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Synthesis of (*Z*)-(2′*R*)-1-*O*-(2′-methoxynonadec-10′-enyl)-*sn*-glycerol, a new analog of bioactive ether lipids

René Pemha [a,b,c], Dieudonné Emmanuel Pegnyemb [c], Paul Mosset [b,d,*]

[a] *Ecole Nationale Supérieure de Chimie de Rennes, CNRS, UMR 6226, Avenue du Général Leclerc, CS 50837, 35708 Rennes Cedex 7, France*
[b] *Université européenne de Bretagne, Rennes, France*
[c] *Département de Chimie Organique, Faculté des Sciences, Université de Yaoundé I, BP 812 Yaoundé, Cameroon*
[d] *Université de Rennes 1, Laboratoire SCR, CNRS, UMR 6226, Avenue du Général Leclerc, 35042 Rennes Cedex, France*

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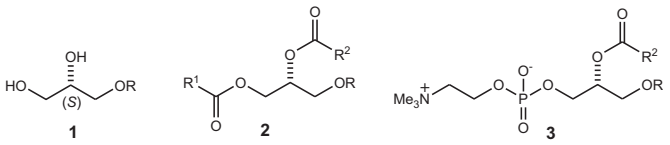
ABSTRACT

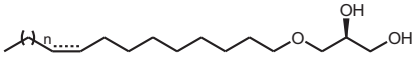
An unsaturated 2-methoxy-substituted 1-*O*-alkylglycerol, (*Z*)-(2′*R*)-1-*O*-(2′-methoxynonadec-10′-enyl)-*sn*-glycerol, a new analog of bioactive ether lipids, was synthesized from oleic acid and 2,3-isopropylidene-*sn*-glycerol. The two key steps of this synthesis were the conversion of oleyl aldehyde to a monounsaturated epoxide using Matteson's method followed by hydrolytic kinetic resolution and a nucleophilic epoxide opening by 2,3-isopropylidene-*sn*-glycerol in the presence of potassium *tert*-butoxide in anhydrous DMF, which appeared to be a good reagent for this purpose. Furthermore, the diol by-product of the HKR process was also easily converted back to the starting epoxide thus almost doubling the amount of target molecule.

1. Introduction

Natural 1-*O*-alkylglycerols **1** are bioactive ether lipids, which are present in various human cells but only in trace quantities. On the contrary, the liver oil of some sharks species and of rat fish (elasmobranch fishes) are rich natural sources and for instance, shark liver oil (SLO) contains 20–25% of 1-*O*-alkylglycerols as diesters **2** and phospholipids **3** but as a mixture of a few species varying by length and unsaturation of the alkyl chain.[1] It was established that the alkyl chain is bound to the glycerol backbone at the *sn*-1 position thus leading to an S configuration at the asymmetric carbon.[2]



In traditional medicine of countries, which are strongly implied in fishing such as Japan, Norway, and Iceland, SLO had been used for strengthening and wound healing. Later in the 20th century, beneficial effects on health of SLO were attributed to 1-*O*-alkylglycerols, which were found to display several useful properties such as stimulating hematopoiesis,[3] lowering radiotherapy-induced injuries,[4] reducing tumor growth,[5] and improving vaccination efficiency.[6,7] Biological testing has been done on natural sources, which are complex mixtures and for which separation of individual components would be tedious. To assess the biological activity of each individual 1-*O*-alkylglycerol, Legrand et al. recently reported the antitumor activity (against lung cancer in mice) of each of the six prominent components **4**–**9** of the natural mixture.[8–10] These derivatives have been obtained in pure form by total synthesis and it was observed that the activity was strongly depending upon the saturation of the alkyl chain. When this chain was saturated, corresponding 1-*O*-alkylglycerols **4**–**7** exhibited little or no activity while it was monounsaturated, a good antitumor activity has been observed for **8** and **9** thus indicating that the antitumor activity of the natural SLO mixture was strongly related to its unsaturated components.



4-7: simple bond, n = 1,3,5,7
8,9: double bond, n = 5,7

In SLO from Greenland, were also identified small amounts (2–4%) of 1-*O*-alkylglycerols with an additional methoxy group in the 2-position (methyl glyceryl ethers: MGE) and containing

* Corresponding author. Tel./fax: +33 2 23 23 69 78; e-mail address: paul.mosset.1@univ-rennes1.fr (P. Mosset).

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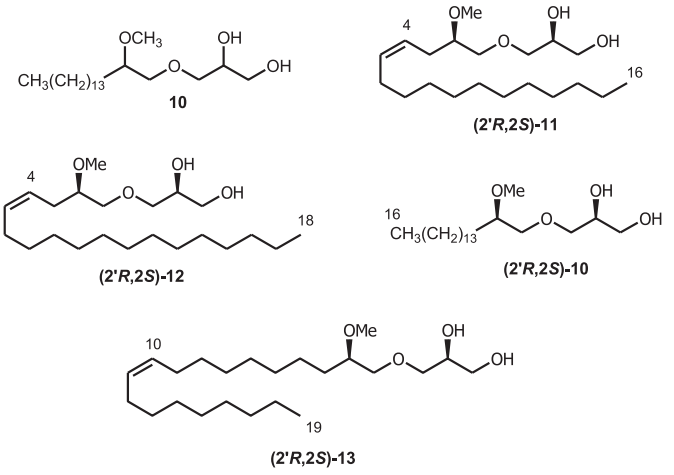
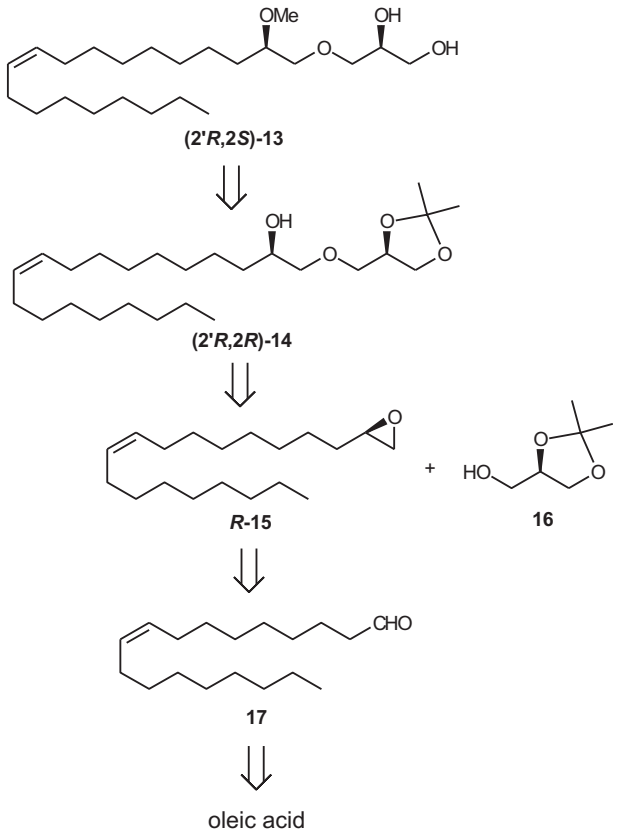
saturated and unsaturated alkyl chains from 14 to 22 carbon atoms.[11–13] Among the four possible stereoisomers, Ställberg has established that the natural product had the 2′*R*,2*S* configuration by comparison of ^{1}H NMR spectra and optical rotations with those of each stereoisomer of 1-*O*-(2′-methoxyhexadecyl)glycerol **10** prepared by chemical synthesis.[14] The most abundant MGE (2′*R*,2*S*)-**11** was found to have 16 carbon atoms in the alkyl chain and a Δ4 unsaturation.[11] A higher homolog (2′*R*,2*S*)-**12** with a 18 carbon atoms alkyl chain was also identified as well as the saturated derivative (2′*R*,2*S*)-**10**. MGE isolated from Greenland SLO was able to inhibit tumor growth and metastasis formation and also to stimulate the immunoreactivity in mice.[15,16] Clearly, the presence of a methoxy group is beneficial to the biological activity thus inducing interest for the synthesis of this kind of valuable lipids. Initially, a saturated MGE had been synthesized as a mixture of stereoisomers in racemic form **10**[11,17] and then the stereoisomer (2′*R*,2*S*)-**10**[14,18] in a stereocontrolled manner. Very recently, the synthesis of MGE (2′*R*,2*S*)-**11**, with a Δ4 unsaturation was reported.[19] For our part, we had observed the good antitumor properties of monounsaturated 1-*O*-alkylglycerols **8** (n-7, Δ9) and **9** (n-9, Δ9).[8–10] Therefore, it was expected that a MGE with a monounsaturated alkyl chain could have an improved biological profile by combining the favorable properties of the unsaturation and of the methoxy group. As oleic acid was used as an affordable precursor in high purity (99%) for the synthesis of bioactive **9**, we became interested in a monounsaturated MGE that would equally be synthesized from oleic acid, namely (2′*R*,2*S*)-**13** with also a n-9 (Δ10) double bond and for which we describe herein the total synthesis.[20]



2. Results and discussion

The retrosynthetic analysis of (2′*R*,2*S*)-**13** indicates that the molecule can be constructed via a regioselective opening of the epoxide *R*-**15** by the primary alcohol group of 2,3-isopropylidene-*sn*-glycerol **16** leading to the secondary alcohol (2′*R*,2*R*)-**14**, which upon methylation followed by acetonide cleavage, would afford the target (2′*R*,2*S*)-**13**. Optically active epoxide *R*-**15** would be obtained by resolution of the racemic epoxide by Jacobsen's method, which is applicable to terminal epoxides.[22] The unknown racemic epoxide *rac*-**15** would be obtained from oleyl aldehyde **17** by a one-carbon homologation method such as reaction with a sulfur ylide for instance (Scheme 1).

Oleyl aldehyde **17** was obtained by a classical two-step sequence. Highly pure (99%) oleic acid was reduced to oleyl alcohol by Red-Al in THF and this alcohol was oxidized by PCC in dichloromethane. The attempted epoxidation of oleyl aldehyde with trimethylsulfonium

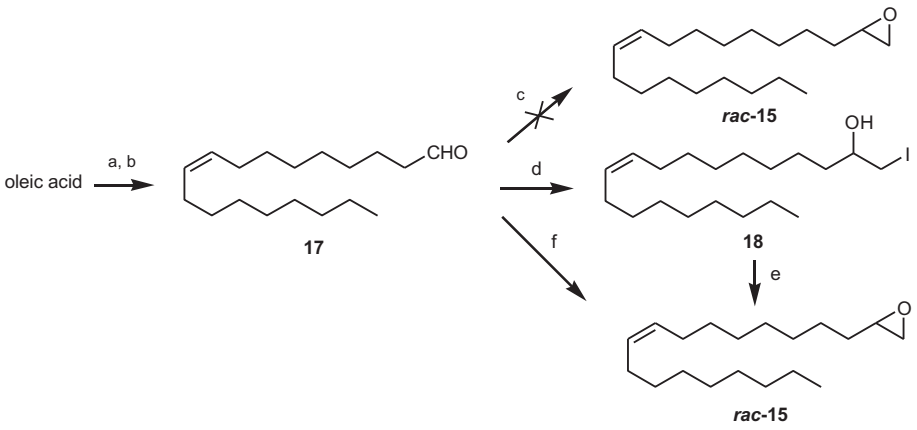


Scheme 1. Retrosynthetic analysis.

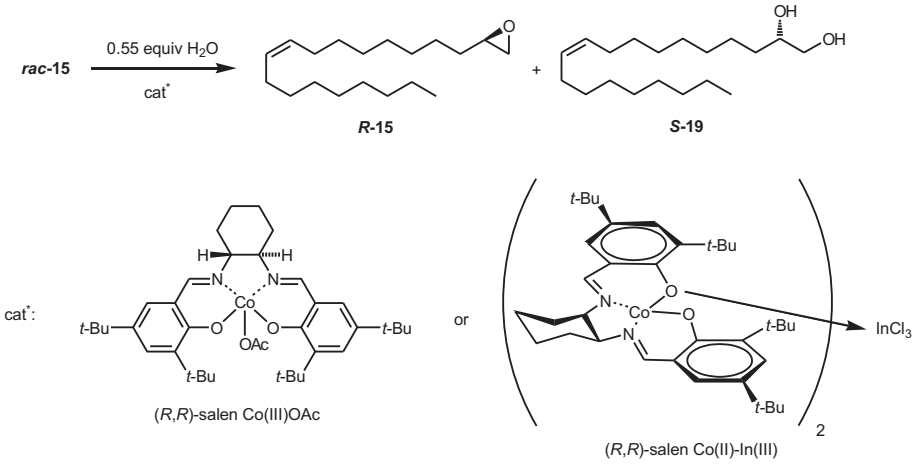
methylsulfate and 50% aqueous sodium hydroxide under phase-transfer conditions[23] did not afford any epoxide but only non-polar by-products were formed probably due to a facile enolization of the methylene group vicinal to the aldehyde. Moreover, it has been reported later that reaction of an aliphatic aldehyde with a sulfur ylide under phase-transfer conditions failed to give any epoxide when there are two hydrogen atoms α to the aldehyde.[24] Thereafter, we were able to react oleyl aldehyde **17** with samarium and diiodomethane[25] to obtain the iodohydrin **18**, which was easily converted to the epoxide *rac*-**15** upon reaction with potassium carbonate in methanol. Unfortunately, the overall yield of this conversion was too low (17%). In fact, an efficient way to obtain the epoxide *rac*-**15** was the reaction of in situ generated (chloromethyl) lithium by the method of Matteson:[26] addition of methyllithium/lithium bromide to a mixture of aldehyde and chloroiodomethane in THF at low temperature (63% yield) (Scheme 2).

