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Evaluation of the Effect of Fluorination on the Property of Monofluorinated Dimyristoylphosphatidylcholines

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The synthesis of three monofluorinated dimyristoylphosphatidylcholines (F-DMPC's), with the fluorine atom located at the extremities of the acyl chain in position 2 of the glycerol (*sn*-2), is described. The synthetic strategy relies on the coupling of 1-myristoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (14:0 lyso-PC) and three different fluorinated fatty acids. FTIR results suggest that the presence of the fluorine atom does not significantly perturb the lipid phase transition temperature and conformational order even though a small increase in the phase transition temperature is observed for the 14F derivative. Overall, comparison with previously reported F-DMPC's where the fluorine atom is located in the middle or close from either side supports the fact that monofluorination of the acyl chain in *sn*-2 brings minimal perturbation to the lipid bilayer. F-DMPC's could therefore potentially be used as NMR probes for the investigation at the molecular level of the interaction between drugs or peptides and lipid membranes and for the study of membrane topology.

Introduction

Fluorine is increasingly used for nuclear magnetic resonance spectroscopy studies of biological systems since this element offers several advantages over other nuclei. ^{19}F is a 100% natural abundant spin-1/2 nucleus with a high gyromagnetic ratio. This allows for fast accumulation of highly resolved spectra which are simplified compared to nuclei with a quadrupolar moment.[1] Notably, ^{19}F relative sensitivity is about 83% that of ^{1}H, which is much greater than the relative sensitivities of ^{13}C (1.6%) and ^{15}N (0.1%). In addition, its large spectral width and the absence of fluorine in native biological components allow respectively the detection of even slight variations of the fluorine chemical environment and the selective detection of the labeled sites.[1] Finally, compared to several other nuclei such as ^{13}C and ^{15}N, for which expensive isotope labeling is necessary,[1b] the use of the 100% abundant ^{19}F nuclei provides a more facile access to the labelled compounds especially given the recent development in synthetic organofluorine chemistry.[2]

Overall, these characteristics make ^{19}F NMR spectroscopy very attractive to study biological systems with fluorine labeled molecules such as drugs, peptides, proteins and nucleic acids.[3,4] While ^{19}F solution NMR spectroscopy has been widely used for structural and functional studies[1b,5] or for drug discovery,[1b,6] ^{19}F solid-state NMR spectroscopy is ideal for the study of complex of biomolecules with lipid bilayers[1a] as exemplified with recent reports.[7] In these systems, the fluorine atom is located directly on the biomolecules under investigation.[8] An interesting complementary alternative is to incorporate the ^{19}F label into the lipid bilayer.[9]

Natural cell membranes contain several components, including various lipids, proteins and cholesterol, which render spectroscopic analyses very difficult.[10] Since the major component of cell membranes is lipid, model membranes composed of phospholipids are widely used in the literature to simplify the study of cell membranes. In particular, dimyristoylphosphatidylcholine (DMPC) is often used to mimic eukaryotic membranes.[11]

The incorporation of fluorine atoms on phospholipids has been explored before and those studies have shown that the number of fluorine atoms and their specific positions influence significantly the perturbation of the lipid bilayers observed. While the introduction of one or two perfluorinated side chains (number of fluorine per side chain > 2) on phosphatidylcholines systematically disturbs the properties of the lipids,[12] less fluorinated lipids behave differently (Figure 1). For instance, the presence of fluorine atoms on DMPC analogs **1**[13] and **2**,[14] containing *gem*-difluorinated groups, and DPPC (dipalmitoylphosphatidylcholine) analogs **3**,[15] which contain one fluorine atom on each acyl chain, induces a significant disorder of the lipid bilayers characterized by a decrease in the phase transition temperature of up to 12, 11 and 5 °C

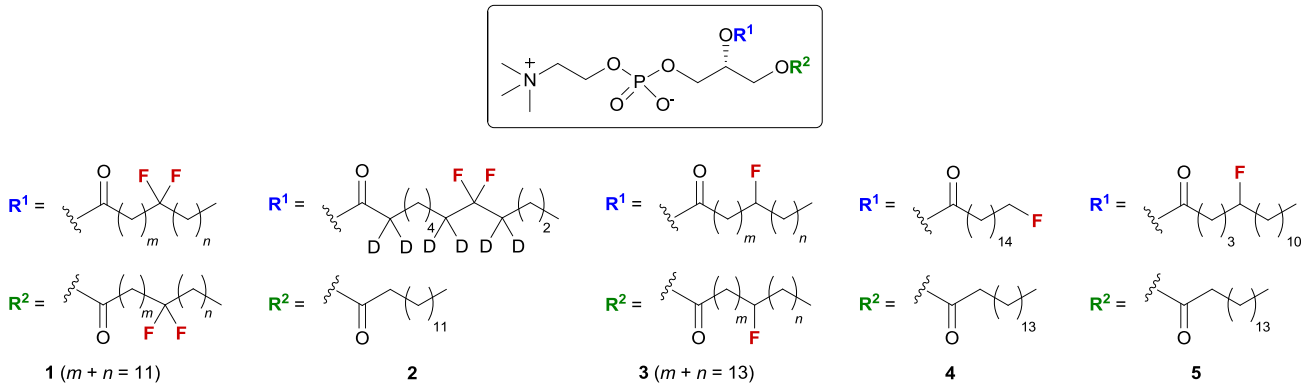


Fig. 1 Polyfluorinated and monofluorinated phosphatidylcholines previously reported.

respectively compared to the non-fluorinated analog. In contrast, DPPC monofluorinated analog **4** was shown to stabilise the lipid bilayers, increasing its phase transition temperature by about 10 °C as a result of the formation of interdigitated bilayers.[16] Nevertheless, it was shown that mixture of fluorinated lipids (**4** and **5**) with non-fluorinated analogs may minimise the perturbation.[17]

With the goal of using fluorinated lipids as molecular probes in ^{19}F solid-state NMR for the study of biomolecules, we have reported the synthesis of three monofluorinated dimyristoylphosphatidylcholines (F-DMPC's) with the fluorine atom located in the middle (7F-DMPC) or close from either side (4F- and 10F-DMPC) on the acyl chain at position two of the glycerol (Figure 2).[18] FTIR studies indicated that the presence of the fluorine atom in pure lipid or in mixtures with DMPC brought minimal perturbation. However, for extensive and complete studies of membrane topology, it would also be of interest to use lipids with the fluorine atom located at the extremities of the lipid acyl chain. Herein, we therefore report the synthesis and characterization by FTIR of three novels F-DMPC's with the fluorine located at both ends of the acyl chain (2F-DMPC, 12F-DMPC and 14F-DMPC) (Figure 2).

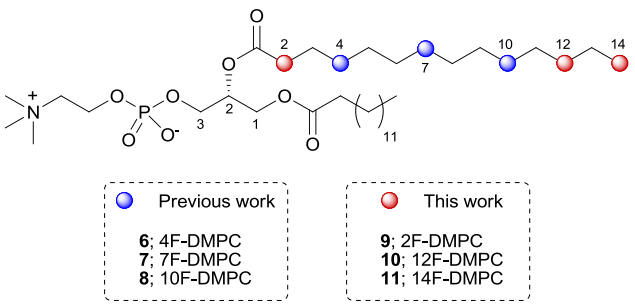


Fig. 2 Previously reported and targeted monofluorinated 1,2-dimyristoyl-*sn*-glycero-3-phosphocholines (F-DMPC's). The colored circle represents the carbon bearing the fluorine atom.

