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Tetrahedron
Tetrahedron 61 (2005) 3659–3669

# Regioselective opening of an oxirane system with trifluoroacetic anhydride. A general method for the synthesis of 2-monoacyl- and 1,3-symmetrical triacylglycerols

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Received 10 November 2004; revised 10 February 2005; accepted 11 February 2005

**Abstract**—A trifluoroacetic anhydride-catalyzed opening of the oxirane system of glycidyl esters with a simultaneous migration of the acyl group provides a new, efficient entry to either 2-monoacylglycerols (2-MAG) or 1,3-symmetrical triglycerides (1,3-STG) as potential prodrug frameworks.


## 1. Introduction

2-Monoacylglycerols (Fig. 1) have recently attracted research interest as unique carriers of fatty acids through intestinal mucosa,[1,2] as metabolic precursors of structured triglycerides having particular fatty acid residues at 2-position in the glycerol backbone[2] as well as biomolecules of importance to human nutrition.[3] Moreover, it was found[4] that a homologue from the same class of lipid mediators, namely 2-arachidonoylglycerol (2-AG), might be an intrinsic, natural ligand for central and peripheral cannabinoid receptors (CB1 and CB2), which had previously been identified as specific targets for a major psychoactive ingredient of marijuana, $\delta^9$-tetrahydrocannabinol. Other 2-MAG, bearing linoleoyl- or palmitoyl fragments, have been suggested 'entourage' co-factors for enhancing the endogenous cannabinoid potential of 2-AG.[5]

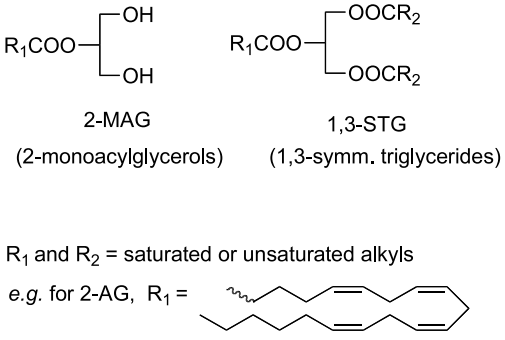


**Figure 1.** Structures of 2-MAG and 1,3-STG.

Complementary to their dual function as carrier molecules and biological effectors per se, 2-monoacylglycerols could be an attractive alternative of the currently employed 1,3-diacylglycerols as key-intermediates in the rational design of prodrugs representing symmetrically substituted 1,3-diacyl isosters of 2-MAG with requisite pharmaceutical moieties at the incipient glycerol 2-position.[2,6] In view of their resemblance to endogenous triglycerides, such a type of micromolecular vectors have already been used in order to confer various drugs to the metabolic pathways of natural lipids thus achieving therapeutic indices better than those of the starting substances (e.g., higher oral bioavailability, reduced ulcerogenity, first-pass metabolism resistance, etc.).[7] Also, 1,3-symmetrical triglycerides have founding interesting applications (e.g., in enzymatic synthesis of structurally modified lipids,[2] molecular modeling,[8] analytical studies,[9] etc.), but the potential of these conjugates has not been exploited to any significant extent due to unsatisfactory efficacy of the known methods of their preparation (e.g., multistep reaction sequences, lengthy isolation and purification steps, etc.).[9,10]

In spite of high demand for isomerically pure 2-MAG for biological studies or as starting material in the synthesis of

*Keywords*: 2-Monoacylglycerols; 2-Arachidonoylglycerol; Glycidyl arachidonate; Acyl migration; 1,3-Symmetrical triacylglycerols; Prodrugs.
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0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.02.034

other lipid derivatives, these compounds are often isolated from natural sources,[11] as chemical[12] and enzymatic methods[13] for their preparations are rather inefficient.

Searching for an alternative methodology that would circumvent shortcomings in the present methods of chemical synthesis of 2-monoacylglycerols, in this paper we describe an efficient and highly regioselective transformation of glycidyl esters **1**–**7** into 2-acyl-1,3-bis(trifluoroacetyl)glycerol derivatives **8**–**14** (Chart 1), from which 2-monoacylglycerols **15**–**21** can be obtained directly without recourse to any additional purification techniques whatsoever.[14] One can also envisage triglycerides **8**–**14** as convenient storage forms of 2-MAG (protection of 1- and 3-hydroxyl groups as trifluoroacetyl esters should prevent scrambling of the acyl moiety) or starting material for the preparation of other lipid mediators, for example, 1,3-STG **22**–**26**.

## 2. Results and discussion

There are two problems that make synthesis of 2-MAG most difficult. First, due to the presence of two adjacent primary hydroxyl functions, 2-monoacylglycerols show high propensity towards isomerisation (acid, base and heat promoted migration of an acyl group)[15] and this poses severe limitations in the choice of synthetic methods as well as means of their isolation, storage, etc. Secondly, a problem specific to 2-MAG with polyunsaturated systems is the pronounced susceptibility to autoxidation affecting integrity of the corresponding, native olefinic system that further reducing the number of available procedures for their preparation.

In this context, 2-AG is probably the most typical synthetic target to which similar acute complications seem to be inherent. Two chemical methods described in literature for the synthesis of this compound are based on the same chemistry: acylation of suitable 1,3-protected glycerol precursors with an arachidonic acid derivative, followed by deprotection and separation of the isomeric arachidonoylglycerols. In the original method developed by Martin[16] and its two most recent modifications,[12,17] 1,3-benzylideneglycerol is used as a substrate and, after introduction of the arachidonoyl moiety, the acetal group is removed using boric acid derivatives. In the other approach,[18] triisopropylsilyl (TIPS) groups are employed for the protection of 1-and 3-hydroxyl functions of glycerol and their removal from 1,3-bissilyl-2-arachidonoyl intermediate is effected by a prolonged treatment with tetra-*n*-butylammonium fluoride (TBAF) and acetic acid at low temperature. The use of 1,3-dibenzyloxy-2-propanol as starting material and β-chlorocatecholborane as a reagent for cleavage of the benzyl group are the latest improvements which do not affect the core of the same strategy.[19]

One should note that these methods provide only fragmentary solution to synthetic drawbacks, for example, extended reaction time, acidic or basic conditions required for the removal of protecting groups, necessity for an aqueous workup after each synthetic step or separation of the intermediates from the accompanying by-products etc, that have frequently been reported to contribute to isomerisation and oxidative or hydrolytic side-reactions during the synthesis of 2-MAGs. To lessen the problem of acyl migrations, in these synthetic procedures, the deprotection steps were either not taken to completion,[18] or the produced isomeric compounds were separated by various chromatographic techniques.[12,18,19] Although useful in general sense, the above approaches have not been evaluated on substances with other structural variations, and thus scope and generality of these methods are unclear.

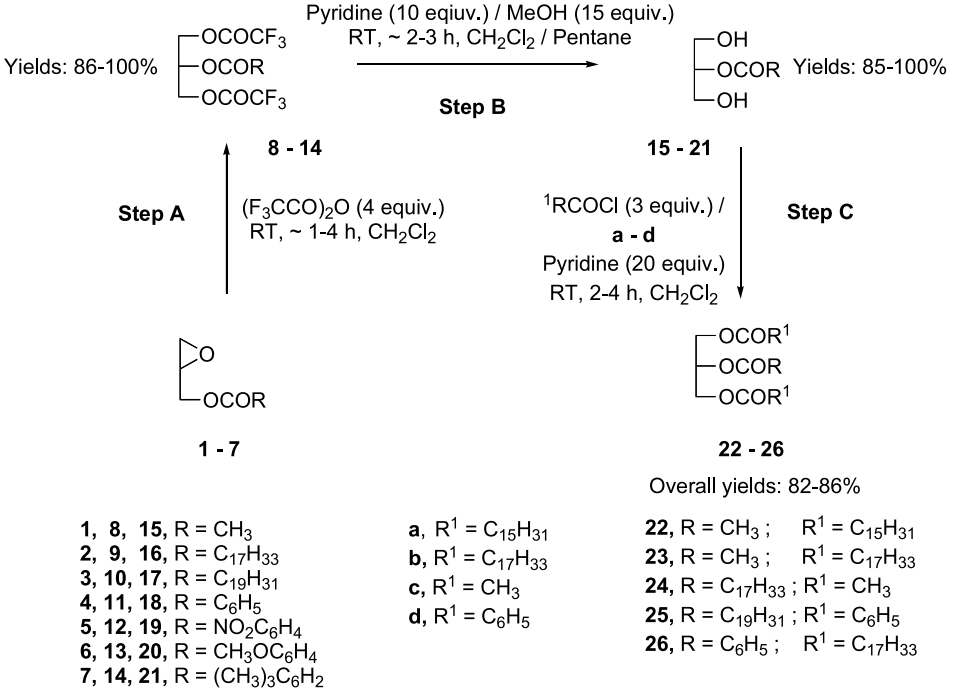



**Chart 1.**

In these studies, therefore, we adopted another strategy and investigated the regioselectivity of a trifluoroacetic anhydride-catalyzed opening of the oxirane system[14] of glycidyl esters **1**–**7** to produce the corresponding 1,3-bis(trifluoroacetyl)-2-acylglycerols as a novel approach to the synthesis of 2-monoacylglycerols (2-MAG) and also 1,3-symmetrical triglycerides (1,3-STG).

