Yokum, G.A. Morales, R.L. Gundry, M.L. McLaughlin, and R.P. Hammer, *J.Org.Chem*, 1996, **61**, 7650.
99 B. Westermann and I. Gedrath, *SynLett.*, 1996, 665.
100 L. Ridvan, N. Abdallah, R. Holakovsky, M. Tichy, and J. Zavada, *Tetrahedron; Asymmetry*, 1996, **7**, 231.
101 U. Buettner, S. Ochs, and T. Severin, *Carbohydr.Res.*, 1996, **291**, 175.
102 K. Davic, B. Cazes, and J. Gore, *J.Chem.Res., Synop.*, 1996, 488.
103 O. Maior and D. Gavriliu, *Rev.Chem.Roum.*, 1996, **47**, 127.

104 C. Hamon and B.J. Rawlings, *Synth.Commun.*, 1996, **26**, 1109.
105 R. Yuan, Y. Zhang, and K. Chen, *Huaxue Tongbao*, 1996, 38 (*Chem.Abs.*, 1996, **125**, 196300).
106 R.D.A. Hudson, S.A. Osborne, and R.G. Stephenson, *SynLett.*, 1996, 845.
107 D.J. Krysan, *Tetrahedron Lett.*, 1996, **37**, 3303.
108 A. Olma, *Pol.J.Chem.*, 1996, **70**, 1442.
109 D. Obrecht, C. Abrecht, M. Altorfer, U. Bohdal, A. Grieder, M. Kleber, P. Pfyffer, and K. Mueller, *Helv.Chim.Acta*, 1996, **79**, 1315.
110 W.Q. Liu, F. Carreaux, H. Mendal, B.P. Roques, and C. Garbay-Jaureguiberry, *Tetrahedron*, 1996, **52**, 4411.
111 E.A. Il'yasov and G.G. Galust'yan, *Khim.Prir.Soedin.*, 1995, 855.
112 P.E. Morgan, A. Whiting, and R. McCague, *Tetrahedron Lett.*, 1996, **37**, 4795.
113 E. Jao, A.B. Cooper, D.F. Rane, A.K. Saksena, J. Desai, J. Wang, V.M. Girijavallabhan, and A.K. Ganguly, *Tetrahedron Lett.*, 1996, **37**, 5661.
114 B.H. Chen, J. Nie, M. Singh, V.W. Pike, and K.L. Kirk, *J.Fluorine Chem.*, 1995, **75**, 93.
115 S. Vadon, J. Custot, J.-L. Boucher, and D. Mansuy, *J.Chem.Soc., Perkin Trans. I*, 1996, 645.
116 M.A. Walker, *Tetrahedron Lett.*, 1996, **37**, 8133.
117 A. Lopez, M. Moreno-Manas, R. Pleixats, A. Roglans, J. Ezquerra, and C. Pedregal, *Tetrahedron*, 1996, **52**, 8365.
118 S.P. Chavan, M.S. Venkatraman, and A.G. Chittiboyina, *Tetrahedron Lett.*, 1996, **37**, 2857.
119 A. Hercouet, B. Bessieres, and M. Le Corre, *Tetrahedron: Asymmetry*, 1996, **7**, 1267.
120 A. Hercouet, B. Bessieres, and M. Le Corre, *Tetrahedron: Asymmetry*, 1996, **7**, 283.
121 K. Miyashita, H. Miyabe, C. Kurozumi, K. Tai, and T.I manishi, *Tetrahedron*, 1996, **52**, 12125.
122 A. Jonczyk and Z. Pakulski, *Tetrahedron Lett.*, 1996, **37**, 8909.
123 J.-P. Mazaleyrat, A. Gaucher, M. Wakselman, L. Tchertanov, and J. Guilhem, *Tetrahedron Lett.*, 1996, **37**, 2971.
124 C. Alvarez-Ibarra, A.G. Csaky, I. Lopez de Silanes, and M.L. Quiroga, *J.Org.Chem*, 1997, **62**, 479.
125 A.G.H. Wee and F. Tang, *Tetrahedron Lett.*, 1996, **37**, 6677.
126 G. Kokotos, J.M. Padron, C. Noula, W.A. Gibbons, and V.S. Martin, *Tetrahedron: Asymmetry*, 1996, **7**, 857.
127 J.-C. Rossi, L. Garrel, J. Taillades, and A. Commeyras, *C.R.Acad.Sci., Ser.II, Mec., Phys., Chim., Astron.*, 1996, **322**, 767.
128 Q. Liu, A.P. Marchington, N. Boden, and C.M. Rayner, *SynLett.*, 1995, 1037.
129 Advances in Asymmetric Synthesis, Ed. R.G. Stephenson, Chapman & Hall, London, 1996; *e.g.* C. Bolm, p.9, (see also Ref. 583) R.M. Williams, p.45.
130 B. Kaptein, W.H.J. Boesten, W.J.J. Van Den Tweel, Q.B. Broxterman, H.E. Schoemaker, F. Formaggio, M. Crisma, C. Toniolo, and J. Kamphuis, *Chim.Oggi*, 1996, **14**, 9.
131 M.S. Iyer, K.M. Gigstad, N.D. Namdev, and M. Lipton, *Amino Acids*, 1996, **11**, 259; *J.Am.Chem.Soc.*, 1996, **118**, 4910.
132 A.V. Rama Rao, K.L. Reddy, A.S. Rao, T.V.S.K. Vittal, M.M. Reddy, and P.L. Pathi, *Tetrahedron Lett.*, 1996, **37**, 3023.
133 F.-J. Volk and A.W. Frahm, *Liebigs Ann.*, 1996, 1893.
134 R. Badorrey, C. Cativiela, D.D. Diaz De Villegas, and J.A. Galvez, *Tetrahedron: Asymmetry*, 1995, **6**, 2787.

135 F.A. Davis, P.S. Portonovo, R.E. Reddy, and Y. Chiu, *J. Org. Chem*, 1996, **61**, 440.
136 L. Yan, Y. Guishu, J. Yaozhong, and Y. Tengkui, *Synth. Commun.*, 1996, **26**, 63.
137 J.Y. Choi and Y.H. Kim, *Tetrahedron Lett.*, 1996, **37**, 7795.
138 C. Greck, F. Ferreira, and J.-P. Genet, *Tetrahedron Lett.*, 1996, **37**, 2031.
139 D.L. Boger, R.M. Borzilleri, and S. Nukui, *J. Org. Chem*, 1996, **61**, 3561.
140 H. Kuang, M.L. Brown, R.R. Davies, E.C. Young, and M.D. Distefano, *J. Am. Chem. Soc.*, 1996, **118**, 10702.
141 R. Chenevert and M.-P. Morin, *Tetrahedron: Asymmetry*, 1996, **7**, 2161.
142 T. Yokomatsu, M. Sato, and S. Shibuya, *Tetrahedron: Asymmetry*, 1996, **7**, 2743.
143 C. Monne, D. Robic, G. Campion, R. Bourbouze, A. Rimbault, M. Masure, V. Langlois, P. Hemery, and P. Guerin, *Chirality*, 1996, **8**, 300.
144 K. Shibata, K. Shingu, V.P. Vassilev, K. Nishide, T. Fujita, M. Node, T. Kajimoto, and C.-H. Wong, *Tetrahedron Lett.*, 1996, **37**, 2791.
145 D. Muller, I. Zeltser, G. Bitan, and C. Gilon, *J. Org. Chem*, 1997, **62**, 411.
146 P. Mantri, D.E. Duffy, and C.A. Kettner, *J. Org. Chem*, 1996, **61**, 5290.
147 C. Lebarbier, F. Carreaux, and B. Carboni, *Synthesis*, 1996, 1371.
148 A.R. Katritzky, J. Wang, and P. Leeming, *Tetrahedron: Asymmetry*, 1996, **7**, 1631.
149 G. Mandville, M. Ahmar, and R. Bloch, *J. Org. Chem*, 1996, **61**, 1122.
150 A. Dondini, F.L. Merchan, P. Merino, I. Rojo, and T. Tejero, *Synthesis*, 1996, 641.
151 A. Arnone, P. Bravo, S. Capelli, G. Fronza, S.V. Meille, M. Zanda, G. Cavicchio, and M. Crucianelli, *J. Org. Chem*, 1996, **61**, 3375.
152 A. Bongini, R. Camerini, and M. Pannuzio, *Tetrahedron: Asymmetry*, 1996, **7**, 1467.
153 C. Cativiela, M.D. Diaz De Villegas, and J.A. Galvez, *Tetrahedron: Asymmetry*, 1996, **7**, 529.
154 D. Braghiroli, E. Mussati, M. Di Bella, and M. Saladini, *Tetrahedron: Asymmetry*, 1996, **7**, 831; D. Braghiroli and M. Di Bella, *Tetrahedron: Asymmetry*, 1996, **7**, 2145; D. Braghiroli and M. Di Bella, *Tetrahedron Lett.*, 1996, **37**, 7319.
155 M.J. O'Donnell, C. Zhou, and X.N. Chen, *Tetrahedron: Asymmetry*, 1996, **7**, 621.
156 D.J. Chalmers, J.A.K. Howard, I.C. Kilpatrick, D.C. Sunter, G.A. Thompson, P. Mudvarhelyi, C. Wilson, and J.C. Watkins, *J. Med. Chem.*, 1996, **39**, 4738.
157 B.S. Moeller, T. Benneche, and K. Undheim, *Tetrahedron*, 1996, **52**, 8807.
158 M. Ohaba, M. Imasho, and T. Fujii, *Heterocycles*, 1996, **42**, 219.
159 D. Heerding, P. Bhatnagar, M. Hartmann, P. Kremminger, and S. Lo Castro, *Tetrahedron: Asymmetry*, 1996, **7**, 237.
160 V. Ojea, M.C. Fernandez, M. Ruiz, and J.M. Quintela, *Tetrahedron Lett.*, 1996, **37**, 5801; see also M. Ruiz, V. Ojea, and J.M. Queintela, *ibid.*, p. 5743.
161 R. Amici, P. Pevarello, M. Colombo, and M. Varasi, *Synthesis*, 1996, 1177.
162 H. Nakao, T. Morimoto, and M. Kirihata, *Biosci. Biotechnol. Biochem.*, 1996, **60**, 683.
163 L.S. Richter and T.R. Gadek, *Tetrahedron: Asymmetry*, 1996, **7**, 427.
164 S.H. Nielsen, *Dan. Kemi*, 1995, **76**, 16.
165 J. Malmquist and S. Sjoberg, *Tetrahedron*, 1996, **52**, 9207.
166 S. Hanessian and R.-Y. Yang, *Tetrahedron Lett.*, 1996, **37**, 5273.
167 S. Hoarau, J.L. Fauchere, L. Pappalardo, M.L. Roumestant, and S. Viallefont, *Tetrahedron: Asymmetry*, 1996, **7**, 2585.
168 T. Gefflaunt, U. Bauer, K. Airola, and M.P. Koskinen, *Tetrahedron: Asymmetry*, 1996, **7**, 3099.
169 L. Bendahl, A. Hammershoei, J. Anders, D.K. Jensen, E. Kaifer, A.M. Sargeson, and A.C. Willis, *Chem. Commun.*, 1996, 1649.

170 V.A. Soloshonok, D.V. Avilov, and V.P. Kukhar, *Tetrahedron: Asymmetry*, 1996, **7**, 1547.
171 V.A. Soloshonok, D.V. Avilov, and V.P. Kukhar, *Tetrahedron*, 1996, **52**, 12433.
172 R. Kliukiene, A. Maroziene, Z. Stumbreviciute, and K. Karpavicius, *Chemija*, 1996, 76 (*Chem.Abs.*, 1996, **125**, 196273).
173 K. Tanaka, M. Ahn, Y. Watanabe, and K. Fujii, *Tetrahedron: Asymmetry*, 1996, **7**, 1771.
174 A. Arnone, D. Gestmann, S.V. Meille, G. Resnati, and G. Sidoti, *Chem.Commun.*, 1996, 2569.
175 V.A. Soloshonok, A.D. Kacharov, and T. Hayashi, *Tetrahedron*, 1996, **52**, 245.
176 P. Dorizon, J. Ollivier, and J. Salauen, *SynLett.*, 1996, 1071.
177 N. Katagiri, M. Okada, Y. Morishita, and C. Kaneko, *Chem.Commun.*, 1996, 2137.
178 F. Machetti, F.M. Cordero, F. De Sarlo, A. Guarna, and A. Brandi, *Tetrahedron Lett.*, 1996, **37**, 4205.
179 D. Obrecht, M. Altorfer, C. Lehmann, P. Schoenholzer, and K. Mueller, *J.Org.Chem*, 1996, **61**, 4080.
180 E. Bunuel, C. Cativiela, M.D. Diaz-de-Villegas, *Tetrahedron: Asymmetry*, 1996, **7**, 1521.
181 E. Bunuel, C. Cativiela, M.D. Diaz-de-Villegas, *Tetrahedron: Asymmetry*, 1996, **7**, 1431.
182 M.N. Keynes, M.A. Earle, M. Sudharshan, and P.G. Hultin, *Tetrahedron*, 1996, **52**, 8685.
183 D. Gestmann, A.J. Laurent, and E.G. Laurent, *J.Fluorine Chem.*, 1996, **80**, 27.
184 R.P. Polniaszek and S.J. Bell, *Tetrahedron Lett.*, 1996, **37**, 575.
185 A. Solladie-Cavallo, J.-L. Koessler, J. Fischer, and A. DeCian, *Gazz.Chim.Ital.*, 1996, **126**, 173.
186 T.Matsumoto, T. Shioiri, and E. Osawa, *Tetrahedron*, 1996, **52**, 5971.
187 T. Matsumoto, T. Shioiri, and E. Osawa, *Tetrahedron*, 1996, **52**, 5961.
188 S.H. Nielsen, *Dan.Kemi*, 1995, **76**, 20.
189 A. Sudo and K. Saigo, *Tetrahedron: Asymmetry*, 1996, **7**, 2939.
190 G.H.P. Roos, S. Balasubramanian, M.P. Doyle, and C.E. Raab, *Synth.Commun.*, 1996, **26**, 2165.
191 M.Falck-Pedersen and K. Undheim, *Tetrahedron*, 1996, **52**, 7761.
192 P.A. Radel and S.B. Kahl, *J.Org.Chem*, 1996, **61**, 4582.
193 D.A. Evans and P.S. Watson, *Tetrahedron Lett.*, 1996, **37**, 3251.
194 P.P. Waid, G.A. Flynn, E.W.Huber, and J.S. Sabol, *Tetrahedron Lett.*, 1996, **37**, 4091.
195 A. Shibuya, M. Kurishita, C. Ago, and T. Tagushi, *Tetrahedron*, 1996, **52**, 271.
196 S. Liao and V.J. Hruby, *Tetrahedron Lett.*, 1996, **37**, 1563.
197 K.J.Hale, J. Cai, V. Delisser, S. Manaviazar, S.A. Peak, G.S. Bhatia, T.C. Collins, and N. Jogiya, *Tetrahedron*, 1996, **52**, 1047.
198 F.M. Rossi, E.T. Powers, R. Yoon, L. Rosenberg, and J. Meinwald, *Tetrahedron*, 1996, **52**, 10279.
199 A.D. Abell, J.M. Taylor, and M.D. Oldham, *J.Chem.Soc., Perkin Trans. I*, 1996, 1299.
200 M.J. Al-Darwich, A. Plenevaux, C. Lemaire, G.D. Fiore, L. Christiaens, D. Comar, and A. Luxen, *J.Fluorine Chem.*, 1996, **80**, 117.
201 A. Kubo, H. Kubota, M. Takahashi, and K. Nunami, *Tetrahedron Lett.*, 1996, **37**, 4957.
202 C. Agami, D. Bihan, and C. Puchot-Kadouri, *Tetrahedron*, 1996, **52**, 9079.

203 K.A. Daslick, R.G.F. Giles, and G.H.P. Roos, *Tetrahedron: Asymmetry*, 1996, **7**, 2525.
204 L.M. Harwood, K. J. Vines, and M.G.B. Drew, *SynLett.*, 1996, 1051.
205 L.M. Harwood and I.A. Lilley, *SynLett.*, 1996, 1010.
206 A. J. Bicknell and N.W. Hird, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2441.
207 A. S. Anslow, L.M. Harwood and I.A. Lilley, *Tetrahedron: Asymmetry*, 1995, **6**, 2465.
208 A. S. Anslow, G.G. Cox, and L.M. Harwood, *Khim. Geterosikl. Soedin.*, 1995, 1393.
209 R.M. Williams, G.J. Fegley, R. Gallegos, F. Schaefer, and D.L. Pruess, *Tetrahedron*, 1996, **52**, 1149.
210 D. Solas, R.L. Hale, and D.V. Patel, *J. Org. Chem*, 1996, **61**, 1537.
211 G. Porzi and S. Sandri, *Tetrahedron: Asymmetry*, 1996, **7**, 189.
212 A.R. Sting and D. Seebach, *Tetrahedron*, 1996, **52**, 279.
213 G. Pandey, P.Y. Reddy, and P. Das, *Tetrahedron Lett.*, 1996, **37**, 3175.
214 A.G. Myers and J.L. Gleason, *J. Org. Chem*, 1996, **61**, 813.
215 R.S. Roy and B. Imperiali. *Tetrahedron Lett.*, 1996, **37**, 2129.
216 A.G.Myers, J.L. Gleason, T. Yoon, and D.W. Kung, *J. Am. Chem. Soc.*, 1997, **119**, 656.
217 H.Y. Kim, K. Stein, and P.L. Toogood, *Chem. Commun.*, 1996, 1683.
218 C.B. Bucher and H.Heimgartner, *Helv. Chim. Acta*, 1996, **79**, 1903.
219 P. Dauban, A. Chiaroni, C. Riche, and R.H. Dodd, *J. Org. Chem*, 1996, **61**, 2488.
220 B.G.M. Burgaud, D.C. Horwell, A. Padova, and M.C. Pritchard, *Tetrahedron*, 1996, **52**, 13035.
221 G. Righi, R. D'Achille, and C. Bonini, *Tetrahedron Lett.*, 1996, **37**, 6893.
222 J.E. Baldwin, C.N. Farthing, A.T. Russell, C.J. Schofield, and A.C. Spivey, *Tetrahedron Lett.*, 1996, **37**, 3761.
223 J. Aires-de-Sousa, A.M. Lobo, and S. Prabhakar, *Tetrahedron Lett.*, 1996, **37**, 3183.
224 C. Palomo, J.M. Aizpurea, I. Gamboa, B. Odriozola, R. Urchegui, and H. Gorls, *Chem. Commun.*, 1996, 1269.
225 K.J. Kreuzfeld, C. Doebler, U. Schmidt, and H.W. Krause, *Amino Acids*, 1996, **11**, 269.
226 H.W. Krause, K.J. Kreuzfeld, U. Schmidt, C. Doebler, M. Michalik, S. Tandien, and C. Fischer, *Chirality*, 1996, 8, 173; C. Doebler, K.J. Kreuzfeld, M. Michalik, and H.W. Krause, *Tetrahedron: Asymmetry*, 1996, **7**, 117.
227 J.A. Ramsden, T.D.W. Claridge, and J.M. Brown, *Chem. Commun.*, 1995, 2469.
228 K. Tamao, K. Nakamura, S. Yamaguchi, M. Shiro, and S. Saito, *Chem. Lett.*, 1996, 1007.
229 P. Pellon, C. Le Goaster, and L. Toupet, *Tetrahedron Lett.*, 1996, **37**, 4713.
230 S.R. Gilbertson and X. Wang, *Tetrahedron Lett.*, 1996, **37**, 6475.
231 K. Borszeky, T. Mallat, R. Aeschiman, W.B. Schmeizer, and A. Baiker, *J. Catal.*, 1996, **161**, 451.
232 M. Oba, S. Nakajima, and K. Nishiyama, *Chem. Commun.*, 1996, 1875.
233 T. Sakai, F. Yan, S. Kashino, and K. Uneyama, *Tetrahedron*, 1996, **52**, 233.
234 D. Enders, A. Haertwig, G. Raabe, and J. Runsink, *Angew. Chem. Int. Ed.*, 1996, **35**, 2388.
235 M. Malumbres and J.F. Martin, *FEMS Microbiol. Lett.*, 1996, **143**, 103.
236 R.S. Hanson, R. Dillingham, P. Olson, G.H. Lee, D. Cue, F.J. Schendel, C. Bremmon, and M.C. Flickinger, in Microbial Growth Conference 1995 (published 1996), Eds. M.E. Lidstrom and F.R. Tabita, Kluwer, Dordrecht, p.227.
237 K. Kawasaki, A. Yokota, and F. Tomita, *Kagaku to Seibutsu*, 1996, **34**, 569.

