Amino Acids

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1 Introduction

As the coverage of Amino Acids did not make it into Volume 34 of these Reports,[1] this Chapter covers the years 2001 and 2002. This inevitably means that the authors this time needed to be a little more selective in the papers reviewed, due to space limitations. The main source of the citations was again Chemical Abstracts (Vols 134–136), CA Selects on Amino Acids Peptides and Proteins[2] and the Web of Knowledge.[3] No references to conference proceedings have been included, and the patent literature has not been scanned. With the addition of an extra author, the style of the Chapter might show minor changes, but in order to preserve continuity for those taking 'year on year' surveys within a field, the pattern of sub-headings have been retained.

2 Reviews

The main aim of this Report is to review the original refereed papers in this subject area, so reporting on reviews covering similar areas is included in 'title-only' format as a token of respect for all those that have similarly laboured through the literature to bring us highlights from specific areas of endeavour. Reviews cited during 2001–2002 were:-

New Strecker Synthesis-Asymmetric Synthesis and Chiral Catalysts[4]
Methods for the Synthesis of Unnatural Amino Acids[5]
Chiral Oxazinones and Pyrazinones as α-Amino Acid Templates[6]
Amino Acid Derivatives by Multicomponent Reactions[7]
Progress on the Asymmetric Synthesis of α–Amino Acids[8]
Comparison of different Chemoenzymatic Process Routes to Enantiomerically Amino Acids[9]

Amino Acids, Peptides and Proteins, Volume 35

α-Imino Esters: Versatile Substrates for the Catalytic, Asymmetric Synthesis of α- and β-Amino Acids and Lactones[10]

The Asymmetric Synthesis of Unnatural α–Amino Acids as building blocks for Complex Synthesis[11]

Asymmetric Hydrogenation and other Methods for the Synthesis of Unnatural Amino Acids[12]

Metabolic Engineering of Glutamate Production[13]

Amino Acids Production Processes[14]

Biotechnological Manufacture of Lysine[15]

The Threonine Story[16]

The Economic Aspects of Amino Acid Production[17]

Synthesis of Enantiometrically pure Pipecolic Acid Derivatives via Bio- and Transition Metal Catalysis[18]

A Journey from Unsaturated Amino Acid Synthesis to Cyclic Peptides[19]

Side-chain modifications and Applications of Aliphatic Unsaturated α-Amino Acids[20]

Fullerene-based Amino Acids and Peptides[21]

Selenocysteine Derivatives for Chemoselective Ligations[22]

Study on Resolution of Chiral Amino Acid Enantiomers[23]

Highly Diastereoselective Michael Reactions between Nucleophilic Glycine Equivalents and β-Substituted α,β-Unsaturated Acids: A General Approach to chi-Constrained Amino Acids[24]

3 Naturally-Occurring Amino Acids

While interest continues in the synthesis of known naturally-occurring amino acids, it has not been a productive period in papers highlighting the existence of amino acids from new sources.

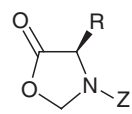
3.1 New Naturally Occurring Amino Acids. – Amongst the new nortropane alkaloids isolated from the fruit of *Morus alba* LINNE in Turkey, six new amino acids have been characterised.[25] They have been allocated pyrrolidinyl dodecanoic and piperidinyl dodecanoic structures: (3*R*)-3-hydroxy-12-{(1*S*,4*S*)-4-[(1-hydroxyethyl-pyrrolidin-1-yl}-dodecanoic acid-3-*O*-β-D-glucopyranoside; its free acid; (3*R*)-3-hydroxy-12-[(1*R*, 4*R*, 5*S*)-4-hydroxy-5-methyl-piperidin-1-yl]-dodecanoic acid-3-*O*-β-D-glucopyranoside; its free acid; (3*R*)-3-hydroxy-12-[(1*R*, 4*R*, 5*S*)-4-hydroxy-5-hydroxymethyl-piperidin-1-yl]-dodecanoic acid-3-*O*-β-D-glucopyranoside and (3*R*)-3-hydroxy-12-[(1*R*, 4*S*, 5*S*)-4-hydroxy-5-methyl-piperidin-1-yl]-dodecanoic acid.

4 Chemical Synthesis and Resolution of Amino Acids

As in past years this remains the core section of the activity in the field, with some aspects already covered by the reviews listed in sub-section 2. Some subject matter also overlaps with material in subsequent sections of this Report.

4.1 General Methods for the Synthesis of α-Amino Acids, including Enantioselective Synthesis. – The development of benzophenone imines of glycine derivatives for the synthesis of α-amino acids has been outlined.[26] Substituted phenylalanines have been prepared[27] using UV photolysis of protected glycines in the presence of di-*t*-butylperoxide, substituted toluenes and the photosensitiser, benzophenone. After removal of the chiral auxiliary by lithium hydroperoxide, *N*-acetyl-D-serine methyl ester was the final product of the rearrangement summarised[28] in Scheme 1.

Reaction of 5-oxazolidinones such as (**1**), with alcohols in bicarbonate solution,[29] and with PLE and HLE[30] has led to good yields of amino acid derivatives. A chiral copper catalyst can catalyse[31] an enantioselective Mannich type reaction as summarised in Scheme 2. Catalysis by L-proline has enabled a general reaction[32] between ketones and PMP-protected α-imino ethyl glyoxylate (Scheme 3) to be made highly stereoselective. Its simplicity would make it an attractive proposal regarding prebiotic synthesis. Either enantiomer of both α- or β-amino acids have been made available[33] if this reaction includes an aldehyde instead of a ketone.



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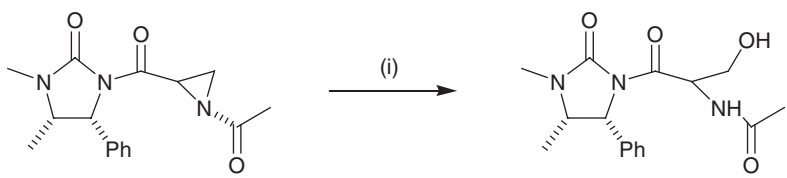
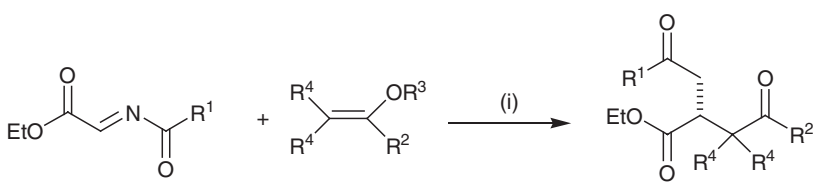
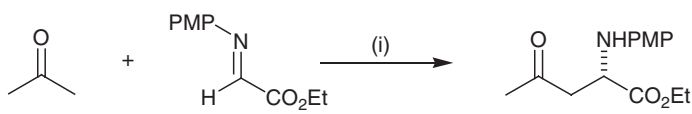


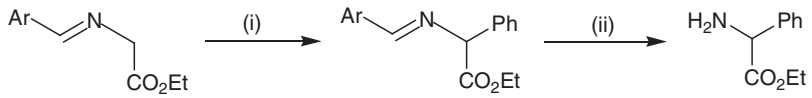
Scheme 1 *Reagents: $CeCl_3\ 6H_2O$, microwaves 240W 50–60°.*



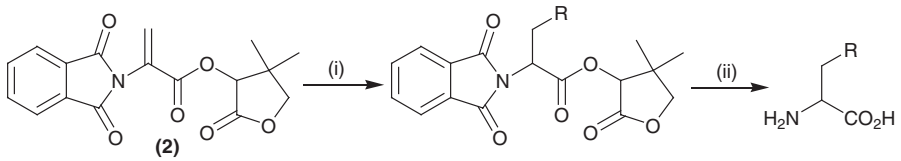
Scheme 2 *Reagents: (i) Cu catalyst.*



Scheme 3 *Reagents: (i) L-Pro (cat), DMSO.*



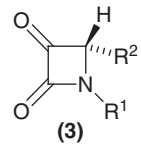
Scheme 4 *Reagents: (i) PhBr/Pd, t-Bu_3P/K_3PO_4 100°C (ii) H^+*



Scheme 5 *Reagents: (i) e.g. RX, Bu_3SnH Et_3B, Lewis acid (ii) 6M HCl/glacial acetic acid.*

A broad-based methodology[34] for the synthesis of non-natural amino acids has used catalytic enantioselective alkylation of α-imino esters and acetals with enol silanes, allyl silanes and olefins using chiral Cu(I) phosphine complexes. With suitable substitution (using 4-methoxybenzylidene) the pathway of Pd-catalysed acrylation can be guided[35] to amino acid esters as summarised in Scheme 4. A novel method, via a radical pathway for the asymmetric synthesis of α-amino acids has been reported.[36] Starting from the pantolactone (**2**) and using the conditions summarised in Scheme 5, it was shown that the absolute configuration of the stereogenic centre was dependent on the nature of the added radical. Rhodium-catalysed conjugated addition of α-aminoacrylates, with organotin and organobismuth reagents have yielded[37] amino acids under ambient conditions of air and water. Similar conditions have been used by the same authors[38] for the zinc-mediated conjugate addition of alkyl halides to α-phthalimidoacrylate.

α- and β-Substituted alanine derivatives have been efficiently produced[39] by α-amidoacrylation or Michael addition reactions using microwave irradiation and catalysis by silica-supported Lewis acids. Diverse functionalities, such as chlorides, nitriles, azides, acetates, thioacetates, thioethers and amines have been inserted[40] at varying chain lengths away from the α-centre, if amino acids (Ala or Phe), attached to a Wang resin, and derivatised with 3,4-dichlorobenzaldehyde were subjected to alkylation by α-bromo-ω-chloroelectrophiles. The one-step conversion[41] of azetidine-2,3-diones (**3**) to amino acids in the presence of cadmium/wet methanol has been explained by chelation of the ketone and amide groups to the metal, which allows for attack of the keto group by methanol followed by CO extrusion. The demands of the chemical libraries fraternity for a fast throughput of synthons, has brought the Ugi 4-component condensation into mainstream activity, and the formation of chiral products has now been made easier through better access[42] to chiral 1-amino carbohydrates. The reductive amination of ketones[43] has been adapted for the synthesis of racemic amino acids from α-keto acids, as shown by the synthesis of phenylglycine, and its 3-indolyl or 2-thienyl analogues.



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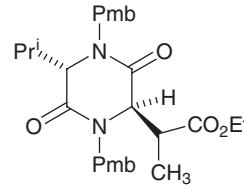


(4)

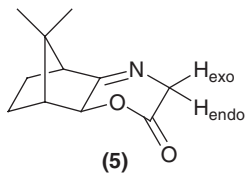
4.1.1 Use of Chiral Synthons in Amino Acid Synthesis. This still represents a booming area of interest and justifies its own sub-section. The Oxford school continues its productivity in this area as exemplified by the chiral glycine enolate, (*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-isopropylpiperazine-2,5-dione.[44] This was able to discriminate between enantiomers of 2-bromopropionate esters in forming (**4**), which on further manipulation resulted in the synthesis of chiral 3-methylaspartates. A more detailed examination of the same chiral synthesis has also been carried out.[45] Diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to α,β-unsaturated esters followed by enolate hydroxylation, reduction and oxidative cleavage has been shown[46] to be a route to α-amino acids in high enantiomeric excess. (*S*)-α-Amino acids in high chiral yields have been obtained[47] from (*S*)-*N*,*N*′-bis(*p*-methoxybenzyl)-3-methylene-6-isopropylpiperazine by reaction with a range of organocuprates.

The imine moiety of (5*S*)-3-([2-methoxycarbonyl]ethyl)-5-phenyl-5,6-dihydro-2H-1,4-oxazin-2-one has been shown[48] to undergo highly diastereocontrolled reduction followed by Lewis-acid-mediated nucleophilic addition of Grignard reagents to give enantiomerically pure glutamic acid analogues. The same authors[49] have also shown that iminium ions derived from (*S*)-5-phenylmorpholine-2-one undergo diastereoselective Strecker reactions using copper(I) cyanide/anhydrous hydrochloric acid, which lead eventually to D-α-amino acids. An inexpensive chiral auxiliary, the imino lactone (**5**), from (1*R*)-(+)-camphor on alkylation afforded[50,51] good yields of monosubstituted products at the H_{endo} position, which on hydrolysis yielded D-α-amino acids. Using camphor of the opposite configuration, or by switching the OH group of the auxiliary from C_2 to C_3, gave the L-enantiomer. *N*-Methyl pseudoephedrine has also been used[52] as a chiral auxiliary, by mediating a dynamic resolution of α-bromo-α-alkyl esters in nucleophilic substitution. Enantiomeric ratios of 98:2 were achieved in the α-amino acids finally produced.

A variety of α-amino acids have been produced[53] diastereoselectively using indium-mediated allylation and alkylation of the Oppolzer camphorsultam derivative of glyoxylic oxime ether. A new chiral auxiliary (*S*)-*N*-(2-benzoylphenyl)-1-(3,4-dichlorobenzyl)-D-pyrrolidine-2-carboxamide, and related halogen-containing auxiliaries as their Ni(II) complexes have been shown[54] to give an increased chiral bias in the formation of (*S*)-α-amino acids, due possibly to the halogen substitution in the *N*-benzyl group. A 5-step asymmetric synthesis[55] of the (2*R*, 4*R*) 4-hydroxy-D-pyroglutamic acid involved the 1,3-dipolar cycloaddition of a chiral nitrone (from glyoxylic and protected D-ribosyl

hydroxylamine) with the acrylamide of Oppolzer's sultam. The scope of this reaction[56] using other analogues has also been studied experimentally and theoretically for the formation of the (2*S*,4*S*)-isomer.

By association with substrates, chiral catalysts can also be considered under the heading 'chiral auxiliaries', and recently together with phase-transfer reagents constitute a popular means of asymmetric synthesis. A novel substrate/catalytic pair under phase-transfer conditions turned out[57] to be based on complex (**6**) which reacted quickly with 2-amino-2′-hydroxy-1,1-binaphthyl (NOBIN) as the phase transfer catalyst and could then be alkylated asymmetrically to give purifiable complexes for further processing to amino acids.



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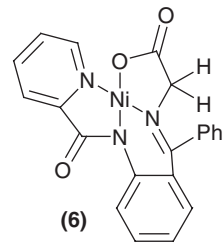

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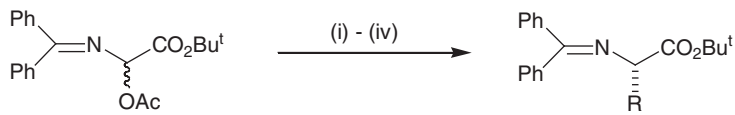
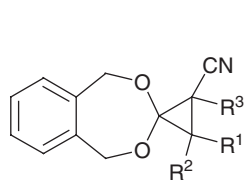
Stereoselective alkylation reactions of *N*′[(*S*)-1′-phenylethyl]-*N*-(diphenylmethylene)glycinamide using 18-crown-6 as catalyst, gave[58] a series of enantioenriched (83:17 ratio) unnatural amino acids. Structures based on the chirality of cinchona alkaloids have a noble track record in this area, and when polymer-supported cinchona alkaloid salts with different spacers were used[59] as catalysts in the *C*-alkylation of *N*-diphenylmethylene glycine *t*-butyl esters, it was found that the best result (81% ee) came from the polymer bearing a 4-carbon spacer. When dimeric cinchonidine- and cinchonine-derived ammonium salts incorporating a dimethylanthracenyl bridge were studied in the same type of asymmetric alkylations, 90% ee was achieved.[60] In the enantioselective synthesis[61] summarised in Scheme 6 cinchonidine is used to control the stereochemistry of the α-carbon when side-chains are introduced using β-alkyl-9-BBN organoborane reagents. In 12 examples studied 54–95% ee's were recorded. A new class of naphthalene-based dimeric cinchona alkaloids have been developed[62] which show excellent enantioselectivity in the alkylation of glycine derivatives and seem good prospects for adoption by industry. Cinchonidinium salts bearing a 3,5-dialkoxybenzyl have been shown[63] to be efficient catalysts for the alkylation of *N*-(diphenylmethylene)glycine Pr^i ester with benzyl bromide, but surprisingly give the (*S*)-enantiomer when KOH is used as base and the (*R*)-enantiomer when NaOH was used. A cinchonidine-based phase-transfer catalyst in the



Scheme 6 *Reagents: (i) cinchonidine/ LiCl (ii) nBuLi (iii)* R—B *(iv) 0°C THF*

presence of KOD/D_2O, provided[64] the means to incorporate deuterium into the α-position of benzophenone-derived glycine imine to produce α-deuterated α-amino acids.

4.1.2 Synthesis via Rearrangements. γ-Amino acids were produced[65] via the hydrogen-mediated ring-opening of (**7**) to the carboxy nitrile, followed by hydrogenation of the nitrile group. *N*-Benzyl-4-acetylproline has been prepared[66] from *N*-(2-hydroxy-2-methyl)but-2-enyl-*N*-benzylamine and glyoxylic acid via a tandem cationic aza-Cope rearrangement and Mannich reaction under mild conditions. A TEMPO-mediated ring expansion to the α-keto-β-lactam (**8**) resulted[67] in the formation of *N*-carboxyanhydrides which could be hydrolysed without loss of chirality to the α-amino acid derivatives as summarised in Scheme 7. *N*-Protected allylic amines produced from allylic alcohols via Overman's [3,3] sigmatropic rearrangement of trichloroacetimidates have been converted[68] to *N*-protected amino acids by using $NaIO_4$ with catalytic amounts of $RuCl_3.3H_2O$ or by ozonolysis, without loss of chirality.



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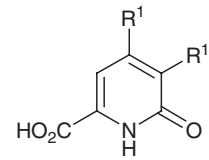
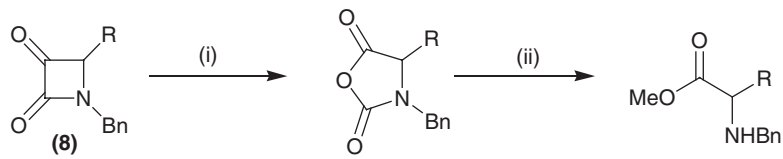


(9) $R^1 = CH_2CH(NH_2)CO_2H$, $R^2 = H$
(10) $R^1 = H$, $R^2 = CH_2CH(NH_2)CO_2H$

4.1.3 Synthesis from Dehydroamino Acids and by Carbohydroamination. Secondary phosphanes have proved[69] to be useful ligands for the asymmetric hydrogenation of acetamidocinnamic and itaconic acids using [rhodium (cycloocta-1,5-diene)$_2$]BF_4 as catalyst. Enantiomeric excesses of up to 97% were found for both the bidentate and monodentate ligands. The asymmetric hydrogenation of dehydroaminoacid precursors was the key step[70] in the synthesis of *S*-(−)-acromelobic acid (**9**) and *S*-(−)-acromelobonic acid (**10**). An ee of >98% was achieved at the key stage in the synthesis of (**9**) through the use of (*R*,*R*)-Rh(DIPAAMP)(COD)]BF_4, while (S,S)-[Rh(Et-DuPHOS)(COD)]BF_4 was used for (**10**) and gave >96% ee. In the hydrogenation of (*Z*)-acetamido-3-arylacrylic acid methyl esters it has been discovered[71] that the introduction of N for O into the binaphthyl chiral ligands allows catalysts such



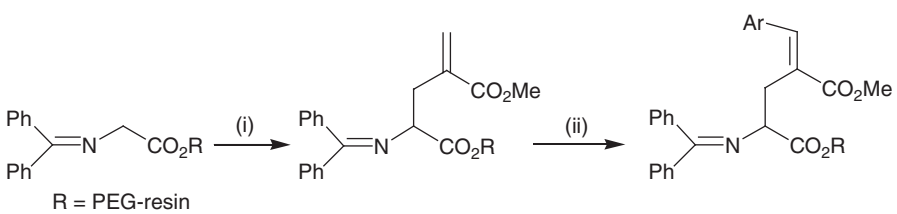
Scheme 7 *Reagents: (i) TEMPO (cat) / NaOCl/ CH_2Cl_2 (ii) MeOH or MeOH/TMSCI*

as [Rh(H_8-BINAPO)] and [Rh(H_8-BDPAB)] to give improved ee values. (2*S*, 6*S*)- and *meso*-Diaminopimelic acids have been synthesised[72] by the asymmetric hydrogenation (95% ee) of their dehydroamino acid precursor under catalysis by [Rh(I))COD)-(*S,S*) or (*R,R*)-Et-DuPHOS]OTf.

No asymmetric bias, but good yields (up to 86%) have been claimed[73] for the interesting formation of PhCH(NHR)CONHR, when various iodoarenes, primary amines and carbon monoxide were condensed together in a Pd-catalysed one-pot double carbonylation reaction.

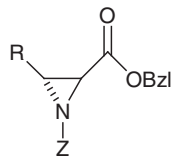
4.2 Synthesis of Protein Amino Acids and Other Naturally Occurring Amino Acids. – The use of enzymes to carry out key conversions in the synthesis of amino acids has been a useful part of the armoury for many years. During this period, examples come from: the formation[74] of L-[4-^{11}C]-aspartate and L-[5-^{11}C]-glutamate by enzymatic catalysis of ^{11}C-hydrogen cyanide into *O*-acetyl-serine and –homoserine respectively; phenylalanine ammonia lyase was used[75] to produce [1-^{14}C]- and [2-^{14}C]-phenylalanine from corresponding cinnamic acids, and these isotopomers converted further to [1-^{14}C]- and [2-^{14}C]-tyrosine using L-phenylalanine hydroxylase; tyrosine phenol lyase from *Citrobacter freundii* can catalyse[76] conversion of 2-aza-1- and 3-aza-1-tyrosine from 3-hydroxy- and 2-hydroxypyridine respectively and ammonium pyruvate; four tritium-labelled isotopomers of L-phenylalanine (2-^{3}H-, 2′,6′-^{3}H, 3*R*-^{3}H and 3*S*-^{3}H-phenylalanine) have been made[77] and converted into [2-^{3}H]-, [2′,6′-^{3}H]-, [3R-^{3}H]- and [3S-^{3}H]-tyrosine using phenylalanine-4′-monooxygenase; reductive amination[78] of pyruvate to form L-alanine using alanine dehydrogenase from the hyperthermophilic archeon, *Archaeoglobus fulgidus*; the biotransformation[79] of *p*-hydroxyphenylpyruvic acid to L-tyrosine using L-aspartate amino transferase from *E. coli*.

The chemical synthesis of well known amino acids and derivatives still commands a great deal of attention. Thus glutamic acid analogues have been prepared[80] from PEG-supported intermediates using a Heck reaction as summarised in Scheme 8, followed by further processing to the amino acid derivatives. Starting from the same Schiff base, conjugative addition[81] of Michael acceptors, either in solution or on solid phase, in the presence of quaternary salts from cinchona alkaloids have also given glutamic acid derivatives. Asymmetric synthesis[82] of β-substituted aspartic acid derivatives has been secured via a catalysed [2+2] cycloaddition of ketenes and imines to form acyl-β-lactams,



Scheme 8 *Reagents: (i) $BrCH_2(C{=}CH_2)CO_2Me$/ Cs_2CO_3/ MeCN (ii) ArX /$Pd(OAc)_2$/10% PPh_3/Cs_2CO_3.*

which ring-open under catalysis by benzoylquinine with high enantio- and diastereo-selectivity. Aziridines, such as (**11**) and cyclic sulfates based on (**12**) were the basis[83] of the asymmetric synthesis of *syn* and *anti* forms of β-substituted cysteines and serines, and reductive amination[84] of phenylpyruvic acid over Pd/C catalyst yielded DL-phenylalanine. Oxazolidinones (**13**) and (**14**) have been shown[85] to be efficient synthons on the pathway to α-amino-aldehydes and α-amino acids respectively.



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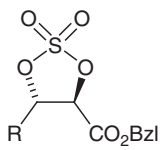

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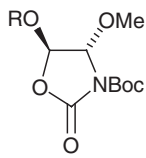
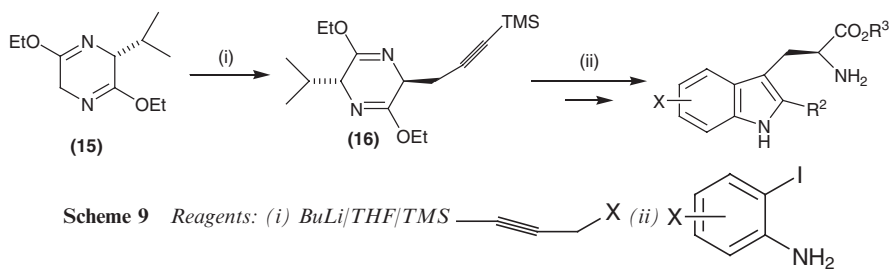


(13) R = Bn
(14) R = Me

The Schollkoff chiral auxiliary (**15**) formed the basis,[86] which on conversion to the alkyne (**16**), and reaction with *o*-iodoanilines gave a series of tryptophan analogues (Scheme 9). Enantiopure 4-substituted prolines have been prepared[87] via intramolecular radical cyclisation of *N*-arylsulfonyl-*N*-allyl-3-bromo-L-alanines, while a practical and convenient enzymatic[88] enantioselective hydrolysis of DL-glycine nitriles with nitrile hydratase from *Rhodococcus* sp. AJ270 cells have yielded amino acids and their amides. Both solution and solid phase versions of the Ugi multicomponent reaction[89] have produced a library of arginine derivatives. Selectively protected L-DOPA derivatives were the products[90] from the hydroformylation of 3-iodo-L-tyrosine followed by Baeyer-Villiger oxidation of the derived 3-formyl group.

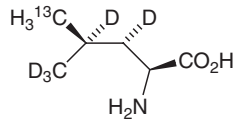
Further investigations[91] have optimised the oxidation conditions required to produce (*R*)-glycine-d-^{15}N from *N*-(*p*-methoxyphenyl methylamine)-2,2,2-trichloroethyl carbamate to be the use of periodic acid.

N-Enriched-L-histidine (99% enrichment in each position) were the products[92] of introduction of the labels into the precursor 1-benzyl-5-hydroxymethylimidazole, and leucine labelled with ^{13}C-carbon and deuterium as shown in (**17**) was the product[93] of a multistep synthesis starting from pyroglutamic acid derivatives. A chiral centre located[94] on a *N*-phthaloyl protecting group has secured control of stereochemistry in the formation of (2-^{2}H)- and (2,3-^{2}H)-phenylalanine, while a chirally deuterated 3-aminopropanol derivative



Scheme 9 *Reagents: (i) BuLi/THF/TMS* —≡— X *(ii)*

proved[95] to be key to the synthesis of L-[2,3,4,5-^{2}H]-ornithine. Synthesis[96,97] of [2*S*, 3*R*]-[3-^{2}H,^{15}N]-phenylalanine involved a key alkylation of the chiral glycine template ^{15}N-labelled 8-phenylmenthyl hippurate with (*S*)-(+)-benzyl-α-d-mesylate, giving 92% de at the 2-position and 74% de at the 3-position.



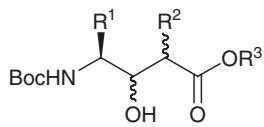
(17)

Starting from a diprotected L-aspartic acid, (2*S*, 4*R*)-4-hydroxyornithine has been synthesised, and from L-aspartic acid itself after esterification, azo-hydrolysis, aminolysis and a Hofmann rearrangement, (*S*)-isoserine has been synthesised.[98] The partially hydrogenated aromatic ring of phenylalanine (1,4-dihydro-L-phenylalanine), produced as a minor product in the Birch reduction of the amino acid, has been shown[99] to be a moderate competitive inhibitor of phenylalanine ammonia lyase rather than a substrate. In an enzyme-assisted[100] preparation of D-*tert*-leucine, it was (±)-*N*-acetyl-*tert*-leucine chloroethyl ester that exhibited the highest rate of hydrolysis.

Amino acid anhydride hydrochlorides have been used[101] for the first time as acylating agents in Friedel-Crafts reactions, resulting in the synthesis of L-homophenylalanine from aspartic acid. Reduction of cystine with Fe/HCl yielded[102] cysteine, while di- and tri-nuclear Cu(II) complexes catalysed[103] the condensation of glycine with HCHO to yield serine. A process (40g-scale) for making enantiomerically pure (*S*)- and (*R*)-valine *t*-butyl esters has been developed[104] from *N*-TFA-valine and 2-methylpropene, but *N*-Boc-4-hydroxymethyl-oxazolidin-2-ones from L-serine[105] undergo rearrangement and racemisation making these unsuitable polymer-mounted auxiliaries. Homolytic free radical alkylations via silver-catalysed oxidative decarboxylation with ammonium persulfate, has been used[106] to convert L-histidine methyl ester to 2,3-dialkylated-histidines. *N*-Boc-Phenylglycine *t*-butyl esters were the result[107] of a 1,2 Boc-migration on treating *N*, *N*-di-Boc-benzylamines with KDA/*t*-BuOLi. Iodine powder/hydrogen peroxide mixtures have furnished[108] L-thyroxine from L-tyrosine.

Non-proteinogenic amino acids now encompass a wide range of structures and are sometimes difficult to retrieve from the literature as they are often referred to only by their 'trivial' name. However statines, due to their pharmacological importance, are well-documented. Thus, all four 2,3 stereoisomers 2-substituted statines (**18**) have been synthesised.[109] Both the *anti* and *syn* forms were obtained from precursor β-ketoesters via reduction and aldol reactions. Both enantiomers of statine (**18**, R^1=Bu^i, R^2=H, R^3=H, without Boc) have been synthesised[110] by exploiting an α-lithiated alkyl sulfoxide as a chiral α-hydroxyalkyl carbanion equivalent, while another method[111] utilised orthogonally protected *syn*-2-amino-1, 3, 4-butantriol as a general *syn*-aminoalcohol building block. A *N*-hydroxymethyl group tethered to the amino group of *N*-Boc-L-leucinal has been shown[112] to undergo intramolecular conjugate

addition to an α,β-unsaturated ester formed by condensation with the aldehyde group of the leucinal. The resulting adduct hydrolysed to (−)-statine.



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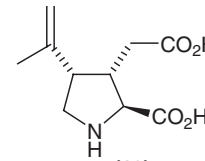
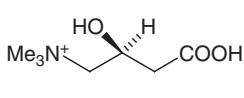


(19)

Interest in the polysubstituted proline family of kainoids for their anthelmintic and insecticidal properties has provided interesting synthetic challenges, since natural sources have been interrupted. Thus (−) kainic acid (**19**) has been synthesised[113] from chiral lithium amide bases which are able to deprotonate *N*-benzyl-*N*-cumylanisamide enantioselectivity to yield enantiomerically enriched benzylic organolithiums. These spontaneously undergo dearomatising cyclisation to yield partially saturated isoindolones, which are processed further in nine steps to (**19**). A potent neuroexcitatory kainoid analogue MFPA (2-methoxyphenyl group in position 4 in **19**) has been synthesised[114] with the proline ring built using a photoinduced benzyl radical cyclisation which had excellent stereoselectivity. Model studies[115] on another photochemical approach to the kainoid ring system have been reported, as well as a formal synthesis[116] of the kainoid amino acid FPA, using a ketyl radical cyclisation as a key step. Some reflections on the synthesis of (−)-kainic acid (**19**) have been recorded in a short review.[117] Full details[118] have now emerged for the synthesis of 4-arylsulfonyl-substituted kainoid analogues starting from 4-hydroxy-L-proline.

(*S*)-(+)-Carnitine (**20**) and analogues have been produced[119] by sequential mono-addition of organometallic reagents to the lactone of (5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one followed by Lewis acid-promoted stereoselective allylation of the resulting hemiacetals. The *R*-(−)-carnitine has also become available[120] from the same oxazinone template but via its reaction in a $TiCl_4$ – promoted Mukaiyama-type aldol reaction of the ketenesilyl acetal of ethyl acetate. A key step in another stereoselective synthesis of *S*-(+)-lycoperdic acid (**21**), was achieved[121] by the stereoselective hydroxylation of the enolate of a bicyclic lactam using oxodiperoxymolybdenum(pyridine)hexamethyl phosphoric triamide as oxidising agent.



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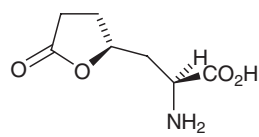

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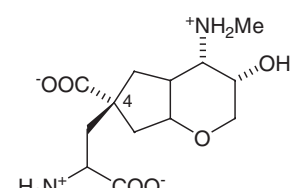

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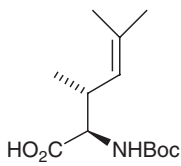
The side-chain component of paclitaxel (taxol), (2*R*, 3*S*)-*N*-benzoyl-3-phenylisoserine, has been synthesised[122] utilising dihydroxylation and regio-and diastereo-selective iminocarbonate rearrangement. *N, N*-Dichlorinated derivatives of taurine, homotaurine, GABA and leucine have been shown[123] to be more lipophilic than their parent compounds, and an asymmetric synthesis[124] of *cis*-α,β-propanoleucine has used a Strecker synthesis as a key step. Another total synthesis[125] of the selective glutamate receptor agonist dysiherbaine (**22**) has been reported, this time in a one-pot halogenation-ring-contraction to prepare the bicyclic ring system with excellent stereochemical control at the C-4 centre. *N*-Methylhydroxyleucine and another three unusual components (**23–25**) of cyclomarin A have been synthesised[126] in protected form ready for further processing to the cyclic peptide. Amino acid (**23**) was derived from diastereoselective methylation of an aspartic acid lactone, while (**24**) was formed via aldol reaction with Schollkopf's chiral glycine enolate, and (**25**) was achieved by the AQN ligand-promoted Sharpless aminohydroxylation protocol. New derivatives of L-canavanine have been produced[127] in order to study the effect of oxygen in the S-position, on their efficiency as nitric oxide synthase inhibitors.



