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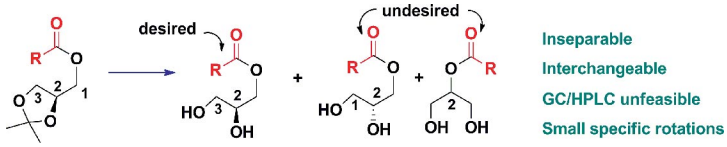
Glycerolipids



Because of facile acyl migrations, the synthesis of enantiopure 1(or 3)-acyl-*sn*-glycerols is much more difficult than their seemingly very simple structures may imply. Even assessment of their optical purity is a difficult task because of the lack of a feasible means of analysis. Now, new findings have changed everything.

C.-Y. Chen, W.-B. Han, H.-J. Chen, Y. Wu,* P. Gao* 1–9

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Optically Active Monoacylglycerols: Synthesis and Assessment of Purity

Chao-Yuan Chen,[a,b] Wei-Bo Han,[a] Hui-Jun Chen,[a] Yikang Wu,*[a] and Po Gao*[b]

Keywords: Lipids / Rearrangement / Protecting groups / Glycerolipids / Esters / Analytical methods

Despite their simple structures, synthesis of 1(or 3)-acyl-*sn*-glycerols remains a challenge that cannot be ignored because of facile acyl migrations, which not only complicate the synthesis but also make direct GC or HPLC analysis unfeasible. Assessment of the optical purity of monoacylglycerols has, to date, relied almost exclusively on specific rotation data, which are small in value and thus insensitive to impurities. Now, a simple means to "magnify" the small specific rotations has been found, along with practical methods for the measurement of both 1,2- and 1,3-acyl migrations, which offer a convenient and straightforward alternative to Mori's NMR analysis of Mosher esters. With the aid of these methods, a range of conditions for deacetonide removal were examined en route to the synthesis of two natural monoacylglycerols. Refined hydrolysis conditions, along with useful knowledge about the solubility and reactivity of substrates with an ultra long alkyl chain are also presented.

Introduction

Naturally occurring monoacylglycerols, an important family of lipids, normally contain a long alkyl group in the acyl subunit, with or without additional functionalities on the chain and/or branching at the chain terminus (Figure 1). Although it is not clear whether all such natural monoacylglycerols are optically active, at least in those cases where optical rotation[1] was measured, the isolated products were indeed optically active. 1(or 3)-Acyl-*sn*-glycerols are also essential precursors for asymmetric di- or triacylglycerols. It is thus understandable that there has been an increasing interest over the years in gaining access to 1(or 3)-acyl-*sn*-glycerols of a predefined absolute configuration.[2]

We became interested in 1(or 3)-acyl-*sn*-glycerols because of a recently identified[3a] natural product (**3**, hyloglycerol; Figure 1) isolated from *Hylodendron gabunensis* Taub. (Fabaceae). This molecule carries the longest (to the best of our knowledge) alkyl chain among all known natural monoacylglycerols, and thus represents an extreme example for this family of lipids.

The hentriacontanoyl chain in **3** is much longer than the chain in any synthetically confirmed 1(or 3)-acyl-*sn*-glycerol (for which the longest is stearoyl). Therefore, it does not seem wise to assign **3**'s configuration by simple comparison of the optical rotation with a known analogue − the ultra long alkyl chain in **3** might behave differently from the shorter ones due to unpredictable chain coiling, folding, and/or aggregation. An enantioselective synthesis thus ap-

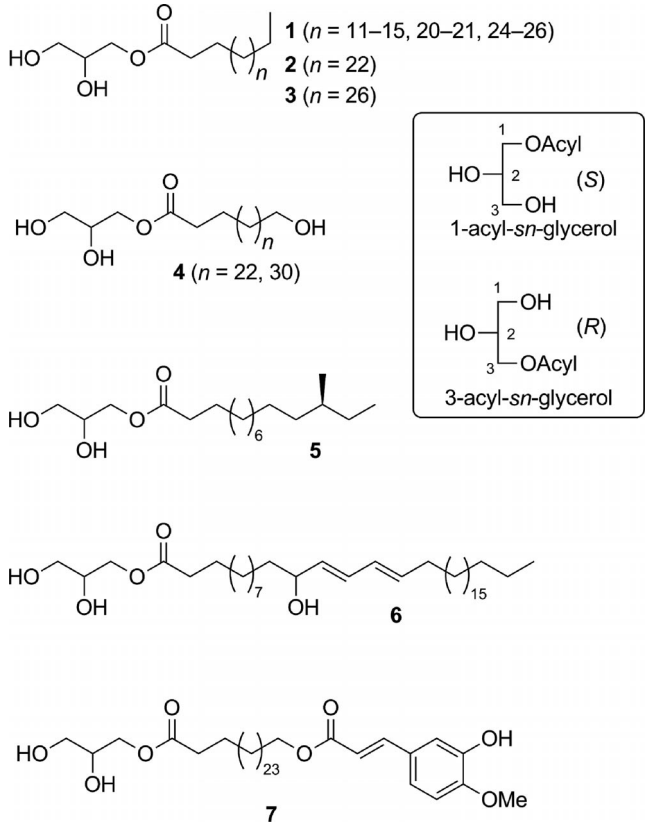

Figure 1. Examples of naturally occurring 1(or 3)-acyl-*sn*-glycerols, with the definitions for 1- and 3-acyl-*sn*-glycerols in lipid chemistry shown in the box. *sn* = stereospecific numbering.

[a] State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
345 Lingling Road, Shanghai 200032, China
E-mail: yikangwu@sioc.ac.cn
[b] School of Chemistry and Materials, Heilongjiang University, Harbin 150080, China

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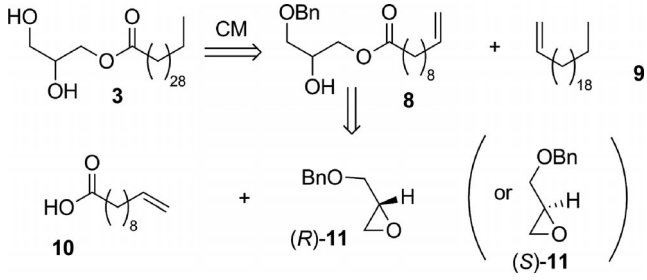
peared to be necessary; this would not only allow the unambiguous assignment of the absolute configuration of natural **3**, but also offer an optical rotation reference for other 1(or 3)-acyl-*sn*-glycerols containing fatty acyl chains of comparable lengths that has been missing so far.

As this apparently rather simple synthetic endeavor proceeded, the intrinsic difficulties [which are greatly belied by the unpretentious molecular architectures of 1(or 3)-acyl-*sn*-glycerols] encapsulated in the assembly of glycerol and acyl fragments gradually surfaced, and this prompted us to extend the original simple synthesis into a more general investigation of optically active monoacylglycerols. Much useful knowledge was thus gained, and the results are presented in this paper.

