Asymmetric Synthesis of L-[β-^{11}C]Amino Acids using a Chiral Nickel Complex of the Schiff Base of (*S*)-*o*-[(*N*-Benzylprolyl)-amino]benzophenone and Glycine

Karl Johan Fasth and Bengt Långström*

Department of Organic Chemistry, Institute of Chemistry, Uppsala University, Box 531, S-751 21, Uppsala, Sweden

Fasth, K. J. and Långström, B., 1990. Asymmetric Synthesis of L-[β-^{11}C]Amino Acids using a Chiral Nickel Complex of the Schiff Base of (*S*)-*o*-[(*N*-Benzylprolyl)-amino]benzophenone and Glycine. – Acta Chem. Scand. 44: 720–725.

Various amino acids have been specifically labelled in the β-position with the short-lived positron-emitting radionuclide ^{11}C ($t_{1/2}$ = 20.4 min) by an asymmetric alkylation reaction using various ^{11}C-labelled organic halides with a nickel(II) complex of a Schiff base derived from (*S*)-*o*-[(*N*-benzylprolyl)amino]benzophenone and glycine. The nickel(II) complex was reacted with [^{11}C]methyl, [α-^{11}C]benzyl and [α-^{11}C]-4-methoxybenzyl iodides, prepared in multistep syntheses starting from $^{11}CO_2$. [β-^{11}C]-Labelled alanine, phenylalanine, tyrosine and *O*-methyltyrosine enriched in the L-form were obtained, after acid hydrolysis, in 12–60 % radiochemical yields (decay corrected) within 30–55 min and with radiochemical purities higher than 98 %. The optical purities were 80–90 % enantiomeric excess (e.e.). Enantiomerically pure L-[β-^{11}C]alanine (> 99 % e.e.) was prepared in 40 % radiochemical yield (decay corrected), after preparative LC-separation of the diastereomeric products obtained from the ^{11}C-methylation reaction and subsequent hydrolysis of the appropriate diastereomer. In a typical synthesis 400 MBq of [β-^{11}C]phenylalanine was obtained, starting from 5.2 GBq $^{11}CO_2$, within 40 min, with 90 % e.e. and a radiochemical purity of more than 98 %.

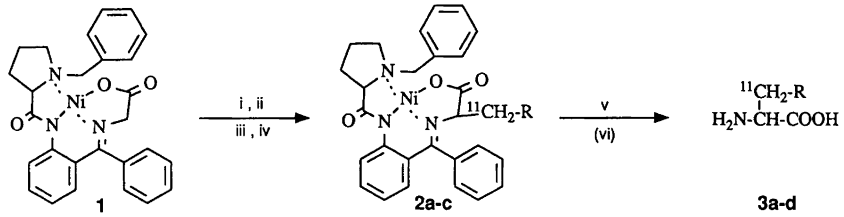
Biomolecules and pharmaceuticals labelled with short-lived positron-emitting radionuclides such as ^{11}C, ^{13}N and ^{18}F ($t_{1/2}$ = 20.4, 10.0 and 110 min, respectively) have become very useful in combination with the positron emission tomography (PET) technique.[1,2] PET is a medical imaging technique that allows non-invasive measurements of the location and concentration of such radiopharmaceuticals *in vivo*. It has been applied extensively in studies of such processes as energy metabolism and receptor binding.[1] Amino acids labelled with ^{11}C, ^{13}N, or ^{18}F, have been used in PET for studies of amino acid transport,[3,4] protein synthesis[5,6] and neurological diseases,[7] and also applied clinically for tumour diagnosis.[8–10]

[β-^{11}C]-Labelled amino acids have been synthesized by various methods in either racemic, enantiomerically enriched or pure form.[11–20] Resolution of enantiomers from a racemic mixture has the disadvantage that 50 % of the radioactivity is lost in the resolution procedure. Asymmetric syntheses of [β-^{11}C]-labelled amino acids have thus been of interest because since the preparation of either enantiomer in high radiochemical yields is made possible. The use of enzymes for [^{11}C]-labelling of amino acids have been shown to be very promising.[19,20] However, there are some disadvantages with their use in labelling synthesis. The high substrate- and stereo-selectivity can be a problem in the synthesis of exogenic amino acids. Furthermore not all enzymes used are easily or commercially available.

