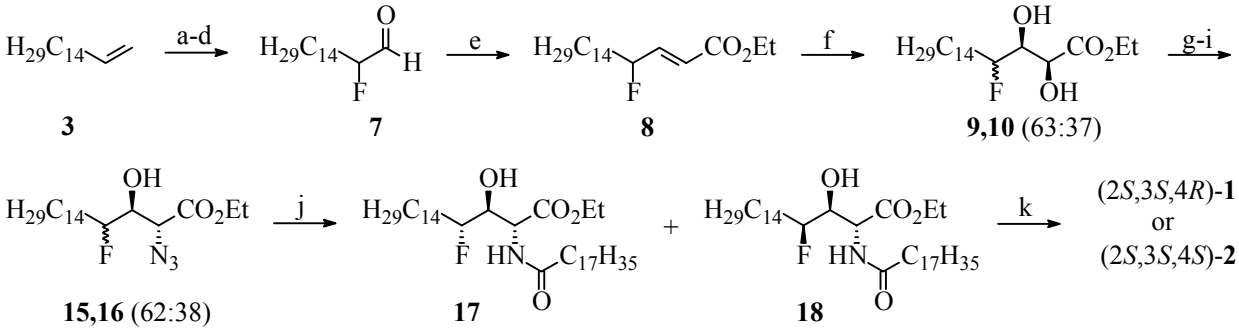
Eur. J. Org. Chem. **2006** · © WILEY-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, 2006 · ISSN 1434–193X

SUPPORTING INFORMATION

Title: Synthesis of Both Enantiomers of Diastereomeric 4-Fluoro-4,5-Dihydroceramides
Author(s): Jens Oldendorf, Günter Haufe*
Ref. No.: O200600456

Synthetic sequence towards 4-fluoro-4,5-dihydroceramides 1 and 2.



3 **7** **8** **9,10** (63:37)

15,16 (62:38) **17** **18**

Reagents and conditions: (a) NBS, $Et_3N{\cdot}3HF$, CH_2Cl_2, r.t., 6 h [refs.1;2] (84 %); (b) KOAc, DMF, reflux, 26 h (67 %) [ref. 3]; (c) KOH, MeOH, r.t., 4 h (92 %); (d) CO_2Cl_2, DMSO, Et_3N, CH_2Cl_2, –60 °C→r.t., 30 min (95 %); (e) NaH, $(EtO)_2P(O)CH_2CO_2Et$, Et_2O, reflux, 2.5 h (69 %); (f) AD-mix-β, $MeSO_2NH_2$, ^{t}BuOH/H_2O (1:1), 0 °C, 7 d (79 %); (g) $SOCl_2$, CCl_4, reflux, 24 h (92%); (h) $NaIO_4$, 1 mol% $RuCl_3{\cdot}3H_2O$, MeCN/H_2O (5:2), r.t., 3–6 h (92 %); (i) NaN_3, acetone/H_2O (2:1), r.t., 24 h, then 20 % H_2SO_4, r.t., 8–12 h (78 %); (j) PPh_3, *p*-nitrophenyl stearate, THF/H_2O (9:1), r.t., 10 h (67 % combined yield of diastereomers), chromatographic separation; (k) $NaBH_4$, THF, MeOH, reflux, 3 h (45 % **1** or 72 % **2**, respectively).

The aldehyde **7** has been synthesized according to a protocol used by us earlier for other fluorinated aldehydes.[4] The bromofluorination was shown to be highly regioselective giving a 92:8 mixture of the Markoffnikoff product 1-bromo-2-fluorohexadecane (**4**)[5] and its regioisomer. Refluxing this mixture with potassium acetate in DMF gave a 98:2 mixture of 1-acetoxy-2-fluorohexadecane (**5**) and its regioisomer with 67 % yield after chromatographic purification. Hydrolysis with potassium hydroxide in methanol yielded the fluorohydrin **6**, which was oxidized under Swern conditions to give the 2-fluorohexadecanal (**7**) almost quantitatively. This aldehyde, as already known for other α-fluoroaldehydes,[6] is fairly unstable and thus was used for the next step without purification. However, for spectroscopic investigations **7** could be purified by quick chromatography using a short (5 cm) silica gel column. The aldehyde proton appears at δ = 9.75 ppm in the ^{1}H NMR spectrum as a doublet of a doublet with typically small coupling constants $^3J_{HF}$ = 6.2 Hz and $^3J_{HH}$ = 1.0 Hz. In the ^{13}C NMR spectrum, the carbonyl carbon is high field shifted by 2.5 ppm (δ = 200.2 ppm, $^2J_{CF}$ = 1.0 Hz) compared to the non-fluorinated parent compound.[7] Also the carbonyl frequency in the IR spectrum is shifted to shorter wave length and appeared at $\tilde{\nu}$ = 1742 cm^{-1} compared to $\tilde{\nu}$ = 1730 cm^{-1} for hexadecanal.[7] A very weak signal at $\tilde{\nu}$ = 3394 cm^{-1} might be a hint on the presence of a small amount of the carbonyl hydrate.

A two carbon chain elongation was accomplished by a slightly modified Horner-Wadsworth-Emmons reaction.[8] Treatment of the aldehyde **7** with triethylphosphonium acetate and sodium hydride gave the *trans*-configured α,β-unsaturated ester **8** almost exclusively (selectivity >95

%). The large $^{3}J_{HH}$ = 16 Hz is characteristic for the *trans*-configuration of the double bond. Subsequently, in a Sharpless dihydroxylation the α,β-unsaturated ester **8** was treated with AD-mix-β similar to a published procedure.[9] However, the fluorine substituent caused a significantly lower reaction rate of compound **8** compared to that of non-fluorinated analogues and even after long reaction time (up to 7 days at 0 °C) the starting material was not consumed completely (about 80 %). Two diastereomers were formed in 63:37 ratio (^{19}F NMR), which could not be separated chromatographically. Depending on the reaction temperature different ratios of the diastereomers varying between 55:45 and 65:35 were observed.

By ^{1}H^{1}H correlation NMR spectroscopy and selective decoupling experiments at 600 MHz the major product was assigned as ethyl (2*S*,3*S*,4*R*)-4-fluoro-2,3-dihydroxyoctadecanoate (**9**). Most indicative for the *anti*-arrangement of the substituents attached to carbons 3 and 4 are the small $^{3}J_{HF}$ = 6.0 Hz between H_3 and F and the relatively large $^{3}J_{HH}$ = 8.6 Hz between H_3 and H_4. In contrast, the corresponding coupling constants for the minor product **10** were determined to be $^{3}J_{HF}$ = 18.2 Hz and $^{3}J_{HH}$ = 5.0 Hz. Thus, in compound **10** the fluorine and the hydroxyl group should be arranged in *syn*-configuration. The enantiomeric excess (ee) of **9** was determined by ^{19}F NMR spectroscopy to be >98% using 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 below). For the minor isomer **10** the ee could neither be determined with Eu(hfc)$_3$ nor with Pr(hfc)$_3$.

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 the crude product mixture) 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** in this case. Again the selectivity varied between 60:40 and 76:24 depending on the reaction temperature, which is basically in line with the results for the other isomers.

In the following steps the mixtures of diols **9** and **10** were transformed to mixtures of the corresponding 2-azido compounds **15** and **16** in a three-steps sequence. After several trials in different solvents such as cyclohexane or methyl *tert*-butyl ether, the reaction of the above-mentioned mixture of (2*S*,3*S*,4*R*)-**9** and (2*S*,3*S*,4*S*)-**10** with excess thionyl chloride in refluxing tetrachloromethane in the presence of triethylamine was successful applying a protocol similar to that published by Sharpless et al.[10] Due to the chirality of sulfur, under these conditions a mixture of four compounds (31:29/22:18, ^{19}F NMR) was obtained in 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) benefiting from different product ratios within the mixture.

This mixture was subsequently oxidized with catalytic amount of ruthenium tetroxide and sodium periodate as a re-oxidant in aqueous acetonitrile at room temperature according to a procedure of Sharpless et al.[10] which was slightly modified. An inseparable 63:37 mixture (^{19}F NMR of the crude product mixture) of methyl (4*S*,5*S*,6*R*)-5-(1-fluoropentadecyl)-2,2-dioxo-2λ^6(1,3,2)dioxolan-4-carboxylate (**13**) and (4*S*,5*S*,6*S*)-5-(1-fluoropentadecyl)-2,2-dioxo-2λ^6(1,3,2)dioxolan-4-carboxylate (**14**) was isolated in 92% yield. Again, the structures of products were assigned from the NMR spectra of mixtures of different product ratios using the above-mentioned NMR techniques.

For the major product (4*S*,5*S*,6*R*)-**13** a quite small coupling constant of $^3J_{HH}$ = 5.1 Hz was observed for H-2 (δ = 5.17 ppm) and H-3 (δ = 5.02 ppm). The $^3J_{HF}$ with H-3 was determined to be 15.0 Hz. The proton H-4 neighboring the fluorine atom at δ = 4.82 ppm showed a $^3J_{HH}$ = 5.1 Hz to H-3. These data suggest an *anti*-configuration of the substituents at carbons 3 and 4. In contrast, having a look on the other diastereomer (4*S*,5*S*,6*S*)-**14** a much larger $^3J_{HF}$ = 23.4 Hz and a much smaller $^3J_{HH}$ = 1.9 Hz with H-3 were detected suggesting the *syn*-arrangement of the substituents at C-3 and C-4. In the ^{13}C NMR spectra of these compounds only marginal differences of chemical shifts and coupling constants were found (see exp. part).

The ring opening of the cyclic sulfites **11** and **12** with sodium azide was shown to be very slow at 20 °C (90 hours, 95 % transformation) giving the 2-azido products almost exclusively. At 50 °C complete consumption of the starting compounds was detected after 18 hours, but significant amounts of the other regioisomers bearing the azido group in 3-position were formed (see below). At even higher temperature partial decomposition occurred.

Significantly higher reactivity and complete regioselectivity of the introduction of azide was observed in ring opening of the cyclic sulfates **13** and **14** with sodium azide. Similarly to a procedure used by Bittman et al.[11] for non-fluorinated cyclic sulfates, treatment of a 54:46 mixture of **13** and **14** with 5 equivalents of sodium azide at room temperature in a 2:1 mixture of acetone and water led to complete conversion of the starting sulphates after 3 hours. Complete regio- and stereoselectivity was observed after acidic hydrolysis of the crude product mixture of ring opening. An inseparable 62:38 mixture (^{19}F NMR of the crude product mixture) of the two diastereomeric fluorinated 2-azido-3-hydroxyoctadecanoic esters **15** and **16** was isolated in 78% yield after chromatographic purification. The stereochemistry of the products was assigned from mixtures containing different shares of the two regioisomers.

As most indicative signals of the major product (2*R*,3*S*,4*R*)-**15** the doublet of H-2 was found at δ = 4.15 ppm showing a small $^3J_{HH}$ = 4.1 Hz to H-3, which suggests *anti*-arrangement of the

azido- and the hydroxyl group. In contrast H-3 (δ = 4.00 ppm) exhibited a slightly larger $^3J_{HH}$ = 7.2 Hz to H-4 and a small $^3J_{HF}$ = 7.2 Hz, which suggest an *anti*-arrangement of the OH-group and fluorine. For the minor product (2*R*,3*S*,4*S*)-**16** a large $^3J_{HF}$ = 24.7 Hz to H-3 and a small $^3J_{HH}$ = 2.1 Hz was found for H-4 (δ = 4.66 ppm) suggesting the *syn*-arrangement of the functional groups at carbons 3 and 4. On the other hand a $^3J_{HH}$ = 7.6 Hz was observed for H-2 (δ = 4.00 ppm) and H-3 (δ = 3.81 ppm). An *anti,syn*-arrangement of the three functional groups is in agreement with these data.

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

Next we tried simultaneous reduction of both the azido and the ester groups using various equivalents of lithium aluminium hydride (up to 3.5 equivalents) in refluxing diethyl ether for ten hours or two days. Instead of the expected two products, complex mixtures of up to ten fluorinated compounds were obtained depending on the reaction conditions. Thus, we decided to reduce the functional groups one after the other selectively.

