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Synthesis and characterization of partially fluorinated stearolic acid analogs: Effect of their fluorine content on the monolayer at the air–water interface

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Abstract

Novel stearolic acid analogs (i.e., 9-octadecynoic acid analogs: **1a**–**d**) containing the shorter perfluoroalkyl groups, CF_3, C_2F_5, n-C_3F_7 or n-C_4F_9 group were synthesized. Equilibrium spreading pressures (π_es) of their monolayers at the air–water interface were measured in order to demonstrate how the fluorine content has an effect on the stability of the fatty acid monolayers. As the fluorine content in stearolic acid molecule increased, its melting points was lowered indicating the solid bulk phase of stearolic acid became thermally unstable, while its monolayer stability evaluated by π_e at 25 °C, dramatically increased and subsequently leveled off above a certain fluorine content. Under this condition, the replacement of at least five hydrogen atoms at the terminal hydrophobic segment in stearolic acid molecule by fluorine atoms (CF_3CF_2 group) was required to alter the bulk property of stearolic acid and exhibit the stabilization of monolayers, whereas further fluorination of stearolic acid had a minor effect on the monolayer stability. This behavior suggests the terminal fluorinated hydrophobic segment exclusively controls the interfacial stability of fatty acid monolayers.

Keywords: Fluorinated fatty acid; Stearolic acid; Equilibrium spreading pressure; Monolayer; Monolayer stability

1. Introduction

Fluorinated compounds exhibit unique properties such as thermal and chemical stability, remarkable hydrophobicity and lipophobicity [1–6]. These characteristics are also the case for fluorinated amphiphiles such as lipids, detergents, emulsifiers, etc., and one of the most remarkable features of these amphiphiles is that these are much more surface active than their hydrogenated counterparts and can lower the surface tension of water below the lower limit reached by hydrogenated counterparts [2–6]. This feature is ascribed to a much weak intermolecular interaction among fluorinated segments in spite of much strong intramolecular bonds in stiff fluorinated segments. Therefore, there is growing interest in fluorinated amphiphiles for use in bioanalysis [7,8], pharmaceuticals [3,9–12] such as pulmonary drug delivery [11,12].

We have previously synthesized C_{18} fatty acids containing $CF_3(CF_2)_7$ group as a terminal hydrophobic segment, and measured equilibrium spreading pressures (π_es) of their monolayers at the air–water interface (Fig. 1) [13]. These highly fluorinated fatty acids formed more stable monolayers with high spreading pressures irrespective of the structural alteration in the hydrophobic segments as compared to their hydrogenated counterparts. In particular, *Z* isomer, i.e., oleic acid analog (π_e = 45.4 mN/m) and the carbon–carbon triple bond form, i.e., stearolic acid, 9-octadecynoic acid analog, **1e** (π_e = 43.7 mN/m) formed liquid expanded monolayers of the highest interfacial stability at the air–water interface.

On the basis of these researches, we planned to synthesize fatty acid analogs containing different length of terminal fluorinated segments in order to demonstrate how the fluorine content has an effect on the stability of fatty acid monolayers. However, it was found in our previous work [13] that the oleic

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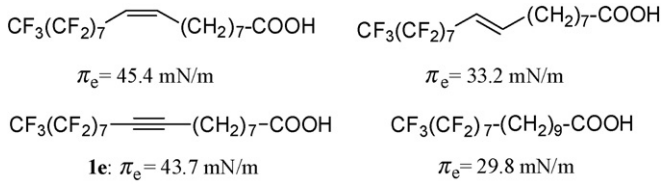


Fig. 1. Equilibrium spreading pressures (π_es) of C_{18} fatty acids containing *n*-C_8F_{17} group at the air–water interface and 25 °C.

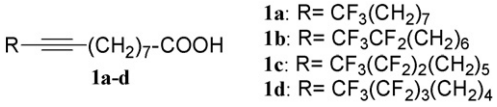


Fig. 2. Novel partially fluorinated stearolic acid analogs.

acid analog containing $CF_3(CF_2)_7$ group should be separated by preparative HPLC and its purity should be confirmed by HPLC. Therefore, we considered that it is efficient to first examine the above-mentioned effect by employing a series of partially fluorinated stearolic acid analogs.

In this paper, we present the synthesis of novel stearolic acid analogs (**1a**, **1b**, **1c** and **1d**) containing the shorter perfluoroalkyl group, CF_3, C_2F_5, *n*-C_3F_7 or *n*-C_4F_9 group, respectively (Fig. 2), and the π_es of their monolayers formed at the air–water interface. On the basis of the results of π_e measurements, we discuss the effect of fluorine content in stearolic acid analog molecules on their monolayer stability.