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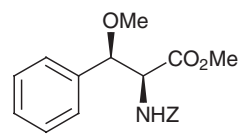

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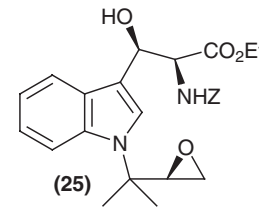
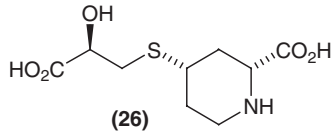


(25)

All eight stereoisomers of puleherrimine (**26**), the bitter principle from a sea urchin ovary have been synthesized,[128] and has resulted in the re-designation of the stereochemistry of the natural pulcherrimine as (2′*S*, 2*R*, 4*S*). The stereoselective synthesis[129] of (+)-myriocin (**27**) from D-mannose has been briefly reported, using an Overman rearrangement as a key step.

5-[4-^{13}C, ^{15}N]- and 5-[5-^{13}C, ^{15}N]-Aminolevulinic acids have been synthesised[130] in 4 steps from labelled glycine, and *N*-Boc-aziridine-2-carboxyIates treated with ^{11}C-cyanide with no carrier added[131] produced DL-2,4-diamino[4-^{11}C]butanoic acid, 4-^{11}C-asparagine and 4-^{11}C-aspartic acid. [l-^{11}C]-γ-Vinyl γ-aminobutyric acid (Vigabatrin®), a suicide inhibitor of GABA-transaminase has been synthesised[132] in order to better understand its pharmokinetics using positron emission tomography. A 7-step synthesis[133] to (*S*, *S*)-dysibetaine (**28**) from a marine sponge, established its natural stereochemistry as well as providing other isomers for testing. A first asymmetric synthesis[134] has been recorded for (2*S*)- and (2*R*)-amino-3,3-dimethoxy propanoic acid through quenching of a chiral glycine titanium enolate with trimethyl orthoformate, and (*S*)-α-aminooleic acid has been formed[135] from Me (2*S*)-2-[bis-(Boc)amino]-5-oxopentanoate.



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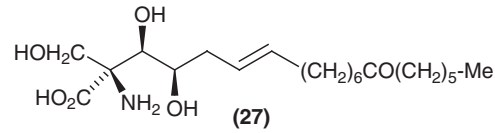

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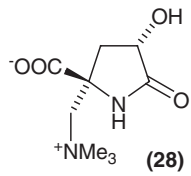

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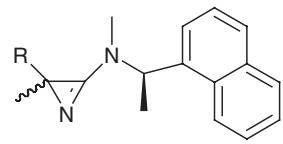

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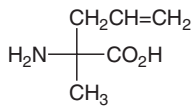
4.3 Synthesis of α-Alky1 α-Amino Acids. – The chromatographically isolatable diastereoisomers of 2, 2-disubstituted 2H-azirin-3-amine (**29**) provided[136] useful synthons for the synthesis of (*R*)- and (*S*)-isomers of isovaline, 2-methylvaline, 2-cyclopentylalanine, 2-methylleucine and 2-methylphenylalanine, and in an extension of the work[137] 2-methyltyrosine and 2-methylDOPA were produced. The latter compound has also been used,[138] to create via its catechol hydroxyls new crown ether carriers. Both enantiomers of α-methyl serine were synthesised[139] with the use of Ni(II) complexes of (*S*)-*N*(2-benzoylphenyl-l-benzylpyrrolidine)-2-carboxamide, and can also be obtained[140] on a multigram scale from the Weinreb amide of 2-methyl-2-propenoic acid via a Sharpless asymmetric di-hydroxylation. The products were also converted to (*S*) and (*R*)-*N*-Boc-*N*, *O*-isopropylidene-α-methylserinals in new approaches to the synthesis of quaternary α-methyl amino acids. (*S*, *S*)-and (*R*, *R*)-Cyclohexane-l,2-diols have been used[141] as chiral auxiliaries in the asymmetric synthesis of (*S*)-butylethylglycine and (*S*)-ethylleucine, while chiral synthons containing metal ions gave α,α-amino acids in a 'one-pot' reaction.[142]

Copper salen complexes have been found[143] to catalyse the asymmetric alkylation of enolates from a variety of amino acids, and after a wide survey of conditions it was concluded that there was a clear relationship between size of the substrate side chain and the enantioselectivity of the process. A chiral nitrone from L-erythrulose has been subjected[144] to reaction by various Grignard reagents, to give protected α,α-disubstituted amino acids and their corresponding *N*-hydroxy derivatives. Using α,β-didehydroglutamates as starting material,[145] α-methyl pyroglutamates have been synthesised via α-methyl-6-oxoperhydropyridazme-3-carboxylates with ring contraction using LiHMDS. A range of chiral α-alkyl-α-phenylglycine derivatives were prepared[146] by alkylation of (3*R*)-phenylpyrazine, which was obtained from the arylation of (*S*)-2, 5-dihydro-3,6-dimethoxy-2-isopropylpiperazine with benzene-$Mn(CO)_3$ complex. Treatment of ethyl nitroacetate with *N*,*N*-diisopropylethylarnine/tetraalkylammonium salt followed by addition of an alkyl halide or Michael acceptor gave the doubly C-alkylated product in good yield which gave the corresponding amido esters on selective nitro group reduction.[147] On *N*-protection, a series of these $C^{\alpha,\alpha}$ -disubstituted amino acids were incorporated into peptides, while in a separate publication[148] esters of Boc- and

Z-α,α,-dialkylamino acids have been prepared via the mixed anhydride method. Large scale syntheses[149] of C^{α}-tetrasubstituted α-amino acids such as (**30**), important for ring closing metathesis have been carried out using phase-transfer catalysed alkylation of *N*-benzylidene-DL-alaninamide using two amidases for the resolution of the amino acid into chirally pure forms. Another synthesis[150] of APCD (**31**), a selective agonist of metabotropic glutamate receptors has appeared which is based upon an alkylidene carbene 1,5-CH insertion reaction as a key step. A Wittig homologation of Garner's aldehyde, with subsequent catalytic hydrogenation gave a precursor ketone which with lithio(trimethylsilyl)diazomethane resulted in the cyclopentene-CH insertion product.



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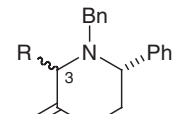


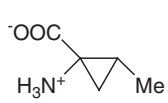
(32)

Chiral α,α-disubstituted amino acid derivatives possessing a vinyl silane synthetic handle have been obtained[151] from aza-[2,3]-Wittig rearrangement precursors derived from Ala, Val, Phe and PhGly. Upon irradiation[152] with suitable α-alkoxy carbon radical precursors plus a sensitiser, substitution occurred onto C═N bonds of ketoxime ethers to form β-oxygenated quaternary α-amino acid derivatives.

Protected α-methyl-α-phenylglycine and α-methylisoleucine have been prepared[153] by oxidative cleavage of *N*-Boc-3-amino-l, 2-diols which had been formed from 3-azido-l, 2-diols. Treatment[154] of enolates of (**32**) with alkyl halides or aldehydes, gave a quaternary C at 3 with *S*-configuration, but with methyl bromoacetate the *R*-configuration predominated. The products were de-protected to form enantiopure α, α-dialkyl amino acids. In the chiral phase transfer-catalysed alkylation of protected amino acids, anaerobic conditions offer advantages[155] of yield and enantioselectivity. 6-Benzyl-piperazine-2, 3, 5-trione has been selectively alkylated[156] at the C-6 position, which is equivalent to the C^{α} position of phenylalanine.

4.4 Synthesis of α-Amino Acids with Alicyclic and Long Aliphatic Side Chains. – There seems to be an increase in activity under this Section during this period, with the 3-membered cyclopropyl ring amongst the most popular. Options for the synthesis of a large class of chiral 2-*S*-alkyl-l-aminocyclopropane carboxylic acids have been made available[157] through the synthesis of (*Z*)-l-benzoylamino-2-tritylsulfanylcyclopropane carboxylic acid, formed from (−) or (+)-menthyl-2-benzoylamino-3-tritylsulfenyl acrylates and diazomethane. (1*S*, 2*R*)- and (1*R*, 2*S*)-Allocoronamic acids (**33**) have been made[158] using Belokon's complex {Ni(II) complex of glycine-(*S*)-2-[*N*′-(*N*-benzylprolyl)amino] benzophenone Schiff base ligands}, and chiral sulfate cyclopropane amino acids have been

reported[159] as products from ylide insertion on the exocyclic double bond of a chiral 5(4H)- oxazolone from D-glyceraldehyde. There is a first report[160] of an enzymatic (pig liver esterase) asymmetrisation of a prochiral precursor in the form of (1*S*)-l-amino-2, 2-dimethylcyclopropane-l-carboxylic acid, and (2*R*, 1′*S*, 2′*S*)-2-(carboxycyclopropyl)glycine has been formed[161] via an extension of Taguchi's protocol for Simmons-Smith cyclopropanation to a chiral amino allyl alcohol. *S*-Cleonin (**34**) from the anti-tumour cleomycin has been prepared[162] from *R*-serine via a Kulinkovich cyclopropanation of the methyl ester of Z-serine acetonide. Of the two novel antagonists of group 2 metabotropic glutamate receptors, synthesised[163] as (2*S*, 1′*S*, 2′*S*, 3′*R*)-2-(3′-xanthenyl, methyl-2′-carboxycyclopropyl)glycine and its xanthenylethyl analogue, it was the latter which had submicromolar activity. *exo*-Nucleophilic addition[164] to (bicyclo [5.1.0] octadienyl)iron (1+) established the stereochemistry of the ring and the α-stereocentre in the synthesis of *cis*-2-(2′-carboxycyclopropyl)glycine (**35**), while the synthesis[165] of (2*S*, 1′*S*, 2′*S*, 3′*R*)-2-(2′-carboxy-3′-methylcyclopropyl)glycine and its epimer at C-3′ has shown the former to be a potent and selective metabotropic group 2 receptor agonist. Cyclopropanation of dehydroamino acid derivatives[166] with alkyl diazoacetates, catalysed by dirhodium tetraacetate gave cyclopropane analogues of aspartic and adipic acids. Full details[167] have appeared for the titanium-mediated cyclopropanation of homoallyl alk-2-enoates to give (Z)-vinylcyclopropanols, which can be processed via azidation and oxidative cleavage to give alkyl 2,3-methanoamino acids such as (**36**). *Syn*- and *anti*- forms of 3,4-cyclopropylarginitie have been produced[168] using diazomethane addition to Z-dehydroglutamate, 4-methyl-2,6,7-trioxabicyclo [2,2,2] ortho ester followed by irradiation of the resulting pyrazoline.



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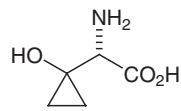

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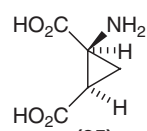

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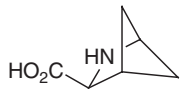
Also generating continuing interest in this sub-section is the conformational constraints offered by the 5-membered ring in proline, so a number of syntheses of substituted prolines have been reported. A number of 3-substituted prolines have been synthesised enantioselectively[169] starting from 3-OH-(*S*)-2-Pro using the enol triflate derived from *N*-trityl-3-oxo-(*S*)-2-proline methyl ester, followed by hydrolysis/hydrogenation. A chirally stabilised azomethine ylide[170] from 5-(*S*)-5-phenylmorpholin-2-one and 2,2-dimethoxypropane has been trapped diastereoselectively with singly and doubly-activated dipolarophiles to give cycloadducts dismantled in one-pot to enantiomerically pure 5,5-dimethylproline derivatives. A reductive cyanation[171] of 2-pyrrolidones with Schwartz's reagent has also given the same disubstituted proline. Two methods have been described for the synthesis of (2*S*, 5*S*)-5-*t*-butylprolin. One

involved[172] converting 2(*S*)-l-*t*-butyldimethylsiloxy-2-*N*-(PhF)amino-5-oxo-6, 6-dimethyl heptane into its imino alcohol followed by reduction of the imine function with >96% enantiomeric purity, while another study[173] made the same 5-substituted proline via the addition of *t*-butylcuprate to 2(*S*)-Boc-Δ^5-dehydroproline ethyl ester with 78:22 diastereoselectivity. Starting from 2,3-disubstituted pentenoic acid derivatives it has been shown[174] that a hydroboration-Swern oxidation sequence created a *N*-acyliminium precursor which could be transformed into 3-phenyl-5-vinylproline in 70% yield. *N*-Alkylated glycine esters[175] with excess acrolein in presence of acid, followed by treatment with Et_3N have provided 4-formyl-5-vinylproline carboxylates with good regio- and stereo-selectivity.

Trans-4-Cyclohexylproline has been obtained[176] by stereoselective alkylation of *N*-benzyl-pyroglutamic acid with 3-bromocyclohexene, which after hydrogenation afforded *trans*-4-cyclohexylpyroglutamic acid and then processed via a thioester (Lawesson's reagent) and Raney Ni to give the proline derivative with 93% ee. A library of 4-alkoxyprolines has been produced[177] using solid phase techniques, and a detailed survey[178] of the phase transfer catalysis conditions required for the cycloaddition of imino esters derived from alanine and glycine with alkenes to form substituted prolines has been carried out. A number of heteroaromatic acromelic acid analogues have been synthesised[179] from (−)-α-kainic acid and (2*S*, 3*R*)-3-hydroxy-3-methylproline a component of the polyoxypeptins has been synthesised[180] via a SmI_2-mediated cyelisation of an iodoketone. Both *syn, exo*, and *anti, exo*-3, 4, 5-trisubstitiued-prolines can separately be prepared[181] from 2, 4, 5-pyrrolidinyl carbene complexes formed from glycine ester aldimines and chiral alkoxyalkenylcarbene complexes of chromium, oxidation producing the former, acid hydrolysis producing the latter. The azabicycle (**39**) with sec-butyllithium/TMEDA at 0°C afforded[182] the C bridgehead anion which could be quenched with e.g. CO_2 to form the naturally-occurring 2, 4-methanoproline (**38**), but when conditions were changed to −78°C the hitherto unknown 3, 5-methanoproline (**37**) was amongst the products. The 2, 4-isomer (**38**) was also synthesised[183] in five steps from allyl benzyl ether. Further bridged analogues of proline have come in the form of (**40**) and (**41**), which were produced[184] from transformations of an azabicyclic intermediate obtained from the asymmetric Diels-Alder reaction of a chiral oxazolone derived from *R*-glyceraldehyde with Danishefsky's diene. Cyclopenta[c]proline derivatives (**42**) were formed[185] from enyne amino acid derivatives in a stereocontrolled manner using catalytic Pauson-Khand reactions. A facile synthesis[186] of protected 3*R*, 5*R*-dihydroxyhomoproline has been achieved using L-threonine aldolase as an enzyme catalyst. The potent metabotropic glutamate receptor agonist (1*S*, 3*R*)-l-aminocyclopentane-l, 3-dicarboxylic acid (**43**) has been prepared[187] from serine via C–H insertion of an alkylidene carbene, and a stereoselective route[188] has been used to form 3-substituted 2-amino cyclopentane carboxylic acid derivatives.



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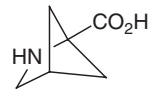

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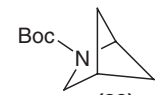

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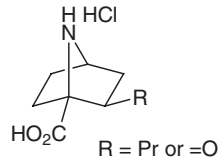
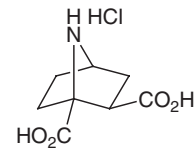


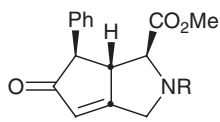
R = Pr or =O

(40)



(41)

Pyroglutamic acid has been the starting point for the synthesis[189] of (3*S*, 4*R*)-3,4-dimethyl-L-pyroglutamic acid and (3*S*, 4*R*)-3,4-dimethylglutamine, with the methyl groups being introduced via a cuprate and enolate addition. *N*-Ts and *N*-Boc derivatives of (2*S*, 4*S*)-4-phenylamino-5-oxoprolines have also been synthesised.[190] A common strategy has been devised[191] for the synthesis of pipecolic acid derivatives (**44**) and (**45**) and involves intramolecular eneiminium cyclisation. Analogue (**45**) has also been prepared[192] using the stereoselective addition of allyltrimethylsilane with *N*-tosyl- and *N*-phenyl-iminoglyoxylates of (*R*)-8-phenylmenthol. Several pipecolic acid derivatives have been synthesised[193] from 2, 3-epoxy-5-hexen-l-ol, followed by regio- and stereo-selective ring opening with allylamine, while the constrained phenylalanine analogue (2*S*, 3*R*)-3-phenylpipecoiic acid has been obtained[194] from the Evans chiral auxiliary (4*S*)-4-benzyl-l, 3-oxazolidin-2-one. (2*R*, 3*R*)-3-Hydroxypipecolic acid has been obtained[195] from the *O*-protected methyl mandelate, *via* the nucleophilic substitution of an azide epoxide.



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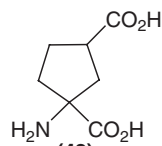

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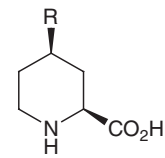


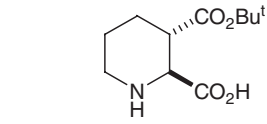
(44) R = Me

(45) R = OH

Both enantiomers of 4-oxo-pipecolic acid have been synthesized[196] via 1, 3-dipolar cycloaddition of C-ethoxycarbonyl-*N*-(1*R*)-phenylethylnitrone to but-3-en-l-ol, and a range of different disubstituted pipecolic acid derivatives have been made[197] via an oxidative cleavage of azabicycloalkene synthesised from an aza Diels-Alder reaction. *Trans*-3,4-Piperidindicarboxylic acid derivative (**46**) and a *trans*-3, 4-analogue have been synthesised[198] asymmetrically in 5 steps starting from aspartic acid *t*-butyl ester and Z-(*S*)-alanine respectively via intermediates which on ozonolysis and reductive animation provided the cyclic structures. Five and six-membered cyclic amino acids can be obtained[199] in a one-pot protocol by a rhodium-catalysed (Rh-DuPHOS) hydroformylation/

cyclisation sequence. Benzocyclic α, α-dialkyl amino acids (**47**) have been constructed[200] via an asymmetric Strecker reaction using *S*-α-methylbenzylamine and *R*-phenylglycinol as chiral auxiliaries, while the benzene ring in the benzocycloheptene α-amino acid derivatives (**48**) was built up[201] from a Diels-Alder reaction of a seven-membered ring diene with various dienophiles. Rigidified bicyclic α-amino acids have also been obtained[202] from appropriate 1,6-heptenynes and the reactions[203] of acyclic and cyclic dehydroalanines with 1,3-dienylcobaloxime complexes have yielded functionalised carbocyclic amino acids. Crown ether macro-rings such as (**49**) have been built up[204] from masked tris(hydroxymethyl)amino methane, and shown to be capable of stacking in the presence and in the absence of alkali metal ions.

Compounds (**50**) with *cis*- and *trans*-relationships between the 2,5-dihydroxy groups have been made[205] starting from Diels-Alder reactions between oxazolones and dienes. Cyclohexylglycine scaffolds have been synthesised[206] and tested for potency as matrix metalloproteinase inhibitors, and *cis*- and *trans* forms of 4-Boc-cyclohexylglycine have been obtained[207] from amino-hydroxylation of styrene. Rhodium-catalysed[208] hydrogenation of enamide (**51**) gave (*R*)-4-piperidinylglycine in good yield. The cyclopentyl glutamate analogue (**52**) formed[209] using a [3 + 2] cycloaddition reaction of dehydroamino acids turned out to be a potent agonist of the mGlu5 and mGlu2 receptors. Methyl substituted cyclohexyl-l-amino-3-hydroxy-l-carboxylic acids have been prepared[210] from 5,5-tethered dienes of (2*R*)-2, 5-dihydro-2-isopropyl-3, 6-dimethylpyrazine.



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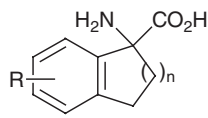
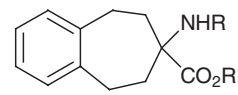


(47) n = 1, 2 or 3



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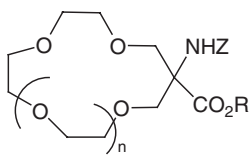
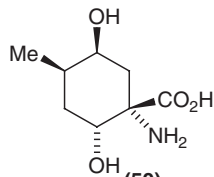


(49) n = 1, 2 or 3



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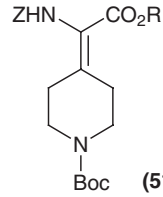

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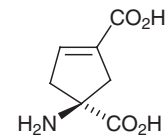


(52)

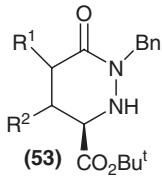
A new class of cyclic amino acids based on (**53**) (6-oxoperhydropyridazine-3-carboxylic acid derivative) has been created[211] by diastereoselective transformation of α, β-didehydroglutamates. An improved synthesis[212] of (−) CIP-AS (**54**), an analogue of glutamic acid has been reported, which involves cycloaddition of ethoxycarbonyl formonitrile oxide to a *N*-(4-methoxybenzyl)α-ethoxycarbonyl nitrone. Further clarification[213] has been given of the conditions that favour cyclopropane *vis à vis* cyclopentene ring formation from a Schiff base derivative of glycine and bis-alkylating alkenes.

The synthesis[214] of 2-cyclopentadienylglycine (**55**) from α-bromohippuric acid with nickelocene, or other cyclopentadienyl complexes has provided a means of studying its dimerisation in Diels-Alder reactions and in ferrocenylene formation. By coupling ethyl isocyanoacetate with 1,2-bis (4-bromoethylphenyl)ethane under phase transfer conditions a macrocyclic cyclophane α-amino acid was produced,[215] and in a Diels-Alder reaction[216] between methyl 2-acetamidoacrylate and anthracene a highly constrained α-amino acid derivative was produced.

Fmoc-Protected lipophilic amino acids with alkyl side chains varying from C_{12}–C_{16} have originated[217] from the alkylation of Schiff bases obtained from 2-hydroxypinan-3-one with Gly-OBu^t. (*S*)-2-Amino-8-oxodecanoic acid a constituent of the cyclic tetrapeptides, the apicidins, has been synthesised[218] from an iodo-ester of glutamic acid which was subjected to photolytic condensation with ethyl vinyl ketone in the presence of tri-*N*-buryltin hydride. (*S*)-2-Amino-oleic acid was obtained[219] from a chiral aldehyde, Bu-(2*S*)-2[bis(Boc-amino)]-5-oxopentanoate, derived from glutamic acid, which underwent a Wittig reaction with appropriate ylides.

4.5 Models for Prebiotic Synthesis of Amino Acids. – Only one publication was found that fitted into this category, and was a report[220] of low energy nitrogen ions being implanted into carboxylic salt solutions to give hplc evidence for the production of amino acids.

4.6 Synthesis of Halogenoalkyl α-Amino Acids. – The only member of the halogen series with the correct stability profile is fluorine, so it commands a monopoly of the papers. The Reformatsky reaction between Garner's aldehyde (from D-serine) and ethyl bromodifluoroacetate[221] followed by further processing yielded L-4, 4-difluoroglutamine, and the same reaction[222] after slight modification gave L-4, 4-difluoroglutamic acid. New approaches[223] for incorporating fluorine stereoselectively have included, alkylation of chiral glycine Schiff bases, intramolecular cyclisation of chiral cyanohydrins and catalytic hydrogenation of fluorinated imino esters. Chiral α-fluoroalkylated mesylates with Boc-Gly-OH in the presence of Pd-catalyst have given[224] γ-fluoroalkylated allyl esters, which after an Ireland-Claisen rearrangement gave α-fluoroalkylated-β,γ-unsaturated amino acids. β, β-Difluoro amino acids have been made[225,226] via the alkylation of a hydroxypinanone glycinate from ethyl trifluoropyruvate, or via carboxamides or substituted ureas.[227] 5, 5, 5, 5′, 5′, 5′-Hexafluoroleucine has been obtained[228] from addition of an organozincate (from Z-L-serine) to hexafluoroacetone followed by a radical-mediated deoxygenation. (2*S*, 3*R*)-Difluorothreonine's synthesis was evolved[229] from 3, 3-difluoroacetaldehyde, an alkenyl or arylboronic acid and an amine in high yield and ee. Hydride reduction stereocontrolled[230] by intramolecular π-stacking of 1-naphthylsulfinyl and *N*-aryl groups, non-oxidative Pummerer rearrangement and ring-closing metathesis, have given both cyclic and acyclic fluorinated α-amino acid derivatives. Ring-closing metathesis using a ruthenium catalyst, also formed[231] the last stage in the synthesis of 5-, 6- and 7-membered cyclic amino esters such as (**56**), and used similarly in another publication.[232]



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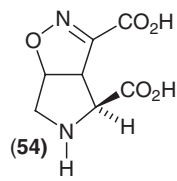

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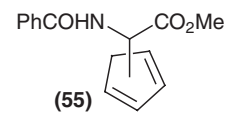

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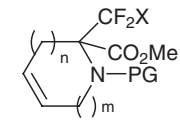

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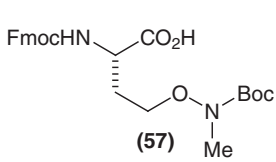
A number of fluorinated proline analogues have been made, such as *cis*- and *trans*-4-trifluoromethyl D-proline from serine[233] involving the reaction between Garner's aldehyde and an ylide, followed by trifluoromethylation. From the same authors[234] comes a report that *N*-Boc-*cis*-4-trifluoromethyl (and difluoromethyl)-L-proline could be made from *N*-Boc-4-oxo-L-proline using either CF_3SiMe_3 or CF_2Br_2/Zn respectively, and in another approach,[235] the 4-oxoproline was again alkylated with CF_3SiMe_3, whose adduct was allowed to dehydrate to a cyclic alkene which was hydrogenated stereoselectively using Ir(cod)(py)PCy_3 (Crabtree's catalyst). Fmoc-(4*R*) and (4*S*)-fluoroprolines have been synthesised[236] from 4(*R*)-hydroxyproline using a Mitsunobu reaction.

4-Fluoro- and 4,4-difluoropipecolic acid have been stereoselectively synthesised[237] from Z-protected 4-OH- and 4-oxopipecolates via fluorodehydroxylation and fluorodeoxygenation. For the preparation[238] of α-fluoromethyltryptophans, highly electrophilic imines derived from methyl bromodifluoro- and trifluoropyruvate were reacted with l-sulfonyl-3-methyleneindolines, and for the synthesis[239] of α,α-difluoro-β-amino acids, starting from aldehydes and ethyl bromodifluoroacetate, a Mitsunobu reaction was again the key step. Similar products were obtained[240] from the solid phase condensation of amines, aldehydes, benzotriazole and a Reformatsky reagent prepared *in situ* from ethyl bromodifluoroacetate, trimethylsilyl chloride and zinc. Using the recently discovered electrophilic *N*-fluoro-cinchona alkaloid reagent, it has been proven[241] that it will carry out α-deprotection/fluorination with enantiomeric excess up to 94% in the synthesis of α-fluoro-*N*-phthaloylphenylglycinonitrile. Taking the pathway summarised in Scheme 10, α-trifluoromethyl α-amino acids have been obtained[242] from sulfinimes and trifluoropyruvates using Grignard reagents with the source of chirality being menthylsulfinate which can be recycled.



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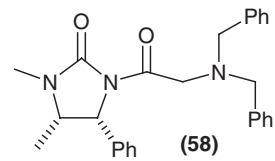

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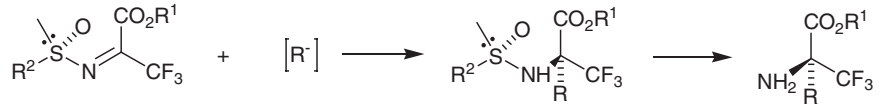
4.7 Synthesis of Hydroxyalkyl α-Amino Acids. – A general method[243] whereby 2-benzyloxyaziridine-2-carboxylates undergo regioselective hydrogenolysis has been shown to yield α-substituted serines. A stereoselective synthesis[244] of Z-D-Ser-OMe involved an intermediate tetrahydrooxazin-4-one generated from a hetero Diels-Alder reaction between 2-aza-3-trimethylsilyloxy-1,3-diene and

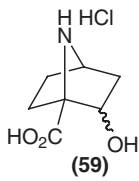


Scheme 10

gaseous formaldehyde. Z- and Boc-(*S*)-Isoserines have been obtained[245] from the appropriate (*S*)-malic acid monoester via an oxazolidin-2-one, and a protected form (**57**) of *N*-methylated amino-homoserine suitable for Fmoc-protocols has been produced.[246]

There have been a number of examples of OH groups generated in the side chains of proteinogenic acids, thus 2*S*, 3*R*, 4*S*-4-hydroxyisoleucine, a potent insulinotropic amino acid from the seeds of fenugreek, has been made[247] by biotransformation of ethyl, 2-methylacetoacetate to (2*S*, 3*S*)-2-methyl-3-hydroxybutanoate followed by an asymmetric Strecker synthesis. Protected β-hydroxyvalines were obtained[248] from *N*-protected serine methyl esters via a Grignard addition (MeMgBr) to the ester group followed by selective oxidation of the diol formed with a hypochlorite cocktail. (2*S*, 3*S*)-3-Hydroxyleucine was the model compound synthesised[249] to test out a stereodivergent approach starting from a symmetrical alk-2-yne-l, 4-diol and using a Pd(0)-catalysed process to select the stereochemistry of the α-carbon in the amino acid produced. Four stereoisomers of 3,4-dihydroxyglutamic acid have been formed[250] as a result of a stereoselective cyanation of an *N*-acyliminium intermediate derived from L- or D-tartaric acid. (2*S*)-2-Hydroxymethyl-glutamic acid (HMG), a potent agonist of metebotropic glutamate receptor mGlu R3 has been obtained[251] from *S*-pyroglutaminol, via a bicyclic siloxypyrrole. Another route to HMG[252] involved starting from D-serine, followed by a tandem Michael addition, a ring-closure protocol, followed by a stereoselective alkylation reaction from the convex face of the bi-cycle. The imidazolidinone (**58**) has been shown[253] to give excellent stereocontrol and can be considered a chiral enolate equivalent, which can undergo diastereoselective aldol reactions which give rise to β-hydroxy-α-amino acids. *Syn*-(*S*)-β-Hydroxy α-amino acids have also been synthesised[254] via asymmetric aldol reactions of aldehydes with a chiral Ni(II) BPB/glycine Schiff base complex in the presence of NaH. A multigram scale preparation of *syn*-(*S*)-β-hydroxyleueine was possible using this method. L-2-Amino-4, 5-dihydroxypentanoic acid has been prepared[255] from L-allylglycine and using appropriate protection it is a good precursor for conversion to an aldehyde side chain in peptides. Enantiopure ω-hydroxy-α-amino acids were key[256] to the synthesis of a number of C-15 α-amino carboxylates and were produced as a result of the Wittig reaction of methyl (2*S*)-2-[bis(Boc-amino)]-5-oxopentanoate with ω-trityloxyalkylidene triphenylphosphoranes. A general strategy[257] has been developed to access α, β-dihydroxy-α-amino acid via N-carboxyanhydrides produced by ring expansion of 3-hydroxy-β-lactams. Enantiomerically and diastereomerically pure 2(*S*)-amino-6(*R*)-hydroxy-l, 7-heptanedioic acid dimethyl ester has been derived[258] from cycloheptadiene using an acylnitroso Diels-Alder reaction as the

key step. *Anti*-β-Hydroxy-α-amino acid esters were obtained[259] as the major diastereoisomer with moderate enantiomeric excess using a direct aldol reaction of glycinate Schiff bases with aldehydes, using heterobimetallic asymmetric complexes as catalyst.



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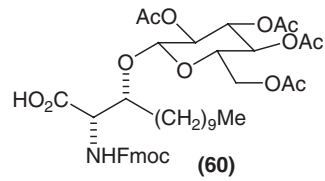


(60)

Two building blocks as part of the structure of the cyclic depsipeptide, callipeltin A, have been synthesised. (2*R*, 3*R*, 4*S*)-3-Hydroxy-2, 4, 6-trimethylpentanoic acid has been obtained[260] from L-valine using the Heathcock variant of the Evans aldol reaction, while a fully protected (2*R*, 3*R*, 4*S*)-4, 7-diamino-2,3-dihydroxyheptanoic acid has been produced[261] by a multistage process from D-glucose. The protease inhibitor statine, continues to be thoroughly researched as in the synthesis of all four 2,3-stereoisomers of 2-substituted statines.[262] The 2,3 *syn*- and *anti*-isomers were synthesised via β-ketoester and aldol reactions. Since Mitsunobu reactions of *syn*-2,3-dihydroxy esters exhibited[263] complete regioselectivity for the β-hydroxyl to give *anti* α-hydroxy β-Nu ester (Nu = OBz, OTs, N_3), which could be processed to form natural *syn*-statine and its *anti* diastereoisomer. Fmoc-(2*S*, 3*S*)-2-hydroxy-3-amino acids have been synthesised[264] starting from 2-furaldehyde, cyanation being catalysed by R-oxynitrilase, and final removal of the furan ring by ozonolysis.