Since many of the chemical methods used in asymmetric synthesis of amino acids involves reaction sequences that are long or reagents that are sensitive to humidity and temperature,[14,16] simpler methods of high reproducibility and involving a minimum of technical handling are required. So far methods that work under mild and simple conditions have produced [β-^{11}C]-labelled amino acids with lower optical yields,[11,18] therefore there is still a need for methods that give high asymmetric induction and allow the simple preparation of enantiomerically pure [β-^{11}C]-amino acids.

In this paper, the asymmetric synthesis of [β-^{11}C]-labelled amino acids using ^{11}C-labelled alkyl iodides and a chiral nickel complex (**1**) of the Schiff base of (*S*)-*o*-[(*N*-benzylprolyl)amino]benzophenone (**6**) and glycine,[21,22] according to Scheme 1, is described. [^{11}C]Methyl,[23,24] [α-^{11}C]benzyl[15,18] and [α-^{11}C] 4-methoxybenzyl iodides[25] have been used in rapid alkylations of **1** in acetone using solid NaOH as the base. The resulting diastereomeric alkylation products (**2**) were hydrolysed to obtain enantiomerically enriched [β-^{11}C]-labelled amino acids (**3**). In one case the diastereomeric products (**2a**) were separated and then hydrolysed to obtain an enantiomerically pure L-[β-^{11}C]-amino acid (**3a**).

* To whom correspondence should be addressed.



Scheme 1.

Reagents: i, NaOH(s); ii, R$^{11}CH_2$I; iii, Acetone; iv, MeOH; v, HCl/H_2O; (vi, HI) R = H (a), Ph (b), C_6H_4OMe (c), C_6H_4OH (d)

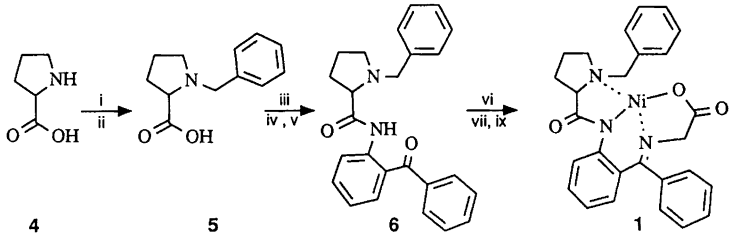
Results and discussion

The nickel(II) complex (**1**) of the Schiff base of (**6**) and glycine was synthesized from L-proline (**4**) according to the procedure described by Belokon *et al.*[21] (Scheme 2). The [^{11}C-]alkyl iodides used were prepared from $^{11}CO_2$ as previously described in detail.[15,18,23,24,25] [^{11}C]Methyl iodide was prepared , in 80 % radiochemical yield, by reduction of the $^{11}CO_2$ with lithium aluminium hydride (LAH) and treatment with hydriodic acid followed by distillation in a specially designed one-pot reactor.[24] The [α-^{11}C]benzyl iodides were obtained, in 45 % radiochemical yield, after trapping of the $^{11}CO_2$ in a Grignard reagent in tetrahydrofuran (THF), reduction with LAH and treatment with hydriodic acid, using the same one-pot reactor, followed by a liquid–liquid extraction work-up procedure[15,18,25] (Scheme 3). The alkylation reactions were carried out in a closed septum-equipped glass vessel and were complete within 5 min at 80 °C. Different substrate concentrations, solvents, sodium hydroxide concentrations and temperatures were investigated in order to optimize the reaction with respect to reaction time, chemical yield and degree of asymmetric induction. Acetone was found to be the best solvent for the reactions using the ^{11}C-labelled alkyl iodides.