2. Results and discussion

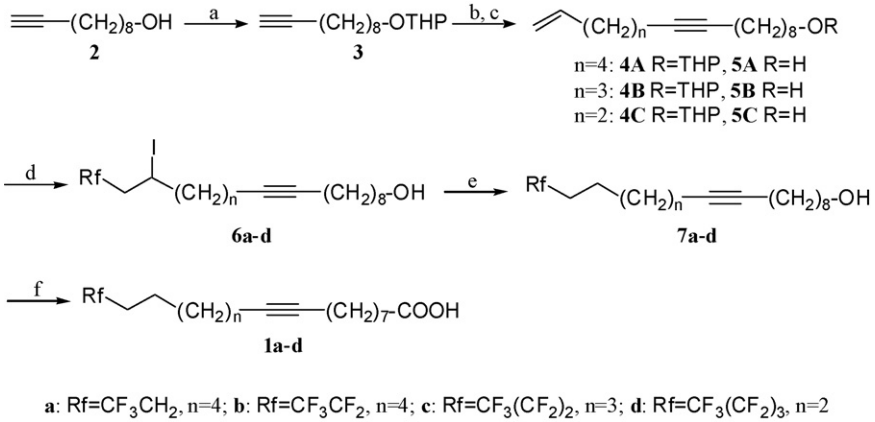
Various investigations of synthesis and behavior of partially fluorinated carboxylic acids at the air–water interface have been reported [14–18]. These acids were, however, limited to saturated fatty acids containing hydrogenated segments of the same chain length (C_{16}) and terminal fluorinated groups of various chain lengths, i.e., $F(CF_2)_n$–$(CH_2)_{16}COOH$ [14,15], in addition, all these acids were in the solid state at 25 °C.

We synthesized novel partially fluorinated stearolic acid analogs (**1a**, **1b**, **1c** and **1d**) by following procedures (Scheme 1).

The hydroxyl group of 9-decyn-1-ol **2** prepared from 3-decyn-1-ol [13,19] was protected by tetrahydropyranyl group to afford **3**. Bromoalkenes (6-bromo-1-hexene, 5-bromo-1-pentene and 4-bromo-1-butene) were reacted with the lithium acetylide of **3** [20–22], and then tetrahydropyranyl group was cleaved to afford alkynols **4A–C**. **4A–C** was reacted with fluorinated alkyl iodide in the presence of $Na_2S_2O_4$ as a free radical initiator to afford fluorinated alkynyl iodide **6a–d** [13,23–25]. **6a**, **6b** and **6d** were deiodinated with Zn–$NiCl_2$ to afford fluorinated alkynols **7a**, **7b** and **7d**, respectively. **6c** was, however, deiodinated with *n*-BuLi to afford **7c**, because a large amount of by-products was obtained when **6c** was deiodinated with Zn–$NiCl_2$. **7a–d** was oxidized with Jones reagent, and successively purified to afford the partially fluorinated stearolic acid analogs **1a–d**.

Among partially fluorinated stearolic acid analogs, **1c**, **1d** and **1e** were in the liquid state at 25 °C, while **1a** (mp 37–41 °C), **1b** (mp 35–38 °C) and stearolic acid (mp 47–48 °C [26]) in the solid state. Because melting point is a measure of the cohesive force in bulk materials, lowering of the melting points of the partially fluorinated stearolic acid analogs with increasing the fluorine content in stearolic acid molecule, suggests the intermolecular interaction among the fatty acid molecules in the solid bulk phase become progressively weaker with increasing the fluorine content in stearolic acid molecule.

The monolayer stability of **1a–d** at the air–water interface can be evaluated by their equilibrium spreading pressures (π_es) because insoluble monolayer collapse occurs at π_e thermodynamically and monolayers cannot be significantly overcompressed when the bulk materials are in the liquid state [27,28]. The value of π_e is routinely calculated from $\pi_e = \gamma_0 - \gamma$, where γ_0 is the surface tension of aqueous substrate in the absence of an insoluble (or an adsorbed) monolayer, and γ is the surface tension of aqueous substrate with the insoluble (or the adsorbed) monolayer in equilibrium with its bulk material at the air–water interface (or molecular assemblies in aqueous phase such as micelles). Therefore, π_e can be also taken as a measure of the maximal surface activity (lowering of substrate surface tension) of the amphiphilic



Scheme 1. Synthesis of partially fluorinated stearolic acid analogs **1a–d**. (a) DHP, *p*-TsOH/CH_2Cl_2, rt, overnight; (b) (i) *n*-BuLi/THF, −40 to −10 °C; (ii) bromoalkene, HMPA, rt, overnight, or (i) *n*-BuLi/THF, −78 to 10 °C; (ii) bromoalkene, NaI, gentle reflux, overnight; (c) PPTS/EtOH, 55 °C, 1.5–2 h; (d) Rf-I, $Na_2S_2O_4$, $NaHCO_3$/CH_3CN, H_2O, rt, 1–3 days; (e) Zn–$NiCl_2$/THF, H_2O, rt, overnight, or *n*-BuLi/ether, −78 °C, 4 h; (f) Jones reagent/acetone, rt.

