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**Synthesis of Highly Fluorinated Fatty Acids
and Sucrose Polyesters**

By

Elena Munteanu, B.Sc. (Hons.)

A thesis submitted to the

Faculty of Graduate Studies and Research

In partial fulfillment of the requirements for the degree of

Master of Science

Department of Chemistry

Carleton University

Ottawa, Ontario, Canada

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2003

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Abstract

When combined with sucrose to produce highly fluorinated sucrose polyesters (HFSPE's), fluorinated fatty acids with at least 10 fluorine atoms per chain may have possible use in the preparation of novel image enhancement agents for hyperpolarized xenon Magnetic Resonance Imaging (MRI).

The synthesis of Z-11,11,12,12,13,13,14,14,15,15,16,16,17,17,18,18-heptafluoro-octadec-8-enoic acid was performed via a procedure which employs a Wittig reaction as its key step and generates the Z isomer almost exclusively. The structure was confirmed by ^{13}C NMR and NOESY spectra.

The stereospecific 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}) was carried out through 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 COSY spectroscopy.

HFSPE's were synthesized using sucrose and Z-13,13,14,14,15,15,16,16,17,17,18,18,18-tridecafluoro-octadec-9-enoic acid as starting materials. The presence of penta, hexa, hepta and octa HFSPE as a mixture, was confirmed via MALDI mass spectrometry. The major product

is the hexa ester and the non-esterified carbons are postulated to be the 3' and 4' sites of the fructose moiety. Molecular mechanics calculations indicate that these sites are the most difficult to esterify due to steric hindrance.

Abbreviations

τ	Molecular life
AIBN	Azobisisobutyronitrile
DCM	Dichloromethane
DMF	Dimethylformamide
DS	Degree of Esterification
HF	Hydrofluoric acid
HFSPE	Highly Fluorinated Sucrose Polyester
MRI	Magnetic Resonance Imaging
PCC	Pyridinium Chlorochromate
PDC	Pyridinium Dichromate
PFOB	Perfluorooctyl Bromide
R_F	Perfluoroalkyl
R_{FI}	Perfluoroalkyl iodide
S	Electron spin
SPE	Sucrose Polyester
SOAC	Sucrose Octa Acetate
SOO	Sucrose Octa Oleate
T	Temperature
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
T_F^{-1}	Rate per Rubidium atom
TFE	Trifluoroethene
THF	Tetrahydrofuran
T_K^{-1}	Rate per Xenon atom
TLC	Thin-Layer Chromatography

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Chapter 1 Introduction

1.1 General and applications

The magnetic polarization of ^{129}Xe nuclei can be enhanced by up to five orders of magnitude by using optical pumping methods (1). The theory of these methods involves the polarization transfer between the electron spins of alkali-metal atoms and the nuclear spins of noble-gas atoms in a gas. Nuclei of ^{129}Xe can be polarized with remarkable efficiency by spin exchange with optically pumped Rb atoms. The spin exchange rates between alkali-metal electron spins and the nuclei of heavy noble gases are completely dominated by van der Waals interactions. The basic process is illustrated in Figure 1.1

Figure 1.1 Rb-Xe molecules are formed in three-body collisions at a rate $(T_F)^{-1}$ per Rb atom and $(T_K)^{-1}$ per Xe atom.

One Rb atom and one Xe atom collide in the presence of a nitrogen molecule and form a weakly bound van der Waals “collision complex”. This “collision complex” evolves freely for a time τ until it is broken up by a collision with another molecule of nitrogen. During the relatively long molecular life τ the weak coupling between the electron spin S of the alkali-metal atom, the rotational angular momentum (not shown in Figure 1) of the molecule and the nuclear spin K of the noble-gas atom causes S to flip down and K to flip partway up. The spin-exchange rates are very slow for noble gases in alkali-metal vapors because of the weakness of the spin interactions and the frequency of three-body collisions. The nuclear-electron spin exchange rate constant for noble-gas atom in an alkali-metal atom vapor depends strongly on the third-body pressure. Also to be mentioned, the noble-gas spin-polarization rate depends linearly on the alkali-metal number density.

The primary source of angular momentum for this system is the beam of circularly polarized light in the presence of an appropriate gas that is absorbed by the Rb atoms.

In conclusion, the polarization of ^{129}Xe and other spin $\frac{1}{2}$ noble gases can be very much enhanced through spin-exchange with optically pumped alkali-metal vapor. In this case, a dilute vapor of Rb is kept spin-polarized by the absorption of circularly polarized 795nm Rb D_1 -resonance light. Gas-phase collisions between the ^{129}Xe and the polarized Rb atoms result in the transfer of angular momentum from the Rb valence electron to the ^{129}Xe nucleus (1).

Laser polarized xenon gas can be imaged directly in the airways of human lungs following introduction into the respiratory system (2-5).

As implemented, magnetic resonance imaging (MRI) relies on the protons of water molecules in tissues to provide the NMR signal. However, protons are very difficult to image in some biological environments of interest, such as the lungs and lipid bilayer membranes. It has been shown (2) that ^{129}Xe gas can be used for high resolution MRI when the nuclear spin polarization of the atoms is increased by laser optical pumping and spin exchange. By introducing hyperpolarized xenon gas into mouse lungs images of the lung gas space have been obtained with a speed and resolution better than those available from proton MRI.

Further efforts (3) have been made to describe the highly polarized noble gas (^3He) enhanced MRI findings of normal pulmonary ventilation in healthy volunteers and to evaluate abnormalities in patients with different lung diseases. After inhalation of the highly polarized gas, airways and alveolar airspaces could be visualized with a strong signal. Signal defects and incomplete or inhomogeneous distribution of the hyperpolarized noble gas were regarded as abnormal findings indicating ventilatory disturbances as shown in Figure 1.2(a). High signal intensity areas seemed to be hyperventilated, representing fast compartments, as shown in Figure 1.2(b).

Figure 1.2 Signal inhomogeneity with hyper intense areas and wedge-shaped defects (a) and healthy patient, upper and lower lung field with high signal intensity (3) (b)

In conclusion, hyperpolarized noble gas MRI may be helpful to recognize and localize these different compartments, which cannot be achieved by other modality.

Most hyperpolarized lung imaging has employed conventional pulse sequences applied during breath holds and excitation angles of $\alpha = 3^\circ$. Such images show signal in the larger airways, gas-exchange areas, as well as an outline of the heart, and pulmonary vasculature. However, there has been little success in imaging individual smaller airways with hyperpolarized noble gases. Some of the parameters that affect the image are the timing of the acquisition with respect to the gas infusion, the duration of the acquisition window, and the excitation angle, in addition to the more traditional acquisition parameters. It has been shown (4) that the use of larger flip angles ($\alpha = 10-45^\circ$), and during inspiration (not at breath holds like in the previous trials), permit the signal from the polarized gas to be captured as it travels through the conducting airways and before it

reaches the distal air spaces. Although applying the radial acquisition technique for this study, required many views to form an image compared to techniques used before, the inherent reduction of motion artifacts was very beneficial for imaging during inspiration. Using the right values for the acquisition window and for the excitation angle, airways could be imaged down to at least fourth-order branching in humans. In figure below it is shown the differences between a “during inhalation” image (a) and “held-breath” image (b).

Figure 1.3 Hyperpolarized gas images of a human volunteer (a) during inspiration ($\alpha = 10^\circ$) and (b) at hold breath ($\alpha = 3^\circ$).

In addition, the high solubility of xenon gas in blood and lipids suggests the possibility of dissolved phase imaging. Xenon MRI allows perfusion imaging of the brain, lung, or other regions (5). Combined imaging of the gas-phase and dissolved-phase xenon provides a high-resolution, cross-sectional ventilation/perfusion study of the lung. Since the solution-phase resonances of xenon are shifted by approximately 200ppm from

the gas-phase resonance, it is possible to collect both gas and dissolved-phase xenon images within a single rapid acquisition. Using a new method for xenon laser-polarization that provides large quantities of hyperpolarized gas, it has been possible to obtain the first ^{129}Xe spectroscopy results from the human chest and head, Figure 1.4 and Figure 1.5 respectively (5).