Results and Discussion

Our initial approach is outlined in Scheme 1. To minimize the potential interference from an extra long linear alkyl chain (vide infra), we planned to access **3** using a cross-metathesis (CM) reaction.



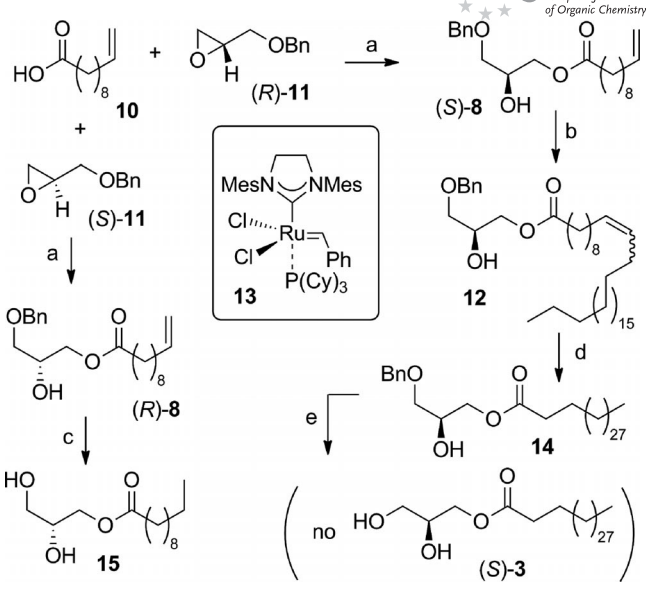
Scheme 1. A retrosynthetic analysis for **3**.

The synthesis (Scheme 2) was executed all the way to **12** without complications. However, debenzylation turned out to be entirely impossible (see Supporting Information), in sharp contrast to the situation with the stearoyl[4] counterpart or (*R*)-**8**.

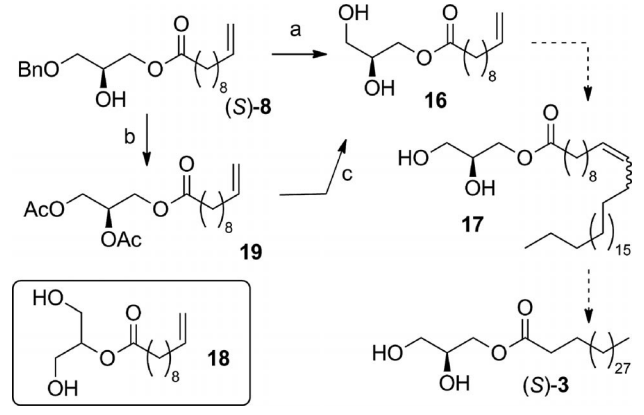
Cleaving the benzyl group with DDQ[5] before the CM reaction was possible (Scheme 3). However, the product (i.e., **16**) contained an extra doublet at δ = 3.81 ppm(arising from the -CH_2- units in the 1,2-acyl migration product according to Haraldsson[6,7]) in its ^{1}H NMR spectrum, while the alternative route[8] via diacetate **19** suffered from difficulties in the removal of the acetyl groups (see Supporting Information).

Using the cleavage of an acetonide group as the final step to access 1(or 3)-*sn*-glycerols is very common. However, acyl migration still is a major and largely unsolved problem,[2a–2c,2f,2k] although in most cases the complications were not described in detail (e.g., without mentioning the doublet at $\delta \approx 3.8$ ppm). The optical purity of the final 1(or 3)-*sn*-glycerol products has almost exclusively been assessed using their specific rotations,[9] which are normally rather small in value (around or less than, say, 5.0) and thus are not sensitive indicators for the presence of impurities.

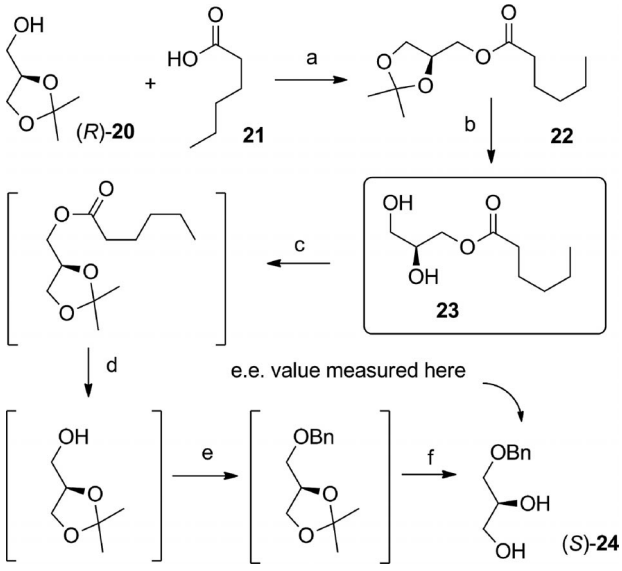
Recently, a distinct advance[2a] was made by Mori. For the first time (to the best of our knowledge) the *ee* (enantiomeric excess) values of the 1(or 3)-*sn*-glycerols were measured in addition to optical rotations to indicate their optical purities. However, the preparation of a Mosher ester was required for each sample. Analysis of the NMR spectra is also cumbersome. Therefore, a more straightforward means for measuring the *ee* values of 1(or 3)-acyl-*sn*-glycerols is still desirable. For this reason, in connection with the removal of the acetonide group from a model system (**22**, readily accessible from commercially available **20** and **21**), we first developed a four-step sequence (Scheme 4, lower half) for converting 1(or 3)-acyl-*sn*-glycerols (in this case, **23**) into the corresponding monobenzylated glycerols (here, **24**) for chiral HPLC analysis.



Scheme 2. *Reagents and conditions:* a) Et_4NBr, 100 °C, 95% for (*S*)-**8**, 94% for (*R*)-**8**; b) **13** (cat.), **9**, CH_2Cl_2, reflux, 3 h, 64%; c) H_2 (1 atm), Pd/C, EtOH, room temp., 4 h, 91%; d) H_2 (50 atm), Pd black, EtOAc, 80 °C, 48 h, 98% for **14**, see Supporting Information; e) see Supporting Information.



Scheme 3. *Reagents and conditions:* a) DDQ, 100 °C, see text; b) TMSOTf, Ac_2O, –40 °C, 82%; c) see text. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. TMSOTf = trimethylsilyl triflate.



Scheme 4. *Reagents and conditions:* a) EDCI, DMAP, CH_2Cl_2, 0 °C, 3 h, 92%; b) different conditions in the literature, see text; for measuring the *ee* value of (*S*)-**23**: c) acetone, *p*TsOH, room temp., 6 h; d) LiOH, THF/H_2O (10:1, v/v), room temp., 12 h; e) BnBr, NaH, DMF, room temp., 2 h; f) AcOH/H_2O (4:1, v/v), 50 °C, 2 h, 91% overall from **23** (4 steps). EDCI = [*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide]; DMAP = 4-(dimethylamino)pyridine; *p*TsOH = *p*-toluenesulfonic acid; DMF = *N*,*N*′-dimethylformamide.

