Regioselective and stereospecific acylation across oxirane- and silyloxy systems as a novel strategy to the synthesis of enantiomerically pure mono-, di- and triglycerides†

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A trifluoroacetate-catalyzed opening of the oxirane ring of glycidyl derivatives bearing allylic acyl or alkyl functionalities with trifluoroacetic anhydride (TFAA), provides an efficient entry to configurationally homogeneous 1(3)-acyl- or 1(3)-*O*-alkyl-*sn*-glycerols. Selective introduction of *tert*-butyldimethylsilyl- (TBDMS), or triisopropylsilyl- (TIPS) transient protections at the terminal sites within these key intermediates secures 1(3)-acyl- or 1(3)-*O*-alkyl-3(1)-*O*-TBDMS (or TIPS)-*sn*-glycerols as general bifunctional precursors to 1,2(2,3)-diacyl-, 1(3)-*O*-alkyl-2-acyl- and 1,3-diacyl-*sn*-glycerols and hence triester isosters. Incorporation of a requisite acyl residue at the central carbon of the silylated synthons with a subsequent $Et_3N{\cdot}3HF$-promoted, direct trichloroacetylation across the siloxy system by trichloroacetic anhydride (TCAA), followed by cleavage of the trichloroacetyl group, affords the respective 1,2(2,3)-diacyl- or 1(3)-*O*-alkyl-2-acyl-*sn*-glycerols. Alternatively, a reaction sequence involving: (i) attachment of a trichloroacetyl fragment at the stereogenic C2-centre of the monosilylated glycerides; (ii) replacement of the silyl moiety by a short- or long-chain carboxylic acid residue by means of the acylating agent: tetra-*n*-butylammonium bromide (TBABr)–carboxylic acid anhydride (CAA)–trimethylsilyl bromide (TMSBr); and (iii) removal of the trichloroacetyl replacement, provides pure 1,3-diacyl-*sn*-glycerols. The TBABr–CAA–TMSBr reagent system allows also a one-step conversion of 1,2-diacylglycerol silyl ethers into homochiral triglycerides with predefined asymmetry and degree of unsaturation. These compounds can also be accessed *via* a two-step one-pot approach where the trichloroacetyl derivatives of 1,2(2,3)- or 1,3-diacyl-*sn*-glycerols serve as triester building blocks for establishing the third ester bond at preselected C3(1)- or C2-positions within the glycerol skeleton at the very last synthetic stage. In all instances, the target compounds were produced under mild conditions, in high enantiomeric purity, and in practically quantitative yields.

1 Introduction

1-Acyl- or 1-*O*-alkyl-,[1] 1,2-diacyl- or 1-*O*-alkyl-2-acyl-,[2,3] 1,3-diacyl-*sn*-glycerols,[4,5] and their triester isosters[6,7] are capable of exerting various host protective and physiopathological effects (*e.g.* antitumour activity, cell-growth inhibition, modulation of signal transduction pathways, activation of protein kinase C, modification of cell membrane properties, *etc.*) on biological systems. Due to this, the aforementioned lipid mediators emerged as synthetic targets of importance in enzymology,[8] nucleic acid-,[9] carbohydrate-,[10] lipid-,[11–14] supramolecular-,[15] and medicinal chemistry,[16] clinical diagnostics,[17–19] and became lead structures in rational drug[20,21] and antioxidant[22] design.

Although attractive as starting materials for numerous chemical and biological applications (*e.g.* development of carrier molecules for therapeutics and gene delivery,[23] or liposomes allowing a triggered release of bioactive agents[24]), access to these classes of natural products is considerably limited as stereospecific introduction of an acyl fragment into the glycerol skeleton has repeatedly been shown to be a complicated task in respect of generation of a defined stereocentre at the incipient glycerol C2-location, and the required chemo- and regioselectivity.[12]

In this context, various three-carbon synthons from either the traditional pool of glycerol/D-mannitol acetals[14,25,26] or glycidol derivatives[27] have been proposed as enantiomerically pure precursors to glycerolipids.[12,28] However, selective incorporation of two different carboxylic acid residues at the primary *vs.* secondary glycerol positions by means of known protocols, requires extensive use of transient protections that must be removable under reaction conditions that do not provoke acyl chain scrambling after exposure of a vicinal hydroxyl group and, in the case of unsaturated fatty acids, should also be compatible with the presence of double bonds.[12,29,30] Failure to meet these requirements adversely affects the total outcome of glyceride synthesis as the phenomenon of acyltropy (acid, base and heat promoted migration of an acyl moiety[31–35]) may result in loss of chirality and formation of positional isomers, while the occurrence of oxidation, hydrogenation, halogenation, *etc.*, of the olefinic systems, introduces harmful structural alterations, affecting the biological activity of the glycerides.[12,36]

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Unfortunately, not only the chemistry employed during protection–deprotection manipulations,[12,26,37,38] but also purification techniques, have frequently been reported to contribute to isomerisation, hydrolysis, oxidation, and other side-reactions within the glycerolipid skeleton.[12,31,33] This poses severe limitations for isolation and storage of glycerolipids, and their utility as structurally defined synthetic intermediates[12,32,34,35,39] or therapeutic agents *per se* for biochemical and medicinal intervention.[3,5,17,40,41]

In light of the above, even highly stereospecific methodologies proposed for the synthesis of mixed-chain glycerides[12–14,26,28,29,42–44] seem to be rather inefficient and usually preclude *in situ* derivatization of labile acylglycerols, or carrying out the synthesis as a one-pot reaction.

In this paper we describe efficient synthesis of 1-mono- (route A), 1,2-di- (route C), 1,3-di- (route D), and triglycerides (routes E and F) with both saturated and unsaturated chains and predesigned asymmetry, obtainable from a single and readily available starting material (*e.g.* an acylated or alkylated glycidol derivative) in highly regioselective and stereospecific manner, under mild conditions and in practically quantitative yields (Scheme 1). Unlike other methods, this protocol is based on two types of alternative chemical transformations, namely, (i) a direct conversion of oxirane[45] or silyloxy systems[46,47] into the corresponding carboxylic esters with variable headgroup functions, which avoids the drawbacks of stepwise generation–acylation of a free alcohol functionality, and (ii) the removal of trifluoroacetyl/trichloroacetyl residues in a way that affords either mono- and diglycerides without recourse to any additional purification,[45–47] or structurally defined triglycerides *via* one-pot procedures.

This strategy minimizes the number of protecting groups used (*e.g.* TBDMS or TIPS groups, to produce a common precursor to di- and triglycerides; route B), and thus may constitute a novel, general method for the synthesis of configurationally pure glycerolipids and related compounds.

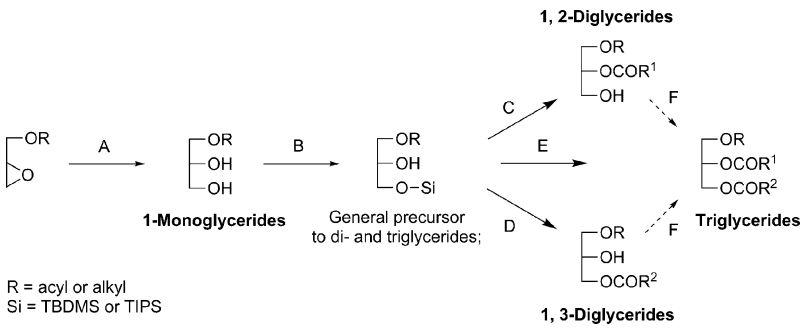
2 Results and discussion

Consistent with generality of our synthetic approach outlined in Scheme 1, special attention was given to glycerides bearing hexadecyl-, acetyl, palmitoyl- and oleoyl substituents as known/prospective precursors to bioactive natural products,[1,7,17,45–49] or model compounds required in structure–activity relationship studies.[41]

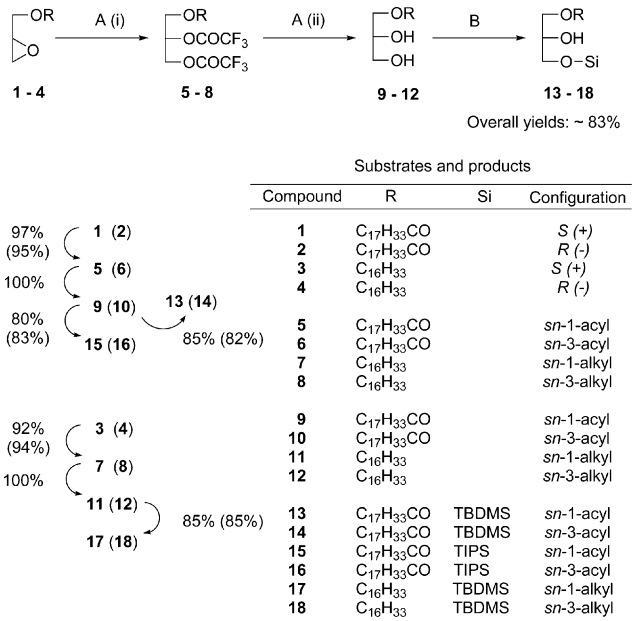
Regioselectivity and stereospecificity of the reactions involved were evaluated on various model acetyl glyceride derivatives, and this was important on two counts. Firstly, since acetyl groups show a high propensity towards migration, transesterification, hydrolysis, *etc.*,[12,50] this type of glycerol derivative provides a rigorous test for efficiency and mildness of the reaction conditions used. Secondly, contrary to acylglycerols with long fatty acid chains, which exhibit only low or no optical activity[28,37] and are hardly distinguishable from their isomers by spectral characteristics,[51] the acetyl derivatives are excellent models for probing isomeric and enantiomeric purity by spectroscopic methods. Supporting arguments in this context are our findings regarding the distinctive chemical shifts of the methyl protons, and the methyl- and carbonyl carbons of an acetyl group at the C1 *vs.* C2 position in the glycerol moiety. These permit the assignment to the corresponding regioisomeric species of a given mono- or bis(acetylated) derivative by ^{1}H and ^{13}C NMR spectroscopy,[52] without recourse to the enzymatic or chemoenzymatic analytical techniques that are usually required for structure elucidation of long-chain triacylglycerols.[32,53–55] The observed spectral regularities also apply to diglycerides where their regioisomeric purity could be additionally assessed by the position of the C–H proton resonances and that of the secondary C2 carbon atom of the glycerol moiety, which are shifted from δ_H ~4.0 to 5.0 ppm and δ_C ~68.5 to 72.6 ppm, respectively, upon acetylation.[56] Similarly, in the presence of the C2-regioisomer of a 1(3)-monoacylated glycerol, new signals at δ_H ~4.9 ppm and δ_C ~75.2 ppm become apparent.[57]

Synthesis of monoacyl- and monoalkyl-*sn*-glycerols (9–12) (Scheme 2, route A)

Despite the apparent structural simplicity of 1(3)-monoacyl-*sn*-glycerols [1(3)-MAG] and their 1(3)-monoalkyl-*sn*-analogues [1(3)-MALKG], an efficient synthesis of these compounds is far from trivial.[45] For example, classical methods for their production *via* 1,2(2,3)-isopropylidene-*sn*-glycerol derivatives[12,28] involve prolonged treatment with concentrated mineral acids at elevated temperature[58] [alternatively with dimethylboronbromide,[59] or trifluoroacetic acid with triethyl borate-2,2,2-trifluoroethanol (8 : 1, v/v)[37]] to remove the isopropylidene group. This entails extensive side-product formation (*e.g.* acyl migration, generation of cyclic systems, racemization, hydrolysis of an ester function, *etc.*),[58,59] and almost always requires additional work-up and chromatographic manipulations,[37,59] which frequently erode the regio- and stereochemical homogeneity of the preparations.[34,60,61]



Scheme 1



Scheme 2 *Reagents and conditions*: route A: (i) $Bu_4N^+CF_3COO^-$ (3.0 equiv.), $(CF_3CO)_2O$ (2.0 equiv.), THF–CH_2Cl_2 (1 : 1, v/v), 80 °C, 5 h; (ii) pyridine (10 equiv.), MeOH (250 equiv.), pentane–CH_2Cl_2, rt, 20 min; route B: TBDMS-Cl or TIPS-Cl (1.3 equiv.), imidazole (6.0 equiv.), THF, rt, 18 h.

An alternative direct approach, involving Lewis-acid-promoted insertions of carboxylic acids,[62] alcohols[63] or phenols[64] into the oxirane system, brings additional synthetic problems due to incompatibility of the reagents (*e.g.* $BF_3{\cdot}OEt_2$)[65] with unsaturated substrates and affords the target compounds in low (*e.g.* ~25% for 1-acyl-*sn*-glycerols)[62] or moderate (*e.g.* ~54–70% for 1-*O*-alkyl-*sn*-glycerols)[63] yields.

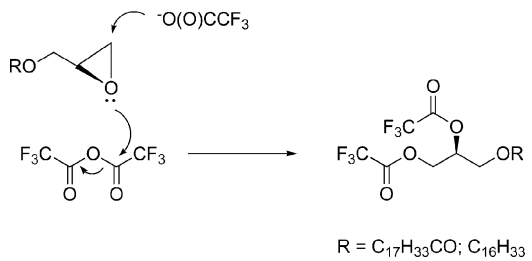
Recently, we have demonstrated the high synthetic utility of a trifluoroacetyl group in glycerolipid synthesis.[66,67] This group can be removed quantitatively under mild conditions without any supplementary purification and thus trifluoroacetate esters can also be considered as storage forms for structurally labile monoacyl glycerols.[66,67]

As a continuation of these studies we investigated a trifluoroacetate-assisted direct trifluoroacetylation across the oxirane system of glycidols bearing a proximal ester function (substrates of type **1** and **2**) or an ether fragment (substrates of type **3** and **4**) by means of trifluoroacetic anhydride (TFAA) as shown in Scheme 2 [route A (i)]. After evaluation of various reaction conditions, the best results were achieved when a solution comprising substrates **1–4** and tetra-*n*-butylammonium trifluoroacetate (TBATFA, 3.0 equiv.) in tetrahydrofuran (THF)–CH_2Cl_2 (1 : 1, v/v), was treated under argon with TFAA (2.0 equiv.) in a tightly stoppered glass ampoule at 80 °C for 5 h.

