Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **XLI**, 287-300 (1998)

SOLID PHASE-SUPPORTED REACTION OF N.C.A. $H^{11}CN$ WITH ARABINOSE: A SIMPLIFIED AUTOMATED SYNTHESIS OF D-[1-^{11}C]GLUCOSE†

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Summary

A simplified, automated synthesis for D-[1-^{11}C]glucose is described by the solid phase-supported reaction of $NH_4{}^{11}CN$ with D-arabinose on an Alumina N Sep-Pak™. ^{11}C-cyanide reacted instantaneously to produce [1-^{11}C]aldonitriles. Reduction with Raney nickel in formic acid and semipreparative HPLC afforded D-[1-^{11}C]glucose with radiochemical purity >95%. Compared with previously reported procedures a pH adjustment and rotary evaporation step is avoided resulting in a shortening of the synthesis time from 55 to 38 min. The radiochemical yield was 5 – 15% (2.5 – 8.5% non-corrected) based on $NH_4{}^{11}CN$. For a typical production starting with 20 GBq of $NH_4{}^{11}CN$ up to 500 MBq D-[1-^{11}C]glucose was obtained at end of synthesis as a sterile, formulated solution.

Key words: ^{11}C, cyanide, solid phase, D-[1-^{11}C]glucose, PET

† Presented in part at the XIIth International Symposium on Radiopharmaceutical Chemistry, Uppsala 1997

CCC 0362–4803/98/040287–14$17.50

Received 13 October 1997
Revised 8 December 1997

Introduction

[2-^{18}F]Fluoro-2-deoxy-D-glucose (FDG) is a widely used radiopharmaceutical for the measurement of in vivo glucose utilisation by PET. These measurements are based on the deoxyglucose (DG) method [1] and have been adapted to PET using FDG and ^{11}C-deoxyglucose [2,3,4]. The method relies on the fact that DG/FDG are taken up in tissue and phosphorylated to DG/FDG-6-phosphate, which are non-substrates for the subsequent enzymatic steps of native glucose metabolism. Therefore these compounds are effectively metabolically trapped in tissue. However DG and FDG are glucose analogues and their rates of transport and phosphorylation are not identical to that of glucose. The estimation of these rate constants requires the use of a conversion factor, the so-called 'Lumped Constant' (LC). This constant has been experimentally determined in healthy tissue, in animals and man [5]; however, there is little indication that the LC has the same value in diseased tissue [6,7]. Indeed there are reports, that the magnitude of the LC can vary significantly even in healthy tissue [8]. The lumped constant is therefore not a constant, but a variable and may be a source of error, when quantitative estimates of glucose metabolism are required. Due to the fact that ^{11}C labelled glucose is biochemically indistinguishable from natural glucose, the analyses of ^{11}C labelled glucose PET data is not affected by problems arising from the LC. To enable the determination of LC values in normal and abnormal physiological states in vivo, a comparison of the FDG results for glucose transport and phosphorylation with those obtained from ^{11}C labelled glucose is required.

In the past several syntheses were developed for the labelling of ^{11}C labelled glucose. These procedures are based either on the biosynthetic methods [9-13], which result in a statistical distribution of the label throughout the molecule [14], or on specific chemical labelling in position 1 [15-18] or 6 [19]. In terms of the metabolism of glucose, it is preferable to use either specifically labelled D-[1-^{11}C] or D-[6-^{11}C]glucose [20-24].

A useful method for the synthesis of D-[1-^{11}C]glucose is an adaptation of the well-known Kiliani-Fischer method for the preparation of carbohydrates [15,16]. This synthesis is based on the reaction

of ^{11}C labelled cyanide with arabinose. The resulting aldonitriles are reduced with Raney nickel/formic acid, resulting in ^{11}C-glucose and ^{11}C-mannose.

