Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **43**, 1289-1300 (2000)

A New Approach for the Synthesis of [^{11}C]-Labeled Fatty Acids

F. Wüst[1,2], C. S. Dence[1], T. J. McCarthy[1], M. J. Welch[1*]

[1]Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri 63110, USA. [2]Institut für Interdisziplinäre Isotopenforschung e.V., Permoserstraße 15, 04318 Leipzig, Germany.

SUMMARY

The synthesis of ω-[^{11}C], ω-1-[^{11}C] and ω-3-[^{11}C] palmitic acid employing a cross-coupling reaction between a functionalized copper-zinc reagent with [^{11}C]MeI, [1-^{11}C]EtI and [1-^{11}C]BuI is described. A *tert.*-butyl-protected ω-iodo fatty acid precursor $^{t}BuO_2C$-$(CH_2)_n$-I (n = 11, 13, 14) was converted into the corresponding dialkylzinc reagent [$^{t}BuO_2C$-$(CH_2)_n$]$_2$Zn which reacts with $Me_2CuI(MgCl)_2$ to give a highly reactive copper reagent [$^{t}BuO_2C$-$(CH_2)_n$]$_2$CuI$(MgCl)_2$·Me_2Zn as the labeling precursor. The cross-coupling reaction with [^{11}C]MeI, [1-^{11}C]EtI and [1-^{11}C]BuI provided the protected palmitic acid, specifically labeled with carbon-11 in several positions. The corresponding carbon-13 labeled compounds were synthesized to verify the labeling position. In a typical synthesis with [1-^{11}C]EtI starting with 250 mCi of [^{11}C]CO_2, 14 mCi (6% decay-corrected based on [^{11}C]CO_2) of ω-1-[^{11}C]palmitic acid was obtained within 30 minutes after EOB in 88% radiochemical purity prior to purification by HPLC. The general feature of this approach allows the convenient synthesis of palmitic acid specifically labeled in the ω, ω-1 or ω-3 positions by using several [^{11}C]-labeled alkyl iodides ([^{11}C]MeI, [1-^{11}C]EtI or [1-^{11}C]BuI) in the same cross-coupling protocol.

Key words: Carbon-11, [^{11}C]-labeled fatty acids, palmitic acid, cross-coupling, copper-zinc reagents, metabolism.

*Author for correspondence: Box 8225, 510 S. Kingshighway Blvd, St. Louis, MO 63110. (welchm@mir.wustl.edu).

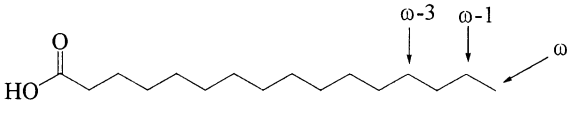
Received 18 July 2000
Revised 24 July 2000
Accepted 17 August 2000

INTRODUCTION

Under normal physiological conditions, fatty acid metabolism provides the major source of energy for the myocardium.[1] The fatty acid metabolism occurs in distinct stages and metabolism is governed by a process termed β-oxidation. In the β-oxidation step, the fatty acid is sequentially broken down into two carbon acetyl increments followed by further oxidation of the resulting AcSCoA subunits to CO_2 in the mitochondria in the tricarboxylic acid (TCA) cycle.[2] Each cycle of β-oxidation is enzymatically controlled by several different acetyl-CoA dehydrogenases and enolhydratases, which are specific for various fatty acid chain lengths. Genetic deficiencies in these enzymes result in an inability to metabolize fatty acids and cause an accumulation of toxic fatty acid metabolic intermediates, which have been identified as probable cause for sudden cardiac arrest.[3] Positron emission tomography (PET) represents an unique tool to monitor dynamic physiological processes by using short-lived positron emitting isotope like ^{11}C, ^{13}N, ^{15}O and ^{18}F. In addition, PET is thought to be an ideal approach for the evaluation and quantification of a myocardial metabolic enzyme deficiency.[1,4,5]

The required radiolabeled fatty acid as the imaging agent should ideally represent a long chain fatty acid like palmitic acid, which exhibits the same structural and biological properties like its parent compound. The incorporation of the positron-emitting isotope carbon-11 into a fatty acid would result in an isotopic substitution, which would neither interfere with the natural structure nor with the normal metabolism of a fatty acid. Furthermore, the half-life of 20.4 min of carbon-11 provides a convenient time-window for the assessment of the kinetics of metabolism. Therefore, carbon-11 is the ideal radiolabel for the design of palmitic acid as a PET imaging agent.