This produced quantitatively and in a highly regioselective and stereospecific manner (>99%, ^{1}H and ^{13}C NMR spectroscopy) trifluoroacetyl esters **5–8**, which were isolated in 92–97% yields after simple solid-phase filtration through a short silica gel pad (see the Experimental part for details). The reaction seemed to be rather general as other glycidol derivatives (linoleoyl, palmitoyl, stearoyl, benzoyl, isopropyl, or methyl) also underwent quantitative conversions into the corresponding bis(trifluoroacetates) without detectable migration of the fatty acid substituents from C1 to C2. Such compounds can either be stored for several months (−20 °C, under argon) without noticeable alterations of their spectral characteristics (^{1}H and ^{13}C NMR spectroscopy).

We also carried out additional experiments to get some insight into a possible mechanism for this transformation. Thus, ^{1}H and ^{13}C NMR spectroscopy revealed that TFAA alone, effected opening of the oxirane system of glycidyl esters of type **1** with migration of the acyl group to produce the corresponding 2-acylglycerols, while alkyl glycidols of type **3**, were completely stable under these conditions. On the other hand, in the absence of TFAA, glycidyl oleate **1** underwent reaction with TBATFA to give, after deprotection of the trifluoroacetyl moieties, a mixture of 1-monoacylglycerol **9** and 2-acylglycerol in a ratio of 85 : 15. When instead of TFAA, acetic or benzoic anhydride with TBATFA (3.0 equiv.) was used, bis(trifluoroacetates) of type **5** or **7** were identified as the only products. Reactions with acyl donors other than TFAA or TBATFA were rather sluggish, *e.g.* for the tetra-*n*-butylammonium acetate–acetic anhydride system, the reaction occurred to only *ca.* 85% completion after 24 h.

The above observations suggest that opening of the oxirane system in acyl and alkyl glycidols probably proceeds *via* a one-step concerted mechanism involving nucleophilic attack of a trifluoroacetate anion on the primary carbon of the oxirane ring, with simultaneous electrophilic catalysis exerted by TFAA, as depicted in Scheme 3. In addition, the nucleophile and electrophile assistance provided by this two-component reagent should facilitate the epoxide fission and prevent acyl migration during the course of the reaction. As no bond breaking takes place at the chiral centre of the glycidol, the transformation should be stereospecific and occur with retention of configuration. The observed formation of bis(trifluoroacetates) of type **5** or **7** in the reaction of glycidyl esters **1** with the acetic or benzoic anhydride–TBATFA reagent system, is also consistent with this mechanism, and indicates generation under the reaction conditions of the mixed acetic- or benzoic-trifluoroacetic anhydrides, which are expected to be stronger electrophiles than the parent carboxylic anhydrides.



Scheme 3

To demonstrate the feasibility of the removal of trifluoroacetyl groups from triglycerides **5–8** under mild conditions, these compounds were treated in CH_2Cl_2–pentane with pyridine (10 equiv.) and methanol (250 equiv.) at room temperature. The reactions were quantitative (completion within 20 min) and after evaporation of the volatile products, afforded positionally homogeneous monoglycerides **9–12** (purity >99%, by ^{1}H and ^{13}C NMR spectroscopy) in 92–95% overall yields (calculated on **1–4**) without any additional purification [route A (ii), Scheme 2].

Synthesis of 3(1)-*O*-silyl intermediates (Schemes 2 and 4)

Aside from their utility as chiral precursors to 1(3)-monoacyl- (*e.g.* **9** and **10**) or 1(3)-monoalkyl-*sn*-glycerols (*e.g.* **11** and **12**), trifluoroacetyl esters **5–8** represent valuable starting materials for the preparation of monosilylated derivatives **13–18** (Scheme 2), that can be viewed as key intermediates in the synthesis of di- and triglycerides (Scheme 4). To this end, trifluoroacetates **5–8** were deprotected as described above, and the resulting monoglycerides **9–12** were treated in anhydrous THF, at room temperature, with TBDMS-Cl or TIPS-Cl (1.3 equiv.) in the presence of imidazole (6.0 equiv.) for *ca.* 18 h. This gave the building blocks **13–18**, with terminal *O*-silyl groups, in high overall yields of *ca.* 80–85% (the yields calculated in relation to **5–8**; see the Experimental part).

These compounds are usually acylated to produce 3-*O*-silylated derivatives **19–27**, which are used as starting materials for the preparation of various di- and triglycerides. The acylation of silyl ethers **13–18** with acyl chlorides (1.5 equiv.) in the presence of pyridine (20 equiv.). was uneventful and produced in high yields (92–95%; Scheme 4) the corresponding esters bearing either long- or short-chain fatty acid residues (**19–23**, **25** and **26**) or 2,2,2-trichloroacetyl functionality (**27**) at the glycerol *sn*-2-position. This type of derivative can also be prepared *via* consecutive silylation and acylation of commercially available chiral monoglycerides, *e.g.* 3-palmitoyl-*sn*-glycerol (MPG), as shown in Scheme 4 (overall yield, 73%).

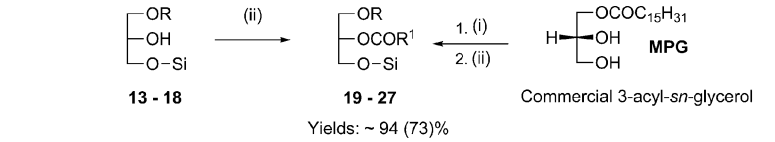
Synthesis of vicinal diacyl- and alkyl-acyl-*sn*-glycerols *via* direct trichloroacetylation across the silyloxy system (Scheme 5)

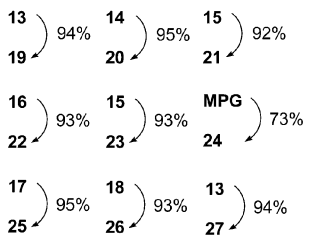
While temporary protection of the terminal hydroxyl group of 1(3)-MAG or 1(3)-MALKG (*e.g.* route B, Scheme 2) followed by the formation of an ester bond at the central carbon atom of such C3-units (Scheme 4), is a well-known approach to 1,2(2,3)-diacyl-*sn*-glycerols [1,2(2,3)-DAG] and their 1(3)-*O*-alkyl-2-acyl-*sn*-analogues [1(3)-AL-2-AG],[12,28] problems usually arise at the end of synthesis as most of the protecting group systems (*e.g.* levulinate,[68] benzyl,[26,42] trityl,[29,41,69] 2,2,2-trichloroethoxycarbonyl,[70] 9-phenylxanthen-9-yl,[37] *etc.*) require deprotection conditions that preclude admission to conjugates with unsaturated or acid–base-sensitive moieties,[12] or cause undesirable intramolecular rearrangements.[12,31,34]

In this situation we turned our attention to silyl groups as alternative transient protecting groups.[71] Unfortunately, cleavage of even relatively labile *tert*-butyldimethylsilyl (TBDMS) ethers having an acyl functionality in a vicinal position, is often impractically slow (*e.g.* 17 h[62] or up to 14 days[72]) or requires reagents that are either incompatible with acid,[73] base,[38] or oxidation–reduction-susceptible substrates,[62,71,74] or trigger an extensive acyl migration process.[38]

As the removal of a trichloroacetyl group can be carried out quantitatively, under mild conditions, and without additional purification,[47] we considered direct transformation between silyl and trichloroacetyl groups as a viable strategy for our purpose, to circumvent drawbacks inherent to a stepwise deprotection of silyl derivatives.[46] However, although the acylation across a silyloxy system of simple alcohols finds ample literature precedents, the current methods (*e.g.* by using $FeCl_3$–acetic anhydride,[75] pyridine–acetic anhydride–acetic acid or methanol–acetic acid,[76] $ZnCl_2$–acetyl chloride,[77] or $SnBr_2$–acetyl bromide[78]) permit only introduction of an acetyl residue and are inapplicable to the synthesis of 1,2(2,3)-DAG and 1(3)-AL-2-AG.

Therefore, reaction conditions for direct trichloroacetylation of monofunctional silyl intermediates (*e.g.* **19**, **22**, **23**, **25**, and **26**) with trichloroacetic anhydride (TCAA) in the presence of triethylamine tris(hydrofluoride) ($Et_3N{\cdot}3HF$), were investigated employing different solvents, ratios of the reactants, *etc.* [Scheme 5, route C (i)]. The best results were obtained when compounds **19**, **22**, **23**, **25**, or **26** were treated under argon with neat TCAA (9.0 equiv.) and $Et_3N{\cdot}3HF$ (2.0 equiv.) in a pressure

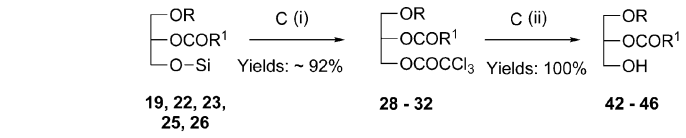


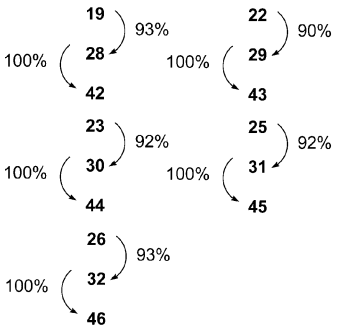


Substrates and products

Compound	R	OH	Si	Configuration
13	$C_{17}H_{33}CO$		TBDMS	*sn*-1-acyl
14	$C_{17}H_{33}CO$		TBDMS	*sn*-3-acyl
15	$C_{17}H_{33}CO$		TIPS	*sn*-1-acyl
16	$C_{17}H_{33}CO$		TIPS	*sn*-3-acyl
17	$C_{16}H_{33}$		TBDMS	*sn*-1-alkyl
18	$C_{16}H_{33}$		TBDMS	*sn*-3-alkyl
		R^1		
19	$C_{17}H_{33}CO$	CH_3	TBDMS	*sn*-1,2-diacyl
20	$C_{17}H_{33}CO$	CH_3	TBDMS	*sn*-2,3-diacyl
21	$C_{17}H_{33}CO$	CH_3	TIPS	*sn*-1,2-diacyl
22	$C_{17}H_{33}CO$	CH_3	TIPS	*sn*-2,3-diacyl
23	$C_{17}H_{33}CO$	$C_{17}H_{33}$	TIPS	*sn*-1,2-diacyl
24	$C_{15}H_{31}CO$	$C_{17}H_{33}$	TIPS	*sn*-2,3-diacyl
25	$C_{16}H_{33}$	CH_3	TBDMS	*sn*-1-alkyl-2-acyl
26	$C_{16}H_{33}$	CH_3	TBDMS	*sn*-3-alkyl-2-acyl
27	$C_{17}H_{33}CO$	CCl_3	TBDMS	*sn*-1,2-diacyl

Scheme 4 *Reagents and conditions*: (i) TIPS-Cl (1.3 equiv.), imidazole (6.0 equiv.), THF, rt, 18 h; (ii) CH_3COCl, $C_{17}H_{33}COCl$ or CCl_3COCl (1.5 equiv.), pyridine (20 equiv.), CH_2Cl_2, rt, 2 h.





Substrates and products

Compound	R	R^1	Si	Configuration
19	$C_{17}H_{33}CO$	CH_3	TBDMS	*sn*-1,2-diacyl
22	$C_{17}H_{33}CO$	CH_3	TIPS	*sn*-2,3-diacyl
23	$C_{17}H_{33}CO$	$C_{17}H_{33}$	TIPS	*sn*-1,2-diacyl
25	$C_{16}H_{33}$	CH_3	TBDMS	*sn*-1-alkyl-2-acyl
26	$C_{16}H_{33}$	CH_3	TBDMS	*sn*-3-alkyl-2-acyl
			CCl_3CO	
28	$C_{17}H_{33}CO$	CH_3		*sn*-1,2-diacyl
29	$C_{17}H_{33}CO$	CH_3		*sn*-2,3-diacyl
30	$C_{17}H_{33}CO$	$C_{17}H_{33}$		*sn*-1,2-diacyl
31	$C_{16}H_{33}$	CH_3		*sn*-1-alkyl-2-acyl
32	$C_{16}H_{33}$	CH_3		*sn*-3-alkyl-2-acyl
			OH	
42	$C_{17}H_{33}CO$	CH_3		*sn*-1,2-diacyl
43	$C_{17}H_{33}CO$	CH_3		*sn*-2,3-diacyl
44	$C_{17}H_{33}CO$	$C_{17}H_{33}$		*sn*-1,2-diacyl
45	$C_{16}H_{33}$	CH_3		*sn*-1-alkyl-2-acyl
46	$C_{16}H_{33}$	CH_3		*sn*-3-alkyl-2-acyl

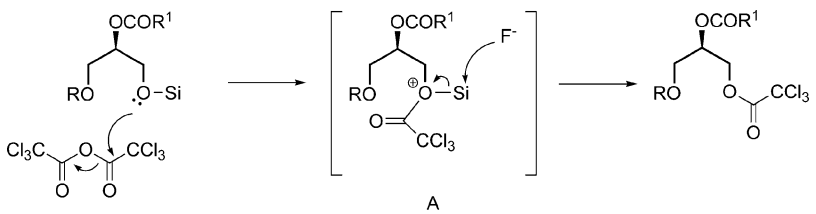
Scheme 5 *Reagents and conditions*: route C: (i) $Et_3N{\cdot}3HF$ (2.0 equiv.), $(CCl_3CO)_2O$ (9.0 equiv.), no solvent, 80 °C, 2 h; (ii) pyridine (50 equiv.), MeOH (500 equiv.), THF, rt, 3 h.

glass ampoule at 80 °C for 2 h. This produced quantitatively and in a highly chemo- and regiospecific manner (>99%, ^1H and ^{13}C NMR spectroscopy) terminal trichloroacetates **28–32**, which were isolated in 90–93% yields after flash column silica gel chromatography. The obtained trichloroacetyl derivatives **28–32** can either be subjected directly to subsequent transformations, or stored for several months (−20 °C, under argon) without detectable alterations of their spectral characteristics (^1H and ^{13}C NMR spectroscopy).

