JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2002; **45**: 423–434.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.569

Research Article

Synthesis of 3-[(2S)-azetidin-2-ylmethoxy]-5-[^{11}C]-methylpyridine, an analogue of A-85380, via a Stille coupling

Farhad Karimi[1] and Bengt Långström[1,2]*
[1] *Institute of Chemistry, Department of Organic Chemistry, Box 531, S-751 21 Uppsala, Sweden*
[2] *Uppsala University PET Centre, Uppsala University, S-751 85 Uppsala, Sweden*

Summary

3-[(2S)-azetidin-2-ylmethoxy]-5-[^{11}C]-methylpyridine **(5d)**, which might be a novel ligand for nicotinic receptors, was synthesized via coupling [^{11}C]iodomethane with *tert*-butyl (2S)-2-({[5-(trimethylstannyl)pyridin-3-yl]oxy}methyl) azetidine-1-carboxylate **(4)** at 80°C for 5 min with tri-*o*-tolylphosphine-bound, unsaturated palladium(0), followed by deprotection using trifluoroacetic acid (TFA). The previous problem (solid-phase extraction before injection on semi-preparative LC) with automation of Stille coupling reactions has been overcome. In a typical experiment, 0.46 GBq of **5d** was obtained from 5.2 GBq of [^{11}C]iodomethane. The decay-corrected radiochemical yield was 39% (based on the quantity [^{11}C]iodomethane trapped). The synthesis time was 43 min from end of radionuclide production. During a production condition using 36 μAh of proton beam irradiation, a specific radioactivity of 50 GBq/μmol of the final product was obtained in biological buffer.

Key Words: [^{11}C]iodomethane; stille coupling; methylation; nicotinic receptor ligand

*Correspondence to: B. Långström, Uppsala University PET Centre, Uppsala University, S-751 85 Uppsala, Sweden.

Received 24 August 2001
Revised 21 September 2001
Accepted 17 December 2001

Introduction

Positron emission tomography (PET) is a powerful tool for clinical diagnosis and research[1–3] and in drug development.[4] Amongst these applications there is a great interest in developing PET tracers for imaging central nicotinic acetylcholine receptors (nAChRs) due to their importance in several neurodegenerative diseases.[5,6]

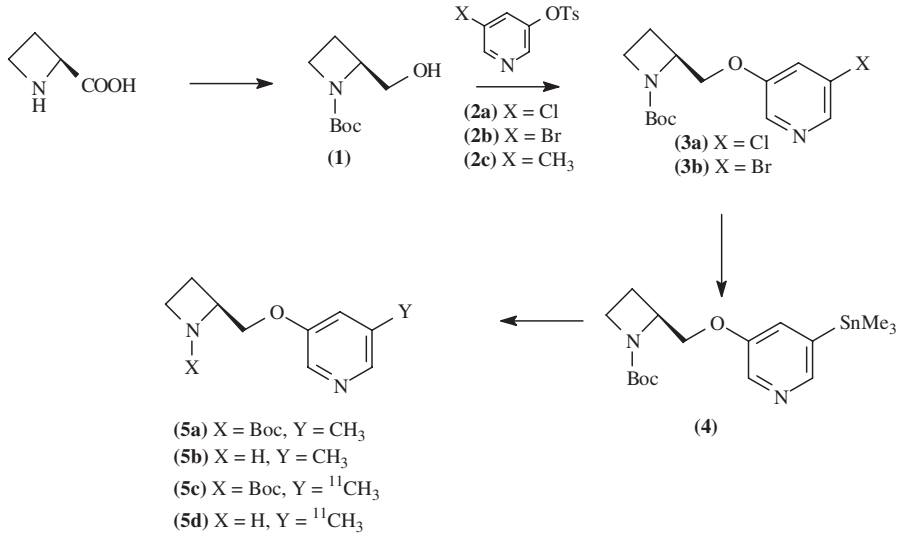
[^{11}C](−)-Nicotine has been used for PET imaging of human nAChRs, but this radiotracer suffers from high non-specific binding, low-affinity and blood-flow dependence.[7,8] Therefore, there has been a continuous search for suitable radioligands with high affinity and selectively.[9–12]