The starting materials were chosen to include model substrates bearing bioactive acyl fragments[4,11,18,20,21] with variable chain length and different degree of unsaturation in the acyl moiety [e.g., 2-(acetyloxymethyl)oxirane **1**, 2-(oleoyloxymethyl)oxirane **2**, and 2-(arachidonoyloxymethyl)oxirane **3**] or aromatic acyl residues with electron-withdrawing and electron-donating groups, and with different steric requirements [e.g., 2-(benzoyloxymethyl)-oxirane **4**, 2-(4-nitrobenzoyloxymethyl)oxirane **5**, and 2-(4-methoxybenzoyloxymethyl)oxirane **6**, and 2-(2,4,6-trimethylbenzoyloxymethyl)-oxirane **7**] (see Chart 1). The choice of palmitoyl **a**, oleoyl **b**, acetyl **c**, and benzoyl **d** chlorides as acylating agents was justified by accessibility of these compounds and their common use in the synthesis of acyl bioconjugates based on glycerol chemistry.[7,21]

At first, the ring-opening of glycidyl esters **1**–**7** with TFAA to produce triacylglycerols **8**–**14** was investigated under various experimental conditions (type of solvents, ratio of reactants, temperature; Chart 1, Step A). The best results were obtained when glycidol derivatives **1**–**7** were allowed to react with TFAA (4 equiv) in $CH_2Cl_2$ at rt for 1–4 h. The rate of the epoxide opening in **1**–**7** was not appreciably affected by electronic and structural features of the acyl group present and the reactions usually were complete within 1 h. The only exception was 2-(4-nitrobenzoyloxymethyl)oxirane **5** whose conversion to **12** required ca. 4 h. $^1H$ and $^{13}C$ NMR analysis revealed that under the investigated reaction conditions the conversion of **1**–**7** to 1,3-bis(trifluoroacetyl)-2-acylglycerols **8**–**14** did not involve any detectable intermediates, and it was quantitative and completely regioselective (>99%). The produced bis(trifluoroacetyl) derivatives **8**–**14** could thus be either directly used for a subsequent reactions, or isolated (~86–96% yields, see Section 3) and stored for several months (−20 °C, under argon) without detectable alterations of their spectral characteristics ($^1H$ and $^{13}C$ NMR spectroscopy).

Since trifluoroacetate esters are known to undergo smooth transesterification with alcohols,[18] as the next step of this synthetic protocol trifluoroacetyl-conjugates **8**–**14** in pentane–$CH_2Cl_2$ were treated with methanol (15 equiv) in the presence of pyridine (10 equiv) (Chart 1, Step B). The reaction was quantitative (completion within 2–3 h) and after removal of volatile products via evaporation, isomerically homogenous 2-monoacylglycerols **15**–**21** (purity >99%, $^1H$ and $^{13}C$ NMR spectroscopy) were obtained in 85–99% overall yields (calculated on **1**–**7**) without any additional purification.

Due to high purity of the monoacylglycerols **15**–**21** produced, these could be directly used for the acylation to afford 1,3-symmetrical triacylglycerols **22**–**26** (Chart 1, Step C) To this end, 2-monoacylglycerols **15**–**18** in dichloromethane were treated with acyl chlorides **a**–**d** (3 equiv) in the presence of pyridine (20 equiv).

Under these conditions, the acylation proceeded without detectable acyl migration[22] and was complete within 2–4 h to give the target products, triglycerides **22**–**26**, in consistently high overall yields (82–86% after silica gel chromatography, see Section 3).

Regarding a possible mechanism for the regioselective epoxide opening, some additional observations are pertinent. Thus, in preliminary model experiments it was established that in methylene chloride at rt other carboxylic anhydrides (e.g., acetic-, benzoic anhydride, etc) were completely unreactive and only trichloroacetic anhydride could act in a similar way as TFAA to give regioselectively the isosteric 1,3-bis(trichloroacetates), although in a significantly slower reaction (ca. 24 h for the completion). The use of trifluoroacetic acid alone afforded variable proportions of 1-acyl- and 2-acyl glycerols under the same conditions. Additional studies (Table 1) revealed that the oxirane system became extremely resistant towards TFAA when the acyl group was replaced by an alkyl one (entry 1). Synthons from the traditional pool of acylated glycerol acetals (e.g., entries 2 and 3) remained unaffected under the same conditions, as well.

In all instances where mixtures of TFAA with up to three equivalent excess of non-halogenated carboxylic acids or carboxylic anhydrides were used, 1,3-bis(trifluoroacetyl)-2-acylglycerols were still formed as the only products of the reaction (e.g., entries 4 and 5).

Organic bases were shown to completely inhibit the epoxide opening, irrespective of their potential to act as nucleophiles or base catalysts, despite the presence of excess TFAA in the reaction mixtures (entries 6, 8–10). All these reactions could be rescued by the addition of trifluoroacetic acid providing the expected products (entry 7). A similar effect was observed for the reaction using tetrabutylammonium trifluoroacetate with TFAA (entry 11).

These data are consistent with a mechanism depicted in Scheme 1, which involves initial coordination of the epoxide oxygen by a strongly electrophilic TFAA, followed by the opening of the activated oxirane ring via an intramolecular attack of the adjacent carbonyl group to form cyclic acyliumglycerol cation **A**. This is apparently the rate-determining step of the reaction as opening of the oxirane ring does not occur under these conditions without assistance of the neighbouring carbonyl group. The produced acylium ion **A** then collapses in a fast reaction to the corresponding 1,3-bis(trifluoroacetyl)-2-acylglycerol by a regioselective attack of a trifluoroacetate ion on the primary carbon atom of the dioxolane ring.

A mechanism by which amines inhibit this reaction is not clear. It is possible that acid catalysis by traces of trifluoroacetic acid most likely present in the reaction mixture is essential for the formation of cyclic intermediate **A**, for example, to facilitate the departure of trifluoroacetoxy group during opening of the oxirane ring. An

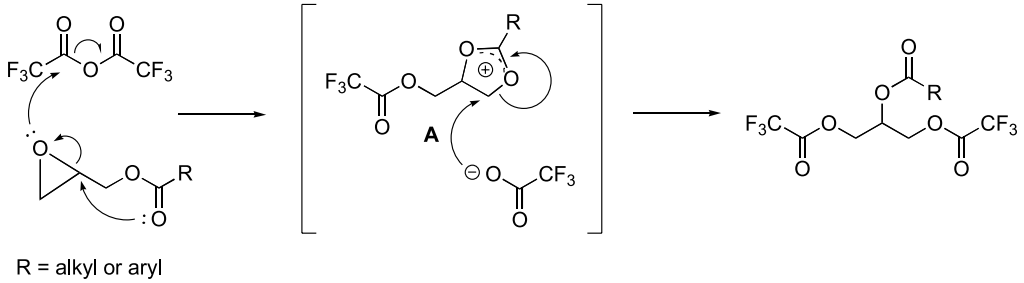
**Table 1**. Mechanistic studies

| No. | Reaction conditions: methylene chloride, rt | Reaction time (remarks) |
|---|---|---|
| 1. | TFAA (4.0 eq) → No reaction | rt/24 h |
| 2. | TFAA (4.0 eq) → No reaction | rt/24 h |
| 3. | TFAA (4.0 eq) → No reaction | rt/24 h |
| 4. | TFAA (4.0 eq), $^1$RCOOH (3.0 eq) | rt/∼4 h (quantitative yield) |
| 5. | TFAA (4.0 eq), ($^1$RCO)$_2$O (4.0 eq) | rt/∼4 h (quantitative yield) |
| 6. | Py (1.0 eq) / TFAA (4.0 eq) → No reaction | 80 °C/∼4 h |
| 7. | Py (1.0 eq) / TFAA (4.0 eq) / $F_3CCOOH$ / (2.0 eq) | rt/∼4 h (quantitative yield) |
| 8. | 2,6-Lutidine (1.0 eq) / TFAA (4.0 eq) → No reaction | rt/24 h |
| 9. | $Bu_3N$ (2.0 eq) / TFAA (4.0 eq) / $F_3CCOOH$ / (2.0 eq) → No reaction | rt/24 h |
| 10. | $Bu_4N(TFA^-)$ (2.0 eq) / TFAA (4.0 eq) → No reaction | rt/24 h |
| 11. | $Bu_4N(TFA^-)$ (2.0 eq) / TFAA (4.0 eq) / $F_3CCOOH$ / (2.0 eq) | rt/∼4 h (quantitative yield) |

R=$C_{16}H_{33}$; RCO=oleoyl; $^1$RCO=Acetyl, benzoyl, etc. $TFA^-$=$F_3CCOO^-$; TFAA=$(F_3CCO)_2O$; Py=pyridine.

alternative scenario could be that due to increased acylating properties of TFAA in the presence of bases, the carbonyl function of the ester group is acylated and thus converted into tetrahedral species that cannot provide an intramolecular nucleophilic assistance necessary for the opening of the oxirane ring. Elucidation of these mechanistic aspects needs further studies.

