Chapter 1. Introduction

1.1 Short review on the use and preparation of PET-labelled amino acids. Importance for PET using new α-substituted amino acids

1.1.1 *Positron emission tomography in oncology*

Tomography is the technique of analysing data as contiguous slices through a part of subject's body. The data are reconstructed to give a steady three dimensional image and, in some cases, time-resolved images. Positron emission tomography (PET) utilises positron emitting radiopharmaceuticals in the study of metabolic and physiological processes. The production of the positron emitting radionuclide by a cyclotron followed by its incorporation into a molecule of a physiologically active compound using the appropriate radiochemical techniques is the starting point for any PET study. After the injection of the labelled tracer, the space- and time-resolved image of positron annihilations is detected externally using rings of coincidence detectors placed around the subject (a PET scanner).

PET investigations using 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) become available in a large number of hospitals worldwide (Figures 1.1, 1.2). FDG-PET is a useful technique for tumour detection, diagnosis of tumour recurrence. However, FDG has disadvantages. It is not only taken up by tumours, but also in the heart and the brain. This phenomenon hampers detection of tumours in these tissues. High physiological FDG uptake can be seen in muscle tissue, macrophages and other cells in inflammatory processes or activated after chemotherapy or radiation therapy causing false positive results. Decreased uptake can cause false negative results in patients with hyperglycaemia. More specific tracers are therefore being developed. An overview is given in Table 1. Of these tracers, amino acids have been extensively studied both clinically and pre-clinically. The incorporation of labelled amino acids into brain tumours and into some other organ with high physiological consumption of glucose is the superior diagnostic method for its much higher selectivity compared to FDG. In Figure 1, a typical example is given showing a comparison of [^{18}F]FDG and [1-^{11}C]-L-tyrosine in the same patient. High physiological uptake of [^{18}F]FDG is observed, but in the tumour region the uptake is lower. [1-^{11}C]-L-Tyrosine uptake correctly visualizes this tumour.

[^{11}C]Amino acids with exception of [^{11}C]methionine are not yet available for routine diagnostics, while fluorine-18 labelled FET and FDOPA are routinely available (Table 1.1).

Tracer	Uptake Mechanism	Refs.
[^{18}F]-FDG, [^{11}C]-glucose	Glucose consumption	[1, 2]
[^{11}C]-Tyrosine	Protein synthesis	[3]
[^{18}F]-Fluoroethyltyrosine, [^{11}C]-methionine	Amino acid transport	[4, 5]
[^{18}F]-Annexin	Apoptosis	[6]
[^{11}C]-Thymidine, [^{18}F]-fluorouracil, [^{18}F]-fluorothymidine	DNA-synthesis	[7-9]
[^{11}C]-Choline, [^{18}F]-fluoromethylcholine	Membrane synthesis	[10, 11]
[^{18}F]-Fluoroazomycine	Hypoxia	[12]

arabinoside			
[^{18}F]-Octreotide, [^{18}F]-fluoroestradiol, [^{18}F]-neuropeptides	Receptor density		[13-15]
[^{18}F]-Phosphonium salts	Membrane potential		[16]
[^{18}F]-FluoroDOPA, β-[^{11}C]-5-Hydroxy-tryptophan, β-[^{11}C]-DOPA, α-[^{11}C]Methyltryptophan	Excretion of neurotransmitters		[17, 18]

Table 1.1 Tracers and uptake mechanisms.

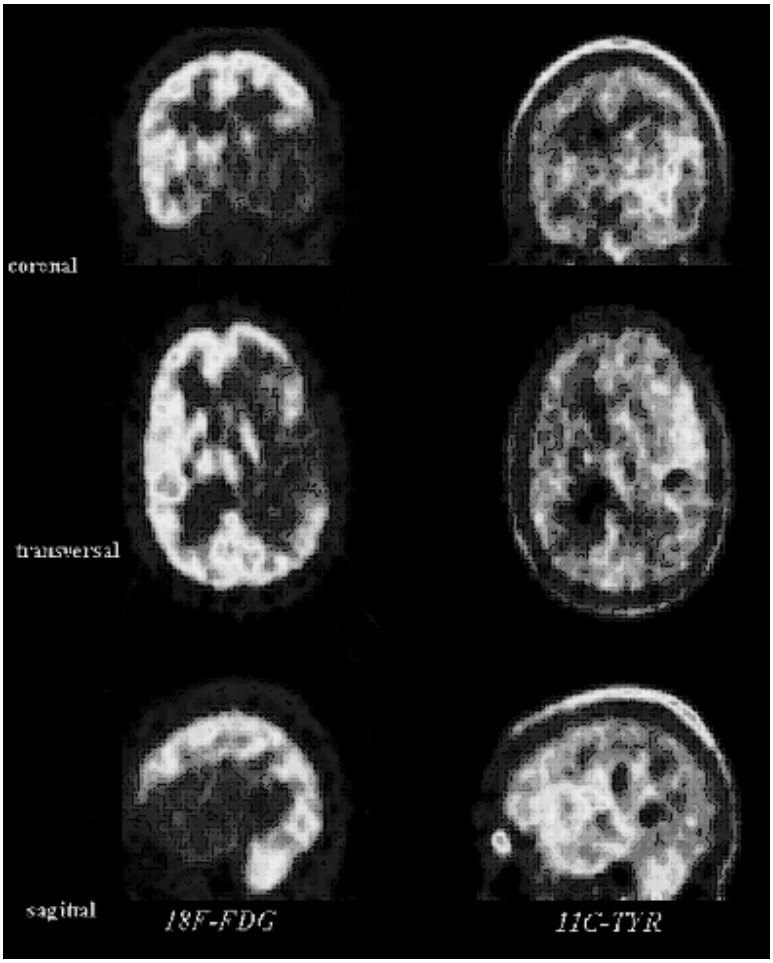


Figure 1.1 Full-color in appendix. Imaging of a human brain with [^{18}F]FDG versus [1-^{11}C]-L-Tyrosine. Courtesy of Dr Jan Pruim, University Medical Center Groningen.

New tomographs allow simultaneously recording of both CT or MRI and PET providing both anatomical information from CT (or MRI) and functionality from PET (Figure 1.2).

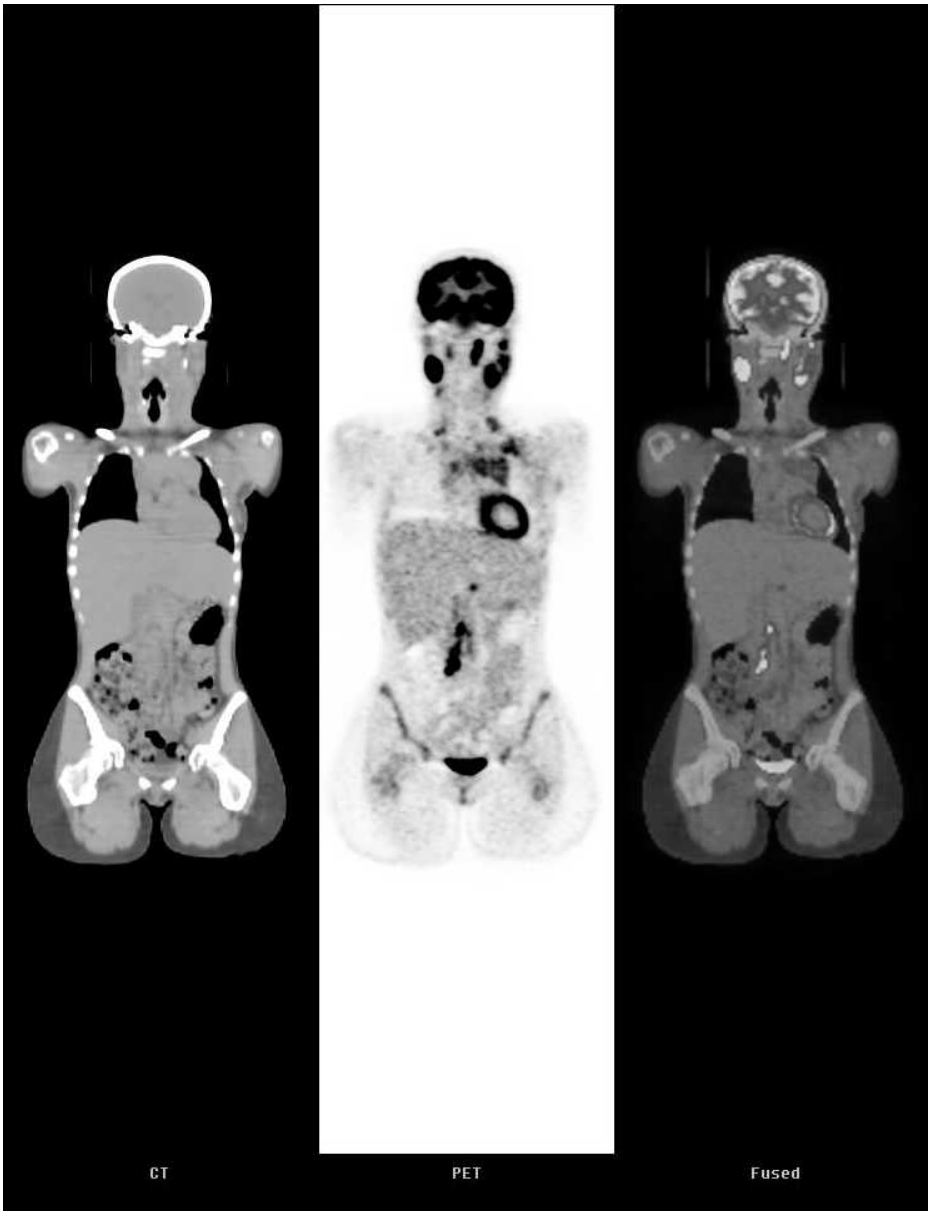


Figure 1.2 Full-color in appendix. Left – CT image, middle – PET image, right – superposition in artificial rcolours. Courtesy of Dr Nicholas Gillings, Copenhagen University Hospital.

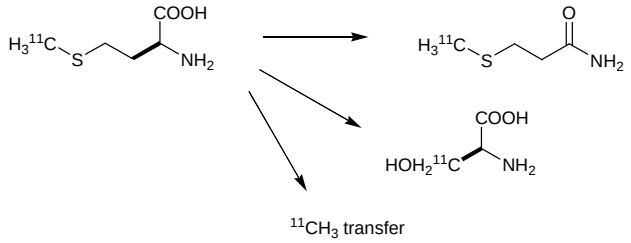
The PET scan clearly shows neck metastases of Hodgkin lymphoma.

