^{18}F-Labeled Octanoates as Potential Agents for Cerebral Fatty Acid Studies. The Influence of 4-Substitution and the Fluorine Position on Biodistribution

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In order to understand the structural features that might lead to an *in vivo* radiotracer for studying cerebral fatty acid metabolism, 8-[^{18}F]fluorooctanoate derivatives with methyl or *gem*-dimethyl branching at the C4 position have been prepared. 3-[^{18}F]Fluoro- and 4-[^{18}F]fluorooctanoic acid have also been synthesized for studying the influence of the fluorine position on the *in vivo* behavior of ^{18}F-labeled octanoic acid analogs. Radiochemical synthesis was achieved by the nucleophilic displacement of a tosylate or mesylate precursor with [^{18}F]fluoride ion. Tissue distribution studies in rats showed low cerebral uptakes of these ^{18}F-labeled fatty acid analogs with poor brain-to-blood ratios. 3-[^{18}F]Fluorooctanoic acid showed considerable defluorination, evident as a high bone activity level. The initial uptake of activity in the brain after injection of ethyl 8-[^{18}F]fluoro-4-methyloctanoate and 4-[^{18}F]-fluorooctanoic acid remained virtually unchanged over an extended time period, similar to that previously observed for the unbranched analogs, ethyl 8-[^{18}F]fluorooctanoate and its free acid. In contrast, the 4-*gem*-dimethyl branched analog was rapidly and preferentially taken up by the liver. It was shown in the metabolite analysis that labeled metabolites produced from 8-[^{18}F]fluoro-4-methyloctanoic acid were found in blood, and that they could enter the brain to a significant degree. Thus, the present studies showed that radioactivity retention in the brain in the case of the 4-methyl branched analog was mainly attributable to its radioactive metabolites.

Key words 8-[^{18}F]fluoro-4-methyloctanoic acid; tissue distribution; cerebral uptake; 3-[^{18}F]fluorooctanoic acid; 4-[^{18}F]fluorooctanoic acid; methyl 4,4-dimethyl-8-[^{18}F]fluorooctanoic acid

Octanoic acid, a saturated fatty acid with eight carbon atoms, can be taken up by the brain and is oxidatively metabolized by brain tissue.[1] Studies with [1-^{14}C]-octanoate in rats have shown that the first acetyl moiety is split from octanoate by β-oxidation in the brain and then is incorporated into pools of glutamate and glutamine, in addition to CO_2 production.[2] Thus, the potential use of [1-^{14}C]octanoate as a fast functional marker in the brain has been proposed by Rowley and Collins.[3] In another study, Edmond *et al.* found that CO_2 and the ketone bodies acetoacetate and D-(−)-3-hydroxybutyrate are produced when cultured astrocytes derived from rat brain are incubated with [1-^{14}C]- and [7-^{14}C]octanoate.[4] We are interested in investigating the feasibility of using octanoic acid analogs labeled with positron-emitting nuclides as tracers for studying cerebral fatty acid metabolism by positron emission tomography. A potential problem with the use of octanoic acid to study cerebral metabolism is that, because of straight-chain fatty acid catabolism by β-oxidation, radioactivity is released from the brain within a short time, as revealed by studies with [1-^{14}C]octanoate,[3] preventing precise imaging of the brain. Our research has been directed toward the development of fluorine-18-labeled octanoic acid analogs exhibiting reasonable uptake and retention of radioactivity in the brain in order to obtain optimal imaging.

One strategy to increase the myocardial residence time of radiolabeled long-chain fatty acids to allow sufficient time for cardiac imaging has been developed,[5,6] based on metabolic blocking by the introduction of methyl branching into a fatty acid. Following this chemical modification approach, we synthesized β-methyl and *gem*-dimethyl branched analogs of terminally ^{18}F-labeled octanoic acid and characterized their biodistribution in rats.[7] These β-branched analogs demonstrated, contrary to expectation, rapid loss of activity from the brain, with no indication of accumulation. On the other hand, unbranched 8-[^{18}F] fluorooctanoic acid and its ethyl ester exhibited prolonged retention of radioactivity in the brain but with relatively low brain uptake. It has also been shown by us that retention in the case of 8-[^{18}F]fluorooctanoic acid is mainly attributed to its radioactive metabolites, which enter the brain from the blood.

In the current study, we have investigated the influence of 4-methyl and 4-geminal dimethyl branching, and a fluorine substituent at the 3- or 4-position of the carbon chain of octanoic acid on brain uptake and retention in order to develop additional structure–*in vivo* behavior relationships for optimal imaging. Herein we describe the radiochemical synthesis, precursor synthesis and evaluation of its distribution properties of these agents in rats.

Results and Discussion

Chemistry We developed synthetic routes to fluorinated analogs of octanoic acid allowing the introduction of fluorine by fluoride ion displacement of a sulfonate ester late in the synthesis, for the ultimate synthesis of the ^{18}F-labeled forms. The first step was the synthesis of the hydroxy derivatives as immediate precursors.

Ethyl 8-hydroxy-4-methyloctanoate (**3**) was prepared by a similar sequence of reactions (Chart 1) to that which we have developed for the synthesis of the unbranched analog, starting from ε-caprolactone.[8] Treatment of ε-caprolactone with lithium diisopropylamide (LDA), followed by addition of CH_3I gave 2-methyl-ε-caprolactone (**1**) in modest yield. Reductive cleavage of the lactone, followed by condensation with the two-carbon fragment, and then reduction of the double bond gave the requisite

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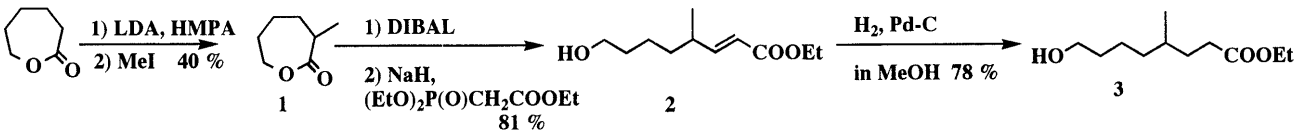
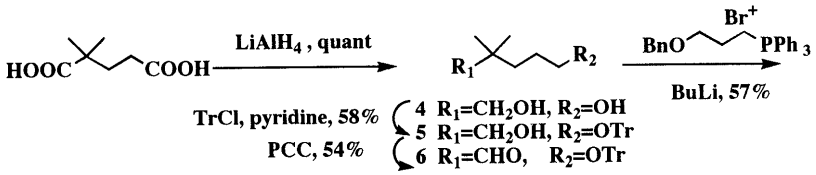


Chart 1



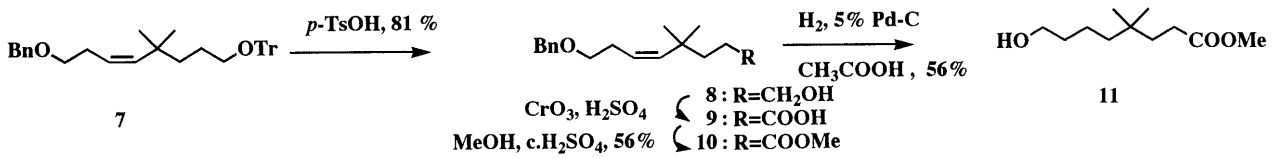


Chart 2

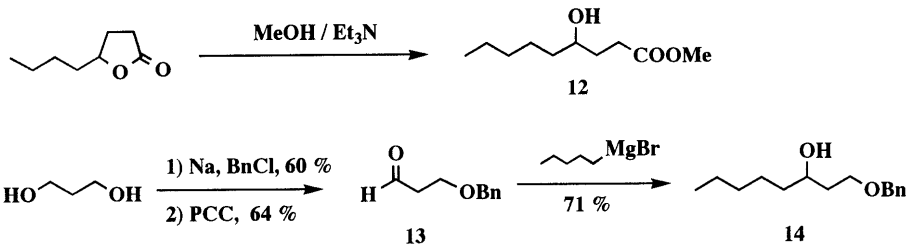


Chart 3

4-methyl-substituted hydroxy ester (**3**) in 26% overall yield from (**1**).

