

Selenated and Sulfurated Analogues of Triacyl Glycerols: Selective Synthesis and Structural Characterization

Damiano Tanini*, Veronica D'Esopo, Duccio Tatini, Moira Ambrosi, Pierandrea Lo Nostro and Antonella Capperucci*

Abstract: The synthesis of sulfur- and selenium-containing isomers of triacyl glycerols is herein described. Regioselective fluoride-induced ring-opening reaction of suitable substituted thiranes with bis(trimethyl)silyl selenide, followed by *in situ* S- and Se-acylation with fatty acid acyl chlorides, enables the *one pot* synthesis of mixed chalcogeno esters in good yield. The key step of this methodology is the functionalization of S-Si and Se-Si bonds of silyl chalcogenides, generated *in situ* under mild conditions. A related procedure for the synthesis of functionalized selenides, bearing two thiol ester and two ester moieties, was also developed through a fine tuning of the reaction conditions. The physico-chemical properties of these novel fatty acid chalcogeno esters have been investigated through DSC, SAXS, WAXS, FTIR and polarized optical microscopy, and compared to those of the common triglycerides in order to highlight the effect of the replacement of oxygen with other chalcogen elements in the polar head of the lipid.

Introduction

Acyl glycerol derivatives represent a large group of molecules, finding wide application in different fields, as pharmaceutical, food, cosmetic, and material sciences.^[1] Suitable substituted acyl glycerols are reported to play important physiological roles in the nervous system^[2] and it is established that acyl glycerols from common oils show antitumor activity and various inhibitory actions.^[3] Furthermore, acyl glycerols and their sulfur- and nitrogen-containing analogues are used for the prevention and the treatment of neurodegenerative diseases.^[4] Triglycerides have been widely investigated also for their physicochemical properties. In particular, triglycerides have been deeply investigated in the past by Luzzatti and Larsson, especially for their peculiar structural properties in the solid state. This topic gave rise to a vivacious debate in the scientific community.^[5] Nanodispersions of triacyl glycerols have been studied as potential drug carrier systems^[6] and for their polymorphism.^[7] In this context, thio-substituted derivatives have been examined for the peculiar properties that sulfur can confer to these thiol esters, like chiroptical properties,^[8] improvement of oxidation and

lubricity properties, and of the friction and wear behaviour.^[9] Likewise, triacyl glycerols composition plays a significant role on their properties and their application. For example the conformational flexibility and absolute stereochemistry affect the biological activity of these molecules and can be investigated through the common chiroptical spectroscopies.^[10] Several studies are reported on triacyl glycerols bearing fatty acids which differ for the kind and the length of the chain.^[11] Ester exchange reactions have been commonly used to prepare triacyl glycerols; however, these procedures lead to a random distribution of triglycerides as isomeric products bearing a mixed short and medium chain fatty acids.

Thus, taking into account that the features of triglycerides can be related both to the fatty acid composition and to the presence of heteroatoms, there is a need for further studies on the preparation of novel heterosubstituted triacyl glycerols, containing saturated and unsaturated fatty acids of different nature and different chain length. For example, the presence of chalcogeno ester groups can open new space, offering the possibility to modulate the lipophilicity and to confer catalytic antioxidant properties. In this regard, very few examples are described on the synthesis of acyl-thioglycerols,^[4,8,11] and usually several steps are required to obtain products in a regio- and stereoselective way. In addition, to the best of our knowledge, only one example is reported to prepare acyl-selenoglycerols,^[4] while no procedure is described to access acyl glycerols containing both sulfur and selenium atoms.

Our long dated interest in the chemistry of thiosilanes led us to develop a general and mild methodology to synthesize differently substituted 1,2-mercapto alcohols, 1,2-mercapto amines, and 1,2-dithiols by ring opening of epoxides and episulfides with bis(trimethylsilyl)sulfide, (Me₃Si)₂S (HMDST).^[12] More recently, we disclosed that the selenated analogue, (Me₃Si)₂Se (bis(trimethylsilyl)selenide, HMDSS), reacted efficiently with strained heterocycles, allowing to access β -substituted selenols.^[13] These functionalized small molecules can be employed as versatile intermediates, enabling the synthesis of a variety of cyclic and acyclic chalcogen-containing derivatives.^[14] In order to further expand the scope and the application of this synthetic approach, we became interested in evaluating the reactivity of bis(trimethylsilyl)selenide with suitably substituted episulfides for the preparation of novel triacyl thio-selenoglycerols.