In conclusion, we have developed an efficient synthetic strategy based on a novel, regioselective transformation of glycidyl esters **1**–**7** into 2-acyl-1,3-bis(trifluoroacetyl)-glycerols **8**–**14**, from which 2-monoacylglycerols **15**–**21** can be retrieved under mild conditions. The main features of this new synthetic protocol are: (i) highly effective and practically quantitative, one-pot synthesis of




**Scheme 1.**

2-monoacylglycerols **15–21** under mild reaction conditions; (ii) the produced compounds **8–14** and **15–21** are of high purity, which alleviates problems of their additional purification, and thus the extent of acyl migration (and of other side-reactions) is minimized; (iii) 2-acyl-1,3-bis(trifluoroacetyl)glycerols **8–14** can be envisaged either as convenient storage forms of 2-MAG or prospective prodrug frameworks for this class of lipid mediators; (iv) the general strategy also introduces 2-monoacylglycerols as common intermediates in the direct synthesis of prodrug isosters that typically represent triglycerides 1,3-STG (e.g., **22–26**); (v) the method makes use of commercially available reactants and it is easy to scale-up.

## 3. Experimental

### 3.1. General

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.[23] Reaction conditions were kept strictly anhydrous.

Column chromatography (CC) was carried out on silica gel 60 (70–230 mesh ASTM, Merck) using the following mobile phases: system A, pentane–toluene–ethyl acetate (40:50:10, v/v/v); system B, pentane–toluene–ethyl acetate (30:20:50, v/v/v); system C, pentane–ethyl acetate (90:10, v/v); system D, dichloromethane–methanol (90:10, v/v); system E, pentane–toluene–ethyl acetate (60:35:5, v/v/v); system F, pentane–ethyl acetate (70:30, 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 visualized using the commercially available 3.5% molybdatophosphoric acid spray reagent (Merck) or 50% sulphuric acid followed by heating at 140 °C.

$^1$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 **1–26** 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. The melting points were determined on a Kofler melting point apparatus and are uncorrected.

Glycidyl esters **1–7** (see below), were obtained in one step from (±)-glycidol (Fluka) and appropriate acyl-donors (e.g., free fatty acids, fatty acid anhydrides, or acyl chlorides), in 74–95% yields as described elsewhere[14] or analogously to conventional approaches.[18,24] No attempts were made to optimize these particular procedures.

**3.1.1. 2-(Acetyloxymethyl)oxirane (1).** To a solution of (±)-glycidol (3.7 g; 50 mmol) and 4-dimethylaminopyridine (4-DMAP, 6.1 g; 50 mmol) in $CH_2Cl_2$ (15 mL) at rt was added acetic anhydride (6.1 g; 60 mmol). After 12 h, the solution was passed through a silica gel pad (~5 g) prepared in $CH_2Cl_2$. The support was washed with $CH_2Cl_2$ (150 mL) and the solvent evaporated in vacuo. Purification of the crude product by flash chromatography ($CH_2Cl_2$) gave the title compound **1** (4.3 g, 74%) as a colorless oil. [Found: C, 51.66; H, 7.00. $C_5H_8O_3$ (116.11) requires C, 51.72; H, 6.94%]; $R_f$ (system A)=0.39; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 4.37 (1H, dd, $J$=2.9, 2.9 Hz, $OCH_2CHCH_aH_bOCO$); 3.87 (1H, dd, $J$=6.6, 6.2 Hz, $OCH_2CHCH_aH_bOCO$); 3.17 (1H, m, $C(O)CH_2CHCH_2O$); 2.81 (1H, t, $J$=4.4 Hz, $C(O)CH_2CHCH_aH_bO$); 2.61 (1H, dd, $J$=2.6, 2.6 Hz, $C(O)CH_2CHCH_aH_bO$); 2.06 (3H, s, 2-$CH_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 170.88 (C1); 20.90 (C2): acetyl fragment; 65.20 (C3); 49.48 (C2); 44.82 (C1): oxirane-2-methyl fragment.

**3.1.2. 2-(Oleoyloxymethyl)oxirane (2).** To a solution of (±)-glycidol (1.1 g; 15 mmol) and 4-DMAP (2.2 g; 18 mmol) in $CH_2Cl_2$ (15 mL) at rt was added oleoyl chloride (5.4 g; 18 mmol). After 4 h, the solution was passed through a silica gel pad (~5 g) prepared in $CH_2Cl_2$. The support was washed with $CH_2Cl_2$ (150 mL) and the solvent evaporated in vacuo. Purification of the crude product by flash chromatography (toluene) gave the title compound **2** (4.4 g, 86%) as a colorless oil. [Found: C, 74.58; H, 11.28. $C_{21}H_{38}O_3$ (338.52) requires C, 74.51; H, 11.31%]; $R_f$ (system C)=0.52; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 5.34 (2H, m, $CH$=$CH$); 4.40 (1H, dd, $J$=2.9, 2.9 Hz, $OCH_2CHCH_aH_bOCO$); 3.91 (1H, dd, $J$=5.9, 6.2 Hz, $OCH_2CHCH_aH_bOCO$); 3.20 (1H, m, $C(O)CH_2CHCH_2O$); 2.84 (1H, dd, $J$=4.0, 4.4 Hz, $C(O)CH_2CHCH_aH_bO$); 2.63 (1H, dd, $J$=2.6, 2.6 Hz, $C(O)CH_2CHCH_aH_bO$); 2.34 (2H, t, $J$=7.3 Hz, 2-$CH_2$); 2.01 (4H, m, 8-$CH_2$, 11-$CH_2$); 1.63 (2H, m, 3-$CH_2$); 1.30 (20H, m, 4-7-$CH_2$, 12-17-$CH_2$); 0.87 (t, $J$=7.0 Hz, 18-$CH_3$, 3H); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 173.73 (C1); 129.95 and 130.23 (C9 andC10); 34.28 (C2); 32.12 (C16); 29.30–29.98 (C4-C7, C12-C15); 27.38 and 27.43 (C11 and C8); 25.08 (C3); 22.90 (C17); 14.32 (C18): oleoyl fragment; 64.97 (C3); 49.60 (C2); 44.88 (C1): oxirane-2-methyl fragment.

**3.1.3. 2-(Arachidonoyloxymethyl)oxirane (3).** To a solution of (±)-glycidol (0.22 g; 3.0 mmol), 4-DMAP (0.49 g; 4.0 mmol) and arachidonic acid (1.22 g; 4.0 mmol) in $CH_2Cl_2$ (15 mL) at rt was added *N*,*N*′-dicyclohexylcarbodiimide (DCC, 0.82 g; 4.0 mmol) and the reaction system was stirred under these conditions for 12 h. After filtration, the solution was passed through a silica gel pad (~5 g) prepared in $CH_2Cl_2$. The support was washed with $CH_2Cl_2$ (150 mL) and the solvent evaporated under reduced pressure. Purification of the crude product by flash chromatography (system C) afforded the target compound **3** (1.03 g, 95%) as a yellowish oil. [Found: C, 76.70; H, 10.04. $C_{23}H_{36}O_3$ (360.54) requires C, 76.62; H, 10.06%]; $R_f$ (system C)=0.33; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 5.36 (8H, m, $CH$=$CH$); 4.40 (1H, dd, $J$=3.3, 2.9 Hz, $OCH_2CHCH_aH_bOCO$); 3.91 (1H, dd, $J$=6.2, 6.2 Hz, $OCH_2CHCH_aH_bOCO$); 3.19 (1H, m, $C(O)CH_2CHCH_2O$); 2.82 (7H, m, 7, 10, 13-$CH_2$, $C(O)CH_2$-$CHCH_aH_bO$); 2.64 (1H, dd, $J$=2.6, 2.6 Hz, $C(O)CH_2$-$CHCH_aH_bO$); 2.36 (2H, t, $J$=7.5 Hz, 2-$CH_2$); 2.11, 2.05 (4H, m, 16-$CH_2$, 4-$CH_2$); 1.71 (2H, p, $J$=7.5 Hz, 3-$CH_2$); 1.31 (6H, m, 17-19-$CH_2$); 0.88 (3H, t, $J$=6.8 Hz, 20-$CH_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 173.47 (C1); 130.71, 129.19, 129.04, 128.80, 128.45, 128.35, 128.07 and

127.76 (C5-6, C8-9, C11-12, C14-15); 33.62 (C2); 31.73 (C17); 29.54 (C18); 27.43 (C4); 26.73 (C16); 25.83 (C7, C10, C13); 24.91 (C3); 22.78 (C19); 14.28 (C20): arachidonoyl fragment; 65.05 (C3); 49.56 (C2); 44.87 (C1): oxirane-2-methyl fragment.