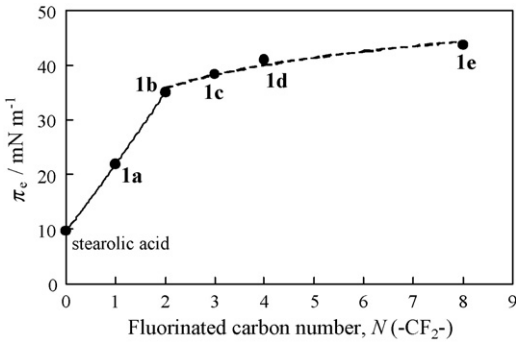


Fig. 3. Effect of the fluorine content in the hydrophobic chain on the equilibrium spreading pressures (π_es) of the partially fluorinated stearolic acid analogs **1a**–**e** at the air–water interface and 25 °C. Subphase is aqueous HCl solution (pH 2.0). Solid line represents monolayers formed from the fatty acid powder in the solid state, while broken line represents monolayers from the fatty acid droplet in the liquid state.

materials at the air–water interface. The π_es of **1a**, **1b**, **1c** and **1d** at 25 °C were 21.9, 35.0, 38.4 and 41.0 mN/m, respectively, and were found much to be higher than that of stearolic acid itself (π_e = 9.7 mN/m), indicating successive fluorination of stearolic acid enhances its maximal surface activity in a striking manner.

Fig. 3 shows a plot of π_e as a function of the fluorinated carbon number (N(–CF_2–)) of partially fluorinated stearolic acid analogs at 25 °C. As mentioned above, since an insoluble monolayer is thermodynamically stable unless the surface pressure beyond π_e is applied to the monolayer [27,28], π_e can be taken as a measure of the monolayer stability. The monolayer stability of partially fluorinated stearolic acid analogs dramatically increased with increasing the fluorine content ranging from N(–CF_2–) = 0–2. The plot, however, broke at N(–CF_2–) = 2 and exhibited the moderate increase in the monolayer stability and/or leveled off with increasing the fluorine content, i.e., N(–CF_2–) $\geq$ 3, i.e., there was only a small difference in the monolayer stability between **1d** and **1e**, while the fluorine content in the molecule was approximately doubled. As π_e is the point where the monolayer is in equilibrium with its bulk material, the break in the plot obviously reflects a change of phase state in the equilibrium bulk fatty acid, i.e., fatty acids with N(–CF_2–) $<$ 3 are in the solid state and those with N(–CF_2–) $\geq$ 3 in the liquid one at 25 °C as mentioned above. It should be noted that π_e is known to be largely affected by their crystal properties such as crystal geometries and crystallographic forms in cases of bulk materials in the solid state [29]. Therefore, it is more desirable for an exact interpretation of this result to compare the π_es of fatty acids all in the liquid state. At this stage, however, it can be considered that the terminal fluorinated group of a certain chain-length, i.e., at least N(–CF_2–) $\approx$ 2, exclusively controls the interfacial stability of monolayers and further fluorination of stearolic acid has a minor effect on the stability. In connection with the monolayer stability, the results concerning the critical surface tension of saturated 17-(perfluoroalkyl)-heptadecanoic acid monolayer-coated metal surfaces are highly suggestive, i.e., the critical surface tension is controlled by the fluorinated outermost segment in the exposed surface and the terminal perfluoroheptyl (N(–CF_2–) = 7) segment is sufficiently long to shield the hydrocarbon segment (heptadecanoyl chain) from the air-side of the monolayer [30]. Interestingly, it was also observed that the critical surface tension of the surface linearly increases as N(–CF_2–) decreases from 7 to 3 and this relationship shows the discontinuity at 3 $>$ N(–CF_2–) $>$ 2 [30]. The linear change in the critical surface tension as a function of N(–CF_2–) was explained by that the packing of the adjacent fatty acid molecules become less compact as N(–CF_2–) decreases and the discontinuity was explained by that the configuration of the fluorinated fatty acid monolayer changes from the lower order in the hydrocarbon segment at N(–CF_2–) = 3, resulting in the decrease in the fluorine atom density in the outermost portion of monolayer, to the higher order in the hydrocarbon segment at N(–CF_2–) = 2, resulting in the increase in the surface fluorine atom density. This situation would be also the case for the monolayers of partially fluorinated stearolic acid analogs, i.e., there would be a threshold chain-length of fluorinated segment where the packing and the configuration of monolayers abruptly change. The fluorinated stearolic acid analogs of N(–CF_2–) $\geq$ 3 are, however, in the liquid state at 25 °C, partly due to the packing irregularity in unsaturated carbon–carbon triple bond region in the monolayer, as is distinct from a series of saturated 17-(perfluoroalkyl)-heptadecanoic acids of which all are in the solid state and form the closely packed monolayers at 20 °C. Therefore, stearolic acid analogs of N(–CF_2–) $\geq$ 3 should form more expanded monolayers comparing to saturated 17-(perfluoroalkyl)-heptadecanoic acids, leading to the reduction of the strong cohesive force between hydrocarbon chains and separation of perfluoroalkyl segments in monolayers. The surface density of fluorine atom for these monolayers should be lower than that for saturated 17-(perfluoroalkyl)-heptadecanoic acid monolayers. This leads to the reduction of surface activity. The surface density of fluorine atom among the fluorinated stearolic acid monolayers in the liquid state, however, may not markedly change irrespective of the fluorinated chain-length, because the fluorinated segments are speculated to be less well oriented and loosely packed in the outermost portion of monolayer so as to minimize the inter-chain space. This may be one of reasons why the monolayer stability of fluorinated stearolic acid analogs is almost constant at N(–CF_2–) $\geq$ 3.