In the present contribution, the synthesis and the main structural and thermal properties (through DSC, SAXS, WAXS, FTIR and polarized optical microscopy studies) of selenated and sulfurated analogues of triglycerides in the solid state will be discussed. Our results suggest that these compounds are promising in view of future biomedical applications as innovative drug delivery devices. In fact the comparison of their physico-chemical properties to those of their fully oxygenated analogues suggest the relevance of the role played by the interactions

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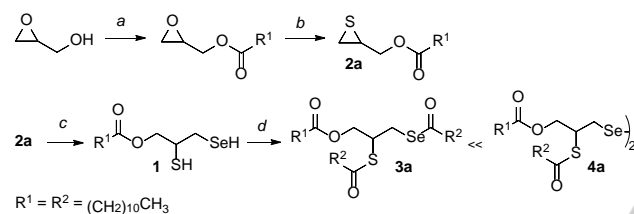
Supporting information for this article, including detailed experimental procedures, products characterization, DSC, SAXS, WAXS curves, FTIR spectra, and copy of NMR spectra of new products, is given via a link at the end of the document.

between the head groups on the phase behavior of these molecules. The consequences of absolute stereochemistry on their self-assembly behavior in different media and on their performances *in vivo* and *in vitro* are of great interest for biomedical and formulation technology applications.

Results and Discussion

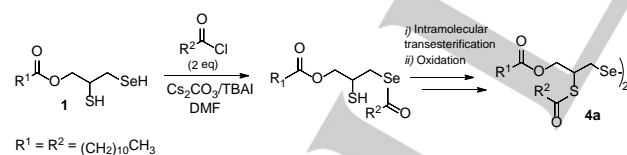
a) Synthesis of fatty acid chalcogeno esters **3** and **7**

We began our investigations by evaluating the possibility to synthesize compound **3a** through the double functionalization of the selenol and thiol moieties of β -mercapto selenol **1**, which can be easily prepared from the corresponding thirane **2a**^[15] and HMDSS following our reported procedure.^[13a] However, when selenol **1** was treated with 2.0 eq. of lauryl chloride under basic conditions in the presence of Cs₂CO₃/TBAI the desired product **3a** was formed only in low yield (15%), while the major observed compound was the corresponding diselenide **4a**, bearing an ester and a thiol ester group on β -positions (Scheme 1).



Scheme 1. Reagents and conditions: a) R²COCl (1.1 eq.), Et₃N (3.0 eq.), MeCN, 0 °C to r.t., 12h; b) Thiourea (1.2 eq.), MeOH, r.t., 24h; c) (Me₃Si)₂Se, TBAF, THF, -15 °C, 10 min; d) R²COCl (2.0 eq.), Cs₂CO₃/TBAI (2.0 eq.), DMF, 0 °C to r.t.

Taking into account the stronger nucleophilic character of the selenol with respect to the thiol, the formation of the diselenide **4a** could be due to a preliminary esterification of the SeH group, followed by an intramolecular attack of the sulfated nucleophile. This transesterification reaction^[16] should afford the thiol ester bearing the selenolate function, which easily undergoes oxidation to diselenide (Scheme 2).

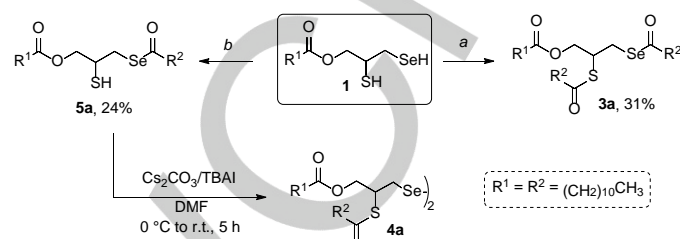


Scheme 2. Hypothesis for the formation of diselenide **4a** from selenol **1a**.