1.1.2 *Potential benefits of using AAs for PET*

Additionally to the applications in oncologic diagnostics (protein synthesis rate, amino acids uptake), the aromatic amino acids tyrosine, 3,4-dihydroxyphenylalanine (DOPA), tryptophan, 5-hydroxytryptophan and their analogues are potential tools for neurological research since they are precursors for the biosynthesis of neurotransmitters dopamine and serotonin in the

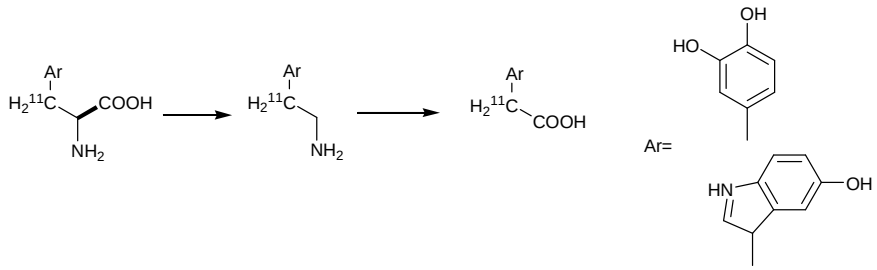
brain following the amine precursor uptake and decarboxylation (APUD) principle (Table 1.1). Cognitive processes and neurological and psychiatric diseases are related to these neurosystems and their possible malfunction.
Nowadays two applications of labelled amino acids for visualisation of tumours attract the main attention: [^{11}C] or [^{18}F]amino acids as substrates of specific membrane transport systems or *in vivo* measurement of protein synthesis rate. Recently we disclosed different mode of interaction of fluorine-containing compounds with biological structures originated in a hydrogen bond H…F formation. (Chapter 2.5) Van-der-Waals interactions between fluorine atoms and aromatic systems are also possible. This argument against non-critical use of [^{18}F]amino acids is more solid for neurological application where pharmacokinetic modelling of biosynthesis and catabolism of neurotransmitters is of crucial importance, but in oncological diagnostics such unnatural interactions should be also avoided if possible. From a clinical point of view, fluorine-labelled amino acids such as (*S*)-3-(4-(2-[^{18}F]fluoroethoxy)phenyl)alanine (FET) or (*S*)-3-(6-[^{18}F]fluoro-3,4-dimethoxyphenyl)alanine (FDOPA) are very useful for detection of tumour lesions nowadays.
Metabolic behaviour of [^{11}C]methionine and four large aromatic ^{11}C-labelled amino acids (Tyr, (*S*)-3-(3,4-dimethoxyphenyl)alanine (DOPA) and Trp or (*S*)-5-hydroxytryptophan (5-HT)) has been intensively studied [19, 20]:

- largest amount of [^{11}C]methionine in blood plasma is incorporated into plasma proteins. A minor part of the tracer is metabolised to ^{11}C-labelled serine and ^{11}C-methyl 4-methylsulphanyl-2-oxobutyrate; important is transmethylation through S-adenosyl-methionine (Scheme 1.1).



Scheme 1.1 Metabolism of [^{11}C]methionine

- β-^{11}C-labelled L-5-hydroxytryptophan is decarboxylated into β-labelled serotonin by L-aromatic amino acid decarboxylase (EC 4.1.1.28) and desaminated into 5-hydroxyindoleacetic acid by monoaminoxidase (EC 1.4.3.4). In the rat brain the distribution of other metabolites such as *N*-acetylserotonin, melatonin, 5-*O*-methylserotonin and 5-*O*-methoxytryptophan is restricted to the pineal gland (Scheme 1.2) [21-23];
- metabolism of β-labelled L-DOPA is similar – decarboxylation to dopamine and desamination to 3,4-dihydroxyphenylacetic acid (Scheme 1.2). Both L-DOPA and 3,4-dihydroxyphenylacetic acid are methylated by catechol-*O*-methyltransferase giving 3-*O*-methyl-L-DOPA and homovanillinic acid, respectively;
- L-tyrosine is *meta*-hydroxylated *in vivo* giving L-DOPA. Tyr and Leu are found to have the highest incorporation rates into mouse brain proteins [24] thus being the most suitable amino acids for measuring protein synthesis rates in brain tumours [20, 25, 26].



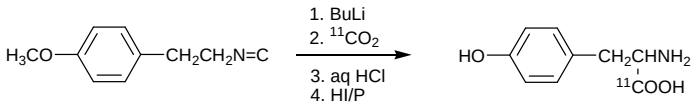
Scheme 1.2 Metabolism of β-^{11}C-labelled L-5-hydroxytryptophan and L-DOPA

1.1.3 *Overview of approaches to ^{11}C amino acids*

A short overview of developed methods of synthesis of [^{11}C]aminoacids has been published [27].

Most of optically pure ^{11}C-labelled amino acids (except [^{11}C]methionine) have been prepared via low-yield non-reliable synthetic procedures. Low availability hampers their evaluation as biological probes. Enantioselective synthesis of large aromatic α-[^{11}C]methyl-α-amino acids by α-radiomethylation of amino acids derivatives is an especially challenging goal due to relatively low steric volume of the methylation agent (methyliodide or methyltriflate). On the other hand, availability of both $^{11}CH_3I$ and $^{11}CH_3OSO_3CF_3$ as starting materials makes the synthesis and disclosure of α-[^{11}C]methylaminoacids diagnostic impact especially attractive for future routine application in PET diagnostics. The possible applications of these amino acids are discussed in more detail in Chapter 1.1.4 "Importance for PET using new α-substituted amino acids"

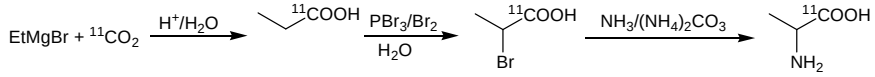
Early asymmetric syntheses of amino acids based on previously developed syntheses of ^{11}C-labelled racemic amino acids, or separation of enantiomers was used. Historically, the first synthesis of a [^{11}C]amino acid precursor - lactic acid - was described as early as in 1941 [28]. At that time no application for both lactic acid and racemic [^{11}C]alanine, which might be easily prepared from lactic acid nitrile, was known. The first synthesis of an [^{11}C]amino acid was published in 1973 [29]. Subsequently preparation of racemic phenylglycine, phenylalanine, DOPA and tyrosine labelled in carboxylic position via isocyanides was reported followed by development of preparative separation procedure for isolation of enantiomerically pure L-tyrosine (Scheme 1.3) [30-33].



Scheme 1.3 Synthesis of ^{11}C-labelled racemic tyrosine

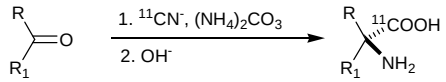
The preparation of L-tyrosine via the isocyanide has been automated for routine production using the robotic devices Anatech® RB-86 [34] and Zymark® with integrated preparative chiral HPLC.

According to PET data, this amino acid penetrates the blood-brain barrier and is accumulated in occipital cortex, limbic cortex and the thalamus. Loss of radioactivity during decarboxylation of the amino acid to tyramine limits longevity of this radiotracer [35-37]. Loss of carbon-11 carbon dioxide is beneficial, because PET-images will not be affected by ^{11}C-metabolites. ^{11}C-Carboxyl labelled L-tyrosine has been also prepared by Strecker synthesis using basic hydrolysis followed by separation of enantiomers on CHIRALPAK WH. The enzymatic approach to ^{11}C-labelled tyrosine is described in Chapter 1.1.3.3 "Enzymatic catalysis"
For the synthesis of racemic [^{11}C]alanine an original multi-step synthetic approach was developed (Scheme 1.4) [38].



Scheme 1.4 Synthesis of ^{11}C-labelled racemic alanine

In the four-step synthetic sequence, radioactivity was introduced in the first step. This makes the procedure less attractive for routine applications. In most cases, the Strecker reaction was used for production of carboxyl-labelled amino acids. In this synthesis [^{11}C]cyanide is reacted with the bisulfite adduct of an aldehyde and ammonium carbonate, followed by basic or acidic [39] hydrolysis of the resulting hydantoin. During physiologic decarboxylation of such amino acids (*e.g.* to neurotransmitters) carbon-11 carbon dioxide is exhaled and does not stay in the body. The first racemic [^{11}C]amino acids prepared by this method were valine, tryptophan and the first [^{11}C]amino acids with a quarternary α-carbon were 1-aminocyclopentanecaboxylic acid (ACPC), 1-aminocyclobutanecarboxylic acid, 1-aminocyclohexanecarboxylic acid (Scheme 1.5) [40].



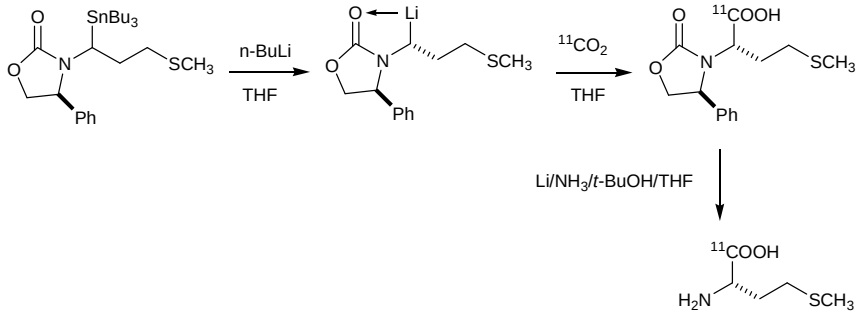
Scheme 1.5 Preparation of ^{11}C-labelled amino acids with a quarternary α-carbon

Racemic [^{11}C]amino acids have been separated to enantiomers by means of chromatography on a chiral stationary phase [38] or enzymes [41, 42]. Now chiral chromatography is a standard laboratory tool due to advent of industrially produced chiral stationary phases. Two disadvantages of this approach are:

- extra chromatography step and loss of half of the prepared labelled amino acid;
- sensitivity of the stationary phase to metals cations which irreversibly complex crown-ether residues of the most common stationary phases. This limit makes impossible direct separation of reaction mixtures of metal-catalysed reactions as well as reactions used metallocomplex synthons using such columns. In all cases, crude reaction mixtures need a C_{18} purification before application onto the chiral column.

