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[F-18]Labeling of 1,2-Diacylglycerols

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Summary

We have developed two kinds of [^{18}F]labeled 1,2-diacylglycerols (1,2-DAGs) such as 1-(ω-[^{18}F]fluoroacyl)-2-acylglycerols (1*,2-[^{18}F]FDAGs) and 2-(ω-[^{18}F]fluoroacyl)-1-acylglycerols (1,2*-[^{18}F]FDAGs) for imaging receptor-mediated phosphatidyl-inositol (PI) turnover responses by positron emission tomography (PET). The 1*,2-[^{18}F]FDAGs were synthesized by the reaction of 2-monoacyl glycerols with ω-[^{18}F]fluoroacyl chlorides (method A) and 1-(16-[^{18}F]fluoro palmitoyl)-2-palmitoylglycerol (1*,2-[^{18}F]FDAG(C16,C16)) and 1-(8-[^{18}F]fluoro octanoyl)-2-palmitoylglycerol (1*,2-[^{18}F]FDAG(C8,C16)) were synthesized using method A. However, during the synthesis of 1,2*-[^{18}F]FDAGs, we adopted the

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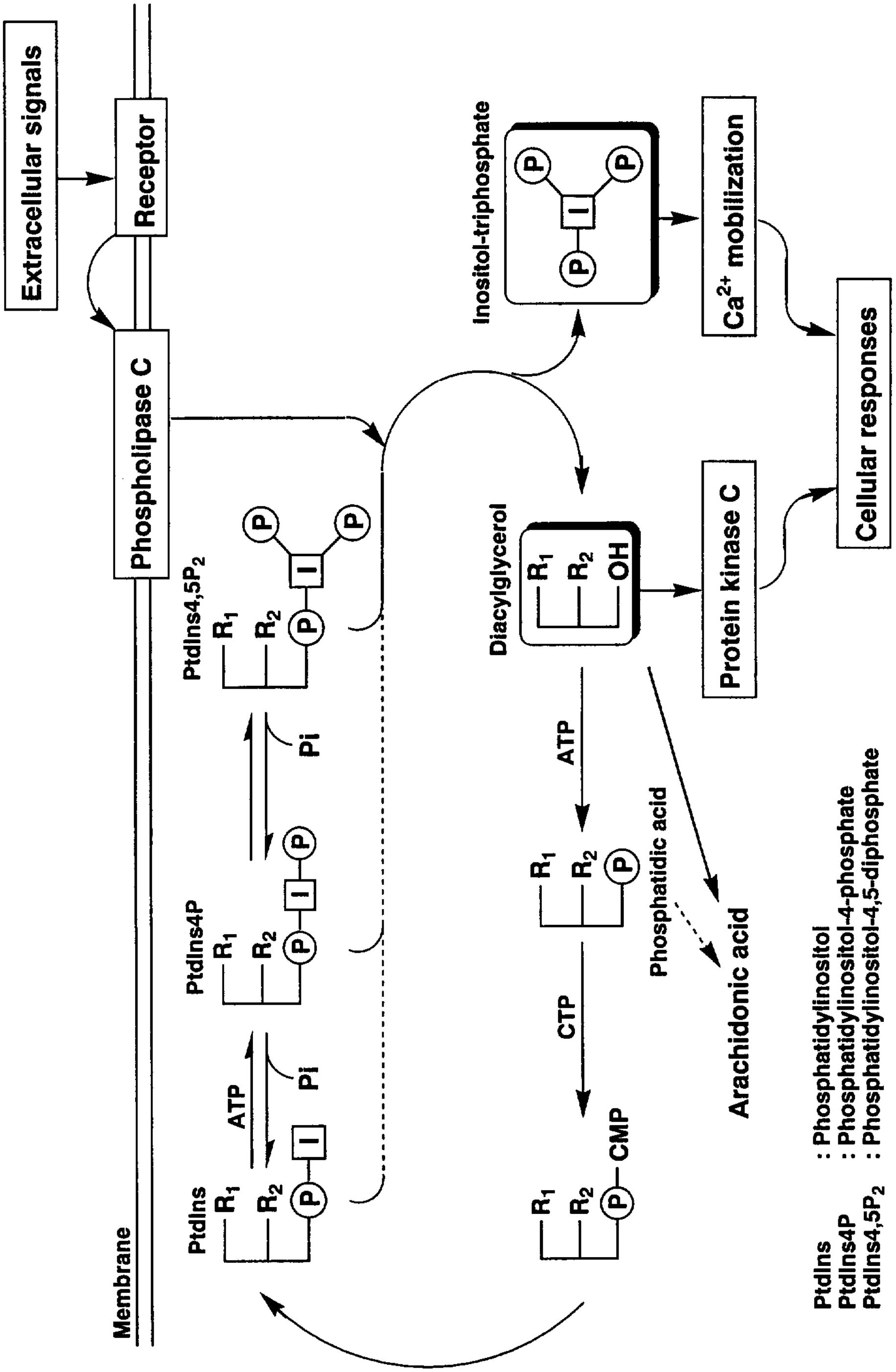
hydrogenolysis to remove a benzyl group from 3-O-benzyl-2-(ω-[^{18}F]fluoroacyl)-1-acylglycerol, which was synthesized by the nucleophilic exchange reaction of 3-O-benzyl-2-(ω-bromoacyl)-1-acylglycerol with [^{18}F]F$^-$ (method B) and 2-(16-[^{18}F]fluoropalmitoyl)-1-palmitoylglycerol (1,2*-[^{18}F]FDAG(C16,C16)) and 2-(8-[^{18}F]fluorooctanoyl)-1-palmitoylglycerol (1,2*-[^{18}F]FDAG(C16,C8)) were produced using method B. The purified 1*,2-[^{18}F]FDAGs were obtained in radiochemical yields of 8-35 % (based on [^{18}F]F$^-$) with radiochemical purities of > 97 % and the purified 1,2*-[^{18}F]FDAGs were in radiochemical yields of 5-15 % with radiochemical purities of > 95 %. The total synthesis time from the start of the reactive [^{18}F]F$^-$ production, including HPLC purification, was 100 - 135 min (method A) and 115 - 175 min (method B), respectively. It has already been used for more than 100 preparations of 1*,2-[^{18}F]FDAG(C16,C16), 1*,2-[^{18}F]FDAG (C8, C16), and 1,2*-[^{18}F]FDAG(C16,C16), 1,2*-[^{18}F]FDAG(C16,C8) for animal studies.

Key words: [^{18}F]labeled 1,2-diacylglycerols, 1-(ω-[^{18}F]fluoroacyl)-2-acylglycerol, 2-(ω-[^{18}F]fluoroacyl)-1-acylglycerol, phosphatidyl-inositol (PI) turnover, positron emission tomography (PET)

Introduction

The receptor-mediated phosphatidyl-inositol (PI) turnover, defined as a second messenger system (Fig. 1), has been recognized as one of the most important systems in the central nervous system. Neuronal manifestations are driven by the second messenger system in synapses through the neurotransmission process. 1)-4) Recently, various intercellular responses by protein kinase C (PKC) linked with PI turnover have been presented. 5)-8) The receptor-mediated PI response images may then reflect neuronal activation in particular neuronal pathways with a high sensitivity based on the common amplifying mechanism of the second messenger system and is suggested to be useful for the study of the mechanism of many neuronal functions and neurological disorders.



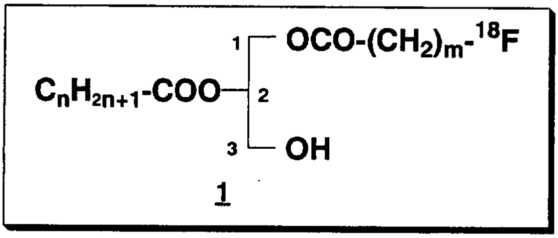
PtdIns : Phosphatidylinositol
PtdIns4P : Phosphatidylinositol-4-phosphate
PtdIns4,5P$_2$: Phosphatidylinositol-4,5-diphosphate