Figure 1.4 Twenty-five consecutive ^{129}Xe spectra (one/second) from the chest of a healthy human volunteer, showing the temporal evolution of the gas-phase and dissolved-phase signal components during and after a 16 s breath-hold period (5).

Figure 1.5 Fifteen consecutive ^{129}Xe spectra (one/5 s) from the head of healthy human volunteer, demonstrating the temporal evolution of the gas-phase and dissolved-phase signal components (5).

However, xenon delivery through the respiratory system is very inefficient for these applications. Large quantities of laser-polarized gas have to be produced. A substantial portion of this remains in the lungs and thus will not contribute to the Magnetic Resonance signal of the tissue of interest. Imaging with hyperpolarized species depends on the transport of sufficient surviving magnetization to target of analysis. Another factor is the interaction between ^{129}Xe hyperpolarized and oxygen because of its paramagnetic properties. This interaction leads to rapid loss of polarization (5).

Accordingly, intravenous injection of xenon dissolved in a bolus injection of a biocompatible liquid is a far more promising method for maintaining the polarization during introduction of the gas to blood and tissues (6,7).

This technique requires the production of small amounts of xenon with high polarization.

The injection of polarized xenon solutions is promising for in vivo localized NMR spectroscopy and chemical-shift imaging. Using injection, the polarized xenon can be administered rapidly, and locally, especially if the experimental situation has an indication for intraarterial or intramuscular injections (6). In comparison with respiration techniques, which are noninvasive, the injection technique is invasive, but it requires a far smaller amount of polarized xenon.

Recently perfluorocarbon emulsions have been used successfully for intravenous delivery of hyperpolarized xenon.

In particular, perfluorooctyl bromide (PFOB), administered as an emulsion stabilized by a phospholipid monolayer has been employed (8). Xenon is known to have a high solubility in perfluorocarbons. Perfluorocarbon emulsions have been designed for use as blood substitutes and as ^{129}Xe carriers for in vivo magnetic resonance applications.

There are some disadvantages with this technique, however, as some PFOB emulsions containing hyper polarized xenon exhibit severely broadened ^{129}Xe NMR spectra. The xenon NMR line width depends on the size distribution of the PFOB droplets in the emulsion.

However, finding perfluorocarbon emulsions that have the droplet size comparable to that of red blood cells and with a better stability could serve as delivery media for hyperpolarized xenon MRI studies (8). As the size of these droplets increases the NMR line width gets narrower as is shown in the figure below.

Figure 1.6 Spectra of two PFOB emulsions with small (a) and bigger (b) size droplet.

Another disadvantage is that this technique is limited by the exchange of xenon with the water environment. In order to obtain a narrow ^{129}Xe spectrum this exchange process has to be slow, and thus, not depending on dilution.

In addition, the xenon present in PFOB droplets exhibits too high a chemical shift difference between exchanging environments, hence peak broadening (9).

Accordingly other biocompatible methods for delivery of hyperpolarized xenon to blood and tissues are worthy of exploration. It is in this context that we have embarked on the synthesis of sucrose polyesters (SPE) with highly fluorinated side chains.

Our rationale for this is based on several known phenomena. It is well established that the human lipase enzymes cannot recognize sucrose esters of fatty acids in which 6 or more of the 8 available hydroxyl functions of sucrose have been esterified.

Sucrose polyesters in a mixture composed of sucrose octaesters with a low amount of sucrose hepta and hexaesters of stearic, palmitic, oleic and linoleic acids are known as the commercial product OLESTRA marketed as a calorie-free fat substitute by Procter & Gamble (10,11).

Recent work from this laboratory (12,13) has studied the interactions of sucrose octapalmitate, and sucrose hexapalmitate with lipid membranes using a variety of NMR methods. During the course of this work, we had occasion to mix the sucrose polyesters with phospholipids and carry out sonication. Emulsions were observed.

Sucrose polyesters have the potential to interact with and insert into biological membranes and change their physical properties. At low concentrations sucrose polyesters insert into membrane, having their carbonyl residues proximal to the aqueous interface and they could exhibit a tendency to aggregate. As a consequence of this property, the local bilayer structure is perturbed to favor formation of nonlamellar structures (12).

A geometry-optimized representation of the suggested bilayer intercalated sucrose octapalmitate and sucrose hexapalmitate conformation is shown in Figure 1.7 (12).

Figure 1.7

The resulting micelle with polyester on the inside, and the phospholipid on the outside should possess a large hydrophobic volume on the inside into which xenon gas may be trapped, provided that the sucrose polyesters can be prepared with a sufficiently high degree of fluorination.

An additional potential use for such highly fluorinated sucrose polyesters (HFSPE's) would be in direct gut imaging by Xenon MRI since these materials will pass unmetabolized through the gastrointestinal system.

Recent computational studies from this laboratory (14) have shown that xenon is likely to bind to the highly fluorinated terminal segment of the fatty acid moiety and hence, there exists the possibility of carrying enough xenon atoms to the tissue of investigation.

Initial synthetic work in this area attempted to use the commercially available perfluorohexadecanoic acid and simply esterify sucrose. However, the perfluorinated

materials suffer from severe solubility problems thus making the esterification reactions impossible.

Accordingly, there is a need to synthesize fatty acids with lesser, yet still substantial degrees of fluorination.

The main focus of this thesis represents such work, with oleic acids as primary target molecules. Subsequent reactions of highly fluorinated oleic acid derivatives with sucrose to produce HFSPE's have been explored.

1.2 Highly fluorinated fatty acid analogs

1.2.1 General

During the 1950s, Neal O. Brace studied different methods of introducing the perfluoroalkyl group into organic molecules. The main purpose of this work was to obtain new organic molecules of unusual chemical and physical properties.

First trials were made towards the initiation of a free radical reaction of a longer chain perfluoroalkyl iodide (R_FI) and vinyl acetate with azobisisobutyronitrile (AIBN) instead of the well-known peroxide or ultraviolet light. The advantage of this reaction was that using only a few percent of AIBN, a vigorous, exothermic reaction takes place, and by quickly cooling it to be kept under control, the pure adduct can be obtained by distillation.

This method requires the use of many hazardous reagents as liquid HF, fluorine, gaseous trifluoroethene (TFE) and other fluoro olefins.

The unique properties of R_FI reside in their easy conversion into R_F radicals and their high reactivity towards unsaturated molecules. Therefore R_FI can be used to obtain specific compounds with R_F groups in many sizes and shapes attached in precise positions in alkenes and alkynes of a large variety of structure (15). The iodine atom is attached to an adjacent carbon, and since iodine may also be readily removed by elimination or substitution, this provides a second point of reactivity (Figure 1.8).

Figure 1.8 Radical addition of R_FI to alkenes and alkynes.

The free radical addition mechanism of R_FI to unsaturated compounds is essentially that proposed by Kharasch, Jensen and Urry (16). A scheme of this mechanism is presented in Figure 1.9.

Figure 1.9 Free radical addition mechanism.

Using a free radical initiator, the initiator molecule is dissociated into radicals. The initiation is promoted by the abstraction of iodine from $R_F I$ by an initiator radical having as result the formation of $R_F^\cdot$ radical, which adds irreversibly to an alkene or alkyne giving an intermediate adduct radical. This is an exothermic step since the π -bond of the alkene or alkyne is broken and a stronger σ -bond is formed. In step three, the iodine is extracted from $R_F I$ by the adduct radical giving the product, and a second $R_F^\cdot$ radical is produced that may continue the chain reaction. This step is reversible and isomerization of the adduct, or equilibration of Z/E isomers may occur. If an excess of alkene or alkyne is present or with highly polymerizable monomers, propagation of the polymer chain takes place, as shown in step four. In step five the reaction chain is terminated by radical coupling reactions, or by radical disproportionation. Iodine has a

very important role in this type of reactions, acting as inhibitor for steps two and three and not allowing these reactions to continue for several hundred or thousand cycles (15).

