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Synthesis of Enantiostructured Triacylglycerols Possessing a Saturated Fatty Acid, a Polyunsaturated Fatty Acid and an Active Drug Intended as Novel Prodrugs

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Abstract: This report describes the asymmetric synthesis of a focused library of enantiopure structured triacylglycerols (TAGs) comprised of a single saturated fatty acid (C6, C8, C10, C12, C14 or C16), a pure bioactive n-3 polyunsaturated fatty acid (EPA or DHA) and a potent drug (ibuprofen or naproxen) intended as a novel type of prodrugs. One of the terminal sn-1 or sn-3 positions of the glycerol backbone is occupyed with a saturated fatty, the remaining one with a PUFA, and the drug entity is present in the sn-2 position. This was accomplished by a six-step chemoenzymatic approach starting from enantiopure (*R*)- and (*S*)-solketals. The highly regioselective immobilized *Candida antarctica* lipase (CAL-B) played a crucial role in the regiocontrol of the synthesis. All combinations, the total of 48 such prodrug TAGs were prepared, isolated and fully characterized, along with 60 acylglycerol intermediates, obtained in very high to excellent yields.

Keywords: asymmetric synthesis; enantiostructured triacylglycerols; Lipase; n-3 PUFAs; acylglycerol prodrugs

1. Introduction

Fish oil and marine fat is the main source of the long-chain omega-3 polyunsaturated fatty acids (n-3 PUFAs) of which eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are largely predominant [1]. Algal oil extracted from marine microalgae biomass grown in contained fermentation vessels has also become a major sustainable vegetarian source of EPA and DHA for human consumption [2,3]. EPA and DHA are attributed to numerous beneficial effects on human health and prevention of various health disorders including inflammation, cardiovascular and brain diseases, and many more [4–6]. They act in membranes, cell signalling, as precursors to potent lipid mediators and regulate gene expression via receptors. EPA and DHA are indeed precursors to various prostanoids and leukotrienes [7] as well as the more recently established highly potent resolvins, protectins and maresins that exhibit potent anti-inflammatory and pro-resolving actions, currently known as the specialized pro-resolving mediators (SPMs) [8–10].

The term structured lipids refers to acylglycerol lipids constituting certain type of fatty acids placed at predetermined positions of the glycerol backbone [11–13]. Structured triacylglycerols (TAGs) carrying long-chain bioactive PUFAs such as EPA and DHA at the 2-position and saturated medium chain (C6:0, C8:0 and C10:0) fatty acids (MCFAs) at the terminal 1,3-positions have acquired a growing interest of scientists because of their properties and nutritional value [14]. In such MLM (medium-long-medium) type TAGs the MCFAs located at the end-positions undergo rapid hydrolysis by pancreatic lipase in the digestive tract. They are rapidly absorbed into the intestines and rapidly carried to the liver where they act as a quick but only moderate source of energy. The remaining 2-monoacylglycerols constituting the n-3 PUFAs are absorbed through the intestinal wall,

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accumulate as TAGs in the adipose tissue and as phospholipids in cell membranes as a source of bioactive PUFAs and essential fatty acids [15,16].

Natural TAGs differ significantly in animals and plants from species to species where the fatty acids by no means happen to be randomly distributed. Classical examples of naturally structured TAGs include cocoa butter [13,17], used in chocolate manufacturing, and TAGs in human milk [12,18]. Generally, in fish oil TAGs, the mid-position of the glycerol backbone is more enriched with the *n*-3 PUFAs, especially DHA, compared to the terminal positions. Notably, in the TAG oil of marine mammals including whale and seal this is the other way around with the mid-position less enriched with these PUFAs than the outer positions [19].

We have reported an efficient two-step chemoenzymatic synthesis of regiopure MLM type structured TAGs constituting pure EPA or DHA in the 2-position and pure short- and medium-chain saturated fatty acids in the 1,3-positions. This was accomplished by aid of a highly regioselective immobilized *Candida antarctica* lipase (CAL-B) that was observed to act exclusively at the end-positions of glycerol [20,21]. We have also reported on a multi-step asymmetric synthesis of what we name enantiostructured TAGs also involving the highly regioselective lipase. Glycerol is prochiral causing a TAG molecule to become chiral when the two fatty acyl groups occupying the terminal 1,3-positions are different, regardless of the acyl group accommodating the 2-position. Accordingly, the two enantiotopic terminal carbons of the glycerol backbone in TAGs are distinguishable by a stereospecific numbering indicated by a prefix, *sn*-, with the *pro-S* hydroxycarbon group of glycerol referring to the *sn*-1 position, the *pro-R* group to the *sn*-3 position, and the central carbon to the *sn*-2 position [22,23]. Numerous tailor-made enantiostructured TAGs have been synthesized with a variety of pre-determined fatty acyl groups occupying the individual stereospecific positions of the glycerol backbone [24–28]. There are multiple reports on stereospecific positioning of fatty acids in animal and plant TAGs [28–31].

The current report describes a further extension of the concept of structured and enantiostructured TAGs, namely our synthesis of enantiostructured TAGs intended as prodrugs possessing a pure saturated fatty acid (SFA), EPA or DHA and a potent drug all attached as carboxylic esters to pre-determined stereospecific positions of the glycerol framework of the TAG molecule. To demonstrate this novel concept, we have selected the well-known non-steroidal anti-inflammatory drugs (NSAIDs) (*S*)-ibuprofen and (*S*)-naproxen and chosen to follow procedures already established for the synthesis of the enantiostructured TAGs previously described. This is illustrated in Figure 1.

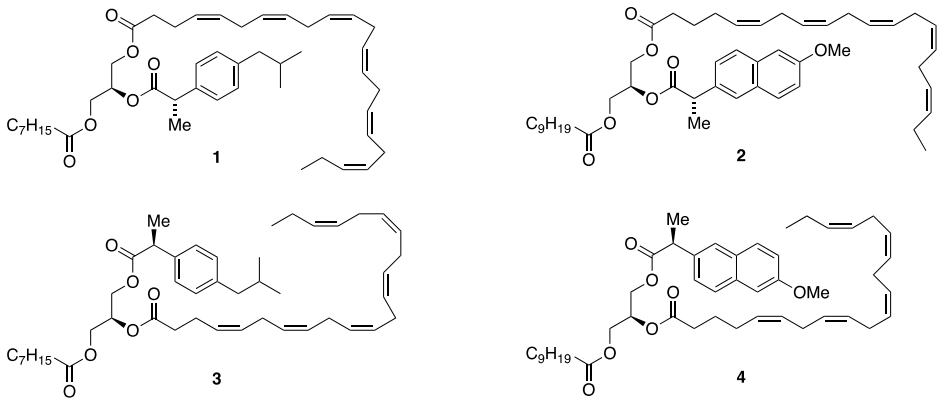

Figure 1. The structure of TAG prodrugs **1** and **2** belonging to the first category prodrugs, and TAG products **3** and **4** belonging to the second category prodrugs.

Two categories of such prodrug designs are shown in Figure 1. Structures **1** and **2** belong to the first category where the active drugs are located in the *sn*-2 position along with EPA or DHA in one of the terminal positions and a SFA in the other. Structure **1** contains (*S*)-ibuprofen esterifed to the *sn*-2 position, DHA in the *sn*-1 position and caprylic acid (C8:0) in the remaining *sn*-3 position. Likewise, structure **2** contains (*S*)-naproxen in the *sn*-2 position, EPA in the *sn*-1 position and capric acid (C10:0) in the *sn*-3 position. In the second prodrug category the location of the n-3 PUFAs and

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the drug has been interchanged with the drugs located in the *sn*-1 position and the PUFAs in the *sn*-2 position as shown in structures **3** and **4**. The current paper reports the synthesis of the first category prodrugs with all combinations of medium- and longer-chain SFAs ranging from C6:0 to C16:0, EPA and DHA, (*S*)-ibuprofen and (*S*)-naproxen for both (*R*)- and (*S*)-TAG diastereomers. The synthesis of all the corresponding diasteromers of the second category prodrugs are also under way to be reported.

2. Results and Discussion

A prodrug is a compound that undergoes an intra- or extracellular bioconversion within the human body to liberate an active drug. Prodrugs are designed to improve the bioavailability of a drug, how it is absorbed, distributed, metabolized and excreted (ADME) [32–34]. Lipid based drug carriers and prodrugs offer advantages such as increased absorption through the intestines and they enhance drug availability and targeting [35,36]. The current report describes the preparation of enantiostructured TAGs constituting even carbon number SFAs ranging from C6:0 to C16:0, EPA and DHA, and an active drug attached to the glycerol backbone, where the benign effects of the n-3 PUFAs, assumed benefits of structured and enantiostructured TAGs, and the pharmaceutical properties of the drug are combined in a single molecule. It is our belief that this approach may offer an interesting and a novel form of a prodrug.

Two regioisomeric prodrug forms are proposed and their general structures are displayed in Figure 1. In the first form (represented by structures **1** and **2**) the active drug is attached as an ester to the *sn*-2 position of the TAG with the PUFA at the *sn*-3 and the SFA at the *sn*-1 positions (*First category TAG prodrugs*). The current report describes the synthesis of TAG prodrugs that belong to this category. All corresponding diastereomers where the acyl groups at the end-positions have been interchanged (the n-3 PUFAs at the *sn*-1 and the SFAs at the *sn*-3 positions) were also synthesized. In the second form (represented by **3** and **4**) the location of the drug and the PUFA has been reversed such that the drug is at the *sn*-3 position with the PUFA at the *sn*-2 position (*Second category TAG prodrugs*). Their synthesis will be addressed in a separate report that is under way to be completed.

A prodrug design of the type described may offer good opportunities for controlling site-specific release of not only the drug, but also the bioactive n-3 PUFA as a combination of the regio- and enantiospecific location of the SFA and its length, the n-3 PUFA and the drug within the TAG backbone and their consequent release. This may result in a higher bioavailability of the drug with less drug needed and therefore less harmful side effects. As far as we know there are currently no reports on acylglycerol-based prodrugs possessing n-3 PUFAs and active drugs attached to the glycerol backbone.

Serving as precursors to the specialized pro-resolving mediators EPA and DHA may be regarded as anti-inflammatory prodrugs [37]. It will be of interest to find out how EPA and DHA may act by their own, or perhaps through some interactive or synergistic effects with the drugs. The non-steroidal anti-inflammatory drugs were an obvious choice to demonstrate this concept, and they offer the prerequisite of a carboxyl group to allow an ester bond formation to the glycerol backbone.

By varying the location of the three counterparts present in the designed prodrugs within the glycerol skeleton a better control may be gained on when (timing) and where (site) these counterparts will be released from the prodrug molecule. In the current prodrug design the saturated fatty acids, located at the terminal positions only, will be most accessible for cleavage at an early stage in the digestive tract by pancreatic lipase. The SFAs are generally a significantly better substrates to lipase than the n-3 PUFAs [38] and will undergo a cleavage ahead of the other counterparts present to deliver a diacylglycerol (DAG) derivative. The DAG delivery rate may depend both on the length of the SFAs ranging from C6:0 to C16:0 as well as their location at the *sn*-1 or the *sn*-3 positions by the pancreatic lipase fatty acid selectivity and its enantioselectivity.

Varying the location of the drug and the bioactive n-3 PUFAs between the terminal and mid positions within the glycerol framework will presumably influence their timing and site of release. In the case of the first category prodrugs with the drug located at the *sn*-2 position and the n-3 PUFAs at the terminal positions it is anticipated that the release of the PUFA from the DAG will take place

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prior to the drug to form a 2-monoacylglycerol (2-MAG) with the drug still attached. The rate of release of the n-3 PUFA will assumingly depend on its stereospecific location between the *sn*-1 and *sn*-3 positions within the DAGs, and it is anticipated that the release of EPA will occur faster than DHA by the fact that lipase prefers EPA over DHA [38]. In case of the second category prodrugs the situation is different and perhaps more complicated when the active drug is located at a terminal position. However, it is anticipated that all parameters discussed above may enable some fine-tuning of the prodrug in terms of release of both the PUFA and the drug.

EPA and DHA are not only regarded as prodrugs, but they are also available in their ethyl ester form as prescription drugs registered as an adjuvant therapy to treat hypertriglyceridemia [39] both as a mixture of EPA and DHA [40,41] as well as virtually pure EPA [42–44]. This may enable a further development of our prodrug concept based on the enantiostructured TAGs into a codrug formula. A codrug constitutes two drug components that display activity against the same disease. When released they may offer various beneficial effects including therapeutic synergy [45–48]. One embodiment of such a codrug might involve a potent statin drug in a combination with EPA and DHA in such a molecule without or, if needed, with a suitable linker to the glycerol moiety.