Fig. 1 Inositol phospholipid turnover and signal transduction

Recent new developments in diagnostic imaging techniques using positron emission tomography (PET) have made it possible to measure the binding capacity of many different kinds of neurotransmitter receptors *in vivo*. Information from these images has contributed to the large amount of clinical knowledge about neurological disorders. Based on this information, second messenger imaging *in vivo* studies using PET have been suggested to be effective for the observation of neuronal functions manifested by the synaptic transmission process. Among some components in the PI turnover system, 1,2-diacylglycerols (1,2-DAGs) may be better characterized ligands for imaging receptor-mediated PI turnover responses because 1,2-DAGs are located in the branched point between the PI-turnover and PKC activation and the endogenous modulators of PKC. Imahori *et al.* synthesized 1-palmitoyl-sn-2-[1-^{11}C]butyrylglycerol using [^{11}C]propyl ketene 9) and applied it by PET for assessing PI turnover in the neurotransmission process and for PI turnover imaging linked to the muscarinic cholinergic receptor in the central nervous system. 10)-13) They also used it as a probe of signal transduction in glioma. 14) Hammadri *et al.* reported the synthesis of [^{18}F] or [^{11}C]1,2-diacylglycerols such as 1-palmitoyl-2-[1-^{11}C]acetylglycerol and 1-[8-[^{18}F]fluorooctanoyl]-2-[3-phenylpropanoyl]glycerol in order to study PKC activity in the brain by PET. 15) Most of these reports are generally [^{11}C]labeling of 1,2-DAGs while the systematic [^{18}F]labeling of 1,2-DAGs has not been reported. The short half-life of ^{11}C is disadvantageous for metabolic studies and radiopharmaceutical synthesis, therefore, the labeling with a longer lived positron emitter such as ^{18}F ($t_{1/2}$ = 109.8 min) seems to be more suitable. In recent animal studies using 1,2-[^{18}F]FDAGs, it has become apparent that 1,2-[^{18}F]FDAGs showed a different tissue distribution depending upon the carbon-chain lengths of the acyl groups bonded to glycerol. Among the various synthesized 1,2-[^{18}F] FDAGs, the 1,2-[^{18}F]FDAGs containing one C8-chain-length acyl group and one C16-chain-length acyl group were the best tracers for PI turnover imaging. Therefore, we noted four [^{18}F]labeled compounds -- [^{18}F]labeled at 1 position: 1-(16-[^{18}F]fluoropalmitoyl)-2-palmitoylglycerol (1*,2-[^{18}F]FDAG(C16,C16)), 1-(8-[^{18}F]fluorooctanoyl)-2-palmitoylglycerol (1*,2-[^{18}F]FDAG(C8,C16)) and [^{18}F] labeled at 2 position: 2-(16-[^{18}F]fluoropalmitoyl)-1-palmitoylglycerol (1,2*-[^{18}F]FDAG(C16,C16)), 2-(8-[^{18}F]fluorooctanoyl)-1-palmitoylglycerol (1,2*-[^{18}F] FDAG(C16,C8) -- as the typical and useful 1,2-[^{18}F]FDAGs and planned to synthesize these 1,2-[^{18}F]FDAGs.

In this paper, we report the general [^{18}F]labeling of 1,2-DAGs such as 1*,2-[^{18}F] FDAG(C16,C16), 1*,2-[^{18}F]FDAG(C8,C16), 1,2*-[^{18}F]FDAG(C16,C16) and 1,2*-[^{18}F]FDAG(C16,C8) (Fig. 2).

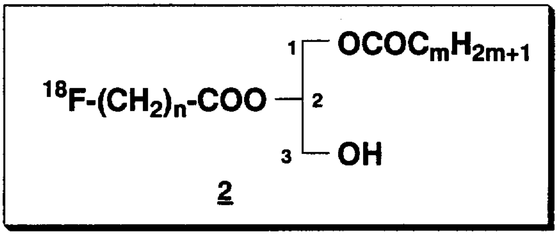
1) 1,2-Diacylglycerols labeled with ^{18}F at 1-position (1*,2-[^{18}F]FDAG)



1c. m=15, n=15 1*,2-[^{18}F]FDAG (C16,C16)
1-(16-[^{18}F]Fluorohexadecanoyl)-2-hexadecanoylglycerol

1d. m=7, n=15 1*,2-[^{18}F]FDAG (C8,C16)
1-(8-[^{18}F]Fluorooctanoyl)-2-hexadecanoylglycerol

2) 1,2-Diacylglycerols labeled with ^{18}F at 2-position (1,2*-[^{18}F]FDAG)



2c. m=15, n=15 1,2*-[^{18}F]FDAG (C16,C16)
2-(16-[^{18}F]Fluorohexadecanoyl)-1-hexadecanoylglycerol

2e. m=15, n=7 1,2*-[^{18}F]FDAG (C16,C8)
2-(8-[^{18}F]Fluorooctanoyl)-1-hexadecanoylglycerol

Fig. 2 Radiopharmaceuticals

footnote: 1-(16-[^{18}F]fluoropalmitoyl)-2-palmitoylglycerol is abbreviated as
1*,2-[^{18}F]FDAG(C16,C16)
1* $^{a)}$,2-[^{18}F]FDAG $^{b)}$ (C16 $^{c)}$,C16 $^{d)}$)
a) *: [^{18}F]labeling position, b) FDAG: fluorodiacylglycerol,
c) carbon-chain number of acyl group bonded at 1-position of glycerol,
d) carbon-chain number of acyl group bonded at 2-position of glycerol

Results and Discussion

The schemes for the synthesis of the starting materials and the standard compounds are shown in Fig. 3.

[^{18}F]Labeling at the 1-position was carried out by the reaction of 2-monoacyl glycerol with ω-[^{18}F]fluoroacyl chloride (Method A) and [^{18}F]labeling at the 2-position by the reaction of 3-O-benzyl-1-acyl-2-(ω-bromoacyl)glycerol with active [^{18}F]F$^-$, followed by removal of the benzyl group by hydrogenolysis (Method B). The [^{18}F]labeling schemes of both methods (Method A and Method B) are shown in Fig. 4 and Fig. 5, respectively.

Preparation of the starting materials and the standard compounds

As shown in Fig. 3, the 3-O-benzyl-1,2-diacylglycerols (8-11) were synthesized from 3-O-benzyl-1,2-isopropylideneglycerol (4) by the stepwise acylation, in which the first acylation at the 1-position proceeded more easily than the second acylation at the 2-position due to the steric hindrance of the O-benzyl group at the 3-position. Compounds 8-11 were characterized by their *i.r.* spectra, ^{1}H-NMR spectra and mass spectra. Generally, their ester groups showed two strong *i.r.* bands at 1730-1740 cm^{-1} and the presence of the bromine atom was strongly supported by the mass fragments. From the ^{1}H-NMR spectra, the signals well-supported the presence of the acyl / ω-bromoacyl (C16, C8) structure, glycerol structure and benzyl structure. These 3-O-benzylglycerol derivatives (8-11) are stable and able to be stored for a long time at room temperature. The synthesized standard fluoro-compounds (13, 14) were also characterized by their *i.r.* spectra, ^{1}H-NMR spectra and mass spectra. Their ester groups and the hydroxy groups showed *i.r.* bands at 1730-1740 and 3300-3600 cm^{-1}, respectively, and based on the mass spectra, their mass fragments showed a pattern similar to those of compounds 8-11. Based on the ^{1}H-NMR spectra, a very high coupling constant derived from the H-F coupling (47 Hz) was observed and the spectra pattern was similar to those of 1,2-dipalmitoylglycerol (8c). Additionary, the elemental analysis

