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Research Article

An efficient catalytic three-step synthesis of enantiopure triacylglycerols

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With the developments in high performance chromatography and mass spectrometry, the analysis of complex mixtures of closely related triacylglycerols has come within reach. Currently, however, the availability of chemically pure triacylglycerols is limited, mainly due to the lack of efficient synthetic methods that allow their synthesis. Here, we report an efficient and operationally simple three-step synthesis of enantiopure triacylglycerols with yields ranging from 79 to 92%, that tolerates a broad range of saturated and unsaturated fatty acids. Furthermore, we developed an automated protocol, which might greatly facilitate the synthesis of triacylglycerol libraries.

Practical applications: The analysis of the composition of milk fat and as analytical standards in lipidomics.

Keywords: Catalysis / Epoxide ringopening / Library synthesis / Milk fat / Triacylglycerols

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1 Introduction

Glycerol is desymmetrized when mono-esterified on one of its primary alcohols, or when a di- or triacylglycerol (di- or triacylglyceride) bears two different acyl chains on the *sn*-1 and the *sn*-3 position. This chirality is frequently overlooked in research connected to di- and triacylglycerols, although it was noted already in 1939 [1]. Furthermore, enantiopure triacylglycerols show only negligible optical rotation [2], and are therefore called *cryptochiral* [3]. In fact, the stereochemistry of triacylglycerols is infrequently considered, although an elaborated review has appeared on the effects of stereochemistry on the physicochemical properties of

fats [4]. Racemic versus enantiopure triacylglycerols, for example, show different crystallization behavior – and, translated to daily life, this means that butter, margarine, and chocolate leave different sensations depending on the stereochemical composition of their triacylglycerols [5].

An unrelated area that recently has been confronted with complex mixtures of triacylglycerols is chemical ecology [6]. The discovery, among others, that sex-specific triacylglycerols are widely conserved in *Drosophila* and mediate mating behavior has elicited research on the composition of these, often complex, mixtures [7].

Over the past 70 years, a considerable effort has been invested into the analysis of mixtures of triacylglycerols as occurring in fats and oils, in particular also in milk fat [8]. These efforts invariably involved chromatographic separation of the triacylglycerols and their subsequent identification. Milk fat is typically composed of triacylglycerols containing dozens of different fatty acids. Of these fatty acids, 13 come at a level of >1% and 9 are present in >2%. This results in an enormous number of different triacylglycerols, e.g., n^3 in which n = the number of fatty acids. Of this number, n^2 triacylglycerols are achiral, the other are chiral. Notably, not all isomers necessarily occur in milk fat. Because the fatty acids are similar in structure, that is, only differ in their chain length

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Abbreviations: CAL, *Candida antarctica* lipase; DCC, dicyclohexylcarbodiimide; DIPEA, diisopropylethyl amine; DMAP, Dimethylamino pyridine; EDC, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; MS-APCI, mass spectrometry-atmospheric pressure chemical ionisation; TBDMSO, tert-butyldimethylsilyloxy

and possible unsaturation, most triacylglycerols are extremely difficult to separate. This severely complicates the analysis.

Complementary to improving resolution in the applied chromatographic techniques [9], one could approach this Gordian knot from a different angle and prepare a library of triacylglycerols in a regio- and stereoselective manner. The availability of such a library provides detailed and precise information on retention times (on different achiral and chiral columns) and for each triacylglycerol a hopefully unique mass spectrum, except for enantiomers. As sighed recently by K. Mori, however, “synthesis of enantiomerically pure triglycerides is not at all a trivial work even at present” [10]. In order to make the preparation of such a library, that should ideally contain several hundreds of triacylglycerols, a reachable target, we decided to develop an efficient and stereochemically unambiguous synthesis of triacylglycerols. The account of this starts with an overview of several procedures known in this area, followed by the description of our approach.

2 Reported syntheses of triacylglycerols

Chemical modification of triacylglycerols to alter the properties of edible fats was first described in the 1920s and subsequently established as an industrial process in the 1940s. To improve the spreadability and baking properties, lard (pig fat) was treated with sodium methoxide. On the molecular level, this results in a random intra- and intermolecular redistribution of the fatty acid residues on glycerol. Today, this process is known as *fat randomization* [11] and it plays an important role in the food industry. Another approach to change triacylglycerol composition is achieved using lipases. As an example, tripalmitoyl glycerol (1), upon treatment with oleic acid (2) undergoes enzymatic interesterification to 1,3-oleoyl-2-palmitoyl-*sn*-glycerol (3) (Scheme 1) [12].

