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Synthesis of $^{11}C/^{13}C$-Labelled Prostacyclins

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A one-pot synthesis of (15*R*)-16-(3-[^{11}C]methylphenyl)-17,18,19,20-tetranorisocarbacyclin methyl ester was performed using a palladium-promoted reaction of [^{11}C]methyl iodide with (15*R*)-16-(3-tri-*n*-butylstannylphenyl)-17,18,19,20-tetranorisocarbacyclin methyl ester. The C-15 epimer (15*S*)-16-(3-[^{11}C]methylphenyl)-17,18,19,20-tetranorisocarbacyclin methyl ester was synthesised in the same way starting from (15*S*)-16-(3-tributylstannylphenyl)-17,18,19,20-tetranorisocarbacyclin methyl ester. The decay-corrected radiochemical yields were 33–45% based on [^{11}C]methyl iodide produced, and the radiochemical purity of the product was >95%. The total synthesis time was 35 min, counted from end of radionuclide production to product ready for administration. The ^{11}C-labelled prostacyclin methyl esters were easily hydrolysed using sodium hydroxide affording the ^{11}C-labelled prostacyclin acids in quantitative yields. The stereoisomers (15*R*)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin [^{11}C]methyl ester and (15*S*)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin [^{11}C]-methyl ester were synthesised by esterification using [^{11}C]methyl iodide and the tetrabutylammonium salts of (15*R*)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin acid and (15*S*)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin acid, respectively. The decay-corrected radiochemical yields were in the range of 55% counting from [^{11}C]methyl iodide produced, and the radiochemical purity of the product was >95%. The total synthesis time was 35 min, counting from end of radionuclide production to product ready for administration. Both of these labelling methods can be used for labelling with ^{13}C when (^{13}C)methyl iodide is used. The methods described herein have already proved important since they enable the *in vivo* use of PET to study the action of prostacyclins in the brain.

Prostaglandins and prostacyclin (prostaglandin I_2) are naturally occurring substances found in animals and man, where they are biosynthesised from C_{20} polyunsaturated fatty acids.[1] Prostacyclin exerts a protective effect against neuronal cell death and damage induced by experimental ischemia. In the search for prostacyclin receptors in the central nervous system, a novel plausible subtype of prostacyclin receptor, with ligand specificity clearly different from that of the known prostacyclin receptors in platelets and peripheral tissues, was found.[2,3] Since (15*R*)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin **1a** was found to be selective for this CNS prostacyclin receptor, **1a** and modified substances might be useful tools for molecular and functional characterisation of this receptor. To provide a means to investigate these substances *in vivo* using positron emission tomography (PET) a method for the labelling of prostaglandins with ^{11}C was developed. PET enables the non-invasive determination of the distribution and pharmacokinetics of biologically active substances labelled with positron-emitting radionuclides. The most commonly used radionuclides are ^{15}O, ^{11}C and ^{18}F with half-lives of 2.0, 20.3 and 109 min, respectively. In the production of ^{11}C-labelled compounds, the short half-lives of the radionuclide and the limited number of ^{11}C-labelled precursors must be considered when developing the synthetic route. The high specific radioactivity, that is the high amount of radioactivity per unit mass,† also needs to be taken into account.

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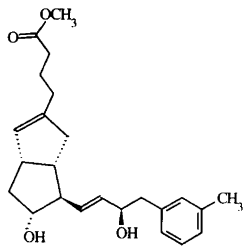
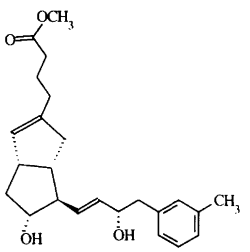
† In the case of ^{11}C, the specific radioactivity is generally in the range of 50–500 GBq μmol^{-1} (1.3–13 Ci μmol^{-1}). The amount of precursor in a reaction with 1 GBq would then be approximately 2–20 nmol.