**3.1.4. 2-(Benzoyloxymethyl)oxirane (4).** Obtained from (±)-glycidol (1.1 g; 15 mmol), 4-DMAP (2.2 g; 18 mmol) and benzoyl chloride (2.5 g; 18 mmol) at rt (reaction time: 4 h) and then purified (system C) in the same way as described for **2**. Yield: 2.3 g (85%, colorless oil). [Found: C, 67.50; H, 5.70. $C_{10}H_{10}O_3$ (178.19) requires C, 67.41; H, 5.66%]; $R_f$ (system C)=0.34; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 8.06 (2H, m, Aryl); 7.57 (1H, m, Aryl); 7.44 (2H, m, Aryl); 4.65 (1H, dd, $J$=2.9, 2.9 Hz, $OCH_2CHCH_aH_b$-OCO); 4.17 (1H, dd, $J$=6.2, 6.2 Hz, $OCH_2CHCH_aH_b$-OCO); 3.34 (1H, m, C(O)$CH_2CHCH_2O$); 2.89 (1H, dd, $J$=4.0, 4.4 Hz, C(O)$CH_2CHCH_aH_bO$); 2.73 (1H, dd, $J$=2.6, 2.6 Hz, C(O)$CH_2CHCH_aH_bO$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 166.48 (–C(O)O); 133.44 (C4); 129.97 (C2, C6); 129.89 (C1); 128.64 (C3 and C5): benzoyl fragment; 65.66 (C3); 49.70 (C2); 44.92 (C1): oxirane-2-methyl fragment.

**3.1.5. 2-(4-Nitrobenzoyloxymethyl)oxirane (5).** Obtained from (±)-glycidol (1.1 g; 15 mmol), 4-DMAP (2.2 g; 18 mmol) and 4-nitrobenzoyl chloride (3.3 g; 18 mmol) at rt (reaction time: 5 h) and then purified (system F) as described for **2** and **4**. Yield: 2.8 g (85%, yellowish crystals, mp 60.3–61.9 °C, from system F; a commercial sample from Fluka: mp 59.9–62 °C). [Found: C, 53.75; H, 3.97; N, 6.19. $C_{10}H_9NO_5$ (223.18) requires C, 53.82; H, 4.06; N, 6.28%]; $R_f$ (system F)=0.42; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 8.28 (4H, m, Aryl); 4.74 (1H, dd, $J$=2.6, 2.9 Hz, $OCH_2CHCH_aH_bOCO$); 4.18 (1H, dd, $J$=6.6, 6.6 Hz, $OCH_2CHCH_aH_bOCO$); 3.37 (1H, m, C(O)$CH_2$-$CHCH_2O$); 2.93 (1H, t, $J$=4.4 Hz, C(O)$CH_2CHCH_aH_bO$); 2.74 (1H, dd, $J$=2.9, 2.6 Hz, C(O)$CH_2CHCH_aH_bO$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 164.63 (–C(O)O); 150.92 (C4); 135.22 (C1); 131.15 (C2, C6); 123.85 (C3 and C5): 4-nitrobenzoyl fragment; 66.70 (C3); 49.43 (C2); 44.91 (C1): oxirane-2-methyl fragment.

**3.1.6. 2-(4-Methoxybenzoyloxymethyl)oxirane (6).** Obtained from (±)-glycidol (1.5 g; 20 mmol), 4-DMAP (2.9 g; 24 mmol) and 4-methoxybenzoyl chloride (4.1 g; 24 mmol) at rt (reaction time: 6 h) and purified (system F) identically as described for **5**. Yield: 3.5 g (83%, colorless oil). [Found: C, 63.55; H, 5.75. $C_{11}H_{12}O_4$ (208.21) requires C, 63.45; H, 5.81%]; $R_f$ (system F)=0.51; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 8.01 (2H, m, Aryl); 6.90 (2H, m, Aryl); 4.62 (1H, dd, $J$=2.9, 2.9 Hz, $OCH_2CHCH_aH_bOCO$); 4.12 (1H, dd, $J$=6.2, 6.2 Hz, $OCH_2CHCH_aH_bOCO$); 3.85 (3H, s, $CH_3O$); 3.32 (1H, m, C(O)$CH_2CHCH_2O$); 2.88 (1H, dd, $J$=4.0, 4.4 Hz, C(O)$CH_2CHCH_aH_bO$); 2.71 (1H, dd, $J$=2.6, 2.6 Hz, C(O)$CH_2CHCH_aH_bO$, 1); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 166.23 (–C(O)O); 163.78 (C4); 132.03 (C2 and C6); 122.24 (C1); 113.89 (C3 and C5); 55.67 (4-$OCH_3$): 4-methoxybenzoyl fragment; 65.39 (C3); 49.83 (C2); 44.94 (C1): oxirane-2-methyl fragment.

**3.1.7. 2-(2,4,6-Trimethylbenzoyloxymethyl)oxirane (7).** Obtained from (±)-glycidol (1.5 g; 20 mmol), 4-DMAP (3.7 g; 30 mmol), 2,4,6-trimethylbenzoic acid (4.9 g; 30 mmol) and DCC (6.2 g; 30 mmol) at rt (reaction time: 24 h) and purified (system C) as described for **3**. Yield: 3.6 g (82%, colorless oil). [Found: C, 70.95; H, 7.40. $C_{13}H_{16}O_3$ (220.26) requires C, 70.89; H, 7.32%]; $R_f$ (system C)=0.31; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 6.86 (2H, s, Aryl); 4.63 (1H, dd, $J$=3.3, 3.3 Hz, $OCH_2CHCH_aH_bOCO$); 4.15 (1H, dd, $J$=6.2, 6.6 Hz, $OCH_2CHCH_aH_bOCO$); 3.32 (1H, m, C(O)$CH_2CHCH_2O$); 2.88 (1H, dd, $J$=4.4, 4.7 Hz, C(O)$CH_2CHCH_aH_bO$); 2.71 (1H, dd, $J$=2.6, 2.6 Hz, C(O)$CH_2CHCH_aH_bO$); 2.32 (6H, s, 2-$CH_3$, 6-$CH_3$); 2.28 (3H, s, 4-$CH_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 169.94 (–C(O)O); 139.83 (C4); 135.61 (C2 and C6); 130.49 (C1); 128.73 (C3 and C5); 21.37 (4-$CH_3$); 20.11 (2-$CH_3$ and 6-$CH_3$): 2,4,6-trimethylbenzoyl fragment; 65.39 (C3); 49.83 (C2); 44.94 (C1): oxirane-2-methyl fragment.

### 3.2. General procedure for the preparation of 2-acyl-1,3-bis(trifluoroacetyl)glycerols 8–14 (step A)

To a solution of a glycidyl ester **1–7** (1.00 mmol), in dichloromethane (3.0 mL), trifluoroacetic anhydride (TFAA, 4.00 mmol), in $CH_2Cl_2$ (3.0 mL), was added at −20 °C, and the reaction mixture was kept at rt for 1–4 h. The solvent and unreacted TFAA were removed under reduced pressure (bath temperature 40–60 °C). Traces of TFAA were removed by co-evaporation with toluene (3× 25 mL) under the same conditions and the residue was kept under vacuum at rt for 2 h to give the target compound **8–14**, in practically quantitative yield.

If necessary, the thus obtained intermediate could additionally be purified by flash, solid-phase filtration through a silica gel pad (~ 5 g) utilizing an appropriate eluant (e.g., toluene or dichloromethane).

