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Content

This review article covers mainly the synthetic approaches for nonproteinogenic heteroarylalanines and therefore it does not include natural proteinogenic amino acids like tryptophan, histidine and their derivatives. There has been an increasing interest in this field as evidenced by many publications which were published during the last decade.

Several review articles on nonproteinogenic amino acids have already appeared in the literature; they include the syntheses and transformations of amino acids substituted with heterocyclic rings as well as the amino acids isolated from various plant sources and fungi [1-5]. To the best of our knowledge no review article has appeared so far covering the syntheses of heteroarylalanines.

The known synthetic methods for the preparation of β-substituted alanines which are based either on conjugate additions to dehydroalanine derivatives or on displacement reactions of β-substituted alanines are neither efficient nor stereospecific and are only partly suitable for the syntheses of heteroarylalanines.

In this article, synthetic methods have been divided into ten chapters. In addition, heteroarylalanines isolated from natural sources, their biosyntheses and resolution methods of their racemates are also reviewed. All synthetic and natural heteroarylalanines described in literature are summarized in the Tables accordingly to the heterocyclic residue attached to the alanine side chain.

For the sake of simplicity, the formulas of amino acids are represented in uncharged (non-dipolar) form; the lactam groups in the Tables are represented in lactim form and the stereochemistry of the alanine side chain is not shown. When necessary, heteroarylalanines are throughout described as *R*- or *S*-, although in the literature descriptors D- and L- are often used. The alanine side chain appears in the Tables abbreviated as A.

The biological activities of some heteroarylalanines which have already found many applications, are only briefly mentioned and are generally not covered in this review article.

I. The Malonate Route.

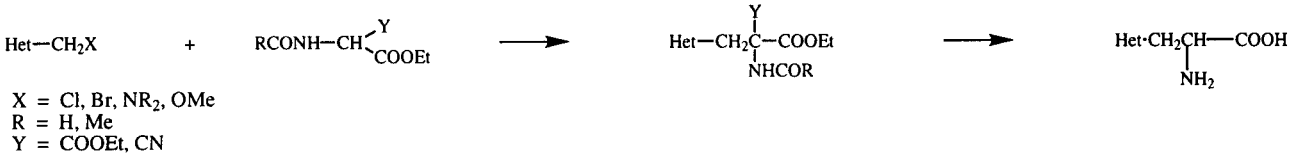
This is the most widely employed synthetic approach for heteroarylalanines. The reaction takes place between a heterocyclic chloro- or bromomethyl compound (in special cases also dialkylaminomethyl or methoxymethyl derivatives were used) and diethyl acetamidomalonate. In a few cases the use of either diethyl formamidomalonate or ethyl acetamidocyanoacetate was found to be advantageous. Hydrolysis of the substituted malonate was in general performed in acidic solution, except in the case of furan derivatives where alkali (or diluted acetic acid) was used. Decarboxylation took place either simultaneously after the hydrolysis or it was induced thermally. The final products are racemates, if not stated otherwise (Scheme 1). The heteroarylalanines prepared by this method are presented in the Tables [6]. Yields are generally good.

II. Syntheses *via* Reactive Methylene Compounds.

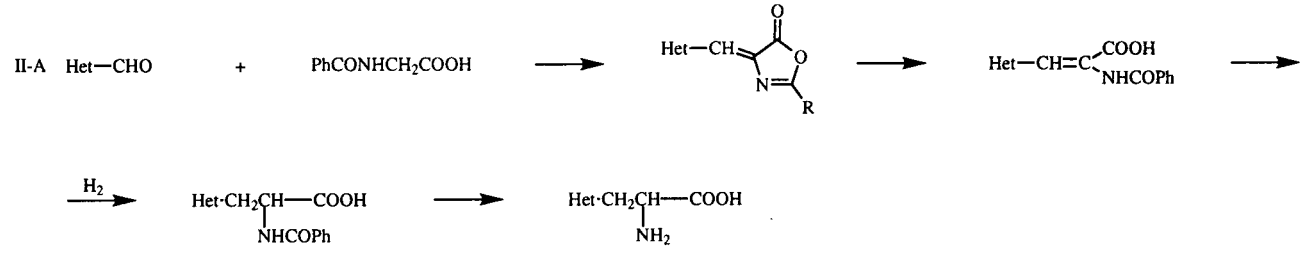
Many compounds with reactive methylene groups can serve as synthons for constructing heteroarylalanines. The majority of them are heterocyclic compounds such as azlactones (oxazolinones), hydantoins (imidazolidine-2,5-diones), imidazolinones, rhodanine, diketopiperazines or oxazinones. The most frequently employed is hippuric acid which is transformed with an aldehyde into the azlactone (Erlenmeyer reaction) which upon reduction and hydrolysis yields the amino acid (Method II-A, Scheme 2).

There are several methods for reductions and hydrolysis of azlactones to the corresponding acylamino or amino acids. These two steps can be combined by using reductive hydrolysis of a suspension of azlactone in alcoholic ammonia over Raney nickel at elevated hydrogen pressure and at room temperature [7].

Scheme 1



Scheme 2



On the other hand, the unsaturated acids obtained from the hydrolysis of azlactones can also be catalytically hydrogenated in the presence of neutral or cationic rhodium 2,3-(*O*-isopropylidene)-2,3-dihydroxy-1,4-[bis(diphenylphosphino)]butane complexes with *e. e.* varying from 3-86% [8]. It has also been observed that unsaturated acids with the heteroaryl moiety such as 2-pyridyl-, 4-pyridyl- or 4(5)-imidazolyl- underwent no hydrogenation.

There are several examples of syntheses starting from hydantoin (Method II-B, Scheme 3) or by alkylation of lithium enolate of a commercially available imidazolinone (Seebach approach) (Method II-C, Scheme 3) or rhodanine (Method II-D, Scheme 4).

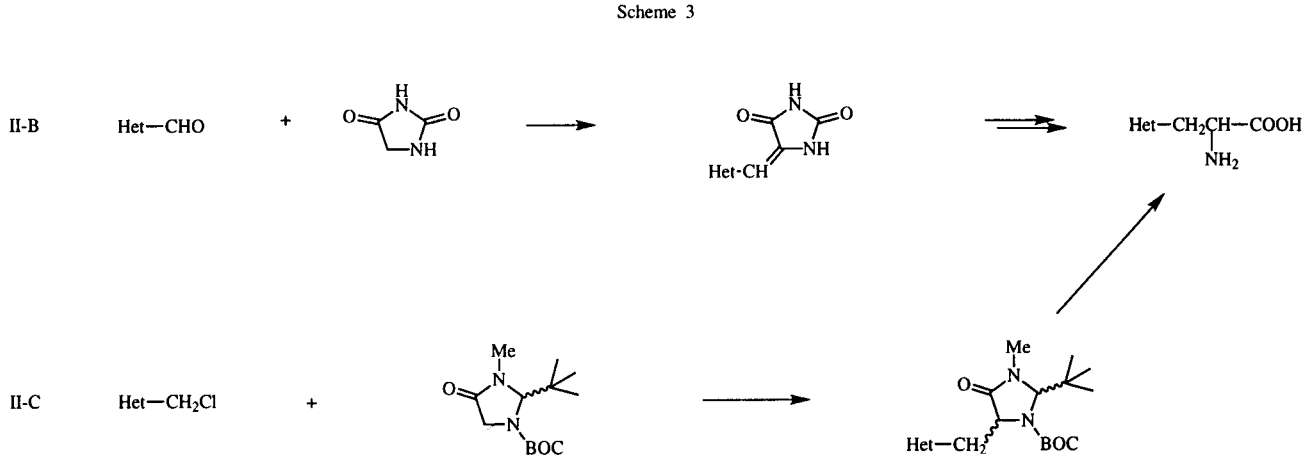
The diketopiperazine (Method II-E, Scheme 4) or 1,4-oxazinone (Method II-F), (Scheme 4) were in certain cases also employed as synthons for heteroarylalanines.

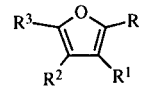
A few cases of using the bis-lactim ether approach (Schöllkopf's method) (Method II-G, Scheme 5) for the preparation of heteroarylalanines were also described in the literature as well as the application of the Schöllkopf-Hartwig bis-lactim ether reagent for the asymmetric synthesis of heteroarylalanines.

Protected glycine imines or amides or their cyclic analogs were used for the preparation of some representatives (Method II-H, Scheme 6). Protected glycine or alanines were either esters of *N*-(diphenylmethylene)glycine, (*R,R*)-pseudoephedrine glycinamide or methyl *N*-benzalalaninate.

Pseudoephedrine glycinamide was used for the synthesis of a protected pyridoxamine coenzyme-amino acid (**183**) which was incorporated into a polypeptide chain. The starting compound was pyridoxamine, its hydroxymethyl side chain was brominated and the product treated

Scheme 3





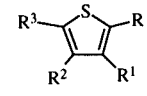
Compound No.	Method of Synthesis	Substituents R	R¹	R²	R³	Remarks	References
1	I	A	H	H	H	as *N*-Cbz, poor yield with DAMM, 25% with EAMC	[89]
						R,S- and *S-*; *N*-Ac	[90]
						poor yield with DAMM or EAMC, good with DFAM, *S-*	[91]
	II-A	A	H	H	H	not suitable for large scale preparation	[7], [8], [92]
	II-B	A	H	H	H		[93], [94]
	II-D, II-E	A	H	H	H	not suitable for large scale preparation	[95], [96]
	V	A	H	H	H	*R-,S-*, >90% *e. e.*	[97]
	V	A	H	H	H	*R-, S-*	[98]
2	I	A	H	COOH	H	with DFMM	[99]
3	V	A	H	H	Me	*R-, S-*	[98]
4	V	A	H	H	NO_2	*R-, S-*	[98]
5	VIII-B	A	H	H	9-pyrenyl	10% yield	[22]
6	V	H	A	H	H	*R-, S-*, >90% *e.e.*	[97]

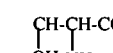
with the chiral auxiliary glycine derivative in the presence of lithium diisopropylamide. Final steps include hydrolysis and deprotection [9].

A pyridone amino acid **178**, isolated from a mushroom, was synthesized from 6-hydroxynicotinic acid. This was transformed into an aldehyde which reacted with Horner-Emmons reagent (Method II-J) to give **287** which was further transformed into the amino acid **178**. The racemate obtained was resolved on chiral tlc plate into both isomers (Scheme 7) [10].

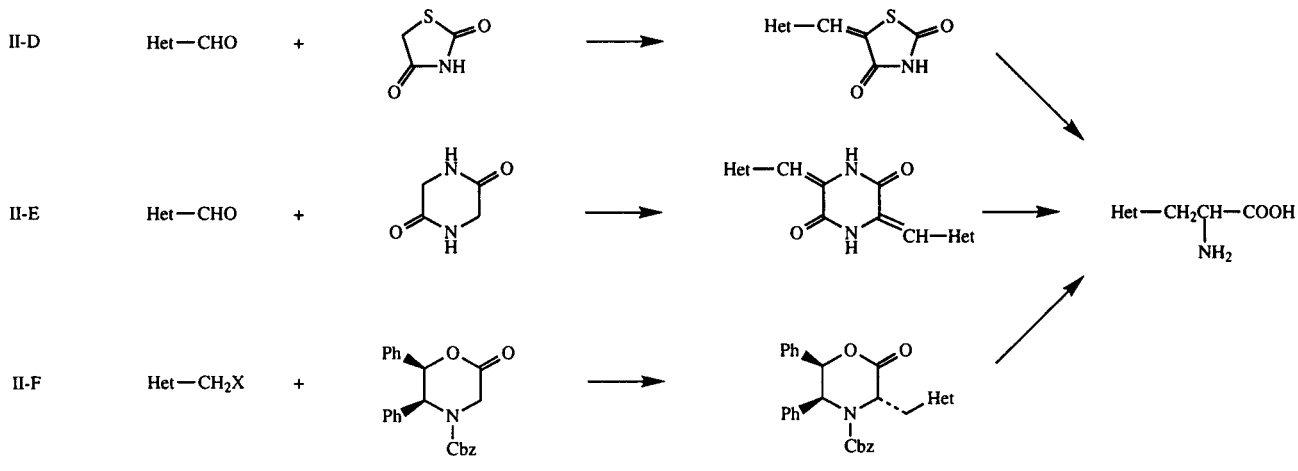
The Horner-Emmons reagent was also used for the preparation of a pyrrole amino acid **27**. The starting compound was 4-formyl-2-methoxycarbonylpyrrole [10,11].

(*R*)-7-Azatryptophan (**130**) was prepared in a multistep reaction sequence from 7-azaindole (pyrrolo[2,3-*b*]pyridine) using (1*R*,4*R*)-camphorimine ester as a chiral tem-

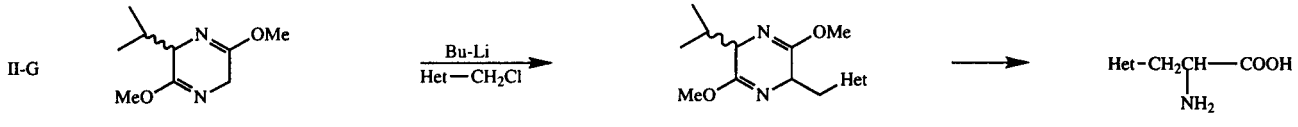


Compound No.	Method of Synthesis	Substituents R	R¹	R²	R³	Remarks	References
7	I	A	H	H	H	*N*-BOC; *S-*	[90]
	I	A	H	H	H	*N*-Bz	[100], [101]
	II-A, II-H	A	H	H	H		[8], [102]
	V	A	H	H	H	*R-*, ≥99% *e. e.*; *R,S-*, >90% *e. e.*	[97], [103], [104]
	VIII-D	A	H	H	H		[24]
8	X	A^1	H	H	H	A^1 = 	[76]
9	VIII-B	A	H	X	H	X = ferrocenyl-CH=CH-	[21]
10	II-D	A	H	H	Me		[105], [106]
	VIII-A	A	H	H	Me	*N*-Ac or *N*-BOC; Me or Bn -ester	[20]
11	II-D	A	H	H	Et		[105], [106]
12	II-D	A	H	H	*n*-Pr		[105], [106]
13	II-D	A	H	H	Cl		[105], [106]
14	I	A	H	H	Br	with EAMC or DAMM	[318]
15	VIII-B	A	H	H	*m*-O_2N-C_6H_4		[21]
16	VIII-B	A	H	H	2-thienyl		[21]
17	I	H	A	H	H	*N*-Bz	[101], [107], [108]
	II-A, II-H	H	A	H	H		[8], [102]
	V	H	A	H	H	*R-, S-*, >90% *e. e.*	[97]
	V	H	A	H	H	*R-*	[104]
18	V	Br	A	H	H		[65]

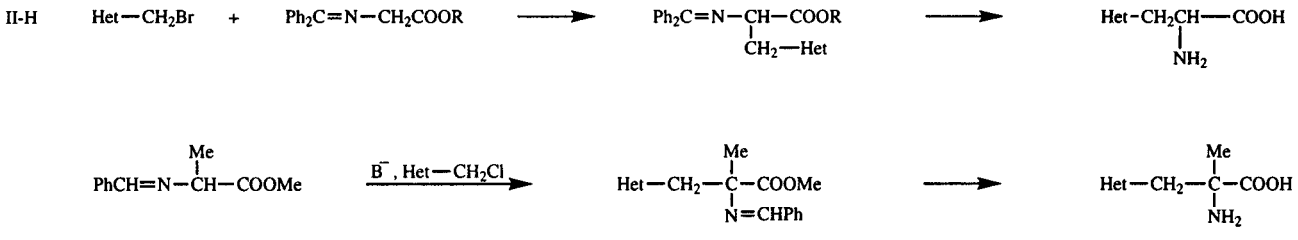
Scheme 4



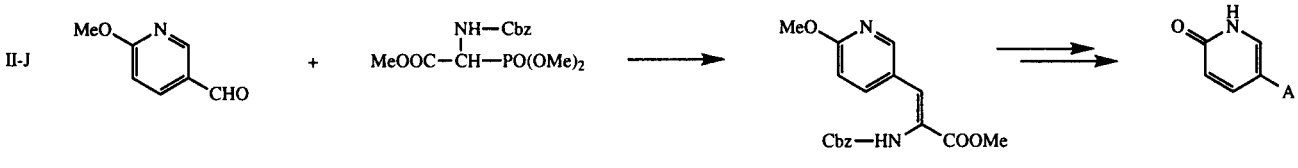
Scheme 5

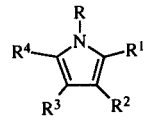


Scheme 6



Scheme 7





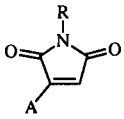
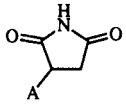
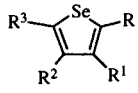
Compound No.	Method of Synthesis	Substituents					Remarks	References
		R	R^1	R^2	R^3	R^4		
19	IX	A	H	H	H	H		[27], [28]
20	IV-A, VII	A		tetrahydro			*S*-	[109], [110]
21	IV-B	A^1	COOMe	H	H	H	A^1 = CH-CH-COOMe; OEt NH_2	[111]
22	I	H	A	H	H	H	from 2-dimethylaminomethylpyrrole and DAMM or EAMC; not obtained pure	[112]
	I	H	A	H	H	H	from 2-dimethylaminomethylpyrrole; *N*-Ac, *N*-BOC, *N*-CBz	[90]
	V, X	H	A	H	H	H	>90% *e. e.*	[75], [97]
	VI	H	A	H	H	H	reduced with Al/Hg; *N*-BOC	[113]
	X	H	A	H	H	H		[75]
23	II-A	Me	A	H	H	H		[8]
24	V	BOC	A	H	H	H		[97]
25	V	Ts	A	H	H	H		[97]
26	VI	H	A	H	H	$COCF_3$	*N*-BOC, Et-ester	[113]
27	II-J	H	H	A	H	COOH		[11]
28								
	IX	H					*N*-Cbz, COOBn	[29], [30]
	IX	Me						[29], [30]
29								
30								
	IX							[29], [30]

plate [12]. Further examples of Method II-H involve alkylation with an aziridine derivative (Scheme 8). Alkylation afforded two isomeric protected products, the *N*-1 and *N*-2 substituted 1,2,4-triazoles in the ratio of about 2:1 [13]. A cyclic sulphamidate (prepared from serine) was also used as a source of reactive methylene group for the preparation of 1-pyrazolylalanine (**67**) (Scheme 9) [14].



Compound No.	Method of Synthesis	Substituents				Remarks	References
		R	R^1	R^2	R^3		
31	I	A	H	H	H		[114]
	V	A	H	H	H	*S*-, 85% yield	[115]
	IX	A	H	H	H	33% yield	[31]
32	I	H	A	H	H		[114]
	V	H	A	H	H	*S*-, 94% yield	[115]

The heteroarylalanines obtained by these procedures are presented in the Tables.