Hydrolysis of the complexes (**2**) was carried out with 6 M hydrochloric acid at 130 °C for ca. 5 min. Addition of hydriodic acid and further heating at 200 °C for 5 min in a closed vessel was required for the hydrolysis of [β-^{11}C]-*O*-methyltyrosine (**3c**) to [β-^{11}C]tyrosine (**3d**). The amino acids were purified using a Sep-Pak C-18 cartridge and a Dowex 50 cation exchange column to give the amino acids in 12–60 % radiochemical yield and with higher than 98 % radiochemical purity. The cation exchange column was used to remove Ni from the solution since it is intended to be, after sterile filtration, administered to humans. Analysis of the solutions with respect to Ni content, using atomic absorption spectroscopy, AAS, showed approximately 130 ppm of nickel before and less than 0.1 ppm of nickel after using the cation exchange column. In a normal batch of about 5 ml that is approximately 0.5 μg of nickel.

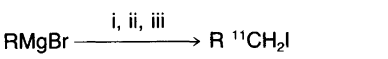
The enantiomeric excesses in the range 80–90 % were determined using *N*-(5-fluoro-2,4-dinitrophenyl)-L-alaninamide (Marfey's reagent).[18,26] With this reagent diastereomeric *N*-derivatives of the amino acids, easily separable by LC, are formed. In the case of tyrosine an additional pair of diastereomers was formed which have been shown, by NMR spectroscopy, to be the disubstituted products in which both the amine and the phenolic oxygen have reacted.[27]

Using a reversed-phase analytical HPLC system, the diastereomeric alkylation products (**2a**) obtained during the synthesis of [β-^{11}C]alanine (**3a**) were separated and the stereochemical outcome of the reaction could be monitored. The two diastereomers were collected and hydrolysed separately to give L- and D-[β-^{11}C]alanine (**3a**). The L-[β-^{11}C]alanine (**3a**) was obtained enantiomerically pure (>99 % e.e.), after preparative separation of the diastereomers (**2a**) on a C-18 column, and subsequent hydrolysis, with approximately 40 % radiochemical yield (decay corrected) within 50 min. The results are summarized in Table 1.



Scheme 2.

Reagents: i, BzCl; ii, Q^+OH^- aq.; iii, *o*-$NH_2PhCOPh$; iv, DCC; v, CH_2Cl_2; vi, $Ni(NO_3)_2$; vii, MeO^-Na^+; ix, Glycine



R = Ph, *p*-$MeOC_6H_4$

Reagents: i, $^{11}CO_2$ ii, LAH/THF; iii, HI/LiI

Scheme 3.

Table 1. Asymmetric induction, radiochemical yields and synthesis times for the syntheses of [β-^{11}C]-labelled amino acids.

[β-^{11}C]-Labelled amino acid	Asymmetric induction[a] (% e.e.)	Radiochemical yield[b] (%)	Synthesis time[c]/min
Alanine (**3a**)	80	60	30
Alanine (**3a**)	<99[d]	40	50
Phenylalanine (**3b**)	90	30	40
O-Methyltyrosine (**3c**)	90	15	45
Tyrosine (**3d**)	90	12	55

[a]LC analysis after derivatisation with *N*-(5-fluoro-2,4-dinitrophenyl)-L-alaninamide. [b]Decay corrected and based on the amount of $^{11}CO_2$ released from the molecular sieves. [c]From the start of the release of $^{11}CO_2$ to the purified product. [d]After preparative HPLC of the diastereoisomers.