Resolution of epoxide *rac*-**15** could be done by hydrolytic kinetic resolution (HKR). Initially, we have used Jacobsen's method with a (salen)cobalt(III) complex[22] as a catalyst. After that to expedite the reaction, we have been used another catalyst, a bimetallic (salen) cobalt(II)–indium(III) complex developed by Geon-Joong Kim et al.[27] (Scheme 3). The latter method presented several advantages: easier handling of the catalyst, faster reaction (overnight versus 3 days) and it was reported to afford a higher enantioselectivity (generally well above 99%).[27,28] The desired *R* enantiomer of **15** was obtained by use of the *R*,*R* enantiomer of the catalyst. It was easily separated by chromatography from the far more polar diol *S*-**19**. HKR using Jacobsen's method afforded 47% *R*-**15** and 42% *S*-**19**. HKR using the bimetallic complex afforded 50% *R*-**15** and 48% *S*-**19**.

The nucleophilic opening of an epoxide by the primary alcohol group of 2,3-isopropylidene-*sn*-glycerol **16** was first investigated by the reaction of an analogous model epoxide, (*R*)-1,2-



Scheme 2. Synthesis of monounsaturated epoxide *rac*-**15**. Reagents and conditions: (a) Red-Al (1.7 equiv), THF, ca. 10 °C to rt, until clear, 97%; (b) PCC (1.5 equiv), CH_2Cl_2, 1 h, rt, 75%; (c) $Me_3S^+MeSO_4^-$, 50% aqueous NaOH, CH_2Cl_2; (d) Sm (2 equiv), CH_2I_2 (3 equiv), THF, 0 °C, addition in 10 min then 20 min, 43%; (e) K_2CO_3 (1.4 equiv), MeOH, rt, 10 min, 39%; (f) $ClCH_2I$ (2 equiv), MeLi·LiBr (1.5 equiv), THF, −80 °C then rt, 17 h, 63%.

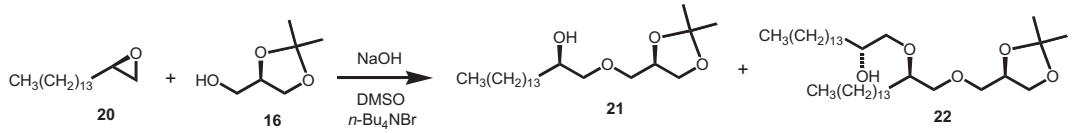


Scheme 3. Resolution of epoxide **15** by HKR.

epoxyhexadecane **20**. In the presence of sodium hydroxide[29] and of tetra-*n*-butylammonium bromide (1 equiv) in DMSO for 30 h at 45 °C, the expected opened product **21** was obtained in 40% yield along with a less polar by-product **22** (23%) arising from a subsequent epoxide opening by the secondary alcohol **21** (Scheme 4).

expected product (2′*R*,2*R*)-**14** but instead by-product **23**, which is the unsaturated analog of **22** (Scheme 5).

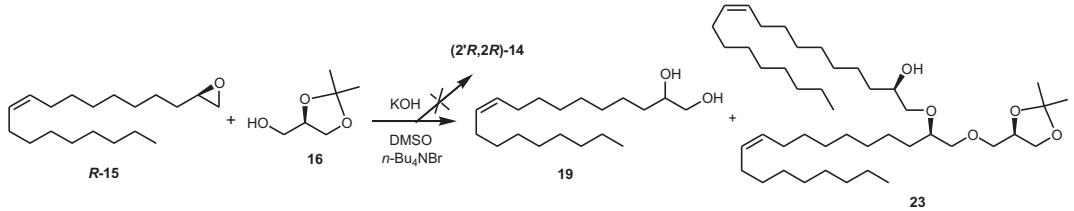
Therefore we turned back to anhydrous conditions using sodium hydride in DMF. In fact, the reaction needed to be performed above room temperature (35 °C) with an appropriate dilution to



Scheme 4. Model nucleophilic opening of (*R*)-1,2-epoxyhexadecane **20** by 2,3-isopropylidene-*sn*-glycerol **16**.

Surprisingly, applying the previous conditions (KOH/*n*-Bu_4NBr cat. in DMSO at 35 °C for 60 h) to unsaturated epoxide *R*-**15** afforded the corresponding diol **19** by hydrolysis[30] with no evidence of

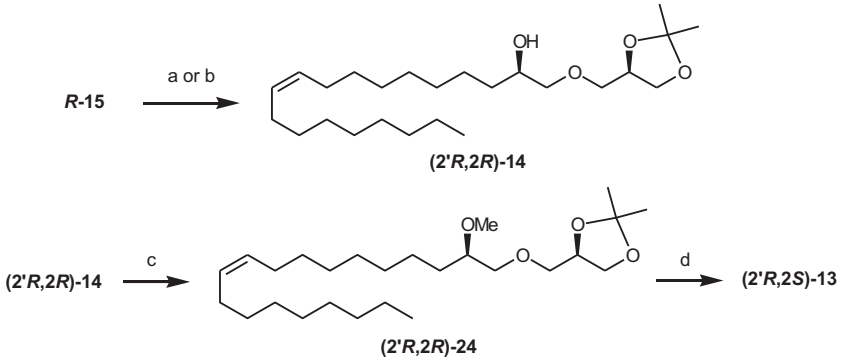
achieve after 2 days, a good conversion to the expected opened product **14**. Interestingly under these conditions, no by-product **23** resulting from a subsequent epoxide opening was observed



Scheme 5. Unsuccessful initial attempt of synthesis of (2′*R*,2*R*)-**14**.

although the yield was fair (only 35%, Scheme 6, step a). It is worthy of note that alcohol (2′*R*,2*R*)-**14** was obtained as a single diastereoisomer with no trace of another isomer being detected by NMR. This result is a very good indication that *R*-**15** was obtained with a high optical purity after HKR.

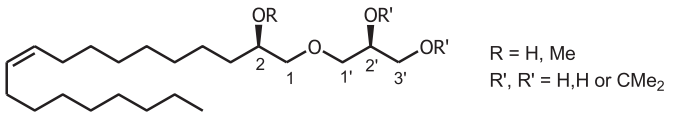
As it has been reported that the optical rotations of the four diastereoisomers of the saturated MGE **10** were noticeably different, those of the MGE (2′*R*,2*S*)-**13** were compared assuming that the nature of the alkyl chain (insaturated or not) would not have a noticeable influence on the order of magnitude. In a chlorinated



Scheme 6. Conversion of epoxide *R*-**15** to monounsaturated MGE (2′*R*,2*S*)-**13**. Reagents and conditions: (a) NaH (5 equiv), 2,3-isopropylidene-*sn*-glycerol **16** (1.25 equiv), DMF, 0 °C then 2 days at 35 °C, 35%; (b) KO*t*-Bu (2.21 equiv), 2,3-isopropylidene-*sn*-glycerol **16** (1.53 equiv), DMF, 5 °C, 3 days, 40% (plus 25% recovered *R*-**15**); (c) KOH (6 equiv), *n*-Bu_4NBr (0.55 equiv), MeI (5 equiv), DMSO, 21 h, darkness, ca. 20 °C, 87%; (d) *p*-TsOH·H_2O (0.05 equiv), MeOH/H_2O 10:1, 60 °C, 3 h, 80%.

The secondary alcohol function could be methylated using practical conditions such as iodomethane and potassium hydroxide in DMSO in the presence of tetra-*n*-butylammonium bromide affording methyl ether (2′*R*,2*R*)-**24** in 87% yield (Scheme 6, step c). Easy acetonide cleavage under acid conditions (0.05 equiv *p*-toluenesulfonic acid monohydrate in MeOH/H_2O 10:1) afforded the targeted monounsaturated MGE (2′*R*,2*S*)-**13** in 80% yield (Scheme 6, step d).

All compounds gave spectroscopic properties (^1H and ^{13}C NMR as well as correlation spectra) in full accordance with their structure. In particular for ^1H NMR of the three last compounds of this synthesis, the presence of the electronegative oxygen atom induces the observation of eight protons at a lower field (from 3.3 to 4.3 ppm). Due to the proximity of the methoxy group to the ether linkage, these eight protons could be distinguished and assigned. Their chemical shifts and coupling constants are given in Table 1 and are in full agreement with those reported for analogous compounds with an unsaturation is another position (Δ4 instead of Δ10).[19] Emphasis could be done on the geminal coupling constants. For the methylene protons, which are vicinal to the ethereal oxygen, they are about 10 Hz. In the acetonide unit, the geminal coupling constants are lowered to 8.3 Hz by the cycle effect. As it could be expected for the MGE (2′*R*,2*S*)-**13**, this value is increased to 11.5 Hz due to the acyclic diol form.



solvent (chloroform or dichloromethane),[31] the values for our material and for the saturated analog (2′*R*,2*S*)-**10** were found to be very close. This is in agreement with the 2′*R*,2*S* stereochemistry of (2′*R*,2*S*)-**13** (Table 2). In THF, the values are less close but of the same order of magnitude and more importantly of opposite signs, in agreement with literature data for 1-*O*-alkylglycerols.[14]

Table 2
Comparison of optical activity data for (2′*R*,2*S*)-**13** and (2′*R*,2*S*)-**10**

Compound	(2′*R*,2*S*)-**13**[a]	(2′*R*,2*S*)-**10**
$[\alpha]_D$	−3.2 (*c* 1, CH_2Cl_2)	−2.6 (*c* 1.3, $CHCl_3$)[b]
		−3.0 (*c* 0.89, $CHCl_3$)[c]
	+1.9 (*c* 1, THF)	+3.4 (*c* 5, THF)[b]

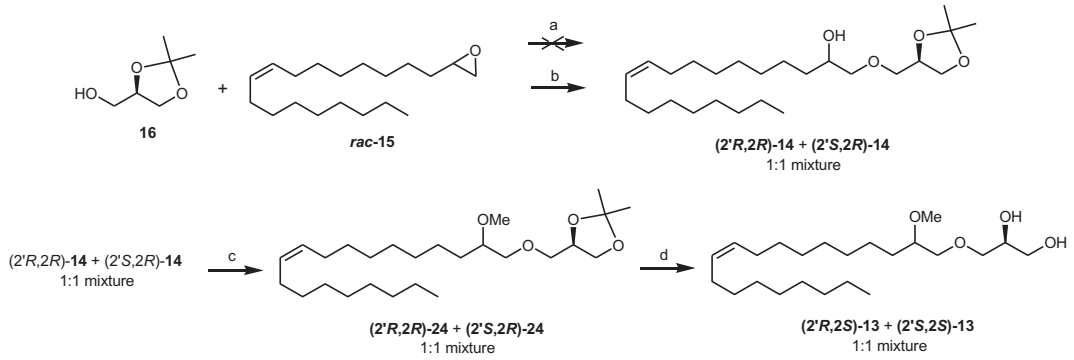
[a] Present study.
[b] According to Ref. 14.
[c] According to Ref. 19.