In conclusion, we have successfully synthesized the novel stearolic acid analogs (i.e., 9-octadecynoic acid analogs: **1a**–**d**) containing the shorter perfluoroalkyl groups. The interfacial stability of the monolayers formed from **1a**–**e** at the air–water interface dramatically increased with increasing fluorine content in the fatty acid molecule. From the viewpoint of the design of fluorinated fatty acid analogs, monolayer stability and/or surface activity can be sufficiently improved so long as hydrogen atoms at the terminal portion of the hydrophobic segment are partially replaced by fluorine, and the replacement of at least five hydrogen atoms by fluorine is required to exhibit the stabilization of monolayers. The present study gave us one of the important information, i.e., what extent the partial fluorination of fatty acid will be required to improve the monolayer stability. To further understand the present results,

examination of interfacial behavior of a series of partially fluorinated fatty acids in the liquid state is in progress.

3. Experimental

3.1. Instruments

^{1}H and ^{19}F NMR spectra were measured on a JEOL JNM-LA 500 FT-NMR system (500 MHz) using TMS and benzotrifluoride as internal standards, respectively. FT-IR spectra were measured on a JASCO FT-IR-680 plus. Mass spectra (ESI-MS) were measured on a JEOL JMS-700T Tandem MStation. Column chromatography was carried out using silica gel 60 (Merck 7734). HPLC purification was carried out on Inertsil ODS-3 columns (20 mm i.d. × 50 mm and 20 mm i.d. × 150 mm, GL Sciences Inc., Tokyo) with MeOH/water (9:1) or acetonitrile/water (9:1) as the mobile phase at a flow rate of 8.0 mL/min and eluate peaks were monitored with a JASCO 870-UV detector at 215 nm and a JASCO 830-RI detector. HPLC analysis was carried out on an HP Model 1100 system equipped with an ERC-7515A RI detector (ERC Inc., Tokyo), and an Inertsil ODS-3 column (4.6 mm i.d. × 150 mm, GL Sciences Inc.), which was maintained at 37 °C in the system itself, with acetonitrile/water/formic acid (90:10:0.05) as the mobile phase at a flow rate of 0.8 mL/min. The eluate was monitored with the UV detector at 215 nm and the RI detector.

3.2. Materials

3.2.1. Synthesis of 18,18,18-trifluorostearolic acid (*1a*)

*3.2.1.1. 1-(2-Tetrahydropyranyloxy)-9-decyne (**3**).* To a solution of 9-decyn-1-ol (**2**) (5.00 g, 32.4 mmol, prepared from 3-decyn-1-ol) in CH_2Cl_2 (100 mL) was added 3,4-dihydro-2*H*-pyrane (DHP, 4.44 mL, 48.6 mmol) and pyridinium *p*-toluenesulfonate (162 mg), and this mixture was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2, washed with satd NaCl aq and dried over $MgSO_4$, affording 1-(2-tetrahydropyranyloxy)-9-decyne (**3**) (7.60 g, 98%) after purification using column chromatography and eluting with *n*-hexane/EtOAc (19:1).

^{1}H NMR ($CDCl_3$) δ: 1.26–1.45 (8H, m), 1.47–1.65 (8H, m), 1.67–1.76 (1H, m), 1.78–1.88 (1H, m), 1.94 (1H, t, J = 2.74 Hz), 2.18 (2H, td, J = 7.00, 2.74 Hz), 3.38 (1H, dt, J = 9.44, 7.00 Hz), 3.47–3.54 (1H, m), 3.73 (1H, dt, J = 9.44, 7.00 Hz), 3.86–3.93 (1H, m), 4.57 (1H, dd, J = 4.27, 2.75 Hz).

*3.2.1.2. 1-(2-Tetrahydropyranyloxy)hexadec-15-en-9-yne (**4A**).* 1.6 M *n*-BuLi/*n*-hexane (1.41 mL, 2.21 mmol) was dropped into a solution of **3** (482 mg, 2.02 mmol) in dry THF (2 mL) at −40 °C under nitrogen. The mixture was stirred for 10 min, and then allowed to −10 °C. To the mixture was added HMPA (1 mL), and then added 6-bromo-1-hexene (300 mg, 1.84 mmol) in dry THF (1.5 mL). The mixture was stirred for 30 min at 0 °C, and then stirred overnight at room temperature. The mixture was poured into iced water, extracted with EtOAc, washed subsequently with satd NaCl aq, 2 M HCl, satd $NaHCO_3$ aq, and satd NaCl aq, and dried over $MgSO_4$, affording 1-(2-tetrahydropyranyloxy)hexadec-15-en-9-yne (**4A**) (771 mg) as a crude product. This was used in the next reaction without further purification.