**3.2.1. 2-Acetyl-1,3-bis(trifluoroacetyl)glycerol (8).** Obtained from 2-(acetyloxymethyl)oxirane (**1**; 0.116 g; 1.00 mmol) and trifluoroacetic anhydride (0.840 g; 4.00 mmol) according to the above general procedure. After 1 h, solid-phase filtration using dichloromethane as eluant gave **8** as a colorless oil (0.280 g, 86%). [Found: C, 33.20; H, 2.50. $C_9H_8O_6F_6$ (326.15) requires C, 33.14; H, 2.47%]; $R_f$ (system C)=0.45; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 5.40 (1H, m, $CH_2CHCH_2$); 4.63 (2H, dd, $J$=4.4, 4.0 Hz, C(O)$OCH_bH_aCHCH_aH_bOCO$); 4.46 (2H, dd, $J$=5.5, 5.5 Hz, C(O)$OCH_bH_aCHCH_aH_bOCO$); 2.10 (3H, s, 2-$CH_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 170.07 (C1); 20.62 (C2): acetyl fragment; 157.19 (C1, q, $J$=43.5 Hz); 114.49 (C2, q, $J$=285.3 Hz): trifluoroacetyl fragment; 67.45 (C2); 64.86 (C1, C3): glycerol fragment.

**3.2.2. 2-Oleoyl-1,3-bis(trifluoroacetyl)glycerol (9).** Obtained by reacting 2-(oleyloxymethyl)oxirane (**2**; 0.169 g; 0.50 mmol) and trifluoroacetic anhydride (0.420 g; 2.00 mmol) for 1 h. Solvents were evaporated in vacuo to give **9** as a yellowish/colorless oil (0.274 g, 100%). [Found: C, 54.62; H, 7.00. $C_{25}H_{38}O_6F_6$ (548.57) requires C, 54.74; H, 6.98%]; $R_f$ (system A)=0.59; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 5.41 (1H, m, $OCH_2CHOCO$); 5.34 (2H, m, $CH{=}CH$); 4.63 (2H, dd, $J$=4.0, 4.4 Hz, C(O)$OCH_bH_aCHCH_aH_bOCO$); 4.46 (2H, dd, $J$=5.5, 5.5 Hz, C(O)$OCH_bH_aCHCH_aH_bOCO$); 2.34 (2H, t,

$J$=7.3 Hz, 2-C$H_2$); 2.00 (4H, m, 8-C$H_2$, 11-C$H_2$); 1.62 (2H, m, 3-C$H_2$); 1.30 (20H, m, 4-7-C$H_2$, 12-17-C$H_2$); 0.88 (3H, t, $J$=6.6 Hz, 18-C$H_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 172.72 (C1); 130.25 and 129.90 (C9 and C10); 34.06 (C2); 32.12 (C16); 29.14–29.98 (C4-C7, C12-C15); 27.42 and 27.36 (C11 and C8); 24.87 (C3); 22.89 (C17); 14.30 (C18): oleoyl fragment; 157.18 (C1, q, $J$=43.5 Hz); 114.51 (C2, q, $J$=285.3 Hz): trifluoroacetyl fragment; 67.15 (C2); 64.94 (C1, C3): glycerol fragment.

**3.2.3. 2-Arachidonoyl-1,3-bis(trifluoroacetyl)glycerol (10).** Obtained from 2-(arachidonyloxymethyl)oxirane (**3**; 0.180 g; 0.50 mmol) and trifluoroacetic anhydride (0.420 g; 2.00 mmol) for 1 h. Evaporation of solvents followed by solid-phase filtration (toluene) afforded **10** as a yellowish oil (0.267 g, 94%). [Found: C, 56.93; H, 6.30. $C_{27}H_{36}O_6F_6$ (570.57) requires C, 56.84; H, 6.36%]; $R_f$ (system A)=0.57; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 5.36 (9H, m, C$H$=C$H$, $CH_2CHCH_2$); 4.63 (2H, dd, $J$=4.2, 4.4 Hz, C(O)OC$H_b$H$_a$CHCH$_a$H$_b$OCO); 4.46 (2H, dd, $J$=5.5, 5.5 Hz, C(O)OCH$_b$H$_a$CHCH$_a$H$_b$OCO); 2.81 (6H, m, 7, 10, 13-C$H_2$); 2.36 (2H, t, $J$=7.5 Hz, 2-C$H_2$); 2.12, 2.05 (4H, m, 16-C$H_2$, 4-C$H_2$, 4H); 1.70 (2H, p, $J$=7.3 Hz, 3-C$H_2$); 1.31 (6H, m, 17-19-C$H_2$); 0.89 (3H, t, $J$=6.9 Hz, 20-C$H_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 172.51 (C1); 130.72, 129.44, 128.83, 128.68, 128.54, 128.22, 128.03 and 127.73 (C5-6, C8-9, C11-12, C14-15); 33.41 (C2); 31.73 (C17); 29.53 (C18); 27.43 (C4); 26.57 (C16); 25.81 (C7, C10, C13); 24.70 (C3); 22.78 (C19); 14.26 (C20): arachidonoyl fragment; 157.17 (C1, q, $J$=43.5 Hz); 114.50 (C2, q, $J$=285.3 Hz): trifluoroacetyl fragment; 67.22 (C2); 64.92 (C1, C3): glycerol fragment.

**3.2.4. 2-Benzoyl-1,3-bis(trifluoroacetyl)glycerol (11).** Obtained by reacting 2-(benzyloxymethyl)oxirane (**4**; 0.089 g; 0.50 mmol) and trifluoroacetic anhydride (0.420 g; 2.00 mmol) for 1 h. Solvents were removed under reduced pressure to give **11** as a colorless oil (0.194 g, 100%). [Found: C, 43.43; H, 2.60. $C_{14}H_{10}O_6F_6$ (388.22) requires C, 43.31; H, 2.60%]; $R_f$ (system A)=0.55; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 8.00 (2H, m, Aryl); 7.60 (1H, m, Aryl); 7.47 (2H, m, Aryl); 5.66 (1H, m, $CH_2CHCH_2$); 4.75 (2H, dd, $J$=4.4, 4.4 Hz, C(O)OC$H_b$H$_a$-CHCH$_a$H$_b$OCO); 4.63 (2H, dd, $J$=5.1, 5.3 Hz, C(O)OCH$_b$-H$_a$CHCH$_a$H$_b$OCO); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 165.44 (–C(O)O); 134.16 (C4); 130.05 (C2, C6); 128.88 (C3 and C5); 128.66 (C1): benzoyl fragment; 157.22 (C1, q, $J$=43.5 Hz); 114.52 (C2, q, $J$=285.3 Hz): trifluoroacetyl fragment; 67.92 (C2); 64.97 (C1, C3): glycerol fragment.

**3.2.5. 2-(4-Nitrobenzoyl)-1,3-bis(trifluoroacetyl)glycerol (12).** Obtained from 2-(4-nitrobenzyloxymethyl)oxirane (**5**; 0.112 g; 0.50 mmol) and trifluoroacetic anhydride (0.420 g; 2.00 mmol) for 4 h. Solid-phase filtration using dichloromethane as eluant gave **12** (0.187 g, 86%) as yellowish crystals, mp 104.9 - 105.8 °C (from $CH_2Cl_2$). [Found: C, 39.00; H, 2.05; N, 3.23. $C_{14}H_9NO_8F_6$ (433.22) requires C, 38.82; H, 2.09; N, 3.23%]; $R_f$ (system A)=0.44; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 8.30 (2H, m, Aryl); 8.20 (2H, m, Aryl); 5.69 (1H, m, $CH_2CHCH_2$); 4.79 (2H, dd, $J$=4.2, 4.2 Hz, C(O)OC$H_b$H$_a$CHCH$_a$H$_b$OCO); 4.65 (2H, dd, $J$=5.5, 5.3 Hz, C(O)OCH$_b$H$_a$CHCH$_a$H$_b$OCO); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 163.73 (–C(O)O); 151.28 (C4); 133.92 (C1); 131.22 (C2 and C6); 124.08 (C3 and C5): 4-nitrobenzoyl fragment; 157.21 (C1, q, $J$=44.2 Hz); 114.46 (C2, q, $J$=285.3 Hz): trifluoroacetyl fragment; 69.02 (C2); 64.77 (C1, C3): glycerol fragment.

