Supplementary Information

Fluorine in fragrances: Exploring the difluoromethylene (CF_2) group as a conformational constraint in macrocyclic musk lactones

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General

All reagents were purchased from commercial suppliers and were used without further purification unless otherwise stated. Tetrahydrofuran, dichloromethane, toluene and diethyl ether were dried and deoxygenated with an MBraun SPS-800 solvent purification system and the moisture content of the solvents was analysed using a Karl Fischer coulometer (Metler Toledo DL32). Dry DMF was purchased from Merck and was used as purchased.

Infra-red spectra were recorded on a Perkin Elmer Spectrum GX FT-IR system. Proton NMR (^{1}H), carbon NMR (^{13}C) and fluorine NMR (^{19}F) were recorded on a Bruker Advance 500 (500 MHz), Bruker Avance II (400 MHz) or a Bruker Avance 300 (300 MHz) spectrometer. Fluorine NMR were were also recorded as proton decoupled (^{19}F{^{1}H}). Using a deptq sequence or an HSQC experiment with multiplicity editing, the ^{13}C NMR signals were assigned to CH_3, CH_2, CH and C. The NMR experiments were carried out in deuterochloroform ($CDCl_3$). The chemical shifts (δ) are quoted in parts per million (ppm). Multiplicities are abbreviated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad for the ^{1}H NMR, ^{19}F NMR, ^{19}F{^{1}H} NMR and ^{13}C NMR spectra. Coupling constants are reported in Hertz (Hz).

High and low resolution mass spectra were recorded at the EPSRC National Mass Spectrometry Service, Swansea or at the University of St Andrews on a Waters Micromass LCT time of flight mass spectrometer coupled to a Waters 2975 HPLC system. Optical rotation values were recorded on a Perkin Elmer Model 341 Polarimeter using a Na/Hal lamp (589 nm) at 20 °C in a 1 dm polarimeter cell and are given in 10^{-1} deg cm^2 g^{-1}. A kdScientific syringe pump (model #KDS-100-CE) was used when required.

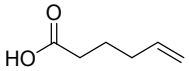
Flash chromatography was performed using silica gel 60 (200-400 mesh). Thin layer chromatography (TLC) was performed using aluminium sheets of silica gel 60 F254 and was visualised under a Mineralight model UVGL-58 lamp (254 nm). The plates were developed with acidic methanolic vanillin solutions, ethanolic phosphomolybdic acid solutions or basic potassium permanganate solutions.

The IUPAC names of some compounds were obtained using Reaxys® (www.reaxys.com).

List of Chemical Abbreviations

4-DMAP	4-Dimethylaminopyridine
9-BBN	9-Borabicyclo(3.3.1)nonane
BAIB	*Bis*(acetoxy)iodobenzene
DAST	Diethylaminosulfur trifluoride
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DME	Dimethoxyethane
DMP	Dess-Martin Periodinane
DMSO	*N*,*N*-Dimethylsulfoxide
mCPBA	m-Chloroperbenzoic acid
NaHMDS	sodium *bis*(trimethylsilyl)amide/ sodium hexamethyldisilazide
nBuLi	*n*-Butyllithium
PMB-Cl	*p*-Methoxybenzyl chloride
TBAI	Tetrabutylammonium iodide
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
THF	Tetrahydrofuran

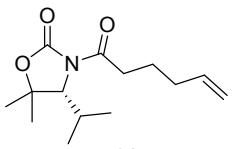
Hex-5-enoic acid 19[1]



19

Hydrogen peroxide (30% in water, 227 mL, 2 mol, 2.0 eq) was added over 30 min to a solution of cyclohexanone **18** (104 mL, 1 mol, 1.0 eq) in methanol (100 mL) at r.t. The mixture was then added to a solution of iron (II) sulfate heptahydrate (278 g, 1 mol, 1.0 eq) and copper (II) sulfate pentahydrate (250 g, 1 mol, 1.0 eq) in water (1.8 L) over 2 h. The reaction mixture was extracted with diethyl ether (3 x 200 mL). The combined ether layers were washed with sodium hydroxide solution (20%, 3 x 100 mL). The combined aqueous layers were acidified to pH 2 with sulfuric acid solution (20%). The aqueous layer was extracted with diethyl ether (3 x 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by distillation (75 °C at 0.1 mbar) gave hex-5-enoic acid **19** (22.4 g, 20%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.76 (2H, tt, *J*(H,H)= 7.6, 7.5 Hz, CH_2), 2.10-2.16 (2H, m, CH_2), 2.38 (2H, t, *J*(H,H)= 7.6 Hz, CH_2), 4.99-5.08 (2H, m, CH_2), 5.74-5.84 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.9 (CH_2), 33.1 (CH_2), 33.3 (CH_2), 115.8 (CH_2), 137.7 (CH), 179.4 (CO); MS (ESI) 113 (100) $[M-H]^-$; HRMS: *m/z* calcd for $C_6H_9O_2$ $[M-H]^-$: 113.0608; found: 113.0604.

(4*R*)-3-(Hex-5-enoyl)-5,5-dimethyl-4-(propan-2-yl)-1,3-oxazolidin-2-one 21

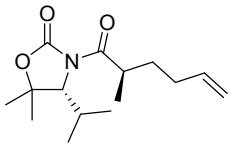


21

*n*BuLi (1.6 M in hexanes, 126 mL, 200.4 mmol, 1.2 eq) was added to a solution of (4*R*)-5,5-dimethyl-4-(propan-2-yl)-1,3-oxazolidin-2-one **20** (26.3 g, 167 mmol, 1.0 eq) in dry THF (500 mL) at -78 °C under argon. In a separate flask, pivaloyl chloride (27 mL, 217.1 mmol, 1.3 eq) and triethylamine (40 mL, 283.9 mmol, 1.7 eq) were added to a solution of hex-5-enoic acid **19** (22.9 g, 200.4 mmol, 1.2 eq) in dry THF (200 mL) at 0 °C under argon and stirred for 30 min. The oxazolidinone solution was added to the mixed anhydride *via* cannula and stirred at 0 °C for 30 min, then warmed to r.t. and stirred for 1.5 h. The reaction mixture

was quenched with sat. NH_4Cl solution (500 mL) and extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution (500 mL), sat. NH_4Cl solution (500 mL) and brine (500 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography (EtOAc/Pet. ether 1:9) gave (4*R*)-3-(hex-5-enoyl)-5,5-dimethyl-4-(propan-2-yl)-1,3-oxazolidin-2-one **21** (39.5 g, 93 %) as a colourless oil; $[\alpha]_D$ -30.6° (c 1.46, $CHCl_3$) [lit.[2] (4*S*)-**21** $[\alpha]_D$ +33.1° (c 1.0, $CHCl_3$)]; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.94 (3H, d, *J*(H,H)= 6.8 Hz, CH_3), 1.02 (3H, d, *J*(H,H)= 7.0 Hz, CH_3), 1.37 (3H, s, CH_3), 1.51 (3H, s, CH_3), 1.72-1.86 (2H, m, CH_2), 2.11-2.16 (3H, m, CH_2, CH), 2.89 (1H, ddd, *J*(H,H)= 16.7, 8.6, 6.4 Hz, CH_AH_B), 3.02 (1H, ddd, *J*(H,H)= 16.7, 8.6, 6.4 Hz, CH_AH_B), 4.15 (1H, d, *J*(H,H)= 3.3 Hz, CH), 5.02 (2H, dddd, *J*(H,H)= 31.3, 16.7, 3.3, 1.7 Hz, CH_2), 5.77-5.85 (1H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.3 (CH_3), 21.6 (CH_3), 21.7 (CH_3), 24.0 (CH_2), 29.0 (CH_3), 29.8 (CH), 33.3 (CH_2), 35.0 (CH_2), 66.4 (CH), 82.9 (C), 115.5 (CH_2), 138.1 (CH), 153.8 (CO), 173.9 (CO); IR (thin film) ν (cm^{-1}) = 2975, 2934, 1780, 1702, 1641, 1465, 1375, 1363, 1315, 1279, 1220, 1172, 1122, 913; MS (ESI) 529 (35) $[2M+Na]^+$, 276 (100) $[M+Na]^+$, 254 (45) $[M+H]^+$; HRMS: *m*/*z* calcd for $C_{14}H_{23}N_1Na_1O_3$ $[M+Na]^+$: 276.1570; found: 276.1562.

(4*R*)- 5,5-Dimethyl-3-((2*R*)-methylhex-5-enoyl)-4-(propan-2-yl)-1,3-oxazolidin-2-one 22

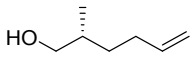


22

NaHMDS (1.0 M in THF, 120 mL, 120 mmol, 1.1 eq) was added to a solution of (4*R*)-3-(hex-5-enoyl)-5,5-dimethyl-4-(propan-2-yl)-1,3-oxazolidin-2-one **21** (27.6 g, 109.1 mmol, 1.0 eq) in dry THF (340 mL) at -78 °C under argon and stirred at -78 °C for 1 h. Iodomethane (34 mL, 546 mmol, 5.0 eq) was added and the reaction mixture was stirred at -78 °C for 1 h, then warmed to r.t. and stirred for 1 h. The reaction mixture was quenched with sat. NH_4Cl solution (250 mL) and extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution (250 mL), sat. NH_4Cl solution (250 mL) and brine (250 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography (EtOAc/Pet. ether 1:9) gave (4*R*)-5,5-dimethyl-3-((2*R*)-methylhex-5-enoyl)-4-(propan-2-yl)-1,3-oxazolidin-2-one **22** (26.9 g, 92%) as a white solid as a single diastereoisomer by ^1H NMR analysis; mp 44-46 °C; $[\alpha]_D$ -52.8° (c 1.23,

$CHCl_3$) [lit.[2] (2*S*,4*S*)-**22** $[\alpha]_D$ +51.4° (c 1.0, $CHCl_3$)]; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.96 (3H, d, *J*(H,H)= 6.8 Hz, CH_3), 1.02 (3H, d, *J*(H,H)= 6.9 Hz, CH_3), 1.27 (3H, d, *J*(H,H)= 6.8 Hz, CH_3), 1.38 (3H, s, CH_3), 1.46-1.52 (1H, m, CH_2), 1.52 (3H, s, CH_3), 1.85-1.92 (1H, m, CH_2), 2.04-2.09 (2H, m, CH_2), 2.11-2.18 (1H, m, CH), 3.75-3.82 (1H, m,CH), 4.19 (1H, d, *J*(H,H)= 3.3 Hz, CH), 4.98 (2H, dddd, *J*(H,H)= 29.2, 17.1, 3.3, 1.5 Hz, CH_2), 5.74-5.82 (1H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.1 (CH_3), 18.7 (CH_3), 21.6 (CH_3), 21.8 (CH_3), 28.9 (CH_3), 29.8 (CH), 31.9 (CH_2), 32.4 (CH_2), 37.5 (CH), 66.3 (CH), 82.8 (C), 115.2 (CH_2), 138.4 (CH), 153.4 (CO), 177.7 (CO); IR (thin film) ν (cm^{-1}) = 2976, 1774, 1700, 1362, 1266, 1173, 1095, 742; MS (ESI) 557 (30) $[2M+Na]^+$, 290 (100) $[M+Na]^+$, 268 (40) $[M+H]^+$; HRMS: *m*/*z* calcd for $C_{15}H_{25}N_1Na_1O_3$ $[M+Na]^+$: 290.1727; found: 290.1720.

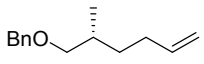
(2*R*)-2-Methylhex-5-en-1-ol 23



23

Lithium aluminium hydride (4.6 g, 122.1 mmol, 4.0 eq) was added to a solution of (4*R*)-5,5-dimethyl-3-((2*R*)-methylhex-5-enoyl)-4-(propan-2-yl)-1,3-oxazolidin-2-one **22** (8.2 g, 30.5 mmol, 1.0 eq) in dry diethyl ether (250 mL) at 0 °C under argon and stirred for 2 h. The reaction mixture was quenched with water (10 mL). Sodium hydroxide solution (2 N, 10 mL) was added, followed by water (10 mL). The resulting white solid was filtered and the filtrate was collected. The solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:9) gave (2*R*)-2-methylhex-5-en-1-ol **23** (2.29 g, 66%) as a colourless oil; $[\alpha]_D$ +10.0° (c 1.05, $CHCl_3$), lit.[3] $[\alpha]_D$ +9.1° (c 3.03, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.94 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.18-1.26 (1H, m, CH_AH_B), 1.41 (1H, bs, OH), 1.49-1.56 (1H, m, CH_AH_B), 1.61-1.72 (1H, m, CH), 2.02-2.18 (2H, m, CH_2), 3.45 (1H, dd, *J*(H,H)= 10.5, 6.4 Hz, CH_AH_B), 3.52 (1H, dd, *J*(H,H)= 10.6, 5.8 Hz, CH_AH_B), 4.94-5.05 (2H, m, CH_2), 5.78-5.86 (1H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 16.6 (CH_3), 31.4 (CH_2), 32.5 (CH_2), 35.4 (CH), 68.4 (CH_2), 114.6 (CH_2), 139.1 (CH); IR (thin film) ν (cm^{-1}) = 3348, 2956, 2925, 2875, 1641, 1458, 1039, 994, 910, 741; MS (CI) 115 (100) $[M+H]^+$; HRMS: *m*/*z* calcd for $C_7H_{15}O_1$ $[M+H]^+$: 115.1117; found: 115.1115.

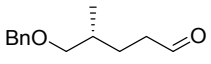
(((2*R*)-2-Methylhex-5-en-1-ol)oxy)methyl)benzene 11



11

A solution of (2*R*)-2-methylhex-5-en-1-ol **23** (2.19 g, 19.2 mmol, 1.0 eq) in dry 1,2-dimethoxyethane (20 mL) was added to a suspension of sodium hydride (60% in oil, 1.0 g, 24.9 mmol, 1.3 eq) in dry 1,2-dimethoxyethane (20 mL) at r.t. under argon. The reaction mixture was stirred for 10 min, then benzyl bromide (2.7 mL, 23.0 mmol, 1.2 eq) was added and the reaction mixture was stirred for 75 min. The reaction mixture was heated at reflux for 20 min, then cooled to r.t. and stirred for 18 h. HCl solution (2 N, 1 mL) was added and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:19) gave (((2*R*)-2-methylhex-5-en-1-ol)oxy)methyl)benzene **11** (3.68 g, 94%) as a colourless oil; $[\alpha]_D$ -2.7° (c 1.20, $CHCl_3$) [lit.[4] (2*S*)-**11** $[\alpha]_D$ +2.6° (c 6.2, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J*(H,H)= 6.8 Hz, CH_3), 1.19-1.27 (1H, m, CH_AH_B), 1.53-1.60 (1H, m, CH_AH_B), 1.76-1.86 (1H, m, CH), 2.01-2.17 (2H, m, CH_2), 3.28 (1H, dd, *J*(H,H)= 9.0, 6.6 Hz, CH_AH_B), 3.35 (1H, dd, *J*(H,H)= 9.0, 6.0 Hz, CH_AH_B), 4.50 (1H, d, *J*(H,H)= 12.3 Hz, CH_AH_B), 4.53 (1H, d, *J*(H,H)= 12.3 Hz, CH_AH_B), 4.94-5.04 (2H, m, CH_2), 5.78-5.86 (1H, m, CH), 7.28-7.39 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 17.2 (CH_3), 31.4 (CH_2), 33.0 (CH), 33.2 (CH_2), 73.2 (CH_2), 76.0 (CH_2), 114.5 (CH_2), 127.6 (CH), 127.7 (CH), 128.5 (CH), 139.0 (C), 139.3 (CH); IR (thin film) ν (cm^{-1}) = 3065, 3030, 2928, 2854, 1641, 1496, 1453, 1363, 1099, 910, 735, 697; MS (ESI) 332 (100), 227 (25) $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{14}H_{20}Na_1O_1$ $[M+Na]^+$: 227.1406; found: 227.1402.

(4*R*)-5-(Benzyloxy)-4-methylpentanal 12

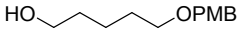


12

Ozone was bubbled through a solution of (((2*R*)-2-methylhex-5-en-1-ol)oxy)methyl)benzene **11** (3.5 g, 17.1 mmol, 1.0 eq) in dry DCM (50 mL) at -78 °C until a pale blue colour appeared (approx. 45 min). Oxygen was bubbled through the reaction until the blue colour disappeared. Triphenylphosphine (4.9 g, 18.8 mmol, 1.1 eq) was added and the reaction was stirred at -78 °C for 1 h, then warmed to r.t. and stirred for 18 h. The solvent was removed *in vacuo*.

Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:19) gave (4*R*)-5-(benzyloxy)-4-methylpentanal **12** (1.93 g, 55%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J*(H,H)= 6.5 Hz, CH_3), 1.47-1.55 (1H, m, CH_AH$_B$), 1.77-1.87 (2H, m, CH$_A$$H_B$, CH), 2.05-2.53 (2H, m, CH_2), 3.29-3.34 (2H, m, CH_2), 4.50 (2H, s, CH_2), 7.27-7.37 (5H, m, ArH), 9.77 (1H, t, *J*(H,H)= 1.7 Hz, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.1 (CH_3), 26.1 (CH_2), 33.3 (CH), 41.8 (CH_2), 73.2 (CH_2), 75.5 (CH_2), 127.7 (CH), 127.8 (CH), 128.6 (CH), 138.7 (C), 203.0 (CO).

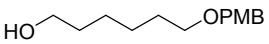
5-((4-Methoxyphenyl)methoxy)pentan-1-ol 25a



25a

Using a modification of the reported[5] procedure, 1,5-pentanediol **24a** (31.4 mL, 300 mmol, 3.0 eq) was added to a suspension of sodium hydride (60% in oil, 4.2 g, 105 mmol, 1.05 eq) in dry THF (400 mL) at 0 °C under argon. The reaction mixture was warmed to r.t. and stirred for 1 h. 4-Methoxybenzyl chloride (13.6 mL, 100 mmol, 1.0 eq) was added, followed by tetrabutylammonium iodide (14.8 g, 40 mmol, 0.4 eq). The reaction mixture was heated to 60 °C and stirred for 18 h. The reaction mixture was cooled to r.t. and quenched with water (400 mL). The organic layer was separated and the aqueous layer was re-extracted with diethyl ether (2 x 200 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:1) gave 5-((4-methoxyphenyl)methoxy)pentan-1-ol **25a** (19.1 g, 85%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.41-1.48 (3H, m, CH_2, OH), 1.56-1.68 (4H, m, CH_2), 3.45 (2H, t, *J*(H,H)= 6.5 Hz, CH_2), 3.65 (2H, t, *J*(H,H)= 6.6 Hz, CH_2), 3.81 (3H, s, CH_3), 4.44 (2H, s, CH_2), 6.87-6.90 (2H, m, ArH), 7.25-7.28 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.7 (CH_2), 29.7 (CH_2), 32.7 (CH_2), 55.5 (CH_3), 63.1 (CH_2), 70.2 (CH_2), 72.8 (CH_2), 114.0 (CH), 129.5 (CH), 130.9 (C), 159.3 (C); IR (thin film) ν (cm^{-1}) = 3404, 2937, 2862, 1613, 1586, 1513, 1464, 1362, 1302, 1248, 1174, 1096, 1035, 820; MS (ESI) 247 (100) $[M + Na]^+$, 121 (30); HRMS: *m*/*z* calcd for $C_{13}H_{20}Na_1O_2$ $[M+Na]^+$: 247.1305; found: 247.1297.

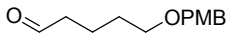
6-((4-Methoxyphenyl)methoxy)hexan-1-ol 25b



25b

Following the same procedure as **25a**, 1,6-hexanediol **24b** (5 g, 42 mmol, 1.0 eq) was reacted to give 6-((4-methoxyphenyl)methoxy)hexan-1-ol **25b** (5.5 g, 55%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.35-1.44 (4H, m, CH_2), 1.46 (1H, bs, OH), 1.54-1.65 (4H, m, CH_2), 3.45 (2H, t, J(H,H)= 6.6 Hz, CH_2), 3.63 (2H, t, J(H,H)= 6.6 Hz, CH_2), 3.81 (3H, s, CH_3), 4.44 (2H, s, CH_2), 6.87-6.90 (2H, m, ArH), 7.25-7.29 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.8 (CH_2), 26.2 (CH_2), 29.9 (CH_2), 32.9 (CH_2), 55.5 (CH_3), 70.2 (CH_2), 72.7 (CH_2), 113.9 (CH), 129.4 (CH), 130.9 (C), 159.3 (C); IR (thin film) ν (cm^{-1}) = 3397, 2935, 2859, 1710, 1612, 1586, 1514, 1464, 1249, 1173, 1095, 1035, 822, 738; MS (ESI) 261 (100) $[M+Na]^+$; HRMS: m/z calcd for $C_{14}H_{22}Na_1O_2$ $[M+Na]^+$: 261.1461; found: 261.1455.