For each of the three last products of this synthesis, namely for (2′*R*,2*R*)-**14**, (2′*R*,2*R*)-**24**, and (2′*R*,2*S*)-**13**, ^{13}C NMR in particular showed one set of signals, which led us to think that these compounds were obtained as single diastereoisomers as the reflect of the high optical purity of *R*-**15**, which was obtained after HKR. To make sure of this point and demonstrate that NMR is capable to distinguish the other diasteroisomer (with an inverted configuration at the 2′ carbon), the three last steps were performed using racemic epoxide *rac*-**15** instead of *R*-**15**. But attempted reaction of *rac*-**15** with 2,3-isopropylidene-*sn*-glycerol **16** in the presence of sodium hydride in anhydrous DMF did not afford any expected product (Scheme 7, step a). This type of reaction was already difficult with *R*-**15** likely due to the insolubility of sodium hydride, which hampers the formation of the sodium alkoxide of **16**. It came

Table 1
^1H NMR parameters of protons, which are α to an oxygen atom

Compound	δ (ppm)					*J* (Hz)					
	H_1	H_2	$H_{1'}$	$H_{2'}$	$H_{3'}$	J_{1-1}	J_{1-2}	$J_{1'-1'}$	$J_{1'-2'}$	$J_{2'-3'}$	$J_{3'-3'}$
(2′*R*,2*R*)-**14**	3.33 and 3.53	3.79	3.56 and 3.56	4.28	3.74 and 4.06	9.7	3.0 and 8.1	?[a]	5.2 and 5.5	6.4 and 6.5	8.3
(2′*R*,2*R*)-**24**	3.48 and 3.52	3.31	3.49 and 3.57	4.27	3.76 and 4.06	10.3	4.2 and 5.9	10.0	5.4 and 5.8	6.3 and 6.4	8.3
(2′*R*,2*S*)-**13**[b]	3.48 and 3.57	3.33	3.54 and 3.61	3.86	3.63 and 3.70	10.5	3.5 and 6.0	10.2	3.8 and 6.3	3.9 and 5.2	11.5

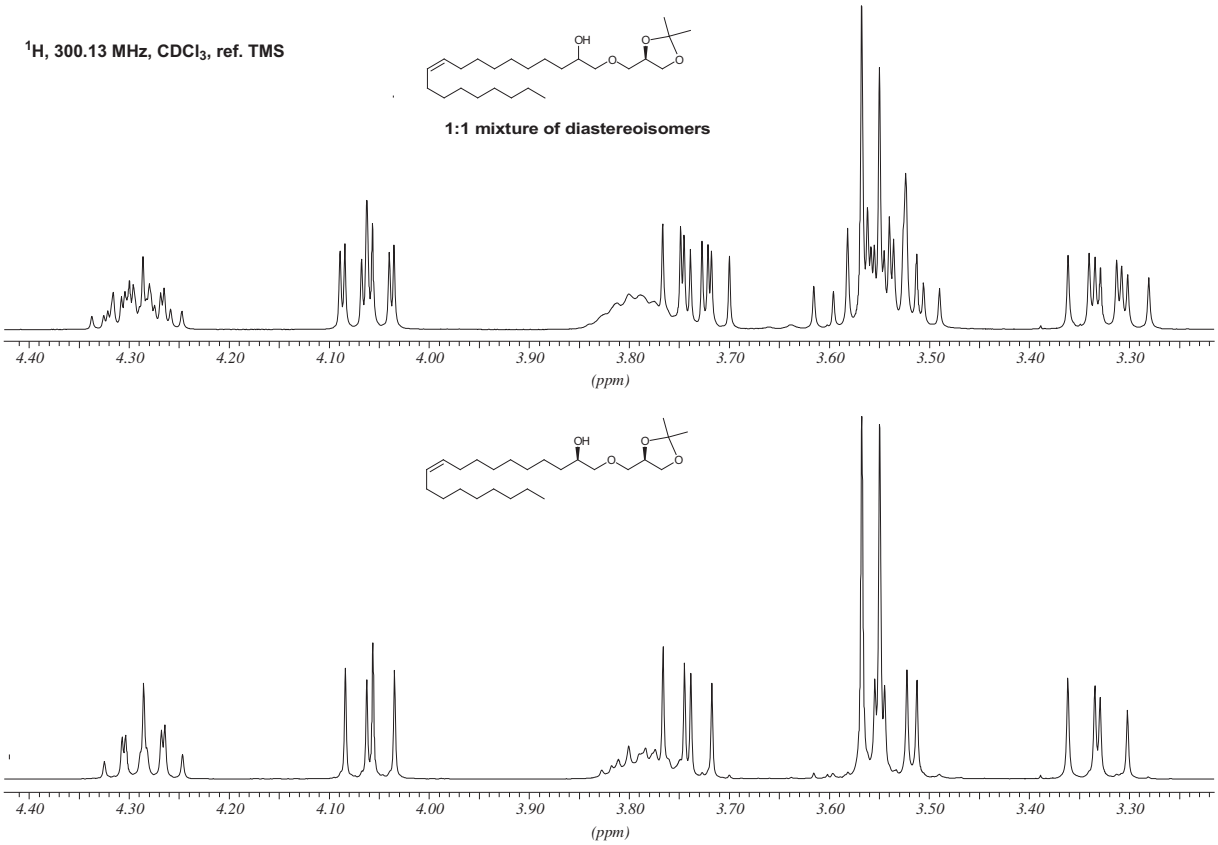
[a] Coupling constant was not seen since the two protons H_1 are equivalent.
[b] After exchange with D_2O to suppress coupling with protons of hydroxyls (see Supplementary data).



Scheme 7. Conversion of racemic epoxide *R*-**15** to a 1:1 mixture of diastereoisomeric MGEs (2′*R*,2*S*)-**13** and (2′*S*,2*S*)-**13**. Reagents and conditions: (a) NaH (5 equiv), 2,3-isopropylidene-*sn*-glycerol **16** (1.25 equiv), DMF, 0 °C then 35 °C, 60 h, 0%; (b) KO*t*-Bu (2.5 equiv), 2,3-isopropylidene-*sn*-glycerol **16** (1.5 equiv), DMF, 5 °C, 2.5 days, 50% (plus 23% recovered *rac*-**15**); (c) KOH (6 equiv), *n*-Bu_4NBr (0.55 equiv), MeI (5 equiv), DMSO, 21 h, darkness, ca. 20 °C, 87%; (d) *p*-TsOH·H_2O (0.05 equiv), MeOH/H_2O 10:1, 60 °C, 3 h, 80%.

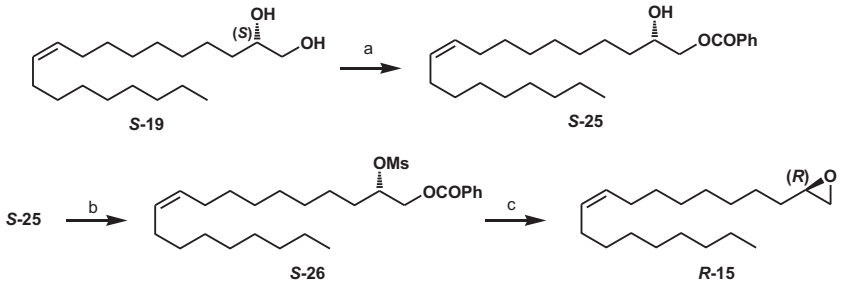
to the idea to use instead potassium *tert*-butoxide whose solubility in DMF is quite good and which would be sufficiently basic to generate potassium alkoxide of **16**. To our delight, potassium *tert*-butoxide efficiently mediated the reaction of *rac*-**15** with **16** affording cleanly a 1:1 mixture of (2′*R*,2*R*)-**14** and (2′*S*,2*R*)-**14** in ca. 40% yield after 3 days at 5 °C (the remaining was almost only unreacted epoxide, Scheme 7, step b).[32,33] Under the same conditions, the reaction of *R*-**15** with **16** also efficiently afforded (2′*R*,2*R*)-**14** (Scheme 6, step b). Further reason of this success is that both potassium *tert*-butoxide and *tert*-butanol, which is generated are not sufficiently nucleophilic by themselves to open the epoxide. It is noteworthy that for this 1:1 mixture, many carbons were clearly distinguished by ^{13}C NMR and even several protons by ^{1}H NMR (Scheme 8). Using the same reaction conditions as previously, the secondary alcohol was methylated affording a 1:1 mixture of (2′*R*,2*R*)-**24** and (2′*S*,2*R*)-**24** (Scheme 7, step c), which upon acetonide cleavage gave a 1:1 mixture of (2′*R*,2*S*)-**13** and (2′*S*,2*S*)-**13** (Scheme 7, step d). In the same manner for these two products, the two diastereoisomers were easily distinguishable by ^{1}H and ^{13}C NMR. That confirmed the diastereoisomeric purity of (2′*R*,2*R*)-**14**, (2′*R*,2*R*)-**24**, and (2′*R*,2*S*)-**13**, which have been previously obtained within of course the limit of detection of high field NMR (ca. 1–2%).

At this point, it also came in mind to assess the optical purity of diol *S*-**19**, which is normally a by-product of the HKR process. The intended solution was to convert it stereospecifically to epoxide *R*-**15** or *S*-**15** followed by reaction with 2,3-isopropylidene-*sn*-glycerol **16** in order to get **14** whose diastereoisomeric purity would reveal the enantiomeric purity of the epoxide **15** and hence that of the



Scheme 8. Comparison of zoomed ^{1}H NMR spectra for protons α to oxygen atoms of the 1:1 mixture of diastereoisomeric (2′*R*,2*R*)-**14** and (2′*S*,2*R*)-**14** (top) and (2′*S*,2*R*)-**14** (bottom, made from diol *S*-**19** and estimated to be of ca. 96% ee, vide supra).

starting diol **19**. The primary alcohol function was easily selectively protected as a benzoate using benzoyl cyanide and a catalytic amount of triethylamine in dichloromethane yielding the monobenzoate *S*-**25** in 76% yield (Scheme 9). The remaining secondary alcohol function was activated by mesylation under classic conditions affording mesylate *S*-**26** in 97% yield. Treating *S*-**26** by potassium *tert*-butoxide in methanol cleaved the benzoate moiety leaving an intermediate potassium alkoxide, which displaced the nucleofugal mesylate with complete inversion of configuration affording epoxide *R*-**15** in 98% yield. Polarimetry confirmed the *R* configuration of *R*-**15**, which was obtained by this process as it was dextrorotatory like *R*-**15** from HKR. In particular, it afforded an optical rotation of +9.2 in toluene compared with +8.9 for the epoxide from HKR.[34] For a real assessment of its optical purity, it was reacted with 2,3-isopropylidene-*sn*-glycerol **16** in the presence of potassium *tert*-butoxide in anhydrous DMF. The alcohol (2′*R*,2*R*)-**14**, which was obtained contained a difficultly detectable amount of ca. 2% (2′*S*,2*R*)-**14** (estimated by integration of protons at 3.31 and 3.33 ppm), which afforded ca. 96% ee for epoxide *R*-**15** and starting diol *S*-**19**.



Scheme 9. Conversion of HKR by-product, diol *S*-**19** into epoxide *R*-**15**. Reagents and conditions: (a) PhCOCN (1.25 equiv), Et_3N (0.4 equiv), CH_2Cl_2, 0 °C, 40 min, 76%; (b) MsCl (1.9 equiv), Et_3N (2.5 equiv), CH_2Cl_2, −40 °C to −10 °C, 55 min, 97%; (c) KO*t*-Bu (1.96 equiv), MeOH, ca. 20 °C, 40 min, 98%.

It is worth of note that by this easily performed three-step sequence, the diol of HKR process could be efficiently converted to epoxide with the same configuration of the one, which is at first produced and also with a good optical purity. The diol, which has been otherwise regarded as a useless by-product is then valorised. Additionally, it almost doubles the amount of optically active epoxide, which is obtained by HKR.

3. Conclusion

In summary, we developed a synthesis of a new unsaturated methyl glyceryl ether, analog of known antitumor derivatives in seven steps from oleic acid. A key intermediate was an unsaturated fatty alkyl epoxide, which was suitably synthesized using Matteson's method and efficiently resolved through HKR process. Another critical step was the nucleophilic opening of this epoxide by 2,3-isopropylidene-*sn*-glycerol. Potassium *tert*-butoxide was showed to be a useful reagent for this reaction with excellent chemoselectivity (primary alcohol of the reactant versus secondary alcohol of the product) being observed in DMF. By an easy and efficient three-step sequence, the diol of an HKR process could be converted to the epoxide with the same configuration than the resolved one. That both valorise the diol and almost double the amount of optically active epoxide, which was obtained by HKR.

