Supporting Information

Organized collapse structures in chiral mixtures of ethyl 2-azido-4-fluoro-3-hydroxystearates

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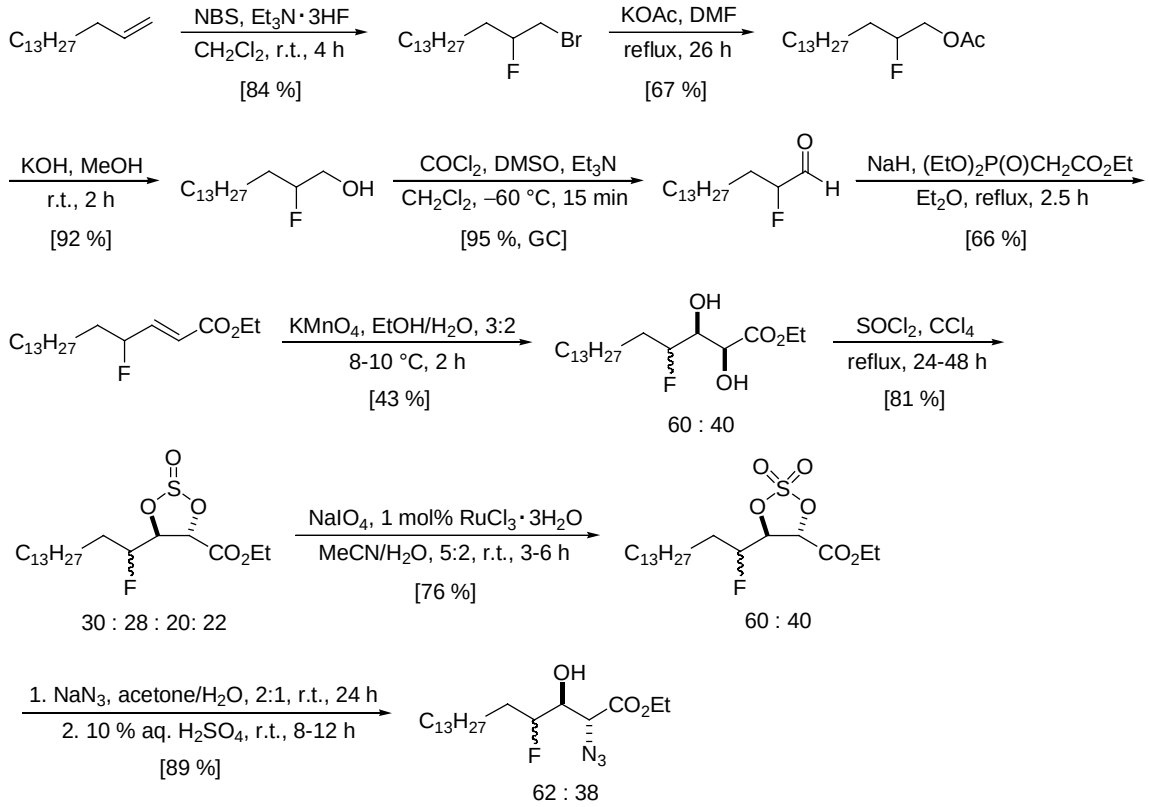
Ethyl *rel*-(2*R*,3*S*,4*R)*-2-Azido-4-fluoro-3-hydroxyoctadecanoate and *rel*-(2*R*,3*S*,4*S)*-2-Azido-4-fluoro-3-hydroxyoctadecanoate have been synthesized according to the sequence depicted in Scheme 1. The optically active compounds were prepared analogously applying a Sharpless bishydroxylation with AD-mix-α or AD-mix-β, respectively, as the key-step.

Scheme 1:



1-Bromo-2-fluorohexadecane

A solution of hexadecene (22.44 g, 100 mmol) and triethylamine tris(hydrogen fluoride) (10 mL, 62 mmol) in CH_2Cl_2 (150 mL) was cooled to 0 °C. Under vigorous stirring *N*-bromosuccinimide (18.58 g, 110 mmol) was added in portions and allowed to warm up to r.t. After four more hours stirring at this temperature, the mixture was poured into ice-water (150 mL) and neutralized with conc. aq. ammonia. The aq. phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layer was washed with 0.1 M HCl (2 × 50 mL) and 5 % aq $NaHCO_3$ (3 × 50 mL) and water (50 mL). After drying ($MgSO_4$) the solvent was evaporated and the residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 20:1); yield: 27.22 g (84 %); mp 38-39 °C.

1-Acetoxy-2-fluorohexadecane

Potassium acetate (14.72 g, 331 mmol) was added to a solution of 1-bromo-2-fluorohexadecane (26.73 g, 82.7 mmol) in DMF (150 mL) and refluxed under argon for 26 h. Then a mixture of cyclohexane and ethylacetate (1:1, 100 mL) was added to the cold reaction mixture and stirred for 10 min. The precipitated solid material was filtered off and washed with the 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); yield: 16.71 g (67 %); mp 37-38 °C.