1a



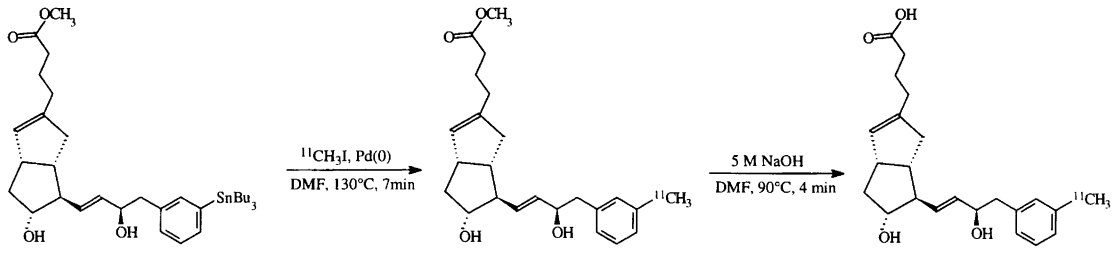
1b

The use of palladium-promoted reactions in synthesis employing the labelled precursors [^{11}C]methyl iodide, hydrogen [^{11}C]cyanide and [^{11}C]carbon monoxide has recently been described.[4–6] In the present paper the palladium-mediated cross-coupling of [^{11}C]methyl iodide with prostacyclin trialkyltin compounds is presented. The cross-coupling of trialkyltin compounds with organic electrophiles in the presence of palladium is often referred to as the Stille reaction.[7] The reagents in this reaction are not particularly sensitive towards oxygen or moisture, and the reaction can be performed in the presence of a wide range of functional groups. The labelling of the two C-15 stereoisomers of the isocarbacyclin derivative (15*R*)- and (15*S*)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin methyl ester **1a** and **1b** with ^{11}C in the tolyl position was carried out as illustrated in Scheme 1. Compounds **1a** and **1b** were also labelled in the methyl ester position via an esterification reaction with the prostacyclin anion acting as a nucleophile on [^{11}C]methyl iodide[8] (Scheme 2). The prostacyclin anion was obtained from a reaction with tetrabutylammonium hydroxide forming an ion pair. The prostacyclins labelled with ^{11}C in different positions have been used in a number of *in vitro* studies and *in vivo* studies using PET and the results from these experiments will be presented elsewhere.[9]

Results and discussion

^{11}C-Labelling of prostacyclins in the tolyl position. (15*R*)-16-(3-[^{11}C]Methylphenyl)-17,18,19,20-tetranorisocarbacyclin methyl ester (**3a**) was synthesised from (15*R*)-16-(3-tributylstannylphenyl)-17,18,19,20-tetranorisocarbacyclin methyl ester (**2a**) and [^{11}C]methyl iodide in the presence of tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] and tri(*o*-tolyl)phosphine[(*o*-Tol)$_3$P] (Scheme 1). The [^{11}C]methyl iodide used was obtained from [^{11}C]carbon dioxide via a reaction with lithium aluminium hydride and subsequent reaction with hydroiodic acid according to a previously described procedure.[10] The conversion of [^{11}C]carbon dioxide to [^{11}C]methyl iodide was performed using an automated system for the production of radiopharmaceuticals.[11] The [^{11}C]methyl iodide was transferred to a solution of the palladium catalyst and **2a** in dimethylformamide (DMF) using nitrogen gas as a carrier. After heating, the labelled product was purified by liquid chromatography (LC). The organic solvent was evaporated and to the residue was added a sterile solution. The resulting solution was sterile filtered and thereafter ready for administration. The decay-corrected radiochemical yield was 33–45% counted from the amount [^{11}C]methyl iodide. The total synthesis time was 35 min counted from the end of radionuclide production to product ready for administration, and the radiochemical purity of the isolated product was >95% as determined by analytical LC. The identity of the labelled compound was assessed by analytical LC, after addition of a reference substance, and by LC–MS. Fragments of mass to charge ratio (*m/z*) 421 and 416 were observed and these represent $[M+Na]^+$ and $[M+NH_4]^+$. These fragments were present during the analysis of both the reference compound and the labelled product by LC–MS. The calculated molecular weight (M_w) was 398.5. The labelled product was fully retained on the column and the selected ion recording of *m/z* 416 $[M+NH_4]^+$ correlated with the signal from the β^+-detector.