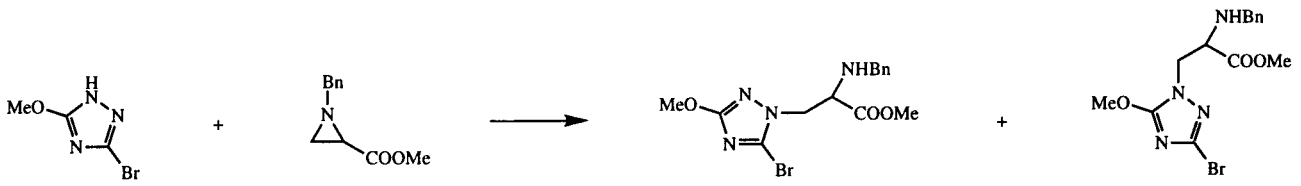
III. The Strecker Synthesis.

This classical approach for the amino acid syntheses has been used mainly for the preparation of at the ring substituted amino acids in the pyrimidine and purine series. The starting *N*-heteroarylacetaldehydes were obtained by alkylation of azines with 2-bromo-1,1-diethoxyethane and they were converted into the corresponding substituted acetaldehydes which were treated with potassium cyanide and ammonia or ammonium chloride or benzylamine (Scheme 10) (for examples see Tables).

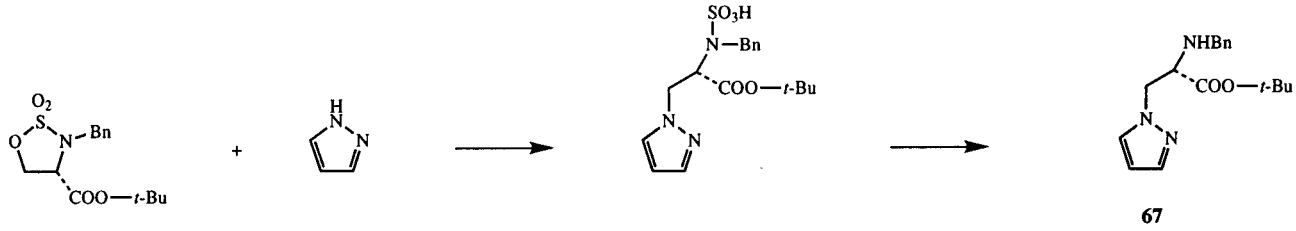
IV. Addition of Secondary Amines to Unsaturated Systems or Addition of Ammonia to Unsaturated Side Chains of Heterocycles.

Catalyzed or uncatalyzed conjugate additions of heterocyclic secondary amino compounds or ammonia to unsaturated heterocyclic acids or esters is a limited synthetic method for the preparation of heteroarylalanines. 2-Acyl-

Scheme 8



Scheme 9



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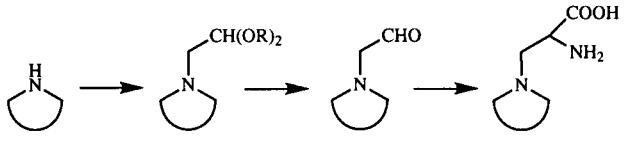
Scheme 10



aminoacrylates (acetyl, trifluoroacetyl or phenylacetyl) were generally used as unsaturated synthons (Method IV-A Scheme 11). A special case of using methyl 3-ethoxy-2-nitroacrylate (Method IV-B) is also described and the nitro group was subsequently reduced. Ethyl α-bromo (or chloro)acrylate (Method IV-C) was used in the following manner. After addition the halogen atom was either replaced directly with ammonia or transformed first into an azido group which was then reduced. A special case represents the Michael addition of a chiral nickel (2)-dehydroalanine complex to imidazole (Method IV-D). Ammonia can also add to an unsaturated side chain of heterocycles (Method IV-E) and, in a special case, 3-chloro-2-(chloromethyl)-1-propene was used to connect two heterocyclic rings (compounds **149** and **263**) (Method IV-F).

Heteroarylalanines prepared by the above methods are presented in the Tables.

V. Hydrogenation of Heteroaryl Acylaminoacrylates.

Enantiomerically pure (*R*)- and (*S*)-heteroarylalanines were prepared by asymmetric hydrogenation of (*Z*)-α-amino-α,β-didehydroesters in the presence of various chiral phosphine-rhodium complexes (Scheme 12). In a special case of dibenzofurylalanine (**126**) cyclization to the tricyclic compound was achieved in the last step.

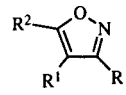
It has been found [15] that the rate of hydrogenation depends on the presence of additional non-complexing acids which can protonate the basic nitrogen of the substrate. This can otherwise interact with the rhodium in the coordination sphere and retard or stop the reaction (for compounds see the Tables).

VI. Syntheses from Methylheterocycles.

A number of racemic heteroarylalanines were prepared from methylazines. These were treated with diethyl oxalate in the presence of a base (Claisen condensation). The pyruvates obtained after the condensation were treated with hydroxylamine and upon reduction the oximino group with tin(II) chloride the corresponding amino acids were obtained (Scheme 13). The compounds prepared are listed in the Tables.

VII. The Use of β-Lactones for the Construction of the Alanine Side Chain and Other *N*-Alkylations.

A great part of *N-tert*-butoxycarbonyl protected heteroarylalanines were synthesized in enantiomerically pure form from *tert*-butoxycarbonyl-serine β-lactone (3-amino-2-oxetanone) by using the method of Vederas [16] (Scheme 14).



Compound No.	Method of Synthesis	Substituents R	R¹	R²	Remarks	References
33	IX	H	A	OH	*N*-Cbz, COOBn	[64]
34	IX	H	A	OAc	*N*-Cbz, COOBn	[64]
35	I	OH	A	Me	abbrev.: AMPA; X-ray of monohydrate [a]	[116]-[118]
					AMP labelled with ^2H in Me group and α- to the COOH	[119]
					N-Methyl-AMPA	[120]
	II-H	OH	A	Me		[121]
36	I	OH	A	Et		[122]
37	I	OH	A	CH_2-OH		[123]
38	I	OH	A	cyclopropyl		[124]
39	I	OH	A	*t*-Bu	abbrev.: ATPA	[125]
40	I	OH	A	CH_2Br		[126]
41	I	OH	A	CF_3		[127]
42	I	OEt	A	Me		[128]
43	I	OCH_2COOH	A	Me		[130]
44	I	OCH_2COOH	A	CF_3		[129]
45	X	COOH	A	Me		[73]
46	X	*p*-$MeOC_6H_4$	A^1	H	A^1 = Ph; CH_2-C-COOMe; $NHCO$-$C_6H_4pNO_2$	[77]
47	I	Cl	A	Me		[127]
48	I, IV-E	OH	H	A	homoibotenic acid (HIBO); 25% yield	[118], [128]
	X	OH	H	A	*R*-, *S*-	[79]
49	II-H, I	OH	Me	A		[121]
50	I	OH	*n*-C_4H_9	A		[132]
51	I	OH	*n*-C_8H_{17}	A		[132]
52	I	OH	CH_2CH_2OH	A		[132]
53	I	OH	CH_2CH_2OMe	A		[132]
54	I	OH	Me	A^1	A^1 = CH(Me)-CH(NH_2)-COOH	[125]
55	I	OH	Br	A		[133]
56	I, IV-E	OMe	H	A	1-2% yield; with $SnCl_2$ added 25% yield	[118]
57	X	CH_2COOH	H	A		[73]
58	X	CH_2CH_2COOH	H	A		[73]
59	X	COOH	H	A		[73]
60	X	COOH	Me	A		[73]
61	I	Cl	Me	A		[127]
62	IX	Ph	H	A	4,5-dihydro derivative	[34]
63	IX	COOH	H	A	2*S*,5'*R* and 2*S*,5'*S*; 4,5-dihydro derivative	[17]
64	IX	A^1	H	CN	4,5-dihydro derivative; A^1 = CH(Me)-CH(NH_2)-COOMe	[60]

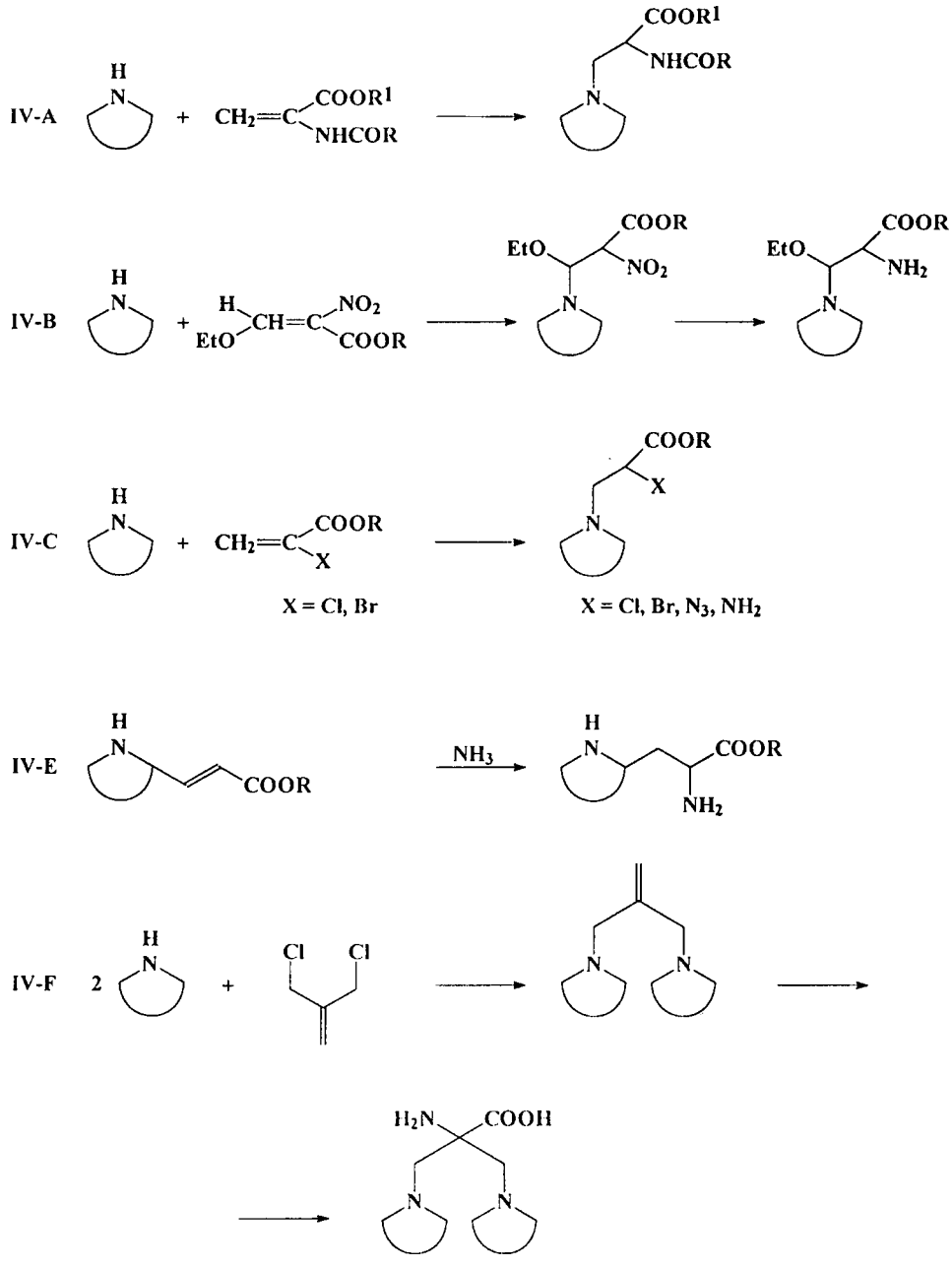
[a] Used as a standard reference for the characterization of neuroreceptors of the non-*N*-methyl-D-aspartic acid type.

The unprotected lactone, (*S*)-3-amino-2-oxetanone in the form of its *p*-toluenesulfonate was also used in a particular case.

If, however, the benzyl ester of imidazole-4-carboxylic acid was treated with *N*-Cbz-(*S*)-serine β-lactone, a mixture of the stereoisomers was obtained in 11% and 18% yield, respectively. After deprotection the (*S*)-isomer **85** was obtained in 81% yield [17]. Compounds prepared by the above methods are listed in the Tables.

Synthetic quisqualic acid (**89**) was prepared by alkylation of 3,5-dioxo-1,2,4-oxazolidine with methyl 3-chloro-2-benzoxycarbonylaminopropionate and subsequent

Scheme 11

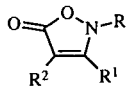


deprotection [18]. In a similar manner isoquisqualic acid was prepared [19].

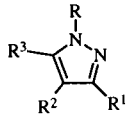
VIII. Metal-Catalyzed Coupling.

Different approaches of metal-catalyzed coupling as a synthetic method for the preparation of heteroarylalanines have been devised.

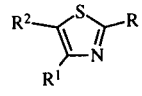
Protected 5-methyl-2-thienylalanines were synthesized by palladium-catalyzed coupling of the corresponding iodothiophene with 2-acetamidoacrylate under phase-transfer conditions. The dehydroamino acid derivatives obtained were hydrogenated in the presence of the Wilkinson catalyst (Method VIII-A) [20]. Other thienyl-



Compound No.	Method of Synthesis	Substituents R	R¹	R²	Remarks	References
65	IX	A	H	H	abbrev. BIA; *S*-, 10% yield, 90% *e. e.*	[32]
	IX	A	H	H	45% yield, 80% *e. e.*	[33]
66	IX	H	H	A	TAN-950A; X-ray	[63]



Compound No.	Method of Synthesis	Substituents R	R¹	R²	R³	Remarks	References
67	I	A	H	H	H	also from 2-^{14}C DAMM	[94], [134]
	II-H	A	H	H	H	*N*-Bn; *t*-Bu ester	[14]
	III	A	H	H	H	*S*-	[135]
	IV-A, IV-C	A	H	H	H		[109], [136], [137]
	VII	A	H	H	H	*R*-, *S*-	[16], [138], [139], [140]
68	IV-C	A	H	Me	H		[141]
69	I	H	A	H	H	from 2-^{14}C DAMM	[94], [131], [142]
70	I	H	H	A	H		[142]
71	IX	H	H	A	OH	*N*-Cbz, COOBn	[64]
72	IX	Me	H	A	OH	*N*-Cbz, COOBn	[64]



Compound No.	Method of Synthesis	Substituents R	R¹	R²	Remarks	References
73	I	A	H	H	16% yield	[143]
74	I	H	A	H		[143]-[145]
	I	H	A	H	*S*-, *N*-BOC	[42],[146]
	IX	H	A	H	*N*-BOC	[42], [66]
75	IX	Me	A	H		[66]
76	IX	Ph	A	H		[40]
77	I	NH_2	A	H		[147], [205]
	IX	NH_2	A	H	also as *N*-BOC, Bn ester	[40], [41], [66]
78	IX	NHCbz	A	H	Me ester	[43]
79	I	NH_2	A	NO_2		[147], [205]
80	I	NH_2	A	NH_2		[147], [205]
81	I	NMe_2	A	H		[147]
82	I	NMe_2	H	NO_2		[147]
83	IX	NHCbz	H	A	Me ester	[43]

alanines were prepared from the corresponding (*R*)-bromo-2-thienylalanines or a furylalanine by tandem catalytic boronic acid coupling in the presence of palladium acetate and tri-(*o*-tolyl)phosphine (Method VIII-B) [21].

Optically pure (*R*)- and (*S*)-3- and 4-pyridylalanines were obtained by transition-metal assisted asymmetric synthesis from the corresponding pyridylacrylates. For coupling of bromopyridines with methyl 2-acetamidoacrylate $Pd_2(dba)_3$ and tri-(*o*-tolyl)phosphine were used. For catalytic hydrogenation a chiral rhodium catalyst was used (Method VIII-C) [22]. The iodozinc reagent, prepared from protected iodoalanine, was used in several cases to react with bromo- or iodopyridines to give protected or deprotected heteroarylalanines (Method VIII-D) [23-25].

All compounds prepared in the described manner are presented in the Tables.

IX. Heteroarylalanines Prepared by Formation of the Heterocyclic Part.

Several synthetic approaches are described in the literature where the heteroarylalanines are formed from compounds already possessing an alanine side chain and the heterocyclic moiety is formed by cyclization in a final step of a particular reaction sequence. In addition, there are cases where the starting heterocyclic compound is rearranged or transformed in another way into a new heterocyclic ring with the alanine side chain.

A furan ring of benzofurylalanines **97-99** is formed from protected 3,5-diiodo-(*S*)-tyrosine and various arylacetylides [26].

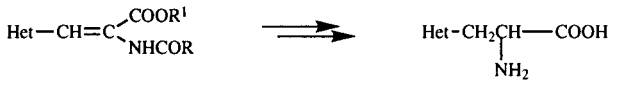
There are several reports on the formation of a pyrrole ring. *N*-Pyrrolo-(*S*)-alanine (**19**) was obtained from N^{α}-tosyl-(*S*)-α,β-diaminopropionic acid and 2,5-diethoxytetrahydrofuran. The *N*-tosyl group was removed with calcium in liquid ammonia [27,28].

Another pyrrole amino acid and its *N*-methyl derivative (**28, 29**) were prepared in a multistep reaction sequence from protected aspartic acid using the Barton method and *N*-hydroxy-2-pyridinethione [29]. In the same manner the protected amino acids were obtained [30] and could be hydrogenated to give a mixture of diastereoisomers **30** in the ratio of 1:1 which could be resolved [29].

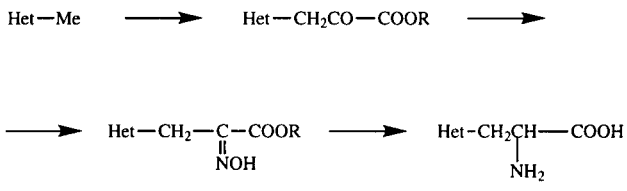
In a novel synthesis 2-selenienylalanine (**31**) was prepared from an acetylenic compound and sodium hydrogenselenide and the obtained *N*-acetyl compound was then converted into **31** [31].

In the isoxazole series, 3-(5-oxo-2*H*-isoxazol-2-yl)alanine (**65**), which was previously synthesized from isoxazolidine-5-one in 10% yield and 90% *e. e.* [32] and also isotopically labeled [33] was prepared in an improved manner from (*S*)-serine. The multistep synthesis involved ring closure of the isoxazolinone ring in the last step.