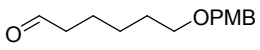
5-((4-Methoxyphenyl)methoxy)pentanal 49a



49a

A solution of DMSO (13.2 mL, 186 mmol, 3.0 eq) in dry DCM (40 mL) was added to a solution of oxalyl chloride (11 mL, 130 mmol, 2.1 eq) in dry DCM (360 mL) at -78 °C under argon and stirred for 30 min. A solution of 5-((4-methoxyphenyl)methoxy)pentan-1-ol **25a** (13.9 g, 62 mmol, 1.0 eq) in dry DCM (100 mL) was slowly added and the reaction mixture was stirred at -78 °C for 1.5 h. Triethylamine (43 mL, 310 mmol, 5.0 eq) was added and the reaction mixture was warmed to 0 °C and stirred for 1 h. Water (500 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (300 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give 5-((4-methoxyphenyl)methoxy)pentanal **49a** (13.8 g, 100%) as a yellow oil, which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.56-1.78 (4H, m, CH_2), 2.46 (2H, dt, J(H,H)= 7.3, 1.7 Hz, CH_2), 3.46 (2H, t, J(H,H)= 6.0 Hz, CH_2), 3.81 (3H, s, CH_3), 4.43 (2H, s, CH_2), 6.87-6.94 (2H, m, ArH), 7.25-7.27 (2H, m, ArH), 9.77 (1H, t, J(H,H)= 1.7 Hz, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.2 (CH_2), 29.3 (CH_2), 43.8 (CH_2), 55.5 (CH_3), 69.6 (CH_2), 72.8 (CH_2), 114.0 (CH), 129.5 (CH), 130.7 (C), 159.3 (C), 202.8 (CHO).

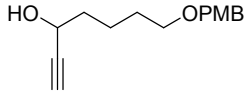
6-((4-Methoxyphenyl)methoxy)hexanal 49b



49b

DMP (10.7 g, 25.2 mmol, 1.2 eq) was added to a solution of 6-((4-methoxyphenyl)methoxy)hexan-1-ol **25b** (5.0 g, 21.0 mmol, 1.0 eq) in DCM (200 mL) at r.t. The reaction mixture was stirred at r.t. for 18 h. The reaction mixture was diluted with diethyl ether (100 mL) and sat. $NaHCO_3$ solution (100 mL). Sodium thiosulfate (12 g) was added and the reaction mixture was stirred vigorously for 30 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give 6-((4-methoxyphenyl)methoxy)hexanal **49b** (5.0 g, 100%) as a yellow oil, which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.38-1.46 (2H, m, CH_2), 1.56-1.69 (4H, m, CH_2), 2.44 (2H, dt, J(H,H)= 7.4, 1.8 Hz, CH_2), 3.45 (2H, t, J(H,H)= 6.5 Hz, CH_2), 3.81 (3H, s, CH_3), 4.43 (2H, s, CH_2), 6.87-6.90 (2H, m, ArH), 7.25-7.28 (2H, m, ArH), 9.77 (1H, t, J(H,H)= 1.8 Hz, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.1 (CH_2), 26.1 (CH_2), 29.7 (CH_2), 44.1 (CH_2), 55.5 (CH_3), 69.9 (CH_2), 72.8 (CH_2), 114.0 (CH), 129.5 (CH), 130.8 (C), 159.3 (C), 202.9 (CHO).

7-((4-Methoxyphenyl)methoxy)hept-1-yn-3-ol 26a

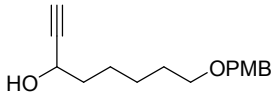


26a

Ethynylmagnesium bromide solution (0.5 M in THF, 150 mL, 74.4 mmol, 1.2 eq) was added to a solution of 5-((4-methoxyphenyl)methoxy)pentanal **49a** (13.8 g, 62.0 mmol, 1.0 eq) in dry THF (200 mL) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 2 h, then allowed to warm to r.t. and stirred for a further 16 h. The reaction mixture was quenched with sat. NH_4Cl solution (300 mL). The organic layer was separated and the aqueous layer was re-extracted with diethyl ether (2 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo.* Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:4) gave 7-((4-methoxyphenyl)methoxy)hept-1-yn-3-ol **26a** (10.9 g, 71%) as a pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.52-1.79 (8H, m, CH_2), 2.47 (1H, d, J(H,H)= 2.1 Hz, CH), 3.47 (2H,

t, *J*(H,H)= 6.5 Hz, CH_2), 3.81 (3H, s, CH_3), 4.38 (1H, td, *J*(H,H)= 6.5, 2.1 Hz, CH), 4.44 (2H, s, CH_2), 6.87-6.90 (2H, m, ArH), 7.26-7.28 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.0 (CH_2), 29.5 (CH_2), 37.5 (CH_2), 55.5 (CH_3), 62.4 (CH), 70.0 (CH_2), 72.8 (CH_2), 73.2 (CH), 85.1 (C), 114.0 (CH), 129.5 (CH), 130.8 (C), 159.3 (C); IR (thin film) ν (cm^{-1}) = 3406, 3290, 2941, 2863, 1612, 1586, 1513, 1464, 1303, 1248, 1174, 1094, 1034, 821, 638; MS (ESI) 271 (100) $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{15}H_{20}Na_1O_3$ $[M+Na]^+$: 271.1305; found: 271.1299.

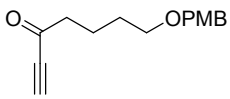
8-((4-Methoxyphenyl)methoxy)oct-1-yn-3-ol 26b



26b

Following the same procedure as **26a**, 6-((4-methoxyphenyl)methoxy)hexanal **49b** (5.0 g, 21.0 mmol, 1.0 eq) was reacted to give 8-((4-methoxyphenyl)methoxy)oct-1-yn-3-ol **26b** (4.2 g, 77%) as a pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.38-1.52 (4H, m, CH_2), 1.60-1.66 (2H, m, CH_2), 1.68-1.77 (2H, m, CH_2), 1.79 (1H, bs, OH), 2.47 (1H, d, *J*(H,H)= 2.1 Hz, CH), 3.45 (2H, t, *J*(H,H)= 6.6 Hz, CH_2), 3.81 (3H, s, CH_3), 4.37 (1H, td, *J*(H,H)= 6.6, 2.1 Hz, CH), 43.44 (2H, s, CH_2), 6.87-6.91 (2H, m, ArH), 7.26-7.28 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.0 (CH_2), 26.1 (CH_2), 29.8 (CH_2), 37.8 (CH_2), 55.5 (CH_3), 62.4 (CH), 70.1 (CH_2), 72.7 (CH_2), 73.1 (CH), 85.1 (C), 114.0 (CH), 129.5 (CH), 130.9 (C), 159.3 (C); IR (thin film) ν (cm^{-1}) = 3398, 3289, 2939, 2861, 2092, 1681, 1612, 1513, 1464, 1303, 1249, 1174, 1090, 1034, 821, 643; MS (ESI) 285 (100) $[M+Na]^+$, 121 (30); HRMS: *m*/*z* calcd for $C_{16}H_{22}Na_1O_3$ $[M+Na]^+$: 285.1461; found: 285.1454.

7-((4-Methoxyphenyl)methoxy)hept-1-yn-3-one 27a

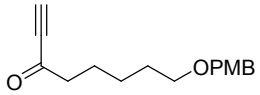


27a

DMP (20.5 g, 48.3 mmol, 1.2 eq) was added to a solution of 7-((4-methoxyphenyl)methoxy)hept-1-yn-3-ol **26a** (10.0 g, 40.3 mmol, 1.0 eq) in DCM (200 mL) at r.t. and stirred at r.t. for 2 h. The reaction mixture was diluted with diethyl ether (200 mL) and sat. $NaHCO_3$ solution (200 mL). Sodium thiosulfate (30 g) was added and the reaction

mixture was stirred vigorously for 30 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (200 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give 7-((4-methoxyphenyl)methoxy)hept-1-yn-3-one **27a** (9.1 g, 85%) as a yellow oil, which was used without further purification; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.62-1.68 (2H, m, CH_2), 1.76-1.82 (2H, m, CH_2), 2.63 (2H, t, *J*(H,H)= 7.4 Hz, CH_2), 3.21 (1H, s, CH), 3.47 (2H, t, *J*(H,H)= 6.3 Hz, CH_2), 3.82 (3H, s, CH_3), 4.44 (2H, s, CH_2), 6.89-6.91 (2H, m, ArH), 7.27-7.28 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.8 (CH_2), 29.1 (CH_2), 45.3 (CH_2), 55.5 (CH_3), 69.6 (CH_2), 72.8 (CH_2), 78.6 (C), 81.6 (C), 114.0 (CH), 129.5 (CH), 130.7 (C), 159.3 (C), 187.4 (CO); IR (thin film) ν (cm^{-1}) = 3261, 2938, 2862, 2092, 1683, 1613, 1513, 1465, 1303, 1248, 1174, 1099, 1035, 821, 737; MS (ESI) 269 (100) $[M+Na]^+$, 259 (20), 121 (25); HRMS: *m*/*z* calcd for $C_{15}H_{18}Na_1O_3$ $[M+Na]^+$: 269.1148; found: 269.1141.

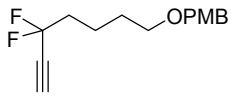
8-((4-Methoxyphenyl)methoxy)oct-1-yn-3-one 27b



27b

Following the same procedure as **27a**, 8-((4-methoxyphenyl)methoxy)oct-1-yn-3-ol (2.09 g, 8.0 mmol, 1.0 eq) was reacted to give 8-((4-methoxyphenyl)methoxy)oct-1-yn-3-one **27b** (1.48 g, 71%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.37-1.45 (2H, m, CH_2), 1.58-1.74 (4H, m, CH_2), 2.60 (1H, d, *J*(H,H)= 7.5 Hz, CH_2), 3.20 (1H, s, CH), 3.45 (2H, t, *J*(H,H)= 6.5 Hz, CH_2), 3.81 (3H, s, CH_3), 4.43 (2H, s, CH_2), 6.87-6.90 (2H, m, ArH), 7.24-7.27 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.8 (CH_2), 25.8 (CH_2), 29.7 (CH_2), 45.6 (CH_2), 55.5 (CH_3), 69.9 (CH_2), 72.8 (CH_2), 78.6 (CH), 81.6 (C), 114.0 (CH), 129.5 (CH), 130.9 (C), 159.4 (C), 187.6 (CO); IR (thin film) ν (cm^{-1}) = 3259, 2938, 2862, 2092, 1683, 1612, 1513, 1248, 1100, 1034, 821; MS (ESI) 283 (100) $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{16}H_{20}Na_1O_3$ $[M+Na]^+$: 283.1305; found: 283.1299.

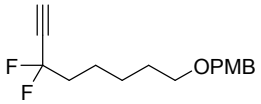
1-(((5,5-Difluorohept-6-yn-1-yl)oxy)methyl)-4-methoxybenzene 28a



28a

DAST (10.6 mL, 80 mmol, 4.0 eq) was added to a Teflon flask containing 7-((4-methoxyphenyl)methoxy)hept-1-yn-3-one **27a** (4.9 g, 20.0 mmol, 1.0 eq) under argon and heated at 50 °C for 18 h. The reaction mixture was cooled to r.t. and poured onto sat. $NaHCO_3$ solution (200 mL). The reaction mixture was extracted with DCM (2 x 200 mL). The combined organic layers were washed with brine (400 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:19) gave 1-(((5,5-difluorohept-6-yn-1-yl)oxy)methyl)-4-methoxybenzene **28a** (3.25 g, 61%) as an orange oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.62-1.78 (4H, m, CH_2), 2.02-2.11 (2H, m, CH_2), 2.76 (1H, t, J(H,F)= 4.9 Hz, CH), 3.47 (2H, t, J(H,H)= 5.5 Hz, CH_2), 3.82 (3H, s, CH_3), 4.45 (2H, s, CH_2), 6.88-6.90 (2H, m, ArH), 7.26-7.28 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.8 (CH_2, t, J(C,F)= 3.7 Hz), 29.2 (CH_2), 39.0 (CH2, t, J(C,F)= 25.6 Hz), 55.5 (CH_3), 69.6 (CH_2), 72.8 (CH_2), 75.4 (CH, t, J(C,F)= 6.8 Hz), 76.8 (C, t, J(C,F)= 41.3 Hz), 114.0 (CH), 114.5 (CF2, t, J(C,F)= 232.9 Hz), 129.5 (CH), 130.7 (C), 159.4 (C); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ = -84.0 (2F, s, CF_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -84.0 (2F, td, J(H,F)= 14.9, 4.8 Hz, CF_2); IR (thin film) ν (cm^{-1}) = 3301, 2939, 2861, 2133, 1613, 1514, 1465, 1303, 1249, 1175, 1101, 1036, 821, 685; MS (ESI) 291 (100) $[M+Na]^+$, 271 (20), 121 (25); HRMS: m/z calcd for $C_{15}H_{18}F_2Na_1O_2$ $[M+Na]^+$: 291.1167; found: 291.1161.

1-(((6,6-Difluorooct-7-yn-1-yl)oxy)methyl)-4-methoxybenzene 28b

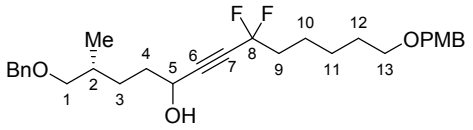


28b

Following the same procedure as **28a**, 8-((4-methoxyphenyl)methoxy)oct-1-yn-3-one (3.51 g, 13.5 mmol, 1.0 eq) was reacted to give 1-(((6,6-difluorooct-7-yn-1-yl)oxy)methyl)-4-methoxybenzene **28b** (1.93 g, 51%) as an orange oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.41-1.67 (6H, m, CH_2), 1.99-2.10 (2H, m, CH_2), 2.75 (1H, t, J(H,F)= 4.9 Hz, CH), 3.46 (2H, t, J(H,H)= 6.4 Hz, CH_2), 3.46 (3H, s, CH_3), 4.44 (2H, s, CH_2), 6.87-6.91 (2H, m, ArH), 7.26-7.29 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.7 (CH_2, t, J(C,F)= 3.4 Hz), 25.8 (CH_2), 29.7 (CH_2), 39.2 (CH_2, t, J(C,F)= 25.6 Hz), 55.5 (CH_3), 69.9 (CH_2), 72.8 (CH_2), 75.3 (CH, t, J(C,F)= 6.8 Hz), 76.8 (C, t, J(C,F)= 41.3 Hz), 114.0 (CH), 114.5 (CF_2, t, J(C,F)= 233.0 Hz), 129.5 (CH), 130.8 (C), 159.3 (C); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = -84.5

(2F, s, CF_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -84.5 (2F, td, J(H,F)= 15.0, 4.9 Hz, CF_2); IR (thin film) ν (cm^{-1}) = 3302, 2940, 2864, 2133, 1722, 1454, 1434, 1363, 1315, 1276, 1176, 1103, 1071, 1028, 738, 698.

(2*R*)-2-((Benzyloxy)methyl)-8,8-difluoro-13-(((4-methoxyphenyl)methoxy) tridec-6-yn-5-ol 15

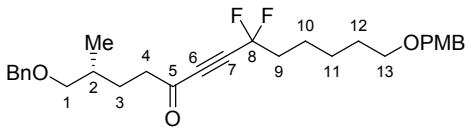


15

*n*BuLi (1.6 M in hexanes, 3.0 mL, 4.8 mmol, 1.0 eq) was added to a solution of (((6,6-difluorooct-7-yn-1-yl)oxy)methyl)benzene **28b** (1.21 g, 4.8 mmol, 1.0 eq) in dry THF (90 mL) at -78 °C under argon and stirred for 30 min. A solution of (4*R*)-5-(benzyloxy)-4-methylpentanal **12** (1.25 g, 5.3 mmol, 1.1 eq) in dry THF (10 mL) was added and the reaction mixture was stirred at -78 °C for 4 h, then allowed to warm to r.t. and stirred for 16 h. The reaction mixture was quenched with sat. NH_4Cl solution (100 mL) and diluted with diethyl ether (50 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:4) gave (2*R*)-13-(benzyloxy)-8,8-difluoro-2-(((4-methoxyphenyl)methoxy)methyl)tridec-6-yn-5-ol **15** (1.44 g, 61%) as a yellow oil, as a mixture of two diastereoisomers; $[\alpha]_D$ +2.3° (c 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.96 (3H, d, J(H,H)= 6.6 Hz, CH_3), 0.97 (3H, d, J(H,H)= 6.6 Hz, CH_3), 1.29-1.38 (1H, m, CH_2-3), 1.44-1.51 (2H, m, CH_2-10), 1.58-1.86 (11H, CH-2, CH_2-3,4,11,12, OH), 2.00-2.09 (2H, m, CH_2-9), 3.30-3.36 (2H, m, CH_2-1), 3.47 (2H, t, J(H,H)= 6.3 Hz, CH_2-13), 3.83 (3H, s, CH_3), 4.39-4.45 (1H, m, CH-5), 4.45 (2H, s, CH_2), 4.52 (2H, s, CH_2), 6.89-6.92 (2H, m, ArH), 7.29-7.38 (7H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.3 and 17.4 (CH_3), 22.8 (CH_2, t, J(C,F)= 2.9 Hz, C10), 25.8 (CH_2, C11), 29.2 and 29.2 (CH_2, C3), 29.6 (CH_2, C12), 33.3 and 33.3 (CH, C2), 34.7 and 34.8 (CH_2, C4), 39.2 (CH_2, t, J(C,F)= 26.0 Hz, C9), 55.5 (CH_3), 62.3 and 62.4 (CH, C5), 69.9 (CH_2, C13), 72.8 (CH_2, Bn), 73.2 (CH_2, PMB), 75.8 (CH_2, C1), 77.9-78.2 (C, m, C7), 88.1-88.3 (C, m, C6), 114.0 (CH), 115.0 (CF_2, d, J(C,F)= 231.8 Hz, C8), 127.7 (CH), 127.8 and 127.8 (CH), 129.5 (CH), 130.7 (C), 138.7

and 138.8 (C), 159.3 (C); $^{19}F\{^{1}H\}$ NMR (282 MHz, $CDCl_3$) δ = -83.09 and -83.10 (2F, s, CF_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -83.09 (2F, t, J(H,F)= 14.9 Hz, CF_2) and -83.11 (2F, t, J(H,F)= 14.9 Hz, CF_2); IR (thin film) ν (cm^{-1}) = 3401, 2936, 2864, 2250, 1613, 1513, 1455, 1248, 1174, 1097, 1033, 739, 699; MS (ESI) 511 (100) $[M+Na]^+$, 491 (20); HRMS: *m*/*z* calcd for $C_{29}H_{38}F_2Na_1O_4$ $[M+Na]^+$: 511.2630; found: 511.2621.

(2*R*)-2-((Benzyloxy)methyl)-8,8-difluoro-13-((4-methoxyphenyl)methoxy)tridec-6-yn-5-one 29

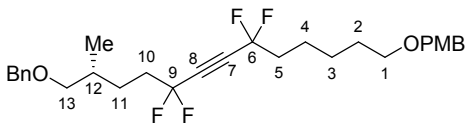


29

DMP (1.46 g, 3.4 mmol, 1.5 eq) was added to a solution of (2*R*)-13-(benzyloxy)-8,8-difluoro-2-(((4-methoxyphenyl)methoxy)methyl)tridec-6-yn-5-ol **15** (1.4 g, 2.9 mmol, 1.0 eq) in DCM (100 mL) at r.t. The reaction mixture was stirred at r.t. for 2 h, then diluted with diethyl ether (50 mL) and sat. $NaHCO_3$ solution (50 mL). Sodium thiosulfate (3 g) was added and the reaction mixture was stirred vigorously for 30 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give (2*R*)-13-(benzyloxy)-8,8-difluoro-13-(((4-methoxyphenyl)methoxy)methyl)-tridec-6-yn-5-one **29** (1.26 g, 89%) as a yellow oil that was used without further purification; $[\alpha]_D$ +0.5° (c 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.96 (3H, d, J(H,H)= 6.7 Hz, CH_3), 1.43-1.67 (7H, m, CH_2-3,10,11,12), 1.78-1.94 (2H, m, CH-2, CH_2-3), 2.04-2.14 (2H, m, CH_2-9), 2.63-2.74 (2H, m, CH_2-4), 3.29-3.35 (2H, m, CH_2-1), 3.46 (2H, t, J(H,H)= 6.4 Hz, CH_2-13), 3.83 (3H, s, CH_3), 4.45 (2H, s, CH_2), 4.51 (2H, s, CH_2), 6.89-6.91 (2H, m, ArH), 7.27-7.39 (7H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.1 (CH_3), 22.5 (CH_2, t, J(C,F)= 2.9 Hz, C10), 25.8 (CH_2, C11), 27.6 (CH_2, C3), 29.6 (CH_2, C12), 33.0 (CH, C2), 38.9 (CH_2, t, J(C,F)= 25.0 Hz, C9), 43.4 (CH_2, C4), 55.5 (CH_3), 69.8 (CH_2, C13), 72.8 (CH_2, PMB), 73.2 (CH_2, Bn), 75.4 (CH_2, C1), 80.8 (C, t, J(C,F)= 42.1 Hz, C7), 82.6 (C, t, J(C,F)= 6.6 Hz, C7), 114.0 (CH), 114.6 (CF_2, t, J(C,F)= 235.1 Hz, C8), 127.8 (CH), 127.8 (CH), 128.6 (CH), 129.4 (CH), 130.8 (C), 138.7 (C), 159.3 (C), 186.5 (CO, C5); $^{19}F\{^{1}H\}$ NMR (470 MHz, $CDCl_3$) δ = -85.5 (2F, s, CF_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -86.0 (2F, t,

J(H,F)= 15.2 Hz, CF_2); MS (ESI) 509 (100) $[M+Na]^+$, 489 (20); HRMS: *m*/*z* calcd for $C_{29}H_{36}F_2Na_1O_4$ $[M+Na]^+$: 509.2474; found: 509.2463.