Regarding the scope and limitations of this particular chemistry, some additional observations are pertinent. The rate of replacement of the silyl groups by a trichloroacetyl moiety was not appreciably influenced by electronic features or the type of molecular fragments present in **19**, **22**, **23**, **25**, or **26** (*e.g.* various acyl, or saturated alkyl substituents). Trimethylsilyl derivatives underwent esterification at comparable rates to those of TBDMS and TIPS ethers. The reactions in organic solvents were considerably slower (*e.g.* in $CHCl_3$; reaction time ~48 h) or produced complex reaction mixtures (*e.g.* the reactions in THF). The rate of trichloroacetylation remained practically within the same range of magnitude upon replacement of $Et_3N{\cdot}3HF$ by tetra-*n*-butylammonium fluoride ($TBAF{\cdot}3H_2O$). In the latter case, however, ^1H and ^{13}C NMR analysis revealed that regioselectivity was eroded due to acyl migration (5–10%), triggered probably by the substantial amounts of free trichloroacetic acid generated from TCAA in the presence of water. Although trifluoroacetic anhydride could be used as a substitute for TCAA, the trifluoroacetyl derivatives were less convenient to work with as they readily decomposed during column chromatography.

It was interesting to note that for TBDMS-ethers of types **19** and **25**, the derivatization could be carried out without the presence of fluoride ions, by using tetra-*n*-butylammonium trichloroacetate with two equivalents of TCAA. Under these conditions, however, the reactions were rather slow (*e.g.* in $CHCl_3$ at rt, *ca.* 24 h; ~90% conversion) and failed for TIPS derivatives (<5% conversion after 24 h; TLC analysis).

On the basis of the above data we can tentatively formulate a mechanism for these reactions, which involves an electrophilic attack by TCAA to form an intermediate of type **A**, followed by a nucleophilic attack by fluoride on the silicon atom (Scheme 6). This rationalizes the replacement of the silyl protection with trichloroacetyl with no migration of the vicinal ester group. Since no bond breaking takes place at the stereogenic C2-centre, the transformation is stereospecific and occurs with retention of configuration. The observed exclusive formation of terminal trifluoroacetates **28–32** with defined stereochemistry (see the Experimental part) and the lack of intramolecular acyl scrambling, are in agreement with this hypothesis.



Si = TBDMS or TIPS; R = acyl or alkyl; R^1 = alkyl

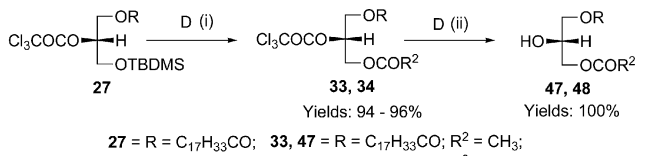
Scheme 6

An alternative mechanism consisting of a nucleophilic attack by a trichloroacetate anion on the silicon centre seems to be less likely as the fluoride ion is orders of magnitude more effective as a nucleophile for silicon then carboxylate. This is also consistent with the experiments carried out in the absence of fluoride (*vide supra*).

As the final stage of this protocol, the trichloroacetates **28–32** were converted into 1,2(2,3)-DAG (**42–44**) and 1(3)-AL-2-AG (**45** and **46**), respectively [route C (ii), Scheme 5]. Due to the high electrophilicity of the carbonyl centre of trichloroacetyl conjugates, this operation could be carried out selectively even in the presence of an acetyl group, by treating compounds **28–32** in THF with pyridine (50 equiv.) and methanol (500 equiv.) at room temperature. The reactions were quantitative (completion within 3 h) and after removal of the volatile products, diglycerides **42–46** of purity >99% (^{1}H and ^{13}C NMR spectroscopy) were obtained directly without any additional work-up.

Synthesis of 1,3-diacyl-*sn*-glycerols *via* direct acylation across the terminal silyloxy system (Scheme 7, route D)

Despite the increasing need for configurationally pure 1,3-diacyl-*sn*-glycerols (1,3-DAG) (physiological effectors,[4,5] micromolecular vectors for directing therapeutics[21,79] or requisite agents[18,19] to the metabolic pathways of natural lipids, *etc.*), the chemical and pharmacological potential of these compounds has not been exploited to any significant extent. There are usually preparative problems in the synthesis of these compounds, and to avoid inconveniences of protection–deprotection procedures[28,37,80] or enzymatic manipulations,[81] several methodologies for direct incorporation of different acyl groups at the terminal sites of a glycerol backbone have been reported. In the original method proposed by Lok *et al.*[82] and its latter modifications,[83–85] glycidyl esters are heated with another fatty acid in the presence of a quaternary ammonium salt (2–4 h, 100–110 °C) to give in variable proportions mixtures of 1,2- and 1,3-diacylglycerols. Although experimentally simple, this approach, suffers from many drawbacks, such as lack of generality, mediocre yields (40–70%[83]), separation problems,[61,86] and rather harsh reaction conditions that contribute to the formation of transesterification products, intramolecular ligand migration, racemization, oxidation, *etc.*[68,82–86] Alternative synthetic protocols based on esterification of 1-monoglycerides with various acyl donors, seem to be equally inefficient due to analogous shortcomings[28] and typically afford unsymmetrical 1,3-DAG in low yields (44–46%).[22,49]



Scheme 7 *Reagents and conditions*: route D: (i) Bu_4NBr (2.0 equiv.), TMSBr (1.5 equiv.), $(CH_3CO)_2O$ or $(C_{15}H_{31}CO)_2O$ (3.0 equiv.), $CHCl_3$, 80 °C, 2 h; (ii) pyridine (50 equiv.), MeOH (500 equiv.), THF, rt, 2 h.

As examples of direct transformation of *O*-silyl groups into *O*-acetates are known from the literature (also, *vide supra*), we reasoned that derivatization of a bifunctional C3-building block (*e.g.* **27**) bearing 2,2,2-trichloroacetyl- and TBDMS-transient protections, *via* direct replacement of the silyl moiety with an acyl residue and subsequent methanolysis of the 2-*O*-trichloroacetyl fragment in the presence of pyridine, could provide a convenient entry to the otherwise difficult-to-access 1,3-diacyl-*sn*-glycerols of type **47** and **48** (Scheme 7). Unfortunately, the reagents available to date[75–78] rely on chemistry that is either incompatible with labile trichloroacetyl derivatives or inapplicable if 1,3-DAG with acyl functionalities different from acetyl are desired.

To overcome the aforementioned complications, we developed a new reagent system consisting of Bu_4NBr–TMSBr–carboxylic acid anhydride, which not only tolerates the presence of a chemically labile trichloroacetyl substituent, but also effects conversion of silyl ethers into short- or long-chain carboxylates without exposure of a free hydroxyl group of the glycerol skeleton.[47]

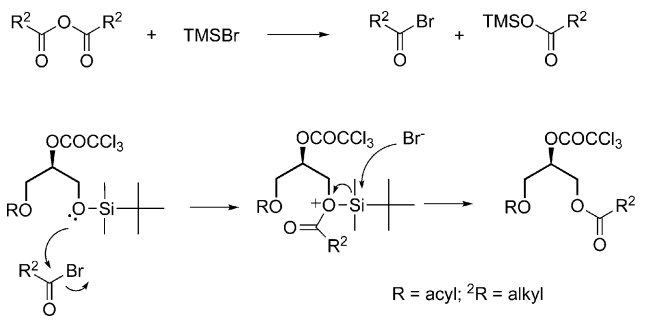
To assess the efficacy of this triester tactic, direct acylation across standard silyl protection in 1-oleoyl-2-trichloroacetyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol (**27**) having a long-chain unsaturated fatty acid residue, was investigated under various experimental conditions (different temperature, ratio of reactants, solvents, *etc.*) using Bu_4NBr, TMSBr, and carboxylic acid anhydrides. The best results were obtained when a carboxylic anhydride (3.0 equiv.) and TMSBr (1.5 equiv.) were mixed together and added to trichloroacetate **27** and Bu_4NBr (2.0 equiv.) in chloroform, and the reaction mixture was heated at 80 °C for 2 h in a tightly stoppered glass ampoule. ^{1}H- and ^{13}C NMR spectral analysis revealed that under these conditions conversion of **27** into triglycerides **33** or **34** bearing a trichloroacetyl group, was practically quantitative and entirely regioselective (>99%). No byproducts due to possible acyl migration or side reactions involving an olefinic system of the oleic acid moiety could be detected [route D (i), Scheme 7].

We also carried out additional studies to elucidate some mechanistic aspects of this direct acylation across a siloxy system. Experiments using model substrates (compound **27**, 1-oleoyl-2-acetyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol, or triisopropylsilyl- and *tert*-butyldimethylsilyl ethers of oleyl alcohol), showed that carboxylic acid anhydrides (CAA) alone (*e.g.* acetic-, palmitic-, oleic anhydride), as well as their mixtures with either Bu_4NBr (TBABr) or TMSBr, were essentially unreactive and only three-component reagent systems, *i.e.* CAA–TBABr–TMSBr, exhibited efficient acylating properties for TBDMS- and TIPS-protected alcohols, although a longer reaction time was required for quantitative functionalization of the TIPS-derivatives (~15 h). Trichloroacetic anhydride could not be used as an acyl donor in conjunction with TBABr–TMSBr, as it underwent partial decomposition under the reaction conditions.

Since ^{1}H- and ^{13}C NMR spectroscopy revealed that treatment of CAA with TMSX (1.0 equiv.) alone, or in the presence of 2.0–4.0 equivalents of Bu_4NX (X = Br, or I), at room temperature led to almost instantaneous production of equimolar amounts of the corresponding acyl halides (ACX) and trimethylsilyl carboxylates (ACOTMS), contribution of these species to the acylolytic cleavage of the aforementioned silyl ethers was examined further. It was found that ACX by themselves (*e.g.* oleoyl chloride or acetyl bromide) or in combination with the respective CAA (*e.g.* oleic or acetic anhydride), in the presence or absence of ACOTMS (*e.g.* trimethylsilyl acetate), were entirely incapable of carrying out conversion of the substrates with a TBDMS or TIPS group into the corresponding carboxylic esters. However, all these

transformations could be rescued, to afford the expected products, *via* the addition of bromide anion to the reaction mixtures. While TMSCl in combination with Bu_4NCl gave inferior results, the corresponding iodo derivatives maintained acylating properties indistinguishable from those provided by the TBABr–TMSBr reagent system. The reactions investigated seemed to be rather general as other silyl ethers (*e.g.* trimethyl-, triethyl- and triisopropylsilyl), with a notable exception of *tert*-butyldiphenylsilyl derivatives, underwent quantitative esterification under the developed reaction conditions. In all instances, no presence of halogenated byproducts could be detected in the reaction mixtures by means of the chromatographic and spectroscopic analytical techniques used.

These observations are consistent with a mechanism shown in Scheme 8. An acyl bromide, generated *in situ* from CAA and TMSBr, is expected to be a powerful electrophile that can coordinate to the oxygen atom of the silyloxy system to form a silyloxonium intermediate, which upon a nucleophilic attack by a bromide ion (from a quaternary ammonium salt) on the silicon centre, collapses to the product. The last two steps can also be synchronous, but this is probably less likely on entropic grounds. The combination of nucleophile and electrophile catalysis in these reactions should facilitate cleavage of the silyl ethers and secure the formation of a new ester bond without scrambling of the adjacent trichloroacetyl moiety, as no free hydroxyl of the glycerol backbone is exposed. The proposed mechanism does not include any C–O bond scission at the stereogenic secondary carbon atom and, therefore, predicts retention of configuration in the glycerol unit.

