1
Amino Acids

BY G.C.BARRETT

1 Introduction

The chemistry and biochemistry of the amino acids, as featured in the 1991 literature, is reviewed in this Chapter. The targeted material could be categorized as the occurrence, chemistry, and analysis of the amino acids, and with the exclusion of routine literature covering the natural distribution of well-known amino acids. As before, the term 'amino acids' is taken to mean [ω]-amino-alkanoic acids, and there is therefore no coverage of amino-phosphonic, -sulphonic, -boronic acids and others of these types.

There continue to be themes in this literature that will be familiar to regular readers of this Specialist Periodical Report, and papers developing these long-running themes are usually given only brief coverage here. However, more thorough discussion is offered for papers where more significant synthetic work, and mechanistically-interesting results, are reported. Patent literature is almost wholly excluded, but this is easily reached through Section 34 of *Chemical Abstracts*, and other Sections (e.g. Section 16: Fermentations etc).

This Chapter is arranged into sections as used in all previous Volumes of this Specialist Periodical Report, and major Journals and *Chemical Abstracts* (to Volume 116, issue 11) have been scanned to reveal the material to be reviewed.

2 Textbooks and Reviews

Most of the citations of textbooks and reviews are located within appropriate Sections of this Chapter. Some books and monographs[1,2] having broad relevance to several Sections of this Chapter, are collected here.

3 Naturally Occurring Amino Acids

3.1 *Methodology of Isolation of Amino Acids from Natural Sources*

This Section covers a number of topics of increasing importance (though mostly simple in themselves). The generation of artefacts through

extraction procedures applied to natural samples, and the ever more sensitive analytical methods used with amino acids, all factors that increase the scope for erroneous conclusions concerning the presence (or absence) of amino acids in natural sources.

Aqueous acidic hydrolysis of peptides can be accelerated by microwave irradiation,[3] and large-scale separation of amino acids from hydrolysates can be achieved using appropriately-designed ion-exchange columns[4] or by reverse-phase flash chromatography.[5] Large-scale crystallisation of L-asparagine from aqueous solutions has received detailed attention.[6]

3.2 *Occurrence of Known Amino Acids*

Topics in reviews include non-protein amino acids,[7] the role of D-amino acids in the biosphere,[8] and N-acylamino acids as components of bacterial lipids.[9] An issue of *Advances in Enzymology and Related Areas in Molecular Biology* includes several reviews relevant to this Chapter [e.g. N^5-(1-carboxyethyl)-L-ornithine and related opines in crown gall tumours, marine invertebrates, microorganisms,[10] and ovothiols[11]].

Perhaps the most spectacular example of the occurrence of a known amino acid is the presence of alanine in the Murchison meteorite – though known for many years, refined analytical methods now allow the additional, even more spectacular, knowledge to emerge, that the amount of the L-enantiomer exceeds that of D-alanine by about 18%.[12] The result needs independent confirmation in another laboratory,[13] but also needs independent proof that the amino acids in a meteorite (or in a fossil,[14] for that matter) are indigenous; this is partly solved by stable isotope analysis, the ^{13}C-content of the meteorite amino acid indicating extraterrestrial origin.[12] The ^{15}N-content of amino acids in fossil samples can be a useful monitor of indigeneity since this isotope is increasingly enriched up the food chain.[14] These are welcome analytical checks on the authenticity of spectacular inferences made, based on the appearance of well-known amino acids in ancient samples – evolution of protein content being one such controversial topic – and another consideration is the chemical stability of the amino acids over such time-spans. The environmental decomposition of aspartic and glutamic acids, serine, alanine, and glycine in 1500y-old molluscan shells has been discussed.[15]

Further examples given later (Section 6.1: Racemization) describe studies of protein amino acids in fossils, but several recent papers report the presence of some uncommon, but known, amino acids in contemporary natural sources. These include L-aminobutyric acid as C-terminal residue in nazumamide A, a thrombin-inhibitory peptide from the marine

sponge *Theonella* sp.,[16] L-thiazolidine-5-carboxylic acid combined with L-proline in a new di-oxopiperazine (1) found in the Bermudan sponge *Tedania ignis*,[17] another new di-oxopiperazine (2), a germacranolide – valine condensation product (the first of its type) from aerial parts of *Centaurea aspera*,[18] and α-methyl-L-serine as a constituent of conagenin (3) from *Streptomyces roseosporus*.[19] Lactacystin (4) is a new microbial metabolite that induces differentiation of neuroblastoma cells.[20]

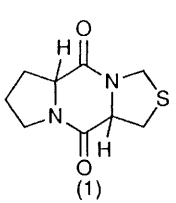
Further bromotyrosine – cysteine condensation products have been found in a marine sponge already shown to be rich in such psammaplins.[21] Far-reaching revision has been necessary for structure assignments made to radish hypocotyl constituents, the raphanusins, thought to be piperidine-2-thiones (see Vol.23, p.3). Raphanusin B is now established to be the pyrrolidinethione (5).[22,23]

3.3 *New Natural Amino Acids*

Relatively simple aliphatic amino acids emerging for the first time include trans-4-methoxypipecolic acid (6) from the tropical legume, *Inga Paterno*,[24] and trans-4-hydroxy-β-proline (7) from the red marine alga *Furcinellaria lumbricalis*.[25] Phenol ring-opening (at C-2 – C-3, and at C-4 – C-5) of L-DOPA by an enzyme from the red peel of *Amanita muscaria* yields two (hitherto hypothetical) intermediates 2,3-secodopa and 4,5-secodopa (8) and (9) respectively. They must be regarded as still elusive since their existence was proved in this study on the basis of the isolation of reaction products muscaflavin and betalamic acid.[26]

A novel addition to the natural biphenyl family is the aldose reductase inhibitor (10) from the fungus *Humicola grisea*,[27] while the similarly-expanding bromotyrosine family has gained two new derivatives (11; R = H) and its ethyl ester.[28]

Heterocyclic systems are represented by L-3-(2-carboxy-4-pyrrolyl) alanine (12) from the poisonous mushroom *Clytocybe acromelalga*,[29] and near relatives (13), a novel fungal antibiotic (TAN-950A) [with (14) as minor component; structural proof supplied by synthesis from L-glutamic acid],[30] and (15),[31] the oxidative adduct from N-acetyl-L-histidine and N-acetyldopamine, but from very different sources. TAN-950A was isolated from *Streptomyces platensis* A-136, while (15) was formed *in vitro* through the action of the cuticle of silkmoth larvae as an enzyme source [(15) is suggested to be widespread in Nature though as yet not recognized to be a natural product]. S-[2-Carboxy-1-(1H-imidazol-4-yl)ethyl]cysteine (16) has been located in normal human urine.[32] It is suggested to be the precursor of its reductive de-amination product, recently discovered also in normal urine.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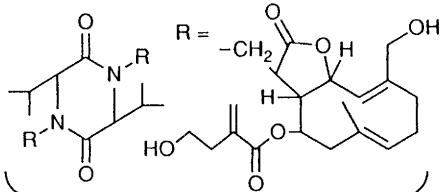
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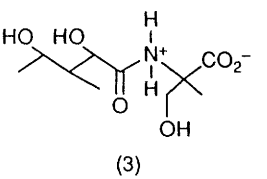
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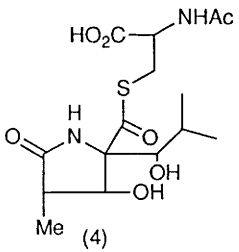
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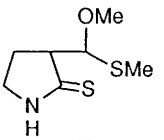
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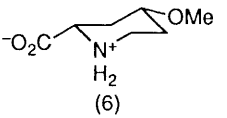
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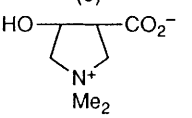
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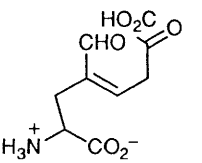
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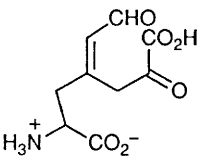
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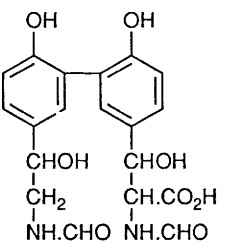
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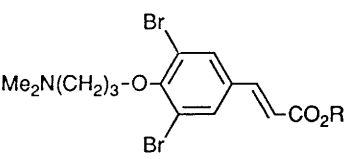
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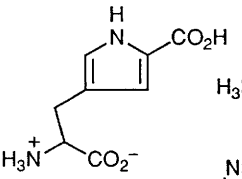
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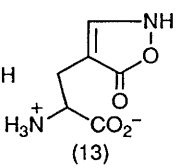
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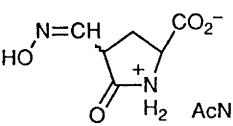
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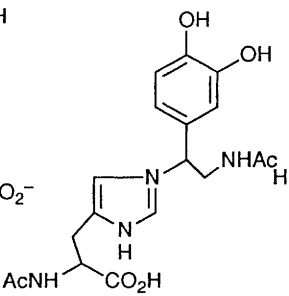
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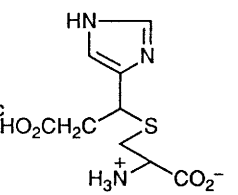
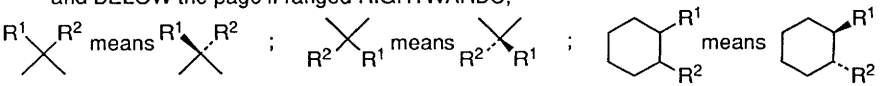

(16)

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

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

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



3.4 *New Amino Acids from Hydrolysates*

As in previous Volumes, this Section is intended to include new amino acids that would be released from condensed structures (i.e. peptides and proteins, mostly) by hydrolysis (in principle if not readily achievable in practice).

Full details are available (*cf.* Vol.23, p.3)[33] of the new protein crosslink allodesmosine (from bovine lung, aorta and skin hydrolysates, as well as from elastin). As the name implies, this pentafunctional amino acid is structurally related to well-known crosslinking amino acid residues, and, like desmosine, contains a pyridinium moiety, being formed from one lysine and four allysine residues in the proteins.

Another reference back to earlier-published material[34] is a correction of the structure of the antibiotic FR900148, revised from the pyrrolone isomer to (17). The opportunity was also taken to establish additional stereochemical details for (17), including the L-configuration shown).

The marine sponge *Theonella* (see also, preceding Section 3.2) biosynthesizes thrombin-inhibitory factors cyclotheonamides A and B made up of proline, phenylalanine 2,3-diaminoptropionic acid, as well as a modified arginine residue (-CO- between the α-methine and COOH groupings) and a modified tyrosine residue (-CH=CH- between the α-methine and COOH groupings).[35] The sea urchin *Tripneustes gratilla* produces o-, m- and p-bromophenylalanine-containing peptides, the p-isomer being the only previously-known isomer.[36]

New cyclic anti-tumour peptides trapoxins A and B (18) contain the surprising α-amino 6-epoxyacylhexanoic acid residue. These differ in the adjacent prolyl or pipecolyl residue.[37]

More complex aliphatic amino acids (often heavily disguised) are represented in the newly-studied pyoverdin-type peptide siderophores (19) from *Pseudomonas fluorescens* E2.[38]

4 Chemical Synthesis and Resolution of Amino Acids

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

This Section offers representative examples from the 1991 literature of mostly well-established general methods. Later sections often reinforce the merits of some of these methods, by giving further examples, and no attempt is made to rank them here; but over the years reviewed in this Specialist Periodical Report, readers will have noticed the growing distinctions between the perennials and the annuals.

Amination reactions, e.g. the reaction of 2-bromopropanamide enantiomers with amines to give alanine amides,[39] and conceptually-

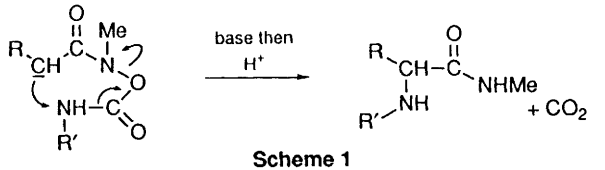
related azidation (3-fluoro-alanine from $BrCH_2CHBrCO_2Me$ by BrF_3, then NaN_3 followed by catalytic hydrogenation)[40] a similar approach to all isomeric 3-phenyl-serines and -iso-serines;[41] and a very useful, long sought – but extremely hazardous! – regiospecific S_N2 ring-opening of an alkoxycarbonyl epoxide using HN_3-di-isopropylethylamine at room temperature (20→21)[42] are conventional ways of introducing a nitrogen functional group into an aliphatic substrate. They are joined by a new reagent, p-Me-C_6H_4-SO_2-O-NHBoc, that may be converted into the N-lithio-derivative so as to offer a Boc-NH^+ equivalent for α-amino acid synthesis; thus, reaction with the zinc enolate $PhCH{=}C(O^iPr)ZnMe$ gives isopropyl N-Boc-phenylglycinate but in only 35% yield.[43] Time will tell whether the methodology can be improved (and simplified) so as to turn this promising method into a generally useful procedure.

A new α-amination method for aliphatic carboxylic acids, would be a suitable way of describing the rearrangement of N-acyl-N-methyl-hydroxylamine O-carbamates to α-amino acid N-methylamides under basic conditions.[44] Yields are in the range 34 – 76% in the cases so far tried for this anionic hetero[3,3]-rearrangement (Scheme 1). Mercury-catalyzed cyclization of chiral amidals is also a new α-amination method, applied to αβ-unsaturated aliphatic carboxylic acids (Scheme 2).[45]

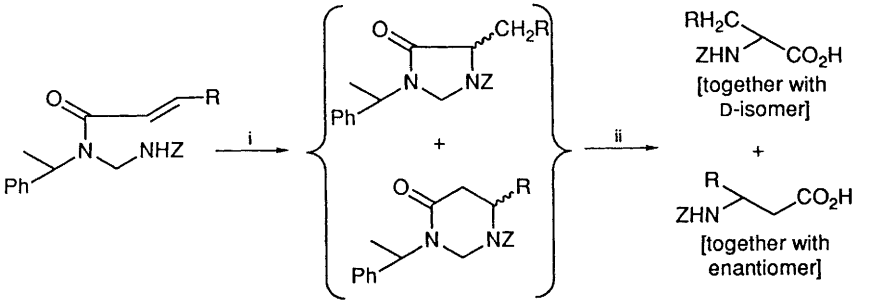
Cobalt-catalyzed aminocarbonylation processes using $Co_2(CO)_8$ with CO and aldehydes,[46,172] or equivalent gem-dihalogenoalkanes,[47] continue to provide effective entry to α-amino acids. Use of acetamide as substrate leads to N-acetyl β-cyclopropylalanines and its β-methyl homologue,[46] and use of diethylamine gives NN-diethylamino acid NN-diethylamides.[47]

Alkylation of glycine derivatives is as popular as ever as a route to target α-amino acids. Diethyl acetamidomalonate has been employed in many laboratories,[e.g.,221] including use in the synthesis of cis- and trans-pyrrolidine-2,4-dicarboxylic acid.[48] These targets are viewed as cyclic analogues of glutamic acid,[48] and similar objectives and methods are involved in the synthesis of all stereoisomers of related substituted prolines.[49] Alkylation of diethyl acetamidomalonate has yielded 4,4-difluoro-threonine,[50] and similar methodology has been applied, to syntheses of 3,6-dimethyldioxopiperazines (from dioxopiperazine and methyl magnesium carbonate),[51] to ethyl α-azidoacetate [aldol reaction with 4-{(bis-t-butoxy)phosphonylmethyl}benzaldehyde and reduction of the resulting cinnamate],[52] and to α-aminonitriles (readily alkylated by epibromhydrin, in contrast with acylated glycine esters, to give 2,3-methanoserines).[53]

Schiff base alkylation is much used, especially in asymmetric synthesis (next Section), notable examples being based on $Ph_2C{=}NCH_2CO_2Et$ [synthesis of a "-CH=CH- for -S-S- replacement", *viz.* 6,6-penta-

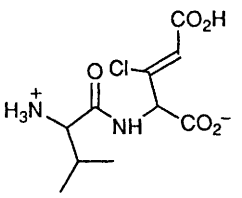


Scheme 1



Reagents; i, $Hg(OTFA)_2$; ii, H_3O^+ with separated products

Scheme 2



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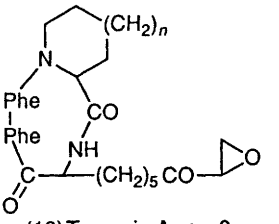
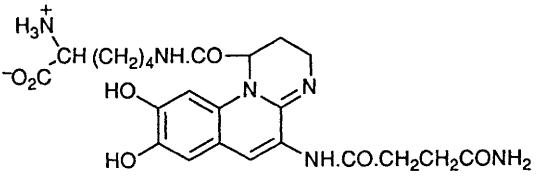


(18) Trapoxin A; $n = 0$
Trapoxin A; $n = 1$



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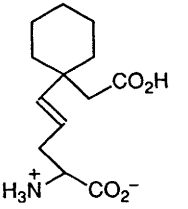


(22)

methylene-2-amino-$\Delta^{4,5}$-suberic acid (22) in a cystine analogue],[54] or on $PhCH{=}NCH_2CO_2Et$ (alkylation in an aqueous organic medium).[55] The imidate $PhC(OEt){=}NCH_2CO_2Et$[56] and the corresponding nitrile $PhC(OEt){=}NCH_2CN$[57] undergo aldol condensation with an aldehyde, elaboration of the resulting oxazoline in conventional ways giving β-hydroxy-α-amino acids[56] and α-hydroxymethylserines.[57]

Interesting applications of the ring expansion of azetidin-2,3-diones to N-carboxyanhydrides, which amounts to a general synthesis of α-amino acids from β-amino acids, have perhaps been slow in coming. The example in Scheme 3 (see also Scheme 30) is representative of the method.[58]

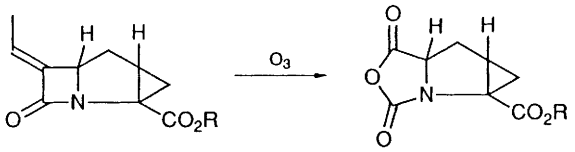
4.2 *Asymmetric Synthesis of α-Amino Acids*

Many of the methods that are familiar to regular readers are found again here. They have, in their own way, become an aspect of general methods of synthesis of α-amino acids, and the text of this Section could be combined with that of the preceding section for readers seeking information on the broader overall current situation.

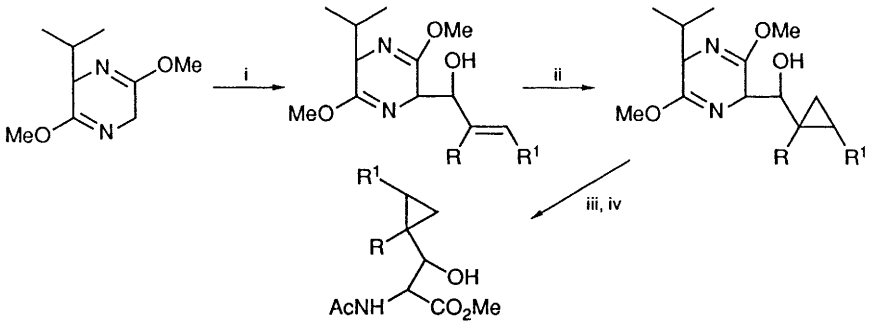
Numerous reviews have appeared: the use of carbohydrates as chiral auxiliaries in asymmetric synthesis of α-amino acids[59-62] including synthesis of prolines and pipecolic acids[60] and β- and γ-amino acids (including polyoxins);[62] amino acids from chiral lithiated amides;[63] and asymmetric hydroformylation.[64] A brief general review of asymmetric synthesis of amino acids is available,[65] accompanied by a review of asymmetric synthesis of statine.[66]

Standard methods are being exercised in a number of laboratories. Alkylation of the bislactim ether illustrated in Scheme 4, and its enantiomer, for the synthesis of (2R)- and (2S)-2-amino-2-methylmalonic acid (chiral on account of ^{13}C-isotopic substitution at one of the carboxyl carbon atoms), has been fully described following last year's preliminary account (Scheme displayed in Vol.23, pp.9,10).[67] The method has also been used in syntheses of (2R,3S)-3-hydroxy-3-(2′,3′-substituted-cyclopropyl)alanines through diastereoselective Simmons-Smith cyclopropanation of the appropriate 1-hydroxy-2-alkenyl bis-lactim ether (Scheme 4).[68] Corresponding (2R,3S)-3-substituted serines have been obtained similarly, exploiting the $ClTi(NEt_2)_3$-catalyzed addition of the bis-lactim ether (*via* 23) to a ketone.[69] Both enantiomers of each member of a series of 2-alkyl-2,3-diaminopropanoic acids,[70] and substituted phenylglycines,[71] have been prepared by bis-lactim ether alkylation, the latter case involving arene-Mn complexes as nucleophiles.

Asymmetric alkylation of Schiff bases also features in several recent papers. The prodigious output continues,[72-78] of examples based on alky-

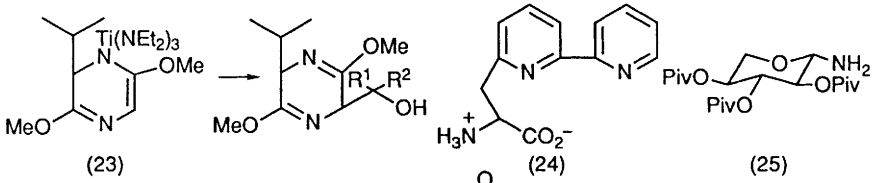


Scheme 3



Reagents: i, $R^1CH{=}CR.CHO$; ii, R^1CuI_2 and Et_2Zn; iii, hydrolysis; iv, protection strategy

Scheme 4



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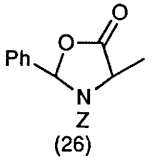

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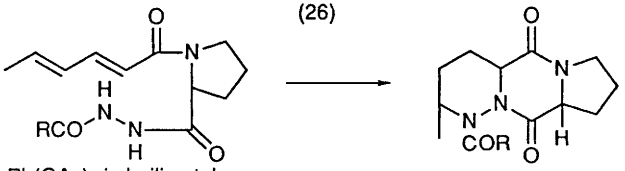
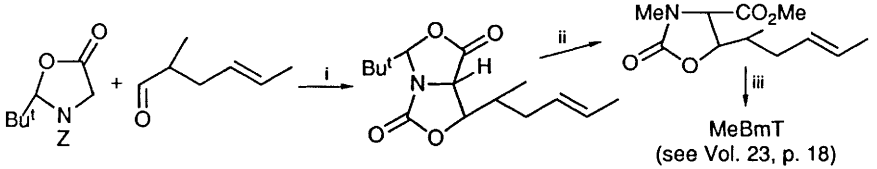


Reagents: i, $Pb(OAc)_4$ in boiling toluene

Scheme 5



Reagents: i, LDA, then $COCl_2$; ii, oxazolidinone cleavage, O,N–methylation;
iii, established methods

Scheme 6

lation of the Ni(II) complex of the (S)-2-[N(N′-benzylprolyl)aminobenzaldehyde] Schiff base of glycine or alanine ethyl ester (*cf.* Vol.23, p.15). Phenylalanine or α-methylphenylalanine obtained in this way through (S)-(2-aminomethyl)pyrrolidine catalysis of benzylation, are obtained in 33-87% yields but only 3-21% optical purity.[72] Hydroxyalkylation using benzaldehydes gives (2S,3R) and (2R,3R)-β-phenylserines from isomeric starting materials.[73] Curiously, while (2S,3S)-perfluoralkylserines are obtained in this way with perfluoroalkanals, the (2R,3S)-alkylserines are obtained when non-fluorinated alkanals are used under otherwise identical conditions with the same starting material.[74] Fluorine-substituted benzaldehydes give a range of (2R,3S)-phenylserines carrying F-, F_2CHO-, F_3CO-, and F_3C-substituents when used in this process.[75] α-Methylserine has been obtained from the process based on the alanine Schiff base,[76] similarly applied to the asymmetric synthesis of α-methylvaline and α-methylglutamic acid through conventional alkyl halide alkylation;[77] however, although aspartic acid and its α-methyl analogue were prepared analogously using ethyl bromoacetate as alkylation agent, the latter target could not be obtained from α-allylalanine.[78]

Related Schiff base alkylation routes established many years ago are also of continuing interest in asymmetric synthesis of α-amino acids. These routes involve substrates with a chiral alkylidene moiety (Schiff bases generated from 2-hydroxypinan-3-one and an amino acid ester[79]), those with a chiral ester or amide function [Schiff bases derived from chiral sultams (Vol.23, p.15) and N-benzophenylideneglycine[80]] in sytheses of L-diphenylalanine and L-9-fluorenylglycine,[80] and those derived from TWO chiral moieties [*e.g.*, the (−)-menthyl ester of the (+)-camphor ketimine of glycine[81-84]]. These studies explore factors determining diastereoselectivity, which is usually not high, though the "double asymmetric induction" study[81-84] includes examples of syntheses of L-amino acids from lithium enolate alkylations in 72-96% optical yields.

Asymmetric alkylation of benzylideneglycine t-butyl ester by α-13-bromomethylbipyridine in the presence of (8S,9R)-(−)-N-benzylcinchonidinium chloride gives modest (53%) enantiomeric excess in favour of the (S)-enantiomer of the novel metal-chelating amino acid (24).[85]

Schiff bases may be used in another way for asymmetric synthesis of α-amino acids, again illustrated in this year's literature in the context of the development of established methods. Asymmetric Strecker synthesis of D-amino acids using imines derived from tetra-O-pivaloyl-α-D-galactosylamine (see Vol.23, pp.28,34)[86] or from tri-O-pivaloyl-α-D-arabinopyranosylamine (25),[87] and an asymmetric Ugi synthesis based on the latter imine,[87] are efficient processes. A diastereoselective Strecker

synthesis the other way round – imines of achiral aldehydes and (−)-α-phenylglycinol – yields chiral N-substituted α-aminonitriles that can be cleaved with lead tetra-acetate (though, unfortunately, with destruction of the chiral auxiliary).[88] Asymmetric synthesis of cyanohydrins [$Me_3SiCN + RCHO \rightarrow RCH(OH)CN$] employs the AlR_3 or $Ti(OR)_4$ complex of the 2-hydroxy-1-naphthylidene Schiff base of L-valyl-L-tryptophan methyl ester as chiral catalyst.[89] The enantiomer excesses achieved are good [71% in one case, better than 94% in the case of (R)-mandelonitrile], and cyanohydrins are suitable for amino acid synthesis in a modification of the Strecker synthesis.

Enantioselective hydration of racemic α-aminonitriles in basic aqueous media has been observed in the presence of a homochiral monoterpene-derived nitrile, reaching 42% enantiomeric excess at half-completion.[90] Although the mechanism is as obscure as the thinking that led to the choice of catalyst, the demonstration by the same group that α-chymotrypsin brings about the same result and completes the overall process by catalyzing the hydrolysis of the amide (the hydration product) is more easily rationalized.[91]

Asymmetric alkylation processes in which the glycine moiety is rendered the electrophilic partner through α-halogenation, are illustrated in a synthesis in high optical yield of (S)-[2-^{2}H]glycine from N-Boc-glycine (−)-menthyl ester, through reaction with N-bromosuccinimide followed by radical formation with Bu_3Sn^2H,[92] and related enantioselective α-substitution of the same substrate with alkenyl- and alkynylstannanes.[93] These results are important in a wider context, since they demonstrate asymmetric induction in radical reactions. Methyl arylacetate – $Cr(CO)_3$ complexes are readily alkylated by N-benzyloxycarbonyl α-halogeno-α-amino acid esters in the presence of sodium hydride, to give β- and δ-arylated α-amino acids.[94] α-Aryl α-amino acids are obtained in optically-pure form in this way using fluorobenzene – $Cr(CO)_3$ with a chiral Schiff base [from L-alanine methyl ester] and (1R,2R,5R)-2-hydroxy-3-pinanone in the presence of LiN^iPr_2 or lithiated 2-t-butyl-4-methyl-1,3-oxazolidin-5-one.[95]

An example of amino acid synthesis by amination,[96] in addition to those described in the preceding Section, describes asymmetric amination of αβ-unsaturated amides (Scheme 5).

Aldol reactions of a conventional type leading to β-hydroxy-α-amino acids from N-protected glycine derivatives and aldehydes or ketones give modest excess of the threo-isomer (33-39%) and poor enantioselection (3-12% excess) when conducted in the presence of a chiral phase transfer catalyst.[97] The chiral trans-oxazolidin-5-one (26), formed from D-alanine and benzaldehyde followed by N-benzyloxy-

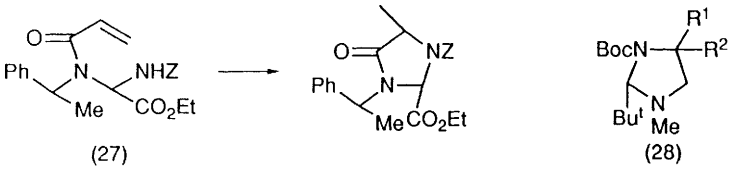
carbonylation, can be used as a source of homochiral α-methyl-α-amino acids through alkylation using an alkyl halide after carbanion formation.[98] X-Ray crystal analysis demonstrates that inversion of configuration occurs.

Numerous studies of alkylation of the glycine homologue of (26), with opposite chirality with t-butyl in place of phenyl, have been reported, mostly from Seebach's group. This chiral synthon, readily resolved by preparative scale chromatography (and readily racemized in boiling MeCN),[99] has been used to prepare threonine analogues by the aldol route, using $LiN(SiMe_3)_2$ for chiral enolate formation.[99] This method is suitable for a synthesis of MeBmT, the threonine homologue that is a component of cyclosporin A (Scheme 6), relying on the high diastereoselectivity of the alkylation step for achieving good optical yields with the correct stereochemistry.[100]

The corresponding imidazolidin-4-one (26; MeN in place of ring O) has been used in a synthesis of threo-3-alkyl- and aryl-glutamic acids[101] and studied for its stereochemical requirements in a number of other simple alkylation processes.[102-105] Aldol condensation gives a 5-alkylidene derivative to which dichlorocarbene or hydrogen (in the presence of a heterogeneous metal catalyst) add completely stereoselectively to the face opposite the t-butyl group.[102] N-Bromosuccinimide-AIBN bromination of the imidazolidin-4-one gives the trans-bromination product, from which the 5-allyl derivative can be prepared using $CH_2{=}CHCH_2SiMe_3$ and $ZnCl_2$, involving inversion of configuration.[103] A careful study of the stereochemical features of Hg-promoted cyclization of chiral unsaturated amidals (27), the basis of a new α-amino acid synthesis (see Scheme 2) to give 2,5-trans-imidazolidin-4-ones, has been reported.[104] The 2R-configuration favours the induction of the 5R-configuration at the new chiral centre.