Results and discussion

Synthesis of monofluorinated dimyristoylphosphatidylcholines.

Our synthetic strategy for the synthesis of the targeted F-DMPC (**9-11**) relied on the coupling of commercially available 1-myristoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (14:0 lyso-PC, **15**) and fluorinated fatty acids (**12-14**) (Figure 3). The latter were obtained from different and complementary synthetic routes.

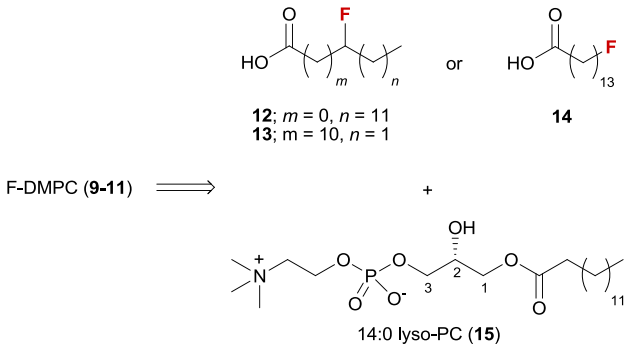
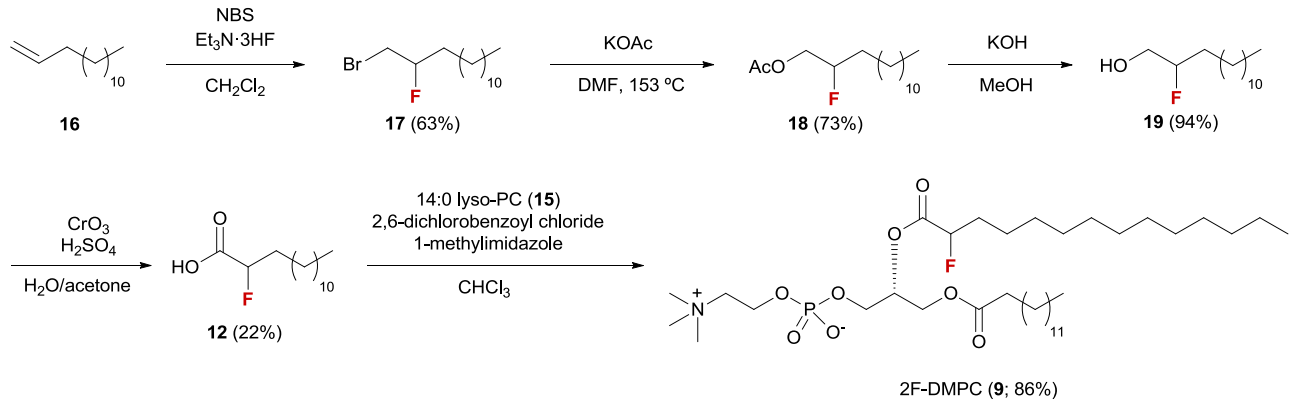


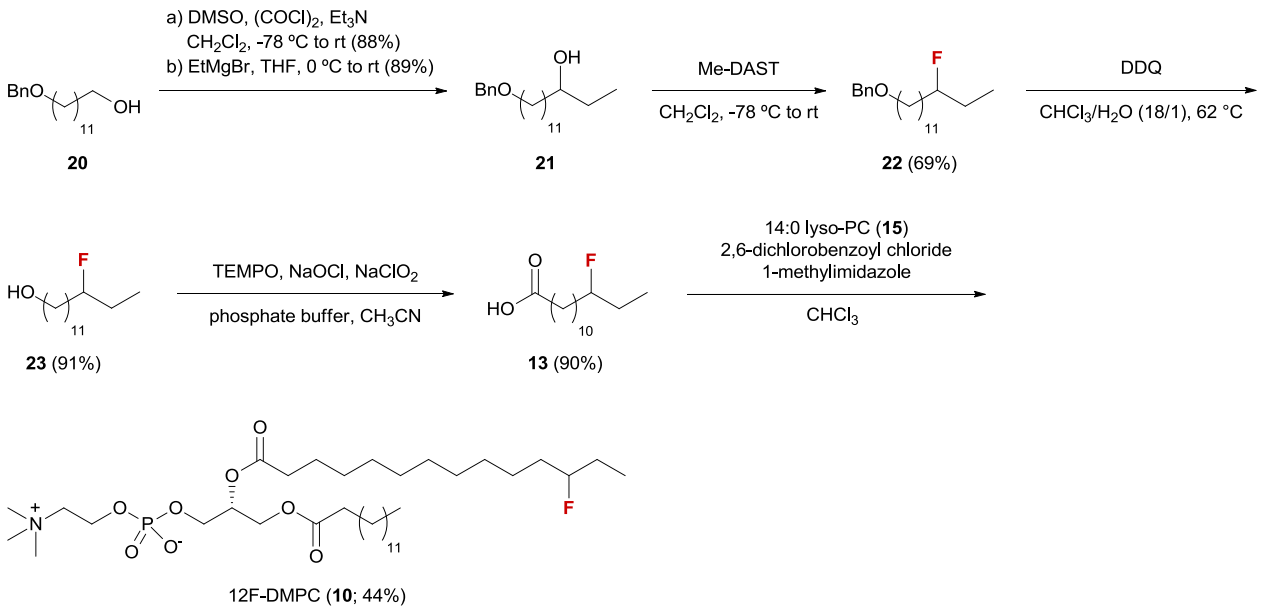
Fig. 3 Retrosynthetic analysis.

The synthesis of 2F-DMPC was inspired by the work performed by Haufe and coworker (Scheme 1).[19] Thus, bromofluorination[20] of commercially available 1-tetradecene (**16**) using NBS and $Et_3N{\cdot}3HF$ produced 1-bromo-2-fluorodotetradecane (**16**) in moderate yield after flash chromatography contaminated with small amount (ca. 2%) of the inseparable regioisomer, 2-bromo-1-fluorotetradecane.[21] Formation of acetate **19** using potassium acetate followed by hydrolysis under basic conditions produced alcohol **19**. Both steps proceeded efficiently. Oxidation of **19** to the carboxylic acid **12** was problematic. Indeed, of the numerous methods investigated, only Jones oxidation provided the desired acid in a poor 22% yield. Finally, the racemic fluorinated fatty acid **12** was coupled with 14:0 lyso-PC (**15**) in good yield[22] to give pure 2F-DMPC (**9**) in 86% yield after purification by flash chromatography on silica gel. An overall yield of 8% was obtained for the 5 synthetic steps.