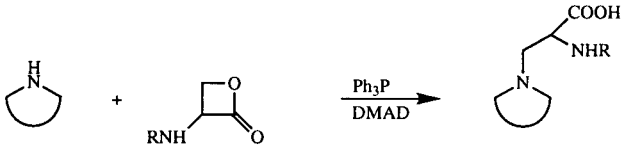
Scheme 12



Scheme 13



Scheme 14



3-(5-Oxo-2*H*-isoxazol-2-yl)alanine was thus prepared in 45% overall yield but with only 80% *e. e.* [33]. In a similar approach diethyl acetamidomalonate was treated with propargyl bromide to give finally (**62**) [34]. (2*S*,5'*R*)- and (2*S*,5'*S*)-2-amino-3-(3-carboxy-2-isoxazolin-5-yl)propionic acid (**63**) were obtained together with 2% of the regioisomers from the reaction between protected (*S*)-allylglycine and a nitrile oxide which was generated *in situ* from methyl chloroximidoacetate. The cycloaddition products were separated (33% and 36% respectively) and hydrolyzed. The structures were determined chemically and by nmr NOE experiments [17].

Condensation of ethyl hippurate with ethyl formate gave an enolic compound which was transformed in a multistep reaction sequence into quisqualic acid (**89**) in an overall yield of 20% [35]. In a similar reaction sequence amino acids containing an imidazole, **87** or a 1,2,4-triazole ring, **94** could be prepared [35]. Benzimidazolylalanines were prepared from the corresponding *o*-aminonitrophenylalanines and after reduction of the nitro group cyclization of the imidazole part to (**122**) and (**123**) was achieved either with formic acid or with phosgene [36-38]. (6-Chloropurin-9-yl)alanine was prepared from 5-amino-4,6-dichloropyrimidine and *N*-tosyl-α,β-diaminopropionic acid followed by ring closure with triethylorthoformate to give **133** [39].

Several thiazolyl- or benzothiazolylalanines were prepared by ring closure of the thiazole part. Thiourea or thioamides were the standard reagents for this purpose. From (*S*)-, (*R*)- or (*R,S*)-*N*-trifluoroacetyl-5-bromo-4-oxonorvaline and thioamides or thiourea the corresponding optically active or racemic **76** was prepared [40]. In a similar manner an α-chloroketone was prepared from protected aspartic acid to give after ring closure with thiourea compound **77** [41].

N-tert-Butoxycarbonyl-3-(4-thiazolyl)-(*S*)-alanine (**74**) was synthesized in a multistep reaction sequence from Cbz-(*S*)-aspartic acid [42]. Two isomeric thiazolylalanines, **78** and **83**, were prepared from the halogenated precursors and thiourea [43]. (*R*)- and (*S*)-aspartic acid were used as the starting material for the preparation of either benzothiazolyl-, benzimidazolyl- or benzoxazolylalanines. Mixed carbonic anhydride coupling was used followed by treatment with either *o*-aminophenyl disulfide, *o*-phenylenediamine or *o*-hydroxyaniline to give compounds **113**, **117** and **112** [44].

Pheomelanin, a red-brown pigment in the skin and hair of fair-skinned humans is photolabile under physiologically relevant conditions. The monomeric part, obtained upon degradation of the protein-free chromophore afforded the amino acid **114**. It was also synthesized from 4-bromomethyl-2-nitroanisole and diethyl acetamidomalonate, the nitro group was reduced and the ring closure of the thiazole part was achieved by thiocyanation [45]. In another synthesis the isomeric amino acid **116** was prepared from 4-acetoxy-7-bromomethylbenzothiazole following the malonate pathway [46].

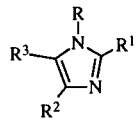
An oxadiazolylalanine **95** was prepared from *p*-benzyloxybenzamide oxime and *N*-protected (*R,S*)-asparagine [47].

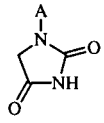
The (*R*)- and (*S*)-enantiomers of tetrazolylalanine (**96**) were prepared from (*R*)- or (*S*)-methyl *N-tert*-butoxycarbonyl-2-amino-3-cyanopropanoate and azido tri-*n*-butyl stannane in over 50% yield [48]. In a similar manner the (*S*)-isomer was prepared with sodium azide in low yield [49].

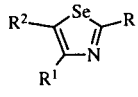
Several azoloazines with bridgehead nitrogen were synthesized from *N*-trifluoroacetyl-3-formylalanine methyl ester and various azinohydrazines, *i. e.* triazolopyridine **154** and triazolopyridazines **155**, **156** [40]. On the other hand, *N*-trifluoroacetyl-5-bromo-4-oxonorvaline yielded with aminoazines the corresponding imidazopyridines **151**, imidazopyrimidines **153** or imidazopyridazines **152** [40].

Quite a number of syntheses proceed by transformations of a heterocyclic system into another one to give various heteroarylalanines.

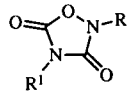
Clavalanine (**157**), a new antibiotic from *Streptomyces clavuligerus* [50-52] was synthesized from D-xylose *via*



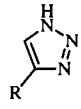
Compound No.	Method of Synthesis	Substituents R	R¹	R²	R³	Remarks	References
84	I	A	H	H	H	1-isohystidine	[148]
	IV-A	A	H	H	H	yield increased by ultrasonic irradiation	[109], [149]
	IV-D	A	H	H	H	*S*-, 85% yield	[150]
	VII	A	H	H	H	*R*-Me ester, *S*-	[110], [139], [151]
85	VII	A	H	COOH	H	*S*-; X-ray data	[17]
86	I	H	A	H	H		[152]
87	IX						[35]



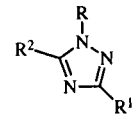
Compound No.	Method of Synthesis	Substituents R	R¹	R²	Remarks	References
88	I	NH_2	A	H	with DFMM	[153]
	IX	NH_2	A	H		[66]

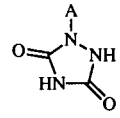


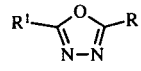
Compound No.	Method of Synthesis	Substituents R	R¹	Remarks	References
89	VII	A	H	quisqualic acid	[18]
	IX	A	H		[35], [54]
90	VII	H	A	isoquisqualic acid	[19]



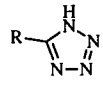
Compound No.	Method of Synthesis	Substituents R	Remarks	References
90a	IIa	A	*R*-, *S*-	[320]



Compound No.	Method of Synthesis	Substituents R	R¹	R²	References
91	II-H	A	OMe	Br	[13]
92	II-H	A	Br	OMe	[13]
93	I	H	A	H	[154], [155]
94	IX				[35]



Compound No.	Method of Synthesis	Substituents R	R¹	References
95	IX	A	*p*-HO-C_6H_4	[47]



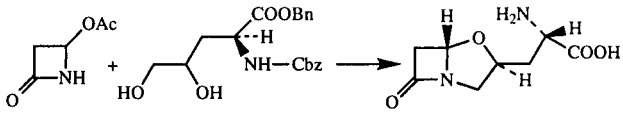
Compound No.	Method of Synthesis	Substituents R	Remarks	References
96	IX	A	*S*-, *R,S*-	[48], [49]

an intermediate which was condensed with 4-acetoxy-2-azetidinone (Scheme 15) [53]. What is remarkable about the structure of **157** is, that it possesses *S*-stereochemistry at the ring juncture. The *R*-isomer was also synthesized [52].

Quisqualic acid (**89**), an exceptionally potent antagonist of the neurotransmitter (*S*)-glutamate was synthesized from a 3-(*S*)-azetidinone derivative (Scheme 16). Isomerization to an oxazolidinone, reaction with ethoxycarbonyl isocyanate to an urea derivative, alkaline ring opening, treatment with trifluoroacetic acid and ion-exchange chromatography afforded the (*S*)-acid **89**. When using the starting (*R*)-azetidinone, (*R*)-quisqualic acid **89** was obtained [54].

(*R,S*)-Stizolobic acid (**282**) was synthesized in a biomimetic fashion from 3,4-dihydroxy-5-methoxybenzaldehyde *via* a dehydrocaffeic acid derivative which formed a

Scheme 15

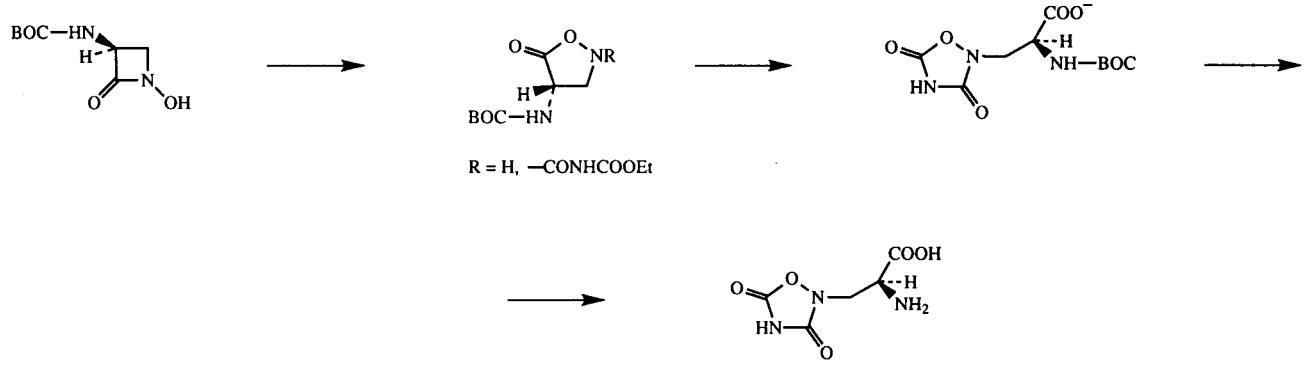


157

butenolide (Scheme 17). This was rearranged in hot hydrochloric acid into desaminostizolobic acid (R = H) which after azidation (R = N_3) and the reduction gave **282** [55]. Upon ammonolysis the pyridine analog, (*R,S*)-acromelobic acid (**190**) was obtained [55]. In a similar transformation compound **190** was prepared directly from stizolobic acid with aqueous ammonia [56].

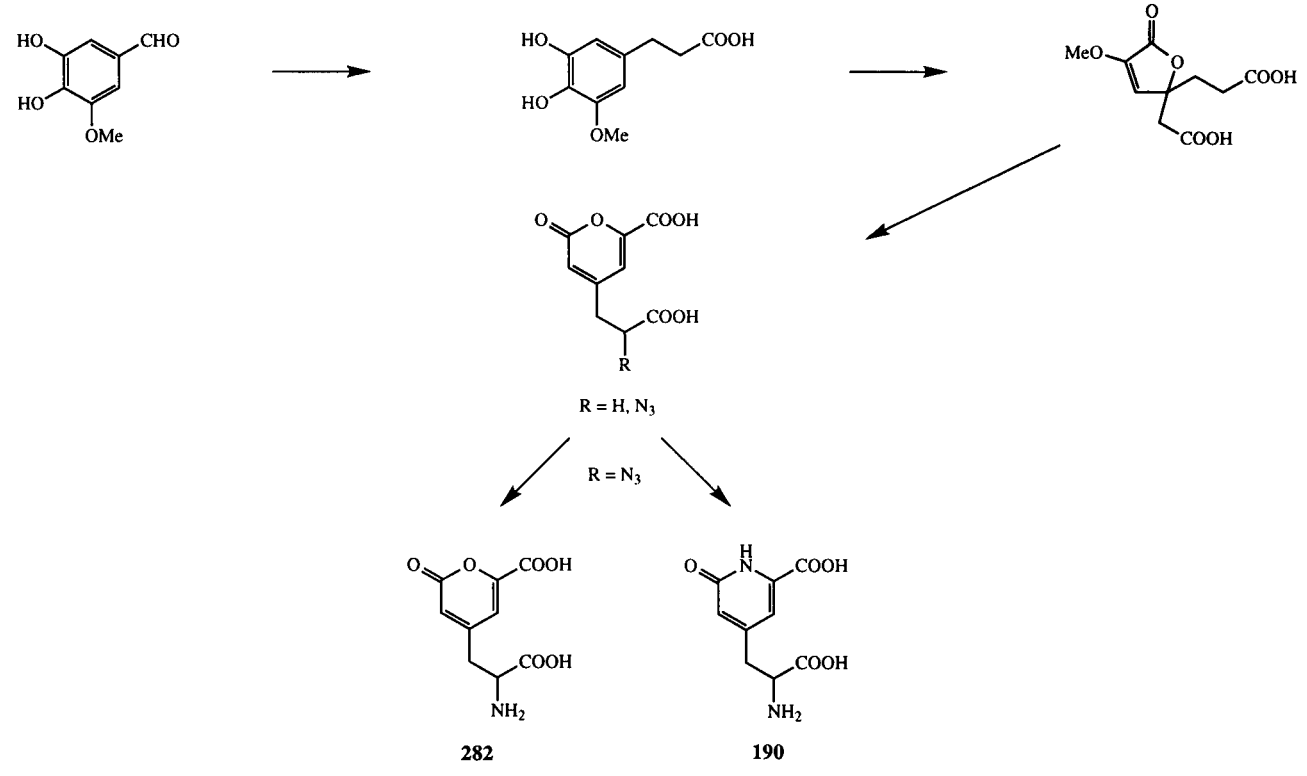
The (*R*)- and (*S*)-deoxymimosines **214** were prepared in two steps from *tert*-butoxycarbonyl-(*R*)- or (*S*)-asparagine, respectively [57].

Scheme 16



R = H, —CONHCOOEt

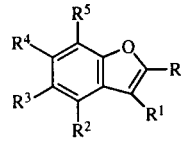
Scheme 17



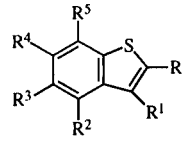
R = H, N_3

R = N_3

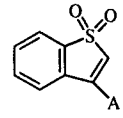
282 190



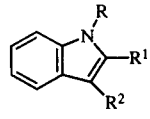
Compound No.	Method of Synthesis	Substituents						Remarks	References
		R	R^1	R^2	R^3	R^4	R^5		
97	II-A	A	Me	H	H	H	H		[157]
98	II-A	A	Me	H	Me	H	H		[157]
99	II-A	A	Me	H	H	H	Me		[157], [158]
100	II-A	A	Me	H	H	H	Cl		[157]
101	IX	Ph	H	H	A	H	I	NHAc	[26]
102	IX	*p*-MeO-C_6H_4	H	H	A	H	I	also as NHAc	[26]
103	IX	3-*i*-Pr-4-Me-C_6H_3	H	H	A	H	I	NHAc	[26]



Compound No.	Method of Synthesis	Substituents						Remarks	References
		R	R^1	R^2	R^3	R^4	R^5		
104	I	A	H	H	H	H	H	with DFMM	[156]
105	I	H	A	H	H	H	H	*R*-, *S*-	[110]
	II-A	H	A	H	H	H	H		[159], [160]
106	II-B	H	A	H	Me	H	H		[160]
107	II-B	H	A	H	Cl	H	H		[160]
108	II-B	H	A	H	Br	H	H		[160]



109	X							NHAc	[85]



Compound No.	Method of Synthesis	Substituents			Remarks	References
		R	R^1	R^2		
110	I	H	A	Me	from 2-dimethyl-aminomethylindole	[161]
111	I	Me	A	H	from 2-dimethyl-aminomethylindole	[162]

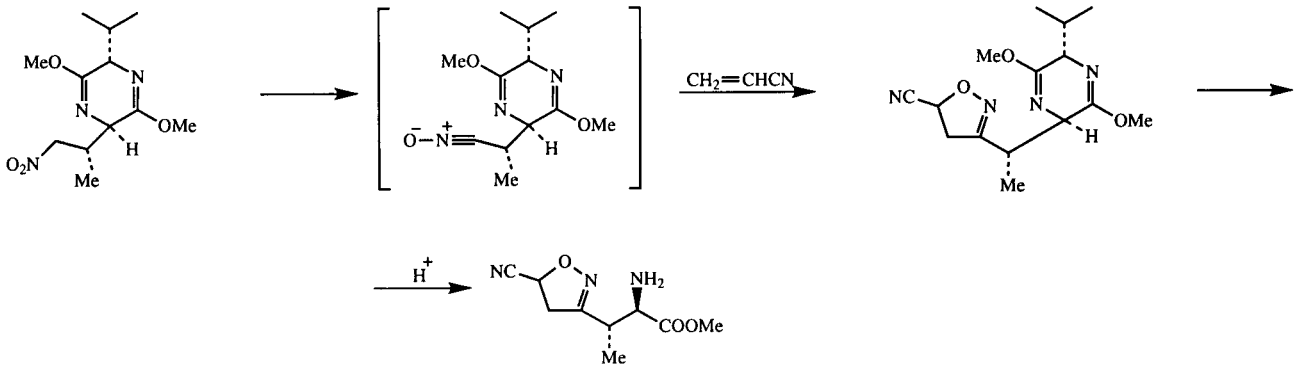
A pyrimidinylalanine derivative was synthesized from β-aminocrotonamide and diethyl *N*-benzoylaspartate. The structure, either an α-**238** or β-alanine derivative has not been firmly established [58].

Numerous α-amino-(3-phosphonoalkyl-2-quinoxalin-3-yl)alanines **271-280** and their benzolog **281** were synthesized [59]. They were prepared from *o*-diaminobenzenes and 1,4-dibromo-2,3-butanedione. The obtained intermediates were phosphorylated by the Arbuzov reaction and the amino acid side chain was introduced by the malonate method. The compounds prepared were found to be potent and selective ligands for the *N*-methyl-D-aspartic acid receptor [59].

There are several cases of rearrangements of heterocycles into other heterocycles with an alanine side chain.

Thus, an isoxazole ring was formed in a [2+3] dipolar cycloaddition of a nitrile oxide derivative (Scheme 18). The initial pyrazine ring afforded upon ring opening the methylalanine side chain of compound **64**. An 1:1 mixture of epimers was obtained [60].

Scheme 18

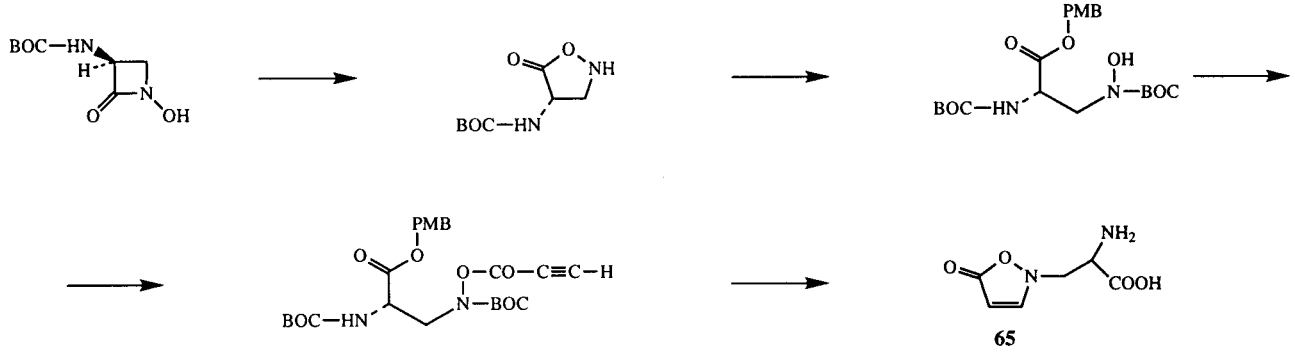


3-(5-Oxo-2*H*-isoxazol-2-yl)alanine (**65**), isolated from roots of pea seedlings [61,62], was synthesized from a β-lactam (Scheme 19). The later was converted into 4-*tert*-butoxycarbonylaminoisoxazolidin-5-one which after ring opening underwent a series of transformations and finally a cyclization with formic acid took place to give **65** [32].