Cyclic amino acids bearing hydroxyl groups have also been the focus of interest. *N*-Boc-(2*S*, 5*R*)-5-(1′-hydroxy-l′-methylethyl)proline was chosen[265] as a *cis*-conformation inducer in Xaa-Pro amide bonds and was synthesised from enantiopure 2, 5-disubstituted pyrrolidine. With the availability of chiral 2-amino-3-hydroxy-4-pentanoate from sugars,[266] cyclisation stages produced both *trans*-3-hydroxy-L-proline and *cis*-3-hydroxy-D-proline. (2*S*, 3*R*)-3-Hydroxy-3-methylproline, found in the polyoxypeptins, has been synthesised[267] via the Sharpless regioselective opening of a cyclic sulfate by NaN_3 and an intramolecular ring closing reaction. By starting with *trans*-4-hydroxy-L-proline and using acetic anhydride, the intermediate lactone contains an inverted stereochemistry at C-4 so that acidic cleavage of the lactone gave *cis*-hydroxy-D-proline.[268] Two independently-reported routes to 3, 4-dihydroxyprolines, involved either a strategy[269] starting with a pentose sugar γ-lactone, or a protocol[270] based on ring-closing metathesis of unsaturated chiral allyl amines. These allyl amines were synthesised from unsaturated epoxy alcohols or from 2,3-epoxy-3-phenylpropanol. All four conformationally constrained analogues (**59**) of 3-hydroxyproline have been synthesised[271] starting from a Diels-Alder reaction between methyl benzamidoacrylate and Danishefsky's diene (1-methoxy-1,3-butadiene) followed by an internal nucleophilic displacement of methanesulfonyl group in the cyclohexane ring. Crystallisation techniques afforded the final resolution to chiral purity.

$RuO_2/NaIO_4$ oxidation[272] of *N*-Boc-4-silyloxy- and 4-acetoxyproline methyl esters under biphasic conditions and after deprotection, have given both *cis* and *trans* methyl, *N*-Boc-4-hydroxypyroglutamates. Constrained serine analogues[273] (1*S*, 2*S*)-, (1*R*, 2*R*), and (1*R*, 2*S*)-1-amino-hydroxy cyclohexane carboxylic acids were synthesised in racemic forms using the Diels-Alder reaction of 2-benzamidoacrylate with Danishefsky's diene, followed by resolution methods. Hydroxylation of 6-substituted piperidine-2-ones has provided[274] an efficient synthesis of (2*S*, 5*R*)-5-hydroxylysine and related amino acids. Lipo-β-hydroxy amino acids and their glycoside derivatives such as (**60**) have been formed[275] by selective oxidation of protected amino diols, formed from a D-serine Schiff base. In order to clarify the configuration of the natural β-methoxytyrosine in the cyclodepsipeptide, the papuamides all four stereoisomers have been synthesised[276] via their β-hydroxy counterparts. The latter were synthesised from Garner's aldehyde [from (*S*)-serine] with 4-benzyloxyphenyllithium at −78°C in presence of LiBr. Ethyl isothiocyanatoacetate and a range of aromatic aldehydes, in the presence of triethylamine, magnesium(II) perchlorate and bipyridine, reacted together[277] to form β-hydroxy-α-amino acids.

4.8 Synthesis of *N*-Substituted α-Amino Acids. – While the *N*-methyl analogues of most of the proteinogenic amino acids are known, their synthesis still demands chemical rigour, so a methodology[278] based on reductive alkylation of Schiff bases both in solution and on solid phase is welcome. Similarly, the unified approach for the methylation of the 20 common acids through 5-oxazolidinones has been researched,[279] and it is concluded that the side-chains of Ser, Thr, Tyr, Cys, Met, Trp, Asn, His and Arg needed protecting groups during the methylation process, but these can be chosen to be compatible with applications for peptide synthesis, A novel solid phase method for monomethylation has also been develop,[280] whereby amino acids supported on Wang or Sasrin resin can be methylated with pinacol chloromethylboronic ester followed by rearrangement of the resulting aminomethylboronate and subsequent cleavage. Both *N*-*Z* and *N*-Fmoc protected MeSer and MeThr have been synthesised[281] via their oxazolidinones, but using *t*-butyldimethylsilyl as the transient side chain protecting group.

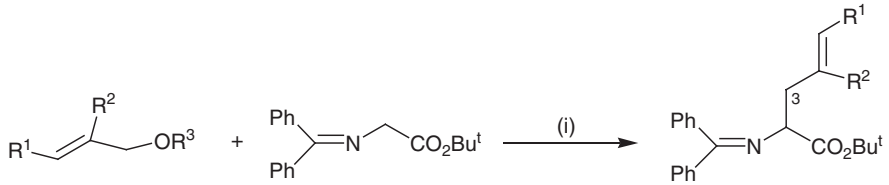
A series of benzylamides of *N*-alkylated and *N*-acylated cyclic and linear amino acids have been synthesised[282] for the testing of their anticonvulsant activity, and *N*-formyl-L-aspartic anhydride has been prepared[283] using $HCOOH/Ac_2O/MgO$. N-Acylated amino acids have been synthesised[284] from *N*-acylamino esters using a polymer-supported amine and scandium triflate, and *N*-phthaloyl derivatives have been obtained[285] in a rapid one-pot procedure involving monomethyl phthalate, BOP and Pr^i_2Net to give an intermediate which then cyclises in aqueous sodium carbonate. A selection of *N*-acyl homoserine lactone analogues have been synthesised[286] and tested for their ability to inhibit bioluminescence, while *N*-acetyl L-glutamic acid was formed[287] efficiently using Ac_2O in alkaline solution. A new reagent 2-[phenyl(methyl)sulfonio]ethyl-4-nitrophenylcarbonate tetrafluoroborate[288] has been introduced for attachment of a water soluble protecting group onto

sulfur-containing amino acids. Scalable syntheses of Z- and Fmoc-Orn have been noted,[289] p-Toluenesulfonamido glutaramides have been prepared[290] from Tos-Cl, Glu and amines, and a novel method[291] has been described for the synthesis of *N*-sulfonyl protected amino acids. Orthogonally protected amino acid building blocks for combinatorial *N*-backbone cyclic peptides have been produced[292] for all amino acids except proline. N^{α}–Aminoallyloxycarbonyl- and carboxyallyl derivatives were first produced, via alkylation (alkyl halides), reductive amination (aldehydes), and Michael addition (α,β-unsaturated carbonyl compound), followed by Fmoc protection of the remaining N–-H bond.

3-*N*-Phthaloyl homophenylalanine lactone has been synthesized,[293] and sodium salts of valine, leucine and phenylalanine when treated[294] with acid chloride of trichlorovinylacetic acid and 3, 3, 4, 4, 4-pentachlorobutanoic gave *N*-chloroacyl derivatives. *N*-Stearylleucine was formed[295] from stearyl chloride under Schotten-Baumann conditions and a number of 2, 6-disubstituted benzoyl derivatives have been prepared[296] in the series N-benzoyl-4-[(2,6-dichlorobenzoylamino)]-L-phenylalanine to test for VCAM/VLA-4 antagonist activity. N-Boc- and N-benzoyl-(*S*)-phenylglycinals have been prepared[297] by the oxidation of the respective alcohols (racemisation free) with Dess-Martin periodinane. *N*-(2-Boc-aminoethyl)glycine esters have been produced[298] from Boc-aminoacetaldehyde and glycine esters, and when a H_2/O_2 flame was blown against an aqueous solution of urea and maleic acid, *N*-carbamoylaspartic acid was generated.[299]

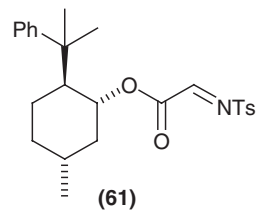
A library of *N*-substituted amino acid esters have been produced[300] by a novel 4-component synthesis using a polymer-bound isocyanide, and when the N^{α} - group is protected[301] by a hydrolysable protecting group (e.g. trifluoroacetyl or an enamine), methyl esters could still be made using Me_2SO_4 with the tetramethylguanidinium salts of the acids. *Threo*-*N*-Benzoyl-3-phenylisoserine has been prepared,[302] and *N*-arachidonyl derivatives of both *O*-phospho-L-serine and *O*-phospho-L-tyrosine have been formed[303] through firstly forming the *N*-arachidonyl derivative followed by phosphorylation with cyanoethylphosphate. A series of *N*-aryl-2, 6-dimethoxybiphenylalanine analogues were prepared[304] for inhibition studies on integrin VLA-4, using aryl halides/$NaOBu^t$/BINAP/Pd_2dba_3 in toluene at 75°C. A 1,4-benzoquinone and three 1,4-naphthaquinones have been directly reacted[305] (2 equivalents) with a series of ω-amino acids to form adducts which have been subjected to electrochemical studies. In model studies[306] for scyphostatin *N*-palmitoylation of the amino group was necessary to produce (*S*)-*N*-(l-benzyl-2-hydroxyethyl)hexadecanamide and *N*-pyrazolidinyl amino acids resulted[307] from reaction of l-acetyl-2-phenyl-5-hydroxypyrazolidine with amino acid esters. Details have been disclosed[308] for the synthesis of N^{α}[4-(2-(2,4-diaminoquinazolin-6-yl)ethyl)]benzoyl-N^{δ}-hemiphthaloyl-L-ornithine and a 4-amino-deoxypteroyl analogue.

4.9 Synthesis of α-Amino Acids carrying Unsaturated Aliphatic Side Chains. – Allylic alkylations have been carried out in different modes, e.g as in Scheme 11, where the alkylations[309] with simple allylic substrates were catalysed by chiral



Scheme 11 *Reagents: (i) Pd/phosphine/PTC/CsOH H_2O/Solvent.*

quaternary ammonium salts giving ee's of up to 61%. In a variation of this approach, the glycine esters were added[310] as zinc enolates. Producing allylic isomers with substitution at position 3 (3 on product in Scheme 11) is more synthetically demanding, but has been achieved[311] by molybdenum-catalysed asymmetric allylic alkylation using azlactones as the 'glycine' element. Good stereoselectivity (*anti*-configured products) has been obtained[312] due to suppression of π-σ-π isomerisation, if zinc enolates of TFA-protected glycine esters were reacted in the presence of [allylPdCl]$_2$.



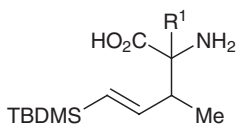
(61)

Asymmetric addition[313] of allyltrimethylsilane to a chiral *N*-tosylimine (**61**) derived from 8-phenylmethyl glyoxylate in the presence of various Lewis acids has been monitored. Good diasteroselectivity was found for $ZnBr_2$, $ZnCl_2$, $TiCl_4$ and $SnCl_4$, but poor selectivity using $BF_3.Et_2O$.

Chiral (*Z*)-α, β-didehydro amino acids have been generated[314] from a chiral iminic cyclic glycine template with 1, 2, 3, 6-tetrahydropyrazin-2-one by condensation with Eschenmoser's salt and Bredereck's reagent. These can be further arylated in the presence of $Pd(OAc)_2$. Enantioselective hydrolysis of amino acid amides using an amidase has been applied[315] to a series of unsaturated amino acids, which can be up-graded to multigram scale. α-Methylene-β-amino acid derivatives have been obtained[316] from aldehydes, sulfonamides and α, β -unsaturated carbonyl compounds using the aza-version of the Baylis-Hillman reaction, with DABCO as base and $La(OTf)_3$ as a Lewis acid. An asymmetric version[317] of the same reaction between *N*-*p*-toluenesulfinimines and methyl acrylate in the presence of $In(OTf)_3$ has also been successfully developed for β-amino-α-methylene esters. The effect of base and solvents on the formation of dehydroalanine through elimination of *p*-Ts from *p*-tosylserine derivatives has been monitored.[318] *N*-Boc- and *N*-Z-α-tosyl ethylglycinates have been reacted[319] with aldehydes in the presence of tributylphosphine and a base under Wittig conditions to give the corresponding α, β-didehydro-amino acid derivatives with high *Z*-selectivity and in good yields.

A concise, scalable route to both isomers of *Z*-2-Boc-amino-6-hydroxyhex-4-enoic acid, has been carried out[320] starting from 2-butyne-l, 4-diol, featuring acylase enzymes in the resolution step. Introduction of allyl groups into the side chain without loss of chirality has been facilitated[321] via the intermediate formation of a terminal aldehyde group in the side chain (generated from the Weinreb amides of aspartic or glutamic acids), which was then subjected to methyl triphenylphosphonium bromide in a Wittig reaction. Starting from L-vinylglycine, enantiomeric purity has been preserved[322] in the making of D- or L-quaternary α-(2-stannylvinyl) amino acids. A series of reaction steps has enabled[323] L-vinylglycine to be synthesised in a novel way from D-xylose. An enolate-Claisen rearrangement of α-acyloxysilane has led[324] to an enantioselective synthesis of compounds such as (**62**) possessing two consecutive chiral centres. A vinylidene-^{3}H analogue of (−)-α-kainic acid has been synthesised[325] via an intermediate keto group substituted in the side-chain of the proline compound, and the 4-keto group in the proline ring of kainic acid was the starting point for transformations[326] leading to (+)-α-allokainic acid. Isoxazolyl and pyrazolyl moieties have been added[327] via 2H-pyran-2-ones to α, β-didehydroamino acid derivatives.

Reaction of *N*-butylsulfonyl, *N*-trimethylsilylethanesulfonyl and *N*-Ts α-imino esters with bis (allyl) titanium complexes, in the presence of $Ti(OPr^i)_4$ and $ClTi(OPr^i)_3$ has given, with high regio- and stereo-selectivity, δ-sulfonimidoyl functionalised β-alkyl-γ,δ-unsaturated amino acids.[328] Dehydrophenylalanine cyclophanes bearing structures such as (**63**) have been synthesised,[329] and the influence of the length of the tethers between the amino acid residues assessed.



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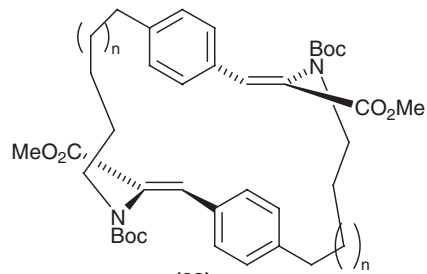


(63)

In synthetic transformations leading to dihydrofurans from amino acids intermediate synthons involved the synthesis[330] of allenic α-amino acid derivatives by 1, 6-addition of the cyano-Gilman reagent, *t*-But-CuLi-LiCN to substituted enynoates, followed by deprotection stages, A convenient route[331] has been found to incorporate alkyne groups into the γ, δ-position of the side chain by treating an aziridine, 1-[(*S*)-l-(2-nitrobenzensulfonyl)-aziridin-2-yl]-4-methyl-2, 6, 7-trioxabicyclo[2,2,2]-octane, with a variety of lithium acetylides. The alkyne-containing amino acids were further transformed to C-glycosyl amino acids. A Heck reaction[332] of (*S*)-*Z*-*N*-allylglycine Bu^t ester with aromatic halides has yielded a series of arylallylglycine derivatives.

Although not strictly side–chain unsaturation, it is appropriate to record the preparation of *N*-allyl amino esters[333] by either reaction of allylamine with $Cl(CH_2)_nCOOEt$ or with ethyl acrylate, and the addition of a range of (hetero)-aryl bromides to the alkyne function in *N*-propargyl alanine[334] using a cross-coupling reaction catalysed by 10% Pd/C.

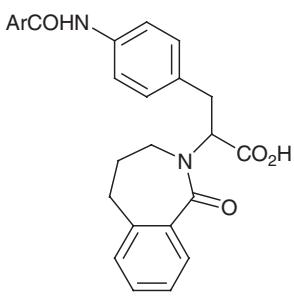
4.10 Synthesis of α-Amino Acids with Aromatic or Heterocyclic Side-Chains. – There has been a flurry of activity in incorporating fluorine into aromatic side-chains, for use as tracers in medical imaging (PET). It has been shown[335] that direct fluorination ($^{18}F_2$) of L-α-methyltyrosine in TFA or in HF, produced 3-^{18}F-α-methyltyrosine in up to 30% radiochemical yield. 3, 5-Difluoro- and α-methyltyrosine could also be produced. Alkylation under phase transfer conditions of the Oppolzer chiral sultam with fluorinated analogues of 3, 4-$(OMe)_2$-benzyl chloride, proceeded[336] diasteroselectively, to produce after deprotection 2-, 5-, 6-fluoro- and 2,6-difluoro-DOPA. Fluorinated DL-phenyl-alanines were synthesised[337] from fluorinated aromatic aldehydes by a 'one-pot' procedure involving Erlenmeyer reactions and subsequent reduction (P/HI). 6-^{18}F-Fluoro-L-DOPA has been synthesised in less than 2 hr, using chiral catalytic transfer alkylation techniques.[338] The Erlenmeyer azlactone strategy has also been employed[339] for the synthesis of 6-fluoro-*meta-tyrosine* from 2-fluoro-5-hydroxybenzaldehyde, and *O*-(2-[^{18}F]-fluoroethyl)-L-tyrosine was made[340] in a remote-controlled 'no carrier added' synthesis. 2-Fluoro- and 6-fluoro-(2*S*, 3*R*)-(3, 4-dihydroxy-phenyl)serines, were also produced[341] via oxazolidine intermediates formed from 3, 4- (and 4, 5)dibenzyloxy-2-fluoro-benzaldehyde respectively. Cell-free extracts from a number of bacterial strains were found to catalyse[342] the transamination of 4-fluorophenylglyoxylic acid to 4-(*S*)- fluorophenylglycine. Aniline derivatives have been the source[343] of halogenated-substituted phenylalanines and radio-iodination techniques for aromatic amino acids have been reviewed.[344]

An efficient 5-step sequence to synthesise optically active 3-arylprolines has been developed[345] starting from aromatic aldehydes and cinnamyl alcohol, with L-proline derivatives as chiral auxiliaries. An aza-Claisen rearrangement with azidoacetyl fluoride became a key stage in the synthesis. 4-*cis*-Phenyl-L-proline has been synthesised[346] starting from naturally-occurring 4-*trans*-HO-L-Pro, via the formation of the 4-oxo derivative which underwent a diastereoselective Grignard reaction with PhMgBr. A novel family of chiral *N*-4-pyridinylproline derivatives have been developed[347] as potential stereoselective catalysts, using nucleophilic displacement of 4-chloropyridine by a proline imino group.

Constraining the flexibility of the aromatic side-chains of amino acids has been actively developed in designing pharmacophores. Over this period examples come from:- the benzazepinone derivative (**64**) which was potent in a VCAM/VLA-4 ELISA assay;[348] indane-based constraints as in (**65**) introduced via a [4+2] cycloaddition, a dialkyne strategy[349] or by starting with phenylglycine;[350] the novel endo-12-aminotricyclo[6.3.2.0(2,7)]trideca-2(7), 3, 5-triene-12-exo-carboxylic acid made from cycloheptadiene;[351] *o*-aryl substituted phenylalanines, naphthylalanines and tryptophan analogues synthesised[352] via

asymmetric hydrogenation of α-enamides using Burke's DuPHOS-based Rh(I) catalyst, followed by Suzuki cross-coupling with boronic acid derivatives. L-2-Naphthylalanine has also been produced[353] from 2-naphthylpyruvate and L-glutamate catalysed by a thermostable aminotransferase. Two separate reports[354,355] summarise different approaches to the synthesis of l, 2, 3, 4,-tetrahydroisoquinoline-carboxylic acid (Tic). A first synthesis[356] of 6-hydroxyoctahydroindole-2-carboxylic acid, a key strategic element in the structure of aeruginosins 298 has been reported. The stereochemical route started with L-tyrosine which underwent a Birch reduction followed by aminocyclisation. Octahydroanthracene amino acids affording conformationally-constrained lysine analogues have also been synthesised (18 steps).[357]

Arylglycines, as components of a number of natural products, have found popularity over recent years. A 'one-pot' novel procedure[358] for their synthesis involved treatment of the side chain OH group of serine with (diacetoxyiodo)benzene and iodine, with the resulting radical being oxidised by a cationic glycine equivalent which can be trapped by nucleophiles (aryl and a number of other types). *N*, *N*′-Di-Boc-protected benzylamines have been shown to undergo[359] 1,2-Boc migration on treatment with KDA/Bu^{t}OLi to give *N*-Boc-phenylglycine Bu^t esters. Mannich-type reaction of phenols with an iminolactone from phenylglycine has given[360] highly stereoselective yields of α-arylglycines. The highly fluorescent L-3-(l-pyrenyl)alanine has been obtained[361] by asymmetric hydrogenaton of 1-acetyl-3-pyrenemethylidene-6-methylpiperazine-2, 5-dione, and novel pyrazolylglycines (**66**) have been produced,[362] including l-hydroxypyrazoleglycine formed[363] by addition of organomagnesium and lithium intermediates to diEt-*N*-Boc-iminomalonate. *N*-Protected arylglycines have been diastereoselectively synthesised[364] via $TiCl_4$ promoted Friedel-Crafts reaction of phenols with chiral *N*, O-hemiacetals. α-Alkyl-α-phenylglycines were obtained[365] by asymmetric synthesis, via phenylation/alkylation of (2*R*, 3*S*)-*N*-Boc-6-oxo-2, 3-diphenylmorpholine followed by hydrolytic ring opening. α-Arylation in high yields has been reported[366] for the reaction of aryl bromides with protected glycinate esters in the presence of Li or Na hexamethyldisilazide and $Pd(dba)_2$/ligand.



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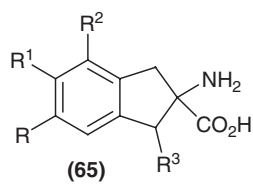

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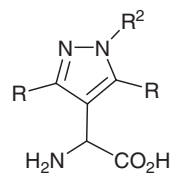

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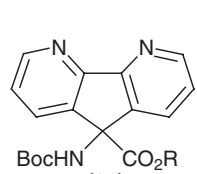
Fmoc-L-*p*-Azidotetrafluorophenylalanine has been prepared[367] from acetamidomalonate, followed by enzymic resolution. 4-Aminophenylalanine has been synthesised[368] from 4-hydroxymethyl anilines via aza quinone methide intermediates, while Boc-L-*p*-aminophenylalanine has been utilised[369] to make FRET cassettes. A practical 'one-pot' catalytic procedure[370] has been developed for both aromatic and heteroaromatic amino acids, utilising a chiral BINAP-Cu catalyst for the addition of aromatic/heteroaromatics to *N*-alkoxycarbonyl α-iminoesters. A cross-enyne metathesis reaction has been the foundation[371] of a synthetic route to many highly substituted phenylalanines. In order to access β-hydroxyphenylalanine, a component of ustiloxin D, use has been made[372] of the Sharpless asymmetric aminohydroxylation of substituted cinnamic acids, using 2-trimethylsilylethyl carbamate with Os(VIII)/$(DHQD)_2AQN$ as catalyst. Homophenylalanine derivatives have been made using cycloaddition[373] of a cyclic nitrone glycine template with styrene derivatives or from L-malic acid.[374] The synthesis of (*S*)-α-methylphenylalanine has featured[375] in the development of better chiral catalysts for C-alkylation of aldimine Schiff bases of alanine esters. (*S*)-3, 3′-Bis[(diethylamino)-methyl]-2, 2′dihydroxy-l, 1′-binaphthalene gave the best ee's. Several α-benzylphenylalanines have been prepared[376] by alkylation of ethyl isocyanoacetate with different benzyl bromides, the products being further derivatised via the Suzuki-Miyaura coupling reaction. The two enantiomers of α-methyldiphenylalanine have been resolved[377] using chiral hplc separation. New photoactivatable phenylalanine analogues have been synthesised[378] via the asymmetric synthesis of (*S*)-Boc-*p*-(propanoyl)phenylalanine from the alkylation of sultam *N*-(diphenylmethylene)glycinate, which was further transformed to Boc-*p*-[3′-(phenylselenenyl)propanoylphenylalanine.

Recent advances in the chemistry of fullerenes (C_{60} buckyballs) have included the synthesis of fullerene-based amino acids, and the developments (especially incorporating proline) have been reviewed.[379] A C_{60}-fullerene unit has been directly attached to the α-position of glycine via the addition[380] of N-(diphenylmethylene)glycine esters to [60] fullerene under Bingel cyclopropanation conditions (C_{60}, DBU, CBr_4, C_6H_5Cl). The sterically constrained 4, 5-diazafluorene amino acid (**67**) has been obtained[381] via the acylation of the anion of *N*-benzyl 4, 5-diazafluorene-9-methylene amine, but incorporation of this building block into peptides could only be done via the azide method due to decarboxylation.

(2*S*, 3*R*)-*N*-(1, 1′-Dimethyl-2′-propenyl)-3-hydroxytryptophan, a constituent of cyclomarin C, has been stereoselectively synthesised[382] from L-tryptophan, and as part of the synthesis of ergot alkaloids the intermediate *N*-Boc-4-bromo-*N*-methyl-1-tosyl-D-tryptophan methyl ester has been synthesized.[383] The Pmc group (2, 2, 5, 7, 8-pentamethylchroman-6-sulfonyl), usually associated with the side chain protection of Arg residues, has been substituted into the 2-position of tryptophan.[384] L-Tryptophanol (COOH → CH_2OH) and indole-substituted analogues have been made[385] from 4(*R*)-iodomethyl-2-oxazolidinone and indolyl magnesium bromide. β-Substituted tryptophans can be

made[386] from an enantiomerically pure 3-phenylaziridine-2-carboxylic ester (made via Sharpless dihydroxylation) followed by ring opening with indole.

There has been quite an interest in amino acids bearing heteroaromatic side chains such as oxazole/thiazole amino acids[387] which have been found widely in marine organisms. The isoaxazole amino acids (**68**) have been prepared[388] on-resin, starting with alkynyl groups attached to tritylchloride resin, then treated with aldoximes (RCH=NOH)/N-chlorosuccinimide. Homologues (**69**) of ibotenic acid have been synthesised[389] with different aryl substituents at R^1 using previously published strategies, and thioanalogues of ibotenic acid have also been made[390] using regioselective lithiation and functionalisation of 3-benzyloxy isothiazole. Both isomers[391] of the neuroexcitant (**70**) have been synthesised asymmetrically. A route[392] to spiroisoxazolino-Pro (**71**) started with nitrile oxides.



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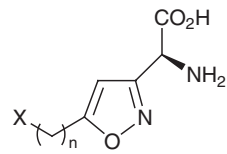
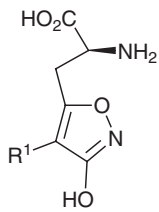


(68) X = CH_2OH, CHO, CO_2H



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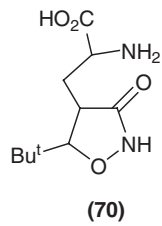

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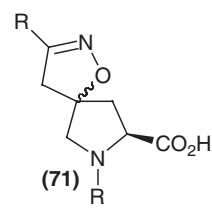
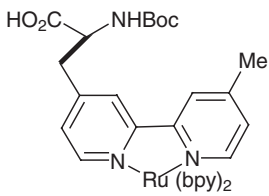


(71)

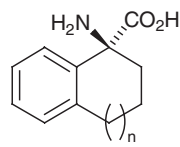
Selective agonists at group II metabotropic glutamate receptors have been found amongst stereoselectively synthesised[393] (*S*)- and (*R*)-2-amino-4-(4-hydroxy[l, 2 5]thiadiazol-3-yl)butyric acids. A soluble polyethylene glycol-supported protecting group related to silylethylsulfonyl has been used[394] to make unsaturated compounds which could be transformed to pyridyl amino acids using ring closing metathesis. Included is a wider study[395] of the application of aza Diels-Alder reactions was a protocol to make anthracenylglycine derivatives. A range of heterocyclic amino acid systems[396] including quinoxalines, pyrazines and 1, 2, 4-triazines have been obtained from the reaction of diamines and amidrazones with α-amino acid vicinal tricarbonyls. *N*-(Iodoethyl)- and *N*-(3-iodopropyl)pyrimidines and purines have shown[397] to undergo conjugate radical addition to chiral oxazolidinone acceptors to give purine and pyrimidine amino acids. A (thymin-l-yl)methyl function at the α-position[398] has been inserted via 2-(N^3-benzoylthymin-l-yl) methyl 1, 3-propanediol using enzymic desymmetrization catalysed by lipase PS. Amongst a series of nucleophiles added[399] to dehydroalanine derivatives were nitrogen heterocycles. The 'organic' stages in the synthesis[400] of ruthenium trisbipyridyl amino

acid (**72**) were achieved using chiral phase transfer catalysis of the reaction between a bromomethylbipyridine and *N*-(diphenylmethylene) glycine t-butyl ester.

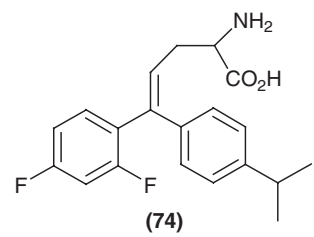
Different benzocycloalkane amino acids (**73**) have been synthesised[401] using (*S*)-α-methylbenzylamine and (*R*)-phenylglycerol as chiral auxiliaries, and which highlighted significant solvent effects in the use of TMSCN. 5, 5-Diaryl-2-amino-4-pentenoates (**74**) have been made[402] using Oppolzer's sultam and a Pd-catalysed stereoselective hydrostannylation. L-2-Amino-3-(6, 7-dimethoxy-4-coumaryl) propionic acid, a fluorescent molecule, has been synthesized,[403] and an analogue, L-2-amino-3-(7-methoxy-4-coumaryl) propionic acid,[404] also a fluorogen, has been made from an oxazinone alkylated with the fluorogenic group. A novel fluorescent amino acid has been synthesised[405] in the form of *N*-Boc-3-[2-(1H-indol-3-yl)benzoxazol-5-yl]-L-alanyl methyl ester from 3-nitro-L-tyrosine and 1H-indole-3-carboxaldehyde.



(**72**)

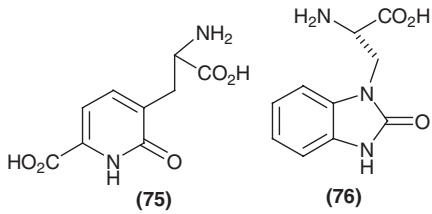


(**73**)



(**74**)

(*S*)-2-Fmoc amino-3-(5-phenyl-8-hydroxyquinoline-2-yl) propionic acid has been made[406] for its fluorescence and ability to act as a sensor for divalent zinc, and 6-(2-methylaminonaphthyl)alanine (DANA) has also been synthesised[407] and used to monitor protein-protein interactions. 6-Aminoquinoline amino acids have been made[408] for antibacterial testing and *N*-(5-hydroxy-3′, 4′-ethylenedioxy-7-isoflavonyloxyacetyl) amino acids have also been synthesized.[409] (S)-Acromelobinic acid (**75**) has been characterised through synthesis.[410] 6-Amino-l, 4, 6, 7-tetrahydroimidazo[4, 5, b]-pyridin-5-ones have been prepared[411] from acetyl-4-nitrohistidine as confromationally restricted His analogues. (1-Benzimidazolonyl) alanine (**76**) has been synthesised[412] as a potential tryptophan mimetic, starting with Z-L-diaminopropanoic acid and building up the benzylimidazolonyl ring from 2-fluoro-l-nitrobenzene. The *cis* isomer of oxazolidinone (**77**), obtained in high purity using $ZnCl_2/SOCl_2$ in the cyclisation step, was alkylated with l-bromobenzylbromide to provide chiral α-(4-bromobenzyl) alanine ethyl ester.[413] (*R*) and (*S*)-α-Hydroxymethylnaphthyl alanine has been made[414] and 3-(3-hydroxy-4-isoamyloxybutyl [and 3-(3-hydroxy)propyl]-4-phenyl-5-mercapto-1, 2, 4-triazoles have been added[415] to dehydroalanine using Ni(II) complexes to form the corresponding phenyltriazolylcysteines. The triazinyl unit itself has also been incorporated into pseudopeptide structures.[416]



4.11 Synthesis of α-Amino Acids carrying Amino Group and related Nitrogen Functional Groups in Aliphatic Side Chains. – This is the sub-section where interest in diamino alkanoic acids can be accommodated. Thus glycine-derived chiral synthons of type (**78**) have been the source of an enantioselective synthesis [417] of (1*R*, 4*R*)- and (1*S*, 4*S*)-forms of 2, 6-diaminopimelic acid, while differentially protected *meso*-2, 6-diaminopimelic acid has been obtained[418] from both aspartic and glutamic acids. The second chiral centre was established by the asymmetric reduction of a pyruvate moiety with Alpine-Borane. All four stereoisomers of *N*, *N*′-protected 2, 3-diaminobutanoic acid have been synthesised[419] using an asymmetric Rh(I)-phosphine-catalysed hydrogenation of isomeric enamides. Desymmetrisation of dimethyl 3-benzyl-aminoglutarate through enzymic ammonolysis[420] has given enantiopure (*R*)-3, 4-diaminobutanoic acid. ^{14}C-Labelled (*S*, *S*)-2, 7-di-Boc-diamino[l, 8 $^{14}C_2$] suberic acid,[421] as well as (*R*, *R*) and (*S*, *S*) isomers[422] have been synthesized, the former by inserting ^{14}CN into 1, 6-hexandial via a thermodynamically-controlled asymmetric Strecker synthesis using (*R*)-2-phenylglycinol as chiral auxiliary. All four stereoisomers of 4-aminoglutamic acid have also been obtained[423] using Ni complex-catalysed Michael-type condensation on to dehydroalanine. (2*R*, 4*S*)-and (2*R*, 4*R*)-Diaminoglutamic acids were obtained[424] in three steps from 6-oxo, 2, 3-diphenyl-4-morpholine carboxylate using a radical reaction of a selenide with methyl 2-acetamidoacrylate.