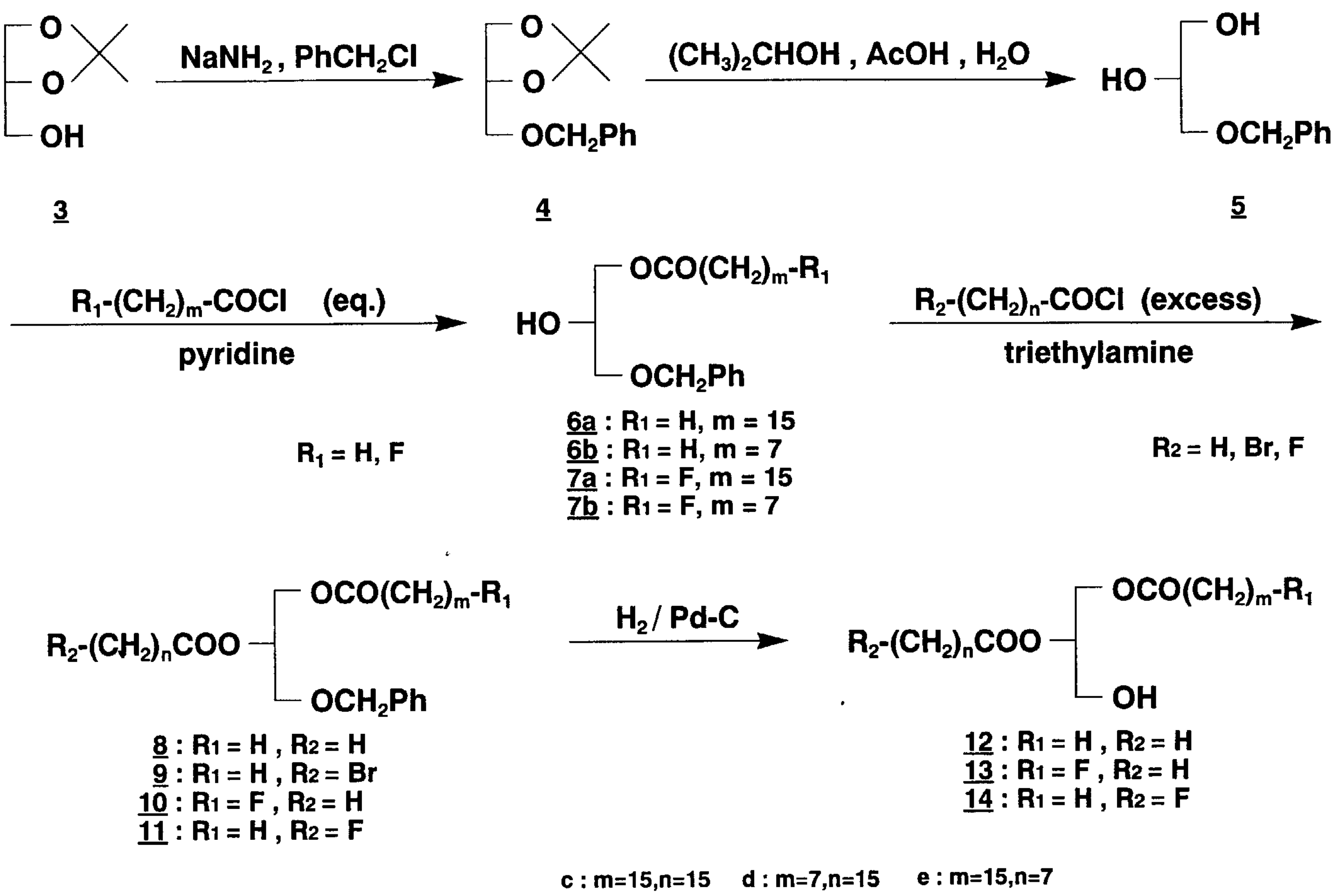


Fig. 3 Preparation of the starting materials and the standard compounds

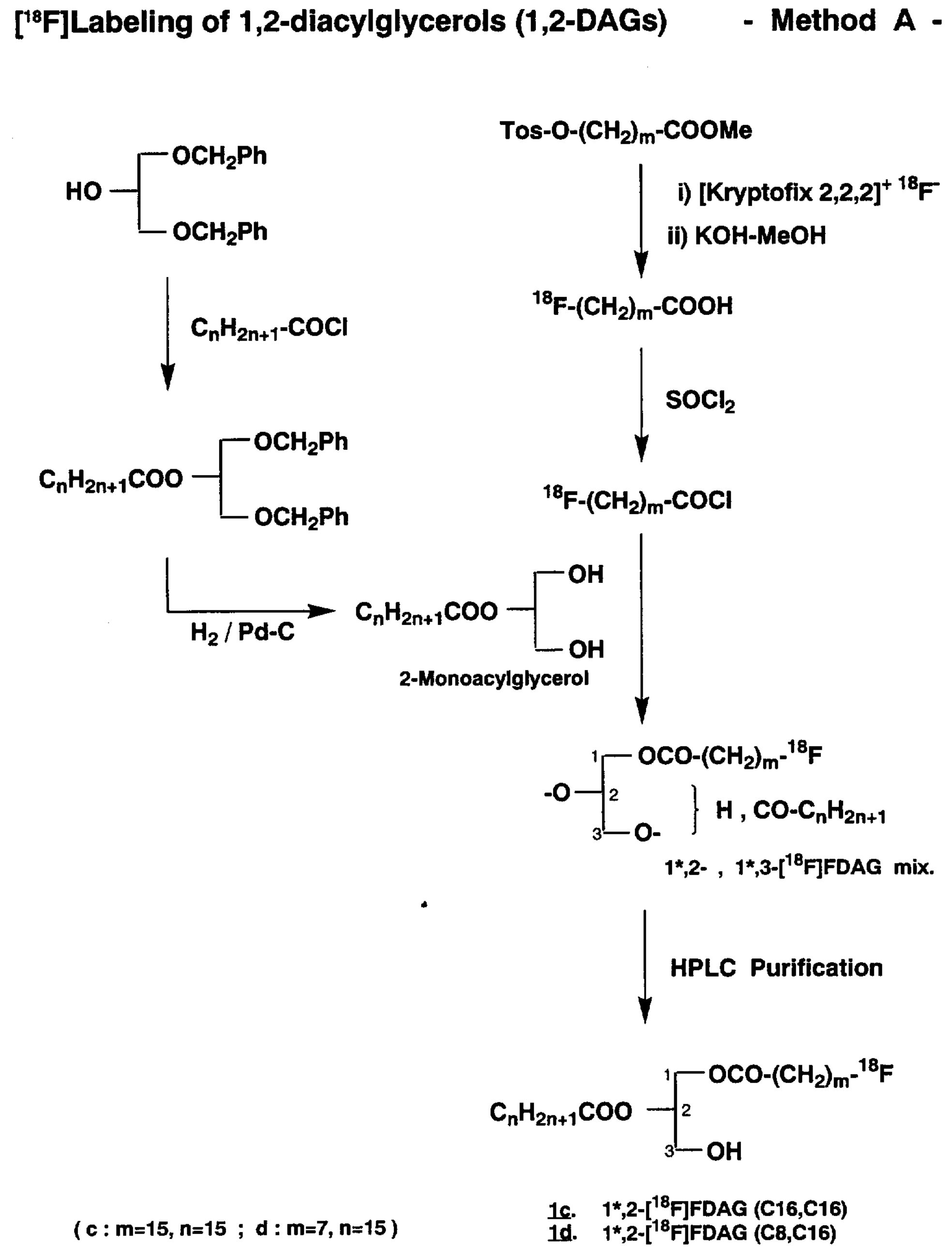


Fig. 4 [^{18}F]Labeling of 1,2-diacylglycerols (1,2-DAGs) - Method A -

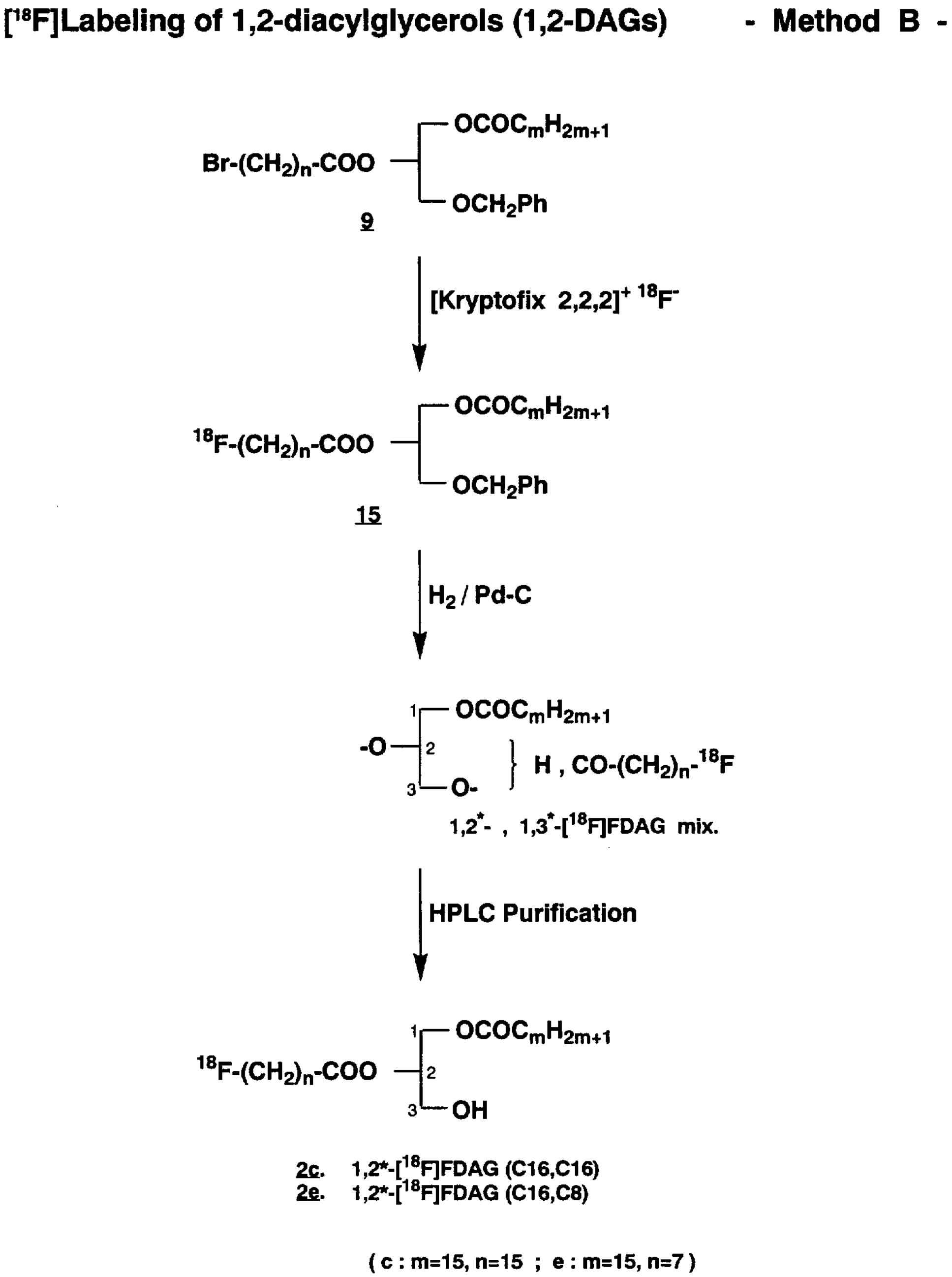


Fig. 5 [^{18}F]Labeling of 1,2-diacylglycerols (1,2-DAGs) - Method B -

of the 3-O-benzyl-compounds (10c and 11c) was carried out because these fluoro-compounds (13c and 14c) are somewhat unstable. These analytical data definitely support their structures.

For [^{18}F]labeling at the 1-position of the 1,2-DAGs, the 2-monoacylglycerols are key compounds (Fig. 4) and the commercially available 2-monoacylglycerols, especially the 2-monoacyl-compounds bonded with lower fatty acids are limited. Therefore, the 2-monoacylglycerol synthesis shown in Fig. 4 seems to be useful for the development of a series of 1,2-[^{18}F]FDAGs with a variety of carbon-chain lengths in spite of the racemic 2-monoacylglycerols formation.