In terms of a comparison of the head-to-tail metabolism, the palmitic acid as an imaging agent for PET should ideally be labeled in either an odd or even position of the carbon chain. The variation of the radiolabel from the 16-(ω) to the 15-(ω-1) or 13-(ω-3)



Carbon-11 labeled palmitic acid **1**

position will result in differences in the retention of radioactivity due to different elimination rates of the CO_2 formed by the TCA cycle.[2]

Since the label is to be incorporated at various positions in the palmitic acid hydrocarbon tail, it is reasonable to use assorted length [1-^{11}C]alkyl iodides to introduce the carbon-11 label. The saturated nature of the fatty acid alkyl chain and the [1-^{11}C]alkyl iodides make a cross-coupling approach between the two Csp^3 centers a promising route for such a ^{11}C-C bond formation.

Several approaches for the synthesis of ω-[^{11}C]-palmitic acid have previously been developed. These methods involve the incorporation of [^{11}C]MeI employing Grignard reactions[6], Pd-catalyzed Suzuki cross-coupling[7], sulfone dianion approach[7] or organocopper chemistry.[8] However, none of these methods have proved to be a reliable and general approach for the synthesis of specifically carbon-11 labeled palmitic acid using longer chain [1-^{11}C]alkyl iodides like [1-^{11}C]EtI and [1-^{11}C]BuI.

Recently, the cross-coupling between functionalized alkylcopper reagents and functionalized alkyl halides has been reported.[9] Several functionalized dialkylzincs $(FG^1R^1)_2Zn$ undergo cross-coupling reactions with several alkyl iodides FG^2R^2I in good to excellent yields when treated with $Me_2Cu(CN)(MgCl)_2$. Furthermore, this procedure allows the presence of many functionalities, such as ester or cyano groups (Scheme 1).

$$(FG^1R^1)_2Zn \xrightarrow[FG^2R^2I]{Me_2Cu(CN)(MgCl)_2} FG^1R^1\text{-}R^2FG^2$$

FG = ester, cyano groups
R = alkyl chain

Scheme 1. Cross-coupling of functionalized dialkylzincs

For a cross-coupling reaction of [^{11}C]MeI, [1-^{11}C]EtI or [1-^{11}C]BuI to give specifically [^{11}C]-labeled palmitic acid, a C_{15}-, C_{14}- or C_{12}-fatty acid precursor is the logical choice as the coupling partner. Due to the known tendency of alkyl iodides to form readily organometallic compounds with zinc and copper as well as the facile cleavage of *tert*-butyl esters, we have synthesized several ω-iodo-*tert*-butyl-alkanoates **2**, **3** and **4** as appropriate starting materials (Scheme 2).

In this paper we report on a novel approach for a ^{11}C-C bond formation that we have investigated for the synthesis of carbon-11 labeled palmitic acid by means of several [1-^{11}C]alkyl iodides.

RESULTS & DISCUSSION

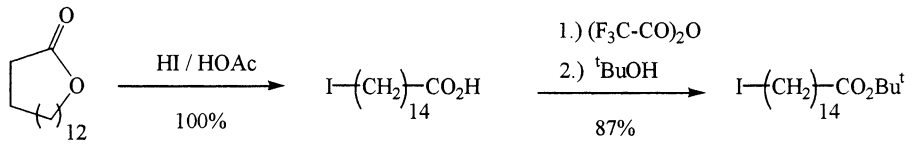
The synthesis of 15-iodo-*tert*-butyl-pentadecanoate **2** was easily accomplished by the treatment of commercially available ω-pentadecalactone **5** with HI in acetic acid. The resulting 15-iodo-pentadecanoic acid **6** was converted into the corresponding *tert*-butyl ester employing a mixed-anhydride method using trifluoroacetic anhydride and *tert*-BuOH.[10] The overall yield for the 2 steps was 87%.