The labelling synthesis of (15*R*)-16-(3-[^{11}C]methylphenyl)-17,18,19,20-tetranorisocarbacyclin **4a** was conducted as above with an additional hydrolysis of the methyl ester using 5 M sodium hydroxide. The solution was neutralised with 6 M hydrochloric acid before semi-preparative LC-purification. The decay-corrected radiochemical yield was 35–40% based on [^{11}C]methyl iodide, and the total synthesis time was 30 min counted from the end of radionuclide production to product ready for administration. The radiochemical purity of the isolated



2a **3a** **4a**

Scheme 1.

product was >90% as determined by analytical LC. The identity of the labelled product was assessed by analytical LC after addition of a reference substance.

(15*S*)-16-(3-[^{11}C]Methylphenyl)-17,18,19,20-tetranorisocarbacyclin methyl ester **3b** and (15*S*)-16-(3-[^{11}C]-methylphenyl)-17,18,19,20-tetranorisocarbacyclin **4b** were obtained according to the methods described above. The decay-corrected radiochemical yields of these compounds were in the range 35–45% and the radiochemical purity of the isolated products was >95% for **3b** and >90% for **4b** as determined by analytical LC.

To verify the position of the ^{11}C-label, a combination of [^{11}C]- and (^{13}C)-methyl iodide was used in an experiment employing the same conditions as described above in the synthesis of **3a**, except for a longer reaction time. The product was purified by semi-preparative LC. After decay of ^{11}C, the solvent was withdrawn and the residue dissolved in $CDCl_3$. The ^{13}C NMR spectrum of the product showed one signal at 21 ppm which corresponded to the position of the tolyl ^{13}C NMR signal of the reference substance **1a**.[2]

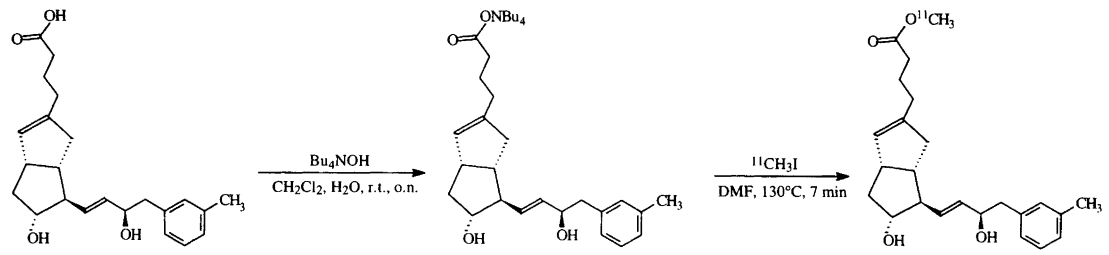
Palladium-mediated cross-coupling of trialkyltin compounds with organic halides or triflates has been reported to be largely influenced by the type of ligand used in the palladium complex.[12] There have been several reports that phosphine ligands are not an optimal choice in these reactions since such ligands are known to coordinate strongly to the palladium centre. This strong coordination may inhibit the transmetallation step and thereby slow down the reaction. Less strongly coordinating ligands such as triphenylarsine and trifurylphosphine, reported[12] to give good results in cross-coupling reactions of Stille type, gave poor results in the present investigation. One reason might be that the conditions employed were too harsh for the palladium complex formed from these ligands. To circumvent these problems, a relatively strong, but not sterically congested, coordinating ligand, (*o*-Tol)$_3$P, was selected.[13]

It has also been reported that an excess amount of ligand, especially phosphine-type of ligands, may slow down the reaction rate.[12] If ligand dissociation is a key step in the transmetallation, the reaction rate would be dependent on the ligand concentration. To avoid an excess amount of ligand the catalyst was prepared *in situ* from one equivalent of $Pd_2(dba)_3$ and four equivalents of the ligand. When using eight equivalents of the ligand, lipophilic ^{11}C-labelled side products were observed chromatographically. The side-products seemed to be formed in a larger amount in diglyme than in DMF, and the reaction afforded low yields under these conditions. No effort was made to investigate the identity of the side products. However since they were very lipophilic and labelled with ^{11}C, one suggestion may be that they were adducts of the catalyst, after oxidative addition of [^{11}C]methyl iodide, with different amounts of ligand and other coordinating species such as the organotin compound or the solvent. It has been shown that [^{11}C]methyl(triphenyl)phosphonium iodide can be formed in the reaction between [^{11}C]methyl iodide and phosphine ligand,[4] however, this type of side product did not prove to be a problem in these cross-coupling reactions. The reaction with two equivalents of (*o*-Tol)$_3$P ligand and one equivalent of palladium(0) gave satisfactory radiochemical yields, a relatively short reaction time, and there was no problem with formation of side products. Since an authentic reference substance was used to verify the identity of the product formed in the cross-coupling reaction, the possibility of alterations in the stereochemistry, caused from the catalyst co-ordinating to, for example, the allylic alcohol moiety, was ruled out.