On the other hand, the observed low reactivity of both the selenol and the thiol moieties with the fatty acid acyl chloride to give the wanted triacyl thio-selenoglycerol could be due to steric hindrance caused by the long chains of the fatty acid residue, which could slow the esterification reaction. The reaction was carried out also under different conditions, varying both the temperature and the reaction time but no appreciable yield improvements were achieved. We also evaluated the effect of different bases and, although strong inorganic bases such as NaOH and KOH led to the formation of compound **3a** in traces amount, the use of Et₃N in CH₂Cl₂ enabled for the first time the isolation of the desired mixed chalcogeno ester **3a** in

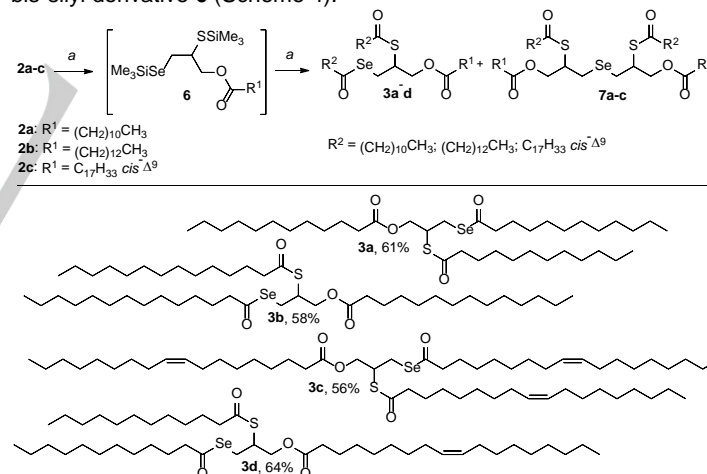
appreciable yield (Scheme 3). Interestingly, slightly modified Et₃N-promoted conditions could also be employed for the synthesis of β -mercapto selenol ester **5a** (Scheme 3).

Pleasingly, treatment of **5a** with Cs₂CO₃/TBAI afforded the diselenide **4a**, thus confirming the proposed mechanism (Scheme 2), involving a thiol/selenol ester transesterification reaction and oxidation sequence. (Scheme 3).



Scheme 3. Synthesis of **3a** and **5a** from selenol **1**. Reagents and conditions: a) R²COCl (2.5 eq.), Et₃N (2.5 eq.), CH₂Cl₂, 0 °C to r.t., 5 h; b) R²COCl (0.8 eq.), Et₃N (0.8 eq.), CH₂Cl₂, 0 °C, 30 min.

In order to develop a direct and operationally easier access to chalcogeno esters **3**, based on our previous results on TBAF induced functionalization of thiosilanes and selenosilanes with electrophiles, we envisaged the plausible bis-silyl intermediate **6** as a suitable species able to *in situ* react with acyl chlorides to afford the desired acyl-2-thio- 3-selenoglycerols through a *one pot* procedure, not involving the isolation of the mercapto selenol **1**. Thus, the episulfide **2a** was cooled at -15 °C and treated, under nitrogen, with HMDSS and TBAF in order to generate the bis-silyl derivative **6** (Scheme 4).



Scheme 4. Synthesis of sulfur- and selenium-containing isosteres of triacyl glycerols **3a-d**. Reagents and conditions: a) (Me₃Si)₂Se (1.2 eq.), TBAF (0.25 eq.), THF, 10 min, -15 °C; b) R²COCl (2.5 eq.), TBAF (0.25 eq.).

After 10 minutes at low temperature, the reaction mixture was *in situ* treated with lauryl chloride and TBAF, warmed to room temperature and stirred for one additional hour. Under these conditions, the mixed bis-chalcogenated triacyl glycerol **3a** was isolated as the major product in appreciable yield (61%), together with ca. 10% of the selenide **7a** (Scheme 4).

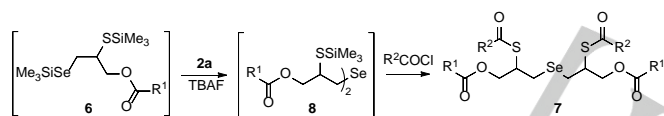
In order to explore the scope of the methodology, the reaction was also carried out with differently substituted thiranes **2b** and **2c**, which were reacted under the same conditions with myristoyl and oleoyl chlorides yielding triacylglycerols **3b** and **3c** in

satisfactory overall yields (58% and 56%) (Scheme 2). In this regard, it is worth to remember that the reaction products are the result of three different consecutive transformations: *i*) episulfide ring opening by HMDSS; *ii*) Se-Si and S-Si bonds F⁻ induced functionalization in **6**; *iii*) esterification reaction with the acyl chloride.