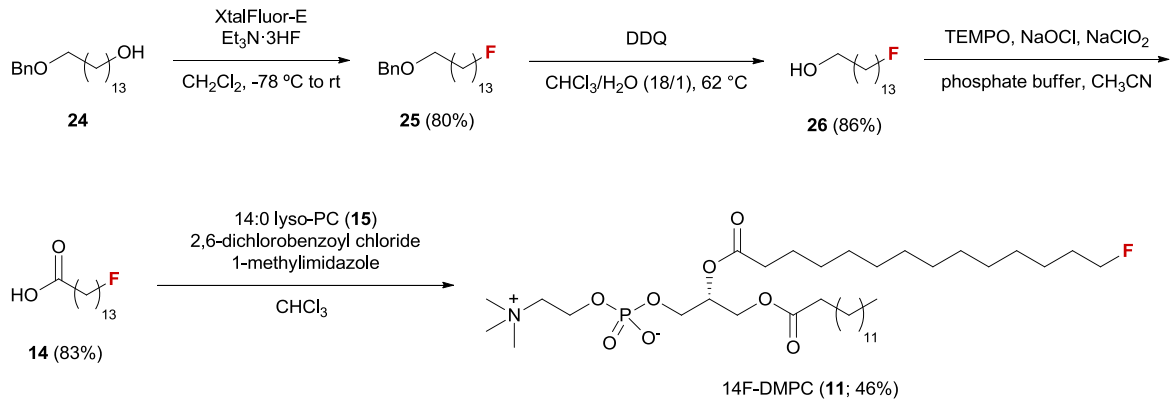


Scheme 1 Synthesis of 2F-DMPC.

The synthesis of 12F-DMPC was conducted similarly to 4F-DMPC (Scheme 2).[18] Readily prepared 1,12-dodecanediol, monobenzyl ether (**20**)[23], was oxidized to the aldehyde[24] followed by addition of ethylmagnesium bromide to give the secondary alcohol (**21**). Deoxofluorination using Me-DAST[25] gave the fluoro compound **22** in moderate yield. Surprisingly, the removal of the benzyl under hydrogenolysis conditions proved difficult and DDQ was employed for this step.[26] Finally, oxidation of the primary alcohol in one step to the carboxylic acid using TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl)[27] provided the racemic fluorinated acid **13** that was coupled with 14:0 lyso-PC (**15**) in moderate yield[22] after purification by flash chromatography on silica gel. An overall yield of 19% was obtained for the 6 synthetic steps starting from **20**. Finally, 14F-DMPC (**11**) was prepared starting from readily available monobenzylether **24** (Scheme 3).[28] Deoxofluorination with XtalFluor-E ($[Et_2NSF_2]BF_4$)[29] and $Et_3N{\cdot}3HF$ as an external source of fluoride provided fluoride **25** in good yield. Deprotection of the benzyl ether with DDQ[26] followed by TEMPO oxidation gave the acid **14**. Finally, coupling with 14:0 lyso-PC (**15**) provided 14F-DMPC (**11**) in 46% yield[22] after purification by flash chromatography on silica gel. An overall yield of 26% was obtained for the 4 synthetic steps starting from **24**.



Scheme 2 Synthesis of 12F-DMPC.



Scheme 3 Synthesis of 14F-DMPC.

Characterization of monofluorinated dimyristoylphosphatidylcholines.

FTIR spectroscopy was used in the present study to investigate how the introduction of a fluorine atom affects the order of the lipid acyl chains. More specifically, monitoring the CH_2 symmetric (2850 cm^{-1}) stretching vibration, which has been shown to be sensitive to *anti/gauche* isomerization in the lipid acyl chains, yields valuable information about the lipid gel-to-fluid phase transition temperature and the conformational order of the acyl chains.[30]

The wavenumbers of the CH_2 stretching vibration as a function of temperature for pure commercial DMPC, for the three novel pure F-DMPC derivatives investigated in the present study (2F-DMPC, 12F-DMPC and 14F-DMPC) and the three previously reported F-DMPC derivatives (4F-DMPC, 7F-DMPC, 10F-DMPC) are shown in Figure 4 and the lipid phase transition temperatures for these six pure F-DMPC derivatives are reported in Table 1. The results first indicate that the properties of the lipid bilayer are not significantly affected by the presence of a fluorine atom at positions 2, 12 and 14 of the lipid acyl chains. The result with 2F-DMPC is somewhat surprising given that the fluorine atom is located closely to the carbonyl group which might influence the conformational possibilities. Nonetheless, the IR results suggest that it is not the case. However, the introduction of a fluorine atom results in a small increase in the CH_2 stretching vibration wavenumber associated with a small increase in the number of gauche conformers for the 12F and 14F derivatives, while a small decrease in the lipid phase transition temperature and a slight broadening of the phase transition are observed for the 2F and 12F derivatives. On the other hand, the lipid phase transition temperature is slightly increased for the 14F derivative. Comparison with results obtained for the previously reported 4F, 7F and 10F derivatives indicates that the increase in the CH_2 stretching vibration wavenumber is more important for the 7F and the 10F-DMPC derivatives than for the other derivatives, suggesting that the perturbation of lipid conformational order induced by the fluorine atom is greater towards the center of the lipid hydrophobic core. However, the results indicate that the lipids form a homogeneous mixture as a single phase transition temperature is observed for all six derivatives.

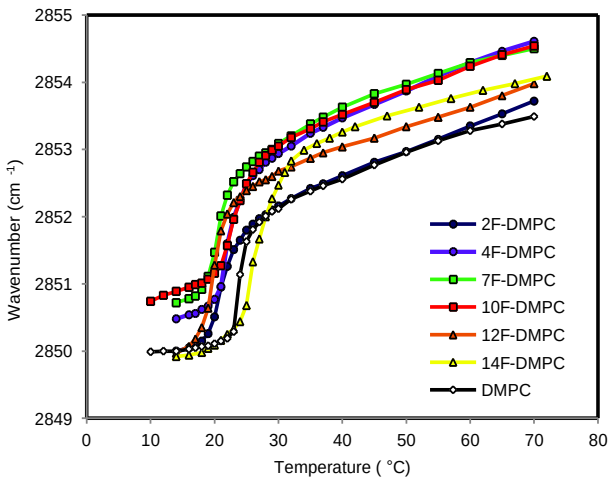


Fig. 4 Temperature dependence of the wavenumber of the CH_2 symmetric stretching vibration for DMPC and F-DMPC's.The error is estimated to be ± 0.1 cm^{-1}.

Previous studies on lipids monofluorinated on both acyl chains have shown that the order of the lipid bilayers is not significantly perturbed by the introduction of the fluorine atom.[15] These results are therefore in agreement with the results obtained in the present study with the three novel monofluorinated lipid derivatives and results previously reported with the 4F, 7F and 10F derivatives. However, other studies have shown a significant decrease of the lipid gel-to-fluid phase transition temperature upon the introduction of more than one fluorine atom on one or two acyl chains.[13,14,31,32] In particular, the introduction of two fluorine atoms on the *sn*-2 acyl chain results in a decrease of the phase transition temperature by about 5-11 °C[31] and the introduction of 13 fluorine atoms on both acyl chains results in a decrease of the phase transition temperature by ~21 °C.[32] On the other hand, an increase of the CH_2 stretching vibration wavenumber of ~2.5