In some of the previously reported work, analogues based on A-85380 (3-(azetidin-2-ylmethoxy)pyridine) as the lead compound were investigated.[9,12,13] A ^{76}Br-labelled analogue, [^{76}Br]BAP (3-(azetidin-2-ylmethoxy)-5-[^{76}Br]-bromopyridine),[13] was also prepared in our lab. However, there are drawbacks with the long half-life of ^{76}Br, for example, when repeated studies are required and the high radiation dosimetry for ^{76}Br. We therefore extended our studies to look at the compound ^{11}C- methylated in the 5-position using the Stille reaction. [^{11}C]-labelled MAP (3-[(2S)-azetidin-2-ylmethoxy]-5-[^{11}C]-methylpyridine) is thus an interesting analogue for further investigation for positron emission tomography studies of nicotinic receptors. The *in vitro* properties of this compound have been reported previously in literature ([^{3}H]cytisine $K_i = 0.047 \pm 0.002$ nM).[14]

Results and discussion

(S)-2-Azetidinecarboxylic acid was reduced and protected with Boc-group in one pot, according to Scheme 1. The crude product was analysed by GC–MS to determine the purity of compound **1** and no trace of impurity was observed. Diborane rapidly reacted with carboxylic acid to form a triacyloxyborane intermediate as a result of protonolysis of the B–H bonds in borane complex.[15] We assumed that the configuration of the final product was the same as (S)-2-azetidinecarboxylic acid, since the stereocentre is not involved in any other step. The compound **1** was synthesized previously in two steps (3 days reaction times).[16]

The compound *tert*-butyl (2S)-2-{[(5-chloropyridin-3-yl)oxy]methyl}-azetidine-1-carboxylate **(3a)** was synthesized by two different methods.



Scheme 1.

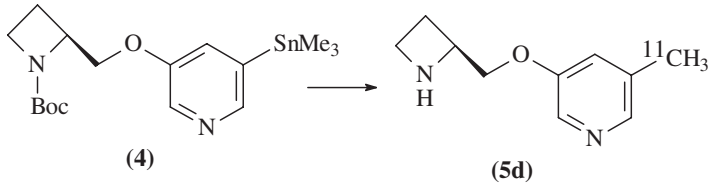
In method A, a reaction between the tosylated pyridine derivative **2a** and Boc-protected azetidinemethanol **(1)** in the presence of anhydrous potassium hydroxide was performed in anhydrous DMF (*N*, *N*-dimethylformamide) at $80 \pm 5^{\circ}$C. This method can be applied if the higher yield is of interest. Method B was based on the transfer catalysis concept using tetra-butylammonium bisulphate ($QHSO_4$).[17] This approach can be used in large-scale synthesis since the starting material (3,5-dichloropyridine) is commercially available. In an attempt using a catalytic amount of $QHSO_4$, only 13% of the desired compound was obtained. When the amount of the $QHSO_4$ was increased to one equivalent compared to the azetidinemethanol **(1)**, the yield increased to 48%. *tert*-Butyl (2S)-2-{[(5-bromopyridin-3-yl)oxy]methyl}azetidine-1-carboxylate (**3b**) and *tert*-butyl (2S)-2-{[(5-methylpyridin-3-yl)oxy]-methyl}azetidine-1-carboxylate **(5a)** were prepared as described in method 'A' using **2b** or **2c**. Method 'B' failed in the synthesis of **3b**. Compounds **3a** and **3b** have been synthesized before using Mitsunobu condition (3 days reactions time).[18]

5-Bromo-3-hydroxypyridine was synthesized according to the literature,[19] followed by tosylation to give **2b**. 5-Methylpyridin-3-yl 4-methylbenzenesulfonate **(2c)** was prepared from **2b** using tetramethyltin and a catalytic amount of tetrakis(triphenylphosphine)palladium(0). An effort to synthesise **2c** from 3-picoline 1-oxide and *p*-toluenesulphfonyl chloride according to literature[20] gave a very poor yield.