^{1}H NMR ($CDCl_3$) δ: 1.26–1.43 (8H, m), 1.43–1.63 (12H, m), 1.67–1.76 (1H, m), 1.78–1.88 (1H, m), 2.03–2.10 (2H, m), 2.11–2.17 (4H, m), 3.38 (1H, dt, J = 9.74, 6.70 Hz), 3.47–3.54 (1H, m), 3.73 (1H, dt, J = 9.74, 7.01 Hz), 3.83–3.92 (1H, m), 4.58 (1H, dd, J = 4.28, 2.74 Hz), 4.95 (1H, ddt, J = 10.35, 1.83, 1.22 Hz), 5.01 (1H, dq, J = 17.05, 1.83 Hz), 5.81 (1H, ddt, J = 17.05, 10.35, 6.70 Hz).

*3.2.1.3. Hexadec-15-en-9-yn-1-ol (**5A**).* To a solution of **4A** (771 mg, 2.41 mmol) in ethanol (16 mL) was added pyridinium *p*-toluenesulfonate (PPTS, 302 mg, 1.20 mmol), and this mixture was stirred for 1.5 h at 55 °C. The reaction mixture was diluted with EtOAc, washed with satd NaCl aq, and dried over $MgSO_4$, affording hexadec-15-en-9-yn-1-ol (**5A**) (386 mg, 89%, two steps) after purification using column chromatography and eluting with *n*-hexane/EtOAc (17:3).

^{1}H NMR ($CDCl_3$) δ: 1.26–1.43 (8H, m), 1.43–1.54 (6H, m), 1.53–1.60 (2H, m), 2.03–2.09 (2H, m), 2.11–2.18 (4H, m), 3.64 (2H, t, J = 6.70 Hz), 4.95 (1H, ddt, J = 10.05, 1.83, 1.22 Hz), 5.01 (1H, dq, J = 17.05, 1.83 Hz), 5.81 (1H, ddt, J = 17.05, 10.05, 6.70 Hz).

*3.2.1.4. 18,18,18-Trifluoro-15-iodooctadec-9-yn-1-ol (**6a**).* **5A** (804 mg, 3.40 mmol), 2,2,2-trifluoroethyl iodide (0.63 mL, 6.87 mmol), $NaHCO_3$ (116 mg, 1.37 mmol), 80% $Na_2S_2O_4$ (299 mg, 1.37 mmol), acetonitrile (2.8 mL) and deionized water (1.4 mL) were placed and filled up with acetonitrile in a 10-mL stainless-steel reactor equipped with a stop valve at 0 °C. Then, the mixture was stirred for 3 days at room temperature. The reaction mixture was diluted with deionized water, extracted with CH_2Cl_2, washed with satd NaCl aq, and dried over $MgSO_4$, affording 18,18,18-trifluoro-15-iodooctadec-9-yn-1-ol (**6a**) (807 mg, 53%) after purification using column chromatography and eluting with *n*-hexane/EtOAc (9:1).

^{1}H NMR ($CDCl_3$) δ: 1.26–1.42 (10H, m), 1.43–1.63 (6H, m), 1.69–1.78 (1H, m), 1.87–2.10 (3H, m), 2.11–2.28 (5H, m), 2.34–2.47 (1H, m), 3.64 (2H, t, J = 6.70 Hz), 4.07 (1H, 7th, J = 4.57 Hz). ^{19}F NMR ($CDCl_3$) ppm: −2.98 (3F, t, J = 10.70 Hz).

*3.2.1.5. 18,18,18-Trifluorooctadec-9-yn-1-ol (**7a**).* **6a** (746 mg, 1.67 mmol) was added to a mixture of Zn powder (219 mg, 3.34 mmol), $NiCl_2{\cdot}6H_2O$ (39.7 mg, 0.17 mmol) in dry THF (2.5 mL), and deionized water (two drops). This mixture was stirred overnight at room temperature. The reaction mixture was quenched with satd $NaHCO_3$ aq, extracted with CH_2Cl_2, washed with satd NaCl aq, and dried over $MgSO_4$, affording 18,18,18-trifluorooctadec-9-yn-1-ol (**7a**) (275 mg, 51%) after purification using column chromatography and eluting with *n*-hexane/EtOAc (3:1).

^{1}H NMR ($CDCl_3$) δ: 1.26–1.43 (14H, m), 1.43–1.52 (4H, m), 1.51–1.60 (4H, m), 2.00–2.12 (2H, m), 2.10–2.20 (4H, m), 3.64

(2H, t, J = 6.70 Hz). ^{19}F NMR ($CDCl_3$) ppm: −3.51 (3F, t, J = 10.70 Hz).

*3.2.1.6. 18,18,18-Trifluorostearolic acid (**1a**).* To **7a** (253 mg, 0.79 mmol) in acetone (4 mL) was added Jones reagent at room temperature until the brownish color of the chromium(VI) ion remained for 30 min. The reaction mixture was quenched with 2-propanol followed by filtration and removal of the solvent. The residue was extracted with EtOAc, washed with satd NaCl aq, and dried over $MgSO_4$, affording 18,18,18-trifluorostearolic acid (**1a**) (233 mg, 88%) after purification using column chromatography and eluting with *n*-hexane/EtOAc (3:1).