Quinazolinone and pyrazolopyrimidone derivatives of *cis*-4-aminoproline have been made,[425] and an improved synthesis[426] of protected *cis* and *trans* 3(and 4)-azido-L(and D)-prolines has been reported. The latter evolved from carrying out Mitsunobu reactions with diphenylphosphoryl azide on hydroxy-prolines. Homochiral building blocks of 4-azalysine (2, 6-diamino-4-aza-hexanoic acid) have been made[427] by exploiting the reductive amination of aldehydes with amines. One route started from L-serine (to form D-isomers) and another route from L-asparagine gave orthogonally protected 4-azalysine derivatives. An enantiomerically pure β-lactone (4-trichloromethyl-2-oxetanone) has been shown[428] to be a versatile synthon leading to a variety of γ-substituted α-amino acids. A synthesis[429] of optically active β-nitro-α-amino esters has provided an entry into α, β-diamino acid derivatives. The former were produced via a copper-bisoxazoline-catalysed aza-Henry (nitroaldol) reaction between silyl nitronates and α-imino esters. 2-Nitromethyl-ornithine has been obtained[430] from ornithine, mediated by cobalt (III), and *S*-nitroso-L-cysteine ethyl ester, known to be involved in *trans* -*S*-nitrosation of thiol

proteins has been made[431] by direct nitrosation of L-cysteine ethyl ester hydrochloride with ethyl nitrite.

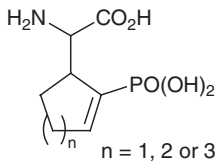
Reaction[432] of unmodified aldehydes with *N*-Pmp-protected α-imino ethyl glyoxylate in the presence of catalytic amounts of L-proline followed by addition of Et_2AlCN has provided enantiometrically pure β-cyanohydroxymethyl α-amino acid derivatives. A good yield of (*S*)-(+)-2-amino-6-(aminoxy)-hexanoic acid was obtained[433] from (*S*)-(−)-6-amino-2-{[(benzyloxy)carbonyl]amino}-hexanoic acid.

4.12 Synthesis of α-Amino Acids with Side-Chains carrying Boron Functional Groups. – A previously published synthesis in 1993 of L-valylpyrrolidine-(2*R*)-boronic acid has been significantly improved[434] by developing efficient recycling of chiral auxiliary (+)-pinanediol. α-Chymotrypsin has been used[435] to resolve p-boronophenylalaninol, while a conference review[436] concentrated on the concise synthesis of enantiomerically pure L-borophenylalanine from L-tyrosine. Both ^{18}F and ^{11}C-labelled *p*-boronophenylalanine[437] and l-amino-3-[2-[7-(6-deoxy-β-galactopyranos-6-yl)-1, 7-dicabododecarboran(12)-l-yl]ethyl cyclobutane carboxylic acid[438] have been synthesised for boron neutron capture therapy.

4.13 Synthesis of α-Amino Acids with Side Chains Carrying Silicon Functional Groups. – Synthesis[439] of racemic and (*R*)-$Me_2Si(CH_2R)CH_2CH(NH_2)CO_2H$, with R=$NH_2$, OH and SH was effected from 3, 6-diethoxy-2, 5-dihydropyrazine and (*R*)-3, 6-diethoxy-2-isopropyl-2, 5-dihydropyrazine respectively. Racemic and non-racemic $NH_2CH(CH_2ElR_3)COOH$ where El = Si or Ge, have been produced[440] starting also from 3, 6-diethoxy-2, 5-dihydropyrazine, using chiral hplc for resolution. Sodium salts of many amino acids have been reacted[441] with dichlorodimethylsilane to form a series of complexes. Esters of three types of silylated amino acids have been prepared[442] from zircona aziridines.

4.14 Synthesis of α-Amino Acids with Side Chains carrying Phosphorus Functional Groups. – Electrophilic fluorinations[443] of lithiated bis-lactim ethers allowed direct access to monofluorinated phosphonate mimetics of naturally-occurring phospho-serine and -threonine, suitable for solid phase peptide synthesis. Facile synthesis[444] and X-ray structural analysis, has been carried out on $Ar_2PCH_2CH(NHBoc)CO_2Me$, the synthesis requiring a nucleophilic phosphination of *N*-(Boc)-3-iodoalanine methyl ester using potassium carbonate as base. Phosphino amino acids were products[445] from the reaction of phosphine with formaldehyde and amino acids. 2*S*-2-(4-Phosphonophenylmethyl)-3-aminopropanoic acid [D-β-2(4-phosphono)-phenylalanine] has been made[446] by the diastereoselective alkylation of a chiral enolate. Access to 4-substituted 2-amino-4-phosphonobutanoic acid was possible[447] either from conjugated addition of the lithiated bis-lactim ether from cyclo (Gly-D-Val) to α-substituted vinyl phosphonates or electrophilic substitution on the lithiated bis-lactim ether from cyclo(2-NH_2-4-phosphonobutanoyl-D-Val). Preliminary

results[448] on the synthesis of constrained analogues of phospho-isostere of glutamic acid (AP4) have been reported. Analogues constructed were (**79**) and (**80**) and their synthesis started from dibromo cycloalkanes. Although stretching the heading of this sub-section the synthesis[449] of proline and pipecolic acid phosphorus analogues such as (**81**) via diastereoselective carboxylation appears to be an interesting concept.



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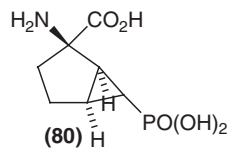

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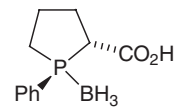
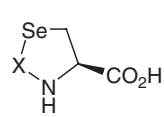
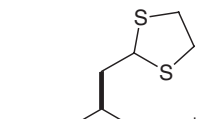


(81)

4.15 Synthesis of α-Amino Acids carrying Sulfur and Selenium Containing Side Chains. – With an increasing number of proteins known to contain selenocysteine (Sec) and the amino acid itself a good source of dehydroamino acids, new methods for its synthesis have been developed. So high yielding upgrades to the synthesis[450] of Fmoc-Sec(PMB) and Fmoc-Sec(Ph) have been reported. The former was synthesised from Fmoc Ser(Ts)-allyl ester, which is treated with p-methoxybenzylselenol, while the latter followed a similar route but using diphenyl methyl ester for carboxyl protection. $(Ac\text{-}Gly\text{-}SecOH)_2$ has been used[451] to test selenocysteine in native chemical ligation. Aromatic selenoamino acids have been made from 4-aminophenylalanine[452] via diazotisation of the 4-amino group and replacement with SCN (polar neutral), SeO_2^- hydrophilic anionic) or SeR(hydrophobic). Selenazolidines, cyclic analogues (**82**) of selenocysteine have been made[453] as masks for the chemically reactive groups. One analogue (**82**, X = C=O) was made from selenocysteine using 1, 1-carbonyldiimidazole, the other (**82**, X = CHMe) using acetaldehyde as the carbonyl donor.



(82) X = C=O or CHMe



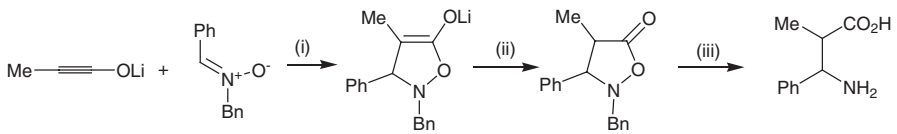
(83)

Asymmetric synthesis[454] of *S*-alkylated cysteines has made use of the nucleophilic addition of alkane thiols to dehydroalanine derivatives using Ni(II) complexes as chiral catalysts, and 4-methoxytrityl-mercapto acids have been trialled[455] in solid phase construction of libraries of mercapto-acyl peptides. The *S*-2-amino-3-(l, 2-dithiolan-4-yl) propanoic acid (**83**) and its dithiolic form have been made[456] using a parallel route to a previously synthesised dihydroxyleucine starting from t-butyl(*S*)-Boc-pGlu. Synthesis of novel N^{α}-(ω-thioalkyl) amino acid building units have been reported[457] and *N*-[2-(indan-l-yl)-3-mercaptopropionyl) amino acids have been made[458] as highly potent

inhibitors of NEP, ACE and ECE. (+)-Biotin was synthesised[459] in 11 steps (25% overall yield) from cysteine using a Lewis base-catalysed cyanosilylation of (2*R*, 4*R*)-*N*-Boc-2-phenylthiazolidine-4-carbaldehyde followed by a Pd-catalysed allylic amination. New routes[460] from homoserine and methionine have been successful for the synthesis of α-amino acid, β, γ-thioenol ether. Suzuki coupling reactions have been applied[461] to the synthesis of several S analogues of dehydrotryptophan e.g. benzo[b]thiophenes.

4.16 Synthesis of β-Amino Acids and Higher Homologous Amino Acids. – Peptides based on the β-amino acid building blocks have acquired renewed interest in the 21st century, and therefore require efficient means of synthesising the building blocks. Thus enantioselective methanolysis[462] of cyclic *meso* anhydrides mediated by cinchona alkaloids provided the monomethyl esters required for further Curtius degradation of acyl azides, to yield *N*-protected β-amino esters. Enantiopure β-amino acids were the result[463] of hydrogenolysis of β-enamino esters, and also the result[464] of the addition of 2 or 3 equivalents of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzamide to α, β-unsaturated ester fragments followed by hydrogenolytic deprotection. Conjugated addition[465] of heteroaromatic amides to ethyl acrylate in a CsF-Si(OEt)$_4$ system gave *N*-substituted β-amino acid ethyl esters, while a mild 2-step synthesis of racemic β-amino acids from Z-alkyl-Δ^2-oxazolines has been shown[466] to take place in high yields. Stereoselective conjugate addition[467] of homochiral lithium *N*-benzyl *N*-α-methyl-4-methoxybenzylamide to α, β-unsaturated esters gave, after mono deprotection either under oxidative or acid-promoted reaction, β-amino acids or β-lactams.

As summarised in Scheme 12 the 1, 3-dipolar cyloaddition of nitrones with ynolates have yielded[468] 5-isoxazolidinones which readily yield β-amino acids. Twenty one 3-amino-3-arylpropanoic acids have been synthesised[469] in a 'one-pot' reaction by refluxing a substituted benzaldehyde derivative with malonic acid and 2 eq. of ammonium acetate in ethanol. Electron-donating groups on the benzaldehyde ring favoured the reaction, as well as solubility in the solvent used. 3-Substituted- and 3, 3-disubstituted aziridine-2-carboxylate esters were a source[470] of β-amino acid and quaternary β-amino acids. The aziridine intermediates were sourced from the aza-Darzens reaction of α-bromoenolates with *N*-sulfinyl imines, and by addition of Grignard reagents to 2H-azirine-2-carboxylate esters. Enantioselective hydrogenation of α, β-unsaturated nitriles, using Rh-DuPHOS as catalyst has given β amino acid precursor, but with only 48% ee.[471] Higher diastereoselectivity (91% ee) was achieved[472] in the synthesis of (*S*)-β-aminophenylpropanoic acid by addition of lithium enolate of



Scheme 12 *Reagents: (i) 0°C 1 hr (ii) HX (iii) H_2/Pd/C 60°C.*

Bu^t-(+)-(*R*)-*p*-toluenesulfinylacetate to *N*-(benzylidene)toluene-4-sulfonamides, followed by reductive cleavage, ester hydrolysis and detosylation. Cyclic β-amino acids, (*S*)-homoproline and (*S*)-homopipecolic acid have been made[473] via the diastereoselective conjugate addition of lithium (*S*)-*N*-allyl-N^{α}-methyl benzamide to α, β-unsaturated esters followed by ring-closing metathesis.

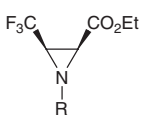
There have been a few examples of conversion of α-amino- to β-amino acids. Thus the Wolff rearrangement of α-aminodiazoketones derived from *N*-urethane protected α-amino acids in the presence of *o*-nitrophenol produced[474] protected β-amino acids. Similarly the Arndt-Eistert homologation method[475] has been applied to protected α-amino acids using *p*-toluenesulfonyl chloride for carboxyl activation, and using Boc_2O as a coupling agent[476] allows for scale up of the homologation process. The β-amino homologue of histidinol has been synthesised[477] utilising the *N*-Mts group for the protection of both the imidazole and amino nitrogens during the transformation of histidinol via its methansulfonate ester and cyanation to its higher homologue.

Several examples of α-substitution of β-amino acids have been reported. Conjugate radical additions[478] and Heck reactions on conjugated double-bonded synthons have yielded a number of α-substituted diverse structures. *N*-Protected α-phenylethyl amides of α-amino acids can be alkylated[479] diastereoselectively (up to 89% ds) in the α-position (via lithium enolates). Following Arndt-Eistert homologation of α-amino acid esters, diastereoselective α-alkylation has been reported,[480] while *anti*-α-methyl-β-amino acid derivatives[481] have emerged from highly enantio- and diastereo-selective Mannich reactions using a zirconium complex of (*R*)-6,6′-bis(pentafluoromethyl)-l, l′-bi-2-naphthol. Asymmetric synthesis[482] of α-phenyl-β-alanine was carried out via intermolecular catalytic C–H insertion of carbenoids derived from aryldiazoacetates. As key compounds in a number of medicinally important compounds, asymmetric synthesis of α-hydroxy-β-amino acids has been a source of increasing interest. One synthesis[483] incorporated the Lewis acid-mediated addition of Z-α-methoxyketene methyltrimethylsilyl acetal to chiral amines, *N*-alkylidene (*S* or *R*)-α-methylbenzyl-amine, followed by demethylation, hydrogenolysis and hydrolysis. In the formation[484] of α-hydroxy-α-methyl-β-amino acids the key steps were a catalytic asymmetric aldol reaction, a modified Curtius reaction to form oxazolidinones, which could be chemoselectively opened.

Ring opening of (2*R*, 3*S*)-2-benzyl-3-vinyl-1-[(*R*)-1-phenylethyl]-aziridine with acetic acid yielded[485] 3-acetyloxy-4-[(*R*)-l-phenylethyl]amino-5-phenyl-pent-l-ene which was transformed using known procedures to (2*S*, 3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid, a key component of bestatin. As part of the demand for aminopeptidase and HIV protease inhibitors as anti-cancer agents, 3-amino-2-hydroxy-4-phenylbutanoates have been synthesised[486] using $H–C(CN)_2OSiR_3$ as a key reagent with protected α-amino aromatic aldehydes. Epoxidation of l-tolylthio-l-nitroalkenes containing an allylic Boc-protected amino group has yielded[487] *cis*-oxazolidinones, which, can be transformed to *anti*-α-hydroxy-β-amino acids. Asymmetric α-hydroxylation[488] of *N*, *N*-diprotected homo-β-amino acid methyl esters has afforded β-amino-α-hydroxy acids

with full orthogonal protection using KHMDS/2-[(4-methylphenyl)sulfonyl]-3-phenyloxaziridine for introduction of the α-OH group.

Among the fluorinated β-amino acids produced were, CF_3-containing amino acids, synthesised[489] via *cis*-3-CF_3 aziridine-2-carboxylate (**84**), β-fluoroalkyl-β-amino acid derivatives starting from 2-alkyl-Δ^2-oxazolines and fluorinated imidoyl chloride.[490] Trifluoromethylated dehydro β-amino acids[491] such as (**85**) were the product of [α-(alkoxycarbonyl)vinyl]diisobutylaluminium with *N*-acylimines of hexafluoroacetone and methyl trifluoropyruvate. (+)-4, 4, 4-Trifluoro-3-aminobutanoic acid has been made[492] from a β-amino ester derived from chiral 2-trifluoromethyl-l, 3-oxazolidine. *p*-Toluene sulfinimines proved to be efficient[493] chiral amine equivalents in the high temperature Reformatsky-type additions with $BrZnCF_2CO_2Et$ which gave enantiomerically pure α, α-difluoro-β-amino acids. Using a similar set of reactions[494] α, α-difluoro-β-amino acid derivatives have been made from *N*-*t*-butylsulfinimines. α-Substituted-β, β-bis(trifluoromethyl)-β-amino acids have been made[495] via a Morita-Baylis-Hillman reaction with the double-bond containing adducts formed, either being hydrogenated or subjected to cuprate addition. Although low yielding, a route[496] to enantiopure conformationally constrained fluorine-containing β-amino acids has been worked out starting from D-glucose. Glycosylated β-amino acid derivatives such as (**86**) have been made via Wittig olefination of xylofuranos-5-ulose and found to be good antitubercular agents.[497] Homochiral β-haloaryl β-amino esters have been obtained[498] by conjugate addition of lithium *N*-benzyl-*N*-α-methyl-4-methoxybenzyl-amide to cinnamates.



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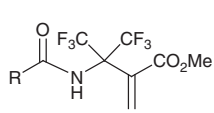

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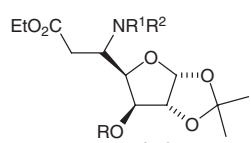

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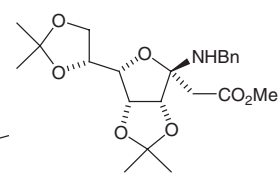

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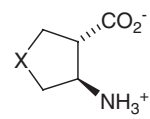
Quite an interest has been shown in cyclic β-amino acids e.g. β-aminocyclopropane carboxylic acids with the side chain functionality of asparagines, arginine, cysteine or serine and have been synthesised[499] via an established route involving the cyclopropanation of *N*-Boc-pyrrole. A photochemical [2 + 2] cycloaddition between ethylene and uracil has furnished[500] *cis*-cyclobutane-β-amino acid, and a chemoenzymatic approach[501] has given both enantiomers of the methyl esters of β-proline by enzymatic resolution of intermediate β-methoxycarbonyl-γ-lactams using α-chymotrypsin. Facile syntheses[502] of fused furanosyl β-amino acids e.g. (**87**) started from protected sugar lactones, and enantiomerically pure *trans*-2-aminocyclohexane acid has been obtained[503] from a 'one-pot' procedure from *trans*-cyclohexane 1, 2-dicarboxylic acid.

Aromatic β-amino acids have been prepared[504] by the Radionow reaction and used as Asp-Phg mimics in VLA-4 antagonism. Nucleophilic addition[505] of

lithium enolates of (*S*)-(−)-4-benzyl-2-oxazolidinones to *N*-tosyl aldimines have given β-aryl-β-amino acid derivatives with excellent diastereoselectivity. Commencing with 4-vinylbenzyl chloride, preparation of suitably protected β-aminophosphotyrosine has been carried out[506,507] for the first time, while use of an acid and aldehydes in 'ring switching' reactions with hydrazines have given β-(l-aminopyrrole)-amino acid and β-(pyrazine)-amino acids respectively.

β-Amino acids have been produced[508] via the opening of *N*-nosyl aziridine rings with cyanide ions, followed by hydrolysis, while base-promoted[509] isomerisation of aziridinyl ethers offer an entry into β-amino acids. All four stereoisomers of 2-alkyl-3, 4-iminobutanoic acid (aziridine ring in β-position) have been synthesised[510] starting from aspartic acid, which underwent alkylation at the β-position, followed by reduction of the α-COOH to the alcohol, which was then subjected to cyclisation and aziridine formation. β-Lactone rings open up quite readily with amine nucleophiles, azides or sulfonamide anions[511] to yield β-amino acid derivatives.

The rhodium complex of an imidazolidinone with bisphosphine ligands was an effective catalyst[512] for hydrogenation of both (*E*) and (*Z*)-forms of 3-acylaminoacrylates, and cyclisation of sulfamate esters using a Rh-catalysed C–H bond oxidation/insertion to form oxathiazinones has provided[513] the pathway to form β-amino acids such as (*R*)-Z-β-Ile in 81% yield. 4-Spiro-3-lactams when treated[514] with KCN/MeOH, gave α, α-disubstituted β-amino esters, and when *trans*- and *cis*-oxazoline-5-carboxylates were reacted[515] with thiol acetic acid *syn* and *anti* forms of *S*-acetyl-*N*-benzoyl-3-phenylisocysteine (2′-sulfur analogues of taxol C-13 side chain) were obtained. Methodology has been developed[516] for the enatitioselective synthesis of differentially protected *erythro* α, β-diamino acids from *N*-tosyloxylactams, made from β-keto esters and enantioselective addition of *t*- butyldimethylsilylketone to nitrones in the presence of isopropoxide and phenols have yielded[517] β amino acid esters. Novel sila-substituted β-amino acids (**88**) have been synthesised[518] via a nucleophilic opening of an intermediate aziridine which generated the *trans* amino/carboxyl relationship. Tritium-labelled β-alanine was formed[519] after solid-phase catalytic hydrogenation of uracil with gaseous tritium to form [5, 5, 6, 6-$^3H_3$]5, 6-dihydrouracil, which was cleaved to the labelled β-alanine. An efficient synthesis[520] of α-dehydro-β-amino esters has been achieved through regioselective palladium(0)-catalysed reactions of primary amines with acetates derived from Baylis-Hillman adducts.



(88) X = Me_2Si or Ph_2Si

4.17 Resolution of DL-Amino Acids. – With this having been one of the most fundamental necessities of amino acid chemistry over the decades, its role recently has received competition from direct methods of asymmetric synthesis. However, while enzymatic resolution remains a staple method, new

developments in chiral recognition for liquid chromatography continue to flourish. In the context of enzymic techniques the following resolutions were reported:

D- and L-forms from *N*-acetyltryptophan (using acylase);[521] L-Phe from *N*-acetyl-Phe-OEt (using aminoacylase);[522] de-racemisation of DL-amino acids (using L-amino acid oxidase[523] or D-amino acid oxidase[524]) followed by amino-borane or hydride reduction of the imino acids; all four diastereoisomers of 4, 4, 4-trifluorovaline and 5, 5, 5-trifluoroleucine by flash chromatography of derivatives followed by enzymic (porcine kidney acylase)[525] deacetylation of *N*-acetylated derivatives; resolution of *N*-Ac-DL-methionine (*Aspergillus*-derived amino acylase);[526,527] enantiopure α-methyl-β-alanine esters by lipase-catalysed (CAL-A and CAL-B) kinetic resolution. Chiral recognition of individual enantiomers forms the basis of a number of chiral hplc separations as listed in Table 1.

Chiral recognition of individual enantiomers is not restricted to CSP's for hplc however. Chiral recognition of D- and L-amino acids was seen[539] in the tandem mass spectrometry of Ni(II)-bound trimeric complexes. Some spontaneous chiral separation[540] of non-covalently bound clusters of amino acids occurred using soft-sampling electrospray ionisation. Amino acids such as hSer, 4OH-Pro, aThr and aIle, underwent guest-exchange reactions when complexed to permethylated β-cyclodextrin in the gas phase.[541] Neutral H-bonding receptors based on a *trans*-benzoxanthene skeleton have shown good stereoselective association towards carbamates of amino acids,[542] and *cis*-tetrahydrobenzoxanthene discriminated[543] between enantiomers of Z-amino

Table 1

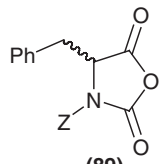
Racemate	*Chiral Stationary Phase (CSP) or complex added to eluant*	*Refs.*
DL-amino acids	Cu(II) complexes of tetradentate diaminodiamido ligands in eluant	528
N-DNB-Leu-deriv.	Secondary and tertiary amide linked CSP's	529
DNP-amino acids	Carboxyethyl-β-cyclodextrin-coated-zirconia(CSP)	530
DNP-amino acid methyl esters	Silica-based CSP-derived from L-Ala and piperidyl cyanuric chloride	531
Aromatic amino acids	Amylose column (CSP)	532
1-Boc-amino 2, 3-diphenyl-l-cyclopropane COOH	Polysaccharide –derived CSP	533
DL-Amino acids	Diphenyl-disubstituted l, l′-binaphthyl crown ether (CSP)	534
DL-Amino acids	Chiral monolithic column (CSP)	535
Boc/Z/Fmoc aminoacid anilides	Modified commercial (*S*)-leucine (CSP)	536
DNP-aminoacid hexyl amide	Macrocycle from (R, R)-l, 2-diphenyl ethylamine and 5-allyloxyphthaloyl chloride on silica	537
DL-Amino acids	Pre-derivatisation by Marfey's reagent-a review	538

acid derivatives. Critical differences in chiral recognition of Z-DL-Asp and -Glu by mono- and bis(trimethylammonio)-β-dextrins have been reported.[544] Chiral molecular tweezers derived[545] from deoxycholic acid have been shown to form 1:1 inclusion complexes with methyl esters of D- and L-Phe and –Leu due to H-bonding and Van der Waals interaction. Cholic acid guanidines and carbamates have been found[546] to extract enantioselectively *N*-acetylated amino acids form aq. buffer into chloroform. Sixty references on enantiomeric amino acid recognition have been compiled in a review.[547] A series of acyclic thiourea derivatives[548] having four H-bond donors showed a moderate enantioselectivity towards *N*-protected amino acid carboxylate salts. (+)-(1*S*)-1, 1′-Binaphthalene-2, 2′-diyl hydrogen phosphate was known[549] to recognise L-α-amino acids and separating them by fractional crystallisation, and X-ray data now confirms the chiral space required for association.

Ultrafiltration through immobilised DNA membranes (channel-type) separated D- from L-phenylalanine,[550] and the same amino acid featured[551] in ultrafiltration using non-ionic micelles containing cholesteryl-L-glutamate at pH 7. Affinity ultrafiltration using bovine serum albumin as a stereoselective ligand has been studied[552] for the separation of D- and L-tryptophan. The D-form of alanine showed[553] preferential flux through a liquid membrane supported polypropylene hollow-fibre molecule using N-3, 5-dinitrobenzoyl-L-alanine octyl ester in toluene as a chiral selector. Enantiomeric discrimination between D- and L-amino acids has been shown[554] to occur using potential changes of optically active membranes. An enantioselective surface-imprinted poly(vinylbenzene)matrix using benzyldimethyl-*n*-tetradecyl ammonium chloride, could recognise[555] the chirality of *N*-protected glutamic acid, and a polypyrrole colloid on over oxidation[556] was able to show higher affinity for L- than for D-alanine.

(*RS*)-2-Benzoylamino-2-benzyl-3-hydroxypropanoic acid has been resolved[557] both by cinchonidine as resolving agent or by preferential crystallisation, while the optical purity[558] of enantioselective reactions can be improved through recrystallisation of Fmoc-α-amino acid *t*-butyl esters. In a dynamic kinetic resolution, (4*S*)-3-(2′-pyrrolidinyl)-3-oxo-2-methylpropanoate hydrochloride underwent[559] asymmetric hydrogenation in the presence of Ru[(*S*)-MeO-BIPHEP$_2$ to yield *anti*-β-hydroxy-α-methyl ester quantitatively. Using micellar electrokinetic chromatography,[560] eleven pairs of DL-amino acids derivatised with *o*-phthalaldehyde and *N*-acylcysteine could be separated using β-cyclodextrin. A kilogram of racemic Z-*t*-leucine could be resolved[561] by continuous chromatography on cellulose-based 'Chiralcel OD' while 0.5 kg Boc-*t*-leucine benzyl ester was resolved using 'Chiralpak AD'. Enantiopure (*R*)- and (*S*)-2-hydroxy-2-methyl-l-tetralone has been efficiently used[562] to epimerise/de-racemise amino acids. A first efficient and general non-enzymatic catalytic method[563] of synthesis involved the asymmetric alcoholysis of urethane *N*-carboxy anhydrides such as (**89**) catalysed by cinchona alkaloids. After its synthesis[564] RS-β^{2,2}-Bin (**90**) could be obtained in enantiomeric forms by benzoylation, coupling with L-Phe-cyclohexamide to give diastereoisomeric dipeptides which could be separated by chromatography. Further

transformation led to the pure enantiomers, which are individually chirally stable due to axial dissymmetry.



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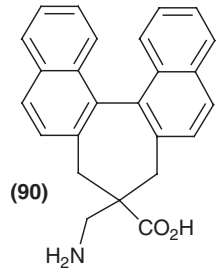

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5 Physico-Chemical Studies of Amino Acids

5.1 X-Ray Crystal Analysis of Amino Acids and Their Derivatives. – A keyword scan of the literature for this sub-section brought in less than the usual harvest of papers, and the ones collected do show an overlap with discussions elsewhere on molecular recognition in this Chapter. Two nearly isomorphous complexes of *N*-acetyl-L-Phe-OMe and its amide with β-cyclodextrin (2:2) have been analysed[565] by X-ray crystallography, which found the former guest molecule showing dynamic disorder, while the latter showed evidence of having shifted position within the complex. No H-bonding existed between host dimer and the guest molecules but hydrophobic interactions involving the phenyl rings were seen[566] in both cases. A perturbation of the aromatic side chain of the guest molecule was seen in a room temperature crystal determination of the 2:2 *N*-acetyl *p*-methoxy-L-Phe-NH^2/β-cyclodextrin complex. Amongst the many physical techniques used to study[567] the selective recognition of amino acids by a novel crown ether (containing pyrillium, thiopyrillium and pyridinium moieties) was X-ray crystallography, which showed the conformation of the aromatic rings to be almost planar, but allowed selective binding to a selection of amino acids. The interaction[568] between a corrugated Langmuir film of cholesteryl-L-glutamate and various α-amino acids at the air-aq. solution interface has been examined by grazing incidence X-ray diffraction (GKD), and the incorporation of the 'guest molecule' within the host monolayer depended on hydrophobicity, shape and chirality of the solute molecules. Silver complexes of Asp, Gly and Asn have also been analysed by X-ray crystallography.[569]

5.2 Nuclear Magnetic Resonance Spectroscopy. – This technique is used widely in the general elucidation of structure, and finds itself as a major study vehicle in only a few papers which can be included in this sub-section. Host-guest NMR studies[570] between β-cyclodextrin and tryptophan enantiomers have revealed that the D-Trp is more strongly bound than its L-enantiomer, The chiral selector (18-crown-6)-tetracarboxylic acid, employed for resolution

of amino acids also showed[571] chemical shift differences for D- and L-phenylglycine and the nature of the association between chiral selector and the 'guest molecules' was due to (i) 3 H-bonds in a tripod arrangement between the crown ether and the ammonium moiety (ii) hydrophobic interaction between polyether ring and Ph ring of the enantiomer and (iii) H-bonding between COOH of the crown ether and the CO oxygen of the D-enantiomer. A three-versus-two point attachment[572] of (*R*)- and (*S*)-amino acid methyl esters to chloro cobalt (III) tetramethyl chiroporphyrin has been used to explain the large diastereomeric dispersions observed with this novel chiral shift reagent. NMR spectroscopy in deuterated mesitylene solution has been used[573] to study the binding between a self-assembled cylindrical capsule and the 'guests', Boc-L-Ala and Boc-β-Ala esters. The most strongly bound to the capsule was Boc-β-Ala-OEt. A study[574] on modified β-cylodextrin,. 6 (A) deoxy 6(AH1) 4, 1, l0-tetreazacyclododecan-10-yl) β-cyclodextrin showed that it formed host-guest complexes with a number of amino acids but only showed enantioselectivity with tryptophan. The structure of liquid-crystalline phases formed from *N*-acetyl-L-glutamic oligopeptide benzyl esters have been examined[575] by NMR, the results indicating that the molecules were in an alignment as in a nematic mesophase.

Solid state NMR has been used[576] to study Lys, Arg and His intercalated into layered zirconium phosphates, and found the ε-NH_2 of Lys and the α-NH_2 of Arg and His interacted with P-OH of the phosphates. H-Bonding in amino acids and peptides as a function of temperature has been monitored[577] by solid state ^{2}H NMR.

5.3 Circular Dichroism. – CD and FT-IR have been used[578] to assess the secondary structure of poly(L-glutamic acid) segments and the binding of α-amino acids onto mixed monolayers. Induced CD signals have been observed[579] in synergistic binding of zwitterionic amino acids to lanthanide porphyrinate crown ethers.

5.4 Mass Spectrometry. – Electrospray mass spectrometry has been applied[580] to the study of Pd(II) complexes of amino acid-substituted calix[4]arenes. ESI-TOF-MS was used[581] in the chiral recognition of D- and L-Tyr and –Trp by cyclodextrins. It was found that D-isomers were more strongly bound than were the L-forms.

5.5 Other Spectroscopic Studies on Amino Acids. – The adsorption of *S*-proline vacuum-deposited on clean Cu(l 1 0) has been investigated[582] using reflective absorption IR and low energy electron diffraction (LEED). Throughout the adsorption, proline bonds to the Cu surface via its COO and N–H functionalities.