The stannyl compound **4** was obtained by reaction between trimethylstannyl lithium and the corresponding halide, **3a**. The trimethylstannyl salt was prepared from stannous chloride (1 equivalent) and methyllithium (3 equivalents). Since the concentration of methyllithium is an important parameter, using the other described method might be of interest.[18] Compound **4** was also prepared from hexamethylditin and the corresponding halide **3b** in the presence of catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Rapid coupling of iodomethane with organostannyl compounds for incorporation of short-lived radionuclides has been reported previously in literature.[21–23] The reaction between tris(dibenzylideneacetone)palladium(0) ($Pd_2(dba)_3$) and tri-*o*-tolylphosphine ((*o*-tol)3P) will generate activated Pd(0) species [(*o*-tol)$_3$P-Pd-P((*o*-tol)$_3$].[21] The bulkiness (cone angle = 194°) of tri-*o*-tolylphosphine is assumed to contribute to the activity of the Pd(0) species formed.[24] According to previous experience we supposed that an excess of ligand [(*o*-tol)3P] might stabilise the activated Pd(0) complex. This species can then undergo oxidative addition to form Pd(II) complex followed by transmetallation, which is the rate limiting step in Stille reactions.[25,26] Due to the stepwise labelling procedure we assumed that scrambling (i.e. interaction of other methyl moieties) was negligible.

A polar aprotic solvent such as DMSO was used for a efficient trapping of [^{11}C]iodomethane. The [^{11}C]iodomethane produced was transferred directly to the reaction vessel using nitrogen gas as a carrier (20 ml /min), and trapped in a solution of $Pd_2(dba)_3$ and (*o*-tol)$_3$P in DMSO (Scheme 2).



(a) CuCl, Pd2dba3, ^{11}CH3I, (O-tol)3P), DMSO
(b) TFA

Scheme 2.

The stannyl compound **4** and copper(I) chloride were then transferred to the reaction vessel. The resulting mixture was heated at 80°C for

5 min, followed by deprotection. The specific radioactivity of compound **5d** (using free base **5b**) was on order of 5.19 ± 0.56 GBq/μmol using 2.0 ± 0.41 μAh proton bombardment (number of runs = 4). The determined specific radioactivity (based on a single experiment) using higher beam (36 μAh) was in the range of 50 GBq/μmol. The low specific radioactivity in the former case was due to the low specific radioactivity of [^{11}C]iodomethane produced. The decay corrected radiochemical yield was 39% calculated from the amount of [^{11}C] iodomethane and the radiochemical purity determined by analytical LC was > 97%. The total synthesis time (including formulation in biological buffer) was less than 50 min from the end of radionuclide production. The identity of **5d** was determined by analytical LC, after addition of authentic reference compound, and by LC–MS analysis.

According to the previous report[22] solid-phase extraction (SPE) was necessary before injection on a semi-preparative LC. The reported synthetic method for the Stille coupling is more easily automated than previous described method.[22]

