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Chemoenzymatic synthesis of a focused library of enantiopure structured 1-*O*-alkyl-2,3-diacyl-*sn*-glycerol type ether lipids

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ABSTRACT

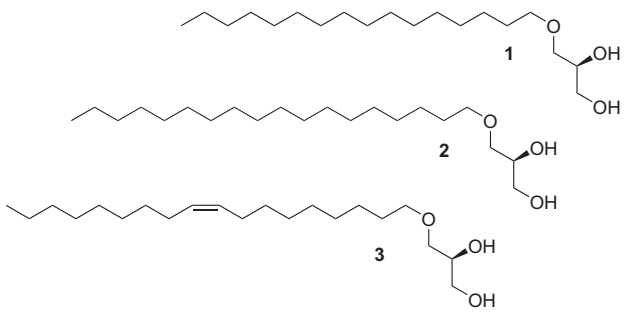
A highly efficient two-step chemoenzymatic synthesis of enantiopure structured ether lipids of the 1-*O*-alkyl-2,3-diacyl-*sn*-glycerol type has been developed. Chimyl, batyl and selachyl alcohols possessing pure saturated fatty acid (SFA) attached to the *sn*-3 position and pure EPA and DHA attached to the *sn*-2 position were obtained under full regiocontrol. This was offered by mild conditions and a highly efficient lipase that operated at room temperature. High-resolution ^{1}H NMR spectroscopy was used to monitor the progress of the reactions and to evaluate the full regiocontrol of the reactions involved by keeping track of all prospective adducts involved in these reactions. This was extended to preparation of a focused library of eight monoacyl intermediate adducts for all even-numbered SFA ranging from C_2–C_{16} and the corresponding EPA and DHA structured diacyl glycerol ethers (DAGE) products for chimyl, batyl and selachyl alcohols, the total of 72 compounds.

1. Introduction

The naturally occurring 1-*O*-alkyl-*sn*-glycerol based ether lipids (EL) are ubiquitously found as 1-*O*-alkyl-2,3-diacyl-*sn*-glycerols in the non-polar lipid fractions of aquatic and terrestrial animals.[1] Such ether lipids are also known as diacyl glycerol ethers (DAGE). In humans, they are widely found in various tissues, usually as minor lipid components.[2] They are present in particularly high amounts in the liver oils of various cartilaginous fish species including sharks, rays and chimaeras. For instance, the liver oil of deep-sea sharks of the Squaliformes order usually contains about 25% DAGE, but up to 89% DAGE has been reported.[3]

The 1-*O*-alkyl-*sn*-glycerols exhibit multiple biological activities and are considered to have high therapeutic potential.[1a,4] They have been demonstrated to possess antineoplastic, immune stimulant and adjuvant properties. 1-*O*-Alkyl-*sn*-glycerols have been shown to prevent leucopenia and thrombocytopenia in patients undergoing cancer radiation therapy.[1a,5] They have been shown to enhance antibody production and stimulate macrophages in vivo, a fact that may explain their relatively high amounts found in human colostrum and milk, presumably to compensate the immature immune system in newborns.[6] Furthermore, studies have shown that 1-*O*-alkyl-*sn*-glycerols reduce tumour growth and metastasis rate of tumour cells in vivo.[7] Besides these biological activities, the amphiphilic and surface active properties of synthetic 1-*O*-alkyl-*rac*-glycerols have been exploited to facilitate the delivery of antibiotics and antineoplastic drugs to the brain by increasing the permeability of the blood–brain barrier.[8]

The *sn*-(stereospecific numbering) terminology[9] implies that the absolute configuration of the natural 1-*O*-alkyl-*sn*-glycerols is *S*. The most prevalent fatty hydrocarbon chains representing the *O*-alkyl moiety found in nature emerge from palmityl ($C_{16:0}$), stearyl ($C_{18:0}$) and oleyl ($C_{18:1}$) alcohols. The corresponding 1-*O*-alkyl-*sn*-glycerols **1**–**3** are known by their trivial names as chimyl, batyl and selachyl alcohols, named after the cartilaginous fish species they were first isolated from, i.e., sharks, chimaeras and rays, respectively.[1]



The long-chain n-3 polyunsaturated fatty acids (PUFA) are characteristic of marine fat[10] and their numerous beneficial effects on human health have been firmly established.[11] These effects are

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almost solely attributed to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the two most prevalent n-3 PUFA in fish.[9] The strongest evidence relates to their cardioprotective effects,[12] various inflammatory and autoimmune disorders,[13] brain function and cognitive health.[14] More recently, EPA and DHA have emerged as anti-carcinogenic nutrients, especially regarding treatment of tumour of the upper digestive tract and pancreas.[15] This has lead to high demands for EPA and DHA concentrates by the health and dietary food industry as dietary supplements as well as the pharmaceutical industry for drugs.[16]

Structured lipids[17] usually refer to lipids offering a predetermined composition and distribution of fatty acids within the glycerol framework. Structured triacylglycerols (TAG) possessing bioactive long-chain PUFA attached to the 2-position and medium-chain fatty acids (MCFA) located at the end-positions have acquired growing attention of scientists as human dietary and health supplements.[17,18] This pertains to MCFA when located at the end-positions undergoing a rapid hydrolysis by 1,3-regioselective pancreatic lipase in the digestive tract and a fast delivery into the liver where they are consumed as a quick source of energy. The remaining 2-monoacylglycerols (2-MAG) become a source of essential fatty acids.[19] Structured MLM (medium-long-medium) type TAG constituting EPA or DHA located at the 2-position with MCFA at the end-positions are strongly desired.[18,20]

The work described in this report aims at possibly combining within the same molecule the beneficial effects of enantiopure ether lipids of the 1-*O*-alkyl-*sn*-glycerol type, the MLM type structured TAG described above, and the long-chain n-3 PUFA. With that in mind a chemoenzymatic synthesis of structured DAGE of the ALM type (alkyl-long-medium) enantiopure ether lipids comprised of pure EPA or DHA at the *sn*-2 position and a pure MCFA (C_6, C_8, C_{10} and C_{12}) at the *sn*-3 position was addressed (Fig. 1). It was decided to base this approach on each of the chimyl, batyl and selachyl type alcohols, optically pure possessing the natural *S* configuration. Furthermore, this work was extended to cover short-chain fatty acids (C_2 and C_4) and longer-chain saturated fatty acids (C_{14} and C_{16}) to complete the task to prepare a focused library of such structured DAGE and all their monoacyl intermediate adducts.

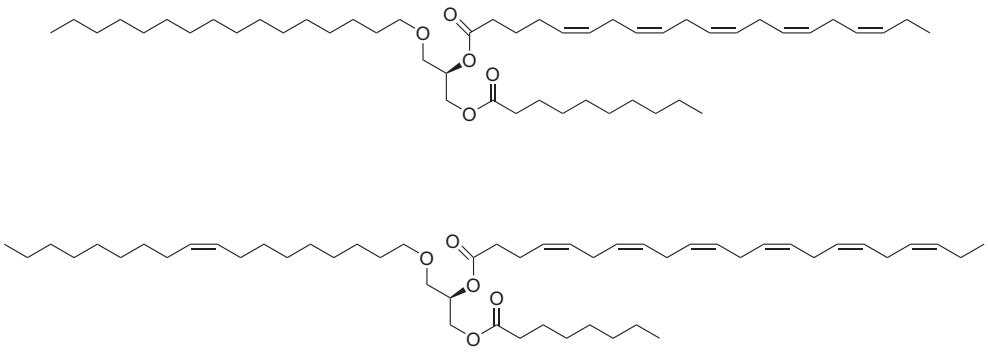


Fig. 1. ALM type structured chimyl alcohol possessing EPA and capric acid (top) and selachyl alcohol possessing DHA and caprylic acid (bottom).

2. Results and discussion

Previous reports describe the synthesis of symmetrically structured TAG of the MLM and the more general ABA type by a highly efficient two-step chemoenzymatic approach starting from glycerol.[21] The synthesis by traditional synthetic organic chemistry methods requires a full regiocontrol that can hardly be accomplished without multi-step protection–deprotection processes. Lipases are well established as powerful bioacatalysts in synthetic organic chemistry.[22] Owing to their regioselectivity and preference to act at the terminal primary alcohol positions of the glycerol backbone lipases are perfectly suited as biocatalysts to prepare structured TAG and DAGE of the type at issue here.[18,23] The low temperature and mild conditions under which they act are also crucial for maintaining the regiocontrol by avoiding acyl-migration side-reactions[21,24] that are common problems when dealing with synthesis involving partially acylated polyols and carbohydrates.

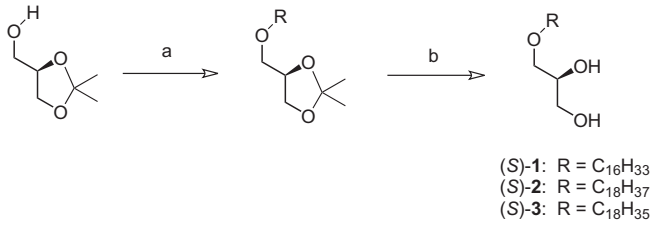
The immobilized *Candida antarctica* lipase B (CAL-B) was observed to display a superb regioselectivity by acting exclusively at the 1,3-positions of glycerol when using activated vinyl esters of the saturated fatty acids in dichloromethane at 0–4 °C. The vinyl esters enabled the lipase to act efficiently at low temperature as well as rendering irreversibility to the transesterification reaction by keto–enol tautomerism undergone by the enolic leaving group. The reaction was completed in 3–5 h and there were no signs of any acyl-migration side reaction taking place. In all cases the 1,3-diacyl glycerol (1,3-DAG) intermediate adducts were accomplished in excellent yields after purification, and were regioisomerically and chemically pure.

Pure EPA and DHA were subsequently introduced to the 2-position of the 1,3-DAG intermediates using EDAC (1-(3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride) as a coupling agent in the presence of dimethylaminopyridine (DMAP). The reaction was completed in only 3–4 h with stoichiometric amounts of EPA and DHA to accomplish the regiopure structured TAG products in excellent yields after purification. There were no indications of any losses in regiocontrol during the coupling reaction as was firmly established by high-resolution ^{1}H and ^{13}C NMR spectroscopy.[21]

The current report describes the synthesis of enantiopure ALM type structured DAGE possessing a pure SFA (C_2, C_4, C_6, C_8, C_{10}, C_{12}, C_{14} and C_{16}) at the *sn*-3 position with a pure bioactive PUFA (EPA or DHA) located at the *sn*-2 position of the 1-*O*-alkyl-*sn*-glycerol backbone of chimyl, batyl and selachyl alcohols. A two-step chemoenzymatic approach similar to that described above for the MLM type structured TAG was followed to introduce the SFA into the *sn*-3 position of the 1-*O*-alkyl-*sn*-glycerol moiety and pure EPA and DHA subsequently to the *sn*-2 position (see Scheme 2). It was anticipated that the CAL would retain its excellent regioselectivity towards the 1-*O*-alkyl-*sn*-glycerols.

2.1. Preparation of chimyl, batyl and selachyl alcohols

Optically pure chimyl, batyl and selachyl alcohols **1**–**3** were prepared in two steps starting from enantiopure (*R*)-solketal (2,3-*O*-isopropylidene-*sn*-glycerol) as a chiral precursor (see Scheme 1). The ether moiety was introduced by alkylation with the corresponding alkyl bromides at 35–40 °C in the absence of a solvent using grounded potassium hydroxide as a base in the presence of tetra-*n*-butylammonium bromide serving as a phase-transfer catalyst.[25] The resulting 1-*O*-alkyl-2,3-*O*-isopropylidene-*sn*-glycerol



Scheme 1. Reagents and conditions: (a) KOH, *n*-Bu_4NBr, R-Br, 35–40 °C, 15 h; (b) *p*-TsOH, THF/water (15:5), reflux, 15 h.

intermediate adducts were usually not purified. A subsequent deprotection of the isopropylidene moiety under acidic conditions afforded the enantiopure 1-*O*-alkyl-*sn*-glycerols **1**–**3**, respectively, for chimyl, batyl and selachyl alcohols, in excellent yields.

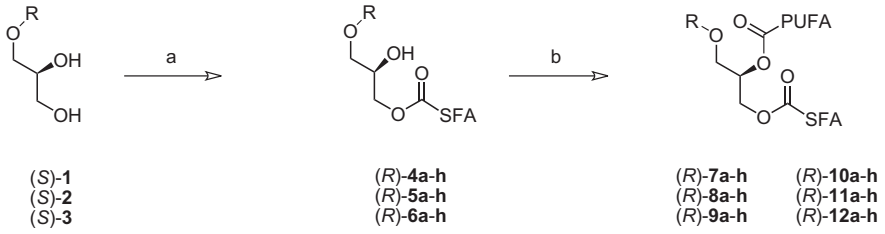
2.2. The enzymatic step

When (*S*)-chimyl, batyl and selachyl alcohols **1**–**3** were treated under similar conditions as described for TAG using vinyl esters of SFA (**a**, **b**, **c**, **d**, **e**, **f**, **g** and **h**, respectively, for C_2, C_4, C_6, C_8, C_{10}, C_{12}, C_{14} and C_{16}) and the CAL-B the excellent degree of regioselectivity was indeed preserved. This resulted in the 3-acyl-1-*O*-alkyl-*sn*-glycerol adducts **4a**–**h**, **5a**–**h** and **6a**–**h**, respectively, for chimyl, batyl and selachyl alcohols (see Scheme 2), that like before were obtained in virtually quantitative yields.

temperature without any deterioration of results. At that temperature only 3 h were required for the reaction to proceed to completion when using 1.25 equiv of the vinyl esters as based on mole EL. This became the condition of choice for all cases addressed in the current report. All monoacyl EL adducts **4a**–**h**, **5a**–**h** and **6a**–**h** were obtained enantio- and regio-pure in excellent yields (90–96%) as can be noticed in Tables 1–3 also showing the specific optical rotation of these compounds, respectively, for chimyl, batyl and selachyl alcohols. Yields are based on highly pure material as was established by high-resolution ^1H and ^{13}C NMR spectroscopy analysis after crystallization from petroleum ether (short-column silica gel treatment for the monounsaturated shortest chain selachyl alcohol adducts **6a**–**c** after distilling off the volatile excessive vinyl ester and by-produced carboxylic acid in vacuo).

2.3. The coupling reaction

The subsequent chemical coupling reaction to introduce pure EPA and DHA into the *sn*-2 position of the 3-acyl-1-*O*-alkyl-*sn*-glycerol adducts **4a**–**h**, **5a**–**h** and **6a**–**h** (see Scheme 2) was performed at room temperature in dichloromethane under similar conditions as described for the TAG synthesis. EDAC (1.4 equiv) was used as a coupling agent in the presence of DMAP (80% as based on mole) with an exact stoichiometric amount of EPA or DHA as based on the 1-*O*-alkyl-*sn*-glycerol adducts. The reactions were completed within 15 h, significantly slower than the 3–4 h required for the TAG synthesis where lower amounts of EDAC (1.2 equiv) and DMAP (20%) were needed.[21] Chemically and regioisomerically pure structured DAGE **7a**–**h**, **8a**–**h** and **9a**–**h** (for EPA) and **10a**–**h**,



SFA = CH_3 (**a**); C_3H_7 (**b**); C_5H_{11} (**c**); C_7H_{15} (**d**); C_9H_{19} (**e**); $C_{11}H_{23}$ (**f**); $C_{13}H_{27}$ (**g**); $C_{15}H_{31}$ (**h**)

1, **4**, **7**, **10**: R = $C_{16}H_{33}$
2, **5**, **8**, **11**: R = $C_{18}H_{37}$
3, **6**, **9**, **12**: R = $C_{18}H_{35}$

7, **8**, **9**: PUFA = EPA
10, **11**, **12**: PUFA = DHA

Scheme 2. Reagents and conditions: (a) *C. antarctica* lipase, SFA as vinyl esters, CH_2Cl_2, rt, 3 h; (b) PUFA, EDAC, DMAP, CH_2Cl_2, rt 15 h.

The highly regioselective acylation of the 1-*O*-alkyl-*sn*-glycerols was initially performed under conditions similar to those described for glycerol in dichloromethane at 0–4 °C. More solvent was needed this time to dissolve the 1-*O*-alkyl-*sn*-glycerols. This slowed down the reaction rate so that more vinyl ester was required for obtaining rates comparable to those obtained before. With 2 M equiv the reactions were completed after 4–5 h reaction time and there were no indications of any acyl-migration products and the lipase was observed to disregard the *sn*-2 position. Comparable results were accomplished when using 1.25 equiv, but the reaction required 15–17 h as was demonstrated for chimyl and batyl alcohols using vinyl caprylate (C_8). A need for modification to lower the excessive use of vinyl esters as well as shortening the reaction time was clearly apparent.

Ether lipids of the DAGE type have been observed to be less prone than TAG to undergo acyl-migration under transesterification conditions when using lipase.[26] Accordingly, the current lipase promoted acylation reaction was observed to tolerate room

11a–**h** and **12a**–**h** (for DHA), respectively, for chimyl, batyl and selachyl alcohols, were afforded as yellowish oils in excellent yields (90–95%) after purification by short-column chromatography treatment on silica gel. The yields are revealed in Tables 1–3 along with their specific optical rotation.

