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Synthesis of Both Enantiomers of Diastereomeric 4-Fluoro-4,5-Dihydroceramides

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Dedicated to Professor Dr. Gerhard Erker with best wishes on the occasion of his 60th birthday

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Two diastereomeric enantiopure 4-fluoro-4,5-dihydroceramides with the natural D-*erythro* configuration at the 2- and 3-carbon atoms have been synthesized in an enantioselective eleven-step sequence. The key step of the synthesis was a diastereoselective asymmetric Sharpless dihydroxylation of ethyl *trans*-4-fluorooctadec-2-enoate (**8**) with AD-mix-β to afford the D-*erythro* arrangement. The diastereomers of the other enantiomeric series were synthesized analogously with the use of AD-mix-α. In all cases, the nitrogen heteroatom was introduced into the 2-position by regio- and stereoselective ring opening of cyclic sulfates **13** and **14** with azide. Staudinger reduction, acylation of the intermediary formed amino group, chromatographic separation of the diastereomers and chemoselective reduction of the ester functionality with sodium borohydride in the presence of methanol afforded both title compounds in an enantiopure form.

Introduction

Besides fatty acids, triglycerides, glycophospholipids and cholesterol, sphingolipids are the most important constituents of the membranes in eukaryotic cells. Because of their amphiphilic character, these compounds are able to form double layers. As a result, they form cell walls that are about 6 nm in diameter. Moreover, sphingolipids are essential for cell-to-cell communication, cell growth and cell differentiation,[1] though the role of particular compounds is difficult to determine because of the very complex nature of these processes.[1a,1f] In recent years, information has been collected that relates to the role of sphingolipids as second messenger molecules.[1c,2] Furthermore, sphingolipids seem to be involved in apoptosis,[3] though its exact role remains to be elucidated.[4–8]

In human skin, sphingolipids crucially contribute to the essential water permeability barrier.[9] The presence of phytosphingosine (D-*ribo*-4-hydroxysphinganine) is characteristic of, and very important for, keratinocytes and constitutes 40% of the membrane content.[10] Because of the additional free hydroxy group in phytosphingosine, additional hydrogen bonds can be formed, which may enhance the rigidity of the multilamellar lipid layer. This in turn leads to a decrease in transepidermal water loss. Furthermore, galactosyl- and glucosyl phytosphingolipids exhibit significant anticancer activity.[11]

The intention of the present work is the synthesis of the enantiopure diastereomeric compounds **1** and **2**, which are 4-fluoro analogues of (2*S*,3*R*)-4,5-dihydroceramide. The latter amide is transformed in nature to the biologically active compound ceramide under the catalytic action of dihydroceramide desaturase.[12] Moreover, compounds **1** and **2** can also be seen as isosters of the mentioned diastereomeric (2*S*,3*S*)-phytoceramides.[13] The title compounds might be able to mimic the properties of phytoceramides. These properties include the ability to act as a hydrogen bridge acceptor, but do not include its ability to act as a donor. Though the role of the C–F group is controversially discussed in relation to hydrogen bonding,[14] the target compounds are expected to exhibit modified bioactivity compared with natural ceramides or phytoceramides. Additionally, compounds **1** and **2** may be suitable to use in the study of biomedical mechanisms. A single fluorine atom in the 4-position has been shown to influence the phase behaviour of different synthetic intermediates that are used in the synthesis of the title compounds. The first results in this area have been recently published.[15]

Results and Discussion

Retrosynthetically, an enantioselective sequence was designed for the synthesis of both diastereomeric 4-fluoro an-

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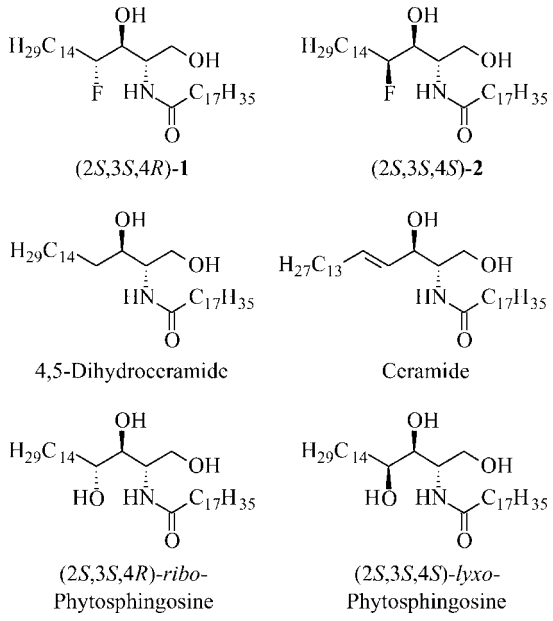
alogues (2*S*,3*S*,4*R*)-**1** and (2*S*,3*S*,4*S*)-**2** of the natural D-*erythro*-configured 4,5-dihydroceramide. These compounds can also be seen as isosters of (2*S*,3*S*,4*R*)-*ribo*- or (2*S*,3*S*,4*S*)-*lyxo*-phytoceramides (Scheme 1). The nonnatural L-*erythro*-isomers (2*R*,3*R*,4*S*)-**1** and (2*R*,3*R*,4*R*)-**2** were prepared analogously.



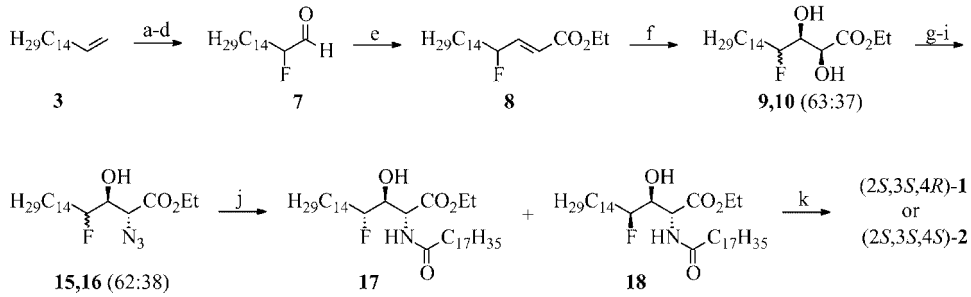
Scheme 1.

The synthetic sequence started with hexadec-1-ene (**3**), which was transformed to 2-fluorohexadecanal (**7**) in four steps analogous to a protocol we used earlier for other α-fluoro aldehydes.[16] Bromofluorination of **3** with *N*-bromosuccinimide (NBS) and triethylamine tris(hydrogen fluoride) complex[17] and subsequent substitution of the bromine functionality of bromofluoride **4**[18] with an acetate group resulted in fluorinated acetate **5**. Hydrolysis and subsequent Swern oxidation of resulting fluorohydrin **6** afforded aldehyde **7** (Scheme 2) in 49% overall yield (see Supporting Information).

Recently, several protocols for the enantioselective α-fluorination of carbonyl compounds with various electrophilic fluorination reagents and chiral secondary amines as catalysts have been described. These methods can also be applied to aliphatic aldehydes.[20] Since, for the mentioned investigation of the organization phenomena at surfaces, we needed both diastereomers of target molecules **1** and **2** our pathway by way of racemic **7** seemed more straightforward in our case.

This aldehyde, as already known for other α-fluoroaldehydes,[21] is fairly unstable and thus was used for the next step without purification. However, for spectroscopic investigations, **7** could be purified by quick chromatography with a short (5 cm) silica gel column.

A two-carbon chain elongation was accomplished by a slightly modified Horner–Wadsworth–Emmons reaction.[22] Treatment of aldehyde **7** with triethylphosphonium acetate and sodium hydride afforded *trans*-configured α,β-unsaturated ester **8** almost exclusively (selectivity >95%). The large $^3J_{H,H}$ = 16 Hz is characteristic of the *trans*-configuration of the double bond. Subsequently, in a Sharpless dihydroxylation, α,β-unsaturated ester **8** was treated with AD-mix-β similar to a published procedure.[23] However, the fluorine substituent caused a significantly lower reaction rate of compound **8** compared to that of nonfluorinated analogues, and even after an extended reaction time (up to 7 days at 0 °C) the starting material was not completely consumed (about 80% conversion). Two diastereomers were formed in 63:37 ratio (^{19}F NMR), which could not be separated chromatographically. The ratio of diastereomers was dependent on the reaction temperature, and the ratios of the diastereomers varied between 55:45 and 65:35. By ^{1}H^{1}H correlation NMR spectroscopy and selective decoupling experiments at an NMR frequency of 600 MHz, the major product was assigned as ethyl (2*S*,3*S*,4*R*)-4-fluoro-2,3-dihydroxyoctadecanoate (**9**). The enantiomeric excess (*ee*) of **9** was determined by ^{19}F NMR spectroscopy and was found to be >98% with 60 mol-% of Eu(hfc)$_3$ ($\Delta\delta$ = 0.25 ppm) or 110 mol-% Pr(hfc)$_3$ ($\Delta\delta$ = 0.75 ppm) as shift reagents (see Supporting Information). For minor isomer **10**, the *ee* could neither be determined with Eu(hfc)$_3$ nor with Pr(hfc)$_3$.



Scheme 2. Synthesis of 4-fluoro-4,5-dihydroceramides **1** and **2**. *Reagents and conditions*: (a) NBS, Et$_3$N·3HF, CH$_2$Cl$_2$, room temp., 6 h (refs.[17,18]) (84%); (b) KOAc, DMF, reflux, 26 h (67%) (ref.[19]); (c) KOH, MeOH, room temp., 4 h (92%); (d) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, –60 °C → room temp., 30 min (95%); (e) NaH, (EtO)$_2$P(O)CH$_2$CO$_2$Et, Et$_2$O, reflux, 2.5 h (69%); (f) AD-mix-β, MeSO$_2$NH$_2$, *t*BuOH/H$_2$O (1:1), 0 °C, 7 d (79%); (g) SOCl$_2$, CCl$_4$, reflux, 24 h (92%); (h) NaIO$_4$, 1 mol-% RuCl$_3$·3H$_2$O, MeCN/H$_2$O (5:2), room temp., 3–6 h (92%); (i) NaN$_3$, acetone/H$_2$O (2:1), room temp., 24 h, then 20% H$_2$SO$_4$, room temp., 8–12 h (78%); (j) PPh$_3$, *p*-nitrophenyl stearate, THF/H$_2$O (9:1), room temp., 10 h (67% combined yield of diastereomers), chromatographic separation; (k) NaBH$_4$, THF, MeOH, reflux, 3 h (45% **1** and 72% **2**).