238 T.K. Maiti, A. Roy, S.K. Mukherjee, S.P. Chatterjee, *Hind. Antibiot. Bull.*, 1995, **37**, 51 (*Chem. Abs.*, 1997, **126**, 46325).
239 R. Kraemer, *J. Biotechnol.*, 1996, **45**, 1.
240 H. Motoyama and H. Anazawa, *Iden*, 1996, **50**, 48.
241 T. Hagishita, R. Yoshida, Y. Izumi, and T. Mitsunaga, *Biosci. Biotechnol. Biochem.*, 1996, **60**, 1604.
242 M. Takagi, Y. Nishio, G. Oh, and T. Yoshida, *Biotechnol. Bioeng.*, 1996, **52**, 653.
243 K. Kawasaki, A. Yokota, and F. Tomita, *J. Ferment. Bioeng.*, 1996, **82**, 604.
244 F. Hasumi, K. Fukuoka, S. Adachi, Y. Miyamoto, and I. Okura, *Appl. Biochem. Biotechnol.*, 1996, **56**, 341.
245 G.B. D'Cunha, V. Satyanarayan, and P.M. Nair, *Enzyme Microb. Technol.*, 1996, **19**, 421.
246 N. Chida, H. Ikemoto, A. Noguchi, S. Amano, and S. Ogawa, *Nat. Prod. Lett.*, 1995, **6**, 295.
247 B.M. Trost, A.C. Krueger, R.C. Bunt, and J. Zambrano, *J. Am. Chem. Soc.*, 1996, **118**, 6520.
248 S.L. Ablaza, N.N. Pai, and P.W. LeQuesne, *Nat. Prod. Lett.*, 1995, **6**, 77.
249 C.M. Evina and G. Guillerm, *Tetrahedron Lett.*, 1996, **37**, 163.
250 C.N. Farthing, J.E. Baldwin, A.T. Russell, C. J.Schofield, and A.C. Spivey, *Tetrahedron Lett.*, 1996, **37**, 5225.
251 J. Yamaguchi and M. Ueki, *Chem. Lett.*, 1996, 621.
252 L. Graziani, G. Porzi, and S. Sandri, *Tetrahedron: Asymmetry*, 1996, **7**, 1341.
253 A. Madan, G. Porzi, and S. Sandri, *Tetrahedron: Asymmetry*, 1996, **7**, 825.
254 Y.Yuasa, J. Ando, and S. Shibuya, *J. Chem. Soc., Perkin Trans. I*, 1996, 793.
255 J. Mulzer, A. Meier, J. Buschmann, and P. Luger, *J. Org. Chem*, 1996, **61**, 566.
256 M.D.Bachi, N. Bar-Ner, and A. Melman, *J. Org. Chem*, 1996, **61**, 7116.
257 M.D.Bachi and A. Melman, *SynLett.*, 1996, 60.
258 S. Hanessian and S. Ninkovic, *J. Org. Chem*, 1996, **61**, 5418.
259 J.E. Baldwin, A.M. Fryer, M.R. Spyvee, R.C. Whitehead, and M.E. Wood, *Tetrahedron Lett.*, 1996, **37**, 6923.
260 M. -P.Bertrand, S. Gastaldi, and R.Nouguier, *Tetrahedron Lett.*, 1996, **37**, 1229.
261 A.FParsons, *Tetrahedron*, 1996, **52**, 4149.
262 Y. Ohfune, S. -H.Moon, and M. Horikawa, *Pure Appl. Chem.*, 1996, **68**, 645; I. Takada and Y. Ohfune, *Kagaku*, 1996, **51**, 334 (*Chem. Abs.*, 1996, **125**, 87120).
263 S. Hatakeyama, H. Fukuyama, Y. Mukugi, and H. Irie, *Tetrahedron Lett.*, 1996, **37**, 4047.
264 A. Kovacs-Kulyassa, P. Herczegh, and F.J. Sztaricskai, *Tetrahedron Lett.*, 1996, **37**, 2499.
265 F.A. Davis, H. Liu, and G.V. Reddy, *Tetrahedron Lett.*, 1996, **37**, 5473.
266 C.R.Noe, M. Knollmueller, H. Voellenkle, M. Noe-Letsching, A. Weigand, and J. Muehl, *Pharmazie*, 1996, **51**, 800.
267 V. Ferey, P. Vedrenne, L. Toupet, T. Le Gall, and C. Mioskowski, *J. Org. Chem.*, 1996, **61**, 7244.
268 Y. Matsumura, T. Kinoshita, Y. Yanagihara, N. Kanemoto, and M. Watanabe, *Tetrahedron Lett.*, 1996, **37**, 8395.
269 D. Ma and H. Tian, *Tetrahedron: Asymmetry*, 1996, **7**, 1567.
270 E. Coudert, F. Acher, and R.Azerad, *Tetrahedron: Asymmetry*, 1996, **7**, 2963.
271 K. Miyashita, H. Miyabe, K. Tai, C. Kurozumi, and T. Imanishi, *Chem. Commun.*, 1996, 1073.

272 S.N. Osipov, A.S. Golubev, N. Sewald, T. Michel, A.F. Kolomiets, A.V.Fokin, and K. Burger, *J. Org. Chem.*, 1996, **61**, 7521.

273 P. Bravo, S. Capelli, S.V. Meille, P. Seresini, A. Volonterio, and M. Zanda, *Tetrahedron: Asymmetry*, 1996, **7**, 2321.

274 P. Bravo, F. Viani, M. Zanda, V.P. Kukhar, V.A. Soloshonok, N. Fokina, O.V. Shishkin, and Y.T. Struchkov, *Gazz. Chim. Ital.*, 1996, **126**, 645.

275 S.N. Osipov, N. Sewald, A.F. Kolomiets, A.V. Fokin, and K. Burger, *Tetrahedron Lett.*, 1996, **37**, 615.

276 U. Kragl, D. Vasic-Racki, and C. Wandrey, *Bioprocess Eng.*, 1996, **14**, 291.

277 A.B. Charette and B. Cote, *J. Am. Chem. Soc.*, 1995, **117**, 12721.

278 J.M. Jimenez and R.M. Ortuno, *Tetrahedron: Asymmetry*, 1996, **7**, 3203.

279 J.M. Jimenez, J.M. Rife, and R.M. Ortuno, *Tetrahedron: Asymmetry*, 1996, **7**, 537.

280 K. Burgess and C.Y. Ke, *Synthesis*, 1996, 1463.

281 S.P. Walford, M.M. Campbell, and D.C. Horwell, *J. Pharm. Pharmacol.*, 1996, **48**, 188.

282 B. Donati, A. Garzon-Aburbeh, B. Natalini, C. Marchioro, and R. Pellicciari, *Tetrahedron*, 1996, **52**, 9901.

283 A. Hercouet, B. Bessieres, M. Le Corre, and L. Toupet, *Tetrahedron Lett.*, 1996, **37**, 4529.

284 S. Hanessian, U. Reinhold, and S. Ninkovic, *Tetrahedron Lett.*, 1996, **37**, 8967.

285 S. Hanessian, S. Ninkovic, and U. Reinhold, *Tetrahedron Lett.*, 1996, **37**, 8971.

286 K. Shimamoto and Y. Ohfune, *J. Med. Chem.*, 1996, **39**, 407.

287 A.M.P. Koskinen and H. Hassila, *Acta Chem. Scand.*, 1996, **50**, 323.

288 M. Calmes, J. Dannis, and F. Escale, *Tetrahedron: Asymmetry*, 1996, **7**, 395.

289 M. Marinozzi, B. Natalini, G. Costantino, P. Tijskens, C. Thomsen, and R. Pellicciari, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2243.

290 R. Pellicciari, M. Marinozzi, B. Natalini, G. Costantino, R. Luneia, G. Giorgi, F. Moroni, and C. Thomsen, *J. Med. Chem.*, 1996, **39**, 2259.

291 R. Pellicciari, M. Raimondo, M. Marinozzi, B. Natalini, G. Costantino, and C. Thomsen, *J. Med. Chem.*, 1996, **39**, 2874.

292 R.D. Allan, R.K. Duke, T.W.Hambley, G.A.R. Johnston, K.N. Mewett, M. Quickert, and H.W. Tran, *Aust. J. Chem.*, 1996, **49**, 785.

293 A. Avenoza, C. Cativiela, M. Paris, and J.M. Peregrina, *Tetrahedron*, 1996, **52**, 4839.

294 R.M. Ortuno, J. Ibarzo, J. d'Angelo, F. Dumas, A. Alvarez-Larena, and J.F. Piniella, *Tetrahedron: Asymmetry*, 1996, **7**, 127.

295 S.G. Pyne and J. Safaei-G. , *J. Chem. Res., Synop.*, 1996, 160.

296 F. Tellier, F. Acher, I. Brabet, J.-P. Pin, J. Bockaert, and R. Azerad, *C.R. Acad. Sci., Ser. II: Mec., Phys., Chim., Astron.*, 1995, **321**, 385; *Bioorg. Med. Chem. Lett.*, 1995, **5**, 2627.

297 M. Carducci, S. Fioravanti, M.A. Loreto, L. Pellacani, and P.A. Tardella, *Tetrahedron Lett.*, 1996, **37**, 3777.

298 H.-J. Ha, K.-H. Kang, J.-M. Suh, and Y.-G. Ahn, *Tetrahedron Lett.*, 1996, **37**, 7069.

299 A.P. Kozikowski, Y. Liao, W. Tueckmantel, S. Wang, S. Pshenichkin, A. Surin, C. Thomsen, and J.T. Wroblewski, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2559.

300 A. Steiner, P. Wessig, and K. Polborn, *Helv. Chim. Acta*, 1996, **79**, 1843.

301 C. Alvarez-Ibarra, A.G. Csaky, M. Martinez, and M.L. Quiroga, *Tetrahedron Lett.*, 1996, **37**, 6573.

302 S.P. Hollinshead, *Tetrahedron Lett.*, 1996, **37**, 9157.

303 B.C. Hamper, D.A. Dukesherer, and M.S. South, *Tetrahedron Lett.*, 1996, **37**, 3671.

304 F. Laduron, C. Ates, and H.G. Viehe, *Tetrahedron Lett.*, 1996, **37**, 5515.

305 J. Bonjoch, J. Catena, E. Isabal, M. Lopez-Canet, and N. Valli, *Tetrahedron: Asymmetry*, 1996, **7**, 1899.
306 M.J. Sodergren and P.G. Andersson, *Tetrahedron Lett.*, 1996, **37**, 7577.
307 J. Mulzer, A. Meier, J. Buschmann, and P. Luger, *Synthesis*, 1996, 123.
308 J.A. Campbell and H. Rapoport, *J. Org. Chem.*, 1996, **61**, 6313.
309 C. Agami, L. Hamon, C. Kadouri-Puchot, and V. Le Guen, *J. Org. Chem.*, 1996, **61**, 5736.
310 C. Agami, F. Couty, and H. Mathieu, *Tetrahedron Lett.*, 1996, **37**, 4001.
311 C. Subramanyam, S. Chattarjee, and J.P. Mallamo, *Tetrahedron Lett.*, 1996, **37**, 459.
312 G.L. Bolton, *Tetrahedron Lett.*, 1996, **37**, 3433.
313 J.C. Estevez, M.D. Smith, M.R. Wormald, G.S. Besra, P.J. Brennan, R.J. Nash, and G.W.J. Fleet, *Tetrahedron: Asymmetry*, 1996, **7**, 391.
314 J.P. Shilvock, J.R. Wheatley, B. Davis, R.J. Nash, R.C. Griffiths, M.G. Jones, M. Muller, S. Crook, D.J. Watkin, C. Smith, G.S. Besra, P.J. Brennan, and G.W.J. Fleet, *Tetrahedron Lett.*, 1996, **37**, 8569.
315 J. Gillard, A. Abraham, P.C. Anderson, P.L. Beaulieu, T. Bogri, Y. Bousquet, L. Grenier, I. Guse, and P. Lavallee, *J. Org. Chem.*, 1996, **61**, 2226.
316 C. Fernandez-Garcia and M.A. McKervey, *Tetrahedron: Asymmetry*, 1995, **6**, 2905.
317 U. Schmidt, C. Braun, and H. Sutoris, *Synthesis*, 1996, 223.
318 K. Kobayashi, *Dojin News*, 1995, **77**, 3 (*Chem. Abs.*, 1996, **124**, 139202).
319 A. Lazcano and S.L. Miller, *Cell*, 1996, **85**, 789.
320 L. Joshi, *Asian J. Chem.*, 1996, **8**, 401 (*Chem. Abs.*, 1996, **125**, 188518).
321 S. Yuasa, T. Fukuhara, M. Isoyama, and M. Tanaka, Evolutionary Biochemistry and Related Areas in Physico-Chemical Biology, Ed. B.F. Poglazov, Bach Institute of Biochemistry, Moscow, 1995, p.105 (*Chem. Abs.*, 1996, **125**, 79514).
322 H. Yanagawa, *Kagaku*, 1996, **66**, 461 (*Chem. Abs.*, 1996, **125**, 79567).
323 L. Rene and B. Badet, *Synth. Commun.*, 1996, **26**, 3237.
324 G. Jiang, L. Simon, and J.E. Rivier, *Protein Pept. Lett.*, 1996, **3**, 219.
325 M. Kawai, K. Hosoda, Y. Omori, K. Yamada, S. Hayakawa, H. Yamamura, and Y. Butsugan, *Synth. Commun.*, 1996, **26**, 1545.
326 M. Seki and K. Matsumoto, *Synthesis*, 1996, 580.
327 V. Tolman, *Amino Acids*, 1996, **11**, 15.
328 K.L. Kirk and J.-Y.Nie, *ACS Symp. Ser.*, 1996, **639** (Biomedical Frontiers of Fluorine Chemistry), 312.
329 G. Haufe and S. Kroeger, *Amino Acids*, 1996, **11**, 409.
330 J.B. Ducep, K. Jund, B. Lesur, S. Sarhan, M. Schliemer, P.R. Zimmerman, and N. Seiler, *ACS Symp. Ser.*, 1996, **639** (Biomedical Frontiers of Fluorine Chemistry), 196.
331 V. A. Soloshonok, *ACS Symp. Ser.*, 1996, **639** (Biomedical Frontiers of Fluorine Chemistry), 26.
332 T. Taguchi, A. Shibuya, and T. Morikawa, *ACS Symp. Ser.*, 1996, **639** (Biomedical Frontiers of Fluorine Chemistry), 73.
333 A.R. Ritter and C.F. Hammer, *J. Fluorine Chem.*, 1996, **77**, 1.
334 F.B. Charvillon and R. Amouroux, *Tetrahedron Lett.*, 1996, **37**, 5103.
335 R. Keese and C. Hinderling, *Synthesis*, 1996, 695.
336 A. Bensadat, C. Felix, A. Laurent, E. Laurent, R. Faure, and T. Thomas, *Bull. Soc. Chim. Fr.*, 1996, **133**, 509.
337 T. Tsukamoto, T. Kitazume, J.J. McGuire, and J.K. Coward, *J. Med. Chem.*, 1996, **39**, 66.
338 B.P. Hart, W.H. Haile, N.T. Licato, W.E. Bolanowska, J.J. McGuire, and J.K. Coward, *J. Med. Chem.*, 1996, **39**, 56.

339 T. Tsukamoto and J.K. Coward, *J. Org. Chem.*, 1996, **61**, 2497.
340 J.-P. Genet, *Pure Appl. Chem.*, 1996, **68**, 593.
341 R. Grandel, U. Kazmeier, and B. Nuber, *Liebigs Ann.*, 1996, 1143.
342 F. Zanardi, L. Battistini, M. Nespi, G. Rassu, F. Spanu, M. Cornia, and G. Casiraghi, *Tetrahedron*, 1996, **52**, 1167.
343 L. Williams, Z. Zhang, F. Shao, P.J. Carroll, and M.M. Jouillie, *Tetrahedron*, 1996, **52**, 11673.
344 Y. Tokunaga, M. Ihara, and K. Fukumoto, *Tetrahedron Lett.*, 1996, **37**, 6157.
345 A.P. Nin, R.M. de Lederkremer, and O.Varela, *Tetrahedron*, 1996, **52**, 12911.
346 T.J. Woltering, G. Weitz-Schmidt, and C.-H. Wong, *Tetrahedron Lett.*, 1996, **37**, 9033.
347 H. Shao and M. Goodman, *J. Org. Chem.*, 1966, **61**, 2582.
348 T. Nagamitsu, T. Sunazuka, H. Tanaka, S. Omura, P.A. Sprengeler, and A.B. Smith, *J. Am. Chem. Soc.*, 1996, **118**, 3584.
349 P.E. Nielsen, *Methods Enzymol.*, 1996, **267** (Combinatorial Chemistry), 426; B. Hyrup and P.E. Nielsen, *Bioorg. Med. Chem.*, 1996, **4**, 5.
350 D.A. Stetsenko. E.N.Lubyako, V.K. Potapov, T.L. Azhikina, and E.D. Sverdlov, *Tetrahedron Lett.*, 1996, **37**, 3571.
351 A. Farese, N. Patino, R. Condom, S. Dalleu, and R. Guedj, *Tetrahedron Lett.*, 1996, **37**, 1413.
352 B. Hyrup, M. Egholm, O. Buchardt, and P.E. Nielsen, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1083.
353 G. Haaima, A. Lohse, O.Buchardt, and P.E. Nielsen, *Angew. Chem., Int. Ed., Engl.*, 1996, **35**, 1939.
354 E. Lioy and H. Kessler, *Liebigs Ann.*, 1996, 201.
355 R.W. Armstrong, J.E. Tellew, and E.J. Moran, *Tetrahedron Lett.*, 1996, **37**, 447.
356 K. Uneyama, F. Yan, S. Hirama, and T. Katagiri, *Tetrahedron Lett.*, 1996, **37**, 2045.
357 A. Hammadi, A. Menerz, and R. Genet, *Tetrahedron Lett.*, 1996, **37**, 3309.
358 D.B. Berkowitz, M.L. Pedersen, and W.-J. Jahng, *Tetrahedron Lett.*, 1996, **37**, 4309.
359 U. Kazmeier, *Amino Acids*, 1996, **11**, 283; U. Kazmeier and S. Maier, *Tetrahedron*, 1996, **52**, 941.
360 U. Kazmeier and C. Schneider, *SynLett.*, 1996, 975.
361 U. Kazmeier, *Tetrahedron Lett.*, 1996, **37**, 5351.
362 U. Kazmeier, *J. Org. Chem.*, 1996, **61**, 3694; U.Kazmeier, *SynLett.*, 1996, 1138.
363 A. Krebs and U. Kazmeier, *Tetrahedron Lett.*, 1996, **37**, 7945.
364 C.H. Goerbitz, *Synthesis*, 1996, 1489.
365 S. Hanessian and R.-Y. Yang, *Tetrahedron Lett.*, 1996, **37**, 8997.
366 P. Meffre and F. Le Goffic, *Amino Acids*, 1996, **11**, 313.
367 M.R. Burns and J.K. Coward, *Bioorg. Med. Chem.*, 1996, **4**, 1455.
368 R.L. Von Tersch, F. Secundo, R.S. Phillips, and M.G. Newton, *ACS Symp. Ser.*, 1996, **639** (Biomedical Frontiers of Fluorine Chemistry), 95.
369 A. Hutinec, A. Ziogas, and A. Rieker, *Amino Acids*, 1996, **11**, 345.
370 A. Torrado and B. Imperiali, *J. Org. Chem.*, 1996, **61**, 8940.
371 N. Galvez, M. Moreno-Manas, A. Vallribera, E. Molins, and A. Cabrero, *Tetrahedron Lett.*, 1996, **37**, 6197.
372 W. Mueller, P. Kipfer, D.A. Lowe, and S. Urwyler, *Helv. Chim. Acta*, 1995, **78**, 2026.
373 N.R. Curtis, J.J. Kulagowski, P.D. Leeson, I.M. Mawer, M.P. Ridgill, M. Rowley, S. Grimwood, and G.R. Marshall, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1145.
374 U. Schmidt, G. Oehme, and H. Krause, *Synth. Commun.*, 1996, **26**, 777.