An efficient way of using the potential for enantioselective alkylation of the racemic 2,5-trans imidazolin-4-ones (26; MeN in place of ring O) as well as recovering one enantiomer of it, requires only a chiral base for deprotonation of the racemic synthon.[105] Thus, (R,R)-$(PhCHMe)_2NLi$ followed by MeI gives the (S,S)-2-t-butyl-5-methylimidazolidinone together with (R)-2-butylimidazolidinone.[105]

Related chiral heterocycles studied in the present context include the imidazolidine (28; R^1 or $R^2 = H$; R^2 or R^1 = alkyl), which is amenable to alkylation after deprotonation with Bu^t Li and used (in the case of R^2 or R^1 $= CO_2Me$; R^1 or $R^2 = H$) to prepare (R)- and (S)-$MeNHCH_2CH(NH_2)CO_2H$.[106] A route from glyoxal to a multi-chiral imidazolidine (Scheme 7) is part of an enantioselective synthesis of α-amino aldehydes.[107] The thiazoline (29) from L-cysteine undergoes



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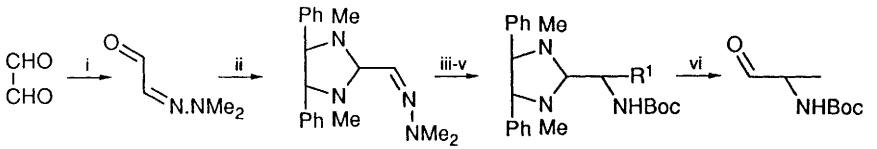
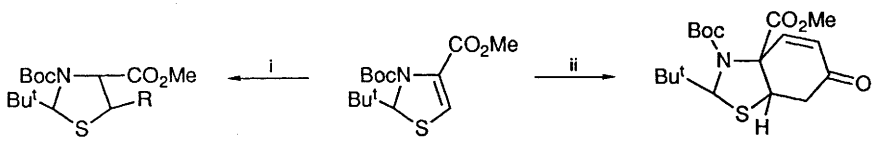


Reagents: i, $NH_2.NMe_2$; ii, $(MeNHCHPh)_2$; iii, R^1M; iv, H_2/Ni; v, $(Boc)_2O$; vi, 2% HCl

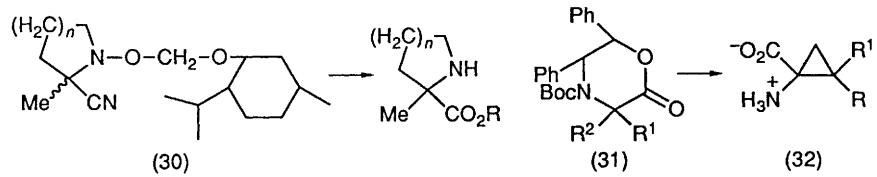
Scheme 7



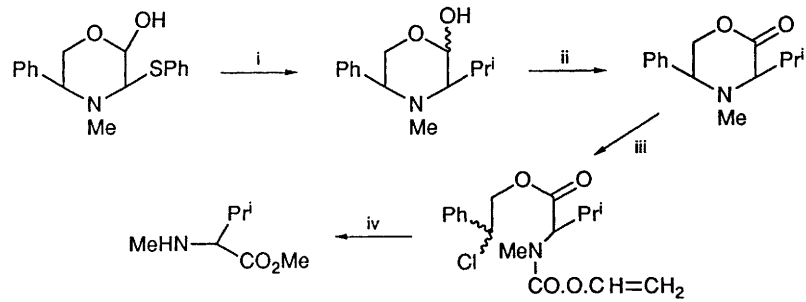
(29)

Reagents: i, $Bu_2Cu(CN)Li_2$-$BF_3.OEt_2$/–30 °C, then $NH_4Cl/NH_3/H_2O$;
ii, $CH_2=C(OSiMe_3)CH=CHOMe$ in PhMe/reflux

Scheme 8



(30) (31) (32)



Reagents: i, Pr^iZnI; ii, $COCl_2/DMSO/Et_3N$; iii, $Cl.CO.OCH=CH_2$; iv, HCl/MeOH

Scheme 9

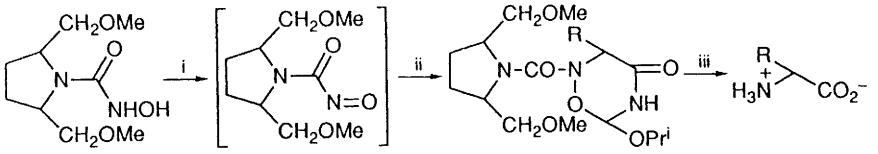
stereoselective trans addition of BuCu and enamines and has been shown to undergo cycloaddition to Danishefsky's diene to give 2-amino-5-hydroxy-3-mercaptoalkanoic acid derivatives after routine work-up (Scheme 8).[108] Chiral oxazolidin-2-ones[109] and thiazolidin-2-thiones[110] seem to be destined for more limited applications. The 4-hydroxymethyl derivatives of the former family [from (R)-glycidol and 2,3-epoxy-carbamates] offer access to homochiral serinols, and 5-methoxycarbonyl derivatives of the sulphur analogues can lead to homochiral α-hydroxy-ethyl-β-lactams. Pyrrolines (30) built up from nitrones, KCN, and chloro-methyl ether, with chirality based on (−)-menthol, can be elaborated into (S)- and (R)-α-methylprolines.[111]

The use of chiral enolates of (5S,6R)- and (5R,6S)-oxazin-3-ones is accompanied with high enantiomeric excesses when used as substrates for alkylation [anti-mono-alkylation of (31; R^1 and $R^2 = H \rightarrow R^1 =$ alkyl, $R^2 = H$) has been established.[112] Further alkylation is feasible; work-up involves Li-ammonia reduction to give Boc-amino acids. (2S,6R)- and (2S,6S)-2,6-di-amino-6-hydroxymethylpimelic acid (a component of the dipeptide antibiotic from *Micromonospora chalcea*) have been synthesized in this way using $ICH_2CH_2CH{=}CH_2$ for alkylation and $MeOCH_2Br$ for inserting the hydroxymethyl group.[113] These synthons give dimethoxy-phosphoryl derivatives (31; $R^1 = PO_3Me_2$, $R^2 = H$) that undergo Wadsworth-Emmons alkylidenation with aldehydes, giving substrates for cyclopropanation with $PhS(O)(N^+Et_2)CH_2^-$ to result in coronamic acid (32; R = Et) and its nor-analogue (32; R = Me) and ^{2}H-analogue.[114]

Homochiral α-(N-methylamino) acids result from nucleophilic dis-placement of thiophenoxide from the tetrahydro-oxazines (Scheme 9), giving an 84:16 diastereoisomer ratio at C-6, with retention when PrZnI is used, but with inversion with alkylcopper reagents.[115]

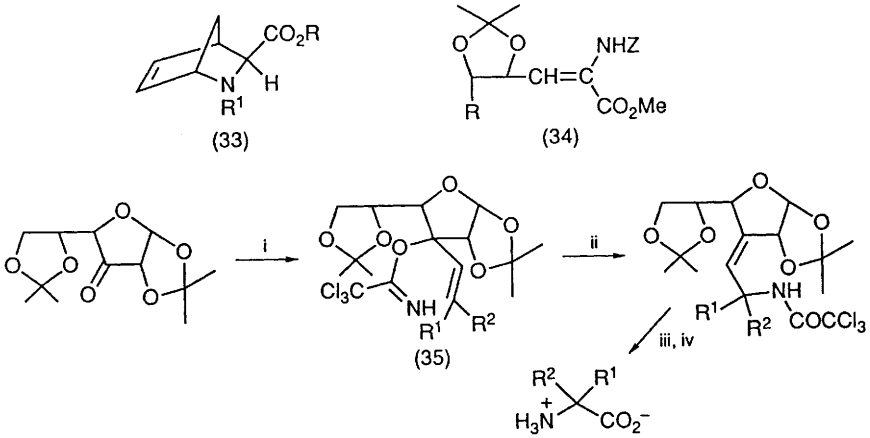
More complex chiral heterocycles are accessible through cyclo-addition reactions of 2-azadienes to chiral nitrones (Scheme 10).[116] The α-amino acid resulting from the particular starting materials shown is of L-configuration and of greater than 98% optical purity, so establishing a novel asymmetric amination procedure.

Aza-Diels-Alder reactions leading to 1-azabicyclo[2.2.1]heptene-2-carboxylic esters (33) based on a chiral iminium ion formed *in situ* from glyoxal and a chiral amine, approach 90% diastereoisomeric excess for exo-isomers, when a non-hindered moiety is introduced with the chiral amine.[117] Related chiral 1-acetamidobicyclo[2.2.1]heptene-1-carboxylates formed by Diels-Alder addition of cyclopentadiene to N-acetyldehydro-alanine (−)-cis-2-neopentyloxyisoborn-3-yl esters exhibit a preference for the isomer with exo-disposition of the carboxylate moiety.[118] A cognate study (that strictly does not fall within the terms of reference of this



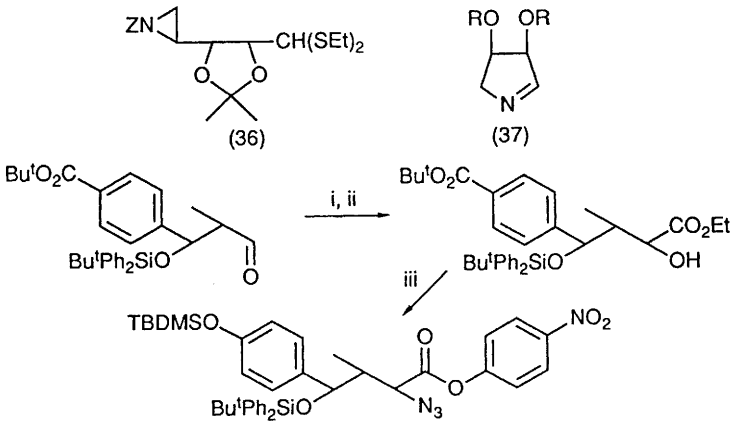
Reagents: i, $NEt_4^+IO_4^-$;
ii, $RCH_2COCl + Pr^iOCH{=}\overset{+}{N}H_2Cl^- \rightarrow\rightarrow R.CH{=}C(OTBDMS)CH{=}N.OPr^i$;
iii, $Mo(CO)_6$ then H_3O^+

Scheme 10



Reagents: i, established methodology; ii, xylene/135 °C; iii, $RuCl_3/NaIO_4$; iv, H_3O^+

Scheme 11



Reagents: i, $CH_2{=}CLi\text{-}OEt$; ii, O_3; iii, routine protection strategy, NaI; iv, NaN_3;
v, ester interchange Et → 4-nitrophenyl for coupling to give nikkomycin B

Scheme 12

Section, but is mechanistically related), succeeds in explaining the diastereofacial selectivity observed in Lewis-acid catalyzed cycloaddition of cyclopentadiene to N-acryloyl-L-amino acids.[119]

Asymmetric hydroformylation of N-acetamidodehydroalanine ethyl ester has been achieved using $HRh(CO)(PPh_3)_3$ as catalyst with a chiral chelating diphosphine [e.g. (−)-DIOP] as chiral selector, giving the protected α-formylalanine.[120] Related studies with acrylate esters of N-acylamino acids have been reported.[121] Chiral rhodium or ruthenium catalysts effect dynamic catalytic resolution during hydrogenation of 2-acylamino-3-oxobutanoates to yield D- or L-threonine.[122]

The substantial record of results on asymmetric (homogeneously catalyzed) hydrogenation of α-acetamidocinnamic acid esters continues to be augmented, studies this year including a report of better than 92% enantiomeric excess with chiral RhX(bichep)(nbd) catalysts [X = Cl, ClO_4; nbd = norbornadiene; bichep = 2,2′-bis(dicyclohexylphosphino)-6,6′-dimethyl-1,1′-biphenyl].[123] Better than 95% stereoselectivity is attributed to the use of a zeolite anchor for the nitrogen-based chiral ligands of the Rh catalyst for the same substrate,[124] and very high stereoselectivity is also achieved with a chiral cyclopentane-1,2-diphosphine.[125] All four stereoisomers of tripalmitoyl γ,δ-dihydroxyamino acids have been prepared through this methodology using an acylamino dehydroamino acid (34) already containing a chiral moiety.[126] More routine studies have appeared,[127,128] in one of which[128] there is mechanistic interest in the fact that a decisive role exists for water, present in a two-phase (EtOAc – H_2O) medium used in deuteration (20 – 70% incorporation) of N-acyldehydroalanine methyl esters.

Better than 95% optical yield, is the extraordinary outcome for hydride transfer from (S)- or (R)-N,N′,1,2,4-pentamethyl-1,4-dihydronicotinamide to the Schiff base $MeO_2CN{=}CPhCO_2Me$ to give the derivatized phenylglycine enantiomers.[129] This provides an excellent model for the *in vivo* action of NADH.

Elaboration of the carbonyl group of the chiral lactone from diacetone-D-glucos-3-ulose provides a versatile intermediate (35 in Scheme 11) that is susceptible to the imidate rearrangement.[130] The resulting αβ-unsaturated amine gives the appropriate α-amino acid enantiomer through $RuCl_3$ – $NaIO_4$ cleavage, and the novel variation of known methodology has been exemplified in the case of a synthesis of (2R)-[2-^{2}H]glycine.

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

The substantial literature on fermentative production of protein

amino acids continues to be represented here only in representative citations, given the availability of authoritative reviews and the accessibility of the literature through *Chemical Abstracts* (mainly within Section 16 – Fermentation and Bio-industrial Chemistry). The reviews this year cover amino acid production mediated by transaminases,[131] by microbial eukaryotes and prokaryotes other than coryneforms,[132] and by acylases, aminopeptidases, and hydantoinases.[133] One of these[133] also covers α-alkyl-α-amino acids. L-Aspartic acid production using the L-aspartase in immobilized microbial cultures,[134] and L-aspartic acid and D-alanine production in pressurized reactors connecting immobilized *Pseudomonas dacunhae* and *Escherichia coli* mediated reactions,[135] have been reviewed.

Representative topics featured in primary research papers include L-phenylalanine production employing *Citrobacter freundii* with L-glutamic acid as NH_2-donor for the transaminase-based process with phenylpyruvic acid[136] (a mathematical model is reported[137] for the corresponding L-tyrosine production from phenol, pyruvate, and NH_3 employing the same organism immobilized on macrocyclic gel granules), L-tryptophan production, from indole-resistant *Corynebacterium glutamicum*,[138] and from tryptophan synthase using L-serine and indole.[139] Less familiar α-amino acids covered, include norvaline and O-ethylhomoserine that accompany L-isoleucine produced by *Brevibacterium flavium* AB-07 (these can be suppressed by using mutant strains),[140] and S-adenosyl-L-methionine and -L-homocysteine production in animal tissues after inactivation of methionine synthase by N_2O.[141]

A number of illustrations of general laboratory methods and asymmetric synthesis methods described in preceding sections have used with protein and other natural amino acids as synthetic targets. Further examples that could have been located here, have instead been collected in a later Section (6.3: Specific Reactions), because they illustrate the synthesis of one amino acid starting from another.

Aliphatic, alicyclic, and saturated heterocyclic examples of particular interest concern polyoxamic acid [enantiospecific ring opening by PhS^-, of an aziridine (36) derived from a protected L-arabinose],[142] and a related synthesis of the γ-hydroxy-β-methyl-α-aminobutanoic acid moiety in nikkomycin B [starting from (−)-(E)-crotyldi-isopinocampheylborane; Scheme 12].[143] Leucinostatine constituents (2S,4S,6S)-2-amino-6-hydroxy-4-methyl-8-oxodecanoic acid and (4S,E)-4-methylhex-2-enoic acid have been synthesized; the amino acid wss prepared through alkylation of a chiral glycine Schiff base with (S)-$CH_2{=}CH.CH_2CH$-$Me.CH_2I$, followed by routine elaboration].[144] A norcoronamic acid synthesis (see also an example in the preceding Section) builds the cyclopropane ring on to a Schiff base, prepared following the illustrative

simpler sequence starting from $ClCH_2CH_2CH(OH)CN \rightarrow ClCH_2CH_2CH(N{=}CHPh)CN \rightarrow$ 1-benzylideneamino-1-cyanocyclopropane.[145] A related natural product, (2S,3S)-(+)-aziridine-2,3-dicarboxylic acid has been synthesized from the corresponding 2,3-dicarbethoxyoxirane (Me_3SiN_3 followed by Ph_3P).[146]

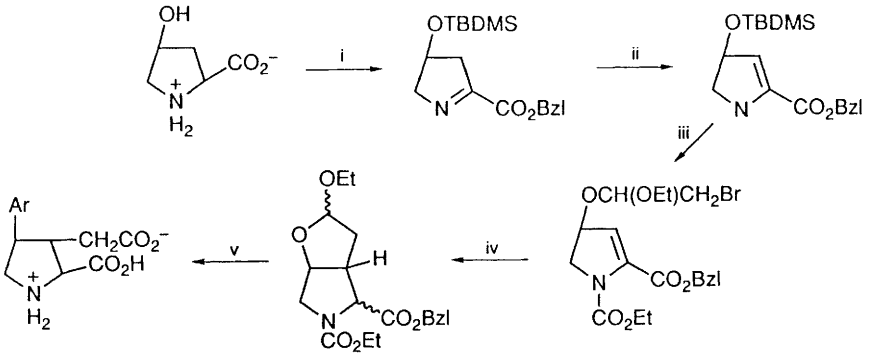
The natural stereoisomer of dihydroxyproline, configuration (2S,3S,4S), and a new isomer [(2R,3S,4S)], have been synthesized from L-tartaric acid by cyanosilylation and routine elaboration of the derived Schiff base (37; R = Bz, TBDMS).[147] These are relatively simple targets compared with members of the kainoid family and near relatives, which continue to stimulate applications of modern synthetic methods. Acromelic acid congeners (carrying an aryl group in place of the 3-pyrid-2-onyl grouping at the 4-position) are accessible through methodology applied to hydroxy-L-proline (Scheme 13; see also Vol.23, p.20).[148] Electrochemical C-5 methoxylation of hydroxy-L-proline carbamates followed by C-5 stereospecific radical homologation ($OMe \rightarrow CH_2OH$) are the crucial steps in a bulgecinine synthesis.[149]

Approaches to kainoids continue to illustrate the best of strategies using interesting new methodology. The Nicholas reaction (Scheme 14) applied to the purpose gives a pyrrolidine carrying all essential substituents.[150] Total syntheses of racemic α-allokainic acid, one involving two allylsilane – N-acyliminium ion reactions (shown in part in Scheme 15),[151] and another based on $Zn(OAc)_2$-catalyzed cyclization of γ-isocyanosilyl enolates $RC(NC)(CO_2Me)CR^1{=}C(OSiMe_3)Me$, use of 6-(TBDMSO)-3-hexen-2-one giving (38), amenable to functional group modification by standard methods.[152]

The interest in a synthesis published for tyrosine[153] lies in its exploration of the feasibility of synthesizing the more complex isodityrosine diaryl ether moieties of the vancomycins. Cycloaddition of Danishefsky's diene (Scheme 16) is possible and the equivalent diene $CH_2{=}C(OTMS).C(OAr){=}CHOTMS$ will be likely to be successful for the more important target. A synthesis of (S)-3,5-dihydroxyphenylglycine (a constituent of the vancomycins and related antibiotics) starts with an apparently routine synthesis of the dihydroxyphenylacetic acid, used to acylate Evans' chiral oxazolidin-2-one followed by α-azidation (trisyl azide).[154]

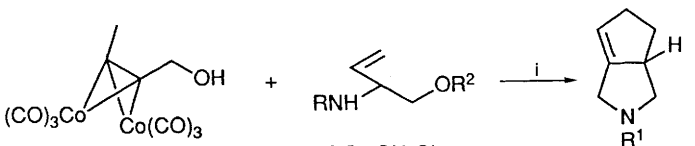
4.4 *α-Alkyl Analogues of Protein Amino Acids*

The long-running interest continues in these homologues, seen as highly hindered compounds potentially capable of modified biological activity in comparison with their natural counterparts. Implicit in this structural feature is the fact that general methods of α-amino acid synthe-



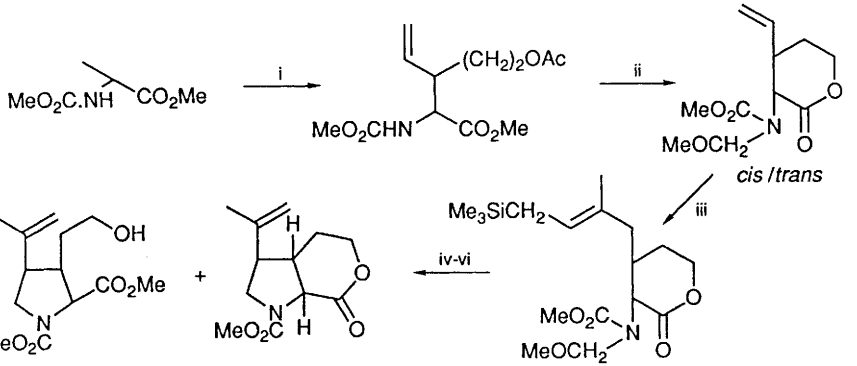
Reagents: i, routine steps; ii, $ClCO_2Et$, py; iii, TBAF, then 1, 2-dibromoethyl ether; iv, $Bu^n{}_3SnH$; v, H_3O^+, then TsCl, then Ar_2CuLi and functional group elaboration

Scheme 13



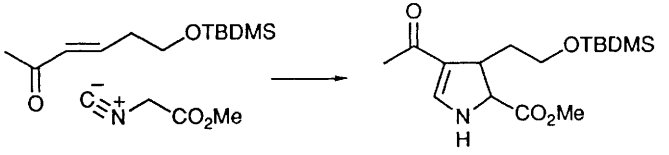
Reagents: i, reactants as shown, with $BF_3.OEt_2/CH_2Cl_2$

Scheme 14



Reagents: i, $Me_3SiCH_2CH{=}CHCH_2CH_2OAc$, and $BF_3.OEt_2$ or $SnCl_4$; ii, TsOH—MeOH, reflux; iii, NaH then $ClCH_2OMe$ with *cis*-isomer; iv, O_3; v, $CHO \rightarrow CH_2CMe{=}CHCH_2SiMe_3$; vi, $BF_3.OEt_2$

Scheme 15



(38)

sis, with the notable exception of the Strecker synthesis, often fail when applied to these homologues.

Alkylation of heterocycles categorises many of the successful routes, and a review of the use of 3-amino-2H-azirene in this way has appeared.[155] A 4,4-diaralkyl-2-phenyloxazol-5-one is obtained from the parent heterocycle through reaction with the aralkyl bromide in the presence of $MeMgCO_3$.[156]

A spectacular achievement is the first synthesis of αα-di-isopropylglycine, through a modified Ugi synthesis ($HCO_2H/PhCH_2N{=}C^iPr_2/C_6H_{11}NC$) but requiring 0.9GPa pressure.[157] All four isomers of α,β-dimethylphenylalanine and 4,5-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-carboxylic acid have been synthesized as "constrained" phenylalanine analogues, through alkylation of the chiral imidazolidin-4-ones (*cf.* 26, NMe in place of ring O) prepared from alanine enantiomers.[158] A similar approach, α-alkylation of an α-amino acid through various means, underlies syntheses of α-benzylproline (hetero-Cope rearrangement of N-trifluoroacetylphenylalanine allyl ester, as established by Steglich many years ago,[159] and subsequent elaboration),[160] and of α-carboxymethyltryptophan (prepared from the isonitrile analogue of N^{im}-Boc-tryptophan benzyl ester by alkylation).[161] A longer route to α-alkylated tryptophans, based on cyclization of suitably protected carbamates followed by enolate alkylation, has been described.[162]

α-[β-(D-C-Allosyl)]-L-alanine (39) and its altrosyl isomer represent a rare type of side-chain-glycosylated amino acid, prepared by Claisen rearrangement (*cf.* Ref 159) and hydration of the resulting unsaturated sugar (Scheme 17).[163]

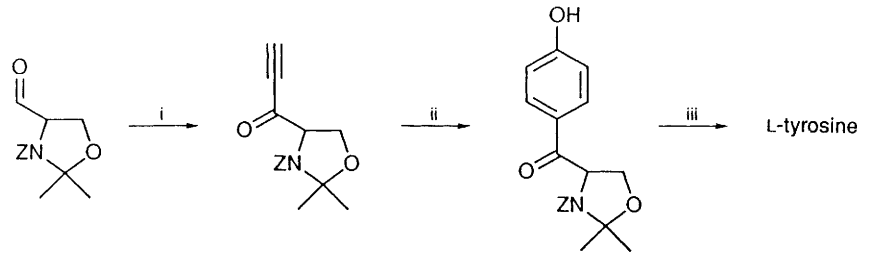
2,6-Di-amino-2-fluoromethylhept-3-ene-1,7-dioic acid, a diaminopimelic acid analogue, has been synthesized by alkylation of fluoroacetonitrile by propenylmagnesium bromide and routine elaboration.[164] Further uses for 5-fluoro-2-phenyl-4-trifluoromethyloxazole, a "hidden" trifluoroalanine synthon, have been found, alkadienylation and ring-opening giving $(E)\text{-}CH_2{=}CH\text{-}CH{=}CH\text{-}CH_2C(CF_3)(CO_2Me)NHCOPh$.[165]

Fluorobenzene chromium tricarbonyl complexes react with chiral esters of Schiff bases of L-alanine, L-leucine, and L-valine, to give the corresponding α-aryl-substituted amino acids.[166,cf.94,95]

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

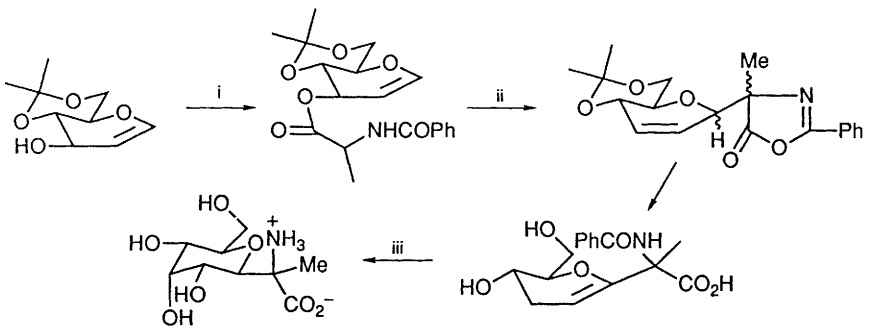
This Section collects examples of syntheses of near-relatives of the familiar natural aliphatic α-amino acids.

Acyclic examples are 3-alkylglutamic acids (potential kainic acid analogues), prepared by moderately diastereoselective alkylation of



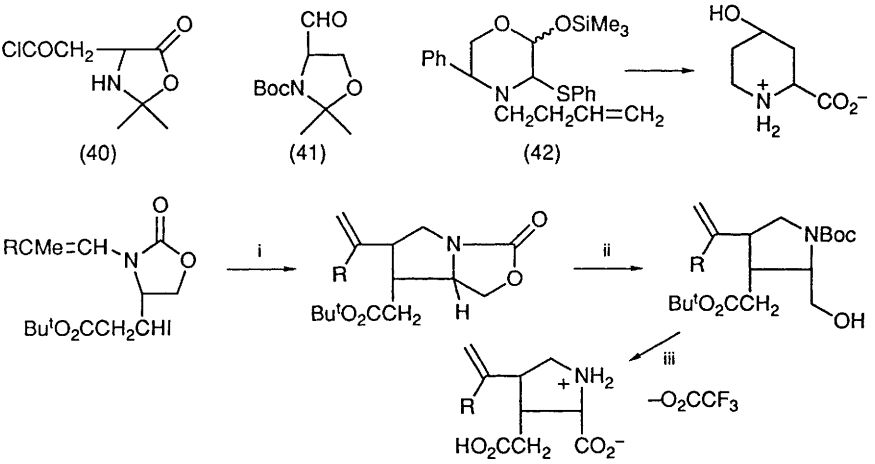
Reagents: i, CHO → CO.C≡CH; ii, CH_2=C($OSiMe_3$)CH=CHOMe/PhMe/110 °C/24h; iii, hydrolysis after C=O → CH_2

Scheme 16



Reagents: i, PhCO.Ala.OH/DCCI; ii, $Ph_3P/CCl_4/Et_3N$; iii, 6M HCl

Scheme 17



Reagents: i, cobaloxime (I); ii, aq. NaOH, then $(Boc)_2O$; iii, [O], then TFA

Scheme 18 (R = Me_2C=$CHCH_2CH_2$—)

(S)-N-Boc-2,2-dimethyl-5-(2′-methoxycarbonylethenyl)oxazolidine using R_2CuLi.[167] (R)- and (S)-2,3-Di-aminopropanoic acids have been prepared through iodocyclization of (S)-RR′C=CH.CH_2.N(CHMePh)CONHTos (chiral on account of the N-phenylethyl moiety) to the N-tosyl-N′-4-α-iodoalkyl-phenylethylimidazolidin-2-one.[168] $HClO_4$-Catalyzed Friedel-Crafts acylation of arenes using the L-aspartic acid derivative (40) yields γ-oxoaralkyl-α-amino acids.[169]

Aliphatic α-amino acids with conformational constraints built in to otherwise flexible acyclic side chains, include the four diastereoisomeric L-α-(carboxycyclopropyl)glycines prepared by cyclopropanation of (S)-CH_2=CH.CH(NHBoc)$CO_2SiMe_2Bu^t$.[170] trans-2-(Phenylcyclopropyl) glycine enantiomers have been synthesized from t-butyl (E,4R)- and (E,4S)-2,2-dimethyl 4-(2′-phenylvinyl)-3-oxazolidinecarboxylates [prepared from the corresponding aldehyde (41)→-CH=CHPh→phenylcyclopropyl].[171]

A substantial collection of papers on the synthesis of members of the proline and pipecolic acid families can be seen in this year's literature, partly covered in earlier sections of this Chapter. This activity is perhaps mainly stimulated by the potential pharmacological activity of the targets, bearing in mind the importance in this context of the kainoids as well as conformationally-constrained analogues of protein amino acids. Following the method used in new syntheses of lysine and ornithine,[46] $Co_2(CO)_8$-catalyzed carboxylation of N-benzoylpyrrolines and -tetrahydropyridines under hydroformylation conditions gives moderate yields of N-benzoylprolines and -pipecolic acids.[172] The mechanism of this process, already exemplified some time ago,[173] is tentative but may involve C – Co bond formation at the C=C group followed by CO insertion and (even more tentatively) may involve participation by the benzoyl oxygen atom to give the carboxy function after hydrolytic work-up.