Staudinger reduction of the azido groups 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 gave the corresponding *N*-stearoylcarboxylic esters **17** and **18** without change of the ratio of isomers in practically quantitative combined yield of the crude products. This mixture could be separated by column chromatography giving (2*R*,3*S*,4*R*)-**17** with 39% yield and (2*R*,3*S*,4*S*)-**18** with 28% yield, both with >99% de and >98% ee (^{19}F NMR, $\Delta\delta$ = 0.33 ppm, 100 mol% Eu(hfc)$_3$ for **17** and $\Delta\delta$ = 0.10 ppm, 100 mol% Eu(hfc)$_3$ for **18**).

Most characteristic for the major product **17** are the very small $^3J_{HH}$ coupling constant of 1.9 Hz between H-2 (δ = 4.72 ppm) and H-3 (δ = 4.13 ppm) suggesting an *anti*-configuration of the functional groups in positions 2 and 3, and the small $^3J_{HF}$ = 3.3 Hz to H-3. Together with the large $^3J_{HH}$ = 8.8 Hz between H-3 and H-4 (δ = 4.30 ppm), these data suggest the *anti*-configuration of the OH- and the fluorine substituents.

The minor product **18** showed similar small $^3J_{HH}$ = 4.1 Hz between H-2 (δ = 4.74 ppm) and H-3 (δ = 3.91 ppm), but in contrast to **17**, a large $^3J_{HF}$ = 21.5 Hz to H-3. The $^3J_{HH}$ of H-3 and H-4 could not be resolved. These data support the *anti*,*syn*-arrangement of the functional groups at carbons C-2, C-3, and C-4.

In the ^{13}C NMR spectra of **17** and **18**, in addition to the carbonyl signals of the ester functions

(δ = 169.2 or δ = 169.8 ppm), two singlets of the amide groups were found at δ = 175.9 ppm or δ = 173.6 ppm, respectively.

To finish the synthetic sequence, the ester functions had to be reduced selectively in the presence of the amido groups. The reactions with 2.2 equivalents of DIBAL-H in diethyl ether at 0 °C according to a protocol of Kumar et al.,[12] or with both 2 equivalents of sodium borohydride and of lithium chloride in ethanol/THF (1:1), according to a procedure of Glunz et al.,[13] or with 12 equivalents of sodium borohydride and 10 equivalents of lithium bromide in THF at room temperature according to a protocol of Bittman et al.,[11] which all were selective with non-fluorinated compounds, were not selective with **17** and **18** but gave complex mixtures of products according to ^{19}F NMR. Finally, modification of a procedure originally published by Soai et al.[14] was successful. Accordingly, the reduction of (2*R*,3*S*,4*R*)-**17** or (2*R*,3*S*,4*S*)-**18**, respectively, with 2.5 equivalents of sodium borohydride in refluxing THF and successive addition of small portions of dry methanol to the refluxing reaction mixture (totally 20 equivalents) gave selectively the expected 4-fluoro 4,5-dihydroceramides **1** or **2**, in 45% and 72% yields. No starting material was detected in the crude product mixtures by ^{19}F NMR spectroscopy.

The structure of the products was determined spectroscopically. The enantiomeric excess of the products could not be determined doubtlessly, because no base line separation of the diastereomeric complexes was detected with up to 200 mol% of Eu(hfc)$_3$ or Pr(hfc)$_3$. However, no racemization occurred during reduction of the ester function. Otherwise a new diastereomer would have been formed.

For (2*S*,3*S*,4*R*)-**1** the diastereotopic protons at C-1 were found as doublets of doublets at δ = 3.72 ppm or δ = 3.90 ppm showing a $^2J_{HH}$ = 11.5 Hz and $^3J_{HH}$ = 3.3 Hz or 4.7 Hz, respectively, to H-2 (δ = 4.02–4.05 ppm, broad). Solely a coupling constant $^3J_{HH}$ = 8.5 Hz of H-2 to the amide proton (δ = 7.08 ppm) could be determined. The neighbouring H-3 (δ = 3.76 ppm) shows the typical $^3J_{HH}$ = 5.9 Hz to H-4 (δ = 4.46 ppm) and a quite small $^3J_{HF}$ = 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 at δ = 174.4 ppm, of carbon C-4 (δ = 94.0 ppm, $^1J_{CF}$ = 172.2 Hz), of carbon C-3 (δ = 73.0 ppm, $^2J_{CF}$ = 23.5 Hz), of carbon C-2 (δ = 51.6 ppm, $^3J_{CF}$ = 2.2 Hz) and of carbon C-1 (δ = 61.4 ppm).

For (2*S*,3*S*,4*S*)-**2** the diastereotopic protons at C-1 were identified as doublets of doublets at δ = 3.67 ppm or δ = 3.87 ppm with $^2J_{HH}$ = 11.5 Hz and $^3J_{HH}$ = 2.6 Hz or 4.3 Hz, respectively, to H-2 (δ = 4.00 ppm). A small $^3J_{HH}$ = 1.2 Hz of H-2 was found to the amide proton at δ = 6.63

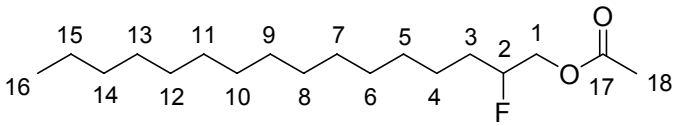
ppm. The $^{3}J_{HH}$ = 4.3 Hz of H-2 to the diastereotopic protons at C-1 and a $^{3}J_{HH}$ = 6.8 Hz to H-3 (δ = 3.66 ppm) were also identified. This proton showed a very large $^{3}J_{HF}$ = 25.6 Hz and a very small $^{3}J_{HH}$ = 2.6 Hz to H-4 (δ = 4.53 ppm). These data suggest the *anti*,*syn*-arrangement 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 at δ = 174.3 ppm, of the carbon C-4 (δ = 93.5 ppm, $^{1}J_{CF}$ = 172.2 Hz), of the carbon C-3 at δ = 72.0 ppm ($^{2}J_{CF}$ = 18.9 Hz), of the carbon C-2 (δ = 61.6 ppm, $^{3}J_{CF}$ = 2.9 Hz) and that of carbon C-1 at δ = 61.6 ppm.

Analogously to this synthetic sequence, also the 4-fluoro-4,5-dihydroceramides of the other enantiomeric series were prepared (see exp. part).

Procedures and Spectroscopic Data

1-Acetoxy-2-fluorohexadecane (5)

Potassium acetate (14.72 g, 331 mmol) was added to a solution of 1-bromo-2-fluorohexadecane (**4**)[15] (26.73 g, 82.7 mmol) in DMF (150 mL) and refluxed under argon for 26 h. Then a mixture of cyclohexane and ethyl acetate (1:1, 100 mL) was added to the reaction mixture and stirred at r.t. for 10 min. The precipitated solid material was filtered off and washed with the mentioned mixture of solvents (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 give **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).



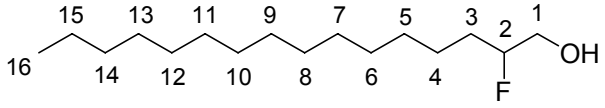
5

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^{3}J_{H,H}$ = 6.7 Hz, 3 H, 16-CH_3), 1.26–1.78 (br m, 26 H, 3-CH_2 to 15-CH_2), 2.10 (s, 3 H, 18-CH_3), 4.12 (ddd, $^{3}J_{H,F}$ = 21.4 Hz, $^{2}J_{H,H}$ = 12.4 Hz, $^{3}J_{H,H}$ = 6.7 Hz, 1 H, 1-CH_2), 4.21 (ddd, $^{3}J_{H,F}$ = 27.4 Hz, $^{2}J_{H,H}$ = 12.4 Hz, $^{3}J_{H,H}$ = 2.9 Hz, 1 H, 1-CH_2), 4.65 (ddddd, $^{2}J_{H,F}$ = 49.6 Hz, $^{3}J_{H,H}$ = 8.1 Hz, $^{3}J_{H,H}$ = 6.7 Hz, $^{3}J_{H,H}$ = 4.8 Hz, $^{3}J_{H,H}$ = 2.9 Hz, 1 H, 2-CH). ^{13}C NMR ($CDCl_3$): δ = 14.0 (q, C-16), 20.7 (q, C-18), 24.7 (dt, $^{3}J_{C,F}$ = 4.8 Hz, C-4), 22.7, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 29.7, 31.9 (t, C-5 to C-15), 31.4 (dt, $^{2}J_{C,F}$ = 20.9 Hz, C-3), 65.8 (dt, $^{2}J_{C,F}$ = 22.5 Hz, C-1), 91.3 (dd, $^{1}J_{C,F}$ = 172.3 Hz, C-2), 170.7 (s, C-17). ^{19}F NMR ($CDCl_3$): δ = –187.5 (dddm, $^{2}J_{F,H}$= 49.6 Hz, $^{3}J_{F,H}$= 22.9 Hz, $^{3}J_{F,H}$= 17.2 Hz); regioisomer: δ = –231.0 (ddd, $^{2}J_{F,H}$= 47.7 Hz, $^{2}J_{F,H}$= 47.7 Hz, $^{3}J_{F,H}$= 22.9 Hz). GC-MS: *m/z* = 302 (1) [M^+], 301 (0.5) [M^+ –

H], 282 (1) [M^+ – HF], 240 (5) [MH^+ – HF – $COCH_3$], 222 (10), 138 (12), 109 (35), 96 (92), 82 (93) [$C_6H_{10}^+$], 69 (70) [$C_5H_9^+$], 57 (85) [$C_4H_9^+$], 43 (100) [$COCH_3^+$, $C_3H_7^+$]. IR: $\tilde{\nu}$ = 2921, 2848 (s, ν -CH_2/CH_3), 1745 (s, ν -C=O), 1475, 1415 (m, δ -CH_2/CH_3), 1276, (m, ν -C–F), 1060, 1072, 1097 (m, br ν -C–F/C–O–C), 920 (m), 724 (m, δ -CH_2). $C_{18}H_{35}FO_2$ (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 r.t. for 2–4 hours. The progress of the reaction was monitored by DC. Then the mixture was poured into water (200 mL) and extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layer was 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 get **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).

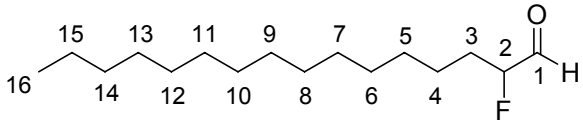


6

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.4 Hz, 3 H, 16-CH_3), 1.26–1.70 (br m, 26 H, 3-CH_2 to 15-CH_2), 1.95 (s, 1 H, OH), 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, 1-CH_2), 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, 2-CH). ^{13}C NMR ($CDCl_3$): δ = 14.1 (q, C-16), 24.9 (dt, $^3J_{C,F}$ = 3.8 Hz, C-4), 22.7, 29.3, 29.4, 29.5, 29.7, 31.9 (t, C-5 to C-15), 31.0 (dt, $^2J_{C,F}$ = 20.3 Hz, C-3), 65.1 (dt, $^2J_{C,F}$ = 21.6 Hz, C-1), 94.8 (dd, $^1J_{C,F}$ = 167.8 Hz, C-2). ^{19}F NMR ($CDCl_3$): 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). GC-MS: *m/z* = 260 (0) [M^+], 222 (2) [M^+ – HF – H_2O], 194 (8), 138 (8), 109 (24), 96 (68), 82 (90) [$C_6H_{10}^+$], 69 (58) [$C_5H_9^+$], 57 (94) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$]. ESI-MS (nanospray): *m/z* = 283 (15) [M + Na^+], 300 (8) [MH + K^+]. IR: $\tilde{\nu}$ = 3400, 3310 (m, br ν -OH), 2960, 2916, 2849 (s, ν -CH_2/CH_3), 1474, 1462, 1380 (m, δ -CH_2/CH_3), 1250 (m, ν -C–F), 1112, 1097, 1074 (m, ν -C–F/C–OH), 845 (m), 820 (m), 729, 721 (m, δ -CH_2). $C_{16}H_{33}FO$ (260.4): calcd. C 73.79, H 12.77; found: C 74.05, H 12.57.