5.6 Measurements on Amino Acids in Solution. – Thermodynamic properties of a number of amino acid situations in solution have been reported and include: dissociation constants of Gly in ethanol/water[583]; stability constants

for complexation of dioxovanadium with Glu in methanol/water[584]; mixing enthalpies of Gly, Ala, Ser, Pro, Thr and Val with 1,3-dimethyIurea[585] and with monomethylurea[586] in aq. solution; densities and sound velocities of Gly in aq. nickel sulphate;[587] enthalpies of solution for α-aminobutyric acid in aq. alkali metal halide solutions;[588] free energies, enthalpies and entropies of transfer of amino acids from water into sodium sulphate;[589] stability constants for complex formation of Cd-amino acid-Vit B systems;[590] enthalpies of dilution of Gly, Ala and Ser in aq. ethylene glycol solution;[591] Gibbs Free energies of Gly zwitterions in hydro-organic solvents (DMSO, EtOH, dioxan and acetonitrile);[592] enthalpies of aq. solutions of Cys, His, Asn, Arg, Trp and Glu in order to determine homogeneous pair interaction coefficients;[593] diffusion coefficients of Pro, Thr and Arg in water at 25°C;[594] activity coefficients of Gly, Ser and Val in aq, sodium and potassium nitrate.[595]

Amongst other parameters reported were; solubility polytherm for Phe-NH_4HPO_4-H_2O systems;[596] extraction equilibrium constants of leucine with di(2-ethylhexyl)phosphonic acid;[597] constant volume combustion energies for Zn-L-threonate and Ca-L-threonate[598]; partial molar volumes of Gly, Ala, Val, Leu and Phe in aq. glycerol solution;[599] stability constants of Cu (II)-glycine complex in mixed solvents;[600] density, viscosity, solubility and diffusivity of N_2O in aq. amino acid solutions;[601] viscosities of amino acid-urea –water systems;[602] activity coefficients of amino acids in variable dielectric permeability media;[603] partial molar volumes of Gly-Gly and Ser at elevated temperatures and pressure[604] and *N*-acetyl-*N*-methylamino acid amides in aq. solution;[605] effect of pH on the diffusion coefficient of Cu(H) ions in Gly and β-Ala aq. Solutions;[606] apparent molar volume and compressibility of Gly in aq. vanadyl sulphate;[607] dissociation functions of Gly and β-Ala in 2-propanol/water mixtures;[608] apparent and partial molar heat capacities and volumes of L-Lys and L-Arg hydrochlorides in aq. solution;[609] water activity, pH and density of aq. amino acid solution;[610] partition coefficients of amino acids in PEG-4000/sodium sulphate 2-phase systems.[611]

Lysine has been extracted with a combination of ion-exchange and membrane ultrafiltration,[612] while N-cholyl amino acid alkyl esters were found[613] to act as potent organogelators for aromatic solvents and cyclohexene. Special surface and aggregation behaviour of the amphiphile *N*-(decyloxy-2-hydroxybenzylidene)glycine has been investigated,[614] and the reactivity of radical dications of protonated amino acids in microsolutions has been investigated.[615] The hydration of amino acids has been found[616] to depend on ion form, the anions of neutral amino acids being the most hydrated. The spatial effect of hydrophobic groups in amino acids on the volume phase transitions of hydrogels has been investigated[617] and new lysine derivatives[618] with positively charged terminal groups could gel water below 1 wt.%. In a survey of chiral aggregation[619] acyl amino acids were found to be present as monomers in acetonitrile, and in a molecular dynamics calculation[620] of solvation properties of non-polar amino acids, the results show that the solvation structure around the amino acids is richer for methanol than for water. Protonation constants and solvation of some α-amino acid methyl and ethyl esters in ethanol-water

mixtures have been determined[621] using potentiometry, and the effect of amino acids on the dynamics of water has been studied.[622] Hydration characteristics of aromatic amino acids have been investigated by an isopiestic method[623] and the effect of additives (ammonium sulfate and dextrose) on the transformation behaviour of phenylalanine has been studied using powder X-ray diffraction.[624] The properties of hydroxy-glycine in aq. solution have been explored[625] and Gly and Lys in a mixed aq. solution[626] demonstrated buffering action, and there was proton transfer from Gly to the Lys zwitterions.

Cystine, being naturally the least soluble of the amino acids, has been subjected[627] to a constant ionic medium of NaCl at different concentrations to study its protonation equilibria, and solvent effects on the conformational behaviour[628] of acetylated amino acids revealed significant differences dependent on the solvent used (DMSO, D_2O, hexafluoroisopropanol or CH_2Cl_2), as determined by IR techniques. The pH dependence of the anisotropy factors (g) for the essential amino acids has been assessed[629] and it was found that g factors at pH 1 were 2–3 times those at pH 7. The results[630] of subjecting Gly to super- and sub-critical water conditions to simulate submarine hydrothermal conditions showed that $(Gly)_2$, $(Gly)_3$ and dioxopiperazine were found in the reaction mixtures. Glycine also decomposed[631] under high temperature and pressure water, by decarboxylation and methylamine formation or by production of ammonia and an organic acid.

The Stark-effect of spectral holes burnt into the long wavelength absorption of phenylalanine in glycerol-water glass showed[632] two protonation-deprotonation transitions. Phenylalanine and aspartic acid can be separated in aq. solution using nanofiltration.[633] Using glycine methyl ester, it has been shown[634] that on forming an iminium adduct with acetone the α-carbon experienced a 7 pK unit increase in acidity, and NMR evidence showed[635] that in α-(benzotriazol-l-yl)-*N*-acylglycines the benzotriazole ring can mop up protons from the ionisation of the carboxyl groups.

5.7 Measurements on Amino Acids in the Solid State. – X-Ray, cyclic voltammetry and IR spectroscopic evidence concurred[636] that the carboxyl group in phthalimido acetic acid preorientates prior to photodecarboxylation by photo induced electron transfer. The crystallisation rates of L-glutamic acid were retarded by the addition of Val, Leu, Ile and Nle, with the effect being larger for Val.[637] Tryptophan was selected[638] for measurement of its permanent electrical dipole in a molecular beam, using a MALDI source coupled to an electron beam deflection setup, and the experimental value agreed with the lowest energy conformation found by calculation. In a study of precipitating agents[639] 3, 4-dimethylbenzene sulfonic acid was highly selective for leucine, and flavianic acid was good for arginine. A novel batch crystallizer[640] has successfully produced large crystals of aspartic acid, while growing glycine crystals at an air-aq. solution interface[641] initiated the occlusion of one α-amino acid enantiomer from an added racemate resulting in enrichment in solution of the other isomer. The latter spontaneous separation of enantiomers has been termed 'chemistry in 2D'.

IR and Inelastic Neutron Vibrational Spectroscopy have been used[642] to examine both the internal and external vibration in crystalline-alanine, and for the first time a splitting of the NH_3^+ torsional band has been seen at a temperature below 220 K. Atomic force microscopy has been applied[643] to study the blocking behaviour of step motion on the (1 0 0) face of an Asp crystal when doped with other amino acids (Ala, Lys, Phe, Asn and GIu). Scanning tunnel microscopy (STM) data[644] on lysine adsorbed on graphite showed that some of its CH groups were located between the hexagonal lattice of the graphite, while the other groups rise above the surface. STM investigations have also been carried out on lipid amino acids on pyrolytic graphite,[645] and on the adsorption and assembly of L-tryptophan on to the Cu (0 0 1) surface.[646]

5.8 Amino Acid Adsorption and Transport Phenomena. – A short review[647] has been noted entitled, 'Adsorption of amino acids at solid/liquid interfaces', and the effect of pH and aluminium content of zeolites on their adsorption and separation of amino acids from aq. solution has been surveyed.[648] Selective adsorption of groups of amino acids occurred from aq. solution using MCM-41 mesoporous molevular sieves.[649] 'Acidic' amino acids were hardly adsorbed, 'basic' amino acids showed high affinity, while adsorption of 'neutral' amino acids increased with side-chain length. The effect of solvophobic interactions[650] on the molecular sorption of four amino acids from water/non-electrolyte binary systems onto mono carboxycellulose has been investigated, and amino acids tested[651] for binding onto calcium materials found in human kidney stones (calcium oxalate, $CaHPO_4.2H_2O$ and Ca_3PO_4), showed maximum binding at pH 5, with the 'acidic' amino acids showing the strongest adsorption.

An investigation[652] for optimising the ion-exchange extraction of amino acids from an L-proline culture liquid has been carried out. Mixed-ligand Cu (II) and Ni (II) chelates have been shown[653] to extract phenylglycine, phenylalanine and tryptophan into dichloroethane from aq. solution. Phenylalanine has been used[654] as test molecule for studying the effect of physical factors on its extraction by Aerosol-OT reverse micelles, and calix[6]arene carboxylic acid derivative was found[655] to be the strongest extractant of the target tryptophan ester in an aliphatic organic solvent. The micellar extraction of tryptophan and tyrosine, using *N*-*n*-dodecyl-L-proline and *trans N*-*n*-dodecyl-4-hydroxyproline as chiral selectors with Cu(II) ions has been evaluated,[656] theoretically and experimentally, and a very similar approach has been applied to study[657] the conditions needed for enantiomeric separations by dense permeation-selective membranes, using the diffusion of phenylalanine through polypropylene beads coated with *N*-dodecyl-L-hydroxyproline:Cu(II), which showed a selectivity value of 1.25 (D/L). The transport of Phe, Tyr and Trp in a buffer solution through Aerosol-OT reverse micelles, has been studied[658] and the conclusion drawn that Tyr does not cross the membrane, but transport rates for Trp and Phe are of the same order. The selectivity of an activated composite membrane containing bis-(2-ethyl-hexyl) phosphoric acid for aromatic amino acids has

been shown[659] to be Trp > Phe > Tyr, and when Langmuir monolayers of N-stearoyl glutamic acid have been investigated by π-A measurements and Atomic Force Microscopy, layers built up from aq $CdCl_2$ solution could aeccomodate the L-*N*-stearoyl glutamic acid better than the racemate.

Distribution coefficients of isomorphic amino acids between a crystal phase and aq. solution have been worked out[660] and indicated that the extent of impurity in a crystal is related to the ratio of the pure compound solubility of the primary solute to that of the impurity in the same solvent Diffusion measurements using NMR[661] have enabled the association constants for weak interactions between cyclodextrin and guest molecules (Phe, Leu and Val) to be worked out, while chiral discrimination between DL-dansyl amino acids and immobilised teicoplanin[662] rely on hydrophobic interactions and H-bond formation.

5.9 Host-Guest Studies with Amino Acids. – Aspects of the complexation of amino acids with macrocyclic receptors such as crown ethers, cryptands, calixerenes have been reviewed,[663] and recent progress on the synthesis/molecular recognition of amino acids/peptides has been reported.[664] The cyclodextrins and crown ether derivatives vie for the top popularity spot as host over this review period and will be reported on first in this sub-section.

Examples having cyclodextrin as host receptor include, calorimetric and NMR studies[665] which showed a direct correlation between complex structure and the thermodynamics of Z-L-Asp and Z-L-Glu inclusion complexes with mono- and bis-(trimethylammonio)-β-cyclodextrins. A β-cyclodextrin derivative bearing a pyridinio on the primary side was synthesised[666] and its complexation stability constants with several aliphatic amino acids determined, with the highest enantioselectivity shown for serine (D/L 5.4). *R*-(−)-2-Phenylglycinol–modified β-cyclodextrin was synthesised[667] under microwave irradiation and showed high chiral discrimination when complexed with amino acids. β-Cyclodextrin bearing nicotinic or isonicotinic moieties have been synthesised[668] and their inclusion complexes with L/D tryptophan, analysed fluorometrically, showed a preference for the D-enantiomer. A kinetic study[669] using ultrasonic relaxational methods on a β-cyclodextrin/L-isoleucine system implied that the departure of the guest molecule from the host cavity was influenced by the amino acid structure. A theoretical study[670] using a fast annealing evolutionary algorithm (FAEA) on the interactions of amino acids with α-cyclodextrin revealed that of the four pairs of L/D-amino acid compared, interaction energies were lower for the L-amino acids than the D-forms which is in agreement with experimental results. Studies have been reported[671] on the separation of the enantiomers of Leu, Val, Tyr and Phe on thin layer chromatography plates modified by β-cyclodextrin, and fluorescence enhancement was recorded[672] in all the examples of coumarin-6-sulfonyl amino acid derivatives on forming inclusion complexes with cyclodextrin. In the latter technique glycine showed the greatest enhancement, tyrosine the least. The association of dansyl amino acids with permethylated β-cyclodextrin has been further investigated[673] using Na^+ as a RPLC retention marker.

Chiral 15-metallacrown-5-complexes, based on L-phenylalaninehydroxamic acid, copper diacetate and lanthanum or gadolinium trinitrate have been prepared and characterized.[674] They adopt a dimeric structure in the solid state, and show selective binding of carboxylate ions. Chiral recognition[675] of carboxylic acids was a feature found in bis-crown ether peptides when complexed with Z-Phe-OH or Z-Ala-OH. The thermodynamics of the complexing of L-Ala-OMe.HCl, L-Phe-OMe.HCl and L-Val-OMe with a series of crown ethers has been reported[676] and the complexation of similar protonated amino acid methyl esters with 18-crown-6 and benzo-18-crown-6 has been studied using calorimetric titrations.[677] 18-Crown-6-tetracarboxylic acid, when used as a chiral additive, has provided[678] simultaneous separation of *o*-, *m*-, *p*-enantiomers of tyrosine and fluorophenylalanine by capillary electrophoresis. Synergistic binding and chiral recognition of unprotected amino acids were properties found[679] for a 18-crown-6 ring connected with a carboxyl group via a ferrocene spacer.

Interactions between calix[4]resorcinarene and amino acids have been studied[680] in Langmuir films and chiral recognition turned out to be a bit patchy depending upon sub-phase conditions. However gas-phase proton bound complexes between chiral resorcin[4]ene and enantiomers of Ala and Ser underwent[681] exchange with the enantiomers of 2-butylamine with significant enantioselectivity. *p*-Tetra *tert*-butyl calix[4]arene derivatives bearing chiral bicyclic guanidinium moieties have served[682] as receptors of amino acid zwitterions and showed selectivity for L-aromatic amino acids. Complexes of tetra-*p*-sulfonated calix[4]arene with racemic Ala, His and Phe, and (*S*)-forms of Ala, His and Tyr have been analysed by X-ray diffraction.[683] The racemates were found in capsules within the host in a bilayer arrangement, while the enantiomers formed a 1:1 complex within the bilayer.

A new kind of threonine-modified porphyrinato zinc(II) host has been shown to form[684] 1:1 and 1:2 adducts with amino acid esters, while a commercially available Zn (II) protoporphyrin has had its binding constants with a series of amino acids analysed by UV-VIS titrations.[685] Three novel chiral zinc porphyrins with protected chiral amino acid substituents, showed[686] enantioselectivity towards amino acid methyl esters, and spectroscopic studies[687] have been carried out on the interactions of Co (II), *N*, *N′*, *N″*, *N‴*-tetramethyltetra-3, 4-tetrapyridinoporphyrazine with amino acids and nitrogen oxides.

Some further selectivity has been incorporated into a pyridyl host molecule with four phosphonate groups[688] attached, which now binds to basic amino acid esters in water. A UV-VIS spectral investigation[689] of chiral SalenCo towards four pairs of enantiomeric amino acid esters showed that 1:1 complexes were formed and the associative constants for the molecular recognition processes were in the order KD > KL > K(LeuOMe) > K(AlaOMe) > K(SerOMe) > K(TyrOMe). The thermodynamic stereoselectivity involved in the chiral recognition of amino acids by the Cu (II) complex of 6-deoxy-6-[4-(2-aminoethyl)imidazolyl]cyclomaltoheptaose has been investigated[690] by a number of techniques. Aromatic amino acids showed stronger binding characteristics with the L-form being favoured. An EPR and molecular mechanics

study[691] of the influence of amino acid side chains on water binding to Cu (II) bis (*N*, *N*-dimethyl-L-isoleucinato) has been carried out, and a 12-reference review has highlighted[692] the intercalation of amino acids and sugars in anionic clays.

A series of unsymmetrical tris-amide receptors, which show a particular affinity for *N*-acetylglycine have been synthesized,[693] and adsorption isotherms for amino acids in BEA zeolites have been analysed.[694] Good chiral recognition properties for enantiomeric amino acid derivatives have been shown[695] by newly synthesised chiral imidazole cyclophane receptors, and enantiomeric recognition[696] could be visualised through development of a purple colour when chiral phenolphthalein derivatives were explored. A synthesised poly (L-glutamic acid) segment grafted on the third generation poly (amidoamine) dendrimer[697] allowed amino acids into its inner core, and showed a preference for the D-forms of Trp, Phe or Tyr.

The thermodynamics of binding of (*R*)- and (*S*)-DNB-Ieueine to cinchona alkaloids and their t-butylcarbamates have been assessed using a number of techniques.[698] The direct intercalation of amino acids into layered double hydroxides of Mg-Al, Mn-Al, Ni-Al and Zn-Al and Zn-Cr has been studied[699] and shown to be dependent on pH and the structure of the amino acid side chains. Reaction of glycine with ninhydrin has been catalysed[700] by cationic micelles, of cetyltrimethylammonium bromide and cetylpyridinium bromide, and the chromatographic performanee[701] in chiral recognition by polymeric amino acid based surfactants has been monitored.

5.10 Theoretical Calculations involving Amino Acids. – Some subject matter covered here will also have found its way into other areas of the Chapter, as theoretical interpretations nowadays are published side by side with experimental deductions. Improved agreement[702] between calculated values and experimental data for the partial molar volume of the 20 amino acids, has been achieved by combining the bridge-corrected ID reference interaction site model (1D-RISM) with the Kirkwood-Buff theory, and even further improvement was gained using a three-dimensional 3D-RISM. The ability of the GROMOS96 force field to reproduce partition constants between water and cyclohexane/chloroform for analogues of 18 of the amino acids has been investigated,[703] and found to work well for non-polar analogues, but overestimates the free energies of polar analogues in water.

Interactions in the contact region of the trypsin-pancreatic trypsin inhibitor complex have been evaluated using simulation methods and thermodynamic cycles,[704] and electrodiffusion of amino acids through fixed charge membranes has been modelled[705] using Nernst-Planck flux equations in the (Goldman) constant electric field assumptions. The formation of various cation radical structures in the irradiated L-Ala crystal has been simulated[706] using a 208-atom cluster, and the relative total energies and equilibrium geometries of various radical conformations were obtained at the PM3 level. The geometries of the 20 genetically encoded amino acids have been optimised[707] at the restricted Hartree-Fock level of theory using 6-31+G* basis set, which turned

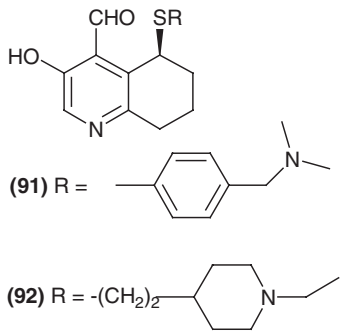
out to be in excellent agreement with those determined by X-ray crystallography.

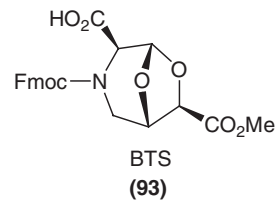
6. Reactions and Analysis of Amino Acids

6.1 General and Specific Reactions of Amino Acids. – Many of the items associated with this topic are really dealt with in other Chapters of this Volume, e.g functional group protection for peptide synthesis (Chapter 2) and metal complexes of amino acids (Chapter 5). So the few papers that remain unattached to other 'sub-sections' are discussed here. The processes involving amino acids, which are catalysed by pyridoxal in nature have been mimicked by pyridoxal analogues such as (**91**) and (**92**) in an attempt to design catalysts that can be applied to organic reactions.[708] Compounds (**91**) and (**92**) steered the reactions of amino acids away from transamination or racemisation towards decarboxylation, retroaldol reaction and aldol reaction. Some enantioselectivity was seen during the protonation of the newly created amino acid carbon chiral centre, but this aspect needs enhancing. Six α-amino acids (Gly, Ala, Abu, iAbu, Val and norVal), β-Ala, and β-aminobutyric acid and γ-amino butyric acid have been subject to nitrosation conditions in aq. media,[709] mimicking the conditions of the stomach lumen. Conclusions there were: dinitrogen trioxide was the main nitrosating agent in aq. media; the reactivity order was α- > β- > γ-amino acids. The kinetics of the oxidation of amino acids by chloramines T in the presence of Fe(II) ion has been studied[710] in aq. sulphuric acid, and show almost identical behaviour with all simple amino acids. Several amino acids were transformed[711] into alkyl esters using triphosgene (trichloromethyl carbonate), and acylation of aromatic amino acids with furancarboxylic acid chlorides was carried out effectively[712] in acetone/water at pH 8–9. In the latter process aliphatic amino acids had to be acylated as methyl esters and then hydrolysed.

To clarify the differences between the reactivity of the γ- and α-COOH's in *N*-phosphorylated glutamic acid, MNDO calculations have been carried out[713] to mimic the results of mixed anhydride activation. Theory and practice agree that it is the α-COOH, via the intermediate 5-membered phosphoric-carboxylic mixed anhydride, that is the most readily activated. A new Fmoc-protected dipeptide isostere, named BTS, (**93**) has been synthesised[714] in 9 steps (11% yield) from *R*, *R*-tartaric acid and *O*-benzyl-L-serine, for use as a peptidomimetic. Chlorination of *N*-acetyl-L-tyrosine with NaOCl and the myeloperoxidase chlorinating system has been investigated[715] and the position of chlorination in the aromatic ring (position 3 and 5) found to be dependent on the reactant concentration ratio and on the pH. FT-IR Spectroscopy has been used to study[716] the decarboxylation of alanine at 280–330°C, as a function of pH, where the rate of decomposition of the zwitterions was found to be 3 × greater than that of the cationic and anionic forms. Pyrolysis of Asn, Pro and Trp has been carried out[717] and the relative formation of polycyclic aromatic amino acids in the products assessed. Seven amino acids have been assessed[718]

as substrates in Belousov-Zhabotinskii oscillation reactions, with mixed results. Asp exhibited typical oscillations, Tyr exhibited oscillations where the metal ion catalyst was not necessary, Cys-Cys, Ala, Gly and Glu gave sustained oscillations only after addition of acetone, while serine showed oscillations even in the absence of acetone. Selective hydroxylation[719] of amino acids in water has been possible with the aid of a catalytic system made up of 5mol % K_2PtCL_4 with 7 eq. $CuCl_2$. The results suggested that the functionalisation of α-amino acids is via a chelate-directed (involving α-NH_2 and COOH groups) C–H bond activation.





BTS
(93)

6.2 Analysis of Amino Acids. – Keyword scanning for papers in this area have brought in very few within this period of reporting, which is out of line with previous periods. This situation could be interpreted in many ways, with the possibility that most analytical methods have over the years been applied to amino acid analysis. The final judgement will have to await the next Volume of these reports to find out what the success rate was during 2003–04.

Better resolution of amino acids by reversed-phase HPLC has been possible using C-18 reverse-phase packing, dynamically coated with 2-aminotetraphenyl porphyrin and in the presence of Zn (II) ion. Twelve of the 20 amino acids could be resolved under isocratic conditions.[720] Ethyl chloroformate in an aq. medium was the derivatisation method[721] chosen in a GC-MS analysis of amino acids and other acids used in artistic paintings. Microchip devices[722] integrating electrophoretic separations, enzymic reactions (amino acid peroxidase), and amperometric detection (of hydrogen peroxide) have been developed.

References

1. *Amino Acids Peptides and Proteins*, eds. G.C. Barrett and J.S. Davies, Royal Society of Chemistry, 2003, Vol. 34.
2. C.A. Selects on *Amino Acids Peptides and Proteins*, published by the American Chemical Society and Chemical Abstracts Service, Columbus, Ohio.
3. '*The ISI Web of Knowledge Service for UK Education*' on http://wok.mimas.ac.uk.
4. T. Lindel, *Nachr. Chem.*, 2000, **48**, 790.
5. D.J. Ager and I.G. Fotheringham, *Curr. Opin. Drug Discovery Dev.*, 2001, **4**, 800.
6. T. Abellan, R. Chinchilla, N. Gallindo, G. Guillena, C. Najera and J. M. Sansano, *Targets in Het. Systems*, 2000, **4**, 57.

7. G. Dyker, *Org. Synth. Highlights IV*, ed. H-G.Schmaltz, Wiley-VCH Verlag, 2000, 53.
8. Y.-h. Cheng, X.-m. Zou, C. Wu and H.-z. Yang, *Jingxi Huagong Zhongjianti*, 2001, **31**, 1.
9. A.S. Bommarius, M. Schwarm and K. Drauz, *Chimia*, 2001, **55**, 50.
10. A. Taggi, A.M. Hafez and T. Lectka, *Acc. Chem. Res.*, 2002, **36**, 10.
11. M.G. Natchus and X. Tian, *Org. Synth: Theory and Applications*, 2001, **5**, 89.
12. D.J. Ager, *Curr. Opin. Drug Discovery Dev.*, 2002, **5**, 892.
13. E. Kimura, *Adv. Biochem.Eng/Biotech.*, 2003, **79**, 37.
14. M. Ikeda, *Adv. Biochem.Eng/Biotech.*, 2003, **79**, 1.
15. W. Pfefferle, B. Mockel, B. Bathe and A. Marx, *Adv. Biochem.Eng/Biotech.*, 2003, **79**, 59.
16. V.G. Debabov, *Adv. Biochem.Eng/Biotech.*, 2003, **79**, 113.
17. U. Mueller and S. Huebner, *Adv. Biochem.Eng/Biotech.*, 2003, **79**, 137.
18. S.S. Kinderman, J.W. van Beijma, L.B. Wolf, H.E Schoemaker, H.R. Hiemstra and F.P.J.T. Rutjes, *Proc. ECSOC-4*, ed E. Pombo-Villar, Mol. Diversity Preservation International, 2000, 709.
19. T. Kimachi, *Farumashia*, 2001, **37**, 920.
20. F.P.J.T. Rutjes, L. B. Wolf and H. E. Schoemaker, *J. Chem. Soc. Trans 1*, 2000, 4197.
21. A. Bianco, T. DaRos, M. Prato and C. Toniolo, *J. Pept. Sci.*, 2001, **7**, 346.
22. M.D. Gieselman, Y. Zhu, H. Zhou, D. Galonic and W.A. Van der Donk, *ChemBiochem.*, 2002, **3**, 709.
23. Y.-X. Fang, Y.-L. Wong, X.-J. Xiong and K. Zhan, *Guangdon Gongye Daxue*, 2002, **19**, 7.
24. V.A. Soloshonok, *Curr. Org. Chem.*, 2002, **6**, 341.
25. G. Kusano, S. Orihara, D. Tsukamoto, M. Shibano, M. Coskun, A. Guvenc and C. S. Erdurak, *Chem. Pharm. Bull.*, 2002, **50**, 185.
26. M.J. O'Donnell, *Aldrichim. Acta*, 2001, **34**, 3.
27. H.S. Knowles, K. Hunt and A.F. Parsons, *Tetrahedron*, 2001, **57**, 8115.
28. G. Cardillo, L. Gentilucci, M. Gianotti and A. Tolemelli, *Tetrahedron*, 2001, **57**, 2807.
29. P. Allevi, G. Cighetti and M. Anastasia, *Tetrahedron Lett.*, 2001, **42**, 5319.
30. C. Tanyeli and B. Sezen, *Enantiomer*, 2001, **6**, 229.
31. S. Kobayashi, R. Matsubara and H. Kitagawa, *Org. Lett.*, 2002, **4**, 143.
32. A. Cordova, W. Notz, G. Zhong, J.M. Betancort and C.F. Barbas III, *J. Am. Chem. Soc.*, 2002, **124**, 1842.
33. A. Cordova, S. Watanabe, F. Tanaka, W. Notz and C.F. Barbas III, *J. Am. Chem. Soc.*, 2002, **124**, 1866.
34. D. Ferraris, B. Young, C. Cox, T. Dudding, W.J. Drury III, L. Ryzhkov, A.E. Taggi and T. Lectka, *J. Am. Chem. Soc.*, 2002, **124**, 67.
35. G.C. Lloyd-Jones, *Angew. Chem. Int. Ed.*, 2002, **41**, 953.
36. A.-M. Yim, Y. Vidal, P. Viallefont and J. Martinez, *Tetrahedron Asymmetry*, 2002, **13**, 503.
37. T.-S. Huang and C.-J. Li, *Org. Lett.*, 2001, **3**, 2037.
38. T.-S. Huang, C.C.K. Keh and C.-J. Li, *Chem. Commun. (Cambridge)*, 2002, 2440.
39. A. de la Hoz, A. Diaz-Ortiz, M.V. Gomez, J.A. Mayoral, M.A. Sanchez-Migallon and A.M. Vazquez, *Tetrahedron*, 2001, **57**, 6421.
40. W.L. Scott, M.J. O'Donnell, F. Delgado and J. Alsina, *J. Org. Chem.*, 2002, **67**, 2960.

41. B. Alcaide, P. Almendros and C. Aragonolo, *Chem.-A Eur. J.*, 2002, **8**, 3646.
42. (*a*) J.M. Drabik, J. Achatz and I. Ugi, *Proc. Estonian Acad. Sci.*, 2002, **51**, 156; (*b*) G. Ross and I. Ugi, *Can. J. Chem.*, 2001, **79**, 1934.
43. M. Kitamura, D. Lee, S. Hayashi, S. Tanaka and M. Yoshimura, *J. Org. Chem.*, 2002, **67**, 8685.
44. S.D. Bull, S.G. Davies, A.C. Garner and N. Mujtaba, *Synlett*, 2001, 781.
45. S.D. Bull, S.G. Davies, M.D. O'Shea, E.D. Savoury and E. Snow, *J. Chem. Soc. Perkin Trans 1*, 2002, 2442.
46. S.G. Davies, S.W. Epstein, O. Ichihara and A.D. Smith, *Synlett*, 2001, 1599.
47. S.D. Bull, S.G. Davies, M.D. O'Shea and A.C. Garner, *J. Chem. Soc. Perkin Trans 1*, 2002, 2442.
48. L.M. Harwood, S.N.G. Tyier, M.G.B. Drew, A. Jahans and I.D. MacGilp, *ARKJVOC*, 2000, **1**, 820.
49. L.M. Harwood, M.G.B. Drew, D.J. Hughes and R.J. Vickers, *J. Chem. Soc. Perkin Trans 1*, 2001, 1581.
50. P.-F. Xu, Y.-S. Chen, S.-I. Lin and T.-J. Lu, *J. Org. Chem.*, 2002, **67**, 2309.
51. P.-F. Xu and T.-J. Lu, *J. Org. Chem.*, 2002, **68**, 658.
52. S.K. Lee, J. Nam and Y.S. Park, *Synlett*, 2002, 790.
53. H. Miyabe, A. Nishimura, M. Ueda and T. Naito, *Chem. Commun. (Cambridge)*, 2002, 1454.
54. (*a*) A.S. Sagiyan, A.A. Petrosyan, A.A. Ambartsumyan, V.I. Maleev and Y.N. Belokon, *Hayastani Kimiak. Handes*, 2002, **55**, 150; (*b*) Y. N. Belokon, V.I. Maleev, A.A. Petrosyan, T.F. Savel'eva, N.S. Ikonnikov, A.S. Peregudov, V.N. Khrustalev and A.S. Saghiyan, *Russ. Chem. Bull.*, 2002, **51**, 1593.
55. P. Merino, J. Revuelta, T. Tejero, U. Chiacchio, A. Rescifina, A. Piperno and G. Romeo, *Tetrahedron Asymmetry*, 2002, **13**, 167.
56. P. Merino, J.A. Mates, J. Revuelta, T. Tejero, U. Ciacchio, G. Romeo, D. Lannazzo and R. Romeo, *Tetrahedron Asymmetry*, 2002, **13**, 173.
57. Y.N. Belokon, K.A. Kochetov, T.D. Churkiana, N.S. Ikonnikov, O.V. Larionov, S.R. Harutyunyan, S. Vyskocil, M. North and H.B. Kagan, *Angew. Chem. Int. Ed.*, 2001, **40**, 1948.
58. H.J. Kim, S.-K. Lee and Y.S. Park, *Synlett*, 2001, 613.
59. B. Thierry, J.C. Plaquevent and D. Cahard, *Tetrahedron: Asymmetry*, 2001, **12**, 983.
60. R. Chinchilla, P. Mazon and C. Najera, *Tetrahedron: Asymmetry*, 2002, **13**, 927.
61. M.J. O'Donnell, M.D. Drew, J.T. Cooper, F. Delgado and C. Zou, *J. Am. Chem. Soc.*, 2002, **124**, 9348.
62. H.-g. Park, B.-S. Jeong, M.-S. Yoo, J.-H. Lee, M.-k. Park, Y.-J. Lee, M.J. Kim and S.-s. Jew, *Angew. Chem. Int. Ed.*, 2002, **41**, 3036.
63. P. Mazon, R. Chinchilla, C. Najera, G. Guillena, R. Kreiter, G. Klein, J.M. Robertus and G. van Koten, *Tetrahedron Asymmetry*, 2002, **13**, 2181.
64. B. Lygo and L.D. Humphreys, *Tetrahedron Lett.*, 2002, **43**, 6677.
65. F. Royer, F.-X. Felpin and E. Doris, *J. Org. Chem.*, 2001, **66**, 6487.
66. A. Cooke, J. Bennett and E. McDaid, *Tetrahedron Lett.*, 2002, **43**, 903.
67. T.B. Durham and M.J. Miller, *J. Org. Chem.*, 2002, **68**, 27.
68. Y.K. Chen, A.E. Lurain and P.J. Walsh, *J. Am. Chem. Soc.*, 2002, **124**, 12225.
69. M. Ostermeier, J. Priess and G. Helmchen, *Angew. Chem. Int. Ed.*, 2002, **41**, 612.
70. M. Adamczyk, S.R. Akireddy and R.E. Reddy, *Tetrahedron*, 2002, **58**, 6951.
71. F.-Y. Zhang, W.H. Kwok and A.S.C. Chan, *Tetrahedron: Asymmetry*, 2001, **12**, 2337.