[^{18}F]Labeling, purification

The alkylketene method reported by Imahori et al. 9) is quite effective for the short carbon-chain-length acylation of hydroxy groups. Using this alkylketene method, we tried the synthesis of 1-(4-[^{18}F]fluorobutyryl)-2-palmitoylglycerol (1*,2-[^{18}F]FDAG(C4,C16)) by the reaction of 2-monopalmitin with 4-[^{18}F]fluoropropyl ketene, but several attempts to prepare the 4-[^{18}F]fluoropropyl ketene were not successful. On the basis of the large amount of free ^{18}F formation, the failure was suggested to be caused by cleavage of the C-F bond before the 4-[^{18}F]fluoropropyl ketene formation. However, another reaction such as the acylation of the 2-monoacylglycerols with ω-[^{18}F]fluoroacyl chlorides (Method A) easily proceeded to give the 1*,2-[^{18}F]FDAGs. In Method A, the omission of the ether extraction for the ω-[^{18}F]fluorofatty acids purification resulted in very low radiochemical yields of 1*,2-[^{18}F]FDAG. This may be due to the degradation of the ω-[^{18}F]fluoroacyl chlorides by the unremoved Kryptofix 2,2,2. The radiochromatogram of the 1*,2-[^{18}F]FDAG(C16,C16) synthesis is shown in Fig. 6.

As shown in Fig. 6, 1*,3-[^{18}F]FDAG was formed as a by-product. On the basis of the fact that the acyl group at the 2-position in the glyceride undergoes rearrangement to the 3-position under acidic conditions, 20) this 1*,3-[^{18}F]FDAG was suggested to form from 1*,2-[^{18}F]FDAG. In method A, further HPLC purification step was needed for removing 1*,3-[^{18}F]FDAG.

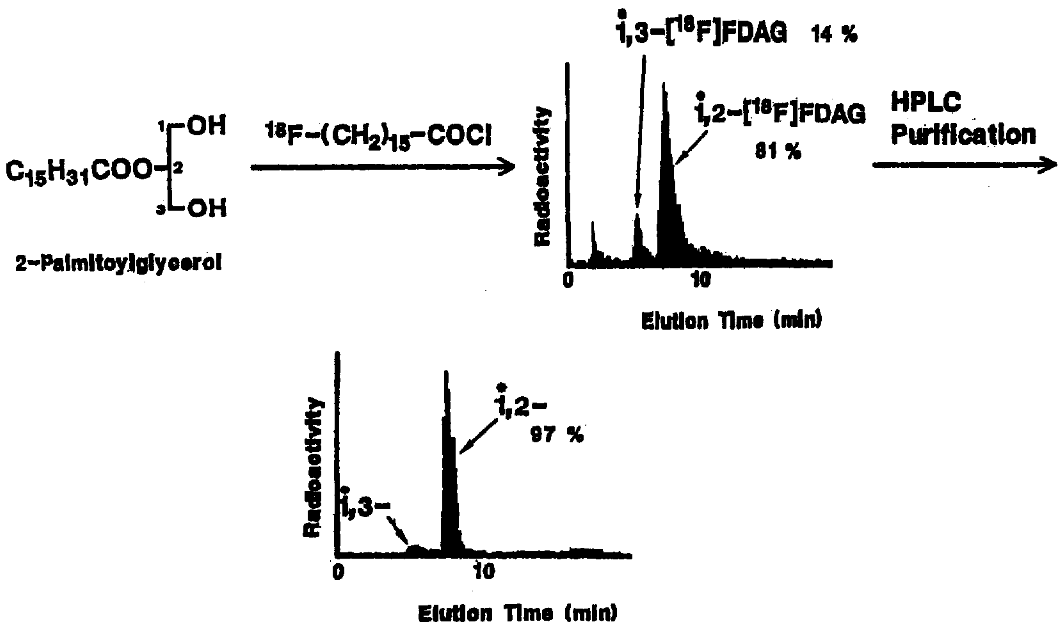


Fig. 6 Radiochromatogram - Synthesis of 1*,2-[^{18}F]FDAG(C16,C16) using Method A -

We then applied Method A to the 1,2*-[^{18}F]FDAG synthesis. The radiochromatogram of the reaction of 16-[^{18}F]fluoropalmitoyl chloride with 1-monopalmitin is shown in Fig. 7.

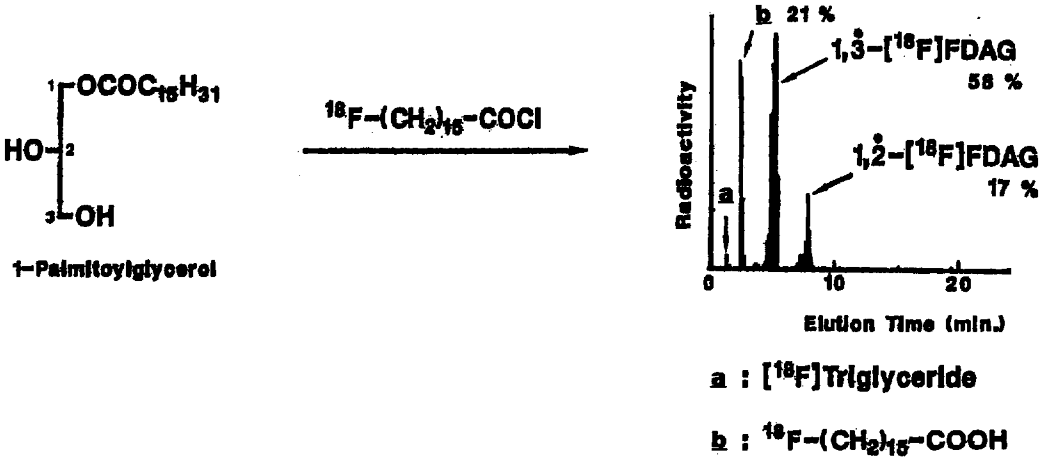


Fig. 7 Radiochromatogram - Synthesis of 1,2*-[^{18}F]FDAG(C16,C16) using Method A -

As shown in Fig. 7, the use of Method A in the 1,2*-[^{18}F]FDAG synthesis is disadvantageous because 1,3*-[^{18}F]FDAG is the main product. This dominant acylation at the 3-position is due to the steric effect of the palmitoyl group at the 1-position. Therefore, for the synthesis of 1,2*-[^{18}F]FDAG, we planned another route using the 3-O-benzyl-2-(ω-bromoacyl)-1-acylglycerols (9c, 9e) (Method B). The radiochromatogram of the 1,2*-[^{18}F]FDAG(C16,C16) synthesis using 3-O-benzyl-2-(16-bromopalmitoyl)-1-palmitoylglycerol(9c) is shown in Fig. 8.

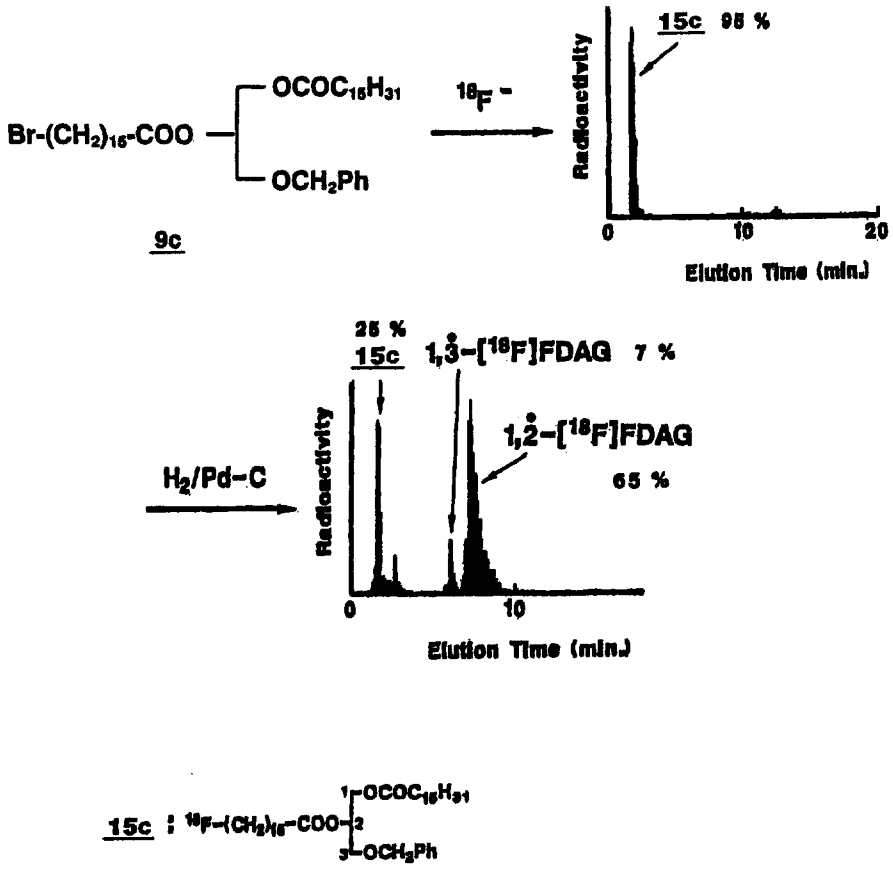


Fig. 8 Radiochromatogram - Synthesis of 1,2*-[^{18}F]FDAG(C16,C16) using Method B -

In this case, 1,2*-[^{18}F]FDAG was the main product, but a small amount of 1,3*-[^{18}F]FDAG was also formed. This 1,3*-[^{18}F]FDAG is suggested to form by rearrangement from 1,2*-[^{18}F]FDAG under acidic hydrogenolysis conditions. In Method B, the removal of the benzyl group by hydrogenolysis at room temperature (for 1 hr) was not effective, but the hydrogenolysis at 45 °C for 20-30 min under acidic conditions gave 1,2*-[^{18}F]FDAG. In this method, the deprotection yields (removal of benzyl group) are not constant and further improvements concerning the protecting groups and deprotection method may be nesessary. The experimental data for the [^{18}F]labeling are summarized in Table 1.