4. Experimental

4.1. General

Moisture sensitive reactions were performed under nitrogen. Anhydrous THF and diethyl ether were obtained by percolating through a column of a drying resin or by distilling over Na/benzophenone. Anhydrous DMF over molecular sieves was used as commercially supplied (Acros). Room temperature (rt) means a temperature generally in the interval 15–20 °C. Basic alumina, which was used for column chromatographies was purchased from Fluka. TLC plates were visualized by UV inspection followed by staining with an acidic ethanolic solution of *p*-anisaldehyde or with a solution of phosphomolybdic acid (5 g in 100 mL 95% ethanol). IR spectra were measured as films between KBr plates for liquids or as KBr disks for solids on a Thermo Nicolet Avatar 250 FTIR spectrometer. ^1H NMR spectra (400.13 and 300.13 MHz) and ^{13}C NMR spectra (100.61 and 75.47 MHz) were recorded on Avance 400 and 300 Bruker spectrometers using TMS as an internal standard. Optical rotations were measured using a Perkin Elmer 341 polarimeter (concentration in g/100 mL). High-resolution mass spectra were recorded using a MicrO-Tof-Q II spectrometer under electrospray using methanol as solvent. Microanalyses were performed with a CHNS analyzer. 2,3-Isopropylidene-*sn*-glycerol **16** (≥95% pure) was purchased from Alfa Aesar.

4.2. Synthesis of oleyl alcohol

In a flamed-dried three-necked flask were introduced oleic acid (20 g, 99% pure, 70.1 mmol) and anhydrous THF (175 mL). Under N_2, this solution was cooled to ca. 10 °C by an ice/water bath and a ca. 3.4 M solution of Red-Al in toluene (35 mL, 1.7 equiv) was added dropwise in ca. 80 min (using a syringe pump or manually if necessary when the Red-Al is too viscous). Escape of hydrogen was noticed when adding the first 0.5 equiv of Red-Al. The resulting white suspension was left under moderate stirring. The progress of the reduction was easy to follow with the gradual disappearance of the white precipitate of carboxylate. The reduction was finished when the reaction mixture became clear: after at least 4 h. It was observed that the reaction time was longer when aged Red-Al was used but the reaction was always complete after overnight. The reaction was cooled by an ice/water bath and petroleum ether (210 mL) was added. When the temperature had dropped to ca. 8 °C, distilled water (ca. 0.5 mL) was added dropwise with caution to destroy excess Red-Al (vigorous escape of hydrogen). A 10% aqueous solution of citric acid was added (175 mL). Stirring at rt was continued until the upper phase (organic), which was initially turbid became clear (in ca. 30 min). The aqueous phase was extracted with petroleum ether (4×100 mL). Combined organic phases were dried (Na_2SO_4) and concentrated. To remove all solvents (including toluene and 2-methoxyethanol arising from Red-Al) with efficiency, the crude oily product was solidified by standing in a freezer. Then, it was put under high vacuum while slowly warming up (thermal isolation). These operations were repeated until boiling was no longer observed on the product during melting. The crude product (19.07 g) was sufficiently pure oleyl alcohol for the next reaction. Reaction on a smaller scale followed by purified

by chromatography on a column of silica gel afforded purified oleyl alcohol in 97% yield. R_f 0.30 (petroleum ether/acetone 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.40–5.30 (m, 2H, C*H*=C*H*), 3.64 (t, J=6.7 Hz, 2H, CH_2OH), 2.08–1.96 (m, 4H, CH_2CH=$CHCH_2$), 1.56 (tt, J=7.2, 6.7 Hz, 2H, CH_2CH_2OH), 1.51–1.41 (br s, 1H, O*H*), 1.40–1.21 (m, 22H, $CH_3(CH_2)_6CH_2CH$=$CHCH_2(CH_2)_5CH_2CH_2OH$), 0.88 (pseudo t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=129.97 and 129.83 (*C*H=*C*H), 63.07 (CH_2OH), 32.80 (CH_2), 31.92 (CH_2), 29.78 (CH_2), 29.76 (CH_2), 29.54 (CH_2), 29.52 (CH_2), 29.43 (CH_2), 29.34 (2 CH_2), 29.25 (CH_2), 27.22 (CH_2), 27.20 (CH_2), 25.75 (CH_2), 22.70 (CH_2), 14.14 (CH_3).

4.3. Synthesis of oleyl aldehyde 17

Pyridinium chlorochromate (485 mg, 1 mmol, 1.5 equiv) was suspended in CH_2Cl_2 (3 mL) by stirring for 1 min. A solution of oleyl alcohol (268.5 mg, 1 mmol) in CH_2Cl_2 (1 mL) was added rapidly. Transfer was completed by CH_2Cl_2 (2×0.5 mL). After 1 h stirring at rt under N_2, *tert*-butyl methyl ether (10 mL) was added. The resulting mixture was filtered over a short plug of silica gel with rinsing of the silica gel by *tert*-butyl methyl ether. Concentration of the filtrate and chromatography on silica gel afforded oleyl aldehyde as a colorless oil (201 mg, 75%). R_f 0.60 (petroleum ether/acetone 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.76 (t, J=1.9 Hz, 1H, C*H*O), 5.40–5.29 (m, 2H, C*H*=C*H*), 2.42 (ddd, J=7.4, 7.3, 1.9 Hz, 2H, CH_2CHO), 2.08–1.94 (m, 4H, CH_2CH=$CHCH_2$), 1.69–1.57 (m, 2H, CH_2CH_2CHO), 1.39–1.19 (m, 20H, $CH_3(CH_2)_6CH_2CH$=$CHCH_2(CH_2)_4CH_2CH_2CHO$), 0.88 (pseudo t, J=6.9 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.92 (*C*HO), 130.06 and 129.71 (*C*H=*C*H), 43.92 (CH_2), 31.92 (CH_2), 29.78 (CH_2), 29.68 (CH_2), 29.53 (CH_2), 29.34 (CH_2), 29.33 (CH_2), 29.26 (CH_2), 29.15 (CH_2), 29.06 (CH_2), 27.23 (CH_2), 27.16 (CH_2), 22.69 (CH_2), 22.09 (CH_2), 14.12 (CH_3).

4.4. Synthesis of (*Z*)-1-iodononadec-10-en-2-ol 18

To freshly scraped samarium powder (using a lime and a samarium ingot) (150 mg, 1 mmol, 2 equiv), was added via syringe in 10 min under stirring at 0 °C, a solution of **17** (133.2 mg, 0.5 mmol), diiodomethane (401.5 mg, 1.5 mmol, 3 equiv) in anhydrous THF (3 mL). The gray samarium was consumed to leave a brown mixture in 20 min. An aqueous solution of citric acid (500 mg in 4 mL) followed by 1 N HCl was added. Extraction with ethyl acetate, washing with aqueous sodium thiosulfate, drying over Na_2SO_4, concentration, and chromatography on silica gel (0→0.5% acetone in petroleum ether) afforded iodohydrin **18** as a colorless oil (87 mg, 43%). R_f 0.24 (petroleum ether/acetone 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.40–5.29 (m, 2H, C*H*=C*H*), 3.51 (br ddddd, J=6.8, 6.1, 6.1, 5.3, 3.5 Hz, 1H, C*H*OH), 3.39 (dd, J=10.1, 3.5 Hz, 1H, CH_2I), 3.23 (dd, J=10.1, 6.8 Hz, 1H, CH_2I), 2.07–1.97 (m, 4H, CH_2CH=$CHCH_2$), 1.94 (br d, J=5.3 Hz, 1H, O*H*), 1.57–1.51 (m, 2H, CH_2CHOH), 1.40–1.19 (m, 22H, $CH_3(CH_2)_6CH_2CH$=$CHCH_2(CH_2)_5$), 0.88 (pseudo t, J=6.9 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=130.00 and 129.77 (*C*H=*C*H), 70.99 (*C*H), 36.61 (CH_2), 31.91 (CH_2), 29.77 (CH_2), 29.72 (CH_2), 29.53 (CH_2), 29.43 (CH_2), 29.40 (CH_2), 29.33 (2 CH_2), 29.19 (CH_2), 27.22 (CH_2), 27.18 (CH_2), 25.68 (CH_2), 22.70 (CH_2), 16.87 (CH_2I), 14.14 (CH_3).

4.5. Synthesis of (*Z*)-2-(heptadec-8-en-1-yl)oxirane *rac*-15

4.5.1. Using ***18****.* Potassium carbonate (42 mg, 0.303 mmol, 1.4 equiv) was added to a solution of iodohydrin **18** (88.4 mg, 0.216 mmol) in methanol (1.73 mL). After 10 min vigorous stirring, 15% aqueous NaCl (3.2 mL) was added. Extraction with petroleum ether, drying (Na_2SO_4), concentration, and chromatography on silica gel afforded epoxide *rac*-**15** as a colorless oil, which solidified in the cold (23.8 mg, 39%). R_f 0.63 (petroleum ether/acetone 19:1).

4.5.2. Using Matteson's method. A solution of chloroiodomethane (353 mg, 2 mmol, 2 equiv) and oleyl aldehyde **17** (266.5 mg, 1 mmol) in anhydrous THF (4 mL) was cooled to −80 °C. Methyllithium lithium bromide complex (2.2 M) in diethylether (0.7 mL, 1.5 equiv) was added dropwise. The mixture was allowed to warm to rt and left 17 h at rt. Brine was added and epoxide *rac*-**15** (colorless oil, 177 mg, 63%) was purified by chromatography on basic alumina (2.5 g, 0→0.2% acetone in petroleum ether). Alternatively on a bigger scale (from 3 g oleyl aldehyde), the epoxide was purified by chromatography on silica gel (15 g, 0.1% triethylamine in petroleum ether). IR (film) ν_{max} 3041, 3003, 2924, 2854, 2730, 1738, 1466, 1258, 723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.40–5.29 (m, 2H, C*H*=C*H*), 2.90 (dddd, J=5.6, 5.3, 4.0, 2.7 Hz, 1H, C*H*–O), 2.75 (dd, J=5.0, 4.0 Hz, 1H, CH_2–O), 2.46 (dd, J=5.0, 2.7 Hz, 1H, CH_2–O), 2.07–1.96 (m, 4H, CH_2CH=$CHCH_2$), 1.56–1.49 (m, 2H), 1.50–1.40 (m, 2H), 1.40–1.19 (m, 20H), 0.88 (pseudo t, J=6.9 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=129.99 and 129.79 (*C*H=CH), 52.42 (*C*H–O), 47.15 (CH_2–O), 32.50 (CH_2), 31.92 (CH_2), 29.78 (CH_2), 29.73 (CH_2), 29.54 (CH_2), 29.46 (CH_2), 29.43 (CH_2), 29.33 (2 CH_2), 29.19 (CH_2), 27.22 (CH_2), 27.18 (CH_2), 25.98 (CH_2), 22.70 (CH_2), 14.13 (CH_3).

4.6. Synthesis of (*R,Z*)-2-(heptadec-8-en-1-yl)oxirane *R*-15

*4.6.1. HKR of rac-****15*** *using Jacobsen's method.* In a 10 mL flask, (*R,R*)-(−)-*N,N′*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (37.8 mg, 0.062 mmol, 0.01 equiv) and toluene (0.37 mL) were introduced followed by acetic acid (7.5 μL, 0.13 mmol, 0.02 equiv). The mixture was stirred upon air exposure for 1 h. It was concentrated and put under high vacuum to remove toluene and acetic acid. The remaining brown oil was redissolved in anhydrous diethyl ether (1.85 mL) and added to *rac*-**15** (1.751 g, 6.24 mmol) followed by distilled water (62 μL, 3.44 mmol, 0.55 equiv). The flask was purged under nitrogen, stoppered, and left under stirring for 3 days at rt. L-Ascorbic acid (15 mg, 2 equiv versus catalyst) was added and stirring was continued for 1 h. Dark brown catalyst was reduced to red salen–cobalt(II) complex, which is catalytically inactive.[35,36] The mixture was taken up with ethyl acetate, dried (Na_2SO_4), and concentrated. Chromatography on silica gel (9 g) afforded epoxide *R*-**15** (830 mg, 47%, eluted by 0.1% triethylamine in petroleum ether) followed by diol *S*-**19** (781 mg, 42%, eluted by 5→10% acetone in petroleum ether).

4.6.2. Synthesis of bimetallic (salen)cobalt(II)–indium(III) complex.- In an oven-dried flask, indium trichloride (91.6 mg, 0.414 mmol) and anhydrous THF (3 mL) were introduced. Under stirring at rt, indium trichloride was partially dissolved. A sufficient small amount of distilled water (ca. 0.006 mL) was added to dissolve completely and rapidly indium trichloride. (*R,R*)-(−)-*N,N′*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (500 mg, 0.828 mmol) was added in three portions. A fast change of color was observed (from red to dark olive green and then to brown). The bimetallic complex precipitated. After 1 h good stirring at rt with the flask left open in air, the resulting mixture was transferred to a separating funnel by means of dichloromethane. Water was added and the separating funnel was vigorously shaked. After this washing with water, the color changed from brown to dark olive green, which are the respective colors of the bimetallic complex in THF and in dichloromethane. The organic phase was withdrawn and rapidly filtered over a short plug of silica gel (height: about 2 cm) with rinsing of the silica gel by dichloromethane. The filtrate was concentrated and the remaining very fine olive green crystalline powder

was put under vacuum to afford bimetallic (salen)cobalt(II)–indium(III) 2:1 complex (0.5413 g, 92%).