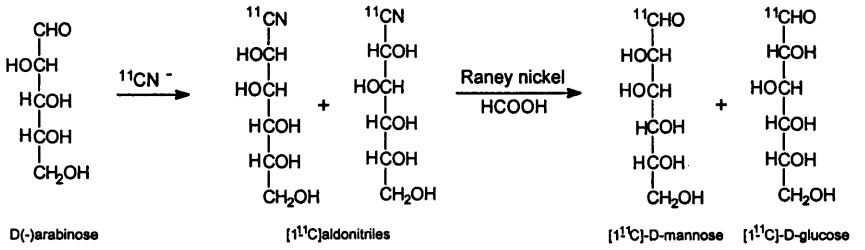

Fig.1: Modified Kiliani-Fischer method for the preparation of D-[1-^{11}C]glucose and D-[1-^{11}C]mannose

However a disadvantage of this approach is the unfavourable glucose/mannose ratio obtained, which is only around 0.65. A major improvement was the use of a borate buffer as reaction medium [18], which afforded a glucose/mannose ratio of between 1.7 and 2.5. The crucial step for the synthesis based on the Kiliani-Fischer method is the reduction of the aldonitriles to the corresponding aldoses. So far the Raney nickel/formic acid method gives the best results, despite large yield losses of up to 50%. Attempts to use alternative reducing reagents such as diborane did not result in an improvement in the efficiency of the reduction [25].

An alternative approach for the synthesis of D-[1-^{11}C]glucose was the reaction of arabinose with ^{11}C labelled nitromethane, followed by the classical Nef reaction [17]. However this approach did not result in better yields of D-[1-^{11}C]glucose.

The published synthesis of D-[6-^{11}C]glucose [19] is based on the Wittig coupling of $^{11}CH_3I$ with an arabinose derivative followed by an osmium tetroxide induced 1,2-hydroxylation and oxidation to glucose. However in terms of automation, this multi-step procedure is too complicated to adapt to a routine labelling procedure. A recently presented synthesis for ^{11}C labelled sugars also uses the Wittig/OsO_4 approach, but the oxidation step is based on an enzyme induced oxidation of the resulting ^{11}C-glucitole [26]. This approach shows no advantage with respect to synthesis time and radiochemical yield.

The aim of our studies was to simplify the automation set-up and to shorten the synthesis time for the production of D-[1-^{11}C]glucose using the Kiliani-Fischer synthesis method for routine PET investigations of glucose metabolism.

Experimental

General

D-Arabinose, D-glucose, D-mannose, formic acid, diethylamine and di-n-butylamine were purchased from Fluka. Sodium tetraborate ($Na_2B_4O_7 \cdot H_2O$), Raney nickel (50% slurry in water), lithium aluminium hydride (1 M solution in THF), sodium borohydride and sodium trimethoxyborohydride were purchased from Aldrich. 0.033 M borate buffer [18], $LiAl(N(C_2H_5)_2)_3H$ [27] and $LiAl(N(C_4H_9)_2)_3H$ [27] were prepared according to literature procedures. All chemicals were used without further purification. The cation exchange resin AG 50 W-X8 (100 – 200 mesh) and the ion retardation resin AG 11A8 (50 – 100 mesh) were obtained from BIO-RAD. The ion exchange resins were washed with sterile water before use. Alumina N Sep-Paks™ (classic Long Body and Plus Light) were purchased from Waters-Millipore.

Analytical HPLC was carried out using two chromatographic systems. System A consisted of a Perkin-Elmer model 250 isocratic pump equipped with a Rheodyne 7725 injector and 20 µl loop, connected in series with a Zorbax NH2 (250 x 4.6 mm) column, a Perkin-Elmer series 200 refractive index detector and a radiodetector of in-house design. The mobile phase was CH_3CN : H_2O (90 : 10) and the flow rate 2 ml/min. To confirm the results a second analytical HPLC system (system B) was used, consisting of a Perkin-Elmer series 200 isocratic pump equipped with a Rheodyne 7725 injector and 20 µl loop connected in series with a Dionex Carbopac PA1 (250 x 4 mm) column, a Dionex PED-2 (electrochemical) detector and a radiodetector of in-house design. The mobile phase was 0.25 M NaOH and the flow rate 0.2 ml/min.