^{1}H NMR ($CDCl_3$) δ: 1.26–1.43 (12H, m), 1.43–1.51 (4H, m), 1.51–1.59 (2H, m), 1.57–1.65 (2H, m), 1.99–2.12 (2H, m), 2.09–2.18 (4H, m), 2.32 (2H, t, J = 7.61 Hz). ^{19}F NMR ($CDCl_3$) ppm: −3.51 (3F, t, J = 10.70 Hz). IR (neat): 1711 cm^{-1} (C=O). ESI-MS (*m/z*): calcd. for $C_{18}H_{29}F_3O_2$ $[M]^+$ 334.2120, found 334.2120.

*3.2.2. Synthesis of 17,17,18,18,18-pentafluorostearolic acid (**1b**)*

*3.2.2.1. 17,17,18,18,18-Pentafluoro-15-iodooctadec-9-yn-1-ol (**6b**).* **5A** (733 mg, 4.03 mmol), perfluoroethyl iodide (0.48 mL, 4.03 mmol), $NaHCO_3$ (130 mg, 1.55 mmol), 80% $Na_2S_2O_4$ (377 mg, 1.55 mmol), acetonitrile (3.1 mL) and deionized water (1.6 mL) were placed and filled up with acetonitrile in the stainless-steel reactor as noted above. Then, the mixture was stirred overnight at room temperature. The reaction mixture was diluted with deionized water, extracted with CH_2Cl_2, washed with satd NaCl aq, and dried over $MgSO_4$, affording 17,17,18,18,18-pentafluoro-15-iodooctadec-9-yn-1-ol (**6b**) (1.58 g) as a crude product. This was used in the next reaction without further purification.

^{1}H NMR ($CDCl_3$) δ: 1.26–1.42 (8H, m), 1.45–1.73 (8H, m), 1.74–1.89 (2H, m), 2.12–2.17 (2H, m), 2.16–2.22 (2H, m), 2.67–2.96 (2H, m), 3.64 (2H, t, J = 6.71 Hz), 4.27–4.36 (1H, m). ^{19}F NMR ($CDCl_3$) ppm: −22.94 (3F, s), −52.39 to −56.43 (2F, m).

*3.2.2.2. 17,17,18,18,18-Pentafluorooctadec-9-yn-1-ol (**7b**).* **6b** (1.58 mg, 3.27 mmol, crude product) was added to a mixture of Zn powder (427 mg, 6.54 mmol), $NiCl_2{\cdot}6H_2O$ (77.7 mg, 3.27 mmol) in dry THF (5.0 mL), and deionized water (five drops). This mixture was stirred overnight at room temperature. The reaction mixture was quenched with satd $NaHCO_3$ aq, extracted with CH_2Cl_2, washed with satd NaCl aq, and dried over $MgSO_4$, 17,17,18,18,18-pentafluorooctadec-9-yn-1-ol (**7b**) (593 mg, 51% two steps yield) after purification using column chromatography and eluting with *n*-hexane/EtOAc (2:3).

^{1}H NMR ($CDCl_3$) δ: 1.26–1.55 (16H, m), 1.51–1.64 (4H, m), 1.94–2.08 (2H, m), 2.10–2.20 (4H, m), 3.64 (2H, t, J = 6.70 Hz). ^{19}F NMR ($CDCl_3$) ppm: −22.57 (3F, s), −55.35 (2F, t, J = 18.74 Hz).

*3.2.2.3. 17,17,18,18,18-Pentafluorostearolic acid (**1b**).* **7b** was oxidized with Jones reagent to afford 17,17,18,18,18-pentafluorostearolic acid (**1b**) in the same manner as **1a** (74%).

^{1}H NMR ($CDCl_3$) δ: 1.28–1.54 (14H, m), 1.55–1.69 (4H, m), 1.94–2.08 (2H, m), 2.11–2.19 (4H, m), 2.35 (2H, t, J = 7.61 Hz). ^{19}F NMR ($CDCl_3$) ppm: −22.54 (3F, s), −55.34 (2F, t, J = 18.73 Hz). IR (neat): 1725 cm^{-1} (C=O). ESI-MS (*m/z*): calcd. for $C_{18}H_{27}F_5O_2$ $[M]^+$ 370.1931, found 370.1923.

*3.2.3. Synthesis of 16,16,17,17,18,18,18-heptafluorostearolic acid (**1c**)*

*3.2.3.1. 1-(2-Tetrahydropyranyloxy)pentadec-14-en-9-yne (**4B**).* **4B** was prepared from **3** and 5-bromo-1-pentene in the same manner as **4A** (not purified).

^{1}H NMR ($CDCl_3$) δ: 1.25–1.43 (8H, m), 1.41–1.64 (10H, m), 1.67–1.76 (1H, m), 1.78–1.88 (1H, m), 2.11–2.22 (6H, m), 3.38 (1H, dt, J = 9.44, 6.70 Hz), 3.47–3.54 (1H, m), 3.73 (1H, dt, J = 9.44, 7.01 Hz, H1), 3.84–3.91 (1H, m), 4.57 (1H, dd, J = 4.27, 3.05 Hz), 4.97 (1H, ddt, J = 10.05, 1.83, 1.22 Hz), 5.03 (1H, dq, J = 17.05, 1.83 Hz), 5.80 (1H, ddt, J = 17.05, 10.05, 6.70 Hz).