The diastereofacial selectivity of the dihydroxylation of **8** is in agreement with the rule of Kishi, who observed *anti* selectivity with respect to the allylic substituent in the Sharpless dihydroxylations of *trans*-configured α,β-unsaturated esters bearing an additional functionality in the allylic position.[24] The transition states of these type of reactions have also been investigated by Stork,[25] Houk[26] and Vedejs.[27] The weak influence of the allylic fluorine substituent on the diastereoselectivity of the Sharpless dihydroxylation has also been observed with similar starting materials.[28]

The diastereoselectivity of the reaction of **8** with AD-mix-α under similar conditions was slightly higher. A 69:31 mixture (^{19}F NMR) of (2*S*,3*S*,4*R*)-**9** and its diastereomer (2*S*,3*S*,4*S*)-**10** was obtained at 0 °C. Again, >98% *ee* was observed for (2*S*,3*S*,4*R*)-**9**. The diastereoselectivity varied between 60:40 and 76:24. The ratio was once again depending on the reaction temperature, which is in line with the results for the other isomers.

In the following steps, mixtures of diols **9** and **10** were transformed to mixtures of corresponding 2-azido compounds **15** and **16** in a three-step sequence. After several trials in different solvents, such as cyclohexane or methyl *tert*-butyl ether, the reaction of (2*S*,3*S*,4*R*)-**9** and (2*S*,3*S*,4*S*)-**10** with excess thionyl chloride heated at reflux in tetrachloromethane in the presence of triethylamine was successful. A protocol similar to that published by Sharpless et al was applied.[29] Because of the chirality of sulfur, under these conditions a mixture of four compounds (31:29/22:18, ^{19}F NMR) was obtained in a 92% yield. This mixture was inseparable by column chromatography. The identity of compounds **11a**, **11b**, **12a** and **12b** was determined by NMR spectroscopy (^{1}H^{1}H, ^{1}H^{13}C correlation and selective decoupling experiments) and was facilitated by the different product ratios within the mixture.

This mixture was subsequently oxidized with a catalytic amount of ruthenium tetroxide with sodium periodate added as a re-oxidant in aqueous acetonitrile at room temperature by a modified procedure of Sharpless et al.[29]. An inseparable 63:37 mixture (^{19}F NMR) of ethyl (4*S*,5*S*,6*R*)-5-(1-fluoropentadecyl)-2,2-dioxo-1,3,2λ^{6}-dioxolan-4-carboxylate (**13**) and ethyl (4*S*,5*S*,6*S*)-5-(1-fluoropentadecyl)-2,2-dioxo-1,3,2λ^{6}-dioxolan-4-carboxylate (**14**) was isolated in 92% yield. Again, the structures of the products were assigned from the different product ratios of the mixtures that were apparent in the NMR spectra (see Experimental Section).

The ring opening of cyclic sulfites **11** and **12** with sodium azide was very slow at 20 °C (90 h, 95% transformation), and afforded the 2-azido products almost exclusively. At 50 °C, complete consumption of the starting compounds was detected after 18 h, but significant amounts of the other regioisomers bearing the azido group in the 3-position were formed (see Supporting Information). At even higher temperatures, partial decomposition of the starting materials occurred. The reactivity of cyclic sulfates **13** and **14** towards sodium azide-induced ring opening was significantly higher, and the azide moiety was introduced with complete regioselectivity. Similar to a procedure used by Bittman et al.[30] for nonfluorinated cyclic sulfates, treatment of a 54:46 mixture of **13** and **14** with 5 equiv. of sodium azide at room temperature in a 2:1 mixture of acetone/water led to complete conversion of the starting sulfates within 3 h. Complete regio- and stereoselectivity was observed after acidic hydrolysis of the crude product mixture of the ring opening reaction. An inseparable 62:38 mixture (^{19}F NMR) of two diastereomeric 2-azido-4-fluoro-3-hydroxyoctadecanoic esters **15** and **16** was isolated in 78% yield after chromatographic purification. The stereochemistry of the products was assigned from mixtures that contained different proportions of the two regioisomers.[15]

In case of regioisomers (2*R*,3*S*,4*R*)-**15** and (2*R*,3*S*,4*S*)-**16**, >98% *ee* for each compound [$\Delta\delta$ = 0.07 ppm, 100 mol-% Eu(hfc)$_3$ for **15**, $\Delta\delta$ = 0.09 ppm, 100 mol-% Eu(hfc)$_3$ for **16**] was determined by ^{19}F NMR shift experiments.

The simultaneous reduction of both the azido- and the ester group was unselective under various conditions and afforded complex mixtures of up to ten fluorinated compounds. In contrast, Staudinger reduction of the azido group of a 60:40 mixture of (2*R*,3*S*,4*R*)-**15** and (2*R*,3*S*,4*S*)-**16**, in the presence of *p*-nitrophenyl stearate, generated corresponding *N*-stearoylcarboxylic esters **17** and **18** without any change in the ratio of the isomers in almost quantitative combined yield of the crude products. This mixture could be separated by column chromatography to afford (2*R*,3*S*,4*R*)-**17** in a 39% yield and (2*R*,3*S*,4*S*)-**18** in a 28% yield, both with >99% *de* and >98% *ee* [^{19}F NMR, $\Delta\delta$ = 0.33 ppm, 100 mol-% Eu(hfc)$_3$ for **17**, $\Delta\delta$ = 0.10 ppm, 100 mol-% Eu(hfc)$_3$ for **18**].

Several methods that selectively reduced the ester functionality in the presence of the amido group in nonfluorinated compounds were not selective for **17** and **18** (see Supporting Information). Finally, modification of a method originally published by Soai et al.[31] was successful. Accordingly, the reduction of (2*R*,3*S*,4*R*)-**17** or (2*R*,3*S*,4*S*)-**18**, with 2.5 equiv. of sodium borohydride in THF heated at reflux coupled with the successive addition of small portions of dry methanol to the refluxing reaction mixture (20 equiv. in total) selectively afforded expected 4-fluoro-4,5-dihydroceramides **1** or **2** in 45% and 72% yields, respectively. No starting material was detected in the crude product mixtures by ^{19}F NMR spectroscopy. The structure of the products was determined spectroscopically, but the *ee*'s could not be determined unequivocally because there was no base line separation of the diastereomeric complexes with the use of up to 200 mol-% of Eu(hfc)$_3$ or Pr(hfc)$_3$. However, no racemization occurred during the reduction of the ester function. Otherwise, a new diastereomer would have been formed and observed in the NMR spectra.

For (2*S*,3*S*,4*R*)-**1**, the diastereotopic protons at C-1 resonate as a doublet of doublets at δ = 3.72 ppm and δ = 3.90 ppm with $^{2}J_{H,H}$ = 11.5 Hz and $^{3}J_{H,H}$ = 3.3 Hz or 4.7 Hz, respectively, to 2-H (δ = 4.02–4.05 ppm, broad). The coupling constant $^{3}J_{H,H}$ = 8.5 Hz for the coupling of 2-H to the amide proton (δ = 7.08 ppm) was determined. The neighbouring 3-H proton (δ = 3.76 ppm) shows the typical

$^3J_{H,H}$ = 5.9 Hz for the coupling to 4-H (δ = 4.46 ppm) and a quite small $^3J_{H,F}$ = 10.5 Hz. From these data, the *anti*,*anti*-configuration, that is the D-*erythro*-configuration, can be deducted. Typical signals in the ^{13}C NMR spectrum are those of the amido group (δ = 174.4 ppm), C-4 (δ = 94.0 ppm, $^1J_{C,F}$ = 172.2 Hz), C-3 (δ = 73.0 ppm, $^2J_{C,F}$ = 23.5 Hz), C-2 (δ = 51.6 ppm, $^3J_{C,F}$ = 2.2 Hz) and C-1 (δ = 61.4 ppm).

For (2*S*,3*S*,4*S*)-**2**, the diastereotopic protons at C-1 resonate as a doublet of doublets at δ = 3.67 ppm and δ = 3.87 ppm with $^2J_{H,H}$ = 11.5 Hz and $^3J_{H,H}$ = 2.6 Hz or 4.3 Hz, respectively, to 2-H (δ = 4.00 ppm). A small $^3J_{H,H}$ = 1.2 Hz for the coupling of 2-H to the amide proton at δ = 6.63 ppm was found. The coupling of 2-H to the diastereotopic protons at C-1 show $^3J_{H,H}$ = 4.3 Hz and $^3J_{H,H}$ = 6.8 Hz to 3-H (δ = 3.66 ppm) was also identified. Proton 2-H shows a very large $^3J_{H,F}$ = 25.6 Hz and a very small $^3J_{H,H}$ = 2.6 Hz for the coupling to 4-H (δ = 4.53 ppm). These data suggest the *anti*,*syn*-arrangement of the functional groups at carbons C-2, C-3, and C-4. Typical signals in the ^{13}C NMR spectrum are those of the amido group (δ = 174.3 ppm), C-4 (δ = 93.5 ppm, $^1J_{C,F}$ = 172.2 Hz), C-3 (δ = 72.0 ppm, $^2J_{C,F}$ = 18.9 Hz), C-2 (δ = 61.6 ppm, $^3J_{C,F}$ = 2.9 Hz) and C-1 (δ = 61.6 ppm).