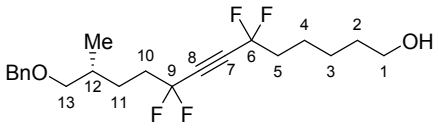
1-(((12*R*)-13-(Benzyloxy)-6,6,9,9-tetrafluoro-12-methyltridec-7-yn-1-yl)oxy)methyl)-4-methoxybenzene 30



30

DAST (1.4 mL, 10.2 mmol, 4.0 eq) was added to a Teflon flask containing (2*R*)-13-(benzyloxy)-8,8-difluoro-2-(((4-methoxyphenyl)methoxy)methyl)tridec-6-yn-5-one **29** (1.24 g, 2.5 mmol, 1.0 eq) under argon and heated at 50 °C for 18 h. The reaction mixture was cooled to r.t. and poured onto sat. $NaHCO_3$ solution (200 mL). The reaction mixture was extracted with DCM (2 x 150 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:9) gave 1-(((12*R*)-13-(benzyloxy)-6,6,9,9-tetrafluoro-12-methyltridec-7-yn-1-yl)oxy)methyl)-4-methoxybenzene **30** (0.90 g, 71%) as a yellow oil; $[\alpha]_D$ +3.5° (c 1.05, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.98 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.42-1.67 (7H, m, CH_2-2,3,4,11), 1.71-1.80 (1H, m, CH_2-11), 1.82-1.88 (1H, m, CH-12), 2.03-2.19 (4H, m, CH_2-5,10), 3.29-3.36 (2H, m, CH_2-13), 3.46 (2H, t, *J*(H,H)= 6.3 Hz, CH_2-1), 3.82 (3H, s, CH_3), 4.45 (2H, s, CH_2), 4.52 (2H, s, CH_2), 6.89-6.91 (2H, m, ArH), 7.27-7.38 (7H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.0 (CH_3), 22.5 (CH_2, t, *J*(C,F)= 3.2 Hz, C4), 25.8 (CH_2, C3), 26.5 (CH_2, t, *J*(C,F)= 3.3 Hz, C11), 29.6 (CH_2, C2), 33.0 (CH, C12), 36.6 (CH_2, t, *J*(C,F)= 25.1 Hz, C10), 38.9 (CH_2, t, *J*(C,F)= 25.1 Hz, C5), 55.5 (CH_3), 69.8 (CH_2, C1), 72.8 (CH_2, PMB), 73.3 (CH_2, Bn), 75.3 (CH_2, C13), 78.8-79.6 (C, m, C7, C8), 114.0 (CH), 114.3 (CF_2, t, *J*(C,F)= 235.3 Hz, C6), 114.5 (CF_2, t, *J*(C,F)= 235.3 Hz, C9), 127.7 (CH), 127.8 (CH), 128.6 (CH), 129.4 (CH), 130.8 (C), 138.7 (C), 159.3 (C); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -85.5 (2F, t, *J*(C,F)= 4.8 Hz, CF_2), -85.6 (2F, t, *J*(C,F)= 4.8 Hz, CF_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -85.4 (2F, tt, *J*(H,F)= 15.2 Hz, *J*(F,F)= 4.8 Hz, CF_2), -85.6 (2F, tt, *J*(H,F)= 15.1 Hz, *J*(F,F)= 4.8 Hz, CF_2); IR (thin film) ν (cm^{-1}) = 2937, 2863, 2243, 1726, 1613, 1586, 1513, 1455, 1364, 1318, 1303, 1248, 1174, 1099, 1036, 822, 737, 699; MS (ESI) 531 (100) $[M+Na]^+$, 511 (45); HRMS: *m*/*z* calcd for $C_{29}H_{36}F_4Na_1O_3$ $[M+Na]^+$: 531.2493; found: 531.2483.

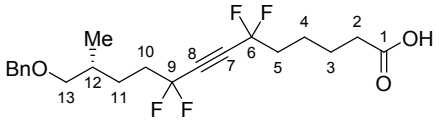
(12*R*)-12-((Benzyloxy)methyl)-6,6,9,9-tetrafluorotridec-7-yn-1-ol 31



31

DDQ (0.54 g, 2.4 mmol, 1.5 eq) was added to a solution of 1-(((12*R*)-13-(benzyloxy)-6,6,9,9-tetrafluoro-12-methyltridec-7-yn-1-yl)oxy)methyl)-4-methoxybenzene **30** (0.8 g, 1.6 mmol, 1.0 eq) in DCM (50 mL) and water (0.5 mL) at r.t. and stirred for 2 h at r.t. The reaction mixture was diluted with diethyl ether (100 mL) and sat. $NaHCO_3$ solution (100 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (100 mL). The combined organic layers were washed with water (150 mL), brine (150 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:4) gave (12*R*)-12-((benzyloxy)methyl)-6,6,9,9-tetrafluorotridec-7-yn-1-ol **31** (0.48 g, 78%) as a colourless oil, with an inseparable impurity; $[\alpha]_D$ +5.4° (c 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.97 (2H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.38-1.50 (8H, m, CH_2-2,3,4,11, OH), 1.56-1.62 (1H, m, CH_2-11), 1.81-1.88 (1H, m, CH_2-12), 2.04-2.16 (4H, m, CH_2-5,10), 3.28-3.36 (2H, m, CH_2-13), 3.65 (2H, t, *J*(H,H)= 6.5 Hz, CH_2-1), 4.51 (2H, s, CH_2), 7.27-7.38 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.0 (CH_3), 22.5 (CH_2, t, *J*(C,F)= 3.3 Hz, C4), 25.3 (CH_2, C2), 26.5 (CH_2, t, *J*(C,F)= 3.3 Hz, C11), 32.5 (CH_2, C3), 33.0 (CH, C12), 36.6 (CH_2, t, *J*(C,F)= 25.0 Hz, C10), 38.9 (CH_2, t, *J*(C,F)= 25.2 Hz, C5), 62.7 (CH_2, C1), 73.3 (CH_2, Bn), 75.3 (CH_2, C13), 78.8-79.5 (C, m, C7/C8), 114.3 (CH_2, t, *J*(C,F)= 235.6 Hz, C6), 114.5 (CH_2, t, *J*(C,F)= 235.6 Hz, C9), 127.8 (CH), 127.8 (CH), 128.6 (CH), 138.6 (C); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -85.4 (2F, t, *J*(C,F)= 4.8 Hz, CF_2), -85.6 (2F, t, *J*(C,F)= 4.8 Hz, CF_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -85.4 (2F, tt, *J*(H,F)= 15.2 Hz, *J*(F,F)= 4.9 Hz, CF_2), -85.6 (2F, tt, *J*(H,F)= 15.1 Hz, *J*(F,F)= 4.9 Hz, CF_2); IR (thin film) ν (cm^{-1}) = 3384, 2936, 2869, 2243, 1663, 1497, 1455, 1319, 1267, 1176, 1075, 1028, 739, 699; MS (ESI) 411 (100) $[M+Na]^+$, 391 (45); HRMS: *m*/*z* calcd for $C_{21}H_{28}F_4Na_1O_2$ $[M+Na]^+$: 411.1918; found: 411.1918.

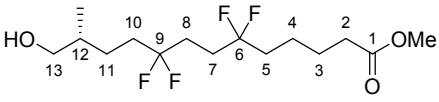
(12*R*)-12-((Benzyloxy)methyl)-6,6,9,9-tetrafluorotridec-7-ynoic acid 32



32

BAIB (2.49 g, 7.7 mmol, 4.0 eq) and TEMPO (0.119 g, 0.8 mmol, 0.4 eq) were added to a solution of (12*R*)-12-((benzyloxy)methyl)-6,6,9,9-tetrafluorotridec-7-yn-1-ol **31** (0.75 g, 1.9 mmol, 1.0 eq) in acetonitrile (6 mL) and water (6 mL) at r.t. and stirred for 7 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:4, 1% AcOH) gave (12*R*)-12-((benzyloxy)methyl)-6,6,9,9-tetrafluoro-tridec-7-ynoic acid **32** (0.45 g, 58%) as a yellow oil; $[\alpha]_D$ +5.5° (c 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.96 (3H, d, *J*(H,H)= 6.8 Hz, CH_3), 1.37-1.44 (1H, m, CH_2-11), 1.59-1.87 (5H, CH_2-3,4,11), 1.81-1.87 (1H, m, CH-12), 2.03-2.18 (4H, m, CH_2-5,10), 2.39 (2H, t, *J*(H,H)= 7.2 Hz, CH_2-2), 3.32 (1H, dd, *J*(H,H)= 7.2, 6.8 Hz, CH_AH$_B$-13), 3.35 (1H, dd, *J*(H,H)= 7.2, 5.8 Hz, CH$_A$$H_B$-13), 4.53 (2H, s, CH_2), 7.27-7.38 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 16.9 (CH_3), 22.2 (CH_2, t, *J*(C,F)= 3.3 Hz, C4), 24.1 (CH_2, C3), 26.5 (CH_2, t, *J*(C,F)= 3.3 Hz, C11), 33.0 (CH, C12), 33.5 (CH_2, C2), 36.6 (CH_2, t, *J*(C,F)= 25.3 Hz, C10), 38.6 (CH_2, t, *J*(C,F)= 25.0 Hz, C5), 73.2 (CH_2, Bn), 75.3 (CH_2, C13), 78.8-79.4 (C, m, C7/C8), 114.2 (CH_2, t, *J*(C,F)= 236.0 Hz, C6), 114.5 (CH_2, t, *J*(C,F)= 236.0 Hz, C9), 127.9 (CH), 127.9 (CH), 128.6 (CH), 138.4 (C), 177.3 (CO, C1); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -85.3-(-85.3) (2F, m, CF_2), -85.4-(-85.4) (2F, m, CF_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -85.3-(-85.4) (4F, m, CF_2); MS (ESI) 425 (100) $[M+Na]^+$, 405 (40); HRMS: *m*/*z* calcd for $C_{21}H_{26}F_4Na_1O_3$ $[M+Na]^+$: 425.1710; found: 425.1702.

Methyl (12*R*)-6,6,9,9-tetrafluoro-13-hydroxy-12-methyltridecanoate 33

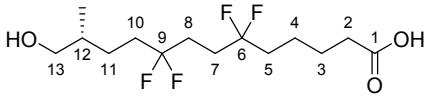


33

A solution of (12*R*)-12-((benzyloxy)methyl)-6,6,9,9-tetrafluorotridec-7-ynoic acid **32** (0.43 g, 1.06 mmol, 1.0 eq) and palladium on carbon (10 wt% on carbon, 0.113 g, 0.11 mmol, 10 mol%) in methanol (20 mL) was stirred under a hydrogen atmosphere (1 atm) for 22 h. The

reaction mixture was filtered through celite and the celite was washed with methanol (20 mL). The methanol layers were combined and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:4, 1% AcOH) gave methyl (12*R*)-6,6,9,9-tetrafluoro-13-hydroxy-12-methyltridecanoate **33** (0.227 g, 65%) as a white solid; mp 40-42 °C; $[\alpha]_D$ +6.2° (c 1.11, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.94 (3H, d, *J*(H,H)= 6.4 Hz, CH_3), 1.29-1.35 (1H, m, CH_2-11), 1.49-1.71 (7H, m, CH-12, CH_2-3,4,11, OH), 1.81-1.96 (4H, m, CH_2-5,10), 1.98-20.8 (4H, m, CH_2-7,8), 2.35 (2H, t, *J*(H,H)= 7.4 Hz, CH_2-2), 3.50 (2H, d, *J*(H,H)= 5.7 Hz, CH_2-13), 3.68 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 16.5 (CH_3), 22.0 (CH_2, t, *J*(C,F)= 4.5 Hz, C4), 24.7 (CH_2, C3), 25.8 (CH_2, t, *J*(C,F)= 4.3 Hz, C11), 29.3 (CH_2, t, *J*(C,F)= 25.8 Hz, C7/C8), 29.3 (CH_2, t, *J*(C,F)= 25.8 Hz, C7/C8), 33.9 (CH_2, C2), 34.5 (CH_2, t, *J*(C,F)= 25.2 Hz, C5/C10), 35.5 (CH, C12), 36.6 (CH_2, t, *J*(C,F)= 25.3 Hz, C5/C10), 51.8 (CH_3), 68.0 (CH_2, C13), 124.4 (CF_2, t, *J*(C,F)= 241.5 Hz, C6/C9), 124.7 (CF_2, t, *J*(C,F)= 241.5 Hz, C6/C9), 174.0 (CO); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -99.8 (2F, s, CF_2), -99.9 (2F, s, CF_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -99.8 (2F, tt, *J*(H,F)= 16.1, 15.5 Hz, CF_2), -99.9 (2F, tt, *J*(H,F)= 16.4, 16.1 Hz, CF_2); IR (thin film) ν (cm^{-1}) = 3276, 2960, 2929, 1734, 1469, 1448, 1257, 1176, 1127, 1028, 980, 899, 799; MS (ESI) 348 (100) $[M+NH_4]^+$, 331 (30); HRMS: *m*/*z* calcd for $C_{15}H_{30}F_4Na_1O_3$ $[M+NH_4]^+$: 348.2156; found: 348.2157.

(12*R*)-6,6,9,9-Tetrafluoro-13-hydroxy-12-methyltridecanoic acid 34

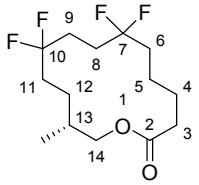


34

Lithium hydroxide (22 mg, 0.93 mmol, 4.2 eq) was added to a solution of methyl (12*R*)-6,6,9,9-tetrafluoro-13-hydroxy-12-methyltridecanoate **33** (73 mg, 0.22 mmol, 1.0 eq) in THF (3 mL) and H_2O (3 mL) at r.t. and stirred for 3 h. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with ethyl acetate (30 mL). The organic layer was separated and washed with brine (20 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give (12*R*)-6,6,9,9-tetrafluoro-13-hydroxy-12-methyltridecanoic acid **34** (70 mg, 94%) as a white solid; mp 90-93 °C; $[\alpha]_D$ +12.6° (c 0.46, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J*(H,H)= 6.5 Hz, CH_3), 1.25-1.37 (2H, m, CH_2-11, OH), 1.52-1.58 (2H, m, CH_2-4), 1.62-1.73 (4H, m, CH-12, CH_2-3,11), 1.82-1.94 (4H, m, CH_2-5,10),

1.99-2.08 (4H, m, CH_2-7,8), 2.40 (2H, t, *J*(H,H)= 7.2 Hz, CH_2-2), 3.49-3.55 (2H, m, CH_2-13); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 16.4 (CH_3), 22.0 (CH_2, t, *J*(C,F)= 4.1 Hz, C4), 24.5 (CH_2, C3), 25.9 (CH_2, t, *J*(C,F)= 4.7 Hz, C11), 29.0-29.5 (CH_2, m, C7, C8), 33.5 (CH_2, C2), 34.4 (CH_2, t, *J*(C,F)= 25.2 Hz, C5/C10), 35.5 (CH, C12), 36.4 (CH_2, t, *J*(C,F)= 25.2 Hz, C5/C10), 68.1 (CH_2, C13), 124.5 (CF_2, t, *J*(C,F)= 240.0 Hz, C6/C9), 124.7 (CF_2, t, *J*(C,F)= 241.4 Hz, C6/C9), 177.5 (CO); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -99.85 (1F, s, CF_2), -78.86 (1F, s, CF_2), -99.2 (2F, s, CF_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -98.8-(-98.9) (2F, m, CF_2), -99.2 (2F, tt, *J*(H,F)= 15.9, 14.5 Hz, CF_2); MS (ESI) 315 (100) $[M-H]^-$, 255 (45); HRMS: *m*/*z* calcd for $C_{14}H_{23}F_4O_3$ $[M-H]^-$: 315.1589; found: 315.1598.

(13*R*)-7,7,10,10-Tetrafluoro-13-methyl-1-oxacyclotetradecan-2-one 8

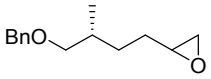


8

Triethylamine (0.48 mL, 3.41 mmol, 15.0 eq) and 2,4,6-trichlorobenzoyl chloride (0.33 mL, 2.28 mmol, 10.0 eq) were added to a solution of (12*R*)-6,6,9,9-tetrafluoro-13-hydroxy-12-methyltridecanoic acid **34** (72 mg, 0.23 mmol, 1.0 eq) in dry THF (100 mL) at r.t. under argon and stirred for 2.5 h. The reaction mixture was diluted with dry toluene (40 mL) and added over 2 h using a syringe pump to a solution of 4-DMAP (0.56 g, 4.55 mmol, 20.0 eq) in dry toluene (60 mL). The reaction mixture was stirred at r.t. for a further 1.5 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution (60 mL) and diluted with DCM (50 mL). The organic layer was separated and the aqueous layer was re-extracted with DCM (50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:19) gave (13*R*)-7,7,10,10-tetrafluoro-13-methyl-1-oxacyclotetradecan-2-one **8** (36.5 mg, 54%) as a white solid; mp 63-65 °C; $[\alpha]_D$ +32.2° (c 0.58, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.98 (3H, d, *J*(H,H)= 6.9 Hz, CH_3), 1.26-2.06 (15H, m, CH-13, CH_2-4,5,6,8,9,11,12), 2.36-2.51 (2H, m, CH_2-3), 3.78 (1H, dd, *J*(H,H)= 11.1, 9.2 Hz, CH_AH_B-14), 4.21 (1H, dd, *J*(H,H)= 11.1, 3.4 Hz, CH_AH_B-14); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 16.2 (CH_3), 22.2 (CH_2, t, *J*(C,F)= 5.8 Hz, C5), 24.4 (CH_2, C4), 26.6 (CH_2, t, *J*(C,F)= 5.0 Hz, C12), 28.1-28.7 (CH_2, m, C7, C8), 31.6 (CH_2, t, *J*(C,F)= 25.2

Hz, C11), 32.3 (CH, C13), 34.3 (CH_2, t, *J*(C,F)= 25.3 Hz, C6), 35.4 (CH_2, C2), 67.9 (CH_2, C14), 125.2 (CF_2, t, *J*(C,F)= 240.9 Hz, C7), 125.5 (CF_2, t, *J*(C,F)= 240.9 Hz, C10), 173.1 (CO, C2); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -91.01 (1F, s, CF_2), -91.04 (1F, s, CF_2), -91.09 (1F, d, *J*(F,F)= 246.9 Hz, CF_AF_B), -92.2 (1F, d, *J*(F,F)= 246.9 Hz, CF_AF_B); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -91.0-(-91.1) (2F, m, CF_2), -91.09 (1F, dm, *J*(F,F)= 246.9 Hz, CF_AF_B), -92.2 (1F, dm, *J*(F,F)= 246.9 Hz, CF_AF_B); MS (ASAP) 316 (60) $[M+NH_4]^+$, 298 (50) $[M]^+$, 279 (100) $[M-F]^+$, 261 (60), 241 (30); HRMS: *m*/*z* calcd for $C_{14}H_{26}F_4N_1O_2$ $[M+NH_4]^+$: 316.1898; found: 316.1894.