In the event, the diol that resulted from hydrolysis of the acetonide was first reprotected as an acetonide. The acyl group was then hydrolyzed, and the primary hydroxy group was benzylated. Finally, the acetonide was hydrolyzed again to give stable diol **24** (91% overall yield from **23**). Because of the ease of its detection by UV light and its suitable polarity, diol **24** can be readily analyzed by chiral HPLC. The *ee* value for **23** (or its counterparts in different cases) can thus be indirectly estimated from the *ee* value of the corresponding **24**.

Having established the means for the rapid detection of 1,2-acyl migration and a feasible and reliable method for measuring the *ee* values of 1(or 3)-acyl-*sn*-glycerols, we went on to examine several sets of promising mild conditions for cleaving acetonides, including CF_3CO_2H (50% aq.)/CH_2Cl_2,[10] H_3BO_3/$HO(CH_2)_2OMe$/reflux,[2c,2f,2k] $Zn(NO_3)_2$/MeCN,[11] and HOAc/H_2O (4:1).[2a] The results are summarized in Table 1.

The results with CF_3CO_2H (aq.)/CH_2Cl_2, which has been widely used in total synthesis with general satisfaction, were discouraging in our system. Before all of the starting material (i.e., **22**) was hydrolyzed, the isolated product (i.e., **23**) already contained significant amounts of the 2-acyl isomer (which is very likely to be "invisible" in the *ee* measuring methods of Mosher ester analysis or chiral HPLC analysis) as revealed by the doublet at δ = 3.81 ppm in the ^{1}H NMR spectrum. Also, chiral HPLC analysis gave an *ee* value of 53% (Table 1, entry 1).

Boric acid in $HO(CH_2)_2OMe$[2c,2f,2k] (Table 1, entry 2) appears to be very mild. However, after 2 h at reflux, when only part of the starting material (i.e., **22**) was consumed, significant amounts of the 2-acyl isomer were already detected in the isolated product (i.e., **23**), with the *ee* value being 46%.

Mori reported[2a] that the $Zn(NO_3)_2$/MeCN conditions gave 1-palmitoyl-*sn*-glycerol with 90% *ee* (measured by the Mosher method). However, in our case with the 1-hexanoyl group (which is much smaller in size than the palmitoyl group), these conditions led to the formation of significant amounts of the 2-acyl-isomer [inseparable from the 1(or 3)-acyl-*sn*-glycerols], as shown by the doublet at δ = 3.81 ppm in the ^{1}H NMR spectrum. The *ee* value for the isolated **23** (measured from the corresponding **24**) was only 14% (Table 1, entry 3).

In 4:1 AcOH/H_2O, excessive acyl migration occurred at 130 °C within 30 min (Table 1, entry 4). At 50 °C, the best temperature found by Mori, a minimum formation of the 2-acyl isomer was observed in our case with the 1-hexanoyl group, with the *ee* value for the isolated **23** being 98% (Table 1, entry 5) when the hydrolysis was run for only 30 min. When the reaction time was prolonged to 2 h as in the literature,[2a] acyl migration occurred to a more significant extent (77% *ee*, Table 1, entry 6); the longer the reaction time, the poorer the optical purity that was observed (Table 1, entries 7–9).

It should be noted that acyl migration also occurred readily under basic conditions. For instance, when **23** (15 mg, obtained under the optimal conditions for aceton-

Table 1. Hydrolysis of the acetonide in **22** under different conditions.

Entry	Conditions	Area for δ = 3.81 ppm[a]	*ee* for **23** [%][b]
1	CF_3CO_2H/CH_2Cl_2/r.t./1 h	0.37	53
2	H_3BO_3/2-ME[c]/reflux/2 h	0.24	46
3	$Zn(NO_3)_2$/MeCN/50 °C/1 h[d]	0.34	14
4	AcOH/H_2O/130 °C/30 min[e]	0.41	15
5	AcOH/H_2O/50 °C/30 min[e]	0.06	98
6	AcOH/H_2O/50 °C/2 h[e]	0.13	77
7	AcOH/H_2O/50 °C/4 h[e]	0.20	61
8	AcOH/H_2O/50 °C/8 h[e]	0.26	37
9	AcOH/H_2O/50 °C/16 h[e]	0.40	20

[a] The integral for the doublet at δ = 3.81 ppm (the methylene groups in the 2-acyl isomer) in the ^{1}H NMR spectrum measured on the crude product mixture, with the multiplet at δ = 3.92 ppm (the methine group in **23**) set to unity for comparison. [b] Measured by chiral HPLC analysis of the **24** derived from **23**. [c] 2-ME = 2-methoxyethanol. [d] $Zn(NO_3)_2 \cdot 6H_2O$ was used. [e] 4:1 (v/v) AcOH/H_2O was used, with 50 °C being the bath temperature.

ide removal) was treated with Et_3N (0.4 mL) and DMAP (2 mg) in CH_2Cl_2 (0.5 mL) at ambient temperature, the relative integral (initially 0.06) for the doublet at δ = 3.81 ppm in the ^{1}H NMR spectrum was measured to be 0.11, 0.19, 0.21, 0.29, and 0.46 at 15 min, 30 min, 1 h, 2 h, and 4 h, respectively.

Efforts were also made to find a better solvent, in which the usually rather small optical rotations for 1(or 3)-acyl-*sn*-glycerols may be substantially "magnified". A few solvents that had not been tested for 1(or 3)-acyl-*sn*-glycerols by previous investigators, including 2,6-lutidine, DMF, and DMSO (dimethyl sulfoxide), were then examined for **23**. The results are summarized in Table 2.

Table 2. Specific rotation for **23** measured in different solvents.

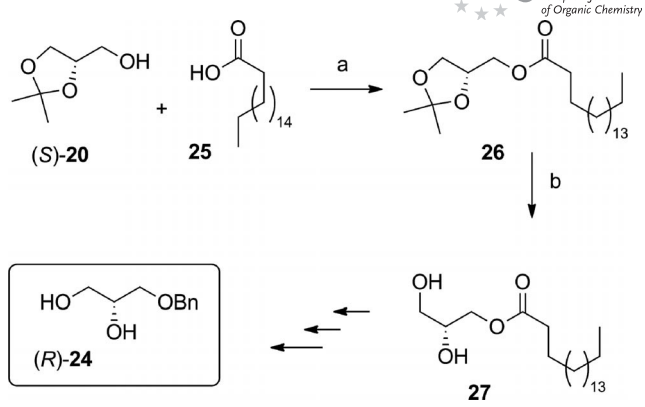
Entry	Solvent (c = 1.0)	$[\alpha]_D^{28}$
1	$CHCl_3$	–1.3
2	CH_2Cl_2	+0.2
3	toluene	+0.8
4	acetone	+5.5
5	2,6-lutidine	+10.7
6	DMF	+10.7
7	DMSO	+11.9

Under otherwise identical conditions, the smallest values were found with $CHCl_3$, CH_2Cl_2, and toluene (Table 2, entries 1–3). In a more polar solvent (acetone), the rotation value was substantially larger (Table 2, entry 4). In 2,6-lutidine or DMF, the rotation for **23** almost doubled. The largest rotation (+11.9) was observed in DMSO. As larger specific rotations lead to smaller errors and thus higher precision in data comparison, DMSO seems to be the solvent of choice for measuring specific rotations for 1(or 3)-acyl-*sn*-glycerols.