1.2.2 Synthesis of long chain alkanolic and alkenolic acids with fluorinated terminal segments

Using this type of process called iodoperfluoroalkylation, which was already presented in the previous chapter, N.O.Brace obtained new perfluoroalkyl-substituted compounds with novel and important uses. Among these compounds, long chain alkanolic and alkenolic acids with fluorinated terminal segments were synthesized (17).

Perfluoroalkanoic acids and their derivatives were obtained through a three-step synthesis: the free radical initiated addition of perfluoroalkyl iodides to unsaturated esters to generate C₁₂ and C₁₄ iodoesters, dehydrohalogenation, and hydrolysis of the ester.

For the first step, peroxide or azonitrile were used as catalysts and only a small amount was necessary to give complete conversion of pure reactants to adduct. Being an exothermic reaction, the heat was controlled by external cooling and by addition of one reactant to the other. The reactant ratio was not important in those cases where the terminal olefin does not readily polymerize. In contrast, in the case of acrylates and to a lesser degree with an allyl compound, telomerization took place. In order to keep the degree of polymerization small, an excess of the unsaturated ester has to be used.

Reduction of the iodo addition compound was carried out using zinc and hydrogen chloride in alcohol solution. Employing alkali, the dehydrohalogenation reaction generated the alkenoic acid, and further hydrogenation using platinum oxide catalyst (under pressure) gave the alkanoic acid in a good yield.

Another method for obtaining the fluorinated alkanoic fatty acids is the peroxide- or azonitrile-induced addition at 80-150°C of R_FI to unsaturated fatty acids (17).

The free radical addition of iodoperfluoroalkanes to terminally unsaturated alcohols generates after dehydrohalogenation, a Z/E mixture (primarily E) of isomers (15).

One route to an all E isomer of fluorinated alkenoic fatty acid in which the unsaturation was adjacent to the R_F group employed the free radical addition of 1-iodoperfluoropropane to 10-hendecynoic acid. The addition occurred smoothly using an azonitrile initiator. The reduction of the iodo adduct by zinc and acid gave a single compound according to gas-liquid chromatography analysis.

More recently, it was found (18) that addition of R_FI to terminal alkynols gives good yield of monounsaturated alcohols, in which the E-isomer predominates. It was found, however, that the E-isomers could be converted efficiently to Z forms. The resulting compound is just one step away, a mild oxidation of the hydroxyl group, from the desired unsaturated fatty acid with a fluorinated terminal segment.

1.2.3 Properties of fatty acids with perfluoroalkyl terminal segment

The perfluoroalkylalkanoic acids have an alkylene segment that separates the strongly electron-withdrawing perfluoroalkyl group from the carboxylic acid function, and therefore these compounds undergo reactions typical of carboxylic acids under normal conditions. The perfluoroalkanoic acids have somewhat a modified chemistry (17). N.O.Brace (17) compared the melting point, surface activity and ionization constants of these new perfluoroalkanoic and perfluoroalkylalkanoic fatty acids with those of alkanoic acids.

The length of the terminal R_F segment and the branching in the R_F influences the melting point and the surface activity, whereas the relative lengths of the two different segments ($-CF_2-$ and $-CH_2-$) and the total chain length affects the melting point to a lesser extent. As expected, a long chain acid with an internal branched R_F segment, melts much lower than do straight chain analogs. This is also the case for acids with unsaturated alkylene segments. The factors that are influencing the melting point behavior in these three series of acids are: the greater stiffness of $(CF_2)_n$ than $(CH_2)_n$ sequence and the larger cross-sectional area, $29 \text{ (\AA)}^2$, for $(CF_2)_n$ versus $20 \text{ (\AA)}^2$ for $(CH_2)_n$ (19).

Surface activity of sodium salts of perfluoroalkyl-segmented alkanoic and alkenoic acids in aqueous solution was also determined. As the length of the perfluoroalkyl segment was increased up to seven carbons, the minimum surface tension dropped from 27 dynes/cm to 14.8 dynes/cm (17). For the unsaturated fluorinated acid with the same number of carbons, the surface activity is even better at lower concentrations of the acid. Conventional surfactants, like soaps of fatty acids, do not

lower the surface tension of water below 26 dynes/cm. The acids having branched chain R_F groups are inferior in surface activity to those having straight chain perfluoroalkyl segments.

The remarkable non-wettability property of these compounds monolayers is caused by the presence of the extremely inert $-CF_3$ group in the surface. As the length of the perfluoro segment decreases the stability of the monolayers falls off rapidly. The change in surface potentials of all films is larger than those of any aliphatic acid because the dipole is oriented in opposite direction (19).

Ionization constants were determined by titration in 50% aqueous ethanol solution (17). The obtained data show that the effect of the strong electron-withdrawing perfluoroalkyl group is transmitted through the alkylene segments by up to the five carbons with decreasing force. The fluorinated alkenoic acids were more ionized than their saturated analogs.

Chapter 2 Results and Discussion

2.1 Synthesis of oleic acid F₁₇ analog

As a starting point for HFSPE synthesis, highly fluorinated analogs of oleic, stearic and palmitic acid are target molecules.

This thesis will concern itself only with oleic acid analogs since these represent a particular stereochemical challenge (i.e. *Z* isomer).

So far, no reports of the synthesis of highly fluorinated oleic acids have appeared in the literature, despite substantial efforts devoted to the preparation of other highly fluorinated unsaturated analogs by means of free radical addition initiated by azobisisobutyronitrile, as discussed in the previous section.

Due to the ready availability of starting materials, the first compound of this kind obtained was *Z*-heptadecafluorooctadec-8-enoic acid via a procedure that employs a Wittig reaction as key step and generates the *Z*-isomer almost exclusively. The double bond position is of course one site removed from the oleic acid skeleton but this represents a useful “model” compound.

The first step in the reaction sequence is the monotetrahydropyranolation of 1,8-octanediol to obtain the known 8-(tetrahydro-2H-pyran-2-yloxy)-octan-1-ol **1** in 64% yield (20). Subsequent oxidation with pyridinium dichromate (PDC) (20) gives the aldehyde **2** in a very good yield 95%.

The highly fluorinated (F_{17}) phosphonium salt **3** can be prepared in high yield (83%) by employing a high boiling point solvent (xylene) and inert atmosphere.

For the key step, the Wittig reaction, between the aldehyde **2** and the fluorinated phosphonium salt **3**, specific conditions were chosen (21, 22) in order to obtain mainly the Z-isomeric olefin **4**: a polar aprotic solvent such as tetrahydrofuran (THF), low reaction temperature (0°C) and a non-lithiated base, potassium t-butoxide. The Z:E isomer ratio was approximately 10:1 as estimated from ^1H NMR integration of the olefinic proton signals. The isomers were separable via column chromatography and the Z-stereochemistry of the major isomer was determined from ^1H NMR NOESY experiment (Figure 2.2).

Removal of the tetrahydropyranyl group from the obtained olefin can be accomplished in a very high yield (99%) using an excess of methanol in presence of Dowex 50 acid resin.

The last step is a mild oxidation of the alcohol using pyridinium dichromate (PDC) to give the target Z-heptadecafluoro-octadec-8-enoic acid **5**, which was identified by ^1H and ^{13}C NMR in solution (Figure 2.1).

2.1.1 Solution NMR studies of Z-heptadecafluoro-octadec-8-enoic acid

The 400MHz ^1H NMR spectrum (Figure 2.1) of **5** shows the broad peak at 11.51ppm characteristic for carboxylic functional group, which is the most deshielded. Two very similar multiplets at 5.79-5.86ppm and 5.43-5.48ppm are indicating the protons from C8, and C9 respectively. The integration of the remaining peaks shows that the triplet of doublets at 3.01-3.12ppm, triplet at 2.35ppm, and the multiplet at 2.12-2.17ppm contain two protons, and the multiplet at 1.36-1.66ppm contains 8 protons. The multiplet situated at 3.01-3.12ppm corresponds to the two protons that are on the C7 carbon, which is adjacent to the double bond. The multiplet at 2.12-2.17ppm represents the two protons

on C10, which is vicinal to the fluorines. The triplet at 2.35ppm corresponds to the protons on C2. The most shielded protons are those corresponding to the aliphatic region of the molecule and are attached to C3-C6. Peak assignments are shown in Table 1.