72. W. Wang, C.Y. Xiong and V.J. Hruby, *Synthesis-Stuttgart*, 2002, **94**.
73. Y.-S. Lin and H. Alper, *Angew. Chem. Int. Ed.*, 2001, **40**, 779.
74. G. Antoni, H. Omura, M. Ikemoto, R. Moulder, Y. Watanabe and B. Langstrom, *J. Labelled Compd. and Radiopharm.*, 2001, **44**, 287.
75. W. Augustyniak, R. Kanski and M. Kanska, *J. Labelled Compd. and Radiopharm.*, 2001, **44**, 553.
76. E.B. Watkins and R.S. Phillips, *Biorg. Med. Chem.Lett.*, 2001, **11**, 2085.
77. (*a*) W. Augustyniak, P. Suchecki, J. Jemielity, R. Kanski and M. Kanska, *J. Labelled Compd. and Radiopharm.*, 2002, **45**, 559; (*b*) J. Jemielity, R. Kanski and M. Kanska, *ibid.*, 2001, **44**, 295.
78. A.J.H. Vadas, I.M. Schroeder and H.G. Monbouquette, *Biotech. Prog.*, 2002, **18**, 909.
79. M. Wu, P. Wei and H. Zhou, *Huaxue Shijie*, 2002, **43**, 476.
80. B. Sauvagnat, F. Lamaty, R. Lazaro and J. Martinez, *Tetrahedron*, 2001, **57**, 9711.
81. M.J. O'Donnell, F. Delgado, E. Dominguez, J. de Blas and W.L. Scott, *Tetrahedron Asymmetry*, 2001, **12**, 821.
82. T. Dudding, A.M. Hafez, A.E. Taggi, T.R. Wagerle and T. Lectka, *Org. Lett.*, 2002, **4**, 387.
83. C. Xiong, W. Wang and V.J. Hruby, *J. Org. Chem.*, 2002, **67**, 3514.
84. G.-x. Li, F.-m. Mei and Y. Juan, *Jingxi Huagong*, 2001, **18**, 579.
85. T. Morita, Y. Nagasawa, S. Yahiro, H. Matsunga and T. Kunieda, *Org. Lett.*, 2001, **3**, 897.
86. C. Ma, X. Liu, X. Li, J. Flippen-Anderson, S. Yu and J. M. Cook, *J. Org. Chem.*, 2001, **66**, 4525.
87. A. Basak, S.S. Bag, K.R. Rudra, J. Barman and S. Dutta, *Chem. Lett.*, 2002, 710.
88. M.-X. Wang and S.-J. Lin, *J. Org. Chem.*, 2002, **67**, 6542.
89. S. Guery, M. Schmitt and J.-J. Bourguignon, *Synlett*, 2002, 2003.
90. E. Morero and G. Ortar, *Synth. Commun.*, 2001, **31**, 2215.
91. J.R. Walker and R.W. Curley, *Tetrahedron*, 2001, **57**, 6695.
92. C. Soede-Huijbregts, M. Van Laren, F.B. Hulsbergen, J. Raap and J. Lugtenburg, *J. Labelled Compd and Radiopharm.*, 2001, **44**, 831.
93. M. Oba, M. Kobayashi, F. Oikawa, K. Nishiyama and M. Kainasho, *J. Org. Chem.*, 2001, **66**, 5919.
94. C.J. Easton, N.L. Fryer, J.B. Kelly and K. Kociuba, *ARKIVOC*, 2001, **2**, U48.
95. M. Oba, T. Ishihara, H. Satake and K. Nishiyama, *J. Labelled Compd. and Radiopharm.*, 2002, **45**, 619.
96. D.W. Barrett, M.J. Panigot and R.W. Curley, *Tetrahedron: Asymmetry*, 2002, **13**, 1893.
97. J. Rudolph, F. Hannig, H. Theis and R. Wischnat, *Org. Lett.*, 2001, **3**, 3153.
98. F.-G. Pan, L.-G. Chen and M. Lu, *Guangzhou Huaxue*, 2001, **26**, 18.
99. A. Skolaut and J. Retey, *Arch. Biochem. Biophys.*, 2001, **393**, 187.
100. K. Laumen, O. Ghisalba and K. Auer, *Biosc. Biotech. Biochem.*, 2001, **65**, 1977.
101. W. Lin, Z. He, H. Zhang, X. Zhang, A. Mi and Y. Jing, *Synthesis*, 2001, 1007.
102. Y. Zhang, X. Liang and Y. Lin, *Huagong Shikan*, 2002, **16**, 46.
103. M. Yashiro, *Bull. Chem. Soc. Jap.*, 2002, **75**, 1383.
104. V.P. Krasnov, G.L. Levit, I.M. Bukrina and A.M. Demin, *Tetrahedron Asymmetry*, 2002, **13**, 1911.
105. S.P. Bew, S.D. Bull, S.G. Davies, E.D. Savory and D.J. Watkin, *Tetrahedron*, 2002, **58**, 9387.
106. S. Narayanan, S. Vangapandu and R. Jain, *Chem. Lett.*, 2001, **11**, 1133.

107. N. Kise, H. Ozaki, H. Terui, K. Ohya and N. Ueda, *Tetrahedron Lett*., 2001, **42**, 7637.
108. Q. Yin, B. Jiang, Z. Mao, X. Sun and Y. Wang, *Huaxue Shijie*, 2001, **42**, 29.
109. J.M. Travins, M.G. Bursavich, D.F. Veber and D.H. Rich, *Org. Lett*., 2001, **3**, 2725.
110. C. Pesenti, P. Bravo, E. Corradi, M. Frigerio, S.V. Meille, W. Panzeri, F. Viani and M. Zanda, *J. Org. Chem*., 2001, **66**, 5637.
111. S.J. Kwon and S.Y. Koo, *Tetrahedron Lett*., 2002, **43**, 639.
112. D. Yoo, J.S. Oh and Y.G. Kim, *Org. Lett*., 2002, **4**, 1213.
113. J. Clayden, C.J. Menet and K. Tchabanenko, *Tetrahedron*, 2002, **58**, 4727.
114. S.-T.S. Itadani, C. Tanigawa, K. Hashimoto and M. Shirahama, *Tetrahedron Lett*., 2002, **43**, 7777.
115. E.S. Greenwood and P.J. Parsons, *Synlett*., 2002, 167.
116. M. Kamabe, T. Miyazaki, K. Hashimoto and H. Shirahama, *Heterocycles*, 2002, **56**, 105.
117. G. Rosini, *Chim. Ind*., 2001, **83**, 75.
118. J.E. Baldwin, G.J. Pritchard and D.S. Williamson, *Tetrahedron*, 2001, **57**, 7991.
119. R.P. Jain and R.M. Williams, *Tetrahedron*, 2001, **57**, 6505.
120. R.P. Jain and R.M. Williams, *Tetrahedron Lett*., 2001, **42**, 4437.
121. K. Makino, K. Shintani, T. Yamatake, O. Hara, K. Hatano and Y. Hamada, *Tetrahedron*, 2002, **58**, 9737.
122. G.Y. Cho, K.M. An and S.Y. Ko, *Bull. Korean Chem. Soc*., 2001, **22**, 432.
123. N.M. Van Gelder and R.J. Bowers, *Neurochem. Res*., 2001, **26**, 575.
124. P. Bisel, E. Breitling, M. Schlauch, F.-J. Volk and A.W. Frahm, *Pharmazie*, 2001, **56**, 770.
125. D. Phillips and A.R. Chamberlain, *J. Org. Chem*., 2002, **67**, 3194.
126. H. Sugiyama, T. Shioiri and F. Yokokawa, *Tetrahedron Lett*., 2002, **43**, 3489.
127. X. Li, R.N. Atkinson and S.B. King, *Tetrahedron*, 2001, **57**, 6557.
128. N.U. Sata, R. Kuwahara and Y. Murata, *Tetrahedron Lett*, 2002, **43**, 115.
129. T. Oishi, K. Ando and N. Chida, *Chem. Commun. (Cambridge)*, 2001, 1932.
130. K. Lida and M. Kajiwara, *J. Labelled Compd. and Radiopharm*., 2002, **45**, 139.
131. N.M. Gillings and A.D. Gee, *J. Labelled Compd. and Radiopharm*., 2001, **44**, 909.
132. Z. Zhang, Y.-S. Ding, A.R. Studenov, M.R. Gerasimov and R.A. Ferrieri, *J. Labelled Compd. and Radiopharm*., 2002, **45**, 199.
133. B.B. Snider and Y. Gu, *Org. Lett*., 2001, **3**, 1761.
134. D.E. DeMong and R.M. Williams, *Tetrahedron Lett*., 2002, **43**, 2355.
135. V. Magrioti and V. Constantinou-Kokotou, *Lipids*, 2002, **37**, 223.
136. K.A. Brun, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, 2001, **84**, 1756.
137. K.A. Brun, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, 2002, **85**, 3422.
138. K. Wright, F. Melandri, C. Cannizzo, M. Wakselman and J.-P. Mazaleyrat, *Tetrahedron*, 2002, **58**, 5811.
139. Y.N. Belekon, V.I. Maleev, T.F. Saveleva and N.S. Ikonnikov, *Russ. Chem. Bull*., 2001, **50**, 1037.
140. A. Avenoza, C. Cativiela, F. Corzana, J.-M. Peregrina, H.D. Sucunza and M.M. Zurbano, *Tetrahedron Asymmetry*, 2001, **12**, 949.
141. M. Tanaka, M. Oba, M. Kurihara, Y. Demizu, S. Nishimura, K. Hayashida and H. Suemune, *Pept. Sci*., 2001, **38**, 263.
142. A.G. Hu, L.-Y. Zhang, S.-W. Ing and J.-T. Wang, *Synth. Commun*., 2002, **32**, 2143.

143. (*a*) Y.N. Belokon, D. Bhave, D. D'Addario, E. Groaz, V. Maleev, M. North and A. Pertrosyan, *Tetrahedron Lett*., 2003, **44**, 2045; (*b*) Y.N. Belokon, R.G. Davies, J.A. Fuentes, M. North and T. Parsons, *ibid*., 2001, **42**, 8093.
144. R. Portoles, J. Murga, E. Falomir, M. Carda, S. Uriel and J. A. Marco, *Synlett*, 2002, **711**.
145. C. Alvarez-Ibarra, A.G. Csaky and C.G. De la Oliva, *Eur. J. Org. Chem*., 2002, 4190.
146. S.-H. Lee and E.-K. Lee, *Bull. Korean Chem. Soc*., 2001, **22**, 551.
147. Y. Fu, L.G.J. Hammarstroem, T.J. Miller, F.R. Fronczek, M.L. McLaughlin and R.P. Hammer, *J. Org. Chem*., 2001, **66**, 7118.
148. V.V.S. Babu, K. Ananda and G.-R. Vasanthakumar, *Protein and Peptide Lett*., 2002, **9**, 345.
149. B. Kaptein, Q.B. Broxterman, H.E. Schoemaker, F.P.J.T. Rutjes, J.J.N. Veerman, J. Kamphuis, C. Peggion, F. Formaggio and C. Toniolo, *Tetrahedron*, 2001, **57**, 6567.
150. D.M. Bradley, R. Mapiste, N.M. Thomson and C.J. Hayes, *J. Org. Chem*., 2002, **67**, 7613.
151. J.C. Anderson and S. Skerratt, *J. Chem. Soc Perkin Trans 1*, 2002, 2871.
152. S. Torrente and R. Alonso, *Org. Lett*., 2001, **3**, 1985.
153. R. Martin, G. Islas, A. Moyana, M.A. Pericas and A. Riera, *Tetrahedron*, 2001, **57**, 6367.
154. K. Ding and D. Ma, *Tetrahedron*, 2001, **57**, 6361.
155. T. Ooi, M. Takeuchi, D. Ohara and K. Maruoka, *Synlett*., 2001, 1185.
156. P.D. Bailey, N. Bannister, M. Bemad, S. Blanchard and N.A. Boa, *J. Chem. Soc. Perkin Trans 1*, 2001, 3245.
157. F. Clerici, M.L. Gelmi, D. Pocar and T. Pilati, *Tetrahedron Asymmetry*, 2001, **12**, 2663.
158. A. Debache, S. Collet, P. Bauchat, D. Danion, L. Euzenat, A. Hercouet and B. Carboni, *Tetrahedron Asymmetry*, 2001, **12**, 761.
159. E. Bunuel, A.I. Jimenez, M.D. Diazde-Villegas and C. Cativiela, *Targets Het. Systems*, 2001, **5**, 79.
160. A. Salgado, T. Huybrechts, A. Eeckhaut, J. Van der Eycken, Z. Szakonyi, F. Fulop, A. Tkachev and N. DeKimpe, *Tetrahedron*, 2001, **57**, 2781.
161. D.K. Mohapatra, *J. Chem. Soc. Perkin Trans 1*, 2001, **1851**.
162. A. Esposito, P.P. Piras, D. Ramazzotti and M. Taddei, *Org. Lett*., 2001, **3**, 3273.
163. R. Pellicciari, G. Constantino, M. Marinozzi, A. Macchiarulo, L. Amori, P. Josef Flor, F. Gasparini, R. Kuhn and S. Urwyler, *Bioorg. Med. Chem. Lett*., 2001, **11**, 3179.
164. N.J. Wallock and W.A. Donaldson, *Tetrahedron Lett*., 2002, **43**, 4541.
165. I. Collado, C. Pedregal, A. Mazon, J. Felix Espinosa, J. Blanco-Urgoiti, D.D. Schoepp, R.A. Wright, B.G. Johnson and A.E. Kingston, *J. Med. Chem*., 2002, **45**, 3619.
166. N.A. Anisimova, G.A. Berkova, T.Y. Paperno and L.I. Deiko, *Russ. J. Gen. Chem*., 2002, **72**, 272.
167. S. Racouchot, I. Sylvestre, J. Ollivier, Y.Y. Kozyrkov, A. Pukin, O.G. Kulinkov and J. Salaun, *Eur. J. Org. Chem*., 2002, 2160.
168. D. Fishlock, J.G. Guillemette and G.A. Lajoie, *J. Org. Chem*., 2002, **67**, 2352.
169. T.M. Kamenecka, Y.-J. Park, L.S. Lin, T. Lanza and W.K. Hagmann, *Tetrahedron Lett*., 2001, **42**, 8571.

170. D.J. Aldous, M.G.B. Drew, E.M.-N. Hamelin, L.M. Harwood, A.B. Jahans and S. Thurairatnam, *Synlett*, 2001, 1836.
171. Q. Xia and B. Ganem, *Tetrahedron Lett*., 2002, **43**, 1597.
172. L. Halab, L. Belec and W.D. Lubell, *Tetrahedron*, 2001, **57**, 6439.
173. E.A.A. Wallen, J.A.M. Christiaans, J. Gynther and J. Vepsalainen, *Tetrahedron Lett*., 2003, **44**, 2081.
174. S. Duan and K.D. Moeller, *Tetrahedron*, 2001, **57**, 6407.
175. Y.G. Gu, Y. Xu, A.C. Krueger, D. Madigan and H.L. Sham, *Tetrahedron Lett*., 2002, **43**, 955.
176. X. Chen, D.-M. Du and W.-T. Hua, *Tetrahedron Asymmetry*, 2002, **13**, 43.
177. A.M. Boldi, J.M. Oener and T.P. Hopkins, *J. Comb. Chem*., 2001, **3**, 367.
178. J. Casas, R. Grigg, C. Najera and J.M. Sansano, *Eur. J. Org. Chem*., 2001, 1971.
179. J.E. Baldwin, A.M. Fryer and G.J. Pritchard, *J. Org. Chem*., 2001, **66**, 2588.
180. K. Makino, A. Kondoh and Y. Hamada, *Tetrahedron Lett*., 2002, **43**, 4695.
181. I. Merino, Y.R. Santosh Laxmi, J. Florez, J. Barluenga, J. Ezquerra and C. Pedregal, *J. Org. Chem*., 2002, **67**, 648.
182. G.R. Crow, S.B. Herzon, G. Lin, F. Qui and P.E. Sonnet, *Org. Lett*., 2002, **4**, 3151.
183. T. Rammeloo and C.V. Stevens, *Chem. Commun. (Cambridge)*, 2002, 250.
184. (*a*) E. Bunuel, A.M. Gil, M.D. Diaz de Villegas and C. Cativiela, *Tetrahedron*, 2001, **57**, 6417; (*b*) A. Avenoza, J.I. Barriobero, J.H. Busto, C. Cativiela and J.S. Peregrina, *Tetrahedron Asymmetry*, 2002, **13**, 625; (*c*) A. Avenoza, C. Cativiela, J.H. Busto, M.A. Fernandez-Recio, J.M. Peregrina and F. Rodriguez, *Tetrahedron*, 2001, **57**, 545.
185. B. Jiang and M. Xu, *Org. Lett*., 2002, **4**, 4077.
186. T. Miura and T. Kajimoto, *Chirality*, 2001, **13**, 577.
187. S. Ohira, M. Akiyama, K. Kamihara, Y. Isoda and A. Kuboki, *Biosci. Biotech. and Biochem*., 2002, **66**, 887.
188. M.G. Woll, J.D. Fisk, P.R. LePlae and S.H. Gellman, *J. Am. Chem. Soc*., 2002, **124**, 12447.
189. C.M. Acevedo, E.F. Kogul and M.A. Lipton, *Tetrahedron*, 2001, **57**, 6353.
190. I.A. Nizova, V.P. Krasnov, G.L. Levit and M.I. Kodess, *Amino Acids*, 2002, **22**, 179.
191. C. Agami, F. Bisaro, S. Comesse, S. Guesne, C. Kadouri-Puchot and R. Morgentin, *Eur. J. Org. Chem*., 2001, 2385.
192. A. Kulesza, A. Mieczkowski and J. Jurczak, *Tetrahedron Asymmetry*, 2002, **13**, 2061.
193. X. Ginesta, M.A. Pericas, A. Riera and F. Marti, *Tetrahedron Lett*., 2002, **43**, 779.
194. D.-G. Liu, Y. Gao, X. Wang, J.A. Kelley and T.R. Burke Jr., *J. Org. Chem*., 2002, **67**, 1448.
195. M. Haddad and M. Larcheveque, *Tetrahedron Lett*., 2001, **42**, 5223.
196. F. Machetti, F.M. Cordero, F. de Sarlo and A. Brandi, *Tetrahedron*, 2001, **57**, 4995.
197. W. Maison and G. Adiwidjaja, *Tetrahedron Lett*., 2002, **43**, 5957.
198. C.-B. Xue, X. He, J. Roderick, R.L. Corbett and C.P. Decicco, *J. Org. Chem*., 2002, **67**, 865.
199. E. Teoh, E.M. Campi, W.R. Jackson and A.J. Robinson, *New J. Chem*., 2003, **27**, 387.
200. R. Warmuth, T.E. Munsch, R.A. Stalker, B. Li and A. Beatty, *Tetrahedron*, 2001, **57**, 6383.
201. S. Kotha, N. Sreenivasachary and E. Brahmachary, *Tetrahedron*, 2001, **57**, 6261.

202. J. Wang, M.L. Falck-Pederson, C. Romming and K. Undheim, *Synth. Commun.*, 2001, **31**, 1141.
203. C.L.L. Chai, R.C. Johnson and J. Koh, *Tetrahedron*, 2002, **58**, 975.
204. M. Belohradsky, I. Cisarova, P. Holy, J. Pastor and J. Zavada, *Tetrahedron*, 2002, **58**, 8811.
205. F. Clerici, M.L. Gelmi, A. Gambini and D. Nava, *Tetrahedron*, 2001, **57**, 6429.
206. J.S. Tulus, M.J. Laufersweiler, J.C. VanRens, M.G. Natchus, R.G. Bookland, N.G. Almstead, S. Pikul, B. De, L.C. Hsieh, M.J. Janusz, T.M. Branch, S.X. Peng, Y.Y. Jin, T. Hudlicky and K. Oppong, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1975.
207. S. Venkatraman, F.G. Njoroge, V. Girijavallabhan and A.T. McPhail, *J. Org. Chem.*, 2002, **67**, 2686.
208. W.-C. Shieh, S. Xue, N. Reel, R. Wu, J. Fitt and O. Repic, *Tetrahedron Asymmetry*, 2001, **12**, 2421.
209. A.T. Ung, K. Schafer, K.B. Lindsay, S.G. Pyne, K. Amornraksa, R. Wouters, U. Van der Linden, U. Biesmans, A.S.J. Lesage, B.W. Skelton and A.H. White, *J. Org. Chem.*, 2001, **67**, 227.
210. S. Krikstolaityte, A. Sackus, C. Roinmilng and K. Undheim, *Tetrahedron Asymmetry*, 2001, **12**, 393.
211. C. Alvarez-Ibarra, A.G. Csaky and C. Gomez de la Oliva, *J. Org. Chem.*, 2002, **67**, 2789.
212. P. Conti, G. Roda and P.F. Barberia Negra, *Tetrahedron Asymmetry*, 2001, **12**, 1363.
213. K.-H. Park, T.M. Kurth, M.M. Olmstead and M.J. Kurth, *Tetrahedron Lett.*, 2001, **42**, 991.
214. H. Dialer, W. Steglich and W. Beck, *Tetrahedron*, 2001, **57**, 4855.
215. S. Kotha, S. Halder, L. Damodharan and V. Pattabhi, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1113.
216. S. Kotha, A.K. Ghosh and M. Behera, *Ind. J. Chem. Section B*, 2002, **41B**, 2330.
217. A.M. Papini, E. Nardi, F. Nuti, I. Uziel, M. Ginanneschi, M. Chelli and A. Brandi, *Eur. J. Org. Chem.*, 2002, 2736.
218. L. Mou and G. Singh, *Tetrahedron Lett.*, 2001, **42**, 6603.
219. V. Constantitinou-Kokotou, V. Magrioti, T. Markidis and G. Kokotos, *J. Pept. Res.*, 2001, **58**, 325.
220. H.-b. Shi, C.-l. Shao and Z.-l. Yu, *Huaxue Yanjiu*, 2001, **12**, 1.
221. P. Meffre, R.H. Dave, J. Leroy and B. Badet, *Tetrahedron Lett.*, 2001, **42**, 8625.
222. Y. Ding, A.J. Wang, K.A. Abboud, Y. Xu, W.R. Dolbier Jr. and N.G.J. Richards, *J. Org. Chem.*, 2001, **66**, 6381.
223. K. Uneyama, T. Katagiri and H. Amii, *Yuki Gosei, Kagaku Kyokaishi*, 2002, **60**, 1069.
224. T. Konno, T.I. Daitoh, T. Ishihara and H. Yamanaka, *Tetrahedron Asymmetry*, 2001, **12**, 2743.
225. T. Katagiri, M. Handa, Y. Matsukawa, J.S. Dileep Kumar and K. Uneyama, *Tetrahedron Asymmetry*, 2001, **12**, 1303.
226. M. Crucianelli, N. Battista, P. Bravo, A. Volonterio and M. Zanda, *Elec.J. Geotech. Eng.*, 2000, **5**, 1251.
227. A.Y. Aksinenko, A.N. Pushin and V.B. Sokolov, *Russ. Chem. Bull.*, 2002, **51**, 2136.
228. J.T. Anderson, P.L. Toogood and E.N.G. Marsh, *Org. Lett*, 2002, **4**, 4281.
229. G.K.S. Prakash, M. Mandal, S. Schweizer, N.A. Petasis and G.A. Olah, *J. Org. Chem.*, 2002, **67**, 3718–6286.

230. S. Fustero, A. Navarro, B. Pina, J.G. Soler, A. Bartolome, A. Asensio, A. Simon, P. Bravo, G. Fronza, A. Volonterio and M. Zanda, *Org. Lett*., 2001, **3**, 2621.
231. S.G. Osipov, O.I. Artyushin, A.F. Kolomiets, C. Brunaeau, M. Picquet and P.H. Dixneuf, *Eur. J. Org. Chem*., 2001, 3891.
232. S.N. Osipov, N.M. Kobelikova, G.T. Shchetnikov, A.F. Kolomeits, C. Bruneau and P.H. Dixneuf, *Synlett*, 2001, 621.
233. X.-l. Qui and F.-l. Qing, *J. Chem. Soc. Perkin Trans*., 2002, 2052.
234. X.-l. Qui and F.-l. Qing, *J. Org. Chem*., 2002, **67**, 7162.
235. J.R. Del Valle and M. Goodman, *Angew. Chem. Int. Ed*., 2002, **41**, 1600.
236. M. Doi, Y. Nishi, N. Kiritoshi, T. Iwata, M. Nago, H. Nakano, S. Uchiyama, T. Nakazawa, T. Wakamiya and Y. Kobayashi, *Tetrahedron*, 2002, **58**, 8453.
237. A.S. Gobulev, H. Schedel, G. Radios, J. Sieler and K. Burger, *Tetrahedron Lett*., 2001, **42**, 7941.
238. S.N. Osipov, N.M. Kobel Kova, A.F. Kolomiets, K. Pumpor, B. Kotsch and K. Burger, *Synlett*, 2001, 1287.
239. N.A. Fokina, A.M. Komilov and V.P. Kukhar, *J. Fluorine Chem*., 2001, **111**, 69.
240. A. Vidal, A. Nefzi and R.A. Houghten, *J. Org. Chem*., 2001, **66**, 8268.
241. B. Mohar, J. Badoux, J.-C. Plaquevent and D. Cahard, *Angew. Chem. Int. Ed*., 2001, **40**, 4214.
242. A. Asensio, P. Bravo, M. Crucianelli, A. Farina, S. Fuslero, J.G. Soler, S.V. Meille, W. Fanzcri, F. Viani. A. Vobnterio and M. Kanda, *Eur. J. Org. Chem*., 2001, 1449.
243. F.A. Davis, Y. Zhang, A. Rao and Z. Zhang, *Tetrahedron*, 2001, **57**, 6345.
244. M. Panunzio, E. Bandini, E. Campana and P. Vicennati, *Tetrahedron Asymmetry*, 2002, **13**, 2113.
245. R. Andruszkiewicz and M. Wyszogrodzka, *Synlett*, 2002, 2101.
246. M.R. Carrasco, R.T. Brown, Y.M. Serafinova and O. Silva, *J. Org. Chem*., 2002, **68**, 195.
247. Q. Wang, J. Ouazzani, N.A. Sasaki and P. Potier, *Eur. J. Org. Chem*., 2002, 834.
248. J.E. Dettwiler and W.D. Lubell, *J. Org. Chem*., 2003, **68**, 177.
249. M. Amador, X. Ariza, J. Garcia and S. Sevilla, *Org. Lett*., 2002, **4**, 4511.
250. M. Oba, S. Koguchi and K. Nishiyama, *Tetrahedron*, 2002, **58**, 9359.
251. P.X. Choudhury, D.X. Le Nguyen and N. Langlois, *Tetrahedron Lett*., 2002, **43**, 463.
252. J. Zhang, J.L. Flippen-Anderson and A.P. Kozikowski, *J. Org. Chem*., 2001, **66**, 7555.
253. S. Caddick, N.J. Parr and M.C. Pritchard, *Tetrahedron*, 2001, **57**, 6615.
254. Y.N. Belokon, K.A. Kochetkov, N.S. Ikannikov, T.V. Strelkova, S.R. Hartyunyan and A.S. Saghiyan, *Tetrahedron Asymmetry*, 2001, **12**, 481.
255. J. Spetzler and T. Hoeg-Jensen, *J. Pept. Sci*., 2001, **7**, 537.
256. T. Markidis and G. Kokotos, *J. Org. Chem*., 2002, **67**, 1685.
257. C. Palomo, M. Oiarhide, A. Landn, A. Esnal and A. Lindtin, *J. Org. Chem*., 2001, **66**, 4180.
258. B.T. Shireman and M.J. Miller, *J. Org. Chem*., 2001, **66**, 4809.
259. N. Yoshikawa and M. Shibasaki, *Tetrahedron*, 2002, **58**, 8289.
260. V. Guerlavais, P.J. Carroll and M.M. Joullie, *Tetrahedron Asymmetry*, 2002, **13**, 675.
261. S. Chandrasekhar, T. Ramachandar, B. Rao and B. Venkateswara, *Tetrahedron Asymmetry*, 2001, **12**, 2315.
262. J.M. Travins, M.G. Bursavich, D.F. Veber and D.H. Rich, *Org. Lett*., 2001, **3**, 2725.

263. S.Y. Ko, *J. Org. Chem.*, 2002, **67**, 2689.
264. R.A. Tromp, M. van der Hoeven, A. Amore, J. Brussee, M. Overhand and G.A. van der Gen, *Tetrahedron Asymmetry*, 2001, **12**, 1109.
265. Q. Wang, M.E. Tran Huu Dau, N. Andre Sasaki and P. Potier, *Tetrahedron*, 2001, **57**, 6455.
266. J.H. Lee, J.E. Kang, M.S. Yang, K.Y. Kang and K.-H. Park, *Tetrahedron*, 2001, **57**, 10071.
267. D.G. Qin, H.-Y. Zha and Z.-J. Yao, *J. Org. Chem.*, 2002, **67**, 1038.
268. P. Dalla Croce and C. La Rosa, *Tetrahedron Asymmetry*, 2002, **13**, 197.
269. C.M. Taylor, W.D. Barker, C.A. Weir and J.H. Park, *J. Org. Chem.*, 2001, **67**, 4466.
270. R. Martin, M. Alcon, M.A. Pericas and A. Riera, *J. Org. Chem.*, 2002, **67**, 6896.
271. A. Avenoza, J. Barriobero, J.H. Busto, C. Cativiela and J.M. Peregrina, *Tetrahedron Asymmetry*, 2002, **13**, 625.
272. X. Zhang, A.C. Schmitt and W. Jiang, *Tetrahedron Lett.*, 2001, **42**, 5335.
273. A. Avenoza, J.I. Barriobero, C. Cativiela, M.A. Fernandez-Recio, J.M. Peregrina and F. Rodriquez, *Tetrahedron*, 2001, **57**, 2745.
274. J. Marin, C. Didierjean, A. Aubry, J.-P. Briand and G. Guichard, *J. Org. Chem.*, 2002, **67**, 8440.
275. M.M. Palian and R. Polt, *J. Org. Chem.*, 2001, **66**, 7178.
276. N. Okamoto, O. Hara, K. Makino and Y. Hamada, *J. Org. Chem.*, 2002, **67**, 9210.
277. M.C. Willis and V.J.-D. Piccio, *Synlett*, 2002, 1625.
278. F. Mutilis, I. Mutule and J.E.S. Wikberg, *Bioorg. Med. Chem. Lett.*, 2001, **12**, 1039.
279. L. Aurelio, J.S. Box, R.T.C. Brownlee, A.B. Hughes and M.M. Sleebs, *J. Org. Chem.*, 2003, **68**, 2652.
280. C. Laplante and D.G. Hall, *Org. Lett.*, 2001, **3**, 1487.
281. Y. Luo, G. Evindar, D. Fishlock and G.A. Lajoie, *Tetrahedron Lett.*, 2001, **42**, 3807.
282. R. Paruszewski, M. Strupinska, J.P. Stables, M. Swiader, S. Czuczwar, Z. Kleinrok and W. turski, *Chem. Pharm. Bull.*, 2001, **49**, 629.
283. Y.-x. Leng, X.-s. Rui, J.-q. Ma, H.-y. Sun and H.-b. Zhou, *Jingxi Huagong*, 2001, **18**, 50.
284. S. Kobayashi, H. Kitagawa and R. Matsubara, *J. Comb. Chem.*, 2001, **3**, 401.
285. J.R. Casimir, G. Guichard, D. Tourwe and J.-P. Briand, *Synthesis-Stuttgart*, 2001, 1985.
286. S. Reverchon, B. Chantegrel, C. Deshayes, A. Doutheau and N. Cotte-Pattat, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1153.
287. Y. Zhang, Q. Yang and Y. Sun, *Huaxue Shijie*, 2002, **43**, 363.
288. K. Hojo, M. Maeda, Y. Takahara, S. Yamamoto and K. Kawasaki, *Tetrahedron Lett.*, 2002, **44**, 2849.
289. E. Masiukiewicz, S. Eiejak and B. Rzeszotarska, *Org. Prep. & Proc. Int.*, 2002, **34**, 521.
290. B.C. Shekar, K. Roy and A.U. De, *J. Het. Chem.*, 2001, **10**, 237.
291. Y. Xu and B. Zhu, *Synthesis*, 2001, **9**, 690.
292. G. Gellenuaii, A. Elgavi, Y. Salitra and M. Kramer, *J. Pept. Res.*, 2001, **57**, 277.
293. H. Shen, A.P. Li, H. Wang, T.X. Wu and X.F. Pan, *Chinese Chem. Lett.*, 2002, **13**, 117.
294. (*a*) V.A. Knizhnikov, V.I. Potkin, S.K. Petkevich, A.S. Skripchenko and A.V. Mikulich, *Vest. Nats. Akad. Navuk. Belarusi*, 2002, 82; (*b*) V.A. Knizhnikov, V.I.