*4.6.3. HKR of rac-**15** using a bimetallic (salen)cobalt(II)–indium(III) complex.* To a stirred mixture of *rac*-**15** (3.847 g, 16 mmol) and bimetallic (salen)cobalt(II)–indium(III) complex (68.6 mg, 0.048 mmol, 0.003 equiv) in anhydrous THF (8 mL), distilled water (159 μL, 8.8 mmol, 0.55 equiv) was added. The flask was purged under nitrogen, stoppered, and left under stirring for 24 h at 25 °C. L-Ascorbic acid (40 mg) was added and stirring was continued for 1 h (ascorbic acid presumably complexed $InCl_3$ of the bimetallic catalyst converting it to the red salen–cobalt(II) complex).[37] After concentration of the resulting suspension (crystalline diol precipitated), chromatography on silica gel (13 g) afforded epoxide *R*-**15** (1.9247 g, 50%) followed by diol *S*-**19** (1.965 g, 48%). After elution of epoxide and before that of diol, elution with 1% and 2% acetone in pentane afforded a small amount (19.2 mg) of a by-product, which was identified as a chlorohydrin, (*Z*)-1-chlorononadec-10-en-2-ol arising by opening of the epoxide by the chloride ions of the bimetallic catalyst.

Physical data for *R*-**15**: ^{1}H and ^{13}C NMR were identical to those of *rac*-**15**. $[\alpha]_D^{20}$ +8.9, $[\alpha]_{578}^{20}$ +9.2, $[\alpha]_{546}^{20}$ +10.4, $[\alpha]_{436}^{20}$ +16.3, $[\alpha]_{365}^{20}$ +22.3 (*c* 4.00, toluene).

4.6.3.1. Data of the chlorohydrin by-product, (Z)-1-chlorononadec-10-en-2-ol. R_f 0.39 (petroleum ether/acetone 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.42–5.28 (m, 2H, C*H*=C*H*), 3.87–3.74 (envelope, which centered at 3.80 ppm, 1H, C*H*OH), 3.64 (dd, *J*=11.1, 3.2 Hz, 1H, CH_2Cl), 3.48 (dd, *J*=11.1, 7.2 Hz, 1H, CH_2Cl), 2.25–2.08 (very br d, which centered at 2.14 ppm, *J*=2.1 Hz, 1H, O*H*), 2.08–1.92 (m, 4H, CH_2CH=CHCH_2), 1.60–1.17 (m, 24H), 0.88 (pseudo t, *J*=6.7 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=130.01 (*C*H=CH), 129.78 (CH=*C*H), 71.46 (*C*HOH), 50.62 (*C*H_2Cl), 34.23 (*C*H_2), 31.92 (*C*H_2), 29.78 (*C*H_2), 29.73 (*C*H_2), 29.53 (*C*H_2), 29.48 (*C*H_2), 29.40 (*C*H_2), 29.33 (2 *C*H_2), 29.20 (*C*H_2), 27.23 (*C*H_2), 27.18 (*C*H_2), 25.53 (*C*H_2), 22.70 (*C*H_2), 14.13 (*C*H_3).

4.7. Synthesis of (*S*,*Z*)-nonadec-10-ene-1,2-diol *S*-19

White crystals. Mp: 44 °C (petroleum ether). R_f 0.05 (petroleum ether/acetone 19:1). IR (KBr) ν_{max} 3382 (br, O–H), 2998, 2955, 2924, 2918, 2849, 1468, 1081, 865, 721 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.41–5.29 (m, 2H, C*H*=C*H*), 3.74–3.67 (well resolved m after exchange with D_2O, 1H, C*H*OH), 3.65 (dd after exchange with D_2O, *J*=11.0, 3.0 Hz, 1H, CH_2OH), 3.42 (dd after exchange with D_2O, *J*=11.0, 7.7 Hz, 1H, CH_2OH), 2.07–1.96 (m, 4H, H–C$_9$, 12), 2.18 (br s, 1H, O*H*), 2.09 (br s, 1H, O*H*), 1.51–1.38 (m, 3H, H–C$_3$ and 1H of H–C$_4$), 1.39–1.19 (m, 21H, H–C5,6,7,12,13,14,15,16,17,18 and 1H of H–C$_4$), 0.88 (pseudo t, *J*=6.9 Hz, 3H, H–C$_{19}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ=129.99 and 129.80 (*C*H=*C*H), 72.33 (*C*H), 66.86 (*C*H_2), 33.21 (*C*H_2), 31.92 (*C*H_2), 29.78 (*C*H_2), 29.75 (*C*H_2), 29.62 (*C*H_2), 29.53 (*C*H_2), 29.45 (*C*H_2), 29.33 (2 *C*H_2), 29.23 (*C*H_2), 27.23 (*C*H_2), 27.19 (*C*H_2), 25.55 (*C*H_2), 22.69 (*C*H_2), 14.13 (*C*H_3). $[\alpha]_D^{23}$ −1.0, $[\alpha]_{578}^{23}$ −1.3, $[\alpha]_{546}^{23}$ −3.4, $[\alpha]_{436}^{23}$ −4.9 (*c* 1.50, CH_2Cl_2). $[\alpha]_D^{23}$ −5.9, $[\alpha]_{578}^{23}$ −6.6, $[\alpha]_{546}^{23}$ −7.4, $[\alpha]_{436}^{23}$ −12.2, $[\alpha]_{365}^{23}$ −17.7 (*c* 3.00, acetone). $[\alpha]_D^{22.5}$ −7.1, $[\alpha]_{578}^{22.5}$ −8.2, $[\alpha]_{546}^{22.5}$ −9.2, $[\alpha]_{436}^{22.5}$ −14.8, $[\alpha]_{365}^{22.5}$ −21.0 (*c* 1.00, acetone). Anal. Calcd for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83. Found: C, 76.17; H, 12.81.

4.8. Synthesis of (*Z*)-(2′*R*)-1-*O*-(2′-hydroxynonadec-10′-enyl)-2,3-*O*-isopropylidene-*sn*-glycerol (2′*R*,2*R*)-14

4.8.1. Using sodium hydride. A 60% dispersion of sodium hydride in mineral oil (210 mg, 5.2 mmol, 5 equiv) was washed three times with petroleum ether under argon. Anhydrous DMF (4.85 mL) was added and the mixture was cooled at 0 °C. A solution of 2,3-isopropylidene-*sn*-glycerol **16** (211 mg, 1.55 mmol, 1.5 equiv) in DMF (0.33 mL) was added dropwise followed by DMF (2×0.2 mL) to complete the transfer of **16**. After 10 min stirring at 0 °C, a solution of epoxide *R*-**15** (290 mg, 1.033 mmol) in DMF (0.4 mL) was added to the resulting white suspension. Transfer of *R*-**15** was completed by rinsing with DMF (2×0.2 mL). This mixture was left under good stirring at 30 °C for 48 h. It was diluted with distilled water (5 mL) and extracted with petroleum ether/ethyl acetate 4:1. After drying (Na_2SO_4) and concentration, chromatography on basic alumina (twice 3 g, 0→5% acetone in petroleum ether) afforded the oily acetonide (2′*R*,2*R*)-**14** (148 mg, 35%). R_f 0.35 (petroleum ether/acetone 9:1). IR (film) ν_{max} 3458, 2925, 2854, 1466, 1458, 1379, 1370, 1257, 1214, 1098, 1057, 845, 723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.40–5.29 (m, 2H, C*H*=C*H*), 4.28 (dddd, *J*=6.5, 6.4, 5.5, 5.2 Hz, 1H), 4.06 (dd, *J*=8.3, 6.5 Hz, 1H), 3.83–3.75 (m, 1H), 3.74 (dd, *J*=8.3, 6.4 Hz, 1H), 3.56 (d, *J*=5.4 Hz, 2H), 3.53 (dd, *J*=9.7, 3.0 Hz, 1H), 3.33 (dd, *J*=9.7, 8.1 Hz, 1H), 2.8–2.0 (br envelope, 1H, OH), 2.06–1.97 (m, 4H), 1.51–1.38 (m, 2H), 1.43 (q, *J*=0.4 Hz, 3H, CH_3), 1.37 (q, *J*=0.4 Hz, 3H, CH_3), 1.38–1.19 (m, 22H), 0.88 (pseudo t, *J*=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=129.96 and 129.83 (*C*H=*C*H), 109.51 (*C*Me_2), 76.20 (*C*H_2), 74.72 (*C*H–O), 72.25 (*C*H_2), 70.32 (*C*HOH), 66.57 (*C*H_2), 33.02 (*C*H_2), 31.92 (*C*H_2), 29.78 (*C*H_2), 29.76 (*C*H_2), 29.66 (*C*H_2), 29.53 (*C*H_2), 29.47 (*C*H_2), 29.33 (2 *C*H_2), 29.25 (*C*H_2), 27.22 (*C*H_2), 27.20 (*C*H_2), 26.73 (C–*C*H_3), 25.52 (*C*H_2), 25.38 (C–*C*H_3), 22.69 (*C*H_2), 14.13 (*C*H_3). $[\alpha]_D^{20}$ −8.9, $[\alpha]_{578}^{20}$ −9.4, $[\alpha]_{546}^{20}$ −10.7, $[\alpha]_{436}^{20}$ −18.5 (*c* 3.03, $CHCl_3$). $[\alpha]_D^{20}$ −7.5, $[\alpha]_{578}^{20}$ −8.9, $[\alpha]_{546}^{20}$ −9.9, $[\alpha]_{436}^{20}$ −16.2 (*c* 1.40, acetone). HRMS (ESI) calcd for $C_{25}H_{48}O_4Na$ $[M+Na]^+$ 435.3448, found 435.3449.

4.8.2. Using potassium tert-butoxide. In a flame-dried 25 mL two-necked flask, potassium *tert*-butoxide (405 mg, 3.54 mmol, 2.21 equiv) was mostly dissolved in anhydrous DMF (3.2 mL) by stirring under nitrogen for 5–10 min at rt. After cooling down to 0 °C by an ice bath, 2,3-isopropylidene-*sn*-glycerol **16** (341.5 mg, ≥95% pure, 2.45 mmol, 1.53 equiv) was added dropwise followed by rinsing with anhydrous DMF (2×0.32 mL) to complete the transfer of **16**. A solution of epoxide *R*-**15** (449 mg, 1.6 mmol) in anhydrous DMF (0.5 mL) was then added dropwise. Transfer of *R*-**15** was completed by rinsing with anhydrous DMF (2×0.4 mL). The two necks of the reaction flask were well stoppered and this one was left aside in a refrigerator at 5 °C for 3 days. It was diluted with distilled water plus little brine and extracted with pentane plus ethyl acetate. Organic extracts were washed with little water and dried (Na_2SO_4). After concentration, the residue was put at the pump and chromatographied on florisil (60–100 mesh, 6 g). Epoxide *R*-**15** was eluted by 0→1% acetone in pentane (110.5 mg, 25%). Then, elution by 2→5% acetone in pentane afforded alcohol (2′*R*,2*R*)-**14** as a colorless oil (264 mg, 40%), which solidified to give a white crystallized solid on storage in a freezer. Mp: −0.5 °C. It contained a small amount of less polar by-product **23**, which had not been possible to separate by chromatography on florisil. On the contrary, it had been possible to separate the by-product **23** (identical with the by-product of another reaction which is showed in Scheme 5) by chromatography on basic alumina (8 g) and to quantify it (9.5 mg, 2%). However, use of florisil was preferred as some loss of (2′*R*,2*R*)-**14** was suspected after chromatography on basic alumina.

