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Synthesis and ^{19}F NMR study of R_F-oleic acid-F_{13}

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Abstract

A seven-step synthesis of *Z*-13,13,14,14,15,15,16,16,17,17,18,18,18-tridecafluoro-octadec-9-enoic acid (oleic acid-F_{13}) is reported. The key step is a Wittig reaction to form the C9–C10 double bond with a *Z*:*E* isomeric ratio greater than 20:1. The ^{19}F nuclear magnetic resonance (NMR) spectrum is included and unambiguous assignments have been made with the aid of ^{19}F–^{19}F correlation NMR spectroscopy (COSY spectra).

Keywords: Terminally perfluorinated oleic acid; ^{19}F NMR

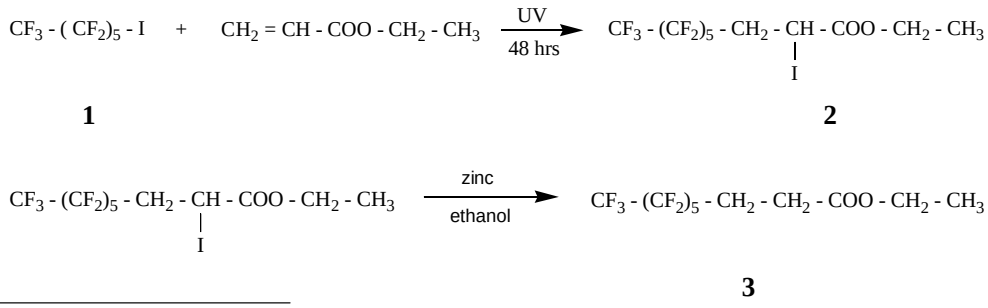
1. Introduction

Present initiatives in this laboratory are directed towards the synthesis of highly fluorinated fatty acids with at least 10 fluorine atoms per chain for possible use in the preparation of novel image enhancement agents in hyperpolarized xenon magnetic resonance imaging (MRI). No reports of the synthesis of highly fluorinated oleic acids have appeared in the literature, although we recently published the synthesis of *Z*-heptadecafluoro-octadec-8-enoic acid via a procedure that utilizes a Wittig reaction as its key step [1]. The present report deals with the stereospecific synthesis of *Z*-tridecafluoro-octadec-9-enoic acid (oleic acid-F_{13}) via a seven-step synthesis. Again a Wittig reaction is the key chain-lengthening step, however the carbonyl component and the phosphonium salt component are reversed from the previously employed procedure and the carboxylic acid function is included in the phosphonium component. The ^{19}F nuclear magnetic resonance (NMR) spectrum of oleic acid-F_{13} has been recorded and unambiguous chemical shift assignments have been made via ^{19}F–^{19}F correlation NMR spectroscopy (COSY spectra).

2. Results and discussion

2.1. Synthesis of oleic acid-F_{13}

The first step in our sequence involves radical addition [2] of the commercially available perfluorohexyl iodide **1** to ethylacrylate via the reaction described below. The known iodoester **2** was obtained in 50% yield and reduced to the known ester **3** in 93% yield via the published method [3].



Preparation of the aldehyde **4** in 48% yield was accomplished by reductive oxidation using the recently reported

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$LiAlH_4$ and PCC method [4].

$$CF_3-(CF_2)_5-CH_2-CH_2-COO-CH_2-CH_3$$

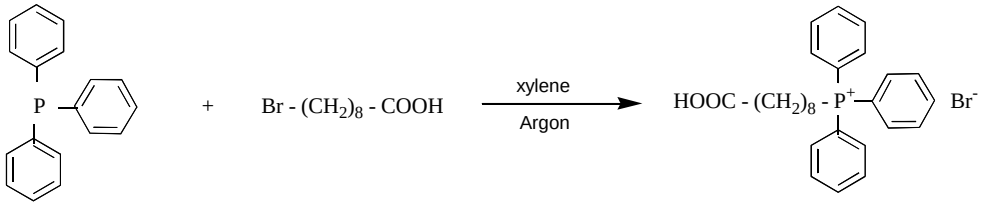
$$\xrightarrow[PCC]{LiAlH_4} CF_3-(CF_2)_5-\underset{\mathbf{4}}{CH_2-CH_2-CHO}$$