From pyroglutamic acid enantiomerically pure isoxazole, pyrazole or isothiazole derivatives of alanine were obtained (Scheme 21) [64,65].

An 1,3-oxazolidine derivative was used for the formation of a thiazole **77** or selenazole ring **88** in a Hantzsch synthesis (Scheme 22). The starting compound was

Scheme 19



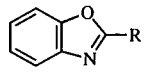
65

An interesting example of a tautomeric amino acid is the antifungal antibiotic 3-(5-oxo-2*H*-isoxazol-4-yl)alanine (TAN-950) (**66**). It was synthesized from γ-formyl-*N*-*tert*-butoxycarbonyl-(*S*)-pyroglutamic acid methyl ester, the product was treated with hydroxylamine, hydrolyzed and deprotected (Scheme 20). When **66** was isolated by cation-exchange chromatography, a mixture of five compounds, **66a**, **b**, **c**, **d** and **e** in the ratio of 2:1:2:1:2 was obtained. Their structures were elucidated on the basis of spectral and X-ray analyses. If the equilibrium mixture of the isoxazolone and rearranged pyrrole derivative was dissolved in 0.5 *N* sodium hydroxide the above compounds were converted to **66a** almost quantitatively in one hour at 60° [63].

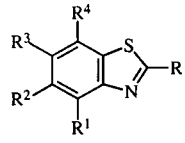
obtained from (*R*)- or (*S*)-aspartic acid using hexafluoroacetone as a protecting reagent [66].

(*R,S*)-5-Hydroxy-2-pyridylalanine (**163**) was prepared in a multistep reaction sequence from kojic acid which was first transformed into a pyridine derivative followed by the malonate route and demethylation and/or dehalogenation to **163** (Scheme 23) [67]. In a similar manner the (*R,S*)-4,5-dihydroxy analog **162** was prepared starting from 2-chloromethyl-5-hydroxy-4-pyrone (chlorokojic acid) *via* the malonate route [68].

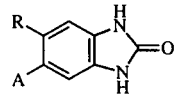
The synthesis of mimosine (**215**) which was previously reported [69] could not be repeated by the described method and a new approach was delineated. The starting compound was 3-benzyloxy-4-pyrone which was con-



Compound No.	Method of Synthesis	Substituent R	Reference
112	IX	A	[44]



Compound No.	Method of Synthesis	Substituents R	R^1	R^2	R^3	R^4	References
113	IX	A	H	H	H	H	[44]
114	IX	H	OH	H	A	H	[45]
115	IX	Me	OH	H	A	H	[72]
116	I, IX	H	OH	H	H	A	[46]



Compound No.	Method of Synthesis	Substituents R	References
123	IX	H	[37], [38]
124	IX	OH	[37], [38]
125	IX	OMe	[37], [38]

densed with (*R,S*)-β-amino-α-tosylaminopropionic acid and after deprotection (*R,S*)-mimosine was obtained in 45% yield [70].

Compounds (*S*)-**182** and (*S*)-**191** which were isolated from a poisonous mushroom, were synthesized from (*S*)-stizolobinic and (*S*)-stizolobic acid, respectively, with ammonia [71].

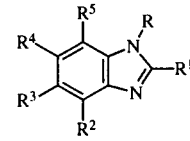
The enol ether derived from protected (*S*)-pyroglutamic acid ester was transformed with amidines into pyrimidinylalanines **245-248** in 39-87% yield (Scheme 24) [65]. The enol ether did not react with 2-aminopyridine, but after being transformed into an aldehyde it afforded a pyrido[1,2-*a*]pyrimidinylalanine (**286**) [65].

An interesting transformation occurred with a pheomelanin precursor which upon irradiation with Pyrex-filtered uv light in a buffered solution underwent a decarboxylative ring contraction giving a benzothiazinylalanine **115** in about 60% yield (Scheme 25) [72]. It was anticipated that the process is a homolytic one.

X. Miscellaneous.

A. Syntheses.

A 1,3-dipolar cycloaddition reaction was employed for the preparation of several compounds, such as **45** and **57-60** (Scheme 26) [73].

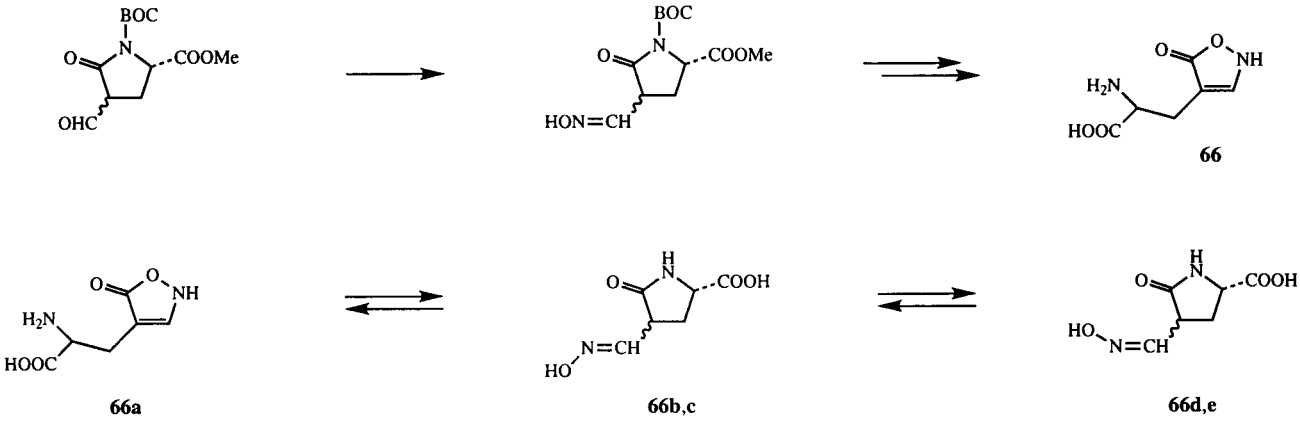


Compound No.	Method of Synthesis	Substituents R	R^1	R^2	R^3	R^4	R^5	Remarks	References
117	IX	H	A	H	H	H	H		[44]
118	IX	H	A	H	H	H	H	4,5,6,7-tetrahydro	[44]
119	II-B	Me	A	H	H	H	H		[163]
120	IX	H	H	H	A	H	H		[36]
121	IX	H	H	H	A	OH	H		[37]
122	IX	H	H	H	A	OMe	H		[38]

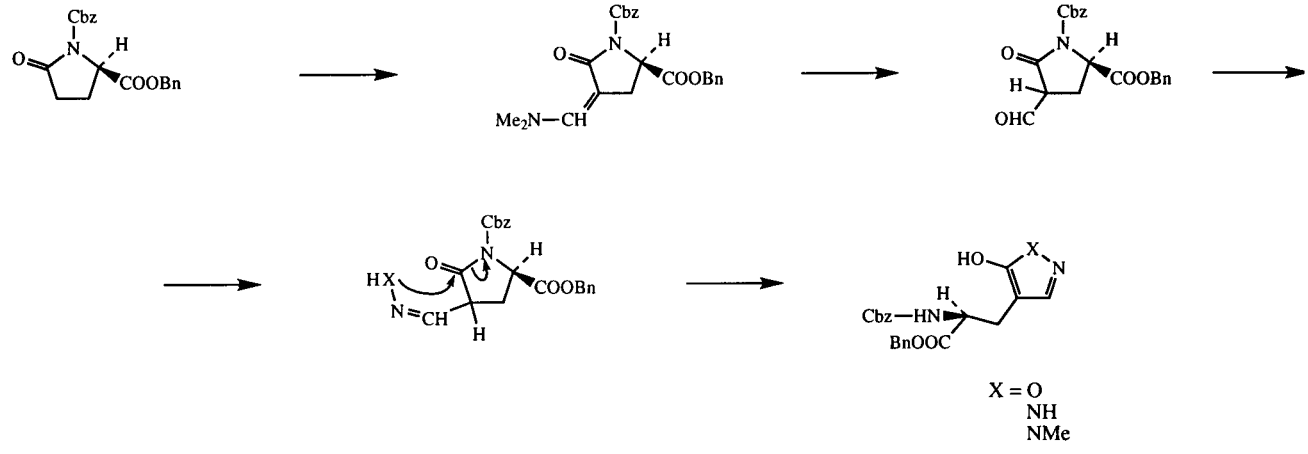
In an Ugi reaction (a four component condensation) (*R,S*)-isowillardiine (**262**) was prepared. A mixture of 1-(2-picolyl-1-oxide)-3-(formylmethyl)uracil and its methyl hemiacetal (an 1:1 mixture as obtained from the synthesis), cyclohexyl cyanide (or better 2-picolylisocyanide 1-oxide) and acetic acid in methanol were reacted at room temperature and an intermediate **288** was formed in 83% yield. After deprotection and hydrolysis the amino acid **262** was obtained in 25% yield (Scheme 27) [74].

Ethyl 2-(diphenylmethyleneamino)acrylate reacted in a Lewis acid catalyzed addition in the presence of ethylaluminium dichloride to give the pyrrole and after deprotection the free amino acid **22** in 60% yield [75].

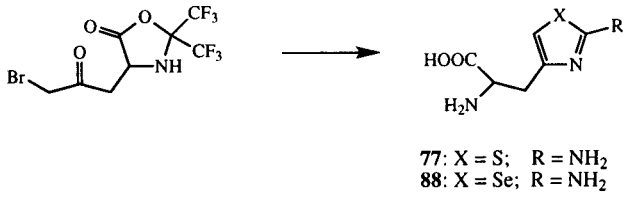
Scheme 20



Scheme 21



Scheme 22



β-(2-Thienyl)serine (**8**) was synthesized from 2-thienaldehyde and glycine in 41% yield. (*R,S*)-*threo* stereochemistry was anticipated [76].

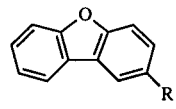
A derivative of an isoxazolylalanine **46** was obtained by the ring opening of the oxazolone ring of isoxazolylmethyloxazolone [77].

A phosphorylated compound **242** was prepared in moderate yield from 4,6-dimethyl-2-phenylpirimidine in a multistep reaction sequence. The phosphonomethyl group was introduced by treating a methyl group with lithium diisopropylamide and thereafter with $(EtO)_2POCl$ and the amino acid side chain was prepared from the hydroxymethyl group [78].

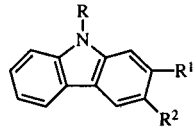
(*R*)- and (*S*)-Homoibotenic acids **48** were synthesized by the use of chiral auxiliary (*S*)-*tert*-butoxycarbonylphenylalanine. The key intermediate in this synthesis was (*R,S*)-2-amino-3-(3-ethoxyisoxazol-5-yl)propionate which was converted into a mixture of **289** and **290** which were separated on preparative tlc plates and then deprotected to give (*R*)- and (*S*)-**48** (Scheme 28) [79].

B. Transformations.

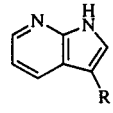
In several publications the conventional methods for the preparation of esters of various *N*-protected derivatives of heteroarylalanines are described. Such derivatives are



Compound No.	Method of Synthesis	Substituents R	Remarks	Reference
126	V	A	*R*-, by cyclization of the diaryl ether with $Pd(OAc)_2$	[164]



Compound No.	Method of Synthesis	Substituents R	R^1	R^2	Remarks	References
127	I	H	A	H		[165]
128	I	H	H	A		[165]
129	II-A	Et	H	A	*S*-	[166]



Compound No.	Method of Synthesis	Substituents R	Remarks	References
130	I, II-H	A	from 3-dimethylamino-methyl compound	[12], [167]

mentioned in the Tables. Transformations of amino acids, including heteroarylalanines into various heterocyclic systems, were also reviewed [80].

N-Protected nonproteinogenic amino acids were condensed with 1-aminoethylphosphonic acid to give phosphonopeptides which were investigated for antibacterial activities [81,82].

A mild alkylation method was used to prepare compounds **206** and **207** from protected (*R*)-3-pyridylalanine by allowing to stand the amino acid and alkyl halide at room temperature for five days [83].

1-Methoxypiridinium perchlorates **208-210** were prepared from the corresponding pyridine derivatives with dimethyl sulfate and perchloric acid. Compound **210** underwent ring opening under the influence of sodium hydroxide and the ring was restored upon acidification [84].

There is also a report on ring sulfur oxidation. *N*-Protected 3-(3-benzo[*b*]thienyl)-(*R,S*)-alanine was oxidized with hydrogen peroxide in acetic acid to give the 1-dioxide **109** in 25% yield [85].

Irradiation of (*R,S*)-(4-pyridyl)alanine yielded (*R,S*)-2-decarboxybetalamic acid imine **291** in 86% yield. This transformation probably takes place *via* a Dewar pyridine intermediate [319].

Dehydrostizolobic acid and its derivatives **292** have been prepared from *N*-acetylstizolobic acid ester *via* the *N*-chloro derivative after dehalogenation with 1,4-diazabicyclo[2.2.2]octane. The obtained *Z*-isomer was isomerized into *E*-isomer in the presence of *p*-toluenesulfonic acid [87].

Stizolobic acid (**282**) was detected among other products when the azide **293** was photolyzed and a mixture of the unsaturated analogs obtained was hydrogenated [88].

XI. Heteroarylalanines Isolated from Natural Sources.

Many heteroarylalanines are found in nature and were isolated from plants and microorganisms.

From the mushroom *Licoperdon perlatum* lycoperdic acid (**294**) was isolated and its structure was determined by X-ray analysis. The (*S*)-configuration at C-2 was determined by chemical methods [238,239].

Compound **295** was isolated from the mushroom *Phyllotopsis nidulans* [240] and from *Tricholomopsis rutilans* [241] and was found to possess the (*S*)-configuration. An isomeric acid **296** was also isolated from *Tricholomopsis rutilans* [242].

(*S*)-Pyrazolyl-1-alanine (**67**) was first isolated from the watermelon *Citrullus vulgaris* [243,244]. It was later found in seeds of many species of *Cucurbitaceae* [245].

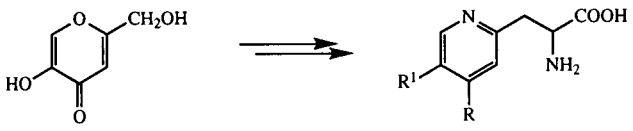
In the isoxazole series, compounds **65** and **297** were isolated from *Pisum sativum* and from *Lathyrus odoratus* seedlings [246,247] and their chemistry and biological aspects have been reviewed [63]. The ^1H and ^{13}C nmr spectra of **65** were recorded [248]. The isomeric amino acid **66** [3-(5-oxo-2*H*-isoxazol-4-yl)alanine] was isolated from culture filtrates of *Streptomyces platensis* A-136 [249]. Quisqualic acid (**89**) was isolated from the seeds of *Quisqualis indica* [250] and its structure was elucidated by X-ray analysis [251].

(*R*)-1-Histidinoalanine (**298**) is a constituent of an antifungal bicyclic dodecapeptide theonellamide F and theonegramide, isolated from the sponges of the genus *Theonella* [252,253].

From a poisonous mushroom *Clitocybe acromelalga* several heteroarylalanines have been isolated. Three of them are pyridine derivatives **178**, **182**, **191** [10,254], and another is a pyrrole derivative **27** [10,11,56].

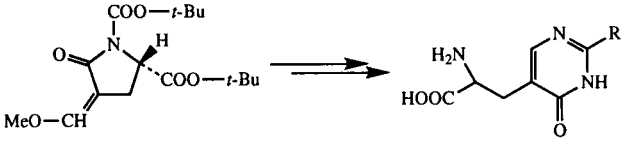
Loss of hair in animals and in native women has been ascribed to a toxic principle in the seeds of a tropical plant

Scheme 23



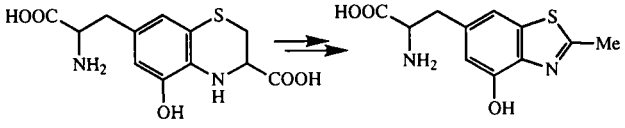
162: R = R^1 = OH
163: R = H, R^1 = OH

Scheme 24



245-248

Scheme 25



115

Leucaena glauca. The active compound leucenol was found to be identical with the mimosine (**215**) from *Mimosa pudica* [141,210,255]. The initially proposed structure [256] was later revised to **215** [141,210,257-259].

Pyridinoline (**299**) and its deoxy derivative **300** are two cross-links of collagen molecules [260-262].

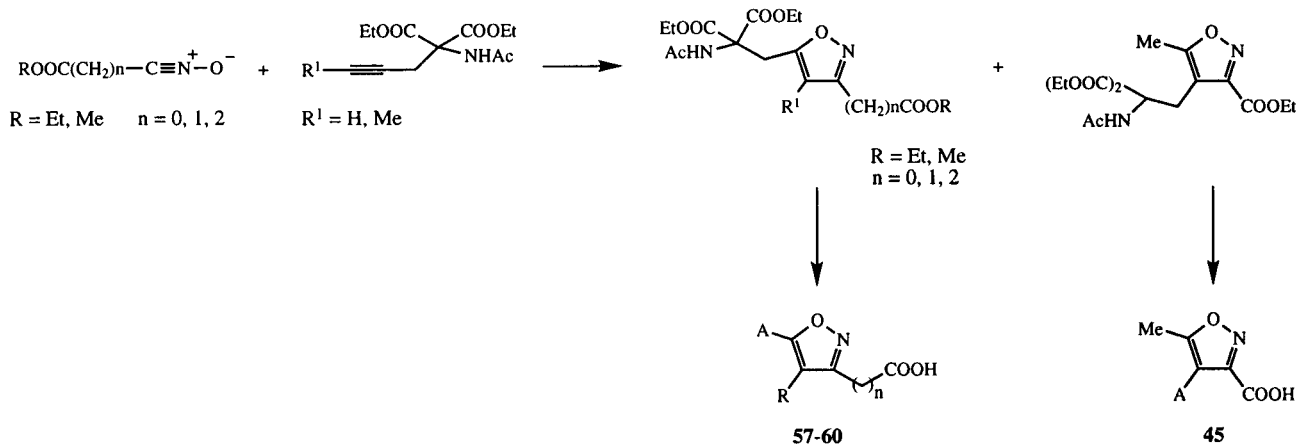
(*S*)-Azatyrosine (**163**) was isolated from a fermentation broth of *Streptomyces chibaensis* [191] and its 2-chloro analog, kedarcidin (**301**), is an antitumor antibiotic [263,264]. Whereas azatyrosine has the (*S*)-configuration, kedarcidin is a *(R)*-stereoisomer as determined by nmr [264].