For the synthesis of 14-iodo-*tert*-butyl-tetradecanoate **3**, 1,12-dibromododecane **7** was converted into the corresponding diiodo compound **8** by a Finkelstein reaction, followed by a malonic ester synthesis to give the ω-iodo alkylated malonic ester **9** in 63% yield for the 2 steps. Ester hydrolysis and decarboxylation of **9** with HI in acetic acid gave 14-iodo-tetradecanoic acid **10** in 65% yield. Employing the mixed-anhydride method, carboxylic acid **10** was converted into the desired *tert*-butyl ester **3** in 70% yield. The formation of *tert*-butyl ester **12** by the same mixed-anhydride procedure with commercially available 12-bromo-dodecanoic acid **11** and a subsequent Finkelstein reaction afforded 12-iodo-*tert*-butyl-dodecanoate **4** in 73% overall yield.

The first step in the radiosynthesis of ^{11}C-labeled palmitic acids [ω]-**1**, [ω-1]-**1** and [ω-3]-**1** involves the formation of functionalized dialkyl reagents **13-15** via an iodine-zinc exchange reaction with ω-iodo-*tert*-butyl alkanoates **2-4** and diethyl zinc (Scheme 3).[7,11] The treatment of dialkylzincs **13**, **14** and **15** with 1 equivalent of $Me_2CuI(MgCl)_2$ resulted in the formation of $[^tBuO_2C\text{-}(CH_2)_n\text{-}]_2CuI(MgCl)_2{\cdot}Me_2Zn$ (n = 11, 13, 14) as the labeling precursor. This highly reactive copper-zinc reagent undergoes a cross-coupling reaction with [^{11}C]-labeled alkyl iodides[12] in the presence of the polar solvent dimethylpropyleneurea (DMPU).

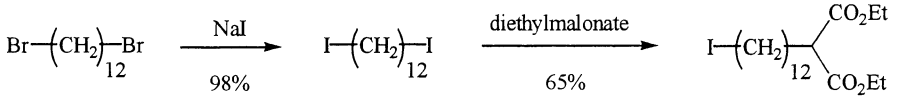
Interestingly, the use of $Me_2CuI(MgCl)_2$ for the formation of the reactive copper-zinc species seems to be essential. If $Me_2Cu(CN)(MgCl)_2$ or $Me_2CuI(MgBr)_2$ are used instead of $Me_2CuI(MgCl)_2$ only the cross-coupling reaction with [^{11}C]MeI is successful.

Synthesis of 15-iodo-*tert.*-butyl-pentadecanoate **2**

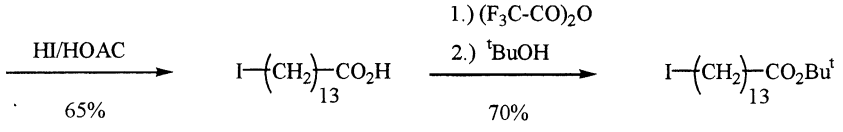


5 **6** **2**

Synthesis of 14-iodo-*tert.*-butyl-tetradecanoate **3**

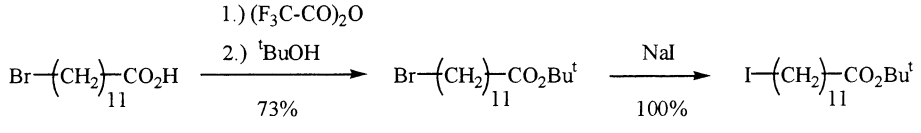


7 **8** **9**



10 **3**

Synthesis of 12-iodo-*tert.*-butyl-dodecanoate **4**



11 **12** **4**

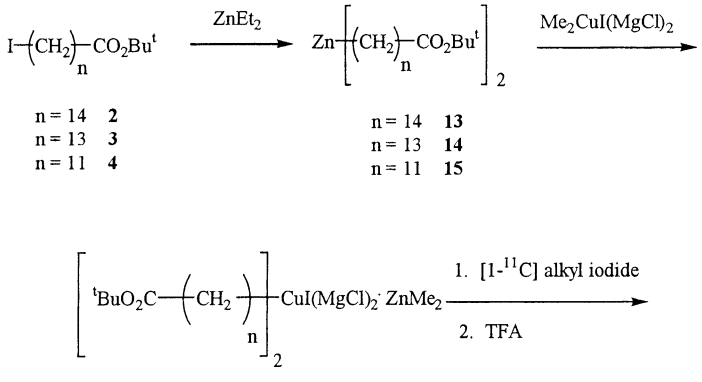
Scheme 2. Synthesis of ω-iodo-*tert.*-butyl-alkanoates **2**, **3** and **4**