Table 1 ^1H NMR chemical shifts and coupling constants for oleic acid F₁₇ analog.

	Chemical shifts (ppm)	Coupling constants (Hz)
- C ¹⁰ <u>H</u> ₂ -	2.12-2.17	
-C ⁹ <u>H</u> =	5.79-5.86	
- C ⁸ <u>H</u> =	5.43-5.48	
- C ⁷ <u>H</u> ₂ -	3.01-3.12	J = 7.7, 19.3
-C ⁶ <u>H</u> ₂ -C ⁵ <u>H</u> ₂ -C ⁴ <u>H</u> ₂ -C ³ <u>H</u> ₂ -	1.36-1.66	
-C ² <u>H</u> ₂ -	2.35	J = 7.5
-COO <u>H</u>	11.51	

In the ^{13}C NMR spectrum (Figure 2.1) the carbons participating to the double bond in the Z-isomer are situated at 137.9ppm and 116.2ppm. Carbons 11-18 contain just fluorine atoms, causing splitting, and therefore the peaks corresponding to them appear as 8 multiplets with low intensities between 122.1ppm and 109.0ppm. The easiest to assign

is, of course, C1 corresponding to the carboxyl group, at 174.6ppm. The nonfluorinated aliphatic carbons appear between 29.8ppm and 25.4ppm.

The existence of the *Z*-isomer is proven by the NOESY spectrum (Figure 2.2), which shows the relaxation between the two *cis* protons of the double bond. Such a NOESY correlation would not be expected in the case of two more spatially remote *trans* protons (23).

With this stereochemistry successful approach in hand, we then embarked on the preparation of a “true” oleic acid analog, in which the C=C is at the C-9, rather than the C-8 position of the chain.

Figure 2.1 400MHz ¹H and 100.6MHz ¹³C NMR spectra of oleic acid F₁₇ analog.

Figure 2.2 ^1H NMR NOESY spectrum of oleic acid F_{17} analog.

2.2 Synthesis of oleic acid F₁₃

The stereospecific synthesis of *Z*-tridecafluoro-octadec-9-enoic acid (oleic acid-F₁₃) was performed 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. In this case the aldehyde employed in the Wittig reaction contains the highly fluorinated terminal segment.

2.2.1 Ethyl-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononanoate

6

7

The first step in this sequence involves radical addition (24) of the commercially available perfluorohexyl iodide **6** to ethylacrylate. The known ethyl-2-iodo-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononanoate **7** was obtained in 50% yield.

In order to obtain primarily the corresponding 1:1 adduct, ethylacrylate was chosen as the unsaturated ester. It is known that ethyl and methyl acrylates exhibit different selectivity. The longer ethyl ester group can shield the terminal carbon of the double bond via steric hindrance than the methyl group, facilitating the extraction of the iodine atom by R_2 (Figure 2.3 B). The steric hindrance of the ethyl group to the radical intermediate also has the effect of lowering the reactivity and increasing the selectivity of the ethyl-substituted R_2 (Figure 2.3) as compared with the methyl analog. This could also partially suppress the reaction of R_2 -Et with a second molecule of alkene to form R_3 (Figure 2.3 A).

Figure 2.3 Reactivity of ethyl and methyl acrylates.

UV light was chosen as initiator to avoid certain disadvantages caused by peroxide or AIBN initiators. The radical chain reaction is exothermic and conditions must be carefully controlled in order to avoid the formation of higher polymeric adducts (15).

In the second step, the iodoester was reduced to the known ester **8** in 93% yield via the published method (17).

2.2.2 4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononal

9

Preparation of the aldehyde **9** was accomplished (25) by reducing the carboxylic ester to the alcohol stage by LiAlH₄ (0.5 equiv.) at 0°C and then room temperature. The

use of the lithium aluminium hydride is more convenient and economical than the use of aluminium hydride because all four equivalents of hydride in LiAlH_4 are utilized for the reduction. This reaction was followed by oxidation of the resultant alkoxyaluminate intermediate (without isolation) with PCC to obtain the aldehyde **9** in 48% yield.

First trials of this method had as result the preparation of the aldehyde in lower yields (20-30%). The actual value of the yield was obtained by employing an excess of the lithium aluminium hydride with 0.25 units than the amount used in (25). Also the reaction time was also increased for the reduction as well as for the oxidation step from three hours to over night time period.

The fraction having the boiling point between 40-43°C at 5mm Hg (reported 40°C at 5mm Hg (26)) was identified as compound **9**.

2.2.3 9-Bromononanol

The other nine carbon component for the key step (Wittig reaction) was obtained starting with 1,9-nonane diol **10** and carrying out selective monobromination (27) with hydrogen bromide 48% and heated at the reflux temperature of toluene, which was used

as solvent, to produce the bromoalcohol **11**. The yield in this reaction was 90% with optimal conditions involving removal of the water as it is formed. By eliminating the water, the reaction mixture is made less polar and thus the monobromoalcohol is obtained in a very good yield.

2.2.4 9-Bromotriphenylphosphonononanoic Acid

Subsequent Jones oxidation (28) of the 9-bromononanol, yielded 9-bromononanoic acid **12** in 72% yield, as a white solid, having the melting point 31.5-33.5°C. In the literature, this compound was reported (28) as colorless oil.

The phosphonium salt **13** was prepared in 84% yield (29). Additional to the solvent free method used in reference 29, both reagents were dissolved in dry xylene and heated at reflux over night in an inert atmosphere. The phosphonium salt **13**, a glassy like solid, is a new compound, not mentioned in the literature before, and was identified by ¹H and ¹³C NMR in solution (Figure 2.4).

^1H NMR spectrum shows five sets of peaks (Table 2). As expected, the multiplet at 7.78-7.83ppm and 7.70-7.74 are characteristic for the three-phenyl ring protons. The triplet at 2.31ppm corresponds to protons attached to C2 carbon, adjacent to carboxyl functional group. The protons on C9, being more deshielded than those on C2, are giving a multiplet peak more downfield at 3.57-3.64ppm. The rest of the 12 protons belonging to the aliphatic chain show two multiplets at the most up-field position, at 1.49-1.60ppm and 1.22-1.28ppm respectively.

Table 2 ^1H NMR resonances and coupling constants for phosphonium salt 13.

	Chemical shift (ppm)	Coupling constant (Hz)
9H aromatic	7.78-7.83	
6H aromatic	7.70-7.74	
-C ⁹ H ₂ -	3.57-3.64	
-C ⁸ H ₂ -C ⁷ H ₂ -C ⁶ H ₂ -	1.49-1.60	
-C ⁵ H ₂ -C ⁴ H ₂ -C ³ H ₂ -	1.22-1.28	
-C ² H ₂ -	2.31	J = 7.4
-COOH	11.1	

The existence of the phosphonium salt is very well proven by the ^{13}C NMR spectrum, which shows (Table 3) the couplings between phosphorus and the aliphatic and aromatic carbons attached to it. In the region 118-140ppm, phosphorus (i.e. ^{31}P with spin $\frac{1}{2}$) is coupling to the aromatic carbons, showing a set of doublets at 135.1-135.2ppm, 133.6-133.7ppm, 130.6-130.7ppm, and 117.8-118.7ppm. The doublets at 30.1ppm, 22.7ppm and 22.4ppm correspond to C8, C9, and C7 respectively. They are due to the influence of phosphorus on these aliphatic carbons.

Table 3 ^{13}C NMR resonances and coupling constants for phosphonium salt 13.