Semipreparative HPLC was performed using a Perkin-Elmer series 200 isocratic pump equipped with a pneumatic actuated Rheodyne 7010 injector and a 2 ml loop connected in series with a Phenomenex RPM monosaccharide column (300 x 7.8 mm) and a radiodetector of in-house design.

The mobile phase was sterile water (flow rate 0.7 ml/min) and the column temperature 85°C. Anion analysis was performed using a Perkin-Elmer series 250 isocratic pump equipped with a Rheodyne 7725 injector and 20 µl loop and connected in series with a Hamilton PRP-X 100 (125 x 4.6 mm) column and an Applied Biosystems 759 A variable UV detector (λ=310 nm). The mobile phase was 4 mM NaOH and 0.15 mM p-hydroxybenzoic acid and the flow rate 1 ml/min. Determination of the content of transition metals in formulated product solutions was performed by AAS.

Automation

Automation was performed using Rheodyne Model 5301 slider valves, equipped with a Rheodyne Model 5300 actuator. Each component was connected to a SMC Model VZ 1120 solenoid valve and compressed air manifold. Syringe drives comprised of SMC pneumatic cylinders CD85N12-50, connected to an appropriate luer lock syringe. Tubing connections were either 1/16 or 1/8 inch PTFE tubes. Heating was achieved using a heating block and oil bath. Valve switching sequences were programmed and controlled using two 16 OPTO –Digital IN and 8 Relay OUT interface cards (inLog Micro systems Co., Ltd Model PI-426) and a PC program of in-house design.

Radionuclide and H^{11}CN production

$^{11}CO_2$ was produced by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction using a nitrogen gas target and 16.5 MeV protons produced by the GEMS PETtrace cyclotron at the Aarhus University Hospital. H^{11}CN was produced by a standard procedure [28]. At end-of-bombardment (EOB) the stream of $^{11}CO_2$ gas was trapped on molecular sieves at room temperature and subsequently released in a stream of nitrogen gas (25 ml/min) by heating to 350°C. The $^{11}CO_2$ was converted to $^{11}CH_4$ by the addition of hydrogen gas (40 ml/min) and passage over a nickel catalyst at 400°C. $NH_4{}^{11}CN$ was formed by the reaction of anhydrous ammonia (5 ml/min) with the $^{11}CH_4$ on a platinum catalyst at 1000°C. $NH_4{}^{11}CN$ was transferred in a stream of N_2 gas to the hot cell.

A schematic of the on-line $NH_4{}^{11}CN$ synthesis system is shown in Fig.2.

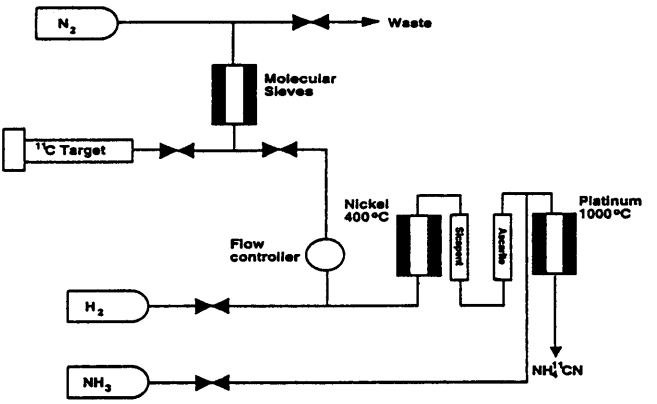

Fig. 2: Schematic of the $NH_4{}^{11}CN$ synthesis system.

