

# New Results on Free Radical Additions to Unsaturated Fatty Compounds\*

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Unsaturated fatty acids such as oleic acid are 1,2-dialkyl substituted alkenes, which can be functionalized by free radical addition to the C,C-double bond. We have been able to add enolizable compounds, e. g. acetone, acetic acid and malonic acid to methyl oleate mediated by manganese(III)acetate. Azide radicals, generated by manganese(III)acetate-oxidation of sodium azide, have also been added to methyl oleate. Perfluoroalkyl iodides have been added via perfluoroalkyl radicals to methyl 10-undecenoate and methyl oleate to form the corresponding addition products. Reduction of the iodides by tributyltin hydride and saponification leads to interesting partially fluorinated fatty acids.

## Introduction

Unsaturated fatty acids such as oleic acid are 1,2-dialkyl substituted alkenes and contain an electron-rich double bond that can be functionalized in many different ways. It is therefore amazing that over 90% of the reactions utilizing fatty acids have been focused on the carboxylic acid functionality<sup>1</sup>.

In this paper we would like to show how the double bond of oleic acid and other unsaturated fatty acids can be functionalized. A common method in organic chemistry is the addition of electrophilic radicals to electron-rich olefines. Such additions are successful when utilizing terminal alkenes in good to excellent yields<sup>2</sup>. We have been particularly interested in developing radical additions to oleic acid, a sterically demanding alkene.

## Manganese(III)acetate mediated free radical additions to methyl oleate

The oxidation of enolizable compounds with manganese(III)acetate is one method of generating electrophilic radicals for the addition to electron rich alkenes<sup>2</sup>. We have recently applied this method to perform the free radical addition of enolizable compounds to methyl oleate<sup>3</sup>.

One example is the addition of acetone to methyl oleate. Acetone is oxidized to the acetyl radical by manganese(III)acetate via the enol intermediate. The acetyl radical attacks the double bond of methyl oleate.

In the presence of H-donors, such as acetone which is used in excess, methyl 9-acetylstearate and the regioisomeric methyl 10-acetylstearate are formed in equal amounts. Formation of an additional double bond at the 8- or 10-position can be achieved by the addition of cupric acetate to the reaction mixture. The intermediate radical is thus oxidized forming both 9- and 10-isomers following loss of a proton (Fig. 1).

This manganese(III)acetate mediated reaction can be used to effect the addition of a wide range of enolizable compounds to electron-rich alkenes<sup>2</sup>. A stoichiometric amount of manganese(III)acetate is required. In many cases it is better to generate Mn(III) *in situ* by adding a potassium permanganate solution to a catalytic amount of

## Neue Ergebnisse der radikalischen Addition an ungesättigte Fettstoffe

Ungesättigte Fettsäuren wie Ölsäure sind 1,2-dialkylsubstituierte Alkene, die durch radikalische Addition an die Doppelbindung funktionalisiert werden können. Enolisierbare Verbindungen wie Aceton, Essigsäure und Malonsäure wurden mittels Mangan(III)acetat an Ölsäuremethylester addiert. Azidradikale, gebildet durch Mangan(III)acetat-Oxidation von Natriumazid, wurden ebenfalls an Ölsäuremethylester addiert. Perfluoralkyliodide wurden über Perfluoralkylradikale unter Bildung der entsprechenden Additionsprodukte an 10-Undecensäuremethylester und Ölsäuremethylester addiert. Reduktion der Iodide mit Tributylzinnhydrid und Verseifung lieferte interessante partiell fluorierte Fettsäuren.

manganese(II)acetate. In this case only 20% of total manganese(III) salt is required<sup>3</sup>. The yields using this procedure are often satisfactory. In comparison to the addition of acetone, the addition of malonic esters to methyl oleate is more facile, proceeding in 55% isolated yield. The formal addition of acetonitrile across an olefin can be achieved by reaction of cyano acetic acid as the active methylene compound. This occurs via manganese(II)acetate mediated decarboxylation to the cyanomethyl radical prior to an attack on the olefin. Using a smaller amount of manganese(II)acetate the formation of  $\alpha$ -substituted  $\gamma$ -lactones is preferred (*vide infra*). Our results are given in Fig. 2.