The knowledge gained from studying model compound **23** was then examined carefully with **27** (3-stearoyl-*sn*-glycerol), which could be generally applicable in the synthesis of biologically relevant 1(or 3)-acyl-*sn*-glycerols. As shown in Scheme 5, condensation of (*S*)-**20** (to make full use of the reagent in hand) and stearic acid gave **26** in 96% yield. The hydrolysis of the acetonide with AcOH/H_2O to deliver **27** was then monitored closely. Aliquot samples were taken out of the reaction flask at selected time points, and the ^{1}H NMR spectra of the crude mixtures were recorded to see the intensity of the doublet at δ = 3.81 ppm. The optical rotations for the purified **27** were then measured in DMSO, and the *ee* values were determined by chiral HPLC analysis of the corresponding (*R*)-**24** prepared by the aforementioned four-step sequence.

The results are shown in Table 3 and Figure 2. After exposure of **26** to AcOH/H_2O at 50 °C for 15 min, more than 80% of the starting acetonide had already reacted. And by 30 min, reaction was complete. Up to 1 h, no 1,2-acyl migration product could be detected (i.e., no doublet at all at δ = 3.84 ppm), and no decrease in the optical rotation or the *ee* value occurred (Table 3, entries 1 and 2).

However, after a further 30 min, acyl migrations became detectable (Table 3, entry 3, see also Figure 1). By 2 h, the changes were substantial (Table 3, entry 4). Further exten-



Scheme 5. *Reagents and conditions:* a) EDCI, DMAP, CH_2Cl_2, 0 °C, 5 h, 96%; b) AcOH/H_2O (4:1, v/v), 50 °C, 30 min, 96%.

Table 3. The results of hydrolysis of the acetonide in **26**.

Entry	Time	Area for δ = 3.84 ppm[a]	$[\alpha]_D^{25}$[b]	*ee* for **27** [%][c]
1	30 min	0	–10.4	>99
2	1 h	0	–10.1	>99
3	1.5 h	0	–9.5	99.6
4	2 h	0.03	–8.6	91
5	4 h	0.12	–6.8	50
6	12 h	0.29	–5.4	35

[a] The integral for the doublet at δ = 3.84 ppm (the methylene groups in the 2-acyl isomer) in the ^{1}H NMR spectrum measured on the crude product mixture after work-up, with the integral for the multiplet at δ = 3.93 ppm (the methine group in **27**) set to unity for comparison. [b] Measured in DMSO at c = 1.0. [c] Measured by chiral HPLC analysis of the **24** derived from **27**.

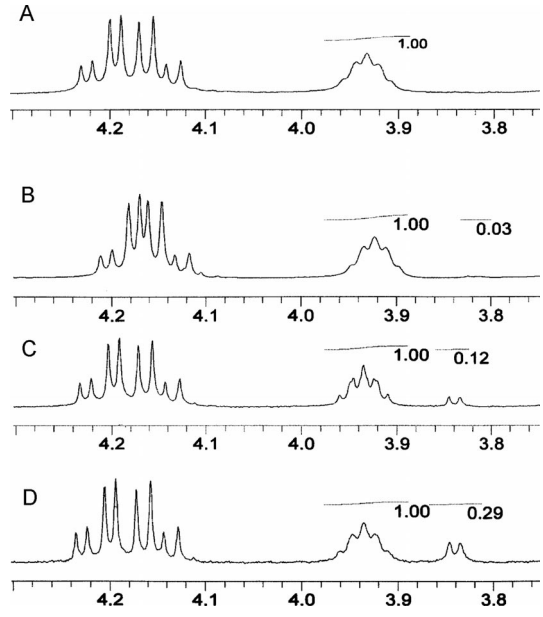
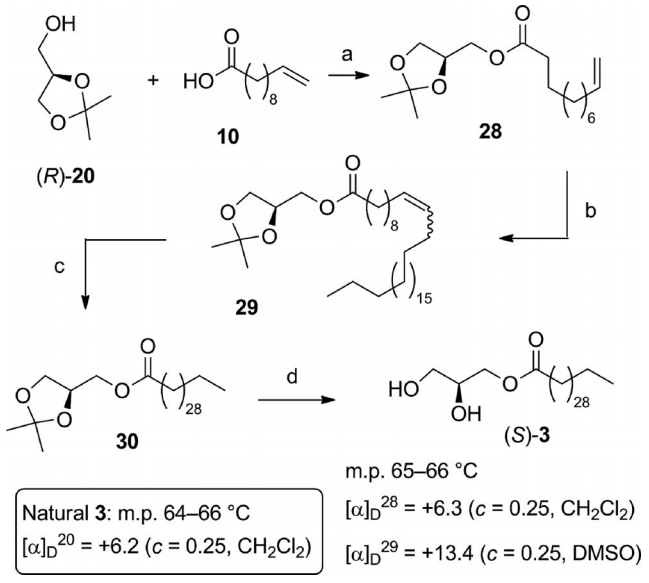


Figure 2. The effect of reaction time on the 1,2-acyl migration in the cleavage of the acetonide in **26** with AcOH/H_2O at 50 °C, as shown by the relative intensity of the doublet at δ = 3.84 ppm in the ^{1}H NMR spectra of the samples taken out of the reaction flask (and worked up immediately) at 30 min (trace A), 2 h (trace B), 4 h (trace C), and 12 h (trace D), respectively. Note that the chemical shifts for such molecules are slightly dependent on the concentration of the NMR sample; see also Table 3.

sion of the reaction time led to very serious isomerization (Table 3, entries 5 and 6).

The optical rotation of **26** in DMSO was also substantially larger than the values measured in e.g., MeOH,[1h] pyridine,[2a] or THF,[12] which unambiguously shows that DMSO may be the generally preferred solvent for measuring the optical rotations of 1(or 3)-acyl-*sn*-glycerols.

Next, we proceeded with the synthesis of **3**. As shown in Scheme 6, condensation of (*R*)-**20** with undec-10-enoic acid **10** gave **28** in 97% yield. Introduction of the additional 21 carbon atoms was effected in a cross-metathesis reaction mediated by the Grubbs II catalyst (**13**). The resulting C=C double bond was saturated by hydrogenation over Pd black under atmospheric H_2 at ambient temperature to deliver **30** in 98% yield.