The other nine carbon component was obtained starting with 1,9-nonane diol **5** and carrying out selective monobromination [5] to produce the bromoalcohol **6**. The yield in this reaction was 90% with optimal conditions involving removal of the water as it is formed.

$$HO-\underset{\mathbf{5}}{(CH_2)_9}-OH \xrightarrow{HBr} Br-\underset{\mathbf{6}}{(CH_2)_9}-OH$$

Subsequent Jones oxidation [6] yielded 9-bromononanoic acid **7** in 72% yield and the phosphonium salt **8** was produced in 84% yield using xylene as solvent in an inert atmosphere.

$$Br-(CH_2)_9-OH \xrightarrow{\text{Jones reagent}} Br-\underset{\mathbf{7}}{(CH_2)_8}-COOH$$



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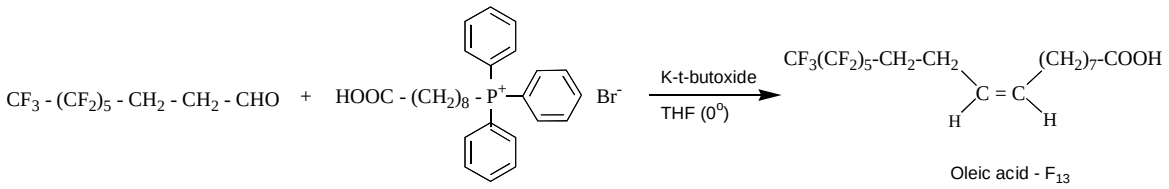
For the key Wittig reaction between **4** and **8**, conditions were chosen [7] to optimize the proportion of the requisite *Z*-isomer **9**, namely a polar aprotic solvent (THF), low reaction temperature (0 °C) and a non-lithiated base, potassium *t*-butoxide. The *Z*:*E* isomer ratio was in excess of 20:1 as estimated from ^1H NMR integration of the olefinic proton signals, since no resonances arising from a possible E-isomer were detected. The *Z*-stereochemistry of the only isolated isomer was determined from a ^1H NMR NOESY experiment. The isolated yield of of *Z*-trideca-fluoro-octadec-9-enoic acid **9** (oleic acid-F_{13}) is 57.6%.



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2.2. ^{19}F NMR results

The 376.4 MHz ^1H decoupled ^{19}F NMR spectrum of **9** is shown in Fig. 1. There are six clearly resolved resonances, consistent with the structure containing six unique fluorinated carbons. Unambiguous assignment is possible using ^{19}F–^{19}F COSY spectroscopy [8]. The resonance for the CF_3 group (C18) is clearly distinguishable from its integrated intensity, characteristic chemical shift [9] (near −81 ppm from $CFCl_3$) and the fact that it has only one COSY connection (to the peak at −123.9 ppm). The C13 position is also expected to show only one COSY correlation since there is just one CF_2 group adjacent. Accordingly, the resonance at −114.9 ppm can be assigned to this site. The −114.9 peak shows a strong COSY connection to the peak at −122.3, thus identifying the C14 site. The −122.3 peak shows a strong COSY connection to the −126.5 ppm peak, thus C15 is assigned. Similarly, the −126.5 ppm peak correlates to the −123.2 peak, indicating that C16 must resonate at the latter chemical shift. Finally, the −123.2 peak connects to −123.9, which identifies C17. This is consistent with the observation that the C18 resonance at −81.1 also exhibits a COSY connection to the C17 peak at −123.9 ppm.

3. Experimental

3.1. General

Melting points are uncorrected. NMR spectra were recorded using a Bruker AMX spectrometer in $CDCl_3$ unless otherwise noted with tetramethylsilane as internal standard for both ^1H (400 MHz) and ^{13}C (100 MHz) spectra. For the NOESY experiment on **9**, the mixing time was selected to be consistent with the $1/T_1$ criterion [8] and in the present case it was set to 1.5 s. An ASPECT 3000 process controller was employed and the NOESY pulse sequence is contained in the standard micro program present in the Bruker Software Library. ^{19}F NMR spectra were recorded with a Bruker AM 400 system operating at 376.4 MHz. ^{19}F chemical shifts are