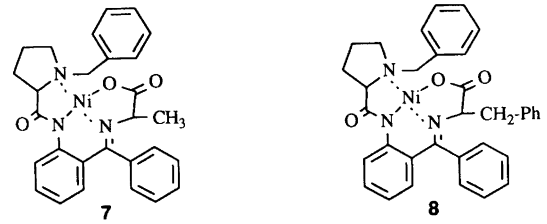
Belokon *et al.*[21,22] claimed that the formation of the diastereoisomers was thermodynamically controlled, with the L-amino acid diastereomer being the favoured one, and that epimerisation of the diastereomeric alkylation products occurred under the reaction conditions when *N,N*-dimethylformamide (DMF) or acetonitrile was used to give, after hydrolysis, amino acids of 70–98 % e.e. Under other conditions, using THF or dichloromethane as solvents, the formations were kinetically controlled to give amino acids of 41–58 % e.e. Compared with the results of Bekolon *et al.* our results show lower optical yields with DMF and acetonitrile. However, using acetone, higher asymmetric induction was obtained as shown in Table 2. Other solvents such as 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidone (DMPU) as well as mixtures of some of the above mentioned solvents were also investigated (Table 2). All reactions were carried out as is described in detail in the Experimental section.

When methanol or water was added and the heating was continued at 80 °C for a few more minutes, the optical yield increased considerably. This could be due to the fact that the increase of solvent polarity made the formation of the (*S*)-amino acid diastereomer even more favourable, leading to an epimerisation with an increased optical yield.

Table 2. Asymmetric induction and radiochemical yield using various solvents in the ^{11}C-methylation reaction of the nickel complex (**1**).

Solvents used	Asymmetric induction[a] (% d.e.)	Radiochemical yield[b] (%)
Acetone[c]	60	75
DMF[c]	35	65
Acetonitrile[c]	40	65
DMPU[c]	45	70
Acetone/acetonitrile (1/1)	40	50
Acetone/methanol (1/1)[d]	80	35
Acetone/water (1/1)[d]	80	30

[a]Determined by separation of the diastereomeric alkylation products. [b]Approximate radiochemical yield of the methylation product, decay corrected and based on the amount of $^{11}CO_2$ released from the molecular sieves. [c]After epimerisation with methanol 80 % d.e. was obtained. [d]Most of the [^{11}C]methyl iodide was hydrolysed to [^{11}C]methanol.



7 8

Scheme 4.

Exposure of a pure diastereomer containing L-[β-^{11}C]alanine to the conditions of the epimerisation [sodium hydroxide in acetone/methanol (1/1, v/v) at 80 °C] led to an equilibration to the same 90/10 ratio of diastereomers (80 % d.e.) that was obtained before the preparative purification. In the absence of methanol a 80/20 ratio of diastereomers (60 % d.e.) was obtained.

The nickel(II) complexes of the Schiff bases (**7**,**8**) of (*S*) of (*S*)-*o*-[(*N*-benzylprolyl)amino]benzophenone and alanine and of (*S*)-*o*-[(*N*-benzylprolyl)amino]benzophenone and phenylalanine were prepared in order to synthesize ^{11}C-labelled α-methyl amino acids (Scheme 4). However all attempts to alkylate these complexes with ^{11}C-labelled alkyl iodides were unsuccessful. The increased steric hindrance makes the alkylation reaction so slow that very little alkylation was observed even when a large excess of substrate was used.

To confirm that the labelling position was correct, methylation of the complex (**1**) using (^{13}C)methyl iodide was carried out. The ^{13}C NMR spectrum of the product was then compared with that of the complex (**7**). It consisted of two peaks at 21.8 and 21.0 ppm which is consistent with the methyl signals from the complex (**7**). The ^{13}C NMR spectrum of the LC-purified diastereomer containing L-(^{13}C)-alanine showed only one peak at 21.8 ppm.

The use of a nickel(II) complex (**1**) of a Schiff base derived from (**6**) and glycine has shown to be a mild, easily performed and reliable method for the asymmetric synthesis of [β-^{11}C]amino acids. This method is attractive as a general procedure for the ^{11}C-labelling of amino acids due to the high chemical and optical yields, the fast reactions and the potential to prepare optically pure [β-^{11}C]amino acids via simple chromatographic separations.

