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A Simple and Efficient Method for Direct Acylation of Acetals with Long Alkyl-Chain Carboxylic Acid Anhydrides

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Abstract—We have developed an efficient and simple method for direct transformation of acetals to carboxylic acid esters. The method consists of treatment of acetals with carboxylic anhydrides in the presence of boron trifluoride etherate as a catalyst and affords the corresponding ester derivatives in high yields with retention of configuration in the alcohol moiety. Some mechanistic aspects of this synthetically useful transformation are also discussed. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Due to its reactivity towards various electrophilic reagents, a hydroxyl function usually has to be protected in long preparative schemes. Although a vast array of protecting groups are available for this purpose,[1] acetals of various degrees of stability are still the most common derivatives that are used in protection–deprotection protocols in carbohydrate, nucleic acid, steroid, and lipid chemistry.[1–7]

Since acyl groups in polyhydroxylic systems have a tendency to undergo facile migration and cleavage,[8,9] acetals are often used as a transient protection that enables subsequent introduction of an ester functionality at the end of a synthesis. Due to this, deprotection conditions for acetals have to be carefully chosen to preserve the integrity of a molecular framework of synthesised products. The moderate to strong acidic conditions required for deprotection of acetals are known to provoke often undesirable molecular rearrangements, elimination processes or other side-reactions.[4–6,10–12] Consequently, the respective polyhydroxylic intermediates obtained after the removal of an acetal-protecting group have to be separated from the accompanying by-products. This is not always an easy task and adversely affects the total yield of the synthesis.

These problems are probably most acute in the synthesis of lipids and their conjugates as it is apparent from repeatedly reported complications in the synthesis of chiral mono-, di-, triacylglycerols, and various phospholipids, where extensive side-reactions (e.g. acyl and phosphoryl migration, formation of cyclic systems, racemization, etc) often occur after exposing the free hydroxyl groups of the glycerol backbone.[4–6,10,13–16] To overcome these difficulties, various attempts have been made to prepare the corresponding carboxylic esters via a one-pot acylolytic cleavage of acetals. For this purpose, the following reagent systems have been proposed: mixtures of acetic anhydride–sulphuric acid,[17] trifluoroacetic anhydride–acetic acid,[12] trifluoroacetic anhydride—a fatty acid (also in combination with $BF_3{\cdot}OEt_2$),[18] carboxylic acids–*p*-toluenesulfonic acid[19] and acid chlorides in conjunction with $ZnCl_2$.[19,20] All these methods, although useful in general context, suffer from various disadvantages, e.g. incompatibility with substrates containing acid-sensitive groups, low to moderate yields (35–68%) of the desired compounds, extended reaction time (1–3 days), and often harsh reaction conditions.[18–20] One should also note that in most instances these methods were evaluated only on racemic substrates with limited structural variations, and thus scope and stereochemical courses of the reactions involved remain obscure.

In this paper we describe an efficient method for stereoselective acylation of acetal-protected hydroxyl functions with long alkyl-chain carboxylic acid anhydrides, in which the replacement of the acetal moiety by the acyl function is mediated by catalytic amounts of $BF_3{\cdot}OEt_2$ to give the target esters in practically quantitative yields under mild reaction conditions.

Results and Discussion

The purpose of our studies was to investigate the reaction of

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acetals with carboxylic anhydrides mediated by $BF_3{\cdot}OEt_2$ for direct preparation of carboxylic acid esters without prior deprotection of the acetal functionality. From a large array of different types of acetals we chose those with different structural features and which are most interesting as substrates for designing lipophilic acyl bioconjugates based on glycerol and glycerophospholipids.[3–6,21–23] As typical representatives we selected three types of acetals: isopropylidene, benzylidene and tetrahydropyranyl derivatives. These included 2,2-dimethoxypropane (**1a**), benzaldehyde dimethylacetal (**1b**), 2-*O*-hexadecyl-1,3-benzylidene glycerol (**1c**), 1-*O*-hexadecyl-2,3-isopropylidene-*sn*-glycerol (**1d**), 1,2-isopropylidene-3-(2′,2′,2′-trichloroethoxy)-carbonyl-*sn*-glycerol (**1e**), 3-*O*-benzyl-1,2-isopropylidene-*sn*-glycerol (**1f**), 1,2-isopropylidene-*sn*-glycero-3-*O*-*p*-toluenesulfonate (**1g**), and cholesteryl-3-*O*-tetrahydro-2*H*-pyran (**1h**) (see Chart 1). The choice of oleic (**2a**), stearic (**2b**) and palmitic (**2c**) anhydrides as acylating agents in these studies was justified by the biological importance of these fatty acids and the synthetic interest they represent as lipid constituents with a different chain length and a different degree of unsaturation.

The reactions were investigated under various experimental conditions by changing solvents and varying amounts of the reactants and the catalyst ($BF_3{\cdot}OEt_2$). Progress of the acylation was monitored by TLC analysis and the products from optimised runs were isolated and their structure and purity were confirmed by ^1H and ^{13}C NMR spectroscopy (see the Experimental).

Best results were obtained when acetals (**1a–h**) were allowed to react with carboxylic anhydrides (**2a–c,** 1 equiv. *per* alcohol moiety) in the presence of boron trifluoride etherate (~0.2 equiv. *per* alcohol moiety) in aprotic solvents (e.g. CH_2Cl_2, $CHCl_3$) with moderate heating (~40–60°C). Under these conditions the expected ester derivatives **3a–k** were produced within 4–6 h in consistently excellent isolated yields (>90%).[24] When the reactions were carried out on enantiomerically pure substrates (e.g. glycerol derivatives **1d–g** and cholesteryl derivative **1h**), the optical rotation of the isolated products indicated that the transformation occurred with complete retention of configuration at the chiral centre in the corresponding alcohol moiety.