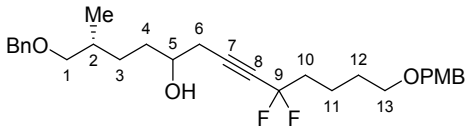
2-((3*R*)-4-(Benzyloxy)-3-methylbutyl)oxirane 13



13

mCPBA (3.45 g, 20 mmol, 2.0 eq) was added to a solution of (((2*R*)-2-methylhex-5-en-1-ol)oxy)methyl)benzene **11** (2.04 g, 10 mmol, 1.0 eq) in DCM (100 mL) at r.t. and stirred for 18 h. The reaction mixture was diluted with DCM (100 mL) and washed with sodium sulfite solution (10%, 200 mL), sat. $NaHCO_3$ solution (200 mL), brine (200 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:19) gave 2-((3*R*)-4-(benzyloxy)-3-methylbutyl)oxirane **13** (1.88 g, 55%) as a colourless oil as a 1:1 mixture of diastereoisomers; $[\alpha]_D$ +3.4° (c 0.99, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J*(H,H)= 6.7 Hz, CH_3) and 0.96 (3H, d, *J*(H,H)= 6.8 Hz, CH_3), 1.24-1.36 (1H, m, CH_2), 1.49-1.69 (3H, m, CH_2), 1.78-1.86 (1H, m, CH), 2.47-2.49 (1H, m, CH_2), 2.74-2.77 (1H, m, CH_2), 2.90-2.93 (1H, m, CH), 3.27-3.35 (2H, m, CH_2), 4.51 (2H, m, CH_2), 7.27-7.37 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.2 and 17.2 (CH_3), 29.9 and 30.0 (CH_2), 30.1 and 30.2 (CH_2), 33.5 and 33.5 (CH), 47.3 and 47.4 (CH_2), 52.7 and 52.7 (CH), 73.2 and 73.2 (CH_2), 75.8 (CH_2), 127.7 (CH), 127.7 (CH), 128.5 (CH), 138.9 (C); IR (thin film) ν (cm^{-1}) = 3032, 2925, 2855, 1496, 1454, 1364, 1260, 1206, 1099, 1029, 835, 737, 698; MS (ESI) 275 (30) $[M+MeOH+Na]^+$, 243 (100) $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{14}H_{20}Na_1O_2$ $[M+Na]^+$: 243.1356; found: 243.1350

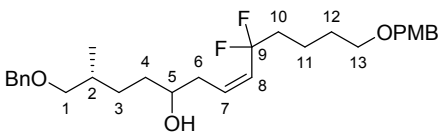
(2*R*)-2-((Benzyloxy)methyl)-9,9-difluoro-13-((4-methoxyphenyl)methoxy)tridec-7-yn-5-ol 16



16

Following the same procedure reported for **15**, 1-(((5,5-difluorohept-6-yn-1-yl)oxy)methyl)-4-methoxybenzene **28a** (3.6 g, 13.5 mmol, 1.0 eq) and 2-((3*R*)-4-(benzyloxy)-3-methylbutyl)oxirane **13** (4.5 g, 20.3 mmol, 1.5 eq) gave (2*R*)-2-((benzyloxy)methyl)-9,9-difluoro-13-((4-methoxyphenyl)methoxy)tridec-7-yn-5-ol **16** (4.0 g, 60%) as a yellow oil, as a mixture of two diastereoisomers; $[\alpha]_D$ +1.8° (c 1.04, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.94 (3H, d, *J*(H,H)= 6.7 Hz, CH_3) and 0.95 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.13-1.33 (1H, m, CH_2-3), 1.46-1.72 (7H, m, CH_2-3,4,11,12), 1.76-1.85 (1H, m, CH-2), 1.91 (1H, bs, OH), 2.00-2.08 (2H, m, CH_2-10), 2.38-2.62 (2H, m, CH_2-6), 3.27-3.33 (2H, m, CH_2-1), 3.45-3.47 (2H, m, CH_2-13), 3.74-3.79 (1H, m, CH-5), 3.81 (3H, s, CH_3), 4.44 (2H, s, CH_2), 4.51 (2H, s, CH_2), 6.88-6.90 (2H, m, ArH), 7.26-7.37 (7H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.3 and 17.3 (CH_3), 20.1 (CH_2, C12), 27.4 and 27.6 (CH_2, C6), 29.2 (CH_2, C11), 29.7 and 29.7 (CH_2, C3), 33.4 and 33.6 (CH, C2), 33.9 and 33.9 (CH_2, C4), 39.3 (CH_2, t, *J*(C,F)= 26.5 Hz, C10), 55.5 (CH_3), 69.6 (CH_2, C13), 69.9 and 70.1 (CH, C5), 72.8 (CH_2, PMB), 73.2 and 73.3 (CH_2, Bn), 75.8 and 75.9 (CH_2, C1), 76.2 (C, t, *J*(C,F)= 41.0 Hz, C8) and 76.2 (C, t, *J*(C,F)= 40.4 Hz, C8), 85.4 and 85.5 (C, C7), 114.0 (CH), 115.0 (CF_2, t, *J*(C,F)= 231.6 Hz, C9), 127.7 and 127.7 (CH), 127.8 and 127.8 (CH), 128.6 (CH), 129.5 (CH), 130.7 (C), 138.7 and 138.8 (C), 159.4 (C); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -81.25 and -81.26 (2F, s, CF_2); MS (ESI) 511 (100) $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{29}H_{38}F_2Na_1O_4$ $[M+Na]^+$: 511.2630; found: 511.2620.

(2*R*,7*Z*)-2-((Benzyloxy)methyl)-9,9-difluoro-13-((4-methoxyphenyl)methoxy)tridec-7-en-1-ol 35

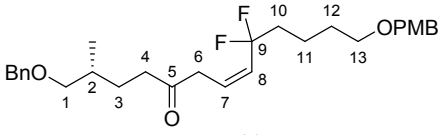


35

A suspension of palladium (5% on barium sulfate, 600 mg) and quinoline (200 mg) in pyridine (80 mL) was evacuated using high vacuum and flushed with hydrogen (1 atm). The

suspension was stirred under a hydrogen atmosphere for 5 minutes. A solution of (2*R*)-2-((benzyloxy)methyl)-9,9-difluoro-13-((4-methoxyphenyl)methoxy)tridec-7-yn-5-ol **16** (2.0 g, 4.1 mmol, 1.0 eq) in pyridine (10 mL) was added and the reaction mixture was evacuated using high vacuum and flushed with hydrogen (1 atm) three times. The reaction mixture was stirred under hydrogen for 22 h. The reaction mixture was filtered through a plug of celite and the celite was washed with ethyl acetate (200 mL). The washing were combined and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:4) gave (2*R*,7*Z*)-2-((benzyloxy)methyl)-9,9-difluoro-13-((4-methoxyphenyl)methoxy)tridec-7-en-1-ol **35** (1.64 g, 82%) as a colourless oil as a 1:1 mixture of two diastereoisomers; $[\alpha]_D$ +0.8° (c 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J*(H,H)= 6.2 Hz, CH_3) and 0.96 (3H, d, *J*(H,H)= 6.3 Hz, CH_3), 1.16-1.34 (1H, m, CH_2-3), 1.40-1.69 (8H, m, CH_2-3,4,11,12, OH), 1.77-1.82 (1H, m, CH-2), 1.90-2.00 (2H, m, CH_2-10), 2.38-2.50 (2H, m, CH_2-6), 3.28-3.36 (2H, m, CH_2-1), 3.47 (2H, t, *J*(H,H)= 6.2 Hz, CH_2-13), 3.67-3.68 (1H, m, CH-5), 3.83 (3H, s, CH_3), 4.45 (2H, s, CH_2), 4.52 (2H, s, CH_2), 5.56-5.64 (1H, m, CH-8), 5.82-5.87 (1H, m, CH-7), 6.89-6.92 (2H, m, ArH), 7.27-7.38 (7H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.3 and 17.4 (CH_3), 19.4 (CH_2, t, *J*(C,F)= 3.9 Hz, C12), 29.6 (CH_2, C11), 29.8 and 29.8 (CH_2, C3), 33.5 and 33.7 (CH, C2), 34.7 and 34.8 (CH_2, C4), 36.3 and 36.4 (CH_2, C6), 38.4 (CH_2, t, *J*(C,F)= 38.4 Hz, C10), 55.5 (CH_3), 69.8 (CH_2, C13), 71.7 and 71.9 (CH, C5), 72.8 (CH_2, PMB), 73.2 and 73.2 (CH_2, Bn), 75.8 and 76.0 (CH_2, C1), 114.0 (CH), 122.7 (CF_2, t, *J*(C,F)= 238.5 Hz, C9), 126.9 (CH, t, *J*(C,F)= 26.8 Hz, C8) and 127.0 (CH, t, *J*(C,F)= 26.8 Hz, C8), 127.7 and 127.7 (CH), 127.8 and 128.0 (CH), 128.5 (CH), 129.5 (CH), 130.7 (C), 134.1-134.2 (CH, m, C7), 138.8 and 138.9 (C), 159.3 (C); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -90.2 and -90.2 (1F, d, *J*(F,F)= 248.0 Hz, CFH_AF_B), -90.7 and -90.7 (1F, d, *J*(F,F)= 248.0 Hz, CF_AH_B); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -90.2 (1F, dm, *J*(F,F)= 248.0 Hz, CH_AF_B), -90.7 (1F, dm, *J*(F,F)= 248.0 Hz, CF_AH_B); MS (ESI) 603 (35), 531 (65), 513 (100) $[M+Na]^+$, 121 (30); HRMS: *m*/*z* calcd for $C_{29}H_{40}F_2Na_1O_4$ $[M+Na]^+$: 513.2787; found: 513.2785.

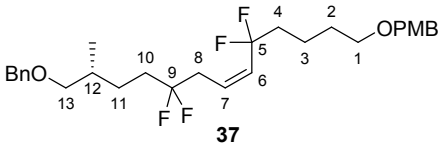
(2*R*,7*Z*)-2-((Benzyloxy)methyl)-9,9-difluoro-13-((4-methoxyphenyl)methoxy)tridec-7-en-1-one 36



36

Following the same procedure reported for **29**, (2*R*,7*Z*)-2-((benzyloxy)methyl)-9,9-difluoro-13-((4-methoxyphenyl)methoxy)tridec-7-en-1-ol **35** (1.6 g, 3.3 mmol, 1.0 eq) gave (2*R*,7*Z*)-2-((benzyloxy)methyl)-9,9-difluoro-13-((4-methoxyphenyl)methoxy)tridec-7-en-1-one **36** (0.90 g, 57%) as a colourless oil; $[\alpha]_D$ -0.4° (c 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.93 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.43-1.84 (7H, m, CH-2, CH_2-3,11,12), 1.86-1.98 (2H, m, CH_2-10), 2.20-2.63 (2H, m, CH_2-6), 3.27-3.347 (2H, m, CH_2-1), 3.42-3.47 (4H, m, CH_2-4,13), 3.81 (3H, s, CH_3), 4.44 (2H, s, CH_2), 4.49 (2H, s, CH_2), 5.58-5.66 (1H, m, CH-8), 6.00-6.07 (1H, m, CH-7), 6.87-6.90 (2H, m, ArH), 7.25-7.37 (7H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.2 (CH_3), 19.3 (CH_2, t, *J*(C,F)= 4.1 Hz, C12), 27.8 (CH_2, C3), 29.5 (CH_2, C11), 33.2 (CH_2, C2), 38.2 (CH_2, t, *J*(C,F)= 26.4 Hz, C10), 40.5 (CH_2, C6), 41.6 (CH_2, C4), 55.5 (CH_3), 69.7 (CH_2, C13), 72.8 (CH_2, PMB), 73.2 (CH_2, Bn), 75.6 (CH_2, C1), 114.0 (CH), 122.6 (CF_2, t, *J*(C,F)= 239.7 Hz, C9), 127.1 (CH_2, t, *J*(C,F)= 26.4 Hz, C8), 127.7 (CH), 127.8 (CH), 128.5 (CH), 129.1 (CH_2, t, *J*(C,F)= 5.4 Hz, C7), 129.4 (CH), 130.7 (C), 138.8 (C), 159.3 (CH), 207.7 (CO, C5); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -91.9 (2F, s, CF_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -91.8-(-91.9) (2F, m, CF_2); MS (ESI) 511 (100) $[M+Na]^+$, 121 (40); HRMS: *m*/*z* calcd for $C_{29}H_{38}F_2Na_1O_4$ $[M+Na]^+$: 511.2630; found: 511.2627.

1-((((6*Z*,12*R*)-13-(Benzyloxy)-5,5,9,9-tetrafluoro-12-methyltridec-6-en-1-yl)oxy)methyl)-4-methoxybenzene 37

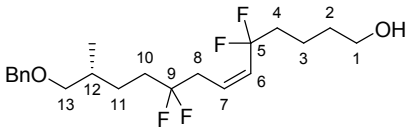


37

Following the same procedure reported for **30**, (2*R*,7*Z*)-2-((benzyloxy)methyl)-9,9-difluoro-13-((4-methoxyphenyl)methoxy)tridec-7-en-1-one **36** (1.0 g, 2.0 mmol, 1.0 eq) gave 1-((((6*Z*,12*R*)-13-(benzyloxy)-5,5,9,9-tetrafluoro-12-methyltridec-6-en-1-yl)oxy)methyl)-4-methoxybenzene **37** (0.29 g, 27%) as a yellow oil; $[\alpha]_D$ -1.2° (c 1.53, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.30-1.70 (6H, m, CH_2-2,3,11), 1.76-1.98 (5H, CH-12, CH_2-4,10), 2.82-3.03 (2H, m, CH_2-8), 3.28-3.36 (2H, m, CH_2-13), 3.45 (2H, t, *J*(H,H)= 6.2 Hz, CH_2-1), 3.81 (3H, s, CH_3), 4.44 (2H, s, CH_2), 4.51 (2H, s, CH_2), 5.54-5.74 (1H, m, CH-6), 5.77-6.02 (1H, m, CH-7), 6.88-6.90 (2H, m, ArH), 7.26-7.38 (7H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.1 (CH_3), 19.3 (CH_2, t, *J*(C,F)= 4.0 Hz, C3), 26.0

(CH_2, t, *J*(C,F)= 4.1 Hz, C11), 29.6 (CH_2, C2), 33.3 (CH_2, C12), 34.1 (CH_2, t, *J*(C,F)= 24.9 Hz, C10), 35.7 (CH_2, t, *J*(C,F)= 26.1 Hz, C8), 38.3 (CH_2, t, *J*(C,F)= 26.5 Hz, C4), 55.5 (CH_3), 69.7 (CH_2, C1), 72.8 (CH_2, PMB), 73.2 (CH_2, Bn), 75.6 (CH_2, C13), 114.0 (CH), 122.5 (CF_2, t, *J*(C,F)= 239.4 Hz, C9), 124.2 (CF_2, t, *J*(C,F)= 240.9 Hz, C5), 127.7 (CH), 127.8 (CH), 128.2-128.3 (CH, m, C7), 128.6 (CH, C6), 128.6 (CH), 129.4 (CH), 130.7 (C), 138.8 (C), 159.4 (C); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -91.8 (2F, s, CF_2), -98.5 (2F, s, CF_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ = = -91.8 (2F, dt, *J*(H,F)= 15.6, 15.6 Hz, CF_2), -98.5 (2F, tt, *J*(H,F)= 16.5, 16.2 Hz, CF_2); MS (ESI) 632 (15), 533 (50) $[M+Na]^+$, 121 (100); HRMS: *m*/*z* calcd for $C_{29}H_{38}F_4Na_1O_3$ $[M+Na]^+$: 533.2649; found: 533.2642.

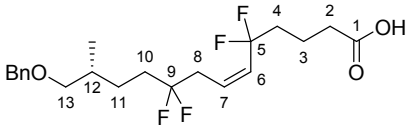
(6*Z*,12*R*)-13-(Benzyloxy)-5,5,9,9-tetrafluoro-12-methyltridec-6-en-1-ol 38



38

Following the same procedure reported for **31**, 1-((((6*Z*,12*R*)-13-(benzyloxy)-5,5,9,9-tetrafluoro-12-methyltridec-6-en-1-yl)oxy)methyl)-4-methoxybenzene **37** (0.28 g, 0.5 mmol, 1.0 eq) gave (6*Z*,12*R*)-13-(benzyloxy)-5,5,9,9-tetrafluoro-12-methyltridec-6-en-1-ol **38** (0.15 g, 70%) as a colourless oil; $[\alpha]_D$ -1.9° (c 1.14, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 13.0-1.44 (1H, m, CH_2-11), 1.54-1.70 (5H, m, CH_2-2,3,11), 1.73-2.00 (5H, CH-12, CH_2-4,10), 2.82-3.02 (2H, m, CH_2-8), 3.28-3.37 (2H, m, CH_2-13), 4.50 (2H, s, CH_2), 5.64-5.72 (1H, m, CH-6), 5.80-5.85 (1H, m, CH-7), 7.26-7.38 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.1 (CH_3), 18.8 (CH_2, t, *J*(C,F)= 4.1 Hz, C3), 26.1 (CH_2, t, *J*(C,F)= 4.0 Hz, C11), 32.4 (CH_2, C2), 33.4 (CH_2, C12), 34.2 (CH_2, t, *J*(C,F)= 25.0 Hz, C10), 35.7 (CH_2, t, *J*(C,F)= 26.3 Hz, C8), 38.3 (CH_2, t, *J*(C,F)= 26.5 Hz, C4), 62.6 (CH_2, C1), 73.3 (CH_2, Bn), 75.6 (CH_2, C13), 122.3 (CF_2, t, *J*(C,F)= 240.1 Hz, C9), 124.2 (CF_2, t, *J*(C,F)= 242.1 Hz, C5), 127.7 (CH), 127.8 (CH), 128.2-128.5 (CH, m, C6 and C7), 128.6 (CH), 129.4 (CH), 138.8 (C); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -91.8 (1F, s, CF_2), -91.8 (1F, s, CF_2), -98.6 (2F, s, CF_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ = = -91.8 (2F, dt, *J*(H,F)= 15.7, 15.4 Hz, CF_2), -98.5 (2F, tt, *J*(H,F)= 16.6, 16.4 Hz, CF_2); MS (ESI) 413 (100) $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{21}H_{30}F_4Na_1O_2$ $[M+Na]^+$: 413.2074; found: 413.2067.

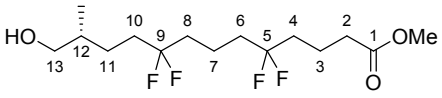
(6*Z*,12*R*)-13-(Benzyloxy)-5,5,9,9-tetrafluoro-12-methyltridec-6-enoic acid 39



39

Following the same procedure reported for **32**, (6*Z*,12*R*)-13-(benzyloxy)-5,5,9,9-tetrafluoro-12-methyltridec-6-en-1-ol **38** (0.15 g, 0.4 mmol, 1.0 eq) gave (6*Z*,12*R*)-13-(benzyloxy)-5,5,9,9-tetrafluoro-12-methyltridec-6-enoic acid **39** (76 mg, 49%) as a colourless oil; $[\alpha]_D$ -0.5° (c 0.40, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.30-1.39 (1H, m, CH_AH$_B$-11), 1.63-1.70 (1H, m, CH$_A$$H_B$-11), 1.76-2.04 (7H, m, CH-12, CH_2-3,4,10), 2.44 (2H, t, *J*(H,H)= 7.3 Hz, CH_2-2), 2.82-2.90 (2H, m, CH_2-8), 3.29-3.34 (2H, m, CH_2-13), 4.52 (2H, s, CH_2), 5.65-5.73 (1H, m, CH-6), 5.82-5.87 (1H, m, CH-7), 7.27-7.40 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.1 (CH_3), 17.6 (CH_2, t, *J*(C,F)= 4.1 Hz, C3), 26.1 (CH_2, t, *J*(C,F)= 4.0 Hz, C11), 33.3 (CH, C12), 33.3 (CH_2, C2), 34.2 (CH_2, t, *J*(C,F)= 24.8 Hz, C10), 35.7 (CH_2, t, *J*(C,F)= 26.2 Hz, C8), 37.5 (CH_2, t, *J*(C,F)= 26.8 Hz, C4), 73.2 (CH_2, Bn), 75.5 (CH_2, C13), 122.2 (CF_2, t, *J*(C,F)= 239.8 Hz, C5), 124.1 (CF_2, t, *J*(C,F)= 241.6 Hz, C9), 127.6 (CH), 127.8 (CH), 128.3 (CH, t, *J*(C,F)= 26.4 Hz, C6), 128.6 (CH), 128.6-128.8 (CH, m, C7), 138.7 (C), 178.9 (CO, C1); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -92.0 (2F, s, CF_2-C5), -98.4 (2F, s, CF_2-C9); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -90.1 (2F, dt, *J*(F,F)= 15.5, 15.4 Hz, CF_2-C5), -98.4 (2F, tt, *J*(F,F)= 16.5, 16.5 Hz, CF_2-C9); MS (ESI) 560 (20), 473 (25), 427 (100) $[M+Na]^+$, 126 (25); HRMS: *m*/*z* calcd for $C_{21}H_{28}F_4Na_1O_3$ $[M+Na]^+$: 427.1867; found: 427.1861.