The Schiff base route using Ph_2C=N.CH_2.CO_2R as nucleophile in a Michael addition to an α,β-unsaturated ketone with 10 mol% Cs_2CO_3 as catalyst gives the adduct, cyclisation leading to 2,5-disubstituted 1-pyrrolinecarboxylates and -prolines.[174] α-Acetoxy-[175,176] and α-chloro-[177] N-methoxycarbonylglycine esters carrying an N-alk-3-enyl grouping undergo cationic π-cyclisation ($SnCl_4$ or HCO_2H)[175,176] or Cu_2Cl_2- 2,2′-bipyridine cyclisation [attempted radical cyclization (Bu_3SnH) merely gives H in place of Cl][177] to give substituted pipecolic acid esters[175,176] and proline esters.[177] There are curious stereochemical results, *viz.* that cis-4-hydroxypipecolic acid esters are formed when the temperature is at −78° throughout the reaction and subsequent quenching, but trans-isomers result if the reaction mixture is allowed to warm before quenching.[176] The formic acid mediated reaction gives 4-formyloxypipecolates with low

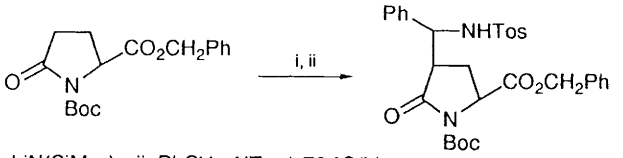
stereoselectivity at the newly-created chiral centre (C-4).[175] Cyclization of the ene-iminium ion derived from the (R)-2-phenylglycinol derivative (42) gives optically-pure 4-substituted pipecolic acids after routine deprotection and hydrolysis stages.[178] Cobaloxime(I)-mediated cyclization of homochiral 2-(α-iodoalkyl) N-alk-1-enyl oxazolidin-2-ones gives the C-8 side-chain analogues of domoic acid shown in Scheme 18.[179] Radical cyclization (Ph_3SnH-AIBN) of N-allyl-N-Boc-L-serine lactone gives 4-alkyl- and 4,4-di-alkylprolines.[180] The (2S,9S)-2-amino-8-oxo-9,10-epoxydecanoic acid moiety of the trapoxins (18) has been prepared by homolytic homologation of protected (S)-2-amino-5-iodopentanoic acid.[181]

Other syntheses of proline derivatives reported this year also start from familiar amino acids. (S)-Pyroglutamic acid can be elaborated into optically-pure homologues containing three chiral centres through addition of the derived enolate to activated imines (Scheme 19).[182] The chiral centre in the side chain is of the configuration shown, in the major (75%) diastereoisomer. The same starting material has been used in a relatively straightforward synthesis of (2S,3R)-2-carboxy-3-pyrrolidine-acetic acid, a simple kainic acid analogue.[183]

Hydroxyproline isomers are convenient as starting materials in a synthesis of all stereoisomers of (43), a conformationally-restricted arginine analogue.[184] The eight-step procedures used in this study, amount to relatively straightforward elaboration of the secondary alcohol chiral centre in the starting material. Azomethine ylide formation from the secondary amine (Scheme 20) derived from L-valine provides a partner for use in asymmetric cycloaddition; e.g. to N-methylmaleimide, giving a homochiral α-isopropyl D-proline derivative though with loss of the L-valine chiral auxiliary (discrepancies exist between absolute configurations in formulae and names in text).[185]

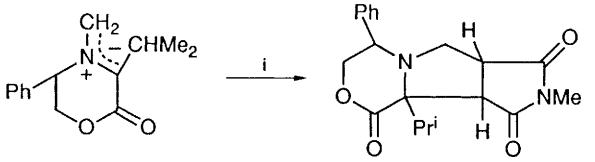
A new synthesis of racemic piperazine-2-carboxylic acid has been described, based on Schmidt rearrangement of N-ethoxycarbonyl-piperidin-4-one to give the seven-membered azalactam. αα-Dibromination at the amide carbonyl followed by Favorskii rearrangement effects the required ring-contraction and simultaneous creation of the α-carboxy group.[186] Azepane-2-carboxylic acid enantiomers are available through Schmidt rearrangement of homochiral 2-substituted cyclohexanones prepared from D- and L-valine-based enamines (Scheme 21).[187]

1-Aminocyclopropanecarboxylic acid is easily prepared from cyclopropanone in a modified one-pot Strecker synthesis.[188] If the ethyl trimethylsilyl acetal of the ketone is treated with NaCN and a chiral amine (phenylethylamine), an asymmetric synthesis opportunity is created. β-Chloroaldimine – HCN adducts prepared using acetone cyanohydrin



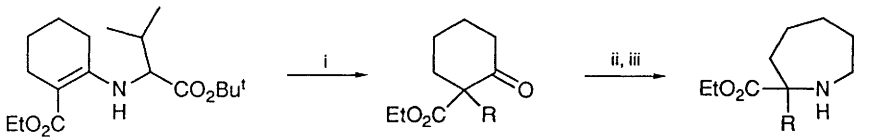
Reagents: i, $LiN(SiMe_3)_2$; ii, PhCH=NTos/–78 °C/l h

Scheme 19



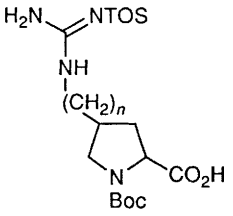
Reagent: i, *N*-methylmaleimide

Scheme 20



Reagents: i, RBr; ii, HN_3; iii, $BH_3.Me_2S$

Scheme 21



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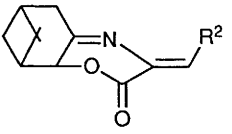

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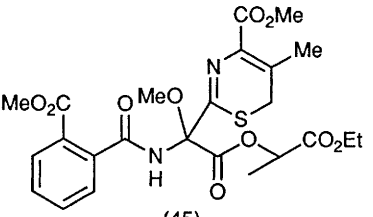

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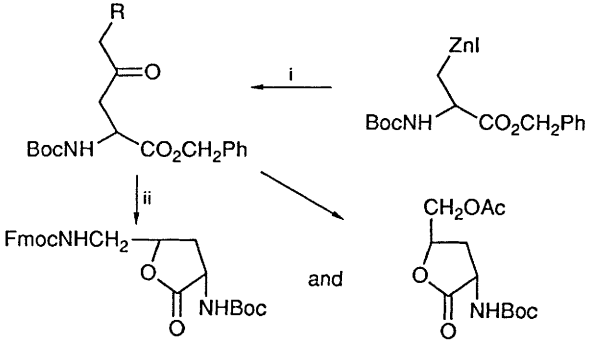


Reagents: i, $R.CH_2COCl/Pd(PPh_3)Cl_2$; ii, [H]

Scheme 22

have been converted into α-amino-γ-chloronitriles that can be cyclized to 1-amino-2,2-dimethylcyclopropanecarboxylic acid.[189] More conventional synthesis routes based on cyclopropanation of alkenes using diazomethane, and giving more flexibility as far as patterns of substituents are concerned, have been described for the Schiff base (44),[190] giving cis- and trans-2-methyl- and -2-ethyl-1-aminocyclopropane carboxylic acids, and for 4-ethylidene-2-phenyloxazol-5-one (giving DL-allocoronamic acid).[191]

First syntheses of 1-amino-3-aza-, 3-oxa-, and 3-thia-cyclobutane-1-carboxylic acids have been announced, starting from 1-chloro-2,3-epoxypropane.[192] These are considered to have potential as NMDA receptor modulators.

A tested procedure for the synthesis of a mixture of cis- and trans-4-aminocyclohexyl-D-alanines, through catalytic hydrogenation of Boc-D-phenylalanine, has been described.[193]

4.6 *Prebiotic Synthesis Models for Amino Acids*

Relevant reviews of the broader topic, within which environmental synthesis of amino acids may have occurred, have been published. One[194] is aimed more at the layman than the other.[13]

Amino acids have been shown to be present in reaction mixtures consisting of 1.0 or 2.2M aqueous KCN kept over kaolinite at 70° during 20 days (glycine, alanine, and aspartic acid),[195] of nitrogen, carbon monoxide, and water subjected to electric discharge over a pool of water (glycine in 5.6% yield based on available carbon, and trace amounts of other amino acids; together with HCN, HCHO, and urea).[196]

Amination of aliphatic carboxylic acids in water occurs under nitrogen with glow discharge, the best yield being seen for maleic acid.[197] This reductive fixation of nitrogen is enhanced by HCl, apparently suffering oxidation to ClO_3^- in the process.

4.7 *α-Alkoxy α-Amino Acids and Related α-Hetero-Atom-Substituted α-Amino Acids*

A useful new synthesis of N-benzyloxycarbonyl α-acetoxyglycine methyl ester from the threonine analogue employs lead tetra-acetate in benzene as reagent.[198] Substitution of acetoxy by thiolate can be effected by a thiol in the presence of DABCO.[198] Twenty-six examples of α-hetero-atom (O, N, S) substituted N-acetylglycine benzylamides have been synthesized to follow up the discovery that the alanine derivative has potent anticonvulsant activity.[199]

The N-methoxyamino- and N-methoxy-N-methylamino- deriva-

tives showed the highest activity. The α-methoxy α-amino acid (45) has been resolved through diastereoisomer formation with ethyl (S)-lactate.[200]

4.8 *α-(Halogenoalkyl) α-Amino Acids*

Aliphatic fluorinated amino acids have been reviewed.[201] Fluorinated analogues, $EtO_2C.CH{=}C[(CF_2)_nCF_3]$-X-$(CH_2)_m.CH(NH_2)CO_2H$, of lysine, arginine and cysteine (X = NH; m = 4,6; X = S; m = 1, n = 4,6) have been prepared from $CF_3(CF_2)_n.C{\equiv}C.CO_2Et$ through Michael addition processes.[202] Trifluoroalanine is obtainable from hexafluoroacetone or trifluoropyruvates, but conveniently from 5-fluoro-2-phenyl-4-trifluoromethyloxazole (see also Refs. 165, 169, 515) by conversion into the 5-t-butoxy analogue and hydrolytic fission, a procedure that allows easy [2 – ^{2} H]-labelling.[203]

D-γγγ-Trichloro-allo-threonine, prepared from the oxazoline from N-benzyloxycarbonyl-L-serinal (*cf.* 41), gives D-allo-threonine by catalytic hydrogenation, a route suitable for preparing the ^{3}H-labelled amino acid.[204]

4.9 *Synthesis of Aliphatic α-Amino Acids Carrying Side-Chain Hydroxy Groups*

Stereoselective reduction of α-([ω]-oxo-alkyl) amino acids is a somewhat neglected route, and is given a useful stimulus in the establishment of methods illustrated in Scheme 22, for γ-hydroxy-compounds.[205] Alternatively, αβ-dehydro-α-amino acids are appropriate starting materials for these targets, demonstrated with an improved route to (2S,4R)-4-hydroxyornithines.[206]

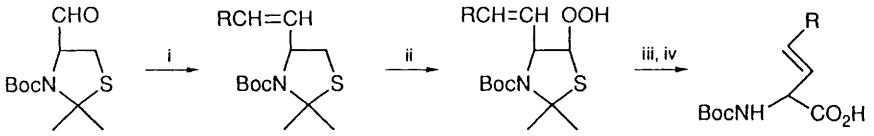
DL-5,5′-Dihydroxyleucine and it 4-fluoro-analogue have been prepared by alkylation of the Schiff base $Ph_2C{=}NCH_2CO_2Et$ with 2,2-dimethyl-5-iodomethyldioxan and the corresponding 6-fluoro-compound.[207] Alkylation of diethyl 2-acetamidomalonate by the same compounds was not so satisfactory.

4.10 *Synthesis of Aliphatic α-Amino Acids Carrying Unsaturated Side-Chains*

As seen in the immediately preceding Section, and elsewhere in this Chapter, alkenyl amino acids are valuable in synthesis and show potential as biologically-active compounds.

Synthesis of βγ-unsaturated amino acids,[208] and synthesis of α- and γ-amino acids containing an acetylenic moiety,[209] have been reviewed.

αβ-Dehydroamino-α-amino acids have been prepared by the time-honoured aldol condensation method, illustrated with the unusual sub-

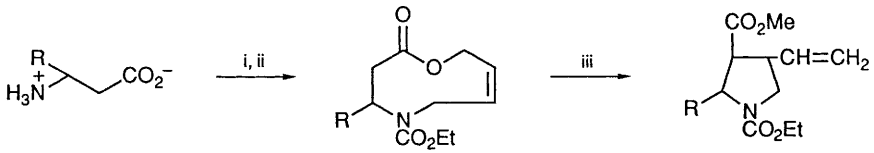


(46)

Reagents: i, Wittig reaction; ii, O_2/*h* v, *meso*-tetraphenyl porphyrin;
iii, Ph_3P reduction (–OOH → –OH); iv, LiOH

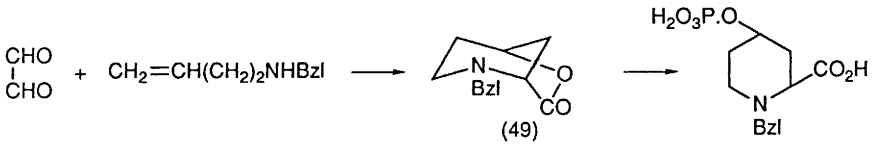
Scheme 23

(47) (48)



Reagents: i, $ClCO_2Et$; ii, (*Z*)-$ClCH_2CH{=}CHCH_2OTHP$;
iii, excess LDA, TBDMSCl, THF/–100 °C

Scheme 24



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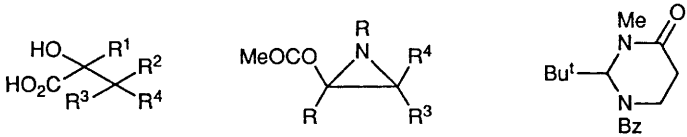

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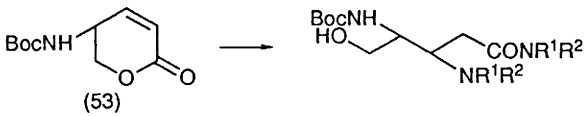

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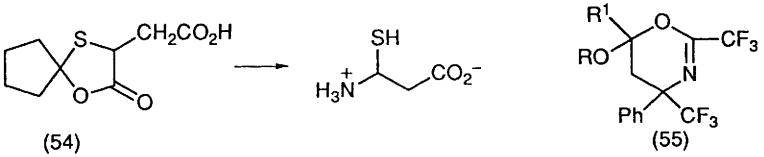


(54) (55)

strate $(HCO)_2NCH_2.CO_2Et$ which requires a strong base (NaOEt in EtOH) for the purpose when benzaldehydes are used.[210] A mixture of (E)- and (Z)-dehydro-compounds is obtained on working up the products of radical bromination (N-bromosuccinimide; there are several examples of this reaction in the year's literature[427,496,497]) of phthaloylphenylalanine t-butyl ester.[211] X-Ray crystal analysis was used to assign stereochemistry to the separated products.

Regioselective α-amination of di-anions of αβ-unsaturated alkanoic acids has been established, employing $H_2N.O.PPh_2$; yields of αβ-dehydro-amino-α-amino acids are modest.[212] The special case situation of L-DOPA is shown in many of its properties covered elsewhere in this Chapter, and in the present context too; the N-acetyl ethyl ester derivative gives the αβ-dehydro-analogue with $NaIO_4$ or with catechol oxidase, through rearrangement of the initially-formed dopaquinone.[213]

Vinylglycine enantiomers are available through effective stereo-selective routes, from the (R)- or (S)-serinal derivative (41), already found to be a valuable synthon in other contexts (Sections 4.5, 4.9, and 4.15),[214] or from the cysteinal analogue (46).[215] Wittig elaboration of (41) gives alkenes that are converted oxidatively into the D-vinylglycines. Similar treatment of the sulphur analogue (46), followed by photo-oxidation (O_2, meso-tetraporphyrin) then Ph_3P reduction to the hemithioacetal, gives D-βγ-unsaturated-α-N-Boc-amino acids (Scheme 23).[215]

Allylation of Schiff bases is also a feasible route, using a Pd catalyst with allylic carbonates, esters or halides,[216] or through Michael addition to 1-alkenes in the case of benzylideneamino nitriles.[217] In the former study, it was shown that the reaction could be biased to the extent of 70% in favour of one enantiomer when $Pd(OAc)_2$ – (+)-DIOP was used as catalyst.[216] N-Benzyl αα-divinylglycine ethyl ester was obtained in an application of the latter route.[217]

Two representative α-amino acids with γ-thioenol ether side-chains have been prepared through a Pummerer-type reaction with S-alkyl-homocysteines effected using N-chlorosuccinimide.[218]

4.11 *Synthesis of α-Amino Acids Carrying Aromatic and Heteroaromatic Side-Chains*

The routine nature of synthetic routes to near-relatives of the aromatic protein amino acids, is accounted for both by the effectiveness of standard methods of α-amino acid synthesis and by the simplicity of methods needed to create the aromatic side-chain precursor from which the α-amino acid is to be prepared. Some natural products in this category, however, offer more challenging problems (e.g. vancomycins,[154])

and examples of these, and of more routine work,[71,94,95,166] have been located elsewhere in this Chapter.

A review of fluorine-containing aromatic amino acids has appeared.[219] Direct fluorination is possible in some cases, e.g. m-tyrosine gives 2- and 6-fluoro-compounds in anhydrous HF;[220] this permits easy ^{18}F-labelling and further examples are collected in the later Section 4.15. DL-2′-Fluoromethyl- and -difluoromethyltyrosines have been prepared from 3,4-dimethylanisole through side-chain radical bromination and use of diethyl acetamidomalonate in the former case, and routine elaboration of ethyl 5-hydroxy-2-methylbenzoate, in the latter case.[221] Iodination of L-DOPA has been achieved through halogen replacement of the 6′-chloro-compound, prepared using $Cl(CH_2CH_2O)_2P^+(NMe_3)_2PF_6^-$.[222] 4′-Substituted phenylalanines are accessible from the N-Boc-4′-iodo-compound, *e.g.* 4′-aminomethyl-L-phenylalanine by Pd-catalyzed carbonylation, followed by oxime formation and catalytic reduction.[223]

Heteroaromatic side-chain creation and manipulation is also often challenging [*e.g.* preparation of D- and L-pyridylalanines from corresponding bromopyridines by Pd(0)-catalyzed substitution of N-acetyldehydroalanine methyl ester, followed by asymmetric hydrogenation,[224] and the 2-pyridiniomethyl-alanine (47) prepared by alkylation of a 5-methyl-2-t-butylimidazolidin-4-one (*cf.* Section 4.2).[225] Standard methods have been used to prepare β-(3-quinolinyl)alanine and its lysine analogue, and 3-pyridylcarbonyl-lysine (by alkylation of diethyl acetamidomalonate),[226] and the fluorescent amino acid, DL-2-amino-1-(7-methoxy-4-coumaryl) propionic acid.[227] The heterocyclic moiety has been built on to the amino acid framework in the cases of β-(4-thiazolyl)-L-alanine [from the L-aspartic-acid derived chloromethyl ketone (48) by Hantszch synthesis – condensation with thioformamide],[228] and of novel analogues of the pharmacologically-interesting β-(3-carboxyalkyl-isoxazol-5-yl)-alanines.[229]

Fischer indole synthesis of 7-fluoro-DL-tryptophan,[230] and routine alkylation methodology [1-hydroxytryptophan from methyl 1-hydroxyindole-3-acetic acid;[231] and 5-bromo-DL-tryptophan from 5-bromoindole and the bromoalanine Schiff base $HON{=}C(CH_2Br)CO_2Et$[232]] have been described.

4.12 *Synthesis of N-Substituted α-Amino Acids*

While this Section excludes peptides, it includes non-routine examples of side-chain N-acyl- and N-alkyl derivatives.

Easy methylation of the ring nitrogen atom in (S)-phthalimido- and -tritylamino -lactams derived from L-lysine and ornithine, has been established using MeI and Ag_2O in DMF.[233] Side-chain N-(α-halogenoacetyl)

derivatives (S)-$RCH_2CONH(CH_2)_nCH(NH_2)CO_2H$ R = Cl, Br, I; n = 1-3 have been prepared for study as enzyme inhibitors.[234] Synthesis of the same iodo-acetyl derivatives of ornithine and lysine (n = 3, 4 respectively) has been reported simultaneously from a different laboratory.[235]

A new synthesis of N^{im}-hydroxytryptophan has been published.[236] N-Amination of α-amino acids under mild conditions using N-methoxycarbonyl phenyloxaziridine offers a useful entry to new carbazates.[237]

4.13 *Synthesis of α-Amino Acids Carrying Phosphorus-Containing Side-Chains*

Organic synthesis is responding more noticeably to the biological importance of glycosylated, phosphated and sulphated side-chains. The enhanced response is also stimulated for other reasons, and has been significantly helped by simplified synthesis methodology.

Together with other examples collected elsewhere in this Chapter, current papers include cis-4-(phosphonoxy)-pipecolic acid (a conformationally-restricted potential antagonist of the NMDA subtype of the glutamate receptor), synthesized from N-benzyl but-3-enylamine and glyoxal through alkene – iminium ion cyclization and ring-opening of the resulting lactone (49).[238] (2R,3S)-β-(Phosphonoxyacetyl)pipecolic acid has been synthesised from N-(3-chloropropyl)-D-aspartic acid for the same purpose.[239]

4.14 *Synthesis of α-Amino Acids Carrying Boron-Containing Side-Chains*

This short new Section is introduced for the first time this year in this Specialist Periodical Report series. This is not intended to imply that these are in any way novel types of α-amino acid, but that their study continues to be recognized as offering useful biological rewards. Uneventful alkylation of the Schiff base $Ph_2C{=}NCH_2CO_2Me$ with 3-[2-methyl-1,2-dicarba-*closo*-dodecaborane(12)-1-yl]propyl iodide gives the corresponding carboranyl amino acid.[240]

4.15 *Synthesis of Labelled α-Amino Acids*

The topic has all the relevance and fascination in this year's literature, that has been illustrated in all recent Volumes of this Report. References are arranged in order of increasing atomic number of the substituting isotope.

^{2}H- and ^{13}C-Labelling of L-cysteine has been accomplished through tryptophan synthase-catalyzed condensation of L-[3-^{13}C]serine with toluenethiol.[241] The corresponding method with 1-^{15}N- and 2-^{13}C-indoles gives labelled tryptophans.[242]

$^2H_2$ or $^3H_2$-Solid-state labelling of amino acids by isotopic exchange

has been extensively studied recently, following a large number of similar earlier studies. Uniform labelling with 80-90% substitution is possible, with retention of stereochemical configuration.[243] The most recent of the Russian studies have concentrated on catalysis[244] and other parameters[245] involved in the $^3H_2$ version of the process, concentrating particularly on L-valine.[245] General $^3H - {}^1H$ exchange using a Pd catalyst with $^3H_2$ is also featured in a preparation of ^{3}H-α-amino-γ-butyrolactone, work-up with HBr-AcOH giving the hydrobromide of labelled α-amino-γ-bromobutyric acid as main product (57% yield) with 23% of the γ-hydroxy-analogue.[246] [4,4-^{3}H]-γ-Aminobutyric acid has been prepared from glutamine by Chloramine-T oxidation to the nitrile, followed by reduction with $^3H_2$.[247] A report on [3-^{3}H]-labelling of S-ribosyl-L-homocysteine has been published,[248] and stereochemical control has been exerted in syntheses of (5R)- and (5S)-[5-^{3}H]-L-ornithines, through crucial stages involving asymmetric reduction of $CH_2{=}CH(CH_2)_3C^3HO$ followed by Evans' azidation methodology,[249] and in a synthesis of [3-$^3H_3$]-L-threonine involving [$^3H_2$-Pd] tritiolysis of the trichloromethyl alcohol derived from the Z-D-serinal oxazoline [41; $CHO \rightarrow CH(OH)CCl_3 \rightarrow CH(OH)C^3H_3$].[250]

^{11}C-Labelling continues to provide valuable derivatives for diagnostic medical studies, but applications are limited by the need for deft organic chemistry in view of the short half-life of the isotope. $^{11}CH_3Cl$ has been used in a synthesis of labelled (R)-carnitine in this context.[251] An improved synthesis of [1,1′-$^{13}C_2$]-L-cystine from $Na^{13}CN$ includes *Aspergillus* acylase resolution.[252] Specific ^{13}C-labelling of each carbon atom is featured in the synthesis of [3-^{13}C]-, [4-^{13}C]-, [5-^{13}C]-, and [3,4-$^{13}C_2$]-2-oxoglutaric acids for use in the synthesis of correspondingly-labelled L-[^{15}N]glutamic acids.[253] Less spectacular are the syntheses of L-[1-^{14}C]phenylalanine (in seven steps from $^{14}CO_2$),[254] and of L-[^{14} C-methyl]-methionine, converted into the S-adenosyl derivative using methionine adenosyl tranferase and ATP in better than 90% yield with relatively high labelling efficiency.[255]

^{18}F-Labelling, referred to elsewhere in this Chapter,[220] is featured in syntheses of 4-[^{18}-F]fluoro-m-tyrosine by regioselective fluorodemercuration of the 4-trifluoroacetoxymercurio derivative using $AcO^{18}F$,[256] and of the isomeric L-[6-^{18}F]fluoroDOPA by the Schiff base alkylation route using similar methods applied to 6-nitroveratraldehyde, to synthesise the labelled 6-fluorobenzyl bromide.[257]

A new synthesis of N-bromoacetyl-[3′-^{125}I]3,3′5-tri-iodo-L-thyronine has been published.[258]

4.16 *Synthesis of β- and Higher Homologous Amino Acids*

Attention continues to be paid to gaps in synthetic methodology in this topic area, so that it can approach the level of sophistication established for the α-amino acids.

The chemistry of β-alanine has been reviewed.[259] Standard methods for the synthesis of β-amino acids exemplified this year for asymmetric synthesis, include addition of nitrogen nucleophiles to αβ-unsaturated esters.[260,261] The presence of baker's yeast achieves up to 60% enantiomeric excesses, enhanced further by the presence of cyclodextrin.[260] N-Lithio (R)-N-benzyl-α-methylbenzylamine adds highly diastereoselectively (better than 95% enantiomeric excess) to (E)-t-butyl but-2-enoate in giving (R)-3-aminobutanoic acid and (S)-β-tyrosine.[261] Efficient and practical syntheses of (R)-3-aminobutanoic acid starting from L-asparagine have been developed,[262] through elaboration of the derived N,N-dibenzyl-L-asparaginol methanesulphonate *via* the nitrile. D-Aspartic acid acts as starting material in a new synthesis of the β-amino acid ADDA, the chiral centres in the derived (4R,5S)-4-methyl-5-phenyloxazolidin-2-one (*cf.* Scheme 18) becoming the (8S)- and (9S)-chiral centres of the synthesis target.[263] Further syntheses in the general category of synthesizing one amino acid from another, include (2S,3R)-3-amino-2-hydroxy-4-(4′-hydroxyphenyl)butanoic acid from Boc-D-tyrosine methyl ester by DIBAL reduction to the aldehyde, and cyanohydrin formation and conventional elaboration,[264] and specifically deuteriated isoserines (50; $R^2 = NH_2$) by Curtius rearrangement of 3-deuteriated malic acid (50; $R^2 = CO_2H$), itself prepared through enzyme-catalyzed methods. Cyclization of an isoserine to the aziridine (51) creates a key intermediate in a versatile route to labelled D-amino acids.[265] An enolate Claisen rearrangement of a β-amino acid allyl ester shown in Scheme 24 has been used for β-proline synthesis.[266]

Examples of homochiral β-amino acid synthesis, building on methods established for α-amino acids, include homoallylamines prepared by addition of allylsilanes or -stannanes to O-pivaloyl-galactosylamine imines (*cf.* the arabinose analogue 25) catalyzed by $SnCl_4$,[267] alkylation of the homologue (52) of the well-established imidazolin-4-ones (Section 4.2) with high diastereoselectivity, and in good yields,[268] and BINAP-Rh(II)-catalyzed asymmetric hydrogenation of β-substituted (E)-β-acylamino-acrylic acids.[269] The Boc-serine-derived δ-lactone (53) undergoes highly diastereoselective 1,4-addition with amines combined with lactone aminolysis.[270]

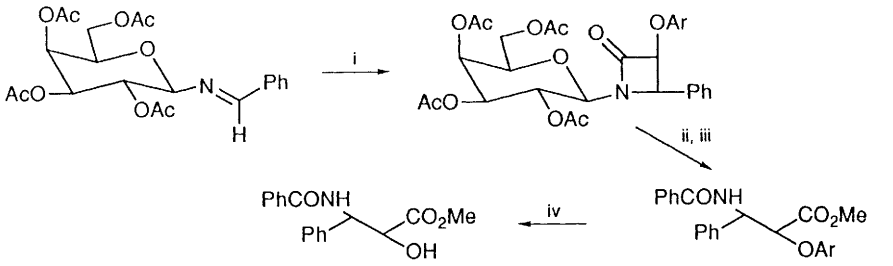
A general asymmetric β-amino acid synthesis exemplified by syntheses of natural β-leucine, β-lysine, and β-phenylalanine, involves

dipolar cycloaddition of nitrones to vinyl acetates, keten acetals and α-chloroalkenyl-nitriles.[271]

Methods reminiscent of standard α-amino acid syntheses are illustrated in a number of recent papers. Ammonolysis of 2-bromo-3-deoxy-D-threonic and -D-arabinoic acids to give 3-aminoalkanoic acids *via* 2,3-epoxycarboxamides.[272] The formation of isomeric α-amino acids is also a feature of this study. Curtius rearrangement of mercaptosuccinic acid oxathiolone (54) gives β-amino-α-mercaptosuccinic acid (*alias* isocysteine), isolated as its S-benzyl derivative.[273] The β-trifluoromethyl derivative of β-phenyl-β-alanine has been synthesized starting from $CF_3CPh{=}NH$, the Schiff base of trifluoroacetophenone, through N-trifluoroacetylation and addition to a vinyl ether to give the oxazinone (55) followed by hydrolysis with concentrated aqueous acid.[274] A chiral Schiff base is employed in an enantioselective Staudinger reaction to give β-lactams from which the corresponding isoserines are obtainable (Scheme 25).[275] A new homochiral β-lactam synthesis from a homochiral diazaborolidine is based on addition to simple Schiff bases as displayed in Scheme 26.[276] Birch reduction of homochiral N-Boc-phenylethylamines followed by ozonolysis and either decarboxylation (to β-amino acid esters) or β-lactam formation is shown in Scheme 27.[277] An alternative, familiar, way to create the carboxy group in the present context is represented in synthesis of 3-amino-2-arylpropanoic acids by N-pivaloylation and benzylic lithiation of 2-arylethylamines and their addition to CO_2.[278] N-Silylated enamines $MeCR^1{=}CHN(SiMe_3)_2$ are a source of 2-aminocyclopropane-1-carboxylic acid derivatives through cyclopropanation using methyl diazoacetate and $Rh_2(OAc)_4$.[279]

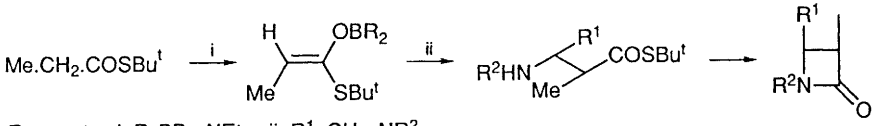
Pharmacologically-interesting β-amino acids are featured in recent synthesis studies, leading to β-proline analogues (agonists at the strychnine-sensitive glycine receptor) through azomethine ylide addition to methylpropiolate (Scheme 28),[280] *Rhodococcus equi*-mediated enantioselective hydrolysis of 6-azabicyclo[3.2.0]hept-3-en-7-one to give a precursor of the antifungal agent (+)-cispentacin,[281] and a synthesis of a series of GABA receptor-binding 2-(thien-2-yl)-3-aminobutanoic acids (56; X = S) and closely related heterocycles.[282] Points of methodological interest in these studies include an effective N-demethylation step in the β-proline synthesis (Scheme 28), using $ClCO_2CHClMe$,[280] and points of interest as far as biological activity is concerned are that 3-carboxy-3,4-dehydropyrrolidines (Scheme 28) are more active than any other isomer,[280] and that the 5-methyl- and 5-chloro-thienyl compounds were the most potent, and also specific for the $GABA_B$ receptor, from the series (56) studied.[282]

Within the γ-amino acid area, there is also considerable interest in



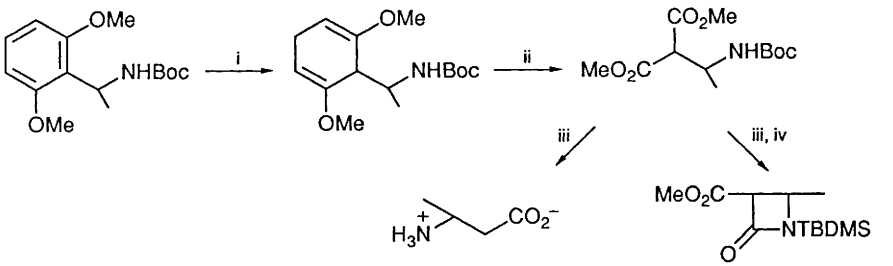
Reagents: i, $ArOCH_2COCl/NEt_3$; ii, H_3O^+, MeOH; iii, $PhCOCl/NEt_3$; iv, NH_4^+ cerium(IV) nitrate

Scheme 25



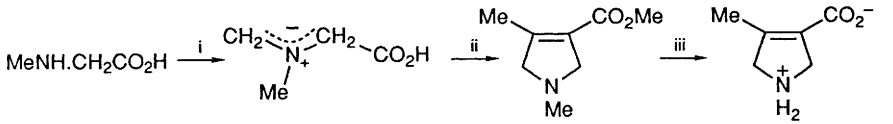
Reagents: i, R_2BBr, NEt_3; ii, $R^1.CH{=}NR^2$

Scheme 26



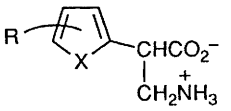
Reagents: i, $Na/NH_3/Et_2O/EtOH/-78$ °C; ii, O_3–EtOH then Pd–C/H_2/–78 °C; iii, deprotection, decarboxylation; iv, $LiN(SiMe_3)_2$, then TBDMSCl

Scheme 27



Reagents: i, paraformaldehyde; ii, $MeC{\equiv}CCO_2Me$; iii, $ClCO_2CHCl.Me$ and hydrolysis

Scheme 28



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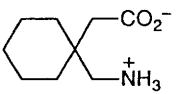


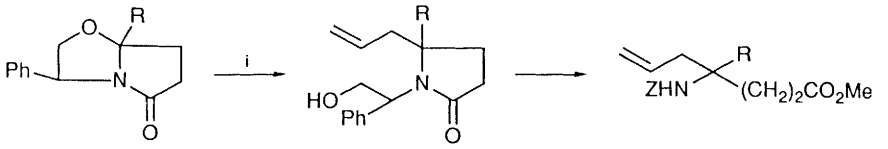
(57)

biologically active compounds. Gabapentin, the anticonvulsive 1-(aminomethyl)cyclohexaneacetic acid (57), is synthesized in a new way through addition of HCN to diethyl cyclohexylidenemalonate, followed by routine elaboration.[283] Other GABA analogues have been synthesized, including γγ-dialkyl homologues (Scheme 29) illustrating acetal alkylation with allyltrimethylsilane,[284] and both enantiomers of Baclofen [4-amino-3-(4-chlorophenyl)butanoic acid, which, unlike GABA, can cross the blood – brain barrier], prepared by α-chymotrypsin-catalyzed hydrolysis of prochiral dimethyl 4-chlorophenylglutarate di-esters to the mono-esters, followed by amination [$-CO_2H \rightarrow NH_2$ *via* azide (Curtius rearrangement), and $-CO_2Me \rightarrow CONH_2$].[285]