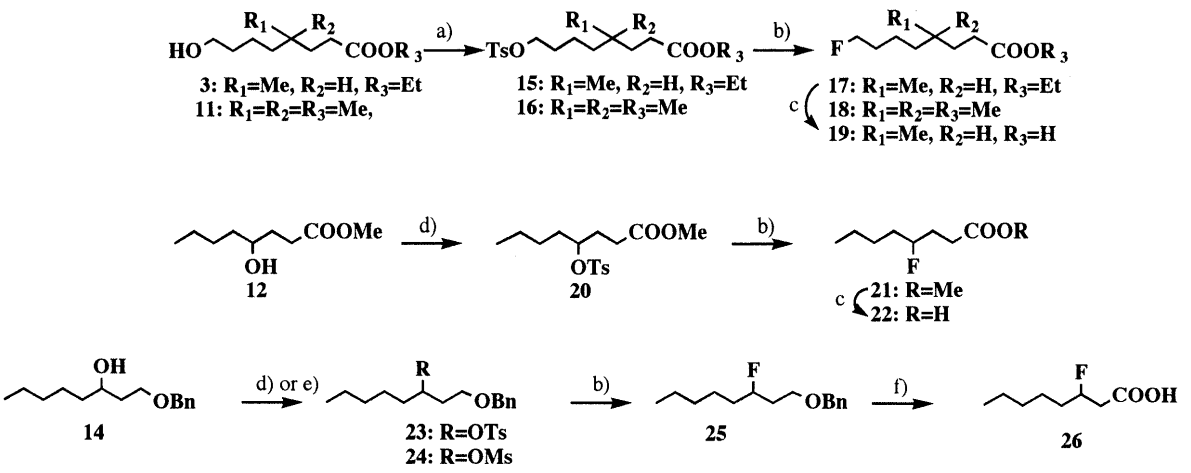
3,3-Dimethyl-5-oxo-1-trityloxypentane (**6**) served as a convenient synthon for the introduction of dimethyl branching. $LiAlH_4$ reduction of 3,3-dimethylglutaric acid gave the diol (**4**) from which **6** was obtained by selective monotritylation followed by oxidation with pyridinium chlorochromate (PCC) of the remaining alcohol. Chain extension using the Wittig reagent derived from 3-benzyloxypropyl triphenylphosphonium bromide and *n*-BuLi[9] gave the alkenyl dimethyl ester (**7**) with a small amount of the *E*-isomer. Deprotection of the trityl group with *p*-TsOH, followed by Jones oxidation and then esterification afforded the alkenyl dimethyl ester (**10**). Subsequent hydrogenation with Pd–C in CH_3COOH with concomitant debenzylation gave the desired hydroxy ester (**11**).

Methyl 4-hydroxyoctanoate (**12**) was synthesized in onestep by ring-opening of commercially available γ-octanoic lactone, and because of its instability, was converted immediately into the tosylate precursor (**20**). Various attempts to fluorinate the tosylate derived from the commercially available 3-hydroxyoctanoic acid for the preparation of 3-fluorooctanoic acid gave only the eliminated product, presumably as a result of facile abstraction of the α-proton to the carbonyl group by fluoride. Therefore, an alternative approach, allowing generation of the carbonyl group after formation of the carbon–fluorine bond, was sought. Thus, benzyloxy-3-octanol (**14**) was prepared as the precursor for the fluoride displacement reaction, starting from propanediol, *via* the Grignard reaction, as shown in Chart 3.

The alcohols thus obtained were converted to the corresponding fluorinated analogs (**17**, **18**, **21**, **25**) in good overall yields, as shown in Chart 4, by tosylation or mesylation followed by fluoride substitution using tetrabutylammonium fluoride. Subsequent hydrolysis of the ester groups gave the desired free acids (**19**, **22**) in almost quantitative yields. On the other hand, the conversion of the fluoro ester (**25**) into 3-fluorooctanoic acid (**26**) was achieved in one step by the use of concentrated HNO_3. The structures of all compounds described here were confirmed by spectral methods.

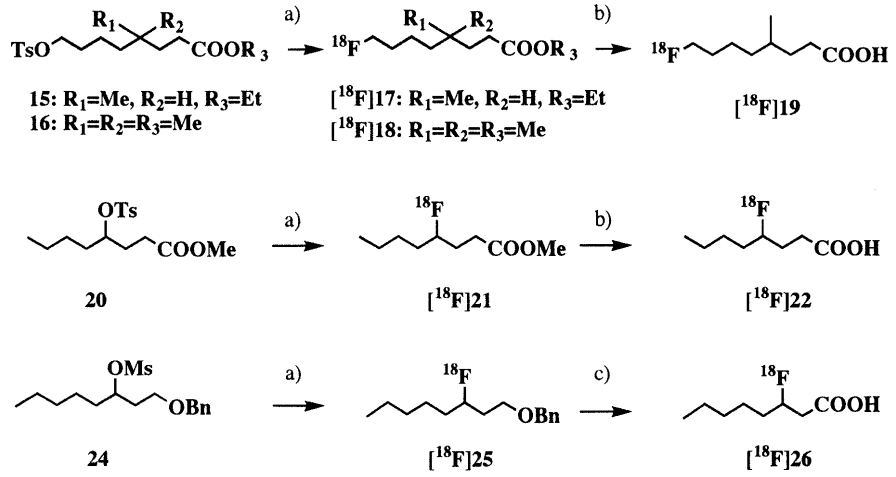
The five fluorinated octanoic acid analogs were labeled with fluorine-18 by the nucleophilic displacement of the tosylate or mesylate precursor with [^{18}F]fluoride ion, as outlined in Chart 5. The non carrier added (NCA) [^{18}F]fluoride activity obtained from the $^{18}O(p, n)^{18}F$ reaction[10] was converted to *n*-$Bu_4N^{18}F$ and $K^{18}F$/Kryptofix 2.2.2 as described earlier.[11,12]

In the preparation of the 8-[^{18}F]fluoro-4-methyl analog ([^{18}F]-**17**) and 8-[^{18}F]fluoro-4,4-dimethyl ester ([^{18}F]-**18**), the tosylate precursors (**15**, **16**) exhibited reasonable substitution behavior with *n*-$Bu_4N^{18}F$. The methyl ester ([^{18}F]-**17**) was further hydrolyzed with 5 N KOH to give the free acid ([^{18}F]-**19**). Synthesis of 4-[^{18}F]fluoro- and 3-[^{18}F]fluorooctanoic acid ([^{18}F]-**22**, [^{18}F]-**26**) proceeded in two steps. [^{18}F]Fluoride displacement of the precursors (**20**, **24**) using $K^{+18}F$/Kryptofix 2.2.2 was followed by hydrolysis with 5 N KOH at room temperature



a) TsCl, pyridine; b) *n*-Bu_4NF, THF; c) 5 N KOH, d) TsCl, DMAP, CH_2Cl_2; e) MsCl, TEA, Et_2O; f) c.HNO_3

Chart 4



a) *n*-$Bu_4N^{18}F$, CH_3CN; b) 5N KOH; c) c.HNO_3

Chart 5

for 30 min, or by oxidation with concentrated HNO_3 at 80 °C for 15 min to the free acid ([^{18}F]-**22**, [^{18}F]-**26**) respectively. This sequence afforded only 4—6% incorporation of the radiolabel in both cases. This was due to the initial [^{18}F]fluorination step. However, alterations in reaction conditions and the use of *n*-$Bu_4N^{18}F$ did not raise the yield. All of the final products were purified by reversed-phase HPLC through the usual Sep-pak procedure. Total time required for synthesis, including HPLC purification, was 60—165 min. Isolated radiochemical yields (not corrected for decay) at the end of synthesis (EOS) were 13—40% for the [^{18}F]fluoro esters ([^{18}F]-**17**, [^{18}F]-**18**) and 5—30% for the free acids ([^{18}F]-**19**, [^{18}F]-**22**, [^{18}F]-**26**) (Table 1). All ^{18}F-labeled compounds obtained in this time were radiochemically pure after the HPLC purification (>99%). The specific activity was not determined but might be around 3700 GBq/mmol at EOS, judging from recent syntheses of other ^{18}F-labeled compounds in our laboratory.