2.1. Synthetic Strategies

A four-step chemoenzymatic approach was designed for the synthesis of the first category TAG prodrugs that is depicted in Figure 2. It is based on the use of 1-*O*-benzyl-*sn*-glycerol (prepared in two steps from (*R*)-solketal [24]) as a chiral precursor of which the *sn*-1 position is protected as a benzyl ether. The first step involves a lipase promoted regioselective acylation of the *sn*-3 hydroxyl group of the diol with a saturated fatty acid. The second step involves an incorporation of the drug into the remaining *sn*-2 position by use of a chemical coupling agent. This is followed by removal of the benzyl protective group, and in the final step the second unsaturated fatty acid is introduced to the *sn*-1 position of the glycerol backbone brought about by the same chemical coupling agent to complete the synthesis.

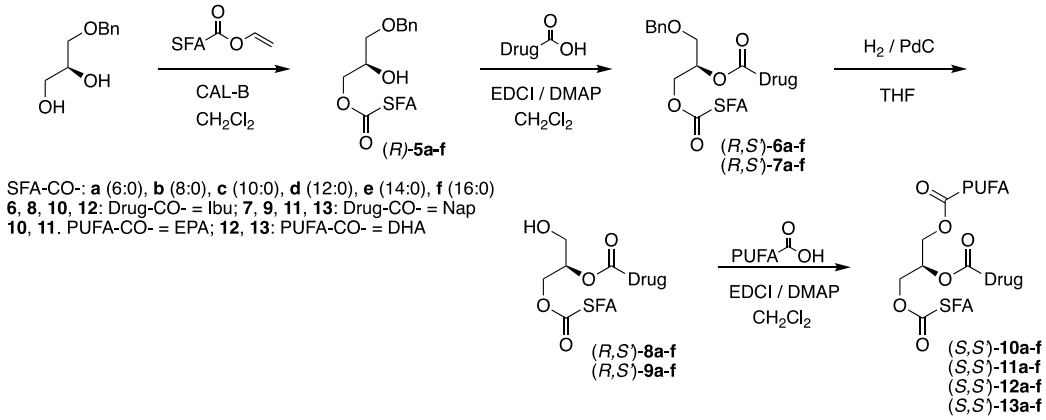

Figure 2. Chemoenzymatic synthesis of the first category TAG prodrug diastereomer series (*S,S'*)-**10a-f – 13a-f**, starting from 1-*O*-benzyl-*sn*-glycerol. In the scheme SFA-CO-, PUFA-CO- and Drug-CO- refer to the corresponding saturated fatty acyl, polyunsaturated fatty acyl and drug acyl group substituents, respectively.

As can be noticed in Figure 2 all combinations of the six saturated fatty acids caproic, caprylic, capric, lauric, myristic and palmitic acids (C6:0, C8:0, C10:0, C12:0, C14:0 and C16:0, respectively) located at the *sn*-3 position, EPA and DHA at the remaining *sn*-1 terminal position, and (*S*)-ibuprofen (Ibu) and (*S*)-naproxen (Nap) at the *sn*-2 position of the glycerol moiety were under the scope to be synthesized. This results in a focused library of the total of 24 targeted enantiostructured TAG prodrugs (*S,S'*)-**10a-f – 13a-f**. This synthetic task also involves the total of 30 enantiopure acylglycerol intermediates.

We were equally interested in the corresponding TAG prodrug products (*R,S'*)-**10a-f – 13a-f**, where the enantiospecific location of the SFAs and the PUFAs has been interchanged with the drugs

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still located at the *sn*-2 position. This results in an identical number of target products and intermediates. It should be noted that the resulting TAG prodrug products are diastereomeric to those shown in Figure 2 and the synthetic route is identical, this time starting from 3-*O*-benzyl-*sn*-gycerol (prepared in two steps from (*S*)-solketal [26]) as a chiral precursor. This is illustrated in Figure 3.

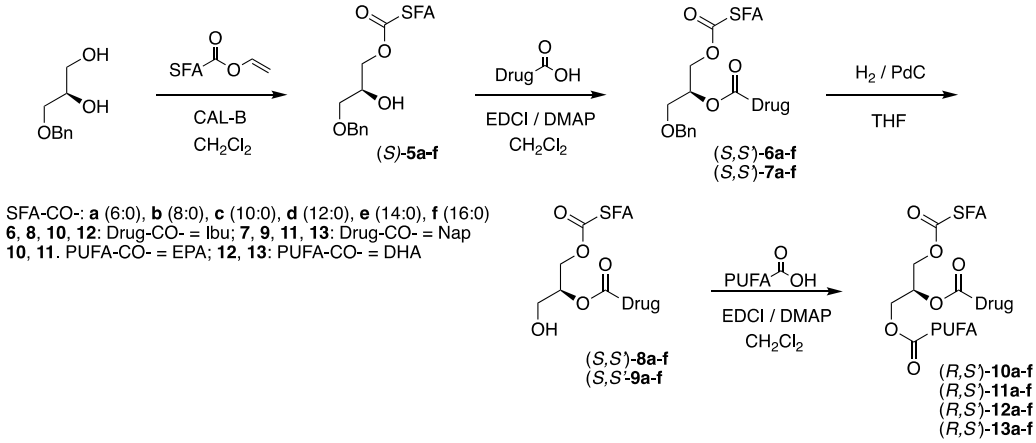

Figure 3. Chemoenzymatic synthesis of the first category TAG prodrug diastereomer series (*R,S'*)-**10a-f – 13a-f**, starting from 3-*O*-benzyl-*sn*-glycerol. In the scheme SFA-CO-, PUFA-CO- and Drug-CO- refer to the corresponding saturated fatty acyl, polyunsaturated fatty acyl and drug acyl group substituents, respectively.

2.2. The Enzymatic Coupling of the SFAs

The first step involved an enzymatic coupling of the saturated fatty acids activated as vinyl esters to the terminal position of the benzyl-protected glycerols. As anticipated and previously described [20,21] the immobilized *Candida antarctica* lipase B (CAL-B) acylated the protected glycerol exclusively at the primary alcohol position. The reaction was performed in dry dichloromethane at r.t. and it took the lipase only 90 minutes to complete the reaction as was confirmed by TLC monitoring and ^{1}H NMR spectroscopy. There were no indications of any acylation taking place at the 2-position of the glycerol backbone.

All the products were obtained as colourless oils in excellent yields (> 94%) in all cases except one (87%) after purification by silica gel chromatography. Tables 1a and 1b show the identity, yields and specific optical activity of the resulting benzyl-protected *sn*-3-MAG intermediates (*R*)-**5a-f** derived from 1-*O*-benzyl-*sn*-glycerol (Table 1a) and the corresponding *sn*-1-MAGs (*S*)-**5a-f** derived from 3-*O*-benzyl-*sn*-glycerol, in accordance with the reaction schemes in Figures 2 and 3.

Table 1a. Summary of the yields and specific rotation of the intermediates (*R*)-**5a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*R*)-**5a**	OBn	OH	6:0	94%	-2.29
(*R*)-**5b**	OBn	OH	8:0	94%	-2.22
(*R*)-**5c**	OBn	OH	10:0	97%	-1.59
(*R*)-**5d**	OBn	OH	12:0	97%	-1.91
(*R*)-**5e**	OBn	OH	14:0	94%	-1.31
(*R*)- **5f**	OBn	OH	16:0	94%	-2.37

Table 1b. Summary of the yields and specific rotation of the intermediates (*S*)-**5a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*S*)-**5a**	6:0	OH	OBn	95%	+2.01
(*S*)-**5b**	8:0	OH	OBn	95%	+2.10
(*S*)-**5c**	10:0	OH	OBn	97%	+1.48

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(*S*)-**5d**	12:0	OH	OBn	96%	+1.31
(*S*)-**5e**	14:0	OH	OBn	94%	+3.64
(*S*)- **5f**	16:0	OH	OBn	87%	+1.11

The use of the saturated fatty acids activated as vinyl esters secures a fast irreversible reaction that is crucial for maintaining the excellent regioselectivity of the lipase [20,21]. Another important parameter offered by the lipase is the mildness under which the lipase acts, especially the low temperature to prevent acyl migration [27,49] that is detrimental to the regiocontrol provided by the lipase.

All partially acylated glycerol intermediates possessing an acyl group adjacent to a free hydroxyl group are prone to undergo such spontaneous thermodynamically controlled acyl migration. Since silica gel is known to promote acyl migration special care had to be taken when it came to purification by means of chromatography that required the use of silica gel impregnated with 4% boric acid which is known to suppress acyl migration [27,50].

The glyceryl proton region of the ^{1}H NMR spectra (δ 5.40-3.60 ppm) is ideally suited to confirm the structure and evaluate the purity of all partial and intermediate acylglycerol derivatives involved in the synthesis as well as the final triacylglycerol products. Quite characteristic patterns of peaks are provided for each of the individual acylglycerols. This is also of great use to accurately detect the level of undesired acyl migration related biproducts as we have demonstrated in detail in numerous previous reports [20,21,24–27].

The structures of the benzyl-protected MAGs were confirmed by the characteristic pattern for the glyceryl proton region of their ^{1}H-NMR spectra. Figure *S1* in the *Supplementary Materials* presents a comparison of the glyceryl region of the benzyl-protected glycerol starting material and the benzyl-protected *sn*-3-MAG (*R*)-**5a**. The characteristic pattern of peaks for the two types of glycerols are clearly evident. Upon acylation the two protons belonging to the *sn*-3 position have undergone a dramatic down-field shift that is also affecting the proton belonging to the *sn*-2 position of the glycerol backbone. No sign of acyl migration was observed in the case of the benzyl-protected *sn*-3-MAG derivatives. Acyl migration side reactions would distort the peak pattern and give additional peaks into their glyceryl proton region.

2.3. The Coupling of the Active Drugs

The second step involved a chemical coupling of the drugs into the *sn*-2 position of the benzyl-protected *sn*-3-MAGs (*R*)-**5a**-**f** and (*S*)-**5a**-**f** by use of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) as a coupling agent in the presence of 4-dimethylaminopyridine (DMAP) serving both as a catalyst and a base. The reactions were performed under conditions identical to those previously described in our syntheses of structured and enantiostructured TAGs using 10% excess of the drugs in dichloromethane at room temperature under which no acyl migration took place [20,21,24–27].

Tables 2a and 2b outline the yields and optical activity of all intermediate products (*R,S′*)-**6a**-**f** and (*S,S′*)-**6a**-**f** obtained from (*R*)-**5a**-**f** and (*S*)-**5a**-**f** acylated with (*S*)-ibuprofen, respectively. This is in full accordance with the schemes shown in Figures 2 and 3 with *R* and *S* referring to the absolute configuration of the glycerol moiety and *S′* to that of the drugs.

Table 2a. Summary of the yields and specific rotation of the intermediates (*R,S′*)-**6a**-**f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*R,S′*)-**6a**	OBn	Ibu	6:0	80%	-0.77
(*R,S′*)-**6b**	OBn	Ibu	8:0	91%	-0.99
(*R,S′*)-**6c**	OBn	Ibu	10:0	98%	-0.58
(*R,S′*)-**6d**	OBn	Ibu	12:0	91%	-0.86
(*R,S′*)-**6e**	OBn	Ibu	14:0	94%	-0.93
(*R,S′*)- **6f**	OBn	Ibu	16:0	98%	-0.57

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As can be noticed from Table 2a the yields obtained for the (*R,S′*)-**6a-f** series were excellent (91-98%) in all cases except one (80%). The diastereomeric (*S,S′*)-**6a-f** series were accomplished in 81-95% yields as can be noticed from Table 2b.

Table 2b. Summary of the yields and specific rotation of the intermediates (*S,S′*)-**6a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*S,S′*)-**6a**	6:0	Ibu	OBn	93%	+22.2
(*S,S′*)-**6b**	8:0	Ibu	OBn	95%	+21.0
(*S,S′*)-**6c**	10:0	Ibu	OBn	81%	+22.0
(*S,S′*)-**6d**	12:0	Ibu	OBn	84%	+19.3
(*S,S′*)-**6e**	14:0	Ibu	OBn	91%	+17.9
(*S,S′*)-**6f**	16:0	Ibu	OBn	84%	+11.6

Similarly, the yields and optical activity of all the intermediate products (*R,S′*)-**7a-f** and (*S,S′*)-**7a-f** obtained from the corresponding acylation of the (*R*)-**5a-f** and (*S*)-**5a-f** with (*S*)-naproxen are outlined in Tables 3a and 3b, respectively. As may be noticed from Table 3a excellent yields were accomplished for the (*R,S′*)-**7a-f** series (90-98%).

Table 3a. Summary of the yields and specific rotation of the intermediates (*R,S′*)-**7a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*R,S′*)-**7a**	OBn	Nap	6:0	90%	-3.90
(*R,S′*)-**7b**	OBn	Nap	8:0	95%	-3.02
(*R,S′*)-**7c**	OBn	Nap	10:0	96%	-3.23
(*R,S′*)-**7d**	OBn	Nap	12:0	92%	-2.00
(*R,S′*)-**7e**	OBn	Nap	14:0	98%	-1.33
(*R,S′*)- **7f**	OBn	Nap	16:0	96%	-2.00

Excellent yields were also obtained in most cases for the corresponding diastereomeric (*S,S′*)-**7a-f** series, but (*S,S′*)-**7e** and **7f** were afforded in lower 75 and 77% yields, respectively. Since these lower yields have not been optimized, we believe they may be significantly improved rather than being associated with diastereomeric issues. Solid products were obtained for all naproxen products constituting the longer-chain SFAs C10:0 to C16:0. They all afforded white, thin needle-like crystals from hexane.