Experimental

General

[^{11}C]Carbon dioxide was produced at the Uppsala University PET Centre via the ^{14}N(p,α)^{11}C reaction in a gas target containing nitrogen (AGA, Nitrogen 6.0) and 0.1% oxygen (AGA. Oxygen 4.8), bombarded with 17 MeV protons produced from the Scanditronix MC-17 cyclotron. [^{11}C]Carbon dioxide was converted in two steps into [^{11}C]iodomethane via reduction with lithium aluminium hydride followed by treatment with hydroiodic acid.[27] Liquid chromatographic analysis (LC) was performed with a Beckman 126 gradient pump and a Beckman 166 variable wavelength UV-detector (Fullerton, CA, USA) in series with a β^+-flow detector.[28] The following mobile phases were used: acetonitrile/water (50:7) (A), 0.01 M trifluoroacetic acid (B). For analytical LC, a Jones chromatography genesis C_{18}, 4 μm, 250 mm × 4.6 mm ID column was used at a flow of 1.5 ml/min. For semi-preparative LC, a Jones chromatography genesis C_{18}, 4 μm, 250 mm × 10 mm (i.d.), was used at a flow of 5 ml/min. Synthia, an automated synthesis system,[29] was used for LC injection and fraction collection. Data collection and LC control were performed with the use of a Beckman system gold chromatography software package (USA). Radioactivity was measured in an ion chamber

(Veenstra Instrumenten bv, VDC-202, Holland). For coarse estimations of radioactivity during synthesis a portable dose-rate metre was used (Långenäs eltekniska AB, Sweden).

In the analysis of the ^{11}C-labelled compound, reference substance was used for comparison in all the LC runs. Identities of synthesized materials were determined using both ^{1}H NMR, ^{13}C NMR, LC–MS and GC–MS. NMR spectra were recorded on a Varian XL 300 (300 MHz) with tetramethylsilane, chloroform-d_1 or acetone-d_6 as internal standards. LC–MS was performed using a Micromass VG Quattro with electrospray ionisation. A Beckman 126 pump, a CMA 240 autosampler and a Beckman Ultrasphere ODS C_{18} column (5 µm, 100 mm × 4.6 mm i.d.) were used. Mass spectra were recorded on Finnigan GCQ mass spectrometer coupled to Finnigan Q-GC using electron impact. THF (tetrahydrofuran) was distilled under nitrogen from sodium/benzophenone. Pyridine was purified by distillation over calcium hydride. All chemicals were purchased from Aldrich (Sweden).

tert-*Butyl (2S)-2-(hydroxymethyl)azetidine-1-carboxylate (1)*

To an ice-cooled solution of (S)-2-azetidinecarboxylic acid (1.00 g, 9.9 mmol) in anhydrous THF (12 ml), borane/THF complex (1 M, 25 ml, 2.5 equiv.) was added at 0°C under argon. The mixture was refluxed for 75 min then was cooled and quenched by addition of aqueous solution of potassium hydrogen sulphate (10%, 10 ml) and refluxed for additional 15 min. The volatiles were removed under reduced pressure. To the cooled reaction mixture $NaOH_{(aq)}$ (1 M, 20 ml), 1,4-dioxane (15 ml), water (20 ml) and di-*tert*-butyl dicarbonate (2.38 g, 10.8 mmol) were added. The mixture was stirred in an ice-bath for 30 min then at room temperature for additional 3 h. The reaction mixture was then poured into ice-cooled saturated solution of sodium bicarbonate at 0°C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 ml × 100 ml), dried ($MgSO_4$) and concentrated *in vacuo*, yielding pure **1** (1.83 g, 99%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 4.44 (1H, m), 3.81 (4H, m), 2.17 (1H, m), 1.93 (1H, m), 1.46 (9H, s). ^{13}C NMR ($CDCl_3$): δ 157.1, 80.3, 66.6, 63.6, 46.6, 28.3, 17.9. MS: $m/z = 188$, 156.