In an analogous synthetic sequence, 4-fluoro-4,5-dihydroceramides of the other enantiomeric series were prepared (see Experimental Section).

With these compounds in hand, we started biological tests and investigations of their physicochemical properties. A manuscript that describes the effect of fluorine on the self organization of **1** and **2** at the air/water interface in comparison to natural ceramide is in preparation.

Conclusions

Diastereomeric 4-fluoro analogues **1** and **2** of the biochemical precursor to ceramide, (2*S*,3*R*)-4,5-dihydroceramide, have been synthesized in eleven steps from hexadec-1-ene (**3**). These compounds can also be seen as isosters of the diastereomeric (2*S*,3*R*)-phytoceramides. The biological properties (potential initiators of apoptosis) of compounds **1** and **2** and their enantiomers are presently under investigation. Results of these studies will be communicated in due course. Shorter chain 3-fluoro-3-deshydroxy analogues of ceramides of different configuration have been shown to be able to initiate apoptosis.[32]

Experimental Section

General Remarks: NMR spectra, if not stated otherwise, were recorded as ca. 20% solutions in $CDCl_3$. Chemical shift values are reported relative to TMS (^{1}H NMR), $CDCl_3$ (^{13}C NMR), or $CFCl_3$ (^{19}F NMR). To assign the structure of the product mixtures, ^{1}H^{1}H and ^{1}H^{13}C correlation spectra and selective decoupling experiments were performed with a 600 MHz NMR spectrometer. Mass spectra were recorded by GC–MS coupling (EI, 70 eV) or by direct inlet. Gas-chromatographic analyses were performed with a HP-5 column (30 m, Ø 0.32 mm, film 0.25 μm, carrier gas N_2). Thin-layer chromatography was performed with coated plate 60 F_{254}. Column chromatography was performed with silica gel 60 (0.063–0.2 mm). Elemental analyses were obtained by Mikroanalytisches Laboratorium, Organische Chemie, University of Münster. All reactions that required the use of air-sensitive reagents were conducted under an argon atmosphere with standard Schlenk techniques. All purchased reagents were used without purification. Solvents and reagents were purified where necessary by literature methods. All melting points are uncorrected.

1-Acetoxy-2-fluorohexadecane (5): Potassium acetate (14.72 g, 331 mmol) was added to a solution of 1-bromo-2-fluorohexadecane[18] (**4**, 26.73 g, 82.7 mmol) in DMF (150 mL) and heated at reflux under an argon atmosphere for 26 h. A mixture of cyclohexane/ethyl acetate (1:1, 100 mL) was then added to the reaction mixture and stirred at room temp. for 10 min. The precipitated solid material was filtered and washed with cyclohexane/ethyl acetate (1:1, 50 mL). The combined organic layer was washed with water (6 × 50 mL) and dried ($MgSO_4$). After evaporation of the solvent, the crude product was purified by column chromatography (cyclohexane/ethyl acetate, 10:1) to afford **5** as a white solid contaminated with 2% of its regioisomer. Yield 16.71 g (67%). M.p. 37–38 °C. R_f = 0.51 (cyclohexane/ethyl acetate, 10:1). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26–1.78 (br. m, 26 H), 2.10 (s, 3 H), 4.12 (ddd, $^3J_{H,F}$ = 21.4 Hz, $^2J_{H,H}$ = 12.4 Hz, $^3J_{H,H}$ = 6.7 Hz Hz, 1 H), 4.21 (ddd, $^3J_{H,F}$ = 27.4 Hz, $^2J_{H,H}$ = 12.4 Hz, $^3J_{H,H}$ = 2.9 Hz, 1 H), 4.65 (ddddd, $^2J_{H,F}$ = 49.6 Hz, $^3J_{H,H}$ = 8.1 Hz, $^3J_{H,H}$ = 6.7 Hz, $^3J_{H,H}$ = 4.8 Hz, $^3J_{H,H}$ = 2.9 Hz, 1 H) ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 14.0 (q), 20.7 (q), 24.7 (dt, $^3J_{C,F}$ = 4.8 Hz), 22.7, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 29.7, 31.9 (all t), 31.4 (dt, $^2J_{C,F}$ = 20.9 Hz), 65.8 (dt, $^2J_{C,F}$ = 22.5 Hz), 91.3 (dd, $^1J_{C,F}$ = 172.3 Hz), 170.7 (s) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –187.5 (dddm, $^2J_{F,H}$ = 49.6 Hz, $^3J_{F,H}$ = 22.9 Hz, $^3J_{F,H}$ = 17.2 Hz); regioisomer: δ = –231.0 (ddd, $^2J_{F,H}$ = 47.7 Hz, $^2J_{F,H}$ = 47.7 Hz, $^3J_{F,H}$ = 22.9 Hz) ppm. GC–MS: *m*/*z* (%) = 302 (1), 301 (0.5) 240 (5) 222 (10), 138 (12), 109 (35), 96 (92), 82 (93), 69 (70), 57 (85), 43 (100). IR (KBr): $\tilde{\nu}$ = 2921, 2848 (s), 1745 (s), 1475, 1415 (m), 1276, (m), 1060, 1072, 1097 (m), 920 (m), 724 (m) cm^{-1}. $C_{18}H_{35}FO_2$ (302.5): calcd. C 71.48, H 11.66; found C 71.46, H 11.45.

2-Fluorohexadecan-1-ol (6): A solution of KOH (4.21 g, 75 mmol) in methanol (100 mL) was treated with 1-acetoxy-2-fluorohexadecane (**5**, 16.32 g, 54 mmol) in methanol (100 mL) and stirred at room temp. for 2–4 h. The progress of the reaction was monitored by DC. The mixture was then poured into water (200 mL) and extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were washed with water (3 × 50 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by column chromatography (cyclohexane/ethyl acetate, 5:1) to afford **3** as a white solid contaminated with 2% of the regioisomer. Yield 12.86 g (92%). M.p. 66–67 °C. R_f = 0.23 (cyclohexane/ethyl acetate, 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.4 Hz, 3 H), 1.26–1.70 (br. m, 26 H), 1.95 (s, 1 H), 3.58–3.78 (dddm, $^2J_{H,H}$ = 12.4 Hz, $^3J_{H,H}$ = 6.2 Hz, $^3J_{H,H}$ = 3.1 Hz, 2 H), 4.56 (ddddd, $^2J_{H,F}$ = 49.6 Hz, $^3J_{H,H}$ = 7.9 Hz, $^3J_{H,H}$ = 6.2 Hz, $^3J_{H,H}$ = 4.8 Hz, $^3J_{H,H}$ = 3.1 Hz, 1 H) ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 14.1 (q), 24.9 (dt, $^3J_{C,F}$ = 3.8 Hz), 22.7, 29.3, 29.4, 29.5, 29.7, 31.9 (all t), 31.0 (dt, $^2J_{C,F}$ = 20.3 Hz), 65.1 (dt, $^2J_{C,F}$ = 21.6 Hz), 94.8 (dd, $^1J_{C,F}$ = 167.8 Hz) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –190.0 (dm, $^2J_{F,H}$ = 49.6 Hz); regioisomer: δ = –228.8 (ddd, $^2J_{F,H}$ = 47.7 Hz, $^2J_{F,H}$ = 47.7 Hz, $^3J_{F,H}$ = 19.1 Hz) ppm. GC–MS: *m*/*z* (%) = 260 (<0.1) [M]$^+$, 222 (2), 194 (8), 138 (8), 109 (24), 96 (68), 82 (90), 69 (58), 57 (94), 43 (100). ESI-MS (nanospray): *m*/*z* (%) = 300 (8), 283 (15). IR (KBr): $\tilde{\nu}$ = 3400, 3310 (m), 2960, 2916, 2849 (s), 1474, 1462, 1380 (m), 1250 (m), 1112, 1097, 1074 (m), 845 (m), 820

(m), 729, 721 (m) cm^{-1}. $C_{16}H_{33}FO$ (260.4): calcd. C 73.79, H 12.77; found C 74.05, H 12.57.

2-Fluorohexadecanal (7): Under an argon atmosphere, oxalyl chloride (2.8 g, 22 mmol) in dry CH_2Cl_2 (100 mL) was cooled to –60 °C and treated with DMSO (3.7 g, 47 mmol). 2-Fluorohexadecan-1-ol (**6**, 2.82 g, 10.8 mmol) dissolved in CH_2Cl_2 (150 mL) was added to the solution very slowly (within 4 h) with vigorous stirring. The solution was stirred for 15 min and triethylamine (10.2 g, 100 mmol) was added. The mixture was warmed to room temp. over a 30 min period and then treated with water (150 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. The crude product (95%) was used without purification in the Wittig reaction. However, aldehyde **7** can be isolated by chromatography by passage through a 5 cm column with silica gel (cyclohexane/ethyl acetate, 10:1). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26–1.82 (br. m, 26 H), 4.72 (dddd, $^2J_{H,F}$ = 49.6 Hz, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 5.0 Hz, $^3J_{H,H}$ = 1.0 Hz, 1 H), 9.75 (dd, $^3J_{H,F}$ = 6.2 Hz, $^3J_{H,H}$ = 1.0 Hz, 1 H) ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 14.1 (q), 24.2 (dt, $^3J_{C,F}$ = 2.6 Hz), 22.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9 (all t), 30.4 (dt, $^2J_{C,F}$ = 20.4 Hz), 95.0 (dd, $^1J_{C,F}$ = 180.6 Hz), 200.2 (dd, $^2J_{C,F}$ = 34.3 Hz) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –199.9 (dddd, $^2J_{F,H}$ = 49.6 Hz, $^3J_{F,H}$ = 22.9 Hz, $^3J_{F,H}$ = 17.2 Hz, $^3J_{F,H}$ = 6.2 Hz) ppm. GC–MS: *m*/*z* (%) = 258 (3) $[M]^+$, 238 (0.5), 220 (0.5), 194 (4), 138 (6), 97 (30), 83 (40), 71 (44), 57 (98), 43 (100). IR (KBr): $\tilde{\nu}$ = 3394 (w), 2960, 2919, 2850 (s), 1742 (m), 1473 (s), 1267 (m), 1074, 1026 (m), 827 (m), 723 (m) cm^{-1}.