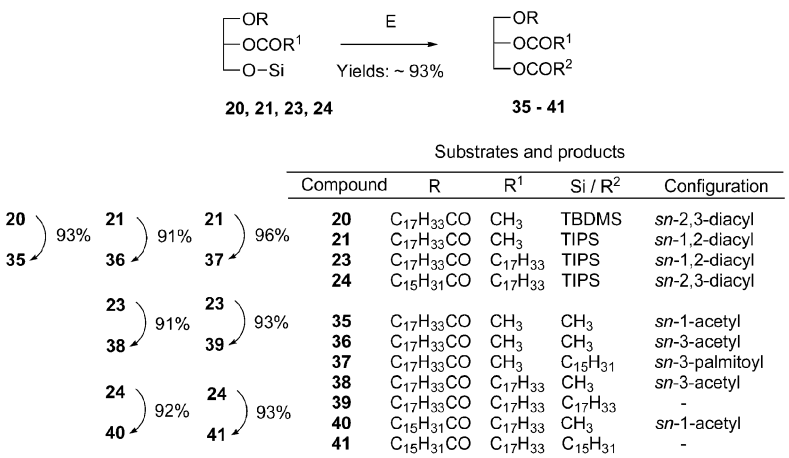


Scheme 8

Since trichloroacetate esters are known to undergo smooth transesterification with alcohols,[46] 1,3-diacylglycerols **47** and **48** could be obtained by treating the precursors **33** and **34**, respectively, with methanol (500 equiv.) at room temperature in the presence of pyridine (50 equiv.) [route D (ii), Scheme 7]. These reactions were quantitative (completion within 2 h) and after removal of the volatile products, afforded 1,3-diacyl-*sn*-glycerol **47** and **48** of purity >99% (^{1}H- and ^{13}C NMR spectroscopy) without supplementary purification. Stereochemical homogeneity of **47** (a new compound) bearing an acetyl group particularly prone to migration, has been additionally confirmed by its conversion into the corresponding Mosher ester **49** [route F (ii), Scheme 10, *vide infra*], and that of **48**, by the lack of depression in melting point upon mixing with various proportions (from 1.0 : 0.5 to 1.0 : 1.5, w/w) with a reference sample of **48**.[82] It is worth noting that 2,2,2-trichloroacetates **33** and **34** can also be considered as a convenient storage form for 1,3-DAG as their spectral characteristics (^{1}H- and ^{13}C NMR spectroscopy) remained unchanged upon prolonged time (several months at −20 °C, under argon).

Synthesis of triacyl-*sn*-glycerols using key silyl intermediates (Scheme 9)

While enzymatic methods can satisfactorily afford only simple triglycerides,[7] the regioselective and enantioselective production of unsymmetrical homologues with different acyl substituents, including both saturated and unsaturated ones, requires access to configurationally pure 1,2(2,3)-DAG or 1,3-DAG as the substrates for the final establishment of the third ester bond.[14,28,82] To this end, the existing synthetic strategies[14,18,22,44,49,53,85,87] resort to a variety of starting materials/intermediates that usually demand lengthy multistep functionalization and work-up procedures to afford the target triacylglycerols (TAG) in rather mediocre overall yields (*e.g.* 7–19%).[49] Even two-step protocols, comprising either LiBr-[88] or LiBr-benzyltributylammonium bromide-assisted[55] fission of the oxirane ring of glycidyl esters with carboxylic acid anhydrides, followed by displacement of the bromine within the produced 3-bromo-1,2-propanediol esters by caesium carboxylates, do not remedy these problems, and do not completely prevent formation of isomeric products.[55]



Substrates and products

Compound	R	R^1	Si / R^2	Configuration
20	$C_{17}H_{33}CO$	CH_3	TBDMS	*sn*-2,3-diacyl
21	$C_{17}H_{33}CO$	CH_3	TIPS	*sn*-1,2-diacyl
23	$C_{17}H_{33}CO$	$C_{17}H_{33}$	TIPS	*sn*-1,2-diacyl
24	$C_{15}H_{31}CO$	$C_{17}H_{33}$	TIPS	*sn*-2,3-diacyl
35	$C_{17}H_{33}CO$	CH_3	CH_3	*sn*-1-acetyl
36	$C_{17}H_{33}CO$	CH_3	CH_3	*sn*-3-acetyl
37	$C_{17}H_{33}CO$	CH_3	$C_{15}H_{31}$	*sn*-3-palmitoyl
38	$C_{17}H_{33}CO$	$C_{17}H_{33}$	CH_3	*sn*-3-acetyl
39	$C_{17}H_{33}CO$	$C_{17}H_{33}$	$C_{17}H_{33}$	-
40	$C_{15}H_{31}CO$	$C_{17}H_{33}$	CH_3	*sn*-1-acetyl
41	$C_{15}H_{31}CO$	$C_{17}H_{33}$	$C_{15}H_{31}$	-

Scheme 9 *Reagents and conditions*: route E: Bu_4NBr (2.0 equiv.), TMSBr (1.5 equiv.), $(CH_3CO)_2O$, $(C_{15}H_{31}CO)_2O$ or $(C_{17}H_{33}CO)_2O$ (3.0 equiv.), $CHCl_3$, 80 °C, 2–15 h.

Because we have already demonstrated that easily accessible 1,2(2,3)-diacyl-3(1)-*O*-silyl-*sn*-glycerols (Scheme 4) are convenient intermediates for the preparation of 1,2(2,3)-DAG[46] (route C, Scheme 5), we wanted to extend this strategy to the synthesis of structured TAG *via* direct replacement of the corresponding *O*-silyl moiety with an acyl group (*e.g.* with saturated/unsaturated or short/long alkyl chains) using the CAA–TBABr–TMSBr[47] reagent system (route E, Scheme 9).

To this end the silyl ethers **20**, **21**, **23**, or **24** and Bu_4NBr (2.0 equiv.) in chloroform, were treated with a mixture of a carboxylic acid anhydride (3.0 equiv.) and TMSBr (1.5 equiv.) in the same solvent at 80 °C for 2 h (15 h for TIPS-derivatives **21**, **23** and **24**), analogously as described for the synthesis of 1,3-DAG (Scheme 7). This gave quantitatively and in a highly chemo- and regioselective way (>99%, ^{1}H- and ^{13}C NMR spectroscopy) the expected triesters **35–41**, which were isolated in 91–96% yields after flash column silica gel chromatography. The longer reaction time required for the displacement of the TIPS group (*ca.* 15 h) had no negative effect on the homogeneity of the triglycerides produced.

One-pot synthesis of triacyl-*sn*-glycerols from the corresponding 2,2,2-trichloroacetyl derivatives (Scheme 10)

Considering possible limitations of a direct acylation across a silyloxy system of glycerol with carboxylic acid anhydrides, we elaborated a complementary methodology based on the use of 1,2(2,3)-diacyl-3(1)-trichloroacetyl- (*e.g.* **28**, **29**) and 1,3-diacyl-2-trichloroacetyl-*sn*-glycerols (*e.g.* **33**, **34**) for the preparation of structurally defined TAG (route F, Scheme 10).

Relevant to the first step of this one-pot approach, trichloroacetates of type **28** and **29**, or **33** and **34**, were converted into 1,2(2,3)-(**42** and **43**), or 1,3-diglycerides (**47** and **48**) by treatment with methanol (500 equiv.) at room temperature in the presence of pyridine (50 equiv.) (Scheme 10), analogous to the method described in Schemes 5 and 7. The volatile byproducts were removed under reduced pressure (see the Experimental part) and the deprotected glycerol intermediates were directly reacted in chloroform with a suitable acyl chloride (2.0 equiv.) in the presence of pyridine (20 equiv.). The ^{1}H- and ^{13}C NMR spectra of the isolated products (flash column silica gel chromatography) revealed that in all instances the transformation to target triacylglycerols **49–53** was practically quantitative (90–95% overall yields, calculated on **28**, **29**, **33**, and **34**) and entirely regioselective (>99%).

In conclusion, we have developed an efficient, general synthetic strategy to configurationally pure 1(3)-mono- (*e.g.* **9–12**), 1,2(2,3)-di- (*e.g.* **42–46**), 1,3-di- (*e.g.* **47**, **48**), and triglycerides (*e.g.* **35–41**, **49–53**), based on direct acylation across the epoxide (*e.g.* **1–4**) and silyloxy systems (*e.g.* **19–27**) of suitable precursors.

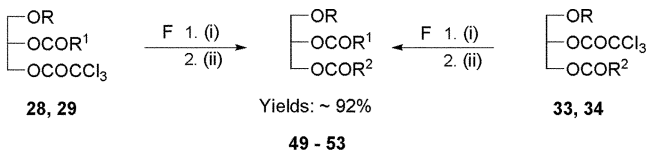
The main features of this new protocol are: (i) access to individual mono-, di- and triacyl-*sn*-glycerols with saturated and unsaturated fatty acid residues, from stable and easily accessible precursors; (ii) highly regioselective and stereospecific introduction of acyl groups without exposure of a free hydroxyl functionality, which eliminates a perennial problem of glyceride chemistry, namely, acyl migration; (iii) a minimal number of chromatographic purifications due to high efficiency of the individual reaction steps and the use of trifluoroacetyl and trichloroacetyl groups as transient protecting groups; (iv) all synthetic intermediates are stable and can be stored for months without noticeable decomposition.

The method seems to be rather general, makes use of commercially available reactants, and can easily be scaled up. The incorporation of 2,2,2-trifluoroacetyl-, 2,2,2-trichloroacetyl- and *O*-silyl groups as versatile protecting groups to the synthetic protocols and the development of efficient methods for their removal, expand the range of biologically important lipid mediators that can be prepared by this methodology.

3 Experimental part

All 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.[89] Reaction conditions were kept strictly anhydrous unless stated otherwise.

Progress of the reactions was monitored by analytical thin-layer chromatography (TLC) on pre-coated silica gel glass plates 60 F_{254} (Merck). The spots were visualized using 3.5% molybdatophosphoric acid spray reagent (Merck) or 50% sulfuric acid followed



Substrates and products

Compound	R	R^1/ CCl_3	R^2/ CCl_3	Configuration
28	$C_{17}H_{33}CO$	CH_3	CCl_3	*sn*-1,2-diacyl
29	$C_{17}H_{33}CO$	CH_3	CCl_3	*sn*-2,3-diacyl
33	$C_{17}H_{33}CO$	CCl_3	CH_3	*sn*-1,3-diacyl
34	$C_{17}H_{33}CO$	CCl_3	$C_{15}H_{31}$	*sn*-1,3-diacyl
49	$C_{17}H_{33}CO$	$C_9H_8F_3O$	CH_3	*sn*-1-oleoyl
50	$C_{17}H_{33}CO$	CH_3	CH_3	*sn*-3-acetyl
51	$C_{17}H_{33}CO$	CH_3	$C_{15}H_{31}$	*sn*-1-palmitoyl
52	$C_{17}H_{33}CO$	$C_{15}H_{31}$	CH_3	*sn*-3-acetyl
53	$C_{17}H_{33}CO$	$C_{15}H_{31}$	$C_{15}H_{31}$	*sn*-3-palmitoyl

28 → **50** 95%; **29** → **51** 94%; **33** → **49** 90%; **33** → **52** 91%; **34** → **53** 91%

Scheme 10 *Reagents and conditions*: route F: (i) pyridine (50 equiv.), MeOH (500 equiv.), THF, rt, 2–3 h; (ii) *R*(−)-MTPA-Cl, CH_3COCl or $C_{15}H_{31}COCl$ (2.0 equiv.), pyridine (20 equiv.), $CHCl_3$, rt, 2–18 h.

by heating at 140 °C. Column chromatography (CC) was carried out on silica gel 60 (70–230 mesh ASTM, Merck) using appropriate solvent systems (see below).

^{1}H- 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 **1–53** was done on the basis of known or expected chemical shifts in conjunction with ^{1}H–^{1}H, ^{1}H–^{13}C, and DEPT correlated NMR spectroscopy. In certain cases, ^{1}H- and ^{13}C NMR spectral characteristics of known compounds were also presented to make up for the lack of appropriate literature information.

Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter. Melting points were determined on a Kofler melting point apparatus and are uncorrected.

Tetra-*n*-butylammonium trifluoroacetate (mp 81.0–82.5 °C) was synthesized according to the method of Weiss and Touchette.[90]

(*S*)-(+)-2-(Oleoyloxymethyl)oxirane **1** [colourless oil; $[\alpha]_D{}^{20}$ = +13.76 (*c* 6.33, $CHCl_3$)] and (*R*)-(−)-2-(oleoyloxymethyl)oxirane **2** [colourless oil; $[\alpha]_D{}^{20} = -13.51$ (*c* 5.03, $CHCl_3$)], were prepared by acylation of chiral glycidols with oleoyl chloride (all from Fluka) as described elsewhere.[67] (*S*)-(+)-2-(Hexadecyloxymethyl)oxirane **3** [white solid; mp 34.3–35.7 °C; $[\alpha]_D^{20}$ = +10.00 (*c* 5.76, C_6H_6)] and (*R*)-(−)-2-(hexadecyloxymethyl)oxirane **4** [white solid; mp 34.1–35.6 °C; $[\alpha]_D^{20}$ = −9.83 (*c* 6.35, C_6H_6)], were obtained from enantiomeric glycidyl tosylates (Fluka) in two steps following a standard approach.[91] Compounds **1–4** had spectral and physicochemical parameters comparable to those reported in the literature.[67,91] For the full characterisation data of the synthesised compounds, see ESI.†

General procedure for the synthesis of bis(trifluoroacetates) 5–8 and 1(3)-monoacyl-/or 1(3)-monoalkyl-*sn*-glycerols thereof 9–12 (route A)

Step (i): a solution of glycidyl derivative **1–4** (1.00 mmol) in alcohol-free dichloromethane–THF (1 : 1, v/v, 2.0 mL) was added to a mixture of tetra-*n*-butylammonium trifluoroacetate (1.066 g; 3.00 mmol) and trifluoroacetic anhydride (TFAA, 0.278 ml; 2.00 mmol) in the same solvent system (3.0 mL), and the reaction was kept under argon, in a pressure-proof glass ampoule at 80 °C (bath temp.) for 5 h. The solvents and unreacted TFAA were removed under reduced pressure (bath temp. 50 °C), the residue was dissolved in toluene (5.0 mL) and passed through a silica gel pad (~5 g) prepared in the same solvent. The support was washed with toluene (100 mL), fractions containing the product were combined, the solvent was removed under reduced pressure, and the residue was kept under high vacuum at room temperature for 2–3 h to provide bis(trifluoroacetate) **5–8** (purity >99%, ^{1}H NMR spectroscopy).