5-chloropyridin-3-yl 4-methylbenzenesulfonate (2a)

Under an argon atmosphere, *p*-toluenesulphfonyl chloride (1.94 g, 10.16 mmol) was added to a solution of 5-chloro-3-hydroxypyridine

(1.01 g, 7.79 mmol) in anhydrous pyridine (20 ml) at room temperature. The resulting mixture was refluxed for 5 h. The volatiles parts were removed *in vacuo* and the residue was partitioned between saturated sodium bicarbonate and dichloromethane. The aqueous layer was extracted with dichloromethane (3 ml × 70 ml) and washed with water (2 ml × 50 ml). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified on flash silica gel column chromatography. Elution with ethyl acetate/pentane (20:80) yielded (2.16 g, 98%) colourless oil that solidified. ^{1}H NMR ($CDCl_3$): δ 8.47 (1H, d), 8.03 (1H, d), 7.72 (2H, d), 7.51 (1H, dd), 7.35 (2H, d), 2.45 (3H, s). ^{13}C NMR ($CDCl_3$): δ 147.3, 141.7, 130.3, 130.2, 128.5, 21.8. MS: $m/z = 283$, 155.

5-bromopyridin-3-yl 4-methylbenzenesulphfonate (2b)

The synthesis was performed as described for **2a** except that 5-bromo-3-hydroxypyridine was used. The reaction mixture was refluxed for 16 h. The purified compound **2b** was obtained (75%) as a colourless solid. ^{1}H NMR ($CDCl_3$): δ 8.55 (1H, d), 8.05 (1H, d), 7.70 (3H, m), 7.35 (2H, d), 2.45 (3H, s). ^{13}C NMR ($CDCl_3$): δ 149.4, 142.0, 133.1, 130.1, 128.5, 21.8. MS: $m/z = 327$, 155.

5-methylpyridin-3-yl 4-methylbenzenesulphfonate (2c)

To a DMF solution (3 ml) of **2b** (300 mg, 914.2 μmol) was added tetramethyltin (196.2 mg, 1.10 mmol) and tetrakis(triphenylphosphine)-palladium(0) (15 mg, 13.0 μmol). The reaction mixture was heated for 17 h at 100°C. The reaction mixture was then poured into brine (100 ml) and extracted with dichloromethane (3 ml × 50 ml). Rotary evaporation followed by silica gel chromatography using ethyl acetate gave (239 mg, 99%) of **2c** as a colourless solid. ^{1}H NMR ($CDCl_3$): δ 8.32 (1H, br), 7.90 (1H, br), 7.68 (2H, dd), 7.31 (3H, dd), 2.45 (3H, s), 2.35 (3H, s). ^{13}C NMR ($CDCl_3$): δ 148.7, 145.9, 140.7, 129.9, 128.4, 21.7, 18.1. MS: $m/z = 263$, 155. LC–MS (ESI^+), solvent (A–B), m/z 263 $[M+H]^+$.

tert-*Butyl (2S)-2-{[(5-chloropyridin-3-yl)oxy]methyl}azetidine-1-carboxylate (3a)*

Method A: A solution of Boc-protected azetidinemethanol **1** (91 mg, 486 μmol), anhydrous potassium hydroxide (58 mg, 1.03 mmol) in

anhydrous DMF (6 ml) was heated at 80°C for 10 min under argon. To this **2a** (157.8 mg, 556 μmol) dissolved in anhydrous DMF (6 ml) was added and the mixture was stirred for 24 h at 80°C. The reaction mixture was diluted with water and extracted with ethyl acetate (3 ml × 50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting crude product was purified by flash chromatography. Elution with ethyl acetate/pentane (1:1) gave (100 mg, 69%) of the title compound. ^{1}H NMR ($CDCl_3$): δ 8.25 (1H, d), 8.20 (1H, d), 7.28 (1H, dd), 4.52 (1H, m), 4.34 (1H, m), 4.13 (1H, m), 3.89 (2H, m), 2.32 (2H, m), 1.43 (9H, s). ^{13}C NMR ($CDCl_3$): δ 140.9, 136.2, 121.4, 79.9, 68.9, 59.9, 28.4, 18.9. MS: $m/z = 298$, 225.