	Chemical shift (ppm)	Coupling constant (Hz)
$^{31}\text{P}-\text{C}^1_{\text{aromatic}}$	118.2	$J = 85.9$
$\text{C}^2_{\text{aromatic}}$	130.6	$J = 12.6$
$\text{C}^3_{\text{aromatic}}$	133.6	$J = 10.0$
$\text{C}^4_{\text{aromatic}}$	135.1	$J = 2.8$
$-\text{C}^9\text{H}_2 - ^{31}\text{P}$	22.7	$J = 42.7$
C8	30.1	$J = 16.0$
C7	22.4	$J = 2.4$
C6	22.9	
C5	24.6	
C4	28.4	
C3	28.5	
C2	34.5	
C1	177.0

Figure 2.4 400MHz ^1H and 100.6MHz ^{13}C NMR spectra of phosphonium salt.

2.2.5 Wittig reaction

The stereochemistry of the Wittig reaction can be affected by solvent, cation stabilization, temperature and type of aldehyde. The reaction mechanism is (Figure 2.5):

Figure 2.5 Mechanism of Wittig reaction.

Cis and trans-oxaphosphetane models were proposed to predict this stereochemistry as shown below ("Organic Synthesis"- M.Smith):

It is known the fact that E stereoselectivity is associated with the reversible dissociation of oxaphosphetane to ylide and aldehyde, a process which will be under thermodynamic control (is assumed to proceed by a late transition state, and the oxaphosphetane has a planar structure II) (21, 22).

In contrast, Z stereoselectivity is maximized by a non-stabilizing substituent (alkyl or alkoxy) on ylide, which has as result the irreversibility of the first step of Wittig reaction. In this case the reaction is under kinetic control (reaction proceeds by an early

transition state and oxophosphetane has a puckered conformation I). The interplay of steric interactions of substituents on P and C2, and steric interactions of substituents on P and C3 will determine cis or trans selectivity. When 1,3 steric-interactions are predominant due to large groups at α -carbon, puckered transition states are formed. Other necessary conditions to obtain the Z isomer are the exclusion of lithium salts, low reaction temperatures and the use of polar aprotic solvents (21, 22).

A standard procedure was employed (29) to obtain the oleic acid F₁₃. The phosphonium salt 13 was treated with potassium tert-butoxide base in dry THF, in a 1:2.05 molar ratio because of the auxiliary acidic group. The formation of the ylide was confirmed by the orange color that appeared immediately after the addition of the base.

The next step was performed by adding the aldehyde 4 at 0°C. Z-13,13,14,14,15,15,16,16,17,17,18,18,18-tridecafluoro-octadec-9-enoic acid was obtained in an excess of 20:1 as estimated from ¹H NMR integration of the olefinic proton signals and in a 28.8% yield. It was identified by ¹H NMR, ¹³C NMR (Figure 2.6), ¹⁹F NMR and ¹⁹F-¹⁹F COSY spectroscopy (Figure 2.7). The Z-stereochemistry of the only isolated isomer was determined from a ¹H NMR NOESY experiment (Figure 2.8). The molecular weight was confirmed to be 516 m/z from the Mass spectrum (Figure 2.9).

¹⁹F NMR results show that there are six clearly resolved resonances, consistent with the structure containing six unique fluorinated carbons. Unambiguous assignment is possible using ¹⁹F-¹⁹F Correlation NMR spectroscopy (COSY) (30). The resonance for the CF₃ group (C18) is clearly distinguishable from its integrated intensity, characteristic chemical shift (31) (near -81 ppm from CFCl₃) 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.

Figure 2.6 400MHz ¹H and 100.6MHz ¹³C NMR spectra of oleic acid F₁₃.

Figure 2.7 376.4 MHz ¹H decoupled ¹⁹F NMR and ¹⁹F-¹⁹F COSY spectra for oleic acid F₁₃.

Figure 2.8 400MHz ¹H NMR NOESY Spectrum for Z-isomer of oleic acid F₁₃.

Figure 2.9 Mass Spectrum of oleic acid F₁₃.

2.2.6 Z-13,13,14,14,15,15,16,16,17,17,18,18,18-tridecafluoro-octadec-9-enoil chloride

In order to synthesize sucrose polyesters the highly fluorinated acid chloride was prepared (32) starting from the oleic acid F₁₃ and oxalyl chloride in a molar ratio of 1 to 1.5. The oleic acid F₁₃ was slowly added to the oxalyl chloride. Both reagents were dissolved in hexane and the reaction carried on at reflux temperature. The pure acid chloride was obtained in 91.7% yield as yellowish oil and used in the HFSPE synthesis without further purification. Highly fluorinated acid chloride was identified by IR (Figure 2.10) and ¹H and ¹³C NMR (Figure 2.11) spectroscopy.

As expected, the absorption band for the carbonyl has shifted from 1705.85cm⁻¹ in the acid 9 IR spectrum, to 1801.73cm⁻¹ for the acid chloride as can be seen from Figure 2.10 (a) and (b) respectively.

a)

b)

Figure 2.10 IR Spectrum for oleic acid F₁₃ (a); IR Spectrum for acid chloride (b).

Figure 2.11 400MHz ^1H NMR and 100MHz ^{13}C NMR Spectra for acid chloride.

2.3 Synthesis of Highly Fluorinated Sucrose Polyesters

2.3.1. Synthesis of Sucrose Octa Oleate

In order to find the most suitable method for synthesizing HFSPE's, model studies involving sucrose and its reactions with methyl oleate and oleoyl chloride have been carried out.

The first trial was carried out using a one stage solvent free method (33). This is a transesterification process involving sucrose octa acetate (SOAC), 2% sodium metal as catalyst, and methyl oleate. The molar ratio of methyl oleate to SOAC was 8:1 to maximize the yield of sucrose octa oleate (SOO). Formation of a one-phase melt was achieved 20 to 30 minutes after the heat was applied. The reaction was carried out at 105°C for 2-3 hours in vacuo (5mm Hg). Volatile methyl acetate formed as a result of the interesterification was trapped in a liquid nitrogen cold trap, thereby driving the synthesis toward the formation of the sucrose octa oleate. Washings with methanol removed the unreacted methyl oleate and the more polar SPE's with low degree of esterification. Sucrose octa oleate was obtained in a 69.3% yield.

The advantage of using SOAC is that the acetate groups are good protecting groups against sucrose degradation and caramelization during synthesis.

Due to the high content of fluorine on the fatty acid chain of our materials, sodium metal could not be used as catalyst for the synthesis of HFSPE, hence, the need of finding another suitable catalyst.

A very good review on transesterification of vegetable oils (34) classifies different kinds of catalysts used for this process. The presence of a catalyst (usually a strong acid or base) accelerates the adjustment of the equilibrium. A great number of organic bases have been developed and used as catalyst. Among these bases 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) seems to have a good catalytic activity due to the fact that its catalytic site (unshared electron pair of the sp^2 N) is practically unhindered, allowing an easy access of the alcohol for proton transfer. The mechanism of the base-catalyzed transesterification is shown in Figure 2.12.

Figure 2.12 Mechanism of the base-catalyzed transesterification (34).

Due to its good performance in the transesterification of vegetable oils, TBD was chosen initially instead of sodium metal as catalyst (34).

The second method (35) applied to synthesize sucrose octa oleate employed sucrose, methyl oleate and TBD as catalyst. The reaction was carried out with a sucrose/methyl oleate molar ratio of 1:8. The reaction mixture was maintained under vigorous stirring at 110°C and reduced pressure for 8 hours. Reaction was monitored by TLC, and no sucrose polyesters were formed.

Accordingly, another attempt of esterification has been carried out using the same reagents but this time the procedure (36) employed DMF as solvent to dissolve sucrose, methyl oleate and TBD. It should be mentioned that in this method (36), potassium carbonate is used as catalyst. During the reaction the pressure was adjusted to 95mm Hg to allow the solvent to reflux while the temperature in the reaction vessel was maintained at 90°C for 9 hours. Again, the reaction was monitored by TLC at different periods of time but only the spots for the starting materials could be seen.

A possible reason for which no product was obtained, could be the high temperature employed, between 90 and 110°C. Sucrose is unstable at high temperatures and decomposes very quickly into glucose and fructose. Additionally, the solvent free interesterification of sucrose, requires that sucrose should be in the molten state. Sucrose melts at 165-185°C and will remain clear and fluid for a brief period of time before starting to degrade to a black, tarry mass (37). This short period of stability may not be sufficient for a transesterification reaction to begin. It was also observed that sucrose recrystallized on the flask walls, shortly after it melted, although the temperature was maintained at same value of 110°C.