Potkin, K.A. Zhavnerko, L.S. Yakubovich, S.K. Petkevich and S.P. Kacherskaya, *Russ. J. Org. Chem.*, 2002, **38**, 915.
295. X.-j. Wang, *Guangzhou Huaxue*, 2001, **26**, 27.
296. A. Sidduri, J.W. Tilley, J.P. Lou, L. Chen, G. Kaplan, F. Mennona, R. Campbell, R. Guthrie, T.-N. Huang, K. Rowan, V. Schwinge and L.M. Renzetti, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2479.
297. A.E. Wroblewski and D.G. Piotrowska, *Tetrahedron Asymmetry*, 2002, **13**, 2509.
298. W.-h. Li, *Hecheng Huaxue*, 2001, **9**, 563.
299. M. Terasaki, S. Nomoto, H. Mita and A. Shimoyama, *Bull. Chem. Soc. Jap.*, 2002, **75**, 855.
300. B. Henkel and L. Weber, *Synlett*, 2002, 1877.
301. S. McGhie, *Synth. Commun.*, 2002, **32**, 1275.
302. Z.-Q. Zhu and X.-G. Mei, *Synth. Commun.*, 2001, **31**, 3609.
303. D.V. Arsenov, M.A. Kisel and O.A. Strel'chenok, *Dokl. Nat. Akad. Nauk. Belarousi*, 2001, **45**, 71.
304. G.A. Doherty, T. Kamenecka, E. McCauley, G. Van Riper, R.A. Mumford, S. Tong and W.K. Hagmann, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 729.
305. S. Bittner, S. Gorovsky, O. Paz-Tal and J.Y. Becker, *Amino Acids*, 2002, **22**, 71.
306. T. Izuhara, W. Yokota, M. Inoue and T. Katoh, *Heterocycles*, 2002, **56**, 553.
307. L.A. Sviridova, I.F. Leschova and G.K. Vertelov, *Khim. Geterotsikl Soedinenii*, 2000, 1335.
308. C.M. Vaidya, J.E. Wright and A. Rosowsky, *J. Med. Chem.*, 2002, **45**, 1690.
309. G. Chen, Y. Deng, L. Gong, A. Mi, X. Cui, Y. Jiang, M.C. K. Choi and A.S.C. Chan, *Tetrahedron Asymmetry*, 2001, **12**, 1567.
310. T.D. Weiss, G. Helmchen and U. Kazmaier, *Chem. Commun. (Cambridge)*, 2002, 1270.
311. B.M. Trost and K. Dogra, *J. Am. Chem. Soc.*, 2002, **124**, 7256.
312. U. Kazmeier and F.L. Zumpe, *Eur. J. Org. Chem.*, 2001, 4067.
313. A. Kulesza and J. Jurczak, *Chirality*, 2001, **13**, 634.
314. T. Abellan, B. Mancheno, C. Najera and J.M. Sansano, *Tetrahedron*, 2001, **57**, 6627.
315. L.B. Wolf, T. Sonke, K.C.M.F. Tjen, B. Kaptein, Q.B. Broxterman, H.E. Schoemaker and F.P.J.T. Rutjes, *Adv. Synth. Catal.*, 2001, **343**, 662.
316. D. Balan and H. Adolfsson, *J. Org. Chem.*, 2001, **66**, 6498.
317. V.K. Aggarwal, A.M.M. Castro, A. Mereu and H. Adams, *Tetrahedron Lett.*, 2002, **43**, 1577.
318. S. Suezen, *Ankara Univ. Eczacilik Fak. Derg.*, 2001, **30**, 17.
319. R. Kimura, T. Nagano and H. Kinoshita, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 2517.
320. K.E. Holt, J.P. Swift, M.E.B. Smith, S.J.C. Taylor and R. McCague, *Tetrahedron Lett.*, 2002, **43**, 1545.
321. C. Douat, A. Heitz, J. Martinez and J.-A. Fehrentz, *Tetrahedron Lett.*, 2001, **42**, 3319.
322. D.B. Berkowitz, E. Chisowa and J.M. McFadden, *Tetrahedron*, 2001, **57**, 6329.
323. S. Chandrasekhar, A. Raza and M. Takhi, *Tetrahedron Asymmetry*, 2002, **13**, 423.
324. K. Sakaguchi, H. Suzuki and Y. Ohfune, *Chirality*, 2001, **13**, 357.
325. D. G. Ahem, R. Seguin and C.N. Filer, *J. Labelled Comp. Radiopharm.*, 2002, **45**, 401.
326. D. Ma, W. Wu and P. Deng, *Tetrahedron Lett.*, 2001, **42**, 6929.
327. L. Vranicar, A. Meden, S. Polanc and M. Kocevar, *J. Chem. Soc. Perkin Trans 1*, 2002, **675**.

328. M. Schleusner, H.-J. Gais, S. Koep and G. Raabe, *J. Am. Chem. Soc.*, 2002, **124**, 7789.
329. S.E. Gibson, J. Jones, S.B. Kalindjian, J.D. Knight, J.W. Steed and M.J. Tozer, *Chem. Commun. (Cambridge)*, 2002, 1938.
330. N. Krause, A. Hoffmann-Roder and J. Canisius, *Synthesis-Stuttgart*, 2002, 1759.
331. J.J. Turner, M.A. Leeuwenburgh, G.A. van der Marel and J.H. van Boom, *Tetrahedron Lett.*, 2001, **42**, 8713.
332. M.K. Gurjar and A. Talukdar, *Synthesis-Stuttgart*, 2002, 315.
333. S.F. Khalilova, Zh.N. Kirbagakova and K.B. Erzhanov, *Izv. Minist. Obraz. Nauki. Resp. Kaz.*, 2000, 94.
334. M.P. Lopez-Deber, L. Castedo and J.R. Granja, *Org. Lett.*, 2001, **3**, 2813.
335. N. Vasdev, R. Chirakal, G.J. Schrobilgen and C. Nahmias, *J. Fluorine Chem.*, 2001, **11**, 17.
336. W.P. Deng, K.A. Wong and K.L. Kirk, *Tetrahedron Asymmetry*, 2002, **13**, 1135.
337. A.V. Samet, D.J. Coughlin, A.C. Buchanan III and A.A. Gakh, *Synth. Commun.*, 2002, **32**, 941.
338. (*a*) G. Tang, L. Zhang, X.-l. Tang, Y.-X. Wang and D. Yin, *He Huaxue Yu Fangshe Huaxue*, 2001, **23**, 211; (*b*) G. Tang, L. Zhang, X.-l. Tang, Y.-X. Wang and D. Yin, *Hejishu*, 2002, **25**, 1019; (*c*) G. Tang, L. Zhang, X.-l. Tang, Y.-X. Wang and D. Yin, *Appl. Rad. Isotop.*, 2002, **57**, 145; (*d*) G. Tang, L. Zhang, X.-l. Tang, Y.-X. Wang and D. Yin, *Zwngguo Yaoke Daxue Xuebao*, 2001, **32**, 166.
339. J.T. Konkel, J. Fan, B. Jayachandran and K.L. Kirk, *J. Fluorine Chem.*, 2002, **115**, 27.
340. K. Hamacher and H.H. Coenen, *Appl. Rad. Isotop.*, 2002, **57**, 853.
341. B. Herbert, I.H. Kim and K.L. Kirk, *J. Org. Chem.*, 2001, **66**, 4892.
342. M. Cameron, D. Cohen, I.F. Cottrell, D.J. Kennedy, C. Roberge and M. Chartrain, *J. Mol. Cat. B: Enz.*, 2001, 1.
343. W.-S. Yu, Y.-J. Liang, K.-L. Liu and Y.-F. Zhao, *Gaodeng Xuexiao Huaxue Xuebao*, 2002, **23**, 1314.
344. J. Vahatalo, M. Kulvik, S. Savolamen and S.-L. Karonen, *Frontiers in Neutron Capture Therapy*, eds. M. F. Hawthorne, K. Shelly and R. J. Wiersema, publ. Kluwer/Plenum, 2001, **2**, 835.
345. S. Laabs, W. Munch, J.W. Bats and U. Nubbemeyer, *Tetrahedron*, 2002, **58**, 1317.
346. M. Tamaki, G. Han and V.J. Hruby, *J. Org. Chem.*, 2001, **66**, 3593.
347. G. Priem, M.S. Anson, S.J.F. MacDonald, B. Pelotier and I.B. Campbell, *Tetrahedron Lett.*, 2002, **43**, 6001.
348. A. Sidduri, J.P. Lou, R. Campbell, K. Rowan and J.W. Tilley, *Tetrahedron Lett.*, 2001, **42**, 8757.
349. (*a*) S. Kotha, N. Bieenivanachary and E. Brahmachary, *Eur. J. Org. Chem.*, 2001, 787; (*b*) S. Kotha and E. Brahmachary, *Bioorg. Med. Chem.*, 2002, **10**, 2291; (*c*) S. Kotha, S. Halder and K. Lahiri, *Synthesis-Stuttgart*, 2002, 339.
350. K. Ding, X.-R. Zhang, D.-W. Ma and B.-M. Wang, *Chin. J. Chem.*, 2001, **19**, 1232.
351. P.A. Crooks and J. Matheru, *Synth. Commun.*, 2002, **32**, 3813.
352. (*a*) W. Wang, C. Xiong, J. Yang and V.J. Hruby, *Tetrahedron Lett.*, 2001, **42**, 7717; (*b*) W. Wang, M. Cai, C. Xiong, J. Zhang, D. Trivedi and V.J. Hruby, *Tetrahedron*, 2002, **58**, 7365; (*c*) W. Wang, M. Cai, C. Xiong, J. Zhang, D. Trivedi and V.J. Hruby, *Tetrahedron Lett.*, 2002, **43**, 2137; (*d*) W. Wang, C. Xiong, J. Zhang and V.J. Hruby, *Tetrahedron*, 2001, **58**, 3101.
353. S. Hanzawa, S. Oe, K. Tokuhisa, K. Kawano, H. Kakidani and T. Ishiguro, *Toso Kenkyu Gijutsu Hokoku*, 2001, **45**, 11.

354. T. Ooi, M. Takeuchi and K. Maruoka, *Synthesis-Stuttgart*, 2001, 1716.
355. J. Spengler, H. Schedel, J. Sieler, P.J.L.M. Quaedser, Q.B. Broxterman, A.L.T. Duchateau and K. Burger, *Synthesis-Stuttgart*, 2001, 1513.
356. N. Vails, M. Lopez-Canet, M. Vallribera and J. Bonjoch, *Chem. -Eur. J.*, 2001, **7**, 3446.
357. R.A. Stalker, T.E. Munsch, J.D. Tran, X. Nie, R. Warmuth, A. Beatty and C.B. Aakeroy, *Tetrahedron*, 2002, **58**, 4837.
358. A. Boto, R. Hernandez, A. Montoya and E. Suarez, *Tetrahedron Lett.*, 2002, **43**, 8269.
359. N. Kise, H. Ozaki, H. Terui, K. Ohya and N. Ueda, *Tetrahedron Lett.*, 2001, **42**, 7637.
360. S. Tohma, A. Endo, T. Kan and T. Fukuyama, *Synlett.*, 2001, 1179.
361. A. Szymanska, W. Wiczk and L. Lankiewicz, *Amino Acids*, 2001, **21**, 265.
362. M. Zia-Ul-Hao, M. Arshad and Saeed-Ur-Reliman, *J. Chin. Chem. Soc.*, 2001, **48**, 45.
363. P. Call and M. Begtrup, *Tetrahedron*, 2002, **58**, 1595.
364. C.-S. Ge, Y.-J. Chen and D. Wang, *Synlett.*, 2002, 37.
365. S.-h. Lee, E.-K. Lee and S.-M. Jeun, *Bull. Korean Chem. Soc.*, 2002, **23**, 931.
366. S. Lee, N.A. Beare and J.F. Hartwig, *J. Am. Chem. Soc.*, 2001, **123**, 8410.
367. J.E. Redman and M.R. Ghadiri, *Org. Lett.*, 2002, **4**, 4467.
368. H. Takahishi, N. Kashiwa, H. Kobayashi, Y. Hashimoto and K. Nagasawa, *Tetrahedron Lett.*, 2002, **43**, 6751.
369. S. Nampalli, W. Zhang, R.T. Sudhakar, H. Xiao, L.P. Kotra and S. Kumar, *Tetrahedron Lett.*, 2002, **43**, 1999.
370. S. Saaby, P. Bayon, P.S. Aburel and K.A. Jorgensen, *J. Org. Chem.*, 2002, **67**, 4352.
371. S. Kotha, S. Halder and E. Brahmachary, *Tetrahedron*, 2002, **58**, 9203.
372. H. Park, B. Cao and M.M. Joullie, *J. Org. Chem.*, 2001, **66**, 7223.
373. A. Long and S.W. Baldwin, *Tetrahedron Lett.*, 2001, **42**, 5343.
374. W.-Q. Lin, Z. He, Y. Jing, X. Cui, H. Liu and A.-Q. Mi, *Tetrahedron Asymmetry*, 2001, **12**, 1583.
375. J. Casas, C. Najera, J.M. Sansano, J. Gonzalez, J.M. Saa and M. Vega, *Tetrahedron Asymmetry*, 2001, **12**, 699.
376. S. Kotha, M. Behera and R.V. Kumar, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 105.
377. S. Royo, P. Lopez, A.I. Jimenez, L. Oliveros and C. Cativiela, *Chirality*, 2002, **14**, 39.
378. V. Jullian, V. Monjardet-Bas, C. Fosse, S. Lavielle and G. Chassaing, *Eur. J. Org. Chem.*, 2002, 1677.
379. A. Bianco, T. DaRos, M. Prato and C. Toniolo, *J. Pept. Sci.*, 2001, **7**, 208.
380. G.A. Burley, P.A. Keller, S.G. Pyne and G.E. Ball, *J. Org. Chem.*, 2002, **67**, 8316.
381. J.-P. Mazaleyrat, K. Wright, M. Wakselman, F. Formaggio, M. Crisma and C. Toniolo, *Eur. J. Org. Chem.*, 2001, 1821.
382. S.-J. Wen, H.W. Zhang and Z.-J. Yao, *Tetrahedron Lett.*, 2002, **43**, 5291.
383. Y. Yokoyama, K. Osanai, M. Mitsuhashi, K. Kondo and Y. Murakami, *Heterocycles*, 2001, **55**, 653.
384. B.E. Haug, J. Andersen, O. Rekdal and J.S. Svendsen, *J. Pept. Sci.*, 2002, **8**, 307.
385. D.K. Pyun, C.H. Lee, H.-J. Ha, C.S. Park, J.-W. Chang and W.K. Lee, *Org. Lett.*, 2001, **3**, 4197.
386. C. Xiong, W. Wang, C. Cai and V.J. Hruby, *J. Org. Chem.*, 2002, **67**, 1399.
387. A. Bertram and G. Pattenden, *Synlett*, 2001, 1873.

388. L. De Luca, G. Giacomelli and A. Riu, *J. Org. Chem.*, 2001, **66**, 6823.
389. H. Kromann, F.A. Slok, T.B. Stensbol, H. Braeuner-Osborne, U. Madsen and P. Krogsgaard-Larsen, *J. Med. Chem.*, 2002, **45**, 988.
390. L. Bunch, P. Krogsgaard-Larsen and U. Madsen, *J. Org. Chem.*, 2002, **67**, 2375.
391. H. Pajouhesli, M. Hosaaini-Meresht, S.H. Pajouhesta and K. Cunry, *Tetrahedron Asymmetry*, 2000, **11**, 4955.
392. W.-C. Cheng, Y. Liu, M. Wong, M.M. Olmstead, K.S. Lam and M.J. Kurth, *J. Org. Chem.*, 2002, **67**, 5673.
393. R.P. Clausen, H. Braeuner-Osborne, J.R. Greenwood, M.B. Hermit, T.B. Stensbol, B. Nielsen and P. Krogsgaard-Larsen, *J. Med. Chem.*, 2002, **45**, 4240.
394. S. Van-ay, R. Lazaro, J. Martinez and F. Lamaty, *Eur. J. Org. Chem.*, 2002, 2308.
395. S.K. Bertilsson, J.K. Ekegren, S.A. Modin and P.G. Andersson, *Tetrahedron*, 2001, **57**, 6399.
396. R.M. Adlington, J.E. Baldwin, D. Catterick and G.J. Pritchard, *J. Chem. Soc. Perkin Trans 1*, 2001, 668.
397. R.C.F. Jones, D.J.C. Berthelot and J.N. Iley, *Tetrahedron*, 2001, **57**, 6539.
398. T. Yokomatsu, K. Takada, Y. Yuasa and S. Shibuya, *Heterocycles*, 2002, **56**, 545.
399. P.M. T. Ferreira, H.L.S. Maia, L.S. Monteiro and J. Sacramento, *J. Chem. Soc. Perkin Trans 1*, 2001, 3167.
400. K.J. Kise Jr. and B.E. Bowler, *Inorg. Chem.*, 2002, **41**, 379.
401. R. Warmuth, T.E. Munsch, R.A. Stalker, B. Li and A. Beatty, *Tetrahedron*, 2001, **57**, 6383.
402. M. Isaac, A. Slassi, K. Da Silva and T. Xin, *Tetrahedron Lett*, 2001, **42**, 2957.
403. G. Sui, P. Kele and J. Orbulescu, *Lett. Pept. Sci.*, 2001, **8**, 47.
404. P. Kele, G. Sui, Q. Huo and R.M. Leblanc, *Tetrahedron Asymmetry*, 2000, **11**, 4959.
405. K. Guzow, M. Szabelski, J. Malicka and W. Wiczk, *Helv. Chim. Acta*, 2001, **84**, 1086.
406. N. Jotterand, D.A. Pearce and B. Imperiali, *J. Org. Chem.*, 2001, **66**, 3224.
407. A.R. Nitz Mark-Mezo, M.H. Ali and B. Imperiali, *Chem. Commun. (Cambridge)*, 2002, 1912.
408. S. Jiranusomkul, B. Sirithun, H. Nemoto and H. Takahata, *Heterocycles*, 2002, **56**, 487.
409. T.V. Shokol, O.S. Ogorodnuchuk, V.V. Shilin, V.B. Milevskaya and V.P. Khilya, *Chem. Het. Comp.*, 2002, **38**, 151.
410. M. Adamczyk, S.R. Akireddy and R.E. Reddy, *Tetrahedron Asymmetry*, 2001, **12**, 2385.
411. C. Escolano, M. Rubiralta and A. Diez, *Tetrahedron Lett.*, 2002, **43**, 4343.
412. V.J. Huber, T.W. Arroll, C. Lum, B.A. Goodman and H. Nakanishi, *Tetrahedron Lett.*, 2002, **43**, 6729.
413. S.K. Kapadia, D.M. Spero and M. Eriksson, *J. Org. Chem.*, 2001, **66**, 1903.
414. A. Olma, A. Gniadzik, A.W. Lipkowski and M. Lachwa, *Acta Biochim. Pol.*, 2001, **48**, 1165.
415. A.S. Sagiyan, A.V. Geolchanyan, N.R. Martiosyan, S.A. Dadayan, V.I. Tararov, Yu.N. Belokon, T.V. Kochikyan, V.S. Arutyunyan and A.A. Avetisyan, *Hayastani Kimiakan Handes*, 2002, **55**, 84.
416. J.A. Zerkowski, L.M. Hensley and D. Abramowitz, *Synlett.*, 2002, 557.
417. F. Paradisi, F. Piccinelli, G. Porzi and S. Sandri, *Tetrahedron Asymmetry*, 2002, **13**, 497.
418. J.L. Roberts and C.K. Chan, *Tetrahedron Lett.*, 2002, **43**, 7679.

419. A. J. Robinson, P. Stanislawski, D. Mulholland, L. He and H.-Y. Li, *J. Org. Chem.*, 2001, **66**, 4148.
420. M. Lobez-Garcia, I. Alfanso and V. Gotor, *J. Org. Chem.*, 2003, **68**, 648.
421. A.J. Villani, D. Saunders, A.Y.L. Shu and R.J. Heys, *J. Labell. Comp. Radiopharm.*, 2002, **45**, 49.
422. F. Paradisi, G. Porzi, S. Rinaldi and S. Sandri, *Tetrahedron Asymmetry*, 2000, **11**, 4617.
423. A.S. Segiyan, A.v. Geolchanyan, L.G. Minasayan, L.L. Manasayan, R.V. Ovspeyan and Yu.N. Belokon, *Hayastani Kimiakan Handes*, 2002, **55**, 103.
424. M.M. Kabat, *Tetrahedron Lett.*, 2001, **42**, 7521.
425. S.K. Das, V.L. Narishima Rao Krowidi, H. Jagadheshan and J. Iqbal, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3579.
426. J.A. Gomez-Vidal and R.B. Silverman, *Org. Lett.*, 2001, **3**, 2481.
427. S.R. Chhabra, A. Mahajan and W.C. Chan, *J. Org. Chem.*, 2002, **67**, 4017.
428. R.L. Tennyson, G.S. Cortez, H.J. Galicia, C.R. Kreiman, C.M. Thomson and D. Romo, *Org. Lett.*, 2002, **4**, 533.
429. (*a*) K.R. Knudsen, T. Risgaard, N. Nishiwaki, K.V. Gothelf and K.A. Jorgenson, *J. Am. Chem. Soc.*, 2001, **123**, 5843; (*b*) K.R. Knudsen, N. Nishiwaki, K.V. Gothelf and K.A. Jorgenson, *Angew. Chem. Int. Ed.*, 2001, **40**, 2992.
430. P.A. Butler, C.G. Crane, B.T. Golding, A. Hammershoi, D.C. Hockless, T.B. Petersen, A.M. Sargeson and D.C. Ware, *Inorg. Chimica Acta*, 2002, **331**, 318.
431. R. Clancy, A.I. Cederbaum and D.A. Stoyanovsky, *J. Med Chem.*, 2001, **44**, 2035.
432. S. Watanabe, A. Cordova, F. Tanaka and C.F. Carlos III, *Org. Lett.*, 2002, **4**, 4519.
433. M. Adamczyk and R.E. Reddy, *Synth. Commun.*, 2001, **31**, 579.
434. F.S. Gibson, A.K. Singh, M.C. Sourmeillant, P.S. Manchant, M. Humora and D.R. Kronenthal, *Org. Proc. Res, Dev.*, 2002, **6**, 814.
435. A. Kumanishi, N. Oaaki, S. Tanfanori, T. Tsuda, M. Tagaguki, K. Ono and M. Kirihata, *KURKI KR*, 2000, **541**, 315.
436. H. Nakamura, M. Figiwara and Y. Yamamoto, *Frontiers in Neutron Capture Therapy*, 2001, **2**, 765.
437. G.W. Kabalka, T.L. Nichols, M. Akula, C.P.D. Longford and L. Miller, '*Synth. and Appl. Isotop.-labelled Compds.*' Proc.7th Int. Symp. Dresden, eds. U. Pless and R. Voges, J. Wiley & Sons Ltd., 2001, 329.
438. B.C. Das, S. Das, G. Li, W. Bao and G.W. Kabalka, *Synlett*, 2001, 1419.
439. R. Tacke and V.I. Handmann, *Organometallics*, 2002, **21**, 2619.
440. M. Merget, K. Gunther, M. Bernd, E. Gunther and R. Tacke, *J. Organomet. Chem.*, 2001, **628**, 183.
441. M. Nath and S. Goyal, *Phosph. Sulfur, Silicon and Rel. Elements*, 2002, **177**, 841.
442. J.-X. Chen, J.A. Tonge and J.R. Norton, *J. Org. Chem.*, 2002, **67**, 4366.
443. M. Ruiz, V. Ojea, J.M. Quintela and J.J. Guillin, *Chem. Commun. (Cambridge)*, 2002, 1600.
444. D.J. Brauer, K.W. Kottsieper, S. Schenk and O. Stelzer, *Z. Anorg. Allg. Chem.*, 2001, **627**, 1151.
445. A.A. Karasik, O.G. Sinyashin, J. Heinicke and E. Hey-Hawkins, *Phosph. Sulfur, Silicon and Rel. Elements*, 2002, **177**, 1469.
446. W.-Q. Liu, C. Olszowy, L. Bischoff and G. Garbay, *Tetrahedron Lett.*, 2002, **43**, 1417.
447. M.C. Feraandez, J.M. Yumtela, M. Ruiz and V. Ojea, *Tetrahedron Asymmetry*, 2001, **13**, 233.

448. B. Bessieres, A. Schoenfelder, C. Verrat, A. Mann, P. Ornstein and C. Pedregal, *Tetrahedron Lett*., 2002, **43**, 7659.
449. S. Kobayashi, N. Shiraishi, W.W.L. Lam and K. Manabe, *Tetrahedron Lett*., 2001, **42**, 7303.
450. M.U. Gieaelman, L. Xie and W.A. van der Donk, *Org. Lett*., 2001, **3**, 1331.
451. R.J. Hondal, B.L. Nilsson and R.T. Raines, *J. Am. Chem. Soc*., 2001, **123**, 5140.
452. H.B. Ganther, *Bioorg. Med. Chem*., 2001, **9**, 1459.
453. Y. Xie, M.D. Short, P.B. Cassidy and J.C. Roberts, *Bioorg. Med. Chem. Lett*., 2001, **11**, 2911.
454. A.S. Sagiyan, A.V. Geolchanyan, S.V. Vardapetvan, A.A. Avetisyan, V.I. Tararov, N.A. Kuzmina, Yu.N. Belakon and M. North, *Russian Chem. Bull*., 2000, **49**, 1460.
455. S. Mourtas, D. Gatos, V. Kalaitzi, C. Katakalou and K. Barlos, *Tetrahedron Lett*., 2001, **42**, 6965.
456. E. Morera, F. Pinnen and G. Lucente, *Org. Lett*., 2002, **4**, 1139.
457. S. Gazal, G. Gellerman, E. Glukhov and C. Gilon, *J. Pept. Res*., 2001, **43**, 527.
458. N. Inguimbert, H. Poras, F. Teffo, F. Beslot, M. Selkti, A. Tomas, E. Scalbert, C. Bennejean, P. Renard, M.-C. Fournie-Zaluski and B.-P. Roques, *Bioorg. Med. Chem. Lett*., 2002, **12**, 2001.
459. M. Seki, M. Hatsuda, Y. Mori and S.-i. Yamada, *Tetrahedron Lett*., 2002, **43**, 3269.
460. P. Meffre and P. Durand, *Synth. Commun*., 2002, **32**, 287.
461. N.O. Silva, A.S. Abreu, P.M.T. Ferreira, L.S. Monteiro and M.-J.R.P. Queiroz, *Eur. J. Org. Chem*., 2002, 2524.
462. C. Bolm, I. Schiffers, C.L. Dinter, L. Defrere, A. Gerlach and G. Raabe, *Synthesis-Stuttgart*, 2001, 1719.
463. C. Cimarelli, G. Palmieri and E. Volpini, *Synth. Commun*., 2001, **31**, 2943.
464. S.D. Bull, S.G. Davies and A.D. Smith, *J. Chem. Soc. Perkin Trans 1*, 2001, 2931.
465. I.L. Iovel, J. Golomba, A. Popelis and E.L. Gaukhmann, *Appl. Organomet. Chem*., 2001, **15**, 67.
466. S. Fuatero, M.D. Diaz, A. Navarro, E. Salavert and E. Aguilar, *Tetrahedron*, 2001, **57**, 703.
467. S.D. Bull, S.G. Davies, P.M. Kelly, M. Gianotti and A.D. Smith, *J. Chem. Soc. Perkin Trans. 1*, 2001, 3106.
468. M. Lindo, K. Itoh, C. Tsuchiya and K. Shishido, *Org. Lett*., 2002, **4**, 3119.
469. C.Y.K. Tan and D.F. Weaver, *Tetrahedron*, 2002, **58**, 7449.
470. F.A. Davis, J. Deng, Y. Zhang and R.C. Haltiwanger, *Tetrahedron*, 2001, **58**, 7135.
471. D. Saylik, E.M. Campi, A.C. Donohue, W.R. Jackson and A.J. Robinson, *Tetrahedron Asymmetry*, 2001, **12**, 657.
472. A.V. Sivakumar, G.S. Babu and S.V. Bhat, *Tetrahedron Asymmetry*, 2001, **12**, 1095.
473. S.G. Davies, K. Iwamoto, C.A.P. Smethurst, A.D. Smith and H. Rodriguez-Solla, *Synlett*, 2002, 1146.
474. K. Ananda, H.N. Gopi and V.V. S. Babu, *Ind. J. Chem. Section B: Org. Chem. Med. Chem*., 2001, **40B**, 790.
475. G.-R. Vasanthakumar and V.V.S. Babu, *Synth. Commun*., 2002, **32**, 651.
476. G.-R. Vasanthakumar, B.S. Patil and V.V.S. Babu, *J. Chem. Soc. Perkin Trans. 1*, 2002, 2087.
477. A. Kumar, S. Ghilagaber, J. Knight and P.B. Wyatt, *Tetrahedron Lett*., 2001, **43**, 6991.

478. J. Huck, J.-M. Receveur, M.-L. Roumestant and J. Martinez, *Synlett*, 2001, 1467.
479. (*a*) V.M. Gutierrez-Garcia, H. Lopez-Ruiz, G. Reyes-Rangel and E. Juaristi, *Tetrahedron*, 2001, **57**, 6487; (*b*) V. M. Gutierrez-Garcia, H. Lopez-Ruiz, G. Reyes-Rangel, O. Munoz-Muniz and E. Juaristi, *J. Braz. Chem. Soc.*, 2001, **12**, 652.
480. Z.H. Ma, C. Liu, Y.H. Zhao, W. Li and J.B. Wang, *Chin. Chem. Lett.*, 2002, **13**, 721.
481. S. Kobayashi, J. Kobayashi, H. Ishiani and M. Ueno, *Chem. –A Eur. J.*, 2002, **8**, 4185.
482. H.M.L. Davies and C. Venkataramani, *Angew. Chem. Int. Ed.*, 2001, **41**, 2197.
483. H.-J. Ha, Y.-G. Ahn, J.-S. Woo, G.S. Lee and W.K. Lee, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 1667.
484. R.V. Roers, *Tetrahedron Lett.*, 2001, **42**, 3563.
485. K.-D. Lee, J.M. Suh, J.H. Park, H.J. Ha, H.G. Choi, C.S. Park, J.W. Chang, W.K. Lee, Y. Dong and H. Yun, *Tetrahedron*, 2001, **57**, 8267.
486. H. Nemoto, R. Ma, X. Li, I. Suzuki and M. Shibuya, *Tetrahedron Lett.*, 2001, **42**, 2145.
487. L. Ambroise, E. Dumez, A. Szeki and R.F.W. Jackson, *Synthesis-Stuttgart*, 2001, 2296.
488. R. Caputo, G. Cecere, A. Guaragna, G. Palumbo and S. Pedatella, *Eur. J. Org. Chem.*, 2002, 3050.
489. B. Crousse, S. Nanzuka, D. Bonnet-Delpon and J.-P. Begue, *Synlett*, 2001, 679.
490. (*a*) S. Fustero, E. Salavert, B. Pina, M.C. Ramirez de Arallano and A. Asensio, *Tetrahedron*, 2001, **57**, 6475; (*b*) S. Fustero, E. Salavert, B. Pina, A. Navarro, M.C. Ramirez de Arallano and A.S. Fuentes, *J. Org. Chem.*, 2002, **67**, 4667.
491. N.N. Sergeeva, A.S. Golubev, L. Hennig, M. Findeisen, E. Paetzold, G. Oehme and K. Burger, *J. Fluorine Chem.*, 2001, **111**, 41.
492. N. Lebouvier, C. Laroche, F. Heguenot and T. Brigaud, *Tetrahedron Lett.*, 2002, **43**, 2827.
493. V.A. Soloshonok, H. Ohkura, A. Sorochinsky, N. Voloshin, A. Markovsky, M. Belik and T. Yamasaki, *Tetrahedron Lett.*, 2002, **43**, 5445.
494. D.D. Staas, K.L. Savage, C.F. Homnik, N.N. Tsou and R.G. Ball, *J. Org. Chem.*, 2001, **67**, 8276.
495. N.N. Sergeeva, A.S. Golubev and K. Burger, *Synthesis-Stuttgart*, 2001, 281.
496. Y. Vera-Ayoso, P. Borrachero, F. Cabrera-Escribano, M.J. Dianez, M.D. Estrada, M. Gomez-Guillen, A. Lopez-Castro and S. Perrez-Garrido, *Tetrahedron Asymmetry*, 2001, **12**, 2031.
497. R.P. Tripathi, R. Tripathi, V.K. Tiwari, L. Bala, S. Sinha, A. Srivastava, R. Srivastava and B.S. Srivastava, *Eur. J. Med. Chem.*, 2002, **37**, 773.
498. S.D. Bull, S.G. Davies, S. Delgado-Ballester, P.M. Kelly, L.J. Kotchie, M. Gianotti, M. Laderas and A.D. Smith, *J. Chem. Soc. Perkin Trans. 1*, 2001, 3112.
499. R. Beumer and O. Reiser, *Tetrahedron*, 2001, **57**, 6497.
500. D.J. Aitken, C. Gauzy and E. Pereira, *Tetrahedron Lett.*, 2002, **43**, 6177.
501. F. Felluga, G. Pitacco, M. Prodan, S. Prici, M. Visintin and E. Valentin, *Tetrahedron Asymmetry*, 2001, **12**, 3241.
502. C. Taillefumier, Y. Lakhrissi and M. Lakhrissi, and Y. Chapleur, *Tetrahedron Asymmetry*, 2002, **13**, 1707.
503. A. Berkessel, K. Glaubitz and J. Lex, *Eur. J. Org. Chem.*, 2002, 2948.
504. V. Wehner, H. Blum, M. Kurz and H.U. Stilz, *Synthesis-Stuttgart*, 2002, 2023.
505. Z. Ma, Y.-h. Zhao, N. Jiang, X. Jin and J. Wang, *Tetrahedron Lett.*, 2002, **43**, 3209.