cm^{-1} in the gel phase and a significant broadening (by about 12 ºC) of the phase transition are observed with the introduction of 13 fluorine atoms on both acyl chains.[32] It has also been shown that the introduction of two fluorine atoms at position 4 of the *sn*-2 acyl chain has less effect than the introduction of two fluorine atoms at positions 8 and 12,[31] which is in agreement with our results with monofluorinated lipids indicating that the most significant perturbation of the lipid conformational order is observed with the 7F and 10F-DMPC derivatives. Similar results have also been obtained upon the introduction of two fluorine atoms at positions 4, 8 and 12 of the two acyl chains.[13] ^{2}H solid-state NMR spectroscopy results also indicate that the order of the methylene groups close to two fluorine atoms at position 8 of the *sn*-2 acyl chain is decreased by about 30% due to the increased size of the ^{19}F label.[14] It is also interesting to note that the introduction of a fluorine atom at position 16 in the *sn*-2 chain of dipalmitoylphosphatidylcholine (DPPC) results in interdigitated lipid bilayers with increased order.[16] However, only a small increase in the phase transition temperature is observed for the novel 14F derivatives investigated in the present study, indicating that, interestingly, the introduction of a fluorine atom at position 14 of the *sn*-2 acyl chain of DMPC does not lead to the formation of fully interdigitated bilayers. The small increase in the phase transition temperature might however be associated with partial interdigitation. Nevertheless, this effect is small and the 14F derivative could therefore be used for membrane topology studies, as opposed to the 16F derivative. Finally, as all the fluorinated fatty acids were racemic (with the exception of 14F-DMPC as the fluorine is not located on a stereocenter), the corresponding F-DMPC's were isolated and characterized as a 1:1 mixture of diastereoisomers. The results obtained so far suggest that this has no impact on the behavior of the lipids. Indeed, 2F-DMPC, for which the C-F stereocenter is the closest to the chiral backbone of the lipid (i.e. the glycerol), does not show a different behavior compared to the other ones, for which the C-F stereocenter is further.

Figure 5 shows the wavenumbers of the CH_2 stretching vibration as a function of temperature obtained for mixture of pure commercial DMPC, for the three novel F-DMPC derivatives and the three previously reported F-DMPC derivatives at different percentages ranging from 2.5 to 100%. (F-DMPC/DMPC). The lipid phase transition temperatures for the pure DMPC and F-DMPC lipids, as well as for various mixtures, are also reported in Table 1. The lipid phase transition temperature and lipid order are slightly decreased at high ratios of fluorinated lipids (percentages of 50 and 100%) for the 2F and 12F derivatives, while the lipid phase transition temperature is slightly increased at high fluorinated lipid ratios for the 14F derivative. Comparison with the results obtained for the three previously reported 4F, 7F and 10F DMPC derivatives indicates that the effect on the phase transition temperature is more important for the 7F and 12F-DMPC derivatives. However, the results presented in Figure 5 and Table 1 clearly indicate that the presence of the fluorine atom does not significantly perturb the lipid phase transition temperature and conformational order at smaller ratios for every fluorinated lipids, namely at F-DMPC percentages between 2.5 and 25%. These results therefore indicate that all F-DMPC derivatives could be successfully used as probes for membrane topology at percentages up to 25% in non-fluorinated lipids without significantly affecting the properties of the lipid bilayers.

Conclusions

Three monofluorinated dimyristoylphosphatidylcholines with the fluorine atom located at the extremities of the acyl chain in position 2 of the glycerol were synthesized in in 4-6 synthetic steps and 8-26% overall yields from commercially or readily available starting materials. FTIR results indicate that the presence of the fluorine atom on the three novel derivatives does not significantly perturb the lipid phase transition temperature and conformational order at ratios of fluorinated lipids up to 25%, in agreement with results previously reported for the 4F, 7F and 10F derivatives. Overall, monofluorination of the acyl chain in *sn*-2 brings minimal perturbation to the lipid bilayer. These monofluorinated lipids could therefore potentially be used as NMR probes for the investigation at the molecular level of the interaction between drugs or peptides and lipid membranes and for the study of membrane topology.

Table 1 Phase transition temperature for pure F-DMPC's, DMPC and for mixtures with DMPC. The error is estimated to be ± 0.5 °C.

F-DMPC:DMPC	Phase transition temperature (°C)					
	2F-DMPC	4F-DMPC	7F-DMPC	10F-DMPC	12F-DMPC	14F-DMPC
100:0	22.1	22.5	20.4	22.0	19.5	25.6
25:75	22.5	22.5	23.5	22.5	21.7	24.5
10:90	22.5	23.5	23.6	22.9	22.2	24.3
5:95	23.2	23.6	24.4	22.6	22.5	23.7
0:100[a]	23.5	23.7	24.5	23.7	23.5	23.5

[a] Different phase transition temperatures are reported for pure DMPC as these temperatures have been measured for every series with the different F-DMPC derivatives.