Dolastatin 10 components (3R,4S,5S)-dolaisoleucine and (2R,3R,4S)-dolaprine have been synthesized from an N-protected isoleucine (*via* the derived β-keto-ester $-CO_2H \rightarrow -COCH_2CO_2Bu^t$) and from N-Boc-L-prolinal [$CHO \rightarrow CH(OH)CHMeCOSPh$] respectively.[286] Several other studies extending the separation of amino and carboxy functions by similar means have been reported, particularly those based on β-keto-esters and using enzyme-catalyzed reduction of the ketone grouping. In this way, baker's yeast and (S)-Boc.NH.CHMe.CO.CH_2 CO_2 Me give the 3R-configuration required for elaboration into sperabillin and negamycin,[287] and the simplest example has been studied further – (R)- and (S)-GABOB from enantiomers of AcO.CH(CN).CH_2-CO_2Et through lipase-catalyzed kinetic resolution (*cf.* Vol 23, p.38).[287a] A different route to these β-keto-esters employs enolate alkylation by N-carboxyanhydrides, newly synthesized by the astonishing ring-expansion of 3-oxolactams (Scheme 30; see also Scheme 3).[288]

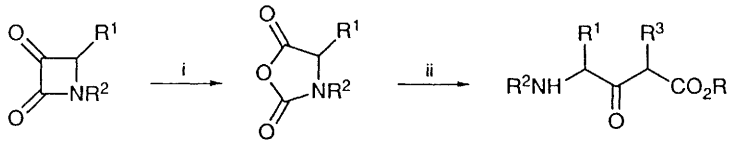
The statine group is of long-standing interest and although many syntheses have been described, still more are evidently in the pipeline. The continuing investigations in this area are of broader interest since light is cast on factors controlling stereoselectivity, especially since standard organic reactions of wide applicability are involved. The aldol condensation of silyl enolates $CH_2=C(OMe)OSiMe_3$ with homochiral aldehydes is better than 95% diastereoselective in the presence of $TiCl_4$, and (3S,4S)-statine and (3S,4S)-cyclohexylstatine have been obtained in this way from L-leucinal and L-phenylalaninal, respectively.[289] 2-Trimethylsilylethylidene triphenylphosphorane adds to Boc-amino aldehydes to give the Cram chelation-controlled product, successive hydration and oxidation of the ethenyl moiety of the adduct, to give a carboxy group providing N-Boc-statine in 36% overall yield from Boc-L-leucine.[290]

Alkylcuprate – BF_3 substitution of 5-methoxy or 5-phenylthio-groups from 4,5-disubstituted oxazolidin-2-ones with retention of configuration has been employed in syntheses of (3S,4S)-statine and (3S,4S)-



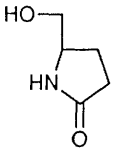
Reagents: i, described in text, and routine elaboration

Scheme 29



Reagents: i, *m*-chloroperbenzoic acid; ii, LDA, then $R^3CH_2CO_2R$

Scheme 30



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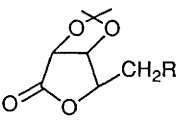

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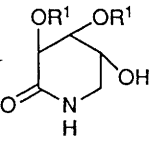

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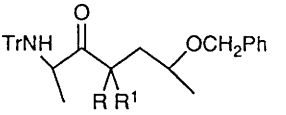

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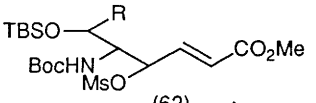

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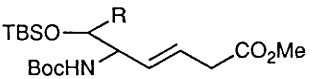

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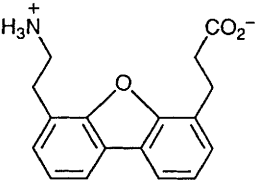

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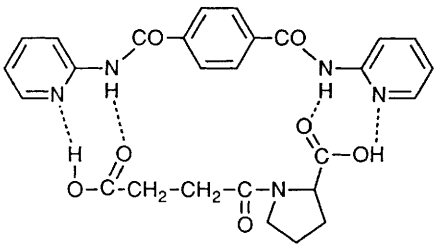

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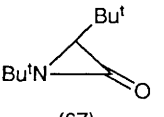

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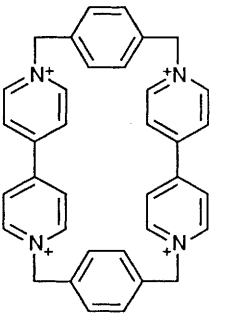


(66)

cyclohexylstatine.[291] Routes *via* these oxazolidinones prepared differently, have been a feature of recent studies (Vol.23, pp.36, 37).

(3S,4S)-Statine and (3S,4R)-statine have been prepared from (S)-malic acid, already used by Bernardi's group (Vol.23, p.34) involving allylation of an α-alkoxy N-acyliminium ion.[292] An "easy" synthesis of cyclohexylnorstatine (3-amino-4-cyclohexyl-2-hydroxybutanoic acid) from D-glucose involves an electro-oxidation and Baeyer-Villiger oxidation sequence.[293] 1,3-Dipolar cycloaddition of a chloronitrile oxide to N-allyl trichloroacetamides gives a diastereoisomer mixture that is not particularly biased (1.4 – 2.2:1) in favour of the stereochemistry of DL-statine.[294] The $C_{33} - C_{38}$ portion of the calyculins is a (2R,3R,4R)-2,3-dihydroxy-4-dimethylamino-5-methoxypentanoic acid residue, and is thus closely related to the statines. Syntheses, incidentally verifying the assigned stereochemistry, have been based on building-up the serine oxazoline (41),[295] and on the pyroglutamate-derived hydroxymethyllactam (58).[296]

δ-Amino acids and higher homologues are generally accessible through standard organic synthesis methodology, as opposed to the particular methods that are recognizable to the protein amino acid chemist. D-Ribonolactone is a convenient starting material for a synthesis of (2R,3R,4R)-5-amino-2,3,4-trihydroxyvaleric acid (60),[297a] employing the key azidation step (59; R = OH→59; R = N_3 in several steps→60) so frequently used in bridging from the carbohydrates across to the amino acids [see also a synthesis of natural trans-5-hydroxypipecolic acid from (S)-5-hydroxy-2-piperidone by the same group,[297b] using the acyliminium ion method[cf.292]]. D-Ribose has been elaborated into the δ-amino acid corresponding to (59) with one fewer OH groups, after reaction of its 5-O-methanesulphonate with NaN_3.[298] Other 2,3-dideoxymonosaccharides can be manipulated in this way, a synthesis of N-Boc-O-benzyl-(4S,5S)-5-amino-4-hydroxy-6-phenylhexanoic acid being crucially dependent upon selective protection of the secondary and anomeric hydroxy groups so that azidation at the C-6 hydroxy group could be accomplished.[299] A lactone almost identical with the above-mentioned lactone (59; $NHCPh_3$ in place of OH) has been prepared from L-phenylalanine for synthetic studies in this area, through the transformation – CO_2Me→-$COCH_2$ P(O)$(OMe)_2$ followed by isopropylidenation, and ring closure.[300] Further connections with statine syntheses are noticeable in this and in a number of other syntheses of higher homologues starting with α-amino acids, such as aldolization of the phenylalanine-derived aldehyde based on (41) with $^iPrCH{=}C(OSiMe_3)SBu^t$,[301] and aldolization of a protected prolinal [reversal of stereoselectivity was observed in this case, compared with experience in the same method applied in a dola-

proine synthesis,[302a] and is ascribed to the use of excess dibutylboron triflate and NEt_3].[302b] Alkylation of diethyl 2-substituted malonates with the chloromethyl ketone derived from a protected ornithine,[303] alkylation of N-t-butyl-D-alanine pyridylthioester with (R)-1-bromopropan-2-ol benzyl ether, giving (61) for further elaboration,[304] and reduction with alkenylcopper reagents $MeCu(CN)Li.BF_3$[305] and $(vinyl)_2Cu(CN)(MgCl)_2$,[306] of δ-amino-γ-methanesulphonyloxy-αβ-enoate esters, (62)→(63)[306] have also been reported.

Full details are available[307] of support by synthesis of the revised structure of galantinic acid, a component of galantin I previously assigned a tetrahydropyran structure now shown to be readily formed from the now-established open-chain structure (see also Vol.23, pp.40,41).

An example of the synthesis of an amino acid with considerably greater separation of amino and carboxy functions, is offered by the compound (64), prepared from the corresponding dicarboxylic acid (from di-iodobenzofuran) through a route employing conversion of the corresponding mono-ester into the t-butyl carbamate with $(PhO)_2P(O)N_3$ and t-butanol.[308] Development of synthetic routes to handle such a separation of functional groups is relevant for residues in some antibiotics but particularly in syntheses of protein cross-linking moieties and their peptide models.

4.7 *Laboratory Resolution of DL-Amino Acids*

All the classical methods for resolution of racemic amino acids in the laboratory, are represented in the recent literature: separations based on diastereoisomer formation and on eutectic phenomena; on enantioselective reactions; and on chromatographic interactions. The last-mentioned category has both preparative and analytical aspects and papers dealing with the latter aspect are mostly covered in later Sections of this Chapter.

Conventional diastereoisomeric salt formation, e.g. between (RS)-2-phenylglycine and (S)-10-camphorsulphonic acid, is accompanied by asymmetric transformation in favour of one enantiomer, when the mixture is allowed to equilibrate in an alkanoic acid solution at 100°.[309] A "replacing crystallization" phenomenon (favoured crystallization of the L-enantiomer) is illustrated for solutions of ammonium salts of N-acetyl-DL-butyrine, norvaline, and norleucine in the presence of ammonium N-acetyl-L-alaninate.[310] Seeding with L-threonine gives optically-impure crystals from a melt of the racemate due to co-crystallization of the D-enantiomer at the crystal surface.[311]

Numerous examples of enzyme-catalyzed "resolution" have appeared in the recent literature for the amino acids area (e.g. papain,[40]

lipase,[41] and α-chymotrypsin[55]), and the topic has been reviewed.[312] Rates of α-chymotrypsin-catalyzed ester hydrolysis differ for (Z)- and (E)-isomers of N-benzoyldehydrophenyalanine methyl ester, with the (Z)-acid predominating in reaction mixtures approaching completion.[313] Urethane protecting groups cause a drop in the selectivity of this process.[313] A new acylase, from *Comamonas testosteroni*, has been used for enantioselective hydrolysis of N-acyl-DL-amino acids;[314] a study of immobilized enzymes for the corresponding role in the resolution of β-(1- and -2-naphthyl)alanines has been reported.[314] Moderate enantiomeric excesses are recorded for the overall process of accumulation of D-ureido acids from hydantoins of L-α[ω]-di-amino acids incubated with *Agrobacterium radiobacter*.[315]

Increasing interest is being shown in resolutions employing chiral chromatographic techniques, a subject endowed with potential commercial reward like others applicable for the resolution of amino acid racemates. Pirkle chiral stationary phases (CSP's) are well established in chromatographic resolutions, and research papers continue to record improvements in their efficiency. A review has appeared in a Symposium Volume.[316] The CSP based on N-(1-naphthyl)-D-leucine has been evaluated for the resolution of N-(3,5-dinitrobenzoyl)-DL-leucinamides,[317,318] and shows improved performance compared with N-(2-naphthyl)-D-alanine.[317] The principle is used the other way round, for the resolution of N-acetyl-DL-leucine 2-naphthylamides over an N-(3,5-dinitrobenzoyl)-L-leucine-based CSP.[319] Interactions involved have been studied, in an attempt to rationalize chromatographic elution order, through collecting physical data (including X-ray analysis) for 1:1-(S,S)- and 1:1 (R,S)-co-crystals of N-(3,5-dinitrobenzoyl)leucine N-methylamide as an analogue of the stationary phase. The spacer groups, typically long-chain aliphatic α,[ω]-diols, connecting the chiral selector group with the inorganic supports, are important in the process, as are the N-protecting groups on the amino acid moiety.[320] Four new CSP's of general form N-(3,5-dinitrobenzoyl)-L-tyrosine[-$(CH_2)_3$ X$(CH_2)_3$ Y-]NHMe have been evaluated for amino acid enantiomer recognition.[321]

Studies employing related principles are featured in separation of DL-N-(2,4-dinitrophenyl)amino acids over a β-cyclodextrin-bonded stationary phase,[322] similar application of crown-ether-bonded columns,[323] and uses of synthetic polymers imprinted through having a derivative of an enantiomer of an amino acid present from the start of the polymerization, and washed out from the polymer at the end (see Vol.23, p.43).[324] Ligand-exchange chromatographic techniques also offer chiral discrimination possibilities, shown in a multi-gram scale resolution of DL-amino acids[325] and in an analytical scale application, monitoring of

the production of L-alanine from DL-aspartic acid by *Pseudomonas dacunhae*.[326] A standard technique, exemplified in resolution of chiral β-amino acids,[327] uses N-dodecyl-hydroxy-L-proline bonded to C-18 silica with a copper(II) acetate buffer, but there are numerous variations of this protocol. Thus, copper(II) acetate and 5′-guanosine monophosphate or cyanocobalamin have been shown to effect resolution of DL-^{3}H-labelled α-amino acids,[328] and copper(II) salts of ribonucleic acids have been used as components of the mobile phase.[329] This last-mentioned study was stimulated by the possible role of homochiral polynucleotides in bringing about the dominance of L-amino acids from prebiotic times, an aspect of resolution featured in the next Section of this Chapter. This explains why there are certain other unexpected aspects to this study, such as the discovery that DNAs work as well as RNAs in this respect, and that L-amino acids seemed to give more stable complexes since they were eluted more slowly than their D-isomers.

4.18 *Models for Prebiotic Enantioselection Relating to α-Amino Acids*

This topic, formerly located within the preceding Section, has strongly established strands of enquiry, and is now given its own identity within this Chapter.

A major prerequisite for a quantum physics background might appear necessary, in coming to terms with currently-discussed models accounting for the discrimination in the contemporary biosphere in favour of L-enantiomers of α-amino acids. However, the basis of the electroweak theory (3×10^{-19} eV energy difference between D- and L-enantiomers due to parity violation) is relatively accessible to all, and has been authoritatively reviewed,[330] even if it is not accepted by all.[13] From this starting point, a specific enhancement factor (i.e. a phase transition into a condensed Bose mode) has been proposed.[331] This, with co-operative and condensation phenomena, could give rise to second-order phase transitions (including equilibration of D-isomers into their L-counterparts) below a critical temperature T_c. This would provide a novel amplification mechanism to transform racemic amino acids into their L-enantiomers. This offers a target, the determination of T_c, that might be the subject of experimental study,[332] though it is considered[331] that the value for T_c might be too low plausibly to account for the occurrence of the process on planet Earth.

The two strands – how did the first small stereochemical bias arise? how did this become amplified? – continue to be fertile fields for speculation and controversy involving different areas of science, and do not depend on the ever-more-enclosed quantum mechanical debate. Long-running theories, all based as they must be on indisputable factors in the

prebiotic environment, continue to be put forward in new forms. It has been suggested[333] that in the course of a day, the planet's surface is bathed in sunlight with a slight predominance of left circularly-polarized light in the morning. In the afternoon, the predominance switches to right circularly-polarized light and because the temperature on the planet's surface is now higher on average than in the morning, chemical reactions will proceed faster (including the destruction of the D-enantiomer within samples of racemic amino acids). The related theory, in which radiolytic or electromagnetic radiative destruction of one enantiomer is proposed to be greater than that of the other, has featured in another new contribution to the debate. Since bi-molecular interactions between two like enantiomers might be such as to suppress their photodegradation, while interactions between opposite enantiomers are likely to be at some different level, there should be a consequence in the selective destruction of one enantiomer faster than the other.[334] This has aspects reminiscent of the respected Frank mechanism (spontaneous chiral selection; see Vol.22), which has now been extended to allow for the racemization that might accompany any amplification mechanism[335] – whether any amplification might be extinguished, or enhanced, as a result of racemization, depends on relative rate constants.[335]

5 Physico-Chemical Studies of Amino Acids

5.1 *X-Ray Crystal Structures*

Familiar amino acids and simple compounds derived from them continue to be subjected to X-ray crystal structure determination, because information on their solid-state structures is relevant in a number of contexts, including the behaviour of heterogeneous systems incorporating amino acids.

Single crystal X-ray analysis of L-alanine has been interpreted to give its total electronic charge density at 23K.[336] More routine motives (solid-state conformations, especially of side-chains) lie behind X-ray studies of DL-histidinium dinitrate,[337] L-lysinamide dihydrochloride,[338] calcium bis-L-pyroglutamate and lithium L-pyroglutamate,[339] N-acetyl-DL-alaninamide and N-acetyl-DL-leucinamide,[340] N-benzoyl α-hydroxymethyltyrosine,[341] and α-hydroxymethyl aspartic acid.[342] In the two last-mentioned cases, assignment of absolute configuration [(+)-isomers have the R-configuration] was the objective, as was the case in an X-ray study of methyl (2R,3S)-N-benzoyl-3-phenylisoserinate.[343] Thialysine hydrochloride[344] provides a further example outside the immediate protein amino acid family.

5.2 *Nuclear Magnetic Resonance Spectrometry*

Proton n.m.r. studies of a non-routine nature concern the interpretation of $^{1}H - {}^{1}H$ coupling constant data for serine, cysteine, and selenocysteine in every conceivable protonation state,[345] and a similar objective for thiazolidine-4-carboxylic acid, assisted by i.r., Raman, and ^{13}C-n.m.r. data.[346] ^{1}H-, ^{13}C-, and ^{17}O-N.m.r. data have assisted X-ray structural studies of calcium L-pyroglutamate.[339] Solid-state high-resolution ^{1}H-n.m.r. of glycine, alanine, N-acetylglycine, and histidine hydrochloride using CRAMPS reveal characteristic line shapes for ^{1}H bonded to ^{14}N, explained by ^{14}N quadrupole effects on $^{14}N - {}^{1}H$ interactions.[347]

Absolute configurational assignments dependent on ^{1}H-n.m.r. measurements have been reported for methyl (S)-(+)-mandelate esters of N,N-dimethylamino acids,[348] confirmed with interpretation of corresponding data for p-nitroanilides of these amino acids in chiral solvents. A modified Mosher method has been developed further, in which shift values for protons in N-(2-methoxy-2-phenyl-2-trifluoromethyl)acetyl derivatives of amines and amino acid esters are determined. A putative extended conformation for these derivatives[349] (CF_3 coplanar with the carbonyl of the chiral acyl group) for chiral amine derivatives of known configuration accounts for consistencies seen in shift values, and establishes a method for configurational assignments that requires less than 0.1 mg of an amino acid. The n-butylamide of (S)-2-(phenylcarbamoyloxy) propionic acid is a suitable chiral solvating agent for determining the enantiomeric composition of N-(3,5-dinitrobenzoyl)amino acid methyl esters.[350]

^{2}H-N.m.r. combined with m.s. data have been used to assess isotope distribution at different locations within amino acid molecules.[351] Glutamic and aspartic acids, alanine, proline, and lysine from different origins show wide variations. ^{13}C-N.m.r. data for aqueous solutions of L-lysine together with a chiral lanthanide shift agent, confirm the adoption of an extended conformation.[352] At a more sophisticated level, ^{14}N – dipole-coupled ^{13}C-n.m.r. powder spectra have been interpreted to give the ^{13}C chemical shift tensor for the indole C-2 in tryptophan.[353]

^{17}O-N.m.r. line widths for carboxy groups of protein amino acids in ^{17}O-enriched water establish the relative hydration numbers for their cationic, anionic, and zwitterionic forms.[354] ^{19}F-N.m.r. data have been determined for diastereoisomeric inclusion complexes formed between fluorinated amino acid derivatives and α-cyclodextrin.[355]

5.3 *Optical Rotatory Dispersion and Circular Dichroism*

Routine spectropolarimetry underpins a study of the dependence of optical activity on structure for L-cysteine, L-histidine, and L-tyrosine.[356]

Chiral aggregates are concluded to be formed in ethanol solutions of N-octadecanoyl-L-glutamic acid, since the positive c.d. feature at 215 nm is replaced by a negative feature at 205 nm in aqueous sodium dodecylsulphate solutions of the same solute.[357] An ordered structure is also claimed for N-acetyl-L-prolyl-D-alanine methylamide in 2,2,2-trifluoroethanol.[358] A more targeted approach is seen in establishment by c.d. of aggregation phenomena involving the L-alanine amphiphile $H_2O_3P(O)$-$(CH_2)_5$-O-p-(C_6H_4)-N=N-(p-C_6H_4)-CO-NH-CHMe-CO-O-$(CH_2)_{11}$Me.[359] A particular feature of interest in this last-mentioned study is the helical bilayer membrane-forming propensity shown by this derivative.

Raman optical activity spectrometry is developing steadily into a technique where the collection of high quality spectra is a routine matter, a point made in a paper dealing with L-alanine.[360]

5.4 *Mass Spectrometry*

The electrospray technique dominates the current non-routine literature in this area, with much remaining to be discovered so as to clarify the physical basis of ionization achieved in this way. As a contribution to this problem, the establishment of a relationhip between log (relative intensity) for ions of protonated amino acid molecules and their standard hydration free energies, is consistent with the ion evaporation theory.[361] A later paper from the same workers[362] modifies the relationship to the difference between hydration free energies and gas-phase binding free energies. Comparison of the atmospheric pressure spray and electrospray techniques has been reported for glycine.[363] While intense ions in the molecular ion region are seen in the spectra for glycine from both methods, atmospheric pressure spray leads to $[M + Na]^+$, $[M + K]^+$, and $[M + H]^+$ ions while electrospray yields only $[M + H]^+$ ions. Electrospray techniques offer several useful advantages over classical ionization techniques for amino acids and peptides,[364] but may give charged clusters; ion masses corresponding to up to 24 molecules have been recorded for arginine.[365]

Positive ion chemical ionization mass spectra of didehydroamino acids give more satisfactory results than those from other conventional ionization modes, and are suitable for structure assignments.[366]

Chemical ionization (isobutane) mass spectra of cyclic D- and L-α-amino acids derivatized with homochiral reagents make interesting comparison.[367] Characteristic ions for diastereoisomers of one configurational type consistently appear to be more abundant in mass spectra, and this opens up a use of mass spectrometry for assignment of absolute configuration using derivatives well-known for this purpose employing

spectrometric techniques based on absorption of electromagnetic radiation.

5.5 *Other Spectroscopic and Related Studies*

Infra-red studies with a traditional objective have established intermolecular hydrogen bonding in Boc-glycine N,N-dimethylamide through its influence on amide absorption features.[368] More sophisticated u.v.-resonance Raman studies applied to N-acetylamino acid amides[369,370] and prolinamides[371] continue to develop new structural insights, including a revision of long-standing dogma that the position of the amide II′-like band is diagnostic of the cis:trans ratio for the amide bond in proline derivatives.[371] A new u.v.- resonance Raman technique used to determine relative Raman intensities as a function of the refractive index of the liquid medium has employed N-acetyl-L-tyrosinamide for comparison purposes.[372] Raman spectra of [N-^{2}H]-labelled histidine salts and C-2 – ^{2}H analogues have shown their usefulness for assessing parameters of hydrogen-bonding in the solid state,[373] information that is potentially transferable to hydrogen-bonding interactions in proteins.

L-Phenylalanine and its methyl ester, derivatized with the nitroxyl spin label 2,2,5,5-tetramethyl-1-oxypyrroline-3-carboxylic acid, yields ENDOR spectra interpreted in terms of conformational details.[374]

Electron diffraction data provide a more traditional basis for gas-phase conformational information, applied to DL-alanine (a unique conformation for the neutral tautomer)[375] and to glycine (a planar structure with OH and NH_2 groups in an anti-relationship).[376]

5.6 *Physico-Chemical Studies*

What might be called 'the thermodynamic properties of wet amino acids' have obvious biological interest since that is one of the normal viewpoints taken *in vivo* by nearby molecules, small and large. It is a growing topic area for this reason, and also because valid data are easily acquired with simple apparatus. Studies of amino acids in homogeneous media include the simplest solubility studies, e.g. of domoic acid,[377] highly relevant information because this proline derivative is a seasonally-dangerous marine toxin (this background is fully described in Ref.179). Solvation of amino acids and small peptides has been reviewed.[378] Hydrogen-bonding pairing (65) involving N-succinoyl L-proline,[379] is revealed by the 32-fold alteration of the amide cis:trans ratio after presentation of the hydrogen-bonding partner. Dissociation constants for valine and norvaline[380] and the corresponding data for the alanine zwitterion together with thermodynamic parameters,[381] have been determined by conductimetric methods; thermodynamic aspects have also been the

primary interest in related calorimetric studies of acid-base reactions in solutions of DL-threonine,[382] and of N-protonation of histidine and other imidazoles.[383]

Determinations of partial molar heat capacities and partial molar volumes,[384] and of enthalpies of interaction,[385] for N-acetylamino acid amides, are accompanied by enthalpies of dilution studies of N-acetyl derivatives of sarcosine and N-methylalanine amides.[386] The last-mentioned topic area has its own fascination in establishing chiral recognition phenomena by continuing studies[387] of ternary aqueous solutions containing two different aliphatic amino acid derivatives of the same or different chirality (see Vol.23, p.49).

A different principle is involved in a study of proton transfers involving amino acids in aqueous solutions using ultrasonic velocity and absorption data.[388]

Strong inclusion complexes are formed in aqueous solutions between amino acids such as DL-tryptophan or DL-tyrosine, or to a lesser extent, DL-phenylalanine, and the rigid cyclophane (66) carrying two acceptor paraquat groups facing each other.[389] The binding constants are two orders of magnitude greater than those involving simple electron acceptors such as methylviologen. Heterogeneous systems are represented in partition and distribution coefficient measurements for amino acids in 1-octanol – water,[390] and transfer free energies of ionic amino acid derivatives (of aspartic and glutamic acids, lysine and arginine) in the same medium.[391] From such distribution coefficient data it can be inferred that amino acids are transferred as their hydrates, from aqueous media into lipid phases.[392]

A similar, and equally important inference,[393] has been drawn, based on comparisons of water-to-vapour and water-to-cyclohexane distribution coefficients for N-acetylpyrrolidine and N-butylacetamide. Proline residues in simple N-acyl amides including peptides and proteins must be taken to be much more hydrophilic than is generally believed.

Amino acid hydrochlorides are well transported through thin sheet supported liquid membranes (polysulphone, polyacrylonitrile, or polyethylene as support in the form of hollow fibres; and long chain alkanols and a choice from various crown ethers to form the membrane).[394] Partition studies of amino acids in micro-emulsion droplets (reversed micelles) have been described, revealing amino acids to have co-surfactant properties.[395] Stable monolayers at the air-water interface, capable of specifically binding amino acids, are formed by long chain alkyl derivatives of Kemp's acid.[396] Monolayer-forming amphiphilic amino acid esters $Me(CH_2)_{17}CH(NH_2)CO_2\,CH_2R$ ($R = Ph$ or $CHCl_2$) must exist in an ordered state since rates of self-condensation to give peptides occur at

much faster rate in the monolayers compared with the process in non-ordered media.[397]

Solid state studies deal with the adsorption of phenylalanine and tyrosine on to activated carbon from water at various pH,[398] and the measurement of latent heat of melting of the oxygen adduct of the eutectic compound formed between NaCl and water in the presence of an L-amino acid (leucine, threonine or aspartic acid).[399] It is puzzling to consider that the value obtained is 5KJ mol^{-1} NaCl lower than that found when a D-amino acid is present.

5.7 *Molecular Orbital Calculations*

The mainstay for this Section over the years continues to be the application of various self-consistent field models to N-acylamino acid N-methylamides.[400-405] However, an authoritative review has now highlighted both the efficiency and limitations of these compounds as models of protein segments, and therefore the limited relevance that such calculations might have in the conformational analysis of peptides.[406] Among the research papers, specific objectives include study of N-alkylamino acid derivatives,[400,401] comparison of hydrated and non-hydrated states from the point of view of changes in free energy and hydration free energy,[402] and consideration of statine as a peptide component.[403]

Calculations relating to the underivatized amino acids have appeared for solvates of zwitterionic glycine, alanine and proline,[406] for five plausible conformations of glycine,[407] and for various models for the interaction of an amino acid with a helical structure.[408] Of course, the latter initial study can only scratch the surface as far as the multitude of possibilities is concerned, but has already shown some features of interest in terms of chiral discrimination related to the geometry of the amino acid alignment within the helix cavity. A less obscure basis is shown by calculations for complexes formed between (S)-methyl N-(2-naphthyl) alaninate and enantiomers of N-(3,5-dinitrobenzoyl)leucine n-propylamide, since they are models for putative interactions occurring on Pirkle CSP's used in chromatographic resolution.[409]

An interesting development in this topic area is the broadening of conformational calculations to compounds resulting from isosteric replacements, and the dithio-acid analogue of N-formylglycine is one such compound.[410]

6 Chemical Studies of Amino Acids

6.1 *Racemization*

There is little to report this year, on the application of amino acid

enantiomer ratios for dating relatively young fossils and similar formerly-living materials, though the subject has been reviewed,[411] and last year's review[412] gives an account of some relevant and extraordinary applications of the method.

Research papers describe long-running mechanistic interests in aldehyde-catalyzed racemization, of proline and pipecolic acid,[413] and of a series of amino acid esters.[414] In the former study, it was shown that solvent acidity affects rates, with higher acidity suppressing racemization,[413] while an unexpected rate enhancement was seen in the other study,[414] and explained to be a consequence of immobilizing of the pyridoxal used as catalyst.

Racemization of pentachlorophenyl esters of amino acids accompanying their use in dipeptide synthesis has been shown to be less than that of corresponding p-nitrophenyl esters.[415] A curious fact that may modify current theories of causes of racemization in reactions of N-protected amino acids, is the optical purity of N-acylureas formed as side-products when dicyclohexylcarbodi-imide is used in peptide synthesis to give partly-racemized peptides.[416]

6.2 *General Reactions of Amino Acids*

This, and the following Section, divide the discussion of reactions of amino acids roughly into: reactions mainly involving amino and carboxy groups (this Section), and reactions mainly involving side-chains (next Section).

Processes causing degradation of amino acids include irradiation by 3KeV helium ions (gradual carbonization of glycine monitored by i.r. spectra)[417] and thermal self-condensation.[418] The latter topic is gaining more momentum because, as well as its 'origins of life' connection, it is becoming clear that there is no uniform pattern of thermal behaviour among protein amino acids, and because mixtures of amino acids are somewhat selective in the range of peptides they form under thermal conditions. Thus, a methionine-phenylalanine bond is not formed in condensation products from mixtures containing these and other amino acids, judging by Edman degradation of cyanogen bromide-cleavage products.[418] Metal ion catalyzed self-condensation occurs under mild conditions in aqueous solutions, glycine giving mixtures of di- and tri-glycine,[419] and alanylglycine predominates in glycine – alanine mixtures containing copper(II) salts.[420] Glycine slowly forms its cyclic dimer, 2,5-dioxopiperazine, when in aqueous solution in the presence of urea,[421] and if alanine is also present, the aminolysis product glycylglycylalanine is formed. De-amination and decarboxylation of glycine ($\rightarrow NH_3 + CO_2$) occur in aqueous solutions containing pyrogallol, a process that is

accelerated strongly by the presence of a mineral, e.g. calcium nontronite.[422]

Further details are available (Vol.23, p.53) of the preparation of quaternary ammonium salts of amino acids, which should be of considerable value in synthesis.[423]

Reactions at the amino group involving simple processes can be followed by further transformations in the special case of α-amino acids. Kinetics of chlorination of aliphatic amino acids, represented by alanine and valine, have been studied;[424] the process leads to N-chloro- and N,N-dichloro-derivatives that decompose to give aldehydes and nitriles. Independently, N-chlorination of proline and hydroxyproline,[425a] and kinetics of the decomposition of the derivatives has been studied, and the same workers have applied themselves to the kinetics of decomposition of N-bromoleucine and N-bromoisoleucine.[425b] Diazotization of (S)-tert-leucine is followed by conversion into the α-chloro- and -hydroxy-acids, as expected, but then successively into the acid chlorides and α-chloro-amides which are sources of the elusive α-lactams, e.g. 67, through treatment with Bu^tOK.[426] Small amounts of N-t-butyl-tert-leucine t-butyl ester also appear among the products.