506. K. Lee, M. Zhang, D. Yang and T.R. Burke, *Bioorg. Med. Chem. Lett*., 2002, **12**, 3399.
507. A. Dinsmore, P.M. Doyle, M. Steger and D.W. Young, *J. Chem. Soc. Perkin Trans. 1*, 2002, 613.
508. J. Fan-as, X. Ginesta, P.W. Sutton, J. Taltavull, F. Egeler, P. Romea, F. Urpi and J. Vilarrasa, *Tetrahedron*, 2001, **57**, 7665.
509. A. Mordini, L. Sbaragli, M. Valacchi, F. Russo and G. Reginato, *Chem. Commun. (Cambridge)*, 2002, **778**.
510. J.-i. Park, G.M. Tian and D.H. Kim, *J. Org. Chem*., 2001, **66**, 3696.
511. S.G. Nelson, K.L. Spencer, W.S. Cheung and S.J. Mamie, *Tetrahedron*, 2002, **58**, 7081.
512. S. Lee and Y.J. Zhang, *Org. Lett*., 2002, **4**, 2429.
513. C.G. Espino, P.M. When, J. Chow and J. DuBois, *J. Am. Chem. Soc*., 2001, **123**, 6935.
514. E. Alonso, C. del Pozo and J. Gonzalez, *Synlett*, 2002, 69.
515. S.-H. Lee, X. Qi, J. Yoon, K. Nakamura and Y.-S. Lee, *Tetrahedron*, 2002, **58**, 2777.
516. T.B. Durham and M.J. Miller, *J. Org. Chem*., 2003, **68**, 35.
517. S. Murahashi, Y. Imada, T. Kawakami, K. Harada, Y. Yonemushi and N. Tomita, *J. Am. Chem. Soc*., 2002, **124**, 2888.
518. J.L. Matthews, D.R. McArthur and K.W. Muir, *Tetrahedron Lett*., 2002, **43**, 5401.
519. G.V. Sidorov and N.F. Myasoedov, *Radiochemistry*, 2002, **44**, 295.
520. S. Rajesh, B. Banerji and J. Iqbal, *J. Org. Chem*., 2002, **67**, 7852.
521. B.-r. Liao, Y.-y. Hong, Zh.-p. Chen and B. Liu, *Uprhing Huaxue*, 2001, 48.
522. Z.-Y. Jiang and H.-F. Chen, *Ymgyong Huaxue*, 2001, **18**, 231.
523. F.-R. Alexandre, D.P. Panteleone, P.P. Taylor, I.G. Fotheringham, D.J. Ager and N.J. Turner, *Tetrahedron Lett*., 2002, **43**, 707.
524. T.M. Beard and N.J. Turner, *Chem. Commun. (Cambridge)*, 2002, 246.
525. X. Xing, A. Fichera and K. Kumar, *J. Org. Chem*., 2002, **67**, 1722.
526. Y. Liu, J.-w. Cao and Z. Chao, *Ziran Kexwban*, 2000, **46**, 769.
527. M. Solymar, A. Liljeblad, L. Lazar, F. Fulop and L.T. Kanerva, *Tetrahedron Asymmetry*, 2002, **13**, 1923.
528. G. Galavema, R. Corradini, F. Dallavalle, G. Folesani, A. Dossena and R. Marchelli, *J. Chromatogr. A*, 2001, **922**, 151.
529. W. Lee, *Anal. Lett*., 2001, **34**, 2785.
530. S.Y. Park, J.K. Park, J.H. Park, C.V. McNeff and P.W. Carr, *Microchem. J*., 2001, **70**, 179.
531. C.-H. Lin, C.-E. Lin, C.-C. Chen and L.-F. Liao, *J. Chin. Chem. Soc*., 2001, **48**, 1069.
532. Y.K. Ye, B.S. Lord, L. Yin and R.W. Stringham, *J. Chromatogr. A*, 2002, **945**, 147.
533. A.I. Jimenez, P. Lopez, L. Ollveroe and C. Cativiela, *Tetrahedron*, 2001, **57**, 6019.
534. M.H. Hyun, S.C. Han, B.H. Lipshutz, Y.-J. Shin and C.J. Welch, *J. Chromatogr. A*, 2001, **910**, 359.
535. K. Hamase, *Farumashia*, 2002, **38**, 437.
536. M.H. Huyn, Y.J. Cho and I.K. Baik, *Bull. Korean. Chem. Soc*., 2002, **23**, 1291.
537. F. Gasparrini, D. Misiti, M. Pierini and C. Villani, *Org. Lett*., 2002, **4**, 3993.
538. C. B'Hymer, M. Montes-Bayon and J.A. Caruso, *J. Sep. Sci*., 2003, **26**, 7.
539. D. Zhang, W.A. Tao and R.G. Cooks, *Int. J. Mass Spectrom*., 2001, **204**, 159.
540. R. Hodyss, R.R. Julian and J.L. Beauchamp, *Chirality*, 2001, **13**, 703.
541. J.F. Gal, M. Stone and C.B. Lebrilla, *Int. J. Mass Spectrom*., 2002, **222**, 259.

542. E.M. Perez, A.I. Oliva, J.V. Hernandez, L. Simon, J.R. Moran and F. Sanz, *Tetrahedron Lett*., 2001, **42**, 5853.
543. A.I. Oliva, L. Simon, J.V. Hernandez, F.M. Muniz, A. Lithgow, A. Jimenez and J.R. Moran, *J. Chem. Soc. Perkin Trans. 2*, 2002, 1050.
544. M. Rekharsky, H. Yamamura, M. Kawai and Y. Inoue, *J. Am. Chem. Soc*., 2001, **123**, 5360.
545. (*a*) H. Zhao, C.-H. Xue, Q.M. Mu, L. Li and S.-H. Chen, *Yingyong Huaxue*, 2001, **18**, 614; (*b*) C.-H. Xue, Q.-M. Mu and S.-H. Chen, *Huaxue Xuebao*, 2002, **60**, 355.
546. L.L. Lawless, A.G. Blackburn, A.J. Ayling, M.N. Perez-Payan and A.P. Davis, *J. Chem. Soc. Perkin Trans. 1*, 2001, 1329.
547. Q. Mu, C. Xie and S. Chen, *Huaxue Yanjiu Yu Yingyong*, 2001, **13**, 473.
548. G.M. Kyne, M.E. Light, M.B. Hursthouse, J. de Mendoza and J. D. Kilburn, *J. Chem. Soc. Perkin Trans. 1*, 2001, 1258.
549. I. Fujii and N. Hirayama, *Helv. Chim. Acta*, 2002, **85**, 2946.
550. A. Higuchi, K. Furuta, H. Yomogita, B.O. Yoon, M. Hara, S. Maniwa and M. Saitoh, *Desalination*, 2002, **148**, 155.
551. P.E.M. Overdevest, T.J.M. de Bruin, E.J.R. Sudhoelter, K. van't Riet, J.T.F. Keurentjes and A. van der Padt, *Ind. Eng. Chem. Res*., 2001, **40**, 5991.
552. J. Romero and A.L. Zydney, *Desalination*, 2002, **148**, 159.
553. (*a*) P. Hadik, L.-P. Szabo and E. Nagy, *Desalination*, 2002, **148**, 193; (*b*) P. Hadik, L.-P. Szabo and E. Nagy, *Bulgarian Chem. Commun*., 2001, **33**, 389.
554. H. Chibvongodze, K. Hayashi and K. Toko, *Sens. Mater*., 2001, **13**, 99.
555. K. Araki, M. Goto and S. Furusaki, *Anal. Chim. Acta*, 2002, **469**, 173.
556. H. Okuno, T. Kitano, H. Yakabe, M. Kishimoto, B.A. Deore, H. Siigi and T. Nagaoka, *Anal. Chem*., 2002, **74**, 4184.
557. T. Shiraiwa, M. Suzuki, Y. Sakai, H. Nagasawa, K. Takatani, D. Noshi and K. Yamanashi, *Chem. Pharm. Bull*., 2002, **50**, 1362.
558. M.J. O'Donnell and F. Delgado, *Tetrahedron*, 2001, **57**, 6641.
559. D. Lavergne, C. Mordant, V. Ratovelomanana-Vidal and J.-P. Genet, *Org. Lett*., 2001, **3**, 1909.
560. L.-l. Yang, D.-q. Zhang and Z.-b. Yuan, *Anal. Chim. Acta*, 2001, **433**, 23.
561. E. Francotte, T. Leutert, L. La Vecchia, F. Ossala, P. Richert and A. Schmidt, *Chirality*, 2002, **14**, 313.
562. A. Solladie-Cavallo, O. Sedy, M. Salisova and M. Schmitt, *Eur. J. Org. Chem*., 2002, 3042.
563. J.-f. Hang, S.-K. Tian, L. Tang and L. Deng, *J. Am. Chem. Soc*., 2001, **123**, 12696.
564. A. Gaucher, Y. Zuliani, D. Cabaret, M. Wakselman and J.-P. Mazaleyrat, *Tetrahedron Asymmetry*, 2001, **12**, 2571.
565. J.L. Clark and J.J. Stezowski, *J. Am. Chem. Soc*., 2001, **123**, 9880.
566. J.L. Clark, B.R. Booth and J.J. Stezowski, *J. Am. Chem. Soc*., 2001, **123**, 9889.
567. M.F. Rastegar, M. Ghandi, M. Taghizadeh, A. Yari, M. Shamsipur, G.P.A. Yap and H. Rahbamoohi, *J. Org. Chem*., 2002, **67**, 2065.
568. C. Alonso, R. Eliash, T.R. Jensen, K. Kjaer, M. Lahav and L. Leiserowitz, *J. Am. Chem. Soc*., 2001, **123**, 10105.
569. K. Nomiya and H. Yokoyama, *J. Chem. Soc. Dalton Trans*., 2002, 2483.
570. Q.-h. Zhu, W.-y. Shao, J.-f. He and Q.-y. Deng, *Bopuxue Zazhi*, 2001, **18**, 377.
571. E. Bang, J.-W. Jung, W. Lee, D.W. Lee and W. Lee, *J. Chem.. Soc. Perkin Trans. 2*, 2001, 1685.
572. M. Claeys-Bruno, D. Toronto, J. Pecaut, M. Bardet and J.-C. Marchon, *J. Am. Chem. Soc*., 2001, **123**, 11067.

573. O. Hayashida, L. Sebo and J. Rebek Jr., *J. Org. Chem.*, 2002, **67**, 8291.
574. S.D. Keane, C.J. Easton, S.F. Lincoln and D. Parker, *Aus. J. Chem.*, 2001, **54**, 535.
575. A. Yoshino, M. Ishida, H. Yuki, H. Okabayashi, H. Masuda and C.J. O'Connor, *Coll. Poly. Sci.*, 2001, **279**, 1144.
576. A. Hayashi, S. Saito, Y. Nakatani, A. Nishiyama, Y. Matsumura, H. Nakayama and M. Tsuhako, *Phosphorus Res. Bull.*, 2001, **12**, 129.
577. S. Ono, T. Taguma, S. Kuroki, I. Ando, H. Kimura and K. Yamauchi, *J. Mol. Struct.*, 2001, **603-;3**, 49.
578. N. Higashi, T. Koga, Y. Fujii and M. Niwa, *Langmuir*, 2001, **17**, 4061.
579. H. Tsukube, M. Wada, S. Shinoda and H. Tamiaki, *J. Alloys Compd.*, 2001, **323-4**, 133.
580. W. He, F. Liu, Y. Mei, Z. Guo and L. Zhu, *New J. Chem.*, 2001, **25**, 1330.
581. Y. Cheng and D.M. Hercules, *J. Mass Spectrom.*, 2001, **36**, 834.
582. M.E. Mateo, S.M. Barlow, S. Haq and R. Raval, *Surface Sci.*, 2002, **501**, 191.
583. Q.-P. Wang, D.-Z. Lu, L. Shen and J.-Z. Yang, *Wuli Huaxue Xuebao*, 2001, **17**, 952.
584. M. Monajjemi, E. Moniri and H.A. Panahi, *J. Chem. Eng. Data.*, 2001, **46**, 1249.
585. S. Shao and R.-S. Lin, *Zhejiang Daxue Xuebao*, 2001, **28**, 269.
586. S. Shao, R.-S. Lin, X.-G. Hu, W.-J. Fang and X.-H. Ying, *Wuli Huaxue Xuebao*, 2001, **17**, 645.
587. P.G. Rohankar and A.S. Aswar, *Indian J. Chem. A, Inorg. Bio-inorg. Phys. Theor. Anal. Chem.*, 2001, **40A**, 1086.
588. Y. Lu, W. Xie and J. Lu, *Thermochim. Acta*, 2002, **385**, 1.
589. M.N. Islam and R.K. Wadi, *Phys. Chem. Liq.*, 2001, **30**, 77.
590. F. Khan and P.L. Sahu, *J. Inst. Chem.*, 2000, **72**, 127.
591. Q. Lau, X. Hu, R. Lin, S. Li and W. Sang, *Thermochim. Acta*, 2001, **369**, 31.
592. A. Al-Khouly, *Roi. Soc. Quim. Peru*, 2000, **66**, 9.
593. B. Palecz, *J. Am. Chem. Soc.*, 2002, **124**, 6003.
594. Y. Wu, P. Ma, Y. Liu and S. Li, *Fluid Phase Equil.*, 2001, **186**, 27.
595. C. Gao and J.H. Vera, *J. Chem. Eng.*, 2001, **79**, 392.
596. B.M. Beglov, B.S. Zakirov and K.N. Karimova, *Uzb. Khim. Zh.*, 2001, **8**.
597. S.-Y. Tan, H. Yang and B. Tang, *Yingywg Huaxue*, 2001, **18**, 252.
598. S. Chen, X. Yang, Z. Ju, H. Li and S. Gao, *Chem. Pap.*, 2001, **55**, 239.
599. T.S. Banipal, G. Singh and B.S. Lark, *J. Solution Chem.*, 2001, **30**, 657.
600. J. Fan, X. Shen and J. Wang, *Electroanalysis*, 2001, **13**, 1115.
601. P.S. Kumar, J.A. Hogendoon, P.H.M. Feron and G.F. Versteeg, *J. Chem. Eng. Data*, 2001, **46**, 1357.
602. B. N. Waris, U. Hassan and N. Shrivastava, *Indian J. Chem. A, Inorg. Bio-inorg. Phys. Theor. Anal. Chem.*, 2001, **40A**, 1218.
603. N.Y. Mokshina, V.F. Selemenev and G.Y. Oros, *Izv. Vyssh. Khimiya Khimicheskaya Technolog.*, 2001, **44**, 17.
604. R.A. Marriott, *J. Chem. Thermodynamics*, 2001, **33**, 959.
605. J.L. Liu, A.W. Hakin and G.R. Hedwig, *J. Solution Chem.*, 2001, **30**, 861.
606. T.I. Lezhava, N.Sh. Ananiashvili, M.P. Kikabidze and N.O. Berdzenishvili, *Russian J. Electrochem.*, 2001, **37**, 1395.
607. P.G. Rohankar and A.S. Aswar, *Indian J. Chem. A, Inorg. Bio-inorg. Phys. Theor. Anal. Chem.*, 2002, **41A**, 312.
608. E.N. Tsurko, T.M. Shihova and N.V. Bondarev, *J. Mol. Liq.*, 2002, **96-7**, 425.
609. A.W. Hakin and G.R. Hedwig, *J. Chem. Thermodynamics*, 2001, **33**, 1709.
610. L. Ninni and A.J.A. Meirelles, *Biotechnol. Progr.*, 2001, **17**, 703.

611. A. Shono, T. Okabe and K. Satoh, *Solvent Ext. Res.Dev. Jpn.*, 2001, **8**, 120.
612. S.-x. Zhang, Y. Yao, X.-k. Yan, Y.-q. Yang and S. Zhang, *Huadong Ugong Daxue Xitebao*, 2000, **26**, 678.
613. H.M. Willemen, T. Vermonden, A.T.M. Marcelis and E.J.R. Sudhölter, *Eur. J. Org. Chem.*, 2001, 2329.
614. C. Wang, J. Huang, S. Tang and B. Zhu, *Langmuir*, 2001, **17**, 6389.
615. M. Sorensen, J.S. Forster, P. Hvelplund, T.J.D. Jorgensen, S.B. Nielsen and S. Tomita, *Chem-Eur. J.*, 2001, **7**, 3214.
616. A.N. Zyablov, T.V. Eliseeva, V.F. Selemenev and N.N. Samoilova, *Zh. Biz. Khim.*, 2001, **75**, 545.
617. J. Hendri, A. Hiroki, Y. Maekawa, M. Yoshida and R. Katakai, *Radiat. Phys. Chem.*, 2001, **61**, 155.
618. M. Suzuki, M. Yumoto, M. Kimura, H. Shirai and K. Hanabusa, *Chem. Commun. (Cambridge)*, 2002, 884.
619. M. Matsuzawa, H. Minami, T. Yano, T. Wakabayashi, M. Iwahashi, K. Sakamoto and D. Kaneko, *Stud. Surface Sci. and Cat.*, 2001, **132**, 137.
620. D. Renzi, C.M. Carlevaro, C. Stoico and F. Vericat, *Mol. Phys.*, 2001, **99**, 913.
621. A. Dogan, F. Koseoglu and E. Kilic, *Indian J. Chem. A, Inorg. Bio-inorg. Phys. Theor. Anal. Chem.*, 2002, **41A**, 960.
622. I.N. Kochnev, A.I. Khaloimov, E.I. Grigor'ev, L.V. Shurpova and V.Kh. Khavinson, *Biofizika*, 2002, **47**, 12.
623. D.L. Kotova, D.S. Beilina, V.F. Selemenev and A. Shepeleva, *Pharm. Chem. J.*, 2001, **35**, 221.
624. R. Mohan, K.-K. Koo, C. Strege and A.S. Myerson, *Ind. Eng. Chem. Res.*, 2001, **40**, 6111.
625. F.-G. Pan, D.-H. Wang, F. Fang, L. Cao, X.-L. Yan and L.-G. Chen, *Youji Huaxue*, 2002, **22**, 341.
626. I.V. Aristov, O.V. Bobreshova and O.Y. Strel'nikova, *Russian J. Electrochem.*, 2002, **38**, 567.
627. F. Apruzzese, E. Bottari and M.R. Festa, *Talanta*, 2002, **56**, 459.
628. M. Plass, C. Griehl and A. Kolbe, *J. Mol. Struct.*, 2001, **570**, 203.
629. H. Nishino, A. Kosaka, G.A. Hembury, K. Matsushima and Y. Inoue, *J. Chem. Soc. Perkin Trans. 2*, 2002, 582.
630. D.K. Alargov, S. Deguchi, K. Tsujii and K. Horikoshi, *Origins of Life Evol. of Biosphere*, 2002, **32**, 1.
631. N. Sato, H. Daimon and K. Fujie, *Kagaku Kogaku Ronbunshu*, 2002, **28**, 113.
632. M. Stuebner, E. Schneider and J. Friedrich, *Phys. Chem. Chem. Phys.*, 2001, **3**, 5369.
633. A.-l. Ying and X. Wang, *Huaihai Gongxueyan Xuebao*, 2001, **10**, 49.
634. A. Rios, J. Crugeiras, T.L. Amyes and R.P. John, *J. Am Chem. Soc.*, 2001, **123**, 7949.
635. A. Khalaj, M. Pirali and R. Dowlatabadi, *J. Chem. Res. Synop.*, 2001, 412.
636. M. Oelgemoeller, A.G. Griesbeck, J. Lex, A. Haeuseler, M. Schmittel, M. Niki, D. Hesek and Y. Inoe, *Org. Lett.*, 2001, **3**, 1593.
637. M. Kitamura and T. Nakamura, *Powder Tech.*, 2001, **121**, 39.
638. I. Compagnon, F.C. Hagemeister, R. Antoine, D. Rayane, M. Broyer, P. Dugourd, R.R. Hudgins and M.F. Jarrold, *J. Am. Chem. Soc.*, 2001, **123**, 8440.
639. G.-c. Yang and X.-r. Chen, *Sichuan Daxue Xuebao*, 2001, **33**, 51.
640. G. Shan, K. Igarashi, H. Noda and H. Ooshima, *Chem. Eng.*, 2002, **85**, 161–169.
641. I. Weissbuch, L. Leiserowitz and M. Lahav, *ACS Symp. Series*, 2002, **810**, 242.

642. M. Barthes, A.F. Vik, A. Spire, H.N. Bordallo and J. Eckert, *J. Phys. Chem.*, 2001, **106**, 5230.
643. M. Yokota, K. Kawaguchi, S. Sakaki and N. Kubota, *Nippon Kaisui Gakkaishi*, 2002, **56**, 261.
644. A.N. Zyablov, D.S. Dolgikh, T.V. Eliseeva, V.F. Selemenev, L.A. Bityutskaya and I.S. Surovtsev, *J. Struct. Chem.*, 2001, **42**, 503.
645. S. Hoeppener, L.F. Chi, J. Wonnemann, G. Erker and H. Fuchs, *Surf. Sci.*, 2001, **487**, 9.
646. X. Zhao, R.G. Zhao and W.S. Yang, *Langmuir*, 2001, **18**, 433.
647. Z. Zhao, *Huaxue Yanjiu Yingyong*, 2001, **13**, 599.
648. S. Munsch, M. Hartmann and S. Ernst, *Chem. Commun. (Cambridge)*, 2001, 1978.
649. S. Ernst, M. Hartmann and S. Munsch, *Stud. Surf. Sci. Catal.*, 2001, **135**, 4566.
650. G.L. Starobinets, T.L. Yurkshtovich, P.M. Bychkovskii and F.N. Kaputskii, *Zhurnal Fizicheskoi Khimii*, 2001, **75**, 1702.
651. D.E. Fleming, W. Van Bronswijk and R.L. Ryall, *Clin. Sci.*, 2001, **101**, 159.
652. A.E. Aghajanyan, K.I. Ygian, A.S. Saghiyan and G.J. Oghanisyan, *Khim. Zh. Arm.*, 2001, **54**, 112.
653. Y. Ihara, S. Kurose and T. Koyama, *Monatsh. für Chem.*, 2001, **132**, 1433.
654. T. Nishiki, K. Nakamura, M. Hisatsune and D. Kato, *Solv. Ext. Res. Dev.*, 2002, **9**, 99.
655. K. Nakashima, T. Oshima and M. Goto, *Solv. Ext. Res. Dev.*, 2002, **9**, 69.
656. M. Hebrant, P. Burgoss, X. Assfeld and J.-P. Joly, *J. Chem. Soc. Perkin Trans. 2*, 2001, 998.
657. E.M. van der Ent, K. van't Riet, J.T.P. Keurentjes and A. van dar Padt, *J. Membr. Sci.*, 2001, **185**, 207.
658. A.M. Antunes, M.M.C. Ferreira and P.L.O. Voipe, *J. Chemometr.*, 2002, **16**, 111.
659. Y.J. Zhang, Y. Song, Y. Zhao, T.J. Li, L. Jiang and D. Zhu, *Langmuir*, 2001, **17**, 1317.
660. J. Givand, B.-K. Chang, A.S. Teja and R.W. Rousseau, *Ind Eng. Chem. Res.*, 2002, **41**, 1873.
661. R. Wimmer, F.L. Aachmann, K.L. Larsen and S.B. Petersen, *Carbohydr. Res.*, 2002, **337**, 841.
662. E. Peyrin, A. Ravel, C. Grosset, A. Villet, C. Ravelet, E. Nicolle and J. Alary, *Chromatographia*, 2001, **53**, 645.
663. H.-J. Buschmann, L. Mutihac and K. Jansen, *J. Incl. Phenom. Macrocycl. Chem.*, 2001, **39**, 1.
664. L.-x. Song and Z.-j. Guo, *Wuji Huaxue Xuebao*, 2001, **17**, 457.
665. H. Yamamura, M. Rekharsky, A. Akasaki, S. Araki, M. Kawai and Y. Inoue, *J. Phys. Org. Chem.*, 2001, **14**, 416.
666. Y. Liu and S. Kang, *Sci. China Ser. B: Chem.*, 2001, **44**, 260.
667. C. Ye, Y. Zhao, J. Chang and W. Liu, *J. Chem. Res. Synopsis*, 2001, 330.
668. Y. Liu, B. Lin, T. Wada and Y. Inoue, *Bioorg. Chem.*, 2001, **29**, 19.
669. T. Ugawa and S. Nishikawa, *J. Phys. Chem. A*, 2001, **105**, 4248.
670. B.-Y. Xia, W.-S. Cai, X.-G. Shao, Q.-X. Guo. B. Maigret and Z.-X. Pan, *THEOCHEM.*, 2001, **546**, 33.
671. S.-C. Xiang, Y. Zheng, J.-b. Weng and Z.-s. Zhu, *Hecheng Huaxue*, 2001, **9**, 499.
672. S.M.Z. Al-Kindy, F.F.O. Suliinan and A.A. Al-Hamadi, *Anal. Sci.*, 2001, **17**, 639.
673. Y.C. Guillaume, E. Peynn, A. Villet, A. Nicolaa, C. Guinchard, J. Millet and J.F. Robert, *Chromatographia*, 2001, **52**, 753.

674. A.D. Cutland, J.A. Halfen, J.W. Kampf and V.L. Pecoraro, *J. Am. Chem. Soc.*, 2001, **123**, 6211.
675. N. Voyer, S. Cote, E. Biron, M. Beaumont, M. Chaput and S. Levac, *J. Supramol. Chem.*, 2001, **1**, 1.
676. J. Al-Mustafa, S. Hamzah and D. Marji, *J. Solution Chem.*, 2001, **30**, 681.
677. H.-J. Buschmann, E. Schollmeyer and L. Mutihac, *J. Incl. Phenom. Macrocycl. Chem.*, 2001, **40**, 199.
678. Z. Chen, K. Uchiyana and T. Hobo, *Enantiomer*, 2001, **6**, 19.
679. H. Tsukube, H. Fukui and S. Shinoda, *Tetrahedron Lett.*, 2001, **42**, 7583.
680. P. Prus, M. Pietraszkiewicz and R. Bilewicz, *Mater. Sci. Eng. C*, 2001, **18**, 157.
681. B. Botta, M. Botta, A. Pilippi, A. Tafi, G. Delle Monache and M. Speranza, *J. Am. Chem. Soc.*, 2002, **124**, 7658.
682. F. Liu, G.-Y. Lu, W.-J. He, Z.S. Wang and L.-G. Zhu, *Chin. J. Chem.*, 2001, **19**, 317.
683. J.L. Atwood, T. Ness, P.J. Nichols and C.L. Raston, *Cryst. Growth and Design*, 2002, **2**, 171.
684. X. Peng, L. Liang, G. Yuan and S. Liu, *Huaxue Tongbao*, 2001, **65**, 126.
685. A. Tung, Q. Yang, H. Dong, L. Li and C.W. Huie, *Anal. Sci.*, 2001, **17**, a207.
686. C.Z. Wang, Z.A. Zhu, Y. Li, Y.T. Chen, F.M. Miao, W.L. Chan, X. Wien and A.S.C. Chan, *New J. Chem.*, 2001, **25**, 801.
687. M. Thamae and T. Nyokong, *J. Porphyrins Phthalocyanins*, 2001, **5**, 839.
688. T. Grawe, T. Schrader, P. Finocchario, G. Consiglio and S. Failla, *Org. Lett.*, 2001, **3**, 1597.
689. T. Liu, W.-J. Ruan, Y. Li, D.-Q. Yang, Z.-A. Zhu, Y.-T. Chen and A.S.C. Chan, *Gaodeng Xuexiao Huaxue Xuebao*, 2001, **22**, 159.
690. R.P. Bonomo, V. Cucinotta, G. Maccarrone, E. Rizzarelli and G. Vecchio, *J. Chem. Soc. Dalton Trans.*, 2001, 1366.
691. J. Sabolovic and V. Noethig-Laslo, *Cell. Mol Biol. Lett.*, 2002, **7**, 151.
692. E. Naritu, *Nendo Kogaku*, 2001, **40**, 173.
693. S. Goswami and R. Mukherjee, *Indian J. Chem. B: Org. Chem. Med. Chem.*, 2001, **40B**, 960.
694. C. Buttersack and A. Perlberg, *Stud. Surf. Sci. Catal.*, 2001, **135**, 2944.
695. J.-S. You, X.-Q. Yu, G.-L. Zhang, Q.-X. Xiang, J.-B. Lan and R.-G. Xie, *Chem. Commun. (Cambridge)*, 2001, 1816.
696. K. Tsubaki, M. Nuruzzaman, T. Kusumoto, N. Hayashi, B.-G. Wang and K. Fuji, *Org. Lett.*, 2001, **3**, 4071.
697. N. Higasi, T. Koga and M. Niwa, *ChemBioChem.*, 2001, **3**, 448.
698. M. Jurij, N.M. Maier, W. Lindner and G. Vesnaver, *J. Phyt. Chem. B*, 2001, **105**, 1070.
699. S. Aisawa, S. Takahishi, W. Ogasawara, Y. Umetsu and E. Narita, *J. Solid State Chem.*, 2001, **162**, 52.
700. Kabir-Ud-Din, J.K.J. Salem, S. Kumar and Z. Khan, *Indian J. Chem. B: Org. Chem. Med. Chem.*, 2001, **40B**, 1196.
701. F. Billiot, E.J. Billiot and I.M. Wamer, *J. Chromat. A*, 2001, **922**, 329.
702. (*a*) M. Kinoshita, T. Imai, A. Kovalenko and F. Hirata, *Chem. Phys. Lett.*, 2001, **348**, 337; (*b*) Y. Harano, T. Imai, A. Kovalenko, M. Kinoshita and F. Hirata, *J. Chem. Phys.*, 2001, **114**, 9606.
703. A. Villa and A.E. Mark, *J. Comput. Chem.*, 2002, **23**, 548.
704. A. Melo and M.J. Ramos, *THEOCHEM*, 2002, **580**, 251.
705. P. Ramirez, A. Alcaraz and S. Mate, *J. Colloid Interface Sci.*, 2001, **242**, 164.

706. T.L. Petrenko, *J. Phys Chem. A*, 2001, **106**, 149.
707. C.F. Matta and R.F.W. Bader, *Proteins-Structure Funct. Genetics*, 2002, **48**, 519.
708. L. Liu, M. Rozenman and R. Breslow, *Bioorg. Med. Chem.*, 2002, **10**, 3973.
709. M.D. Garcia-Santos, S. Gonzalez-Mancebo, J. Hernandez-Benito, E. Calle and J. Casado, *J. Am. Chem. Soc.*, 2002, **124**, 2177.
710. S.D. Quine and B.T. Gowda, *Oxid. Commun.*, 2001, **24**, 450.
711. I.A. Rivero, S. Heredia and A. Ochao, *Synth. Commun.*, 2001, **31**, 2169.
712. I.M. Lapina and L.M. Pevzner, *Russ. J. Gen. Chem.*, 2001, **71**, 1479.
713. Z.Z. Chen, C.-M. Chen and Y.-F. Zhao, *THEOCHEM*, 2001, **574**, 163.
714. N. Cini, F. Machetti, G. Menchi, E.G. Occhiato and A. Guarna, *Eur. J. Org. Chem.*, 2002, 873.
715. G. Drabik and J.W. Nashalski, *Acta Biochim. Pol.*, 2001, **48**, 271.
716. J. Li, X. Wang, M.T. Klein and T.B. Brill, *Int. J. Chem. Kinetics*, 2002, **34**, 271.
717. R.K. Sharma, W.G. Chan, J.I. Seeman and M.R. Hajaligol, *Preprints of Symposia ACS.*, 2002, **47**, 398.
718. H.X. Li, Y.P. Xu and M.H. Wang, *Int. J. Chem. Kinetics*, 2002, **34**, 405.
719. B.D. Dangel, J.A. Johnson and D. Sames, *J. Am. Chem. Soc.*, 2001, **123**, 8149.
720. M. Soleimani and M.N. Sarbolouki, *Chromatographia*, 2002, **56**, 505.
721. R. Mateo-Castro, J.V. Gimeno-Adelantado, F. Bosch-Reig, A. Domenech-Carbo, M.J. Casas-Catalan, L. Osete-Cortina, J. De La Cruz-Canizares and M.T. Domenech-Carbo, *Fresnius J. Anal. Chem.*, 2001, **369**, 642.
722. J. Wang, A.P. Chatrathi, A. Ibanez and A. Escarpa, *Electroanalysis*, 2002, **14**, 400.