Table 1. [^{18}F]Fluorooctanoic Acid Analogs Synthesis by Nucleophilic Displacement of Tosylate or Mesylate and [^{18}F]Fluoride Ion

Labeled compound	Radiochemical yield[d] (%)	Synthetic time[e] (min)
Ethyl 8-[^{18}F]fluoro-4-methyloctanoate ([^{18}F]-**17**)[a]	39—41	60
8-[^{18}F]Fluoro-4-methyloctanic acid ([^{18}F]-**19**)[a]	26—30	120
Methyl 8-[^{18}F]fluoro-4,4-dimethyloctanoate ([^{18}F]-**18**)[b]	13—25	60
4-[^{18}F]Fluorooctanoic acid ([^{18}F]-**22**)[b]	4—6	110
3-[^{18}F]Fluorooctanoic acid ([^{18}F]-**26**)[c]	4—5	165

a) The corresponding tosylate was reacted with *n*-$Bu_4N^{18}F$ in CH_3CN at 80 °C for 15 min. *b*) The corresponding tosylate was reacted with K ^{18}F/Kryptofix 2.2.2 in CH_3CN at 80 °C for 15 min. *c*) The corresponding mesylate was reacted with K ^{18}F/Kryptofix 2.2.2 in CH_3CN at 110 °C for 20 min. *d*) Radiochemical yields refer to those after separation by HPLC. Not corrected for decay. *e*) Including HPLC purification. *f*) Including hydrolysis with KOH in MeOH to give the free acid. *g*) Including oxidation with concentrated HNO_3 to give the acid.

Biodistribution Studies The tissue distribution of the five [^{18}F]fluorinated analogs of octanoic acid in Wistar male rats under starvation at various times after intravenous injection is shown in Table 2. Figure 1 shows the brain uptakes as a function of time after the injection of the labeled compounds. Radioactivity was substantially retained in the brain after injection of ethyl 8-[^{18}F]fluoro-4-methyloctanoate ([^{18}F]-**17**) and 4-[^{18}F]fluorooctanoic acid ([^{18}F]-**22**) throughout the observation period,

Table 2. Tissue Distribution in Rats Following i.v. Administration of the [^{18}F]Fluorinated Analogs of Octanoic Acid Derivatives

	Time (min)	Uptake (% dose/g)[a]					
		Brain[b]	Blood	Liver	Kidney	Heart	Bone
Ethyl 8-[^{18}F]fluoro-4-methyl octanoate ([^{18}F]**18**)	10	0.28±0.05	0.87±0.10	1.49±0.15	2.67±0.11	0.79±0.11	0.69±0.14
	30	0.24±0.02	0.44±0.01	0.34±0.01	0.78±0.04	0.34±0.00	0.88±0.05
	60	0.36±0.06	0.45±0.04	0.32±0.04	0.57±0.02	0.36±0.06	1.79±0.20
	120	0.39±0.03	0.35±0.03	0.25±0.02	0.38±0.03	0.30±0.05	2.23±0.04
Methyl 8-[^{18}F]fluoro-4,4-dimethyl octanoate ([^{18}F]**18**)	5	0.06±0.03	0.53±0.18	7.17±1.19	0.87±0.04	0.26±0.09	0.04±0.02
	10	0.04±0.005	0.47±0.05	9.26±0.28	0.66±0.23	0.21±0.02	0.05±0.005
	30	0.03±0.01	0.26±0.14	6.74±0.85	0.71±0.14	0.19±0.07	0.18±0.05
3-[^{18}F]Fluorooctanoic acid ([^{18}F]**26**)	5	0.06±0.00	0.76±0.00	2.29±0.24	2.39±0.20	0.53±0.15	0.52±0.07
	30	0.06±0.01	0.16±0.03	0.15±0.04	0.41±0.08	0.07±0.01	2.29±0.09
4-[^{18}F]Fluorooctanoic acid ([^{18}F]**22**)	5	0.12±0.04	0.75±0.17	1.23±0.47	2.02±0.62	0.67±0.15	0.19±0.11
	30	0.16±0.03	0.61±0.08	0.47±0.07	1.38±0.08	0.35±0.05	0.62±0.23
	60	0.13±0.02	0.47±0.04	0.33±0.02	0.93±0.10	0.24±0.02	0.84±0.12
8-[^{18}F]Fluoro-4-methyloctanoic acid ([^{18}F]**19**)	5	0.15±0.01	0.77±0.06	0.41±0.24	3.17±0.3	1.13±0.05	0.21±0.04

a) Mean±S.D. of three rats. *b*) Corrected for the contribution from blood.

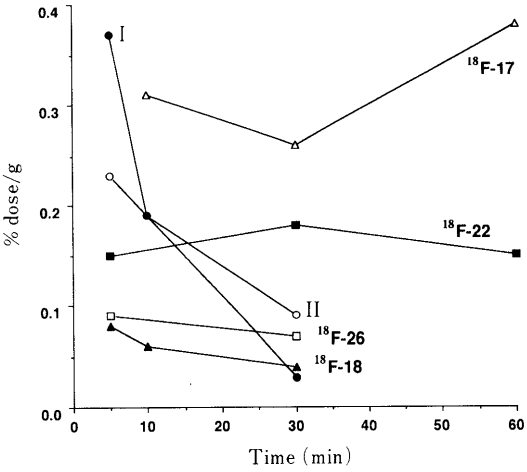


Fig. 1. Brain Uptake of [^{18}F]Fluorooctanoic Acid Analogs at Different Times after Intravenous Injection

Brain uptake data of methyl-3,3-dimethyl-8-[^{18}F]fluorooctanoate (I, ●—●) and ethyl-3-methyl-8-[^{18}F]fluorooctanoate (II, ○—○) are included for comparison.[7]

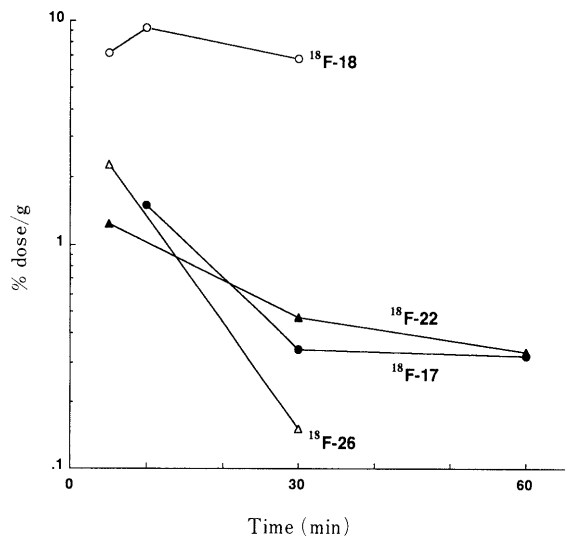


Fig. 2. Liver Uptake of [^{18}F]Fluorooctanoic Acid Analogs at Different Times after Intravenous Injection

although the radioactivity levels in blood were higher than in the brain for both compounds even at later time points after injection.

In our earlier study, we observed that both β-methyl and dimethylbranching of 8-fluorooctanoic acid led to fast cerebral washout of radioactivity.[7] In the present studies, we found that a monomethyl substituent at C4 position allowed better retention of radioactivity in brain tissue, with brain uptake being similar to that observed for the unbranched analog. Furthermore, fluorination at either C3 or C4 of the octanoic acid molecule produced lower brain activity compared to the chain-terminal fluorination, suggesting that the position of the fluorine atom is a critical factor affecting cerebral uptake.

Interestingly, the 4,4-dimethyl analog ([^{18}F]-**18**) was rapidly and preferentially taken up by the liver, with a concentration of 7.17% dose/g after only 5 min, and this concentration did not change significantly at 30 min, indicative of trapping of the substance in the liver. The other three analogs described here exhibited a similar time course with fast elimination of radioactivity from the liver, as shown in Fig. 2. It is known that fatty acid activation, the initial stage of β-oxidation, is the highest in the liver over almost the whole range of fatty acid chain length.[13] Accordingly in the liver, 4,4-dimethyloctanoate ([^{18}F]-**18**) would be actively converted to the corresponding acyl CoA derivative, which could be accumulated and retained in the cells due to the low membrane permeability, if the subsequent steps of metabolism were inhibited in the liver. This is one possible explanation for the long hepatic retention of radioactivity in the case of [^{18}F]-**18**, although further investigations are necessary to clarify this issue.