Early examples of asymmetric synthesis of [^{11}C]amino acids demonstrated only moderate enantiomeric excess, up to 82% [43-46]. The first asymmetric synthesis of [^{11}C]alanine [44] was based on the known isocyanoacetate methylation reaction; 8-phenylmenthyl ester was used

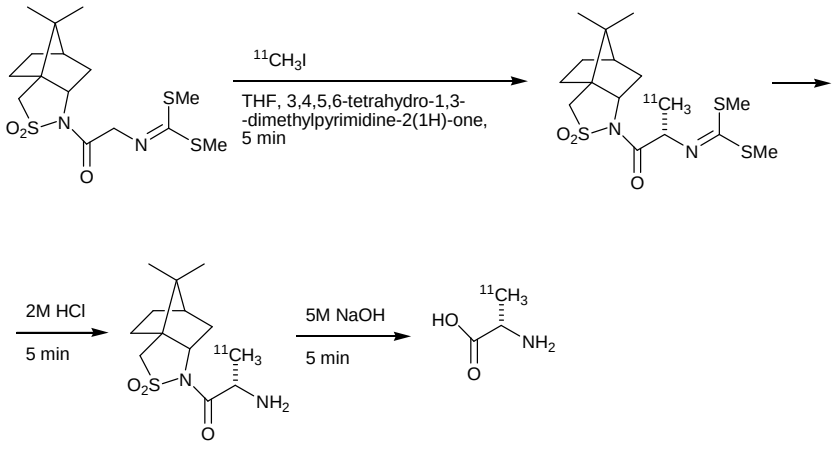
in order to induce preferrable formation of one diastereomer. As expected, alkylation of a chiral acyclic precursor results in only moderate asymmetric induction, 48 *% e.e.*
For the preparation of *carboxy*-^{11}C-labelled amino acids 4-phenylsubstituted oxazolidin-2-ones were also used. Their *N*-(α-tributylstannylalkyl) derivatives were transmetallated with *n*-butyllithium followed by trapping of labelled carbon dioxide and deprotection. In the case of labelled methionine, radiochemical yield was 15-25%. Extention of this procedure to synthesis of other amino acids was not very successful. Overall yields of model reactions with non-labelled carbon dioxide varied from 1 to 33%, and for phenylalanine synthesis 3.6% overall yield was reported (Scheme 1.6) [47].



Scheme 1.6 Asymmetric synthesis of *carboxy*-^{11}C-labelled amino acids

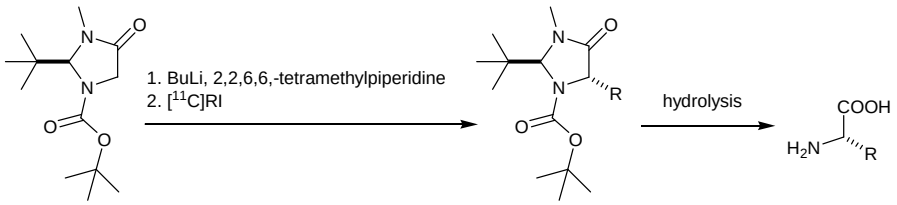
1.1.3.1 *Oppolzer's synthon and Seebach's BMI and BDI*

Commercially available Oppolzer's synthon [48, 49] provides higher asymmetric induction then Schölkopf's bis-lactim ethers [50]. In the synthesis of unlabelled alanine 96.4% *e.e.* has been reported [48]. Different conditions of [^{11}C]alanine radiosynthesis led to 94% *e.e.* (Scheme 1.7) [51].

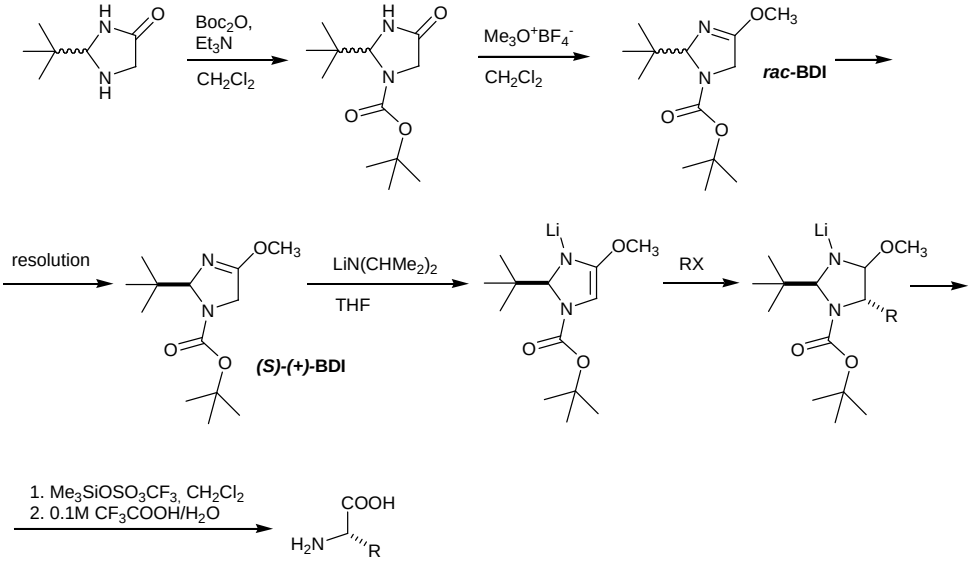


Scheme 1.7 Oppolzer's approach

Several [^{11}C]amino acids were prepared using 2-*tert*-butyl-3-methyl-1, 3-imidazolidin-4-one (BMI, Scheme 1.8) [52]: L-β-[^{11}C]-β-*para*-chlorophenylalanine (>97% *e.e.*) and L-β-[^{11}C]-α-methyl-β-*para*-chlorophenylalanine (>97% *e.e.*) [53], L-β-[^{11}C]alanine (98% *e.e.*), L-β-[^{11}C]phenylalanine (98% *e.e.*), L-ω-[^{11}C]-2-aminoadipic acid (98% *e.e.*), and L-ω-[^{11}C]lysin (96% *e.e.*) [54]



Scheme 1.8 PET radiochemical application of BMI



Scheme 1.9 Preparation and use of BDI

The new compound 2-*tert*-butyl-4-methoxy-2,5-dihydroimidazol-1-carboxylate (BDI) demonstrates even higher asymmetric induction in amino acids synthesis [55]. Hydrolysis of alkylated BDI takes place in milder conditions then hydrolysis of BMI (Scheme 1.9).
All asymmetric routes described above have the same disadvantage - they require application of very small amounts of lithium compounds to generate intermediate carbanions at low temperatures.

1.1.3.2 *Catalytic alkylation of an achiral glycine synthon*

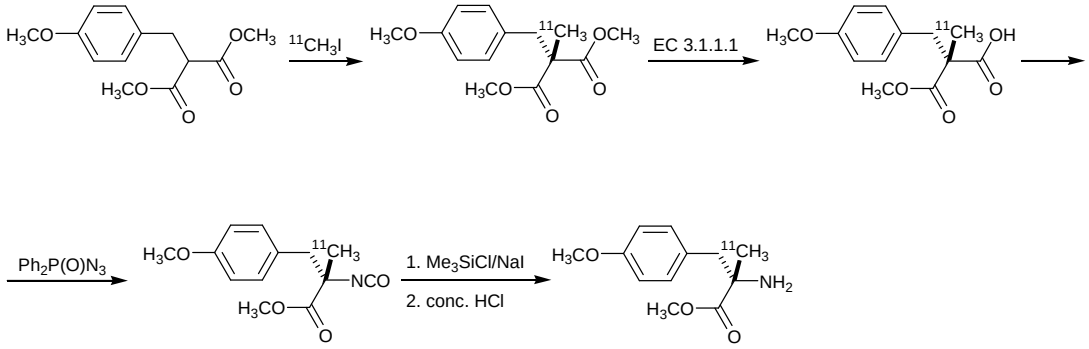
Alkylation of the Schiff base of benzophenone and *tert*-butyl ester of glycine by various ^{11}C-labelled alkyl iodides followed by hydrolysis and depletion of D-amino acids by co-

immobilised catalase (EC 1.11.1.6) and D-amino acid oxidase (EC 1.4.3.3), led to enantiomerically pure amino acids ^{11}C-labelled in the β-position of the side chain.
A similar synthesis of the labelled racemic phenylalanine starting from the ethyl ester of glycine instead of the *tert*-butyl ester led to 23-31% radiochemical yield [56]. Comparison of both $^{11}CH_3I$ [57] and $^{11}CH_3OSO_3CF_3$ [58] as alkylating agents for the Schiff base of benzophenone and *tert*-butyl ester of glycine confirmed that the second one is much more active. It should be useful to combine the catalyst with the most efficient methylation agent. Recently a catalyst for stereospecific alkylation of the Schiff base of benzophenone and *t*-butyl ester of alanine was suggested [59, 60]. The authors claimed stereospecific methylation due to 'locking' of the intermediate carbanion configuration by the lithium bridge between the imine nitrogen and the originally carboxylic oxygen [61, 62]. It has been reported [63], that similar non-catalytic [^{11}C]methylation of the Schiff base of benzophenone and methyl ester of tryptophan [62] is not reproducible. [^{14}C]Methylation of the racemic Schiff base of benzaldehyde and methyl ester of *O*-methyltyrosine carbanion followed by acidic hydrolysis and chiral HPLC of the enantiomers led to enantiomerically pure L- and D-α-[^{14}C]methyltyrosin [64]. The authors were working on generalisation of this approach for the preparation of α-[^{11}C]methylated and α-[^{3}H]methylated tyrosin, but the corresponding procedures have never been published. An auxiliary chiral catalyst was used for efficient asymmetric synthesis of [^{18}F]amino acids [65].

1.1.3.3 *Enzymatic catalysis*

Enzymes have been used in a number of syntheses of ^{13}N- and ^{11}C-labelled amio acids. Apart from the resolution of racemates by the conversion of one of the enantiomers to another compound [41, 42], enzymes can also be used as enantioselective catalysts in the formation of the radiotracer. L-Glutamic acid has been labelled with ^{11}C in both carboxylic positions using multi-enzymatic procedures [66], and L-[4-^{11}C]aspartic acid has been obtained from [^{11}C]carbon dioxide by the use of immobilised phosphoenolpyruvate carboxylase (DTP, EC 4.1.1.32) and glutamic-oxaloacetic transaminase (GOT, EC 2.6.1.1) [67]. Immobilised GOT has also been used for the conversion of chemically-produced [3-^{11}C]phenylpyruvic acid to L-[3-^{11}C]phenylalanine [68]. L-[3-^{11}C]Serine has been prepared from [^{11}C]methanol using a combination of immobilised alcoholoxidase (EC 1.1.3.13), catalase (EC 1.11.1.6) and serine-hydroxymethyl transferase (EC 2.1.2.1) [69]. ^{11}C-Labelled pyruvic acid as a precursor of aromatic amino acids has been prepared from racemic alanine using D-amino acid oxidase/catalase (EC 1.4.3.3) and glutamic-pyruvic transaminase (EC 2.6.1.2) in a one-pot system [70]. Application of carbon-carbon lyases (EC 4.1) led to production of both carboxy- and β-^{11}C-labelled aromatic amino acids including tyrosine [18, 71-75]. The only published synthesis of ^{11}C-methyl labelled α-metyltyrosine has been done using a very original combined chemical and enzymatic approach [76]. The amino acid core was built by malonic esters chemistry; dimethyl 2-(4-methoxybenzyl)malonate was methylated with [^{11}C]methyliodide. Hydrolysis of the prochiral diester using pig liver esterase (EC 3.1.1.1) led to the enantiomerically enriched monoester. After transformation of the free carboxylic group into an amino group via isocyanate and deprotection, the labelled α-methyltyrosine was obtained in 62 % *e.e.* (Scheme 1.10). The decay-corrected radiochemical yield was 12-20% in a synthesis time of 45-50 min. However, low enantiomeric excess and long synthesis does not allow the use of this approach for routine clinical production of the amino acid. Application of the same

reaction sequence for preparation of ^{11}C-methyl labelled α-methylphenylalanine gave racemic amino acid.