There are two isomeric uracilylalanines, the 1-substituted (willardiine, **252**) and a 3-substituted one (isowillardiine, **262**), which were both found in plants. Willardiine (**252**) was first isolated from seeds of *Acacia willardiana* but it was later also found in other species of *Acacia*, in *Mimosa asperata* and in *Pisum sativum*. Isowillardiine (**262**) was isolated later from pea seedlings [265] and the initially proposed structure was later reassigned.

The structure of willardiine was also confirmed by the independent chemical synthesis [227]. The biosynthesis of both amino acids was studied *in vivo* and *in vitro* [266]. The crystal structure of willardiine methyl ester was also determined [267] and the ^{1}H and ^{13}C nmr spectra of both amino acids were recorded [248].

From *Lathyrus tingitanus* lathyrine (**243**) was isolated [268,269]. The isotope incorporation studies showed that the precursor of the pyrimidine moiety is 2-aminopirimidine-4-carboxylic acid which is simultaneously decarboxylated and alanylated by serine at position 4 of the pyrimidine ring [270].

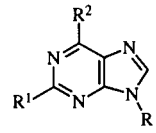
Scheme 26

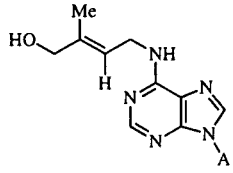
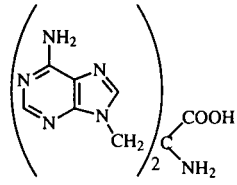
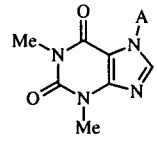


R = Et, Me n = 0, 1, 2 R^1 = H, Me

R = Et, Me
n = 0, 1, 2

57-60 **45**



Compound No.	Method of Synthesis	Substituents			Remarks	References
		R	R^1	R^2		
131	III	A	H	Me		[168]
132	III	A	H	*i*-Pr		[168]
133	VII	A	H	Cl	*S*-, no details given	[169]
	IX	A	H	Cl		[39]
134	III	A	H	NH_2	*N*-BOC, also Me ester	[168], [170]-[173]
	IV-C	A	H	NH_2	4.7% yield	[174]
	VII	A	H	NH_2	*R*-, *S*-; no details given	[169]
135	III	A	H	NHMe		[168]
136	III	A	H	NMe_2		[168]
137	III	A	H	$NH(CH_2)_3Cl$		[168]
138	IV-A	A	H	$NHCH_2Ph$		[175]
139	III, IX	A	H	OH		[39], [168]
140	III	A	H	SH		[168]
141	III	A	NH_2	NH_2		[176], [177]
142	III	A	NH_2	NMe_2		[176], [177]
143	III	A	NH_2	OH		[176], [177]
144	III	*A*	NH_2	SH		[176], [177]
145	III	A	NH_2	SMe		[176], [177]
146	VII	A	NH_2	Cl	no details given	[169]
147	I	Me	A	H		[178]
					lupinic acid	[179]
148	IV-A				low yield	[180]
						[181]
149	IV-F					[182]
150	III					[183]

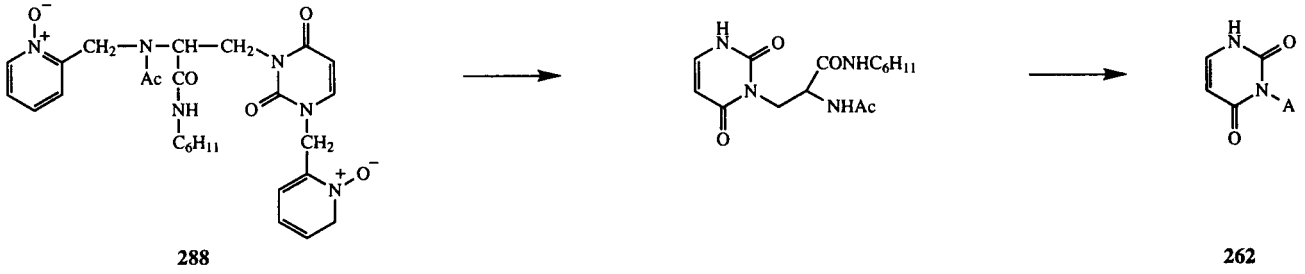
Stizolobic (**282**) and stizolobinic acid (**302**) were isolated from seedlings of *Stizolobium hassjo* [271] and hydrolysis of musca-aurins, the betalain pigments from *Amanita muscaria* (fly agaric) gave among other amino acids also both above mentioned amino acids [236].

XII. Biosyntheses of Heteroarylalanines.

The biosynthetic pathways have been thoroughly studied in the case of on the endocyclic nitrogen substituted heteroarylalanines. Pyrazol-1-yl-(*S*)-alanine (**19**) is synthesized in plants from pyrazole and *O*-acetyl-(*S*)-serine [272-275]. Biosynthesis is achieved by overexpressed cystein synthase [274,276] and the pyrazole part is formed from 1,3-diaminopropane [272]. It was found that biosynthesis can also occur in some microorganisms when pyrazole is added [273].

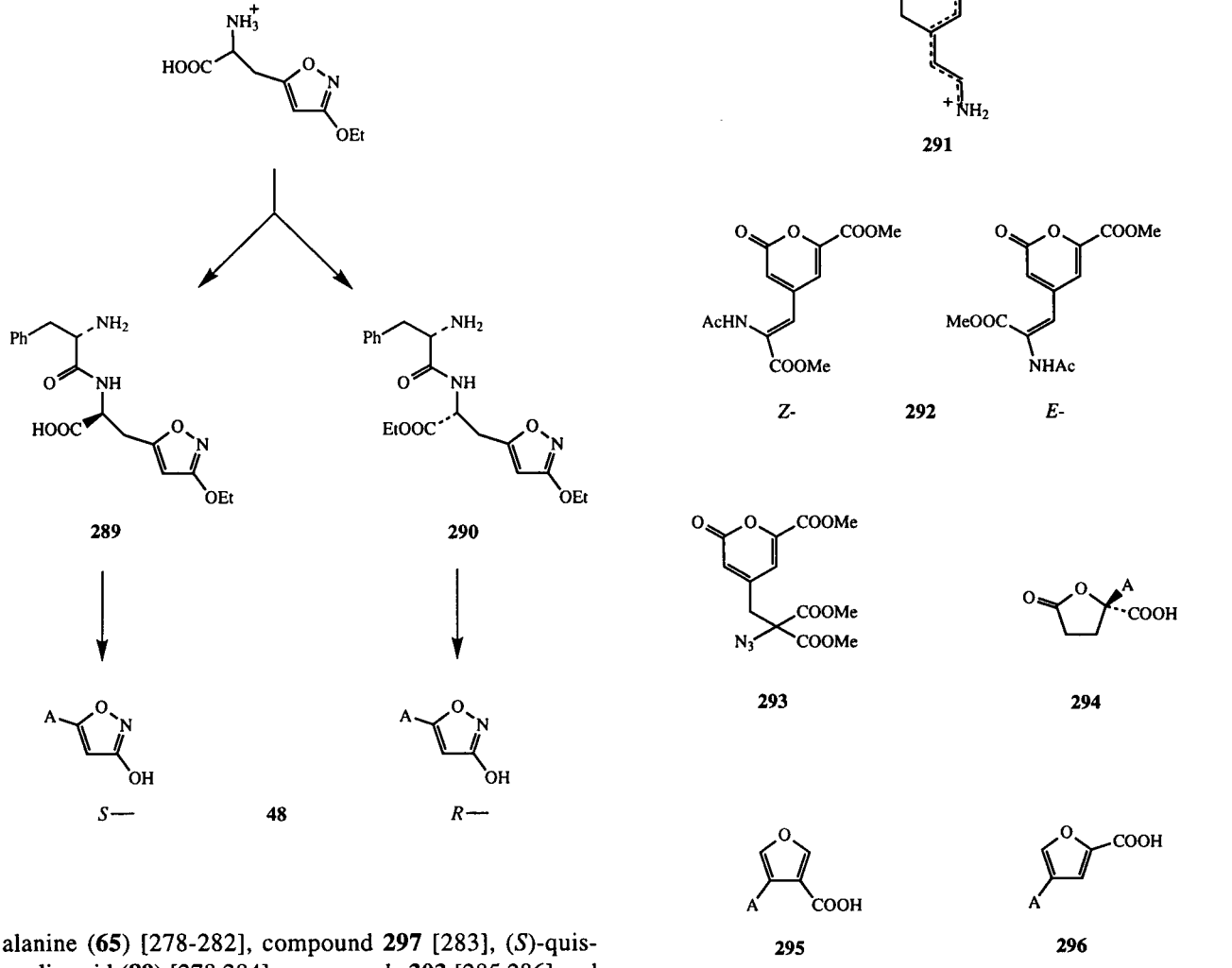
O-Acetyl-(*S*)-serine is also involved in biosyntheses of other heterarylalanines, *i. e.* 3-(5-oxo-2*H*-isoxazol-2-yl)-

Scheme 27



288 262

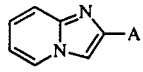
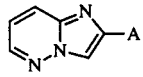
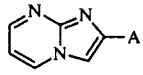
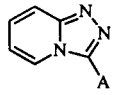
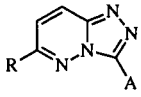
Scheme 28

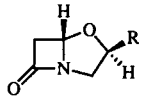


289 290 291 292 293 294 295 296 48

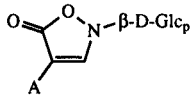
alanine (**65**) [278-282], compound **297** [283], (*S*)-quisqualic acid (**89**) [278,284], compounds **303** [285,286] and **304** [277], willardiine (**252**) and isowillardiine (**262**) from uracil [287], mimosine (**215**) [275], (*S*)-lupinic acid (**148**) from zeatin [288] in 1.5% yield, compound **138** from 6-benzylaminopurine [289-291] and compound **305** of which biosynthesis was studied also by pyridoxal-5'-phosphate catalysis [292,293].

Benzopyrazole is *N*-substituted with (*S*)-serine in the presence of the tryptophan synthase complex from *E. coli* giving the compound **306** [294]. A strain of *Streptomyces* species was found to produce compound **93** [295] and radio-labeling studies showed that stizolobic acid (**282**) is biosynthesized from L-DOPA [296-298].

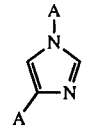
Compound No.	Method of Synthesis	Compounds	Remarks	References
151	IX			[40]
152	IX		$NHCOCF_3$, Me ester	[40]
153	IX			[40]
154	IX			[40]
155, 156	IX		**155**: R = Cl; **156**: R = Ph	[40]



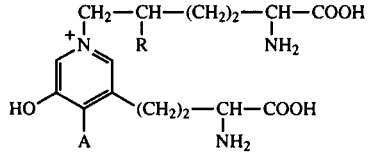
Compound No.	Method of Synthesis	Substituents R	Remarks	References
157	IX	A	*R*-, *S*-	[52], [53]



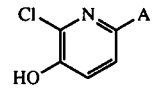
297



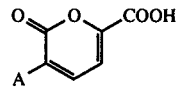
298



299 R = OH
300 R = H



301



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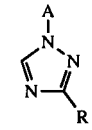
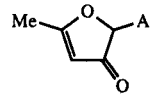


303 R = NH_2
304 R = H



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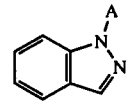

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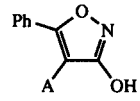


307

XIII. Resolution of Racemates.

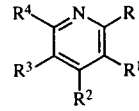
Synthetic heteroarylalanines were generally prepared as racemates, except for enantioselective methods. Either chemical methods, but for the most part the enzymatic methods were employed for the resolution of racemates.

The importance of preparing the single enantiomers can be emphasized in the case of heteroarylalanines which are glutamate agonists and resolution revealed [299,300] that the (*S*)-isomer is the most potent agonist.

Amines such as (+)-α-methylphenetylamine for willardiine (**252**) [227] and a (thimin-1-yl)alanine (**255**) were used for the chemical resolution [301]. (*R,S*)-3-(3-Hydroxy-5-phenylisoxazol-4-yl)alanine (**307**) was resolved using (*R*)- or (*S*)-1-phenylethylamine [302] and *tert*-butoxycarbonyl-2-thienylalanine with the same reagent [303].

(*S*)-Glutamic acid was used for a thiazolyl derivative **77** [304]. Chiral tlc plates were used to obtain (*R*)- and (*S*)-isomers of **178** [10] and for homoibotenic acid, (**48**) [79].

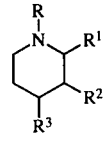
For the determination of the enantiomeric purity of different heteroarylalanines in the form of their *N*-acetyl, *N*-benzoyl derivatives or methyl esters by ^1H nmr tri(3-trifluoromethylhydroxymethylene-d-camphorato)europium(III) was used. A direct correlation between the configuration and the chemical shift differences between the methyl singlets was observed [305].



Compound No.	Method of Synthesis	Substituents					Remarks	References
		R	R^1	R^2	R^3	R^4		
158	I	A	H	H	H	H		[184], [185]
	I	A	H	H	H	H	with phtalimidomalonic ester	[186]
	I	A	H	H	H	H	with benzimidomalonic ester	[187]
	I	A	H	H	H	H	*R*-, *N*-BOC	[188]
	II-A	A	H	H	H	H	azlactone only from 2-pyridine aldehyde acetal in 22% yield	[189]
	II-H	A	H	H	H	H		[102]
	VIII-D	A	H	H	H	H		[24]
159	VIII-D	A	H	CN	H	H	*N*-BOC, benzyl ester	[23]
160	I, IX	A	H	Cl	OH	H		[190], [68]
161	IX	A	H	Cl	OMe	H		[67]
162	IX	A	H	OH	OH	H		[68]
163	VIII-D	A	H	H	OH	H	*S*-, azatyrosine	[25]
	I, IX	A	H	H	OH	H		[190], [191], [67]
	II-F, II-H	A	H	H	OH	H	*S*-	[192]-[194]
164	IX	A	H	H	OMe	H		[67]
165	I	A	H	H	OH	I		[190]
166	I	A	H	H	H	Me		[185]
167	VIII-D	A	H	H	H	CN		[23]
168	I	A	H	H	H	F		[195]
169	I	A	H	H	H	Cl		[196]
170	I	A	H	H	H	Br		[196]
171	I, VI	A	H	H	H	OH		[195], [197]
172	I	H	A	H	H	H	*R*-, also *N*-BOC	[110], [188], [198]
	I	H	A	H	H	H	with DFMM	[156], [160], [199]
	II-A	H	A	H	H	H		[8], [159], [189], [200], [201]
	II-A	H	A	H	H	H	synthesis suitable only on larger scale	[202]
	II-B, II-E, II-H	H	A	H	H	H		[185], [187], [203], [102]
	VIII-C	H	A	H	H	H	*R*-, *S*-	[22]
	V	H	A	H	H	H	*R*, >99% *e. e.*	[15]
173	I	F	A	H	H	H		[195]
174	I	Cl	A	H	H	H		[196]
175	I	Br	A	H	H	H		[196]
176	I	OH	A	H	H	H		[195]
177	I	H	A	H	H	COOH		[84], [204]
178	I	H	A	H	H	OH		[195]
	II-H, II-J	H	A	H	H	OH	*R*-, *S*-	[102], [10]
179	I	H	A	H	H	F		[195], [206]
180	I, II-H	H	A	H	H	Cl		[196], [102]
181	I	H	A	H	H	Br		[196]
182	IX	OH	A	H	H	COOH	*S*-	[71]
183	II-H	H	A	CH_2NHBOC	*O*-BOC	Me	*N*-Fmoc	[3]
184	I	H	H	A	H	H		[185], [207], [208]
	I	H	H	A	H	H	with benzimidomalonic ester; 4% yield	[187]
	I	H	H	A	H	H	*R*-, *N*-BOC	[188]
	II-A, II-B, II-H	H	H	A	H	H		[189], [185], [102]
	V	H	H	A	H	H	*R*-, 99% *e. e.*	[15]
	VI	H	H	A	H	H		[208]
	VIII-C	H	H	A	H	H	*R*-, *S*-	[22]

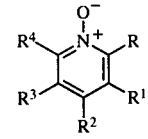
Continued next page.

Compound No.	Method of Synthesis	Substituents					Remarks	References
		R	R^1	R^2	R^3	R^4		
185	I	COOH	H	A	H	H		[204]
186	I	Cl	H	A	H	H		[196]
187	I	Br	H	A	H	H		[196]
188	I	OH	H	A	H	H		[195]
189	VIII-D	CN	H	A	H	H	*N*-BOC, Bn ester	[23]
190	X	COOH	H	A	H	OH	acromelobic acid	[55]
191	X	OH	H	A	H	COOH	*S*-	[71]

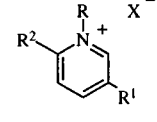


Compound No.	Method of Synthesis	Substituents				References
		R	R^1	R^2	R^3	
192	IV-A	A	H	H	H	[109]
193	IV-A	A	H	COOMe	H	[109]
194	IV-A	A	H	H	COOMe	[109]
195	IV-A	A	COOMe	H	H	[109]

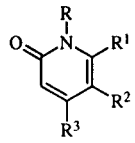
For enzymatic resolution heteroarylalanines were transformed into their *N*-acetyl derivatives or amides and under the action of enzymes they afforded the corresponding (*S*)-amino acids. The (*R*)-amides were separated and hydrolyzed chemically into (*R*)-acids. Acylase I enzymes from porcine kidney were used for kinetic resolution of many heteroarylalanines. This was the case when the heterocyclic part was a furan ring [90,306,308,309] or a pyrazole [307], pyridine [206,310], thiophene [90], uracil and adenine [311] or carbazole [166]. Immobilized aminoacylase was used in the case of isoxazoles [299,300] and an acylase from *Aspergillus oryzae* for pyrazoles [135,312].