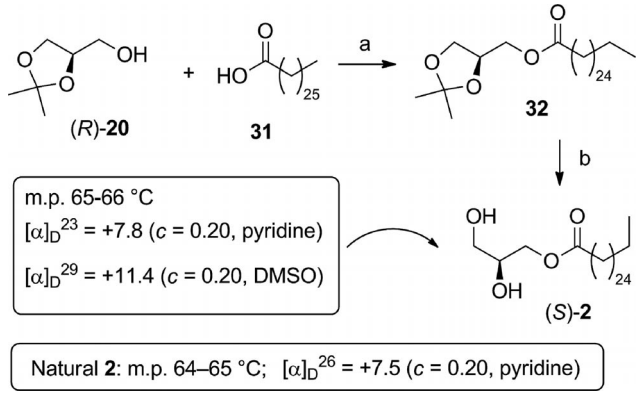


Scheme 6. *Reagents and conditions:* a) EDCI, DMAP, CH_2Cl_2, 0 °C, 2 h, 97%; b) Grubbs II (cat. **13**), **9**, CH_2Cl_2, reflux, 6 h, 45%; c) H_2 (1 atm), Pd black, EtOAc, room temp., 48 h, 98%; d) AcOH/H_2O (4:1, v/v), 65 °C, 8 min, 91%.

Cleavage of the acetonide with AcOH/H_2O deserves further remarks. At 50 °C, the substrate (i.e., **30**) did not dissolve at all, which made it impossible to run the reaction. Reducing the water content in the solvent mixture to almost pure acetic acid did not lead to any improvement. Fortunately, the problem was solved by raising the bath temperature to 65 °C. At this temperature, complete hydrolysis could be achieved in 8 min without any discernible formation of the 2-acyl isomer. This required pre-warming the solvent mixture in a 65 °C bath to allow precise control of the reaction time at 65 °C. The *ee* value of the **24** derived from (*S*)-**3** was determined to be 93%.

The spectroscopic data for the synthetic (*S*)-**3** generally agreed well with the data reported for natural **3**. However, in the ^{1}H NMR spectrum, the protons of the CH_2O group bonded to the acyl group appeared in the synthetic sample at δ = 4.15 (dd, J = 11.5, 6.0 Hz, 1 H) and 4.22 (dd, J = 11.8, 4.8 Hz, 1 H) ppm, whereas those for the natural compound were at δ = 4.37 (dd, J = 11.2, 5.5 Hz, 1 H) and 4.40 (dd, J = 11.2, 3.5 Hz, 1 H) ppm, respectively.[3a] In the ^{13}C NMR spectra, a difference of 0.9 ppm was also observed for a carbon at $\delta \approx$ 32 ppm between the two sets of data (δ = 31.9 ppm for synthetic **3** and δ = 32.8 ppm for natural **3**). It thus seemed that the data for natural **3** contained some minor errors. To confirm this, we looked into the NMR spectroscopic data for other known 1(or 3)-fatty acyl-*sn*-glycerols, including **27**, for supporting evidence. And indeed, all the corresponding data are consistent with the data for the synthetic but not the natural **3**.

To be on the safe side, we also synthesized (*S*)-**2**, a natural product[1a] closely related to **3**, by the sequence shown in Scheme 7.



Scheme 7. *Reagents and conditions:* a) EDCI, DMAP, CH_2Cl_2, 0 °C, 10 h, 95%; b) AcOH/H_2O (4:1, v/v), 65 °C, 10 min, 91%.

All the data for the synthetic and natural **2** were in good agreement with each other, which thus proved that natural **2** has an (*S*) configuration. Neither the synthetic nor the natural **2** has any signals in the δ = 4.30–4.40 ppm region of their ^{1}H NMR spectra. And in the ^{13}C NMR spectrum, the signal in question appeared at δ = 31.8 ppm. As the structural difference between **2** and **3** is almost negligible, the data for **2**, along with those for other closely related 1(or 3)-acyl-*sn*-glycerols including **27**, clearly show that either the reported data for natural **3** contain minor errors (as mentioned above) or, which is less likely, the structure of the natural hyloglycerol was incorrectly assigned.[3b]

Conclusions

Two natural monoacylglycerols both containing an ultra long alkyl chain (hentriacontanoyl and heptacosanoyl) were synthesized using enantiopure (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol as a chiral building block. Comparison of the physical and spectroscopic data confirmed the previously assigned structure for natural **2** and established the absolute configuration to be (*S*). Data comparison also showed that the ^{1}H and ^{13}C NMR spectroscopic data reported for the natural hyloglycerol (i.e., **3**) might contain some minor errors (see also Tables S1 and S2, Supporting Information). In connection with the syntheses of **2** and **3**, the general problems in accessing optically active monoacylglycerols, namely control and detection of acyl

migrations and assessment of optical purity of the final products, were also addressed. A simple means to "magnify" the normally rather small specific rotations for the monoacylglycerols was found (i.e., recording the optical rotations in DMSO). Methods for the quantitative measurement of the 1,2- and 1,3-acyl migrations were also introduced. With the aid of these measures, several sets of mild conditions for the removal of acetonides developed by previous investigators were re-examined. Some of them led to significant acyl migration. The conditions reported by Mori were shown to be the mildest, and these conditions were further refined in this work for the individual substrates, especially those bearing an ultra long alkyl chain and thus having a poor solubility. The methods developed and the knowledge gained may facilitate studies of similar compounds in general.

Experimental Section

General: NMR spectra were recorded with a Bruker Avance NMR spectrometer operating at 400 MHz (^{1}H). IR spectra were measured with a Nicolet 380 Infrared spectrophotometer. ESI-MS data were acquired with a Shimadzu LCMS-2010EV mass spectrometer. HRMS data were obtained with a Bruker APEXIII 7.0 Tesla FT-MS spectrometer. Optical rotations were measured with a Jasco P-1030 polarimeter. Melting points were measured with a hot-stage melting point apparatus equipped with a microscope. CH_2Cl_2 was dried with activated 4 Å MS (molecular sieves). All chemicals were reagent grade and used as purchased. Column chromatography was performed on silica gel (300–400 mesh) under slightly positive pressure. PE = petroleum ether (b.p. 60–90 °C).

Condensation of (*R*)-20 with 21 To Give 22: A mixture of (*R*)-**20** [L-(–)-1,2-isopropylideneglycerol; 400 mg, 3.03 mmol], *n*-hexanoic acid (351 mg, 3.03 mmol), EDCI (640 mg, 3.33 mmol), and DMAP (19 mg, 0.15 mmol) in dry CH_2Cl_2 (25 mL) was stirred at ambient temperature for 3 h. The mixture was concentrated on a rotary evaporator. The residue was purified by chromatography (30:1, PE/EtOAc) on silica gel to give known ester **22** (636 mg, 2.78 mmol, 92%) as a colorless oil. $[\alpha]_D^{27}$ = –12.1 (*c* = 1.25, hexane) {ref.[13] $[\alpha]_D^{25}$ = –12.2 (*c* = 1.20, hexane)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.29 (quint, *J* = 5.3 Hz, 1 H), 4.14 (dd, *J* = 11.5, 4.6 Hz, 1 H), 4.10–4.03 (m, 2 H), 3.72 (dd, *J* = 8.3, 6.4 Hz, 1 H), 2.32 (t, *J* = 7.7 Hz, 2 H), 1.61 (quint, *J* = 7.2 Hz, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.32–1.23 (m, 4 H), 0.87 (t, *J* = 7.1 Hz, 3 H) ppm. ESI-MS: *m*/*z* = 253.3 $[M + Na]^+$.