Addition of stoichiometric amounts of cupric acetate, an oxidizing reagent for nucleophilic radicals, to the reaction mixture results in the stereospecific formation of two regioisomeric (*E*)-alkenes. Attack at C-9 results in the formation of a *trans* double bond at C-10, whereas attack at C-10 forms a *trans*-olefin at C-8. This reaction is particularly valuable as one can effect alkylation with overall retention of the olefin functionality. At this point the yields are low, due to the incomplete conversion of the methyl oleate; often 50% or more of methyl oleate are recovered. The overall addition of acetone, dialkyl malonates and cyano acetic acid has been achieved (Fig. 3).

Another use of this manganese(III)acetate mediated addition reaction is the one step synthesis of  $\gamma$ -lactones by the addition of short chain carboxylic acids and their derivatives to electron-rich olefins<sup>2</sup>. In the first step the carboxymethyl radical attacks the double bond. Oxidation of the resultant radical by a second equivalent of manganese(III)acetate, followed by cyclization results in  $\gamma$ -lactone formation. This  $\gamma$ -lactone synthesis with methyl oleate as olefin is illustrated in Fig. 4. In all cases a mixture of stereoisomers of the two regioisomers is obtained. The yields of the  $\gamma$ -lactones are about 40%. Our results are given in Fig. 4.

Addition of azide radicals allows the introduction of a nitrogen functionality at the C-9 or C-10 position of the methyl oleate. The azide radicals are generated by manganese(III)acetate oxidation of sodium azide. After addition to methyl oleate the intermediate radical is further oxidized by a second equivalent of manganese(III)acetate to form isomeric olefins (yield 50%). Both the azide and the olefin functionalities can be hydrogenated catalytically to form methyl 9(10)-aminostearate. Alternatively, selective reduction of the azide can also be achieved using the *Staudinger* reaction<sup>4</sup>: Treatment with triphenylphosphine followed by hydrolysis produces the methyl 9(10)-aminooctadec-10(8)-enoate (Fig. 5).

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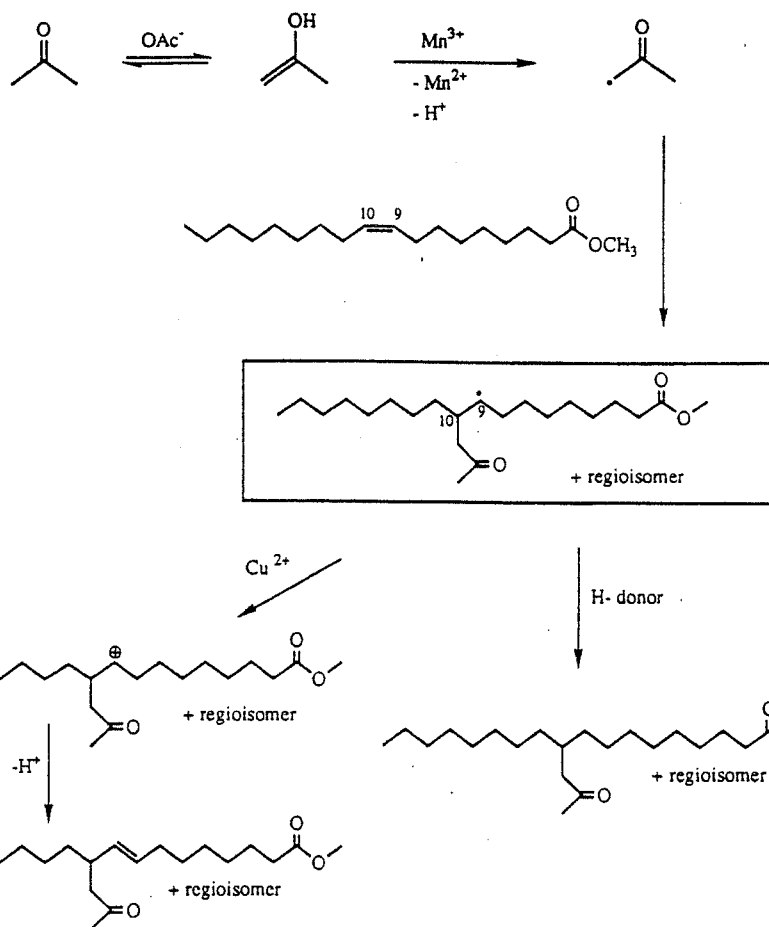
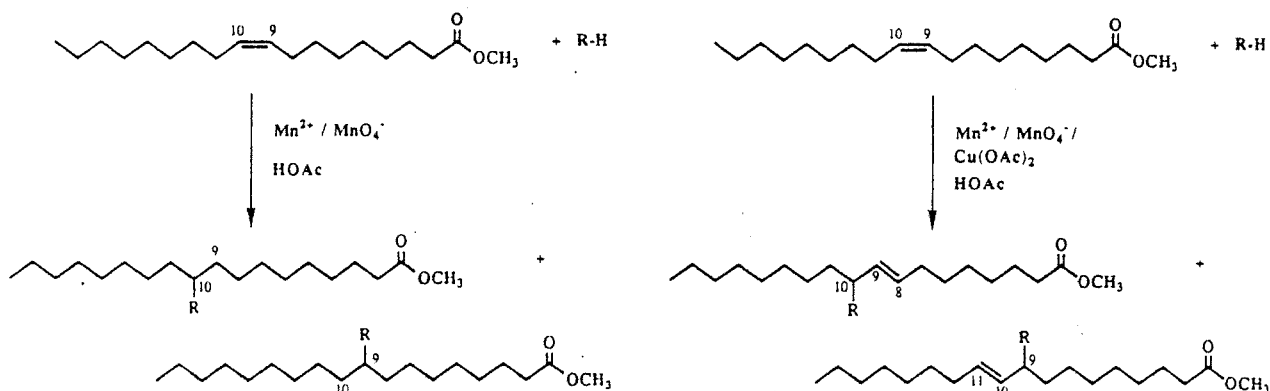