(12*R*)-5,5,9,9-Tetrafluoro-13-hydroxy-12-methyltridecanoate 40

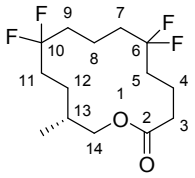


40

Following the same procedure reported for **33**, (6*Z*,12*R*)-13-(benzyloxy)-5,5,9,9-tetrafluoro-12-methyltridec-6-enoic acid **39** (75 mg, 0.19 mmol, 1.0 eq) gave methyl (12*R*)-5,5,9,9-tetrafluoro-13-hydroxy-12-methyltridecanoate **40** (36 g, 59%) as a white solid; $[\alpha]_D$ +4.4° (c 0.25, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.25-1.34 (1H, m, CH_2-11), 1.55 (1H, bs, OH), 1.60-1.72 (4H, m, CH-12, CH_2-7,11), 1.77-1.95 (10H, m, CH_2-3,4,6,8,10), 2.39 (2H, t, *J*(H,H)= 6.9 Hz, CH_2-2), 3.47-3.54 (2H, m, CH_2-13), 3.69 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 15.5-15.7 (CH_2, m, C7), 16.6 (CH_3), 18.0

(CH_2, t, *J*(C,F)= 4.7 Hz, C3), 25.8 (CH_2, t, *J*(C,F)= 4.2 Hz, C11), 33.5 (CH_2, C2), 34.1 (CH_2, t, *J*(C,F)= 25.5 Hz, C10), 35.6 (CH_2, C12), 35.8 (CH_2, t, *J*(C,F)= 26.1 Hz, C8), 36.0 (CH_2, t, *J*(C,F)= 25.5 Hz, C4/C6), 36.1 (CH_2, t, *J*(C,F)= 25.5 Hz, C4/C6), 51.9 (CH_3), 68.0 (CH_2, C13), 124.8 (CF_2, t, *J*(C,F)= 240.7 Hz, C5/C9), 125.2 (CF_2, t, *J*(C,F)= 240.7 Hz, C5/C9), 173.7 (CO, C1); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -98.5 (2F, s, CF_2), -98.6 (2F, s, CF_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -98.5 (2F, tt, *J*(H,F)= 16.5, 16.5 Hz, CF_2), -98.6 (2F, tt, *J*(H,F)= 16.3, 16.3 Hz, CF_2); MS (ESI) 353 (100) $[M+Na]^+$, 316 (15); HRMS: *m*/*z* calcd for $C_{15}H_{26}F_4Na_1O_3$ $[M+Na]^+$: 353.1710; found: 353.1699.

(13*R*)-6,6,10,10-Tetrafluoro-13-methyl-1-oxacyclotetradecan-2-one 9



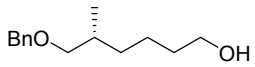
9

Lithium hydroxide (11 mg, 0.46 mmol, 4.2 eq) was added to a solution of methyl (12*R*)-5,5,9,9-tetrafluoro-13-hydroxy-12-methyltridecanoate **40** (36 mg, 0.11 mmol, 1.0 eq) in THF (1 mL) and H_2O (1 mL) at r.t. and stirred for 3 h. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with ethyl acetate (30 mL). The organic layer was separated and washed with brine (20 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give (12*R*)-6,6,9,9-tetrafluoro-13-hydroxy-12-methyltridecanoic acid **41** (24 mg, 70%) as a white solid that was immediately used for the next stage without further purification.

Triethylamine (0.16 mL, 1.14 mmol, 15.0 eq) and 2,4,6-trichlorobenzoyl chloride (0.11 mL, 0.76 mmol, 10.0 eq) were added to a solution of (12*R*)-5,5,9,9-tetrafluoro-13-hydroxy-12-methyltridecanoic acid **41** (24 mg, 0.08 mmol, 1.0 eq) in dry THF (5 mL) at r.t. under argon and stirred for 2.5 h. The reaction mixture was diluted with dry toluene (20 mL) and added over 2 h using a syringe pump to a solution of 4-DMAP (0.19 g, 1.52 mmol, 20.0 eq) in dry toluene (30 mL). The reaction mixture was stirred at r.t. for 18 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution (50 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:19) gave (13*R*)-6,6,10,10-tetrafluoro-13-methyl-1-oxacyclotetradecan-2-one **9** (12 mg, 52%) as a colourless oil; $[\alpha]_D$ +9.2° (c 0.59, $CHCl_3$); ^1H NMR (500

MHz, $CDCl_3$) δ = 1.00 (3H, d, *J*(H,H)= 7.0 Hz, CH_3), 1.35-1.58 (4H, m, CH_2-8,12), 1.77-2.02 (11H, m, CH-13, CH_2-4,5,7,9,11), 2.40-2.46 (1H, m, CH_2-3), 2.49-2.54 (1H, m, CH_2-3), 3.86 (1H, dd, *J*(H,H)= 11.3, 7.8 Hz, CH_2-14), 4.20 (1H, dd, *J*(H,H)= 11.3, 3.4 Hz, CH_2-14); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 16.9 (CH_3), 17.9 (CH_2, tt, *J*(C,F)= 5.5, 5.5 Hz, C8), 19.0 (CH_2, t, *J*(C,F)= 5.5 Hz, C4), 25.8 (CH_2, t, *J*(C,F)= 5.3 Hz, C12), 30.9 (CH_2, t, *J*(C,F)= 25.9 Hz, C11), 31.8 (CH, C13), 33.8 (CH_2, t, *J*(C,F)= 26.0 Hz), 33.9 (CH_2, t, *J*(C,F)= 25.9 Hz), 34.3 (CH_2, t, *J*(C,F)= 25.9 Hz), 34.3 (CH_2, C3), 67.2 (CH_2, C14), 125.6 (CF_2, t, *J*(C,F)= 240.4 Hz, C6), 126.1 (CF_2, t, *J*(C,F)= 240.4 Hz, C10), 172.7 (CO, C2); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -91.0 (2F, s, CF_2), -91.2 (1F, d, *J*(F,F)= 248.5 Hz, CF_AF$_B$), -91.8 (1F, d, *J*(F,F)= 248.5 Hz, CF$_A$$F_B$); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -91.0 (2F, tt, *J*(H,F)= 14.7, 14.6 Hz, CF_2), -91.2 (1F, dm, *J*(F,F)= 248.5 Hz, CF_AF$_B$), -91.8 (1F, dm, *J*(F,F)= 248.5 Hz, CF$_A$$F_B$); HRMS: *m*/*z* calcd for $C_{14}H_{26}F_4N_1O_2$ $[M+NH_4]^+$: 316.1894; found: 316.1888.

(5*R*)-6-(Benzyloxy)-5-methylhexan-1-ol 50

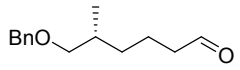


50

9-BBN dimer (3.66 g, 15 mmol, 1.0 eq) was added to a solution of (((2*R*)-2-methylhex-5-en-1-ol)oxy)methyl)benzene **11** (3.06 g, 15 mmol, 1.0 eq) in dry THF (75 mL) under argon at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then warmed to r.t. and stirred for 22 h. The reaction mixture was cooled to 0 °C. Ethanol (10 mL), sodium hydroxide solution (2 N, 10 mL) and hydrogen peroxide (30%, 10 mL) were added. The reaction mixture was warmed to r.t. and stirred for 3 h, and then the solvent was removed *in vacuo*. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (200 mL), brine (200 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:4) gave (5*R*)-6-(benzyloxy)-5-methylhexan-1-ol **50** (1.99 g, 59%) as a colourless oil; $[\alpha]_D$ +0.7° (c 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.94 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.13-1.69 (7H, m, CH_2, OH), 1.74-1.82 (1H, m, CH), 3.26 (1H, dd, *J*(H,H)= 9.1, 6.7 Hz, CH_AH$_B$), 3.33 (1H, dd, *J*(H,H)= 9.1, 6.1 Hz, CH$_A$$H_B$), 3.64 (2H, t, J(H,H)= 6.7 Hz, CH_2), 4.50 (1H, d, *J*(H,H)= 12.8 Hz, CH_AH$_B$), 4.52 (1H, dd, *J*(H,H)= 12.8 Hz, CH$_A$$H_B$), 7.27-7.37 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.3 (CH_3), 23.3 (CH_2), 33.2 (CH_2), 33.6 (CH_2), 33.6 (CH), 63.2 (CH_2), 73.2 (CH_2), 76.1 (CH_2), 127.7 (CH), 127.8 (CH), 128.5 (CH), 138.9 (C); MS (ESI) 277 (100)

[M+MeOH+Na]$^+$, 245 (60) [M+Na]$^+$; HRMS: *m/z* calcd for $C_{14}H_{22}Na_1O_2$ [M+Na]$^+$: 245.1512; found: 245.1509.

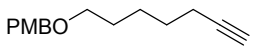
(5*R*)-6-(Benzyloxy)-5-methylhexanal 14



14

DMP (4.53 g, 10.7 mmol, 1.2 eq) was added to a solution of (5*R*)-6-(benzyloxy)-5-methylhexan-1-ol **50** (1.98 g, 8.9 mmol, 1.0 eq) in DCM (100 mL) at r.t. The reaction mixture was stirred at r.t. for 1 h, then diluted with diethyl ether (50 mL) and sat. $NaHCO_3$ solution (100 mL). Sodium thiosulfate (7 g) was added and the reaction mixture was stirred vigorously for 30 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give (5*R*)-6-(benzyloxy)-5-methylhexanal **12** (2.0 g, 100%) as a yellow oil that was used without further purification; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J*(H,H)= 6.9 Hz, CH_3), 1.14-1.22 (1H, m, CH_2), 1.46-1.82 (4H, m, CH_2, CH), 2.43 (2H, t, *J*(H,H)= 7.2 Hz, CH_2), 3.28 (1H, dd, *J*(H,H)= 9.0, 6.3 Hz, CH_AH$_B$), 3.32 (1H, dd, *J*(H,H)= 9.1, 6.3 Hz, CH$_A$$H_B$), 4.51 (2H, s, CH_2), 7.27-7.37 (5H, m, ArH), 9.77 (1H, t, *J*(H,H)= 1.6 Hz, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.2 (CH_3), 19.7 (CH_2), 33.4 (CH_2), 33.6 (CH), 44.4 (CH_2), 73.2 (CH_2), 75.8 (CH_2), 127.7 (CH), 127.8 (CH), 128.6 (CH), 138.9 (C), 203.0 (CHO).

1-((Hept-6-yn-1-yloxy)methyl)-4-methoxybenzene 43

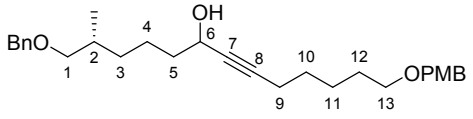


43

6-Heptyn-1-ol **42** (2.0 g, 17.8 mmol, 1.0 eq) was added to a suspension of sodium hydride (60% in oil, 0.78 g, 19.6 mmol, 1.1 eq) in dry DMF (100 mL) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 30 min, then 4-methoxybenzyl chloride (2.7 mL, 19.6 mmol, 1.1 eq) was added. The reaction mixture was warmed to r.t. and stirred for 18 h. The reaction mixture was quenched with water (200 mL) and diluted with ethyl acetate (250 mL). The organic layer was separated and washed with water (3 x 250 mL), brine (250 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:9) gave 1-((hept-6-yn-1-yloxy)methyl)-

4-methoxybenzene **43** (3.58 g, 87%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.45-1.66 (6H, m, CH_2), 1.95 (1H, t, *J*(H,H)= 2.6 Hz, CH), 2.20 (2H, dt, *J*(H,H)= 6.9, 2.6 Hz, CH_2), 3.46 (2H, t, *J*(H,H)= 6.5 Hz, CH_2), 3.81 (3H, s, CH_3), 4.44 (2H, s, CH_2), 6.88-6.90 (2H, m, ArH), 7.26-7.28 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 18.6 (CH_2), 25.6 (CH_2), 28.5 (CH_2), 29.4 (CH_2), 55.5 (CH_3), 68.4 (CH), 70.1 (CH_2), 72.8 (CH_2), 84.8 (C), 114.0 (CH), 129.4 (CH), 130.9 (C), 159.3 (C); IR (thin film) ν (cm^{-1}) = 3302, 2939, 2861, 2116, 1613, 1513, 1248, 1098, 1036, 821, 738, 637; MS (ESI) 287 (80) $[M+MeOH+Na]^+$, 255 (100) $[M+Na]^+$, 121 (45); HRMS: *m*/*z* calcd for $C_{15}H_{20}Na_1O_2$ $[M+Na]^+$: 255.1356; found: 255.1350.

(2*R*)-2-((Benzyloxy)methyl)-13-((4-methoxyphenyl)methoxy)tridec-7-yn-6-ol 17

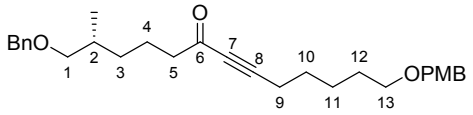


17

Following the same procedure reported for **15**, 1-((hept-6-yn-1-yloxy)methyl)-4-methoxybenzene **43** (1.88 g, 8.1 mmol, 1.0 eq) and (5*R*)-6-(benzyloxy)-5-methylhexanal **14** (1.96 g, 8.9 mmol, 1.1 eq) gave (2*R*)-2-((benzyloxy)methyl)-13-((4-methoxyphenyl)methoxy)tridec-7-yn-6-ol **17** (2.92 g, 80%) as a colourless oil, as a mixture of two diastereoisomers; $[\alpha]_D$ +1.1° (c 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.94 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.14-1.16 (1H, m, CH_2-3), 1.38-1.71 (12H, m, CH_2-3,4,5,10,11,12, OH), 1.76-1.82 (1H, m,CH-2), 2.21 (2H, t, *J*(H,H)= 7.1 Hz, CH_2-9, diastereomer A), 2.21 (2H, t, *J*(H,H)= 7.0 Hz, CH_2-9, diastereomer B), 3.26 (1H, dd, *J*(H,H)= 8.9, 6.5 Hz, CH_AH$_B$-1), 3.31-3.35 (1H, m, CH_AH$_B$-1), 3.44 (2H, t, *J*(H,H)= 6.6 Hz, CH_2-13), 3.81 (3H, s, CH_3), 4.33-4.36 (1H, m, CH-6), 4.43 (2H, s, CH_2), 4.49 (1H, d, *J*(H,H)= 12.5 Hz, CH_AH$_B$), 4.52 (1H, d, *J*(H,H)= 12.5 Hz, CH$_A$$H_B$), 6.88-6.89 (2H, m, ArH), 7.26-7.37 (7H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.3 and 17.3 (CH_3), 18.9 (CH_2, C9), 22.8 and 22.8 (CH_2, C5), 25.7 (CH_2, C10), 28.7 (CH_2, C11), 29.5 (CH_2, C12), 33.4 (CH_2, C3), 33.6 (CH, C2), 38.6 (CH_2, C4), 55.5 (CH_3), 62.9 and 62.9 (CH, C6), 70.1 (CH_2, C13), 72.8 (CH_2, PMB), 73.2 (CH_2, Bn), 76.1 and 76.1 (CH_2, C1), 81.6 and 81.6 (C, C7), 85.5 and 85.6 (C, C8), 114.0 (CH), 127.6 (CH), 127.7 (CH), 128.5 (CH), 129.5 (CH), 130.9 (C), 139.0 (C), 159.3 (C); IR (thin film) ν (cm^{-1}) = 3413, 2935, 2862, 2212, 1613, 1513, 1454, 1248, 1097,

821, 737, 699; MS (ESI) 507 (50) $[M+MeOH+Na]^+$, 475 (100) $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{29}H_{40}Na_1O_4$ $[M+Na]^+$: 475.2819; found: 475.2809.

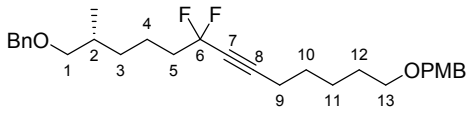
(2*R*)-2-((Benzyloxy)methyl)-13-((4-methoxyphenyl)methoxy)tridec-7-yn-6-one 44



44

Following the same procedure reported for **29**, (2*R*)-2-((benzyloxy)methyl)-13-((4-methoxyphenyl)methoxy)tridec-7-yn-6-ol **17** (2.8 g, 6.2 mmol, 1.0 eq) gave (2*R*)-2-((benzyloxy)methyl)-13-((4-methoxyphenyl)methoxy)tridec-7-yn-6-one **44** (1.72 g, 61%) as a colourless oil; $[\alpha]_D$ +0.2° (c 1.03, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.11-1.19 (1H, m, CH_2-3), 1.43-1.81 (11H, m, CH-2, CH_2-3,4,10,11,12), 2.36 (2H, t, *J*(H,H)= 7.1 Hz, CH_2-9), 2.47-2.57 (2H, m, CH_2-5), 3.26 (1H, dd, *J*(H,H)= 8.9, 6.4 Hz, CH_AH_B-1), 3.32 (1H, dd, *J*(H,H)= 9.1, 6.2 Hz, CH_AH_B-1), 3.45 (2H, t, *J*(H,H)= 6.7 Hz, CH_2-13), 3.81 (3H, s, CH_3), 4.43 (2H, s, CH_2), 4.49 (1H, d, *J*(H,H)= 12.6 Hz, CH_AH_B), 4.51 (1H, d, *J*(H,H)= 12.6 Hz, CH_AH_B), 6.87-6.89 (2H, m, ArH), 7.26-7.37 (7H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.2 (CH_3), 19.1 (CH_2, C9), 21.8 (CH_2, C4), 25.8 (CH_2, C11), 27.8 (CH_2, C10), 29.4 (CH_2, C12), 33.1 (CH_2, C3), 33.6 (CH, C2), 46.0 (CH_2, C5), 55.5 (CH_3), 69.9 (CH_2, C13), 72.8 (CH_2, PMB), 73.2 (CH_2, Bn), 75.9 (CH_2, C1), 81.1 (C, C7), 94.2 (C, C8), 114.0 (CH), 127.7 (CH), 127.7 (CH), 128.5 (CH), 129.5 (CH), 130.8 (C), 138.9 (C), 159.3 (C), 188.6 (CO, C6); IR (thin film) ν (cm^{-1}) = 2936, 2861, 2211, 1671, 1613, 1513, 1454, 1248, 1172, 1098, 1035, 822, 738, 699; MS (ESI) 505 (25) $[M+MeOH+Na]^+$, 487 (40), 473 (100) $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{29}H_{38}Na_1O_4$ $[M+Na]^+$: 473.2662; found: 473.2650.

1-((((12*R*)-13-(Benzyloxy)-8,8-difluoro-12-methyltridec-6-yn-1-ol)oxy)methyl)-4-methoxybenzene 45

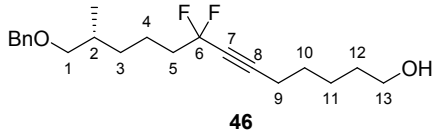


45

Following the same procedure reported for **30**, (2*R*)-2-((benzyloxy)methyl)-13-((4-methoxyphenyl)methoxy)tridec-7-yn-6-one **44** (1.7 g, 3.8 mmol, 1.0 eq) gave 1-((((12*R*)-13-

(benzyloxy)-8,8-difluoro-12-methyltridec-6-yn-1-ol)oxy)methyl)-4-methoxybenzene **45** (1.01 g, 62%) as a yellow oil; $[\alpha]_D$ -0.6° (c 1.09, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.96 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.15-1.22 (1H, m ,CH_2-3), 1.45-1.67 (9H, CH_2-3,4,10,11,12), 1.76-1.83 (1H, m, CH-2), 1.95-2.05 (2H, m, CH_2-5), 2.25-2.30 (2H, m, CH_2-9), 3.28 (1H, dd, *J*(H,H)= 9.0, 6.3 Hz, CH_AH_B-1), 3.32 (1H, dd, *J*(H,H)= 9.0, 6.3 Hz, CH_AH_B-1), 3.45 (2H, t, *J*(H,H)= 6.5 Hz, CH_2-13), 3.81 (3H, s, CH_3), 4.44 (2H, s, CH_2), 4.51 (2H, s, CH_2), 6.88-6.91 (2H, m, ArH), 7.26-7.38 (7H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.1 (CH_3), 18.5 (CH_2, C9), 20.6 (CH_2, C4), 25.7 (CH_2, C10), 27.9 (CH_2, C11), 29.4 (CH_2, C12), 33.1 (CH_2, C3), 33.5 (CH, C2), 39.9 (CH_2, t, *J*(C,F)= 26.7 Hz, C5), 55.5 (CH_3), 70.0 (CH_2, C13), 72.8 (CH_2, PMB), 73.2 (CH_2, Bn), 74.3 (C, t, *J*(C,F)= 40.3 Hz, C7), 75.9 (CH_2, C1), 88.6 (C, t, *J*(C,F)= 6.4 Hz, C7), 114.0 (CH), 115.2 (CF_2, t, *J*(C,F)= 230.1 Hz, C6), 127.7 (CH), 127.7 (CH), 128.5 (CH), 129.4 (CH), 130.8 (C), 138.9 (C), 159.3 (C); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = -81.1 (1F, d, *J*(F,F)= 267.0 Hz, CF_AF_B), -81.9 (1F, d, *J*(F,F)= 267.0 Hz, CF_AF_B); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -80.7 (1F, dm, *J*(F,F)= 267.3 Hz, CF_AF_B), -81.3 (1F, dm, *J*(F,F)= 267.3 Hz, CF_AF_B); IR (thin film) ν (cm^{-1}) = 2936, 2859, 2252, 1725, 1613, 1513, 1454, 1248, 1099, 821, 738, 699; MS (ESI) 527 (10) $[M+MeOH+Na]^+$, 495 (100) $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{29}H_{38}F_2Na_1O_3$ $[M+Na]^+$: 495.2681; found: 495.2671.