Removal of the Acetonide in 22 To Give 23: A solution of acetonide **22** (50 mg, 0.22 mmol) in AcOH/H_2O (4:1, v/v; 2.5 mL) was stirred at 50 °C (bath) for 30 min. The heating bath was removed, and $NaHCO_3$ (saturated aq.; 5 mL) was added. The mixture was extracted with EtOAc (3× 10 mL). The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and chromatography (2:1, PE/EtOAc) on silica gel gave known[14] diol **23** (39 mg, 0.21 mmol, 93%) as a colorless oil. $[\alpha]_D^{28}$ = –1.3 (*c* = 1.00, $CHCl_3$); $[\alpha]_D^{28}$ = +11.9 (*c* = 1.00, DMSO). *ee* = 98%, as shown by chiral HPLC analysis of the compound **24** derived from **23** by the four-step sequence developed in this work. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.23–4.07 (m, 2 H), 3.92 (quint, *J* = 5.6 Hz, 1 H), 3.68 (dd, *J* = 11.5, 3.8 Hz, 1 H), 3.58 (dd, *J* = 11.6, 5.8 Hz, 1 H), 2.72 (br. s, 2 H), 2.34 (t, *J* = 7.5 Hz, 2 H), 1.62 (quint, *J* = 7.6 Hz, 2 H), 1.38–1.19 (m, 4 H), 0.87 (t, *J* = 6.9 Hz, 3 H) ppm. FT-IR (film): $\tilde{\nu}$ = 3316, 2960, 2925, 2854, 1730, 1417, 1260, 1099, 799 cm^{-1}. ESI-MS: *m*/*z* = 213.0 $[M + Na]^+$.

Condensation of (*S*)-20 with Stearic Acid (25) To Give 26: A mixture of (*S*)-**20** [D-(+)-1,2-isopropylideneglycerol; 1.03 g, 7.58 mmol], stearic acid (2.22 g, 7.58 mmol), EDCI (1.62 g, 8.34 mmol), and DMAP (46 mg, 0.38 mmol) in dry CH_2Cl_2 (60 mL) was stirred at ambient temperature for 5 h. The mixture was concentrated on a rotary evaporator. Water (15 mL) and was added. The mixture was extracted with Et_2O (3× 15 mL). The combined organic extracts were washed with brine, and dried with anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator left an oily residue, which was purified by chromatography (30:1, PE/EtOAc) on silica gel to give known[2a] ester **26** (2.91 g, 7.31 mmol, 96%) as a white solid, m.p. 41–43 °C (ref.[2a] m.p. 40–41 °C). $[\alpha]_D^{26}$ = –2.4 (*c* = 0.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.35–4.28 (m, 1 H), 4.17 (dd, *J* = 11.3, 4.5 Hz, 1 H), 4.12–4.05 (m, 2 H), 3.79–3.66 (m, 1 H), 2.34 (t, *J* = 7.5 Hz, 2 H), 1.68–1.56 (m, 2 H), 1.44 (s, 3 H), 1.37 (s, 3 H), 1.40–1.20 (m, 28 H), 0.88 (t, *J* = 6.5 Hz, 3 H) ppm. ESI-MS: *m*/*z* = 421.5 $[M + Na]^+$.

Removal of the Acetonide in 26 To Give 27: A solution of acetonide **26** (103 mg, 0.26 mmol) in AcOH/H_2O (4:1, v/v; 2.5 mL) was stirred at 50 °C (bath) for 30 min. The heating bath was removed, and $NaHCO_3$ (saturated aq.; 5 mL) was added. The mixture was extracted with EtOAc (3× 10 mL). The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and chromatography (2:1, PE/EtOAc) on silica gel gave known[2a] diol **27** (90 mg, 0.25 mmol, 96%) as a white solid, m.p. 74–76 °C (ref.[2a] m.p. 73–74 °C). $[\alpha]_D^{25}$ = +1.4 (*c* = 20.00, $CHCl_3$); $[\alpha]_D^{29}$ = –7.4 (*c* = 0.65, DMSO); $[\alpha]_D^{29}$ = –4.2 (*c* = 2.55, pyridine) {ref.[2a] $[\alpha]_D^{23}$ = –3.83 (*c* = 2.63, pyridine)}. *ee* >99%, as shown by chiral HPLC analysis of the compound **24** derived from **27** using the four-step sequence developed in this work. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21 (dd, *J* = 11.7, 4.7 Hz, 1 H), 4.15 (dd, *J* = 11.7, 6.2 Hz, 1 H), 3.98–3.89 (m, 1 H), 3.70 (dd, *J* = 11.2, 3.7 Hz, 1 H), 3.60 (dd, *J* = 11.5, 5.7 Hz, 1 H), 2.54 (br. s, 1 H), 2.35 (t, *J* = 7.6 Hz, 2 H), 2.10 (br. s, 1 H), 1.68–1.53 (m, 2 H), 1.45–1.20 (m, 28 H), 0.88 (t, *J* = 6.8 Hz, 3 H) ppm. ESI-MS: *m*/*z* = 381.4.

Condensation of Alcohol (*R*)-20 with Undec-10-enoic Acid (10) To Give Ester 28: A mixture of (*R*)-**20** [L-(+)-1,2-Isopropylideneglycerol, 103 mg, 0.76 mmol], undec-10-enoic acid (**10**; 140 mg, 0.76 mmol), EDCI (162 mg, 0.84 mmol), and DMAP (5 mg, 0.04 mmol) in dry CH_2Cl_2 (8 mL) was stirred at ambient temperature for 2 h. The mixture was concentrated on a rotary evaporator. Water (15 mL) and was added. The mixture was extracted with Et_2O (3× 15 mL). The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator left an oily residue, which was purified by chromatography (30:1, PE/EtOAc) on silica gel to give ester **28** (220 mg, 0.74 mmol, 97%) as a colorless oil. $[\alpha]_D^{28}$ = –1.40 (*c* = 3.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.88–5.71 (m, 1 H), 5.06–4.86 (m, 2 H), 4.36–4.26 (m, 1 H), 4.16 (dd, *J* = 11.6, 4.8 Hz, 1 H), 4.12–4.02 (m, 2 H), 3.73 (dd, *J* = 8.3, 6.4 Hz, 1 H), 2.34 (t, *J* = 7.6 Hz, 2 H), 2.03 (q, *J* = 6.9 Hz, 2 H), 1.65–1.59 (m, 2 H), 1.43 (s, 3 H), 1.37 (s, 3 H), 1.35–1.24 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 139.2, 114.1, 109.8, 73.7, 66.3, 64.5, 34.1, 33.7, 29.24, 29.15, 29.1, 29.0, 28.9, 26.7, 25.4, 24.9 ppm. FT-IR (film): $\tilde{\nu}$ = 2986, 2928, 2856, 1742, 1640, 1456, 1371, 1161, 1057, 910, 843 cm^{-1}. ESI-MS: *m*/*z* = 321.3 $[M + Na]^+$. ESI-HRMS: calcd. for $C_{17}H_{30}O_4Na$ $[M + Na]^+$ 321.20363; found 321.20371.