In these reactions the catalytic effect of $BF_3{\cdot}OEt_2$ is most likely due to Lewis acid properties of the catalyst, which exhibited a maximum activity when ca. 0.2 equiv. of $BF_3{\cdot}OEt_2$ *per* alcohol moiety were used. In the acylation of typical substrates **1c**, **1d** and **1h**, $BF_3{\cdot}OEt_2$ exerted only negligible catalytic effect when used in less than 0.1 equiv./alcohol moiety, as judged from the exceedingly slow formation of the acylated products **3** (>5 days at ~60°C). The rate

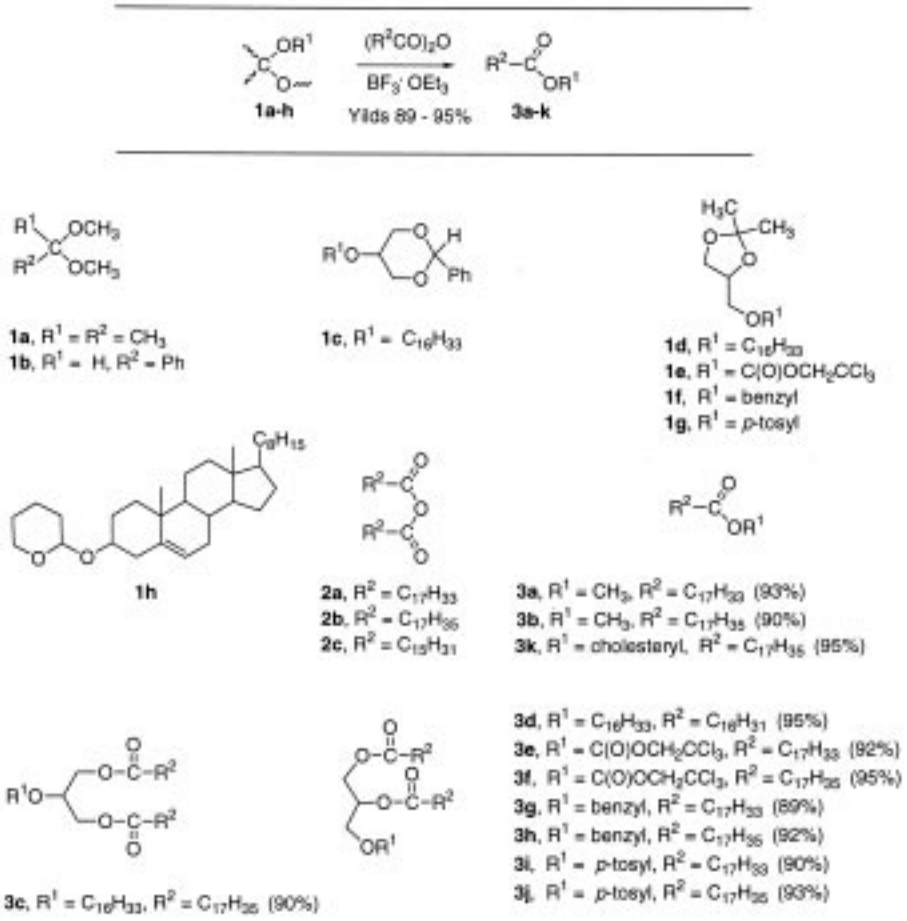
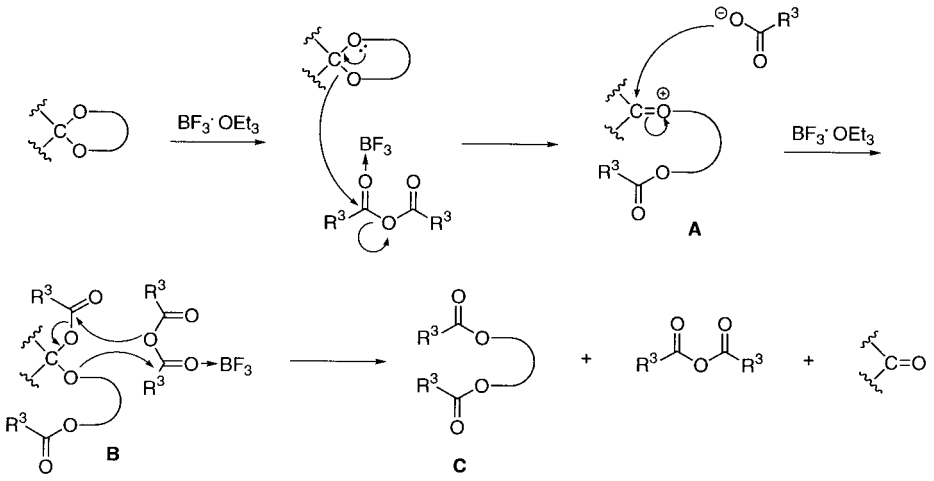


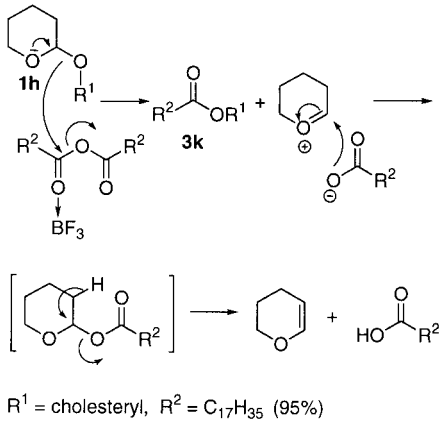
Chart 1.