With the aim to prepare triglycerides with different ester groups on the oxygen and on the chalcogen atoms thiiran-2-yl-methyl oleate **2c** was reacted with lauryl chloride, leading to the isolation of the mixed triacyl glycerol **3d** in good yield (Scheme 2).

These results demonstrate the versatility of the procedures towards the synthesis of both simple and mixed chalcogenated isomers of triglycerides, bearing saturated and unsaturated alkyl chains.

Having developed a convenient *one pot* silicon-mediated procedure to access 2-seleno-1-thioglycerol esters **3**, we sought to evaluate whether the chemistry of silyl chalcogenides could also be exploited to disclose a selective access to selenides tetraesters **7**, obtained as side products in the previous reactions (Scheme 4). Selenides are indeed valuable compounds for their application as key intermediates in organic synthesis^[17] and, more recently, as antioxidants,^[18] carbonic anhydrase inhibitors^[19] and for their thiol peroxidase catalytic activity.^[18] In this context, the selective synthesis of functionalized selenides, bearing two fatty acid esters and two fatty acid thioesters would be highly desirable in order to modulate the lipophilicity of these systems. The formation of these compounds can be rationalised through the mechanism depicted in the Scheme 5.

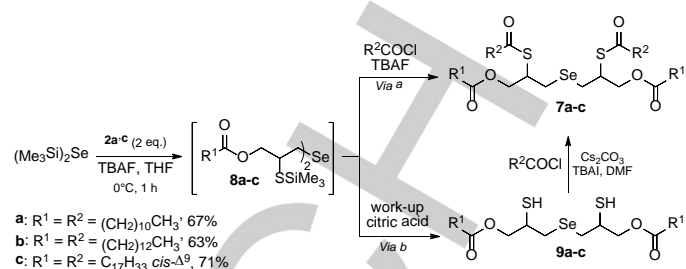


Scheme 5. Plausible formation of selenide tetraesters **7** through the bis-silyl derivative **8**.

The Se-Si bond of intermediate **6** can be activated by the fluoride ion, allowing the nucleophilic attack of selenium on a second molecule of thiirane **2a**. This reaction leads to the formation of the selenide intermediate **8** containing two thiosilane moieties, which in turn react with the acyl chloride, affording the product **7**, isolated in low yield. We reasoned that the formation of selenides **7** could be optimized simply tuning the stoichiometry of the ring-opening reaction of **2** with HMDSS towards the complete conversion of **6** into **8**. Therefore, bis(trimethylsilyl)selenide was reacted with an excess of thiirane **2a** in the presence of TBAF to generate the thiosilane **8**, which was *in situ* S-acylated upon treatment with lauroyl chloride and an additional amount of TBAF, affording the desired tetraester **7a** in good yield. (Scheme 6, *via a*). Pleasingly, this *one pot* route proved to be general, enabling the synthesis of functionalised selenides **7a-c** in good yield (Scheme 6) and confirming the synthetic utility and versatility of silyl chalcogenides.

Interestingly, intermediates **8** can also undergo proto-desilylation upon treatment with citric acid to afford the corresponding β -mercapto selenides **9**, which can be isolated and employed as precursors of selenide tetraesters **7** through a multi-step procedure (Scheme 6, *via b*). Indeed, Cs₂CO₃/TBAI-promoted S-acylation of **9a-c** led smoothly to the formation of polysubstituted

selenides **7a-c**, bearing lauroyl, mirystoyl and oleoyl chains, in comparable yields with respect to the *in situ* functionalization methodology. (Scheme 6, *via b*).



Scheme 6. Synthesis of selenides tetraesters **7a-c**.

b) Physico-chemical properties of fatty acid chalcogeno esters **3** and **7**.

The pure solids were investigated through DSC, SAXS-WAXD and FTIR in order to provide a physico-chemical characterization of these novel compounds and to compare their properties to the oxygenated analogues. Table 1 lists the main findings.

Table 1. Melting point (*mp*, in °C), enthalpy of fusion (ΔH_m , in kJ/mol), spacing (*d*, in nm).