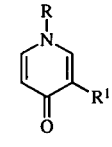
Compound No.	Method of Synthesis	Substituents					Remarks	References
		R	R^1	R^2	R^3	R^4		
196	I, II-H	A	H	H	H	H		[209], [102]
197	I	A	H	Cl	OH	H		[190]
198	I	A	H	H	OH	H		[190]
199	I	A	H	H	OH	I		[190]
200	I, II-H	H	A	H	H	H		[209], [102]
210	II-H	H	A	H	H	Cl		[102]
202	II-H	H	A	H	H	OH		[102]
203	I, II-H, VI	H	H	A	H	H		[209], [102]
	II-G	H	H	A	H	H	mixture of *N*-BOC derivatives in 33% yield; *S*:*R* ≈ 96:4	[211]
204	II-H	H	H	A	H	Cl		[102]
205	II-H	H	H	A	H	OH		[102]



Compound No.	Method of Synthesis	Substituents				Remarks	References
		R	R^1	R^2	X^-		
206	X	Me	A	H	I	*N*-BOC	[83]
207	X	$PhCH_2$	A	H	Br	*N*-BOC	[83]
208	X	OMe	A	COOH	ClO_4		[84]
209	I	OMe	A	COOMe	ClO_4		[84]
210	X	OMe	A^1	COOMe	ClO_4	A^1 = $CH_2-C(COOMe)_2$ (NHAc)	[84]



Compound No.	Method of Synthesis	Substituents				References
		R	R^1	R^2	R^3	
211	I	H	A	H	OH	[192]
212	I	H	H	A	H	[206]
213	I	OH	H	H	A	[192]



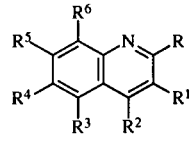
Compound No.	Method of Synthesis	Substituents		Remarks	References
		R	R^1		
214	IX	A	H	*R-*, *S-*; *N*-BOC	[57]
215	IV-A, IX	A	OH	mimosine (leucenol); 4% yield; from 3-methoxy-4-pyridone 25% yield	[69], [70], [210]

Aminopeptidase from *Pseudomonas putida* was used in the case of lupinic acid [181]. Carboxypeptidase and a papaia extract (papain) were used for thienylalanine [106,313,314], alkaline protease or alcalase for the bipyridine and furan derivatives [235,315].

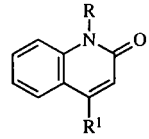
The 2-chloroethyl ester of (*Z*)-4-thienylalanine was converted into enantiomerically enriched (*Z*)-amino acid by lipases from *Aspergillus niger* (94% *e. e.*), *Pseudomonas fluorescens* (70% *e. e.*) or *Candida cylindracea* (43% *e. e.*). The (*S*)-enantiomer was hydrolyzed preferentially [316].

Chymotrypsin was also used in some cases, as for (*R,S*)-3-(3-hydroxy-5-methylisoxazol-4-yl)alanine (**35**) [317], pyridine [198] or pyridine-1-oxide derivatives [207] and a thiazole [42].

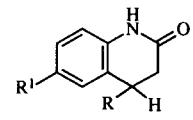
Subtilisin was used for a thiazole [42], pyridine [110,200], benzothiophene [110] or quinoline derivatives [55,213].



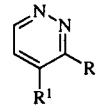
Compound No.	Method of Synthesis	Substituents							Remarks	References
		R	R^1	R^2	R^3	R^4	R^5	R^6		
216	II-C	A	H	H	H	H	H	H	*S-*, 98% *e. e.* using commercially available (*S*)-2-*t*-butyloxycarbonyl-3-methyl-4-imidazolinone	[212]
217	I, II-A	H	A	H	H	H	H	H	*R-*, *S-*; *N*-BOC	[213], [8]
218	I	OH	A	H	H	H	H	H		[214]
219	II-A, VI	H	H	A	H	H	H	H		[215], [208]
220	I, II-G	OH	H	A	H	H	H	H	*R-*, *S-*	[214], [216], [219]
221	VI	H	H	A	H	OMe	H	H		[208]
222	I	OH	H	A	H	OH	H	H		[217]
223	I	OH	H	A	H	H	H	OH		[217]
224	I	OH	H	H	A	H	H	H		[214]
225	I	H	H	H	H	A	H	H	*R-*, *S-*	[218]



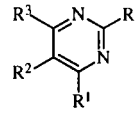
Compound No.	Method of Synthesis	Substituents R	Substituents R^1	References
226	I	Me	A	[214]
227	I	Et	A	[214]
228	I	n-C_4H_9	A	[214]
229	I	CH_2=$CHCH_2$	A	[214]
230	I	CH≡CCH_2	A	[214]
231	I	$PhCH_2$	A	[214]



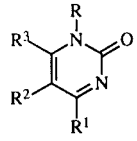
Compound No.	Method of Synthesis	Substituents R	Substituents R^1	References
232	I	A	H	[214]
233	I	H	A	[214]

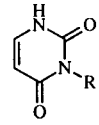
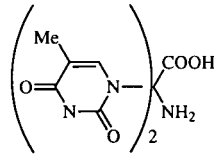
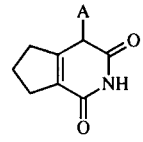


Compound No.	Method of Synthesis	Substituents R	Substituents R^1	References
234	VI	A	H	[86]
235	VI	H	A	[86]

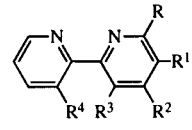


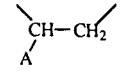
Compound No.	Method of Synthesis	Substituents R	Substituents R^1	Substituents R^2	Substituents R^3	Remarks	References
236	VI	A	H	H	H		[86]
237	I	A	OH	H	H		[220]
238	IX	A	OH	H	Me	NHCOPh; or alternative structure: A = CH−CH_2COOH / NHCOPh	[58]
239	I	A	OH	OH	H		[221]
240	VI	A	OH	H	OH		[222]
241	VI	H	A	H	H		[86]
242	X	Ph	A	H	$CH_2PO(OH)_2$		[78]
243	VI	NH_2	A	H	H	lathyrine	[223]
244	I, VI	H	H	A	H	with diethyl *N*-(carbobenzoylamino)malonate (method I)	[86]
245	IX	H	OH	A	H		[65]
246	IX	Me	OH	A	H		[65]
247	IX	Ph	OH	A	H		[65]
248	IX	NH_2	OH	A	H		[65]
249	I	OH	NH_2	A	H		[224]
250	I	OH	OH	A	H		[222]
251	VI	OH	OH	H	A		[222]

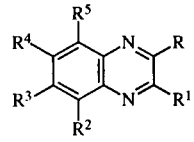


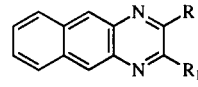
Compound No.	Method of Synthesis	Substituents R	R¹	R²	Remarks	References
252	III, VII	A	OH	H	*S*-, willardine	[225]-[227], [168]
253	III	A	NH_2	H	also Me ester	[170]. [171], [228], [229]
	VII	A	NH_2	H	*S*-, no details given	[169]
254	III	A	$NHCH_2$-COOH	H		[229]
255	III	A	OH	Me	also as *N*-BOC, Me ester	[160]. [170]. [172]
256	VII	A	OH	Me	S-, no details given [169]	[168], [228], [229]
257	III	A	OH	NO_2		[230]
258	III	A	OH	$N(CH_2CH_2Cl)_2$		[230]
259	III	A	OH	F		[228], [229]
260	III	A	OH	Cl		[228], [229]
261	III	A	OH	Br	X-ray of racemate	[228], [229]
262	X	A			isowillardine	[74]
263	IV-F					[182]
264	III				low yield	[172]

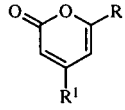
Compound No.	Method of Synthesis	Substituents R	Remarks	References
265	I	A	*S*-	[231]

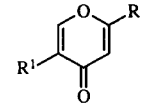


Compound No.	Method of Synthesis	Substituents R	R¹	R²	R³	R⁴	Remarks	References
266	II-H	A	H	H	H	H	*S*-, >99% *e. e.*	[232]-[234]
267	II-H	H	A	H	H	H		[235]
268	II-H	H	H	A	H	H		[235]
269	II-C	H	H	H			*S*-, using commercially available (*S*)-2-*t*-butyl-1-*t*-butyloxycarbonyl-3-methyl-4-imidazolinone	[213]



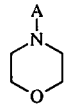
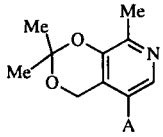
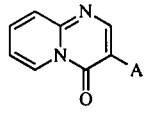
Compound No.	Method of Synthesis	Substituents R	R^1	R^2	R^3	R^4	R^5	Remarks	References
270	II-C	A	H	H	H	H	H	*S*-, using commercially available (*S*)-2-*t*-butyl-1-*t*-butyloxycarbonyl-3-methyl-4-imidazolinone	[213]
271	IX	$CH_2PO(OH)_2$	A	H	H	H	H	*R*-, *S*-	[59]
272	IX	$CH_2PO(OH)_2$	A	H	Cl	H	H		[59]
273	IX	$CH_2PO(OH)_2$	A	H	H	Cl	H		[59]
274	IX	$CH_2PO(OH)_2$	A	H	Me	Me	H		[59]
275	IX	$CH_2PO(OH)_2$	A	H	F	F	H		[59]
276	IX	$CH_2PO(OH)_2$	A	H	Cl	Cl	H		[59]
277	IX	$CH_2PO(OH)_2$	A	H	OMe	OMe	H		[59]
278	IX	$CH_2PO(OH)_2$	A	Cl	H	H	Cl		[59]
279	IX	$(CH_2)_2PO(OH)_2$	A	H	H	H	H		[59]
280	IX	$CH{=}CHPO(OH)_2$	A	H	H	H	H		[59]
281	IX	$CH_2PO(OH)_2$	A						[59]





Compound No.	Method of Synthesis	Substituents R	R^1	Remarks	References
282	I	COOH	A	stizolobic acid	[55], [236]

Compound No.	Method of Synthesis	Substituents R	R^1	References
283	II-H	A	OH	[102]

Compound No.	Method of Synthesis		Remarks	References
284	IV-A, VII			[110], [109]
285	II-H		*S*-, >99% *e. e.*	[237]
286	IX			[65]

REFERENCES AND NOTES

[1] E. A. Bell, The Non-protein Amino Acids Occurring in Plants, in: Progress in Phytochemistry, Vol **7**, Pergamon, Oxford, 1981, p 171.

[2] G. C. Barrett, ed., Chemistry and Biochemistry of the Amino Acids, Chapman and Hall, London, 1985.

[3] S.-I. Hatanaka, Progress in the Chemistry of Organic Natural Products, Vol **59**, Springer Verlag, 1992, p 1.

[4] G. A. Rosenthal, Plant Nonprotein Amino and Imino Acids, Biological, Biochemical and Toxicological Properties. Academic Press, New York, 1982.

[5] L. Fowden, P. J. Lea and E. A. Bell, *Adv. Enzymol.*, **50**, 117 (1979).

[6] In many cases the final products are not amino acids but their derivatives. Under Remarks are represented in Tables the following abbreviations for derivatives: Ac = acetyl, Bn = benzyl, BOC = *t*-butoxycarbonyl, Bz = benzoyl, Cbz = benzyloxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl and Ts = *p*-toluenesulfonyl. Some dihydro and tetrahydro derivatives of heteroarylalanines are also included.

[7] A. Badshah, N. H. Khan and A. R. Kidwai, *J. Org. Chem.*, **37**, 2916 (1972).

[8] C. Cativiela, J. A. Mayoral, E. Meléndez, L. A. Oro, M. T. Pinillos and R. Usón, *J. Org. Chem.*, **49**, 2502 (1984).

[9] R. S. Roy and B. Imperiali, *Tetrahedron Letters*, **37**, 2129 (1996).

[10] K. Yamano and H. Shirahama, *Tetrahedron*, **48**, 1457 (1992).

[11] K. Yamano, K. Konno and H. Shirahama, *Chem. Letters*, 1541 (1991).

[12] R. Sanchez-Obregón, A. G. Fallis and A. G. Szabo, *Can. J. Chem.*, **70**, 1531 (1992).

[13] S. Farooq, W. E. Swain, Jr., R. Daeppen and G. Rihs, *Tetrahedron: Asymmetry*, **3**, 51 (1992).

[14] J. E. Baldwin, A. C. Spivey and C. J. Schofield, *Tetrahedron: Asymmetry*, **1**, 881 (1990).

[15] C. Döbler, H.-J. Kreuzfeld, M. Michalik and H. W. Krause, *Tetrahedron: Asymmetry*, **7**, 117 (1996).

[16] L. D. Arnold, T. H. Kalantar and J. C. Vederas, *J. Am. Chem. Soc.*, **107**, 7105 (1985).

[17] S. D. Abbott, P. Lane-Bell, K. P. S. Sidhu and J. C. Vederas, *J. Am. Chem. Soc.*, **116**, 6513 (1994).

[18] T. Takemoto, K. Koike, T. Nakajima and S. Arihara, *Yakugaku Zasshi*, **95**, 448 (1975); *Chem. Abstr.*, **83**, 97875 (1975).

[19] T. Takemoto, T. Nakajima, S. Arihara and K. Koike, *Yakugaku Zasshi*, **95**, 326 (1975); *Chem. Abstr.*, **83**, 43706 (1975).

[20] A.-S. Carlström and T. J. Freid, *Synthesis*, 414 (1981).

[21] M. J. Burk, J. R. Lee and J. P. Martinez, *J. Am. Chem. Soc.*, **116**, 10847 (1994).

[22] J. J. Bozell, C. E. Vogt and J. Gozum, *J. Org. Chem.*, **56**, 2584 (1991).

[23] M. J. Dunn, R. F. W. Jackson, J. Pietruszka, N. Wishart, D. Ellis and M. J. Wythes, *Synlett*, 499 (1993).

[24] R. F. W. Jackson, M. J. Wythes and A. Wood, *Tetrahedron Letters*, **30**, 5941 (1989).

[25] B. Ye and T. R. Burke, Jr., *J. Org. Chem.*, **60**, 2640 (1995).

[26] M. T. Cox and J. J. Holohan, *Tetrahedron*, **31**, 633 (1975).

[27] K. Poduška, J. Glöde, V. Lisý, J. Škoda, H. Gross and J. Rudinger, *Experientia*, **22**, 809 (1966).

[28] K. Poduška, J. Rudinger, J. Gloede and H. Gross, *Collect. Czech. Chem. Commun.*, **34**, 1002 (1969).

[29] N. Subasinghe, M. Schulte, R. J. Roon, J. F. Koerner and R. L. Johnson, *J. Med. Chem.*, **35**, 4602 (1992).

[30] D. H. R. Barton, Y. Hervé, P. Potier and J. Thierry, *Tetrahedron*, **43**, 4297 (1987).

[31] P. M. Jacobs and M. Davis, *J. Org. Chem.*, **44**, 178 (1979).

[32] J. E. Baldwin, R. M. Adlington and D. J. Birch, *Tetrahedron Letters*, **26**, 5931 (1985).

[33] J. E. Baldwin, R. M. Adlington and L. C. Mellor, *Tetrahedron*, **50**, 5049 (1994).

[34] G. Lo Vecchio, M. P. Conti and G. Cum, *Biochem. Appl.*, **10**, 192 (1963).

[35] B. W. Bycroft, S. R. Chhabra, R. J. Grout and P. C. Crowley, *J. Chem. Soc., Chem. Commun.*, 1156 (1984).

[36] J. D. Milkowski, F. M. Miller, E. M. Johnson and N. Zenker, *J. Med. Chem.*, **13**, 741 (1970).

[37] N. Zenker, C. N. Talaty, P. S. Callery, J. Wright, L. S. Hubbard and E. M. Johnson, Jr., *J. Heterocyclic Chem.*, **20**, 435 (1983).

[38] N. Zenker, V. H. Morgenroth and J. Wright, *J. Med. Chem.*, **17**, 1223 (1974).

[39] S. E. Poritere, J. J. Shluke, M. Yu. Lidak and M. K. Kilevica, *Khim. Geterotsikl. Soedin.*, 1690 (1982).

[40] J. Svete, B. Stanovnik and M. Tišler, *J. Heterocyclic Chem.*, **31**, 1259 (1994).

[41] W. C. Patt, R. W. Skeean and B. A. Steinbaugh, *Synth. Commun.*, **20**, 3097 (1990).

[42] C.-N. Hsiao, M. R. Leanna, L. Bhagavatula, E. De Lara, T. M. Zydowsky, B. W. Horrom and H. E. Morton, *Synth. Commun.*, **20**, 3507 (1990).

[43] K. Konno, H. Shirahama and T. Matsumoto, *Heterocycles*, **15**, 1033 (1981).

[44] J. J. Nestor, Jr., B. L. Horner, T. L. Ho, G. H. Jones, G. I. McRae and B. H. Vickery, *J. Med. Chem.*, **27**, 320 (1984).

[45] I. A. Ismail, D. E. Sharp and M. R. Chedekel, *J. Org. Chem.*, **45**, 2243 (1980).

[46] D. G. Patil and M. R. Chedekel, *J. Org. Chem.*, **49**, 997 (1984).

[47] C. D. Moussebois, J. F. Heremans, R. Merenyi and W. Rennerts, *Helv. Chim. Acta*, **60**, 237 (1977).

[48] P. L. Ornstein, M. B. Arnold, D. Evrard, J. D. Leander, D. Lodge and D. D. Schoepp, *Bioorg. Med. Chem. Letters*, **3**, 43 (1993).

[49] Z. Grzonka, *Rocz. Chem.*, **46**, 1265 (1972).

[50] R. H. Evans, H. Ax, A. Jacoby, T. H. Williams, E. Jenkins and J. P. Scannell, *J. Antibiot.*, **36**, 213 (1983).

[51] D. L. Pruess and M. Kellett, *J. Antibiot.*, **36**, 208 (1983).

[52] J. C. Müller, V. Toome, D. L. Pruess, J. F. Blount and M. Weigele, *J. Antibiot.*, **36**, 217 (1983).

[53] S. De Bernardo, J. P. Tengi, G. J. Sasso and M. Weigele, *J. Org. Chem.*, **50**, 3457 (1985).

[54] J. E. Baldwin, R. M. Adlington and D. J. Birch, *J. Chem. Soc., Chem. Commun.*, 256 (1985).

[55] J. E. Baldwin, M. R. Spyvee and R. C. Whitehead, *Tetrahedron Letters*, **35**, 6575 (1994).

[56] K. Yamano, K. Hashimoto and H. Shirahama, *Heterocycles*, **34**, 445 (1992).

[57] E.-S. Lee, J. Jurayj and M. Cushman, *Tetrahedron*, **50**, 9873 (1994).

[58] N. Katagiri, A. Koshihara, S. Atsuumi and T. Kato, *Chem. Pharm. Bull.*, **31**, 2288 (1983).

[59] R. B. Baudy, L. P. Greenblatt, I. L. Jirkovsky, M. Conklin, R. J. Russo, D. R. Bramlett, T. A. Emrey, J. T. Simmonds, D. M. Kowal, R. P. Stein and R. P. Tasse, *J. Med. Chem.*, **36**, 331 (1993).

[60] K. Busch, U. M. Groth, W. Kühnle and U. Schöllkopf, *Tetrahedron*, **48**, 5607 (1992).