Table 1. Experimental Data of 1,2-[^{18}F]FDAG Synthesis

Compounds	Radiochemical [a] yield (%)	Radiochemical [b] purity (%)	Synthesis time [c] (min.)
[^{18}F]Labeling of 1,2-DAGs at 1 position (Method A)			
1c 1*,2-[^{18}F]FDAG (C16,C16)	8 - 30	> 97	104 - 135
1d 1*,2-[^{18}F]FDAG (C8,C16)	13 - 35	> 97	110 - 127
[^{18}F]Labeling of 1,2-DAGs at 2 position (Method B)			
2c 1,2*-[^{18}F]FDAG (C16,C16)	10 - 15	> 96	145 - 160
2e 1,2*-[^{18}F]FDAG (C16,C8)	5 - 10	> 95	117 - 172

a) based on ^{18}F. decay corrected
b) determined by analytical HPLC (Conditions: See text)
c) including the time required for HPLC purification

Quality control

The radiochemical purities were determined by analytical HPLC. The HPLC retention times of acylglycerol derivatives are listed in Table 2.

1,2- and 1,3-[^{18}F]FDAG could be well-separated by preparative HPLC. The time required for HPLC purification was 15-20 min and the recovery of radioactivity ranged from 47-58 %. Both purified 1*,2-[^{18}F]FDAGs and 1,2*-[^{18}F]FDAGs were obtained with radiochemical purities of > 95 %. Based on the measurement of the cold fluoro-compounds in the final products with a UV-205 nm absorption, the specific activities were calculated to be 11.1-48.1 GBq/μmol (0.3-1.3 Ci/μmol) at the end of the bombardment (EOB).

Table 2. HPLC Retention Times of Fatty Acid / Acylglycerol Derivatives

Compounds	Retention Times (min.)	
	Analytical HPLC $^{a)}$	Preparative HPLC
1,2-Dipalmitin $^{b)}$	9.3	5.7
1,3-Dipalmitin $^{b)}$	5.8	4.2
16-[^{18}F]Fluoropalmitic Acid	3.2	——
8-[^{18}F]Fluorooctanoic Acid	4.0	——
1^*,2-[^{18}F]FDAG (C16,C16) (1c)	8.7	5.4
1^*,3-[^{18}F]FDAG (C16,C16)	5.5	3.9
1^*,2-[^{18}F]FDAG (C8,C16) (1d)	11.5	6.8
1,2^*-[^{18}F]FDAG (C16,C16) (2c)	9.0	5.5
1,2^*-[^{18}F]FDAG (C16,C8) (2e)	12.0	6.6

a) Conditions: See text b) Detected by Refractive Index Detector

Conclusion

We have developed two [^{18}F]labeling methods for the 1,2-diacylglycerols. One is the reaction of the 2-monoacylglycerols with ω-[^{18}F]fluoroacyl chlorides for [^{18}F]labeling at the 1-position of the 1,2-diacylglycerols and the other is the removal of a benzyl group from 3-O-benzyl-2-(ω-[^{18}F]fluoroacyl)-1-acylglycerol for [^{18}F]labeling at the 2-position of the 1,2-diacylglycerols. This result can be applied to the synthesis of 1-(16-[^{18}F]fluoropalmitoyl)-2-palmitoylglycerol (1^*,2-[^{18}F]FDAG (C16,C16)), 1-(8-[^{18}F]fluorooctanoyl)-2-palmitoylglycerol (1^*,2-[^{18}F]FDAG(C8, C16)), 2-(16-[^{18}F]fluoropalmitoyl)-1-palmitoylglycerol (1,2^*-[^{18}F]FDAG(C16,C16)) and 2-(8-[^{18}F]fluorooctanoyl)-1-palmitoylglycerol (1,2^*-[^{18}F]FDAG(C16,C8)) to give sufficient mutimilicurie amounts and purities to allow preparation for medical studies. These two methods have been already used for more than 100 preparations of the above-mentioned four radiopharmaceuticals for animal studies. Now the emulsification of these 1,2-[^{18}F]FDAGs using liposome has been developed and the studies regarding sterility or the presence of endotoxins are also in progress.

Quite recently, Hatano et al. reported interesting data related to the [^{18}F]labeling of the ether-linked analogs of 1,2-DAGs. 21)

Experimental

General

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JNM-FX 100 or JNM-GX 500 spectrometer with TMS as the internal standard, mass spectra on a JMS-DX 303 or JMS-AX 500 mass spectrometer and i.r. spectra on a Jasco A-202 i.r. spectrometer.

Chromatography

Column chromatography and preparative TLC were carried out on silica gel (column chromatography: Wakogel C-200 (Wako Pure Chem. Ind. Ltd.), preparative TLC: DC-Fertig platten Kieselgel 60 F254, Art. 5744 (Merck) using the solvent indicated below. Preparative HPLC was performed using a silica column (YMC-Pack Sil-06, RCM 10 mm i.d. x 25 cm long) with hexane/isoPrOH=9/1 (V/V) as the solvent (flow rate: 5 mL/min) and analytical HPLC using a silica column (Zorbax SIL, 4.6 mm i.d. x 25 cm long) with hexane/ether/isoPrOH=400/80/1.5 (V/V) as the solvent (flow rate: 3 mL/min).

Preparation of the starting materials and the standard compounds

1-Monopalmitin, 2-monopalmitin, 1,2-dipalmitin and 1,3-dipalmitin were purchased from Funakoshi Co., Ltd., 1,2-isopropylideneglycerol (3) and 4-(N,N-dimethyl amino)pyridine were from Tokyo Kasei Kogyo Co., Ltd., sodium amide and palmitoyl chloride were from Wako Pure Chem. Ind., Ltd., 16-hydroxy-hexadecanoic acid, 8-bromooctanoic acid and 1,3-dibenzyloxy-2-propanol were from Aldrich Chem. Co., Inc., and Kryptofix 2,2,2 (K 2,2,2) was from Merck. The benzene and chloroform used were additionary dried from commercially available special grade (Wako Pure Chem. Ind., Ltd.) using 4Å molecular sieves.

Synthesis of 2-monooctanoylglycerol

To a solution of 1,3-dibenzyloxy-2-propanol (1.36 g, 5 mmol) dissolved in benzene (35 mL), a solution of octanoyl chloride (1.22 g, 7.5 mmol) dissolved in benzene (30 mL) and triethylamine (776 mg, 7.7 mmol) were added at room temperature and the mixture was refluxed for 1.5 hr. After removal of the solvent *in vacuo*, H_2O (100 mL) and conc. HCl (20 mL) were added, followed by ether extraction (100 mL x 3). The residue obtained by the evaporation was purified by column chromatography (hexane/CH_2Cl_2=1/1) to give 1,3-di-O-benzyl-2-octanoyl glycerol (1.25 g). Yield: 72 % (from 1,3-dibenzyloxy-2-propanol). colorless oil. MS (m/z) : 307 (M^+ - CH_2Ph), 291 (M^+ - OCH_2Ph), 271 (M^+ - COC_7H_{15}).

To a suspension of 5% Pd-C (20 mg) in ethanol (2 mL), a solution of 1,3-di-O-benzyl-2-octanoylglycerol (70 mg, 0.18 mmol) dissolved in dioxane (2 mL) was added and the mixture was hydrogenated at atmospheric pressure with stirring at room temperature for 3 hr. After removal of the catalyst by filtration, the filtrate was concentrated. The obtained residue was purified by preparative TLC (CH_2Cl_2/ CH_3OH=100 mL/150 drops) to give 2-monooctanoylglycerol (26 mg). Yield: 67 %. pale yellow oil.

Synthesis of 3-O-benzyl-1,2-dipalmitoylglycerol (8c) and 3-O-benzyl-2-(16-bromo palmitoyl)-1-palmitoylglycerol (9c)

16-Bromopalmitoyl chloride: 16-Bromopalmitic acid was synthesized by a method similar to that described in the literature. 16) To the obtained 16-bromopalmitic acid (102 mg, 0.3 mmol), thionyl chloride (5 mL) was added and the mixture was stirred at room temperature for 1 hr. After removal of the excess thionyl chloride *in vacuo*, the residue was used for the next reaction without further purification.

3-O-Benzyl-1,2-isopropylideneglycerol (4): Compound 4 was prepared by a method similar to that described in the literature. 17) To a solution of 1,2-isopropylidene glycerol (3) (44 g, 0.33 mol) dissolved in benzene (83 mL), sodium amide (13 g, 0.33 mol) was added in portions and the mixture was refluxed for 1 hr under an Ar atmosphere. After cooling, benzyl chloride (61 mL, 0.53 mol) was added dropwise and the mixture was refluxed again for 1 day under an Ar atmosphere. After cooling to room temperature, the benzene layer was washed with water (100 mL x 3) and the residue obtained by the evaporation was distilled twice under reduced pressure to give 4 (42 g). Yield: 57 %. b.p.: 120-124 °C/3 torr.

3-O-Benzyl-1-palmitoylglycerol (6a): To 4 (2.2 g, 9.9 mmol), isopropanol (2.2 mL), acetic acid (0.2 mL) and water (1 mL) were added and the mixture was refluxed for 6 hr. After removal of the solvent, the residue (crude 1-O-benzylglycerol (5), colorless oil) was used for the next synthesis without further purification.