(*E*)-4-(Fluoro)ethyloctadec-2-enoate (8): Freshly prepared aldehyde **7** (see above) in diethyl ether (10 mL), was slowly added under an argon atmosphere to a stirred solution of sodium hydride (0.6 g, 20 mmol) and ethyl phosphonium acetate (2.25 g, 10 mmol) in dry diethyl ether (250 mL) at 0 °C. The solution was warmed to room temp. over a 30 min period and heated at refluxed for 4 h. The mixture was subsequently hydrolyzed at room temp. with water (250 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (3×150 mL). The combined organic layers were washed with water (2×25 mL) and dried ($MgSO_4$). The solvent was evaporated, and the residue was purified by column chromatography (cyclohexane/ethyl acetate, 20:1). Yield: 2.56 g (66%, over two steps). R_f = 0.26 (cyclohexane/ethyl acetate, 20:1). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26–1.53 (br. m, 24 H), 1.29 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.62–1.82 (m, 2 H), 4.21 (q, $^3J_{H,H}$ = 6.7 Hz, 2 H), 5.06 (ddddd, $^2J_{H,F}$ = 48.4 Hz, $^3J_{H,H}$ = 8.1 Hz, $^3J_{H,H}$ = 4.3 Hz, $^3J_{H,H}$ = 2.6 Hz, $^4J_{H,H}$ = 1.7 Hz, 1 H), 6.04 (ddd, $^3J_{H,H}$ = 15.7 Hz, $^4J_{H,H}$ = 1.7 Hz, $^4J_{H,F}$ = 1.7 Hz, 1 H), 6.88 (ddd, $^3J_{H,F}$ = 20.0 Hz, $^3J_{H,H}$ = 15.7 Hz, $^3J_{H,H}$ = 4.3 Hz, 1 H) ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 14.0 (q), 14.1 (q), 24.3 (dt, $^3J_{C,F}$ = 3.8 Hz), 22.7, 29.3, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 31.9 (all t), 34.8 (dt, $^2J_{C,F}$ = 20.3 Hz), 60.5 (t), 91.3 (dd, $^1J_{C,F}$ = 174.2 Hz), 121.1 (dd, $^3J_{C,F}$ = 10.2 Hz), 145.1 (dd, $^2J_{C,F}$ = 19.1 Hz), 166.0 (s) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –184.3 (m) ppm. GC–MS: *m*/*z* (%) = 328 (15) $[M]^+$, 308 (10), 283 (14), 262 (10), 234 (14), 220 (22), 135 (22), 125 (30), 109 (30), 95 (46), 81 (54), 69 (38), 57 (66), 43 (100). IR (NaCl palets): $\tilde{\nu}$ = 2932, 2853 (s), 1732 (s), 1667 (m), 1466, 1366 (m), 1304, 1270, 1179, 1035 (m), 981 (m), 726, 714 (m) cm^{-1}. $C_{20}H_{37}FO_2$ (328.5): calcd. C 73.12, H 11.35; found C 72.74, H 11.89.

Ethyl *rel*-(2*S*,3*S*,4*R*)-4-Fluoro-2,3-dihydroxyoctadecanoate (9) and Ethyl *rel*-(2*S*,3*S*,4*S*)-4-Fluoro-2,3-dihydroxyoctadecanoate (10): Ethyl (*E*)-4-fluorooctadec-2-enoate (**8**, 264 mg, 0.8 mmol) in ethanol (6 mL) was cooled to 9±1 °C and treated with $KMnO_4$ (120 mg, 0.8 mmol) in water (4 mL) with vigorous stirring. The mixture was stirred for 1 h at this temperature and then extracted (continuous extraction) with ethyl acetate. The combined extracts were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 5:2) to afford a 60:40 diastereomeric mixture of products as a white waxy solid. Yield: 121 mg (43%). M.p. 71–72 °C. R_f = 0.22 (cyclohexane/ethyl acetate, 5:2). Compound *rel*-(2*S*,3*S*,4*R*)-**9**: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26–1.48 (br. m, 24 H), 1.35 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.60–1.90 (m, 2 H), 3.87 (ddd, $^3J_{H,H}$ = 8.6 Hz, $^3J_{H,F}$ = 6.0 Hz, $^3J_{H,H}$ = 1.0 Hz, 1 H), 4.31 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.44 (br. s, 1 H), 4.47 (dddd, $^2J_{H,F}$ = 47.8 Hz, $^3J_{H,H}$ = 8.7 Hz, $^3J_{H,H}$ = 8.7 Hz, $^3J_{H,H}$ = 2.4 Hz, 1 H) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –190.7 (dddd, $^2J_{F,H}$ = 48.2 Hz, $^3J_{F,H}$ = 21.0 Hz, $^3J_{F,H}$ = 12.4 Hz, $^3J_{F,H}$ = 5.7 Hz) ppm. Compound *rel*-(2*S*,3*S*,4*S*)-**10**: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26–1.48 (br. m, 24 H), 1.31 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.60–1.90 (m, 2 H), 3.90 (ddd, $^3J_{H,F}$ = 18.2 Hz, $^3J_{H,H}$ = 5.0 Hz, $^3J_{H,H}$ = 2.7 Hz, 1 H), 4.31 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.23 (d, $^3J_{H,H}$ = 2.1 Hz 1 H), 4.63 (dddd, $^2J_{H,F}$ = 49.8 Hz, $^3J_{H,H}$ = 8.8 Hz, $^3J_{H,H}$ = 5.1 Hz, $^3J_{H,H}$ = 4.1 Hz, 1 H) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –197.8 (dddd, $^2J_{F,H}$ = 49.6 Hz, $^3J_{F,H}$ = 17.2 Hz, $^3J_{F,H}$ = 17.2 Hz, $^3J_{F,H}$ = 15.3 Hz) ppm.

Mixture of Compounds *rel*-(2*S*,3*S*,4*R*)-9 and *rel*-(2*S*,3*S*,4*S*)-10: Several signals in the ^{13}C NMR spectra overlap each other and could not be assigned unequivocally to one of the isomeric compounds. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 14.0 (q), 14.1 (q), 24.8 and 24.9 (dt, $^3J_{C,F}$ = 5.1 Hz, $^3J_{C,F}$ = 5.1 Hz), 22.7, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9 (all t), 31.0 and 31.7 (dt, $^2J_{C,F}$ = 22.9 Hz, $^2J_{C,F}$ = 20.3 Hz), 62.4 (t), 69.7 and 70.7 (t or dt, $^3J_{C,F}$ = 5.1 Hz), 72.9 and 73.6 (dt, $^2J_{C,F}$ = 25.4 Hz, $^2J_{C,F}$ = 20.3 Hz), 92.1 and 93.9 (dd, $^1J_{C,F}$ = 172.9 Hz, $^1J_{C,F}$ = 170.4 Hz), 172.7 and 173.4 (s) ppm. ESI-MS (nanospray): *m*/*z* (%) = 385 (44) $[M + Na]^+$. IR (KBr): $\tilde{\nu}$ = 3477 (s br), 2954, 2926, 2851 (s), 1742, 1728, 1707 (s), 1473, 1391, 1377 (m), 1301, 1205, 1143, 1033 (s), 1067 (m), 971 (m), 868 (m), 826, 723 (m) cm^{-1}. HRMS: calcd. for $C_{20}H_{39}FO_4Na$ 385.2730; found 385.2727. $C_{20}H_{39}FO_4$ (362.5): calcd. C 66.26, H 10.84; found C 66.02, H 10.54.

Ethyl (2*S*,3*S*,4*R*)-4-Fluoro-2,3-dihydroxyoctadecanoate (9) and Ethyl (2*S*,3*S*,4*S*)-4-Fluoro-2,3-dihydroxyoctadecanoate (10): A mixture of AD-mix-β (3.07 g, 8.8 μmol OsO_4) and methanesulfonyl amide (209 mg, 2.19 mmol) in *tert*-butyl alcohol/H_2O (1:1, 50 mL) was stirred at room temp. until the solution became clear. This solution was cooled to 0 °C, and whilst stirring ethyl (*E*)-4-fluorooctadec-2-enoate (**8**, 720 mg, 2.19 mmol) was slowly added. The mixture was stirred at 0 °C for 7 d. Sodium sulfite (3.12 g, 25 mmol) was then added at room temp., and the reaction was stirred for 30 min until all of the salts were dissolved (addition of some water might be necessary). The solution was transferred to a separatory funnel, and ethyl acetate (100 mL) was added. After vigorous shaking, the phases were separated, and the aqueous layer was extracted with ethyl acetate (4×50 mL). The combined organic layers were washed with NaOH (2 N, 2×25 mL) water (25 mL) and then dried ($MgSO_4$). The solvent was evaporated in vacuo, and the dirty-white residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 5:2) to afford a 63:37 diastereomeric mixture of products (2*S*,3*S*,4*R*)-**9** and (2*S*,3*S*,4*S*)-**10** as a white waxy solid. Yield 613 mg (77%). M.p. 75 °C. >98% *ee* for **9** [^{19}F NMR, 103 mol-% Eu(hfc)$_3$]. The spectroscopic data are in agreement with those of the racemic compounds.

Ethyl (2*R*,3*R*,4*S*)-4-Fluoro-2,3-dihydroxyoctadecanoate (9) and Ethyl (2*R*,3*R*,4*R*)-4-Fluoro-2,3-dihydroxyoctadecanoate (10): According to the above procedure from ethyl (*E*)-4-fluorooctadec-2-enoate (**8**, 720 mg, 2.19 mmol) and AD-mix-α (3.07 g, 8.8 μmol OsO_4). A 69:31 diastereomeric mixture (^{19}F NMR) of compounds (2*R*,3*R*,4*S*)-**9** and (2*R*,3*R*,4*R*)-**10** was obtained. Yield 375 mg (47%). After repeated column chromatography, a 74:26 diastereomeric mixture was isolated. M.p. 82–83 °C. >98% *ee* for (2*R*,3*R*,4*S*)-**9** [^{19}F NMR, 95 mol-% Eu(hfc)$_3$].