Polar aprotic solvents enhance the coupling rates[14] and these solvents are also the most efficient in trapping‡ of [^{11}C]methyl iodide, so DMF was a natural choice of solvent. In a previous report on ^{11}C-labelling of model compounds, using palladium-promoted cross-coupling of organotin compounds with [^{11}C]methyl iodide,[4] a temperature of 90 °C and a reaction time of 4 min was used. However, these reaction conditions were not suitable for ^{11}C-labelling of the prostacyclins in this study. The radiochemical yield was improved tenfold at a temperature of 130 °C and a reaction time of 7 min. In spite of the instability of the prostacyclin, no major degradation was observed with an increase in reaction temperature. Formation of polar ^{11}C-labelled side products such as [^{11}C]methanol could be minimised if the palladium complex solution was prepared only a few minutes before trapping of the [^{11}C]methyl iodide. In addition it was observed that it was important to use a fresh Sicapent® drying tower to remove traces of water, from the hydroiodic acid, along with [^{11}C]methanol, formed in the [^{11}C]methyl iodide reaction.

^{11}C-Labelling of prostacyclins in the methyl ester position. (15*R*)-16-(3-Methylphenyl)-17,18,19,20-tetranorisocarbacyclin [^{11}C]methyl ester (**7a**) and (15*S*)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin [^{11}C]-methyl ester (**7b**) were synthesised by direct esterification of a tetrabutylammonium ion pair with [^{11}C]methyl iodide. The tetrabutylammonium salt was prepared from the prostacyclin acid and tetrabutylammonium hydroxide according to a published method.[15] The [^{11}C]methyl iodide was transferred to a DMF solution of the tetrabutylammonium salt of the prostacyclin acid **6a** or **6b**. The reaction mixture was heated and the product purified by semi-preparative LC. The organic solvent was evaporated and the residue was dissolved in a sterile propylene glycol–ethanol solution and sterile filtered after which it was ready for administration. The decay-corrected radiochemical yield was in the range of 55% based on [^{11}C]methyl iodide, and the product was obtained within 35 min counted from the end of the radionuclide production to product ready for administration. The radio-

‡ In this case trapping is the retention of [^{11}C]methyl iodide in the solvent with >90% of the radioactivity remaining in the solution after transfer of the radioactivity through the reaction mixture.



5a **6a** **7a**

Scheme 2.

chemical purity of the isolated product was >95% as determined by analytical LC. The identity of the labelled compounds was assessed by analytical LC after addition of reference compounds, and by LC–MS. The fragments *m/z* 421 and 416 represent $[M+Na]^+$ and $[M+NH_4]^+$. These fragments were present during analysis of both the reference compounds and the labelled products by LC–MS. The calculated molecular weight was $M_w = 398.5$. The labelled products were fully retained on the column and the selected ion recording of *m/z* 416 $[M+NH_4]^+$ correlated with the signal from the β^+-detector.