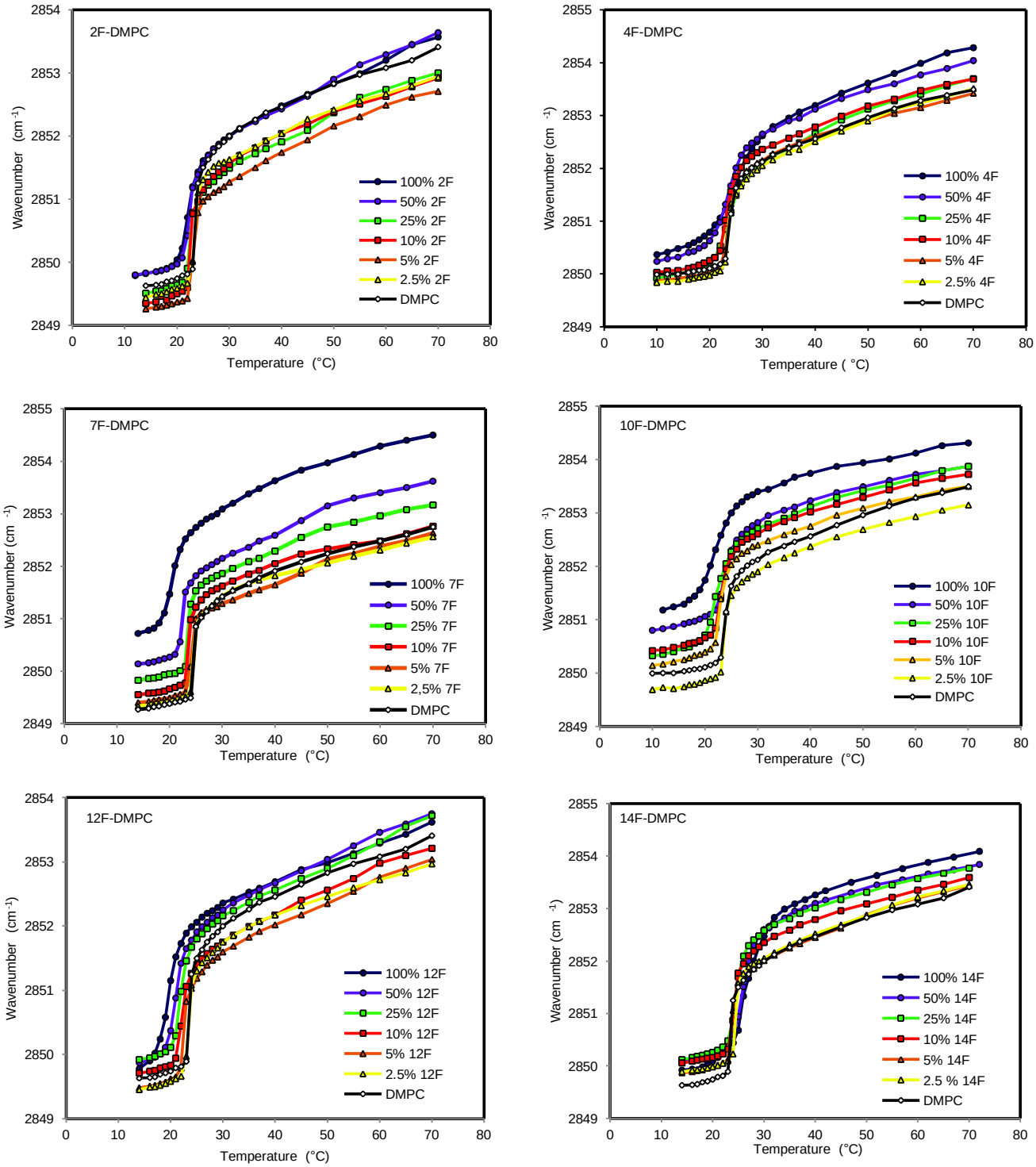


Fig. 5 Temperature dependence of the wavenumber of the CH_2 symmetric stretching vibration for various mixtures of F-DMPC and DMPC. The error is estimated to be ± 0.1 cm^{-1}.

Experimental

Materials and Methods

All reactions were carried out under a nitrogen or argon atmosphere with dry solvents under anhydrous conditions. Unless otherwise noted, all commercial reagents were used without further purification. Dichloromethane, toluene, ether, tetrahydrofuran and acetonitrile were purified by using a Vacuum Atmospheres Inc. Solvant Purification System. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed using Silicyle silica gel 60Å F254 TLC plates, and visualized under UV or by staining with ceric ammonium molybdate, phosphomolybdic acid or molybdenium blue. Flash column chromatography was carried out on Silicycle Silica Gel 60 Å, 230 X 400 mesh. ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded on a Agilent DD2 500 or a Varian Inova 400 in $CDCl_3$ at ambient temperature using tetramethylsilane (^{1}H NMR) or residual $CHCl_3$ (^{1}H and ^{13}C NMR) as the internal standard, $CFCl_3$ (^{19}F NMR) and H_3PO_4 (^{31}P NMR) as external standards. Coupling constants (*J*) are measured in hertz (Hz). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance. High-resolution mass spectra were obtained on a LC/MS-TOF Agilent 6210 using electrospray ionization (ESI). A low-resolution mass spectrum was obtained using EI ionization on a GC-MS. Infrared spectra were recorded on a Thermo Scientific Nicolet 380 FT-IR spectrometer (for characterization) and on a Nicolet Magna-IR 560 or 760 spectrometer (for the lipid phase temperature study). Melting points were recorded on a Stanford ResearchSystem OptiMelt capillary melting point apparatus and are uncorrected. Lyso-PC was purchased from Avanti Polar Lipids (Alabaster, AL). The synthesis of 4F-DMPC, 7F-DMPC and 10F-DMPC has been reported previously.[18]

Synthesis of 2F-DMPC

1-Bromo-2-fluorotetradecane (17). To a solution of 1-tetradecene (**16**) (333 mg, 1.69 mmol) and $Et_3N{\cdot}3HF$ (0.43 mL, 2.63 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added NBS (332 mg, 1.86 mmol). The reaction was stirred at 0 °C for 15 min and then warmed to room temperature over 6 h. The reaction mixture was then poured into 20 mL of ice/water, neutralized with 25% aq. NH_4OH and extracted three times with CH_2Cl_2. The organic layer was then washed with twice with 0.1 N HCl, three times with 5% aq. $NaHCO_3$, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by silica gel chromatography (100% hexane) affording **17** as a colorless solid (314 mg, 63%) contaminated with 2% of 2-bromo-1-fluorotetradecane. mp 30-31 °C; IR (ATR, ZnSe) 2915, 2848, 1464, 1131, 1097, 817, 719, 666 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (dm, 1H, $J_{H\text{-}F}$ = 48 Hz), 3.47 (ddd, 2H, *J* = 19.7, 5.2, 1.9 Hz), 1.79-1.61 (m, 2H), 1.53-1.19 (m, 20H), 0.88 (t, 3H, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) □ 92.2 (d, $J_{C\text{-}F}$ = 175 Hz), 33.9 (d, $J_{C\text{-}F}$ = 25.4 Hz), 33.5 (d, $J_{C\text{-}F}$ = 20.5 Hz), 32.1, 29.81, 29.79, 29.77, 29.7, 29.6, 29.5, 29.4, 24.9, 24.8, 22.8, 14.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -178.1 (m, 1F); regioisomer: δ -210.0 (td, 1F, $J_{F\text{-}H}$ = 47.2, 13.7 Hz). GC-MS calcd for $C_{14}H_{28}Br$ $[M\text{-}F]^+$ 275 found 275.[33]

1-Acetoxy-2-fluorotetradecane (18). Potassium acetate (417 mg, 4.3 mmol) was added to a solution of **17** (314 mg, 1.1 mmol) in DMF (6 mL) and heated at reflux under an argon atmosphere for 26 h. The reaction mixture was then cooled down to room temperature and 10 mL of a 1:1 mixture of hexane and ethyl acetate was added and the solid was filtered off and washed carefully with the same solvent. The organic layer was then washed six times with water, dried over $MgSO_4$ and the solvent was removed under reduced pressure, affording **18** as a yellow oil (212 mg, 73%) contaminated with 2% of 2-acetoxy-1-fluorotetradecane. IR (ATR, ZnSe) 2923, 2854, 1746, 1466, 1368, 1230, 1048, 722 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (dm, 1H, $J_{H\text{-}F}$ = 49.5 Hz), 4.26-4.09 (m, 2H), 2.11 (s, 2H), 1.75-1.44 (m, 4H), 1.40-1.21 (m, 19H), 0.88 (t, 3H, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 91.6 (d, $J_{C\text{-}F}$ = 172 Hz), 66.1 (d, $J_{C\text{-}F}$ = 21.9Hz), 32.1, 31.5 (d, $J_{C\text{-}F}$ = 20.4Hz), 29.81, 29.79, 29.77, 29.67, 29.57, 29.50, 29.49, 24.9 (d, $J_{C\text{-}F}$ = 4.5Hz), 22.9, 21.0, 14.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ -187.4 (m, 1F, major regioisomer), -230.6 (td, 1F, $J_{F\text{-}H}$ = 47.5, 21.8 Hz, minor regioisomer). HRMS-ESI calcd for $C_{16}H_{32}O_2F$ $[M+H]^+$ 275.2381 found 275.2396.