Ethyl *rel*-(4*S*,5*S*,6*R*)-5-(1-Fluoropentadecyl)-2-oxo-1,3,2λ^4-dioxathiolan-4-carboxylates (11) and Ethyl *rel*-(4*S*,5*S*,6*S*)-5-(1-Fluoropentadecyl)-2-oxo-1,3,2λ^4-dioxathiolan-4-carboxylates (12): A solution of racemic diols *rel*-(2*S*,3*S*,4*R*)-**9** and *rel*-(2*S*,3*S*,4*S*)-**10** (60:40, 190 mg, 0.52 mmol) in CCl_4 (15 mL) was treated with freshly distilled thionylchloride (300 mg, 2.51 mmol) under an argon atmosphere, and the mixture was heated at reflux until the starting material was no longer detected by TLC (about 24 h). The solvent and excess $SOCl_2$ was removed in vacuo, and the crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 10:1) to afford a mixture of diastereomeric sulfites **11a**, **11b**, **12a** and **12b**. Yield 173 mg (81%). M.p. 41 °C.

Ethyl *rel*-(4*S*,5*S*,6*R*)-5-(1-Fluoropentadecyl)-2-oxo-1,3,2λ^4-dioxathiolan-4-carboxylate (11a) (first diastereomer): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26–1.48 (br. m, 24 H), 1.33 or 1.34 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.60–1.84 (m, 2 H), 4.30 or 4.32 or 4.33 or 4.33 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.71 (ddd, $^3J_{H,F}$ = 8.9 Hz, $^3J_{H,H}$ = 8.0 Hz, $^3J_{H,H}$ = 4.0 Hz, 1 H), 4.80 (dddd, $^2J_{H,F}$ = 47.8 Hz, $^3J_{H,H}$ = 8.6 Hz, $^3J_{H,H}$ = 8.0 Hz, $^3J_{H,H}$ = 2.8 Hz, 1 H), 5.35 (dd, $^3J_{H,H}$ = 4.0 Hz, $^4J_{H,F}$ = 1.4 Hz, 1 H) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –185.7 (dddd, $^2J_{F,H}$ = 45.8 Hz, $^3J_{F,H}$ = 21.0 Hz, $^3J_{F,H}$ = 15.3 Hz, $^3J_{F,H}$ = 9.5 Hz) ppm. GC–MS: *m*/*z* (%) = 408 (0) [M]$^+$, 337 (8), 335 (20), 289 (8), 271 (16), 251 (22), 233 (15), 135 (34), 109 (30), 94 (55), 83 (88), 69 (84), 57 (100), 43 (84).

Ethyl *rel*-(4*S*,5*S*,6*R*)-5-(1-Fluoropentadecyl)-2-oxo-1,3,2λ^4-dioxathiolan-4-carboxylate (11b) (second diastereomer): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26–1.48 (br. m, 24 H), 1.33 or 1.34 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.60–1.84 (m, 2 H), 4.30 or 4.32 or 4.33 or 4.33 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.60–4.84 (m, 1 H), 4.99 (d, $^3J_{H,H}$ = 5.1 Hz, 1 H), 5.27 (ddd, $^3J_{H,F}$ = 18.4 Hz, $^3J_{H,H}$ = 5.2 Hz, $^3J_{H,H}$ = 3.8 Hz, 1 H) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –194.5 (dddd, $^2J_{F,H}$ = 47.7 Hz, $^3J_{F,H}$ = 22.9 Hz, $^3J_{F,H}$ = 15.3 Hz, $^3J_{F,H}$ = 7.6 Hz) ppm. GC–MS: *m*/*z* (%) = 408 (<0.1) [M]$^+$, 359 (4), 324 (4), 251 (24), 233 (6), 135 (12), 109 (18), 95 (38), 83 (55), 69 (55), 57 (82), 43 (100).

Ethyl *rel*-(4*S*,5*S*,6*S*)-5-(1-Fluoropentadecyl)-2-oxo-1,3,2λ^4-dioxathiolan-4-carboxylates (12a) (first diastereomer): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26–1.48 (br. m, 24 H), 1.33 or 1.34 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.60–1.84 (m, 2 H), 4.30 or 4.32 or 4.33 or 4.33 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.61 (ddd, $^3J_{H,F}$ = 22.4 Hz, $^3J_{H,H}$ = 7.9 Hz, $^3J_{H,H}$ = 2.9 Hz, 1 H), 4.71–4.80 (dm, $^2J_{H,F}$ = 48.0 Hz, 1 H), 5.32 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –195.0 (dddd, $^2J_{F,H}$ = 49.6 Hz, $^3J_{F,H}$ = 19.1 Hz, $^3J_{F,H}$ = 17.2 Hz, $^3J_{F,H}$ = 11.5 Hz) ppm. GC–MS: *m*/*z* (%) = 408 (<0.1) [M]$^+$, 365 (6), 343 (2), 306 (4), 251 (26), 233 (8), 229 (10), 135 (14), 111 (22), 96 (52), 83 (56), 69 (62), 57 (90), 43 (100).

Ethyl *rel*-(4*S*,5*S*,6*S*)-5-(1-Fluoropentadecyl)-2-oxo-1,3,2λ^4-dioxathiolan-4-carboxylates (12b) (second diastereomer): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26–1.48 (br. m, 24 H), 1.33 or 1.34 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.60–1.84 (m, 2 H), 4.30 or 4.32 or 4.33 or 4.33 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.60–4.84 (m, 1 H), 4.97 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H), 5.14 (ddd, $^3J_{H,F}$ = 24.3 Hz, $^3J_{H,H}$ = 6.9 Hz, $^3J_{H,H}$ = 1.7 Hz, 1 H) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –199.2 (dddd, $^2J_{F,H}$ = 45.8 Hz, $^3J_{F,H}$ = 24.8 Hz, $^3J_{F,H}$ = 15.3 Hz, $^3J_{F,H}$ = 7.6 Hz) ppm. GC–MS: *m*/*z* (%) = 408 (<0.1) [M]$^+$, 390 (2), 337 (8), 336 (20), 271 (15), 251 (40), 233 (6), 135 (16), 95 (44), 83 (42), 69 (68), 57 (80), 43 (100).

Mixture of Compounds *rel*-(4*S*,5*S*,6*R*)-11a,b and *rel*-(4*S*,5*S*,6*S*)-12a,b: Several signals in the ^{13}C NMR spectra overlap each other and could not be assigned unequivocally to one of the isomeric compounds. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 13.9 and 14.0 and 14.1 (q), 24.3 and 24.7 and 24.9 and 25.0 (dt, $^3J_{C,F}$ = 2.5 Hz, $^3J_{C,F}$ = 3.8 Hz, $^3J_{C,F}$ = 3.8 Hz), 22.7, 29.2, 29.3, 29.5, 29.6, 29.6, 31.9 (t), 31.0 and 31.7 (dt, $^2J_{C,F}$ = 22.9 Hz, $^2J_{C,F}$ = 20.3 Hz), 62.8 and 62.9 (t), 76.2 and 77.3 and 77.6 and 79.7 (dd, $^3J_{C,F}$ = 6.4 Hz, $^3J_{C,F}$ = 5.1 Hz, $^3J_{C,F}$ = 6.4 Hz, $^2J_{C,F}$ = 2.5 Hz), 82.4 and 83.2 and 84.8 and 86.0 (dd, $^2J_{C,F}$ = 19.1 Hz, $^2J_{C,F}$ = 24.2 Hz, $^2J_{C,F}$ = 29.2 Hz, $^2J_{C,F}$ = 20.3 Hz), 89.9 and 90.2 and 91.2 and 91.7 (dd, $^1J_{C,F}$ = 181.9 Hz, $^1J_{C,F}$ = 181.9 Hz, $^1J_{C,F}$ = 178.1 Hz, $^1J_{C,F}$ = 174.2 Hz), 166.6 and 167.0 and 167.5 and 167.7 (s) ppm. IR (KBr): $\tilde{\nu}$ = 2926, 2857 (s br), 1762, 1749 (s), 1470, 1384 (m), 1281, 1232, 1033 (m br), 1033, 1035 (m br) cm^{-1}. $C_{20}H_{37}FO_5S$ (408.6): calcd. C 58.80, H 9.13, S 7.85; found C 58.93, H 9.20, S 8.08.

Analogously, the mixtures of enantiomers **11** and **12** were prepared from (2*S*,3*S*,4*R*)-**9** and (2*S*,3*S*,4*S*)-**10** or (2*R*,3*R*,4*S*)-**9** and (2*R*,3*R*,4*R*)-**10**.

Ethyl (4*S*,5*S*,6*R*)-5-(1-Fluoropentadecyl)-2-oxo-1,3,2λ^4-dioxathiolan-4-carboxylates (11) and Ethyl (4*S*,5*S*,6*S*)-5-(1-Fluoropentadecyl)-2-oxo-1,3,2λ^4-dioxathiolan-4-carboxylates (12): From a 56:44 mixture of (2*S*,3*S*,4*R*)-**9** and (2*S*,3*S*,4*S*)-**10** (230 mg, 0.57 mmol) the title compounds were prepared. Yield 240 mg (92%). The spectroscopic data are in agreement with those of the racemic mixture.