D-[1-^{11}C]glucose

A schematic of the automated apparatus for the production of D-[1-^{11}C]glucose is shown in Fig. 3. 15 mg (1.15×10^{-4} mol) of D(-)arabinose was dissolved in 0.1 ml of 0.033 M borate buffer and loaded on an Alumina N Sep-Pak™ preconditioned with 10 ml of 0.033 M borate buffer. $NH_4{}^{11}CN$

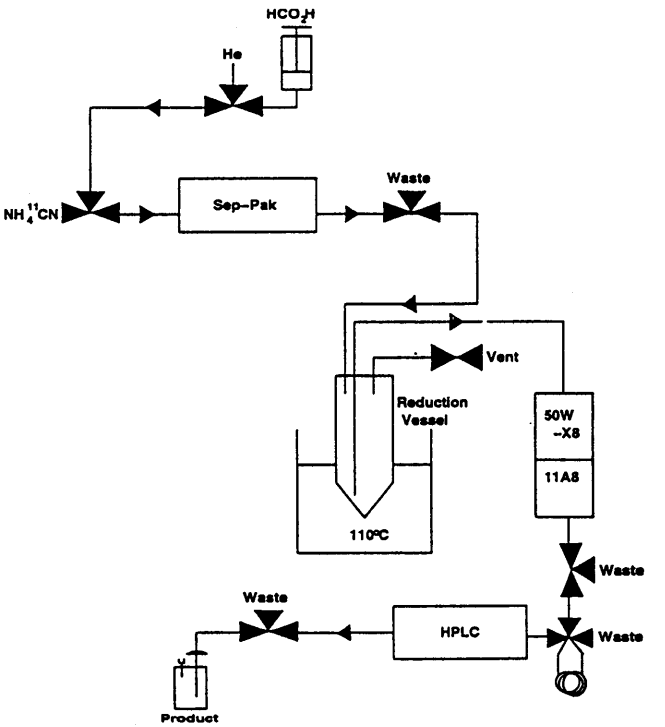

Fig. 3: Experimental set-up for the production of D-[1-^{11}C]glucose

was passed directly from the $NH_4{}^{11}CN$ process system over the Sep-Pak™. After the end of the $NH_4{}^{11}CN$ delivery (7 min after EOB) the radioactivity was eluted using 2.5 ml of 30 % HCO_2H directly into a reduction vessel containing ca. 0.5 g of Raney nickel slurry. After heating for 7 min at 110°C an overpressure of He gas was applied to transfer the solution through a column filled with 0.8 g BIO-RAD AG® 50W-X8 (100 – 200 mesh) cation exchange resin, 1.5 g BIO-RAD AG® 11A8 (50 – 100 mesh) ion retardation resin and a vented Millipore filter directly into a 2 ml HPLC loop [29]. After injection onto the column the [1-^{11}C]-D-glucose fraction was collected and the total volume adjusted to 10 ml, using isotonic saline.

On-line reduction experiments using complex hydrides

In order to simplify the synthesis and shorten the overall synthesis time, attempts were made to perform the reduction of the intermediate ^{11}C labelled aldonitriles directly on the Sep-Pak™ used for the reaction of $NH_4{}^{11}CN$ with arabinose. After trapping of the $NH_4{}^{11}CN$, the Sep-Pak™ was flushed with 5 ml of anhydrous tetrahydrofuran to remove traces of water. 1 ml of a solution of the complex hydride (lithium aluminiumhydride, sodium trimethoxyborohydride, $LiAl(N(C_2H_5)_2)_3H$ or $LiAl(N(C_4H_9)_2)_3H$; concentrations 0.01, 0.05, 0.75 and 1 mmol respectively) in tetrahydrofuran was subsequently passed over the Sep-Pak™ at room temperature with a flow rate of 1 ml/min. In the case of sodium borohydride as reducing reagent, 1 ml of a solution of 0.130 mmol (5 mg) sodium borohydride in ethanol was passed over the Sep-Pak™ at a flow rate of 1 ml/min directly after end of trapping of the $NH_4{}^{11}CN$ at room temperature. The radioactivity was eluted from the Sep-Pak™ using 5 ml of 0.1 M acetic acid and the eluent analysed by HPLC.

On-line reduction experiments using Raney nickel/HCO_2H

In these experiments $NH_4{}^{11}CN$ was trapped on the Sep-Pak™ and the radioactivity eluted as described above. The formic acid eluent was passed directly with a flow rate of 1 ml/min over a column filled with ca. 0.5 g of Raney nickel heated to 150°C, followed by a column filled with 0.8

g BIO-RAD AG® 50W-X8 (100 – 200 mesh) cation exchange resin, 1.5 g BIO-RAD AG® 11A8 (50 – 100 mesh) ion retardation resin. The eluent was analysed by HPLC.