	<i>mp</i>	ΔH_m	ΔS_m^c	<i>d</i>
3a	55.8	66.5	202	3.3
3b	65.2	104.6	309	3.7
3c	-5.2	54.5	204	
7a	22.3	70.2	237	3.4
7b	42.0 48.4	66.4 36.9	211 115	4.0 3.7
7c	-48.3	58.2	259	
LLL	15.0 (α_H) ^a	123.5 ^b	386 ^b	3.6
	35.0 (β_O) ^a			3.3
	46.4.0 (β_T) ^a			3.1
MMM	33.0 (α_H) ^a	148.1 ^b	446 ^b	4.1
	46.5 (β_O) ^a			3.8
	57.0 (β_T) ^a			3.6
OOO	-37.0 (α_H) ^c	107.9 ^c	388 ^c	
	-12.0 (β_{O3}) ^c			
	-8.0 (β_{O2}) ^c			
	-5.0 (β_{O1}) ^c			
	5.0 (β_T) ^c			

[a] See reference 22. [b] See reference 23. [c] See reference 24.

The DSC analysis provides interesting information on the thermal behavior. In particular, besides the evaluation of the melting temperature and enthalpy change, the DSC thermograms can reveal the presence of different crystalline phases (polymorphs).^[20] Long chain hydrocarbons form different crystalline phases: hexagonal (α_H), orthorhombic (β_O), triclinic (β_T), and monoclinic (β_M), that produce specific peaks between 3 and 5 Å in WAXD spectra, and typical bands between 750 and 710 cm⁻¹ in FTIR spectra.^[21] In more detail, the orthorhombic packing of the hydrocarbon chains has dual absorptions at 719

and 727 cm^{-1} . The hexagonal α_{H} and the triclinic β_{T} structures have only one band, at 720 and 717 cm^{-1} , respectively.

In WAXD profiles the α_{H} structure has a main diffraction at 0.42 nm ($2\theta = 21.5^\circ$); the β_{O} shows two main diffractions at 0.42 and 0.38 nm ($2\theta = 21.5^\circ$ and 23.9°). In the case of β_{T} packing, there are three main diffractions at 0.45 , 0.38 , and 0.36 nm ($2\theta = 19.5^\circ$, 22.5° , and 24.6°).

DSC analysis. **3a**, **3b**, and **7b** look like crystalline solids at room temperature, while **3c** and **7c** are colorless liquids at room temperature and **7a** melts at 22°C . **3a** and **3b** produce sharp peaks in the thermograms while **7a** and **7b** give broader peaks (Figure 1). **7b** shows the presence of two peaks at 42.0°C (62.5 J/g) and 48.4°C (31.2 J/g), suggesting the coexistence of two different crystalline phases. The **3c** and **7c** liquid samples gave very broad DSC peaks that could be narrowed and separated by using a 0.5°C/min scanning rate (Figure 2).

Apparently the presence of four chains linked to the same head group in the "7" series of homologues brings about a less ordered and less dense state as compared to the "3" series that contain only three aliphatic tails, in fact the calculation of the entropy change of melting per single chain provides values that are always higher for "3" derivatives as compared to their "7" analogues, including the oleic lipids (items "c"). In other words the four-chain "7" derivatives are less packed than the corresponding three-chain "3" compounds. Concerning the parameters of fusion, the data indicate that the melting points increase with the chain length within each series and drop abruptly in the case of the oleic moieties. The enthalpy changes of fusion increases in a similar way within each series according to the trend oleoyl < lauroyl < myristoyl. Interestingly a close look at the experimental findings shows that **3a** and **7a**, **3b** and **7b**, **3c** and **7c** possess very similar values of ΔH_m , although they contain either 3 or 4 chains per molecule. This result is unexpected and counterintuitive because the presence of another chain should bring about a larger enthalpy of melting. We speculate that the effect of a larger number of hydrophobic moieties is compensated by the different composition and interaction properties of the head groups. A comparison between the "3" series and the common fully oxygenated triglycerides (trilaurin, trimyristin and triolein, indicated as LLL, MMM, and OOO respectively in Table 1) shows that the melting point of **3a** and **3b** is higher than that of LLL and MMM respectively probably because of the larger polar region, while in the case of **3c** the different head group leads to a lower point respect to OOO. On the other hand, the enthalpy and entropy changes of triglycerides are significantly larger than those of **3a**, **3b** and **3c**, due to the replacement of the oxygenated polar group of triglycerides with the larger calchogen-mixed (OSSe) residue that results in weaker inter-chain interactions and therefore in a more disordered crystalline phase as confirmed by the lower ΔS_m values. In the case of the oleic derivatives we note that the **3c** derivative has a much lower melting point, enthalpy and entropy of melting compared to the β_{T} form of triolein due to a different packing of the chains and arrangement of the polar groups in the solid state.