Step (ii): a mixture of pyridine (0.8 mL, 10 mmol) and methanol (10.1 mL, 250 mmol) in pentane–CH_2Cl_2 (3 : 1, v/v, 5.0 mL) was added at 0 °C to a solution of trifluoroacetate **5–8** in the same solvent, and the reaction was left at room temperature for 20 min. The solvents were evaporated under reduced pressure (bath temp. 50 °C) and the residue was kept under high vacuum at room temperature for 2–3 h to give the deprotected monoglyceride **9–12** (purity >99%, ^{1}H NMR spectroscopy).

1-Oleoyl-2,3-bis(trifluoroacetyl)-*sn*-glycerol 5. Obtained from (*S*)-(+)-2-(oleoyloxymethyl)oxirane (**1**; 0.338 g, 1.00 mmol). Yield: 0.532 g (97%, yellowish oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.60; $[\alpha]_D^{20} = -3.49$ (*c* 10.14, $CHCl_3$); found: C, 54.64; H, 7.03%. $C_{25}H_{38}F_6O_6$ (548.57) requires C, 54.74; H, 6.98%. ^{1}H- and ^{13}C NMR spectra identical with those reported in the literature.[45]

3-Oleoyl-1,2-bis(trifluoroacetyl)-*sn*-glycerol 6. Obtained from (*R*)-(−)-2-(oleoyloxymethyl)oxirane (**2**; 0.338 g, 1.00 mmol). Yield: 0.521 g (95%, yellowish oil); $[\alpha]_D^{20}$ = +3.54 (*c* 11.28, $CHCl_3$). All other physicochemical and spectral characteristics were identical with those of **5**.

1-*O*-Hexadecyl-2,3-bis(trifluoroacetyl)-*sn*-glycerol 7. Obtained from (*S*)-(+)-2-(hexadecyloxymethyl)oxirane (**3**; 0.299 g, 1.00 mmol). Yield: 0.468 g (92%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.76; $[\alpha]_D^{20} = -9.55$ (*c* 10.89, $CHCl_3$); found: C, 54.40; H, 7.47%. $C_{23}H_{38}F_6O_5$ (508.53) requires C, 54.32; H, 7.53%. ^{1}H- and ^{13}C NMR spectra identical with those reported in the literature.[45]

3-*O*-Hexadecyl-1,2-bis(trifluoroacetyl)-*sn*-glycerol 8. Obtained from (*R*)-(−)-2-(hexadecyloxymethyl)oxirane (**4**; 0.299 g, 1.00 mmol). Yield: 0.478 g (94%, colourless oil); $[\alpha]_D^{20}$ = +9.67 (*c* 10.03, $CHCl_3$). All other physicochemical and spectral characteristics were identical with those of **7**.

1-Oleoyl-*sn*-glycerol 9. Obtained from (*S*)-(+)-2-(oleoyloxymethyl)oxirane (**1**; 0.338 g, 1.00 mmol) *via* **5**. Overall yield: 0.338 g (95%, calculated in relation to**1**); white solid; mp 34.5–36.0 °C (identical with that of a commercial sample from Fluka); R_f (pentane–toluene–EtOAc = 30 : 20 : 50, v/v/v) = 0.34; $[\alpha]_D^{20}$ = −1.32 (*c* 11.76, $CHCl_3$); found: C, 70.66; H, 11.40%. $C_{21}H_{40}O_4$ (356.54) requires C, 70.74; H, 11.31%. ^{1}H- and ^{13}C NMR spectra identical with those reported in the literature.[45]

3-Oleoyl-*sn*-glycerol 10. Obtained from (*R*)-(−)-2-(oleoyloxymethyl)oxirane (**2**; 0.338 g, 1.00 mmol) *via* **6**. Overall yield: 0.335 g (94%, calculated in relation to **2**). While all other physicochemical and spectral characteristics were identical with those of **9**, $[\alpha]_D^{20}$ = +1.28 (*c* 10.64, $CHCl_3$); $[\alpha]_D^{20} = -3.33$ (*c* 7.33, pyridine); lit.[59] $[\alpha]_D^{20}$ = −3.2 (*c* 5, pyridine).

1-*O*-Hexadecyl-*sn*-glycerol 11. Obtained from (*S*)-(+)-2-(hexadecyloxymethyl)oxirane (**3**; 0.299 g, 1.00 mmol) *via* **7**. Overall yield: 0.297 g (94%, calculated in relation to **3**); white solid; mp 62.9–63.9 °C; R_f (pentane–toluene–EtOAc = 30 : 20 : 50, v/v/v) = 0.26; $[\alpha]_D^{20} = -2.10$ (*c* 3.00, THF); lit.[63] mp 63.0–64.0 °C; $[\alpha]_D^{25}$ = −2.68 (*c* 3.5, THF); found: C, 72.00; H, 12.80%. $C_{19}H_{40}O_3$ (316.52) requires C, 72.10; H, 12.74%. ^{1}H- and ^{13}C NMR spectra identical with those reported in the literature.[45]

3-*O*-Hexadecyl-*sn*-glycerol 12. Obtained from (*R*)-(−)-2-(hexadecyloxymethyl)oxirane (**4**; 0.299 g, 1.00 mmol) *via* **8**. Overall yield: 0.291 g (92%, calculated in relation to **4**). Identical physicochemical and spectral characteristics as those of **11**. $[\alpha]_D^{20}$ = +2.72 (*c* 3.66, THF); lit.[63] $[\alpha]_D^{25}$ = +2.69 (*c* 3.5, THF).

General procedure for the one-pot, two-step synthesis of a common precursor of di- and triglycerides (13–18) [routes A (ii) and B]

Step A(ii). A mixture of pyridine (1.6 mL, 20 mmol) and methanol (20.2 mL, 500 mmol) in pentane–CH_2Cl_2 (3 : 1, v/v, 10.0 mL) was added at 0 °C to a solution of trifluoroacetate **5–8**

(2.00 mmol) in the same solvent system (10.0 mL). The reaction was left at room temperature for 20 min, and the solvents were evaporated under reduced pressure as described above.

Step B. The residue from the previous step (deprotected monoglyceride **9–12**) was dissolved in anhydrous THF (25.0 mL), and imidazole (0.817 g, 12.00 mmol) and a trialkylchlorosilane (*e.g.* TBDMS-Cl 0.392 g or TIPS-Cl 0.550 mL, 2.60 mmol) were added successively. The reaction mixture was stirred at room temperature for 18 h, the solvent was removed under reduced pressure and the target silyl ethers **13–18** were isolated by flash column silica gel chromatography (mobile phase: toluene–EtOAc = 95 : 5, v/v) with purity >99% (^{1}H NMR spectroscopy).

1-Oleoyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol 13. Acquired from 1-oleoyl-2,3-bis(trifluoroacetyl)-*sn*-glycerol (**5**; 1.097 g, 2.00 mmol) *via* **9**. Overall yield: 0.800 g (85%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.43; $[\alpha]_D^{20}$ = +1.76 (*c* 9.45, $CHCl_3$); found: C, 68.92; H, 11.50%. $C_{27}H_{54}O_4Si$ (470.80) requires C, 68.88; H, 11.56%.

1-*O*-*tert*-Butyldimethylsilyl-3-oleoyl-*sn*-glycerol 14. Obtained from 3-oleoyl-1,2-bis(trifluoroacetyl)-*sn*-glycerol (**6**; 1.097 g, 2.00 mmol) *via* **10**. Overall yield: 0.772 g (82%, colourless oil); $[\alpha]_D^{20}$ = −1.73 (*c* 9.63, $CHCl_3$). All other physicochemical and spectral characteristics were identical with those of **13**.

1-Oleoyl-3-*O*-triisopropylsilyl-*sn*-glycerol 15. Synthesized from 1-oleoyl-2,3-bis(trifluoroacetyl)-*sn*-glycerol (**5**; 1.097 g, 2.00 mmol) *via* **9**. Overall yield: 0.821 g (80%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.53; $[\alpha]_D^{20}$ = +1.39 (*c* 13.36, $CHCl_3$); found: C, 70.25; H, 11.63%. $C_{30}H_{60}O_4Si$ (512.88) requires C, 70.25; H, 11.79%.

1-*O*-Triisopropylsilyl-3-oleoyl-*sn*-glycerol 16. Acquired from 3-oleoyl-1,2-bis(trifluoroacetyl)-*sn*-glycerol (**6**; 1.097 g, 2.00 mmol) *via* **10**. Overall yield: 0.851 g (83%, colourless oil); $[\alpha]_D^{20}$ = −1.38 (*c* 10.17, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **15**.

1-*O*-Hexadecyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol 17. Prepared from 1-*O*-hexadecyl-2,3-bis(trifluoroacetyl)-*sn*-glycerol (**7**; 1.017 g, 2.00 mmol) *via* **11**. Overall yield: 0.732 g (85%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.47; $[\alpha]_D^{20}$ = +0.40 (*c* 12.97, $CHCl_3$); found: C, 69.93; H, 12.55%. $C_{25}H_{54}O_3Si$ (430.78) requires C, 69.70; H, 12.63%.

1-*O*-*tert*-Butyldimethylsilyl-3-*O*-hexadecyl-*sn*-glycerol 18. Synthesized from 3-*O*-hexadecyl-1,2-bis(trifluoroacetyl)-*sn*-glycerol (**8**; 1.017 g, 2.00 mmol) *via* **12**. Overall yield: 0.735 g (85%, colourless oil); $[\alpha]_D^{20}$ = −0.49 (*c* 8.66, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **17**.

General procedure for the synthesis of acylated C3-chirons bearing terminal *O*-silyl- (19–26) or 2-*O*-trichloroacetyl transient protection (27) (Scheme 4)

A solution of the corresponding acyl chloride (2.25 mmol) in dichloromethane was added at −20 °C to a mixture of monosilylated compound **13–18** (1.50 mmol) and pyridine (2.42 mL, 30.0 mmol) in the same solvent (10.0 mL). The reaction mixture was kept at room temperature for 2 h, the solvents were removed under reduced pressure and the required C3-synthons **19–23** or **25–27** were obtained after flash column silica gel chromatography (mobile phase: toluene–EtOAc = 95 : 5, v/v) with purity >99% (^{1}H NMR spectroscopy).

Similarly, the terminally-protected 2,3-DAG **24** was synthesized in two-steps by consecutive silylation and acylation of the commercially available 3-palmitoyl-*sn*-glycerol (Fluka) as described below.

1-Oleoyl-2-acetyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol 19. Obtained from 1-oleoyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol (**13**; 0.706 g, 1.50 mmol) and acetyl chloride (0.161 mL, 2.25 mmol). Yield: 0.723 g (94%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.62; $[\alpha]_D^{20}$ = +9.75 (*c* 11.05, $CHCl_3$); found: C, 67.88; H, 11.08%. $C_{29}H_{56}O_5Si$ (512.84) requires C, 67.92; H, 11.01%.

1-*O*-*tert*-Butyldimethylsilyl-2-acetyl-3-oleoyl-*sn*-glycerol 20. Acquired from 1-*O*-*tert*-butyldimethylsilyl-3-oleoyl-*sn*-glycerol (**14**; 0.706 g, 1.50 mmol) and acetyl chloride (0.161 mL, 2.25 mmol). Yield: 0.731 g (95%, colourless oil); $[\alpha]_D^{20}$ = −9.47 (*c* 9.90, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **19**.

1-Oleoyl-2-acetyl-3-*O*-triisopropylsilyl-*sn*-glycerol 21. Prepared from 1-oleoyl-3-*O*-triisopropylsilyl-*sn*-glycerol (**15**; 0.769 g, 1.50 mmol) and acetyl chloride (0.161 mL, 2.25 mmol). Yield: 0.766 g (92%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.61; $[\alpha]_D^{20}$ = +11.28 (*c* 9.87, $CHCl_3$); found: C, 69.20; H, 11.30%. $C_{32}H_{62}O_5Si$ (554.92) requires C, 69.26; H, 11.26%.

1-*O*-Triisopropylsilyl-2-acetyl-3-oleoyl-*sn*-glycerol 22. Synthesized from 1-*O*-triisopropylsilyl-3-oleoyl-*sn*-glycerol (**16**; 0.769 g, 1.50 mmol) and acetyl chloride (0.161 mL, 2.25 mmol). Yield: 0.774 g (93%, colourless oil); $[\alpha]_D^{20}$ = −11.81 (*c* 10.91, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **21**.

1,2-Dioleoyl-3-*O*-triisopropylsilyl-*sn*-glycerol 23. Obtained from 1-oleoyl-3-*O*-triisopropylsilyl-*sn*-glycerol (**15**; 0.769 g, 1.50 mmol) and oleoyl chloride (0.744 mL, 2.25 mmol). Yield: 1.084 g (93%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.83; $[\alpha]_D^{20}$ = +10.00 (*c* 10.12, $CHCl_3$); found: C, 74.23; H, 11.88%. $C_{48}H_{92}O_5Si$ (777.33) requires C, 74.17; H, 11.93%.

1-*O*-Triisopropylsilyl-2-oleoyl-3-palmitoyl-*sn*-glycerol 24. Prepared in two steps by silylation of 3-palmitoyl-*sn*-glycerol (0.661 g, 2.00 mmol) with triisopropylchlorosilane (0.550 mL, 2.60 mmol), identically to **16** (see General procedure 3.3), followed by acylation of the intermediary 1-*O*-triisopropylsilyl-3-palmitoyl-*sn*-glycerol with oleoyl chloride (0.661 mL, 2.00 mmol), as described for **23**. Overall yield: 1.097 g (73%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.63; $[\alpha]_D^{20}$ = −10.18 (*c* 9.31, $CHCl_3$); found: C, 73.60; H, 12.00%. $C_{46}H_{90}O_5Si$ (751.29) requires C, 73.54; H, 12.07%.