Finally it was decided that the ester functional group on the methyl oleate should be changed into an acid chloride function, since it is known that the acid halides are more

reactive than esters. Another advantage is the fact that the conditions employed in this case are milder: no catalysts and no high temperatures.

The esterification reaction of sucrose with oleoyl chloride was carried out using anhydrous DMF as solvent (38). Oleoyl chloride dissolved in acetonitrile was added dropwise to a solution of sucrose in DMF in a molar ratio of 8 to 1. The sucrose was dissolved in dimethylformamide at a concentration of 0.16 mol of sucrose per 100mL of DMF, and then pyridine was added in an excess of 3 mol per 1 mol of acid chloride. The resulting mixture was stirred for 24 hours at room temperature. Oleoyl chloride must be added as an acetonitrile solution to prevent extensive degradation of sucrose esters to glucose esters.

The polar DMF activates the hydroxyl groups of the sucrose and the acyl groups of the acid chloride, while pyridine traps the hydrochloric acid formed during the esterification. In this DMF/pyridine solvent mixture, sucrose was readily acylated by oleoyl chloride without requirement of catalyst.

Pure sucrose octa oleate was obtained in a yield of 38% and was confirmed by ^{13}C NMR spectrum (Figure 2.13 a) and b)). The signals corresponding to methyl and methylene carbons of the oleyl segment appear between 14-35ppm, carbons of the sucrose skeleton show at 62-110ppm, the two carbons participating at the double bond at 129.2-130.0ppm and carbonyl carbons at 172.7-173.5ppm. As it can be seen from the enlarged area of carbonyl carbons spectrum (Figure 2.13 b)) there are seven peaks, one of them, at 172.4ppm, having double intensity of the other six, counting for two carbonyl carbons, hence proving the existence of eight ester groups on the sucrose.

a)

Figure 2.13 a) 100MHz ^{13}C NMR Spectrum for sucrose octa oleate.

b)

Figure 2.13 b) enlarged carbonyl carbons area for sucrose octa oleate.

With these results in hand, the next step was made towards the synthesis of highly fluorinated sucrose polyesters, using the process of esterification of sucrose with oleoyl F_{13} chloride.

2.3.2 Highly Fluorinated Sucrose Polyesters

The same procedure as for the esterification of sucrose with oleoyl chloride was applied. The only difference was a longer period of time and higher temperature, at which the reaction was performed, such as: three days at room temperature, followed by 12 hours at 40°C. These conditions were employed in an attempt to push the reaction towards the formation of HFSPE's with a higher degree of esterification (DS).

After working up the reaction, 2.7g of orange viscous oil was obtained, which was further purified by column chromatography on silica gel, using methylene chloride/ethyl acetate 12:1 as eluent. Three fractions were collected, representing HFSPE's with varying degree of esterification. The amount of unreacted acid chloride was 0.7g, which means that approximately 75% of this compound was converted into HFSPE's.

Evidence of HFSPE structure was obtained from IR spectra analysis (Figure 2.14 a) and b)). Absorption bands are observed at 3000-2850cm⁻¹ (C-H stretch in CH₃/CH₂), 1740cm⁻¹ (ester carbonyl), 1454cm⁻¹ (C-H deformation in CH₃/CH₂), 1020-1240cm⁻¹ (C-O-C vibrations).

An indication of the degree of esterification in these two fractions can be obtained by IR spectroscopy (Figure 2.14 a) and b)). As can be seen from figure (a), the absorption band for the hydroxyl groups has a low intensity confirming that the first fraction corresponds to HFSPE's with higher degree of esterification. The larger intensity of this absorption band in figure (b) indicates the presence of higher number of free hydroxyl groups in later fractions.

a)

b)

Figure 2.14 a) IR Spectrum for HFSPE with high DS; b) IR Spectrum for HFSPE with low DS.

The first fraction having R_f value of 0.97 in DCM/ethyl acetate 12:1 appeared as a single spot on TLC. However, TLC performed using a different solvent mixture, such as hexane:ether:acetic acid = 70:30:1, showed four spots very close one to each other, having R_f values between 0.11 and 0.18. This behavior could be explained by the very similar polarities of these compounds.

It should be mentioned that in the same solvent mixture, sucrose octa oleate shows on TLC only one spot at $R_f = 0.94$. This difference in polarity between SOO and HFSPE is due to the presence of fluorine atoms on the fatty acid moieties.

As our interest is the obtaining of HFSPE's with a degree of esterification of 6, 7, or 8, only this first fraction will be further characterized.

The ^{13}C NMR spectrum (Figure 2.15 a)) of this first mixture indicates that esterification reaction took place and a mixture of HFSPE's has been obtained.

Approximately, 15 peaks corresponding to carbonyl carbons at 171.2-175.4ppm (Figure 2.15 b)), are consistent with this interpretation. The carbons of the sucrose skeleton show peaks at 63.5-102.9ppm and those participating at the double bond at 126.1 and 132.2ppm.

a)

b)

Figure 2.15 a) 100MHz ^{13}C NMR Spectrum for HFSPE, and b) carbonyl peaks for HFSPE.

In order to determine the degree of esterification of the HFSPE mixture a MALDI mass spectrum was obtained.

Matrix-assisted laser desorption ionization mass spectrometry (MALDI) is a relatively new soft ionization method that allows desorption and ionization of large molecules even if they exist in complex mixtures. The sample is embedded in a chemical matrix that greatly facilitates the production of intact gas-phase ions from these large, nonvolatile, and thermally labile compounds. The matrix plays a key role in this technique by absorbing the laser light energy and causing a small part of the target substrate to vaporize (39). The matrix used to determine the molecular weight of HFSPE was 3,5-dimethoxy-4-hydroxycinnamic acid, known as sinapinic acid. Its structure is shown below.

Sinapinic Acid

This compound meets the requirements for a good MALDI matrix, such as: solubility in solvents compatible with analyte, ability to co-crystallize with analyte, stability to vacuum, absorption of the laser wave length, ability to cause co-desorption of the analyte upon laser irradiation and promotion of analyte ionization.

The MALDI spectrum (Figure 2.17, and enhanced area of interest Figure 2.18 a) and b)) of the fraction containing a mixture of HFSPE with high degree of esterification was taken in the linear mode and the resolution was 44.6 at 1000 m/z. The calculated molecular weights for penta, hexa, hepta and octa HFSPE are 2832.3, 3330.3, 3828.3,

and 4326.3 respectively. In Table 4, are shown the calculated values for the molecular weight and the obtained values from the MALDI experiment.

Table.4 Calculated and found values for HFSPEs molecular weights.

HFSPE	Calculated Molecular Weight	Found value from MALDI Spectrum
Penta HFSPE	2832.3	2856.1
Hexa HFSPE	3330.3	3354.9
Hepta HFSPE	3828.3	3854.0
Octa HFSPE	4326.3	4345.8

The precision of the experimental measurements was calculated using the expression: $\Delta M = M/R$ (39), where M is 1000 m/z and R is the resolution, which has the value 44.6. The calculated ΔM is approx. 22.4 m/z, a value that may explain the difference of approx. 23m/z (average), between the calculated and found values for the molecular weights. One very important piece of information provided by MALDI spectrum is that all these four values are approx. 500 units apart, which represents the mass of one highly fluorinated fatty acid moiety.

An attempt was made to assign the other peaks from this spectrum. As it has been already established via ^{13}C NMR methods (40), for the hexa and hepta isomers of sucrose poly oleates, it is the fructose ring that is most likely to be less esterified due to its flat shape and to hydroxy groups in position 3' and 4' which are less reactive due to steric

hindrance. Therefore the calculations of molecular weight for fructose ring with, two, three and four ester groups were done. As it can be seen from Table 5, the calculated values are very close to those found by experiment, which lead to the conclusion that are fragments from hexa, hepta and octa HFSPE's.