2-Fluorohexadecanal (7)

Under argon oxalylchloride (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 (about 4 h) with vigorous stirring. The solution was stirred for 15 min and triethylamine (10.2 g, 100 mmol) was added. Within 30 min the mixture was allowed to warm up to r.t. and then treated with water (150 mL). The organic phase was separated and the aq layer was extracted with CH_2Cl_2 (20 mL). The combined organic layer was dried ($MgSO_4$) and the solvent was evaporated. The crude product (95 %) was used for the subsequent Wittig reaction without purification. However, the aldehyde **7** can be isolated by chromatography through a 5 cm column with silica gel (cyclohexane/ethyl acetate 10:1).

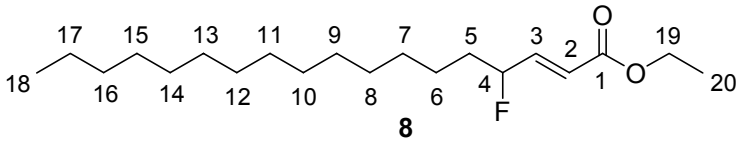


7

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H, 16-CH_3), 1.26–1.82 (br m, 26 H, 3-CH_2 to 15-CH_2), 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, 2-CH), 9.75 (dd, $^3J_{H,F}$ = 6.2 Hz, $^3J_{H,H}$ = 1.0 Hz, 1 H, 1-CHO). ^{13}C NMR ($CDCl_3$): δ = 14.1 (q, C-16), 24.2 (dt, $^3J_{C,F}$ = 2.6 Hz, C-4), 22.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9 (t, C-5 to C-15), 30.4 (dt, $^2J_{C,F}$ = 20.4 Hz, C-3), 95.0 (dd, $^1J_{C,F}$ = 180.6 Hz, C-2), 200.2 (dd, $^2J_{C,F}$ = 34.3 Hz, C-1). ^{19}F NMR ($CDCl_3$): 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, 2-CHF). GC-MS: *m/z* = 258 (3) [M^+], 238 (0.5) [M^+ – HF], 220 (0.5) [M^+ – HF – H_2O], 194 (4), 138 (6), 97 (30), 83 (40) [$C_6H_{11}^+$], 71 (44) [$C_5H_{11}^+$], 57 (98) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$]. IR: $\tilde{\nu}$ = 3394 (w, br ν -OH), 2960, 2919, 2850 (s, ν -CH_2/CH_3), 1742 (m, ν -C=O), 1473 (s, δ -CH_2/CH_3), 1267 (m, ν -C–F), 1074, 1026 (m, br ν -C–F/C–OH), 827 (m), 723 (m, δ -CH_2).

Ethyl (*E*)-4-fluorooctadec-2-enoate (8)

The freshly prepared aldehyde **7** (see above) in diethyl ether (10 mL), was added slowly under argon to a stirred solution of sodium hydride (0.6 g, 20 mmol) and ethyl phosphonoacetate (2.25 g, 10 mmol) in dry diethyl ether (250 mL) at 0 °C. The solution was allowed to warm up to r.t. within 30 min and refluxed for 4 h. The mixture was subsequently hydrolyzed with water (250 mL) at r.t. The phases were separated and the aqueous was extracted with diethyl ether (3 × 150 mL). The combined organic layer was 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).



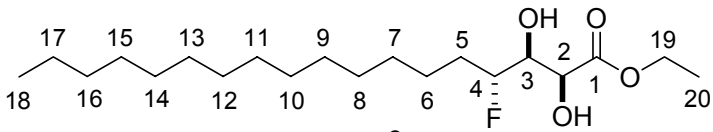
8

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^{3}J_{H,H}$ = 6.7 Hz, 3 H, 18-CH_3), 1.26–1.53 (br m, 24 H, 6-CH_2 to 17-CH_2), 1.29 (t, $^{3}J_{H,H}$ = 6.7 Hz, 3 H, 20-CH_3), 1.62–1.82 (m, 2 H, 5-CH_2), 4.21 (q, $^{3}J_{H,H}$ = 6.7 Hz, 2 H, 19-CH_2), 5.06 (ddddd, $^{2}J_{H,F}$ = 48.4 Hz, $^{3}J_{H,H}$ = 8.1 Hz, $^{3}J_{H,H}$ = 4.3 Hz, $^{3}J_{H,H}$ = 2.6 Hz, $^{4}J_{H,H}$ = 1.7 Hz, 1 H, 4-CH), 6.04 (ddd, $^{3}J_{H,H}$ = 15.7 Hz, $^{4}J_{H,H}$ = 1.7 Hz, $^{4}J_{H,F}$ = 1.7 Hz, 1 H, 2-CH), 6.88 (ddd, $^{3}J_{H,F}$ = 20.0 Hz, $^{3}J_{H,H}$ = 15.7 Hz, $^{3}J_{H,H}$ = 4.3 Hz, 1 H, 3-CH). ^{13}C NMR ($CDCl_3$): δ = 14.0 (q, C-18), 14.1 (q, C-20), 24.3 (dt, $^{3}J_{C,F}$ = 3.8 Hz, C-6), 22.7, 29.3, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 31.9 (t, C-7 to C-17), 34.8 (dt, $^{2}J_{C,F}$ = 20.3 Hz, C-5), 60.5 (t, C-19), 91.3 (dd, $^{1}J_{C,F}$ = 174.2 Hz, C-4), 121.1 (dd, $^{3}J_{C,F}$ = 10.2 Hz, C-2), 145.1 (dd, $^{2}J_{C,F}$ = 19.1 Hz, C-3), 166.0 (s, C-1). ^{19}F NMR ($CDCl_3$): δ = –184.3 (m). GC-MS *m/z* (%) 328 (15) [M^+], 308 (10) [M^+ – HF], 283 (14) [M^+ – OC_2H_5], 262 (10), 234 (14) [MH^+ – HF – $CO_2C_2H_5$], 220 (22), 135 (22), 125 (30), 109 (30), 95 (46), 81 (54) [$C_6H_9^+$], 69 (38) [$C_5H_9^+$], 57 (66) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$]. IR (NaCl palets): $\tilde{\nu}$ = 2932, 2853 (s, ν -CH_2/CH_3), 1732 (s, ν -C=O), 1667 (m, ν -C=C), 1466, 1366 (m, *δ* -CH_2/CH_3), 1304, 1270, 1179, 1035 (m, ν -C–F/-O–C–O), 981 (m), 726, 714 (m, *δ* -CH_2). $C_{20}H_{37}FO_2$ (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 down to 9 °C ± 1 °C and treated with $KMnO_4$ (120 mg, 0.8 mmol) in water (4 mL) under vigorous stirring. The mixture was stirred for one more hour at this temperature and then extracted (continuous extraction) with ethyl acetate. After drying ($MgSO_4$) and evaporation of the solvent, the residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate 5:2) to give a 60:40 of the diastereomeric 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*)-4-fluoro-2,3-dihydroxyoctadecanoate (9).

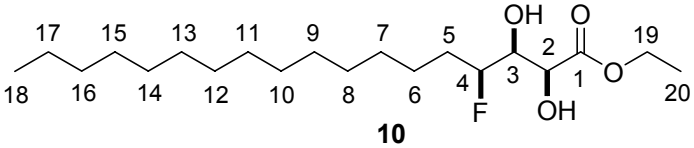


9

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^{3}J_{H,H}$ = 6.7 Hz, 3 H, 18-CH_3), 1.26–1.48 (br m, 24 H, 6-CH_2 to 17-CH_2), 1.35 (t, $^{3}J_{H,H}$ = 7.2 Hz, 3 H, 20-CH_3), 1.60–1.90 (m, 2 H, 5-CH_2), 3.87 (ddd, $^{3}J_{H,H}$ =

8.6 Hz, $^{3}J_{H,F}$ = 6.0 Hz, $^{3}J_{H,H}$ = 1.0 Hz, 1 H, 3-CH), 4.31 (q, $^{3}J_{H,H}$ = 7.2 Hz, 2 H, 19-CH_2), 4.44 (br s,1 H, 2-CH), 4.47 (dddd, $^{2}J_{H,F}$ = 47.8 Hz, $^{3}J_{H,H}$ = 8.7 Hz, $^{3}J_{H,H}$ = 8.7 Hz, $^{3}J_{H,H}$ = 2.4 Hz, 1 H, 4-CH). ^{19}F NMR ($CDCl_3$): δ = –190.7 (dddd, $^{2}J_{F,H}$ = 48.2 Hz, $^{3}J_{F,H}$ = 21.0 Hz, $^{3}J_{F,H}$ = 12.4 Hz, $^{3}J_{F,H}$ = 5.7 Hz).

Compound *rel*-(2*S*,3*S*,4*S*)-4-fluoro-2,3-dihydroxyoctadecanoate (10).



10

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^{3}J_{H,H}$ = 6.7 Hz, 3 H, 18-CH_3), 1.26–1.48 (br m, 24 H, 6-CH_2 to 17-CH_2), 1.31 (t, $^{3}J_{H,H}$ = 7.2 Hz, 3 H, 20-CH_3), 1.60–1.90 (m, 2 H, 5-CH_2), 3.90 (ddd, $^{3}J_{H,F}$ = 18.2 Hz, $^{3}J_{H,H}$ = 5.0 Hz, $^{3}J_{H,H}$ = 2.7 Hz, 1 H, 3-CH), 4.31 (q, $^{3}J_{H,H}$ = 7.2 Hz, 2 H, 19-CH_2), 4.23 (d, $^{3}J_{H,H}$ = 2.1 Hz 1 H, 2-CH), 4.63 (dddd, $^{2}J_{H,F}$ = 49.8 Hz, $^{3}J_{H,H}$ = 8.8 Hz, $^{3}J_{H,H}$ = 5.1 Hz, $^{3}J_{H,H}$ = 4.1 Hz, 1 H, 4-CH). ^{19}F NMR ($CDCl_3$): δ = –197.8 (dddd, $^{2}J_{F,H}$ = 49.6 Hz, $^{3}J_{F,H}$ = 17.2 Hz, $^{3}J_{F,H}$ = 17.2 Hz, $^{3}J_{F,H}$ = 15.3 Hz).

Compounds *rel*-(2*S*,3*S*,4*R*)-9 and *rel*-(2*S*,3*S*,4*S*)-10. ^{13}C NMR ($CDCl_3$) (several signals are overlapping and could not be assigned doubtlessly to one or the other isomer): δ = 14.0 (q, C-18 or C-20), 14.1 (q, C-20 or C-18), 24.8 and 24.9 (dt, $^{3}J_{C,F}$ = 5.1 Hz, $^{3}J_{C,F}$ = 5.1 Hz, C-6), 22.7, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9 (t, C-7 to C-17), 31.0 and 31.7 (dt, $^{2}J_{C,F}$ = 22.9 Hz, $^{2}J_{C,F}$ = 20.3 Hz, C-5), 62.4 (t, C-19), 69.7 and 70.7 (t or dt, $^{3}J_{C,F}$ = 5.1 Hz, C-2), 72.9 and 73.6 (dt, $^{2}J_{C,F}$ = 25.4 Hz, $^{2}J_{C,F}$ = 20.3 Hz, C-3), 92.1 and 93.9 (dd, $^{1}J_{C,F}$ = 172.9 Hz, $^{1}J_{C,F}$ = 170.4 Hz, C-4), 172.7 and 173.4 (s, C-1). ESI-MS (nanospray): *m/z* = 385 (44) [M + Na^+]. IR (KBr): $\tilde{\nu}$ = 3477 (s br, ν -O–H), 2954, 2926, 2851 (s, ν -CH_2/CH_3), 1742, 1728, 1707 (s, ν -C=O), 1473, 1391, 1377 (m, *δ* -CH_2/CH_3), 1301, 1205, 1143, 1033 (s, ν -C–F/-O–C–O), 1067 (m, ν -C–OH), 971 (m), 868 (m), 826, 723 (m, *δ* -CH_2); High resolution MS: $C_{20}H_{39}FO_4Na$ [ESI] (g/mol). Calcd. 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.