2.4. Regiocontrol and investigation of acyl-migration

Acyl-migration[24] is a major problem in regioselective acylations of polyhydroxy compounds, such as glycerols and carbohydrates. This is a spontaneous intramolecular rearrangement, independent of the lipase, that competes against regioselectivity and regiocontrol. The acyl-migration processes are accelerated by various parameters such as temperature, the most prominent one in the current case,[21b] the presence of acid and base, type of solvent and immobilized enzyme carrier material.[24] Obviously, the increased reaction rate offered by the activated vinyl esters and their irreversibility is of importance in terms of shorter reaction time. The

Table 1
Type of intermediates (**4a**–**h**) and structured DAGE products constituting pure SFA and EPA (**7a**–**h**) or DHA (**10a**–**h**) for the chimyl alcohol series

Compound	SFA	PUFA	Yield (%)	$[\alpha]_D$
(*R*)-**4a**	$-CH_3$	—	95	−3.7
(*R*)-**4b**	$-C_3H_7$	—	92	−3.5
(*R*)-**4c**	$-C_5H_{11}$	—	91	−3.8
(*R*)-**4d**	$-C_7H_{15}$	—	90	−3.3
(*R*)-**4e**	$-C_9H_{19}$	—	92	−3.5
(*R*)-**4f**	$-C_{11}H_{23}$	—	95	−3.7
(*R*)-**4g**	$-C_{13}H_{27}$	—	92	−4.0
(*R*)-**4h**	$-C_{15}H_{31}$	—	91	−2.5
(*R*)-**7a**	$-CH_3$	EPA	90	−5.0
(*R*)-**7b**	$-C_3H_7$	EPA	90	−5.4
(*R*)-**7c**	$-C_5H_{11}$	EPA	91	−4.8
(*R*)-**7d**	$-C_7H_{15}$	EPA	90	−3.9
(*R*)-**7e**	$-C_9H_{19}$	EPA	90	−2.9
(*R*)-**7f**	$-C_{11}H_{23}$	EPA	90	−4.1
(*R*)-**7g**	$-C_{13}H_{27}$	EPA	91	−3.7
(*R*)-**7h**	$-C_{15}H_{31}$	EPA	91	−4.5
(*R*)-**10a**	$-CH_3$	DHA	91	−5.8
(*R*)-**10b**	$-C_3H_7$	DHA	92	−5.2
(*R*)-**10c**	$-C_5H_{11}$	DHA	92	−4.7
(*R*)-**10d**	$-C_7H_{15}$	DHA	91	−3.3
(*R*)-**10e**	$-C_9H_{19}$	DHA	92	−3.0
(*R*)-**10f**	$-C_{11}H_{23}$	DHA	91	−3.1
(*R*)-**10g**	$-C_{13}H_{27}$	DHA	93	−3.7
(*R*)-**10h**	$-C_{15}H_{31}$	DHA	91	−3.4

Table 2
Type of intermediates (**5a**–**h**) and structured DAGE products constituting pure SFA and EPA (**8a**–**h**) or DHA (**11a**–**h**) for the batyl alcohol series

Compound	SFA	PUFA	Yield (%)	$[\alpha]_D$
(*R*)-**5a**	$-CH_3$	—	91	−3.6
(*R*)-**5b**	$-C_3H_7$	—	90	−3.2
(*R*)-**5c**	$-C_5H_{11}$	—	91	−4.3
(*R*)-**5d**	$-C_7H_{15}$	—	94	−3.4
(*R*)-**5e**	$-C_9H_{19}$	—	95	−3.5
(*R*)-**5f**	$-C_{11}H_{23}$	—	90	−3.0
(*R*)-**5g**	$-C_{13}H_{27}$	—	91	−2.5
(*R*)-**5h**	$-C_{15}H_{31}$	—	90	−2.3
(*R*)-**8a**	$-CH_3$	EPA	90	−6.1
(*R*)-**8b**	$-C_3H_7$	EPA	91	−5.6
(*R*)-**8c**	$-C_5H_{11}$	EPA	90	−4.7
(*R*)-**8d**	$-C_7H_{15}$	EPA	92	−5.0
(*R*)-**8e**	$-C_9H_{19}$	EPA	92	−4.5
(*R*)-**8f**	$-C_{11}H_{23}$	EPA	90	−4.3
(*R*)-**8g**	$-C_{13}H_{27}$	EPA	92	−3.7
(*R*)-**8h**	$-C_{15}H_{31}$	EPA	90	−4.7
(*R*)-**11a**	$-CH_3$	DHA	90	−6.0
(*R*)-**11b**	$-C_3H_7$	DHA	92	−4.0
(*R*)-**11c**	$-C_5H_{11}$	DHA	92	−3.7
(*R*)-**11d**	$-C_7H_{15}$	DHA	90	−3.5
(*R*)-**11e**	$-C_9H_{19}$	DHA	95	−2.8
(*R*)-**11f**	$-C_{11}H_{23}$	DHA	90	−3.0
(*R*)-**11g**	$-C_{13}H_{27}$	DHA	93	−3.8
(*R*)-**11h**	$-C_{15}H_{31}$	DHA	90	−4.1

Table 3
Type of intermediates (**6a**–**h**) and structured DAGE products constituting pure SFA and EPA (**9a**–**h**) or DHA (**12a**–**h**) for the selachyl alcohol series

Compound	SFA	PUFA	Yield (%)	$[\alpha]_D$
(*R*)-**6a**	$-CH_3$	—	96	−3.5
(*R*)-**6b**	$-C_3H_7$	—	95	−3.6
(*R*)-**6c**	$-C_5H_{11}$	—	93	−3.6
(*R*)-**6d**	$-C_7H_{15}$	—	90	−3.3
(*R*)-**6e**	$-C_9H_{19}$	—	90	−2.8
(*R*)-**6f**	$-C_{11}H_{23}$	—	90	−3.1
(*R*)-**6g**	$-C_{13}H_{27}$	—	90	−2.7
(*R*)-**6h**	$-C_{15}H_{31}$	—	95	−2.3
(*R*)-**9a**	$-CH_3$	EPA	90	−5.8
(*R*)-**9b**	$-C_3H_7$	EPA	90	−5.1
(*R*)-**9c**	$-C_5H_{11}$	EPA	91	−4.7
(*R*)-**9d**	$-C_7H_{15}$	EPA	91	−4.6
(*R*)-**9e**	$-C_9H_{19}$	EPA	90	−4.5
(*R*)-**9f**	$-C_{11}H_{23}$	EPA	90	−4.4
(*R*)-**9g**	$-C_{13}H_{27}$	EPA	91	−3.5
(*R*)-**9h**	$-C_{15}H_{31}$	EPA	92	−4.8
(*R*)-**12a**	$-CH_3$	DHA	90	−5.5
(*R*)-**12b**	$-C_3H_7$	DHA	90	−4.7
(*R*)-**12c**	$-C_5H_{11}$	DHA	90	−4.3
(*R*)-**12d**	$-C_7H_{15}$	DHA	90	−4.1
(*R*)-**12e**	$-C_9H_{19}$	DHA	91	−3.7
(*R*)-**12f**	$-C_{11}H_{23}$	DHA	90	−3.8
(*R*)-**12g**	$-C_{13}H_{27}$	DHA	90	−3.5
(*R*)-**12h**	$-C_{15}H_{31}$	DHA	91	−3.8

results from previous and current studies also indicate that longer-chain acyl groups are less prone to undergo acyl-migration than the shorter-chain.

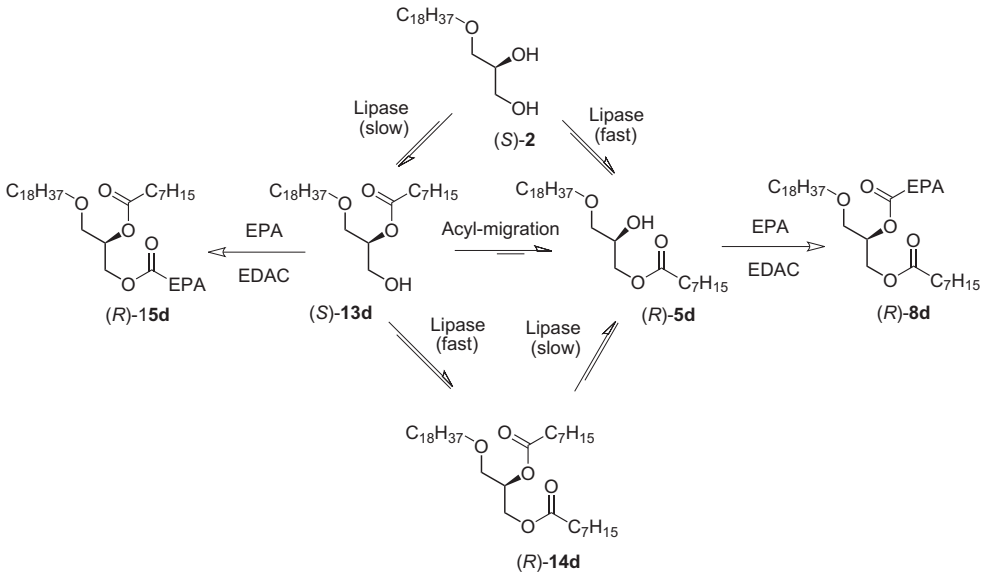
Scheme 3 covers all possible interrelated reactions involved in the enzymatic and coupling steps, including those of the lipase acting directly at the *sn*-2 position and the acyl-migration side reactions, as illustrated for batyl alcohol **2**, caprylic acid C_8 and EPA. The desired two-step pathway consists of the regioselective lipase promoted conversion of **2** into **5d** and the subsequent chemical coupling of EPA to the *sn*-2 position by EDAC to form **8d**. Unwanted acyl-migration is possible in both reaction steps resulting in the wrong regioisomeric adduct **13d**. Once formed that adduct may undergo a fast lipase promoted acylation to form the unwanted DAGE **14d** possessing two MCFA under the enzymatic conditions or the reverse regioisomeric structured DAGE product **15d** through the coupling step.

There were no indications of any losses in regiocontrol during the enzymatic and coupling reactions (Scheme 2) as was established after careful collection of samples from the progressing reactions and their analysis by high-resolution ^1H (400 MHz) and ^{13}C NMR spectroscopy. This prompted further investigations on the stability of the 3-acyl-1-*O*-alkyl-*sn*-glycerol adducts under the conditions of the coupling reaction and to what extent a possible acyl-migration to the corresponding 2-acyl-1-*O*-alkyl-*sn*-glycerol might occur. Investigations involving 3-acyl-1-*O*-alkyl-*sn*-glycerol (batyl alcohol with C_8) revealed only traces of the acyl-migration adduct **13d** after 48 h stirring at room temperature under the exact background conditions of the coupling reaction in dichloromethane in the presence of EDAC and DMAP with the 3-acyl-1-*O*-alkyl-*sn*-glycerol initial concentration thus remaining virtually constant throughout the experiment. After 120 h there were indications of 0.6% presence of the 2-acyl adduct.

This compares to less than 0.5% acyl-migration observed in analogous investigations for 1,3-DAG comprising C_{10} under similar condition after 24 h.[21b] In that case the coupling reaction proceeded to completion in less than 4 h, whereas the current case required 15 h. All this supports a full regiocontrol of these reactions. It should be added that the equilibrium level of 2-acyl-1-*O*-alkyl-*sn*-glycerol was determined to remain at approximately 11% in dichloromethane at room temperature as obtained after 7 days by the use of catalytic amount of Amberlyst 15 when starting with pure 3-acyl-1-*O*-alkyl-*sn*-glycerol. This is comparable to the corresponding equilibrium levels of 1-MAG and 2-MAG with 1-MAG dominating.[24d,e]

2.5. Regiocontrol evaluation by ^1H NMR spectroscopic analysis

All four types of compounds potentially involved in the current structured EL synthesis displayed characteristic resonance pattern in the glyceryl moiety proton region of their ^1H NMR spectra. The spectra may be easily assigned thus making it quite straightforward to track down all individual EL constituents present in a reaction mixture at a time and quantifying them by reasonable or good



Scheme 3. A pathway showing all reactions potentially involved in the enzymatic and coupling reactions.

accuracy by integration of appropriate signals. This became an excellent tool to monitor in detail the progress of the reactions as they proceeded and evaluating their regiocontrol in a similar manner as was described in the previous structured TAG synthesis.[21a,27]

The adducts involved include 1-*O*-alkyl-*sn*-glycerol starting material, both 3-acyl- and 2-acyl-1-*O*-alkyl-*sn*-glycerol monoacyl intermediates and the DAGE product. Fig. 2 presents the glyceryl proton segment of their ^{1}H NMR spectra that were acquired from reference samples obtained from the current synthesis (batyl alcohol, C_8 and EPA). The 2-acyl-1-*O*-alkyl-*sn*-glycerol adduct (**13d** in accordance with Scheme 3) is the prospective acyl-migration product of 3-acyl-1-*O*-alkyl-*sn*-glycerol. It was generated from **5d** as the minor fraction (11%) after inducing acyl-migration equilibrium under acidic conditions (Amberlyst 15 or *p*-TsOH as a catalyst) in dichloromethane at room temperature and a subsequent separation and purification by preparative TLC on silica gel.

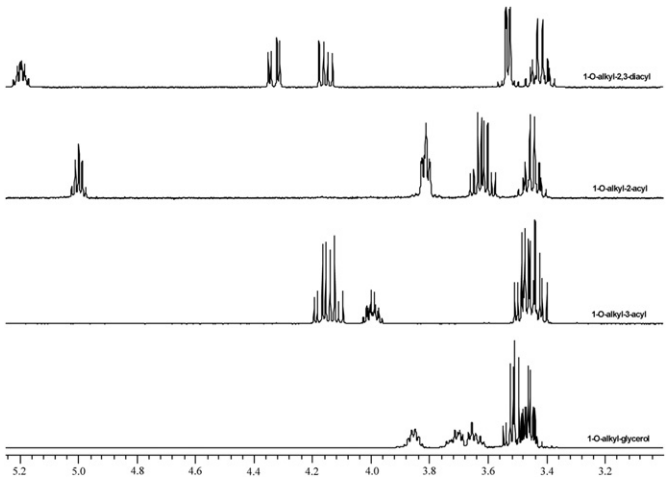


Fig. 2. The glyceryl proton segment of the ^{1}H NMR spectra of all 1-*O*-alkyl-*sn*-glycerol type adducts involved in the synthesis of structured DAGE.

As may be noticed from Fig. 2 there are three main categories of signals present in the glyceryl proton region that are readily assignable for each of the individual adducts. The five protons involved include the methylene proton pair of the *sn*-1 position as the first category, the single proton that belongs to the *sn*-2 methine group as the second one, and the two methylene protons representing the *sn*-3 position as the third one. The protons that belong to the methylene group next to oxygen in the alkoxy moiety resonating as two very close ABX_2-type doublets of triplets[28] at δ 3.50–3.40 ppm interfere with the *sn*-1 methylene protons in the up-field part of that region. This was particularly prominent in the cases of 1-*O*-alkyl-*sn*-glycerol and 3-acyl-1-*O*-alkyl-*sn*-glycerol, where the *sn*-2 position remained non-acylated.

The chemical shift of the glyceryl protons was much dependent upon whether the attached hydroxyl groups were free or acylated. This was particularly evident for the proton at the *sn*-2 position. Acylation was also observed to result in a down-field shift of the protons of adjacent carbons. Very similar trends were also observed for individual acylglycerols in the structured TAG synthesis.[21a]

For the 1-*O*-alkyl-*sn*-glycerol there is a multiplet at δ 3.89–3.83 ppm corresponding to the proton located at the *sn*-2 position. The non-substituted methylene group protons of the *sn*-3 position resonated as two distinct multiplets at 3.75–3.69 and 3.67–3.62 ppm. Each of the methylene protons of the ether substituted glyceryl *sn*-1 carbon resonated as an ABX-type doublet of doublets at 3.54 and 3.48 ppm in close vicinity to the protons belonging to the methylene group next to the oxygen atom of the alkyl moiety.

Substantial changes were observed in the glyceryl proton region when an acyl group was introduced to the *sn*-3 hydroxyl group of 1-*O*-alkyl-*sn*-glycerol. Upon acylation, the methylene protons belonging to the *sn*-3 position underwent nearly 0.5 ppm down-field shift, now resonating as two distinguishable ABX-type doublets of doublets at δ 4.17 and 4.12 ppm. The proton belonging to the *sn*-2 position also underwent a significant shift as a result of acylation of the vicinal methylene group, this time resonating as a multiplet at 4.03–3.95 ppm. The remaining *sn*-1 methylene protons resonated at chemical shift values close to those obtained for the 1-*O*-alkyl-*sn*-glycerol as two distinguishable ABX-type doublets of doublets at 3.49 and 3.42 ppm with the methylene protons next to oxygen in the alkoxy moiety still strongly interfering.

More dramatic changes occurred in the glyceryl proton region upon the second acylation as can be noticed from the corresponding spectrum for 1-*O*-alkyl-2,3-diacyl-*sn*-glycerol. Now, all the protons are very well separated and distinct and easily assigned. This time the

proton located at the *sn*-2 position resonated as a multiplet at δ 5.22–5.17 ppm. This down-field shift of more than 1.3 ppm upon acylation is comparable to that observed in the synthesis of the corresponding triacylglycerols by stepwise acylation of glycerol.[21a] There was also a further down-field shift of the vicinal *O*-acyl substituted *sn*-3 methylene group protons, now appearing as two well separated ABX-type doublets of doublets at 4.33 and 4.16 ppm. It is of interest to notice changes occurring to the 1-*O*-alkyl substituted *sn*-1 methylene group protons now resonating as two close ABX-type doublets of doublets at 3.57–3.50 ppm, this time showing stronger second order behaviour.

In the glyceryl proton region of the 2-acyl-1-*O*-alkyl-*sn*-glycerol adduct the proton at the *sn*-2 position resonated as a quintet at δ 5.00 ppm. The protons belonging to the non-acylated *sn*-3 methylene group resonated as a multiplet at 3.83–3.80 ppm. There are two doublets of doublets representing each of the two *sn*-1 methylene protons at 3.64 and 3.60 ppm, well apart from the two ABX_2-type doublets of triplets belonging to the alkoxy group.

It is evident that the high-resolution ^{1}H NMR spectroscopy is of great importance for monitoring the reactions involved in the chemoenzymatic synthesis of structured ether lipids, both in terms of their progress as well as evaluating the chemical and regioisomeric purity of the compounds and the regiocontrol in these reactions. The limit of quantification as detected by 400 MHz ^{1}H NMR spectroscopy has been determined for a possible acyl-migration of 1,3-DAG to 1,2-DAG as well as 1-MAG to 2-MAG in previous work.[21b] The results indicate that the levels of 2-MAG and 1,2-DAG acyl-migration products can be accurately quantified down to 0.25 mol % for practical sample concentration levels. Obviously, the limit of detection is well below that. The detection degree in the current case involving the structured EL synthesis is estimated to be close to that in the above acylglycerol studies and regiopurity levels of the minimum of 99.9% can be confidently asserted.

2.6. ^{13}C NMR spectroscopy

^{13}C NMR spectroscopy was also useful to aid evaluating the regiocontrol of the reactions, although offering lower accuracy than ^{1}H NMR spectroscopy.[21a,29] This relates to the carbonyl group carbons of each of the three types of fatty acids involved (MCFA and longer-chain SFA, EPA and DHA) displaying two distinct resonance peaks depending upon whether the fatty acid is located at the *sn*-3 position or the *sn*-2 position of the glyceryl backbone. The carbonyl carbons of all four MCFA types and two longer-chain fatty acids involved in the current work were observed to resonate at δ 173.41 ppm when located at the *sn*-3 position of the DAGE. The corresponding resonance for EPA located at the *sn*-2 position remained at 172.84 ppm and that for DHA at 172.37 ppm.

3. Conclusion

Previous work was aimed at preparing libraries of MLM type structured TAG possessing pure MCFA, EPA and DHA at the predetermined positions. This has more recently been extended to cover the shortest chain fatty acids as well as the longer-chain saturated fatty acids.[21] This means that synthesis of such ABA type structured TAG possessing all even number saturated fatty acids ranging from C_2–C_{16} has been completed for both EPA and DHA. Work towards synthesis of asymmetrically structured TAG of the ABC type possessing different saturated fatty acids at the *sn*-1 and *sn*-3 positions and EPA or DHA at the *sn*-2 position has also been initiated.[30]

The current work presents a similar generation of a focused library of enantiopure structured EL of the ALM (alkyl-long-medium) type for chimyl, batyl and selachyl alcohols possessing pure SFA (C_2, C_4, C_6, C_8, C_{10}, C_{12}, C_{14} and C_{16}) attached to the *sn*-3 position and both EPA and DHA to the *sn*-2 position, highly efficiently and under firm regiocontrol. The resulting focused libraries of structured TAG and EL and their intermediate adducts may be exploited for various purposes, such as to compare the biological effects of these compounds and individual fatty acids by screening, as standards for analysis, as various drug supplements, to develop prodrugs as well as serving as potential drugs.