Experimental

General. The ^{11}C was prepared by the ^{14}N(p,α)^{11}C nuclear reaction using a nitrogen gas target bombarded with 10 MeV protons produced by the tandem van de Graaff accelerator at the 'The Svedberg Laboratory,' University of Uppsala. The [^{11}C]carbon dioxide formed was trapped in 4Å molecular sieves kept in a quartz vessel in a lead-

shielded oven and then transported to the chemistry laboratory.

Analytical LC was performed on a Hewlett-Packard 1090 liquid chromatograph equipped with a UV-diode-array detector in series with a β-flow detector[28] and a 250×4.6 mm C-18 (Nucleosil) 10 μ column (A) or a 250×4.6 mm LC-NH_2 (Nucleosil) 10 μ column (B). Preparative LC was carried out using a Waters M-45 pump and a 250×10 mm C-18 (Nucleosil) 10 μ column (C) in series with a Pharmacia dual path monitor UV-2 and tubing passing a GM tube connected to a rate meter. Ammonium formate (0.05 M, pH 3.50) (D), methanol (E), potassium dihydrogen phosphate (0.01 M, pH 4.6) (F) and acetonitrile/water (50:7, v/v) (G) were used as mobile phases.

The identity of the [^{11}C]alkyl iodides and the [β-^{11}C]-amino acids were confirmed by the addition of reference substances. In all cases the response from the UV detector was simultaneous with the radiodetector response, corrected for a delay (owing to the detectors being coupled in series) between the detectors.

Tetrahydrofuran (THF) was dried by distillation over sodium/benzophenone into a glass vessel containing activated 4Å molecular sives. The hydriodic acid (HI, 54 %) was distilled less than a month prior to use and stored in a freezer. A solution of lithium aluminium hydride (LAH) in THF (ca. 1 M) was prepared by addition of a pellet (0.5 g) of LAH to approximately 15 ml degassed and dried THF. NMR spectroscopy was performed on a Varian XL-300 NMR spectrometer. For the atomic absorption spectrometry (AAS) a Perkin-Elmer 2380 atomic absorption spectrometer equipped with a Ni lamp operating at 232 nm was used.

Synthesis of the nickel(II) complex (**1**) *of the Schiff base of glycine and* (**6**). (*S*)-*o*-([*N*-Benzylprolyl)amino]benzophenone (**6**), synthesized in a two-step synthesis starting with (*S*)-proline (**4**), was treated with nickel(II) nitrate and glycine to give a red complex (**1**) as described earlier by Belokon *et al.*[21] A slight modification of the purification procedures were that 'dry flash chromatography'[29] was used instead of ordinary column chromatography. The reactions were followed by TLC, and NMR spectroscopy was used to identify the products. The yield was approximately 90 %. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.5, 30.5, 57.4 (CH_2Pro), 61.1 (CH_2Gly), 63.0 (NCH_2), 69.7 (CHPro), 120.7, 124.0, 125.5, 126.1, 128.9, 129.1, 129.4, 129.5, 132.0, 132.9 (ArCH), 128.7, 131.5 (2×ArCH), 125.0, 133.2, 134.3, 142.2 (ArC), 171.3 (C=N), 177.1, 181.1 (C=O).