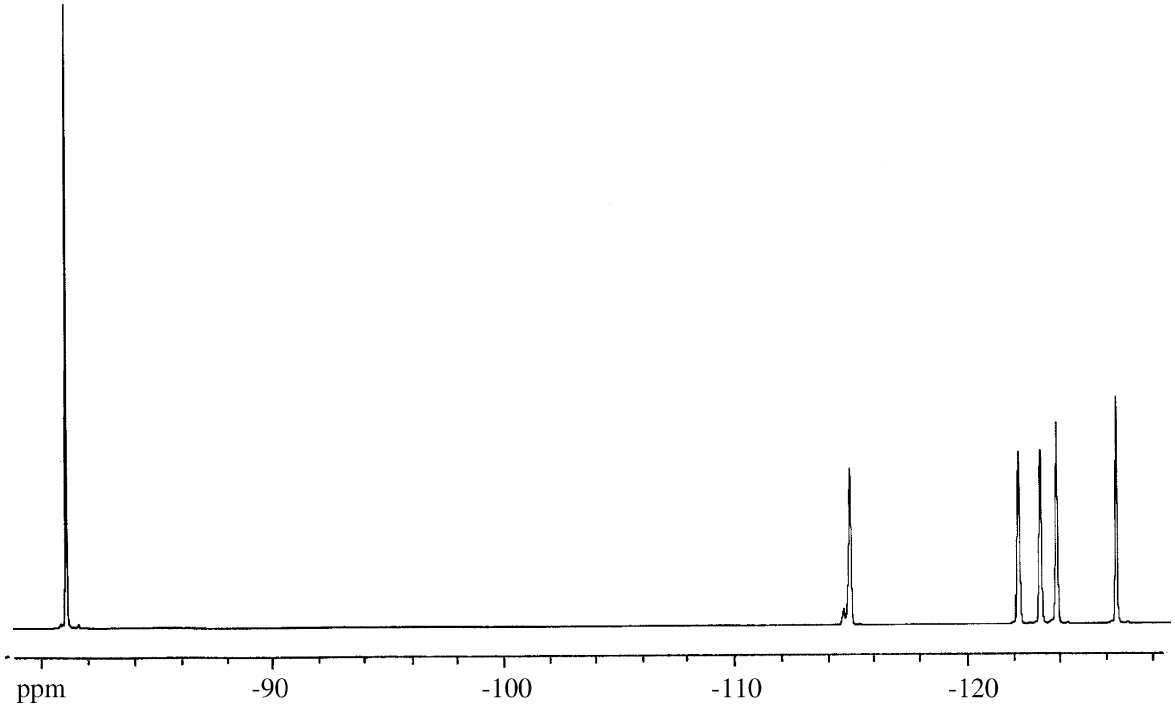

Fig. 1. ^{19}F NMR spectrum of oleic acid-F_{13} (**9**).

upfield relative to an external $CFCl_3$ reference. All reagents and solvents were commercial grade (Aldrich) and purified according to established convention. Elemental analyses were performed by Guelph Analytical Laboratories.

*3.2. Ethyl-2-iodo-4,4,5,5,6,6,7,7,8,8,9,9, 9-tridecafluorononanoate (**2**)*

To a 50 ml quartz tube were added perfluorohexyl iodide (2.65 g, 5.9 mmol) and ethyl acrylate (1.78 g, 17.8 mmol). The reactants were continuously mixed by running nitrogen gas through the quartz tube. The mixture was irradiated in a Rayonet photochemical reactor with 254 nm UV light at room temperature for 48 h. The reaction mixture was purified by fractional distillation under vacuum and gave 1.62 g (50% yield) of ethyl-2-iodo-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononanoate (**2**), bp 60–62 °C (1 mmHg), reported [2] bp 86–90 °C (2.3 mmHg).

*3.3. Ethyl-4,4,5,5,6,6,7,7,8,8,9,9, 9-tridecafluorononanoate (**3**)*

To a 100 ml double-necked round bottom flask equipped a condenser and a dropping funnel, **2** (1 g, 0.0018 mol) was added in absolute ethanol (1.2 ml). After heating the solution to reflux temperature, zinc dust (10 to 20 mesh), (0.119 g, 0.0018 mol) was added, while stirring. Foaming and exothermic reaction were observed. To this reaction mixture hydroiodic acid (55%) was then added dropwise until the zinc was dissolved. After 1 h at 65–70 °C another 0.119 g of zinc was added, the slurry was resaturated with 55% HI, and the reaction carried on for a further 2 h. The colorless solution was cooled, filtered and poured into water (10 ml), and extracted with diethyl ether (3 × 10 ml). The collected organic extracts were washed with water (2 × 10 ml), then with brine (10 ml), dried over magnesium sulfate and the solvent evaporated by rotary evaporation. The product (**3**) obtained in a 94% yield (0.7 g) was used in the next step without further purification.