Although powerful tools in modifying triacylglycerols, enzymes give enantioenriched products only in a very limited number of cases [13]. Another limitation of the enzymatic synthesis of triacylglycerols is that different fatty acid chain lengths often require different lipases.

Chemical synthesis can provide enantiopure triglycerides. Kristinsson and Haraldsson [14, 15] reported a 6-step approach (Scheme 2). (*S*)-Solketal 4 (from mannitol) was first benzylated and then hydrolyzed in acidic aqueous ethanol affording 5 in 87% yield. An *sn*-3 selective acylation of 5 by immobilized *Candida antarctica* lipase (CAL) and vinyl stearate, followed by hydrogenolysis with Pd/C gave monoacylglycerol 6 in 85% yield over 2 steps. A second esterification with the same enzyme and vinyl capriate afforded 7 in 85% yield. Finally, esterification of 7 with eicosapentaenoic acid led to triacylglycerol 8 in 91% yield. A careful choice of protecting groups and the use of a selective lipase circumvented acyl migration.

Stamatov and Stawinski [16] presented a different strategy. Heating glycidyl ether 9 (Scheme 3I) with an excess of trifluoroacetic anhydride and Bu₄NI afforded the iodohydrin, which after esterification in the same pot yielded 11 in 90%. Substitution of iodide 10 by acetate yielded 11 in 92% yield. The TBDMSO- group in 11 was directly converted into the ester, yielding triacylglycerol 12 in 90% yield. In case the authors applied 13 as starting material (Scheme 3II), the silyl substitution could be omitted, thus affording 14 in only three steps. In this approach, the application of iodohydrines and direct substitution of TBDMSO- group for an ester circumvents acyl migration.

Despite both approaches avoid acyl migration and yield the triacylglycerols in high yields, some characteristics make them less suitable for library synthesis. The shorter approach presented by Stamatov and Stawinski uses significant excess of the reagents (3–5 equiv), not economical in case of expensive (i.e., polyunsaturated) fatty acids. The approach presented by Kristinsson and Haraldsson uses nearly stoichiometric (1.1–1.25 equiv) conditions, but requires two protecting groups and six steps.

Recently, we reported [17] that 1 mol% of (*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) catalyses the ring opening of glycidyl ethers with a stoichiometric amount of a fatty acid under basic conditions with remarkable regioselectivity. If glycidyl esters would exhibit the same reactivity, this would afford triacylglycerols by the same procedure in three steps

Scheme 1. Lipase-mediated interesterification of a triacylglycerol.

Scheme 2. Synthesis of enantiopure triacylglycerols according to Kristinsson and Haraldsson.

Scheme 3. (I) Synthesis of triacylglycerols according to Stamatov and Stawinski; (II) in case glycidyl esters are applied, the synthesis is one step shorter.

Table 1. Prepared glycidyl esters

Entry-label	Fatty acid	Yield (%)
1–16a	Butyric acid	86
2–16b	Caproic acid	92
3–16c	Capric acid	86
4–16d	Myristic acid	82
5–16e	Palmitic acid	92
6–16f	Stearic acid	88
7–16g	Oleic acid	81

and without utilization of a large excess of reagents or protecting groups.

3 Results and discussion

3.1 Co[(*R,R*)-salen] catalyzed ring opening of glycidyl esters

Glycidyl esters **16a–g** were prepared under Steglich conditions (Table 1). In the presence of DCC and catalytic amounts of DMAP, (*S*)-glycidol **15** was conveniently esterified with a small excess of fatty acid (1.2 equiv). Homologous glycidyl esters **16a–f** (Table 1, entries 1–6) were obtained in high yields (82–92%). In addition to the saturated derivatives, unsaturated glycidyl oleate **16g** was prepared in 81% yield (Table 1, entry 7).