Ethyl (4*R*,5*R*,6*S*)-5-(1-Fluoropentadecyl)-2-oxo-1,3,2λ^4-dioxathiolan-4-carboxylates (11) and Ethyl (4*R*,5*R*,6*R*)-5-(1-Fluoropentadecyl)-2-oxo-1,3,2λ^4-dioxathiolan-4-carboxylates (12): From a 74:26 mixture of (2*R*,3*R*,4*S*)-**9** and (2*R*,3*R*,4*R*)-**10** (232 mg, 0.58 mmol) the title compounds were prepared. Yield 239 mg (88%). The spectroscopic data are in agreement with those of the racemic mixture.

Ethyl *rel*-(4*S*,5*S*,6*R*)-5-(1-Fluoropentadecyl)-2,2-dioxo-1,3,2λ^6-dioxathiolan-4-carboxylate (13) and Ethyl *rel*-(4*S*,5*S*,6*S*)-5-(1-Fluoropentadecyl)-2,2-dioxo-1,3,2λ^6-dioxathiolan-4-carboxylate (14): A solution of a mixture of racemic sulfites **11** and **12** (151 mg, 0.37 mmol) in acetonitrile/water (25:1, 35 mL) was vigorously stirred with sodium periodate (130 mg, 0.60 mmol) and ruthenium trichloride trihydrate (1.3 mg, 1 mol-%) at room temp. until the starting material was no longer detected by TLC (3–6 h). The reaction mixture was treated with diethyl ether (50 mL) and stirred for some minutes. After separation of the phases, the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with water (50 mL) and dried ($MgSO_4$). The solvent was evaporated, and the residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 5:1) to afford a 60:40 mixture of compounds **13** and **14** as a white waxy solid. Yield 120 mg (76%). M.p. 37–38 °C.

Ethyl *rel*-(4*S*,5*S*,6*R*)-5-(1-Fluoropentadecyl)-2,2-dioxo-1,3,2λ^6-dioxathiolan-4-carboxylate (13): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26–1.62 (br. m, 24 H), 1.36 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.64–1.94 (m, 2 H), 4.33–4.39 (br. m, 2 H), 4.82 (dddd, $^2J_{H,F}$ = 47.9 Hz, $^3J_{H,H}$ = 8.9 Hz, $^3J_{H,H}$ = 5.1 Hz, $^3J_{H,H}$ = 5.1 Hz, 1 H), 5.02 (ddd, $^3J_{H,F}$ = 15.0 Hz, $^3J_{H,H}$ = 5.1 Hz, $^3J_{H,H}$ = 5.1 Hz, 1 H), 5.17 (d, $^3J_{H,H}$ = 5.1 Hz, 1 H) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –195.7 (dddd, $^2J_{F,H}$ = 49.6 Hz, $^3J_{F,H}$ = 19.1 Hz, $^3J_{F,H}$ = 15.3 Hz, $^3J_{F,H}$ = 5.7 Hz) ppm. GC–MS: *m*/*z* (%)

= 424 (0.5) $[M]^+$, 395 (0.2), 269 (0.5), 251 (5), 233 (15), 133 (5), 109 (6), 9 (12), 85 (20), 71 (46), 57 (98), 43 (100).

Ethyl *rel*-(4*S*,5*S*,6*S*)-5-(1-Fluoropentadecyl)-2,2-dioxo-1,3,2λ⁶-dioxathiolan-4-carboxylate (14): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26–1.62 (br. m, 24 H), 1.37 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H), 1.64–1.94 (m, 2 H), 4.33–4.39 (br. m, 2 H), 4.73 (dddd, $^2J_{H,F}$ = 46.4 Hz, $^3J_{H,H}$ = 9.1 Hz, $^3J_{H,H}$ = 4.6 Hz, $^3J_{H,H}$ = 1.9 Hz, 1 H), 4.94 (ddd, $^3J_{H,F}$ = 23.4 Hz, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 1.9 Hz, 1 H), 5.26 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –198.5 (dddd, $^2J_{F,H}$ = 45.8 Hz, $^3J_{F,H}$ = 22.9 Hz, $^3J_{F,H}$ = 17.2 Hz, $^3J_{F,H}$ = 15.3 Hz) ppm. GC–MS: *m*/*z* (%) = 424 (0.5) $[M]^+$, 351 (1), 306 (2), 271 (4), 251 (10), 233 (5), 133 (10), 111 (16), 95 (22), 85 (55), 71 (76), 57 (100), 43 (100).

Mixture of Compounds *rel*-(4*S*,5*S*,6*S*)-13 and *rel*-(4*S*,5*S*,6*S*)-14: Several signals in the ^{13}C NMR spectra overlap each other and could not be assigned unequivocally to one of the isomeric compounds. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 13.9 and 14.0 or 14.1 (q), 24.4 and 24.8 (dt, $^3J_{C,F}$ = 3.8 Hz, $^3J_{C,F}$ = 3.8 Hz), 22.7, 29.1, 29.3, 29.3, 29.4, 29.6, 29.6, 31.9 (t), 30.5 and 30.6 (dt, $^2J_{C,F}$ = 20.3 Hz, $^2J_{C,F}$ = 21.6 Hz), 63.6 and 63.6 (t), 75.5 and 75.8 (dd, $^3J_{C,F}$ = 6.4 Hz, $^3J_{C,F}$ = 5.1 Hz), 82.0 and 82.5 (dd, $^2J_{C,F}$ = 26.7 Hz, $^2J_{C,F}$ = 19.1 Hz), 89.4 and 90.4 (dd, $^1J_{C,F}$ = 183.1 Hz, $^1J_{C,F}$ = 179.3 Hz), 165.1 and 165.3 (s) ppm. IR (KBr): $\tilde{\nu}$ = 2918, 2851 (s br), 1744 (s), 1472 (m), 1403 (s), 1312, 1217, 1034 (m br), 1034 (m br), 859 (m), 820 (m) cm^{-1}. $C_{20}H_{37}FO_6S$ (424.6): calcd. C 56.58, H 8.78, S 7.55; found C 56.52, H 8.82, S 7.97.

Analogously, the mixtures of enantiomers **13** and **14** were prepared from (2*S*,3*S*,4*R*)-**11** and (2*S*,3*S*,4*S*)-**12** or (2*R*,3*R*,4*S*)-**11** and (2*R*,3*R*,4*R*)-**12**.

Ethyl (4*S*,5*S*,6*R*)-5-(1-Fluoropentadecyl)-2,2-dioxo-1,3,2λ⁶-dioxathiolan-4-carboxylate (13) and Ethyl (4*S*,5*S*,6*S*)-5-(1-Fluoropentadecyl)-2,2-dioxo-1,3,2λ⁶-dioxathiolan-4-carboxylate (14): From a 60:40 mixture of (2*S*,3*S*,4*R*)-**11** and (2*S*,3*S*,4*S*)-**12** (169 mg, 0.41 mmol) the title compounds were prepared as a 63:37 mixture. Yield 162 mg (92%). The spectroscopic data are in agreement with those of the racemic mixture.

Ethyl (4*R*,5*R*,6*S*)-5-(1-Fluoropentadecyl)-2,2-dioxo-1,3,2λ⁶-dioxathiolan-4-carboxylate (13) and Ethyl (4*R*,5*R*,6*R*)-5-(1-Fluoropentadecyl)-2,2-dioxo-1,3,2λ⁶-dioxathiolan-4-carboxylate (14): From a 62:38 mixture of (2*R*,3*R*,4*S*)-**11** and (2*R*,3*R*,4*R*)-**12** (278 mg, 0.68 mmol) the title compounds were prepared as a 61:39 mixture. Yield 261 mg (90%). The spectroscopic data are in agreement with those of the racemic mixture.

Ethyl *rel*-(2*R*,3*S*,4*R*)-2-Azido-4-fluoro-3-hydroxyoctadecanoate (15) and Ethyl *rel*-(2*R*,3*S*,4*S*)-2-Azido-4-fluoro-3-hydroxyoctadecanoate (16): A solution of the racemic mixture of sulfates *rel*-(2*R*,3*S*,4*R*)-**13** and *rel*-(2*R*,3*S*,4*S*)-**14** (98 mg, 0.23 mmol) in acetone/water (2:1, 30 mL) was treated with sodium azide (72 mg, 1.1 mmol) and vigorously stirred at room temp. until the starting material was no longer detected by TLC (about 24 h). The solvent was removed in vacuo and the crude solid material was dissolved with stirring in diethyl ether/20% aq. H_2SO_4 (1:1, 40 mL) until the starting material was no longer found by TLC (8–12 h). The mixture was diluted with diethyl ether (40 mL), and the clear ethereal layer was separated. The aqueous phase was extracted with diethyl ether (4 × 25 mL), and the combined organic layers were washed with 5% aq. $NaHCO_3$ solution (2 × 20 mL) and water (20 mL) and dried ($MgSO_4$). The solvent was removed, and the crude product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 5:1) to afford a 62:38 mixture of diastereomeric azides *rel*-(2*R*,3*S*,4*R*)-**15** and *rel*-(2*R*,3*S*,4*S*)-**16**. Yield 80 mg (89%). M.p. 41–42 °C.

Ethyl *rel*-(2*R*,3*S*,4*R*)-2-Azido-4-fluoro-3-hydroxyoctadecanoate (15): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26–1.85 (br. m, 26 H), 1.33 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 4.00 (ddd, $^3J_{H,F}$ = 7.2 Hz, $^3J_{H,H}$ = 7.2 Hz, $^3J_{H,H}$ = 4.1 Hz, 1 H), 4.15 (d, $^3J_{H,H}$ = 4.1 Hz, 1 H), 4.32 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.58 (dddd, $^2J_{H,F}$ = 47.7 Hz, $^3J_{H,H}$ = 8.8 Hz, $^3J_{H,H}$ = 7.2 Hz, $^3J_{H,H}$ = 3.1 Hz) ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 14.1 (q), 24.8 (t), 22.7, 29.4, 29.5, 29.5, 29.7, 31.9 (t), 31.2 (dt, $^2J_{C,F}$ = 20.3 Hz), 62.2 (t), 62.8 (dd, $^3J_{C,F}$ = 3.1 Hz), 73.4 (dd, $^2J_{C,F}$ = 25.4 Hz), 92.9 (dd, $^1J_{C,F}$ = 170.4 Hz), 168.2 (s) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –191.1 (dddd, $^2J_{F,H}$ = 47.7 Hz, $^3J_{F,H}$ = 35.5 Hz, $^3J_{F,H}$ = 21.0 Hz, $^3J_{F,H}$ = 7.2 Hz) ppm.