1-*O*-Hexadecyl-2-acetyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol 25. Obtained from 1-*O*-hexadecyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol (**17**; 0.646 g, 1.50 mmol) and acetyl chloride (0.161 mL, 2.25 mmol). Yield: 0.674 g (95%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.58; $[\alpha]_D^{20}$ = +4.51

(c 14.60, $CHCl_3$); found: C, 68.67; H, 11.87%. $C_{27}H_{56}O_4Si$ (472.82) requires C, 68.59; H, 11.94%.

1-*O*-*tert*-Butyldimethylsilyl-2-acetyl-3-*O*-hexadecyl-*sn*-glycerol 26. Acquired from 1-*O*-*tert*-butyldimethylsilyl-3-*O*-hexadecyl-*sn*-glycerol (**18**; 0.646 g, 1.50 mmol) and acetyl chloride (0.161 mL, 2.25 mmol). Yield: 0.659 g (93%, colourless oil); $[\alpha]_D^{20} = -5.00$ (c 8.83, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **25**.

1-Oleoyl-2-trichloroacetyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol 27. Synthesized from 1-oleoyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol (**13**; 0.706 g, 1.50 mmol) and trichloroacetyl chloride (0.252 mL, 2.25 mmol). Yield: 0.868 g (94%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.70; $[\alpha]_D^{20} = +11.87$ (c 10.26, $CHCl_3$); found: C, 56.67; H, 8.60; Cl, 17.30%. $C_{29}H_{53}Cl_3O_5Si$ (616.17) requires C, 56.53; H, 8.67; Cl, 17.26%.

General procedure for the direct conversion of silyl ethers 19, 22, 23, 25, and 26 into trichloroacetate educts of 1,2(2,3)-DAG (28–30) and 1(3)-AL-2-AG (31, 32) [route C (i)]

A mixture containing a silyl ether (**19**, **22**, **23**, **25**, or **26**; 1.00 mmol), neat trichloroacetic anhydride (TCAA, 1.644 ml, 9.00 mmol) and triethylamine tris(hydrofluoride) ($Et_3N{\cdot}3HF$, 0.326 ml, 2.00 mmol) was kept under argon, in a pressure-proof glass ampoule at 80 °C (bath temp.). After 2 h, the reaction mixture was diluted with toluene–ethyl acetate (98 : 2, v/v; 5 mL), and the target trichloroacetyl derivatives **28–32** were isolated in pure state (>99%, ^{1}H NMR spectroscopy) by flash column silica gel chromatography (mobile phase: toluene–EtOAc = 98 : 2, v/v).

1-Oleoyl-2-acetyl-3-trichloroacetyl-*sn*-glycerol 28. Obtained from 1-oleoyl-2-acetyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol (**19**; 0.513 g, 1.00 mmol). Yield: 0.506 g (93%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.56; $[\alpha]_D^{20} = -0.40$ (c 7.18, $CHCl_3$); found: C, 55.00; H, 7.70; Cl, 19.73%. $C_{25}H_{41}Cl_3O_6$ (543.95) requires C, 55.20; H, 7.60; Cl, 19.55%.

1-Trichloroacetyl-2-acetyl-3-oleoyl-*sn*-glycerol 29. Obtained from 1-*O*-triisopropylsilyl-2-acetyl-3-oleoyl-*sn*-glycerol (**22**; 0.555 g, 1.00 mmol). Yield: 0.489 g (90%, colourless oil); $[\alpha]_D^{20} = +0.42$ (c 9.47, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **28**.

1,2-Dioleoyl-3-trichloroacetyl-*sn*-glycerol 30. Obtained from 1,2-dioleoyl-3-*O*-triisopropylsilyl-*sn*-glycerol (**23**; 0.777 g, 1.00 mmol). Yield: 0.705 g (92%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.64; $[\alpha]_D^{20} = -0.21$ (c 5.33, $CHCl_3$); found: C, 64.20; H, 9.40; Cl, 13.90%. $C_{41}H_{71}Cl_3O_6$ (766.36) requires C, 64.26; H, 9.34; Cl, 13.88%.

1-*O*-Hexadecyl-2-acetyl-3-trichloroacetyl-*sn*-glycerol 31. Obtained from 1-*O*-hexadecyl-2-acetyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol (**25**; 0.473 g, 1.00 mmol). Yield: 0.464 g (92%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.54; $[\alpha]_D^{20} = -5.81$ (c 11.81, $CHCl_3$); found: C, 54.82; H, 8.27; Cl, 21.00%. $C_{23}H_{41}Cl_3O_5$ (503.93) requires C, 54.82; H, 8.20; Cl, 21.11%.

1-Trichloroacetyl-2-acetyl-3-*O*-hexadecyl-*sn*-glycerol 32. Obtained from 1-*O*-*tert*-butyldimethylsilyl-2-acetyl-3-*O*-hexadecyl-*sn*-glycerol (**26**; 0.473 g, 1.00 mmol). Yield: 0.470 g (93%, colourless oil); $[\alpha]_D^{20} = +6.00$ (c 5.44, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **31**.

General procedure for the direct conversion of silyl ethers 20, 21, 23, 24, and 27 into esters of short- or long-chain fatty acids to produce 1,3-DAG (33, 34) [route D (i)] or structured TAG (35–41) (route E)

A mixture of the appropriate carboxylic acid anhydride (3.00 mmol) and trimethylbromosilane (TMSBr; 0.195 mL; 1.50 mmol) in alcohol-free chloroform (2 mL) was added to a solution of silyl ether **20**, **21**, **23**, **24** or **27** (1.00 mmol) and tetra-*n*-butylammonium bromide (0.645 g; 2.00 mmol) (3.0 mL) in the same solvent (3.0 mL). The reaction mixture was kept under argon, in a pressure-proof glass ampoule at 80 °C (bath) for 2 h (reaction time for TIPS-derivatives: 15 h). Chloroform was removed under reduced pressure and the triglycerides **33–41** were isolated (purity >99%, ^{1}H NMR spectroscopy) by flash column chromatography (silica gel; mobile phase for **33**, **34**, **37–41**: toluene–EtOAc = 98 : 2, v/v; mobile phase for **35** and **36**: pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v).

1-Oleoyl-2-trichloroacetyl-3-acetyl-*sn*-glycerol 33. Obtained from 1-oleoyl-2-trichloroacetyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol (**27**; 0.616 g, 1.00 mmol) and acetic anhydride (0.284 mL, 3.00 mmol). Yield: 0.511 g (94%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.49; $[\alpha]_D^{20} = -0.68$ (c 9.77, $CHCl_3$); found: C, 55.30; H, 7.55; Cl, 19.47%. $C_{25}H_{41}Cl_3O_6$ (543.95) requires C, 55.20; H, 7.60; Cl, 19.55%.

1-Oleoyl-2-trichloroacetyl-3-palmitoyl-*sn*-glycerol 34. Obtained from 1-oleoyl-2-trichloroacetyl-3-*O*-*tert*-butyldimethylsilyl-*sn*-glycerol (**27**; 0.616 g, 1.00 mmol) and palmitic anhydride (1.484 g, 3.00 mmol). Yield: 0.711 g (96%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.58; $[\alpha]_D^{20} = 0.00$ (c 4.26, $CHCl_3$); found: C, 63.35; H, 9.50; Cl, 14.30%. $C_{39}H_{69}Cl_3O_6$ (740.32) requires C, 63.27; H, 9.39; Cl, 14.37%.

1,2-Diacetyl-3-oleoyl-*sn*-glycerol 35. Obtained from 1-*O*-*tert*-butyldimethylsilyl-2-acetyl-3-oleoyl-*sn*-glycerol (**20**; 0.513 g, 1.00 mmol) and acetic anhydride (0.284 mL, 3.00 mmol). Yield: 0.410 g (93%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.25; $[\alpha]_D^{20} = +1.23$ (c 10.83, $CHCl_3$); found: C, 68.08; H, 10.12%. $C_{25}H_{44}O_6$ (440.61) requires C, 68.15; H, 10.06%.

1-Oleoyl-2,3-diacetyl-*sn*-glycerol 36. Obtained from 1-oleoyl-2-acetyl-3-*O*-triisopropylsilyl-*sn*-glycerol (**21**; 0.555 g, 1.00 mmol) and acetic anhydride (0.284 mL, 3.00 mmol). Yield: 0.401 g (91%, colourless oil); $[\alpha]_D^{20} = -1.29$ (c 8.93, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **35**.

1-Oleoyl-2-acetyl-3-palmitoyl-*sn*-glycerol 37. Synthesized from 1-oleoyl-2-acetyl-3-*O*-triisopropylsilyl-*sn*-glycerol (**21**; 0.555 g, 1.00 mmol) and palmitic anhydride (1.484 g, 3.00 mmol). Yield: 0.611 g (96%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.57; $[\alpha]_D^{20} = 0.00$ (c 5.11, $CHCl_3$); found: C, 73.66; H, 11.20%. $C_{39}H_{72}O_6$ (636.98) requires C, 73.54; H, 11.39%.

1,2-Dioleoyl-3-acetyl-*sn*-glycerol 38. Acquired from 1,2-dioleoyl-3-*O*-triisopropylsilyl-*sn*-glycerol (**23**; 0.777 g, 1.00 mmol) and acetic anhydride (0.284 mL, 3.00 mmol). Yield: 0.603 g

(91%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.53; $[\alpha]_D^{20} = -0.68$ (*c* 7.60, $CHCl_3$); found: C, 74.22; H, 11.28%. $C_{41}H_{74}O_6$ (663.02) requires C, 74.27; H, 11.25%.

1,2,3-Trioleoyl glycerol 39. Obtained from 1,2-dioleoyl-3-*O*-triisopropylsilyl-*sn*-glycerol (**23**; 0.777 g, 1.00 mmol) and oleic anhydride (1.641 g, 3.00 mmol). Yield: 0.823 g (93%, colourless oil); R_f (pentane–EtOAc = 90 : 10, v/v) = 0.72; found: C, 77.37; H, 11.81%. $C_{57}H_{104}O_6$ (885.43) requires C, 77.32; H, 11.84%.

1-Acetyl-2-oleoyl-3-palmitoyl-*sn*-glycerol 40. Obtained from 1-*O*-triisopropylsilyl-2-oleoyl-3-palmitoyl-*sn*-glycerol (**24**; 0.751 g, 1.00 mmol) and acetic anhydride (0.284 mL, 3.00 mmol). Yield: 0.586 g (92%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.52; $[\alpha]_D^{20} = +0.72$ (*c* 11.73, $CHCl_3$); found: C, 73.57; H, 11.40%. $C_{39}H_{72}O_6$ (636.98) requires C, 73.54; H, 11.39%.

1,3-Dipalmitoyl-2-oleoyl glycerol 41. Obtained from 1-*O*-triisopropylsilyl-2-oleoyl-3-palmitoyl-*sn*-glycerol (**24**; 0.751 g, 1.00 mmol) and palmitic anhydride (1.484 g, 3.00 mmol). Yield: 0.775 g (93%); white solid: mp 37.4–38.0 °C; R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.56; lit.[28] mp 35.0–37.5 °C; found: C, 76.43; H, 12.04%. $C_{53}H_{100}O_6$ (833.36) requires C, 76.39; H, 12.09%.

General procedure for the preparation of 1,2(2,3)-diglycerides (42–46) [route C (ii)] and 1,3-DAG (47, 48) [route D (ii)] from the corresponding 2,2,2-trichloroacetyl isosters (28–34)

To a solution of **28–34** (1.00 mmol) in tetrahydofuran (5.0 mL), a mixture of pyridine (4.0 mL, 50 mmol) and methanol (20.3 mL, 500 mmol) was added and the reaction mixture was left at room temperature for 3 h. Solvents were evaporated under reduced pressure (bath temp. 50 °C) and the residue was kept under high vacuum at room temperature for 2–3 h to give the unprotected diglyceride **42–48** (purity >99%, ^{1}H NMR spectroscopy).

1-Oleoyl-2-acetyl-*sn*-glycerol 42. Acquired from 1-oleoyl-2-acetyl-3-trichloroacetyl-*sn*-glycerol (**28**; 0.544 g, 1.00 mmol). Yield: 0.398 g (100%, colourless oil); R_f (toluene–EtOAc = 80 : 20, v/v) = 0.24; $[\alpha]_D^{20} = -5.42$ (*c* 5.07, $CHCl_3$); found: C, 70.01; H, 10.60%. $C_{23}H_{42}O_5$ (398.58) requires C, 69.31; H, 10.62%.

2-Acetyl-3-oleoyl-*sn*-glycerol 43. Obtained from 1-trichloroacetyl-2-acetyl-3-oleoyl-*sn*-glycerol (**29**; 0.544 g, 1.00 mmol). Yield: 0.399 g (100%, colourless oil); $[\alpha]_D^{20} = +5.48$ (*c* 3.25, $CHCl_3$). All other physicochemical and spectral characteristics were identical with those of **42**.

1,2-Dioleoyl-*sn*-glycerol 44. Produced from 1,2-dioleoyl-3-trichloroacetyl-*sn*-glycerol (**30**; 0.766 g, 1.00 mmol). Yield: 0.621 g (100%, colourless oil); R_f (toluene–EtOAc = 80 : 20, v/v) = 0.50; $[\alpha]_D^{20} = -2.85$ (*c* 4.16, $CHCl_3$); lit.[92] $[\alpha]_D^{20} = -2.5$ (*c* 3.0, $CHCl_3$); found: C, 75.50; H, 11.66%. $C_{39}H_{72}O_5$ (620.99) requires C, 75.43; H, 11.69%.