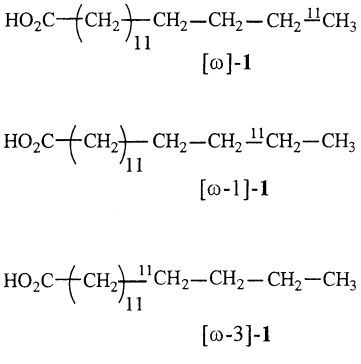
After the cleavage of the *tert*-butyl ester with trifluoroacetic acid (TFA), the corresponding [^{11}C]-labeled palmitic acids [ω]-**1**, [ω-1]-**1** and [ω-3]-**1** were isolated by SPE purification and analyzed by analytical HPLC (t_R palmitic acid = 5.1 min).

Table 1 summarizes the average radiochemical yields (decay-corrected, based on trapped [^{11}C]CO_2, number of runs in parentheses) and the obtained radiochemical purities. The total synthesis time was 25-35 minutes from the end of radionuclide production.

The identity of the carbon-11 labeled palmitic acids [ω]-**1**, [ω-1]-**1** and [ω-3]-**1** was confirmed by comparison of the retention times with a standard unlabeled palmitic acid via coinjection on an analytical HPLC column.

Furthermore, synthesizing and analyzing the corresponding carbon-13 labeled palmitic acids by ^{13}C-NMR confirmed the position of the carbon-11 label. The carbon-13 labeled palmitic acids were synthesized employing the same protocol described for the carbon-11 labeled compounds by simultaneous addition of [^{13}C]MeI and [1-^{13}C]EtI, respectively. The carbon-13 signals at 13.99 ppm and 22.58 ppm correspond with the chemical shift of the ω- and ω-1 carbon atom in authentic palmitic acid.





[ω]-**1**

[ω-1]-**1**

[ω-3]-**1**

Scheme 3. Radiosynthesis of [^{11}C]-labeled palmitic acids [ω]-**1**, [ω-1]-**1** and [ω-3]-**1**

Compound	Radiochemical yield	Radiochemical purity
[ω]-**1**	16% (n=2)	98%
[ω-1]-**1**	6% (n=4)	88%
[ω-3]-**1**	10% (n=3)	90%

Table 1. Radiochemical yields and purities of ^{11}C-labeled palmitic acid **1**

The highest radiochemical purity (98%) and yield (16%, decay-corrected for [^{11}C]CO_2) for the cross-coupling reaction were achieved with [^{11}C]MeI, due to its higher reactivity and simpler synthesis. The use of [1-^{11}C]EtI and [1-^{11}C]BuI decreases the yield of [ω-1]-**1** and [ω-3]-**1** to 6% and 10%, respectively. In addition, the radiochemical purities for [ω-1]-**1** and [ω-3]-**1** are also diminished (88-90%) by using [1-^{11}C]BuI and [1-^{11}C]EtI as the coupling partner. The main impurity in the synthesis of [ω-1]-**1** was a C_{15}-fatty acid (10%, t_R = 4.3 min) which was formed by the reaction of **14** with contaminant [^{11}C]MeI present in the used [1-^{11}C]EtI. The preparation of [ω-3]-**1** required the use of [1-^{11}C]BuI. In this case we found a 10% impurity corresponding to the [^{11}C]MeI-coupling product (C_{13}-fatty acid, t_R = 2.8 min). Both mixtures were analyzed by reversed phase HPLC using and analytical C-8 column (see experimental for details). The resolution function, R_s, between C-15 and C-16 fatty acids was calculated to be 1.22.

CONCLUSIONS

We have described a novel approach for the synthesis of [^{11}C]-fatty acids specifically labeled in the ω, ω-1 or ω-3 positions, employing highly reactive copper-zinc reagents. The general feature of this approach allows the convenient synthesis of ^{11}C-labeled fatty acids by using several [^{11}C]-labeled alkyl iodides ([^{11}C]MeI, [1-^{11}C]EtI or [1-^{11}C]BuI) in the same cross-coupling protocol. Furthermore, we have shown a novel route for a ^{11}C-C bond formation which expands the scope of carbon-11 labeled compounds.