To a solution of crude 5 dissolved in chloroform (2 mL), a solution of palmitoyl chloride (2.76 g, 10 mmol) dissolved in chloroform (2 mL) and a solution of pyridine (787 mg, 10 mmol) dissolved in chloroform (1 mL) were added and the mixture was stirred at room temperature for 2 days. After removal of the solvent, 1N HCl (15 mL) was added, followed by ether extraction (15 mL x 3). The residue obtained by the evaporation was purified by column chromatography (hexane/ CH_2Cl_2=1/1) to give 6a (1.25 g). Yield: 30 % (from 4). A small amount of the obtained 6a was characterized after further purification by preparative TLC (hexane /CH_2Cl_2=1/1). m.p.: < 30 °C. IR (KBr): 3470 cm^{-1} (-$\underline{OH}$), 1740 cm^{-1} (-O$\underline{CO}$-). MS (m/z): 420 (M^+), 313 (M^+ - OCH_2Ph), 181 (M^+ - $COC_{15}H_{31}$).

3-O-Benzyl-1,2-dipalmitoylglycerol (8c): To a solution of 6a (141 mg, 0.34 mmol) dissolved in benzene (4 mL), a solution of palmitoyl chloride (250 mg, 0.91 mmol) dissolved in benzene (3 mL) and triethylamine (130 μL, 0.93 mmol) were added and the mixture was refluxed for 1 hr. After removal of the solvent, water (10 mL) and conc. HCl (2 mL) were added, followed by ether extraction (15 mL x 3). The residue obtained by the evaporation was purified by preparative TLC (hexane/ CH_2Cl_2=1/1) to give 8c (174 mg). Yield: 79 %. m.p.: 40-43 °C. IR ($CHCl_3$): 1735, 1730 cm^{-1} (-O$\underline{CO}$- x 2). MS (m/z) : 658 (M^+), 551 (M^+ - OCH_2Ph), 419 (M^+ - $COC_{15}H_{31}$). ^{1}H-NMR ($CDCl_3$) : δ 0.42-1.76 [58H ; m ; -$COCH_2$-$\underline{C_{14}H_{29}}$ x 2], 2.04-2.42 [4H ; m ; -CO-$\underline{CH_2}$-$C_{14}H_{29}$ x 2], 3.58 [2H ; d (J_{HH}=5 Hz) ; -$\underline{CH_2}$-OCH_2Ph], 4.16 , 4.36 [1H , 1H ; d-d ($J_{H_AH_B}$=12 Hz, J_{H_AH}=6 Hz), d-d ($J_{H_BH_A}$=12 Hz, J_{H_BH}=4 Hz) ; -COO-$\underline{CH_AH_B}$-CH(-O-)-CH_2O-], 4.52 [2H ; s ; -O-$\underline{CH_2}$-Ph], 5.22 [1H ; m ; -OCH_2-$\underline{CH}$(-O-)-CH_2O-], 7.32 [arom. 5H].

3-O-Benzyl-2-(16-bromopalmitoyl)-1-palmitoylglycerol (9c): 16-Bromopalmitoyl chloride (0.3 mmol) was reacted with 6a (90 mg, 0.21 mmol) and treated in a manner similar to 8c. The obtained residue was purified by preparative TLC (hexane /CH_2Cl_2=1/4) to give 9c (59 mg). Yield: 37 %. m.p.: < 36 °C. IR ($CHCl_3$): 1740, 1735 cm^{-1} (-O$\underline{CO}$- x 2). MS (m/z) : 631 , 629 (M^+ - OCH_2Ph), 419 (M^+ - CO $(CH_2)_{15}Br$). ^{1}H-NMR ($CDCl_3$): δ 0.88 [3H ; t (J_{HH}=7 Hz) ; -$\underline{CH_3}$), 0.48-2.00 [52H ; m ; $-CH_2\text{-}\underline{(CH_2)_{13}}\text{-}CH_3$ and $-CH_2\text{-}\underline{(CH_2)_{13}}\text{-}CH_2Br$], 2.14, 2.36 [2H, 2H ; t (J_{HH}=7.5 Hz), t (J_{HH}=7.5 Hz) ; $-CO\text{-}\underline{CH_2}\text{-}C_{14}H_{29}$ and $-CO\text{-}\underline{CH_2}\text{-}(CH_2)_{14}Br$], 3.38 [2H ; t ($J_{HH}$=7 Hz) ; $-\underline{CH_2}\text{-}Br$], 3.58 [2H ; d ($J_{HH}$=5 Hz), $-\underline{CH_2}\text{-}OCH_2Ph$], 4.16, 4.36 [1H, 1H ; d-d ($J_{H_AH_B}$=12 Hz, J_{H_AH}=6.5 Hz), d-d ($J_{H_BH_A}$=12 Hz, J_{H_BH}=4 Hz) ; $-COO\text{-}\underline{CH_AH_B}\text{-}CH(\text{-}O\text{-})CH_2O\text{-}$], 4.52 [2H ; s ; $-O\text{-}\underline{CH_2}\text{-}Ph$], 5.22 [1H ; m ; $-OCH_2\text{-}\underline{CH}(\text{-}O\text{-})\text{-}CH_2O\text{-}$], 7.24-7.38 [arom. 5H].

Synthesis of 3-O-benzyl-2-(8-bromooctanoyl)-1-palmitoylglycerol (9e)

8-Bromooctanoyl chloride: 8-Bromooctanoyl chloride was synthesized from 8-bromo octanoic acid (254 mg, 1.14 mmol) in a manner similar to the synthesis of 16-bromopalmitoyl chloride. The obtained residue was used for the next reaction without further purification.

3-O-Benzyl-2-(8-bromooctanoyl)-1-palmitoylglycerol (9e): 8-Bromooctanoyl chloride (1.14 mmol) was reacted with 6a (330 mg, 0.79 mmol) and treated in a manner similar to 8c. The obtained residue was purified by preparative TLC (hexane /CH_2Cl_2=1/1) to give 9e (236 mg). Yield: 48 %. pale yellow oil. IR ($CHCl_3$): 1740, 1735 cm^{-1} (-O$\underline{CO}$- x 2). MS (m/z): 519 , 517 (M^+ - OCH_2Ph), 419 (M^+ - $CO(CH_2)_7$ Br). ^{1}H-NMR ($CDCl_3$): δ 0.88 [3H ; t (J_{HH}=7 Hz) ; -$\underline{CH_3}$), 0.52-2.00 [36H ; m ; $-CH_2\text{-}\underline{(CH_2)_{13}}\text{-}CH_3$ and $-CH_2\text{-}\underline{(CH_2)_5}\text{-}CH_2Br$], 2.16, 2.36 [2H, 2H ; t (J_{HH}=7.5 Hz), t (J_{HH}=7.5 Hz) ; $-CO\text{-}\underline{CH_2}\text{-}C_{14}H_{29}$ and $-CO\text{-}\underline{CH_2}\text{-}(CH_2)_6Br$], 3.40 [2H ; t ($J_{HH}$=7 Hz) ; $-\underline{CH_2}\text{-}Br$], 3.58 [2H ; d ($J_{HH}$=5 Hz), $-\underline{CH_2}\text{-}OCH_2Ph$], 4.16, 4.34 [1H, 1H ; d-d ($J_{H_AH_B}$=12 Hz, J_{H_AH}=6.5 Hz), d-d ($J_{H_BH_A}$=12 Hz, J_{H_BH}=4 Hz) ; $-COO\text{-}\underline{CH_AH_B}\text{-}CH(\text{-}O\text{-})CH_2O\text{-}$], 4.54 [2H ; s ; $-O\text{-}\underline{CH_2}\text{-}Ph$], 5.22 [1H ; m ; $-OCH_2\text{-}\underline{CH}(\text{-}O\text{-})\text{-}CH_2O\text{-}$], 7.23-7.38 [arom. 5H].

Synthesis of 1-(16-Fluoropalmitoyl)-2-palmitoylglycerol (13c)

16-Fluoropalmitoyl chloride: 16-Fluoropalmitic acid was synthesized by a method similar to that described in the literature. 16) To the obtained 16-fluoropalmitic acid (374 mg, 1.4 mmol), thionyl chloride (15 mL) was added and the mixture was stirred at room temperature for 1 hr. After removal of the excess thionyl chloride *in vacuo*, the residue was used for the next reaction without further purification.

3-O-Benzyl-1-(16-fluoropalmitoyl)glycerol (7a): 7a was synthesized from 4 (1.1 g, 5 mmol) and 16-fluoropalmitoyl chloride (1.4 mmol) in a manner similar to the synthesis of 6a. The obtained residue was purified by preparative TLC (hexane/ CH_2Cl_2=3/7) to give 7a (294 mg). Yield: 48 % (from 16-fluoropalmitoyl chloride). colorless oil. IR (KBr): 3470 cm^{-1} (-OH), 1740 cm^{-1} (-OCO-).