1-*O*-Hexadecyl-2-acetyl-*sn*-glycerol 45. Synthesized from 1-*O*-hexadecyl-2-acetyl-3-trichloroacetyl-*sn*-glycerol (**31**; 0.504 g, 1.00 mmol). Yield: 0.359 g (100%); white solid, mp 35.5–36.0 °C (from pentane); R_f (toluene–EtOAc = 80 : 20, v/v) = 0.23; $[\alpha]_D^{20} = -5.44$ (*c* 2.39, $CHCl_3$); lit.[93] $[\alpha]_D^{20} = -11.1$ (*c* 0.4, $CHCl_3$); found: C, 70.51; H, 11.77%. $C_{21}H_{42}O_4$ (358.56) requires C, 70.34; H, 11.81%.

2-Acetyl-3-*O*-hexadecyl-*sn*-glycerol 46. Obtained from 1-trichloroacetyl-2-acetyl-3-*O*-hexadecyl-*sn*-glycerol (**32**; 0.504 g, 1.00 mmol). Yield: 0.359 g (100%, white solid); $[\alpha]_D^{20} = +5.98$ (*c* 2.08, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **45**.

1-Oleoyl-3-acetyl-*sn*-glycerol 47. Obtained from 1-oleoyl-2-trichloroacetyl-3-acetyl-*sn*-glycerol (**33**; 0.544 g, 1.00 mmol). Yield: 0.398 g (100%, colourless oil); R_f (toluene–EtOAc = 80 : 20, v/v) = 0.29; $[\alpha]_D^{20} = -0.28$ (*c* 9.15, $CHCl_3$); found: C, 69.19; H, 10.70%. $C_{23}H_{42}O_5$ (398.58) requires C, 69.31; H, 10.62%.

1-Oleoyl-3-palmitoyl-*sn*-glycerol 48. Produced from 1-oleoyl-2-trichloroacetyl-3-palmitoyl-*sn*-glycerol (**34**; 0.740 g, 1.00 mmol). Yield: 0.595 g (100%); white solid, mp 45.5–47.0 °C (from pentane); lit.[82] mp 45–46 °C; R_f (toluene–EtOAc = 80 : 20, v/v) = 0.52; found: C, 74.81; H, 11.80%. $C_{37}H_{70}O_5$ (594.95) requires C, 74.69; H, 11.86%.

General procedure for the one-pot, two-step synthesis of TAG (49–53) from their terminal- (28, 29) or 2-*O*-trichloroacetyl derivatives (33, 34) (route F)

Step (i). To a solution of trichloroacetate **28**, **29**, **33** or **34** (1.00 mmol) in tetrahydrofuran (5.0 mL), a mixture of pyridine (4.0 mL, 50 mmol) and methanol (20.3 mL, 500 mmol) was added and the reaction mixture was left at room temperature for 2–3 h. The solvents and volatile materials were removed under reduced pressure, and the resulting gum was subjected to acylation in the next step.

Step (ii). The residue containing the deprotected diacylglycerol species was dissolved in alcohol-free chloroform (10.0 mL) containing pyridine (1.61 mL, 20.0 mmol), and the mixture was treated at −20 °C with a solution of a requisite acyl chloride (2.00 mmol) in alcohol-free chloroform (10.0 mL). After keeping the reaction mixture at room temperature for 2 h, the solvents were removed under reduced pressure, dichloromethane (10.0 mL) was added and the solution was passed through a dichloromethane-filled aluminium oxide pad (~20 g), which was washed with the same solvent (~150 mL). Dichloromethane was removed under reduced pressure and the target triacylglycerols **50–53** were isolated in pure state (>99%, ^{1}H NMR spectroscopy) by flash column silica gel chromatography (mobile phase for **50**: pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v; mobile phase for **51–53**: toluene–EtOAc = 98 : 2, v/v).

The Mosher ester **49** of 1,3-DAG **47**, also representing a model triacylglycerol with a sterically hindered chiral substituent at the C2-position, was obtained in a similar way as described below.

1-Oleoyl-2-[*R*-(−)-α-methoxy-α-trifluoromethylphenylacetyl]-3-acetyl-*sn*-glycerol 49. The compound was prepared from 1-oleoyl-3-acetyl-*sn*-glycerol (**47**; 0.399 g, 1.00 mmol) and *R*-(−)-α-methoxy-α-trifluoromethylphenylacetyl chloride (0.224 mL, 1.20 mmol) at room temperature for 18 h according to the above general procedure with the exception that after removing the solvents, the residue was dissolved in toluene–ethyl acetate (98 : 2, v/v, 5 mL) and the solution was passed through a silica gel pad (~5 g) prepared in the same solvent system. The support was washed with this eluent (50 mL), fractions containing the product were combined and the solution was concentrated under

reduced pressure to afford the crude Mosher ester **49**, which was examined next by ^{1}H and ^{13}C NMR without further purification. Yield calcd for $C_{33}H_{49}F_3O_7$ (614.73): 0.553 g (90%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.45.

1-Oleoyl-2,3-diacetyl-*sn*-glycerol 50. Obtained from 1-oleoyl-2-acetyl-3-trichloroacetyl-*sn*-glycerol (**28**; 0.544 g, 1.00 mmol) *via* **42** and acetyl chloride (0.142 mL; 2.00 mmol). Overall yield: 0.418 g (95%, colourless oil); $[\alpha]_D^{20} = -1.25$ (*c* 9.33, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **35** and **36**.

1-Palmitoyl-2-acetyl-3-oleoyl-*sn*-glycerol 51. Synthesized from 1-trichloroacetyl-2-acetyl-3-oleoyl-*sn*-glycerol (**29**; 0.544 g; 1.00 mmol) *via* **43** and palmitoyl chloride (0.606 mL; 2.00 mmol). Overall yield: 0.598 g (94%, colourless oil); $[\alpha]_D^{20} = 0.00$ (*c* 8.69, $CHCl_3$). All other physicochemical and spectral characteristics were identical to those of **37**.

1-Oleoyl-2-palmitoyl-3-acetyl-*sn*-glycerol 52. Acquired from 1-oleoyl-2-trichloroacetyl-3-acetyl-*sn*-glycerol (**33**; 0.544 g, 1.00 mmol) *via* **47** and palmitoyl chloride (0.606 mL; 2.00 mmol). Yield: 0.580 g (91%, colourless oil); R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.55; $[\alpha]_D^{20} = -0.64$ (*c* 8.15, $CHCl_3$); found: C, 73.50; H, 11.31%. $C_{39}H_{72}O_6$ (636.98) requires C, 73.54; H, 11.39%.

1-Oleoyl-2,3-palmitoyl-*sn*-glycerol 53. Obtained from 1-oleoyl-2-trichloroacetyl-3-palmitoyl-*sn*-glycerol (**34**; 0.740 g; 1.00 mmol) *via* **48** and palmitoyl chloride (0.606 mL; 2.00 mmol). Yield: 0.758 g (91%); white solid, mp 34.0–35.0 °C; R_f (pentane–toluene–EtOAc = 40 : 50 : 10, v/v/v) = 0.54; $[\alpha]_D^{20} = 0.00$ (*c* 7.05, $CHCl_3$); lit.[28] mp 29.8–34.5 °C; found: C, 76.40; H, 12.12%. $C_{53}H_{100}O_6$ (833.36) requires C, 76.39; H, 12.09%.

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References and Notes

1 F. Philippoussis, C. Arguin, M. Fortin, A.-M. Steff and P. Hugo, *Immunol. Lett.*, 2002, **83**, 221–230; F. Philippoussis, E. Przybytkowski, M. Fortin, C. Arguin, S. V. Pande, A.-M. Steff and P. Hugo, *Cell Death Differ.*, 2001, **8**, 1103–1112; M. I. Tyler and M. E. H. Howden, *Naturwissenschaften*, 1985, **72**, 373–375; *Ether Lipids: Biochemical and Biomedical Aspects*, ed. H. K. Mangold, F. Paltauf, Academic Press, New York, 1983.
2 E. Oancea and T. Meyer, *Cell Death Differ.*, 1998, **95**, 307–318; K. Urata and N. Takaishi, *J. Am. Oil Chem. Soc.*, 1996, **73**, 819–830; A. H. Merrill, *Nutr. Rev.*, 1989, **47**, 161–169; N. Weber, *Prog. Biochem. Pharmacol.*, 1988, **22**, 48–57.
3 R. M. Bell and D. J. Burns, *J. Biol. Chem.*, 1991, **266**, 4661–4664.
4 D. P. Siegel, J. Banschbach, D. Alford, H. Ellens, L. J. Lis, P. J. Quinn, P. L. Yeagle and J. Bentz, *Biochemistry*, 1989, **28**, 3703–3709.
5 H. Kido, N. Fukussen, K. Ishidoh and N. Katunuma, *Biochem. Biophys. Res. Commun.*, 1986, **138**, 275–282.
6 J. Prades, S. S. Funari, P. V. Escriba and F. Barcelo, *J. Lipid Res.*, 2003, **44**, 1720–1727; G. S. Denyer, *Med. J. Aust.*, 2002, **176**(Suppl.), 109–110; E. Maury, N. C. Guerineau, C. Commingers, P. Mollard, M. C. Prevost and H. Chap, *FEBS Lett.*, 2000, **466**, 228–232.
7 Y. Iwasaki and T. Yamane, *J. Mol. Catal. B: Enzym.*, 2000, **10**, 129–140.
8 R. Haftendorn, G. Schwarze and R. Ulbrich-Hofmann, *Chem. Phys. Lipids*, 2000, **104**, 57–66; G. H. de Haas and L. M. van Deenen, *Biochim. Biophys. Acta*, 1964, **84**, 469–471; L. M. Van Deenen and G. H. De Haas, *Biochim. Biophys. Acta*, 1963, **70**, 538–553.
9 K. Parang, L. I. Wiebe and E. E. Knaus, *Curr. Med. Chem.*, 2000, **7**, 995–1039; D. W. Will and T. Brown, *Tetrahedron Lett.*, 1992, **33**, 2729–2732.
10 H. M. VonMinden, M. Morr, G. Milkereit, E. Heinz and V. Vill, *Chem. Phys. Lipids*, 2002, **114**, 55–80; P. Ferraboschi, D. Colombo, F. Compostella and S. Reza-Elahi, *Synlett*, 2001, **9**, 1379–1382.
11 N. M. Carballeira, *Prog. Lipid Res.*, 2002, **41**, 437–456.
12 F. Paltauf and A. Hermetter, *Prog. Lipid Res.*, 1994, **33**, 239–328.
13 B. T. Golding, A. L. Griffin and D. H. Robinson, *Tetrahedron Lett.*, 1993, **34**, 6459–6462.
14 H. Eibl and P. Woolley, *Chem. Phys. Lipids*, 1988, **47**, 47–53.
15 D. Frense, R. Haftendorn and R. Ulbrich-Hofmann, *Chem. Phys. Lipids*, 1995, **78**, 81–87; T. Kunitake, Y. Okahata and S. I. Tawaki, *J. Colloid Interface Sci.*, 1984, **103**, 190–201.
16 V. E. Marquez, K. Nacro, S. Benzaria, J. Lee, R. Sharma, K. Teng, G. W. A. Milne, B. Bienfait, S. Wang, N. E. Lewin and P. M. Blumberg, *Pharmacol. Ther.*, 1999, **82**, 251–261; E. L. Arrese and M. A. Wells, *J. Lipid Res.*, 1997, **38**, 68–76; A. Brohult, J. Brohult and S. Brohult, *Experientia*, 1973, **29**, 81–82.
17 S. J. Slater, J. L. Seiz, B. A. Stagliano, A. C. Cook, S. K. Milano, C. Ho and C. D. Stubbs, *Biochemistry*, 2001, **40**, 6085–6092.
18 J. P. Weichert, M. A. Longino, D. A. Bakan, M. G. Spigarelli, T. Chou, S. W. Schwendner and R. E. Counsell, *J. Med. Chem.*, 1995, **38**, 636–646.
19 B. Gallez, R. Demeure, R. Debuyst, D. Leonard, F. Dejehet and P. Dumont, *Magn. Reson. Imaging*, 1992, **10**, 445–455.
20 D. M. Lambert, L. Neuvens, F. Mergen, B. Gallez, J. H. Poupaert, J. Ghyselburton, J. M. Maloteaux and P. Dumont, *J. Pharm. Pharmacol.*, 1993, **45**, 186–191; G. Y. Paris, D. L. Garmaise, D. G. Cimon, L. Swett, G. W. Carter and P. Young, *J. Med. Chem.*, 1979, **22**, 683–687.
21 G. Y. Paris, D. L. Garmaise, D. G. Cimon, L. Swett, G. W. Carter and P. Young, *J. Med. Chem.*, 1980, **23**, 9–13.
22 H. Houte, V. Partali, H.-R. Sliwka and E. G. K. Quartey, *Chem. Phys. Lipids*, 2000, **105**, 105–113.
23 J. A. Boomer and D. H. Thompson, *Chem. Phys. Lipids*, 1999, **99**, 145–153; A. Chonn and P. R. Cullis, *Adv. Drug Delivery Rev.*, 1998, **30**, 73–83.
24 O. V. Gerasimov, Y. Rui and D. H. Thompson, *Surfactant Sci. Ser.*, 1996, **62**, 679–746.
25 W. Srisiri, H. G. Lamparski and D. F. O'Brien, *J. Org. Chem.*, 1996, **61**, 5911–5915; W. Srisiri, Y. S. Lee and D. F. O'Brien, *Tetrahedron Lett.*, 1995, **36**, 8945–8948; N. Hebert, A. Beck, R. B. Lennox and G. Just, *J. Org. Chem.*, 1992, **57**, 1777–1783; S. F. Martin and J. A. Josey, *Tetrahedron Lett.*, 1988, **29**, 3631–3634.
26 S. F. Martin, J. A. Josey, Y. L. Wong and D. W. Dean, *J. Org. Chem.*, 1994, **59**, 4805–4820.
27 H.-S. Byun and R. Bittman, *Tetrahedron Lett.*, 1989, **30**, 2751–2754; Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. H. M. Ko and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765–5780.
28 L. Hartman, *Chem. Rev.*, 1958, **58**, 845–867.
29 F. S. Roodsari, D. Wu, G. S. Pum and J. Hajdu, *J. Org. Chem.*, 1999, **64**, 7727–7737.
30 D. R. Kodali and R. I. Duclos, *Chem. Phys. Lipids*, 1992, **61**, 169–173; C. M. Lok, *Chem. Phys. Lipids*, 1978, **22**, 323–337.
31 B. J. Sjursnes and B. Anthonsen, *Biocatalysis*, 1994, **9**, 285–297.
32 P. E. Sonnett and R. L. Dudley, *Chem. Phys. Lipids*, 1994, **72**, 185–191.
33 D. R. Kodali, A. Tercyak, D. A. Fahey and D. M. Small, *Chem. Phys. Lipids*, 1990, **52**, 163–170.
34 B. Serdarevich, *J. Am. Oil Chem. Soc.*, 1967, **44**, 381–393.
35 F. H. Mattson and R. A. Volpenhein, *J. Lipid Res.*, 1962, **3**, 281–296; J. B. Martin, *J. Am. Chem. Soc.*, 1953, **75**, 5483–5486.
36 *Antioxidants in food (practical applications)*, ed. J. Pokorny, N. Yanishlieva and M. Gordon, Woodhead Publishing Ltd. and CRC Press LLC, Cambridge, England, 2001.
37 P. R. J. Gaffney and C. B. Reese, *Tetrahedron Lett.*, 1997, **38**, 2539–2542.
38 G. H. Dodd, B. T. Golding and P. V. Ioannou, *J. Chem. Soc., Chem. Commun.*, 1975, 249–250.
39 D. Buchnea, *Lipids*, 1974, **9**, 55–57.
40 S. Bhattacharya and A. Bajaj, *Curr. Opin. Chem. Biol.*, 2005, **9**, 647–655.
41 L. M. Strawn, R. E. Martell, R. U. Simpson, K. L. Leach and R. E. Counsell, *J. Med. Chem.*, 1989, **32**, 2104–2110.