EXPERIMENTAL

General

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Gemini-300 spectrometer (Varian Associates, Palo Alto, CA) at 300 MHz and 75 MHz, respectively, with $CDCl_3$ as the internal standard. High resolution fast atom bombardment (FAB) spectra were performed by the Washington University Mass Spectroscopy Resource. Elemental analyses were performed by Galbraith Laboratories (Knoxville, TN). Flash chromatography was performed as described by Still and co-workers[13] using silica gel (0.040-0.063 mm, EM Science). All solvents and reagents were purchased from Sigma-Aldrich or Fluka. The dialkylzincs **13**, **14** or **15** were synthesized according to Knochel and co-workers[11] by the reaction of an excess of $ZnEt_2$ with ω-iodo-*tert.*-butyl-alkanoates **2**, **3** or **4**.

Chemical syntheses

15-Iodo-pentadecanoic acid 6. 5g (20.8 mmol) of lactone **5** was refluxed in 20 ml HI (57%) and 40 ml HOAc for 3 h. Afterwards, the mixture was cooled to room temperature when it solidified. The brown solid was dissolved in CH_2Cl_2, and the solution was washed with 10% $Na_2S_2O_3$ solution. The organic layer was separated and flushed through a short silica gel plug. After removal of the solvent, the residue was purified by flash chromatography (1. 20% EtOAc-n-hexane; 2. CH_2Cl_2) to give 7.8 g (100%) of **6** as white crystals. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.24 (m, 18H), 1.34 (m, 2H), 1.61 (quint., 2H, J = 7.2 Hz) 1.80 (quint. 2H, J = 7.2 Hz), 2.33 (t, 2H, J = 7.4 Hz), 3.17 (t, 2H, J = 7.1 Hz). Anal. Calcd. for $C_{15}H_{29}IO_2$: C, 48.92; H, 7.94. Found: C, 49.04; H, 8.08.

15-Iodo-*tert.*-butyl-pentadecanoate 2. 1 g (2.7 mmol) of 15-iodo-pentadecanoic acid **6** in 10 ml of dry THF was cooled to 0°C and 850 µl (6 mmol) of trifluoroacetic anhydride was slowly added. After 30 minutes, 5 ml of *tert.*-BuOH was added all at once and the mixture was stirred at room temperature for 2 h. The reaction was quenched with 50 ml of saturated $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 extract was flushed through a short silica-gel plug and the solvent was evaporated under reduced pressure to give 1 g (87%) of **2** as a clear oil which solidified on cooling.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.24 (bs, 18 H), 1.36 (m, 2H), 1.42 (s, 9H), 1.55 (m, 2H), 1.80 (quint. 2H , J = 7.2 Hz), 2.18 (t, 1H, J = 7.4 Hz), 3.17, (t, 2H, J = 7.1 Hz). Anal. Calcd. for $C_{19}H_{37}IO_2$: C, 53.77; H, 8.79. Found: C, 53.98; H, 8.97.

1,12-Diiododododecane 8. 9.14 g (61 mmol) of NaI was dissolved in a minimum amount of acetone. 5 g (15.2 mmol) of 1,12-dibromododecane was added all at once and the mixture was stirred at room temperature overnight. 100 ml of 10% $Na_2S_2O_3$ solution was added and the aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 extract was flushed through a SiO_2 plug and the solvent was evaporated under reduced pressure to give 6.3 g (98%) of **8** as a colorless solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.26 (bs, 12H), 1.37 (m, 4H), 1.81 (quint. 4H, J = 7.1 Hz), 3.17 (t, 4H, J = 7.0 Hz). Anal. Calcd. for $C_{12}H_4I_2$: C, 34.14; H, 5.75. Found: C, 35.00; H, 5.97.

12-Iodo-dodecylmalonic acid diethyl ester 9. 322 mg (14 mmol) of sodium was dissolved in 25 ml of EtOH. 2.25 g (14 mmol) of diethyl malonate was added and the mixture was stirred for 30 minutes at room temperature. 5.9 g (14 mmol) of diiodide **8** was dissolved in 50 ml EtOH and the sodium ester enolate was slowly added at 40-50°C. After stirring for 3 h the EtOH was evaporated under reduced pressure, and the oily residue was purified by flash chromatography (5% EtOAc-hexane) to yield 2.7 g of the starting material and 2.3 g (65% corrected) of product **9** as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.25 (bs, 16 H), 1.26 (t, 2H, J = 7.1 Hz), 1.29 (m, 2H), 1.81 (quint. 2H , J = 7.4 Hz), 1.83 (m, 2H), 3.18, (t, 2H, J = 7.1 Hz), 3.30 (t, 1H, J = 7.5 Hz), 4.18 (q, 4H, J = 7.1 Hz). HRMS (FAB, 3-NBA) Calcd. for $C_{19}H_{36}IO_4$ [M+H]: 455.1658; Found: 455.1639.