3-O-Benzyl-1-(16-fluoropalmitoyl)-2-palmitoylglycerol (10c): Palmitoyl chloride (268 mg, 0.97 mmol) was reacted with 7a (264 mg, 0.6 mmol) and treated in a manner similar to 8c. The obtained residue was purified by preparative TLC (hexane /CH_2Cl_2=1/1) to give 10c (218 mg). Yield: 54 % (from 7a). A small amount of the obtained 10c was characterized after further purification by preparative TLC (hexane/CH_2Cl_2 =2/3). m.p.: 43-45 °C. IR (KBr): 1740, 1735 cm^{-1} (-OCO- x 2). MS (m/z): 419 (M^+ - $CO(CH_2)_{15}F$). ^{1}H-NMR ($CDCl_3$): δ 0.86 [3H ; t (J_{HH}=7 Hz) ; -CH_3), 1.05-1.72 [52H ; m ; -CH_2-$(CH_2)_{13}$-CH_2F and -CH_2-$(CH_2)_{13}$-CH_3], 2.25, 2.30 [2H, 2H ; t (J_{HH}=7.5 Hz), t (J_{HH}=7.5 Hz) ; -CO-CH_2-$(CH_2)_{14}F$ and -CO-CH_2-$C_{14}H_{29}$], 3.58 [2H ; d (J_{HH}=5 Hz) ; -CH_2-OCH_2Ph], 4.17, 4.32 [1H, 1H ; d-d ($J_{H_AH_B}$=12 Hz , J_{H_AH}=6.5 Hz), d-d ($J_{H_BH_A}$ =12 Hz, J_{H_BH}=4 Hz) ; -COO-CH_AH_B-CH(-O-)CH_2O-], 4.41 [2H ; d-t (J_{FH} =47 Hz, J_{HH}=6 Hz) ; -CH_2-F], 4.52 [2H ; s ; -O-CH_2-Ph], 5.22 [1H ; m ; -OCH_2-CH(-O-)-CH_2O-], 7.23-7.38 [arom. 5H]. Anal. calcd for $C_{42}H_{73}O_5F$: C= 74.56, H=10.80. Found: C=74.79, H=10.90.

1-(16-Fluoropalmitoyl)-2-palmitoylglycerol (13c): To a suspension of 5% Pd-C (20 mg) in ethanol (2 mL), a solution of 10c (53 mg, 78 mmol) dissolved in dioxane (2 mL) and conc. HCl (1 drop) were added and the mixture was hydrogenated at atmospheric pressure with stirring at room temperature for 20 hr. After removal of the catalyst by filtration, the filtrate was concentrated. The obtained residue was purified by preparative TLC (CH_2Cl_2 only) to give 13c (17 mg). Yield: 37 %. m.p.:

56-60 °C. IR (KBr): 1740, 1735 cm^{-1} (-OCO- x 2). MS (FAB) (m/z): 587 (M^{+}+1), 331 (M^{+} - $\mathrm{OCOC_{15}H_{31}}$), 313 (M^{+} - $\mathrm{OCO(CH_2)_{15}F}$). ^{1}H-NMR ($\mathrm{CDCl_3}$): δ 0.86 [3H ; t (J_{HH}=7 Hz) ; -$\mathrm{CH_3}$), 1.05-1.72 [52H ; m ; -$\mathrm{CH_2}$-$\mathrm{(CH_2)_{13}}$-$\mathrm{CH_2F}$ and -$\mathrm{CH_2}$-$\mathrm{(CH_2)_{13}}$-$\mathrm{CH_3}$], 2.32, 2.32 [2H, 2H ; t (J_{HH}=7.5 Hz), t (J_{HH}=7.5 Hz) ; -CO-$\mathrm{CH_2}$-$\mathrm{(CH_2)_{14}F}$ and -CO-$\mathrm{CH_2}$-$\mathrm{C_{14}H_{29}}$], 3.71 [2H ; t (J_{HH}=6 Hz) ; -$\mathrm{CH_2}$-OH], 4.21, 4.30 [1H, 1H ; d-d ($J_{H_AH_B}$=12 Hz, J_{H_AH}=6 Hz), d-d ($J_{H_BH_A}$=12 Hz, J_{H_BH}=4.5 Hz) ; -COO-$\mathrm{CH_AH_B}$-CH(-O-)$\mathrm{CH_2OH}$], 4.41 [2H ; d-t (J_{HF}=47 Hz, J_{HH}=6 Hz) ; -$\mathrm{CH_2}$-F], 5.10 [1H ; m ; -$\mathrm{OCH_2}$-CH(-O-)-$\mathrm{CH_2O}$-]

Synthesis of 1-(8-Fluorooctanoyl)-2-palmitoylglycerol (13d)

8-Fluorooctanoyl chloride: 8-Fluorooctanoic acid was synthesized by a method similar to that described in the literature. $^{16)}$ 8-Fluorooctanoyl chloride was prepared from 8-fluorooctanoic acid (243 mg, 1.5 mmol) in a manner similar to the synthesis of 16-bromopalmitoyl chloride. The obtained residue was used for the next reaction without further purification.

3-O-Benzyl-1-(8-fluorooctanoyl)glycerol (7b): 7b was synthesized from 4 (1.1 g, 5 mmol) and 8-fluorooctanoyl chloride (1.5 mmol) in a manner similar to the synthesis of 6a. The obtained residue was purified by preparative TLC (hexane/ $\mathrm{CH_2Cl_2}$=3/7) to give 7b (264 mg). Yield: 54 % (from 8-fluorooctanoyl chloride). colorless oil. IR (KBr): 3460 cm^{-1} (-OH), 1735 cm^{-1} (-OCO-).

3-O-Benzyl-1-(8-fluorooctanoyl)-2-palmitoylglycerol (10d): Palmitoyl chloride (355 mg, 1.3 mmol) was reacted with 7b (261 mg, 0.8 mmol) and treated in a manner similar to 8c. The obtained residue was purified by preparative TLC (hexane/$\mathrm{CH_2Cl_2}$ =1/1) to give 10d (262 mg). Yield : 58 % (from 7b). A small amount of the obtained 10d was characterized after further purification by preparative TLC (hexane/ $\mathrm{CH_2Cl_2}$=2/3). colorless oil. IR (KBr): 1740, 1735 cm^{-1} (-OCO- x 2). MS (m/z): 420 (M^{+} - $\mathrm{CO(CH_2)_7F}$), 326 (M^{+} - $\mathrm{COC_{15}H_{31}}$). ^{1}H-NMR ($\mathrm{CDCl_3}$): δ 0.88 [3H ; t (J_{HH}=7 Hz) ; -$\mathrm{CH_3}$), 1.20-1.72 [36H ; m ; -$\mathrm{CH_2}$-$\mathrm{(CH_2)_5}$-$\mathrm{CH_2F}$ and -$\mathrm{CH_2}$-$\mathrm{(CH_2)_{13}}$-$\mathrm{CH_3}$], 2.33, 2.34 [2H, 2H ; t (J_{HH}=7.5 Hz), t (J_{HH}=7.5 Hz) ; -CO-$\mathrm{CH_2}$-$\mathrm{(CH_2)_6F}$ and -CO-$\mathrm{CH_2}$-$\mathrm{C_{14}H_{29}}$], 3.74 [2H ; d (J_{HH}=6 Hz) ; -$\mathrm{CH_2}$-$\mathrm{OCH_2Ph}$], 4.24, 4.32 [1H, 1H ;

d-d ($J_{H_AH_B}$=12 Hz , J_{H_AH}=6.5 Hz), d-d ($J_{H_BH_A}$=12 Hz, J_{H_BH}=4 Hz) ; -COO-CH_AH_B-CH(-O-)-CH_2O-], 4.43 [2H ; d-t (J_{FH}=47 Hz, J_{HH}=6 Hz) ; -CH_2-F], 4.52 [2H ; s ; -O-CH_2-Ph], 5.09 [1H ; m ; -OCH_2-CH(-O-)-CH_2O-], 7.23-7.38 [arom. 5H].

1-(8-Fluorooctanoyl)-2-palmitoylglycerol (13d): To a suspension of 5% Pd-C (25 mg) in ethanol (2 mL), a solution of 10d (52 mg, 92 mmol) dissolved in dioxane (2 mL) and conc. HCl (1 drop) were added and treated in a manner similar to the synthesis of 13c. The obtained residue was purified by preparative TLC (CH_2Cl_2 only) to give 13d (18 mg). Yield: 41 %. colorless oil. IR (KBr): 1740, 1735 cm^{-1} (-OCO- x 2). MS (m/z): 456 (M^+ - H_2O), 313 (M^+ - $OCO(CH_2)_7F$), 219 (M^+ - OCO $C_{15}H_{31}$). ^{1}H-NMR ($CDCl_3$): δ 0.88 [3H ; t (J_{HH}=7 Hz) ; -CH_3), 1.20-1.72 [36H ; m ; -CH_2-$(CH_2)_5$-CH_2F and -CH_2-$(CH_2)_{13}$-CH_3], 2.03 [1H ; broad ; -OH], 2.33, 2.34 [2H, 2H ; t (J_{HH}=7.5 Hz), t (J_{HH}=7.5 Hz) ; -CO-CH_2-$(CH_2)_6$F and -CO-CH_2-$C_{14}H_{29}$], 3.72 [2H ; t (J_{HH}=6 Hz) ; -CH_2-OH], 4.24, 4.32 [1H, 1H ; d-d ($J_{H_AH_B}$=12 Hz, J_{H_AH}=6.5 Hz), d-d ($J_{H_BH_A}$=12 Hz, J_{H_BH}=4 Hz) ; -COO-CH_AH_B-CH (-O-)-CH_2OH], 4.43 [2H ; d-t (J_{FH}=47 Hz, J_{HH}=6 Hz) ; -CH_2-F], 5.09 [1H ; m ; -OCH_2-CH(-O-)-CH_2O-].