Results and discussion

D-[1-^{11}C]glucose

D-[1-^{11}C]glucose was produced using the solid phase-supported reaction of $NH_4{}^{11}CN$ with arabinose and reduction with Raney nickel/HCO_2H within 38 min after EOB and in acceptable radiochemical yields of 5 – 15% (2.5 – 8.5% non-corrected, based on $NH_4{}^{11}CN$). Compared with previously reported procedures [16,18] our method removes the need for a 5 min reaction time for the cyanation step, a pH adjustment and a rotary evaporation step prior to HPLC purification: The reaction parameters are summarised in Table 1. For a typical production 200 – 500 MBq (6 – 14 mCi) D-[1-^{11}C]glucose were obtained at EOS as a sterile and pyrogen free solution. The radiochemical purity of the isolated D-[1-^{11}C]glucose was greater than 95%. Levels of non-radioactive arabinose and D-[1-^{11}C]mannose were below detection limits. In 10 ml formulations of D-[1-^{11}C]glucose, the concentration of borate anions was typically between 0.4 and 0.6 mg/ml and of formate anions between 0.008 and 0.017 mg/ml. The concentration of nickel ions was less than 0.005 µg/ml and of lead ions between 0.0129 and 0.0139 µg/ml.

Reaction parameters:	solid phase synthesis	previous report [18]
Syntheses time:	38 min (EOB)	50 – 55 min
Trapping efficiency:	>99% on Sep-Pak™	>99% in buffer
Elution efficiency from Sep-Pak™:	>95%	------
Aldonitrile yield:	>90%	>95%
RCY of [1-^{11}C]glucose and [1-^{11}C]mannose after exchange resin work-up:	10 – 30%	approx. 20 – 30%
Yield of [1-^{11}C]glucose (non-corrected):	2.5 – 8.5%	1.5 – 3.5%
Yield of [1-^{11}C]glucose (decay-corrected):	5 – 15% (EOB)	10 – 20% (EOB)
Ratio glucose/mannose:	1.2 – 1.7	1.5 – 2.1
Radiochemical purity:	>95%	>95%

Table 1: Reaction parameters of the solid phase-supported synthesis compared with ref. 18.

$NH_4{}^{11}CN$ production

Up to 20 GBq (540 mCi) of $NH_4{}^{11}CN$ was produced after a 30 minute (40 μA) bombardment within 7 min after EOB. Interestingly the increase in the amount of D-[1-^{11}C]glucose was not linearly related to an increase in the starting radioactivity. This may be due to a dose dependent radiolysis of $NH_4{}^{11}CN$ as reported by Dence et al. [30].

Trapping efficiency of $NH_4{}^{11}CN$ on Sep-Paks™ and ^{11}C-aldonitrile formation

Trapping of $NH_4{}^{11}CN$ on the Alumina N Sep-Pak™ was almost quantitative (>98%). In addition to the Alumina Sep-Pak™, C-18 and Silica Sep-Paks™ were tested with respect to trapping efficiency for $NH_4{}^{11}CN$. The Alumina N Sep-Pak™ was chosen for the labelling experiments because of the slightly higher trapping efficiency for $NH_4{}^{11}CN$ (98 – 100%) compared to C-18 (86 – 92%) and Silica Sep-Paks™ (94 – 98%).

The reaction of ^{11}C cyanide with arabinose on the preconditioned Alumina N Sep-Pak™ gave labelled ^{11}C-aldonitriles in radiochemical yields higher than 90%. The formation of the ^{11}C-aldonitriles was instantaneous. After cessation of $NH_4{}^{11}CN$ trapping, 2.5 ml of 30% formic acid was sufficient to remove more than 95% of the trapped radioactivity from the Sep-Pak™. No further treatment or pH control of the ^{11}C-aldonitrile solution was necessary before proceeding to the reduction step. HPLC analysis of the reaction mixture eluted from the Sep-Pak™ is shown in Fig. 5.