High bone activity (*ca.* 20% of the injected dose at 30 min) was observed with 3-[^{18}F]fluorooctanoic acid ([^{18}F]-**26**), indicative of *in vivo* defluorination. The low brain uptake by [^{18}F]-**26** may derive, in part, from its significant metabolic lability to defluorination. Bone activity was the lowest for 4-[^{18}F]fluorooctanoic acid ([^{18}F]-**22**) among the three ^{18}F-labeled unbranched analogs. This may be due to the formation of α-[^{18}F]fluoro acid, which is known to resist defluorination,[14] by one cycle of β-oxidation of 4-[^{18}F]fluorooctanoic acid

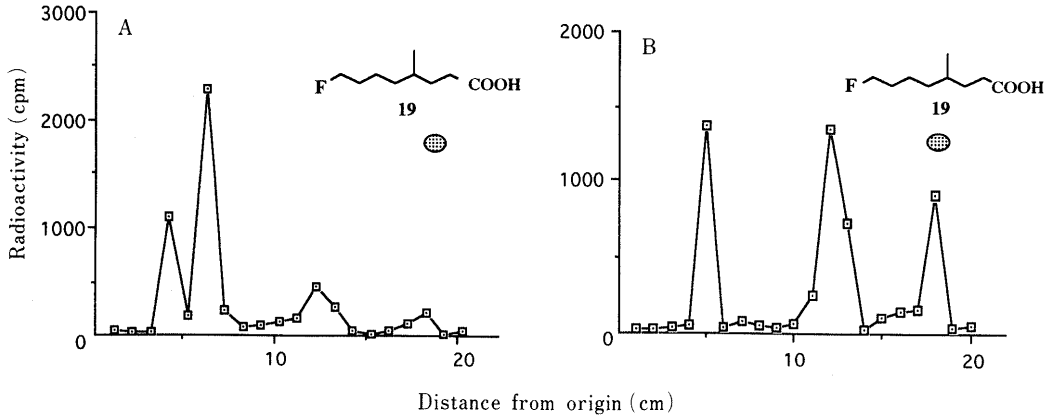


Fig. 3. Radio-TLC Chromatograms of Metabolites in Protein-Free Plasma at 5 min Postinjection of 8-[^{18}F]Fluoro-4-methyloctanoic Acid ([^{18}F]-**19**)

TLC was performed on a TLC plate using chloroform : methanol = 9 : 1 (A) or chloroform : methanol : H_2O : CH_3COOH = 25 : 15 : 4 : 2 (B). The location of 8-fluoro-4-methyloctanoic acid (**19**) on the TLC plate was determined by co-spotting with an authentic sample and is shown by dotted circles in the figures.

([^{18}F]-**22**).

In our previous study, it was shown that the distribution profile of radioactivity with ester compounds of 8-[^{18}F]fluorooctanoic acid and its free acid were similar even at early time points, suggesting that most of the radioactivity found in the tissues, when the ester compounds of 8-[^{18}F]fluorooctanoic acids were injected, was due to uptake of the free acid produced by rapid hydrolysis in the body.[7] Table 2 also shows the tissue concentrations of radioactivity at 5 min after injection of 8-[^{18}F]fluoro-4-methyloctanoic acid ([^{18}F]-**19**) indicating similar biodistribution to its ethyl ester ([^{18}F]-**17**). Therefore, we investigated the extent of metabolism of the free acid ([^{18}F]-**19**) instead of the ester ([^{18}F]-**17**), by TLC examination of rat blood.

Blood samples, obtained from the heart of rats 5 min after injection of [^{18}F]-**19**, were examined to determine the distribution of activity in the plasma and the red blood cells; we found 59% of the activity in the plasma, of which 94% was distributed in the protein-free plasma fraction, and 41% in the red blood cell fraction. TLC analysis of protein-free plasma at 5 min post injection revealed that only 10—15% of radioactivity co-migrated with unmetabolized [^{18}F]-**19** (this value was estimated from TLC analysis of protein-free plasma), and at least three radioactive peaks were found at very low *Rf* values on TLC, suggestive of the formation of polar metabolites (Fig 3). These results clearly demonstrated the very rapid appearance of peripheral radioactive metabolites.

To examine whether the metabolites can penetrate into the brain and contribute to the radioactivity values obtained after i.v. injection of [^{18}F]-**19**, plasma samples obtained 5 min after the injection of [^{18}F]-**19**, were re-injected into other rats. The recipient rats were then killed at 5 min, and the biodistribution is summarized in Table 3. If only the unmetabolized [^{18}F]-**19** in the donor plasma samples can cross the blood-brain barrier (BBB), then only 0.02±0.01% dose/g was predicted to be distributed in the brain, since 10—15% of radioactivity in the donor plasma samples was estimated to be unmetabolized [^{18}F]-**19**. The brain uptake observed in the plasma-injected rats was higher than the predicted value (0.10 *vs.* 0.01% dose/g, respectively), suggesting that the

Table 3. Tissue Distribution of 8-[^{18}F]Fluoro-4-Methyloctanoic Acid Metabolites in Rats[a]

Tissue	% dose/g
Brain[b]	0.10±0.00 (0.02±0.01)[c]
Blood	0.59±0.14
Liver	0.85±0.22
Kidney	1.40±0.50
Heart	0.48±0.11
Bone	0.37±0.11

a) One Wistar male rat was injected with 8-[^{18}F]fluoro-4-methyloctanoic acid. At 5 min, blood was removed from the donor rat. Aliquots of blood containing 10—15% of the original compound, was reinjected into another rat. The recipient rat was then killed at 5 min. All values are means ± S.D. of three rats. *b*) Corrected for radioactivity present in the brain blood pools. *c*) Predicted % dose/g is the uptake that would be expected if the metabolites were fully excluded from crossing the BBB.

labeled metabolites of [^{18}F]-**19** enter the brain to a significant degree. Thus, the re-injection experiments have indicated that the radioactivity in the brain with [^{18}F]-**19**, and probably also [^{18}F]-**17**, may be mainly attributable to radioactive metabolites which enter the brain from the blood. The metabolites were not identified in the present work.

We have described here the synthesis of C4-substituted 8-^{18}F-labeled analogs of octanoic acid and 3- or 4-^{18}F-labeled octanoic acid, and their tissue distribution in rats. None of the labeled analogs exhibited favorable distribution characteristics in rats for imaging of cerebral fatty acid metabolism. The activity of medium-chain acyl CoA synthetase in rat brain has been reported to be low for octanoate.[15] It is likely that the rapid cerebral washout of radioactivity we observed may be related to the low or zero activation rate of the ^{18}F-labeled octanoic acid analogs to the acyl CoA in the brain. The ^{18}F-labeled octanoic acid analogs exhibiting retention of radioactivity in brain did so *via* peripheral formation of labeled metabolites, which appear to enter the brain and contribute to the radioactivity distribution. The present results not only add to our understanding of the structural features that affect cerebral uptake and retention of ^{18}F-labeled octanoic acid analogs, but also help us define the limitations imposed on the design of related derivatives based on the octanoic acid molecule.

Experimental

Unless otherwise stated, chemical reagents were obtained from commercial sources and were used directly. The melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were taken in deuteriochloroform on a JEOL GX-270 (270 MHz), JEOL PS-100 (100 MHz), or Hitachi (60 MHz) spectrometer, Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Infrared (IR) spectra were taken on a JASCO IR Report-100 spectrometer and mass spectra were obtained with a JEOL JMS DX-300 or D-300 mass spectrometer. The elemental analyses were performed by the staff of the microanalytical section of Kyushu University. Analytical TLC was carried out on TLC plates (Merck, Kieselgel 60 F_{254}, 0.2 mm) and visualization was achieved by heating after spraying with 10% ethanol solution of sodium phosphomolybdate. Column chromatography was done by using Merck Kieselgel 60 (70—230 mesh) or Fuji Davison BW-200. Analysis of radioactivity on TLC plates was performed with an Aloka radiochromatogram scanner. HPLC was done using a Waters model M-45 fitted with a YMC pack AQ-323 S-5 ODS (10 × 250 mm) with monitoring of the radioactivity (RCL-500 NaI scintillation, Aloka) as well as the refractive index (Differential T401, Waters). The radioactivity was also quantified with a Capintec radioisotope calibrator (CRC-30). The identification of radiolabeled compounds was supported by HPLC co-injection studies and TLC.

Fluorine-18 was produced from 8 or 16% enriched [^{18}O] H_2O by the $^{18}O(p, n)^{18}F$ reaction as described previously[10]. Aminopolyether (Kryptofix 2.2.2)-supported potassium fluoride ($K^{18}F$/Kryptofix 2.2.2) and tetra-*n*-butylammonium [^{18}F]fluoride (*n*-$Bu_4N^{18}F$) were prepared by the addition of $K_2CO_3 \cdot 1.5H_2O$ (1.6 mg), Kryptofix 2.2.2 (7.2 mg) and 1 M tetrabutylammonium hydroxide in MeOH (2.4 μl), respectively, to irradiated water in a TPX (polymethylpentene) vessel and subsequent removal of the water under a stream of argon at 110 °C by azeotropic distillation using dry CH_3CN. Radiochemical yields were expressed at the EOS (not corrected for decay), relative to the amount of the [^{18}F]fluorinating agent measured as total radioactivity present in the reaction vessel.