Scheme 1.

of esterification was sharply increased in a very narrow range of the concentration of the catalyst (0.1–0.2 equiv.) and then showed a certain tendency to decreasing when the amount of $BF_3{\cdot}OEt_2$ exceeded 0.25 equiv. *per* alcohol moiety. This dependency on the concentration of boron trifluoride, is most likely due to involvement of the catalyst in complex equilibria systems resulting from its co-ordination to various nucleophilic centres in substrates, products and intermediates. It is worth noting, however, that acetals **1** (e.g. **1c**, **1d** and **1h**) and carboxylic anhydride **2a–c**, when treated separately in deuterated chloroform with equimolar amounts of $BF_3{\cdot}OEt_2$, remained completely unchanged within 24 h at rt, as judged from the ^1H- and ^{13}C NMR spectra of the corresponding reaction mixtures.

As to a possible mechanism for the replacement of an acetal group by an acyl group under the investigated reaction conditions, some additional observations are pertinent. Although acetals **1a–g** in the presence of $BF_3{\cdot}OEt_2$ required at least 1 equiv. of carboxylic anhydride **2** *per* alcohol moiety for the reaction to go to completion,[25] the TLC analysis and ^{13}C NMR spectra did not reveal any formation of the corresponding fatty acids, but instead, partially unreacted anhydrides **2** were still present at the end of the reaction (TLC and ^{13}C NMR analyses).[26] Only for the tetrahydropyranyl derivative **1h**, both TLC and ^{13}C NMR data clearly indicated the formation of free fatty acids during the course of the reaction.



Scheme 2.

In the acylation of glycerol derivatives **1c–g** with carboxylic anhydrides **2** we observed that the starting acetals disappeared within a few minutes upon addition of $BF_3{\cdot}OEt_2$ with little formation of the final products **3**. Instead, TLC analysis revealed formation of polar intermediates (one or two spots with R_f values ca 0.2–0.4; System B) that gradually underwent conversion to the corresponding final products **3**. Since the observed intermediates had chromatographic mobility identical to those of the reference mono-deacylated compounds derived from products of type **3** (structures not shown) we assumed that these were artefacts and arose via hydrolysis on TLC plates of some other reactive species initially present in the reaction mixtures.

The above findings permitted us to propose a tentative mechanism for a $BF_3{\cdot}OEt_2$-catalysed direct acylation of acetals with carboxylic anhydrides (Schemes 1 and 2).

According to the mechanism in Scheme 1, the reaction commences with a $BF_3{\cdot}OEt_2$-assisted transfer of the first acyl group to an alcohol moiety of an acetal. The cleavage of the latter and the formation of oxocarbenium ion (intermediate A) can occur simultaneously or may involve the Lewis acid-mediated generation of an acylium ion from the carboxylic anhydride followed by reaction with the acetal. This transformation is apparently fast and may explain the observed rapid disappearance of the starting material upon addition of $BF_3{\cdot}OEt_2$ to the reaction mixtures. The oxocarbenium ion may co-ordinate the carboxylate formed and collapses to intermediate B, which reaction with another molecule of the anhydride is apparently the rate determining step of the whole transformation.

For glycerol derivatives, transfer of the second acyl group could, in principle, occur as an intramolecular reaction of intermediate B, but this is probably not the case on two counts. First, an intramolecular acyl transfer would require a four-membered cyclic transition state and this, probably, is not kinetically favoured. Second, the reaction should be relatively insensitive to the concentration of the carboxylic

anhydride used and would require only 0.5 equiv. of **2** *per* alcohol moiety for the completion. Since these possibilities disagree with the experimental data, a more likely pathway for collapsing of intermediate B into product C probably is an intermolecular reaction of B with **2**, which ultimately regenerates equimolar amounts of the carboxylic anhydride. Since none of the reaction steps in Scheme 1 involve the C–O bond scission of an alcohol moiety, the proposed mechanism predicts retention of configuration in the alcohol unit.

A similar tentative mechanism, consistent with experimental data, can also be proposed for the conversion of tetrahydropyranylated derivative **1h** to the corresponding ester **3k** (Scheme 2).

In this instance, the transfer of an acyl group leads directly to product **3k** or may involve the initial generation of an acylium ion from the carboxylic anhydride mediated by $BF_3{\cdot}OEt_2$. The observed formation of free fatty acids during the course of this reaction can probably occur either by a direct abstraction of proton from the oxocarbenium ion or may involve an acylacetal as an intermediate.[27]

In summary, direct acylation of acetals **1** with carboxylic anhydrides **2** in the presence of $BF_3{\cdot}OEt_2$ represents a general protocol that secures synthesis of the corresponding carboxylic esters **3** in consistently high yields and with retention of configuration in the alcohol moiety. The main advantages of the method are: (i) high efficiency and mild reaction conditions, (ii) the method makes use of commercially available reactants and is easy to scale-up, (iii) it alleviates problems of deprotection of an acetal function prior to acylation, and thus minimises the possibility of occurrence of side reactions due to generation of free hydroxyl functions.

Experimental

1,2-Isopropylidene-3-(2′,2′,2′-trichloroethoxy)carbonyl-*sn*-glycerol, 1-*O*-hexadecyl-2,3-isopropylidene-*sn*-glycerol, 2-*O*-hexadecyl-1,3-benzylidene glycerol, and cholesteryl-3-*O*-tetrahydro-2*H*-pyran were synthesised according to published procedures.[28–32] The reference samples of acetals **3c**, **3d**, and **3i** were prepared via acylation of the corresponding glycerol derivatives (i.e. 2-*O*-hexadecyglycerol, 1-*O*-hexadecyl-*sn*-glycerol, and 3-*O*-*p*-toluenesulfonyl-*sn*-glycerol, respectively) with the corresponding fatty acids in the presence of dicyclohexylcarbodiimide,[33] and their melting points or specific rotation were identical to those of compounds synthesised via a direct acylation protocol (see below). All other reagents were commercial grade (Fluka, Lancaster, Merck, Sigma) with purity >98% and were used as provided without further purification. Solvents were dried and distilled prior to use according to standard protocols.[34]

Column chromatography (CC) was carried out on silica gel 60 (70–230 mesh ASTM, Merck) using the following mobile phases: System A, *n*-hexane–ethyl acetate (95:5, v/v); System B, *n*-hexane–ethyl acetate (90:10, v/v); System C, *n*-hexane–toluene–ethyl acetate (70:20:10, v/v/v); System D, *n*-hexane–CH_2Cl_2 (80:20, v/v). Progress of the reactions was monitored by analytical thin-layer chromatography (TLC) on pre-coated glass plates of silica gel 60 F_{254} (Merck) using the same solvent systems as for CC. The spots were visualised using the commercially available 3.5% molybdatophosphoric acid spray reagent (Merck) or 50% sulphuric followed by heating at 140°C.