4. Experimental

4.1. General

^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker Avance 400 spectrometer in deuterated chloroform as a solvent at 400.12 and 100.61 MHz, respectively. Chemical shifts (δ) are quoted in parts per million (ppm) and the coupling constants (J) in hertz (Hz). The following abbreviations are used to describe the multiplicity: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet. The number of carbon nuclei behind each ^{13}C signal is indicated in parentheses after each chemical shift value, when there is more than one carbon responsible for the peak. Two dimensional ^{1}H–^{1}H COSY and HETCOR correlation analysis were utilized for unequivocally assigning ^{13}C NMR peaks. All Infrared spectra were conducted on a Nicolet Avatar 360 FT-IR (E.S.P.) Spectrophotometer on a ZnSe plate and on KBr pellets for neat liquid and solid compounds, respectively. The optical activities were measured on an Autopol V from Rudolph Research Analytical, New Jersey USA. Melting points were determined on a Büchi 520 melting point apparatus and are uncorrected. The high-resolution mass spectra (HRMS) were acquired on a Bruker micrOTOF-Q mass spectrometer equipped with an atmospheric pressure chemical ionization chamber (APCI) or an E-spray atmospheric pressure ionization chamber (ESI). All data analyses were done on Bruker software.

The immobilized *C. antarctica* lipase (Novozym 435; CAL-B) was supplied as a gift from Novozyme A/S (Bagsvaerd, Denmark). All chemicals and solvents were used without further purification unless otherwise stated. (*R*)-2,3-*O*-Isopropylidene-*sn*-glycerol (98%, 99% ee) and EDAC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) were obtained from Sigma–Aldrich (Steinheim, Germany). 1-bromohexadecane (97%), 1-bromooctadecane (98%), *cis*-1-bromohexadec-9-ene (≤99%) and tetrabutyl ammonium bromide were purchased from Sigma Chemicals (St. Louis, Missouri, USA). Vinyl butanoate (>97%), vinyl hexanoate (>99%), vinyl octanoate (>99%), vinyl decanoate (>99%), vinyl tetradecanoate (>99%) and vinyl hexadecanoate (96%) were obtained from TCI Europe (Zwijndrecht, Belgium), vinyl acetate (≥99%), and vinyl dodecanoate (≥99%) from Fluka Chemie GmbH (Buchs, Switzerland) and 4-dimethylaminopyridine (99%) from Acros Organics (Geel, Belgium). EPA (98%) and DHA (≥95%) were obtained as ethyl esters from Pronova Biocare (Sandefjord, Norway) and were hydrolysed to their corresponding free acids. Dichloromethane (dried over CaH_2) chloroform, diethyl ether, benzene and tetrahydrofuran were all obtained HPLC grade from Sigma–Aldrich (Steinheim, Germany). Silica gel (Silica gel 60), potassium hydroxide and *p*-toluenesulfonic acid monohydrate were purchased from Merck (Darmstadt, Germany) and preparative TLC plates (250 μm, F-254) from Silicycle (Quebec, Canada).

*4.1.1. Synthesis of (S)-1-O-hexadecyl-sn-glycerol (**1**), (S)-1-O-octadecyl-sn-glycerol (**2**) and (S)-1-O-cis-octadec-9-enyl-sn-glycerol (**3**).* Chimyl (**1**), batyl (**2**) and selachyl (**3**) alcohols were prepared by a previously published procedure by Halldorsson et al.[25] The existence of all these compounds is manifested in the literature.[31] Full experimental details are provided in Supplementary data.

*4.1.2. Synthesis of (R)-1-O-hexadecyl-3-acetyl-sn-glycerol (**4a**).* To a mixture of 1-*O*-hexadecyl-*sn*-glycerol **1** (500 mg, 1.58 mmol) and

vinyl ethanoate (170 mg, 1.97 mmol) in dichloromethane (5 ml), *C. antarctica* lipase (67 mg) was added and the resulting mixture stirred for 3 h at room temperature. After filtration of the lipase the reaction solution was concentrated to dryness in vacuo and the residue introduced to crystallization in petroleum ether at −18 °C, affording the product as white crystals (538 mg, 95% yield); $[\alpha]_D^{20}$ −3.7 (*c* 1.10, benzene); mp 49.5–50.0 °C; IR (KBr) 3404 (O–H), 2917 (C–H), 1702 (C=O), 1123 (C–O–C ether) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (dd, *J*=11.5, 4.3 Hz, 1H, CH_2OCO), 4.11 (dd, *J*=11.5, 6.2 Hz, 1H, CH_2OCO), 4.03–3.97 (m, 1H, CH_2CHCH_2), 3.50 (dd, *J*=9.7, 4.2 Hz, 1H, CHCH_2O), 3.50–3.42 (2×dt, *J*=9.8, 6.2 Hz, 2H, OCH_2CH_2), 3.42 (dd, *J*=9.7, 6.3 Hz, 1H, CHCH_2O), 2.47 (d (br), *J*=4.3 Hz, 1H, CHO*H*), 2.10 (s, 3H, CH_3COO), 1.57 (quintet (br), *J*=6.9 Hz, 2H, OCH_2CH_2), 1.36–1.21 (m, 26H, CH_2), 0.88 (br t, *J*=6.9 Hz, 3H, CH_3 in 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 171.11 (*C*=O), 71.78 (OCH_2CH_2), 71.33 ($CHCH_2O$), 68.80 (CH_2CHCH_2), 65.67 (CH_2OCO), 31.92, 29.69 (3), 29.67, 29.66 (2), 29.61, 29.58, 29.57, 29.46, 29.36, 26.07, 22.69, 20.87, 14.11 ppm; HRMS (APCI): *m*/*z* calcd for $C_{21}H_{42}O_4$/OH: 341.3050; found 341.3050 amu.

*4.1.3. Synthesis of (R)-1-O-hexadecyl-3-butanoyl-sn-glycerol (**4b**).* Full details are provided in Supplementary data. The product **4b** was afforded as white crystals (92% yield); $[\alpha]_D^{20}$ −3.5 (*c* 0.92, benzene); mp 31.7–32.2 °C; HRMS (APCI): *m*/*z* calcd for $C_{23}H_{46}O_4$/OH: 369.3363; found 369.3379 amu.

*4.1.4. Synthesis of (R)-1-O-hexadecyl-3-hexanoyl-sn-glycerol (**4c**).* A procedure identical to the one described above for **4a** was followed using 1-*O*-hexadecyl-*sn*-glycerol **1** (500 mg, 1.58 mmol), vinyl hexanoate (280 mg, 1.97 mmol), dichloromethane (5 ml) and *C. antarctica* lipase (78 mg). The product was afforded as white crystals (593 mg, 91% yield); $[\alpha]_D^{20}$ −3.8 (*c* 1.08, benzene); mp 33.6–33.9 °C; IR (KBr) 3439 (O–H), 2917 (C–H), 1731 and 1717 (C=O), 1132 (C–O–C ether) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (dd, *J*=11.5, 4.4 Hz, 1H, CH_2OCO), 4.12 (dd, *J*=11.5, 6.1 Hz, 1H, CH_2OCO), 4.03–3.96 (m, 1H, CH_2CHCH_2), 3.49 (dd, *J*=9.6, 4.3 Hz, 1H, CHCH_2O), 3.50–3.42 (2×dt, *J*=9.3, 6.1 Hz, 2H, OCH_2CH_2), 3.42 (dd, *J*=9.6, 6.3 Hz, 1H, CHCH_2O), 2.47 (d (br), *J*=4.6 Hz, 1H, CHO*H*), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO), 1.64 (quintet, *J*=7.5 Hz, 2H, CH_2CH_2COO), 1.57 (quintet (br), *J*=6.9 Hz, 2H, OCH_2CH_2), 1.38–1.20 (m, 30H, CH_2), 0.90 (br t, *J*=6.9 Hz, 3H, CH_3 in hexanoic acid), 0.88 (br t, *J*=6.9 Hz, 3H, CH_3 in 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.93 (*C*=O), 71.76 (OCH_2CH_2), 71.36 ($CHCH_2O$), 68.87 (CH_2CHCH_2), 65.41 (CH_2OCO), 34.14, 31.92, 31.28, 29.69 (3), 29.67, 29.65 (2), 29.61, 29.58, 29.57, 29.46, 29.35, 26.07, 24.61, 22.68, 22.30, 14.11, 13.89 ppm; HRMS (ESI): *m*/*z* calcd for $C_{25}H_{50}O_4$/OH: 432.4047; found 432.4068 amu.

*4.1.5. Synthesis of (R)-1-O-hexadecyl-3-octanoyl-sn-glycerol (**4d**).* Full details are provided in Supplementary data. The product **4d** was afforded as white crystals (90% yield); $[\alpha]_D^{20}$ −3.3 (*c* 0.92, benzene); mp 38.5–39.0 °C; HRMS (APCI): *m*/*z* calcd for $C_{27}H_{54}O_4$/OH: 425.3989; found 425.4005 amu.

*4.1.6. Synthesis of (R)-1-O-hexadecyl-3-decanoyl-sn-glycerol (**4e**).* A procedure identical to the one described above for **4a** was followed using 1-*O*-hexadecyl-*sn*-glycerol **1** (500 mg, 1.58 mmol), vinyl decanoate (391 mg, 1.97 mmol), dichloromethane (5 ml) and *C. antarctica* lipase (89 mg). The product was afforded as white crystals (684 mg, 92% yield); $[\alpha]_D^{20}$ −3.5 (*c* 1.13, benzene); mp 44.8–45.5 °C; IR (KBr) 3391 (O–H), 2918 (C–H), 1730 (C=O), 1128 (C–O–C ether) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (dd, *J*=11.5, 4.4 Hz, 1H, CH_2OCO), 4.12 (dd, *J*=11.5, 6.1 Hz, 1H, CH_2OCO), 4.03–3.96 (m, 1H, CH_2CHCH_2), 3.49 (dd, *J*=9.7, 4.3 Hz, 1H, CHCH_2O), 3.50–3.42 (2×dt, *J*=9.3, 6.2 Hz, 2H, OCH_2CH_2), 3.42 (dd, *J*=9.7, 6.3 Hz, 1H, CHCH_2O), 2.47 (d, *J*=4.7 Hz, 1H, CHO*H*), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO), 1.63 (quintet (br), *J*=7.6 Hz, 2H, CH_2CH_2COO) 1.57 (quintet (br), *J*=7.4 Hz, 2H, OCH_2CH_2), 1.37–1.19 (m, 38H, CH_2), 0.88 (br t, *J*=6.8 Hz, 6H, CH_3 in decanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.94 (*C*=O), 71.76 (OCH_2CH_2), 71.37 ($CHCH_2O$), 68.88 (CH_2CHCH_2), 65.41 (CH_2OCO), 34.18, 31.92, 31.85, 29.69 (3), 29.68, 29.66 (2), 29.62, 29.59, 29.58, 29.46, 29.41, 29.36, 29.25 (2), 29.13, 26.07, 24.94, 22.69, 22.66, 14.11, 14.10 ppm; HRMS (APCI): *m*/*z* calcd for $C_{29}H_{58}O_4$/OH: 453.4302; found 453.4300 amu.

*4.1.7. Synthesis of (R)-1-O-hexadecyl-3-dodecanoyl-sn-glycerol (**4f**).* Full details are provided in Supplementary data. The product **4f** was afforded as white crystals (95% yield); $[\alpha]_D^{20}$ −3.7 (*c* 1.01, benzene); mp 57.0–57.5 °C; HRMS (APCI): *m*/*z* calcd for $C_{31}H_{62}O_4$/OH: 481.4615; found 481.4594 amu.

*4.1.8. Synthesis of (R)-1-O-hexadecyl-3-tetradecanoyl-sn-glycerol (**4g**).* A procedure identical to the one described above for **4a** was followed using 1-*O*-hexadecyl-*sn*-glycerol **1** (500 mg, 1.58 mmol), vinyl tetradecanoate (501 mg, 1.97 mmol), dichloromethane (10 ml) and *C. antarctica* lipase (100 mg). The product was afforded as white crystals (766 mg, 92% yield); $[\alpha]_D^{20}$ −4.0 (*c* 0.63, benzene); mp 62.6–63.1 °C; IR (KBr) 3391 (O–H), 2917 (C–H), 1730 (C=O), 1135–1113 (C–O–C ether) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (dd, *J*=11.5, 4.4 Hz, 1H, CH_2OCO), 4.12 (dd, *J*=11.5, 6.1 Hz, 1H, CH_2OCO), 4.03–3.96 (m, 1H, CH_2CHCH_2), 3.49 (dd, *J*=9.7, 4.3 Hz, 1H, CHCH_2O), 3.50–3.42 (2×dt, *J*=9.3, 6.2 Hz, 2H, OCH_2CH_2), 3.42 (dd, *J*=9.7, 6.3 Hz, 1H, CHCH_2O), 2.48 (d (br), *J*=4.6 Hz, 1H, CHO*H*), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO), 1.63 (quintet (br), *J*=7.5 Hz, 2H, CH_2CH_2COO), 1.57 (quintet (br), *J*=7.3 Hz, 2H, OCH_2CH_2), 1.35–1.18 (m, 46H, CH_2), 0.88 (br t, *J*=6.9 Hz, 6H, CH_3 in tetradecanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.94 (*C*=O), 71.76 (OCH_2CH_2), 71.36 ($CHCH_2O$), 68.88 (CH_2CHCH_2), 65.41 (CH_2OCO), 34.18, 31.92 (2), 29.69 (3), 29.67 (2), 29.66, 29.64 (2), 29.62, 29.60 (3), 29.58, 29.46 (2), 29.35 (2), 29.26, 29.13, 26.07, 24.94, 22.69 (2), 14.11 (2) ppm; HRMS (APCI): *m*/*z* calcd for $C_{35}H_{66}O_4$/OH: 509.4928; found 509.4919 amu.

*4.1.9. Synthesis of (R)-1-O-hexadecyl-3-hexadecanoyl-sn-glycerol (**4h**).* Full details are provided in Supplementary data. The product **4h** was afforded as white crystals (91% yield); $[\alpha]_D^{20}$ −2.5 (*c* 0.91, benzene); mp 69.0–69.3 °C; HRMS (APCI): *m*/*z* calcd for $C_{35}H_{70}O_4$/OH: 537.5241; found 537.5238 amu.

*4.1.10. Synthesis of (R)-1-O-octadecyl-3-acetyl-sn-glycerol (**5a**).* Full details are provided in Supplementary data. The product **5a** was afforded as white crystals (91% yield); $[\alpha]_D^{20}$ −3.6 (*c* 1.05, benzene); mp 56.6–57.0 °C; HRMS (APCI): *m*/*z* calcd for $C_{23}H_{46}O_4$/OH: 369.3363; found 369.3376 amu.

*4.1.11. Synthesis of (R)-1-O-octadecyl-3-butanoyl-sn-glycerol (**5b**).* A procedure identical to the one described above for **4a** was followed using 1-*O*-octadecyl-*sn*-glycerol **2** (500 mg, 1.45 mmol), vinyl butanoate (207 mg, 1.81 mmol), dichloromethan (5 ml) and *C. antarctica* lipase (70 mg). The product was afforded as white crystals (542 mg, 90% yield); $[\alpha]_D^{20}$ −3.2 (*c* 0.99, benzene); mp 40.2–40.7 °C; IR (KBr) 3445 (O–H), 2917 (C–H), 1735 and 1718 (C=O), 1132 (C–O–C ether) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (dd, *J*=11.6, 4.4 Hz, 1H, CH_2OCO), 4.12 (dd, *J*=11.6, 6.1 Hz, 1H, CH_2OCO), 4.03–3.97 (m, 1H, CH_2CHCH_2), 3.49 (dd, *J*=9.6, 4.3 Hz, 1H, CHCH_2O), 3.50–3.42 (2×dt, *J*=9.3, 6.1 Hz, 2H, OCH_2CH_2), 3.42 (dd, *J*=9.6, 6.3 Hz, 1H, CHCH_2O), 2.46 (d, *J*=4.8 Hz, 1H, CHO*H*), 2.33 (t, *J*=7.5 Hz, 2H, CH_2COO), 1.67 (sextet, *J*=7.4 Hz, 2H, CH_2CH_2COO) 1.57 (quintet (br), *J*=6.9 Hz, 2H, OCH_2CH_2), 1.36–1.21 (m, 30H, CH_2), 0.96 (t, *J*=7.3 Hz, 3H in butanoic acid), 0.88 (br t, *J*=6.9 Hz, 3H, CH_3 in 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.75 (*C*=O), 71.77 (OCH_2CH_2), 71.36 ($CHCH_2O$), 68.89 (CH_2CHCH_2), 65.40 (CH_2OCO), 36.04, 31.93, 29.70 (6), 29.67 (2), 29.62, 29.59, 29.58, 29.46, 29.36, 26.08, 22.69,

18.42, 14.12, 13.65 ppm; HRMS (APCI): *m*/*z* calcd for $C_{25}H_{50}O_4$/OH: 397.3676; found 397.3680 amu.

*4.1.12. Synthesis of (R)-1-O-octadecyl-3-hexanoyl-sn-glycerol (**5c**).* Full details are provided in Supplementary data. The product **5c** was afforded as white crystals (91% yield); $[\alpha]_D^{20}$ −4.3 (*c* 1.04, benzene); mp 41.2–41.5 °C; HRMS (APCI): *m*/*z* calcd for $C_{27}H_{54}O_4$/OH: 425.3989; found 425.3993 amu.

*4.1.13. Synthesis of (R)-1-O-octadecyl-3-octanoyl-sn-glycerol (**5d**).* A procedure identical to the one described above for **4a** was followed using 1-*O*-octadecyl-*sn*-glycerol **2** (500 mg, 1.45 mmol), vinyl octanoate (309 mg, 1.81 mmol), dichloromethane (5 ml) and *C. antarctica* lipase (81 mg). The product was afforded as white crystals (642 mg, 94% yield); $[\alpha]_D^{20}$ −3.4 (*c* 0.94, benzene); mp 45.2–45.7 °C; IR (KBr) 3444 (O–H), 2918 (C–H), 1731 and 1717 (C=O), 1133 (C–O–C ether) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (dd, *J*=11.5, 4.4 Hz, 1H, C*H*$_2$OCO), 4.12 (dd, *J*=11.5, 6.2 Hz, 1H, C*H*$_2$OCO), 4.03–3.96 (m, 1H, CH_2CHCH_2), 3.49 (dd, *J*=9.6, 4.3 Hz, 1H, CHC*H*$_2$O), 3.50–3.42 (2×dt, *J*=9.3, 5.9 Hz, 2H, OC*H*$_2$CH$_2$), 3.42 (dd, *J*=9.6, 6.4 Hz, 1H, CHC*H*$_2$O), 2.46 (d, *J*=4.8 Hz, 1H, CHO*H*), 2.34 (t, *J*=7.6 Hz, 2H, C*H*$_2$COO), 1.63 (quintet (br), *J*=7.4 Hz, 2H, C*H*$_2$CH$_2$COO) 1.57 (quintet (br), *J*=7.0 Hz, 2H, OCH$_2$C*H*$_2$), 1.37–1.19 (m, 38H, C*H*$_2$), 0.88 (br t, *J*=6.9 Hz, 6H, C*H*$_3$ in octanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.94 (*C*=O), 71.77 (OCH$_2$CH$_2$), 71.36 (CHCH$_2$O), 68.88 (CH_2CHCH_2), 65.41 (*C*H$_2$OCO), 34.18, 31.92, 31.65, 29.70 (6), 29.66 (2), 29.62, 29.59, 29.58, 29.47, 29.36, 29.08, 28.91, 26.08, 24.93, 22.69, 22.59, 14.11, 14.05 ppm; HRMS (APCI): *m*/*z* calcd for $C_{29}H_{58}O_4$/OH: 453.4302; found 453.4322 amu.