A. Synthesis. 2-Methyl ε-Caprolactone (1) *n*-Butyllithium (1.5 M/hexane, 5.4 ml) was added to a solution of diisopropylamine (1.4 mmol) in tetrahydrofuran (THF, 15 ml) at −78 °C. The solution was stirred for 30 min and a solution of ε-caprolactone (0.5 ml, 4.52 mmol) in THF (10 ml) was added dropwise over a period of 20 min. The reaction mixture was stirred for 1 h at −78 °C and hexamethylphosphoramide (HMPA, 0.87 ml, 5.0 mmol) was added. Stirring was continued for 30 min, then methyl iodide (1.5 ml, 22.6 mmol) was added. The reaction mixture stirred for 2 h at −78—50 °C, then poured into cold 10% HCl (5 ml) and diluted with ether. The separated organic layer was washed with H_2O, brine, and dried Na_2SO_4. Evaporation of the solvent gave a crude oil, which was chromatographed (hexane : ethyl acetate = 3 : 1→2 : 1) to give **1** as a colorless oil (222 mg, 40%). IR (neat): 1730 cm^{-1}. ^{1}H-NMR δ: 4.43—4.20 (2H, m), 2.89—2.55 (1H, m), 2.17—1.43 (6H, m), 1.21 (3H, t, J = 6.6 Hz). EIMS *m/z*: 128 (M^+).

Ethyl 8-Hydroxy-4-methyl-2-octenoate (2) A solution of diisobutylaluminium hydride (DIBAL, 1.5 M solution in toluene, 17 ml) was added under argon to a solution of 2-methyl-ε-caprolactone (**1**) (287 mg, 2.24 mmol) in toluene (60 ml) at −78 °C over a period of 30 min, and the reaction mixture was stirred at the same temperature for an additional 4 h. In parallel, a mineral oil dispersion of NaH (134 mg, 3.4 mmol) was washed with toluene and suspended in benzene (4 ml), then triethyl phosphonoacetate (0.67 ml, 3.4 mmol) was added to this suspension at 5—10 °C over a period of 20 min and the mixture was stirred at room temperature for 30 min. The resulting solution was added at −78 °C to the solution of the aldehyde in toluene described above. The mixture was stirred at ambient temperature overnight and then the reaction was quenched by the addition of H_2O. The precipitates were filtered off and washed with ether. The combined ether layer was washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude oil, which was chromatographed (hexane : ethyl acetate = 3 : 1→2 : 1) to give **2** as a colorless oil (362 mg, 81%, containing a trace amount of *Z* isomer). IR (neat) 3400, 1720, 1640 cm^{-1}. ^{1}H-NMR δ: 6.88 (1H, dd, J = 15.8, 7.8 Hz), 5.76 (1H, dd, J = 15.8, 1.6 Hz), 4.19 (2H, q, J = 7.2 Hz), 3.64 (2H, t, J = 6.1 Hz), 2.60—2.10 (2H, m), 1.35 (3H, d, J = 7.1 Hz), 1.70—1.11 (6H, m), 1.11 (3H, t, J = 6.6 Hz). EIMS *m/z*: 200 (M^+), 154 ($M^+ - C_2H_6O$).

Ethyl 8-Hydroxy-4-methyloctanoate (3) A solution of the olefin (**2**) (362 mg, 1.81 mmol) in MeOH (2 ml) was added to a suspension of 5% Pd–C (25 mg) in MeOH (3 ml). The reaction mixture was stirred vigorously at room temperature for 5 h under an atmosphere of hydrogen. The catalyst was then removed by filtration and washed with ethyl acetate. The combined filtrate and washing were concentrated under reduced pressure. The product was purified by column chromatography on silica gel using hexane–ethyl acetate (3 : 1) to give the alcohol (**3**) (286 mg, 78%) as a colorless oil. IR (neat): 3400, 1740 cm^{-1}. ^{1}H-NMR δ: 4.13 (2H, q, J = 7.2 Hz), 3.63 (2H, t, J = 5.9 Hz), 2.31 (2H, t, J = 7.0 Hz), 2.35 (1H, br s), 1.85—1.34 (9H, m), 1.26 (3H, t, J = 7.2 Hz), 0.89 (3H, d, J = 4.4 Hz). EIMS *m/z*: 184 ($M^+ - H_2O$).

2,2-Dimethyl-8-trityloxy-pentan-1-ol (5) A solution of 3,3-dimethylglutaric acid (1.0 g, 6.25 mmol) in THF (10 ml) was added dropwise to a a solution of $LiAlH_4$ (500 mg, 12.5 mmol) in THF (20 ml) under argon. The mixture was stirred at room temperature for 2 h and quenched by slow addition of water (0.5 ml), aqueous 15% NaOH (0.5 ml), and water again (1.5 ml). A small amount of anhydrous potassium carbonate was added and the precipitate was filtered off and washed with THF. The solvent was removed *in vacuo*, and the product was purified by column chromatography on silica gel ($CHCl_3$: MeOH = 9 : 1) to give the diol (**4**) (812 mg, quant.) as a colorless oil. IR (neat): 3400 cm^{-1}. ^{1}H-NMR δ: 3.62 (2H, t, J = 5.7 Hz), 3.31 (2H, s), 1.63 (2H, br, D_2O exchangeable), 1.47 (4H, br), 0.87 (6H, s).

A solution of the diol (1.01 g, 7.7 mmol) in pyridine (20 ml) was treated with trityl chloride (1.27 g, 3.8 mmol). The reaction mixture was stirred at room temperature overnight, diluted with ether, then washed with saturated aqueous NH_4Cl and brine. The organic phase was dried ($MgSO_4$). Evaporation of the solvent gave a crude oil, which was chromatographed on silica gel (hexane : ethyl acetate = 20 : 1) to give the 8-trityloxy alcohol (**5**) as colorless needles, mp 82—84 °C (1.66 g, 58%). IR (neat): 3400 cm^{-1}. ^{1}H-NMR δ: 7.38—7.26 (15H, m), 3.30 (2H, s), 3.06 (2H, t, J = 6.4 Hz), 1.64—1.12 (5H, m), 0.86 (6H, s). FDMS *m/z*: 374 (M^+).

3,3-Dimethyl-5-oxo-1-trityloxypentane (6) Pyridinium chlorochromate (0.8 mmol, 173 mg) and Celite (500 mg) were suspended in dichloromethane (4 ml) containing sodium acetate (100 mg) under argon and a solution of alcohol (**5**) (150 mg, 0.4 mmol) in dichloromethane (5 ml) was added. The mixture was stirred at room temperature overnight, then ether was added and stirring was continued for 30 min at room temperature. The mixture was passed through Florisil (20 g) and washed with ether. The combined filtrate and washing were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel using hexane–ethyl acetate (10 : 1) to give the aldehyde **6** (81 mg, 54%) as a colorless needles, mp. 67—73 °C. IR (Nujol): 1720 cm^{-1}. ^{1}H-NMR δ: 9.48 (1H, s), 7.42—7.25 (15H, m), 3.08 (2H, t, J = 2.0 Hz), 1.51 (4H, br), 1.04 (6H, s). FDMS *m/z*: 372 (M^+)

8-Benzyloxy-4,4-dimethyl-1-trityloxy-2-octene (7) *n*-Butyllithium (1.5 M/hexane, 0.22 ml) was added to a stirred suspension of 3-benzyloxypropyl triphenylphosphonium bromide (140 mg, 0.29 mmol) in THF (1 ml) at 0 °C over a period of 15 min. The resulting dark red solution was stirred for an additional 45 min at 0 °C. A solution of the aldehyde **6** (0.22 mmol, 80 mg) in dry THF (1 ml) was added dropwise over a period of 20 min at 0 °C. The reaction mixture was stirred at room temperature overnight, diluted with ether, then washed with H_2O and brine. The organic phase was dried ($MgSO_4$). Evaporation of the solvent gave a crude oil, which was chromatographed on silica gel (hexane : ethyl acetate = 20 : 1) to give compound **7** as a colorless oil (63 mg, 57%, containing a trace amount of *E* isomer). IR (neat): 1740 cm^{-1}. ^{1}H-NMR δ: 7.45—7.18 (20H, m), 5.30 (1H, d, J = 12.2 Hz), 5.22 (1H, dt, J = 11.9, 5.9 Hz), 4.50 (2H, s), 3.47 (2H, t, J = 7.2 Hz), 3.02 (2H, t, J = 6.6 Hz), 2.49 (2H, dt, J = 6.4, 5.9 Hz), 1.63—1.55 (2H, m), 1.39—1.33 (2H, m), 1.08 (6H, s). FDMS *m/z*: 504 (M^+).