Fig. 1. Manganese(III)acetate mediated addition of acetone to methyl oleate and addition-elimination in the presence of cupric acetate

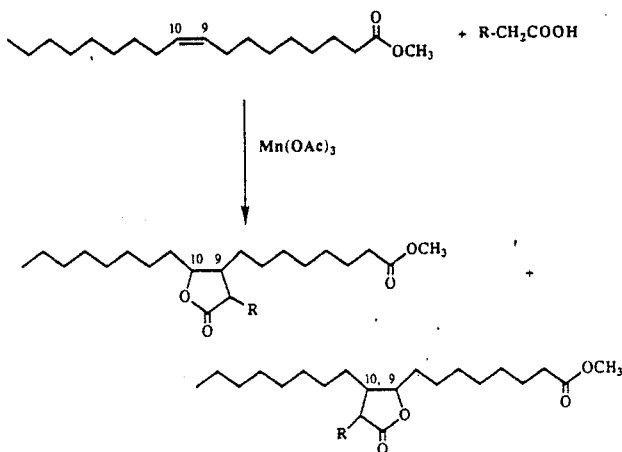


R-H	reaction-conditions	yield
CH <sub>3</sub> COCH <sub>3</sub>	Mn <sup>2+</sup> (cat.) / Mn <sup>7+</sup> 90°C	44%
CH <sub>2</sub> (COOEt) <sub>2</sub>	Mn <sup>2+</sup> (cat.) / Mn <sup>7+</sup> 70°C	55%
CH <sub>2</sub> (COOMe) <sub>2</sub>		
CNCH <sub>2</sub> COOH (-CO <sub>2</sub> )	Mn <sup>2+</sup> / Mn <sup>7+</sup> 70°C	24%

R-H	reaction-conditions	yield
CH <sub>3</sub> COCH <sub>3</sub>	Mn <sup>2+</sup> (cat.) / Mn <sup>7+</sup> / Cu <sup>2+</sup> 90°C	39%
CH <sub>2</sub> (COOEt) <sub>2</sub>	Mn <sup>2+</sup> (cat.) / Mn <sup>7+</sup> / Cu <sup>2+</sup> 70°C	35%
CH <sub>2</sub> (COOMe) <sub>2</sub>		
CNCH <sub>2</sub> COOH (-CO <sub>2</sub> )	Mn <sup>2+</sup> / Mn <sup>7+</sup> / Cu <sup>2+</sup> 70°C	23%

Fig. 2. Addition of enolizable compounds to methyl oleate with manganese(III)acetate prepared *in situ* with catalytic amounts of manganese(II)acetate and potassium permanganate (isolated yields based on charged methyl oleate are given)