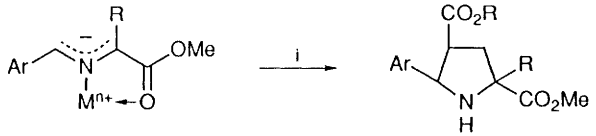
Radical N-methylation of Boc- and phenyloxycarbonylamino acid methyl esters is achieved in 47 – 57% yields using t-butyl perbenzoate in the presence of copper(II) octanoate (Boc-valine methyl ester does not react).[427] More conventional processes are reductive benzylation of amino acids and esters using benzaldehyde and sodium hydrotelluride,[428] and Eschweiler – Clarke N,N-dimethylation using $HCHO/HCO_2H$.[429,430] These latter reports concern unexpected reaction products with β-alanine (N,N,N-trimethylation to give the betaine[429]) and describe fragmentation products formed with polyamines.[430] In contrast with these thwarted alkylation processes, an unintended N-methylation, with some N,N-dimethylation, has occurred during hydrogenolytic deprotection operations of threonine derivative in MeOH-AcOH.[431] N-(1-Ethoxycarbonyl)-1-acetonylation of amino acid esters can be effected by their NEt_3-catalyzed addition to $HO.CHMe.C{\equiv}C.CO_2Et$ and its homologues.[432] Improved N-protecting group protocols have been reported for N-benzyloxycarbonylation of γ-benzyl glutamate and β-benzyl aspartate as their O,N-bis(trimethylsilyl) derivatives, using Z-Cl and N-methylmorpholine,[433] for preparing 4-azidomethyleneoxy-Z-protected amino acids,[434] and for polymeric reagents for 3,5-dinitrobenzoylation[435] and for the introduction of Fmoc, 4-nitrobenzoyl, and acetylsalicyloyl groups.[436]

Photolysis of N-2,4,6-trinitrophenylamino acids in weakly basic alkaline solution causes cleavage into 2-nitroso-4,6-dinitroaniline, CO_2, and the aldehyde corresponding to the decarboxylated amino acid.[437]

Schiff base formation between pyridoxal 5′-phosphate and L-serine, and its subsequent transamination to pyridoxamine 5′-phosphate and ketoacetate, has been subjected to kinetic study.[438] Formation equilibria for the initial step in this process have been determined for several amino acids over a range of pH.[439] In this[439] and another study,[440] spectrometric characteristics have been collected for these particular Schiff bases, including estimation by u.v. spectrometry of their tautomerization equilibria and acid dissociation constants.[439] A detailed study has appeared[441] of the oxidative deamination of (p-sulphophenyl)glycine by copper(II)-mediated Vitamin B_6 coenzymes with pyridoxal 5′-phosphate or 5′-deoxypyridoxal phosphate. The deamination product, (p-sulphophenyl) glyoxylic acid, becomes a focus in this study for a demonstration by ^{18}O-labelling that $^{18}O_2$ is a reactant and is incorporated into hydroxylamine released after conversion of its Schiff base into the oxime, followed by hydrolysis.[441] It seems reasonable from this impressive study, to assume that hydroxylamine is the precursor of the eventual product, NH_3.

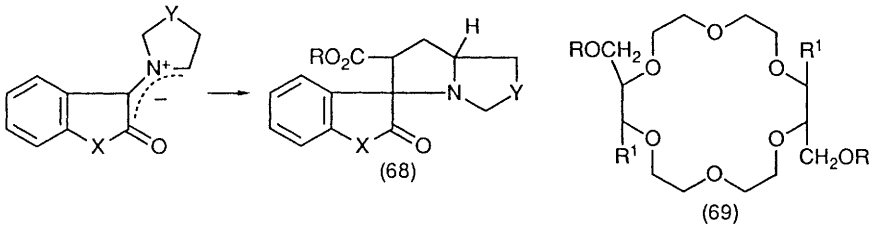
[2 + 2]-Cycloaddition reactivity of chiral Schiff bases of amino acid esters have been reviewed.[442] Chiral-catalyzed addition of derived azomethine ylides to acrylic esters to give proline homologues (Scheme 31) has been explored,[443a] using $CoCl_2$ or $MnBr_2$ with (1R,2S)-N-methylephedrine; up to 96% enantiomeric excess is claimed. Isatin-derived azomethine ylides undergo decarboxylative cycloaddition to (−)-menthyl acrylate to give (68).[443b] These extend the scope of earlier results that established the wider usefulness of Schiff bases of amino acids, and Grigg's group has combined the process with a cyclization by using a mixture of N-methylmaleimide, an N-allylglycine ester, and o-bromobenzaldehyde (to provide the intermediate azomethine ylide that undergoes cycloaddition to N-methylmaleimide, but with the bromine atom to provide the point for cyclization to the allyl moiety). Catalysis by $Pd(OAc)_2$ /Ph_3 P/Et_4 NCl/K_2 CO_3) is involved, and gives a product with four chiral centres.[444]

Extensive studies of Maillard reactions between amino acids and carbohydrates continue to give increasing insights into this most complex of processes. The Schiff base formed between glucose and proline rearranges in the usual way to the fructose – proline Amadori product, which is the main intermediate from which ensuing steps develop, leading to numerous products.[445] About 40 compounds were identified in this study, and a detailed study of products from glucose – N^{α}-protected lysine reaction mixtures has been published.[446] The mechanistic detail of the release of ammonia from the Amadori product is one of the difficult problems, and some attention is given to this aspect in this[445] and in other recent papers. 1,2- and 1,3-Enolization of the open-chain form of the



Reagents: i, $CH_2{=}CHCO_2R$, (1*R*, 2*S*)-*N*-methylephedrine

Scheme 31



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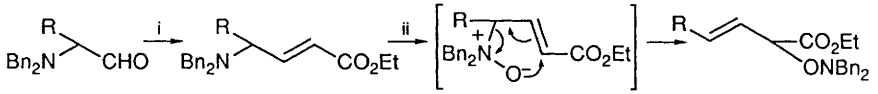
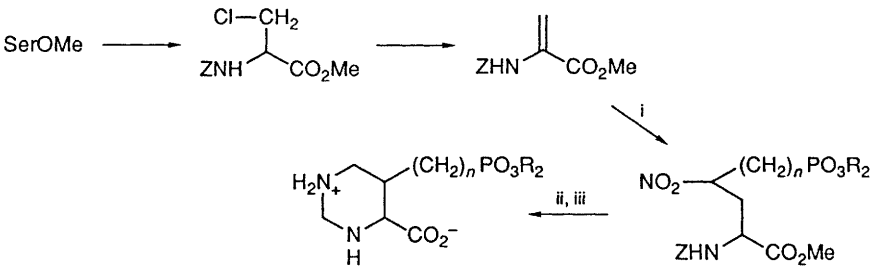


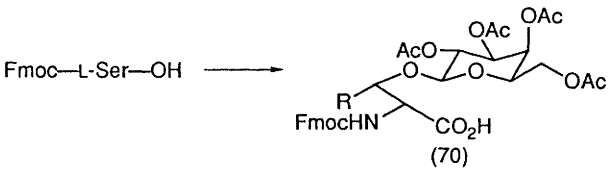
Reagents: i, see *Angew. Chem.*, 1987, **99**, 1186; ii, *m*-chloroperbenzoic acid/–50 °C

Scheme 32



Reagents: i, $NO_2(CH_2)_{n+1}PO_3R_2$-KF/Al_2O_3; ii, H_2/10 % Pd-C, HCl;
iii, $AcOCH(OEt)_2$ and routine steps

Scheme 33



(70)

Amadori compound is followed by dehydration, and then an avalanche of processes, in the currently-adopted mechanism, but it has long been realized that this does not adequately account for most of the ultimate products. An alternative dehydration mode involving cyclic forms of the Amadori compound is suggested.[447] Another interesting development is the verification of azomethine ylide behaviour by isolation of cycloadducts with the dipolarophile, norbornene, targeting the pyrylium betaines derived from initially-formed Schiff bases (Schiff bases are already known to exhibit this reactivity profile – see preceding paragraphs).[448] The original amino acids can be recovered from the fructose -β-alanine, -phenylalanine, and -N^{α}-Boc-N^{γ}-fructosyl-lysine Amadori compounds, by oxidation in the presence of copper(II) salts to release D-arabino-hexos-2-ulose.[449] The generation of fluorescent compounds and non-enzymic browning processes, based on interactions of ascorbic acid with amino acids, has been surveyed.[450] Furfural formed between L-ascorbic acid and simple amino acids accounts for the 'browning reaction' products through further condensations with the amino acids.[451] The Maillard process has been reviewed from the carbohydrate point of view, concentrating on the behaviour of 3-, 4-, and 1-deoxyosones in the presence of particular amino acids and amines.[452] The physiological role of the Maillard reaction is also important, especially in protein cross-linking processes, and the formation of the recently-discovered fluorescent crosslinking residue, pentosidine (containing the 2-amino-imidazo[4,5-b]pyridinium chromophore) in human extracellular matrix protein has been modelled with D-ribose and N^{α}-Boc-L-lysine and N^{α}-Boc-L-arginine.[453] Ribated (sic!) Boc-lysine gives a compound identical with pentosidine, which could also be obtained using glucose or ascorbic acid as carbohydrate[453] (note the link with work outside the physiological context[450]).

Relatively superficial reports still appear in the food chemistry and in the physiology contexts, but are rarer, as shown in an excellent overview of the presently greater chemical sophistication seen in the current approaches to this topic.[454]

Reactions at the carboxy group of amino acids include routine hydrolysis of Schiff base methyl esters, and re-alkylation with an alkyl halide, with the purpose of establishing the survival of the Schiff base function through these steps.[455] Crown ethers have been shown to enhance α-chymotrypsin-catalyzed transesterification of N-acetyl-L-phenylalanine ethyl ester in isopropanol,[456] while ethyl ester formation from N-protected tyrosines can be effected easily by suspending α-chymotrypsin in 95% ethanol containing an appropriate buffer.[457] Industrial-scale Fischer-type synthesis of L-phenylalanine methyl ester hydro-

chloride has been described, using DL-phenylalanine and (−)-camphor-10-sulphonic acid.[458]

In the biosynthesis of proteins, each amino acid passes from the aminoacyl adenylate to become an amino acid ester, and finally a 2′(3′)-peptidyl ester of AMP at the end of a tRNA. Because of the stereochemical situation, it would be expected and has now been established, that bis(2′,3′-aminoacyl)esters of AMP should react faster with N-acetyl-L-phenylalanine than with its D-isomer.[459] Conventional methods for preparing active esters of N-protected amino acids for use in peptide synthesis are led by dicyclohexylcarbodi-imide condensation of the acid with the alkanol or phenol. However, a way of avoiding the use of this reagent exploits the high acylation reactivity, free from side-reactions, recently established for Fmoc-amino acid chlorides.[460] While DHBt esters are made in a simple one-pot way, from the Fmoc-amino acid, thionyl chloride, and HODHBt, in the case of pentafluorophenyl esters a workable procedure requires separation of the acid chloride formation step from the acylation step.

An alternative method to that recently established ($SOCl_2$) for the preparation of Fmoc-amino acid chlorides involves reaction of an Fmoc-amino acid anhydride with anhydrous HCl, though some contamination with simple esters is inevitable, as the alkanol liberated along with the displaced anhydride grouping reacts with other components.[461] These acid chlorides are sensitive to atmospheric moisture,[462] and corresponding fluorides, which are readily prepared from Fmoc- and Z-amino acids using cyanuryl fluoride,[462] are more stable. Polymers prepared from bis(N-chloroformylmethyl)pyromellitimide bis(acid chloride)s in which the acid chlorides are based on amino acids, have been described.[463]

Cleavage by $Bu_4N^+F^-$, of 4-nitrobenzyl, 2,2,2-trichloroethyl, and phenacyl esters of N-protected amino acids,[464] and use of aqueous alcoholic alkali metal carbonates (*e.g.* Cs_2CO_3) and bicarbonates for cleavage of methyl, ethyl, and benzyl esters,[465] are useful practical procedures. The extensive studies of recent years (Vol.23, p.59) of enantioselective hydrolysis of N-acylamino acid esters continues with results using aqueous emulsions containing Z-L-histidyl-L-leucine as chiral catalyst, with a series of long chain N-acyl D- and L-phenylalanine p-nitrophenyl esters[466] and Z-L-leucine p-nitrophenyl ester[467] as substrates. A thoughtful approach to the former system[468] leads to the suggestion that the micellar interface discriminates between transition states that have different hydrophilic and hydrophobic properties. Thiolysis of hydrobromides of amino acid p-nitrophenyl esters is more effectively catalyzed by bridged crown ethers (69; 2R = p-CH_2-C_6H_4-CH_2-, R′ = Me or CH_2SH) than by unbridged analogues (R = 2-MeO-C_6H_4-).[469]

Reduction of carboxy functions is represented in the preparation of β-aminoalkanols from N-protected amino acid mixed anhydrides using $NaBH_4$ in an aqueous organic medium (see also the same results of G.Kokotis cited in Vol.23, p.58),[470] and in polarography of chiral metal complexes *fac*[Cr(L-aminoacidato)$_3$], in which the first reduction wave at the Hg surface in the presence of the tetraethylammonium ion is more positive for the (+)-isomer.[471]

Homochiral α-amino-aldehydes have been mentioned several times earlier in this Chapter, and as conveniently-available compounds nowadays, they are useful in Wittig reactions leading to γ-amino esters[472] that undergo [2,3-[σ]] rearrangement after N-oxide formation (Scheme 32) to give homochiral α-aminoxy esters.[473]

Oxidative decarboxylation of N-acylamino acids with lead tetraacetate followed by quenching with MeOH gives N,O-acetals RCONH.CHR′.CH(OMe)NHAc which can be used in α-amidoalkylation reactions with Me_3 SiCN to give α-amino nitriles.[474] There is some mechanistic interest involved in this process, since diastereoisomeric excesses in the range 5 – 72% are obtained with homochiral amino acid derivatives.[474] The ninhydrin reagent protocol has been modified for use in t.l.c., by preceding its use by a (+)-camphor-10-sulphonic acid spray, and heating the plates;[475] this produces a range of distinctive colours rather than the familiar, relatively uniform, blue-purple of the usual ninhydrin system. Since it is claimed that the colours appear in the cold, from 0.4 – 2.0 μg samples, no doubt some will be tempted to try to repeat this strange protocol. It is incorrectly claimed in this paper that secondary amines are formed from amino acids in this procedure.

α-Amino acids are useful sources of heterocyclic compounds,[476] and examples additional to those already cited above, illustrate 4-alkyloxazol-5(4*H*)-one formation from mixed anhydrides of N-formylamino acids (prepared using isopropenyl chloroformate with N-methylmorpholine),[477] and from N-acylamino acids using cyanuric chloride and triethylamine[478] (see above, for discussion of acid chloride formation with this reagent). Since oxazolones are implicated as side-reaction-introducing species in peptide synthesis, their aminolysis reactions are of considerable interest; diastereoisomer ratios disclosed for dicyclohexylcarbodiimide coupling products of N-benzoyl-L- or D-amino acids with L-amino acid esters give false indications of the racemization accompanying this standard peptide bond-forming procedure, considered to be introduced through oxazolone intermediates, unless corrected for asymmetric induction.[479] Easy assessment of diastereoisomer ratios is possible using h.p.l.c.[480] 2-Phenyloxazolones give N-benzamido-acyl 2-thiothazolidines, usable in peptide synthesis, through reaction with 2-thiothiazolidine in

boiling dichloromethane in the presence of NEt_3.[481] Oxidative dimerization of oxazolones, giving 4,4′-bis-oxazolones, can be achieved using nickel peroxide or DMSO.[482]

N-Protected oxazolidines are readily prepared from N-protected amino acids by $LiAlH_4$ reduction and *in situ* condensation of the resulting β-amino alkanols with a carbonyl compound.[483] Condensation of an N-arylalanine methyl ester with an isocyanide gives an imidazolidin-2,4-dione,[484] while N-sulphonylisocyanate gives 1,2,5-thiadiazolin-1,1-dioxides.[485] Heterocyclic synthesis from higher homologous amino acids includes β-amino acid cyclodehydration to β-lactams (methanesulphonyl chloride/$NaHCO_3$ /MeCN/80°),[486] and active ester cyclization of γ-keto-δ-amino acids to piperidin-2,5-diones.[487]

The flow of routine, often repetitive, work on simple oxidation processes involving amino acids, continues with accounts of peroxomonophosphoric acid,[488] alkaline hexacyanoferrate(II),[489] and electrooxidation at a Pt electrode.[490] Potassium permanganate continues as front-runner in this pack,[491-494] with attention to autocatalytic effects of colloidal MnO_2[491] and Mn(II),[492] Mn(III) and Mn(IV)[493] species. An exceptional interest attaches to a study of the oxidation of amino acids by Fenton's reagent [H_2O_2 and an Fe(II) salt] leading to the expected products NH_4^+, α-keto-acid, and CO_2, but also to oximes and aldehydes, and the carboxylic acid containing one fewer carbon atom than the starting amino acid.[495] The process has a dependence on bicarbonate ion and appears to involve an undefined iron chelate with an (undefined) role.

6.3 *Specific Reactions of Amino Acids*

Some reactions that are specific to a particular amino acid are occasionally extendable to homologues of that amino acid, though the distinctive functional group distribution in the familiar protein amino acids usually ensures a unique profile for each structural type. The aliphatic side-chains might have been expected to show a general group of radical substitution reactions, but there are structural influences such as the finding that phthaloylamino acids show much less α-halogen substitution than corresponding N-acylamino acids.[496] Regioselective H-transfer from β- and γ-positions of N-acetylvaline and from the N-methyl group of N-acetylsarcosine has been established by e.p.r., providing direct evidence of polar effects in radical reactions of amino acid derivatives.[497] New results indirectly demonstrating α-hydroxylation of α-amino acids, a key step in one theory for C-terminal amidation of peptides, relate to copper(II)-mediated oxygenation of N-salicoylglycine.[498] Although this substrate is a poor model for a peptide, more support is given for

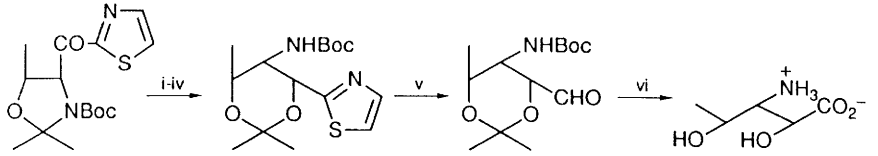
non-enzymatic processing in accordance with the original proposal for the biogenesis of peptide amides.[499]

Michael addition reactions to dehydroalanine have proved useful over the years, and another example is a synthesis of 6-phosphono-alkyl tetrahydro-4-pyrimidinecarboxylic acids (Scheme 33) as NMDA receptor antagonists.[500]

A surge of papers relating to side-chain hydroxy groups is mostly accounted for by growing interests in glycosylated amino acids, especially in protected versions suitable for peptide synthesis. β-Glucosidase from almonds, and β-xylosidase, have been employed in preparations of β-glycosides from N-acetyl-L-serine methyl ester.[501α-502] and β-Galactosidases[502,503] have been used in the corresponding transglycosylations from lactose[502,503] and raffinose,[503] employing mild deprotection procedures. Non-enzymic procedures require protection of the carbohydrate moiety, illustrated in $SnCl_4$-catalyzed transglycosylation (Fmoc-L-serine→70),[504] and a variation of the Koenigs-Knorr process with a glycosyl bromide/AgOTfl/L-serine methyl ester Schiff base.[505] In the last-mentioned study,[505] the interesting suggestion seems to be validated, that a hydrogen bond between the side-chain OH and the imine nitrogen atom of a serine Schiff base increases the nucleophilicity of the oxygen lone pair, thereby catalyzing electrophilic attack as required in non-enzymic O-glycosylation.

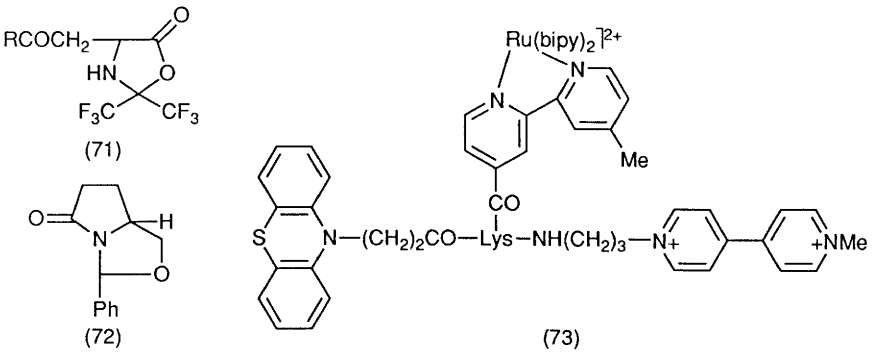
O-Phosphorylation methodology for serine, threonine and tyrosine continues to be developed for similar reasons to those stimulating glycosylation studies, a recent example being (S,S-diaryl)phosphorodithioylation.[506] O-t-Butylation of N-Fmoc derivatives has been effected for methyl esters of serine and threonine using isobutene and toluene-p-sulphonic acid (H_2SO_4 catalysis for non-esterified Fmoc-tyrosine), followed by mild, non-racemizing, ester saponification (NaOH or Na_2CO_3).[507] The overall process is suitable for large scale operations, improving on the current route based on benzyl esters.

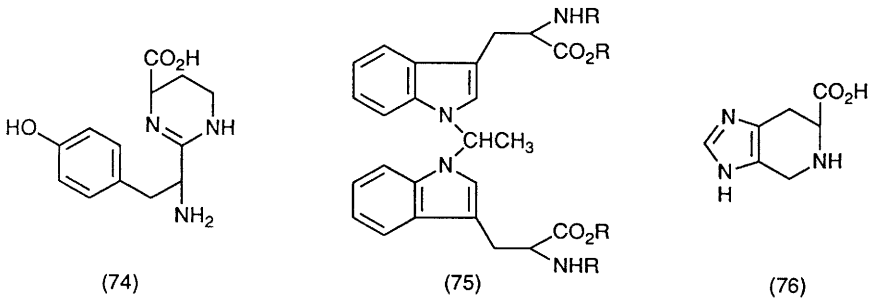
"Homologation of L-threonine", a somewhat inaccurate term used[508] for a procedure (Scheme 34) based on oxazolidin-4-yl thiazol-2-yl ketones, depends on the use of the thiazole as a latent aldehyde function.[508] Poly(ester)s $[-OCH_2\ CH(NHZ)CO-]_n$ (n [≃] 100) are obtained by heating benzotriazolyl esters of Z-serine at 105° during 3h.[509] A lengthy process involved in bridging two protected serine molecules through side-chain hydroxy groups with $-CH_2CH_2-$ starts with the conversion of N-tritylserine methyl ester into the aziridine; in this and in other steps, the synthesis is based on routine methodology.[510] L-Homoserine lactone has been prepared from L-aspartic acid through selective reduction with $LiBH_4$.[511] N-Benzoyl [3,4-$^2H_2$]-L-homoserine, subjected to 6M-HCl hydrolysis (reflux 14h) and conversion into its 3,5-dinitrobenzoate was

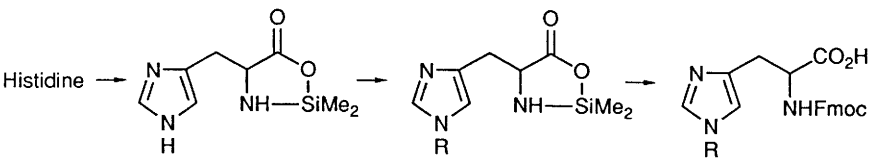


Reagents: i, TFA-CH_2Cl_2; ii, TBDMSCl; iii, L-Selectride/–78°C, then $Bu^n{}_4NF$, room temp; iv, $Me_2C(OMe)_2$, (+)-camphor sulfonic acid; v, hydrolysis; vi, [O], then TFA, then acetal cleavage

Scheme 34







Reagents: i, Me_2SiCl_2; ii, MeOTrCl, or MeTrCl (R = methoxytrityl or methyltrityl, respectively); iii, H_2O, then FmocCl

Scheme 35

surprisingly epimerized at C-4, but not at C-3.[512] The possible explanation, cyclization involving the benzoyl group (to give a 2-phenyloxazole) has been discussed.

No tritylamide derivatives of amino acids have so far been reported, but they may be prepared using triphenylmethanol with Ac_2O/AcOH; N-tritylasparagines and other derivatives are stable to strong mineral acids in aqueous media but may be cleaved with trifluoroacetic acid.[513] 1-Glycosylamines [easily prepared by dissolving a reducing sugar in saturated aqueous $(NH_4)_2CO_3$] have been condensed with α-t-butyl β-pentafluorophenyl Fmoc-L-aspartate to give N^{β} -glycosides of Fmoc-L-asparagine for use in peptide synthesis.[514]

L-Aspartic acid condenses with hexafluoroacetone to give the oxazolidin-4-one (71), proposed to be a useful synthon for regiospecific reactions leading to α- or β-substituted aspartates.[515] D-Isoglutamine, a component of peptidoglycans of the bacterial cell wall, has been synthesized from dicyclopentyl D-glutamate through lipase-catalyzed selective hydrolysis of the side-chain ester group followed by ammonolysis of the other ester group.[516] A useful recipe for the preparation of γ-benzyl Boc-L-glutamate that avoids the pyroglutamic acid side-reaction involves minor changes to an established procedure.[517] L-Pyroglutamic acid continues to provide the starting point in syntheses of interest to several research groups. The derived acetal (72) is readily prepared, and has been used in syntheses of 2,4- and 2,3,4-substituted pyrrolidinones.[518] The related pyroglutaminol (58), as its N-Boc O-TBDPS derivative, has been shown to be susceptible to stereoselective functionalization at C-3 and C-4.[519] After introduction of a C-3 – C-4 double bond (LDA/PhSeCl), 3,4-dihydroxy- and 4-methyl-derivatives were prepared by standard methods; alternatively, 3-hydroxylation could be accomplished (LDA/MoOPH). Methylation (Me_2SO_4/K_2CO_3) gives methyl N-methyl-L-pyroglutamate, and methyl L-pyroglutamate with $MeOCH_2$ OMe/$MeSO_3$ H gives a mixture of the N-methoxymethyl derivative and the bis[N,N-(methyl pyroglutamyl)]methane.[520]

Biogenetic interests are reflected in a study of the finer details (oxidative decarboxylation involves loss of the 3-pro-(R) proton, *i.e.* anti-geometry for the eliminated atom and group) of the conversion of (2S,6R)-(−)-S-(2-carboxypropyl)cysteine into trans-S-1-propenyl-L-cystine sulphoxide.[521] S-Protected cysteines are converted into cystines through reaction with sulphoxides and trimethylsilyl chloride in TFA.[522,523] Simpler methods are involved in reactions with NN′-diacetyl L-cystine bismethylamide (thermolysis gives trisulphides; aqueous alkali causes elimination to dehydroalanine).[524] Tyrosinase catalyzes attack by cysteine through the side-chain sulphur atom, at the 4-position of 5,6-

dihydroxytryptamine;[525] in the absence of the enzyme, 5,6-dihydroxytryptamine protects cysteine against oxidation to cystine, because it is more readily oxidized to the o-quinone.

Lysine is represented in detailed recipe for conversion into the N^{ε}-Z-derivative of its methyl ester through successive copper complexation, reaction with ZCl, and MeOH-$SOCl_2$ esterification[526] (errors in this account are corrected later[527]). Extraordinary lysine derivatives, the (εεε-tribenzyl-EDTA) ester of Boc-L-lysine,[528] and the heavily-loaded amino acid (73),[529] have been prepared. The latter derivative in MeCN displays net electron transfer between the bipyridinium group and the phenothiazine moiety when subjected to 6ns 460 nm laser pulses.

One-pot syntheses in about 50% yields, of N^{3} -Boc-$N^{\delta}N^{[\omega]}$-di-Z-arginine and of tri-Z-arginine have been reported, based on the reaction of ZCl with appropriate di- and tri-N-trimethylsilyl derivatives.[530] Established routes enjoying detailed description concern synthesis of side-chain Pmc-protected arginine,[531] and multi-gram synthesis of $N^{[\omega]}$-methyl arginine (in the classical way from ornithine and $MeNH.C(SMe)=NH_2^+I^-$ in the presence of aqueous NaOH).[532] Lysine is the starting material in a synthesis of Boc-homoarginine through regiospecific amidation with $EtN=C(NHEt)SO_3H$.[533] Synthesis of $N^{[\omega]}$-hydroxy-arginine from N-Boc-ornithine t-butyl ester, proceeds *via* the thiourea [-NH_2 with $CSCl_2 \rightarrow$-NH.CS.$NH_2 \rightarrow$-NH.C(=NOR).NH_2],[534] or alternatively[535] -$NH_2 \rightarrow$-NHC≡N with BrCN, $\rightarrow$NHC(=NH)NHOH. This arginine derivative has created interest as the source, in tissue, of the vasorelaxing agent nitric oxide; the work of D.J.Stuehr and co-workers on this topic has been surveyed.[536]

Aromatic and heteroaromatic side-chain modifications have been mentioned in earlier Sections (4.11 and 4.15) of this Chapter, a spectacular example[38] being the biogenesis from L-tyrosine, of the pyoverdin chromophore (19) *via* (74) in *Pseudomonas fluorescens* E2.[537] Mass-spectrometric confirmation of the structure has been published.[538] The propensity to form 1,1′-ethylidene bis(L-tryptophan) (75) with acetaldehyde[539] led to the unfortunate outbreak of eosinophilia myalgia syndrome when this compound, Contaminant "97", was discovered in commercial L-tryptophan used as a nutritional additive in health foods.[540]

4-Methoxy- and 4-methyltrityl side-chain protection of histidine has been proposed,[541] removable under mild conditions compared with trityl groups, employing novel temporary protection of NH_2 and CO_2H groups (Scheme 35). Unprotected histidine readily forms spinacine (76) with aqueous formaldehyde, and several of its analogues have been prepared from N^{im} -benzyl-L-histidine.[542] The histidine side-chain can be degraded using Ru(VIII) reagents to cleave the 4,5-π-bond, leading to $N^{[\omega]}$-

carbamoyl-L-asparagine, $N^{[\omega]}$-formyl-L-asparagine, N^{α}-benzoyl-β-cyanoalanine, and aspartic acid.[543]

6.4 *Effects of Electromagnetic Radiation on Amino Acids*

Familiar theses for this Section continue to be represented, with studies of fluorescence quenching of dityrosine with boric acid and borates,[544] and similar quenching studies for 3-nitrotyrosine and N-acetyltryptophanamide.[545] Lumiflavin-sensitized photo-CIDNP study of tryptophan has to take account of accompanying irreversible photolysis processes since these reduce the intensity of the CIDNP.[546] Similarly, the presence of the anti-oxidant spermine suppresses the formation of u.v.-generated radicals in aqueous tryptophan,[547] as shown by e.s.r. monitoring. Generation of the azide radical, and radical anions from bromine and dithiocyanogen, has been assessed in relation to the formation of the tryptophan radical and the protonated tryptophan radical cation.[548]

7 Analytical Methods

7.1 *General*

Reviews have appeared covering recent advances[549] and broad areas: liquid chromatographic methods of amino acid analysis,[550] determination of L-DOPA in physiological fluids.[551] Certain drugs interfere with analytical methods for amino acids, particularly when blood and urine samples are involved.[552]

7.2 *Gas-Liquid Chromatography*

The topic has been reviewed.[553] Pre-treatment of amino acid samples for g.l.c. analysis has received attention,[554] and so it should, to improve reliability which so often depends on rigid protocols and calibration. n-Propyl esters are best extracted from an NH_4Cl/NH_4OH buffer with propan-1-ol – chloroform mixtures, increased extraction efficiency accompanying higher proportions of propan-1-ol. This is the typical first step in g.l.c. analysis of amino acids, and esterification is followed by N-derivatization with a variety of reagents. N-Trifluoroacetyl-,[555] pentafluoropropionyl-,[556,557] and heptafluorobutyroyl-,[558] derivatives are continuing in use after many years, and are being shadowed by N-alkoxycarbonyl derivatives[556,559-561] that have the benefit of being formed from an alkyl chloroformate very rapidly.[560,561]

Different workers distribute their favours differently as far as esterifying groups are concerned for g.l.c. analysis of amino acids, and isopropyl,[556] isobutyl,[558] propyl,[557] and methyl[561] esters are typical.