Ethyl *rel*-(2*R*,3*S*,4*S*)-2-Azido-4-fluoro-3-hydroxyoctadecanoate (16): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H), 1.26–1.85 (br. m, 26 H), 1.35 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 3.81 (ddd, $^3J_{H,F}$ = 24.7 Hz, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 2.1 Hz, 1 H), 4.00 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H), 4.30 or 4.30 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.66 (dddd, $^2J_{H,F}$ = 48.2 Hz, $^3J_{H,H}$ = 6.9 Hz, $^3J_{H,H}$ = 4.7 Hz, $^3J_{H,H}$ = 2.1 Hz) ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 14.1 (q), 25.0 (dt, $^3J_{C,F}$ = 5.1 Hz), 22.7, 29.4, 29.5, 29.5, 29.7, 31.9 (t), 30.7 (dt, $^2J_{C,F}$ = 20.3 Hz), 62.3 (t), 62.4 (d), 72.3 (dd, $^2J_{C,F}$ = 20.3 Hz), 92.3 (dd, $^1J_{C,F}$ = 172.9 Hz), 169.3 (s) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –200.8 (dddd, $^2J_{F,H}$ = 48.2 Hz, $^3J_{F,H}$ = 32.3 Hz, $^3J_{F,H}$ = 24.8 Hz, $^3J_{F,H}$ = 15.3 Hz) ppm.

Mixture of Compounds *rel*-(2*R*,3*S*,4*R*)-15 and *rel*-(2*R*,3*S*,4*S*)-16: IR (KBr): $\tilde{\nu}$ = 3388 (s br), 2927, 2854 (s br), 2111 (s), 1735 (s), 1669 (m), 1468, 1377 (m), 1261, 1202, 1067, 1019 (m br), 1067 (m br), 984 (m), 822, 721 (m) cm^{-1}. HRMS: calcd. for $C_{20}H_{38}FN_3O_3Na$ 410.2795; found 410.2843. $C_{20}H_{38}FN_3O_3$ (387.5): calcd. C 61.99, H 9.88, N 10.84; found C 62.14, H 9.74, N 10.91.

Analogously, the mixtures of enantiomers **15** and **16** were prepared from (4*S*,5*S*,64*R*)-**13** and (4*S*,5*S*,6*S*)-**14** or (4*R*,5*R*,6*S*)-**13** and (4*R*,5*R*,6*R*)-**14**.

Ethyl (2*R*,3*S*,4*R*)-2-Azido-4-fluoro-3-hydroxyoctadecanoate (15) and Ethyl (2*R*,3*S*,4*S*)-2-Azido-4-fluoro-3-hydroxyoctadecanoate (16): From a 63:37 mixture of (4*S*,5*S*,6*R*)-**13** and (4*S*,5*S*,6*S*)-**14** (105 mg, 0.25 mmol) the title compounds were prepared as a 62:38 mixture. Yield 75 mg (78%). >98% *ee* for (2*R*,3*S*,4*R*)-**15** [^{19}F NMR, 65 mol-% Eu(hfc)$_3$], >98% *ee* for (2*R*,3*S*,4*S*)-**16** [^{19}F NMR, 65 mol-% Eu(hfc)$_3$]. The spectroscopic data are in agreement with those of the racemic mixture.

Ethyl (2*S*,3*R*,4*S*)-2-Azido-4-fluoro-3-hydroxyoctadecanoate (15) and Ethyl (2*S*,3*R*,4*R*)-2-Azido-4-fluoro-3-hydroxyoctadecanoate (16): From a 61:39 mixture of (4*R*,5*R*,6*S*)-**13** and (4*R*,5*R*,6*R*)-**14** (209 mg, 0.49 mmol) the title compounds were prepared as a 61:39 mixture. Yield 173 mg (91%). 97% *ee* for (2*S*,3*R*,4*S*)-**15** [^{19}F NMR, 90 mol-% Eu(hfc)$_3$], >98% *ee* for (2*S*,3*R*,4*R*)-**16** [^{19}F NMR, 90 mol-% Eu(hfc)$_3$]. The spectroscopic data are in agreement with those of the racemic mixture.

Ethyl *rel*-(2*R*,3*S*,4*R*)-4-Fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (17) and Ethyl *rel*-(2*R*,3*S*,4*S*)-4-Fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (18): A 64:36 mixture of **15** and **16** (162 mg, 0.42 mmol) in THF/water (9:1, 20 mL) was stirred and treated successively with 4-nitrophenylstearate (255 mg, 0.63 mmol) and triphenylphosphane (131 mg, 0.50 mmol) under an argon atmosphere at room temp. The mixture was stirred at this temperature until all of the starting material was consumed (about 10 h). Diethyl ether (60 mL) was then added, and the phases were separated. The aqueous layer was extracted with diethyl ether (2 × 15 mL). The combined organic layers were washed with 1% aq. $NaHCO_3$ solution (5 × 15 mL), dried ($MgSO_4$), and the solvent was evaporated. The

yellow product mixture was separated by column chromatography (silica gel, cyclohexane/ethyl acetate, 5:1) to afford diastereopure compounds **17** and **18**.

Ethyl *rel*-(2*R*,3*S*,4*R*)-4-Fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (17): Yield 101 mg (39%). M.p. 89–90 °C. R_f = 0.45 (pentane/diethyl ether, 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 6 H), 1.26–1.53 (br. m, 54 H), 1.30 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.58–1.85 (m, 2 H), 2.32 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H), 4.13 (ddd, $^3J_{H,H}$ = 8.8 Hz, $^3J_{H,F}$ = 3.3 Hz, $^3J_{H,H}$ = 1.9 Hz, 1 H), 4.25 or 4.26 (q, each $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.30 (dddd, $^2J_{H,F}$ = 47.7 Hz, $^3J_{H,H}$ = 8.8 Hz, $^3J_{H,H}$ = 8.8 Hz, $^3J_{H,H}$ = 3.1 Hz, 1 H), 4.72 (dd, $^3J_{H,H}$ = 5.0 Hz, $^3J_{H,H}$ = 1.9 Hz, 1 H), 6.70 (d, $^3J_{H,H}$ = 5.0 Hz, 1 H) ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 14.1 (q), 24.8 (t), 22.7, 25.6, 29.2, 29.3, 29.4, 29.5, 29.7, 31.9 (t), 31.6 (t), 36.3 (t), 57.4 (d), 62.4 (t), 74.7 (dd, $^2J_{C,F}$ = 25.4 Hz), 93.2 (dd, $^1J_{C,F}$ = 170.4 Hz), 169.2 (s), 175.9 (s) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –189.3 (dddd, $^2J_{F,H}$ = 47.7 Hz, $^3J_{F,H}$ = 38.6 Hz, $^3J_{F,H}$ = 21.0 Hz, $^3J_{F,H}$ = 3.8 Hz) ppm.

Ethyl *rel*-(2*R*,3*S*,4*S*)-4-Fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (18): Yield 39 mg (15%). M.p. 91–92 °C. R_f = 0.19 (pentane/diethyl ether, 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 6 H), 1.26–1.53 (br. m, 54 H), 1.29 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.58–1.90 (m, 2 H), 2.25 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H), 3.91 (ddm, $^3J_{H,F}$ = 21.5 Hz, $^3J_{H,H}$ = 4.1 Hz, 1 H), 4.23 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 4.54 (dddd, $^2J_{H,F}$ = 48.7 Hz, $^3J_{H,H}$ = 8.4 Hz, $^3J_{H,H}$ = 4.2 Hz, $^3J_{H,H}$ = 4.2 Hz, 1 H), 4.74 (dd, $^3J_{H,H}$ = 8.1 Hz, $^3J_{H,H}$ = 4.1 Hz, 1 H), 6.36 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H) ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 14.1 (q), 24.9 (t), 22.7, 25.5, 29.2, 29.3, 29.5, 29.7, 31.9 (t), 31.0 (dt, $^2J_{C,F}$ = 20.3 Hz), 36.5 (t), 54.6 (d), 61.9 (t), 73.6 (dd, $^2J_{C,F}$ = 20.3 Hz), 94.1 (dd, $^1J_{C,F}$ = 170.4 Hz), 169.8 (s), 173.6 (s) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$): δ = –196.0 (dddd, $^2J_{F,H}$ = 48.7 Hz, $^3J_{F,H}$ = 21.0 Hz, $^3J_{F,H}$ = 17.2 Hz, $^3J_{F,H}$ = 15.3 Hz) ppm.

Mixture of Compounds *rel*-(2*R*,3*S*,4*R*)-17 and *rel*-(2*R*,3*S*,4*S*)-18: IR (KBr): $\tilde{\nu}$ = 3428 (s br), 2929, 2850 (s br), 1758 (m), 1637 (m br), 1537 (m), 1471 (m), 1378 (m), 1200, 1096, 1030 (m br), 872 (m), 727 (m) cm^{-1}. HRMS: calcd. for $C_{38}H_{74}FNO_4Na$ 650.5500; found 650.5524. $C_{38}H_{74}FNO_4$ (628.0): calcd. C 72.68, H 11.88, N 2.23; found C 72.66, H 11.84, N 2.40.

Analogously, from a 62:38 mixture of (2*R*,3*S*,4*R*)-**15** and (2*R*,3*S*,4*S*)-**16** (209 mg, 0.54 mmol) after chromatographic separation, diastereo- and enantiopure products (2*R*,3*S*,4*R*)-**17** and (2*R*,3*S*,4*S*)-**18** were isolated.