Method B: A solution of Boc-protected azetidinemethanol **1** (100 mg, 534 μmol), 3,5-dichloropyridine (176 mg, 1.19 mmol) and tetra-butylammonium bisulphate (181 mg, 534 μmol) in 50% aqueous sodium hydroxide (6 ml) and THF (6 ml) was heated at 80 ± 5°C for 11 h. The volatile fraction was removed under reduced pressure. The residue was diluted by water (30 ml) and extracted with ethyl acetate (3 ml × 70 ml). The pooled organic phases were washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by flash chromatography. Elution with ethyl acetate/pentane (1:1) yielded (78 mg, 49%) of the desired pyridine derivative.

tert-*Butyl (2S)-2-{[(5-bromopyridin-3-yl)oxy]methyl}azetidine-1-carboxylate (3b)*

The synthesis was performed as described for **3a** (method A) except that **2b** was used instead of **2a**. The title compound was obtained (73%) as colourless oil. ^{1}H NMR ($CDCl_3$): δ 8.28 (2H, m), 7.42 (1H, dd), 4.51 (1H, m), 4.33 (1H, m), 4.13 (1H, m), 3.89 (2H, m), 2.32 (2H, m), 1.43 (9H, s). ^{13}C NMR ($CDCl_3$): δ 156.1, 143.1, 136.6, 124.1, 79.8, 69.4, 59.9, 28.4, 18.9. MS: $m/z = 343$, 270.

tert-*Butyl (2S)-2-({[5-(trimethylstannyl)pyridin-3-yl]oxy}methyl) azetidine-1-carboxylate (4)*

Method A: A diluted solution of methyllithium (1.4 M in ether, 21.1 ml, 3 eqv., in ether 50 ml) was added dropwise to a stirred suspension of anhydrous stannous chloride (1.87 g, 9.88 mmol) in 20 ml of ether at

−10°C. The reaction mixture was transferred by cannula to a solution of **3a** (0.59 g, 1.98 mmol) in anhydrous DME (ethylene glycol dimethyl ether) (10 ml) and stirred at room temperature for 3 h. The solvent was removed in vacuo and the residue extracted with ether (4 ml × 10 ml). The ether was evaporated and the crude material was purified by flash chromatography (pentane- ethyl acetate, 1:1) to give **4** (0.41 g, 49%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 8.23 (2H, m), 7.33 (1H, d), 4.52 (1H, m), 4.33 (1H, m), 4.15 (1H, m), 3.91 (2H, m), 2.32 (2H, m), 1.42 (9H, s), 0.34 (9H, m). ^{13}C NMR($CDCl_3$): δ 147.8, 137.6, 129.0, 79.7, 68.6, 60.1, 28.4, 19.1, −9.5. MS: $m/z = 428$, 355. LC–MS (ESI^+), solvent (A–B), m/z 428 $[M+H]^+$.

Method B: Hexamethylditin (190.8 mg, 582.6 μmol) and tetrakis(triphenylphosphine)-palladium(0) (9 mg, 7.8 μmol) were added to a solution of **3b** (100 mg, 291.3 μmol) in degassed toluene (3 ml). The reaction was heated for 12 h at 90°C under argon atmosphere and the solvent was evaporated under reduced pressure. The residue was extracted with ether and purified as described in method A, to give **4** (47%).

tert-*Butyl (2S)-2-{[(5-methylpyridin-3-yl)oxy]methyl}azetidine-1-carboxylate (5a)*

Method A: A solution of tris(dibenzylideneacetone)palladium(0) (131 mg, 144 μmol), tri-*o*-tolylphosphine (176 mg, 577 μmol), anhydrous potassium carbonate (78.7 mg, 577 μmol) and copper(I) chloride (57.7 mg, 577 μmol)) in anhydrous DMF (2 ml) was stirred at room temperature for 30 min under argon atmosphere. To this mixture was added a solution of stannyl compound **4a** (90 mg, 211 μmol) in anhydrous DMF (2 ml) followed by methyl iodide (60 mg, 423 μmol). This was heated at 60°C for 1 h then poured into brine (30 ml) and extracted with ethyl acetate (3 ml × 30 ml). The pooled extracts were dried ($MgSO_4$) and concentrated to give compound **5a** (50 mg, 85%). ^{1}H NMR ($CDCl_3$): δ 8.18 (1H, d), 8.06 (1H, s), 7.04 (1H, s), 4.51 (1H, m), 4.31 (1H, m), 4.14 (1H, m), 3.90 (2H, t), 2.30 (5H, m), 1.42 (9H, s). ^{13}C NMR($CDCl_3$): δ 156.1, 142.6, 122.1, 79.7, 68.5, 63.6, 60.1, 28.3, 19.0, 18.0. MS: $m/z = 278$, 205.