Configurational assignments based on enantioselection over chiral

g.l.c. columns have been made to N-methylphenylalanine using Chirasil-L-Val capillary g.l.c.[556] The topic of enantioselective g.l.c. of amino acids has been reviewed.[562] Other points of interest in these accounts include m.s. monitoring,[555] and a special derivatization protocol for g.l.c. analysis of cysteic acid [N-isobutoxycarbonylation followed by methylation (MeI/Me_2SO_4/Ag_2O) of the silver salt to give the dimethyl ester].[561] One study[557] focuses on α-aminoisobutyric acid and isovaline, non-protein amino acids that are, in fact, quite common in the biosphere.

7.3 *Ion Exchange and Related Forms of Chromatography*

New techniques are being assessed for ion-exchange separation of amino acids, employing poly(hydroxyethyl methacrylate) modified with various weak acid and strong acid functional groups such as carboxyalkyl and sulphobutyl, respectively,[563] employing hollow fibres made from a perfluorinated ion-exchange membrane of the Nafion type,[564] and using a strong cation exchange polymer gel (Polyspher PE-A).[565]

Ion-pair chromatography has been used for the analysis of N-oxalylcysteine through conversion into a highly-fluorescent derivative using monobrombimane.[566]

7.4 *Thin-Layer Chromatography*

A routine subject for evermore, perhaps, in the context of amino acid analysis, but valid new papers continue to appear that are welcome when they describe improvements, however small, such as ICT-Empore silica gel plates capable of separating glutamic and aspartic acids, and serine and glycine.[567] Mention could be made of a modified ninhydrin spray reagent (prior spraying an heating with (+)-camphor-10-sulphonic acid) that is claimed to give distinctively different blue colours for the different common amino acids.[475]

7.5 *High Performance Liquid Chromatography*

This too might almost have become a routine topic by now, like the subject of the preceding Section, but the number of relevant papers exploring new aspects shows no sign of declining. Most of the current papers reflect benefits associated with newer derivatization regimes that are proposed to take the place of older, but not necessarily displaced, methods.

The o-phthaldialdehyde (OPA) – mercaptoethanol reagent,[568-574] and its highly sensitive relative, naphthalene-1,2-dialdehyde,[575] are still dominant in amino acid analysis, as far as the volume of current literature is concerned. Comparisons are being made with Fmoc derivatives, often in favour of the latter, and with N- phenylthiocarbamoyl derivatives.

The favoured OPA derivatization routine continues to have among its supporters a number of research groups which strive to expunge some of its problematical details. Good housekeeping shows up many of these problems to be somewhat illusory,[568] and attention to sample preparation, and the incorporation of nitrilotri-acetic acid to stabilize the OPA reagent,[569] are beneficial. Better fluorescence response accompanies the sequential use of dithiothreitol and iodoacetic acid in OPA derivatization-based assays of cysteine and cystine.[570] Among studies of general application of the OPA procedure in amino acid analysis,[571-573] accurate assay of 3-methylhistidine[571] continues to have special clinical importance. Commercial samples of L-amino acids estimated for their D-enantiomer content, as OPA derivatives separated in an achiral – chiral coupled column configuration, all show at least traces of the 'wrong' enantiomer.[574] In some of these cases, the levels of D-amino acids reach several percent.

A combination of OPA with Fmoc-Cl derivatization using piperidine-4-carboxylic acid as internal standard allows estimation of both primary and secondary amino acids (the OPA protocol cannot derivatize amino acids in the latter category) with improved quantification of secondary amino acids compared with classical ion exchange techniques,[576] though h.p.l.c. shows lower reproducibility levels for some amino acids. Other assays based on fluorescence measured at 315 nm (excitation at 265 nm) for Fmoc-amino acids[577,578] include an assay of basic amino acids extracted from mixtures with the use of a weakly acidic cation exchanger.[577]

Automated derivatization of amino acid mixtures using phenyl isothiocyanate (PITC) has been compared with Fmoc-Cl derivatization,[579] with the finding that Fmoc-Cl is more sensitive to the deleterious effects of buffers and solvents. Routine uses of PITC derivatization continue to be reported, for quantifying amino acids in hydrolysates,[580] in aminopeptidase – carboxypeptidase – mineral acid[581] or trypsin[582] digests, and in wine.[583] Use of the PITC method for estimating the crosslinking amino acids desmosine and isodesmosine in elastin hydrolysates[584,585] illustrates the growing realization, that h.p.l.c. analysis offers a reliable method for the assay of trace components in tissue samples, from which clinically useful conclusions can be drawn. Assays of collagen cross-linking amino acids pyridinoline and deoxypyridinoline in physiological fluids gives early diagnosis of bone loss in osteoporosis.[586]

Enantiomer ratios are quantifiable from the use of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate as a chiral reagent, recently applied to α-methyl α-amino acids with the finding that the elution order

for enantiomers of these is the opposite of that for their parent α-amino acids of the 'same' configuration.[587]

The PITC method has been found to compare favourably with the OPA – Fmoc-Cl combination for h.p.l.c. analysis of amino acids.[583] However, PITC and OPA methods are unsatisfactory for asparagine, glutamine, N^{γ}-methylasparagine and N^{γ}-methylglutamine (protein constituents that are the products of post-translational processing). Indeed, careful studies of deamidation of these compounds in solutions at various temperatures and pH (glutamine reacts [≃] 12 – 14 times faster than N^{γ}-methylglutamine, and N^{γ}-methylasparagine undergoes cyclisation in preference to de-amidation) suggests that there must be several errors in the literature due to previous lack of this knowledge.[588]

Ninhydrin derivatization of asparagine and glutamine and their methylation products mentioned in the preceding paragraph is, however, the basis of a satisfactory analytical procedure, and this faithful standby has been used for estimating S-methylmethionine, methionine, and lysine in corn,[589] and 2,6-di-aminopimelic acid as a marker for bacterial protein.[590]

A review has appeared covering the role of h.p.l.c. in identifying phenylthiohydantoins (PTHs) for protein sequence analysis.[591] DOPA-PTH co-elutes with alanine-PTH, but such overlaps can be dealt with by varying chromatographic parameters.[592]

Isolated examples of alternative derivatization reagents arise with an assay of homocysteine in plasma, using 7-fluorobenzo-2-oxa-1,3-diazole-4-sulphonate,[593] and of general uses for dabsyl chloride, claimed to be a simple, stable reagent, capable of offering sensitive assays for amino acids.[594] No derivatization is involved in assays of histidine, tyrosine and tryptophan based on their u.v. absorption at 220 nm;[595] of cystine, arginine, lysine and ornithine based on intense $[M + H]^+$ ions formed using a mass spectrometer equipped with an atmospheric pressure ion interface;[596] and of cysteine and N-acetylcysteine using indirect amperometric detection based on I_2 oxidation.[597] N-Acetylamino acids have been determined at 0.5 nmol levels using a mobile phase containing trisphenanthrolinyliron(II) salts.[598]

Examples have been given in foregoing paragraphs of reports of analytical enantiomer separation by standard method. A more experimental approach is illustrated in an application of an 18-crown-6 silica gel stationary phase for analyzing unusual amino acids.[599]

7.6 *Other Analytical Methods*

High performance capillary electrophoresis (h.p.c.e) is now an established technique in many areas, and especially in the field of amino

acid analysis. Less than one picomole of phosphotyrosine PTH can be detected,[600] and similar levels can be reached for the analysis of underivatized amino acids.[601] Enantiomer composition of amino acid samples can be determined by h.p.c.e., after derivatization with Marfey's reagent.[602]

7.7 *Assay of Specific Amino Acids*

Many examples have been given elsewhere in this Chapter, of analytical information being acquired for particular amino acids. However, this Section's title as used over the years, is not meant to have hidden meaning; its purpose is to collect papers describing methods based on specific amino acid-modifying enzymes by whose action some simple compound is released in amounts indicative of the level of the particular amino acid.

A flexible redox polymer biosensor responsive to L-glutamic acid has been developed, employing immobilized L-glutamate oxidase.[603] Improvements to details of a standard hydroxyproline assay capable of detecting levels in urine, have been announced.[604]

Instrumentation for flow-injection analysis has reached levels of sophistication that allow reliable analysis of specific L- and D-amino acids in the presence of all other L-amino acids in serum samples, based on immobilized enzymes.[605,606] In one of these accounts,[605] an assay for L-lysine is described in detail; the other[606] indicates the scope of the technique, which allows the analysis of nineteen 50μL samples per hour. A sensitive flow-injection analysis, in which L-aspartic and L-glutamic acids are enzymatically coupled with NADH that activates immobilized bacterial bioluminescence enzymes, has been described.[607] The aspartate assay depends on the aspartate aminotransferase – malate dehydrogenase combination, while glutamate is quantified through the corresponding glutamate aminotransferase – dehydrogenase system.

References

1. Methods in Plant Biochemistry. Volume 5: Amino Acids, Proteins, and Nucleic Acids, Ed. L.J.Rogers, Academic Press, London, 1991.
2. Molecules Through Time: Fossil Molecules and Biochemical Systematics, Proceedings of The Royal Society Discussion on Biomolecular Palaeontology, *Phil.Trans. Roy.Soc.London, Ser.B*, 1991, Vol.353 (No 1286), Eds. G. Eglinton and G.B.Curry, The Royal Society, London, 1991.
3. W.G.Engelhart, *Am.Biotechnol.Lab.*, 1990, **8**, 30, 32, 34.
4. Y.Takahashi and S.Goto, *Sep.Sci.Technol.*, 1991, **26**, 1.
5. I.A.O'Neil, *SynLett.*, 1991, 651.
6. A.J.Mahajan, C.J.Orella, and D.J.Kirwan, *A.I.Ch.E.Symp. Ser.*, 1991, **87**, 143.
7. S.Hunt, *Methods Plant Biochem.*, 1991, **5**, 1.

8. K.Harada, *Viva Origino*, 1991, **18**, 97 (*Chem.Abs.*, 1991, **115**, 24514).
9. J.Asselineau, *Progr.Chem.Org.Nat.Prod.*, 1991, **56**, 1.
10. J.Thompson and S.P.F.Miller, *Adv.Enzymol., Relat.Areas Mol.Biol.*, 1991, **64**, 317.
11. B.M.Shapiro and P.B.Hopkins, *Adv.Enzymol., Relat.Areas Mol.Biol.*, 1991, **64**, 291.
12. M.H.Engel, S.A.Macko, and J.A.Siffer, *Nature*, 1990, **348**, 47.
13. W.A.Bonner, *Origins Life Evol.Biosphere*, 1991, **21**, 59.
14. S.A.Macko and M.H.Engel, *Philos.Trans.Roy.Soc.London, Ser.B*, 1991, 333, 367.
15. E.N.Powell, J.A.King, and S.Boyles, *Archaeometry*, 1991, **33**, 57.
16. N.Fusetani, Y.Nakao, and S.Matsunaga, *Tetrahedron Lett.*, 1991, **32**, 7073.
17. R.L.Dillman and J.H.Cardinella, *J.Nat.Prod.*, 1991, **54**, 1159.
18. J.A.Marco, J.F.Sanz, A.Yuste, and J.Jakupovic, *Tetrahedron Lett.*, 1991, **32**, 5193.
19. K.Isshiki, H.Naganawa, S.Hattori, M.Hamada, and M.Ishizuka, *J.Antibiot.*, 1991, **44**, 557.
20. S.Omura, K.Matsuzaki, T.Fujimoto, K.Kosuge, T.Furuya, S.Fujita, and A.Nakagawa, *J.Antibiot.*, 1991, **44**, 117.
21. C.Jiminez and P.Crews, *Tetrahedron*, 1991, **47**, 2097.
22. S.Nishiyama, S.Yamamura, K.Hasegawa, M.Sakoda, and K.Harada, *Tetrahedron Lett.*, 1991, **32**, 6753.
23. N.Harada, H.Hagiwara, H.Ono, H.Uda, S.Ohba, M.Kubisa, S.Nishiyama, S.Yamamura, K.Hasegawa, and M.Sakoda, *Tetrahedron Lett.*, 1991, **32**, 6757.
24. T.C.Morton, A.S.Zektzer, J.P.Rife, and J.T.Romeo, *Phytochemistry*, 1991, **30**, 2397.
25. G.Blunden, B.E.Smith, and P.D.Carey, *J.Appl.Phycol.*, 1989, **1**, 1.
26. F.Terradas and H.Wyler, *Helv.Chim.Acta*, 1991, **74**, 124.
27. M.Nishikawa, Y.Tsurumi, H.Murai, K.Yoshida, M.Okamoto, S.Takase, H.Tanaka, K.Hirota, M.Hashimoto, and M.Kohsaka, *J.Antibiot.*, 1991, **44**, 130.
28. K.Kassuhlke and D.J.Faulkner, *Tetrahedron*, 1991, **47**, 1809.
29. K.Yamano, K.Konno, and H.Shirahama, *Chem.Lett.*, 1991, 1541.
30. S.Tsubotani, Y.Funabashi, M.Takamoto, S.Hakoda, and S.Harada, *Tetrahedron*, 1991, 47, 8079.
31. S.O.Andersen, J.P.Jacobsen, P.Roepstorff, and M.G.Peter, *Tetrahedron Lett.*, 1991, 32, 4287.
32. M.Kinuta, N.Masuoka, K.Yao, J.Ohta, S.Yoshida, S.Futani, and T.Ubuka, *Amino Acids*, 1991, **1**, 259; M.Kinuta, K.Yao, N.Masaoka, J.Ohta, T.Teraoka, and T.Ubuka, *Biochem.J.*, 1991, **275**, 617.
33. F.Nakamura and K.Suyama, *Agric.Biol.Chem.*, 1991, **55**, 547.
34. N.Yasuda and K.Sakane, *J.Antibiot.*, 1991, **44**, 801.
35. N.Fusetani and S.Matsunaga, *Tennen Yuki Kagobutsu Koen Yashishu*, 1990, **32**, 65 (*Chem.Abs.*, 1991, **114**, 244530).
36. K.Yoshino, T.Takao, M.Suhara, T.Kitai, K.Hori, K.Nomura, M.Yamaguchi, Y.Shimonishi, and N.Suzuki, *Biochemistry*, 1991, **30**, 6203.
37. H.Itazaki, K.Nagashima, K.Sugita, H.Yoshida, Y.Kawamura, Y.Yasuda, K.Matsumoto, K.Ishii, N.Uotani, et al., *J.Antibiot.*, 1990, **43**, 1524.
38. K.Taraz, D.Seinschen, and H.Budzikiewicz, *Z.Naturforsch.C: Biosci.*, 1991, **46**, 522.
39. F.D'Angeli, P.Marchetti, G.Cavicchioni, V.Bertolasi, and F.Maran, *Tetrahedron: Asymmetry*, 1991, **2**, 1111.
40. I.I.Gerus, Y.L.Yagupolsk'ii, V.P.Khukhar, L.S.Boguslavskaya, N.N.Chuvatkin, A.V.Kartashov, and Yu.V.Mitin, *Zh.Org.Khim.*, 1991, **27**, 537.
41. H.Hoenig, P.Seufer-Wasserthal, and H.Weber, *Tetrahedron*, 1990, **46**, 3841.
42. S.Saito, H.Yokoyama, T.Ishikawa, N.Niwa, and T.Moriwake, *Tetrahedron Lett.*, 1991, **32**, 663; S.Saito, N.Takahashi, T.Ishikawa, and T.Moriwake, *Idem.* p.667.

43. J.P.Genet, S.Mallart, C.Greck, and E.Piveteau, *Tetrahedron Lett.*, 1991, **32**, 2359.
44. Y.Endo, S.Hizatate, and K.Shudo, *SynLett.*, 1991, 649.
45. R.Amoroso, G.Cardillo, C.Tomasini, and P.Tortoreto, *J.Org.Chem.*, 1992, **57**, 1082.
46. Y.Amino and K.Izawa, *Bull.Chem.Soc.Jpn.*, 1991, **64**, 613, 1040.
47. A.Miyashita, T.Kawashima, S.Kaji, K.Nomura, and H.Nohira, *Tetrahedron Lett.*, 1991, **32**, 781.
48. F.Trigalo, C.Molliex, B.Champion, and R.Azerad, *Tetrahedron Lett.*, 1991, **32**, 3049.
49. R.J.Bridge, M.S.Stanley, M.W.Andersonm, C.W.Cotman, and A.R.Chamberlain, *J.Med.Chem.*, 1991, **34**, 717.
50. T.Yamazaki, J.Haga, and T.Kitazume, *Bioorg.Med.Chem.Lett.*, 1991, **1**, 271.
51. Y.Shi, X.Zhou, Z.Du, and H,Hu, *Youji Huaxue*, 1991, **11**, 78 (*Chem.Abs.*, 1991, **114**, 207200).
52. T.R.Burke, P.Russ, and B.Lim, *Synthesis*, 1991, 1019.
53. D.Guillaume, D.J.Aitken, and H.P.Husson, *SynLett.*, 1991, 747.
54. J.F.Callahan, K.A.Newlander, and W.F.Huffmann, *Tetrahedron Lett.*, 1991, **32**, 7203.
55. Yu.N.Belokon, K.A.Kochetkov, V.I.Tararov, T.F.Savel'eva, Z.B.Bakasova, and A.G.Raik, *Bioorg.Khim.*, 1991, **17**, 773.
56. Y.Rong, Y.Shi, W.Lu, Z.Du, H.Hu, and M.Wu, *Youji Huaxue*, 1991, **11**, 170 (*Chem.Abs.*, 1991, **115**, 50243).
57. Y.Shi, Y.Rong, W.Jiang, W.Lu, and H.Hu, *Chin.Chem.Lett.*, 1991, **2**, 213 (*Chem.Abs.*, 1991, **115**, 159701).
58. J.H.Bateson, A.C.Kaura, and R.Southgate, *Tetrahedron Lett.*, 1991, **32**, 2065.
59. P.Cintas, *Tetrahedron*, 1991, **47**, 6079.
60. K.A.Kochetkov and A.F.Sviridov, *Bioorg.Khim.*, 1991, **17**, 5.
61. K.A.Kochetkov and A.F.Sviridov, *Bioorg.Khim.*, 1991, **17**, 293.
62. K.A.Kochetkov and A.F.Sviridov, *Bioorg.Khim.*, 1991, **17**, 149.
63. F.Reed, *Spec.Chem.*, 1991, **11**, 148 (*Chem.Abs.*, 1991, **115**, 92843).
64. C.Botteghi, S.Paganelli, A.Schionato, and M.Marchetti, *Chirality*, 1991, **3**, 355.
65. H.J.Altenbach, *Org.Synth.Highlights*, 1991, 300 (*Chem.Abs.*, 1991, **115**, 136665).
66. H.J.Altenbach, *Org.Synth.Highlights*, 1991, 309.
67. N.R.Thomas and D.Gani, *Tetrahedron*, 1991, **47**, 497.
68. U.Groth, U.Schollkopf, and T.Tiller, *Liebigs Ann,Chem.*, 1991, 857.
69. T.Beulshausen, U.Groth, and U.Schollkopf, *Liebigs Ann,Chem.*, 1991, 1207.
70. W.Hartwig and J.Mittendorf, *Synthesis*, 1991, 939.
71. A.J.Pearson and P.R.Bruhn, *J.Org.Chem.*, 1991, **56**, 7092.
72. Yu.N.Belokon, U.I.Maleev, S.O.Videnskaya, M.B.Saporovskaya, V.A.Tsyryapkin, and V.M.Belikov, *Izv.Akad.Nauk S.S.S.R., Ser.Khim.*, 1991, 126.
73. V.A.Soloshonok, V.P.Khukhar, S.V.Galushko, A.B.Rozhenko, N.A.Kuz'mina, M.T.Kolycheva, and Yu.N.Belokon, *Izv.Akad.Nauk S.S.S.R., Ser.Khim.*, 1991, 126.
74. V.A.Soloshonok, V.P.Khukhar, A.S.Batsanov, M.A.Galakhov, Yu.N.Belokon, and Yu.T.Struchkov, *Izv.Akad.Nauk S.S.S.R., Ser.Khim.*, 1991, 1548.
75. V.A.Soloshonok, V.P.Khukhar, S.V.Galushko, M.T.Kolycheva, A.B.Rozhenko, and Yu.N.Belokon, *Izv.Akad.Nauk S.S.S.R., Ser.Khim.*, 1991, 1166.
76. Yu.N.Belokon, V.I.Tararov, and T.F.Savel'eva, *Izv.Akad.Nauk S.S.S.R., Ser.Khim.*, 1991, 1175.
77. Yu.N.Belokon, S.C.Mociskite, V.I.Tararov, and V.I.Maleev, *Izv.Akad.Nauk S.S.S.R., Ser.Khim.*, 1991, 1536.
78. Yu.N.Belokon, V.I.Tararov, V.I.Maleev, S.C.Mociskite, S.V.Vitt, N.I.Chernogla-

zova, T.F.Savel'eva, and M.B.Saporovskaya,*Izv.Akad.Nauk S.S.S.R., Ser.Khim.*, 1991, 1542.
79. M.Tabcheh, A.El Achqar, L.Pappalardo, M.L.Roumestant, and P.Viallefont, *Tetrahedron*, 1991, **47**, 4611.
80. H.Josien, A.Martin, and G.Chassaing, *Tetrahedron Lett.*, 1991, **32**, 6547.
81. A.Mi, Z.Ma, L.Wu, and Y.Jiang, *Chin.Chem.Lett.*, 1991, **2**, 115 (*Chem.Abs.*, 1991, **115**, 159700).
82. Y.Jiang, G.Liu, C.Zhou, H.Piao, L.Wu, and A.Mi, *Synth.Commun.*, 1991, **2**, 115.
83. G.Liu, J.Deng, and Y.Jiang, *Huaxue Tongbao*, 1991, 34.
84. Y.Jiang, G.Liu, R.Deng, and S.Wu, *Tianran Chanwu Yanjiu Yu Kaifa*, 1989, **1**, 1 (*Chem.Abs.*, 1992, **116**, 59914).
85. B.Imperiali and S.L.Fisher, *J.Org.Chem.*, 1992, 57, 757; *J.Am.Chem.Soc.*, 1991, 113, 8527.
86. H.Kunz, W.Sagar, D.Schanzenbach and M.Decker, *Liebigs Ann,Chem.*, 1991, 649.
87. H.Kunz, W.Pfrengle, K.Rueck, and W.Sagar, *Synthesis*, 1991, 1039.
88. T.K.Chakraborty, G.V.Reddy, and K.A.Hussain, *Tetrahedron Lett.*, 1991, **32**, 7597.
89. A.Mori, H.Ohno, H.Nitta, K.Tanaka, and S.Inoue, *SynLett.*, 1991, 563; A.Mori, H.Nitta, M.Kudo, and S.Inoue, *Tetrahedron Lett.*, 1991, **32**, 4333.
90. Z.Tadros, P.H.Langriffont, L.Mion, J.Taillades, and A.Commeyras, *J.Chem.Soc., Chem.Commun.*, 1991, 1373.
91. J.Taillades, P.Boussac, H.Collet, J.Brugidou, and A.Commeyras, *Bull.Soc.Chim.Fr.*, 1991, 423.
92. D.P.G.Hamon, P.Razzino, and R.A.Massy-Westropp, *J.Chem.Soc., Chem.Commun.*, 1991, 332.
93. D.P.G.Hamon, R.A.Massy-Westropp, and P.Razzino, *J.Chem.Soc., Chem.Commun.*, 1991, 722.
94. A.Jenhi, J.P.Lavergne, and P.Viallefont, *J.Organomet.Chem.*, 1991, **401**, C10.
95. M.Chaari, A.Jenhi, J.P.Lavergne, and P.Viallefont, *J.Organomet.Chem.*, 1991, **401**, C14.
96. T.Sheradsky, J.Milvitskaya, and I.E.Pollak, *Tetrahedron Lett.*, 1991, **32**, 133.
97. C.M.Gasparski and M.J.Miller, *Tetrahedron*, 1991, **47**, 5367.
98. E.Altmann, K.Nebel, and M.Mutter, *Helv.Chim.Acta*, 1991, **74**, 800.
99. D.Blaser and D.Seebach, *Liebigs Ann,Chem.*, 1991, 1067
100. D.Blaser, S.Y.Ko, and D.Seebach, *J.Org.Chem.*, 1991, **56**, 6230.
101. K.Suzuki and D.Seebach, *Liebigs Ann,Chem.*, 1992, 51.
102. D.Seebach, H.M.Burger, and C.P.Schickli, *Liebigs Ann,Chem.*, 1991, 669.
103. C.P.Schickli and D.Seebach, *Liebigs Ann,Chem.*, 1991, 655.
104. R.Amoroso, G.Cardillo, and C.Tomasini, *Tetrahedron Lett.*, 1991, **32**, 1971.
105. P.Coggins and N.S.Simpkins, *SynLett.*, 1991, 515.
106. E.Pfammater and D.Seebach, *Liebigs Ann,Chem.*, 1991, 1323.
107. A.Alexakis, N.Lensen, and P.Mangeney, *Tetrahedron Lett.*, 1991, **32**, 1171.
108. A.Jeanguenat and D.Seebach, *J.Chem.Soc., Perkin Trans.1*, 1991, 2291.
109. S.Katsumura, A.Kondo, and Q.Han, *Chem. Lett.*, 1991, 1245.
110. C.Ma and M.J.Miller, *Tetrahedron Lett.*, 1991, **32**, 2577.
111. S.Shatzmiller, B.Z.Dulithzki, and E.Behar, *Liebigs Ann,Chem.*, 1991, 375.
112. R.M.Williams and M.N.Im, *J.Am.Chem.Soc.*, 1991, **113**, 9276.
113. R.M.Williams, M.N.Im, and J.Cao, *J.Am.Chem.Soc.*, 1991, **113**, 6976.
114. R.M.Williams and G.F.Fegley, *J.Am.Chem.Soc.*, 1991, **113**, 8796.
115. C.Agami, F.Couty, B.Prince, and C.Puchot, *Tetrahedron*, 1991, **47**, 4343.
116. V.Gouverneur and L.Ghosez, *Tetrahedron Lett.*, 1991, **32**, 5349.

117. H.Waldmann and M.Braun, *Liebigs Ann,Chem.*, 1991, 1045.
118. C.Cativiela, P.Lopez, and J.A.Mayoral, *Tetrahedron: Asymmetry*, 1991, **2**, 449.
119. M.P.Bueno, C.A.Cativiela, J.A.Mayoral, and A.Avenoza, *J.Org.Chem.*, 1991, **56**, 6551.
120. S.Gladiali and L.Pinna, *Tetrahedron: Asymmetry*, 1991, **2**, 693.
121. S.Gladiali and L.Pinna, *Tetrahedron: Asymmetry*, 1991, **2**, 623.
122. J.P.Genet, C.Pinel, S.Mallart, S.Juge, S.Thorimbert, and J.A.Lafitte, *Tetrahedron: Asymmetry*, 1991, **2**, 555.
123. T.Chiba, A.Miyashita, H.Nohira, and H.Takaya, *Tetrahedron Lett.*, 1991, **32**, 4745.
124. A.Corma, M.Iglesias, C.Del Pino, and F.Sanchez, *J.Chem.Soc., Chem.Commun.*, 1991, 1253.
125. K.Inoguchi and K.Achiwa, *SynLett.*, 1991, 49.
126. U.Schmidt, A.Lieberknecht, U.Kazmaier, H.Griesser, G.Jung, and J.Metzger, *Synthesis*, 1991, 49.
127. J.G.Andrade, G.Prescher, A.Schaefer, and U.Nagel, *Chem.Ind.(Dekker)*, 1990, 40 (Catalyzed Organic Reactions), 33 (*Chem.Abs.*, 1991, **114**, 249685).
128. M.Laghmari and D.Sinou, *J.Mol.Catal.*, 1991, 66, L15.
129. J.A.J.M.Vekemans, J.P.G.Versleijen, and H.M.Buck, *Tetrahedron: Asymmetry*, 1991, **2**, 949.
130. K.Kakinuma, T.Koudate, H.-Y.Li, and T.Eguchi, *Tetrahedron Lett.*, 1991, **32**, 5801.
131. S.P.Crump, J.S.Heier, and J.D.Rozzell, in "Biocatalysis", Ed.D.A.Abramowicz, Van Nostrand Reinhold, New York, 1990, p.115.
132. P.Niederberger, *Symp.Soc.Gen.Microbiol.*, 1989, 44 (Microbiological Production: New Approaches), 1.
133. J.Kamphuis, W.H.J.Boesten, Q.B.Broxterman, H.F.M.Hermes, J.A.M.Van Balken, E.M.Meijer, and H.E.Schoemaker, *Adv.Biochem.Eng.,Biotechnol.*, 1990, **42**, 133 (*Chem.Abs.*, 1991, **114**, 141469).
134. K.Dilova and P.Aleksieva, *Biotekhnol.Biotekh.*, 1991, 12.
135. T.Tosa, *Nippon Nogei Kagaku Kaishi*, 1991, **65**, 185.
136. H.Anazawa, K.Araki, Y.Ito, and T.Ozeki, *J.Gen.Appl.Microbiol.*, 1991, **37**, 71.
137. V.P.Gachok and I.V.Gachok, *Zh.Fiz.Khim.*, 1991, **65**, 476.
138. J.Plachy and S.Ulbert, *Acta Biotechnol.*, 1990, **10**, 517.
139. M.Terasawa, M.Inui, Y.Uchida, M.Kobayashi, Y.Kurusu, and H.Yukawa, *Appl. Microbiol.Biotechnol.*, 1991, **34**, 623.
140. M.Terasawa, M.Inui, M.Goto, Y.Kurusu, and H.Yukawa, *Appl.Microbiol.Biotechnol.*, 1991, **34**, 623.
141. T.Bottiglieri, *Biomed.Chromatogr.*, 1990, **4**, 239; see also A.M.Molloy, D.G.Weir, G.Kennedy, S.Kennedy, and J.M.Scott, *Ibid.*, p.257.
142. A.Dureault, F.Carreaux, and J.C.Depezay, *Synthesis*, 1991, 150.
143. A.G.M.Barrett and S.A.Lebold, *J.Org.Chem.*, 1991, **56**, 4875.
144. M.El Hadrami, J.-P.Lavergne, P.Viallefont, M.Y.A.Itto, and A.Hasnaoui, *Tetrahedron Lett.*, 1991, **32**, 3985.
145. A.Gaucher, J.Ollivier, and J.Salaun, *SynLett.*, 1991, 151.
146. J.Legters, L.Thijs, and B.Zwanenburg, *Tetrahedron*, 1991, **47**, 5287.
147. Y.Arakawa and S.Yoshifuji, *Chem.Pharm.Bull.*, 1991, **39**, 2219.
148. K.Hashimoto and H.Shirahama, *Tetrahedron Lett.*, 1991, **32**, 2625.
149. A.G.M.Barrett and D.Pilipauskas, *J.Org.Chem.*, 1991, **56**, 2787.
150. N.Jeong, S.Yoo, S.J.Lee, S.H.Lee, and Y.K.Chung, *Tetrahedron Lett.*, 1991, **32**, 2137.
151. H.H.Mooiweer, H.Hiemstra, and W.N.Speckamp, *Tetrahedron*, 1991, **47**, 3451.