*4.1.14. Synthesis of (R)-1-O-octadecyl-3-decanoyl-sn-glycerol (**5e**).* Full details are provided in Supplementary data. The product **5e** was afforded as white crystals (95% yield); $[\alpha]_D^{20}$ −3.5 (*c* 1.12, benzene); mp 50.8–51.5 °C; HRMS (APCI): *m*/*z* calcd for $C_{31}H_{62}O_4$/OH: 481.4615; found 481.4604 amu.

*4.1.15. Synthesis of (R)-1-O-octadecyl-3-dodecanoyl-sn-glycerol (**5f**).* A procedure identical to the one described above for **4a** was followed using 1-*O*-octadecyl-*sn*-glycerol **2** (500 mg, 1.45 mmol), vinyl dodecanoate (410 mg, 1.81 mmol), dichloromethan (5 ml) and *C. antarctica* lipase (91 mg). The product was afforded as white crystals (688 mg, 90% yield); $[\alpha]_D^{20}$ −3.0 (*c* 0.94, benzene); mp 55.1–55.6 °C; IR(KBr) 3444 (O–H), 2918 (C–H), 1730 and 1717 (C=O), 1133 (C–O–C ether) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (dd, *J*=11.5, 4.4 Hz, 1H, C*H*$_2$OCO), 4.12 (dd, *J*=11.5, 6.1 Hz, 1H, C*H*$_2$OCO), 4.03–3.96 (m, 1H, CH_2CHCH_2), 3.49 (dd, *J*=9.7, 4.3 Hz, 1H, CHC*H*$_2$O), 3.50–3.42 (2×dt, *J*=9.3, 6.1 Hz, 2H, OC*H*$_2$CH$_2$), 3.42 (dd, *J*=9.7, 6.3 Hz, 1H, CHC*H*$_2$O), 2.47 (d, *J*=4.7 Hz, 1H, CHO*H*), 2.34 (t, *J*=7.6 Hz, 2H, C*H*$_2$COO), 1.62 (quintet (br), *J*=7.5 Hz, 2H, C*H*$_2$CH$_2$COO) 1.57 (quintet (br), *J*=7.3 Hz, 2H, OCH$_2$C*H*$_2$), 1.37–1.19 (m, 46H, C*H*$_2$), 0.88 (br t, *J*=6.9 Hz, 6H, C*H*$_3$ in dodecanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.94 (*C*=O), 71.77 (OCH$_2$CH$_2$), 71.36 (CHCH$_2$O), 68.88 (CH_2CHCH_2), 65.41 (*C*H$_2$OCO), 34.18, 31.92, 31.91, 29.70 (6), 29.66 (2), 29.62, 29.60 (3), 29.58, 29.46 (2), 29.36, 29.33, 29.26, 29.14, 26.08, 24.94, 22.69 (2), 14.11 (2) ppm; HRMS (APCI): *m*/*z* calcd for $C_{33}H_{66}O_4$/OH: 509.4928; found 509.4916 amu.

*4.1.16. Synthesis of (R)-1-O-octadecyl-3-tetradecanoyl-sn-glycerol (**5g**).* Full details are provided in Supplementary data. The product **5g** was afforded as white crystals (91% yield); $[\alpha]_D^{20}$ −2.5 (*c* 0.67, benzene); mp 64.2–64.8 °C; HRMS (APCI): *m*/*z* calcd for $C_{35}H_{70}O_4$/OH: 537.5241; found 537.5249 amu.

*4.1.17. Synthesis of (R)-1-O-octadecyl-3-hexadecanoyl-sn-glycerol (**5h**).* Full details are provided in Supplementary data. The product **5h** was afforded as white crystals (90% yield); $[\alpha]_D^{20}$ −2.3 (*c* 0.26, benzene); mp 69.0–69.3 °C; HRMS (APCI): *m*/*z* calcd for $C_{37}H_{74}O_4$/OH: 565.5554; found 565.5549 amu.

*4.1.18. Synthesis of (R)-1-O-cis-octadec-9-enyl-3-acetyl-sn-glycerol (**6a**).* To a mixture of (*S*)-1-*O*-*cis*-octadec-9-enyl-*sn*-glycerol **3** (350 mg, 1.02 mmol), vinyl ethanoate (110 mg, 1.28 mmol) in dry dichloromethane (3 ml), immobilized *C. antarctica* lipase (46 mg) was added and the reaction mixture stirred for 3 h at room temperature. After filtration of the lipase the volatile components were first removed on a rotary evaporator and then on an oil vacuum pump system at 10^{-2} mm Hg. The purified residue was obtained as clear oil that, if needed, could be further purified by passing it through a short silica gel column using petroleum ether/ethyl acetate (80:20) as eluent (375 mg, 96% yield); $[\alpha]_D^{20}$ −3.5 (*c* 1.33, benzene); IR (ZnSe) 3457 (O–H), 3003 (=C–H *cis*), 2922 (C–H), 1743 (C=O), 1655 (C=C), 1117 (C–O–C ether) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.39–5.31 (m, 2H, =C*H*) 4.18 (dd, *J*=11.6, 4.3 Hz, 1H, C*H*$_2$OCO), 4.12 (dd, *J*=11.6, 6.3 Hz, 1H, C*H*$_2$OCO), 4.03–3.97 (m, 1H, CH_2CHCH_2), 3.50 (dd, *J*=9.6, 4.3 Hz, 1H, CHC*H*$_2$O), 3.50–3.42 (2×dt, *J*=9.7, 6.2 Hz, 2H, OC*H*$_2$CH$_2$), 3.42 (dd, *J*=9.6, 6.3 Hz, 1H, CHC*H*$_2$O), 2.46 (d (br), *J*=4.5 Hz, 1H, CHO*H*), 2.10 (s, 3H, C*H*$_3$COO), 2.01 (quartet (br), *J*=6.4 Hz, 4H, =CHC*H*$_2$), 1.57 (quintet (br), *J*=6.9 Hz, 2H, OCH$_2$C*H*$_2$), 1.38–1.22 (m, 22H, C*H*$_2$), 0.88 (br t, *J*=6.8 Hz, 3H, C*H*$_3$ in 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 171.10 (*C*=O), 129.95, 129.81, 71.76 (OCH$_2$CH$_2$), 71.33 (CHCH$_2$O), 68.80 (CH_2CHCH_2), 65.67 (*C*H$_2$OCO), 31.90, 29.77, 29.75, 29.57, 29.52, 29.48, 29.43, 29.32 (2), 29.25, 27.21, 27.19, 26.06, 22.68, 20.87, 14.11 ppm; HRMS (APCI): *m*/*z* calcd for $C_{23}H_{44}O_4$/OH: 367.3207; found 367.3192 amu.

*4.1.19. Synthesis of (R)-1-O-cis-octadec-9-enyl-3-butanoyl-sn-glycerol (**6b**).* Full details are provided in Supplementary data. The product **6b** was obtained as clear oil (95% yield); $[\alpha]_D^{20}$ −3.6 (*c* 1.34, benzene); HRMS (APCI): *m*/*z* calcd for $C_{25}H_{48}O_4$+H: 413.3625; found: 413.3637 amu.

*4.1.20. Synthesis of (R)-1-O-cis-octadec-9-enyl-3-hexanoyl-sn-glycerol (**6c**).* A procedure identical to the one described above for **6a** was followed using (*S*)-1-*O*-*cis*-octadec-9-enyl-*sn*-glycerol **3** (350 mg, 1.02 mmol), vinyl hexanoate (181 mg, 1.28 mmol), dry dichloromethane (3 ml) and immobilized *C. antarctica* lipase (53 mg). The volatile components were first removed on a rotary evaporator and then on a Kugelrohr apparatus (70 °C, 10^{-2} mm Hg). The purified residue was obtained as clear oil that, if needed, could be further purified by passing it through a short silica gel column using petroleum ether/ethyl acetate (80:20) as eluent (418 mg, 93% yield); $[\alpha]_D^{20}$ −3.6 (*c* 1.32, benzene); IR (ZnSe) 3446 (O–H), 3004 (=C–H *cis*), 2923 (C–H), 1739 (C=O), 1655 (C=C), 1111 (C–O–C ether) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.39–5.31 (m, 2H, =C*H*), 4.18 (dd, *J*=11.5, 4.4 Hz, 1H, C*H*$_2$OCO), 4.12 (dd, *J*=11.5, 6.2 Hz, 1H, C*H*$_2$OCO), 4.02–3.97 (m, 1H, CH_2CHCH_2), 3.49 (dd, *J*=9.6, 4.2 Hz, 1H, CHC*H*$_2$O), 3.49–3.40 (2×dt, *J*=9.3, 6.1 Hz, 2H, OC*H*$_2$CH$_2$), 3.42 (dd, *J*=9.6, 6.3 Hz, 1H, CHC*H*$_2$O), 2.53–2.45 (s (br), 1H, CHO*H*), 2.34 (t, *J*=7.6 Hz, 2H, C*H*$_2$COO), 2.01 (quartet (br), *J*=6.4 Hz, 4H, =CHC*H*$_2$), 1.64 (quintet (br), *J*=7.5 Hz, 2H, C*H*$_2$CH$_2$COO), 1.57 (quintet (br), *J*=6.8 Hz, 2H, OCH$_2$C*H*$_2$), 1.38–1.21 (m, 26H, C*H*$_2$), 0.90 (br t, *J*=6.9 Hz, 3H, C*H*$_3$ in hexanoic acid), 0.88 (br t, *J*=6.9 Hz, 3H, C*H*$_3$ in 1-*O*-alkyl) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.93 (*C*=O), 129.94, 129.80, 71.75 (OCH$_2$CH$_2$), 71.37 (CHCH$_2$O), 68.87 (CH_2CHCH_2), 65.41 (*C*H$_2$OCO), 34.13, 31.90, 31.28, 29.76, 29.75, 29.57, 29.52, 29.48, 29.43, 29.31 (2), 29.25, 27.20, 27.19, 26.06, 24.61, 22.67, 22.30, 14.10, 13.89 ppm; HRMS (APCI): *m*/*z* calcd for $C_{27}H_{52}O_4$/OH: 423.3833; found: 423.3842 amu.

*4.1.21. Synthesis of (R)-1-O-cis-octadec-9-enyl-3-octanoyl-sn-glycerol (**6d**).* To a mixture of (*S*)-1-*O*-*cis*-octadec-9-enyl-*sn*-glycerol **3** (350 mg, 1.02 mmol), vinyl octanoate (218 mg, 1.28 mmol) in dry

dichloromethane (3 ml), immobilized *C. antarctica* lipase (57 mg) was added and the reaction mixture stirred for 3 h at room temperature. After filtration of the lipase, the reaction solution was concentrated and introduced to crystallization in petroleum ether at −40 °C (acetonitrile cooling bath) affording the product as white solid that melted into clear oil at room temperature (430 mg, 90% yield); $[\alpha]_D^{20}$ −3.3 (*c* 1.16, benzene); IR (ZnSe) 3454 (O–H), 3004 (=C–H *cis*), 2923 (C–H), 1740 (C=O), 1655 (C=C), 1113 (C–O–C ether) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.39–5.31 (m, 2H, =C*H*), 4.17 (dd, *J*=11.6, 4.4 Hz, 1H, CH_2OCO), 4.12 (dd, *J*=11.6, 6.0 Hz, 1H, CH_2OCO), 4.03–3.95 (m (br), 1H, CH_2CHCH_2), 3.49 (dd, *J*=9.6, 4.3 Hz, 1H, CHCH_2O), 3.50–3.41 (2×dt, *J*=9.3, 6.1 Hz, 2H, OCH_2CH_2), 3.42 (dd, *J*=9.6, 6.3 Hz, 1H, CHCH_2O), 2.47 (d (br), *J*=3.8 Hz, 1H, CHO*H*), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO), 2.01 (quartet (br), *J*=6.4 Hz, 4H, =CHCH_2), 1.63 (quintet (br), *J*=7.4 Hz, 2H, CH_2CH_2COO), 1.57 (quintet (br), *J*=7.0 Hz, 2H, OCH$_2$CH_2), 1.38–1.20 (m, 30H, CH_2), 0.88 (br t, *J*=6.8 Hz, 6H, CH_3 in octanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.94 (*C*=O), 129.94, 129.80, 71.75 (OCH_2CH_2), 71.38 (CHCH_2O), 68.88 (CH_2CHCH_2), 65.41 (CH_2OCO), 34.18, 31.90, 31.65, 29.77, 29.75, 29.58, 29.52, 29.48, 29.43, 29.32 (2), 29.25, 29.08, 28.91, 27.21, 27.20, 26.07, 24.93, 22.68, 22.59, 14.11, 14.05 ppm; HRMS (APCI): *m*/*z* calcd for $C_{29}H_{56}O_4$/OH: 451.4146; found: 451.4153 amu.

*4.1.22. Synthesis of (R)-1-O-cis-octadec-9′-enyl-3-decanoyl-sn-glycerol (**6e**).* Full details are provided in Supplementary data. The product **6e** was afforded as white solid that melted into clear oil at room temperature after crystallization in petroleum ether at −18 °C (90% yield); $[\alpha]_D^{20}$ −2.8 (*c* 1.35, benzene); HRMS (APCI): *m*/*z* calcd for $C_{31}H_{60}O_4$/OH: 479.4459; found: 479.4441 amu.

*4.1.23. Synthesis of (R)-1-O-cis-octadec-9-enyl-3-dodecanoyl-sn-glycerol (**6f**).* A procedure identical to the one described above for **6d** was followed using (*S*)-1-*O*-*cis*-octadec-9-enyl-*sn*-glycerol **3** (350 mg, 1.02 mmol), vinyl dodecanoate (290 mg, 1.28 mmol), dry dichloromethane (3 ml) and immobilized *C. antarctica* lipase (64 mg). The product was afforded as a white solid after crystallization in petroleum ether at −18 °C (481 mg, 90% yield); $[\alpha]_D^{20}$ −3.1 (*c* 0.91, benzene); mp 28.7–29.1 °C; IR (KBr) 3511 (O–H), 3004 (=C–H *cis*), 2920 (C–H), 1725 (C=O), 1654 (C=C), 1123 (C–O–C ether) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.39–5.31 (m, 2H, =C*H*), 4.17 (dd, *J*=11.5, 4.4 Hz, 1H, CH_2OCO), 4.12 (dd, *J*=11.5, 6.0 Hz, 1H, CH_2OCO), 4.03–3.96 (m, 1H, CH_2CHCH_2), 3.49 (dd, *J*=9.6, 4.3 Hz, 1H, CHCH_2O), 3.50–3.42 (2×dt, *J*=9.2, 6.1 Hz, 2H, OCH_2CH_2), 3.42 (dd, *J*=9.6, 6.5 Hz, 1H, CHCH_2O), 2.46 (d (br), *J*=4.5 Hz, 1H, CHO*H*), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO), 2.01 (quartet, *J*=6.4 Hz, 4H, =CHCH_2), 1.63 (quintet (br), *J*=7.4 Hz, 2H, CH_2CH_2COO), 1.57 (quintet (br), *J*=7.1 Hz, 2H, OCH$_2$CH_2), 1.38–1.19 (m, 38H, CH_2), 0.88 (br t, *J*=6.8 Hz, 6H, CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 173.95 (*C*=O), 129.95, 129.80, 71.75 (OCH_2CH_2), 71.37 (CHCH_2O), 68.89 (CH_2CHCH_2), 65.42 (CH_2OCO), 34.18, 31.90 (2), 29.77, 29.75, 29.60 (2), 29.58, 29.52, 29.48, 29.46, 29.44, 29.32 (3), 29.26 (2), 29.14, 27.21, 27.20, 26.07, 24.94, 22.68 (2), 14.11 (2) ppm; HRMS (APCI): *m*/*z* calcd for $C_{33}H_{64}O_4$/OH: 507.4772; found: 507.4748 amu.

*4.1.24. Synthesis of (R)-1-O-cis-octadec-9-enyl-3-tetradecanoyl-sn-glycerol (**6g**).* Full details are provided in Supplementary data. The product **6g** was afforded as a white solid (90% yield); $[\alpha]_D^{20}$ −2.7 (*c* 1.06, benzene); mp 32.6–33.1 °C; HRMS (APCI): *m*/*z* calcd for $C_{35}H_{68}O_4$/OH: 535.5085; found: 535.5083 amu.

*4.1.25. Synthesis of (R)-1-O-cis-octadec-9′-enyl-3-hexadecanoyl-sn-glycerol (**6h**).* A procedure identical to the one described above for **6d** was followed using (*S*)-1-*O*-*cis*-octadec-9-enyl-*sn*-glycerol **3** (350 mg, 1.02 mmol), vinyl hexadecanoate (360 mg, 1.28 mmol), dry dichloromethane (3 ml) and immobilized *C. antarctica* lipase (71 mg). The product was afforded as a white solid after crystallization in petroleum ether at −18 °C (564 mg, 95% yield); $[\alpha]_D^{20}$ −2.3 (*c* 1.05, benzene); mp 37.8–38.3 °C; IR(KBr) 3404 (O–H), 2998 (=C–H *cis*), 2918 (C–H), 1742 (C=O), 1660 (C=C), 1119 (C–O–C ether) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.39–5.31 (m, 2H, =C*H*), 4.17 (dd, *J*=11.5, 4.4 Hz, 1H, CH_2OCO), 4.12 (dd, *J*=11.5, 6.2 Hz, 1H, CH_2OCO), 4.02–3.97 (m, 1H, CH_2CHCH_2), 3.49 (dd, *J*=9.8, 4.3 Hz, 1H, CHCH_2O), 3.50–3.42 (2×dt, *J*=9.2, 6.1 Hz, 2H, OCH_2CH_2), 3.42 (dd, *J*=9.8, 6.3 Hz, 1H, CHCH_2O), 2.52–2.43 (s (br), 1H, CHO*H*), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO), 2.01 (quartet (br), *J*=6.3 Hz, 4H, =CHCH_2), 1.62 (quintet (br), *J*=7.3 Hz, 2H, CH_2CH_2COO), 1.57 (quintet (br), *J*=7.1 Hz, 2H, OCH$_2$CH_2), 1.38–1.18 (m, 46H, CH_2), 0.88 (t, *J*=6.9 Hz, 6H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.95 (*C*=O), 129.94, 129.80, 71.75 (OCH_2CH_2), 71.38 (CHCH_2O), 68.88 (CH_2CHCH_2), 65.41 (CH_2OCO), 34.18, 31.92, 31.91, 29.77, 29.76, 29.69 (2), 29.68, 29.65 (2), 29.60, 29.58, 29.52, 29.49, 29.47, 29.44, 29.36, 29.32 (2), 29.26 (2), 29.14, 27.22, 27.20, 26.07, 24.94, 22.69 (2), 14.11 (2) ppm; HRMS (APCI): *m*/*z* calcd for $C_{37}H_{72}O_4$/OH: 563.5398; found: 563.5396 amu.