(12*R*)-13-(Benzyloxy)-8,8-difluoro-12-methyltridec-6-yn-1-ol 46

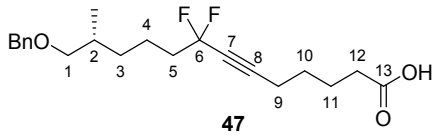


46

Following the same procedure reported for **31**, 1-((((12*R*)-13-(benzyloxy)-8,8-difluoro-12-methyltridec-6-yn-1-ol)oxy)methyl)-4-methoxybenzene **45** (0.5 g, 1.1 mmol, 1.0 eq) gave (12*R*)-13-(benzyloxy)-8,8-difluoro-12-methyltridec-6-yn-1-ol **46** (0.33 g, 88%) as a colourless oil; $[\alpha]_D$ -0.5° (c 0.97, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.16-1.22 (1H, m, CH_2-3), 1.44-1.67 (10H, m, CH_2-3,4,10,11,12, OH), 1.75-1.83 (1H, m, CH-2), 1.95-2.04 (2H, m, CH_2-5), 2.27-2.32 (2H, m, CH_2-9), 3.27-3.34 (2H, m, CH_2-1), 3.65 (2H, t, *J*(H,H)= 6.5 Hz, CH_2-13), 4.51 (2H, s, CH_2), 7.27-7.37 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.1 (CH_3), 18.5 (CH_2, C9), 20.7 (CH_2, C4), 25.2 (CH_2, C10), 27.8 (CH_2, C11), 32.3 (CH_2, C12), 33.2 (CH_2, C3), 33.6 (CH, C2), 39.9 (CH_2, t, *J*(C,F)= 26.7 Hz, C5), 62.8 (CH_2, C13), 73.3 (CH_2, Bn), 74.4 (C, t, *J*(C,F)= 40.2 Hz,

C7), 75.9 (CH_2, C1), 88.5 (C, t, *J*(C,F)= 6.5 Hz, C8), 115.2 (CF_2, t, *J*(C,F)= 230.7 Hz, C6), 127.7 (CH), 127.8 (CH), 128.6 (CH), 138.8 (C); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = -81.1 (1F, d, *J*(F,F)= 267.4 Hz, CF_AF_B), -81.9 (1F, d, *J*(F,F)= 267.4 Hz, CF_AF_B); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -81.1 (1F, dm, *J*(F,F)= 267.1 Hz, CF_AF_B), -81.9 (1F, dm, *J*(F,F)= 267.1 Hz, CF_AF_B); IR (thin film) ν (cm^{-1}) = 3396, 2936, 2863, 2252, 1454. 1319, 1157, 1097, 738, 699; MS (ESI) 407 (20) $[M+MeOH+Na]^+$, 375 (100) $[M+Na]^+$; HRMS: *m/z* calcd for $C_{21}H_{30}F_2Na_1O_2$ $[M+Na]^+$: 375.2106; found: 375.2096.

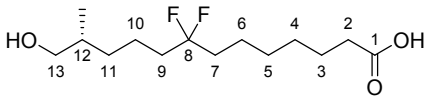
(12*R*)-13-(Benzyloxy)-8,8-difluoro-12-methyltridec-6-ynoic acid 47



47

Following the same procedure reported for **32**, (12*R*)-13-(benzyloxy)-8,8-difluoro-12-methyltridec-6-yn-1-ol **46** (280 mg, 0.8 mmol, 1.0 eq) gave (12*R*)-13-(benzyloxy)-8,8-difluoro-12-methyltridec-6-ynoic acid **47** (0.14 g, 48%) as a yellow oil; $[\alpha]_D$ +1.0° (c 0.64, $CHCl_3$) ; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.94 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.15-1.25 (1H, m, CH_2-3), 1.48-1.65 (5H, m, CH_2-3,4,10), 1.73-1.82 (3H, m, CH-2, CH_2-11), 1.95-2.04 (2H, m, CH_2-5), 2.29-2.33 (2H, m, CH_2-9), 2.39 (2H, t, *J*(H,H)= 7.3 Hz, CH_2-12), 3.27-3.33 (2H, m, CH_2-1), 4.52 (2H, s, CH_2), 7.27-7.37 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.1 (CH_3), 18.3 (CH_2, C9), 20.7 (CH_2, C4), 24.0 (CH_2, C11), 27.3 (CH_2, C10), 33.2 (CH_2, C3), 33.4 (CH_2, C12), 33.6 (CH, C2), 39.9 (CH_2, t, *J*(C,F)= 26.4 Hz, C5), 73.2 (CH_2, Bn), 74.7 (C, t, *J*(C,F)= 40.4 Hz, C7), 75.9 (CH_2, C1), 87.9 (C, t, *J*(C,F)= 6.8 Hz, C8), 115.2 (CF_2, t, *J*(C,F)= 231.2 Hz, C6), 127.7 (CH), 127.8 (CH), 128.6 (CH), 138.7 (C); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -80.8 (1F, d, *J*(F,F)= 267.2 Hz, CF_AF_B), -81.6 (1F, d, *J*(F,F)= 267.2 Hz, CF_AF_B); ^{19}F NMR (376 MHz, $CDCl_3$) δ = -81.3 (1F, dtt, *J*(F,F)= 267.7 Hz, *J*(H,F)= 14.4, 5.0 Hz, CF_AF_B), -82.1 (1F, dtt, *J*(F,F)= 267.7 Hz, *J*(H,F)= 15.0, 5.0 Hz, CF_AF_B); MS (ESI) 365 (100) $[M-H]^-$, 345 (30); HRMS: *m/z* calcd for $C_{21}H_{27}F_2O_3$ $[M-H]^-$: 365.1934; found: 365.1929.

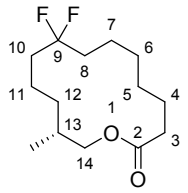
(12*R*)-8,8-Difluoro-13-hydroxy-12-methyltridecanoic acid 48



48

A solution of (12*R*)-13-(benzyloxy)-8,8-difluoro-12-methyltridec-6-ynoic acid **47** (0.12 g, 0.33 mmol, 1.0 eq) and palladium hydroxide (20 wt% on wet carbon, 23 mg, 0.03 mmol, 10 mol%) in THF (20 mL) was stirred under an atmosphere of hydrogen for 20 h. The reaction mixture was filtered through celite and the celite was washed with THF (30 mL). The THF layers were combined and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:1) gave (12*R*)-8,8-difluoro-13-hydroxy-12-methyltridecanoic acid **48** (42 mg, 46%) as a white solid; mp 67-68 °C; $[\alpha]_D$ +8.0° (c 0.23, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.94 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.12-1.22 (1H, m, CH_2-11), 1.36-1.69 (13H, m, CH_2-3,4,5,6,10,11, CH-12), 1.76-1.85 (4H, m, CH_2-7,9), 2.36 (2H, t, *J*(H,H)= 7.4 Hz, CH_2-2), 3.47 (1H, dd, *J*(H,H)= 10.5, 6.2 Hz, CH_AH$_B$-1), 3.52 (1H, dd, *J*(H,H)= 10.5, 6.0 Hz, CH$_A$$H_B$-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 16.6 (CH_3), 20.0 (CH_2, t, *J*(C,F)= 4.5 Hz, C10), 22.3 (CH_2, t, *J*(C,F)= 4.5 Hz, C6), 24.6 (CH_2, C3), 28.9 (CH_2, C4/C5), 29.1 (CH_2, C4/C5), 33.0 (CH_2, C11), 34.0 (CH_2, C2), 35.7 (CH, C12), 36.4 (CH_2, t, *J*(C,F)= 25.5 Hz, C9), 36.7 (CH_2, t, *J*(C,F)= 25.5 Hz, C7), 68.3 (CH_2, C13), 125.5 (CF_2, t, *J*(C,F)= 239.2 Hz, C8), 179.3 (CO_2H, C1); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -97.7 (2F, s); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -97.7 (2F, tt, *J*(H,F)= 16.6, 16.5 Hz, CF_2); MS (ESI) 559 (15) $[2M-H]^-$, 279 (100) $[M-H]^-$; HRMS: *m*/*z* calcd for $C_{14}H_{25}F_2O_3$ $[M-H]^-$: 279.1777; found: 279.1773.

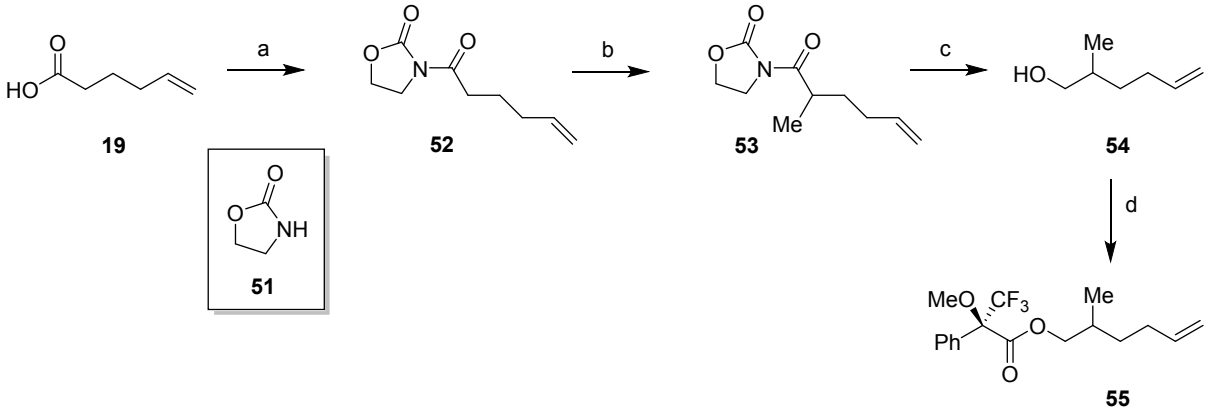
(13*R*)-9,9-Difluoro-13-methyl-1-oxacyclotetradecan-2-one 10



10

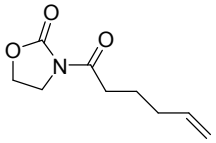
Triethylamine (0.29 mL, 2.01 mmol, 15.0 eq) and 2,4,6-trichlorobenzoyl chloride (0.19 mL, 1.34 mmol, 10.0 eq) were added to a solution of (12*R*)-8,8-difluoro-13-hydroxy-12-methyltridecanoic acid **48** (38 mg, 0.13 mmol, 1.0 eq) in dry THF (5 mL) at r.t. under argon and stirred for 2.5 h. The reaction mixture was diluted with dry toluene (20 mL) and added

over 2 h using a syringe pump to a solution of 4-DMAP (0.33 g, 2.68 mmol, 20.0 eq) in dry toluene (30 mL). The reaction mixture was stirred at r.t. for 18 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution (50 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:19) gave (13*R*)-9,9-difluoro-13-methyl-1-oxacyclotetradecan-2-one **10** (24 mg, 67%) as a white solid; mp 51-53 °C; $[\alpha]_D$ +5.9° (c 0.59, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.97 (3H, d, *J*(H,H)= 7.0 Hz, CH_3), 1.32-1.52 (10H, m, CH_2-5,6,7,11,12), 1.63-1.71 (2H, m, CH_2-4), 1.76-1.99 (5H, m, CH-13, CH_2-8,10), 2.33-2.45 (2H, m, CH_2-3), 3.80 (1H, dd, *J*(H,H)= 11.2, 7.4 Hz, CH_AH$_B$-14), 4.13 (1H, dd, *J*(H,H)= 11.2, 3.9 Hz, CH_AH$_B$-14); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.7 (CH_3), 19.9 (CH_2, t, *J*(C,F)= 5.3 Hz, C7/C11), 20.2 (CH_2, t, *J*(C,F)= 4.8 Hz, C7/C11), 24.3 (CH_2, C4), 26.1 (CH_2, C5), 26.5 (CH_2, C6), 31.6 (CH, C13), 32.4 (CH_2, t, *J*(C,F)= 25.7 Hz, C8/C10), 32.6 (CH_2, C12), 35.0 (CH_2, C3), 35.1 (CH_2, t, *J*(C,F)= 25.0 Hz, C8/C10), 68.0 (CH_2, C14), 126.7 (CF_2, *J*(C,F)= 240.4 Hz, C9), 174.0 (CO, C2); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -90.4 (1F, d, *J*(F,F)= 243.5 Hz, CF_AF$_B$), -91.0 (1F, d, *J*(F,F)= 243.5 Hz, CF$_A$$F_B$); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -90.4 (1F, dm, *J*(F,F)= 243.5 Hz, CF_AF$_B$), -91.0 (1F, dm, *J*(F,F)= 243.5 Hz, CF$_A$$F_B$); HRMS: *m*/*z* calcd for $C_{14}H_{28}F_2N_1O_3$ $[M+NH_4]^+$: 280.2083; found: 280.2086



Synthesis of Moshers derivative **55**. *Reagents and conditions*: a) (i) 2-Oxazolidinone **51**, *n*BuLi, THF, -78 °C, 30 min. (ii) Pivaloyl chloride, NEt_3, THF, 0 °C, 30 min, r.t., 1.5 h, 50%; b) NaHMDS, MeI, THF, -78 °C, 3 h, 34%; c) $LiAlH_4$, Et_2O, 0 °C, 2 h, 24%; d) (*R*)-(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride, NEt_3, 4-DMAP, DCM, r.t., 18 h, 78%.

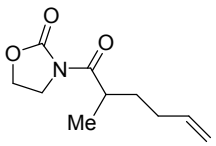
3-(Hex-5-enoyl)-1,3-oxazolidin-2-one 52



52

*n*BuLi (1.48 M in hexanes, 10.1 mL, 13.8 mmol, 1.2 eq) was added to a solution of 2-oxazolidinone **51** (1.0 g, 11.5 mmol, 1.0 eq) in dry THF (30 mL) at -78 °C under argon. In a separate flask, pivaloyl chloride (1.8 mL, 15.0 mmol, 1.3 eq) and triethylamine (2.7 mL, 19.6 mmol, 1.7 eq) were added to a solution of hex-5-enoic acid **19** (1.57 g, 13.8 mmol, 1.2 eq) in dry THF (10 mL) at 0 °C under argon and stirred for 30 min. The oxazolidinone solution was added to the mixed anhydride *via* cannula and stirred at 0 °C for 30 min, then warmed to r.t. and stirred for 18 h. The reaction mixture was quenched with sat. NH_4Cl solution (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution (50 mL), sat. NH_4Cl solution (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography (EtOAc 100%) gave 3-(hex-5-enoyl)-1,3-oxazolidin-2-one **52** (1.05 g, 50 %) as a colourless oil, as a mixture of two regioisomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.78 (2H, tt, *J*(H,H)= 7.5, 7.4 Hz, CH_2), 1.78 (2H, tt, *J*(H,H)= 7.4, 7.2 Hz, CH_2), 2.12-2.16 (2H, m, CH_2), 2.93 (2H, t, *J*(H,H)= 7.5 Hz, CH_2), 2.94 (2H, t, *J*(H,H)= 7.4 Hz, CH_2), 4.00-4.04 (2H, m, CH_2), 4.40-4.44 (2H, m, CH_2), 4.98-5.07 (2H, m, CH_2), 5.77-5.85 (1H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.6 (CH_2), 33.2 (CH_2), 34.6 (CH_2), 42.7 (CH_2), 62.2 (CH_2), 115.5 (CH_2), 138.0 (CH), 153.7 (CO), 173.6 (CO); MS (ESI) 206 (100) $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_9H_{13}N_1Na_1O_3$ $[M+Na]^+$: 206.0788; found: 206.0781.

3-(2-Methylhex-5-enoyl)-1,3-oxazolidin-2-one 53

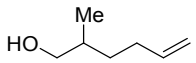


53

NaHMDS (1.0 M in THF, 3.0 mL, 3.0 mmol, 1.1 eq) was added to a solution of 3-(hex-5-enoyl)-1,3-oxazolidin-2-one **52** (0.5 g, 2.7 mmol, 1.0 eq) in dry THF (20 mL) at -78 °C under argon and stirred at -78 °C for 1 h. Iodomethane (0.8 mL, 13.5 mmol, 5.0 eq) was added and the reaction mixture was stirred at -78 °C for 1 h, then warmed to r.t. and stirred for 1 h. The

reaction mixture was quenched with sat. NH_4Cl solution (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution (50 mL), sat. NH_4Cl solution (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography (EtOAc/Pet. ether 1:4) gave 3-(2-methylhex-5-enoyl)-1,3-oxazolidin-2-one **53** (0.18 g, 34%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.18 (3H, d, *J*(H,H)= 6.8 Hz, CH_3), 1.47-1.54 (1H, m, CH_AH_B), 1.83-1.90 (1H, m, CH_AH_B), 2.05-2.13 (2H, m, CH_2), 3.76 (1H, tq, *J*(H,H)= 6.9, 6.8 Hz, CH), 4.00-4.04 (2H, m, CH_2), 4.39-4.42 (2H, m, CH_2), 4.94-5.03 (2H, m, CH_2), 5.75-5.83 (1H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 17.3 (CH_3), 31.6 (CH_2), 32.8 (CH_2), 37.1 (CH), 43.0 (CH_2), 62.0 (CH_2), 115.1 (CH_2), 138.3 (CH), 153.4 (CO), 177.5 (CO); MS (ESI) 220 (100) $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{10}H_{15}N_1Na_1O_3$ $[M+Na]^+$: 220.0944; found: 220.0938.

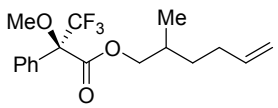
2-Methylhex-5-en-1-ol 54



54

Lithium aluminium hydride (0.12 g, 3.2 mmol, 4.0 eq) was added to a solution of 3-(2-methylhex-5-enoyl)-1,3-oxazolidin-2-one **53** (0.16 g, 0.8 mmol, 1.0 eq) in dry diethyl ether (10 mL) at 0 °C under argon and stirred for 2 h. The reaction mixture was quenched with water (0.5 mL). Sodium hydroxide solution (2 N, 0.5 mL) was added, followed by water (0.5 mL). The resulting white solid was filtered and the filtrate was collected. The solvent was removed *in vacuo*. Purification by column chromatography using silica gel (EtOAc/Pet. ether 1:9) gave 2-methylhex-5-en-1-ol **54** (22 mg, 24%) as a colourless oil. The NMR data was identical to that reported for (2*R*)-2-methylhex-5-en-1-ol **23**.