The position of the ^{11}C-label was verified by synthesis with a combination of [^{11}C]- and (^{13}C)methyl iodide using the same reaction conditions as described above for the synthesis of **7a**, with a reaction time of 15 min. The product was purified by semi-preparative LC. After decay of ^{11}C the solvent was withdrawn and the residue dissolved in $CDCl_3$. The ^{13}C NMR signal of the product showed a signal at 51 ppm. This signal corresponds to the signal of the methyl ester group of the reference compound, **1a**.[2]

It has been reported that the esterification of a prostacyclin acid with [^{11}C]methyl iodide can be performed in DMF using trimethylpiperidine as the base.[16] However, in the present investigation esterification with an ion pair, formed from the prostacyclin acid and tetrabutylammonium hydroxide, acting as a nucleophile on [^{11}C]methyl iodide afforded a better result. The isocarbacyclin acid was easily converted into the tetrabutylammonium salt.[8]

Experimental

General. [^{11}C]CO_2 was prepared by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction in a nitrogen (AGA Nitrogen 6.0) gas target containing 0.1% oxygen (AGA Oxygen 4.8), with 17 MeV protons produced by the Scanditronix MC-17 Cyclotron at the Uppsala University PET Centre. The [^{11}C]CO_2 was converted into [^{11}C]CH_3I via a reaction with lithium aluminium hydride and subsequent reaction with hydroiodic acid,[10] using an automated system for the production of radiopharmaceuticals.[11] $CDCl_3$ was used as the solvent when recording ^{13}C NMR spectra at 75.4 MHz on a Varian XL-300 spectrometer. Chemical shifts are reported in ppm with $CDCl_3$ as an internal standard (77.0 ppm). The LC–MS equipment consisted of a Beckman 126 solvent delivery module, a CMA 240 autosampler (CMA Microdialysis, Stockholm, Sweden) and a Fison VG Quattro mass spectrometer equipped with pneumatically assisted electrospray and an RF ion bridge. The column in the LC–MS system was a C-18 Beckman Ultrasphere ODS 5 μm (250 × 4.5 mm). A post column 1 : 100 split was used, with 1% of the total flow delivered to the electrospray probe and 99% delivery to a Bioscan Flow-count β^+-detector. Mobile phases were (A) 25 mM ammonium formate buffer pH 3.5 and (B) methanol. Isocratic elution 0–8 min with 70% B and thereafter a linear gradient to 90% B after 8 min at a flow of 1 ml min^{-1} was used.

Chromatography. Semi-preparative and analytical LC was performed using a Beckman 126 Pump and a Beckman 166 UV detector in a series with a β^+-flow detector. Data collections were performed using the Beckman System Gold chromatography software package. A C-18 Beckman Ultrasphere ODS 5 μm (250 × 10 mm) column was used for semi-preparative LC. The analytical column was a Beckman Ultrasphere Octyl 5 μm (250 × 4.5 mm). Mobile phases were 50 mM ammonium formate pH 3.5 (A) and acetonitrile–water (50/7 v/v) (B). LC was performed at room temperature and the UV-detection wavelengths were 230 nm for semi-preparative LC and 220 nm for analytical LC.

The following LC conditions were used for all substances. The semi-preparative LC purification of the reaction mixtures was performed with isocratic elution 0–6 min 65% B, linear gradient to 95% B after 6 min with a flow of 5 ml min^{-1}. The analytical LC system used for identification and determination of radiochemical purity was isocratic elution 0–6 min 65% B and a linear gradient to 90% B after 6 min with a flow of 1.5 ml min^{-1}.

Chemicals. (15*R*)-16-(3-Tributylstannylphenyl)-17,18,19,20-tetranorisocarbacyclin methyl ester (**2a**) and (15*S*)-16-(3-tributylstannylphenyl)-17,18,19,20-tetranorisocarbacyclin methyl ester (**2b**) and the reference compounds (15*R*)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin methyl ester (**1a**) and (15*S*)-16-(3-

methylphenyl)-17,18,19,20-tetranorisocarbacyclin methyl ester (**1b**) were prepared according to a described procedure.[2]

A sterile PPG solution containing 400 mg of propylene glycol and 100 mg of ethanol in an aqueous solution with a total volume of 10 ml, was purchased from Apoteksbolaget, Sweden. $Pd_2(dba)_3$ (without chloroform) and the $(o\text{-Tol})_3P$ were purchased from Aldrich. All other chemicals and solvents were of analytical or gradient grade purity and used as received.