*4.1.26. Synthesis of (R)-1-O-hexadecyl-2-eicosapentaenoyl-3-acetyl-sn-glycerol (**7a**).* To a solution of (*R*)-1-*O*-hexadecyl-3-acetyl-*sn*-glycerol **4a** (100 mg, 0.279 mmol), DMAP (27 mg, 0.223 mmol) and EDAC (75 mg, 0.391 mmol) in dry dichloromethane (2.5 ml) was added EPA as a free acid (84 mg, 0.279 mmol) and the resulting solution stirred at room temperature for 15 h under nitrogen atmosphere. The reaction mixture was passed through a short silica gel column with ether/dichloromethane (10:90) as eluent, affording the product as yellowish oil (161 mg, 90% yield) after concentration in vacuo; $[\alpha]_D^{20}$ −5.0 (*c* 1.43, chloroform); IR (ZnSe) 3012 (=C–H *cis*), 2922 (C–H), 1743 (C=O), 1653 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44–5.28 (m, 10H, =CH), 5.22–5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.6 Hz, 1H, CH_2OCO), 4.15 (dd, *J*=11.9, 6.5 Hz, 1H, CH_2OCO), 3.57–3.50 (2×dd, *J*=10.6, 5.3 Hz, 2H, CHCH_2O), 3.47–3.37 (2×dt, *J*=9.4, 7.4 Hz, 2H, OCH_2CH_2), 2.88–2.77 (m, 8H, =CCH_2C=), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO), 2.14–2.04 (m, 4H, =CCH_2CH_2 and =CCH_2CH_3), 2.05 (s, 3H, CH_3COO), 1.71 (quintet, *J*=7.5 Hz, 2H, CH_2CH_2COO), 1.53 (quintet (br), *J*=6.8 Hz, 2H, OCH$_2$CH_2), 1.35–1.20 (m, 26H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in EPA), 0.88 (br t, *J*=6.9 Hz, 3H, CH_3 in 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 172.87 (β, C=O), 170.62 (α, C=O), 132.01, 128.88, 128.85, 128.55, 128.25, 128.18, 128.15, 128.06, 127.84, 126.99, 71.75 (OCH_2CH_2), 70.10 (CH_2CHCH_2), 68.88 (CHCH_2O), 63.04 (CH_2OCO), 33.70, 31.91, 29.69 (4), 29.67, 29.65, 29.62, 29.60, 29.53, 29.45, 29.35, 26.48, 26.02, 25.61 (2), 25.59, 25.53, 24.80, 22.68, 20.75, 20.54, 14.26, 14.10 ppm; HRMS (APCI): *m*/*z* calcd for $C_{41}H_{70}O_5$+H: 643.5296; found 643.5285 amu.

*4.1.27. Synthesis of (R)-1-O-hexadecyl-2-eicospentaenoyl-3-butanoyl-sn-glycerol (**7b**).* Full details are provided in Supplementary data. The product **7b** was afforded as yellowish oil (90% yield); $[\alpha]_D^{20}$ −5.4 (*c* 1.08, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{43}H_{74}O_5$+H: 671.5609; found 671.5637 amu.

*4.1.28. Synthesis of (R)-1-O-hexadecyl-2-eicosapentaenoyl-3-hexanoyl-sn-glycerol (**7c**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-hexadecyl-3-hexanoyl-*sn*-glycerol **4c** (100 mg, 0.241 mmol), DMAP (24 mg, 0.193 mmol), EDAC (65 mg, 0.337 mmol), dry dichloromethane (2.5 ml) and EPA as a free acid (73 mg, 0.241 mmol). The product was afforded as yellowish oil after concentration (153 mg, 91% yield); $[\alpha]_D^{20}$ −4.8 (*c* 1.21, chloroform); IR (ZnSe) 3013 (=C–H *cis*), 2923 (C–H), 1740 (C=O), 1654 (C=C); ^1H NMR (400 MHz, $CDCl_3$) δ 5.43–5.28 (m, 10H, =CH), 5.22–5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.4 Hz, 1H, CH_2OCO), 3.57–3.50 (2×dd, *J*=10.6, 5.3 Hz, 2H, CHCH_2O), 3.47–3.37 (2×dt, *J*=9.4, 7.5 Hz, 2H, OCH_2CH_2), 2.88–2.76 (m, 8H, =CCH_2C=), 2.34 (t, *J*=7.8 Hz, 2H, CH_2COO in EPA), 2.30 (t, *J*=7.4 Hz, 2H, CH_2COO in hexanoic acid),

2.14–2.04 (m, 4H, =CCH_2CH$_2$ and =CCH_2CH$_3$), 1.70 (quintet, J=7.5 Hz, 2H, CH_2CH$_2$COO in EPA), 1.61 (quintet, J=7.5 Hz, 2H, CH_2CH$_2$COO in hexanoic acid), 1.54 (quintet (br), J=6.9 Hz, 2H, OCH$_2$CH_2), 1.37–1.18 (m, 30H, CH_2), 0.97 (t, J=7.5 Hz, 3H, CH_3 in EPA), 0.89 (br t, J=6.2 Hz, 3H, CH_3 in hexanoic acid), 0.88 (br t, J=6.3 Hz, 3H, CH_3 in 1-*O*-alkyl) ppm; ^{13}C NMR (CDCl$_3$) δ 173.41 (α, C=O), 172.84 (β, C=O), 132.02, 128.89, 128.84, 128.55, 128.25, 128.19, 128.15, 128.06, 127.85, 127.00, 71.75 (OCH$_2$CH$_2$), 70.16 (CH$_2$CHCH$_2$), 68.90 (CHCH$_2$O), 62.75 (CH$_2$OCO), 34.08, 33.72, 31.92, 31.25, 29.69 (5), 29.65, 29.63, 29.61, 29.55, 29.46, 29.35, 26.50, 26.03, 25.61 (2), 25.60, 25.53, 24.81, 24.57, 22.68, 22.30, 20.55, 14.26, 14.11, 13.89 ppm; HRMS (APCI): m/z calcd for $C_{45}H_{78}O_5$+NH_4: 716.6188; found 716.6185 amu.

*4.1.29. Synthesis of (R)-1-O-hexadecyl-2-eicosapentaenoyl-3-octanoyl-sn-glycerol (**7d**).* Full details are provided in Supplementary data. The product **7d** was afforded as yellowish oil (90% yield); $[\alpha]_D^{20}$ −3.9 (*c* 1.58, chloroform); HRMS (APCI): m/z calcd for $C_{47}H_{82}O_5$+H: 727.6235; found 727.6250 amu.

*4.1.30. Synthesis of (R)-1-O-hexadecyl-2-eicosapentaenoyl-3-decanoyl-sn-glycerol (**7e**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-hexadecyl-3-decanoyl-*sn*-glycerol **4e** (100 mg, 0.212 mmol), DMAP (21 mg, 0.170 mmol), EDAC (57 mg, 0.297 mmol), dry dichloromethane (2.5 ml) and EPA as a free acid (64 mg, 0.212 mmol). The product was afforded as yellowish oil after concentration (145 mg, 90% yield); $[\alpha]_D^{20}$ −2.9 (*c* 1.03, chloroform); IR (ZnSe) 3013 (=C–H *cis*), 2921 (C–H), 1741 (C=O), 1653 (C=C) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.43–5.28 (m, 10H, =CH), 5.22–5.17 (m, 1H, CH$_2$CHCH$_2$), 4.33 (dd, J=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, J=11.9, 6.4 Hz, 1H, CH_2OCO), 3.57–3.50 (2×dd, J=10.6, 5.3 Hz, 2H, CHCH_2O), 3.47–3.37 (2×dt, J=9.4, 7.5 Hz, 2H, OCH_2CH$_2$), 2.88–2.76 (m, 8H, =CCH_2C=), 2.34 (t, J=7.6 Hz, 2H, CH_2COO in EPA), 2.30 (t, J=7.6 Hz, 2H, CH_2COO in decanoic acid), 2.14–2.04 (m, 4H, =CCH_2CH$_2$ and =CCH_2CH$_3$), 1.70 (quintet, J=7.5 Hz, 2H, CH_2CH$_2$COO in EPA), 1.60 (quintet (br), J=7.3 Hz, 2H, CH_2CH$_2$COO in decanoic acid), 1.53 (quintet (br), J=6.4 Hz, 2H, OCH$_2$CH_2), 1.35–1.18 (m, 38H, CH_2), 0.98 (t, J=7.5 Hz, 3H, CH_3 in EPA), 0.88 (t, J=6.8 Hz, 6H, CH_3 in decanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR (CDCl$_3$) δ 173.42 (α, C=O), 172.85 (β, C=O), 132.02, 128.89, 128.85, 128.56, 128.26, 128.19, 128.16, 128.07, 127.85, 127.00, 71.76 (OCH$_2$CH$_2$), 70.17 (CH$_2$CHCH$_2$), 68.91 (CHCH$_2$O), 62.74 (CH$_2$OCO), 34.13, 33.73, 31.92, 31.86, 29.70 (5), 29.66, 29.64, 29.62, 29.55, 29.47, 29.43, 29.36, 29.28 (2), 29.12, 26.51, 26.04, 25.62 (2), 25.61, 25.54, 24.90, 24.82, 22.69, 22.66, 20.55, 14.27, 14.11, 14.10 ppm; HRMS (APCI): m/z calcd for $C_{49}H_{86}O_5$+H: 755.6548; found 755.6567 amu.

*4.1.31. Synthesis of (R)-1-O-hexadecyl-2-eicosapentaenoyl-3-dodecanoyl-sn-glycerol (**7f**).* Full details are provided in Supplementary data. The product **7f** was afforded as yellowish oil (90% yield); $[\alpha]_D^{20}$ −4.1 (*c* 1.44, chloroform); HRMS (APCI): m/z calcd for $C_{51}H_{90}O_5$+H: 783.6861; found 783.6900 amu.

*4.1.32. Synthesis of (R)-1-O-hexadecyl-2-eicosapentaenoyl-3-tetradecanoyl-sn-glycerol (**7g**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-hexadecyl-3-tetradecanoyl-*sn*-glycerol **4 g** (100 mg, 0.190 mmol), DMAP (19 mg, 0.152 mmol), EDAC (51 mg, 0.266 mmol), dry dichloromethane (2.5 ml) and EPA as a free acid (57 mg, 0.190 mmol). The product was afforded as yellowish oil after concentration (140 mg, 91% yield); $[\alpha]_D^{20}$ −3.7 (*c* 1.13, chloroform); IR (ZnSe) 3013 (=C–H *cis*), 2922 (C–H), 1741 (C=O), 1654 (C=C) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.44–5.28 (m, 10H, =CH), 5.22–5.17 (m, 1H, CH$_2$CHCH$_2$), 4.33 (dd, J=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, J=11.9, 6.4 Hz, 1H, CH_2OCO), 3.57–3.50 (2×dd, J=10.6, 5.3 Hz, 2H, CHCH_2O), 3.47–3.37 (2×dt, J=9.4, 7.5 Hz, 2H, OCH_2CH$_2$), 2.88–2.77 (m, 8H, =CCH_2C=), 2.34 (t, J=7.6 Hz, 2H, CH_2COO in EPA), 2.30 (t, J=7.6 Hz, 2H, CH_2COO in tetradecanoic acid), 2.14–2.04 (m, 4H, =CCH_2CH$_2$ and =CCH_2CH$_3$), 1.70 (quintet, J=7.5 Hz, 2H, CH_2CH$_2$COO in EPA), 1.60 (quintet (br), J=7.3 Hz, 2H, CH_2CH$_2$COO in tetradecanoic acid), 1.54 (quintet (br), J=6.9 Hz, 2H, OCH$_2$CH_2), 1.35–1.15 (m, 46H, CH_2), 0.98 (t, J=7.5 Hz, 3H, CH_3 in EPA), 0.88 (br t, J=6.9 Hz, 6H, CH_3 in tetradecanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR (CDCl$_3$) δ 173.43 (α, C=O), 172.85 (β, C=O), 132.03, 128.90, 128.85, 128.57, 128.26, 128.20, 128.16, 128.07, 127.86, 127.00, 71.76 (OCH$_2$CH$_2$), 70.17 (CH$_2$CHCH$_2$), 68.91 (CHCH$_2$O), 62.74 (CH$_2$OCO), 34.14, 33.73, 31.92 (2), 29.70 (4), 29.69 (3), 29.66 (3), 29.63 (2), 29.55, 29.49, 29.47, 29.36 (2), 29.29, 29.13, 26.50, 26.04, 25.62 (2), 25.61, 25.54, 24.91, 24.82, 22.69 (2), 20.56, 14.27, 14.12 (2) ppm; HRMS (APCI): m/z calcd for $C_{53}H_{94}O_5$+NH_4: 828.7440; found 828.7459 amu.

*4.1.33. Synthesis of (R)-1-O-hexadecyl-2-eicosapentaenoyl-3-hexadecanoyl-sn-glycerol (**7h**).* Full details are provided in Supplementary data. The product **7h** was afforded as yellowish oil (91% yield); $[\alpha]_D^{20}$ −4.5 (*c* 1.04, chloroform); HRMS (APCI): m/z calcd for $C_{55}H_{98}O_5$+NH_4: 856.7753; found 856.7784 amu.

*4.1.34. Synthesis of (R)-1-O-octadecyl-2-eicosapentaenoyl-3-acetyl-sn-glycerol (**8a**).* Full details are provided in Supplementary data. The product **8a** was afforded as yellowish semisolid oil (90% yield); $[\alpha]_D^{20}$ −6.1 (*c* 0.85, chloroform); HRMS (APCI): m/z calcd for $C_{43}H_{74}O_5$+NH_4: 688.5875; found 688.5857 amu.

*4.1.35. Synthesis of (R)-1-O-octadecyl-2-eicosapentaenoyl-3-butanoyl-sn-glycerol (**8b**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-octadecyl-3-butanoyl-*sn*-glycerol **5b** (100 mg, 0.241 mmol), DMAP (24 mg, 0.193 mmol), EDAC (65 mg, 0.337 mmol), dry dichloromethane (2.5 ml) and EPA as a free acid (73 mg, 0.241). The product was afforded as yellowish semisolid oil after concentration (153 mg, 91% yield); $[\alpha]_D^{20}$ −5.6 (*c* 1.14, chloroform); IR(ZnSe) 3012 (=C–H *cis*), 2922 (C–H), 1740 (C=O), 1653 (C=C) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.44–5.28 (m, 10H, =CH), 5.23–5.18 (m, 1H, CH$_2$CHCH$_2$), 4.34 (dd, J=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, J=11.9, 6.4 Hz, 1H, CH_2OCO), 3.57–3.50 (2×dd, J=10.6, 5.3 Hz, 2H, CHCH_2O), 3.47–3.38 (2×dt, J=9.4, 7.5 Hz, 2H, OCH_2CH$_2$), 2.88–2.77 (m, 8H, =CCH_2C=), 2.34 (t, J=7.6 Hz, 2H, CH_2COO in EPA), 2.29 (t, J=7.4 Hz, 2H, CH_2COO in butanoic acid), 2.14–2.04 (m, 4H, =CCH_2CH$_2$ and =CCH_2CH$_3$), 1.71 (quintet, J=7.1 Hz, 2H, CH_2CH$_2$COO in EPA), 1.64 (sextet, J=7.1 Hz, 2H, CH_2CH$_2$COO in butanoic acid), 1.54 (quintet (br), J=6.8 Hz, 2H, OCH$_2$CH_2), 1.35–1.20 (m, 30H, CH_2), 0.98 (t, J=7.5 Hz, 3H, CH_3 in EPA), 0.94 (t, J=7.4 Hz, 3H, CH_3 in butanoic acid), 0.88 (br t, J=6.9 Hz, 3H, CH_3 in 1-*O*-alkyl) ppm; ^{13}C NMR (CDCl$_3$) δ 173.23 (α, C=O), 172.86 (β, C=O), 132.03, 128.90, 128.85, 128.57, 128.26, 128.20, 128.16, 128.07, 127.86, 127.00, 71.76 (OCH$_2$CH$_2$), 70.17 (CH$_2$CHCH$_2$), 68.91 (CHCH$_2$O), 62.75 (CH$_2$OCO), 36.00, 33.73, 31.92, 29.70 (7), 29.66, 29.64, 29.61, 29.55, 29.47, 29.36, 26.51, 26.04, 25.62 (2), 25.61, 25.54, 24.82, 22.69, 20.56, 18.38, 14.27, 14.12, 13.62 ppm; HRMS (APCI): m/z calcd for $C_{45}H_{78}O_5$+NH_4: 716.6188; found 716.6201 amu.

*4.1.36. Synthesis of (R)-1-O-octadecyl-2-eicosapentaenoyl-3-hexanoyl-sn-glycerol (**8c**).* Full details are provided in Supplementary data. The product **8c** was afforded as yellowish semisolid oil (90% yield); $[\alpha]_D^{20}$ −4.7 (*c* 1.16, chloroform); HRMS (APCI): m/z calcd for $C_{47}H_{82}O_5$+NH_4: 744.6501; found 744.6473 amu.

*4.1.37. Synthesis of (R)-1-O-octadecyl-2-eicosapentaenoyl-3-octanoyl-sn-glycerol (**8d**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-octadecyl-3-octanoyl-*sn*-glycerol **5d** (100 mg, 0.212 mmol), DMAP (21 mg, 0.170 mmol), EDAC (57 mg, 0.297 mmol), dry dichloromethane (2.5 ml) and EPA as a free acid (64 mg, 0.212). The product was afforded as yellowish

oil after concentration (147 mg, 92% yield); $[\alpha]_D^{20}$ −5.0 (*c* 1.02, chloroform); IR (ZnSe) 3013 (=C−H *cis*), 2923 (C−H), 1740 (C=O), 1653 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44−5.28 (m, 10H, =C*H*), 5.22−5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.4 Hz, 1H, CH_2OCO), 3.57−3.50 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.47−3.38 (2×dt, *J*=9.4, 7.5 Hz, 2H, OCH_2CH_2), 2.88−2.77 (m, 8H, =CCH_2C=), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO in EPA), 2.30 (t, *J*=7.6 Hz, 2H, CH_2COO in octanoic acid), 2.14−2.04 (m, 4H, =CCH_2CH_2 and =CCH_2CH_3), 1.71 (quintet, *J*=7.5 Hz, 2H, CH_2CH_2COO in EPA), 1.61 (quintet (br), *J*=7.4 Hz, 2H, CH_2CH_2COO in octanoic acid), 1.54 (quintet (br), *J*=6.6 Hz, 2H, OCH_2CH_2), 1.37−1.18 (m, 38H, CH_2), 0.98 (t, *J*=7.5 Hz, 3H, CH_3 in EPA), 0.88 (br t, *J*=6.9 Hz, 6H, CH_3 in octanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.43 (α, C=O), 172.86 (β, C=O), 132.01, 128.88, 128.83, 128.54, 128.24, 128.18, 128.14, 128.05, 127.84, 126.98, 71.73 (OCH_2CH_2), 70.13 (CH_2CHCH_2), 68.88 ($CHCH_2O$), 62.72 (CH_2OCO), 34.11, 33.70, 31.91, 31.64, 29.69 (7), 29.64 (2), 29.60, 29.53, 29.46, 29.35, 29.05, 28.92, 26.48, 26.02, 25.60 (3), 25.52, 24.88, 24.79, 22.68, 22.59, 20.54, 14.26, 14.11, 14.06 ppm; HRMS (APCI): *m*/*z* calcd for $C_{49}H_{86}O_5$+H: 755.6548; found 755.6550 amu.