375 C.G. Wermuth, A. Mann, A. Schoenfelder, R.A. Wright, B.G. Johnson, J.P. Burnett, N.G. Mayne, and D.D. Schoepp, *J. Med. Chem.*, 1996, **39**, 814.
376 H. Braeuner-Osborne, F. A. Slok, N.Skjaerback, B. Ebert, N. Sekiyama, S. Nakanishi, and P. Krogsgaard-Larsen, *J. Med. Chem.*, 1996, **39**, 3188.
377 U. Diederichsen, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 445.
378 R.P. Cheng, S.L. Fisher, and B. Imperiali, *J. Am. Chem. Soc.*, 1996, **118**, 11349.
379 D. Wensbo and S. Gronowitz, *Tetrahedron*, 1996, **52**, 14975.
380 B. Basu and T. Frejd, *Acta Chem. Scand.*, 1996, **50**, 316.
381 R.L. Rich, A.V. Smirnov, A.W. Schwabacher, and J.W. Petrich, *J. Am. Chem. Soc.*, 1995, **117**, 11850.
382 S.W. Wright, R.L. Dow, L.D. McClure, and D.L. Hageman, *Tetrahedron Lett.*, 1996, **37**, 6965.
383 I. Kavrakova and M.J. Lyapova, *Org. Prep. Proced. Int.*, 1996, **28**, 333.
384 T. Hayashi, E. Kishi, V.A. Soloshonok, and Y. Uozumi, *Tetrahedron Lett.*, 1996, **37**, 4969.
385 A.K. Bose, M. Jayaraman, A. Okawa, S.S. Bari, E.W. Robb, and M.S. Manhas, *Tetrahedron Lett.*, 1996, **37**, 6989.
386 C. Palomo, J.M. Aizpurua, R. Galarza, and A. Mielgo, *Chem. Commun.*, 1996, 633.
387 J.A. Robl, E. Sieber-McMaster, and R. Sulsky, *Tetrahedron Lett.*, 1996, **37**, 8985.
388 M. Cowart, E.A. Kowaluk, K.L. Kohlhaas, K.M. Alexander, and J.F. Kerwin, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 999.
389 M.J. Thompson, A. Mekhalfia, D.L. Jakeman, S.E.V. Phillips, K. Phillips, J. Porter, and G.M. Blackburn, *Chem. Commun.*, 1996, 791.
390 N. Shibata, J.E. Baldwin, A. Jacobs, and M.E. Wood, *SynLett.*, 1996, 519.
391 W. Karnbrock, E. Weyher, N. Budisa, R. Huber, and L. Moroder, *J. Am. Chem. Soc.*, 1996, **118**, 913.
392 B. Swahn, A. Claesson, B. Pelemann, Y. Besidski, H. Molin, M.P. Sandberg, and O. Berge, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1635.
393 F.C. Ross, N.P. Botting, and P.D. Leeson, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2643.
394 M.S. Smyth and T.R. Burke, *Org. Prep. Proced. Int.*, 1996, **28**, 77.
395 A.K. Szardenings, M.F. Gordeev, and D.V. Patel, *Tetrahedron Lett.*, 1996, **37**, 3635.
396 J.W. Skiles, P.P. Giannoussis, and K.R. Fales, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 963.
397 I.M. Wyzlic, W. Tjarks, A.H. Soloway, D.J. Perkins, M. Burgos, and K.P. O'Reilly, *Inorg. Chem.*, 1996, **35**, 4541.
398 S.B. Kahl and R.A. Kaser, *J. Am. Chem. Soc.*, 1996, **118**, 1223.
399 M.M. Kessels and B. Qualmann, *J. Prakt. Chem./Chem.-Ztg.*, 1996, **338**, 89.
400 C. Malan and C. Morin, *SynLett.*, 1996, 167.
401 M. Kirihata, T. Morimoto, T. Mizuta, I. Ichimoto, Y. Kitaoka, and M. Kobayashi, *Kyoto Daogaku Genshiro Jikkensho, Tech. Rep.*, 1995, 43 (*Chem. Abs.*, 1996, **125**, 143259); M. Kirihata, T. Morimoto, I. Ichimoto, M. Kobayashi, and Y. Kitaoka, *Biosci., Biotechnol., Biochem.*, 1996, **60**, 157.
402 M. Kirihata, T. Morimoto, T. Mizuta, and I. Ichimoto, *Biosci. Biotechnol. Biochem.*, 1996, **60**, 2317.
403 F.J. Winkler, K. Kuehnl, R. Medina, R. Schwarz-Kaske, and H.-L. Schmidt, *Ist. Environ. Health Stud.*, 1995, **31**, 161.
404 Y. Yang and R.F. Evila, *J. Supercrit. Fluids*, 1996, **9**, 161.
405 Y. Yang and R.F. Evila, *J. Supercrit. Fluids*, 1996, **9**, 113.
406 M. Oba, T. Terauchi, and K. Nishiyama, *J. Deuterium Sci.*, 1996, **5**, 35.
407 J.J. Milne and J.P.G. Malthouse, *Biochem. Soc. Trans.*, 1996, **24**, 133S.
408 F.C. Ross, N.P. Botting, and P.D. Leeson, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 875.

409 F. Barclay, E. Chrystal, and D. Gani, *J. Chem.Soc., Perkin Trans. I*, 1996, 683.
410 K.J.M. Beresford and D.W. Young, *Tetrahedron*, 1996, **52**, 9891.
411 X.Durand, P. Hudhomme, J.A. Khan, and D.W. Young, *J. Chem.Soc., Perkin Trans. I*, 1996, 1131.
412 R.A. August, J.A. Khan, C.M. Moody, and D.W. Young, *J. Chem.Soc., Perkin Trans. I*, 1996, 507.
413 Y. Maeda, K. Tago, T. Eguchi, and K. Kakinuma, *Biosci.Biotechnol.Biochem.*, 1996, **60**, 1248.
414 T. Tsuzuki, T. Mashimo, M. Mukumoto, S. Mataka, J. Udagawa, and M. Tashiro, *J. Chem.Res.Synop.*, 1996, 412.
415 T.J. Ruth and M.J. Adam, *J. Radioanal.Nucl.Chem.*, 1996, **203**, 457.
416 C. Prenant, A. Theobald, U. Haberkorn, M.G. Bellemann, K. Weber, and F. Oberdorfer, *Nucl.Med.Biol.*, 1996, **23**, 359.
417 D. Roeda, C. Crouzel, E. Brouiller, and H. Valette, *Nucl.Med.Biol.*, 1996, **23**, 509.
418 B. Schmall, P.S. Conti, and M.M. Alauddin, *Nucl.Med.Biol.*, 1996, **23**, 263.
419 P.K. Chakraborty, T.J. Manguer, D.C. Chugani, O. Muzik, and H.T. Chugani, *Nucl.Med.Biol.*, 1996, **23**, 1005.
420 M. Kurosawa and K. Nishioka, *Radioisotopes*, 1996, **45**, 685.
421 N.M. Kelly, R.G. Reid, C.L. Willis, and P.L. Winton, *Tetrahedron Lett.*, 1996, **37**, 1517.
422 Y. Elemes and U. Ragnarsson, *J. Chem.Soc., Perkin Trans. I*, 1996, 537.
423 Y. Elemes and U. Ragnarsson, *Chem.Commun.*, 1996, 935.
424 S.N. Lodwig and C.J. Unkefer, *J. Labelled Compd.Radiopharm.*, 1996, **38**, 239.
425 A. Sutherland and C.L. Willis, *J. Labelled Compd.Radiopharm.*, 1996, **38**, 95.
426 Y. Yost and T. Conway, *Nucl.Med.Biol.*, 1996, **23**, 857.
427 K. Ishiwata, M. Shinoda, S. Ishii, T. Nozaki, and M. Senda, *Nucl.Med.Biol.*, 1996, **23**, 301.
428 K. Hatano, K. Ishiwata, and T. Yanagisawa, *Nucl.Med.Biol.*, 1996, **23**, 101.
429 K. Kawai, H. Ohta, A. Kubodera, M.A. Channing, and W.C. Eckelman, *Nucl.Med.Biol.*, 1996, **23**, 251.
430 J. Schmaljohan, *Ber.Forschungszent.Juelich*, 1995 (no page given; information from *Chem.Abs.*, 1996, **124**, 176859).
431 G. Cardillo and C. Tomasini, *Chem.Soc.Rev.*, 1996, **25**, 117.
432 N. Sewald, *Amino Acids*, 1996, **11**, 397.
433 J. Escalante and E. Juaristi, *Ciencia*, 1996, **47**, 259 (*Chem.Abs.*, 1997, **126**, 89712).
434 S. Kourtal and J. Paris, *Lett.Pept.Sci.*, 1996, **3**, 73.
435 A. Mann, L. Quaranta, G. Reginato, and M. Taddei, *Tetrahedron Lett.*, 1996, **37**, 2651.
436 A. Barco, S. Benetti, C. De Risi, G.P. Pollini, G. Spalluto, and V. Zanirato, *Tetrahedron*, 1996, **52**, 4719.
437 J. Zygmunt, R. Gancarz, B. Lejczak, P. Wieczorek, and P. Kafarski, *Bioorg.Med.Chem.Lett.*, 1996, **6**, 2989.
438 C. Guibourdenche, J. Podlech, and D. Seebach, *Liebigs Ann.*, 1996, 1121.
439 C.W. Jefford, J. McNulty, Z.H. Lu, and J.B. Wang, *Helv.Chim.Acta*, 1996, **79**, 1203.
440 M. Seki and K. Matsumoto, *Biosci., Biotechnol., Biochem.*, 1996, **60**, 916.
441 P. Gmeiner, E. Hummel, and C. Haubmannn, *Liebigs Ann.*, 1996, 1987.
442 F.J. Lakner, K.S. Chu, G.R. Negrete, and J.P. Konopelski, *Org.Synth.*, 1996, **73**, 201.
443 F. Beaulieu, J. Arova, U. Veith, N.J. Taylor, B.J. Chapell, and V. Snieckus, *J. Am.Chem.Soc.*, 1996, **118**, 8727.

444 F. D'Aniello, A. Mann, and M. Taddei, *J. Org. Chem.*, 1996, **61**, 4870.
445 H.Y. Kim and P.L. Toogood, *Tetrahedron Lett.*, 1996, **37**, 2349.
446 N. Sin and J. Kallmerten, *Tetrahedron Lett.*, 1996, **37**, 5645.
447 P. Pires and K. Burger, *Synthesis*, 1996, 1277.
448 A. Tuch, M. Saniere, Y. Le Merrer, and J.-C. Depezay, *Tetrahedron: Asymmetry*, 1996, **7**, 2901.
449 L. Pegorier, M. Haddad, and M. Larcheveque, *SynLett.*, 1996, 621.
450 K. Danielmeier, K. Schierle, and E. Steckhan, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2247.
451 M. Shiozaki, T. Mochizuki, R. Wakabayashi, S. Kurakata, T. Tatsuta, and M. Nishijima, *Tetrahedron Lett.*, 1996, **37**, 7271.
452 G.A. Kraus, H. Maeda, and L. Chen, *Tetrahedron Lett.*, 1996, **37**, 7245.
453 Y. Igarashi, M. Ichikawa, and Y. Ichikawa, *Tetrahedron Lett.*, 1996, **37**, 2707.
454 R. Pires and K. Burger, *Tetrahedron Lett.*, 1996, **37**, 8159.
455 E. Arvanitis, M. Motevalli, and P.B. Wyatt, *Tetrahedron Lett.*, 1996, **37**, 4277.
456 S.G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1996, **7**, 1919.
457 A.J. Burke, S.G. Davies, and C.J.R. Hedgcock, *SynLett.*, 1996, 621.
458 T. Ishikawa, K. Nagai, T. Kudoh, and S. Saito, *SynLett.*, 1995, 1171.
459 G. Li, H.-T. Chang, and K.B. Sharpless, *Angew. Chem. Int., Ed. Engl.*, 1996, **35**, 451.
460 L. Banfi, G. Guanti, and M.T. Zannetti, *Tetrahedron Lett.*, 1996, **37**, 521.
461 V.A. Soloshonok and V.P. Kukhar, *Tetrahedron*, 1996, **52**, 6953.
462 H. Sugimura and N. Yamada, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, 1996, **38th**, 625.
463 C. Cimarelli and G. Palmieri, *J. Org. Chem.*, 1996, **61**, 5557.
464 E.G.J.C. Warmerdam, R.D. van Rijn, J. Brussel, C.G. Kruse, and A. van der Gen, *Tetrahedron: Asymmetry*, 1996, **7**, 1723.
465 S. Hanessian and J.-Y. Sanceau, *Can. J. Chem.*, 1996, **74**, 621.
466 B. Bhatia, A. Jain, A. De, I. Bagchi, and J. Iqbal, *Tetrahedron Lett.*, 1996, **37**, 7311.
467 G. Righi, G. Rumboldt, and C. Bonini, *J. Org. Chem.*, 1996, **61**, 3557.
468 F. Junquera, F.L. Merchan, P. Merino, and T. Tejero, *Tetrahedron*, 1996, **52**, 7045.
469 L. Ambroise and R.F.W. Jackson, *Tetrahedron Lett.*, 1996, **37**, 2311.
470 M. Tsuda, Y. Muraoka, M. Nagai, T. Aoyagi, and T. Takeuchi, *J. Antibiot.*, 1996, **49**, 281.
471 H. Harayama, H. Okuno, Y. Takahashi, M. Kimura, K. Fugami, S. Tanaka, and Y. Tamaru, *Tetrahedron Lett.*, 1996, **37**, 7287.
472 G. Heinisch, T. Langer, J. Tonnel, K. Mereiter, and K. Wurst, *Heterocycles*, 1996, **43**, 1057.
473 P.G. Cozzi, B. Di Simone, and A. Umani-Ronchi, *Tetrahedron Lett.*, 1996, **37**, 1691.
474 S. Kobayashi, H. Ishitani, S. Komiyama, D.C. Oniciu, and A.R. Katritzky, *Tetrahedron Lett.*, 1996, **37**, 3731.
475 Y. Kodama, M. Okumura, N. Yanabu, and T. Taguchi, *Tetrahedron Lett.*, 1996, **37**, 1061.
476 B.B. Shankar, M.P. Kirkup, S.W. McCombie, J.W. Clader, and A.K. Ganguly, *Tetrahedron Lett.*, 1996, **37**, 4095.
477 C. Gennari and G. Pain, *Tetrahedron Lett.*, 1996, **37**, 3747.
478 S. Kobayashi, I. Hachiya, S. Suzuki, and M. Moriwaki, *Tetrahedron Lett.*, 1996, **37**, 2809.
479 K. Fuji, T. Kawabata, Y. Diryu, and Y. Sugiura, *Heterocycles*, 1996, **42**, 701.
480 A. Abouabdellah, J.-P. Begue, and D. Bonnet-Delpon, *SynLett.*, 1996, 399.