In an initial experiment (Scheme 4), neat glycidyl myristate **16d** was treated with a stoichiometric amount of stearic acid in the presence of **17** (1 mol%) and Hünigs base (diisopropylethyl amine, DIPEA). These conditions resulted in quantitative formation of the 1,3-diacylglycerol. Progress of this reaction (Scheme 4) was monitored by ^1H NMR by following the attenuation of the signals corresponding to the protons of the primary epoxide carbon ($\delta = 2.63$ and 2.83 ppm). As the reaction afforded ring-opened product **18** exclusively, after dilution with heptane the crude residue was esterified in the same flask with stearic acid, DCC and DMAP.

After full conversion of **18**, the reaction mixture was transferred directly onto a silica column and chromatographed to afford chemically pure triacylglycerol **19** in 83% yield. The scope of this two-step-one-pot procedure was further investigated with various acids for ring opening and final esterification (Table 2).

The synthesized triacylglycerols were obtained in yields ranging from 79 to 92% over two steps in high purity. The obtained yields are similar or higher than those described by Kristinsson and Haraldsson, and by Stamatov and Stawinski. Furthermore, the fatty acids are used in stoichiometric or nearly stoichiometric amounts. Compared to the enzymatic synthesis of triacylglycerols, the developed reaction conditions tolerate different chain lengths in all three positions (Table 2). A pair of isomeric triacylglycerols (entry 8 vs. 9) was prepared in very similar yields. The unsaturated oleic acid is tolerated on all 3 (*sn*-1, *sn*-2, *sn*-3) positions (entries 1, 3, 4, 6, 7, 10, 13, 14). The double bonds of the polyunsaturated linoleic acid (18:2 *cis,cis*-9,12, entry 5) remained intact. And finally, these conditions allow the synthesis of a pair of enantiomers (entry 2 and 11) both from (*S*)-glycidol **16**, if the fatty acids are introduced in reversed order.

Scheme 4. Triacylglycerols, prepared according to the described method. Reagents and conditions: a) stearic acid (1.0 equiv), Hünigs base (1 equiv), **17** (1 mol%), neat, 20 h, RT; b) stearic acid (1.2 equiv), DCC (1.1 equiv), DMAP (5 mol%) heptane, 20 h, RT.

Table 2. Synthetized triacylglycerols (for the synthesis by automated protocol see below)

Entry-label	Starting glycidyl ester (<i>sn</i> -3 position)	Fatty acid used in ring opening (<i>sn</i> -1 position)	Fatty acid in final esterification (<i>sn</i> -2 position)	Yield manual protocol (%)	Yield automated protocol (%)
1–19a	glycidyl butyrate 16a	myristic acid	oleic acid	86	62
2–19b	glycidyl butyrate 16a	stearic acid	palmitic acid	79	67
3–19c	glycidyl butyrate 16a	oleic acid	stearic acid	86	56
4–19d	glycidyl butyrate 16a	oleic acid	oleic acid	83	58
5–19e	glycidyl butyrate 16a	linoleic acid	myristic acid	85	–
6–19f	glycidyl caproate 16b	oleic acid	palmitic acid	82	–
7–19g	glycidyl caprate 16c	oleic acid	palmitic acid	88	–
8–19h	glycidyl palmitate 16e	myristic acid	stearic acid	80	33
9–19i	glycidyl palmitate 16e	stearic acid	myristic acid	79	48
10–19j	glycidyl palmitate 16e	oleic acid	oleic acid	92	–
11–19k	glycidyl stearate 16f	butyric acid	palmitic acid	82	70
12–19l	glycidyl stearate 16f	myristic acid	palmitic acid	80	60
13–19m	glycidyl stearate 16f	oleic acid	oleic acid	80	62
14–19n	glycidyl oleate 16g	palmitic acid	stearic acid	80	74

3.2 Towards the automated synthesis of triacylglycerols

The 15 triacylglycerols prepared (Table 2) correspond to only 2% of the estimated number of triacylglycerols in milk fat [18]. The time required for the synthesis of the remaining 98% may well be reduced by the development of an automated protocol. Commercially available liquid-handling platforms can perform up to 96 reactions in the same batch, although the options for work-up and purification are limited. Given that the cobalt catalyst is soluble in a variety of organic solvents, its removal is a challenge. Thanks to the wide application of the Co(salen) catalysts, a lot of groups developed protocols for its facile removal from the reaction mixture and recycling. One of the options, reported by Annis and Jacobsen, is immobilization of the catalyst on polystyrene beads [19]. The catalyst modified in this way can be easily removed by filtration. The authors also studied the influence of immobilization on the performance of the catalyst, and did not observe any detrimental effect. We decided to prepare and apply the same immobilized catalyst in the automated synthesis of a set of 10 triacylglycerols.