^1H NMR 4.19 (q, $J = 7.2$, 2H), 2.63 (m, 2H), 2.18 (m, 2H), 1.28 (t, $J = 7.2$, 3H). ^{13}C NMR 171.3, 120.6 (m), 118.7 (m), 118.0 (m), 115.6 (m), 111.1 (m), 108.5 (m), 61.3, 26.7 (t, $J = 22.1$), 25.6 (t, $J = 4.0$), 14.2.

*3.4. 4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononal (**4**)*

To an oven dried 250 ml double-necked round bottom flask equipped with a condenser, flashed with dry nitrogen gas and maintained under static pressure of nitrogen, was transferred a 1.0 M solution of lithium aluminum hydride (20.2 ml, 0.0202 mol) in THF. To this stirred solution at 0 °C, ethyl-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononanoate (**3**) (11.3 g, 0.026 mol) was added dropwise and the reaction mixture was stirred overnight at room temperature. Subsequently, this solution was added to a well-stirred suspension of pyridinium chlorochromate (PCC) (12.8 g, 0.059 mol) in methylene chloride (100 ml) dropwise using a syringe. The mixture was stirred again overnight at room temperature. The reaction mixture was diluted with diethyl ether (50 ml) and the supernatant liquid was filtered through Florisil (60 g) contained in a sintered glass funnel; the solid residue was triturated with diethyl ether (3 × 30 ml) and passed through the same Florisil column. The solvent was removed by

rotary evaporation and the yellowish oil was further purified by fractional distillation to give **4** (4.86 g, 48% yield) bp 40–43 °C (5 mmHg), reported [10] bp 40 °C (5 mmHg).

^{1}H NMR 9.83 (t, $J = 1.2$, 1H), 2.84 (d, t, $J = 1.2, 7.2$, 2H), 2.45 (m, 2H). ^{13}C NMR 197.9, 120.9 (m), 118.4 (m), 115.8 (m), 113.3 (m), 111.1 (m), 108.3 (m), 34.8, 23.4 (t, $J = 22.3$).

3.5. 9-Bromononanol (*6*)

1,9-Nonane diol (Aldrich) (20 g, 0.124 mol) was dissolved in toluene (250 ml) by heating the solution at about 60 °C, in a 500 ml round bottom flask. To this solution was added hydrobromic acid (48%, 14.1 ml), dropwise with stirring and the mixture was heated at reflux (178–180 °C) for 28 h. The water formed during the reaction was removed using a Dean–Stark trap. After cooling to room temperature, the mixture was washed with 6N sodium hydroxide solution (100 ml), 10% hydrochloric acid (100 ml), water (2×200 ml), and finally with brine (150 ml). The organic layer was dried over anhydrous magnesium sulfate, filtered by gravity and the solvent was removed by rotary evaporation. The resulting yellowish oil was applied to a silica gel column (grade 40, 6–12 mesh) and eluted with 4:1 hexane:ethylacetate. The second fraction contained 9-bromo-1-nonanol (24.9 g, 90% yield) as a white solid with mp 33–35 °C.

^{1}H NMR 3.63 (t, $J = 6.6$, 2H), 3.41 (t, $J = 6.8$, 2H), 1.85 (m, 2H), 1.74 (s, 1H), 1.56 (m, 2H), 1.42 (m, 2H), 1.31 (m, 8H). ^{13}C NMR 62.9, 34.0, 32.8, 32.7, 29.4, 29.3, 28.7, 28.1, 25.7.

3.6. 9-Bromononanoic acid (*7*)

To chromium trioxide (10.3 g, 0.102 mol) in water (10 ml) at 0 °C was added dropwise concentrated sulfuric acid (8.8 ml, 0.133 mol) followed by water (19 ml). The resulting mixture was slowly added to a solution of **6** (15.2 g, 0.0682 mol) in acetone (50 ml) at −5 °C. After stirring for 2 h at 0 °C, the solution was left overnight at room temperature. The mixture was extracted with diethyl ether (3×60 ml) and the combined organic extracts were washed with water (2×60 ml), brine (70 ml), then dried over anhydrous magnesium sulfate, and filtrated through Florisil (200 mesh). The solvent was removed by rotary evaporation. Column chromatography on silica gel with dichloromethane was carried out on the resulting yellowish oil and the fraction having the R_f value of 0.48 in DCM on TLC was collected, yielding 9-bromo-nonanoic acid (**7**) (11.6 g, 72%) as a white solid, mp 31.5–33.5 °C, reported [6], colorless oil.