152. M.Murakami, N.Hasegawa, M.Hayashi, and Y.Ito, *J.Org.Chem.*, 1991, **56**, 7356.
153. R.K.Olsen and X.Feng, *Tetrahedron Lett.*, 1991, **32**, 5721.
154. M.J.Stone, R.A.Maplestone, S.K.Rahman, and D.H.Williams, *Tetrahedron Lett.*, 1991, **32**, 2663.
155. H.Heimgartner, *Angew.Chem.Int.Ed.*, 1991, **30**, 238.
156. J.J.Chen, Z.M.Du, Y.Z.Shi, and H.W.Wu, *Chin.Chem.Lett.*, 1991, **2**, 193 (*Chem.Abs.*, 1991, **115**, 136691).
157. T.Yamada, T.Yanagi, Y.Omote, T.Miyazawa, S.Kuwata, M.Sugiura, and K.Matsumoto, *Chem.Express*, 1991, **6**, 575.
158. W.M.Kazmierski and V.J.Hruby, *Tetrahedron Lett.*, 1991, **32**, 5769.
159. N.Engel, B.Kubel, and W.Steglich, *Angew.Chem.Int.Ed.*, 1977, *16*, 394.
160. M.W.Holladay and A.M.Nadzan, *J.Org.Chem.*, 1991, **56**, 3900.
161. G.T.Bourne, D.Crich, J.W.Davies, and D.C.Horwell, *J.Chem.Soc., Perkin Trans.1*, 1991, 1693.
162. G.T.Bourne, D.C.Horwell, and M.C.Pritchard, *Tetrahedron*, 1991, **47**, 4763.
163. L.Colombo, G.Casiraghi, A.Pittalis, and G.Rassu, *J.Org.Chem.*, 1991, **56**, 3897.
164. L.van Assche, A.Haemers, and M.Hooper, *Eur.J.Med.Chem.*, 1991, **26**, 363.
165. K.Burger, K.Gaa, and K.Muetze, *Chem.-Ztg.*, 1991, **115**, 292.
166. M.Chaari, A.Jenhi, J.P.Lavergne, and P.Viallefont, *Tetrahedron*, 1991, **47**, 4619.
167. I.Jako, P.Uiber, A.Mann, C.G.Wermuth, T.Boulanger, B.Norberg, G.Evrard, and F.Durant, *J.Org.Chem* , 1991, **56**, 5729.
168. G.Cardillo, M.Orena, M.Penna, S.Sandri, and C.Tomalini, *Tetrahedron*, 1991, **47**, 2263.
169. K.Burger, M.Rudolph, and H.Neuhauser, *Liebigs Ann,Chem.*, 1991, 1365.
170. K.Shimamoto, M.Ishida, H.Shimozaki, and Y.Ohfune, *J.Org.Chem.*, 1991, **56**, 4167.
171. P.de Frutos, D.Fernandez, E.Fernandez-Alvarez, and M.Bernabe, *Tetrahedron Lett.*, 1991, **32**, 541.
172. Y.Amino, S.Nishi, and K.Izawa, *Bull.Chem.Soc.Jpn.*, 1991, **64**, 620.
173. J.K.Stille and Y.Becker, *J.Org.Chem.*, 1980, *45*, 2139.
174. A.van der Werf and R.M.Kellogg, *Tetrahedron Lett.*, 1991, **32**, 3727.
175. P.M.Esch, R.F.de Boer, H.Hiemstra, I.M.Boska, and W.N.Speckamp, *Tetrahedron*, 1991, **47**, 4063.
176. P.M.Esch, I.M.Boska, H.Hiemstra, R.F.De Boer, and W.N.Speckamp, *Tetrahedron*, 1991, **47**, 4039.
177. J.H.Udding, H.Hiemstra, M.N.A.van Zanden, and W.N.Speckamp, *Tetrahedron Lett.*, 1991, **32**, 3123.
178. C.Agami and F.Couty, *Tetrahedron*, 1991, **47**, 155.
179. J.E.Baldwin, M.G.Moloney, and A.F.Parsons, *Tetrahedron*, 1991, **47**, 155.
180. F.Soucy, D.Wernic, and P.Beaulieu, *J.Chem.Soc., Perkin Trans.1.*,1991, 2885.
181. J.E.Baldwin, R.M.Adlington, C.R.A.Godfrey, and V.K.Patel, *J.Chem.Soc., Chem. Commun.*, 1991, 1277.
182. A.N.Bowler, P.M.Doyle, P.B.Hitchcock, and D.W.Young, *Tetrahedron Lett.*, 1991, **32**, 2679.
183. N.Langlois and R.Z.Andriamialisoa, *Tetrahedron Lett.*, 1991, **32**, 3057.
184. T.R.Webb and C.Eigenbrot, *J.Org.Chem.*, 1991, **56**, 3009.
185. A.S.Anslow, L.M.Harwood, H.Phillips and D.Watkin, *Tetrahedron: Asymmetry*, 1991, **2**, 997.
186. J.Y.Merour and J.Y.Coadou, *Tetrahedron Lett.*, 1991, **32**, 2469.
187. G.Georg, X.Guan, and J.Kant, *Bioorg.Med.Chem.Lett.*, 1991, **1**, 125.
188. A.Fadel, *Tetrahedron*, 1991, **47**, 6265.

189. N.De Kimpe, P.Sulmon, and C. Stevens, *Tetrahedron*, 1991, **47**, 4723.
190. A.Alami, J.Calmes, J.Daunis, F.Escale, R.Jacquier, M.L.Roumestant, and P.Viallefont, *Tetrahedron: Asymmetry*, 1991, **2**, 175.
191. J.L.Marco, B.Sanchez, M.D.Fernandez, and M.Bernabe, *Liebigs Ann,Chem.*, 1991, 1099.
192. A.P.Kozikowski and A.H.Fauq, *SynLett.*, 1991, 783.
193. P.N.Rao, D.M.Peterson, C.K.Acosta, M.L.Bahr, and H.K.Kim, *Org.Prep.Proced. Int.*, 1991, **23**, 103.
194. J.Horgan, *Sci.Am.*, 1991, 243, 101.
195. P.Menendez Aparicio, A.De Andres Gomez de Barreda, and F.Aragon de la Cruz, *An.Quim.*, 1991, **87**, 240.
196. Y.Hirose, K.Ohmuro, M.Saigoh, T.Nakayama, and Y.Yamagata, *Origins Life Evol. Biosphere*, 1991, **20**, 471.
197. K.Harada, S.Igari, T.Munegumi, M.Takasaki, and A.Shimoyama, *Bull.Soc. Chem.Jpn.*, 1991, **64**, 1776.
198. G.Apitz and W.Steglich, *Tetrahedron Lett.*, 1991, **32**, 3163.
199. H.Kohn, K.N.Sawhney, P.Le Gall, D.W.Robertson, and J.O.Leander, *J.Med. Chem.*, 1991, **34**, 2444.
200. A.Boussoufi, P.Hudhomme, P.Hitchcock, and G.Duguay, *Tetrahedron*,1991, **2**, 157.
201. V.P.Kukhar and V.A.Soloshonok, *Usp.Khim.*, 1991, **60**, 1680.
202. M.Haddach, R.Pastor, and J.G.Riess, *J.Fluorine Chem.*, 1991, **51**, 197.
203. K.Burger, E.Hoess, K.Gaa, N.Sewald, and C.Schierlinger, *Z.Naturforsch. B: Chem.Sci.*, 1991, **46**, 361.
204. P.L.Beaulieu, *Tetrahedron Lett.*, 1991, **32**, 1031.
205. R.F.Jackson, A.Wood, and M.Wythes, *SynLett.*, 1990, 735.
206. U.Schmidt, R.Meyer, V.Leitenberger, F.Staebler, and A.Lieberknecht, *Synthesis*, 1991, 409.
207. J.Dubois, C.Foures, S.Bory, S.Falcon, M.Gaudry, and A.Marquet, *Tetrahedron*, 1991, **47**, 1001.
208. L.Havlicek and J.Hanus, *Coll.Czech.Chem.Commun.*, 1991, **56**, 1365.
209. S.A.Abdulganeva and K.B.Erzhanov, *Usp.Khim.*, 1991, **60**, 1318.
210. Y.Han, H.Hu, Z.Zhou, and K.Yu, *Chin.J.Chem.*, 1991, **9**, 60.
211. C.J.Easton, C.A.Hutton, P.D.Rosell, and E.R.T.Tiekink, *Aust.J.Chem.*, 1991, **44**, 687.
212. M.J.Aurell, S.Gil, P.V.Martinez, M.Parra, A.Tortajada, and R.Mestres, *Synth.Commun.*, 1991, **21**, 1833.
213. L.M.Raepecki, T.Nagafuchi, and J.H.Waite, *Arch.Biochem.Biophys.*, 1991, **285**, 17.
214. P.Beaulieu, J.S.Duceppe, and C.Johnson, *J.Org.Chem.*, 1991, **56**, 4196.
215. R.O.Duthaler, *Angew.Chem.Int.Ed.*, 1991, **30**, 705.
216. J.P.Genet, S.Juge, I.Besnier, J.Uziel, D.Ferroud, N.Kardos, S.Achi, J.Ruiz-Montes, and S.Thorimbert, *Bull.Soc.Chim.Fr.*, 1991, 781.
217. J.O.Opio, S.Labidalle, H.Galous, M.Miocque, A.Zaparucha, and A.Loupy, *Synth. Commun.*, 1991, **21**, 1743.
218. P.Meffre, H.Lhermitte, L.Vo-Quang, Y.Vo-Quang, and F.Le Goffic, *Tetrahedron Lett.*, 1991, **32**, 4717.
219. V.P.Kukhar, Yu.L.Yagupol'skii, I.I.Gerus, and M.T.Kolycheva, *Usp.Khim.*, 1991, **60**, 2047.
220. R.Chirakal, G.J.Schrobilgen, G.Firnan, and S.Garnetti, *Appl.Radiat.Isot.*, 1991, **42**, 113.

221. I.A.MacDonald, P.L.Nyce, M.J.Jung, and J.S.Sabol, *Tetrahedron Lett.*, 1991, **32**, 887.
222. B.Escoula, I.Rico, A.Lattes, J.Simon, and R.Guiraud, *New J.Chem.*, 1991, **15**, 75.
223. G.D.Hartman and W.Halczenko, *Synth.Commun.*, 1991, **21**, 2103.
224. J.J.Bozell, C.E.Vogt, and J.Gozum, *J.Org.Chem.*, 1991, **56**, 2584.
225. H.Pervez and C.J.Suckling, *J.Nat.Sci.Math.*, 1990, **30**, 83 (*Chem.Abs.*, 1991, **115**, 50247).
226. C.K.Acosta, M.L.Bahr, J.E.Burdett, J.W.Cessac, R.A.MArtinez, P.N.Rao, and H.K.Kim, *J.Chem.Res.,Synop.*, 1991, 110.
227. C.G.Knight, *Biochem.J.*, 1991, **274**, 45.
228. C.N.Hsaio, M.R.Leanna, L.Bhagavatula, E.DeLara, T.M.Zydowsky, W.Horrom, and H.E.Morton, *Synth.Commun.*, 1990, **20**, 3507.
229. U.Madsen and E.H.F.Wong, *J.Med.Chem.*, 1992, **35**, 107.
230. M.Lee and R.S.Phillips, *Bioorg.Med.Chem.Lett.*, 1991, **1**, 477.
231. M.Somei, T.Kawasaki, K.Shimizu, Y.Fukui, and T.Ohta, *Chem.Pharm.Bull.*, 1991, **39**, 1905.
232. N.Prasitpan, M.E.Johnson, and B.L.Currie, *Synth.Commun.*, 1990, **20**, 3459.
233. E.V.Krasko, *Synthesis*, 1991, 417.
234. S.Auvin, O.Cochet, N.Kucharczyk, F.Le Goffic, and B.Badet, *Bioorg.Chem.*, 1991, **19**, 143.
235. J.G.Trujillo, G.Ceballos, R.Yanez, and P.Joseph-Nathan, *Synth.Commun.*, 1991, **21**, 683.
236. R.Rajagopal, I.Moeller, and C.E.Olsen, *Phytochemistry*, 1991, **30**, 1405.
237. J.Vidal, J.Drouin, and A.Collet, *J.Chem.Soc., Chem.Commun.*, 1991, 435.
238. S.J.Hays, T.C.Malone, and G.Johnson, *J.Org.Chem.*, 1991, **56**, 4084.
239. J.P.Whitten, D.Muench, R.V.Cube, P.L.Nyce, B.M.Baron, and I.A.MacDonald, *Bioorg.Med.Chem.Lett.*, 1991, **1**, 441.
240. A.Varadarajan and M.F.Hawthorne, *Bioconjugate Chem.*, 1991, **2**, 242 (*Chem.Abs.*, 1991, **115**, 92903).
241. C.J.Unkefer, J.L.Hanners, and D.S.Ehler, *J.Labelled Compd.Radiopharm.*, 1991, **29**, 1241.
242. C.J.Unkefer, S.N.Lodwig, L.A.Silks, J.L.Hanners, D.S.Ehler, and R.Gibson, *J.Labelled Compd.Radiopharm.*, 1991, **29**, 1247.
243. Yu.A.Zolotarev, N.F.Myasoedov, D.A.Zaitsev, M.Yu.Lyubnin, V.Yu.Tatur, V.S.Kozic, E.M.Dorokhova, and S.N.Rozenberg, *Radioisotopy*, 1990, **31**, 110.
244. Yu.A.Zolotarev, V.S.Kozic, D.A.Zaitsev, E.M.Dorokhova, and N.F.Myasoedov, *J.Labelled Compd.Radiopharm.*, 1991, **29**, 507.
245. Yu.A.Zolotarev, V.S.Kozik, E.M.Dorokhova, N.F.Myasoedov, and S.N.Rozenberg, *J.Labelled Compd.Radiopharm.*, 1991, **29**, 997.
246. E.Mittag, S.Noll, and B,Grosse, *Isotopenpraxis*, 1991, **27**, 262.
247. M.Dong and R.Cao, *Hejishu*, 1991, **14**, 372 (*Chem.Abs.*, 1991, **115**, 208494).
248. G.Guillerm and B.Allart, *J.Labelled Compd.Radiopharm.*, 1991, **29**, 1027.
249. R.J.Parry, S.Ju, and B.J.Baker, *J.Labelled Compd.Radiopharm.*, 1991, **29**, 633.
250. J.M.Delacotte, H.Galous, D.Schott,and J.L.Morgat, *J.Labelled Compd.Radiopharm.*, 1991, **29**, 1141.
251. M.Holschbach, W.Hamkens, W.Roden, and L.E.Feinendegen, *J.Labelled Compd. Radiopharm.*, 1991, **29**, 599.
252. K.Uchida and M.Kainisho, *J.Labelled Compd.Radiopharm.*, 1991, **29**, 867.
253. J.J.Cappon, J.Baart, G.A.M.van der Walle, J.Raap, and J.Lugtenburg, *Recl.Trav. Chim.Pays-Bas*, 1991, **110**, 158.

254. H.T.Lee, J.L.Hicks, and D.R.Johnson, *J.Labelled Compd.Radiopharm.*, 1991, **29**, 1065.
255. H.Rhim, I.Park, and M.U.Choi, *Han'guk Saenghwa Hakkoechi*, 1991, **24**, 478 (*Chem.Abs.*, 1991, **116**, 79778).
256. M.Perlmutter, N.Iatyamurthy, A.Luxen, M.E.Phelps, and J.R.Barrio, *Appl.Radiat. Isot.*, 1990, **41**, 801.
257. C.Lemaire, M.Guillaume, R.Cantineau, A.Plenevaux, and L.Christaiens, *Appl. Radiat.Isot.*, 1991, **42**, 629.
258. H.J.Cahnmann, E.Goncalves, Y.Ito, H.M.Fales, and E.A.Sokoloski, *J.Chromatogr.*, 1991, **538**, 165.
259. S.A.Kazaryan, E.A.Ekmedzhyan, and Z.O.Mndzhoyan, *Khim.- Farm.Zh.*, 1991, **25**, 57.
260. K.R.Rao, Y.V.D.Nageswar, and H.M.S.Kumar, *Tetrahedron Lett.*, 1991, **32**, 6611.
261. S.G.Davies and O.Ichihara, *Tetrahedron: Asymmetry*, 1991, **2**, 183.
262. P.Gmeiner, *Liebigs Ann.Chem.*, 1991, 1501; *Arch.Pharm.*, 1991, **324**, 551.
263. M.F.Beatty, C.Jennings-White, and M.A.Avery, *J.Chem.Soc., Chem.Commun.*, 1991, 351.
264. B.J.Moon and K.L.Huh, *Bull.Korean Chem.Soc.*, 1991, **12**, 71.
265. R.S.Axelsson, K.J.O'Toole, P.A.Spencer, and D.W.Young, *J.Chem.Soc., Chem. Commun.*, 1991, 1085.
266. J.Cooper, D.W.Knight, and P.T.Gallagher, *J.Chem.Soc., Perkin Trans.1*,1991, 705.
267. S.Laschat and H.Kunz, *J.Org.Chem.*, 1991, **56**, 5883.
268. E.Juaristi, D.Quintama, B.Lamatsch, and D.Seebach, *J.Org.Chem.*, 1991, **56**, 2553.
269. W.D.Lubell, M.Kitamura, and R.Noyori, *Tetrahedron: Asymmetry*, 1991, **2**, 543.
270. H.Yoda, T.Shirai, T.Kawasaki, T.Katagiri, K.Takabe, K.Kimita, and K.Hosoya, *Chem.Lett.*, 1991, 793.
271. D.Keirs, D.Moffat, K.Overton, and R.Tomanek, *J.Chem.Soc., Perkin Trans.1*, 1991, 1041.
272. M.Bols and I.Lundt, *Acta Chem.Scand.*, 1991, **45**, 280.
273. L.M.Gustavson and A.Srinivasan, *Synth.Commun.*, 1991, **21**, 265.
274. M.T.Kolycheva, I.I.Gerus, Yu.L.Yagupolskii, and V.P.Khukhar, *Zh.Org.Khim.*, 1991, **27**, 117.
275. G.I.Georg, P.M.Mashava, E.Akgün, and W.M.Milstead, *Tetrahedron Lett.*, 1991, **32**, 3151.
276. E.J.Corey, C.P.Decicco, and R.C.Newbold, *Tetrahedron Lett.*, 1991, **32**, 5287.
277. G.Bringman and T.Gender, *Synthesis*, 1991, 829.
278. G.Simig and M.Schlosser, *Tetrahedron Lett.*, 1991, **32**, 1963.
279. K.Paulini and H.Reissig, *Liebigs Ann.Chem.*, 1991, 455.
280. G.Johnson, J.T.Drummond, P.A.Boxer, and R.F.Bruns, *J.Med.Chem.*, 1992, **35**, 233.
281. C.Evans, R.McCague, S.M.Roberts, A.G.Sutherland, and R.Wisdom, *J.Chem.Soc., Perkin Trans.1*, 1991, 2276.
282. P.Berthelot, C.Vaccher, N.Flouquet, M.Debaert, M.Luyckx, and C.Brunel, *J.Med. Chem.*, 1991, **34**, 2557.
283. G.Griffiths, H.Mettler, L.S.Mills, and F.Previdoli, *Helv.Chim.Acta*, 1991, **74**, 309.
284. L.E.Burgess and A.I.Meyers, *J.Am.Chem.Soc.*, 1991, **113**, 9858.
285. R.Chênevert and M.Desjardins, *Tetrahedron Lett.*, 1991, **32**, 4249.
286. K.Tomioka, M.Kanai, and K.Koga, *Tetrahedron Lett.*, 1991, **32**, 2395.
287. S.Hashiguchi, A.KAwada, and H.Natsugari, *J.Chem.Soc., Perkin Trans.1*, 1991, 2435.

287a Y.Lu, C.Miet, N.Kunesch, and J.Poisson, *Tetrahedron: Asymmetry*, 1990, **1**, 707.
288. A.Palomo, F.P.Cossio, G.Rubiales, and S.Aparicio, *Tetrahedron Lett.*, 1991, **32**, 3115.
289. Y.Takemoto, T.Matsumoto, Y.Ito, and S.Terashima, *Chem.Pharm.Bull.*, 1991, **39**, 2425.
290. M.Franciotti, A.Mann, and M.Taddei, *Tetrahedron Lett.*, 1991, **32**, 6783.
291. S.Ishibuchi, Y.Ikematsu, T.Ishizuka, and T.Kunieda, *Tetrahedron Lett.*, 1991, **32**, 3523.
292. W.-J.Koot, R.van Ginkel, M.Kranenburg, H.Hiemstra, S.Louwrier, M.J.Moolenaar, and W.N.Speckamp, *Tetrahedron Lett.*, 1991, **32**, 401.
293. T.Inokuchi, S.Tanigawa, M.Kamazaki, and S.Torii, *SynLett.*, 1991, 707.
294. K.Halling, K.B.G.Torsell, and R.G.Hazell, *Acta Chem.Scand.*, 1991, **45**, 736.
295. A.M.P.Koskinen and J.Chen, *Tetrahedron Lett.*, 1991, **32**, 6977.
296. Y.Hamada, Y.Tanada, F.Yokokawa, and T.Shioiri, *Tetrahedron Lett.*, 1991, **32**, 5983.
297. (a) C.Herdeis and D.Waibel, *Arch.Pharm.*, 1991, **324**, 269; (b) C.Herdeis and W.Engel, *Tetrahedron: Asymmetry*, 1991, 2, 945.
298. H.Kotsuki, A.Miyazaki, and M.Ochi, *Tetrahedron Lett.*, 1991, **32**, 4503.
299. T.Chakraborty and K.K.Gangakhedkar, *Tetrahedron Lett.*, 1991, **32**, 1097.
300. D.J.Plata, M.R.Leanna, and H.E.Morton, *Tetrahedron Lett.*, 1991, **32**, 3623.
301. S.H.Rosenberg, S.A.Boyd, and R.A.Mantei, *Tetrahedron Lett.*, 1991, **32**, 6507.
302. (a) Y.Hamada, K.Hayashi, and T.Shioiri, *Tetrahedron Lett.*, 1991, **32**, 931; (b) K.Hayashi, Y.Hamada, and T.Shioiri, *Tetrahedron Lett.*, 1991, **32**, 7287.
303. I.Gomez-Monterrey, M.J.Dominguez, R.Gonzalez-Muniz, J.R.Harto, and M.T.Garcia-Lopez, *Tetrahedron Lett.*, 1991, **32**, 1089.
304. G.S.Garrett, T.J.Emge, S.C.Lee, E.M.Fischer, K.Dyehouse, and J.M.McIver, *J.Org. Chem.*, 1991, **56**, 4823.
305. T.Ibuka, H.Habashita, A.Otaka, N.Fujii, Y.Oguchi, T.Uyehara, and Y.Yamamoto, *J.Org.Chem.*, 1991, **56**, 4370.
306. N.Fujii, H.Habashita, N.Shigemori, A.Otaka, T.Ibuka, M.Tanaka, and Y.Yamamoto, *Tetrahedron Lett.*, 1991, **32**, 4969.
307. N.Sakai and Y.Ohfune, *J.Am.Chem.Soc.*, 1992, **114**, 998.
308. H.Diaz and J.W.Kelly, *Tetrahedron Lett.*, 1991, **32**, 5725.
309. T.Shiraiwa, S.Sakata, K.Fujishima, and H.Kurokawa, *Bull.Chem.Soc.Jpn.*, 1991, **64**, 191.
310. T.Shiraiwa, M.Yamauchi, T.Yamauchi, T.Yamana, M.Nagata, and H.Kurokawa, *Bull.Chem.Soc.Jpn.*, 1991, **64**, 1057.
311. M.Matsuoka, H.Hasegawa, and K.Ohori, *ACS Symp.Ser.* (Crystallization and Separation Processes), 1990, **438**, 251.
312. M.A.Verkhovskaya and I.A.Yamskov, *Usp.Khim.*, 1991, **60**, 2250.
313. K.Drauz, U.Gröger, M.Schäfer, and H.Klenk, *Chem.-Ztg.*, 1991, **115**, 97.
314. M.Pugniere, B.Castro, and A.Previero, *Chirality*, 1991, **3**, 170.
315. K.Drauz, M.Kottenhahn, K.Makryaleas, H.Klenk, and M.Bernd, *Angew.Chem.Int. Ed.*,1991, **30**, 712.
316. S.R.Perrin and W.H.Pirkle, *ACS Symp.Ser.* (Chiral Separations in Liquid Chromatography), 1991, **471**, 43.
317. W.H.Pirkle, K.C.Derning, and J.A.Burke, *Chirality*, 1991, **3**, 183.
318. S.R.Perrin, *Chirality*, 1991, **3**, 188.
319. R.Daeppen, G.Rihs, and C.W.Mayer, *Chirality*, 1990, **2**, 185.
320. C.D.Haurou, G.Declercq, P.Ramiandrasoa, and J.L.Millet, *J.Chromatogr.*, 1991, **547**, 31.

321. L.Siret, A.Tambute, A.Begos, J.Rouden, and M.Caude, *Chirality*, 1991, **3**, 427.
322. S.Li and W.C.Purdy, *J.Chromatogr.*, 1991, **543**, 105.
323. M.Hilton and D.W.Armstrong, *J.Liq.Chromatogr.*, 1991, **14**, 9.
324. B.Sellergren and K.G.I.Nilsson, *Methods Mol.Cell.Biol.*, 1989, **1**, 59.
325. G.Jeanneret-Gris, C.Soerensen, H.Su, and J.Porret, *Spec.Chem.*, 1991, **11**, 142 (*Chem.Abs.*, 1991, **115**, 136681).
326. C.Cheng and L.H.Huang, *J.Chromatogr.*, 1991, **555**, 272.
327. S.Yamazaki, T.Takeuchi, and T.Tanimura, *J.Chromatogr.*, 1991, **540**, 169.
328. T.Fukuhara, M.Isoyama, M.Tanaka, and S.Yuasa, *Appl.Radiat.Isot.*, 1991, **42**, 457.
329. T.Fukuhara and S.Yuasa, *J.Mol.Evol.*, 1991, **32**, 304.
330. S.F.Mason, *Chirality*, 1991, **3**, 223.
331. A.Salam, *J.Mol.Evol.*, 1991, **33**, 105.
332. J.Chela-Flores, *Chirality*, 1991, **3**, 389.
333. D.H.Deutsch, *J.Mol.Evol.*, 1991, **33**, 295.
334. K.Tennakone, *Origins Life Evol.Biosphere*, 1991, **220**, 515.
335. P.Jungwirth and I.Gutman, *J.Serb.Chem.Soc..*, 1991, **56**, 253 (*Chem.Abs.*, 1991, **115**, 44636).
336. R.Destro, R.Bianchi, C.Gatti, and F.Merati, *Chem.Phys.Lett.*, 1991, 186, 47.
337. S.A.Bahadur, R.K.Rajaram, and M.Nethali, *Acta Crystallogr., Sect.C: Cryst.Struct. Commun.*, 1991, *C47*, 1705.
338. X.De La Cruz, J.Tormo, I.Fita, and J.A.Subirama, *Acta Crystallogr., Sect.C: Cryst. Struct.Commun.*, 1991, *C47*, 1705.
339. H.Schmidbauer, P.Kiprof, O.Kumberger, and J.Reide, *Chem.Ber.*, 1991, **124**, 1083.
340. R.Puliti, C.A.Mattia, G.Barone, and C.Giancola, *Acta Crystallogr., Sect.C: Cryst. Struct.Commun.*, 1991, *C47*, 1658.
341. W.Wieczorek, M.Bukowska-Strzyzewska, M.T.Leplawy, and A.Olma, *J.Crystallogr.Spectrosc.Res.*, 1991, **21**, 209.
342. W.Wieczorek, M.Bukowska-Strzyzewska, A.Olma, Z.Kaminski, and M.T.Leplawy, *J.Crystallogr.Spectrosc.Res.*, 1991, **21**, 107.
343. J.R.Peterson, H.D.Do, and R.O.Rogers, *Pharm.Res.*, 1991, **8**, 908.
344. H.L.Ammon, S.M.Prasad, and J.A.Gerit, *Acta Crystallogr., Sect.C: Cryst.Struct. Commun.*, 1991, *C47*, 1476.
345. B.Noszal, W.Guo, and D.L.Rabenstein, *J.Phys.Chem.*, 1991, **95**, 9609.
346. H.E.Howard-Lock, C.J.L.Lock, and M.L.Martins, *Can.J.Chem.*, 1991, **69**, 1721.
347. A.Naito, A.Root, and C.A.McDowell, *J.Phys.Chem.*, 1991, **95**, 3578.
348. S.G.Ang and S.H.Low, *Aust.J.Chem.*, 191, *44*, 1591.
349. T.Kusumi, T.Fukushima, I.Ohtani, and H.Kakisawa, *Tetrahedron Lett.*, 1991, **32**, 2939.
350. D.Pini, G.Uccello-Barretta, C.Rosini, and P.Salvadori, *Chirality*, 1991, **3**, 174.
351. C.Vallet, M.Arendt, P.Mabon, N.Naulet, and G.J.Martin, *J.Sci.Food Agric.*, 1991, **56**, 167.
352. J.Ren, F.Pei, and W.Wang, *Chin.J.Chem.*, 1990, 423 (*Chem.Abs.*, 1992, **114**, 164786).
353. F.Separovic, K.Hayamizu, R.Smith, and B.A.Cornell, *Chem.Phys.Lett.*, 1991, 181, 157.
354. J.Lauterwein, I.P.Gerothanassis, R.N.Hunston, and M.Schumacher, *J.Phys.Chem.*, 1991, **95**, 3804.
355. S.E.Brown, J.H.Coates, S.F.Lincoln, D.Coghlan, and C.J.Easton, *J.Chem.Soc., Faraday Trans.*, 1991, **87**, 2699.
356. C.Mandravel and L.Ionescu, *Rev.Roum.Chim.*, 1990, **35**, 961.
357. F.Tanaka, *Fukuoka Joshi Daigaku Kaseigakubu Kiyo*, 1991, **22**, 43.