For optimal performance of resin-bound catalysts, the applied solvent must swell the resin. For this purpose we screened resin swelling solvents like THF, CH₂Cl₂, CH₂ClCH₂Cl, and toluene. From these solvents, CH₂Cl₂ turned out to be the best option. A reaction of (*R*)-glycidyl palmitate with butyric acid, diisopropylethyl amine and the immobilized catalyst went to full conversion in 3 days. Again, the ring-opened product formed as the only product in quantitative yield based on ¹H NMR. Subsequently, we could apply these conditions in an automated protocol. All liquid components were added automatically, followed by shaking on a shaking device, which gave full conversion in 3 days. Subsequently, the resin was filtered off and the

volatiles were evaporated. The obtained 1,3-diacylglycerols were directly used on the liquid handling machine to perform the final esterification. Pure triacylglycerols were subsequently obtained by column chromatography. The yields are summarized in Table 2. In general, the yields are acceptable but somewhat lower compared to the protocol with “free” catalyst **17**. As the variation in yield in the automated protocol is larger compared to the manual protocol, we suspect solubility differences of the various components to play a major role. In particular the volatility of the solvent CH₂Cl₂ is challenging to cope with in a liquid handling system.

As the preparation of the immobilized catalyst is laborious, the recyclability of the catalyst was studied as well. In an experiment with glycidyl palmitate, oleic acid, and diisopropylethyl amine, the immobilized catalyst was filtered off after full conversion and recycled in a next experiment. In total, 3 cycles were carried out, and in each the reaction got to completion within 72 h. After each reaction, the Co loading of the resin was determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES). After a drop between the first and second cycle, from 1.36 to 0.99%, the cobalt loading kept constant.

3.3 Identification of triacylglycerols by mass spectrometry

Chemically pure triacylglycerols are frequently used as analytical standards [20], therefore their MS data are valuable tools that might facilitate their identification. For this reason, we acquired the MS spectra using a standard MS-APCI technique. The acquired data are summarized in the Table 3. In general, the ionization pattern is in agreement with the findings of Turk [21], who reported that the primary positions (*sn*-1 and *sn*-3) in triacylglycerols cleave

Table 3. Summary of MS–APCI data

Entry	Triacylglycerol	Relative intensity of the resulting ion		
		<i>sn</i> -1	<i>sn</i> -2	<i>sn</i> -3
1	LiMB (19e)	28	25	100
2	MOB (19a)	30	20	100
3	MSP (19h)	100	50	82
4	OOb (19d)		55 ^a	100
5	OOP (19j)		100 ^a	40
6	OSB (19c)	37	26	100
7	PSO (19n)	47	26	100
8	SMP (19i)	42	60	53
9	SPB (19b)	16	17	100
10	BPS (19k)	100	68	12

^aCleavage at the *sn*-1 and *sn*-2 position results in ions of same mass.

preferentially. From our data, it is notable that in the case of fully saturated triacylglycerols the preference for cleavage at the *sn*-1 or *sn*-3 position corresponds to the molecular weight of the cleaved fatty acid. In cases, where the triacylglycerols bear butyric acid at the *sn*-1 or *sn*-3 position, this is cleaved preferentially and the resulting ion corresponds to the base peak. This is demonstrated in entry 9 and 10, where the triacylglycerols are enantiomers and in both cases, the base peak corresponds to the cleavage of butyric acid. In case the triacylglycerol bears the unsaturated oleic acid, this was cleaved preferentially over saturated palmitic acid (entry 7).

4 Conclusions

We developed an efficient protocol for the synthesis of triacylglycerols. The straightforward two-step-one-pot procedure, starting from glycidyl esters, affords the triacylglycerols in 79–92% yields and tolerates unsaturations. Furthermore, we modified the protocol in such a way that it can be operated by liquid handling platforms to prepare libraries of triacylglycerols. The use of a removable and recyclable catalyst simplifies this automated synthesis.

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