2-Fluorotetradecan-1-ol (19). A mixture of **18** (212 mg, 0.77 mmol) in 1.5 mL of methanol is added to a mixture of potassium hydroxide (130 mg, 2.31 mmol) in 2.5 mL of methanol. After stirring 4 h, the solution is poured into 15 mL of ice/water and extracted five times with CH_2Cl_2. The combined organic layers are washed three times with water, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product **19** is obtained as a white solid (322 mg, 94%) contaminated with 2% of 1-fluorotetradecan-2-ol. mp 56-58 °C; IR (ATR, ZnSe) 2952, 2924, 2847, 1470, 1099, 1061, 1000, 728 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (dm, 1H, $J_{H\text{-}F}$ = 50 Hz), 3.76-3.61 (m, 2H), 2.29 (bs, 1H), 1.73-1.40 (m, 4H), 1.36-1.21 (m, 18H), 0.88 (t, 3H, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 95.0 (d, $J_{C\text{-}F}$ = 168 Hz), 65.2 (d, $J_{C\text{-}F}$ = 21.7 Hz), 32.1, 31.1 (d, $J_{C\text{-}F}$ = 20.3 Hz), 29.79, 29.77, 29.7, 29.59, 29.56, 29.5, 25.1, 25.0, 22.8, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -190.0 (m, 1F, major regioisomer), -228.6 (td, 1F, $J_{F\text{-}H}$ = 47.8, 18.0 Hz, minor regioisomer). HRMS-ESI calcd for $C_{14}H_{33}NOF$ $[M+NH_4]^+$ 250.2541 found 250.2540.

2-Fluorotetradecanoic acid (12). To a mixture of **19** (201 mg, 0.87 mmol) in acetone (0.5 mL) at 0 °C was added Jones reagent (prepared from CrO_3 (173 mg, 1.73 mmol), 1.7 mL of concentrated H_2SO_4 and 6 mL of water) dropwise. The reaction was stirred for 70 h at room temperature. Afterward, the reaction mixture was extracted three times with ether. The combined organic layers were washed once with water, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by silica gel chromatography (10% EtOAc/hexane) affording **12** as a white solid (47 mg, 22%). mp 72-74 °C; IR (ATR, ZnSe) 2916, 2848, 1709, 1468,

1097, 1075, 720, 679 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 4.97 (dm, 1H, J_{H-F} = 39.6 Hz), 2.04-1.86 (m, 2H), 1.54-1.46 (m, 2H), 1.40-1.21 (m, 18H), 0.89 (t, 3H, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3 (d, J_{C-F} = 21.7 Hz), 88.7 (d, J_{C-F} = 185 Hz), 32.4 (d, J_{C-F} = 20.8 Hz), 32.1, 29.79, 29.78, 29.7, 29.6, 29.50, 29.46, 29.2, 24.5 (d, J_{C-F} = 2.7 Hz), 22.8, 14.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ -192.2 (m, 1F). HRMS-ESI calcd for $C_{14}H_{31}NO_2F$ $[M+NH_4]^+$ 264.2333 found 264.2331.

1-Myristoyl-2-(2-fluoromyristoyl)-*sn*-glycero-3-phosphocholine (9, 2F-DMPC). To a solution of **12** (30 mg, 0.12 mmol), 14:0 lyso-PC (**15**) (58 mg, 0.12 mmol) and 1-methylimidazole (29 µL, 0.37 mmol) in $CHCl_3$ (1.3 ml) was added 2,6-dichlorobenzoyl chloride (54 µL, 0.38 mmol) and the resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then concentrated under reduced pressure. The crude was purified by silica gel chromatography (1:1 MeOH:CH_2Cl_2) affording **9** as a light yellow wax (74 mg, 86%) in a 1:1 diastereoisomeric mixture. IR (ATR, ZnSe) 2916, 1737, 1090, 1051, 969, 823, 763, 720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (m, 1H), 5.14-4.78 (m, 1H), 4.40 (td, J = 12.5, 2.9 Hz, 1H), 4.30 (bs, 2H), 4.23-4.09 (m, 1H), 4.00 (t, J = 6.0 Hz, 2H), 3.78 (bs, 2H), 3.43 (s, 2H), 3.34 (bs, 7H), 2.37-2.21 (m, 2H), 1.92-1.78 (m, 2H), 1.63-1.52 (m, 2H), 1.49-1.37 (m, 2H), 1.34-1.21 (m, 38H), 0.88 (t, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 173.4, 169.8 (d, J_{C-F} = 25.0 Hz), 169.7 (d, J_{C-F} = 23.2 Hz), 89.3 (d, J = 186 Hz), 89.0 (d, J_{C-F} = 181 Hz), 72.2, 72.1, 66.4, 63.6 (d, J = 15.6 Hz), 63.5 (d, J_{C-F} = 15.7 Hz), 62.7, 59.5, 54.5 (3C), 34.2, 32.6, 32.5 (d, J_{C-F} = 20.8 Hz), 32.0 (2C), 30.0-29.2 (m, 15C), 25.0, 24.6 (d, J_{C-F} = 12.3 Hz), 24.5 (d, J_{C-F} = 12.2 Hz), 22.8 (2C), 14.2 (2C). ^{19}F NMR (470 MHz, $CDCl_3$) δ -192.3 (m, 1F). ^{31}P NMR, (152 MHz, $CDCl_3$) δ -0.96 (s, 0.5P), -1.05 (s, 0.5P). HRMS-ESI calcd for $C_{36}H_{72}NO_8FP$ $[M+H]^+$ 696.4974 found 696.4993.

Synthesis of 12F-DMPC

12-(Benzyloxy)tetradecan-1-ol (21). To a solution of 12-(benzyloxy)dodecanal (93 mg, 0.32 mmol, prepared from the Swern oxidation of 10-(benzyloxy)decan-1-ol (**20**)[23] as previously described)[24] in THF (3 mL) at 0 °C was added a solution of ethyl magnesium bromide (214 µL, 0.64 mmol, 3 M in Et_2O). The resulting mixture was stirred 1 hour at 0 °C and then warmed to room temperature over 1 hour. The reaction mixture was then cooled to 0 °C and quenched with 5% aq. H_2SO_4. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed twice with a sat. aq. Na_2SO_3, once with water, dried over $MgSO_4$ and concentrated under reduced pressure. The product **21** is obtained as a colorless oil (605 mg, 89%). IR (ATR, ZnSe) 2924, 2853, 1455, 1239, 1101, 1046, 733, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.25 (m, 5H), 4.52 (s, 2H), 3.53 (bs, 1H), 3.48 (t, 2H, J = 6.7 Hz), 1.68-1.1.59 (m, 2H), 1.57-1.33 (m, 8H), 1.33-1.24 (m, 12H), 0.95 (t, 3H, J = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 128.5 (2C), 127.8 (2C), 127.6, 73.5, 73.0, 70.7, 37.1, 30.3, 29.91, 29.89, 29.8, 29.7 (4C), 29.6, 26.3, 25.8, 10.0. HRMS-ESI calcd for $C_{21}H_{37}O_2$ $[M+H]^+$ 321.2788 found 321.2784.