*4.8.2.1. Data of by-product **23**.* R_f 0.38 (pentane/acetone 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.42–5.26 (m, 4H, C*H*=C*H*), 4.26 (dddd, *J*=6.4, 6.2, 5.6, 5.6 Hz, 1H), 4.06 (dd, *J*=8.3, 6.4 Hz, 1H), 3.75 (dd, *J*=8.3, 6.2 Hz, 1H), 3.85–3.65 (m, 1H, C*H*OH), 3.62–3.43 (m, 6H), 3.35 (dd, *J*=10.2, 7.7 Hz, 1H), 3.05–2.72 (br envelope, which topped at 2.90 ppm [appeared in another sample as a br d at 2.88 ppm with *J*=3.0 Hz], 1H, O*H*), 2.10–1.94 (m, 8H), 1.42 (q, *J*=0.6 Hz, 3H, CH_3), 1.36 (q, *J*=0.6 Hz, 3H, CH_3), 1.54–1.17 (m, 48H), 0.88 (pseudo t,

J=6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=129.99 (1*C*H), 129.94 (1*C*H), 129.85 (1*C*H), 129.80 (1*C*H), 109.42 (1*C*Me$_2$), 78.99 (1*C*H), 74.56 (1*C*H), 74.47 (1*C*H$_2$), 74.43 (1*C*H$_2$), 72.31 (1*C*H$_2$), 70.19 (1*C*H), 66.79 (1*C*H$_2$), 33.01 (1*C*H$_2$), 31.93 (1*C*H$_2$), 31.92 (2*C*H$_2$), 29.78 (3*C*H$_2$), 29.76 (2*C*H$_2$), 29.73 (1*C*H$_2$), 29.54 (2*C*H$_2$), 29.52 (1*C*H$_2$), 29.48 (1*C*H$_2$), 29.33 (4*C*H$_2$), 29.30 (1*C*H$_2$), 29.26 (1*C*H$_2$), 27.22 (3*C*H$_2$), 27.20 (1*C*H$_2$), 26.77 (C–*C*H$_3$), 25.71 (1*C*H$_2$), 25.54 (1*C*H$_2$), 25.37 (C–*C*H$_3$), 22.69 (2*C*H$_2$), 14.13 (2*C*H$_3$).

4.9. Synthesis of (*Z*)-(2′*R*)-1-*O*-(2′-methoxynonadec-10′-enyl)-2,3-*O*-isopropylidene-*sn*-glycerol (2′*R*,2*R*)-24

To alcohol **14** (219.0 mg, 0.53 mmol) was added tetra-*n*-butylammonium bromide (94 mg, 0.292 mmol, 0.55 equiv) and DMSO (0.85 mL) followed after stirring by finely and freshly grounded potassium hydroxide (210 mg, 3.18 mmol, 6 equiv, ~85% KOH) and iodomethane (165 μL, 2.65 mmol, 5 equiv). The flask was purged under nitrogen and stoppered. It was dipped in an ultrasonic bath while rotating by hand in order to finely divide potassium hydroxide, which required 1–2 min. It was wrapped with an aluminum foil for protection against light and left under stirring for 21 h at rt (ca. 20 °C). Distilled water was added and a little bit of sodium thiosulfate. The resulting mixture was extracted four times with pentane/ethyl acetate ca. 4:1 and each organic extract was washed with a little bit of water. Drying (Na_2SO_4), concentration, and chromatography on basic alumina (5 g, pentane+0.5% Et_3N and then pentane+1% acetone) afforded methyl ether (2′*R*,2*R*)-**24** as a colorless oil (197.1 mg, 87%). R_f 0.62 (pentane/acetone 9:1). IR (film) ν_{max} 3004, 2925, 2855, 1466, 1458, 1379, 1370, 1256, 1214, 1098, 847, 723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.40–5.30 (m, 2H, C*H*=C*H*), 4.27 (dddd, J=6.4, 6.3, 5.6, 5.5 Hz, 1H), 4.06 (dd, J=8.3, 6.4 Hz, 1H), 3.76 (dd, J=8.3, 6.3 Hz, 1H), 3.57 (dd, J=10.0, 5.4 Hz, 1H), 3.52 (dd, J=10.3, 5.9 Hz, 1H), 3.49 (dd, J=10.0, 5.8 Hz, 1H), 3.48 (dd, J=10.3, 4.2 Hz, 1H), 3.40 (s, 3H), 3.31 (dddd, J=6.1, 5.9, 5.9, 4.2 Hz, 1H), 2.05–1.97 (m, 4H), 1.51–1.44 (m, 2H), 1.42 (q, J=0.6 Hz, 3H, C*H*$_3$), 1.36 (q, J=0.6 Hz, 3H, C*H*$_3$), 1.40–1.20 (m, 22H), 0.88 (pseudo t, J=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=129.96 and 129.84 (*C*H=*C*H), 109.35 (*C*Me$_2$), 80.19 (*C*H), 74.69 (*C*H–O), 73.83 (*C*H$_2$), 72.38 (*C*H$_2$), 66.88 (*C*H$_2$), 57.60 (*C*H$_3$), 31.92 (*C*H$_2$), 31.42 (*C*H$_2$), 29.78 (2 *C*H$_2$), 29.77 (*C*H$_2$), 29.53 (*C*H$_2$), 29.50 (*C*H$_2$), 29.33 (2 *C*H$_2$), 29.27 (*C*H$_2$), 27.23 (*C*H$_2$), 27.21 (*C*H$_2$), 26.78 (C–*C*H$_3$), 25.43 (C–*C*H$_3$), 25.36 (*C*H$_2$), 22.69 (*C*H$_2$), 14.12 (*C*H$_3$). $[\alpha]_D^{22}$ −6.8; $[\alpha]_{578}^{20}$ −7.2; $[\alpha]_{546}^{20}$ −8.2; $[\alpha]_{436}^{20}$ −14.6; $[\alpha]_{365}^{20}$ −23.7 (*c* 1.10, $CHCl_3$). $[\alpha]_D^{20}$ −5.8; $[\alpha]_{578}^{20}$ −7.3; $[\alpha]_{546}^{20}$ −13.2; $[\alpha]_{436}^{20}$ −21.2 (*c* 0.86, acetone). HRMS (ESI) calcd for $C_{26}H_{50}O_4Na$ [M+Na]$^+$ 449.36013, found 449.3601.

4.10. Synthesis of (*Z*)-(2′*R*)-1-*O*-(2′-methoxynonadec-10′-enyl)-*sn*-glycerol (2′*R*,2*S*)-13

To acetonide (2′*R*,2*R*)-**24** (128 mg, 0.3 mmol) and methanol (1.5 mL) were added *p*-toluenesulfonic acid monohydrate (4 mg, 0.02 mmol, 0.07 equiv) and distilled water (0.15 mL). The flask was purged under nitrogen, stoppered, and dipped in a preheated bath at 60 °C. After 5 h at 60 °C, sodium bicarbonate (6 mg, 0.071 mmol, 0.24 equiv) was added and stirring was continued for 1 h at 60 °C. Methanol and water were removed by concentration using a rotary evaporator using sufficiently high vacuum. Chromatography of the residue on basic alumina (3.15 g) first eluting impurities with 0→4% acetone in pentane and then with pentane/acetone 4:1 afforded alkylglycerol (2′*R*,2*S*)-**13** (93 mg, 80%) as a colorless oil, which solidified giving a white solid after overnight storage in a freezer. Mp: 21.5–23 °C. R_f 0.09 (petroleum ether/acetone 9:1). IR (film) ν_{max} 3402, 2956, 2925, 2854, 1466, 1457, 1378, 1364, 1135, 1118, 852, 722 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.40–5.30 (m, 2H, C*H*=C*H*), 3.86 (dddd after exchange with D_2O, m centered at 3.87 ppm before exchange with D_2O, J=6.3, 5.2, 3.9, 3.8 Hz, 1H), 3.70 (dd after exchange with D_2O, br dd at 3.71 ppm before exchange with D_2O, J=11.5, 3.9 Hz, 1H), 3.63 (dd after exchange with D_2O, 3.64 ppm before exchange with D_2O, J=11.5, 5.2 Hz, 1H), 3.61 (dd, J=10.2, 3.8 Hz, 1H), 3.57 (dd, J=10.5, 3.5 Hz, 1H), 3.54 (dd, J=10.2, 6.2 Hz, 1H), 3.48 (dd, J=10.5, 6.0 Hz, 1H), 3.40 (s, 3H), 3.33 (dddd, J=6.2, 6.1, 6.0, 3.5 Hz, 1H), 3.05 (envelope from 3.21 to 2.82 ppm, 1H, CHO*H*), 2.36 (envelope from 2.53 to 2.22 ppm, 1H, CH$_2$O*H*), 2.09–1.94 (m, 4H), 1.58–1.40 (m, 2H), 1.40–1.19 (m, 22H), 0.88 (pseudo t, J=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=129.99 and 129.81 (*C*H=*C*H), 80.37 (*C*H), 73.62 (*C*H$_2$), 73.40 (*C*H$_2$), 70.58 (*C*H), 64.07 (*C*H$_2$), 57.36 (*C*H$_3$), 31.92 (*C*H$_2$), 30.89 (*C*H$_2$), 29.78 (2*C*H$_2$), 29.76 (*C*H$_2$), 29.53 (*C*H$_2$), 29.49 (*C*H$_2$), 29.33 (2*C*H$_2$), 29.25 (*C*H$_2$), 27.23 (*C*H$_2$), 27.20 (*C*H$_2$), 25.35 (*C*H$_2$), 22.69 (*C*H$_2$), 14.13 (*C*H$_3$). $[\alpha]_D^{20}$ −3.2; $[\alpha]_{578}^{20}$ −3.8; $[\alpha]_{546}^{20}$ −4.2; $[\alpha]_{536}^{20}$ −6.8; $[\alpha]_{365}^{20}$ −10.4 (*c* 1.00, CH_2Cl_2). $[\alpha]_D^{20}$ +1.9; $[\alpha]_{578}^{20}$ +1.2; $[\alpha]_{546}^{20}$ +1.4; $[\alpha]_{436}^{20}$ +2.5; $[\alpha]_{365}^{20}$ +3.5 (*c* 1.00, THF). HRMS (ESI) calcd for $C_{23}H_{46}O_4Na$ [M+Na]$^+$ 409.32883, found 409.3289.

4.11. Synthesis of (*Z*)-(2′*R*)-1-*O*-(2′-hydroxynonadec-10′-enyl)-2,3-*O*-isopropylidene-*sn*-glycerol+(*Z*)-(2′*S*)-1-*O*-(2′-hydroxynonadec-10′-enyl)-2,3-*O*-isopropylidene-*sn*-glycerol (2′*R*,2*R*)-14+(2′*S*,2*R*)-14

Using the same procedure as described for the synthesis of (2′*R*,2*R*)-**14** (paragraph 4.8.2) with potassium *tert*-butoxide (2.5 equiv), 2,3-isopropylidene-*sn*-glycerol **16** (1.5 equiv), and epoxide *rac*-**15** instead of *R*-**15** in anhydrous DMF at 5 °C for 2.5 days afforded a 1:1 mixture of (2′*R*,2*R*)-**14** and (2′*S*,2*R*)-**14** (50% plus 23% recovered *rac*-**15**). R_f 0.27 (pentane/acetone 9:1). Mp: −1.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.41–5.28 (m, 2H, C*H*=C*H*), 4.298 (dddd, J=6.5, 6.4, 5.9, 4.8, Hz, 0.5H, *S*,*R*), 4.286 (dddd, J=6.5, 6.3, 5.5, 5.2, Hz, 0.5H, *R*,*R*), 4.064 (dd, J=8.3, 6.5 Hz, 0.5H, *S*,*R*), 4.059 (dd, J=8.3, 6.5 Hz, 0.5H, *R*,*R*), 3.86–3.73 (m, 1H, C*H*OH), 3.741 (dd, J=8.3, 6.4 Hz, 0.5H, *R*,*R*), 3.724 (dd, J=8.3, 6.5 Hz, 0.5H, *S*,*R*), 3.589 (dd, J=10.2, 5.9 Hz, 0.5H, *S*,*R*), 3.559 (d, J=5.4 Hz, 1H, *R*,*R*), 3.547 (dd, J=9.8, 3.0 Hz, 0.5H, *S*,*R*), 3.515 (dd, J=10.2, 4.8 Hz, 0.5H, *S*,*R*), 3.534 (dd, J=9.7, 3.0, Hz, 0.5H, *R*,*R*), 3.33 (dd, J=9.7, 8.1 Hz, 0.5H, *R*,*R*), 3.31 (dd, J=9.7, 8.2 Hz, 0.5H, *S*,*R*), 2.62–2.35 (br envelope, which topped at 2.47 ppm, 1H, O*H*), 2.10–1.94 (m, 4H), 1.436 (q, J=0.6 Hz, 1.5H, C*H*$_3$, *S*,*R*), 1.432 (q, J=0.6 Hz, 1.5H, C*H*$_3$, *R*,*R*), 1.371 (q, J=0.6 Hz, 1.5H, C*H*$_3$, *S*,*R*), 1.368 (q, J=0.6 Hz, 1.5H, C*H*$_3$, *R*,*R*), 1.52–1.19 (m, 24H), 0.88 (pseudo t, J=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=129.96 (*C*H=CH), 129.83 (CH=*C*H), 109.58 (0.5 *C*Me$_2$, *S*,*R*), 109.52 (0.5 *C*Me$_2$, *R*,*R*), 76.22 (0.5 *C*H$_2$, *S*,*R*), 76.20 (0.5 *C*H$_2$, *R*,*R*), 74.78 (0.5 *C*H–O, *S*,*R*), 74.72 (0.5 *C*H–O, *R*,*R*), 72.34 (0.5 *C*H$_2$, *S*,*R*), 72.24 (0.5 *C*H$_2$, *R*,*R*), 70.32 (0.5 *C*HOH, *R*,*R*), 70.25 (0.5 *C*HOH, *S*,*R*), 66.56 (0.5 *C*H$_2$, *R*,*R*), 66.48 (0.5 *C*H$_2$, *S*,*R*), 33.01 (0.5 *C*H$_2$, *R*,*R*), 32.93 (0.5 *C*H$_2$, *S*,*R*), 31.91 (*C*H$_2$), 29.78 (*C*H$_2$), 29.76 (*C*H$_2$), 29.66 (0.5 *C*H$_2$, *R*,*R*), 29.65 (0.5 *C*H$_2$, *S*,*R*), 29.53 (*C*H$_2$), 29.46 (*C*H$_2$), 29.33 (2 *C*H$_2$), 29.25 (*C*H$_2$), 27.22 (*C*H$_2$), 27.20 (*C*H$_2$), 26.72 (C–*C*H$_3$), 25.52 (*C*H$_2$), 25.38 (C–*C*H$_3$), 22.69 (*C*H$_2$), 14.13 (*C*H$_3$). Anal. Calcd for $C_{25}H_{48}O_4$: C, 72.77; H, 11.72. Found: C, 73.34; H, 11.70.