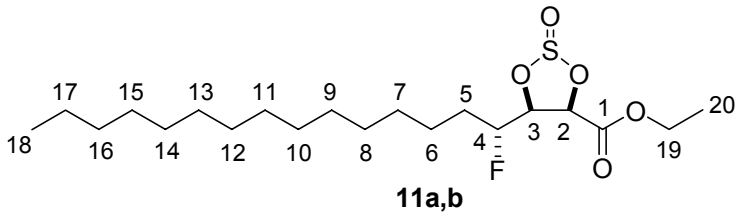
Ethyl (2*S*,3*S*,4*R*)-4-fluoro-2,3-dihydroxyoctadecanoate (9) and ethyl (2*S*,3*S*,4*S*)-4-fluoro-2,3-dihydroxyoctadecanoate (10). A mixture of AD-mix-β (3.07 g, 8.8 μmol OsO_4) and methanesulfonyl amide (209 mg, 2.19 mmol) in *tert*-butanol/H_2O (1:1, 50 mL) was stirred at r.t. until became a clear solution. This solution was cooled to 0 °C and under stirring ethyl (*E*)-4-fluorooctadec-2-enoate (**8**) (720 mg, 2.19 mmol) was added slowly. The mixture was stirred at 0 °C for further 7 days. Then sodium sulfite (3.12 g, 25 mmol) was added at r.t. and stirred for 30 min until all salts were dissolved (addition of some amount of water might be necessary). The

solution was transferred to a separation funnel and ethyl acetate (100 mL) was added. After vigorous shaking the phases were separated and the aqueous was extracted with ethyl acetate (4 × 50 mL). The combined organic layer was washed with 2 N aq NaOH (2 × 25 mL), water (25 mL) and 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 give a 63:37 mixture of the two diastereomers (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 agree 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 mixture (^{19}F NMR) of the two diastereomeric compounds (2*R*,3*R*,4*S*)-**9** and (2*R*,3*R*,4*R*)-**10** was prepared. Yield: 375 mg (47 %); after repeated column chromatography a 74:26 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-2λ^4-(1,3,2)dioxathiolan-4-carboxylates (11) and ethyl *rel*-(4*S*,5*S*,6*S*)-5-(1-fluoropentadecyl)-2-oxo-2λ^4-(1,3,2)dioxathiolan-4-carboxylates (12)

A solution of the 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 argon and refluxed until starting material was no longer detected by DC (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 get a mixture of the four diastereomeric sulfites **11a**, **11b**, **12a**, and **12b**. Yield: 173 mg (81 %). m.p. 41 °C.

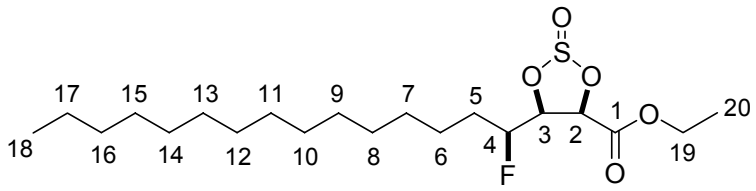


11a,b

Ethyl *rel*-(4*S*,5*S*,6*R*)-5-(1-fluoropentadecyl)-2-oxo-2λ^4-(1,3,2)dioxathiolan-4-carboxylate (11a) (first diastereomer). ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H, 20-CH_3), 1.26–1.48 (br m, 24 H, 8-CH_2 to 19-CH_2), 1.33 or 1.34 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, 23-CH_3), 1.60–1.84 (m, 2 H, 7-CH_2), 4.30 or 4.32 or 4.33 or 4.33 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, 22-CH_2), 4.71 (ddd, $^3J_{H,F}$ = 8.9 Hz, $^3J_{H,H}$ = 8.0 Hz, $^3J_{H,H}$ = 4.0 Hz, 1 H, 5-CH), 4.80 (dddd, $^2J_{H,F}$ = 47.8 Hz,

$^{3}J_{H,H}$ = 8.6 Hz, $^{3}J_{H,H}$ = 8.0 Hz, $^{3}J_{H,H}$ = 2.8 Hz, 1 H, 6-CH), 5.35 (dd, $^{3}J_{H,H}$ = 4.0 Hz, $^{4}J_{H,F}$ = 1.4 Hz, 1 H, 4-CH). ^{19}F NMR ($CDCl_3$): δ = –185.7 (dddd, $^{2}J_{F,H}$ = 45.8 Hz, $^{3}J_{F,H}$ = 21.0 Hz, $^{3}J_{F,H}$ = 15.3 Hz, $^{3}J_{F,H}$ = 9.5 Hz). GC-MS: *m/z* = 408 (0) [M^+], 337 (8) [$M^+ - C_5H_{11}$], 335 (20) [$M^+ - CO_2C_2H_5$], 289 (8), 271 (16) [$M^+ - SO_2 - CO_2C_2H_5$], 251 (22) [$M^+ - SO_2 - CO_2C_2H_5 - HF$], 233 (15) [$M^+ - SO_2 - CO_2C_2H_5 - HF - H_2O$], 135 (34), 109 (30), 94 (55), 83 (88) [$C_6H_9^+$], 69 (84) [$C_5H_9^+$], 57 (100) [$C_4H_9^+$], 43 (84) [$C_3H_7^+$].

Ethyl *rel*-(4*S*,5*S*,6*R*)-5-(1-fluoropentadecyl)-2-oxo-2λ^4-(1,3,2)dioxathiolan-4-carboxylate (11b) (second diastereomer). ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^{3}J_{H,H}$ = 6.7 Hz, 3 H, 20-CH_3), 1.26–1.48 (br m, 24 H, 8-CH_2 to 19-CH_2), 1.33 or 1.34 (t, $^{3}J_{H,H}$ = 7.2 Hz, 3 H, 23-CH_3), 1.60–1.84 (m, 2 H, 7-CH_2), 4.30 or 4.32 or 4.33 or 4.33 (q, $^{3}J_{H,H}$ = 7.2 Hz, 2 H, 22-CH_2), 4.60–4.84 (m, 1 H, 6-CH), 4.99 (d, $^{3}J_{H,H}$ = 5.1 Hz, 1 H, 4-CH), 5.27 (ddd, $^{3}J_{H,F}$ = 18.4 Hz, $^{3}J_{H,H}$ = 5.2 Hz, $^{3}J_{H,H}$ = 3.8 Hz, 1 H, 5-CH). ^{19}F NMR ($CDCl_3$): δ = –194.5 (dddd, $^{2}J_{F,H}$ = 47.7 Hz, $^{3}J_{F,H}$ = 22.9 Hz, $^{3}J_{F,H}$ = 15.3 Hz, $^{3}J_{F,H}$ = 7.6 Hz). GC-MS: *m/z* = 408 (0) [M^+], 359 (4), 324 (4), 251 (24) [$M^+ - SO_2 - CO_2C_2H_5 - HF$], 233 (6) [$M^+ - SO_2 - CO_2C_2H_5 - HF - H_2O$], 135 (12), 109 (18), 95 (38), 83 (55) [$C_6H_9^+$], 69 (55) [$C_5H_9^+$], 57 (82) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$].



12a,b

Ethyl *rel*-(4*S*,5*S*,6*S*)-5-(1-fluoropentadecyl)-2-oxo-2λ^4-(1,3,2)dioxathiolan-4-carboxylates (12a) (first diastereomer). ^{1}H NMR ($CDCl_3$): *δ* = 0.88 (t, $^{3}J_{H,H}$ = 6.7 Hz, 3 H, 20-CH_3), 1.26–1.48 (br m, 24 H, 8-CH_2 to 19-CH_2), 1.33 or 1.34 (t, $^{3}J_{H,H}$ = 7.2 Hz, 3 H, 23-CH_3), 1.60–1.84 (m, 2 H, 7-CH_2), 4.30 or 4.32 or 4.33 or 4.33 (q, $^{3}J_{H,H}$ = 7.2 Hz, 2 H, 22-CH_2), 4.61 (ddd, $^{3}J_{H,F}$ = 22.4 Hz, $^{3}J_{H,H}$ = 7.9 Hz, $^{3}J_{H,H}$ = 2.9 Hz, 1 H, 5-CH), 4.71–4.80 (dm, $^{2}J_{H,F}$ = 48.0 Hz, 1 H, 6-CH), 5.32 (d, $^{3}J_{H,H}$ = 7.9 Hz, 1 H, 4-CH). ^{19}F NMR ($CDCl_3$): δ = –195.0 (dddd, $^{2}J_{F,H}$ = 49.6 Hz, $^{3}J_{F,H}$ = 19.1 Hz, $^{3}J_{F,H}$ = 17.2 Hz, $^{3}J_{F,H}$ = 11.5 Hz). GC-MS: *m/z* = 408 (0) [M^+], 365 (6) [$M^+ - C_3H_7$], 343 (2), 306 (4) [$M^+ - SO_2 - HF - H_2O$] 251 (26) [$M^+ - SO_2 - CO_2C_2H_5 - HF$], 233 (8) [$M^+ - SO_2 - CO_2C_2H_5 - HF - H_2O$], 229 (10), 135 (14), 111 (22), 96 (52), 83 (56) [$C_6H_9^+$], 69 (62) [$C_5H_9^+$], 57 (90) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$].

Ethyl *rel*-(4*S*,5*S*,6*S*)-5-(1-fluoropentadecyl)-2-oxo-2λ^4-(1,3,2)dioxathiolan-4-carboxylates (12b) (second diastereomer). ^{1}H NMR ($CDCl_3$): *δ* = 0.88 (t, $^{3}J_{H,H}$ = 6.7 Hz, 3 H, 20-CH_3), 1.26–1.48 (br m, 24 H, 8-CH_2 to 19-CH_2), 1.33 or 1.34 (t, $^{3}J_{H,H}$ = 7.2 Hz, 3 H, 23-CH_3),

1.60–1.84 (m, 2 H, 7-CH_2), 4.30 or 4.32 or 4.33 or 4.33 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, 22-CH_2), 4.60–4.84 (m, 1 H, 6-CH), 4.97 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H, 4-CH), 5.14 (ddd, $^3J_{H,F}$ = 24.3 Hz, $^3J_{H,H}$ = 6.9 Hz, $^3J_{H,H}$ = 1.7 Hz, 1 H, 5-CH). ^{19}F NMR ($CDCl_3$): 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); GC-MS: *m/z* = 408 (0) [M^+], 390 (2) [$M^+ - H_2O$], 337 (8) [$M^+ - C_5H_{11}$], 336 (20) [$MH^+ - CO_2C_2H_5$], 271 (15) [$M^+ - SO_2 - CO_2C_2H_5$], 251 (40) [$M^+ - SO_2 - CO_2C_2H_5 - HF$], 233 (6) [$M^+ - SO_2 - CO_2C_2H_5 - HF - H_2O$], 135 (16), 95 (44), 83 (42) [$C_6H_9^+$], 69 (68) [$C_5H_9^+$], 57 (80) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$].

Compounds *rel*-(4*S*,5*S*,6*R*)-11a,b and *rel*-(4*S*,5*S*,6*S*)-12a,b: ^{13}C NMR ($CDCl_3$) (several signals are overlapping and could not be assigned doubtlessly to the isomeric compounds): ^{13}C NMR ($CDCl_3$): δ = 13.9 and 14.0 and 14.1 (q, C-20 and C-23), 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, C-8), 22.7, 29.2, 29.3, 29.5, 29.6, 29.6, 31.9 (t, C-9 to C-19), 31.0 and 31.7 (dt, $^2J_{C,F}$ = 22.9 Hz, $^2J_{C,F}$ = 20.3 Hz, C-7), 62.8 and 62.9 (t, C-22), 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, C-4), 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, C-5), 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, C-6), 166.6 and 167.0 and 167.5 and 167.7 (s, C-21); IR (KBr): $\tilde{\nu}$ = 2926, 2857 (s br, ν -CH_2/CH_3), 1762 , 1749 (s, ν -C=O), 1470, 1384 (m, *δ* -CH_2/CH_3), 1281, 1232, 1033 (m br, ν -C–F/-O–C–O), 1033, 1035 (m br, ν -S=O). $C_{20}H_{37}FO_5S$ (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 enantiomeric compounds **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**.