Scheme 1.10 Enzymatic approach to α-[^{11}C]metyltyrosine

Despite the high selectivity and versatility of enzymes and the mild reaction conditions used, there are some disadvantages to their use:

- α-methyl amino acids require application of uncommon enzymes, which are not readily available from commercial sources or are difficult to isolate;
- the enzymes are often unstable under laboratory conditions, neither application of immobilised enzymes is reliable.

1.1.3.4 *Biotechnologic approach*

A very specific and simple approach was described for production of L-[^{11}C]phenylalanine using a mutant strain of a cyanobacterium (*Synechocystis* PCC 6803). Labelled carbon dioxide was trapped by phosphate buffer solution which was introduced into the cyanobacterium culture. *Synechocystis* rapidly absorbed the carbonate and secreted uniformly labelled L-[^{11}C]phenylalanine into the culture medium. The medium was filtered, and the filtrate was purified by HPLC, giving the enantiomerically pure amino acid in up to 6% radiochemical yield [77]. This approach is a good candidate for further adaptation for biotechnologic preparation of other amino acids. However, extensive work must to be done in order to select effective strains of cyanobacterium.

1.1.3.5 *Catalytic hydrogenation*

Another approach is based on modification of labelled precursors by catalytic hydrogenation [78-81]. This approach has two disadvantages:

- necessity to prepare quickly an [^{11}C]precursor and use it in a next reaction step;
- α-methyl amino acids may not be prepared by hydrogenation of α, β-unsaturated precursors.

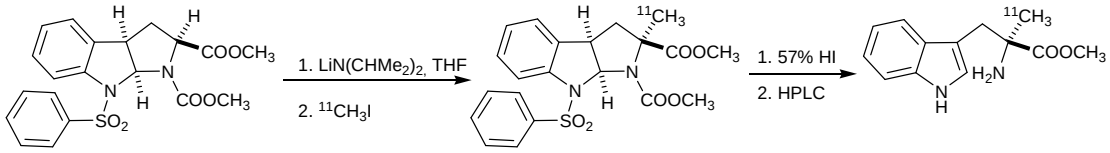
Radiochemical yields are low, up to 15%; enantiomeric excesses are moderate, up to 80%.

1.1.3.6 *Side-chain modification*

A limited number of [^{11}C]amino acids, including the widely used [^{11}C]methionine, were prepared by introduction of carbon-11 into a side-chain of an amino acid-derived precursor [43, 82]. In this case, an asymmetric centre was not created during the radiosynthesis.

1.1.3.7 *α-[^{11}C]Methyltryptophan*

Based on an original approach initially developed for industrial production of optically pure α-methyltryptophan [83, 84], a specialised asymmetric synthesis of α-[^{11}C]methyltryptophan has been developed (Scheme 1.11) [85]:



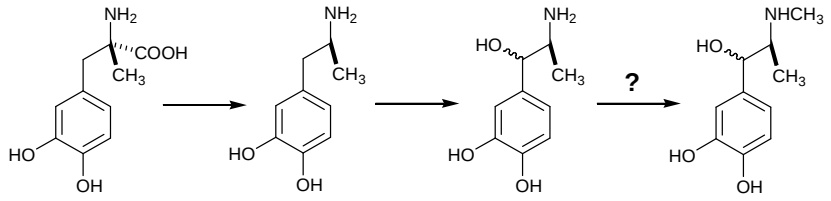
Scheme 1.11 Asymmetric synthesis of α-[^{11}C]methyltryptophan

Up to date this is the only α-[^{11}C]methyl-α-amino acid which has been prepared in enantiomerically pure form. Complicated synthetic setup and use of micromolar amount of LDA and sensitivity of the intermediate carbanion to traces of oxygen limits routine preparation of this tracer to two PET centres in the world – Montreal and Detroit.

1.1.4 *Importance for PET using new α-substituted amino acids*

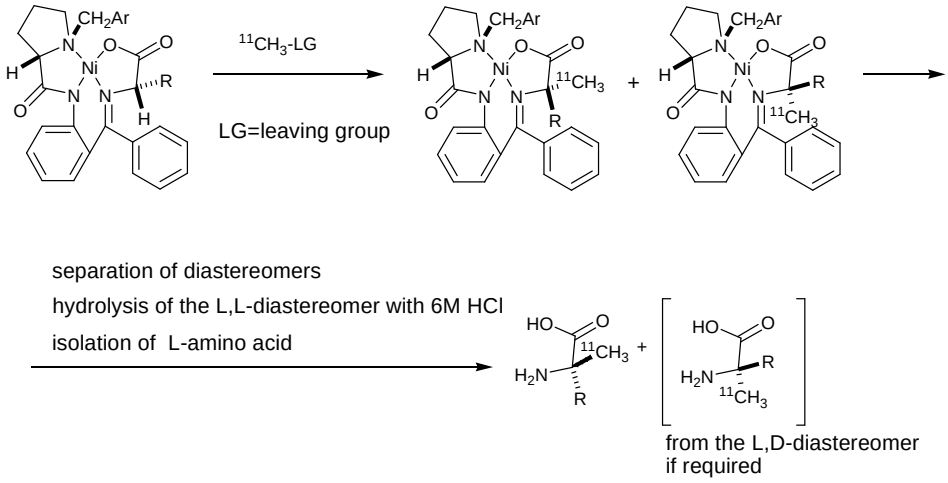
While clinical applications of α-[^{11}C]methyltryptophan are well developed due to its usefulness in diagnostics of neurological, psychiatric and oncologic diseases and availability of the labelled amino acid in two North American PET Centres, evaluation of potential application of other large aromatic ^{11}C-labelled α-methyl amino acid is limited by the lack of reliable preparative approaches to these compounds. Each large aromatic α-[^{11}C]methyl amino acid has specific (potential) advantage based on its metabolic behaviour. *In vivo*, α-[^{11}C]methyltryptophan is converted to the corresponding 5-hydroxyderivative followed by decarboxylation to α-[^{11}C]methylserotonin [86-93]. For this reason it is very useful for quantitative measurement of serotonin biosynthesis. Unlabelled α-methyltyrosine (α-MeTyr) is routinely used for pre-surgery treatment of pacients with pheochromocytomas due to its high accumulation in this tumour followed by competitive suppression of uptake of tyrosine leading to lower biosynthesis of catecholamines [94-96]. Thus α-[^{11}C]MeTyr could be useful for diagnostics of pheochromocytomas, similar to application of fluorine-18 labelled α-MeTyr [97, 98] and the SPECT radiotracer ^{123}I-IMT ((*S*)-enantiomer of α-MeTyr labelled with iodine-123 in position 3 of the aromatic ring) [99-101]. This compound is not decarboxylated *in vivo* thus being a promising radiodiagnostic drug candidate for measurement of LAT expression in tumour cell membranes [102-104]. Similarly to widely used FDOPA [105-107] and β-

[^{11}C]DOPA [108], (*S*)-3-(3,4-dimethoxyphenyl)-2-methylalanine (α-[^{11}C]MeDOPA) may be applied for diagnostics of other neuroendocrine tumours [17, 109-113] and visualisation and possibly quantification of dopamine metabolism in the brain [114, 115]. It is a substrate for enzymes involved in catecholamine biosynthesis and metabolism (Scheme 1.12).



Scheme 1.12 Metabolism of α-methylDOPA

As a non-fluorinated radioligand, α-[^{11}C]MeDOPA should be a good tool for measuring of dopamine metabolism in the brain using pharmacokinetic modelling (see Chapter 2.5). At the same time, pharmacokinetics of α-MeDOPA is not well understood in spite of worldwide use of this compound as a hypertensive drug since 1960 [116, 117]. Similar [^{18}F]fluorinated α-MeDOPA was prepared in 1995, but has never been biologically evaluated [118].
Up to date the development of synthetic approaches to non-labelled α-methyl amino acids did not result in any procedure which could be used in asymmetric α-[^{11}C]methyl amino acids preparation. Even the most efficient approaches suffer from long reaction times and application of air- and moisture-sensitive reagents [60, 119-125]. The current work describes synthetic approaches aimed to overcome these shortcomings by stereoselective alkylation of chiral nickel complexes (Scheme 1.13).