**3.2.6. 2-(4-Methoxybenzoyl)-1,3-bis(trifluoroacetyl)glycerol (13).** Obtained from 2-(4-methoxybenzyloxymethyl)-oxirane (**6**; 0.208 g; 1.00 mmol) and trifluoroacetic anhydride (0.840 g; 4.00 mmol) for 2 h. Solid-phase filtration employing toluene as the mobile phase provided **13** as a colorless oil (0.401 g, 96%). [Found: C, 43.13; H, 2.92. $C_{15}H_{12}O_7F_6$ (418.25) requires C, 43.08; H, 2.89%]; $R_f$ (system A)=0.50; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 7.92 (2H, m, Aryl); 6.86 (2H, m, Aryl); 5.62 (1H, tt, $J$=4.8, 5.1 Hz, $CH_2CHCH_2$); 4.73 (2H, dd, $J$=4.4, 4.4 Hz, C(O)OC$H_b$H$_a$CHCH$_a$H$_b$OCO); 4.62 (2H, dd, $J$=5.3, 5.1 Hz, C(O)OCH$_b$H$_a$CHCH$_a$H$_b$OCO); 3.87 (3H, s, 4-C$H_3$OC$_6$H$_4$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 165.08 (–C(O)O); 164.38 (C4); 132.21 (C2 and C6); 114.17 (C3 and C5); 55.73 (4-$CH_3$): 4-methoxybenzoyl fragment; 157.22 (C1, q, $J$=43.5 Hz); 114.53 (C2, q, $J$=284.6 Hz): trifluoroacetyl fragment; 67.57 (C2); 65.03 (C1, C3): glycerol fragment.

**3.2.7. 2-(2,4,6-Trimethylbenzoyl)-1,3-bis(trifluoroacetyl)glycerol (14).** Obtained from 2-(2,4,6-Trimethylbenzyloxymethyl)oxirane (**7**; 0.110 g; 0.50 mmol) and trifluoroacetic anhydride (0.420 g; 2.00 mmol) for 2 h. Solid-phase filtration (toluene) afforded **14** as a colorless oil (0.201 g, 93%). [Found: C, 47.52; H, 3.70. $C_{17}H_{16}O_6F_6$ (430.30) requires C, 47.45; H, 3.75%]; $R_f$ (system A)=0.53; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 6.88 (2H, m, Aryl); 5.69 (1H, m, $CH_2CHCH_2$); 4.74 (2H, dd, $J$=3.8, 3.8 Hz, C(O)OC$H_b$H$_a$CHCH$_a$H$_b$OCO); 4.56 (2H, dd, $J$=5.9, 6.0 Hz, C(O)OCH$_b$H$_a$CHCH$_a$H$_b$OCO); 2.28, 2.29 (9H, s, s, C$H_3$-C$_6$H$_2$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 168.97 (–C(O)O); 140.56 (C4); 135.74 (C2 and C6); 129.25 (C1); 128.91 (C3 and C5); 21.36 (4-$CH_3$); 19.86 (2-, 6-$CH_3$): 2,4,6-trimethylbenzoyl fragment; 157.16 (C1, q, $J$=43.5 Hz); 114.48 (C2, q, $J$=285.3 Hz): trifluoroacetyl fragment; 67.96 (C2); 65.31 (C1, C3): glycerol fragment.

### 3.3. General procedure for the preparation of 2-monoacylglycerols 15–21 (step B)

To a solution of **8–14** (1.00 mmol) in pentane–$CH_2Cl_2$ (3:1, v/v. 5.0 mL), a mixture of pyridine (10.0 mmol) and methanol (15.0 mmol) in the same solvent (5.0 mL) was added at −20 °C, and the reaction mixture was left at rt for 2–3 h. Solvents were evaporated under reduced pressure (bath 40–60 °C) and the residue was kept under vacuum at rt for 2–3 h to give the target 2-monoacylglycerol **15–21**.

The product could also be retrieved from the corresponding bis(trifluoroacetyl)-intermediate **8–14** directly in a one-pot procedure.

**3.3.1. 2-Acetylglycerol (15).** Synthesized in a one-pot procedure comprising:

*Step A*. Reaction of 2-(acetyloxymethyl)oxirane (**1**; 0.116 g; 1.00 mmol) and trifluoroacetic anhydride (0.840 g;

4.00 mmol) in $CH_2Cl_2$ at rt for 1 h followed by evaporation of volatile products in vacuo to give 2-acetyl-1,3-bis(trifluoroacetyl)glycerol **8** as described above.

*Step B*. Direct treatment of the thus obtained intermediate **8** with pyridine (0.79 g; 10 mmol) and methanol (0.48 g; 15 mmol) in pentane–$CH_2Cl_2$ (3:1, v/v) at rt for 2 h and then removing solvents under reduced pressure to give the title compound **15** as a colorless oil (0.134 g, 100%). [Found: C, 44.71; H, 7.57. $C_5H_{10}O_4$ (134.13) requires C, 44.77; H, 7.51%]; $R_f$ (system D)=0.33; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 4.89 (1H, tt, $J$=4.8, 4.8 Hz, $OCH_2CHOCO$); 3.80 (4H, d, $J$=4.6 Hz, $OCH_2CHCH_2O$); 2.11 (3H, s, 2-$CH_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 171.58 (C1); 21.32 (C2): acetyl fragment; 75.31 (C2); 62.30 (C1, C3): glycerol fragment.

**3.3.2. 2-Oleoylglycerol (16).** Synthesized in a one-pot procedure from 2-(oleyloxymethyl)oxirane (**2**; 0.338 g; 1.00 mmol), (Step B: rt/3 h), as described for **15**. Yield: 0.356 g (100%, yellowish/colorless oil). [Found: C, 70.71; H, 11.35. $C_{21}H_{40}O_4$ (356.55) requires C, 70.74; H, 11.31%]; $R_f$ (system B)=0.32; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 5.34 (2H, m, C*H*=C*H*); 4.92 (1H, tt, $J$=4.8, 4.8 Hz, $OCH_2CHOCO$); 3.83 (4H, d, $J$=4.8 Hz, $OCH_2CHCH_2O$); 2.36 (2H, t, $J$=7.7 Hz, 2-$CH_2$); 1.99 (4H, m, 8-$CH_2$, 11-$CH_2$); 1.63 (2H, m, 3-$CH_2$); 1.30 (20H, m, 4-7-$CH_2$, 12-17-$CH_2$); 0.87 (3H, t, $J$=7.0 Hz, 18-$CH_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 174.29 (C1); 130.26 and 129.92 (C9 and C10); 34.55 (C2); 32.12 (C16); 29.98–29.29 (C4-C7, C12-C15); 27.43 and 27.37 (C8 and C11); 25.16 (C3); 22.90 (C17); 14.32 (C18): oleoyl fragment; 75.22 (C2); 62.70 (C1, C3): glycerol fragment.

**3.3.3. 2-Arachidonoylglycerol (17).** Synthesized in two steps: (a) treatment of 2-(arachidonyloxymethyl)oxirane (**3**; 0.180 g; 0.50 mmol) with trifluoroacetic anhydride (0.420 g; 2.00 mmol) in $CH_2Cl_2$ (reaction time: rt/1 h); b) isolation of intermediate **10** by solid-phase filtration (toluene) followed by its hydrolysis (reaction time: rt/3 h) in pentane–$CH_2Cl_2$ (3:1, v/v) using pyridine (0.39 g; 5.0 mmol) and methanol (0.24 g; 7.5 mmol). Yield: 0.175 g (92%, yellowish oil). [Found: C, 73.00; H, 10.18. $C_{23}H_{38}O_4$ (378.56) requires C, 72.98; H, 10.12%]; $R_f$ (system B)=0.33; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 5.37 (8H, m, C*H*=C*H*); 4.92 (1H, tt, $J$=4.6, 4.6 Hz, $OCH_2CHOCO$); 3.82 (4H, d, $J$=4.8 Hz, $OCH_2CHCH_2O$); 2.81 (6H, m, 7, 10, 13-$CH_2$); 2.39 (2H, t, $J$=7.6 Hz, 2-$CH_2$); 2.13, 2.05 (4H, m, 4-$CH_2$, 16-$CH_2$); 1.73 (2H, p, $J$=7.3 Hz, 3-$CH_2$); 1.32 (6H, m, 17-19-$CH_2$); 0.88 (3H, t, $J$=6.8 Hz, 20-$CH_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 174.03 (C1); 130.76, 129.26, 128.99, 128.85, 128.54, 128.32, 128.06 and 127.75 (C5-6, C8-9, C11-12, C14-15); 33.90 (C2); 31.74 (C17); 29.54 (C18); 27.43 (C4); 26.71 (C16); 25.83 (C7, C10, C13); 24.97 (C3); 22.78 (C19); 14.29 (C20): arachidonoyl fragment; 75.28 (C2); 62.67 (C1, C3): glycerol fragment.