Assuming that the enthalpy of melting can be divided into two independent contributions, related to the hydrophilic and to the hydrophobic portion of the lipid in the β polymorphs, Timms fitted the experimental values of ΔH_m for triglycerides and other similar compounds as a function of the number of carbons in the lipid through a linear equation.^[23,25] Zacharis reported similar data

and discussion in another paper.^[26] One of the main results of such reports is the negative term due to the presence of the polar heads, that in the case of triglycerides is about 33 kJ/mol . The (positive) contribution of the hydrocarbon chains in triglycerides to ΔH_m is about 4 kJ per carbon atom in each chain. Interestingly, the presence of hydrogen bonding between the polar heads in the case of 1-monoglycerides leads to a positive value of the term related to hydrophilic portion, and therefore contributes in increasing the enthalpy of melting of this class of compounds. As stated by Timms, "Because of the negative heats of fusion and almost zero entropies of fusion of the end groups of methyl esters and fatty acids, there is a marked tendency for these end groups to enter the liquid state. In Garner and King's words the end groups are in a "more expanded state" in the solid than in the liquid. Hence, in the process of melting energy is required only to separate the methylene groups, energy is released in converting the end groups from the solid to the liquid state."^[23,27] This is in line with our observations concerning the enthalpy of melting of the OSSe derivatives, where the values of ΔH_m follow a similar trend with a negative contribution from the polar heads. We recall here that upon melting, triglycerides form dimers in the liquid state, that brings about a quite strong head-to-head interaction between two adjacent lipid molecules.^[20,28] While in the case of mono- and diglycerides the free -OH groups in the heads can produce hydrogen bonding, in the case of triglycerides the head-to-head interactions are mainly of dipolar electrostatic origin. However in the case of OSSe derivatives the substitution of oxygen atoms with the more polarizable sulfur and especially selenium atoms enhances the contribution related to dispersion and induction forces acting between the hydrophilic moieties.

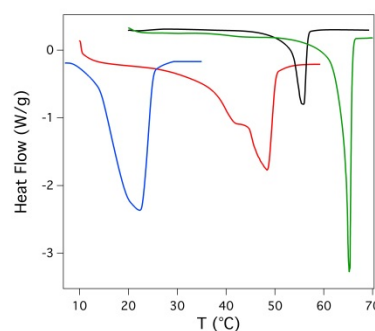


Figure 1. DSC curves for compound **3a** (black), **3b** (green), **7a** (blue), **7b** (red).

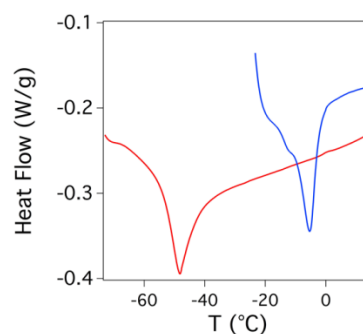


Figure 2. DSC curves for compound **3c** (blue), **7c** (red).

SAXS and WAXS analysis. The analysis of small and wide angle X-ray scattering data provide the structural organization in the solid at long and short range, respectively. Figures S1 and S2 (see ESI) report the $I(q)$ versus q SAXS profiles for **3a** (black), **3b** (green), **7a** (blue) and **7b** (red). All samples show a lamellar structure with spacing values (d in nm) listed in Table 1. Figures S3 and S4 (see ESI) show the $I(q)$ versus d WAXS patterns for the same specimen.

In the case of **3a** we recorded the presence of a single lamellar structure with 3 reflections. In the case of the longer chain derivatives (**3b** and **7b**) the results reflect the presence of different polymorphs. In fact the SAXS pattern for **3b** suggests the coexistence of at least two different phases, with a dominant structure centred at 3.7 nm and additional peaks that cannot be univocally ascribed to another lamellar arrangement.