2-Fluorohexadecan-1-ol

A solution of KOH (4.21 g, 75 mmol) in methanol (100 mL) was treated with 1-acetoxy-2-fluorohexadecane (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); yield: 12.86 g (92 %); mp 66-67 °C.

2-Fluorohexadecanal

Under argon oxalylchloride (82.8 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 (2.82 g, 10.8 mmol) dissolved in CH_2Cl_2 (150 mL) was added 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 was used for the subsequent Wittig reaction without purification.

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

The freshly prepared aldehyde (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 cold mixture was subsequently hydrolyzed with water (250 mL). 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).

Ethyl *rel*-(2*S*,3*S*,4*R*)-4-Fluoro-2,3-dihydroxyoctadecanoate and ethyl *rel*-(2*S*,3*S*,4*S*)-4-fluoro-2,3-dihydroxyoctadecanoate

Ethyl (*E*)-4-fluorooctadec-2-enoate (264 mg, 1.25 mmol) in ethanol (6 mL) was cooled down to 9 °C ± 1 °C and treated with $KMnO_4$ (188 mg, 1.25 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 get a 60:40 of the diastereomeric products as a white waxy solid, yield: 121 mg (43 %); mp 71-72 °C.

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

A Solution of the diastereomeric diols (see above) (190 mg, 0.52 mmol) in CCl_4 (15 mL) was treated with freshly distilled thionylchloride ($SOCl_2$) (300 mg, 2.51 mmol) under argon and refluxed until starting material is 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; yield: 173 mg (81 %); mp 41 °C.

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

A vigorously stirred solution of the above mixture of sulfites (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

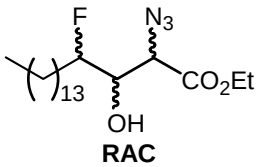
material was detected by DC (3-6 h). The reaction mixture was treated with diethyl ether (50 mL) and stirred for some minutes. After separation of the phases, the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layer was washed with water (50 mL) and dried ($MgSO_4$). 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 as a white waxy solid; yield: 120 mg (76 %); mp 37-38 °C.

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

A vigorously stirred solution of the above mixture of sulfates (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; yield: 80 mg (89 %); mp 41-42 °C.

Characterization of ethyl 2-azido-4-fluoro-3-hydroxy-stearates

RAC



RAC

(*RSR/SRS*)/(*RSS/SRR*)

Yield: 80 mg (0.21 mmol, 89 %) (±)-(2R,3S,4R) und (±)-(2R,3S,4S)
dr: 62:38 (^{19}F-NMR, decoupled)

^{1}H-NMR (CDCl3):

[(±)-(2*R*,3*S*,4*R*]
δ [ppm]: 0.88 (t, $^{3}J_{H,H}$ = 6.7 Hz, 3 H, 18-CH_3), 1.26-1.85 (br m, 26 H, 5-CH_2 - 17-CH_2), 1.33 (t, $^{3}J_{H,H}$ = 7.2 Hz, 3 H, 20-CH_3), 4.00 (ddd, $^{3}J_{H,F}$ = 7.2 Hz, $^{3}J_{H,H}$ = 7.2 Hz, $^{3}J_{H,H}$ = 4.1 Hz, 1 H, 3-CH), 4.15 (d, $^{3}J_{H,H}$ = 4.1 Hz, 1 H, 2-CH), 4.32 (q, $^{3}J_{H,H}$ = 7.2 Hz, 2 H, 19-CH_2), 4.58 (dddd, $^{2}J_{H,F}$ = 47.7 Hz, $^{3}J_{H,H}$ = 8.8 Hz, $^{3}J_{H,H}$ = 7.2 Hz, $^{3}J_{H,H}$ = 3.1 Hz, 4-CH).

[(±)-(2*R*,3*S*,4*S*)]
0.88 (t, $^{3}J_{H,H}$ = 6.7 Hz, 3 H, 18-CH_3), 1.26-1.85 (br m, 26 H, 5-CH_2 - 17-CH_2), 1.35 (t, $^{3}J_{H,H}$ = 7.2 Hz, 3 H, 20-CH_3), 3.81 (ddd, $^{3}J_{H,F}$ = 24.7 Hz, $^{3}J_{H,H}$ = 7.6 Hz, $^{3}J_{H,H}$ = 2.1 Hz, 1 H, 3-CH), 4.00 (d, $^{3}J_{H,H}$ = 7.6 Hz, 1 H, 2-CH), 4.30 bzw. 4.30 (q,$^{3}J_{H,H}$ = 7.2 Hz, 2 H, je 19-CH_2), 4.66 (dddd, $^{2}J_{H,F}$ = 48.2 Hz, $^{3}J_{H,H}$ = 6.9 Hz, $^{3}J_{H,H}$= 4.7 Hz, $^{3}J_{H,H}$ = 2.1 Hz, 4-CH).