Scheme 1.13 Supposed application of chiral nickel complexes for stereoselective preparation of α-[^{11}C]methyl-α-amino acids

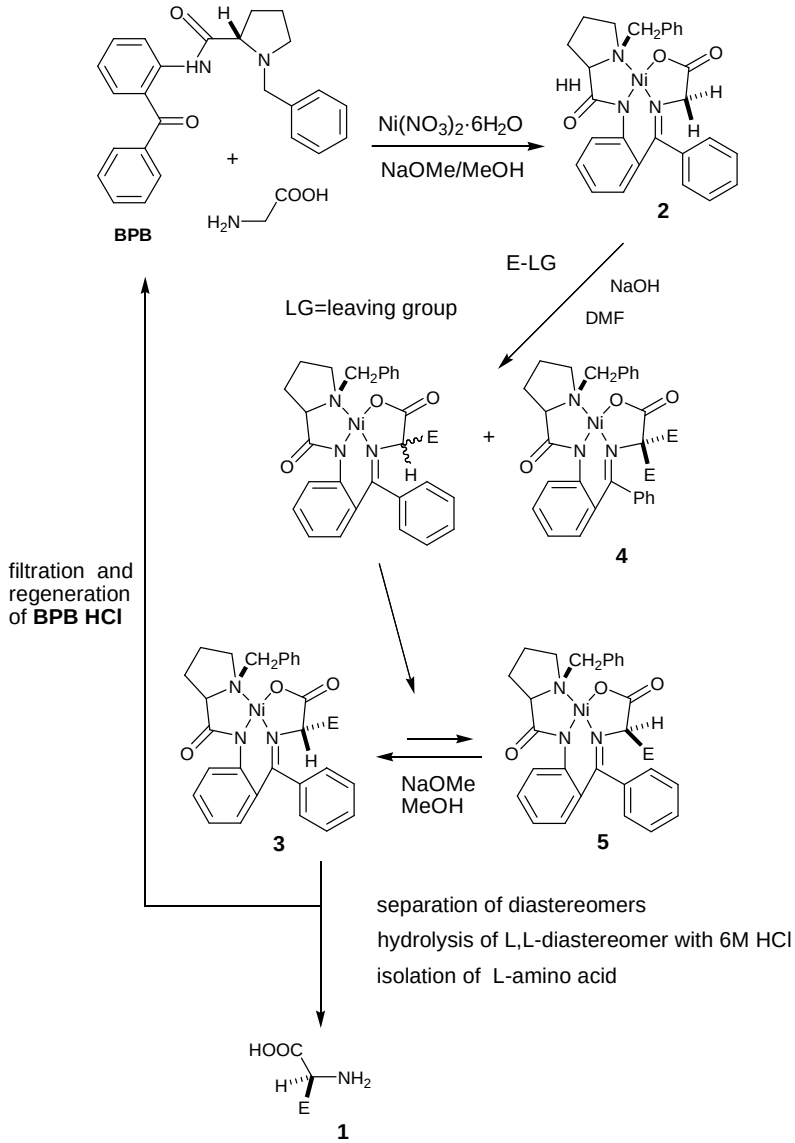
For broadening the scope of available tools for carbon-11 labelling it is important to develop new approaches for the creation of a quaternary asymmetric centre via alkylation of tertiary carbanions by $^{11}CH_3I$ or $^{11}CH_3OTf$. In the future such synthetic methods can be used for other

synthetic targets as well. This is especially important because nowadays the mainstream research in organic chemistry of carbon-11 lies in methylation of highly nucleophilic heteroatoms or development of carbonylation reactions.

1.2 *General aspects on nickel complexes and synthesis of α-amino acids*

1.2.1 *Early development of chiral nickel complexes*

Chiral α-amino acid synthons are often the optimal choice for preparation of small batches of new α-amino acids [48, 52, 55, 84, 126-132] and for special application like preparation of radiolabelled α-amino acids [27, 133].



Scheme 1.14 Overview of application of chiral nickel complexes for stereoselective preparation of α-amino acids

While efficient catalytic approaches have been suggested for a large number of α-amino acids [60, 134, 135], development of such catalytic syntheses often requires time-consuming screening for an optimal catalyst, precursor and reaction conditions. Application of nickel(II) complexes of Schiff bases of (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide (BPB) and α-amino acids for asymmetric synthesis of α-amino acids becomes a popular synthetic method (Scheme 1.14, Figure 1.3) due to cheap starting compounds, easy chromatographic detection (λ=330 nm) of starting and alkylated complexes and re-usage of BPB without loss of enantiomeric purity of its stereogenic centre after several turnovers [136, 137]. The complexes provide easy generation of an intermediate carbanion due to high acidity of α-hydrogen of an amino acid fragment ($pK_a \approx 19$) [138].

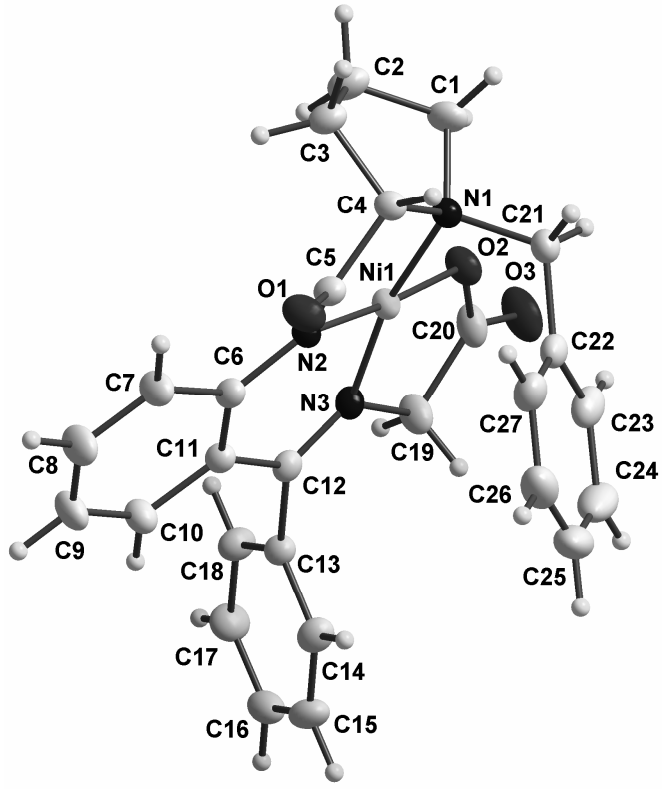


Figure 1.3 Full-color in appendix. Nickel(II) complex of the Schiff base of BPB and glycine. Numbering scheme

Two decades of worldwide research dealing with this chemistry led to a number of synthetic applications [139-164]. The core structure (nickel(II) complex of the Schiff base of BPB and glycine (GK), Figure 1.3) was suggested by a Moscow group led by Professor Belokon. Main synthetic applications were also developed by this group. They include reaction of glycine synthon with:

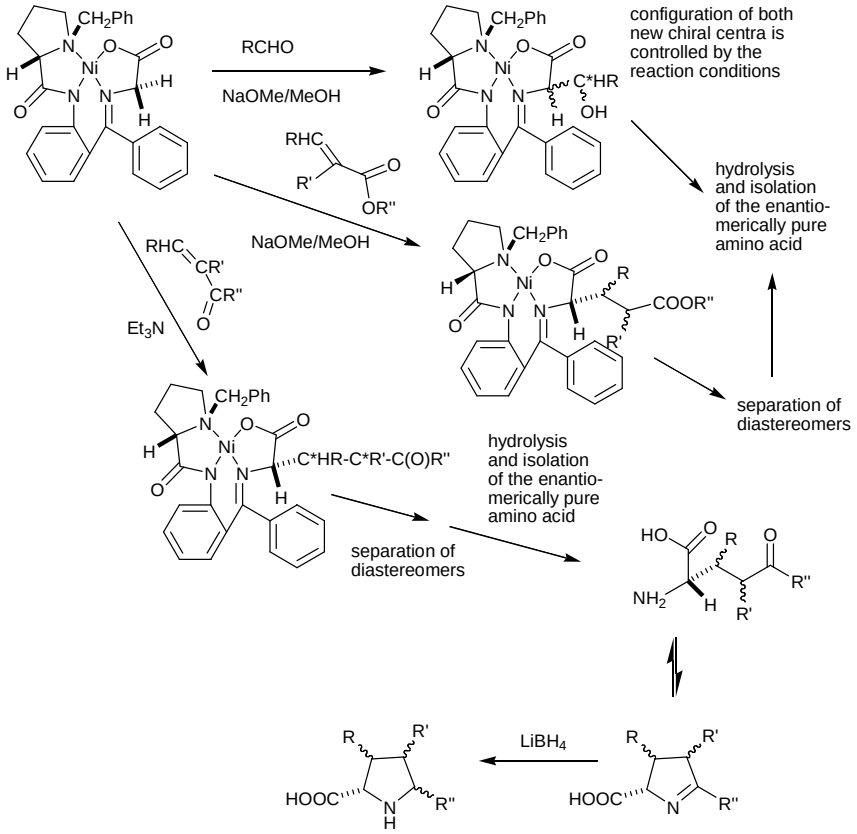
- aldehydes leading to α-amino-β-hydroxy acids [155];
- α,β-unsaturated esters leading to β- or γ-substituted glutamic acids (Scheme 1.15) [156];
- α,β-unsaturated aldehydes and ketones leading to β-, γ- or δ-substituted prolines (Scheme 1.15) [157].

Alkylation of glycine or alanine synthons with alkyl-, benzyl- or allylhalogenides leads to analogues of aromatic α-amino acids or α-amino acids with aliphatic side chains [158]. Original procedures were further developed by a group led by Professor Soloshonok. They prepared a number of fluoro-substituted analogues of phenylalanine [159] and some phosphor-containing α-amino acids [160, 161]. This group suggested a procedure for gentle control of stereochemistry of both asymmetric centres of α-amino-β-hydroxy acids [162]. Application of the second chiral auxiliary attached to α,β-unsaturated electrophile allowed them to improve significantly control of stereochemistry of β- and γ-carbons of resulting pyroglutamic acids (they did not suggest a procedure for preparation of similarly substituted glutamic acids, Scheme 1.16) [163]. A group led by Professor Danion [164] suggested an original one-pot formation of a cyclic core of a quaternary amino acid containing two stereogenic centres. This approach was further developed by the Moscow group [165].

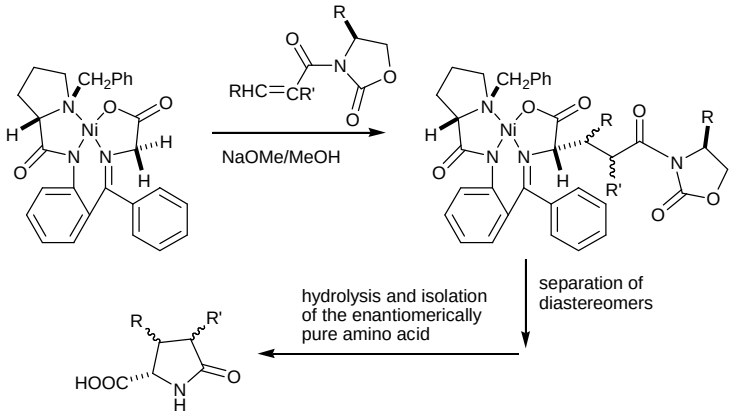
The most common application of nickel complexes as chiral amino acids synthons for preparation of analogues of aromatic α-amino acids or α-amino acids with aliphatic side chains consists of several standard steps (Scheme 1.14):

1. Template preparation of the starting complex **2** from glycine, nickel salt and re-usable chiral auxiliary BPB.
2. Alkylation of complex **2** with an electrophile in an aprotic solvent resulting in relatively low ratio of diastereomers.
3. Epimerisation of the reaction mixture in MeONa/MeOH [158].
4. Separation of diastereomers of the alkylated complex **3** and **5**, starting complex **2** and a minor amount of a product of bis-alkylation **4**.
5. Optional epimerisation of the undesired diastereomer **5** in MeONa/MeOH.
6. Selective acid hydrolysis of diastereomerically pure complex **3**, isolation of the amino acid and regeneration of BPB.