2-Methylhex-5-en-1-yl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 55

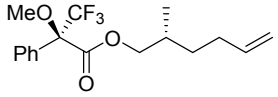


55

(*R*)-(-)-*α*-Methoxy-*α*-trifluoromethylphenylacetyl chloride (0.03 mL, 0.18 mmol, 2.0 eq) was added to a solution of 2-methylhex-5-en-1-ol **54** (10 mg, 0.09 mmol, 1.0 eq), triethylamine

(0.02 mL, 0.13 mmol, 1.5 eq) and 4-DMAP (43 mg, 0.35 mmol, 4.0 eq) in dry DCM (1.0 mL) at r.t. and stirred for 18 h. The solvent was removed *in vacuo*. Purification by column chromatography using silica gel (Pet. ether 100%) gave 2-methylhex-5-en-1-yl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **55** (23 mg, 78%) as a colourless oil, as a 1:1 mixture of diastereoisomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.94 (3H, d, *J*(H,H)= 6.7 Hz, CH_3, (*R*,*S*)-**55**), 0.95 (3H, d, *J*(H,H)= 6.7 Hz, CH_3, (*R*,*R*)-**55**), 1.21-1.31 (1H, m, CH_AH_B), 1.42-1.51 (1H, m, CH_AH_B), 1.85-1.94 (1H, m, CH), 1.98-2.15 (2H, m, CH_2), 3.56 (3H, bq, *J*(H,F)= 1.0 Hz, CH_3), 4.11 (1H, dd, *J*(H,H)= 10.8, 6.5 Hz, CH_AH_B, (*R*,*S*-**55**), 4.16 (1H, dd, *J*(H,H)= 10.8, 5.8 Hz, CH_AH_B, (*R*,*R*)-**55**), 4.20 (1H, dd, *J*(H,H)= 10.8, 6.5 Hz, CH_AH_B, (*R*,*S*)-**55**), 4.25 (1H, dd, *J*(H,H)= 10.8, 5.6 Hz, CH_AH_B, (*R*,*R*)-**55**), 4.95-5.03 (2H, m, CH_2), 5.71-5.80 (1H, m, CH), 7.40-7.43 (3H, m, ArH), 7.52-7.53 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 16.8 and 16.8 (CH_3), 31.1 (CH_2), 32.0 and 32.0 (CH_2), 32.3 and 32.4 (CH), 55.6 (CH_3), 71.2 and 71.2 (CH_2), 115.0 (CH_2), 123.6 (q, *J*(C,F)= 287.9 Hz, CF_3), 127.6 (CH), 128.6 (CH x 2), 129.8 (CH), 132.5 (C), 138.4 (C), 166.9 (CO); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -71.54 (3F, s, CF_3, (*R*,*S*)-**55**), -71.56 (3F, s, CF_3, (*R*,*R*)-**55**); MS (ESI) 683 (15) $[2M+Na]^+$, 353 (100) $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{17}H_{21}F_3Na_1O_3$ $[M+Na]^+$: 353.1335; found: 353.1331.

(2*R*)-2-Methylhex-5-en-1-yl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 56



56

(*R*)-(-)-*α*-Methoxy-*α*-trifluoromethylphenylacetyl chloride (0.03 mL, 0.18 mmol, 2.0 eq) was added to a solution of 2-methylhex-5-en-1-ol **54** (10 mg, 0.09 mmol, 1.0 eq), triethylamine (0.02 mL, 0.13 mmol, 1.5 eq) and 4-DMAP (43 mg, 0.35 mmol, 4.0 eq) in dry DCM (1.0 mL) at r.t. and stirred for 18 h. The solvent was removed *in vacuo*. Purification by column chromatography using silica gel (Pet. ether 100%) gave (2*R*)-2-Methylhex-5-en-1-yl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **56** (14 mg, 49%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J*(H,H)= 6.8 Hz, CH_3), 1.20-1.30 (1H, m, CH_AH_B), 1.41-1.50 (1H, m, CH_AH_B), 1.83-1.95 (1H, m, CH), 1.98-2.15 (2H, m, CH_2), 3.56 (3H, q, *J*(C,F)= 1.1 Hz, CH_3), 4.16 (1H, dd, *J*(H,H)= 10.7, 5.8 Hz, CH_AH_B), 4.20 (1H, dd, *J*(H,H)= 10.7, 6.3 Hz, CH_AH_B), 4.94-5.03 (2H, m, CH_2), 5.70-5.80 (1H, m, CH), 7.40-7.43 (3H, m, ArH), 7.52-7.54 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 16.8 (CH_3), 31.1 (CH_2), 32.0 (CH_2),

32.3 (CH), 55.6 (CH_3), 71.2 (CH_2), 115.0 (CH_2), 123.6 (q, J(C,F)= 287.3 Hz, CF_3), 127.5 (CH), 128.6 (CH x 2), 129.8 (CH), 132.5 (C), 138.4 (C), 166.9 (CO); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -71.56 (3F, s, CF_3, (*R*,*R*)-**56**); MS (ESI) 683 (10) $[2M+Na]^+$, 353 (100) $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{17}H_{21}F_3Na_1O_3$ $[M+Na]^+$: 353.1335; found: 353.1331.

1. Y. N. Ogibin, E. K. Starostin, A. V. Aleksandrov, K. K. Piunitsky, G. I. Nikishin, *Synthesis,* **1994**, 901-903.
2. L. Tomas, G. B. af Gennäs, M. A. Hiebel, P. Hampson, D. Gueyrard, B. Pelotier, J. Yli-Kauhaluoma, O. Piva, J. M. Lord, P. G. Goekjian, *Chem. Eur. J.*, **2012**, *18*, 7452-7466.
3. R. K. Boeckman, Jr., A. B. Charette, T. Asberom, B. H. Johnston, *J. Am. Chem. Soc*., **1991**, *113*, 5337-5353.
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Theoretical Calculations Section

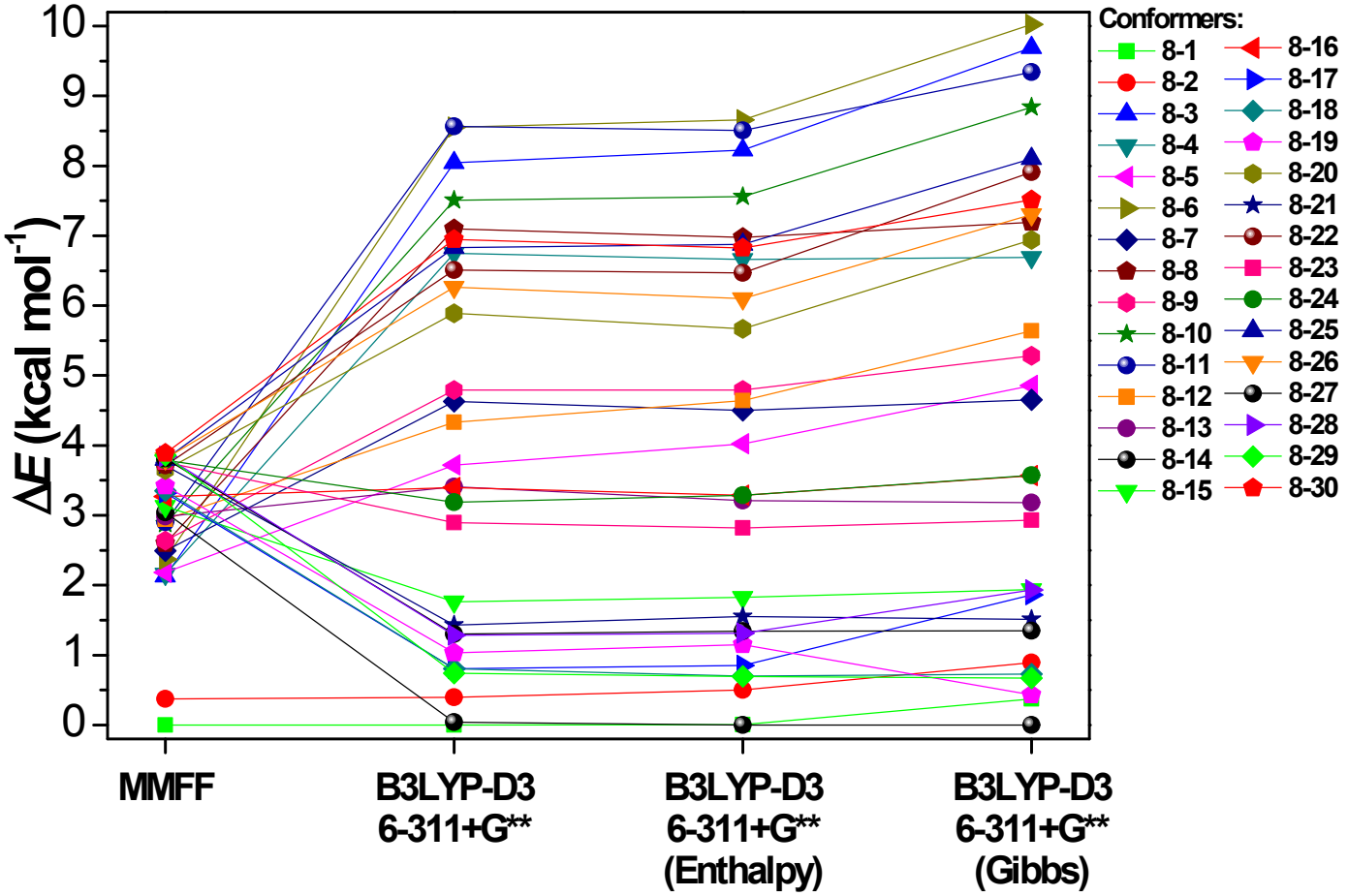
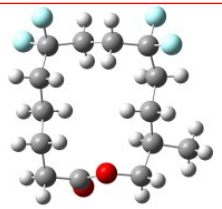
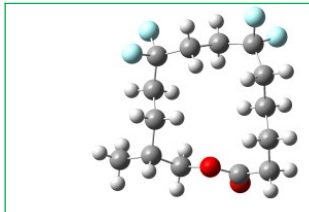


Figure S1: Compound **8** conformer relative energies for the 30 lowest energy minima (from 9650 conformers found in the MM calculations in the gas phase) obtained at different theoretical levels. MMFF and B3LYP/6-311+G** energies correspond to optimised geometries on the same levels, respectively. B3LYP/6-311+G** corrected energies with enthalpies and Gibbs free energies were obtained from B3LYP/6-311+G** frequency calculations.

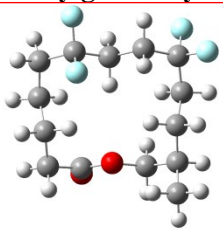
Table S1: Compound **8** lowest energy conformer geometry representations calculated at the B3LYP-D3/6-311+G** level. B3LYP-D3/6-311+G**(Gibbs) energies are given between parenthesis in kcal mol^{-1} for each conformer. X-ray geometries and corresponding calculated geometries are highlighted in red for X-ray geometry 1 and in green for X-ray geometry 2.



X-ray geometry 1



X-ray geometry 2



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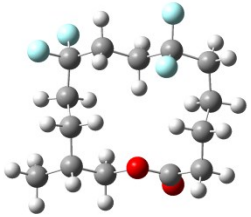

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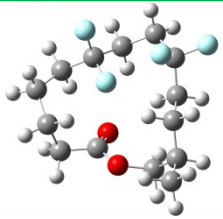

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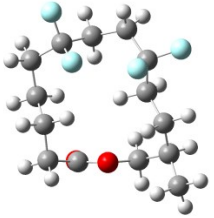
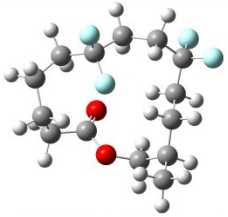


Conformer 8-4 (6.69)



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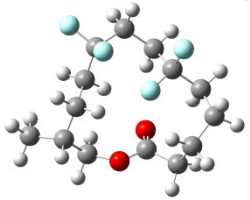

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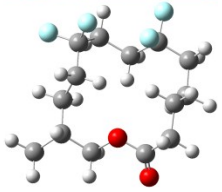

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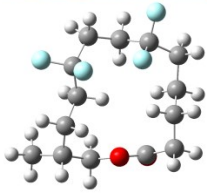

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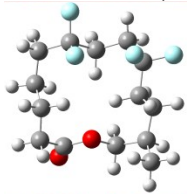

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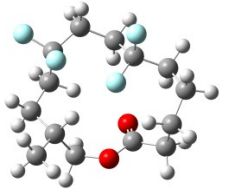

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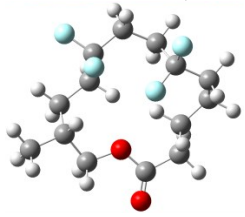

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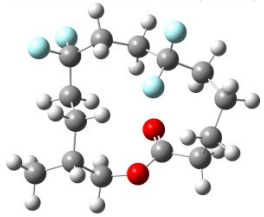

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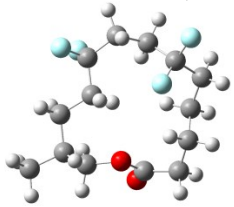

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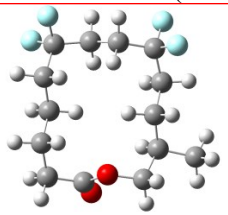

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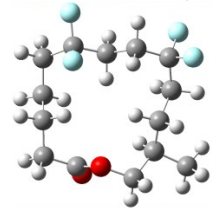

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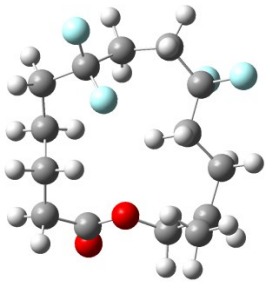

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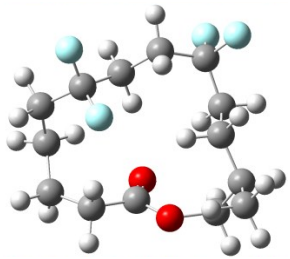

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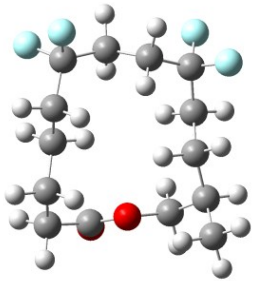

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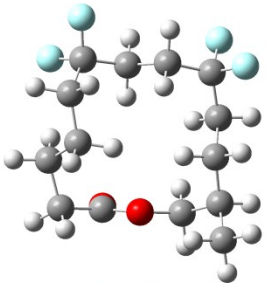

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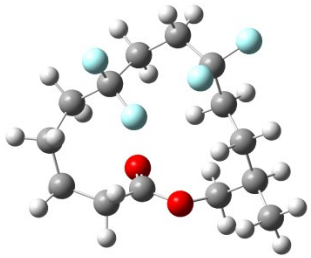

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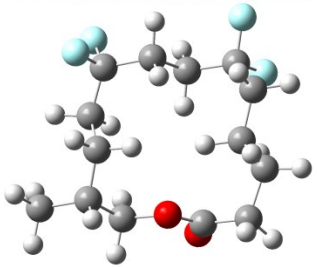

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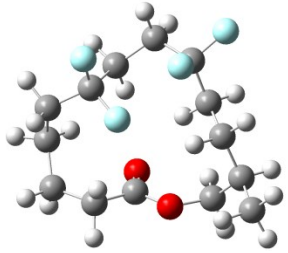

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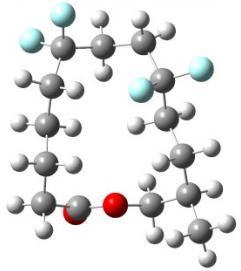

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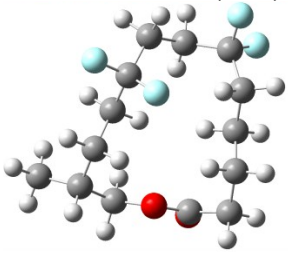

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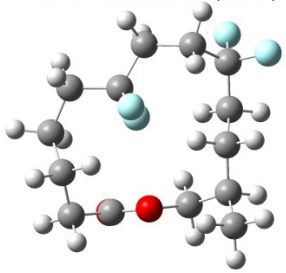

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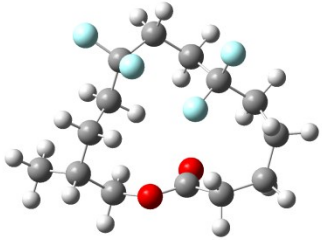

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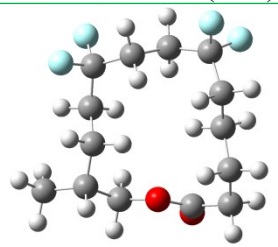

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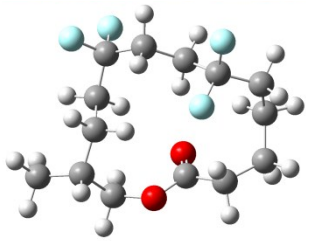

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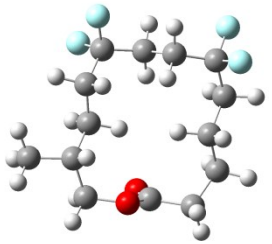
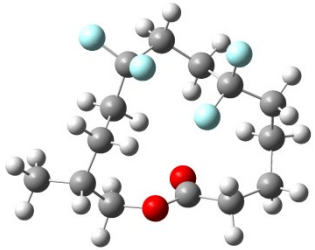


Conformer 8-29 (0.67)



Conformer 8-30 (7.51)

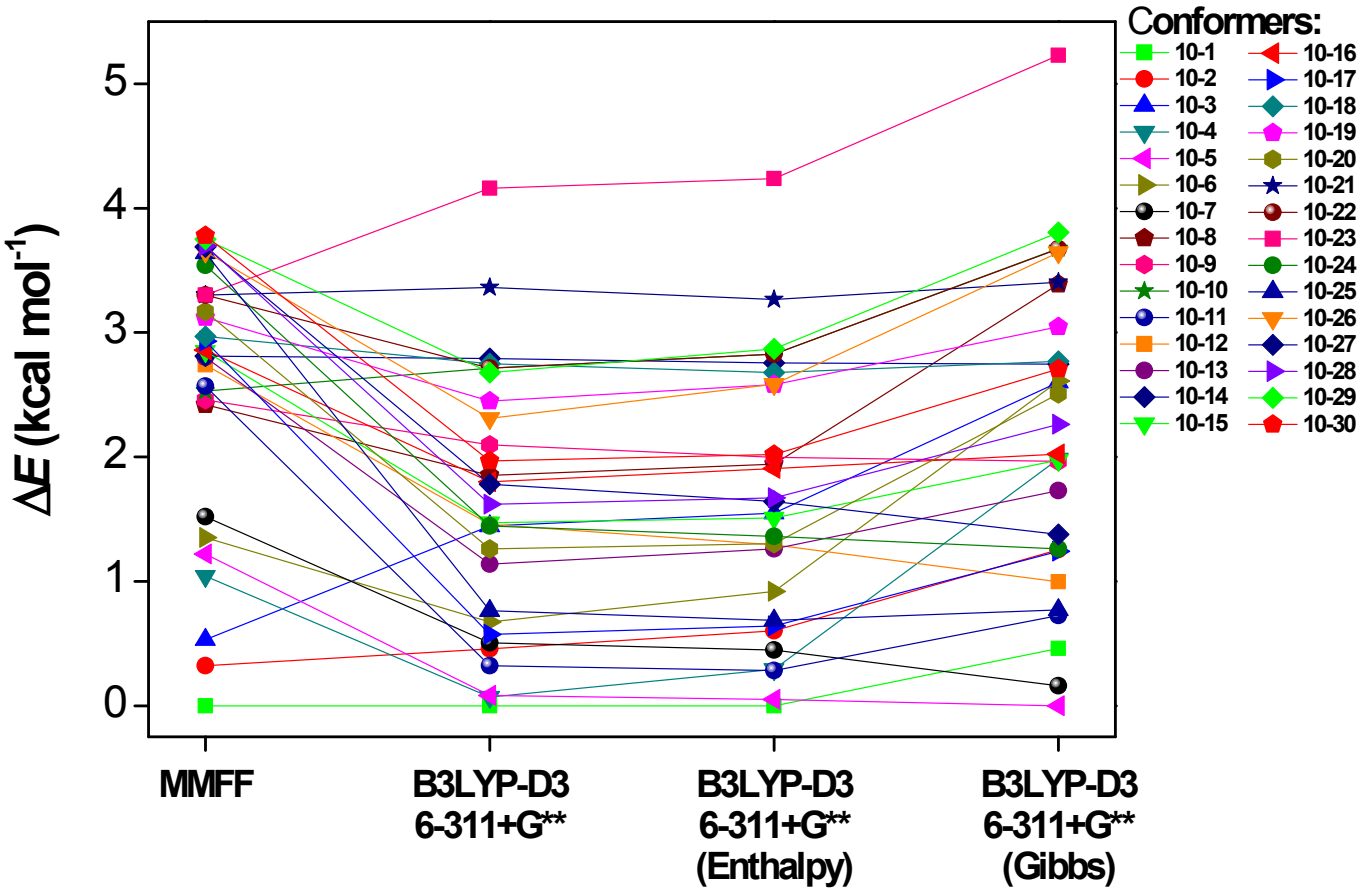
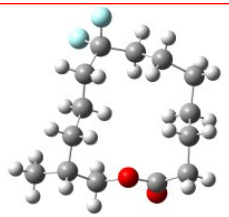
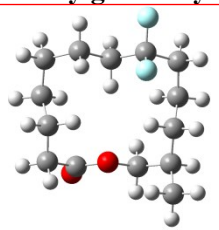


Figure S2: Compound **10** conformer relative energies for the 30 lowest energy minima (from 7948 conformers found in the MM calculations in the gas phase) obtained at different theoretical levels. MMFF and B3LYP/6-311+G** energies correspond to optimised geometries on the same levels, respectively. B3LYP/6-311+G** corrected energies with enthalpies and Gibbs free energies were obtained from B3LYP/6-311+G** frequency calculations.