*3.2.3.2. Pentadec-14-en-9-yn-1-ol (**5B**).* **5B** was prepared from **4B** in the same manner as **5A** (87%, two steps).

^{1}H NMR ($CDCl_3$) δ: 1.26–1.42 (8H, m), 1.42–1.51 (2H, m), 1.53–1.61 (4H, m), 2.11–2.19 (6H, m), 3.64 (2H, t, J = 6.70 Hz), 4.97 (1H, ddt, J = 10.05, 1.83, 1.22 Hz), 5.03 (1H, dq, J = 17.05, 1.83 Hz), 5.80 (1H, ddt, J = 17.05, 10.05, 6.70 Hz).

*3.2.3.3. 16,16,17,17,18,18,18-Heptafluoro-14-iodooctadec-9-yn-1-ol (**6c**).* **6c** was prepared from **5B** and perfluoropropyl iodide in the same manner as **6b** (86%).

^{1}H NMR ($CDCl_3$) δ: 1.25–1.41 (8H, m), 1.42–1.51 (2H, m), 1.52–1.67 (3H, m), 1.70–1.80 (1H, m), 1.86–1.99 (2H, m), 2.14 (2H, tt, J = 7.00, 2.44 Hz), 2.22 (2H, tt, J = 7.00, 2.44 Hz), 2.70–2.87 (1H, m), 2.84–3.02 (1H, m), 3.64 (2H, t, J = 6.70 Hz), 4.33–4.40 (1H, m). ^{19}F NMR ($CDCl_3$) ppm: −17.42 (3F, t, J = 10.70 Hz), −49.12 to −53.43 (2F, m), −64.84 to −65.07 (2F, m).

*3.2.3.4. 16,16,17,17,18,18,18-Heptafluorooctadec-9-yn-1-ol (**7c**).* 1.6 M *n*-BuLi/hexane (4.61 mL, 7.19 mmol) was dropped into a solution of **6c** (1.69 g, 3.27 mmol) in dry Et_2O (25 mL) at −78 °C under nitrogen, and then stirred for 4 h. To the mixture was added pre-cooled (−78 °C) MeOH (4.6 mL), and then allowed to 0 °C. The reaction mixture was poured into satd NH_4Cl aq, extracted with EtOAc, washed with satd NaCl aq, dried over $MgSO_4$, affording 16,16,17,17,18,18,18-heptafluorooctadec-9-yn-1-ol (**7c**) (660 mg, 51%) after purification using column chromatography and eluting with *n*-hexane/EtOAc (3:1).

^{1}H NMR ($CDCl_3$) δ: 1.25–1.42 (8H, m), 1.43–1.67 (10H, m), 1.98–2.13 (2H, m), 2.10–2.21 (4H, m), 3.64 (2H, t, J = 6.70 Hz). ^{19}F NMR ($CDCl_3$) ppm: −17.69 (3F, t, J = 10.57 Hz), −52.38 to −52.62 (2F, m), −64.94 (2F, brs).

*3.2.3.5. 16,16,17,17,18,18,18-Heptafluorostearolic acid (**1c**).* **7c** was oxidized with Jones reagent to afford

16,16,17,17,18,18,18-heptafluorostearolic acid (**1c**) in the same manner as **1a** (84%).

^{1}H NMR ($CDCl_3$) δ: 1.27–1.42 (6H, m), 1.42–1.57 (6H, m), 1.57–1.69 (4H, m), 1.99–2.12 (2H, m), 2.11–2.21 (4H, m), 2.35 (2H, t, J = 7.61 Hz). ^{19}F NMR ($CDCl_3$) ppm: −17.40 (3F, t, J = 10.70 Hz), −52.11 to −52.30 (2F, m), −64.65 (2F, brs). IR (neat): 1730 cm^{-1} (C=O). ESI-MS (*m/z*): calcd. for $C_{18}H_{25}F_7O_2$ $[M]^+$ 406.1743, found 406.1747.

*3.2.4. Synthesis of 15,15,16,16,17,17,18,18,18-nonafluorostearolic acid (**1d**)*

*3.2.4.1. 1-(2-Tetrahydropyranyloxy)tetradec-13-en-9-yne (**4C**).* 1.6 M *n*-BuLi/hexane (5.38 mL, 8.39 mmol) was dropped into a solution of **3** (2.00 g, 8.39 mmol) in dry THF (25 mL) at −78 °C under nitrogen. The mixture was stirred for 10 min, and then allowed to 10 °C. To the mixture was added sodium iodide (252 mg, 1.68 mmol), and then added 4-bromo-1-butene (2.27 g, 16.8 mmol) in dry THF (10 mL). The mixture was heated to gentle reflux (70 °C) and stirred overnight. The reaction mixture was cooled to 0 °C, quenched with satd NH_4Cl aq, extracted with EtOAc, washed with satd NaCl aq, and dried over with $MgSO_4$, affording 1-(2-tetrahydropyranyloxy)tetradec-13-en-9-yne (**4C**) (1.09 g, 45%) after purification using column chromatography and eluting with *n*-hexane/EtOAc (9:1).