*4.1.38. Synthesis of (R)-1-O-octadecyl-2-eicosapentaenoyl-3-decanoyl-sn-glycerol (**8e**).* Full details are provided in Supplementary data. The product **8e** was afforded as yellowish oil (92% yield); $[\alpha]_D^{20}$ −4.5 (*c* 0.82, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{51}H_{90}O_5$+NH_4: 800.7127; found 800.7100 amu.

*4.1.39. Synthesis of (R)-1-O-octadecyl-2-eicosapentaenoyl-3-dodecanoyl-sn-glycerol (**8f**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-octadecyl-3-dodecanoyl-*sn*-glycerol **5f** (100 mg, 0.190 mmol), DMAP (19 mg, 0.152 mmol), EDAC (51 mg, 0.266 mmol), dry dichloromethane (2.5 ml) and EPA as a free acid (57 mg, 0.190). The product was afforded as yellowish oil after concentration (139 mg, 90% yield); $[\alpha]_D^{20}$ −4.3 (*c* 1.17, chloroform); IR (ZnSe) 3013 (=C−H *cis*), 2922 (C−H), 1741 (C=O), 1655 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43−5.28 (m, 10H, =C*H*), 5.22−5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.15 (dd, *J*=11.9, 6.4 Hz, 1H, CH_2OCO), 3.58−3.51 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.48−3.38 (2×dt, *J*=9.4, 7.5 Hz, 2H, OCH_2CH_2), 2.88−2.77 (m, 8H, =CCH_2C=), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO in EPA), 2.30 (t, *J*=7.6 Hz, 2H, CH_2COO in dodecanoic acid), 2.14−2.04 (m, 4H, =CCH_2CH_2 and =CCH_2CH_3), 1.70 (quintet, *J*=7.5 Hz, 2H, CH_2CH_2COO in EPA), 1.60 (quintet (br), *J*=7.1 Hz, 2H, CH_2CH_2COO in dodecanoic acid), 1.53 (quintet (br), *J*=6.5 Hz, 2H, OCH_2CH_2), 1.35−1.20 (m, 46H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in EPA), 0.88 (br t, *J*=6.9 Hz, 6H, CH_3 in dodecanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.41 (α, C=O), 172.84 (β, C=O), 132.02, 128.89, 128.84, 128.56, 128.26, 128.19, 128.16, 128.07, 127.85, 127.00, 71.75 (OCH_2CH_2), 70.16 (CH_2CHCH_2), 68.90 ($CHCH_2O$), 62.73 (CH_2OCO), 34.13, 33.72, 31.92, 31.91, 29.70 (7), 29.66, 29.65, 29.62 (3), 29.55, 29.48 (2), 29.36, 29.34, 29.29, 29.13, 26.51, 26.04, 25.62 (2), 25.61, 25.54, 24.91, 24.82, 22.69 (2), 20.55, 14.27, 14.11 (2) ppm; HRMS (APCI): *m*/*z* calcd for $C_{53}H_{94}O_5$+NH_4: 828.7440; found 828.7437 amu.

*4.1.40. Synthesis of (R)-1-O-octadecyl-2-eicosapentaenoyl-3-tetradecanoyl-sn-glycerol (**8g**).* Full details are provided in Supplementary data. The product **8g** was afforded as yellowish oil (92% yield); $[\alpha]_D^{20}$ −3.7 (*c* 0.95, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{55}H_{98}O_5$+NH_4: 856.7753; found 856.7751 amu.

*4.1.41. Synthesis of (R)-1-O-octadecyl-2-eicosapentaenoyl-3-hexadecanoyl-sn-glycerol (**8h**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-octadecyl-3-hexadecanoyl-*sn*-glycerol **5h** (100 mg, 0.172 mmol), DMAP (17 mg, 0.137 mmol), EDCI (46 mg, 0.241 mmol), dry dichloromethane (2.5 ml) and EPA as a free acid (52 mg, 0.172). The product was afforded as yellowish oil after concentration (134 mg, 90% yield); $[\alpha]_D^{20}$ −4.7 (*c* 0.91, chloroform); IR (ZnSe) 3013 (=C−H *cis*), 2922 (C−H), 1742 (C=O), 1655 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43−5.28 (m, 10H, =C*H*), 5.22−5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.15 (dd, *J*=11.9, 6.4 Hz, 1H, CH_2OCO), 3.58−3.51 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.49−3.39 (2×dt, *J*=9.4, 7.5 Hz, 2H, OCH_2CH_2), 2.88−2.77 (m, 8H, =CCH_2C=), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO in EPA), 2.30 (t, *J*=7.6 Hz, 2H, CH_2COO in hexadecanoic acid), 2.14−2.04 (m, 4H, =CCH_2CH_2 and =CCH_2CH_3), 1.70 (quintet, *J*=7.5 Hz, 2H, CH_2CH_2COO in EPA), 1.60 (quintet (br) *J*=7.2 Hz, 2H, CH_2CH_2COO in hexadecanoic acid), 1.53 (quintet (br), *J*=6.8 Hz, 2H, OCH_2CH_2), 1.35−1.17 (m, 54H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in EPA), 0.88 (br t, *J*=6.9 Hz, 6H, CH_3 in hexadecanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.41 (α, C=O), 172.83 (β, C=O), 132.01, 128.89, 128.84, 128.55, 128.26, 128.19, 128.15, 128.06, 127.85, 127.00, 71.75 (OCH_2CH_2), 70.16 (CH_2CHCH_2), 68.90 ($CHCH_2O$), 62.73 (CH_2OCO), 34.13, 33.72, 31.92 (2), 29.70 (8), 29.69 (2), 29.66 (3), 29.64, 29.63, 29.62, 29.55, 29.49, 29.47, 29.36 (2), 29.29, 29.13, 26.51, 26.04, 25.62 (2), 25.60, 25.53, 24.91, 24.82, 22.69 (2), 20.55, 14.26, 14.11 (2) ppm; HRMS (APCI): *m*/*z* calcd for $C_{57}H_{102}O_5$+NH_4: 884.8066; found 884.8066 amu.

*4.1.42. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-eicosapentaenoyl-3-acetyl-sn-glycerol (**9a**).* Full details are provided in Supplementary data. The product **9a** was afforded as yellowish oil (90% yield); $[\alpha]_D^{20}$ −5.8 (*c* 1.58, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{43}H_{72}O_5$+NH_4: 686.5718; found: 686.5715 amu.

*4.1.43. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-eicosapentaenoyl-3-butanoyl-sn-glycerol (**9b**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-*cis*-octadec-9-enyl-3-butanoyl-*sn*-glycerol **6b** (120 mg, 0.291 mmol), DMAP (25 mg, 0.236 mmol), EDAC (78 mg, 0.407 mmol), dry dichloromethane (2 ml) and EPA as a free acid (88 mg, 0.291). The product was afforded as yellowish oil after concentration (183 mg, 90% yield). $[\alpha]_D^{20}$ −5.1 (*c* 1.61, chloroform); IR (ZnSe) 3012 (=C−H *cis*), 2924 (C−H), 1742 (C=O), 1655 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44−5.28 (m, 12H, =C*H*), 5.23−5.18 (m, 1H, CH_2CHCH_2), 4.34 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.4 Hz, 1H, CH_2OCO), 3.57−3.50 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.47−3.38 (2×dt, *J*=9.4, 7.5 Hz, 2H, OCH_2CH_2), 2.88−2.77 (m, 8H, =CCH_2C=), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO in EPA), 2.29 (t, *J*=7.4 Hz, 2H, CH_2COO in butanoic acid), 2.14−2.03 (m, 4H, =CCH_2CH_2 and =CCH_2CH_3), 2.01 (quartet (br), *J*=6.3 Hz, 4H, =$CHCH_2$ in 1-*O*-alkyl), 1.71 (quintet, *J*=7.1 Hz, 2H, CH_2CH_2COO in EPA), 1.64 (sextet, *J*=7.1 Hz, 2H, CH_2CH_2COO in butanoic acid), 1.53 (quintet (br), *J*=6.6 Hz, 2H, OCH_2CH_2), 1.38−1.19 (m, 22H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in EPA), 0.94 (t, *J*=7.4 Hz, 3H, CH_3 in butanoic acid), 0.88 (br t, *J*=6.8 Hz, 3H, CH_3 in 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.22 (α, C=O), 172.84 (β, C=O), 132.01, 129.92, 129.81, 128.89, 128.84, 128.56, 128.25, 128.19, 128.15, 128.06, 127.85, 127.00, 71.74 (OCH_2CH_2), 70.15 (CH_2CHCH_2), 68.91 ($CHCH_2O$), 62.74 (CH_2OCO), 35.99, 33.71, 31.90, 29.776 (2), 29.54, 29.52, 29.50, 29.43, 29.31 (2), 29.27, 27.20 (2), 26.50, 26.02, 25.62 (2), 25.60, 25.53, 24.81, 22.67, 20.55, 18.37, 14.26, 14.10, 13.62 ppm; HRMS (APCI): *m*/*z* calcd for $C_{45}H_{76}O_5$+H: 697.5779; found: 697.5782 amu.

*4.1.44. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-eicosapentaenoyl-3-hexanoyl-sn-glycerol (**9c**).* Full details are provided in Supplementary data. The product **9c** was afforded as yellowish oil (91% yield); $[\alpha]_D^{20}$ −4.7 (*c* 1.54, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{47}H_{80}O_5$+H: 725.6079: found: 725.6062 amu.

*4.1.45. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-eicosapentaenoyl-3-octanoyl-sn-glycerol (**9d**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-*cis*-octadec-9-enyl-3-octanoyl-*sn*-glycerol **6d** (100 mg, 0.213 mmol), DMAP

(21 mg, 0.170 mmol), EDAC (57 mg, 0.298 mmol), dry dichloromethane (2 ml) and EPA as a free acid (65 mg, 0.213). The product was afforded as yellowish oil after concentration (146 mg, 91% yield); $[\alpha]_D^{20}$ −4.6 (*c* 1.58, chloroform); IR (ZnSe) 3012 (=C−H *cis*), 2924 (C−H), 1740 (C=O), 1653 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44−5.28 (m, 12H, =C*H*), 5.22−5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.4 Hz, 1H, CH_2OCO), 3.57−3.50 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.47−3.37 (2×dt, *J*=9.4, 7.5 Hz, 2H, OCH_2CH_2), 2.87−2.77 (m, 8H, $=CCH_2C=$), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO in EPA), 2.30 (t, *J*=7.6 Hz, 2H, CH_2COO in octanoic acid), 2.14−2.04 (m, 4H, $=CCH_2CH_2$ and $=CCH_2CH_3$), 2.01 (quartet (br), *J*=6.4 Hz, 4H, $=CHCH_2$ in 1-*O*-alkyl), 1.70 (quintet, *J*=7.5 Hz, 2H, CH_2CH_2COO in EPA), 1.61 (quintet (br), *J*=7.4 Hz, 2H, CH_2CH_2COO in octanoic acid), 1.54 (quintet (br), *J*=6.8 Hz, 2H, OCH_2CH_2), 1.39−1.18 (m, 30H, CH_2), 0.98 (t, *J*=7.5 Hz, 3H, CH_3 in EPA), 0.88 (br t, *J*=6.9 Hz, 6H, CH_3 in octanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.42 (α, C=O), 172.84 (β, C=O), 132.03, 129.93, 129.81, 128.89, 128.85, 128.56, 128.26, 128.19, 128.16, 128.07, 127.86, 127,00, 71.75 (OCH_2CH_2), 70.16 (CH_2CHCH_2), 68.92 ($CHCH_2O$), 62.75 (CH_2OCO), 34.13, 33.73, 31.90, 31.66, 29.77 (2), 29.55, 29.52, 29.51, 29.44, 29.32 (2), 29.28, 29.07, 28.93, 27.21 (2), 26.51, 26.03, 25.62 (2), 25.61, 25.54, 24.90, 24.82, 22.68, 22.60, 20.56, 14.27, 14.11, 14.06 ppm; HRMS (APCI): *m*/*z* calcd for $C_{49}H_{84}O_5+NH_4$: 770.6657; found: 770.6647 amu.

*4.1.46. Synthesis of (R)-1-O-cis-octadec-9′-enyl-2-eicosapentaenoyl-3-decanoyl-sn-glycerol (**9e**).* Full details are provided in Supplementary data. The product **9e** was afforded as yellowish oil (90% yield); $[\alpha]_D^{20}$ −4.5 (*c* 1.52, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{51}H_{88}O_5+NH_4$: 798.6970; found: 798.6976 amu.

*4.1.47. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-eicosapentaenoyl-3-dodecanoyl-sn-glycerol (**9f**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-*cis*-octadec-9-enyl-3-dodecanoyl-*sn*-glycerol **6f** (100 mg, 0.191 mmol), DMAP (19 mg, 0.153 mmol), EDAC (52 mg, 0.267 mmol), dry dichloromethane (2 ml) and EPA as a free acid (58 mg, 0.191 mmol). The product was afforded as yellowish oil after concentration (139 mg, 90% yield); $[\alpha]_D^{20}$ −4.4 (*c* 1.17, chloroform); IR (ZnSe) 3012 (=C−H *cis*), 2922 (C−H), 1741 (C=O), 1655 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44−5.28 (m, 12H, =C*H*), 5.22−5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.15 (dd, *J*=11.9, 6.4 Hz, 1H, CH_2OCO), 3.58−3.51 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.48−3.38 (2×dt, *J*=9.4, 7.5 Hz, 2H, OCH_2CH_2), 2.88−2.77 (m, 8H, $=CCH_2C=$), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO in EPA), 2.30 (t, *J*=7.6 Hz, 2H, CH_2COO in dodecanoic acid), 2.14−2.04 (m, 4H, $=CCH_2CH_2$ and $=CCH_2CH_3$), 2.01 (quartet (br), *J*=6.4 Hz, 4H, $=CHCH_2$ in 1-*O*-alkyl), 1.70 (quintet, *J*=7.5 Hz, 2H, CH_2CH_2COO in EPA), 1.60 (quintet (br), *J*=7.3 Hz, 2H, CH_2CH_2COO in dodecanoic acid), 1.53 (quintet (br), *J*=6.7 Hz, 2H, OCH_2CH_2), 1.38−1.19 (m, 38H, CH_2), 0.98 (t, *J*=7.5 Hz, 3H, CH_3 in EPA), 0.88 (t, *J*=6.8 Hz, 6H, CH_3 in dodecanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.42 (α, C=O), 172.84 (β, C=O), 132.02, 129.92, 129.81, 128.89, 128.85, 128.56, 128.26, 128.19, 128.16, 128.07, 127.85, 127.00, 71.75 (OCH_2CH_2), 70.16 (CH_2CHCH_2), 68.92 ($CHCH_2O$), 62.74 (CH_2OCO), 34.13, 33.72, 31.91 (2), 29.77 (2), 29.62 (2), 29.55, 29.52, 29.51, 29.48, 29.44, 29.34, 29.32 (2), 29.28 (2), 29.13, 27.21 (2), 26.51, 26.03, 25.62 (2), 25.61, 25.54, 24.91, 24.82, 22.68 (2), 20.56, 14.27, 14.11 (2) ppm; HRMS (APCI): *m*/*z* calcd for $C_{53}H_{92}O_5+NH_4$: 826.7283; found: 826.7280 amu.

*4.1.48. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-eicosapentaenoyl-3-tetradecanoyl-sn-glycerol (**9g**).* Full details are provided in Supplementary data. The product **9g** was afforded as yellowish oil (91% yield); $[\alpha]_D^{20}$ −3.5 (*c* 1.06, chloroform); HRMS (ESI): *m*/*z* calcd for $C_{55}H_{96}O_5+NH_4$: 854.7596; found: 854.7573 amu.

*4.1.49. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-eicosapentaenoyl-3-hexadecanoyl-sn-glycerol (**9h**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-*cis*-octadec-9-enyl-3-hexadecanoyl-*sn*-glycerol **6h** (100 mg, 0.172 mmol), DMAP (17 mg, 0.138 mmol), EDCI (46 mg, 0.241 mmol), dry dichloromethane (2 ml) and EPA as a free acid (52 mg, 0.172 mmol). The product was afforded as yellowish oil after concentration (137 mg, 92% yield); $[\alpha]_D^{20}$ −4.8 (*c* 0.95, chloroform); IR (ZnSe) 3012 (=C−H *cis*), 2923 (C−H), 1742 (C=O), 1655 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43−5.28 (m, 12H, =C*H*), 5.22−5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.15 (dd, *J*=11.9, 6.4 Hz, 1H, CH_2OCO), 3.58−3.51 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.48−3.38 (2×dt, *J*=9.3, 7.5 Hz, 2H, OCH_2CH_2), 2.88−2.77 (m, 8H, $=CCH_2C=$), 2.34 (t, *J*=7.6 Hz, 2H, CH_2COO in EPA), 2.29 (t, *J*=7.6 Hz, 2H, CH_2COO in hexadecanoic acid), 2.14−2.04 (m, 4H, $=CCH_2CH_2$ and $=CCH_2CH_3$), 2.01 (quartet (br), *J*=6.4 Hz, 4H, $=CHCH_2$ in 1-*O*-alkyl), 1.70 (quintet, *J*=7.5 Hz, 2H, CH_2CH_2COO in EPA), 1.60 (quintet (br), *J*=7.2 Hz, 2H, CH_2CH_2COO in hexadecanoic acid), 1.53 (quintet (br), *J*=6.8 Hz, 2H, OCH_2CH_2), 1.38−1.20 (m, 46H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in EPA), 0.88 (t, *J*=6.9 Hz, 6H, CH_3 in hexadecanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.39 (α, C=O), 172.82 (β, C=O), 132.00, 129.91, 129.79, 128.88, 128.84, 128.55, 128.25, 128.18, 128.15, 128.05, 127.84, 126.99, 71.73 (OCH_2CH_2), 70.16 (CH_2CHCH_2), 68.91 ($CHCH_2O$), 62.73 (CH_2OCO), 34.12, 33.71, 31.91, 31.90, 29.76 (2), 29.69 (3), 29.65 (2), 29.62, 29.54, 29.51, 29.50, 29.48, 29.43, 29.35, 29.31 (2), 29.28 (2), 29.12, 27.20 (2), 26.50, 26.02, 25.61 (2), 25.60, 25.53, 24.90, 24.81, 22.68 (2), 20.54, 14.26, 14.10 (2) ppm; HRMS (ESI): *m*/*z* calcd for $C_{57}H_{100}O_5+NH_4$: 882.7909; found 882.7923 amu.