Table 3b. Summary of the yields and specific rotation of the intermediates (*S,S′*)-**7a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*S,S′*)-**7a**	6:0	Nap	OBn	97%	+20.8
(*S,S′*)-**7b**	8:0	Nap	OBn	97%	+4.82
(*S,S′*)-**7c**	10:0	Nap	OBn	92%	+6.69
(*S,S′*)-**7d**	12:0	Nap	OBn	92%	+17.1
(*S,S′*)-**7e**	14:0	Nap	OBn	75%	+15.3
(*S,S′*)-**7f**	16:0	Nap	OBn	77%	+15.3

Figure *S2* in the *Supplementary Materials* provides a comparison of the glyceryl proton region of the ^{1}H NMR spectrum of (*R,S′*)-**6a**, that is typical for a benzyl-protected glycerol possessing a drug in the 2-position and an SFA in a terminal position, and the precursor (*R*)-**5a**. As can be noticed the proton belonging to the *sn*-2 position has undergone a dramatic down-field shift upon acylation into that position by the drug. This is also significantly affecting the two protons belonging to the *sn*-1 position. Evidently, there are no signs of an acyl migration taking place. The dramatic change in the peak pattern for the benzyl protons is also noteworthy from the figure from a singlet in the precursor to a typical AB-quartet that is interfering with one of the protons belonging to the *sn*-3 position.

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2.4. The Removal of the Benzyl Protective Group

The third step of the first category prodrug synthesis involved the removal of the benzyl protective group. All compounds of the ibuprofen and naproxen series (*R,S′*)-**6a-f**, (*S,S′*)-**7a-f**, (*R,S′*)-**7a-f** and (*R,S′*)-**7a-f** were subjected to catalytic hydrogenolysis by use of a Pd/C catalyst in a mixture of THF and n-hexane under atmospheric pressure at r.t. Catalytic amount of perchloric acid was used to initiate the reaction by following a procedure previously described [26]. It was noted that the reaction involving the starting material as liquids proceeded significantly faster than those in the solid form and required 15 minutes as compared to 35 minutes.

The yields and specific optical rotation values are revealed in Tables 4a and 4b for the ibuprofen adducts (*R,S′*)-**8a-f** and (*S,S′*)-**8a-f** obtained from the deprotection reaction, respectively. All products were obtained as liquids, and as can be noticed, in very high to excellent yields (84-98%).

Table 4a. Summary of the yields and specific rotation of the intermediates (*R,S′*)-**8a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*R,S′*)-**8a**	OH	Ibu	6:0	84%	+23.9
(*R,S′*)-**8b**	OH	Ibu	8:0	86%	+18.3
(*R,S′*)-**8c**	OH	Ibu	10:0	98%	+7.50
(*R,S′*)-**8d**	OH	Ibu	12:0	92%	+2.43
(*R,S′*)-**8e**	OH	Ibu	14:0	84%	+8.00
(*R,S′*)- **8f**	OH	Ibu	16:0	90%	+0.75

Table 4b. Summary of the yields and specific rotation of the intermediates (*S,S′*)-**8a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*S,S′*)-**8a**	6:0	Ibu	OH	95%	+5.65
(*S,S′*)-**8b**	8:0	Ibu	OH	86%	+18.8
(*S,S′*)-**8c**	10:0	Ibu	OH	89%	+20.2
(*S,S′*)-**8d**	12:0	Ibu	OH	93%	+13.8
(*S,S′*)-**8e**	14:0	Ibu	OH	94%	+4.20
(*S,S′*)-**8f**	16:0	Ibu	OH	90%	+15.0

Tables 5a and 5b similarly display the corresponding results for the naproxen adducts (*R,S′*)-**9a-f** and (*S,S′*)-**9a-f**, respectively. Again, very high to excellent yields were obtained for all products (84-98%). As before, the products having SFAs of chain-length C10:0 to C16:0 were all obtained as crystalline material after crystallization from n-hexane.

Table 5a. Summary of the yields and specific rotation of the intermediates (*R,S′*)-**9a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*R,S′*)-**9a**	OBn	Nap	6:0	98%	+5.63
(*R,S′*)-**9b**	OBn	Nap	8:0	94%	+7.17
(*R,S′*)-**9c**	OBn	Nap	10:0	84%	+5.70
(*R,S′*)-**9d**	OBn	Nap	12:0	94%	+3.00
(*R,S′*)-**9e**	OBn	Nap	14:0	89%	+2.04
(*R,S′*)- **9f**	OBn	Nap	16:0	91%	+4.95

Table 5b. Summary of the yields and specific rotation of the intermediates (*S,S′*)-**9a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*S,S′*)-**9a**	6:0	Nap	OH	97%	+8.60
(*S,S′*)-**9b**	8:0	Nap	OH	97%	+17.6
(*S,S′*)-**9c**	10:0	Nap	OH	92%	+8.56
(*S,S′*)-**9d**	12:0	Nap	OH	87%	+17.2

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(*S,S′*)-**9e**	14:0	Nap	OH	90%	+17.9
(*S,S′*)-**9f**	16:0	Nap	OH	90%	+17.0

No acyl migration was observed to take place, despite the use of the perchloric acid, but special care had to be taken to neutralize the reaction immediately after the reaction had proceeded to completion by use of sodium bicarbonate. This was evident from the glyceryl proton region of the ^{1}H NMR spectra of the products showing no signs of acyl migration that are easily detected in the glyceryl proton region. Shortly after the reactions described herein were performed, we discovered that the use of the perchloric acid to initiate the reaction was not necessary when running the reaction in a pure THF as a solvent instead of mixing it with n-hexane [25].

As can be noticed in Figure *S3* of the *Supplementary Materials* providing a comparison between the glyceryl proton region of the product (*R,S′*)-**9d** and its precursor (*R,S′*)-**7d** it is evident that the removal of the benzyl protective moiety has resulted in a slight down-field shift of the protons belonging to the *sn*-1 carbon with the two doublets of doublets merging closer together to give a multiplet. Only minor changes occurred to the protons belonging to the *sn*-3 carbon, whereas the proton belonging to the *sn*-2 carbon underwent a slight up-field shift.

2.5. The Coupling of the PUFA

The fourth and last step of the prodrug synthesis involved a chemical coupling of EPA and DHA into the open end-position of the diacylglycerols possessing the drug and the SFA obtained from the previous step. Previously described procedures involving approximately 5-10% excess of EPA and DHA using EDCI as a coupling agent in the presence of DMAP in dichloromethane at r.t. were followed under which conditions no acyl migration took place [20,21,26].

All products were obtained as yellowish to yellow oils in very high to excellent yields with a few exceptions. The reactions involving DHA were observed to require longer reaction time than those of EPA and afforded somewhat lower yields. Tables 6 – 9 outline the yields and the specific optical activity of the products in accordance with the reaction schemes in Figures 2 and 3. The TAG prodrug products (*S,S′*)-**10a-f** and (*R,S′*)-**10a-f** possessing an SFA, EPA and ibuprofen are shown in Tables 6a and 6b, respectively.

Table 6a. Summary of the yields and specific rotation of the TAG prodrug products (*S,S′*)-**10a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_{D}$
(*S,S′*)-**10a**	EPA	Ibu	6:0	90%	+11.7
(*S,S′*)-**10b**	EPA	Ibu	8:0	91%	+9.60
(*S,S′*)-**10c**	EPA	Ibu	10:0	88%	+8.40
(*S,S′*)-**10d**	EPA	Ibu	12:0	87%	+7.98
(*S,S′*)-**10e**	EPA	Ibu	14:0	89%	+6.58
(*S,S′*)-**10f**	EPA	Ibu	16:0	86%	+6.68

Table 6b. Summary of the yields and specific rotation of the TAG prodrug products (*R,S′*)-**10a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_{D}$
(*R,S′*)-**10a**	6:0	Ibu	EPA	74%	+6.50
(*R,S′*)-**10b**	8:0	Ibu	EPA	91%	+9.11
(*R,S′*)-**10c**	10:0	Ibu	EPA	88%	+7.44
(*R,S′*)-**10d**	12:0	Ibu	EPA	87%	+7.57
(*R,S′*)-**10e**	14:0	Ibu	EPA	89%	+7.12
(*R,S′*)-**10f**	16:0	Ibu	EPA	86%	+7.43

Similarly, the corresponding TAG prodrug products (*S,S′*)-**11a-f** and (*R,S′*)-**10a-f** possessing an SFA, EPA and naproxen are shown in Tables 7a and 7b, respectively.

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Table 7a. Summary of the yields and specific rotation of the TAG prodrug products (*S,S′*)-**11a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*S,S′*)-**11a**	EPA	Nap	6:0	91%	+8.12
(*S,S′*)-**11b**	EPA	Nap	8:0	94%	+6.00
(*S,S′*)-**11c**	EPA	Nap	10:0	84%	+6.58
(*S,S′*)-**11d**	EPA	Nap	12:0	96%	+4.89
(*S,S′*)-**11e**	EPA	Nap	14:0	90%	+5.29
(*S,S′*)-**11f**	EPA	Nap	16:0	91%	+5.44

Table 7b. Summary of the yields and specific rotation of the TAG prodrug products (*R,S′*)-**11a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*R,S′*)-**11a**	6:0	Nap	EPA	80%	+4.20
(*R,S′*)-**11b**	8:0	Nap	EPA	80%	+4.97
(*R,S′*)-**11c**	10:0	Nap	EPA	86%	+8.76
(*R,S′*)-**11d**	12:0	Nap	EPA	74%	+5.20
(*R,S′*)-**11e**	14:0	Nap	EPA	76%	+6.30
(*R,S′*)-**11f**	16:0	Nap	EPA	89%	+6.23

Tables 8a and 8b outline the TAG prodrug products (*S,S′*)-**12a-f** and (*R,S′*)-**12a-f** possessing an SFA, DHA and ibuprofen, respectively.

Table 8a. Summary of the yields and specific rotation of the TAG prodrug products (*S,S′*)-**12a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*S,S′*)-**12a**	DHA	Ibu	6:0	81%	+9.95
(*S,S′*)-**12b**	DHA	Ibu	8:0	86%	+4.44
(*S,S′*)-**12c**	DHA	Ibu	10:0	95%	+4.05
(*S,S′*)-**12d**	DHA	Ibu	12:0	89%	+5.30
(*S,S′*)-**12e**	DHA	Ibu	14:0	82%	+7.54
(*S,S′*)-**12f**	DHA	Ibu	16:0	85%	+3.16

Table 8b. Summary of the yields and specific rotation of the TAG prodrug products (*R,S′*)-**12a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*R,S′*)-**12a**	6:0	Ibu	DHA	81%	+6.73
(*R,S′*)-**12b**	8:0	Ibu	DHA	86%	+7.96
(*R,S′*)-**12c**	10:0	Ibu	DHA	80%	+4.57
(*R,S′*)-**12d**	12:0	Ibu	DHA	78%	+6.57
(*R,S′*)-**12e**	14:0	Ibu	DHA	82%	+7.01
(*R,S′*)-**12f**	16:0	Ibu	DHA	79%	+3.93

Finally, the TAG prodrug products (*S,S′*)-**13a-f** and (*R,S′*)-**13a-f** possessing an SFA, DHA and naproxen are outlined in Tables 9a and 9b, respectively.

Table 9a. Summary of the yields and specific rotation of the TAG prodrug products (*S,S′*)-**13a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*S,S′*)-**13a**	DHA	Nap	6:0	84%	+6.81
(*S,S′*)-**13b**	DHA	Nap	8:0	85%	+2.78
(*S,S′*)-**13c**	DHA	Nap	10:0	89%	+6.60
(*S,S′*)-**13d**	DHA	Nap	12:0	92%	+3.67
(*S,S′*)-**13e**	DHA	Nap	14:0	93%	+7.54
(*S,S′*)-**13f**	DHA	Nap	16:0	92%	+3.60

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Table 9b. Summary of the yields and specific rotation of the TAG prodrug products (*R,S'*)-**13a-f**.

Compound	*sn*-1	*sn*-2	*sn*-3	Yields	$[\alpha]^{20}_D$
(*R,S'*)-**13a**	6:0	Nap	DHA	74%	+8.80
(*R,S'*)-**13b**	8:0	Nap	DHA	72%	+2.01
(*R,S'*)-**13c**	10:0	Nap	DHA	80%	+3.93
(*R,S'*)-**13d**	12:0	Nap	DHA	92%	+3.50
(*R,S'*)-**13e**	14:0	Nap	DHA	88%	+4.58
(*R,S'*)-**13f**	16:0	Nap	DHA	89%	+2.14

As may be noticed from Figure *S4* of the *Supplementary Materials* providing a comparison of the glyceryl proton region of the product (*R,S'*)-**11c** and the precursor (*R,S'*)-**9c** changes anticipated for TAGs have taken place with significant down-field shift of the protons belonging to the *sn*-1 position upon acylation into that position. They now resonate as two well dispersed doublets of doublets with one of them merging with one of the peaks from the protons belonging to the *sn*-3 position.