Fig. 3. Addition of enolizable compounds to methyl oleate with manganese(III)acetate and cupric acetate (isolated yields based on charged methyl oleate are given)



R	reaction-conditions	yield
H	Mn(OAc) <sub>3</sub> 90°C	40%
COOH	Mn(OAc) <sub>3</sub> 70°C	55%
COOC <sub>2</sub> H <sub>5</sub>	Mn(OAc) <sub>3</sub> 70°C	42%
CN	Mn <sup>2+</sup> (cat.) / Mn <sup>7+</sup>	44%

Fig. 4. One step synthesis of  $\gamma$ -lactones by addition of short chain carboxylic acids to methyl oleate in the presence of manganese(III)acetate (isolated yields based on charged methyl oleate are given)

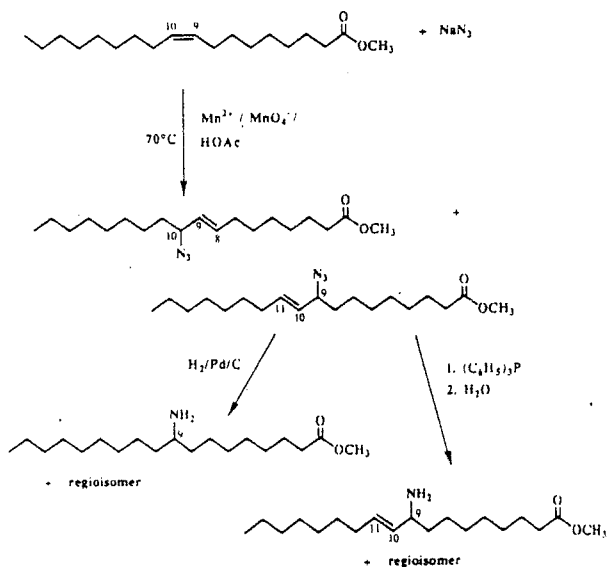


Fig. 5. Addition of sodium azide to methyl oleate with manganese(III)-acetate prepared *in situ* and reduction of the addition products to the corresponding methyl aminostearates

Addition of perfluoroalkyl iodides to methyl 10-undecenoate and to methyl oleate

We have been interested in developing a method to introduce perfluoroalkyl groups onto the side chain of fatty acids. We believe that such partially fluorinated fatty acids

could display interesting characteristics, such as surface properties.

A known method for the generation of semifluorinated hydrocarbons is the free radical addition of perfluoroalkyl iodides to 1-alkenes. Rabold *et al.*<sup>5</sup> heated perfluorododecyl iodide in the presence of 1-octene with AIBN (azobisisobutyronitrile) as initiator to form the addition product in a yield of 82%. After reduction of the iodide with Zn/HCl the semifluorinated hydrocarbon is obtained (Fig. 6). Addition of perfluoroalkyl iodides to terminal unsaturated acids i.e. 10-undecenoic acid gave 90–100% yields of the addition product<sup>6</sup>.

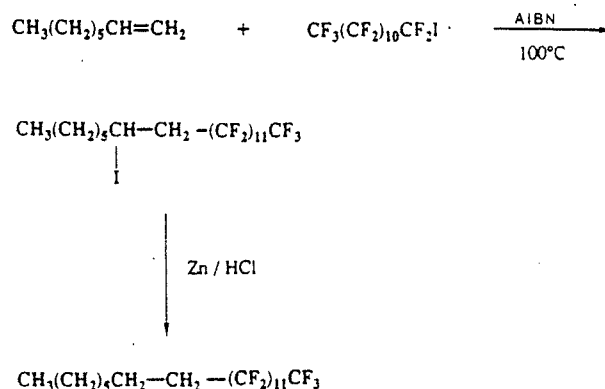


Fig. 6. AIBN induced free radical addition of perfluorododecyl iodide to 1-octene<sup>5</sup>

We investigated the free radical addition of perfluoroalkyl iodides to unsaturated fatty acids. Perfluorohexyl iodide and methyl 10-undecenoate were heated in the presence of AIBN at 80°C, to give the addition product in a yield of 72%. However, attempts to add perfluorohexyl iodide to methyl oleate using this procedure were unsuccessful. After heating at 100°C we could detect the addition product only by GC (yield 6%) (Fig. 7).