*4.1.50. Synthesis of (R)-1-O-hexadecyl-2-docosahexaenoyl-3-acetyl-sn-glycerol (**10a**).* Full details are provided in Supplementary data. The product **10a** was afforded as yellowish oil (91% yield); $[\alpha]_D^{20}$ −5.8 (*c* 1.46, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{43}H_{72}O_5+NH_4$: 686.5718; found 686.5720 amu.

*4.1.51. Synthesis of (R)-1-O-hexadecyl-2-docosahexaenoyl-3-butanoyl-sn-glycerol (**10b**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-hexadecyl-3-butanoyl-*sn*-glycerol **4b** (100 mg, 0.259 mmol), DMAP (25 mg, 0.207 mmol), EDAC (70 mg, 0.363 mmol), dry dichloromethane (2.5 ml) and DHA as a free acid (85 mg, 0.259 mmol). The product was afforded as yellowish oil after concentration (166 mg, 92% yield); $[\alpha]_D^{20}$ −5.2 (*c* 1.16, chloroform); IR (ZnSe) 3013 (=C−H *cis*), 2922 (C−H), 1741 (C=O), 1653 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43−5.28 (m, 12H, =CH), 5.23−5.18 (m, 1H, CH_2CHCH_2), 4.34 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.4 Hz, 1H, CH_2OCO), 3.57−3.50 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.47−3.38 (2×dt, *J*=9.4, 7.4 Hz, 2H, OCH_2CH_2), 2.90−2.78 (m, 10H, $=CCH_2C=$), 2.41−2.37 (m, 4H, CH_2CH_2COO in DHA), 2.29 (t, *J*=7.4 Hz, 2H, CH_2COO in butanoic acid), 2.08 (quintet (br), *J*=7.4 Hz, 2H ,$=CCH_2CH_3$), 1.64 (sextet, *J*=7.4 Hz, 2H, CH_2CH_2COO in butanoic acid), 1.52 (quintet (br), *J*=6.8 Hz, 2H, OCH_2CH_2), 1.35−1.19 (m, 26H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in DHA), 0.94 (t, *J*=7.4 Hz, 3H, CH_3 butanoic acid), 0.88 (br t, *J*=6.8 Hz, 3H, CH_3 in 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.22 (α, C=O), 172.37 (β, C=O), 132.02, 129.29, 128.56, 128.27 (2), 128.23, 128.09, 128.06, 128.03, 127.86, 127.79, 127.00, 71.76 (OCH_2CH_2), 70.28 (CH_2CHCH_2), 68.87 ($CHCH_2O$), 62.71 (CH_2OCO), 36.00, 34.16, 31.92, 29.70 (5), 29.66, 29.64, 29.61, 29.55, 29.46, 29.36, 26.03, 25.62 (3), 25.59, 25.54, 22.72, 22.69, 20.55, 18.38, 14.27, 14.11, 13.63 ppm; HRMS (APCI): *m*/*z* calcd for $C_{45}H_{76}O_5+NH_4$: 714.6031; found 714.6044 amu.

*4.1.52. Synthesis of (R)-1-O-hexadecyl-2-docosahexaenoyl-3-hexanoyl-sn-glycerol (**10c**).* Full details are provided in Supplementary

data. The product **10c** was afforded as yellowish oil (92% yield); $[\alpha]_D^{20}$ −4.7 (*c* 1.44, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{47}H_{80}O_5$+H: 725.6079; found 725.6091 amu.

*4.1.53. Synthesis of (R)-1-O-hexadecyl-2-docosahexaenoyl-3-octanoyl-sn-glycerol (**10d**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-hexadecyl-3-octanoyl-*sn*-glycerol **4d** (100 mg, 0.226 mmol), DMAP (22 mg, 0.181 mmol), EDAC (61 mg, 0.316 mmol), dry dichloromethane (2.5 ml) and DHA as a free acid (74 mg, 0.226 mmol). The product was afforded as yellowish oil after concentration (155 mg, 91% yield); $[\alpha]_D^{20}$ −3.3 (*c* 1.35, chloroform); IR (ZnSe) 3013 (=C−H *cis*), 2922 (C−H), 1742 (C=O), 1653 (C=C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.43−5.28 (m, 12H ,=CH), 5.22−5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.3 Hz, 1H, CH_2OCO), 3.57−3.50 (2×dd, 10.7, 5.3 Hz, 2H, $CHCH_2O$), 3.47−3.38 (2×dt, 9.4, 7.4 Hz, 2H, OCH_2CH_2), 2.91−2.77 (m, 10H, $=CCH_2C=$), 2.42−2.37 (m, 4H, CH_2CH_2COO in DHA), 2.30 (t, *J*=7.5 Hz, 2H, CH_2COO in octanoic acid), 2.08 (quintet (br), *J*=7.3 Hz, 2H, $=CCH_2CH_3$), 1.61 (quintet (br), *J*=7.4 Hz, 2H, CH_2CH_2COO in octanoic acid), 1.54 (quintet (br), *J*=6.6 Hz, 2H, OCH_2CH_2), 1.36−1.18 (m, 34H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in DHA), 0.88 (br t, *J*=6.9 Hz, 6H, CH_3 in octanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) *δ* 173.41 (*α*, C=O), 172.37 (*β*, C=O), 132.02, 129.29, 128.56, 128.27 (2C), 128.23, 128.09, 128.06, 128.03, 127.86, 127.79, 127.00, 71.76 (OCH_2CH_2), 70.29 (CH_2CHCH_2), 68.87 ($CHCH_2O$), 62.70 (CH_2OCO), 34.16, 34.13, 31.92, 31.66, 29.70 (5C), 29.66, 29.64, 29.61, 29.55, 29.47, 29.36, 29.07, 28.93, 26.03, 25.62 (3C), 25.59, 25.53, 24.90, 22.72, 22.69, 22.60, 20.55, 14.26, 14.11, 14.06 ppm; HRMS (APCI): *m*/*z* calcd for $C_{49}H_{84}O_5$+H: 753.6392; found 753.6388 amu.

*4.1.54. Synthesis of (R)-1-O-hexadecyl-2-docosahexaenoyl-3-decanoyl-sn-glycerol (**10e**).* Full details are provided in Supplementary data. The product **10e** was afforded as yellowish oil (92% yield); $[\alpha]_D^{20}$ −3.0 (*c* 1.16, chloroform); HRMS (ESI): *m*/*z* calcd for $C_{51}H_{88}O_5$+NH_4: 798.6970; found 798.6967 amu.

*4.1.55. Synthesis of (R)-1-O-hexadecyl-2-docosahexaenoyl-3-dodecanoyl-sn-glycerol (**10f**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-hexadecyl-3-dodecanoyl-*sn*-glycerol **4f** (100 mg, 0.200 mmol), DMAP (20 mg, 0.160 mmol), EDAC (54 mg, 0.280 mmol), dry dichloromethane (2.5 ml) and DHA as a free acid (66 mg, 0.200 mmol). The product was afforded as yellowish oil after concentration (147 mg, 91% yield); $[\alpha]_D^{20}$ −3.1 (*c* 1.43, chloroform); IR (ZnSe) 3013 (=C−H *cis*), 2922 (C−H), 1742 (C=O), 1653 (C=C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.43−5.28 (m, 12H, =CH), 5.22−5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.3 Hz, 1H, CH_2OCO), 3.57−3.50 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.47−3.38 (2×dt, *J*=9.4, 7.4 Hz, 2H, OCH_2CH_2), 2.91−2.77 (m, 10H, $=CCH_2C=$), 2.44−2.36 (m, 4H, CH_2CH_2COO in DHA), 2.30 (t, *J*=7.5 Hz, 2H, CH_2COO in dodecanoic acid), 2.08 (quintet (br), *J*=7.3 Hz, 2H, $=CCH_2CH_3$), 1.60 (quintet, *J*=7.3 Hz, 2H, CH_2CH_2COO in dodecanoic acid), 1.53 (quintet (br), *J*=6.8 Hz, 2H, OCH_2CH_2), 1.37−1.18 (m, 42H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in DHA), 0.88 (br t, *J*=6.9 Hz, 6H, CH_3 in dodecanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) *δ* 173.42 (*α*, C=O), 172.37 (*β*, C=O), 132.02, 129.29, 128.56, 128.27(2), 128.24, 128.09, 128.07, 128.04, 127.86, 127.79, 127.00, 71.76 (OCH_2CH_2), 70.29 (CH_2CHCH_2), 68.87 ($CHCH_2O$), 62.70 (CH_2OCO), 34.16, 34.14, 31.93, 31.91, 29.70 (5), 29.66, 29.64, 29.62 (3), 29.55, 29.48 (2), 29.36, 29.34, 29.29, 29.13, 26.04, 25.63 (3), 25.60, 25.54, 24.91, 22.72, 22.69 (2), 20.56, 14.27, 14.11 (2) ppm; HRMS (APCI): *m*/*z* calcd for $C_{53}H_{92}O_5$+NH_4: 826.7283; found 826.7285 amu.

*4.1.56. Synthesis of (R)-1-O-hexadecyl-2-docosahexaenoyl-3-tetradecanoyl-sn-glycerol (**10g**).* Full details are provided in Supplementary data. The product **10g** was afforded as yellowish oil (93% yield); $[\alpha]_D^{20}$ −3.7 (*c* 1.25, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{55}H_{96}O_5$+NH_4: 854.7596; found 854.7598 amu.

*4.1.57. Synthesis of (R)-1-O-hexadecyl-2-docosahexaenoyl-3-hexadecanoyl-sn-glycerol (**10h**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-hexadecyl-3-hexadecanoyl-*sn*-glycerol **4h** (100 mg, 0.180 mmol), DMAP (18 mg, 0.144 mmol), EDAC (48 mg, 0.252 mmol), dry dichloromethane (2.5 ml) and DHA as a free acid (59 mg, 0.180 mmol). The product was afforded as yellowish oil after concentration (142 mg, 91% yield); $[\alpha]_D^{20}$ −3.4 (*c* 0.93, chloroform); IR (ZnSe) 3013 (=C−H *cis*), 2922 (C−H), 1742 (C=O), 1656 (C=C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.43−5.28 (m, 12H, =CH), 5.22−5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.8 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.3 Hz, 1H, CH_2OCO), 3.57−3.50 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.47−3.38 (2×dt, *J*=9.4, 7.4 Hz, 2H, OCH_2CH_2), 2.91−2.77 (m, 10H, $=CCH_2C=$), 2.42−2.37 (m, 4H, CH_2CH_2COO in DHA), 2.30 (t, *J*=7.5 Hz, 2H, CH_2COO in hexadecanoic acid), 2.08 (quintet (br), *J*=7.4 Hz, 2H, $=CCH_2CH_3$), 1.61 (quintet (br), *J*=7.3 Hz, 2H, CH_2CH_2COO in hexadecanoic acid), 1.54 (quintet (br), *J*=6.9 Hz, 2H, OCH_2CH_2), 1.37−1.17 (m, 50H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in DHA), 0.88 (br t, *J*=6.9 Hz, 6H, CH_3 in hexadecanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) *δ* 173.40 (*α*, C=O), 172.35 (*β*, C=O), 132.00, 129.29, 128.55, 128.26 (2), 128.23, 128.09, 128.06, 128.03, 127.85, 127.79, 127.00, 71.76 (OCH_2CH_2), 70.28 (CH_2CHCH_2), 68.87 ($CHCH_2O$), 62.69 (CH_2OCO), 34.16, 34.13, 31.92 (2), 29.70 (8), 29.66 (3), 29.64, 29.63, 29.61, 29.55, 29.49, 29.47, 29.36 (2), 29.29, 29.13, 26.03, 25.62 (3), 25.59, 25.53, 24.90, 22.72, 22.69 (2), 20.55, 14.26, 14.11 (2) ppm; HRMS (APCI): *m*/*z* calcd for $C_{57}H_{100}O_5$+NH_4: 882.7909; found 882.7906 amu.

*4.1.58. Synthesis of (R)-1-O-octadecyl-2-docosahexaenoyl-3-acetyl-sn-glycerol (**11a**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-octadecyl-3-acetyl-*sn*-glycerol **5a** (100 mg, 0.259 mmol), DMAP (25 mg, 0.207 mmol), EDAC (70 mg, 0.363 mmol), dry dichloromethane (2.5 ml) and DHA as a free acid (85 mg, 0.259). The product was afforded as yellowish semisolid oil after concentration (162 mg, 90% yield); $[\alpha]_D^{20}$ −6.0 (*c* 0.80, chloroform); IR (ZnSe) 3013 (=C−H *cis*), 2922 (C−H), 1744 (C=O), 1656 (C=C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.43−5.28 (m, 12H, =CH), 5.23−5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.5 Hz, 1H, CH_2OCO), 3.57−3.50 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.47−3.38 (2×dt, *J*=9.4, 7.4 Hz, 2H, OCH_2CH_2), 2.88−2.77 (m, 10H, $=CCH_2C=$), 2.42−2.36 (m, 4H, CH_2CH_2COO), 2.11−2.04 (m, 2H, $=CCH_2CH_3$), 2.05 (s, 3H, CH_3COO), 1.54 (quintet (br), *J*=7.0 Hz, 2H, OCH_2CH_2), 1.35−1.19 (m, 30H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in DHA), 0.88 (br t, *J*=6.9 Hz, 3H, CH_3 in 1-*O*-alkyl) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.40 (*β*, C=O), 170.62 (*α*, C=O), 132.01, 129.30, 128.55, 128.26 (2), 128.23, 128.08, 128.06, 128.02, 127.85, 127.77, 127.00, 71.76 (OCH_2CH_2), 70.23 (CH_2CHCH_2), 68.85 ($CHCH_2O$), 63.00 (CH_2OCO), 34.16, 31.92, 29.69 (7), 29.65, 29.63, 29.60, 29.54, 29.46, 29.35, 26.02, 25.62 (3), 25.59, 25.53, 22.72, 22.68, 20.76, 20.55, 14.26, 14.11 ppm; HRMS (APCI): *m*/*z* calcd for $C_{45}H_{76}O_5$+NH_4: 714.6031; found 714.6008 amu.

*4.1.59. Synthesis of (R)-1-O-octadecyl-2-docosahexaenoyl-3-butanoyl-sn-glycerol (**11b**).* Full details are provided in Supplementary data. The product **11b** was afforded as yellowish semisolid oil (92% yield); $[\alpha]_D^{20}$ −4.0 (*c* 1.07, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{47}H_{80}O_5$+NH_4: 742.6344; found 742.6324 amu.

*4.1.60. Synthesis of (R)-1-O-octadecyl-2-docosahexaenoyl-3-hexanoyl-sn-glycerol (**11c**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-octadecyl-3-hexanoyl-*sn*-glycerol **5c** (100 mg, 0.226 mmol), DMAP (22 mg, 0.181 mmol), EDAC (61 mg, 0.316 mmol), dry dichloromethane (2.5 ml) and EPA as a free acid (74 mg, 0.226). The product was afforded as yellowish

semisolid oil after concentration (157 mg, 92% yield); $[\alpha]_D^{20}$ −3.7 (*c* 1.36, chloroform); IR (ZnSe) 3013 (=C−H *cis*), 2922 (C−H), 1742 (C=O), 1654 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43−5.28 (m, 12H, =C*H*), 5.23−5.18 (m, 1H, CH_2CHCH_2), 4.34 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.4 Hz, 1H, CH_2OCO), 3.57−3.50 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.47−3.38 (2×dt, *J*=9.4, 7.4 Hz, 2H, OCH_2CH_2), 2.88−2.78 (m, 10H, $=CCH_2C=$), 2.42−2.37 (m, 4H, CH_2CH_2COO in DHA), 2.30 (t, *J*=7.5 Hz, 2H, CH_2COO in hexanoic acid), 2.08 (quintet, *J*=7.3 Hz, 2H, $=CCH_2CH_3$), 1.62 (quintet, *J*=7.5 Hz, 2H, CH_2CH_2COO in hexanoic acid), 1.54 (quintet (br), *J*=6.9 Hz, 2H, OCH_2CH_2), 1.35−1.20 (m, 34H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in DHA), 0.89 (br t, *J*=6.2 Hz, 3H, CH_3 hexanoic acid), 0.88 (br t, *J*=6.2 Hz, 3H, CH_3 in 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.42 (α, C=O), 172.37 (β, C=O), 132.03, 129.30, 128.56, 128.27 (2), 128.24, 128.10, 128.07, 128.04, 127.87, 127.80, 127.00, 71.77 (OCH_2CH_2), 70.29 (CH_2CHCH_2), 68.88 ($CHCH_2O$), 62.72 (CH_2OCO), 34.17, 34.10, 31.93, 31.26, 29.71 (7), 29.66, 29.65, 29.62, 29.56, 29.47, 29.36, 26.04, 25.63 (3), 25.60, 25.54, 24.58, 22.72, 22.69, 22.31, 20.56, 14.27, 14.12, 13.90 ppm; HRMS (APCI): *m*/*z* calcd for $C_{49}H_{84}O_5+NH_4$: 770.6657; found 770.6676 amu.

*4.1.61. Synthesis of (R)-1-O-octadecyl-2-docosahexaenoyl-3-octanoyl-sn-glycerol (**11d**).* Full details are provided in Supplementary data. The product **11d** was afforded as yellowish oil (, 90% yield); $[\alpha]_D^{20}$ −3.5 (*c* 1.11, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{51}H_{88}O_5+NH_4$: 798.6970; found 798.6961 amu.

*4.1.62. Synthesis of (R)-1-O-octadecyl-2-docosahexaenoyl-3-decanoyl-sn-glycerol (**11e**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-octadecyl-3-decanoyl-*sn*-glycerol **5e** (100 mg, 0.200 mmol), DMAP (20 mg, 0.160 mmol), EDCI (54 mg, 0.280 mmol), dry dichloromethane (2.5 ml) and DHA as a free acid (66 mg, 0.200). The product was afforded as yellowish oil after concentration (155 mg, 95% yield); $[\alpha]_D^{20}$ −2.8 (*c* 0.76, chloroform); IR (ZnSe) 3013 (=C−H *cis*), 2922 (C−H), 1742 (C=O), 1655 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43−5.28 (m, 12H, =C*H*), 5.22−5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.3 Hz, 1H, CH_2OCO), 3.57−3.50 (2×dd, *J*=10.7, 5.3 Hz, 2H, $CHCH_2O$), 3.47−3.38 (2×dt, *J*=9.4, 7.4 Hz, 2H, OCH_2CH_2), 2.89−2.78 (m, 10H, $=CCH_2C=$), 2.42−2.36 (m, 4H, CH_2CH_2COO in DHA), 2.30 (t, *J*=7.5 Hz, 2H, CH_2COO in decanoic acid), 2.08 (quintet (br), *J*=7.4 Hz, 2H, $=CCH_2CH_3$), 1.61 (quintet (br), *J*=7.4 Hz, 2H, CH_2CH_2COO in decanoic acid), 1.54 (quintet (br), *J*=6.5 Hz, 2H, OCH_2CH_2), 1.36−1.18 (m, 42H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in DHA), 0.88 (br t, *J*=6.8 Hz, 6H, CH_3 in decanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.42 (α, C=O), 172.37 (β, C=O), 132.02, 129.29, 128.56, 128.27 (2), 128.24, 128.10, 128.07, 128.04, 127.86, 127.80, 127.01, 71.77 (OCH_2CH_2), 70.29 (CH_2CHCH_2), 68.88 ($CHCH_2O$), 62.70 (CH_2OCO), 34.17, 34.14, 31.93, 31.87, 29.71 (7), 29.66, 29.65, 29.62, 29.55, 29.48, 29.44, 29.36, 29.28 (2), 29.13, 26.04, 25.63 (3), 25.60, 25.54, 24.91, 22.72, 22.69, 22.67, 20.56, 14.27, 14.12, 14.10 ppm; HRMS (APCI): *m*/*z* calcd for $C_{53}H_{92}O_5+NH_4$: 826.7283; found 826.7294 amu.