**3.3.4. 2-Benzoylglycerol (18).** Obtained from 2-(benzyloxymethyl)oxirane (**4**; 0.089 g; 0.50 mmol) in the same way as described for **17**. Yield: 0.094 g (96%, colorless oil). [Found: C, 61.19; H, 6.20. $C_{10}H_{12}O_4$ (196.20) requires C, 61.22; H, 6.16%]; $R_f$ (system B)=0.21; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 8.04 (2H, m, Aryl); 7.56 (1H, m, Aryl); 7.43 (2H, m, Aryl); 5.16 (1H, tt, $J$=4.8, 4.8 Hz, $OCH_2CHOCO$); 3.95 (4H, d, $J$=4.9 Hz, $OCH_2CHCH_2O$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 166.89 (–C(O)O); 133.57 (C4); 129.99 (C2 and C6); 128.66 (C1, C3, C5): benzoyl fragment; 75.97 (C2); 62.60 (C1, C3): glycerol fragment.

**3.3.5. 2-(4-Nitrobenzoyl)glycerol (19).** Obtained from 2-(4-nitrobenzyloxymethyl)oxirane (**5**; 0.112 g; 0.50 mmol) identically with **17** and **18**. Yield: 0.109 g (90%, yellowish crystals, mp 115.9–117.8 °C, from pentane–$CH_2Cl_2$=3:1, v/v). [Found: C, 49.75; H, 4.67; N, 5.78. $C_{10}H_{11}NO_6$ (241.20) requires C, 49.80; H, 4.60; N, 5.81%]; $R_f$ (system B)=0.15; $^1$H NMR $\delta_H$ (in ppm, $CD_3OD$, 400 MHz) 8.31 (4H, m, Aryl); 5.18 (1H, tt, $J$=4.9, 4.9 Hz, $OCH_2CHOCO$); 3.83 (4H, m, $OCH_2CHCH_2O$); $^{13}$C NMR $\delta_C$ (in ppm, $CD_3OD$, 100 MHz) 164.76 (–C(O)O); 150.88 (C4); 135.95 (C1); 130.80 (C2 and C6); 123.34 (C3 and C5): 4-nitrobenzoyl fragment; 77.20 (C2); 60.47 (C1, C3): glycerol fragment.

**3.3.6. 2-(4-Methoxybenzoyl)glycerol (20).** Obtained from 2-(4-Methoxybenzyloxy-methyl)oxirane (**6**; 0.104 g; 0.50 mmol) in a synonymous way as described for **17**–**19**. Yield: 0.107 g (95%, white crystals, mp 78.9–80.1 °C, from pentane–$CH_2Cl_2$=3:1, v/v). [Found: C, 58.48; H, 6.30. $C_{11}H_{14}O_5$ (226.23) requires C, 58.40; H, 6.24%]; $R_f$ (system B)=0.17; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 7.95 (2H, m, Aryl); 6.85 (2H, m, Aryl); 5.12 (1H, tt, $J$=4.8, 4.8 Hz, $OCH_2CHOCO$); 3.93 (4H, d, $J$=4.8 Hz, $OCH_2CHCH_2O$); 3.85 (3H, s, 4-$CH_3OC_6H_4$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 166.70 (–C(O)O); 163.94 (C4); 132.09 (C2, C6); 122.25 (C1); 113.93 (C3 and C5); 55.69 (4-$CH_3$): 4-methoxybenzoyl fragment; 75.79 (C2); 62.72 (C1, C3): glycerol fragment.

**3.3.7. 2-(2,4,6-Trimethylbenzoyl)glycerol (21).** Obtained from 2-(2,4,6-trimethylbenzyloxymethyl)oxirane (**7**; 0.110 g; 0.50 mmol) identically with **17**–**20**. Yield: 0.113 g (95%, white crystals, mp 85.9–90.5 °C, from pentane–$CH_2Cl_2$=3:1, v/v). [Found: C, 65.50; H, 7.69. $C_{13}H_{18}O_4$ (238.29) requires C, 65.53; H, 7.61%]; $R_f$ (system B)=0.35; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 6.85 (2H, m, Aryl); 5.18 (1H, tt, $J$=4.8, 4.8 Hz, $OCH_2CHOCO$); 3.93 (4H, m, $OCH_2CHCH_2O$); 2.28, 2.30 (9H, s, s, $CH_3$-$C_6H_2$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 170.35 (–C(O)O); 139.83 (C4); 135.28 (C2 and C6); 130.77 (C1); 128.69 (C3 and C5); 21.34 (4-$CH_3$); 19.97 (2-, 6-$CH_3$): 2,4,6-trimethylbenzoyl fragment; 75.88 (C2); 62.59 (C1, C3): glycerol fragment.

### 3.4. General procedure for the preparation of 1,3-symmetrical triacylglycerols 22–26 (step C)

A solution of 2-monoacylglycerol **15**–**18** (1.00 mmol) and pyridine (20.0 mmol), in dichloromethane (10.0 mL), was treated with a solution of acyl chloride **a**–**d** (3.00 mmol) in dichloromethane (10.0 mL) at −20 °C, and the reaction mixture was kept at rt for 2–4 h. Solvents were removed under reduced pressure. The residue was taken in dichloromethane (10.0 mL), solution was passed through a dichloromethane-filled aluminium oxide pad (~20 g) and the

support was washed with the same solvent (~150 mL). Dichloromethane was removed under reduced pressure and triglyceride formed **22**–**26** was isolated in pure state by flash column chromatography (CC).

The latter compound could also be obtained via a one-pot procedure by conveniently combining steps A, B and C.

**3.4.1. 1,3-Dipalmitoyl-2-acetylglycerol (22).** Synthesized in a one-pot procedure by consecutively performing:

*Step A*. Transformation of 2-(acetyloxymethyl)oxirane (**1**; 0.058 g; 0.50 mmol) by means of trifluoroacetic anhydride (0.420 g; 2.00 mmol) to 2-acetyl-1,3-bis(trifluoroacetyl)-glycerol **8** (reaction time: rt/1 h).

*Step B*. Direct hydrolysis of the thus obtained intermediate **8** with pyridine (0.39 g; 5.0 mmol) and methanol (0.24 g; 7.5 mmol) to 2-acetylglycerol **15** (reaction time: rt/2 h).

*Step C*. Treatment of **15** in the presence pyridine (0.79 g; 10.0 mmol) with palmitoyl chloride (**a**; 0.412 g; 1.50 mmol) (reaction time: rt/4 h). Finally, purification of the crude triglyceride by flash column chromatography (system E) gave the title compound **22** (0.254 g, 83%) as a white solid, mp 58.2–60.9 °C (from system E). [Found: C, 72.74; H, 11.60. $C_{37}H_{70}O_6$ (610.97) requires C, 72.74; H, 11.55%]; $R_f$ (system E)=0.36; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 5.24 (1H, m, $OCH_2CHOCO$); 4.29 (2H, dd, $J$=4.2, 4.2 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 4.15 (2H, dd, $J$=5.9, 5.9 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 2.31 (4H, t, $J$=7.3 Hz, 2-$CH_2$); 2.07 (3H, s, $CH_3CO$); 1.60 (4H, m, 3-$CH_2$); 1.28 (48H, m, 4-15-$CH_2$); 0.87 (6H, t, $J$=6.8 Hz, 16-$CH_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 173.54 (C1); 34.26 (C2); 32.14 (C14); 29.91–29.32 (C4-13); 25.07 (C3); 14.33 (C16): palmitoyl fragment; 170.28 (C1); 21.09 (C2): acetyl fragment; 69.40 (C2); 62.23 (C1, C3): glycerol fragment.

**3.4.2. 1,3-Dioleoyl-2-acetylglycerol (23).** Synthesized in a one-pot, three-step procedure from 2-(acetyloxymethyl)-oxirane (**1**; 0.058 g; 0.50 mmol), pyridine (0.79 g; 10.0 mmol), and oleoyl chloride (**b**; 0.451 g; 1.50 mmol) as described for **22**. The crude product was purified by flash CC (system E) to give the title compound **23** (0.271 g, 82%) as a colorless oil. [Found: C, 74.32; H, 11.22. $C_{41}H_{74}O_6$ (663.04) requires C, 74.27; H, 11.25%]; $R_f$ (system E)=0.35; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 5.35 (4H, m, $CH$=$CH$); 5.24 (1H, m, $OCH_2CHOCO$); 4.30 (2H, dd, $J$=4.4, 4.4 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 4.14 (2H, dd, $J$=5.9, 5.9 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 2.31 (4H, t, $J$=7.5 Hz, 2-$CH_2$); 2.07 (3H, s, $CH_3CO$); 2.00 (8H, m, 8-$CH_2$, 11-$CH_2$); 1.61 (4H, m, 3-$CH_2$); 1.30 (40H, m, 4-7-$CH_2$, 12-17-$CH_2$); 0.87 (6H, t, $J$=6.9 Hz, 18-$CH_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 173.49 (C1); 130.23, 129.93 (C9, C10); 34.24 (C2); 32.12 (C16); 29.98–29.29 (C4-C7, C12-C15); 27.43 and 27.38 (C8 and C11); 25.06 (C3); 22.90 (C17); 14.32 (C18): oleoyl fragment; 170.26 (C1); 21.09 (C2): acetyl fragment; 69.40 (C2); 62.24 (C1, C3): glycerol fragment.