3. Materials and Methods

3.1. General Information

The ^{1}H- and ^{13}C-NMR spectra were recorded on a 400 MHz Bruker Avance spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance used as an internal standard. In all cases the solvent was deuterochloroform which had been filtered through aluminium oxide to get rid of acid contamination. The coupling constants (*J*) are given in Hertz (Hz). The following abbreviations are used to describe the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; AB q, AB-quartet; m, multiplet. For ^{13}C-NMR, the number of carbon nuclei contributing to each signal is indicated in parentheses after the chemical shift value. Infrared spectra were recorded on a Nicolet Avatar FT-IR (E.S.P.) spectrometer using sodium chloride windows (NaCl) for liquid compounds or potassium bromide pellets (KBr) for solids. The following abbreviations are used to describe the peaks: s, strong; vs, very strong; m, medium; w, weak; br, broad. The high-resolution mass spectra (HMRS) were recorded on a Bruker micrOTOF-Q mass spectrometer. Optical activity was measured on an Autopol V automatic Polarimeter from Rudolph Research Analytical using a 40T-2.5-100-0.7 Temp Trol polarimetric cell with 2.5 mm inside diameter, 100 mm optical length and 0.7 mL volume with c (concentration) referring to g sample/100mL. Melting points were determined using a Büchi m-560 melting point apparatus. TLC monitoring was done on silica plates from SiliCycle and the plates were developed in 4% PMA solution in methanol. Boric acid impregnated silica gel was prepared by dissolving 4g of boric acid in 100 mL methanol and then adding 55g of silica and swirling the resulting slurry for a few minutes. The methanol was then evaporated off and the silica dried *in vacuo* for 6h at 40°C.

All chemicals and solvents were used without further purification unless otherwise stated. All solvents used, deuterated chloroform (99.8% D), diethyl ether (≥99.8%), ethyl acetate (≥99.7%), dichloromethane (99.8%), ethanol (≥99.8%), hexane (>99%), methanol (99.9%) and tetrahydrofuran (99.9%), were from Sigma-Aldrich. Tetrahydrofuran was dried over natrium wire in the presence of benzophenone under dry nitrogen atmosphere prior to use. Dichloromethane was stored over molecular sieves under nitrogen after taken to use. All the following chemicals: boric acid (≥99.5%), hydrochloric acid (37%), magnesium sulfate (≥99.5%), phosphomolybdic acid, sodium bicarbonate (≥99.0%), sodium hydride (60% dispersion in mineral oil), sodium sulfate (≥99%), (*R*)-solketal (98%, 98% ee), (*S*)-solketal (98%, 99% ee), (*S*)-ibuprofen (99%), vinyl dodecanoate (≥99%), palladium on carbon catalyst, perchloric acid (>70%), benzyl bromide (98%), EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, >99%), DMAP (4-dimethylaminopyridine, >99%) were obtained from Sigma-Aldrich. Vinyl hexanoate (>99%), vinyl octanoate (>99%), vinyl decanoate (>99%), vinyl tetradecanoate (>99%) and vinyl hexadecanoate (>96%) were purchased from TCI Europe. The immobilized *Candida antarctica* lipase B (CAL-B, Novozym 435) was obtained as a gift

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from Novozymes Denmark. EPA (98%) and DHA (≥95%) were obtained as ethyl esters from Pronova Biopharma (Sandefjord, Norway) and were hydrolyzed to their corresponding free acids [51]. (*S*)-Naproxen was acquired from Prof. Thorsteinn Loftsson at the Faculty of Pharmaceutical Sciences at the University of Iceland. The silica gel for the chromatography (40-63 mm, 0.060-0.300, F60) were obtained from Silicycle. The TLC plates were dipped into methanol solution of phosphomolybdic acid (PMA) to develop the spots.

3.2. The Enzymatic Coupling of the SFAs: Synthesis of (R)-5a-f and (S)-5a-f

3.2.1. Synthesis of 1-O-benzyl-3-hexanoyl-sn-glycerol, (R)-5a

Immobilized CAL-B (18 mg) was added to a solution of 1-*O*-benzyl-*sn*-glycerol (150 mg, 0.823 mmol) and vinyl hexanoate (134 mg, 0.940 mmol) in CH_2Cl_2 (3 mL). The resulting mixture was stirred at room temperature for approx. 90 min when TLC monitoring indicated a complete reaction. The lipase preparation was separated by filtration and the solvent was removed in vacuo on rotary evaporator. The concentrate was applied to a 4% boric acid impregnated flash silica gel chromatography using petroleum ether/ethyl acetate (7:3) as eluent. This afforded the product (*R*)-**5a** as a colorless liquid in 94% yield (216 mg, 0.770 mmol). $[\alpha]^{20}_D$ = -2.29 (c. 10.0, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3459 (br), 2957 (vs), 2930 (vs), 2861 (vs), 1737 (vs). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.38-7.28 (m, 5H, Ph-H), 4.56 (s, 2H, $PhCH_2$), 4.19 (dd, *J*=11.5, 4.5 Hz, 1H, CH_2 *sn*-3), 4.14 (dd, *J*=11.5, 6.0 Hz, 1H, CH_2 *sn*-3), 4.05-4.00 (m, 1H, CH *sn*-2), 3.56 (dd, *J*=9.6, 4.3 Hz, 1H, CH_2 *sn*-1), 3.50 (dd, *J*=9.6, 6.1 Hz, 1H, CH_2 *sn*-1), 2.48 (bs, 1H, OH), 2.32 (t, *J*=7.6 Hz, 2H, CH_2COO), 1.66-1.58 (m, 2H, CH_2CH_2COO), 1.38-1.24 (m, 4H, CH_2), 0.89 (t, *J*=6.9 Hz, 3H, CH_3) ppm. ^{13}C{H} NMR (101 MHz, $CDCl_3$) δ_C: 174.1, 137.8, 128.6 (2), 128.0, 127.9 (2), 73.6, 71.0, 69.1, 65.5, 34.2, 31.4, 24.7, 22.4, 14.0 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{24}O_4Na$ 303.1567; found, 303.1557.

3.2.2–6. Synthesis of (R)-5b – (R)-5f

See full experimental details in *Supplementary Materials*

3.2.7. Synthesis of 3-O-benzyl-1-hexanoyl-sn-glycerol, (S)-5a

The same procedure was followed as described for (*R*)-**5a** using immobilized CAL-B (6 mg), 3-*O*-benzyl-*sn*-glycerol (50 mg, 0.274 mmol), vinyl hexanoate (44 mg, 0.309 mmol) and CH_2Cl_2 (3 mL). Purification on a 4% boric acid impregnated flash silica gel chromatography using pet. ether/ethyl acetate (7:3) as eluent afforded the product (*S*)-**5a** as a colorless liquid in 95% yield (73 mg, 0.260 mmol). Spectroscopic data identical to those for (*R*)-**5a** were obtained. $[\alpha]^{20}_D$ = -2.29 (c. 10.0, CH_2Cl_2). HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{24}O_4Na$ 303.1567; found, 303.1565.

3.2.8–12. Synthesis of (S)-5b – (S)-5f

See full experimental details in *Supplementary Materials*

3.3. The Coupling of the Active Drugs: Synthesis of (R,S')-6a-f, (S,S')-6a-f, (R,S')-7a-f and (S,S')-7a-f

3.3.1. Synthesis of 1-O-benzyl-3-hexanoyl-2-[(S)-2-(4-isobutylphenyl)propanoyl]-sn-glycerol, (R,S')-6a

To a solution of 1-*O*-benzyl-3-hexanoyl-*sn*-glycerol (*R*)-**5a** (93 mg, 0.332 mmol) and (*S*)-ibuprofen (83 mg, 0.401 mmol) in CH_2Cl_2 (3 mL) were added DMAP (36 mg, 0.292 mmol) and EDCI (68 mg, 0.352 mmol). The solution was stirred on a magnetic stirrer at room temperature for 12 h. The reaction was disconnected by passing the reaction mixture through a short column packed with silica gel by use of Et_2O/CH_2Cl_2 (1:9). The solvent was removed in vacuo on a rotary evaporator. The concentrate was applied to a silica gel chromatography using petroleum ether/ethyl acetate (7:3) as eluent, which afforded the product (*R,S'*)-**6a** as a pale-yellow oil, in 80% yield (152 mg, 0.267 mmol). $[\alpha]^{20}_D$ = -0.77 (c. 9.7, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3028 (s), 2956 (vs), 2932 (vs), 2869 (vs), 1740 (vs), 1162 (br s). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.34-7.25 (m, 3H, Ph-H), 7.21 (m, 2H, Ibu-2,6 and 2H, Ph-H), 7.07 (d, *J*=8.1

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Hz, 2H, Ibu-3,5), 5.27-5.21 (m, 1H, CH *sn*-2), 4.42-4.34 (m, 1H, CH_2 *sn*-3 and 2H, $PhCH_2$), 4.20 (dd, *J*=11.9, 6.6 Hz, 1H, CH_2 *sn*-3), 3.72 (q, *J*=7.2 Hz, 1H, $CHCH_3$), 3.55-3.46 (m, 2H, CH_2 *sn*-1), 2.43 (d, *J*=7.2 Hz, 2H, $CH_2CH(CH_3)_2$), 2.26 (t, *J*=7.5 Hz, 2H, CH_2COO), 1.83 (nonet, *J*=6.7 Hz, 1H, $CH(CH_3)_2$), 1.64-1.54 (m, 2H, CH_2CH_2COO), 1.50 (d, *J*=7.2 Hz, 3H, $CHCH_3$), 1.36-1.25 (m, 4H, CH_2), 0.90 (t, *J*=6.8 Hz, 3H, CH_2CH_3), 0.89 (d, *J*=6.6 Hz, 6H, $CH(CH_3)_2$) ppm. $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 174.0 (Ibu), 173.4 (SFA), 140.5, 137.7, 137.5, 129.3 (2), 128.3 (2), 127.6 (2), 127.5 (2), 127.2, 73.3, 70.6, 68.2, 62.6, 45.1, 45.0, 34.0, 31.2, 30.1, 24.5, 22.4 (2), 22.3, 18.5, 13.9 ppm. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{29}H_{40}O_5Na$ 491.2768; found, 491.2764.

3.3.2–6. Synthesis of (R,S′)-6b – (R,S′)-6f

See full experimental details in *Supplementary Materials*

3.3.7. Synthesis of 3-O-benzyl-1-hexanoyl-2-[(S)-2-(4-isobutylphenyl)propanoyl]-sn-glycerol, (S,S′)-6a

The same procedure was followed as described for (*R,S′*)-**6a** using 3-*O*-benzyl-1-hexanoyl-*sn*-glycerol (*S*)-**5a** (36 mg, 0.128 mmol), (*S*)-ibuprofen (30 mg, 0.145 mmol), CH_2Cl_2 (2 mL), DMAP (14 mg, 0.115 mmol) and EDCI (26 mg, 0.136 mmol). Purification on a silica gel chromatography using pet. ether/ethyl acetate (4:1) as eluent afforded the product (*S,S′*)-**6a** as a pale-yellow oil, in 93% yield (56 mg, 0.119 mmol). $[\alpha]^{20}_D$ = +22.2 (c. 5.6, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3024 (s), 2957 (vs), 2934 (vs), 2865 (vs), 1743 (vs), 1162 (br s). ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.37-7.26 (m, 5H, Ph-H), 7.19 (d, *J*=8.1 Hz, 2H, Ibu-2,6), 7.06 (d, *J*=8.1 Hz, 2H, Ibu-3,5), 5.26-5.20 (m, 1H, CH *sn*-2), 4.51 (AB q, *J*=12.1 Hz, 2H, $PhCH_2$), 4.24 (dd, *J*=11.6, 3.9 Hz, 1H, CH_2 *sn*-1), 4.12 (dd, J=11.9, 6.8 Hz, 1H, CH_2 *sn*-1), 3.72 (q, *J*=7.2 Hz, 1H, $CHCH_3$), 3.63-3.55 (m, 2H, CH_2 *sn*-3), 2.43 (d, *J*=7.2 Hz, 2H, $CH_2CH(CH_3)_2$), 2.11 (t, *J*=7.6 Hz, 2H, CH_2COO), 1.83 (nonet, *J*=6.7 Hz, 1H, $CH(CH_3)_2$), 1.48 (m, 2H, CH_2CH_2COO and 3H, $CHCH_3$), 1.33-1.20 (m, 4H, CH_2), 0.90 (t, *J*=6.9 Hz, 3H, CH_2CH_3), 0.88 (d, *J*=6.6 Hz, 6H, $CH(CH_3)_2$) ppm. $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 174.2 (Ibu), 173.4 (SFA), 140.6, 137.9, 137.6, 129.4 (2), 128.6 (2), 127.9 (2), 127.7 (2), 127.3, 73.5, 70.6, 68.5, 62.7, 45.3, 45.2, 34.0, 31.4, 30.1, 24.6, 22.5 (2), 22.4, 18.4, 14.1 ppm. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{29}H_{40}O_5Na$ 491.2768; found, 491.2764.