Method B. The synthesis was performed as described for **3a** (method A) except that **2c** was used instead of **2a**. The title compound was obtained (66%) as oil.

3-[(2s)-azetidin-2-ylmethoxy]-5-methylpyridine, salt with trifluoroactetic acid (5b)

To a mixture of **5a** (17 mg, 61.1 μmol) in anhydrous dichloromethane (0.4 ml) at 0°C TFA (1 ml) was added. After stirring for 2 h at room temperature the volatile fraction was removed under reduced pressure. The crude product was purified by semi-preparative LC, solvent A–B (2%:98%) isocratic at 2% for 3 min, linear gradient to 50%:50% during 10 min then ramped up to 90%:10% over 2 min, flow 5 ml/min, $t_R = 10.4$ min. The collected fractions were repeatedly evaporated with HPLC-grade acetone for azeotropical removal of water to yield the title compound **5b** (16.5 mg, 92%).

^{1}H NMR (Acetone-*d6*): δ 8.50 (1H, br), 8.40 (1H, br), 7.97 (1H, s), 5.78 (1H, m), 5.08 (1H, m), 4.85 (3H, m), 2.95 (1H, m), 2.65 (2H, m), 2.5 (3H, s). ^{13}C NMR(Acetone-*d6*): δ 138.1, 130.1, 129.6, 70.1, 96.1, 56.7, 18.6. LC–MS (ESI^+), solvent (A–B) m/z 179 $[M+H]^+$. The salt **5b** was treated with aqueous NaOH (3M) and extracted with CH_2Cl_2. The solvent was evaporated under reduced pressure to give the free base of **5b** which was later used for determination of specific radioactivity.

3-[(2s)-azetidin-2-ylmethoxy]-5-[^{11}C]-methylpyridine (5d)

A solution containing Pd_2(dba)3 (1.1 mg, 1.2 μmol) and (*o*-Tol)3P (6.7 mg, 22.2 μmol) in DMSO (350 μl) that was kept at room temperature for 10 min was filtered (ThermoHypersil F2513-3, PTFE syringe filter 0.45 μm) before use. [^{11}C]Iodomethane was trapped in the resulting yellowish solution (300 μl) and heated at 80°C for 2 min. To this was added a solution of the tin compound **4** (1 mg, 2.3 μmol) and CuCl (1.0 mg, 10 μmol) in DMSO (50 μl). The reaction mixture was vigorously shaken before heating at 80°C for 5 min. TFA (0.45 ml) was then added followed by heating at 80°C for 7 min. The reaction mixture was diluted by water (0.15 ml) and then separated on a semi-preparative LC column, as described for **5b**. The product was collected after 10.4 min. The organic solvent was evaporated and the residue was dissolved in sterile phosphate buffer (pH = 7.5, 5 ml). Sterile filtration of the final product solution through a filter (Dynagard ME, 0.22 μm pore size) into a sterile vial was performed. Radiochemical purity (> 97%) was determined by analytical LC. Analytical LC, same method as semi-preparative LC, flow 1.5 ml/min, wavelength 254 nm, $t_R = 5.3$ min. LC–MS (ESI^+), solvent (A–B), m/z 179 $[M+H]^+$.