Synthesis of the nickel(II) complexes of the Schiff bases (**7**,**8**) *of alanine and* (**6**) *and of phenylalanine and* (**6**). For the synthesis of these complexes the procedure described by Belokon *et al.*[18] for the synthesis of the nickel(II) complex (**7**) between alanine and (**6**) was used. The reactions were followed by TLC, and NMR spectroscopy was used to identify the products. DL-Alanine and DL-phenylalanine were used and the complexes were obtained in approximately 90 % yield and with 80 % and 90 % d.e., respectively. ^{13}C NMR (75.5 MHz, $CDCl_3$); Alanine complex (**7**): δ 20.9, 21.8 (CH_3), 24.1, 30.7, 57.3 (CH_2Pro), 63.1 (NCH_2), 66.5 (CHAla), 70.3 (CHPro), 120.9, 123.9, 127.1, 127.4, 128.8, 129.7, 132.0, 133.1 (ArCH), 131.4 (2×ArCH), 128.9 (4×ArCH), 126.5, 141.7 (ArC), 133.3 (2×ArC), 171.4 (C=N), 180.5, 180.8 (C=O). Phenylalanine complex (**8**): δ 23.1, 30.6, 57.1 (CH_2Pro), 39.6 (CH_2Phe), 63.2, (NCH_2), 70.2 (CHPro), 71.4 (CHPhe), 120.5, 123.3, 127.1, 127.4, 127.8, 129.0, 129.7, 132.3, 133.5 (ArCH), 128.7, 128.8, 128.9, 130.6, 131.5 (2×ArCH), 126.1, 133.1, 134.1, 135.8, 142.8 (ArC), 171.1 (C=N), 178.5, 180.3 (C=O).

[^{11}C]Methyl iodide. [^{11}C]Methyl iodide was prepared by reduction of $^{11}CO_2$ with LAH and treatment with hydriodic acid followed by distillation in a stream of nitrogen gas, using a one-pot reactor as described in detail elsewhere,[23,24] to the reaction vessel.

[α-^{11}C]Benzyl iodides. The [α-^{11}C]benzyl iodides were obtained after trapping of the $^{11}CO_2$ in a Grignard reagent in THF, reduction with LAH and treatment with hydriodic acid followed by a liquid–liquid extraction work-up procedure using light petroleum as the organic phase as described in detail elsewhere.[15,18,25] The light petroleum was removed and the benzyl iodides were redissolved in acetone and used directly in the subsequent alkylation procedure.

Enantiomerically enriched [β-^{11}C]amino acids. The complex (**1**) (10 mg, 0.02 mmol) and pulverized sodium hydroxide (2 mg, 0.05 mmol) were dissolved in acetone (0.3 ml). To this solution were added the [^{11}C]alkyl iodides either in a stream of nitrogen gas or directly as an acetone solution. The reactions was heated at 80 °C for 5 min, methanol (0.3 ml) was added and the heating was continued for another 3 min. 6 M Hydrochloric acid (0.4 ml) was added and the solution was then heated at 130 °C for 5 min. For the hydrolysis of [β-^{11}C]*O*-methyltyrosine (**3c**) to [β-^{11}C]tyrosine (**3d**), hydriodic acid (0.6 ml, 54 %) was added and the solution was heated at 200 °C for a further 5 min in a closed vessel. The resulting solution was diluted with 4 ml of water and then passed through a Sep-Pak C-18 column and a cation-exchange resin (Bio-Rad Ag 50W-X4, 200–400 mesh, 40×9 mm). The [β-^{11}C]amino acids (**3**) were eluted from the cation-exchange column with 2 M aqueous ammonia. This solution was evaporated to dryness and the amino acids were redissolved in approximately 5 ml of saline and sterile-filtered. The alkylation reaction and hydrolysis were followed by LC [(column A, solvents D/E (35/65 v/v), flow 2 ml min^{-1}, column temp. 40 °C, wavelength 254 nm]. The identity and radiochemical purity were determined by LC using column B [solvents F/G (5/95 v/v linear gradient to 40/60 over 0–8 min), flow 2 ml min^{-1}, column temp. 40 °C, wavelength 254 nm]. The retention times were 6.2, 4.5, 4.2 and 4.9 min for the [β-^{11}C]-labelled alanine (**3a**), phenyl-

alanine (**3b**), *O*-methyltyrosine (**3c**) and tyrosine (**3d**), respectively.