Synthesis of (15R)-16-{3-[^{11}C]methylphenyl}-17,18,19,20-tetranorisocarbacyclin methyl ester (**3a**) *and (15S)-16-(3-[^{11}C]methylphenyl)-17,18,19,20-tetranorisocarbacyclin methyl ester* (**3b**). A solution of 0.9 mg (1 μmol) of $Pd_2(dba)_3$ and 1.2 mg (4 μmol) of $(o\text{-Tol})_3P$ in 350 μl of DMF was prepared in a dry 0.8 ml septum-equipped vial and purged with nitrogen gas for 10 min. [^{11}C]CH_3I was passed through a Sicapent® drying tower and trapped in the solution at room temperature. After trapping the reaction mixture was transferred to a septum-equipped vial containing 1 mg (1.4 μmol) of **2a** or **2b**. The reaction vessel was heated at 130 °C for 7 min and the reaction mixture was then injected onto the semi-preparative column. The product fraction was collected after 10.6 min for **3a** and after 10.8 min for **3b** and the organic solvent was evaporated. To the residue were added 6 ml of sterile PPG solution. The resulting solution was passed through a sterile filter (Dynagard ME, 0.22 μm pore size) into a sterile vial. Radiochemical purity was determined by analytical LC; the retention time for **3a** was 9.5 min and the retention time for **3b** was 9.3 min. The identity was determined by adding an authentic reference compound to the solution and analysing by analytical LC.

Synthesis of (15R)-16-(3-[^{11}C]methylphenyl)-17,18,19,20-tetranorisocarbacyclin (**4a**) *and (15S)-16-(3-[^{11}C]methylphenyl)-17,18,19,20-tetranorisocarbacyclin* (**4b**). A solution of 0.9 mg (1 μmol) of $Pd_2(dba)_3$ and 1.2 mg (4 μmol) of $(o\text{-Tol})_3P$ in 350 μl of DMF was prepared in a dry 0.8 ml septum-equipped vial and purged with nitrogen gas for 10 min. [^{11}C]CH_3I was passed through a Sicapent® drying tower and trapped in the solution at room temp. After trapping the reaction mixture was transferred to a septum-equipped vial containing 1 mg (1.4 μmol) of **2a** or **2b**. The reaction vessel was heated at 130 °C for 7 min, 200 μl of 5 M NaOH were added to the mixture and the resulting solution was heated for an additional 4 min at 90 °C. The mixture was neutralised with 6 M HCl before purification by semi-preparative LC, the product fraction was collected at 5.8 min for **4a** and 6.0 min for **4b**, and the organic eluent was evaporated. To the residue were added 5 ml of a sterile PPG solution, and the resulting solution was passed through a sterile filter (Dynagard ME, 0.22 μm pore size) into a sterile vial. The retention time for **4a** during analytical LC was 4.5 min and the retention time for **4b** was 4.3 min. The identity was assessed by adding an authentic reference compound to the solution and analysing by analytical LC.

Synthesis of (15R)-16-{3-[^{11}C]/(^{13}C)methylphenyl}-17,18,19,20-tetranorisocarbacyclin methyl ester (**3a**). The synthesis was performed as described above with the modification that 10 μl of 10% (^{13}C)CH_3I (15 μmol) were added to the solution when the [^{11}C]CH_3I was trapped. The subsequent solution was transferred to the reaction vessel and the reaction time was prolonged to 15 min. The product fraction with a retention time of 10.6 min during semi-preparative LC was collected. The experiment was repeated four times and the product fractions were combined. After decay of the ^{11}C the residue was dried *in vacuo* and dissolved in $CDCl_3$. ^{13}C NMR ($CDCl_3$): δ 21.0 ($^{13}CH_3$).

Synthesis of (15R)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin tetrabutylammonium salt (**6a**) *and (15S)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin tetrabutylammonium salt* (**6b**). Three mg (7.8 μmol) of (15*R*)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin **5a** or (15*S*)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin **5b** were dissolved in 1 ml of H_2O and 1 ml of CH_2Cl_2. Tetrabutylammonium hydroxide [10 μl of 1.5 M (15 μmol)] was added and the mixture was stirred overnight at room temperature. The organic layer was withdrawn and the aqueous layer extracted twice with CH_2Cl_2. The combined organic phases were filtered through a small column (5 ml syringe) of anhydrous $MgSO_4$. The filtrate was transferred to an 0.8 ml septum-equipped vial, the solvent evaporated and the remaining salt stored in a dessicator at −5 °C.