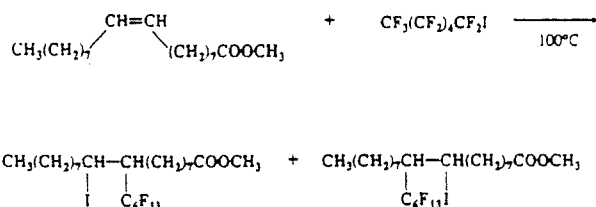
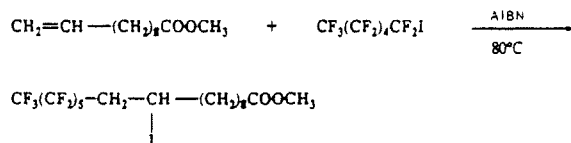


Fig. 7. AIBN induced free radical addition of perfluorohexyl iodide to methyl 10-undecenoate and methyl oleate

AIBN initiated free radical chain addition of perfluoroalkyl iodides seems to be successful only with terminal olefins. Therefore we searched for a new method for the introduction of perfluoroalkyl groups to the more sterically demanding oleic acid.

In 1989 Ishihara and Kuroboshi<sup>7</sup> reported a method for the addition of perfluoroalkyl iodides to olefins using tin(II)

chloride and silver (I) acetate. The addition of perfluorobutyl iodide to 1-octene leads to the addition product in essentially quantitative yield. The addition of perfluorobutyl iodide to 3-hexene under these conditions was also successful, giving the addition product in a yield of 45%. Although the yield is moderate this seems to be the best of the known methods for the introduction of perfluoroalkyl groups to 1,2-disubstituted olefins. We therefore investigated the reaction of perfluoroalkyl iodides with methyl 10-undecenoate and methyl oleate. In the presence of tin(II)chloride and silver (I) acetate the perfluorobutyl iodide is added across the double bond of methyl 10-undecenoate in a yield of 85%. The resulting product is a liquid, with a boiling point slightly higher than methyl 10-undecenoate. Reductive removal of the iodide is the best achieved with tributyltin hydride. The final product, methyl nonafluoropentadecanoate, is obtained as a low melting solid, with a melting point of 22°C. After saponification nonafluoropentadecanoic acid is obtained with a melting point of 53°C. Alternatively, treatment of methyl 10-iodo-nonafluoropentadecanoate with KOH results in the elimination of HI and saponification in one step. The elimination is regioselective, forming the 10-unsaturated fatty acid. In contrast to the saturated product the unsaturated semifluorinated fatty acid is a liquid at room temperature (Fig. 8).

Table 1 shows the isolated products and the reactions we have already carried out with methyl 10-undecenoate and perfluoroalkyl iodides using the tin(II)chloride/silver (I) acetate method. Good yields are obtained in all cases.

Perfluoroalkyl iodides, i.e. perfluorohexyl iodide, can

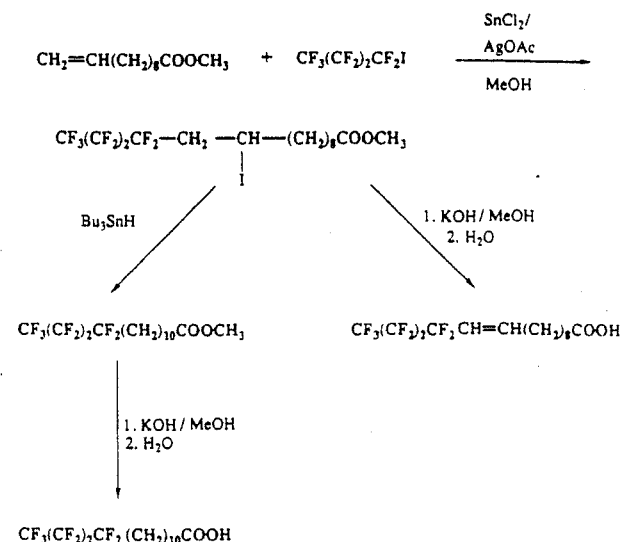


Fig. 8. Addition of perfluorobutyl iodide to methyl 10-undecenoate initiated by tin(II)chloride/silver(I)acetate and further synthetic transformations of the addition product

also be added to methyl oleate in the presence of SnCl<sub>2</sub> and AgOAc, resulting in the non separable regioisomers methyl 9-perfluorohexyl-10-iodostearate and methyl 10-perfluorohexyl-9-iodostearate in a yield of 50%. Reduction with tributyltin hydride forms both methyl 9- and 10-perfluorohexylstearate, isolated as an oil. In comparison methyl tridecafluoroheptadecanoate has a melting point of 31°C. Saponification provides methyl 9(10)-perfluorohex-