^1H and ^{13}C NMR spectra were recorded on a Varian 400 MHz machine and chemical shifts are reported in ppm relative to TMS. The assignment of proton and carbon resonances of **3a**–**k** was done on the basis of known or expected chemical shifts in conjunction with ^1H–^1H, ^1H–^{13}C, and DEPT correlated NMR spectroscopy. Infrared (IR) spectra were recorded on a Perkin–Elmer FT-IR 1750 spectrometer and positions of the absorption bands are reported in cm^{-1}. Optical rotations were measured on a Perkin–Elmer 241 digital polarimeter. The melting points were determined on a Kofler melting point apparatus and are uncorrected.

General procedure for direct acylation of acetals 1

To a solution of acetal **1** (0.20 mmol) and carboxylic acid anhydride **2** (0.50 mmol) in alcohol-free chloroform (10 mL), was added boron trifluoride etherate (0.014 g; 0.10 mmol) and the reaction mixture was refluxed (~61°C) with stirring under nitrogen for 4 h. After cooling to room temperature, triethylamine (0.101 g, 1.00 mmol) was added and the mixture was stirred for 30 min. To remove $BF_3{\cdot}OEt_2$, the reaction mixture was passed through an aluminium oxide pad (15 g; weakly acidic, type 506 C from Fluka) and the support was washed with ethyl acetate (3×50 mL). Fractions containing crude product **3** were combined, the solvents removed under reduced pressure, and the residue was chromatographed on a silica gel column using solvent systems A–D.

Methyl oleate 3a. Obtained from benzaldehyde dimethylacetal (**1b**; 0.030 g; 0.20 mmol), oleic anhydride (**2a**; 0.273 g; 0.50 mmol) and boron trifluoride etherate (0.014 g; 0.10 mmol). CC system A. Yield:0.109 g (93%, colourless oil); R_f (system B)=0.60. Anal. Calcd for $C_{19}H_{36}O_2$ (296.50): C, 76.96; H, 12.26. Found: C, 76.74; H, 12.38. ^1H NMR δ_H (in ppm, $CDCl_3$) 0.88 (t, J=6.7 Hz, CH_3, 3H); 1.24–1.38 (m, $(CH_2)_4$; $(CH_2)_6$; 20H); 1.56–1.66 (m, CH_2CH_2CO, 2H); 1.94–2.06 (m, CH_2CH=, 4H); 2.30 (t, J=7.3 Hz, CH_2CO, 2H); 5.30–5.39 (m, CH=, 2H): oleoyl fragment; 3.66 (m, CH_3, 3H): methyl fragment. ^{13}C NMR δ_C (in ppm, $CDCl_3$) 14.50 (18-CH_3); 23.06 (C-17); 25.33 (C-3); 27.53, 27.59 (C-11, C-8); 29.46–30.14 (C-4–C-7, C-12–C-15); 32.27 (C-16); 34.45 (C-2); 129.86, 130.11 (C-9, C-10) 174.27 (C-1): oleoyl fragment; 51.71 (CH_3): methyl fragment. IR (film) ν 3004 (CH=); 1745 (C=O); 1171 cm^{-1} (C–O–C).

Methyl stearate 3b. Obtained from 2,2-dimethoxypropane (**1a**; 0.021 g; 0.20 mmol), stearic anhydride (**2b**; 0.275 g; 0.50 mmol) and boron trifluoride etherate (0.014 g; 0.10 mmol). CC system D. Yield: 0.108 g (90%, white crystals); mp=46.7–48.3°C (from system D, identical to that of a commercial sample from Fluka); R_f (system B)=0.61. Anal. Calcd for $C_{19}H_{38}O_2$ (298.51): C, 76.45; H, 12.83.

Found: C, 76.53; H, 12.80. ^{1}H NMR δ_H (in ppm, $CDCl_3$) 0.87 (t, J=6.6 Hz, CH_3, 3H); 1.22–1.34 (m, $(CH_2)_{14}$; 28H); 1.56–1.66 (m, CH_2CH_2CO, 2H); 2.30 (t, J=7.7 Hz, CH_2CO, 2H): stearoyl fragment; 3.66 (m, CH_3, 3H): methyl fragment. ^{13}C NMR δ_C (in ppm, $CDCl_3$) 14.51 (18-CH_3); 23.07 (C-17); 25.35 (C-3); 29.53–30.06 (C-4–C-15); 32.29 (C-16); 34.48 (C-2); 174.33 (C-1): stearoyl fragment; 51.71 (CH_3): methyl fragment. IR (KBr) ν 1742 (C=O); 1177 cm^{-1} (C–O–C).