[61] F. Lambein, N. Schamp, L. Vandendriessche and R. Van Parijs, *Biochem. Biophys. Res. Commun.*, **37**, 375 (1969).

[62] F. Lambein, Y.-H. Kuo and R. Van Parijs, *Heterocycles*, **4**, 567 (1976).

[63] S. Tsubotani, Y. Funabashi, M. Takamoto, S. Hakoda and S. Harada, *Tetrahedron*, **47**, 8079 (1991).

[64] A. N. Bowler, P. M. Doyle and D. W. Young, *J. Chem. Soc., Chem. Commun.*, 314 (1991).

[65] A. Dinsmore, P. M. Doyle and D. W. Young, *Tetrahedron Letters*, **36**, 7503 (1995).

[66] K. Burger, M. Gold, H. Neuhauser, M. Rudolph and E. Höss, *Synthesis*, 1145 (1992).

[67] S. J. Norton, C. G. Skinner and W. Shive, *J. Org. Chem.*, **26**, 1495 (1961).

[68] S. J. Norton and E. Sanders, *J. Med. Chem.*, **10**, 961 (1967).

[69] R. Adams and J. L. Johnson, *J. Am. Chem. Soc.*, **71**, 705 (1949).

[70] I. D. Spenser and A. D. Notation, *Can. J. Chem.*, **40**, 1374 (1962).

[71] K. Yamano and H. Shirahama, *Tetrahedron*, **49**, 2427 (1993).

[72] C. Costantini, G. Testa, O. Crescenzi and M. d' Ischia, *Tetrahedron Letters*, **35**, 3365 (1994).

[73] U. Madsen and E. H. F. Wong, *J. Med. Chem.*, **35**, 107 (1992).

[74] K. Tsuchida, K. Ikeda and Y. Mizuno, *Chem. Pharm. Bull.*, **28**, 2748 (1980).

[75] G. Tarzia, C. Balsamini, G. Spadoni and E. Duranti, *Synthesis*, 514 (1988).

[76] M. E. Dullaghan and F. F. Nord, *J. Am. Chem. Soc.*, **73**, 5455 (1951).

[77] E. Erba and D. Pocar, *Liebigs Ann. Chem.*, 853 (1990).

[78] C. Chengzhi, D. Buechler, D. Lowe, S. Urwyler and G. Shapiro, *Tetrahedron*, **50**, 5735 (1994).

[79] F. Bischoff, T. N. Johansen, B. Ebert, P. Krogsgaard-Larsen and U. Madsen, *Bioorg. Med. Chem.*, **3**, 553 (1995).

[80] M. Tišler and P. Kolar, *Adv. Heterocyclic Chem.*, **64**, 1 (1995).

[81] T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, S. Haga, H. Sugi, K. Tanigawa, Y. Suzuki, K. Fukawa, O. Irino, O. Saita and S. Yamabe, *Heterocycles*, **16**, 1205 (1981).

[82] T. Kametani, Y. Suzuki, K. Kigasawa, M. Hiiragi, K. Wakisaka, H. Sugi, K. Tanigawa, K. Fukawa, O. Irino, O. Saita and S. Yamabe, *Heterocycles*, **18**, 295 (1982).

[83] Y. Zhang, Z. Tian, M. Kowalczuk, P. Edwards and R. W. Roeske, *Tetrahedron Letters*, **34**, 3659 (1993).

[84] H. Barth, G. Burger, H. Döpp, M. Kobayashi and H. Musso, *Liebigs Ann. Chem.*, 2164 (1981).

[85] Y. Yabe, C. Miura, H. Horikoshi and Y. Baba, *Chem. Pharm. Bull.*, **24**, 3149 (1976).

[86] W. J. Haggerty, Jr., R. H. Springer and C. C. Cheng, *J. Heterocyclic Chem.*, **2**, 1 (1965).

[87] G. Stoll, J. Frank, H. Musso, H. Henke and W. Herrendorf, *Liebigs Ann. Chem.*, 1968 (1986).

[88] J. Frank, G. Stoll and H. Musso, *Liebigs Ann. Chem.*, 1990 (1986).

[89] W. Herz, K. Dittmer and S. J. Cristol, *J. Biol. Chem.*, **171**, 383 (1947).

[90] C. M. Bladon, *J. Chem. Soc., Perkin Trans. 1*, 1151 (1990).

[91] H. Watanabe, S. Kuwata, S. Nakajima, K. Koshida and M. Hayashi, *Bull. Chem. Soc. Japan*, **38**, 1461 (1965).

[92] L. Flatow, *Z. Physiol. Chem.*, **64**, 367 (1910).

[93] V. Deulofeu, *Z. Physiol. Chem.*, **204**, 214 (1932).

[94] V. Tolman, J. Hanuš and K. Vereš, *J. Labelled Compd.*, **4**, 243 (1968).

[95] C. Gränacher, *Helv. Chim. Acta*, **5**, 610 (1922).

[96] T. Sasaki, *Chem. Ber.*, **54**, 2056 (1921).

[97] T. Masquelin, E. Broger, K. Müller, R. Schmid and D. Obrecht, *Helv. Chim. Acta*, **77**, 1395 (1994).

[98] H. W. Krause, F. W. Wilcke, H.-J. Kreuzfeld and C. Döbler, *Chirality*, **4**, 110 (1992).

[99] Y. Niimura and S. Hatanaka, *Sci. Pap. Coll. Gen. Educ., Univ. Tokyo*, **25**, 39 (1975); *Chem. Abstr.*, **84**, 74593 (1976).

[100] T. T. Otani and M. R. Briley, *J. Pharm. Sci.*, **68**, 260 (1979).

[101] T. T. Otani and M. R. Briley, *J. Pharm. Sci.*, **68**, 1366 (1979).

[102] J. W. Tilley, P. Levitan and R. W. Kierstead, *J. Heterocyclic Chem.*, **16**, 333 (1979).

[103] M. J. Burk, J. E. Feaster, W. A. Nugent and R. L. Harlow, *J. Am. Chem. Soc.*, **115**, 10125 (1993).

[104] C. Döbler, H.-J. Kreuzfeld, H. W. Krause and M. Michalik, *Tetrahedron: Asymmetry*, **4**, 1833 (1993).

[105] B. F. Crowe and F. F. Nord, *J. Org. Chem.*, **15**, 81 (1950).

[106] B. F. Crowe and F. F. Nord, *J. Org. Chem.*, **15**, 688 (1950).

[107] E. Campaigne, R. C. Bourgeois, R. Garst, W. C. McCarthy, R. L. Patrick and H. G. Day, *J. Am. Chem. Soc.*, **70**, 2611 (1948).

[108] K. Dittmer, *J. Am. Chem. Soc.*, **71**, 1205 (1949).

[109] M. Pérez and R. Pleixats, *Tetrahedron*, **51**, 8355 (1995).

[110] E. S. Ratemi and J. C. Vederas, *Tetrahedron Letters*, **35**, 7605 (1994).

[111] M. A. Brimble and D. D. Rowan, *J. Chem. Soc., Chem. Commun.*, 978 (1988).

[112] W. Herz, K. Dittmer and S. J. Cristol, *J. Am. Chem. Soc.*, **70**, 504 (1948).

[113] T. L. Gilchrist and A. Lemos, *Tetrahedron*, **48**, 7655 (1992).

[114] T. Frejd, M. A. Davis, S. Gronowitz and T. Sadeh, *J. Heterocyclic Chem.*, **17**, 759 (1980).

[115] S. Gronowitz and A. Svensson, *Chem. Scripta*, **27**, 249 (1987).

[116] M. Begtrup and F. A. Slok, *Synthesis*, 861 (1993).

[117] T. Honoré and J. Lauridsen, *Acta Chim. Scand.*, **B34**, 235 (1980).

[118] J. J. Hansen and P. Krogsgaard-Larsen, *J. Chem. Soc., Perkin Trans. 1*, 1826 (1980).

[119] J. Lauridsen and T. Honoré, *J. Labelled Compd.-Radiopharmaceuticals*, **18**, 1479 (1981).

[120] P. Krogsgaard-Larsen, E. O. Nielsen and D. R. Curtis, *J. Med. Chem.*, **27**, 585 (1984).

[121] P. Pevarello, R. Amici, M. Colombo and M. Varasi, *J. Chem. Soc., Perkin Trans. 1*, 2151 (1993).

[122] U. Madsen, B. Frolund, T. M. Lund, B. Ebert and P. Krogsgaard-Larsen, *Eur. J. Med. Chem.*, **28**, 791 (1993).

[123] T. N. Johansen, K. Frydenvang, B. Ebert, P. Krogsgaard-Larsen and U. Madsen, *J. Med. Chem.*, **37**, 3252 (1994).

[124] N. Skjaerbaek, B. Ebert, E. Falch, L. Brehm and P. Krogsgaard-Larsen, *J. Chem. Soc., Perkin Trans. 1*, 221 (1995).

[125] J. Lauridsen, T. Honoré and P. Krogsgaard-Larsen, *J. Med. Chem.*, **28**, 668 (1985).

[126] P. Krogsgaard-Larsen, L. Brehm, J. S. Johansen, P. Vinzents, J. Lauridsen and D. R. Curtis, *J. Med. Chem.*, **28**, 673 (1985).

[127] U. Madsen, B. Ebert, P. Krogsgaard-Larsen and E. H. F. Wong, *Eur. J. Med. Chem.*, **27**, 479 (1992).

[128] U. Madsen, K. Schaumburg, L. Brehm, D. R. Curtis and P. Krogsgaard-Larsen, *Acta Chem. Scand.*, **B40**, 92 (1986).

[129] U. Madsen, L. Andresen, G. A. Poulsen, T. B. Rasmussen, B. Ebert, P. Krogsgaard-Larsen and L. Brehm, *Bioorg. Med. Chem. Letters*, **3**, 1649 (1993).

[130] P. Krogsgaard-Larsen, J. W. Ferkany, E. O. Nielsen, U. Madsen, B. Ebert, J. S. Johansen, N. H. Diemer, T. Bruhn, D. T. Beattie and D. R. Curtis, *J. Med. Chem.*, **34**, 123 (1991).

[131] K. Hofmann, R. Andreatta and H. Bohn, *J. Am. Chem. Soc.*, **90**, 6207 (1968).

[132] I. T. Christensen, B. Ebert, U. Madsen,B. Nielsen, L. Brehm and P. Krogsgaard-Larsen, *J. Med. Chem.*, **35**, 3512 (1992).

[133] J. J. Hansen and P. Krogsgaard-Larsen, *J. Chem. Soc., Chem. Commun.*, 87 (1979).

[134] I. L. Finar and K. Utting, *J. Chem. Soc.*, 5272 (1960).

[135] N. Sugimoto, H. Watanabe and A. Ide, *Tetrahedron*, **11**, 231 (1960).

[136] I. Murakoshi, S. Ohmiya and J. Haginiwa, *Chem. Pharm. Bull.*, **20**, 609 (1972).

[137] H. Reimlinger and J. F. M. Oth, *Chem. Ber.*, **97**, 331 (1964).

[138] L. D. Arnold, R. G. May and J. C. Vederas, *J. Am. Chem. Soc.*, **110**, 2237 (1988).

[139] S. H. Rosenberg, K. P. Spina, K. W. Woods, J. Polakowski, D. L. Martin, Z. Yao, H. H. Stein, J. Cohen, J. L. Barlow, D. A. Egan, K.

A.Tricarico, W. R. Baker and H. D. Kleinert, *J. Med. Chem.*, **36**, 449 (1993).

[140] S. V. Pansare, G. Huyer, L. D. Arnold and J. C. Vederas, *Org. Synth.*, **70**, 1 (1992).

[141] C. J. Bish and J. H. Jones, *J. Chem. Res., Synop.*, 338 (1988).

[142] R. G. Jones, *J. Am. Chem. Soc.*, **71**, 3994 (1949).

[143] R. G. Jones, E. C. Kornfeld and K. C. McLaughlin, *J. Am. Chem. Soc.*, **72**, 4526 (1950).

[144] H. Watanabe, S. Kuwata, T. Sakata and K. Matsumura, *Bull. Chem. Soc. Japan.*, **39**, 2473 (1966).

[145] W. T. Caldwell and S. M. Fox, *J. Am. Chem. Soc.*, **73**, 2935 (1951).

[146] T. Nishi, F. Saito, H. Nagahori, M. Kataoka, Y. Morisawa, Y. Yabe, M. Sakurai, S. Higashida, M. Shoji, Y. Matsushita, Y. Iijima, K. Ohizumi and H. Koike, *Chem. Pharm. Bull.*, **38**, 103 (1990).

[147] A. Silberg, M. Ruse, E. Hamburg and I. Cîrdan, *Chem. Ber.*, 102, 423 (1969).

[148] G. E. Trout, *J. Med. Chem.*, **15**, 1259 (1972).

[149] T. Wieland, G. Ohnacker and W. Ziegler, *Chem. Ber.*, **90**, 194 (1957).

[150] Yu. N. Belokon, A. S. Sagyan, S. M. Djamgaryan, V. I. Bakhmutov and V. M. Belikov, *Tetrahedron*, **44**, 5507 (1988).

[151] K. Tohdo, Y. Hamada and T. Shioiri, *Synlett*, 247 (1994).

[152] R. G. Jones, *J. Am. Chem. Soc.*, **71**, 383 (1949).

[153] R. N. Hanson and M. A. Davis, *J. Heterocyclic Chem.*, **18**, 205 (1981).

[154] R. G. Jones and C. Ainsworth, *J. Am. Chem. Soc.*, **77**, 1538 (1955).

[155] A. A. Ogrel, E. N. Zvonkova and R. G. Gafurov, *Bioorg. Khim.*, **19**, 880 (1993).

[156] S. Avakian, J. Moss and G. J. Martin, *J. Am. Chem. Soc.*, **70**, 3075 (1948).

[157] B. Sila, J. Wojtanis and T. Lesiak, *Rocz. Chem.*, **47**, 1281 (1973).

[158] B. Sila, J. Wojtanis and T. Lesiak, *Rocz. Chem.*, **49**, 1661 (1975).

[159] D. F. Elliott and C. Harington, *J. Chem. Soc.*, 1374 (1949).

[160] N. B. Chapman, R. M. Scrowston and R. Westwood, *J. Chem. Soc. (C)*, 1855 (1969).

[161] G. A. Bhat and S. Sidappa, *J. Karnatak Univ., Sci.*, **19**, 184 (1974); *Chem. Abstr.*, **83**, 192993 (1975).

[162] J. Ø. Madsen, M. Meldal, S. Mortensen and B. Olsson, *Acta Chem. Scand.*, **B35**, 77 (1981).

[163] D. D. Dalgatov and A. M. Simonov, *Khim. Geterotsikl. Soedin.*, 908 (1967).

[164] A. Ljungqvist, C. Y. Bowers and K. Folkers, *Int. J. Peptide Protein Res.*, **41**, 427 (1993).

[165] A. Salifou, M. E. Johnson and D. Nagarathnam, *Synth. Commun.*, **23**, 2435 (1993).

[166] K. Taku, H. Sasaki, S. Kimura and Y. Imanishi, *Amino Acids*, **7**, 311 (1994).

[167] M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.*, **77**, 457 (1955).

[168] M. Yu. Lidak, Ya. Ya. Shluke and S. E. Poritere, *Khim. Geterotsikl. Soedin.*, 1561 (1972).

[169] I. Lewis, *Tetrahedron Letters*, **34**, 5697 (1993).

[170] M. T. Doel, A. S. Jones and N. Taylor, *Tetrahedron Letters*, 2285 (1969).

[171] M. T. Doel, A. S. Jones and R. T. Walker, *Tetrahedron*, **30**, 2755 (1974).

[172] M. Draminski and J. Pitka, *Makromol. Chem.*, **179**, 2195 (1978).

[173] M. Yu. Lidak, V. E. Straume, D. E. Shnore and R. A. Paegle, *Khim. Geterotsikl. Soedin.*, 705 (1972).

[174] A. J. H. Nollet and U. K. Pandit, *Tetrahedron*, **25**, 5983 (1969).

[175] D. S. Letham, R. E. Summons, C. W. Parker and J. K. MacLeod, *Planta*, **146**, 71 (1979).

[176] M. Yu. Lidak, Ya. Ya. Shluke, S. E. Poritere and Yu. P. Shvachkin, *Khim. Geterotsikl. Soedin.*, 529 (1970).

[177] M. Yu. Lidak, Ya. Ya. Shluke and Yu. P. Shvachkin, *Khim. Geterotsikl. Soedin.*, 995 (1968).

[178] I. M. Ovcharova and E. S. Golovchinskaya, *Khim.-Farm. Zh.*, **8**, 26 (1974); *Chem. Abstr.*, **81**, 25636 (1974).

[179] J. K. MacLeod, R. E. Summons, C. W. Parker and D. S. Letham, *J. Chem. Soc., Chem. Commun.*, 809 (1975).

[180] C. C. Duke, J. K. MacLeod, R. E. Summons, D. S. Letham and C. W. Parker, *Aust. J. Chem.*, **31**, 1291 (1978).

[181] B. Shadid, H. C. van der Plas, W. H. J. Boesten, J. Kamphuis, E. M. Meijer and H. E. Schoemaker, *Tetrahedron*, **46**, 913 (1990).

[182] S. Kubik, R. S. Meissner and J. Rebek, Jr., *Tetrahedron Leters.*, **35**, 6635 (1994).

[183] K. Takemoto, H. Tahara, A. Yamada, Y. Inaki and N. Ueda, *Makromol. Chem.*, **169**, 327 (1973).

[184] H. Watanabe, S. Kuwata, K. Naoe and Y. Nishida, *Bull. Chem. Soc. Japan*, **41**, 1634 (1968).

[185] F. Zymalkowski, *Arch. Pharm.*, **291**, 436 (1958).

[186] J. Overhoff, J. Boeke and A. Gorter, *Recl. Trav. Chim. Pays-Bas*, **55**, 293 (1936).

[187] C. Niemann, R. N. Lewis and J. T. Hays, *J. Am. Chem. Soc.*, **64**, 1678 (1942).

[188] K. Folkers, C. Y. Bowers, T. Kubiak and J. Stepinski, *Biochem. Biophys. Res. Commun.*, **111**, 1089 (1983).

[189] G. Slater and A. W. Somerville, *Tetrahedron*, **23**, 2823 (1967).

[190] S. J. Norton and P. T. Sullivan, *J. Heterocyclic Chem.*, **7**, 699 (1970).

[191] S. Inouye, T. Shomura, T. Tsuruoka, Y. Ogawa, H. Watanabe, J. Oshida and T. Niida, *Chem. Pharm. Bull.*, **23**, 2669 (1975).

[192] R. L. N. Harris and T. Teitei, *Aust. J. Chem.*, **30**, 649 (1977).