4.12. Synthesis of (*Z*)-(2′*R*)-1-*O*-(2′-methoxynonadec-10′-enyl)-2,3-*O*-isopropylidene-*sn*-glycerol+(*Z*)-(2′*S*)-1-*O*-(2′-methoxynonadec-10′-enyl)-2,3-*O*-isopropylidene-*sn*-glycerol (2′*R*,2*R*)-24+(2′*S*,2*R*)-24

The 1:1 mixture of (2′*R*,2*R*)-**14** and (2′*S*,2*R*)-**14** was methylated using the same procedure as described for the synthesis of (2′*R*,2*R*)-**14** (paragraph 4.9) affording a 1:1 mixture of (2′*R*,2*R*)-**24** and (2′*S*,2*R*)-**24**. R_f 0.62 (pentane/acetone 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.41–5.28 (m, 2H, C*H*=C*H*), 4.28 (dddd, J=6.4, 6.3, 5.6, 5.6 Hz, 0.5H, *S*,*R*), 4.27 (dddd, J=6.4, 6.3, 5.6, 5.5 Hz, 0.5H, *R*,*R*), 4.06 (dd, J=8.3, 6.4 Hz, 1H), 3.76 (dd, J=8.3, 6.3 Hz, 0.5H, *R*,*R*), 3.75 (dd, J=8.3, 6.3 Hz, 0.5H, *S*,*R*), 3.570 (dd, J=10.1, 5.4 Hz, 0.5H, *R*,*R*), 3.568

(dd, *J*=9.8, 5.4 Hz, 0.5H, *S*,*R*), 3.525 (dd, *J*=10.4, 5.8 Hz, 0.5H, *R*,*R*), 3.53–3.44 (m, 2.5H), 3.404 (s, 1.5H, OCH_3, *S*,*R*), 3.401 (s, 1.5H, OCH_3, *R*,*R*), 3.321 (dddd, *J*=6.0, 5.8, 5.8, 4.2 Hz, 0.5H, *S*,*R*), 3.315 (dddd, *J*=6.0, 5.9, 5.9, 4.2 Hz, 0.5H, *R*,*R*), 2.10–1.93 (m, 4H), 1.54–1.40 (m, 2H), 1.42 (br q, *J*=0.6 Hz, 3H, CH_3), 1.36 (q, *J*=0.6 Hz, 3H, CH_3), 1.40–1.20 (m, 22H), 0.88 (pseudo t, *J*=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=129.96 (*C*H=CH), 129.83 (CH=*C*H), 109.37 (0.5 *C*Me_2, *S*,*R*), 109.35 (0.5 *C*Me_2, *R*,*R*), 80.19 (0.5 *C*H–OMe, *R*,*R*), 80.15 (0.5 *C*H–OMe, *S*,*R*), 74.74 (0.5 *C*H–O, *S*,*R*), 74.69 (0.5 *C*H–O, *R*,*R*), 73.99 (0.5 *C*H_2, *S*,*R*), 73.82 (0.5 *C*H_2, *R*,*R*), 72.46 (0.5 *C*H_2, *S*,*R*), 72.37 (0.5 *C*H_2, *R*,*R*), 66.89 (0.5 *C*H_2, *S*,*R*), 66.87 (0.5 *C*H_2, *R*,*R*), 57.63 (0.5 OCH_3, *S*,*R*), 57.59 (0.5 OCH_3, *R*,*R*), 31.92 (CH_2), 31.41 (0.5 *C*H_2, *R*,*R*), 31.34 (0.5 *C*H_2, *S*,*R*), 29.78 (2 CH_2), 29.77 (CH_2), 29.54 (CH_2), 29.50 (CH_2), 29.33 (2 CH_2), 29.27 (CH_2), 27.22 (CH_2), 27.21 (CH_2), 26.782 (0.5C–CH_3, *S*,*R*), 26.774 (0.5C–CH_3, *R*,*R*), 25.43 (C–CH_3), 25.38 (0.5 *C*H_2, *S*,*R*), 25.36 (0.5 *C*H_2, *R*,*R*), 22.69 (CH_2), 14.13 (CH_3).

4.13. Synthesis of (*Z*)-(2′*R*)-1-*O*-(2′-methoxynonadec-10′-enyl)-*sn*-glycerol (2′*R*,2*S*)-13+(*Z*)-(2′*S*)-1-*O*-(2′-methoxynonadec-10′-enyl)-*sn*-glycerol (2′*S*,2*S*)-13

Using the same procedure as described for the synthesis of (2′*R*,2*S*)-**13** (paragraph 4.10) with the 1:1 mixture of (2′*R*,2*R*)-**24** and (2′*S*,2*R*)-**24** afforded a 1:1 mixture of (2′*R*,2*S*)-**13** and (2′*S*,2*S*)-**13**. ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.40–5.29 (m, 2H, C*H*=C*H*), 3.91–3.83 (m, 1H, C*H*OH), 3.708 (dd, *J*=11.4, 4.0 Hz, 0.5H), 3.705 (dd, *J*=11.4, 3.9 Hz, 0.5H), 3.67–3.45 (m, 5H), 3.400 (s, 1.5H, OCH_3, *R*,*S*), 3.398 (s, 1.5H, OCH_3, *S*,*S*), 3.324 (dddd, *J*=6.2, 6.1, 6.0, 3.5 Hz, 0.5H, C*H*OMe, *R*,*S*), 3.323 (dddd, *J*=6.1, 6.0, 5.5, 4.1 Hz, 0.5H, C*H*OMe, *S*,*S*), 3.10 (envelope from 3.27 to 2.85 ppm, 1H, CHO*H*), 2.45 (envelope from 2.70 to 2.22 ppm, 1H, CH_2O*H*), 2.09–1.95 (m, 4H), 1.57–1.41 (m, 2H), 1.40–1.20 (m, 22H), 0.88 (pseudo t, *J*=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=129.98 (*C*H=CH), 129.80 (CH=*C*H), 80.36 (0.5 *C*H–O, *R*,*S*), 80.29 (0.5 *C*H–O, *S*,*S*), 73.55 (0.5 *C*H_2, *R*,*S*), 73.39 (0.5 *C*H_2, *S*,*S*), 73.34 (0.5 *C*H_2, *R*,*S*), 73.22 (0.5 *C*H_2, *S*,*S*), 70.61 (0.5 *C*HOH, *R*,*S*), 70.51 (0.5 *C*HOH, *S*,*S*), 64.04 (0.5 *C*H_2OH, *R*,*S*), 64.01 (0.5 *C*H_2OH, *S*,*S*), 57.34 (0.5 OCH_3, *R*,*S*), 57.29 (0.5 OCH_3, *S*,*S*), 31.92 (CH_2), 30.89 (0.5 *C*H_2, *R*,*S*), 30.88 (0.5 *C*H_2, *S*,*S*), 29.78 (2CH_2), 29.76 (CH_2), 29.53 (CH_2), 29.49 (CH_2), 29.33 (2CH_2), 29.25 (CH_2), 27.23 (CH_2), 27.20 (CH_2), 25.36 (CH_2), 22.69 (CH_2), 14.13 (CH_3). $[\alpha]_D^{21}$ +2.5; $[\alpha]_{578}^{21}$ +2.5; $[\alpha]_{546}^{21}$ +2.8; $[\alpha]_{436}^{21}$ +4.4; $[\alpha]_{365}^{21}$ +6.6 (*c* 1.38, CH_2Cl_2).

4.14. Synthesis of (*S*,*Z*)-1-benzoyloxynonadec-10-en-2-ol *S*-25

A solution of diol *S*-**19** (913.1 mg, 3.06 mmol) and triethylamine (0.17 mL, 1.22 mmol, 0.4 equiv) in dichloromethane (24.5 mL) was cooled at 0 °C under nitrogen. A solution of benzoyl cyanide (528 mg, 3.82 mmol, 1.25 equiv, 95% pure) in dichloromethane (1.84 mL) was then slowly added dropwise under stirring. Transfer of PhCOCN was completed by rinsing with dichloromethane (2×0.25 mL). After 40 min reaction at 0 °C, methanol (0.155 mL) was added. After 15 additional minutes at 0 °C, distilled water (30 mL) was added and the resulting mixture was well shaken in a separating funnel. The organic phase was withdrawn and the aqueous phase was extracted twice with dichloromethane. Combined organic phases were dried (Na_2SO_4) and concentrated. The residue was subjected to a flash-chromatography on silica gel (25 g). It was transferred onto silica gel after dissolving in hot toluene (0.6 mL) followed by rinsing with pentane. First, elution with 0→2% acetone in pentane removed the dibenzoate of *S*-**19** (yellow oil, 157 mg). Then, elution with 2→10% acetone in pentane afforded a fraction containing a mixture of dibenzoate and monobenzoate followed by the monobenzoate *S*-**25** alone as a white crystallized powder (937.8 mg, 76%). Mp: 49 °C. R_f 0.35 (petroleum ether/acetone 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.09–8.02 (m, 2H, H aromatic *ortho*), 7.58 (ddt, *J*=8.2, 6.7, 1.4 Hz, 1H, H aromatic *para*), 7.49–7.41 (m, 2H, H aromatic *meta*), 5.41–5.28 (m, 2H, C*H*=C*H*), 3.99 (dddd, *J*=7.1, 6.5, 5.9, 3.1 Hz, 1H, C*H*OH), 4.40 (dd, *J*=11.4, 3.1 Hz, 1H, CH_2O), 4.23 (dd, *J*=11.4, 7.1 Hz, 1H, CH_2O), 2.28–2.0 (br envelope centered at 2.13 ppm, 1H, O*H*), 2.09–1.92 (m, 4H), 1.62–1.45 (m, 3H), 1.45–1.18 (m, 21H), 0.88 (pseudo t, *J*=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.76 (*C*O), 133.17 (*C*H aromatic *para*), 129.99 (*C*H=CH), 129.92 (*C ipso* aromatic), 129.80 (CH=*C*H), 129.67 (2 *C*H aromatic *ortho*), 128.44 (2 *C*H aromatic *meta*), 70.18 (CHOH), 69.25 (CH_2O), 33.48 (CH_2), 31.91 (CH_2), 29.78 (CH_2), 29.75 (CH_2), 29.56 (CH_2), 29.53 (CH_2), 29.45 (CH_2), 29.33 (2 CH_2), 29.23 (CH_2), 27.23 (CH_2), 27.20 (CH_2), 25.43 (CH_2), 22.69 (CH_2), 14.12 (CH_3). Anal. Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.51. Found: C, 77.69; H, 10.38. $[\alpha]_D^{22.5}$ +4.3; $[\alpha]_{578}^{22.5}$ +4.5; $[\alpha]_{546}^{22.5}$ +5.1; $[\alpha]_{436}^{22.5}$ +8.8; $[\alpha]_{365}^{22.5}$ +14.0 (*c* 1.99, CH_2Cl_2). $[\alpha]_D^{22.5}$ +4.3; $[\alpha]_{578}^{22.5}$ +4.5; $[\alpha]_{546}^{22.5}$ +5.1; $[\alpha]_{436}^{22.5}$ +8.8; $[\alpha]_{365}^{22.5}$ +14.0 (*c* 2.00, $CHCl_3$). $[\alpha]_D^{22.5}$ −1.4; $[\alpha]_{578}^{22.5}$ −1.5; $[\alpha]_{546}^{22.5}$ −1.7; $[\alpha]_{436}^{22.5}$ −2.6; $[\alpha]_{365}^{22.5}$ −3.7 (*c* 2.01, acetone) (note the identity of the optical rotation in CH_2Cl_2 and in $CHCl_3$ as well as the reversal of sign in acetone).