Less attention has been paid to physical-chemical investigation of the complexes. Due to former lack of analytical equipment, scientists had to use simple mechanistic ideas on the improvement of stereodiscriminative properties of the complexes; the early attempts to prepare better synthons met with a little success [166]. This is why in 1993 we started to study conformations of the complexes in solutions and in the solid state.



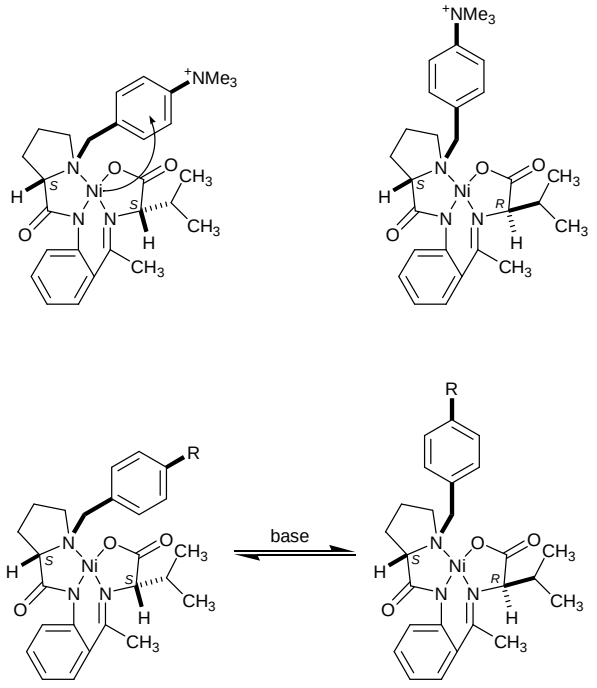
Scheme 1.15 Asymmetric syntheses of substituted glutamic acids and prolines.



Scheme 1.16 Approach to enantiomerically pure substituted pyroglutamic acids.

Ni(II) complex of BPB and glycine [136, 140, 155] was one of the first glycine synthons used for asymmetric synthesis of [^{11}C]alanine, [^{11}C]phenylalanine and [^{11}C]tyrosine [167]. An optimised one-pot procedure included alkylation of the chiral complex with [^{11}C]methyl- or [^{11}C]benzyliodide followed by epimerisation of the alkylated complex. Asymmetric induction

of 80% *d.e.* for alanine and 90% *d.e.* for the other amino acids was achieved (Scheme 1.14). Others applied the same approach for preparation of [β-^{11}C]DOPA [168, 169] and improved conditions for the complexes' epimerization in alanine synthesis (92-99% *d.e.* after epimerization) by applying KOBu-t/MeCN instead of NaOH/aceton [170].
Two attempts to further increase the asymmetric induction achieved with the complexes were published. First, authors hypothesised that introduction of an electron-acceptor substituent into the benzyl group of a similar complex would result in formation of a charge-transfer complex, thus resulting in additional stabilisation of the (*S*,*S*)-diastereomer of the complex. In the (*S*,*R*)-diastereomer steric repulsion of bulky isopropyl- and trimethylamino-groups should disable this kind of stabilisation (Scheme 1.17).
Experimental evidence did not support this hypothesis. The complex with the electron-withdrawing substituent demonstrated lower asymmetric induction, than did a similar complex with the electron-donor substituents (R=H 76% *e.e.*; R=$^{+}$NMe$_3$ 78% *e.e.*; R=NMe$_2$ 84% *e.e.*, Scheme 1.17) [171].



(*S*,*S*)-diastereomer (*S*,*R*)-diastereomer

Scheme 1.17 Supposed intramolecular interactions in a complex bearing bulky substituent in *para*-position of the benzyl group

A second hypothesis was suggested; stabilisation of the (*S*,*S*)-diastereomer of the complex might be achieved by replacement of the benzyl group by a coordinating picolyl group. Introduction of the picolyl group in many cases decreased the observed asymmetric induction [141]. The authors have also prepared and tested a polymer-bound form of the Ni(II) complex of Schiff base of BPB and (*R*,*S*)-phenylalanine. Epimerisation and hydrolysis of this immobilised complex led to the amino acid with *e.e.* 61 %. Non-immobilised complex gave

the amino acid with *e.e.* 96 %. Regeneration of the polymer-bond reagent was not practically useful due to even lower optical purity of the amino acid obtained with regenerated complex – only *e.e.* 43 %.

For successful application of chiral nickel complexes in PET radiochemistry one needs to improve the stereochemical outcome of the alkylation reactions and evaluate their applicability for preparation of carbon-11 labelled α-methyl amino acids.

For progress of methodology of PET radiochemistry it is important to develop new approaches to creation of quaternary asymmetric centre via alkylation of a chiral tertiary carbanion by $^{11}CH_3I$ or $^{11}CH_3OTf$. In the future such synthetic methods can be used for other synthetic targets, not only for α-[^{11}C]methyl-α-amino acids [172]. This is especially important because nowadays the mainstream research in organic chemistry of carbon-11 lies in methylation of heteroatom-based nucleophiles or development of carbonylation reaction.

1.3 References

1. Pieterman R. M., van Putten J. W., Meuzelaar J. J., Mooyaart E. L., Vaalburg W., Koeter G. H., Fidler V., Pruim J., Groen H. J. M. *N. Engl. J. Med.* **2000**, *343*, 254
2. Spence A. M., Muzi M., Graham M. M., O'Sullivan F., Krohn K. A., Link J. M., Lewellen T. K., Lewellen B., Freeman S. D., Berger M. S., Ojeman G. A. *J. Nucl. Med*. **1998**, *39*, 440
3. Kole A. C., Plaat B. E., Hoekstra H. J., Vaalburg W., Molenaar W. M. *J. Nucl. Med*. **1999**, *40*, 381
4. Weber W. A., Wester H. J., Grosu A. L., Herz M., Dzewas B., Feldmann H. J., Molls M., Stocklin G., Schwaiger M. *Eur. J. Nucl. Med.* **2000**, *27*, 542
5. Jager P. L., Vaalburg W., Pruim J., de Vries E. G. E., Langen K. J., Piers D. A. *J. Nucl. Med.* **2001**, *42*, 432
6. Lahorte C. M. M., Vanderheyden J. L., Steinmetz N., van de Wiele C., Dierckx R. A., Slegers G. *Eur. J. Nucl. Med.* **2004**, *31*, 887
7. Krohn K. A., Mankoff D. A., Eary J. F. *J. Clin. Pharmacol.* **2001**, S96
8. Bading J. R., Alauddin M. M., Fissekis J. D., Shahinian A. H., Joung J., Spector T., Conti P. S. *J. Nucl. Med*, **2000**, *41*, 1714
9. Been L. B., Suurmeijer A. J. H., Cobben D. C. P., Jager P. L., Hoekstra H. J., Elsinga P. H. *Eur J Nucl Med Mol Imaging*. **2004**, *31*, 1659
10. de Jong I. J., Pruim J., Elsinga P. H., Vaalburg W., Mensink H. J. A. *Eur. Urol.* **2003**, *44*, 32
11. Hara T. *J. Nucl. Med.* **2001**, *42*, 1815
12. Souvatzoglou M., Grosu A. L., Röper B., Krause B. J., Beck R., Reischl G., Picchio M., Machulla H. J., Wester H. J., Piert M. *Eur. J. Nucl. Med.* **2007**, *34*, 1566
13. Wester H. J., Schottelius M., Scheidhauer K., Meisetschlager G., Herz M., Rau F. C., Reubi J. C., Schwaiger M. *Eur. J. Nucl. Med.* **2003**, *30*, 117
14. Jonson S. D., Welch M. J. *Q. J. Nucl. Med.* **1998**, *42*, 8
15. Varagnolo L., Stokkel M. P., Mazzi U., Pauwels E. K. *Nucl. Med. Biol*. **2000**, *27*, 103
16. Madar I., Weiss L., Izbicki G. *J. Nucl. Med.* **2002**, *43*, 234
17. Koopmans K. P., de Vries E. G. E., Kema I. P., Elsinga P. H., Neels O. C., Sluiter W. J., van der Horst-Schrivers A. N. A., Jager P.L. *Lancet Oncology* **2006**, *7*, 728
18. Neels O. C., Jager P. L., Koopmans K. P., Eriks E., de Vries E. G. E., Kema I. P., Elsinga P. H. *J. Lab. Compnds. Radiopharm*. **2006**, *49*, 889
19. Lindner K.-J. PhD Thesis, Uppsala University, Acta Universitatis Upsaliensis, 1995
20. Willemsen A. T., van Waarde A., Paans A. M., Pruim J., Luurtsema G., Go K. G., Vaalburg W. *J. Nucl. Med.* **1995**, *36*, 411
21. Axelrod J., Weisbach H. *Science* **1960**, *131*, 1312
22. Roberge A., Missala K., Sourkes T. L. *Neuropharmacology* **1972**, *11*, 197
23. Sugden D. *Experentia* **1989**, *45*, 923
24. Banker G., Cotman C. W. *Arch. Biochem. Biophys.* **1971**, *142*, 565
25. Daemen B. J. G., Elsinga P. H., Paans A. M. J., Lemstra W., Konings A. W. T., Vaalburg W. *Nucl. Med. Biol.* **1991**, *18*, 503
26. Jager P. L., Groen H. J. M., van der Leest A., van Putten J. W. G., Pieterman R. M., de Vries E. G. E., Piers D. A. *J. Nucl. Med.* **2001**, *42*, 579
27. Antoni G., Kihlberg T., Långström B., in *Handbook of Radiopharmaceuticals*, ed. Welch M. J. and Redvanly C. S., Wiley, Chichester, 2003, ch. 5, pp. 151-153, 164-166