The WAXS curve for **3a** (Figure S3, ESI) shows the presence of three peaks, suggesting a triclinic packing of the chains. The **3b** derivative (Figure S3, ESI) shows the same structure and other minor contributions. The selenide tetraesters **7a** and **7b** provide different patterns, in fact **7a** shows the presence of a single lamella with a spacing of 3.4 nm, while **7b** shows three reflection peaks of two distinct and coexistent lamellar phases (at 3.7 and 4.0 nm). This behaviour is present also in the WAXS profiles (see Figures S3 and S4, ESI) that suggests the presence of hexagonal arrangements for **7a** and **7b**. Additional peaks appear in the WAXS profile for **7b** indicating the presence of other forms.

FTIR. Figures S5 and S6 (see ESI) illustrate the FTIR spectra of **3a**, **3b**, **7a** and **7b** between 600 and 1000 cm^{-1} . The results are in line with the conclusions drawn from DSC and X-ray experiments. In fact, **3a** and **3b** show the presence of a single peak at 718 cm^{-1} confirming the triclinic structure. While in the spectra of **7a** and **7b** we observe a single peak at 721 cm^{-1} that agrees with an hexagonal arrangement.

Polarized optical microscopy. Figure 3 shows the preliminary micrographs taken on solid samples of **3a**, **3b**, **7a** and **7b** under crossed polarizers. The pictures suggest the presence of spherulites. Such structures may reflect the chiroptical properties of these compounds in the solid state. These are currently investigated and will be the object of a future dedicated paper.

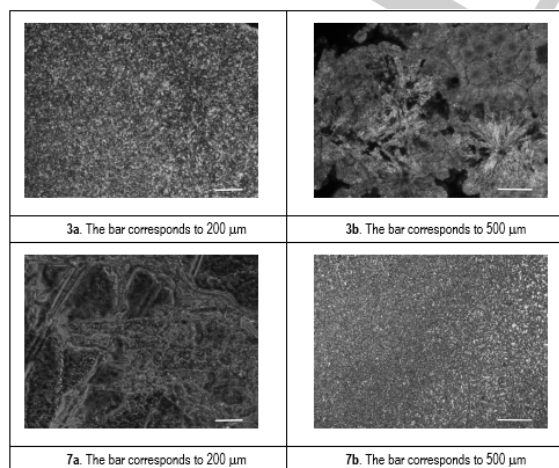


Figure 3. Polarized optical microscopy studies. Micrographs of compounds **3a**, **3b**, **7a**, **7b**.

Conclusions

In conclusion, we have developed a general and efficient procedure for the synthesis of simple and mixed acyl-thio, seleno-glycerol derivatives of different nature, containing saturated and unsaturated fatty acid chains, with different length, esterified to selenol and thiol groups at selected positions on carbons 2 and 3 of the glycerol. Furthermore, through a fine tuning of the reaction conditions and of the stoichiometric ratio of the reagents, a straightforward synthesis of polyfunctionalized selenides, bearing both ester and thiol ester groups was also achieved. The presence of S and/or Se instead of O in the polar heads of the lipids results in relatively small differences in the intermolecular interactions that involve the hydrophilic residues but that in turn significantly modify their physico-chemical properties respect to their fully oxygenated analogues. For their potential applications in the fields of pharmaceuticals and stereochemistry of bioactive molecules, these chalcogen-containing derivatives appear to be interesting candidates for the development of new chemical building blocks for self-assembled nanostructures. Further studies, based on birefringence, UV-vis spectroscopy and circular dichroism will be the subject of a future work.

Experimental Section

General. All reactions were carried out in an oven-dried glassware under inert atmosphere (N_2). Solvents were dried using a solvent purification system (Pure-Solv™). All commercial materials were purchased from various commercial sources and used as received, without further purification. Thiiranes **2a-c** were synthesized from the corresponding epoxides following a reported procedures.^[29] Bis(trimethyl)silyl selenide was prepared according the literature.^[30] Flash column chromatography purifications were performed with Silica gel 60 (230-400 mesh). Thin layer chromatography was performed with TLC plates Silica gel 60 F₂₅₄, which was visualised under UV light, or by staining with an ethanolic acid solution of *p*-anisaldehyde followed by heating. High resolution mass spectra (HRMS) were recorded by Electrospray Ionization (ESI).