2-*O*-Hexadecyl-1,3-distearoyl glycerol 3c. Obtained from 2-*O*-hexadecyl-1,3-benzylidene glycerol (**1c**; 0.081 g; 0.20 mmol), stearic anhydride (**2b**; 0.275 g; 0.50 mmol) and boron trifluoride etherate (0.014 g; 0.10 mmol). CC system C. Yield: 0.153 g (90%, white crystals); mp=54.5–56.3°C (from system C); R_f (system B)=0.71. Anal. Calcd for $C_{55}H_{108}O_5$ (849.63): C, 77.75; H, 12.84. Found: C, 77.85; H, 12.77. ^{1}H NMR δ_H (in ppm, $CDCl_3$) 0.87 (t, J=6.6 Hz, CH_3, 9H); 1.22–1.34 (m, $(CH_2)_{14}$; $(CH_2)_{13}$, 82H); 1.51–1.67 (m, CH_2CH_2CO, CH_2CH_2O, 6H); 2.32 (t, J=7.7 Hz, CH_2CO, 4H); 3.54 (t, J=6.2 Hz, $CH_2OCH_2(CH_2)_{14}$, 2H); 3.67 (p, J=5.5 Hz, $CHO(CH_2)_{15}$, 1H); 4.11, 4.18 (dd, J=5.9, 5.5 Hz, J=4.8, 4.8 Hz, CH_2CHCH_2, 4H). ^{13}C NMR δ_C (in ppm, $CDCl_3$) 14.53 (18-CH_3); 23.09 (C-17); 25.32 (C-3); 29.54–30.06 (C-4–C-15); 32.31 (C-16); 34.57 (C-2); 173.6 (C-1): stearoyl fragment; 14.53 (16-CH_3); 23.09–30.30 (C-3–C-15); 32.31 (C-2); 70.96 (C-1): hexadecyl fragment; 63.36 (C-1, C-3); 75.45 (C-2): glycerol fragment. IR (KBr) ν 1743 (C=O); 1179 (C–O–C); 1118 cm^{-1} (C–O–C_{ether}).

1-*O*-Hexadecyl-2, 3-dipalmitoyl-*sn*-glycerol 3d. Obtained from 1-*O*-hexadecyl-2,3-isopropylidene-*sn*-glycerol (**1d**; 0.071 g; 0.20 mmol), palmitic anhydride (**2c**; 0.247 g; 0.50 mmol) and boron trifluoride etherate (0.014 g; 0.10 mmol). CC system C. Yield: 0.150 g (95%, white crystals); mp=47.9–48.0°C (from system C); R_f (system B)=0.73; $[\alpha]_D^{20}$=−4.2 (c, 2.02, $CHCl_3$). Anal. Calcd for $C_{51}H_{100}O_5$ (793.51): C, 77.19; H, 12.73; Found: C, 77.01; H, 12.80. ^{1}H NMR δ_H (in ppm, $CDCl_3$) (t, J=6.6 Hz, CH_3, 9H); 1.22–1.34 (m, $(CH_2)_{12}$; $(CH_2)_{13}$, 74H); 1.50–1.66 (m, CH_2CH_2CO, CH_2CH_2O, 6H); 2.30 (q, J=7.3 Hz, CH_2CO, 4H); 3.42 (m, $CH_2OCH_2(CH_2)_{14}$, 2H); 3.53 (m, $CH_2CHCH_2OCH_2(CH_2)_{14}$, 2H); 4.15, 4.33 (dd, J=6.6, 6.2 Hz, J=3.7, 3.7 Hz, CH_2CHCH_2, 1H, 1H). 5.19 (m, CH_2CHCH_2, 1H). ^{13}C NMR δ_C (in ppm, $CDCl_3$) 14.54 (16-CH_3); 23.09 (C-15); 25.31, 25.38 (C-3, both acyl chains); 29.54–30.09 (C-4–C-13); 32.31 (C-14); 34.53, 34.73 (C-2, both acyl chains); 173.2, 173.5 (C-1, both acyl chains): palmitoyl fragment; 14.54 (16-CH_3); 23.09–30.09 (C-3–C-15); 32.31 (C-2); 69.23 (C-1): hexadecyl fragment; 63.08, 72.03 (C-1, C-3); 70.35 (C-2): glycerol fragment. IR (KBr) ν 1732 (C=O); 1184 (C–O–C); 1105 cm^{-1} (C–O–C_{ether}).

1,2-Dioleoyl-*sn*-glycero-3-*O*-2′,2′,2′-trichloroethylcarbonate 3e. Obtained from 1,2-isopropylidene-*sn*-glycero-3-*O*-2′,2′,2′-trichloroethyl–carbonate (**1e**; 0.062 g; 0.20 mmol), oleic anhydride (**2a**; 0.273 g; 0.50 mmol), and boron trifluoride etherate (0.014 g; 0.10 mmol) in CH_2Cl_2. Stirred and refluxed (~40°C) for 6 h under nitrogen. CC system B. Yield: 0.148 g (92%, colourless oil); R_f (system B)=0.66; $[\alpha]_D^{20}$=−1.42 (c, 1.54, $CHCl_3$); Lit. [35]: $[\alpha]_D^{25}$=−1.40 (c, 0.88, $CHCl_3$). Anal. Calcd for $C_{42}H_{73}O_7Cl_3$ (796.50): C, 63.33; H, 9.26; Found: C, 63.50; H, 9.20. ^{1}H NMR δ_H (in ppm, $CDCl_3$) 0.88 (t, J=6.6 Hz, CH_3, 6H); 1.22–1.38 (m, $(CH_2)_4$; $(CH_2)_6$; 40H); 1.56–1.66 (m, CH_2CH_2CO, 4H); 1.94–2.06 (m, CH_2CH=, 8H); 2.31 (sxt, J=3.3 Hz, CH_2CO, 4H); 4.18 (dd, J=5.9, 5.5 Hz, $CH_2CHCH_aH_bO$-C(O)O, 1H); 4.34 (m, $CH_2CHCH_2OC(O)O$, 2H); 4.44 (dd, J=4.0, 4.0 Hz, $CH_2CHCH_aH_bOC(O)O$, 1H); 4.77 (m, CH_2CCl_3, 2H); 5.27–5.39 (m, CH=, CH_2CHCH_2, 5H). ^{13}C NMR δ_C (in ppm, $CDCl_3$) 14.53 (18-CH_3); 23.08 (C-17); 25.20, 25.22 (C-3, both acyl chains); 27.56, 27.61 (C-11, C-8); 29.40–30.14 (C-4–C-7, C-12–C-15); 32.27 (C-16); 34.36, 34.48 (C-2, both acyl chains); 129.83, 130.16 (C-9, C-10) 172.83, 173.19 (C-1, both acyl chains): oleoyl fragment; 62.00, 66.98 (C-1, C-3); 68.76 (C-2): glycerol fragment; 77.25 (C-2): 2′,2′,2′-trichloroethylcarbonyl fragment. IR (film) ν 3005 (CH=); 1747 (C=O, O(O)C=O); 1164 (C–O–C); 727 cm^{-1} (C–Cl).