**3.4.3. 1,3-Diacetyl-2-oleoylglycerol (24).** Synthesized in a one-pot procedure from 2-(oleyloxymethyl)oxirane (**2**; 0.169 g; 0.50 mmol), pyridine (0.79 g; 10.0 mmol), and acetyl chloride (**c**; 0.118 g; 1.50 mmol) in $CH_2Cl_2$ (rt/2 h), as described for **22**–**23**. Purification of the crude product by flash CC (system A) afforded the title compound **24** (0.187 g, 85%) as a colorless oil. [Found: C, 68.20; H, 10.10. $C_{25}H_{44}O_6$ (440.63) requires C, 68.15; H, 10.07%]; $R_f$ (system A)=0.37; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 5.33 (2H, m, $CH$=$CH$); 5.26 (1H, m, $OCH_2CHOCO$); 4.27 (2H, dd, $J$=4.4, 4.4 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 4.14 (2H, dd, $J$=6.0, 6.0 Hz, $C(O)OCH_bH_aCHCH_aH_b$-OCO); 2.32 (2H, t, $J$=7.3 Hz, 2-$CH_2$); 2.06 (6H, s, $CH_3CO$); 1.99 (4H, m, 8-$CH_2$, 11-$CH_2$); 1.62 (2H, m, 3-$CH_2$); 1.30 (20H, m, 4-7-$CH_2$, 12-17-$CH_2$); 0.87 (3H, t, $J$=7.0 Hz, 18-$CH_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 173.12 (C1); 130.25 and 129.90 (C10 and C9); 34.39 (C2); 32.11 (C16); 29.97–29.22 (C4-C7, C12-C15); 27.43 and 27.37 (C8 and C11); 25.08 (C3); 22.88 (C17); 14.32 (C18): oleoyl fragment; 170.70 (C1); 20.89 (C2): acetyl fragment; 68.95 (C2); 62.53 (C1, C3): glycerol fragment.

**3.4.4. 1,3-Dibenzoyl-2-arachidonoylglycerol (25).** Obtained according to the general procedure from 2-arachidonoylglycerol (**17**; 0.189 g; 0.50 mmol), pyridine (0.79 g; 10.0 mmol), and benzoyl chloride (**d**; 0.211 g; 1.50 mmol) in $CH_2Cl_2$ (reaction time: rt/4 h). The crude triglyceride was purified by flash CC (system A) to give the target compound **25** (0.252 g, 86%) as a colorless oil. [Found: C, 75.63; H, 7.95. $C_{37}H_{46}O_6$ (586.78) requires C, 75.74; H, 7.90%]; $R_f$ (system A)=0.60; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 8.03 (4H, m, Aryl); 7.57 (2H, m, Aryl); 7.44 (4H, m, Aryl); 5.60 (1H, m, $OCH_2CHOCO$); 5.36 (8H, m, $CH$=$CH$); 4.63 (2H, dd, $J$=4.4, 4.4 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 4.52 (2H, dd, $J$=5.9, 5.9 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 2.90–2.70 (6H, m, 7, 10, 13-$CH_2$); 2.37 (2H, t, $J$=7.5 Hz, 2-$CH_2$); 2.07 (4H, m, 16-$CH_2$, 4-$CH_2$); 1.70 (2H, p, $J$=7.3 Hz, 3-$CH_2$); 1.30 (6H, m, 17-19-$CH_2$); 0.88 (3H, t, $J$=6.8 Hz, 20-$CH_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 172.96 (C1); 130.71, 129.72, 129.72, 128.96, 128.80, 128.47, 128.32, 128.07, 127.76 (C5-6, C8-9, C11-12, C14-15); 33.85 (C2); 31.73 (C17); 29.54 (C18); 27.43 (C4); 26.70 (C16); 25.86, 25.83 and 25.80 (C13, C7 and C10); 24.98 (C3); 22.78 (C19); 14.29 (C20): arachidonoyl fragment; 166.26 (–C(O)O); 133.53 (C4); 129.95 (C6, C2); 129.10 (C1); 128.71 (C5, C3): benzoyl fragment; 69.23 (C2); 63.18 (C1, C3): glycerol fragment.

**3.4.5. 1,3-Dioleoyl-2-benzoylglycerol (26).** Obtained in a one-pot procedure from 2-(benzyloxymethyl)oxirane (**4**; 0.089 g; 0.50 mmol), pyridine (0.79 g; 10.0 mmol), and oleoyl chloride (**b**; 0.451 g; 1.50 mmol) followed by purification of the crude product (CC system E) as described for **22**–**24**. Overall yield of **26**: 0.308 g (85%, colorless oil). [Found: C, 76.32; H, 10.60. $C_{46}H_{76}O_6$ (725.11) requires C, 76.20; H, 10.56%]; $R_f$ (system E)=0.43; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 8.04 (2H, m, Aryl); 7.58 (1H, m, Aryl); 7.44 (2H, m, Aryl); 5.52 (1H, m, $OCH_2CHOCO$); 5.35 (4H, m, $CH$=$CH$); 4.39 (2H, dd, $J$=4.4, 4.4 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 4.33 (2H, dd, $J$=6.0, 6.0 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 2.31 (4H, t, $J$=7.5 Hz, 2-$CH_2$); 1.99 (8H, m, 8-$CH_2$, 11-$CH_2$); 1.60 (4H, m, 3-$CH_2$); 1.30 (40H, m, 4-7-$CH_2$, 12-17-$CH_2$); 0.88 (6H, t, $J$=7.0 Hz, 18-$CH_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$,

100 MHz) 173.53 (C1); 130.21, 129.96 (C10, C9); 34.28 (C2); 32.12 (C16); 29.98–29.29 (C12-C15, C4-C7); 27.44, 27.38 (C8 and C11); 25.07 (C3); 22.90 (C17); 14.33 (C18): oleoyl fragment; 165.84 (–C(O)O); 133.53 (C4); 130.01 (C2, C6); 129.82 (C1); 128.65 (C3, C5): benzoyl fragment; 70.00 (C2); 62.36 (C1, C3): glycerol fragment.

**3.4.6. 2-Oleoyl-1,3-bis(trichloroacetyl)glycerol.** Obtained from 2-(oleyloxymethyl)oxirane (**2**; 0.169 g; 0.50 mmol) and trichloroacetic anhydride (0.617 g; 2.00 mmol) according to the general procedure (reaction time: rt/24 h). Flash CC using toluene–EtOAc (95:5, v/v) as eluant gave the pure trichloroacetylated product (0.317 g, 98%) as a colorless oil. [Found: C, 46.44; H, 6.00. $C_{25}H_{38}O_6Cl_6$ (647.28) requires C, 46.39; H, 5.92%]; $R_f$ (system A)=0.64; $^1$H NMR $\delta_H$ (in ppm, $CDCl_3$, 400 MHz) 5.47 (1H, m, $OCH_2CHOCO$); 5.34 (2H, m, $CH{=}CH$); 4.64 (2H, dd, $J$=4.4, 4.4 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 4.50 (2H, dd, $J$=5.7, 5.5 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 2.34 (2H, t, $J$=7.7 Hz, 2-$CH_2$); 2.00 (4H, m, 8-$CH_2$, 11-$CH_2$); 1.62 (2H, m, 3-$CH_2$); 1.30 (20H, m, 4-7-$CH_2$, 12-17-$CH_2$); 0.87 (3H, t, $J$=7.1 Hz, 18-$CH_3$); $^{13}$C NMR $\delta_C$ (in ppm, $CDCl_3$, 100 MHz) 172.69 (C1); 130.27 and 129.90 (C10 and C9); 34.16 (C2); 32.12 (C16); 29.98–29.22 (C12-C15, C4-C7); 27.44 and 27.37 (C8 and C11); 24.91 (C3); 22.90 (C17); 14.33 (C18): oleoyl fragment; 161.74 (s, C1): trichloroacetyl fragment; 67.70 (C2); 65.99 (C1, C3): glycerol fragment.

## Acknowledgements

We are indebted to Prof. P. J Garegg for his interest in this work. Financial support from the Swedish Natural Science Research Council and the Swedish Foundation for Strategic Research is gratefully acknowledged.

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in the glycerol backbone. For example, for compounds **23** and **24**, the relevant chemical shifts in $CDCl_3$ are: 2.07 ppm ($CH_3$); 170.26 ppm (1-C) and 2.06 ppm ($CH_3$-) and 170.70 ppm (1-C), respectively.

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