481 M. Pasto, A. Moyano, M.A. Pericas, and A. Rieri, *Tetrahedron: Asymmetry*, 1996, **7**, 243.
482 Y. Ahn, *J. Korean Chem.Soc.*, 1995, **39**, 881 (*Chem.Abs.*, 1996, **124**, 176838).
483 C. Cativiela, M.D. Diaz De Villegas, and J.A. Galvez, *Tetrahedron*, 1996, **52**, 687.
484 H. Tsuge, T. Okano, and S. Eguchi, *J. Chem.Soc., Perkin Trans. I*, 1995, 2761.
485 Q. Li, R. Huang, W. Li, and X. Shen, *Zhongguo Yaowu Huaxue Zazhi*, 1995, **5**, 276 (*Chem.Abs.*, 1996, **124**, 344039).
486 R. Castagnani, F. De Angelis, E. De Fusco, F. Giannessi, D. Misiti, D. Meloni, and M.O. Tinti, *J. Org.Chem.*, 1995, **60**, 8318.
487 G.R. Pettit, D.D. Burkett, J. Barkoczy, G.L. Breneman, and W.E. Pettit, *Synthesis*, 1996, 719.
488 G.R. Pettit, D.D. Burkett, and M.D. Williams, *J. Chem.Soc., Perkin Trans.I*, 1996, 853.
489 A. Rottmann and J. Liebscher, *Tetrahedron Lett.*, 1996, **37**, 359.
490 N. Langlois and N. Dahuron, *Tetrahedron Lett.*, 1996, **37**, 3993.
491 N. Langlois and N. Dahuron, *SynLett.*, 1996, 51.
492 D. Savithri, C. Leumann, and R. Scheffold, *Helv.Chim.Acta*, 1996, **79**, 288.
493 N.I. Carruthers, S.-C. Wong, and T.-M. Chan, *J. Chem.Res., Synop.*, 1996, 430.
494 S. Shuto, S. Ono, Y. Hase, N. Kamiyama, and A. Matsuda, *Tetrahedron Lett.*, 1996, **37**, 641.
495 V.N. Leibzon, L.M. Makarenkova, M.Y. Leonova, T.I. Egorova, and S.L. Ioffe, *Russ.J. Electrochem.*, 1996, **32**, 1120.
496 B.M. Trost and R.C. Lemoine, *Tetrahedron Lett.*, 1996, **37**, 9161.
497 B.B. Lohray, A.J. Reddy, and V. Bhushan, *Tetrahedron: Asymmetry*, 1996, **7**, 2411.
498 S. Azam, A.A. D'Souza, and P.B. Wyatt, *J. Chem.Soc., Perkin Trans. I*, 1996, 621.
499 K. Shinozaki, K. Mizuno, H. Wakamatsu, and Y. Masaki, *Chem.Pharm.Bull.*, 1996, **44**, 1823; K. Shinozaki, K. Mizuno, and Y. Masaki, *Heterocycles*, 1996, **43**, 11.
500 K. Shinozaki, K. Mizuno, H. Oda, and Y. Masaki, *Bull.Chem.Soc.Jpn.*, 1996, **69**, 1737.
501 P. Castejon, A. Moyano, M.A. Pericas, and A. Riera, *Tetrahedron*, 1996, **52**, 7063.
502 M. Pasto, P. Castejon, A. Moyano, M.A. Pericas, and A. Riera, *J. Org.Chem.*, 1996, **61**, 6033.
503 P. Castejon, A. Moyano, M.A. Pericas, and A. Riera, *Chem.-Eur.J.*, 1996, **2**, 1001
504 S.H. Kang and D.H. Ryu, *Bioorg.Med.Chem.Lett.*, 1995, **5**, 2959.
505 N. Meunier, U. Veith, and V. Jaeger, *Chem.Commun.*, 1996, 331.
506 D. Enders and U. Reinhold, *Liebigs Ann.*, 1996, 11.
507 D.Ma, J. Ma, W. Ding, and L. Dai, *Tetrahedron: Asymmetry*, 1996, **7**, 2365.
508 M. Prein and A. Padwa, *Tetrahedron Lett.*, 1996, **37**, 6981.
509 P. Nebois and A.E. Greene, *J. Org.Chem.*, 1996, **61**, 5210.
510 C. Shin, Y. Nakamura, Y. Yamada, Y. Yonezawa, K. Umemura, and J. Yoshimura, *Bull.Chem.Soc.Jpn.*, 1995, **68**, 3151.
511 R.A. Aitken and N. Karodia, *Chem.Commun.*, 1996, 2079.
512 M.T. Reetz, T.J. Strack, J. Kanand, and R. Goddard, *Chem.Commun.*, 733.
513 D.M. David, G.W. O'Meara, and S.G. Pyne, *Tetrahedron Lett.*, 1996, **37**, 5417.
514 F. Garro-Helion and F. Guibe, *Chem.Commun.*, 1996, 641.
515 B.M. Trost, D. Stenkamp, and S.R. Pulley, *Chem.-Eur.J.*, 1995, **1**, 568.
516 G.M. Davies, P.B. Hitchcock, D. Loakes, and D.W. Young, *Tetrahedron Lett.*, 1996, **37**, 5601.
517 M.M. Martinez, M.T. Garcia-Lopez, R. Herranz, and R. Gonzalez-Muniz, *Tetrahedron Lett.*, 1996, **37**, 2471.

518 B.H. Kim, Y.J. Chung, H.J. Ahn, and T.-K. Ha, *Bull.Korean Chem.Soc.*, 1996, **17**, 401.
519 C.S. Lee, N. Choy, Y.C. Son, C. Park, H. Choi, K.Y. Moon, W.H. Jung, S.C. Kim, and H. Yoon, *Bull.Korean Chem.Soc.*, 1996, **17**, 294.
520 M. Kranz and H. Kessler, *Tetrahedron Lett.*, 1996, **37**, 5359.
521 Y. Takemoto, J. Takeuchi, E. Matsui, and C. Iwata, *Chem.Pharm.Bull.*, 1996, **44**, 948.
522 B. Hartzoulakis, T.J. Rutherford, M.D. Ryan, and D. Gani, *Tetrahedron Lett.*, 1996, **37**, 6911.
523 M. Ohno, S. Kojima, Y. Shirakawa, and S. Eguchi, *Tetrahedron Lett.*, 1996, **37**, 9211.
524 R.M. Smith, D.P. Weiner, N.C. Chaturvedi, M.D. Thimblin, S.J. Raymond, and D.E. Hansen, *Bioorg.Chem.*, 1995, **23**, 397.
525 C.L. Nesloney and J.W. Kelly, *J. Org.Chem.*, 1996, **61**, 3127.
526 T. Shiraiwa, H. Miyazaki, M. Ohkubo, A. Ohta, A. Yoshioka, T. Yamane, and H. Kurokawa, *Chirality*, 1996, **8**, 197.
527 R. Kliukiene and A. Maroziene, *Chemija*, 1996, 80 (*Chem.Abs.*, 1996, **125**, 196274).
528 D.C.R. Hockless, R.C. Mayadunne, and S.B. Wild, *Tetrahedron: Asymmetry*, 195, **6**, 3031.
529 E. Toyota, K. Itoh, H. Sekizaki, and K. Tamizawa, *Bioorg.Chem.*, 1996, **24**, 150.
530 M. Calmes, J. Daunis, N. Mai, and F. Natt, *Tetrahedron Lett.*, 1996, **37**, 379.
531 C. Morice, P. Le Maux, and G. Simonneaux, *Tetrahedron Lett.*, 1996, **37**, 6701.
532 S. Caddick and K. Jenkins, *Tetrahedron Lett.*, 1996, **37**, 1301.
533 H.T. Stock and N.J. Turner, *Tetrahedron Lett.*, 1996, **37**, 6575.
534 F. Orsini, F. Pelizzoni, and C. Ghioni, *Amino Acids*, 1995, **9**, 135.
535 C. Lan and H. Jiaxin, *Zhongguo Yiyao Gongye Zazhi*, 1996, **27**, 274 (*Chem.Abs.*, 1997, **126**, 75212.
536 M.S. Cooper, A.W. Seton, M.F.G. Stevens, and A.D. Westwell, *Bioorg.Med.Chem. Lett.*, 1996, **6**, 2613.
537 L. Antolini, A. Forni, I. Moretti, F. Prati, E. Laurent, and D. Gestmann, *Tetrahedron: Asymmetry*, 1996, **7**, 3309.
538 K. Kawashiro, H. Sugahara, S. Sugiyama, and H. Hayashi, *Biotechnol.Bioeng.*, 1997, **53**, 26.
539 P. Clapes, I. Valverde, C. Jaime, and J.L. Torres, *Tetrahedron Lett.*, 1996, **37**, 417.
540 E. Pera, J.L. Torres, and P. Clapes, *Tetrahedron Lett.*, 1996, **37**, 3609.
541 Y.-F. Wang, K. Yakovlevsky, and A.L. Margolin, *Tetrahedron Lett.*, 1996, **37**, 5317.
542 Y. Kokuryo, T. Nakatani, K. Kobayashi, Y. Tamura, K. Kawada, and M. Ohtani, *Tetrahedron: Asymmetry*, 1996, **7**, 3545.
543 G. Cardillo, A. Tolomelli, and C. Tomasini, *J. Org.Chem.*, 1996, **61**, 8651.
544 S. Takayama, W.J. Moree, and C.-H. Wong, *Tetrahedron Lett.*, 1996, **37**, 6287.
545 S. Tokuyama and K. Hatano, *Baiosaiensu to Indatsutori*, 1996, **54**, 790.
546 H.E. Schoemaker, W.H.J. Boesten, B. Kaptein, E.C. Roos, Q.B. Broxterman, W.J. J. van der Tweel, and J. Kamphuis, *Acta Chem.Scand.*, 1996, **50**, 225.
547 N. Nishino, T. Arai, Y. Ueno, and M. Ohta, *Chem.Pharm.Bull.*, 1996, **44**, 212.
548 C.-K. Lee and K. Chin, *Enzyme Microb.Technol.*, 1996, **19**, 623.
549 D.V. Gokhale, K.B. Bastawde, S.G. Patil, U.R. Kalkote, R.R. Joshi, T. Ravindranathan, B.G. Gaikwad, V.V. Jogdand, and S. Nene, *Enzyme Microb.Technol.*, 1996, **18**, 353.
550 D.-C. Lee, S.-G. Lee, and H.-S. Kim, *Enzyme Microb.Technol.*, 1996, **18**, 35.
551 J.-Y. Houng , M.-L. Wu, and S.-T. Chen, *Chirality*, 1996, **8**, 418.

552 L.T. Kanerva, P. Csomos, O. Sundholm, G. Bernath, and F. Fueloep, *Tetrahedron: Asymmetry*, 1996, **7**, 1705.
553 F. Theil and S. Bauschuh, *Tetrahedron: Asymmetry*, 1996, **7**, 3565.
554 J.-Y. Houng, C.-L. Hsieh, and S.-T. Chen, *Biotechnol. Technol.*, 1996, **10**, 353.
555 V.S. Parmar, A. Singh, K.S. Bish, N. Kumar, Y.N. Belokon, K.A. Kochetkov, N.S. Ikonnikov, S.A. Orlova, V.I. Tararov, and T.F. Saveleva, *J. Org. Chem.*, 1996, **61**, 1223.
556 R. Ravichandran and S. Divakar, *Indian J. Chem., Sect. A: Inorg., Bioinorg., Phys., Theor., Anal. Chem.*, 1996, **35A**, 504.
557 T. Aoki, K. Shinohara, T. Kaneko, and E. Oikawa, *Macromolecules*, 1996, **29**, 4192.
558 N. Ogata, *Proc. SPIE-Int. Soc. Opt. Eng.*, 1996, 2779.
559 S. Tone, T. Masawaki, and K. Eguchi, *J. Membr. Sci.*, 1996, **118**, 31.
560 M. Yoshikawa, J. Izumi, and T. Kitao, *Chem. Lett.*, 1996, 611.
561 S. Kiyohara, M. Sasaki, K. Saito, K. Sugita, and T. Sugo, *J. Membr. Sci.*, 1996, **109**, 87.
562 A. Berthod, Y. Liu, C. Bagwill, and D.W. Armstrong, *J. Chromatogr. A*, 1996, **731**, 123.
563 J.H. Kennedy, *J. Chromatogr. A*, 1996, **725**, 219.
564 D. Kriz, M. Kempe, and K.H. Mosbach, *Sens. Actuators B*, 1996, **33**, 178; K.H. Mosbach and O. Ramstroem, *Bio/Technology*, 1996, **14**, 163; L.I. Anderson, I.A. Nicholls, and K.H. Mosbach, in Highly Selective Separations in Biotechnology, Ed. G. Street, Blackie, Glasgow, 1994, p.207.
565 M. Yoshikawa, J. Izumi, T. Kitao, and S. Sakamoto, *Macromolecules*, 1996, **29**, 8197.
566 M. Yoshikawa, J. Izumi, T. Kitao, S. Koya, and S. Sakamoto, *J. Membr. Sci.*, 1995, **108**, 171.
567 M. Kempe, *Anal. Chem.*, 1996, **68**, 1948.
568 A.L. Creagh, B.B.E. Hasenack, A. Van der Padt, E.J.R. Sudhoelter, and K. van't Riet, *Biotechnol. Bioeng.*, 1994, **44**, 690 (*Chem. Abs.*, 1994, **121**, 256262); see *Idem, Ibid.*, 1995, **45**, 95.
569 W.H. Pirkle, P.G. Murray, D.J. Rausch, and S.T. McKenna, *J. Org. Chem.*, 1996, **61**, 4769.
570 W.H. Pirkle, P.G. Murray, and S.R. Wilson, *J. Org. Chem.*, 1996, **61**, 4775.
571 M.H. Hyun, C.-S. Min, and K.K. Jyung, *Bull. Korean Chem. Soc.*, 1996, **17**, 409.
572 W.H. Pirkle and W.E. Bowen, *Tetrahedron: Asymmetry*, 1994, **5**, 773 (see also *Chem. Abs.*, 1994, **121**, 83936).
573 H. Bruckner and M. Leitenberger, *Chromatographia*, 1996, **42**, 683.
574 H. Ihara, K. Shudo, C. Hirayama, H. Hachisako, and K. Yamada, *Liq. Cryst.*, 1996, **20**, 807.
575 H. Bruckner and M. Wachsman, *J. Chromatogr. A*, 1996, **728**, 447.
576 J. Ma, L. Chen, and B. He, *J. Appl. Polym.*, 1996, **61**, 2029.
577 T. Kakuchi, T. Satoh, and K. Yokota, *Polym. Prepr.*, 1996, **37**, 487.
578 M.H. Hyun and J.-J. Ryoo, *J. Liq. Chromatogr. Relat. Technol.*, 1996, **19**, 2635.
579 G. Galaverna, R. Corradini, A. Dossena, R. Marchelli, and F. Dallavalle, *Chirality*, 1996, **8**, 189.
580 R.D. Lins, T.A. Soares, and R. Ferreira, *Z. Naturforsch. Teil. C: Biosci.*, 1996, **51**, 70.
581 Physical Origin of Homochirality in Life, AIP Conference Proceedings, 1996, AIP Press [*e.g.* W. A. Bonner, The Quest for Chirality (*Chem. Abs.*, 1997, **126**, 3168); A.J. McDermott, Resolution through parity violation mechanisms, p. 241 (*Chem. Abs.*, 1997, **126**, 16065)].

582 L. Keszthelyi, *Q. Rev. Biophys.*, 1995, **28**, 473.
583 P. Pabinec and M. Babincova, *ACH-Models Chem.*, 1995, **132**, 853 (*Chem. Abs.*, 1996, **124**, 168817) C. Bolm, F. Bienewald, and A. Seger, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1657; see also Ref. 129.
584 W.A. Bonner, *Origins Life Evol. Biosphere*, 1996, **26**, 27.
585 V. Avetisov and V. Goldanski, *Proc. Natl. Acad. Sci. USA*, 1996, **93**, 11435.
586 W. Wang and X. Sheng, *Wuli*, 1995, **24**, 595 (*Chem. Abs.*, 1996, **124**, 335757).
587 C.H. Goerbitz and B. Dahlus, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 1464.
588 C.H. Goerbitz and B. Dahlus, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 1754.
589 C.H. Goerbitz and B. Dahlus, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 1756.
590 B. Dahlus and C.H. Goerbitz, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 1759.
591 B. Dahlus and C.H. Goerbitz, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 1761.
592 B. Dahlus and C.H. Goerbitz, *Acta Chem. Scand.*, 1996, **50**, 544.
593 S. Suresh, S. Padmanabhan, and M. Vijayan, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 1313.
594 A. Pawlukojc, J. Leciejewicz, and I. Natkaniec, *Spectrochim. Acta, Part A*, 1996, **52**, 29.
595 A. Pertsemlidis, A.M. Saxena, A.K. Soper, T. Head-Gordon, and R.M. Glaeser, *Proc. Natl. Acad. Sci. USA*, 1996, **93**, 10769.
596 A. Mostad and S. Natarajan, *Cryst. Res. Technol.*, 1996, **31**, 295.
597 O. Angelova, V. Velikova, T. Kolev, and V. Radomirska, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 3252.
598 O. Angelova, R. Petrova, V. Radomirska, and T. Kolev, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 2218..
599 H. Nagata, Y. In, K. Tomoo, M. Doi, T. Ishida, and A. Wakahara, *Chem. Pharm. Bull.*, 1995, **43**, 1836.
600 E.A. Sudbeck, W.B. Gleason, and M.C. Etter, *J. Chem. Crystallogr.*, 1995, **25**, 555.
601 W. Ojala, E.A. Sudbeck, L.K. Lu, T.I. Richardson, R.E. Lovrien, and W.B. Gleason, *J. Am. Chem. Soc.*, 1996, **118**, 2131.
602 S. Suresh and M. Vijayan, *Acta Crystallogr., Sect. B: Struct. Sci.*, 1996, **C52**, 3252.
603 C.H. Goerbitz and J. Husdal, *Acta Chem. Scand.*, 1996, **50**, 796.
604 R.V. Krishnakumar and S. Natarajan, *Carbohydr. Res.*, 1996, **287**, 117 (for a correction, see *Idem, Ibid.*, **296**, C1.
605 W. Maniukiewicz, W. Kwiatkowski, and R.H. Blessing, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 1736.
606 A.M. Gonzalez-Cameno, D. Badia, E. Dominguez, M.I. Arriortua, M.K. Urtiaga, and X. Solans, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 3169.
607 L. Van Meervelt, K. De Wael, and T. Zeegers-Huyskens, *J. Mol. Struct.*, 1995, **356**, 183.
608 M. Crisma, G. Valle, V. Monaco, F. Formaggio, and C. Toniolo, *Z. Kristallogr.*, 1996, **211**, 557.
609 M. Crisma, G. Valle, F. Formaggio, C. Toniolo, and J. Kamphuis, *Z. Kristallogr.*, 1996, **211**, 559.
610 R. Chen, H. Li, H. Wang, and R. Wang, *Jiegou Huazue*, 1996, **15**, 273 (*Chem. Abs.*, 1996, **125**, 181974).

611 V.H. Vilchiz, R.E. Norman, and S.-C. Chang, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 696.
612 E. Bunuel, C. Cataviela, M.D. Diaz de Villegas, and J.A. Galvez, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 1456.
613 H. Beck and E. Egert, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 2253.
614 J. Wang, X.Yang, J. Cheng, Y. Xu, B. Liu, H. Wang, and D. Zhang, *J. Chem. Soc., Dalton Trans.*, 1996, 3889.
615 T. Ishida, Y. In, E. Kawamoto, T. Amano, J. Kanaya, M. Doi, T. Iwashita, and K. Nomoto, *Chem. Pharm. Bull.*, 1996, **44**, 1387.
616 A.S. Kolaskar and S. Sansant, *Int. J. Pept. Protein Res.*, 1996, **47**, 110.
617 Z. Gu, K. Ebisawa, and A. McDermott, *Solid State Nucl. Magn. Reson.*, 1996, **7**, 161.
618 G. Metz, M. Ziliox, and S.O. Smith, *Solid State Nucl. Magn. Reson.*, 1996, **7**, 155.
619 M.A.K. Rogers, R.D. Keenan, and T.K. Halstead, *Solid State Nucl. Magn. Reson.*, 1996, **6**, 47.
620 W. Kolodziejski and A. Corma, *Solid State Nucl. Magn. Reson.*, 1996, **7**, 67.
621 K. Schmidt-Rohr, *J. Am. Chem. Soc.*, 1996, **118**, 7601.
622 T.K. Pratum, *J. Magn. Reson., Ser. A*, 1995, **117**, 132.
623 V. Doetsch, R.E. Oswald, and G. Wagner, *J. Magn. Reson., Ser. B*, 1996, **110**, 107.
624 K. Hashimoto, K. Konno, and H. Shirahama, *J. Org. Chem.*, 1996, **61**, 4685.
625 V.T. Panushkin, A.V. Vashuk, and M.A. Maruson, *Zh. Strukt. Khim.*, 1996, **37**, 390.
626 N. Todeschi, J. Gharby-Benarous, F. Acher, R. Azerad, and J.-P. Girault, *J. Chem. Soc., Perkin Trans. II*, 1996, 1337.
627 V. Larue, J. Gharby-Benarous, N. Todeschi, F. Acher, R. Azerad, and J.-P. Girault, *J. Chim. Phys., Phys.-Chim., Biol.*, 1995, **92**, 1809.
628 V. Prabhu, B. Chatson, G. Abrams, and J. King, *J. Plant Physiol.*, 1996, **149**, 246.
629 D. Marcovici-Mizrahi, H.E. Gottlieb, V. Marks, and A. Nudelman, *J. Org. Chem.*, 1996, **61**, 8402.
630 E. Beausoleil and W.D. Lubell, *J. Am. Chem. Soc.*, 1996, **118**, 12902.
631 B.W. Gung and Z. Zhu, *J. Org. Chem.*, 1996, **61**, 6482.
632 R.S. Herrick, R.M. Jarret, T.P. Curran, D.R. Dragoli, M.B. Flaherty, S.E. Lindyberg, R.A. Slate, and L.C. Thornton, *Tetrahedron Lett.*, 1996, **37**, 5289.
633 R. Chinchilla, L.R. Falvello, and C. Najera, *J. Org. Chem.*, 1996, **61**, 7285.
634 B. Staubach and J. Buddrus, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1344.
635 Y. Fukushi, K. Shigematsu, J. Mizutani, and S. Tahara, *Tetrahedron Lett.*, 1996, **37**, 4737.
636 T. Asahi, H. Utsumi, Y. Itagaki, I. Kagomiya, and J. Kobayashi, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 1996, **A52**, 766.
637 V.F. Avila, *J. Laser Appl.*, 1996, **8**, 43.
638 O. Cantin, C. Cativiela, M.D. Diaz de Villegas, R. Navarro, and E.P. Urriolabeitia, *Tetrahedron: Asymmetry*, 1996, **7**, 2695.
639 T. Mizutani, S. Yagi, A. Honmanu, and H. Ogoshi, *J. Am. Chem. Soc.*, 1996, **118**, 5318.
640 Z. Deng, P.L. Polavarapu, S.J. Ford, L. Hecht, L.D. Barron, C.S. Ewig, and K. Jalkanen, *J. Phys. Chem.*, 1996, **100**, 2025.
641 H. Yazawa, R. Shishido, T. Nozawa, and T. Arikawa, *J. Mass Spectrom. Soc. Jpn.*, 1996, **44**, 229.
642 T. Arikawa and H. Yazawa, *Jpn. J. Appl. Phys., Part 1*, 1996, **35**, 2332.
643 A. Meffert and J. Grotemeyer, *Eur. Mass Spectrom.*, 1995, **1**, 594.
644 K.H. Lund and G. Bojesen, *Int. J. Mass Spectrom. Ion Processes*, 1996, **156**, 203.