358. S.Ramaprasad, *Proc.Arkansas Acad.Sci.*, 1990, **44**, 94 (*Chem.Abs.*, 1991, **115**, 29900).
359. T.Kunitake, J.M.Kim, and Y.Ishikawa, *J.Chem.Soc., Perkin Trans.2*, 1991, 885.
360. L.A.Nafie, D.Che, G.S.Yu, and T.B.Freedman, *Proc.SPIE Int.Soc.Opt.Eng.*, 1991, 1432 (Biomolecular Spectroscopy II), 37.
361. M.Sakairi, A.L.Yergey, K.W.M.Siu, J.C.Y.Le Blanc, R.Guevremont, and S.S.Berman, *Anal.Sci.*, 1991, **7**, 199.
362. M.Sakairi, A.L.Yergey, K.W.M.Siu, J.C.Y.Le Blanc, R.Guevremont, and S.S.Berman, *Anal.Chem.*, 1991, **63**, 1488.
363. M.Sakairi and A.L.Yergey, *Anal.Sci.*, 1991, **7**, 589.
364. C.K.Meng, C.N.McEwen, and B.S.Larsen, *Rapid Commun.Mass.Spectrom.*, 1990, **4**, 147.
365. C.K.Meng and J.B.Fenn, *Org.Mass Spectrom.*, 1991, **26**, 542.
366. M.Hamdan, M.Scandola, G.Gaviraghi, G.Tarzia, A.L.Bedini, G.Spadoni, O.Curcuruto, and P.Traldi, *Rapid.Commun.Mass Spectrom.*,1991, **5**, 291.
367. J.Martens, S.Luebben, and W.Schwarting, *Z.Naturforsch.B: Chem.Sci.*, 1991, **46**, 320.
368. J.Parmentier, C.Samyu, M. van Beylen, and T.Zeegers- Huyskens, *J.Chem.Soc., Perkin Trans.2*, 1991, 387.
369. Y.Wang, R.Purrello, T.Jordan, and T.G.Spiro, *J.Am.Chem.Soc.*, 1991, **113**, 6359.
370. Y.Wang, R.Purrello, S.Georgiu, and T.G.Spiro, *J.Am.Chem.Soc.*, 1991, **113**, 6368.
371. G.P.Harhay and B.S.Hudson, *J.Phys.Chem.*, 1991, **95**, 3511.
372. P.J.Larkin, W.G.Gustafson, and S.A.Asher, *J.Chem.Phys.*, 1991, **94**, 5324.
373. H.Takeuchi, Y.Kimura, I.Koitabashi, and I.Harada, *J.Raman Spectrosc.*, 1991, **22**, 233.
374. H.Joela, D.Mustafi, C.C.Fair, and M.W.Makinen, *J.Phys.Chem.*, 1991, **95**, 9135.
375. K.Iijima and B.Beagley, *J.Mol.Struct.*, 1991, **248**, 133.
376. K.Iijima, K.Tanaka, and S.Onuma, *J.Mol.Struct.*, 1991, **246**, 257.
377. M.Falk, P.F.Seto, and J.A.Walter, *Can.J.Chem.*, 1991, **69**, 1740.
378. T.H.Lilley, *Water Sci.Rev.*, 1990, **5**, 137 (*Chem.Abs.*, 1991, **115**, 201247).
379. C.Vicent, S.C.Hirst, F.Garcia-Tellado, and A.D.Hamilton, *J.Am.Chem.Soc.*, 1991, **113**, 5466.
380. J.U.Hwang, Y.W.Kwak, J.W.Jung, and C.H.Kil, *J.Korean Chem.Soc.*, 1991, **35**, 105 (*Chem.Abs.*, 1991, **114**, 229334).
381. M.A.Slifkin and S.M.Ali, *J.Chem.Soc., Faraday Trans.*, 1991, **87**, 3241.
382. V.P.Vasil'ev, L.A.Kochergina, S.G.Grosheva, and O.N.Korneva, *Izv.Vyssh.Uchebn. Zaved., Khim., Khim.Tekhnol.*, 1991, **34**, 48 (*Chem.Abs.*, 1991, **115**, 100584).
383. B.Noszal and D.L.Rabenstein, *J.Phys.Chem.*, 1991, **95**, 4761.
369.
384. G.R.Hedwig, J.F.Reading, and T.H.Lilley, *J.Chem.Soc., Faraday Trans.*, 1991, **87**, 1751.
385. A.H.Sijpkes, G.Somsen, and S.G.J.Blankenberg, *J.Chem.Soc., Faraday Trans.*, 1990, **86**, 3737.
386. A.H.Sijpkes and G.Somsen, *J.Solution Chem.*, 1991, **20**, 445.
387. G.Castronuovo, V.Elia, and M.Magliulo, *Can.J.Chem.*, 1991, **69**, 794.
388. T.V.Chalikyan, D.P.Kharakoz, A.P.Sarvazyan, C.A.Cain, R.J.McGough, I.V. Pogosova, and T.N.Gareginyan, *J.Phys,Chem.*, 1992, **96**, 876.
389. T.J.Goodnow, M.V.Reddington, J.F.Stoddart, and A.E.Kaifer, *J.Am.Chem.Soc.*, 1991, **113**, 4335.
390. J.Chmelik, J.Hudzcek, K.Putyeva, J.Mankovicka, V.Kalous, and J.Chmelikova, *Coll.Czech.Chem.Commun.*, 1991, **56**, 2030.

391. H.Hirashima and K.Soda, *J.Phys.Soc.Jpn.*, 1991, **60**, 2783 (*Chem.Abs.*, 1992, **115**, 177714).
392. R.S.Tsai, B.Testa, N.El Tayar, and P.A.Carrupt, *J.Chem.Soc., Perkin Trans.2*, 1991, 1797.
393. P.Gibbs, A.Radzicka, and R.Wolfenden, *J.Am.Chem.Soc.*, 1991, **113**, 4714.
394. M.Bryjak, P.Wieczorek, P.Kafarski, and B.Lejczak, *J.Membr.Sci.*, 1991, **56**, 167.
395. E.B.Leodidis, A.S.Bommarius, and T.A.Hatton, *J.Phys.Chem.*, 1991, **95**, 5943; E.B.Leodidis and T.A.Hatton, *Ibid.*, p.5957.
396. Y.Ikeura, K.Kurihara, and T.Kunitake, *J.Am.Chem.Soc.*, 1991, **113**, 7342.
397. T.Miyasaka, N.Nishikawa, K.Hashimoto, and M.Ono, *Chem.Lett.*, 1991, 619.
398. O.Dusart, H.Bouabane, and M.Mazett, *J.Chim.Phys., Phys.- Chim.Biol.*, 1991, **88**, 259.
399. S.Fujiwara and Y.Nishimoto, *Anal.Sci.*, 1991, **7**, 683, 687.
400. H.J.Boehm and S.Brode, *J.Am.Chem.Soc.*, 1991, **113**, 7129.
401. J.Hlavacek, V.Matejka, and P.Carsky, *J.Comput.Chem.*, 1991, **12**, 829.
402. Y.K.Kang and M.S.Jhou, *Bull.Korean Chem.Soc.*, 1991, **12**, 495.
403. F.Lelj, P.Grimaldi, and P.L.Cristinziano, *Biopolymers*, 1991, **31**, 663.
404. M.Souhassou, C.Lecomte, R.H.Blessing, A.Aubry, M.M.Rohmer, R.Wiest, M.Benard, and M.Marraud, *Acta Crystallogr., Sect.B: Struct.Sci.*, 1991, *B47*, 253.
405. L.Schaefer, S.Q.Newton, F.A.Momany, and V.J.Klimkowski, *Theochem.*, 1991, **78**, 275.
406. H.S.Rzepa and M.Y.Yi, *J.Chem.Soc., Perkin Trans.2*, 1991, 531.
407. V.K.W.Cheng, R.F.Frey, S.Q.Newton, and L.Schaefer, *Theochem*, 1991, **81**, 1.
408. A.Alvira, J.Breton, J.Plata, and C.Girardet, *Chem.Phys.*, 1991, **155**, 7.
409. M.Sabio and S.Topiol, *Chirality*, 1991, **3**, 56.
410. R.Fausto, J.J.C.Teixeira-Dias, and P.R.Carey, *J.Am.Chem.Soc.*, 1991, **113**, 2471.
411. V.R.Meyer, *ACS Symp.Ser.* (Chiral Separation and Liquid Chromatography), 1991, **471**, 217.
412. G.C.Barrett, in *Amino Acids and Peptides*, Vol.23, The Royal Society of Chemistry, London, 1991, pp. 51,52.
413. T.Shiraiwa, K.Shinjo, and H.Kurokawa, *Bull.Chem.Soc.Jpn.*, 1991, **64**, 3251.
414. L.Mion, A.-M.Honnoraty, A.Rousset, and A.Previero, *Tetrahedron Lett.*, 1991, **32**, 7401.
415. G.N.Jham, R.E.Cover, and J.Kovacs, *J.Indian Inst.Sci.*, 1990, **70**, 419 (*Chem.Abs.*, 1991, **114**, 186054).
416. M.Slebioda, Z.Wodecki, and A.M.Kolodziesczyk, *Int.J.Pept.Protein Res.*, 1990, **35**, 539.
417. A.M.Foti, G.A.Baratta, G.Leto, and G.Strazzulla, *Europhys.Lett.*, 1991, 16, 201.
418. P.Melius and C.Srisomsap, *J.Appl.Polym.Sci.*, 1991, **42**, 1167.
419. B.M.Rode and M.G.Schwendinger, *Origins Life Evol.Biosphere*, 1990, **20**, 401.
420. M.G.Schwendinger and B.M.Rode, *Inorg.Chim Acta , 1991*, **186**, 247.
421. M.Nagayama, O.Takaoka, K.Inomata, and Y.Yamagata, *Origins Life Evol.Biosphere*, 1990, **20**, 249.
422. M.C.Wang, *Clays Clay Miner.*, 1991, **39**, 202 (*Chem.Abs.*, 1991, **115**, 50244).
423. S.T.Chen, C.H.Chang, and K.T.Wang, *J.Chem.Res.Synop.*, 1991, 206.
424. F.Benoufella, A.Gaid, and A.Laplanche, *J.Fr.Hydrol.*, 1990, **21**, 41 (*Chem.Abs.*, 1991, **114**, 149820).
425. (a) J.M.Antelo, F.Arce, J.Crugeiras, J.Franco, F.Lopez, P.Rodriguez, and A.Varela, *An.Quim.*, 1991, **87**, 195; (b) J.M.Antelo, F.Arce, J.Crugeiras, J.Franco, P.Rodriguez, and A.Varela, *Idem*, p.21.

426. H.Quast and H.Leybach, *Chem.Ber.*, 1991, **124**, 849.
427. C.J.Easton, K.Kociuba, and S.C.Peters, *J.Chem.Soc., Chem.Commun.*, 1991, 1475.
428. D.Zhou, Y.Guan, and S.Jin, *Chin.Chem.Lett.*, 1990, **1**, 209 (*Chem.Abs.*, 1991, **115**, 280493).
429. S.Rahal and L.Badache, *Tetrahedron Lett.*, 1991, **32**, 3847.
430. R.W.Alder, D.Colclough, and R.W.Mowlam, *Tetrahedron Lett.*, 1991, **32**, 7755.
431. F.Filira, L.Biondi, M.Gobbo, and R.Rocchi,*Tetrahedron Lett.*, 1991, **32**, 7463.
432. A.Arcadi, E.Bernocchi, S.Cacchi, F.Marinelli, and A.Scarinci, *SynLett.*, 1991, 177.
433. A.A.Gershkovich, *Bioorg.Khim.*, 1991, **17**, 546.
434. B.Lonbinoux and P.Gerardin, *Tetrahedron Lett.*, 1991, **32**, 351.
435. A.J.Bourque and I.S.Krull, *J.Chromatogr.*, 1991, **537**, 123.
436. C.X.Gao, D.Schmalzing, and I.S.Krull, *Biomed.Chromatogr.*, 1991, **5**, 23.
437. J.Frederiksen, B.D.Larsen, and N.Harrit, *Tetrahedron Lett.*, 1991, **32**, 5823.
438. M.A.Vazquez, F.Munoz, J.Donoso, and F.Garcia Blanco, *J.Mol.Catal.*, 1991, **68**, 105.
439. M.A.Vazquez, F.Munoz, J.Donoso, and F.Garcia Blanco, *J.Chem.Soc., Perkin Trans.2*, 1991, 275.
440. N.F.Bazhulina, V.A.Bokovoi, Yu.V.Morozov, L.I.Fedorova, and V.O.Chekhov, *Mol.Biol.(Moscow)*, 1991, **23**, 678.
441. V.M.Shanbhag and A.E.Martell, *J.Am.Chem.Soc.*, 1991, **113**, 6479.
442. H.Waldmann and M.Braun, *Gazz.Chim.Ital.*, 1991, **121**, 277.
443. (a) P.Allway and R.Grigg, *Tetrahedron Lett.*, 1991, **32**, 5817; (b) T.Coulter, R.Grigg, J.F.Malone, and V.Sridharan, *Tetrahedron Lett.*, 1991, **32**, 5417.
444. R.Grigg and T.Coulter, *Tetrahedron Lett.*, 1991, **32**, 1359.
445. L.Debrauwer, G.Vernin, J.Metzger, A.M.Siouffi, and J.L.Larice, *Bull.Soc.Chim.Fr.*, 1991, 244.
446. A.Lapolla, C.Gerhardinger, G.Crepaldi, D.Fedele, M.Palumbo, D.Datzoppo, C.J.Porter, E.Ghezzo, R.Seraglia, and P.Traldi, *Talanta*, 1991, **38**, 405.
447. V.Yaylayan, *Trends Food Sci.Technol.*, 1990, **1**, 20.
448. V.Yaylayan and S.Lachambre, *J.Food.Sci.*, 1990, **55**, 1124.
449. S.Kawakishi, J.Tsunehiro, and K.Uchida, *Carbohydr.Res.*, 1991, **211**, 162.
450. D.Yin and U.T.Brunk, *Mech.Ageing Dev.*, 1991, **61**, 99 (*Chem.Abs.*, 1992, **116**, 53813).
451. J.Loescher, L.Kroh, G.Westphal, and J.Vogel, *Z.Lebensm.Unters.Forsch.*, 1991, **192**, 323,452. F.Ledl, *Z.Ernaehrungswiss.*, 1991, **30**, 4.
453. S.K.Grandhee and V.M.Monnier, *J.Biol.Chem.*, 1991, **266**, 11649.
454. "Maillard Reactions in Food Processing, Human Nutrition and Physiology", Ed. P.A.Finot, Birkhauser, Basel, 1990.
455. M.J.O'Donnell, K.Cook, and D.B.Rusterholz, *Synthesis*, 1991, 983.
456. J.Broos, M.N.Martin, I.Rouwenhorst, W.Verboom, and S.N.Reinhoudt, *Recl.Trav. Chim.Pays-Bas*, 1991, **110**, 222.
457. F.C.Theobaldo, E.Lira, E.Chang, A.Irokawa, and M.Tominaga, *Biotechnol.Tech.*, 1991, **5**, 73.
458. M.Portelli, *Farmaco*, 1991, **46**, 839 (*Chem.Abs.*, 1992, **116**, 23331).
459. J.C.Lacey, R.D.Thomas, M.P.Staves, and C.L.Watkins, *Biochim.Biophys.Acta*, 1991, **1076**, 395.
460. M.H.Jacobsen, O.Buchardt, T.Engdahl, and A.Hohn, *Tetrahedron Lett.*, 1991, **32**, 6199.
461. F.M.F.Chen, Y.C.Lee, and N.L.Benoiton, *Int.J.Pept.Protein Res.*, 1991, **38**, 97.

462. J.N.Bertho, A.Loffet, C.Pinel, F.Reuther, and G.Sennyey, *Tetrahedron Lett.*, 1991, **32**, 1303.
463. A.Orzeszko, *J.Appl.Polym.Sci.*, 1991, **42**, 2349.
464. M.Namikoshi, B.Kundu, and K.L.Rinehart, *J.Org.Chem.*, 1991, **56**, 5464.
465. K.L.Kaestle, M.K.Anwer, T.K.Audhya, and G.Goldstein, *Tetrahedron Lett.*, 1991, **32**, 327.
466. K.Ohkubo, H.Ishida, K.Yamaki, and M.Kawata, *Chem.Lett.*, 1991, 1723.
467. J.P.Couvercelle, J.Huguet, and M.Vert, *Macromolecules*, 1991, **24**, 6452.
468. M.C.Cleij, W.Drenth, and R.J.M.Nolte, *J.Org.Chem.*, 1991, **56**, 3883.
469. T.Yasukata, S.Sasaki, and K.Koga, *Chem.Pharm.Bull.*, 1991, **39**, 530.
470. M.Rodriguez, M.Llinares, S.Doulur, A.Heitz, and J.Martinez, *Tetrahedron Lett.*, 1991, **32**, 923.
471. H.Oki, H.Gersoh, and R.Nakata, *Chem.Lett.*, 1991, 789.
472. M.T.Reetz and E.H.Lauterbach, *Tetrahedron Lett.*, 1991, **32**, 4477.
473. M.T.Reetz and E.H.Lauterbach, *Tetrahedron Lett.*, 1991, **32**, 4481.
474. K.E.Harding, L.T.Liu, D.G.Farrar, M.T.Coleman, and S.K.Tansey, *Synth.,Commun.*, 1991, **21**, 1409.
475. S.Laskar, U.Bhattacharya, and B.Basak, *Analyst*, 1991, **116**, 625.
476. G.C.Barrett, in 'Chemistry and Biochemistry of the Amino Acids', Ed. G.C.Barrett, Chapman and Hall, London, 1985, p.366.
477. N.L.Benoiton, *Int.J.Pept.Protein Res.*, 1991, **38**, 285.
478. H.Huang, J.Zhang, and J.Wang, *Gaodeng Xuexiao Huaxue Xuebao*, 1990, **11**, 958 (*Chem.Abs.*, 1991, **115**, 49475).
479. T.Miyazawa, T.Otomatsu, T.Yamada, and S.Kuwata, *Chem.Express*, 1991, **6**, 61.
480. T.Miyazawa, T.Yamada, and S.Kuwata, *Chem.Express*, 1991, **6**, 137.
481. H.Huang, J.Zhang, K.Mao, and J.Wang, *Jilin Dazue Ziran Kexue Xuebao*, 1990, 106 (*Chem.Abs.*, 1991, **114**, 247192).
482. H.Rodriguez, A.Marquez, C.A.Chuaqui, and B.Gomez, *Tetrahedron*, 1991, **47**, 5681.
483. A.Correa, J.N.Denis, and A.E.Greene, *Synth.Commun.*, 1991, **21**, 1.
484. D.Martin, *J.Prakt.Chem.*, 1991, **333**, 261.
485. N.Aouf, G.Dewynter, and J.-L.Montero, *Tetrahedron Lett.*, 1991, **32**, 6545.
486. M.F.Loewe, R.J.Cvetovich, and G.G.Hazen, *Tetrahedron Lett.*, 1991, **32**, 2299.
487. I.Gomez-Monterrey, J.Dominguez, R.Gonzalez-Muniz, J.R.Harto, and T.Garcia-Lopez, *Tetrahedron Lett.*, 1991, **32**, 3563.
488. G.P.Panigrahi and R.C.Paichha, *Int.J.Chem.Kinet.*, 1991, **23**, 345.
489. D.Laloo and M.K.Mahanti, *Afinidad*, 1991, **48**, 45.
490. D.G.Marangoni, I.G.N.Wylie, and S.G.Roscoe, *Bioelectrochem.Bioenerg.*, 1991, **25**, 269.
491. M.J.Insansti, F.Mata-Perez, and M.P.Alvarez-Macho, *Int.J.Chem.Kinet.*, 1991, **23**, 593.
492. F.Andres, A.Arrizabalaga, J.Casado, and R.Peche, *React.Kinet.Catal.Lett.*, 1991, **44**, 293.
493. R.M.Hassan, *Can.J.Chem.*, 1991, **69**, 2018.
494. A.Mucientes, F.J.Poblete, and J.Casado, *React.Kinet.Catal.Lett.*, 1991, **43**, 249.
495. E.R.Stadtman and B.S.Berlett, *J.Biol.Chem.*, 1991, **266**, 17201.
496. C.J.Easton, C.A.Hutton, G.Rositano, and E.W.Tarr, *J.Org.Chem.*, 1991, **56**, 5614.
497. V.A.Burgess and C.J.Easton, *Spectrosc.Lett.*, 1991, **24**, 1059.
498. P.Capdevielle and M.Maumy, *Tetrahedron Lett.*, 1991, **32**, 3831.
499. G.C.Barrett, M.L.A.Choudhury, and A.A.Usmani, *Tetrahedron Lett.*, 1978, 2063.
500. C.F.Bigge, J.-P.Wu, and J.R.Drummond, *Tetrahedron Lett.*, 1991, **32**, 7659.

501. N.J.Turner and M.C.Webberley, *J.Chem.Soc., Chem.Commun.*, 1991, 1349.
502. D.Cantacazune and S.Attal, *Carbohydr.Res.*, 1991, **211**, 327.
503. D.Cantacazune, S.Attal, and S.Bay, *Bioorg.Med.Chem.Lett.*, 1991, **1**, 197.
504. M.Elofsson, B.Walse, and J.Kihlberg, *Tetrahedron Lett.*, 1991, **32**, 7613.
505. L.Szabo, Y.Li, and R.Polt, *Tetrahedron Lett.*, 1991, **32**, 585.
506. Y.Ueno, R.Saito, and T.Hata, *Tetrahedron Lett.*, 1991, **32**, 1347.
507. H.Groenevelt and G.A.Lajoie, *J.Org.Chem.*, 1991, **56**, 3447.
508. A.Dondoni, D.Perrone, and P.Merino, *J.Chem.Soc., Chem.Commun.*, 1991, 1313.
509. M.E.Gelbin and J.Kohn, *Polym.Prep.*, 1991, **32**, 241.
510. M.Ho, W.Wang, M.Douvlos, T.Pham, and T.Klock, *Tetrahedron Lett.*, 1991, **32**, 1283.
511. H.C.Uzar, *Synthesis*, 1991, 526.
512. J.A.Moore and J.M.Schwab, *Tetrahedron Lett.*, 1991, **32**, 2331.
513. P.Sieber and B.Riniker, *Tetrahedron Lett.*, 1991, **32**, 739.
514. L.Urge, E.Kollat, M.Hollosi, I.Laczko, K.Wroblewski, J.Thurin, and L.Otvos, *Tetrahedron Lett.*, 1991, **32**, 3445.
515. K.Burger, M.Gold, H.Neuhauser, and M.Rudolph, *Chem.-Ztg.*, 1991, **115**, 77.
516. S.-H.Wu, F.-Y.Chu, C.-H.Chang, and K.-T.Wang, *Tetrahedron Lett.*, 1991, **32**, 3529.
517. S.Honda, *Chem.Express*, 1991, **6**, 743.
518. J.E.Baldwin, M.G.Moloney, and S.B.Shim, *Tetrahedron Lett.*, 1991, **32**, 1379.
519. K.-C.Woo and K.Jones, *Tetrahedron Lett.*, 1991, **32**, 6949.
520. P.Cauliez, B.Rigo, D.Fasseur, and D.Couturier, *J.Heterocycl.Chem.*, 1991, **28**, 1143.
521. R.J.Parry and F.L.Lii, *J.Am.Chem.Soc.*, 1991, **113**, 4704.
522. T.Koide, A.Otaka, H.Suzuki, and N.Fujii, *Synlett.*, 1991, 345.
523. J.P.Tam, C.R.Wu, and J.W.Chang, *J.Am.Chem.Soc.*, 1991, **113**, 6657.
524. M.Ghadimi and R.R.Hill, *J.Chem.Soc., Chem.Commun.*, 1991, 903.
525. S.Singh and G.Dryhurst, *Bio-org.Chem.*, 1991, **19**, 274.
526. Z.Balajthy, *Org.Prep.Proced.Int.*, 1991, **23**, 375.
527. Z.Balajthy, *Org.Prep.Proced.Int.*, 1991, **23**, 569.
528. B.Cuenoud and A.Schepartz, *Tetrahedron*, 1991, **47**, 2535.
529. S.L.Mecklenburg, B.M.Peek, W.B.Erickson, and T.J.Meyer, *J.Am.Chem.Soc.*, 1991, **113**, 8540.
530. M.Jetten, C.A.M.Peters, J.W.F.M. van Nispen, and H.C.J.Ottenheijm, *Tetrahedron Lett.*, 1991, **32**, 6025.
531. R.Ramage, J.Green, and A.J.Blake, *Tetrahedron*, 1991, **47**, 6353.
532. F.Ferrario, S.Levi, A.Sala, and F.Trupiano, *Synth.Commun.*, 1991, **21**, 99.
533. H.B.Arzeno, W.Bingenheimer, and D.J.Morgans, *Synth.Commun.*, 1990, **20**, 3433.
534. P.L.Feldman, *Tetrahedron Lett.*, 1991, **32**, 875.
535. G.C.Wallace and J.M.Fukuto, *J.Med.Chem.*, 1991, **34**, 1746.
536. A.J.L.Cooper, *ChemTracts: Biochem.Mol.Biol.*, 1991, **2**, 214.
537. K.Taraz, R.Tappe, H.Schroeder, U.Hohenreicher, I.Gwose, H.Budzikiewicz, G.Mohn, and J.F.Lefevre, *Z.Naturforsch C: Biosci.*, 1991, **46**, 527.
538. J.Michels and K.Taraz, *Org.Mass Spectrom.*, 1991, **26**, 899.
539. M.J.Smith, E.P.Mazzola, T.J.Farrell, J.A.Sphon, S.W.Page, D.Ashley, S.R.Sirimanne, R.H.Hill, and L.L.Needham, *Tetrahedron Lett.*, 1991, **32**, 991.
540. B.Ganem, *Chemtracts: Org.Chem.*, 1991, **4**, 239.
541. K.Barlos, O.Chatzi, D.Gatos, G.Stavropoulos, and T.Tsegenides, *Tetrahedron Lett.*, 1991, **32**, 475.

542. S.Klutchko, J.C.Hodges, C.J.Blankley, and N.L.Colbry, *J.Heterocycl.Chem.*, 1991, **28**, 97.
543. S.Ranganathan, D.Ranganathan, and D.Bhattacharyya, *Tetrahedron Lett.*, 1991, **32**, 5615.
544. D.A.Malencik and S.R.Anderson, *Biochim.Biophys.Res.Commun.*, 1991, **178**, 60.
545. R.V.Prigodich and A.Sanaulla, *J.Chem.Res., Synop.*, 1991, 66.
546. P.J.Connolly and J.C.Hoch, *J.Magn.Reson.*, 1991, **95**, 165.
547. G.S.Mahmoud, *J.Photochem.Photobiol.*, 1991, **10**, 353.
548. S.Solar, N.Getoff, P.S.Surdhar, S.A.Armstrong, and A.Singh, *J.Phys.Chem.*, 1991, **95**, 3639.
549. R.S.Ersser and J.F.Davey, *Med.Lab.Sci.*, 1991, **48**, 59.
550. Y.Ishida, *J.Chromatogr.Libr.*, Liquid Chromatography in Biomedical Analysis, *50*, 47.
551. N.Dizdar, A.Henriksson and B.Kaagedal, *J.Chromatogr.*, 1991, **565**, 1.
552. K.R.Ulrey and M.C.Nahata, *J.Pharm.Technol.*, 1990, **6**, 64.
553. S.L.Mackenzie, *Chem.Anal.*, Gas Chromatography, *111*, 267.
554. I.Abe and T.Wasa, *Chem.Express*, 1991, **6**, 253.
555. C.A.Hamann, D.P.Myers, K.J.Rittle, E.F.Wirth, and O.A.Moe, *J.Chem.Educ.*, 1991, **68**, 438.
556. D.Arbain, J.Langley, K.Picker, and W.C.Taylor, *Aust.J.Chem.*, 1991, **44**, 887.
557. H.Bruckner, J.Maisch, C.Reinecke, and A.Kimonyo, *Amino Acids*, 1991, **1**, 251.
558. T.M.Moodie, L.van der Westhuizen, and D.Labadarios, *J.High Resol.Chromatogr.*, 1991, **14**, 579.
559. P.Husek, *J.Chromatogr.*, 1991, **552**, 289.
560. P.Husek, *FEBS Lett.*, 1991, **280**, 354.
561. N.Masuoka, T.Ubuka, K.Yao, M.Kinuta, S.Yamada, and H.Fujiwara, *Amino Acids*, 1991, **1**, 375.
562. W.A.Koenig, *Modern Methods in Protein and Nucleic Acids Research*, Ed.H.Tschesche, de Gruyter, Berlin, 1990, p. 213.
563. K.Stulik, V.Pacakova, and H.Wang, *J.Chromatogr.*, 1991, **552**, 439.
564. A.Berthod, W.Y.Li, and D.W.Armstrong, *Anal.Chim.Acta*, 1991, **244**, 21.
565. T.Konishi, M.Kamada, and H.Nakamura, *Anal.Sci.*, 1989, **5**, 667.
566. S.S.Skorczynski, C.S.Yang, and G.A.Hamilton, *Anal.Biochem.*, 1991, **192**, 403.
567. J.Jentsch, *Amino Acids*, 1991, **1**, 279.
568. K.A.Krok and S.S.Seaver, *Biotechniques*, 1991, **10**, 664.
569. A.M.Uhe, C.R.Collier, E.A.McLennan, D.J.Tucker, and K.O'Dea, *J.Chromatogr.*, 1991, **564**, 81.
570. H.Birwe and A.Hesse, *Clin.Chim.Acta*, 1991, **199**, 33.
571. I.Fermo, E.De Vecchi, C.Arcelloni, P.Brambilla, A.Pastoris, and R.Paroni, *J.Liq.Chromatogr.*, 1991, **14**, 1715.
572. E.Martinez-Force and T.Benitez, *Biotechnol.Tech.*, 1991, **5**, 209.
573. J.Schmidt and C.J.McClain, *J.Chromatogr.*, 1991, **568**, 207.
574. D.W.Armstrong, J.D.Duncan, and S.H.Lee, *Amino Acids*, *1*, 97.
575. S.M.Lunte and O.S.Wong, *Current Sep.*, 1990, **10**, 19.
576. U.Buetikofer, D.Fuchs, J.O.Bosset, and W.Gmuer, *Chromatographia*, 1991, **31**, 441.
577. R.S.Gilbert, G.G.Gonzalez, L.Harwell, and C.V.Byus, *Anal.Biochem.*, 1991, **199**, 86.
578. A.Pecavar, A.Golc-Wondra, M.Prosek, and E.Skocir, *Vestn.Slov.Kem.Drus.*, 1991, **38**, 183. (*Chem.Abs.*, 1991, **115**, 159714).
579. F.Lai, A.Mayer, and T.Sheehan, *Biotechniques*, 1991, **11**, 236.

580. A.S.Inglis, N.A.Bartone, and J.P.Finlayson, *J.Biochem.Biophys.Meth.*, 1988, **15**, 249.
581. R.S.Thoma and D.L.Crimmins, *J.Chromatogr.*, 1991, **537**, 153.
582. F.J.Colilla, S.P.Yadav, K.Brew, and E.Mendez, *J.Chromatogr.*, 1991, **548**, 303.
583. M.Calull, J.Fabregas, R.M.Marce, and F.Bonull, *Chromatographia*, 1991, **31**, 272.
584. T.Hanis, Z.Deyl, R.Struzinsky, and I.Miksik, *J.Chromatogr.*, 1991,*553*, 93.
585. M.Salomoni, M.Muda, E.Zuccato, and E.Mussini, *J.Chromatogr.*, 1991, **572**, 312.
586. S.Osborne, *Lab.Pract.*, 1991, **40**, 75.
587. Z.Tian, T.Hrinyo-Pavlina, R.W.Roeske, and P.N.Rao, *J.Chromatogr.*, 1991, **541**, 297.
588. A.V.Klotz and B.N.Higgins, *Arch.Biochim.Biophys.*, 1991, **291**, 113.
589. J.A.Grunan and J.M.Swiader, *Commun.Soil.Sci. Plant Anal.*, 1991, **22**, 1873.
590. T.Voelker, J.Wuensche, E.Bergmann, and W.B.Souffrant, *Arch.Anim.Nutr.*, 1991, **41**, 615.
591. C.Lazure, J.A.Rochemont, N.G.Siedah, and M.Chretien, *Chromatogr.Sci.*, 1990, **51**, 263.
592. J.H.Waite, *Anal.Biochem.*, 1991, 192, 429.
593. B.Vester and K.Rasmussen, *Eur.J.Chem.Clin.Biochem.*, 1991, **29**, 549.
594. E.H.J.M.Jansen, R.H.van den Berg, B.Roth-Miedema, and L.Doorn, *J.Chromatogr.*, 1991, **553**, 123.
595. I.Papadoyannis, V.Samanidou, and G.Theodoridis, *J.Liq.Chromatogr.*, 1991, **14**, 1409.
596. H.Watanabe, K.Sugahara, K.Inoue, Y.Fujita, and H.Kodama, *J.Chromatogr.*, 1991, **568**, 445.
597. X.Huang and W.T.Kok, *J.Liq.Chromatogr.*, 1991, **14**, 2207.
598. T.Miyazawa, H.Iwanaga, T.Yamada, and S.Kuwata, *Chem.Express*, 1991, **6**, 887.
599. D.Yuan and D.J.Pietrzyk, *J.Chromatogr.*, 1991, **557**, 315.
600. H.E.Meyer, E.Hoffmann-Posorske, H.Korte, A.Donella-Deana, A.M.Buanati, L.A.Pinna, J.Coull, J.Perich, R.M.Valerio, and R.B.Johns, *Chromatographia*, 1990, **30**, 691.
601. T.Bergman, B.Agerberth, and H.Joernvall, *FEBS Lett.*, 1991, **283**, 100.
602. E.Leopold amd L.Gonesclou, *Spectra 2000*, 1991, **156**, 27.
603. P.D.Hale, H.S.Lee, Y.Okamoto, and T.A.Skotheim, *Anal.Lett.*, 1991, **24**, 345.
604. B.A.Sela and R.Doolman, *Clin.Chim.Acta*, 1991, **203**, 91.
605. G.Marko-Varga, E.Dominguez, and M.Carlsson, *GBF Monogr.*, 1991, **14**, 101.
606. G.Marko-Varga, E.Dominguez, and M.Carlsson, *GBF Monogr.*, 1991, **14**, 165 (*Chem.Abs.*, 1992, **116**, 79582).
607. K.Kurkijarvi, T.Vierijoki, and T.Korpela, *Ann. N.Y.Acad.Sci.*, 1990, **585**, 394.