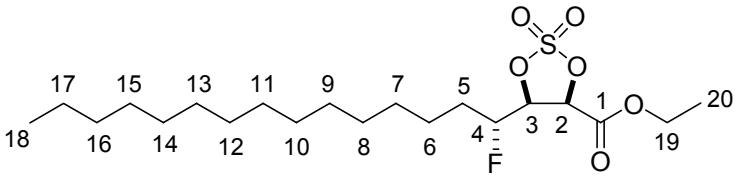
(4*S*,5*S*,6*R*)-5-(1-fluoropentadecyl)-2-oxo-2λ^4-(1,3,2)dioxathiolan-4-carboxylates (11) and ethyl (4*S*,5*S*,6*S*)-5-(1-fluoropentadecyl)-2-oxo-2λ^4-(1,3,2)dioxathiolan-4-carboxylates (12). From a 56:44 mixture of (2*S*,3*S*,4*R*)-**9** and (2*S*,3*S*,4*S*)-**10** (230 mg, 0.57 mmol) the title compounds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

(4*R*,5*R*,6*S*)-5-(1-fluoropentadecyl)-2-oxo-2λ^4-(1,3,2)dioxathiolan-4-carboxylates (11) and ethyl (4*R*,5*R*,6*R*)-5-(1-fluoropentadecyl)-2-oxo-2λ^4-(1,3,2)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 agree with those of the racemic mixture.

Ethyl *rel*-(4*S*,5*S*,6*R*)-5-(1-fluoropentadecyl)-2,2-dioxo-2λ^6-(1,3,2)dioxathiolan-4-carboxylate (13) and ethyl *rel*-(4*S*,5*S*,6*S*)-5-(1-fluoropentadecyl)-2,2-dioxo-2λ^6-(1,3,2)-dioxathiolan-4-carboxylate (14)

A vigorously stirred solution of the above mixture of the racemic sulfites **11** and **12** (151 mg, 0.37 mmol) in a mixture of acetonitrile and water (25:1, 35 mL) was stirred with sodium periodate (130 mg, 0.60 mmol) and rutheniumtrichloride trihydrate (1.3 mg, 1 mol%) at r.t. until no more starting material was detected by DC (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 layer was 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 give a 60:40 mixture of the title compounds **13** and **14** as a white waxy solid. Yield: 120 mg (76 %). m.p. 37–38 °C.

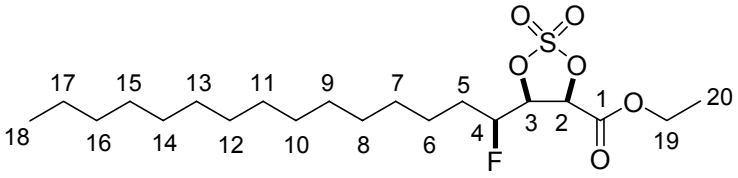
Ethyl *rel*-(4*S*,5*S*,6*R*)-5-(1-fluoropentadecyl)-2,2-dioxo-2λ^6-(1,3,2)dioxathiolan-4-carboxylate (13).



13

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H, 20-CH_3), 1.26–1.62 (br m, 24 H, 8-CH_2 to 19-CH_2), 1.36 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, 23-CH_3), 1.64–1.94 (m, 2 H, 7-CH_2), 4.33–4.39 (br m, 2 H, 22-CH_2), 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, 6-CHF), 5.02 (ddd, $^3J_{H,F}$ = 15.0 Hz, $^3J_{H,H}$ = 5.1 Hz, $^3J_{H,H}$ = 5.1 Hz, 1 H, 5-CH), 5.17 (d, $^3J_{H,H}$ = 5.1 Hz, 1 H, 4-CH). ^{19}F NMR ($CDCl_3$): 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); GC-MS: *m/z* = 424 (0.5) [M^+], 395 (0.2) [$M^+ - C_2H_5$], 269 (0.5), 251 (5) [$M^+ - SO_3 - CO_2C_2H_5 - HF$], 233 (15) [$M^+ - SO_3 - CO_2C_2H_5 - HF - H_2O$], 133 (5), 109 (6), 9 (12), 85 (20) [$C_6H_{13}^+$], 71 (46) [$C_5H_{11}^+$], 57 (98) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$].

Ethyl *rel*-(4*S*,5*S*,6*S*)-5-(1-fluoropentadecyl)-2,2-dioxo-2λ^6-(1,3,2)-dioxathiolan-4-carboxylate (14).



14

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^{3}J_{H,H}$ = 6.7 Hz, 3 H, 20-CH_3), 1.26–1.62 (br m, 24 H, 8-CH_2 to 19-CH_2), 1.37 (t, $^{3}J_{H,H}$ = 7.4 Hz, 3 H, 23-CH_3), 1.64–1.94 (m, 2 H, 7-CH_2), 4.33–4.39 (br m, 2 H, 22-CH_2), 4.73 (dddd, $^{2}J_{H,F}$ = 46.4 Hz, $^{3}J_{H,H}$ = 9.1 Hz, $^{3}J_{H,H}$ = 4.6 Hz, $^{3}J_{H,H}$ = 1.9 Hz, 1 H, 6-CHF), 4.94 (ddd, $^{3}J_{H,F}$ = 23.4 Hz, $^{3}J_{H,H}$ = 7.4 Hz, $^{3}J_{H,H}$ = 1.9 Hz, 1 H, 5-CH), 5.26 (d, $^{3}J_{H,H}$ = 7.4 Hz, 1 H, 4-CH). ^{19}F NMR ($CDCl_3$): δ = –198.5 (dddd, $^{2}J_{F,H}$ = 45.8 Hz, $^{3}J_{F,H}$ = 22.9 Hz, $^{3}J_{F,H}$ = 17.2 Hz, $^{3}J_{F,H}$ = 15.3 Hz). GC-MS: *m/z* = 424 (0.5) [M^+], 351 (1) [$M^+ - CO_2C_2H_5$], 306 (2), 271 (4) [$M^+ - SO_3 - CO_2C_2H_5$], 251 (10) [$M^+ - SO_3 - CO_2C_2H_5 - HF$], 233 (5) [$M^+ - SO_3 - CO_2C_2H_5 - HF - H_2O$], 133 (10), 111 (16), 95 (22), 85 (55) [$C_6H_{13}^+$], 71 (76) [$C_5H_{11}^+$], 57 (100) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$].

Compounds *rel*-(4*S*,5*S*,6*S*)-13 and *rel*-(4*S*,5*S*,6*S*)-14: ^{13}C NMR ($CDCl_3$) (several signals are overlapping and could not be assigned doubtlessly to the isomeric compounds): δ = 13.9 and 14.0 or 14.1 (q, C-20 and C-23), 24.4 and 24.8 (dt, $^{3}J_{C,F}$ = 3.8 Hz, $^{3}J_{C,F}$ = 3.8 Hz, C-8), 22.7, 29.1, 29.3, 29.3, 29.4, 29.6, 29.6, 31.9 (t, C-9 to C-19), 30.5 and 30.6 (dt, $^{2}J_{C,F}$ = 20.3 Hz, $^{2}J_{C,F}$ = 21.6 Hz, C-7), 63.6 and 63.6 (t, C-22), 75.5 and 75.8 (dd, $^{3}J_{C,F}$ = 6.4 Hz, $^{3}J_{C,F}$ = 5.1 Hz, C-4), 82.0 and 82.5 (dd, $^{2}J_{C,F}$ = 26.7 Hz, $^{2}J_{C,F}$ = 19.1 Hz, C-5), 89.4 and 90.4 (dd, $^{1}J_{C,F}$ = 183.1 Hz, $^{1}J_{C,F}$ = 179.3 Hz, C-6), 165.1 and 165.3 (s, C-21); IR (KBr): $\tilde{\nu}$ = 2918, 2851 (s br, ν -CH_2/CH_3), 1744 (s, ν -C=O), 1472 (m, *δ* -CH_2/CH_3), 1403 (s, ν -SO_2), 1312, 1217, 1034 (m br, ν -C–F/-O–C–O), 1034 (m br, ν -S=O), 859 (m), 820 (m). $C_{20}H_{37}FO_6S$ (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 enantiomeric compounds **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-2λ^6-(1,3,2)dioxathiolan-4-carboxylate (13) and ethyl (4*S*,5*S*,6*S*)-5-(1-fluoropentadecyl)-2,2-dioxo-2λ^6-(1,3,2)-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 agree with those of the racemic mixture.

Ethyl (4*R*,5*R*,6*S*)-5-(1-fluoropentadecyl)-2,2-dioxo-2λ^6-(1,3,2)dioxathiolan-4-carboxylate (13) and ethyl (4*R*,5*R*,6*R*)-5-(1-fluoropentadecyl)-2,2-dioxo-2λ^6-(1,3,2)-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 agree with those of the racemic mixture.

Selectivity of ring opening of the cyclic sulfites *rel*-(4*S*,5*S*,6*R*)-11 and *rel*-(4*S*,5*S*,6*S*)-12 with sodium azide

According to a protocol, which was used by Fernandez and Kumar for non-fluorinated cyclic sulfites,[16] we treated a 55:45 mixture of the diastereomeric cyclic sulfites *rel*-(4*S*,5*S*,6*R*)-**11a,b** and *rel*-(4*S*,5*S*,6*S*)-**12a,b** (considering the stereochemistry at sulfur this was a 27.5:27.5/15:30 mixture of diastereomers) with excess sodium azide in DMF at 0 °C, 10 °C, 20 °C, 50 °C and 75 °C. The reaction was highly regio- and stereoselective at low temperatures. Exclusive attack at the 2-position with complete inversion of the configuration was observed at 0 °C and 10 °C, however with lower conversion. Moreover, the diastereomers *rel*-(4*S*,5*S*,6*R*)-**11a,b** reacted faster than the *rel*-(4*S*,5*S*,6*S*)-isomers **12a,b** giving a 88:12 mixture of the products *rel*-(2*R*,3*S*,4*R*)-**15** and *rel*-(2*R*,3*S*,4*S*)-**16** at conversion lower than 10 %. At higher conversion (>30%), the ratio of diastereomers approaches the original 55:45 mixture (see diagram 1).

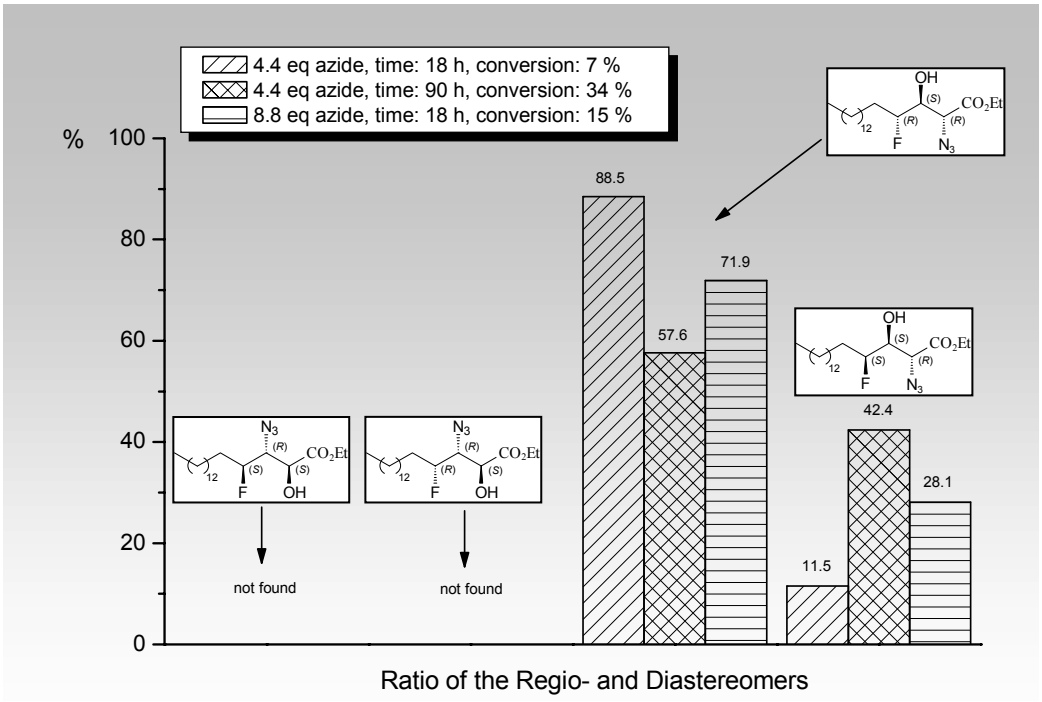


Diagram 1: Ratio of products formed from diastereomers *rel*-(4*S*,5*S*,6*R*)-**11a,b** and *rel*-(4*S*,5*S*,6*S*)-isomers **12a,b** with sodium azide in DMF at 10 °C

At 20 °C and conversion >40 % the ratio was close to 55:45, but a very small amount of another regioisomer, most properly *rel*-(2*S*,3*R*,4*S*)-3-azido-4-fluoro-2-hydroxyoctadecanoate was also formed. At a reaction temperature as high as 50 °C and complete conversion of the starting cyclic sulfites **11a,b** and **12a,b** significant amounts of both 3-azido isomers were formed in addition to the regioisomers **15** and **16**. At 75 °C the 3-azido regioisomers became the major products of the reaction.