645 L. Prokai, R. Ramanathan, J. Nawrocki, and J. Eyler, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1996, **25**, 117.
646 S.N. Davey, D.A. Leigh, J.P. Smart, L.W. Tetler, and A.M. Truscello, *Carbohydr. Res.*, 1996, **290**, 117.
647 M. Saraswathi and J.M. Miller, *Rapid Commun. Mass Spectrom.*, 1996, **10**, 1706.
648 Q.P. Lei and I.J. Amster, *J. Am. Soc. Mass Spectrom.*, 1996, **7**, 722.
649 M.A. Freitas, R.A.J. O'Hair, J.A.R. Schmidt, S.E. Tichy, and B.E. Plashko, *J. Mass Spectrom.*, 1996, **31**, 1086.
650 R.A.J. O'Hair, M.A. Freitas, and T.D. Williams, *J. Org. Chem.*, 1996, **61**, 2374.
651 R.D. Kinser, D.P. Ridge, G. Hvistendahl, B. Rasmussen, and E. Uggerud, *Chem. Eur. J.*, 1996, **2**, 1143.
652 S.R. Carr and C.J. Cassady, *J. Am. Soc. Mass Spectrom.*, 1996, **7**, 1203.
653 MN. Dookeran, T. Yakin, and A.G. Harrison, *J. Mass Spectrom.*, 1996, **31**, 500.
654 M. d'Ischia, A. Pezzella, G. Prota, D. Favretto, and P. Traldi, *J. Mass Spectrom.*, 1996, **31**, 885.
655 D. Favretto, P. Traldi, G. Resnati, and V.A. Soloshonok, *J. Fluorine Chem.*, 1996, **80**, 41.
656 S. Chen, *J. Trace Microprobe Tech.*, 1996, **14**, 399.
657 R. Opreau, L. Roman, and R. Sandulescu, *J. Pharm. Biomed. Anal.*, 1996, **14**, 1031.
658 C. Perier, J. Doumit, and J. Frey, *Amino Acids*, 1996, **10**, 273.
659 S.L. Ramsay, R.J. Waugh, T. Blumenthal, and J.H. Bowie, *Eur. J. Mass. Spectrom.*, 1995, **1**, 381.
660 R. Murugan and S. Mohan, *Indian J. Phys. B*, 1996, **70**, 67.
661 F. Gosselin, M. Di Renzo, T.H. Ellis, and W.D. Lubell, *J. Org. Chem.*, 1996, **61**, 7980.
662 M. Tsuboi, T. Ueda, K. Ushizawa, Y. Ezaki, S.A. Overman, and G.J. Thomas, *J. Mol. Struct.*, 1996, **379**, 43.
663 S.P. Robins, A. Duncan, N. Wilson, and B.J. Evans, *Clin. Chem.*, 1996, **42**, 1621.
664 M.M. Vorob'ev, A.A. Baranov, V.M. Belikov, and Y.I. Khurgin, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 618.
665 A.D. Headley, B. Patel, and E.T. Cheung, *Tetrahedron Lett.*, 1996, **37**, 6673.
666 V. Chis, O. Cozar, G. Damian, L. David, C. Cosma, R. Semeniuc, and R. Dragiou, *Stud. Univ. Babes-Bolyai, Phys.*, 1994, **39**, 17 (*Chem. Abs.*, 1997, **126**, 31601).
667 I. Kartal, F. Koksal, and F. Ucun, *J. Chem. Res., Synop.*, 1996, 118.
668 M. Kikuchi, M. Sakurai, and K. Nitta, *J. Chem. Eng. Data*, 1996, **41**, 1439.
669 M.K. Khoshkbarchi and J.H. Vera, *Ind. Eng. Chem. Res.*, 1996, **35**, 2735.
670 M.K. Khoshkbarchi and J.H. Vera, *A. I. Chem. J.*, 1996, **42**, 2354.
671 I. Brandariz, S. Fiol, and M. de V. Sastre, *J. Solution Chem.*, 1995, **24**, 1049.
672 J.S. Sukumar, G.N. Rao, K.V. Ramana, and M.S.P. Rao, *Indian J. Chem., Sect. A: Inorg., Bio-inorg., Phys., Theor., Anal. Chem.*, 1996, **35A**, 121.
673 S.P. Verevkin, S. Zueffle, H.-D. Beckhaus, and C. Ruechardt, *Thermochim. Acta*, 1996, **285**, 1.
674 P. Del Vecchio, R. Sabbah, L. Abate, G. Barone, and G. Della Gatta, *Calorim. Anal. Therm.*, 1995, **26**, 168.
675 G. Castronuovo, V. Elia, and F. Velleca, *J. Solution Chem.*, 1996, **25**, 971.
676 G. Castronuovo, V. Elia, and F. Velleca, *J. Solution Chem.*, 1995, **24**, 1209.
677 Y. Liu, B. Li, Y. Zhang, X. Bu, Y. Li, and R. Chen, *Chin. Sci. Bull.*, 1996, **412**, 117 (*Chem. Abs.*, 1996, **125**, 196298).
678 X.Chasseray, S.M. Lo, and D. Lemordant, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1995, **23**, 127.

679 A. Geiger, P. Burgstaller, H. von der Eltz, A. Roeder, and M. Famulok, *Nucleic Acids Res.*, 1996, **24**, 1029.
680 A. Stroinski and W. Kedzierski, *Rocz. Acad. Rol. Poznaniu*, 1994, **264**, 71 (*Chem. Abs.*, 1996, **125**, 320768).
681 H. Yang and C. Bohne, *J. Phys. Chem.*, 1996, **100**, 14533.
682 I.S. Antipin, I.I. Stoikov, A.R. Garifzyanov, and A. Konovalov, *Zh. Obshch. Khim.*, 1996, **66**, 402.
683 L. Mutihac, R. Mutihac, and H.-J. Buschmann, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1995, **23**, 167.
684 H. Tsukube, S. Shinoda, K. Uenishi, M. Shiode, and O. Yonemitsu, *Chem. Lett.*, 1996, 969.
685 T. Shinbo, T. Kanamori, K. Ogasawara, A. Yamasaki, T. Iwatsubo, T. Masuoka, and T. Yamaguchi, *Sen'i Gakkaishi*, 1996, **52**, 105 (*Chem. Abs.*, 1996, **124**, 291471).
686 S.S. Bodhankar, V. Harihar, and V.G. Gaikar, *Bioseparation*, 1996, **6**, 47.
687 F. Zhou, S. Yamada, K. Kakisaka, T. Furuya, Y. Iwai, and Y. Arai, *Solvent Extr. Res. Dev., Jpn.*, 1996, **3**, 56.
688 H. Johansson, G. Karlstrohm, B. Mattiasson, and F. Tjerneld, *Bioseparation*, 1995, **5**, 269.
689 K.J. Stine, A.R. Leventhal, D.P. Parazak, and J.Y.-J. Uang, *Enantiomers*, 1996, **1**, 41.
690 T. Cserhati and E. Forgacs, *Biochem. Mol. Biol. Int.*, 1995, **37**, 555.
691 S. Alaeddine and H. Nguyen, *Colloids Surf. B*, 1996, **6**, 71.
692 V. Basiuk and T.Y. Gromovoy, *Adsorption*, 1996, **2**, 145.
693 D.S. Grzegrczyk and G. Carta, *Chem. Eng. Sci.*, 1996, **51**, 807, 819.
694 F.N. Kapytsky, G.L. Starobinet, T.L. Yurkshtovish, and T.I. Borschchenskaya, *Vestn. Beloruss. Gos. Univ., Ser.2*, 1995, 6 (*Chem. Abs.*, 1996, **125**, 59023).
695 A. de Lucas, J.L. Valverde, P. Canizares, and L. Rodriguez, *Solvent Extr. Ion. Exch.*, 1996, **14**, 1115.
696 S. Melis, J. Markos, G. Cao, and M. Morbidelli, *Ind. Eng. Chem. Res.*, 1996, **35**, 1912.
697 W.R. Bowen and E.B. Moran, *Biotechnol. Bioeng.*, 1995, **48**, 559; *Ind. Eng. Chem. Res.*, 1996, **35**, 573.
698 M.T. Gude, H.H.J. Meuwissen, L.A.M. van der Wielen, and K.C.A.M. Luyben, *Ind. Eng. Chem. Res.*, 1996, **35**, 4700.
699 M.T. Gude, L.A.M. van der Wielen, and K.C.A.M. Luyben, *Fluid Phase Equilib.*, 1996, **116**, 110.
700 O.V. Kulikov and P.V. Lapschev, *Mendeleev Commun.*, 1996, 255.
701 A. Kumar and A. Maitra, *J. Indian Chem. Soc.*, 1996, **73**, 516.
702 R.J. Pieters and F. Diederich, *Chem. Commun.*, 1996, 2255.
703 M. Asakawa, C.L. Brown, D. Pasini, J.F. Stoddart, and P.G. Wyatt, *J. Org. Chem.*, 1996, **61**, 7234.
704 K. Araki, K. Inada, and S. Shinkai, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 72.
705 A. Metzger, K. Gloe, H. Stephan, and F.P. Schmidtchen, *J. Org. Chem.*, 1996, **61**, 2051.
706 T. Kawabata, A. Kuroda, E. Nakata, K. Takasu, and K. Fuji, *Tetrahedron Lett.*, 1996, **37**, 4153.
707 H. Chen, S. Ogo, and R.H. Fish, *J. Am. Chem. Soc.*, 1996, **118**, 4993.
708 S. Bhattacharya, S.N.G. Acharya, and A.R. Raju, *Chem. Commun.*, 1996, 2101.
709 K.T. Madhusan, N. Huang, E.H. Braswell, and J.R. Sokatch, *J. Bacteriol.*, 1997, **179**, 276.

710 S. Padmanabhan, E.J. York, J.M. Stewart, and R.L. Baldwin, *J. Mol.Biol.*, 1996, **257**, 726.
711 L. Misoguti, A.T. Varela, F.D. Nunes,V.S. Bagnato, F.E.A. Melo, J.M. Fillio, and S.C. Zilio, *Opt.Mater.*, 1996, **6**, 147.
712 A. Perczel, O. Farkas, and I.G. Csizmadia, *J. Am.Chem.Soc.*, 1996, **118**, 7809; *J. Comput.Chem.*, 1996, **17**, 821.
713 J.J. Navas, C. Aleman, and S. Munoz-Guerra, *J. Org.Chem.*, 1996, **61**, 6849.
714 E. Marcus, D.A. Keller, M. Shibata, R.L. Ornstein, and R. Rein, *Chem.Phys.*, 1996, **204**, 157.
715 V.N. Balaji, M.F. Chan, K. Ramnarayan, and S.N. Rao, *J. Struct.Biol.*, 1995, **115**, 267.
716 T.J. Marrone, M.K. Gilson, and J.A. McCammon, *J. Phys.Chem.*, 1996, **100**, 1439.
717 D.A. MacDonaill and D.A. Morton-Blake, *Philos.Mag.B*, 1996, **73**, 139.
718 Y. Ding and K. Krogh-Jespersen, *J. Comput.Chem.*, 1996, **17**, 338.
719 H. Nakajima, O. Takahashi, and O. Kikuchi, *J. Comput.Chem.*, 1996, **17**, 790.
720 A.G. Csaszar, *J. Phys.Chem.*, 1996, **100**, 3541.
721 M. Luo, H. Wang, X. Yan, S. Qu, and L. Ouyang, *Wuhan Daxue Xuebao, Ziran Kexueban*, 1995, **41**, 439.
722 L. Pogliani, *Croat.Chim.Acta*, 1996, **69**, 95.
723 G.A. Heal, P.D. Walker, M. Ramek, and P.G. Mezey, *Can.J. Chem.*, 1996, **74**, 1660.
724 J. Rulewski, P. Skurski, P. Dokurno, and J. Blazejowski, *Mol.Cryst.Liq.Cryst.Sci.-Technol., Sect.A*, 1996, **279**, 219.
725 M.K. Khoshkbarchi and J.H. Vera, *Ind.Eng.Chem.Res.*, 1996, **35**, 4319.
726 L. Serrano-Andres and M.P. Fuelscher, *J. Am.Chem.Soc.*, 1996, **118**, 12200.
727 P. Tarakeshwar and S. Manogoran, *Theochem*, 1996, **365**, 117.
728 J. Casado, J.T.L. Navarrete, and F.J. Ramirez, *Spectrochim.Acta, Part A*, 1995, **51**, 2347.
729 A.F. Weir, A.H. Lowrey, and R.W. Williams, *Theochem*, 1996, **362**, 339.
730 V. Barone, C. Adamo, A. Grand, F. Jolibois, Y. Brunel, and R. Subra, *J. Am.Chem.Soc.*, 1995, **117**, 12618.
731 P.D. Godfrey, R.D. Brown, and F.M. Rogers, *J. Mol.Struct.*, 1996, **376**, 65.
732 J.J. Queralt, V.S. Safont, V. Molinez, and J. Andres, *Theor.Chim.Acta*, 1996, **94**, 247; J. Andres, J.J. Queralt, V.S. Safont, M. Canle, and J.A. Santaballa, *J. Phys.Chem.*, 1996, **100**, 3561.
733 J. Andres, J.J. Queralt, V.S. Safont, M. Canle, and J.A. Santaballa, *J. Phys.Org. Chem.*, 1996, **9**, 371.
734 J.L. Radkiewicz, S. Clare, and K.N. Houk, *J. Am.Chem.Soc.*, 1996, **118**, 9148
735 H. Qian and S.I. Chan, *J. Mol.Biol.*, 1996, **261**, 279.
736 I. Luque, O.I. Mayorga, and E. Friere, *Biochemistry*, 1996, **35**, 13681.
737 M. Rakocevic, *J. Theor.Biol.*, 1996, **183**, 345.
738 T.O. Zaikova, O.I. Lomovskii, and A.V. Rukavishnikov, *Zh.Obshch.Khim.*, 1996, **66**, 643.
739 N. Fujii, *Seikagaku*, 1996, **68**, 1641 (*Chem.Abs.*, 1996, **125**, 320697).
740 N. Fujii, Y. Momose, and K. Harada, *Int.J. Pept.Protein Res.*, 1996, **48**, 118.
741 S. Duan, X.Zhang, N. Xie, C. Fan, J. Liu, and S. Fu, *Sepu*, 1996, **14**, 484 (*Chem.Abs.*, 1996, **125**, 28691).
742 H.N. Poinar, M. Hoess, and J.L. Bada, *Science*, 1996, **272**, 864.
743 A.M. Child, *ACS Symp.Ser.*, 1996, **625**(Archaeological Chemistry), 366.
744 A.F. Spatola, K. Darlak, and P. Romanovskis, *Tetrahedron Lett.*, 1996, **37**, 591.

745 T. Kaiser, G.J. Nicholson, H.J. Kohlbau, and W. Voelter, *Tetrahedron Lett.*, 1996, **37**, 1187.
746 M. Reist, P.-A. Carrupt, B. Testa, S. Lehmann, and J.J. Hansen, *Helv. Chim. Acta*, 1996, **79**, 767.
747 H. Matsunaga, T. Iida, T. Santa, T. Fukushima, H. Homma, and K. Imai, *Anal. Chem.*, 1996, **68**, 2850.
748 J.M. Antelo, F. Arce, and J. Crugeiras, *J. Chem. Soc., Perkin Trans. II*, 1995, 2275.
749 X.L. Armesto, L.M. Canle, M.V. Garcia, M. Losada, and J.A. Santaballa, *J. Phys. Org. Chem.*, 1996, **9**, 552.
750 L. Abia, X.L. Armesto, L.M. Canle, M.V. Garcia, M. Losada, and J.A. Santaballa, *Bull. Soc. Chim. Belg.*, 1996, **105**, 349.
751 M.C. Brown, J.M. Lepree, and K.A. Connors, *Int. J. Chem. Kinet.*, 1996, **28**, 791.
752 M.S. Ramachandran, D. Easwaramoorthy, and S. Vasanthkumar, *J. Org. Chem.*, 1996, **61**, 4336.
753 B.T. Gowda and K. Geetha, *Oxid. Commun.*, 1996, **19**, 75.
754 M.N. Qabar and M. Kahn, *Tetrahedron Lett.*, 1996, **37**, 965.
755 M. Peric, B. Vercek, and A. Petric, *Acta Chim. Slov.*, 1996, **43**, 163.
756 R.S. Atkinson, E. Barker, and M.J. Sutcliffe, *Chem. Commun.*, 1996, 1051.
757 Y. Kato, H. Yamada, and Y. Asano, *J. Mol. Catal. B: Enzym.*, 1996, **1**, 151.
758 W. Duczek, J. Deutsch, S. Vieth, and H.-J. Niclas, *Synthesis*, 1996, 37.
759 C. Ebert, L. Gardossi, and P. Linda, *Tetrahedron Lett.*, 1996, **37**, 9377.
760 J.S. Debenham and B. Fraser-Reid, *J. Org. Chem.*, 1996, **61**, 432.
761 J.C. Pelletier and D.P. Hesson, *SynLett.*, 1995, 1141.
762 M. Dekhane, K.T. Douglas, and P. Gilbert, *Tetrahedron Lett.*, 1996, **37**, 1883.
763 M. Adamczyk and J.E. Fishpaugh, *Tetrahedron Lett.*, 1996, **37**, 7171.
764 R.A. Bank, E.J. Jansen, B. Beckman, and J.M. te Koppele, *Anal. Biochem.*, 1996, **240**, 167.
765 H. Nakamura, S. Asai, and M. Yamada, *Chem. Eng. Sci.*, 1996, **51**, 1343.
766 H. Li, T. Sakamoto, M. Kato, and Y. Kikugawa, *Synth. Commun.*, 1995, **25**, 4045.
767 E.M. Khalil, N.L. Subasinghe, and R.L. Johnson, *Tetrahedron Lett.*, 1996, **37**, 3441.
768 M. Gormanns and H. Ritter, *Tetrahedron*, 1995, **51**, 3525.
769 T. Apelqvist and D. Wensbo, *Tetrahedron Lett.*, 1996, **37**, 1471.
770 F. Cavelier and C. Enjalbal, *Tetrahedron Lett.*, 1996, **37**, 5131.
771 J.R. Hwu, M.L. Jain, S.-C. Tsay, and G.H. Hakimelahi, *Tetrahedron Lett.*, 1996, **37**, 2035.
772 K.M. Sivanandaiah, V.V.S. Babu, and B.P. Gangadhar, *Tetrahedron Lett.*, 1996, **37**, 5989.
773 R. Frank and M. Schutkowski, *Chem. Commun.*, 1996, 2509.
774 S. Lemaire-Andoire, M. Savignac, J.-P. Genet, and J.-M. Bernard, *Ind. Chem. Libr.*, 1996, **8**, 416.
775 D. Ma and J. Yao, *Tetrahedron: Asymmetry*, 1996, **7**, 3075.
776 F.R. Hewgill, U. Hoefler, R.C. Power, and H.B. Stegmann, *Magn. Reson. Chem.*, 1996, **34**, 47.
777 D. Barbry and S. Torchy, *Synth. Commun.*, 1996, **26**, 3919.
778 R.W.A. Luke, P.G.T. Boyce, and E.K. Dorling, *Tetrahedron Lett.*, 1996, **37**, 263.
779 N.J. Ede, K.H. Ang, I.W. James, and A.M. Bray, *Tetrahedron Lett.*, 1996, **37**, 9097.
780 P. Pevarello, R. Amici, V. Pinciroli, and M. Varasi, *Org. Prep. Proced. Int.*, 1996, **28**, 179.
781 J.M. Ramanjulu and M.M. Joullie, *Synth. Commun.*, 1996, **26**, 1379.