4.14.1. Data of the dibenzoate of S-19, (S,Z)-1,2-di(benzoyloxy)nonadec-10-ene. R_f 0.66 (petroleum ether/acetone 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.09–8.03 (m, 2H, H aromatic *ortho*), 8.03–7.97 (m, 2H, H aromatic *ortho*), 7.56 (ddt, *J*=8.1, 6.7, 1.4 Hz, 1H, H aromatic *para*), 7.54 (ddt, *J*=8.2, 6.6, 1.4 Hz, 1H, H aromatic *para*), 7.48–7.37 (m, 4H, H aromatic *meta*), 5.50 (dddd, *J*=7.4, 6.6, 5.9, 3.5 Hz, 1H, C*H*OBz), 5.40–5.26 (m, 2H, C*H*=C*H*), 4.56 (dd, *J*=11.9, 3.5 Hz, 1H, CH_2OBz), 4.47 (dd, *J*=11.9, 6.6 Hz, 1H, CH_2OBz), 2.10–1.92 (m, 4H), 1.92–1.71 (m, 2H), 1.54–1.16 (m, 22H), 0.87 (pseudo t, *J*=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.33 (*C*O), 166.13 (*C*O), 133.06 (*C*H aromatic *para*), 133.00 (*C*H aromatic *para*), 130.23 (*C ipso* aromatic), 129.98 (*C*H=CH), 129.85 (*C ipso* aromatic), 129.76 (CH=*C*H), 129.68 (4 *C*H aromatic *ortho*), 128.38 (2 *C*H aromatic *meta*), 128.37 (2 *C*H aromatic *meta*), 72.22 (CHOBz), 65.73 (CH_2OBz), 31.91 (CH_2), 30.99 (CH_2), 29.77 (CH_2), 29.71 (CH_2), 29.53 (CH_2), 29.42 (CH_2), 29.34 (CH_2), 29.32 (2 CH_2), 29.18 (CH_2), 27.22 (CH_2), 27.18 (CH_2), 25.20 (CH_2), 22.69 (CH_2), 14.12 (CH_3).

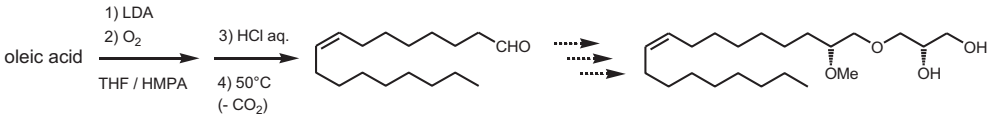
4.15. Synthesis of (*S*,*Z*)-1-benzoyloxy-2-methanesulfonyloxynonadec-10-ene *S*-26

To a cooled solution at −40 °C under nitrogen of alcohol *S*-**25** (728.6 mg, 1.81 mmol) and triethylamine (0.63 mL, 4.52 mmol, 2.5 equiv) in dichloromethane (7.25 mL, distilled over CaH_2) was added dropwise under stirring a solution of methanesulfonyl chloride (395 mg, 3.44 mmol, 1.9 equiv) in dichloromethane (1.15 mL). Transfer of MsCl was completed by rinsing with dichloromethane (2×0.15 mL). The cooling bath was allowed to warm up slowly. After 55 min, the temperature had risen to −10 °C and a TLC control showed that the reaction was complete (R_f of the mesylate=0.60 with dichloromethane versus 0.34 for the starting alcohol). Distilled water was added. After transferring into a separating funnel and shaking, the organic phase was withdrawn. The remaining aqueous phase was extracted three times with a small amount of dichloromethane. After drying over Na_2SO_4 and concentration, the remaining oily yellow residue was subjected to a chromatography on silica gel (21 g) eluting with dichloromethane. After long standing under high vacuum while repeating several cycles of crystallizing by the cold and slow melting (Dewar insulating), mesylate *S*-**26** was obtained as a slightly yellow oil (842.9 mg, 97%). R_f 0.60 (dichloromethane). Mp: 8–8.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.11–8.03 (m, 2H, H aromatic *ortho*), 7.59 (ddt, *J*=8.2, 6.6, 1.4 Hz, 1H, H aromatic *para*), 7.51–7.42 (m, 2H, H aromatic *meta*), 5.41–5.28 (m, 2H, C*H*=C*H*), 5.02 (dddd, *J*=7.2, 7.1, 5.9, 2.9 Hz, 1H, C*H*OMs), 4.54 (dd, *J*=12.4, 2.9 Hz, 1H, CH_2O), 4.39 (dd, *J*=12.4, 7.1 Hz, 1H, CH_2O), 3.03 (s, 3H, CH_3 of OMs), 2.10–1.93 (m, 4H), 1.91–1.67 (m, 2H), 1.57–1.41 (m, 2H), 1.41–1.18 (m, 20H), 0.88 (pseudo t, *J*=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$):

δ=166.14 (*C*O), 133.40 (*C*H aromatic *para*), 130.04 (*C*H=CH), 129.74 (2 *C*H aromatic *ortho*), 129.72 (CH=*C*H), 129.47 (*C ipso* aromatic), 128.56 (2 *C*H aromatic *meta*), 80.31 (*C*HOMs), 65.57 (*C*H_2O), 38.80 (*C*H_3 of OMs), 31.91 (*C*H_2), 31.74 (*C*H_2), 29.77 (*C*H_2), 29.70 (*C*H_2), 29.53 (*C*H_2), 29.33 (*C*H_2), 29.32 (*C*H_2), 29.28 (*C*H_2), 29.25 (*C*H_2), 29.17 (*C*H_2), 27.23 (*C*H_2), 27.17 (*C*H_2), 24.96 (*C*H_2), 22.69 (*C*H_2), 14.13 (*C*H_3). Anal. Calcd for $C_{27}H_{44}O_5S$: C, 67.46; H, 9.23; S, 6.67. Found: C, 67.51; H, 9.23; S, 6.33. $[\alpha]_D^{27}$ +9.8; $[\alpha]_{578}^{27}$ +9.7; $[\alpha]_{546}^{27}$ +11.2; $[\alpha]_{436}^{27}$ +19.3; $[\alpha]_{365}^{27}$ +30.6 (*c* 1.90, CH_2Cl_2). $[\alpha]_D^{18}$ +10.9; $[\alpha]_{578}^{18}$ +11.6; $[\alpha]_{546}^{18}$ +13.2; $[\alpha]_{536}^{18}$ +22.8; $[\alpha]_{365}^{18}$ +36.0 (*c* 2.02, $CHCl_3$). $[\alpha]_D^{17.5}$ +7.8; $[\alpha]_{578}^{17.5}$ +8.2; $[\alpha]_{546}^{17.5}$ +9.2; $[\alpha]_{436}^{17.5}$ +14.9; $[\alpha]_{365}^{17.5}$ +22.5 (*c* 2.01, acetone).

4.16. Synthesis of (*R*,*Z*)-2-(heptadec-8-en-1-yl)oxirane *R*-15

To a solution of mesylate *S*-**26** (718.9 mg, 1.495 mmol) in methanol (15 mL) was added under stirring potassium *tert*-butoxide (329 mg, 2.93 mmol, 1.96 equiv). This reaction mixture was left under stirring at rt. A gelatinous white precipitate rapidly appeared, which was thereafter divided in ca. 20 min. A TLC control after 30 min showed that the reaction was complete (R_f with pentane+4% acetone=0.65 for the epoxide and 0.50 for methyl benzoate, which is formed at the same time). After 40 min, distilled water was added and some brine. The resulting mixture was extracted with ethyl acetate+pentane and then three times with pentane. After drying over Na_2SO_4 and concentration, the remaining oily residue was subjected to a short column chromatography on silica gel (3.5 g) eluting with pentane+0.5% Et_3N. After collecting the fractions and concentration, methyl benzoate was removed by putting under high vacuum for 2–3 h. Epoxide *R*-**15** was obtained as a quite mobile colorless oil (410.0 mg, 98%), which solidified to give a white crystallized solid on storage in a freezer. It was estimated to have ca. 96% ee as reaction with 2,3-isopropylidene-*sn*-glycerol afforded (2′*R*,2*S*)-**13** with ca. 96% de. Mp: −10.5 °C. $[\alpha]_D^{18}$ +4.7; $[\alpha]_{578}^{18}$ +4.8; $[\alpha]_{546}^{18}$ +5.4; $[\alpha]_{536}^{18}$ +8.0; $[\alpha]_{365}^{18}$ +10.2 (*c* 2.12, $CHCl_3$). $[\alpha]_D^{18.5}$ +5.7, $[\alpha]_{578}^{18.5}$ +5.8, $[\alpha]_{546}^{18.5}$ +6.4, $[\alpha]_{436}^{18.5}$ +9.5; $[\alpha]_{365}^{18.5}$ +11.9 (*c* 2.10, acetone). $[\alpha]_D^{18}$ +9.2; $[\alpha]_{578}^{18}$ +9.4; $[\alpha]_{546}^{18}$ +10.5; $[\alpha]_{436}^{18}$ +16.6; $[\alpha]_{365}^{18}$ +23.4 (*c* 2.12, benzene). $[\alpha]_D^{18.5}$ +9.2; $[\alpha]_{578}^{18.5}$ +9.5; $[\alpha]_{546}^{18.5}$ +10.6; $[\alpha]_{436}^{18.5}$ +16.7; $[\alpha]_{365}^{18.5}$ +23.4 (*c* 2.10, toluene).



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Supplementary data

Supplementary data associated with this article including copies of ^{1}H and ^{13}C NMR (1D and some 2D) spectra can be found in the online version, at doi:10.1016/j.tet.2012.02.033. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

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20. In target (2′*R*,2*S*)-**13**, the double bond is Δ10 instead of Δ9 for oleic acid due to homologation of oleyl aldehyde to epoxide **15**. After the beginning of our study, an efficient conversion of carboxylic acids to one-carbon degraded aldehydes was reported.[21] Moreover, this method had been applied to oleic acid affording (*Z*)-heptadec-8-enal, which would replace oleyl aldehyde to give a one-carbon lower homolog of (2′*R*,2*S*)-**13** where the double bond is Δ9.
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28. However, bimetallic (salen)cobalt(II)–indium(III) complex had showed to be less enantioselective after aging by several months storage in a freezer.
29. Potassium hydroxide gave the same result with nearly identical yields.
30. KOH in aqueous DMSO is known to promote epoxide hydrolysis: Berti, G.; Macchia, B.; Macchia, F. *Tetrahedron Lett.* **1965**, *6*, 3421–3427.
31. We observed in many instances that optical rotations are very close or equal in chloroform and in dichloromethane, see the example of *S*-**25**.
32. It was observed that upon repeated use of potassium *tert*-butoxide, conversion gradually decreased to about 20% and more and more epoxide was recovered unreacted. This problem was obviously due to the highly hygroscopic character of potassium *tert*-butoxide and that absorbed moisture destroyed *t*-BuOK by DMF liberating dimethylamine. Handling *t*-BuOK in a glove-box would solve this problem.
33. Use of anhydrous NMP afforded similar results than that of anhydrous DMF. On the other hand, use of anhydrous DMSO had resulted in a better conversion but the reaction of *R*-**15** with **16** was not selective and resulted in a mixture of (2′*R*,2*R*)-**14**, **23**, and even of smaller amounts of other by-products probably resulting of subsequent reaction of the secondary hydroxy group with the epoxide. The same absence of selectivity between primary and secondary hydroxy groups was already observed for the reaction of epoxide **20** with **16** in the presence of KOH or NaOH and *n*-Bu_4NBr in DMSO. Obviously, this could be explained by the enhancement of the nucleophilic reactivity of the alcoholates
34. Optical rotation of epoxide from HKR was a little bit lower than that of epoxide, which was made from diol. That could likely be due to a trace of salen ligand arising from the decomposition of the catalyst ((*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine), which is strongly levorotatory and quite hard to remove completely from epoxide by chromatography
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37. Without adding ascorbic acid, the bimetallic catalyst decomposed during chromatography on silica gel leading to brown impurities, which were hard to remove.