8-Benzyloxy-1-hydroxy-4,4-dimethyl-2-octene (8) The trityl ether **7** (50 mg, 0.1 mmol) was dissolved in MeOH–THF (1 ml–1 ml) containing a catalytic amount of *p*-TsOH, and the mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with ether, then washed with saturated aqueous $NaHCO_3$, H_2O and brine, and the organic layer was dried ($MgSO_4$). Evaporation of the solvent gave a crude oil, which was chromatographed on silica gel (hexane : ethylacetate = 9 : 1→4 : 1) afford **8** as a colorless oil (20 mg, 81%). IR (neat) 3400 cm^{-1}. ^{1}H-NMR δ: 7.33 (5H, s), 5.33—5.19 (2H, m), 4.52 (2H, s), 3.65 (2H, t, J = 6.9 Hz), 3.49 (2H, t, J = 6.5 Hz), 2.65—2.22 (2H, m), 1.42—1.47 (5H, m), 1.10 (6H, s).

Methyl 8-Benzyloxy-1-hydroxy-4,4-dimethyl-2-octenoate (10) The

CrO_3–H_2SO_4 reagent[16] was added to a solution of the alcohol **8** (20 mg, 0.08 mmol) in acetone (0.5 ml) at 0 °C until the mixture showed an orange color. The reaction mixture was stirred for 2 h at the same temperature and 2-propanol was added to decompose excess oxidizing agent. The mixture was diluted with $CHCl_3$, then washed with H_2O and brine. The organic phase was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was dissolved in MeOH (1 ml), and concentrated H_2SO_4 (0.1 ml) was added to the solution. The mixture was stirred at room temperature overnight, then potassium carbonate (1.0 g) was added and stirring was continued for 30 min. The reaction mixture was diluted with ether and washed with H_2O and brine. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was chromatographed on silica gel (hexane : ethyl acetate = 10 : 1) to give the ester compound **10** (13 mg, 56%) as a colorless oil. IR (neat): 1740 cm^{-1}. ^{1}H-NMR δ: 7.39—7.26 (5H, m), 5.28 (1H, d, J=8.5 Hz), 5.20 (1H, dt, J=10.0, 3.8 Hz), 4.52 (2H, s), 3.64 (3H, s), 3.49 (2H, t, J=7.1 Hz), 2.59—2.30 (4H, m), 1.78—1.61 (2H, m), 1.11 (6H, s). EIMS m/z: 290 (M^+), 199 ($M^+ - C_7H_7$).

Methyl 8-Hydroxy-4,4-dimethyloctanoate (11) A solution of **10** (274 mg, 0.94 mmol) in CH_3COOH (2 ml) was hydrogenated over 5% palladium carbon catalyst (30 mg). The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The product was purified by column chromatography on silica gel (hexane : ethyl acetate = 3 : 1) to give **11** (107 mg, 56%) as a colorless oil. IR (neat): 3400, 1740 cm^{-1}. ^{1}H-NMR δ: 3.67 (3H, s), 3.65 (2H, t, J=6.3 Hz), 2.26 (1H, dt, J=8.2, 4.6 Hz), 2.25 (1H, ddd, J=8.2, 6.4, 4.6 Hz), 1.89 (1H, br s, D_2O exchangeable), 1.58—1.51 (4H, m), 1.37—1.18 (4H, m), 0.86 (6H, s). FDMS m/z: 203 ($M^+ + 1$).

1-Benzyloxy-3-propanal (13) PCC (60 mmol, 13.5 g) and Celite (25.6 g) were suspended in dichloromethane (30 ml) under argon and a solution of 1-benzyloxy-3-propanol (150 mg, 0.4 mmol)[17] in dichloromethane (5 ml) was added. The mixture was stirred at room temperature overnight, ether was added, and stirring was continued for 30 min at room temperature. The mixture was filtered and the filtrate was washed with ether. The combined filtrate and washing were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel using hexane–ethyl acetate (3 : 1) to give the aldehyde **13** (4.4 g, 64%) as a colorless oil. IR (Nujol): 1720 cm^{-1}. ^{1}H-NMR δ: 9.82 (1H, t, J=1.7 Hz), 7.34 (5H, s), 4.53 (2H, s), 3.82 (2H, t, J=6.0 Hz) 2.67 (2H, dt, J=1.7, 6.1 Hz).

1-Benzyloxy-3-octanol (14) A solution of aldehyde (**13**) (380 mg, 2.35 mmol) in dry ether (4 ml) was added at 0 °C to a Grignard solution prepared from *n*-amyl bromide (1.2 ml) and magnesium (240 mg) in dry ether (2 ml). The reaction mixture was stirred at 0 °C—room temperature overnight and diluted with ether. The ether solution was poured into 10% HCl and the organic layer was washed with H_2O and brine. The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel using hexane–ethyl acetate (93 : 7) to give the alcohol **14** (388 mg, 71%) as a colorless oil. IR (Nujol): 3400 cm^{-1}. ^{1}H-NMR δ: 7.32 (5H, s), 4.52 (2H, s), 3.70 (3H, m), 2.66 (1H, br), 1.74 (1H, q, J=5.6 Hz), 1.43—1.26 (8H, m), 0.88 (3H, m). FDMS m/z: 236 (M^+).

Ethyl 4-Methyl-8-(*p*-toluenesulfonyloxy)octanoate (15) Pyridine (0.02 ml, 0.26 mmol) and *p*-toluenesulfonyl chloride (*p*-TsCl, 38 mg, 0.19 mmol) were added to a solution of the alcohol **3** (26 mg, 0.13 mmol) in dichloromethane (1 ml), and the reaction mixture was stirred at room temperature for 12 h. It was then diluted with ether and washed with H_2O and brine. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was chromatographed on silica gel with a mixture of hexane and ethyl acetate (10 : 1→5 : 1) to give the tosylate **15** (41 mg, 92%) as a colorless oil. IR (neat): 1740, 1360 cm^{-1}. ^{1}H-NMR δ: 7.79 (2H, d, J=8.3 Hz), 7.35 (2H, d, J=8.6 Hz), 4.12 (2H, q, J=7.1 Hz), 4.08 (2H, d, J=7.1 Hz), 2.45 (3H, s), 2.26 (2H, t, J=6.7 Hz), 1.82—1.02 (9H, m) 1.25 (3H, t, J=7.1 Hz), 0.83 (3H, d, J=5.9 Hz). FDMS m/z: 356 (M^+).

Methyl 4,4-Dimethyl-8-(*p*-toluenesulfonyloxy)octanoate (16) The alcohol **11** (150 mg, 0.75 mmol) was allowed to react with *p*-TsCl (210 mg, 1.12 mmol) in a mixture of CH_2Cl_2 (3 ml) and pyridine (0.1 ml) for 12 h, and work-up as described for **15** gave the tosylate **16** (246 mg, 90%) as a colorless oil. IR (neat): 1740, 1360 cm^{-1}. ^{1}H-NMR δ: 7.80 (2H, d, J=8.2 Hz), 7.35 (2H, d, J=7.9 Hz), 4.03 (1H, t, J=6.6 Hz), 3.76 (3H, s), 2.45 (3H, s), 2.21 (1H, dt, J=8.3, 4.6 Hz), 2.18 (1H, ddd, J=8.4, 8.2, 4.6 Hz), 1.63—1.55 (2H, m), 1.49 (1H, dt, J=8.2, 4.3 Hz), 1.48 (1H, ddt, J=8.3, 8.2, 4.1 Hz), 1.11—1.32 (4H, m), 0.80 (6H, s). FDMS m/z: 356 (M^+).

Ethyl 8-Fluoro-4-methyloctanoate (17) A solution of the tosylate **15** (153 mg, 0.43 mmol) in dry THF (2 ml) was treated with *n*-Bu_4NF (1 M THF solution, 1.72 mmol) under argon. The mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue was chromatographed on silica gel using hexane–ethyl acetate (10 : 1) to give **17** (74 mg, 85%) as a colorless oil. IR (neat): 1740 cm^{-1}. ^{1}H-NMR δ: 4.46 (2H, dt, J=44.6, 6.1 Hz), 4.12 (2H, q, J=7.1 Hz), 2.23 (2H, t, J=6.4 Hz), 1.26 (3H, t, J=7.2 Hz), 1.89—1.09 (9H, m), 0.89 (3H, d, J=5.6 Hz). EIMS m/z: 205 ($M^+ + 1$), 189 ($M^+ - Me$), 184 ($M^+ - HF$). *Anal.* Calcd for $C_{11}H_{21}FO_2$: C, 64.61; H, 10.15. Found: C, 64.71; H, 10.29.