^{1}H NMR 11.1 (bs, 1H), 3.40 (t, $J = 6.8$, 2H), 2.35 (t, $J = 7.5$, 2H), 1.85 (m, 2H), 1.63 (m, 2H), 1.42 (m, 2H), 1.32 (m, 6H). ^{13}C NMR 180.1, 34.0, 33.9, 32.8, 29.0, 28.9, 28.5, 28.1, 24.6.

3.7. 9-Bromotriphenylphosphononononanoic acid (*8*)

In a 250 ml round bottom flask were added **7** (11.6 g, 0.048 mol) and triphenylphosphine (12.8 g, 0.048 mol) in dry xylene (50 ml). The solution was heated at reflux overnight under argon. After cooling to room temperature a thick, glassy-like solid came out of solution. The solvent was removed by rotary evaporation and the resulting crude product was further purified by column chromatography on silica gel with 5% methanol in chloroform to yield 9-bromo-triphenylphosphononononanoic acid **8** (20.5 g, 84% yield) as a glassy solid.

^{1}H NMR 11.1 (bs, 1H), 7.82 (m, 9H), 7.73 (m, 6H), 3.61 (m, 2H), 2.31 (t, $J = 7.4$, 2H), 1.56 (m, 6H), 1.24 (m, 6H). ^{13}C NMR 177.0, 135.1 (d, $J = 2.8$), 133.6 (d, $J = 10.0$), 130.6 (d, $J = 12.6$), 118.2 (d, $J = 85.9$), 34.5, 30.1 (d, $J = 16.0$), 28.5, 28.5, 28.4, 24.6, 22.7 (d, $J = 47.0$), 22.4 (d, $J = 2.4$).

3.8. Z-13,13,14,14,15,15,16,16,17,17,18,18,18-Tridecafluoro-octadec-9-enoic acid (*9*)

To a double-necked round bottom flask was added **8** (3.0 g, 0.006 mol). The flask was equipped with a heating mantle and connected to a high vacuum pump. The phosphonium salt was dried at 110 °C under high vacuum for 5 h. To this dried phosphonium salt, was added freshly distilled THF (100 ml) and the resulting slurry was stirred under argon atmosphere until the salt completely dissolved. Subsequently, potassium *t*-butoxide (1.38 g, 0.0123 mol) was added under argon. The resulting orange solution was stirred for 30 min at room temperature after which time **4** (2.26 g, 0.006 mol) in 10ml of dry THF was added dropwise with stirring at 0 °C under argon. After all the aldehyde was added the cooling bath was removed and the slurry further stirred for 48 h. The reaction mixture was then triturated with 50 ml of diethyl ether, acidified with 2 M hydrochloric acid and extracted with diethyl ether. The collected organic extracts were washed with water, then with brine, dried over magnesium sulfate and the solvent removed by rotary evaporation. The crude product was purified by column chromatography on silica gel with 3:1 hexane:ethyl acetate to yield *Z*-13,13,14,14,15,15,16,16,17,17,18,18,18-tridecafluoro-octadec-9-enoic acid (**9**) (1.78 g, 57.6%) as a white solid with mp 17.6–18.1 °C.

^{1}H NMR 10.8 (bs 1H), 5.48 (m, 1H), 5.34 (m, 1H), 2.36 (m, 4H), 2.05 (m, 4H), 1.64 (m, 2H), 1.32 (m, 8H). ^{13}C NMR 180.6, 132.4, 126.3, 121.2 (m), 119.2 (m), 116.4 (m), 113.9 (m), 111.3 (m), 108.6 (m), 34.2, 31.2 (t, $J = 22.1$), 29.5, 29.3, 29.1, 29.0, 27.2, 24.8, 18.4 (t, $J = 4.2$). Anal. Calcd. for $C_{18}H_{21}F_{13}O_2$: C 41.86, H 4.10, F 47.84, O 6.20. Found C 41.62, H 4.32, F 47.98.

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