Also the relative amount of the applied sodium azide did influence the ratio of regio- and diastereomers to some extend (see diagrams at 10, 20, 50, and 75 °C. At even higher temperature (100 °C) almost complete destruction occurred.

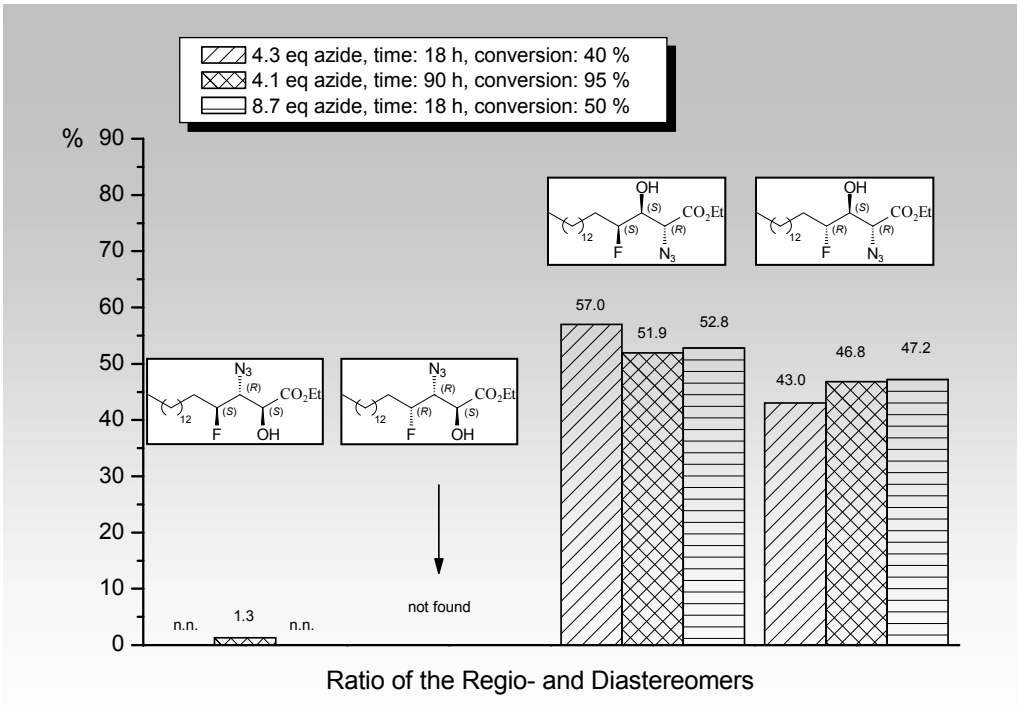


Diagram 2: Ratio of products formed from diastereomers *rel*-(4*S*,5*S*,6*R*)-**11a,b** and *rel*-(4*S*,5*S*,6*S*)-isomers **12a,b** with sodium azide in DMF at 20 °C

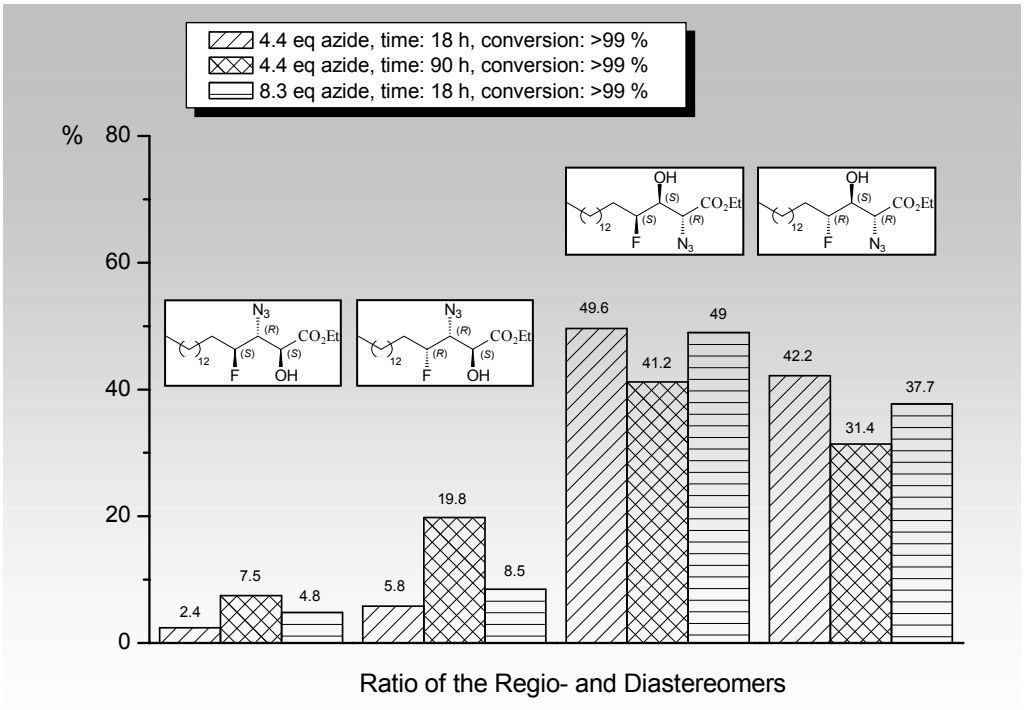


Diagram 3: Ratio of products formed from diastereomers *rel*-(4*S*,5*S*,6*R*)-**11a,b** and *rel*-(4*S*,5*S*,6*S*)-isomers **12a,b** with sodium azide in DMF at 50 °C

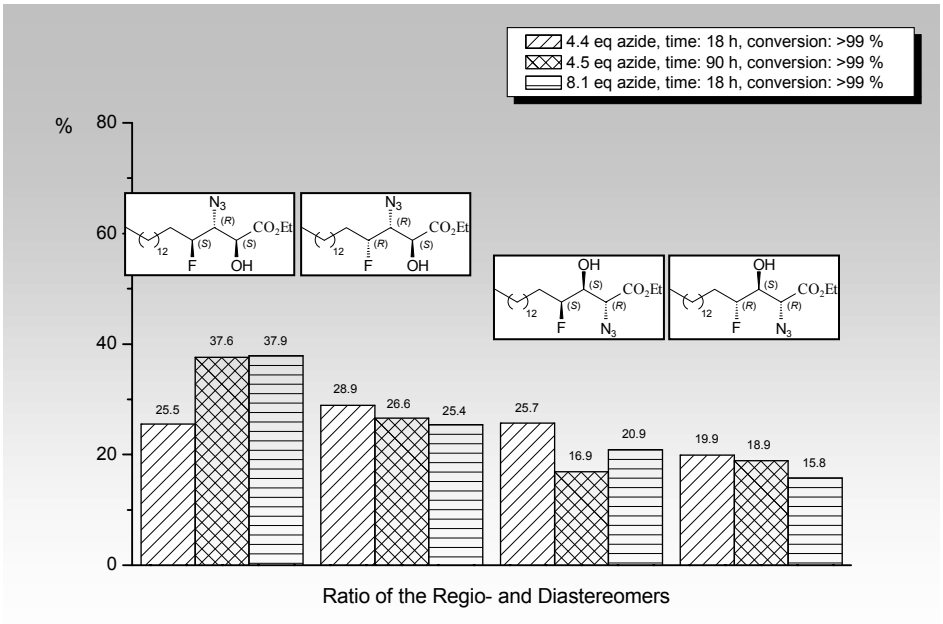


Diagram 4: Ratio of products formed from diastereomers *rel*-(4*S*,5*S*,6*R*)-**11a,b** and *rel*-(4*S*,5*S*,6*S*)-isomers **12a,b** with sodium azide in DMF at 75 °C

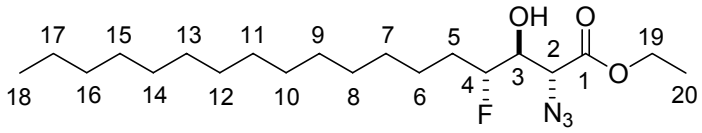
Procedure: A solution of the above racemic 55:45 mixture of cyclic sulfites *rel*-(2*R*,3*S*,4*R*)-**11** and *rel*-(2*R*,3*S*,4*S*)-**12** (1 mL of a 38.1 mM solution in DMF, 15.5 mg, 38.1 μmol) in DMF (1 mL) and sodium azide (10.9 mg or 21.8 mg, 168 μmol or 336 μmol, 4.4 or 8.8 equivalents, respectively) was vigorously stirred at the given temperature for the given time (see diagrams 1–4). The solvent was evaporated in vacuo and the crude product was extracted with diethyl ether (5 mL). The ethereal solution was treated with 20 % aq H_2SO_4 (5 mL) and stirred until no starting material was detectable by DC (8–12 h). The reaction mixture was dissolved with diethyl ether (5 mL) and the organic layer was separated and the aqueous phase was extracted with diethyl ether (2 × 5 mL). The combined organic layer was washed with 5 % aq $NaHCO_3$ solution (2 × 5 mL) and dried ($MgSO_4$). After evaporation of the solvent, the product ratio in the crude material was determined ^{19}F NMR spectroscopically.

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 vigorously stirred solution of the above 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 stirred at r.t. until no more starting material was detectable by DC (about 24 h). The solvent was removed in vacuo and the crude solid material was dissolved with stirring in a 1:1 mixture of diethyl ether and 20 % aq. H_2SO_4 (40 mL) until no starting material was found by DC (8–12 hours). The mixture was diluted with diethyl ether (40 mL) and the

clear ethereal layer was separated. The aq phase was extracted with diethyl ether (4 × 25 mL) and the combined organic layer was washed with 5 % aq $NaHCO_3$ solution (2 × 20 mL) and water (20 mL). After drying ($MgSO_4$) the solvent was removed and the crude product was purified by column chromatography (silic gel, cyclohexane/ethyl acetate 5:1) to give a 62:38 mixture of the 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.

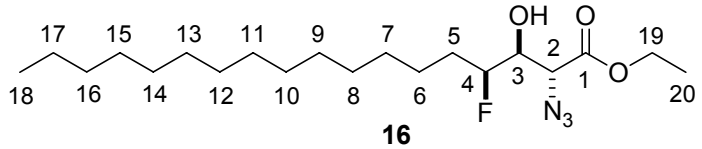
Ethyl *rel*-(2*R*,3*S*,4*R*)-2-azido-4-fluoro-3-hydroxyoctadecanoate (15)



15

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H, 18-CH_3), 1.26–1.85 (br m, 26 H, 5-CH_2 to 17-CH_2), 1.33 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, 20-CH_3), 4.00 (ddd, $^3J_{H,F}$ = 7.2 Hz, $^3J_{H,H}$ = 7.2 Hz, $^3J_{H,H}$ = 4.1 Hz, 1 H, 3-CH), 4.15 (d, $^3J_{H,H}$ = 4.1 Hz, 1 H, 2-CH), 4.32 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, 19-CH_2), 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, 4-CH). ^{13}C NMR ($CDCl_3$): δ = 14.1 (q, C-18 and C-20), 24.8 (t, C-6), 22.7, 29.4, 29.5, 29.5, 29.7, 31.9 (t, C-7 to C-17), 31.2 (dt, $^2J_{C,F}$ = 20.3 Hz, C-5), 62.2 (t, C-19), 62.8 (dd, $^3J_{C,F}$ = 3.1 Hz, C-2), 73.4 (dd, $^2J_{C,F}$ = 25.4 Hz, C-3), 92.9 (dd, $^1J_{C,F}$ = 170.4 Hz, C-4), 168.2 (s, C-1). ^{19}F NMR ($CDCl_3$): 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).