42 F. Marguet, J.-F. Cavalier, R. Verger and G. Buono, *Eur. J. Org. Chem.*, 1999, 1671–1678.
43 A. B. Kazi, S. Shidmand and J. Hajdu, *J. Org. Chem.*, 1999, **64**, 9337–9347.
44 H. Eibl and P. Woolley, *Chem. Phys. Lipids*, 1986, **41**, 53–63.
45 S. D. Stamatov and J. Stawinski, *Tetrahedron Lett.*, 2005, **46**, 1601–1605.
46 S. D. Stamatov, M. Kullberg and J. Stawinski, *Tetrahedron Lett.*, 2005, **46**, 6855–6859.
47 S. D. Stamatov and J. Stawinski, *Synlett*, 2005, 2587–2590.
48 T. Murase, T. Hase, I. Tokimitsu, Jp Patent: 2001354558, CAN 136:48454, 2001; N. Ikegawa, T. Ikegawa, Jp Patent 02247125, CAN 114:157190, 1990; A. Kadota, Jp Patent: 61191619, CAN 106:72911, 1986; S. M. Innis, R. Dyer and C. M. Nelson, *Lipids*, 1994, **29**, 541–545.
49 S.-Y. Han, S.-H. Cho, S.-Y. Kim, J.-T. Seo, S.-J. Moon and G.-J. Jhon, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 59–64.
50 C. A. A. van Boeckel, G. A. van der Marel, P. Westerduin and J. H. van Boom, *Synthesis*, 1982, 399–402.
51 L. Mannina, C. Luchinat, M. Patumi, M.-C. Emanuele, E. Rossi and A. Segre, *Magn. Reson. Chem.*, 2000, **38**, 886–890; G. Vlahov, *Magn. Reson. Chem.*, 1998, **36**, 359–362; M. M. Bergana and T. W. Lee, *J. Am. Oil Chem. Soc.*, 1996, **73**, 551–556.
52 For example, (i) 1,2-diacetyl-3-oleoyl- (**35**), the CH_3CO group at the 1-*sn* position: $\delta_H = 2.06$ ppm and $\delta_C = 20.89$ & 170.69 ppm; at the 2-*sn* position: $\delta_H = 2.07$ ppm and $\delta_C = 21.09$ & 170.28 ppm; (ii) 1-oleoyl-2-acetyl-3-palmitoyl- (**37**), the CH_3CO group at the 2-*sn* position: $\delta_H = 2.07$ ppm and $\delta_C = 21.09$ & 170.28 ppm; (iii) 1-acetyl-2-oleoyl-3-palmitoyl-*sn*-glycerol- (**40**), the CH_3CO group at the 1-*sn* position: $\delta_H = 2.06$ ppm and $\delta_C = 20.90$& 170.68 ppm.
53 R. O. Adlof and G. R. List, *J. Agric. Food Chem.*, 2003, **51**, 2096–2099.
54 F. Turon, F. Bonnot, Y. Caro, M. Pina and J. Graille, *Chem. Phys. Lipids*, 2003, **125**, 41–48; J. J. Myher, A. Kuksis, K. Geher, P. W. Park and D. A. Diersen-Schade, *Lipids*, 1996, **31**, 207–215; J. D. Baty and N. W. Rawle, *J. Chromatogr.*, 1987, **395**, 395–402.
55 P. Villeneuve, M. Pina, D. Montet, G. Renard and J. Graille, *Chem. Phys. Lipids*, 1994, **72**, 135–141.
56 For example, (i) 1-oleoyl-2-acetyl- (**42**), the acetyl group: $\delta_H = 2.10$ ppm and $\delta_C = 21.21$ & 170.78 ppm; the glycerol fragment C1: $\delta_H = 5.06$ ppm, (CHOAc) and $\delta_C = 72.58$ ppm, C2; (ii) 1-oleoyl-3-acetyl-*sn*-glycerol- (**47**), the acetyl group $\delta_H = 2.09$ ppm and $\delta_C = 20.99$ & 171.26 ppm; the glycerol fragment C2: $\delta_H = 4.04$ ppm (CHOH) and $\delta_C = 68.49$ ppm.
57 For example, (i) 1-oleoyl-*sn*-glycerol- (**9**), the glycerol fragment: $\delta_H = 3.93$ ppm (CHOH) and $\delta_C = 70.48$ ppm; (ii) a reference compound, 2-oleoylglycerol, the glycerol fragment: $\delta_H = 4.92$ ppm (CHOCOR) and $\delta_C = 75.22$ ppm.
58 D. R. Kodali, T. G. Redgrave, D. M. Small and D. Atkinson, *Biochemistry*, 1985, **24**, 519–525; L. Hartman, *J. Chem. Soc.*, 1959, 4134–4135; E. Baer and H. O. L. Fisher, *J. Am. Chem. Soc.*, 1945, **67**, 2031–2037.
59 D. R. Kodali, *J. Lipid Res.*, 1987, **28**, 464–469.
60 S. Murgia, F. Caboi, M. Monduzzi, H. Ljusberg-Wahren and T. Nylander, *Prog. Colloid Polym. Sci.*, 2002, **120**, 41–46; B. G. Sempore and J. A. Bezard, *J. Liq. Chromatogr.*, 1994, **17**, 1679–1694; A. E. I. Thomas, J. E. Scharoun and H. Ralston, *J. Am. Oil Chem. Soc.*, 1965, **42**, 789–792.
61 R. G. Jensen and R. A. Ferraina, *J. Am. Oil Chem. Soc.*, 1989, **65**, 135–136; J. D. Pollack, D. S. Clark and N. L. Somerson, *J. Lipid Res.*, 1971, **12**, 563–569.
62 C. E. Burgos, D. E. Ayer and R. A. Johnson, *J. Org. Chem.*, 1987, **52**, 4973–4977.
63 P. N. Guivisdalsky and R. Bittman, *J. Org. Chem.*, 1989, **54**, 4637–4642.
64 S. Y. Ko and B. Sharpless, *J. Org. Chem.*, 1986, **51**, 5413–5415.
65 J.-L. Gras and J.-F. Bonfanti, *Synlett*, 2000, 248–250.
66 S. D. Stamatov and J. Stawinski, *Tetrahedron Lett.*, 2002, **43**, 1759–1761.
67 S. D. Stamatov and J. Stawinski, *Tetrahedron*, 2005, **61**, 3659–3669.
68 A. Froling, H. J. J. Pabon and J. P. Ward, *Chem. Phys. Lipids*, 1984, **36**, 29–38.
69 J. E. Browne, R. T. Freeman, J. C. Russell and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 2000, 645–652; A. Hermetter and F. Paltauf, *Chem. Phys. Lipids*, 1981, **29**, 191–195.
70 F. R. Pfeiffer, C. K. Miao and J. A. Weisbach, *J. Org. Chem.*, 1970, **35**, 221–224.
71 M. Lalonde and T. H. Chan, *Synthesis*, 1985, 817–845.
72 J. Xia and Y.-Z. Hui, *Tetrahedron: Asymmetry*, 1997, **8**, 3131–3142.
73 W.-H. Leung, T. K. T. Wong, J. C. H. Tran and L.-L. Yeung, *Synlett*, 2000, 677–679.
74 J. S. Bajwa, J. Vivelo, J. Slade, O. Repic and T. Blacklock, *Tetrahedron Lett.*, 2000, **41**, 6021–6024; W. Zhang and M. J. Robins, *Tetrahedron Lett.*, 1992, **33**, 1177–1180.
75 S. J. Danishefsky and N. Mantlo, *J. Am. Chem. Soc.*, 1988, **110**, 8129–8133; B. Ganem and V. R. Small, *J. Org. Chem.*, 1974, **39**, 3728–3730.
76 E.-F. Fuchs and J. Lehmann, *Chem. Ber.*, 1974, **107**, 721–724.
77 S. Kim and W. J. Lee, *Synth. Commun.*, 1986, **16**, 659–665.
78 T. Oriyama, M. Oda, J. Gono and G. Koga, *Tetrahedron Lett.*, 1994, **35**, 2027–2030.
79 A. Patra and S. K. Chaudhuri, *J. Indian Chem. Soc.*, 1988, **65**, 367–368; A. Garzon-Aburbeh, J. H. Poupaert, M. Claesen and P. Dumont, *J. Med. Chem.*, 1986, **29**, 687–691; A. Garzon-Aburbeh, J. H. Poupaert, M. Claesen, P. Dumont and G. Atassi, *J. Med. Chem.*, 1983, **26**, 1200–1203; G. Y. Paris, D. L. Garmaise, D. G. Cimon, L. Swett, G. W. Carter and P. Young, *J. Med. Chem.*, 1980, **23**, 79–82.
80 P. H. Bentley and W. McCrae, *J. Org. Chem.*, 1970, **35**, 2082–2083.
81 C. Waldinger and M. Schneider, *J. Am. Oil Chem. Soc.*, 1996, **73**, 1513–1519.
82 C. M. Lok, J. P. Ward and D. A. van Dorp, *Chem. Phys. Lipids*, 1976, **16**, 115–122.
83 W. T. M. de Groot, C. M. Lok and J. P. Ward, *Chem. Phys. Lipids*, 1988, **47**, 75–80.
84 C. M. Lok, A. P. J. Mank and J. P. Ward, *Chem. Phys. Lipids*, 1985, **36**, 329–334.
85 A. P. J. Mank, J. P. Ward and D. A. VanDorp, *Chem. Phys. Lipids*, 1976, **16**, 107–114.
86 I. Ikeda, X. P. Gu, I. Miyamoto and M. Okahara, *J. Am. Oil Chem. Soc.*, 1989, **66**, 822–824.
87 T. Naalsund, K. E. Malterud, V. Partali and H.-R. Sliwka, *Chem. Phys. Lipids*, 2001, **112**, 59–65; J.-L. Gras and J.-F. Bonfanti, *Synlett*, 1999, 1835–1837; A. Bhati, R. J. Hamilton, D. A. Steven, R. Aneja and F. B. Padley, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1553–1558; J.-P. Carreau, *Bull. Soc. Chim. Fr.*, 1970, **11**, 4111–4114.
88 P. E. Sonnet, *Chem. Phys. Lipids*, 1991, **58**, 35–39.
89 *Purification of Laboratory Chemicals*, ed. D. D. Perrin, W. L. F. Armarego, Pergamon Press, New York, 1988.
90 H. M. Weiss and K. M. Touchette, *J. Chem. Soc., Perkin Trans. 2*, 1998, 1517–1522.
91 R. Bittman, H.-S. Byun, B. Mercier and H. Salari, *J. Med. Chem.*, 1994, **37**, 425–430.
92 S. Rakhit, J. F. Bagli and R. Deghenghi, *Can. J. Chem.*, 1969, **47**, 2906–2910.
93 D.-S. Wang, A.-L. Hsu and C.-S. Chen, *Bioorg. Med. Chem.*, 2001, **9**, 133–139.