3.3.8–12. Synthesis of (S,S′)-6b – (S,S′)-6f

See full experimental details in *Supplementary Materials*

3.3.13. Synthesis of 1-O-benzyl-3-hexanoyl-2-[(S)-2-(6-methoxynaphthalen-2-yl)propanoyl]-sn-glycerol, (R,S′)-7a

To a solution of 1-*O*-benzyl-3-hexanoyl-*sn*-glycerol (*R*)-**5a** (93 mg, 0.332 mmol) and (*S*)-naproxen (92 mg, 0.401 mmol) in CH_2Cl_2 (3 mL) were added DMAP (36 mg, 0.292 mmol) and EDCI (68 mg, 0.352 mmol). The solution was stirred on a magnetic stirrer at room temperature for 12 h. The reaction was disconnected by passing the reaction mixture through a short column packed with silica gel by use of Et_2O/CH_2Cl_2 (1:9). The solvent was removed in vacuo on a rotary evaporator. The concentrate was applied to a silica gel chromatography using petroleum ether/ethyl acetate (7:3) as eluent, which afforded the product (*R,S′*)-**7a** as a clear oil, in 90% yield (147 mg, 0.299 mmol). $[\alpha]^{20}_D$ = -3.9 (c. 10.0, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3062 (s), 3031 (s), 2957 (vs), 2935 (vs), 2871 (vs), 1739 (vs), 1634 (vs), 1174 (br s). ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.70-7.65 (m, 3H, H-1,4,8 Nap), 7.41 (dd, *J*=8.5, 1.8 Hz, 1H, H-3 Nap), 7.24-7.21 (m, 3H, Ph-H), 7.14 (dd, *J*=8.9, 2.6 Hz, 1H, H-7 Nap), 7.12-7.09 (m, 2H, Ph-H and 1H, Nap-5), 5.27 (dtd, *J*=6.6, 5.0, 3.7 Hz, 1H, CH *sn*-2), 4.39-4.27 (m, 1H, CH_2 *sn*-3 and 2H, $PhCH_2$), 4.21 (dd, *J*=11.9, 6.6 Hz, 1H, CH_2 *sn*-3), 3.91 (s, 3H, OCH_3), 3.89 (q, *J*=7.2, 1H, $CHCH_3$), 3.54-3.44 (m, 2H, CH_2 *sn*-1), 2.22 (t, *J*=7.5 Hz, 2H, CH_2COO), 1.64-1.54 (m, 2H, CH_2CH_2COO and 3H, $CHCH_3$), 1.33-1.21 (m, 4H, CH_2), 0.89 (t, *J*=6.9 Hz, 3H, CH_2CH_3) ppm. $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 173.9 (Nap), 173.4 (SFA), 157.6, 137.7, 135.4, 133.68, 129.2, 128.9, 128.2 (2), 127.6, 127.4 (2), 127.1, 126.2, 126.0, 118.9, 105.6, 73.2, 70.7, 68.2, 62.6, 55.3, 45.4, 34.0, 31.2, 24.58, 22.3, 18.5, 13.9 ppm. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{30}H_{36}O_6Na$ 515.2404; found, 515.2396.

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3.3.14–18. Synthesis of (R,S′)-7b – (R,S′)-7f

See full experimental details in *Supplementary Materials*

3.3.19. Synthesis of 3-O-benzyl-1-hexanoyl-2-[(S)-2-(6-methoxynaphthalen-2-yl)propanoyl]-sn-glycerol, (S,S′)-7a

To a solution of 3-*O*-benzyl-1-hexanoyl-*sn*-glycerol (*S*)-**5a** (36 mg, 0.128 mmol) and (*S*)-naproxen (34 mg, 0.147 mmol) in CH_2Cl_2 (2.3 mL) were added DMAP (15 mg, 0.121 mmol) and EDCI (28 mg, 0.145 mmol). The solution was stirred on a magnetic stirrer at room temperature for 16 h. The reaction was disconnected by passing the reaction mixture through a short column packed with silica gel by use of Et_2O/CH_2Cl_2 (1:9). The solvent was removed in vacuo on a rotary evaporator. The concentrate was applied to a silica gel chromatography using petroleum ether/ethyl acetate (8.5:1.5) as eluent, which afforded the product (*S,S′*)-**7a** as a clear oil, in 97% yield (58 mg, 0.124 mmol). $[\alpha]^{20}_D$ = +20.8 (c. 3.4, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3058 (s), 3028 (s), 2956 (vs), 2932 (vs), 2855 (vs), 1742 (vs), 1635 (vs), 1170 (br s). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.73-7.63 (m, 3H, H-1,4,8 Nap), 7.41 (dd, *J*=8.6, 1.8 Hz, 1H, H-3 Nap), 7.36-7.26 (m, 5H, Ph-H), 7.14 (dd, *J*=8.9, 2.5 Hz, 1H, H-7 Nap), 7.10 (d, *J*=2.5 Hz, 1H, Nap-5) 5.26-5.20 (m, 1H, CH *sn*-2), 4.51 (AB q, *J*=12.1 Hz, 2H, $PhCH_2$), 4.23 (dd, *J*=11.9, 3.7 Hz, 1H, CH_2 *sn*-1), 4.13 (dd, *J*=11.9, 6.9 Hz, 1H, CH_2 *sn*-1), 3.91 (s, 3H, OCH_3), 3.72 (q, *J*=7.1, 1H, C*H*CH_3), 3.61-3.59 (m, 2H, CH_2 *sn*-3), 1.94-1.87 (m, 2H, CH_2COO), 1.58 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$), 1.40-1.31 (m, 2H, C*H*$_2CH_2COO$), 1.23-1.15 (m, 2H, C*H*$_2CH_2CH_3$), 1.13-1.03 (m, 2H, C*H*$_2CH_3$), 0.85 (t, *J*=7.2 Hz, 3H, CH_2C*H*$_3$) ppm. ^{13}C{H} NMR (101 MHz, $CDCl_3$) δ_C: 174.1 (Nap), 173.4 (SFA), 157.8, 137.8, 135.6, 133.8, 129.4, 129.1, 128.5 (2), 127.9, 127.7 (2), 127.2, 126.4, 126.1, 119.1, 105.7, 73.4, 70.7, 68.5, 62.6, 55.4, 45.6, 33.8, 31.3, 24.4, 22.4, 18.5, 14.0 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{36}O_6Na$ 515.2404; found, 515.2405.

3.3.20–24. Synthesis of (S,S′)-7b – (S,S′)-7f

See full experimental details in *Supplementary Materials*

3.4. The Removal of the Benzyl Protective Group: Synthesis of (R,S′)-8a-f, (S,S′)-8a-f, (R,S′)-9a-f and (S,S′)-9a-f

3.4.1. Synthesis of 3-hexanoyl-2-[(S)-2-(4-isobutylphenyl)propanoyl]-sn-glycerol, (R,S′)-8a

Pd/C catalyst (26 mg) was placed into a 25 mL flame-dried two-necked round-bottom flask equipped with a magnetic stirrer under nitrogen atmosphere at room temperature and the flask sealed with a septum. A solution of 1-*O*-benzyl-3-hexanoyl-2-[(*S*)-2-(4-isobutylphenyl)propanoyl]-*sn*-glycerol, (*R,S′*)-**6a** (116 mg, 0.236 mmol) dissolved in dry THF (7 mL) was added with a syringe, followed by n-hexane (11.2 mL). A balloon filled with hydrogen gas was then mounted on a syringe and stuck through the septum. The mixture was stirred while the hydrogen gas was blown through the flask to replace the nitrogen atmosphere with hydrogen. Then a tiny drop of perchloric acid was added and the solution stirred vigorously at room temperature while being monitored with TLC. When the reaction came to completion according to the TLC (approximately 15 minutes) the flask was promptly opened and the acid neutralized by adding $NaHCO_3$ (s). Then the solution was filtered, and the solvent removed in vacuo on a rotary evaporator. The crude product was applied to a 4% boric acid impregnated flash silica gel chromatography using petroleum ether/ethyl acetate (7:3) as eluent, wich afforded the product (*R,S′*)-**8a** as a pale-yellow oil, in 84% yield (75 mg, 0.198 mmol). $[\alpha]^{20}_D$ = +23.9 (c. 4.0, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3500 (br), 2956 (vs), 2932 (vs), 2870 (vs), 1739 (vs), 1165 (br s). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.19 (d, *J*=8.2 Hz, 2H, Ibu-2,6), 7.10 (d, *J*=8.1 Hz, 2H, Ibu-3,5), 5.07-5.02 (m, 1H, CH *sn*-2), 4.30 (dd, *J*=11.9, 4.4 Hz, 1H, CH_2 *sn*-3), 4.21 (dd, *J*=11.9, 5.9 Hz, 1H, CH_2 *sn*-3), 3.73 (q, *J*=7.1 Hz, 1H, C*H*CH_3), 3.61-3.56 (m, 2H, CH_2 *sn*-1), 2.44 (d, *J*=7.1 Hz, 2H, C*H*$_2$CH(CH_3)$_2$), 2.29 (t, *J*=7.6 Hz, 2H, CH_2COO), 1.84 (nonet, *J*=6.7 Hz, 1H, C*H*(CH_3)$_2$), 1.67-1.57 (m, 2H, C*H*$_2CH_2COO$), 1.50 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$), 1.34-1.27 (m, 4H, CH_2), 0.90 (t, *J*=6.1 Hz, 3H, CH_2C*H*$_3$), 0.88 (d, *J*=6.6 Hz, 6H, CH(C*H*$_3$)$_2$) ppm. ^{13}C{H} NMR (101 MHz, $CDCl_3$) δ_C: 174.3 (Ibu), 173.8

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(SFA), 140.9, 137.8, 129.6 (2), 127.1 (2), 72.7, 62.1, 61.5, 45.3, 45.1, 34.2, 31.4, 30.3, 24.7, 22.5 (2), 22.4, 18.4, 14.1 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{34}O_5Na$ 401.2298; found, 401.2297.

3.4.2–6. Synthesis of (R,S′)-8b – (R,S′)-8f

See full experimental details in *Supplementary Materials*

3.4.7. Synthesis of 1-hexanoyl-2-[(S)-2-(4-isobutylphenyl)propanoyl]-sn-glycerol, (S,S′)-8a

The same procedure was followed as described for (*R,S′*)-**8a** using Pd/C catalyst (13 mg), 3-*O*-benzyl-1-hexanoyl-2-[(*S*)-2-(4-isobutylphenyl)propanoyl]-*sn*-glycerol (*S,S′*)-**6a** (30 mg, 0.064 mmol), THF (4 mL) and n-hexane (5.6 mL). Purification on 4% boric acid impregnated flash silica gel chromatography using pet. ether/ethyl acetate (3:2) as eluent, afforded the product (*S,S′*)-**8a** as a pale-yellow oil, in 95% yield (23 mg, 0.061 mmol). $[\alpha]^{20}_D$ = +5.65 (c. 2.3, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3474 (br), 2956 (vs), 2870 (vs), 1740 (vs), 1513 (vs), 1165 (br s). ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.19 (d, *J*=8.2 Hz, 2H, Ibu-2,6), 7.10 (d, *J*=8.1 Hz, 2H, Ibu-3,5), 5.07-5.02 (m, 1H, CH *sn*-2), 4.30 (dd, *J*=11.9, 4.4 Hz, 1H, CH_2 *sn*-1), 4.14 (dd, *J*=11.9, 6.0 Hz, 1H, CH_2 *sn*-1), 3.72-3.63 (m, 2H, CH_2 *sn*-3 and 1H, C*H*CH_3), 2.44 (d, *J*=7.1 Hz, 2H, C*H*$_2$CH$(CH_3)_2$), 2.18 (t, *J*=7.6 Hz, 2H, CH_2COO), 1.91 (t, *J*=6.5 Hz, 1H, OH), 1.84 (nonet, *J*=6.8 Hz, 1H, C*H*$(CH_3)_2$), 1.55 (m, 2H, C*H*$_2$CH$_2$COO), 1.50 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$), 1.34-1.27 (m, 4H, CH_2), 0.90 (t, *J*=6.1 Hz, 3H, CH_2C*H*$_3$), 0.88 (d, *J*=6.6 Hz, 6H, CH(C*H*$_3$)$_2$) ppm. $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 174.5 (Ibu), 173.8 (SFA), 140.8, 137.4, 129.5 (2), 127.2 (2), 72.7, 62.0, 61.7, 45.2, 45.2, 34.1, 31.4, 30.3, 24.6, 22.5 (2), 22.4, 18.4, 14.0 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{34}O_5Na$ 401.2298; found, 401.2295.