782 S.G. Zlotin, I.V. Sharova, and O.A. Lukyanov, *Izv.Akad.Nauk, Ser.Khim.*, 1996, 1761.
783 I. Ugi, A. Demharter, W. Hoerl, and T. Schmid, *Tetrahedron*, 1996, **52**, 11657.
784 J.-D. Bourzat, M. Vuilhorgne, L.P. Rivory, J. Robert, and A. Commercon, *Tetrahedron Lett.*, 1996, **37**, 6327.
785 V. Ferey, L. Toupet, T. Le Gall, and C. Mioskowski, *Angew.Chem., Int.Ed.Engl.*, 1996, **35**, 430.
786 Y. Fukuyama, Y. Kiriyama, and M. Kodama, *Tetrahedron Lett.*, 1996, **37**, 1261.
787 G. Alvaro and D. Savoia, *Tetrahedron: Asymmetry*, 1996, **7**, 2083.
788 C.F. Jones, K.J. Howard, and J.S. Smith, *Tetrahedron Lett.*, 1996, **37**, 1707, 1711.
789 T. Henle, R. Deppisch, and E. Ritz, *Nephrol., Dial., Transplant.*, 1996, **11**, 1718.
790 T. Iwamoto, T. Kan, S. Katsumura, and Y. Ohfune, *SynLett.*, 1996, 269.
791 B. Kojic-Prodic, V. Milinkovic, J. Kidric, P. Pristovsek, S. Horvat, and A. Jakas, *Carbohydr.Res.*, 1995, **279**, 21.
792 V.A. Yaylayan and A. Huyghues-Despointes, *Carbohydr.Res.*, 1996, **286**, 179.
793 A. Lapolla, D. Fedele, R. Aronica, O. Curcuruto, M. Hamdan, S. Catinella, R. Seraglia, and P. Traldi, *J. Mass Spectrom.*, 1995, **30**, 569.
794 X. Zhang and P. Ulrich, *Tetrahedron Lett.*, 1996, **37**, 4667.
795 A.F. Parsons and R.M. Pettifer, *Tetrahedron Lett.*, 1996, **37**, 1667.
796 C.M. Thompson and J. Lin, *Tetrahedron Lett.*, 1996, **37**, 8979.
797 Q. Wang, G. Luo, R. Wang, W. Zhou, and Y. Zhao, *J. Chromatogr., A*, 1996, **745**, 263.
798 B. Lal and A.K. Gangopadhyay, *Tetrahedron Lett.*, 1996, **37**, 2483.
799 D.R. Kent, W.L. Cody, and A.M. Doherty, *Tetrahedron Lett.*, 1996, **37**, 8711.
800 L. Beyer, J.J. Criado, E. Garcia, F. Lessmann, M. Medarde, R. Richter, and E. Rodriguez, *Tetrahedron*, 1996, **52**, 6233.
801 C.W. Jefford, F. de Villedon de Naide, and K. Sienkiewicz, *Tetrahedron: Asymmetry*, 1996, **7**, 1069.
802 R. Grigg and G. Yoganathan, *Tetrahedron: Asymmetry*, 1996, **7**, 273.
803 A.G. Griesbeck, *Liebigs Ann.*, 1996, 1953.
804 J.D. Rush and B.H. Bielski, *Free Radical Res.*, 1995, **22**, 571.
805 L.A. Carpino, M. Beyermann, H. Wenschuh, and M. Bienert, *Acc.Chem.Res.*, 1996, **29**, 268.
806 H. Wenschuh, M. Beyermann, R. Winter, M. Bienert, D. Ionescu, and L. A. Carpino, *Tetrahedron Lett.*, 1996, **37**, 5483.
807 C. Kaduk, H. Wenschuh, M. Beyermann, K. Forner, L. A. Carpino, and M. Bienert, *Lett.Pept.Sci.*, 1996, **2**, 285.
808 J.A. Sowinski and P.L. Toogood, *J. Org.Chem.*, 1996, **61**, 7671.
809 S. Sengupta and D. Das, *Synth.Commun.*, 1996, **26**, 113.
810 C.A. Busacca, Y. Dong, and E.M. Spinelli, *Tetrahedron Lett.*, 1996, **37**, 2935.
811 Z. Khan, Z.A. Rafiquee, and A.A. Khan, *J. Indian Chem.Soc.*, 1996, **73**, 305.
812 R. Rodriguez and F. Bermejo, *Tetrahedron Lett.*, 1996, **37**, 5581.
813 G.M. Taylor, S.J. Baker, A. Gedney, D.J. Pearson, and G.E.M. Sibley, *Tetrahedron Lett.*, 1996, **37**, 1297.
814 M. Adamczyk and J. R. Fishpaugh, *Tetrahedron Lett.*, 1996, **37**, 4305.
815 L.M. Gayo and M.J. Suto, *Tetrahedron Lett.*, 1996, **37**, 4915.
816 K.M. Sliedregt, A. Schouten, J. Kroon, and R.M.J. Liskamp, *Tetrahedron Lett.*, 1996, **37**, 4237.
817 P. Ruzza, A. Calderan, and G. Borin, *Tetrahedron Lett.*, 1996, **37**, 5191.
818 A. Karlstrom and A. Unden, *Tetrahedron Lett.*, 1996, **37**, 4243.

819 N. Galeotti, J. Coste, P. Bedos, and P. Jouin, *Tetrahedron Lett.*, 1996, **37**, 3997.
820 T.R. Boehlow and C.D. Spilling, *Nat. Prod. Lett.*, 1995, **7**, 1.
821 D.J. Ager and I. Prakas, *Synth. Commun.*, 1996, **26**, 3865.
822 M.C. Cleij, P. Scrimin, P. Tecilla, and U. Tonellato, *Langmuir*, 1996, **12**, 2956.
823 Y. Fukushima, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 2269.
824 N. Ohtani, I. Takeishi, Y. Ioue, and S. Matingami, *Nihon Yukagakkaishi*, 1996, **45**, 181 (*Chem. Abs.*, 1996, **124**, 317810).
825 K. Ohjubo, Y. Funakoshi, and T. Sagawa, *Polymer*, 1996, **37**, 3993.
826 C.J. Salomon, E.G. Mata, and O.A. Mascaretti, *J. Chem. Soc., Perkin Trans. I*, 1996, 995.
827 A. Trecziak and W. Bannwarth, *Synthesis*, 1996, 1433.
828 P.D. Howes and P.W. Smith, *Tetrahedron Lett.*, 1996, **37**, 6595.
829 A. Mordini, M. Valacchi, S. Pecchi, A. Degl'Innocenti, and G. Reginato, *Tetrahedron Lett.*, 1996, **37**, 5209.
830 S.Y. Tamura, J.E. Semple, R.J. Ardecky, P. Leon, S.H. Carpenter, Y. Ge, B.M. Shamblin, M.I. Weinhouse, W.C. Ripka, and R.F. Nutt, *Tetrahedron Lett.*, 1996, **37**, 4109.
831 P. Nagafuji and M. Cushman, *J. Org. Chem.*, 1996, **61**, 4999.
832 Y. Takeuchi, A. Yamada, T. Suzuki, and T. Koizumi, *Tetrahedron*, 1996, **52**, 225.
833 S. Laschat, R. Froelich, and B. Wibberling, *J. Org. Chem.*, 1996, **61**, 2829.
834 A. Spaltenstein, J.J. Leban, J.J. Huang, K.R. Reinhardt, O.H. Viveros, J. Sigafoos, and R. Crouch, *Tetrahedron Lett.*, 1996, **37**, 1343.
835 S. Hanessian and P.V. Devasthale, *Tetrahedron Lett.*, 1996, **37**, 987.
836 A. Kamal, B.S.P. Reddy, and B.S.N. Reddy, *Tetrahedron Lett.*, 1996, **37**, 2281.
837 D.L. Wright, M. Weekly, R. Groff, and M.C. McMills, *Tetrahedron Lett.*, 1996, **37**, 2165.
838 E. Lee, K.S. Li, and J. Lim, *Tetrahedron Lett.*, 1996, **37**, 1445.
839 P. O'Brien and S. Warren, *Tetrahedron Lett.*, 1996, **37**, 4271.
840 S. Narasimhan, S. Madhavan, and K.G. Prasad, *Synth. Commun.*, 1996, **26**, 703.
841 S. Devadder, P. Verheyden, H.C.M. Jaspers, G. Van Binst, and D. Tourwe, *Tetrahedron Lett.*, 1996, **37**, 703.
842 B. Wagner, R. Beugelmans, and J. Zhu, *Tetrahedron Lett.*, 1996, **37**, 6557.
843 L.F. Captain, X. Xia, and D.C. Liotta, *Tetrahedron Lett.*, 1996, **37**, 4293.
844 K.A. Novachek and A.I. Meyers, *Tetrahedron Lett.*, 1996, **37**, 1743.
845 M. Gude, U. Piarulli, D. Potenza, B. Salom, and C. Gennari, *Tetrahedron Lett.*, 1996, **37**, 8589; see also D.W.P.M. Lowik, S.J.E. Mulders, Y. Cheng, Y. Shao, and R.M.J. Liskamp, *Tetrahedron Lett.*, 1996, **37**, 8253.
846 A.P. Mehrotra and D. Gani, *Tetrahedron Lett.*, 1996, **37**, 6915.
847 J. Nielsen and L.O. Lyngso, *Tetrahedron Lett.*, 1996, **37**, 8439.
848 M.P. Doyle and A.V. Kalinin, *Tetrahedron Lett.*, 1996, **37**, 1371.
849 L.M. Harwood, T.T. Tucker, R. Angell, and H. Finch, *Tetrahedron Lett.*, 1996, **37**, 4217.
850 M.P. Gamble, J.R. Studley, and M. Wills, *Tetrahedron Lett.*, 1996, **37**, 2853.
851 J. Wang, Y.Okada, Z. Wang, Y. Wang, and W. Li, *Chem. Pharm. Bull.*, 1996, **44**, 2189.
852 R. Pires, S. Fehn, A. Golubev, D. Winkler, and K. Burger, *Amino Acids*, 1996, **11**, 301.
853 M.R. Paleo and F.J. Sardina, *Tetrahedron Lett.*, 1996, **37**, 3403.
854 H. Collet, C. Bied, L. Mion, J. Taillades, and A. Commeyras, *Tetrahedron Lett.*, 1996, **37**, 9043.

855 W.D. Fuller, M. Goodman, F.R. Naider, and Y.-F. Zhu, *Biopolymers*, 1996, **40**, 183.
856 M. Paris, J.-A. Fehrentz, A. Heitz, A. Loffet, and J. Martinez, *Tetrahedron Lett.*, 1996, **37**, 8489.
857 P. Chevallet, J.-A. Fehrentz, K. Kiec-Kononowicz, C. Devin, J. Castel, A. Loffet, and J. Martinez, *Lett. Pept. Sci.*, 1996, **2**, 297.
858 C. Pothion, J.-A. Fehrentz, A. Aumelas, A. Loffet, and J. Martinez, *Tetrahedron Lett.*, 1996, **37**, 1027.
859 J.J. Leban and K.L. Colson, *J. Org. Chem.*, 1996, **61**, 228.
860 F.J. Sardina and H. Rapoport, *Chem. Rev.*, 1996, **96**, 1825; M. Tisler and P. Kolar, *Adv. Heterocyclic Chem.*, 1995, **64**, 1.
861 A. Studer, *Synthesis*, 1996, 793.
862 D.K. Mohapatra and A. Datta, *SynLett.*, 1996, 1129.
863 N.L. Benoiton, *Biopolymers*, 1996, **40**, 245.
864 J. Ezquerra, C. Lamas, A. Pastor, P. Alvarez, J.J. Vaquero, and W.G. Prowse, *Tetrahedron Lett.*, 1996, **37**, 5813.
865 B. Jung, H. Kim, and B.S. Park, *Tetrahedron Lett.*, 1996, **37**, 4019.
866 R.M. Ortuno, J. Ibarzo, A. Alvarez-Larena, and J.F. Piniella, *Tetrahedron Lett.*, 1996, **37**, 4059.
867 M. Adachi, T. Sasatani, N. Chomei, and S. Takada, *Tetrahedron Lett.*, 1996, **37**, 8871.
868 D.R. Hutchison, N.K. Nayyar, and M.J. Martinelli, *Tetrahedron Lett.*, 1996, **37**, 2887.
869 A. Detsi, J. Markopoulos, and O. Igglessi-Markopoulou, *Chem. Commun.*, 1996, 1323.
870 E. Kawamoto, T. Amano, J. Kanayama, Y. In, M. Doi, T. Ishida, T. Iwashita, and K. Nomoto, *J. Chem. Soc., Perkin Trans. II*, 1996, 1331.
871 B.A. Dressman, L.A. Spangle, and S.W. Kaldor, *Tetrahedron Lett.*, 1996, **37**, 937.
872 N.-X.Wang, J.-S. Li, and D.-B. Zhu, *Chin. J. Chem.*, 1996, **14**, 167.
873 A. Bianco, M. Maggini, G. Scorrano, C. Toniolo, G. Marconi, C. Villani, and M. Prato, *J. Am. Chem. Soc.*, 1996, 118, 4072.
874 L. Gan, D. Zhon, C. Luo, H. Tan, C. Huang, M. Lue, J. Pan, and Y. Wu, *J. Org. Chem.*, 1996, **61**, 1954.
875 S.R. Wilson, Y. Wang, J. Cao, and X. Tan, *Tetrahedron Lett.*, 1996, **37**, 775.
876 R.-H. Mattern, *Tetrahedron Lett.*, 1996, **37**, 291.
877 T. Okawa and S. Eguchi, *Tetrahedron Lett.*, 1996, **37**, 81.
878 J. Howarth and K. Gillespie, *Tetrahedron Lett.*, 1996, **37**, 6011.
879 A.W. Schwartz, *Chem. Biol.*, 1996, **3**, 515.
880 J. Bujdak, E. Eder, Y. Yongyai, K. Faybikova, and B.M. Rode, *J. Inorg. Biochem.*, 1996, **61**, 69; J. Bujdak, H.L. Son, Y. Yongyai, and B.M. Rode, *Catal. Lett.*, 1996, **37**, 267.
881 E. Imai, S. Sakurazawa, H. Honda, and K. Matsuno, *Viva Origino*, 1996, **24**, 159.
882 P. Brungs, K. Danielmeier, J. Jakobi, C. Nothhelfer, A. Stahl, A. Zietlow, and E. Steckhan, *J. Chim. Phys., Phys.-Chim., Biol.*, 1996, **93**, 575.
883 D.A. Frey, N. Wu, and K.D. Moeller, *Tetrahedron Lett.*, 1996, **37**, 8317.
884 I. Ojima, *Adv. Asymmetric Synth.*, 1995, **1**, 95.
885 C. Palomo, J.M. Aizpurua, C. Cuevas, R. Urchegui, and A. Linden, *J. Org. Chem.*, 1996, **61**, 4400.
886 K. Hervouet and A. Guingant, *Tetrahedron: Asymmetry*, 1996, **7**, 421.
887 G. Delle Monache, M.C. Di Giovanni, F. Maggio, D. Misiti, and G. Zappia, *Synthesis*, 1995, 1155.