Coupling of 28 with Docos-1-ene (9) To Give 29: A mixture of **28** (70 mg, 0.23 mmol), docos-1-ene (**9**; 434 mg, 1.41 mmol), and

Grubbs II catalyst **13** (9 mg, 0.01 mmol) in dry CH_2Cl_2 (3 mL) was stirred at reflux under argon for 6 h. The solids were filtered off. The filtrate was concentrated on a rotary evaporator. The residue was purified by chromatography (40:1, PE/EtOAc) on silica gel to give **29** (60 mg, 0.10 mmol, 45%; a mixture of the *cis*/*trans* isomers) as a white solid, m.p. 76–79 °C. $[\alpha]_D^{28}$ = –0.9 (*c* = 1.33, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.44–5.31 (m, 2 H), 4.31 (quint, *J* = 5.0 Hz, 1 H), 4.16 (dd, *J* = 11.6, 4.8 Hz, 1 H), 4.12–4.03 (m, 2 H), 3.73 (dd, *J* = 8.3, 6.1 Hz, 1 H), 2.33 (t, *J* = 7.5 Hz, 2 H), 2.03–1.91 (m, 4 H), 1.66–1.58 (m, 2 H), 1.43 (s, 3 H), 1.37 (s, 3 H), 1.40–1.20 (m, 46 H), 0.87 (t, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 130.5, 130.4, 130.23, 130.16, 109.8, 73.7, 66.3, 64.5, 34.1, 32.59, 32.55, 32.53, 31.9, 29.8–29.1 (many unresolved C's), 26.7, 25.4, 24.9, 22.7, 14.1 ppm. FT-IR (film of a concentrated solution in CH_2Cl_2): $\tilde{\nu}$ = 2924, 2853, 1745, 1465, 1371, 1260, 1087, 801 cm^{-1}. All attempts to acquire mass spectra for this compound failed.

Hydrogenation of 29 To Give 30: A mixture of **29** (26 mg, 0.04 mmol) and Pd black (5 mg) in EtOAc (2 mL) was stirred at ambient temperature under H_2 (1 atm) for 2 d. The solids were filtered off. The filtrate was concentrated on a rotary evaporator. The residue was purified by chromatography (10:1, PE/EtOAc) on silica gel to give **30** (27 mg, 0.05 mmol, 98%) as a white solid, m.p. 69–71 °C. $[\alpha]_D^{27}$ = –0.7 (*c* = 2.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.31 (quint, *J* = 5.9 Hz, 1 H), 4.16 (dd, *J* = 11.6, 4.6 Hz, 1 H), 4.12–4.03 (m, 2 H), 3.73 (dd, *J* = 8.3, 6.4 Hz, 1 H), 2.34 (t, *J* = 7.6 Hz, 2 H), 1.65–1.58 (m, 2 H), 1.43 (s, 3 H), 1.37 (s, 3 H), 1.40–1.20 (m, 54 H), 0.88 (t, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 109.8, 73.7, 66.4, 64.5, 34.1, 31.9, 29.7–29.1 (many unresolved C's), 26.7, 25.4, 24.9, 22.7, 14.1 ppm. FT-IR (film of a concentrated solution in CH_2Cl_2): $\tilde{\nu}$ = 2917, 2849, 1740, 1463, 1261, 1095, 760 cm^{-1}. All attempts to acquire mass spectra for this compound failed.

Removal of the Acetonide in 30 To Give (*S*)-3: Acetonide **30** (20 mg, 0.03 mmol) was dissolved in AcOH/H_2O (4:1, v/v; 2.5 mL). The solvent was taken from a stock solution that had been pre-warmed to 65 °C in another bath for >30 min to more precisely control the hydrolysis time at 65 °C. The mixture was stirred at 65 °C (bath) for 8 min. The heating bath was removed, and $NaHCO_3$ (saturated aq.; 5 mL) was added. The mixture was extracted with EtOAc (3× 10 mL). The combined organic extracts were washed with brine, and dried with anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and chromatography (2:1, PE/EtOAc) on silica gel gave diol **3** (17 mg, 0.03 mmol, 91%) as a white solid, m.p. 65–66 °C (ref.[3a] 64–66 °C). $[\alpha]_D^{28}$ = +6.3 (*c* = 0.25, CH_2Cl_2) {ref.[3a] $[\alpha]_D^{20}$ = +6.2 (*c* = 0.25, CH_2Cl_2)}; $[\alpha]_D^{29}$ = +13.4 (*c* = 0.25, DMSO). *ee* = 93%, as determined by chiral HPLC analysis of the compound **24** prepared from (*S*)-**3** by the four-step sequence described in this work. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.22 (dd, *J* = 11.8, 4.8 Hz, 1 H), 4.15 (dd, *J* = 11.5, 6.0 Hz, 1 H), 3.97–3.90 (m, 1 H), 3.70 (dd, *J* = 11.5, 4.0 Hz, 1 H), 3.60 (dd, *J* = 11.6, 5.7 Hz, 1 H), 2.45 (br. s, 1 H), 2.35 (t, *J* = 7.6 Hz, 2 H), 1.70–1.52 (m, 2 H), 1.40–1.20 (m, 54 H), 0.87 (t, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 70.3, 65.1, 63.3, 34.1, 31.9, 29.7–29.1 (many unresolved C's), 24.9, 22.7, 14.1 ppm. FT-IR (film of a concentrated solution in CH_2Cl_2): $\tilde{\nu}$ = 3307, 2918, 2849, 1736, 1463, 1256, 1108, 799 cm^{-1}. ESI-MS: *m*/*z* = 563.9 $[M + Na]^+$. ESI-HRMS: calcd. for $C_{34}H_{68}O_4Na$ $[M + Na]^+$ 563.50098; found 563.49871.