((12-Fluorotetradecyloxy)methyl)benzene (22). To a solution of **21** (605 mg, 1.89 mmol) in CH_2Cl_2 (19 mL) at -78 °C was added Me-DAST (210 µL, 1.89 mmol) dropwise. The reaction mixture was stirred for 3 h at -78 °C and allowed to warm up to room temperature over 3 h. The solution was carefully poured to a sat. aq. $CaCO_3$ cooled at 0 °C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (1% Et_2O/hexane) affording **22** as a colorless oil (418 mg, 69%). IR (ATR, ZnSe) 2925, 2853, 1455, 1239, 1101, 943, 733, 696 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 4.51 (s, 1H), 4.50-4.42 (m, 0.5H), 4.39-4.30 (m, 0.5H), 3.47 (t, 2H, J = 6.7 Hz), 1.68-1.46 (m, 6H), 1.45-1.25 (m, 16H), 0.97 (t, 3H, J = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.5 (2C), 127.7 (2C), 127.6, 95.8 (d, J_{C-F} = 167 Hz), 73.0, 70.7, 34.8 (d, J_{C-F} = 20.9 Hz), 29.9, 29.71, 29.71, 29.69, 29.68, 29.66, 29.62, 28.2 (d, J_{C-F} = 21.5 Hz), 26.3, 25.3 (d, J_{C-F} = 4.5 Hz), 9.54 (d, J = 5.7 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -181.2 (m, 1F). HRMS-ESI calcd for $C_{21}H_{39}NOF$ $[M+NH_4]^+$ 340.3010 found 340.3013.

12-Fluorotetradecan-1-ol (23). DDQ (126 mg, 0.55 mmol) was added to a solution of **22** (90 mg, 0,28 mmol) in a 18:1 mixture of chloroform:distilled water (3 mL) and heated at reflux for 48 h. The reaction mixture was then cooled down to room temperature and 10 mL of distilled water was added. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic layers were washed twice with sat. aq. $NaHCO_3$. The organic layer was then dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by silica gel chromatography (10% EtOAc/hexane) affording **23** as a white solid (59 mg, 91%). mp 43-44 °C; IR (ATR, ZnSe) 3266, 2914, 2847, 1462, 1061, 935, 856, 729 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 4.48-4.42 (m, 0.5H), 4.38-4.32 (m, 0.5H), 3.65 (t, 2H, J = 6.6 Hz), 1.70-1.40 (m, 8H), 1.37-1.24 (m, 14H), 0.97 (t, 3H, J = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 95.9 (d, J_{C-F} = 167 Hz), 63.2, 34.8 (d, J_{C-F} = 20.8 Hz), 33.0, 29.73, 29.69, 29.68, 29.67, 29.66, 29.6, 28.2 (d, J_{C-F} = 21.5 Hz), 25.9, 25.3 (d, J_{C-F} = 4.5 Hz), 9.54 (d, J_{C-F} = 5.8 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -181.2 (m, 1F). HRMS-ESI calcd for $C_{14}H_{33}NOF$ $[M+NH_4]^+$ 250.2541 found 250.2541.

12-Fluorotetradecanoic acid (13). To a mixture of TEMPO (3 mg, 0.02 mmol) in CH_3CN (1.1 mL) and a phosphate buffer (pH 6.7, 0.67 M, 360 µL) at 35 °C was added **23** (56.3 mg, 0.24 mmol). Solutions of sodium chlorite (44 mg, 0.49 mmol) in distilled water (228 µL) and sodium hypochlorite (37 µL of a 10% aqueous solution, 5 µmol) diluted in distilled water (117 µL) were added dropwise over 2 h in two separate syringe. The reaction was stirred for 4 h at 35 °C and then cooled to room temperature. Water (1 mL) was added and the pH was adjusted to 8 with a 2 M NaOH solution. The reaction mixture was poured in sat. aq. Na_2SO_3 and maintained under 20 °C (pH was around 8.5-9.0) After stirring for 10 minutes, the solution was extracted with Et_2O (1 mL) and the organic phase was discarded. The aqueous phase was then

acidified to pH 3-4 using a 2 M HCl solution. Sat. aq. NaCl was added to the mixture before extracting with EtOAc (3×). Organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (20% EtOAc/hexane) affording **13** as a white solid (53 mg, 90%). mp 65-66 °C; IR (ATR, ZnSe) 2912, 2847, 1699, 1471, 1265, 1216, 929, 718 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 4.48-4.43 (m, 0.5H), 4.39-4.33 (m, 0.5H), 2.36 (t, 2H, J = 7.5 Hz), 1.68-1.42 (m, 8H), 1.38-1.25 (m, 12H), 0.97 (t, 3H, J = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6, J_{C-F} = 167 Hz), 34.8 (d, J_{C-F} = 20.9 Hz), 34.2, 29.64 (2C), 29.62, 29.5, 29.4, 29.2, 28.2 (d, J_{C-F} = 21.5 Hz), 25.3 (d, J_{C-F} = 4.5 Hz), 24.8, 9.5 (d, J_{C-F} = 5.8 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -181.3 (m, 1F). HRMS-ESI calcd for $C_{14}H_{31}NO_2F$ $[M+NH_4]^+$ 264.2333 found 264.2332.

1-Myristoyl-2-(12-fluoromyristoyl)-*sn*-glycero-3-phosphocholine (10, 12F-DMPC). To a solution of **13** (28 mg, 0.11 mmol), 14:0 lyso-PC (**15**) (54 mg, 0.11 mmol) and 1-methylimidazole (27 µL, 0.34 mmol) in $CHCl_3$ (1.1 ml) was added 2,6-dichlorobenzoyl chloride (50 µL, 0.35 mmol) and the resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then concentrated under reduced pressure. The crude was purified by silica gel chromatography (1:1 MeOH:CH_2Cl_2) affording **10** as a light yellow wax (35 mg, 44%). IR (ATR, ZnSe) 2918, 1736, 1238, 1089, 1064, 969, 760, 691 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.21 (m, 1H), 4.48-4.43 (m, 4H), 4.18-4.10 (m, 1H), 4.01-3.91 (m, 2H), 3.89-3.78 (bs, 2H), 3.48 (s, 1H), 3.39 (s, 9H), 2.34-2.48 (m, 2H), 1.69-1.51 (m, 8H), 1.36-1.21 (m, 34H), 0.97 (t, 3H, J = 7.5 Hz), 0.89 (t, 3H, J = 6.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 173.2, 95.7 (d, J_{C-F} = 168 Hz), 71.1 (d, J_{C-F} = 7.2 Hz), 67.0, 63.7 (d, J_{C-F} = 5.0 Hz), 63.3, 59.5 (d, J_{C-F} = 4.7 Hz), 54.9, 34.9 (d, J_{C-F} = 21.0 Hz), 34.5 (d, J_{C-F} = 25.0 Hz), 32.1 (2C), 29.9-29.3 (m, 14C), 28.3 (d, J_{C-F} = 21,7 Hz), 25.3 (d, J_{C-F} = 4.6 Hz), 25.15 (d, J_{C-F} = 7.4 Hz), 22.8 (2C), 14.1, 9.4 (d, J_{C-F} = 5.9 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -181.2 (m, 1F). ^{31}P NMR, (152 MHz, $CDCl_3$) δ 0.76 (s, 1P). HRMS-ESI calcd for $C_{36}H_{72}NO_8FP$ $[M+H]^+$ 696.4974 found 696.4985.