Methyl 8-Fluoro-4,4-dimethyloctanoate (18) The tosylate (**16**) (100 mg, 0.29 mmol) was reacted with *n*-Bu_4NF (1 M THF solution, 1.16 mmol) in THF (4 ml) for 4 h at room temperature according to the procedure described for **17**, to give **18** (52 mg, 88%) as a colorless oil. IR (neat): 1740 cm^{-1}. ^{1}H-NMR δ: 4.45 (2H, dt, J=47.1, 6.3 Hz), 3.67 (3H, s), 2.26 (1H, dt, J=8.2, 4.6 Hz), 2.25 (1H, ddd, J=8.4, 8.2, 4.6 Hz), 1.76—1.52 (4H, m), 1.48—1.21 (4H, m), 0.86 (6H, s). FABMS m/z: 205 ($M^+ + 1$). FAB HR-MS m/z: 205.1592 [Calcd for $C_{11}H_{22}FO_2$ (M^+): 205.1580]

8-Fluoro-4-methyloctanoic Acid (19) The fluoroester (**17**) (40 mg, 0.2 mmol) was treated with 1 N methanolic KOH (3 ml). The reaction mixture was stirred at room temperature for 2 h, neutralized with 5% H_2SO_4 and extracted with chloroform. The organic phase was dried and concentrated under reduced pressure. The residue was chromatographed on silica gel using $CHCl_3$ to give **19** (27 mg, 78%) as a colorless oil. IR (neat): 3200, 1740 cm^{-1}. ^{1}H-NMR δ: 9.7 (br, 1H), 4.48 (2H, dt, J=44.6, 6.1 Hz), 2.24 (2H, t, J=6.4 Hz), 1.89—1.09 (9H, m), 0.89 (3H, d, J=5.6 Hz).

Methyl 4-*p*-Toluenesulfonyloxy Octanoate (20) Triethylamine (12 ml, 86 mmol) was added to a solution of γ-octanoic lactone (2.0 g, 14.3 mmol) in dry MeOH (10 ml). The reaction mixture was stirred at room temperature for 3 h and evaporated *in vacuo*. The residue containing methyl 4-hydroxyoctanoate (**12**) was dissolved in CH_2Cl_2 (30 ml) and then 4-dimethylaminopyridine (DMAP) (3.5 g, 29 mmol) and *p*-TsCl (2.7 g, 14 mmol) were added. Stirring was continued for 2 h at room temperature, then the reaction mixture was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave a crude oil, which was chromatographed on silica gel with a mixture of hexane and ethyl acetate (9 : 1) to give γ-octanoic lactone (1.58 g, 79%) and the tosylate **20** (497 mg, 11%) as a colorless oil. IR (neat): 1730, 1350 cm^{-1}. ^{1}H-NMR δ: 7.79 (2H, d, J=8.6 Hz), 7.34 (2H, d, J=8.6 Hz), 4.62 (2H, q, J=5.8 Hz), 3.64 (3H, s), 2.45 (3H, s), 2.30 (2H, d, J=7.8 Hz), 2.01—1.77 (2H, m), 1.71—1.47 (2H, m) 1.26—1.11 (2H, m), 0.81 (3H, t, J=5.7 Hz). FDMS m/z: 328 (M^+).

4-Fluorooctanoic Acid (22) A solution of the tosylate (**20**) (100 mg, 0.30 mmol) in dry THF (2 ml) was treated with *n*-Bu_4NF (1 M THF solution, 0.46 mmol) under argon. The mixture was refluxed for 20 min then diluted with ether, and washed with brine. The organic layer was dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel with hexane–ethyl acetate (10 : 1) to give the ester (**21**) (22 mg, 41%) as a colorless oil. IR (neat): 1740 cm^{-1}. ^{1}H-NMR δ: 4.50 (2H, dtt, J=49.6, 7.9, 4.0 Hz), 3.69 (3H, s), 2.47 (2H, m), 2.06—1.82 (2H, m), 1.74—1.57 (2H, m) 1.57—1.27 (4H, m), 0.91 (3H, t, J=7.1 Hz). EIMS m/z: 175 ($M^+ - 1$). A solution of methyl 4-fluorooctanoate (**21**) (50 mg, 0.28 mmol) in MeOH (2 ml) was treated with 5 N aqueous KOH (1 ml), and the mixture was stirred for 30 min at room temperature, neutralized with 5% H_2SO_4 and extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane–ethyl acetate (10 : 1→1 : 1) to give **22** (16.7 mg, 36%) as a colorless oil. IR (neat): 3600, 1710 cm^{-1}. ^{1}H-NMR δ: 8.19 (1H, m), 4.38 (1H, dm, J=47.6 Hz), 2.6—2.3 (2H, m), 2.2—1.1 (8H, m), 0.84 (3H, t, J=7.1 Hz).

1-Benzyloxy-3-(*p*-toluenesulfonyloxy)octane (23) The alcohol **14** (100 mg, 0.42 mmol) was allowed to react with *p*-TsCl (121 mg, 0.64 mmol) in a mixture of CH_2Cl_2 (3 ml) and 4-methylaminopyridine (0.1 ml) for 12 h at room temperature, after work-up as described for **15**, to give the tosylate **23** (106 mg, 64%) as a colorless oil: IR (neat) 1360 cm^{-1}. ^{1}H-NMR δ: 7.78 (2H, d, J=8.3 Hz), 7.33—7.24 (7H, m), 4.76 (1H, q, J=6.0 Hz), 4.37 (2H, s), 3.42 (2H, dt, J=6.1, 2.7 Hz), 2.41 (3H, s), 1.89 (2H, q, J=6.3 Hz), 1.33—1.04 (8H, m), 0.82 (3H, br t, J=5.9 Hz). EIMS m/z: 390 (M^+).

1-Benzyloxy-3-(methanesulfonyloxy)octane (24) The alcohol **14** (4.16

g, 18 mmol) was allowed to react with MsCl (1.65 ml, 21 mmol) in a mixture of ether (35 ml) and triethylamine (TEA) (3.7 ml) for 3 h at room temperature. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was dried ($MgSO_4$) and evaporated to give **24** as a colorless oil, which was used for the next reaction without further purification. IR (neat): 1350 cm^{-1}. ^{1}H-NMR δ: 7.36—7.33 (7H, m), 4.89 (1H, q, J=6.1 Hz), 4.50 (2H, s), 3.58 (2H, t, J=6.1 Hz), 2.94 (3H, s), 1.97 (2H, dt, J=6.1 Hz), 1.85—1.29 (8H, m), 0.88 (3H, br t, J=6.1 Hz). FDMS m/z: 314 (M^+).

3-Fluorooctanoic Acid (26) A solution of the mesylate (**24**) (5.77 g, 18 mmol) in dry THF (50 ml) was treated with n-Bu_4NF (1 M THF solution, 28 mmol) under argon. The mixture was refluxed for 6 h, then diluted with ether, and washed with brine. The organic layer was dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel with hexane–ethyl acetate (500 : 1) to give 1-benzyloxy-3-fluorooctane (**25**) (2.3 g, 52%) as a colorless oil. IR (neat): 920, 780 cm^{-1}. ^{1}H-NMR δ: 7.33 (5H, m), 4.67 (1H, dtt, J=49.5, 8.0, 4.0 Hz), 4.52 (2H, s), 3.67—3.54 (2H, m), 1.96—1.79 (2H, m), 1.70—1.26 (8H, m), 0.89 (3H, t, J=6.8 Hz). FDMS m/z: 238 (M^+).

1-Benzyloxy-3-fluorooctane (**25**) was allowed to react with 70% nitric acid at 90 °C for 15 min and the mixture was cooled to room temperature, and diluted with water. It was extracted with ether and the extract was dried (Na_2SO_4). Evaporation of the solvent gave a crude oil, which was chromatographed on silica gel with hexane-ethyl acetate (19 : 1) to give 3-fluorooctanoic acid (**26**) (57 mg, 42%) as colorless plates (mp 54—55 °C). IR (neat): 3200, 1690 cm^{-1}. ^{1}H-NMR δ: 4.94 (1H, dtt, J= 48.2, 8.1, 4.1 Hz), 2.74 (1H, dt, J=15.8, 8.0 Hz), 2.60 (1H, ddd, J= 29.9, 16.2, 4.5 Hz), 1.81—1.30 (9H, m), 0.89 (3H, t, J=6.6 Hz). FDMS m/z: 163 (M^++1). *Anal.* Calcd for $C_8H_{15}FO_2$: C, 59.24; H, 9.32. Found: C, 59.32; H, 9.36.