3.4.8–12. Synthesis of (S,S′)-8b – (S,S′)-8f

See full experimental details in *Supplementary Materials*

3.4.13. Synthesis of 3-hexanoyl-2-[(S)-2-(6-methoxynaphthalen-2-yl)propanoyl]-sn-glycerol, (R,S′)-9a

Pd/C catalyst (24 mg) was placed into a 25 mL flame-dried two-necked round-bottom flask equipped with a magnetic stirrer under nitrogen atmosphere at room temperature and the flask sealed with a septum. A solution of 1-*O*-benzyl-3-hexanoyl-2-[(*S*)-2-(6-methoxynaphthalen-2-yl)propanoyl]-*sn*-glycerol, (*R,S′*)-**7a** (107 mg, 0.217 mmol) dissolved in dry THF (6.4 mL) was added with a syringe, followed by n-hexane (10.3 mL). A balloon filled with hydrogen gas was then mounted on a syringe and stuck through the septum. The mixture was stirred while the hydrogen gas was blown through the flask to replace the nitrogen atmosphere with hydrogen. Then a tiny drop of perchloric acid was added and the solution stirred vigorously at room temperature while being monitored with TLC. When the reaction came to completion according to the TLC (approximately 15 minutes) the flask was promptly opened and the acid neutralized by adding $NaHCO_3$ (s). Then the solution was filtered, and the solvent removed in vacuo on a rotary evaporator. The crude product was applied to a 4% boric acid impregnated flash silica gel chromatography using petroleum ether/ethyl acetate (1:1) as eluent, wich afforded the product (*R,S′*)-**9a** as a pale-yellow oil, in 98% yield (86 mg, 0.213 mmol). $[\alpha]^{20}_D$ = +5.63 (c. 1.6, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3358 (br), 2926 (vs), 2856 (vs), 1739 (vs), 1632 (vs). 1606 (vs). ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.71-7.66 (m, 3H, Nap-1,4,8), 7.38 (dd, *J*=8.5, 1.9 Hz, 1H, Nap-3), 7.14 (dd, *J*=8.9, 2.5 Hz, 1H, Nap-7), 7.10 (d, *J*=2.5 Hz, 1H, Nap-5), 5.14-5.01 (m, 1H, CH *sn*-2), 4.31 (dd, *J*=11.9, 4.3 Hz, 1H, CH_2 *sn*-3), 4.27-4.19 (m, 1H, CH_2 *sn*-3), 3.91 (s, 3H, OCH_3), 3.91-3.82 (m, 1H, C*H*CH_3), 3.61-3.57 (m, 2H, CH_2 *sn*-1), 2.27-2.24 (m, 2H, CH_2COO), 2.23-2.20 (bs, 1H, OH), 1.58 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$), 1.56 (quint, *J*=7.2 Hz, 2H, C*H*$_2$CH$_2$COO), 1.38-1.22 (m, 4H, CH_2), 0.89 (t, *J*=7.0 Hz, 3H, CH_2C*H*$_3$) ppm. $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 174.3 (Nap), 173.8 (SFA), 157.9, 135.6, 133.9, 129.4, 129.0, 127.4, 126.1, 126.0, 119.3, 105.8, 72.8, 62.1, 61.5, 55.5, 45.6, 34.2, 31.1, 24.7, 22.4, 18.5, 14.0 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{30}O_6Na$ 425.1935; found, 425.1934.

3.4.14–18. Synthesis of (R,S′)-9b – (R,S′)-9f

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See full experimental details in *Supplementary Materials*

3.4.19. Synthesis of 1-hexanoyl-2-[(S)-2-(6-methoxynaphthalen-2-yl)propanoyl]-sn-glycerol, (S,S′)-9a

The same procedure was followed as described for (*R,S′*)-**9a** using Pd/C catalyst (3 mg), 3-*O*-benzyl-1-hexanoyl-2-[(*S*)-2-(6-methoxynaphthalen-2-yl)propanoyl]-*sn*-glycerol, (*S,S′*)-**7a** (14 mg, 0.028 mmol), THF (1 mL) and n-hexane (1.5 mL). Purification on 4% boric acid impregnated flash silica gel chromatography using pet. ether/ethyl acetate (3:2) as eluent, afforded the product (*S,S′*)-**9a** as a pale-yellow oil, in 97% yield (11 mg, 0.027 mmol). $[\alpha]^{20}_{D}$ = +8.60 (c. 1.0, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3421 (br), 3060 (s), 2925 (vs), 2856 (vs), 1739 (vs), 1634 (s), 1607 (vs), 1162 (br s). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.73-7.65 (m, 3H, Nap-1,4,8), 7.39 (dd, *J*=8.5, 1.9 Hz, 1H, Nap-3), 7.14 (dd, *J*=8.9, 2.6 Hz, 1H, Nap-7), 7.10 (d, *J*=2.6 Hz, 1H, Nap-5), 5.08 (m, 1H, CH *sn*-2), 4.19 (dd, *J*=11.9, 4.4 Hz, 1H, CH_2 *sn*-1), 4.27-4.13 (dd, *J*=11.9, 6.1, Hz, 1H, CH_2 *sn*-1), 3.91 (s, 3H, OCH_3), 3.96-3.84 (m, 1H, C*H*CH_3), 3.74-3.69 (m, 2H, CH_2 *sn*-3), 2.23-2.20 (bs, 1H, OH), 2.05-1.89 (m, 2H, CH_2COO), 1.59 (d, *J*=7.1 Hz, 3H, CHC*H*$_3$), 1.44-1.33 (m, 2H, C*H*$_2$CH$_2$COO), 1.38-1.06 (m, 4H, CH_2), 0.85 (t, *J*=7.2 Hz, 3H, CH_2CH_3) ppm. ^{13}C{H} NMR (101 MHz, $CDCl_3$) δ_C: 174.5 (Nap), 173.7 (SFA), 157.9, 135.4, 133.9, 129.4, 129.1, 127.3, 126.2, 126.1, 119.2, 105.7, 72.8, 61.9, 61.7, 55.5, 45.6, 33.9, 31.3, 29.9, 24.5, 18.5, 14.0 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{30}O_6Na$ 425.1935; found, 425.1932.

3.4.20–24. Synthesis of (S,S′)-9b – (S,S′)-9f

See full experimental details in *Supplementary Materials*

3.5. Coupling of EPA: Synthesis of (S,S′)-10a-f, (R,S′)-10a-f, (S,S′)-11a-f and (R,S′)-11a-f

3.5.1. Synthesis of 1-[5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoyl]-3-hexanoyl-2-[(S)-2-(4-isobutylphenyl)propanoyl]-sn-glycerol, (S,S′)-10a

To a solution of 3-hexanoyl-2-[(*S*)-2-(4-isobutylphenyl)propanoyl]-*sn*-glycerol (*R,S′*)-**8a** (45 mg, 0.118 mmol) and EPA as a free acid (33 mg, 0.108 mmol) in CH_2Cl_2 (4 mL) were added DMAP (13 mg, 0.106 mmol) and EDCI (28 mg, 0.143 mmol). The solution was stirred on a magnetic stirrer at room temperature for 12 h. The reaction was disconnected by passing the reaction mixture through a short column packed with silica gel by use of Et_2O/CH_2Cl_2 (1:9). The solvent was removed in vacuo on a rotary evaporator. The residue was applied to a silica gel chromatography using petroleum ether/ethyl acetate (8.5:1.5) as eluent, which afforded the product (*S,S′*)-**10a** as a yellow oil, in 90% yield (70 mg, 0.106 mmol). $[\alpha]^{20}_{D}$ = +11.7 (c. 6.0, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3013 (s), 2959 (vs), 2933 (vs), 2871 (vs), 1743 (vs), 1656 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.18 (d, *J*=8.1 Hz, 2H, Ibu-2,6), 7.07 (d, *J*=8.1 Hz, 2H, Ibu-3,5), 5.44-5.28 (m, 10H, =CH), 5.35-5.32 (m, 1H, CH *sn*-2), 4.30 (dd, *J*=11.9, 4.2 Hz, 1H, CH_2 *sn*-1/3), 4.19 (dd, *J*=11.9, 4.5 Hz, 1H, CH_2 *sn*-1/3), 4.13 (dd, J=11.9, 6.0 Hz, 1H, CH_2 *sn*-1/3), 4.07 (dd, J=11.9, 6.4 Hz, 1H, CH_2 *sn*-1/3), 3.70 (q, *J*=7.1 Hz, 1H, C*H*CH_3), 2.86-2.78 (m, 8H, =CHC*H*$_2$CH=), 2.43 (d, *J*=7.2 Hz, 2H, C*H*$_2$CH(CH$_3$)$_2$), 2.28 (t, *J*=7.2 Hz, 2H, CH_2COO EPA), 2.18 (t, *J*=7.5 Hz, 2H, CH_2COO), 2.10-2.05 (m, 4H, CH_2CH_2CH= and =CHC*H*$_2$CH3), 1.84 (nonet, *J*=6.8 Hz, 1H, C*H*(CH$_3$)$_2$), 1.63-1.48 (m, 4H, C*H*$_2$CH$_2$COO SFA and C*H*$_2$CH$_2$COO EPA), 1.49 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$), 1.32-1.29 (m, 4H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 EPA), 0.90 (t, *J*=7.2 Hz, 3H, CH_3 SFA), 0.89 (d, *J*=6.6 Hz, 6H, CH(C*H*$_3$)$_2$) ppm. ^{13}C{H} NMR (101 MHz, $CDCl_3$) δ_C: 173.9 (Ibu), 173.4 (SFA), 173.0 (EPA), 140.7, 137.4, 132.2, 129.4 (2), 129.0, 128.71, 128.4, 128.3, 128.3, 128.2, 128.0, 128.3, 127.3 (2), 127.2, 69.3, 62.2, 62.1, 45.2, 45.2, 34.1, 33.4, 31.4, 30.3, 26.6, 25.8 (2), 25.7 (2), 24.7, 24.7, 22.5 (2), 22.4, 20.7, 18.5, 14.4, 14.0 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{42}H_{62}O_6Na$ 685.4439; found, 685.4439.

3.5.2–6. Synthesis of (S,S′)-10b – (S,S′)-10f

See full experimental details in *Supplementary Materials*

3.5.7. Synthesis of 3-[5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoyl]-1-hexanoyl-2-[(S)-2-(4-isobutylphenyl)propanoyl]-sn-glycerol, (R,S′)-10a

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The same procedure was followed as described for (*S,S′*)-**10a** using 1-hexanoyl-[(*S*)-2-(4-isobutylphenyl)propanoyl]-*sn*-glycerol (*S,S′*)-**8a** (19 mg, 0.050 mmol), EPA (16 mg, 0.053 mmol), CH_2Cl_2 (3 mL), DMAP (7 mg, 0.054 mmol) and EDCI (14 mg, 0.073 mmol). Purification on a silica gel chromatography using pet. ether/ethyl acetate (8.5:1.5) as eluent afforded the product (*R,S′*)-**10a** as a pale-yellow oil, in 74% yield (25 mg, 0.037 mmol). $[\alpha]^{20}_D$ = +6.50 (c. 2.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.18 (dd, *J*=8.1, 1.7 Hz, 2H, Ibu-2,6), 7.07 (dd, *J*=8.1, 3.8 Hz, 2H, Ibu-3,5), 5.45-5.29 (m, 10H, =CH), 5.28-5.22 (m, 1H, CH *sn*-2), 4.30 (dd, *J*=11.9, 4.3 Hz, 1H, CH_2 *sn*-1/3), 4.21 (dd, *J*=11.9, 4.3 Hz, 1H, CH_2 *sn*-1/3), 4.15 (dd, J=11.9, 6.4 Hz, 1H, CH_2 *sn*-1/3), 4.06 (dd, J=11.9, 6.3 Hz, 1H, CH_2 *sn*-1/3), 3.70 (q, *J*=7.1 Hz, 1H, C*H*CH_3), 2.87-2.77 (m, 8H, =CHC*H*$_2$CH=), 2.44 (d, *J*=7.2 Hz, 2H, C*H*$_2$CH$(CH_3)_2$), 2.33-2.22 (m, 2H, CH_2COO EPA), 2.18-2.04 (m, 6H, CH_2COO SFA, CH_2C*H*$_2$CH= and =CHC*H*$_2$$CH_3$), 1.84 (nonet, *J*=6.8 Hz, 1H, C*H*$(CH_3)_2$), 1.74-1.58 (m, 2H, C*H*$_2$$CH_2$COO EPA), 1.57-1.50 (m, 2H, C*H*$_2$$CH_2$COO SFA), 1.49 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$), 1.33-1.20 (m, 4H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 EPA), 0.89 (d, *J*=6.6 Hz, 6H, CH(C*H*$_3$)$_2$), 0.88 (t, *J*=6.5 Hz, 3H, CH_3 SFA) ppm. ^{13}C{H} NMR (101 MHz, $CDCl_3$) δ_C: 173.9 (Ibu), 173.3 (SFA), 173.1 (EPA), 140.7, 137.4, 132.2, 129.4 (2), 129.1, 129.0, 128.7, 128.4, 128.4, 128.3, 128.2, 128.0, 127.3 (2), 127.2, 69.4, 62.3, 62.1, 45.2, 45.2, 34.0, 33.5, 31.4, 30.3, 26.7, 25.8 (2), 25.7 (2), 24.8, 24.6, 22.5 (2), 22.4, 20.7, 18.5, 14.4, 14.0 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{42}H_{62}O_6Na$ 685.4439; found, 685.4430.