888 D. Misiti, G. Zappia, and G. Delle Monache, *Liebigs Ann.*, 1996, 235; see also N. Dell'Uomo, M.C. Di Giovanni, D. Misiti, G. Zappia, and G. Delle Monache, *Tetrahedron: Asymmetry*, 1996, **7**, 181.
889 D.A. Goff and R.N. Zuckermann, *Tetrahedron Lett.*, 1996, **37**, 6247.
890 I. Bernabei, R. Castagnani, F. De Angelis, E. De Fusco, F. Giannessi, D. Misiti, S. Muck, N. Scafetta, and M.O. Tinti, *Chem.-Eur.J.*, 1996, **2**, 826.
891 S. Nomoto, A. Shimoyama, S. Shiraishi, and D. Sahara, *Biosci.Biotechnol.Biochem.*, 1996, **60**, 1851.
892 J. Matsubara, K. Otsubo, S. Morita, T. Ohtani, T. Kawano, and M. Uchida, *Heterocycles*, 1996, **43**, 133.
893 C.J. Easton, C.A. Hutton, M.C. Merrett, and E.R.T. Tiekink, *Tetrahedron*, 1996, **52**, 7025.
894 B. Moissec, H. Rudyk, L. Toupet, R. Danion-Bougot, and D. Danion, *J. Chem.Soc., Perkin Trans. I*, 1996, 1833.
895 M. Yamada, K. Nakao, T. Fukui, and K. Nunami, *Tetrahedron*, 1996, **52**, 5751.
896 K. Goodall and A.F. Parsons, *Tetrahedron*, 1996, **52**, 6739.
897 P. Molina, P.M. Fresneda, and S. Garcia-Zafra, *Tetrahedron Lett.*, 1996, **37**, 9353.
898 K. Kubo, S. Yaegashi, K. Sasaki, T. Sakurai, and H. Inoue, *Tetrahedron Lett.*, 1996, **37**, 5917.
899 A. Avenoza, C. Cativiela, and M.A. Fernandez-Recio, *Tetrahedron: Asymmetry*, 1996, **7**, 721.
900 S. Hanessian, W. Wang, and Y. Gai, *Tetrahedron Lett.*, 1996, **37**, 7477.
901 M.T. Reetz, T.J. Strack, F. Mutulis, and R. Goddard, *Tetrahedron Lett.*, 1996, **37**, 9293.
902 T. Ibuka, M. Akaji, N. Mimura, H. Habashita, K. Nakai, H. Tamamura, N. Fujii, and Y. Yamamoto, *Tetrahedron Lett.*, 1996, **37**, 2849.
903 V. Denniel, P. Bauchat, D. Danion, and R. Danion-Bougot, *Tetrahedron Lett.*, 1996, **37**, 5111.
904 M. Kirihata, M. Fukuari, T. Izukawa, and I. Ichimoto, *Amino Acids*, 1995, **9**, 317.
905 K. David, A. Greiner, J. Gore, and B. Cazes, *Tetrahedron Lett.*, 1996, **37**, 3333.
906 K. David, C. Ariente, A. Greiner, J. Gore, and B. Cazes, *Tetrahedron Lett.*, 1996, **37**, 3335.
907 J.M. Receveur, M.L. Roumestant, and P. Viallefont, *Amino Acids*, 1995, **9**, 391.
908 M. Marinozzi, B. Natalini, G. Costantio, R. Pellicciari, V. Bruno, and F. Nicoletti, *Farmaco*, 1996, **51**, 121.
909 P. Meffre, L. Gauzy, E. Branquet, P. Durand, and F. Le Goffic, *Tetrahedron*, 1996, **52**, 11215.
910 A.R. Vaino and W. A. Szarek, *Chem.Commun.*, 1996, 2351.
911 T. Wakamiya, T. Nishida, R. Togashi, K. Saruta, J. Yasuoka, and S. Kusumoto, *Bull.Chem.Soc.Jpn.*, 1996, **69**, 465.
912 B.M. Duggan, R. Laslett, and J.F.K. Wilshire, *Aust.J. Chem.*, 1996, **49**, 541.
913 S.A. Kolodziej and G.R. Marshall, *Int.J. Pept.Protein Res.*, 1996, **48**, 274.
914 P. Wipf and S. Vankatraman, *Tetrahedron Lett.*, 1996, **37**, 4659.
915 R. Tokunoh, H. Tomiyama, M. Sodeoka, and M. Shibasaki, *Tetrahedron Lett.*, 1996, **37**, 2449.
916 A. Barco, S. Benetti, C. De Risi, G.P. Pollini, R. Romagnoli, and V. Zanirato, *Tetrahedron Lett.*, 1996, **37**, 7599.
917 L. Williams, D.B. Hauze, and M.M. Joullie, *Heterocycl.Commun.*, 1996, **2**, 55.
918 N.G. Anderson, D.A. Lust, K.A. Colapret, J.H. Simpson, M.F. Malley, and J.Z. Gougoutas, *J. Org.Chem.*, 1996, **61**, 7955.

919 G. Stavropoulos, V. Magafa, K. Karagiannis, and S. Papaioannou, *Epitheor.Klin. Farmacokokinet., Int.Ed.*, 1995, **9**, 103 (*Chem.Abs.*, 1996, **125**, 59016).
920 M.E. Solomon, C.L. Lynch, and D.H. Rich, *Synth.Commun.*, 1996, **26**, 2723.
921 R.J. Cherney and L. Wang, *J. Org.Chem.*, 1996, **61**, 2544.
922 K.J. Hale, J. Cai, and V.M. Delisser, *Tetrahedron Lett.*, 1996, **37**, 9345.
923 C. Dugave and A. Menez, *J. Org.Chem.*, 1996, **61**, 6067.
924 R.F.W. Jackson, D. Turner, and M.H. Block, *SynLett.*, 1996, 862.
925 B.J. Dorgan and R.F.W. Jackson, *SynLett.*, 1996, 859.
926 F. D'Aniello, M. Falorni, A. Mann, and M. Taddei, *Tetrahedron: Asymmetry*, 1996, **7**, 1217.
927 D.B. Berkowitz, M. Eggen, Q. Shen, and R.K. Shoemaker, *J. Org.Chem.*, 1996, **61**, 4666.
928 A. Avenoza, C. Cativiela, J.M. Peregrina, and M.M. Zurbano, *Tetrahedron: Asymmetry*, 1996, **7**, 1555.
929 A.P. Kozikowski, Q. Ding, and S. Spiegel, *Tetrahedron Lett.*, 1996, **37**, 3279.
930 F.A. Davis and G.V. Reddy, *Tetrahedron Lett.*, 1996, **37**, 4349.
931 D.B. Berkowitz and M.K. Smith, *Synthesis*, 1996, 39.
932 A.G. Griesbeck and J. Hirt, *Liebigs Ann.*, 1995, 1957.
933 M. Seki and K. Matsumoto, *Tetrahedron Lett.*, 1996, **37**, 3165.
934 T.P. Curran, N.M. Chandler, R.J. Kennedy, and M.T. Keaney, *Tetrahedron Lett.*, 1996, **37**, 1933.
935 K.M.J. Brands, G. Marchesini, J.M. Williams, U.-H. Dolling, and P.J. Reider, *Tetrahedron Lett.*, 1996, **37**, 2919.
936 K. Hashimoto, Y. Shima, and H. Shirahama, *Heterocycles*, 1996, **42**, 489.
937 M. Horikawa and H. Shirahama, *SynLett.*, 1996, 95.
938 S. Yoshifuji and M. Kaname, *Chem.Pharm.Bull.*, 1995, **43**, 1617.
939 G. Pandey and D. Chakrabarti, *Tetrahedron Lett.*, 1996, **37**, 2285.
940 R. Sharma and W.D. Lubell, *J. Org.Chem.*, 1996, **61**, 202.
941 K. Tanaka, H. Suzuki, and H. Sawanishi, *Heterocycles*, 1996, **43**, 205.
942 T. Nagasaka and T. Imai, *Chem.Pharm.Bull.*, 1995, **43**, 1081.
943 R.M. Williams and J. Cao, *Tetrahedron Lett.*, 1996, **37**, 5441.
944 A. Karlstroem and A. Unden, *Int.J. Pept.Protein Res.*, 1996, **48**, 305.
945 R. Shankar and A.I. Scott, *Heterocycles*, 1996, **42**, 145.
946 D.R. Adams, P.D. Bailey, I.D. Collier, J.D. Heffernan, and S. Stokes, *Chem. Commun.*, 1996, 349.
947 H.Y. Kim, K. Stein, and P.L. Toogood, *Chem.Commun.*, 1996, 1683.
948 P.J. Murray and I.D. Starkey, *Tetrahedron Lett.*, 1996, **37**, 1875.
949 E. Juaristi, D. Quintana, M. Balderas, and E. Garcia-Perez, *Tetrahedron: Asymmetry*, 1996, **7**, 2233.
950 A.T. Ung and S.G. Pyne, *Tetrahedron Lett.*, 1996, **37**, 6209.
951 D. Schirlin and J.-M. Altenburger, *Synthesis*, 1995, 1351.
952 C.V. Coulter, J.A. Gerrard, J.A.E. Kraunsoe, D.J. Moore, and A.J. Pratt, *Tetrahedron*, 1996, **52**, 7127.
953 A.S. Golubev, N. Sewald, and K. Burger, *Tetrahedron*, 1996, **52**, 14757.
954 D. Winkler and K. Burger, *Synthesis*, 1996, 1419.
955 N. Shibata, J.E. Baldwin, A. Jacobs, and M.E. Wood, *Tetrahedron*, 1996, **52**, 12839.
956 U. Bratusek, I. Kejzar, J. Svete, and B. Stanovnik, *Acta Chim.Slov.*, 1996, **43**, 105.
957 E. Beausoleil, B. L'Archeveque, L. Belec, M. Aftani, and W.D. Lubell, *J. Org.Chem.*, 1996, **61**, 9447.
958 H.-G. Lombart and W.D. Lubell, *J. Org.Chem.*, 1996, **61**, 9437.

959 C. Pedregal, J. Ezquerra, and C. Ramirez, *J. Chem. Res., Synop.*, 1996, 294.
960 N. Langlois, A. Rojas-Rousseau, and O. Decavallas, *Tetrahedron: Asymmetry*, 1996, **7**, 1095.
961 B. Rigo, S. El Ghammarti, and D. Couturier, *Tetrahedron Lett.*, 1996, **37**, 485.
962 C. Herdeis, W.A. Held, A. Kirfel, and F. Schabenlaender, *Tetrahedron*, 1996, **52**, 6409.
963 P.L. Feldman, S. Chi, N. Sennequier, and D.J. Stuehr, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 111.
964 B. Rigo, R. Dolaine, S. El Ghammarti, and D. Couturier, *J. Heterocycl. Chem.*, 1996, **33**, 1063.
965 T. Simandan and M.B. Smith, *Synth. Commun.*, 1996, **26**, 1827.
966 J.-B. Behr, A. Defoin, J. Pires, J. Streith, L. Macko, and M. Zehnder, *Tetrahedron*, 1996, **52**, 3283.
967 J. Ezquerra, A. Escribano, A. Rubio, M.J. Remuinan, and J.J. Vaquero, *Tetrahedron: Asymmetry*, 1996, **7**, 2613.
968 W. Fleischhacker, T. Riede, H. Voellenkle, and C.R. Noe, *Arch. Pharm.*, 1996, **329**, 41.
969 M. Hashimoto, K. Hashimoto, and H. Shirahama, *Tetrahedron*, 1996, **52**, 1931.
970 C. Zhang, E.J. Moran, T.F. Woiwode, K.M. Short, and A.M.M. Mjalli, *Tetrahedron Lett.*, 1996, **37**, 751.
971 C. Cativiela, M.D. Diaz De Villegas, and A.I. Jimenez, *Tetrahedron*, 1996, **52**, 5881.
972 H. Ito, N. Imai, S. Tanikawa, and S. Kobayashi, *Tetrahedron Lett.*, 1996, **37**, 1795.
973 S. Goldstein and G. Czapski, *J. Am. Chem. Soc.*, 1996, **118**, 3419.
974 A.F. Vanin and I.V. Malenkova, *Biokhimiya*, 1996, **61**, 505.
975 A.F. Vanin and I.V. Malenkova, *Portland Press Proc.*, 1996, **10** (Biology of Nitric Oxide, Part 5), 107.
976 D.R. Arnelle and J.S. Stamler, *Portland Press Proc.*, 1996, **10** (Biology of Nitric Oxide, Part 5), 181.
977 A.P. Dicks, H.R. Swift, D.L.H. Williams, A.R. Butler, I.H. Al-Sa'doni, and B.G. Cox, *J. Chem. Soc., Perkin Trans. II*, 1996, 481.
978 R.J.Singh, N. Hogg, J. Joseph, and B. Kalyanaraman, *J. Biol. Chem.*, 1996, **271**, 18596.
979 K. Briviba, I. Roussyn, V.S. Sharov, and H. Sies, *Biochem. J.*, 1996, **319**, 13.
980 S. Padmaja, G.C. Squadrito, J.-N. Lemercier, R. Cueto, and W.A. Pryor, *Free Radical Biol. Med.*, 1996, **21**, 317.
981 H. Zainal, D.E. LaCroix, and W.R. Wolf, *Fresenius' J. Anal. Chem.*, 1996, **356**, 311.
982 L. Pecci, A. Antonucci, M. Fontana, G. Montefoschi, and D. Cavallini, *Amino Acids*, 1996, **10**, 379.
983 P. Bravo, M. Zanda, and C. Zappala, *Tetrahedron Lett.*, 1996, **37**, 6005.
984 M.P. Gamble, G.M.P. Giblin, J.G. Montana, P. O'Brien, T.P. Ockendon, and R.J.K. Taylor, *Tetrahedron Lett.*, 1996, **37**, 7457.
985 L. Kaesbeck and H. Kessler, *Liebigs Ann./Recl.*, 1997, 165.
986 J.M. Probert, D. Rennex, and M. Bradley, *Tetrahedron Lett.*, 1996, **37**, 1101.
987 R. Xu, X. Huang, K.J. Kramer, and M.D. Hawley, *Bioorg. Chem.*, 1996, **24**, 110.
988 H.T. Nagasawa, J.F. Cohen, and W.B. Rathbun, *Org. Prep. Proced. Int.*, 1996, **28**, 237.
989 V.J. Shah, I.D. Duntz, and G.L. Kenyon, *Bioorg. Chem.*, 1996, **24**, 194.
990 A. Eltarra and I. Hwang, *Chem. Res. Toxicol.*, 1996, **9**, 654.
991 J.J. Acton and A.B. Jones, *Tetrahedron Lett.*, 1996, **37**, 4319.
992 P. Chen, D. Wielser, J. Chmelik, and M. Novotny, *Chem. Res. Toxicol.*, 1996, **9**, 970.

993 E. Brinkmann, K.J. Wells-Knecht, S.R. Thorpe, and J.W. Baynes, *J. Chem. Soc., Perkin Trans. I*, 1995, 2817.
994 L. Graham, *Biochim. Biophys. Acta*, 1996, **1297**, 9.
995 V. Nagaraj and V. Monnier, *Biochim. Biophys. Acta*, 1992, **1116**, 34.
996 Y. El-Abed, T. Mitsuhashi, P. Ulrich, and R. Bucala, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1577.
997 N. Ruis, K. Maeda and A.L. Demain, *FEMS Microbiol. Lett.*, 1996, **144**, 207.
998 J. Kowalski and M.A. Lipton, *Tetrahedron Lett.*, 1996, **37**, 5839.
999 J. Deng, Y. Hamada, and T. Shioiri, *Tetrahedron Lett.*, 1996, **37**, 2261.
1000 J.F. Fukuto, *Methods Enzymol.*, 1996, **268** (Nitric Oxide, Part A), 365.
1001 B.H. Klein and J.W. Dudenhausen, *Eur. J. Clin. Chem., Clin. Biochem.*, 1996, **34**, 805.
1002 E. Masuikiewicz and B. Rzeszotarska, *Org. Prep. Proced. Int.*, 1996, **28**, 711.
1003 R. Jain and L.A. Cohen, *Tetrahedron*, 1996, **52**, 5363.
1004 M.S. Bolgar and S.J. Gaskell, *Anal. Chem.*, 1996, **68**, 2325.
1005 D.A. Kuhl, J.T. Methvin, and R.N. Dickerson, *J. Chromatogr., B: Biomed. Appl.*, 1996, **681**, 390.
1006 T. Hino, *Yakugaku Zasshi*, 1996, **116**, 566 (*Chem. Abs.*, 1996, **125**, 143246).
1007 E.D. Cox, J. Li, L.K. Hamaker, P. Yu, and J.M. Cook, *Chem. Commun.*, 1996, 2477.
1008 V. Moreaux, I. Birlouez-Aragon, and C. Ducauze, *Redox Rep.*, 1996, **2**, 191.
1009 U. Schmidt and S. Weinbrenner, *Synthesis*, 1996, 28.
1010 Z.Wu and G. Dryhurst, *Bioorg. Chem.*, 1996, **24**, 127.
1011 R. Lock and H. Waldmann, *Tetrahedron Lett.*, 1996, **37**, 2753.
1012 Y. Yokoyama, K. Kondo, M. Mitsuhashi, and Y. Murakami, *Tetrahedron Lett.*, 1996, **37**, 9309.
1013 S.C. Benson, L. Lee, and J.K. Snyder, *Tetrahedron Lett.*, 1996, **37**, 5061.
1014 W.-M. Dai, H.J. Zhu, and X.-J. Hao, *Tetrahedron Lett.*, 1996, **37**, 5971.
1015 Y. Nishiuchi, H. Nishio, T. Inui, T. Kimura, and S. Sakakibara, *Tetrahedron Lett.*, 1996, **37**, 7529.
1016 C. Luca, A. Zarna, D. Anghel, and T. Constantinescu, *Rev. Roum. Chim.*, 1996, **41**, 125.
1017 H. Hara, T. Inoue, M. Endoh, H. Nakamura, H. Takahashi, and O. Hoshino, *Heterocycles*, 1996, **42**, 445.
1018 H. Fretz, *Tetrahedron Lett.*, 1996, **37**, 8475 (see also *Idem, Ibid.*, p.8479).
1019 W. Wang, N.U. Obeyesekere, and J.S. McMurray, *Tetrahedron Lett.*, 1996, **37**, 6661.
1020 S.R. Gilbertson and G.W. Starkey, *J. Org. Chem.*, 1996, **61**, 2922.
1021 T. Yokomatsu, T. Yamagishi, K. Matsumoto, and S. Shibuya, *Tetrahedron*, 1996, **52**, 11725.
1022 A.J. Pearson and G. Bignan, *Tetrahedron Lett.*, 1996, **37**, 735.
1023 H. Konishi, T. Okuno, S. Nishiyama, S. Yamamura, K. Koyasu, and Y. Terada, *Tetrahedron Lett.*, 1996, **37**, 8791.
1024 J.H. Lai, H. Pham, and D.G. Hangauer, *J. Org. Chem.*, 1996, **61**, 1872.
1025 D.W. Larden and H.T.A. Cheung, *Tetrahedron Lett.*, 1996, **37**, 7581.
1026 S. Rajagopalan, G. Radke, M. Evans, and J.M. Tomich, *Synth. Commun.*, 1996, **26**, 1431.
1027 C.W. Alexander and D.C. Liotta, *Tetrahedron Lett.*, 1996, **37**, 1961.
1028 A. Katoh, S. Jyumonji, and J. Ohkanda, *Seikei Daigaku Kogaku, Kenkyu Hokoku*, 1995, **32**, 53 (*Chem. Abs.*, 1996, **124**, 233043).
1029 B.P. Zhao, G.P. Panigrahi, P.D. Sadowski, and J.J. Krepinsky, *Tetrahedron Lett.*, 1996, **37**, 3093.