B. Radiochemical Synthesis.

Ethyl 8-[^{18}F]Fluoro-4-methyloctanoate ([^{18}F]-17) Ethyl 4-methyl-8-(*p*-toluenesulfonyloxy)octanoate (**15**) (1—3 mg) dissolved in dry CH_3CN (300 μl) was added to a TPX vessel containing n-$Bu_4N^{18}F$ (37—74 Bq). The vessel was closed and heated in an oil bath at 80 °C for 15 min, then cooled to room temperature. The mixture was applied to a silica Sep-Pak (Waters). The Sep-Pak was eluted with 2 ml of $CHCl_3$–MeOH (9 : 1). The elute was evaporated *in vacuo* and the residue was dissolved in MeOH, then purified by reversed-phase HPLC (eluent: MeOH : H_2O = 80 : 20; flow rate: 3.0 ml/min) to give radiochemically pure [^{18}F]-**17** (t_R=18 min) in 39—41% radiochemical yield (total time for synthesis: 60 min).

Methyl 8-[^{18}F]Fluoro-4,4-dimethyloctanoate ([^{18}F]-18) Methyl 4,4-dimethyl-8-(*p*-toluenesulfonyloxy)octanoate (**16**) (1—3 mg) dissolved in dry CH_3CN (300 μl) was added to a TPX vessel containing n-$Bu_4N^{18}F$ (37—74 Bq). The vessel was closed and heated in an oil bath at 80 °C for 15 min, then cooled to room temperature. The mixture was applied to a silica gel Sep-Pak (Waters). The Sep-Pak was then eluted with 2 ml of $CHCl_3$–MeOH (9 : 1). The elute was evaporated *in vacuo*. The residue was re-dissolved in MeOH, then purified by reversed-phase HPLC (eluent: MeOH : H_2O = 80 : 20; flow rate: 3.0 ml/min) to give radiochemically pure [^{18}F]-**18** (t_R=19 min) in 13—25% radiochemical yield (total time for synthesis: 60 min).

8-[^{18}F]Fluoro-4-methyloctanoic Acid ([^{18}F]-19) Following the reaction of **15** with n-$Bu_4N^{18}F$ (37—74 MBq) as described above, the fraction containing ethyl 8-[^{18}F]fluoro-4-methyloctanoate ([^{18}F]-**17**) obtained through the Sep-Pak procedure was evaporated, and the residue was taken up in 5 N KOH in MeOH (150 μl). The mixture was heated at 90 °C for 5 min. After cooling to room temperature, the mixture was applied to a resin column (1.2 × 4.0 cm, Dowex 50W-X8) and eluted with MeOH (3—5 ml). The elute was evaporated *in vacuo* and the crude product was purified by reversed-phase HPLC (eluent: MeOH : H_2O : CH_3COOH = 260 : 140 : 0.3; flow rate: 3.0 ml/min) to give radiochemically pure [^{18}F]-**19** (t_R=18 min) in 26—30% radiochemical yield (total time for synthesis: 120 min).

4-[^{18}F]Fluorooctanoic Acid ([^{18}F]-22) Methyl 4-(*p*-toluenesulfonyloxy)octanoate (**20**) (1—3 mg) dissolved in dry CH_3CN (300 μl) was added to a TPX vessel containing K^{18}F/Kryptofix 2.2.2 (37—74 Bq). The vessel was closed, heated in an oil bath at 85 °C for 15 min, and cooled to room temperature. The mixture was applied to a silica gel Sep-Pak (Waters). The Sep-Pak was then eluted with 2 ml of $CHCl_3$–MeOH (9 : 1). The elute was evaporated *in vacuo*. The residue was dissolved in MeOH (300 μl) and aqueous 5 N KOH (200 μl) was added. The mixture was allowed to stand for 30 min, applied to a resin column (1.2 × 4.0 cm, Dowex 50W-X8), and eluted with MeOH (3—5 ml). The elute was evaporated *in vacuo* and the crude product was purified by reversed-phase HPLC (eluent: MeOH : H_2O : CH_3COOH = 300 : 100 : 0.2; flow rate: 3.0 ml/min) to give radiochemically pure [^{18}F]-**22** (t_R=15 min) in 4—6% radiochemical yield (total time for synthesis: 110 min).

3-[^{18}F]Fluorooctanoic Acid ([^{18}F]-26) 1-Benzyloxy-3-methanesulfonyloxyoctane (**24**) (1—3 mg) dissolved in dry CH_3CN (300 μl) was added to a TPX vessel containing K^{18}F/Kryptofix 2.2.2 (37—74 Bq). The vessel was closed, heated in an oil bath at 110 °C for 20 min, and cooled to room temperature. The mixture was applied to a silica gel Sep-Pak (Waters). The Sep-Pak was then eluted with 2 ml of $CHCl_3$–MeOH (9 : 1). The elute was evaporated *in vacuo*, the residue was taken up in 70% nitric acid (5 μl) and the mixture was heated to 90 °C for 15 min in a glass vial. The mixture was cooled to room temperature and diluted with saturated $NaHCO_3$ (20 μl) and water (30 μl), then extracted with hexane. The solvent was removed *in vacuo* and the crude product was purified by reversed-phase HPLC (eluent: MeOH : H_2O : CH_3COOH = 295 : 105 : 0.2; flow rate: 3.0 ml/min) to give radiochemically pure [^{18}F]-**26** (t_R=15 min) in 4—6% radiochemical yield (total time for synthesis: 165 min).

Biodistribution of ^{18}F-Labeled Octanoates in Rats Male Wistar rats (150—200 g), deprived of food for 24—48 h prior to initiation of the experiments, were used in this investigation. Purified radiofluorinated fatty acids dissolved in 0.5 ml of normal saline (including less than 1% MeOH) with activities ranging from 370—740 kBq were injected through the tail vein of the unanesthetized rats. Under light ether anesthesia, the animals were killed at the indicated times after the injection. Samples of blood and the organs of interest were taken, blotted free of blood, weighed and assayed for radioactivity in a Packard Auto-gamma 500 scintillation counter (corrected for decay). The values of % injected dose/g tissue was calculated for each tissue. The blood activity contribution to the brain tissues was estimated based on whole body and brain blood volumes taken from the literature[18] (4%) for the rat and the values for the brain uptake were corrected accordingly. Toxic effects were not apparent in rats injected with the ^{18}F-labeled fatty acids.

The procedure of plasma-reinjection was as follows. 8-[^{18}F]Fluoro-4-methyloctanoic acid ([^{18}F]-**19**) was dissolved in 1.0 ml of normal saline (including less than 1% MeOH) and injected *via* a tail vein into the unanesthetized animals (7.4—14.8 MBq). The animals were anesthetized with ether, and killed at 5 min after the injection. Blood samples from the heart were placed in heparinized vials, centrifuged (2000 rpm, 10 min) to separate the plasma fraction from red blood cells and the plasma fraction was collected. Biodistribution experiments identical to those done with [^{18}F]-**19** were performed by injecting into recipient rats 1.0—2.0 ml (59—93 kBq) of the donor plasma fraction. Five minutes later, the animal was killed and tissue activity concentration was assayed as described above.

Metabolite Analyses Blood samples, obtained from the heart at 5 min after injection of 8-[^{18}F]fluoro-4-methyloctanoic acid ([^{18}F]-**19**), were placed in heparinized vials, and centrifuged (3000 rpm, 10 min), and the plasma was removed. The red blood cells (RBC) were washed with a small amount of ice-cold saline and the wash was added to the plasma. Aliquots of the plasma solution and the total RBC pellet were counted for ^{18}F activity. An equal volume of freshly prepared 1 M $HClO_4$ (PCA) was added to the plasma and the combined mixture was centrifuged (3000 rpm, 10 min) to remove precipitated proteins. The supernatant and one PCA washing were combined. The plasma protein and the protein-free plasma were also counted for ^{18}F activity. Aliquots of the protein free-plasma was spotted on TLC plates, then developed with the following two solvent systems: $CHCl_3$: MeOH = 9 : 1 and $CHCl_3$: MeOH : H_2O : CH_3COOH = 25 : 15 : 4 : 2. The TLC plates were cut into 0.5 cm wide strips after counting with the TLC analyzer, and their radioactivity were counted manually with a γ-well counter. The location of 8-fluoro-4-methyloctanoic acid on the plates was determined by co-spotting with an authentic cold sample.

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