3.5.8–12. Synthesis of (R,S′)-10b – (R,S′)-10f

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3.5.13. Synthesis of 1-[5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoyl]-3-hexanoyl-2[(S)-2-(6-methoxynaphthalen-2-yl)propanoyl]-sn-glycerol, (S,S′)-11a

To a solution of 3-hexanoyl-2-[(*S*)-2-(6-methoxynaphthalen-2-yl)propanoyl]-*sn*-glycerol (*R,S′*)-**9a** (35 mg, 0.087 mmol) and EPA as a free acid (28 mg, 0.093 mmol) in CH_2Cl_2 (4 mL) were added DMAP (11 mg, 0.094 mmol) and EDCI (24 mg, 0.127 mmol). The solution was stirred on a magnetic stirrer at room temperature for 12 h. The reaction was disconnected by passing the reaction mixture through a short column packed with silica gel by use of Et_2O/CH_2Cl_2 (1:9). The solvent was removed in vacuo on a rotary evaporator. The residue was applied to a silica gel chromatography using petroleum ether/ethyl acetate (7:3) as eluent, which afforded the product (*S,S′*)-**11a** as a yellow oil, in 91% yield (54 mg, 0.079 mmol). $[\alpha]^{20}_D$ = +8.12 (c. 5.0, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3012 (s), 2960 (vs), 2933 (vs), 2872 (vs), 1735 (vs), 1634 (vs), 1607 (vs). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.72-7.65 (m, 3H, Nap-1,4,8), 7.38 (dd, *J*=8.5, 1.9 Hz, 1H, Nap-3), 7.14 (dd, *J*=8.9, 2.5 Hz, 1H, Nap-7), 7.10 (d, *J*=2.5 Hz, 1H, Nap-5), 5.46-5.31 (m, 10H, =CH), 5.33-5.19 (m, 1H, CH *sn*-2), 4.30 (dd, *J*=11.9, 4.2 Hz, 1H, CH_2 *sn*-1/3), 4.20-4.10 (m, 2H, CH_2 *sn*-1/3), 4.07 (dd, J=11.9, 6.4 Hz, 1H, CH_2 *sn*-1/3), 3.90 (s, 3H, OCH_3), 3.85 (q, *J*=7.5 Hz, 1H, C*H*CH_3), 2.87-2.71 (m, 8H, =CHC*H*$_2$CH=), 2.30-2.19 (m, 2H, CH_2COO EPA), 2.12-2.04 (m, 2H, CH_2COO SFA), 2.00 (td, *J*=7.6, 5.6 Hz, 2H, CH_2C*H*$_2$CH=), 1.96-1.90 (m, 2H, =CHC*H*$_2$$CH_3$), 1.62-1.52 (m, 5H, C*H*$_2$$CH_2$COO SFA and CHC*H*$_3$), 1.46 (quint, *J*=7.3 Hz, 2H, C*H*$_2$$CH_2$COO EPA), 1.35-1.19 (m, 4H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 EPA), 0.89 (t, *J*=7.0 Hz, 3H, CH_3 SFA) ppm. ^{13}C{H} NMR (101 MHz, $CDCl_3$) δ_C: 173.8 (Nap), 173.3 (SFA), 172.9 (EPA), 157.8, 135.3, 133.8, 132.1, 129.4, 129.0, 128.93, 128.89, 128.7, 128.4, 128.3, 128.3, 128.2, 128.0, 127.2, 127.1, 126.2, 126.1, 119.1, 105.6, 69.5, 62.1, 62.1, 55.4, 45.5, 34.1, 33.2, 31.3, 26.5, 25.7, 25.7 (2), 25.7, 24.6, 24.5, 22.4, 20.7, 18.4, 14.4, 14.0 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{43}H_{58}O_7Na$ 709.4075; found, 709.4062.

3.5.14-18. Synthesis of (S,S′)-11b – (S,S′)-11f

See full experimental details in *Supplementary Materials*

3.5.19. Synthesis of 3-[5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoyl]-1-hexanoyl-2[(S)-2-(6-methoxynaphthalen-2-yl)propanoyl]-sn-glycerol, (R,S′)-11a

To a solution of 1-hexanoyl-2-[(*S*)-2-(6-methoxynaphthalen-2-yl)propanoyl]-*sn*-glycerol (*S,S′*)-**9a** (12 mg, 0.030 mmol) and EPA as a free acid (10 mg, 0.033 mmol) in CH_2Cl_2 (1.3 mL) were added

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DMAP (4 mg, 0.033 mmol) and EDCI (8 mg, 0.044 mmol). The solution was stirred on a magnetic stirrer at room temperature for 12 h. The reaction was disconnected by passing the reaction mixture through a short column packed with silica gel by use of Et_2O/CH_2Cl_2 (1:9). The solvent was removed in vacuo on a rotary evaporator. The residue was applied to a silica gel chromatography using petroleum ether/ethyl acetate (7:3) as eluent, which afforded the product (*R,S'*)-**11a** as a yellow oil, in 80% yield (16 mg, 0.024 mmol). $[\alpha]^{20}_D$ = +4.20 (c. 1.0, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3059 (br), 3012 (s), 2958 (vs), 2872 (vs), 1740 (vs, 1634 (s), 1607 (s). ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.72-7.63 (m, 3H, Nap-1,4,8), 7.38 (dd, *J*=8.5, 1.8 Hz, 1H, Nap-3), 7.14 (dd, *J*=8.9, 2.4 Hz, 1H, Nap-7), 7.10 (d, *J*=2.4 Hz, 1H, Nap-5), 5.45-5.31 (m, 10H, =CH), 5.33-5.19 (m, 1H, CH *sn*-2), 4.30 (dd, *J*=11.9, 4.2 Hz, 1H, CH_2 *sn*-1/3), 4.17 ((dd, *J*=8.2, 3.7 Hz, 2H, CH_2 *sn*-1/3), 4.14 (dd, *J*=8.2, 3.6 Hz, 1H, CH_2 *sn*-1/3), 4.06 (dd, J=11.9, 6.4 Hz, 1H, CH_2 *sn*-1/3), 3.91 (s, 3H, OCH_3), 3.86 (q, *J*=7.1 Hz, 1H, C*H*CH_3), 2.80-2.76 (m, 8H, =CHC*H*$_2$CH=), 2.29-2.23 (m, 2H, CH_2COO EPA), 2.12-2.03 (m, 4H, CH_2COO SFA and CH_2CH_2CH=), 1.97-1.91 (m, 2H, =CHC*H*$_2CH_3$), 1.65 (quint, *J*=7.4 Hz, 2H, C*H*$_2CH_2$COO SFA), 1.57 (d, *J*=7.1 Hz, CHC*H*$_3$), 1.44-1.33 (m, 2H, C*H*$_2CH_2$COO EPA), 1.32-1.07 (m, 4H, CH_2), 0.97 (t, *J*=7.6 Hz, 3H, CH_3 EPA), 0.89 (t, *J*=7.2 Hz, 3H, CH_3 SFA) ppm. $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 173.9 (Nap), 173.3 (SFA), 173.1 (EPA), 157.9, 135.4, 133.9, 132.2, 131.0, 129.4, 129.08, 129.05, 129.0, 128.9, 128.7, 128.4, 128.4, 128.2, 128.0, 127.24, 127.17, 126.3, 126.1, 119.2, 105.7, 69.5, 62.3, 62.0, 55.4, 45.5, 34.1, 33.2, 31.3, 26.5, 25.8, 25.70 (2), 25.66, 24.8, 24.6, 22.4, 20.7, 18.5, 14.4, 14.0 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{43}H_{58}O_7Na$ 709.4075; found, 709.4075.

3.5.20-24. Synthesis of (R,S')-11b – (R,S')-11f

See full experimental details in *Supplementary Materials*

3.6. Coupling of DHA: Synthesis of (S,S')-12a-f, (R,S')-12a-f, (S,S')-13a-f and (R,S')-13a-f

3.6.1. Synthesis of 1-[4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl]-3-hexanoyl-2-[(S)-2-(4-isobutylphenyl)propanoyl]-sn-glycerol, (S,S')-12a

To a solution of 3-hexanoyl-2-[(*S*)-2-(4-isobutylphenyl)propanoyl]-*sn*-glycerol (*R,S'*)-**8a** (23 mg, 0.061 mmol) and DHA as a free acid (36 mg, 0.108 mmol) in CH_2Cl_2 (4 mL) were added DMAP (13 mg, 0.106 mmol) and EDCI (28 mg, 0.143 mmol). The solution was stirred on a magnetic stirrer at room temperature for 12 h. The reaction was disconnected by passing the reaction mixture through a short column packed with silica gel by use of Et_2O/CH_2Cl_2 (1:9). The solvent was removed in vacuo on a rotary evaporator. The residue was applied to a silica gel chromatography using petroleum ether/ethyl acetate (8.5:1.5) as eluent, which afforded the product (*S,S'*)-**12a** as a yellow oil, in 81% yield (35 mg, 0.049 mmol). $[\alpha]^{20}_D$ = +9.95 (c. 2.0, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3013 (vs), 2957 (vs), 2928 (vs), 2870 (vs), 1743 (vs). ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.18 (d, *J*=8.1 Hz, 2H, Ibu-2,6), 7.07 (d, *J*=8.1 Hz, 2H, Ibu-3,5), 5.44-5.28 (m, 12H, =CH), 5.35-5.32 (m, 1H, CH *sn*-2), 4.30 (dd, *J*=11.9, 4.2 Hz, 1H, CH_2 *sn*-1/3), 4.19 (dd, *J*=11.9, 4.5 Hz, 1H, CH_2 *sn*-1/3), 4.13 (dd, J=11.9, 6.0 Hz, 1H, CH_2 *sn*-1/3), 4.08 (dd, J=11.9, 6.4 Hz, 1H, CH_2 *sn*-1/3), 3.70 (q, *J*=7.2 Hz, 1H, C*H*CH_3), 2.90-2.78 (m, 10H, =CHC*H*$_2$CH=), 2.43 (d, *J*=7.2 Hz, 2H, C*H*$_2$CH(CH_3)$_2$), 2.34-2.19 (m 6H, CH_2CH_2COO DHA and CH_2COO SFA), 2.10-2.06 (m, 2H, =CHC*H*$_2CH_3$), 1.83 (nonet, *J*=6.8 Hz, 1H, C*H*(CH_3)$_2$), 1.65-1.55 (m, 2H, C*H*$_2CH_2$COO SFA), 1.49 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$), 1.37-1.24 (m, 4H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 DHA), 0.90 (t, *J*=7.2 Hz, 3H, CH_3 SFA), 0.89 (d, *J*=6.6 Hz, 6H, CH(C*H*$_3$)$_2$) ppm. $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 173.8 (Ibu), 173.3 (SFA), 172.5 (DHA), 140.6, 137.3, 132.1, 129.4 (2), 129.3, 128.6, 128.4, 128.32, 128.29, 128.14, 128.12, 128.05, 127.9, 127.7 (2), 127.2, 127.1, 69.2, 62.1, 62.1, 45.09, 45.07, 34.0, 33.8, 31.3, 30.2, 25.7 (2), 25.63, 25.59 (2), 24.6, 22.6, 22.4 (2), 22.3, 20.6, 18.4, 14.3, 13.9 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{44}H_{64}O_6Na$ 711.4595; found, 711.4584.