1030 T.R. Burke, B. Ye, M. Akamatsu, H. Ford, X. Yan, H.K. Kole, G. Wolf, S.E. Shoelson, and P.B. Roller, *J. Med. Chem.*, 1996, **39**, 1021.
1031 N.L. Adams and J.M. Schick, *Photochem. Photobiol.*, 1996, **64**, 149.
1032 R. Schadowski, K. Schaefer, and H. Hoecker, *DWI Rep.*, 1996, **117**, 601 (*Chem. Abs.*, 1996, **125**, 11410).
1033 G. Cambron, J.M. Sevilla, T. Pineda, and M. Blazquez, *J. Fluoresc.*, 1996, **6**, 1.
1034 E. Silva and A.M. Edwards, *Cienc. Cult.*, 1996, **48**, 47.
1035 C.R. Lambert and I.E. Kochevar, *J. Am. Chem. Soc.*, 1996, **118**, 3297.
1036 S. Criado, S.G. Bertolotti, and N.A. Garcia, *J. Photochem. Photobiol.*, 1996, **34**, 79.
1037 I. Gryczynski, H. Malak, and J.R. Lakowicz, *Biospectroscopy*, 1996, **2**, 9.
1038 D.M. Davis, D. McLoskey, D.J.J. Birch, P.R. Gellett, R.S. Kittlety, and R.M. Swart, *Biophys. Chem.*, 1996, **60**, 63.
1039 L. Lankiewicz, J. Lanoszaka, S. Oldziej, and W. Wiczk, *Amino Acids*, 1996, **10**, 192.
1040 T. Sakurai, K. Miyoshi, M. Obitsu, and H. Inoue, *Ber. Bunsen-Ges.*, 1996, **100**, 46.
1041 J.Q. Wu, A. Ozarowski, S.K. Davis, and A.H. Maki, *J. Phys. Chem.*, 1996, **100**, 11496.
1042 M. Novo, G. Huettmann, and H. Diddens, *J. Photochem. Photobiol., B*, 1996, **34**, 143.
1043 I. Shevchuk, V. Chekulayev, J. Moan, and K. Berg, *Int. J. Cancer*, 1996, **67**, 791.
1044 K.F.M. Fau, C. Hopper, P.M. Speight, G. Buonaccorsi, A.J. MacRobert, and S.G. Brown, *Cancer*, 1996, **78**, 1374.
1045 B. Zhang, J. Zhang, D.-D.H. Yang, and N.C. Yang, *J. Org. Chem.*, 1996, **61**, 3236.
1046 C.I. Simionescu, S. Manolache, C. Romanescu, and G. Cobileac, *Rev. Roum. Biochim.*, 1995, **32**, 149 (*Chem. Abs.*, 1996, **125**, 321070).
1047 Highly Selective Separations in Biotechnology, Ed. G. Street, Blackie, Glasgow, 1996 (*e.g.* Chiral Separations, C.M. Heard and I.C.R. Brain, pp.179-206).
1048 K. Kobayashi, *Bunseki Kagaku*, 1996, **45**, 811.
1049 I.T. James, A.J. Walne, and D. Perrett, *Ann. Clin. Biochem.*, 1996, **33**, 397; *Anal. Biochem.*, 1996, **240**, 29; S. Ibrahim, S. Mojiminiyi, and J. L. Barron, *Ann. Clin. Biochem.*, 1996, **33**, 31.
1050 J. Pietzsch, S. Nitzsche, B. Wiedemann, U. Julius, W. Leonhardt, and M. Hanefeld, *J. Mass Spectrom.*, 1995, **30**, S129.
1051 S. Matsumura, H. Kataoka, and M. Makita, *J. Chromatogr. B: Biomed. Appl.*, 1996, **681**, 375.
1052 H. Demmelmair and H.-L. Schmidt, *Isotopenpraxis*, 1993, **29**, 237 (*Chem. Abs.*, 1996, **124**, 140082).
1053 D. Hofmann, K. Jung, H.-J. Segschnieder, M. Gehre, and G. Schueuermann, *Isot. Environ. Health Stud.*, 1995, **31**, 367.
1054 I. Abe and T. Nakahara, *J. High Resolut. Chromatogr.*, 1996, **19**, 511.
1055 U.F. da Silva, C.D. Cardoso, N. Zanatta, A.F. Morel, D. Icheln, and B. Gehrcke, *Phytochem. Anal.*, 1996, **7**, 20.
1056 E. Benicka, J. Krupcik, I. Spanik, J. Hrouzek, and P. Sandra, *J. Microcolumn Sep.*, 1996, **8**, 57.
1057 A. Ayala and R.G. Cutler, *Free Radical Biol. Med.*, 1996, **21**, 65.
1058 Y. Shigematsu, I. Hata, Y. Kikawa, Y. Tanaka, and M. Sudo, *Nippon Iyo Masu Supekutoru Gakkai Koenshu*, 1996, **21**, 205 (*Chem. Abs.*, 1996, **125**, 269804).
1059 M.G. Thompson, R.M. Palmer, A. Thom, K. Garden, G.E. Lobley, and G. Calder, *Am. J. Physiol.*, 1996, **270**, C1875.
1060 K. Sugahara, S. Yu, J. Zhang, and H. Kodama, *Nippon Iyo Masu Supekutoru Gakkai Koenshu*, 1996, **21**, 149 (*Chem. Abs.*, 1996, **125**, 269803).

1061 R.M. Matarese, A. Macone, A. Maggio, and D. Cavallini, *J. Chromatogr. B: Biomed. Appl.*, 1996, **683**, 269.
1062 D. Tsikas, S. Rossa, D.O. Stichtenoth, M. Raida, F.-M. Gutzki, and J.C. Frelich, *Biochem. Biophys. Res. Commun.*, 1996, **220**, 939
1063 L.H. de Jonge and M. Breuer, *J. Chromatogr. B: Biomed. Appl.*, 1996, **677**, 61.
1064 D.C. DeMeglio and G.K. Svanberg, *J. Liq. Chromatogr. Relat. Technol.*, 1996, **19**, 969.
1065 R.L. Aponte, J.A. Diaz, A.A. Perera, and V.G. Diaz, *J. Liq. Chromatogr. Relat. Technol.*, 1996, **19**, 687.
1066 P. Vyas, M. Attur, G.-M. Ou, K.A. Haines, S.B. Abramson, and A.R. Amin, *Portland Press Proc.*, **10** (Biology of Nitric Oxide, Part V), 44.
1067 I.T. Malakhova, B.V. Tyaglov, V. Degterev, V.D. Krasikov, and W.G. Degtiar, *J. Planar Chromatogr., Mod. TLC*, 1996, **9**, 375.
1068 P.A. de Witte, J.F. Cuveele, W.J. Merlevede, and P.M. Agostinis, *J. Pharm. Biomed. Anal.*, 1996, **14**, 1063.
1069 G. Matysik, *Chromatographia*, 1996, **43**, 301.
1070 E. Pyra and S. Wawrzycki, *Acta Pol. Pharm.*, 1996, **53**, 147.
1071 HPLC: Principles and Methods in Biotechnology, Ed. E.D. Katz, Wiley, Chichester, 1996.
1072 D. Fekkes, *J. Chromatogr. B: Biomed. Appl.*, 1996, **682**, 3.
1073 K.-J. Lindner, P. Hartvig, C. Akesson, N. Tyrefors, A. Sundin, and B. Langstroem, *J. Chromatogr. B: Biomed. Appl.*, 1996, **679**, 13.
1074 Y. Yuan, M. Shen, and J. Lu, *Sepu*, 1996, **14**, 274 (*Chem. Abs.*, 1996, **125**, 189722).
1075 C. Herve, P. Beyne, H. Jamault, and E. Delacoux, *J. Chromatogr. B: Biomed. Appl.*, 1996, **675**, 157.
1076 M. Takahashi, H. Hoshino, K. Kushida, K. Kawana, and T. Inoue, *Clin. Chem.*, 1996, **42**, 1439.
1077 A. Colwell and R. Eastell, *J. Bone Mineral Res.*, 1996, **11**, 1976; M. Takahashi, H. Hoshino, K. Kushida, and T. Inoue, *Anal. Biochem.*, 1995, **232**, 158.
1078 K. Suyama, *Connect. Tissue*, 1995, **27**, 221.
1079 U.M. Casserly, A. O'Rorke, M.J. Power, and P.F. Fottrell, *Anal. Biochem.*, 1996, **242**, 255.
1080 A. Toriba, H. Kubo, and T. Kinoshita, *Bunseki Kugaku*, 1996, **45**, 315 (*Chem. Abs.*, 1996, **125**, 306001); B.M. Polanuer, and S.V. Ivanov, *J. Chromatogr., A*, 1996, **722**, 311.
1081 W. Maruyama, Y. Hashizume, K. Matsubara, and M. Naoi, *J. Chromatogr. B: Biomed. Appl.*, 1996, **676**, 153.
1082 B. Sandee, C.A. Schipper, and R.H.M. Eertman, *J. Chromatogr. B: Biomed. Appl.*, 1996, **685**, 176.
1083 A.L. Jensen and B. Foltmann, *Scand. J. Clin. Lab. Invest.*, 1996, **56**, 69.
1084 Y. Yokoyama, O. Ozaki, and H. Sato, *J. Chromatogr., A*, 1996, **739**, 333.
1085 L.A. Kartsova, I.N. Krasnova, and A.I. Pimenov, *J. Anal. Chem.* (translation of *Zh. Anal. Khim.*), 1996, **51**,976.
1086 Y. Xu, X. Xu, and Y. Wang, *Hebei Yixueyuan Xuebao*, 1996, **17**, 132 (*Chem. Abs.*, 1996, **125**, 136815).
1087 V. Rizzo, A. Anesi, L. Montalbetti, R. Trotti, and G.V. Melzi d'Eril, *J. Chromatogr., A*, 1996, **729**, 181.
1088 A.L.L. Duchateau, J.M.M. Boesten, and B.B. Coussens, *Chirality*, 1995, **7**, 547.
1089 M. Aminuddin and N.R. Rana, *Pak. J. Sci. Ind. Res.*, 1994, **37**, 408; M. Aminuddin, M.A. Shah, and Z.H. Chohan, *J. Chem. Soc. Pak.*, 1996, **18**, 8.

1090 V. Gopalakrishnan, PJ. Burton, and T. F. Blaschke, *Anal. Chem.*, 1996, **68**, 3520.
1091 C. Carducci, M. Birarelli, V. Leuzzi, G. Santagata, P. Serafini, and I. Antonozzi, *J. Chromatogr., A*, 1996, **729**, 173.
1092 J. Diaz, J.L. Lliberia, L. Comellas, and F. Broto-Puig, *J. Chromatogr., A*, 1996, **719**, 171.
1093 H. Inoue, Y. Date, K. Kohashi, Y. Yoshitomi, and Y. Tsurata, *Biol. Pharm. Bull.*, 1996, **19**, 163.
1094 K.-L. Woo and Y.-K. Ahan, *J. Chromatogr., A*, 1996, **738**, 785.
1095 D.A. Malencik, J.F. Sprouse, C.A. Swanson, and S.R. Anderson, *Anal. Biochem.*, 1996, **242**, 202.
1096 C.-S. Liu, C.-C. Lin, J.-M. Chen, C.-H. Chang, and T.-B. Lo, *J. Chin. Biochem. Soc.*, 1993, **22**, 69 (*Chem. Abs.*, 1996, **125**, 29462).
1097 J. Kirschbaum and H. Bruckner, *Chromatographia*, 1996, **43**, 2275.
1098 T. Takeuchi and T. Miwa, *Chromatographia*, 1996, **43**, 143; *Kuromatogurafi*, 1995, **16**, 276 (*Chem. Abs.*, 1996, **124**, 218964); A.R. Martins and A.P. Padovan, *J. Liq. Chromatogr. Relat. Technol.*, 1996, **19**, 467.
1099 D.R. Skotty, W.-Y. Lee, and T.A. Niemann, *Anal. Chem.*, 1996, **68**, 1530.
1100 G.N. Chen, X.Q. Xu, J.P. Duan, R.E. Lin, and F. Zhang, *Anal. Commun.*, 1996, **33**, 99.
1101 J. Saurina and S. Hernandez-Cossou, *J. Chromatogr., A*, 1996, **740**, 21.
1102 P. Durand, L.J. Fortin, C.S. Lussier, J. Davignon, and D. Blache, *Clin. Chim. Acta*, 1996, **252**, 83.
1103 I. Daskalakis, M.D. Lucock, A. Anderson, J. Wild, C.J. Schorah, and M.I. Levene, *Biomed. Chromatogr.*, 1996, **10**, 205.
1104 N.P.B. Dudman, X.W. Guo, R. Crooks, L. Xie, and J.S. Silberberg, *Clin. Chem.*, 1996, **42**, 2028.
1105 Y. Kamisaki, K. Wade, K. Nakamoto, Y. Kishimoto, M. Kitano, and T. Itoh, *J. Chromatogr. B: Biomed. Appl.*, 1996, **685**, 343.
1106 K. Ou, M.R. Wilkins, J.X. Yan, A.A. Gooley, Y. Fung, D. Scheumack, and K.L. Williams, *J. Chromatogr., A*, 1996, **723**, 219.
1107 G. Li, J. Yu, I.S. Krull, and S. Cohen, *J. Liq. Chromatogr. Relat. Technol.*, 1995, **18**, 3889.
1108 A. Bongo, G. Bruno, S. Curti, A. Mancinelli, and G. Miotto, *J. Chromatogr. B: Biomed. Appl.*, 1996, **686**, 129.
1109 G. Felix, C. Cachau, A. Thienpout, and M.-H. Soulard, *Chromatographia*, 1996, **42**, 583.
1110 J.-Y. Lin, *J. Chromatogr., A*, 1996, **740**, 183.
1111 K. Kuromizu, O. Abe, N. Izumiya, and Y. Kodera, *Fukuoka Shika Daigaku Gakkai Zasshi*, 1995, **22**, 359 (*Chem. Abs.*, 1996, **124**, 197372).
1112 T. Hanai, H. Harano, N. Nimura, and T. Kinoshita, *J. Liq. Chromatogr., Relat.-Technol.*, 1996, **19**, 1189.
1113 A. Peter, G. Toth, G. Toeroek, and D. Tourwe, *J. Chromatogr., A*, 1996, **728**, 455.
1114 K. Ishida, H. Matsuda, M. Murakami, and K. Yamaguchi, *Tetrahedron Lett.*, 1996, **37**, 9225.
1115 K. Harada, K. Fujii, K. Hayashi, and M. Suzuki, *Tetrahedron Lett.*, 1996, **37**, 3001.
1116 E. Itoh, Y. Nishida, Y. Togashi, H. Ohrui, and H. Meguro, *Anal. Sci.*, 1996, **12**, 551.
1117 T. Toyooka, T. Suzuki, T. Watanabe, and Y. M. Liu, *Anal. Sci.*, 1996, **12**, 779.
1118 A. Khedr, *Biomed. Chromatogr.*, 1996, **10**, 167.
1119 Y.P. Belov, A.Y. Aksinenko, B. Blessington, and A.H. Newman, *Chirality*, 1996, **8**, 122.

1120 R.R. Hill, C.W. Richenburg, and D.R. Roberts, *J. Photochem.Photobiol.*, 1996, **97**, 109.
1121 M.A. Jenkins and M.D. Guerin, *J. Chromatogr. B: Biomed.Appl.*, 1996, **682**, 23.
1122 A. Meulemans, *J. Chromatogr. B: Biomed.Appl.*, 1996, **683**, 273.
1123 S.P.D. Lalljie, J. Vindevogel, G. Murugan, H.J. Dumont, and P. Sandra, *Hydrobiologia*, 1996, **319**, 103 (*Chem.Abs.*, 1996, **125**, 29461).
1124 W.R. La Course and G.S. Owens, *Electrophoresis*, 1996, **17**, 310.
1125 M.G. Zeece, Q. Chu, S.J. Jones, T.L. Woods, and W.J. Reville, *J. Capillary Electrophor.*, 1996, **3**, 55.
1126 M.W. Lada and R.T. Kennedy, *Anal.Chem.*, 1996, **68**, 2790.
1127 A. Taga, M. Sugimura, and S. Honda, *Kuromatogurafi*, 1995, **16**, 302 (*Chem.Abs.*, 1996, **124**, 127654).
1128 C.M. Jariego and A. Hernanz, *Clin.Chem.*, 1996, **42**, 427.
1129 N.G. Sundrin, T.M. Dowling, N. Grinberg, and G. Bicker, *J. Microcolumn Sep.*, 1996, **8**, 323.
1130 E.V. Hove and P. Sandra, *J. Liq.Chromatogr., Relat.Technol.*, 1995, **18**, 3675.
1131 L. Zhang, R.H. Yang, and S. Jin, *Am.Biotechnol.Lab.*, 1996, **14**, 32.
1132 S.-Y. Liao and C.-W. Whang, *J. Chromatogr., A*, 1996, **736**, 247.
1133 M.G. Schmid and G. Gubitz, *Enantiomer*, 1996, **1**, 23 (*Chem.Abs.*, 1996, **125**, 211428).
1134 M. Jung, K.O. Boernson, and E. Francotte, *Electrophoresis*, 1996, **17**, 130.
1135 K.D. Altria, P. Harkin, and M.G. Hindson, *J. Chromatogr. B: Biomed.Appl.*, 1996, **686**, 103.
1136 M. Sanchez Pena, Y. Zhang, S. Thibodeaux, M.L. McLaughlin, A. Munoz de la Pena, and I. M. Warner, *Tetrahedron Lett.*, 1996, **37**, 5841.
1137 I.E. Valko, H. Siren, and M.-L. Riekkola, *Chromatographia*, 1996, **43**, 242; *J. Chromatogr., A*, 1996, **737**, 263.
1138 H. Wan, A. Engstroem, and L.G. Blomberg, *J. Chromatogr., A*, 1996, **731**, 92.
1139 S. Anselmi, D. Braghiroli, M. DiBella, M.G. Schmid, R. Wintersteiger, and G. Guebitz, *J. Chromatogr. B: Biomed.Appl.*, 1996, **681**, 83.
1140 P.L. Desbene and C.E. Fulchic, *J. Chromatogr., A*, 1996, **749**, 257.
1141 T.J. Ward, *LC-GC*, 1996, **14**, 886, 890, 891, 892, 894 (*Chem.Abs.*, 1996, **125**, 322112).
1142 Y. Kurosu, K. Murayama, N. Shindo, Y. Shisa, and N. Ishioka, *J. Chromatogr., A*, 1996, **752**, 279.
1143 R. Vespalec, H.A.H. Billiet, J. Frank, and P. Bocek, *Electrophoresis*, 1996, **17**, 1214.
1144 M. Morita and O. Niwa, *NTT Rev.*, 1996, **8**, 77 (*Chem.Abs.*, 1996, **125**, 29454).
1145 A.S. Baranski, P. Norouzi, and L.J. Nelson, *Proc.Electrochem.Soc.*, 1996, **96**, 41 (*Chem.Abs.*, 1996, **125**, 296471).
1146 J.M. Marioli and L.E. Sereno, *J. Liq.Chromatogr., Relat.Technol.*, 1996, **19**, 2505.
1147 O. Nieto, P. Hernandez, and L. Hernandez, *Talanta*, 1996, **43**, 1201.
1148 W. Roth and E. Reh, *CLB Chem.Labor.Biotech.*, 1996, **47**, 298 (*Chem.Abs.*, 1996, **125**, 237178).
1149 G.K. Reddy and C.S. Enwemeka, *Clin.Biochem.*, 1996, **29**, 225.
1150 M. Hecker and T.R. Billiar, Methods in Nitric Oxide Research, Eds. M. Feelisch and J.S. Stamler, Wiley, Chichester, 1996, p.259.
1151 J. Komlenovic and N. Radic, *Analusis*, 1996, **24**, 63.
1152 A. Giannousios and C. Papadopoulos, *Analyst*, 1996, **121**, 413.
1153 A. Mulchandani and A.S. Bassi, *Biosens.Bioelectron.*, 1996, **11**, 271.
1154 T. Yao, S. Suzuki, H. Nishino, and T. Nakahara, *Electroanalysis*, 1995, **7**, 1114.
1155 R. Koncki, I Walcerz, F. Ruchruh, and S. Glab, *Anal.Chim.Acta*, 1996, **333**, 215.

1156 K. Nakamura, T. Fujii, Y. Kato, Y. Asano, and A.J.L. Cooper, *Anal.Biochem.*, 1996, **234**, 19.

1157 P.R. Beckett, D.S. Hardin, T.A. Davis, H.V. Nguyen, D. Wray-Cohen, and K. C. Copeland, *Anal.Biochem.*, 1996, **240**, 45.