Reduction of ^{11}C-aldonitriles to the corresponding ^{11}C- aldoses and purification

The best results for the reduction of the ^{11}C-aldonitriles were obtained using batch-wise Raney nickel reduction in formic acid at 110°C for 7 min. The glucose/mannose ratio was between 1.2 and 1.7. However, we observed large losses of radioactivity up to 50% on the ion-exchange resins during the precleaning procedure, particularly on the cation exchange resin. This is in accordance with previously reported results and indicates an insufficient reduction of the intermediate amides to the corresponding aldoses. Moreover, we observed high losses of radioactivity on the

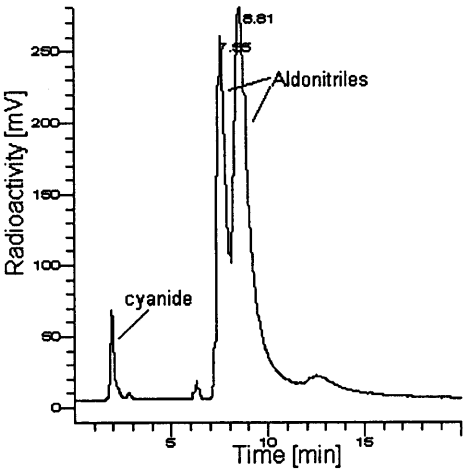

Fig. 5: HPLC analysis of the reaction mixture of the solid phase reaction of $^{11}CN^-$ with D-arabinose eluted from the Alumina N Sep-Pak™. (HPLC conditions: Zorbax NH2 (250 x 4.6 mm) column, CH_3CN : H_2O (90 : 10), 2 ml/min)

semipreparative HPLC column as previously observed. HPLC analysis of the reaction mixture after the ion exchange purification is shown in Fig. 6, the semipreparative separation in Fig.7 and a QC radiochromatogram in Fig.8.

The use of complex hydrides as reducing reagents did not result in an improvement. In the reduction step, lithium aluminium hydride and sodium trimethoxyborohydride resulted in either an over-reduction or a non-reduction depending on the hydride concentration. $LiAl(N(C_2H_5)_2)_3H$ and $LiAl(N(C_4H_9)_2)_3H$ are reported to be selective for the reduction of amides and nitriles to aldehydes [27]. However, even with a large molar excess of these reducing reagents, no reduction occurred. Only with sodium borohydride were we able to produce radiolabelled sugars in radiochemical yields of up to 10%. These results were, however, difficult to reproduce. Furthermore, the batch-wise Raney nickel/formic acid reduction method gave higher radiochemical yields.

Attempts to achieve an on-line reduction of the aldonitriles by passing the formic acid/aldonitrile eluent directly over a column filled with 0.5 g of Raney nickel at 150°C. did not result in an improvement due to uncontrollable pressure build ups and temperature fluctuations. However, we were able to produce radiolabelled sugars with this on-line method in radiochemical yields of about 2 – 3%.

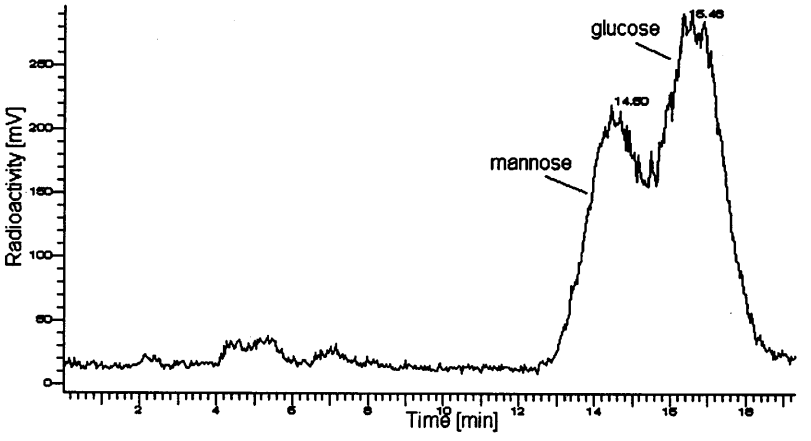

Fig. 6: HPLC analysis of the reaction mixture after ion-exchange purification (HPLC conditions: Zorbax NH2 (250 x 4.6 mm) column, CH_3CN : H_2O (90 : 10), 2 ml/min).