3.6.2–6. Synthesis of (S,S')-12b – (S,S')-12f

See full experimental details in *Supplementary Materials*

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3.6.7. Synthesis of 3-[4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl]-1-hexanoyl-2-[(S)-2-(4-isobutylphenyl)propanoyl]-sn-glycerol, (R,S′)-12a

To a solution of 1-hexanoyl-2-[(*S*)-2-(4-isobutylphenyl)propanoyl]-*sn*-glycerol (*S,S′*)-**8a** (12 mg, 0.032 mmol) and DHA as a free acid (12 mg, 0.035 mmol) in CH_2Cl_2 (1.5 mL) were added DMAP (4 mg, 0.029 mmol) and EDCI (7 mg, 0.035 mmol). The solution was stirred on a magnetic stirrer at room temperature for 12 h. The reaction was disconnected by passing the reaction mixture through a short column packed with silica gel by use of Et_2O/CH_2Cl_2 (1:9). The solvent was removed in vacuo on a rotary evaporator. The residue was applied to a silica gel chromatography using petroleum ether/ethyl acetate (9:1) as eluent, which afforded the product (*R,S′*)-**12a** as a yellow oil, in 81% yield (18 mg, 0.026 mmol). $[\alpha]^{20}_D$ = +6.73 (c. 1.8, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 2973 (vs), 2926 (vs), 1742 (vs). ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.18 (d, *J*=7.7 Hz, 2H, Ibu-2,6), 7.07 (d, *J*=7.7 Hz, 2H, Ibu-3,5), 5.54-5.27 (m, 12H, =CH), 5.27-5.23 (m, 1H, CH *sn*-2), 4.30 (dd, *J*=11.9, 4.3 Hz, 1H, CH_2 *sn*-1/3), 4.19-4.13 (m, 2H, CH_2 *sn*-1/3), 4.06 (dd, J=11.9, 6.3 Hz, 1H, CH_2 *sn*-1/3), 3.70 (q, *J*=7.2 Hz, 1H, C*H*CH_3), 2.90-2.78 (m, 10H, =CHC*H*$_2$CH=), 2.43 (d, *J*=7.1 Hz, 2H, C*H*$_2$CH$(CH_3)_2$), 2.40-2.27 (m 4H, CH_2CH_2COO DHA), 2.15 (m, 2H, =CHC*H*$_2$$CH_3$), 2.08 (t, *J*=7.4 Hz, 2H, CH_2COO SFA), 1.83 (nonet, *J*=6.8 Hz, 1H, C*H*$(CH_3)_2$), 1.65-1.55 (m, 2H, C*H*$_2$$CH_2COO$ SFA), 1.49 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$), 1.37-1.24 (m, 4H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 DHA), 0.90 (d, *J*=6.6 Hz, 6H, CH(C*H*$_3$)$_2$), 0.89 (t, *J*=7.2 Hz, 3H, CH_3 SFA) ppm. $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 174.0 (Ibu), 173.3 (SFA), 172.7 (DHA), 140.6, 137.3, 132.2, 129.6 (2), 129.4, 128.7, 128.4, 128.3, 128.23 (2), 128.16, 128.0, 127.9, 127.8, 127.7 (2), 127.3, 69.3, 62.4, 62.1, 45.2, 45.1, 34.0, 33.8, 32.1, 30.3, 29.8 (2), 25.8, 25.7 (2), 24.9, 22.9, 22.8 (2), 22.5, 20.7, 18.5, 14.31, 14.27 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{44}H_{64}O_6Na$ 711.4595; found, 711.4590.

3.6.8–12. Synthesis of (R,S′)-12b – (R,S′)-12f

See full experimental details in *Supplementary Materials*

3.6.13. Synthesis of 1-[4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl]-3-hexanoyl-2-[(S)-2-(6-methoxynaphthalen-2-yl)propanoyl]-sn-glycerol, (S,S′)-13a

To a solution of 3-hexanoyl-2-[(*S*)-2-(6-methoxynaphthalen-2-yl)propanoyl]-*sn*-glycerol (*R,S′*)-**9a** (35 mg, 0.087 mmol) and DHA as a free acid (31 mg, 0.093 mmol) in CH_2Cl_2 (4 mL) were added DMAP (11 mg, 0.094 mmol) and EDCI (24 mg, 0.127 mmol). The solution was stirred on a magnetic stirrer at room temperature for 12 h. The reaction was disconnected by passing the reaction mixture through a short column packed with silica gel by use of Et_2O/CH_2Cl_2 (1:9). The solvent was removed in vacuo on a rotary evaporator. The residue was applied to a silica gel chromatography using petroleum ether/ethyl acetate (7:3) as eluent, which afforded the product (*S,S′*)-**13a** as a yellow oil, in 84% yield (52 mg, 0.073 mmol). $[\alpha]^{20}_D$ = +6.81 (c. 5.2, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3013 (vs), 2961 (vs), 2934 (vs), 2873 (vs), 1743 (vs), 1607 (vs). ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.72-7.62 (m, 3H, Nap-1,4,8), 7.38 (dd, *J*=8.5, 1.9 Hz, 1H, Nap-3), 7.13 (dd, *J*=8.9, 2.5 Hz, 1H, Nap-7), 7.09 (d, *J*=2.5 Hz, 1H, Nap-5), 5.43-5.23 (m, 12H, =CH), 5.21-5.14 (m, 1H, CH *sn*-2), 4.30 (dd, *J*=11.9, 4.2 Hz, 1H, CH_2 *sn*-1/3), 4.18 (dd, *J*=11.9, 4.3 Hz, 1H, CH_2 *sn*-1/3), 4.14 (dd, *J*=11.9, 6.1 Hz, 1H, CH_2 *sn*-1/3), 4.07 (dd, J=11.9, 6.5 Hz, 1H, CH_2 *sn*-1/3), 3.90 (s, 3H, OCH_3), 3.86 (q, *J*=7.5 Hz, 1H, C*H*CH_3), 2.88-2.74 (m, 10H, =CHC*H*$_2$CH=), 2.27-2.21 (m, 2H, CH_2COO DHA), 2.20-2.13 (m, 2H, CH_2COO DHA), 2.12-1.99 (m, 4H, CH_2COO SFA and =CHC*H*$_2$$CH_3$), 1.61-1.52 (m, 5H, C*H*$_2$$CH_2COO$ SFA and CHC*H*$_3$), 1.35-1.20 (m, 4H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 DHA), 0.89 (t, *J*=7.0 Hz, 3H, CH_3 SFA) ppm. $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 173.9 (Nap), 173.4 (SFA), 172.5 (DHA), 157.8, 135.3, 133.9, 132.2, 129.4 (2), 129.0, 128.7, 128.6, 128.41, 128.38, 128.3, 128.21, 128.16, 128.0, 127.8, 127.23, 127.15, 126.2, 126.1, 119.2, 105.7, 69.5, 62.18, 62.15, 55.4, 45.5, 34.1, 33.7, 31.4, 25.8 (2), 25.7, 25.6 (2), 24.6, 22.5, 22.4, 20.7, 18.4, 14.1, 14.0 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{45}H_{60}O_7Na$ 735.4231; found, 735.4227.

3.6.14–18. Synthesis of (S,S′)-13b – (S,S′)-13f

See full experimental details in *Supplementary Materials*

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3.6.19. Synthesis of 3-[4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoyl]-1-hexanoyl-2-[(S)-2-(6-methoxynaphthalen-2-yl)propanoyl]-sn-glycerol, (R,S′)-13a

To a solution of 1-hexanoyl-2-[(*S*)-2-(6-methoxynaphthalen-2-yl)propanoyl]-*sn*-glycerol (*S,S′*)-**9a** (12 mg, 0.030 mmol) and DHA as a free acid (11 mg, 0.033 mmol) in CH_2Cl_2 (1.3 mL) were added DMAP (4 mg, 0.033 mmol) and EDCI (8 mg, 0.044 mmol). The solution was stirred on a magnetic stirrer at room temperature for 12 h. The reaction was disconnected by passing the reaction mixture through a short column packed with silica gel by use of Et_2O/CH_2Cl_2 (1:9). The solvent was removed in vacuo on a rotary evaporator. The residue was applied to a silica gel chromatography using petroleum ether/ethyl acetate (8.5:1.5) as eluent, which afforded the product (*R,S′*)-**13a** as a yellow oil, in 74% yield (22 mg, 0.022 mmol). $[\alpha]^{20}_D$ = +8.80 (c. 0.6, CH_2Cl_2). IR (NaCl, ν_{max} / cm^{-1}): 3013 (vs), 2960 (vs), 2932 (vs), 1732 (vs), 1634 (s), 1607 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.72-7.62 (m, 3H, Nap-1,4,8), 7.38 (dd, *J*=8.5, 1.9 Hz, 1H, Nap-3), 7.13 (dd, *J*=8.9, 2.5 Hz, 1H, Nap-7), 7.10 (d, *J*=2.5 Hz, 1H, Nap-5), 5.46-5.26 (m, 12H, =CH), 5.31-5.21 (m, 1H, CH *sn*-2), 4.30 (dd, *J*=11.9, 4.2 Hz, 1H, CH_2 *sn*-1/3), 4.21-4.10 (m, 2H, CH_2 *sn*-1/3), 4.06 (dd, J=11.9, 6.4 Hz, 1H, CH_2 *sn*-1/3), 3.91 (s, 3H, OCH_3), 3.70 (q, *J*=7.2 Hz, 1H, C*H*CH_3), 2.89-2.77 (m, 10H, =CHC*H*$_2$CH=), 2.46-2.28 (m, 4H, CH_2COO DHA), 2.14-2.01 (m, 2H, CH_2COO SFA), 2.01-1.88 (m, 2H, =CHC*H*$_2$$CH_3$), 1.58 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$), 1.37 (quint, *J*=7.5 Hz, 2H, C*H*$_2$$CH_2$COO SFA), 1.30-1.20 (m, 4H, CH_2), 0.97 (t, *J*=7.5 Hz, 3H, CH_3 DHA), 0.84 (t, *J*=7.0 Hz, 3H, CH_3 SFA) ppm. ^{13}C{H} NMR (101 MHz, $CDCl_3$) δ_C: 173.9 (Nap), 173.3 (SFA), 172.7 (DHA), 157.9, 135.4, 133.9, 132.2, 129.6, 129.4, 129.1, 128.7, 128.5, 128.44, 128.41, 128.3, 128.23, 128.16, 128.0, 127.8, 127.24, 127.17, 126.3, 126.1, 119.2, 105.7, 69.5, 62.4, 62.0, 55.4, 45.5, 34.0, 33.8, 31.3, 25.8 (2), 25.7, 25.7 (2), 24.4, 22.7, 22.4, 20.7, 18.5, 14.4, 14.0 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{45}H_{60}O_7Na$ 735.4231; found, 735.4231.

3.6.20–24. Synthesis of (R,S′)-13b – (R,S′)-13f

See full experimental details in *Supplementary Materials*

4. Conclusions

The synthesis of a focused library of enantiostructured TAGs comprised of a SFA, a bioactive PUFA, and a potent drug has been successfully executed by a six-step chemo-enzymatic approach, starting from enantiopure (*R*)- and (*S*)-solketals as chiral precursors. All combinations of even number saturated fatty acids ranging from C6:0 to C16:0, EPA and DHA, and (S)-ibuprofen and (S)-naproxen, were prepared with the SFA and the PUFA accommodating each of the terminal positions and the drug entity located at the mid position of the glycerol backbone of the molecule. The total of 48 such enantiostructured TAG molecular species were prepared. They may be divided into two series of diastereomeric analogs, 24 each, of the (*R,S′*) and the (S,*S′*)-stereochemistry by interconversion of the SFA and the PUFA at the end position.

The immobilized lipase, CAL-B, played a crucial role in the regiocontrol of the synthesis. All products and intermediates were obtained in a high chemical, regio- and stereoisomeric purity, and in very high to excellent yields in almost all cases. All products (48) and intermediates (60) were isolated, purified and fully characterized.

It is anticipated that the resulting structured TAGs may possibly find use as an interesting and novel type of prodrugs. An acylglycerol based prodrug possessing a potent NSAID along with a bioactive n-3 PUFA that also is considered as a prodrug offering pro-inflammatory properties, but also a drug, may offer some interesting properties, perhaps by some synergistic effects. The idea of introducing a saturated fatty acyl group to the molecule may indeed offer some interesting properties in terms of the timing of the release of the different acyl groups including the drug and hence some site-specificity. An alternative type of related prodrugs, namely those possessing the potent drug in one of the terminal positions, with the SFA in the remaining one, and the PUFA this time in the mid position, is under way to be reported. That second category enantiostructured TAG prodrugs may offer some complementary possibilities in modifying the time of release and a subsequent site of release of the drug and the acyl counterparts.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Figure S1: Comparison of the glyceryl proton region of the ^{1}H NMR spectra for the 1-*O*-benzyl-*sn*-glycerol starting material and the benzyl-protected monoacylglycerol (*R*)-**5a** (p*S1*); Figure S2: Comparison of the glyceryl proton region of the ^{1}H NMR spectra for (*R*)-**5a** and (*R,S'*)-**6a** possessing (*S*)-ibuprofen(p*S2*); Figure S3: Comparison of the glyceryl proton region of the ^{1}H NMR spectra for (*R,S'*)-**6a** and its deprotected product (*R,S'*)-**8a** (p*S3*); Figure S4: Comparison of the glyceryl proton region of the ^{1}H NMR spectra for (*R,S'*)-**9c** and its product (*R,S'*)-**11c** acylated with EPA (p*S4*); Experimental Information: p*S5-S45*; NMR spectra (^{1}H and ^{13}C NMR, ^{1}H-^{1}H COSY and ^{13}C-^{1}H HSQC shown for all compounds belonging to **5a – 13a**): p*S46-S81*.

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