Ethyl *rel*-(2*R*,3*S*,4*S*)-2-azido-4-fluoro-3-hydroxyoctadecanoate (16)



16

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3 H, 18-CH_3), 1.26–1.85 (br m, 26 H, 5-CH_2 to 17-CH_2), 1.35 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, 20-CH_3), 3.81 (ddd, $^3J_{H,F}$ = 24.7 Hz, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 2.1 Hz, 1 H, 3-CH), 4.00 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 2-CH), 4.30 bzw. 4.30 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, je 19-CH_2), 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, 4-CH). ^{13}C NMR ($CDCl_3$): δ = 14.1 (q, C-18 and C-20), 25.0 (dt, $^3J_{C,F}$ = 5.1 Hz, C-6), 22.7, 29.4, 29.5, 29.5, 29.7, 31.9 (t, C-7 to C-17), 30.7 (dt, $^2J_{C,F}$ = 20.3 Hz, C-5), 62.3 (t, C-19), 62.4 (d, C-2), 72.3 (dd, $^2J_{C,F}$ = 20.3 Hz, C-3), 92.3 (dd, $^1J_{C,F}$ = 172.9 Hz, C-4), 169.3 (s, C-1). ^{19}F NMR ($CDCl_3$): 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).

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, ν -OH), 2927, 2854 (s br, ν -CH_2/CH_3), 2111 (s, ν -N_3), 1735 (s, ν -C=O), 1669 (m), 1468, 1377 (m, δ

-CH_2/CH_3), 1261, 1202, 1067, 1019 (m br, ν -C–F/-O–C–O), 1067 (m br, ν -C–OH), 984 (m), 822, 721 (m, δ -CH_2); High resolution MS: $C_{20}H_{38}FN_3O_3Na$ [ESI] (g/mol): Calcd. 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 enantiomeric compounds **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**.

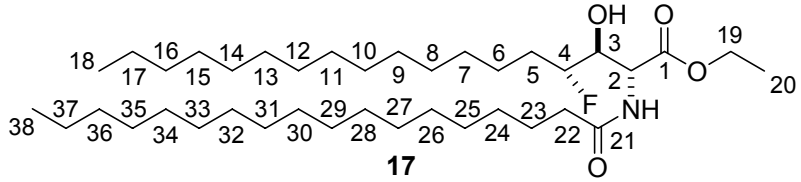
Ethyl (2*R*,3*S*,4*R*)-2-azido-4-fluoro-3-hydroxyoctadecanoate (15) and ethyl (2*R*,3*S*,4*S*)-2-azido-4-fluoro-3-hydroxyoctadecanoate (16). From a 63:37 mixture of (4*S*,5*S*,6*R*)-**13** and (4*S*,5*S*,6*S*)-**14** (105 mg, 0.25 mmol) the title compounds were prepared as a 62:38 mixture. Yield: 75 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 agree 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 agree 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 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**) (162 mg, 0.42 mmol) in a 9:1 mixture of THF and water (20 mL) under stirring was treated successively with 4-nitrophenylstearate (255 mg, 0.63 mmol) and triphenylphosphine (131 mg, 0.50 mmol) under argon at r.t. Stirring was continued at this temperature until all starting material was consumed (about 10 h). Then diethyl ether (60 mL) was added, the phases were separated and the aqueous was extracted with diethyl ether (2 × 15 mL). The combined organic layer was washed with 1 % aq $NaHCO_3$ solution (5 × 15 mL), dried ($MgSO_4$) and evaporated. The yellow product mixture was separated by column chromatography (silica gel, cyclohexane/ ethyl acetate 5:1) to give the diastereopure title compounds **17** and **18**.

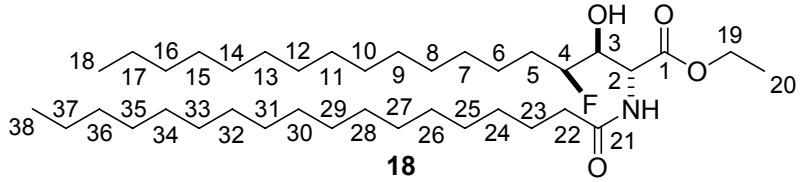
Ethyl *rel*-(2*R*,3*S*,4*R*)-4-fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (17).



17

Yield: 101 mg (39 %). m.p. 89–90 °C. R_f 0.45 (pentane/diethyl ether, 5:1). ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 6 H, 18-CH_3 and 38-CH_3), 1.26–1.53 (br m, 54 H, 6-CH_2 to 17-CH_2 and 23-CH_2 to 37-CH_2), 1.30 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, 20-CH_3), 1.58–1.85 (m, 2 H, 5-CH_2), 2.32 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, 22-CH_2), 4.13 (ddd, $^3J_{H,H}$ = 8.8 Hz, $^3J_{H,F}$ = 3.3 Hz, $^3J_{H,H}$ = 1.9 Hz, 1 H, 3-CH), 4.25 or 4.26 (q, je $^3J_{H,H}$ = 7.2 Hz, 2 H, je 19-CH_2), 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-CH), 4.72 (dd, $^3J_{H,H}$ = 5.0 Hz, $^3J_{H,H}$ = 1.9 Hz, 1 H, 2-CH), 6.70 (d, $^3J_{H,H}$ = 5.0 Hz, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ = 14.1 (q, C-18, C-20 and C-38), 24.8 (t, C-6), 22.7, 25.6, 29.2, 29.3, 29.4, 29.5, 29.7, 31.9 (t, C-7 to C-17 and C-23 to C-37), 31.6 (t, C-5), 36.3 (t, C-22), 57.4 (d, C-2), 62.4 (t, C-19), 74.7 (dd, $^2J_{C,F}$ = 25.4 Hz, C-3), 93.2 (dd, $^1J_{C,F}$ = 170.4 Hz, C-4), 169.2 (s, C-1), 175.9 (s, C-21). ^{19}F NMR ($CDCl_3$): 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).

Ethyl *rel*-(2*R*,3*S*,4*S*)-4-fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (18).



18

Yield: 39 mg (15 %). m.p. 91–92 °C. R_f 0.19 (pentane/diethyl ether, 5:1). ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 6 H, 18-CH_3 and 38-CH_3), 1.26–1.53 (br m, 54 H, 6-CH_2 to 17-CH_2 and 23-CH_2 to 37-CH_2), 1.29 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, 20-CH_3), 1.58–1.90 (m, 2 H, 5-CH_2), 2.25 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H, 22-CH_2), 3.91 (ddm, $^3J_{H,F}$ = 21.5 Hz, $^3J_{H,H}$ = 4.1 Hz, 1 H, 3-CH), 4.23 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, 19-CH_2), 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-CH), 4.74 (dd, $^3J_{H,H}$ = 8.1 Hz, $^3J_{H,H}$ = 4.1 Hz, 1 H, 2-CH), 6.36 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ = 14.1 (q, C-18, C-20 and C-38), 24.9 (t, C-6), 22.7, 25.5, 29.2, 29.3, 29.5, 29.7, 31.9 (t, C-7 to C-17 and C-23 to C-37), 31.0 (dt, $^2J_{C,F}$ = 20.3 Hz, C-5), 36.5 (t, C-22), 54.6 (d, C-2), 61.9 (t, C-19), 73.6 (dd, $^2J_{C,F}$ = 20.3 Hz, C-3), 94.1 (dd, $^1J_{C,F}$ = 170.4 Hz, C-4), 169.8 (s, C-1), 173.6 (s, C-21). ^{19}F NMR ($CDCl_3$): 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).

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, ν -OH and/or -NH), 2929, 2850 (s br, ν -CH_2/CH_3), 1758 (m, ν -C=O), 1637 (m br, ν -C=O, amide), 1537 (m, δ -N-H, amide), 1471, 1378 (m, δ -CH_2/CH_3), 1200, 1096, 1030 (m br, ν -C–F/-O–C–O), 872 (m), 727 (m, δ -CH_2). High resolution MS: $C_{38}H_{74}FNO_4Na$ [ESI] (g/mol). Calcd. 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 ethyl (2*R*,3*S*,4*R*)-2-azido-4-fluoro-3-hydroxy-octadecanoate (**15**) and ethyl (2*R*,3*S*,4*S*)-2-azido-4-fluoro-3-hydroxyoctadecanoate (**16**) (209 mg, 0.54 mmol) after chromatographic separation the 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% $Eu(hfc)_3$).

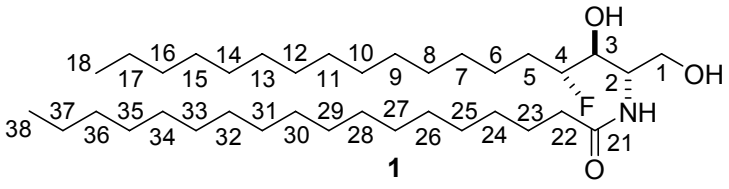
Ethyl (2*R*,3*S*,4*S*)-4-fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (18). Yield: 95 mg (28 %). m.p. 92–93 °C. $[\alpha]_D^{20}$ = –14.9 (c 0.83, $CHCl_3$), ee >98 % (^{19}F NMR, decoupled, 89 mol% $Eu(hfc)_3$).

Analogously, from a 61:39 mixture of 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**) (151 mg, 0.39 mmol) after chromatographic separation the 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)**.

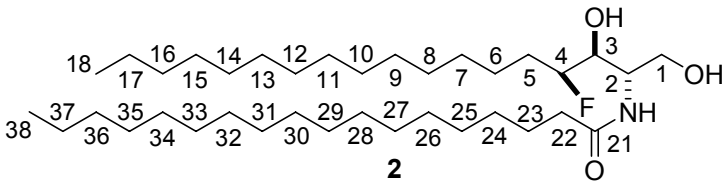


1

A solution of ethyl (2*R*,3*S*,4*R*)-4-fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (**17**) (123 mg, 0.20 mmol) in freshly distilled dry THF (10 mL) was treated with $NaBH_4$ (19 mg, 0.50

mmol) under argon and refluxed. To the refluxing mixture dry methanol (128 μL, 4.0 mmol) was added dropwise using a syringe over a periode of 10 min. The mixture was refluxed for two more hours and then cooled to r.t. Then water (20 mL) was added and the mixture was stirred until becoming turbid. This mixture was extracted with a $CHCl_3$/methanol mixture (5 × 20 mL, gradient 50:1 to 10:1). The combined organic layer was 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 ($CDCl_3$:MeOH-d_4 = 5:1 to 9:1): δ = 0.89 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H, 18-CH_3 and 36-CH_3), 1.27–1.45 (br m, 54 H, 6-CH_2 to 17-CH_2 and 21-CH_2 to 35-CH_2), 1.51–1.81 (m, 2 H, 5-CH_2), 2.23 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H, 20-CH_2), 3.72 (dd, $^2J_{H,H}$ = 11.5 Hz, $^3J_{H,H}$ = 3.3 Hz, 1 H, 1-CH), 3.76 (dd, $^3J_{H,F}$ = 10.5 Hz, $^3J_{H,H}$ = 5.9 Hz, 1 H, 3-CH), 3.90 (dd, $^2J_{H,H}$ = 11.5 Hz, $^3J_{H,H}$ = 4.7 Hz, 1 H, 1-CH), 4.02-4.05 (br m, 1 H, 2-CH), 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, 4-CH), 7.08 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, NH). ^{13}C NMR ($CDCl_3$:MeOH-d_4 = 5:1 to 9:1): δ = 13.6 (q, C-18 and C-36), 24.8 (dt, $^3J_{C,F}$ = 2.8 Hz, C-6), 22.3, 25.5, 29.0, 29.0, 29.0, 29.1, 29.2, 29.3, 31.6 (t, C-7 to C-17, C-21 to C-35), 30.5 (dt, $^2J_{C,F}$ = 21.2 Hz, C-5), 36.2 (t, C-20), 51.6 (dd, $^3J_{C,F}$ = 2.2 Hz, C-2), 61.4 (t, C-1), 73.0 (dd, $^2J_{C,F}$ = 23.5 Hz, C-3), 94.0 (dd, $^1J_{C,F}$ = 171.2 Hz, C-4), 174.4 (s, C-19). ^{19}F NMR ($CDCl_3$:MeOH-d_4 = 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).