1,2-Distearoyl-*sn*-glycero-3-*O*-2′,2′,2′-trichloroethylcarbonate 3f. Obtained from 1,2-isopropylidene-*sn*-glycero-3-*O*-2′,2′,2′-trichloroethylcarbonate (**1e**; 0.062 g; 0.20 mmol), stearic anhydride (**2b**; 0.275 g; 0.50 mmol) and boron trifluoride etherate (0.014 g; 0.10 mmol) in CH_2Cl_2. Stirred and refluxed (~40°C) for 6 h under nitrogen. CC system B. Yield: 0.152 g (95%, white crystals); mp=55.2–56.4°C (from system C); Lit. [36]: mp=54–55°C; R_f (system B)=0.70; $[\alpha]_D^{20}$=−1.69 (c, 2.20, $CHCl_3$); Lit.[35]: $[\alpha]_D^{25}$=−1.70 (c, 1.050, $CHCl_3$). Anal. Calcd for $C_{42}H_{77}O_7Cl_3$ (800.54): C, 63.01; H, 9.71; Found: C, 63.07; H, 9.63. ^{1}H NMR δ_H (in ppm, $CDCl_3$) 0.88 (t, J=6.6 Hz, CH_3, 6H); 1.22–1.32 (m, $(CH_2)_{14}$; 56H); 1.56–1.66 (m, CH_2CH_2CO, 4H); 2.32 (sxt, J=3.3 Hz, CH_2CO, 4H); 4.18 (dd, J=5.5, 5.9 Hz, $CH_2CHCH_aH_bOC(O)O$, 1H); 4.35 (m, $CH_2CHCH_2OC(O)O$, 2H); 4.44 (dd, J=4.0, 4.0 Hz, $CH_2CHCH_aH_bOC(O)O$, 1H); 4.77 (m, CH_2CCl_3, 2H); 5.30 (m, CH_2CHCH_2, 1H). ^{13}C NMR δ_C (in ppm, $CDCl_3$) 14.54 (18-CH_3); 23.09 (C-17); 25.22, 25.24 (C-3, both acyl chains); 29.45–30.08 (C-4–C-15); 32.31 (C-16); 34.40, 34.51 (C-2, both acyl chains); 172.9, 173.2 (C-1, both acyl chains): stearoyl fragment; 62.01, 66.98 (C-1, C-3); 68.75 (C-2): glycerol fragment; 77.25 (C-2): 2′,2′,2′-trichloro–ethylcarbonyl fragment. IR (KBr) ν 1770 (O(O)C=O) 1732 (C=O); 1156 (C–O–C); 728 cm^{-1} (C–Cl).

3-*O*-Benzyl-1,2-dioleoyl-*sn*-glycerol 3g. Obtained from 3-*O*-benzyl-1,2-isopropy-lidene-*sn*-glycerol (**1f**; 0.044 g; 0.20 mmol), oleic anhydride (**2a**; 0.273 g; 0.50 mmol) and boron trifluoride etherate (0.014 g; 0.10 mmol). CC system B. Yield: 0.126 g (89%, colourless oil); R_f (system B)=0.65; $[\alpha]_D^{20}$=+5.94 (c, 2.02, $CHCl_3$); Lit.[37]: $[\alpha]_D$=+6.20 (c, 10.0, $CHCl_3$). Anal. Calcd for $C_{46}H_{78}O_5$ (711.24): C, 77.68; H, 11.08; Found: C, 77.75; H, 11.15. ^{1}H NMR δ_H (in ppm, $CDCl_3$) 0.86 (t, J=6.6 Hz, CH_3, 6H); 1.20–1.38 (m, $(CH_2)_4$; $(CH_2)_6$; 40H); 1.57–1.66 (m, CH_2CH_2CO, 4H); 1.96–2.05 (m, CH_2CH=, 8H); 2.30 (m, CH_2CO, 4H); 3.58 (d, J=5.1 Hz, $CH_2CHCH_2OCH_2C_6H_5$, 2H); 4.18 (dd, J=6.4, 6.4 Hz, $CH_2CHCH_aH_bOCH_2C_6H_5$, 1H); 4.34 (dd, J=3.7, 3.7 Hz, $CH_2CHCH_aH_bOCH_2C_6H_5$, 1H); 4.54 (m, $CH_2C_6H_5$, 2H); 5.24 (m, CH_2CHCH_2, 1H); 5.34 (m, CH=, 4H); 7.31 (m, $CH_2C_6H_5$, 5H). ^{13}C NMR δ_C (in ppm, $CDCl_3$) 14.58 (18-CH_3); 23.12 (C-17); 25.27, 25.35

(C-3, both acyl chains); 27.58, 27.62 (C-11, C-8); 29.47–30.17 (C-4–C-7, C-12–C-15); 32.31 (C-16); 34.47, 34.69 (C-2, both acyl chains); 129.9, 130.2 (C-9, C-10) 173.17, 173.5 (C-1, both acyl chains): oleoyl fragment; 62.96, 68.51 (C-1, C-3); 70.27 (C-2): glycerol fragment; 73.58 (C-7); 127.8, 127.9, 128.6 (C-2–C-6); 137.8 (C-1): benzyl fragment. IR (film) ν 3004 (CH═); 1742 (C═O); 1497 (C═C_{aryl}); 1168 (C–O–C); 1115 cm^{-1} (C–O–C_{ether}).