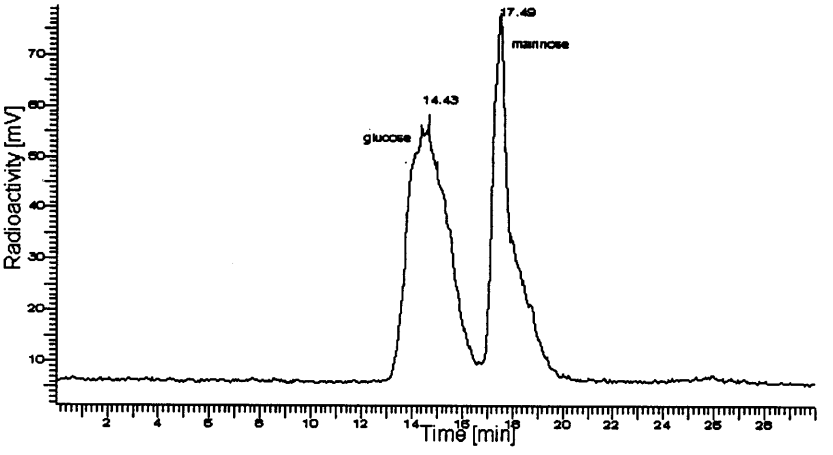

Fig. 7: Semipreparative separation of D-[1-^{11}C]glucose and D-[1-^{11}C]mannose (HPLC conditions: Phenomenex RPM monosaccharide column (300 x 7.8 mm), sterile water, flow rate 0.7 ml/min, column temperature 85°C).

Conclusions

The solid phase-supported synthesis simplifies the previously reported procedures [16,18] for the preparation of D-[1-^{11}C]glucose, as a pH control and rotary evaporation step before HPLC is avoided. Due to the instantaneous reaction of the cyanide with the arabinose/borate complex on the

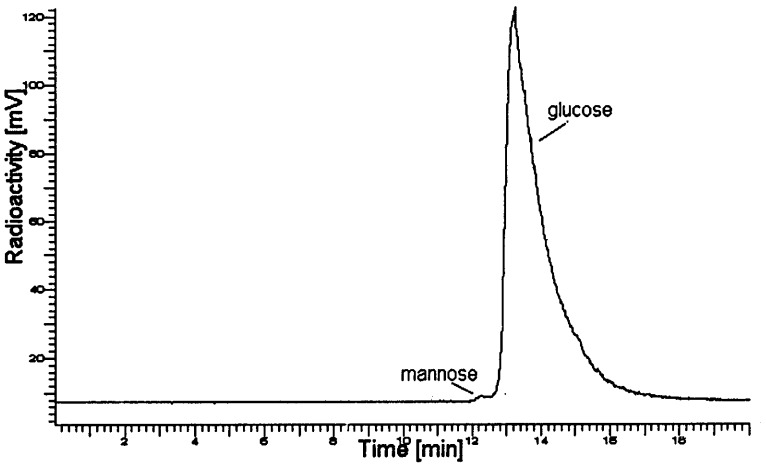

Fig. 8: QC radiochromatogram of the isolated D-[1-^{11}C]glucose fraction (HPLC conditions: Dionex Carbopac PA1 (250 x 4 mm) column, 0.25 M NaOH, flow rate 0.2 ml/min).

Al-N Sep-Pak™, this simplified synthesis procedure reduces the overall reaction time by 12 – 17 min. The yield-determining step of this synthesis is the reduction of the aldonitriles to the corresponding aldoses. Further improvements in the synthesis of D-[1-^{11}C]glucose may be obtained, if a more efficient reduction procedure can be implemented.

The solid-phase labelling technique may be generally applicable for rapid labelling reactions using ^{11}C cyanide.

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