***rel*-(2*S*,3*S*,4*S*)-4-Fluoro-2-(stearoylamido)octadecane-1,3-diol (2)**.



2

Analogously to the above procedure from ethyl *rel*-(2*R*,3*S*,4*S*)-4-fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (**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 ($CDCl_3$:MeOH-d_4 = 5:1 to 9:1): δ = 0.88 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, 18-CH_3 and 36-CH_3), 1.26–1.55 (br m, 54 H, 6-CH_2 to 17-CH_2 and 21-CH_2 to 35-CH_2), 1.58–1.85 (m, 2 H, 5-CH_2), 2.21 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H, 20-CH_2), 3.67 (dd, $^2J_{H,H}$ = 11.5 Hz, $^3J_{H,H}$ = 4.3 Hz, 1 H, 1-CH), 3.66 (ddd, $^3J_{H,F}$ = 25.6 Hz, $^3J_{H,H}$ = 6.8 Hz, $^3J_{H,H}$ = 2.6 Hz, 1 H, 3-CH), 3.87 (dd, $^2J_{H,H}$ = 11.5 Hz, $^3J_{H,H}$ = 4.3 Hz, 1 H, 1-CH), 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, 2-CH), 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, 4-CH), 6.63 (br d, $^3J_{H,H}$ = 1.2 Hz, 1 H, NH). ^{13}C NMR ($CDCl_3$:MeOH-d_4 = 5:1 to 9:1): δ = 13.7 (q, C-18 and C-36), 24.8

(dt, $^{3}J_{C,F}$ = 4.8 Hz, C-6), 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, C-7 to C-17, C-21 to C-35), 31.0 (dt, $^{2}J_{C,F}$ = 20.7 Hz, C-5), 36.4 (t, C-20), 52.0 (dd, $^{3}J_{C,F}$ = 2.9 Hz, C-2), 61.6 (t, C-1), 72.0 (dd, $^{2}J_{C,F}$ = 18.9 Hz, C-3), 93.5 (dd, $^{1}J_{C,F}$ = 172.2 Hz, C-4), 174.3 (s, C-19). ^{19}F NMR ($CDCl_3$:MeOH-d_4 = 5:1 to 9:1): δ = –196.7 (dddd, $^{2}J_{F,H}$ = 47.9 Hz, $^{3}J_{F,H}$ = 24.8 Hz, $^{3}J_{F,H}$ = 15.3 Hz, $^{3}J_{F,H}$ = 9.5 Hz); IR (KBr): $\tilde{\nu}$ = 3418 (s br, ν -OH and/or -NH), 2916, 2849 (s br, ν -CH_2/CH_3), 1640 (s, ν -C=O, amide), 1576 (m, δ -N–H, amide), 1472, 1388 (m, δ -CH_2/CH_3), 1080, 1040 (m br, ν -C–OH), 734 (m, δ -CH_2); High resolution MS: $C_{36}H_{72}FNO_3Na$ [ESI] (g/mol). Calcd. 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 ethyl (2*R*,3*S*,4*R*)-4-fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (**17**) (104 mg, 0.18 mmol) the title compound was 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 to the above procedure from ethyl (2*R*,3*S*,4*S*)-4-fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (**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 ethyl (2*S*,3*R*,4*S*)-4-fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (**17**) (55 mg, 0.088 mmol) the title compound was 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 to the above procedure from ethyl (2*S*,3*R*,4*R*)-4-fluoro-3-hydroxy-2-(stearoylamido)octadecanoate (**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).

Determination of the enantiomeric excesses of the diols 9 and 10, the azides 15 and 16, the esters 17 and 18 and the fluoroceramides 1 and 2.

The enantiomeric excesses of the diols **9** and **10**, the azides **15** and **16**, and the esters **17** and **18** were determined ^{19}F NMR spectroscopically in $CDCl_3$ using Eu(hfc)$_3$ and Pr(hfc)$_3$ as chiral shift reagents. For the fluoroceramides **1** and **2** the same method was tested in several solvent combinations. However, only in $CDCl_3$/methanol-d_4 a partial separation of the signals of the diastereomeric complexes of compound **1** was possible using up to 200 mol% of Pr(hfc)$_3$ not

allowing the precise determination of the ee value. For compound **2** no separation of the signals was observed neither with $Eu(hfc)_3$ nor with $Pr(hfc)_3$. However, partial racemization would have resulted in the formation of diastereomers. This was not observed.

Table 1: Results of the shift experiments to determine the enantiomeric excess of products

Compound	Shift reagent (mol%)	δ [ppm]		$\Delta\delta$ [ppm]	Baseline separation
rel-(2*S*,3*S*,4*R*)-**9**	-	–190.7		-	-
rel-(2*S*,3*S*,4*R*)-**9**	$Pr(hfc)_3$ (43)	–192.668	–192.945	0.277	no
rel-(2*S*,3*S*,4*R*)-**9**	$Pr(hfc)_3$ (109)	–195.957	–196.706	0.749	yes
rel-(2*S*,3*S*,4*R*)-**9**	$Eu(hfc)_3$ (59)	–189.034	–198.284	0.250	yes
rel-(2*S*,3*S*,4*R*)-**9**	$Eu(hfc)_3$ (108)	broad		-	no
rel-(2*S*,3*S*,4*S*)-**10**	-	–197.8		-	-
rel-(2*S*,3*S*,4*S*)-**10**	$Pr(hfc)_3$ (43–143)	broad		-	no
rel-(2*S*,3*S*,4*S*)-**10**	$Eu(hfc)_3$ (59–108)	broad		-	no
rel-(2*R*,3*S*,4*R*)-**15**	-	–191.1		-	-
rel-(2*R*,3*S*,4*R*)-**15**	$Pr(hfc)_3$ (38)	–193.114 (broad)		-	no
rel-(2*R*,3*S*,4*R*)-**15**	$Pr(hfc)_3$ (144)	–194.403 (broad)		-	no
rel-(2*R*,3*S*,4*R*)-**15**	$Eu(hfc)_3$ (17)	–190.999 (broad)		-	no
rel-(2*R*,3*S*,4*R*)-**15**	$Eu(hfc)_3$ (57)	–189.684	–189.738	0.054	no
rel-(2*R*,3*S*,4*R*)-**15**	$Eu(hfc)_3$ (96)	–189.534	–189.608	0.074	yes
rel-(2*R*,3*S*,4*S*)-**16**	-	–202.8		-	-
rel-(2*R*,3*S*,4*S*)-**16**	$Pr(hfc)_3$ (38)	–202.758	–203.204	0.446	no
rel-(2*R*,3*S*,4*S*)-**16**	$Pr(hfc)_3$ (144)	–204.129	–204.838	0.709	yes
rel-(2*R*,3*S*,4*S*)-**16**	$Eu(hfc)_3$ (57)	–199.511	–199.585	0.074	no
rel-(2*R*,3*S*,4*S*)-**16**	$Eu(hfc)_3$ (167)	–199.158	–199.253	0.095	no
rel-(2*R*,3*S*,4*R*)-**17**	-	–189.3		-	-
rel-(2*R*,3*S*,4*R*)-**17**	$Pr(hfc)_3$ (53)	–193.512 (broad)		-	no
rel-(2*R*,3*S*,4*R*)-**17**	$Pr(hfc)_3$ (164)	–197.510	–197.767	0.257	no
rel-(2*R*,3*S*,4*R*)-**17**	$Pr(hfc)_3$ (320)	–198.422	–198.908	0.468	yes
rel-(2*R*,3*S*,4*R*)-**17**	$Eu(hfc)_3$ (51)	–188.217	–188.420	0.203	no
rel-(2*R*,3*S*,4*R*)-**17**	$Eu(hfc)_3$ (103)	–187.325	–187.650	0.325	yes
rel-(2*R*,3*S*,4*S*)-**18**	-	–196.0		-	-
rel-(2*R*,3*S*,4*S*)-**18**	$Pr(hfc)_3$ (52)	–201.500 (broad)		-	-
rel-(2*R*,3*S*,4*S*)-**18**	$Pr(hfc)_3$ (307)	–208.641	–208.790	0.149	no
rel-(2*R*,3*S*,4*S*)-**18**	$Eu(hfc)_3$ (52)	–194,917	–195.011	0.096	no
rel-(2*R*,3*S*,4*S*)-**18**	$Eu(hfc)_3$ (104)	–193,789	–194.086	0.297	yes
rel-(2*S*,3*S*,4*R*)-**1**	-	–191.1		-	-
rel-(2*S*,3*S*,4*R*)-**1**	$Pr(hfc)_3$ (54)	–191.256	–191.270	0.014	no
rel-(2*S*,3*S*,4*R*)-**1**	$Pr(hfc)_3$ (200)	–191.364	–191.391	0.027	no
rel-(2*S*,3*S*,4*S*)-**2**	-	–196.7		-	-
rel-(2*S*,3*S*,4*S*)-**2**	$Pr(hfc)_3$ (54-196)	broad		-	-

[1] [1a] G. Alvernhe, A. Laurent, G. Haufe, *Synthesis* **1987**, 562–564. [1b] G. Haufe, G. Alvernhe, A. Laurent, T. Ernet, O. Goj, S. Kröger, A. Sattler, *Org. Synth.* **1999**, *76*, 159–168.

[2] F. Tranel, G. Haufe, *J. Fluorine Chem.* **2004**, *125*, 1593–1608.

[3] [18a] A. Burchardt, T. Takahashi, Y. Takeuchi, G. Haufe, *J. Org. Chem.* **2001**, *66*, 2078–2084. [18b] G. Haufe, A. Burchardt, *Eur. J. Org. Chem.* **2001**, 4501–4507. [18c] G. Haufe, A. Burchardt, *Synthesis* **2002**, 648–654.

[4] J. Oldendorf, G. Haufe, *J. Prakt. Chem.* **2000**, *342*, 52–57.

[5] F. Tranel, G. Haufe, *J. Fluorine Chem.* **2004**, *125*, 1593–1608.

[6] [3a] S. T. Purrington, N. V. Lazaridis, C. L. Bumgardner, *Tetrahedron Lett.* **1986**, *27*, 2715–2716. [3b] H. Suga, M. Schlosser, *Tetrahedron* **1990**, *46*, 4261–4264. [3c] F. A. Davis, P. V. N. Kasu, G. Sundarababu, H. Qi, *J. Org. Chem.* **1997**, *62*, 7546–7547. [3d] Review: F. A. Davis, P. V. N. Kasu, *Org. Prep. Proc. Int.* **1999**, *31*, 125–143.

[7] D. F. Taber, J. C. Amedio, jr., K.-Y. Jung, *J. Org. Chem.* **1987**, *52*, 5621–5622.

[8] [5a] W. S. Wadsworth, jr., W. D. Emmons, *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738. [5b] W. S. Wadsworth, *Org. React.* **1977**, *25*, 73–353.

[9] R. A. Fernandes, P. Kumar, *Tetrahedron:Asymmetry* **1999**, *10*, 4797–4802.

[10] Y. Gao, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539.

[11] L. He, H.-S. Byun, R. Bittman, *J. Org. Chem.* **2000**, *65*, 7618–7626.

[12] R. A. Fernandes, P. Kumar, *Eur. J. Org. Chem.* **2000**, 3447–3449.

[13] P. W. Glunz, D. H. Rich, *Synth. Commun.* **1999**, *5*, 835–842.

[14] K. Soai, S. Yokoyama, A. Ookawa, *Synthesis* **1987**, 48–49.

[15] F. Tranel, G. Haufe, *J. Fluorine Chem.* **2004**, *125*, 1593–1608.

[16] R. A. Fernandes, P. Kumar, *Eur. J. Org. Chem.* **2000**, 3447–3449.