3-*O*-Benzyl-1,2-distearoyl-*sn*-glycerol 3h. Obtained from 3-*O*-benzyl-1,2-isopropylidene-*sn*-glycerol (**1f**; 0.044 g; 0.20 mmol), stearic anhydride (**2b**; 0.275 g; 0.50 mmol) and boron trifluoride etherate (0.014 g; 0.10 mmol). CC system C. Yield: 0.130 g (92%, white crystals); mp=50.2–50.6°C (from system C); Lit.[38]: mp=50.5–51.0°C; R_f (system B)=0.68; $[\alpha]_D^{20}$=+5.80 (*c*, 1.50, $CHCl_3$); Lit.[38] $[\alpha]_D$=+6.10 (*c*, 7.48, $CHCl_3$). Anal. Calcd for $C_{46}H_{82}O_5$ (715.28): C, 77.24; H, 11.58; Found: C, 77.05; H, 11.62. ^{1}H NMR δ_H (in ppm, $CDCl_3$) 0.88 (t, *J*=6.6 Hz, CH_3, 6H); 1.20–1.36 (m, $(CH_2)_{14}$; 56H); 1.54–1.68 (m, C$H_2$$CH_2$CO, 4H); 2.30 (m, CH_2CO, 4H); 3.58 (d, *J*=5.1 Hz, CH_2CHCH_2OC$H_2$$C_6H_5$, 2H); 4.18 (dd, *J*=6.2, 6.6 Hz, CH_2CHC$H_a$$H_bOCH_2$$C_6H_5$, 1H); 4.34 (dd, *J*=3.7, 4.0 Hz, CH_2CHC$H_a$$H_bOCH_2$$C_6H_5$, 1H); 4.54 (m, C$H_2$$C_6H_5$, 2H); 5.24 (m, CH_2C$H$$CH_2$, 1H); 7.31 (m, $CH_2$$C_6H_5$, 5H). ^{13}C NMR δ_C (in ppm, $CDCl_3$) 14.52 (18-CH_3); 23.09 (C-17); 25.28, 25.36 (C-3, both acyl chains); 29.48–30.08 (C-4–C-15); 32.31 (C-16); 34.50, 34.71 (C-2, both acyl chains); 173.12, 173.42 (C-1, both acyl chains): stearoyl fragment; 62.96, 68.57 (C-1, C-3); 70.30 (C-2): glycerol fragment; 73.59 (C-7); 127.8, 127.9, 128.6 (C-2–C-6); 137.9 (C-1): benzyl fragment. IR (KBr) ν 1734 (C═O); 1473 (C═C_{aryl}); 1178 (C–O–C); 1112 cm^{-1} (C–O–C_{ether}).

1,2-Dioleoyl-*sn*-glycero-3-*O*-*p*-toluenesulfonate 3i. Obtained from 1,2-isopropylidene-*sn*-glycero-3-*O*-*p*-toluenesulfonate (**1g**; 0.057 g; 0.20 mmol), oleic anhydride (**2a**; 0.273 g; 0.50 mmol) and boron trifluoride etherate (0.014 g; 0.10 mmol) in CH_2Cl_2. Stirred and refluxed (~40°C) for 5 h under nitrogen. Yield: 0.139 g (90%, colourless oil); R_f (system B)=0.53; $[\alpha]_D^{20}$=+5.20 (*c*, 0.635, $CHCl_3$–CH_3OH, 1:1). Anal. Calcd for $C_{46}H_{78}O_7S$ (775.30): C, 71.26; H, 10.16; S, 4.13. Found: C, 71.35; H, 10.10; S, 4.21. ^{1}H NMR δ_H (in ppm, $CDCl_3$) 0.87 (t, *J*=7.0 Hz, CH_3, 6H); 1.20–1.37 (m, $(CH_2)_4$; $(CH_2)_6$; 40H); 1.57 (m, C$H_2$$CH_2$CO, 4H); 2.0 (m, C$H_2$CH═, 8H); 2.30 (m, CH_2CO, 4H); 2.45 (s, C$H_3$$C_6H_4$, 3H); 4.08–4.20 (m, CH_2CHC$H_a$$H_b$OS(O)$_2$$C_6H_4CH_3$, C$H_2CHCH_2$OS(O)$_2$$C_6H_4CH_3$, 3H); 4.24 (dd, *J*=4.8, 4.8 Hz, CH_2CHC$H_a$$H_b$OS(O)$_2$$C_6H_4CH_3$, 1H); 5.15 (p, *J*=4.8 Hz, CH_2C$H$$CH_2$, 1H); 5.34 (m, CH═, 4H); 7.34–7.80 (dd, *J*=8.1, 8.4 Hz, $CH_3C_6H_4$, 4H). ^{13}C NMR δ_C (in ppm, $CDCl_3$) 14.53 (18-CH_3); 23.07 (C-17); 25.12, 25.17 (C-3, both acyl chains); 27.56, 27.61 (C-11, C-8); 29.41–30.14 (C-4–C-7, C-12–C-15); 32.27 (C-16); 34.29, 34.37 (C-2, both acyl chains); 130.07, 130.17 (C-9, C-10) 172.68, 173.07 (C-1, both acyl chains): oleoyl fragment; 61.67, 67.57 (C-1, C-3); 68.57 (C-2): glycerol fragment; 22.06 (7-CH_3); 128.1, 129.8 (C-2, C-3, C-5, C-6); 132.8 (C-1); 145.2 (C-4): tosyl fragment. IR (film) ν 3004 (CH═); 1747 (C═O);.1599 (C═C_{aryl}); 1373, 1191, 1179 cm^{-1} (SO_2).