^1H and ^{13}C NMR spectra were recorded in CDCl_3 using Varian Mercury 400, Bruker 400 Ultrashield, and Varian Gemini 200 spectrometers operating at 400 MHz and 200 MHz (for ^1H), 100 MHz and 50 MHz (for ^{13}C). ^{77}Se NMR spectra were recorded using a Bruker 400 Ultrashield spectrometer, operating at 76 MHz. NMR signals were referenced to nondeuterated residual solvent signals (7.26 ppm for ^1H , 77.0 ppm for ^{13}C). Diphenyl diselenide (PhSe)₂ was used as an external reference for ^{77}Se NMR ($\delta = 461$ ppm).

DSC experiments were performed on a Q2000 differential scanning calorimeter (TA Instruments) by using hermetic aluminium pans.

SAXS and WAXS measurements were performed with a HECUS S3-MICRO camera (Kratky-type) equipped with two position-sensitive detectors (OED 50m) containing 1024 channels of 54 mm in width.

FTIR experiments were performed by using a Nexus 970-FTIR spectrometer (Thermo-Nicolet) with a KBr beam splitter and MCT/A detector. All spectra were background corrected.

General procedure for the synthesis of fatty acid chalcogeno esters

3. A solution of thiirane **2a-c** (1.0 mmol) and bis(trimethylsilyl)selenide (HMDSS) (1.2 mmol) in dry THF (10 mL) was cooled under inert atmosphere at -15°C , and treated with TBAF (0.30 mL of 1M THF solution, 0.3 mmol). After stirring for 10 minutes at -15°C , the acyl chloride (2.5 mmol) was added drop-wise and the reaction mixture was warmed to room temperature and stirred for 1h. Afterwards, a second portion of TBAF (0.30 mL of 1M THF solution, 0.3 mmol) was added and the reaction was stirred for 1h. The mixture was quenched with a

saturated aq. NH_4Cl (5 mL) and diluted with H_2O (5 mL) and Et_2O (10 mL). The layers were separated and the organic layer was washed with brine (2×10 mL). The organic layer was dried over Na_2SO_4 , filtered, concentrated *in vacuo* and purified by column chromatography to afford compounds **3a-d**.

General procedure of selenides fatty acid tetraesters 7. TBAF (0.068 mL of 1M THF solution, 0.068 mmol) was added to a solution of thirane **2a-c** (0.5 mmol) and bis(trimethylsilyl)selenide (HMDSS) (0.27 mmol) in dry THF (5 mL) at 0°C under inert atmosphere. After stirring for 15 minutes at 0°C , the acyl chloride (1.2 mmol) was added drop-wise and the reaction mixture was warmed to room temperature and stirred for 1h. Afterwards, a second portion of TBAF (0.068 mL of 1M THF solution, 0.068 mmol) was added and the reaction was stirred for 1h. The mixture was quenched with a saturated aq. NH_4Cl (2 mL) and diluted with H_2O (2 mL) and Et_2O (5 mL). The layers were separated and the organic layer was washed with brine (5 mL). The organic layer was dried over Na_2SO_4 , filtered, concentrated *in vacuo* and purified by column chromatography to afford compounds **7a-c**.

Full experimental details, synthetic procedures, products characterization, DSC, SAXS, WAXS curves, FTIR spectra, and copy of NMR spectra of new products, are reported in the supplementary material.

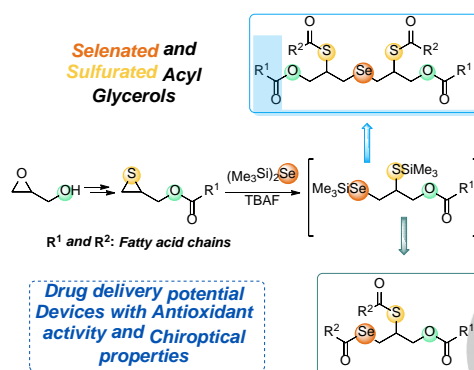
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Keywords: selenol esters • thiol esters • thiiranes • triglyceride(s) • thermal behaviour • polymorphism

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A direct and selective access to fatty acid chalcogeno ester glycidol derivatives through the fluoride-induced reaction of thiiranes with bis(trimethylsilyl)selenide and fatty acid chlorides has been developed. Sulfurated and selenated isomers of triglycerides and selenide fatty acid tetraesters have been obtained and their physicochemical properties have been investigated.



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**Novel Selenated and Sulfurated
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