14-Iodo-tetradecanoic acid 10. 3 g (6.6 mmol) of malonic ester **9** was refluxed with 15 ml of HI (57%) and 30 ml acetic acid for 3 h. The mixture was cooled to room temperature and 200 ml of water was added. The mixture was extracted with CH_2Cl_2, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (20% EtOAc-hexane) to give 1.5 g (65%) of **10** as a solid. ^{1}H-NMR

(300 MHz, $CDCl_3$) δ 1.26 (bs, 16 H), 1.35 (m, 2H), 1.63 (quint. 2H , J = 7.2 Hz), 1.82 (quint. 2H , J = 7.4 Hz), 2.35 (t, 1H, J = 7.4 Hz), 3.18 (t, 2H, J = 7.1 Hz). Anal. Calcd. for $C_{14}H_{27}IO_2$: C, 47.46; H, 7.68. Found: C, 47.41; H, 7.82.

14-Iodo-*tert.*-butyl-tetradecanoate 3. 750 mg (2.1 mmol) of 14-iodo-tetradecanoic acid **10** in 25 ml of dry THF was cooled to 0°C and 966 mg (4.6 mmol) of trifluoroacetic anhydride was slowly added. After 30 minutes, 4 ml of *tert.*-BuOH was added all at once and the mixture was stirred at room temperature for 2 h. .The reaction was quenched with 100 ml of saturated $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. After evaporation of the solvent the residue was purified by flash chromatography (5% EtOAc-hexane) to give 600 mg (70%) of **2** as an oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.26 (bs, 16 H), 1.39 (m, 2H), 1.44 (s, 9H), 1.55 (m, 2H), 1.81 (quint. 2H , J = 7.1 Hz), 2.19 (t, 1H, J = 7.4 Hz), 3.14 (t, 2H, J = 7.0 Hz); HRMS (FAB, 3-NBA) Calcd. for $C_{18}H_{36}IO_2$ [M+H]: 411.1760; Found: 411.1781.

12-Bromo-*tert.*-butyl-dodecanoate 12. To 12-bromododecanoic acid **11** (4.5 g, 16.1 mmol) in 50 ml of THF was slowly added trifluoroacetic anhydride (5 ml, 35.5 mmol) at 0°C. After 0.5 h *tert.*-BuOH (20 ml) was added, and the solution was stirred for 2 h at room temperature. Then, the mixture was poured into 250 ml of saturated $NaHCO_3$ solution and was extracted with CH_2Cl_2. The extract was flushed through a short silica gel plug, the solvent was removed, and the residue was purified by flash chromatography (10% EtOAc-hexane) to give 3.92 g (73%) of **12** as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.20-1.28 (m, 22H), 1.40 (m, 2H), 1.80-1.87 (m, 4H), 3.29 (t, 1H, J = 8.3 Hz), 3.39 (t, 2H, J = 7.6 Hz), 4.17 (q, 4H, J = 8.0 Hz). HRMS (FAB, 3-NBA) Calcd. for $C_{16}H_{32}BrO_2$ [M+H]: 335.1585; Found: 335.1581.

12-Iodo-*tert.*-butyl-dodecanoate 4. NaI (1.8 g, 12 mmol) was dissolved in a minimum amount of acetone. The solution was added all at once to 12-bromo-*tert.*-butyl-dodecanoate **12** (1 g, 3 mmol) and the mixture was stirred overnight at room temperature. Then, 50 ml of a 5% $Na_2S_2O_3$-solution was added and the mixture was extracted with CH_2Cl_2. The extract was flushed through a short silica gel plug. The solvent was removed

to afford 1.15 g (100%) of **4** as a pale yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.26 (m, 16H), 1.39 (m, 2H), 1.44 (s, 9H), 1.55 (m, 2H), 1.81 (quint., 2H, J = 7.1 Hz), 2.19 (t, 2H, J = 7.4 Hz), 3.14 (t, 2H, J = 7.0 Hz). HRMS (FAB, 3-NBA) Calcd. for $C_{16}H_{32}IO_2$ [M+H]: 383.1447; Found: 383.1449.