L-[β-^{11}C]Alanine. The solution obtained after alkylation and epimerisation was injected into the preparative LC system [column C, solvents D/E (30/70 v/v), flow 6 ml min^{-1}, room temperature, wavelength 254 nm] and the appropriate radioactive peak (7 min) was collected. After evaporation to dryness, 2 M hydrochloric acid (2 ml) was added and the solution was heated at 130 °C for 5 min. The purification and identity and purity control was performed as described above.

Alkylation of complex **1** *with (^{13}C)methyl iodide.* The complex (**1**) (20 mg, 0.04 mmol) and pulverized sodium hydroxide (4 mg, 0.10 mmol) were dissolved in acetone (0.4 ml). (^{13}C)Methyl iodide (3 µl, 0.05 mmol) was added and after the reaction had been heated at 80 °C for 5 min, analysis by LC showed that the alkylation was complete. The reaction mixture was diluted with 25 ml of water and extracted with 3×25 ml of chloroform. The combined organic phases were washed with 25 ml of water and evaporated to dryness. The residue was dissolved in $CDCl_3$ and a ^{13}C NMR spectrum was taken. After evaporation the complex was dissolved in 2 ml of methanol and injected into the preparative LC system [column C, solvents D/E (30/70 v/v), flow 6 ml min^{-1}, room temperature, wavelength 254 nm] and the appropriate peak (7–8 min) was collected. The methanol was evaporated and the residue extracted with chloroform. The organic phase was evaporated to dryness and then redissolved in $CDCl_3$ and another ^{13}C NMR spectrum was taken.

Determination of the stereochemical purities. The diastereomeric alkylation products (**2a**) obtained during the synthesis of [β-^{11}C]-labelled alanine were separated using the above-mentioned conditions for column A. For the determination of the enantiomeric purity, the [β-^{11}C]-labelled amino acids (**3**) were converted into diastereomeric derivatives by reaction with *N*-(5-fluoro-2,4-dinitrophenyl)-L-alaninamide (Marfey's reagent) as described in detail elsewhere.[18,26] The derivatives were separated by LC [column A, solvents D/E (70/30 v/v linear gradient to 50/50 over 0–10 min for alanine and 60/40 to 35/65 over 0–15 min for phenylalanine, *O*-methyltyrosine and tyrosine), flow 2 ml min^{-1}, column temp. 40 °C, wavelength 340 nm]. The retention times were 6.0 and 9.0 min for the diastereomers of L- and D-[β-^{11}C]alanine, 8.2 and 12.2 min for phenylalanine, 7.2 and 10.9 min for O-methyltyrosine and 4.4 and 6.3 min for tyrosine. The retention times for the disubstituted derivatives of tyrosine were 12.5 and 17.2 min.

Determination of the nickel content in the solutions of the [β-^{11}C]amino acids. Two standard solutions were prepared with nickel contents of 1 µg ml^{-1} and 0.1 µg ml^{-1}. These samples together with the [β-^{11}C]amino acid solutions were analysed by atomic absorption spectroscopy.

Acknowledgements. We are indebted to Fil. lic. Petter Malmborg for radionuclide production. This work was supported financially by the Swedish Natural Science Research Council. We would also like to thank Ms. Christina Ericzon for assistance with the AAS analysis.