Synthesis of 2-(16-fluoropalmitoyl)-1-palmitoylglycerol (14c)

3-O-Benzyl-2-(16-fluoropalmitoyl)-1-palmitoylglycerol (11c): 16-Fluoropalmitoyl chloride (1.3 mmol) was reacted with 6a (374 mg, 0.89 mmol) and treated in a manner similar to 8c. The obtained residue was purified by preparative TLC (hexane/CH_2Cl_2=1/1) to give 11c (225 mg). Yield: 37 % (from 6a). A small amount of the obtained 11c was characterized after further purification by preparative TLC (hexane/CH_2Cl_2=2/3). m.p.: 40-42 °C. IR (KBr) : 1740, 1735 cm^{-1} (-OCO- x 2). MS (m/z): 676 (M^+), 569 (M^+ - OCH_2Ph), 437 (M^+ - $COC_{15}H_{31}$), 419 (M^+ - $CO(CH_2)_{15}$ F). ^{1}H-NMR ($CDCl_3$): ^{1}H-NMR chart very similar to that of 10c. δ 0.86 [3H ; t (J=7 Hz)], 1.03-1.73 [52H ; m], 2.25, 2.30 [2H, 2H ; t (J=7.5 Hz), t (J=7.5 Hz)], 3.57 [2H ; d (J=5 Hz)], 4.17, 4.32 [1H, 1H ; d-d (J=12 and 6.5 Hz), d-d (J=12 and 4 Hz)], 4.41 [2H ; d-t (J_{HF}=47 and 6 Hz)], 4.52 [2H ; s], 5.22 [1H ; m], 7.23-7.38 [arom. 5H]. Anal. calcd for $C_{42}H_{73}O_5F$: C=74.56, H=10.80. Found: C=74.30, H=11.00.

2-(16-Fluoropalmitoyl)-1-palmitoylglycerol (14c): To a suspension of 5% Pd-C (20 mg) in ethanol (2 mL), a solution of 11c (51 mg, 76 mmol) dissolved in dioxane (2 mL) and conc. HCl (1 drop) were added and treated in a manner similar to 13c. The obtained residue was purified by preparative TLC (CH_2Cl_2 only) to give 16a (14 mg). Yield: 32 %. m.p.: 56-60 °C. IR (KBr): 1740, 1735 cm^{-1} (-OCO- x 2). MS (m/z): 587 (M^++1), 331(M^+ - $OCOC_{15}H_{31}$), 313 (M^+ - $OCO(CH_2)_{15}F$). ^{1}H-NMR ($CDCl_3$): ^{1}H-NMR chart very similar to that of 13c. δ 0.86 [3H ; t (J=7 Hz)], 1.05-1.75 [52H ; m], 2.32, 2.33 [2H, 2H ; t (J=7.5 Hz), t (J=7.5 Hz)], 3.71 [2H ; t (J=6 Hz)], 4.21, 4.30 [1H, 1H ; d-d (J=12 and 6 Hz), d-d (J=12 and 4.5 Hz)], 4.41 [2H ; d-t (J=47 and 6 Hz)], 5.09 [1H ; m]..

Synthesis of 2-(8-fluorooctanoyl)-1-palmitoylglycerol (14e)

3-O-Benzyl-2-(8-fluorooctanoyl)-1-palmitoylglycerol (11e): 8-Fluorooctanoyl chloride (1.6 mmol) was reacted with 6a (462 mg, 1.1 mmol) and treated in a manner similar to 8c. The obtained residue was purified by preparative TLC (hexane/CH_2Cl_2=1/1) to give 11e (298 mg). Yield: 48 % (from 6a). A small amount of the obtained 11e was characterized after further purification by preparative TLC (hexane/CH_2Cl_2=2/3). colorless oil. IR (KBr): 1740, 1735 cm^{-1} (-OCO- x 2). MS (m/z): 420 (M^+ - $CO(CH_2)_7F$), 326 (M^+ - $COC_{15}H_{31}$). ^{1}H-NMR ($CDCl_3$): ^{1}H-NMR chart very similar to that of 10d. δ 0.88 [3H ; t (J=7 Hz)], 1.18-1.76 [36H ; m], 2.31, 2.32 [2H, 2H ; t (J=7.5 Hz), t (J=7.5 Hz)], 3.73 [2H ; d (J=6 Hz)], 4.26, 4.34 [1H, 1H ; d-d (J=12 and 6.5 Hz), d-d (J=12 and 4 Hz)], 4.43 [2H ; d-t (J= 47 and 6 Hz)], 4.53 [2H ; s], 5.09 [1H ; m], 7.20-7.35 [arom. 5H].

2-(8-Fluorooctanoyl)-1-palmitoylglycerol (14e): To a suspension of 5% Pd-C (25 mg) in ethanol (2 mL), a solution of 11e (50 mg, 88 mmol) dissolved in dioxane (2 mL) and conc. HCl (1 drop) were added and treated in a manner similar to the synthesis of 13c. The obtained residue was purified by preparative TLC (CH_2Cl_2 only) to give 14e (16 mg). Yield: 38 %. colorless oil. IR (KBr): 1740, 1735 cm^{-1} (-OCO- x 2). MS (m/z): 456 (M^+ - H_2O), 313 (M^+ - $OCO(CH_2)_7F$), 219 (M^+ - $OCO C_{15}H_{31}$). ^{1}H-NMR ($CDCl_3$): ^{1}H-NMR chart very similar to that of 13d. δ 0.88 [3H ; t (J=7 Hz)], 1.18-1.76 [36H ; m], 2.33, 2.34 [2H, 2H ; t (J=7.5 Hz), t (J=7.5

Hz)], 2.84 [1H ; broad ; -<u>OH</u>], 3.72 [2H ; t (J=6 Hz)], 4.24, 4.32 [1H, 1H ; d-d (J=12 and 6.5 Hz), d-d (J=12 and 4 Hz)], 4.43 [2H ; d-t (J=47 and 6 Hz)], 5.10 [1H ; m].

^{18}F-Labeling

Production of [^{18}F]fluoride

[^{18}F]Fluoride was produced via the ^{18}O(p,n)^{18}F reaction by proton bombardment (18 MeV, 10 μA) of a circulating 20 % enriched [^{18}O]water target using the CGR-MeV model 680 Cyclotron located at Tohoku University. 18)

Synthesis of 1-(ω-[^{18}F]Fluoroacyl)-2-acylglycerols (1*,2-[^{18}F]FDAGs) (1)

The [^{18}F]labeling scheme is shown in Fig. 4. As a typical example, the synthetic procedure for 1*,2-[^{18}F]FDAG(C16,C16) is described.

<u>1-(16-[^{18}F]Fluoropalmitoyl)-2-palmitoylglycerol (1*,2-[^{18}F]FDAG(C16,C16) (1o)</u>: 16-[^{18}F]Fluoropalmitic acid was prepared using K 2,2,2 (25 mg, 66 μmol) and methyl 16-O-tosylpalmitate (6 mg, 14 μmol) by a method similar to that described in the literature. 16),19) To the obtained 16-[^{18}F]fluoropalmitic acid, thionyl chloride (500 μL) was added and the mixture was stirred at room temperature for 5 min. After complete removal of the excess thionyl chloride in vacuo, a solution of 2-mono palmitin dissolved in dry CH_2Cl_2 (1 mL) and 4-(N,N-dimethylamino)pyridine (1-2 pieces) were added and the mixture was stirred again for another 5 min at room temperature. Afer removal of the solvent, water (10 mL) and 2N HCl (1 mL) were added, followed by ether extraction (10 mL x 3). The residue obtained by the evaporation was redissolved in chloroform (ca. 1 mL) and subsequent purification was done by preparative HPLC.

Synthesis of 1-acyl-2-(ω-[^{18}F]Fluoroacyl)glycerols (1,2*-[^{18}F]FDAGs) (2)

The [^{18}F] labeling scheme is shown in Fig. 5. As a typical example, the synthetic procedure for 1,2*-[^{18}F]FDAG(C16,C16) is described.

2-(16-[^{18}F]Fluoropalmitoyl)-1-palmitoylglycerol (1,2*-[^{18}F]FDAG(C16,C16) (2c): ^{18}F was introduced in a manner similar to the synthesis of 16-[^{18}F]fluoropalmitic acid. 16), 19) To the [^{18}F]water (100-400 μL), 0.15M K_2CO_3 aq. sol. (200 μL) and a solution of K 2,2,2 (25 mg, 66 μmol) dissolved in acetonitrile (1 mL) were added. While purging with flowing N_2, the solvent was completely evaporated to dryness at 120 °C. To the residue, a solution of compound 9c (7.5 mg, 12 μmol) dissolved in acetonitrile (1 mL) was added and then the mixture was refluxed for 10 min at 120 °C. After removal of the solvent, water (10 mL) and 2N HCl (1 mL) were added, followed by ether extraction (10 mL x 3). The crude 3-O-benzyl-2-(16-[^{18}F]fluoro palmitoyl)-1-palmitoylglycerol (15c) obtained by the evaporation was used for the next reaction without further purification.

To a suspension of 5% Pd-C (20 mg) in ethanol (2 mL), a solution of 15c dissolved in dioxane (2 mL) and conc. HCl (1 drop) were added and the mixture was hydrogenated at atmospheric pressure with stirring at 45 °C for 30 min. After removal of the catalyst by filtration, the filtrate was concentrated. The residue was redissolved in chloroform (ca. 1 mL) and the purification was performed using the same preparative HPLC system as that for the 1*,2-[^{18}F]FDAG(C16,C16) synthesis.

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