[193] S. R. Schow, S. Q. DeJoy, M. M. Wick and S. S. Kerwar, *J. Org. Chem.*, **59**, 6850 (1994).

[194] A. G. Myers and J. L. Gleason, *J. Org. Chem.*, **61**, 813 (1996).

[195] P. T. Sullivan, C. B. Sullivan and S. J. Norton, *J. Med. Chem.*, **14**, 211 (1971).

[196] P. T. Sullivan and S. J. Norton, *J. Med. Chem.*, **14**, 557 (1971).

[197] R. B. Greenwald and C. L. Zirkle, *J. Org. Chem.*, **33**, 2118 (1968).

[198] J. E. Rivier, J. Porter, C. L. Rivier, M. Perrin, A. Corrigan, W. A. Hook, R. P. Siraganian and W. W. Vale, *J. Med. Chem.*, **29**, 1846 (1986).

[199] H. M. Rajh, J. H. Uitzetter, L. W. Westerhuis, C. L. Van den Dries and G. I. Tesser, *Int. J. Peptide Protein Res.*, **14**, 68 (1979).

[200] K. Folkers, T. Kubiak and J. Stepinski, *Int. J. Peptide Protein Res.*, **24**, 197 (1984).

[201] J. P. Wibaut, H. P. Wallingford, H. J. Rang and D. K. Kettenes, *Recl. Trav. Chim. Pays-Bas*, **74**, 1049 (1955).

[202] R. K. Griffith and H. J. Harwood, *J. Org. Chem.*, **29**, 2658 (1964).

[203] M. Ali, N. H. Khan and A. A. Siddiqui, *Synth. Commun.*, **6**, 227 (1976).

[204] H. Hilpert, *Helv. Chim. Acta*, **70**, 1307 (1987).

[205] A. Silberg, M. Ruse, H. Mantsch and S. Csontos, *Chem. Ber.*, **97**, 1767 (1964).

[206] D. M. Andrews, M. Gregoriou, T. C. M. Page, J. M. Peach and A. J. Pratt, *J. Chem. Soc., Perkin Trans 1*, 1335 (1995).

[207] R. L. Bixler and C. Niemann, *J. Org. Chem.*, **23**, 575 (1958).

[208] D. F. Elliott, A. T. Fuller and C. R. Harington, *J. Chem. Soc.*, 85 (1948).

[209] P. T. Sullivan, M. Kester and S. J. Norton, *J. Med. Chem.*, **11**, 1172 (1968).

[210] A. F. Bickel, *J. Am. Chem. Soc.*, **69**, 1805 (1947).

[211] M. Cushman, P. Chinnasamy, A. K. Chakraborti, J. Jurayj, R. L. Geahlen and R. D. Haugwitz, *Int. J. Peptide Protein Res.*, **36**, 538 (1990).

[212] G. Y. Krippner and M. M. Harding, *Tetrahedron: Asymmetry*, **5**, 1793 (1994).

[213] 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.*, 110 (1991).

[214] M. Uchida, F. Tabusa, M. Komatsu, S. Morita, T. Kanbe and K. Nakagawa, *Chem. Pharm. Bull.*, **33**, 3775 (1985).

[215] K. Matsumura, T. Kasai and H. Tashiro, *Bull. Chem. Soc. Japan.*, **42**, 1741 (1969).

[216] D. O. Shah and K. N. Trivedi, *Curr. Sci.*, **41**, 876 (1972); *Chem. Abstr.*, **78**, 72547 (1973).

[217] M. Uchida, F. Tabusa, M. Komatsu, S. Morita, T. Kanbe and K. Nakagawa, *Chem. Pharm. Bull.*, **34**, 4821 (1986).

[218] A. Berger, M. Smolarsky, N. Kurn and H. R. Bosshard, *J. Org. Chem.*, **38**, 457 (1973).

[219] K. Otsubo, S. Morita, M. Uchida, K. Yamasaki, T. Kanbe and T. Shimizu, *Chem. Pharm. Bull.*, **39**, 2906 (1991).

[220] Yu. P. Shvachkin, L. A. Syrtsova and M. P. Filatova, *Zh. Obsch. Khim.*, **33**, 2487 (1963).

[221] R. L. N. Harris, *Aust. J. Chem.*, **29**, 1335 (1976).

[222] R. H. Springer, W. J. Haggerty, Jr. and C. C. Cheng, *J. Heterocyclic Chem.*, **2**, 49 (1965).

[223] Yu. P. Shvachkin, G. A. Korshunova, N. A. Bashkirova and M. A. Prokofjev, *Dokl. Akad. Nauk SSSR*, **179**, 1127 (1968).

[224] B. Blank and W. T. Caldwell, *J. Org. Chem.*, **24**, 1137 (1959).

[225] R. A. Paegle, I. Zh. Lulle, S. E. Poritere and M. Yu. Lidak, *Khim. Geterotsikl. Soedin.*, 954 (1990).

[226] A. P. Martinez and W. W. Lee, *J. Org. Chem.*, **30**, 317 (1965).

[227] J. H. Dewar and G. Shaw, *J. Chem. Soc.*, 583 (1962).

[228] M. Yu. Lidak, R. A. Paegle, M. G. Plata, K. Ya. Pets and Yu. P. Shvachkin, *Khim. Geterotsikl. Soedin.*, 379 (1968).

[229] M. Yu. Lidak, R. A. Paegle, M. G. Plata and Yu. P. Shvachkin, *Khim. Geterotsikl. Soedin.*, 530 (1971).

[230] A. P. Martinez, W. W. Lee and L. Goodman, *J. Med. Chem.*, **11**, 60 (1968).

[231] C. Petermann and J.-L. Fauchere, *Helv. Chim. Acta*, **66**, 1513 (1983).

[232] B. Imperiali and S. L. Fisher, *J. Am. Chem. Soc.*, **113**, 8527 (1991).

[233] B. Imperiali and S. L. Fisher, *J. Org. Chem.*, **57**, 757 (1992).

[234] S. R. Wilson, A. Yasmin and Y. Wu, *J. Org. Chem.*, **57**, 6941 (1992).

[235] B. Imperiali, T. J. Prins and S. L. Fisher, *J. Org. Chem.*, **58**, 1613 (1993).

[236] H. Döpp, S. Maurer, A. N. Sasaki and H. Musso, *Liebigs Ann. Chem.*, 254 (1982).

[237] B. Imperiali and R. S. Roy, *J. Org Chem.*, **60**, 1891 (1995).

[238] N. Rhugenda-Banga, A. Welter, J. Jadot and J. Casimir, *Phytochemistry*, **18**, 482 (1979).

[239] J. Lamotte, B. Oleksyn, L. Dupont, O. Dideberg, H. Campsteyn, M. Vermeire and N. Rhugenda-Banga, *Acta Cryst.*, **B34**, 3635 (1978).

[240] R.R. Doyle and B. Levenberg, *Phytochemistry*, **13**, 2813 (1974).

[241] S.-I. Hatanaka and Y. Niimura, *Phytochemistry*, **14**, 1436 (1975).

[242] H. Oogishi, *Japan Kokai* 76 22,886; *Chem. Abstr.*, **85**, 30796 (1976).

[243] L. Fowden, F. F. Noe, J. H. Ridd and R. F. M. White, *Proc. Chem. Soc.*, 131 (1959).

[244] F. F. Noe and L. Fowden, *Nature*, **184**, 69 (1959).

[245] F. F. Noe and L. Fowden, *Biochem. J.*, **77**, 543 (1960).

[246] F. Lambein and R. Van Parijs, *Biochem. Biophys. Res. Commun.*, **40**, 557 (1970).

[247] F. Lambein and R. Van Parijs, *Biochem. Biophys. Res. Commun.*, **61**, 155 (1974).

[248] A. De Bruyn, G. Verhegge and F. Lambein, *Org. Magn. Reson.*, **29**, 641 (1991).

[249] T. Iwama, Y. Nagai, N. Tamura, S. Harada and A. Nagaoka, *Eur. J. Pharmacol.*, **197**, 187 (1991).

[250] H. Shinozaki and I. Shibuya, *Neuropharmacology*, **13**, 665 (1974).

[251] J. L. Flippen and R. D. Gilardi, *Acta Cryst.*, **B32**, 951 (1976).

[252] S. Matsunaga, N. Fusetani, K. Hashimoto and M. Wälchli, *J. Am. Chem. Soc.*, **111**, 2582 (1989).

[253] C. A. Bewley and D.J. Faulkner, *J. Org. Chem.*, **59**, 4849 (1994); and correction, *J. Org. Chem.*, **60**, 2644 (1995).

[254] K. Yamano, K. Konno and H. Shirahama, *Heterocycles*, **35**, 125 (1993).

[255] R. J. C. Kleipool and J. Wibaut, *Recl. Trav. Chim. Pays-Bas*, **69**, 37 (1950).

[256] R. Adams, S. J. Cristol, A. A. Anderson, and A. A. Albert, *J. Am. Chem. Soc.*, **67**, 89 (1945).

[257] R. Adams and T. R. Govindachari, *J. Am. Chem. Soc.*, **69**, 1806 (1947).

[258] R. Adams, V. V. Jones and J. L. Johnson, *J. Am. Chem. Soc.*, **69**, 1810 (1947).

[259] R. G. Crounse, J. D. Maxwell and H. Blank, *Nature*, **194**, 694 (1962).

[260] D. Fujimoto, T. Moriguchi, T. Ishida and H. Hayashi, *Biochem. Biophys. Res. Commun.*, **84**, 52 (1978).

[261] S. P. Robins, *Biochem. J.*, **215**, 167 (1983).

[262] T. Ogawa, T. Ono, M. Tsuda and Y. Kawanishi, *Biochem. Biophys. Res. Commun.*, **107**, 1252 (1982).

[263] J. E. Leet, D. R. Schroeder, S. J. Hofstead, J. Golik, K. L. Colson, S. Huang, S. E. Klohr, T. W. Doyle and J. A. Matson, *J. Am. Chem. Soc.*, **114**, 7946 (1992).

[264] J. E. Leet, D. R. Schroeder, D. R. Langley, K. L. Colson, S. Huang, S. E. Klohr, M. S. Lee, J. Golik, S. J. Hofstead, T. W. Doyle and J. A. Matson, *J. Am. Chem. Soc.*, **115**, 8432 (1993).

[265] F. Lambein and R. Van Parijs, *Biochem. Biophys. Res. Commun.*, **32**, 474 (1968).

[266] T. S. Ashworth, E. G. Brown and F. M. Roberts, *Biochem. J.*, **129**, 897 (1972).

[267] N. V. Nazimova and G. N. Tishchenko, *Kristallografiya*, **28**, 817 (1983).

[268] E. A. Bell, *Biochim. Biophys. Acta*, **47**, 602 (1961).

[269] E. A. Bell and R. G. Foster, *Nature*, **194**, 91 (1962).

[270] E. G. Brown and J. Mohamad, *Phytochemistry*, **29**, 3117 (1990).

[271] S. Hattori and A. Komamine, *Nature*, **183**, 1116 (1959).

[272] E. G. Brown, K. A. M. Flayeh and J. R. Gallon, *Phytochemistry*, **21**, 863 (1982).

[273] D. M. Frisch, P. M. Dunnill, A. Smith and L. Fowden, *Phytochemistry*, **6**, 921 (1967).

[274] K. Saito, R. Kanda, M. Kurosawa and I. Murakoshi, *Can. J. Chem.*, **72**, 188 (1994).

[275] I. Murakoshi, H. Kuramoto, J. Haginiwa and L. Fowden, *Phytochemistry*, **11**, 177 (1972).

[276] M. Noji, I. Murakoshi and K. Saito, *Biochem. Biophys. Res. Commun.*, **197**, 1111 (1993).

[277] F. Ikegami, Y. Komada, M. Kobori, D. R. Hawkins and I. Murakoshi, *Phytochemistry*, **29**, 2507 (1990).

[278] F. Ikegami, S. Itagaki, T. Ishikawa, G. Ongena, Y.-H. Kuo, F. Lambein and I. Murakoshi, *Chem. Pharm. Bull.*, **39**, 3376 (1991).

[279] F. Ikegami, S. Horiuchi, M. Kobori, I. Morishige and I. Murakoshi, *Phytochemistry*, **31**, 1991 (1992).

[280] F. Ikegami, G. Ongena, R. Sakai, S. Itagaki, M. Kobori, T. Ishikawa, Y.-H. Kuo, F. Lambein and I. Murakoshi, *Phytochemistry*, **33**, 93 (1993).

[281] F. Ikegami, K. Kusama-Eguchi, E. Sugiyama, K. Watanabe, F. Lambein and I. Murakoshi, *Biol. Pharm. Bull.*, **18**, 360 (1995).

[282] I. Murakoshi, F. Kato, J. Haginiwa and L. Fowden, *Chem. Pharm. Bull.*, **21**, 918 (1973).

[283] I. Murakoshi, F. Ikegami, F. Kato, J. Haginiwa, F. Lambein, L. Van Rompuy and R. Van Parijs, *Phytochemistry*, **14**, 1515 (1975).

[284] I. Murakoshi, F. Kato, J. Haginiwa and T. Takemoto, *Chem. Pharm. Bull.*, **22**, 473 (1974).

[285] I. Murakoshi, F. Kato and J. Haginiwa, *Chem. Pharm. Bull.*, **22**, 480 (1974).

[286] P. Massini, *Biochem. Biophys. Acta*, **36**, 548 (1959).

[287] I. Murakoshi, F. Ikegami, N. Ookawa, T. Ariki, J. Haginiwa, Y.-H. Kuo and F. Lambein, *Phytochemistry*, **17**, 1571 (1978).

[288] I. Murakoshi, F. Ikegami, N. Ookawa, J. Haginiwa and D. S. Letham, *Chem. Pharm. Bull.*, **25**, 520 (1977).

[289] I. Murakoshi, C. Koide, F. Ikegami and K. Nasu, *Chem. Pharm. Bull.*, **31**, 1777 (1983).

[290] I. Murakoshi, F. Ikegami, Y. Hinuma and Y. Hanma, *Phytochemistry*, **23**, 973 (1984).

[291] I. Murakoshi, F. Ikegami, Y. Hinuma and Y. Hanma, *Phytochemistry*, **23**, 1905 (1984).

[292] I. Murakoshi, F. Ikegami, T. Nishimura and K. Tomita, *Phytochemistry*, **24**, 1693 (1985).

[293] I. Murakoshi, F. Ikegami, Y. Yoneda, H. Ihara, K. Sakata and C. Koide, *Chem. Pharm. Bull.*, **34**, 1473 (1986).

[294] H. Tanaka, K. Tanizawa, T. Arai, K. Saito, T. Arai and K. Soda, *FEBS Letters*, **196**, 357 (1986).

[295] N. Imamura, M. Murata, T. Yao, R. Ōiwa, H. Tanaka and S. Omura, *J. Antibiot.*, **38**, 1110 (1985).

[296] K. Saito, A. Komamine and S. Hatanaka, *Z. Naturforsch.*, **33C**, 793 (1978).

[297] K. Saito, A. Komamine and S. Senoh, *Z. Naturforsch.*, **30C**, 659 (1975).

[298] B. E. Ellis, *Phytochemistry*, **15**, 489 (1976).

[299] J. J. Hansen, J. Lauridsen, E. Nielsen and P. Krogsgaard-Larsen, *J. Med. Chem.*, **26**, 901 (1983).

[300] J. J. Hansen, B. Nielsen, P. Krogsgaard-Larsen, L. Brehm, E. O. Nielsen and D. R. Curtis, *J. Med. Chem.*, **32**, 2254 (1989).

[301] J. D. Buttrey, A. S. Jones and R. T. Walker, *Tetrahedron*, **31**, 73 (1975).

[302] B. Ebert, S. Lenz, L. Brehm, P. Bregnedal, J. J. Hansen, K. Frederiksen, K. P. Bogeso and P. Krogsgaard-Larsen, *J. Med. Chem.*, **37**, 878 (1994).

[303] A. W. Lipkowski and G. Flouret, *Pol. J. Chem.*, **54**, 2225 (1980).

[304] D. T. Belmont, V. Hendrickson and M. J. Hoehman, *US Patent* 5,089,616; *Chem. Abstr.*, **116**, 214924 (1992).

[305] C. Cativiela, M. D. Diaz de Villegas, J. I. Garcia, J. A. Mayoral and E. Mélendez, *Bull. Soc. Chim. Belg.*, **93**, 479 (1984).

[306] H. K. Chenault, J. Dahmer and G. M. Whitesides, *J. Am. Chem. Soc.*, **111**, 6354 (1989).

[307] K. Hofmann and H. Bohn, *J. Am. Chem. Soc.*, **88**, 5914 (1966).

[308] G. Kretzschmar, H. U. Hoppe, H. Wicke, M. Schlingmann, R. Keller and B. Sachse, *German Patent* 3,820,302; *Chem. Abstr.*, **113**, 23677 (1990).

[309] G. Kretzschmar, H. Wicke and B. Sachse, *German Patent*, 3,829,451; *Chem. Abstr.*, **113**, 115862 (1990).

[310] K. Hsieh, E. C. Jorgensen and T. C. Lee, *J. Med. Chem.*, **22**, 1199 (1979).

[311] Yu. P. Shvachkin, N. A. Voskova, G. A. Korshunova, Yu. A. Semiletov and V. Savelova, *Vestn. Mosk. Univ., Khim.*, **17**, 598 (1976); *Chem. Abstr.*, **87**, 23697 (1977).

[312] D. H. Coy, Y. Hirotsu, T. W. Redding, E. J. Coy and A. V. Schally, *J. Med. Chem.*, **18**, 948 (1975).

[313] F. W. Dunn, *J. Org. Chem.*, **21**, 1525 (1956).

[314] F. W. Dunn, *J. Biol. Chem.*, **234**, 802 (1959).

[315] S. T. Chen, S. C. Hsiao, A. J. Chiou, S. H. Wu and K. T. Wang, *J. Chin. Chem. Soc. (Taipei)*, **39**, 91 (1992); *Chem. Abstr.*, **116**, 236119 (1992).

[316] T. Miyazawa, T. Takitani, S. Ueiji, T. Yamada and S. Kuwata, *J. Chem. Soc., Chem. Commun.*, 1214 (1988).

[317] B. Nielsen, H. Fisker, B. Ebert, U. Madsen, D. R. Curtis, P. Krogsgaard-Larsen and J. J. Hansen, *Bioorg. Med. Chem. Leters.*, **3**, 107 (1993).

[318] K. Dittmer, R. P. Martin, W. Herz and S. J. Cristol, *J. Am. Chem. Soc.*, **71**, 1201 (1949).

[319] H. Hilpert, M. A. Siegfried and A. S. Dreiding, *Helv. Chim. Acta*, **68**, 1670 (1985).

[320] J. C. Sheehan and C. A. Robinson, *J. Am. Chem. Soc*, **71**, 1436 (1949).