28. Cramer R. D., Kistiakowsky G. B. *J. Biol. Chem.* **1941**, *137*, 549
29. Weimer K. PhD Thesis, University of Darmstadt, 1973
30. Vaalburg W., Strating M. G., Woldring M. G., Wynberg H. *Synth. Commun.* **1972**, *2*, 423 (this article describes preparation of the non-labelled amino acid)
31. Vaalburg W., Beerling-van der Molen H. D., Reiffers S., Rijskamp A., Woldring M. G., Wynberg H. *Int. J. Appl. Radiat. Isot.* **1976**, *27*, 153
32. Vaalburg W., Beerling-van der Molen H. D., Woldring M. G. *Nuclearmedizin* **1975**, *14*, 60
33. Reiffers S., Beerling-van der Molen H. D., Vaalburg W., Ten Hoeve W., Paans A. M. J., Korf J., Woldring M. G., Wynberg H. *Int. J. Appl. Radiat. Isot.* **1977**, *28*, 955
34. G. Luurtsema, Medema J., Elsinga P. H., Visser G. M., Vaalburg W. *Appl. Radiat. Isot.* **1994**, *45*, 821
35. Bolster J. M., Vaalburg W., Paans A. M. J., van Dijk Th. H., Elsinga P. H., Zijlstra J. B., Piers D. A., Mulder N. H., Woldring M. G., Wynberg H. *Eur. J. Nucl. Med.* **1986**, 12, 321
36. Halldin C., Schoeps K.-O., Stone-Elander S., Wiezel F.-A. *Eur. J. Nucl. Med.* **1987**, *13*, 288
37. Vaalburg W., Coenen H. H., Crouzel C., Elsinga P. H., Långström B., Lemaire C., Meyer G. J. *Nucl. Med. Biol.* **1992**, *19*, 227
38. Machulla H.-J., Dutschka K. *Radiochem. Radioamal. Letters* **1976**, *25*, 309
39. Iwata R., Ido T., Takahashi T., Nakanishi H., Iida S. *Appl. Radiat. Isot.* **1987**, *38*, 97
40. Hayes R. L., Washburn L. C., Wieland B. W., Sun T. T., Anon J. B., Butler T. A., Callahan A. P. *Int. J. Appl. Radiat. Isot.* **1978**, *29*, 186.
41. Casey D. L., Digenis G. A., Wesner D. A., Washburn L. C., Chaney J. E., Hayes R. L., Callahan A. P. *Int. J. Appl. Radiat. Isotop.* **1981**, *32*, 325
42. Antoni G., Långström B. *Int. J. Appl. Radiat. Isotop.* **1987**, *38*, 655
43. Ding Y. - S., Antoni G., Fowler J. S., Wolf A. P., Långström B. *J. Labelled Compd. Radiofarm.* **1989**, *32*, 1079
44. Långström B., Stridsberg B. *Int. J. Appl. Radiat. Isot.* **1979**, *30*, 151
45. Antoni G., Långström B. *Acta Chem. Scand.* **1986**, *B40*, 152
46. Antoni G., Långström B. *Acta Chem. Scand.* **1987**, *B41*, 511.
47. Jeanjean F., Fournet G., Le Bars D., Gore J. *Eur. J. Org. Chem.* **2000**, 1297
48. Oppolzer W., Moretti R., Zhou C. *Helv. Chim. Acta* **1994**, *77*, 2363
49. Knight C. G. *Lett. Pept. Sci.* **1998**, *5*, 1
50. Lankiewicz L., Barthélémy N., Franson B., Grehn L., Ragnarsson U. *J. Chem. Soc., Perkin Trans 1* **1994**, 2503
51. Någren K. Proceedings of the XIIth International Symposium on Radiopharmaceutical Chemistry, Uppsala, Sweden, June 15 - 19, 1997 *J. Labelled Compd. Radiofarm.* **1997**, *40*, 758
52. Seebach D., Sting A. R., Hoffmann M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708
53. Plenevaux A., Al-Darwich M. J., Lemaire C., Delfiore G., Comar D. *Appl. Radiat. Isot.* **1994**, *45*, 361
54. Fasth K. J., Hörnfeldt K., Långström B. *Acta Chem. Scand.* **1995**, *49*, 301
55. Seebach D., Hoffmann M. *Eur. J. Org. Chem.* **1998**, 1137
56. Kilbourn M. R., Dischino D. D., Welch M. *Int. J. Appl. Radiat. Isot.* **1984**, *35*, 559
57. Antoni G., Långström B. *J. Labelled Compd. Radiofarm.* **1987**, *24*, 125

58. Någren K. Proceedings of XIIth International Symposium on Radiopharmaceutical Chemistry, Uppsala, Sweden, June 15 - 19, 1997 *J. Labelled Compd. Radiofarm.* **1997**, *40*, 760.
59. Ooi T., Takeuchi M., Kameda M., Maruoka K. *J. Am. Chem. Soc*. **2000**, *122*, 5228
60. For a review see: Ooi T., Maruoka K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222
61. Fitt J. J., Gswend H. W. *J. Org. Chem.* **1977**, *42*, 2639
62. Chaly T., Diksic M. *J. Nucl. Med.* **1988**, *29*, 370
63. Suehiro, M., Ravert H. T., Wilson A. A., Scheffel U., Dannals R. F., Wagner Jr. H. N. *J. Labelled Compd. Radiofarm.* **1992**, *31*, 151
64. Rajagopal S., Venkatachalam T. K., Conway T., Diksic M. *Appl. Radiat. Isot.* **1992**, *43*, 979
65. Krasikova R. N., Zaitsev S. M., Ametamey S. M., Kuznetsova O. F., Fedorova O. S., Mosevich I. K., Belokon Y. N., Vyskočil Š., Shatik S. V., Nader M., Schubiger P. A. *Nucl. Med. Biol.* **2004**, *31*, 597
66. Cohen M. B., Spolter L., Chang C. C., Behrendt D., Cook J., MacDonald N. S. *Int. J. Appl. Radiat. Isotop.* **1982**, *33*, 613
67. Barrio J. R., Egbert J. E., Henze E., Schelbert H. R., Baumgartner F. J. *J. Med. Chem.* **1982**, *25*, 93
68. Halldin C., Långström B. *J. Labelled Compd. Radiofarm.* **1986**, *23*, 715
69. Svård H., Jigerius S. B., Långström B. *Appl. Radiat. Isotop.* **1990**, *41*, 587
70. Bjurling P., Watanabe Y., Långström B. *Appl. Radiat. Isotop.* **1988**, *39*, 627
71. Bjurling P., Watanabe Y., Malmborg P., Långström B. *J. Labelled Compd. Radiofarm.* **1989**, *26*, 243
72. Bjurling P., Watanabe Y., Tokushide M., Långström B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1331
73. Bjurling P., Watanabe Y., Oka S., Nasagawa T., Yamada H., Långström B. *Acta Chem. Scand.* **1990**, *44*, 183
74. Bjurling P., Malmborg P., Långström B.: *J. Labelled Compd. Radiofarm.* **1991**, *30*, 399
75. Antoni G., Omura H., Bergström M., Sundin A., Watanabe Y., Långström B. *J. Labelled Compd. Radiofarm.* **1995**, *37*, 182
76. Gee A. D., Långström B. *J. Chem. Soc., Perkin Trans. 1* **1991**, 215
77. Labarre J., Donie P., Crouzel C. *Appl. Radiat. Isotop.* **1991**, *42*, 659
78. Halldin C., Långström B.: *Int. J. Appl. Radiat. Isotop.* **1984**, *35*, 779
79. Halldin C., Långström B.: *Int. J. Appl. Radiat. Isotop.* **1984**, *35*, 945
80. Halldin C. PhD Thesis, Uppsala University, Acta Universitatis Upsaliensis 1984
81. Nagel U., Albrecht J. *Topics in Catalysis* **1998**, *5*, 3
82. Långström B., Lundquist H. *Int. J. Appl. Radiat. Isot.* **1976**, *27*, 357
83. Crich D., Davies J. W. *J. Chem. Soc., Chem. Commun.* **1989**, 1418
84. Bourne G. T., Crich D., Davies J. W., Horwell. D. C. *J. Chem. Soc., Perkin Trans.1* **1991**, 1693
85. Plenevaux A., Lemaire C., Delfiore G., Comar D. *Appl. Radiat. Isot.* **1994**, *45*, 651
86. Lundquist P., Hartvig P., Blomqvist G., Hammarlund-Udenes M., Langstrom B. *Neuroimage* **2006**, *31*, T133
87. Sakai Y., Nishikawa M., Leyton M., Benkelfat C., Young S. N., Diksic M. *Neuroimage* **2006**, *33*, 815

88. Natsume J., Kumakura Y., Bernasconi N., Soucy J. P., Nakai A., Rosa P., Fedi M., Dubeau F., Andermann F., Lisbona R., Bernasconi A., Diksic M. *Neurology* **2003**, *60*, 756
89. Fedi M., Reutens D., Okazawa H., Andermann F., Boling W., Dubeau F., White C., Nakai A., Gross D. W., Andermann E., Diksic M. *Neurology* **2001**, *57*, 1629
90. Diksic M. *J. Psychiatry Neurosci.* **2001**, *26*, 293
91. Shoaf S. E., Carson R. E., Hommer D., Williams W. A., Higley J. D., Schmall B., Herscovitch P., Eckelman W. C., Linnoila M. *J. Cereb. Blood Flow Metab.* **2000**, *20*, 244
92. Nishizawa S., Benkelfat C., Young S. N., Leyton M., Mzengeza S., DeMontigny C., Blier P., Diksic M. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 5308
93. Diksic M. *J. Chem. Neuroanat.* **1992**, *5*, 349
94. Pacak K. *The Journal of Clinical Endocrinology & Metabolism* **2007**, *92*, 4069
95. Louthan O. *Neuroendocrine tumours. Clinical views*, Grada Publishing, Praha, 2006, pp. 311-322 (in Czech)
96. Manger W. M. *The Journal of Clinical Endocrinology & Metabolism* **2003**, *88*, 4080
97. Inoue T., Tomiyoshi K., Higuichi T., Ahmed K., Sarwar M., Aoyagi K., Amano S., Alyafei S., Zhang H.N., Endo K. *J. Nucl. Med.* **1998**, *39*, 663
98. Kaira K., Oriuchi N., Otani Y., Shimizu K., Tanaka S., Imai H., Yanagitani N., Sunaga N., Hisada T., Ishizuka T., Dobashi K., Kanai Y., Endou H., Nakajima T., Endo K., Mori M. *Clinical Cancer Research* **2007**, *13*, 6369
99. Jager P. L., Meijer WG, Kema I. P., Willemse P. H., Piers D. A., de Vries E. G. *J. Nucl. Med.* **2000**, 41, 1793
100. Shikano N., Kanai Y., Kawai K., Inatomi J., Kim D. K., Ishikawa N., Endou H. *J. Nucl. Med.* **2003**, *44*, 244
101. Lahoutte T, Caveliers V, Camargo SMR, Franca R, Ramadan T, Veljkovic E, Mertens J, Bossuyt A, Verrey F *J. Nucl. Med.* **2004**, *45*, 1591
102. Sjoerdsma A., Engelman K., Spector S., Udenfriend S. *Lancet* **1965**, *2*, 1092
103. Engelman K., Horwitz D., Jéquier E., Sjoerdsma A. *J. Clin. Iinvestigation* **1968**, *47*, 577
104. Brogden R. N., Heel R. C., Speight T. M., Avery G. S. *Drugs* **1981**, *21*, 81
105. Chirakal R., Vasdev N., Asselin M.-C., Schrobilgen G. J., Nahmias C. *J. Fluorine Chem.* **2002**, *115*, 33
106. Melega W. P., Luxen A., Perlmutter M. M., Nissenson C. H. K., Phelps M. E., Barrio J. R. *Biochemical Pharmacology*, **1990**, *39*, 1853
107. Yee R. E., Cheng D. W., Huang S.-C., Namavari M., Satyamurthy N., Barrio J. R. *Biochemical Pharmacology*, **2001**, *62*, 1409
108. Bjurling P., Watanabe Y., Tokushige M., Oda T., Långström B. *J Chem Soc Perkin Trans I* **1989**, 1331
109. For review see: Oberg K. *Lancet Oncology* **2006**, *7*, 790
110. For review see: Groves A. M., Win T., Ben Haim S., Ell P. J. *Lancet Oncology* **2007**, *8*, 822
111. For review see: Sundin A., Garske U., Orlefors H. *Best Practice & Research Clinical Endocrinology & Metabolism* **2007**, *21*, 69
112. For review see: Seibyl J. P., Chen W., Silverman D. H. S. *Sem. Nucl. Med*. **2007**, *37*, 440