Figure 2.16 Fragmentation of sucrose polyester parent ion.

The C-O bond between glucose and fructose ring is not very strong and can break as shown in Figure 2.16. The result of this breakage is a glucose ring fragment, totally esterified, with a calculated mass of 2155 (which is in concordance with the peak found at 2157.7) and fructose ring fragment totally and partially esterified having the values shown in Table 5.

These results lead to the conclusion that this analyzed fraction is a mixture of penta, hexa, hepta and octa HFSPE. As estimated from MALDI spectrum calculation of relative peak areas, the mixture content was: hexa highly fluorinated sucrose ester 56.6%, penta 25.9%, hepta 16.5% and octa ester 0.9%.

Table 5. Calculated and found values for the fructose mass with different degree of esterification.

Fructose esters	Calculated mass value	Found mass value
Fructose tetra ester	2155	2157.7
Fructose triester	1657	1659.9
Fructose diester	1159	1160.8

Figure 2.17 MALDI Mass Spectrum on HFSPE's mixture with high degree of esterification.

a)

b)

Figure 2.18 a) MALDI Mass Spectrum for penta, hexa and hepta HFSPE, and b) for hepta and octa HFSPE's.

Attempts to separate the mixture of HFSPE's with higher degree of esterification were performed through high performance liquid chromatograph (HPLC) methods (41, 42). No satisfactory results were obtained although different mobile phases and different wavelengths were used. One possible reason could be the fact that the UV absorbtion at 230nm of these compounds is too broad and of too low intensity, characteristic that appear in the HPLC chromatograms as well.

Molecular mechanics calculations on the hepta HFSPE isomers (Figure 2.19-2.23) total energy confirmed that 3' and 4' sites on the fructose moiety are the most difficult to esterify due to steric hindrance. As it can be seen from Table 6 the structures having the free hydroxyl on these positions, have lower values for the total energy, which means a better stability and a higher probability of formation.

Table 6 Total energy values for hepta HFSPE isomers.

Sucrose with free hydroxyl in position	Energy value (Kcal/mol)
3'	1790.1
4'	1776.3
2	1816.7
3	1815.6
4	1814.8

Figure 2.19 Structure of HFSPE with free hydroxyl at 4' position obtained from energy minimization (molecular mechanics).

Figure 2.20 Structure of HFSPE with free hydroxyl at 3' position obtained from energy minimization (molecular mechanics)

Figure 2.21 Structure of HFSPE with free hydroxyl at 2 position obtained from energy minimization (molecular mechanics)

Figure 2.22 Structure of HFSPE with free hydroxyl at 3 position obtained from energy minimization (molecular mechanics).

Figure 2.23 Structure of HFSPE with free hydroxyl at 4 position obtained from energy minimization (molecular mechanics).

Chapter 3 Experimental Section

All reagents and solvents used in this study were commercial grade (Aldrich) and purified according to established convention

- 1,9-nonane diol, 98%
- hydrogen bromide 48%
- chromium trioxide
- concentrated sulfuric acid
- triphenylphosphine
- perfluorohexyl iodide, 99%
- ethyl acrylate, 99%
- lithium aluminium hydride, 1.0M solution in tetrahydrofuran
- pyridinium chlorochromate, 98%
- potassium tert-butoxide, 95%
- oxalyl chloride, 98%
- sucrose, 98%
- sucrose octaacetate, 98%
- oleoyl chloride, 85%
- oleic acid, 90%
- sodium, pieces, 3-20mm in mineral spirits
- 1,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-a]pyrimidine, 98%

3.1 Synthesis of 9-bromo-1-nonanol

1,9-nonane diol (20g, 0.124 mol) was dissolved in toluene (250mL) by heating the solution at about 60°C, in a 500mL round bottom flask. To this solution was added hydrobromic acid (48%, 14.1mL), dropwise and the mixture was heated at reflux (178 - 180°C) for 28 hours. The water formed during the reaction was trapped using a Dean-Stark trap.

After cooling to room temperature, the mixture was washed with 6 N sodium hydroxide solution (100mL), 10% hydrochloric acid (100mL), water (2x200mL), and finally with brine (150mL). 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 (24.89g, 90% yield) as a white solid mp 31.4-33.8°C, reported 33-35°C (Aldrich).

¹H 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).

¹³C NMR 62.9, 34.0, 32.8, 32.7, 29.4, 29.3, 28.7, 28.1, 25.7.

3.2 Synthesis of 9-bromo-nonanoic acid

To chromium trioxide (10.24g, 0.1023 mol) in water (10mL) at 0°C was added dropwise concentrated sulfuric acid (8.8mL, 0.133) followed by water (19mL). The molar ratio between chromium trioxide and 9-bromo-1-nonanol was 1.5:1, and between chromium trioxide and sulfuric acid was 1:1.3. The resulting mixture was slowly added to a solution of 9-bromo-1-nonanol (15.2g, 0.0682 mol) in acetone (50mL) at -5°C. After stirring for 2 hours at 0°C, the solution was left over night at room temperature.

To the resulting mixture was added diethyl ether (60mL) and the mixture was extracted several times with diethyl ether (3x60mL). The combined organic extracts were washed with water (2x60mL), brine (70mL), 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 resulted yellowish oil and the fraction having the R_f value of 0.48 in DCM on TLC was collected, yielding 9-bromo-nonanoic acid (11.6g, 71.8%), as a solid, having the melting point 31.5-33.5°C. This compound is reported in the literature as being a liquid (28).

¹H 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).

¹³C NMR 180.1, 34.0, 33.9, 32.8, 29.0, 28.9, 28.5, 28.1, 24.6.

3.3 Synthesis of 9-bromotriphenylphosphonononanoic acid

In a 250mL round bottom flask were added 9-bromo-nonanoic acid (11.58g, 0.048 mol) and triphenylphosphine (12.81g, 0.048 mol) and dissolved in dry xylene (50mL).

The solution was heated at reflux over night 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. 9-bromo-triphenylphosphonononanoic acid (20.47g) was obtained in a 83.9% yield as a glassy solid.

^1H 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, $J=2.4$).

3.4 Synthesis of Ethyl-2-iodo-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononanoate

To a 50mL quartz tube were added perfluorohexyl iodide (2.65g, 5.9mmol) and ethyl acrylate (1.78g, 17.8mmol). The reactants were continuously mixed by running nitrogen gas through the quartz tube. The mixture was irradiated in a Rayonet photochemical reactor with 254nm UV light at room temperature for 48 hours. The ambient temperature was maintained by the cooling finger situated inside the quartz tube.

The reaction mixture was purified by fractional distillation under vacuum and gave 1.622g (50%, yield) of ethyl-2-iodo-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononanoate, boiling point 60-62°C (1mm Hg), reported (24) boiling point 86-90°C (2.3mm Hg).

3.5 Synthesis of Ethyl-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononanoate

To a 100mL double necked round bottom flask equipped with a condenser and a dropping funnel ethyl-2-iodo-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononanoate (1g, 0.0018 mol) was added in absolute ethanol (1.2mL). After heating the solution to reflux temperature, zinc dust (10 to 20 mesh), (0.119g, 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 one hour at 65-70°C another 0.119g of zinc was added, the slurry was resaturated with hydroiodic acid (55%), and the reaction carried on for a further two hours. The colorless solution was cooled, filtered from excess of zinc and poured into water (10mL), and extracted with diethyl ether (3x10mL). The collected organic extracts were washed with water (2x10mL), then with brine (10mL), dried over magnesium sulfate and the solvent evaporated by rotary evaporation. The product obtained in a 93.3% yield (0.7g) 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.