Table 1

Addition of perfluoroalkyl iodides to methyl 10-undecenoate initiated by tin(II)chloride/silver(I)acetate.  
Reduction and saponification of the addition products  
Isolated yields and refractive index or melting point of the products are given

	C <sub>4</sub> F <sub>9</sub> I	C <sub>6</sub> F <sub>13</sub> I	C <sub>8</sub> F <sub>17</sub> I
$\text{H}_2\text{C}=\text{CH}-\text{R}^1$	$\text{C}_4\text{F}_9-\text{CH}_2-\underset{\text{I}}{\text{CH}}-\text{R}^1$	$\text{C}_6\text{F}_{13}-\text{CH}_2-\underset{\text{I}}{\text{CH}}-\text{R}^1$	$\text{C}_8\text{F}_{17}-\text{CH}_2-\underset{\text{I}}{\text{CH}}-\text{R}^1$
	$n_D^{25}: 1,4215$ yield: 85%	$n_D^{23}: 1,4085$ yield: 85%	$n_D^{22}: 1,4005$ yield: 90%
Reduction with Bu <sub>3</sub> SnH yields: 90 - 95%	$\text{H}_2\text{C}-\text{CH}_2-\text{R}^1$   C <sub>4</sub> F <sub>9</sub> m.p.: 22,3°C	$\text{H}_2\text{C}-\text{CH}_2-\text{R}^1$   C <sub>6</sub> F <sub>13</sub> m.p.: 31°C	$\text{H}_2\text{C}-\text{CH}_2-\text{R}^1$   C <sub>8</sub> F <sub>17</sub> m.p.: 49,6°C
Saponification with KOH/CH <sub>3</sub> OH yields: 85 - 93 %	$\text{H}_2\text{C}-\text{CH}_2-\text{R}^2$   C <sub>4</sub> F <sub>9</sub> m.p.: 52,5°C	$\text{H}_2\text{C}-\text{CH}_2-\text{R}^2$   C <sub>6</sub> F <sub>13</sub> m.p.: 68°C	$\text{H}_2\text{C}-\text{CH}_2-\text{R}^2$   C <sub>8</sub> F <sub>17</sub> m.p.: 88,2°C

R<sup>1</sup>: (CH<sub>2</sub>)<sub>8</sub>COOCH<sub>3</sub>

R<sup>2</sup>: (CH<sub>2</sub>)<sub>8</sub>COOH

Table 2

Addition of perfluoroalkyl iodides to methyl oleate initiated by tin(II)chloride/silver(I)acetate. Reduction and saponification of the addition products  
Isolated and GC-yields and the refractive index of the products are given