Synthesis of 14F-DMPC

((14-Fluorotetradecyloxy)methyl)benzene (25). To a solution of XtalFluor-E, $[Et_2NSF_2]BF_4$, (288 mg, 1.3 mmol) in CH_2Cl_2 (4.5 mL) at -78 °C was added $Et_3N{\cdot}3HF$ (170 mg, 1.68 mmol). A mixture of **24**[28] (268 mg, 0.84 mmol) in CH_2Cl_2 (4.5 mL) was slowly added and the reaction mixture was stirred and allowed to warm up to room temperature for 22 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (1% EtOAc/hexane) affording **25** as a yellow oil (217 mg, 80%). IR (ATR, ZnSe) 2925, 2854, 1455, 1362, 1101, 1028, 909 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.22 (m, 5H), 4.52 (s, 1H), 4.50 (t, J = 6.3 Hz), 4.40 (t, J = 6.2 Hz), 3.48 (t, J = 6.7 Hz), 1.75-1.59 (m, 4H), 1.44-1.25 (m, 20H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 128.5 (2C), 127.8 (2C), 127.6, 84.4 (d, J_{C-F} = 164 Hz), 73.0, 70.7, 30.6 (d, J_{C-F} = 19.4 Hz), 29.9, 29.78, 29.77, 29.74 (2C), 29.69, 29.66, 29.6, 29.4, 26.3, 25.3 (d, J_{C-F} = 5.6 Hz). ^{19}F NMR (475 MHz, $CDCl_3$) δ -218.0 (m, 1F). HRMS-ESI calcd for $C_{21}H_{39}NOF$ $[M+NH_4]^+$ 340.3010 found 340.3006.

14-Fluorotetradecan-1-ol (26). DDQ (187 mg, 0.82 mmol) was added to a solution of **25** (132 mg, 0.41 mmol) in a 18:1 mixture of chloroform:distilled water (4.2 mL) and heated at reflux for 48 h. The reaction mixture was then cooled down to room temperature and 10 mL of distilled water was added. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic layers were washed twice with sat. aq. $NaHCO_3$. The organic layer was then dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified by silica gel chromatography (10% EtOAc/hexane) affording **26** as a white solid (82 mg, 86%). mp 41-43 °C; IR (ATR, ZnSe) 3322, 2915, 2848, 1463, 1059, 1049, 1030, 730 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 4.48 (t, 1H, J = 6.2 Hz), 4.38 (t, 1H, J = 6.2 Hz), 3.62 (t, 2H, J = 6.7 Hz), 1.75-1.61 (m, 3H), 1.60-1.50 (m, 2H), 1.42-1.23 (m, 19H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.4 (d, J_{C-F} = 164 Hz), 63.1, 32.9, 30.5 (d, J_{C-F} = 19.3 Hz), 29.74, 29.73 (2C), 29.70, 29.66, 29.63, 29.56, 29.4, 25.9, 25.3 (d, J_{C-F} = 5.5 Hz). ^{19}F NMR (475 MHz, $CDCl_3$) δ -218.0 (m, 1F). HRMS-ESI calcd for $C_{14}H_{33}NOF$ $[M+NH_4]^+$ 250.2541 found 250.2535.

14-Fluorotetradecanoic acid (14). To a mixture of TEMPO (8.3 mg, 0.05 mmol) in CH_3CN (0.22 mL) and a phosphate buffer (pH 6.7, 0.67 M, 0.67 mL) at 35 °C was added **26** (155 mg, 0.67 mmol). Solutions of sodium chlorite (121 mg, 1.33 mmol) in distilled water (0.63 mL) and sodium hypochlorite (96 µL of a 10% aqueous solution, 13 µmol) diluted in distilled water (0.32 mL) were added dropwise over 2 h in two separate syringe. The reaction was stirred for 4 h at 35 °C and then cooled to room temperature. Water (1 mL) was added and the pH was adjusted to 8 with a 2 M NaOH solution. The reaction mixture was poured in sat. aq. Na_2SO_3 and maintained under 20 °C (pH was around 8.5-9.0). After stirring for 10 minutes, the solution was extracted with Et_2O (1 mL) and the organic phase was discarded. The aqueous phase was then acidified to pH 3-4 using a 2 M HCl solution. Some sat. aq. NaCl was added to the mixture before extracting with EtOAc (3×). Organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel chromatography (20% EtOAc/hexane) affording **14** as a white solid (135 mg, 83%). mp 65-67 °C; IR (ATR, ZnSe) 2912, 2847, 1704, 1470, 1250, 1210, 948, 718 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.49 (t, 1H, J = 6.2 Hz), 4.37 (t, 1H, J = 6.2 Hz), 2.34 (t, 2H, J = 7.5 Hz), 1.77-1.56 (m, 4H), 1.46-1.18 (m, 20H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7, 84.4 (d, J_{C-F} = 164 Hz), 34.2, 30.5 (d, J_{C-F} = 19.3 Hz), 29.71, 29.69, 29.66, 29.6, 29.5, 29.4 (2C), 29.2, 25.3 (d, J_{C-F} = 5.6 Hz), 24.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -217.9 (m, 1F). HRMS-ESI calcd for $C_{14}H_{31}NO_2F$ $[M+NH_4]^+$ 264.2333 found 264.2329.

1-Myristoyl-2-(14-fluoromyristoyl)-*sn*-glycero-3-phosphocholine (11, 14F-DMPC). To a solution of **14** (40 mg,

0.16 mmol), 14:0 lyso-PC (**15**) (73 mg, 0.15 mmol) and 1-methylimidazole (37 µL, 0.46 mmol) in $CHCl_3$ (1.6 ml) was added 2,6-dichlorobenzoyl chloride (69 µL, 0.48 mmol) and the resulting mixture was stirred for 16 h at room temperature and for 6 h at 45 °C. The reaction mixture was then concentrated under reduced pressure. The crude was purified by silica gel chromatography (1:1 MeOH:CH_2Cl_2) affording **11** as a light yellow wax (49 mg, 46%). IR (ATR, ZnSe) 3356, 2918, 2850, 1651, 1469, 1094, 765, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.19 (bs, 1H), 4.47 (t, 1H, *J* = 6.1 Hz), 4.38 (m, 2H), 4.30 (bs, 2H), 4.12 (m, 1H), 3.93 (bs, 2H), 3.76 (bs, 2H), 3.33 (s, 9H), 2.34-2.22 (m, 4H), 1.74-1.62 (m, 2H), 1.57 (bs, 4H), 1.43-1.13 (m, 38H), 0.87 (t, 3H, *J* = 6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 173.3, 84.3 (d, *J* = 164 Hz), 70.5 (d, *J* = 6.4 Hz), 63.4, 63.6, 63.0, 59.5, 54.4 (3C), 34.4, 34.2, 32.1, 30.5 (d, *J* = 19.3 Hz), 29.9-29.3 (m, 16C), 25.3 (d, *J* = 5.6 Hz), 25.1, 25.0, 22.8, 14.3. ^{19}F NMR (475 MHz, $CDCl_3$) δ -218.0 (m, 1F). ^{31}P NMR, (152 MHz, $CDCl_3$) δ -1.06 (s, 1P). HRMS-ESI calcd for $C_{36}H_{72}NO_8FP$ $[M+H]^+$ 696.4974 found 696.4985.

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