Radiochemical syntheses

A remote gantry system[14] was used to prepare the [^{11}C]-alkyl iodides and [^{11}C]palmitic acids [ω]-**1**, [ω-1]-**1** and [ω-3]-**1**. [^{11}C]CO_2 was produced by the ^{14}N(p,α)^{11}C reaction and trapped under vacuum in a copper coil cooled with liquid nitrogen. HPLC (Phenomenex Luna, 5μm, C_8, 150 mm x 4.6 mm; CH_3CN/THF/HOAc 87/3/0.1, 2 ml/min) for the radiochemical experiments was performed on a chromatograph equipped with a refractive index detector and a NaI(Tl) radioactivity detector. [^{11}C]MeI was synthesized according to Crouzel and co-workers.[15] [1-^{11}C]EtI and [1-^{11}C]BuI were synthesized according to Långström and co-workers,[12] but replacing THF as the solvent with diethyl ether.

Carbon-11 labeled palmitic acids [ω]-1, [ω-1]-1 and [ω-3]-1 Ten minutes before the end of radionuclide production, 100 μl (50 μmol, 0.5 mM solution in THF) of the dialkylzincs **13**, **14** or **15** and 100 μl (50 μmol, 0.5 mM solution in THF) of $Me_2CuI(MgCl)_2$ were combined in a 5 ml reaction vessel at approx. –50°C. After 5 minutes, the mixture was cooled to –78°C and 100 μl of DMPU was added. The synthesis of the [^{11}C]-alkyl iodides was started. The cooling-bath (acetone/dry-ice) was removed, and the [^{11}C]-alkyl iodides were transferred in a stream of nitrogen into the reaction vessel. After the completion of the transfer (10-15 minutes) the reaction vessel was heated for 1 minute at 130°C. Then, 1 ml of TFA was added and the mixture was heated for 5 minutes at 130°C. The reaction mixture was removed from the gantry, diluted to a volume of 10 ml with H_2O and applied to a solid-phase extraction (SPE, C8, 300 mg). The SPE column was eluted with 2.4 ml of acetonitrile and the eluate was analyzed by HPLC (Phenomenex Luna, 5μm, C_8, 150 mm x 4.6 mm; CH_3CN/THF/HOAc 87/3/0.1, 2 ml/min, t_R [^{11}C]palmitic acid 5.1 min).

ACKNOWLEDGMENTS

We thank the National Institute of Health (HL13851) for generous financial support. We wish to thank Bill Margenau and Dave Ficke for radioisotope production and Keith Lechner for analytical assistance. Mass spectrometry was provided by the Washington University Mass Spectrometry Resource with support from the NIH National Center for Research Resources (Grant No. P41RR0954).

REFERENCES

(1) Bergmann, S.R. *et al. J. Nucl. Med.*, **37:** 1723 (1996)

(2) Stryer, L., Ed. *Biochemistry,* W. H. Freeman & Co. New York, 1995; (606-612)

(3) Van Hove, J.L. *et al. Am. J. Hum. Genet.* **52:** 958 (1993)

(4) Schwaiger, M. *et al. J. Nucl. Med.* **32:** 565 (1991)

(5) Saha, G. B. *et al. Nucl. Med. Biol.* **19:** 1 (1992)

(6) Buckman, B. O. *et al. J. Med. Chem.* **37:** 2481-2485 (1994)

(7) Hostetler, E. D. *et al. J. Org. Chem.* **63:** 1348-1351 (1998)

(8) Neu, H. *et al. J. Labelled Cpd. Radiopharm.* **39:** 509 (1997)

(9) Tucker, C. E *et al. J. Org. Chem.* **58:** 4781 (1993)

(10) Morin, C. *et al. Tetrahedron.* **48:** 9277 (1992).

(11) Rozema, M. J. *et al. J. Org. Chem.* **57:** 1956 (1992)

(12) Långström, B. *et al. Appl. Radiat. Isot.* **37:** 1141 (1986)

(13) Still, W. C. *et al. J. Org. Chem.* **43:** 2923 (1978)

(14) Dence, C.S. *et al. J. Labelled Cpd. Radiopharm.* **33:** 174 (1993)

(15) Crouzel, C. *et al. Appl. Radiat. Isot.* **38:** 601 (1987)