Synthesis of (15R)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin [^{11}C]methyl ester (**7a**) *and (15S)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin [^{11}C]methyl ester* (**7b**). One mg (1.6 μmol) of **6a** or **6b** was dissolved in 300 μl of DMF and the septum-equipped vial purged with nitrogen gas for 1–5 min. [^{11}C]CH_3I was passed through a Sicapent® drying tower and trapped in the solution at room temperature, and the reaction mixture was heated at 130 °C for 7 min. The mixture was injected into a semi-preparative LC column, from which the product fraction was collected after 10.6 min for **7a** and 10.8 min for **7b**, and the organic solvent was evaporated. The residue was dissolved in sterile PPG solution and passed through a sterile filter (Dynagard ME, 0.22 μm pore size) into a sterile vial. The radiochemical purity was determined by analytical LC, the retention time for **7a** was 9.5 min and the retention time for **7b** was 9.3 min. The identity was assessed by adding an authentic reference sample to the solution and analysing by analytical LC.

Synthesis of (15R)-16-(3-methylphenyl)-17,18,19,20-tetranorisocarbacyclin [^{11}C]/(^{13}C)methyl ester (**7a**). The

synthesis was performed in the same way as described above with the modification that 10 µl of 10% (^{13}C)CH_3I (15 µmol) were added to the solution when the [^{11}C]CH_3I was trapped and the reaction time was prolonged to 15 min. The product fraction with retention time of 10.6 min during semi-preparative LC was collected. After decay of ^{11}C the residue was dried *in vacuo* and dissolved in $CDCl_3$. ^{13}C NMR ($CDCl_3$): δ 51.0 ($^{13}CH_3$).

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References

1. Collins, P. W. and Djuric, S. W. *Chem. Rev. 93* (1993) 1533.
2. Suzuki, M., Kato, K., Noyori, R., Watanabe, Yu., Takechi, H., Matsumura, K., Långström, B. and Watanabe, Y. *Angew. Chem., Int. Ed. Engl. 35* (1996) 334.
3. Takechi, H., Matsumura, K., Watanabe, Yu., Kato, K., Noyori, R., Suzuki, M. and Watanabe, Y. *J. Biol. Chem. 271* (1996) 5901.
4. Andersson, Y., Cheng, A. and Långström, B. *Acta Chem. Scand. 49* (1995) 683.
5. Andersson, Y. and Långström, B. *J. Chem. Soc., Perkin Trans. 1* (1994) 1395.
6. Andersson, Y. and Långström, B. *J. Chem. Soc., Perkin Trans. 1* (1995) 287.
7. Stille, J. K. *Angew. Chem., Int. Ed. Engl. 25* (1986) 508; Mitchell, T. N. *Synthesis* (1992) 803.
8. Brändström, A. *Preparative Ion Pair Extraction*, Swedish Academy of Pharmaceutical Sciences, Stockholm 1976, pp. 109.
9. Watanabe, Y. *In preparation.*
10. Långström, B., Antoni, G., Gullberg, P., Haldin, C., Malmborg, P., Någren, K., Rimland, A. and Svärd, H. *J. Nuclear Med. 28* (1987) 1037.
11. Bjurling, P., Reineck, R., Westerberg, G., Schultz, J., Gee, A., Sutcliff, J. and Långström, B. *Proceedings from VIth Workshop on Targetry and Target Chemistry*, Vancouver, BC, Canada, August 1995.
12. Farina, V. and Roth, G. P. *Adv. Met. Org. Chem. 5* (1996) 1.
13. Suzuki, M., Doi, H., Björkman, M., Andersson, Y., Långström, B., Watanabe, Y. and Noyori, R. *Chem. Eur. J. In press.*
14. Scott, W. J. and Stille, J. K. *J. Am. Chem. Soc. 108* (1986) 3033.
15. Brändström, A. *Preparative Ion Pair Extraction*, Swedish Academy of Pharmaceutical Sciences, Stockholm 1976, pp. 83.
16. Gullberg, P., Watanabe, Y., Svärd, H., Hayaishi, O. and Långström, B. *Appl. Radiat. Isot. 38* (1987) No. 8, 647.

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