*4.1.63. Synthesis of (R)-1-O-octadecyl-2-docosaenoyl-3-dodecanoyl-sn-glycerol (**11f**).* Full details are provided in Supplementary data. The product **11f** was afforded as yellowish oil (90% yield); $[\alpha]_D^{20}$ −3.0 (*c* 1.26, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{55}H_{96}O_5+NH_4$: 854.7596; found 854.7566 amu.

*4.1.64. Synthesis of (R)-1-O-octadecyl-2-docosahexaenoyl-3-tetradecanoyl-sn-glycerol (**11g**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-octadecyl-3-tetradecanoyl-*sn*-glycerol **5g** (100 mg, 0.180 mmol), DMAP (18 mg, 0.144 mmol), EDAC (48 mg, 0.252 mmol), dry dichloromethane (2.5 ml) was added DHA as a free acid (59 mg, 0.180). The product was afforded as yellowish oil after concentration (145 mg, 93% yield); $[\alpha]_D^{20}$ −3.8 (*c* 1.04, chloroform); IR (ZnSe) 3013 (=C−H *cis*), 2922 (C−H), 1742 (C=O), 1655 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43−5.28 (m, 12H, =C*H*), 5.22−5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.8 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.3 Hz, 1H, CH_2OCO), 3.57−3.50 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.47−3.38 (2×dt, *J*=9.4, 7.4 Hz, 2H, OCH_2CH_2), 2.88−2.78 (m, 10H, $=CCH_2C=$), 2.42−2.37 (m, 4H, CH_2CH_2COO in DHA), 2.30 (t, *J*=7.6 Hz, 2H, CH_2COO in tetradecanoic acid), 2.07 (quintet (br), *J*=7.3 Hz, 2H, $=CCH_2CH_3$), 1.60 (quintet, *J*=7.3 Hz, 2H, CH_2CH_2COO in tetradecanoic acid), 1.53 (quintet (br), *J*=6.9 Hz, 2H, OCH_2CH_2), 1.35−1.20 (m, 50H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in DHA), 0.88 (br t, *J*=6.9 Hz, 6H, CH_3 in tetradecanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.41 (α, C=O), 172.38 (β, C=O), 132.02, 129.30, 128.56, 128.27 (2), 128.24, 128.10, 128.07, 128.04, 127.87, 127.80, 127.01, 71.77 (OCH_2CH_2), 70.30 (CH_2CHCH_2), 68.88 ($CHCH_2O$), 62.70 (CH_2OCO), 34.17, 34.14, 31.93 (2), 29.71 (6), 29.69 (2), 29.66 (4), 29.63 (2C), 29.56, 29.50, 29.48, 29.36 (2), 29.30, 29.14, 26.04, 25.63 (3), 25.60, 25.54, 24.91, 22.73, 22.69 (2), 20.56, 14.27, 14.12 (2) ppm; HRMS (APCI): *m*/*z* calcd for $C_{57}H_{100}O_5+H$: 865.7644; found 865.7647 amu.

*4.1.65. Synthesis of (R)-1-O-octadecyl-2-docosahexaenoyl-3-hexadecanoyl-sn-glycerol (**11h**).* Full details are provided in Supplementary data. The product **11h** was afforded as yellowish oil (90% yield); $[\alpha]_D^{20}$ −4.1 (*c* 1.02, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{59}H_{104}O_5+NH_4$: 910.8222; found 910.8239 amu.

*4.1.66. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-docosahexaenoyl-3-acetyl-sn-glycerol (**12a**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-*cis*-octadec-9-enyl-3-acetyl-*sn*-glycerol **6a** (100 mg, 0.260 mmol), DMAP (25 mg, 0.208 mmol), EDAC (70 mg, 0.364 mmol), dry dichloromethane (2 ml) and DHA as a free acid (85 mg, 0.260 mmol). The product was afforded as yellowish oil after concentration (163 mg, 90% yield); $[\alpha]_D^{20}$ −5.5 (*c* 1.68, chloroform); IR (ZnSe) 3012 (=C−H *cis*), 2924 (C−H), 1744 (C=O), 1654 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43−5.28 (m, 14H, =C*H*), 5.23−5.18 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.5 Hz, 1H, CH_2OCO), 3.58−3.51 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.49−3.39 (2×dt, *J*=9.3, 7.3 Hz, 2H, OCH_2CH_2), 2.88−2.80 (m, 10H, $=CCH_2C=$), 2.42−2.39 (m, 4H, CH_2CH_2COO in DHA), 2.11−2.03 (m, 2H, $=CCH_2CH_3$), 2.05 (s, 3H, CH_3COO), 2.01 (quartet (br), *J*=6.5 Hz, 4H, $=CHCH_2$ in 1-*O*-alkyl), 1.54 (quintet (br), *J*=6.8 Hz, 2H, OCH_2CH_2), 1.38−1.21 (m, 22H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in DHA), 0.88 (br t, *J*=6.9 Hz, 3H, CH_3 in 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 172.41 (β, C=O), 170.64 (α, C=O), 132.03, 129.93, 129.82, 129.32, 128.57, 128.28 (2), 128.24, 128.10, 128.07, 128.04, 127.87, 127.78, 127.01, 71.77 (OCH_2CH_2), 70.23 (CH_2CHCH_2), 68.87 ($CHCH_2O$), 63.01 (CH_2OCO), 34.17, 31.91, 29.77 (2), 29.55, 29.52, 29.51, 29.44, 29.32 (2), 29.28, 27.21 (2), 26.03, 25.63 (3), 25.60, 25.54, 22.73, 22.68, 20.78, 20.56, 14.27, 14.11 ppm; HRMS (APCI): *m*/*z* calcd for $C_{45}H_{74}O_5+NH_4$: 712.5875; found: 712.5870 amu.

*4.1.67. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-docosahexaenoyl-3-butanoyl-sn-glycerol (**12b**).* Full details are provided in Supplementary data. The product **12b** was afforded as yellowish oil (90% yield); $[\alpha]_D^{20}$ −4.7 (*c* 1.54, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{47}H_{78}O_5+NH_4$: 740.6188; found: 740.6190 amu.

*4.1.68. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-docosahexaenoyl-3-hexanoyl-sn-glycerol (**12c**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-*cis*-octadec-9-enyl-3-hexanoyl-*sn*-glycerol **6c** (120 mg, 0.272 mmol), DMAP (26 mg, 0.218 mmol), EDAC (73 mg, 0.380 mmol), dry dichloromethane (2 ml) and DHA as a free acid (89 mg, 0.272). The product was afforded as yellowish oil after concentration (184 mg, 90% yield); $[\alpha]_D^{20}$ −4.3 (*c* 1.26, chloroform); IR (ZnSe) 3012 (=C−H *cis*),

2924 (C–H), 1741 (C=O), 1653 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43–5.28 (m, 14H, =C*H*), 5.23–5.18 (m, 1H, CH_2CHCH_2), 4.34 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.4 Hz, 1H, CH_2OCO), 3.57–3.50 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.47–3.38 (2×dt, *J*=9.4, 7.4 Hz, 2H, OCH_2CH_2), 2.88–2.78 (m, 10H, $=CCH_2C=$), 2.42–2.36 (m, 4H, CH_2CH_2COO in DHA), 2.30 (t, *J*=7.5 Hz, 2H, CH_2COO in hexanoic acid), 2.07 (quintet, *J*=7.5 Hz, 2H, $=CCH_2CH_3$), 2.01 (quartet (br), *J*=6.4 Hz, 4H, $=CHCH_2$ in 1-*O*-alkyl), 1.61 (quintet, *J*=7.5 Hz, 2H, CH_2CH_2COO in hexanoic acid), 1.54 (quintet (br), *J*=7.2 Hz, 2H, OCH_2CH_2), 1.38–1.19 (m, 26H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in DHA), 0.89 (br t, *J*=6.9 Hz, 3H, CH_3 hexanoic acid), 0.88 (br t, *J*=6.1 Hz, 3H, CH_3 in 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.43 (α, C=O), 172.38 (β, C=O), 132.01, 129.91, 129.80, 129.28, 128.54, 128.25 (2), 128.22, 128.07, 128.05, 128.02, 127.84, 127.77, 126.99, 71.73 (OCH_2CH_2), 70.25 (CH_2CHCH_2), 68.85 ($CHCH_2O$), 62.70 (CH_2OCO), 34.13, 34.07, 31.89, 31.23, 29.75 (2), 29.51 (2), 29.49, 29.42, 29.30 (2), 29.26, 27.19 (2), 26.01, 25.60 (3), 25.57, 25.51, 24.56, 22.69, 22.67, 22.29, 20.54, 14.26, 14.11, 13.89 ppm; HRMS (APCI): *m*/*z* calcd for $C_{49}H_{82}O_5$+H: 751.6235; found: 751.6230 amu.

*4.1.69. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-docosahexaenoyl-3-octanoyl-sn-glycerol (**12d**).* Full details are provided in Supplementary data. The product **12d** was afforded as yellowish oil (90% yield); $[\alpha]_D^{20}$ −4.1 (*c* 1.25, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{51}H_{86}O_5$+H: 779.6548; found: 779.6552 amu.

*4.1.70. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-dodecahexaenoyl-3-decanoyl-sn-glycerol (**12e**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-*cis*-octadec-9-enyl-3-decanoyl-*sn*-glycerol **6e** (100 mg, 0.201 mmol), DMAP (20 mg, 0.161 mmol), EDAC (54 mg, 0.281 mmol), dry dichloromethane (2 ml) and DHA as a free acid (66 mg, 0.201). The product was afforded as yellowish oil after concentration (148 mg, 91% yield); $[\alpha]_D^{20}$ −3.7 (*c* 1.55, chloroform); IR (ZnSe) 3013 (=C–H *cis*), 2923 (C–H), 1741 (C=O), 1654 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43–5.28 (m, 14H, =C*H*), 5.22–5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.3 Hz, 1H, CH_2OCO), 3.58–3.51 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.48–3.39 (2×dt, *J*=9.4, 7.4 Hz, 2H, OCH_2CH_2), 2.88–2.78 (m, 10H, $=CCH_2C=$), 2.42–2.36 (m, 4H, CH_2CH_2COO in DHA), 2.30 (t, *J*=7.5 Hz, 2H, CH_2COO in decanoic acid), 2.07 (quintet (br), *J*=7.4 Hz, 2H, $=CCH_2CH_3$), 2.01 (quartet (br), *J*=6.5 Hz, 4H, $=CHCH_2$ in 1-*O*-alkyl), 1.60 (quintet (br), *J*=7.3 Hz, 2H, CH_2CH_2COO in decanoic acid), 1.54 (quintet (br), *J*=6.8 Hz, 2H, OCH_2CH_2), 1.38–1.18 (m, 34H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in DHA), 0.88 (br t, *J*=7.2 Hz, 6H, CH_3 in decanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.42 (α, C=O), 172.37 (β, C=O), 132.02, 129.92, 129.81, 129.29, 128.56, 128.27 (2), 128.24, 128.09, 128.06, 128.03, 127.86, 127.79, 127.01, 71.75 (OCH_2CH_2), 70.29 (CH_2CHCH_2), 68.89 ($CHCH_2O$), 62.70 (CH_2OCO), 34.16, 34.14, 31.90, 31.86, 29.77 (2), 29.56, 29.52, 29.51, 29.44 (2), 29.32 (2), 29.28 (3), 29.13, 27.21 (2), 26.04, 25.63 (3), 25.60, 25.54, 24.91, 22.72, 22.68, 22.66, 20.56, 14.27, 14.11 (2) ppm; HRMS (APCI): *m*/*z* calcd for $C_{53}H_{90}O_5$+H: 807.6861; found: 807.6888 amu.

*4.1.71. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-docosahexaenoyl-3-dodecanoyl-sn-glycerol (**12f**).* Full details are provided in Supplementary data. The product **12f** was afforded as yellowish oil (90% yield); $[\alpha]_D^{20}$ −3.8 (*c* 1.64, chloroform); HRMS (APCI): *m*/*z* calcd for $C_{55}H_{94}O_5$+NH_4: 852.7440; found: 852.7423 amu.

*4.1.72. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-docosahexaenoyl-3-tetradecanoyl-sn-glycerol (**12g**).* A procedure identical to the one described above for **7a** was followed using (*R*)-1-*O*-*cis*-octadec-9-enyl-3-tetradecanoyl-*sn*-glycerol **6g** (100 mg, 0.181 mmol), DMAP (18 mg, 0.145 mmol), EDAC (49 mg, 0.253 mmol), dry dichloromethane (2 ml) and DHA as a free acid (59 mg, 0.181 mmol). The product was afforded as yellowish oil after concentration (140 mg, 90% yield); $[\alpha]_D^{20}$ −3.5 (*c* 1.29, chloroform); IR (ZnSe) 3013 (=C–H *cis*), 2923 (C–H), 1742 (C=O), 1654 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43–5.28 (m, 14H, =C*H*), 5.22–5.17 (m, 1H, CH_2CHCH_2), 4.33 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2OCO), 4.16 (dd, *J*=11.9, 6.3 Hz, 1H, CH_2OCO), 3.57–3.50 (2×dd, *J*=10.6, 5.3 Hz, 2H, $CHCH_2O$), 3.47–3.38 (2×dt, *J*=9.4, 7.4 Hz, 2H, OCH_2CH_2), 2.88–2.77 (m, 10H, $=CCH_2C=$), 2.42–2.36 (m, 4H, CH_2CH_2COO in DHA), 2.30 (t, *J*=7.5 Hz, 2H, CH_2COO in tetradecanoic acid), 2.08 (quintet (br), *J*=7.4 Hz, 2H, $=CCH_2CH_3$), 2.01 (quartet (br), *J*=6.4 Hz, 4H, $=CHCH_2$ in 1-*O*-alkyl), 1.60 (quintet (br), *J*=7.3 Hz, 2H, CH_2CH_2COO in tetradecanoic acid), 1.54 (quintet (br), *J*=6.7 Hz, 2H, OCH_2CH_2), 1.38–1.20 (m, 42H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 in DHA), 0.88 (br t, *J*=6.9 Hz, 6H, CH_3 in tetradecanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.42 (α, C=O), 172.37 (β, C=O), 132.02, 129.93, 129.81, 129.30, 128.56, 128.27 (2), 128.24, 128.10, 128.07, 128.04, 127.86, 127.79, 127.01, 71.76 (OCH_2CH_2), 70.29 (CH_2CHCH_2), 68.89 ($CHCH_2O$), 62.70 (CH_2OCO), 34.16, 34.14, 31.92, 31.91, 29.77 (2), 29.69, 29.66, 29.65, 29.63, 29.56, 29.53, 29.51, 29.49, 29.45, 29.34, 29.32 (2), 29.29 (2), 29.14, 27.22 (2), 26.04, 25.63 (3), 25.60, 25.54, 24.91, 22.72, 22.69 (2), 20.56, 14.27, 14.12 (2) ppm; HRMS (ESI): *m*/*z* calcd for $C_{57}H_{98}O_5$+NH_4: 880.7753; found: 880.7755 amu.

*4.1.73. Synthesis of (R)-1-O-cis-octadec-9-enyl-2-docosahexaenoyl-3-hexadecanoyl-sn-glycerol (**12h**).* Full details are provided in Supplementary data. The product **12h** was afforded as yellowish oil (91% yield); $[\alpha]_D^{20}$ −3.8 (*c* 0.90, chloroform); HRMS (ESI): *m*/*z* calcd for $C_{59}H_{102}O_5$+NH_4: 908.8066; found 908.8102 amu.

4.1.74. Calculation of the equilibrium level of 2-monoacyl-1-O-alkyl-sn-glycerol. To a solution of pure 1-*O*-octadecyl-3-octanoyl-*sn*-glycerol **5d** (100 mg, 0.212 mmol) in dry CH_2Cl_2 (3 ml), Amberlyst 15 (10 mg) was added and the resulting mixture stirred at room temperature for 7 days. Aliquots (0.8 ml) were withdrawn from the reaction mixture, with 56 h intervals, passed through a Pasteur pipette packed with a plug of cotton wool and concentrated in vacuo. The afforded white crystals were subsequently dissolved in 0.7 ml of $CDCl_3$ and submitted to ^1H NMR measurements.

*4.1.75. Preparation of (S)-1-O-octadecyl-2-octanoyl-sn-glycerol (**13d**).* To a 10 ml round-bottomed flask containing (*R*)-1-octadecyl-3-octanoyl-*sn*-glycerol **5d** (100 mg, 0.212 mmol) dissolved in chloroform (5 ml), *p*-toluenesulfonic acid monohydrate (4 mg, 0.0212 mmol) was added and the solution stirred for 1 h at room temperature. After evaporation of the solvent the crude mixture was applied to preparative TLC and eluted with petroleum ether/ether/acetic acid (80:20:2). The product (R_f=0.45) was finally afforded as white crystals. ^1H NMR (400 MHz, $CDCl_3$) δ 5.00 (quintet, *J*=4.8, 1H, CH_2CHCH_2), 3.83–3.80 (m, 2H, CH_2OH), 3.64 (dd, *J*=10.5, 4.9 Hz, 1H, $CHCH_2O$), 3.60 (dd, *J*=10.5, 5.1 Hz, 1H, $CHCH_2O$), 3.50–3.40 (dt, *J*=9.3, 7.1 Hz, 2H, OCH_2CH_2), 2.36 (t, *J*=7.5 Hz, 2H, CH_2COO), 2.18 (t, *J*=6.2 Hz, 1H, CH_2OH), 1.64 (quintet (br), *J*=7.4 Hz, 2H, CH_2CH_2COO), 1.57–1.52 (m, 2H, OCH_2CH_2), 1.37–1.18 (m, 38H, CH_2), 0.88 (br t, *J*=6.9 Hz, 6H, CH_3 in octanoic acid and 1-*O*-alkyl) ppm; ^{13}C NMR ($CDCl_3$) δ 173.70 (*C*=O), 72.81, 71.92, 70.04, 63.08, 34.40, 31.93, 31.66, 29.70 (6), 29.66 (2), 29.63, 29.60, 29.55, 29.45, 29.36, 29.05, 28.92, 26.05, 24.99, 22.69, 22.60, 14.12, 14.06 ppm.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.01.032.

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