1,2-Distearoyl-*sn*-glycero-3-*O*-*p*-toluenesulfonate 3j. Obtained from 1,2-isopropylidene-*sn*-glycero-3-*O*-*p*-toluenesulfonate (**1g**; 0.057 g; 0.20 mmol), stearic anhydride (**2b**; 0.275 g; 0.50 mmol) and boron trifluoride etherate (0.014 g; 0.10 mmol). CC system C. Yield: 0.144 g (93%, white crystals); mp=73.5–74.6°C (from system C); Lit.[14]: mp=73.0–75.0°C; R_f (system B)=0.60; $[\alpha]_D^{20}$=+5.18 (*c*, 0.675, $CHCl_3$–CH_3OH, 1:1); Lit.[14]: $[\alpha]_D^{25}$=+5.50 (*c*, 0.545, $CHCl_3$–CH_3OH, 1:1). Anal. Calcd for $C_{46}H_{82}O_7S$ (779.34): C, 70.89; H, 10.63; S, 4.11. Found: C, 70.71; H, 10.69; S, 4.09. ^{1}H NMR δ_H (in ppm, $CDCl_3$) 0.88 (t, *J*=7.0 Hz, CH_3, 6H); 1.20–1.34 (m, $(CH_2)_{14}$; 56H); 1.54 (m, C$H_2$$CH_2$CO, 4H); 2.25 (m, CH_2CO, 4H); 2.45 (s, C$H_3$$C_6H_4$, 3H); 4.08–4.20 (m, CH_2CHC$H_a$$H_b$OS(O)$_2$$C_6H_4CH_3$, C$H_2CHCH_2$OS(O)$_2$$C_6H_4CH_3$, 3H); 4.24 (dd, *J*=4.4, 4.8 Hz, CH_2CHC$H_a$$H_b$OS(O)$_2$$C_6H_4CH_3$, 1H); 5.16 (p, *J*=4.8 Hz, CH_2C$H$$CH_2$, 1H); 7.34–7.80 (dd, *J*=8.1, 8.4 Hz, $CH_3C_6H_4$, 4H). ^{13}C NMR δ_C (in ppm, $CDCl_3$) 14.54 (18-CH_3); 23.09 (C-17); 25.14, 25.19 (C-3, both acyl chains); 29.44–30.09 (C-4–C-15); 32.31 (C-16); 34.32, 34.40 (C-2, both acyl chains); 172.71, 173.10 (C-1, both acyl chains): stearoyl fragment; 61.67, 67.58 (C-1, C-3); 68.56 (C-2): glycerol fragment; 22.07 (7-CH_3); 128.13, 130.07 (C-2, C-3, C-5, C-6); 132.76 (C-1); 145.21 (C-4): tosyl fragment. IR (KBr) ν 1738 (C═O);.1598 (C═C_{aryl}); 1368, 1192, 1174 cm^{-1} (SO_2).

Cholesteryl stearate 3k. Obtained from cholesteryl-3-*O*-tetrahydro-2*H*-pyran (**1h**; 0.094 g; 0.20 mmol), stearic anhydride (**2b**; 0.138 g; 0.25 mmol) and boron trifluoride etherate (0.007 g; 0.05 mmol). CC system D. Yield of **3k**: 0.124 g (95%, white crystals); mp=80.2–81.3°C (from system D); R_f (system D)=0.40; $[\alpha]_D^{20}$=−23.6 (*c*, 3.41, $CHCl_3$) (the same as of a commercially available sample from Fluka). Anal. Calcd for $C_{45}H_{80}O_2$ (653.25): C, 82.73; H, 12.37. Found: C, 82.89; H, 12.28. ^{1}H NMR δ_H (in ppm, $CDCl_3$) 0.68 (s, 18-CH_3, 3H); 4.61 (m, C-3, 1H); 5.37 (m, C-6, 1H): cholesteryl fragment; 0.87 (CH_3); 1.25 ($(CH_2)_{14}$); 2.30 (CH_2CO): stearoyl fragment (overlapping with signals from cholesteryl fragment). ^{13}C NMR δ_C (in ppm, $CDCl_3$) 12.28 (18-CH_3); 19.12 (C-21); 19.73 (C-19); 21.43 (C-11); 22.96 (C-26); 23.22 (C-27); 73.94 (C-3); 122.72 (C-6); 139.84 (C-5): cholesteryl fragment; 14.54 (18-CH_3); 23.09 (C-17); 25.47 (C-3); 29.50–30.09 (C-4–C-15); 32.28 (C-16); 35.10 (C-2); 173.4 (C-1): stearoyl fragment IR (KBr) ν 1741 (C═O); 1178 cm^{-1} (C–O–C).

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24. The reactions can also be effected at room temperature but this usually requires extended reaction time (overnight or longer).
25. When anhydrides **2** were used in a lower proportion, part of the starting material remained either unreacted or underwent some decomposition, regardless of the amount of boron trifluoride etherate (up to 0.50 equiv./alcohol moiety) present in the reaction mixture.
26. The carbonyl and the adjacent methylene carbons in free fatty acids, the corresponding carboxylic anhydrides, and in fatty acid esters, have distinctive chemical shifts permitting their assignment to the appropriate species. For example, for ester **3c**, anhydride **2b**, and for stearic acid, these chemical shifts in $CDCl_3$ are: 173.8 and 34.8 ppm; 169.6 and 35.7 ppm; 180.1 and 34.3 ppm; respectively.
27. One can also envisage a one-step synchronous mechanism for this reaction.
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