Acknowledgements

We thank Dr. Robert Moulder for checking the language. The Swedish Nature Research Council is acknowledged for its support through Grant No. K3464 (B.L.).

References

1. Wagner HN, Szabo Z, Buchanan JW. *Principles of Nuclear Medicine*. W. B. Saunders Company: Philadelphia, 1995.
2. Jones T. *Eur J Nucl Med* 1996; **23**: 207–211.
3. Jones T. *Eur J Nucl Med* 1996; **23**: 807–813.
4. Comar C. *Developments in Nuclear Medicine*. Kluwer Academic Publishers: Dordrecht, 1995.
5. Flynn D, Mash D. *J Neurochem* 1986; **47**: 1948–1954.
6. Warpman U, Nordberg A. *NeuroReport* 1995; **6**: 2419–2423.
7. Grünwald F, Biersack HJ, Kuchinsky W. *Eur J Nucl Med* 1996; **23**: 1012–1013.
8. Muzic Jr RF, Berridge MS, Friendland RP, Zhu N, Nelson AD. *J Nucl Med* 1998; **39**: 2048–2054.
9. Ding YS, Liu N, Wang T, *et al*. *Nucl Med & Biol* 2000; **27**: 381–389.
10. Horti A, Scheffel U, Finely P, Ravert HT, London ED, Dannals RF. *J Nucl Med* 1997, **38**: 1260–1265.
11. Musachio JL, Villemange VL, Scheffel UA, Dannals RF, Dogan SA, Yokoi F, Wong DF. *Nucl Med & Biol* 1999; **26**: 201–207.
12. Koren AO, Horti AG, Mukhin AG, Guendisch D, Dannals RF, London ED. *J Label Compd Radiopharm* 2000; **43**: 413–424.
13. Sihver W, Fasth KJ, Horti AG, *et al*. *Journal of Neurochemistry* 1999; **73**: 1264–1272.
14. Holladay MW, Bai H, Li Y, *et al*. *Bioorg & Med Chem Lett* 1998, **8**: 2797–2802.
15. Yoon MN, Pak SC, Brown CH, Krishamurthy S, Stocky PT. *J Org Chem* 1973; **38**: 2786–2792.
16. Abreo MA, Lin NH, Garvey DS, *et al*. *J Med Chem* 1996; **39**: 817–825.
17. Freedman HH, Dubois RA. *Tetrahedron Lett* 1975; **38**: 3251–4354.
18. Koren A, Horti AG, Mukhin AG, *et al*. *J Med Chem* 1998; **41**: 3690–3698.
19. Clauson-Kaas N, Mattern G, Traber W. *United State Patent* 4,192,946.
20. Matsumura N, Nippon KZ. *Chem Abstr* 1953; **74**: 446; *Chem Abstr* 1954; 6442.
21. Suzuki M, Doi H, Björkman M, *et al*. *Chem Eur J* 1997; **12**: 2039–2042.
22. Björkman M, Andersson Y, Doi H, *et al*. *Acta Chem Scand* 1998; **52**: 635–640.

23. Björkman M, Doi H, Resul B, Suzuki M, Noyori R, Watanabe Y, Långström B. *J Label Compd Radiopharm* 2000; **43**: 1327–1334.
24. Tolman CA. Chem Rev 1997; **77**: 313–348.
25. Farina V, Roth GP. *Adv Met Org Chem* 1996; **5**: 1.
26. Labadie JW, Stille JK. *J Am Chem Soc* 1983; **105**: 6129.
27. Långström B, Antoni G, Gullberg P, *et al. J Nuclear Med* 1987; **28**: 1037.
28. Långström B, Lundquist H. *Radiochem Radioanal Lett* 1979; **41**: 375.
29. Bjurling P, Reineck R, Westerberg G, Gee A. D, Sutcliffe J, Långström B. *Proceedings of the VIth Workshop on Targetry and Target Chemistry*. Vancouver, Canada, 1995; 282–284.