113. Hartvig P., Lindner K.J., Tedroff J., Bjurling P., Hornfelt K., Långström B. *J. Neural Transmission-General Section* **1992**, *87*, 15
114. For a review see: Cumming P, Gjedde A. *Synapse* **1998**, *29*, 37
115. Ames M. M., Melmon K. L., Castagnoli N. *Biochemical Pharmacology* **1977**, *26*, 1757
116. For a review see: Myhre E., Rugstad H. E., Hansen T. *Clinical Pharmacokinetics* **1982**, *7*, 221
117. Yost Y., Conway T. *Nucl. Med. Biol.* **1996**, *23*, 857
118. For a review see: Duthaler R. O. *Tetrahedron*, **1994**, *50*, 1539
119. For a review see: Bailey P. D., Clayson J., Boa A. N. *Contemp. Org. Synth*., **1995**, *2*, 173
120. For a review see: Cativiela C., Días-de-Villegas D. *Tetrahedron: Asymmetry*, **1998**, *9*, 3517
121. For a review see: Cativiela C., Días-de-Villegas D. *Tetrahedron: Asymmetry*, **2000**, *11*, 645
122. For a review see: Ohfune Y., Shinada T. *Eur. J. Org. Chem*., **2005**, 5127
123. For a review see: Vogt H., Bräse S. *Org. Biomol. Chem*., **2007**, *7*, 406
124. For a review see: Najera C.; Sansano J. M. *Chem. Rev.*, **2007**, *107*, 4584
125. For a review see: C. Cativiela, D. Días-de-Villegas, *Tetrahedron: Asymmetry* **2007**, *18*, 569
126. Schölkopf U. *Tetrahedron* **1983**, *39*, 2085
127. Bull S. D., Davies S. G., Epstein S. W., Leech M. A., Ouzman J. V. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2321
128. Evans D. A., Bartroli H., Shih T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127
129. Evans D. A., Weber A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757
130. Hintermann T., Seebach D. *Helv. Chim. Acta* **1998**, *81*, 2093
131. Bourne G. T., Crich D., Davies J. W., Horwell. D. C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1693
132. Dastlik K. A., Sundermeier U., Johns D. M., Chen Y., Williams R. M. *Synlett* **2005**, 693
133. Krasikova R. N., Fedorova O. S., Mosevich I. K., Kuznetsova O. F., Korsakov M. V., Ametamey S. M., Schubiger P. A. *J. Label. Compds. Radiopharm.* **1999**, *42*, S102
134. Ma J. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4290;
135. Maruoka K., Takashi O. *Chem. Rev.* **2003**, *103*, 3013
136. For preparation of complex 1 see: Belokon Y. N., Tararov V. I., Maleev V. I., Saveleva T. F., Ryzhov M. G. *Tetrahedron: Asymmetry* **1998**, *9*, 4249
137. For preparation of complex 1 see: Tararov V. I., Kadyrov R., Fischer C., Börner A. *Synlett* **2004**, 1961
138. Terekhova M. I., Belokon Y. N., Maleev V. I., Chernoglazova N. I., Kochetkov K. A., Belikov V. M., Petrov E. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 905
139. For a review see: Belokon Y. N. *Izv. Acad. Nauk, Ser. Khim.* **1992**, 1106; *Bull. Russ. Acad. Sci., Div. Chem. Sci.* **1992**, *41*, 868 (Engl. Trans.); and references therein
140. For a review see: Belokon Y. N. *Pure Appl. Chem.* **1992**, *64*, 191
141. De B.B., Thomas N.R. *Tetrahedron: Asymmetry* **1997**, *8*, 2687
142. Collet S., Bauchat P., Danion - Bougot D., Danion R.: *Tetrahedron: Asymmetry* **1998**, *9*, 2121
143. Soloshonok V. A., Cai C. Z., Hruby V. J. *Tetrahedron* **1999**, *55*, 12045

144. Tang X., Soloshonok V.A., Hruby V. J. *Tetrahedron: Asymmetry* **2000**, *11*, 2917
145. Cai C., Soloshonok V. A., Hruby V. J. *J. Org. Chem.* **2001**, *66*, 1339
146. Belokon Y. N., Kochetkov K. A., Ikonnikov N. S., Strelkova T. V., Harutyunyan S. R., Saghiyan A. S. *Tetrahedron: Asymmetry* **2001**, *12*, 481
147. Larionov O. V., Saveleva T. F., Kochetkov K. A., Ikonnokov N. S., Kozhushkov S. I., Yufit D. S., Howard J. A. K., Khrustalev V. N., Belokon Y. N., de Meijere A. *Eur. J. Org. Chem.* **2003**, 869
148. Belokon Y. N., Kochetkov K. A., Borkin D. A. *Mendeleev Commun.* **2003**, 132
149. Ueki H., Ellis T. K., Martin C. H., Boettiger T. U., Bolene S. B., Soloshonok V. A. *J. Org. Chem.* **2003**, *68*, 7104
150. Saghiyan A. S., Geolchanyan A. V., Petrosyan S. G., Ghochikyan T. V., Haroutunyan V. S., Avetisyan A. A., Belokon Y. N., Fischer K. *Tetrahedron: Asymmetry* **2004**, *15*, 705
151. Gu X. Y., Ndungu J. A., Qiu W., Ying J. F., Carducci M. D., Wooden H., Hruby V. J. *Tetrahedron* **2004**, *60*, 8233
152. Vadon-Legoff S., Dijols S., Mansuy D., Boucher J.-L. *Organic Process Research & Development* **2005**, *9*, 677
153. Saghiyan A. S., Hambardzumyan H. H., Manasyan L. L., Petrosyan A. A., Maleev V. I., Peregudov A. S. *Synth. Commun*. **2005**, *35*, 449
154. Saghiyan A. S., Dadayan S. A., Petrosyan S. G., Manasyan L. L., Geolchanyan A. V., Djamgaryan S. M., Andreasyan S. A., Maleev V. I., Khrustalev V. N. *Tetrahedron: Asymmetry* **2006**, *17*, 455
155. Belokon Y. N., Bulychev A. G., Vitt S. V., Struchkov Yu. T., Batsanov A. S., Timofeeva T. V., Tsyryapkin V. A., Ryzhov M. G., Lysova L. A., Bakhmutov V. I., Belikov V. I. *J. Am. Chem. Soc.* **1985**, *107*, 4252
156. Belokon Y. N., Bulychev A. G., Ryzhov M. G., Vitt S. V., Batsanov A. S., Struchkov Y. T., Bakhmutov V. I., Belikov V. I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1865
157. Belokon Y. N., Bulychev A. G., Pavlov V. A., Fedorova E. B., Tsyryapkin V. A., Bakhmutov V. I., Belikov V. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2075
158. Belokon Y. N., Bakhmutov V. I., Chernoglazova N. I., Kochetkov K. A., Vitt S. V., Garbalinskaya N. S., Belikov V. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 305
159. Kukhar V. P., Belokon Y. N., Soloshonok V. A., Svistunova N. Y., Rozhenko A. B., Kuzmina N. A. *Synthesis* **1993**, 117
160. Soloshonok V. A, Belokon Y. N., Kuzmina N. A., Maleev V. I., Svistunova N. Y., Solodenko V. A., Kukhar V. P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1525
161. For a review see: Kukhar V. P., Soloshonok V. A, Solodenko V. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *92*, 239
162. Soloshonok V. A., Avilov D. V., Kukhar V. P., Tararov V. I., Saveleva T. F., Churkina T. D., Ikonnikov N. S., Kochetkov K. A., Orlova S. A., Pysarevsky A. P., Strutchkov Y. T., Raevsky N. I., Belokon Y. N. *Tetrahedron: Asymmetry* **1995**, *6*, 1741
163. Soloshonok V. A., Cai C., Yamada T., Ueki H., Ohfune Y., Hruby V. J. *J. Am. Chem. Soc.* **2005**, *127*, 15296
164. Debache A., Collet S., Bauchat P., Danion D., Euzenat L., Hercouet A., Carboni B. *Tetrahedron: Asymmetry* **2001**, *12*, 761

165. Belokon Y. N., Maleev V. I., Saveleva T. F., Moskalenko M. A., Pripadchev D. A., Khrustalev V. N., Vorontsov E. V., Sagiyan A. S., Babayan E. P. *Russ. Chem. Bull.* **2005**, *54*, 981
166. Belokon Y. N., Maleev V. I., Saporovskaya M. B., Backhmutov V. I., Timofeeva T. V., Batsanov A. S., Struchkov Y. T., Belikov V. M. Koord. Khim. 1988, 14, 1565
167. Fasth K. J., Långström B. *Acta Chem. Scand.* **1990**, *44*, 720
168. Mosevich I. K., Kuznetsova O. F., Fedorova O. S., Korsakov M. V. *Radiochemistry* **1996**, *38*, 511
169. Mosevich I. K., Kuznetsova O. F., Fedorova O. S., Korsakov M. V. *Radiochemistry* **1997**, *39*, 552
170. Mosevich I. K., Kuznetsova O. F., Vasilev D. A., Anichkov A. A., Korsakov M. V. *Radiochemistry* **1999**, *41*, 273
171. Maleev V. I. PhD Thesis, A. N. Nesmeyanov Institute of Organoelement Compounds, Acad. Sci. USSR, 1991
172. *Quaternary Stereocenters – Challenges and Solutions for Organic Synthesis*, eds. Christoffers J., Baro A., Wiley-VCH, Weinheim, 2005