3.6 Synthesis of 4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononal

To an oven dried 250mL double necked round bottom flask equipped with a condenser, flashed with dry nitrogen gas and maintained under static pressure of nitrogen was transferred a 1.0M solution of lithium aluminum hydride (20.24mL, 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 (11.31g, 0.026 mol) was added dropwise and the reaction mixture was stirred over night at room temperature. To a well-stirred suspension of PCC (12.76g, 0.059 mol) in methylene chloride (100mL) taken in a 500mL round bottom flask equipped as described above, the solution of alkoxyaluminate intermediate in THF previously obtained by the reduction with lithium aluminum hydrate was added dropwise using a syringe. The mixture was stirred again over night at room temperature. The

reaction mixture was diluted with diethyl ether (50mL) and the supernatant liquid was filtered through Florisil (60g) contained in a sintered glass funnel; the solid residue was triturated with diethyl ether (3x30mL) 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 the fluorinated aldehyde, (4.86g , 48% yield) boiling point 40-43°C (5mm Hg), reported (26) boiling point 40°C (5mm Hg).

^1H 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, $J=22.3$).

3.7 Synthesis of Z-13,13,14,14,15,15,16,16,17,17,18,18,18-tridecafluoro-octadec-9-enoic acid

To a double-necked round bottom flask was added 9-bromotriphenylphosphonononanoic acid (3g, 0.006 mol). The flask was equipped with a mantle and connected to a high vacuum pump. A cold trap was used to collect all traces of water. The phosphonium salt was dried at 110°C under high vacuum for 5 hours. To this dried phosphonium salt, was added freshly distilled THF (100mL) and stirred under argon atmosphere until the salt completely dissolved. Subsequently, potassium tert-butoxide (1.38g, 0.0123 mol) was added under argon. The molar ratio base/phosphonium salt was 2.05:1. The resulting orange solution was stirred for 30 minutes at room temperature after which time 4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononanal (2.26g, 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 hours.

The reaction mixture was then triturated with 50mL of diethyl ether, acidified with 2M 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 further purified by column chromatography on silica gel with hexane as eluent until all less polar fractions were washed out. Then the polarity of the eluent was slowly increased using ethyl acetate using a final amount of 20% ethyl acetate in hexane.

A second purification by column chromatography on silica gel with 3:1 hexane: ethyl acetate was performed on the resulted yellowish oil. The fraction having a R_f value of 0.2 in DCM on TLC was collected, yielding Z-

13,13,14,14,15,15,16,16,17,17,18,18,18-tridecafluoro-octadec-9-enoic acid (0.89g, 28.3%) as a white solid, melting point 17.6-18.1°C.

^1H 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), 118.4 (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 $\text{C}_{18}\text{H}_{21}\text{F}_{13}\text{O}_2$: C 41.86, H 4.10, F 47.84, O 6.20. Found C 41.62, H 4.32, F 47.98.

3.8 Synthesis of Z-13,13,14,14,15,15,16,16,17,17,18,18,18-tridecafluoro-octadec-9-enoil chloride

To a round bottom flask equipped with a condenser was added 0.8522mL of oxalyl chloride dissolved in hexane. To this solution was added dropwise, over a period of 30 minutes, using a dropping funnel, 3.37g (0.0065 mol) Z-

13,13,14,14,15,15,16,16,17,17,18,18,18-tridecafluoro-octadec-9-enoic acid dissolved in approximately 1mL of hexane. The molar ratio between acid and oxalyl chloride was 1:1.5. After stirring for 30 minutes at 40°C, the mixture was slowly heated and kept at reflux temperature for 4 hours. The reaction mixture was cooled and the solvent and the excess of oxalyl chloride were removed by rotary evaporation. The remaining yellowish oil was heated at 60-70°C for another hour in vacuo to remove the last traces of oxalyl chloride. The acid chloride, yellowish oil, was obtained in a 91.7% yield, being used in the next step without further purification.

¹H NMR 5.48 (m, 1H), 5.35 (m, 1H), 2.88 (t, J = 1.8 , 2H), 2.34 (m, 2H), 2.07 (m, 4H), 1.7 (m, 2H), 1.33 (m, 8H).

¹³C NMR 173.8, 132.2, 126.2, 121.0 (m), 118.5 (m), 115.8 (m), 113.4 (m), 110.8 (m), 108.4 (m), 47.1, 31.0 (t, J = 21.9), 29.3, 29.0, 28.9, 28.4, 27.0, 25.0, 18.3 (t, J = 3.9)

3.9 Synthesis of sucrose polyesters

To a round bottom flask was added sucrose 0.24g (0.0007 mol) and dissolved in 1mL of dimethylformamide (DMF) with gentle heating until all sucrose dissolved. Then, 1.5mL of pyridine was added and the solution was cooled to room temperature. The pyridine was added in an excess of 3:1 to acid chloride. To this solution, the acid chloride solution was added under vigorous stirring. Acid chloride, 3g (0.0056 mol) was dissolved in acetonitrile 2.5mL, poured into a dropping funnel and added at a fast drop rate (20 minutes) to the sucrose solution.

The completion of the reaction was checked by TLC. After three days at room temperature the flask was heated at 40°C and kept for another 12 hours.

Over the reaction mixture water (25mL) and ether (25mL) were added. The aqueous phase was extracted three times with ether (25mL). The combined organic phases were washed with water and brine, dried over magnesium sulfate and filtered by gravity filtration. The solvent was removed by rotary evaporation and an orange viscous liquid was obtained. This reaction mixture was further purified by column chromatography on silica gel with 12:1 dichloromethane:ethyl acetate. The resulting chromatographic fractions were concentrated to dryness on rotary evaporator in round bottom flasks.

Attempts to separate the HFSPE mixture were performed via high performance liquid chromatograph (HPLC) methods. A HPLC-DAD (diode array detector) equipped with a commercially available reversed phase C12 Synergi 4 μ Max-RP 250x4.6mm column was used. The mobile phases were: a) methanol:isopropanol = 95:5 (v/v), at a flow rate of 1.0mL/min. and an injection volume of 10 μ l; samples were dissolved in THF at 5-20wt%.

b) methylene chloride, acetonitrile and isopropanol used in a mixture as shown in table bellow at a flow rate of 1.0 to 1.5mL/min; sample concentrations were 1.5 to 5mg/mL in DCM.

Table 7. Reverse phase HPLC gradient

Time (min.)	DCM	Acetonitrile	Isopropanol	Flow (mL/min.)
0	45.5	52.5	2.0	1.0
5	45.5	52.5	2.0	1.0
5.5	98.0	0	2.0	1.5
11.5	98.0	0	2.0	1.5
12.0	45.5	52.5	2.0	1.5
15.0	45.5	52.5	2.0	1.5
30.0	45.5	52.5	2.0	1.0

Chapter 4 Conclusions and Future Work

During this work, two highly fluorinated (F_{17} and F_{13}) oleic acid analogs were synthesized.

Z-11,11,12,12,13,13,14,14,15,15,16,16,17,17,18,18-heptadecafluoro-octadec-8-enoic acid (F_{17}) was obtained via a procedure, which employs a Wittig reaction as its key step and generates the Z isomer almost exclusively. The Z-stereochemistry of the major isomer was determined from ^1H NMR NOESY experiment.

Z-13,13,14,14,15,15,16,16,17,17,18,18,18-tridecafluoro-octadec-9-enoic acid (F_{13}) was obtained in an excess of 20:1 as estimated from ^1H NMR integration of the olefinic proton signals and in a 28.8% yield. ^{19}F NMR results show that there are six clearly resolved resonances, consistent with the structure containing six unique fluorinated carbons. Unambiguous assignment is possible using ^{19}F - ^{19}F Correlation NMR spectroscopy (COSY) ^{19}F NMR and ^{19}F - ^{19}F COSY spectroscopy. The Z-stereochemistry of the only isolated isomer was determined from a ^1H NMR NOESY experiment. The molecular weight was confirmed to be 516 from the Mass spectrum.

In the next step, a mixture of penta, hexa, hepta and octa HFSPE was obtained. The molecular masses for these polyesters and the major compound (the hexa ester) were confirmed via MALDI mass spectroscopy. The non-esterified carbons of this main polyester are assumed to be at 3' and 4' positions of the fructose ring, as demonstrated by molecular mechanics calculations and ^{13}C NMR spectroscopy.

As future work, efforts will be made to find a suitable method for the separation of these highly fluorinated sucrose polyesters.

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