	C <sub>4</sub> F <sub>9</sub> I	C <sub>6</sub> F <sub>13</sub> I	C <sub>8</sub> F <sub>17</sub> I
R <sup>1</sup> CH=CHR <sup>2</sup> yields: 30 - 50% GC-yields: 42 - 67%	R <sup>1</sup> CH—CHR <sup>2</sup>   C <sub>4</sub> F <sub>9</sub>   n <sub>D</sub> <sup>21</sup> : 1,4344	R <sup>1</sup> CH—CHR <sup>2</sup>   C <sub>6</sub> F <sub>13</sub>   n <sub>D</sub> <sup>23</sup> : 1,4238	R <sup>1</sup> CH—CHR <sup>2</sup>   C <sub>8</sub> F <sub>17</sub>   n <sub>D</sub> <sup>23</sup> : 1,4005
Reduction with Bu <sub>3</sub> SnH yields: 85 - 90%	R <sup>1</sup> CH—CH <sub>2</sub> R <sup>2</sup>   C <sub>4</sub> F <sub>9</sub> n <sub>D</sub> <sup>22</sup> : 1,4075	R <sup>1</sup> CH—CH <sub>2</sub> R <sup>2</sup>   C <sub>6</sub> F <sub>13</sub> n <sub>D</sub> <sup>23</sup> : 1,3950	R <sup>1</sup> CH—CH <sub>2</sub> R <sup>2</sup>   C <sub>8</sub> F <sub>17</sub> n <sub>D</sub> <sup>22</sup> : 1,3912
Saponification with KOH / CH <sub>3</sub> OH yields: 85%	R <sup>1</sup> CH—CH <sub>2</sub> R <sup>3</sup>   C <sub>4</sub> F <sub>9</sub> n <sub>D</sub> <sup>21</sup> : 1,4146	R <sup>1</sup> CH—CH <sub>2</sub> R <sup>3</sup>   C <sub>6</sub> F <sub>13</sub> n <sub>D</sub> <sup>22</sup> : 1,4015	R <sup>1</sup> CH—CH <sub>2</sub> R <sup>3</sup>   C <sub>8</sub> F <sub>17</sub> n <sub>D</sub> <sup>21</sup> : 1,3994

R<sup>1</sup>: CH<sub>3</sub>(CH<sub>2</sub>)<sub>7</sub>  
R<sup>2</sup>: (CH<sub>2</sub>)<sub>7</sub>COOCH<sub>3</sub>  
R<sup>3</sup>: (CH<sub>2</sub>)<sub>7</sub>COOH

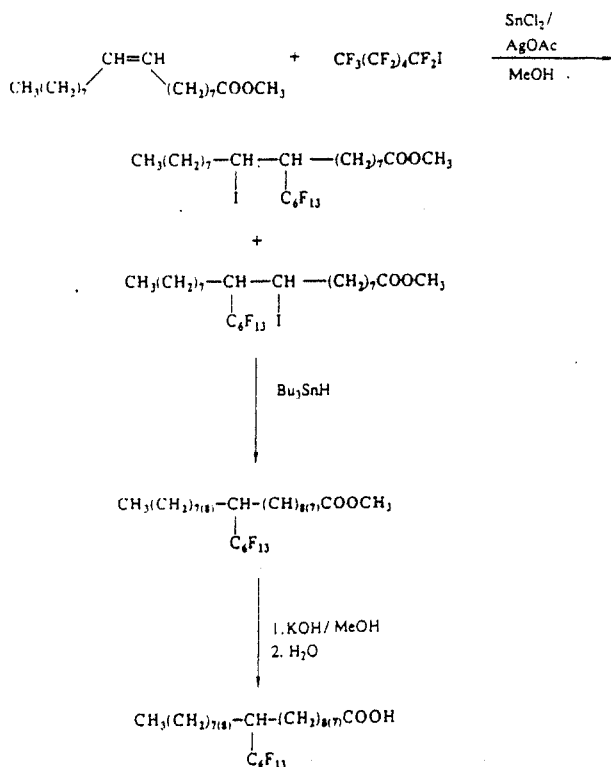


Fig. 9. Addition of perfluorohexyl iodide to methyl oleate. Reduction and saponification of the addition product

ylstearate as a liquid product (Fig. 9). In comparison tridecafluoro pentadecanoic acid melts at 68 °C.

Table 2 displays the results of reactions of methyl oleate with perfluoroalkyl iodides. The isolated yields are generally moderate; the GC-yields are higher. Loss of product is due to difficulties in separation of the product from starting material.

### Conclusion

The manganese(III)acetate mediated addition of enolizable compounds e.g. acetone, dialkyl malonates, acetic acid, cyanoacetic acid to the double bond of methyl oleate is a convenient and valuable method to synthesize branched and functionalized stearic acid derivatives in good to moderate yields. Nitrogen functionalities can be introduced in the alkyl chain by addition of azide to oleic acid mediated by manganese(III)acetate as well. Partially fluorinated linear fatty acids can be synthesized in very good yields by tin(II)chloride/silver(I)acetate induced addition of perfluoroalkyl iodides to 10-undecenoic acid. Perfluoroalkyl branched stearic acids can be obtained by addition of perfluoroalkyl iodides to oleic acid by the same method. A great variety of branched and partially fluorinated fatty compounds which may have interesting properties are now available.

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