^{1}H NMR ($CDCl_3$) δ: 1.24–1.43 (8H, m), 1.43–1.64 (8H, m), 1.68–1.75 (1H, m), 1.79–1.88 (1H, m), 2.11–2.16 (2H, m), 2.22–2.25 (4H, m), 3.38 (1H, dt, J = 9.74, 6.70 Hz), 3.47–3.54 (1H, m), 3.73 (1H, dt, J = 9.44, 7.00 Hz), 3.84–3.91 (1H, m), 4.58 (1H, dd, J = 4.57, 2.74 Hz), 4.99–5.03 (1H, m), 5.04–5.09 (1H, m), 5.81–5.92 (1H, m).

*3.2.4.2. Tetradec-14-en-9-yn-1-ol (**5C**).* **5C** was prepared from **4C** in the same manner as **5A** (98%).

^{1}H NMR ($CDCl_3$) δ: 1.25–1.43 (8H, m), 1.43–1.51 (2H, m), 1.53–1.61 (2H, m), 2.11–2.16 (2H, m), 2.22–2.25 (4H, m), 3.64 (2H, t, J = 6.70 Hz), 4.99–5.03 (1H, m), 5.04–5.10 (1H, m), 5.81–5.92 (1H, m).

*3.2.4.3. 15,15,16,16,17,17,18,18,18-Nonafluoro-13-iodooctadec-9-yn-1-ol (**6d**).* **6d** was prepared from **5C** and perfluorobutyl iodide in the same manner as **6b** (92%).

^{1}H NMR ($CDCl_3$) δ: 1.26–1.42 (8H, m), 1.44–1.51 (2H, m), 1.53–1.63 (2H, m), 1.87–2.02 (2H, m), 2.14 (2H, tt, J = 7.00, 2.44 Hz), 2.30–2.47 (2H, m), 2.75–3.05 (2H, m), 3.64 (2H, t, J = 6.70 Hz), 4.46–4.53 (1H, m). ^{19}F NMR ($CDCl_3$) ppm: −18.11 to −18.18 (3F, m), −48.36 to −52.10 (2F, m), −61.65 (2F, brs), −62.95 to −63.11 (2F, m).

*3.2.4.4. 15,15,16,16,17,17,18,18,18-Nonafluorooctadec-9-yn-1-ol (**7d**).* **7d** was prepared from **6d** in the same manner as **7a** (67%).

^{1}H NMR ($CDCl_3$) δ: 1.25–1.42 (8H, m), 1.43–1.52 (2H, m), 1.52–1.62 (4H, m), 1.69–1.77 (2H, m), 2.02–2.15 (2H, m), 2.14 (2H, tt, J = 7.00, 2.44 Hz), 2.21 (2H, tt, J = 7.00, 2.44 Hz), 3.64 (2H, t, J = 6.70 Hz). ^{19}F NMR ($CDCl_3$) ppm: −18.21 to −18.31 (3F, m), −51.74 to −51.95 (2F, m), −61.64 to −61.78 (2F, m), −63.20 to −63.34 (2F, m).

*3.2.4.5. 15,15,16,16,17,17,18,18,18-Nonafluorostearolic acid (**1d**).* **7d** was oxidized with Jones reagent to afford 15,15,16,16,17,17,18,18,18-nonafluorostearolic acid (**1d**) in the same manner as **1a** (69%).

^{1}H NMR ($CDCl_3$) δ: 1.26–1.43 (6H, m), 1.44–1.51 (2H, m), 1.52–1.68 (4H, m), 1.68–1.77 (2H, m), 2.02–2.16 (2H, m), 2.14 (2H, tt, J = 7.00, 2.44 Hz), 2.21 (2H, tt, J = 7.00, 2.44 Hz), 2.35 (2H, t, J = 7.61 Hz). ^{19}F NMR ($CDCl_3$) ppm: −18.13 to −18.22 (3F, m), −51.65 to −51.84 (2F, m), −61.52 to −62.68 (2F, m), −63.12 to −63.24 (2F, m). IR (neat): 1730 cm^{-1} (C=O). ESI-MS (*m/z*): calcd. for $C_{18}H_{23}F_9O_2$ $[M]^+$ 442.1554, found 442.1551.

3.3. Method

3.3.1. Equilibrium spreading pressure measurements

The purity of fluorinated fatty acids was checked by ^{1}H NMR, ^{19}F NMR and HPLC analysis in 99% purity. Oleic acid (99%) as a standard fatty acid was obtained from Sigma. A fatty acid sample was sprinkled onto the clean surface of aqueous hydrochloric acid solution (pH 2.0) in a thermostated Teflon vessel as one or more visible droplets or powders remained on the surface. The surface pressure was monitored by the Wilhelmy plate technique using a sandblasted platinum plate attached to a KSV electronic balance (pressure sensitivity: 0.01 mN/m; KSV Instruments, Helsinki, Finland) at 25.0 ± 0.2 °C. This set-up was housed in a clean box to reduce any contaminations. The equilibrium spreading pressures, π_es were reproduced within ±0.2 mN/m.

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