^{13}C-NMR ($CDCl_3$):

[(±)-(2*R*,3*S*,4*R*)]
δ [ppm]: 14.1 (q, C-18 und C-20), 24.8 (t, C-6), 22.7, 29.4, 29.5, 29.5, 29.7, 31.9 (t, C-7 -C-17), 31.2 (dt, $^{2}J_{C,F}$ = 20.3 Hz, C-5), 62.2 (t, C-19), 62.8 (dd, $^{3}J_{C,F}$ = 3.1 Hz, C-2), 73.4 (dd, $^{2}J_{C,F}$ = 25.4 Hz, C-3), 92.9 (dd, $^{1}J_{C,F}$ = 170.4 Hz, C-4), 168.2 (s, C-1).
[(±)-(2*R*,3*S*,4*S*)]
14.1 (q, C-18 und C-20), 25.0 (dt, $^{3}J_{C,F}$ = 5.1 Hz, C-6), 22.7, 29.4, 29.5, 29.5, 29.7, 31.9 (t, C-7 - C-17), 30.7 (dt, $^{2}J_{C,F}$ = 20.3 Hz, C-5), 62.3 (t, C-19), 62.4 (d,C-2), 72.3 (dd, $^{2}J_{C,F}$ = 20.3 Hz, C-3), 92.3 (dd, $^{1}J_{C,F}$ = 172.9 Hz, C-4), 169.3 (s,C-1).

^{19}F-NMR ($CDCl_3$):

[(±)-(2*R*,3*S*,4*R*)]
δ [ppm]: -191.1 (dddd, $^{2}J_{F,H}$ = 47.7 Hz, $^{3}J_{F,H}$ = 35.5 Hz, $^{3}J_{F,H}$ = 21.0 Hz, $^{3}J_{F,H}$ = 7.2 Hz).

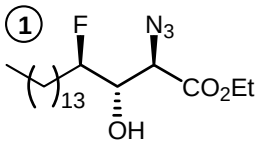
[(±)-(2*R*,3*S*,4*S*)]
-200.8 (dddd, $^{2}J_{F,H}$ = 48.2 Hz, $^{3}J_{F,H}$ = 32.3 Hz, $^{3}J_{F,H}$ = 24.8 Hz, $^{3}J_{F,H}$ = 15.3 Hz).

ESI-MS (Nanospray, 1.32 kV Kapillar- u. 35 V Konusspannung):
m/z (%): 426 (6) [M + K^+], 410 (100) [M + Na^+], 405 (16) [M + NH_4^+].
[(±)-(2*R*,3*S*,4*R*)-] and [(±)-(2*R*,3*S*,4*S*)]
424/422 (100/36) [M + Cl^-]. [(±)-(2*R*,3*S*,4*R*)] and [(±)-(2*R*,3*S*,4*S*)]

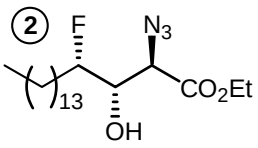
exact mass: $C_{20}H_{38}FN_3O_3Na$ [ESI]
(g/mol) calc.: 410.2795 meas.: 410.2843

C,H,N-analysis: $C_{20}H_{38}FN_3O_3$ (387.53)
(%) calc.: C 61.99 H 9.88 N 10.84
meas.: C 62.14 H 10.78 N 10.91
meas.: C 61.64 H 9.74 N 10.38

RDIA



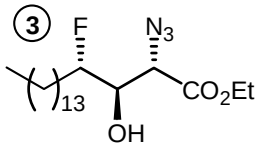
2R*,3*S*,4*R



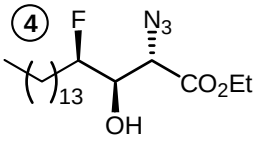
2R*,3*S*,4*S

Yield: 75 mg (0.19 mmol, 78 %) (2*R*,3*S*,4*R*) and (2*R*,3*S*,4*S*)
dr: 62:38 (^{19}F-NMR, decoupled)
ee: > 98 % (^{19}F-NMR, decoupled, shift with 65 mol% Eu(hfc)$_3$) [(2*R*,3*S*,4*R*)]
> 98 % (^{19}F-NMR, entkoppelt, shift with 65 mol% Eu(hfc)$_3$) [(2*R*,3*S*,4*S*)]

SDIA



2S*,3*R*,4*S



2S*,3*R*,4*R

Yield: 173 mg (0.45 mmol, 91 %) (2*S*,3*R*,4*S*) und (2*S*,3*R*,4*R*)
dr: 61:39 (^{19}F-NMR, decoupled)
ee: > 97 % (^{19}F-NMR, decoupled, shift with 90 mol% Eu(hfc)$_3$)$_{xix}$ [(2*S*,3*R*,4*S*]
> 98 % (^{19}F-NMR, decoupled, shift with 90 mol% Eu(hfc)$_3$)$_{xix}$ [(2*S*,3*R*,4*R*]