Ethyl (2*R*,3*S*,4*R*)-4-Fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (17): Yield 133 mg (39%). M.p. 88–89 °C. $[\alpha]_D^{20}$ = –20.9 (c = 0.90, $CHCl_3$). *ee* >98% [^{19}F NMR, decoupled, 124 mol-% Eu(hfc)$_3$].

Ethyl (2*R*,3*S*,4*S*)-4-Fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (18): Yield 95 mg (28%). M.p. 92–93 °C. $[\alpha]_D^{20}$ = –14.9 (c = 0.83, $CHCl_3$). *ee* >98% [^{19}F NMR, decoupled, 89 mol-% Eu(hfc)$_3$].

Analogously, from a 61:39 mixture of (2*S*,3*R*,4*S*)-**15** and (2*S*,3*R*,4*R*)-**16** (151 mg, 0.39 mmol) after chromatographic separation, diastereo- and enantiopure products (2*R*,3*S*,4*R*)-**17** and (2*R*,3*S*,4*S*)-**18** were isolated.

Ethyl (2*S*,3*R*,4*S*)-4-Fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (17): Yield 124 mg (51%). $[\alpha]_D^{20}$ = +21.4 (c = 0.86, $CHCl_3$). *ee* >98% [^{19}F NMR, decoupled, 153 mol-% Pr(hfc)$_3$].

Ethyl (2*S*,3*R*,4*R*)-4-Fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (18): Yield 41 mg (17%). $[\alpha]_D^{20}$ = +15.7 (c = 0.88, $CHCl_3$). *ee* >98% [^{19}F NMR, decoupled, 117 mol-% Eu(hfc)$_3$].

***rel*-(2*S*,3*S*,4*R*)-4-Fluoro-2-(stearoylamido)octadecane-1,3-diol (1):** A solution of **17** (123 mg, 0.20 mmol) in freshly distilled dry THF (25 mL) was treated with $NaBH_4$ (19 mg, 0.50 mmol) under an argon atmosphere and heated at reflux. Dry methanol (128 μL, 4.0 mmol) was added dropwise with a syringe over a period of 10 min. The mixture was heated at reflux for 2 h and then cooled to room temp. Water (20 mL) was then added, and the mixture was stirred until it became turbid. This mixture was extracted with a $CHCl_3$/methanol mixture (gradient 50:1 to 10:1, 5×20 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by column chromatography (silica gel, $CHCl_3$/methanol, 50:1). Yield 96 mg (84%). M.p. 100–101 °C. R_f = 0.15 ($CHCl_3$/MeOH, 50:1). ^{1}H NMR (300.13 MHz, $CDCl_3$/[D$_4$]MeOH,5:1 to 9:1): δ = 0.89 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H), 1.27–1.45 (br. m, 54 H), 1.51–1.81 (m, 2 H), 2.23 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H), 3.72 (dd, $^2J_{H,H}$ = 11.5 Hz, $^3J_{H,H}$ = 3.3 Hz, 1 H), 3.76 (dd, $^3J_{H,F}$ = 10.5 Hz, $^3J_{H,H}$ = 5.9 Hz, 1 H), 3.90 (dd, $^2J_{H,H}$ = 11.5 Hz, $^3J_{H,H}$ = 4.7 Hz, 1 H), 4.02–4.05 (br. m, 1 H), 4.46 (dddd, $^2J_{H,F}$ = 48.2 Hz, $^3J_{H,H}$ = 9.1 Hz, $^3J_{H,H}$ = 6.3 Hz, $^3J_{H,H}$ = 2.7 Hz, 1 H), 7.08 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H) ppm. ^{13}C NMR: (75.48 MHz, $CDCl_3$/[D$_4$]MeOH, 5:1 to 9:1): δ = 13.6 (q), 24.8 (dt, $^3J_{C,F}$ = 2.8 Hz), 22.3, 25.5, 29.0, 29.0, 29.0, 29.1, 29.2, 29.3, 31.6 (t), 30.5 (dt, $^2J_{C,F}$ = 21.2 Hz), 36.2 (t), 51.6 (dd, $^3J_{C,F}$ = 2.2 Hz), 61.4 (t), 73.0 (dd, $^2J_{C,F}$ = 23.5 Hz), 94.0 (dd, $^1J_{C,F}$ = 171.2 Hz), 174.4 (s) ppm. ^{19}F NMR: (282.37 MHz, $CDCl_3$/[D$_4$]MeOH, 5:1 to 9:1): δ = –191.1 (dddm, $^2J_{F,H}$ = 47.9 Hz, $^3J_{F,H}$ = 19.1 Hz, $^3J_{F,H}$ = 11.5 Hz) ppm.

***rel*-(2*S*,3*S*,4*S*)-4-Fluoro-2-(stearoylamido)octadecane-1,3-diol (2):** Analogously, from **18** (65 mg, 0.10 mmol) compound **2** was prepared. Yield 44 mg (73%). M.p. 118–119 °C. R_f = 0.15 ($CHCl_3$/MeOH, 50:1). ^{1}H NMR (300.13 MHz, $CDCl_3$/[D$_4$]MeOH, 5:1 to 9:1): δ = 0.88 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H), 1.26–1.55 (br. m, 54 H), 1.58–1.85 (m, 2 H), 2.21 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H), 3.67 (dd, $^2J_{H,H}$ = 11.5 Hz, $^3J_{H,H}$ = 4.3 Hz, 1 H), 3.66 (ddd, $^3J_{H,F}$ = 25.6 Hz, $^3J_{H,H}$ = 6.8 Hz, $^3J_{H,H}$ = 2.6 Hz, 1 H), 3.87 (dd, $^2J_{H,H}$ = 11.5 Hz, $^3J_{H,H}$ = 4.3 Hz, 1 H), 4.00 (dddd, $^3J_{H,H}$ = 6.8 Hz, $^3J_{H,H}$ = 4.3 Hz, $^3J_{H,H}$ = 4.3 Hz, $^3J_{H,H}$ = 1.2 Hz, 1 H), 4.53 (dddd, $^2J_{H,F}$ = 47.9 Hz, $^3J_{H,H}$ = 12.1 Hz, $^3J_{H,H}$ = 8.1 Hz, $^3J_{H,H}$ = 3.9 Hz, 1 H), 6.63 (br. d, $^3J_{H,H}$ = 1.2 Hz, 1 H) ppm. ^{13}C NMR: (75.48 MHz, $CDCl_3$/[D$_4$]MeOH, 5:1 to 9:1): δ = 13.7 (q), 24.8 (dt, $^3J_{C,F}$ = 4.8 Hz), 22.4, 25.6, 29.1, 29.1, 29.2, 29.2, 29.3, 29.4, 29.4, 29.4, 29.5, 31.7 (t), 31.0 (dt, $^2J_{C,F}$ = 20.7 Hz), 36.4 (t), 52.0 (dd, $^3J_{C,F}$ = 2.9 Hz), 61.6 (t), 72.0 (dd, $^2J_{C,F}$ = 18.9 Hz), 93.5 (dd, $^1J_{C,F}$ = 172.2 Hz), 174.3 (s) ppm. ^{19}F NMR (282.37 MHz, $CDCl_3$/[D$_4$]MeOH, 5:1 to 9:1): δ = –196.7 (dddd, $^2J_{F,H}$ = 47.9 Hz, $^3J_{F,H}$ = 24.8 Hz, $^3J_{F,H}$ = 15.3 Hz, $^3J_{F,H}$ = 9.5 Hz) ppm. IR (KBr): $\tilde{\nu}$ = 3418 (s br), 2916, 2849 (s br), 1640 (s), 1576 (m), 1472, 1388 (m), 1080, 1040 (m br), 734 (m) cm^{-1}. HRMS: calcd. for $C_{36}H_{72}FNO_3Na$ 608.5394; found 608.5418. $C_{36}H_{72}FNO_3$ (586.0): calcd. C 73.79, H 12.39, N 2.39; found C 73.50, H 12.43, N 2.19.

(2*S*,3*S*,4*R*)-4-Fluoro-2-(stearoylamido)octadecane-1,3-diol (1): Analogously, from **17** (104 mg, 0.18 mmol) compound **1** was prepared and purified by column chromatography (silica gel, $CHCl_3$/methanol, 50:1). Yield 44 mg (45%). $[\alpha]_D^{20}$ = +7.2 (c = 1.00, $CHCl_3$/MeOH, 9:1).

(2*S*,3*S*,4*S*)-4-Fluoro-2-(stearoylamido)octadecane-1,3-diol (2): Analogously, from **18** (68 mg, 0.11 mmol) compound **2** was prepared. Yield: 46 mg (72%). $[\alpha]_D^{20}$ = +1.1 (c = 1.14, $CHCl_3$/MeOH, 9:1).

(2*R*,3*R*,4*S*)-4-Fluoro-2-(stearoylamido)octadecane-1,3-diol (1): Analogously, from **17** (55 mg, 0.088 mmol) compound **1** was prepared and purified by column chromatography (silica gel, $CHCl_3$/

methanol, 50:1). Yield 46 mg (90%). M.p. 110–111 °C. $[\alpha]_D^{20}$ = –4.8 (c = 0.87, $CHCl_3$/MeOH, 9:1).

(2*R*,3*R*,4*R*)-4-Fluoro-2-(stearoylamido)octadecane-1,3-diol (2): Analogously, from **18** (48 mg, 0.076 mmol) compound **2** was prepared. Yield 36 mg (81%). M.p. 114–115 °C. $[\alpha]_D^{20}$ = –0.6 (c = 0.92, $CHCl_3$/MeOH, 9:1).

Supporting Information (see footnote on the first page of this article): ^1H, ^{13}C, and ^{19}F NMR spectroscopic data including assignments of the signals and EI mass spectrometric data of all new compounds of this paper; optimization experiments for the ring opening reaction of cyclic sulfites **11** and **12** with azide, and data on the determination of the enantiomeric excesses.

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