References

1. Greitz, T., Ingvar, D. H. and Widén, L. *The Metabolism of the Human Brain Studied with Positron Emission Tomography,* Raven Press, New York 1985.
2. Phelps, M., Mazziotta, I. and Schelbert, H. *Positron Emission Tomography and Autoradiography: Principles and Applications for the Brain and Heart,* Raven Press, New York 1986.
3. Lundqvist, H., Pråhl, M., Stålnacke, C.-G., Malmborg, P., Långström, B., Antoni, G., Svärd, H., Fasth, K. J., Lilja, A. and Bergström, M. *Ann. Univ. Turku. Ser. D 27* (1988) 279.
4. Berglund, L., Andersson, J., Lilja, A., Lindberg, B., Gebre-Medhin, M., Antoni, G., Bjurling, P., Långström, B. and Lundqvist, H. *Am. J. Obstet. Gynecol.* (1989). *Submitted.*
5. Ref. 1, pp. 215–249.
6. Coenen, H. H., Kling, P. and Stöcklin, G. *J. Nucl. Med. 30* (1989) 1367.
7. Nahmias, C., Garnett, E. S., Firnau, G. and Lang, A. *J. Neurol. Neurosurg. Psychiatry 69* (1986) 223.
8. Lilja, A., Bergström, K., Hartvig, P., Spännare, B., Halldin, C., Lundqvist, H. and Långström, B. *Am. J. Neuroradiol. 6* (1985) 505.
9. Bergström, M., Muhr, C., Lundberg, P. O., Bergström, K., Gee, A., Fasth, K. J. and Långström, B. *J. Comput. Assist. Tomogr. 11* (1987) 815.
10. Bergström, M., Muhr, C., Lundberg, P. O., Bergström, K., Lundqvist, H., Antoni, G., Fasth, K. J. and Långström, B. *J. Comput. Assist. Tomogr. 11* (1987) 348.
11. Långström, B., Stridsberg, B. and Bergson, G. *Chem. Scr. 13* (1979) 49.
12. Kilbourn, M., Dischino, D. and Welch, M. *Int. J. Appl. Radiat. Isot. 35* (1984) 603.
13. Halldin, C. and Långström, B. *Int. J. Appl. Radiat. Isot. 35* (1984) 779.
14. Halldin, C. and Långström, B. *Int. J. Appl. Radiat. Isot. 35* (1984) 945.
15. Antoni, G. and Långström, B. *J. Labelled Compd. Radiopharm. 24* (1987) 125.
16. Antoni, G. and Långström, B. *Acta Chem. Scand., Ser. B 41* (1987) 511.
17. Antoni, G. and Långström, B. *Int. J. Appl. Radiat. Isot. 38* (1987) 655.
18. Fasth, K. J., Antoni, G. and Långström, B. *J. Chem. Soc., Perkin Trans. 1* (1988) 3081.
19. Bjurling, P., Watanabe, Y., Tokushige, M., Oda, T. and Långström, B. *J. Chem. Soc. Perkin Trans. 1* (1989) 1331.
20. Bjurling, P., Watanabe, Y., Oka, S., Nagasawa, T., Yamada, H. and Långström, B. *Acta Chem. Scand. 44* (1990). *In press.*
21. Belokon, Y., Bulychev, A., Vitt, S., Struchkov, Y., Batsanov, A., Timofeeva, T., Tsyryapkin, V., Ryzhov, M., Lysova, L., Bakhmutov, V. and Belikov, V. *J. Am. Chem. Soc. 107* (1985) 4252.
22. Belokon, Y., Bakhmutov, V., Chernoglazova, N., Kochetkov, K., Vitt, S., Garbalinskaya, N. and Belikov, V. *J. Chem. Soc., Perkin Trans. 1* (1988) 305.
23. Crouzel, C., Coenen, H., Pike, V. and Långström, B. *Int. J. Appl. Radiat. Isot. 38* (1987) 601.
24. Långström, B., Antoni, G., Gullberg, P., Halldin, C., Malmborg, P., Någren, K., Rimland, A. and Svärd, H. *J. Nucl. Med. 28* (1987) 1037.

25. Fasth, K. J., Antoni, G. and Långström, B. *Appl. Radiat. Isot. A* (1989). *In press.*
26. Marfey, P. *Carlsberg Res. Commun. 49* (1984) 591.
27. Bjurling, P., Gogoll, A. and Långström, B. *Unpublished results.*
28. Långström, B. and Lundqvist, H. *Radiochem. Radioanal. Lett. 41* (1979) 375.
29. Harwood, L. *Aldrichim. Acta 18* (1985) No. 1.

Received December 27, 1989.