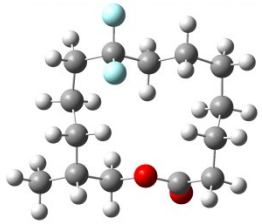
Table S2: Compound **10** lowest energy conformer geometry representations calculated at the B3LYP-D3/6-311+G** level. B3LYP-D3/6-311+G**(Gibbs) energies are given between parenthesis in kcal mol^{-1} for each conformer. The X-ray geometry and corresponding calculated geometry are highlighted in red.



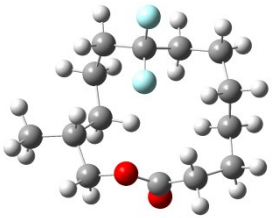
X-ray geometry



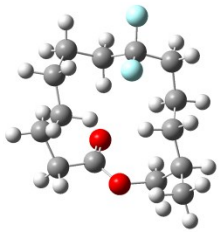
Conformer 10-1 (0.46)



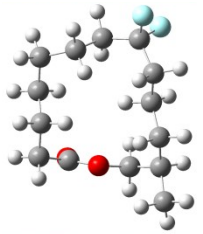
Conformer 10-2 (1.25)



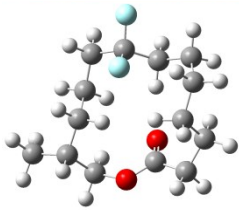
Conformer 10-3 (2.60)



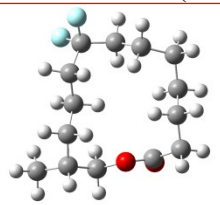
Conformer 10-4 (1.98)



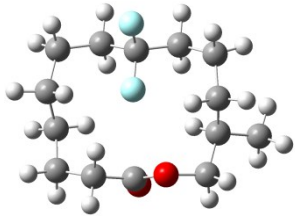
Conformer 10-5 (0.00)



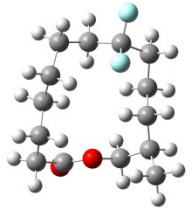
Conformer 10-6 (2.61)



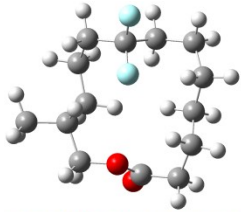
Conformer 10-7 (0.16)



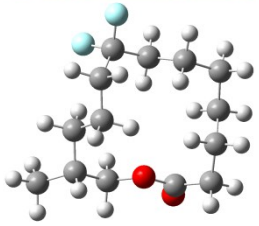
Conformer 10-8 (3.39)



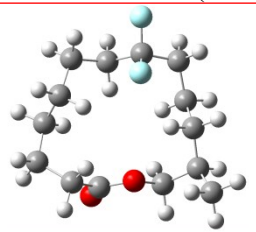
Conformer 10-9 (1.96)



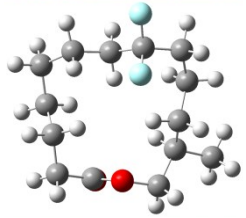
Conformer 10-10 (3.68)



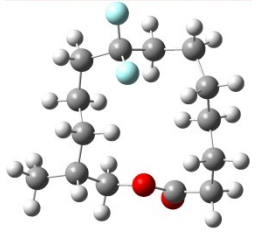
Conformer 10-11 (0.73)



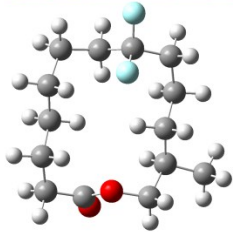
Conformer 10-12 (1.00)



Conformer 10-13 (1.73)

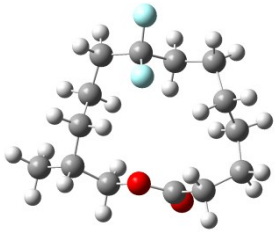


Conformer 10-14 (2.75)

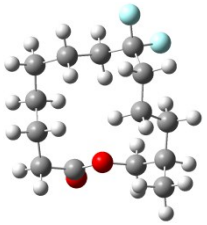


Conformer 10-15 (1.97)

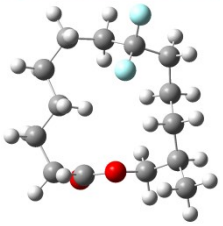
Continuation of **Table S2**:



Conformer 10-16 (2.02)



Conformer 10-17 (1.24)



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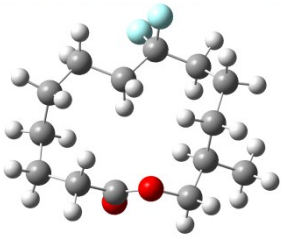
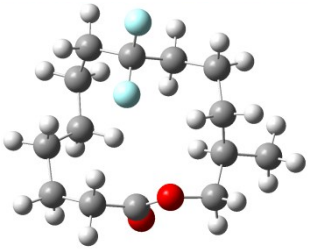
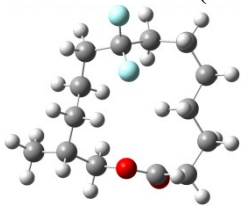


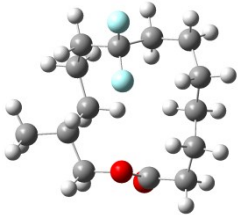
Conformer 10-19 (3.05)



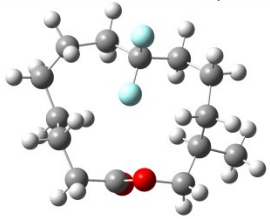
Conformer 10-20 (2.51)



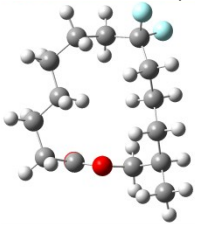
Conformer 10-21 (3.40)



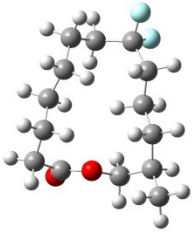
Conformer 10-22 (3.67)



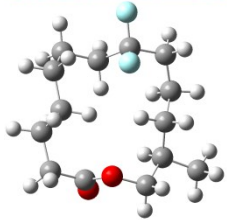
Conformer 10-23 (5.23)



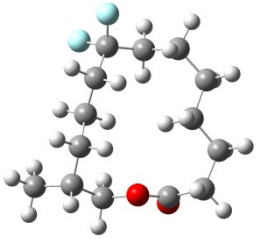
Conformer 10-24 (1.26)



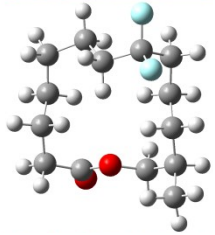
Conformer 10-25 (0.77)



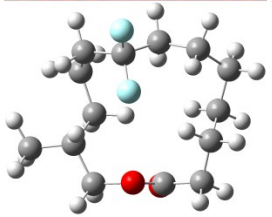
Conformer 10-26 (3.64)



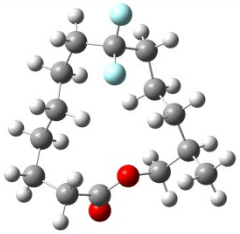
Conformer 10-27 (1.38)



Conformer 10-28 (2.26)



Conformer 10-29 (3.81)



Conformer 10-30 (2.71)

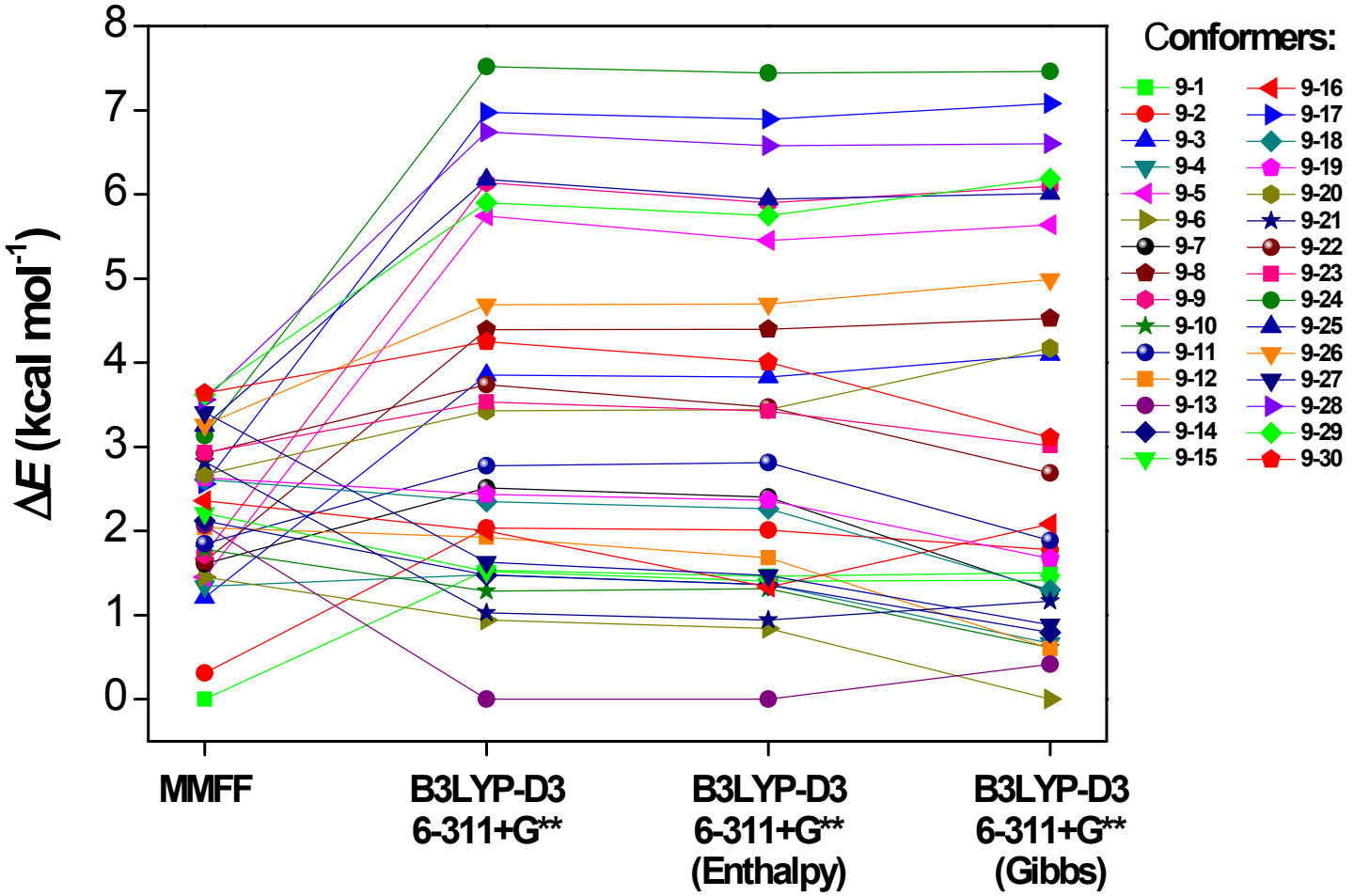
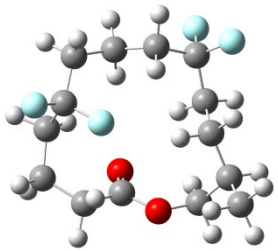
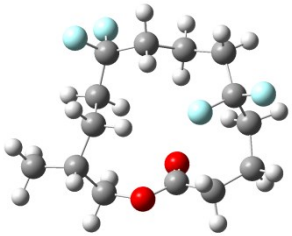


Figure S3: Compound **9** conformer relative energies for the 30 lowest energy minima (from 9714 conformers found in the MM calculations in the gas phase) obtained at different theoretical levels. MMFF and B3LYP/6-311+G** energies correspond to optimised geometries on the same levels, respectively. B3LYP/6-311+G** corrected energies with enthalpies and Gibbs free energies were obtained from B3LYP/6-311+G** frequency calculations.

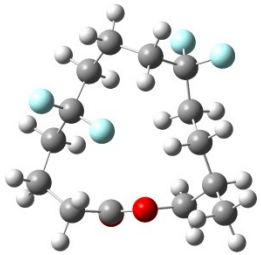
Table S3: Compound **9** lowest energy conformer geometry representations calculated at the B3LYP-D3/6-311+G** level. B3LYP-D3/6-311+G**(Gibbs) energies are given between parenthesis in kcal mol^{-1} for each conformer.



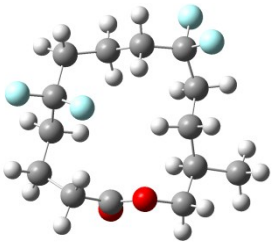
Conformer 9-1 (1.52)



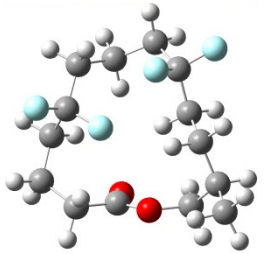
Conformer 9-2 (1.78)



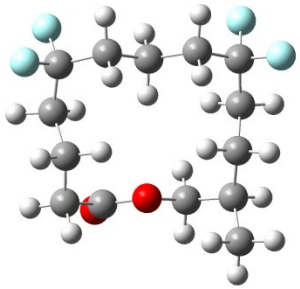
Conformer 9-3 (4.09)



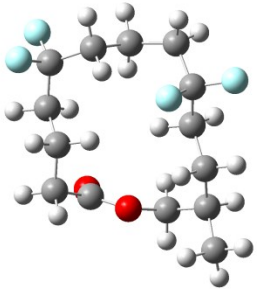
Conformer 9-4 (0.66)



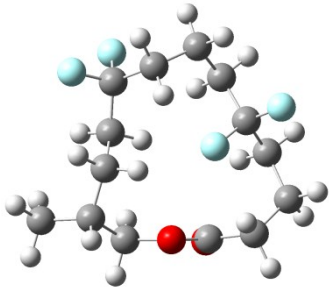
Conformer 9-5 (5.64)



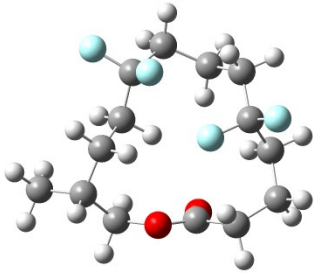
Conformer 9-6 (0.00)



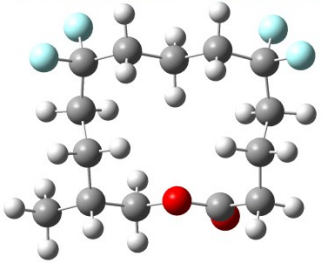
Conformer 9-7 (1.28)



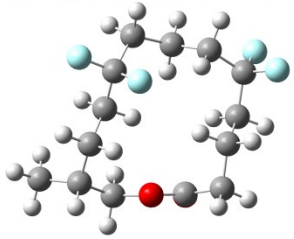
Conformer 9-8 (4.52)



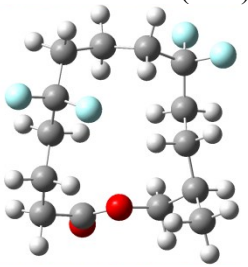
Conformer 9-9 (6.09)



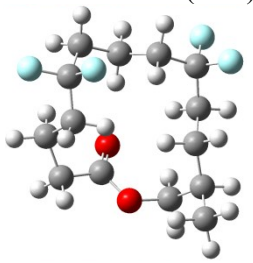
Conformer 9-10 (0.61)



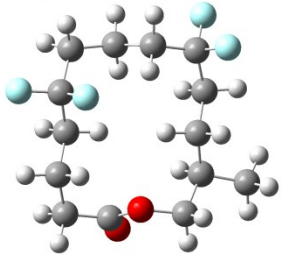
Conformer 9-11 (1.89)



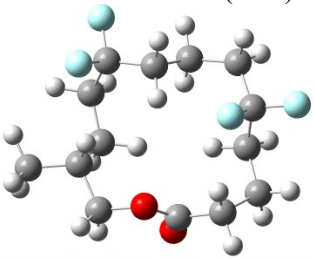
Conformer 9-12 (0.60)



Conformer 9-13 (0.42)

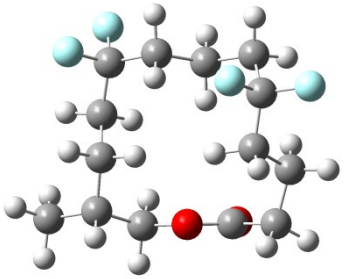


Conformer 9-14 (0.79)

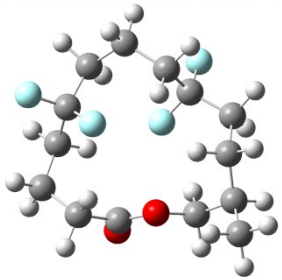


Conformer 9-15 (1.41)

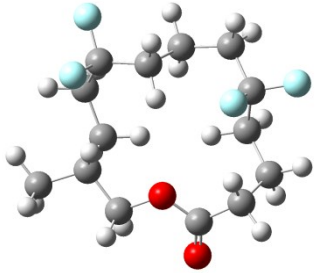
Continuation of **Table S3**:



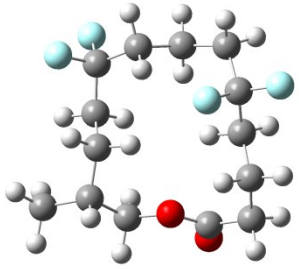
Conformer 9-16 (2.08)



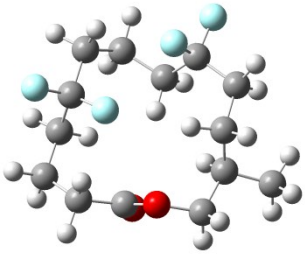
Conformer 9-17 (7.08)



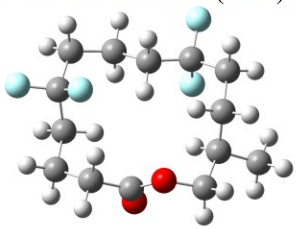
Conformer 9-18 (1.30)



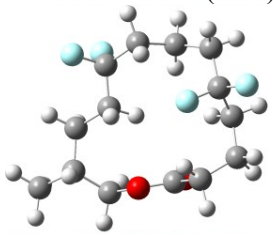
Conformer 9-19 (1.67)



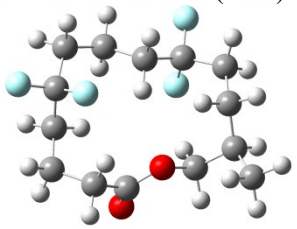
Conformer 9-20 (4.17)



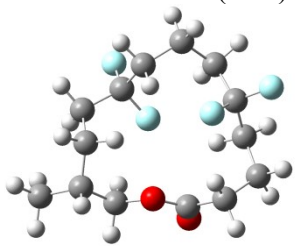
Conformer 9-21 (1.16)



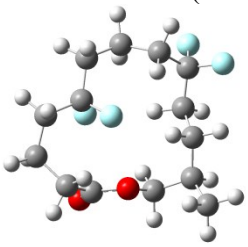
Conformer 9-22 (2.69)



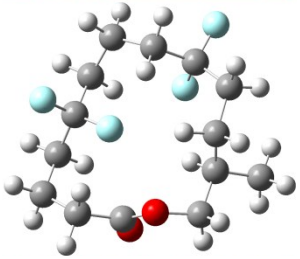
Conformer 9-23 (3.01)



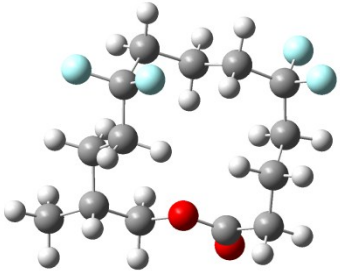
Conformer 9-24 (7.46)



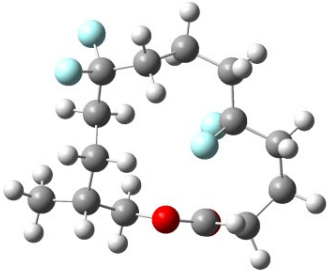
Conformer 9-25 (6.01)



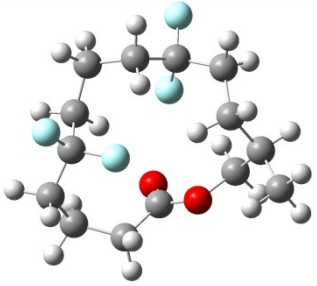
Conformer 9-26 (4.99)



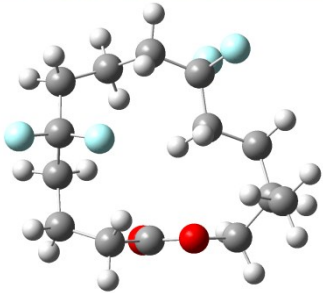
Conformer 9-27 (0.88)



Conformer 9-28 (6.60)



Conformer 9-29 (6.19)



Conformer 9-30 (3.11)