Condensation of Alcohol (*R*)-20 with Heptacosanoic Acid (31) To Give Ester 32: A mixture of (*R*)-**20** [L-(+)-1,2-Isopropylideneglycerol; 32 mg, 0.24 mmol], heptacosanoic acid (**31**; 100 mg, 0.24 mmol), EDCI (50 mg, 0.26 mmol), and DMAP (20 mg, 0.12 mmol) in dry CH_2Cl_2 (5 mL) was stirred at ambient temperature for 10 h. The mixture was concentrated on a rotary evaporator. Water (15 mL) and was added. The mixture was extracted with Et_2O (3× 15 mL). The combined organic extracts were washed with brine (20 mL), and dried with anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator left an oily residue, which was purified by chromatography (25:1, PE/EtOAc) on silica gel to give ester **32** (120 mg, 0.23 mmol, 95%) as a white solid, m.p. 66–67 °C. $[\alpha]_D^{28}$ = –2.5 (*c* = 0.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.29 (quint, *J* = 6.0 Hz, 1 H), 4.14 (dd, *J* = 11.4, 4.7 Hz, 1 H), 4.11–4.02 (m, 2 H), 3.72 (dd, *J* = 8.5, 6.1 Hz, 1 H), 2.32 (t, *J* = 7.5 Hz, 2 H), 1.65–1.55 (m, 2 H), 1.41 (s, 3 H), 1.34 (s, 3 H), 1.40–1.20 (m, 46 H), 0.86 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 109.7, 73.6, 66.3, 64.4, 34.0, 31.9, 29.7–29.1 (many unresolved C's), 26.6, 25.3, 24.8, 22.6, 14.0 ppm. FT-IR (film of a concentrated solution in CH_2Cl_2): $\tilde{\nu}$ = 2916, 2848, 1741, 1473, 1261, 1089, 799 cm^{-1}. ESI-MS: *m*/*z* = 547.6 $[M + Na]^+$. ESI-HRMS: calcd. for $C_{33}H_{64}O_4Na$ $[M + Na]^+$ 547.46968; found 547.47035.

Removal of the Acetonide in 32 To Give (*S*)-2: The same procedure for the conversion of **30** to (*S*)-**3** given above was used, and gave (*S*)-**2** (17 mg, 0.03 mmol, 91%) after chromatography (2:1, PE/EtOAc) on silica gel, m.p. 65–66 °C (ref.[1a] 64–65 °C). $[\alpha]_D^{23}$ = +7.8 (*c* = 0.20, pyridine) {ref.[1a] $[\alpha]_D^{26}$ = +7.5 (*c* = 0.20, pyridine)}; $[\alpha]_D^{29}$ = +11.4 (*c* = 0.20, DMSO). *ee* = 96% as determined by chiral HPLC analysis of the compound **24** derived from (*S*)-**2** by the four-step sequence described in the text. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.24–4.11 (m, 2 H), 3.98–3.89 (m, 1 H), 3.70 (dd, *J* = 11.3, 3.6 Hz, 1 H), 3.60 (dd, *J* = 11.7, 5.8 Hz, 1 H), 2.36 (t, *J* = 7.1 Hz, 2 H), 1.70–1.59 (m, 2 H), 1.40–1.20 (m, 46 H), 0.87 (t, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 70.3, 65.1, 63.3, 34.1, 31.9, 29.7–29.1 (many unresolved C's), 24.9, 22.6, 14.1 ppm. FT-IR (film): $\tilde{\nu}$ = 3332, 2917, 2848, 1735, 1461, 1257, 1052, 799 cm^{-1}. ESI-MS: *m*/*z* = 507.7 $[M + Na]^+$. ESI-HRMS calcd. for $C_{30}H_{60}O_4Na$ $[M + Na]^+$ 507.43838; found 507.43759.

Conversion of the 1(3)-Acyl-*sn*-Glycerol Into 24 (Representative Procedure, with 23 as the Substrate) and Chiral HPLC Analysis for the *ee* Values: A solution of **23** (30 mg, 0.16 mmol) and *p*TsOH (monohydrate, 0.5 mg) in acetone (2 mL) was stirred at ambient temperature for 6 h. Na_2HCO_3 (saturated aq.; 5 mL) was added. The mixture was extracted with EtOAc (3× 10 mL). The combined organic extracts were washed with brine (10 mL), and dried with anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue (a colorless oil) was dissolved in THF/H_2O (10:1, v/v; 2.2 mL) containing LiOH (10 mg, 0.25 mmol). The mixture was stirred at ambient temperature for 12 h. Water (5 mL) was added. The mixture was extracted with EtOAc (3× 10 mL). The combined organic extracts were washed with brine (10 mL), and dried with anhydrous Na_2SO_4. The residue (a colorless oil) was dissolved in dry DMF (2 mL). NaH (60% in mineral oil; 10 mg, 0.4 mmol) was then added. The yellowish mixture was stirred in an ice-water bath for 40 min. BnBr (20 μL, 0.18 mmol) was added dropwise. The mixture was stirred at ambient temperature for 2 h. NH_4Cl (saturated aq.; 5 mL) was added, followed by water (5 mL). The mixture was extracted with EtOAc (3× 10 mL). The combined organic extracts were washed with brine (10 mL), and dried with anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The yellowish oily residue was dissolved in AcOH/H_2O (4:1, v/v; 2.5 mL) and the mixture was stirred at 50 °C for 2 h. Water (5 mL) was added, followed by $NaHCO_3$ (saturated aq.; 5 mL). The mixture was extracted with EtOAc (3× 10 mL). The combined organic extracts were washed with brine (10 mL) and dried with anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator

and column chromatography (2:1, PE/EtOAc) on silica gel gave **24** (26 mg, 0.15 mmol, 91% overall from **23**) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 5 H), 4.54 (s, 2 H), 3.93–3.84 (m, 1 H), 3.68 (dd, J = 11.4, 3.6 Hz, 1 H), 3.60 (dd, J = 11.4, 5.6 Hz, 1 H), 3.57–3.49 (m, 2 H), 2.78 (br. s, 2 H) ppm. ESI-MS m/z = 205.1 $[M + Na]^+$. The optical rotation and *ee* values depended on the source of the starting 1(3)-acyl-*sn*-glycerol.

The *ee* values of the samples of **24** prepared using the above procedure were measured by chiral HPLC on a CHIRALPAK AD-H column (0.46 × 25 cm, particle size 5 μm) eluting with 95:5 *n*-hexane/*i*PrOH at a flow rate of 0.7 mL/min with the detector set to 214 nm.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra, chiral HPLC traces for **24**, tabular data comparison for natural and synthetic **2** and **3**, detailed information about the unsuccessful routes to **3** and related experimental procedures.

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[7] It is interesting to note that although the acyl migration problem has been discussed, in: many papers on the synthesis of monoacylglycerols, ref.[6] was never cited. Also, the doublet at $\delta \approx 3.8$ ppm was neither mentioned nor included in the ^{1}H NMR spectroscopic data listings, although in the scanned spectra in the Supporting Information of a few recent publications, this doublet was apparently present. See, for example: a) R. J. Kubiak, K. S. Bruzik, *J. Org. Chem.* **2003**, *68*, 960–968; b) H. Nakamura, N. Ueda, H. S. Ban, M. Ueno, S. Tachikawa, *Org. Biomol. Chem.* **2012**, *10*, 1374–1380; c) Z. Li, D. L. Baker, G. Tigyi, R. Bittman, *J. Org. Chem.* **2006**, *71*, 629–635. The multiplet at $\delta \approx 3.9$ ppm (the C-2 methine group of 2-acyl-*sn*-glycerols) may be partially overlapping with the olefinic protons for C=C double-bond(s)-containing 1(or 3)-acyl-*sn*-glycerols, and hence not so useful/sensitive as the doublet at $\delta \approx 3.8$ ppm in the detection of 2-acyl-*sn*-glycerols.

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